



Kent Academic Repository

Alexander, Stephen P. H., Davenport, Anthony P., Kelly, Eamonn, Gibb, Alasdair J., Mathie, Alistair A., Peach, Chloe J., Veale, Emma L., Armstrong, Jane F., Faccenda, Elena, Harding, Simon D. and others (2025) *The Concise Guide to PHARMACOLOGY 2025/26: G protein-coupled receptors*. *British Journal of Pharmacology*, 182 (S1). S24-S151. ISSN 0007-1188.

Downloaded from

<https://kar.kent.ac.uk/114870/> The University of Kent's Academic Repository KAR

The version of record is available from

<https://doi.org/10.1111/bph.70230>

This document version

Publisher pdf

DOI for this version

Licence for this version

CC BY (Attribution)

Additional information

Versions of research works

Versions of Record

If this version is the version of record, it is the same as the published version available on the publisher's web site. Cite as the published version.

Author Accepted Manuscripts

If this document is identified as the Author Accepted Manuscript it is the version after peer review but before type setting, copy editing or publisher branding. Cite as Surname, Initial. (Year) 'Title of article'. To be published in **Title of Journal**, Volume and issue numbers [peer-reviewed accepted version]. Available at: DOI or URL (Accessed: date).
























Enquiries

If you have questions about this document contact ResearchSupport@kent.ac.uk. Please include the URL of the record in KAR. If you believe that your, or a third party's rights have been compromised through this document please see our [Take Down policy](https://www.kent.ac.uk/guides/kar-the-kent-academic-repository#policies) (available from <https://www.kent.ac.uk/guides/kar-the-kent-academic-repository#policies>).

The Concise Guide to PHARMACOLOGY 2025/26: G protein-coupled receptors

Stephen P. H. Alexander¹ , Anthony P. Davenport² , Eamonn Kelly³ , Alasdair J. Gibb⁴ , Alistair A. Mathie⁵ , Chloe J. Peach⁶ , Emma L. Veale⁷ , Jane F. Armstrong⁸ , Elena Faccenda⁸ , Simon D. Harding⁸ , Christopher Southan⁸ , Jamie A. Davies⁸ , Maria Pia Abbracchio⁹ , George R. Abraham¹⁰ , Alexander Agoulnik¹¹, Wayne Alexander¹², Khaled Al-hosaini¹³, Magnus Bäck¹⁴ , Jillian G. Baker¹⁵, Nicholas M. Barnes¹⁶, Ross Bathgate¹⁷ , Jean-Martin Beaulieu¹⁸ , Annette G. Beck-Sickinger¹⁹ , Maik Behrens²⁰ , Kirstie A. Bennett²¹ , Kenneth E. Bernstein²² , Bernhard Bettler²³ , Nigel J. M. Birdsall²⁴ , Victoria A. Blaho²⁵ , Pascal Bonaventure²⁶ , Francois Boulay²⁷, Corinne Bousquet²⁸ , Hans Bräuner-Osborne²⁹ , Andrew J. Brown³⁰ , Geoffrey Burnstock³¹ , Marta Busnelli³² , Girolamo Caló³³, Vanni Caruso³⁴ , Justo P. Castaño³⁵, Kevin J. Catt³⁶, Stefania Ceruti⁹ , Paul Chazot³⁷ , Nan Chiang¹²⁴ , Bice Chini³² , Arthur Christopoulos³⁸ , Jerold Chun³⁹ , Antonia Cianciulli⁴⁰, Olivier Civelli⁴¹, Lucie H. Clapp³¹ , Réjean Couture⁴², Helen M. Cox⁴³ , Zsolt Csaba⁴⁴, Claes Dahlgren⁴⁵ , Frank M. Dautzenberg⁴⁶, Gordon Dent⁴⁷ , Steven D. Douglas⁴⁸, Pascal Dournaud⁴⁴, Margarita L. Dubocovich⁴⁹ , Satoru Eguchi⁵⁰, Emanuel Escher⁵¹, Edward J. Filardo⁵² , Tung Fong⁵³, Huamei Fu Forsman⁴⁵ , Marta Fumagalli⁹ , Raul R. Gainetdinov⁵⁴ , Michael L. Garelja⁵⁵ , Marc de Gasparo⁵⁶, Florence Gbahou⁴⁴ , Craig Gerard¹²⁴, Marvin Gershengorn³⁶, Michelle Glass⁵⁵ , David E. Gloriam²⁹ , Fernand Gobeil⁵¹, Theodore L. Goodfriend⁵⁷, Cyril Goudet⁵⁸ , Lukas Grätz⁵⁹, Karen J. Gregory³⁸ , Christian Gruber⁶⁰ , Andrew L. Gundlach¹⁷ , Jörg Hamann⁶¹ , Julien Hanson⁶² , Deborah S. Hartman⁶³ , Richard L. Hauger³⁹ , Debbie L. Hay⁵⁵ , Akos Heinemann⁶⁴ , Laura Heitman⁶⁵ , Deron R. Herr⁶⁶ , Morley D. Hollenberg⁶⁷, Nicholas D. Holliday¹⁵ , Birgitte Holst²⁹ , Mastgugu Horiuchi⁶⁹, Daniel Hoyer⁷⁰ , László Hunyady⁷¹, Ahsan Husain¹², Adriaan P. IJzerman⁶⁵ , Tadashi Inagami⁷², Paul A. Insel³⁹ , Kenneth A. Jacobson³⁶ , Laura H. Jacobson¹⁷ , Robert T. Jensen³⁶, Ralf Jockers⁴⁴ , Deepa Jonnalagadda²⁵ , Sadashiva Karnik⁷³ , Klemens Kaupmann⁷⁴ , Jacqueline Kemp⁷⁵, Charles Kennedy⁷⁶ , Yasuyuki Kihara²⁵ , Julia Kinsolving⁵⁹ , Takio Kitazawa⁷⁷, Pawel Kozielowicz⁵⁹ , Hans-Jürgen Kreienkamp⁷⁸, Jyrki P. Kukkonen⁷⁹ , Luxmichan Laishram⁷⁵, Tobias Langenhan¹⁹ , Christopher J. Langmead³⁸ , Dan Larhammar⁸⁰ , Katie Leach³⁸ , Davide Lecca⁹ , John D. Lee⁸¹ , Susan E. Leeman⁸², Jérôme Leprince⁸³ , Rob Leurs⁸⁴ , Xaria X. Li⁸⁵ , Ines Liebscher¹⁹ , Stephen J. Lolait⁸⁶ , Amelie Lupp⁸⁷, Robyn Macrae¹⁰, Janet J. Maguire¹⁰ , Davide Malfacini³³, Maurice Manning⁸⁸, Davide Marangon⁹ , Kirill Martemyanov⁸⁹ , Jean Mazella⁹⁰ , Craig A. McArdle⁸⁶ , Shlomo Melmed⁹¹, Martin C. Michel⁹² , Laurence J. Miller⁹³ , Vincenzo Mitolo⁴⁰, Bernard Mouillac⁵⁸ , Christa E. Müller⁹⁴ , Philip M. Murphy³⁶, Jean-Louis Nahon⁹⁰ , Richard R. Neubig⁹⁵ , Tony Ngo²⁵ , Xavier Norel⁴⁴ , Duuamene Nyimamu¹⁰, Anne-Marie O'Carroll⁸⁶ , Stefan Offermanns⁹⁶ , Maria Antonietta Panaro⁴⁰ , Marc Parmentier⁹⁷, Nicole Perry-Hauser⁹⁸ , Roger G. Pertwee⁹⁹ , Jean-Philippe Pin¹⁰⁰ , Eric R. Prossnitz¹⁰¹ , Helena Chengxue Qin¹⁰², Mark Quinn¹⁰³, Stefano Raffaele⁹ , Rithwik Ramachandran⁶⁷ , Manisha Ray²⁵ , Rainer K. Reinscheid⁸⁷, Alejandro Romeral Buzón²⁹ , Philippe Rondard¹⁰⁰ , Mette M. Rosenkilde²⁹ , G. Enrico Rovati⁹ , Chiara Ruzza¹⁰⁴ 



Gareth J. Sanger¹⁰⁵ , Nicole Scholz¹⁹ , Torsten Schöneberg¹⁹ , Gunnar Schulte⁵⁹ , Stefan Schulz⁸⁷, Deborah L. Segaloff¹⁰⁶, Charles N. Serhan¹²⁴, Arun K. Shukla¹⁰⁷ , Khuraijam Dhanachandra Singh⁷⁵ , Craig M. Smith¹⁰⁸, Nicola J. Smith¹⁰⁹ , Claudia Stäubert¹⁹ , Leigh A. Stoddart¹¹⁰ , Yukihiko Sugimoto¹¹¹ , Roger Summers¹⁰² , Valerie P. Tan³⁹ , David M. Thal¹⁰² , Walter (Wally) Thomas⁸⁵, Pieter B. M. W. M. Timmermans¹¹², Kalyan Tirupula⁷⁵, Lawrence Toll¹¹³ , Giovanni Tulipano¹¹⁴, Hamiyet Unal⁷⁵, Thomas Unger¹¹⁵, Celine Valant¹⁰² , Patrick Vanderheyden⁹⁷, David Vaudry⁸³, Hubert Vaudry⁸³, Joseph G. Verbalis¹¹⁶ , Jean-Pierre Vilardaga¹¹⁷ , Christopher S. Walker¹¹⁸ , Ji Ming Wang³⁶, Donald T. Ward¹¹⁹ , Hans-Jürgen Wester²⁰, Gary B. Willars¹²⁰, Tom Lloyd Williams¹⁰, Trent M. Woodruff⁸⁵ , Huixian Wu¹²¹ , Cheng Yang³⁴, Chengcan Yao¹²² , Richard D. Ye¹²³ and Nathan Zaidman¹⁰¹ 

¹Division of Physiology, Pharmacology & Neuroscience, School of Life Sciences, University of Nottingham Medical School, Nottingham, NG7 2UH, UK, ²Clinical Pharmacology Unit, University of Cambridge, Cambridge, CB2 0QQ, UK, ³School of Psychology and Neuroscience, University of Bristol, Bristol, BS8 1TD, UK, ⁴Research Department of Neuroscience, Physiology and Pharmacology, Division of Biosciences, University College London, Gower Street, London, WC1E 6BT, UK, ⁵School of Life Sciences, University of Westminster, London, W1W 6UW, UK, ⁶Division of Physiology, Pharmacology & Neuroscience, School of Life Sciences, Centre of Membrane Proteins and Receptors (COMPARE), University of Nottingham Medical School, Nottingham, NG7 2UH, UK, ⁷Medway School of Pharmacy, Universities of Kent and Greenwich, Chatham Maritime, Kent, ME4 4TB, UK, ⁸Institute for Neuroscience and Cardiovascular Research, University of Edinburgh, Edinburgh, EH8 9XD, UK, ⁹University of Milan, Milan, Italy, ¹⁰University of Cambridge, Cambridge, UK, ¹¹Florida International University, Miami, USA, ¹²Emory University, Atlanta, USA, ¹³King Saud University, Riyadh, Kingdom of Saudi Arabia, ¹⁴Karolinska University Hospital, Stockholm, Sweden, ¹⁵University of Nottingham, Nottingham, UK, ¹⁶University of Birmingham, Birmingham, UK, ¹⁷Florey Institute of Neuroscience and Mental Health, Melbourne, Australia, ¹⁸University of Toronto, Toronto, Canada, ¹⁹Leipzig University, Leipzig, Germany, ²⁰Technical University of Munich, Freising, Germany, ²¹Nxera Pharma UK Ltd, Cambridge, UK, ²²Cedars-Sinai Medical Center, Los Angeles, USA, ²³University of Basel, Basel, Switzerland, ²⁴The Francis Crick Institute, London, UK, ²⁵Sanford Burnham Prebys Medical Discovery Institute, La Jolla, USA, ²⁶Janssen Research & Development, San Diego, USA, ²⁷University of Grenoble Alpes, Grenoble, France, ²⁸French Institute of Health and Medical Research (INSERM), Toulouse, France, ²⁹University of Copenhagen, Copenhagen, Denmark, ³⁰Ikherma Consulting Ltd, Hitchin, UK, ³¹University College London, London, UK, ³²University of Milan Bicocca, Veduggio al Lambro, Italy, ³³University of Padova, Padova, Italy, ³⁴University of Tasmania School of Medicine, Hobart, Australia, ³⁵University of Córdoba, Córdoba, Spain, ³⁶National Institutes of Health, Bethesda, USA, ³⁷Durham University, Durham, UK, ³⁸Monash Institute of Pharmaceutical Sciences and Department of Pharmacology, Parkville, Australia, ³⁹University of California San Diego, La Jolla, USA, ⁴⁰University of Bari, Bari, Italy, ⁴¹University of California Irvine, Irvine, USA, ⁴²University of Montréal, Montréal, Canada, ⁴³King's College London, London, UK, ⁴⁴French Institute of Health and Medical Research (INSERM), Paris, France, ⁴⁵University of Gothenburg, Gothenburg, Sweden, ⁴⁶Novaliq GmbH, Konstanz, Germany, ⁴⁷Keele University, Newcastle-under-Lyme, UK, ⁴⁸University of Pennsylvania, Pennsylvania, USA, ⁴⁹University at Buffalo, Buffalo, USA, ⁵⁰Temple University, Philadelphia, USA, ⁵¹University of Sherbrooke, Sherbrooke, Canada, ⁵²Rhode Island Hospital, Providence, USA, ⁵³Labcorp Drug Development, Somerset, USA, ⁵⁴Saint Petersburg State University, Saint Petersburg, Russia, ⁵⁵University of Otago, Dunedin, New Zealand, ⁵⁶MG Consulting Co, Basel, Switzerland, ⁵⁷University of Wisconsin, Madison, USA, ⁵⁸French National Centre for Scientific Research, Montpellier, France, ⁵⁹Karolinska Institute, Stockholm, Sweden, ⁶⁰Medical University of Vienna, Vienna, Austria, ⁶¹Amsterdam University, Amsterdam, The Netherlands, ⁶²University of Liège, Liège, Belgium, ⁶³Takeda Development Center Americas, Inc., Boston, USA, ⁶⁴Medical University of Graz, Graz, Austria, ⁶⁵Leiden University, Leiden, The Netherlands, ⁶⁶Indiana State University Foundation, Terre Haute, USA, ⁶⁷University of Calgary, Calgary, Canada, ⁶⁹Ehime University, Ehime, Japan, ⁷⁰University of Melbourne, Melbourne, Australia, ⁷¹Semmelweis University, Budapest, Hungary, ⁷²Vanderbilt University, Nashville, USA, ⁷³Lerner Research Institute, Cleveland, USA, ⁷⁴Novartis, Basel, Switzerland, ⁷⁵Cleveland Clinic Lerner Research Institute, Cleveland, USA, ⁷⁶Strathclyde University, Glasgow, UK, ⁷⁷Rakumo Gakuen University, Ebetsu, Japan, ⁷⁸University of Hamburg, Hamburg, Germany, ⁷⁹University of Helsinki, Helsinki, Finland, ⁸⁰Uppsala University, Uppsala, Sweden, ⁸¹University of Queensland, Brisbane, Australia, ⁸²Boston University, Boston, USA, ⁸³University of Rouen, Rouen, France, ⁸⁴Vrije Universiteit Amsterdam, Amsterdam, The Netherlands, ⁸⁵University of Queensland, Queensland, Australia, ⁸⁶University of Bristol, Bristol, UK, ⁸⁷Friedrich Schiller University Jena, Jena, Germany, ⁸⁸University of Toledo College of Medicine, Toledo, USA, ⁸⁹Scripps Research Institute, Jupiter, USA, ⁹⁰French National Centre for Scientific Research (CNRS), Valbonne, France, ⁹¹Cedars-Sinai Medical Center, Los Angeles, USA, ⁹²Johannes Gutenberg University, Mainz, Germany, ⁹³Mayo Foundation for Medical Education and Research, Scottsdale, USA, ⁹⁴University of Bonn, Bonn, Germany, ⁹⁵Michigan State University, East Lansing, USA, ⁹⁶Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany, ⁹⁷Free University of Brussels, Brussels, Belgium, ⁹⁸University of Glasgow, Glasgow, UK, ⁹⁹University of Aberdeen, Aberdeen, UK, ¹⁰⁰University of Montpellier, Montpellier, France, ¹⁰¹University of New Mexico, Albuquerque, USA, ¹⁰²Monash University, Melbourne, Australia, ¹⁰³Montana State University, Bozeman, USA, ¹⁰⁴University of Ferrara, Ferrara, Italy, ¹⁰⁵Queen Mary University of London, London, UK, ¹⁰⁶University of Iowa, Iowa City, USA, ¹⁰⁷Indian Institute of Technology, Kanpur, India, ¹⁰⁸Deakin University, Waurn Ponds, Australia, ¹⁰⁹University of New South Wales, Sydney, Australia, ¹¹⁰Excellerate Bioscience, Nottingham, UK, ¹¹¹Kumamoto University, Kumamoto, Japan, ¹¹²Kosan Biosciences Inc., San Francisco, USA, ¹¹³Florida Atlantic University, Jupiter, USA, ¹¹⁴University of Brescia, Brescia, Italy, ¹¹⁵Maastricht University, Maastricht, The Netherlands, ¹¹⁶Georgetown University Medical Center, Washington, DC, USA, ¹¹⁷University of Pittsburgh, Pittsburgh, USA, ¹¹⁸University of Auckland, Auckland, New Zealand, ¹¹⁹University of Manchester, Manchester, UK, ¹²⁰University of Leicester, Leicester, UK, ¹²¹Pfizer Research & Development, Groton, USA, ¹²²University of Edinburgh, Edinburgh, UK, ¹²³The Chinese University of Hong Kong, Shenzhen, China, ¹²⁴Harvard University, Boston, USA

Abstract

The Concise Guide to Pharmacology 2025/26 marks the seventh edition in this series of biennial publications in the *British Journal of Pharmacology*. Presented in landscape format, the guide provides a comparative overview of the pharmacology of drug target families. The concise nature of the Concise Guide refers to the style of presentation, being clear, accessible, and well-structured, rather than the scope of the content, which spans approximately 500 pages. The Concise Guide summarises the key pharmacological properties of around 1900 human drug targets, and nearly 7000 interactions, involving around 4400 ligands. While the content is a substantially condensed version of the more detailed information and links available at the www.guidetopharmacology.org website, the printed guide serves as a permanent, citable, point-in-time record, that remains stable despite ongoing updates to the online database. The full contents of this publication can be found at <https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.70230>.

The Concise Guides provide expert-curated recommendations of 'Gold Standard' selective pharmacological tools, available either commercially or as donations, which enable the identification of individual drug targets or families of drug targets. While the Concise Guide offers a more streamlined overview, more comprehensive information, including detailed pharmacological profiles and links to multiple online databases, is available through the Guide to Pharmacology website. The 2025/26 edition of the Concise Guide is based on material current as of mid-2025, and supersedes all previous editions, including the 2023/24 Guide, and earlier Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), and as such provides official IUPHAR classification and nomenclature for human drug targets, where applicable.

G protein-coupled receptors are one of the six major pharmacological targets into which the Guide is divided, with the others being: ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. Each section includes nomenclature guidance, concise summaries, information of the best available pharmacological tools, key references, and suggestions for further reading.

Conflict of interest

The authors state that there are no conflicts of interest to disclose.

© 2025 The Author(s). *British Journal of Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Introduction: G protein-coupled receptors (GPCRs) are the largest class of membrane proteins in the human genome. The term "7TM receptor" is commonly used interchangeably with "GPCR", although there are some receptors with seven transmembrane domains that do not signal through G proteins. GPCRs share a common architecture, each consisting of a single polypeptide with an extracellular N-terminus, an intracellular C-terminus and seven hydrophobic transmembrane domains (TM1-TM7) linked by three extracellular loops (ECL1-ECL3) and three intracellular loops (ICL1-ICL3). About 800 GPCRs have been identified in man, of which about half have sensory functions, mediating olfaction (~400), taste (33), light perception (10) and pheromone signalling (5) [1943]. The remaining ~350 non-sensory GPCRs mediate signalling by ligands that range in size from small molecules to peptides to large proteins; they are the targets for the majority of drugs in clinical usage [2148, 2346], although only a minority of these receptors are exploited therapeutically. The first classification scheme to be proposed for GPCRs [1464] divided them, on the basis of sequence homology, into six classes. These classes and their prototype members were as follows: **Class A** (rhodopsin-like), **Class B** (secretin receptor family), **Class C** (metabotropic glutamate), **Class D** (fungal mating pheromone receptors), **Class E** (cyclic AMP receptors) and **Class F** (frizzled/smoothed). Of these, classes D and E are not found in vertebrates. An alternative classification scheme "GRAFS" [2510] divides vertebrate GPCRs into five classes, overlapping with the A-F nomenclature, *viz*:

Glutamate family (class C), which includes metabotropic glutamate receptors, a calcium-sensing receptor and GABA_B receptors, as well as three taste type 1 receptors and a family of pheromone receptors (V2 receptors) that are abundant in rodents but absent in man [1943].

Rhodopsin family (class A), which includes receptors for a wide variety of small molecules, neurotransmitters, peptides and hormones, together with olfactory receptors, visual pigments, taste type 2 receptors and five pheromone receptors (V1 receptors).

Adhesion family GPCRs are phylogenetically related to class B receptors, from which they differ by possessing large extracellular N-termini that are autoproteolytically cleaved from their 7TM domains at a conserved "GPCR proteolysis site" (GPS) which lies within a much larger (~320 residue) "GPCR autoproteolysis-inducing" (GAIN) domain, which in terms of evolution is an ancient motif also found in polycystic kidney disease 1 (PKD1)-like proteins, which has been suggested to be both required and sufficient for autoproteolysis [2288].

Frizzled family consists of 10 Frizzled proteins (FZD₁₋₁₀) and Smoothed (SMO). The FZDs are activated by secreted lipoglycoproteins of the WNT family, whereas SMO is indirectly activated by the Hedgehog (HH) family of proteins acting on the transmembrane protein Patched (PTCH).

Secretin family, encoded by 15 genes in humans. The ligands for receptors in this family are polypeptide hormones of 27-141 amino acid residues; nine of the mammalian receptors respond to ligands that are structurally related to one another (glucagon, glucagon-like peptides (GLP-1, GLP-2), glucose-dependent insulinotropic polypeptide (GIP), secretin, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP) and growth-hormone-releasing hormone (GHRH)) [1053].

GPCR families

Family	Class A	Class B (Secretin)	Class C (Glutamate)	Adhesion	Frizzled
Receptors with known ligands	197	15	12	0	11
Orphans	87 (54) ^a	-	8 (1) ^a	33 (7) ^a	0
Sensory (olfaction)	390 ^{b,c}	-	-	-	-
Sensory (vision)	10 ^d opsins	-	-	-	-
Sensory (taste)	30 ^c taste 2	-	3 ^c taste 1	-	-
Sensory (pheromone)	5 ^c vomeronasal 1	-	-	-	-
Total	719	15	23	33	11

^aNumbers in brackets refer to orphan receptors for which an endogenous ligand has been proposed in at least one publication, see [586]; ^b[2130]; ^c[1943]; ^d[2803].

Pseudogenes

A number of pseudogenes have been identified in the human genome, which, in some cases, have a shared ancestry with functional G protein-coupled receptors in other species, including rats and mice. A curated list includes:

ADGRE4P, *GNRHR2*, *GPR79*, *HTR5BP*, *NPY6R*, *TAAR3P*, *TAAR4P*, *TAAR7P*, *TAS2R12P*, *TAS2R15P*, *TAS2R18P*, *TAS2R2P*, *TAS2R62P*, *TAS2R63P*, *TAS2R64P*, *TAS2R67P*, *TAS2R68P*, *TAS2R6P*. A more detailed listing containing further information can be viewed [here](#).

Odorant receptors

Odorant receptors are also seven-transmembrane spanning G protein-coupled receptors, responsible for the detection of odorant, generally volatile compounds associated with olfaction. These are not currently included as they are not yet associated with extensive pharmacological data but are curated in the following databases: The gene list of odorant receptors at [HGNC](#), and curated by [HORDE](#) and [ORDB](#).

Family structure

S28	5-Hydroxytryptamine receptors	S55	Chemokine receptors	S74	Dopamine receptors
S31	Acetylcholine receptors (muscarinic)	S59	Cholecystokinin receptors	S76	Endothelin receptors
S33	Adenosine receptors	S61	Class A Orphans	S77	Formylpeptide receptors
S35	Adhesion Class GPCRs	S61	Class A Orphans with no pharmacology	S79	Free fatty acid receptors
S40	Adrenoceptors	S61	Class A Orphans with only surrogate ligands	S80	G protein-coupled estrogen receptor
S45	Angiotensin receptors	S62	Class A Orphans with emerging pharmacology	S81	GABA _B receptors
S46	Apelin receptor	S67	GPR42, GPR84	S82	Galanin receptors
S47	Bile acid receptor	S67	LGR4, LGR5, LGR6	S83	Ghrelin receptor
S47	Bombesin receptors	S68	Mas1, BB3/brs3, GPR17	S84	Glucagon receptor family
S49	Bradykinin receptors	-	Class B Orphans	S85	Glycoprotein hormone receptors
S50	Calcitonin receptors	S69	Class C Orphans	S86	Gonadotrophin-releasing hormone receptors
S52	Calcium-sensing receptor	S69	Class Frizzled GPCRs	S87	GPR143
S53	Cannabinoid receptors	S71	Complement peptide receptors	S88	GPR18, GPR55 and GPR119
S54	Chemerin receptors	S73	Corticotropin-releasing factor receptors	S89	Histamine receptors

S90 Hydroxycarboxylic acid receptors	S105 Neuropeptide Y receptors	S121 Relaxin family peptide receptors
S91 Kisspeptin receptor	S107 Neurotensin receptors	S123 Somatostatin receptors
S92 Leukotriene receptors	S108 Opioid receptors	S124 Succinate receptor
S94 Lysophospholipid (LPA) receptors	S110 Opsin receptors	S125 Tachykinin receptors
S95 Lysophospholipid (S1P) receptors	S110 Orexin receptors	S126 Taste 1 receptors
S96 Melanin-concentrating hormone receptors	S111 Oxoglutarate receptor	S126 Taste 2 receptors
S97 Melanocortin receptors	S112 P2Y receptors	S129 Thyrotropin-releasing hormone receptors
S98 Melatonin receptors	S114 Parathyroid hormone receptors	S130 Trace amine receptor
S99 Metabotropic glutamate receptors	S115 Platelet-activating factor receptor	S131 TAAR2, TAAR3, TAAR4p, TAAR5, TAAR6, TAAR8, TAAR9
S101 Motilin receptor	S115 Prokineticin receptors	S131 Urotensin receptor
S102 Neuromedin U receptors	S116 Prolactin-releasing peptide receptor	S132 Vasopressin and oxytocin receptors
S103 Neuropeptide FF/neuropeptide AF receptors	S117 Prostanoid receptors	S133 VIP and PACAP receptors
S104 Neuropeptide S receptor	S119 Proteinase-activated receptors	S134 Other non-GPCR 7TM proteins
S105 Neuropeptide W/neuropeptide B receptors	S121 QRFP receptor	

5-Hydroxytryptamine receptors

G protein-coupled receptors → 5-Hydroxytryptamine receptors

Overview: 5-HT receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-HT receptors [1176] and subsequently revised [1058]**) are, with the exception of the ionotropic 5-HT₃ class, GPCRs where the endogenous agonist is 5-hydroxytryptamine. The diversity of metabotropic 5-HT recep-

tors is increased by alternative splicing that produces isoforms of the 5-HT_{2A} (non-functional), 5-HT_{2C} (non-functional), 5-HT₄, 5-HT₆ (non-functional) and 5-HT₇ receptors. Unique amongst the GPCRs, RNA editing produces 5-HT_{2C} receptor isoforms that differ in function, such as efficiency and specificity of coupling

to G_{q/11} and also pharmacology [241, 3052]. Most 5-HT receptors (except 5-HT_{1e} and 5-HT_{5b}) play specific roles mediating functional responses in different tissues (reviewed by [2334, 2945]).

Nomenclature	5-HT _{1A} receptor	5-HT _{1B} receptor	5-HT _{1D} receptor	5-HT _{1e} receptor	5-HT _{1F} receptor
HGNC, UniProt	<i>HTR1A</i> , P08908	<i>HTR1B</i> , P28222	<i>HTR1D</i> , P28221	<i>HTR1E</i> , P28566	<i>HTR1F</i> , P30939
Agonists	U92016A [1856], vilazodone (Partial agonist) [596], vortioxetine (Partial agonist) [140]	L-694,247 [959], naratriptan (Partial agonist) [2031], eletriptan [2031], frovatriptan [3139], zolmitriptan (Partial agonist) [2031], vortioxetine (Partial agonist) [140], rizatriptan (Partial agonist) [2031]	dihydroergotamine [1028, 1633, 1642], ergotamine [922], L-694,247 [3114], naratriptan [661, 2031, 2377], zolmitriptan [2031], frovatriptan [3139], rizatriptan [2031]	BRL-54443 [320]	BRL-54443 [320], eletriptan [2031], sumatriptan [15, 16, 2031, 2969]
Selective agonists	8-OH-DPAT [608, 1029, 1330, 1620, 1904, 2062, 2064, 2065], NLX-101 [2063]	CP94253 [1453]	PNU109291 [727] – Gorilla, eletriptan [2031]	–	lasmiditan [2049], LY334370 [2969], 5-BODMT [1443], LY344864 [2237]
Antagonists	(S)-UH 301 (pK _i 7.9) [2062]	–	–	–	–
Selective antagonists	WAY-100635 (pK _i 7.9–9.2) [2062, 2064], robalzotan (pK _i 9.2) [1298]	SB 224289 (Inverse agonist) (pK _i 8.2–8.6) [869, 2060, 2557], SB236057 (Inverse agonist) (pK _i 8.2) [1896], GR-55562 (pK _B 7.4) [1177]	SB 714786 (pK _i 9.1) [3017]	–	–

Labelled ligands	³ H]robalzotan (Antagonist) (pK _d 9.8) [1283], ³ H]WAY100635 (Antagonist) (pK _d 9.5) [1388], ³ H]8-OH-DPAT (Agonist) [234, 1330, 2061, 2064], ³ H]NLX-112 (Agonist) [1118], [¹¹ C]WAY100635 (Antagonist) [2876], p-[¹⁸ F]MPPF (Antagonist) [540]	³ H]N-methyl-AZ10419369 (Agonist, Partial agonist) [1785], ³ H]GR 125,743 (Selective Antagonist) (pK _d 8.6–9.2) [959, 3123], ³ H]alniditan (Agonist) [1633], [¹²⁵ I]GTI (Agonist) [278, 327] – Rat, ³ H]eletriptan (Agonist, Partial agonist) [2031], ³ H]sumatriptan (Agonist, Partial agonist) [2031], [¹¹ C]AZ10419369 (Agonist, Partial agonist) [2931]	³ H]eletriptan (Agonist) [2031], ³ H]alniditan (Agonist) [1633], [¹²⁵ I]GTI (Selective Agonist) [278, 327] – Rat, ³ H]GR 125,743 (Selective Antagonist) (pK _d 8.6) [3123], ³ H]sumatriptan (Agonist) [2031]	³ H]5-HT (Agonist) [1852, 2172]	³ H]LY334370 (Agonist) [2969], [¹²⁵ I]LSD (Agonist) [61] – Mouse
------------------	--	---	--	--	---

Nomenclature	5-HT _{2A} receptor	5-HT _{2B} receptor	5-HT _{2C} receptor
HGNC, UniProt	<i>HTR2A</i> , P28223	<i>HTR2B</i> , P41595	<i>HTR2C</i> , P28335
Agonists	DOI [294, 2048, 2633]	methysergide (Partial agonist) [1448, 2425, 2970], DOI [1529, 2048, 2500]	DOI [706, 2048, 2500], Ro 60-0175 [1421, 1448]
Selective agonists	–	BW723C86 [169, 1448, 2500], Ro 60-0175 [1448]	WAY-163909 [696], lorcaserin [2825]
Antagonists	risperidone (Inverse agonist) (pK _i 9.3–10) [1467, 1503, 2527], mianserin (pK _i 7.7–9.6) [1448, 1485, 1904], ziprasidone (pK _i 8.8–9.5) [1467, 1503, 2527, 2570], volinanserin (pIC ₅₀ 6.5–9.3) [1448, 1732, 2362], blonanserin (pK _i 9.1) [2105], clozapine (Inverse agonist) (pK _i 7.6–9) [1448, 1503, 1901, 2527, 2923], H05 (pIC ₅₀ 7.2) [3135]	mianserin (pK _i 7.9–8.8) [261, 1448, 2970]	mianserin (Inverse agonist) (pK _i 8.3–9.2) [783, 1448, 1904], methysergide (pK _i 8.6–9.1) [706, 1448], ziprasidone (Inverse agonist) (pK _i 7.9–9) [1111, 1503, 2570], olanzapine (Inverse agonist) (pK _i 8.1–8.4) [1111, 1503, 2570], loxapine (Inverse agonist) (pK _i 7.8–8) [1111, 1503]
Selective antagonists	compound 3b (pK _i 10.6) [779], ketanserin (pK _i 8.1–9.7) [332, 1448, 2345], pimavanserin (Inverse agonist) (pK _i 9.3) [854, 2923]	BF-1 (pK _i 10.1) [2516], RS-127445 (pK _i 9–9.5) [261, 1448], EGIS-7625 (pK _i 9) [1485]	FR260010 (pK _i 9) [1048], SB 242084 (pK _i 8.2–9) [1382, 1448], RS-102221 (pK _i 8.3–8.4) [262, 1448]
Labelled ligands	³ H]fananserin (Antagonist) (pK _d 9.9) [1790] – Rat, ³ H]ketanserin (Antagonist) (pK _d 8.6–9.7) [1448, 2345], [¹¹ C]volinanserin (Antagonist) [1020], [¹⁸ F]altanserin (Antagonist) [2421]	³ H]LSD (Agonist) [2345], ³ H]5-HT (Agonist) [2968] – Rat, ³ H]mesulergine (Antagonist, Inverse agonist) (pK _d 7.9) [1448], [¹²⁵ I]DOI (Agonist)	³ H]mesulergine (Antagonist, Inverse agonist) (pK _d 8.7–9.3) [783, 2345], [¹²⁵ I]DOI (Agonist) [783], ³ H]LSD (Agonist)

Nomenclature	5-HT ₄ receptor	5-HT _{5A} receptor	5-HT _{5B} receptor
HGNC, UniProt	<i>HTR4</i> , Q13639	<i>HTR5A</i> , P47898	<i>HTR5BP</i> , –
Agonists	cisapride (Partial agonist) [115, 193, 895, 1887, 1888, 2910]	–	–
Selective agonists	TD-8954 [1866], ML 10302 (Partial agonist) [206, 238, 1887, 1888, 1889], RS67506 [1093] – Rat, relenopride (Partial agonist) [908], velusetrag [1728, 2642], BIMU 8 [511]	–	–
Selective antagonists	RS 100235 (pK _i 8.7–12.2) [511, 2396], SB 204070 (pK _i 9.8–10.4) [193, 1887, 1888, 2910], GR 113808 (pK _i 9.3–10.3) [115, 193, 238, 511, 1888, 2396, 2910]	SB 699551 (pK _i 8.2) [536]	–
Labelled ligands	[³ H]GR 113808 (Antagonist) (pK _d 9.7–10.3) [115, 193, 1889, 2910], [¹²⁵ I]SB 207710 (Antagonist) (pK _d 10.1) [321] – Pig, [³ H]RS 57639 (Selective Antagonist) (pK _d 9.7) [260] – Guinea pig, [¹¹ C]SB207145 (Antagonist) (pK _d 8.6) [1772]	[¹²⁵ I]LSD (Agonist) [961], [³ H]5-CT (Agonist) [961]	[¹²⁵ I]LSD (Agonist) [1844] – Mouse, [³ H]5-CT (Agonist) [2967] – Mouse

Nomenclature	5-HT ₆ receptor	5-HT ₇ receptor
HGNC, UniProt	<i>HTR6</i> , P50406	<i>HTR7</i> , P34969
Selective agonists	WAY-181187 [2505], E6801 (Partial agonist) [1147], WAY-208466 [205], EMD-386088 [1845]	LP-12 [1627], LP-44 [1627], LP-211 [1628] – Rat, AS-19 [1414], E55888 [298]
Antagonists	–	lurasidone (pK _i 9.3) [1235], pimozide (pK _i 9.3) [2424] – Rat, vortioxetine (pK _i 6.3) [140]
Selective antagonists	SB399885 (pK _i 9) [1135], SB 271046 (pK _i 8.9) [317], cerlapirdine (pK _i 8.9) [525], SB357134 (pK _i 8.5) [318], Ro 63-0563 (pK _i 7.9–8.4) [244, 2632]	SB269970 (pK _i 8.6–8.9) [2817], SB656104 (pK _i 8.7) [790], DR-4004 (pK _i 8.7) [921, 1397], JNJ-18038683 (pK _i 8.2) [257], SB 258719 (Inverse agonist) (pK _i 7.5) [2818]
Labelled ligands	[¹¹ C]GSK215083 (Antagonist) (pK _d 9.8) [2171], [¹²⁵ I]SB258585 (Selective Antagonist) (pK _d 9) [1135], [³ H]LSD (Agonist) [243], [³ H]Ro 63-0563 (Antagonist) (pK _d 8.3) [244], [³ H]5-CT (Agonist)	[³ H]5-CT (Agonist) [2817], [³ H]5-HT (Agonist) [143, 2687], [³ H]SB269970 (Selective Antagonist) (pK _d 8.9) [2817], [³ H]LSD (Agonist) [2687]

Comments: Tabulated pK_i and K_D values refer to binding to human 5-HT receptors unless indicated otherwise. The nomenclature of 5-HT_{1B}/5-HT_{1D} receptors has been revised [1058]. Only the non-rodent form of the receptor was previously called 5-HT_{1D}; the human 5-HT_{1B} receptor (tabulated) displays a different pharmacology to the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors [1040]. Wang *et al.* (2013) report X-ray structures which reveal the binding modality of ergotamine and dihydroergotamine (DHE) to the 5-HT_{1B} receptor in comparison with the structure of the 5-HT_{2B} receptor [2984]; some of these drugs adopt rather different conformations depending on the target receptor [2207]. Various

5-HT receptors have multiple partners in addition to G proteins, which may affect function and pharmacology [1817]. NAS181 is a selective antagonist of the rodent 5-HT_{1B} receptor. Fananserin (LSD) and ketanserin bind with high affinity to dopamine D4 and histamine H₁ receptors respectively, and ketanserin is a potent α1 adrenoceptor antagonist, in addition to blocking 5-HT_{2A} receptors. Lysergic acid (LSD) and ergotamine show a strong preference for arrestin recruitment over G protein coupling at the 5-HT_{2B} receptor, with no such preference evident at 5-HT_{1B} receptors, and they also antagonise 5-HT_{7A} receptors [2965]. DHE (dihydroergocryptine), pergolide and cabergoline also show significant preference for arrestin recruitment over G protein coupling at 5-HT_{2B}

receptors [2965]. The 5-HT_{2B} (and other 5-HT) receptors interact with immunocompetent cells [2153]. The serotonin antagonist mesulergine was key to the discovery of the 5-HT_{2C} receptor [2192], initially known as 5-HT_{1C} [110]. The human 5-HT_{5A} receptor may couple to several signal transduction pathways when stably expressed in C6 glioma cells [2089] and rodent prefrontal cortex (layer V pyramidal neurons) [939]. The human orthologue of the mouse 5-HT_{5B} receptor is non-functional (stop codons); the 5-HT_{5C} receptor has not been cloned from mouse, or rat, impeding definition of its function [1040]. In addition to accepted receptors, an 'orphan' receptor, unofficially termed 5-HT_{1P}, has been described [900].

Further reading on 5-Hydroxytryptamine receptors

Bockaert J *et al.* (2011) 5-HT(4) receptors, a place in the sun: act two. *Curr Opin Pharmacol* **11**: 87-93 [PMID:21342787] Hayes DJ *et al.* (2011) 5-HT receptors and reward-related behaviour: a review. *Neurosci Biobehav Rev* **35**: 1419-49 [PMID:21402098]

Hoyer D *et al.* (1994) International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacol Rev* **46**: 157-203 [PMID:7938165]
 Leopoldo M *et al.* (2011) Serotonin 5-HT7 receptor agents: Structure-activity relationships and potential therapeutic applications in central nervous system disorders. *Pharmacol Ther* **129**: 120-48 [PMID:20923682]

Meltzer HY *et al.* (2011) The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr Opin Pharmacol* **11**: 59-67 [PMID:21420906]
 Roberts AJ *et al.* (2012) The 5-HT(7) receptor in learning and memory. *Hippocampus* **22**: 762-71 [PMID:21484935]

Acetylcholine receptors (muscarinic)

G protein-coupled receptors → Acetylcholine receptors (muscarinic)

Overview: Muscarinic acetylcholine receptors (mAChRs) (**no-nomenclature as agreed by the NC-IUPHAR Subcommittee on Muscarinic Acetylcholine Receptors** [398]) are activated by the endogenous agonist **acetylcholine** [460, 1263, 1384]. All five (M1-M5) mAChRs are ubiquitously expressed in the hu-

man body and are therefore attractive targets for many disorders. Functionally, M₁, M₃, and M₅ mAChRs preferentially couple to G_{q/11} proteins, whilst M₂ and M₄ mAChRs predominantly couple to G_{i/o} proteins. Both agonists and antagonists of mAChRs are clinically approved drugs, including **pilocarpine** for the treat-

ment of elevated intra-ocular pressure and glaucoma, and **atropine** for the treatment of bradycardia and poisoning by muscarinic agents such as organophosphates. Of note, it has been observed that mAChRs dimerise reversibly [1108] and that dimerisation/oligomerisation can be affected by ligands [1661, 1821].

Nomenclature	M ₁ receptor	M ₂ receptor
HGNC, UniProt	<i>CHRM1</i> , P11229	<i>CHRM2</i> , P08172
Endogenous agonists	acetylcholine [1263, 1384]	acetylcholine [460, 1263, 1384]
Agonists	xanomeline (Partial agonist) [497, 2276, 3029, 3091], methacholine [2196, 2387] – Rat, arecoline [1263, 2150, 2387], oxotremorine (Partial agonist) [1263, 2387], carbachol [497, 1263, 3091], pilocarpine (Partial agonist) [1263, 2387], bethanechol [1263, 2387], iperoxo [2528]	iperoxo [2528, 2529], xanomeline [2276, 3029, 3091], methacholine [2196, 2387] – Rat, oxotremorine [1263, 2387], arecoline [1263, 2150, 2387], pilocarpine (Partial agonist) [1263, 2387], bethanechol [1263, 2387]
Antagonists	tiotropium (pK _i 9.6–10.7) [654, 2280, 2753, 2796], aclidinium (pIC ₅₀ 10.1–10.2) [2280, 2796], glycopyrrolate (pIC ₅₀ 9.6–10.1) [2701, 2753], ipratropium (pK _i 9.3–9.8) [1132, 2280], atropine (pK _i 8.5–9.6) [497, 823, 1132, 1190, 2209, 2641], biperiden (pK _d 9.3) [250], 4-DAMP (pK _i 9.3) [672], darifenacin (pK _i 8.9–9.1) [911, 1132, 2623], scopolamine (pK _i 9) [560, 1190], oxybutynin (pK _i 8.6) [617, 2623], tolterodine (pK _i 8.4–8.5) [911, 2623], droxidopa (pK _i 7.1) [560]	tiotropium (pK _i 9.9–10.7) [654, 2280, 2753, 2796], aclidinium (pIC ₅₀ 10.1) [2280, 2796], ipratropium (pK _i 9.3–9.8) [1132, 2280], glycopyrrolate (pIC ₅₀ 8.7–9.5) [2701, 2753], atropine (pK _i 7.8–9.2) [560, 1132, 1190, 2209], scopolamine (pK _i 8.7) [250, 1190], tolterodine (Inverse agonist) (pK _i 8.4–8.5) [911, 2623], 4-DAMP (pK _i 8.4) [672], biperiden (pK _d 8.2) [250], oxybutynin (pK _i 7.9–8.1) [617, 2623], darifenacin (Inverse agonist) (pK _i 7.2–7.3) [911, 1132, 2623], tropicamide (pK _i 7.2) [560]
Selective antagonists	pirenzepine (pK _i 7.6–8.3) [336, 672, 1092, 1190, 1302, 3053], VU0255035 (pK _i 7.8) [2580]	AFDX384 (pK _i 8.1–8.2) [560, 672]
Allosteric modulators (Positive)	benzoquinazolinone 12 (pK _B 6.6) [4], VU0486846 (pEC ₅₀ 6.5) [211, 2414], KT 5720 (pK _d 6.4) [1575], brucine (pK _d 4.5–5.8) [225, 1263, 1574], BQCA (pK _B 4–4.8) [4, 5, 372, 1760], MIPS1780 [1249, 1385], TAK-071 [1527, 2459], VU0467319 [2268]	BAY2413555 (pK _d 7.8) [2902], LY2119620 (pK _d 5.5–5.7) [561, 1505], LY2033298 (pK _d 4.4) [2903]
Allosteric modulators (Negative)	muscarinic toxin 7 (pK _i 11–11.1) [823, 2033, 2133]	gallamine (pK _i 5.8–7.6) [512, 1486, 1572, 1952, 2865], W-84 (pK _d 6–7.5) [1934, 2865], C ₇ /3-phth (pK _d 7.1) [108, 498], alcuronium (pK _d 6.1–6.9) [108, 1263, 2865]
Selective allosteric modulators	PF-06767832 (Positive) (pEC ₅₀ 7.2) [595, 1385, 2975]	–

Labelled ligands	[³H]QNB (Antagonist) (pK _d 10.6–10.8) [1264, 2209], [³H]N-methyl scopolamine (Antagonist) (pK _d 9.4–10.3) [406, 497, 499, 1132, 1263, 1265, 1302, 1387, 1572], [³H]iperoxo (Agonist) [2528], [³H]pirenzepine (Selective Antagonist) (pK _d 7.9) [410, 2496, 2908, 3030], [³H]acetylcholine (Agonist)	[³H]QNB (Antagonist) (pK _d 10.1–10.6) [1264, 2209], [³H]iperoxo (Agonist) [2528], [³H]N-methyl scopolamine (Antagonist) (pK _d 9.3–9.9) [406, 1132, 1264, 1265, 1387, 1572, 3009], [³H]AF DX-384 (Selective Antagonist) (pK _d 9) [410, 1910, 2908], [³H]acetylcholine (Agonist) [1573]
Comments	Atypical agonists: AC-42 [109, 1555, 1556, 2469, 2672, 2673], 77-LH-28-1 [109, 1555], N-desmethylozapine [2469, 2672, 2737], TBPB [1305, 1384, 2469], McN-A-343 [1263, 2387]	Atypical agonists: AC-42 [1555, 1848], 77-LH-28-1 [1555, 1848], N-desmethylozapine [2737], McN-A-343 [1263, 1848, 2387]

Nomenclature	M ₃ receptor	M ₄ receptor	M ₅ receptor
HGNC, UniProt	CHRM3 , P20309	CHRM4 , P08173	CHRM5 , P08912
Endogenous agonists	acetylcholine [460, 1263, 1384]	acetylcholine [1263, 1384]	acetylcholine [460]
Agonists	xanomeline (Partial agonist) [2276, 3029, 3091], methacholine [2196, 2387] – Rat, arecoline [1263, 2150, 2387], oxotremorine [1263, 2387], pilocarpine (Partial agonist) [1263, 2387], carbachol [460, 1263, 3091], bethanechol [1263, 2387], iperoxo [2528]	xanomeline (Partial agonist) [1860, 2276, 3029, 3091], methacholine [2196, 2387] – Rat, arecoline [1263, 2150, 2387], oxotremorine [1263, 2387], pilocarpine (Partial agonist) [1263, 2387], carbachol [1263, 3091], bethanechol [1263, 2387], iperoxo [2528]	xanomeline (Partial agonist) [965, 2276, 3029, 3091], pilocarpine (Partial agonist) [203, 665, 965], carbachol [203, 965, 3091], arecoline [2150, 2387], bethanechol [2387], iperoxo [2528], methacholine [2387]
Antagonists	tiotropium (pK _i 9.5–11.1) [654, 676, 2280, 2753, 2796], aclidinium (pK _i 10.1–10.2) [2280, 2796], atropine (pK _i 8.5–9.8) [560, 1132, 1190, 2209], glycopyrrolate (pIC ₅₀ 9.6–9.8) [2701, 2753], ipratropium (pK _i 9.3–9.8) [676, 1132, 2280], scopolamine (pK _i 9.4) [250, 1190], 4-DAMP (pK _i 9.3) [672], darifenacin (pK _i 8.9–9.1) [911, 1132, 2623], oxybutynin (pK _i 8.8) [617, 2623], tolterodine (pK _i 8.4–8.5) [911, 2623], biperiden (pK _d 8.4) [250], tropicamide (pK _i 7) [560]	tiotropium (pK _i 10.2–10.6) [2753, 2796], aclidinium (pK _i 10) [2796], glycopyrrolate (pK _i 9.1–10) [2701, 2753], atropine (pK _i 8.7–9.5) [560, 1132, 1190, 2209], scopolamine (pK _i 9.1–9.5) [250, 1190], ipratropium (pK _i 9.2) [1132], 4-DAMP (pK _i 8.9) [672], oxybutynin (pK _i 8.4–8.7) [617, 2623], biperiden (pK _d 8.6) [250], tolterodine (pK _i 8.3–8.4) [911, 2623], darifenacin (pK _i 7.3–8.1) [911, 1132, 2623], tropicamide (pK _i 6.9) [386]	tiotropium (pK _i 9.8–10.2) [2753, 2796], aclidinium (pK _i 9.9) [2796], glycopyrrolate (pK _i 8.9–9.9) [2701, 2753], atropine (pK _i 8.3–9.3) [560, 1132, 1974], 4-DAMP (pK _i 9) [672], ipratropium (pK _i 8.8) [1132], tolterodine (pK _i 8.5–8.8) [911, 2623], scopolamine (pK _i 8.7) [250], darifenacin (pK _i 7.9–8.6) [911, 1132, 2623], biperiden (pK _d 8.2) [250], oxybutynin (pK _i 7.9) [617, 2623], tropicamide (pK _i 6.4) [560]
Selective antagonists	–	PCS1055 (pK _i 8.2) [560], AFDX384 (pK _i 7.3–8) [560, 672], PD 102807 (pK _i 7.4–7.6) [560, 2134]	ML381 (pK _i 6.3) [888]
Allosteric modulators (Positive)	WIN 62,577 (pK _d 5.1) [1576], N-chloromethyl-brucine (pK _d 3.3) [1574]	VU0152100 (pEC ₅₀ 6.4) [291] – Rat, VU0467154 (pEC ₅₀ 6.2) [335, 2162, 2963], LY2033298 (pK _B 4.9–5.5) [417, 2737, 2963], LY2119620 (pK _d 5.5) [561], thiochrome (pK _d 4) [1573], MK-6884 [1653, 2848], emraclidine [191, 350, 2011]	amiodarone (pK _B 7.2) [2684], ML380 (pK _B 4.8) [203, 890], VU6007678 [202, 345]
Allosteric modulators (Negative)	–	muscarinic toxin 3 (pK _i 8.7) [1302, 2132]	–
Selective allosteric modulators	–	–	ML375 (Negative) (pK _B 6.2–6.6) [203, 344, 889]
Labelled ligands	[³H]QNB (Antagonist) (pK _d 10.4) [1264, 2209], [³H]N-methyl scopolamine (Antagonist) (pK _d 9.7–10.2) [406, 1132, 1263, 1264, 1387, 1572], [³H]4-DAMP (Selective Antagonist) (pK _i 8.8–9.4) [410, 1282], [³H]iperoxo (Agonist) [2528], [³H]acetylcholine (Agonist)	[³H]QNB (Antagonist) (pK _d 9.7–10.5) [1264, 2208], [³H]N-methyl scopolamine (Antagonist) (pK _d 9.9–10.2) [406, 1263, 1264, 1387, 1572, 3009], [³H]iperoxo (Agonist) [2528], [³H]AF DX-384 (Selective Antagonist) (pK _d 8.7) [410, 1910, 2908], [³H]acetylcholine (Agonist) [1573]	[³H]QNB (Antagonist) (pK _d 10.2–10.7) [1264], [³H]N-methyl scopolamine (Antagonist) (pK _d 9.3–9.7) [406, 460, 1132, 1264, 1387, 2962, 3009], [³H]iperoxo (Agonist) [2528], [³H]acetylcholine (Agonist)
Comments	Atypical agonists: AC-42 [1555], 77-LH-28-1 [1555], N-desmethylozapine [2737], McN-A-343 [1263, 2387]	Atypical agonists: AC-42 [1555], 77-LH-28-1 [1555], N-desmethylozapine [2737], McN-A-343 [1263, 2387]	Atypical agonists: AC-42 [1555], 77-LH-28-1 [1555], McN-A-343 [2387]

Comments: Atomic structures for all five mAChRs bound to antagonists have been determined [1012, 2736, 2807, 2962, 3173]. Structures of agonist-bound M₁, M₂, M₃, and M₄ mAChRs [345, 1505, 2995, 3130, 3232] and β₂-arrestin-bound M₂ mAChR have been reported [2688]. These structures show that the orthosteric binding site of this family of receptor is absolutely conserved and, as a consequence, explain why highly selective orthosteric ligand binding to any specific mAChR has been notoriously difficult to achieve. As such, it is common to assess the rank order of affinity for a range of antagonists with limited selectivity (*e.g.*, 4-DAMP, darifenacin, pirenzepine, AFDX384) to identify the involvement of particular subtypes- although caution should be used in the design and interpretation of such experiments due to the lack of absolute ligand subtype selectivity [2009]. Some ligands may display selectivity at the level of function (*e.g.*, xanomeline) or

binding kinetics (*e.g.*, tiotropium) [2276, 2571, 2799]. In addition, structures of the M₃ and M₄ mAChR DREADDS (designer receptors exclusively activated by designer drugs) have been reported providing insights into orthosteric ligand selectivity for these chemogenetic tools [3232]. Structures of the M₂ and M₄ mAChRs in complex with allosteric modulators [1505, 1779, 2963, 2995] have validated numerous pharmacological studies that indicated the presence of a common mAChR allosteric site located at the extracellular entrance to these receptors. In addition, a structure of the M₁ mAChR with muscarinic toxin 7 (MT7) bound to the common allosteric site has provided insight into the extreme subtype selectivity of MT7 [1779]. Allosteric ligands proposed to bind to this common allosteric site include gallamine, strychnine, C₇/3-phth, brucine. Additionally, a second allosteric site has been proposed on the

mAChRs based on pharmacological analyses of the actions of compounds such as KT 5720, WIN 62,577, WIN 51,708, staurosporine and amiodarone [344, 1575, 1576, 2684]. In the presence of the orthosteric ligand, allosteric modulators can exert positive, negative, or neutral cooperativity with that ligand. Direct receptor activation *via* an allosteric site has been reported for a number of allosteric ligands of the mAChRs [595, 1587, 1590, 1760, 2037, 2038]. 'Atypical agonists' are ligands that have been suggested to have bitopic binding modes for at least one subtype whereby the agonist occupies both the orthosteric and allosteric sites [109, 1383, 2904]. Several mAChR subtype selective PET radioligands have been reported, with [¹¹C]MK-6884 showing specific activity in patients with Alzheimer's disease [568, 1653].

Further reading on Acetylcholine receptors (muscarinic)

Burger WAC *et al.* (2018) Toward an understanding of the structural basis of allostery in muscarinic acetylcholine receptors. *J Gen Physiol* **150**: 1360-1372 [PMID:30190312]
 Caulfield MP *et al.* (1998) International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacol Rev* **50**: 279-90 [PMID:9647869]
 Eglen RM. (2012) Overview of muscarinic receptor subtypes. *Handb Exp Pharmacol* 3-28 [PMID:22222692]
 Kaoullas MG *et al.* (2024) Ligand bias at the muscarinic acetylcholine receptor family: Opportunities and challenges. *Neuropharmacology* **258**: 110092 [PMID:39067666]

Kruse AC *et al.* (2014) Muscarinic acetylcholine receptors: novel opportunities for drug development. *Nat Rev Drug Discov* **13**: 549-60 [PMID:24903776]
 Leach K *et al.* (2012) Structure-function studies of muscarinic acetylcholine receptors. *Handb Exp Pharmacol* 29-48 [PMID:22222693]
 Tobin AB. (2024) A golden age of muscarinic acetylcholine receptor modulation in neurological diseases. *Nat Rev Drug Discov* **23**: 743-758 [PMID:39143241]
 Valant C *et al.* (2012) The best of both worlds? Bitopic orthosteric/allosteric ligands of g protein-coupled receptors. *Annu Rev Pharmacol Toxicol* **52**: 153-78 [PMID:21910627]

Adenosine receptors

G protein-coupled receptors → Adenosine receptors

Overview: Adenosine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Adenosine Receptors** [809]) are activated by the endogenous ligand adenosine (potentially inosine also at A₃ receptors). Crystal and cryo-EM structures for all four adenosine receptors have been solved, occupied by either agonists (sometimes in the presence of an allosteric modu-

lator) or antagonists. Many of these structures were incorporated in a recent review [1219]. More recently, structures for the A_{2B} receptor [360, 452] and the A₃ receptor [359, 2144] were elucidated. The A_{2A} receptor is used as a workhorse in GPCR structure elucidation: almost 100 structures are available in the Protein Data Bank (www.rcsb.org). Istradefylline, a selective A_{2A} recep-

tor antagonist, is on the market for the treatment of Parkinson's disease, while caffeine's mechanism of action is largely due to its antagonism of at least three of the four adenosine receptor subtypes. Allosteric modulators, particular PAMs of A₁ and A₃ receptors, have been explored chemically and structurally [678, 2279].

Nomenclature	A ₁ receptor	A _{2A} receptor	A _{2B} receptor	A ₃ receptor
HGNC, UniProt	<i>ADORA1</i> , P30542	<i>ADORA2A</i> , P29274	<i>ADORA2B</i> , P29275	<i>ADORA3</i> , P0DMS8
Endogenous agonists	adenosine [3153]	adenosine [807, 808, 3153]	adenosine [807, 808, 3153]	adenosine [807, 808, 3153]
Agonists	NECA [852, 1296, 2400, 2861, 3153]	NECA [273, 653, 852, 1407, 1520, 3153]	NECA [214, 273, 1284, 1691, 2697, 2926, 3153]	NECA [273, 852, 1257, 2467, 2927, 3153]
Selective agonists	cyclopentyladenosine [573, 603, 852, 1099, 1254, 1296, 2400], 5-Cl-5-deoxy-(±)-ENBA [803], 2'-Me-CCPA [377], CCPA [1254, 2103], MRS7469 [2856]	apadenoson [2197], UK-432,097 [1002, 3129], compound 4g [529], CGS 21680 [273, 653, 852, 1254, 1407, 1445, 1520, 2103], regadenoson [1254]	BAY 60-6583 [701]	piclidenoson [765, 839, 1445, 2927], Cl-IB-MECA [292, 1257, 1403], MRS5980 [2855], MRS5698 [2854]
Antagonists	CGS 15943 (pK _i 8.5) [2138], xanthine amine congener (pK _d 7.5) [803]	CGS 15943 (pK _i 7.7–9.4) [653, 1407, 1445, 2138], xanthine amine congener (pK _i 8.4–9) [653, 1445]	xanthine amine congener (pK _i 6.9–8.8) [214, 1284, 1285, 1445, 1691, 2697], CGS 15943 (pK _i 6–8.1) [96, 1284, 1285, 1445, 2138, 2697]	MRS7799 (pK _d 9.3) [2738], CGS 15943 (pK _i 7–7.9) [1416, 1445, 2138, 2927], xanthine amine congener (pK _i 7–7.4) [1445, 2467, 2927]
Selective antagonists	PSB36 (pK _i 9.9) [8] – Rat, DPCPX (pK _i 7.4–9.2) [603, 1230, 2103, 2400, 3056], derenofylline (pK _i 9) [1331], WRC-0571 (pK _i 8.8) [1825], DU172 (pK _i 7.4) [923]	SCH442416 (pK _i 8.4–10.3) [2598, 2839], ZM-241385 (pK _i 8.8–9.1) [2138]	PSB-0788 (pK _i 9.4) [272], PSB603 (pK _i 9.3) [272], MRS1754 (pK _i 8.8) [1284, 1415], PSB1115 (pK _i 7.3) [1078]	MRS1220 (pK _i 8.2–9.2) [1257, 1416, 2726, 3175], VUF5574 (pK _i 8.4) [2915], MRS1523 (pK _i 7.7) [1643], MRS1191 (pK _i 7.5) [1257, 1288, 1663]
Allosteric modulators (Positive)	MIP5521 (pK _B 5) [102, 678], VPC171 (pEC ₅₀ 4.8) [102, 1225, 2066], PD81723 [329]	–	–	MRS8247 (pEC ₅₀ 4.8) [2279], LUF6000 [927], LUF6096 [1098], MRS8054 [746]
Labelled ligands	[³ H]CCPA (Agonist) [1445, 2400], [³ H]DP-CPX (Antagonist) (pK _d 8.4–9.2) [573, 765, 1445, 2138, 2400, 2861], ABEA-X-BY630 (Selective Agonist) [3169]	[³ H]ZM 241385 (Antagonist) (pK _d 8.7–9.1) [47, 850], [³ H]CGS 21680 (Agonist) [1272, 2981]	[³ H]MRS1754 (Antagonist) (pK _d 9.8) [1284], PSB-12105 (Selective Antagonist) (pK _i 8.7) [3169]	[¹²⁵ I]AB-MECA (Agonist) [2138, 2927], CA200645 (Selective Antagonist) (pK _i 8.2) [3169]

Comments: Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A_{2B} adenosine receptor (*ADORA2BPI*) with 79% identity to the A_{2B} adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor [1258]. DPCPX

also exhibits antagonism at A_{2B} receptors (pK_i ca. 7, [45, 1445]). Antagonists at A₃ receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A₃ receptor. In the absence of other adenosine receptors, [³H]DPCPX and [³H]ZM 241385 can also be used to label A_{2B} receptors (K_D

ca. 30 and 60 nM respectively). [¹²⁵I]AB-MECA also binds to A₁ receptors [1445]. [³H]CGS 21680 is relatively selective for A_{2A} receptors, but may also bind to other sites in cerebral cortex [565, 1297]. [³H]NECA binds to other non-receptor elements, which also recognise adenosine [1734].

Further reading on Adenosine receptors

- Borea PA *et al.* (2015) The A₃ adenosine receptor: history and perspectives. *Pharmacol Rev* **67**: 74–102 [PMID:25387804]
- Cai H *et al.* (2024) Cryo-EM structures of adenosine receptor A₃AR bound to selective agonists. *Nat Commun* **15**: 3252 [PMID:38627384]
- Chen Y *et al.* (2022) Cryo-EM structure of the human adenosine A_{2B} receptor-G_s signaling complex. *Sci Adv* **8**: eadd3709 [PMID:36563137]
- Draper-Joyce CJ *et al.* (2021) Positive allosteric mechanisms of adenosine A₁ receptor-mediated analgesia. *Nature* **597**: 571–576 [PMID:34497422]
- Guo D *et al.* (2017) Kinetic Aspects of the Interaction between Ligand and G Protein-Coupled Receptor: The Case of the Adenosine Receptors. *Chem Rev* **117**: 38–66 [PMID:27088232]
- Ijzerman AP *et al.* (2022) International Union of Basic and Clinical Pharmacology. CXII: Adenosine Receptors: A Further Update. *Pharmacol Rev* **74**: 340–372 [PMID:35302044]
- Jacobson KA *et al.* (2022) Adenosine A_{2A} receptor antagonists: from caffeine to selective non-xanthines. *Br J Pharmacol* **179**: 3496–3511 [PMID:32424811]
- Oshima HS *et al.* (2024) Structural insights into the agonist selectivity of the adenosine A₃ receptor. *Nat Commun* **15**: 9294 [PMID:39511145]
- Pradhan B *et al.* (2024) Lipid Trolling to Optimize A₃ Adenosine Receptor-Positive Allosteric Modulators (PAMs). *J Med Chem* **67**: 12221–12247 [PMID:38959401]

Adhesion Class GPCRs

G protein-coupled receptors → Adhesion Class GPCRs

Overview: Adhesion GPCRs are structurally identified on the basis of a large extracellular region, similar to the Class B GPCR, but which is linked to the 7TM region by a GPCR autoproteolysis-inducing (GAIN) domain [74] containing a GPCR proteolysis site (GPS). The N-terminal extracellular region often shares structural

homology with adhesive domains (e.g. cadherins, immunoglobulin, lectins) facilitating inter- and matricellular interactions and leading to the term adhesion GPCR [811, 3193]. Several receptors have been suggested to function as mechanosensors [285, 2229, 2250, 2525, 3072]. Cryo-EM structures of the 7-transmembrane

domain of several adhesion GPCRs have been determined recently [150, 1683, 2249, 2250, 2308, 2313, 3122, 3268]. **The nomenclature of these receptors was revised in 2015 as recommended by NC-IUPHAR and the Adhesion GPCR Consortium** [1024].

Nomenclature	ADGRA1	ADGRA2
HGNC, UniProt	ADGRA1, Q86SQ6	ADGRA2, Q96PE1
Comments	Receptor knockout in mice results in increased anxiety-like behaviours and increased neuron dendritic density [3241] as well as increased metabolic rates and thermogenesis [3242].	Required to assemble higher-order Reck/Gpr124/Frizzled/ Lrp5/6 complexes [738, 2269, 2907, 2922, 3261]. Interacts with Reck [479, 738, 2922], Syndecan-1, -2 [483], Integrin- $\alpha\beta$ 3 [2906] and heparin [2906]. Principal signal transduction involves Dishevelled [738], β -catenin [2269] and Cdc42 [422]. Required for CNS vascularization and blood-brain barrier formation [422, 1824, 2922]. In endothelial cells ADGRA2 mediates pyroptosis [3136] and lipid deposition [933].

Nomenclature	ADGRA3	ADGRB1	ADGRB2	ADGRB3
HGNC, UniProt	ADGRA3, Q8IWK6	ADGRB1, O14514	ADGRB2, O60241	ADGRB3, O60242
Endogenous agonist peptides and proteins	–	Peptides derived from the ADGRB1 (BAI1) <i>Stachel</i> sequence STFALLAQL-SADANMEKAT; reticulon 4 (<i>RNT4</i>); neuroligin-1 (<i>CHRDLI</i>) [2873, 2990]	–	–
Endogenous agonist proteins	–	–	–	reticulon 4 (<i>RNT4</i>) [2990]
Endogenous agonists	–	phosphatidylserine [2170]	–	–
Comments	ADGRA3 is a stem and progenitor cell marker in the male reproductive tract [2548]. It controls fluid homeostasis, sperm maturation and storage in the male reproductive tract [2098]. Principal signal transduction involves recruitment of Dishevelled [1654]. Classical G protein-mediated signaling has also been reported [122].	Reported to mediate phagocytosis through binding of phosphatidylserine [2170] and lipopolysaccharide [578]. Interaction with reticulon 4 (<i>RNT4</i>) [2990], <i>Stachel</i> -peptide or neuroligin-1 (<i>CHRDLI</i>) [2873] mediates synapse formation. Suppresses medulloblastoma formation [3263] and is involved in dendrite development [694]. A recent study disputes the previously reported expression of ADGRB1 by macrophages [1181].	Principal signal transduction involves $G\alpha_z$ [2299]. A R1465W mutation confers increased coupling to $G\alpha_i$ [2299].	Reported to bind C1q-like molecules [254]. Promotes myoblast fusion in vertebrates [1031].

Nomenclature	CELSR1	CELSR2	CELSR3
Systematic nomenclature	ADGRC1	ADGRC2	ADGRC3
HGNC, UniProt	CELSR1 , Q9NYQ6	CELSR2 , Q9HCU4	CELSR3 , Q9NYQ7
Agonists	–	tumour necrosis factor shed form (<i>TNF</i> , P01375) [848] – Mouse	–
Comments	Principal signal transduction involves Rho kinase [2081]. Interacts with Vangl-2 [631, 1617], Frizzled-6 [631] and LRRK2 [2464]. In the presence of calcium the extracellular region (ECR) forms an antiparallel dimer [138].	Mutated in Joubert syndrome patients [2944]. Signal transduction is potentially mediated through G $\alpha_{q/11}$ [2590]. Interacts homomerically with CELSR2/ADGRC2 [2590]. TNF α stimulation of ADGRC2 in monocytes leads to p65 increase [848].	High-confidence risk gene for Tourette syndrome [3008]. Signal transduction is potentially mediated through G $\alpha_{q/11}$ [2590]. Interacts with Frizzled-3 [2806], Dystroglycan [1692] and homomerically with CELSR3/ADGRC3 [2590]. Variants are associated with febrile seizures [1646]. Expressed in the brain [228], CNS [793, 2836], pancreas [539], and testis [167]. Does not undergo autoproteolysis.

Nomenclature	ADGRD1	ADGRD2
HGNC, UniProt	ADGRD1 , Q6QNK2	ADGRD2 , Q7Z7M1
Allosteric modulator	protein tyrosine kinase 7 (PTK7) [816]	–
Endogenous agonists	Peptides derived from the <i>Stachel</i> sequence: THLTNFAILMQVV; PLXDC2 is an activating ligand for mouse ADGRD1; dihydrotestosterone [220, 1670]	–
Comments	ADGRD1 a G $_s$ protein-coupled receptor [246, 1670]. 5- α - dihydrotestosterone regulates skeletal muscle strength through the receptor. The same study establishes the small molecule agonist AP503 as an ADGRD1 specific and G $_s$ -biased agonist [3171]. Couples also to G $_i$ proteins [1671]. Strong association with body height [1408, 1418, 2849] and bone mineral density [2454]. Regulates oviductal fluid flow in mice [220]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [2250, 2313]. Expressed in the CNS [2925], gastric antrum [978], thymus and adrenal glands [647], and intestinal epithelium [1451]. ADGRD1 is highly expressed in glioblastoma [166]. Candidate SNP in lipid profiling [1492] and SNP affecting electrocardiographic RR and QT interval [1819]	ADGRD2 mRNA may be prognostic for head and neck squamous cell carcinoma [2161].

Nomenclature	ADGRE1	ADGRE2	ADGRE3	ADGRE4P
HGNC, UniProt	ADGRE1 , Q14246	ADGRE2 , Q9UHX3	ADGRE3 , Q9BY15	ADGRE4P , Q86SQ3
Comments	The structure of β -arrestin-1 in complex with ADGRE1 has been reported [66]. Expressed in eosinophilic granulocytes [1025, 1611] and mouse macrophages [941, 1685, 1867]. Associated with familial eosinophilic esophagitis [52]; risk factor for lymph node metastasis and colorectal cancer [34]; SNPs found in patients with neuroblastoma [120].	Principal signal transduction involves G protein-coupling [216] and the phospholipase C pathway [1231]. Coupling to $G_{\alpha 16}/G_{\alpha z}$ has been reported [217]. A mutation destabilizing the GAIN domain sensitizes mast cells to IgE-independent vibration-induced degranulation [285]. Reported to bind chondroitin sulfate B [2681]. Interacts with FHR1 [1231]. Expressed in spleen, lymph node, peripheral blood leukocytes, lung, bone marrow, and fetal liver [103, 419, 787, 1475, 1535, 1684, 2913]. Associated with risk of diverticulosis disease [3218]; high expression in acute myeloid leukemia [1189].	Highest expression in the spleen, peripheral blood leukocytes, and lung [2683]; no rat or mouse orthologues exist. Potential mediator of glioblastoma [1338]; hypomethylation correlates with breast cancer in Chinese women [3259].	Probable pseudogene; expression in thymus, spleen, monocytes [369, 370, 1026, 2682].
Nomenclature	ADGRES	ADGRF1		
HGNC, UniProt	ADGRES , P48960	ADGRF1 , Q5T601		
Endogenous agonists	–	synaptamide [1536] Peptides derived from the <i>Stachel</i> sequence TSFSILMSFPVPTIFPV-VKWIT [622, 2708]		
Comments	Interacts with $G_{\alpha 12/13}$ [216, 1811, 3003, 3003, 3018, 3019]. Reported to bind CD55 [1027], chondroitin sulfate B [2681], $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins [3010], and CD90 [2983]. Expressed in macrophages, dendritic cells, and lymphocytes [709, 1273, 1476, 1535, 1837, 2913], and smooth muscle [104, 1710, 2364, 2938]. Expression levels on leukocytes are regulated by shear stress-dependent interaction with CD55 on red blood cells [1351]. Promotes the retention of blood-exposed dendritic cells in the spleen by interaction with CD55 on red blood cells [1710]. Potential therapeutic target in glioblastoma [2354, 2634, 3258]; negative regulator of the innate immune response [421], with predicted roles in preeclampsia [94] and osteoporosis [1822].	Coupling with all major G protein families is reported [1306], including G_s and G_q [622, 2708], and $G_{\alpha s}$ and $G_{\alpha q/11}$ [3268]. N-Docosahexaenoyl ethanolamine (synaptamide) is an agonist at ADGRF1 supporting neurogenesis [1604]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [2313, 3268]. Furthermore, the domain structure of the N terminus (SEA, HormR, GAIN) has been solved by X-ray crystallography [2988]. The structural basis for G protein-coupling has also been reported [1306]. Expressed in kidney and prostate [1744, 2690], spleen, liver, and adrenal gland [2289]. ADGRF1 may be a prognostic marker for uterine corpus endometrial cancer [1616]. Tumour-promoting function in HER2-positive breast cancer has been reported [6, 7], as has a role in non-alcoholic fatty liver disease progression [3109].		
Nomenclature	ADGRF2	ADGRF3		
HGNC, UniProt	ADGRF2P , Q8IZF7	ADGRF3 , Q8IZF5		
Comments	ADGRF2 is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [2289]. It is also expressed in heart, skin, spleen, testis, brain, tongue, esophagus, forestomach [2289]. Potential therapeutic target in breast cancer [2584].	Expressed in kidney, small bowel, pancreas [387, 1602], and testis [1733]. ADGRF3 is highly expressed in gastrointestinal neuroendocrine tumours [387].		

Nomenclature	ADGRF4	ADGRF5	
HGNC, UniProt	ADGRF4 , Q8IZF3	ADGRF5 , Q8IZF2	
Endogenous agonists	Peptides derived from the ADGRF5 (GPR116) <i>Stachel</i> sequence: TSFSILMSPDSPD [622]	Peptides derived from the <i>Stachel</i> sequence: TSFSILMSPDSPD [622]	
Comments	ADGRF4 couples to G _{q/11} proteins [622] and constitutively activates G _{α15} G protein [1004]. Expression has been detected in the lung, heart, skin, kidney, testis, brain, ovaries, epididymis, and thymus [2289], and in adult ameloblasts [472]. It is highly expressed in squamous epithelia and gene deficiency did not result in detectable defects [2289]. ADGRF4 is required for enamel mineralization mediated by ameloblasts [472]. It is a potential therapeutic target in breast cancer [2584] and is a regulator of non-small cell lung cancer cell invasiveness [3194].	ADGRF5 controls alveolar surfactant secretion via G _{q/11} pathway [323, 622, 1447, 2791]. ADGRF5 acts as a receptor of soluble fibronectin type III domain-containing protein 4 (<i>FNDC4</i>) in the white adipose tissue [891] and it is a critical regulator of V-ATPase in the kidney [3211]. ADGRF5 deficiency leads to dysregulation of lung surfactant homeostasis [303, 830, 3165].	
Nomenclature	ADGRG1	ADGRG2	
HGNC, UniProt	ADGRG1 , Q9Y653	ADGRG2 , Q8IZP9	
Endogenous agonists	Peptides derived from the <i>Stachel</i> sequence: TYFAVLM [2708]	Peptides derived from the <i>Stachel</i> sequence: TSFGVLLDLRSLSLPP [621]	
Comments	ADGRG1 (GPR56) is a collagen-responsive platelet receptor sensing shear forces [3181]. Reported to bind tissue transglutaminase 2 [3131] and collagen, which activates the G _{12/13} pathway [1751]. Interacts with heparin [471]. Couples to G13 proteins [2708]. GAIN domain-mediated cleavage is required for activation of ADGRG1 by its natural ligands and a small-molecule agonist [3262]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [150]. 3- α -acetoxydihydrodeoxygedunin is a partial agonist [2709], and hexahydroquinoline derivatives act as selective agonists for ADGRG1 [2951]. Dihydrumunduletone, a rotenoid derivative, is an antagonist [2707]. ADGRG1 negatively regulates immediate effector functions in human NK cells [420]. Deficiency leads to dysregulation of central and peripheral myelination [12, 906] and ADGRG1 deficiency in humans leads to bilateral frontoparietal polymicrogyria [2239].	ADGRG2 is coupled to G _q and G _s pathways [621, 3225] and gene deficiency causes congenital obstructive azoospermia [2179]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [1683, 3122].	
Nomenclature	ADGRG3	ADGRG4	ADGRG5
HGNC, UniProt	ADGRG3 , Q86Y34	ADGRG4 , Q8IZF6	ADGRG5 , Q8IZF4
Endogenous agonists	–	–	Peptides derived from the <i>Stachel</i> sequence: TYFAVLMQLSGDPVPAEL [2707, 3072]
Comments	ADGRG3 couples to G _o proteins [1004], G α_s and G $\alpha_{o/i}$ signaling [1180]. The 7-helix transmembrane domain structure has been determined by cryo-EM [2249]. Binds to exogenous ligands beclomethasone dipropionate and cortisol [1004, 2249], ezetimibe, flunarizine and zeranol [2669].	ADGRG4 is highly expressed in enterochromaffin cells and gastrointestinal neuroendocrine tumors [1619]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [3122].	ADGRG5 is a constitutively active G _s protein-coupled receptor [1004, 2707, 3072]. Dihydrumunduletone is an antagonist [2707]. The cryo-EM structure of the 7-helix transmembrane domain with its intramolecular agonist has been determined [2250].

Nomenclature	ADGRG6	ADGRG7	
HGNC, UniProt	ADGRG6, Q86SQ4	ADGRG7, Q96K78	
Endogenous agonists	Peptides derived from the <i>Stachel</i> sequence: THFGVLMDLPRASQL; Progesterone and 17-hydroxyprogesterone seem to activate Gi signaling via GPR126 (ADGRG6). [62, 1670]	–	
Comments	ADGRG6 (GPR126) is a key regulator of Schwann cell-mediated myelination [1945], and couples to G _s and G _{i/o} pathways [1670, 1931, 2229]. Apomorphine hydrochloride is an exogenous agonist [289]. Binds to Laminin-211 [2229]. ADGRG6 is essential for normal differentiation of promyelinating Schwann cells and for normal myelination of axons [1931, 1945, 1946, 2229], normal placenta development [2851], and for proper heart development [2185, 2976]. Furthermore, conditional deletion of <i>Adrg6</i> revealed that this adhesion GPCR is involved in regulation of body length and bone mass [2729] and intervertebral disc function [1721]. Involved in arthrogryposis multiplex congenita (lethal congenital contracture syndrome-9) [2353]. Types VI and IV collagen are agonists of ADGRG6 [1322, 3071], with type VI exhibiting G _i -biased signalling [1322]. The prion protein is an ADGRG6 agonist [1322].	ADGRG7 is expressed in intestine and involved in regulation of intestinal contractility [2068].	
Nomenclature	ADGRL1	ADGRL2	
HGNC, UniProt	ADGRL1, O94910	ADGRL2, O95490	
Endogenous agonist proteins	–	teneurin 2 (<i>TENM2</i>) [619]	
Agonists	α -latrotoxin [1493, 2955] – Rat	α -latrotoxin [1209] – Rat	
Comments	Couples to G _s and G _q pathways [1621, 1996]. Principal signal transduction involves G α_s [1996], G α_o [1621, 2327] and G α_q [2327]. Interacts with Teneurin-2 [2613], FLRT-1, -3 [2101], Neurexin-1 α , -1 β , -2 β , -3 β [276], Contactin-6 [3277], Shank [1497], TRIP8b [2262, 2263] and glucose [467]. <i>ADGRL1</i> haploinsufficiency has been linked to intellectual disability and developmental delay [2950].	<i>ADGRL2</i> variants are associated with cocaine use disorder [2728]. Also known to interact with teneurin 3 (<i>TENM3</i>) [2194, 2195].	
Nomenclature	ADGRL3	ADGRL4	ADGRV1
HGNC, UniProt	ADGRL3, Q9HAR2	ADGRL4, Q9HBW9	ADGRV1, Q8WXG9
Agonists	α -latrotoxin [594] – Rat	–	–
Comments	Principal signal transduction involves G $\alpha_{12/13}$ [1833] and G α_q [1833]. Interacts with teneurin-2 and -3 [1647, 2101], FLRT-1, -3 [2101], LRG1 [3183], UNC5A [1251] and synthetic binder LK30 [1479]. <i>ADGRL3</i> (formerly LPHN3; latrophilin 3) gene variants in humans are associated with attention-deficit-hyperactivity disorder [3076] and Tourette disorder [77]. Associations with substance use disorder [78] and autism spectrum disorder [1346] have been reported.	ADGRL4 (ELTD1) extracellular domain (ECD) closely resembles class E adhesion GPCRs [754].	Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder [1259]. Interacts with Harmonin [2368] and Whirlin [2920].

Further reading on Adhesion Class GPCRs

- Bassilana F *et al.* (2019) Adhesion G protein-coupled receptors: opportunities for drug discovery. *Nat Rev Drug Discov* **18**: 869-884 [PMID:31462748]
- Gupta C *et al.* (2023) Structural clarity is brought to adhesion G protein-coupled receptor tethered agonism. *Basic Clin Pharmacol Toxicol* **133**: 295-300 [PMID:36585032]
- Hamann J *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G protein-coupled receptors. *Pharmacol Rev* **67**: 338-67 [PMID:25713288]
- Kleinau G *et al.* (2023) Intramolecular activity regulation of adhesion GPCRs in light of recent structural and evolutionary information. *Pharmacol Res* **197**: 106971 [PMID:38032292]
- Langenhan T *et al.* (2013) Sticky signaling—adhesion class G protein-coupled receptors take the stage. *Sci Signal* **6**: re3 [PMID:23695165]
- Liessmann F *et al.* (2024) Targeting adhesion G protein-coupled receptors. Current status and future perspectives. *Structure* **32**: 2188-2205 [PMID:39520987]
- Monk KR *et al.* (2015) Adhesion G Protein-Coupled Receptors: From In Vitro Pharmacology to In Vivo Mechanisms. *Mol Pharmacol* **88**: 617-23 [PMID:25956432]
- Purcell RH *et al.* (2018) Adhesion G Protein-Coupled Receptors as Drug Targets. *Annu Rev Pharmacol Toxicol* **58**: 429-449 [PMID:28968187]

Adrenoceptors

G protein-coupled receptors → Adrenoceptors

Overview: The nomenclature of the Adrenoceptors has been agreed by the NC-IUPHAR Subcommittee on Adrenoceptors [355, 1123].**Adrenoceptors, α_1**

The three α_1 -adrenoceptor subtypes α_{1A} , α_{1B} and α_{1D} are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. (-)-phenylephrine, methoxamine and cirazoline are agonists and prazosin and doxazosin antagonists considered selective for α_1 -relative to α_2 -adrenoceptors. [³H]prazosin and HEAT (BE2254) (BE2254) are relatively selective radioligands. S(+)-niguldipine also has high affinity for L-type Ca²⁺ channels. Fluorescent de-

rivatives of prazosin (Bodipy FLprazosin- QAPB) are used to examine cellular localisation of α_1 -adrenoceptors. α_1 -Adrenoceptor agonists are used as nasal decongestants; antagonists to treat symptoms of benign prostatic hyperplasia (alfuzosin, doxazosin, terazosin, tamsulosin and silodosin, with the last two compounds being α_{1A} -adrenoceptor selective and claiming to relax bladder neck tone with less hypotension); and to a lesser extent hyperten-

sion (doxazosin, terazosin). The α_1 - and β_2 -adrenoceptor antagonist carvedilol is used to treat congestive heart failure, although the contribution of α_1 -adrenoceptor blockade to the therapeutic effect is unclear. Several anti-depressants and anti-psychotic drugs are α_1 -adrenoceptor antagonists contributing to side effects such as orthostatic hypotension.

Nomenclature	α_{1A} -adrenoceptor	α_{1B} -adrenoceptor	α_{1D} -adrenoceptor
HGNC, UniProt	ADRA1A, P35348	ADRA1B, P35368	ADRA1D, P25100
Potency order of endogenous ligands	(-)-noradrenaline = (-)-adrenaline	–	–
Endogenous agonists	(-)-adrenaline [1165, 2295, 2541, 2585], (-)-noradrenaline [569, 739, 1165, 2295, 2541, 2585, 2794]	(-)-adrenaline [2295, 2585], (-)-noradrenaline [2295, 2585]	(-)-noradrenaline [1165, 2295, 2585], (-)-adrenaline [1165, 2295, 2585]
Agonists	phenylephrine [569, 739, 2295, 2794], methoxamine [569, 739, 2295, 2541, 2585, 2794]	phenylephrine [792, 1914]	methoxamine [2295, 2585], phenylephrine [2295]
Selective agonists	A61603 [569, 739, 1446, 2295], oxymetazoline [569, 739, 1165, 2104, 2295, 2541, 2585, 2794], dabuzalgron [239]	–	–

Antagonists	prazosin (Inverse agonist) (pK _i 9–9.9) [418, 574, 792, 2296, 2585, 3074], doxazosin (pK _i 8.4–9.3) [1035, 2296, 2315], terazosin (pK _i 7.9–8.7) [1881, 2296, 2315], phentolamine (pK _i 8.2–8.6) [2296, 2585], alfuzosin (pK _i 7.8–8.1) [1121, 2296, 2315]	prazosin (Inverse agonist) (pK _i 8.7–9.9) [792, 2296, 2585, 3074], tamsulosin (Inverse agonist) (pK _i 8.1–9.7) [792, 2296, 2585, 3074], doxazosin (pK _i 8.5–9.1) [1035, 2296], alfuzosin (pK _i 7.6–8.6) [1122, 2296], terazosin (pK _i 8–8.6) [1881, 2296], phentolamine (pK _i 6.6–7.5) [2296, 2585]	prazosin (Inverse agonist) (pK _i 9.1–10.2) [792, 2296, 2585, 3074], tamsulosin (pK _i 9.2–10.2) [792, 2296, 2585, 3074], doxazosin (pK _i 8.3–9.1) [1035, 2296], terazosin (pK _i 7.7–9.1) [1881, 2296], alfuzosin (pK _i 7.7–8.4) [1121, 2296], dapiprazole (pK _i 8.4) [100, 2296], phentolamine (Inverse agonist) (pK _i 6.8–8.2) [2296, 2585], RS-100329 (pK _i 7.6–7.9) [2296, 3074], labetalol (pK _i 6.1–6.6) [100, 2296]
Selective antagonists	tamsulosin (pK _i 9.4–10.7) [418, 574, 792, 2296, 2315, 2541, 2585, 3074], silodosin (pK _i 9.6–10.4) [2296, 2315, 2585], S(+)-niguldipine (pK _i 9.1–10) [792, 2296, 2585], RS-100329 (pK _i 9.6) [2296, 3074], ρ-Da1a (pK _i 9.2–9.5) [1786, 2319], SNAP5089 (pK _i 8.8–9.4) [1121, 1626, 2296, 3055], RS-17053 (pK _i 8.3–9.3) [418, 574, 791, 792, 2296]	Rec 15/2615 (pK _i 7.8–9.5) [2296, 2804], L-765314 (pK _i 7.7) [2177], AH 11110 (pK _i 7.5) [2489]	BMY-7378 (pK _i 8.6–9.1) [389, 2296, 3199]

Comments: Adrenoceptors, α₁

The three α₁-adrenoceptor subtypes are α_{1A}, α_{1B} and α_{1D}. The previously described α_{1C}-adrenoceptor is a species homologue that corresponds to the pharmacologically defined α_{1A}-adrenoceptor [1123]. Some tissues possess α_{1A}-adrenoceptors (termed α_{1L}-adrenoceptors [792, 1973]) that display relatively low affinity in functional and binding assays for [prazosin](#) indicative of different receptor states or locations. α_{1A}-Adrenoceptor C-terminal splice variants form homo- and heterodimers, and do not gen-

erate a functional α_{1L}-adrenoceptor [2340]. Recombinant α_{1D}-adrenoceptors have been shown in some heterologous systems to be mainly located intracellularly but cell-surface localization is encouraged by truncation of the N-terminus, or by co-expression and formation of heterodimers of with α_{1B}-α_{1B}- or β₂-β₂-adrenoceptors [1014, 2879]. In blood vessels all three α₁-adrenoceptor subtypes are located both at the cell surface and intracellularly [1878, 1879]. Signalling is predominantly *via* G_{q/11}

but α₁-adrenoceptors also couple to G_{i/o}, G_s and G_{12/13}. Several α_{1A}-adrenoceptor agonists display ligand directed signalling bias relative to noradrenaline [739] although some bias appears to relate to off-target activity [569]. There are also differences between subtypes in coupling efficiency to different pathways. In vascular smooth muscle, the potency of agonists is related to the predominant subtype, α_{1D}- conveying greater agonist sensitivity compared to α_{1A}-adrenoceptors [785].

Adrenoceptors, α₂

The three α₂-adrenoceptor subtypes α_{2A}, α_{2B} and α_{2C} are activated by (-)-adrenaline and with lower potency by (-)-noradrenaline. [Brimonidine](#) (UK14304) and [talipexole](#) are agonists and [rauwolscine](#) and [yohimbine](#) antagonists selective for α₂- relative to α₁-adrenoceptors. [³H]rauwolscine, [³H]brimonidine (UK14304) and [³H]RX821002 are relatively selective radioligands. There are species variations in the pharmacology of the α_{2A}-adrenoceptor. Multiple mutations of α₂-adrenoceptors have been described, some associated with alterations in function. Presynaptic α₂-

adrenoceptors regulate many functions in the nervous system. The α₂-adrenoceptor agonists [clonidine](#), [guanabenz](#) and [brimonidine](#) (UK14304) affect central baroreflex control (hypotension and bradycardia), induce hypnotic effects and analgesia, and modulate seizure activity and platelet aggregation. [Clonidine](#) is an anti-hypertensive (relatively little used) and counteracts opioid withdrawal. [Dexmedetomidine](#) (also [xylazine](#)) is increasingly used as a sedative and analgesic in human [145] and veterinary medicine and has sympatholytic and anxiolytic properties.

The α₂-adrenoceptor antagonist [mirtazapine](#) is used as an anti-depressant. The α_{2B} subtype appears to be involved in neurotransmission in the spinal cord and α_{2C} in regulating catecholamine release from adrenal chromaffin cells. Although subtype-selective antagonists have been developed, none are used clinically and they remain experimental tools.

Nomenclature	α_{2A} -adrenoceptor	α_{2B} -adrenoceptor	α_{2C} -adrenoceptor
HGNC, UniProt	ADRA2A, P08913	ADRA2B, P18089	ADRA2C, P18825
Endogenous agonists	(-)-adrenaline [1275, 2240, 2293], (-)-noradrenaline [1275, 2240, 2293]	(-)-noradrenaline [1275, 2240, 2293], (-)-adrenaline [1275, 2293]	(-)-noradrenaline [1275, 1528, 2240, 2293], (-)-adrenaline [1275, 2293]
Agonists	dexmedetomidine (Partial agonist) [1275, 1766, 2200, 2240, 2293], clonidine [1275, 2200, 2240, 2293], brimonidine (UK14304) [1275, 1766, 2200, 2240, 2293], apraclonidine [1998], guanabenz [100, 2293], guanfacine (Partial agonist) [1275, 1770, 2293], tizanidine [2293], moxonidine [2293]	dexmedetomidine [1275, 1766, 2200, 2240, 2293], clonidine (Partial agonist) [1275, 2200, 2240, 2293], brimonidine (UK14304) (Partial agonist) [1275, 2200, 2240, 2293], guanfacine [1275, 2293], oxymetazoline [1275, 2293, 2884], guanabenz [2293], tizanidine [2293], moxonidine [2293]	dexmedetomidine [1275, 2200, 2240, 2293], guanabenz [100, 1528, 2293], brimonidine (UK14304) [1275, 1766, 2200, 2240, 2293], apraclonidine [1998, 2293], oxymetazoline [1275, 1528, 2293, 2884], guanfacine [1275, 2293], moxonidine [2293]
Selective agonists	oxymetazoline (Partial agonist) [1275, 1766, 2293, 2884]	–	–
Antagonists	RX821002 (pK _i 8.1–9.2) [2294, 2884], yohimbine (pK _i 8.4–9.2) [354, 630, 2294, 2884], atipamezole (pK _i 8.5) [2294], idazoxan (pK _i 7.2) [2294]	lisuride (pK _i 8.5–9.9) [1903, 2294], yohimbine (pK _i 7.7–8.9) [354, 630, 2294, 2884], phenoxybenzamine (pK _i 8.5) [3037], RX821002 (pK _i 7.5–8.4) [2294, 2884], atipamezole (pK _i 7.9) [2294], idazoxan (pK _i 6.4) [2294], tolazoline (pK _i 5.5) [1275]	MK-912 (pK _i 9.8–10) [2294], lisuride (pK _i 9.3–9.9) [1766, 1903, 2294], yohimbine (pK _i 8.5–9.5) [354, 630, 2294, 2884], WB 4101 (pK _i 8.2–9.4) [354, 630, 2294, 2884], spiroxatrine (pK _i 8.7–9) [2294, 2884], RX821002 (pK _i 8.1–8.7) [2294, 2884], atipamezole (pK _i 8.5) [2294], mirtazapine (pK _i 7–7.7) [767, 2294], idazoxan (pK _i 7.2) [2294], tolazoline (pK _i 5.4) [1275]
Selective antagonists	BRL 44408 (pK _i 7.2–8.8) [2294, 2884, 3201]	ARC-239 (pK _i 6.8–8.6) [354, 630, 2294, 2884], imiloxan (pK _i 7.3) [1892] – Rat	JP1302 (pK _B 6.9–7.8) [2294, 2465]
Labelled ligands	–	–	[³ H]MK-912 (Antagonist) (pK _d 10.1) [2884]

Adrenoceptors, α_2

The three α_2 -adrenoceptor subtypes are termed α_{2A} , α_{2B} and α_{2C} . ARC-239 and prazosin show some selectivity for α_{2B} - and α_{2C} -adrenoceptors over α_{2A} -adrenoceptors. Oxymetazoline is an imidazoline partial agonist that also binds to non-GPCR binding sites for imidazolines, classified as I₁, I₂ and I₃ [576] at which catecholamines have a low affinity, while rilmenidine and moxonidine are selective ligands with hypotensive effects *in vivo*. I₁-imidazoline recognition sites cause central inhibition of sympathetic tone, I₂-imidazoline sites are an allosteric binding site on monoamine oxidase B, and I₃-imidazoline sites regulate insulin

secretion from pancreatic β -cells. α_{2A} -adrenoceptor stimulation reduces insulin secretion from β -islets [3162], with a polymorphism in the 5'-UTR of the ADRA2A gene being associated with increased receptor expression in β -islets and heightened susceptibility to diabetes [2419]. The α_{2A} - and α_{2C} -adrenoceptors form homodimers [2638]. Heterodimers between α_{2A} - and either the α_{2C} -adrenoceptor or μ opioid peptide receptor exhibit altered signalling and trafficking properties compared to the individual receptors [2638, 2782, 2943]. Signalling by α_2 -adrenoceptors is primarily via G_{1/O}, although the α_{2A} -adrenoceptor also couples

to G_s [700]. Imidazoline compounds display bias relative to each other at the α_{2A} -adrenoceptor [2189]. The noradrenaline reuptake inhibitor desipramine acts directly on α_{2A} -adrenoceptors to promote internalisation *via* recruitment of β -arrestin [543]. The structure of the α_{2B} -adrenoceptor has recently been determined by cryo-EM in complex with dexmedetomidine and G α_o at a resolution of 2.9 Å providing insights into the structural requirements required for interactions with α_2 -adrenoceptor agonists [3204].

Adrenoceptors, β

The three β -adrenoceptor subtypes β_1 , β_2 and β_3 are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline. Isoprenaline is selective for β -adrenoceptors relative to α_1 - and α_2 -adrenoceptors, while propranolol (pK_i 8.2–9.2) and cyanopindolol (pK_i 10.0–11.0) are relatively selective antagonists for β_1 - and β_2 - relative to β_3 -adrenoceptors. (-)-noradrenaline, xamoterol and (-)-Ro 363 show selectivity for β_1 - relative to β_2 -

adrenoceptors. Pharmacological differences exist between human and mouse β_3 -adrenoceptors, and the 'rodent selective' agonists BRL 37344 and CL316243 have low efficacy at the human β_3 -adrenoceptor whereas CGP 12177 (low potency) and L 755507 activate human β_3 -adrenoceptors [88]. β_3 -Adrenoceptors are resistant to blockade by propranolol, but can be blocked by high concentrations of bupranolol. SR59230A has reasonably high

affinity at β_3 -adrenoceptors, but does not discriminate between the three β - subtypes [1895] whereas L-748337 is more selective. [¹²⁵I]-cyanopindolol, [¹²⁵I]-hydroxy benzylpindolol and [³H]-alprenolol are high affinity radioligands that label β_1 - and β_2 -adrenoceptors and β_3 -adrenoceptors can be labelled with higher concentrations (nM) of [¹²⁵I]-cyanopindolol together with β_1 - and β_2 -adrenoceptor antagonists. Fluorescent ligands such as

BODIPY-TMR-CGP12177 can be used to track β -adrenoceptors at the cellular level [8]. Somewhat selective β_1 -adrenoceptor agonists (**denopamine**, **dobutamine**) are used short term to treat cardiogenic shock but, chronically, reduce survival. β_1 -Adrenoceptor-preferring antagonists are used to treat cardiac arrhythmias (**atenolol**, **bisoprolol**, **esmolol**) and cardiac failure (**metoprolol**,

nebivolol) but also in combination with other treatments to treat hypertension (**atenolol**, **betaxolol**, **bisoprolol**, **metoprolol** and **nebivolol**) [3087]. Cardiac failure is also treated with carvedilol that blocks β_1 - and β_2 -adrenoceptors, as well as α_1 -adrenoceptors. Short (**salbutamol**, **terbutaline**) and long (**formoterol**, **salmeterol**) acting β_2 -adrenoceptor-selective agonists are powerful bronchodilators used to treat respiratory disorders. Many first generation

β -adrenoceptor antagonists (**propranolol**) block both β_1 - and β_2 -adrenoceptors and there are no β_2 -adrenoceptor-selective antagonists used therapeutically. The β_3 -adrenoceptor agonist **mira-begron** is used to control overactive bladder syndrome. There is evidence to suggest that β -adrenoceptor antagonists can reduce metastasis in certain types of cancer [1127].

Nomenclature	β_1 -adrenoceptor	β_2 -adrenoceptor
HGNC, UniProt	<i>ADRB1</i> , P08588	<i>ADRB2</i> , P07550
Potency order of endogenous ligands	(-)-noradrenaline > (-)-adrenaline	(-)-adrenaline > (-)-noradrenaline
Endogenous agonists	(-)-adrenaline [125, 820, 1144], (-)-noradrenaline [125, 820, 1144], noradrenaline [820]	(-)-adrenaline [125, 820, 1144, 1270], (-)-noradrenaline [125, 820, 1144]
Agonists	isoprenaline [125, 820, 2488], cimaterol [125], dobutamine (Partial agonist) [125, 1238], fenoterol [125]	indacaterol [162, 168], fenoterol [81, 125, 133, 604], isoprenaline [125, 129, 2488], cimaterol [125]
Selective agonists	(-)-Ro 363 [1936], xamoterol (Partial agonist) [126, 1238], denopamine (Partial agonist) [125, 1238, 2743]	formoterol [49, 125, 133, 162, 1700], olodaterol [279], zinterol [125], vilanterol [2285], salmeterol (Partial agonist) [125, 133, 604], abediterol [73], clenbuterol [125], procaterol [125], salbutamol (Partial agonist) [125, 126, 133, 604, 1238, 2667], terbutaline (Partial agonist) [125, 126], orciprenaline [2668]
Antagonists	carvedilol (pK _i 8.8–9.5) [126, 373], bupranolol (pK _i 7.3–9) [126, 373, 1735], (-)-propranolol (pK _i 7.9–8.9) [126, 1312, 1735, 2653], SR59230A (pK _i 7.5–8.6) [125, 126, 373], bunolol (pK _i 8.4) [100], labetalol (pK _i 7.6–8.2) [100, 126, 130], metoprolol (pK _i 7–7.9) [126, 130, 373, 1144, 1735], esmolol (pK _i 6.7–6.9) [100, 2034], nadolol (pK _i 6.9) [373], practolol (pK _i 6.1–6.8) [126, 1735], propafenone (pK _i 6.7) [100], sotalol (pK _i 5.8–6.1) [100, 126]	bupranolol (pK _i 8.3–9.9) [126, 373, 1735], carvedilol (pK _i 9.4–9.9) [126, 373], timolol (pK _i 9.7) [126], propranolol (pK _i 9.1–9.5) [126, 131, 1238, 1735], SR59230A (pK _i 8.5–9.3) [126, 373], bunolol (pK _i 9.3) [100], alprenolol (Partial agonist) (pK _i 9) [126], nadolol (pK _i 7–8.6) [126, 373], labetalol (Partial agonist) (pK _i 8) [100, 126], propafenone (pK _i 7.4) [100], sotalol (pK _i 6.5–6.9) [100, 126]
Selective antagonists	CGP 20712A (pK _i 7.8–9.2) [126, 373, 1735, 2487, 2653], betaxolol (pK _i 8.2–9.1) [126, 1735, 2575], nebivolol (pK _i 9.1) [125], NDD-825 (pK _i 8.3–9) [128], ICI-89406 (Partial agonist) (pK _i 8.8) [1917], nebivolol (pIC ₅₀ 8.1–8.7) [2188] – Rabbit, NDD-713 (pK _i 7.8–8.5) [128], bisoprolol (pK _i 7.8) [128]	ICI 118551 (Inverse agonist) (pK _i 9.2–9.5) [126, 131, 1735]
Allosteric modulators	–	AS408 [1719]
Labelled ligands	[¹²⁵ I]ICYP (Antagonist) (pK _d 10.4–11.3) [1238, 1313, 1735, 2488]	[¹²⁵ I]ICYP (Antagonist) (pK _d 11.1–11.4) [1735, 2488, 2752]
Comments	The agonists indicated have less than two orders of magnitude selectivity [125].	–

Nomenclature	β_3 -adrenoceptor
HGNC, UniProt	<i>ADRB3</i> , P13945
Potency order of endogenous ligands	(-)-noradrenaline = (-)-adrenaline
Endogenous agonists	(-)-noradrenaline [1144, 2264, 2712], (-)-adrenaline [125, 1144]
Agonists	carazolol (Partial agonist) [125], isoprenaline [125, 1144, 1874, 1936, 2264, 2488, 2712], fenoterol [125]
Selective agonists	L 755507 [125], vibegron [326, 641, 704], mirabegron [326, 616, 1064, 2768], L742791 [3033], solabegron [1210, 1894, 2882], SB251023 [1206] – Mouse, BRL 37344 [237, 659, 1144, 1874], CL316243 [3158]
Antagonists	SR59230A (pK _i 6.9–8.4) [125, 373, 605, 1144], bupranolol (pK _i 6.8–7.3) [237, 373, 1735, 1874], propranolol (pK _i 6.3–7.2) [126, 1735, 2264], bunolol (pK _i 6.8) [2264]
Selective antagonists	L-748328 (pK _i 8.4–8.6) [125, 373], L-748337 (pK _i 8–8.4) [125, 373]
Labelled ligands	[¹²⁵ I]ICYP (Agonist, Partial agonist) [1735, 1936, 2264, 2488, 2712], [³ H]CGP12177 (Agonist, Partial agonist) [125]
Comments	Agonist SB251023 has a pEC ₅₀ of 6.9 for the splice variant of the mouse β_3 receptor, β_{3b} [1206]. [³ H] L-748337 is a selective antagonist that is used to label β_3 -AR [2919].

Adrenoceptors, β

The three β -adrenoceptors are termed β_1 , β_2 and β_3 . [¹²⁵I]ICYP can be used to define either β_1 - or β_2 -adrenoceptors when conducted in the presence of a β_1 - or a β_2 -adrenoceptor-selective antagonist. A fluorescent analogue of CGP 12177 is used to study β -adrenoceptors in living cells [132]. [¹²⁵I]ICYP at higher (nM) concentrations has been used to label β_3 -adrenoceptors in systems with few if any other β -adrenoceptor subtypes. The β_3 -adrenoceptor has an intron in the coding region, but splice variants have only been described for the mouse [740], where the isoforms display different signalling characteristics [1206]. There are three β -adrenoceptors in turkey (termed the t β , t β_3c and t β_4c) with pharmacology that differs from the human β -adrenoceptors [127]. Numerous polymorphisms have been described for the β -adrenoceptors; some are associated with altered signalling and trafficking, susceptibility to disease and/or altered responses to pharmacotherapy [1672]. All β -adrenoceptors couple to G_s (activating adenylyl cyclase and elevating cAMP levels),

but the β_2 - and β_3 -adrenoceptors in particular can also activate G_i and the β_2 -adrenoceptor activates β -arrestin-mediated signalling. Many β_1 - and β_2 -adrenoceptor antagonists are agonists at β_3 -adrenoceptors (CL316243, CGP 12177 and carazolol). Many 'antagonists' of cAMP accumulation, for example carvedilol and bucindolol, weakly activate MAP kinase pathways [130, 741, 835, 836, 2485, 2486] and thus display biased agonism. Bupranolol acts as a neutral antagonist in most systems so far examined. Agonists also display biased signalling at the β_2 -adrenoceptor via G_s or arrestins [677]. X-ray crystal structures have been described of the agonist bound [3020] and antagonist bound forms of the β_1 - [3021], agonist-bound [464] and antagonist-bound forms of the β_2 -adrenoceptor [2347, 2418], as well as a fully active agonist-bound, G_s protein-coupled β_2 -adrenoceptor [2348], as well as providing insights into the structural requirements for agonist, partial agonist, antagonist, G protein and β -arrestin coupling [3038]. Structures have also been described for negative allosteric mod-

ulators of the β_2 -adrenoceptor [1719]. Cryo-EM studies have also been recently described that provide a structural framework for agonist mediated signal transduction [2716]. The agonists carvedilol and bucindolol bind to a site on the β_1 -adrenoceptor involving contacts in TM2, 3, and 7 and extracellular loop 2 that may facilitate coupling to arrestins [3021]. Compounds displaying β -arrestin-biased signalling at the β_2 -adrenoceptor have a greater effect on the conformation of TM7, whereas full agonists for G_s coupling promote movement of TM5 and TM6 [1713]. Recent studies using NMR spectroscopy demonstrate significant conformational flexibility in the β_2 -adrenoceptor that is stabilized by both agonist and G proteins highlighting the dynamic nature of interactions with both ligand and downstream signalling partners [1410, 1802, 2099]. Such flexibility likely has consequences for our understanding of allostereism and biased agonism, and for the future therapeutic exploitation of these phenomena.

Further reading on Adrenoceptors

- Baker JG *et al.* (2011) Evolution of β -blockers: from anti-anginal drugs to ligand-directed signalling. *Trends Pharmacol Sci* **32**: 227-34 [PMID:21429598]
- Bylund DB *et al.* (1994) International Union of Pharmacology nomenclature of adrenoceptors. *Pharmacol Rev* **46**: 121-36 [PMID:7938162]
- Evans BA *et al.* (2010) Ligand-directed signalling at beta-adrenoceptors. *Br J Pharmacol* **159**: 1022-38 [PMID:20132209]
- Jensen BC *et al.* (2011) Alpha-1-adrenergic receptors: targets for agonist drugs to treat heart failure. *J Mol Cell Cardiol* **51**: 518-28 [PMID:21118696]
- Kobilka BK. (2011) Structural insights into adrenergic receptor function and pharmacology. *Trends Pharmacol Sci* **32**: 213-8 [PMID:21414670]
- Langer SZ. (2015) α_2 -Adrenoceptors in the treatment of major neuropsychiatric disorders. *Trends Pharmacol Sci* **36**: 196-202 [PMID:25771972]
- Michel MC *et al.* (2015) Selectivity of pharmacological tools: implications for use in cell physiology. A review in the theme: Cell signaling: proteins, pathways and mechanisms. *Am J Physiol, Cell Physiol* **308**: C505-20 [PMID:25631871]

Angiotensin receptors

G protein-coupled receptors → Angiotensin receptors

Overview: The actions of **angiotensin II (AGT, P01019)** (Ang II) are mediated by AT₁ and AT₂ receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Angiotensin receptors** [599, 1350]), which have around 30% sequence similarity. The octapeptide **angiotensin II (AGT, P01019)** and the heptapeptide **angiotensin III (AGT, P01019)** are endogenous ligands. The “sartan” family drugs such as **losartan**, **candesartan**, **olmesartan**, **telmisartan**, etc. are clinically used AT₁ receptor blockers.

Nomenclature	AT ₁ receptor	AT ₂ receptor
HGNC, UniProt	AGTR1, P30556	AGTR2, P50052
Endogenous agonists	angiotensin II (AGT, P01019) [600, 1350, 2921], angiotensin III (AGT, P01019) [600, 1350], angiotensin IV (AGT, P01019) (Partial agonist) [1584]	angiotensin III (AGT, P01019) [554, 600, 3059], angiotensin II (AGT, P01019) [600, 2649, 3059], angiotensin-(1-7) (AGT, P01019) [274]
Agonists	[Sar ¹ ,Cha ⁴]Ang-II [1152, 1922] – Rat	–
Selective agonists	L-162,313 [2215], L-163,101 [2891], TRV027 [1271, 2947, 3213]	CGP42112 [274], [p-aminoPhe ⁶]ang II [600, 2676] – Rat, compound 21 [2940]
Antagonists	saprisartan (pK _i 9.1) [1124] – Rat, 5-oxo-1-2-4-oxadiazol biphenyl (pIC ₅₀ 8.8) [2071] – Rat, 5-butyl-methyl imidazole carboxylate 30 (pIC ₅₀ 8.5) [19], sparsentan (Dual antagonist of endothelin type A (ET _A) and AT ₁ receptors) (pK _i 8.4) [2749], TRV027 (pK _d 7.7) [2947]	saralasin (pIC ₅₀ 9) [477] – Rat
Selective antagonists	candesartan (pIC ₅₀ 9.5–9.7) [2921], eprosartan (pIC ₅₀ 8.4–8.8) [705], losartan (pIC ₅₀ 7.4–8.7) [600, 1350, 2834], telmisartan (pIC ₅₀ 8.4) [1857], olmesartan (pIC ₅₀ 8.1) [1461]	PD123177 (pIC ₅₀ 8.5–9.5) [424, 477, 691] – Rat, PD123319 (pK _d 8.7–9.2) [600, 690, 3069], olodanrigan (pK _d 7.4) [2220]
Labelled ligands	[³ H]candesartan (Antagonist) (pK _d 10.3) [770], [¹²⁵ I][Sar ¹]Ang-II (Agonist) [764] – Rat, [¹²⁵ I][Sar ¹ ,Ile ⁸]Ang-II (Agonist, Partial agonist) [764] – Rat, [³ H]eprosartan (Antagonist) (pK _d 9.1) [28] – Rat, [³ H]losartan (Antagonist) (pK _d 8.2) [428] – Rat	[¹²⁵ I]CGP42112 (Agonist) [600, 3059, 3060], [¹²⁵ I][Sar ¹ ,Ile ⁸]Ang-II (Agonist) [2780] – Rat
Comments	Telmisartan and candesartan are also reported to be agonists of PPAR _γ [2705]. Nanobodies that acts as AT ₁ antagonists (AT118-H and AT118-L) have been reported [2626, 2627].	Compounds have been generated with enhanced AT ₂ receptor selectivity and proteolytic stability by imposing conformational constraints at position 6 of Angiotensin II [2859].

Comments: AT₁ receptors are predominantly coupled to G_{q/11} [599, 1350, 3223], however they also recruit β-arrestins and stimulate G protein-independent β-arrestin signaling [1271, 1755, 3213]. Most species express a single *AGTR1* gene located on chromosome 3, but two related *Agtr1a* and *Agtr1b* receptor genes are expressed in rodents. Expression of the X chromosome-linked *AGTR2* gene is higher in females than males [2468]. AT₁ receptor antagonists bearing substituted biphenyl tetrazolium moieties are clinically used to treat hypertension and other cardiovascular disorders. They bind to AT₁ receptors with nanomolar affinity and are more potent than losartan in functional studies [1350]. High-resolution crystal structures of AT₁ receptor bound to non-peptide antagonists (PDB id: 4ZUD, 4YAY), peptide agonists (PDB

id: 6DO1, 6OSO, 6OS1, 6OS2) and G protein G_q (7F6G) are deposited in the protein structure database [2620, 3223]. Structural details of nanobodies (PDB id: 8TH4, 9EAH, 9EAI, 9EAJ) acting as AT₁ receptor antagonists are reported [2626, 2627]. The AT₁ and bradykinin B2 receptors have been proposed to form a heterodimeric complex [3]. β-arrestin1 prevents AT₁-B2 receptor heteromerization [2320]. The AT₂ receptor counteracts several of the growth responses initiated by AT₁ receptors. The AT₂ receptor is much less abundant than the AT₁ receptor in adult tissues and is upregulated in pathological conditions. Agonist activation of AT₂ receptors promotes anti-fibrotic tissue protection in cardiovascular and renal diseases [3012]. AT₂ receptors are involved in pain modulation [63, 2383] and AT₂ receptor antagonists relieve

peripheral neuropathic pain in chronic diseases such as diabetes [2383, 2647]. High-resolution structures of the AT₂ receptor bound to non-peptide antagonists (PDB id: 5UNF, 7JN1) and peptide agonists (PDB id: 5XJM, 6JOD) are available in the protein structure database [2620]. An AT₃ receptor was proposed based on cDNA isolated from a neuroblastoma cell line, but existence of a genuine *AGTR3* gene and AT₃ receptor are not confirmed at this time. However, there is evidence for an AT₄ receptor that specifically binds **angiotensin IV (AGT, P01019)** (AGT; P01019) and is located in the brain and kidney. An additional putative endogenous ligand for the AT₄ receptor has been described (**LVV-hemorphin (HBB, P68871)** [HBB, P68871], a globin decapeptide) [1930].

Further reading on Angiotensin receptors

- Asada H *et al.* (2020) The Crystal Structure of Angiotensin II Type 2 Receptor with Endogenous Peptide Hormone. *Structure* **28**: 418-425.e4 [PMID:31899086]
- Balogh M *et al.* (2021) Angiotensin receptors and neuropathic pain. *Pain Rep* **6**: e869 [PMID:33981922]
- Karnik SS *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCIX. Angiotensin Receptors: Interpreters of Pathophysiological Angiotensinergic Stimuli [corrected]. *Pharmacol Rev* **67**: 754-819 [PMID:26315714]
- Singh KD *et al.* (2021) Novel allosteric ligands of the angiotensin receptor AT1R as autoantibody blockers. *Proc Natl Acad Sci U S A* **118**: [PMID:34380734]
- Singh KD *et al.* (2022) Structural perspectives on the mechanism of signal activation, ligand selectivity and allosteric modulation in angiotensin receptors: IUPHAR Review 34. *Br J Pharmacol* **179**: 4461-4472 [PMID:35318654]
- Wingler LM *et al.* (2020) Angiotensin and biased analogs induce structurally distinct active conformations within a GPCR. *Science* **367**: 888-892 [PMID:32079768]

Apelin receptor

G protein-coupled receptors → Apelin receptor

Overview: The apelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the apelin receptor [2252] and subsequently updated [2361]**) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. Apelin-36 (APLN, Q9ULZ1), apelin-13 (APLN, Q9ULZ1) and [Pyr¹]apelin-13 (APLN, Q9ULZ1) are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide

(APLN, Q9ULZ1) [2798]. A second family of peptides discovered independently and named Elabela [478] or Toddler, that has little sequence similarity to apelin, is present, and functional at the apelin receptor in the adult cardiovascular system [2187, 3167]. The enzymatic pathways generating biologically active apelin and Elabela isoforms have not been determined but both pro-peptides include sites for potential proprotein convertase pro-

cessing [2596]. Structure-activity relationship Elabela analogues have been described [2006, 2863]. The stoichiometry of apelin receptor-heterotrimeric G protein complexes has been studied using cryogenic-electron microscopy [3206]. A crystal structure for the apelin receptor in complex with a G protein-biased agonist has been reported [3075].

Nomenclature	apelin receptor
HGNC, UniProt	APLNR, P35414
Potency order of endogenous ligands	[Pyr ¹]apelin-13 (APLN, Q9ULZ1) ≥ apelin-13 (APLN, Q9ULZ1) > apelin-36 (APLN, Q9ULZ1) [748, 2798]
Endogenous agonists	apelin-13 (APLN, Q9ULZ1) [748, 1169, 1871], apelin receptor early endogenous ligand (APELA, P0DMC3) [623], apelin-17 (APLN, Q9ULZ1) [711, 1871], [Pyr ¹]apelin-13 (APLN, Q9ULZ1) [1362, 1871], Elabela/Toddler-21 (APELA, P0DMC3) [3166], Elabela/Toddler-32 (APELA, P0DMC3) [3166], apelin-36 (APLN, Q9ULZ1) [748, 1169, 1362, 1871], Elabela/Toddler-11 (APELA, P0DMC3) [3166]
Selective agonists	CMF-019 (Biased agonist) [2360], MM07 (Biased agonist) [293], azelaprag [93, 443]
Antagonists	MM54 (pK _i 8.2) [1765]
Labelled ligands	[¹²⁵ I][Nle ⁷⁵ , Tyr ⁷⁷]apelin-36 (human) (Agonist) [1362], [¹²⁵ I][Glp ⁶⁵ Nle ⁷⁵ , Tyr ⁷⁷]apelin-13 (Agonist) [1169], [¹²⁵ I](Pyr ¹)apelin-13 (Agonist) [1356], [¹²⁵ I]ape- lin-13 (Agonist) [748], [³ H](Pyr ¹)[Met(0)11]-apelin-13 (Agonist) [1871]

Comments: Potency order determined for heterologously expressed human apelin receptor (pD₂ values range from 9.5 to 8.6). The apelin receptor may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function [403]. A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* [1600], however, this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant apelin receptor [748]. The apelin receptor antagonist, MM54, was reported to suppress tumour growth and increase survival in an intracranial xenograft mouse model of glioblastoma [1050].

Further reading on Apelin receptor

- Chapman FA *et al.* (2023) Targeting the apelin system for the treatment of cardiovascular diseases. *Cardiovasc Res* **119**: 2683-2696 [PMID:37956047]
- de Oliveira AA *et al.* (2022) Apelin pathway in cardiovascular, kidney, and metabolic diseases: Therapeutic role of apelin analogs and apelin receptor agonists. *Peptides* **147**: 170697 [PMID:34801627]
- Huang Z *et al.* (2025) Effects and mechanisms of Apelin in treating central nervous system diseases. *Neuroscience* **566**: 177-189 [PMID:39681256]
- Marsault E *et al.* (2019) The apelinergic system: a perspective on challenges and opportunities in cardiovascular and metabolic disorders. *Ann N Y Acad Sci* **1455**: 12-33 [PMID:31236974]
- Naldi L *et al.* (2025) Apelin/APJ: Another Player in the Cancer Biology Network. *Int J Mol Sci* **26**: [PMID:40243599]
- Wagenaar GTM *et al.* (2025) Advances in the therapeutic potentials of ligands of the apelin receptor APJ. *Eur J Pharmacol* **991**: 177302 [PMID:39870231]
- Wen R *et al.* (2023) Beneficial effects of Apelin-13 on metabolic diseases and exercise. *Front Endocrinol (Lausanne)* **14**: 1285788 [PMID:38089606]

Bile acid receptor

G protein-coupled receptors → Bile acid receptor

Overview: The bile acid receptor (GPBA) responds to bile acids produced during the liver metabolism of **cholesterol**. Selective agonists are promising drugs for the treatment of metabolic disorders, such as type II diabetes, obesity and atherosclerosis.

Nomenclature	GPBA receptor
HGNC, UniProt	GPBAR1, Q8TDU6
Potency order of endogenous ligands	lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid [1361, 1830]
Selective agonists	S-EMCA [2199] – Mouse, betulinic acid [884], oleanolic acid [2483]

Comments: The triterpenoid natural product **betulinic acid** has also been reported to inhibit inflammatory signalling through the NFκB pathway [2761]. Disruption of GPBA expression is reported to protect from cholesterol gallstone formation [2933]. A new series of 5-phenoxy-1,3-dimethyl-1H-pyrazole-4-carboxamides have been reported as highly potent agonists [1727].

Further reading on Bile acid receptor

- Duboc H *et al.* (2014) The bile acid TGR5 membrane receptor: from basic research to clinical application. *Dig Liver Dis* **46**: 302-12 [PMID:24411485]
- Lefebvre P *et al.* (2009) Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev* **89**: 147-91 [PMID:19126757]
- Lieu T *et al.* (2014) GPBA: a GPCR for bile acids and an emerging therapeutic target for disorders of digestion and sensation. *Br J Pharmacol* **171**: 1156-66 [PMID:24111923]
- van Nierop FS *et al.* (2017) Clinical relevance of the bile acid receptor TGR5 in metabolism. *Lancet Diabetes Endocrinol* **5**: 224-233 [PMID:27639537]

Bombesin receptors

G protein-coupled receptors → Bombesin receptors

Overview: Mammalian bombesin (Bn) receptors comprise 3 subtypes: BB₁, BB₂, BB₃ (**nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors**, [44, 1280]). BB₁ and BB₂ are activated by the endogenous ligands **neuromedin B (NMB, P08949)** (NMB), **gastrin-releasing peptide (GRP, P07492)** (GRP), and **GRP-(18-27) (GRP, P07492)**. Bombesin is a tetra-decapeptide, originally derived from amphibians and structurally closely related to GRP. The three Bn receptor subtypes couple primarily to the G_{q/11} and G_{12/13} family of G proteins [1280]. Each of these receptors is widely distributed in the CNS and peripheral tissues [48, 936, 1279, 1280, 1334, 1955, 2338, 2477, 3231, 3251]. Activation of BB₁ and BB₂ receptors causes a

wide range of physiological/pathophysiological actions, including the stimulation of normal and neoplastic tissue growth, smooth-muscle contraction, respiration, gastrointestinal motility, feeding behavior, secretion and many central nervous system effects including regulation of circadian rhythm, body temperature control, sighing, behavioral disorders and mediation of pruritus [43, 458, 564, 1280, 1955, 1964, 1966, 1966, 2338, 3251]. BB₃ is an

orphan receptor, although some propose it is constitutively active [2786]. BB₃ receptor knockout studies show it has important roles in glucose and insulin regulation, metabolic homeostasis, feeding, regulation of body temperature, obesity, diabetes mellitus and growth of normal/neoplastic tissues [43, 936, 1650, 1962, 1962, 2114]. Bn receptors are one of the most frequently overexpressed receptors in cancers and are receiving increased attention

for their roles in tumor growth, as well as for tumour imaging and for receptor-targeted cytotoxicity especially for advanced prostate and breast cancer [164, 1530, 1787, 1964, 3226, 3276]. Bn receptors are also receiving attention because they are one of the primary neurotransmitters for pruritus [458, 1395, 2206].

Nomenclature	BB ₁ receptor	BB ₂ receptor	BB ₃ receptor
HGNC, UniProt	<i>NMBR</i> , P28336	<i>GRPR</i> , P30550	<i>BRS3</i> , P32247
Endogenous agonist rank potency	neuromedin B (<i>NMB</i> , P08949) >> gastrin-releasing peptide (<i>GRP</i> , P07492)	gastrin-releasing peptide (<i>GRP</i> , P07492) > neuromedin C, gastrin releasing peptide(14-27) (human)	–
Endogenous agonists	neuromedin B (<i>NMB</i> , P08949) [1280, 2338, 2881], gastrin releasing peptide(14-27) (human) [2881]	neuromedin C [2881], gastrin releasing peptide(14-27) (human) [2881], gastrin-releasing peptide (<i>GRP</i> , P07492) [196, 2448, 2881]	–
Selective agonists	–	[D-Tyr ⁶ ,β-Ala ¹¹ ,N-Me-Ala ¹³ ,Nle ¹⁴]bombesin-(6-14) [1162]	compound 9g [1839, 2336, 2339], MK-7725 [481], MK-5046 [1963, 2549], dimethyl shikonin oxime 5a [3107], [D-Tyr ⁶ ,Apa-4Cl ¹¹ ,Phe ¹³ ,Nle ¹⁴]bombesin-(6-14) [1809], compound 17c [1838], bag-1 [989], compound 22e [1086], oridonin [3270]
Antagonists	D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal-NH ₂ (pIC ₅₀ 6.2–6.6) [935]	–	–
Selective antagonists	PD 176252 (pIC ₅₀ 9.3–9.8) [935], PD 168368 (pIC ₅₀ 9.3–9.6) [935], dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH ₂	[D-Phe ⁶ , Leu ¹³ , Cpa ¹⁴ ,ψ13-14]bombesin-(6-14) (pK _i 9.8) [935], JMV641 (pIC ₅₀ 9.3) [2842] – Mouse, [(3-Ph-Pr ⁶), His ⁷ ,D-Ala ¹¹ ,D-Pro ¹³ ,ψ13-14],Phe ¹⁴]bombesin-(6-14) (pIC ₅₀ 9.2) [935, 1594], JMV594 (pIC ₅₀ 8.9) [1722, 2842] – Mouse, [D-Tpi ⁶ , Leu ¹³ ψ(CH ₂ NH)-Leu ¹⁴]bombesin-(6-14) (pIC ₅₀ 8.9) [935], [D-Phe ⁶ , Stat ¹³ , Leu ¹⁴]Bn(6-14) (pIC ₅₀ 8.1) [1807]	bantag-1 (pIC ₅₀ 8.6–8.7) [989, 1963, 2337], licoisoflavone A (pIC ₅₀ 6.2) [1737], ML-18 (pIC ₅₀ 5.3) [1954]
Labelled ligands	[¹²⁵ I]BH-NMB (human, mouse, rat) (Agonist), [¹²⁵ I][Tyr ⁴]bombesin (Agonist)	[¹²⁵ I][D-Tyr ⁶]bombesin-(6-13)-methyl ester (Selective Antagonist) (pK _d 9.3) [1808] – Mouse, BAY86-7548 (Antagonist) (pIC ₅₀ 8.6) [1325, 2881], [¹²⁵ I][Tyr ⁴]bombesin (Agonist) [196], BAY86-7548 (Selective Antagonist) (pIC ₅₀ 8.1) [1530, 1806, 1807], [¹²⁵ I]GRP (human) (Agonist)	[¹²⁵ I]bantag-1 (Selective Antagonist) (pK _i 9.6) [2337], [³ H]bag-2 (Agonist) [989] – Mouse, [¹²⁵ I][D-Tyr ⁶ ,β-Ala ¹¹ ,Phe ¹³ ,Nle ¹⁴]bombesin-(6-14) (Agonist) [1810, 1963]

Comments: All three human subtypes may be activated by [D-Phe⁶,β-Ala¹¹,Phe¹³,Nle¹⁴]bombesin-(6-14) [1810, 2338]. A recent study [2336] shows that MK-5046 functions as an allosteric agonist for hBRS-3 (the first for any BnR). In a recent study the crystal structure of inactive hGRPR (BB₂) was reported, as well as two active state GRPR structures bound to GRP or [D-Phe⁶,β-Ala¹¹,Phe¹³,Nle¹⁴]bombesin-(6-14) [2206]. An additional recent study [1644] reported the cryo-EM structures of BRS3 in complex with the heterotrimeric Gq protein in its active states: one bound to the pan-BnR agonist BA1 and the other bound to the synthetic BRS3-specific agonist MK-5046.

Further reading on Bombesin receptors

- Aloj L *et al.* (2024) Radiolabeled peptides and their expanding role in clinical imaging and targeted cancer therapy. *J Pept Sci* **30**: e3607 [PMID:38710638]
- Chen XJ *et al.* (2020) Central circuit mechanisms of itch. *Nat Commun* **11**: 3052 [PMID:32546780]
- D'Onofrio A *et al.* (2023) GRPR-targeting radiotheranostics for breast cancer management. *Front Med (Lausanne)* **10**: 1250799 [PMID:38020178]
- Gajjar S *et al.* (2017) Neuromedin: An insight into its types, receptors and therapeutic opportunities. *Pharmacol Rep* **69**: 438-447 [PMID:28315588]
- Mohseninia N *et al.* (2025) Diagnostic Value of Gastrin-Releasing Peptide Receptor-Targeted PET Imaging in Oncology: A Systematic Review. *Semin Nucl Med* **55**: 776-788 [PMID:39855939]
- Morgat C *et al.* (2025) A Vision for Gastrin-Releasing Peptide Receptor Targeting for Imaging and Therapy: Perspective from Academia and Industry. *J Nucl Med* **66**: 1160-1167 [PMID:40341094]
- Sun HL *et al.* (2023) Novel insight on GRP/GRPR axis in diseases. *Biomed Pharmacother* **161**: 114497 [PMID:36933382]

Bradykinin receptors

G protein-coupled receptors → Bradykinin receptors

Overview: Bradykinin (or kinin) receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Bradykinin (kinin) Receptors** [1608]) are activated by the endogenous peptides bradykinin (*KNG1*, P01042) (BK), [des-Arg⁹]bradykinin (*KNG1*, P01042), Lys-BK (kallidin (*KNG1*, P01042)), [des-Arg¹⁰]

kallidin (*KNG1*, P01042), [Phospho-Ser⁶]-Bradykinin, T-kinin (*KNG1*, P01042) (Ile-Ser-BK), [Hyp³]bradykinin (*KNG1*, P01042) and Lys-[Hyp³]-bradykinin (*KNG1*, P01042). Variation in pharmacology and activity of B₁ and B₂ receptor antagonists at species orthologs has been documented. Icatibant (Hoe140, Firazir

is approved in North America and Europe for the treatment of acute attacks of hereditary angioedema. Inhibition of bradykinin with icatibant in COVID-19 infection is under clinical evaluation, with trial NCT05407597.

Nomenclature	B ₁ receptor	B ₂ receptor
HGNC, UniProt	<i>BDKRB1</i> , P46663	<i>BDKRB2</i> , P30411
Potency order of endogenous ligands	[des-Arg ¹⁰]kallidin (<i>KNG1</i> , P01042) > [des-Arg ⁹]bradykinin (<i>KNG1</i> , P01042) = kallidin (<i>KNG1</i> , P01042) > bradykinin (<i>KNG1</i> , P01042)	kallidin (<i>KNG1</i> , P01042) > bradykinin (<i>KNG1</i> , P01042) ≫ [des-Arg ⁹]bradykinin (<i>KNG1</i> , P01042), [des-Arg ¹⁰]kallidin (<i>KNG1</i> , P01042)
Endogenous agonists	[des-Arg ¹⁰]kallidin (<i>KNG1</i> , P01042) [105, 158, 925, 1303]	bradykinin (<i>KNG1</i> , P01042) [75, 1114]
Selective agonists	NG29 [2493], [Sar,D-Phe ⁸ ,des-Arg ⁹]bradykinin [97, 1303]	NG291 [185], labradimil [2494], [Hyp ³ ,Tyr(Me) ⁸]BK, [Phe ⁸ ,ψ(CH ₂ -NH)Arg ⁹]BK
Selective antagonists	B-9958 (pK _i 9.2–10.3) [894, 2365], [Leu ⁹ ,des-Arg ¹⁰]kallidin (pK _i 9.1–9.3) [105, 158], SSR240612 (pK _i 9.1–9.2) [952], R-954 (pA ₂ 8.6) [926], R-715 (pA ₂ 8.5) [924]	icatibant (pK _i 10.2) [55], deucricitabant (pK _i 9.3) [1631, 1632], FR173657 (pA ₂ 8.2) [2401], anatiabant (pK _i 8.2) [2297]
Labelled ligands	[¹²⁵ I]Hpp-desArg ¹⁰ HOE140 (Antagonist) (pK _d 10), [¹²⁵ I]Hpp-desArg ¹⁰ HOE140 (Antagonist) (pK _d 10) [606, 2137], [³ H]Lys-[des-Arg ⁹]BK (Agonist), [³ H]Lys-[Leu ⁸][des-Arg ⁹]BK (Antagonist)	[³ H]BK (human, mouse, rat) (Agonist) [3081] – Mouse, [³ H]NPC17731 (Antagonist) (pK _d 9.1–9.4) [3236, 3237], [¹²⁵ I]HPP-HOE140 (Antagonist) [606, 2137], [¹²⁵ I][Tyr ⁸]bradykinin (Agonist) [1730]

Further reading on Bradykinin receptors

- Blaes N *et al.* (2013) Targeting the 'Janus face' of the B2-bradykinin receptor. *Expert Opin Ther Targets* **17**: 1145-66 [PMID:23957374]
- Brusco I *et al.* (2023) Kinins and their B₁ and B₂ receptors as potential therapeutic targets for pain relief. *Life Sci* **314**: 121302 [PMID:36535404]
- Couture R *et al.* (2025) *In Bradykinin From Vasodilation to Neuroinflammation* Edited by Couture R: Academic Press/ELSEVIER: 528 [ISBN: 9780443289071]
- Couture R *et al.* (2014) Kinin receptors in vascular biology and pathology. *Curr Vasc Pharmacol* **12**: 223-48 [PMID:24568157]
- Marceau F *et al.* (2020) Bradykinin receptors: Agonists, antagonists, expression, signaling, and adaptation to sustained stimulation. *Int Immunopharmacol* **82**: 106305 [PMID:32106060]
- Paquet JL *et al.* (1999) Pharmacological characterization of the bradykinin B2 receptor: inter-species variability and dissociation between binding and functional responses. *Br J Pharmacol* **126**: 1083-90 [PMID:10204994]
- Thornton E *et al.* (2010) Kinin receptor antagonists as potential neuroprotective agents in central nervous system injury. *Molecules* **15**: 6598-618 [PMID:20877247]

Searchable database: <https://www.guidetopharmacology.org/>Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

Bradykinin receptors S49

Calcitonin receptors

G protein-coupled receptors → Calcitonin receptors

Overview: This receptor family comprises a group of receptors for the calcitonin/CGRP family of peptides. The calcitonin (CT), amylin (AMY), calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on CGRP, AM, AMY, and CT receptors** [1074, 1076, 2278]) are generated by the genes *CALCR* (which codes for the calcitonin receptor, CTR) and *CALCRL* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying proteins), which are single TM domain proteins of *ca.* 150 amino

acids, identified as a family of three members; RAMP1, RAMP2 and RAMP3. There are splice variants of the CTR; these in turn produce variants of amylin receptors [2278], some of which can be potently activated by CGRP. The endogenous agonists are the peptides calcitonin (*CALCA*, P01258), α -CGRP (*CALCA*, P06881) (formerly known as CGRP-I), β -CGRP (*CALCB*, P10092) (formerly known as CGRP-II), amylin (*IAPP*, P10997) (occasionally called islet-amyloid polypeptide, diabetes-associated polypeptide), adrenomedullin (*ADM*, P35318) and adrenomedullin 2/intermedin (*ADM2*, Q7Z4H4). There are species differences in peptide sequences, particularly for the calcitonins. CTR-stimulating peptide

[Pig] (CRSP) is another member of the family with selectivity for the CTR but it is not expressed in humans [1353]. CLR (calcitonin receptor-like receptor) by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, adrenomedullin and adrenomedullin 2/intermedin. There are several approved drugs that target this receptor family, such as pramlintide, erenumab, and the “gepant” class of CGRP receptor antagonists. There are also species differences in agonist pharmacology; for example, CGRP displays potent activity at multiple rat and mouse receptors [124, 861]. The summary table only reflects human receptor pharmacology.

Complexes

Nomenclature	AMY ₁ receptor	AMY ₂ receptor	AMY ₃ receptor	CGRP receptor	AM ₁ receptor	AM ₂ receptor
Subunits	CT receptor, RAMP1 (Accessory protein)	CT receptor, RAMP2 (Accessory protein)	CT receptor, RAMP3 (Accessory protein)	calcitonin receptor-like receptor, RAMP1 (Accessory protein)	calcitonin receptor-like receptor, RAMP2 (Accessory protein)	calcitonin receptor-like receptor, RAMP3 (Accessory protein)
Potency order of endogenous ligands	amylin (<i>IAPP</i> , P10997) \geq α -CGRP (<i>CALCA</i> , P06881), β -CGRP (<i>CALCB</i> , P10092) > adrenomedullin 2/intermedin (<i>ADM2</i> , Q7Z4H4) \geq calcitonin (<i>CALCA</i> , P01258) > adrenomedullin (<i>ADM</i> , P35318)	amylin (<i>IAPP</i> , P10997) \geq calcitonin (<i>CALCA</i> , P01258) = α -CGRP (<i>CALCA</i> , P06881)	amylin (<i>IAPP</i> , P10997) > α -CGRP (<i>CALCA</i> , P06881), β -CGRP (<i>CALCB</i> , P10092) \geq adrenomedullin 2/intermedin (<i>ADM2</i> , Q7Z4H4) \geq calcitonin (<i>CALCA</i> , P01258) > adrenomedullin (<i>ADM</i> , P35318)	α -CGRP (<i>CALCA</i> , P06881), β -CGRP (<i>CALCB</i> , P10092) > adrenomedullin (<i>ADM</i> , P35318) \geq adrenomedullin 2/intermedin (<i>ADM2</i> , Q7Z4H4) > amylin (<i>IAPP</i> , P10997)	adrenomedullin (<i>ADM</i> , P35318) > adrenomedullin 2/intermedin (<i>ADM2</i> , Q7Z4H4) > α -CGRP (<i>CALCA</i> , P06881), β -CGRP (<i>CALCB</i> , P10092), amylin (<i>IAPP</i> , P10997)	adrenomedullin (<i>ADM</i> , P35318) \geq adrenomedullin 2/intermedin (<i>ADM2</i> , Q7Z4H4) \geq α -CGRP (<i>CALCA</i> , P06881), β -CGRP (<i>CALCB</i> , P10092) > amylin (<i>IAPP</i> , P10997)
Endogenous agonists	α -CGRP (<i>CALCA</i> , P06881) [1072, 1533, 1534, 1637, 2974], amylin (<i>IAPP</i> , P10997) [915], β -CGRP (<i>CALCB</i> , P10092)	amylin (<i>IAPP</i> , P10997) [915]	amylin (<i>IAPP</i> , P10997) [915]	β -CGRP (<i>CALCB</i> , P10092) [27, 1868], α -CGRP (<i>CALCA</i> , P06881) [27, 1868]	adrenomedullin (<i>ADM</i> , P35318) [27, 1868], adrenomedullin 2/intermedin (<i>ADM2</i> , Q7Z4H4) [1074]	adrenomedullin 2/intermedin (<i>ADM2</i> , Q7Z4H4) [1074], adrenomedullin (<i>ADM</i> , P35318) [27, 806]
Agonists	pramlintide [915], calcitonin (salmon)	–	pramlintide [915], calcitonin (salmon)	–	–	–

Antagonists	rimegepant (pK _B 8.1) [2158], AC187 (pK _B 8) [1072], calcitonin-(8-32) (salmon) (pK _B 7.8) [1072], olcegepant (pK _B 7.5) [1073]	–	calcitonin-(8-32) (salmon) (pK _B 7.9) [1072], AC187 (pK _B 7.7) [1072]	olcegepant (pK _i 10.7–11) [668, 1073, 1075, 1314, 1797], ubrogepant (pK _B 10.8) [1956], rimegepant (pK _B 9.6) [2158], erenumab (pK _B 8.3–9.1) [860], telcagepant (pK _i 9.1) [2466]	adrenomedullin-(22-52) (human) (pK _i 7–7.8) [1075]	adrenomedullin-(22-52) (human)
Labelled ligands	[¹²⁵ I]αCGRP (Agonist), [¹²⁵ I]amylin (Agonist)	[¹²⁵ I]amylin (Agonist)	[¹²⁵ I]amylin (Agonist)	[¹²⁵ I]αCGRP (Agonist)	[¹²⁵ I]adrenomedullin (Agonist)	[¹²⁵ I]adrenomedullin (Agonist)

Subunits

Nomenclature	CT receptor	calcitonin receptor-like receptor
HGNC, UniProt	CALCR, P30988	CALCRL, Q16602
Potency order of endogenous ligands	calcitonin (CALCA, P01258) ≥ amylin (IAPP, P10997), α-CGRP (CALCA, P06881), β-CGRP (CALCB, P10092) > adrenomedullin (ADM, P35318), adrenomedullin 2/intermedin (ADM2, Q7Z4H4)	–
Endogenous agonists	calcitonin (CALCA, P01258) [41, 84, 1072, 1534, 1637, 1991]	–
Agonists	calcitonin (salmon) [41, 521, 945, 2236], pramlintide [915]	–
Antagonists	calcitonin-(8-32) (salmon) (pK _B 8.2) [1072], AC187 (pK _B 7.2) [1072]	–
Labelled ligands	[¹²⁵ I]calcitonin (Agonist)	–

Comments: It is important to note that a complication with the interpretation of pharmacological studies with AMY receptors in transfected cells is that most of this work has likely used a mixed population of receptors, encompassing RAMP-coupled CTR as well as CTR alone. This means that although in binding assays human calcitonin (CALCA, P01258) has low affinity for ¹²⁵I-amylin binding sites, cells transfected with CTR and RAMPs can display potent calcitonin functional responses. Transfection of human CTR with any RAMP can generate receptors with a high affinity for both salmon calcitonin and amylin and varying affinity for different antagonists [500, 1072, 1073]. The major human CTR splice variant (hCT_(a), which does not contain an insert) with RAMP1 (*i.e.* the AMY_{1(a)} receptor) has a high affinity for CGRP [2974], unlike hCT_(a)-RAMP3 (*i.e.* AMY_{3(a)} receptor) [500, 1072].

However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent [1965, 2305, 2833]. Emerging data suggests that AMY₁ could be a second CGRP receptor [2443]. The ligands described have limited selectivity. In addition to its high affinity at both the AM₁ and AM₂ receptors, adrenomedullin also has appreciable affinity for the CGRP receptor. CGRP can show significant cross-reactivity at AMY receptors and AM₂ receptors. Adrenomedullin 2/intermedin also has high affinity for the AM₂ receptor [1074]. CGRP-(8-37) acts as an antagonist of CGRP (pK_i ~8) and inhibits some adrenomedullin and amylin responses (pK_i ~6–7). It is weak at CT receptors. Adrenomedullin-(22-52) (human) has some selectivity towards AM receptors, but with modest potency (pK_i ~7), limiting its use [1075]. Olcegepant (also known as BIBN4096BS, pK_i ~10.5) and telcagepant (also known

as MK0974, pK_i ~9) are examples of the “gepant” class of small molecule antagonists. These are selective for the CGRP receptor over the AM receptors but depending on the compound, have variable affinity for the AMY₁ receptor [862]. These antagonists tend to have higher affinity at primate receptors, compared to rodent receptors [1957, 2974].

G_s is a prominent route for effector coupling for CLR and CTR but other pathways (*e.g.* Ca²⁺, ERK, Akt), and G proteins can be activated [2443]. There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein; O75575) is important for the coupling of CLR to adenylyl cyclase [742].

[¹²⁵I]-Salmon calcitonin is the most common radioligand for CTR but it has high affinity for AMY receptors and is also poorly reversible.

Further reading on Calcitonin receptors

Hay DL *et al.* (2015) Amylin: Pharmacology, Physiology, and Clinical Potential. *Pharmacol Rev* **67**: 564–600 [PMID:26071095] Hay DL *et al.* (2018) Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25. *Br J Pharmacol* **175**: 3–17 [PMID:29059473]

Kotliar IB *et al.* (2023) Elucidating the Interactome of G Protein-Coupled Receptors and Receptor Activity-Modifying Proteins. *Pharmacol Rev* **75**: 1-34 [PMID:36757898]
 Russell FA *et al.* (2014) Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev* **94**: 1099-142 [PMID:25287861]
 Russo AF *et al.* (2023) CGRP physiology, pharmacology, and therapeutic targets: migraine and beyond. *Physiol Rev* **103**: 1565-1644 [PMID:36454715]

Schönauer R *et al.* (2017) Adrenomedullin - new perspectives of a potent peptide hormone. *J Pept Sci* **23**: 472-485 [PMID:28150464]
 Walker CS *et al.* (2025) Amylin: emergent therapeutic opportunities in overweight, obesity and diabetes mellitus. *Nat Rev Endocrinol* **21**: 482-494 [PMID:40360789]

Calcium-sensing receptor

G protein-coupled receptors → Calcium-sensing receptor

Overview: The calcium-sensing receptor (CaS, **provisional nomenclature as recommended by NC-IUPHAR [789] and subsequently updated [1589]**) responds to multiple endogenous ligands, including extracellular calcium and other divalent/trivalent cations, polyamines and polycationic peptides, L-amino acids (particularly L-Trp and L-Phe), glutathione and various peptide analogues, ionic strength and extracellular pH (reviewed in

[1591]). While divalent/trivalent cations, polyamines and polycations are CaS receptor agonists [322, 2318], L-amino acids, glutamyl peptides, ionic strength and pH are allosteric modulators of agonist function [531, 789, 1138, 2316, 2317]. Indeed, L-amino acids have been identified as "co-agonists", with both concomitant calcium and L-amino acid binding required for full receptor activation [886, 3220]. The sensitivity of the CaS receptor to

primary agonists is increased by elevated extracellular pH [371] or decreased extracellular ionic strength [2317] while sensitivity is decreased by pathophysiological phosphate concentrations [408]. This receptor bears no sequence or structural relation to the plant calcium receptor, also called CaS.

Nomenclature	CaS receptor
HGNC, UniProt	CASR, P41180
Amino-acid rank order of potency	L-phenylalanine, L-tryptophan, L-histidine > L-alanine > L-serine, L-proline, L-glutamic acid > L-aspartic acid (not L-lysine, L-arginine, L-leucine and L-isoleucine) [531]
Cation rank order of potency	Gd ³⁺ > Ca ²⁺ > Mg ²⁺ [322]
Glutamyl peptide rank order of potency	S-methylglutathione ≈ γGlu-Val-Gly > glutathione > γGlu-Cys [311, 2116, 3001]
Polyamine rank order of potency	spermine > spermidine > putrescine [2318]
Allosteric modulators (Positive)	upacalcet (pIC ₅₀ 8.1) [2484], evocalcet (pEC ₅₀ 7) [1925], nanobody Nb4 (pEC ₅₀ 6.7) [682], cinacalcet (pK _B 5.9–6.6) [534, 590, 1588, 1592], tecalcet (pK _B 6.2–6.6) [534, 590], AC265347 (pK _B 6.3–6.4) [534, 1588], calindol (pK _B 6.3) [534], etelcalcetide (pEC ₅₀ 4.6) [2978]
Allosteric modulators (Negative)	ATF936 (pIC ₅₀ 8.9) [3064], encalret (pIC ₅₀ 7.9) [2597], SB-423562 (pIC ₅₀ 7.1) [1524], ronacalret (pIC ₅₀ 6.5–6.8) [135], NPS 2143 (pK _B 6.2–6.7) [590, 1588, 1592], nanobody NB32 (pIC ₅₀ 6.7) [563], calhex 231 (pIC ₅₀ 6.4) [2231]

Comments: The CaS receptor has a number of physiological functions, but it is best known for its central role in parathyroid and renal regulation of extracellular calcium homeostasis [1038]. This is seen most clearly in patients with loss-of-function CaS receptor mutations who develop familial hypocalcaemic hypercalcaemia (heterozygous mutations) or neonatal severe hyperparathyroidism (heterozygous, compound heterozygous or homozygous mutations) [1038] and in *Casr* null mice [426, 1138], which exhibit similar increases in PTH secretion and blood calcium levels. Gain-of-function CaS mutations are associated with autosomal dominant hypocalcaemia and Bartter syndrome type V [1038].

The CaS receptor primarily couples to G_{q/11}, G_{12/13} and G_{i/o} [590, 898, 1188, 2823], but in some cell types can couple to G_s [1799]. The CaS receptor acts as a homodimer [849, 3220], but which can only couple one G protein at a time [1081, 3278]. However, the CaS receptor can also form heteromers with Class C GABA_B [427, 463] and mGlu1/5 receptors [843], which may introduce further complexity in its signalling capabilities. Multiple other small molecule chemotypes are positive and negative allosteric modulators of the CaS receptor [1392, 2052]. Further, etelcalcetide is a peptide positive allosteric modulator of the receptor, that also displays weak agonist activity [2978]. Agonists

and positive allosteric modulators of the CaS receptor are termed Type I and II calcimimetics, respectively, and can suppress parathyroid hormone (PTH (PTH, P01270)) secretion [2054]. Computational docking using large library screens has recently identified additional potent CaS receptor positive allosteric modulators [1712]. Negative allosteric modulators are called calcilytics and can act to increase PTH (PTH, P01270) secretion [2053]. Recently, nanobodies have been developed as both positive and negative allosteric modulators [563, 682]. Where functional pK_B values are provided for allosteric modulators, this refers to ligand affinity determined in an assay that

measures a functional readout of receptor activity (*i.e.* a receptor signalling assay), as opposed to affinity determined in a radioligand binding assay. The functional pK_B may differ depending on the signalling pathway studied. Consult the 'More detailed page' for the assay description, as well as other functional readouts.

Further reading on Calcium-sensing receptor

- Brown EM. (2013) Role of the calcium-sensing receptor in extracellular calcium homeostasis. *Best Pract Res Clin Endocrinol Metab* **27**: 333-43 [PMID:23856263]
- Centeno PP *et al.* (2023) Inhibition of the calcium-sensing receptor by extracellular phosphate ions and by intracellular phosphorylation. *Front Physiol* **14**: 1154374 [PMID:37064904]
- Conigrave AD *et al.* (2013) Calcium-sensing receptor (CaSR): pharmacological properties and signaling pathways. *Best Pract Res Clin Endocrinol Metab* **27**: 315-31 [PMID:23856262]
- Hannan FM *et al.* (2018) The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. *Nat Rev Endocrinol* **15**: 33-51 [PMID:30443043]
- Leach K *et al.* (2020) International Union of Basic and Clinical Pharmacology. CVIII. Calcium-Sensing Receptor Nomenclature, Pharmacology, and Function. *Pharmacol Rev* **72**: 558-604 [PMID:32467152]
- Nemeth EF *et al.* (2018) Discovery and Development of Calcimimetic and Calcilytic Compounds. *Prog Med Chem* **57**: 1-86 [PMID:29680147]
- Newey PJ *et al.* (2022) Genetics of monogenic disorders of calcium and bone metabolism. *Clin Endocrinol (Oxf)* **97**: 483-501 [PMID:34935164]

Cannabinoid receptors

G protein-coupled receptors → [Cannabinoid receptors](#)

Overview: Cannabinoid receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Cannabinoid Receptors** [2223]) are activated by endogenous ligands that include N-arachidonylethanolamine (anandamide), N-homo- γ -linolenylethanolamine, N-docosatetra-7,10,13,16-enylethanolamine and 2-arachidonoylglycerol. Potency determinations of endogenous agonists at these receptors are

complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion [46]. There are currently three licenced cannabinoid medicines each of which contains a compound that can activate CB₁ and CB₂ receptors [2221]. Two of these medicines were developed to suppress nausea and vomiting produced by chemotherapy. These are nabilone (Cesamet®), a synthetic CB₁/CB₂ receptor agonist,

and synthetic Δ^9 -tetrahydrocannabinol (Marinol®; dronabinol), which can also be used as an appetite stimulant. The third medicine, Sativex®, contains mainly Δ^9 -tetrahydrocannabinol and cannabidiol, both extracted from cannabis, and is used to treat multiple sclerosis and cancer pain.

Nomenclature	CB ₁ receptor	CB ₂ receptor
HGNC, UniProt	CNRI, P21554	CNR2, P34972
Agonists	HU-210 [759, 2604], CP55940 [759, 2422, 2604], WIN55212-2 [759, 2600, 2604], Δ^9 -tetrahydrocannabinol (Partial agonist) [759, 2604], cannabinol (Partial agonist) [759, 2604]	HU-210 [759, 2379, 2604], WIN55212-2 [759, 2600, 2604], CP55940 [759, 2422, 2604], Δ^9 -tetrahydrocannabinol (Partial agonist) [165, 759, 2379, 2604]
Selective agonists	arachidonyl-2-chloroethylamide [1126] – Rat, arachidonylcyclopropylamide [1126] – Rat, O-1812 [637] – Rat, R-(+)-methanandamide [1386] – Rat	JWH-133 [1199, 2222], L-759,633 [859, 2422], AM1241 [3172], L-759,656 [859, 2422], onternabez [1046], GW405833 (Partial agonist) [1818]
Selective antagonists	JD5037 (pK _i 9.5) [2778], rimonabant (pK _i 7.9–8.7) [758, 759, 2391, 2437, 2604], AM6545 (pK _i 8.5) [283], AM251 (pK _i 8.1) [1549] – Rat, AM281 (pK _i 7.9) [1548] – Rat, LY320135 (pK _i 6.9) [758]	SR144528 (pK _i 8.3–9.2) [2392, 2422], AM-630 (pK _i 7.5) [2422]
Allosteric modulators (Positive)	ZCZ011 (pEC ₅₀ 6.3) [1216] – Mouse, GAT211 [1563]	pepcan-12 (pK _i ~7.3) [2234], compound C2 [834]
Allosteric modulators (Negative)	GAT100 (pEC ₅₀ 7.7) [1519], cannabidiol [1562]	–
Labelled ligands	[³ H]rimonabant (Antagonist) (pK _d 8.9–10) [297, 1133, 1318, 2230, 2393, 2615, 2816] – Rat	–

Comments: Both CB₁ and CB₂ receptors may be labelled with [³H]CP55940 (0.5 nM; [2604]) and [³H]WIN55212-2 (2-2.4 nM; [2636, 2666]). Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs [2102, 3279]. There is evidence for an allosteric site on the CB₁ receptor [2282]. All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems [2223]. For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have been identified [2223]. Moreover, GPR18, GPR55 and GPR119, although showing little structural similarity to CB₁ and CB₂ receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands [2223].

Further reading on Cannabinoid receptors

Howlett AC *et al.* (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* **54**: 161-202 [PMID:12037135]
 Pertwee RG. (2010) Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. *Curr Med Chem* **17**: 1360-81 [PMID:20166927]
 Pertwee RG *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB₁ and CB₂. *Pharmacol Rev* **62**: 588-631 [PMID:21079038]

Chemerin receptors

G protein-coupled receptors → Chemerin receptors

Overview: Nomenclature for the chemerin receptors is presented as **recommended by NC-IUPHAR** [586, 1375]). The chemoattractant protein and adipokine, chemerin (*RARRES2*, Q99969), has been shown to be the endogenous ligand for both chemerin family receptors. Chemerin₁ was the founding family member, and when *GPR1* was de-orphanised it was re-named Chemerin₂ [1375]. Chemerin₁ is also activated by the lipid-derived, anti-inflammatory ligand *resolvin E1* (RvE1), which is formed *via* the sequential metabolism of *EPA* by aspirin-modified cyclooxygenase and lipoxygenase [82, 83]. In addition, two GPCRs for *resolvin D1* (RvD1) have been identified: FPR2 and *GPR32*, an orphan receptor [1500].

Nomenclature	chemerin receptor 1	chemerin receptor 2
Common abbreviation	Chemerin ₁	Chemerin ₂
HGNC, UniProt	<i>CMKLR1</i> , Q99788	<i>CMKLR2</i> , P46091
Potency order of endogenous ligands	resolvin E1 > chemerin C-terminal peptide > 18R-HEPE > EPA [82]	–
Endogenous agonists	–	chemerin (<i>RARRES2</i> , Q99969) [147]
Selective agonists	resolvin E1	–
Labelled ligands	[³ H]resolvin E1 (Agonist) [82, 83]	–
Comments	–	Reported to act as a co-receptor for HIV [2591]. See review [586] for discussion of pairing with chemerin.

Comments: CCX832 (structure not disclosed) is a selective antagonist, pK_i=9.2 [1377].

Further reading on Chemerin receptors

Kennedy AJ *et al.* (2018) International Union of Basic and Clinical Pharmacology CIII: Chemerin Receptors CMKLR1 (Chemerin1) and GPR1 (Chemerin2) Nomenclature, Pharmacology, and Function. *Pharmacol Rev* **70**: 174-196 [PMID:29279348]
 Shin WJ *et al.* (2018) Mechanisms and Functions of Chemerin in Cancer: Potential Roles in Therapeutic Intervention. *Front Immunol* **9**: 2772 [PMID:30555465]

Chemokine receptors

G protein-coupled receptors → Chemokine receptors

Overview: Chemokine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Chemokine Receptors** [116, 465, 2004, 2005]) comprise a large subfamily of 7TM proteins that bind one or more chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes. Additional hematopoietic and non-hematopoietic roles have been identified for many chemokines in the areas of embryonic development, immune cell proliferation, activation and death, viral infection, and as antibacterials, among others. Chemokine receptors can be divided by function into two main groups: G protein-coupled chemokine receptors, which mediate leukocyte trafficking, and “Atypical chemokine receptors”, which may signal through non-G protein-coupled mechanisms and act as chemokine scavengers to downregulate inflammation or shape

chemokine gradients [116].

Chemokines in turn can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as β -chemokines; $n=28$), CXC (also known as α -chemokines; $n=17$) and CX3C ($n=1$) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines respectively. C chemokines ($n=2$) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high-affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically

highly promiscuous with regard to ligand specificity, and may lack a selective endogenous ligand. G protein-coupled chemokine receptors are named according to the class of chemokines bound, whereas ACKR is the root acronym for atypical chemokine receptors [117, 465]. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and microbial non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, but CCR5 is the only one demonstrated to play an essential role in HIV/AIDS pathogenesis. The tables include both standard chemokine receptor names [3273] and aliases.

Nomenclature	CCR1	CCR2	CCR3
HGNC, UniProt	CCR1, P32246	CCR2, P41597	CCR3, P51677
Endogenous agonists	CCL3 (CCL3, P10147) [485, 524, 1116, 3275], CCL23 (CCL23, P55773) [485], CCL5 (CCL5, P13501) [524, 1116], CCL7 (CCL7, P80098) [485, 1008], CCL15 (CCL15, Q16663) [545], CCL14 (CCL14, Q16627) [485], CCL13 (CCL13, Q99616), CCL8 (CCL8, P80075)	CCL2 (CCL2, P13500) [545, 1754, 1916, 2173, 2883], CCL13 (CCL13, Q99616) [1754, 2883], CCL7 (CCL7, P80098) [545, 1754, 2883], CCL11 (CCL11, P51671) (Partial agonist) [1754, 2173], CCL16 (CCL16, O15467)	CCL13 (CCL13, Q99616) [1979, 2883], CCL24 (CCL24, O00175) [1979, 2173], CCL5 (CCL5, P13501) [580], CCL7 (CCL7, P80098) [580], CCL11 (CCL11, P51671) [693, 1435, 1979, 2455, 2883], CCL26 (CCL26, Q9Y258) [1435, 1979, 2173], CCL15 (CCL15, Q16663) [545], CCL28 (CCL28, Q9NRJ3), CCL8 (CCL8, P80075)
Agonists	–	–	CCL11 [Mouse] [580]
Endogenous antagonists	CCL4 (CCL4, P13236) (pK_i 7.1–7.8) [485, 524]	CCL26 (CCL26, Q9Y258) (pIC_{50} 8.5) [2173]	CXCL10 (CXCL10, P02778), CXCL11 (CXCL11, O14625), CXCL9 (CXCL9, Q07325)
Selective antagonists	BX 471 (pK_i 8.2–9) [1664], compound 2b-1 (pIC_{50} 8.7) [2039], UCB35625 (pIC_{50} 8) [2455], CP-481,715 (pK_d 8) [918]	GSK Compound 34 (pK_i 7.6)	banyu (I) (Inverse agonist) (pK_i 8.5) [2982], SB328437 (pK_i 8.4), BMS compound 87b (pK_i 8.1) [2966]
Labelled ligands	[¹²⁵ I]CCL7 (human) (Agonist) [192], [¹²⁵ I]CCL3 (human) (Agonist) [192, 934, 2482], [¹²⁵ I]CCL5 (human) (Agonist) [2482]	[¹²⁵ I]CCL2 (human) (Agonist), [¹²⁵ I]CCL7 (human) (Agonist)	[¹²⁵ I]CCL11 (human) (Antagonist) (pK_d 8.3) [2982], [¹²⁵ I]CCL5 (human) (Agonist), [¹²⁵ I]CCL7 (human) (Agonist)

Nomenclature	CCR4	CCR5	CCR6	CCR7	CCR8	CCR9	CCR10
HGNC, UniProt	CCR4 , P51679	CCR5 , P51681	CCR6 , P51684	CCR7 , P32248	CCR8 , P51685	CCR9 , P51686	CCR10 , P46092
Endogenous agonists	CCL22 (CCL22 , O00626) [1223], CCL17 (CCL17 , Q92583) [1223]	CCL5 (CCL5 , P13501) [114, 2030, 2434], CCL4 (CCL4 , P13236) [2030, 2434], CCL8 (CCL8 , P80075) [2434], CCL3 (CCL3 , P10147) [2030, 2434, 3275], CCL11 (CCL11 , P51671) [235], CCL2 (CCL2 , P13500) [2030], CCL14 (CCL14 , Q16627) [2030], CCL16 (CCL16 , O15467)	CCL20 (CCL20 , P78556) [26, 113, 2274], beta-defensin 4A (DEFB4ADEFB4B , O15263) [3160]	CCL21 (CCL21 , O00585) [3196], CCL19 (CCL19 , Q99731) [2145, 3195, 3196]	CCL1 (CCL1 , P22362) [572, 1060, 1226], CCL8 (CCL8 , P80075)	CCL25 (CCL25 , O15444)	CCL27 (CCL27 , Q9Y4X3) [1157], CCL28 (CCL28 , Q9NRJ3)
Agonists	vMIP-III	R5-HIV-1 gp120	–	–	vMIP-I [572, 1226]	–	–
Endogenous antagonists	–	CCL7 (CCL7 , P80098) (pK _i 7.5) [2030]	–	–	–	–	–
Antagonists	–	vMIP-II (pIC ₅₀ 8.3) [1441]	–	–	vMIP-II (pIC ₅₀ 8.1) [572]	–	–
Selective antagonists	compound 8ic (pIC ₅₀ 7.7) [3192]	vicriviroc (pK _i 9.1) [2711], E913 (pIC ₅₀ 8.7) [1777], ancriviroc (pK _i 7.8–8.7) [1776, 2155, 2711], aplaviroc (pK _i 8.5) [1776], maraviroc (pIC ₅₀ 8.1) [2030], TAK-779 (pK _i 7.5) [1776], MRK-1 [1523] – Rat	–	–	–	–	–
Selective allosteric modulators	–	–	–	–	–	vercimon (Antagonist) (pIC ₅₀ 8.2) [2979]	–
Antibodies	mogamulizumab (Inhibition) [72, 2602]	leronlimab (Binding) [2136]	–	–	–	–	–
Labelled ligands	[¹²⁵ I] CCL17 (human) (Agonist), [¹²⁵ I] CCL27 (human) (Agonist)	[¹²⁵ I] CCL4 (human) (Agonist) [2030], [¹²⁵ I] CCL3 (human) (Agonist), [¹²⁵ I] CCL5 (human) (Agonist), [¹²⁵ I] CCL8 (human) (Agonist)	[¹²⁵ I] CCL20 (human) (Agonist) [967]	[¹²⁵ I] CCL19 (human) (Agonist), [¹²⁵ I] CCL21 (human) (Agonist) [1278]	[¹²⁵ I] CCL1 (human) (Agonist) [1226, 2416]	[¹²⁵ I] CCL25 (human) (Agonist)	–

Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6	CX ₃ CR1
HGNC, UniProt	CXCR1 , P25024	CXCR2 , P25025	CXCR3 , P49682	CXCR4 , P61073	CXCR5 , P32302	CXCR6 , O00574	CX3CR1 , P49238
Endogenous agonists	CXCL8 (CXCL8 , P10145) [210, 1019, 1603, 3079, 3108], CXCL6 (CXCL6 , P80162) [3115]	CXCL1 (CXCL1 , P09341) [1019, 1603, 3108], CXCL8 (CXCL8 , P10145) [210, 1019, 1603, 3079, 3108], CXCL7 (PPBP , P02775) [24], CXCL3 (CXCL3 , P19876) [24], CXCL2 (CXCL2 , P19875) [24], CXCL5 (CXCL5 , P42830) [24], CXCL6 (CXCL6 , P80162) [3115]	CXCL11 (CXCL11 , O14625) [1096], CXCL10 (CXCL10 , P02778) [1096, 3046], CXCL9 (CXCL9 , Q07325) [1096, 3046]	CXCL12α (CXCL12 , P48061) [1115, 1725], CXCL12β (CXCL12 , P48061) [1115]	CXCL13 (CXCL13 , O43927) [151]	CXCL16 (CXCL16 , Q9H2A7) [3070]	CX₃CL1 (CX₃CL1 , P78423) [863]
Agonists	vCXCL1 [1753]	vCXCL1 [1753], HIV-1 matrix protein p17 [903]	–	–	–	–	–
Selective agonists	–	–	–	ALX40-4C (Partial agonist) [3239], X4-HIV-1 gp120	–	–	–
Endogenous antagonists	–	–	CCL11 (CCL11 , P51671) (pK _i 7.2) [3046], CCL7 (CCL7 , P80098) (pK _i 6.6) [3046]	–	–	–	–
Antagonists	–	–	–	plerixafor (pK _i 7) [3239]	–	–	–
Selective antagonists	–	navarixin (pIC ₅₀ 10.3) [116, 699], danirixin (pIC ₅₀ 7.9) [1909], SB 225002 (pIC ₅₀ 7.7) [3057], elubirixin (pIC ₅₀ 7.7) [116], SX-517 (pIC ₅₀ 7.2) [1775]	–	T134 (pIC ₅₀ 8.4) [2779], mavorixafor (pIC ₅₀ 7.9) [2625], HIV-Tat	–	–	–
Allosteric modulators (Negative)	–	reparixin (pIC ₅₀ 6.4) [210]	–	–	–	–	–
Labelled ligands	[¹²⁵ I] CXCL8 (human) (Agonist) [1019, 2388]	[¹²⁵ I] CXCL8 (human) (Agonist) [1019, 2388], [¹²⁵ I] CXCL1 (human) (Agonist), [¹²⁵ I] CXCL5 (human) (Agonist), [¹²⁵ I] CXCL7 (human) (Agonist)	[¹²⁵ I] CXCL10 (human) (Agonist), [¹²⁵ I] CXCL11 (human) (Agonist)	[¹²⁵ I] CXCL12α (human) (Agonist) [640, 1115]	[¹²⁵ I] CXCL13 (mouse) (Agonist) [315] – Mouse	[¹²⁵ I] CXCL16 (human) (Agonist)	[¹²⁵ I] CX₃CL1 (human) (Agonist) [404]

Nomenclature	XCRI
HGNC, UniProt	XCRI , P46094
Endogenous agonists	XCL1 (XCL1 , P47992) [800], XCL2 (XCL2 , Q9UBD3) [800]
Comments	XCL1 cannot be iodinated, but a secreted alkaline phosphatase (SEAP)-XCL1 fusion peptide can be used as a probe at XCR1.

Nomenclature	ACKR1	ACKR2	ACKR3	ACKR4	ACKR5
HGNC, UniProt	ACKR1 , Q16570	ACKR2 , O00590	ACKR3 , P25106	ACKR4 , Q9NPB9	ACKR5 , O15218
Non-chemokine ligands	–	–	–	–	GPR15L (GPR15LG , Q6UWK7), big dynorphin (PDYN , P01213), ape-lin-36 (APLN , Q9ULZ1), PACAP-38 (ADCYAPI , P18509)
Endogenous ligands	CXCL5 (CXCL5 , P42830), CXCL6 (CXCL6 , P80162), CXCL8 (CXCL8 , P10145), CXCL11 (CXCL11 , O14625), CCL2 (CCL2 , P13500), CCL5 (CCL5 , P13501), CCL7 (CCL7 , P80098), CCL11 (CCL11 , P51671), CCL14 (CCL14 , Q16627), CCL17 (CCL17 , Q92583)	–	–	–	CXCL10 (CXCL10 , P02778), CXCL11 (CXCL11 , O14625), CXCL12α (CXCL12 , P48061), CXCL13 (CXCL13 , O43927), CXCL14 (CXCL14 , O95715), CXCL17 (CXCL17 , Q6UXB2), CCL1 (CCL1 , P22362), CCL11 (CCL11 , P51671), CCL19 (CCL19 , Q99731), CCL25 (CCL25 , O15444), CCL26 (CCL26 , Q9Y258), CXCL1 (CXCL1 , P09341)
Endogenous agonists	–	CCL2 (CCL2 , P13500), CCL3 (CCL3 , P10147), CCL4 (CCL4 , P13236), CCL5 (CCL5 , P13501), CCL7 (CCL7 , P80098), CCL8 (CCL8 , P80075), CCL11 (CCL11 , P51671), CCL13 (CCL13 , Q99616), CCL14 (CCL14 , Q16627), CCL17 (CCL17 , Q92583), CCL22 (CCL22 , O00626)	CXCL12α (CXCL12 , P48061) [966, 2669], CXCL11 (CXCL11 , O14625)	CCL19 (CCL19 , Q99731) [3032], CCL25 (CCL25 , O15444) [3032], CCL21 (CCL21 , O00585) [3032]	–
Antagonists	–	–	canverixin (pIC ₅₀ 8.5) [2386]	–	–
Selective antagonists	–	–	LIH383 (pEC ₅₀ 9.2) [1886]	–	–

Comments	ACKR1 is used by <i>Plasmodium vivax</i> and <i>Plasmodium knowlesi</i> for entering erythrocytes.	Several lines of evidence have suggested that CGRP and adrenomedullin could be ligands for ACKR3; however, classical direct binding to the receptor has not yet been convincingly demonstrated [2755]. CCX771 (Chemocentryx; structure not disclosed) is an ACKR3 antagonist (IC ₅₀ ~4 nM in a ¹²⁵ I-CXCL12 radioligand displacement binding assay) [3208].	Rat GPR182 was first proposed as the adrenomedullin receptor [1345]. However, it was later reported that rat and human GPR182 did not respond to adrenomedullin [1381] and GPR182 is not currently considered to be a genuine adrenomedullin receptor [1077]. Proposed as a scavenger for the chemokines CXCL10, CXCL12, and CXCL13 [1583]. Nomenclature for <i>GPR182</i> was revised in 2024 to ACKR5, to reflect its function as an atypical chemokine receptor [263, 465, 466, 2754].
----------	--	---	---

Comments: Specific chemokine receptors facilitate cell entry by microbes, such as ACKR1 for *Plasmodium vivax*, and CCR5 and CXCR4 for HIV-1. Virally encoded chemokine receptors are known (*e.g.* US28, a homologue of CCR1 from human cytomegalovirus and ORF74, which encodes a homologue of CXCR2 in *Herpesvirus saimiri* and gamma-Herpesvirus-68), but their role

in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers. Three chemokine receptor antagonists have now been approved by the FDA: 1) the CCR5 antagonist **maraviroc** (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains; and 2) the CXCR4 antagonist **plerixafor** (Sanofi) for he-

matopoietic stem cell mobilization with **G-CSF** (*CSF3*, **P09919**) in patients undergoing transplantation in the context of chemotherapy for Hodgkins' Disease and multiple myeloma; and 3) the CCR4 blocking antibody Poteligeo (**mogamulizumab-kpkc**, Kyowa Kirin, Inc.) for mycosis fungoides or Sezary syndrome; and the CXCR4 antagonist **mavorixafor** for WHIM syndrome.

Further reading on Chemokine receptors

Bachelierie F *et al.* (2014) International Union of Pharmacology. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors. *Pharmacol Rev* **66**: 1-79 [PMID:24218476]
 Bachelierie F *et al.* (2015) An atypical addition to the chemokine receptor nomenclature: IUPHAR Review 15. *Br J Pharmacol* **172**: 3945-9 [PMID:25958743]
 Koelink PJ *et al.* (2012) Targeting chemokine receptors in chronic inflammatory diseases: an extensive review. *Pharmacol Ther* **133**: 1-18 [PMID:21839114]

Murphy PM. (2002) International Union of Pharmacology. XXX. Update on chemokine receptor nomenclature. *Pharmacol Rev* **54**: 227-9 [PMID:12037138]
 Murphy PM *et al.* (2000) International union of pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev* **52**: 145-76 [PMID:10699158]
 Scholten DJ *et al.* (2012) Pharmacological modulation of chemokine receptor function. *Br J Pharmacol* **165**: 1617-43 [PMID:21699506]

Cholecystokinin receptors

G protein-coupled receptors → Cholecystokinin receptors

Overview: Cholecystokinin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on CCK receptors** [2088]) are activated by the endogenous peptides cholecystokinin-8 (**CCK-8** (*CCK*, **P06307**)), **CCK-33** (*CCK*, **P06307**), **CCK-58** (*CCK*, **P06307**) and gastrin (*gastrin-17* (*GAST*, **P01350**)). There are

only two distinct subtypes of CCK receptors, CCK₁ and CCK₂ receptors [1478, 3016], with some alternatively spliced forms most often identified in neoplastic cells. The CCK receptor subtypes are distinguished by their peptide selectivity, with the CCK₁ receptor requiring the carboxyl-terminal heptapeptide-amide that

includes a sulfated tyrosine for high affinity and potency, while the CCK₂ receptor requires only the carboxyl-terminal tetrapeptide shared by each CCK and gastrin peptides. These receptors have characteristic and distinct distributions, with both present in both the central nervous system and peripheral tissues.

Nomenclature	CCK ₁ receptor	CCK ₂ receptor
HGNC, UniProt	CCKAR, P32238	CCKBR, P32239
Potency order of endogenous ligands	CCK-8 (CCK, P06307), CCK-58 (CCK, P06307), CCK-39 (CCK, P06307), CCK-33 (CCK, P06307) >> gastrin-17 (GAST, P01350), desulfated cholecystokinin-8 > CCK-4 (CCK, P06307)	CCK-8 (CCK, P06307), CCK-39 (CCK, P06307), CCK-33 (CCK, P06307), CCK-58 (CCK, P06307) >gastrin-17 (GAST, P01350), desulfated cholecystokinin-8, CCK-4 (CCK, P06307)
Endogenous agonists	CCK-33 (CCK, P06307), CCK-39 (CCK, P06307), CCK-58 (CCK, P06307), CCK-8 (CCK, P06307)	desulfated cholecystokinin-8 [1606], CCK-4 (CCK, P06307) [1240], desulfated gastrin-14 (GAST, P01350), desulfated gastrin-17 (GAST, P01350), desulfated gastrin-34 (GAST, P01350), desulfated gastrin-71 (GAST, P01350), gastrin-14 (GAST, P01350), gastrin-34 (GAST, P01350), gastrin-71 (GAST, P01350)
Selective agonists	A-71623 [92] – Rat, JMV180 [1379], GW-5823 [1104]	RB-400 [189] – Rat, PBC-264 [1260] – Rat, gastrin-17 (GAST, P01350) [1201] – Mouse
Antagonists	linitript (pIC ₅₀ 8.3) [953]	–
Selective antagonists	devazepide (pIC ₅₀ 9.7) [1201] – Rat, T-0632 (pIC ₅₀ 9.6) [2792] – Rat, PD-140548 (pIC ₅₀ 8.6) [2621] – Rat, lorglumide (pIC ₅₀ 6.7–8.2) [1201, 1246] – Rat	YF-476 (pIC ₅₀ 9.7) [284, 2776], GV150013 (pIC ₅₀ 9.4) [2897], L-740093 (pIC ₅₀ 9.2) [2077], YM-022 (pIC ₅₀ 9.2) [2077], JNJ-26070109 (pIC ₅₀ 8.5) [1984], L-365260 (pIC ₅₀ 8.4) [1606], RP73870 (pIC ₅₀ 8) [1696] – Rat, LY262691 (pIC ₅₀ 7.5) [2347] – Rat
Labelled ligands	[³ H]devazepide (Antagonist) (pK _d 9.7) [425], [¹²⁵ I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist) [2277]	[³ H]PD140376 (Antagonist) (pK _i 9.7–10) [1205] – Guinea pig, [¹²⁵ I]PD142308 (Antagonist) (pK _d 9.6) [1166] – Guinea pig, [¹²⁵ I]DTyr-Gly-[(Nle28,31)CCK-26-33 (Agonist) [2277], [¹²⁵ I]gastrin (Agonist), [³ H]gastrin (Agonist), [³ H]L365260 (Antagonist) (pK _d 8.2–8.5) [2077], [¹²⁵ I]-BDZ ₂ (Antagonist) (pK _i 8.4) [32]

Comments: While a cancer-specific CCK receptor has been postulated to exist, which also might be responsive to incompletely processed forms of CCK (Gly-extended forms), this has never been isolated. An alternatively spliced form of the CCK₂ receptor in which intron 4 is retained, adding 69 amino acids to the in-

tracellular loop 3 (ICL3) region, has been described to be present particularly in certain neoplasms where mRNA mis-splicing has been commonly observed [2643], but it is not clear that this receptor splice form plays a special role in carcinogenesis. Another alternative splicing event for the CCK₂ receptor was reported

[2665], with alternative donor sites in exon 4 resulting in long (452 amino acids) and short (447 amino acids) forms of the receptor differing by five residues in ICL3, however, no clear functional differences have been observed.

Further reading on Cholecystokinin receptors

- Cawston EE *et al.* (2010) Therapeutic potential for novel drugs targeting the type 1 cholecystokinin receptor. *Br J Pharmacol* **159**: 1009-21 [PMID:19922535]
- Dockray GJ. (2009) Cholecystokinin and gut-brain signalling. *Regul Pept* **155**: 6-10 [PMID:19345244]
- Dufresne M *et al.* (2006) Cholecystokinin and gastrin receptors. *Physiol Rev* **86**: 805-47 [PMID:16816139]
- Herranz R. (2003) Cholecystokinin antagonists: pharmacological and therapeutic potential. *Med Res Rev* **23**: 559-605 [PMID:12789687]
- Miller LJ *et al.* (2008) Structural basis of cholecystokinin receptor binding and regulation. *Pharmacol Ther* **119**: 83-95 [PMID:18558433]
- Noble F *et al.* (1999) International Union of Pharmacology. XXI. Structure, distribution, and functions of cholecystokinin receptors. *Pharmacol Rev* **51**: 745-781 [PMID:10581329]

Class A Orphans

G protein-coupled receptors → Class A Orphans

Overview: The class A orphan GPCRs have been organised into the subfamilies listed below, to better segregate them based on evidence (or lack of evidence) for endogenous ligand or surrogate ligand interactions, and potential for deorphanization.

Class A Orphans with no pharmacology

G protein-coupled receptors → Class A Orphans → Class A Orphans with no pharmacology

Overview: The table below contains Class A 'orphan' G protein-coupled receptors where the endogenous ligand(s) is not known.

<i>GPR20</i>	<i>GPR22</i>	<i>GPR26</i>	<i>GPR33</i>	<i>GPR45</i>	<i>GPR50</i>	<i>GPR62</i>
<i>GPR78</i>	<i>GPR82</i>	<i>GPR135</i>	<i>GPR141</i>	<i>GPR148</i>	<i>GPR149</i>	<i>GPR150</i>
<i>GPR152</i>	<i>GPR153</i>	<i>GPR161</i>	<i>GPR176</i>	<i>MRGPRF</i>	<i>MRGPRG</i>	<i>MRGPRX3</i>

Information on members of this family may be found in the [online database](#).

Class A Orphans with only surrogate ligands

G protein-coupled receptors → Class A Orphans → Class A Orphans with only surrogate ligands

Overview: Preliminary pairings with surrogate ligands have been described for these GPCRs. Endogenous ligands have not been identified.

Nomenclature	<i>GPR21</i>	<i>GPR27</i>
HGNC, UniProt	<i>GPR21</i> , Q99679	<i>GPR27</i> , Q9NS67
Agonists	–	compound 5128535 [2241], PT-91 [2241], compound 1a (Inverse agonist) [3159]
Comments	Positive benefit in models of diabetes/obesity [858, 2142] were not observed in another study [2993]. A cryo-EM structure of unliganded GPR21 bound to G proteins has been reported [1688]. GRA2 is reported as an inverse agonist [267].	A complex mix of plasmalogens evoked phosphorylation of ERK and PKB in mouse cultured hippocampal neurones that could be inhibited with shRNA directed against GPR27 [1175]. Compound 5128535 [660, 698, 2241] and PT-91 [2241] function as surrogate agonists, while compound 1a is reported as an inverse agonist [3159]. Knockdown of Gpr27 reduces endogenous mouse insulin promoter activity and glucose-stimulated insulin secretion [1506].

Nomenclature	GPR52	GPR85	GPR88
HGNC, UniProt	GPR52 , Q9Y2T5	GPR85 , P60893	GPR88 , Q9GZN0
Agonists	NXE0041178 [2271]	–	–
Antagonists	comp-43 (pIC ₅₀ 6.2) [2987]	–	–
Comments	A number of agonists have been described, including compound 7a and 7m [2563], FTBMT [2082], derivative 17 [2017], BD442618 , BD502657 [2440], HTL0041178 [2271] and sucralose [2275]. Additionally, multiple antagonists/inverse agonists have been reported, including cannabidiol O1918 [2706] and comp-43 [2987].	Compound 1a [3159] and compound 3i [2458] are reported as inverse agonists. Proposed to regulate hippocampal neurogenesis in the adult, as well as neurogenesis-dependent learning and memory [444].	A number of small molecule agonists have been reported including 2-PCCA [1649], RTI-122 [2328], RTI-13951-33 [1292, 1292], compound 2 [1292], compound 99 [219] and BI-9508 [766]. Gene disruption results in altered striatal signalling [1726].

Class A Orphans with emerging pharmacology

G protein-coupled receptors → Class A Orphans → Class A Orphans with emerging pharmacology

Overview: There are plausible grounds for considering deorphanization of some of these GPCRs. Preliminary pairings with an endogenous/physiological ligand have been described for some of these receptors, but confirmatory evidence is required to validate any deorphanization and subsequent re-naming of the receptors.

GPR3	GPR4	GPR6	GPR12	GPR15	GPR19	GPR25
GPR31	GPR32	GPR34	GPR35	GPR37	GPR37L1	GPR39
GPR61	GPR63	GPR65	GPR68	GPR75	GPR83	GPR87
GPR101	GPR132	GPR139	GPR142	GPR146	GPR151	GPR160
GPR162	GPR171	GPR173	GPR174	GPR183	MASIL	MRGPRD
MRGPRF	MRGPRX1	MRGPRX2	MRGPRX4	P2RY8	P2RY10	

Nomenclature	GPR3	GPR4	GPR6	GPR12	GPR15
HGNC, UniProt	GPR3 , P46089	GPR4 , P46093	GPR6 , P46095	GPR12 , P47775	GPR15 , P49685
Endogenous ligands	–	Protons	–	–	–
Agonists	RTI-19318-32 [875], diphenyl-eneiodonium chloride [3177]	–	–	–	–

Comments	Sphingosine 1-phosphate was reported to be an endogenous agonist [2885], but this finding was not replicated in subsequent studies [3184]. Reported to activate adenylyl cyclase constitutively through G _s [707]. Gene disruption results in premature ovarian ageing [1596], reduced β-amyloid deposition [2809] and hypersensitivity to thermal pain [2439] in mice. First small molecule inverse agonist [1281] and agonists identified [3177]. Agonist RTI-19318-32 proposed for therapeutic potential to aid nicotine cessation [1933].	An initial report suggesting activation by lysophosphatidylcholine and sphingosylphosphorylcholine [3267] has been retracted [2087]. <i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as proton-sensing receptors detecting acidic pH [586, 2564]. Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation [3164]. Negative allosteric modulators of <i>GPR4</i> have been reported [2837].	An initial report that sphingosine 1-phosphate (S1P) was a high-affinity ligand (EC ₅₀ value of 39nM) [1214, 2885] was not repeated in arrestin-based assays [2669, 3184]. Reported to activate adenylyl cyclase constitutively through G _s and to be located intracellularly [2152]. <i>GPR6</i> -deficient mice showed reduced striatal cyclic AMP production <i>in vitro</i> and selected alterations in instrumental conditioning <i>in vivo</i> . [1723].	Reports that sphingosine 1-phosphate is a ligand of <i>GPR12</i> [1213, 2885] have not been replicated in arrestin-based assays [2669, 3184]. Gene disruption results in dyslipidemia and obesity [229].	Reported to act as a co-receptor for HIV [703]. In an infection-induced colitis model, <i>Gpr15</i> knockout mice were more prone to tissue damage and inflammatory cytokine expression [1409].
----------	---	---	---	---	---

Nomenclature	<i>GPR19</i>	<i>GPR25</i>	<i>GPR31</i>	<i>GPR32</i>	<i>GPR34</i>
HGNC, UniProt	<i>GPR19</i> , Q15760	<i>GPR25</i> , O00155	<i>GPR31</i> , O00270	<i>GPR32</i> , O75388	<i>GPR34</i> , Q9UPC5
Potency order of endogenous ligands	–	–	–	resolvin D1 > LXA ₄	–
Endogenous agonists	–	–	12S-HETE [1003] – Mouse	resolvin D1 [1500], LXA ₄ [1500]	lysophosphatidylserine [1434, 2725]
Agonists	adropin (<i>ENHO</i> , Q6U-WT2) [2343]	–	–	–	–
Antagonists	–	–	–	–	YL-365 (pIC ₅₀ 7.8) [3118]
Labelled ligands	–	–	–	[³ H]resolvin D1 (Agonist) [1500]	–
Comments	–	–	See [586] for discussion of pairing.	Resolvin D1 has been demonstrated to activate <i>GPR32</i> in two publications [470, 1500]. The pairing was not replicated in a recent study based on arrestin recruitment [2669]. <i>GPR32</i> is a pseudogene in mice and rats. See reviews [119] and [586].	Lysophosphatidylserine has been reported to be a ligand of <i>GPR34</i> in several publications, but the pairing was not replicated in a recent study based on arrestin recruitment [2669]. Fails to respond to a variety of lipid-derived agents [3184]. Gene disruption results in an enhanced immune response [1669]. Characterization of agonists at this receptor is discussed in [1220] and [586].

Nomenclature	<i>GPR35</i>	<i>GPR37</i>	<i>GPR37L1</i>	<i>GPR39</i>	<i>GPR61</i>
HGNC, UniProt	<i>GPR35</i> , Q9HC97	<i>GPR37</i> , O15354	<i>GPR37L1</i> , O60883	<i>GPR39</i> , O43194	<i>GPR61</i> , Q9BZJ8
Endogenous agonists	2-oleoyl-LPA [2121], kynurenic acid [2669, 2994]	–	–	Zn ²⁺ [1154]	–
Agonists	–	neuropeptide head activator [2378]	–	–	–
Selective agonists	–	–	–	–	compound 1 (Inverse agonist) [1609]
Comments	Several studies have shown that kynurenic acid is an agonist of <i>GPR35</i> but it remains controversial whether the proposed endogenous ligand reaches sufficient tissue concentrations to activate the receptor [1507]. 2-oleoyl-LPA has also been proposed as an endogenous ligand [2121] but these results were not replicated in an arrestin assay [2669]. The phosphodiesterase inhibitor zaprinast [2795] has become widely used as a surrogate agonist to investigate <i>GPR35</i> pharmacology and signalling [2795]. <i>GPR35</i> is also activated by the pharmaceutical adjunct pamoic acid [3249]. See reviews [586] and [655].	Reported to associate and regulate the dopamine transporter [1815] and to be a substrate for parkin [1813]. Gene disruption results in altered striatal signalling [1814]. The peptides prosaptide and prosaposin are proposed as endogenous ligands for <i>GPR37</i> and <i>GPR37L1</i> [1883].	The peptides prosaptide and prosaposin are proposed as endogenous ligands for <i>GPR37</i> and <i>GPR37L1</i> [1883].	Zn ²⁺ has been reported to be a potent and efficacious agonist of human, mouse and rat <i>GPR39</i> [3174]. Obestatin (<i>GHRL</i> , <i>Q9UBU3</i>), a fragment from the ghrelin precursor, was reported initially as an endogenous ligand, but subsequent studies failed to reproduce these findings. <i>GPR39</i> has been reported to be down-regulated in adipose tissue in obesity-related diabetes [394]. Gene disruption results in obesity and altered adipocyte metabolism [2228]. Reviewed in [586].	<i>GPR61</i> deficient mice exhibit obesity associated with hyperphagia [2026]. Although no endogenous ligands have been identified, 5-(nonyloxy) tryptamine has been reported to be a low affinity inverse agonist [2774].

Nomenclature	<i>GPR63</i>	<i>GPR65</i>	<i>GPR68</i>	<i>GPR75</i>	<i>GPR83</i>
HGNC, UniProt	<i>GPR63</i> , Q9BZJ6	<i>GPR65</i> , Q8IYL9	<i>GPR68</i> , Q15743	<i>GPR75</i> , O95800	<i>GPR83</i> , Q9NYM4
Endogenous ligands	–	Protons	Protons	–	–
Agonists	–	–	–	–	PEN {Mouse} [931] – Mouse, Zn ²⁺ [1994] – Mouse
Allosteric modulators (Positive)	–	–	ogerin (pK _B 5) [1194], lorazepam (lorazepam characterised as a non-selective <i>GPR68</i> positive allosteric modulator for the agonist proton in cAMP production) [1194]	–	–

Comments	Sphingosine 1-phosphate and dioleoylphosphatidic acid have been reported to be low affinity agonists for <i>GPR63</i> [2072] but this finding was not replicated in an arrestin-based assay [3184].	<i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as proton-sensing receptors detecting acidic pH [586, 2564]. Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease [1484].	<i>GPR68</i> was previously identified as a receptor for sphingosylphosphorylcholine (SPC) [3137], but the original publication has been retracted [3138]. <i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as proton-sensing receptors detecting acidic pH [586, 2564]. A family of 3,5-disubstituted isoxazoles were identified as agonists of <i>GPR68</i> [2442].	<i>CCL5</i> (<i>CCL5</i> , <i>P13501</i>) was reported to be an agonist of <i>GPR75</i> [1215], but the pairing could not be repeated in an arrestin assay [2669].	One isoform has been implicated in the induction of CD4(+) CD25(+) regulatory T cells (Tregs) during inflammatory immune responses [1043]. The extracellular N-terminal domain is reported as an intramolecular inverse agonist [1995].
----------	---	--	--	--	---

Nomenclature	GPR87	GPR101	GPR132	GPR139	GPR142
HGNC, UniProt	GPR87 , Q9BY21	GPR101 , Q96P66	GPR132 , Q9UNW8	GPR139 , Q6DWJ6	GPR142 , Q7Z601
Endogenous ligands	–	–	Protons	–	–
Endogenous agonists	LPA [2003, 2756]	–	–	–	–
Comments	–	Mutations in <i>GPR101</i> have been linked to gigantism and acromegaly [2869].	<i>GPR4</i> , <i>GPR65</i> , <i>GPR68</i> and <i>GPR132</i> are now thought to function as proton-sensing receptors detecting acidic pH [586, 2564]. Reported to respond to lysophosphatidylcholine [1323], but later retracted [3085].	Peptide agonists have been reported [1234].	Small molecule agonists have been reported [2838, 3203].

Nomenclature	GPR146	GPR151	GPR160	GPR162	GPR171
HGNC, UniProt	GPR146 , Q96CH1	GPR151 , Q8TDV0	GPR160 , Q9UJ42	GPR162 , Q16538	GPR171 , O14626
Comments	Yosten <i>et al.</i> demonstrated inhibition of proinsulin C-peptide (<i>INS</i> , P01308)-induced stimulation of cFos expression following knock-down of <i>GPR146</i> in KATO III cells, suggesting proinsulin C-peptide as an endogenous ligand of the receptor [3200]. Reviewed in [1693].	<i>GPR151</i> responded to galanin with an EC ₅₀ value of 2 μM, suggesting that the endogenous ligand shares structural features with galanin (<i>GAL</i> , P22466) [1212].	–	<i>Putative pairing</i> : direct interaction between <i>GPR162</i> and cocaine and amphetamine-regulated transcript (CART; <i>CARTPT</i>) has been demonstrated in three different assay systems, and siRNA <i>Cartpt</i> knockdown reduces this detected binding [1694]. Functionally the <i>GPR162</i> /CART appears to be involved in insulin exocytosis in pancreatic beta cells.	<i>GPR171</i> has been shown to be activated by the endogenous peptide BigLEN (Mouse). This receptor-peptide interaction is believed to be involved in regulating feeding and metabolism responses [930].

Nomenclature	<i>GPR173</i>	<i>GPR174</i>	<i>GPR183</i>	<i>MAS1L</i>	<i>MRGPRD</i>
HGNC, UniProt	<i>GPR173</i> , Q9NS66	<i>GPR174</i> , Q9BXC1	<i>GPR183</i> , P32249	<i>MAS1L</i> , P35410	<i>MRGPRD</i> , Q8TDS7
Endogenous agonists	–	lysophosphatidylserine [1227]	7 α ,25-dihydroxycholesterol [1039, 1709], 7 α ,27-dihydroxycholesterol [1709], 7 β ,25-dihydroxycholesterol [1709], 7 β ,27-dihydroxycholesterol [1709]	–	β -alanine [2599, 2669]
Comments	–	See [1220] which discusses characterization of agonists at this receptor.	Two independent publications have shown that 7 α ,25-dihydroxycholesterol is an agonist of <i>GPR183</i> and have demonstrated by mass spectrometry that this oxysterol is present endogenously in tissues [1039, 1709]. <i>Gpr183</i> -deficient mice show a reduction in the early antibody response to a T-dependent antigen. <i>GPR183</i> -deficient B cells fail to migrate to the outer follicle and instead stay in the follicle centre [1372, 2211].	–	An endogenous peptide with a high degree of sequence similarity to angiotensin-(1-7) (<i>AGT</i> , P01019), alamandine (<i>AGT</i>), was shown to promote NO release in <i>MRGPRD</i> -transfected cells. The binding of alamandine to <i>MRGPRD</i> was shown to be blocked by D-Pro ⁷ -angiotensin-(1-7), β-alanine and PD123319 [1568]. Genetic ablation of <i>MRGPRD</i> + neurons of adult mice decreased behavioural sensitivity to mechanical stimuli but not to thermal stimuli [402]. See reviews [586] and [2662].

Nomenclature	<i>MRGPRX1</i>	<i>MRGPRX2</i>	<i>MRGPRX4</i>	<i>P2RY8</i>	<i>P2RY10</i>
HGNC, UniProt	<i>MRGPRX1</i> , Q96LB2	<i>MRGPRX2</i> , Q96LB1	<i>MRGPRX4</i> , Q96LA9	<i>P2RY8</i> , Q86VZ1	<i>P2RY10</i> , O00398
Endogenous agonists	bovine adrenal medulla peptide 8-22 (<i>PENK</i> , P01210) [438, 1622, 2669]	PAMP-20 (<i>ADM</i> , P35318) [1335]	–	–	sphingosine 1-phosphate [2003], LPA [2003]
Agonists	–	cortistatin-14 {Mouse, Rat} [1335, 1559, 2403, 2669]	–	–	–
Selective agonists	–	PAMP-12 (human) [1335]	–	–	–
Comments	Reported to mediate the sensation of itch [1716, 2611]. Reports that bovine adrenal medulla peptide 8-22 (<i>PENK</i> , P01210) was the most potent of a series of proenkephalin A-derived peptides as an agonist of <i>MRGPRX1</i> in assays of calcium mobilisation and radioligand binding [1622] were replicated in an independent study using an arrestin recruitment assay [2669]. See reviews [586] and [2662].	A diverse range of substances has been reported to be agonists of <i>MRGPRX2</i> , with cortistatin 14 the highest potency agonist in assays of calcium mobilisation [2403], also confirmed in an independent study using an arrestin recruitment assay [2669]. See reviews [586] and [2662].	See reviews [586] and [2662]. <i>MRGPRX4</i> is expressed by a subset of pruriceptive neurons that innervate the skin in response to activation by bile acids, bilirubin, and urobilin. As an attractive therapeutic strategy for the treatment of cholestatic and uremic pruritus caused by cholestatic liver diseases and chronic kidney disease, respectively, the small molecule <i>MRGPRX4</i> antagonist EP547 (Escient Pharmaceuticals) was progressed to clinical evaluation for these indications.	–	–

Further reading on Class A Orphans with emerging pharmacology

Han J *et al.* (2025) GPR75: Advances, Challenges in Deorphanization, and Potential as a Novel Drug Target for Disease Treatment. *Int J Mol Sci* **26**: [PMID:40362321]

Mackenzie AE *et al.* (2017) The emerging pharmacology and function of GPR35 in the nervous system. *Neuropharmacology* **113**: 661-671 [PMID:26232640]

GPR42, GPR84

G protein-coupled receptors → Class A Orphans → GPR42, GPR84

Overview: There is some evidence to suggest that GPR42 and GPR84 may be free fatty acid receptors.

Nomenclature	<i>GPR42</i>	<i>GPR84</i>
HGNC, UniProt	<i>GPR42</i> , O15529	<i>GPR84</i> , Q9NQS5
Agonists	–	DL-175 (orthosteric) [1820, 3004], decanoic acid [2669, 2996], undecanoic acid [2996], lauric acid [2996], 6-nonylpyridine-2,4-diol (orthosteric) [1820], Embelin (orthosteric) [1820], PSB-16434 (orthosteric) [1820], ZQ-16 (orthosteric) [1820]
Allosteric modulators	–	DIM (Agonist) [1820]
Comments	–	Medium chain free fatty acids with carbon chain lengths of 9-14 activate <i>GPR84</i> [2741, 2996]. A surrogate ligand for <i>GPR84</i> , 6-n-octylaminouracil has also been proposed [2741]. See review [586] for discussion of classification. Mutational analysis and molecular modelling of <i>GPR84</i> has been reported [2075].

LGR4, LGR5, LGR6

G protein-coupled receptors → Class A Orphans → LGR4, LGR5, LGR6

Overview: This set of orphan GPCRs contain leucine rich repeat domains which suggests potential for participation in protein-protein interactions.

Nomenclature	<i>LGR4</i>	<i>LGR5</i>	<i>LGR6</i>
HGNC, UniProt	<i>LGR4</i> , Q9BXB1	<i>LGR5</i> , O75473	<i>LGR6</i> , Q9HBX8
Endogenous agonists	R-spondin-2 (<i>RSPO2</i> , Q6UXX9) [383], R-spondin-1 (<i>RSPO1</i> , Q2MKA7) [383], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) [383], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) [383]	R-spondin-2 (<i>RSPO2</i> , Q6UXX9) [383], R-spondin-1 (<i>RSPO1</i> , Q2MKA7) [383], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) [383], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) [383]	R-spondin-1 (<i>RSPO1</i> , Q2MKA7) [383, 601], R-spondin-2 (<i>RSPO2</i> , Q6UXX9) [383, 601], R-spondin-3 (<i>RSPO3</i> , Q9BXY4) [383, 601], R-spondin-4 (<i>RSPO4</i> , Q2I0M5) [383, 601]
Comments	<i>LGR4</i> does not couple to heterotrimeric G proteins or recruit arrestins when stimulated by the R-spondins, indicating a unique mechanism of action. R-spondins bind to <i>LGR4</i> , which specifically associates with Frizzled and LDL receptor-related proteins (LRPs) that are activated by the extracellular Wnt molecules and then trigger canonical Wnt signalling to increase gene expression [383, 601, 2435]. Gene disruption leads to multiple developmental disorders [1293, 1749, 2664, 3045].	The four R-spondins can bind to <i>LGR4</i> , <i>LGR5</i> , and <i>LGR6</i> , which specifically associate with Frizzled and LDL receptor-related proteins (LRPs), proteins that are activated by extracellular Wnt molecules and which then trigger canonical Wnt signalling to increase gene expression [383, 601].	–

Comments: *LGR4/5/6* have been identified as components of the Wnt/ β -catenin signaling complexes [146, 2592, 2905, 3000]. *LGR4* and -5 are recognised as markers of cancer stem cells. These receptors are active targets for anti-tumour drug development [445, 1109, 1746, 2840, 2841].

Mas1, BB3/brs3, GPR17

G protein-coupled receptors → Class A Orphans → Mas1, BB3/brs3, GPR17

Overview: These 3 orphan GPCRs are considered 'foster children' of well established GPCR families and are reviewed by the corresponding subcommittee members; *Mas1* (Angiotensin receptors), *BB₃* receptor (Bombesin receptors), *GPR17* (P2Y receptors/Leukotriene receptors).

Nomenclature	<i>MAS1</i>	<i>BB₃</i> receptor	<i>GPR17</i>
HGNC, UniProt	<i>MAS1</i> , P04201	<i>BRS3</i> , P32247	<i>GPR17</i> , Q13304
Endogenous agonists	–	–	UDP-glucose [195, 506], LTC ₄ [506], UDP-galactose [195, 506], UDP [195, 506], LTD ₄ [506]
Agonists	angiotensin-(1-7) (<i>AGT</i> , P01019) [917] – Mouse	–	–
Selective agonists	–	compound 9g [1839, 2336, 2339], MK-7725 [481], MK-5046 [1963, 2549], dimethyl shikonin oxime 5a [3107], [D-Tyr ⁶ , Apa-4Cl ¹¹ , Phe ¹³ , Nle ¹⁴]bombesin-(6-14) [1809], compound 17c [1838], bag-1 [989], compound 22e [1086], oridonin [3270]	–
Selective antagonists	–	bantag-1 (pIC ₅₀ 8.6–8.7) [989, 1963, 2337], licoisoflavone A (pIC ₅₀ 6.2) [1737], ML-18 (pIC ₅₀ 5.3) [1954]	–
Labelled ligands	–	[¹²⁵ I]bantag-1 (Selective Antagonist) (pK _i 9.6) [2337], [³ H]bag-2 (Agonist) [989] – Mouse, [¹²⁵ I][D-Tyr ⁶ , β-Ala ¹¹ , Phe ¹³ , Nle ¹⁴]bombesin-(6-14) (Agonist) [1810, 1963]	–
Comments	–	–	Reported to be a dual leukotriene and UDP receptor [506]. Another group instead proposed that <i>GPR17</i> functions as a negative regulator of the CysLT ₁ receptor response to leukotriene D ₄ (LTD ₄). For further discussion, see [586]. Reported to antagonize CysLT ₁ receptor signalling <i>in vivo</i> and <i>in vitro</i> [1780]. See reviews [119] and [586].

Further reading on Class A Orphans

- Akbari P *et al.* (2021) Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity. *Science* **373**: [PMID:34210852]
- Hershfinkel M. (2024) Cross-talk between zinc and calcium regulates ion transport: A role for the zinc receptor, ZnR/GPR39. *J Physiol* **602**: 1579-1594 [PMID:37462604]
- McNeil BD *et al.* (2015) Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* **519**: 237-41 [PMID:25517090]
- Wirthgen E *et al.* (2017) Kynurenic Acid: The Janus-Faced Role of an Immunomodulatory Tryptophan Metabolite and Its Link to Pathological Conditions. *Front Immunol* **8**: 1957 [PMID:29379504]

Class C Orphans

G protein-coupled receptors → Class C Orphans

Overview: This set contains class C 'orphan' G protein coupled receptors where the endogenous ligand(s) is not known.

Nomenclature	<i>GPR156</i>	<i>GPR158</i>	<i>GPR179</i>	<i>GPRC5A</i>	<i>GPRC5B</i>	<i>GPRC5C</i>	<i>GPRC5D</i>	<i>GPRC6</i> receptor
HGNC, UniProt	<i>GPR156</i> , Q8N-FN8	<i>GPR158</i> , Q5T848	<i>GPR179</i> , Q6PRD1	<i>GPRC5A</i> , Q8N-FJ5	<i>GPRC5B</i> , Q9NZH0	<i>GPRC5C</i> , Q9NQ84	<i>GPRC5D</i> , Q9NZD1	<i>GPRC6A</i> , Q5T6X5
Comments	–	–	Forms a complex with the extracellular matrix protein pikachurin (<i>EGFLAM</i> ; <i>Q63HQ2</i>) in retinal photoreceptor synapses [2183].	–	–	–	–	<i>GPRC6</i> is a G _q -coupled receptor which responds to basic amino acids [3040].

Further reading on Class C Orphans

Harpsoe K *et al.* (2017) Structural insight to mutation effects uncover a common allosteric site in class C GPCRs. *Bioinformatics* **33**: 1116-1120 [PMID:28011766]

Class Frizzled GPCRs

G protein-coupled receptors → Class Frizzled GPCRs

Overview: Receptors of the Class Frizzled (FZD, **nomenclature as agreed by the NC-IUPHAR subcommittee on the Class Frizzled GPCRs** [2531]), are GPCRs highly conserved across species and were originally identified in *Drosophila* [416]. While SMO shows structural resemblance to the 10 FZDs, it is functionally separated as it is involved in Hedgehog signaling [2531]. SMO exerts its effects by activating heterotrimeric G proteins or stabilization of G₁₂ by sequestering catalytic PKA subunits [89, 1047, 2581]. While SMO itself is bound by sterols and oxysterols [537, 1423], FZDs are activated by WNTs, which are cysteine-rich lipoglycoproteins with fundamental functions in ontogeny and tissue homeostasis. FZD signaling was initially divided into two pathways, being either dependent on the accumulation of the transcription regulator β -catenin (*CTNNB1*, *P35222*) or being β -catenin-independent (often referred to as canonical vs. non-canonical WNT/FZD signaling, respectively). Nevertheless, it makes pharmacologically more sense to define downstream signaling by transducer coupling to either DVL or heterotrimeric G

proteins [2532]. WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors *LRP5* (*O75197*) and *LRP6* (*O75581*), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β -catenin and subsequently its translocation to the nucleus. β -catenin, in turn, modifies gene transcription by interacting with TCF/LEF transcription factors. WNT/ β -catenin-dependent signaling can also be activated by FZD subtype-specific WNT surrogates [1890]. β -catenin-independent FZD signalling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the activation of heterotrimeric G proteins [648, 2226, 2533], the elevation of intracellular calcium [2637], activation of cGMP-specific PDE6 [25] and elevation of cAMP as well as RAC-1, JNK, Rho and Rho kinase signalling [1042]. Novel resonance energy transfer-based tools have allowed the study of the GPCR-like nature of FZDs in greater detail. Upon ligand stimulation, FZDs undergo conformational changes and signal *via* heterotrimeric G proteins [282, 958, 1488, 1491, 2508,

3098, 3099]. Furthermore, the phosphoprotein Dishevelled constitutes a key transducer in WNT/FZD signaling towards planar-cell-polarity-like pathways. Importantly, FZDs adopt distinct conformational landscapes that regulate pathway selection [956, 3099]. As with other GPCRs, members of the Frizzled family are functionally dependent on the arrestin scaffolding protein for internalization [450], as well as for β -catenin-dependent [333] and -independent [334, 1402] signalling. The pattern of cell signalling is complicated by the presence of additional ligands, which can enhance or inhibit FZD signalling (secreted Frizzled-related proteins (sFRP), *Wnt-inhibitory factor* (*WIF1*, *Q9Y5W5*) (WIF), *sclerostin* (*SOST*, *Q9BQB4*) or Dickkopf (DKK)), as well as modulatory (co)-receptors with *Ryk*, *ROR1*, *ROR2* and *PTK7*, which may also function as independent signaling proteins. An important FZD₄-selective non-WNT agonist is the *norrin* (*NDP*, *Q00604*) cysteine knot protein, which is a key player in FZD₄-mediated vascularization for example in the retina and which is functionally related to familial exudative vitreoretinopathy (FEVR).

Nomenclature	FZD ₁	FZD ₂	FZD ₃	FZD ₄	FZD ₅
HGNC, UniProt	FZD1 , Q9UP38	FZD2 , Q14332	FZD3 , Q9NPG1	FZD4 , Q9ULV1	FZD5 , Q13467
Agonists	–	–	–	norrin (<i>NDP</i> , Q00604)	–
Allosteric modulators (Negative)	–	–	–	FzM1 (pIC ₅₀ 6.2) [883 , 2382]	–
Antibodies	vantictumab (Antagonist) (pIC ₅₀ ~9.1) [1005]	vantictumab (Antagonist) (pIC ₅₀ ~9) [1005]	–	–	vantictumab (Antagonist) (pIC ₅₀ ~9) [1005]
Comments	–	–	–	–	IgG-2919 and IgG-2921 are FZD ₅ antibodies that have exhibited antitumour activities <i>in vitro</i> and <i>in vivo</i> (inhibiting the growth of RNF43-mutant pancreatic ductal adenocarcinoma cells/xenograft tumours), by blocking autocrine Wnt-β-catenin signalling in these mutant, FZD ₅ -dependent cells [2692].

Nomenclature	FZD ₆	FZD ₇	FZD ₈	FZD ₉	FZD ₁₀
HGNC, UniProt	FZD6 , O60353	FZD7 , O75084	FZD8 , Q9H461	FZD9 , O00144	FZD10 , Q9ULW2
Selective antagonists	–	Fz7-21 (pIC ₅₀ 7) [2076]	–	–	–
Antibodies	–	vantictumab (Antagonist) (pIC ₅₀ ~9) [1005]	vantictumab (Antagonist) (pIC ₅₀ ~8) [1005]	–	–
Comments	SAG1.3 and purmorphamine have been described as weak partial agonists with varying potencies depending on a read-out [1491].	–	FZD8-Fc/OMP-54F28 is a FZD ₈ antagonist [612].	–	Radio-labelled murine monoclonal antibody Mab 92-13 has been used to demonstrate the therapeutic potential of targeting FZD ₁₀ -positive tumours [826].

Nomenclature	SMO
HGNC, UniProt	SMO , Q99835
Agonists	SAG1.3 [441] – Mouse, purmorphamine [2622]
Antagonists	MRT-92 (pK _d 9.5) [1143], SANT-1 (pK _i 7.7) [441] – Mouse, cyclopamine-KAAD (pIC ₅₀ 7.7) [2760] – Mouse, cyclopamine (pIC ₅₀ ~7) [2877] – Mouse
Selective antagonists	vismodegib (pK _i 7.8) [2992]
Allosteric modulators (Positive)	GSA-10 (pEC ₅₀ 5.9) [946]
Comments	SANT-3 and SANT-4 are SMO antagonists [441]. Cyclopamine-KAAD can act as an inverse agonist [3099].

Comments: There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. Recent insights into protein dynamics, activation mechanisms, conserved microswitches, and co-receptor involvement of FZDs have advanced our understanding in being able to target this enigmatic class of receptors as drug targets [282, 956, 958, 1426, 2961]. Findings with recent reported small molecules were not reproducible, including

FzM1.8 and carbamazepine, highlighting the limitations in the assays available [1427, 2824]. Understanding of FZD and SMO coupling to heterotrimeric G proteins is incomplete, but progress has been made [88, 628, 648, 1398, 1805, 2306, 2307, 2395, 2581, 2959, 3098]. Development of pharmacological tools [1490] for SMO has been facilitated by successful determination of several SMO structures [356, 628, 1191, 1490, 2306, 2307, 2985, 2986, 3229, 3240]. The increase in FZD structures including FZD_{1,3,6,7}

in *apo* and active states and a recent FZD₄ complex with DEP have provided insights into FZD transmembrane organization and intracellular transducer coupling [1426, 2309, 2872, 3132, 3168, 3244]. FZD₇ has emerged as a particularly interesting WNT receptor by primarily modulating carcinogenesis, metastasis, and chemoresistance [1564]. Recent pharmacological and structural studies highlight FZD₇ in the context of intestinal cancer and its interaction with the virulence factor, TcdB [957, 1426].

Further reading on Class Frizzled GPCRs

- Angers *S et al.* (2009) Proximal events in Wnt signal transduction. *Nat Rev Mol Cell Biol* **10**: 468-77 [PMID:19536106]
- Kozielewicz *P et al.* (2020) Molecular Pharmacology of Class F Receptor Activation. *Mol Pharmacol* **97**: 62-71 [PMID:31591260]
- Schulte *G.* (2024) International Union of Basic and Clinical Pharmacology CXV: The Class F of G Protein-Coupled Receptors. *Pharmacol Rev* **76**: 1009-1037 [PMID:38955509]
- Schulte *G et al.* (2021) *In Pharmacology of the WNT Signaling System* Edited by Schulte *G*, Kozielewicz *P*: Springer Cham: 422 [ISBN: 9783030854980]
- Schulte *G et al.* (2024) Frizzleds act as dynamic pharmacological entities. *Trends Pharmacol Sci* **45**: 419-429 [PMID:38594145]
- Schulte *G et al.* (2018) Frizzleds as GPCRs - More Conventional Than We Thought! *Trends Pharmacol Sci* **39**: 828-842 [PMID:30049420]
- van Amerongen *R.* (2012) Alternative Wnt pathways and receptors. *Cold Spring Harb Perspect Biol* **4**: [PMID:22935904]
- Wang *Y et al.* (2016) Frizzled Receptors in Development and Disease. *Curr Top Dev Biol* **117**: 113-39 [PMID:26969975]

Complement peptide receptors

G protein-coupled receptors → Complement peptide receptors

Overview: Complement peptide receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Complement peptide receptors [1444]**) are activated by the endogenous ⁷⁵ amino-acid anaphylatoxin polypeptides **C3a** (**C3**, **P01024**) and **C5a** (**C5**, **P01031**), generated upon stimulation of the complement cascade. C3a and C5a exert their functions through binding to their receptors (C3a receptor, C5a receptor 1 and C5a receptor 2), causing cell recruitment and triggering cellular degranulation that contributes to local inflammation.

Nomenclature	C3a receptor
HGNC, UniProt	C3AR1 , Q16581
Potency order of endogenous ligands	C3a (C3 , P01024) > C5a (C5 , P01031) [57]
Agonists	E7 [59, 718, 2547], compound 17 [2367], JR14a [1406, 1750], compound 21 [2366], casoxin C [2762, 3198], TLQP-21 (VEGF , O15240) (Partial agonist) [1659], TLQP-21 (VEGF , O15240) [1659] – Mouse, albutensin A [2113, 3198], oryzatensin [1294, 2763, 3198]
Antagonists	SB290157 (SB290157 has also been reported to have agonist properties at the C3a receptor, and act as a weak C5aR2 activator) (pIC ₅₀ 7.6) [56, 1657]
Labelled ligands	[¹²⁵ I]C3a (human) (Agonist) [429], Eu-DTPA-hC3a (Agonist) [575]
Comments	Dual pro- and anti-inflammatory roles of C3a receptor have been reported in pathological conditions [548]. In particular, C3 and the C3a receptor have been identified as being involved in regulating the intestinal immune response during chronic colitis [2733, 3044]. Protective roles of the C3a receptor were reported for traumatic spinal cord injury [299], melanoma [2010] and systemic lupus erythematosus [1399]. C3a-C3a receptor signalling inhibits neural progenitor cell proliferation during neurodevelopment, playing a critical role in the normal development of the mammalian brain [448]. Inactivation of C3a receptor leads to decreased cytotoxic NK-cell infiltration into tumors [2029]. Moreover, a protective role for C3a receptor is described in experimental chronic pyelonephritis [3250].

Nomenclature	C5a ₁ receptor	C5a ₂ receptor
HGNC, UniProt	CSARI, P21730	C5AR2, Q9P296
Potency order of endogenous ligands	C5a (C5, P01031), C5a des-Arg (C5) > C3a (C3, P01024) [57]	C5a (C5, P01031), C5a des-Arg (C5) > C3a (C3, P01024) [57]
Endogenous agonists	C5a des-Arg (C5) (Partial agonist) [363], ribosomal protein S19 (RPS19, P39019) [3146]	C5a des-Arg (C5) (Partial agonist) [363, 2127], ribosomal protein S19 (RPS19, P39019) [3146]
Agonists	BM221 [943], NDT9513727 (Inverse agonist) [314], N-methyl-Phe-Lys-Pro-D-Cha-Cha-D-Arg-CO ₂ H [1360, 1472], BM213 (Biased agonist) [943], lactomedin 1 [2164, 3198]	C5a ^{pep} (Partial agonist) [2164]
Selective agonists	–	P59 (Biased agonist) [557], P32 (Biased agonist) [557]
Antagonists	avacopan (pIC ₅₀ 9.7) [184], W54011 (pK _i 8.7) [2727], DF2593A (pIC ₅₀ 8.3) [1970], ACT-1014-6470 (pIC ₅₀ 8) [1030], AcPhe-Orn-Pro-D-Cha-Trp-Arg (pIC ₅₀ 7.9) [3088], PMX205 (pIC ₅₀ 7.5) [1660, 1816], DF3016A (pIC ₅₀ 7.3) [295], N-methyl-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO ₂ H (pIC ₅₀ 7.2) [1472], DF3966A [555]	A8 ^{A71-73} (pIC ₅₀ ~6) [2146] – Mouse
Labelled ligands	[¹²⁵ I]C5a (human) (Agonist) [1198], Eu-DTPA-[Ser ²⁷ , Nle ⁷⁰]hC5a (Agonist) [944]	Eu-DTPA-[Ser ²⁷ , Nle ⁷⁰]hC5a (Agonist) [942], [¹²⁵ I]C5a (human) (Agonist)
Comments	The C5a ₁ receptor is currently referred to as C5aR1 in the literature. C5a ₁ has been an attractive target for pharmacological inhibition to treat a myriad of inflammatory and neurodegenerative diseases. Several C5a ₁ antagonists have been reported that have progressed to various stages of clinical development [1071, 1660, 1947], although none are yet approved for use in humans. The non-peptide C5aR1 inhibitor CCX168 (Avacopan®), developed by ChemoCentryx/Amgen, is currently the most clinically advanced C5aR ₁ inhibitor [184]. The drug was approved by the FDA in October 2021, as an adjunctive treatment in adults for severe active ANCA-associated vasculitis (specifically microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA)) in combination with standard therapy including glucocorticoids [1598]. Considering the potential benefits of blocking the C5a-C5a ₁ axis to limit myeloid infiltration and prevent excessive lung inflammation in Coronavirus disease 2019 (COVID-19) [391], the two anti-C5a/C5a ₁ blocking antibodies, avdoralimab (IPH5401) and vilobelimab (IFX-1), were studied in patients with COVID-19 severe pneumonia (NCT04371367 and NCT04333420) [2952]. Vilobelimab was provided emergency use authorization by the FDA (in April 2023) for the treatment of COVID-19 in hospitalized adults [755].	The C5a ₂ receptor is commonly referred to as C5L2 and C5aR2 in the literature. C5a ₂ was traditionally recognized as a decoy receptor for C5a, as it has no reported G protein signalling capacity. New research however, shows C5a ₂ is capable of mediating its own set of signalling events and immunomodulatory actions, not only towards C5a ₁ but also other complement, chemokine and pattern recognition receptors [1656].

Comments: SB290157 has also been reported to have agonist properties at the C3a receptor [1657, 1836]. JR14a, originally reported as an antagonist, has since been shown to exert full agonist activity [1406]. The chemoattractant receptor C5a₂ (also known as GPR77, C5L2) binds C5a and has putative roles in either opposing or promoting inflammatory responses [363, 847, 873, 1658, 2165]. Binding to this site may be displaced with the rank order C5a des-Arg (C5) > C5a (C5, P01031) [363, 2127] while there is controversy over the ability of C3a (C3, P01024) and C3a des Arg (C3, P01024) to compete [1158, 1327, 1328, 2127]. C5a₂ appears to lack G protein signalling and has been termed a decoy receptor

[2542]. However, C5a₂ does recruit β-arrestin 2 after ligand binding, which might provide a signalling pathway for this receptor [137, 2914], and forms heteromers with C5a₁. A recent study has identified p90RSK (90kDa ribosomal s6 kinase) phosphorylation as a potential signalling pathway for C5a₂ [2163]. C5a, but not C5a des Arg, induces upregulation of heterodimer formation between complement C5a receptors C5a₁ and C5a₂ [556]. There are also reports of pro-inflammatory activity of C5a₂, mediated by HMGB1, likely through AKT and MAPK signalling pathways (reviewed in [1651, 3238]). In T cells it has been shown that C5a₁ and C5a₂ act in opposition to each other and that altering the

equilibrium between the two receptors, by differential expression or production of C5a des Arg (which favours C5a₂), can affect the final cellular response [76]. In human macrophages, C5a₂ was observed to modulate multiple complement and chemokine receptor-mediated signalling and pattern recognition-induced cytokine responses, independent of C5a₁ [1656]. In addition, C5a₂ is reported to act as a C5a transporter on endothelial cells, and is required for the transport of C5a into the vessel lumen and the subsequent neutrophil arrest in arthritis [1924].

Further reading on Complement peptide receptors

- Coulthard LG *et al.* (2015) Is the complement activation product C3a a proinflammatory molecule? Re-evaluating the evidence and the myth. *J Immunol* **194**: 3542-8 [PMID:25848071]
- Cui CS *et al.* (2025) Colon-targeted complement C5a₁ receptor inhibition using pH-sensitive nanoparticles ameliorates experimental colitis. *Br J Pharmacol* **182**: 3852-3869 [PMID:40288760]
- Hubler F *et al.* (2024) Discovery and Characterization of a New Class of C5aR1 Antagonists Showing *In Vivo* Activity. *J Med Chem* **67**: 4100-4119 [PMID:38482828]
- Laumonier Y *et al.* (2017) Novel insights into the expression pattern of anaphylatoxin receptors in mice and men. *Mol Immunol* **89**: 44-58 [PMID:28600003]
- Li F *et al.* (2025) Knockdown of C3aR alleviates age-related bone loss via activation of YAP1/β-catenin signaling. *J Biol Chem* **301**: 108500 [PMID:40216253]
- Li XX *et al.* (2025) The complement system: Biology, pathology, and therapeutic interventions. *Pharmacol Rev* **77**: 100079 [PMID:40683108]
- Mishra S *et al.* (2025) Molecular fingerprints of a convergent mechanism orchestrating diverse ligand recognition and species-specific pharmacology at the complement anaphylatoxin receptors. *bioRxiv* [PMID:40501890]
- West EE *et al.* (2024) Complement in human disease: approved and up-and-coming therapeutics. *Lancet* **403**: 392-405 [PMID:37979593]
- Yadav MK *et al.* (2023) Molecular basis of anaphylatoxin binding, activation, and signaling bias at complement receptors. *Cell* **186**: 4956-4973.e21 [PMID:37852260]

Corticotropin-releasing factor receptors

G protein-coupled receptors → Corticotropin-releasing factor receptors

Overview: Corticotropin-releasing factor (CRF, **nomenclature as agreed by the NC-IUPHAR subcommittee on Corticotropin-releasing Factor Receptors** [1068]) receptors are activated by the endogenous peptides **corticotrophin-releasing hormone** (*CRH*, P06850), a 41 amino-acid peptide, **urocortin 1** (*UCN*, P55089), 40 amino-acids, **urocortin 2** (*UCN2*, Q96RP3), 38 amino-acids and **urocortin 3** (*UCN3*, Q969E3), 38 amino-acids. CRF₁ and CRF₂ receptors are activated non-selectively by CRH

and UCN. CRF₂ receptors are selectively activated by UCN2 and UCN3. Binding to CRF receptors can be conducted using radioligands [¹²⁵I]Tyr⁰-CRF or [¹²⁵I]Tyr⁰-sauvagine with K_d values of 0.1-0.4 nM. CRF₁ and CRF₂ receptors are non-selectively antagonized by α-helical CRF, **D-Phe-CRF-(12-41)** and **astressin**. CRF₁ receptors are selectively antagonized by small molecules **NBI27914**, **R121919**, **antalarmin**, **CP 154,526**, **CP 376,395**. CRF₂ receptors are selectively antagonized by **antisauvagine** and **astressin 2B**. Al-

though selective small molecule CRF₁ receptor antagonists were not effective in treating major depressive disorder, posttraumatic stress disorder, or alcohol use disorder in clinical trials, recent phase 2 studies have found that CRF₁ receptor antagonists effectively reduce adrenocortical androgens and precursors in congenital adrenal hyperplasia [2059].

Nomenclature	CRF ₁ receptor	CRF ₂ receptor
HGNC, UniProt	<i>CRHR1</i> , P34998	<i>CRHR2</i> , Q13324
Endogenous agonists	urocortin 1 (<i>UCN</i> , P55089) [582, 584, 663], corticotrophin-releasing hormone (<i>CRH</i> , P06850) [446, 581, 584, 663, 2156, 2936]	urocortin 1 (<i>UCN</i> , P55089) [582, 584], urocortin 2 (<i>UCN2</i> , Q96RP3) [582], urocortin 3 (<i>UCN3</i> , Q969E3) [582], corticotrophin-releasing hormone (<i>CRH</i> , P06850) [584]
Antagonists	crinecerfont (pK _i 8.7) [998], astressin (pK _i 8.7) [2399], tildacerfont (pK _i >8.3) [457], verucerfont (pK _i 8.2) [2801], pexacerfont (pIC ₅₀ 6.5) [1929]	astressin (pIC ₅₀ 9.2) [2397]
Selective antagonists	CP 154,526 (pIC ₅₀ 9.3-10.4) [1748] – Rat, DMP696 (pK _i 8.3-9) [1085], NBI27914 (pK _i 8.3-9) [435], R121919 (pK _i 8.3-9) [3274], antalarmin (pK _i 8.3-9) [3034], NBI-35965 (pK _i 8.4) [1912] – Rat, CP 376,395 (pIC ₅₀ 8.3) [455] – Rat, CRA1000 (pIC ₅₀ 6.4-7.1) [414]	antisauvagine (pK _d 8.8-9.6) [584], K41498 (pK _i 9.2) [1571], astressin 2B (pIC ₅₀ 8.9) [2397], K31440 (pK _i 8.7-8.8) [2436]

Comments: A CRF binding protein has been identified (*CRHBP*, P24387) to which both **corticotrophin-releasing hormone** (*CRH*, P06850) and **urocortin 1** (*UCN*, P55089) bind with high affinities, which has been suggested to bind and inactivate circulating **corticotrophin-releasing hormone** (*CRH*, P06850) [591, 2214].

Further reading on Corticotropin-releasing factor receptors

- Deussing JM *et al.* (2018) The Corticotropin-Releasing Factor Family: Physiology of the Stress Response. *Physiol Rev* **98**: 2225-2286 [PMID:30109816]
- Grammatopoulos DK *et al.* (2017) CRH Receptor Signalling: Potential Roles in Pathophysiology. *Curr Mol Pharmacol* **10**: 296-310 [PMID:28103786]
- Hauger RL *et al.* (2003) International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. *Pharmacol Rev* **55**: 21-6 [PMID:12615952]
- Liapakis G *et al.* (2011) Members of CRF family and their receptors: from past to future. *Curr Med Chem* **18**: 2583-600 [PMID:21568890]
- Ma S *et al.* (2020) Molecular Basis for Hormone Recognition and Activation of Corticotropin-Releasing Factor Receptors. *Mol Cell* **77**: 669-680.e4 [PMID:32004470]
- Matsoukas MT *et al.* (2024) Structural and Functional Insights into CRF Peptides and Their Receptors. *Biology (Basel)* **13**: [PMID:38392338]
- Parra-Mercado GK *et al.* (2019) CRF₁ Receptor Signaling via the ERK1/2-MAP and Akt Kinase Cascades: Roles of Src, EGF Receptor, and PI3-Kinase Mechanisms. *Front Endocrinol (Lausanne)* **10**: 869 [PMID:31920979]
- Slater PG *et al.* (2016) Corticotropin-Releasing Factor Receptors and Their Interacting Proteins: Functional Consequences. *Mol Pharmacol* **90**: 627-632 [PMID:27612874]

Dopamine receptors

G protein-coupled receptors → Dopamine receptors

Overview: Dopamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Dopamine Receptors** [2534]) are commonly divided into D₁-like (D₁ and D₅) and D₂-like (D₂, D₃ and D₄) families, where the endogenous agonist is **dopamine**.

Nomenclature	D ₁ receptor	D ₂ receptor
HGNC, UniProt	<i>DRD1</i> , P21728	<i>DRD2</i> , P14416
Sub/family-selective labelled ligands	[¹²⁵ I]SCH23982 (Antagonist) (pK _d 9.5) [613], [³ H]SCH-23390 (Antagonist) (pK _d 9.5) [3257]	[³ H]spiperone (Antagonist) (pK _d 10.2) [340, 1141, 3253] – Rat
Endogenous agonists	dopamine [2732, 2830]	dopamine [346, 813, 2490]
Agonists	fenoldopam [2830]	rotigotine [649], cabergoline (Partial agonist) [1903], aripiprazole (Partial agonist) [3212], bromocriptine [813, 1903, 2490], MLS1547 (Biased agonist) [812], ropinirole [1094], apomorphine (Partial agonist) [346, 813, 1903, 2490, 2659], pramipexole [1897, 2490], benzquinamide [970]
Sub/family-selective agonists	A68930 [2055], SKF-38393 (Partial agonist) [2732, 2830]	quinpirole [346, 1897, 2181, 2659, 2661, 2918]
Selective agonists	SKF-83959 (Biased agonist) [533], A77636 [2450], SKF-81297 [65] – Rat	sumanirole [1855]
Antagonists	flupentixol (pK _i 7–8.4) [2732, 2830]	blonanserin (pK _i 9.9) [2105], pipotiazine (pK _i 9.7) [2660], perphenazine (pK _i 8.9–9.6) [1503, 2552], risperidone (pK _i 9.4) [86], perospirone (pK _i 9.2) [2553], trifluoperazine (pK _i 8.9–9) [1503, 2554], quetiapine (pK _i 7.2) [86]
Sub/family-selective antagonists	SCH-23390 (pK _i 7.4–9.5) [2732, 2830], SKF-83566 (pK _i 9.5) [2732], ecopipam (pK _i 8.3) [2831]	haloperidol (pK _i 7.4–8.8) [813, 1769, 1897, 2659, 2831]
Selective antagonists	–	L-741,626 (pK _i 7.9–8.5) [985, 1518], domperidone (pK _i 7.9–8.4) [813, 2659], raclopride (pK _i 8) [1905], ML321 (pK _i 7) [3120, 3121]
Labelled ligands	–	[³ H]raclopride (Antagonist) (pK _d 8.9) [1459] – Rat

	D ₃ receptor	D ₄ receptor	D ₅ receptor
Nomenclature	D ₃ receptor	D ₄ receptor	D ₅ receptor
HGNC, UniProt	DRD3 , P35462	DRD4 , P21917	DRD5 , P21918
Sub/family-selective labelled ligands	–	[³ H]spiperone (Antagonist) (pK _d 9.5) [1120 , 2918]	[³ H]SCH-23390 (Antagonist) (pK _d 9.2) [2380]
Endogenous agonists	dopamine [346 , 813 , 2490 , 2661]	dopamine [2918]	dopamine [2732]
Agonists	cariprazine (Partial agonist) [1432], pramipexole [1897 , 2490], bromocriptine (Partial agonist) [813 , 1903 , 2490], ropinirole [1094], apomorphine (Partial agonist) [346 , 813 , 1903 , 2490 , 2659]	apomorphine (Partial agonist) [1903]	–
Sub/family-selective agonists	quinpirole [346 , 1897 , 1905 , 2181 , 2490 , 2659 , 2661 , 2918]	quinpirole [1903 , 2181 , 2918]	A68930 [2055]
Selective agonists	PD 128907 [2298 , 2490]	PD168,077 (Partial agonist) [1480] – Rat, A412997 [1959] – Rat, A412997 [1959]	–
Antagonists	perospirone (pK _i 9.6) [2659], sertindole (pK _i 8–8.8) [86 , 2527 , 2552], prochlorperazine (pK _i 8.4) [100], (-)-sulpiride (pK _i 6.7–7.7) [813 , 2659 , 2787], loxapine (pK _i 7.7) [2552], domperidone (pK _i 7.1–7.6) [813 , 2659], promazine (pK _i 6.8) [347]	perospirone (pK _i 10.1) [2555], sertindole (pK _i 7.8–9.1) [347 , 2552 , 2554 , 2555], sonepiprazole (pK _i 8.9) [2513], loxapine (pK _i 8.1) [2554]	–
Sub/family-selective antagonists	haloperidol (pK _i 7.5–8.6) [813 , 2570 , 2659 , 2831]	haloperidol (pK _i 8.7–8.8) [1541 , 2570 , 2831]	SCH-23390 (pK _i 7.5–9.5) [2732], SKF-83566 (pK _i 9.4) [2732], ecopipam (pK _i 8.3) [2732]
Selective antagonists	S33084 (pK _i 9.6) [1902], nafadotride (pK _i 9.5) [2491], PG01037 (pK _i 9.2) [986], NGB 2904 (pK _i 8.8) [3117], SB 277011-A (pK _i 8) [2363], (+)-S-14297 (pK _i 6.9–7.9) [1900 , 1905]	L745870 (pK _i 9.4) [1518], A-381393 (pK _i 8.8) [2023], L741742 (pK _i 8.5) [2431], ML398 (pK _i 7.4) [207]	–
Selective allosteric modulators	SB269652 (Negative) (pK _i ~9) [831]	–	–
Labelled ligands	[³ H]spiperone (Antagonist) (pK _d 9.9) [1141 , 3253] – Rat, [³ H]7-OH-DPAT (Agonist) [2381], [³ H]PD128907 (Agonist) [35]	[¹²⁵ I]L750667 (Antagonist) (pK _d 9.8) [2181], [³ H]NGD941 (Antagonist) (pK _d 8.3) [2284]	[¹²⁵ I]SCH23982 (Antagonist) (pK _d 9.1)

Comments: The selectivity of many of these agents is less than two orders of magnitude. [³H]raclopride exhibits similar high affinity for D₂ and D₃ receptors (low affinity for D₄), but has been used to label D₂ receptors in the presence of a D₃-selective antagonist. [³H]7-OH-DPAT has similar affinity for D₂ and D₃ receptors, but labels only D₃ receptors in the absence of divalent cations. The pharmacological profile of the D₅ receptor is similar to, yet distinct from, that of the D₁ receptor. The splice variants of the D₂ receptor are commonly termed D_{2S} and D_{2L} (short and long). The *DRD4* gene encoding the D₄ receptor is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 to 515.

Further reading on Dopamine receptors

- Beaulieu JM *et al.* (2015) Dopamine receptors - IUPHAR Review 13. *Br J Pharmacol* **172**: 1-23 [[PMID:25671228](#)]
- Beaulieu JM *et al.* (2011) The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev* **63**: 182-217 [[PMID:21303898](#)]
- Bonifazi A *et al.* (2019) Novel and Potent Dopamine D₂ Receptor Go-Protein Biased Agonists. *ACS Pharmacol Transl Sci* **2**: 52-65 [[PMID:30775693](#)]
- Cumming P. (2011) Absolute abundances and affinity states of dopamine receptors in mammalian brain: A review. *Synapse* **65**: 892-909 [[PMID:21308799](#)]
- Dorogan M *et al.* (2024) Natural Product-Inspired Dopamine Receptor Ligands. *J Med Chem* **67**: 12463-12484 [[PMID:39038276](#)]
- Moritz AE *et al.* (2018) Advances and challenges in the search for D₂ and D₃ dopamine receptor-selective compounds. *Cell Signal* **41**: 75-81 [[PMID:28716664](#)]
- Urs NM *et al.* (2017) New Concepts in Dopamine D₂ Receptor Biased Signaling and Implications for Schizophrenia Therapy. *Biol Psychiatry* **81**: 78-85 [[PMID:27832841](#)]
- Zhuang Y *et al.* (2021) Structural insights into the human D1 and D2 dopamine receptor signaling complexes. *Cell* **184**: 931-942.e18 [[PMID:33571431](#)]

Endothelin receptors

G protein-coupled receptors → Endothelin receptors

Overview: Endothelin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Endothelin Receptors** [585]) are activated by the endogenous 21 amino-acid peptides endothelins 1-3 (**endothelin-1** (*EDN1*, P05305), **endothelin-2** (*EDN2*, P20800) and **endothelin-3** (*EDN3*, P14138)).

Nomenclature	ET _A receptor	ET _B receptor
HGNC, UniProt	<i>EDNRA</i> , P25101	<i>EDNRB</i> , P24530
Potency order of endogenous ligands	endothelin-1 (<i>EDN1</i> , P05305) = endothelin-2 (<i>EDN2</i> , P20800) > endothelin-3 (<i>EDN3</i> , P14138) [1782]	endothelin-1 (<i>EDN1</i> , P05305) = endothelin-2 (<i>EDN2</i> , P20800), endothelin-3 (<i>EDN3</i> , P14138) [2463]
Selective agonists	–	sarafotoxin S6c [1508, 2441], BQ 3020 [2376], [Ala ^{1,3,11,15}]ET-1 [1935], sovateltide [2342, 3023]
Antagonists	SB209670 (pK _B 9.4) [717] – Rat, TAK 044 (pA ₂ 8.4) [3026] – Rat, bosentan (pA ₂ 7.2) [519] – Rat, aprocitentan (pA ₂ 6.7) [1211]	SB209670 (pK _B 9.4) [717] – Rat, TAK 044 (pA ₂ 8.4) [3026] – Rat, bosentan (pK _i 7.1) [519], aprocitentan (pA ₂ 5.5) [1211]
Selective antagonists	clazosentan (pA ₂ 9.5) [2429], macitentan (pIC ₅₀ 9.3) [252], atrasentan (pA ₂ 9.2) [2140], zibotentan (pIC ₅₀ 8.3) [1982], sitaxsentan (pA ₂ 8) [3100], FR139317 (Inverse agonist) (pIC ₅₀ 7.3–7.9) [1782], BQ123 (pA ₂ 6.9–7.4) [1782], ambrisentan (pA ₂ 7.1) [253]	K-8794 (pIC ₅₀ 8.2) [2589], A192621 (pK _d 8.1) [2957], BQ788 (pK _d 7.9–8) [2441], IRL 2500 (pK _d 7.2) [2441], Ro 46-8443 (pIC ₅₀ 7.2) [301]
Labelled ligands	[¹²⁵ I]PD164333 (Antagonist) (pK _d 9.6–9.8) [588], [³ H]S0139 (Antagonist) (pK _d 9.2) [1899], [¹²⁵ I]PD151242 (Antagonist) (pK _d 9–9.1) [589], [³ H]BQ123 (Antagonist) (pK _d 8.5) [1217]	[¹²⁵ I]IRL1620 (Agonist) [2025], [¹²⁵ I]BQ3020 (Agonist) [1052, 1935, 2224], [¹²⁵ I][Ala ^{1,3,11,15}]ET-1 (Agonist) [1935]

Comments: Splice variants of the ET_A receptor have been identified in rat pituitary cells; one of these, ET_AR-C13, appeared to show loss of function with comparable plasma membrane expression to wild type receptor [1063]. Subtypes of the ET_B receptor have been proposed, although gene disruption studies in mice suggest that only a single gene product exists [1926]. Cryogenic-electron microscopy structures of ET_A and ET_B bound to **endothelin-1** (*EDN1*, P05305) and ET_B bound to **sovateltide** (IRL1620)

[1286] and crystal structures of the ET_B receptor complexed with non-selective agonists **endothelin-1** (*EDN1*, P05305) [2588] and **sarafotoxin S6b** [1248], ET_B selective agonists **endothelin-3** (*EDN3*, P14138) and **sovateltide** (IRL1620) [2587], inverse agonist **IRL 2500** [2015], and clinically relevant non-selective antagonist **bosentan** and the ET_B selective analogue **K-8794** [2589] have been reported. **Sparsentan** is a combined ET_A and AT₁ receptor antagonist [1487]. ET_A-selective (**ambrisentan**) and mixed ET_A/

ET_B (**bosentan**, **macitentan**) antagonists are approved for use in pulmonary arterial hypertension (PAH) [9, 2576]. The mixed antagonist, **aprocitentan** has been approved for use in resistant hypertension [634]. **Atrasentan**, an ET_A selective antagonist is approved for use in primary IgA nephropathy [1366] and the ET_B selective agonist, **sovateltide** is approved for use in cerebral ischaemic stroke [1367].

Further reading on Endothelin receptors

- Abraham GR *et al.* (2023) Current and future strategies for targeting the endothelin pathway in cardiovascular disease. *Nat Cardiovasc Res* **2**: 972-990 [PMID:39196099]
- Davenport AP *et al.* (2016) Endothelin. *Pharmacol Rev* **68**: 357-418 [PMID:26956245]
- Dhaun N *et al.* (2019) Endothelins in cardiovascular biology and therapeutics. *Nat Rev Cardiol* **16**: 491-502 [PMID:30867577]
- Harrison M *et al.* (2024) Endothelin-1 and Its Role in Cancer and Potential Therapeutic Opportunities. *Biomedicines* **12**: [PMID:38540124]
- Hou J *et al.* (2024) Structural basis of antagonist selectivity in endothelin receptors. *Cell Discov* **10**: 79 [PMID:39075075]
- Ko CJ *et al.* (2022) Endothelin 2: a key player in ovulation and fertility. *Reproduction* **163**: R71-R80 [PMID:35167488]
- Maguire JJ *et al.* (2014) Endothelin@25 - new agonists, antagonists, inhibitors and emerging research frontiers: IUPHAR Review 12. *Br J Pharmacol* **171**: 555S-72 [PMID:25131455]
- Smeijer JD *et al.* (2025) Endothelin receptor antagonists in chronic kidney disease. *Nat Rev Nephrol* **21**: 175-188 [PMID:39643698]

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

Endothelin receptors S76

Formylpeptide receptors

G protein-coupled receptors → Formylpeptide receptors

Overview: The human formylpeptide receptor subfamily of GPCRs (FPR: nomenclature described in [2311, 3179] [1, 2]) comprises three members (FPR1, FPR2, and FPR3). Two of these, FPR1 and FPR2, recognize peptides bearing N-terminal formyl-Met from invading bacteria [1498] or mitochondria. These peptides func-

tion as danger signals in innate immunity. FPR1 and FPR2 are promiscuous and also recognize several non-formylated peptides, proteins, lipids and small molecules [1498, 2311, 3179] of which some are able to initiate signals (balanced or biased) that mediate pro-inflammatory and/or inflammation resolving effects [1880,

2218]. In contrast, FPR3 remains less well-characterized in part due to the absence of selective ligands which has significantly impeded progress in its functional characterization [632, 2324].

Nomenclature	FPR1	FPR2	FPR3
HGNC, UniProt	<i>FPR1</i> , P21462	<i>FPR2</i> , P25090	<i>FPR3</i> , P25089
Potency order of endogenous agonists	–	Lipid mediators for resolution of inflammation: LXA_4 = aspirin triggered lipoxin A4 = ATLa2 = resolvin D1 > LTC_4 = LTD_4 >> 15-deoxy- LXA_4 >> C16:0 ceramide Proteins and peptides for balanced activation: fMLKLIV = fMTPMRKINPLMKLIN > serum amyloid A (<i>SAAI</i> , <i>PODJI8</i>) > LL-37 (<i>CAMP</i> , P49913) [517, 610, 776, 778, 833, 979, 1682, 2717, 2765]	–
Potency order of endogenous ligands	mitochondrial peptide fMMYALF > fMLKLIV > mitochondrial peptide fMFADRW > annexin I-(2-26) (<i>ANXA1</i> , P04083) [833, 1083]	–	–
Potency order of endogenous ligands and other agonists	fMet-Leu-Phe-Ile-Ile > fMet-Leu-Phe > compound 43 > AG-14 > annexin I-(2-26) (<i>ANXA1</i> , P04083) > compound 17b [1083, 2323, 2658, 3179, 3182]	For lipid mediators (resolving) LXA_4 = aspirin triggered lipoxin A4 = ATLa2 = resolvin D1 >> 15-deoxy- LXA_4 > C16:0 ceramide For other ligands: WKYMVm > BMS-986235 > ACT-389949 > mitochondrial formyl peptides [517, 776, 778, 833, 853, 979, 1586, 1682, 2204, 2217, 2310, 2323, 2765]	–
Endogenous agonists	–	LXA_4 [776], resolvin D1 [1500], serum amyloid A (<i>SAAI</i> , <i>PODJI8</i>) [2717], annexin I-(2-26) (<i>ANXA1</i> , P04083) [872, 1080, 2216, 2980], LL-37 (<i>CAMP</i> , P49913) [610], LTC_4 , LTD_4 , resolvin D3 [2097]	F2L (<i>HEBP1</i> , Q9NRV9) [632, 1898]
Agonists	compound 43 [1082] – Mouse, AG-14 [2507], annexin I-(2-26) (<i>ANXA1</i> , P04083) [872, 2980], compound 17b [507, 3182], mitochondrial peptide fMMYALF [833, 2323], mitochondrial peptide fMFADRW [833, 2323]	WKYMVm [1586], ACT-389949 [2685]	–
Selective agonists	fMet-Leu-Phe [815, 2605], fMet-Leu-Phe-Ile-Ile [1083]	BMS-986235 [91], ATLa2 [996]	–
Antagonists	t-Boc-FLFLF (pK _i 6–6.5) [3049], T-0080 [1662]	WRWWWW (pIC ₅₀ 6.6) [121], t-Boc-FLFLF (pIC ₅₀ 4.3–6) [814, 2693]	–
Selective antagonists	AZ2158 (pK _d 7.7) [1976], cyclosporin H (pK _i 6.1–7.1) [3049, 3154]	PBP10 (pIC ₅₀ 7) [795], quin-C7 (pEC ₅₀ 5.2) [3254]	–
Labelled ligands	[³ H]fMet-Leu-Phe (Agonist) [1474]	[³ H] LXA_4 (Agonist) [776, 777], [¹²⁵ I-Tyr]Ac2-26 (Agonist) [2216]	–

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

Formylpeptide receptors S77

Comments	A FITC-conjugated fMLF analogue has been used for binding to the mouse recombinant receptor [1082]. Agonist non-mitochondrial formyl peptides are also reported [1400]. Natural and synthetic compounds (<i>e.g.</i> T-0080) are described as antagonists [1662, 2506, 2693].	Ceramide (C14:0, C16:0, C18:0) [1682], formyl peptides (fMLKLIV, fMTPMRKINPLMKLIN) [833, 2323] and A β ₄₂ are endogenous agonists [2832]. Other agonists include PSM α peptides [2351], HIVgp120 [624] and synthetic molecules such as BMS-986235, ACT-389949 and Quin-C1 [2028]. New potent FPR2 agonists confirm this receptor's anti-inflammatory, pro-resolving and neuroprotective functions [802].
----------	--	--

Comments: Note that the data for FPR2 are also reproduced on the leukotriene receptor page under the heading "the FPR2/ALX receptor". It should also be noted that some of the specialized pro-resolving mediators are, in addition to the FPRs, also recognized by other GPCRs and they are present at very low levels as endogenous mediators for resolution of inflammation [2504]. Since potency for different FPR agonists determined in many different research laboratories is dependent on the assay systems used, direct comparison of potency may be difficult for FPR agonists with anti-inflammatory and pro-resolving activities. For this reason, the pro-resolving lipid mediators are listed in one group and ligands with balanced agonistic activities are listed in another group for potency comparison. The biased signaling characteristics of some of the FPR agonists must be taken into consider-

ation when their potencies are compared [880, 1690, 2734]. FPR1 has been reported to be the plague receptor on host immune cells [2143] and as co-receptor for HIV [3036], but these findings have to be further explored [879]. Some FPR2 ligands suggested to allosterically modulate receptor function activate the receptor in a classical but functionally selective mode [3083], whereas allosteric modulatory effects of other compounds cause changes in receptor conformational states and receptor signaling [880]. The 3-D structure of FPR1/2 has been solved and the FPR2 structure reveals a large binding pocket that can accommodate ligands of different shapes and sizes for the generation of different conformational changes [1665]. Studies have been conducted to explore the mechanisms by which primarily FPR2 mediates both pro-inflammatory and anti-inflammatory signaling in a ligand-

dependent manner. It should be noted, however, that some of the not yet clearly identified anti-inflammatory signals, are generated by agonists that preferentially activate FPR1 [2310]. The status of FPR2 dimerization is a determining factor for ligand-specific conformational changes leading to biased signaling [535]. There is also a report on ligand concentration-dependent dual modulation of FPR2 for receptor-activation vs. anti-inflammatory activities [872], and ligand concentration-dependent modulation of FPR1 functions has also been reported [2997]. FPR ligands are attractive candidates for promoting the resolution of inflammation, enhancing innate immune defense and tuning immune responses in inflammatory/auto-immune diseases and tumor microenvironments [571, 2991].

Further reading on Formylpeptide receptors

- Dahlgren C *et al.* (2016) Basic characteristics of the neutrophil receptors that recognize formylated peptides, a danger-associated molecular pattern generated by bacteria and mitochondria. *Biochem Pharmacol* **114**: 22-39 [PMID:27131862]
- Dorward DA *et al.* (2015) The Role of Formylated Peptides and Formyl Peptide Receptor 1 in Governing Neutrophil Function during Acute Inflammation. *Am J Pathol* **185**: 1172-1184 [PMID:25791526]
- Krepel SA *et al.* (2019) Chemotactic Ligands that Activate G-Protein-Coupled Formylpeptide Receptors. *Int J Mol Sci* **20**: [PMID:31336833]
- Mun B *et al.* (2024) Structural basis for the access and binding of resolvin D1 (RvD1) to formyl peptide receptor 2 (FPR2/ALX), a class A GPCR. *bioRxiv* [PMID:39386527]
- Nunes VS *et al.* (2023) ALX/FPR2 Activation by Stereoisomers of D1 Resolvins Elucidating with Molecular Dynamics Simulation. *J Phys Chem B* **127**: 6479-6486 [PMID:37428488]
- Nunes VS *et al.* (2025) ALX/FPR2 Receptor Activation by Inflammatory (fMLFII) and Pro-resolving (LXA₄ and RvD3) Agonists. *ACS Phys Chem Au* **5**: 367-374 [PMID:40727226]
- Perretti M *et al.* (2020) Formyl peptide receptor type 2 agonists to kick-start resolution pharmacology. *Br J Pharmacol* **177**: 4595-4600 [PMID:32954491]
- Yazid S *et al.* (2012) Anti-inflammatory drugs, eicosanoids and the annexin A1/FPR2 anti-inflammatory system. *Prostaglandins Other Lipid Mediat* **98**: 94-100 [PMID:22123264]
- Ye RD *et al.* (2009) International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol Rev* **61**: 119-61 [PMID:19498085]

Free fatty acid receptors

G protein-coupled receptors → Free fatty acid receptors

Overview: Free fatty acid receptors (FFA, **nomenclature as agreed by the NC-IUPHAR Subcommittee on free fatty acid receptors** [586, 2703]) are activated by free fatty acids. Long-chain saturated and unsaturated fatty acids (including C14:0 (myristic acid), C16:0 (palmitic acid), C18:1 (oleic acid), C18:2 (linoleic acid), C18:3, (α -linolenic acid), C20:4 (arachidonic acid), C20:5,n-3 (EPA) and C22:6,n-3 (docosahexaenoic acid)) activate FFA1 [308, 1241, 1483] and FFA4 receptors [1130, 1208, 2111], while short chain fatty acids (C2 (acetic acid), C3 (propanoic acid), C4 (butyric acid) and C5 (pentanoic acid)) activate FFA2 [319, 1585, 2078] and FFA3 [319, 1585] receptors. The crystal structure for agonist bound FFA1 has been described [2679].

Nomenclature	FFA1 receptor	FFA2 receptor
HGNC, UniProt	<i>FFAR1</i> , O14842	<i>FFAR2</i> , O15552
Endogenous agonists	docosahexaenoic acid [308, 1241], α -linolenic acid [308, 1241, 1483], oleic acid [308, 1241, 1483], myristic acid [308, 1241, 1483]	propanoic acid [319, 1585, 2078, 2515], acetic acid [319, 1585, 2078, 2515], butyric acid [319, 1585, 2078, 2515], <i>trans</i> -2-methylcrotonic acid [2515]
Agonists	HWL-088 [451]	1-methylcyclopropanecarboxylic acid [2515]
Selective agonists	AMG-837 [1679], compound 4 [493], TUG-770 [492], TUG-905 [491], GW9508 (Partial agonist) [307], fasiglifam [1326, 2045, 2679, 2871]	TUG-1375 [1041]
Selective antagonists	GW1100 (pIC ₅₀ 6) [307, 2702]	GLPG0974 (pIC ₅₀ 8.1) [2027, 2254], CATPB (pIC ₅₀ 6.5) [1196]
Comments	A wide range of both saturated and unsaturated fatty acids containing from 6 to 22 carbons have been shown to act as agonists at FFA1 [308, 1241, 1483]. Antagonist GW1100 is also an oxytocin receptor antagonist [307]. Fasiglifam, TUG-770 and GW9508 are approximately 100 fold selective for FFA1 over FFA4 [307, 492, 2045]. AMG-837 and the related analogue AM6331 have been suggested to have an allosteric mechanism of action at FFA1, with respect to the orthosteric fatty acid binding site [1679, 3128].	–

Nomenclature	FFA3 receptor	FFA4 receptor	<i>GPR42</i>
HGNC, UniProt	<i>FFAR3</i> , O14843	<i>FFAR4</i> , Q5NUL3	<i>GPR42</i> , O15529
Endogenous agonists	propanoic acid [319, 1585, 2515, 3127], butyric acid [319, 1585, 2515, 3127]	α -linolenic acid [2595], myristic acid [3031], α -linolenic acid [2783] – Rat, oleic acid [3031]	–
Agonists	1-methylcyclopropanecarboxylic acid [2515], acetic acid [319, 1585, 2515, 3127]	–	–
Selective agonists	–	compound A [2110], TUG-891 [2595], NCG21 [2742]	–
Comments	Beta-hydroxybutyrate has been reported to antagonise FFA3 responses to short chain fatty acids [1419]. A range of FFA3 selective molecules with agonist and antagonist properties, but which bind at sites distinct from the short chain fatty acid binding site (<i>i.e.</i> allosteric modulators), have been described [256, 1195, 1761].	A wide range of both saturated and unsaturated fatty acids containing from 6 to 22 carbons have been shown to act as agonists at FFA4 [494] with a small subset listed above. Compound A [PMID 24997608] exhibits more than 1000 fold selectivity [2110], and TUG-891 50-1000 fold selectivity for FFA4 over FFA1 [2595], dependent on the assay. NCG21 exhibits approximately 15 fold selectivity for FFA4 over FFA1 [2730].	–

Comments: Short (361 amino acids) and long (377 amino acids) splice variants of human FFA4 have been reported [1958], which differ by a 16 amino acid insertion in intracellular loop 3, and exhibit differences in intracellular signalling properties in recombinant systems [3031]. The long FFA4 splice variant has not been identified in other primates or rodents to date [1130, 1958]. *GPR42* was originally described as a pseudogene within the family (ENSM0025000002583), but the discovery of several polymorphisms suggests that some versions of *GPR42* may be functional [1666]. *GPR84* is a structurally-unrelated G protein-coupled receptor which has been found to respond to medium chain fatty acids [2996].

Further reading on Free fatty acid receptors

- Bolognini D *et al.* (2016) The Pharmacology and Function of Receptors for Short-Chain Fatty Acids. *Mol Pharmacol* **89**: 388-98 [PMID:26719580]
- Mancini AD *et al.* (2013) The fatty acid receptor FFA1/GPR40 a decade later: how much do we know? *Trends Endocrinol Metab* **24**: 398-407 [PMID:23631851]
- Milligan G *et al.* (2017) Complex Pharmacology of Free Fatty Acid Receptors. *Chem Rev* **117**: 67-110 [PMID:27299848]
- Moniri NH. (2016) Free-fatty acid receptor-4 (GPR120): Cellular and molecular function and its role in metabolic disorders. *Biochem Pharmacol* **110-111**: 1-15 [PMID:26827942]
- Stoddart LA *et al.* (2008) International Union of Pharmacology. LXXI. Free fatty acid receptors FFA1, -2, and -3: pharmacology and pathophysiological functions. *Pharmacol Rev* **60**: 405-17 [PMID:19047536]
- Watterson KR *et al.* (2014) Treatment of type 2 diabetes by free Fatty Acid receptor agonists. *Front Endocrinol (Lausanne)* **5**: 137 [PMID:25221541]

G protein-coupled estrogen receptor

G protein-coupled receptors → G protein-coupled estrogen receptor

Overview: The G protein-coupled estrogen receptor (GPER, **nomenclature as agreed by the NC-IUPHAR Subcommittee on the G protein-coupled estrogen receptor** [2291]) was identified following observations of estrogen-evoked **cyclic AMP** signalling in breast cancer cells [87], which mirrored the differential expression of an orphan 7-transmembrane receptor

GPR30 [382]. There are observations of both cell-surface and intracellular expression of the GPER receptor [2371, 2821]. Selective agonist/ antagonists for GPER have been characterized [2291]. Antagonists of the nuclear estrogen receptor, such as **fulvestrant** [773], **tamoxifen** [2371, 2821] and **raloxifene** [2233], as well as the flavonoid 'phytoestrogens' **genistein** and **quercetin** [1781],

are agonists of GPER. Reviews of GPER pharmacology have been published [2291]. The roles of GPER in (patho)physiological systems throughout the body (cardiovascular, metabolic, endocrine, immune, reproductive) and in cancer have also been reviewed [772, 1561, 1882, 2291, 2292]. The GPER-selective agonist G-1 is currently in Phase I/II clinical trials for cancer (NCT04130516).

Nomenclature	GPER
HGNC, UniProt	<i>GPER1</i> , Q99527
Endogenous agonists	17 β -estradiol [2371, 2821]
Agonists	fulvestrant [2821], raloxifene [2233], 4-hydroxytamoxifen [2371]
Selective agonists	G-1 [255]
Selective antagonists	G36 (pIC ₅₀ 6.8–6.9) [626], G15 (pIC ₅₀ 6.7) [625]
Labelled ligands	[³ H]17 β -estradiol (Agonist) [2821]

Further reading on G protein-coupled estrogen receptor

- Arterburn JB *et al.* (2023) G Protein-Coupled Estrogen Receptor GPER: Molecular Pharmacology and Therapeutic Applications. *Annu Rev Pharmacol Toxicol* **63**: 295-320 [PMID:36662583]
- Barton M *et al.* (2018) Twenty years of the G protein-coupled estrogen receptor GPER: Historical and personal perspectives. *J Steroid Biochem Mol Biol* **176**: 4-15 [PMID:28347854]
- Gaudet HM *et al.* (2015) The G-protein coupled estrogen receptor, GPER: The inside and inside-out story. *Mol Cell Endocrinol* **418 Pt 3**: 207-19 [PMID:26190834]
- Prossnitz ER *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCVII. G Protein-Coupled Estrogen Receptor and Its Pharmacologic Modulators. *Pharmacol Rev* **67**: 505-40 [PMID:26023144]
- Prossnitz ER *et al.* (2023) The G protein-coupled oestrogen receptor GPER in health and disease: an update. *Nat Rev Endocrinol* **19**: 407-424 [PMID:37193881]
- Prossnitz ER *et al.* (2015) What have we learned about GPER function in physiology and disease from knockout mice? *J Steroid Biochem Mol Biol* **153**: 114-26 [PMID:26189910]

GABA_B receptors

G protein-coupled receptors → GABA_B receptors

Overview: Functional GABA_B receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on GABA_B receptors** [280, 2247]) are formed from the heterodimerization of two similar 7TM subunits termed GABA_{B1} and GABA_{B2} [280, 721, 2246, 2247, 2889]. GABA_B receptors are widespread in the CNS and regulate both pre- and postsynaptic activity. The GABA_{B1} subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10-100-fold less than for the native receptor. Co-expression of GABA_{B1} and GABA_{B2} subunits allows transport of GABA_{B1} to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca²⁺ channels (Ca_v2.1, Ca_v2.2), or inwardly rectifying potassium channels (Kir3) [213, 280, 281]. The GABA_{B1} subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA_{B2} subunit mediates G protein-coupled signalling [280, 885, 887, 2246]. The cryo-electron microscopy structures of the human full-length GABA_{B1}-GABA_{B2}

heterodimer have been solved in the inactive apo state, two intermediate agonist-bound forms and an active state in which the heterodimer is bound to an agonist and a positive allosteric modulator [2577]. Phospholipids bound within the central cavity of the transmembrane domains stabilize the inactive state. The positive allosteric modulator binds to the transmembrane interface and stabilizes the active state. Recent evidence indicates that higher order assemblies of GABA_B receptors comprising dimers of heterodimers occur in recombinant expression systems and *in vivo*, and that such complexes exhibit negative functional cooperativity between heterodimers [528, 2244]. Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the GABA_{B2} subunit to impart altered signalling kinetics and agonist potency to the receptor complex [156, 2537, 2875] and are reviewed by [2248]. The molecular complexity of GABA_B receptors is further increased through association with trafficking and effector proteins [2538] and reviewed by [2243]. The

predominant GABA_{B1a} and GABA_{B1b} isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA_{B1a}-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas GABA_{B1b}-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [2212, 2942]. Amyloid precursor protein (APP) and soluble APP (sAPP) bind to the N-terminal sushi domain of the GABA_{B1a} isoform to regulate axonal trafficking of GABA_B receptors and release of neurotransmitters [2384]. *AJAP1* (Q9UKB5) is a dendritic protein that trans-synaptically recruits GABA_{B1a}-containing receptors to presynaptic sites [801]. Missense variants in *GABABR* and *AJAP1* genes as well as autoantibodies link receptor dysfunction to neurodevelopmental disorders and epileptic encephalopathies [405, 801, 1550].

Complexes

Nomenclature	GABA _B receptor
Subunits	GABA _{B1} , GABA _{B2} , KCTD8 (Accessory protein), KCTD12 (Accessory protein), KCTD12b (Accessory protein), KCTD16 (Accessory protein)
Agonists	CGP44532 [822] – Rat, (-)-baclofen [822] – Rat, 3-APPA [1134], baclofen [1134, 3092], 3-APMPA [3092], γ -hydroxybutyrate (Partial agonist) [3039]
Antagonists	CGP62349 (pK _i 8.5–8.9) [1134, 3092], CGP55845 (pK _i 7.8) [3092], SCH50911 (pK _i 5.5–6) [1134, 3092], CGP35348 (pK _i 4.4) [3092], 2-hydroxy-saclofen (pIC ₅₀ 4.1) [1358] – Rat
Allosteric modulators (Positive)	<i>rac</i> -BHFF (pEC ₅₀ 6.6) [1794], GS39783 (pK _B 4.7) [1102, 2899], CGP7930 [2898]
Labelled ligands	[³ H]CGP54626 (Antagonist) (pK _i 9.1) [1307] – Rat, [³ H]CGP62349 (Antagonist) (pK _d 9.1) [1368] – Rat, [¹²⁵ I]CGP64213 (Antagonist) (pK _d 9) [842] – Rat, [¹²⁵ I]CGP71872 (Antagonist) (pK _d 9) [1358] – Rat, [³ H](R)-(-)-baclofen (Agonist)

Subunits

Nomenclature	GABA _{B1}	GABA _{B2}
HGNC, UniProt	GABBR1, Q9UBS5	GABBR2, O75899

Comments: Potencies of agonists and antagonists listed in the table, quantified as IC₅₀ values for the inhibition of [³H]CGP27492 binding to rat cerebral cortex membranes, are from [280, 821, 822]. Radioligand K_D values relate to binding to rat brain membranes. CGP 71872 is a photoaffinity ligand for the GABA_{B1} subunit [188]. CGP27492 (3-APPA), CGP35024 (3-APMPA) and CGP44532 act as antagonists at human GABA_A ρ1 receptors, with potencies in the low micromolar range [821]. In addition to the ligands listed in the table, Ca²⁺ binds to the VTM of the GABA_{B1}

subunit to act as a positive allosteric modulator of GABA [842]. Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF-177 [2953] and (+)-BHF [13, 213, 223, 821]. The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the GABA_{B2} subunit [697, 2246]. In the presence of CGP7930 or GS39783, CGP35348 and 2-hydroxy-saclofen behave as partial agonists [821]. A negative allosteric modulator of GABA_B activity has been reported [442]. Knock-out of the GABA_{B1} subunit in C57B mice

causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA_{B1}^{-/-} BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion (in a novel, but not familiar, environment), hyperdopaminergia, memory impairment and behaviours indicative of anxiety [726, 2901]. A similar phenotype has been found for GABA_{B2}^{-/-} BALB/c mice [868].

Further reading on GABA_B receptors

Bowery NG *et al.* (2002) International Union of Pharmacology. XXXIII. Mammalian gamma-aminobutyric acid(B) receptors: structure and function. *Pharmacol Rev* **54**: 247-64 [PMID:12037141]
 Froestl W. (2011) An historical perspective on GABAergic drugs. *Future Med Chem* **3**: 163-75 [PMID:21428811]

Gassmann M *et al.* (2012) Regulation of neuronal GABA(B) receptor functions by subunit composition. *Nat Rev Neurosci* **13**: 380-94 [PMID:22595784]
 Pin JP *et al.* (2016) Organization and functions of mGlu and GABAB receptor complexes. *Nature* **540**: 60-68 [PMID:27905440]

Galanin receptors

G protein-coupled receptors → Galanin receptors

Overview: Galanin receptors (**provisional nomenclature as recommended by NC-IUPHAR** [789]) are activated by the endogenous peptides galanin (*GAL*, P22466) and galanin-like peptide (*GALP*, Q9UBC7). Human galanin (*GAL*, P22466) is a 30 amino-acid non-amidated peptide [743]; in other species, it is 29 amino acids long and C-terminally amidated. Amino acids

1-14 of galanin are highly conserved in mammals, birds, reptiles, amphibia and fish. Shorter peptide species (*e.g.* human galanin-1-19 [208] and porcine galanin-5-29 [2612]) and N-terminally extended forms (*e.g.* N-terminally seven and nine residue elongated forms of porcine galanin [209, 2612]) have been reported. More recently, the newly-identified peptide, spexin (SPX), has been

reported to activate human GAL2 and GAL3 (but not GAL1) receptors in heterologous expression systems; and to alter GAL2/3 receptor-related behaviours in animals [1401]. Galanin and spexin neuropeptides are important regulators of energy homeostasis [838].

Nomenclature	GAL ₁ receptor	GAL ₂ receptor	GAL ₃ receptor
HGNC, UniProt	<i>GALR1</i> , P47211	<i>GALR2</i> , O43603	<i>GALR3</i> , O60755
Potency order of endogenous ligands	galanin (<i>GAL</i> , P22466) > galanin-like peptide (<i>GALP</i> , Q9UBC7) >> spexin-1 (<i>SPX</i> , Q9BT56) [1401, 2118]	galanin-like peptide (<i>GALP</i> , Q9UBC7) ≥ galanin (<i>GAL</i> , P22466) > spexin-1 (<i>SPX</i> , Q9BT56) [1401, 2118]	galanin-like peptide (<i>GALP</i> , Q9UBC7) > galanin (<i>GAL</i> , P22466) [1551]
Endogenous agonists	–	spexin-1 (<i>SPX</i> , Q9BT56) [1401]	spexin-1 (<i>SPX</i> , Q9BT56) [1401]
Agonists	–	galanin(2-29) (rat/mouse) [2166, 3005, 3006, 3007] – Rat	–
Selective agonists	–	[D-Trp ²]galanin-(1-29) [2644] – Rat, Qu-SPX [1607]	–
Selective antagonists	2,3-dihydro-1,4-dithiin-1,1,4,4-tetroxide (pIC ₅₀ 5.6) [2546]	M871 (pK _i 7.9) [2663]	SNAP 398299 (pK _i 8.3) [1468, 1469, 2746], SNAP 37889 (pK _i 7.8–7.8) [1468, 1469, 2746]
Selective allosteric modulators	–	CYM2503 (Positive) (pEC ₅₀ 9.2) [1739] – Rat	–

Labelled ligands	^[125I] [Tyr ²⁶]galanin (human) (Agonist) [784], ^[125I] [Tyr ²⁶]galanin (human) (Agonist) [784]	^[125I] [Tyr ²⁶]galanin (human) (Agonist) [3006] – Rat, ^[125I] spexin-1 (Agonist) [1401]	^[125I] [Tyr ²⁶]galanin (pig) (Agonist) [271, 2645], ^[125I] spexin-1 (Agonist) [1401]
Comments	–	The CYM2503 PAM potentiates the anticonvulsant activity of endogenous galanin in mouse seizure models [1739]. Activation and binding potency of spexin at human GAL ₂ receptor is less than galanin (GAL) [1401].	Activation and binding potency of spexin at human GAL ₃ receptor is higher than galanin (GAL) [1401].

Comments: Galanin-(1-11) is a high-affinity agonist at GAL₁/GAL₂ (pK_i 9), and galanin(2-11) is selective for GAL₂ and GAL₃ compared with GAL₁ [1738]. [^{125I}]-[Tyr²⁶]galanin binds to all three subtypes with K_d values generally reported to range from 0.05 to 1 nM, depending on the assay conditions used [784, 2629, 2644, 2645, 3006]. Porcine galanin-(3-29) does not bind to cloned GAL₁, GAL₂ or GAL₃ receptors, but a receptor that is functionally activated by porcine galanin-(3-29) has been reported in pituitary and gastric smooth muscle cells [987, 3116]. Additional galanin

receptor subtypes are also suggested from studies with chimeric peptides (*e.g.* M15, M35 and M40), which act as antagonists in functional assays in the cardiovascular system [2887], spinal cord [3068], locus coeruleus, hippocampus [154] and hypothalamus [155, 1618], but exhibit agonist activity at some peripheral sites [155, 987]. The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL₁ receptors expressed endogenously in Bowes human melanoma cells [2118], and at heterologously expressed recombinant GAL₁, GAL₂ and GAL₃ receptors [784, 2644, 2645].

Further studies described the synthesis of a series of novel, systemically-active, galanin analogues, with modest preferential binding at the GAL₂ receptor. Specific chemical modifications to the galanin backbone increased brain levels of these peptides after *i.v.* injection and several of these peptides exerted a potent antidepressant-like effect in mouse models of depression [2452]. More recent studies have identified synthetic spexin (SPX)-based peptides that are selective GAL₂ receptor agonists [1607, 2374].

Further reading on Galanin receptors

- Fonseca-Rodrigues D *et al.* (2022) A New Gal in Town: A Systematic Review of the Role of Galanin and Its Receptors in Experimental Pain. *Cells* **11**: [PMID:35269462]
- Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]
- Lang R *et al.* (2015) Physiology, signaling, and pharmacology of galanin peptides and receptors: three decades of emerging diversity. *Pharmacol Rev* **67**: 118-75 [PMID:25428932]
- Lang R *et al.* (2011) The galanin peptide family in inflammation. *Neuropeptides* **45**: 1-8 [PMID:21087790]
- Lawrence C *et al.* (2011) Galanin-like peptide (GALP) is a hypothalamic regulator of energy homeostasis and reproduction. *Front Neuroendocrinol* **32**: 1-9 [PMID:20558195]
- Rich K *et al.* (2023) Investigating the potential of GalR2 as a drug target for neuropathic pain. *Neuropeptides* **98**: 102311 [PMID:36580831]
- Webling KE *et al.* (2012) Galanin receptors and ligands. *Front Endocrinol (Lausanne)* **3**: 146 [PMID:23233848]
- Zhu S *et al.* (2022) Galanin family peptides: Molecular structure, expression and roles in the neuroendocrine axis and in the spinal cord. *Front Endocrinol (Lausanne)* **13**: 1019943 [PMID:36561569]

Ghrelin receptor

G protein-coupled receptors → Ghrelin receptor

Overview: The ghrelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor** [587]) is activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (*GHRL*, *Q9UBU3*). A unique post-translational modification (octanoylation of Ser³, catalysed by ghrelin O-acyltransferase (*MBOAT4*, *Q96T53*) [3161] is essential for binding and activation of ghrelin receptors in all tissues, including the hypothalamus and pituitary [1463]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for

binding [175], and receptor mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin (*GHRL*, *Q9UBU3*) function [1155]. The authorities in Japan have in 2020 approved the orally active agonist anamorelin, for the treatment of anorexia in cancer patients [2971]. *PF-05190457* is a small-molecule inverse agonist targeting the ghrelin receptor that has been progressed to phase I clinical trial for the treatment of alcoholism and has been demonstrated to decrease appetite [752]. An endogenous antagonist and inverse agonist called Liver enriched antimicro-

bial peptide 2 (Leap2), expressed primarily in hepatocytes and in enterocytes of the proximal intestine [878, 1758] inhibits ghrelin receptor-induced GH secretion and food intake [878]. The secretion of Leap2 and ghrelin is inversely regulated under various metabolic conditions [1804]. In cell systems the ghrelin receptor is constitutively active [1156], and this property is responsible for modulation of D₂ receptor signalling [615], and is attenuated by a naturally occurring mutation (A204E) that is associated with familial short stature [2167].

Nomenclature	ghrelin receptor
HGNC, UniProt	<i>GHSR</i> , Q92847
Potency order of endogenous ligands	ghrelin (<i>GHRL</i> , Q9UBU3) = [des-Gln ¹⁴]ghrelin (<i>GHRL</i> , Q9UBU3) [174, 1840]
Endogenous antagonists	liver enriched antimicrobial peptide 2 (<i>LEAP2</i> , Q969E1) (pIC ₅₀ 8.2) [878]
Selective antagonists	PF-05190457 (pK _i 8.9) [1466]
Labelled ligands	[¹²⁵ I][His ⁹]ghrelin (human) (Agonist) [1357], [¹²⁵ I][Tyr ⁴]ghrelin (human) (Agonist) [1989]

Comments: A potent inverse agonist has been identified ([D-Arg¹,D-Phe⁵,D-Trp^{7,9},Leu¹¹]substance P, pD₂ 8.3; [1153]). **Ulimorelin**, described as a ghrelin receptor agonist (pK_i 7.8 and pD₂ 7.5 at human recombinant ghrelin receptors), has been shown to stimulate ghrelin receptor mediated food intake and gastric emp-

tying but not elicit release of growth hormone, or modify ghrelin stimulated growth hormone release, thus pharmacologically discriminating the orexigenic and gastrointestinal actions of **ghrelin** (*GHRL*, Q9UBU3) from the release of growth hormone [805]. Similar discrimination of ghrelin receptor mediated physiologi-

cal functions can be obtained by activation of distinct signaling pathways [1875]. A number of selective antagonists have been reported, including peptidomimetic [1988] and non-peptide small molecules including **GSK1614343** [2190, 2210, 2453].

Further reading on Ghrelin receptor

- Andrews ZB. (2011) The extra-hypothalamic actions of ghrelin on neuronal function. *Trends Neurosci* **34**: 31-40 [PMID:21035199]
- Angelidis G *et al.* (2010) Current and potential roles of ghrelin in clinical practice. *J Endocrinol Invest* **33**: 823-38 [PMID:21293171]
- Callaghan B *et al.* (2014) Novel and conventional receptors for ghrelin, desacyl-ghrelin, and pharmacologically related compounds. *Pharmacol Rev* **66**: 984-1001 [PMID:25107984]
- Davenport AP *et al.* (2005) International Union of Pharmacology. LVI. Ghrelin receptor nomenclature, distribution, and function. *Pharmacol Rev* **57**: 541-6 [PMID:16382107]
- Ge X *et al.* (2018) LEAP2 Is an Endogenous Antagonist of the Ghrelin Receptor. *Cell Metab* **27**: 461-469.e6 [PMID:29233536]
- Hedegaard MA *et al.* (2020) The Complex Signaling Pathways of the Ghrelin Receptor. *Endocrinology* **161**: [PMID:32049280]

Glucagon receptor family

G protein-coupled receptors → Glucagon receptor family

Overview: The glucagon family of receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the Glucagon receptor family** [1850]) are activated by the endogenous peptide (27-44 aa) hormones glucagon (*GCG*, P01275), glucagon-like peptide 1 (*GCG*, P01275), glucagon-like peptide 2 (*GCG*,

P01275), glucose-dependent insulinotropic polypeptide (also known as **gastric inhibitory polypeptide** (*GIP*, P09681)), **GHRH** (*GHRH*, P01286) and **secretin** (*SCT*, P09683). One common precursor (*GCG*) generates glucagon (*GCG*, P01275), glucagon-like peptide 1 (*GCG*, P01275) and glucagon-like peptide 2 (*GCG*,

P01275) peptides [1233]. For a recent review on the current understanding of the structures of GLP-1 and GLP-1R, the molecular basis of their interaction, and the associated signaling events see de Graaf *et al.*, 2016 [960].

Nomenclature	GHRH receptor	GIP receptor	GLP-1 receptor
HGNC, UniProt	<i>GHRHR</i> , Q02643	<i>GIPR</i> , P48546	<i>GLP1R</i> , P43220
Endogenous agonists	GHRH (<i>GHRH</i> , P01286)	gastric inhibitory polypeptide (<i>GIP</i> , P09681) [2956]	glucagon-like peptide 1-(7-36) amide (<i>GCG</i> , P01275) [1311], glucagon-like peptide 1-(7-37) (<i>GCG</i> , P01275) [650]
Agonists	J1-38 [361], sermorelin	–	liraglutide [1450], lixisenatide [3051], WB4-24 [747]
Selective agonists	BIM28011 [553], tesamorelin	–	semaglutide [1565], exendin-4 [1915], exendin-4 [1311], exendin-3 (P20394) [2350]

Selective antagonists	JV-1-36 (pK _i 10.1–10.4) [2503 , 2929 , 2930] – Rat, JV-1-38 (pK _i 10.1) [2503 , 2929 , 2930] – Rat	[Pro³]GIP [871] – Mouse	exendin-(9-39) (pK _i 8.1) [1311], GLP-1-(9-36) (pIC ₅₀ 6.9) [1951] – Rat, T-0632 (pIC ₅₀ 4.7) [2829]
Labelled ligands	[¹²⁵I]GHRH (human) (Agonist) [277] – Rat	[¹²⁵I]GIP (human) (Agonist) [840] – Rat	[¹²⁵I]GLP-1-(7-36)-amide (Agonist) [1311], [¹²⁵I]exendin-(9-39) (Antagonist) (pK _d 8.3) [1311], [¹²⁵I]GLP-1-(7-37) (human) (Agonist)

Nomenclature	GLP-2 receptor	glucagon receptor	secretin receptor
HGNC, UniProt	GLP2R , O95838	GCGR , P47871	SCTR , P47872
Endogenous agonists	glucagon-like peptide 2 (GCG, P01275) [2826]	glucagon (GCG, P01275) [2257]	secretin (SCT, P09683) [486]
Agonists	teduglutide [1865]	NNC1702 [3227]	–
Selective agonists	apraglutide [1051 , 2635]	–	–
Selective antagonists	–	L-168,049 (pIC ₅₀ 8.4) [392], adomeglivant (pK _i 8.2) [1365 , 1373], des-His¹-[Glu⁹]glucagon-NH₂ (pA ₂ 7.2) [2892 , 2893] – Rat, NNC 92-1687 (pK _i 5) [1773], BAY27-9955 [2227]	[(CH₂NH)⁴⁻⁵]secretin (pK _i 5.3) [1010]
Labelled ligands	–	[¹²⁵I]glucagon (human, mouse, rat) (Agonist)	[¹²⁵I](Tyr¹⁰)secretin-27 (rat) (Agonist) [2888] – Rat

Comments: The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically [RAMP2](#), in heterologous expression systems [[496](#)], although the physiological significance of this has yet to be established.

Further reading on Glucagon receptor family

- Chang R *et al.* (2020) Cryo-electron microscopy structure of the glucagon receptor with a dual-agonist peptide. *J Biol Chem* **295**: 9313–9325 [[PMID:32371397](#)]
- Dong M *et al.* (2020) Structure and dynamics of the active Gs-coupled human secretin receptor. *Nat Commun* **11**: 4137 [[PMID:32811827](#)]
- Drucker DJ. (2019) The Discovery of GLP-2 and Development of Teduglutide for Short Bowel Syndrome. *ACS Pharmacol Transl Sci* **2**: 134–142 [[PMID:32219218](#)]
- Holst JJ *et al.* (2020) GIP as a Therapeutic Target in Diabetes and Obesity: Insight From Incretin Co-agonists. *J Clin Endocrinol Metab* **105**: [[PMID:32459834](#)]
- Liang YL *et al.* (2020) Toward a Structural Understanding of Class B GPCR Peptide Binding and Activation. *Mol Cell* **77**: 656–668.e5 [[PMID:32004469](#)]
- Zhang X *et al.* (2020) Differential GLP-1R Binding and Activation by Peptide and Non-peptide Agonists. *Mol Cell* **80**: 485–500.e7 [[PMID:33027691](#)]
- Zhou F *et al.* (2020) Structural basis for activation of the growth hormone-releasing hormone receptor. *Nat Commun* **11**: 5205 [[PMID:33060564](#)]

Glycoprotein hormone receptors

G protein-coupled receptors → Glycoprotein hormone receptors

Overview: Glycoprotein hormone receptors (**provisional nomenclature** [[789](#)]) are activated by a non-covalent heterodimeric glycoprotein made up of a common α chain (**glycoprotein hormone common alpha subunit** ([CGA, P01215](#)) [CGA, P01215](#)), with a unique β chain that confers the biological specificity to [FSH](#) ([CGAFSHB, P01215 P01225](#)), [LH](#) ([CGALHB, P01215 P01229](#)), [hCG](#) ([CGACGB3, P01215 P01233](#)) or [TSH](#) ([CGATSHB, P01215 P01222](#)). There is binding cross-reactivity across the endogenous agonists for each of the glycoprotein hormone receptors. The deglycosylated hormones appear to exhibit reduced efficacy at these receptors [[591](#), [2456](#)].

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

Glycoprotein hormone receptors S85

Nomenclature	FSH receptor	LH receptor	TSH receptor
HGNC, UniProt	<i>FSHR</i> , P23945	<i>LHCGR</i> , P22888	<i>TSHR</i> , P16473
Potency order of endogenous ligands	FSH (<i>CGAFSHB</i> , P01215P01225)	LH (<i>CGALHB</i> , P01215P01229), hCG (<i>CGACGB3</i> , P01215P01233) [1287, 1997]	TSH (<i>CGATSHB</i> , P01215P01222)
Labelled ligands	[¹²⁵ I]FSH (human) (Agonist)	[¹²⁵ I]LH (Agonist), [¹²⁵ I]chorionic gonadotropin (human) (Agonist)	[¹²⁵ I]TSH (human) (Agonist)

Further reading on Glycoprotein hormone receptors

- Jiang X *et al.* (2012) Structure of follicle-stimulating hormone in complex with the entire ectodomain of its receptor. *Proc Natl Acad Sci USA* **109**: 12491-6 [PMID:22802634]
- Kleinau G *et al.* *Thyroid Disease Manager*. Accessed on 2017-02-23.
- Tao YX *et al.* (2009) Follicle stimulating hormone receptor mutations and reproductive disorders. *Prog Mol Biol Transl Sci* **89**: 115-31 [PMID:20374735]
- Troppmann B *et al.* (2013) Structural and functional plasticity of the luteinizing hormone/choriogonadotropin receptor. *Hum Reprod Update* **19**: 583-602 [PMID:23686864]

Gonadotrophin-releasing hormone receptors

G protein-coupled receptors → Gonadotrophin-releasing hormone receptors

Overview: GnRH₁ and GnRH₂ receptors (**provisional nomenclature** [789], also called Type I and Type II GnRH receptor, respectively [1908]) have been cloned from numerous species, most of which express two or three types of GnRH receptor [1907, 1908, 2614]. GnRH I (*GNRHI*, P01148) (p-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂) is a hypothalamic decapeptide also known as luteinizing hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin or simply as GnRH. It is a member of a family of similar peptides found in many species [1907, 1908, 2614] including GnRH II (*GNRH2*, O43555) (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH₂ (which is also known as chicken GnRH-II). Receptors for three forms of GnRH exist in some spe-

cies but only GnRH I and GnRH II and their cognate receptors have been found in mammals [1907, 1908, 2614]. GnRH₁ receptors are expressed by pituitary gonadotrophs, where they mediate the effects of GnRH on gonadotropin hormone synthesis and secretion that underpin central control of mammalian reproduction. GnRH analogues are used in assisted reproduction and to treat steroid hormone-dependent conditions [1393]. Notably, agonists cause desensitization of GnRH-stimulated gonadotropin secretion and the consequent reduction in circulating sex steroids is exploited to treat hormone-dependent cancers of the breast, ovary and prostate [1393]. GnRH₁ receptors are selectively activated by GnRH I and all lack the COOH-terminal tails

found in other GPCRs. GnRH₂ receptors do have COOH-terminal tails and (where tested) are selective for GnRH II over GnRH I. GnRH₂ receptors are expressed by some primates but not by humans [1967]. Phylogenetic classifications divide GnRH receptors into three [1908] or five groups [3073] and highlight examples of gene loss through evolution, with humans retaining only one ancient gene. The structure of the GnRH₁ receptor in complex with *elagolix* has been elucidated [3155]. Cryo-EM structures of GnRH bound to both pig and frog GnRH₁ receptors have also been reported [2583].

Nomenclature	GnRH ₁ receptor	GnRH ₂ receptor
HGNC, UniProt	<i>GNRHR</i> , P30968	<i>GNRHR2</i> , Q96P88
Potency order of endogenous ligands	GnRH I (<i>GNRHI</i> , P01148) > GnRH II (<i>GNRH2</i> , O43555) [1908]	GnRH II (<i>GNRH2</i> , O43555) > GnRH I (<i>GNRHI</i> , P01148) [1906]
Endogenous agonists	GnRH I (<i>GNRHI</i> , P01148) [1740], GnRH II (<i>GNRH2</i> , O43555) [782, 1740, 2696]	–
Agonists	–	GnRH I (<i>GNRHI</i> , P01148) [1906, 1908] – Monkey
Selective agonists	buserelin [2041, 2042], triptorelin [171], leuprolide [2713], goserelin, histrelin, nafarelin	GnRH II (<i>GNRH2</i> , O43555) [1906] – Monkey
Antagonists	relugolix (pIC ₅₀ 9.5) [1923], iturelix (pK _i 9.5) [2398], linzagolix (pIC ₅₀ 7.4) [2805]	–
Selective antagonists	cetorelix (pK _i 9.3–10) [172, 173, 2713], abarelix (pK _i 9.1–9.5) [2713], elagolix (pK _i 9.1) [436, 1545], degarelix (pK _i 8.8) [2916], ganirelix	trptorelix-1 [1788] – Monkey
Labelled ligands	[¹²⁵ I]cetorelix (Antagonist) (pK _d 9.7) [1145], [¹²⁵ I]triptorelin (Agonist) [620] – Rat, [¹²⁵ I]buserelin (Agonist) [1526] – Rat, [¹²⁵ I]GnRH I (human, mouse, rat) (Agonist)	–

Comments: GnRH₁ and GnRH₂ receptors couple primarily to G_{q/11} [981] but coupling to G_s and G_i is evident in some systems [1504, 1526]. GnRH₂ receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases [399]. There is increasing evidence for expression of GnRH receptors on hormone-dependent cancer cells where they can exert antiproliferative and/or proapoptotic effects and mediate effects of cytotoxins conjugated to GnRH analogues [459, 1056, 1677, 2502]. In some human cancer cell models GnRH II (GNRH2, O43555) is more potent than GnRH I (GNRH1, P01148), implying mediation by GnRH₂ receptors [984], but GnRH₂ receptors are not expressed

by humans because the human GNRHR2 gene contains a frame shift and internal stop codon [1967]. The possibility remains that this gene generates GnRH₂ receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (GNRH2, O43555) (see [2047]). Alternatively, evidence for multiple active GnRH receptor conformations [399, 400, 774, 1847, 1908] raises the possibility that GnRH₁ receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon a conformation that couples to G_i rather than G_{q/11} proteins as in pituitary cells [400, 1847]. Loss-of-function mutations in the GnRH₁ receptor and deficiency of GnRH I (GNRH1,

P01148) are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' GnRH₁ receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists [1593]. Human GnRH₁ receptors are poorly expressed at the cell surface because of failure to meet structural quality control criteria for endoplasmic reticulum exit [775, 1593], and this increases susceptibility to point mutations that further impair trafficking [775, 1593]. GnRH receptor signalling may require receptor oligomerisation [532, 1502].

Further reading on Gonadotrophin-releasing hormone receptors

- Desaulniers AT *et al.* (2017) Expression and Role of Gonadotropin-Releasing Hormone 2 and Its Receptor in Mammals. *Front Endocrinol (Lausanne)* **8**: 269 [PMID:29312140]
- Limonta P *et al.* (2012) GnRH receptors in cancer: from cell biology to novel targeted therapeutic strategies. *Endocr Rev* **33**: 784-811 [PMID:22778172]
- McArdle CA and Roberson MS. (2015) *In Knobil and Neill's Physiology of Reproduction (4th edition)*. Edited by Plant TM and Zeleznik AJ.: Elsevier Inc.: [ISBN: 9780123971753]
- Millar RP *et al.* (2004) Gonadotropin-releasing hormone receptors. *Endocr Rev* **25**: 235-75 [PMID:15082521]
- Tao YX *et al.* (2014) Chaperoning G protein-coupled receptors: from cell biology to therapeutics. *Endocr Rev* **35**: 602-47 [PMID:24661201]

GPR143

G protein-coupled receptors → GPR143

GPR143 is an orphan GPCR with a preliminary pairing for an endogenous candidate. NC-IUPHAR considers it to be structurally distinct from existing classes of GPCR.

Nomenclature	GPR143
HGNC, UniProt	GPR143 , P51810
Endogenous agonists	levodopa [1731]
Comments	Loss-of-function mutations underlie ocular albinism type 1 [157].

Further reading on GPR143

- Kim YJ *et al.* (2024) L-DOPA Promotes Functional Proliferation Through GPR143, Specific L-DOPA Receptor of Astrocytes. *ACS Chem Neurosci* **15**: 4132-4142 [PMID:39509688]
- Tajika R *et al.* (2024) Opposite regulation by L-DOPA receptor GPR143 of the long and short forms of the dopamine D2 receptors. *J Pharmacol Sci* **156**: 77-81 [PMID:39179337]

GPR18, GPR55 and GPR119

G protein-coupled receptors → GPR18, GPR55 and GPR119

Overview: *GPR18*, *GPR55* and *GPR119* (**provisional nomenclature**), although showing little structural similarity to CB₁ and CB₂ cannabinoid receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands [2223]. Although there are multiple reports to indicate that *GPR18*, *GPR55* and *GPR119* can be activated *in vitro* by *N*-arachidonoylglycine, lysophosphatidylinositol and *N*-oleoylethanolamide, respectively, there is a lack of evidence for activation by these lipid messengers *in vivo*. As such, therefore, these receptors retain their orphan status.

Nomenclature	<i>GPR18</i>	<i>GPR55</i>	<i>GPR119</i>
HGNC, UniProt	<i>GPR18</i> , Q14330	<i>GPR55</i> , Q9Y2T6	<i>GPR119</i> , Q8T5V5
Potency order of endogenous ligands	–	–	<i>N</i> -oleoylethanolamide, <i>N</i> -palmitoylethanolamine > SEA (anandamide is ineffective) [2149]
Endogenous agonists	<i>N</i> -arachidonoylglycine [1460]	lysophosphatidylinositol [1105, 2120, 2669], 2-arachidonoylglycerolphosphoinositol [2122]	<i>N</i> -oleoylethanolamide [501, 2149, 2669], <i>N</i> -palmitoylethanolamine, SEA
Selective agonists	–	AM251 [1105, 1347, 2449]	AS1269574 [3197], PSN632408 [2149], PSN375963 [2149]
Selective antagonists	–	CID16020046 (apparent pA ₂) (pA ₂ 7.3) [1349], ML193 (pIC ₅₀ 6.7) [1119]	–
Comments	The pairing of <i>N</i> -arachidonoylglycine with GPR18 was not replicated in two studies based on arrestin assays [2669, 3184]. See [586] for discussion.	See reviews [586] and [2603].	In addition to those shown above, further small molecule agonists have been reported [1033].

Comments: *GPR18* failed to respond to a variety of lipid-derived agents in an *in vitro* screen [3184], but has been reported to be activated by Δ^9 -tetrahydrocannabinol [1864]. *GPR55* responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB₁ receptor antagonists/

inverse agonists [2223]. It has been reported that lysophosphatidylinositol acts at other sites in addition to *GPR55* [3150]. *N*-Arachidonoylserine has been suggested to act as a low efficacy agonist/antagonist at *GPR18* *in vitro* [1862]. It has also been suggested oleoyl-lysophosphatidylcholine acts, at least in part,

through *GPR119* [2079]. Although PSN375963 and PSN632408 produce *GPR119*-dependent responses in heterologous expression systems, comparison with *N*-oleoylethanolamide-mediated responses suggests additional mechanisms of action [2079].

Further reading on GPR18, GPR55 and GPR119

Davenport AP *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacol Rev* **65**: 967-86 [PMID:23686350]
 Hassing HA *et al.* (2016) Biased signaling of lipids and allosteric actions of synthetic molecules for GPR119. *Biochem Pharmacol* **119**: 66-75 [PMID:27569424]

Liu B *et al.* (2015) GPR55: from orphan to metabolic regulator? *Pharmacol Ther* **145**: 35-42 [PMID:24972076]
 Pertwee RG *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB₁ and CB₂. *Pharmacol Rev* **62**: 588-631 [PMID:21079038]

Histamine receptors

G protein-coupled receptors → Histamine receptors

Overview: Histamine receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Histamine Receptors** [1125, 2168]) are activated by the endogenous ligand **histamine**. Marked species differences exist between histamine receptor orthologues [1125]. The human and rat H_3 receptor genes are subject to significant splice variance [134]. The potency order of histamine at histamine receptor subtypes is $H_3 = H_4 > H_2 > H_1$ [2168]. Some agonists at the human H_3 receptor display significant ligand bias [2389]. Antagonists of all 4 histamine receptors have clinical uses: H_1 antagonists for allergies (e.g. **cetirizine**), H_2 antagonists for acid-reflux diseases (e.g. **ranitidine**), H_3 antagonists for narcolepsy (e.g. **pitolisant**/WAKIX; Registered) and H_4 antagonists for atopic dermatitis (e.g. **adriforant**; Phase IIa) [2168] and vestibular neuritis (AUV) (SENS-111 (Seliforant, previously UR-63325), entered and completed vestibular neuritis (AUV) Phase IIa efficacy and safety trials, respectively) [95, 2937]. Histamine receptor photopharmacology has provided both ag-

onist and antagonist tools to achieve optical control over H_3 receptor function. The best-characterized agonist is VUF15000, an azobenzene-containing compound in which the trans-isomer binds the H_3 receptor with nanomolar affinity ($K_i = 4$ nM) and behaves as a full agonist. Its cis-isomer is approximately 10-fold less active, thereby creating a reversible light-controlled switch for receptor activation that has been validated in binding, NanoBRET biosensor, and electrophysiology assays [1070]. Also several photoswitchable antagonists have been established as tools for histamine H_3 receptor photopharmacology. The first-generation azobenzene-based antagonists included VUF14738 and VUF14862, which are part of a bidirectional toolbox [1069]. VUF14738 (trans: $K_i = 631$ nM) shows a light-induced 10-fold increase in affinity, while VUF14862 (trans: $K_i = 1.6$ nM) displays the opposite, with more than a tenfold change upon illumination. Both compounds are highly fatigue-resistant, underwent rapid trans-cis isomerization, and had long thermal half-lives, al-

lowing reversible optical control in binding and electrophysiological assays. Building on these scaffolds, recently 2nd generation ligands were developed to overcome limitations of azobenzenes [224]. The arylazopyrazole-based antagonist VUF26063 displayed subnanomolar affinity at the H_3 receptor in its trans isomer ($K_i = 0.5$ nM) and a 50-fold lower affinity in the cis state. This compound showed robust switching with high photostationary state efficiency and improved aqueous solubility compared to earlier analogues. Importantly, radiolabeling yielded [3 H]VUF26063, the first radiolabeled photoswitchable GPCR ligand, enabling the direct study of ligand binding kinetics and photoisomerization inside the receptor pocket in real time. These antagonists, together with the agonist VUF15000, provide a well-characterized toolkit of photosensitive ligands that can be used to dissect H_3 receptor pharmacology with spatiotemporal precision.

Nomenclature	H_1 receptor	H_2 receptor
HGNC, UniProt	<i>HRH1</i> , P35367	<i>HRH2</i> , P25021
Selective agonists	methylhistaprodifen [2556], histaprodifen [1676]	amthamine [1494]
Antagonists	cyproheptadine (pK_i 10.2) [1932], promethazine (pK_i 9.6) [902], mepyramine (Inverse agonist) (pK_i 8.7–9) [266, 2349], cetirizine (Inverse agonist) (pK_i 8.2) [1932], diphenhydramine (pK_i 7.9) [266]	–
Selective antagonists	clemastine (pK_i 10.3) [100], desloratadine (pK_i 9) [1641], triprolidine (pK_i 8.5–9) [266, 1932], azelastine (pK_i 8.9) [2286], astemizole (pK_i 8.5) [2193]	tiotidine (pK_i 7.5) [215] – Rat, ranitidine (pK_i 7.1) [1636], cimetidine (pK_i 6.8) [378]
Labelled ligands	[3 H]pyrilamine (Antagonist, Inverse agonist) (pK_d 8.4–9.1) [598, 1932, 2527, 2556], [14 C]doxepin (Antagonist) (pK_d 9) [1237], [14 C]pyrilamine (Antagonist, Inverse agonist)	[125 I]iodoaminopotentidine (Antagonist) (pK_d 8.7) [1510] – Rat, [3 H]tiotidine (Antagonist) (pK_d 7.7–8.7) [1944]

Nomenclature	H_3 receptor	H_4 receptor
HGNC, UniProt	<i>HRH3</i> , Q9Y5N1	<i>HRH4</i> , Q9H3N8
Agonists	VUF15000 [1070]	–
Selective agonists	GSK-189254 (Inverse agonist) [1870], immethridine [1439], methimepip [1438], MK-0249 (Inverse agonist) [2013]	clobenpropit (Partial agonist) [734, 1676, 1706, 1707, 1983], 4-methylhistamine [877, 1676], ST-1006 [2168], VUF 8430 [1675]
Antagonists	VUF26063 (pK_i 9.3) [224], iodophenpropit (pK_i 8.2–8.7) [3067, 3112], VUF14862 (pK_i 7.7) [1069], VUF14738 (pK_i 7.3) [1069]	SENS-111 [2232]

Selective antagonists	pitolisant (pK _i 8.1–8.6) [1579, 2168], A331440 (pK _i 8.5) [1034], conessine (pK _i 8.3) [2168], MK-0249 (pK _i 8.2) [2168], thioperamide (Selective for H ₃ /H ₄ compared to H ₁ and H ₃ .) (pK _i 7.1–7.7) [520, 733, 734, 1673, 1736, 3067, 3112], ciproxifan (pK _i 6.7–7.3) [520, 733, 734, 1673, 2168, 3112]	adrioforant (pK _i 8.3) [2168], INCB-38579 (pK _i 8.3) [2168], JNJ 7777120 (pK _i 7.8–8.3) [1676, 2650, 2827], JNJ-39758979 (pK _i 7.9) [2168, 2492], thioperamide (Selective for H ₃ /H ₄ compared to H ₁ and H ₃ .) (pK _i 6.3–7.6) [733, 734, 1706, 1707, 1983, 3269]
Labelled ligands	[123I]iodoproxyfan (Antagonist) (pK _d 10.2) [1673], [125I]iodophenpropit (Antagonist) (pK _d 9.2) [1268] – Rat, [3H](R)-α-methylhistamine (Agonist) [1706], N-[3H]α-methylhistamine (Agonist) [440] – Mouse	[3H]JNJ 7777120 (Antagonist) (pK _d 8.4) [2827]

Comments: [Histaprodifen](#) and [methylhistaprodifen](#) are reduced efficacy agonists. The H₄ receptor appears to exhibit broadly similar pharmacology to the H₃ receptor for imidazole-containing ligands, although [\(R\)-α-methylhistamine](#) and [N-α-methylhistamine](#) are less potent, while [clobenpropit](#) acts as a reduced efficacy agonist at the H₄ receptor and an antagonist at the H₃ receptor [1706, 2022, 2067, 2106, 3269]. Moreover, [4-methylhistamine](#) is identified as a high affinity, full agonist for the human H₄ receptor [1676]. [\[3H\]histamine](#) has been used to label the H₄ receptor in heterologous expression systems.

Further reading on Histamine receptors

- Gbahou F *et al.* (2012) The histamine autoreceptor is a short isoform of the H₃ receptor. *Br J Pharmacol* **166**: 1860-71 [PMID:22356432]
- Nieto-Alamilla G *et al.* (2016) The Histamine H3 Receptor: Structure, Pharmacology, and Function. *Mol Pharmacol* **90**: 649-673 [PMID:27563055]
- Panula P *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCVIII. Histamine Receptors. *Pharmacol Rev* **67**: 601-55 [PMID:26084539]
- van Rijn RM *et al.* (2008) Cloning and characterization of dominant negative splice variants of the human histamine H4 receptor. *Biochem J* **414**: 121-31 [PMID:18452403]

Hydroxycarboxylic acid receptors

G protein-coupled receptors → Hydroxycarboxylic acid receptors

Overview: The hydroxycarboxylic acid family of receptors (ENSMF00500000271913, nomenclature as agreed by the [NC-IUPHAR Subcommittee on Hydroxycarboxylic acid receptors](#) [586, 2108]) respond to organic acids, including the endogenous hydroxy carboxylic acids 3-hydroxy butyric acid and [L-lactic acid](#), as well as the lipid lowering agents [nicotinic acid](#) (niacin), [acipimox](#) and [acifran](#) [2656, 2874, 3084]. These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA₂ receptors only and is unlikely to be the natural ligand [2874, 3084].

Nomenclature	HCA ₁ receptor	HCA ₂ receptor	HCA ₃ receptor
HGNC, UniProt	HCAR1 , Q9BXC0	HCAR2 , Q8TDS4	HCAR3 , P49019
Potency order of endogenous ligands	–	β-D-hydroxybutyric acid > butyric acid	–
Endogenous agonists	L-lactic acid [21, 362, 1708, 2669]	β-D-hydroxybutyric acid [2757], butyric acid	3-hydroxyoctanoic acid [20]
Agonists	compound 2 [2461], 3,5-dihydroxybenzoic acid [1705]	SCH 900271 [2154], GSK256073 [2678]	D-phenyllactic acid [2225]
Selective agonists	–	MK 6892 [2582], MK 1903 [240], nicotinic acid [2656, 2874, 3084], acipimox [2656, 3084], monomethyl fumarate [2785]	compound 6o [2628], IBC 293 [2558]
Labelled ligands	–	[3H]nicotinic acid (Agonist) [2656, 2874, 3084]	–

Comments: Further closely-related GPCRs include the **5-oxoeicosanoid receptor** (*OXER1*, *Q8TDSS*) and *GPR31* (*O00270*). Lactate activates HCA₁ on adipocytes in an autocrine manner. It inhibits lipolysis and thereby promotes anabolic effects. HCA₂ and HCA₃ regulate adipocyte lipolysis and immune functions under conditions of increased FFA formation through lipolysis (e.g., during fasting). HCA₂ agonists acting mainly through the receptor on immune cells exert antiatherogenic and anti-inflammatory effects. HCA₂ is also a receptor for butyrate and mediates some of the beneficial effects of short-chain fatty acids produced by gut microbiota. HCA₃ has been shown to be activated by aromatic D-amino acids, and by D-phenyllactic acid, a metabolite of gut lactic acid bacteria [2225].

Further reading on Hydroxycarboxylic acid receptors

- Boatman PD *et al.* (2008) Nicotinic acid receptor agonists. *J Med Chem* **51**: 7653-62 [PMID:18983141]
 Graff EC *et al.* (2016) Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2. *Metab Clin Exp* **65**: 102-13 [PMID:26773933]
 Kennedy L *et al.* (2022) Lactate receptor HCAR1 regulates neurogenesis and microglia activation after neonatal hypoxia-ischemia. *Elife* **11**: [PMID:35942676]
 Offermanns S. (2017) Hydroxy-Carboxylic Acid Receptor Actions in Metabolism. *Trends Endocrinol Metab* **28**: 227-236 [PMID:28087125]
 Offermanns S *et al.* (2011) International Union of Basic and Clinical Pharmacology. LXXXII: Nomenclature and Classification of Hydroxy-carboxylic Acid Receptors (GPR81, GPR109A, and GPR109B). *Pharmacol Rev* **63**: 269-90 [PMID:21454438]
 Offermanns S *et al.* (2015) Nutritional or pharmacological activation of HCA(2) ameliorates neuroinflammation. *Trends Mol Med* **21**: 245-55 [PMID:25766751]
 Park JH *et al.* (2023) Structural basis for ligand recognition and signaling of hydroxy-carboxylic acid receptor 2. *Nat Commun* **14**: 7150 [PMID:37932263]
 Wang J *et al.* (2025) Insights into the Activation Mechanism of HCA1, HCA2, and HCA3. *J Med Chem* **68**: 4527-4539 [PMID:39936872]

Kisspeptin receptor

G protein-coupled receptors → Kisspeptin receptor

Overview: The kisspeptin receptor (nomenclature as agreed by the **NC-IUPHAR Subcommittee on the kisspeptin receptor** [1428]), like neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) responds to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. **Kisspeptin-54** (*KISS1*, *Q15726*) (KP54, originally named metastatin), **kisspeptin-13** (*KISS1*, *Q15726*) (KP13) and **kisspeptin-10** (*KISS1*) (KP10) are biologically-active peptides cleaved from the *KISS1* (*Q15726*) gene product. Kisspeptins have roles in, for example, cancer metastasis, fertility/puberty regulation and glucose homeostasis.

Nomenclature	kisspeptin receptor
HGNC, UniProt	<i>KISS1R</i> , Q969F8
Endogenous agonists	kisspeptin-10 (<i>KISS1</i>) [1481, 2119], kisspeptin-54 (<i>KISS1</i> , <i>Q15726</i>) [1481, 2119], kisspeptin-14 (<i>KISS1</i> , <i>Q15726</i>) [1481], kisspeptin-13 (<i>KISS1</i> , <i>Q15726</i>) [1481]
Selective agonists	4-fluorobenzoyl-FGLRW-NH2 [2847], [dY] ¹ KP-10 [566] – Mouse, TAK-448 [2083]
Selective antagonists	peptide 234 [2420]
Labelled ligands	[¹²⁵ I]Tyr ⁴⁵ -kisspeptin-15 (Agonist) [2119], [¹²⁵ I]kisspeptin-13 (human) (Agonist) [1869], [¹²⁵ I]kisspeptin-10 (human) (Agonist) [1481], [¹²⁵ I]kisspeptin-14 (human) (Agonist) [1869], [d-Tyr- ¹⁴ C]TAK-448 (Agonist) [1975]

Comments: 2-acylamino-4,6-diphenylpyridine derivatives have been described and are the first small molecule kisspeptin receptor antagonists reported with potential for treatment of sex-hormone dependent diseases such as prostate cancer and endometriosis [591, 1452].

Further reading on Kisspeptin receptor

- Harter CJL *et al.* (2018) The role of kisspeptin neurons in reproduction and metabolism. *J Endocrinol* **238**: R173-R183 [PMID:30042117]
- Kanda S *et al.* (2013) Structure, synthesis, and phylogeny of kisspeptin and its receptor. *Adv Exp Med Biol* **784**: 9-26 [PMID:23550000]
- Kirby HR *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXVII. Kisspeptin receptor nomenclature, distribution, and function. *Pharmacol Rev* **62**: 565-78 [PMID:21079036]
- Oakley AE *et al.* (2009) Kisspeptin signaling in the brain. *Endocr Rev* **30**: 713-43 [PMID:19770291]
- Pasquier J *et al.* (2014) Molecular evolution of GPCRs: Kisspeptin/kisspeptin receptors. *J Mol Endocrinol* **52**: T101-17 [PMID:24577719]

Leukotriene receptors

G protein-coupled receptors → Leukotriene receptors

Overview: The leukotriene receptors (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene Receptors** [118, 119]) are activated by the endogenous ligands leukotrienes (LT), synthesized from lipoxygenase metabolism of arachidonic acid. The human BLT1 receptor is the high affinity LT_{B4} receptor whereas the BLT2 receptor in addition to being a low-affinity LT_{B4} receptor also binds several other lipoxygenase-products, such as 12S-HETE, 12S-HPETE, 15S-HETE, and the thromboxane synthase product 12-hydroxyheptadecatrienoic acid. The BLT receptors mediate chemotaxis and immunomodulation in several leukocyte populations and are in addition

expressed on non-myeloid cells, such as vascular smooth muscle and endothelial cells. In addition to BLT receptors, LT_{B4} has been reported to bind to the peroxisome proliferator activated receptor (PPAR) α [1686] and the vanilloid TRPV1 ligand-gated nonselective cation channel [1863]. The crystal structure of the BLT1 receptor was initially determined in complex with selective antagonists [1164, 1891] and extended to the cryo-electron microscopy structure of LT_{B4}-bound human BLT1 receptor at 2.91 Å resolution [3002]. The receptors for the cysteinyl-leukotrienes (*i.e.* LTC₄, LTD₄ and LTE₄) are termed CysLT1 and CysLT2 and exhibit distinct expression patterns in human tissues, mediating for

example smooth muscle cell contraction, regulation of vascular permeability, and leukocyte activation. The crystal structures of both receptors have been solved; CysLT1 in complex with **zafirlukast** and **pranlukast** [1742] and CysLT2 in complex with three dual CysLT1/CysLT2 antagonists [1006]. There is also evidence in the literature for additional CysLT receptor subtypes, derived from functional *in vitro* studies, radioligand binding and in mice lacking both CysLT1 and CysLT2 receptors [119]. Cysteinyl-leukotrienes have also been suggested to signal through the P2Y12 receptor [810, 2090, 2174], GPR17 [506] and the oxoglutarate receptor OXGR1 (previously referred to as GPR99) [1336].

Nomenclature	BLT1 receptor	BLT2 receptor	CysLT1 receptor	CysLT2 receptor
HGNC, UniProt	<i>LTBR</i> , Q15722	<i>LTBR2</i> , Q9NPC1	<i>CYSLTR1</i> , Q9Y271	<i>CYSLTR2</i> , Q9NS75
Potency order of endogenous ligands	LT _{B4} > 20-hydroxy-LT _{B4} >> 12R-HETE [3191]	12-hydroxyheptadecatrienoic acid > LT _{B4} > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE > 20-hydroxy-LT _{B4} [2129, 3191]	LTD ₄ > LTC ₄ > LTE ₄ [1757, 2479]	LTC ₄ > LTD ₄ >> LTE ₄ [1095, 2095, 2766]
Antagonists	–	–	pranlukast (pK _i 7.1–8.8) [379, 2352], pobilukast (pK _i 7.1) [381]	pranlukast (pA ₂ 7.1) [380], pobilukast (pA ₂ 6.2) [380]
Selective antagonists	BIIL 260 (pK _i 8.8) [226, 643], CP105696 (pIC ₅₀ 8.1) [2606], U75302 (pK _i 6.4) [249]	LY255283 (pIC ₅₀ 6–7.1) [1112, 3191]	ICI198615 (pK _i 9.7) [837] – Guinea pig, zafirlukast (zafirlukast is only about 100-fold selective for CysLT ₁) (pK _i 8.9) [379, 2352], montelukast (pK _i 8.6) [2352], MK-571 (pIC ₅₀ 8) [1757]	BayCysLT ₂ (pA ₂ 8.4) [384], Bay-CysLT ₂ (pA ₂ 8.3) [384], HAMI3379 (pIC ₅₀ 7.4) [3113]
Labelled ligands	[³ H]LT _{B4} (Agonist) [3190], [³ H]CGS23131 (Antagonist) (pK _d 7.9) [1250]	[³ H]LT _{B4} (pK _d 7.6–9.7)	[³ H]LTD ₄ (Agonist), [³ H]ICI-198615 (Antagonist) (pK _d 10.6) [2430]	[³ H]LTD ₄ (Agonist) [1095]

Nomenclature	OXER1	FPR2
HGNC, UniProt	OXER1, Q8TDS5	FPR2, P25090
Potency order of endogenous agonists	–	Lipid mediators for resolution of inflammation: LXA ₄ = aspirin triggered lipoxin A ₄ = ATLa ₂ = resolvin D1 > LTC ₄ = LTD ₄ >> 15-deoxy-LXA ₄ >> C16:0 ceramide Proteins and peptides for balanced activation: fMLKLIV = fMTPMRKINPLMKLIN > serum amyloid A (SAA1, PODJ18) > LL-37 (CAMP, P49913) [517, 610, 776, 778, 833, 979, 1682, 2717, 2765]
Potency order of endogenous and other ligands	5-oxo-EETE, 5-oxo-C20:3, 5-oxo-ODE > 5-oxo-15-HETE > 5S-HPETE > 5S-HETE [964, 1168, 1304, 2100, 2180, 2273, 2539]	For lipid mediators (resolving) LXA ₄ = aspirin triggered lipoxin A ₄ = ATLa ₂ = resolvin D1 >> 15-deoxy-LXA ₄ > C16:0 ceramide For other ligands: WKYVMm > BMS-986235 > ACT-389949 > mitochondrial formyl peptides [517, 776, 778, 833, 853, 979, 1586, 1682, 2204, 2217, 2310, 2323, 2765]
Endogenous agonists	–	LXA ₄ [776], resolvin D1 [1500], serum amyloid A (SAA1, PODJ18) [2717], annexin I-(2-26) (ANXA1, P04083) [872, 1080, 2216, 2980], LL-37 (CAMP, P49913) [610], LTC ₄ , LTD ₄ , resolvin D3 [2097]
Agonists	–	WKYVMm [1586], ACT-389949 [2685]
Selective agonists	–	BMS-986235 [91], ATLa ₂ [996]
Endogenous antagonists	5-oxo-12-HETE (pIC ₅₀ 6.3) [2272]	–
Antagonists	S-Y048 (pIC ₅₀ 10.7) [3178]	WRWWWW (pIC ₅₀ 6.6) [121], t-Boc-FLFLF (pIC ₅₀ 4.3–6) [814, 2693]
Selective antagonists	–	PBP10 (pIC ₅₀ 7) [795], quin-C7 (pEC ₅₀ 5.2) [3254]
Labelled ligands	[³ H]5-oxo-EETE (Agonist) [2100]	[³ H]LXA ₄ (Agonist) [776, 777], [¹²⁵ I-Tyr]Ac2-26 (Agonist) [2216]
Comments	–	Ceramides (C14:0, C16:0, C18:0) [1682], formyl peptides (fMLKLIV, fMTPMRKINPLMKLIN) [833, 2323] and Aβ ₄₂ are endogenous agonists [2832]. Other agonists include PSMα peptides [2351], HIVgp120 [624] and synthetic molecules such as BMS-986235, ACT-389949 and Quin-C1 [2028]. New potent FPR2 agonists confirm this receptor's anti-inflammatory, pro-resolving and neuroprotective functions [802].

Comments: The FPR2 receptor (**nomenclature as agreed by the NC-IUPHAR subcommittee on Leukotriene and Lipoxin Receptors** [119]) is activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A₄ (LXA₄) and 15-epi-LXA₄ (aspirin triggered lipoxin A₄, ATL). The FPR2/ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide [469] as well as annexin I (ANXA1, P04083) (ANXA1) and its N-terminal peptides [535, 2216]. In addition, a soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has been reported to activate the FPR2/ALX receptor [2370]. Furthermore, FPR2/ALX has been suggested to act as a receptor medi-

ating the proinflammatory actions of the acute-phase reactant, serum amyloid A [2654, 2717]. FPR2/ALX has also been reported to be activated by resolvin D1 [2051] and resolvin D3 [2097]. The agonist activity of the lipid mediators described has been questioned [1044, 2255], which may derive from batch-to-batch differences, partial agonism or biased agonism. Results from Co-oray *et al.* (2013) [535] have addressed this issue and the role of homodimers and heterodimers in intracellular signaling. ATL-induced conformational changes of recombinant human ALX was demonstrated using FRET analysis [880]; ATL gives a bell-shaped concentration-response relationship, inducing maximal conformational changes of ALX at 0.1–1 nM. In addition, the

crystal structure of ALX was reported at 2.8 Å resolution [449]. A receptor selective for LXB₄ has been suggested from functional studies [80, 1771, 2413]. Note that the data for FPR2/ALX are also reproduced on the [Formylpeptide receptor pages](#). Oxoeicosanoid receptors (OXER1, **nomenclature agreed by the NC-IUPHAR subcommittee on Leukotriene receptors** [305]) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-EETE the most potent agonist identified for this receptor. Initial characterization of the heterologously expressed OXER1 suggested that polyunsaturated fatty acids, such as docosahexaenoic acid and EPA, acted as receptor antagonists [1168].

Further reading on Leukotriene receptors

- Brink C *et al.* (2003) International Union of Pharmacology XXXVII. Nomenclature for leukotriene and lipoxin receptors. *Pharmacol Rev* **55**: 195-227 [PMID:12615958]
- Brink C *et al.* (2004) International Union of Pharmacology XLIV. Nomenclature for the oxoecosanoid receptor. *Pharmacol Rev* **56**: 149-57 [PMID:15001665]
- Bäck M *et al.* (2011) International Union of Basic and Clinical Pharmacology. LXXXIV: leukotriene receptor nomenclature, distribution, and pathophysiological functions. *Pharmacol Rev* **63**: 539-84 [PMID:21771892]
- Bäck M *et al.* (2014) Update on leukotriene, lipoxin and oxoecosanoid receptors: IUPHAR Review 7. *Br J Pharmacol* **171**: 3551-74 [PMID:24588652]
- Laidlaw TM *et al.* (2012) Cysteinyl leukotriene receptors, old and new; implications for asthma. *Clin Exp Allergy* **42**: 1313-20 [PMID:22925317]

Lysophospholipid (LPA) receptors

G protein-coupled receptors → Lysophospholipid (LPA) receptors

Overview: Lysophosphatidic acid (LPA) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid Receptors** [586, 1396, 1927, 3157]) are activated by the endogenous phospholipid LPA. The first receptor, LPA₁, was identified as *ventricular zone gene-1* (*vzg-1*) [1091]. This discovery represented the beginning of the de-orphanisation of members of the endothelial differentiation gene (*edg*) family, as other LPA and sphingosine 1-phosphate (S1P) receptors were found. Five additional LPA receptors (LPA_{2,3,4,5,6}) have since been identified [1927] and their gene nomenclature codified for human *LPAR1*, *LPAR2*, *etc.* (HUGO Gene Nomenclature Committee, HGNC) and *Lpar1*, *Lpar2*, *etc.* for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function of their corresponding proteins. The high-resolution structures

of LPA₁ [29, 30, 489, 1717] and LPA₆ [683, 2793] determined by both X-ray crystallography and cryo-electron microscopy, are solved and indicate that LPA accesses the extracellular binding pocket, consistent with its proposed delivery via autotaxin [489]. These studies have also implicated crosstalk with endocannabinoids *via* phosphorylated intermediates that can also activate these receptors. The binding affinities to LPA₁ of unlabeled, natural LPA and anandamide phosphate (AEAp) were measured using backscattering interferometry (pK_d = 9) [1928, 2357]. Utilization of this method indicated affinities that were 77-fold lower than when measured using radioactivity-based protocols [3156]. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. admilparant (BMS-986278) [538], a selective LPA₁ receptor antagonist,

is currently in Phase III trials for pulmonary fibrosis. Other LPA₁-targeting drugs such as BMS-986020 were discontinued due to hepatotoxicity [2157], while preclinical candidates like PIPE 791 [2260] are being explored for neurological and fibrotic diseases. Multiple groups have independently published validation of all six LPA receptors described in these tables, and further validation was achieved using a distinct read-out *via* a novel TGFα “shedding” assay [1227]. Moreover, LPA has also been described as an agonist for the transient receptor potential (Trp) ion channels TRPV1 [2074] and TRPA1 [1440]. All of these proposed non-GPCR receptor identities require confirmation and are not currently recognized as *bona fide* LPA receptors.

Nomenclature	LPA ₁ receptor	LPA ₂ receptor	LPA ₃ receptor	LPA ₄ receptor	LPA ₅ receptor	LPA ₆ receptor
HGNC, UniProt	<i>LPAR1</i> , Q92633	<i>LPAR2</i> , Q9HBW0	<i>LPAR3</i> , Q9UBYS	<i>LPAR4</i> , Q99677	<i>LPAR5</i> , Q9H1C0	<i>LPAR6</i> , P43657
Agonists	UCM-05194 [938]	–	–	–	–	–
Selective agonists	–	dodecylphosphate [2948], decyl dihydrogen phosphate [2948], GRI977143 [1433]	OMPT [1059]	–	–	–
Antagonists	Ki16425 (pIC ₅₀ 6.6–6.9) [2117] – Mouse, VPC12249 (pK _i 5.2–6.9) [1097] – Mouse, VPC32179 [1090]	–	VPC12249 (pK _i 6.4) [1097], VPC32179 [1090]	–	compound 66 (pIC ₅₀ 7.5) [3221], compound 65 (pIC ₅₀ 7.2) [3221]	–
Sub/family-selective antagonists	–	–	Ki16425 (pK _i 6.4) [2117]	–	–	–
Selective antagonists	BMS-986020 (pIC ₅₀ 8.9), AM966 (pIC ₅₀ 6.7–7.8) [2745], ONO-7300243 (pIC ₅₀ 6.8) [2802], AM095 (pIC ₅₀ 6–6.1) [2745]	H2L5186303 (pIC ₅₀ 8.1) [760, 761], UCM-14216 (pIC ₅₀ 5.7) [1389]	dioctanoylglycerol pyrophosphate (pK _i 5.5–7) [780, 2117]	–	AS2717638 (pIC ₅₀ 7.4) [2001], TCLPAS (pIC ₅₀ 6.1) [1489]	–

Comments: Ki16425 [2117], VPC12249 [1097] and VPC32179 [1090] have dual antagonist activity at LPA₁ and LPA₃ receptors. There is growing evidence for *in vivo* efficacy of these chemical antagonists in several disorders, including fetal hydrocephalus [3207], fetal hypoxia [1110], lung fibrosis [2112], systemic sclerosis [2112] and atherosclerosis progression [1501]. LPA₂ selective antagonist SAR100842 [1595], and LPA₁ selective agonist UCM-05194 [938], are proposed for therapy of systemic sclerosis and neuropathic pain, respectively. The LPA₂ selective agonist, GRI977143, shows efficacy in an animal model of multiple sclerosis [2517]. The LPA₅ selective antagonist, AS2717638, is effective in pain models [1364]. Antidepressants, amitriptyline, clomipramine, and mianserin, are reported to show profibrotic responses *via* LPA₁ [2131].

Further reading on Lysophospholipid (LPA) receptors

- Chun J *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol Rev* **62**: 579-87 [PMID:21079037]
 Mizuno H *et al.* (2020) Druggable Lipid GPCRs: Past, Present, and Prospects. *Adv Exp Med Biol* **1274**: 223-258 [PMID:32894513]
 Kihara Y *et al.* (2014) Lysophospholipid receptor nomenclature review: IUPHAR Review 8. *Br J Pharmacol* **171**: 3575-94 [PMID:24602016]
 Yung YC *et al.* (2015) Lysophosphatidic Acid signaling in the nervous system. *Neuron* **85**: 669-82 [PMID:25695267]

Lysophospholipid (S1P) receptors

G protein-coupled receptors → Lysophospholipid (S1P) receptors

Overview: Sphingosine 1-phosphate (S1P) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid receptors** [1396]) are activated by the endogenous lipid sphingosine 1-phosphate (S1P). Originally cloned as orphan members of the endothelial differentiation gene (*edg*) family [231, 1927], the receptors are currently designated as S1P₁R through S1P₅R [231, 1137, 1927]. Their gene nomenclature has been codified as human *S1PR1*, *S1PR2*, *etc.* (HUGO Gene Nomenclature Committee, HGNC) and *S1pr1*, *S1pr2*, *etc.* for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function. All S1P receptors (S1PRs) have been knocked-out in mice constitutively and in some cases, conditionally. S1P receptors, particularly S1P₁, are expressed throughout all mammalian organ systems. Ligand delivery occurs *via* two

known carriers (or “chaperones”): albumin and HDL-bound apolipoprotein M (ApoM), the latter of which elicits biased agonist signaling by S1P₁ in multiple cell types [233, 841]. The five S1PRs, two chaperones, and active cellular metabolism have complicated analyses of receptor ligand binding in native systems. Signaling pathways and physiological roles have been characterized through radioligand binding in heterologous expression systems, targeted deletion of the different S1PRs, and most recently, mouse models that report *in vivo* S1P₁R activation [1470, 1471]. The structures of S1P₁ [1045, 1717, 3141, 3202], S1P₂ [437], S1P₃ [1778, 3245], and S1P₅ [1756, 3205] are solved, and confirmed aspects of ligand binding, specificity, and receptor activation, determined previously through biochemical and genetic studies [232, 1045]. Fingolimod (FTY720), the first FDA-approved

drug to target any of the lysophospholipid receptors, binds as a phosphorylated metabolite to four of the five S1PRs, and was the first oral therapy for multiple sclerosis (MS) [502]. Second-generation S1PR modulators siponimod and ozanimod target S1P₁ and S1P₅, while etrasimod targets S1P₁, S1P₄ and S1P₅; and ponesimod targets S1P₁ alone, and all are FDA approved for the treatment of various MS forms [231, 1927] and/or ulcerative colitis for ozanimod and etrasimod [2470, 2601]. The mechanisms of action of fingolimod and other S1PR-modulating drugs now in development include binding S1PRs in multiple organ systems, *e.g.*, immune and nervous systems, although the precise nature of their receptor interactions requires clarification, although most S1P₁ effects appear to involve functional antagonism [522, 982, 983, 2287].

Nomenclature	S1P ₁ receptor	S1P ₂ receptor	S1P ₃ receptor	S1P ₄ receptor	S1P ₅ receptor
HGNC, UniProt	<i>S1PR1</i> , P21453	<i>S1PR2</i> , O95136	<i>S1PR3</i> , Q99500	<i>S1PR4</i> , O95977	<i>S1PR5</i> , Q9H228
Potency order of endogenous ligands	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [64, 2123]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [64, 2123]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [2123]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [2909]	sphingosine 1-phosphate > dihydro-sphingosine 1-phosphate [1222]

Agonists	fingolimod-phosphate [306, 794], siponimod [919, 2159], BMS-986166 (Partial agonist) [914], BMS-986104 derivative 12 (Biased agonist) [913], BMS-986104 derivative 24 (Biased agonist) [913], etrasimod [352], SAR247799 (Biased agonist) [2258], ST-2191 [2694], ST-1478 [1224], ST-1505 [1224]	S1P d20:1 (Partial agonist) [2964]	fingolimod-phosphate [306, 794], fingolimod-phosphate [306, 794]	fingolimod-phosphate [306, 794, 2160, 2475, 3145], etrasimod [351, 352]	fingolimod-phosphate [306, 794, 2160], siponimod [870, 899, 2895], etrasimod [352]
Selective agonists	RP-001 [358], cenerimod [2238], CYM5442 [937], ponesimod [251], SEW2871 [2475] – Mouse	–	CYM-5541 [1295]	CYM-50308 [2896], SLB736 [1160]	A-971432 [638, 1142]
Antagonists	VPC23019 (pK _i 7.9) [592], VPC03090-P (pK _i 7.6–7.7) [1380], VPC44116 (pIC ₅₀ 7.6) [796]	–	VPC44116 (pK _i 6.5) [796], VPC23019 (pK _i 5.9) [592]	–	–
Selective antagonists	NIBR-0213 (pIC ₅₀ 8.6) [2314], W146 (pK _i 7.1) [2476]	JTE-013 (pIC ₅₀ 7.8) [2141]	TY-52156 (pK _i 7) [2002]	CYM-50358 (pIC ₅₀ 7.6) [407, 991]	compound 15 (pIC ₅₀ 10) [1759]

Comments: The FDA-approved immunomodulator [fingolimod](#) (FTY720) is phosphorylated *in vivo* [39] to generate an agonist with activity at S1P₁, S1P₃, S1P₄ and S1P₅ receptors [306, 1801]. Many of the physiological consequences of [fingolimod-phosphate](#) administration, as well as those of other currently described S1P₁ agonists, may involve functional antagonism *via* ubiquitination and subsequent degradation of S1P₁ [231, 2139]. Additionally, receptor specificities of the different compounds may depend on the functional assay system utilized and from which species the receptor sequence originated.

Further reading on Lysophospholipid (S1P) receptors

- Cartier A *et al.* (2019) Sphingosine 1-phosphate: Lipid signaling in pathology and therapy. *Science* **366**: [PMID:31624181]
- Chew WS *et al.* (2016) To fingolimod and beyond: The rich pipeline of drug candidates that target S1P signaling. *Pharmacol Res* **113**: 521-532 [PMID:27663260]
- Chun J *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol Rev* **62**: 579-87 [PMID:21079037]
- Pyne NJ *et al.* (2017) Sphingosine 1-Phosphate Receptor 1 Signaling in Mammalian Cells. *Molecules* **22**: [PMID:28241498]
- Rosen H *et al.* (2013) Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. *Annu Rev Biochem* **82**: 637-62 [PMID:23527695]
- Yanagida K *et al.* (2017) Vascular and Immunobiology of the Circulatory Sphingosine 1-Phosphate Gradient. *Annu Rev Physiol* **79**: 67-91 [PMID:27813829]

Melanin-concentrating hormone receptors

G protein-coupled receptors → Melanin-concentrating hormone receptors

Overview: Melanin-concentrating hormone (MCH) receptors (**provisional nomenclature as recommended by NC-IUPHAR** [789]) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRQCQV; mammalian MCH) generated from a precursor (*PMCH*, P20382), which also produces [neuropeptide EI](#) (*PMCH*, P20382) and [neuropeptide GE](#) (*PMCH*, P20382).

Nomenclature	MCH ₁ receptor	MCH ₂ receptor
HGNC, UniProt	MCH1 , Q99705	MCH2 , Q969V1
Selective antagonists	GW803430 (pIC ₅₀ 9.3) [1113], SNAP-7941 (pA ₂ 9.2) [270], T-226296 (pIC ₅₀ 8.3) [2775], ATC0175 (pIC ₅₀ 7.9–8.1) [413]	–
Labelled ligands	[¹²⁵I]S36057 (Antagonist) (pK _d 9.2–9.5) [98], [¹²⁵I][Phe¹³,Tyr¹⁹]MCH (Agonist) [343], [³H]MCH (human, mouse, rat) (Agonist) [343]	–

Comments: The MCH₂ receptor appears to be a non-functional pseudogene in rodents [[2781](#)].

Further reading on Melanin-concentrating hormone receptors

Chung S *et al.* (2011) Recent updates on the melanin-concentrating hormone (MCH) and its receptor system: lessons from MCH1R antagonists. *J Mol Neurosci* **43**: 115-21 [[PMID:20582487](#)]

Eberle AN *et al.* (2010) Cellular models for the study of the pharmacology and signaling of melanin-concentrating hormone receptors. *J Recept Signal Transduct Res* **30**: 385-402 [[PMID:21083507](#)]

Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [[PMID:15914470](#)]

Takase K *et al.* (2014) Meta-analysis of melanin-concentrating hormone signaling-deficient mice on behavioral and metabolic phenotypes. *PLoS ONE* **9**: e99961 [[PMID:24924345](#)]

Melanocortin receptors

G protein-coupled receptors → Melanocortin receptors

Overview: Melanocortin receptors (**provisional nomenclature as recommended by NC-IUPHAR** [[789](#)]) are activated by members of the melanocortin family (α -MSH ([POMC](#), [P01189](#)), β -MSH ([POMC](#), [P01189](#)) and γ -MSH ([POMC](#), [P01189](#)) forms; δ form is not found in mammals) and adrenocorticotrophin (ACTH

([POMC](#), [P01189](#))). Endogenous antagonists include [agouti](#) ([ASIP](#), [P42127](#)) and [agouti-related protein](#) ([AGRP](#), [O00253](#)). ACTH(1-24) was approved by the US FDA as a diagnostic agent for adrenal function test. [Setmelanotide](#) was approved by the US FDA for weight management in patients with POMC, PCSK1 or LEPR de-

fiency, [bremelanotide](#) was approved by the US FDA for generalized hypoactive sexual desire disorder in premenopausal women, and NDP-MSH ([afamelanotide](#)) was approved by the EMA for the treatment of erythropoietic protoporphyria. Several synthetic melanocortin receptor agonists are under clinical development.

Nomenclature	MC ₁ receptor	MC ₂ receptor	MC ₃ receptor	MC ₄ receptor	MC ₅ receptor
HGNC, UniProt	MC1R , Q01726	MC2R , Q01718	MC3R , P41968	MC4R , P32245	MC5R , P33032
Potency order of endogenous agonists	α -MSH (POMC , P01189) > β -MSH (POMC , P01189) > ACTH (POMC , P01189), γ -MSH (POMC , P01189)	ACTH (POMC , P01189)	γ -MSH (POMC , P01189), β -MSH (POMC , P01189) > ACTH (POMC , P01189), α -MSH (POMC , P01189)	β -MSH (POMC , P01189) > α -MSH (POMC , P01189), ACTH (POMC , P01189) > γ -MSH (POMC , P01189)	α -MSH (POMC , P01189) > β -MSH (POMC , P01189) > ACTH (POMC , P01189) > γ -MSH (POMC , P01189)
Selective agonists	–	corticotropin zinc hydroxide	[D-Trp ⁸] γ -MSH [973]	THIQ [2550], setmelanotide [516 , 1522]	–
Antagonists	–	–	PG-106 (pIC ₅₀ 6.7) [974]	–	–
Selective antagonists	–	–	–	MBP10 (pIC ₅₀ 10) [176], HS014 (pK _i 8.5) [2512]	–
Labelled ligands	[¹²⁵I]NDP-MSH (Agonist) [1477]	[¹²⁵I]ACTH-(1-24) (Agonist) [1477]	[¹²⁵I]NDP-MSH (Agonist) [1477], [¹²⁵I]SHU9119 (Antagonist) [2069]	[¹²⁵I]SHU9119 (Antagonist) (pK _d 9.2) [2069], [¹²⁵I]NDP-MSH (Agonist) [1477 , 2511]	[¹²⁵I]NDP-MSH (Agonist) [1477]

Comments: Polymorphisms of the MC₁ receptor have been linked to variations in skin pigmentation. Defects of the MC₂ receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC₄ receptor have been linked to obesity [412, 751].

Further reading on Melanocortin receptors

- Caruso V *et al.* (2014) Synaptic changes induced by melanocortin signalling. *Nat Rev Neurosci* **15**: 98-110 [PMID:24588018]
- Renquist BJ *et al.* (2011) Physiological roles of the melanocortin MC₃ receptor. *Eur J Pharmacol* **660**: 13-20 [PMID:21211527]
- Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]

Melatonin receptors

G protein-coupled receptors → Melatonin receptors

Overview: Melatonin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Melatonin Receptors** [687]) are activated by the endogenous ligands **melatonin** and clinically used drugs like **ramelteon**, **agomelatine** and **tasimelteon**.

Nomenclature	MT ₁ receptor	MT ₂ receptor
HGNC, UniProt	<i>MTNR1A</i> , P48039	<i>MTNR1B</i> , P49286
Endogenous agonists	melatonin [99, 686, 688]	melatonin [99, 686, 688]
Agonists	ramelteon [1355], agomelatine [99, 199], tasimelteon [2329]	agomelatine [99, 199], tasimelteon [2329], ramelteon [1355, 2355]
Selective agonists	–	UCM1014 [2670], IIK7 [753, 2722], 5-methoxy-luzindole (Partial agonist) [688]
Selective antagonists	UCSF7447 (Inverse agonist) (pEC ₅₀ 7.3) [2691]	4P-PDOT (pK _i 8.8–9.4) [99, 688, 689], K185 (pK _i 9.3) [753, 2722], DH97 (pK _i 8) [2800]
Labelled ligands	[¹²⁵ I]SD6 (Agonist) [1612], 2-[¹²⁵ I]melatonin (Agonist) [99, 688], [³ H]melatonin (Agonist) [324]	[¹²⁵ I]SD6 (Agonist) [1612], 2-[¹²⁵ I]melatonin (Agonist) [99, 688], [¹²⁵ I]DIV880 (Agonist, Partial agonist) [1612], [³ H]melatonin (Agonist) [324], PBI-8192 (Selective Agonist) [876]

Comments: **Melatonin**, **2-iodo-melatonin**, **agomelatine**, **GR 196429**, **LY 156735** and **ramelteon** [1355] are nonselective agonists for MT₁ and MT₂ receptors. (-)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT₁ receptors (see **AMMTC** for structure) [2835]. **Luzindole** is an MT₁/MT₂ non-selective competitive melatonin receptor antagonist with about 15-25 fold selectivity for the MT₂ receptor [689]. MT₁/MT₂ heterodimers present different pharmacological profiles from MT₁ and MT₂ receptors [111].

The MT₃ binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML₂ receptor, binds selectively **2-iodo-[¹²⁵I]5MCA-NAT** [1937]. Pharmacological investigations of MT₃ binding sites have primarily been conducted in hamster tissues. At this site, The endogenous ligand **N-acetylserotonin** [710, 1741, 1937, 2261] and **5MCA-NAT** [2261] appear to function as agonists, while **prazosin** [1741] functions as an antagonist. The MT₃ binding site of hamster kidney was also identified as the hamster homologue of human quinone reductase 2 (**NQO2**,

P16083[2092, 2093]). The MT₃ binding site activated by **5MCA-NAT** in eye ciliary body is positively coupled to adenylyl cyclase and regulates chloride secretion [1197]. *Xenopus* melanophores and chick brain express a distinct receptor (x420, P49219; c346, P49288, initially termed Mel_{1C}) coupled to the G_{i/o} family of G proteins, for which GPR50 has recently been suggested to be a mammalian counterpart [692] although **melatonin** does not bind to GPR50 receptors. Several variants of the *MTNR1B* gene have been associated with increased type 2 diabetes risk [1348].

Further reading on Melatonin receptors

- Bedini A *et al.* (2024) Industrial and academic approaches to the search for alternative melatonin receptor ligands: An historical survey. *J Pineal Res* **76**: e12953 [PMID:38682544]
- Cecon E *et al.* (2018) Melatonin receptors: molecular pharmacology and signalling in the context of system bias. *Br J Pharmacol* **175**: 3263-3280 [PMID:28707298]
- Dubocovich ML *et al.* (2010) International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. *Pharmacol Rev* **62**: 343-80 [PMID:20605968]
- Jockers R *et al.* (2016) Update on melatonin receptors: IUPHAR Review 20. *Br J Pharmacol* **173**: 2702-25 [PMID:27314810]
- Karamitri A *et al.* (2019) Melatonin in type 2 diabetes mellitus and obesity. *Nat Rev Endocrinol* **15**: 105-125 [PMID:30531911]
- Liu J *et al.* (2016) MT1 and MT2 Melatonin Receptors: A Therapeutic Perspective. *Annu Rev Pharmacol Toxicol* **56**: 361-83 [PMID:26514204]
- Okamoto HH *et al.* (2024) Melatonin receptor structure and signaling. *J Pineal Res* **76**: e12952 [PMID:38587234]

Metabotropic glutamate receptors

G protein-coupled receptors → Metabotropic glutamate receptors

Overview: Metabotropic glutamate (mGlu) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors** [2521]) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate [971]. The mGlu family is composed of eight members (named mGlu₁ to mGlu₈) which are divided in three groups based on similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I (mGlu₁ and mGlu₅), Group-II (mGlu₂ and mGlu₃) and Group-III (mGlu₄, mGlu₆, mGlu₇ and mGlu₈) (see Further reading). Structurally, mGlu are composed of three juxtaposed domains: a core G protein-activating seven-transmembrane domain (TM), common to all GPCRs, is linked *via* a rigid cysteine-rich domain (CRD) to the Venus Flytrap domain (VFTD), a large bi-lobed extracellular domain where glutamate binds. mGlu form constitutive dimers, cross-linked by a disulfide bridge. The structures of the VFTD of mGlu₁, mGlu₂, mGlu₃, mGlu₅ and mGlu₇ have been solved [1525, 1948, 2008, 2870]. The structure of the 7

transmembrane (TM) domains of both mGlu₁ and mGlu₅ have been solved, and confirm a general helical organisation similar to other GPCRs, although the helices appear more compacted [495, 671, 3105]. Recent advances in cryo-electron microscopy have provided structures of full-length mGlu receptor homodimers [1454, 1687], heterodimers [681, 1192], and new insights into activation mechanisms [374, 375, 1499]. Studies have revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [675]. First characterised in transfected cells, co-localisation and specific pharmacological properties suggest the existence of such heterodimers in the brain [1009, 1689, 1876, 1961, 2086, 3189]. Beyond heteromerisation with other mGlu receptor subtypes, increasing evidence suggests mGlu receptors form heteromers and larger order complexes with class A GPCRs (reviewed in [971]). The endogenous ligands of mGlu are **L-glutamic acid**, **L-serine-O-phosphate**, **N-acetylaspartylglutamate (NAAG)** and **L-cysteine sulphonic acid**. Group-I mGlu receptors may be acti-

vated by **3,5-DHPG** and **(S)-3HPG** [287] and antagonised by **(S)-hexylhomobotenic acid** [1774]. Group-II mGlu receptors may be activated by **LY389795** [1949], **LY379268** [1949], **eglumegad** (also referred to as LY354470) [2523, 3111], **DCG-IV** and **(2R,3R)-APDC** [2524], and antagonised by **eGlu** [1267] and **LY307452** [735, 3050]. Group-III mGlu receptors may be activated by **L-AP4** and **(R,S)-4-PPG** [865]. An example of an antagonist selective for mGlu receptors is **LY341495**, which blocks mGlu₂ and mGlu₃ at low nanomolar concentrations, mGlu₈ at high nanomolar concentrations, and mGlu₄, mGlu₅, and mGlu₇ in the micromolar range [1422]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that recognise distinct sites primarily within the TM domain have been described. Negative allosteric modulators are listed separately. Positive allosteric modulators potentiate orthosteric agonist responses solely, or may also possess intrinsic agonist activity.

Nomenclature	mGlu ₁ receptor	mGlu ₂ receptor	mGlu ₃ receptor	mGlu ₄ receptor	mGlu ₅ receptor
HGNC, UniProt	GRM1 , Q13255	GRM2 , Q14416	GRM3 , Q14832	GRM4 , Q14833	GRM5 , P41594
Endogenous agonists	L-glutamic acid [2245]	L-glutamic acid [2245]	L-glutamic acid [2245], NAAG [2536]	L-serine-O-phosphate [3111], L-glutamic acid [2245]	L-glutamic acid [2245]
Agonists	3,5-DHPG [1569, 2522] – Rat	eglumegad [1299, 1949]	eglumegad [1299, 1949]	L-AP4 [3111]	3,5-DHPG (Partial agonist) [2007, 2522] – Rat
Selective agonists	–	–	–	LSP4-2022 [951]	CHPG [2007]
Antagonists	LY367385 (pIC ₅₀ 5.1) [513]	–	–	MAP4 (pK _i 4.6) [1032] – Rat	–

Selective antagonists	3-MATIDA (pIC ₅₀ 5.2) [1980] – Rat, AIDA (pA ₂ 4.2) [1981]	–	–	–	ACDPP (pIC ₅₀ 6.9) [264]
Allosteric modulators (Positive)	–	CBiPES (pEC ₅₀ 7) [1301], 4-MPPTS (pIC ₅₀ 5.8) [144, 1300, 1301, 2501]	–	SIB-1893 (obtained in the presence of L-AP4) (pEC ₅₀ 6.3–6.8) [1835], MPEP (obtained in the presence of L-AP4) (pEC ₅₀ 6.3–6.6) [1835], PHCCC (obtained in the presence of L-AP4) (pEC ₅₀ 4.5) [1789]	CDPPB (pEC ₅₀ 7.6–8) [1424, 1695]
Allosteric modulators (Negative)	–	–	MNI-137 (pIC ₅₀ 7.7) [1103] – Rat, VU0650786 (pIC ₅₀ 6.4) [723]	–	alloswitch-1 (pIC ₅₀ 8.1) [2253] – Rat, MTEP (pK _i 7.8) [316], MPEP (pIC ₅₀ 7.4–7.7) [864, 866], fenobam (pIC ₅₀ 7.2) [2265]
Selective allosteric modulators	BAY 367620 (Negative) (pK _i 9.5) [388] – Rat, JNJ16259685 (Negative) (pIC ₅₀ 8.9) [1570], Ro01-6128 (Positive) (pK _i 7.5–7.7) [1449] – Rat, LY456236 (Negative) (pIC ₅₀ 6.9) [480], CPCCOEt (Negative) (pIC ₅₀ 5.2–5.8) [1698]	Ro64-5229 (Negative) (pIC ₅₀ 7) [1465] – Rat, biphenylindanone A (Positive) (pEC ₅₀ 7) [265]	ML337 (Negative) (pIC ₅₀ 6.2) [3047] – Rat	VU0361737 (Positive) (pEC ₅₀ 6.6) [722], VU0155041 (Positive) (pEC ₅₀ 6.1) [2085]	VU0409551 (Positive) (pK _B 7.1) [2415], VU0360172 (Positive) (pK _B 6.6–7) [972, 2406]

Nomenclature	mGlu₆ receptor	mGlu₇ receptor	mGlu₈ receptor
HGNC, UniProt	GRM6 , O15303	GRM7 , Q14831	GRM8 , O00222
Endogenous agonists	L-glutamic acid [2245]	L-glutamic acid [2245]	L-serine-O-phosphate [1793, 3111], L-glutamic acid [2245]
Agonists	L-AP4 [1567, 2018, 2820]	LSP4-2022 [951], L-serine-O-phosphate [3111], L-AP4 [3111]	(S)-3,4-DCPG [2820], L-AP4 [1793]
Selective agonists	homo-AMPA [296]	–	–
Antagonists	MAP4 (pIC ₅₀ 3.5) [2242] – Rat	–	MPPG (pIC ₅₀ 4.3) [3111]
Allosteric modulators (Positive)	–	AMN082 (pEC ₅₀ 6.5–6.8) [1921]	VU0422288 (pK _B 6.7) [1266], VU0155094 (pK _B 5) [1266]
Allosteric modulators (Negative)	–	MMPiP (pIC ₅₀ 6.1–7.6) [2084, 2740] – Rat, ADX71743 (pIC ₅₀ 7.2) [1329], XAP044 (pIC ₅₀ 5.6) [881]	–

Comments: The activity of [NAAG](#) as an agonist at mGlu₃ receptors was questioned on the basis of contamination with glutamate [484, 817], but this has been refuted [2040]. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors and may have unappreciated biased or neutral activity at other subtypes [1102]. Potential differences linked to the species (*e.g.* human *versus* rat or mouse) of the receptors and the receptor splice variants are generally not known.

The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling. [DCG-IV](#) also exhibits agonist activity at NMDA glutamate receptors [2900], and is an antagonist at all Group-III mGluRs with an IC₅₀ of 30 μM. A potential novel metabotropic glutamate receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by [4-methylhomobotenic acid](#) (ineffective

as an agonist at recombinant Group I metabotropic glutamate receptors), but is resistant to [LY341495](#) [503]. There are also reports of a distinct metabotropic glutamate receptor coupled to phospholipase D in rat brain, which does not readily fit into the current classification [1442, 2198]. A related class C receptor composed of two distinct subunits, T1R1 + T1R3 is also activated by glutamate and is responsible for umami taste detection.

Further reading on Metabotropic glutamate receptors

- Ferraguti F *et al.* (2006) Metabotropic glutamate receptors. *Cell Tissue Res* **326**: 483-504 [PMID:16847639]
- Gregory KJ *et al.* (2021) International Union of Basic and Clinical Pharmacology. CXI. Pharmacology, Signaling, and Physiology of Metabotropic Glutamate Receptors. *Pharmacol Rev* **73**: 521-569 [PMID:33361406]
- Nicoletti F *et al.* (2011) Metabotropic glutamate receptors: from the workbench to the bedside. *Neuropharmacology* **60**: 1017-41 [PMID:21036182]
- Niswender CM *et al.* (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol* **50**: 295-322 [PMID:20055706]
- Pin JP *et al.* (2016) Organization and functions of mGlu and GABAB receptor complexes. *Nature* **540**: 60-68 [PMID:27905440]
- Rondard P *et al.* (2011) The complexity of their activation mechanism opens new possibilities for the modulation of mGlu and GABAB class C G protein-coupled receptors. *Neuropharmacology* **60**: 82-92 [PMID:20713070]

Motilin receptor

G protein-coupled receptors → Motilin receptor

Overview: Motilin receptors (**provisional nomenclature**) are activated by **motilin** (*MLN*, P12872), a 22 amino-acid peptide derived from a precursor (*MLN*, P12872), which may also generate a **motilin-associated peptide** (*MLN*, P12872). There are significant species differences in the structure of motilin and its receptor, and in the functions of motilin. In humans and large mammals such as dog, activation of these receptors by motilin

released from endocrine cells in the duodenal mucosa during fasting, induces propulsive phase III movements. This activity is associated with promoting hunger in humans. In humans and other mammals drugs and other non-peptide compounds which activate the motilin receptor may generate a more long-lasting ability to increase cholinergic activity within the upper gut, to promote upper gastrointestinal motility; this activity is suggest-

ed to be responsible for the gastrointestinal prokinetic effects of certain macrolide antibacterials (often called motilides; *e.g.* erythromycin, azithromycin), although for many of these molecules the evidence is sparse. Relatively high doses may induce vomiting and in humans, nausea.

Nomenclature	motilin receptor
HGNC, UniProt	<i>MLNR</i> , O43193
Endogenous agonists	motilin (<i>MLN</i> , P12872) [544, 1841, 1842, 1843]
Agonists	alemcinol [2814], erythromycin [757, 2814], azithromycin [310]
Selective agonists	camicinal [153, 2474], mitemcinol [1456, 2764] – Rabbit
Selective antagonists	MA-2029 (pA ₂ 9.2) [2718], GM-109 (pIC ₅₀ 8) [1049] – Rabbit
Labelled ligands	[¹²⁵ I]motilin (human) (Agonist) [757]

Comments: In terms of structure, the motilin receptor has closest homology with the ghrelin receptor. Thus, the human motilin receptor shares 52% overall amino acid identity with the human ghrelin receptor and 86% in the transmembrane regions [1084, 2764, 2814]. However, differences between the N-terminus regions of these receptors means that their cognate peptide ligands do not readily activate each other [579, 2474]. Where studied the motilin receptor does not appear to have constitutive activity [1153]. Although not proven, the existence of biased agonism at the receptor has been suggested [1843, 1918, 2471]. A truncated 5-transmembrane structure has been identified but this is without activity when transfected into a host cell [5]. Receptor dimerisation has not been reported. It must be noted that for the complex mac-

rolide structures, selectivity of action has often not been rigorously examined and other actions are possible (*e.g.* P2X inhibition by erythromycin; [3246]). Small molecule and selective motilin receptor agonists are now described [1648, 2474, 3054]. Significant species-dependent variations exist. Among mammals, the gene encoding the motilin precursor is absent in laboratory rodents, while the receptor appears to be a pseudogene [1084, 2472]. Functions of motilin are not usually detected in rodents, although brain and other responses to motilin and macrolides continue to be reported and the mechanism of these actions is obscure. In some non-laboratory rodents (*e.g.* North American kangaroo rat (*Dipodomys*) and mouse (*Microdipodops*) a functional form of motilin may exist but the motilin receptor is non-functional [1648]. Marked dif-

ferences in ligand affinities for the motilin receptor in dogs and humans may be explained by significant differences in receptor structure [2473]. Among birds, chicken (*Gallus gallus domesticus*) motilin differs from human motilin at positions 4, 7-10, and 12, and contracts avian upper gastrointestinal tissues more potently than human motilin; in rabbit duodenum, the reverse is apparent [1436]. Chicken motilin receptor has 59% sequence homology with the human motilin receptor [3144]. In chicken, motilin does not mediate phase III activity of the gastric MMC but initiates rhythmic oscillating complexes in the small intestine [2407]. Responsiveness to motilin in the ileum is highest in avian gastrointestinal tract. Among reptiles, caiman/alligator motilin is similar to avian motilin, but markedly different forms of motilin exist in

turtles, anole/lizard and snake. Their activities have not been examined in reptiles. Among amphibians, a motilin-like peptide has been identified in newts but not in frogs, with a structure differing from mammalian motilin. There may be some diversity among the anuran, urodelal and gymnophional species. Although endog-

enous motilin is not present in frogs, human motilin caused contraction of the upper gastrointestinal tract [3235]. However, newt but not human motilin caused strong contraction of the stomach of Japanese fire belly newts [3234]. Among teleost fish, sequences for motilin peptide and motilin receptor have been identified (ze-

brafish, ballan wrasse, spotted sea bass) but the motilin peptides are short and the structure of motilin receptor differs from that of mammals. Zebrafish motilin activates its cognate motilin receptor but fails to cause contraction of gastrointestinal strips *in vitro*, perhaps because of low expression of the motilin receptor [1437].

Further reading on Motilin receptor

- Kitazawa T *et al.* (2021) Motilin Comparative Study: Structure, Distribution, Receptors, and Gastrointestinal Motility. *Front Endocrinol (Lausanne)* **12**: 700884 [PMID:34497583]
 Sanger GJ *et al.* (2016) Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* **13**: 38-48 [PMID:26392067]
 Singaram K *et al.* (2020) Motilin: a panoply of communications between the gut, brain, and pancreas. *Expert Rev Gastroenterol Hepatol* **14**: 103-111 [PMID:31996050]

Neuromedin U receptors

G protein-coupled receptors → Neuromedin U receptors

Overview: Neuromedin U receptors (**provisional nomenclature as recommended by NC-IUPHAR** [789]) are activated by the endogenous 25 amino acid peptide neuromedin U (**neuromedin U-25 (NMU, P48645)**), NmU-25, a peptide originally isolated from pig spinal cord [1913]. In humans, NmU-25 appears to be the sole product of a precursor gene (**NMU, P48645**) showing a broad tissue distribution, but which is expressed at highest levels in the

upper gastrointestinal tract, CNS, bone marrow and fetal liver. Much shorter versions of NmU are found in some species, but not in human, and are derived at least in some instances from the proteolytic cleavage of the longer NmU. Despite species differences in NmU structure, the C-terminal region (particularly the C-terminal pentapeptide) is highly conserved and contains biological activity. Neuromedin S (**neuromedin S-33 (NMS, Q5H8A3)**) has also been

identified as an endogenous agonist [1968]. Nms-33 is, as its name suggests, a 33 amino-acid product of a precursor protein derived from a single gene and contains an amidated C-terminal heptapeptide identical to NmU. Nms-33 appears to activate NMU receptors with equivalent potency to NmU-25.

Nomenclature	NMU1 receptor	NMU2 receptor
HGNC, UniProt	NMUR1, Q9HB89	NMUR2, Q9GZQ4
Agonists	CPN-223 (Partial agonist) [2769]	–
Selective agonists	–	CPN-219 [2771], CPN-116 [2770]
Antagonists	–	R-PSOP (pK _B 7) [1714]
Comments	CPN-267 is a selective hexapeptidic NMUR1 agonist, but the sequence is obscure.	–

Comments: NMU1 and NMU2 couple predominantly to G_{q/11} although there is evidence of good coupling to G_{i/o} [304, 1170, 1182]. NMU1 and NMU2 can be labelled with [¹²⁵I]-NmU and [¹²⁵I]-NmS (of various species, *e.g.* [1877]), **BODIPY® TMR-NMU** or **Cy3B-NMU-8** [304]. A range of radiolabelled (¹²⁵I-), fluorescently labelled (*e.g.* Cy3, Cy5, rhodamine and FAM) and **biotin** labelled versions of **neuromedin U-25 (NMU, P48645)** and **neuromedin S-33 (NMS, Q5H8A3)** are now commercially available.

Further reading on Neuromedin U receptors

- Brighton PJ *et al.* (2004) Neuromedin U and its receptors: structure, function, and physiological roles. *Pharmacol Rev* **56**: 231-48 [PMID:15169928]
 Budhiraja S *et al.* (2009) Neuromedin U: physiology, pharmacology and therapeutic potential. *Fundam Clin Pharmacol* **23**: 149-57 [PMID:19645813]
 Mitchell JD *et al.* (2009) Emerging pharmacology and physiology of neuromedin U and the structurally related peptide neuromedin S. *Br J Pharmacol* **158**: 87-103 [PMID:19519756]
 Novak CM. (2009) Neuromedin S and U. *Endocrinology* **150**: 2985-7 [PMID:19549882]

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

Neuromedin U receptors S102

Neuropeptide FF/neuropeptide AF receptors

G protein-coupled receptors → Neuropeptide FF/neuropeptide AF receptors

Overview: The Neuropeptide FF receptor family contains two subtypes, NPFF1 and NPFF2 (**provisional nomenclature** [789]), which exhibit high affinities for neuropeptide FF (*NPFF*, O15130) and RFamide related peptides (RFRP: precursor gene symbol *NPVF*, Q9HCQ7). NPFF1 is broadly distributed in the central nervous system with the highest levels found in the limbic system and the hypothalamus. NPFF2 is present in high density in the superficial layers of the mammalian spinal cord where it is involved in nociception and modulation of opioid functions.

	NPFF1 receptor	NPFF2 receptor
Nomenclature	NPFF1 receptor	NPFF2 receptor
HGNC, UniProt	<i>NPFFR1</i> , Q9GZQ6	<i>NPFFR2</i> , Q9Y5X5
Potency order of endogenous ligands	RFRP-1 (<i>NPVF</i> , Q9HCQ7) > RFRP-3 (<i>NPVF</i> , Q9HCQ7) > FMRFneuropeptide FF (<i>NPFF</i> , O15130) > neuropeptide AF (<i>NPFF</i> , O15130) > neuropeptide SF (<i>NPFF</i> , O15130), QRFP43 (43Rfa) (<i>QRFP</i> , P83859), PrRP-31 (<i>PRLH</i> , P81277) [948]	neuropeptide AF (<i>NPFF</i> , O15130), neuropeptide FF (<i>NPFF</i> , O15130) > PrRP-31 (<i>PRLH</i> , P81277) > FMRF, QRFP43 (43Rfa) (<i>QRFP</i> , P83859) > neuropeptide SF (<i>NPFF</i> , O15130) [948]
Endogenous agonists	neuropeptide FF (<i>NPFF</i> , O15130) [948, 949, 1940], RFRP-3 (<i>NPVF</i> , Q9HCQ7) [949, 950, 1940]	neuropeptide FF (<i>NPFF</i> , O15130) [949, 1939]
Selective agonists	–	dNPA [2428], AC263093 [1546]
Antagonists	RF9 (pK _i 7.2) [2617]	–
Selective antagonists	AC262620 (pK _i 7.7–8.1) [1546], AC262970 (pK _i 7.4–8.1) [1546]	–
Labelled ligands	[¹²⁵ I]Y-RFRP-3 (Agonist) [949], [³ H]NPVF (Agonist) [2777], [¹²⁵ I]NPFF (Agonist) [948]	[¹²⁵ I]EYF (Agonist) [1940], [³ H]EYF (Agonist) [2777], [¹²⁵ I]NPFF (Agonist) [948]

Comments: An orphan receptor *GPR83* (Q9NYM4) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors. The antagonist RF9 is selective for NPFF receptors, but does not distinguish between the NPFF1 and NPFF2 subtypes (pK_i 7.1 and 7.2, respectively, [591, 2617]).

Further reading on Neuropeptide FF/neuropeptide AF receptors

- Moulédous L *et al.* (2010) Opioid-modulating properties of the neuropeptide FF system. *Biofactors* **36**: 423-9 [PMID:20803521]
- Nguyen T *et al.* (2020) Neuropeptide FF and Its Receptors: Therapeutic Applications and Ligand Development. *J Med Chem* **63**: 12387-12402 [PMID:32673481]
- Vyas N *et al.* (2006) Structure-activity relationships of neuropeptide FF and related peptidic and non-peptidic derivatives. *Peptides* **27**: 990-6 [PMID:16490282]
- Yang HY *et al.* (2008) Modulatory role of neuropeptide FF system in nociception and opiate analgesia. *Neuropeptides* **42**: 1-18 [PMID:17854890]

Neuropeptide S receptor

G protein-coupled receptors → Neuropeptide S receptor

Overview: The neuropeptide S receptor (NPS receptor) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (*NPS*, *POCOP6*). NPS activates its receptor at low nanomolar concentrations elevating intracellular cAMP and calcium levels [2369]. Currently, some peptidic and small molecule NPS receptor antagonists are available as research tools [368, 995, 2124, 2444]. No NPS receptor ligands are currently used clinically.

Nomenclature	NPS receptor
HGNC, UniProt	NPSR1 , Q6W5P4
Endogenous agonists	neuropeptide S (<i>NPS</i> , <i>POCOP6</i>) [3140]
Selective agonists	PWT1-NPS [2445] – Mouse, SFKN-NH₂ [515]
Selective antagonists	SHA 68 (pA ₂ 8.1) [2446] – Mouse, [³H]-Bu-D-Gly⁵NPS (pA ₂ 7.1) [995] – Mouse
Labelled ligands	[¹²⁵I]Tyr¹⁰NPS (human) (Agonist) [3140]

Comments: Multiple single-nucleotide polymorphisms (SNP) and several splice variants have been identified in the human NPS receptor (NPSR1). The most common of these is an Asn-Ile exchange at position 107 (Ile107Asn, rs324981). Both variants displayed similar binding affinity but NPSR Ile107 shows higher NPS potency (by approx. 10-fold) than NPSR1 Asn107 [2369]. Several epidemiological studies reported an association between the Ile107Asn receptor variant and susceptibility to panic disorders

[662, 666, 2125, 2325]. The SNP Ile107Asn (rs324981) has also been linked to sleep behavior [947], inflammatory bowel disease [567], schizophrenia [1623], increased impulsivity and ADHD symptoms [1537]. Interestingly, a carboxy-terminal splice variant of human NPS receptor was found to be overexpressed in asthmatic patients [1544]. Additionally, the gain-of-function variant NPSR1 Tyr206His has been described in a single family where it dramatically reduces total sleep time [3125]. In preclinical ani-

mal models, NPS was found to increase arousal, reduce sleep and anxiety, enhance learning and memory, enhance extinction of conditioned fear, facilitate self-administration of addictive drugs, and attenuate feeding [1320, 1332, 1625, 2519, 2646, 3140]. All of these effects could be blocked by NPSR1 antagonists. NPSR1 or NPS precursor knockout mice displayed mildly increased anxiety levels, impaired learning and memory, but no changes in sleep phenotypes or respiratory functions [51, 684, 1720, 3126].

Further reading on Neuropeptide S receptor

- Guerrini R *et al.* (2010) Neurobiology, pharmacology, and medicinal chemistry of neuropeptide S and its receptor. *Med Res Rev* **30**: 751-77 [PMID:19824051]
- Reinscheid RK *et al.* (2021) Pharmacology, Physiology and Genetics of the Neuropeptide S System. *Pharmaceuticals (Basel)* **14**: [PMID:33922620]
- Reinscheid RK *et al.* (2005) Pharmacological characterization of human and murine neuropeptide S receptor variants. *J Pharmacol Exp Ther* **315**: 1338-45 [PMID:16144971]
- Ruzza C *et al.* (2015) Neuropeptide S reduces mouse aggressiveness in the resident/intruder test through selective activation of the neuropeptide S receptor. *Neuropharmacology* **97**: 1-6 [PMID:25979487]
- Ruzza C *et al.* (2017) Neuropeptide S receptor ligands: a patent review (2005-2016). *Expert Opin Ther Pat* **27**: 347-362 [PMID:27788040]
- Xu YL *et al.* (2004) Neuropeptide S: a neuropeptide promoting arousal and anxiolytic-like effects. *Neuron* **43**: 487-97 [PMID:15312648]

Neuropeptide W/neuropeptide B receptors

G protein-coupled receptors → Neuropeptide W/neuropeptide B receptors

Overview: The neuropeptide BW receptor 1 (NPBW1, **provisional nomenclature** [789]) is activated by two 23-amino-acid peptides, neuropeptide W (**neuropeptide W-23** (NPW, Q8N729)) and neuropeptide B (**neuropeptide B-23** (NPB, Q8NG41)) [825, 2593]. C-terminally extended forms of the peptides (**neuropeptide W-30** (NPW, Q8N729)) and **neuropeptide B-29** (NPB,

Q8NG41)) also activate NPBW1 [302]. Unique to both forms of neuropeptide B is the N-terminal bromination of the first tryptophan residue, and it is from this post-translational modification that the nomenclature NPB is derived. These peptides were first identified from bovine hypothalamus and therefore are classed as neuropeptides. Endogenous variants of the peptides without

the N-terminal bromination, **des-Br-neuropeptide B-23** (NPB, Q8NG41) and **des-Br-neuropeptide B-29** (NPB, Q8NG41), were not found to be major components of bovine hypothalamic tissue extracts. The NPBW2 receptor is activated by the short and C-terminal extended forms of neuropeptide W and neuropeptide B [302].

Nomenclature	NPBW1 receptor	NPBW2 receptor
HGNC, UniProt	NPBWR1, P48145	NPBWR2, P48146
Potency order of endogenous ligands	neuropeptide B-29 (NPB, Q8NG41) > neuropeptide B-23 (NPB, Q8NG41) > neuropeptide W-23 (NPW, Q8N729) > neuropeptide W-30 (NPW, Q8N729) [302]	neuropeptide W-23 (NPW, Q8N729) > neuropeptide W-30 (NPW, Q8N729) > neuropeptide B-29 (NPB, Q8NG41) > neuropeptide B-23 (NPB, Q8NG41) [302]
Selective agonists	Ava3 [1340], Ava5 [1340]	–
Labelled ligands	[¹²⁵ I]NPW-23 (human) (Agonist) [2619]	[¹²⁵ I]NPW-23 (human) (Agonist) [2593]

Comments: Potency measurements were conducted with heterologously-expressed receptors with a range of 0.14–0.57 nM (NPBW1) and 0.98–21 nM (NPBW2). NPBW1^{−/−} mice show changes in social behavior, suggesting that the NPBW1 pathway may have an important role in the emotional responses of social inter-

action [2014]. For a review of the contribution of neuropeptide B/W to social dominance, see Watanabe and Yamamoto, 2015 [3025]. It has been reported that neuropeptide W may have a key role in the gating of stressful stimuli when mice are exposed to novel environments [1986]. Two antagonists have been dis-

covered and reported to have affinity for NPBW1, ML181 and ML250, the latter exhibiting improved selectivity (~100 fold) for NPBW1 compared to MCH1 receptors [992, 993]. Computational insights into the binding of antagonists to this receptor have also been described [2186, 2190].

Further reading on Neuropeptide W/neuropeptide B receptors

Sakurai T. (2013) NPBWR1 and NPBWR2: Implications in Energy Homeostasis, Pain, and Emotion. *Front Endocrinol (Lausanne)* **4**: 23 [PMID:23515889] Singh G *et al.* (2006) Neuropeptide B and W: neurotransmitters in an emerging G-protein-coupled receptor system. *Br J Pharmacol* **148**: 1033–41 [PMID:16847439]

Neuropeptide Y receptors

G protein-coupled receptors → Neuropeptide Y receptors

Overview: Neuropeptide Y (NPY) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Neuropeptide Y Receptors** [1893]) are activated by the endogenous peptides **neuropeptide Y** (NPY, P01303), neuropeptide Y-(3–36), peptide YY (PYY, P10082), PYY-(3–36) and **pancreatic polypeptide** (PPY, P01298) (PP). The receptor originally identified as the Y3 receptor has been identified as the **CXCR4 chemokine receptor** (originally named LESTR, [1724]). The y6 receptor is a functional

gene product in mouse, absent in rat, but contains a frame-shift mutation in primates producing a truncated non-functional gene [969]. Three-dimensional structures have been determined for subtype active receptors Y₁, Y₂ and Y₄ [1341, 2789] and inactive antagonist bound Y₁ and Y₂ receptors [2788, 3170]. Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the potency of PP is greater at the rat Y₄ receptor than at the human receptor [729]. In addition,

many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [¹²⁵I]-PYY or [¹²⁵I]-NPY can be used to label Y₁, Y₂, Y₅ and y₆ subtypes non-selectively, while [¹²⁵I][cPP(1–7), NPY(19–23), Ala³¹, Aib³², Gln³⁴] hPP may be used to label Y₅ receptors preferentially (note that cPP denotes chicken peptide sequence and hPP is the human sequence).

Nomenclature	Y_1 receptor	Y_2 receptor	Y_4 receptor	Y_5 receptor	y_6 receptor
HGNC, UniProt	<i>NPY1R</i> , P25929	<i>NPY2R</i> , P49146	<i>NPY4R</i> , P50391	<i>NPY5R</i> , Q15761	<i>NPY6R</i> , Q99463
Potency order of endogenous ligands	neuropeptide Y = peptide YY \gg pancreatic polypeptide	peptide YY = peptide YY(3-36) = neuropeptide Y = neuropeptide Y(3-36) \gg pancreatic polypeptide	pancreatic polypeptide \gg neuropeptide Y = peptide YY	neuropeptide Y > peptide YY > pancreatic polypeptide	neuropeptide Y = peptide YY > pancreatic polypeptide
Endogenous agonists	neuropeptide Y (<i>NPY</i> , P01303), peptide YY (<i>PYY</i> , P10082)	<i>PYY</i> (3-36) (<i>PYY</i> , P10082) [882, 897], neuropeptide Y (<i>NPY</i> , P01303), neuropeptide Y-(3-36) (<i>NPY</i> , P01303), peptide YY (<i>PYY</i> , P10082)	pancreatic polypeptide (<i>PPY</i> , P01298) [142, 1747, 2858, 3152]	–	–
Agonists	[Leu ³¹ ,Pro ³⁴]NPY [552], [Leu ³¹ ,Pro ³⁴]PYY (human), [Pro ³⁴]NPY, [Pro ³⁴]PYY (human)	–	–	–	–
Selective agonists	–	–	–	[Ala ³¹ ,Aib ³²]NPY (pig) [357]	–
Selective antagonists	<i>BIBO3304</i> (pIC ₅₀ 9.5) [3065], <i>BIBP3226</i> (pK _i 8.1–9.3) [669, 3066]	<i>BIIE0246</i> (pIC ₅₀ 8.5) [667], <i>JNJ-5207787</i> (pIC ₅₀ 6.9–7.1) [258]	–	<i>L-152,804</i> (pK _i 7.6) [1337]	–
Selective allosteric modulators	–	–	<i>VU0506013</i> (Positive) (pEC ₅₀ 6.9) [2497], (<i>S</i>)- <i>VU0637120</i> (Negative) (pIC ₅₀ 5.6) [2498]	–	–
Labelled ligands	[³ H] <i>BIBP3226</i> (Antagonist) (pK _d 8.7), [¹²⁵ I][Leu ³¹ ,Pro ³⁴]NPY (Agonist)	[¹²⁵ I] <i>PYY</i> (3-36) (human) (Agonist)	[¹²⁵ I] <i>PP</i> (human) (Agonist)	[¹²⁵ I][cPP(1-7), <i>NPY</i> (19-23), Ala ³¹ , Aib ³² , Gln ³⁴]hPP (Agonist) [695] – Rat	–
Comments	Note that Pro ³⁴ -containing NPY and PYY can also bind Y_4 and Y_5 receptors, so strictly speaking are not selective, but are the 'preferred' agonists.	–	–	–	–

Comments: The Y_1 agonists indicated are selective relative to Y_2 receptors. *BIBP3226* is selective relative to Y_2 , Y_4 and Y_5 receptors [896]. *NPY*-(13-36) is Y_2 selective relative to Y_1 and Y_5 receptors. *PYY*-(3-36) is Y_2 selective relative to Y_1 receptors, and new long-acting analogues of *PYY*(3-36) exhibit improved Y_2 selectivity. Note that Pro³⁴-containing NPY and PYY can also bind Y_4 and Y_5 , thus they are selective only relative to Y_2 . The y_6 receptor is a pseudogene in humans, but is functional in mouse, rabbit and some other mammals. Human Y_4 has several naturally occurring sequence variants [2579] and the human *NPY4R* gene displays extensive gene copy number variation [2578].

Further reading on Neuropeptide Y receptors

- Østergaard S *et al.* (2025) Variant screening of PYY₃₋₃₆ leads to potent long-acting PYY analogs with superior Y₂ receptor selectivity. *Sci Transl Med* **17**: eadq6392 [PMID:40138456]
- Bowers ME *et al.* (2012) Neuropeptide regulation of fear and anxiety: Implications of cholecystokinin, endogenous opioids, and neuropeptide Y. *Physiol Behav* **107**: 699-710 [PMID:22429904]
- Michel MC *et al.* (1998) XVI. International Union of Pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY, and pancreatic polypeptide receptors. *Pharmacol Rev* **50**: 143-50 [PMID:9549761]
- Pedragosa-Badia X *et al.* (2013) Neuropeptide Y receptors: how to get subtype selectivity. *Front Endocrinol (Lausanne)* **4**: 5 [PMID:23382728]
- Shebanits K *et al.* (2018) Copy number of pancreatic polypeptide receptor gene NPY4R correlates with body mass index and waist circumference. *PLoS One* **13**: e0194668 [PMID:29621259]
- Shebanits K *et al.* (2019) Functional characterization in vitro of twelve naturally occurring variants of the human pancreatic polypeptide receptor NPY4R. *Neuropeptides* **76**: 101933 [PMID:31230758]
- Zhang L *et al.* (2011) The neuropeptide Y system: pathophysiological and therapeutic implications in obesity and cancer. *Pharmacol Ther* **131**: 91-113 [PMID:21439311]

Neurotensin receptors

G protein-coupled receptors → Neurotensin receptors

Overview: Neurotensin receptors (**nomenclature as recommended by NC-IUPHAR [789]**) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (*NTS*, 30990), which also generates neuromedin N, an agonist at the NTS₂ receptor. [³H]neurotensin (human, mouse, rat) and [¹²⁵I]neurotensin (human, mouse, rat) may be used to label NTS₁ and NTS₂ receptors at 0.1-0.3 and 3-5 nM concentrations respectively.

Nomenclature	NTS ₁ receptor	NTS ₂ receptor
HGNC, UniProt	<i>NTSR1</i> , P30989	<i>NTSR2</i> , O95665
Potency order of endogenous ligands	neurotensin (<i>NTS</i> , P30990) > neuromedin N (<i>NTS</i> , P30990) [1107]	neurotensin (<i>NTS</i> , P30990) = neuromedin N (<i>NTS</i> , P30990) [1851]
Agonists	ABS-201 [482, 3252] – Mouse, ABS-212 [1200, 1645] – Rat	–
Selective agonists	JMV449 [2630] – Rat	levocabastine [1851, 2385]
Selective antagonists	meclinertant (pIC ₅₀ 7.5–8.2) [999]	–
Labelled ligands	[³ H]meclinertant (Antagonist) (pK _d 8.5) [1539] – Rat	–

Comments: Neurotensin (*NTS*, P30990) appears to be a low-efficacy agonist at the NTS₂ receptor [2949], while the NTS₁ receptor antagonist meclinertant is an agonist at NTS₂ receptors [2949]. An additional protein, provisionally termed NTS₃ (also known as NTR3, gp95 and sortilin; *ENSG00000134243*), has been

suggested to bind lipoprotein lipase and mediate its degradation [2073]. It has been reported to interact with the NTS₁ receptor [1826] and the NTS₂ receptor [198], and has been implicated in hormone trafficking and/or neurotensin uptake. A splice variant of the NTS₂ receptor bearing 5 transmembrane domains has been

identified in mouse [275] and later in rat [2219]. The neurotensinergic system is implicated in various physiological and pathological processes related to neuropsychiatric and metabolic functions, cancer growth, food, and drug intake [1247].

Further reading on Neurotensin receptors

- Boules M *et al.* (2013) Diverse roles of neurotensin agonists in the central nervous system. *Front Endocrinol (Lausanne)* **4**: 36 [PMID:23526754]
- Christou N *et al.* (2020) Neurotensin pathway in digestive cancers and clinical applications: an overview. *Cell Death Dis* **11**: 1027 [PMID:33268796]
- Mazella J *et al.* (2012) Neurotensin and its receptors in the control of glucose homeostasis. *Front Endocrinol (Lausanne)* **3**: 143 [PMID:23230428]
- Myers RM *et al.* (2009) Cancer, chemistry, and the cell: molecules that interact with the neurotensin receptors. *ACS Chem Biol* **4**: 503-25 [PMID:19462983]
- Ouyang Q *et al.* (2017) Oncogenic role of neurotensin and neurotensin receptors in various cancers. *Clin Exp Pharmacol Physiol* **44**: 841-846 [PMID:28556374]
- Schroeder LE *et al.* (2018) Role of central neurotensin in regulating feeding: Implications for the development and treatment of body weight disorders. *Biochim Biophys Acta Mol Basis Dis* **1864**: 900-916 [PMID:29288794]

Opioid receptors

G protein-coupled receptors → Opioid receptors

Overview: Opioid and opioid-like receptors are activated by a variety of endogenous peptides including [Met]enkephalin (*PENK*, P01210) (met), [Leu]enkephalin (*PENK*, P01210) (leu), β -endorphin (*POMC*, P01189) (β -end), α -neodyorphin (*PDYN*, P01213), dynorphin A (*PDYN*, P01213) (dynA), dynorphin B (*PDYN*, P01213) (dynB), big dynorphin (*PDYN*, P01213) (Big dyn), nociceptin/orphanin FQ (*PNOC*, Q13519) (N/OFQ); endomorphin-1 and endomorphin-2 are also potential endogenous peptides. The Greek letter nomenclature for the opioid receptors,

μ , δ and κ , is well established, and **NC-IUPHAR** considers this nomenclature appropriate, along with the symbols spelled out (μ , δ , and κ), and the acronyms, MOP, DOP, and KOP [550, 633, 789]. However the acronyms MOR, DOR and KOR are still widely used in the literature. The human N/OFQ receptor, NOP, is considered 'opioid-related' rather than opioid because, while it exhibits a high degree of structural homology with the conventional opioid receptors [550, 1942], it displays a distinct pharmacology. Currently there are numerous clinically used

drugs, such as morphine and many other opioid analgesics, as well as antagonists such as naloxone. The majority of clinically used opiates are relatively selective μ agonists or partial agonists, though there are some μ/κ compounds, such as butorphanol, in clinical use. κ opioid agonists, such as the alkaloid nalfurafine and the peripherally acting peptide difelikefalin, are in clinical use for itch.

Nomenclature	δ receptor	κ receptor
HGNC, UniProt	<i>OPRD1</i> , P41143	<i>OPRK1</i> , P41145
Principal endogenous agonists	β -endorphin (<i>POMC</i> , P01189), [Leu]enkephalin (<i>PENK</i> , P01210), [Met]enkephalin (<i>PENK</i> , P01210)	big dynorphin (<i>PDYN</i> , P01213), dynorphin A (<i>PDYN</i> , P01213)
Agonists	DADLE [2845], etorphine [2845], PN6047 (Biased agonist) [530]	nalfurafine [3013, 3260], (-)-cyclazocine (Partial agonist) [2845], etorphine [2845], ethylketocyclazocine [2845, 3266]
Selective agonists	UFP-512 [2941], BW373U86 [1581], ADL5859 [1581], DPDPE [1985, 2845], [D-Ala ²]deltorphin II [732], ADL5747 [1582], SNC80 [364, 2321]	difelikefalin [2530], U50488 [432, 2191, 2616, 2845, 2960, 3264, 3266], enadoline [1204, 2057], U69593 [1542, 2845], salvinorin A [177, 2423], probe 1.1 (Biased agonist) [3256]
Antagonists	UFP-505 (pK _i 9.8) [645, 646], naltrexone (pK _i 8) [2845], AT-076 (pK _i 7.7) [2845, 3215], naloxone (pK _i 7.2) [2845]	buprenorphine (pK _i 9.1–10.2) [2845, 3266], nalmefene (pK _i 9.5) [2845], naltrexone (pK _i 8.4–9.4) [2191, 2616, 2845], AT-076 (pK _i 8.9) [2845, 3216], naloxone (pK _i 7.6–8.6) [2191, 2616, 2845, 3264, 3266]
Selective antagonists	naltriben (pK _i 10) [2655, 2845], naltrindole (pK _i 9.7) [2267, 2845], TIPPP ψ (Inverse agonist) (pK _i 9) [2509, 2845]	nor-binaltorphimine (pK _i 8.9–11) [2191, 2266, 2616, 2845, 3264, 3266], 5'-guanidinonaltrindole (pK _i 9.7–9.9) [1308, 2191, 2695], JDTC (pK _i 9–9.4) [2000, 2819, 3216], aticaprant (pK _i 9.1) [2417]
Labelled ligands	[³ H]naltrindole (Antagonist) (pK _d 10.4) [3147] – Rat, [³ H][D-Ala ²]deltorphin I (Agonist) [2689], [³ H]diprenorphine (Agonist) [70, 2845], [³ H]DPDPE (Agonist) [33], [³ H]deltorphin II (Agonist) [353], [³ H]naltriben (Antagonist) [1638]	[³ H]diprenorphine (Antagonist) (pK _d 9.1) [70, 2616], [³ H]U69593 (Agonist) [1542, 2191, 2616], [³ H]enadoline (Agonist) [2618]

Nomenclature	μ receptor	NOP receptor
HGNC, UniProt	<i>OPRM1</i> , P35372	<i>OPRL1</i> , P41146
Potential endogenous agonists	endomorphin-1, endomorphin-2	–
Principal endogenous agonists	β -endorphin (<i>POMC</i> , P01189), [Met]enkephalin (<i>PENK</i> , P01210), [Leu]enkephalin (<i>PENK</i> , P01210)	nociceptin/orphanin FQ (<i>PNOC</i> , Q13519) [14, 222, 2126]
Endogenous agonists	Several additional extended enkephalin peptides or truncated beta-endorphin peptides. [932]	–
Agonists	levorphanol [1037], hydromorphone [3048], etorphine [2845], cebranopadol [1697], BU10038 (Partial agonist) [1394], morphine [929, 2845], buprenorphine (Partial agonist) [2845], BU08028 (Partial agonist) [1390], methadone [2270], UFP-505 [645, 646], AT-121 (Partial agonist) [651], codeine [2845], tapentadol [2878], pethidine [2270]	cebranopadol [1697], AT-121 (Partial agonist) [651], BU08028 (Partial agonist) [1390], BU10038 (Partial agonist) [1394]
Selective agonists	sufentanil [2954], etonitazene [2845], DAMGO [1036, 2845], loperamide [456], fentanyl [2845], PL017 [423, 2845]	N/OFQ-(1-13)-NH ₂ [222, 994, 1859, 2126], MCOPPB [1079], Ac-RYYRWK-NH ₂ (Partial agonist) [670, 1859], UFP-112 [367, 2402], SCH221510 [2932], Ro64-6198 [1277, 3063], AT-403 [79], sunobinop (Partial agonist) [3061]
Antagonists	naltrexone (pK _i 9.1–9.7) [1371, 2845], nalmefene (pK _i 9.5) [2845], nalorphine (pK _i 8.9) [2845], naloxone (pK _i 8.9) [2845], AT-076 (pK _i 8.8) [2845, 3216], methylnaltrexone (pK _i 8.7) [3048]	AT-076 (pK _i 8.8) [3216]
Selective antagonists	CTOP (pK _i 9.7) [1000, 2359], β -FNA (irreversible at μ receptor) (pK _i 9.5) [2845, 3256], alvimopan (peripheral) (pK _i 9.3) [1580], CTAP (pK _i 8.6) [423, 2845]	UFP-101 (pK _i 10.2) [366], LY2940094 (pK _i 10) [769, 2843], compound 24 (pK _i 9.6) [781], SB 612111 (pK _i 9.2–9.5) [2671, 3214], J-113397 (pIC ₅₀ 8.3) [1363]
Allosteric modulators (Positive)	BMS-986121 (pK _B 5.7) [341], BMS-986122 (pK _B 5.3) [341]	–
Allosteric modulators (Neutral)	BMS-986123 (pK _B 6) [341], BMS-986124 (pK _B 5.7) [341]	–
Labelled ligands	[³ H]diprenorphine (Antagonist) (pK _d 10.1) [2359] – Mouse, [³ H]DAMGO (Agonist) [2359] – Rat, [³ H]CTOP (Antagonist) [2844]	[³ H]N/OFQ (Agonist) [670, 1941]

Comments: Three genes for naloxone-sensitive opioid receptors have been identified in humans, and while the μ receptor in particular may be subject to extensive alternative splicing [2175], these putative isoforms have not been correlated with any of the subtypes of receptor proposed in years past. Opioid receptors may heterodimerize with each other or with other 7TM receptors [1310], and give rise to complexes with a unique pharmacology, however, evidence for such heterodimers in native cells is equivocal and the consequences of this heterodimerization for signalling remains largely unknown. For μ -opioid receptors at least, dimerization does not seem to be required for signalling [1531]. A distinct met-enkephalin receptor lacking structural resemblance to the opioid receptors listed has been identified (*OGFR*, *9NZT2*) and termed an opioid growth factor receptor [3210]. endomorphin-1 and endomorphin-2 have been identified as highly selective, putative endogenous agonists for the μ -opioid

receptor. At present, however, the mechanisms for endomorphin synthesis *in vivo* have not been established, and there is no gene identified that encodes for either. Thus, the status of these peptides as endogenous ligands remains unproven.

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human μ -receptors [2107] and the identification of biased signalling by opioid receptor ligands, both agonists and antagonists [325, 1370]. Despite the identification of biased ligands for the μ receptor, the relevance with respect to physiological and behavioral actions *in vivo* is not clear [912]. Pathway bias for agonists makes general rank orders of potency and efficacy somewhat obsolete, so these do not appear in the table. As ever, the mechanisms underlying the acute and long term regulation of opioid receptor function are the subject of intense investigation and debate.

The richness of opioid receptor pharmacology has been enhanced with the recent discovery of allosteric modulators of μ and δ receptors, notably the positive allosteric modulators and silent allosteric “antagonists” outlined in [341, 342]. Negative allosteric modulation of opioid receptors has been previously suggested [1354], whether all compounds are acting at a similar site remains to be established.

In the last decade, several opioid receptors structures have been solved in their inactive and active forms: δ receptor [762, 763, 963, 3015]; κ receptor [433, 434, 3015, 3104]; μ receptor [749, 1193, 1455, 1803, 2312, 2405, 2989, 3015, 3271]; NOP [1911, 2822, 3015]. More recently, and importantly, cryoEM has been used to identify ligand-receptor interactions and design novel ligands [1339, 2928].

Further reading on Opioid receptors

- Butelman ER *et al.* (2012) κ -opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. *Trends Neurosci* **35**: 587-96 [PMID:22709632]
- Cox BM *et al.* (2015) Challenges for opioid receptor nomenclature: IUPHAR Review 9. *Br J Pharmacol* **172**: 317-23 [PMID:24528283]
- Gendron L *et al.* (2016) Molecular Pharmacology of δ -Opioid Receptors. *Pharmacol Rev* **68**: 631-700 [PMID:27343248]
- Gillis A *et al.* (2020) Intrinsic Efficacy of Opioid Ligands and Its Importance for Apparent Bias, Operational Analysis, and Therapeutic Window. *Mol Pharmacol* **98**: 410-424 [PMID:32665252]
- Pradhan AA *et al.* (2011) The delta opioid receptor: an evolving target for the treatment of brain disorders. *Trends Pharmacol Sci* **32**: 581-90 [PMID:21925742]
- Toll L *et al.* (2016) Nociceptin/Orphanin FQ Receptor Structure, Signaling, Ligands, Functions, and Interactions with Opioid Systems. *Pharmacol Rev* **68**: 419-57 [PMID:26956246]
- Valentino RJ *et al.* (2020) Opioid Research: Past and Future. *Mol Pharmacol* **98**: 389-391 [PMID:32660966]
- Williams JT *et al.* (2013) Regulation of μ -opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev* **65**: 223-54 [PMID:23321159]

Opsin receptors

G protein-coupled receptors → Opsin receptors

Nomenclature	<i>OPN3</i>	<i>OPN4</i>	<i>OPN5</i>
HGNC, UniProt	<i>OPN3</i> , <i>Q9H1Y3</i>	<i>OPN4</i> , <i>Q9UHM6</i>	<i>OPN5</i> , <i>Q6U736</i>
Comments	–	–	Evidence indicates that UV light triggers OPN5 to activate G _i -mediated signalling in mammalian tissues [1462].

Orexin receptors

G protein-coupled receptors → Orexin receptors

Overview: Orexin receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Orexin receptors** [1516]) are activated by the endogenous polypeptides **orexin-A** (*HCRT*, [O43612](#)) and **orexin-B** (*HCRT*, [O43612](#)) (also known as hypocretin-1 and -2; 33 and 28 aa) derived from a common precursor, **prepro-orexin** or **orexin precursor**, by proteolytic cleavage and

some typical peptide modifications [1516, 2460]. Orexin signaling has been associated with regulation of sleep and wakefulness, reward and addiction, appetite and feeding, pain gating, stress response, anxiety and depression. Currently the orexin receptor ligands in clinical use are the dual orexin receptor antagonists **suvorexant**, **lemborexant** and **daridorexant**, which are used as hyp-

notics, and several dual, as well as OX₁- and OX₂-selective antagonists are under development for different indications. Multiple orexin agonists are in development for the treatment of narcolepsy and other sleep disorders. Orexin receptor 3D structures have been solved [90, 1101, 1159, 2344, 2735, 3185, 3187, 3188].

Nomenclature	OX₁ receptor	OX₂ receptor
HGNC, UniProt	<i>HCRTR1</i> , O43613	<i>HCRTR2</i> , O43614
Potency order of endogenous ligands	orexin-A (<i>HCRT</i> , O43612) > orexin-B (<i>HCRT</i> , O43612) (for Ca ²⁺ elevation, unclear/variable for other responses)	orexin-A (<i>HCRT</i> , O43612) = orexin-B (<i>HCRT</i> , O43612) (for Ca ²⁺ elevation, unclear/variable for other responses)
Agonists	<i>RTOXA-43</i> [3224]	<i>RTOXA-43</i>
Selective agonists	<i>(R)</i> -YNT-3708 [1218]	<i>oveporexton</i> [1920], <i>firazorexton</i> [1236], <i>YNT-185</i> [1232, 2012]

Antagonists	SB-649868 (pK _i 9.1–9.6) [365 , 551 , 635], daridorexant (pK _B 8.8–9.3) [2868], suvorexant (pK _i 8.7–9.3) [365 , 551 , 1987 , 2344], filorexant (pK _i 8.4–9.2) [365 , 551 , 2344 , 3082], TCS 1102 (pK _B 8–8.5) [201 , 2394], almorexant (pK _i 8.3–8.5) [1792 , 1795 , 2868]	SB-649868 (pK _i 8.9–9.8) [365 , 551], TCS 1102 (pK _B 8.8–9.7) [201 , 2394], filorexant (pK _i 9.7) [2344], suvorexant (pK _i 8.9–9.5) [365 , 551 , 1987 , 2344], almorexant (pK _i 8.6–9.4) [1791 , 1792 , 1795 , 2868], daridorexant (pK _B 8.9–9.1) [2344 , 2868], filorexant (pK _i 8.9–9.1) [365 , 551 , 3082], seltorexant (pK _B 8.8) [259]
Selective antagonists	SB-674042 (70–120-fold selective pro-OX ₁) (pK _i 8.7–9.3) [1557 , 1792], 1-SORA-51 (560-fold selective pro-OX ₁) (pK _i 8.7) [2714], CVN766 (1800-fold selective pro-OX ₁) (pK _i 8.1) [920], CVN45502 (1600-fold selective pro-OX ₁) (pK _i 7.9) [2520], SB-408124 (32–65-fold selective pro-OX ₁) (pK _i 7.5) [1792]	MK-1064 (3000-fold selective pro-OX ₂) (pK _i 9.3) [2408], EMPA (790–3500-fold selective pro-OX ₂) (pK _i 8.4–9.2) [1791 , 1792 , 2344], JNJ-10397049 (500–630-fold selective pro-OX ₂) (pK _i 7.7–8.4) [1853], seltorexant (70–320-fold selective pro-OX ₂) (pK _i 8) [259]
Labelled ligands	[³H]SB-674042 (Antagonist) (pK _d 8.3–9.1) [1557 , 1792 , 1795], [³H]-almorexant (Antagonist) (pK _d 8.6–8.9) [1792 , 1795], [¹²⁵I]orexin A (human, mouse, rat) (Useful working concentration sub nM–low nM.) [1512 , 2302 , 2460]	[³H]-almorexant (Antagonist) (pK _d 8.9–9.8) [1792 , 1795], [³H]EMPA (Selective Antagonist) (pK _d 8.6–9) [1791 , 1795 , 1919], [¹²⁵I]orexin A (human, mouse, rat) (Useful working concentration sub nM–low nM.) [1512 , 2302 , 2460]

Comments: The primary coupling of orexin receptors to G_{q/11} proteins is rather speculative and based on the strong activation of phospholipase C, though recent studies in recombinant cells also stress the importance of G_{q/11} [[1513](#)]. Coupling of both receptors to G_{i/o}, G_s and and G_{12/13} has also been reported [[1228](#),

[1352](#), [1517](#), [1624](#), [2341](#)]. For most native cellular responses observed, the G protein pathway is unknown. The selectivity of agonist ligands may depend on the cellular signal transduction machinery [[1514](#), [2303](#), [2394](#), [3143](#)]. Thorough characterization of many antagonists and radioligands has not been published,

but the situation has recently improved for many commercially available ones. Orexin receptors have been reported to be able to form complexes with each other and some other GPCRs as well as σ 1-receptors, which might affect the signaling and pharmacology [[1515](#), [2035](#)].

Further reading on Orexin receptors

Štefková-Mazochová K *et al.* (2022) Pharmacokinetic, pharmacodynamic, and behavioural studies of deschloroketamine in Wistar rats. *Br J Pharmacol* **179**: 65–83 [[PMID:34519023](#)]
 Burdakov D. (2019) Reactive and predictive homeostasis: Roles of orexin/hypocretin neurons. *Neuropharmacology* **154**: 61–67 [[PMID:30347195](#)]
 Jacobson LH *et al.* (2022) Hypocretins (orexins): The ultimate translational neuropeptides. *J Intern Med* **291**: 533–556 [[PMID:35043499](#)]

James MH *et al.* (2022) Orexin Reserve: A Mechanistic Framework for the Role of Orexins (Hypocretins) in Addiction. *Biol Psychiatry* **92**: 836–844 [[PMID:36328706](#)]
 Sakurai T *et al.* (2021) Interaction between Orexin Neurons and Monoaminergic Systems. *Front Neurol Neurosci* **45**: 11–21 [[PMID:34052806](#)]

Oxoglutarate receptor

G protein-coupled receptors → Oxoglutarate receptor

Overview: Nomenclature as recommended by NC-IUPHAR [[586](#)].

Nomenclature	oxoglutarate receptor
HGNC, UniProt	OXGR1 , Q96P68
Endogenous agonists	α -ketoglutaric acid [1088 , 2669]

Further reading on Oxoglutarate receptor

Davenport AP *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacol Rev* **65**: 967-86 [PMID:23686350]

P2Y receptors

G protein-coupled receptors → P2Y receptors

Overview: P2Y receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on P2Y Receptors** [1, 2, 1253]) are activated by the endogenous ligands ATP, ADP, UTP, UDP, and UDP-sugars. The eight mammalian P2Y receptors are activated by distinct nucleotides: P2Y₁, P2Y₁₁, P2Y₁₂ and P2Y₁₃ are activated by adenosine-nucleotides; P2Y₂, P2Y₄ can be activated by both adenosine and uridine nucleotides, with some species-specific differences; P2Y₆ is mainly activated by UDP; P2Y₁₄ is preferentially activated by sugar-uracil nucleotides. The missing numbers

in the receptor nomenclature refer either to non-mammalian orthologs or receptors having some sequence homology to P2Y receptors but for which there is no functional evidence of responsiveness to nucleotides [2958]. Based on their G protein coupling P2Y receptors can be divided into two subfamilies: P2Y₁, P2Y₂, P2Y₄, P2Y₆ and P2Y₁₁ receptors couple *via* Gq proteins to stimulate phospholipase C followed by increases in inositol phosphates and mobilization of Ca²⁺ from intracellular stores. P2Y₁₁ receptors couple in addition to Gs proteins followed by increased

adenylate cyclase activity. In contrast, P2Y₁₂, P2Y₁₃, and P2Y₁₄ receptors signal primarily through activation of Gi proteins and inhibition of adenylate cyclase activity or control of ion channel activity [2958]. Clinically used drugs acting on these receptors include the dinucleoside polyphosphate **diquafosol**, agonist of the P2Y₂ receptor subtype, approved in Japan and South Korea for the management of dry eye disease [1566], and the P2Y₁₂ receptor antagonists **clopidogrel**, **prasugrel**, **cangrelor** and **ticagrelor**, all approved as antiplatelet drugs [376, 2281].

Nomenclature	P2Y ₁ receptor	P2Y ₂ receptor	P2Y ₄ receptor	P2Y ₆ receptor	P2Y ₁₁ receptor
HGNC, UniProt	<i>P2RY1</i> , P47900	<i>P2RY2</i> , P41231	<i>P2RY4</i> , P51582	<i>P2RY6</i> , Q15077	<i>P2RY11</i> , Q96G91
Potency order of endogenous ligands	ADP>ATP	UTP > ATP	UTP>ATP (at rat recombinant receptors, UTP = ATP)	UDP≫ UTP > ADP	ATP>ADP
Endogenous agonists	ATP (Partial agonist) [2499, 2972], ADP [2499, 2972]	UTP [1405, 1577]	UTP [1378], ATP [1256]	UDP [526]	ATP [527, 1256, 3058], UTP [3058], ADP [527]
Agonists	ADPβS [2767], 2MeSADP [2499, 2972]	–	–	–	ATPγS [527]
Sub/family-selective agonists	–	diquafosol [2203], denufosol [1578, 2203, 3180], UTPγS [1577]	diquafosol [330], denufosol [3180], UTPγS [1578]	–	ADPβS [527]
Selective agonists	MRS2365 [468], 2-CI-ADP(α-BH ₃) [112]	MRS2698 [1243], 2-thioUTP [713], PSB1114 (EC ₅₀ value determined using an IP ₃ functional assay) [713, 714, 1242]	MRS4062 [1828], MRS2927 [1828], (N)methanocarba-UTP [1405]	Rp-5-OMe-UDPαB [916, 1007], MRS2957 [1827], MRS2693 [212]	AR-C67085 [136, 527], NF546 [1873]
Antagonists	suramin (pK _i 5.3) [2972], PPADS (pK _i 5.2) [2972]	–	–	MRS4841 (pIC ₅₀ 5.5) [2135]	NF157 (pK _i 7.3) [2886]
Sub/family-selective antagonists	–	reactive blue-2 (pIC ₅₀ 6) [1269], suramin (pIC ₅₀ 4.3) [1269, 2499]	PPADS (pEC ₅₀ 2–5) [1255], reactive blue-2 (pIC ₅₀ 4.7) [245] – Rat	reactive blue-2 (pK _B 6) [2958], PPADS (pK _B 4) [2958], suramin (pK _B 4) [2958]	suramin (pIC ₅₀ 4.8–6) [527], reactive blue-2 (pIC ₅₀ 5) [527]

Selective antagonists	MRS2500 (pK _i 8.8–9.1) [396, 1404], MRS2279 (pK _i 7.9) [2972], MRS2179 (pK _i 7–7.1) [286, 2972]	AR-C118925XX (pIC ₅₀ ~6) [1374], AR-C126313 (pEC ₅₀ 6) [1243], PSB-416 (pIC ₅₀ 4.7) [1128]	PSB-16133 (pIC ₅₀ 6.6) [2326], ATP (pK _d 6.2) [1378]	MRS2578 (pIC ₅₀ 7.4) [1798], MRS2567 (pIC ₅₀ 6.9) [1798], TIM-38 (pIC ₅₀ 5.4) [1239]	NF340 (pIC ₅₀ 6.4–7.1) [1873]
Selective allosteric modulators	BMS compound 16 (Negative) (pK _i 6.9) [3222], 2,2'-pyridylisatogen tosylate (Negative) (pIC ₅₀ 6.8) [851]	–	–	–	–
Labelled ligands	[³ H]MRS2279 (Antagonist) (pK _d 8.1) [2972], [³ H]2MeSADP (Agonist) [2767], [³⁵ S]ADPβS (Agonist)	–	–	MRS4162-BODIPY conjugate (Selective Agonist) [1276]	–

Nomenclature	P2Y ₁₂ receptor	P2Y ₁₃ receptor	P2Y ₁₄ receptor
HGNC, UniProt	P2RY12, Q9H244	P2RY13, Q9BPV8	P2RY14, Q15391
Potency order of endogenous ligands	ADP>ATP	ADP≫ATP	UDP= UDP-glucose
Endogenous agonists	ADP [1151]	ADP [1823]	UDP [390], UDP-glucose [818], UDP-galactose [415]
Sub/family-selective agonists	2MeSADP [1151], ADPβS [2767]	2MeSADP [1823], 2MeSATP [1823], ADPβS [1823]	–
Selective agonists	–	–	MRS2905 [1252], 2-thio-UDP [577], α,β-difluoromethylene-UDP [577]
Antagonists	cangrelor (pIC ₅₀ 9.4) [1256], Ap ₄ A (pIC ₅₀ 6) [1823], 2MeSAMP (pIC ₅₀ 5.4) [2767]	cangrelor (pIC ₅₀ 8.3) [1823], Ap ₄ A (pIC ₅₀ 6.7) [1823], 2MeSAMP (pIC ₅₀ 5.6) [1823]	–
Selective antagonists	selatogrel (pK _d 8.7) [163, 2301], AZD1283 (pIC ₅₀ 8.5) [3228], PSB-22219 (pK _i 8.3) [37], ARL66096 (pIC ₅₀ 7.9) [1202, 1203], ticagrelor (pK _i 7.8) [3217], PSB-0702 (pIC ₅₀ 7.7) [141], PSB-0739 (pK _i 7.6) [141]	MRS2603 (pIC ₅₀ 6.2) [1417], MRS2211 (pIC ₅₀ 6) [1417]	PPTN (pK _i 10.1) [148], MRS4738 (pIC ₅₀ 8.5) [3043], MRS4833 (pIC ₅₀ 8.2) [3042], MRS4654 (pIC ₅₀ 7.8) [1319], compound A (pIC ₅₀ 7.6) [3035], MRS4625 (pIC ₅₀ 7.6) [1992]
Labelled ligands	[³ H]2MeSADP (Agonist) [2767], [³ H]AZ12464237 (Selective Antagonist) (pK _d 8.5) [2680], [³ H]PSB-0413 (Antagonist) (pK _d 8.3–8.5) [712, 2115], [³ H]PSB-22219 (Selective Antagonist) (pK _d 8.3) [37], [³ H]PSB-22219 (Selective Antagonist) (pK _d 8.3) [37]	[³³ P]2MeSADP (Agonist) [1823]	MRS4174 (Selective Antagonist) (pK _i 10.1) [1431], MRS4183 (Selective Agonist) [1430]

Comments: A series of 4-alkyloxyimino derivatives of uridine-5'-triphosphate which could be useful for derivatization as fluorescent P2Y_{2/4/6} receptor probes has been synthesized [1276]. Recently, selatogrel, a potent and reversible P2Y₁₂ receptor antagonist in clinical trials for acute myocardial infarction and chronic coronary syndromes, showed potent platelet inhibition, rapid onset, suitable duration, and good safety [2624, 2704]. Cryo-EM structures of the apo P2Y₂ receptor in complex with G_q, the ATP-bound P2Y₂ receptor in complex with G_q or G_o, and the UTP-bound P2Y₄ receptor in complex with G_q have been determined

[1547]. A helix-like segment within the N-terminus of the apo P2Y₂ receptor has been found to occupy the orthosteric ligand-binding pocket, revealing a novel mechanism of receptor self-activation [1547]. The human P2Y₁₂ receptor has been structurally resolved in complex with the antagonist AZD1283 [3230] and the agonist 2MeSADP [3228].

Single nucleotide polymorphisms of the P2Y₁ gene have been associated to different platelet reactivity to ADP [1117]. Three frequent nonsynonymous P2Y₂ receptor polymorphisms have been identified, one of which was significantly more common in cystic

fibrosis patients. This polymorphism is linked to increases in Ca²⁺ influx in transfected cells, and might therefore play a role in disease development [348]. ATP acts as partial agonist/antagonist at the human P2Y₄ receptor [2958]. A frequent loss-of-function P2Y₄ variant was found associated with less severe coronary artery atherosclerosis and lower fasting plasma glucose in coronary patients [1163]. A group of single nucleotide polymorphisms in the P2Y₁₂ gene, forming the so called P2Y₁₂ H2 haplotype, has been associated with increased platelet responsiveness to ADP, increased risk of peripheral arterial disease and with coronary

artery disease [401]. The platelet-type bleeding disorder due to P2Y₁₂ receptor defects is an autosomal recessive condition characterized by mild to moderate mucocutaneous bleeding and excessive bleeding after surgery or trauma. The defect is due to the

inability of ADP to induce platelet aggregation [397]. The P2Y₁₃ receptor Met-158-Thr polymorphism, which is in linkage disequilibrium with the P2Y₁₂ locus, is not associated with acute myocardial infarction, diabetes mellitus or related risk factors [60]. The

P2Y₁₄ receptor, previously known to bind sugar nucleotides such as UDP-glucose and its derivatives, has also been shown to bind UDP [390], which competitively antagonizes the UDP-glucose response at the human recombinant receptor [819].

Further reading on P2Y receptors

Abbracchio MP *et al.* (2006) International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. *Pharmacol Rev* **58**: 281-341 [PMID:16968944]

Jacobson KA *et al.* (2020) Update of P2Y receptor pharmacology: IUPHAR Review 27. *Br J Pharmacol* **177**: 2413-2433 [PMID:32037507]

Jacobson KA *et al.* (2015) Nucleotides Acting at P2Y Receptors: Connecting Structure and Function. *Mol Pharmacol* **88**: 220-30 [PMID:25837834]

von Kügelgen I *et al.* (2016) Pharmacology and structure of P2Y receptors. *Neuropharmacology* **104**: 50-61 [PMID:26519900]

Parathyroid hormone receptors

G protein-coupled receptors → Parathyroid hormone receptors

Overview: The parathyroid hormone receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Parathyroid Hormone Receptors** [857]) are class B G protein-coupled receptors. The parathyroid hormone (PTH)/parathyroid hormone-related protein (PTHrP) receptor (PTH1 receptor) is activated by: PTH (PTH, P01270) (84 amino acids),

and PTHrP (PTHLH, P12272) (141 amino-acids) and related N-terminal peptides (PTH-(1-34), PTHrP-(1-36) (PTHLH, P12272)). The parathyroid hormone 2 receptor (PTH2 receptor) is activated by the precursor-derived peptide TIP39 (PTH2, Q96A98) (39 amino acids) and PTH. [¹²⁵I]PTH may be used to label both PTH1 and PTH2 receptors. The structure of a long-active PTH analogue (LA-

PTH, an hybrid of PTH-(1-13) and PTHrP-(14-36)) bound to the PTH1 receptor-G_s complex has been resolved by cryo-electron microscopy [3247]. Another structure of a PTH-(1-34) analog bound to a thermostabilized inactive PTH1 receptor has been obtained with X-ray crystallography [708].

Nomenclature	PTH1 receptor	PTH2 receptor
HGNC, UniProt	PTH1R, Q03431	PTH2R, P49190
Potency order of endogenous ligands	PTH (PTH, P01270) = PTHrP (PTHLH, P12272)	TIP39 (PTH2, Q96A98), PTH (PTH, P01270) ≫ PTHrP (PTHLH, P12272)
Agonists	teriparatide [855]	TIP39 (PTH2, Q96A98) [940, 1140]
Selective agonists	PTHrP-(1-34) (human) [856] – Rat, abaloparatide [101]	–

Comments: The parathyroid hormone type 1 receptor (PTH1R) is the canonical GPCR for PTH and PTHrP. It is coupled to G_s and G_q and regulates the development of bone, heart, mammary glands and other tissues in response to PTHrP, and blood concentrations of calcium and phosphate ions, as well as vitamin D, in response to PTH. Another important action of the PTH/PTHrP system is to stimulate bone formation when the hormone is intermittently administered (daily injection).

Although PTH (PTH, P01270) is an agonist at human PTH2 receptors, it fails to activate the rodent orthologues. TIP39 (PTH2, Q96A98) is a weak antagonist at PTH1 receptors [1309].

Further reading on Parathyroid hormone receptors

- Cheloha RW *et al.* (2015) PTH receptor-1 signalling-mechanistic insights and therapeutic prospects. *Nat Rev Endocrinol* **11**: 712-24 [PMID:26303600]
- Gardella TJ *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCIII. The Parathyroid Hormone Receptors-Family B G Protein-Coupled Receptors. *Pharmacol Rev* **67**: 310-37 [PMID:25713287]
- Sutkeviciute I *et al.* (2020) Structural insights into emergent signaling modes of G protein-coupled receptors. *J Biol Chem* **295**: 11626-11642 [PMID:32571882]
- Villardaga JP *et al.* (2023) Molecular Mechanisms of PTH/PTHrP Class B GPCR Signaling and Pharmacological Implications. *Endocr Rev* **44**: 474-491 [PMID:36503956]
- Villardaga JP *et al.* (2014) Endosomal generation of cAMP in GPCR signaling. *Nat Chem Biol* **10**: 700-6 [PMID:25271346]

Platelet-activating factor receptor

G protein-coupled receptors → Platelet-activating factor receptor

Overview: Platelet-activating factor (PAF, 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is an ether phospholipid mediator associated with platelet coagulation, but also subserves inflammatory roles. The PAF receptor (**provisional nomenclature recommended by NC-IUPHAR** [789]) is activated by PAF and other suggested endogenous ligands are oxidized phosphatidylcholine [1812] and lyso-phosphatidylcholine [2109]. It may also be activated by bacterial lipopolysaccharide [2020].

Nomenclature	PAF receptor
HGNC, UniProt	PTAFR, P25105
Selective agonists	methylcarbamyl PAF
Selective antagonists	foropafant (pK _i 10.3) [1106], ABT-491 (pK _i 9.2) [38], CV-6209 (pIC ₅₀ 8.1–8.3) [928, 2019], L659989 (pK _i 7.8) [1207], apafant (pK _i 5.2–7.5) [2169, 2744]
Labelled ligands	[³ H]PAF (Agonist) [827, 2019]

Comments: Note that a previously recommended radioligand ([³H]apafant; K_d 44.6 nM) is currently unavailable.

Further reading on Platelet-activating factor receptor

- Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]
- Ishii S *et al.* (2000) Platelet-activating factor (PAF) receptor and genetically engineered PAF receptor mutant mice. *Prog Lipid Res* **39**: 41-82 [PMID:10729607]
- Prescott SM *et al.* (2000) Platelet-activating factor and related lipid mediators. *Annu Rev Biochem* **69**: 419-45 [PMID:10966465]

Prokineticin receptors

G protein-coupled receptors → Prokineticin receptors

Overview: Prokineticin receptors, PKR₁ and PKR₂ (**provisional nomenclature as recommended by NC-IUPHAR** [789]) respond to the cysteine-rich 81-86 amino-acid peptides **prokineticin-1** (PROK1, Q9HC23) (also known as endocrine gland-derived vascular endothelial growth factor, mambakine) and **prokineticin-2** (PROK2, Q9HC23) (protein Bv8 homologue). An orthologue of PROK1 from black mamba (*Dendroaspis polylepis*) venom, mamba intestinal toxin 1 (MIT1, [2535]) is a potent, non-selective agonist at prokineticin receptors [1832], while **Bv8**, an orthologue of PROK2 from amphibians (*Bombina sp.*, [1938]), is equipotent at recombinant PKR₁ and PKR₂ [2046], and has high potency in macrophage chemotaxis assays, which are lost in PKR₁-null mice.

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

Platelet-activating factor receptor S115

Nomenclature	PKR ₁	PKR ₂
HGNC, UniProt	<i>PROKR1</i> , Q8TCW9	<i>PROKR2</i> , Q8NEJ6
Potency order of endogenous ligands	prokineticin-2 (<i>PROK2</i> , Q9HC23) > prokineticin-1 (<i>PROK1</i> , Q9HC23) > prokineticin-2β (<i>PROK2</i> , Q9HC23) [439, 1678, 1832, 2657]	prokineticin-2 (<i>PROK2</i> , Q9HC23) > prokineticin-1 (<i>PROK1</i> , Q9HC23) > prokineticin-2β (<i>PROK2</i> , Q9HC23) [439, 1678, 1832, 2657]
Agonists	MIT1 [1832]	MIT1 [1832]
Selective agonists	IS20 [867], IS1 [867]	–
Labelled ligands	[¹²⁵ I]BH-MIT1 (Agonist) [1832]	[¹²⁵ I]BH-MIT1 (Agonist) [1832]

Comments: Genetic mutations in *PROKR1* are associated with Hirschsprung's disease [2438], while genetic mutations in *PROKR2* are associated with hypogonadotropic hypogonadism with anosmia [658], hypopituitarism with pituitary stalk interruption [2375] and Hirschsprung's disease [2438]. PKR₂ has been recently identified as a receptor for *T. cruzi* natural infection [1391]. *PROK2* neuropeptide signalling via PKR₂ on spinal neurons generates pleasant touch sensation [1701].

Further reading on Prokineticin receptors

- Boulberdaa M *et al.* (2011) Prokineticin receptor 1 (PKR1) signalling in cardiovascular and kidney functions. *Cardiovasc Res* **92**: 191-8 [PMID:21856786]
- Lattanzi R *et al.* (2022) Non-Peptide Agonists and Antagonists of the Prokineticin Receptors. *Curr Issues Mol Biol* **44**: 6323-6332 [PMID:36547092]
- Lattanzi R *et al.* (2024) Genetic Polymorphisms of Prokineticins and Prokineticin Receptors Associated with Human Disease. *Life (Basel)* **14**: [PMID:39459554]
- Negri L *et al.* (2018) The Prokineticins: Neuromodulators and Mediators of Inflammation and Myeloid Cell-Dependent Angiogenesis. *Physiol Rev* **98**: 1055-1082 [PMID:29537336]
- Negri L *et al.* (2012) Bv8/PK2 and prokineticin receptors: a druggable pronociceptive system. *Curr Opin Pharmacol* **12**: 62-6 [PMID:22136937]
- Negri L *et al.* (2007) Bv8/Prokineticin proteins and their receptors. *Life Sci* **81**: 1103-16 [PMID:17881008]
- Ngan ES *et al.* (2008) Prokineticin-signaling pathway. *Int J Biochem Cell Biol* **40**: 1679-84 [PMID:18440852]
- Vincenzi M *et al.* (2023) Therapeutic Potential of Targeting Prokineticin Receptors in Diseases. *Pharmacol Rev* **75**: 1167-1199 [PMID:37684054]

Prolactin-releasing peptide receptor

G protein-coupled receptors → Prolactin-releasing peptide receptor

Overview: The precursor (*PRLH*, P81277) for PrRP generates 31 and 20-amino-acid versions. QRFP43 (43RFa) (*QRFP*, P83859) (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from *QRFP* (P83859) and is also known as P518 or 26RFa. RFRP is an RF amide-related peptide [1129] derived from a FMRFamide-related peptide precursor (*NPVF*, Q9HCQ7), which is cleaved to generate neuropeptide SF (*NPFF*, O15130), neuropeptide RFRP-1 (*NPVF*, Q9HCQ7), neuropeptide RFRP-2 (*NPVF*, Q9HCQ7) and neuropeptide RFRP-3 (*NPVF*, Q9HCQ7) (neuropeptide NPVF).

Nomenclature	PrRP receptor
HGNC, UniProt	<i>PRLHR</i> , P49683
Potency order of endogenous ligands	PrRP-20 (<i>PRLH</i> , P81277) = PrRP-31 (<i>PRLH</i> , P81277) [1558]
Endogenous agonists	PrRP-20 (<i>PRLH</i> , P81277) [724, 1558], PrRP-31 (<i>PRLH</i> , P81277) [724, 1558]
Agonists	compound 18-S4 [2235]
Endogenous antagonists	neuropeptide Y (<i>NPY</i> , P01303) (pK _i 5.4) [1540]
Labelled ligands	[¹²⁵ I]PrRP-20 (human) (Agonist) [1558], [¹²⁵ I]PrRP31 (Agonist) [716]

Comments: The orphan receptor *GPR83* (*Q9NYM4*) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors.

Further reading on Prolactin-releasing peptide receptor

- Jørgensen SK *et al.* (2024) An analogue of the Prolactin Releasing Peptide reduces obesity and promotes adult neurogenesis. *EMBO Rep* **25**: 351-377 [PMID:38177913]
- Macías M *et al.* (2023) Liquid Biopsy in Alzheimer's Disease Patients Reveals Epigenetic Changes in the *PRLHR* Gene. *Cells* **12**: [PMID:38067107]
- Morgan A *et al.* (2024) Deficiency of GPR10 and NPFFR2 receptors leads to sex-specific prediabetic syndrome and late-onset obesity in mice. *Biosci Rep* **44**: [PMID:39440369]
- Mráziková L *et al.* (2025) Anti-inflammatory effects of palm11-PrRP31 in a rat model of lipopolysaccharide-induced acute inflammation. *J Mol Endocrinol* **74**: [PMID:39869505]
- Vas S *et al.* (2023) Prolactin-Releasing Peptide Contributes to Stress-Related Mood Disorders and Inhibits Sleep/Mood Regulatory Melanin-Concentrating Hormone Neurons in Rats. *J Neurosci* **43**: 846-862 [PMID:36564184]

Prostanoid receptors

G protein-coupled receptors → Prostanoid receptors

Overview: Prostanoid receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors** [3095]) are activated by the endogenous ligands prostaglandins *PGD₂*, *PGE₁*, *PGE₂*, *PGF_{2α}*, *PGH₂*, prostacyclin [*PGI₂*] and *thromboxane A₂*. Differences and similarities between human and rodent prostanoid receptor orthologues, and their specific roles in pathophysiological conditions are reviewed in [2091]. Measurement of the potency of *PGI₂* and *thromboxane A₂* is hampered by their instability in physiological salt solution; they are often replaced by *cicaprost* and *U46619*, respectively, in receptor characterization studies.

Nomenclature	<i>DP₁</i> receptor	<i>DP₂</i> receptor
HGNC, UniProt	<i>PTGDR</i> , Q13258	<i>PTGDR2</i> , Q9Y5Y4
Potency order of endogenous ligands	<i>PGD₂</i> > <i>PGE₁</i> >> <i>PGE₂</i> > <i>PGF_{2α}</i> > <i>PGI₂</i> , <i>thromboxane A₂</i>	<i>PGD₂</i> >> <i>PGF_{2α}</i> , <i>PGE₂</i> > <i>PGI₂</i> , <i>thromboxane A₂</i>
Agonists	treprostinil [1089, 2748, 3062]	–
Selective agonists	BW 245C [248, 3096, 3097], L-644,698 [3096, 3097]	15(R)-15-methyl- <i>PGD₂</i> [1062, 1950, 2723]
Antagonists	laropiprant (p <i>K_i</i> 10.1) [1543, 2715]	fevipiprant (p <i>K_i</i> 9) (p <i>K_d</i> 9) [2750, 2751], AZD1981 (p <i>IC₅₀</i> 8.4) [1743], ramatroban (p <i>K_i</i> 7.4) [2723]
Selective antagonists	BWA868C (p <i>K_i</i> 8.6–9.3) [248, 907, 3096], ONO-AE3-237 (p <i>K_i</i> 7.7) [1131, 2850, 2853]	TM30089 (p <i>K_i</i> 9.2) (p <i>IC₅₀</i> 8.9) [2205, 2432, 2890]
Labelled ligands	[³ H] <i>PGD₂</i> (Agonist) [3077, 3096]	[³ H] <i>PGD₂</i> (Agonist) [1834, 2586], [¹⁸ F]TM30089 (Antagonist) [2205]

Nomenclature	<i>EP₁</i> receptor	<i>EP₂</i> receptor	<i>EP₃</i> receptor	<i>EP₄</i> receptor
HGNC, UniProt	<i>PTGER1</i> , P34995	<i>PTGER2</i> , P43116	<i>PTGER3</i> , P43115	<i>PTGER4</i> , P35408
Potency order of endogenous ligands	<i>PGE₂</i> > <i>PGE₁</i> > <i>PGF_{2α}</i> , <i>PGI₂</i> > <i>PGD₂</i> , <i>thromboxane A₂</i>	<i>PGE₂</i> = <i>PGE₁</i> > <i>PGF_{2α}</i> , <i>PGI₂</i> > <i>PGD₂</i> , <i>thromboxane A₂</i>	<i>PGE₂</i> , <i>PGE₁</i> > <i>PGF_{2α}</i> , <i>PGI₂</i> > <i>PGD₂</i> , <i>thromboxane A₂</i>	<i>PGE₂</i> = <i>PGE₁</i> > <i>PGF_{2α}</i> , <i>PGI₂</i> > <i>PGD₂</i> , <i>thromboxane A₂</i>
Endogenous agonists	<i>PGE₂</i> [10]	<i>PGE₂</i> [10, 2698, 3077]	<i>PGE₂</i> (<i>EP₃</i> -III isoform) [10]	<i>PGE₂</i> [10, 593, 2024, 2698, 3077]

Agonists	17-phenyl- ω -trilor-PGE ₂ [2572]	treprostinil [2748, 3062], PGE ₁ [159]	ONO-AE-248 (EP ₃ α isoform) [2739, 3209] – Mouse, ralinepag [2864], misoprostol (methyl ester) (EP ₃ -III isoform) [10]	17-phenyl- ω -trilor-PGE ₂ [2810]
Selective agonists	ONO-DI-004 [2739] – Mouse	ONO-AE1-259 [2739] – Mouse, omidenepag [1429], butaprost (free acid form) [10, 2698]	sulprostone (EP ₃ -III isoform) [10], ONO-AE-248 [798, 1729]	L902688 [799, 1597], KMN-159 [149], ONO-AE1-329 [798, 799]
Selective antagonists	ONO-8711 (pK _i 9.2) [3024], MF266-1 (pK _i 8.4) [514], SC-51322 (pK _i 7.9) [10]	PF-04418948 (PF-04418948 has weaker affinity at the EP ₂ -receptor in guinea-pigs) (pK _B 8.3) [17, 227], TG6-129 (pK _B 8.1) [846], TG8-260 (pK _B 7.9) [54, 2356]	L-826266 (EP ₃ -III isoform (pK _i =8.04 in the presence of HSA)) (pK _i 9.1) [1321], ONO-AE3-240 (pIC ₅₀ 8.8) [53] – Mouse, DG-041 (pK _i 8.4) [1317]	MF 498 (pK _i 9.1) [514, 756], ONO-AE3-208 (pK _i 8.9) [1324, 2862], palupiprant (pK _i 8.2) [42, 1161], L-161,982 (EP ₄ A) (pK _i 7.6) [1767, 2178], GW 627368 (pK _i 7–7.1) [3077, 3078]
Labelled ligands	[³ H]PGE ₂ (Agonist) [10, 2572, 3077]	[³ H]PGE ₂ (Agonist) [10, 3077]	[³ H]PGE ₂ (Agonist) [10, 3077]	[³ H]PGE ₂ (Agonist) [10, 593, 3062, 3077]

Nomenclature	FP receptor	IP receptor	TP receptor
HGNC, UniProt	<i>PTGFR</i> , P43088	<i>PTGIR</i> , P43119	<i>TBXA2R</i> , P21731
Potency order of endogenous ligands	PGF _{2α} > PGD ₂ > PGE ₂ > PGI ₂ , thromboxane A ₂	PGI ₂ >> PGE ₁ > PGD ₂ , PGF _{2α} > thromboxane A ₂	thromboxane A ₂ = PGH ₂ >> PGD ₂ , PGE ₂ , PGF _{2α} , PGI ₂
Endogenous agonists	–	PGI ₂ [2607], PGE ₁ [1829, 2700]	–
Agonists	ONO-9054 [3149]	iloprost [10, 3077], treprostinil [3062]	–
Selective agonists	fluprostenol [10], latanoprost (free acid form) [10]	cicaprost [10], MRE-269 [197, 1532]	U46619 [10]
Antagonists	–	–	ramatroban (pK _i 8) [2811], GW 627368 (pK _i 6.9) [3078] – Pig, laropiprant (pK _i 6.1) [1543]
Selective antagonists	AS604872 (pK _i 7.5) [509], AL-8810 (pA ₂ 6.7) [2573] – Rat, AL-8810 (pK _i 6.4–6.6) [2573] – Rat	CAY10441 (pK _i 8.7) [236], RO3244794 (pA ₂ 8.5) [236]	vapiprost (pK _i 8.3–9.4) [85, 1745], SQ-29548 (pK _i 8.1–9.1) [10, 2747, 3077]
Labelled ligands	[³ H]PGF _{2α} (Agonist) [10, 11, 3077], [³ H](+)-fluprostenol (Agonist)	[³ H]iloprost (Agonist) [10, 247, 3062, 3077]	[¹²⁵ I]SAP (Antagonist) (pK _d 7.7–9.3) [2016], [¹²⁵ I]BOP (Agonist) [1971], [³ H]SQ-29548 (Antagonist) (pK _d 7.4–8.2) [10, 3077]

Comments: Whilst **cicaprost** is selective for IP receptors, it does exhibit moderate agonist potency at EP₄ receptors [10]. Apart from IP receptors, **iloprost** also binds to EP₁ receptors.

The EP₁ agonist **17-phenyl- ω -trilor-PGE₂** also shows agonist activity at EP₃ and EP₄ receptors [798, 2810]. **Butaprost** and **SC46275** may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP [1674] and TP receptors [1496, 2358]. mRNA for the EP₃ receptor undergoes alternative splicing to produce variants which can interfere with

signalling [2128] or generate complex patterns of G-protein (G_{i/o}, G_{q/11}, G_s and G_{12/13}) coupling (e.g. [1482, 2044]). The number of EP₃ receptor (protein) variants are variable depending on species. For the human prostaglandin EP₃ receptor, there exist five different EP₃ isoform proteins (EP₃-I, EP₃-II, EP₃-III, EP₃-IV and EP₃-e). Three isoforms exist in rat and mouse. Putative receptor(s) for prostamide F (which as yet lack molecular correlates) and which preferentially recognize **PGF2-1-ethanolamide** and its analogues (e.g. **Bimatoprost**) have been identified, together with moderate-

potency antagonists (e.g. **AGN 211334**) [3094].

The free acid form of **AL-12182**, **AL12180**, used in *in vitro* studies, has a EC₅₀ of 15nM which is the concentration of the compound giving half-maximal stimulation of inositol phosphate turnover in HEK-293 cells expressing the human FP receptor [2574]. References given alongside the TP receptor agonists **I-BOP** [1849] and **STA₂** [85] use human platelets as the source of TP receptors for competition radio-ligand binding assays to determine the indicated activity values.

Pharmacological evidence for a second IP receptor, denoted IP₂, in the central nervous system [2773, 3027] and in the BEAS-2B human airway epithelial cell line [3080] is available. This receptor

is selectively activated by 15R-17,18,19,20-tetranor-16-m-tolyl-isocarbacyclin (15R-TIC) and 15R-deoxy 17,18,19,20-tetranor-16-m-tolyl-isocarbacyclin (15-deoxy-TIC). However, molecular bi-

ological evidence for an IP₂ subtype is currently lacking. The IP antagonist CAY10441 also exhibits affinity for some alpha adrenoceptors (rat/human pK_i 5.9-6.5) [236].

Further reading on Prostanoid receptors

Baudouin C *et al.* (2025) Adherence and Persistence on Prostaglandin Analogues for Glaucoma: A Systematic Review and Meta-Analysis. *Am J Ophthalmol* **275**: 99-113 [PMID:40113120]
 Cheng H *et al.* (2021) Role of prostaglandin E2 in tissue repair and regeneration. *Theranostics* **11**: 8836-8854 [PMID:34522214]
 Ganesh T. (2014) Prostanoid receptor EP2 as a therapeutic target. *J Med Chem* **57**: 4454-65 [PMID:24279689]
 Humbert M *et al.* (2022) 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* **43**: 3618-3731 [PMID:36017548]

Norel X *et al.* (2020) International Union of Basic and Clinical Pharmacology. CIX. Differences and Similarities between Human and Rodent Prostaglandin E₂ Receptors (EP1-4) and Prostacyclin Receptor (IP): Specific Roles in Pathophysiological Conditions. *Pharmacol Rev* **72**: 910-968 [PMID:32962984]
 Santiso A *et al.* (2024) Prostaglandin E2 in the Tumor Microenvironment, a Convolved Affair Mediated by EP Receptors 2 and 4. *Pharmacol Rev* **76**: 388-413 [PMID:38697857]
 Woodward DF *et al.* (2011) International union of basic and clinical pharmacology. LXXXIII: classification of prostanoid receptors, updating 15 years of progress. *Pharmacol Rev* **63**: 471-538 [PMID:21752876]

Proteinase-activated receptors

G protein-coupled receptors → Proteinase-activated receptors

Overview: Proteinase-activated receptors (PARs, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Proteinase-activated Receptors** [1148]) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmasks a tethered ligand (TL) at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. TL sequences

at human PAR1-4 are SFLLRN-NH₂, SLIGKV-NH₂, TFRGAP-NH₂ and GYPGQV-NH₂, respectively. With the exception of PAR3, synthetic peptides with these sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors. Several proteinases, including neutrophil elastase, cathepsin G and chymotrypsin can have inhibitory effects at PAR1 and PAR2 such that they cleave the exodomain of the receptor without inducing activation of Gαq-coupled calcium signalling, thereby preventing

activation by activating proteinases but not by agonist peptides. Neutrophil elastase (NE) cleavage of PAR1 and PAR2 can however activate MAP kinase signaling by exposing a TL that is different from the one revealed by trypsin [2333]. PAR2 activation by NE regulates inflammation and pain responses [1993, 3248] and triggers mucin secretion from airway epithelial cells [3255].

Nomenclature	PAR1	PAR2	PAR3	PAR4
HGNC, UniProt	<i>F2R</i> , P25116	<i>F2RL1</i> , P55085	<i>F2RL2</i> , O00254	<i>F2RL3</i> , Q96RI0
Agonist proteases	thrombin (<i>F2</i> , P00734), activated protein C (<i>PROC</i> , P04070), matrix metalloproteinase 1 (<i>MMP1</i> , P45452), matrix metalloproteinase 13 (<i>MMP13</i> , P45452) [106]	Trypsin, tryptase, TF/VIIa, Xa; elastase, neutrophil expressed; cathepsin S [1291, 2331]	thrombin (<i>F2</i> , P00734)	thrombin (<i>F2</i> , P00734), trypsin, cathepsin G (<i>CTSG</i> , P08311)
Agonists	F16357	–	–	–
Selective agonists	TFLLR-NH ₂ [1150]	Isox-Cha-Chg-Ala-Arg-Dpr(4FB)-NH ₂ [1635], AY77 [3176], AZ2429 [1376], GB110 [152], 2-furoyl-LIGRLO-amide [1861], SLIGKV-NH ₂ [1605], SLIGRL-NH ₂ [1605]	–	AYPGKF-NH ₂ , GYPGKF-NH ₂ , GYPGQV-NH ₂

Selective antagonists	vorapaxar (pK _i 8.1) [411], atopaxar (pIC ₅₀ 7.7) [1457], SCH-79797 (pIC ₅₀ 7.2) [23], RWJ-56110 (pIC ₅₀ 6.4) [67]	I-191 (pIC ₅₀ 7.1) [1290], AZ8838 (pK _d 6.5) [462], GB88 (pIC ₅₀ 5.7) [2720], P2pal18S (pIC ₅₀ 5.4)	–	BMS-986120 (pIC ₅₀ 9.3) [2283, 3090], BMS-986141 (pIC ₅₀ 9.3) [2283], YD-3 (pIC ₅₀ 6.9) [3041], ML354 (pIC ₅₀ 6.8) [3041], P4pal-10 [549], RAG8 [2332]
Allosteric modulators (Negative)	–	AZ3451 (pIC ₅₀ 7.6) [462], I-287 (functionally selective) (pIC ₅₀ 7.1) [107], I-287 (functionally selective) (pIC ₅₀ 6.4) [107]	–	–
Labelled ligands	[³H]haTRAP (Agonist) [22]	Isox-Cha-Chg-ARK(Sulfo-Cy5)-NH₂ (Selective Agonist) [1634], 2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH₂ (Agonist) [1149], 2-furoyl-LIGRL[N(³H)propionyl]-O-NH₂ (Agonist) [1149], [³H]2-furoyl-LIGRL-NH₂ (Selective Agonist) [1344], trans-cinnamoyl-LIGRLO [N-(³H)propionyl]-NH₂ (Agonist) [36]	–	–
Comments	TFLLR-NH₂ is selective relative to the PAR ₂ receptor [230, 1359].	2-Furoyl-LIGRLO-NH ₂ activity was measured via calcium mobilisation in HEK 293 cells which constitutively coexpress human PAR ₁ and PAR ₂ .	–	–

Comments: Endogenous serine proteases (EC 3.4.21.) active at the proteinase-activated receptors include: [thrombin](#) ([F2](#), [P00734](#)), generated by the action of Factor X ([F10](#), [P00742](#)) on liver-derived prothrombin ([F2](#), [P00734](#)); trypsin, generated by the action of enterokinase ([TMPRSS15](#), [P98073](#)) on pancreatic-derived trypsinogen ([PRSSI](#), [P07477](#)); tryptase, a family of enzymes (α/β 1 [TPSABI](#), [Q15661](#); γ 1 [TPSG1](#), [Q9NRR2](#); δ 1 [TPSD1](#), [Q9BZJ3](#)) secreted from mast cells; cathepsin G ([CTSG](#), [P08311](#)) generated from leukocytes; liver-derived protein C ([PROC](#), [P04070](#)) generated in plasma by [thrombin](#) ([F2](#), [P00734](#)) and [matrix metalloproteinase 1](#) ([MMP1](#), [P45452](#)).

Further reading on Proteinase-activated receptors

- Adams MN *et al.* (2011) Structure, function and pathophysiology of protease activated receptors. *Pharmacol Ther* **130**: 248-82 [PMID:21277892]
- Canto I *et al.* (2012) Allosteric modulation of protease-activated receptor signaling. *Mini Rev Med Chem* **12**: 804-11 [PMID:22681248]
- Hollenberg MD *et al.* (2002) International Union of Pharmacology. XXVIII. Proteinase-activated receptors. *Pharmacol Rev* **54**: 203-17 [PMID:12037136]
- Peach CJ *et al.* (2023) Protease-activated receptors in health and disease. *Physiol Rev* **103**: 717-785 [PMID:35901239]
- Ramachandran R *et al.* (2012) Targeting proteinase-activated receptors: therapeutic potential and challenges. *Nat Rev Drug Discov* **11**: 69-86 [PMID:22212680]
- Soh UJ *et al.* (2010) Signal transduction by protease-activated receptors. *Br J Pharmacol* **160**: 191-203 [PMID:20423334]

QRFP receptor

G protein-coupled receptors → QRFP receptor

Overview: The human gene encoding the QRFP receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on the QRFP receptor** [1629]; QRFP, formerly known as the Peptide P518 receptor), previously designated as an orphan GPCR receptor was identified in 2001 by Lee *et al.* from a hypothalamus cDNA library [1599]. However, the reported cDNA (AF411117) is

a chimera with bases 1-127 derived from chromosome 1 and bases 155-1368 derived from chromosome 4. When corrected, QRFP (also referred to as SP9155 or AQ27) encodes a 431 amino acid protein that shares sequence similarities in the transmembrane spanning regions with other peptide receptors. These include neuropeptide FF2 (38%), neuropeptide Y₂ (37%) and galanin Gal₁

(35%) receptors. QRFP receptor was identified as a Gs-coupled GPCR [430, 1289] that's activated by the endogenous peptides QRFP43 (43RFa) and QRFP26 (26RFa) [430, 829, 1289]. However, Gq- and Gi/o-mediated signaling was also reported [829, 2335]. Two naturally occurring mutations in the human QRFP receptor lead to distinct and opposite 26RFa-evoked signaling bias [1762].

Nomenclature	QRFP receptor
HGNC, UniProt	QRFP, Q96P65
Endogenous agonists	QRFP43 (43RFa) (QRFP, P83859) [828, 2669], QRFP26 (26RFa) (QRFP, P83859) [430, 1289]
Agonists	LV-2186 [50], LV-2172 [2058], LV-2211 [1610]
Selective antagonists	compound 25e (pIC ₅₀ 7.3) [892, 893]
Labelled ligands	[¹²⁵ I]QRFP43 (human) (Agonist) [829, 2772], [¹²⁵ I]26RFa (human) (Agonist) [331]

Comments: The orphan receptor *GPR83* (9NYM4) shows sequence similarities with the QRFP receptor, as well as with the NPFF1, NPFF2, and PrRP receptors.

Further reading on QRFP receptor

Chartrel N *et al.* (2011) The RFamide neuropeptide 26RFa and its role in the control of neuroendocrine functions. *Front Neuroendocrinol* **32**: 387-97 [PMID:21530572]
 Devère M *et al.* (2025) The 26RFa (QRFP)/GPR103 Neuropeptidergic System: A Key Regulator of Energy and Glucose Metabolism. *Neuroendocrinology* **115**: 111-127 [PMID:38599200]
 Fukusumi S *et al.* (2006) Recent advances in mammalian RFamide peptides: the discovery and functional analyses of PrRP, RFRPs and QRFP. *Peptides* **27**: 1073-86 [PMID:16500002]

Iwama A *et al.* (2024) Structure and dynamics of the pyroglutamylated RF-amide peptide QRFP receptor GPR103. *Nat Commun* **15**: 4769 [PMID:38897996]
 Leprince J *et al.* (2017) The Arg-Phe-amide peptide 26RFa/glutamine RF-amide peptide and its receptor: IUPHAR Review 24. *Br J Pharmacol* **174**: 3573-3607 [PMID:28613414]

Relaxin family peptide receptors

G protein-coupled receptors → Relaxin family peptide receptors

Overview: Relaxin family peptide receptors (RXFP, **nomenclature as agreed by the NC-IUPHAR Subcommittee on Relaxin family peptide receptors** [160, 1021]) may be divided into two pairs, RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are heterodimeric peptide hormones structurally related to insulin: relaxin-1 (*RLN1*, P04808), relaxin (*RLN2*, P04090), relaxin-3 (*RLN3*, Q8WXF3) (also known as INSL7), insulin-like peptide 3 (*INSL3* (*INSL3*, P51460)) and *INSL5* (*INSL5*,

Q9Y5Q6). Species homologues of relaxin have distinct pharmacology and relaxin (*RLN2*, P04090) interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 [2544]. Relaxin-3 (*RLN3*, Q8WXF3) is the ligand for RXFP3 but it also binds to RXFP1 and RXFP4 and has differential affinity for RXFP2 between species [2543]. *INSL5* (*INSL5*, *Q9Y5Q6*) is the ligand for RXFP4 but is a weak antagonist of RXFP3. Relaxin (*RLN2*, P04090) and *INSL3* (*INSL3*, P51460) have

multiple complex binding interactions with RXFP1 [2562] and RXFP2 [1139], which together with the N-terminal linker and LDLa module drive receptor activation by an unknown mechanism [730, 2545]. *INSL5* (*INSL5*, *Q9Y5Q6*) and relaxin-3 (*RLN3*, Q8WXF3) interact with their receptors using distinct residues in their B-chains for binding, and activation, respectively [453, 454, 1186, 3089].

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

QRFP receptor S121

Nomenclature	RXFP1	RXFP2
HGNC, UniProt	<i>RXFP1</i> , Q9HBX9	<i>RXFP2</i> , Q8WXD0
Potency order of endogenous ligands	relaxin (<i>RLN2</i> , P04090) = relaxin-1 (<i>RLN1</i> , P04808) > relaxin-3 (<i>RLN3</i> , Q8WXF3) [2719]	INSL3 (<i>INSL3</i> , P51460) > relaxin (<i>RLN2</i> , P04090) ≫ relaxin-3 (<i>RLN3</i> , Q8WXF3) [1521, 2719]
Agonists	LY3540378 [2939], R2R01 [2259], SA10SC-RLX [1221, 1796], SE301 [731], AZD5462 [962], (B7-33)H2 [629, 1171]	compound 6641 [737]
Antagonists	B-R13HR H2 relaxin (pK _i 7.4) [1172], B-R13/17K H2 relaxin (pIC ₅₀ 5.7–6.7) [1174, 2056]	–
Selective antagonists	–	A(9-26)INSL3 (pK _i 9.1) [1173], A(10-24)INSL3 (pK _i 8.7) [1173], A(C10/15S)INSL3 (pK _i 8.6) [3233], INSL3 B chain dimer analogue 8 (pK _i 8.5) [2569], A(Δ10/15C)INSL3 (pK _i 8.3) [3233], cyclic INSL3 B-chain analogue 6 (pK _i 6.7) [2567], INSL3 B-chain analogue (pK _i 5.1) [618], (des 1-8) A-chain INSL3 analogue [339]
Labelled ligands	[³³ P]relaxin (human) (Agonist) [1022, 2719], europium-labelled relaxin (Agonist) [2566], TamRLX (Agonist) [1139], Nanoluciferase-labelled relaxin (Agonist) [3110], [¹²⁵ I]relaxin (human) (Agonist)	[¹²⁵ I]INSL3 (human) (Agonist) [1990], [³³ P]relaxin (human) (Agonist) [1022, 2719], europium-labelled INSL3 (Agonist) [2568], TamRLX (Agonist) [1139]

Nomenclature	RXFP3	RXFP4
HGNC, UniProt	<i>RXFP3</i> , Q9NSD7	<i>RXFP4</i> , Q8TUD9
Potency order of endogenous ligands	relaxin-3 (<i>RLN3</i> , Q8WXF3) > relaxin-3 (B chain) (<i>RLN3</i> , Q8WXF3) > relaxin (<i>RLN2</i> , P04090) [1704]	INSL5 (<i>INSL5</i> , Q9Y5Q6) = relaxin-3 (<i>RLN3</i> , Q8WXF3) > relaxin-3 (B chain) (<i>RLN3</i> , Q8WXF3) [1702, 1703]
Agonists	compound 4 [614], compound 10d [988], H3B10-27(13/17αF) [161], B1-27 [1601], WNN0109-C011 [1680]	A13:B7-24-GG [3102], compound 4 [614], compound 10d [988], hINSL5: A8-21 (T15K) [2184], DC591053 [453], JK1 [1681]
Endogenous antagonists	INSL5 (<i>INSL5</i> , Q9Y5Q6) (pK _i 7) [3265]	–
Antagonists	R3(BΔ23-27)R/I5 chimeric peptide (pIC ₅₀ 9.2) [1509], R3 B1-22R (pK _i 7.7) [1067]	R3(BΔ23-27)R/I5 chimeric peptide (pIC ₅₀ 8–8.6) [1066, 1509], INSL5-A13nRbW (pK _i 8.4) [3101], INSL5-A13NR (pIC ₅₀ 7.4) [2300]
Selective antagonists	R3 B1-22R (pK _i 7.4) [1066], RLX-33 (pIC ₅₀ 5.6) [874]	minimised relaxin-3 analogue 3 (pIC ₅₀ 6.6) [2565]
Labelled ligands	[¹²⁵ I]relaxin-3 (human) (Agonist) [1704], [¹²⁵ I]relaxin-3-B/INSL5 A chimera (Agonist) [1702], europium-labelled relaxin-3-B/INSL5 A chimera (Agonist) [1066], NanoLuc R3/I5 chimera (Agonist) [2998, 2999, 3103]	[¹²⁵ I]relaxin-3 (human) (Agonist) [1703], [¹²⁵ I]relaxin-3-B/INSL5 A chimera (Agonist) [1702], europium-labelled mouse INSL5 (Agonist) [186], europium-labelled relaxin-3-B/INSL5 A chimera (Agonist) [1066], europium-labelled INSL5 (pK _d 8.3) [1066], NanoLuc R3/I5 chimera (Agonist) [1185, 2998, 3103]

Comments: Relaxin (*RLN2*, P04090) is the cognate peptide ligand for RXFP1. It has potent vasodilatory, anti-fibrotic, angiogenic, anti-apoptotic and anti-inflammatory effects which has led to the use of RXFP1 agonists for the treatment of acute heart failure (AHF) [680]. There are numerous long-acting RXFP1 agonists in clinical development for AHF, including small molecule agonist AZD5462 [962], relaxin fusion peptide SE301 [731] and a relaxin peptidomimetic R2R01 [2259]. The antifibrotic actions of relaxin are dependent on the angiotensin receptor AT₂ [487] and

are blocked by either AT₁ or AT₂ receptor antagonists [488]. INSL3 (*INSL3*, P51460) is the cognate peptide for RXFP2 and is a circulating hormone that in males is essential for testicular descent in utero [2043] and in females has important roles in ovarian follicle function [1244]. In adults, INSL3 has potential roles in testicular function [1245] and the musculo-skeletal system [607]. RXFP2 is also present in brain, associated with cortico-thalamic motor circuits [2551]. cAMP elevation is the major signalling pathway for both RXFP1 and RXFP2 [1183, 1184], but RXFP1 also activates

MAP kinases, nitric oxide signalling, and tyrosine kinase phosphorylation; and relaxin can interact with the glucocorticoid receptor [1023]. RXFP1 displays ultra-sensitive responses to sub picomolar levels of relaxin [510].

relaxin-3 (*RLN3*, Q8WXF3) is the cognate ligand for RXFP3 but also has high affinity for RXFP4, whereas INSL5 (*INSL5*, Q9Y5Q6) is the cognate ligand for RXFP4 and is a weak antagonist at RXFP3. Receptor expression profiles suggest that RXFP3 is a brain neuro-peptide receptor [1763, 1764, 2640] and RXFP4 a gut hormone

receptor [768, 845, 1473]. The brain relaxin-3/RXFP3 system modulates feeding [844, 845, 1066, 2565, 2639] *via* effects in the hypothalamus [597, 844, 1342, 1343], anxiety [1831, 2447, 2451, 3219], reward and motivated, goal-directed behaviours [1167, 2447, 2973], and spatial, social and fear memory [40, 1015, 1016, 2036]. Furthermore, RXFP3 activation in the brainstem, nucleus of the solitary tract, modulates respiration at baseline and during reflex behaviour [832]. INSL5 is secreted from colonic and rectal enteroendocrine L cells, while RXFP4 is expressed by colonic 5-hydroxytryptamine (5-HT)-producing enterochromaffin cells [768, 1473], consistent with actions of RXFP4 agonists on colon

motility [656]. The INSL5/RXFP4 system has also been reported to affect food intake [980] and glucose homeostasis [1752]. RXFP3 and RXFP4 couple to G_{i/o} and inhibit adenylyl cyclase [1704, 2911], and also cause Erk1/2 phosphorylation [2911]. RXFP4 also causes phosphorylation of p38MAPK, Akt and S6RP [69] and GLP-1 secretion *in vitro* [68]. There is evidence that at RXFP3, relaxin (RLN2, P04090) is a biased ligand compared to the cognate ligand relaxin-3 (RLN3, Q8WXF3) [2911]. Single chain or two-chain peptide agonists and antagonists have been developed for RXFP3 [161, 1065, 1601] and RXFP4 [3101, 3102]. The first small molecule agonist of these receptors, com-

pound 4 [614] has nanomolar activity on both receptors. A subsequent lead optimization study resulted in compound 10d [988] which demonstrates higher specificity for RXFP3. The same group also developed a small molecule negative allosteric modulator of RXFP3, RLX-33 [874]. A specific RXFP3 small molecule agonist, WNN0109-C011 was discovered in a high throughput screening campaign [1680], while specific small molecule agonists for RXFP4, JK0621-D008 [1681] and DC591053 [453], have also been developed.

Further reading on Relaxin family peptide receptors

- Bathgate RA *et al.* (2013) Relaxin family peptides and their receptors. *Physiol Rev* **93**: 405-80 [PMID:23303914]
- Bathgate RAD *et al.* (2018) The relaxin receptor as a therapeutic target - perspectives from evolution and drug targeting. *Pharmacol Ther* **187**: 114-132 [PMID:29458108]
- Du XJ *et al.* (2010) Cardiovascular effects of relaxin: from basic science to clinical therapy. *Nat Rev Cardiol* **7**: 48-58 [PMID:19935741]
- Esteban-Lopez M *et al.* (2020) Diverse functions of insulin-like 3 peptide. *J Endocrinol* **247**: R1-R12 [PMID:32813485]
- Gil-Miravet I *et al.* (2021) Involvement of the *Nucleus Incertus* and Relaxin-3/RXFP3 Signaling System in Explicit and Implicit Memory. *Front Neuroanat* **15**: 637922 [PMID:33867946]
- Halls ML *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCV. Recent advances in the understanding of the pharmacology and biological roles of relaxin family peptide receptors 1-4, the receptors for relaxin family peptides. *Pharmacol Rev* **67**: 389-440 [PMID:25761609]
- Ivell R *et al.* (2011) Relaxin family peptides in the male reproductive system—a critical appraisal. *Mol Hum Reprod* **17**: 71-84 [PMID:20952422]
- Klonisch T. (2019) Editorial to the mini-review series on relaxin, related peptides and receptors? *Mol Cell Endocrinol* **487**: 1 [PMID:30831203]
- Samuel CS *et al.* (2022) Relaxin as an anti-fibrotic treatment: Perspectives, challenges and future directions. *Biochem Pharmacol* **197**: 114884 [PMID:34968489]

Somatostatin receptors

G protein-coupled receptors → Somatostatin receptors

Overview: Somatostatin (somatotropin release inhibiting factor) is an abundant neuropeptide, which acts on five subtypes of somatostatin receptor (SST₁-SST₅; **nomenclature as agreed by the NC-IUPHAR Subcommittee on Somatostatin Receptors** [1001]). Activation of these receptors produces a wide range of physiological effects throughout the body including the inhibition of secretion of many hormones. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14 (SST, P61278)) and somatostatin-28 (SRIF-28 (SST, P61278)). **Cortistatin-14**{Mouse, Rat} has also been suggested to be an endogenous ligand for somatostatin receptors [602].

Nomenclature	SST ₁ receptor	SST ₂ receptor	SST ₃ receptor	SST ₄ receptor	SST ₅ receptor
HGNC, UniProt	<i>SSTR1</i> , P30872	<i>SSTR2</i> , P30874	<i>SSTR3</i> , P32745	<i>SSTR4</i> , P31391	<i>SSTR5</i> , P35346
Agonists	pasireotide [2514]	pasireotide [2514], veldoreotide [18]	pasireotide [2514]	NNC269100 [1718], veldoreotide [18]	pasireotide [2514], veldoreotide [18]
Selective agonists	L-797,591 [2409], Des-Ala ^{1,2,5} -[D-Trp ⁸ ,Iamp ⁹]SRIF [728]	L-054,522 [3163], BIM 23027 [393], L-779,976 [2409], octreotide [328, 2182, 2608, 2609, 2610, 3163], lanreotide [328, 2182, 2608, 2609, 2610]	L-796,778 [2409]	L-803,087 [2409], J-2156 [725]	BIM 23052 [1884, 2608, 2609, 2610], L-817,818 [2409]
Selective antagonists	SRA880 (pK _d 8–8.1) [1178]	DOTA- ₇ RR11 [409]	MK-4256 (pIC ₅₀ 9.2) [1087], ACQ090 (pK _i 7.9) [1179]	–	SSA1 (pK _i 9.3) [750]

Comments: [¹²⁵I]Tyr¹¹-SRIF-14, [¹²⁵I]LTT-SRIF-28, [¹²⁵I]CGP 23996 and [¹²⁵I]Tyr¹⁰-CST14 may be used to label somatostatin receptors nonselectively. A number of nonpeptide subtype-selective agonists have been synthesised [2409]. Octreotide and lanreotide are being used in the treatment of SST₂-expressing neuroendocrine tumors and pasireotide for SST₅-expressing neuroendocrine tumors. A novel peptide somatostatin analogue, veldoreotide (COR-005), has affinity for SST₂, SST₄ and SST₅ receptors and is a potent inhibitor of GH secretion [2256, 2594].

Further reading on Somatostatin receptors

- Colao A *et al.* (2011) Resistance to somatostatin analogs in acromegaly. *Endocr Rev* **32**: 247-71 [PMID:21123741]
- Günther T *et al.* (2018) International Union of Basic and Clinical Pharmacology. CV. Somatostatin Receptors: Structure, Function, Ligands, and New Nomenclature. *Pharmacol Rev* **70**: 763-835 [PMID:30232095]
- Hoyer D *et al.* (2000) *In The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edn.* Edited by Watson SP, Girdlestone D: IUPHAR Media: 354-364
- Schulz S *et al.* (2014) Fine-tuning somatostatin receptor signalling by agonist-selective phosphorylation and dephosphorylation: IUPHAR Review 5. *Br J Pharmacol* **171**: 1591-9 [PMID:24328848]
- Weckbecker G *et al.* (2003) Opportunities in somatostatin research: biological, chemical and therapeutic aspects. *Nat Rev Drug Discov* **2**: 999-1017 [PMID:14654798]

Succinate receptor

G protein-coupled receptors → Succinate receptor

Overview: Nomenclature as recommended by NC-IUPHAR [586]. The succinate receptor (GPR91, *SUCNR1*) is activated by the tricarboxylic acid (or Krebs) cycle intermediate succinate and other dicarboxylic acids with less clear physiological relevance such as maleate [1088]. Since its pairing with its endogenous ligand in 2004, intense research has focused on the receptor-ligand pair role in various (patho)physiological processes such as regulation of renin production [1088, 2846], ischemia injury [1088], fibrosis

[1768], retinal angiogenesis [2478], inflammation [1699, 1768], immune response [2433], obesity [1369, 1858, 2946], diabetes [1652, 2846, 2912], platelet aggregation [2674, 2790] or cancer [322, 3106]. The succinate receptor is coupled to G_{i/o} [909, 1088] and G_{q/11} protein families [1088, 2404, 2866], whilst coupling to these G proteins is dependent on the cellular, metabolic and spatial context [1668, 2866]. Although the receptor is, upon ligand addition, rapidly desensitized [1146, 2404], and in some cells in-

ternalized [1088], it seems to recruit arrestins weakly [901]. The cellular activation of the succinate receptor triggers various signalling pathways such as decrease of cAMP levels, [Ca²⁺]ⁱ mobilization and activation of kinases (ERK, c-Jun, Akt, Src, p38, PI3Kβ, *etc.*) [910]. The receptor is broadly expressed but is notably abundant in immune cells (M2 macrophages [1369, 2866], monocytes [2433], immature dendritic cells [2433], adipocytes [2946], platelets [2674, 2790], *etc.*) and in the kidney [1088].

Nomenclature	succinate receptor
HGNC, UniProt	<i>SUCNR1</i> , Q9BXA5
Endogenous agonists	succinic acid [1088, 2669]
Agonists	compound 31 (Partial agonist) [2373], compound 130 (Partial agonist) [2867], <i>cis</i> -epoxysuccinic acid [901], maleic acid [901, 909, 1088]
Antagonists	NF-56-EJ40 (pK _i 7.8) [1011], compound 4c (pIC ₅₀ 7.5) [218]

Comments: In humans, there is the possibility of two open-reading frames (ORFs) for *SUCNR1*, one giving a protein of 330 amino acids (AA) and the other one 334-AA. Wittenberger *et al.* [3086] noted that the 330-AA protein was more likely to be expressed given the Kozak sequence surrounding the second ATG. Some databases report *SUCNR1* as being 334-AA long.

Further reading on Succinate receptor

- de Castro Fonseca M *et al.* (2016) GPR91: expanding the frontiers of Krebs cycle intermediates. *Cell Commun Signal* **14**: 3 [PMID:26759054]
- Gilissen J *et al.* (2016) Insight into *SUCNR1* (GPR91) structure and function. *Pharmacol Ther* **159**: 56-65 [PMID:26808164]
- Grimolizzi F *et al.* (2018) Multiple faces of succinate beyond metabolism in blood. *Haematologica* **103**: 1586-1592 [PMID:29954939]
- Krzak G *et al.* (2021) Succinate Receptor 1: An Emerging Regulator of Myeloid Cell Function in Inflammation. *Trends Immunol* **42**: 45-58 [PMID:33279412]
- Lückmann M *et al.* (2020) Structural basis for GPCR signaling by small polar versus large lipid metabolites-discovery of non-metabolite ligands. *Curr Opin Cell Biol* **63**: 38-48 [PMID:31951921]

Tachykinin receptors

G protein-coupled receptors → Tachykinin receptors

Overview: Tachykinin receptors (**provisional nomenclature as recommended by NC-IUPHAR** [789]) are activated by the endogenous peptides **substance P** (*TAC1*, P20366) (SP), **neurokinin A** (*TAC1*, P20366) (NKA; previously known as substance K, neurokinin α , neuromedin L), **neurokinin B** (*TAC3*, Q9UHF0) (NKB; previously known as neurokinin β , neuromedin K), **neuro-**

peptide K (*TAC1*, P20366) and **neuropeptide γ** (*TAC1*, P20366) (N-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in *in vitro* pharmacology exist for all three re-

ceptors, in the context of nonpeptide ligands. Antagonists such as **aprepitant** and **fosaprepitant** were approved by FDA and EMA, in combination with other antiemetic agents, for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.

Nomenclature	NK ₁ receptor	NK ₂ receptor	NK ₃ receptor
HGNC, UniProt	<i>TACR1</i> , P25103	<i>TACR2</i> , P21452	<i>TACR3</i> , P29371
Potency order of endogenous ligands	substance P (<i>TAC1</i> , P20366) > neurokinin A (<i>TAC1</i> , P20366) > neurokinin B (<i>TAC3</i> , Q9UHF0)	neurokinin A (<i>TAC1</i> , P20366) > neurokinin B (<i>TAC3</i> , Q9UHF0) \gg substance P (<i>TAC1</i> , P20366)	neurokinin B (<i>TAC3</i> , Q9UHF0) > neurokinin A (<i>TAC1</i> , P20366) > substance P (<i>TAC1</i> , P20366)
Agonists	substance P-OMe [2828]	–	–
Selective agonists	[Sar ⁹ ,Met(O ₂) ¹¹]SP [2828], septide [190, 1061], [Pro ⁹]SP [2852] – Rat	[Lys ⁵ ,Me-Leu ⁹ ,Nle ¹⁰]NKA-(4-10) [1846] – Rat, GR64349 [611] – Rat, [β Ala ⁸]neurokinin A-(4-10) [720]	[Phe(Me) ⁷]neurokinin B [2480, 2481], senktide [2480, 2481, 2828]
Antagonists	L760735 (pIC ₅₀ 9.7) [1057]	–	–
Selective antagonists	aprepitant (pK _i 10.1) [1017, 1018], CP 99994 (pK _i 9.3–9.7) [71, 2481], RP67580 (pIC ₅₀ 7.7) [788]	GR94800 (pK _i 9.8) [290], saredutant (pK _i 9.4–9.7) [71, 720, 2481], GR 159897 (pK _d 7.8–9.5) [200, 720, 2648], MEN10627 (pK _i 9.2) [904], nepadutant (pK _i 8.5–8.7) [395, 505]	osanetant (pK _i 8.4–9.7) [71, 170, 504, 719, 1333, 2147, 2480, 2481, 2828], talnetant (pK _i 7.4–9) [194, 905, 2480, 2481], PD157672 (pIC ₅₀ 7.8–7.9) [242, 2828]
Labelled ligands	[¹²⁵ I]L703,606 (Antagonist) (pK _d 9.5) [804], [¹²⁵ I]BH-[Sar ⁹ ,Met(O ₂) ¹¹]SP (Agonist) [2860] – Rat, [³ H]SP (human, mouse, rat) (Agonist) [123], [¹²⁵ I]SP (human, mouse, rat) (Agonist), [¹⁸ F]SPARQ (Antagonist) [473]	[³ H]saredutant (Antagonist) (pK _d 9.7) [977] – Rat, [¹²⁵ I]NKA (human, mouse, rat) (Agonist) [3022], [³ H]GR100679 (Antagonist) (pK _d 9.2) [1013]	[³ H]osanetant (Antagonist) (pK _d 9.9), [³ H]senktide (Agonist) [990] – Guinea pig, [¹²⁵ I][MePhe ⁷]NKB (Agonist)

Comments: The NK₁ receptor has also been described to couple to G proteins other than G_{q/11} [2427]. The crystal structure of the human NK₁ receptor in complex with antagonists has been determined [2526, 3186]. The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to **substance P** (*TAC1*, P20366) on the NK₁ receptor. There are additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK₃ receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells [664, 1495]. NK₁ receptor antagonists affect cellular physiology including inflammation, apoptosis and cell trafficking and have a role in therapeutics [1999, 2677].

Further reading on Tachykinin receptors

Douglas SD *et al.* (2011) Neurokinin-1 receptor: functional significance in the immune system in reference to selected infections and inflammation. *Ann NY Acad Sci* **1217**: 83-95 [PMID:21091716]
 Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]
 Jones S *et al.* (2008) The neurokinin 1 receptor: a potential new target for anti-platelet therapy? *Curr Opin Pharmacol* **8**: 114-9 [PMID:18296119]

Steinhoff MS *et al.* (2014) Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol Rev* **94**: 265-301 [PMID:24382888]
 Yin J *et al.* (2018) Crystal structure of the human NK₁ tachykinin receptor. *Proc Natl Acad Sci USA* **115**: 13264-13269 [PMID:30538204]

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.70230/full>

Tachykinin receptors S125

Taste 1 receptors

G protein-coupled receptors → Taste 1 receptors

Overview: Whilst the taste of acid and salty foods appear to be sensed by regulation of ion channel activity, bitter, sweet and umami tastes are sensed by specialised GPCR. Two classes of taste GPCR have been identified, T1R and T2R, which are similar in sequence and structure to Class C and Class A GPCR, respectively. Activation of taste receptors appears to involve gustducin- ($G\alpha 3$) and $G\alpha 14$ -mediated signalling, although the precise mechanisms

remain obscure. Gene disruption studies suggest the involvement of PLC $\beta 2$ [3243], TRPM5 [3243] and IP3 [1136] receptors in post-receptor signalling of taste receptors. Although predominantly associated with the oral cavity, taste receptors are also located elsewhere, including further down the gastrointestinal system, in the lungs and in the brain.

Sweet/Umami: T1R3 acts as an obligate partner in T1R1/T1R3

and T1R2/T1R3 heterodimers, which sense umami or sweet, respectively. T1R1/T1R3 heterodimers respond to L-glutamic acid and may be positively allosterically modulated by 5'-nucleoside monophosphates, such as 5'-GMP [1655]. T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin [2050] and aspartame [1316].

Nomenclature	<i>TAS1R1</i>	<i>TAS1R2</i>	<i>TAS1R3</i>
HGNC, UniProt	<i>TAS1R1</i> , Q7RTX1	<i>TAS1R2</i> , Q8TE23	<i>TAS1R3</i> , Q7RTX0
Comments	–	Cryo-EM structures of TAS1R2 bound to sucralose and aspartame have been determined [1316].	–

Comments: Positive allosteric modulators of T1R2/T1R3 have been reported [3142]. Such compounds enhance the sweet taste of sucrose mediated by these receptors, but are tasteless on their own.

Further reading on Taste 1 receptors

Behrens M *et al.* (2020) Structure-Function Analyses of Human Bitter Taste Receptors-Where Do We Stand? *Molecules* **25**: 4423 [PMID:32993119]

Egan JM. (2024) Physiological Integration of Taste and Metabolism. *N Engl J Med* **390**: 1699-1710 [PMID:38718360]

Juen Z *et al.* (2025) The structure of human sweetness. *Cell* **188**: 4141-4153.e18 [PMID:40339580]

Palmer RK. (2019) A Pharmacological Perspective on the Study of Taste. *Pharmacol Rev* **71**: 20-48 [PMID:30559245]

Shi Z *et al.* (2025) Structural and functional characterization of human sweet taste receptor. *Nature* [PMID:40555359]

Taste 2 receptors

G protein-coupled receptors → Taste 2 receptors

Overview: Taste 2 receptors or Bitter taste receptors (TAS2Rs) are G protein-coupled receptors expressed in oral sensory cells and a variety of non-gustatory tissues. The ~25 human TAS2Rs share low amino acid sequence identities with other GPCR families and are classified as broadly tuned “generalist” receptors with numerous, chemically diverse bitter agonists, as narrowly

tuned “specialist” receptors with very few activators, as intermediately tuned receptors with an average number of agonists, or receptors specialized to interact with chemically defined activators [1885]. The number of functional bitter taste receptor genes varies among species and orthologues might not be functionally conserved. Due to their expression in various tissues, the signal

transduction of TAS2Rs is complex. Some TAS2Rs interact with drugs such as analgesic, anti-inflammatory, and antibacterial compounds. The specialist database BitterDB contains additional information on bitter compounds and receptors [570]. Recently, several experimental cryo-electron structures of TAS2Rs have been published [2213].

Nomenclature	<i>TAS2R1</i>	<i>TAS2R3</i>	<i>TAS2R4</i>	<i>TAS2R5</i>	<i>TAS2R7</i>	<i>TAS2R8</i>	<i>TAS2R9</i>
HGNC, UniProt	<i>TAS2R1</i> , Q9NYW7	<i>TAS2R3</i> , Q9NYW6	<i>TAS2R4</i> , Q9NYW5	<i>TAS2R5</i> , Q9NYW4	<i>TAS2R7</i> , Q9NYW3	<i>TAS2R8</i> , Q9NYW2	<i>TAS2R9</i> , Q9NYW1
Agonists	cohumulone [1229], L-Phe-Phe-Phe [2894], L-Trp-Trp-Trp [1458], dextromethorphan [1885], nirmatrelvir [385], ritonavir [447], tauroolithocholic acid-3-sulphate [3272]	chloroquine [1885]	L-Trp-Trp-Trp [1458], azithromycin [1261], stevioside [1100], colchicine [1885]	epigallocatechin-3-gallate [2652], Procyanidin C2 [2651], 1,10-Phenanthroline [1885]	grandinin [2652], malvidin-3-glucoside [2651], cromoglicic acid [1885]	oleuropein [562], andrographolide [797], chloramphenicol [1885], parthenolide [1885], ritonavir [447]	ofloxacin [673], pirenzepine [673], procainamide [673]
Antagonists	–	–	abscisic acid (pIC ₅₀ 4.5) [2304]	–	–	S6821 (pIC ₅₀ 7.7) [797], S7958 (pIC ₅₀ 7.2) [797]	–
Comments	–	–	–	–	Aluminum sulfate and magnesium sulfate act as <i>TAS2R7</i> agonists; EC ₅₀ values are 29 μM [3014] and 14900 μM [183] respectively.	–	–

Nomenclature	<i>TAS2R10</i>	<i>TAS2R13</i>	<i>TAS2R14</i>
HGNC, UniProt	<i>TAS2R10</i> , Q9NYW0	<i>TAS2R13</i> , Q9NYV9	<i>TAS2R14</i> , Q9NYV8
Agonists	bergapten [1800], cucurbitacin B [268], strychnine [1885], denatonium [268], haloperidol [1885]	denatonium [1885], diphenidol [1885]	flufenamic acid [639, 1187], aristolochic acid [1187, 2096], lupulone [1229], nobiletin [181], luteolin [2411], santonin [2096], datsicetin [2411], parthenolide [2096], (-)-α-thujone [180], picrotoxinin [180], N-octanoyl-L-homoserine lactone [1262], phloretin [2411], resveratrol [2411], tributyrin [1639], eriodictyol chalcone [2411], (±)-Equol [2412], silibinin [2411], (+/-)-Eriodictyol [2411], genistein [2096], homoeriodictyol [2411], coumestrol [2412], vanillin [1972], L-Trp-Trp-Trp [1458], compound 28.1 [3028], infractopicrin [2518], quinine [1885], ritonavir [447], tauroolithocholic acid-3-sulphate [3272]
Antagonists	–	–	LF22 [771]
Comments	–	–	<i>TAS2R14</i> is involved in detecting a broad range of bitter substances, of both natural and pharmaceutical origin. Expression in extra-gustatory tissues suggests additional physiological functions. Cryo-electron microscopy has been used in 4 independent approaches to solve <i>TAS2R14</i> structures in complex with different ligands and coupled to different G protein subtypes [1187, 1412, 1413, 2213, 2797].

Nomenclature	<i>TAS2R16</i>	<i>TAS2R19</i>	<i>TAS2R20</i>	<i>TAS2R30</i>	<i>TAS2R31</i>	<i>TAS2R38</i>
HGNC, UniProt	<i>TAS2R16</i> , Q9NYV7	<i>TAS2R19</i> , P59542	<i>TAS2R20</i> , P59543	<i>TAS2R30</i> , P59541	<i>TAS2R31</i> , P59538	<i>TAS2R38</i> , P59533
Agonists	4-Nitrophenyl- β -D-mannopyranoside [2815], Phenyl- β -D-glucopyranoside [338], salicin [338], beta-gentiobiose [2462], D-(-)-Amygdalin [338], sinigrin [1885]	–	ritanserin [1800], methoxsalen [1800], cromoglicic acid [1885], tobramycin [1261], vanillin [1972], diphenidol [1885]	denatonium [1885], absinthin [1885], amarogentin [2426]	aristolochic acid [1511], saccharin [1511], acesulfame [1511], famotidine [1885]	phenylthiocarbamide [337], propylthiouracil [337], goitrin [3093], methimazole [182], sinigrin [1885]
Antagonists	probenecid (pIC ₅₀ 3.5) [968]	–	–	–	GIV3727 (pIC ₅₀ 5.5) [2631], sakuranetin (pIC ₅₀ 5.3) [786], cyclamate (pIC ₅₀ 1.8) [178]	probenecid (pIC ₅₀ 3.7) [968]
Comments	Cryo-electron microscopy has been used to solve the <i>TAS2R16</i> structure in complex with the agonist salicin [3011].	–	–	–	–	Of the two main variants of <i>TAS2R38</i> , only the taster-variant (<i>TAS2R38-PAV</i>) is exquisitely sensitive to the listed agonists as well as to structurally related bitter substances from cruciferous vegetables. The non-taster variant (<i>TAS2R38-AVI</i>) is non-functional [337, 1411].

Nomenclature	<i>TAS2R39</i>	<i>TAS2R40</i>	<i>TAS2R41</i>	<i>TAS2R42</i>
HGNC, UniProt	<i>TAS2R39</i> , P59534	<i>TAS2R40</i> , P59535	<i>TAS2R41</i> , P59536	<i>TAS2R42</i> , Q7RTR8
Agonists	theaflavin-3'-O-gallate [3151], theaflavin [3151], luteolin [2411], epicatechin gallate [3151], naringenin [2411], scutellarein [2411], datiscetin [2411], phloretin [2411], genistein [2412], (\pm)-Equol [2412], epigallocatechin [2032], (-)-Epicatechin [2032], vanillin [1972], L-Trp-Trp-Trp [1458], tenofovir alafenamide [2540]	cohumulone [1229], dapsone (Threshold=30 μ M) [1885], quinine [1885]	chloramphenicol [2808]	–
Antagonists	6-Methylflavone (pIC ₅₀ 4.7) [2410, 2540]	GIV3727 (pIC ₅₀ 5.2) [2631]	–	–

Nomenclature	TAS2R43	TAS2R45	TAS2R46	TAS2R50	TAS2R60
HGNC, UniProt	TAS2R43 , P59537	TAS2R45 , P59539	TAS2R46 , P59540	TAS2R50 , P59544	TAS2R60 , P59551
Agonists	aristolochic acid [1511], lactucopicrin [1552], aloin [2290], Cyclolinopeptide 1-Mso,3-Met-CL6 [1553], bengalensol [1554], grosheimin [2426], amarogentin [1885], saccharin [1511], acesulfame [1511]	–	lactucopicrin [1552], strychnine [312], oligopirin D [2518], grosheimin [2426], absinthin [312], bengalensol [1554], andrographolide [2426], amarogentin [2426], picrotoxinin [312], denatonium [1885], colchicine [1885], L-Trp-Trp-Trp [1458], tauroolithocholic acid-3-sulphate [3272]	andrographolide [179], amarogentin [179]	–
Antagonists	GIV3727 (pIC ₅₀ 4.9) [2631], 3-methylhexanal (pIC ₅₀ 4.1) [2721], citronellal (pIC ₅₀ 4.1) [2721], cyclamate (pIC ₅₀ 2.3) [178]	–	3β-hydroxydihydrocostunolide (pIC ₅₀ 5.3) [313]	–	–
Comments	–	–	Cryo-electron microscopy has been used to solve the TAS2R46 structure in complex with the agonist strychnine [3133, 3134].	–	–

Further reading on Taste 2 receptors

- Behrens M. (2025) International Union of Basic and Clinical Pharmacology. CXVII: Taste 2 receptors—Structures, functions, activators, and blockers. *Pharmacol Rev* **77**: 100001 [PMID:39952694]
- Egan JM. (2024) Physiological Integration of Taste and Metabolism. *N Engl J Med* **390**: 1699-1710 [PMID:38718360]
- Palmer RK. (2019) A Pharmacological Perspective on the Study of Taste. *Pharmacol Rev* **71**: 20-48 [PMID:30559245]
- Wooding SP et al. (2021) Bitter taste receptors: Genes, evolution and health. *Evol Med Public Health* **9**: 431-447 [PMID:35154779]

Thyrotropin-releasing hormone receptors

G protein-coupled receptors → Thyrotropin-releasing hormone receptors

Overview: Thyrotropin-releasing hormone (TRH) receptors (**provisional nomenclature as recommended by NC-IUPHAR** [789]) are activated by the endogenous tripeptide TRH (*TRH*, [P20396](#)) (pGlu-His-ProNH₂). TRH (*TRH*, [P20396](#)) and TRH analogues fail to distinguish TRH₁ and TRH₂ receptors [2731]. [³H]TRH (human, mouse, rat) is able to label both TRH₁ and TRH₂ receptors with K_d values of 13 and 9 nM respectively. Synthesis and biology of ring-modified L-Histidine containing TRH analogues has been reported [1872].

Nomenclature	TRH₁ receptor	TRH₂ receptor
HGNC, UniProt	TRHR , P34981	–
Antagonists	diazepam (pK _i 5.2) [679] – Rat	–
Selective antagonists	midazolam (pK _i 5.5) [679] – Rat, chlordiazepoxide (pK _i 4.8) [679] – Rat, chlordiazepoxide (pK _i 4.7) [2710] – Mouse	–
Comments	–	A class A G protein-coupled receptor: not present in man

Further reading on Thyrotropin-releasing hormone receptorsBílek R *et al.* (2011) TRH-like peptides. *Physiol Res* **60**: 207-15 [PMID:21114375]Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]Nillni EA. (2010) Regulation of the hypothalamic thyrotropin releasing hormone (TRH) neuron by neuronal and peripheral inputs. *Front Neuroendocrinol* **31**: 134-56 [PMID:20074584]

Trace amine receptor

G protein-coupled receptors → Trace amine receptor

Overview: Trace amine-associated receptors were discovered from a search for novel 5-HT receptors [269], where 15 mammalian orthologues were identified and divided into two families. The TA₁ receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Trace amine receptor**[1784]) has affinity for the endogenous trace amines **tyramine**, **β-phenylethylamine** and **octopamine** in addition to the classical amine **dopamine** [269]. Emerging evidence suggests that TA₁ is a modulator of monoaminergic activity in the brain [3124] with TA₁ and dopamine D₂ receptors shown to form constitutive het-

erodimers when co-expressed [736]. In addition to trace amines, receptors can be activated by amphetamine-like psychostimulants, and endogenous thyronamines.

Nomenclature	TA ₁ receptor
HGNC, UniProt	TAAR1, Q96RJ0
Potency order of endogenous ligands	tyramine > β-phenylethylamine > octopamine = dopamine [269]
Agonists	RO5166017 [2372]
Antagonists	EPPTB (Inverse agonist) (pIC ₅₀ 5.1) [288]
Labelled ligands	[³ H]tyramine (Agonist) [269]

Comments: In addition to TA₁, in man there are up to 5 functional TAAR genes (TAAR2,5,6,8,9). See [269] for detailed discussion. The product of the gene TAAR2 (also known as GPR58) appears to respond to **β-phenylethylamine** > **tyramine** and to couple through G_s [269]. **TAAR3**, in some individuals, and **TAAR4** are pseudogenes in man,although functional in rodents. The signalling characteristics and pharmacology of TAAR₅ (PNR, Putative Neurotransmitter Receptor: **TAAR5**, O14804), **TAAR₆** (Trace amine receptor 4, TaR-4: **TAAR6**, 96RI8), **TAAR₈** (Trace amine receptor 5, GPR102: **TAAR8**, Q969N4) and **TAAR₉** (trace amine associated receptor 9: **TAAR9**, 96RI9) are lacking. The thyronamines, endogenous derivatives ofthyroid hormone, have affinity for rodent cloned trace amine receptors, including TA₁ [2495]. An antagonist **EPPTB** has recently been described with a pK_i of 9.1 at the mouse TA₁ but >5.3 for human TA₁ [2686].**Further reading on Trace amine receptor**Liu H *et al.* (2023) Recognition of methamphetamine and other amines by trace amine receptor TAAR1. *Nature* **624**: 663-671 [PMID:37935377]Maguire JJ *et al.* (2009) International Union of Pharmacology. LXXII. Recommendations for trace amine receptor nomenclature. *Pharmacol Rev* **61**: 1-8 [PMID:19325074]Pei Y *et al.* (2016) Trace Amines and the Trace Amine-Associated Receptor 1: Pharmacology, Neurochemistry, and Clinical Implications. *Front Neurosci* **10**: 148 [PMID:27092049]Xu Z *et al.* (2023) Ligand recognition and G-protein coupling of trace amine receptor TAAR1. *Nature* **624**: 672-681 [PMID:37935376]

TAAR2, TAAR3, TAAR4p, TAAR5, TAAR6, TAAR8, TAAR9

G protein-coupled receptors → TAAR2, TAAR3, TAAR4p, TAAR5, TAAR6, TAAR8, TAAR9

Overview: This set of orphan GPCRs are under review by the NC-IUPHAR subcommittee for the Trace amine receptors.

Nomenclature	<i>TAAR2</i>	<i>TAAR3</i>	<i>TAAR4P</i>	<i>TAAR5</i>	<i>TAAR6</i>	<i>TAAR8</i>	<i>TAAR9</i>
HGNC, UniProt	<i>TAAR2</i> , Q9PIP5	<i>TAAR3P</i> , Q9PIP4	<i>TAAR4P</i> , –	<i>TAAR5</i> , O14804	<i>TAAR6</i> , Q96R18	<i>TAAR8</i> , Q969N4	<i>TAAR9</i> , Q96R19
Potency order of endogenous ligands	β-phenylethylamine > tryptamine [269]	–	–	–	–	–	–
Comments	Probable pseudogene in 10-15% of Asians due to a polymorphism (rs8192646) producing a premature stop codon at amino acid 168 [586].	<i>TAAR3</i> is thought to be a pseudogene in man though functional in rodents [586].	Pseudogene in man but functional in rodents [586].	Trimethylamine is reported as an agonist [2977] and 3-iodothyronamine an inverse agonist [652].	–	–	<i>TAAR9</i> appears to be functional in most individuals but has a polymorphic premature stop codon at amino acid 61 (rs2842899) with an allele frequency of 10-30% in different populations [2924].

Urotensin receptor

G protein-coupled receptors → Urotensin receptor

Overview: The urotensin-II (U-II) receptor (UT, **nomenclature as agreed by the NC-IUPHAR Subcommittee on the Urotensin receptor** [674, 789, 2935]) is activated by the endogenous dodecapeptide urotensin-II (*UTS2*, O95399), originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish [204, 2934]. Several structural forms of U-II exist in fish and amphibians [2935]. The goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene *gpr14* [58, 547,

1715, 1969, 2094]. Human urotensin-II (*UTS2*, O95399), an 11-amino-acid peptide [547], retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding [309, 1425, 1630]. This sequence is also conserved in the deduced amino-acid sequence of rat urotensin-II {Rat} (14 amino-acids) and mouse urotensin-II{Mouse} (14 amino-acids), although the N-terminal is more divergent from the human sequence [546]. A second endogenous ligand for the UT has been discovered in rat [2724]. This is the urotensin II-related peptide

(*UTS2B*, Q76510), an octapeptide that is derived from a different gene, but shares the C-terminal sequence (CFWKYCV) common to U-II from other species. Identical sequences to rat urotensin II-related peptide (*UTS2B*, Q76510) are predicted for the mature mouse and human peptides [685]. UT exhibits relatively high sequence identity with somatostatin, opioid and galanin receptors [2935]. The urotensinergic system displays an unprecedented repertoire of four or five ancient UT in some vertebrate lineages and five U-II family peptides in teleost fish [2857].

Nomenclature	UT receptor
HGNC, UniProt	<i>UTS2R</i> , Q9UKP6
Endogenous agonists	urotensin II-related peptide (<i>UTS2B</i> , Q76510) [685, 2724], urotensin-II (<i>UTS2</i> , O95399) [58, 1715, 1969, 2094]
Selective agonists	[Pen ⁵]U-(4-11) (human) [975], U-II-(4-11) (human) [975], [3-iodo-Tyr ⁶]U-II-(4-11) (human) [1538], Urolinin [139], FL104 [1613, 1615], AC-7954 [559, 1614]
Selective antagonists	DS37001789 (pIC ₅₀ 9.1) [2080], RCI-0879 (pIC ₅₀ 9) [2784], urantide (pK _i 8.3) [2176], SR101099 (pIC ₅₀ 8) [2151], [Orn ⁵]URP (pK _i 7.2) [642] – Rat, palosuran (pIC ₅₀ 7.1) [518], SB-611812 (pK _i 6.6) [2330], [Cha ⁶]U-II-(4-11) (pK _i 6.4) [431] – Rat
Labelled ligands	[¹²⁵ I]U-II (human) (Agonist) [58, 431, 1783], [¹²⁵ I]N-biotin-[Ahx ⁰ , Bpa ³]U-II (human) [657]

Comments: In the human vasculature, human **urotensin-II** (*UTS2*, [O95399](#)) elicits both vasoconstrictor (pD₂ 9.3-10.1, [\[1783\]](#)) and vasodilator (pIC₅₀ 10.3-10.4, [\[2699\]](#)) responses.

Further reading on Urotensin receptor

- Foord SM *et al.* (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [[PMID:15914470](#)]
- Hunt BD *et al.* (2010) A rat brain atlas of urotensin-II receptor expression and a review of central urotensin-II effects. *Naunyn Schmiedebergs Arch Pharmacol* **382**: 1-31 [[PMID:20422157](#)]
- Maryanoff BE *et al.* (2010) Urotensin-II receptor modulators as potential drugs. *J Med Chem* **53**: 2695-708 [[PMID:20043680](#)]
- Ross B *et al.* (2010) Role of urotensin II in health and disease. *Am J Physiol Regul Integr Comp Physiol* **298**: R1156-72 [[PMID:20421634](#)]
- Vaudry H *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCII. Urotensin II, urotensin II-related peptide, and their receptor: from structure to function. *Pharmacol Rev* **67**: 214-58 [[PMID:25535277](#)]

Vasopressin and oxytocin receptors

G protein-coupled receptors → Vasopressin and oxytocin receptors

Overview: Vasopressin (AVP) and oxytocin (OT) receptors (**nomenclature as recommended by NC-IUPHAR** [\[789\]](#)) are activated by the endogenous cyclic nonapeptides **vasopressin** (*AVP*, [P01185](#)) and **oxytocin** (*OXT*, [P01178](#)). These peptides are derived from precursors which also produce neurophysins (neurophysin I for oxytocin; neurophysin II for vasopressin). Vasopressin and oxytocin differ at only 2 amino acids (positions 3 and 8). There are metabolites of these neuropeptides that may be biologically active [\[609\]](#).

Nomenclature	V _{1A} receptor	V _{1B} receptor	V ₂ receptor	OT receptor
HGNC, UniProt	<i>AVPR1A</i> , P37288	<i>AVPR1B</i> , P47901	<i>AVPR2</i> , P30518	<i>OXR</i> , P30559
Potency order of endogenous ligands	vasopressin (<i>AVP</i> , P01185) > oxytocin (<i>OXT</i> , P01178) [31 , 461 , 541 , 2021 , 2457 , 2758 , 2812]	vasopressin (<i>AVP</i> , P01185) > oxytocin (<i>OXT</i> , P01178) [31 , 461 , 627 , 976 , 2021 , 2457 , 2758 , 2813]	vasopressin (<i>AVP</i> , P01185) > oxytocin (<i>OXT</i> , P01178) [31 , 461 , 475 , 2202 , 2559 , 2758 , 3148]	oxytocin (<i>OXT</i> , P01178) > vasopressin (<i>AVP</i> , P01185) [31 , 475 , 476 , 508 , 976 , 1274 , 1420]
Selective agonists	selepressin [1560]	d[Leu ⁴ Lys ⁸]VP [2201] – Rat, d[Cha ⁴]AVP [627 , 976]	VNA932 [745], OPC-51803 [2021], d[Val ⁴ ,DArg ⁸]VP	[Thr ⁴ ,Gly ⁷]OT [349 , 476 , 715 , 1274]
Antagonists	d(CH ₂) ₅ [Tyr(Me) ² ,Arg ⁸]VP (pK _i 9), conivaptan (pK _i 8.2–8.4) [2758 , 2759]	nelivaptan (pK _i 8.4–9.3) [976 , 2561]	–	L-371,257 (pK _i 8.8) [976]
Selective antagonists	SRX246 (pK _i 9.5) [744 , 997], [D-Arg ⁸]inotocin (pK _i 8.9) [636]	–	conivaptan (pK _i 9.4) [558], tolvaptan (pK _i 9.4) [3148], d(CH ₂) ₅ [D-Ile ² ,Ile ⁴]AVP (pK _i 6.9–8.4) [542 , 2559], mozavaptan (Inverse agonist) (pK _i 7.4–8.1) [542 , 2559 , 2758 , 2813 , 3148]	retosiban (pK _i 9–9.2) [1667 , 1854], SSR126768A (pK _i 8.8–9.1) [2560], desGlyNH ₂ -d(CH ₂) ₅ [Tyr(Me) ² ,Thr ⁴ ,Orn ⁸]OT (pK _i 8.5), L-372662 (pK _i 8.4) [187]
Labelled ligands	[¹²⁵ I]OH-LVA (Antagonist) (pK _d 10.3–10.4) [475 , 541], [³ H]AVP (human, mouse, rat) (Agonist) [300 , 475 , 2758 , 2759 , 2812]	[³ H]AVP (human, mouse, rat) (Agonist) [627 , 2457 , 2758 , 2759 , 2813]	[³ H]AVP (human, mouse, rat) (Agonist) [542 , 2021 , 2758 , 2759 , 3148]	[¹²⁵ I]d(CH ₂) ₅ [Tyr(Me) ² ,Thr ⁴ ,Orn ⁸ ,Tyr-NH ₂ ⁹]OVT (Antagonist) (pK _d 10), [³ H]OT (human, mouse, rat) (Agonist) [475 , 824 , 1274 , 1420]

Comments: Vasopressin and OT receptors have a characteristic and sometimes overlapping distribution in a number of tissues including brain. There are phylogenetic, ontogenetic and sex-specific differences in the levels and distribution of these receptors, particularly in the brain. The receptors display significant species-specific differences, with many ligands demonstrating varying affinity and/or efficacy at human receptors in comparison to those of other species [349, 474]. For example **desmopressin** (dDAVP) is more V_2 se-

lective in the rat than in the human [2457], agonist **d[Cha⁴]AVP** is selective only for the human and bovine V_{1B} receptors [627], while **d[Leu⁴Lys⁸]VP** has high affinity for the rat V_{1B} receptor [2202], and agonist **[Thr⁴,Gly⁷]OT** is selective at mouse, rat and human OT receptors [349]. **Terlipressin** is a V_{1A} , V_{1B} and V_2 receptor agonist with relevant clinical applications [523, 1711]. The gene encoding the V_2 receptor is polymorphic in man, underlying Arginine Vasopressin Deficiency (AVP-D; formerly nephrogenic diabetes insipi-

du) [221, 490, 1640]. Knockouts of vasopressin and OT receptors have system-specific defects (*e.g.*, impaired ability to concentrate urine in V_2 receptor knockouts) which include behavioural deficits (principally in V_{1A} , V_{1B} and OT receptor knockouts) [2390]. **[³H]d(CH₂)₅[Tyr(Me)²]AVP** (V_{1A} antagonist), **[³H]desGly-NH₂[D-Ile²,Ile⁴]VP** and **[³H]dDAVP** (V_2 agonists) radiolabelled compounds formerly used to pharmacologically characterize vasopressin and OT receptors are no longer available.

Further reading on Vasopressin and oxytocin receptors

Carter CS *et al.* (2020) Is Oxytocin "Nature's Medicine"? *Pharmacol Rev* **72**: 829-861 [PMID:32912963]
Grinevich V *et al.* (2021) Brain oxytocin: how puzzle stones from animal studies translate into psychiatry. *Mol Psychiatry* **26**: 265-279 [PMID:32514104]
Gulliver D *et al.* (2019) Targeting the Oxytocin System: New Pharmacotherapeutic Approaches. *Trends Pharmacol Sci* **40**: 22-37 [PMID:30509888]
Knepper MA. (2012) Systems biology in physiology: the vasopressin signaling network in kidney. *Am J Physiol, Cell Physiol* **303**: C1115-24 [PMID:22932685]

Koshimizu TA *et al.* (2012) Vasopressin V1a and V1b receptors: from molecules to physiological systems. *Physiol Rev* **92**: 1813-64 [PMID:23073632]
Manning M *et al.* (2012) Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics. *J Neuroendocrinol* **24**: 609-28 [PMID:22375852]
Perisic M *et al.* (2024) Oxytocin and vasopressin signaling in health and disease. *Trends Biochem Sci* **49**: 361-377 [PMID:38418338]
Rigney N *et al.* (2022) Oxytocin, Vasopressin, and Social Behavior: From Neural Circuits to Clinical Opportunities. *Endocrinology* **163**: [PMID:35863332]

VIP and PACAP receptors

G protein-coupled receptors → VIP and PACAP receptors

Overview: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors** [1054, 1055]) are activated by the endogenous peptides **VIP** (*VIP*, P01282), **PACAP-38** (*ADCYAPI*, P18509), **PACAP-27** (*ADCYAPI*, P18509), peptide histidine isoleucineamide (PHI {Mouse, Rat}), peptide histidine methionineamide (PHM (*VIP*, P01282)) and peptide histidine valine (PHV (*VIP*, P01282)). VPAC₁ and VPAC₂ receptors

display comparable affinity for the PACAP peptides, **PACAP-27** (*ADCYAPI*, P18509) and **PACAP-38** (*ADCYAPI*, P18509), and **VIP** (*VIP*, P01282), whereas **PACAP-27** (*ADCYAPI*, P18509) and **PACAP-38** (*ADCYAPI*, P18509) are >100 fold more potent than **VIP** (*VIP*, P01282) as agonists of most isoforms of the PAC₁ receptor. However, one splice variant of the human PAC₁ receptor has been reported to respond to **PACAP-38** (*ADCYAPI*, P18509), **PACAP-27** (*ADCYAPI*, P18509) and **VIP** (*VIP*, P01282) with comparable affinity [583]. **PG 99-465** [1960] has been used as a selective VPAC₂

receptor antagonist in a number of physiological studies, but has been reported to have significant activity at VPAC₁ and PAC₁ receptors [644]. The selective PAC₁ receptor agonist **maxadilan**, was extracted from the salivary glands of sand flies (*Lutzomyia longipalpis*) and has no sequence homology to **VIP** (*VIP*, P01282) or the PACAP peptides [1977]. Two deletion variants of **maxadilan**, **M65** [2880] and **Max.d.4** [1978] have been reported to be PAC₁ receptor antagonists, but these peptides have not been extensively characterised.

Nomenclature	PAC ₁ receptor	VPAC ₁ receptor	VPAC ₂ receptor
HGNC, UniProt	<i>ADCYAPI1</i> , P41586	<i>VIPRI</i> , P32241	<i>VIPR2</i> , P41587
Potency order of endogenous ligands	PACAP-27 (<i>ADCYAPI</i> , P18509), PACAP-38 (<i>ADCYAPI</i> , P18509) ≫ VIP (<i>VIP</i> , P01282)	VIP (<i>VIP</i> , P01282), PACAP-27 (<i>ADCYAPI</i> , P18509), PACAP-38 (<i>ADCYAPI</i> , P18509) ≫ GHRH (<i>GHRH</i> , P01286), PHI {Pig} (pig), secretin (<i>SCT</i> , P09683)	VIP (<i>VIP</i> , P01282), PACAP-38 (<i>ADCYAPI</i> , P18509), PACAP-27 (<i>ADCYAPI</i> , P18509) > PHI {Pig} (pig) ≫ GHRH (<i>GHRH</i> , P01286), secretin (<i>SCT</i> , P09683)
Selective agonists	maxadilan [644], maxadilan [644]	[Lys¹⁵,Arg¹⁶,Leu²⁷]VIP-(1-7)/GRF-(8-27)-NH₂ [1953], [Ala^{11,22,28}]VIP [2070]	Ro 25-1553 [955, 1315, 1953], Ro 25-1392 [3119]
Selective antagonists	–	PG 97-269 (pIC ₅₀ 8.7) [954, 1315]	–
Labelled ligands	[¹²⁵I]PACAP-27 (Agonist) [2251]	[¹²⁵I]VIP (human, mouse, rat) (Agonist) [2070], [¹²⁵I]PACAP-27 (Agonist)	[¹²⁵I]VIP (human, mouse, rat) (Agonist) [2070], [¹²⁵I]PACAP-27 (Agonist)

Comments: Subtypes of PAC₁ receptors have been proposed based on tissue differences in the potencies of PACAP-27 (*ADCYAP1*, P18509) and PACAP-38 (*ADCYAP1*, P18509); these might result from differences in G protein coupling and second messenger mechanisms [2917], or from alternative splicing of PAC₁ receptor mRNA [2675].

Further reading on VIP and PACAP receptors

- Harmar AJ *et al.* (1998) International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide. *Pharmacol Rev* **50**: 265-70 [PMID:9647867]
- Harmar AJ *et al.* (2012) Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: IUPHAR review 1. *Br J Pharmacol* **166**: 4-17 [PMID:22289055]
- Reglodi D *et al.* (2012) Effects of pituitary adenylate cyclase activating polypeptide in the urinary system, with special emphasis on its protective effects in the kidney. *Neuropeptides* **46**: 61-70 [PMID:21621841]
- Smith CB *et al.* (2012) Is PACAP the major neurotransmitter for stress transduction at the adrenomedullary synapse? *J Mol Neurosci* **48**: 403-12 [PMID:22610912]

Other non-GPCR 7TM proteins

G protein-coupled receptors → Other non-GPCR 7TM proteins

Overview: These proteins are predicted to have 7TM domains, but functional studies have yet to confirm them as G protein-coupled receptors.

Nomenclature	<i>GPR107</i>	<i>GPR137</i>	<i>TPRA1</i>	<i>GPR157</i>
HGNC, UniProt	<i>GPR107</i> , Q5VW38	<i>GPR137</i> , Q96N19	<i>TPRA1</i> , Q86W33	<i>GPR157</i> , Q5UAW9
Comments	<i>GPR107</i> is a member of the LUSTR family of proteins found in both plants and animals, having similar topology to G protein-coupled receptors [702]	–	<i>TPRA1</i> shows no homology to known G protein-coupled receptors.	<i>GPR157</i> has ambiguous sequence similarities to several different GPCR families (class A, class B and the slime mould cyclic AMP receptor). Because of its distant relationship to other GPCRs, it cannot be readily classified.

Further reading on G protein-coupled receptors

- Kenakin T. (2018) Is the Quest for Signaling Bias Worth the Effort? *Mol Pharmacol* **93**: 266-269 [PMID:29348268]
- Michel MC *et al.* (2018) Biased Agonism in Drug Discovery-Is It Too Soon to Choose a Path? *Mol Pharmacol* **93**: 259-265 [PMID:29326242]
- Roth BL *et al.* (2017) Discovery of new GPCR ligands to illuminate new biology. *Nat Chem Biol* **13**: 1143-1151 [PMID:29045379]
- Sriram K *et al.* (2018) G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs? *Mol Pharmacol* **93**: 251-258 [PMID:29298813]

References

1. Abbracchio MP *et al.* (2003) [12559763]
2. Abbracchio MP *et al.* (2006) [16968944]
3. AbdAlla S *et al.* (2000) [10993080]
4. Abdul-Ridha A *et al.* (2014) [25326383]
5. Abdul-Ridha A *et al.* (2014) [24443568]
6. Abdulkareem NM *et al.* (2025) [39965212]
7. Abdulkareem NM *et al.* (2021) [34110646]
8. Abo-Salem OM *et al.* (2004) [14563788]
9. Abraham GR *et al.* (2023) [39196099]
10. Abramovitz M *et al.* (2000) [10634944]
11. Abramovitz M *et al.* (1994) [8300593]
12. Ackerman SD *et al.* (2018) [29367382]
13. Adams CL *et al.* (2007) [17894647]
14. Adapa ID *et al.* (1997) [9413015]
15. Adham N *et al.* (1997) [9225282]
16. Adham N *et al.* (1993) [8380639]
17. af Forselles KJ *et al.* (2011) [21595651]
18. Afargan M *et al.* (2001) [11145612]
19. Agelis G *et al.* (2012) [22889560]
20. Ahmed K *et al.* (2009) [19561068]
21. Ahmed K *et al.* (2010) [20374963]
22. Ahn HS *et al.* (1997) [9203642]
23. Ahn HS *et al.* (2000) [11020444]
24. Ahuja SK *et al.* (1996) [8702798]
25. Ahumada A *et al.* (2002) [12471263]
26. Ai LS *et al.* (2002) [12081481]
27. Aiyar N *et al.* (2001) [11693189]
28. Aiyar N *et al.* (1993) [8463997]
29. Akasaka H *et al.* (2024) [39506093]
30. Akasaka H *et al.* (2022) [36109516]
31. Akerlund M *et al.* (1999) [10519430]
32. Akgün E *et al.* (2009) [19271701]
33. Akiyama K *et al.* (1985) [2986120]
34. Akter R *et al.* (2022) [36551877]
35. Akunne HC *et al.* (1995) [7674830]
36. Al-Ani B *et al.* (1999) [10411588]
37. Al-Hroub H *et al.* (2025) [40367388]
38. Albert DH *et al.* (1997) [9151941]
39. Albert R *et al.* (2005) [16078855]
40. Albert-Gasco H *et al.* (2019) [30368554]
41. Albrandt K *et al.* (1995) [75886285]
42. Albu DI *et al.* (2017) [28920002]
43. Alcantara IC *et al.* (2024) [39091749]
44. Alexander SP *et al.* (2021) [34529832]
45. Alexander SP *et al.* (1996) [8937736]
46. Alexander SP *et al.* (2007) [17876303]
47. Alexander SP *et al.* (2001) [11164377]
48. Alexander SPH *et al.* (2023) [38123151]
49. Alikhani V *et al.* (2004) [15324892]
50. Alim K *et al.* (2018) [30358997]
51. Allen IC *et al.* (2006) [16829631]
52. Allen-Brady K *et al.* (2025) [39914776]
53. Amano H *et al.* (2003) [12538661]
54. Amaradhi R *et al.* (2022) [35187419]
55. Amblard M *et al.* (1999) [10514288]
56. Ames RS *et al.* (2001) [11342658]
57. Ames RS *et al.* (1996) [8898085]
58. Ames RS *et al.* (1999) [10499587]
59. Ames RS *et al.* (1997) [9476119]
60. Amisten S *et al.* (2008) [18213371]
61. Amlaiki N *et al.* (1992) [1328180]
62. An W *et al.* (2022) [35394864]
63. Anand U *et al.* (2015) [26111701]
64. Ancellin N *et al.* (1999) [10380399]
65. Andersen PH *et al.* (1990) [1973652]
66. Anderson PJ *et al.* (2025) [40236194]
67. Andrade-Gordon P *et al.* (1999) [10535908]
68. Ang SY *et al.* (2018) [29535183]
69. Ang SY *et al.* (2017) [27243554]
70. Ann DK *et al.* (1992) [1313812]
71. Anthes JC *et al.* (2002) [12206858]
72. Antoniu SA. (2010) [21154168]
73. Aparici M *et al.* (2012) [22588259]
74. AraÅSD *et al.* (2012) [22333914]
75. Aramori I *et al.* (1997) [9203620]
76. Arbore G *et al.* (2016) [27313051]
77. Arcos-Burgos M *et al.* (2010) [20157310]
78. Arcos-Burgos M *et al.* (2019) [30696812]
79. Arcuri L *et al.* (2018) [29232769]
80. Ariel A *et al.* (2003) [12794159]
81. Aristotelous T *et al.* (2013) [24454993]
82. Arita M *et al.* (2005) [15753205]
83. Arita M *et al.* (2007) [17339491]
84. Armour SL *et al.* (1999) [11033437]
85. Armstrong RA *et al.* (1993) [3824228]
86. Arnt J *et al.* (1998) [9430133]
87. Aronica SM *et al.* (1994) [8078914]
88. Arthofer E *et al.* (2016) [27458145]
89. Arveseth CD *et al.* (2021) [33886552]
90. Asada H *et al.* (2022) [36417909]
91. Asahina Y *et al.* (2020) [32407089]
92. Asin KE *et al.* (1992) [1636779]
93. Ason B *et al.* (2020) [32208384]
94. Atigan A *et al.* (2022) [36572878]
95. Attali P *et al.* (2016) [27673668]
96. Auchampach JA *et al.* (2009) [19141710]
97. Audet R *et al.* (1997) [8996175]
98. Audinot V *et al.* (2001) [11375253]
99. Audinot V *et al.* (2003) [12764576]
100. Auerbach SS *et al.* *DrugMatrix*. Accessed on 02/05/2014.
101. Augustine M *et al.* (2013) [24078470]
102. Aurelio L *et al.* (2009) [19514477]
103. Aust G *et al.* (2003) [12761622]
104. Aust G *et al.* (2006) [16408199]
105. Austin CE *et al.* (1997) [9111052]
106. Austin KM *et al.* (2013) [23086754]
107. Avet C *et al.* (2020) [33247181]
108. Avlani VA *et al.* (2007) [17591774]
109. Avlani VA *et al.* (2010) [20413650]
110. Ayme-Dietrich E *et al.* (2017) [28806488]
111. Ayoub MA *et al.* (2004) [15266022]
112. Azran S *et al.* (2013) [23751098]
113. Baba M *et al.* (1997) [9169459]
114. Baba M *et al.* (1999) [10318947]
115. Bach T *et al.* (2001) [11218067]
116. Bachelier F *et al.* (2014) [24218476]
117. Bachelier F *et al.* (2015) [25958743]
118. Bäck M *et al.* (2011) [21771892]
119. Bäck M *et al.* (2014) [24588652]
120. Bae JS *et al.* (2020) [32599975]
121. Bae YS *et al.* (2004) [15210823]
122. Bagger SM *et al.* (2025) *JBC*
123. Bahouth SW *et al.* (1985) [2410593]
124. Bailey RJ *et al.* (2012) [22014233]
125. Baker JG. (2010) [20590599]
126. Baker JG. (2005) [15655528]
127. Baker JG. (2010) [21152092]
128. Baker JG *et al.* (2017) [28400472]
129. Baker JG *et al.* (2002) [12237261]
130. Baker JG *et al.* (2003) [14645666]
131. Baker JG *et al.* (2003) [12920204]
132. Baker JG *et al.* (2003) [12770928]
133. Baker JG *et al.* (2015) [25324048]
134. Bakker RA *et al.* (2006) [16415177]
135. Balan G *et al.* (2009) [19442519]
136. Balogh J *et al.* (2005) [15893764]
137. Bamberg CE *et al.* (2010) [20044484]
138. Bandekar SJ *et al.* (2025) [40295529]
139. Bandholtz S *et al.* (2016) [27791374]
140. Bang-Andersen B *et al.* (2011) [21486038]
141. Baqi Y *et al.* (2009) [19463000]
142. Bard JA *et al.* (1995) [7592911]
143. Bard JA *et al.* (1993) [8226867]
144. Barda DA *et al.* (2004) [15149652]
145. Barends CR *et al.* (2017) [28107373]
146. Barker N *et al.* (2010) [20085740]
147. Barnea G *et al.* (2008) [18165312]
148. Barrett MO *et al.* (2013) [23592514]
149. Barrett SD *et al.* (2019) [30964292]
150. Barros-Álvarez X *et al.* (2022) [35418682]
151. Barroso R *et al.* (2012) [22913878]
152. Barry GD *et al.* (2010) [20873792]
153. Barshop K *et al.* (2015) [25341626]
154. Bartfai T *et al.* (1991) [1720557]
155. Bartfai T *et al.* (1993) [7504301]
156. Bartoi T *et al.* (2010) [20406808]
157. Bassi MT *et al.* (1995) [7647783]
158. Bastian S *et al.* (1997) [9313952]
159. Bastien L *et al.* (1994) [8163486]
160. Bathgate RA *et al.* (2006) [16507880]
161. Bathgate RAD *et al.* (2023) [37439676]
162. Battram C *et al.* (2006) [16434564]
163. Baumann M *et al.* (2022) [33427002]
164. Baun C *et al.* (2024) [38342656]
165. Bayewitch M *et al.* (1996) [8626625]
166. Bayin NS *et al.* (2016) [27775701]
167. Beall SA *et al.* (2005) [15955893]
168. Beattie D *et al.* (2012) [22932315]
169. Beattie DT *et al.* (2004) [15466450]
170. Beaujouan JC *et al.* (1997) [9042606]
171. Beckers T *et al.* (2001) [11726197]
172. Beckers T *et al.* (1995) [7649152]
173. Beckers T *et al.* (1997) [9300077]
174. Bedendi I *et al.* (2003) [12969753]
175. Bednarek MA *et al.* (2000) [11087562]
176. Bednarek MA *et al.* (2001) [11606131]
177. Béguin C *et al.* (2005) [15869877]
178. Behrens M *et al.* (2017) [28919036]
179. Behrens M *et al.* (2009) [19817411]
180. Behrens M *et al.* (2004) [15178431]
181. Behrens M *et al.* (2018) [28834122]
182. Behrens M *et al.* (2013) [23632915]
183. Behrens M *et al.* (2019) [30928101]
184. Bekkers P *et al.* (2016) [27768695]
185. Bélanger S *et al.* (2009) [19111586]
186. Belgi A *et al.* (2011) [21866895]
187. Bell IM *et al.* (1998) [9622556]
188. Belley M *et al.* (1999) [10658574]
189. Bellier B *et al.* (2004) [14698161]
190. Bellucci F *et al.* (2002) [11786503]
191. Belov V *et al.* (2024) [38477292]

192. Ben-Baruch A *et al.* (1995) [7545673]
 193. Bender E *et al.* (2000) [10646498]
 194. Bennacef I *et al.* (2004) [15265501]
 195. Benned-Jensen T *et al.* (2010) [20148890]
 196. Benya RV *et al.* (1995) [7838118]
 197. Benyahia C *et al.* (2013) [23850788]
 198. Béraud-Dufour S *et al.* (2009) [19891061]
 199. Beresford IJ *et al.* (1998) [9618428]
 200. Beresford IJ *et al.* (1995) [7713168]
 201. Bergman JM *et al.* (2008) [18207395]
 202. Berizzi AE *et al.* (2018) [29683647]
 203. Berizzi AE *et al.* (2016) [27461343]
 204. Bern HA *et al.* (1985) [2864726]
 205. Bernotas RC *et al.* (2009) [19523834]
 206. Berque-Bestel I *et al.* (2003) [12801225]
 207. Berry CB *et al.* (2014) [25221667]
 208. Bersani M *et al.* (1991) [1710578]
 209. Bersani M *et al.* (1991) [1718731]
 210. Bertini R *et al.* (2004) [15282370]
 211. Bertron JL *et al.* (2018) [29754948]
 212. Besada P *et al.* (2006) [16942026]
 213. Bettler B *et al.* (2004) [15269338]
 214. Beukers MW *et al.* (2000) [11093773]
 215. Beukers MW *et al.* (1997) [9384502]
 216. Bhudia N *et al.* (2020) [32184438]
 217. Bhudia N *et al.* (2020) [31969668]
 218. Bhuniya D *et al.* (2011) [21571530]
 219. Bi Y *et al.* (2015) [25754495]
 220. Bianchi E *et al.* (2021) [33623007]
 221. Bichet DG *et al.* (1998) [9756088]
 222. Bigoni R *et al.* (2002) [12070757]
 223. Binet V *et al.* (2004) [15126507]
 224. Binkhorst LCP *et al.* (2025) [40568883]
 225. Birdsall NJ *et al.* (1999) [10101037]
 226. Birke FW *et al.* (2001) [11259574]
 227. Birrell MA *et al.* (2013) [22747912]
 228. Bjarnadóttir TK *et al.* (2007) [17056209]
 229. Bjursell M *et al.* (2006) [16887097]
 230. Blackhart BD *et al.* (1996) [8663335]
 231. Blaho VA. (2020) [32894509]
 232. Blaho VA *et al.* (2018) [30343728]
 233. Blaho VA *et al.* (2015) [26053123]
 234. Blair JB *et al.* (2000) [11101361]
 235. Blanpain C *et al.* (1999) [10477718]
 236. Bley KR *et al.* (2006) [16331286]
 237. Blin N *et al.* (1993) [7903415]
 238. Blondel O *et al.* (1998) [9603189]
 239. Blue DR *et al.* (2004) [14678390]
 240. Boatman PD *et al.* (2012) [22435740]
 241. Bockaert J *et al.* (2006) [16896947]
 242. Boden P *et al.* (1996) [8648606]
 243. Boess FG *et al.* (1997) [9284367]
 244. Boess FG *et al.* (1998) [9730917]
 245. Bogdanov YD *et al.* (1998) [9647463]
 246. Bohnkamp J *et al.* (2011) [22025619]
 247. Boie Y *et al.* (1994) [7512962]
 248. Boie Y *et al.* (1995) [7642548]
 249. Boie Y *et al.* (1999) [10513580]
 250. Bolden C *et al.* (1992) [1346637]
 251. Bolli MH *et al.* (2010) [20446681]
 252. Bolli MH *et al.* (2012) [22862294]
 253. Bolli MH *et al.* (2004) [15139756]
 254. Bolliger MF *et al.* (2011) [21262840]
 255. Bologa CG *et al.* (2006) [16520733]
 256. Bolognini D *et al.* (2016) [27385588]
 257. Bonaventure P *et al.* (2012) [22570363]
 258. Bonaventure P *et al.* (2004) [14617685]
 259. Bonaventure P *et al.* (2015) [26177655]
 260. Bonhaus DW *et al.* (1997) [9225293]
 261. Bonhaus DW *et al.* (1999) [10455251]
 262. Bonhaus DW *et al.* (1997) [9225287]
 263. Bonnavion R *et al.* (2023) [38026988]
 264. Bonnefous C *et al.* (2005) [15686941]
 265. Bonnefous C *et al.* (2005) [16046122]
 266. Booth RG *et al.* (2002) [12065734]
 267. Bordano V *et al.* (2022) [35537492]
 268. Born S *et al.* (2013) [23283334]
 269. Borowsky B *et al.* (2001) [11459929]
 270. Borowsky B *et al.* (2002) [12118247]
 271. Borowsky B *et al.* (1998) [9880084]
 272. Borrmann T *et al.* (2009) [19569717]
 273. Bosch MP *et al.* (2004) [15267242]
 274. Bosnyak S *et al.* (2011) [21542804]
 275. Botto JM *et al.* (1997) [9001400]
 276. Boucard AA *et al.* (2012) [22262843]
 277. Boulanger L *et al.* (2002) [11814616]
 278. Boulenguez P *et al.* (1992) [1738002]
 279. Bouyssou T *et al.* (2010) [20371707]
 280. Bowery NG *et al.* (2002) [12037141]
 281. Bowery NG *et al.* (2000) [10604925]
 282. Bowin CF *et al.* (2023) [37014927]
 283. Bowles NP *et al.* (2015) [25535367]
 284. Boyce M *et al.* (2012) [22607579]
 285. Boyden SE *et al.* (2016) [26841242]
 286. Boyer JL *et al.* (1996) [8913364]
 287. Brabet I *et al.* (1995) [8532171]
 288. Bradaia A *et al.* (2009) [19892733]
 289. Bradley EC *et al.* (2019) [31529518]
 290. Bradshaw CG *et al.* (1994) [8027981]
 291. Brady AE *et al.* (2008) [18772318]
 292. Brambilla R *et al.* (2000) [10731034]
 293. Brame AL *et al.* (2015) [25712721]
 294. Branchek T *et al.* (1990) [2233697]
 295. Brandolini L *et al.* (2019) [30953275]
 296. Bräuner-Osborne H *et al.* (1996) [8759641]
 297. Breivogel CS *et al.* (1997) [9316881]
 298. Brenchat A *et al.* (2009) [19118950]
 299. Brennan FH *et al.* (2019) [31045582]
 300. Breton C *et al.* (2001) [11337500]
 301. Breu V *et al.* (1996) [8612786]
 302. Brezillon S *et al.* (2003) [12401809]
 303. Bridges JP *et al.* (2013) [23590306]
 304. Brighton PJ *et al.* (2004) [15331768]
 305. Brink C *et al.* (2004) [15001665]
 306. Brinkmann V *et al.* (2002) [11967257]
 307. Briscoe CP *et al.* (2006) [16702987]
 308. Briscoe CP *et al.* (2003) [12496284]
 309. Brkovic A *et al.* (2003) [12807997]
 310. Broad J *et al.* (2013) [23190027]
 311. Broadhead GK *et al.* (2011) [21187282]
 312. Brockhoff A *et al.* (2007) [17595105]
 313. Brockhoff A *et al.* (2011) [21994393]
 314. Brodbeck RM *et al.* (2008) [18753409]
 315. Brodfuehrer J *et al.* (2014) [24190631]
 316. Brodtkin J *et al.* (2002) [12473093]
 317. Bromidge SM *et al.* (1999) [9925723]
 318. Bromidge SM *et al.* (2001) [11140733]
 319. Brown AJ *et al.* (2003) [12496283]
 320. Brown AM *et al.* (1998) *Br J Pharmacol* **123**: 233
 321. Brown AM *et al.* (1993) *Br J Pharmacol* **110**: 10
 322. Brown EM *et al.* (1993) [8255296]
 323. Brown K *et al.* (2017) [28570277]
 324. Browning C *et al.* (2000) [10696085]
 325. Bruchas MR *et al.* (2007) [17702750]
 326. Brucker BM *et al.* (2022) [35693456]
 327. Bruinvels AT *et al.* (1993) [8361548]
 328. Bruns C *et al.* (1996) [8769372]
 329. Bruns RF *et al.* (1990) [2174510]
 330. Brunschweiler A *et al.* (2006) [16475938]
 331. Bruzzzone F *et al.* (2007) [17534937]
 332. Bryant HU *et al.* (1996) [8845011]
 333. Bryja V *et al.* (2007) [17426148]
 334. Bryja V *et al.* (2008) [18953287]
 335. Bubser M *et al.* (2014) [25137629]
 336. Buckley NJ *et al.* (1989) [2704370]
 337. Bufe B *et al.* (2005) [15723792]
 338. Bufe B *et al.* (2002) [12379855]
 339. Büllesbach EE *et al.* (2005) [15708846]
 340. Bunzow JR *et al.* (1988) [2974511]
 341. Burford NT *et al.* (2013) [23754417]
 342. Burford NT *et al.* (2015) [25901762]
 343. Burgaud JL *et al.* (1997) [9434758]
 344. Burger WAC *et al.* (2021) [34351123]
 345. Burger WAC *et al.* (2025) [39975287]
 346. Burris KD *et al.* (1995) [7576010]
 347. Burstein ES *et al.* (2005) [16135699]
 348. Büscher R *et al.* (2006) [16495779]
 349. Busnelli M *et al.* (2013) [23723434]
 350. Butler CR *et al.* (2024) [38888621]
 351. Buvinic S *et al.* (2002) [12110609]
 352. Buzard DJ *et al.* (2014) [25516790]
 353. Búzás B *et al.* (1992) [1313131]
 354. Bylund DB *et al.* (1992) [1353247]
 355. Bylund DB *et al.* (1994) [7938162]
 356. Byrne EFX *et al.* (2016) [27437577]
 357. Cabrele C *et al.* (2002) [12069595]
 358. Cahalan SM *et al.* (2011) [21445057]
 359. Cai H *et al.* (2024) [38627384]
 360. Cai H *et al.* (2022) [36575181]
 361. Cai R *et al.* (2014) [24373935]
 362. Cai TQ *et al.* (2008) [18952058]
 363. Cain SA *et al.* (2002) [11773063]
 364. Calderon SN *et al.* (1994) [8035418]
 365. Callander GE *et al.* (2013) [24376396]
 366. Calo G *et al.* (2002) [12010780]
 367. Camarda V *et al.* (2009) [19183962]
 368. Camarda V *et al.* (2009) [18971372]
 369. Caminschi I *et al.* (2001) [11564768]
 370. Caminschi I *et al.* (2006) [16753812]
 371. Campion KL *et al.* (2015) [25556167]
 372. Canals M *et al.* (2012) [22086918]
 373. Candelore MR *et al.* (1999) [10411574]
 374. Cannone G *et al.* (2025) [39805839]
 375. Cao AM *et al.* (2021) [34521824]
 376. Capodanno D *et al.* (2013) [23809135]
 377. Cappellacci L *et al.* (2005) [15743197]
 378. Cappelli A *et al.* (2013) [23466604]
 379. Capra V *et al.* (1998) [9504401]
 380. Capra V *et al.* (2015) [25839425]
 381. Capra V *et al.* (1998) [9547367]
 382. Carmeci C *et al.* (1997) [9367686]
 383. Carmon KS *et al.* (2011) [21693646]
 384. Carmini C *et al.* (2011) [21753081]
 385. Caronia L *et al.* (2023) [37806252]
 386. Carr BJ *et al.* (2018) [29860464]
 387. Carr JC *et al.* (2012) [23158174]
 388. Carroll FY *et al.* (2001) [11306677]
 389. Carroll WA *et al.* (2001) [11354357]

390. Carter RL *et al.* (2009) [19759354]
 391. Carvelli J *et al.* (2020) [32726800]
 392. Cascieri MA *et al.* (1999) [10085108]
 393. Castro SW *et al.* (1996) [8646408]
 394. Catalán V *et al.* (2007) [17371481]
 395. Catalioto RM *et al.* (1998) [9484857]
 396. Cattaneo M *et al.* (2004) [15476670]
 397. Cattaneo M *et al.* (2003) [12578987]
 398. Caulfield MP *et al.* (1998) [9647869]
 399. Caunt CJ *et al.* (2004) [15059960]
 400. Caunt CJ *et al.* (2012) [22808094]
 401. Cavallari U *et al.* (2007) [17803810]
 402. Cavanaugh DJ *et al.* (2009) [19451647]
 403. Cayabyab M *et al.* (2000) [11090199]
 404. Cederblad L *et al.* (2016) [26656484]
 405. Cediel ML *et al.* (2022) [36103875]
 406. Cembala TM *et al.* (1998) [9846649]
 407. Cencetti F *et al.* (2013) [23913862]
 408. Centeno PP *et al.* (2019) [31619668]
 409. Cescato R *et al.* (2008) [18543899]
 410. Ch'ng SS *et al.* (2020) [32079174]
 411. Chackalamannil S *et al.* (2008) [18447380]
 412. Chagnon YC *et al.* (1997) [9392003]
 413. Chaki S *et al.* (2005) [15677346]
 414. Chaki S *et al.* (1999) [10357258]
 415. Chambers JK *et al.* (2000) [10753868]
 416. Chan SD *et al.* (1992) [1334084]
 417. Chan WY *et al.* (2008) [18678919]
 418. Chang DJ *et al.* (1998) [9490024]
 419. Chang GW *et al.* (2007) [17174274]
 420. Chang GW *et al.* (2016) [27184850]
 421. Chang H *et al.* (2023) [37978243]
 422. Chang J *et al.* (2017) [28288111]
 423. Chang KJ *et al.* (1983) [6313901]
 424. Chang RS *et al.* (1990) [2314387]
 425. Chang RS *et al.* (1986) [3018478]
 426. Chang W *et al.* (2008) [18765830]
 427. Chang W *et al.* (2007) [17591780]
 428. Chansel D *et al.* (1993) [8282008]
 429. Chao TH *et al.* (1999) [10092660]
 430. Chartrel N *et al.* (2003) [14657341]
 431. Chatenet D *et al.* (2006) [17125276]
 432. Chavkin C *et al.* (2004) [14718611]
 433. Che T *et al.* (2020) [32123179]
 434. Che T *et al.* (2018) [29307491]
 435. Chen C *et al.* (1996) [8893829]
 436. Chen C *et al.* (2008) [19006286]
 437. Chen H *et al.* (2022) [35353559]
 438. Chen H *et al.* (2004) [15163697]
 439. Chen J *et al.* (2005) [15772293]
 440. Chen J *et al.* (2003) [12706455]
 441. Chen JK *et al.* (2002) [12391318]
 442. Chen LH *et al.* (2014) [25050158]
 443. Chen N *et al.* (2016) Patent number: WO2016187308A1.
 444. Chen Q *et al.* (2012) [22697179]
 445. Chen Q *et al.* (2024) [38355778]
 446. Chen R *et al.* (1993) [7692441]
 447. Chen S *et al.* (2023) [37625013]
 448. Chen T *et al.* (2020) [32568214]
 449. Chen T *et al.* (2020) [32139677]
 450. Chen W *et al.* (2003) [12958365]
 451. Chen Y *et al.* (2020) [31971610]
 452. Chen Y *et al.* (2022) [36563137]
 453. Chen Y *et al.* (2023) [36717591]
 454. Chen Y *et al.* (2025) [40410443]
 455. Chen YL *et al.* (2008) [18288792]
 456. Chen Z *et al.* (2004) [15454210]
 457. Chen Z *et al.* (2008) Patent number: WO2008036579A1.
 458. Chen ZF. (2021) [34663954]
 459. Cheng CK *et al.* (2005) [15561800]
 460. Cheng K *et al.* (2002) [12235229]
 461. Cheng LL *et al.* (2004) [15084136]
 462. Cheng RKY *et al.* (2017) [28445455]
 463. Cheng Z *et al.* (2007) [17615148]
 464. Cherezov V *et al.* (2007) [17962520]
 465. Chevigné A *et al.* (2025) [39952689]
 466. Chevigné A *et al.* (2024) [39375046]
 467. Chhabra KH *et al.* (2024) [37712955]
 468. Chhatriwala M *et al.* (2004) [15345752]
 469. Chiang N *et al.* (2000) [10748237]
 470. Chiang N *et al.* (2012) [22538616]
 471. Chiang NY *et al.* (2016) [27068534]
 472. Chiba Y *et al.* (2020) [32868297]
 473. Chin FT *et al.* (2006) *J Label Comp Radiopharm* 17-31
 474. Chini B *et al.* (2008) [18655904]
 475. Chini B *et al.* (1995) [7774575]
 476. Chini B *et al.* (1996) [8955347]
 477. Chiu AT *et al.* (1989) [2590220]
 478. Chng SC *et al.* (2013) [24316148]
 479. Cho C *et al.* (2017) [28803732]
 480. Cho HP *et al.* (2014) [24798819]
 481. Chobanian HR *et al.* (2012) [24900461]
 482. Choi KE *et al.* (2012) [22459147]
 483. Chong ZS *et al.* (2018) [30477585]
 484. Chopra M *et al.* (2009) [19389924]
 485. Chou CC *et al.* (2002) [12381680]
 486. Chow BK. (1995) [7612008]
 487. Chow BS *et al.* (2014) [24429402]
 488. Chow BSM *et al.* (2019) [31511361]
 489. Chrencik JE *et al.* (2015) [26091040]
 490. Christ-Crain M *et al.* (2019) [31395885]
 491. Christiansen E *et al.* (2012) [22724451]
 492. Christiansen E *et al.* (2013) [23687558]
 493. Christiansen E *et al.* (2016) [27074625]
 494. Christiansen E *et al.* (2015) [25916176]
 495. Christopher JA *et al.* (2019) [29455526]
 496. Christopoulos A *et al.* (2003) [12446722]
 497. Christopoulos A *et al.* (1998) [9614217]
 498. Christopoulos A *et al.* (1999) [9890565]
 499. Christopoulos A *et al.* (2001) [11578621]
 500. Christopoulos G *et al.* (1999) [10385705]
 501. Chu ZL *et al.* (2010) [19901198]
 502. Chun J *et al.* (2019) [30625282]
 503. Chung DS *et al.* (1997) [9353394]
 504. Chung FZ *et al.* (1995) [7476898]
 505. Cialdai C *et al.* (2006) [16979621]
 506. Ciana P *et al.* (2006) [16990797]
 507. Cilibrizzi A *et al.* (2009) [19639995]
 508. Cirillo R *et al.* (2003) [12660315]
 509. Cirillo R *et al.* (2007) [17618756]
 510. Civciristov S *et al.* (2019) [30801691]
 511. Claeysens S *et al.* (1997) [9351641]
 512. Clark AL *et al.* (1976) [990587]
 513. Clark BP *et al.* (1997) *Bioorg Med Chem Lett* 7: 2777-2780
 514. Clark P *et al.* (2008) [18287210]
 515. Clark SD *et al.* (2017) [28267583]
 516. Clément K *et al.* (2020) [33137293]
 517. Clish CB *et al.* (1999) [10393980]
 518. Clozel M *et al.* (2004) [15146030]
 519. Clozel M *et al.* (1994) [8035319]
 520. Cogé F *et al.* (2001) [11284713]
 521. Cohen DP *et al.* (1996) [8828514]
 522. Cohen JA *et al.* (2011) [21520239]
 523. Colson PH *et al.* (2016) [27586252]
 524. Combadiere C *et al.* (1995) [8530354]
 525. Commy TA. (2010) *Alzheimers Dement* 6: S548-S549
 526. Communi D *et al.* (1996) [8670200]
 527. Communi D *et al.* (1999) [10578132]
 528. Comps-Agrar L *et al.* (2011) [21552208]
 529. Congreve M *et al.* (2012) [22220592]
 530. Conibear AE *et al.* (2020) [31594792]
 531. Conigrave AD *et al.* (2000) [10781086]
 532. Conn PM *et al.* (1982) [6282571]
 533. Conroy JL *et al.* (2015) [25660762]
 534. Cook AE *et al.* (2015) [25220431]
 535. Cooray SN *et al.* (2013) [24108355]
 536. Corbett DF *et al.* (2005) [16002289]
 537. Corcoran RB *et al.* (2006) [16707575]
 538. Corte TJ *et al.* (2021) [34969771]
 539. Cortijo C *et al.* (2012) [23177622]
 540. Costes N *et al.* (2005) [16330560]
 541. Cotte N *et al.* (2000) [10866830]
 542. Cotte N *et al.* (1998) [9792651]
 543. Cottingham C *et al.* (2011) [21859713]
 544. Coulie B *et al.* (2001) [11461914]
 545. Coulin F *et al.* (1997) [9346309]
 546. Coulouarn Y *et al.* (1999) [10486557]
 547. Coulouarn Y *et al.* (1998) [9861051]
 548. Coulthard LG *et al.* (2015) [25848071]
 549. Covic L *et al.* (2002) [12357249]
 550. Cox BM *et al.* (2015) [24528283]
 551. Cox CD *et al.* (2010) [20565075]
 552. Cox HM *et al.* (1995) [8590988]
 553. Coy DH *et al.* (1996) [8993400]
 554. Cristiano L *et al.* (1993) [8242249]
 555. Cristiano C *et al.* (2023) [37722320]
 556. Croker DE *et al.* (2013) [24060963]
 557. Croker DE *et al.* (2016) [27108698]
 558. Crombie AL *et al.* (2010) [20471258]
 559. Croston GE *et al.* (2002) [12408704]
 560. Croy CH *et al.* (2016) [27085897]
 561. Croy CH *et al.* (2014) [24807965]
 562. Cui Q *et al.* (2021) [34785711]
 563. Cui Q *et al.* (2024) [38154264]
 564. Cui Y *et al.* (2025) [40553099]
 565. Cunha RA *et al.* (1996) [8692280]
 566. Curtis AE *et al.* (2010) [19934405]
 567. D'Amato M *et al.* (2007) [17854592]
 568. d'Orchymont F *et al.* (2024) [38500748]
 569. da Silva Junior ED *et al.* (2017) [28444738]
 570. Dagan-Wiener A *et al.* (2019) [30357384]
 571. Dahlgren C *et al.* (2025) [40437796]
 572. Dairaghi DJ *et al.* (1999) [10419462]
 573. Dalpiaz A *et al.* (1998) [9827575]
 574. Daniels DV *et al.* (1999) [10334511]
 575. Dantas de Araujo A *et al.* (2017) [28562031]
 576. Dardonville C *et al.* (2004) [15224384]
 577. Das A *et al.* (2010) [19902968]
 578. Das S *et al.* (2011) [21245295]
 579. Dass NB *et al.* (2003) [14504130]
 580. Daugherty BL *et al.* (1996) [8642344]
 581. Dautzenberg FM *et al.* (1997) [9326293]
 582. Dautzenberg FM *et al.* (2004) [15450949]
 583. Dautzenberg FM *et al.* (1999) [10583729]
 584. Dautzenberg FM *et al.* (2001) [11123370]

585. Davenport AP. (2002) [12037137]
 586. Davenport AP *et al.* (2013) [23686350]
 587. Davenport AP *et al.* (2005) [16382107]
 588. Davenport AP *et al.* (1998) [9489609]
 589. Davenport AP *et al.* (1994) [8012722]
 590. Davey AE *et al.* (2012) [22210744]
 591. Davidson JS *et al.* (1997) [9335546]
 592. Davis MD *et al.* (2005) [15590668]
 593. Davis TL *et al.* (2000) [10952683]
 594. Davletov BA *et al.* (1996) [8798521]
 595. Davoren JE *et al.* (2016) [27275946]
 596. Dawson LA *et al.* (2009) [19499624]
 597. de Ávila C *et al.* (2018) [28864207]
 598. De Backer MD *et al.* (1998) [9794809]
 599. de Gasparo M *et al.* (2000) [10977869]
 600. de Gasparo M *et al.* (1994) *In Medicinal Chemistry of the Renin-Angiotensin System*. Edited by Timmermanns PBMWM, Wexler RR: Elsevier: 269-294 [ISBN: 0444820531]
 601. de Lau W *et al.* (2011) [21727895]
 602. de Lecea L *et al.* (1996) [8622767]
 603. de Ligt RA *et al.* (2005) [15740718]
 604. De Pascali F *et al.* (2022) [35732075]
 605. De Ponti F *et al.* (1996) [8730277]
 606. de Sousa Buck H *et al.* (2002) [12025957]
 607. De Toni L *et al.* (2019) [30625346]
 608. De Vry J *et al.* (1998) [9495870]
 609. de Wied D *et al.* (1993) [8258377]
 610. De Yang *et al.* (2000) [11015447]
 611. Deal MJ *et al.* (1992) [1331460]
 612. DeAlmeida VI *et al.* (2007) [17545618]
 613. Dearry A *et al.* (1990) [2144334]
 614. DeChristopher B *et al.* (2019) [30824200]
 615. Dehkhoda F *et al.* (2025) [40441153]
 616. Dehvari N *et al.* (2020) [32813332]
 617. Del Bello F *et al.* (2012) [22243489]
 618. Del Borgo MP *et al.* (2006) [16547350]
 619. Del Toro D *et al.* (2020) [31928845]
 620. Delahaye R *et al.* (1997) [9484907]
 621. Demberg LM *et al.* (2015) [26188515]
 622. Demberg LM *et al.* (2017) [28154189]
 623. Deng C *et al.* (2015) [25995451]
 624. Deng X *et al.* (1999) [10438703]
 625. Dennis MK *et al.* (2009) [19430488]
 626. Dennis MK *et al.* (2011) [21782022]
 627. Derick S *et al.* (2002) [12446593]
 628. Deshpande I *et al.* (2019) [31263273]
 629. Devarakonda T *et al.* (2020) [32295457]
 630. Devedian JC *et al.* (1994) [7908642]
 631. Devenport D *et al.* (2011) [21743464]
 632. Devosse T *et al.* (2011) [21709160]
 633. Dhawan BN *et al.* (1996) [8981566]
 634. Dhillon S. (2024) [38833193]
 635. Di Fabio R *et al.* (2011) [21831639]
 636. Di Giglio MG *et al.* (2017) [28145450]
 637. Di Marzo V *et al.* (2001) [11181068]
 638. Di Pardo A *et al.* (2018) [29688337]
 639. Di Pizio A *et al.* (2020) [31236627]
 640. Di Salvo J *et al.* (2000) [11104827]
 641. Di Salvo J *et al.* (2017) [27965369]
 642. Diallo M *et al.* (2008) [18082287]
 643. Díaz-González F *et al.* (2007) [17170051]
 644. Dickson L *et al.* (2006) [16930633]
 645. Dietis N *et al.* (2012) [22194444]
 646. Dietis N *et al.* (2018) [29524334]
 647. Diez-Roux G *et al.* (2011) [21267068]
 648. Dijksterhuis JP *et al.* (2013) [24032637]
 649. Dijkstra D *et al.* (2002) [12086487]
 650. Dillon JS *et al.* (1993) [8404634]
 651. Ding H *et al.* (2018) [30158150]
 652. Dinter J *et al.* (2015) [25706283]
 653. Dionisotti S *et al.* (1997) [9179373]
 654. Disse B *et al.* (1993) [8441333]
 655. Divorty N *et al.* (2015) [25805994]
 656. Diwakarla S *et al.* (2020) [31989750]
 657. Doan ND *et al.* (2012) [22044114]
 658. Dodé C *et al.* (2013) [23596439]
 659. Dolan JA *et al.* (1994) [7912272]
 660. Dolanc D *et al.* (2022) [35326460]
 661. Doménech T *et al.* (1997) [9303569]
 662. Domschke K *et al.* (2011) [20603625]
 663. Donaldson CJ *et al.* (1996) [8612563]
 664. Donaldson LF *et al.* (1996) [8947459]
 665. Dong GZ *et al.* (1995) [7616422]
 666. Donner J *et al.* (2010) [20705147]
 667. Doods H *et al.* (1999) [10611450]
 668. Doods H *et al.* (2000) [10711339]
 669. Doods HN *et al.* (1995) [7562541]
 670. Dooley CT *et al.* (1997) [9353393]
 671. Doré AS *et al.* (2014) [25042998]
 672. Dörje F *et al.* (1991) [1994002]
 673. Dotson CD *et al.* (2008) [19092995]
 674. Douglas SA Ohlstein EH. (2000) *In The IUPHAR Receptor Compendium of Receptor Characterization and Classification*. Edited by Girdlestone D: IUPHAR Media Ltd: 365-372
 675. Doumazane E *et al.* (2011) [20826542]
 676. Dowling MR *et al.* (2006) [16847442]
 677. Drake MT *et al.* (2008) [18086673]
 678. Draper-Joyce CJ *et al.* (2021) [34497422]
 679. Drummond AH *et al.* (1989) [2566295]
 680. Dschietzig TB. (2019) [30659842]
 681. Du J *et al.* (2021) [34135509]
 682. Du W *et al.* (2025) [39522703]
 683. Duan Y *et al.* (2025) [39847322]
 684. Duangdao DM *et al.* (2009) [19646487]
 685. Dubessy C *et al.* (2008) [18710417]
 686. Dubocovich ML. (1985) [2991499]
 687. Dubocovich ML *et al.* (2010) [20605968]
 688. Dubocovich ML *et al.* (1997) [9089668]
 689. Dubocovich ML *et al.* (1998) [9737724]
 690. Dudley DT *et al.* (1990) [2402226]
 691. Dudley DT *et al.* (1993) [8469774]
 692. Dufourny L *et al.* (2008) [18400093]
 693. Duggal P *et al.* (2003) [12761559]
 694. Duman JG *et al.* (2019) [31461398]
 695. Dumont Y *et al.* (2004) [15337369]
 696. Dunlop J *et al.* (2005) [15705738]
 697. Dupuis DS *et al.* (2006) [16966477]
 698. Dupuis N *et al.* (2017) [28314853]
 699. Dwyer MP *et al.* (2006) [17181143]
 700. Eason MG *et al.* (1995) [7559592]
 701. Eckle T *et al.* (2007) [17353435]
 702. Edgar AJ. (2007) [17454009]
 703. Edinger AL *et al.* (1997) [9405683]
 704. Edmondson SD *et al.* (2016) [26709102]
 705. Edwards RM *et al.* (1992) [1309870]
 706. Egan C *et al.* (2000) [10611640]
 707. Eggerickx D *et al.* (1995) [7639700]
 708. Ehrenmann J *et al.* (2018) [30455434]
 709. Eichler W *et al.* (1997) [9389316]
 710. Eison AS *et al.* (1993) [8246675]
 711. El Messari S *et al.* (2004) [15341513]
 712. El-Tayeb A *et al.* (2005) [16213725]
 713. El-Tayeb A *et al.* (2006) [17125260]
 714. El-Tayeb A *et al.* (2011) [21417463]
 715. Elands J *et al.* (1988) [2827511]
 716. Ellacott KL *et al.* (2005) [15752583]
 717. Elliott JD *et al.* (1994) [8201588]
 718. Ember JA *et al.* (1991) [2015217]
 719. Emonds-Alt X *et al.* (1995) [7830490]
 720. Emonds-Alt X *et al.* (1993) [7682062]
 721. Emson PC. (2007) [17499108]
 722. Engers DW *et al.* (2009) [19469556]
 723. Engers JL *et al.* (2015) [26335039]
 724. Engström M *et al.* (2003) [12606605]
 725. Engström M *et al.* (2005) [15333679]
 726. Enna SJ *et al.* (2004) [15451397]
 727. Ennis MD *et al.* (1998) [9632349]
 728. Erchehyi J *et al.* (2005) [15658864]
 729. Eriksson H *et al.* (1998) [9802391]
 730. Erlandson SC *et al.* (2023) [37081311]
 731. Erlandson SC *et al.* (2024) [39134056]
 732. Erspamer V *et al.* (1989) [2544892]
 733. Esbenshade TA *et al.* (2004) [15294456]
 734. Esbenshade TA *et al.* (2003) [12606603]
 735. Escribano A *et al.* (1998) [9871538]
 736. Espinoza S *et al.* (2011) [21670104]
 737. Esteban-Lopez M *et al.* (2022) [36333465]
 738. Eubelen M *et al.* (2018) [30026314]
 739. Evans BA *et al.* (2011) [20978120]
 740. Evans BA *et al.* (1999) [10455305]
 741. Evans BA *et al.* (2010) [20132209]
 742. Evans BN *et al.* (2000) [10903324]
 743. Evans HF *et al.* (1991) [1714839]
 744. Fabio KM *et al.* (2013) [23471831]
 745. Failli AA *et al.* (2006) [16297621]
 746. Falloot LB *et al.* (2022) [36367749]
 747. Fan H *et al.* (2015) [25176008]
 748. Fan X *et al.* (2003) [12939143]
 749. Faouzi A *et al.* (2023) [36450356]
 750. Farb TB *et al.* (2017) [28938487]
 751. Farooqi IS *et al.* (2008) [18779842]
 752. Faulkner ML *et al.* (2024) [39704175]
 753. Faust R *et al.* (2000) [10737738]
 754. Favara DM *et al.* (2019) [31299890]
 755. FDA. [fda.gov](https://www.fda.gov). Accessed on 01/09/2025.
 756. Feehan KT *et al.* (2024) [38773113]
 757. Feighner SD *et al.* (1999) [10381885]
 758. Felder CC *et al.* (1998) [9435190]
 759. Felder CC *et al.* (1995) [7565624]
 760. Fells JI *et al.* (2008) [18467108]
 761. Fells JI *et al.* (2009) [19800804]
 762. Fenalti G *et al.* (2014) [24413399]
 763. Fenalti G *et al.* (2015) [25686086]
 764. Feng YH *et al.* (1995) [7759541]
 765. Feoktistov I *et al.* (2001) [11705449]
 766. Fer M *et al.* (2024) [38949964]
 767. Fernández J *et al.* (2005) [15771415]
 768. Fernando SJA *et al.* (2023) [36947541]
 769. Ferrari F *et al.* (2020) [31937563]
 770. Fierens F *et al.* (1999) [10079018]
 771. Fierro F *et al.* (2023) [37012410]
 772. Filardo EJ. (2018) [28595943]
 773. Filardo EJ *et al.* (2000) [11043579]
 774. Finch AR *et al.* (2010) [20009083]
 775. Finch AR *et al.* (2010) [19888967]
 776. Fiore S *et al.* (1994) [8006586]
 777. Fiore S *et al.* (1992) [1322894]
 778. Fiore S *et al.* (1995) [8527441]

779. Fiorino F *et al.* (2017) [28943244]
 780. Fischer DJ *et al.* (2001) [11562440]
 781. Fischetti C *et al.* (2009) [19445927]
 782. Fister S *et al.* (2009) [19638591]
 783. Fitzgerald LW *et al.* (1999) [10217294]
 784. Fitzgerald LW *et al.* (1998) [9808667]
 785. Flacco N *et al.* (2013) [23373597]
 786. Fletcher JN *et al.* (2011) [22059530]
 787. Florian S *et al.* (2006) [16918507]
 788. Fong TM *et al.* (1992) [1281470]
 789. Foord SM *et al.* (2005) [15914470]
 790. Forbes IT *et al.* (2002) [12392747]
 791. Ford AP *et al.* (1996) [8632751]
 792. Ford AP *et al.* (1997) [9249248]
 793. Formstone CJ *et al.* (2001) [11677057]
 794. Forrest M *et al.* (2004) [14747617]
 795. Forsman H *et al.* (2012) [22706076]
 796. Foss FW *et al.* (2007) [17113298]
 797. Fotsing JR *et al.* (2020) [32330040]
 798. Foudi N *et al.* (2011) [21323896]
 799. Foudi N *et al.* (2008) [18516068]
 800. Fox JC *et al.* (2015) [25497737]
 801. Früh S *et al.* (2024) [38985877]
 802. Francavilla F *et al.* (2025) [40847912]
 803. Franchetti P *et al.* (2009) [19317449]
 804. Francis BE *et al.* (1994) [8287060]
 805. Fraser GL *et al.* (2008) [18719021]
 806. Fraser NJ *et al.* (1999) [10347248]
 807. Fredholm BB. (1995) [7346802]
 808. Fredholm BB *et al.* (2005) [15822182]
 809. Fredholm BB *et al.* (2001) [11734617]
 810. Fredman G *et al.* (2010) [20702811]
 811. Fredriksson R *et al.* (2003) [12761335]
 812. Free RB *et al.* (2014) [24755247]
 813. Freedman SB *et al.* (1994) [8301582]
 814. Freer RJ *et al.* (1982) [6280748]
 815. Freer RJ *et al.* (1980) [7387981]
 816. Frenster JD *et al.* (2023) [37354459]
 817. Fricker AC *et al.* (2009) [19285517]
 818. Fricks IP *et al.* (2009) [19339661]
 819. Fricks IP *et al.* (2008) [18252808]
 820. Frielle T *et al.* (1988) [2849109]
 821. Froestl W. (2011) [21428811]
 822. Froestl W *et al.* (1997) *In The GABA Receptors* Edited by Enna SJ, Bowery NG: Humana Press: 271-296 [ISBN: 0896034585]
 823. Fruchart-Gaillard C *et al.* (2006) [16439611]
 824. Fuchs AR *et al.* (1982) [6278592]
 825. Fujii R *et al.* (2002) [12118011]
 826. Fukukawa C *et al.* (2008) [18271942]
 827. Fukunaga K *et al.* (2001) [11560941]
 828. Fukusumi S *et al.* (2006) [16500002]
 829. Fukusumi S *et al.* (2003) [12960173]
 830. Fukuzawa T *et al.* (2013) [23922714]
 831. Furman CA *et al.* (2015) [25583363]
 832. Furuya WI *et al.* (2020) [31568840]
 833. Gabl M *et al.* (2018) [29602776]
 834. Gado F *et al.* (2019) [29990428]
 835. Galandrin S *et al.* (2006) [16901982]
 836. Galandrin S *et al.* (2008) [18403719]
 837. Galembo RA Jr *et al.* (1990) [2170649]
 838. Gallagher DM *et al.* (2024) [37714335]
 839. Gallo-Rodriguez C *et al.* (1994) [8126704]
 840. Gallwitz B *et al.* (1996) [8795084]
 841. Galvani S *et al.* (2015) [26268607]
 842. Galvez T *et al.* (2000) [10692480]
 843. Gama L *et al.* (2001) [11489900]
 844. Ganella DE *et al.* (2013) [23135160]
 845. Ganella DE *et al.* (2012) [22854307]
 846. Ganesh T *et al.* (2013) [23914286]
 847. Gao H *et al.* (2005) [15784721]
 848. Gao W *et al.* (2025) [40373963]
 849. Gao Y *et al.* (2021) [34194040]
 850. Gao ZG *et al.* (2000) [10267024]
 851. Gao ZG *et al.* (2004) [15193955]
 852. Gao ZG *et al.* (2004) [15476669]
 853. Garcia RA *et al.* (2021) [34466754]
 854. Gardell LR *et al.* (2007) [17519387]
 855. Gardella TJ *et al.* (1996) [7802701]
 856. Gardella TJ *et al.* (1995) [7896796]
 857. Gardella TJ *et al.* (2015) [25713287]
 858. Gardner J *et al.* (2012) [22155242]
 859. Gareau Y *et al.* (1996) *Bioorg Med Chem Lett* 6: 189-194
 860. Garelja ML *et al.* (2024) [37580864]
 861. Garelja ML *et al.* (2022) [34289083]
 862. Garelja ML *et al.* (2022) [34076887]
 863. Garin A *et al.* (2003) [14607932]
 864. Gasparini F *et al.* (2002) [11814808]
 865. Gasparini F *et al.* (1999) [10336568]
 866. Gasparini F *et al.* (1999) [10530811]
 867. Gasser A *et al.* (2015) [25831128]
 868. Gassmann M *et al.* (2004) [15240800]
 869. Gaster LM *et al.* (1998) [9548813]
 870. Gates E. (1998) [9735753]
 871. Gault VA *et al.* (2003) [12627321]
 872. Gavins FN *et al.* (2003) [12560218]
 873. Gavrilyuk V *et al.* (2005) [15715664]
 874. Gay EA *et al.* (2022) [35594150]
 875. Gay EA *et al.* (2023) [37541631]
 876. Gbahou F *et al.* (2022) [35983281]
 877. Gbahou F *et al.* (2006) [16432504]
 878. Ge X *et al.* (2018) [29233536]
 879. Ge Y *et al.* (2025) [40698130]
 880. Ge Y *et al.* (2020) [32239559]
 881. Gee CE *et al.* (2014) [24596089]
 882. Gehlert DR *et al.* (1996) [8632753]
 883. Generoso SF *et al.* (2015) [25751279]
 884. Genet C *et al.* (2010) [19911773]
 885. Geng Y *et al.* (2013) [24305054]
 886. Geng Y *et al.* (2016) [27434672]
 887. Geng Y *et al.* (2012) [22660477]
 888. Gentry PR *et al.* (2014) [24692176]
 889. Gentry PR *et al.* (2013) [24164599]
 890. Gentry PR *et al.* (2014) [25147929]
 891. Georgiadi A *et al.* (2021) [34016966]
 892. Georgsson J *et al.* (2014) [24937104]
 893. Georgsson J *et al.* (2015) [25875054]
 894. Gera L *et al.* (2006) [16368899]
 895. Gerald C *et al.* (1995) [7796807]
 896. Gerald C *et al.* (1996) [8700207]
 897. Gerald C *et al.* (1995) [7592910]
 898. Gerbino A *et al.* (2005) [16247029]
 899. Gergely P *et al.* (2012) [22646698]
 900. Gershon MD. (1999) [10429737]
 901. Geubelle P *et al.* (2017) [28160606]
 902. Ghoneim OM *et al.* (2006) [16782354]
 903. Giannuli C *et al.* (2012) [22262769]
 904. Giannotti D *et al.* (2000) [11063600]
 905. Giardina GA *et al.* (1996) [8691422]
 906. Giera S *et al.* (2015) [25607655]
 907. Giles H *et al.* (1989) [2924081]
 908. Gilet M *et al.* (2014) [25316608]
 909. Gilissen J *et al.* (2015) [26386312]
 910. Gilissen J *et al.* (2016) [26808164]
 911. Gillberg PG *et al.* (1998) [9671109]
 912. Gillis A *et al.* (2020) [32665252]
 913. Gilmore JL *et al.* (2021) [33492963]
 914. Gilmore JL *et al.* (2019) [30785748]
 915. Gingell JJ *et al.* (2014) [24169554]
 916. Ginsburg-Shmuel T *et al.* (2012) [22901672]
 917. Gironacci MM *et al.* (2011) [21670420]
 918. Gladue RP *et al.* (2003) [12909630]
 919. Glazenz U *et al.* (2018) [29735753]
 920. Glen A *et al.* (2024) [38295907]
 921. Glennon RA. (2003) [12825922]
 922. Glennon RA *et al.* (2000) [10715164]
 923. Glukhova A *et al.* (2017) [28235198]
 924. Gobeil F *et al.* (1996) [8901831]
 925. Gobeil F *et al.* (1996) [8735629]
 926. Gobeil Jr F *et al.* (2014) [24361511]
 927. Göblyös A *et al.* (2006) [16722654]
 928. Goldring WP *et al.* (2005) [15922596]
 929. Goldstein A *et al.* (1989) [2549383]
 930. Gomes I *et al.* (2013) [24043826]
 931. Gomes I *et al.* (2016) [27117253]
 932. Gomes I *et al.* (2020) [32393639]
 933. Gong DM *et al.* (2018) [29402834]
 934. Gong X *et al.* (1997) [9115216]
 935. González N *et al.* (2009) [19463875]
 936. González N *et al.* (2015) [26066663]
 937. Gonzalez-Cabrera PJ *et al.* (2008) [18708635]
 938. González-Gil I *et al.* (2020) [31790581]
 939. Goodfellow NM *et al.* (2012) [22539842]
 940. Goold CP *et al.* (2001) [11602681]
 941. Gordon S *et al.* (2011) [21952799]
 942. Gorlov IP *et al.* (2002) [12217959]
 943. Gorman DM *et al.* (2021) [34762432]
 944. Gorman DM *et al.* (2021) [34927012]
 945. Gorn AH *et al.* (1995) [7769107]
 946. Gorojankina T *et al.* (2013) [23448715]
 947. Gottlieb DJ *et al.* (2007) [17903308]
 948. Gouardères C *et al.* (2007) [17011599]
 949. Gouardères C *et al.* (2002) [12421602]
 950. Gouardères C *et al.* (2007) [17337079]
 951. Goudet C *et al.* (2012) [22223752]
 952. Gougat J *et al.* (2004) [14747609]
 953. Gouldson P *et al.* (2000) [10988332]
 954. Gourlet P *et al.* (1997) [9437716]
 955. Gourlet P *et al.* (1997) [9145428]
 956. Grätz L *et al.* (2023) [37516754]
 957. Grätz L *et al.* (2024) [37055379]
 958. Grätz L *et al.* (2024) [39213612]
 959. Grånäs C *et al.* (1999) [10513577]
 960. Graaf Cd *et al.* (2016) [27630114]
 961. Grailhe R *et al.* (2001) [11343685]
 962. Granberg KL *et al.* (2024) [38502782]
 963. Granier S *et al.* (2012) [22596164]
 964. Grant GE *et al.* (2009) [19450703]
 965. Grant MK *et al.* (2005) [16002459]
 966. Gravel S *et al.* (2010) [20956518]
 967. Greaves DR *et al.* (1997) [9294138]
 968. Greene TA *et al.* (2011) [21629661]
 969. Gregor P *et al.* (1996) [8641440]
 970. Gregori-Puigjané E *et al.* (2012) [22711801]
 971. Gregory KJ *et al.* (2021) [33361406]
 972. Gregory KJ *et al.* (2012) [22863693]
 973. Grieco P *et al.* (2000) [11150170]
 974. Grieco P *et al.* (2007) [17482720]

975. Grieco P *et al.* (2002) [12238917]
 976. Griffante C *et al.* (2005) [16158071]
 977. Grisshammer R *et al.* (1994) [7719707]
 978. Gromova P *et al.* (2009) [19453770]
 979. Gronert K *et al.* (2001) [11141472]
 980. Grosse J *et al.* (2014) [25028498]
 981. Grosse R *et al.* (2000) [10734055]
 982. Groves A *et al.* (2013) [23518370]
 983. Groves A *et al.* (2018) [30255127]
 984. Gründker C *et al.* (2002) [12237622]
 985. Grundt P *et al.* (2007) [17095222]
 986. Grundt P *et al.* (2007) [17672446]
 987. Gu ZF *et al.* (1995) [7529309]
 988. Guan D *et al.* (2021) [34855388]
 989. Guan XM *et al.* (2010) [20096642]
 990. Guard S *et al.* (1990) [1694464]
 991. Guerrero M *et al.* (2011) [21570287]
 992. Guerrero M *et al.* (2010) [22834040]
 993. Guerrero M *et al.* (2010) [23762933]
 994. Guerrini R *et al.* (1997) [9191955]
 995. Guerrini R *et al.* (2009) [19473027]
 996. Guilford WJ *et al.* (2004) [15056011]
 997. Guillon CD *et al.* (2007) [17234419]
 998. Gully D *et al.* (2002) [11907190]
 999. Gully D *et al.* (1997) [9023294]
 1000. Gulya K *et al.* (1986) [2872570]
 1001. Günther T *et al.* (2018) [30232095]
 1002. Guo D *et al.* (2012) [22324512]
 1003. Guo Y *et al.* (2011) [21712392]
 1004. Gupte J *et al.* (2012) [22575658]
 1005. Gurney A *et al.* (2012) [22753465]
 1006. Gusach A *et al.* (2019) [31811124]
 1007. Haas M *et al.* (2014) [24970757]
 1008. Habasque C *et al.* (2002) [11994538]
 1009. Habrian CH *et al.* (2019) [31804469]
 1010. Haffar BM *et al.* (1991) [1702423]
 1011. Haffke M *et al.* (2019) [31645725]
 1012. Haga K *et al.* (2012) [22278061]
 1013. Hagan RM *et al.* (1993) [8210508]
 1014. Hague C *et al.* (2004) [14718583]
 1015. Haidar M *et al.* (2017) [28100033]
 1016. Haidar M *et al.* (2019) [30906254]
 1017. Hale JJ *et al.* (2000) [10737756]
 1018. Hale JJ *et al.* (1998) [9804700]
 1019. Hall DA *et al.* (1999) [10188995]
 1020. Hall H *et al.* (2000) [11044889]
 1021. Halls ML *et al.* (2015) [25761609]
 1022. Halls ML *et al.* (2005) [15649866]
 1023. Halls ML *et al.* (2007) [17293890]
 1024. Hamann J *et al.* (2015) [25713288]
 1025. Hamann J *et al.* (2007) [17823986]
 1026. Hamann J *et al.* (2003) [12731063]
 1027. Hamann J *et al.* (1996) [9064337]
 1028. Hamblin MW *et al.* (1991) [1652050]
 1029. Hameg A *et al.* (2003) [12527336]
 1030. Hammann-Hänni A *et al.* (2023) [36285509]
 1031. Hamoud N *et al.* (2014) [24567399]
 1032. Han G *et al.* (1999) [10187777]
 1033. Han S *et al.* (2015) [26048791]
 1034. Hancock AA *et al.* (2004) [15033391]
 1035. Hancock AA *et al.* (1998) *Drug Development Research* **44**: 140-162
 1036. Handa BK *et al.* (1981) [6263640]
 1037. Hanessian S *et al.* (2003) [12502358]
 1038. Hannan FM *et al.* (2016) [27647839]
 1039. Hannedouche S *et al.* (2011) [21796212]
 1040. Hannon J *et al.* (2008) [18571247]
 1041. Hansen AH *et al.* (2018) [30247908]
 1042. Hansen C *et al.* (2009) [19651774]
 1043. Hansen W *et al.* (2010) [20200545]
 1044. Hanson J *et al.* (2013) [23643932]
 1045. Hanson MA *et al.* (2012) [22344443]
 1046. Hanus L *et al.* (1999) [10588688]
 1047. Happ JT *et al.* (2022) [36202993]
 1048. Harada K *et al.* (2006) [17074317]
 1049. Haramura M *et al.* (2002) [11806718]
 1050. Harford-Wright E *et al.* (2017) [29053791]
 1051. Hargrove DM *et al.* (2020) [32075870]
 1052. Harland SP *et al.* (1995) [8587429]
 1053. Harmar AJ. (2001) [11790261]
 1054. Harmar AJ *et al.* (1998) [9647867]
 1055. Harmar AJ *et al.* (2012) [122289055]
 1056. Harrison GS *et al.* (2004) [15613448]
 1057. Harrison T *et al.* (2001) [11708932]
 1058. Hartig PR *et al.* (1996) [8936345]
 1059. Hasegawa Y *et al.* (2003) [12554733]
 1060. Haskell CA *et al.* (2006) [16221874]
 1061. Hastrup H *et al.* (1996) [8985159]
 1062. Hata AN *et al.* (2003) [12721327]
 1063. Hatae N *et al.* (2007) [17312275]
 1064. Hatanaka T *et al.* (2013) [23239087]
 1065. Haugaard-Kedström LM *et al.* (2018) [30131342]
 1066. Haugaard-Kedström LM *et al.* (2011) [21384867]
 1067. Haugaard-Kedström LM *et al.* (2015) [25792111]
 1068. Hauger RL *et al.* (2003) [12615952]
 1069. Hauwert NJ *et al.* (2018) [29470065]
 1070. Hauwert NJ *et al.* (2019) [30735597]
 1071. Hawsworth OA *et al.* (2017) [28576324]
 1072. Hay DL *et al.* (2005) [15692146]
 1073. Hay DL *et al.* (2006) [16959943]
 1074. Hay DL *et al.* (2018) [29059473]
 1075. Hay DL *et al.* (2003) [12970090]
 1076. Hay DL *et al.* (2008) [18552275]
 1077. Hay DL *et al.* (2011) [21051558]
 1078. Hayallah AM *et al.* (2002) [11906291]
 1079. Hayashi S *et al.* (2009) [19125610]
 1080. Hayhoe RP *et al.* (2006) [16278303]
 1081. He F *et al.* (2024) [38326620]
 1082. He HQ *et al.* (2013) [23160941]
 1083. He HQ *et al.* (2017) [28335409]
 1084. He J *et al.* (2010) [19696113]
 1085. He L *et al.* (2000) [10669572]
 1086. He S *et al.* (2010) [20167483]
 1087. He S *et al.* (2012) [24900499]
 1088. He W *et al.* (2004) [15141213]
 1089. He Y *et al.* (2020) [31917615]
 1090. Heasley BH *et al.* (2004) [15125924]
 1091. Hecht JH *et al.* (1996) [8922387]
 1092. Hegde SS *et al.* (1997) [9113359]
 1093. Hegde SF *et al.* (1996) [8903510]
 1094. Heier RR *et al.* (1997) [9057850]
 1095. Heise CE *et al.* (2000) [10851239]
 1096. Heise CE *et al.* (2005) [15761110]
 1097. Heise CE *et al.* (2001) [11723223]
 1098. Heitman LH *et al.* (2009) [19161279]
 1099. Heitman LH *et al.* (2006) [16444290]
 1100. Hellfritsch C *et al.* (2012) [22616809]
 1101. Hellmann J *et al.* (2020) [32669442]
 1102. Hellyer SD *et al.* (2018) [29514854]
 1103. Hemstapat K *et al.* (2007) [17416742]
 1104. Henke BR *et al.* (1997) [9276016]
 1105. Henstridge CM *et al.* (2010) [20136841]
 1106. Herbert JM *et al.* (1993) [8395255]
 1107. Hermans E *et al.* (1997) [9283723]
 1108. Hern JA *et al.* (2010) [20133736]
 1109. Herpers B *et al.* (2022) [35469014]
 1110. Herr KJ *et al.* (2011) [21878565]
 1111. Herrick-Davis K *et al.* (2000) [10991983]
 1112. Herron DK *et al.* (1992) [1316967]
 1113. Hertzog DL *et al.* (2006) [16870432]
 1114. Hess JF *et al.* (1994) [8302267]
 1115. Hesselgesser J *et al.* (1998) [9551924]
 1116. Hesselgesser J *et al.* (1998) [9624164]
 1117. Hetherington SL *et al.* (2005) [15514209]
 1118. Heusler P *et al.* (2010) [20799027]
 1119. Heynen-Genel S *et al.* (2010) [22091481]
 1120. Hidaka K *et al.* (1995) [7777184]
 1121. Hieble JP. (2000) [10812954]
 1122. Hieble JP *et al.* (1995) [7658428]
 1123. Hieble JP *et al.* (1995) [7568329]
 1124. Hilditch A *et al.* (1995) [7853190]
 1125. Hill SJ *et al.* (1997) [9311023]
 1126. Hillard CJ *et al.* (1999) [10336536]
 1127. Hiller JG *et al.* (2020) [31754048]
 1128. Hillmann P *et al.* (2009) [19419204]
 1129. Hinuma S *et al.* (2000) [11025660]
 1130. Hirasawa A *et al.* (2005) [15619630]
 1131. Hirata T *et al.* (2011) [21819041]
 1132. Hirose H *et al.* (2001) [11303071]
 1133. Hirst RA *et al.* (1996) [8981483]
 1134. Hirst WD *et al.* (2003) [12663046]
 1135. Hirst WD *et al.* (2006) [17069795]
 1136. Hisatsune C *et al.* (2007) [17925404]
 1137. Hla T *et al.* (1990) [2160972]
 1138. Ho C *et al.* (1995) [7493018]
 1139. Hoare BL *et al.* (2019) [30594862]
 1140. Hoare SR *et al.* (2000) [10854439]
 1141. Hoare SR *et al.* (2000) [10882389]
 1142. Hobson AD *et al.* (2015) [26509640]
 1143. Hoch L *et al.* (2015) [25636740]
 1144. Hoffmann C *et al.* (2004) [14730417]
 1145. Hoffmann SH *et al.* (2000) [10894158]
 1146. Högberg C *et al.* (2011) [21143371]
 1147. Holenz J *et al.* (2005) [15771424]
 1148. Hollenberg MD *et al.* (2002) [12037136]
 1149. Hollenberg MD *et al.* (2008) [18477767]
 1150. Hollenberg MD *et al.* (1997) [9315351]
 1151. Hoppel G *et al.* (2001) [11196645]
 1152. Holloway AC *et al.* (2002) [11901215]
 1153. Holst B *et al.* (2003) [12907757]
 1154. Holst B *et al.* (2007) [16959833]
 1155. Holst B *et al.* (2009) [18923064]
 1156. Holst B *et al.* (2004) [15383539]
 1157. Homey B *et al.* (2000) [10725697]
 1158. Honczarenko M *et al.* (2005) [15990859]
 1159. Hong C *et al.* (2021) [33547286]
 1160. Hong CH *et al.* (2022) [34890841]
 1161. Hong DS *et al.* (2020) [32554609]
 1162. Hoppenz P *et al.* (2019) [31743956]
 1163. Horckmans M *et al.* (2022) [36532779]
 1164. Hori T *et al.* (2018) [29309055]
 1165. Horie K *et al.* (1995) [8564227]
 1166. Horwell DC *et al.* (1995) *Bioorg Med Chem Lett* **5**: 2501-2506
 1167. Hosken IT *et al.* (2015) [25257104]
 1168. Hosoi T *et al.* (2002) [12065583]

1169. Hosoya M *et al.* (2000) [10777510]
 1170. Hosoya M *et al.* (2000) [10887190]
 1171. Hossain MA *et al.* (2016) [30155023]
 1172. Hossain MA *et al.* (2023) [37200817]
 1173. Hossain MA *et al.* (2008) [18434306]
 1174. Hossain MA *et al.* (2010) [20043231]
 1175. Hossain MS *et al.* (2016) [26934370]
 1176. Hoyer D *et al.* (1994) [7938165]
 1177. Hoyer D *et al.* (2002) [11888546]
 1178. Hoyer D *et al.* (2004) [15135911]
 1179. Hoyer D *et al.* (2004) *Soc Neurosci Abstracts* -
 1180. Hsiao CC *et al.* (2018) [30559745]
 1181. Hsiao CC *et al.* (2019) [31130954]
 1182. Hsu SH *et al.* (2007) [17652154]
 1183. Hsu SY *et al.* (2000) [10935549]
 1184. Hsu SY *et al.* (2002) [11809971]
 1185. Hu MJ *et al.* (2018) [29770870]
 1186. Hu MJ *et al.* (2017) [28274616]
 1187. Hu X *et al.* (2024) [38776963]
 1188. Huang C *et al.* (2004) [12954603]
 1189. Huang D *et al.* (2024) [39082681]
 1190. Huang F *et al.* (2001) [12049493]
 1191. Huang P *et al.* (2018) [29804838]
 1192. Huang W *et al.* (2024) [39609406]
 1193. Huang W *et al.* (2015) [26245379]
 1194. Huang XP *et al.* (2015) [26550826]
 1195. Hudson BD *et al.* (2014) [24870406]
 1196. Hudson BD *et al.* (2012) [23066016]
 1197. Huet-Toral F *et al.* (2015) [25344385]
 1198. Huey R *et al.* (1985) [4202139]
 1199. Huffman JW *et al.* (1999) [10658595]
 1200. Hughes FM *et al.* (2010) [20481538]
 1201. Hughes J *et al.* (1990) [1975695]
 1202. Humphries RG *et al.* (1995) [7582510]
 1203. Humphries RG *et al.* (1994) [7858849]
 1204. Hunter JC *et al.* (1990) [2178014]
 1205. Hunter JC *et al.* (1993) [8474432]
 1206. Hutchinson DS *et al.* (2002) [11959793]
 1207. Hwang SB *et al.* (1988) [2841449]
 1208. Ichimura A *et al.* (2012) [22343897]
 1209. Ichtchenko K *et al.* (1999) [10026162]
 1210. Igawa Y *et al.* (2013) [23263450]
 1211. Iglarz M *et al.* (2008) [18780830]
 1212. Ignatov A *et al.* (2004) [15111018]
 1213. Ignatov A *et al.* (2003) [12574419]
 1214. Ignatov A *et al.* (2003) [14592418]
 1215. Ignatov A *et al.* (2006) [17001303]
 1216. Ignatowska-Jankowska BM *et al.* (2015) [26052038]
 1217. Ihara M *et al.* (1995) [7768260]
 1218. Iio K *et al.* (2023) [37043436]
 1219. IJzerman AP *et al.* (2022) [35302044]
 1220. Ikubo M *et al.* (2015) [25970039]
 1221. Illiano S *et al.* (2022) [36443381]
 1222. Im DS *et al.* (2000) [10799507]
 1223. Imai T *et al.* (1998) [9430724]
 1224. Imeri F *et al.* (2021) [33460688]
 1225. Imlach WL *et al.* (2015) [26104547]
 1226. Inngjerd M *et al.* (2001) [11154210]
 1227. Inoue A *et al.* (2012) [22983457]
 1228. Inoue A *et al.* (2019) [31160049]
 1229. Intelmann D *et al.* (2009) *Chemosensory Perception* 2: 118-132
 1230. Iredale PA *et al.* (1994) [8032613]
 1231. Irmscher S *et al.* (2019) [31273197]
 1232. Irukayama-Tomobe Y *et al.* (2017) [28507129]
 1233. Irwin DM. (2001) [11179772]
 1234. Isberg V *et al.* (2014) [24826842]
 1235. Ishibashi T *et al.* (2010) [20404009]
 1236. Ishikawa T *et al.* (2023) [37001988]
 1237. Ishiwata K *et al.* (2004) [15093820]
 1238. Isogaya M *et al.* (1999) [10531390]
 1239. Ito M *et al.* (2017) [28527783]
 1240. Ito M *et al.* (1993) [8349705]
 1241. Itoh Y *et al.* (2003) [12629551]
 1242. Ivanov AA *et al.* (2007) [17088057]
 1243. Ivanov AA *et al.* (2007) [17302398]
 1244. Ivell R *et al.* (2018) [30204868]
 1245. Ivell R *et al.* (2011) [20952422]
 1246. Iwamoto Y *et al.* (1987) [2437574]
 1247. Iyer MR *et al.* (2021) [33393392]
 1248. Izume T *et al.* (2020) [32001000]
 1249. Jörg M *et al.* (2021) [32851779]
 1250. Jackson RH *et al.* (1992) [1320692]
 1251. Jackson VA *et al.* (2016) [27091502]
 1252. Jacobson KA *et al.* (2011) [21484092]
 1253. Jacobson KA *et al.* (2020) [32037507]
 1254. Jacobson KA *et al.* (2006) [16518376]
 1255. Jacobson KA *et al.* (2009) [18600475]
 1256. Jacobson KA *et al.* (2002) [12213051]
 1257. Jacobson KA *et al.* (1997) [9364471]
 1258. Jacobson MA *et al.* (1995) [7558011]
 1259. Jacobson SG *et al.* (2008) [18463160]
 1260. Jagerschmidt A *et al.* (1996) [8720482]
 1261. Jaggupilli A *et al.* (2019) [30011231]
 1262. Jaggupilli A *et al.* (2018) [29799189]
 1263. Jakubík J *et al.* (1997) [9224827]
 1264. Jakubík J *et al.* (1995) [7562472]
 1265. Jakubík J *et al.* (2006) [16675658]
 1266. Jalan-Sakrikar N *et al.* (2014) [25225882]
 1267. Jane DE *et al.* (1996) [9121605]
 1268. Jansen FP *et al.* (1994) [7834183]
 1269. Janssens R *et al.* (1999) [10401562]
 1270. January B *et al.* (1997) [9295336]
 1271. Jara ZP *et al.* (2023) [36440576]
 1272. Jarvis MF *et al.* (1989) [2600819]
 1273. Jaspars LH *et al.* (2001) [11380941]
 1274. Jasper JR *et al.* (1995) [7475979]
 1275. Jasper JR *et al.* (1998) [9605427]
 1276. Jayasekara PS *et al.* (2014) [24712832]
 1277. Jenck F *et al.* (2000) [10758169]
 1278. Jenh CH *et al.* (1999) [10201891]
 1279. Jennings CA *et al.* (2003) [12890504]
 1280. Jensen RT *et al.* (2008) [18055507]
 1281. Jensen T *et al.* (2014) [25442311]
 1282. Jeon WJ *et al.* (2013) [23962466]
 1283. Jerning E *et al.* (1998) [9851589]
 1284. Ji X *et al.* (2001) [11266650]
 1285. Ji XD *et al.* (1999) [10624567]
 1286. Ji Y *et al.* (2023) [36882417]
 1287. Jia XC *et al.* (1991) [1922095]
 1288. Jiang JL *et al.* (1996) [8917655]
 1289. Jiang Y *et al.* (2003) [12714592]
 1290. Jiang Y *et al.* (2018) [29263243]
 1291. Jimenez-Vargas NN *et al.* (2018) [30012612]
 1292. Jin C *et al.* (2018) [30011199]
 1293. Jin C *et al.* (2008) [18487371]
 1294. Jinsmaa Y *et al.* (2001) [111179594]
 1295. Jo E *et al.* (2012) [22971058]
 1296. Jockers R *et al.* (1994) [7798201]
 1297. Johansson B *et al.* (1995) [7566470]
 1298. Johansson L *et al.* (1997) [9336327]
 1299. Johnson BG *et al.* (1999) [10530814]
 1300. Johnson MP *et al.* (2003) [12852748]
 1301. Johnson MP *et al.* (2005) [15717213]
 1302. Jolkonen M *et al.* (1994) [7925952]
 1303. Jones C *et al.* (1999) [10422787]
 1304. Jones CE *et al.* (2003) [12606753]
 1305. Jones CK *et al.* (2008) [18842902]
 1306. Jones DTD *et al.* (2023) [37120430]
 1307. Jones KA *et al.* (1998) [9872315]
 1308. Jones RM *et al.* (2000) [10822054]
 1309. Jonsson KB *et al.* (2001) [11159842]
 1310. Jordan BA *et al.* (1999) [10385123]
 1311. Jorgensen R *et al.* (2005) [15528268]
 1312. Joseph SS *et al.* (2004) [15060759]
 1313. Joseph SS *et al.* (2004) [15037517]
 1314. Joshi P *et al.* (2014) [24405707]
 1315. Juarranz MG *et al.* (1999) [10570056]
 1316. Juen Z *et al.* (2025) [40339580]
 1317. Jugus MJ *et al.* (2009) [19486006]
 1318. Jung M *et al.* (1997) [8978752]
 1319. Jung YH *et al.* (2021) [33787273]
 1320. Jüngling K *et al.* (2008) [18667157]
 1321. Juteau H *et al.* (2001) [11504634]
 1322. Küffer A *et al.* (2016) [27501152]
 1323. Kabarowski JH *et al.* (2001) [11474113]
 1324. Kabashima K *et al.* (2002) [11927615]
 1325. Kähkönen E *et al.* (2013) [23935037]
 1326. Kaku K *et al.* (2015) [25787200]
 1327. Kalant D *et al.* (2003) [12540846]
 1328. Kalant D *et al.* (2005) [15833747]
 1329. Kalinichev M *et al.* (2013) [23257312]
 1330. Kalipatnapu S *et al.* (2004) [15628665]
 1331. Kalk P *et al.* (2007) [17558436]
 1332. Kallupi M *et al.* (2010) [20974945]
 1333. Kamali F. (2001) [11757797]
 1334. Kamichi S *et al.* (2005) [15680955]
 1335. Kamohara M *et al.* (2005) [15823563]
 1336. Kanaoka Y *et al.* (2013) [23504326]
 1337. Kanatani A *et al.* (2000) [10872822]
 1338. Kane AJ *et al.* (2010) [20827226]
 1339. Kaneko S *et al.* (2024) [38740791]
 1340. Kanesaka M *et al.* (2007) [17486669]
 1341. Kang H *et al.* (2023) [36525977]
 1342. Kania A *et al.* (2017) [28098344]
 1343. Kania A *et al.* (2020) [32532885]
 1344. Kanke T *et al.* (2005) [15765104]
 1345. Kapas S *et al.* (1995) [7592696]
 1346. Kappel DB *et al.* (2019) [30652248]
 1347. Kapur A *et al.* (2009) [19723626]
 1348. Karamitri A *et al.* (2019) [30531911]
 1349. Kargl J *et al.* (2013) [23639803]
 1350. Karnik SS *et al.* (2015) [26315714]
 1351. Karpus ON *et al.* (2013) [23447688]
 1352. Karteris E *et al.* (2005) [15687100]
 1353. Katafuchi T *et al.* (2003) [12556539]
 1354. Kathmann M *et al.* (2006) [16489449]
 1355. Kato K *et al.* (2005) [15695169]
 1356. Katugampola SD *et al.* (2001) [11250876]
 1357. Katugampola SD *et al.* (2001) [11522606]
 1358. Kaupmann K *et al.* (1997) [9069281]
 1359. Kawabata A *et al.* (1999) [9862790]
 1360. Kawai M *et al.* (1992) [1732540]
 1361. Kawamata Y *et al.* (2003) [12524422]
 1362. Kawamata Y *et al.* (2001) [11336787]
 1363. Kawamoto H *et al.* (1999) [10602690]

1364. Kawamoto Y *et al.* (2018) [29208511]
 1365. Kazda CM *et al.* (2016) [26681715]
 1366. Keam SJ. (2025) [40760295]
 1367. Keam SJ. (2023) [37486545]
 1368. Keir MJ *et al.* (1999) [10521582]
 1369. Keiran N *et al.* (2019) [30962591]
 1370. Kelly E *et al.* (2023) [36170657]
 1371. Kelly E *et al.* (2015) [24973897]
 1372. Kelly LM *et al.* (2011) [21844396]
 1373. Kelly RP *et al.* (2015) [25656305]
 1374. Kemp PA *et al.* (2004) [15231488]
 1375. Kennedy AJ *et al.* (2018) [29279348]
 1376. Kennedy AJ *et al.* (2020) [33335291]
 1377. Kennedy AJ *et al.* (2016) [27742615]
 1378. Kennedy C *et al.* (2000) [10779375]
 1379. Kennedy K *et al.* (1995) [7654246]
 1380. Kennedy PC *et al.* (2011) [21632869]
 1381. Kennedy SP *et al.* (1998) [9535752]
 1382. Kennett GA *et al.* (1997) [9225286]
 1383. Keov P *et al.* (2014) [25006252]
 1384. Keov P *et al.* (2013) [23798605]
 1385. Khajehali E *et al.* (2018) [29777683]
 1386. Khanolkar AD *et al.* (1996) [8893848]
 1387. Khattar SK *et al.* (2006) [16369696]
 1388. Khawaja X *et al.* (1997) [9048968]
 1389. Khier-Fernández N *et al.* (2022) [35948083]
 1390. Khroyan TV *et al.* (2011) [21177476]
 1391. Khusal KG *et al.* (2015) [25324134]
 1392. Kiefer L *et al.* (2011) [21406038]
 1393. Kiesel LA *et al.* (2002) [12072036]
 1394. Kiguchi N *et al.* (2019) [30916003]
 1395. Kiguchi N *et al.* (2022) [35189108]
 1396. Kihara Y *et al.* (2014) [24602016]
 1397. Kikuchi C *et al.* (1999) [10052959]
 1398. Kilander MB *et al.* (2014) [24873871]
 1399. Kildsgaard J *et al.* (2000) [11067891]
 1400. Kim D *et al.* (2023) [36990220]
 1401. Kim DK *et al.* (2014) [24517231]
 1402. Kim GH *et al.* (2007) [17476309]
 1403. Kim HO *et al.* (1994) [7932588]
 1404. Kim HS *et al.* (2003) [14584948]
 1405. Kim HS *et al.* (2002) [11754592]
 1406. Kim J *et al.* (2025) [40195498]
 1407. Kim J *et al.* (1995) [7775460]
 1408. Kim JJ *et al.* (2012) [21959382]
 1409. Kim SV *et al.* (2013) [23661644]
 1410. Kim TH *et al.* (2013) [23721409]
 1411. Kim UK *et al.* (2003) [12595690]
 1412. Kim Y *et al.* (2024) [38600377]
 1413. Kim Y *et al.* (2024) [38789678]
 1414. Kim Y *et al.* (2013) [23541835]
 1415. Kim YC *et al.* (2000) [10737749]
 1416. Kim YC *et al.* (1996) [8863790]
 1417. Kim YC *et al.* (2005) [15913566]
 1418. Kim YK *et al.* (2013) [23147675]
 1419. Kimura I *et al.* (2011) [21518883]
 1420. Kimura T *et al.* (1994) [7921228]
 1421. Kimura Y *et al.* (2004) [14709324]
 1422. Kingston AE *et al.* (1998) [9680254]
 1423. Kinnebrew M *et al.* (2022) [35658032]
 1424. Kinney GG *et al.* (2005) [15608073]
 1425. Kinney WA *et al.* (2002) [12203418]
 1426. Kinsolving J *et al.* (2024) [38308843]
 1427. Kinsolving J *et al.* (2024) [39670643]
 1428. Kirby HR *et al.* (2010) [21079036]
 1429. Kirihara T *et al.* (2018) [29332128]
 1430. Kiselev E *et al.* (2015) [26303895]
 1431. Kiselev E *et al.* (2014) [25299434]
 1432. Kiss B *et al.* (2010) [20093397]
 1433. Kiss GN *et al.* (2012) [22968304]
 1434. Kitamura H *et al.* (2012) [22343749]
 1435. Kitaura M *et al.* (1999) [10488147]
 1436. Kitazawa T *et al.* (1997) [9416990]
 1437. Kitazawa T *et al.* (2017) [28242309]
 1438. Kitbunnadaj R *et al.* (2005) [15771452]
 1439. Kitbunnadaj R *et al.* (2004) [15115383]
 1440. Kittaka H *et al.* (2017) [28176353]
 1441. Kledal TN *et al.* (1997) [9287217]
 1442. Klein J *et al.* (1997) [9175608]
 1443. Klein MT *et al.* (2011) [21422162]
 1444. Klos A *et al.* (2013) [23383423]
 1445. Klotz KN *et al.* (1998) [9459566]
 1446. Knepper SM *et al.* (1995) [7616455]
 1447. Knierim AB *et al.* (2019) [31363148]
 1448. Knight AR *et al.* (2004) [15322733]
 1449. Knoflach F *et al.* (2001) [11606768]
 1450. Knudsen LB *et al.* (2000) [10794683]
 1451. Kobayashi A *et al.* (2012) [22991451]
 1452. Kobayashi T *et al.* (2010) [20580563]
 1453. Koe BK *et al.* (1992) *Drug Dev Res* **26**: 241-250
 1454. Koehl A *et al.* (2019) [30675062]
 1455. Koehl A *et al.* (2018) [29899455]
 1456. Koga H *et al.* (1994) *Bioorg Med Chem Lett* **4**: 1347-1352
 1457. Kogushi M *et al.* (2011) [21300059]
 1458. Kohl S *et al.* (2013) [23214402]
 1459. Köhler C *et al.* (1985) [4015674]
 1460. Kohno M *et al.* (2006) [16844083]
 1461. Koike H *et al.* (2001) [11451212]
 1462. Kojima D *et al.* (2011) [22043319]
 1463. Kojima M *et al.* (1999) [10604470]
 1464. Kolakowski Jr LF. (1994) [8081729]
 1465. Kolczewski S *et al.* (1999) [10465539]
 1466. Kong J *et al.* (2016) [26784385]
 1467. Kongsamut S *et al.* (2002) [12176106]
 1468. Konkel MJ *et al.* (2006) [16789730]
 1469. Konkel MJ *et al.* (2006) [16730981]
 1470. Kono M *et al.* (2017) [29079828]
 1471. Kono M *et al.* (2014) [24667638]
 1472. Konteatis ZD *et al.* (1994) [7930622]
 1473. Koo A *et al.* (2022) [35596811]
 1474. Koo C *et al.* (1982) [6285921]
 1475. Kop EN *et al.* (2005) [15693006]
 1476. Kop EN *et al.* (2009) [19428565]
 1477. Kopanchuk S *et al.* (2005) [15840392]
 1478. Kopin AS *et al.* (1992) [1373504]
 1479. Kordon SP *et al.* (2023) [36746957]
 1480. Kontagere S *et al.* (2004) [15448188]
 1481. Kotani M *et al.* (2001) [11457843]
 1482. Kotani M *et al.* (1995) [7476918]
 1483. Kotarsky K *et al.* (2003) [12565875]
 1484. Kottyan LC *et al.* (2009) [19641187]
 1485. Kovács A *et al.* (2003) [15107597]
 1486. Kovacs I *et al.* (1998) [9454790]
 1487. Kowala MC *et al.* (2004) [14718594]
 1488. Kowalski-Jahn M *et al.* (2021) [34757789]
 1489. Kozián DH *et al.* (2012) [22801643]
 1490. Koziélewicz P *et al.* (2020) [31707356]
 1491. Koziélewicz P *et al.* (2020) [31964872]
 1492. Kraja AT *et al.* (2013) [23192668]
 1493. Krasnoperov VG *et al.* (1997) [9208860]
 1494. Kraus A *et al.* (2009) [19072936]
 1495. Krause JE *et al.* (1997) [8990205]
 1496. Kraus AH *et al.* (1996) [8882612]
 1497. Kreienkamp HJ *et al.* (2000) [10964907]
 1498. Krepel SA *et al.* (2019) [31336833]
 1499. Krishna Kumar K *et al.* (2024) [38632403]
 1500. Krishnamoorthy S *et al.* (2010) [20080636]
 1501. Kritikou E *et al.* (2016) [27883026]
 1502. Kroeger KM *et al.* (2001) [11278883]
 1503. Kroeze WK *et al.* (2003) [12629531]
 1504. Krsmanovic LZ *et al.* (2003) [12591945]
 1505. Kruse AC *et al.* (2013) [24256733]
 1506. Ku GM *et al.* (2012) [22253604]
 1507. Kuc D *et al.* (2008) [18235993]
 1508. Kuc RE *et al.* (1995) [8587419]
 1509. Kuei C *et al.* (2007) [17606621]
 1510. Kühn B *et al.* (1996) [8961278]
 1511. Kuhn C *et al.* (2004) [15537898]
 1512. Kukkonen JP. (2016) [26582739]
 1513. Kukkonen JP. (2016) [27237973]
 1514. Kukkonen JP. (2013) [23034387]
 1515. Kukkonen JP. (2017) [27909990]
 1516. Kukkonen JP *et al.* (2024) [38902035]
 1517. Kukkonen JP *et al.* (2014) [23902572]
 1518. Kulagowski JJ *et al.* (1996) [8642550]
 1519. Kulkarni PM *et al.* (2016) [26529344]
 1520. Kull B *et al.* (1999) [9920286]
 1521. Kumagai J *et al.* (2002) [12114498]
 1522. Kumar KG *et al.* (2009) [19646498]
 1523. Kumar S *et al.* (2003) [12604693]
 1524. Kumar S *et al.* (2010) [19786130]
 1525. Kunishima N *et al.* (2000) [11069170]
 1526. Kupal D *et al.* (1994) [8013367]
 1527. Kurimoto E *et al.* (2019) [30856192]
 1528. Kurko D *et al.* (2014) [25080296]
 1529. Kursar JD *et al.* (1994) [8078486]
 1530. Kurth J *et al.* (2022) [35668669]
 1531. Kuzak AJ *et al.* (2009) [19542234]
 1532. Kuwano K *et al.* (2007) [17545310]
 1533. Kuwasako K *et al.* (2004) [14722252]
 1534. Kuwasako K *et al.* (2003) [12565884]
 1535. Kwakkenbos MJ *et al.* (2002) [11994511]
 1536. Kwon HS *et al.* (2023) [36982411]
 1537. Laas K *et al.* (2014) [23325374]
 1538. Labarrère P *et al.* (2003) [12943190]
 1539. Labbé-Jullié C *et al.* (1995) [7746272]
 1540. Lagerström MC *et al.* (2005) [15885496]
 1541. Lahti RA *et al.* (1993) [8102973]
 1542. Lahti RA *et al.* (1985) [2986999]
 1543. Lai E *et al.* (2008) [17882161]
 1544. Laitinen T *et al.* (2004) [15073379]
 1545. Lamb YN. (2018) [30194661]
 1546. Lameh J *et al.* (2010) [20354177]
 1547. Lan B *et al.* (2025) [40360475]
 1548. Lan R *et al.* (1999) [11741201]
 1549. Lan R *et al.* (1999) [10052983]
 1550. Lancaster E *et al.* (2010) [19962348]
 1551. Lang R *et al.* (2005) [15944009]
 1552. Lang R *et al.* (2022) [36601079]
 1553. Lang T *et al.* (2022) [35364812]
 1554. Lang T *et al.* (2020) [32437139]
 1555. Langmead CJ *et al.* (2008) [18454168]
 1556. Langmead CJ *et al.* (2006) [16207821]
 1557. Langmead CJ *et al.* (2004) [14691055]
 1558. Langmead CJ *et al.* (2000) [11030716]
 1559. Lansu K *et al.* (2017) [28288109]
 1560. Laporte R *et al.* (2011) [21411496]

1561. Lappano R *et al.* (2018) [28249728]
 1562. Laprairie RB *et al.* (2015) [26218440]
 1563. Laprairie RB *et al.* (2017) [28103441]
 1564. Larasati Y *et al.* (2022) [34915171]
 1565. Lau J *et al.* (2015) [26308095]
 1566. Lau OC *et al.* (2014) [24511227]
 1567. Laurie DJ *et al.* (1997) [9144651]
 1568. Lautner RQ *et al.* (2013) [23446738]
 1569. Lavreysen H *et al.* (2003) [12695537]
 1570. Lavreysen H *et al.* (2004) [15555631]
 1571. Lawrence AJ *et al.* (2002) [12110614]
 1572. Lazareno S *et al.* (1995) [7651370]
 1573. Lazareno S *et al.* (2004) [14722259]
 1574. Lazareno S *et al.* (1998) [9495826]
 1575. Lazareno S *et al.* (2000) [10860942]
 1576. Lazareno S *et al.* (2002) [12435818]
 1577. Lazarowski ER *et al.* (1995) [8564228]
 1578. Lazarowski ER *et al.* (1996) [8825364]
 1579. Łazewski D *et al.* (2009) [19329325]
 1580. Le Bourdonnec B *et al.* (2008) [18313920]
 1581. Le Bourdonnec B *et al.* (2008) [18788723]
 1582. Le Bourdonnec B *et al.* (2009) [19694468]
 1583. Le Mercier A *et al.* (2021) [33875597]
 1584. Le MT *et al.* (2002) [12006574]
 1585. Le Poul E *et al.* (2003) [12711604]
 1586. Le Y *et al.* (1999) [10586077]
 1587. Leach K *et al.* (2011) [21300722]
 1588. Leach K *et al.* (2016) [27002221]
 1589. Leach K *et al.* (2020) [32467152]
 1590. Leach K *et al.* (2010) [19940843]
 1591. Leach K *et al.* (2014) [24111791]
 1592. Leach K *et al.* (2013) [23372019]
 1593. Leños-Miranda A *et al.* (2003) [12843188]
 1594. Leban JJ *et al.* (1993) [8446610]
 1595. Ledein L *et al.* (2020) [32627178]
 1596. Ledent C *et al.* (2005) [15956199]
 1597. Leduc M *et al.* (2009) [19584306]
 1598. Lee A. (2022) [34826105]
 1599. Lee DK *et al.* (2001) [11574155]
 1600. Lee DK *et al.* (2005) [15486224]
 1601. Lee HS *et al.* (2020) [32133341]
 1602. Lee J *et al.* (2005) [15955843]
 1603. Lee J *et al.* (1992) [1379593]
 1604. Lee JW *et al.* (2016) [27759003]
 1605. Lee MC *et al.* (2008) [181379608]
 1606. Lee YM *et al.* (1993) [7681836]
 1607. Lee YN *et al.* (2020) [32231393]
 1608. Leeb-Lundberg LM *et al.* (2005) [15734727]
 1609. Lees JA *et al.* (2023) [37741852]
 1610. Lefranc B *et al.* (2021) [34299587]
 1611. Legrand F *et al.* (2014) [24530099]
 1612. Legros C *et al.* (2013) [23698757]
 1613. Lehmann F *et al.* (2009) [19481466]
 1614. Lehmann F *et al.* (2005) [15781415]
 1615. Lehmann F *et al.* (2007) [17112638]
 1616. Lei P *et al.* (2022) [35413679]
 1617. Lei Y *et al.* (2014) [24632739]
 1618. Leibowitz SF *et al.* (1992) [1283559]
 1619. Leja J *et al.* (2009) [18953328]
 1620. Lejeune F *et al.* (1997) [9067310]
 1621. Lelianaova VG *et al.* (1997) [9261169]
 1622. Lembo PM *et al.* (2002) [11850634]
 1623. Lennertz L *et al.* (2012) [22078257]
 1624. Leonard CS *et al.* (2014) [23848055]
 1625. Leonard SK *et al.* (2008) [18311561]
 1626. Leonardi A *et al.* (1997) [9190863]
 1627. Leopoldo M *et al.* (2007) [17649988]
 1628. Leopoldo M *et al.* (2008) [18800769]
 1629. Leprince J *et al.* (2017) [28613414]
 1630. Leprince J *et al.* (2008) [17931747]
 1631. Lesage A *et al.* (2020) [32636746]
 1632. Lesage A *et al.* (2022) [35086057]
 1633. Lesage AS *et al.* (1998) [9605573]
 1634. LeSarge JC *et al.* (2019) [31312406]
 1635. LeSarge JC *et al.* (2023) [36527934]
 1636. Leurs R *et al.* (1994) [7921611]
 1637. Leuthauser K *et al.* (2000) [11023820]
 1638. Lever JR *et al.* (1998) [9696425]
 1639. Levit A *et al.* (2014) [24285091]
 1640. Levchenko E *et al.* (2025) [39438674]
 1641. Lewis TA *et al.* (2004) [15482930]
 1642. Leyens JE *et al.* (1996) [8967979]
 1643. Li AH *et al.* (1998) [9703464]
 1644. Li C *et al.* (2024) [39024101]
 1645. Li H *et al.* (2019) [30986796]
 1646. Li J *et al.* (2022) [34951123]
 1647. Li J *et al.* (2020) [32358586]
 1648. Li JJ *et al.* (2004) [15027861]
 1649. Li JX *et al.* (2013) [23123351]
 1650. Li M *et al.* (2019) [31911345]
 1651. Li R *et al.* (2013) [23239822]
 1652. Li T *et al.* (2014) [25324681]
 1653. Li W *et al.* (2022) [35020407]
 1654. Li X *et al.* (2013) [23821037]
 1655. Li X *et al.* (2002) [12013525]
 1656. Li XX *et al.* (2020) [32611725]
 1657. Li XX *et al.* (2020) [33551801]
 1658. Li XX *et al.* (2019) [31160390]
 1659. Li XX *et al.* (2023) [36776827]
 1660. Li XX *et al.* (2020) [32682759]
 1661. Li Y *et al.* (2018) [30131171]
 1662. Li Z *et al.* (2021) [34349037]
 1663. Liang BT *et al.* (2010) *In A3 Adenosine Receptors from Cell Biology to Pharmacology and Therapeutics* Edited by Borea PA: Springer: [ISBN: 9789048131440]
 1664. Liang M *et al.* (2000) [10748002]
 1665. Liao Q *et al.* (2022) [35385323]
 1666. Liaw CW *et al.* (2009) [19630535]
 1667. Liddle J *et al.* (2008) [18032036]
 1668. Liebing AD *et al.* (2025) [39838520]
 1669. Liebscher I *et al.* (2011) [21097509]
 1670. Liebscher I *et al.* (2014) [25533341]
 1671. Liebscher I *et al.* (2013) [23518449]
 1672. Liggett SB. (2003) [15090197]
 1673. Ligneau X *et al.* (2000) [11090094]
 1674. Liljebriis C *et al.* (1995) [7830272]
 1675. Lim HD *et al.* (2006) [17154494]
 1676. Lim HD *et al.* (2005) [15947036]
 1677. Limonta P *et al.* (2003) [14726258]
 1678. Lin DC *et al.* (2002) [11886876]
 1679. Lin DC *et al.* (2012) [22859723]
 1680. Lin G *et al.* (2021) [34946593]
 1681. Lin GY *et al.* (2020) [32235863]
 1682. Lin H *et al.* (2025) [40080544]
 1683. Lin H *et al.* (2022) [35982227]
 1684. Lin HH *et al.* (2000) [10903844]
 1685. Lin HH *et al.* (2010) [21618834]
 1686. Lin Q *et al.* (1999) [9890897]
 1687. Lin S *et al.* (2021) [34135510]
 1688. Lin X *et al.* (2023) [36639690]
 1689. Lin X *et al.* (2022) [36063995]
 1690. Lind S *et al.* (2019) [31085160]
 1691. Linden J *et al.* (1999) [10496952]
 1692. Lindenmaier LB *et al.* (2019) [30758284]
 1693. Lindfors L *et al.* (2020) [32354568]
 1694. Lindqvist A *et al.* (2023) [38077141]
 1695. Lindsley CW *et al.* (2004) [15537338]
 1696. Lindström E *et al.* (1999) [10385255]
 1697. Linz K *et al.* (2014) [24713140]
 1698. Litschig S *et al.* (1999) [10051528]
 1699. Littlewood-Evans A *et al.* (2016) [27481132]
 1700. Littmann T *et al.* (2015) [26306764]
 1701. Liu B *et al.* (2022) [35482870]
 1702. Liu C *et al.* (2005) [15465925]
 1703. Liu C *et al.* (2003) [14522967]
 1704. Liu C *et al.* (2003) [14522968]
 1705. Liu C *et al.* (2012) [22434674]
 1706. Liu C *et al.* (2001) [11179434]
 1707. Liu C *et al.* (2001) [11561071]
 1708. Liu C *et al.* (2009) [19047060]
 1709. Liu C *et al.* (2011) [21796211]
 1710. Liu D *et al.* (2022) [35143305]
 1711. Liu D *et al.* (2025) [40178480]
 1712. Liu F *et al.* (2024) [39298584]
 1713. Liu JJ *et al.* (2012) [22267580]
 1714. Liu JJ *et al.* (2009) [19369576]
 1715. Liu Q *et al.* (1999) [10581185]
 1716. Liu Q *et al.* (2009) [20004959]
 1717. Liu S *et al.* (2022) [35136060]
 1718. Liu S *et al.* (1998) [9822540]
 1719. Liu X *et al.* (2020) [32483378]
 1720. Liu X *et al.* (2017) [28548278]
 1721. Liu Z *et al.* (2019) [31652254]
 1722. Llinares M *et al.* (1999) [10231715]
 1723. Lobo MK *et al.* (2007) [17934457]
 1724. Loetscher M *et al.* (1994) [8276799]
 1725. Loetscher P *et al.* (1998) [19712844]
 1726. Logue SF *et al.* (2009) [19796684]
 1727. Londregan AT *et al.* (2013) [23337601]
 1728. Long DD *et al.* (2012) [22959244]
 1729. Longrois D *et al.* (2012) [22342278]
 1730. Lopes P *et al.* (1995) [8577380]
 1731. Lopez VM *et al.* (2008) [18828673]
 1732. Lopez-Gimenez JF *et al.* (2001) [11562430]
 1733. LopezJimenez ND *et al.* (2005) [15780750]
 1734. Lorenzen A *et al.* (1996) [8937447]
 1735. Louis SN *et al.* (1999) [10079020]
 1736. Lovenberg TW *et al.* (2000) [10869375]
 1737. Lu J *et al.* (2025) [40141387]
 1738. Lu X *et al.* (2005) [15944007]
 1739. Lu X *et al.* (2010) [20660766]
 1740. Lu ZL *et al.* (2007) [17452338]
 1741. Lucchelli A *et al.* (1997) [9283717]
 1742. Luginina A *et al.* (2019) [31633023]
 1743. Luker T *et al.* (2011) [21944852]
 1744. Lum AM *et al.* (2010) [20149256]
 1745. Lumley P *et al.* (1989) [2527074]
 1746. Lundberg AS *et al.* (2025) [40427162]
 1747. Lundell I *et al.* (1995) [7493937]
 1748. Lundkvist J *et al.* (1996) [8874139]
 1749. Luo J *et al.* (2009) [19605502]
 1750. Luo P *et al.* (2025) [39788969]
 1751. Luo R *et al.* (2011) [21768377]
 1752. Luo X *et al.* (2015) [25514935]
 1753. Lüttichau HR. (2010) [20044480]
 1754. Lüttichau HR *et al.* (2003) [12554737]
 1755. Luttrell LM *et al.* (2010) [20427692]

1756. Lyapina E *et al.* (2022) [35961984]
 1757. Lynch KR *et al.* (1999) [10391245]
 1758. M'Kadmi C *et al.* (2019) [30543423]
 1759. Ma B *et al.* (2021) [33738061]
 1760. Ma L *et al.* (2009) [19717450]
 1761. Ma L *et al.* (2016) [26808470]
 1762. Ma Q *et al.* (2021) [33872671]
 1763. Ma S *et al.* (2007) [17071007]
 1764. Ma S *et al.* (2017) [27774604]
 1765. Macaluso NJ *et al.* (2011) [21560248]
 1766. MacDonald E *et al.* (1997) [9227000]
 1767. Machwate M *et al.* (2001) [11408598]
 1768. Macias-Ceja DC *et al.* (2019) [30279517]
 1769. MacKenzie RG *et al.* (1994) [7907989]
 1770. MacLennan SJ *et al.* (1997) [9283709]
 1771. Maddox JF *et al.* (1996) [8551217]
 1772. Madsen K *et al.* (2011) [21831646]
 1773. Madsen P *et al.* (1998) [9857085]
 1774. Madsen U *et al.* (2005) [15996690]
 1775. Maeda DY *et al.* (2014) [25254640]
 1776. Maeda K *et al.* (2006) [16476734]
 1777. Maeda K *et al.* (2001) [11454872]
 1778. Maeda S *et al.* (2021) [34108205]
 1779. Maeda S *et al.* (2020) [32646996]
 1780. Maekawa A *et al.* (2009) [19561298]
 1781. Maggiolini M *et al.* (2004) [15090535]
 1782. Maguire JJ *et al.* (1995) [7647976]
 1783. Maguire JJ *et al.* (2000) [11015293]
 1784. Maguire JJ *et al.* (2009) [19325074]
 1785. Maier DL *et al.* (2009) [19401496]
 1786. Maïga A *et al.* (2013) [23935897]
 1787. Maina T *et al.* (2017) [28267454]
 1788. Maiti K *et al.* (2003) [14651258]
 1789. Maj M *et al.* (2003) [14573382]
 1790. Malgouris C *et al.* (1993) [8472747]
 1791. Malherbe P *et al.* (2009) [19751316]
 1792. Malherbe P *et al.* (2009) [19542319]
 1793. Malherbe P *et al.* (1999) [10216218]
 1794. Malherbe P *et al.* (2008) [18536733]
 1795. Malherbe P *et al.* (2010) [20404073]
 1796. Mallart S *et al.* (2021) [33555858]
 1797. Mallee JJ *et al.* (2002) [11847213]
 1798. Mamedova LK *et al.* (2004) [15081875]
 1799. Mamillapalli R *et al.* (2010) [20032198]
 1800. Mancuso G *et al.* (2015) [26501253]
 1801. Mandala S *et al.* (2002) [11923495]
 1802. Manglik A *et al.* (2015) [25981665]
 1803. Manglik A *et al.* (2012) [22437502]
 1804. Mani BK *et al.* (2019) [31424424]
 1805. Manning DR *et al.* (2015) [26179037]
 1806. Mansi R *et al.* (2021) [34830920]
 1807. Mansi R *et al.* (2011) [20717822]
 1808. Mantey S *et al.* (1993) [7684815]
 1809. Mantey SA *et al.* (2004) [15102928]
 1810. Mantey SA *et al.* (1997) [9325344]
 1811. Mao C *et al.* (2024) [38215752]
 1812. Marathe GK *et al.* (1999) [10497200]
 1813. Marazziti D *et al.* (2009) [19398891]
 1814. Marazziti D *et al.* (2011) [21372109]
 1815. Marazziti D *et al.* (2007) [17519329]
 1816. March DR *et al.* (2004) [15044616]
 1817. Martin P *et al.* (2012) [21777185]
 1818. Marini P *et al.* (2013) [23711022]
 1819. Marroni F *et al.* (2009) [20031603]
 1820. Marsango S *et al.* (2022) [32869860]
 1821. Marsango S *et al.* (2018) [29146505]
 1822. Martínez-Gil N *et al.* (2022) [35434450]
 1823. Marteau F *et al.* (2003) [12815166]
 1824. Martin M *et al.* (2022) [35175798]
 1825. Martin PL *et al.* (1996) [8632314]
 1826. Martin S *et al.* (2002) [12360476]
 1827. Maruoka H *et al.* (2010) [20446735]
 1828. Maruoka H *et al.* (2011) [21528910]
 1829. Maruyama T *et al.* (2001) [11454473]
 1830. Maruyama T *et al.* (2002) [12419312]
 1831. Marwari S *et al.* (2019) [31220339]
 1832. Masuda Y *et al.* (2002) [12054613]
 1833. Mathiasen S *et al.* (2020) [32778842]
 1834. Mathiesen JM *et al.* (2006) [16418339]
 1835. Mathiesen JM *et al.* (2003) [12684257]
 1836. Mathieu MC *et al.* (2005) [16154494]
 1837. Matmati M *et al.* (2007) [17108056]
 1838. Matsufuji T *et al.* (2015) [25497965]
 1839. Matsufuji T *et al.* (2014) [24412111]
 1840. Matsumoto M *et al.* (2001) [11549267]
 1841. Matsuura B *et al.* (2005) [15677347]
 1842. Matsuura B *et al.* (2002) [11781320]
 1843. Matsuura B *et al.* (2006) [16531413]
 1844. Matthes H *et al.* (1993) [8450829]
 1845. Mattsson C *et al.* (2005) [16055331]
 1846. Matuszek MA *et al.* (1998) [9718274]
 1847. Maudsley S *et al.* (2004) [15492280]
 1848. May LT *et al.* (2007) [17525129]
 1849. Mayeux PR *et al.* (1991) [1830308]
 1850. Mayo KE *et al.* (2003) [12615957]
 1851. Mazella J *et al.* (1996) [8795617]
 1852. McAllister G *et al.* (1992) [1608964]
 1853. McAtee LC *et al.* (2004) [15261275]
 1854. McCafferty GP *et al.* (2007) [17395790]
 1855. McCall RB *et al.* (2005) [15980060]
 1856. McCall RB *et al.* (1994) [7965808]
 1857. McClellan KJ *et al.* (1998) [9878991]
 1858. McCreath KJ *et al.* (2015) [25352636]
 1859. McDonald J *et al.* (2003) [12967935]
 1860. McDonald JK *et al.* (2022) [35380782]
 1861. McGuire JJ *et al.* (2004) [14976230]
 1862. McHugh D *et al.* (2010) [20346144]
 1863. McHugh D *et al.* (2006) [16207832]
 1864. McHugh D *et al.* (2012) [21595653]
 1865. McKeage K. (2015) [25859983]
 1866. McKinnell RM *et al.* (2013) [23756062]
 1867. McKnight AJ *et al.* (1996) [8550607]
 1868. McLatchie LM *et al.* (1998) [9620797]
 1869. Mead EJ *et al.* (2007) [17023533]
 1870. Medhurst AD *et al.* (2007) [17327487]
 1871. Medhurst AD *et al.* (2003) [12603839]
 1872. Meena CL *et al.* (2016) [26854379]
 1873. Meis S *et al.* (2010) [19815812]
 1874. Méjean A *et al.* (1995) [8719421]
 1875. Mende F *et al.* (2018) [30301804]
 1876. Meng J *et al.* (2022) [35681029]
 1877. Meng T *et al.* (2008) [18358099]
 1878. Methven L *et al.* (2009) [19572943]
 1879. Methven L *et al.* (2009) [19888965]
 1880. Metzemaekers M *et al.* (2020) [32238918]
 1881. Meyer MD *et al.* (1997) [9379432]
 1882. Meyer MR *et al.* (2018) [28343901]
 1883. Meyer RC *et al.* (2013) [23690594]
 1884. Meyerhof W. (1998) [9600011]
 1885. Meyerhof W *et al.* (2010) [20022913]
 1886. Meyrath M *et al.* (2020) [32561830]
 1887. Miale J *et al.* (2000) [10683202]
 1888. Miale J *et al.* (2000) [11030734]
 1889. Miale J *et al.* (2000) [10821780]
 1890. Miao Y *et al.* (2020) [32818433]
 1891. Michaelian N *et al.* (2021) [34016973]
 1892. Michel AD *et al.* (1990) [1970500]
 1893. Michel MC *et al.* (1998) [9549761]
 1894. Michel MC *et al.* (2016) [26808167]
 1895. Michel MC *et al.* (2010) [20517594]
 1896. Middlemiss DN *et al.* (1999) [10443589]
 1897. Mierau J *et al.* (1995) [7664822]
 1898. Migeotte I *et al.* (2005) [15623572]
 1899. Mihara S *et al.* (1998) [9548403]
 1900. Millan MJ *et al.* (1994) [7988633]
 1901. Millan MJ *et al.* (1998) [9732398]
 1902. Millan MJ *et al.* (2000) [10869410]
 1903. Millan MJ *et al.* (2002) [12388666]
 1904. Millan MJ *et al.* (2000) [10611634]
 1905. Millan MJ *et al.* (1995) [7473180]
 1906. Millar R *et al.* (2001) [11493674]
 1907. Millar RP. (2005) [16140177]
 1908. Millar RP *et al.* (2004) [15082521]
 1909. Miller BE *et al.* (2015) [26092545]
 1910. Miller JH *et al.* (1991) [1941609]
 1911. Miller RL *et al.* (2015) [26526853]
 1912. Million M *et al.* (2003) [12957366]
 1913. Minamino N *et al.* (1985) [3839674]
 1914. Minneman KP *et al.* (1994) [7969082]
 1915. Miranda LP *et al.* (2008) [18412318]
 1916. Mirzadegan T *et al.* (2000) [10770925]
 1917. Mistry SN *et al.* (2013) [23614528]
 1918. Mitselos A *et al.* (2007) [17074305]
 1919. Mitsukawa K *et al.* (2022) [35589803]
 1920. Mitsukawa K *et al.* (2024) [39242684]
 1921. Mitsukawa K *et al.* (2005) [16339898]
 1922. Miura S *et al.* (1999) [10066768]
 1923. Miwa K *et al.* (2011) [21657270]
 1924. Miyabe Y *et al.* (2019) [31076525]
 1925. Miyazaki H *et al.* (2018) [29724589]
 1926. Mizuguchi T *et al.* (1997) [9113361]
 1927. Mizuno H *et al.* (2020) [32894513]
 1928. Mizuno H *et al.* (2019) [30463988]
 1929. Mochizuki M *et al.* (2017) [28174066]
 1930. Moeller I *et al.* (1997) [9166749]
 1931. Mogha A *et al.* (2013) [24227709]
 1932. Moguevsky N *et al.* (1994) [7925364]
 1933. Mogul AS *et al.* (2025) [40866560]
 1934. Mohr M *et al.* (2004) [15163212]
 1935. Molenaar P *et al.* (1992) [1472961]
 1936. Molenaar P *et al.* (1997) [9117106]
 1937. Molinari EJ *et al.* (1996) [8773460]
 1938. Mollay C *et al.* (1999) [10422759]
 1939. Mollereau C *et al.* (2001) [11325787]
 1940. Mollereau C *et al.* (2002) [12242085]
 1941. Mollereau C *et al.* (1996) [8849681]
 1942. Mollereau C *et al.* (1994) [8137918]
 1943. Mombaerts P. (2004) [15034552]
 1944. Monczor F *et al.* (2003) [12869657]
 1945. Monk KR *et al.* (2009) [19745155]
 1946. Monk KR *et al.* (2011) [21613327]
 1947. Monk PN *et al.* (2007) [17603557]
 1948. Monn JA *et al.* (2015) [25602126]
 1949. Monn JA *et al.* (1999) [10090786]
 1950. Monneret G *et al.* (2003) [12490611]
 1951. Montrose-Rafizadeh C *et al.* (1997) [9261127]
 1952. Moo EV *et al.* (2018) [30213802]
 1953. Moody TW *et al.* (2002) [11931347]
 1954. Moody TW *et al.* (2015) [25554218]

1955. Moody TW *et al.* (2004) [15134870]
 1956. Moore E *et al.* (2020) [31992609]
 1957. Moore EL *et al.* (2012) [21871019]
 1958. Moore K *et al.* (2009) [19723586]
 1959. Moreland RB *et al.* (2005) [16153699]
 1960. Moreno D *et al.* (2000) [11068102]
 1961. Moreno Delgado D *et al.* (2017) [28661401]
 1962. Moreno P *et al.* (2018) [29410320]
 1963. Moreno P *et al.* (2013) [23892571]
 1964. Moreno P *et al.* (2016) [26981612]
 1965. Morfis M *et al.* (2008) [18599553]
 1966. Morgado-Valle C *et al.* (2023) [35066612]
 1967. Morgan K *et al.* (2003) [12538601]
 1968. Mori K *et al.* (2005) [15635449]
 1969. Mori M *et al.* (1999) [10548501]
 1970. Moriconi A *et al.* (2014) [25385614]
 1971. Morinelli TA *et al.* (1989) [2530338]
 1972. Morini G *et al.* (2021) [34307435]
 1973. Morishima S *et al.* (2007) [17162094]
 1974. Moriya H *et al.* (1999) [10374898]
 1975. Moriya Y *et al.* (2019) [30044673]
 1976. Morley AD *et al.* (2012) [22094028]
 1977. Moro O *et al.* (1997) [8995389]
 1978. Moro O *et al.* (1999) [10438479]
 1979. Morokata T *et al.* (2006) [16339911]
 1980. Moroni F *et al.* (2002) [12015200]
 1981. Moroni F *et al.* (1997) [9152378]
 1982. Morris CD *et al.* (2005) [15956965]
 1983. Morse KL *et al.* (2001) [11181941]
 1984. Morton MF *et al.* (2011) [21493750]
 1985. Mosberg HI *et al.* (1983) [6310598]
 1986. Motoike T *et al.* (2016) [27140610]
 1987. Mould R *et al.* (2014) [23692283]
 1988. Moulin A *et al.* (2013) [22798076]
 1989. Muccioli G *et al.* (2001) [11314756]
 1990. Muda M *et al.* (2005) [16051677]
 1991. Muff R *et al.* (1999) [10342886]
 1992. Mufti F *et al.* (2020) [32551012]
 1993. Muley MM *et al.* (2016) [26140667]
 1994. Müller A *et al.* (2013) [23335960]
 1995. Müller A *et al.* (2014) [25516095]
 1996. Müller A *et al.* (2015) [26505631]
 1997. Müller T *et al.* (2003) [12727981]
 1998. Munk SA *et al.* (1996) [8784451]
 1999. Muñoz M *et al.* (2020) [32401556]
 2000. Munro TA *et al.* (2013) [23976952]
 2001. Murai N *et al.* (2017) [28859883]
 2002. Murakami A *et al.* (2010) [20097776]
 2003. Murakami M *et al.* (2008) [18466763]
 2004. Murphy PM. (2002) [12037138]
 2005. Murphy PM *et al.* (2000) [10699158]
 2006. Murza A *et al.* (2016) [26986036]
 2007. Mutel V *et al.* (2000) [11080213]
 2008. Muto T *et al.* (2007) [17360426]
 2009. Myslivecek J. (2022) [36148314]
 2010. Nabizadeh JA *et al.* (2016) [27183625]
 2011. Nag S *et al.* (2023) [37375167]
 2012. Nagahara T *et al.* (2015) [26267383]
 2013. Nagase T *et al.* (2008) [18598020]
 2014. Nagata-Kuroiwa R *et al.* (2011) [21390312]
 2015. Nagiri C *et al.* (2019) [31263780]
 2016. Naka M *et al.* (1992) [1386885]
 2017. Nakahata T *et al.* (2018) [29478803]
 2018. Nakajima Y *et al.* (1993) [8389366]
 2019. Nakamura M *et al.* (1991) [1657923]
 2020. Nakamura M *et al.* (1992) [1333988]
 2021. Nakamura S *et al.* (2000) [10780976]
 2022. Nakamura T *et al.* (2000) [11118334]
 2023. Nakane M *et al.* (2005) [15992586]
 2024. Nakao K *et al.* (2007) [17495127]
 2025. Nambi P *et al.* (1994) [8301559]
 2026. Nambu H *et al.* (2011) [21971119]
 2027. Namour F *et al.* (2016) [26852904]
 2028. Nanamori M *et al.* (2004) [15308762]
 2029. Nandagopal S *et al.* (2022) [34819308]
 2030. Napier C *et al.* (2005) [16298345]
 2031. Napier C *et al.* (1999) [10193663]
 2032. Narukawa M *et al.* (2011) [21272567]
 2033. Näsman J *et al.* (2000) [10799315]
 2034. Nasrollahi-Shirazi S *et al.* (2016) [27451411]
 2035. Navarro G *et al.* (2015) [25926444]
 2036. Navarro-Sánchez M *et al.* (2024) [38710334]
 2037. Nawaratne V *et al.* (2010) [20406819]
 2038. Nawaratne V *et al.* (2008) [18628403]
 2039. Naya A *et al.* (2003) [12614873]
 2040. Neale JH. (2011) [21740441]
 2041. Nederpelt I *et al.* (2016) [26398856]
 2042. Nederpelt I *et al.* (2016) [26774084]
 2043. Nef S *et al.* (1999) [10391220]
 2044. Negishi M *et al.* (1995) [7608175]
 2045. Negoro N *et al.* (2010) [24900210]
 2046. Negri L *et al.* (2005) [16113687]
 2047. Neill JD. (2002) [11861490]
 2048. Nelson DL *et al.* (1999) [9933142]
 2049. Nelson DL *et al.* (2010) [20855361]
 2050. Nelson G *et al.* (2001) [11509186]
 2051. Nelson JW *et al.* (2014) [24259417]
 2052. Nemeth EF. (2013) [24050279]
 2053. Nemeth EF *et al.* (2001) [11561095]
 2054. Nemeth EF *et al.* (1998) [9520489]
 2055. Nergårdh R *et al.* (2005) [13718870]
 2056. Neschadim A *et al.* (2014) [24812057]
 2057. Neumeier JL *et al.* (2003) [14613319]
 2058. Neveu C *et al.* (2012) [22800498]
 2059. Newfield RS *et al.* (2023) [37216921]
 2060. Newman-Tancredi A *et al.* (2000) [11040052]
 2061. Newman-Tancredi A *et al.* (1999) [10431754]
 2062. Newman-Tancredi A *et al.* (1998) [9760039]
 2063. Newman-Tancredi A *et al.* (2009) [19154445]
 2064. Newman-Tancredi A *et al.* (1998) [9550290]
 2065. Newman-Tancredi A *et al.* (1992) [1386736]
 2066. Nguyen AT *et al.* (2016) [27683013]
 2067. Nguyen T *et al.* (2001) [11179435]
 2068. Ni YY *et al.* (2014) [24574718]
 2069. Nickolls SA *et al.* (2003) [12604699]
 2070. Nicole P *et al.* (2000) [10801840]
 2071. Nie YY *et al.* (2012) [22410249]
 2072. Niedernberg A *et al.* (2003) [12618218]
 2073. Nielsen MS *et al.* (1999) [10085125]
 2074. Nieto-Posadas A *et al.* (2012) [22101604]
 2075. Nikaido Y *et al.* (2015) [25425658]
 2076. Nile AH *et al.* (2018) [29632413]
 2077. Nilsson I *et al.* (2002) [11738246]
 2078. Nilsson NE *et al.* (2003) [12684041]
 2079. Ning Y *et al.* (2008) [18724386]
 2080. Nishi M *et al.* (2019) [30608334]
 2081. Nishimura T *et al.* (2012) [22632972]
 2082. Nishiyama K *et al.* (2017) [28851764]
 2083. Nishizawa N *et al.* (2016) [27589480]
 2084. Niswender CM *et al.* (2010) [20026717]
 2085. Niswender CM *et al.* (2008) [18664603]
 2086. Niswender CM *et al.* (2016) [27441572]
 2087. No authors listed. (2005) [16498716]
 2088. Noble F *et al.* (1999) [10581329]
 2089. Noda M *et al.* (2003) [12558985]
 2090. Nonaka Y *et al.* (2005) [16185654]
 2091. Norel X *et al.* (2020) [32962984]
 2092. Nosjean O *et al.* (2000) [10913150]
 2093. Nosjean O *et al.* (2001) [11331072]
 2094. Nothacker HP *et al.* (1999) [10559967]
 2095. Nothacker HP *et al.* (2000) [11093801]
 2096. Nowak S *et al.* (2018) [30009876]
 2097. Nunes VS *et al.* (2025) [40727226]
 2098. Nybo ML *et al.* (2023) [36688818]
 2099. Nygaard R *et al.* (2013) [23374348]
 2100. O'Flaherty JT *et al.* (1998) [9829988]
 2101. O'Sullivan ML *et al.* (2012) [22405201]
 2102. O'Sullivan SE. (2007) [17704824]
 2103. Obiefuna PC *et al.* (2005) [16020631]
 2104. Obika K *et al.* (1995) [8719417]
 2105. Ochi T *et al.* (2005) [15686911]
 2106. Oda T *et al.* (2000) [10973974]
 2107. Oertel BG *et al.* (2009) [19116204]
 2108. Offermanns S *et al.* (2011) [21454438]
 2109. Ogita T *et al.* (1997) [9038918]
 2110. Oh da Y *et al.* (2014) [24997608]
 2111. Oh DY *et al.* (2010) [20813258]
 2112. Ohashi T *et al.* (2015) [25959255]
 2113. Ohinata K *et al.* (2002) [11814627]
 2114. Ohki-Hamazaki H *et al.* (1997) [9367152]
 2115. Ohlmann P *et al.* (2013) [22892887]
 2116. Ohsu T *et al.* (2010) [19892707]
 2117. Ohta H *et al.* (2003) [14500756]
 2118. Ohtaki T *et al.* (1999) [10601261]
 2119. Ohtaki T *et al.* (2001) [11385580]
 2120. Oka S *et al.* (2007) [17765871]
 2121. Oka S *et al.* (2010) [20361937]
 2122. Oka S *et al.* (2009) [18845565]
 2123. Okamoto H *et al.* (1998) [9765227]
 2124. Okamura N *et al.* (2008) [18337476]
 2125. Okamura N *et al.* (2007) [17669576]
 2126. Okawa H *et al.* (1999) [10369464]
 2127. Okinaga S *et al.* (2003) [12899627]
 2128. Okuda-Ashitaka E *et al.* (1996) [8940129]
 2129. Okuno T *et al.* (2008) [18378794]
 2130. Olender T *et al.* (2008) [19129093]
 2131. Olianias MC *et al.* (2020) [32007501]
 2132. Olianias MC *et al.* (1999) [9862767]
 2133. Olianias MC *et al.* (2000) [11015294]
 2134. Olianias MC *et al.* (1999) [10576595]
 2135. Oliva P *et al.* (2024) [39195256]
 2136. Olson WC *et al.* (2006) Patent number: US7122185B2.
 2137. Ongali B *et al.* (2006) [16689671]
 2138. Ongini E *et al.* (1999) [9933143]
 2139. Oo ML *et al.* (2007) [17237497]
 2140. Opgenorth TJ *et al.* (1996) [8632312]
 2141. Osada M *et al.* (2002) [12445827]
 2142. Osborn O *et al.* (2012) [22653059]
 2143. Osei-Owusu P *et al.* (2019) [31534221]
 2144. Oshima HS *et al.* (2024) [39511145]

2145. Ott TR *et al.* (2006) [16904643]
 2146. Otto M *et al.* (2004) [14570896]
 2147. Oury-Donat F *et al.* (1995) [7616392]
 2148. Overington JP *et al.* (2006) [17139284]
 2149. Overton HA *et al.* (2006) [16517404]
 2150. Ozenil M *et al.* (2020) [32717485]
 2151. Ozoux ML *et al.* (2020) [32332113]
 2152. Padmanabhan S *et al.* (2009) [19059244]
 2153. Palacios JM *et al.* (2017) [28265714]
 2154. Palani A *et al.* (2012) [24900372]
 2155. Palani A *et al.* (2001) [11585437]
 2156. Palchaudhuri MR *et al.* (1998) [9851694]
 2157. Palmer SM *et al.* (2018) [30201408]
 2158. Pan KS *et al.* (2020) [32973499]
 2159. Pan S *et al.* (2013) [24900670]
 2160. Pan S *et al.* (2006) [17114004]
 2161. Pan Y *et al.* (2019) [30886579]
 2162. Pancani T *et al.* (2015) [26508634]
 2163. Pandey S *et al.* (2021) [34582793]
 2164. Pandey S *et al.* (2019) [31036565]
 2165. Pandey S *et al.* (2020) [32402749]
 2166. Pang L *et al.* (1998) [9832122]
 2167. Pantel J *et al.* (2006) [16511605]
 2168. Panula P *et al.* (2015) [26084539]
 2169. Parent JL *et al.* (1996) [8798529]
 2170. Park D *et al.* (2007) [17960134]
 2171. Parker CA *et al.* (2012) [22223878]
 2172. Parker EM *et al.* (1996) [8863519]
 2173. Parody TR *et al.* (2004) [15207250]
 2174. Paruchuri S *et al.* (2009) [19822647]
 2175. Pasternak GW *et al.* (2013) [24076545]
 2176. Patacchini R *et al.* (2003) [14645137]
 2177. Patane MA *et al.* (1998) [9548811]
 2178. Patankar JV *et al.* (2021) [34239062]
 2179. Patat O *et al.* (2016) [27476656]
 2180. Patel P *et al.* (2008) [18292294]
 2181. Patel S *et al.* (1996) [8967990]
 2182. Patel YC *et al.* (1994) [7988476]
 2183. Patil DN *et al.* (2023) [37490546]
 2184. Patil NA *et al.* (2016) [26824523]
 2185. Patra C *et al.* (2013) [24082093]
 2186. Patra MC *et al.* (2014) [24938207]
 2187. Pauli A *et al.* (2014) [24407481]
 2188. Pauwels PJ *et al.* (1988) [2462161]
 2189. Pauwels PJ *et al.* (2003) [12649300]
 2190. Pawson AJ *et al.* (2008) [18039780]
 2191. Payza K. (2003) *In The Delta Receptor*
 Edited by Chang KJ: CRC Press: 261-275 [ISBN:
 0824740319]
 2192. Pazos A *et al.* (1984) [6519175]
 2193. Pearlstein R *et al.* (2003) [12747773]
 2194. Pederick DT *et al.* (2021) [34083484]
 2195. Pederick DT *et al.* (2023) [36939320]
 2196. Pei XF *et al.* (1998) [9622546]
 2197. Peirce SM *et al.* (2001) [11406470]
 2198. Pellegrini-Giampietro DE *et al.* (1996)
 [8799579]
 2199. Pellicciari R *et al.* (2009) [20014870]
 2200. Peltonen JM *et al.* (1998) [9760042]
 2201. Pena A *et al.* (2007) [17495006]
 2202. Pena A *et al.* (2007) [17300166]
 2203. Pendergast W *et al.* (2001) [11206448]
 2204. Peng C *et al.* (2024) [39154373]
 2205. Peng J *et al.* (2023) [37895951]
 2206. Peng S *et al.* (2023) [36724251]
 2207. Peng Y *et al.* (2018) [29398112]
 2208. Peralta EG *et al.* (1988) [2841607]
 2209. Peralta EG *et al.* (1987) [3443095]
 2210. Perdonà E *et al.* (2011) [21034740]
 2211. Pereira JP *et al.* (2009) [19597478]
 2212. Pérez-García E *et al.* (2006) [16701210]
 2213. Peri L *et al.* (2024) [39557861]
 2214. Perkins AV *et al.* (1995) [7595134]
 2215. Perlman S *et al.* (1995) [7829475]
 2216. Perretti M *et al.* (2002) [12368905]
 2217. Perretti M *et al.* (1995) [7610983]
 2218. Perretti M *et al.* (2020) [32954491]
 2219. Perron A *et al.* (2005) [15637074]
 2220. Perryman R *et al.* (2022) [35917342]
 2221. Pertwee RG. (2012) [23108552]
 2222. Pertwee RG. (2000) [11060760]
 2223. Pertwee RG *et al.* (2010) [21079038]
 2224. Peter MG *et al.* (1995) [7881728]
 2225. Peters A *et al.* (2019) [31120900]
 2226. Petersen J *et al.* (2017) [28790300]
 2227. Petersen KF *et al.* (2001) [11719833]
 2228. Petersen PS *et al.* (2011) [21784784]
 2229. Petersen SC *et al.* (2015) [25695270]
 2230. Petitet F *et al.* (1996) [8733746]
 2231. Petrel C *et al.* (2003) [14506236]
 2232. Petremann M *et al.* (2020) [31347148]
 2233. Petrie WK *et al.* (2013) [24379833]
 2234. Petrucci V *et al.* (2017) [28842619]
 2235. Pflimlin E *et al.* (2019) [31413801]
 2236. Pham V *et al.* (2004) [14623894]
 2237. Phebus LA *et al.* (1997) [9395253]
 2238. Piali L *et al.* (2017) [29226621]
 2239. Piao X *et al.* (2004) [15044805]
 2240. Pihlavisto M *et al.* (1998) [9824686]
 2241. Pillaiyar T *et al.* (2023) [38060818]
 2242. Pin JP *et al.* (2002) [12769621]
 2243. Pin JP *et al.* (2016) [27905440]
 2244. Pin JP *et al.* (2009) [19723778]
 2245. Pin JP *et al.* (1999) [10443583]
 2246. Pin JP *et al.* (2004) [15451400]
 2247. Pin JP *et al.* (2007) [17329545]
 2248. Pinard A *et al.* (2010) [20655485]
 2249. Ping YQ *et al.* (2021) [33408414]
 2250. Ping YQ *et al.* (2022) [35418678]
 2251. Pisegna JR *et al.* (2000) [11193823]
 2252. Pitkin SL *et al.* (2010) [20605969]
 2253. Pittolo S *et al.* (2014) [25173999]
 2254. Pizzonero M *et al.* (2014) [25380412]
 2255. Planagumà A *et al.* (2013) [23607720]
 2256. Plöckinger U *et al.* (2012) [22065857]
 2257. Pohl SL *et al.* (1969) [4305077]
 2258. Poirier B *et al.* (2020) [32487716]
 2259. Poirier B *et al.* (2024) [38450758]
 2260. Poon MM *et al.* (2024) [38719983]
 2261. Popova JS *et al.* (1995) [7798909]
 2262. Popova NV *et al.* (2007) [17695324]
 2263. Popova NV *et al.* (2008) [18620529]
 2264. Popp BD *et al.* (2004) [14744619]
 2265. Porter RH *et al.* (2005) [16040814]
 2266. Portoghese PS *et al.* (1987) [2444704]
 2267. Portoghese PS *et al.* (1988) [2832195]
 2268. Poslunsey MS *et al.* (2025) [39660766]
 2269. Posokhova E *et al.* (2015) [25558062]
 2270. Poulain R *et al.* (2001) [11585433]
 2271. Poulter S *et al.* (2023) [37077397]
 2272. Powell WS *et al.* (1999) [9920859]
 2273. Powell WS *et al.* (1992) [1326548]
 2274. Power CA *et al.* (1997) [9294137]
 2275. Power ME *et al.* (2024) [37748201]
 2276. Powers AS *et al.* (2023) [36782010]
 2277. Powers SP *et al.* (1988) [3410633]
 2278. Poyner DR *et al.* (2002) [12037140]
 2279. Pradhan B *et al.* (2024) [38959401]
 2280. Prat M *et al.* (2009) [19653626]
 2281. Price MJ. (2017) [27886821]
 2282. Price MR *et al.* (2005) [16113085]
 2283. Priestley ES *et al.* (2022) [35729784]
 2284. Primus RJ *et al.* (1997) [9262371]
 2285. Procopiou PA *et al.* (2010) [20462258]
 2286. Procopiou PA *et al.* (2011) [21381763]
 2287. Proia RL *et al.* (2015) [25831442]
 2288. Prömel S *et al.* (2013) [23850273]
 2289. Prömel S *et al.* (2012) [22837050]
 2290. Pronin AN *et al.* (2007) [17702579]
 2291. Prossnitz ER *et al.* (2015) [26023144]
 2292. Prossnitz ER *et al.* (2015) [26189910]
 2293. Proudman RGW *et al.* (2022) [36101495]
 2294. Proudman RGW *et al.* (2022) [35224877]
 2295. Proudman RGW *et al.* (2021) [34355529]
 2296. Proudman RGW *et al.* (2020) [32608144]
 2297. Pruneau D *et al.* (1999) [10596852]
 2298. Pugsley TA *et al.* (1995) [8531103]
 2299. Purcell RH *et al.* (2017) [28891236]
 2300. Pustovit RV *et al.* (2021) [34661082]
 2301. Puthanveedu M *et al.* (2025) [40289379]
 2302. Putula J *et al.* (2014) [25132134]
 2303. Putula J *et al.* (2011) [21362456]
 2304. Pydi SP *et al.* (2015) [25844797]
 2305. Qi T *et al.* (2013) [22946511]
 2306. Qi X *et al.* (2020) [32929279]
 2307. Qi X *et al.* (2019) [31168089]
 2308. Qian Y *et al.* (2022) [36309016]
 2309. Qian Y *et al.* (2024) [39223191]
 2310. Qin CX *et al.* (2017) [28169296]
 2311. Qin CX *et al.* (2022) [35797341]
 2312. Qu Q *et al.* (2023) [36411392]
 2313. Qu X *et al.* (2022) [35418679]
 2314. Quancard J *et al.* (2012) [22999882]
 2315. Quaresma BMCS *et al.* (2019) [31285236]
 2316. Quinn SJ *et al.* (2004) [15201280]
 2317. Quinn SJ *et al.* (1998) [9677383]
 2318. Quinn SJ *et al.* (1997) [9357776]
 2319. Quinton L *et al.* (2010) [20015090]
 2320. Quitterer U *et al.* (2019) [30503206]
 2321. Quock RM *et al.* (1997) [9178661]
 2322. Rabe P *et al.* (2022) [34813893]
 2323. Rabiet MJ *et al.* (2005) [16025565]
 2324. Rabiet MJ *et al.* (2011) [21543323]
 2325. Raczka KA *et al.* (2010) [20628342]
 2326. Rafahi M *et al.* (2017) [28306255]
 2327. Rahman MA *et al.* (1999) [10212487]
 2328. Rahman MT *et al.* (2023) [36749855]
 2329. Rajaratnam SM *et al.* (2009) [19054552]
 2330. Rakowski E *et al.* (2005) [16171813]
 2331. Ramachandran R *et al.* (2011) [21576245]
 2332. Ramachandran R *et al.* (2017) [28126849]
 2333. Ramachandran R *et al.* (2012) [22212680]
 2334. Ramage AG *et al.* (2008) [19086344]
 2335. Ramanjaneya M *et al.* (2013) [23964068]
 2336. Ramos-Alvarez I *et al.* (2022) [35644465]
 2337. Ramos-Alvarez I *et al.* (2019) [30971479]
 2338. Ramos-Álvarez I *et al.* (2015) [25976083]
 2339. Ramos-Álvarez I *et al.* (2016) [26524625]
 2340. Ramsay D *et al.* (2004) [15266013]
 2341. Randeve HS *et al.* (2001) [11600545]

2342. Ranjan AK *et al.* (2022) [35328566]
 2343. Rao A *et al.* (2017) [28476646]
 2344. Rappas M *et al.* (2020) [31860301]
 2345. Rashid M *et al.* (2003) [12738034]
 2346. Rask-Andersen M *et al.* (2014) [24016212]
 2347. Rasmussen SG *et al.* (2011) [21228869]
 2348. Rasmussen SG *et al.* (2011) [21772288]
 2349. Ratnala VR *et al.* (2004) [15206929]
 2350. Raufman JP *et al.* (1991) [1704369]
 2351. Rautenberg M *et al.* (2011) [21183593]
 2352. Ravasi S *et al.* (2002) [11996896]
 2353. Ravenscroft G *et al.* (2015) [26004201]
 2354. Ravn-Boess N *et al.* (2023) [37938973]
 2355. Rawashdeh O *et al.* (2011) [21182402]
 2356. Rawat V *et al.* (2023) [36654746]
 2357. Ray M *et al.* (2020) [32513900]
 2358. Raychowdhury MK *et al.* (1994) [8034687]
 2359. Raynor K *et al.* (1994) [8114680]
 2360. Read C *et al.* (2016) [27475715]
 2361. Read C *et al.* (2019) [31492821]
 2362. Reavill C *et al.* (1999) [10188965]
 2363. Reavill C *et al.* (2000) [10945872]
 2364. Regard JB *et al.* (2008) [18984166]
 2365. Regoli D *et al.* (1998) [9650825]
 2366. Reid RC *et al.* (2014) [25259874]
 2367. Reid RC *et al.* (2013) [24257095]
 2368. Reiners J *et al.* (2005) [16301216]
 2369. Reinscheid RK *et al.* (2005) [16144971]
 2370. Resnati M *et al.* (2002) [11818541]
 2371. Revankar CM *et al.* (2005) [15705806]
 2372. Revel FG *et al.* (2011) [21525407]
 2373. Rexen Ulven E *et al.* (2018) [29968758]
 2374. Reyes-Alcaraz A *et al.* (2016) [26907960]
 2375. Reynaud R *et al.* (2012) [22466334]
 2376. Reynolds EE *et al.* (1995) [7733918]
 2377. Reynolds GP *et al.* (1995) [7780656]
 2378. Rezagoum M *et al.* (2006) [16443751]
 2379. Rhee MH *et al.* (1997) [9379442]
 2380. Ricci A *et al.* (1994) [8051291]
 2381. Ricci A *et al.* (1995) [7759603]
 2382. Riccio G *et al.* (2018) [29293331]
 2383. Rice AS *et al.* (2014) [24507377]
 2384. Rice HC *et al.* (2019) [30630900]
 2385. Richard F *et al.* (2001) [11723247]
 2386. Richard-Bildstein S *et al.* (2020) [33314938]
 2387. Richards MH *et al.* (1995) [7620715]
 2388. Richardson RM *et al.* (2003) [12626541]
 2389. Riddy DM *et al.* (2017) [27864425]
 2390. Rigney N *et al.* (2022) [35863332]
 2391. Rinaldi-Carmona M *et al.* (1994) [8070571]
 2392. Rinaldi-Carmona M *et al.* (1998) [9454810]
 2393. Rinaldi-Carmona M *et al.* (1996) [8614277]
 2394. Rinne MK *et al.* (2018) [30194937]
 2395. Riobo NA *et al.* (2006) [16885213]
 2396. Rivaail L *et al.* (2004) [15351779]
 2397. Rivier J *et al.* (2002) [12361401]
 2398. Rivier J *et al.* (1991) [1850267]
 2399. Rivier JE *et al.* (2014) [24269930]
 2400. Rivkees SA *et al.* (1999) [9920910]
 2401. Rizzi A *et al.* (1997) [9095082]
 2402. Rizzi A *et al.* (2007) [17532097]
 2403. Robas N *et al.* (2003) [12915402]
 2404. Robben JH *et al.* (2009) [19776718]
 2405. Robertson MJ *et al.* (2022) [36396979]
 2406. Rodriguez AL *et al.* (2010) [20923853]
 2407. Rodriguez-Sinovas A *et al.* (1997) [9142926]
 2408. Roecker AJ *et al.* (2014) [24376006]
 2409. Rohrer SP *et al.* (1998) [9784130]
 2410. Roland WS *et al.* (2014) [24722342]
 2411. Roland WS *et al.* (2013) [24117141]
 2412. Roland WS *et al.* (2011) [21942422]
 2413. Romano M *et al.* (1996) [8757340]
 2414. Rook JM *et al.* (2018) [29701957]
 2415. Rook JM *et al.* (2015) [25937172]
 2416. Roos RS *et al.* (1997) [9211859]
 2417. Rorick-Kehn LM *et al.* (2014) [24071566]
 2418. Rosenbaum DM *et al.* (2011) [21228876]
 2419. Rosengren AH *et al.* (2010) [19965390]
 2420. Roseweir AK *et al.* (2009) [19321788]
 2421. Rosier A *et al.* (1996) [9027929]
 2422. Ross RA *et al.* (1999) [10188977]
 2423. Roth BL *et al.* (2002) [12192085]
 2424. Roth BL *et al.* (1994) [7908055]
 2425. Rothman RB *et al.* (2000) [11104741]
 2426. Roudnitzky N *et al.* (2015) [26406243]
 2427. Roush ED *et al.* (1998) [9654151]
 2428. Roussin A *et al.* (2005) [16129413]
 2429. Roux S *et al.* (1997) [9399983]
 2430. Rovati GE *et al.* (1992) [1329767]
 2431. Rowley M *et al.* (1996) [8642551]
 2432. Royer JF *et al.* (2007) [17714552]
 2433. Rubic T *et al.* (2008) [18820681]
 2434. Ruffing N *et al.* (1998) [9790730]
 2435. Ruffner H *et al.* (2012) [22815884]
 2436. Rühmann A *et al.* (2002) [11835994]
 2437. Ruiu S *et al.* (2003) [12663689]
 2438. Ruiz-Ferrer M *et al.* (2011) [21858136]
 2439. Ruiz-Medina J *et al.* (2011) [21352831]
 2440. Russell B *et al.* (2021) [33119328]
 2441. Russell FD *et al.* (1996) [8904635]
 2442. Russell JL *et al.* (2012) [22462679]
 2443. Russo AF *et al.* (2023) [36454193]
 2444. Ruzza C *et al.* (2012) [22342393]
 2445. Ruzza C *et al.* (2015) [25692025]
 2446. Ruzza C *et al.* (2010) [20172007]
 2447. Ryan PJ *et al.* (2013) [24297931]
 2448. Ryan RR *et al.* (1999) [10454496]
 2449. Ryberg E *et al.* (2007) [17876302]
 2450. Ryman-Rasmussen JP *et al.* (2007) [17067639]
 2451. Rytova V *et al.* (2019) [30891856]
 2452. Saar I *et al.* (2013) [23600864]
 2453. Sabbatini FM *et al.* (2010) [20593439]
 2454. Sabik OL *et al.* (2020) [32937138]
 2455. Sabroe I *et al.* (2000) [10854442]
 2456. Sairam MR. (1989) [2542111]
 2457. Saito M *et al.* (1997) [9264324]
 2458. Sakai A *et al.* (2022) [35194900]
 2459. Sako Y *et al.* (2019) [30089885]
 2460. Sakurai T *et al.* (1998) [9491897]
 2461. Sakurai T *et al.* (2014) [24486398]
 2462. Sakurai T *et al.* (2010) [20965151]
 2463. Sakurai T *et al.* (1990) [2175397]
 2464. Salašová A *et al.* (2017) [28697798]
 2465. Sallinen J *et al.* (2007) [17220913]
 2466. Salvatore CA *et al.* (2008) [18039958]
 2467. Salvatore CA *et al.* (1993) [8234299]
 2468. Sampson AK *et al.* (2008) [18711010]
 2469. Sams AG *et al.* (2010) [20684563]
 2470. Sandborn WJ *et al.* (2021) [34587385]
 2471. Sanger GJ. (2014) [24438586]
 2472. Sanger GJ *et al.* (2011) [21531468]
 2473. Sanger GJ *et al.* (2013) [23189978]
 2474. Sanger GJ *et al.* (2009) [19374732]
 2475. Sanna MG *et al.* (2004) [14732717]
 2476. Sanna MG *et al.* (2006) [16829954]
 2477. Sano H *et al.* (2004) [15203211]
 2478. Sapiëha P *et al.* (2008) [18836459]
 2479. Sarau HM *et al.* (1999) [10462554]
 2480. Sarau HM *et al.* (2001) [11226387]
 2481. Sarau HM *et al.* (1997) [9190866]
 2482. Sarau HM *et al.* (1997) [9336350]
 2483. Sato H *et al.* (2007) [17825251]
 2484. Sato H *et al.* (2022) [36122913]
 2485. Sato M *et al.* (2007) [17717109]
 2486. Sato M *et al.* (2008) [18684840]
 2487. Sato T *et al.* (2015) [26385885]
 2488. Sato Y *et al.* (1996) [8982677]
 2489. Saussy Jr DL *et al.* (1996) [8764344]
 2490. Sautel F *et al.* (1995) [7756621]
 2491. Sautel F *et al.* (1995) [8531087]
 2492. Savall BM *et al.* (2014) [24495018]
 2493. Savard M *et al.* (2016) [26565554]
 2494. Savard M *et al.* (2013) [23362191]
 2495. Scanlan TS *et al.* (2004) [15146179]
 2496. Scarr E *et al.* (2008) [18957051]
 2497. Schüß C *et al.* (2023) [37339079]
 2498. Schüß C *et al.* (2021) [33595306]
 2499. Schachter JB *et al.* (1997) [9154346]
 2500. Schaeferling B *et al.* (2003) [12970106]
 2501. Schaffhauser H *et al.* (2003) [14500736]
 2502. Schally AV *et al.* (2004) [15350601]
 2503. Schally AV *et al.* (1999) [10542394]
 2504. Schebb NH *et al.* (2022) [35308198]
 2505. Schechter LE *et al.* (2008) [17625499]
 2506. Schepetkin IA *et al.* (2014) [25450672]
 2507. Schepetkin IA *et al.* (2007) [17229869]
 2508. Schiöth H *et al.* (2021) [33486136]
 2509. Schiller PW *et al.* (1993) [8230106]
 2510. Schiöth HB *et al.* (2005) [15862553]
 2511. Schiöth HB *et al.* (1995) [7774675]
 2512. Schiöth HB *et al.* (1998) [9630346]
 2513. Schlachter SK *et al.* (1997) [9098699]
 2514. Schmid HA *et al.* (2004) [15477717]
 2515. Schmidt J *et al.* (2011) [21220428]
 2516. Schmitz B *et al.* (2015) [25666387]
 2517. Schmitz K *et al.* (2017) [28578681]
 2518. Schmitz LM *et al.* (2025) [39945763]
 2519. Schmoutz CD *et al.* (2012) [22982682]
 2520. Schneeberger M *et al.* (2022) [36411386]
 2521. Schoepp DD *et al.* (2000) *In* IUPHAR Compendium of Receptor Characterization and Classification Edited by Watson SP, Girdlestone D: IUPHAR Press: 195-208
 2522. Schoepp DD *et al.* (1994) [8035201]
 2523. Schoepp DD *et al.* (1997) [9144636]
 2524. Schoepp DD *et al.* (1996) [9076745]
 2525. Scholz N *et al.* (2015) [25937282]
 2526. Schöppe J *et al.* (2019) [30604743]
 2527. Schotte A *et al.* (1996) [8935801]
 2528. Schrage R *et al.* (2014) [24863257]
 2529. Schrage R *et al.* (2013) [23062057]
 2530. Scheingart CD *et al.* (2008) Patent number: US7402564 B1.
 2531. Schulte G. (2010) [21079039]
 2532. Schulte G. (2024) [38955509]
 2533. Schulte G *et al.* (2018) [30049420]
 2534. Schwartz JC Carlsson A Caron M Scatton

- B Civelli O, Kebebian JW, Langer SZ, Sedvall G, Seeman P, Spano PF, Sokoloff P, Van Tol H. (1998) *In The IUPHAR Compendium of Receptor Characterization and Classification* Edited by Girdlestone D: IUPHAR media: 141-151
2535. Schweitz H *et al.* (1999) [10567694]
2536. Schweitzer C *et al.* (2000) [10884552]
2537. Schwenk J *et al.* (2010) [20400944]
2538. Schwenk J *et al.* (2016) [26691831]
2539. Schwenk U *et al.* (1995) [7797484]
2540. Schwiebert E *et al.* (2021) [33824185]
2541. Schwinn DA *et al.* (1995) [7815325]
2542. Scola AM *et al.* (2009) [19100624]
2543. Scott DJ *et al.* (2005) [15956681]
2544. Scott DJ *et al.* (2005) [15956680]
2545. Scott DJ *et al.* (2006) [16963451]
2546. Scott MK *et al.* (2000) [10896115]
2547. Scully CC *et al.* (2010) [20527893]
2548. Seandel M *et al.* (2007) [17882221]
2549. Seebhat IK *et al.* (2011) [24900253]
2550. Seebhat IK *et al.* (2002) [12361385]
2551. Sedaghat K *et al.* (2008) [18706979]
2552. Seeman P. (2001) *Clinical Neuroscience Research* **1**: 53-60
2553. Seeman P *et al.* (1975) [1060115]
2554. Seeman P *et al.* (1997) [9015795]
2555. Seeman P *et al.* (1998) [9577836]
2556. Seifert R *et al.* (2003) [12626648]
2557. Selkirk JV *et al.* (1998) [9776361]
2558. Semple G *et al.* (2006) [16480258]
2559. Serradeil-Le Gal C *et al.* (2000) [11012895]
2560. Serradeil-Le Gal C *et al.* (2004) [14722330]
2561. Serradeil-Le Gal C *et al.* (2002) [11861823]
2562. Sethi A *et al.* (2016) [27088579]
2563. Setoh M *et al.* (2014) [24884590]
2564. Seuwen K *et al.* (2006) [17118800]
2565. Shabanpoor F *et al.* (2012) [22257012]
2566. Shabanpoor F *et al.* (2012) [22425984]
2567. Shabanpoor F *et al.* (2007) [17120268]
2568. Shabanpoor F *et al.* (2008) [18529069]
2569. Shabanpoor F *et al.* (2011) [20560146]
2570. Shahid M *et al.* (2009) [18308814]
2571. Shannon HE *et al.* (1994) [7909557]
2572. Sharif NA *et al.* (2002) [11999132]
2573. Sharif NA *et al.* (2019) [29679483]
2574. Sharif NA *et al.* (2006) [17076623]
2575. Sharif NA *et al.* (2001) [11572462]
2576. Sharma M *et al.* (2025) [40141775]
2577. Shaye H *et al.* (2021) [34049877]
2578. Shebanits K *et al.* (2018) [29621259]
2579. Shebanits K *et al.* (2019) [31230758]
2580. Sheffler DJ *et al.* (2009) [19407080]
2581. Shen F *et al.* (2013) [23292797]
2582. Shen HC *et al.* (2010) [20184326]
2583. Shen S *et al.* (2025) [40523184]
2584. Shi W *et al.* (2024) [38834774]
2585. Shibata K *et al.* (1995) [7651358]
2586. Shichijo M *et al.* (2003) [12975488]
2587. Shihoya W *et al.* (2018) [30413709]
2588. Shihoya W *et al.* (2016) [27595334]
2589. Shihoya W *et al.* (2017) [28805809]
2590. Shima Y *et al.* (2007) [17618280]
2591. Shimizu N *et al.* (1999) [10233994]
2592. Shimokawa M *et al.* (2017) [28355176]
2593. Shimomura Y *et al.* (2002) [12130646]
2594. Shimon I *et al.* (2004) [15636423]
2595. Shimpukade B *et al.* (2012) [22519963]
2596. Shin K *et al.* (2017) [29357134]
2597. Shinagawa Y *et al.* (2011) [24900301]
2598. Shinkre BA *et al.* (2010) [20801028]
2599. Shinohara T *et al.* (2004) [15037633]
2600. Shire D *et al.* (1996) [8679694]
2601. Shirley M. (2024) [38388871]
2602. Shitara K *et al.* (2009) Patent number: US7504104.
2603. Shore DM *et al.* (2015) [25926795]
2604. Showalter VM *et al.* (1996) [8819477]
2605. Showell HJ *et al.* (1976) [1262785]
2606. Showell HJ *et al.* (1995) [7714764]
2607. Siegl AM *et al.* (1979) [372237]
2608. Siehler S *et al.* (1998) [9650799]
2609. Siehler S *et al.* (1998) [9652348]
2610. Siehler S *et al.* (1999) [10598788]
2611. Sikand P *et al.* (2011) [21593341]
2612. Sillard R *et al.* (1992) [1283627]
2613. Silva JP *et al.* (2011) [21724987]
2614. Silver MR *et al.* (2005) [15878963]
2615. Sim LJ *et al.* (1996) [8987831]
2616. Simonin F *et al.* (1995) [7624359]
2617. Simonin F *et al.* (2006) [16407169]
2618. Simonin F *et al.* (2001) [11239198]
2619. Singh G *et al.* (2004) [15261118]
2620. Singh KD *et al.* (2022) [35318654]
2621. Singh L *et al.* (1995) [8605955]
2622. Sinha S *et al.* (2006) [16408088]
2623. Sinha S *et al.* (2010) [20590605]
2624. Sinnavee P *et al.* (2020) [32439008]
2625. Skerlj RT *et al.* (2010) [20297846]
2626. Skiba MA *et al.* (2025) [40067891]
2627. Skiba MA *et al.* (2024) [38744986]
2628. Skinner PJ *et al.* (2009) [19524438]
2629. Skofitsch G *et al.* (1986) [2436195]
2630. Skrzydelski D *et al.* (2003) [12869647]
2631. Slack JP *et al.* (2010) [20537538]
2632. Sleight AJ *et al.* (1998) [9647481]
2633. Sleight AJ *et al.* (1996) [8534270]
2634. Slepak TI *et al.* (2023) [37517698]
2635. Slim GM *et al.* (2019) [30614011]
2636. Slipetz DM *et al.* (1995) [7651369]
2637. Slusarski DC *et al.* (1997) [9389482]
2638. Small KM *et al.* (2006) [16605244]
2639. Smith CM *et al.* (2012) [21899720]
2640. Smith CM *et al.* (2010) [20737598]
2641. Smith CM *et al.* (1997) [9029489]
2642. Smith JA *et al.* (2008) [18415081]
2643. Smith JP *et al.* (2002) [12429993]
2644. Smith KE *et al.* (1997) [9305929]
2645. Smith KE *et al.* (1998) [9722565]
2646. Smith KL *et al.* (2006) [16574794]
2647. Smith MT *et al.* (2016) [26785154]
2648. Smith PW *et al.* (1995) [7562907]
2649. Smith RD *et al.* (1994) [7850406]
2650. Smits RA *et al.* (2006) [16854056]
2651. Soares S *et al.* (2013) [23311874]
2652. Soares S *et al.* (2018) [30056706]
2653. Soave M *et al.* (2016) [27588207]
2654. Sodin-Semrl S *et al.* (2004) [15171815]
2655. Sofuoglu M *et al.* (1991) [1851833]
2656. Soga T *et al.* (2003) [12646212]
2657. Soga T *et al.* (2002) [12427552]
2658. Sogawa Y *et al.* (2011) [21173551]
2659. Sokoloff P *et al.* (1992) [1354163]
2660. Sokoloff P *et al.* (1992) [1586393]
2661. Sokoloff P *et al.* (1990) [1975644]
2662. Solinski HJ *et al.* (2014) [24867890]
2663. Sollenberg UE *et al.* (2006) *Int J Pept Res* **12**: 115-119
2664. Song H *et al.* (2008) [18955481]
2665. Song I *et al.* (1993) [8415658]
2666. Song ZH *et al.* (1996) [8622639]
2667. Soriano-Ursúa MA *et al.* (2012) [22182578]
2668. Soriano-Ursúa MA *et al.* (2009) [19168263]
2669. Southern C *et al.* (2013) [23396314]
2670. Spadoni G *et al.* (2015) [26334942]
2671. Spagnolo B *et al.* (2007) [17329552]
2672. Spalding TA *et al.* (2006) [16959945]
2673. Spalding TA *et al.* (2002) [12021390]
2674. Spath B *et al.* (2012) [21736422]
2675. Spengler D *et al.* (1993) [8396727]
2676. Speth RC *et al.* (1990) [2194459]
2677. Spitsin S *et al.* (2017) [28978797]
2678. Sprecher D *et al.* (2015) [25773497]
2679. Srivastava A *et al.* (2014) [25043059]
2680. Stéen EJL *et al.* (2025) [40179990]
2681. Stacey M *et al.* (2003) [12829604]
2682. Stacey M *et al.* (2002) [12023293]
2683. Stacey M *et al.* (2001) [11279179]
2684. Stahl E *et al.* (2010) [20348203]
2685. Stalder AK *et al.* (2017) [27730665]
2686. Stalder H *et al.* (2011) [21237643]
2687. Stam NJ *et al.* (1997) [9303561]
2688. Staus DP *et al.* (2020) [31945772]
2689. Stefano GB *et al.* (1992) [1329092]
2690. Steichen H *et al.* (2025) [40372763]
2691. Stein RM *et al.* (2020) [32040955]
2692. Steinhart Z *et al.* (2017) [27869803]
2693. Stenfeldt AL *et al.* (2007) [17687636]
2694. Stepanovska Tanturovska B *et al.* (2021) [34500564]
2695. Stevens WC *et al.* (2000) [10893314]
2696. Stewart AJ *et al.* (2008) [17942747]
2697. Stewart M *et al.* (2004) [15194002]
2698. Stillman BA *et al.* (1999) [10462542]
2699. Stirrat A *et al.* (2001) [11158995]
2700. Stitham J *et al.* (2007) [17704830]
2701. Stocks MJ *et al.* (2010) [21036043]
2702. Stoddart LA *et al.* (2007) [17200419]
2703. Stoddart LA *et al.* (2008) [19047536]
2704. Storey RF *et al.* (2020) [31994703]
2705. Storka A *et al.* (2008) [19021699]
2706. Stott LA *et al.* (2021) [34189291]
2707. Stoveken HM *et al.* (2016) [27338081]
2708. Stoveken HM *et al.* (2015) [25918380]
2709. Stoveken HM *et al.* (2018) [29476042]
2710. Straub RE *et al.* (1990) [2175902]
2711. Strizki JM *et al.* (2005) [16304152]
2712. Strosberg AD. (1997) [9131260]
2713. Struthers RS *et al.* (2007) [17095587]
2714. Stump CA *et al.* (2016) [27818110]
2715. Sturino CF *et al.* (2007) [17300164]
2716. Su M *et al.* (2020) [32818430]
2717. Su SB *et al.* (1999) [9892621]
2718. Sudo H *et al.* (2008) [18164286]
2719. Sudo S *et al.* (2003) [12506116]
2720. Suen JY *et al.* (2012) [21806599]
2721. Suess B *et al.* (2018) [27569025]
2722. Sugden D *et al.* (1999) [10420436]
2723. Sugimoto H *et al.* (2005) [16256979]
2724. Sugo T *et al.* (2008) [17628210]
2725. Sugo T *et al.* (2006) [16460680]

2726. Sullivan GW *et al.* (2001) [11226132]
 2727. Sumichika H *et al.* (2002) [12384495]
 2728. Sun J *et al.* (2020) [31490055]
 2729. Sun P *et al.* (2020) [32219165]
 2730. Sun Q *et al.* (2010) [20685848]
 2731. Sun Y *et al.* (2003) [12683933]
 2732. Sunahara RK *et al.* (1991) [1826762]
 2733. Sünderhauf A *et al.* (2017) [28843904]
 2734. Sundqvist M *et al.* (2017) [29375548]
 2735. Suno R *et al.* (2018) [29225076]
 2736. Suno R *et al.* (2018) [30420692]
 2737. Sur C *et al.* (2003) [14595031]
 2738. Suresh RR *et al.* (2022) [35450351]
 2739. Suzawa T *et al.* (2000) [10746663]
 2740. Suzuki G *et al.* (2007) [17609420]
 2741. Suzuki M *et al.* (2013) [23449982]
 2742. Suzuki T *et al.* (2008) [19007110]
 2743. Suzuki T *et al.* (1993) [7902433]
 2744. Svetlov S *et al.* (1993) [8380690]
 2745. Swaney JS *et al.* (2011) [21159750]
 2746. Swanson CJ *et al.* (2005) [16287967]
 2747. Swayne GT *et al.* (1988) [2975605]
 2748. Syed NI *et al.* (2015) [25542069]
 2749. Syed YY. (2023) [37022667]
 2750. Sykes D *et al.* (2014) *Eur Respir J* **44**: 4074
 2751. Sykes DA *et al.* (2016) [26916831]
 2752. Sykes DA *et al.* (2012) [21883146]
 2753. Sykes DA *et al.* (2012) [22854200]
 2754. Szpakowska M *et al.* (2025) [39900975]
 2755. Szpakowska M *et al.* (2018) [29530506]
 2756. Tabata K *et al.* (2007) [17905198]
 2757. Taggart AK *et al.* (2005) [15929991]
 2758. Tahara A *et al.* (1998) [9884074]
 2759. Tahara A *et al.* (1998) [9459574]
 2760. Taipale J *et al.* (2000) [10984056]
 2761. Takada Y *et al.* (2003) [12960358]
 2762. Takahashi M *et al.* (1997) [9145417]
 2763. Takahashi M *et al.* (1994) [7804141]
 2764. Takanashi H *et al.* (2007) [17183187]
 2765. Takano T *et al.* (1997) [9151906]
 2766. Takasaki J *et al.* (2000) [10913337]
 2767. Takasaki J *et al.* (2001) [11502873]
 2768. Takasu T *et al.* (2007) [17293563]
 2769. Takayama K *et al.* (2020) [32721452]
 2770. Takayama K *et al.* (2014) [24999562]
 2771. Takayama K *et al.* (2020) [32247748]
 2772. Takayasu S *et al.* (2006) [16648250]
 2773. Takechi H *et al.* (1996) [8621463]
 2774. Takeda S *et al.* (2004) [15173198]
 2775. Takekawa S *et al.* (2002) [11909603]
 2776. Takinami Y *et al.* (1997) [9042983]
 2777. Talmont F *et al.* (2009) [19682524]
 2778. Tam J *et al.* (2012) [22841573]
 2779. Tamamura H *et al.* (1998) [9918823]
 2780. Tamura M *et al.* (1999) [10024318]
 2781. Tan CP *et al.* (2002) [12036292]
 2782. Tan M *et al.* (2009) [19126537]
 2783. Tanaka T *et al.* (2008) [18320172]
 2784. Tandon R *et al.* (2020) [32745605]
 2785. Tang H *et al.* (2008) [18722346]
 2786. Tang H *et al.* (2019) [30840614]
 2787. Tang L *et al.* (1994) [8301592]
 2788. Tang T *et al.* (2021) [33531491]
 2789. Tang T *et al.* (2022) [35507650]
 2790. Tang X *et al.* (2020) [31930602]
 2791. Tang X *et al.* (2013) [24008316]
 2792. Taniguchi H *et al.* (1996) [8813597]
 2793. Taniguchi R *et al.* (2017) [28792932]
 2794. Taniguchi T *et al.* (1999) [10433504]
 2795. Taniguchi Y *et al.* (2006) [16934253]
 2796. Tanis SP *et al.* (2010) [21036042]
 2797. Tao L *et al.* (2024) [38969802]
 2798. Tatemoto K *et al.* (1998) [9792798]
 2799. Tautermann CS *et al.* (2013) [24088171]
 2800. Teh MT *et al.* (1998) [9840420]
 2801. Tellew JE *et al.* (2010) [21074436]
 2802. Terakado M *et al.* (2016) [27774128]
 2803. Terakita A. (2005) [15774036]
 2804. Testa R *et al.* (1997) [9190864]
 2805. Tezuka M *et al.* (2022) [35690889]
 2806. Thakar S *et al.* (2017) [28057866]
 2807. Thal DM *et al.* (2016) [26958838]
 2808. Thalmann S *et al.* (2013) [23632330]
 2809. Thathiah A *et al.* (2009) [19213921]
 2810. Theiler A *et al.* (2016) [27664754]
 2811. Theis JG *et al.* (1992) [1387312]
 2812. Thibonnier M *et al.* (1994) [8106369]
 2813. Thibonnier M *et al.* (1997) [9322919]
 2814. Thielemans L *et al.* (2005) [15764739]
 2815. Thomas A *et al.* (2017) [28798468]
 2816. Thomas BF *et al.* (1998) [9536023]
 2817. Thomas DR *et al.* (2000) [10807680]
 2818. Thomas DR *et al.* (1998) [9720804]
 2819. Thomas JB *et al.* (2001) [11495579]
 2820. Thomas NK *et al.* (2001) [11166323]
 2821. Thomas P *et al.* (2005) [15539556]
 2822. Thompson AA *et al.* (2012) [22596163]
 2823. Thomsen AR *et al.* (2012) [22192592]
 2824. Thomsen HK *et al.* (1985) [3969828]
 2825. Thomsen WJ *et al.* (2008) [18252809]
 2826. Thulesen J *et al.* (2002) [11738243]
 2827. Thurmond RL *et al.* (2004) [14722321]
 2828. Tian Y *et al.* (1996) [8702757]
 2829. Tibaduiza EC *et al.* (2001) [11498540]
 2830. Tiberi M *et al.* (1994) [7525564]
 2831. Tice MA *et al.* (1994) [7862709]
 2832. Tiffany HL *et al.* (2001) [11316806]
 2833. Tilakaratne N *et al.* (2000) [10871296]
 2834. Timmermans PB *et al.* (1993) [8372104]
 2835. Ting KN *et al.* (1999) [10433507]
 2836. Tissir F *et al.* (2002) [11850187]
 2837. Tobo A *et al.* (2015) [26070068]
 2838. Toda N *et al.* (2013) [24900747]
 2839. Todde S *et al.* (2000) [11087559]
 2840. Toh Y *et al.* (2025) [40894780]
 2841. Toh Y *et al.* (2025) [40825849]
 2842. Tokita K *et al.* (2001) [11463790]
 2843. Toledo MA *et al.* (2014) [24678969]
 2844. Toll L. (1990) [1968847]
 2845. Toll L *et al.* (1998) [9686407]
 2846. Toma I *et al.* (2008) [18535668]
 2847. Tomita K *et al.* (2008) [18302161]
 2848. Tong L *et al.* (2020) [32101422]
 2849. Tönjes A *et al.* (2009) [19729412]
 2850. Torisu K *et al.* (2004) [15388164]
 2851. Torregrosa-Carrión R *et al.* (2021) [34767447]
 2852. Torrens Y *et al.* (1997) [9243521]
 2853. Torres D *et al.* (2008) [18178816]
 2854. Tosh DK *et al.* (2012) [22559880]
 2855. Tosh DK *et al.* (2024) [39022354]
 2856. Tosh DK *et al.* (2019) [30605331]
 2857. Tostivint H *et al.* (2014) [24740737]
 2858. Tough IR *et al.* (2006) [16807358]
 2859. Tourwé D *et al.* (2021) [33965531]
 2860. Tournant C *et al.* (1990) [1705465]
 2861. Townsend-Nicholson A *et al.* (1994) [8300561]
 2862. Toyoda Y *et al.* (2019) [30510193]
 2863. TrÅ%on K *et al.* (2021) [33350824]
 2864. Tran TA *et al.* (2017) [28072531]
 2865. Tränkle C *et al.* (2003) [12815174]
 2866. Trauelsen M *et al.* (2021) [34133934]
 2867. Trauelsen M *et al.* (2017) [29157600]
 2868. Treiber A *et al.* (2017) [28663311]
 2869. Trivellini G *et al.* (2014) [25470569]
 2870. Tsuchiya D *et al.* (2002) [11867751]
 2871. Tsuchihata Y *et al.* (2011) [21752941]
 2872. Tsutsumi N *et al.* (2020) [32762848]
 2873. Tu YK *et al.* (2018) [30120207]
 2874. Tunaru S *et al.* (2003) [12563315]
 2875. Turecek R *et al.* (2014) [24836506]
 2876. Turner MR *et al.* (2005) [15689356]
 2877. Turner MW *et al.* (2016) [27338657]
 2878. Tzschentke TM *et al.* (2007) [17656655]
 2879. Uberti MA *et al.* (2005) [15615865]
 2880. Uchida D *et al.* (1998) [9928019]
 2881. Uehara H *et al.* (2011) [21729729]
 2882. Uehling DE *et al.* (2006) [16640337]
 2883. Uguccioni M *et al.* (1997) [9276730]
 2884. Uhlén S *et al.* (1994) [7996470]
 2885. Uhlenbrock K *et al.* (2002) [12220620]
 2886. Ullmann H *et al.* (2005) [16250663]
 2887. Ulman LG *et al.* (1993) [7693918]
 2888. Ulrich 2nd CD *et al.* (1998) [9843782]
 2889. Ulrich D *et al.* (2007) [17433877]
 2890. Ulven T *et al.* (2005) [15715457]
 2891. Underwood DJ *et al.* (1994) [9383393]
 2892. Unson CG *et al.* (1987) [3035568]
 2893. Unson CG *et al.* (1989) [2560175]
 2894. Upadhyaya J *et al.* (2010) [20599705]
 2895. Urbano M *et al.* (2013) [24125884]
 2896. Urbano M *et al.* (2011) [21982495]
 2897. Ursini A *et al.* (2000) [11020274]
 2898. Urwyler S *et al.* (2001) [11641424]
 2899. Urwyler S *et al.* (2003) [12954816]
 2900. Uyama Y *et al.* (1997) [9106476]
 2901. Vacher CM *et al.* (2006) [16606363]
 2902. Vakalopoulos A *et al.* (2024) [39463278]
 2903. Valant C *et al.* (2012) [21989256]
 2904. Valant C *et al.* (2008) [18723515]
 2905. Valenzuela-Bezanilla D *et al.* (2025) [39432578]
 2906. Vallon M *et al.* (2006) [16982628]
 2907. Vallon M *et al.* (2018) [30304675]
 2908. Valuskova P *et al.* (2018) [29515448]
 2909. Van Brocklyn JR *et al.* (2000) [10753843]
 2910. Van den Wyngaert I *et al.* (1997) [9349523]
 2911. van der Westhuizen ET *et al.* (2010) [20159943]
 2912. van Diepen JA *et al.* (2017) [28382382]
 2913. van Eijk M *et al.* (2010) [20167235]
 2914. Van Lith LH *et al.* (2009) [19641221]
 2915. van Muijlwijk-Koezen JE *et al.* (2000) [10841801]
 2916. Van Poppel H. (2010) [21188095]
 2917. Van Rampelbergh J *et al.* (1996) [8967982]
 2918. Van Tol HH *et al.* (1991) [1840645]
 2919. van Wieringen JP *et al.* (2013) [24183974]

2920. van Wijk E *et al.* (2006) [16434480]
 2921. Vanderheyden PM *et al.* (1999) [10193788]
 2922. Vanhollenbeke B *et al.* (2015) [26051822]
 2923. Vanover KE *et al.* (2004) [15102927]
 2924. Vanti WB *et al.* (2003) [14559210]
 2925. Vanti WB *et al.* (2003) [12732197]
 2926. Varani K *et al.* (2005) [16219300]
 2927. Varani K *et al.* (2000) [10779381]
 2928. Varga BR *et al.* (2025) [40082451]
 2929. Varga JL *et al.* (1999) [9892695]
 2930. Varga JL *et al.* (2004) [14755056]
 2931. Varnäs K *et al.* (2011) [20424633]
 2932. Varty GB *et al.* (2008) [18492950]
 2933. Vassileva G *et al.* (2006) [16724960]
 2934. Vaudry H *et al.* (2010) [20633133]
 2935. Vaudry H *et al.* (2015) [25535277]
 2936. Vaughan J *et al.* (1995) [7477349]
 2937. Venail F *et al.* (2018) [30152527]
 2938. Veninga H *et al.* (2008) [18941248]
 2939. Verdino P *et al.* (2011) [20424633]
 2940. Verdonk K *et al.* (2012) [22802221]
 2941. Vergura R *et al.* (2008) [18069089]
 2942. Vigot R *et al.* (2006) [16701209]
 2943. Vilardaga JP *et al.* (2008) [18193048]
 2944. Vilboux T *et al.* (2017) [28052552]
 2945. Villalón CM *et al.* (2007) [17703282]
 2946. Villanueva-Carmona T *et al.* (2023) [36977414]
 2947. Violin JD *et al.* (2010) [20801892]
 2948. Virag T *et al.* (2003) [12695531]
 2949. Vita N *et al.* (1998) [9851594]
 2950. Vitobello A *et al.* (2022) [35907405]
 2951. Vizurraga AL *et al.* (2023) [37290962]
 2952. Vlaar APJ *et al.* (2020) [33015643]
 2953. Vlachou S *et al.* (2011) [21181127]
 2954. Volpe DA *et al.* (2011) [21215785]
 2955. Volynski KE *et al.* (2003) [12782639]
 2956. Volz A *et al.* (1995) [7589426]
 2957. von Geldern TW *et al.* (1999) [10479298]
 2958. von Kügelgen I *et al.* (2016) [26519900]
 2959. von Maltzahn J *et al.* (2012) [22179044]
 2960. Vonvoigtlander PF *et al.* (1983) [6129321]
 2961. Voss JH *et al.* (2025) [40413190]
 2962. Vuckovic Z *et al.* (2019) [31772027]
 2963. Vuckovic Z *et al.* (2023) [37248726]
 2964. Vutukuri R *et al.* (2020) [31944406]
 2965. Wacker D *et al.* (2013) [23519215]
 2966. Wacker DA *et al.* (2002) [12067561]
 2967. Waeber C *et al.* (1998) [9928243]
 2968. Wainscott DB *et al.* (1993) [8450835]
 2969. Wainscott DB *et al.* (2005) [15900510]
 2970. Wainscott DB *et al.* (1998) [9459568]
 2971. Wakabayashi H *et al.* (2021) [33382205]
 2972. Waldo GL *et al.* (2002) [12391289]
 2973. Walker AW *et al.* (2015) [25849482]
 2974. Walker CS *et al.* (2015) [26125036]
 2975. Walker LC *et al.* (2022) [34962108]
 2976. Waller-Evans H *et al.* (2010) [21124978]
 2977. Wallrabenstein I *et al.* (2013) [23393561]
 2978. Walter S *et al.* (2013) [23674604]
 2979. Walters MJ *et al.* (2010) [20660125]
 2980. Walther A *et al.* (2000) [10882119]
 2981. Wan W *et al.* (1990) [2213023]
 2982. Wan Y *et al.* (2002) [12450563]
 2983. Wandel E *et al.* (2012) [22210915]
 2984. Wang C *et al.* (2013) [23519210]
 2985. Wang C *et al.* (2014) [25008467]
 2986. Wang C *et al.* (2013) [23636324]
 2987. Wang C *et al.* (2021) [33185430]
 2988. Wang F *et al.* (2023) [36716818]
 2989. Wang H *et al.* (2022) [35385593]
 2990. Wang J *et al.* (2021) [34758294]
 2991. Wang J *et al.* (2025) [40102363]
 2992. Wang J *et al.* (2012) [23063522]
 2993. Wang J *et al.* (2016) [27081476]
 2994. Wang J *et al.* (2006) [16754668]
 2995. Wang J *et al.* (2022) [35606397]
 2996. Wang J *et al.* (2006) [16966319]
 2997. Wang J *et al.* (2022) [35878025]
 2998. Wang JH *et al.* (2018) [30102931]
 2999. Wang JH *et al.* (2017) [28631012]
 3000. Wang L *et al.* (2025) [39753551]
 3001. Wang M *et al.* (2006) [16455645]
 3002. Wang N *et al.* (2022) [35241677]
 3003. Wang N *et al.* (2023) [37673067]
 3004. Wang P *et al.* (2024) [38146625]
 3005. Wang S *et al.* (1998) [9742938]
 3006. Wang S *et al.* (1997) [9281594]
 3007. Wang S *et al.* (1997) [9405385]
 3008. Wang S *et al.* (2018) [30257206]
 3009. Wang SZ *et al.* (1993) [7687290]
 3010. Wang T *et al.* (2005) [15576472]
 3011. Wang X *et al.* (2025) [40261795]
 3012. Wang Y *et al.* (2017) [28912715]
 3013. Wang Y *et al.* (2005) [15383632]
 3014. Wang Y *et al.* (2019) [31066447]
 3015. Wang Y *et al.* (2023) [36638794]
 3016. Wank SA *et al.* (1992) [1313582]
 3017. Ward SE *et al.* (2005) [15887956]
 3018. Ward Y *et al.* (2013) [22797060]
 3019. Ward Y *et al.* (2011) [21978933]
 3020. Warne T *et al.* (2011) [21228877]
 3021. Warne T *et al.* (2008) [18594507]
 3022. Warner FJ *et al.* (1999) [10455255]
 3023. Watakabe T *et al.* (1992) [1320877]
 3024. Watanabe K *et al.* (1999) [10537280]
 3025. Watanabe N *et al.* (2015) [26136644]
 3026. Watanabe T *et al.* (1995) [7780649]
 3027. Watanabe Y *et al.* (1999) [10349870]
 3028. Waterloo L *et al.* (2023) [36847646]
 3029. Watson J *et al.* (1998) [9884068]
 3030. Watson M *et al.* (1984) [6546354]
 3031. Watson SJ *et al.* (2012) [22282525]
 3032. Watts AO *et al.* (2013) [23341447]
 3033. Weber AE *et al.* (1998) [9873496]
 3034. Webster EL *et al.* (1996) [8940412]
 3035. Wei Z *et al.* (2025) [40037063]
 3036. Weiß E *et al.* (2018) [30195466]
 3037. Weinshank RL *et al.* (1991) [1834671]
 3038. Weis WI *et al.* (2018) [29925258]
 3039. Wellendorph P *et al.* (2025) [40449125]
 3040. Wellendorph P *et al.* (2005) [15576628]
 3041. Wen W *et al.* (2014) [25176330]
 3042. Wen Z *et al.* (2023) [37382926]
 3043. Wen Z *et al.* (2022) [35113556]
 3044. Wende E *et al.* (2013) [23638016]
 3045. Weng J *et al.* (2008) [18424556]
 3046. Weng Y *et al.* (1998) [9660793]
 3047. Wenthur CJ *et al.* (2013) [23718281]
 3048. Wentland MP *et al.* (2009) [19282177]
 3049. Wenzel-Seifert K *et al.* (1993) [8387097]
 3050. Wermuth CG *et al.* (1996) [8632404]
 3051. Werner U *et al.* (2010) [20570597]
 3052. Werry TD *et al.* (2008) [18554725]
 3053. Wess J *et al.* (1991) [2043926]
 3054. Westaway SM *et al.* (2009) [21544957]
 3055. Westzel JM *et al.* (1995) [7752182]
 3056. Weyler S *et al.* (2006) [16902942]
 3057. White JR *et al.* (1998) [9553055]
 3058. White PJ *et al.* (2003) [12761346]
 3059. Whitebread S *et al.* (1989) [2775266]
 3060. Whitebread SE *et al.* (1991) [1764088]
 3061. Whiteside GT *et al.* (2024) [37883189]
 3062. Whittle BJ *et al.* (2012) [22480736]
 3063. Wichmann J *et al.* (2000) [11006485]
 3064. Widler L *et al.* (2010) [20158186]
 3065. Wieland HA *et al.* (1998) [9806339]
 3066. Wieland HA *et al.* (1995) [7562543]
 3067. Wieland K *et al.* (2001) [11714875]
 3068. Wiesenfeld-Hallin Z *et al.* (1992) [1373497]
 3069. Wiest SA *et al.* (1991) [1709220]
 3070. Wilbanks A *et al.* (2001) [11290797]
 3071. Wilde C *et al.* (2023) [37296671]
 3072. Wilde C *et al.* (2016) [26499266]
 3073. Williams BL *et al.* (2014) [25344287]
 3074. Williams TJ *et al.* (1999) [10369480]
 3075. Williams TL *et al.* (2024) [39730334]
 3076. Willsey AJ *et al.* (2017) [28472652]
 3077. Wilson RJ *et al.* (2006) [16604093]
 3078. Wilson RJ *et al.* (2005) [15655509]
 3079. Wilson S *et al.* (2005) [15946947]
 3080. Wilson SM *et al.* (2011) [21173040]
 3081. Windischhofer W *et al.* (1997) [9333122]
 3082. Winrow CJ *et al.* (2012) [22019562]
 3083. Winther M *et al.* (2017) [28934373]
 3084. Wise A *et al.* (2003) [12522134]
 3085. Witte ON *et al.* (2005) [15653487]
 3086. Wittenberger T *et al.* (2001) [11273702]
 3087. Wiysonge CS *et al.* (2017) [28107561]
 3088. Wong AK *et al.* (1998) [9719594]
 3089. Wong LLL *et al.* (2018) [30131340]
 3090. Wong PC *et al.* (2017) [28053157]
 3091. Wood MD *et al.* (1999) [10323594]
 3092. Wood MD *et al.* (2000) [11082110]
 3093. Wooding S *et al.* (2010) [20551074]
 3094. Woodward DF *et al.* (2008) [18700152]
 3095. Woodward DF *et al.* (2011) [21752876]
 3096. Wright DH *et al.* (1998) [9579253]
 3097. Wright DH *et al.* (1999) [10448933]
 3098. Wright SC *et al.* (2018) [30514810]
 3099. Wright SC *et al.* (2019) [30737406]
 3100. Wu C *et al.* (1997) [9171878]
 3101. Wu H *et al.* (2024) [38679208]
 3102. Wu H *et al.* (2024) [39568362]
 3103. Wu H *et al.* (2024) [38677442]
 3104. Wu H *et al.* (2012) [22437504]
 3105. Wu H *et al.* (2014) [24603153]
 3106. Wu JY *et al.* (2020) [31735641]
 3107. Wu L *et al.* (2023) [37272653]
 3108. Wu L *et al.* (1996) [8940121]
 3109. Wu M *et al.* (2023) [37580962]
 3110. Wu QP *et al.* (2016) [26767372]
 3111. Wu S *et al.* (1998) [9473604]
 3112. Wulff BS *et al.* (2002) [12393057]
 3113. Wunder F *et al.* (2010) [20423349]
 3114. Wurch T *et al.* (1998) [9855638]
 3115. Wuyts A *et al.* (1998) [9692902]
 3116. Wynick D *et al.* (1993) [7683428]
 3117. Xi ZX *et al.* (2007) [17627675]
 3118. Xia A *et al.* (2023) [37733739]

3119. Xia M *et al.* (1997) [9152366]
 3120. Xiao J *et al.* (2010) [24260782]
 3121. Xiao J *et al.* (2014) [24666157]
 3122. Xiao P *et al.* (2022) [35418677]
 3123. Xie Z *et al.* (1999) [10452531]
 3124. Xie Z *et al.* (2009) [19482011]
 3125. Xing L *et al.* (2019) [31619542]
 3126. Xing L *et al.* (2024) [38381789]
 3127. Xiong Y *et al.* (2004) [14722361]
 3128. Xiong Y *et al.* (2013) [23403053]
 3129. Xu F *et al.* (2011) [21393508]
 3130. Xu J *et al.* (2023) [36690613]
 3131. Xu L *et al.* (2006) [16757564]
 3132. Xu L *et al.* (2021) [34239071]
 3133. Xu W *et al.* (2022) [36108005]
 3134. Xu W *et al.* (2025) [40273273]
 3135. Xu X *et al.* (2018) [29615471]
 3136. Xu Y *et al.* (2024) [38042462]
 3137. Xu Y *et al.* (2000) [10806476]
 3138. Xu Y *et al.* (2006) [16508674]
 3139. Xu YC *et al.* (1999) [9986723]
 3140. Xu YL *et al.* (2004) [15312648]
 3141. Xu Z *et al.* (2022) [34937912]
 3142. Yamada K *et al.* (2019) [31098002]
 3143. Yamamoto H *et al.* (2022) [35867683]
 3144. Yamamoto I *et al.* (2008) [18433751]
 3145. Yamamoto R *et al.* (2014) [25347187]
 3146. Yamamoto T. (2000) [11107061]
 3147. Yamamura MS *et al.* (1992) [1313133]
 3148. Yamamura Y *et al.* (1998) [9864265]
 3149. Yamane S *et al.* (2015) [25788650]
 3150. Yamashita A *et al.* (2013) [23714700]
 3151. Yamazaki T *et al.* (2014) [25273142]
 3152. Yan H *et al.* (1996) [8643460]
 3153. Yan L *et al.* (2003) [14662005]
 3154. Yan P *et al.* (2006) [17082621]
 3155. Yan W *et al.* (2020) [33082324]
 3156. Yanagida K *et al.* (2009) [19386608]
 3157. Yanagida K *et al.* (2020) [32894510]
 3158. Yanagisawa T *et al.* (2000) [11249148]
 3159. Yanai T *et al.* (2016) [27184081]
 3160. Yang D *et al.* (1999) [10521347]
 3161. Yang J *et al.* (2008) [18267071]
 3162. Yang J *et al.* (2012) [22645144]
 3163. Yang L *et al.* (1998) [9724791]
 3164. Yang LV *et al.* (2007) [17145776]
 3165. Yang MY *et al.* (2013) [23684610]
 3166. Yang P *et al.* <https://bit.ly/2RpvLqB>. Accessed on 07/07/2015.
 3167. Yang P *et al.* (2017) [28137936]
 3168. Yang S *et al.* (2018) [30135577]
 3169. Yang X *et al.* (2021) [33313997]
 3170. Yang Z *et al.* (2018) [29670288]
 3171. Yang Z *et al.* (2025) [39884271]
 3172. Yao BB *et al.* (2006) [16894349]
 3173. Yao XC *et al.* (2012) [22358838]
 3174. Yasuda H *et al.* (2007) [17214962]
 3175. Yates L *et al.* (2006) [16553647]
 3176. Yau MK *et al.* (2016) [26819675]
 3177. Ye C *et al.* (2014) [24633425]
 3178. Ye Q *et al.* (2020) [31655025]
 3179. Ye RD *et al.* (2009) [19498085]
 3180. Yerxa BR *et al.* (2002) [12183642]
 3181. Yeung J *et al.* (2020) [33097663]
 3182. Yi X *et al.* (2024) [38199163]
 3183. Yin GN *et al.* (2022) [35562586]
 3184. Yin H *et al.* (2009) [19286662]
 3185. Yin J *et al.* (2016) [26950369]
 3186. Yin J *et al.* (2018) [30538204]
 3187. Yin J *et al.* (2022) [35614071]
 3188. Yin J *et al.* (2015) [25533960]
 3189. Yin S *et al.* (2014) [24381270]
 3190. Yokomizo T *et al.* (1997) [9177352]
 3191. Yokomizo T *et al.* (2001) [11278893]
 3192. Yokoyama K *et al.* (2009) [19081254]
 3193. Yona S *et al.* (2008) [18789697]
 3194. Yoon JH *et al.* (2020) [33288575]
 3195. Yoshida R *et al.* (1997) [9153236]
 3196. Yoshida R *et al.* (1998) [9507024]
 3197. Yoshida S *et al.* (2010) [20804735]
 3198. Yoshikawa M. (2015) [26297549]
 3199. Yoshio R *et al.* (2001) [11459121]
 3200. Yosten GL *et al.* (2013) [23759446]
 3201. Young P *et al.* (1989) [2573535]
 3202. Yu L *et al.* (2022) [35412894]
 3203. Yu M *et al.* (2013) [24900757]
 3204. Yuan D *et al.* (2020) [32152538]
 3205. Yuan Y *et al.* (2021) [34526663]
 3206. Yue Y *et al.* (2022) [35817871]
 3207. Yung YC *et al.* (2011) [21900594]
 3208. Zabel BA *et al.* (2009) [19641136]
 3209. Zacharowski K *et al.* (1999) [10479656]
 3210. Zagon IS *et al.* (2002) [11890982]
 3211. Zaidman NA *et al.* (2020) [33004624]
 3212. Zajdel P *et al.* (2013) [23279866]
 3213. Zanaty M *et al.* (2021) [33249862]
 3214. Zaratin PF *et al.* (2004) [14593080]
 3215. Zaveri N. (2003) [12801588]
 3216. Zaveri NT *et al.* (2015) [25635572]
 3217. Zech G *et al.* (2012) [22984835]
 3218. Zhan D *et al.* (2025) [39400547]
 3219. Zhang C *et al.* (2015) [26057358]
 3220. Zhang C *et al.* (2016) [27746744]
 3221. Zhang D *et al.* (2022) [36126387]
 3222. Zhang D *et al.* (2015) [25822790]
 3223. Zhang D *et al.* (2023) [37038975]
 3224. Zhang D *et al.* (2021) [34101446]
 3225. Zhang DL *et al.* (2018) [29393851]
 3226. Zhang H *et al.* (2024) [38442298]
 3227. Zhang H *et al.* (2018) [29300013]
 3228. Zhang J *et al.* (2014) [24784220]
 3229. Zhang K *et al.* (2022) [35902590]
 3230. Zhang K *et al.* (2014) [24670650]
 3231. Zhang L *et al.* (2013) [22911445]
 3232. Zhang S *et al.* (2022) [36450989]
 3233. Zhang S *et al.* (2010) [20570702]
 3234. Zhang S *et al.* (2023) [36228737]
 3235. Zhang S *et al.* (2021) [33153968]
 3236. Zhang SP *et al.* (1998) [9651119]
 3237. Zhang SP *et al.* (2001) [11379050]
 3238. Zhang T *et al.* (2020) [32191644]
 3239. Zhang WB *et al.* (2002) [11923301]
 3240. Zhang X *et al.* (2017) [28513578]
 3241. Zhang XH *et al.* (2022) [36115515]
 3242. Zhang XH *et al.* (2021) [33824276]
 3243. Zhang Y *et al.* (2003) [12581520]
 3244. Zhang Z *et al.* (2024) [38182578]
 3245. Zhao C *et al.* (2022) [34545189]
 3246. Zhao DM *et al.* (2000) [10749750]
 3247. Zhao LH *et al.* (2019) [30975883]
 3248. Zhao P *et al.* (2015) [25878251]
 3249. Zhao P *et al.* (2010) [20826425]
 3250. Zhao SJ *et al.* (2022) [36250902]
 3251. Zhao T *et al.* (2023) [37702025]
 3252. Zhao Y *et al.* (2020) [31770520]
 3253. Zhen J *et al.* (2010) [20122961]
 3254. Zhou C *et al.* (2007) [17652444]
 3255. Zhou J *et al.* (2013) [23392769]
 3256. Zhou L *et al.* (2013) [24187130]
 3257. Zhou QY *et al.* (1990) [2168520]
 3258. Zhou S *et al.* (2024) [39637858]
 3259. Zhou X *et al.* (2021) [34755660]
 3260. Zhou Y *et al.* (2022) [33834276]
 3261. Zhou Y *et al.* (2014) [25373781]
 3262. Zhu B *et al.* (2019) [31628191]
 3263. Zhu D *et al.* (2018) [29894688]
 3264. Zhu J *et al.* (1995) [7869844]
 3265. Zhu J *et al.* (2008) [18582868]
 3266. Zhu J *et al.* (1997) [9262330]
 3267. Zhu K *et al.* (2001) [11535583]
 3268. Zhu X *et al.* (2022) [36127364]
 3269. Zhu Y *et al.* (2001) [11179436]
 3270. Zhu Y *et al.* (2022) [35405616]
 3271. Zhuang Y *et al.* (2022) [36368306]
 3272. Ziegler F *et al.* (2023) [37286811]
 3273. Zlotnik A *et al.* (2000) [10714678]
 3274. Zobel AW *et al.* (2000) [10867111]
 3275. Zoffmann S *et al.* (2001) [111170631]
 3276. Zou Y *et al.* (2024) [39219355]
 3277. Zuko A *et al.* (2016) [28018171]
 3278. Zuo H *et al.* (2024) [38632411]
 3279. Zygmunt PM *et al.* (1999) [10440374]