CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

Accepted Article

Title: Thiourea and Guanidine Compounds and their Iridium Complexes in Drug-Resistant Cancer Cell Lines: Structure-Activity Relationships and Direct Luminescent Imaging

Authors: Samuel J Thomas, Barbora Balónová, Jindrich Cinatl, Mark Wass, Christopher Serpell, Barry Blight, and Martin Michaelis

To be cited as: *ChemMedChem* 10.1002/cmdc.201900591

Link to VoR: http://dx.doi.org/10.1002/cmdc.201900591

A Journal of

ChemPubSoc Europe

WILEY-VCH

www.chemmedchem.org

WILEY-VCH

COMMUNICATION

Thiourea and Guanidine Compounds and their Iridium Complexes in Drug-Resistant Cancer Cell Lines: Structure-Activity Relationships and Direct Luminescent Imaging

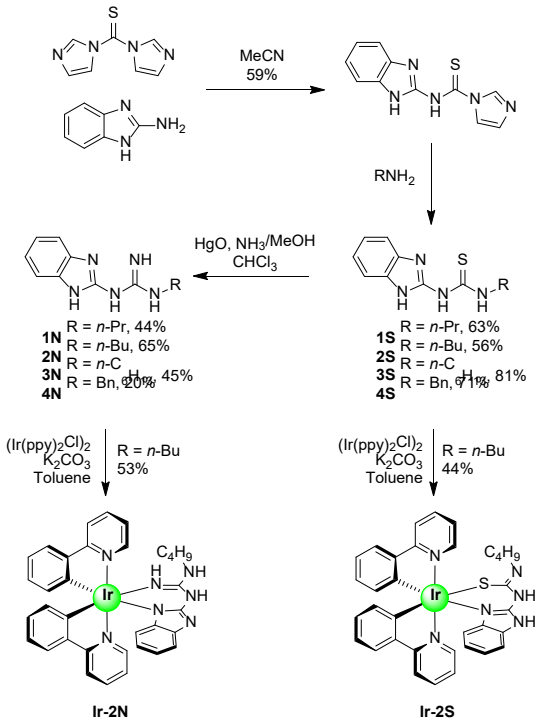
Samuel J. Thomas,[a] Barbora Balónová,[b] Jindrich Cinatl jr.,[c] Mark N. Wass,[a] Christopher J. Serpell,*[d] Barry A. Blight,*[b] Martin Michaelis*[a]

[a] S. J. Thomas, Mark N. Wass, Martin Michaelis
School of Biosciences
University of Kent
Stacey Building, Canterbury, Kent, CT2, 7NJ, UK
E-mail: M.Michaelis@kent.ac.uk
[b] Dr Barbora Balónová, Assoc. Prof Barry A. Blight
Department of Chemistry
University of New Brunswick
Fredericton, New Brunswick, E3B 5A3, Canada
Email: b.blight@unb.ca
[c] Prof Jindrich Cinatl jr,
Institute of Medical Viralology
Goethe University Frankfurt,
Paul-Ehrlich-Strasse 40, 60596 Frankfurt am Main, Germany
[d] Dr Christopher J. Serpell
School of Physical Sciences
University of Kent
Ingram Building, Canterbury, Kent, CT2 7NH, UK,

Supporting information for this article is given via a link at the end of the document.

Abstract: Thiourea and guanidine units are found in nature, medicine, and materials. Their continued exploration in applications as diverse as cancer therapy, sensors, and electronics means that their toxicity is an important consideration. Iridium complexes present new opportunities for drug development imaging in terms of structure and photoactivity. We have systematically synthesised a set of thiourea and guandine compounds and iridium complexes thereof, and elucidated structure-activity relationships in terms of cellular toxicity in three ovarian cancer cell lines and their cisplatin-resistant sub-lines. We have been able to use the intrinsic luminescence of iridium complexes to visualise the effect of both structure alteration and cellular resistance mechanisms. These findings provide starting points for the development of new drugs and consideration of safety issues for novel thiourea-, guanidine-, and iridium-based materials.

Introduction: Thiourea and guanidine derivatives are versatile compounds that are used in industries from materials manufacturing to medical research. The two functional groups represent modifications of urea, with the oxygen being replaced by a sulfur, or by an NH unit, respectively. Compared to urea, thioureas are more acidic and poorer hydrogen bond acceptors. In contrast, guanidines are basic and protonated under most aqueous conditions (pK_a = 13.6 for unsubstituted guanidine). While urea is of low toxicity (oral LD50 in rats of 8471 mg/kg[1]), showing only irritant properties at high concentrations, guanidine is listed as harmful, with an LD50 of 1120 mg/kg for the hydrochloride.[2] Thiourea (LD50 of 1750 mg/kg) is a carcinogen and teratogen and has harmful effects on the thyroid.[3]



Scheme 1. Synthesis of guanidine and thiourea compounds and their iridium complexes.

Guanidines occur in biology in the form of the nucleobase guanine and the amino acid arginine, and are also found in urine.[4,5] These compounds have also been employed in the catalytic synthesis in

green chemistry,[6] as potential antivirals for the treatment of poliovirus,[7] and as adhesive promotors in the materials industry.[8] A focal point of guanidine research has been in medicinal chemistry. For example, metformin (*N*,*N*-dimethylbiguanide) is widely used in the treatment of type 2 diabetes.[9] Further research has been conducted on their antimicrobial and anticancer properties.[10–12] In these cases, the compounds studied included chalcones[13] and also platinum centred derivatives.[14] Findings like these support advances in synthesising further derivatives of guanidine compounds to target new areas of cancer therapeutics, and further illustrate the biological importance of these simple and easily manipulatable structures.

Compared to guanidines, thioureas are found more rarely, for example in 2-thiouridine in tRNAs.[15] Within chemistry, interest has centred on their hydrogen bonding capability which has enabled sensing of anions,[16] self-assembly,[17] and organocatalysis,[18] for example. The thiourea functional group has been used widely in medicine, with 2-thiouracil itself used to treat thyroid disorders for some time.[19] Thioureas are investigated as antiviral agents,[20] including non-nucleoside HIV-1 reverse transcriptase inhibitors,[21] insecticidal growth regulators,[22] anti-inflammatory,[22] and anticancer drugs.[20] Thioureas show promise as anticancer drug candidates due to their sulfur atoms,[23] with sulfur itself being a versatile and biologically important element to all living organisms.[24] Thiourea derivatives have been synthesised with an assortment of partnering organic structures and demonstrated to exert anti-cancer effects in human cancer cell lines from different entities including breast and lung cancer as well as leukaemia[25–27] [28]

We are currently investigating guanidine- and thiourea-based molecules as components in advanced organic LED materials through formation of luminescent iridium complexes.[29,30] Iridium complexes themselves are of great interest as potential cancer therapeutics because they generate a 3D scaffold, enabling structural diversity beyond the 'flatter' organic molecules or platinum complexes used in cancer therapy; they offer an opportunity for simultaneous imaging due to their rich and tuneable luminescence properties;[31] and they offer an opportunity for photogeneration of singlet oxygen within cells.[32] Furthermore, cyclometallated iridium complexes similar to those we investigate for organic LEDs have been shown to interfere with protein-protein interactions,[33] bind G-quadruplexes in oncogene promoters,[34] and can be used to target either the mitochondria[35] or endoplasmic reticulum.[36] Mechanisms of action for cell death caused by iridium complexes include generation of reactive oxygen species (ROS)[32] and interference with NF-κB.[33,37]

Given the broad application of guanidines, thioureas, and iridium complexes in upcoming drugs and materials, their toxicity is of interest both from the standpoint of potentially beneficial or detrimental effects. In this light, we decided to perform a systematic screen of a series of thiourea and guanidine compounds and their iridium complexes for toxicity in ovarian cancer cell lines, including those which display resistance to cisplatin, the mainstay of ovarian cancer therapies and one of the most commonly used anticancer drugs.[38,39] These studies identify trends which could be used as first pointers for initial toxicity predictions of similar compounds. We have also been able to make use of the intrinsic luminescence of iridium complexes to observe extent and distribution of uptake, and its relationship to guanidine or thiourea function.

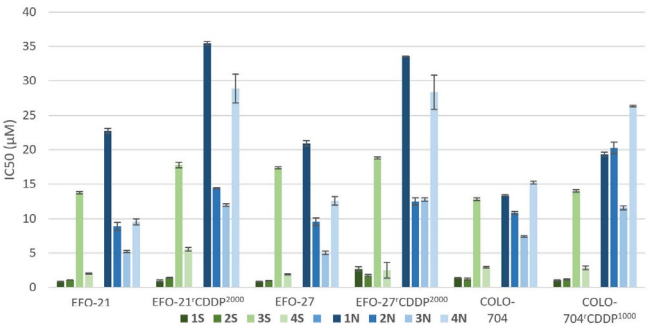


Figure 1. IC50 values for compounds **1S-4S** and **1N-4N** against six cancer cell lines. Error bars represent one standard deviation, over three repeats.

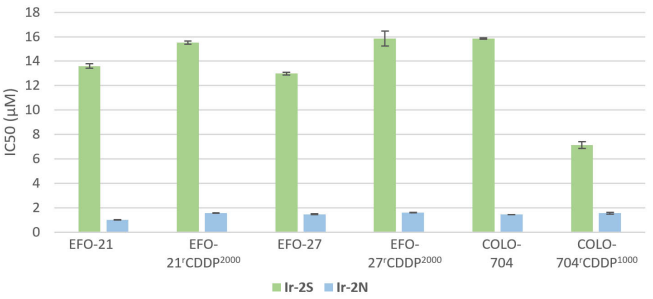


Figure 2. IC50 values for compounds **Ir-2S** and **Ir-2N** against six cancer cell lines. Error bars represent one standard deviation over three repeats.

Results and Discussion: A series of guanidine and thiourea compounds was synthesised based upon a 2-aminobenzimidazole unit; this was selected since it is a 'drug-like' unit which also has capacity to form the type of metal complexes which could be used in OLED materials. Monosubstitution of 1,1'-thiocarbonyldiimidazole was achieved by reaction with substoichiometric 2-aminobenzimidazole in acetonitrile. The second imidzoyl unit was displaced by a selection of amines (n-propylamine, n-butylamine,[40] n-hexylamine, and benzylamine) in the presence of dimethylaminopyridine (DMAP) in dimethylformamide (DMF) to give compounds **1S** to **4S** in 63 - 81 % yield after purification.[21] Portions of these compounds were converted to the corresponding guanidines by reaction with mercury(II) oxide and methanolic ammonia in chloroform to give **1N** to **4N**[41,42] in 40 – 65% yield.[43] Two iridium complexes based on these systems were previously prepared by reacting **2S** and **2N** separately with $[Ir(ppy)_2Cl]_2$ in toluene in the presence of potassium carbonate, giving bright yellow powders **Ir-2S** and **Ir-2N** in 53 % and 44 % yield respectively as racemates (confirmed for **Ir-2N**, confirmed by single crystal X-ray diffraction).[29,30] All new compounds were characterised by ^{1}H and ^{13}C NMR, EI-MS, and elemental analysis (see supplementary information).

To examine the biological activity of the compounds synthesised, they were tested for effects on the viability of the human ovarian cancer cell lines EFO-21, EFO-27 and COLO-704 and their cisplatin-resistant sublines EFO-21^{r}CDDP^{2000}, EFO-27^{r}CDDP^{2000} (both adapted to cisplatin at 2 μg/mL), and COLO-704^{r}CDDP^{1000} (adapted to cisplatin at 1 μg/mL) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphennyltetrazolium bromide) (MTT) assay modified after Mosmann[44] as previously described.[45] Cisplatin is one of the most commonly used anticancer drugs, and resistance formation to cisplatin represents a major obstacle to the development of improved anticancer therapies.[38,46,47]. The assay principle is based on metabolization of the yellow MTT reagent

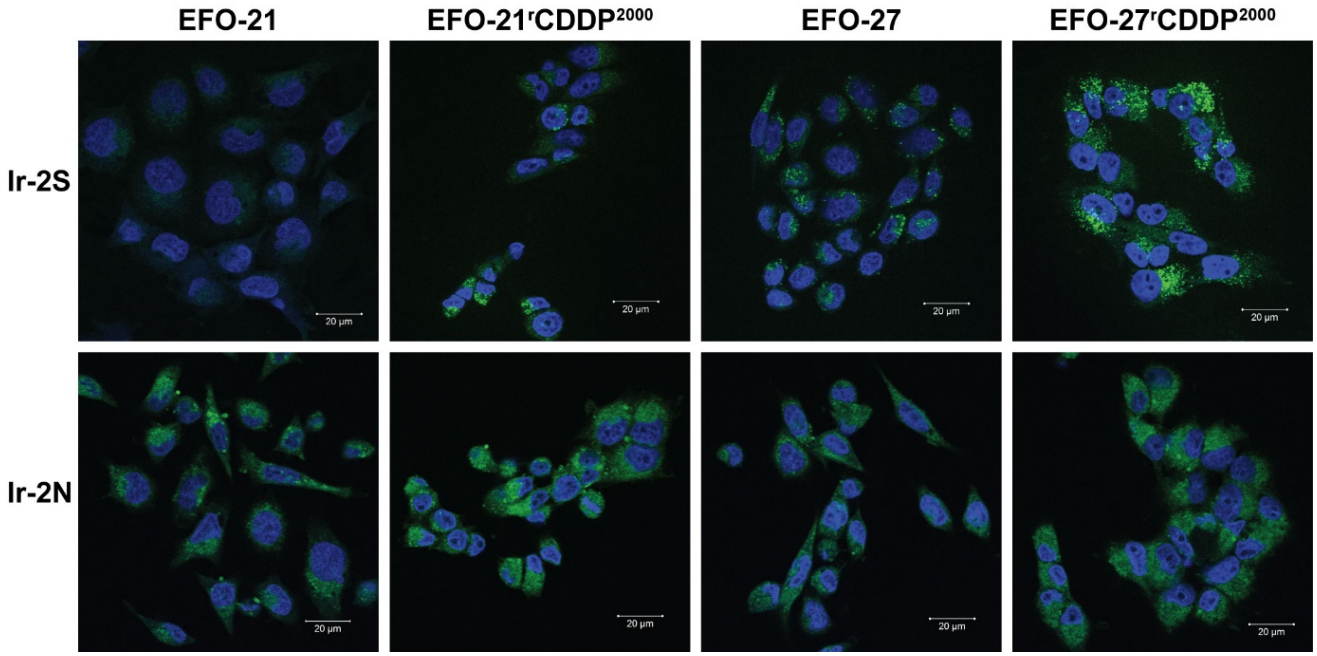


Figure 3. Confocal images of cells treated with **Ir-2S** and **Ir-2N**. Emission from metal complexes are green, and nuclei are shown in blue (stained with DAPI). All cells were treated with compounds at their IC50 concentrations. The brightness, gain and excitation of the confocal microscopes laser for compound expression was kept consistent throughout the assays, although slight adjustments were made to the brightness of the DAPI stain to achieve a clear nuclei mapping image. Individual channels and control images can be found in Fig. S7-S18 in the Supplementary Information.

into a purple insoluble formazan compound within the mitochondria of viable cells.[44] This colour change from yellow to purple enables for the collection of rapid and coherent cell proliferation data.[48] Concentrations that reduce cell viability by 50% relative to an untreated control (IC50) were calculated by treating the cell lines with sequential dilutions of the compounds. All of the unmetallated compounds examined showed toxicity in all cell lines, with IC50 values in the low micromolar range (Fig. 1). While thioureas **1S**, **2S**, and **4S** (IC50s across all cell lines averaging 1.29, 1.26, and 2.96 µM, respectively) were notably more toxic than their guanidine counterparts **1N**, **2N**, and **4N** (averaging 18.7, 10.1, 6.8 µM respectively), the hexyl-appended **3S** (average IC50 across all cell lines 15.8 µM) was less effective at inhibiting cell proliferation than **3N** (9.0 µM average). We propose that these differences relate to the impact that the longer chain makes on the hydrophobicity balance of the molecule. The guanidine compounds are expected to be protonated under these conditions, and addition of a long chain will produce a cationic surfactant-type molecule which could disrupt biological membranes.[49] With other side chains, the charged guanidiniums may not be sufficiently lipophilic to enter the biological membranes when compared to the neutral thioureas. This is supported by ClogP value calculation (Table S1, supplementary information) – only **3N** (ClogP = 2.75) is as lipophilic as any of the S series (lowest ClogP is for **1S**, at 2.58). In the case of **3S**, the lipophilicity may be so high that it prevents the compound leaving the membrane and entering the cells. Despite the variation in activity of the individual compounds, the average sensitivity of the cell lines was remarkably consistent, with the parental EFO-21, EFO-27, and COLO-704 lines have average IC50s of 8.0, 8.7, and 8.1 µM, and their cisplatin-resistant sublines having average IC50s of 14.5, 14.1, and 12.1 µM, respectively. Hence overall, the cisplatin resistant sublines were also more resistant to our compounds, however this effect was larger with **1N**-**4N** than with **1S**-**4S** (average ratio of resistant/parental IC50s = 1.81 versus 1.23).

The same studies were then conducted with the iridium complexes **Ir-2S** and **Ir-2N** (Fig. 2). Here, the guanidine compound (average IC50 = 1.4 µM) was approximately ten times more toxic across the board than **Ir-2S** (average IC50 = 13.5 µM). This is a reverse of what was seen for the unmetallated compounds **2S** and **2N**. For both EFO-21 and EFO-27 lines, the cisplatin-resistant sublines were slightly more tolerant of all compounds (IC50s on average 25% higher), but when COLO-704rCDDP^{1000} cells were treated with **Ir-2S** the IC50 was reduced to 45% of the value of the parental cell line, suggesting that a different mechanism of resistance is in place here. In this case, both complexes are uncharged at pH 7, and since the chemical difference is on the interior of the molecule, they could be expected to have similar cell penetration properties, with the difference in toxicity being due to processing within the cell.

Taking advantage of the intrinsic luminescence of the iridium complexes, we were able to study whether the difference in toxicity related to cell uptake or internal processing using confocal microscopy (Fig. 3). Using EFO-21, EFO-21rCDDP^{2000}, EFO-27, and EFO-27rCDDP^{2000} cells, which were amenable to this technique due to good adhesion properties, cell lines were dosed with **Ir-2S** and **Ir-2N** at their IC50 concentrations. **Ir-2S** and **Ir-2N** have similar excitation and emission spectra in terms of peak position and shape, but the quantum yield of **Ir-2N** is roughly ten times that of **Ir-2S** (Fig. S1-S6, Supplementary Information), since the IC50s of **Ir-2S** are approximately ten times higher than those of **Ir-2N** (Table S2, supplementary information), the total brightness for full uptake of either molecule should be similar,

enabling an approximate comparison of uptake efficiency. Cell nuclei were stained with DAPI. In all cases, the compounds were observed to be primarily located in the cytoplasm, with little change in cell morphology compared to untreated cells. In EFO-21 and EFO-21^{r}CDDP^{2000} cells, there was clearly greater uptake of the more toxic **Ir-2N** compared to **Ir-2S**. This is impressive given the tenfold difference in concentrations. In EFO-27 cells, the **Ir-2N** uptake was only slightly higher than that of **Ir-2S**, while in EFO-27^{r}CDDP^{2000} cells, the total level of uptake was approximately equal. Across all cell lines, the distribution of the two different complexes differed considerably, with **Ir-2S** displaying a distinctively punctate distribution, while **Ir-2N** was more evenly dispersed and network-like, in some cases forming a bridge across the nucleus (e.g. Fig S9). Through comparison with reported images for other Ir complexes in cells, these distributions suggest that **Ir-2S** resides primarily in lysosomes[50] and the endoplasmic reticulum (ER)[51] is the target of **Ir-2N**. This difference in distribution is likely to relate to the difference in cytotoxicity – hydrophobic Ir complexes are known to accumulate in the membrane of the ER, inducing stress which results in apoptosis.[36] We believe that these observations may also shed light on the behaviour of the non-metallated molecules; there is already precedent for minor components of the Ir coordination sphere to drive subcellular location,[51] and in our case, due to reduced bond rotation arising from intramolecular hydrogen bonding in the free ligands, it is possible that the metal complex also preserves the conformation of the uncoordinated molecule. Complex stability, a prerequisite for this hypothesis, is reported to be good for similar Ir complexes.[52,53]

Conclusion: All compounds tested showed notable toxicity. On the one hand, this shows that use of similar thiourea and guanidine structures in materials applications should be accompanied by caution about release. On the other hand, these structures could be useful scaffolds for cancer chemotherapeutics; in particular for drug resistance. Cisplatin is a mainstay of ovarian cancer therapy: although initial response is common, resistance formation and therapy failure are typically inevitable[46,47,54]. Hence, cisplatin-resistant ovarian cancer is an unmet clinical need and novel therapies are urgently needed. Our series **1S-4S** showed minimal reduction in efficacy in cisplatin resistant cell lines. **Ir-2N** displayed nearly nanomolar activity across the panel of cell lines, an effect which may be due to apparent accumulation within the ER. **Ir-2S** was in fact more effective in the cisplatin resistant COLO-704 subline than it was in the parental line.

We have shown that the seemingly minor change of an S to NH can have significant effects upon the biological action of the molecules. This may relate to changes in conformation of the molecules due to intramolecular hydrogen bond formation.[29,30] In the case of the iridium complexes, the toxicity trend was reversed, but we were able to observe a dramatic difference in subcellular distribution of the complexes according to the S/NH substitution. The mechanism of action of these compounds is unknown, but we have shown that uptake of the metal complexes at least is efficient, and that their biological properties are tuned by even small changes in structure.

In summary, our investigation of thiourea and guanidine derivatives, and their iridium complexes, has uncovered promising low dose responses in the early research stages of human *in vitro* cell assays, with the data collected providing a start to new potential therapeutic pathways in the battle against drug-resistant ovarian cancer.

Acknowledgements

SJT thanks SACO AEI Polymers UK for funding. JC thanks Frankfurter Stiftung für krebskranke Kinder, and Hilfe für krebskranke Kinder Frankfurt e.V for funding.

Keywords: keyword 1 • keyword 2 • keyword 3 • keyword 4 • keyword 5

[1] National Library of Medicine, “ChemIDplus,” can be found under https://chem.nlm.nih.gov/chemidplus/rn/startswith/57-13-6, **n.d.**

[2] T. Güthner, B. Mertschenk, B. Schulz, in *Ullmann’s Encycl. Ind. Chem.*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2006**.

[3] B. Mertschenk, A. Knott, W. Bauer, in *Ullmann’s Encycl. Ind. Chem.*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2013**, pp. 1–15.

[4] C. J. Weber, *J Biol Chem* **1928**, *78*, 465–473.

[5] J. F. Van Pilsum, E. A. Wolin, *J. Lab. Clin. Med.* **1958**, *51*, 219–223.

[6] T. Ishikawa, T. Isobe, *Chem. - A Eur. J.* **2002**, *8*, 552–557.

[7] W. A. Rightsel, J. R. Dice, R. J. McAlpine, E. A. Timm, I. W. McLean, G. J. Dixon, F. M. Schabel, *Science* **1961**, *134*, 558–9.

[8] W. Huang, X. Sun, *J. Am. Oil Chem. Soc.* **2000**, *77*, 101–104.

[9] C. J. Dunn, D. H. Peters, *Drugs* **1995**, *49*, 721–749.

[10] M. Said, A. Badshah, N. Shah, H. Khan, G. Murtaza, B. Vabre, D. Zargarian, M. Khan, *Molecules* **2013**, *18*, 10378–10396.

[11] F. Sączewski, Ł. Balewski, *Expert Opin. Ther. Pat.* **2013**, *23*, 965–995.

[12] R. G. S. Berlinck, A. E. Trindade-Silva, M. F. C. Santos, *Nat. Prod. Rep.* **2012**, *29*, 1382.

[13] Y. Qian, H.-J. Zhang, P.-C. Lv, H.-L. Zhu, *Bioorg. Med. Chem.* **2010**, *18*, 8218–8225.

[14] A. A. Legin, M. A. Jakupec, N. A. Bokach, M. R. Tyan, V. Y. Kukushkin, B. K. Keppler, *J. Inorg. Biochem.* **2014**, *133*, 33–39.

[15] R. K. Kumar, D. R. Davis, *Synthesis and Studies on the Effect of 2-Thiouridine and 4-Thiouridine on Sugar Conformation and RNA Duplex Stability*, Oxford University Press, **1997**.

[16] C. J. Serpell, P. D. Beer, in *Compr. Supramol. Chem. II*, **2017**.

[17] L. J. White, S. N. Tyuleva, B. Wilson, H. J. Shepherd, K. K. L. Ng, S. J. Holder, E. R. Clark, J. R. Hiscock, *Chem. – A Eur. J.* **2018**, *24*, 7761–7773.

[18] Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187.

[19] A. Nagasaka, H. Hidaka, *J. Clin. Endocrinol. Metab.* **1976**, *43*, 152–158.

[20] W. Liu, J. Zhou, T. Zhang, H. Zhu, H. Qian, H. Zhang, W. Huang, R. Gust, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2701–2704.

[21] R. Vig, C. Mao, T. . Venkatachalam, L. Tuel-Ahlgren, E. A. Sudbeck, F. M. Uckun, *Bioorg. Med. Chem.* **1998**, *6*, 1789–1797.

[22] A. Shakeel, *J. Drug Des. Med. Chem.* **2016**, *2*, 10.

[23] I. L. Goncalves, G. O. de Azambuja, D. F. Kawano, V. L. Eifler-Lima, *Mini. Rev. Org. Chem.* **2017**, *15*, 28–35.

[24] *Nat. Chem. Biol.* **2006**, *2*, 169.

[25] R. Tokala, S. Bale, I. P. Janrao, A. Vennela, N. P. Kumar, K. R. Senwar, C. Godugu, N. Shankaraiah, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1919–1924.

[26] P. Liao, S.-Q. Hu, H. Zhang, L.-B. Xu, J.-Z. Liu, B. He, S.-G. Liao, Y.-J. Li, *Bull. Korean Chem. Soc.* **2018**, *39*, 300–304.

[27] H. Hu, C. Lin, M. Ao, Y. Ji, B. Tang, X. Zhou, M. Fang, J. Zeng, Z. Wu, *RSC Adv.* **2017**, *7*, 51640–51651.

[28] R. Pingaew, N. Sinthupoom, P. Mandi, V. Prachayasittikul, R. Cherdtrakulkiat, S. Prachayasittikul, S. Ruchirawat, V. Prachayasittikul, *Med. Chem. Res.* **2017**, *26*, 3136–3148.

[29] B. Balónová, D. R. Martir, E. R. Clark, H. J. Shepherd, E. Zysman-Colman, B. A. Blight, *Inorg. Chem.* **2018**, *57*, 8581–8587.

[30] B. Balónová, H. J. Shepherd, C. J. Serpell, B. A. Blight, *Supramol. Chem.* **2019**, 1–12.

[31] D.-L. Ma, C. Wu, K.-J. Wu, C.-H. Leung, *Molecules* **2019**, *24*, 2739.

[32] Z. Liu, P. J. Sadler, *Acc. Chem. Res.* **2014**, *47*, 1174–1185.

[33] T.-S. Kang, Z. Mao, C.-T. Ng, M. Wang, W. Wang, C. Wang, S. M.-Y. Lee, Y. Wang, C.-H. Leung, D.-L. Ma, *J. Med. Chem.* **2016**, *59*, 4026–4031.

[34] K. J. Castor, K. L. Metera, U. M. Tefashe, C. J. Serpell, J. Mauzeroll, H. F. Sleiman, *Inorg. Chem.* **2015**, *54*, 6958–6967.

[35] L. He, K.-N. Wang, Y. Zheng, J.-J. Cao, M.-F. Zhang, C.-P. Tan, L.-N. Ji, Z.-W. Mao, *Dalt. Trans.* **2018**, *47*, 6942–6953.

[36] R. Cao, J. Jia, X. Ma, M. Zhou, H. Fei, *J. Med. Chem.* **2013**, *56*, 3636–3644.

[37] T. S. Kang, W. Wang, H. J. Zhong, Z. Z. Dong, Q. Huang, S. W. F. Mok, C. H. Leung, V. K. W. Wong, D. L. Ma, *Cancer Lett.* **2017**, *396*, 76–84.

[38] S. Ghosh, *Bioorg. Chem.* **2019**, *88*, 102925.

[39] S. Dasari, P. Bernard Tchounwou, *Eur. J. Pharmacol.* **2014**, *740*, 364–378.

[40] M. I. Rodríguez-Franco, I. Dorronsoro, A. Martínez, A. Castro, *J. Heterocycl. Chem.* **2001**, *38*, 435–441.

[41] N. Sato, S. Matsumoto, A. Tsunoda, N. Ishida, *J Antibiot* **1966**, *19*, 172–174.

[42] T. Mukherjee, C. Ganzmann, N. Bhuvanesh, J. A. Gladysz, *Organometallics* **2014**, *33*, 6723–6737.

[43] B. A. Blight, C. A. Hunter, D. A. Leigh, H. McNab, P. I. T. Thomson, *Nat. Chem.* **2011**, *3*, 244–248.

[44] T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55–63.

[45] M. Michaelis, J. Matousek, J. U. Vogel, T. Slavik, K. Langer, J. Cinatl, J. Kreuter, D. Schwabe, J. Cinatl, *Anticancer. Drugs* **2000**, *11*, 369–76.

[46] B. van Zyl, D. Tang, N. A. Bowden, *Endocr. Relat. Cancer* **2018**, *25*, R303–R318.

[47] G. Damia, M. Broggini, *Cancers (Basel)*. **2019**, *11*, 119.

[48] D. Gerlier, N. Thomasset, *J. Immunol. Methods* **1986**, *94*, 57–63.

[49] S. Zhang, S. Ding, J. Yu, X. Chen, Q. Lei, W. Fang, *Langmuir* **2015**, *31*, 12161–12169.

[50] A. Sansee, S. Meksawangwong, K. Chainok, K. J. Franz, M. Gál, L.-O. Pålsson, W. Puniyan, R. Traiphol, R. Pal, F. Kielar, *Dalt. Trans.* **2016**, *45*, 17420–17430.

[51] C. Caporale, C. A. Bader, A. Sorvina, K. D. M. MaGee, B. W. Skelton, T. A. Gillam, P. J. Wright, P. Raiteri, S. Stagni, J. L. Morrison, et al., *Chem. - A Eur. J.* **2017**, *23*, 15666–15679.

[52] M.-H. Chen, Y. Zheng, X.-J. Cai, H. Zhang, F.-X. Wang, C.-P. Tan, W.-H. Chen, L.-N. Ji, Z.-W. Mao, *Chem. Sci.* **2019**, *10*, 3315–3323.

[53] W. Wang, K. Vellaisamy, G. Li, C. Wu, C.-N. Ko, C.-H. Leung, D.-L. Ma, *Anal. Chem.* **2017**, *89*, 11679–11684.

[54] U. A. Matulonis, A. K. Sood, L. Fallowfield, B. E. Howitt, J. Sehouli, B. Y. Karlan, *Nat. Rev. Dis. Prim.* **2016**, *2*, 16061.

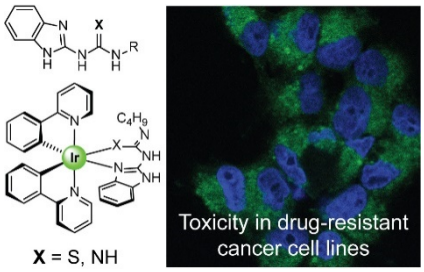
10.1002/cmdc.201900591

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents

Insert graphic for Table of Contents here.



Thiourea and guanidine compounds, and iridium complexes thereof, have been screened against drug-resistant cancer cell lines, showing toxicity against cis-platin resistant strains. The compounds display toxicity trends which are strongly dependent upon S/NH substitution. The patterns of toxicity are illuminated through use of the intrinsic luminescence of the complexes as a handle for cellular imaging.

Institute and/or researcher Twitter usernames: @SJ_Thomas93 @BarboraBalonova @markwassy @CJSerpell @DrBarryChem @MartMichaelis