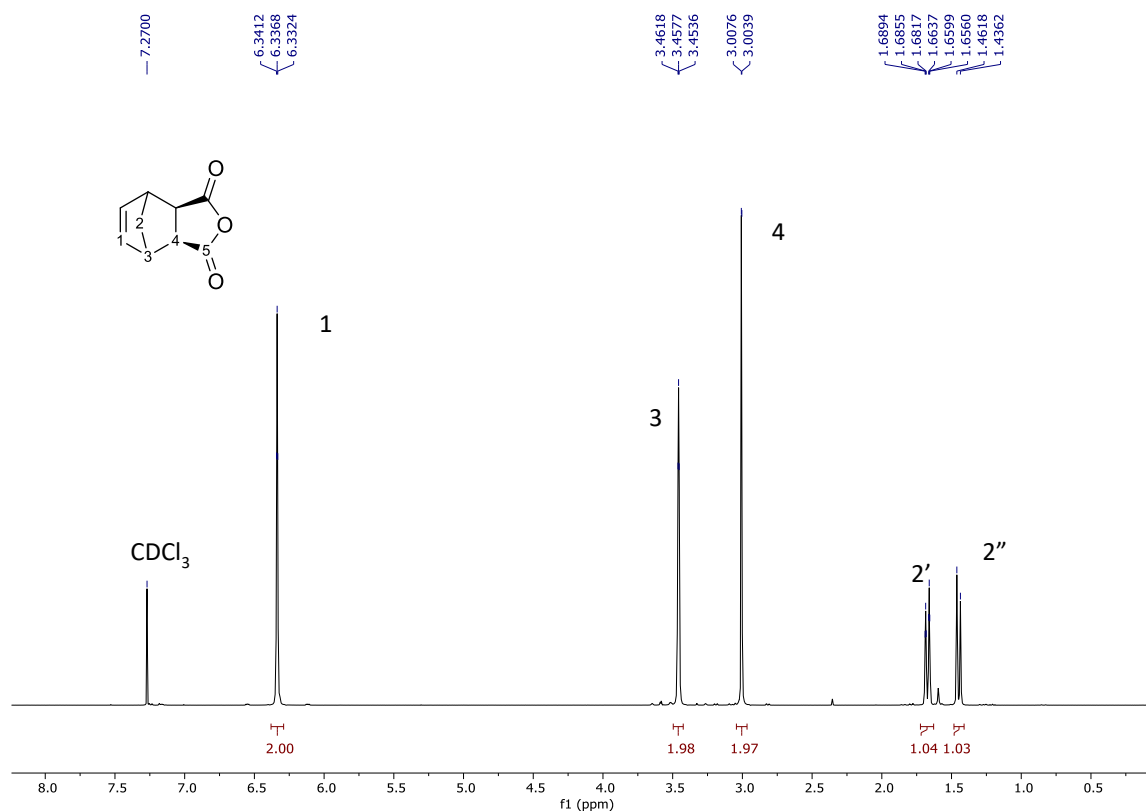


# APPENDIX 1. NSAIDs BASED ROMP NANOPARTICLES: SYNTHESIS, SELF-ASSEMBLY AND DRUG RELEASE.

## 1. NMR spectra



**Fig. S1.** <sup>1</sup>H NMR in CDCl<sub>3</sub> of *exo*-carbic anhydride, **1b**

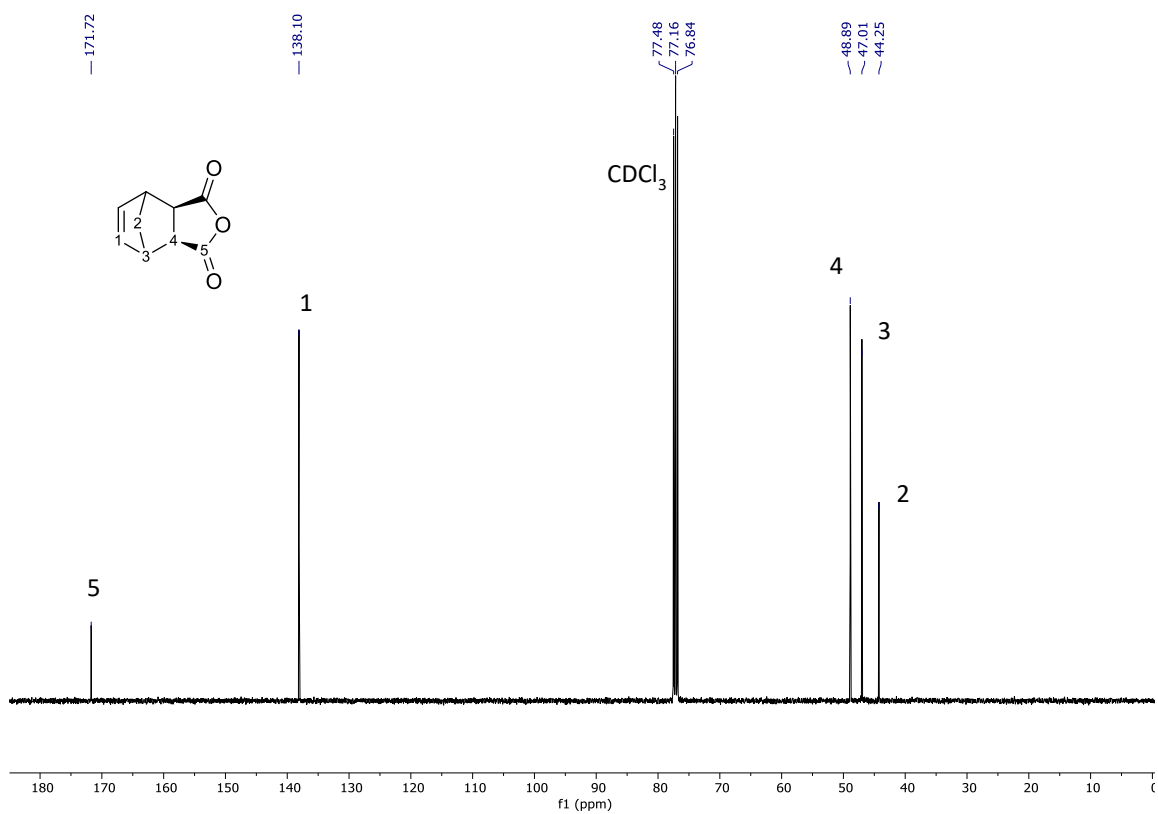


Fig. S2.  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  of *exo*-carbocyclic anhydride, **1b**

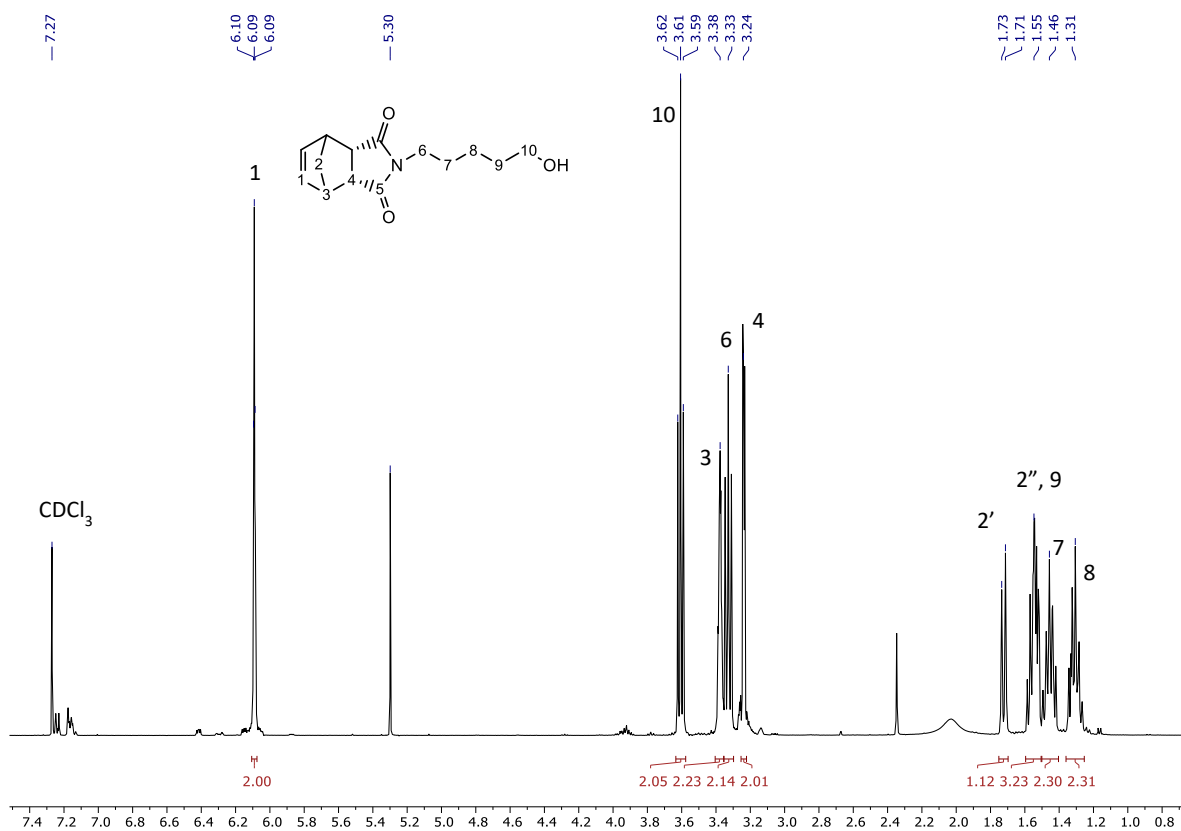
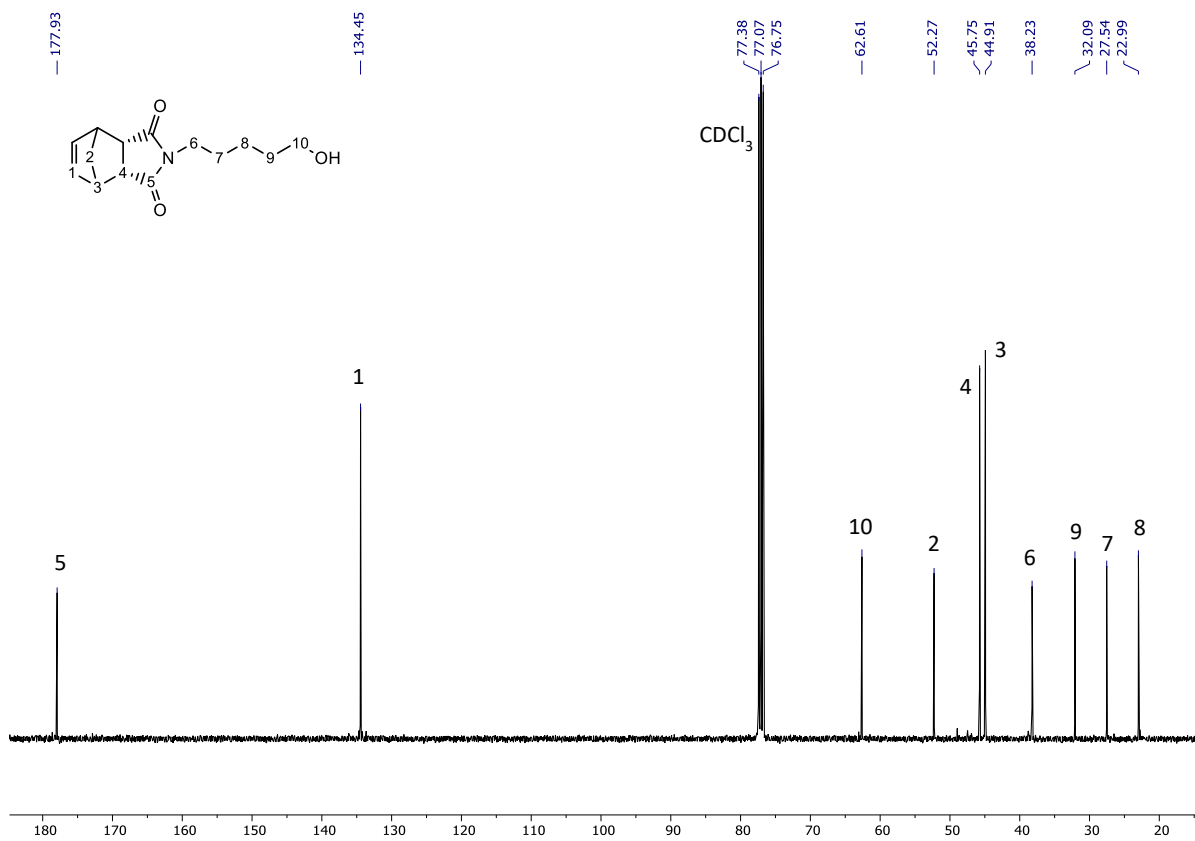
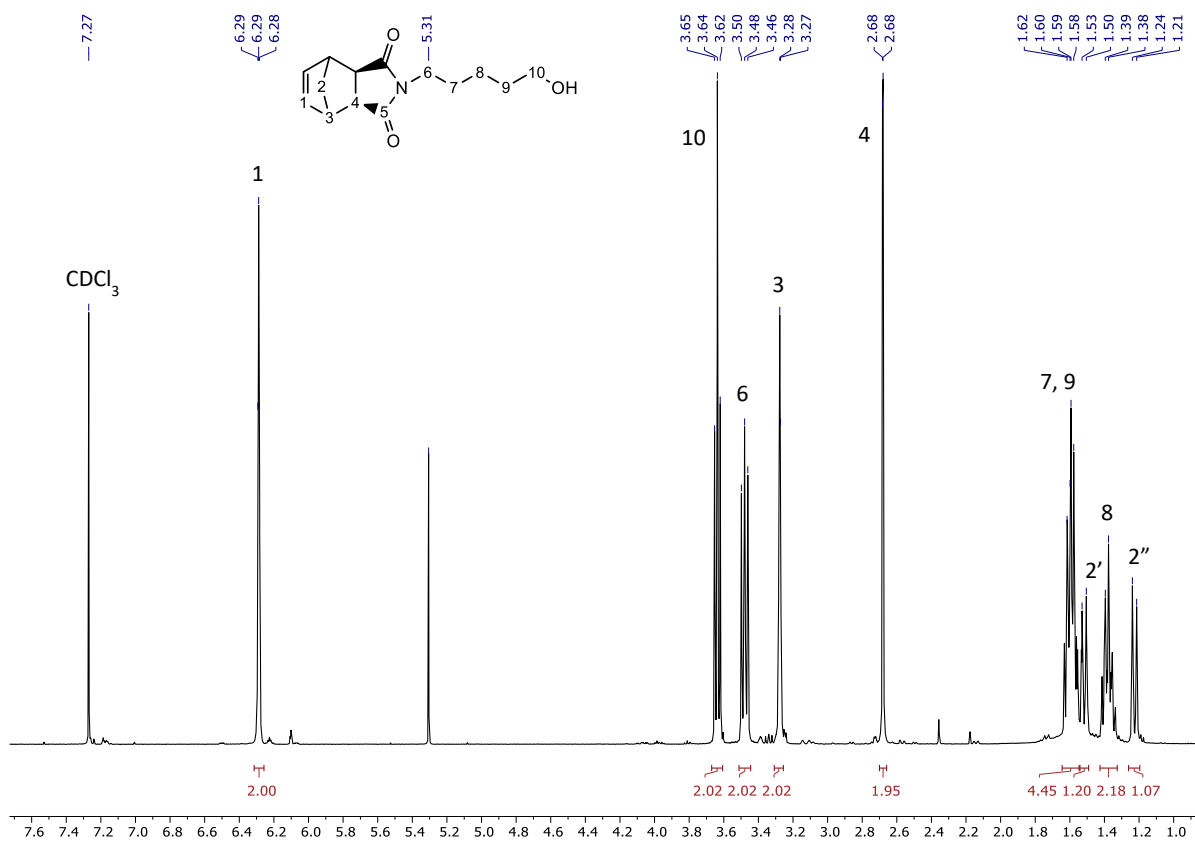


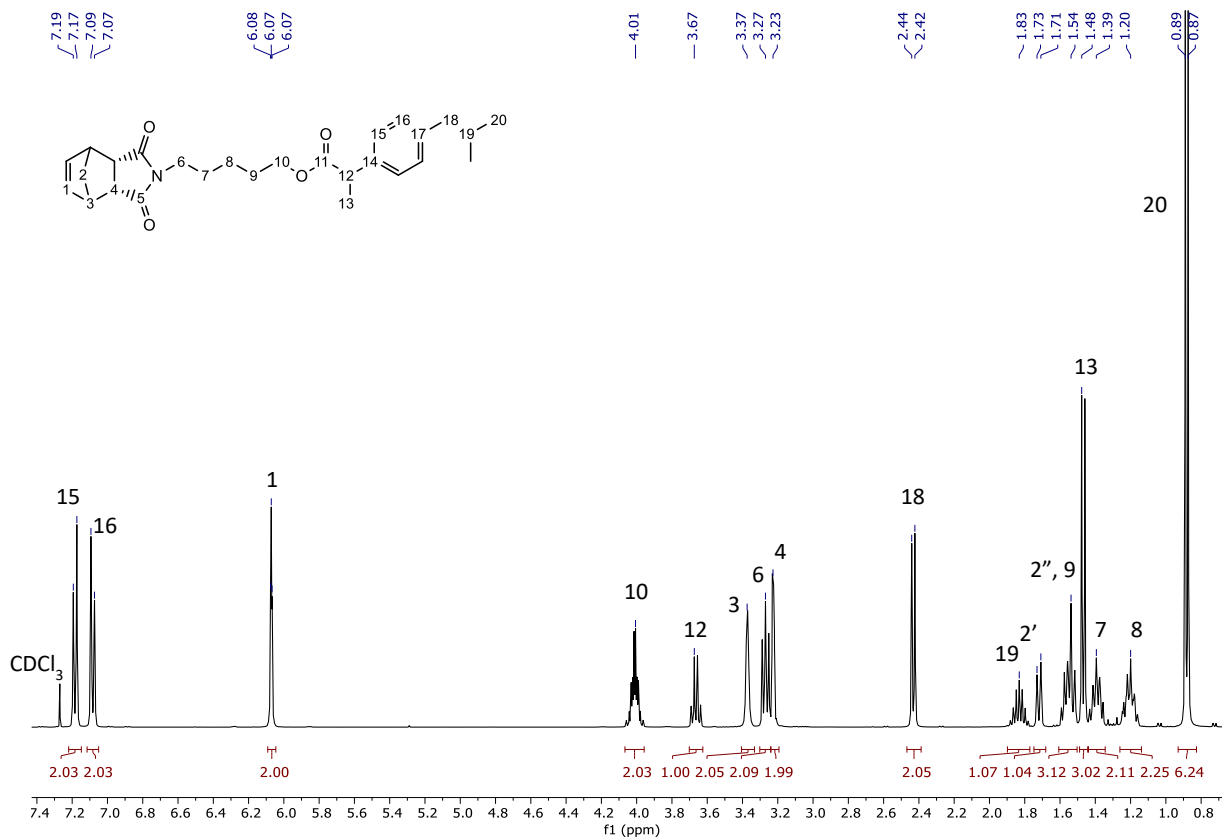
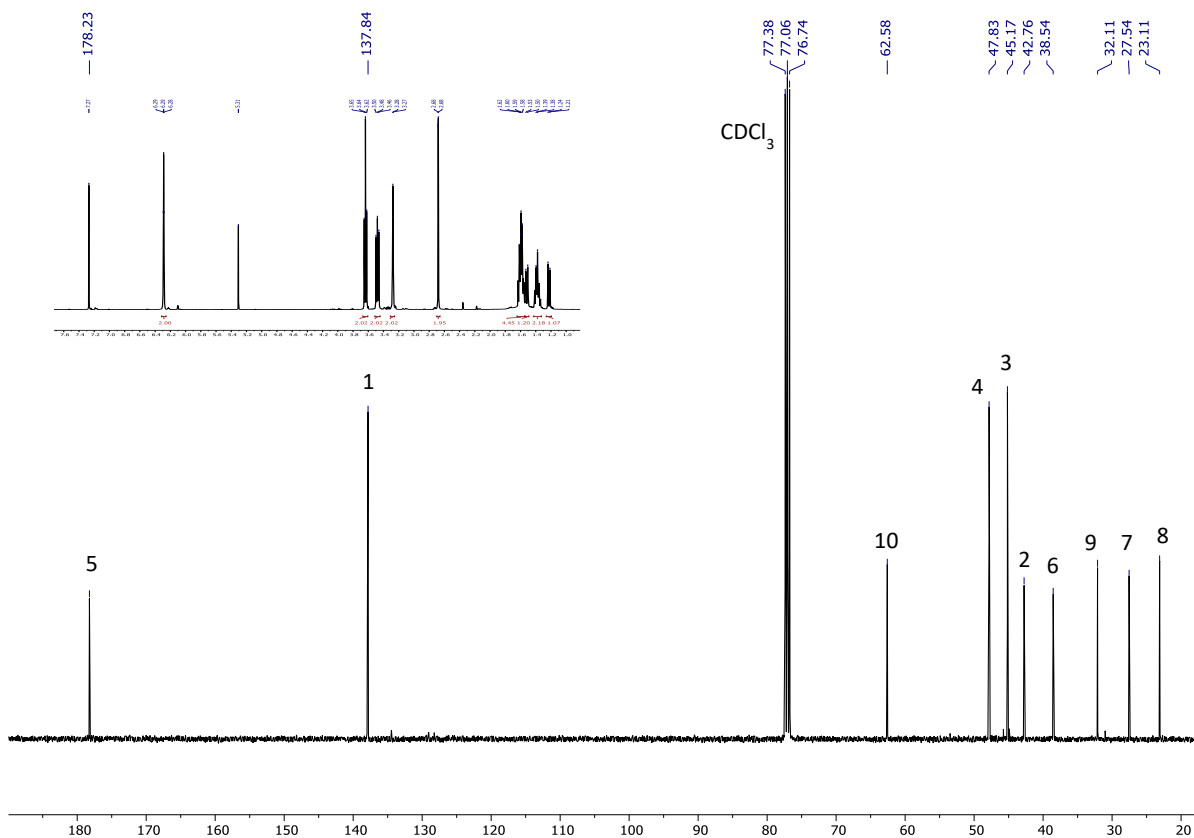
Fig. S3.  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of *N*-(hydroxypentanyl)-*cis*-5-norbornene-*endo*-2,3-dicarboximide, **3a**



**Fig. S4.**  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  of *N*-(hydroxypentanyl)-*cis*-5-norbornene-*endo*-2,3-dicarboximide, **3a**



**Fig. S5.**  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of *N*-(hydroxypentanyl)-*cis*-5-norbornene-*exo*-2,3-dicarboximide **3b**



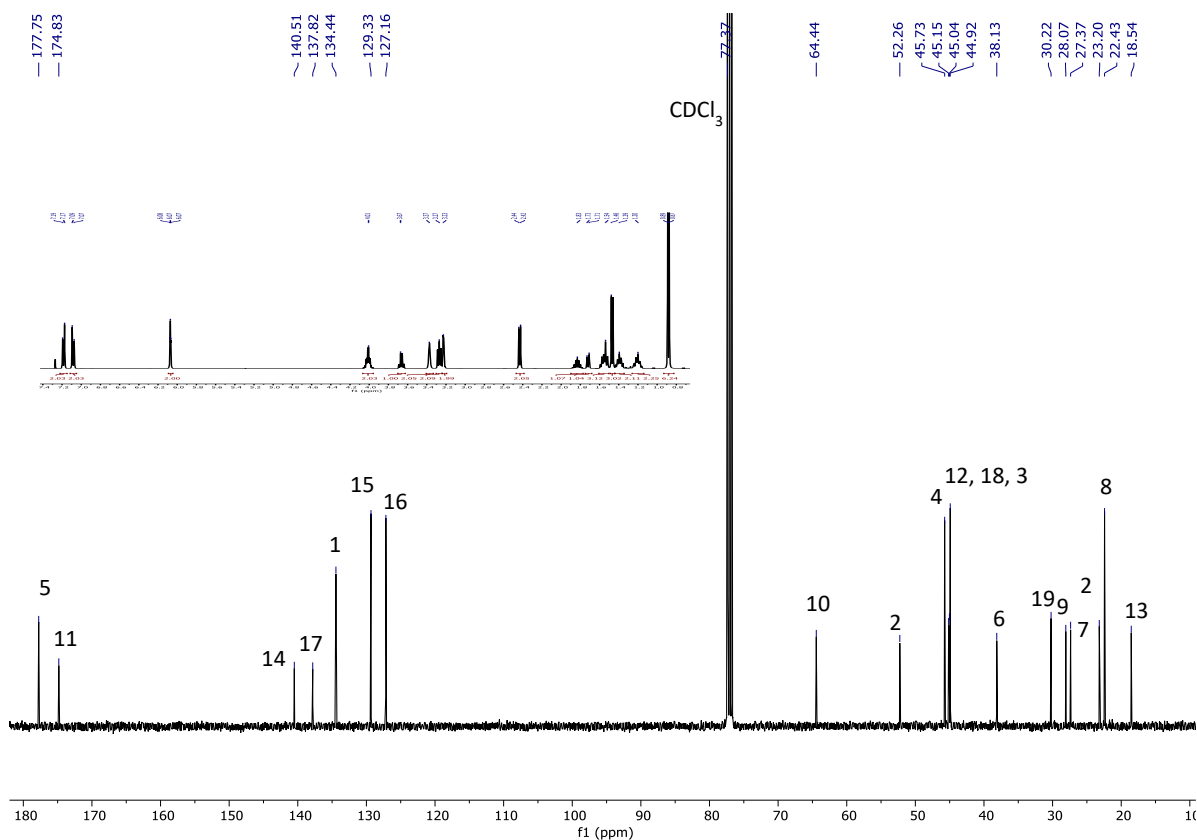


Fig. S8. <sup>13</sup>C NMR in CDCl<sub>3</sub> of Ibuprofen ester of compound 3a, 5a

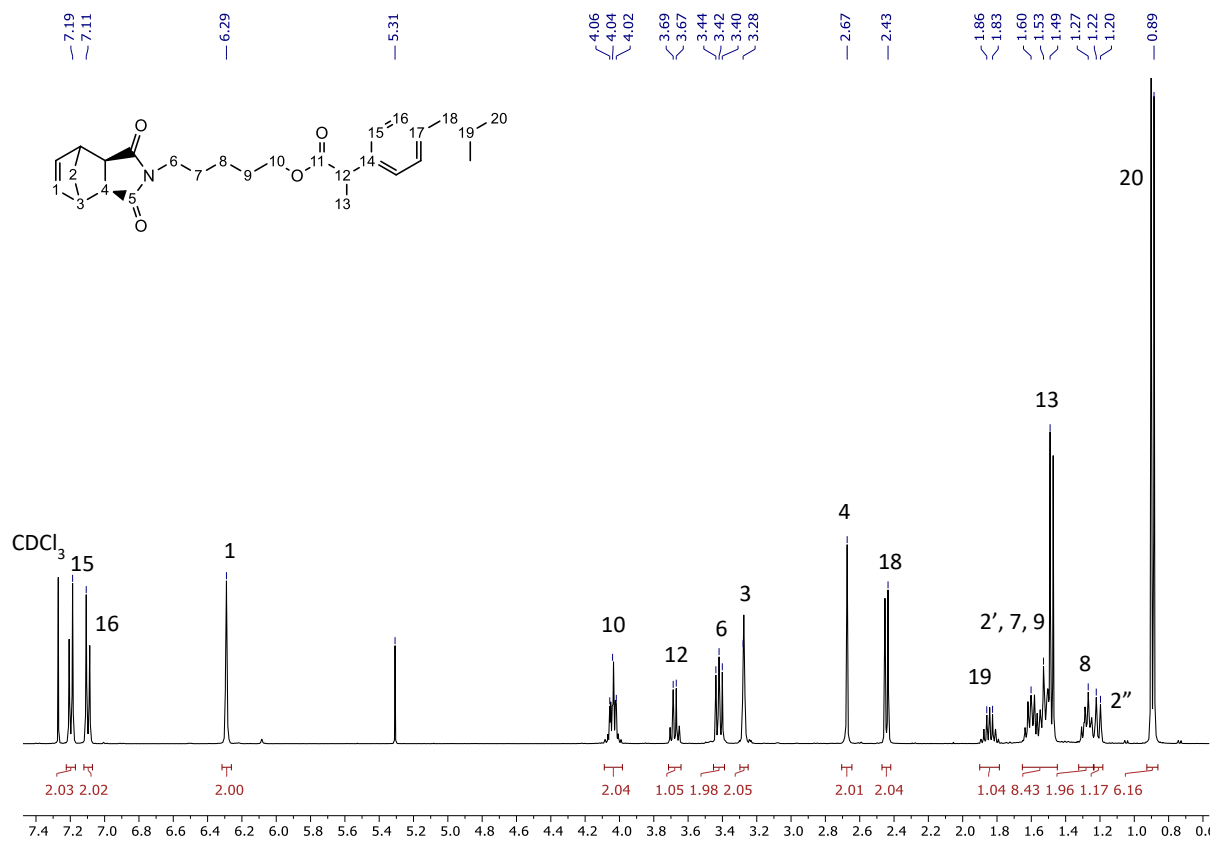
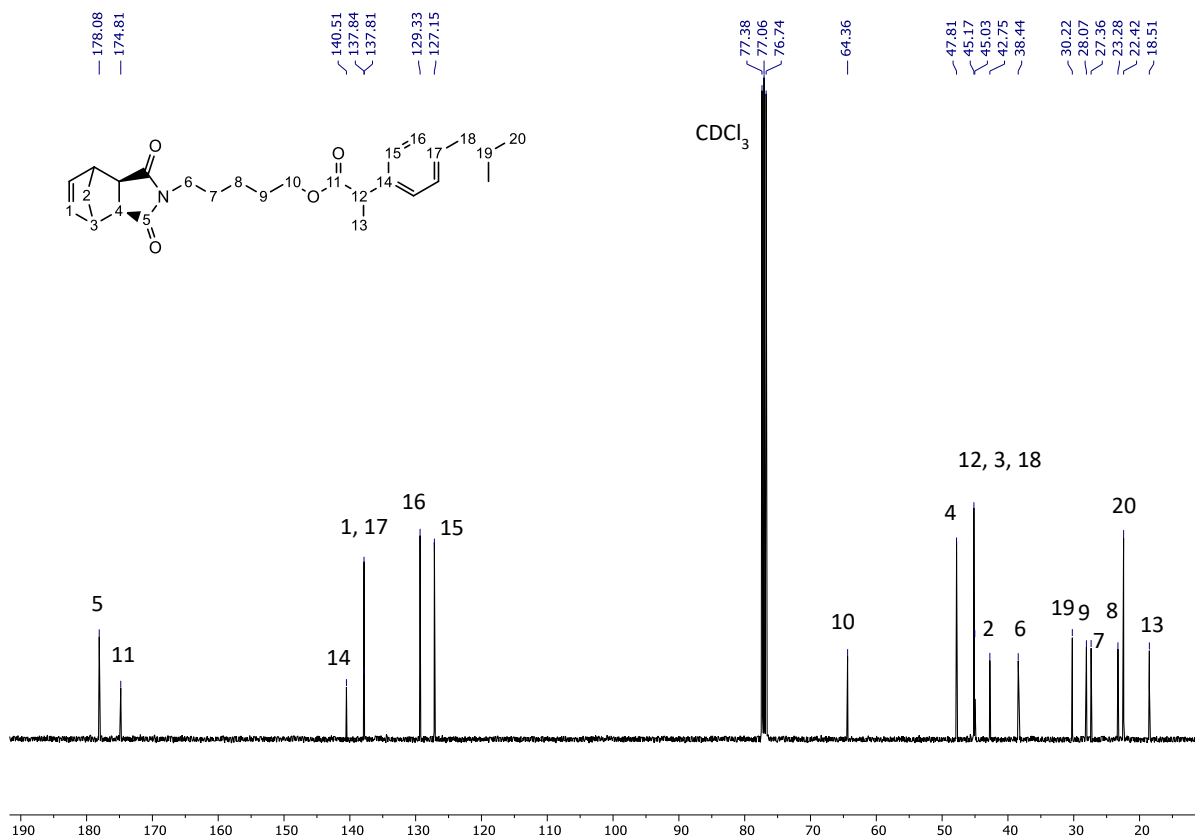
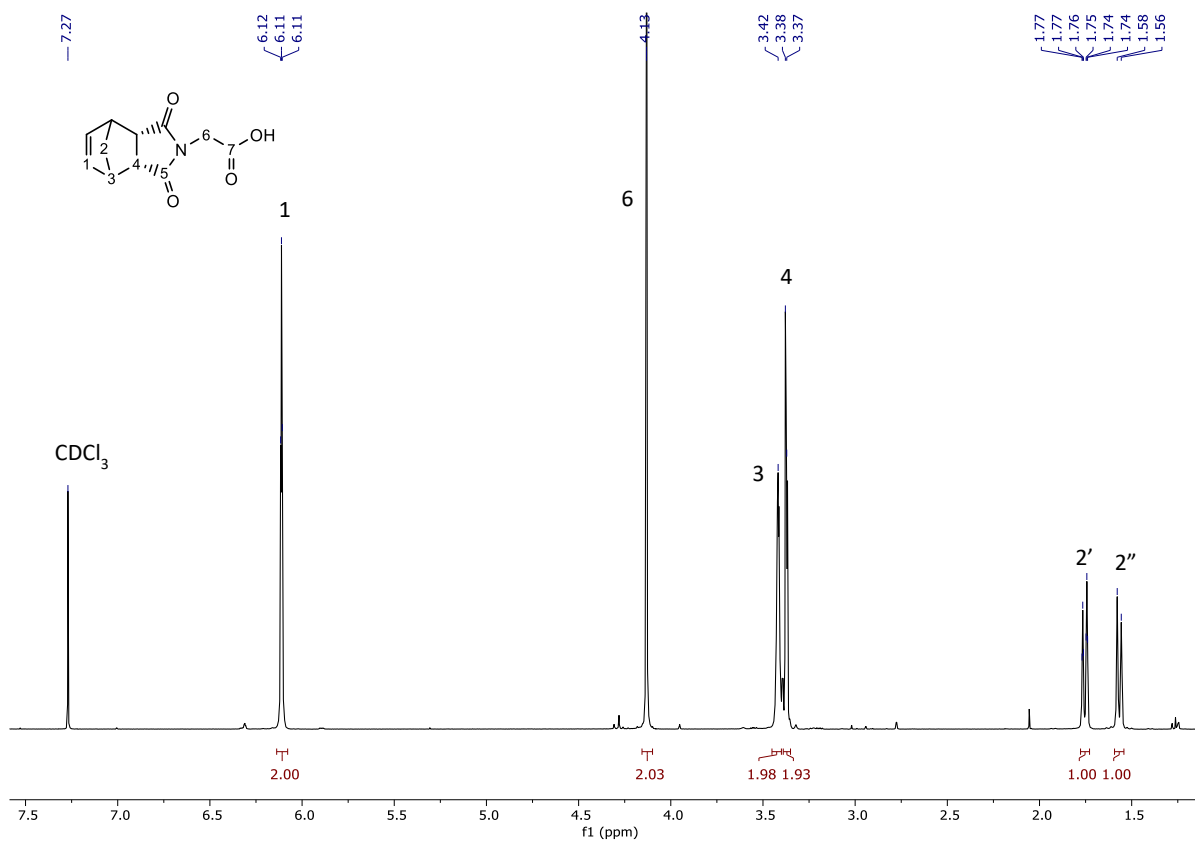


Fig. S9. <sup>1</sup>H NMR in CDCl<sub>3</sub> of Ibuprofen ester of compound 3b, monomer 5b (NB-Ibu)



**Fig. S10.** <sup>13</sup>C NMR in CDCl<sub>3</sub> of Ibuprofen ester of compound **3b**, monomer **5b** (NB-Ibu)



**Fig. S11.** <sup>1</sup>H NMR in CDCl<sub>3</sub> of *N*-(endo-himoyl)-glycine, **7a**

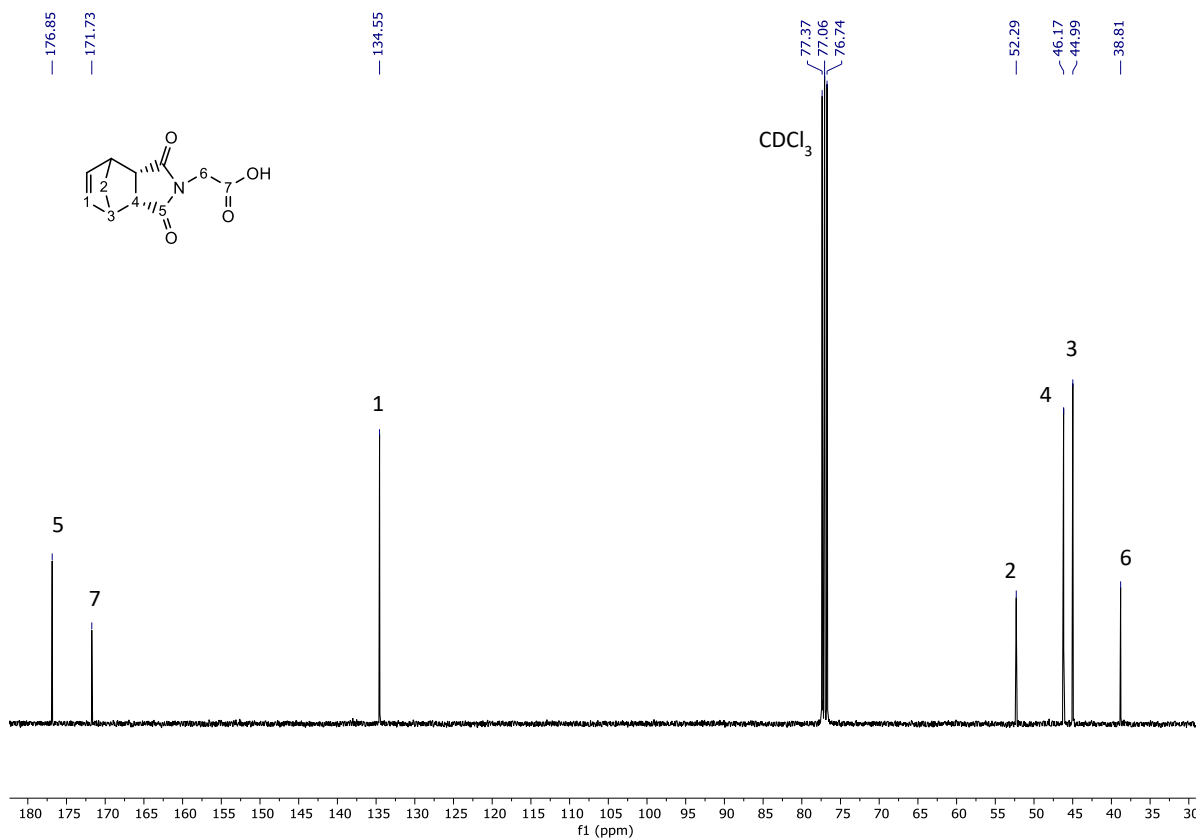


Fig. S12. <sup>13</sup>C NMR in CDCl<sub>3</sub> of *N*-(endo-himoyl)-glycine, **7a**

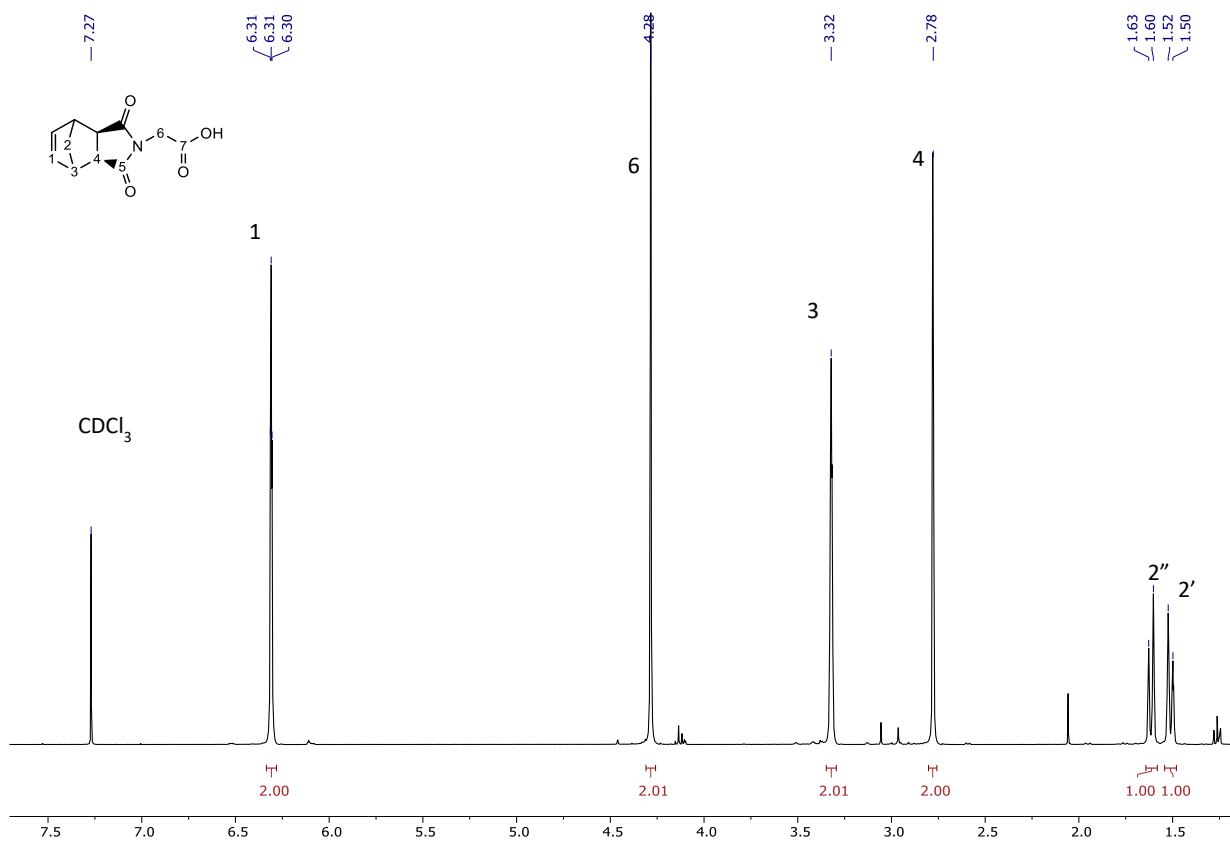
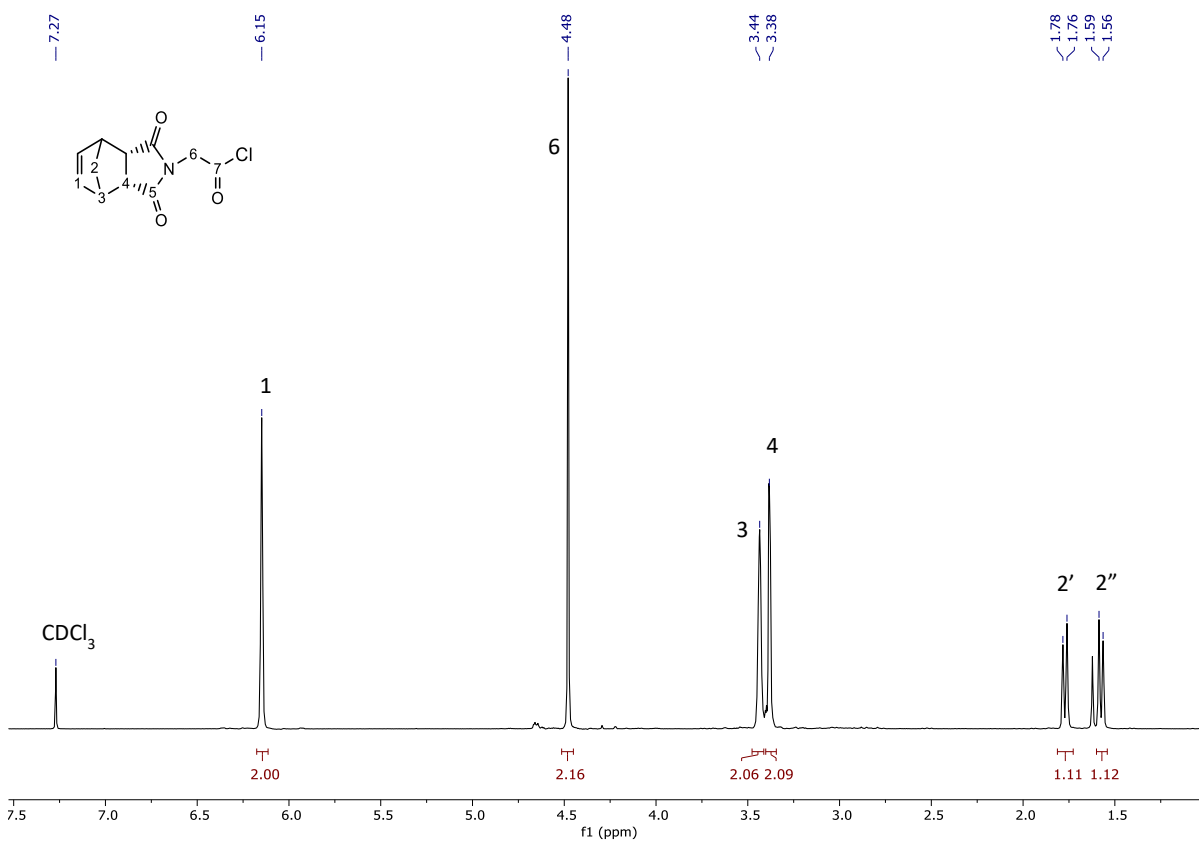
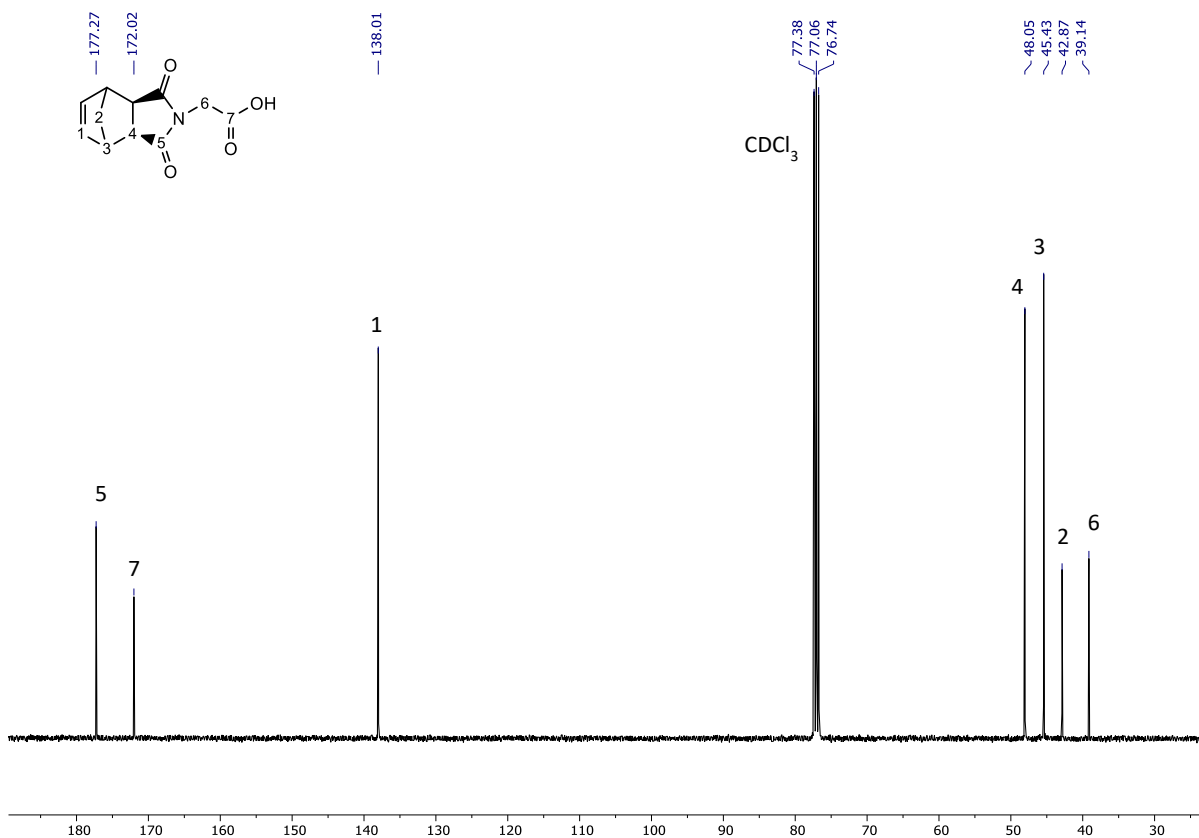


Fig. S13. <sup>1</sup>H NMR in CDCl<sub>3</sub> of *N*-(exo-himoyl)-glycine, **7b**





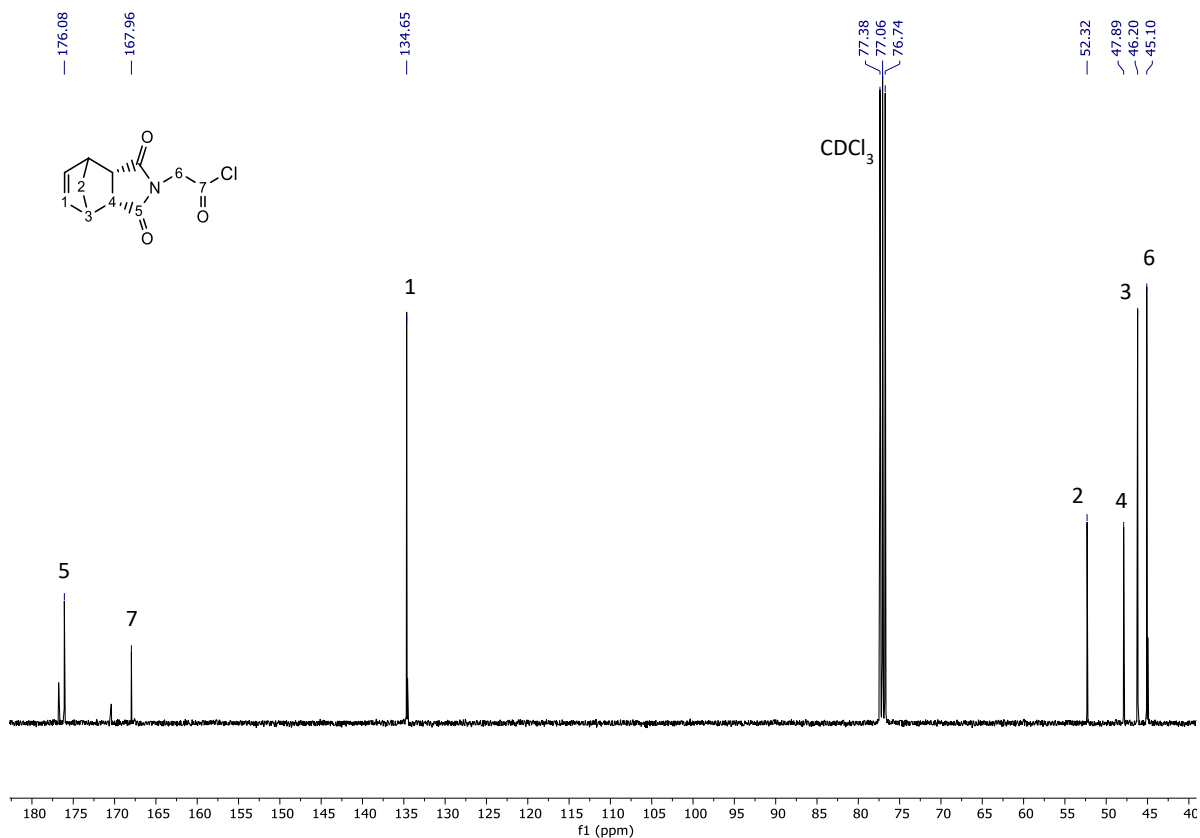


Fig. S16. <sup>13</sup>C NMR in CDCl<sub>3</sub> of *N*-(endo-himoyl)-glycinoyl chloride, **8a**

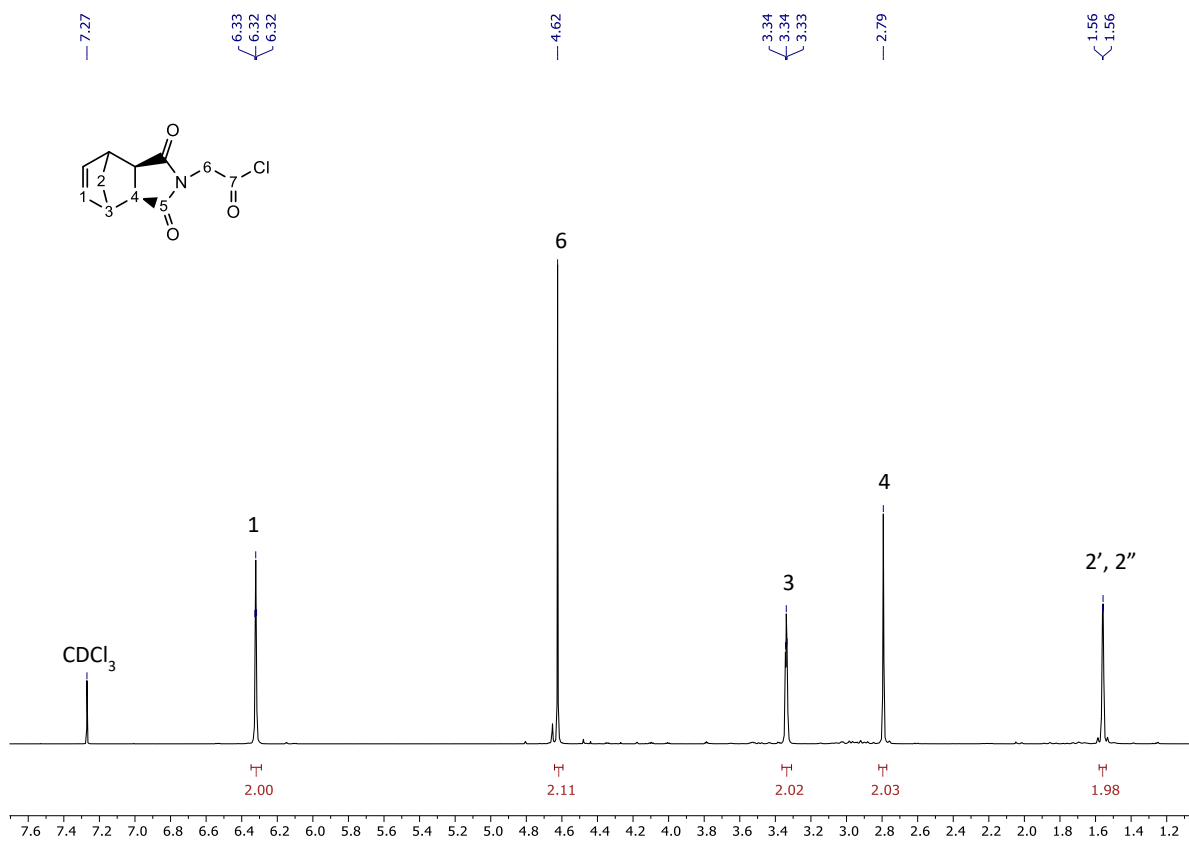


Fig. S17. <sup>1</sup>H NMR in CDCl<sub>3</sub> of *N*-(exo-himoyl)-glycinoyl chloride, **8b**

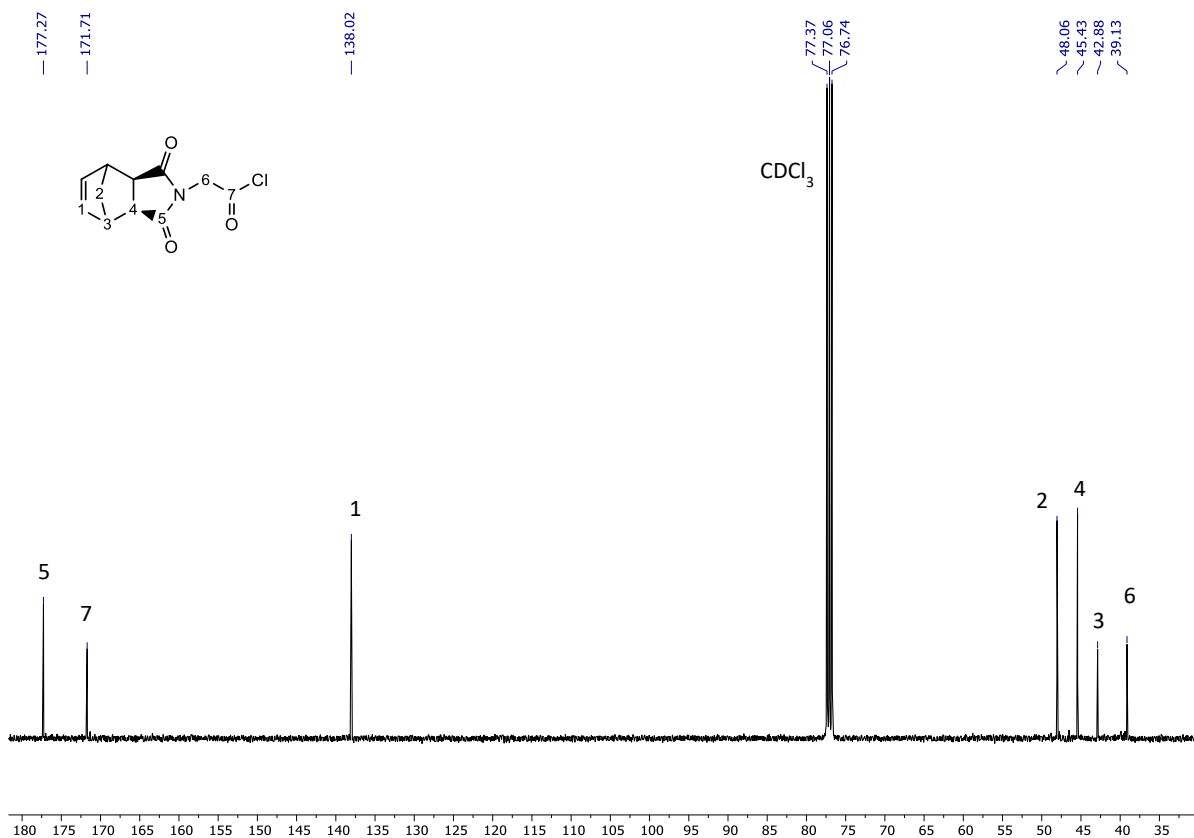


Fig. S18. <sup>13</sup>C NMR in CDCl<sub>3</sub> of *N*-(*exo*-himoyl)-glycinoyl chloride, **8b**

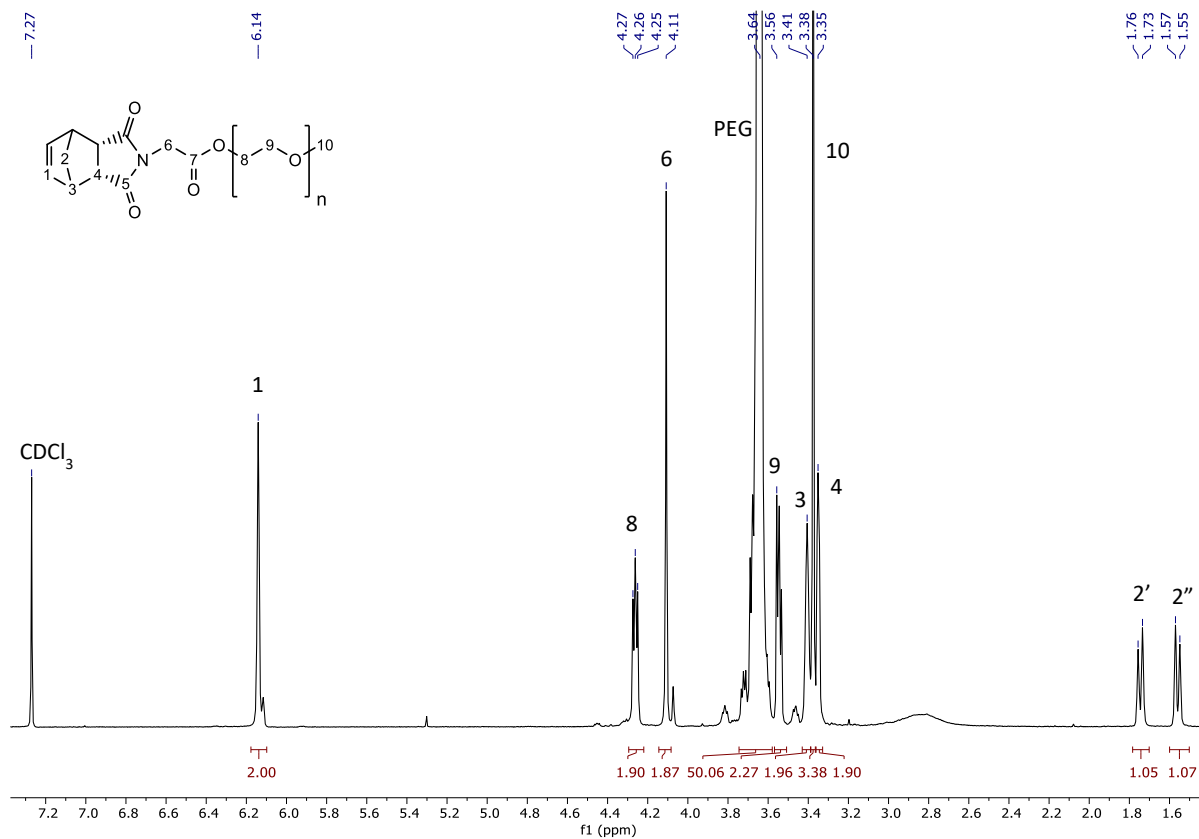
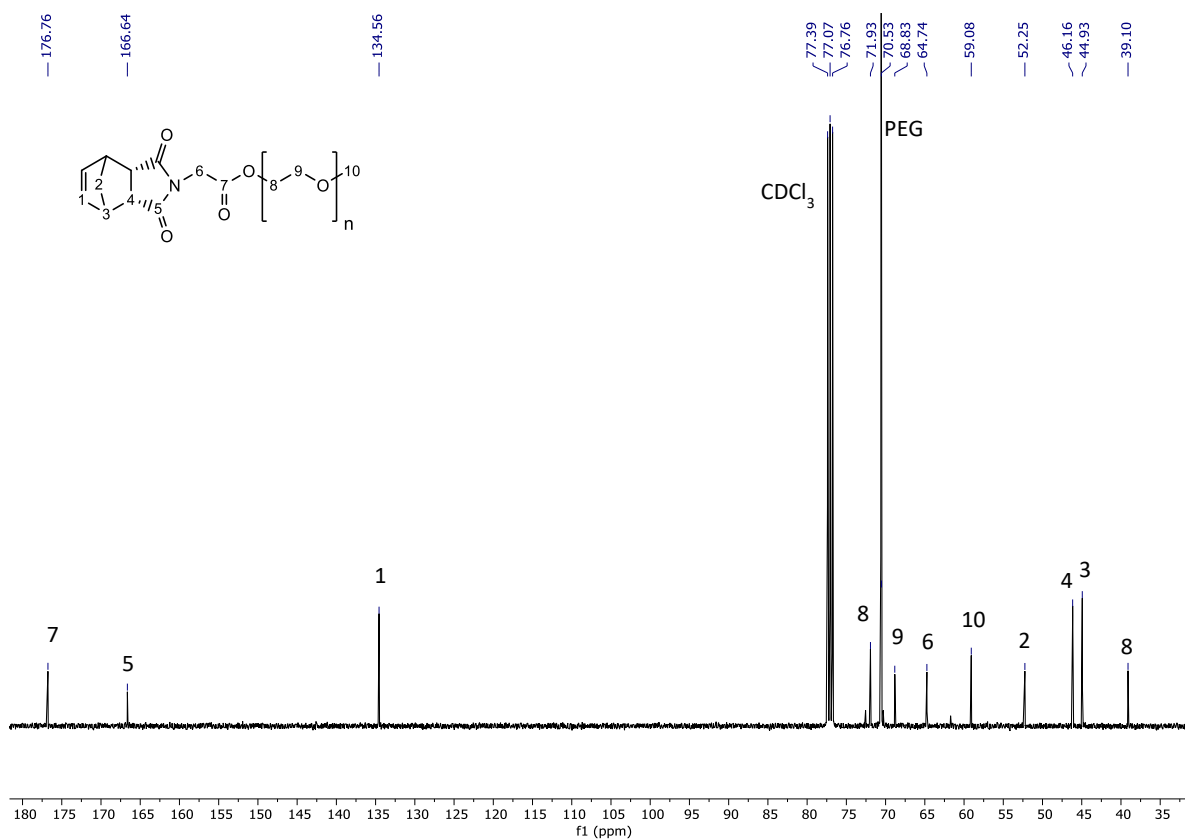
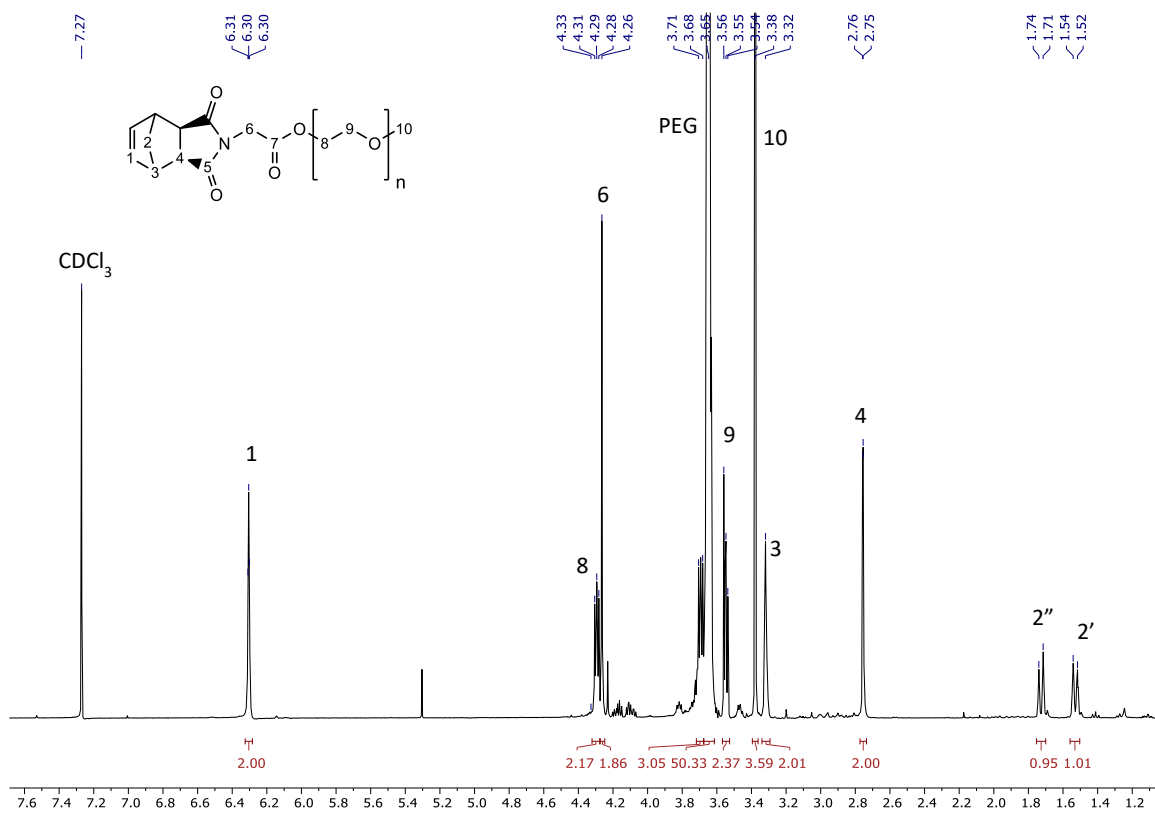


Fig. S19. <sup>1</sup>H NMR in CDCl<sub>3</sub> of *N*-(*endo*-himoyl)-glycine PEG-OMe ester, **10a**



**Fig. S20.** <sup>13</sup>C NMR in CDCl<sub>3</sub> of *N*-(endo-himoyl)-glycine PEG-OMe ester, **10a**



**Fig. S21.** <sup>1</sup>H NMR in CDCl<sub>3</sub> of *N*-(exo-himoyl)-glycine PEG-OMe ester, monomer **10b** (NB-PEG)

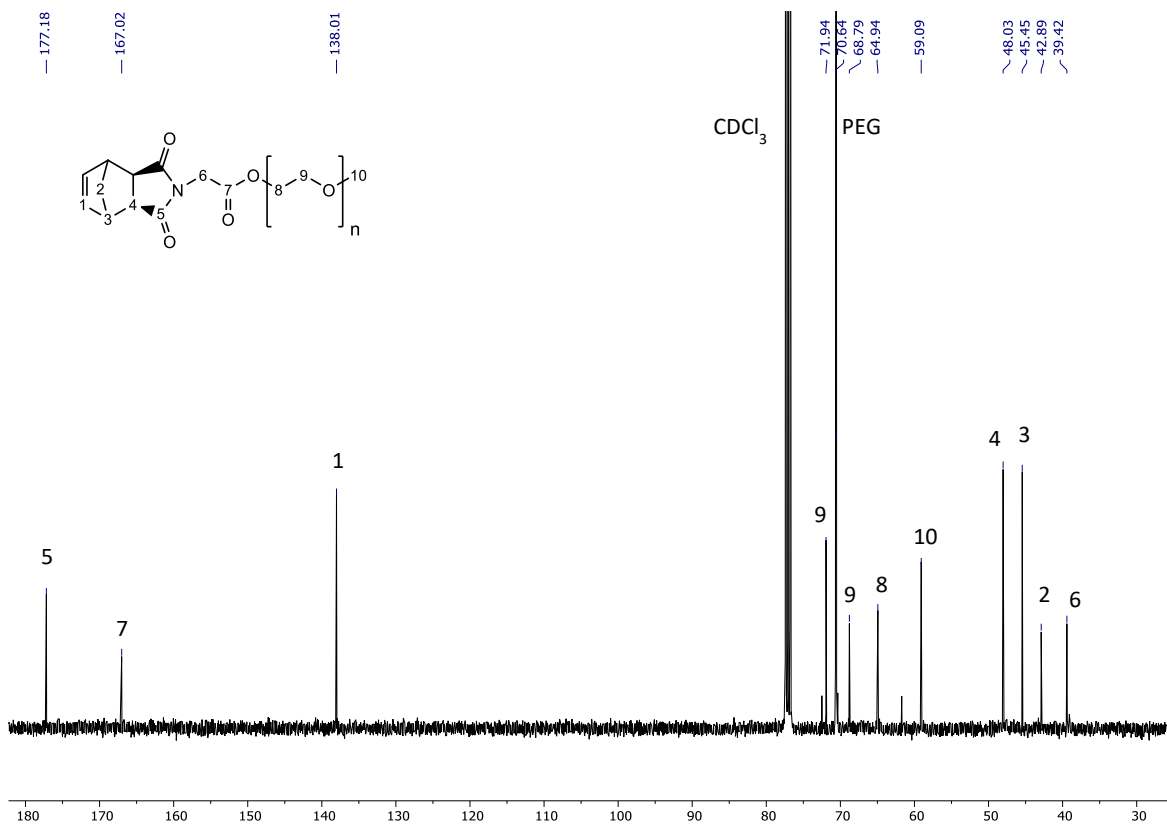


Fig. S22. <sup>13</sup>C NMR in CDCl<sub>3</sub> of *N*-(*exo*-himoyl)-glycine PEG-OMe ester, monomer **10b** (NB-PEG)

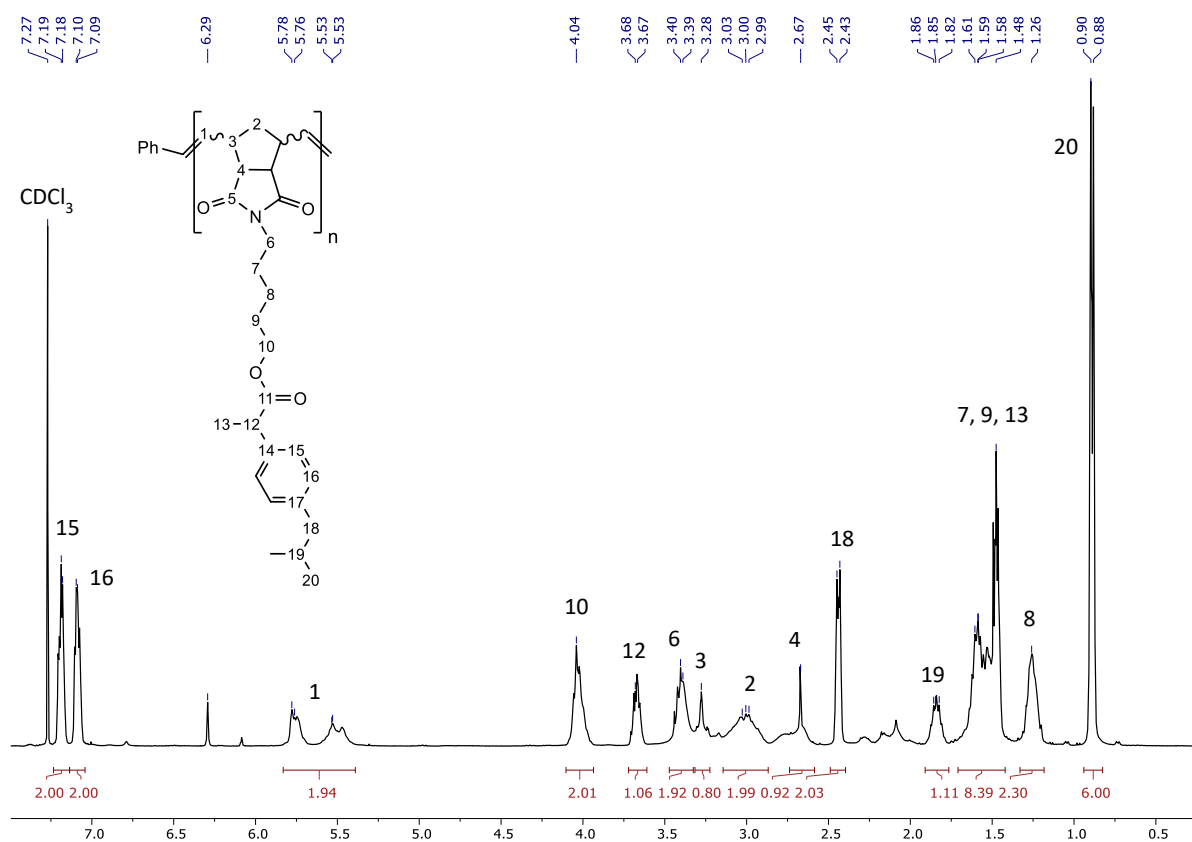


Fig. S23. <sup>1</sup>H NMR in CDCl<sub>3</sub> of homopolymer **poly5b**

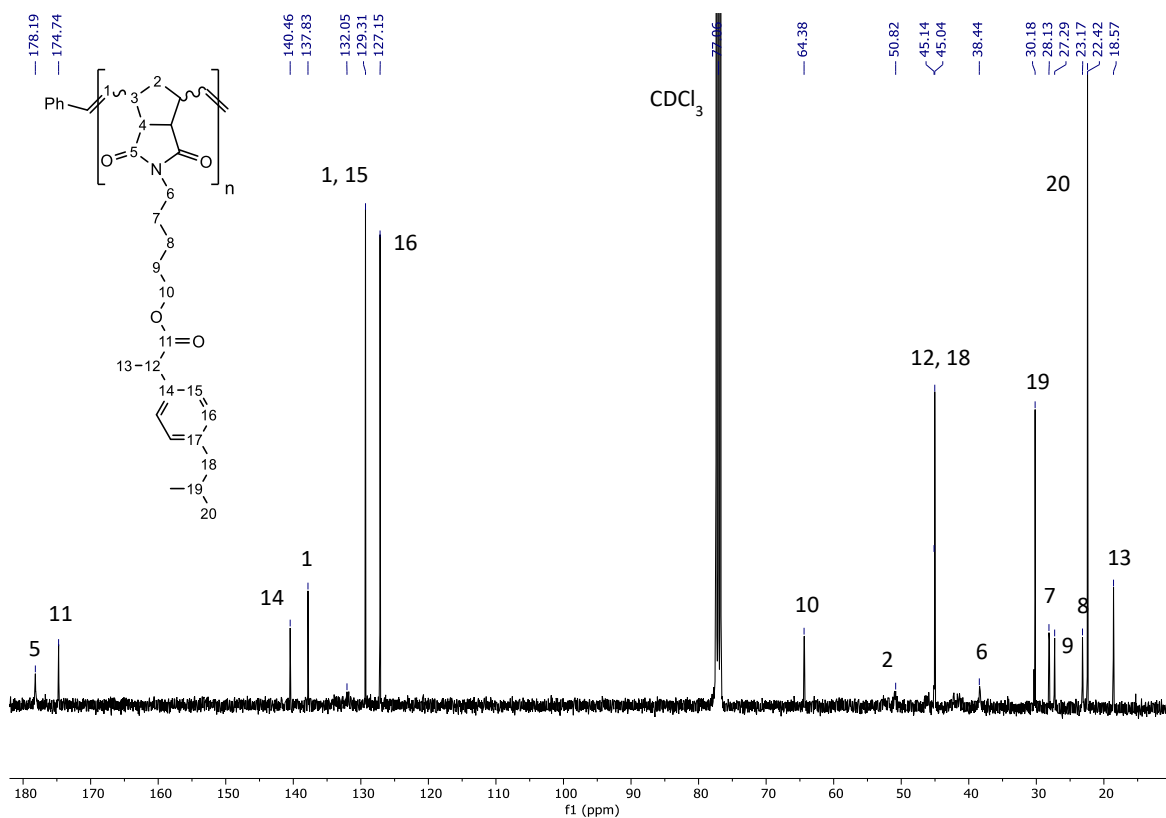


Fig. S24.  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  of homopolymer **poly5b**

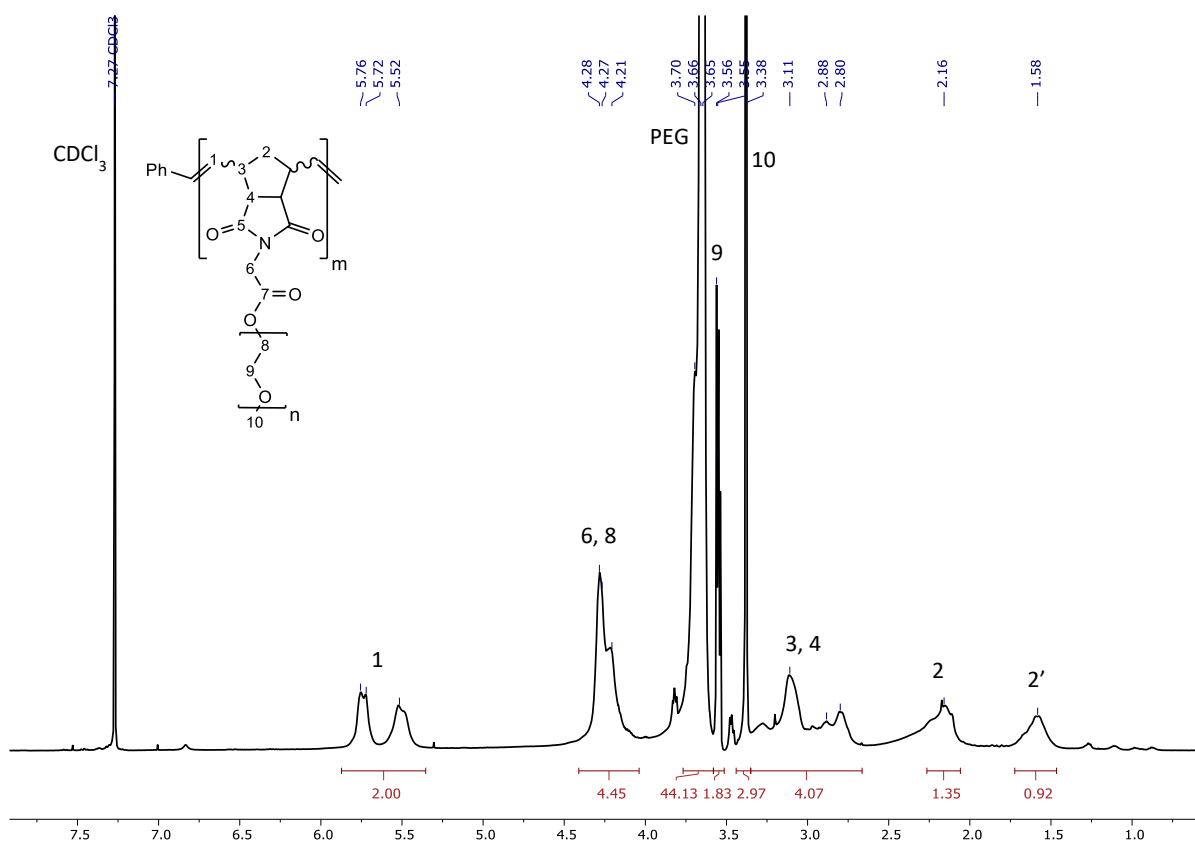


Fig. S25.  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of homopolymer **poly10b**

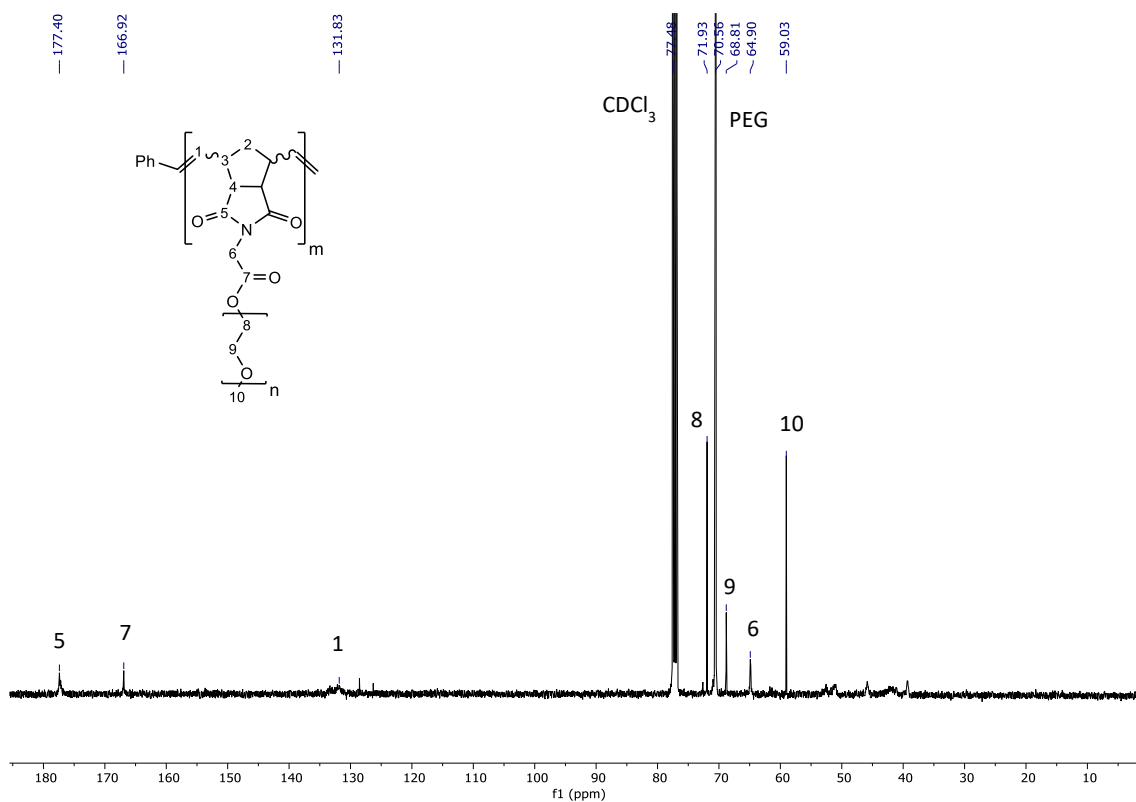


Fig. S26.  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  of homopolymer **poly10b**

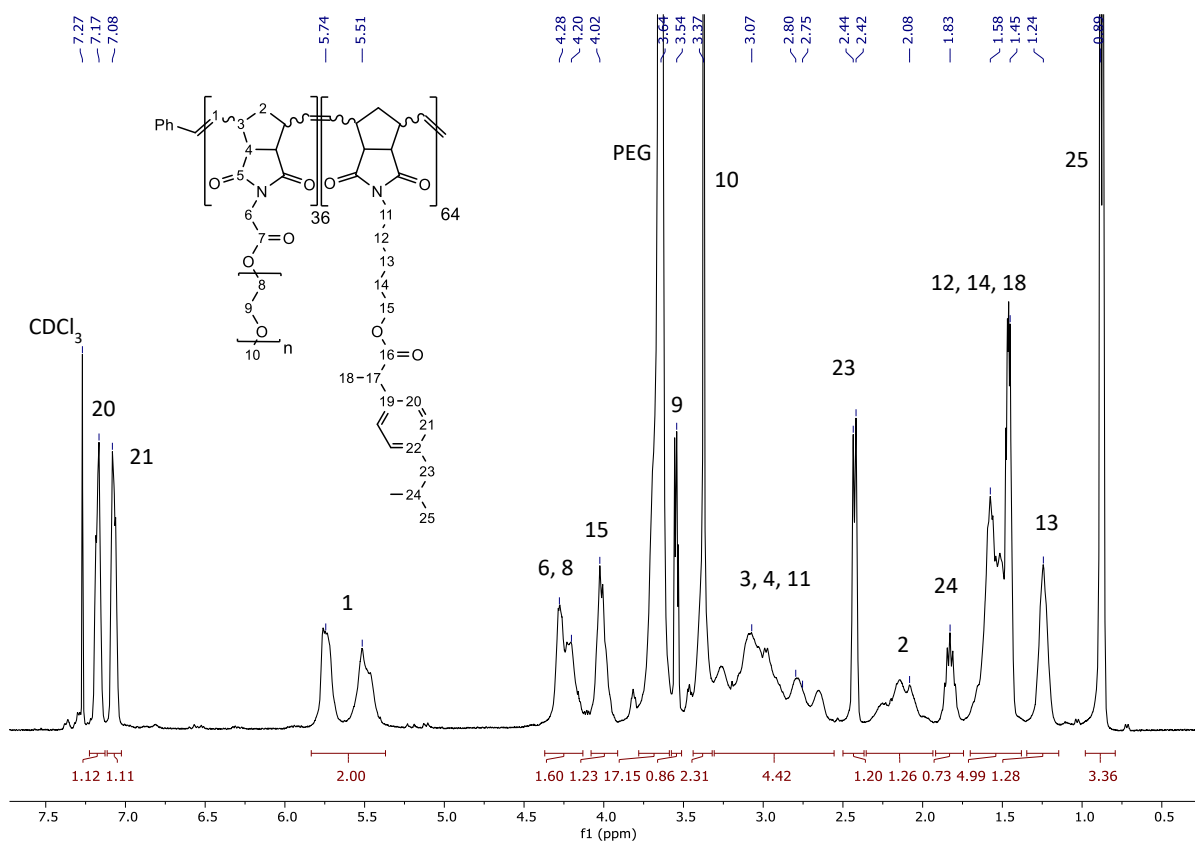


Fig. S27.  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of block copolymer, **poly5b-b-poly10b [64:36]**

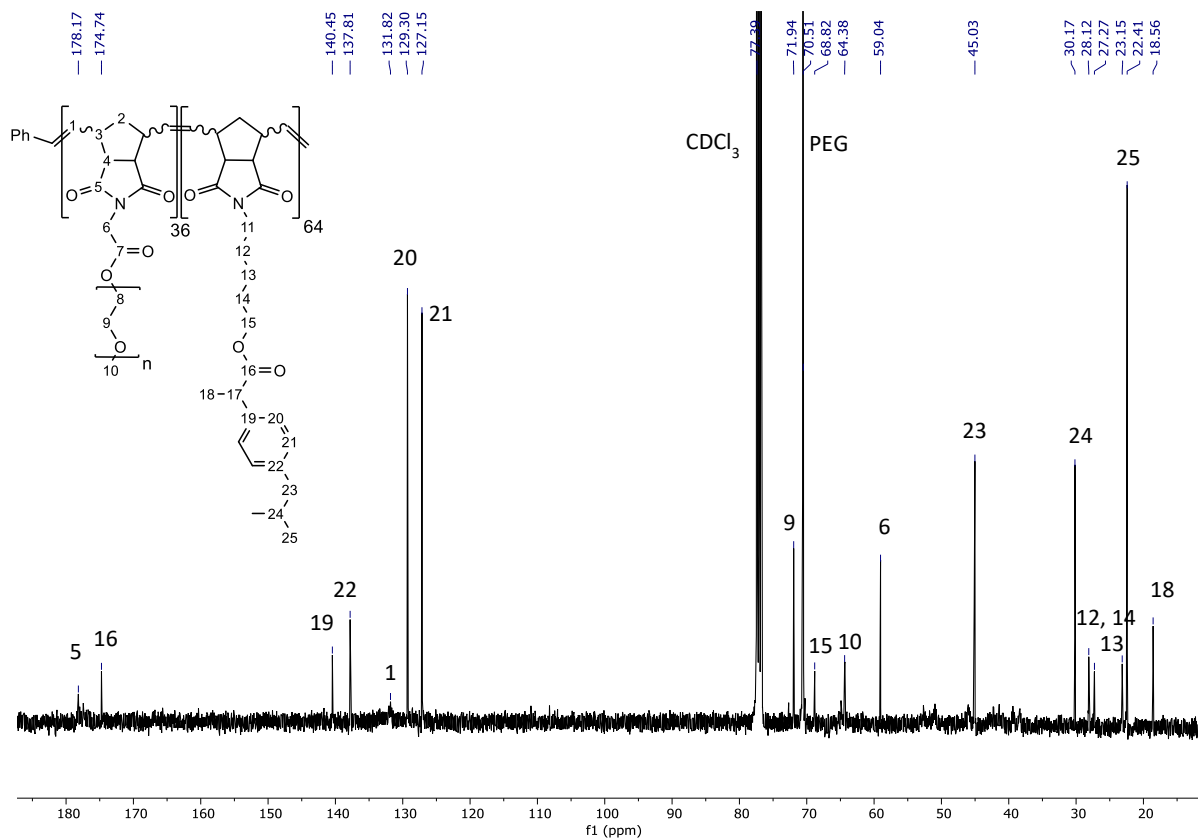


Fig. S28. <sup>13</sup>C NMR in CDCl<sub>3</sub> of block copolymer, **poly5b-b-poly10b [64:36]**

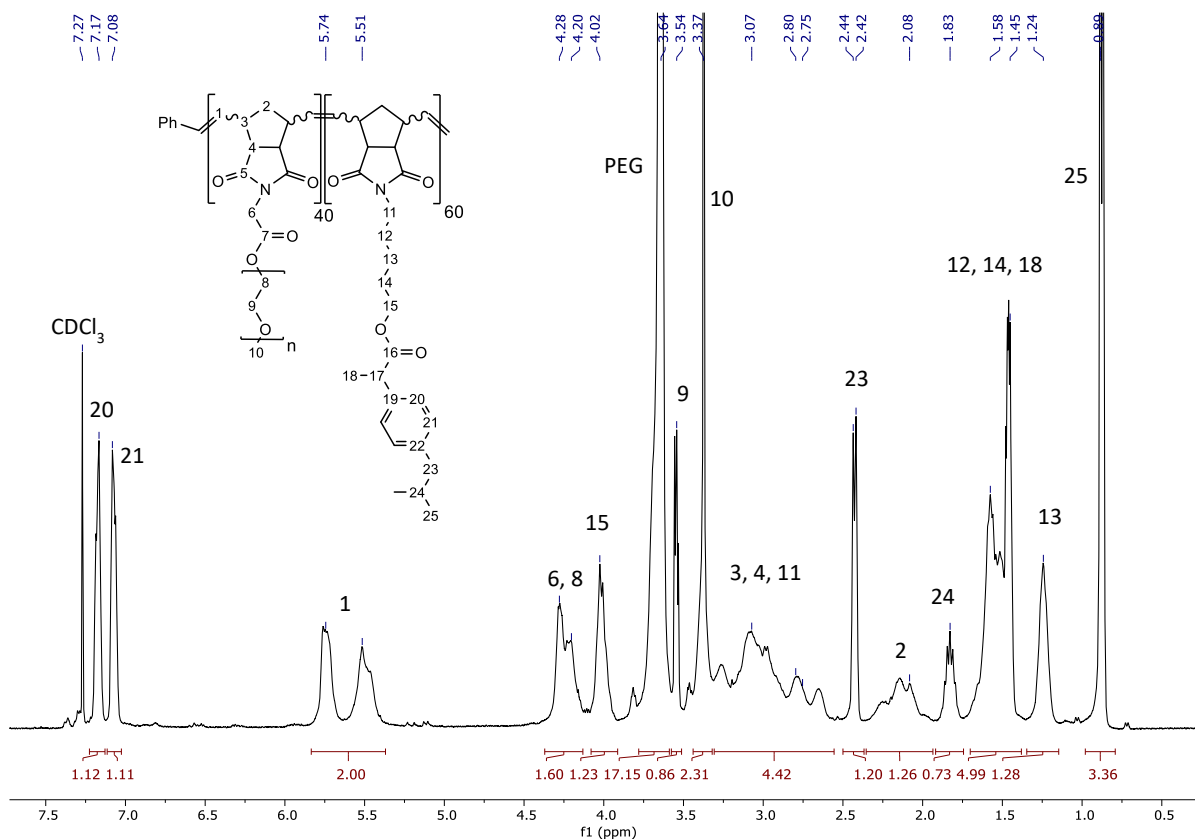
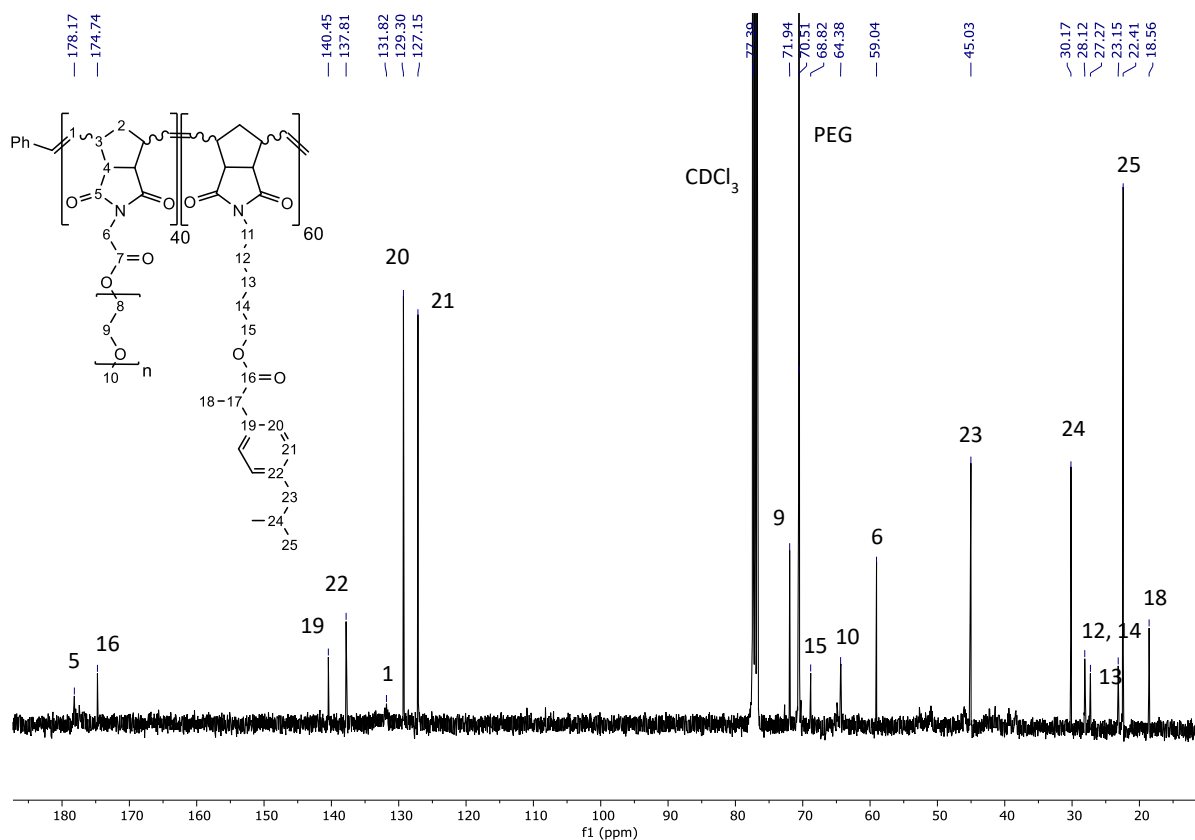
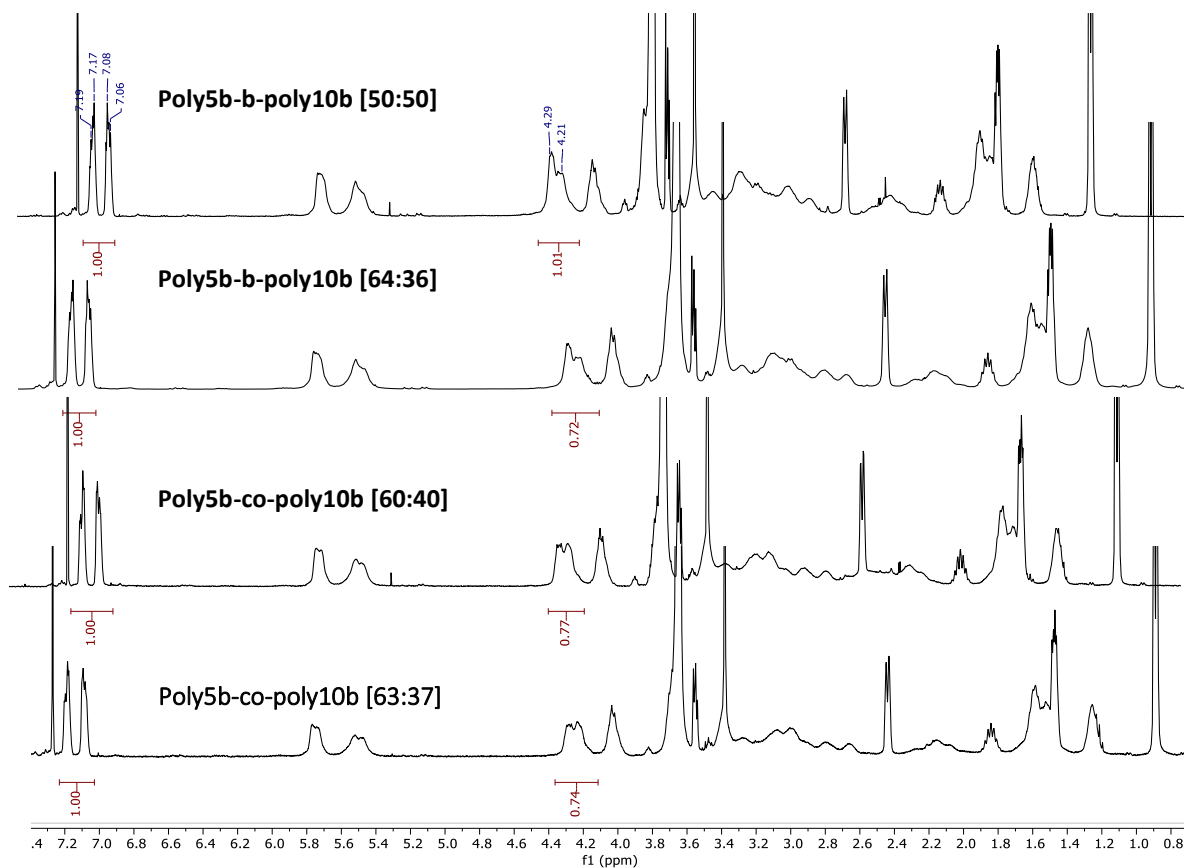


Fig. S29. <sup>1</sup>H NMR in CDCl<sub>3</sub> of statistical copolymer, **poly5b-co-poly10b [60:40]**

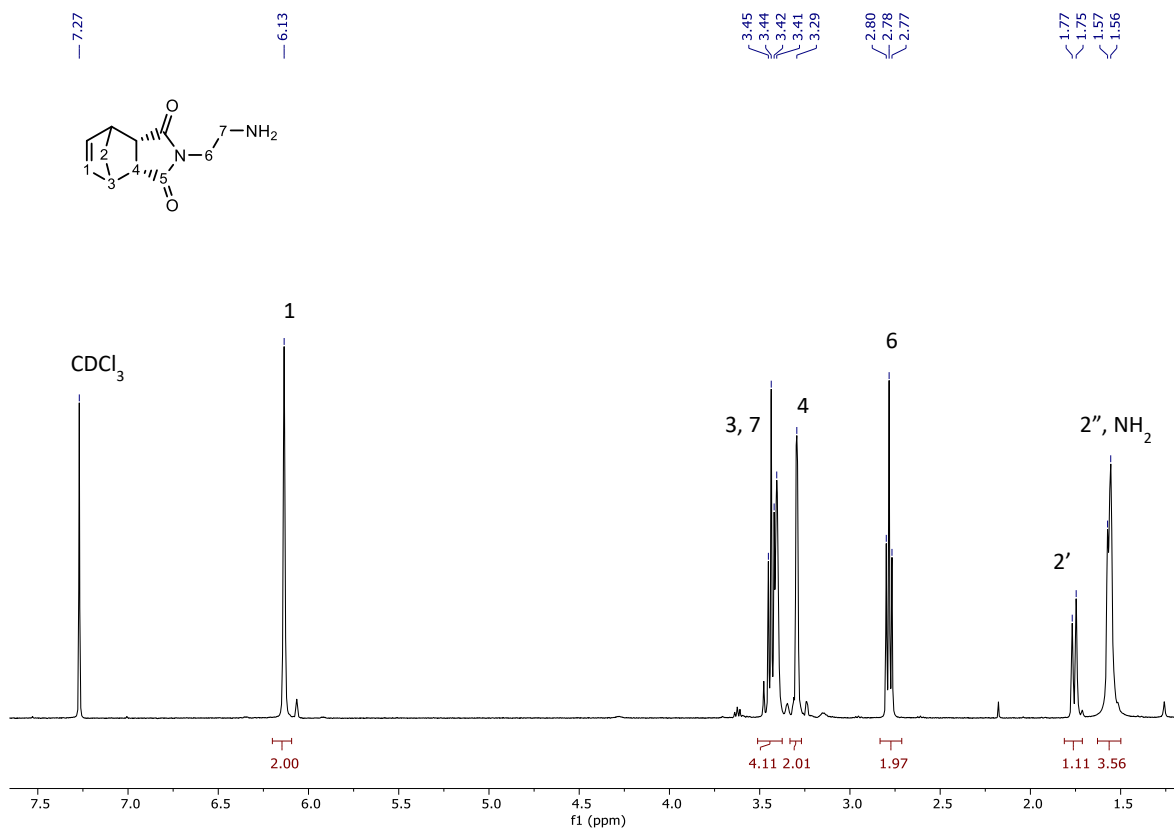


**Fig. S30.**  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  of statistical copolymer, **poly5b-co-poly10b [60:40]**

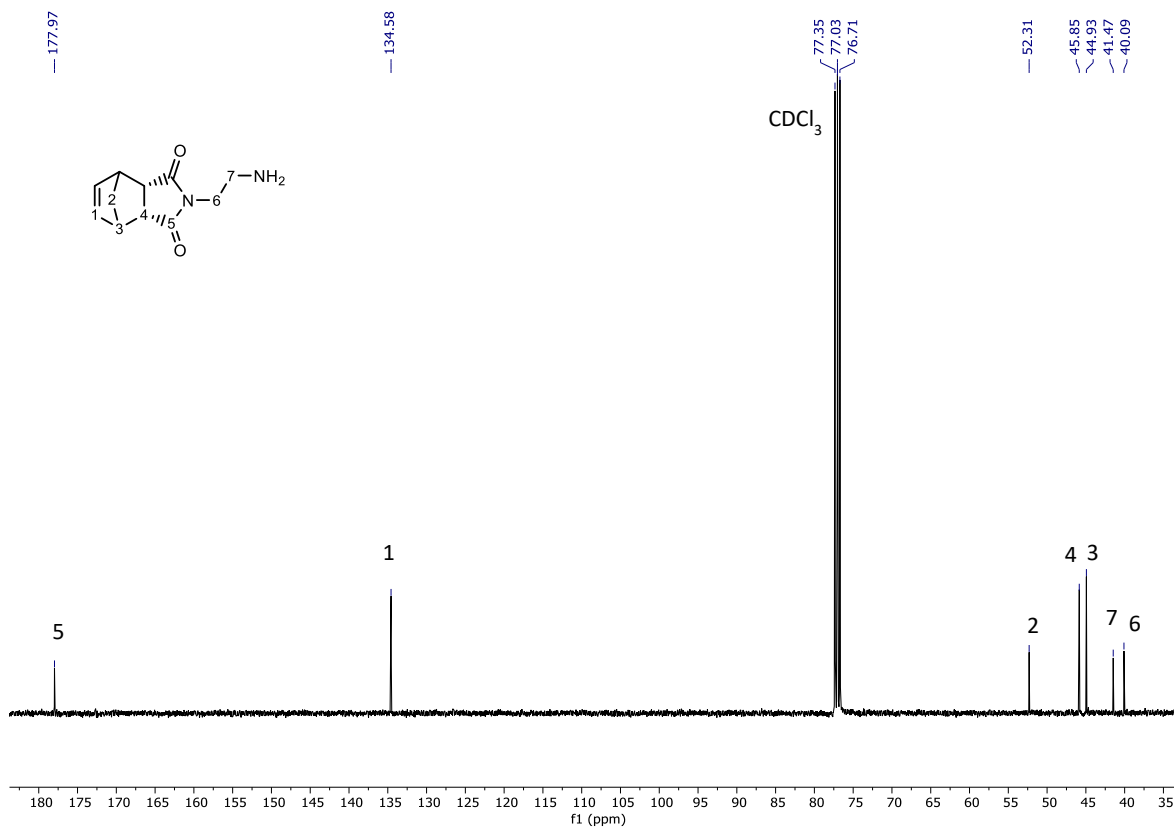


**Fig. S31.** Quantitative NMR analysis of block and statistical copolymers. The ratio between the highlighted integrals afforded the relative percentages of ibuprofen and PEG containing monomers (NB-Ibu/NB-PEG) within the polymer backbone of each polymer sequence.





**Fig. S32.**  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of *endo*-N-(2-aminoethyl)-5-norbornene-2,3-dicarboximide, **11**



**Fig. S33.**  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  of *endo*-N-(2-aminoethyl)-5-norbornene-2,3-dicarboximide, **11**

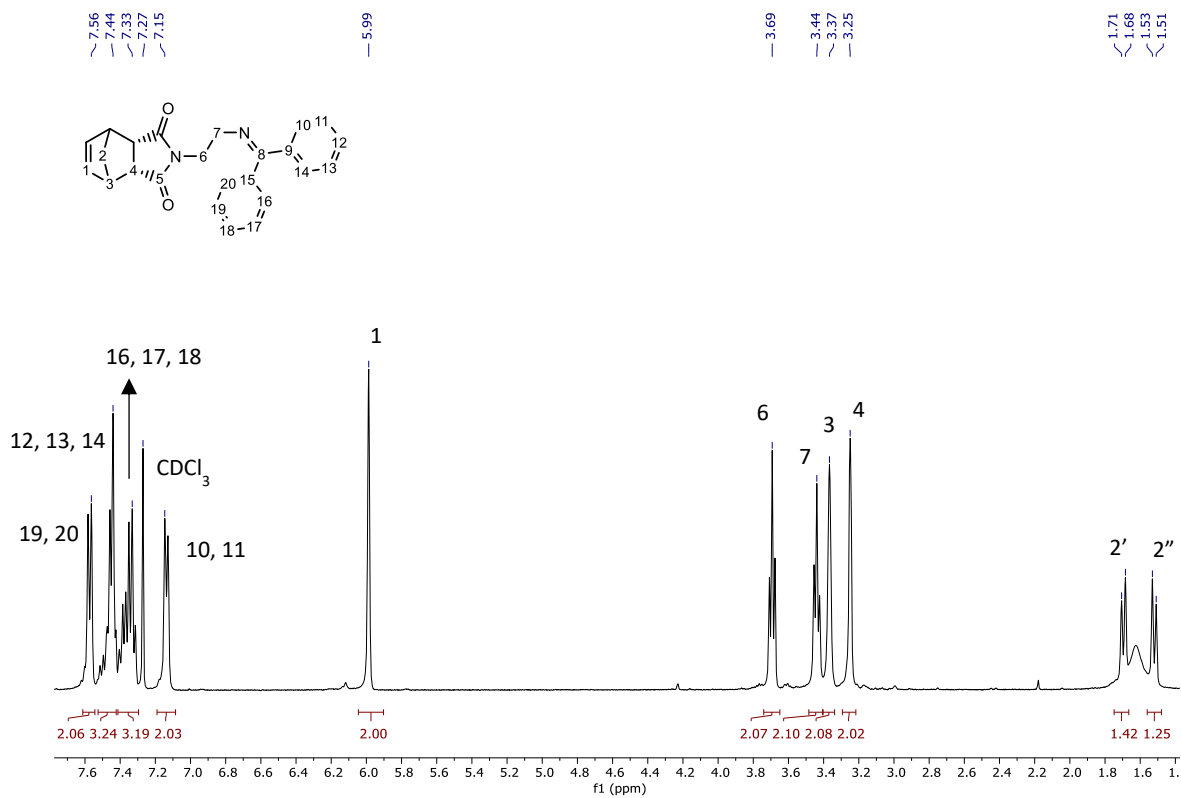


Fig. S34. <sup>1</sup>H NMR in CDCl<sub>3</sub> of compound **13a**

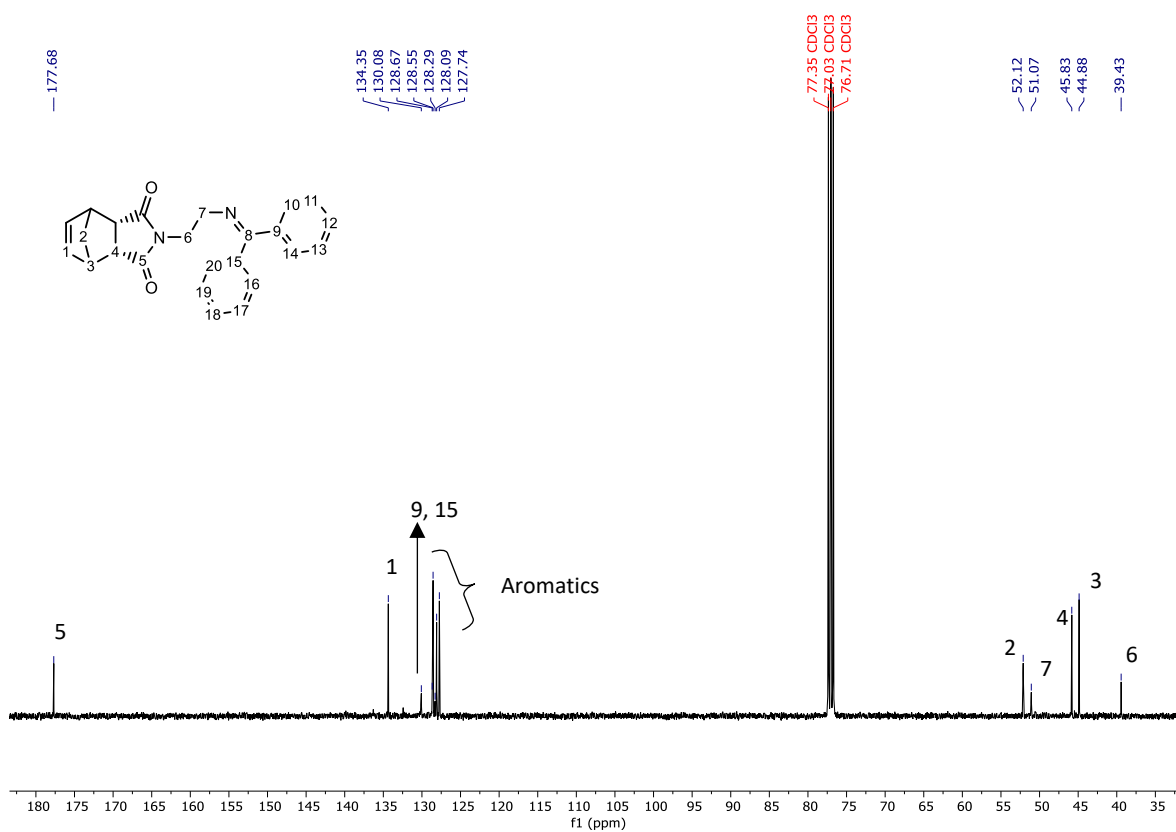


Fig. S35. <sup>13</sup>C NMR in CDCl<sub>3</sub> of compound **13a**

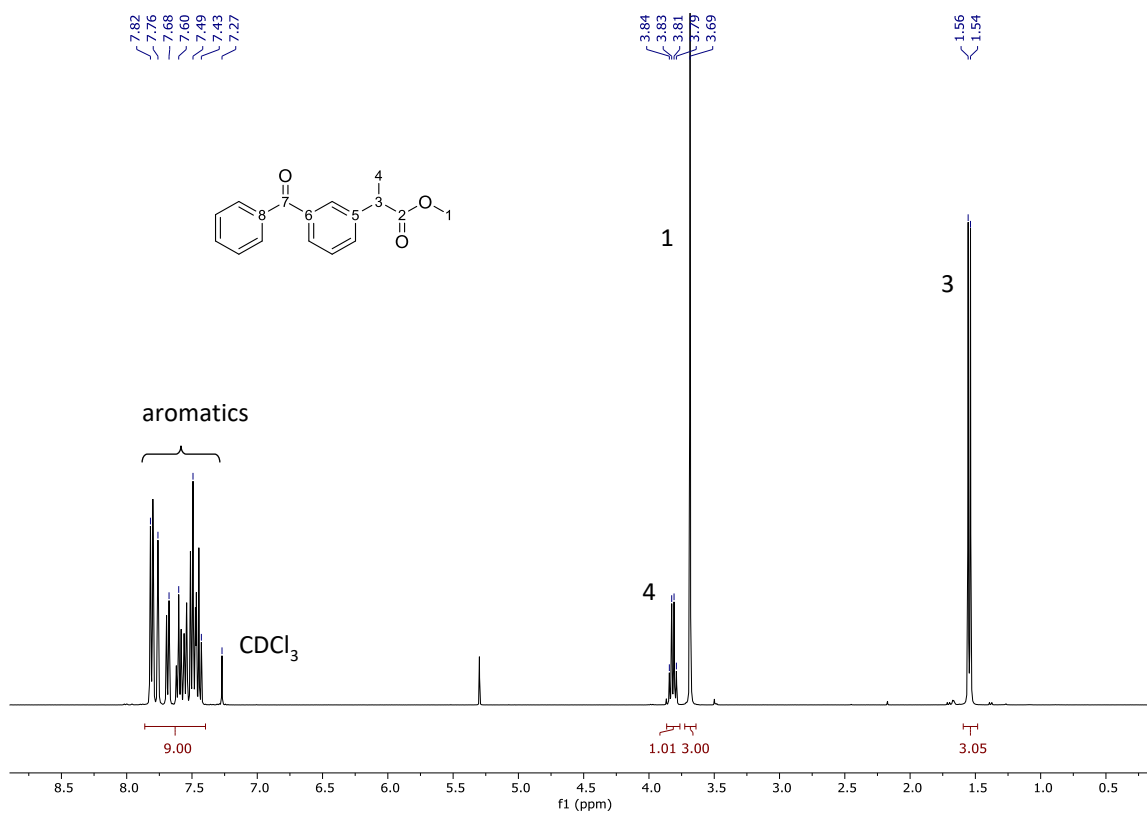


Fig. S36.  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of ketoprofen ester, **12c**

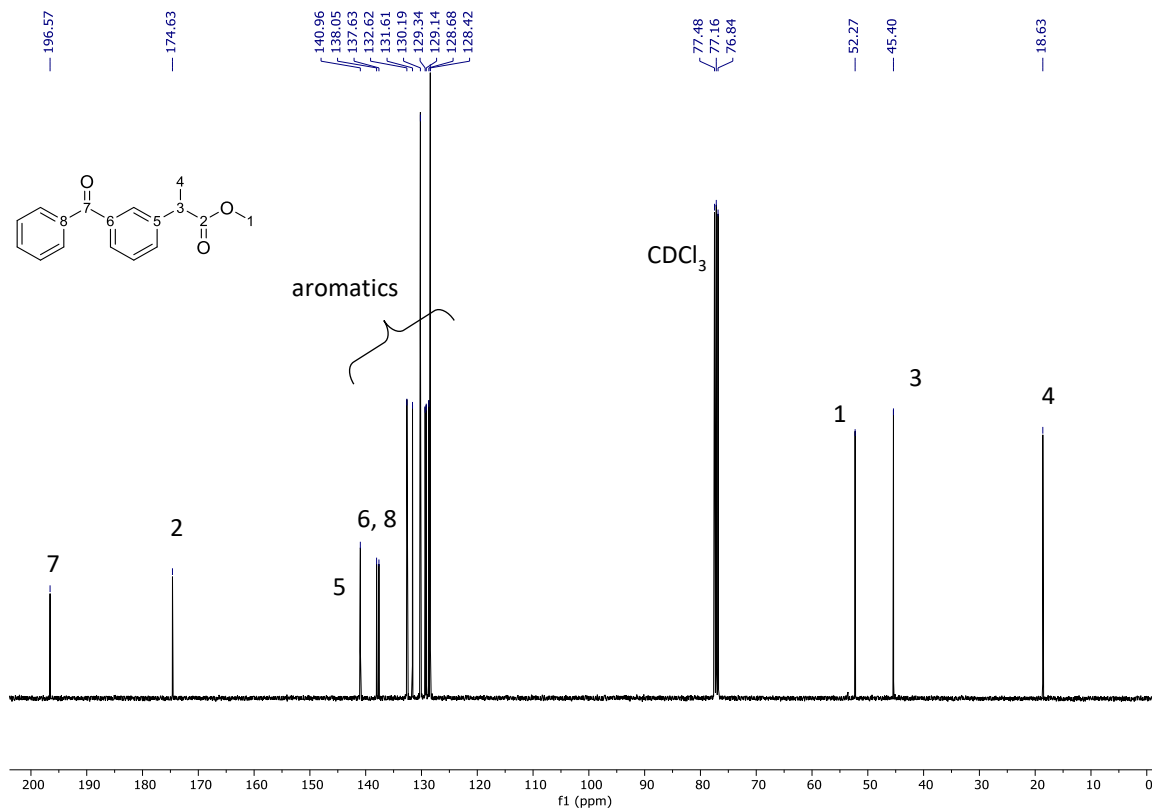
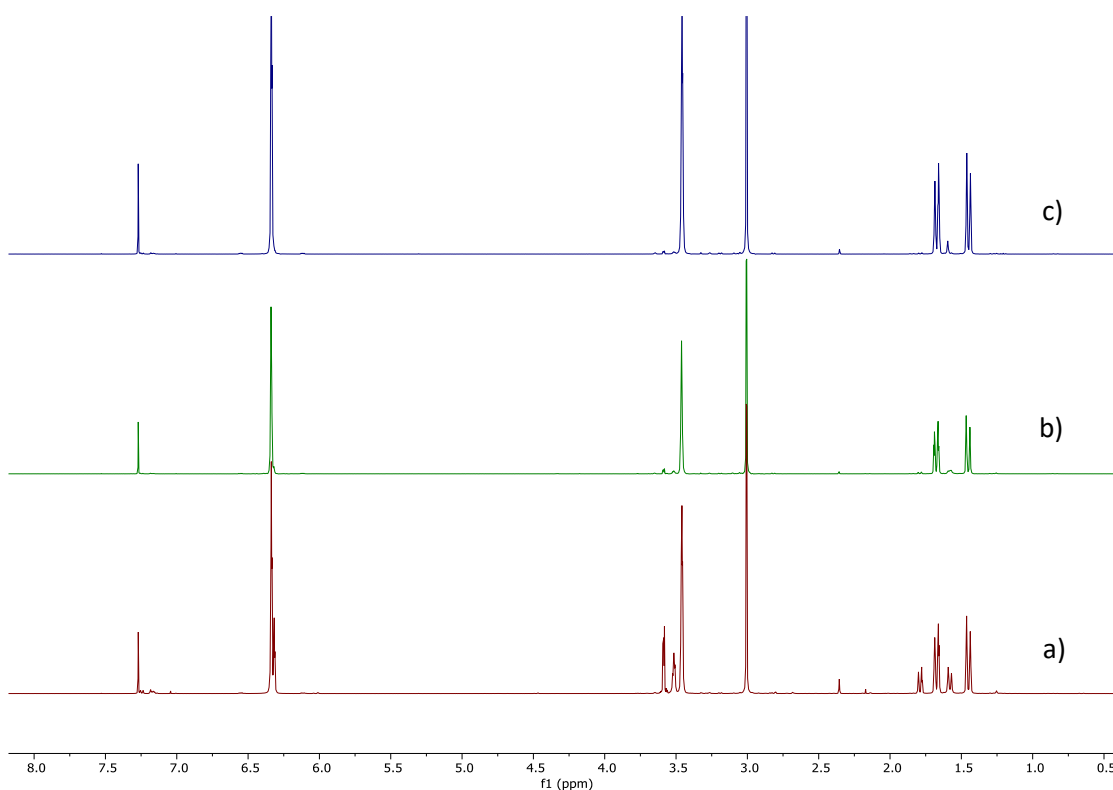
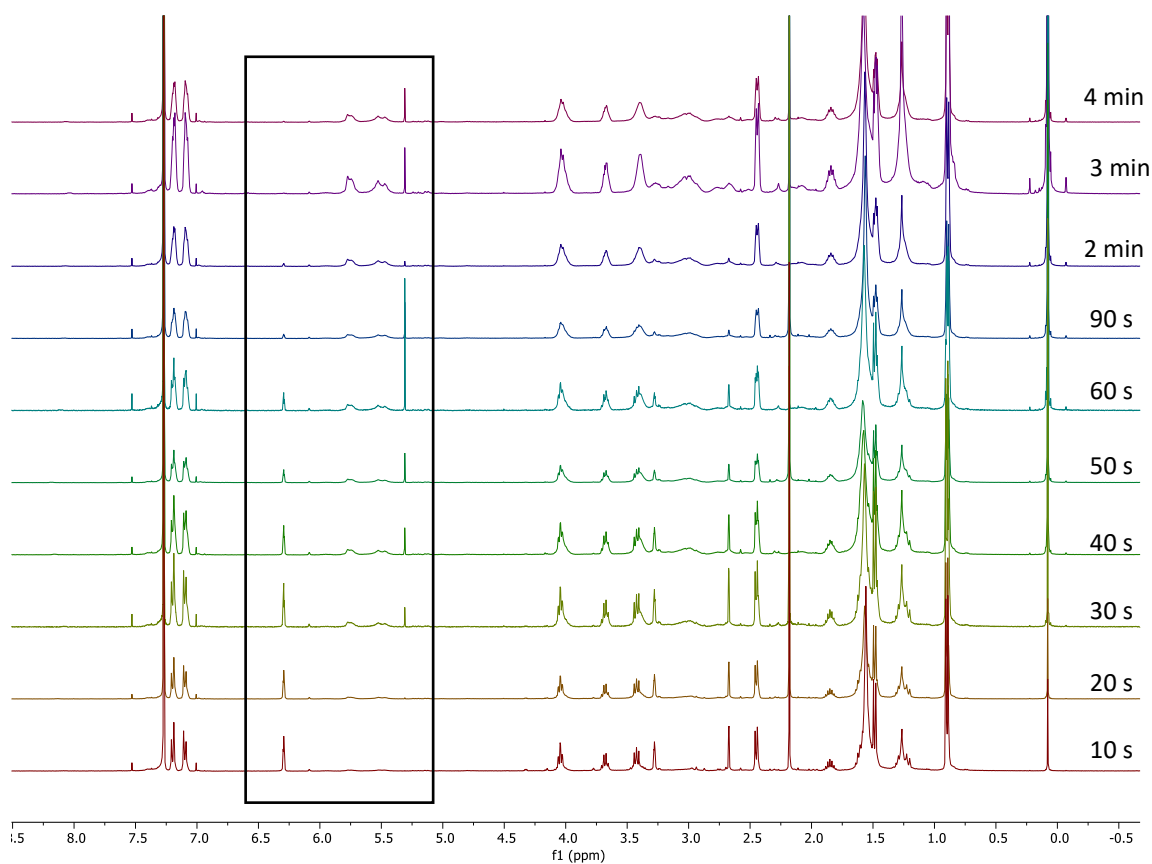


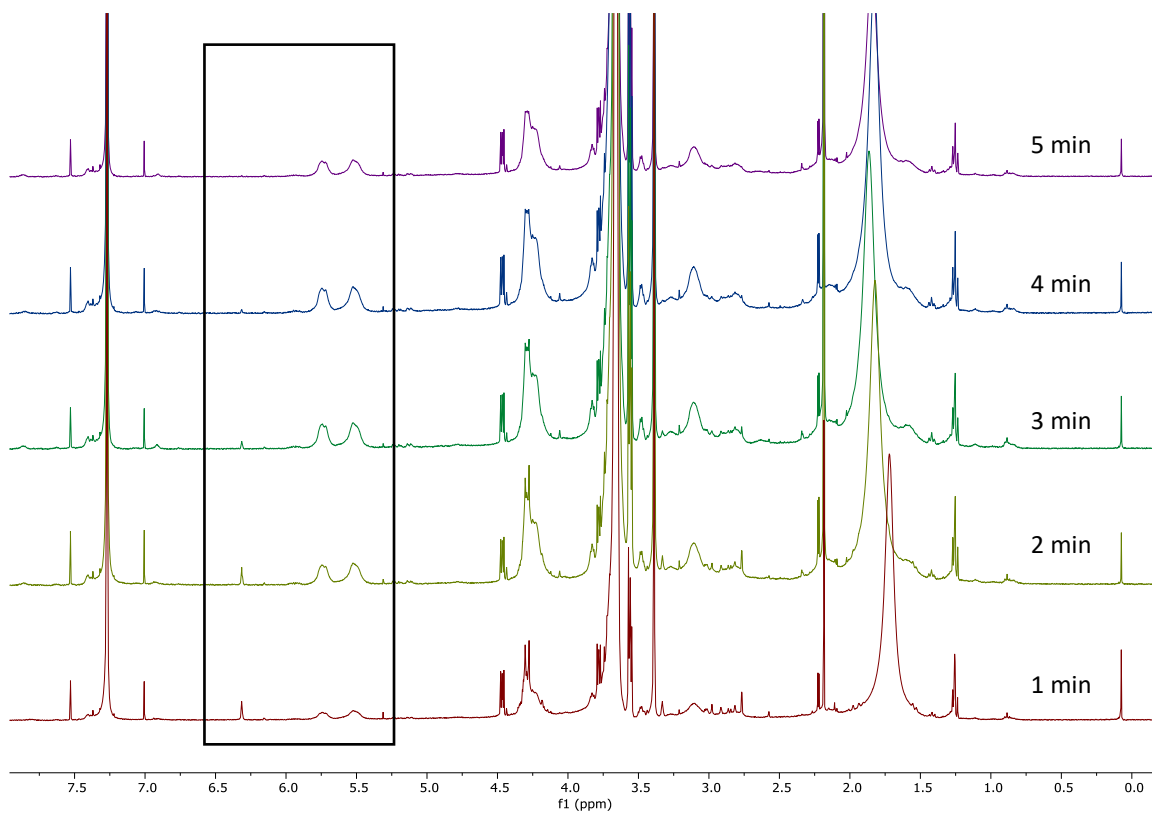
Fig. S37.  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  of ketoprofen ester, **12c**



**Fig. S38.** Stacked  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of endo/exo carbic anhydride conversion. a) 1<sup>st</sup> recrystallisation afforded exo-carbic anhydride with 78 % purity; b) 2<sup>nd</sup> recrystallisation with 97 % of exo purity; c) 3<sup>rd</sup> recrystallisation with 99 % of exo purity. The purity of exo carbic anhydride is calculated by the integration of the bridgehead protons of endo and exo between 2.0 ppm and 1.25 ppm.

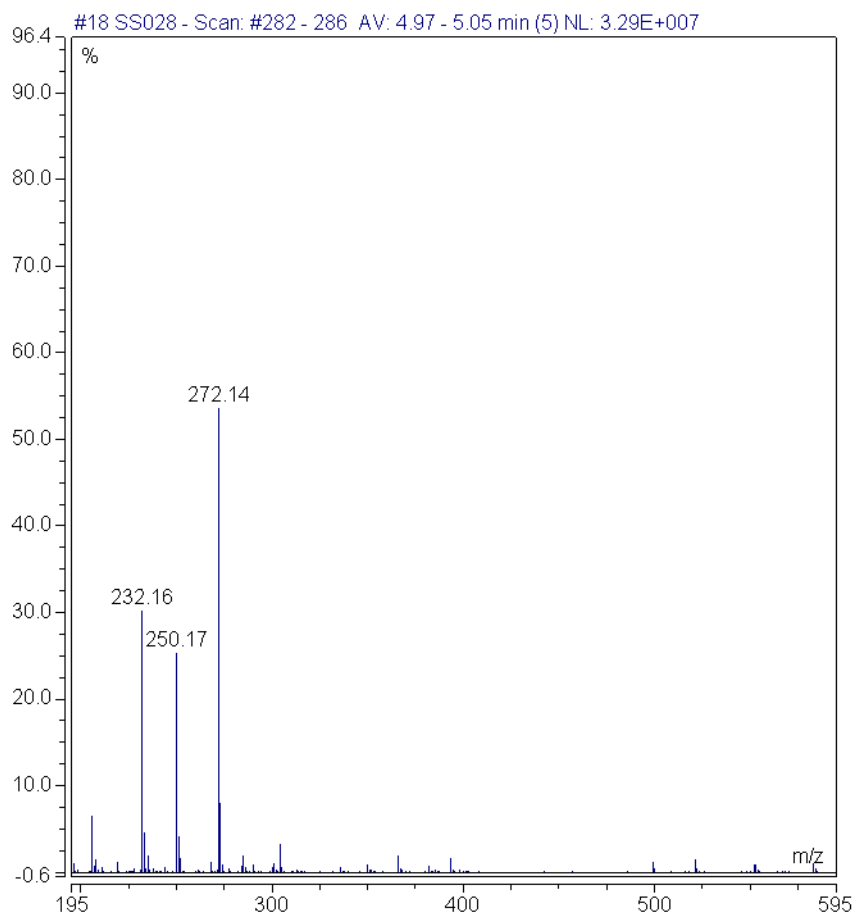


**Fig. S39.** Stacked  $^1\text{H}$  NMR spectra in  $\text{CDCl}_3$  showing monomer **5b** conversion into homopolymer **poly5b**.

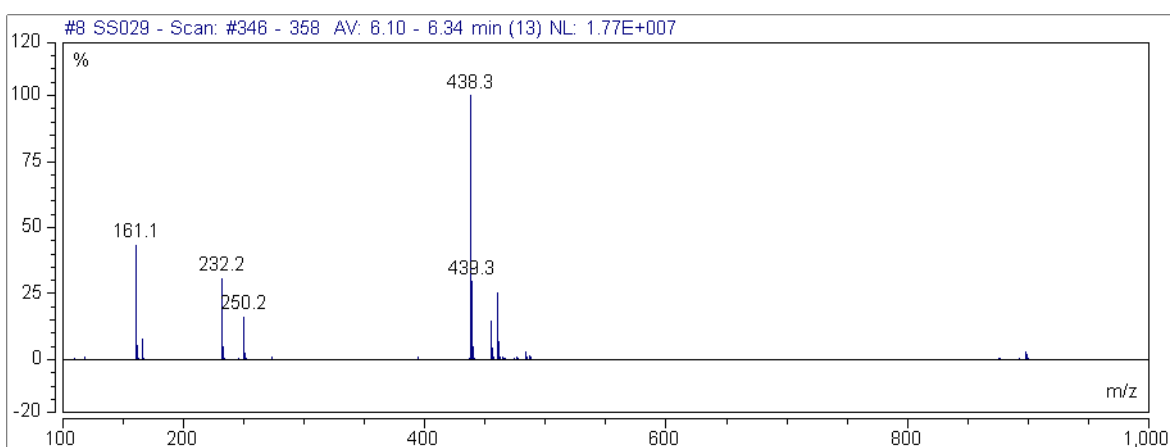


**Fig. S40.** Stacked <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> showing monomer **10b** conversion into homopolymer **poly10b**.

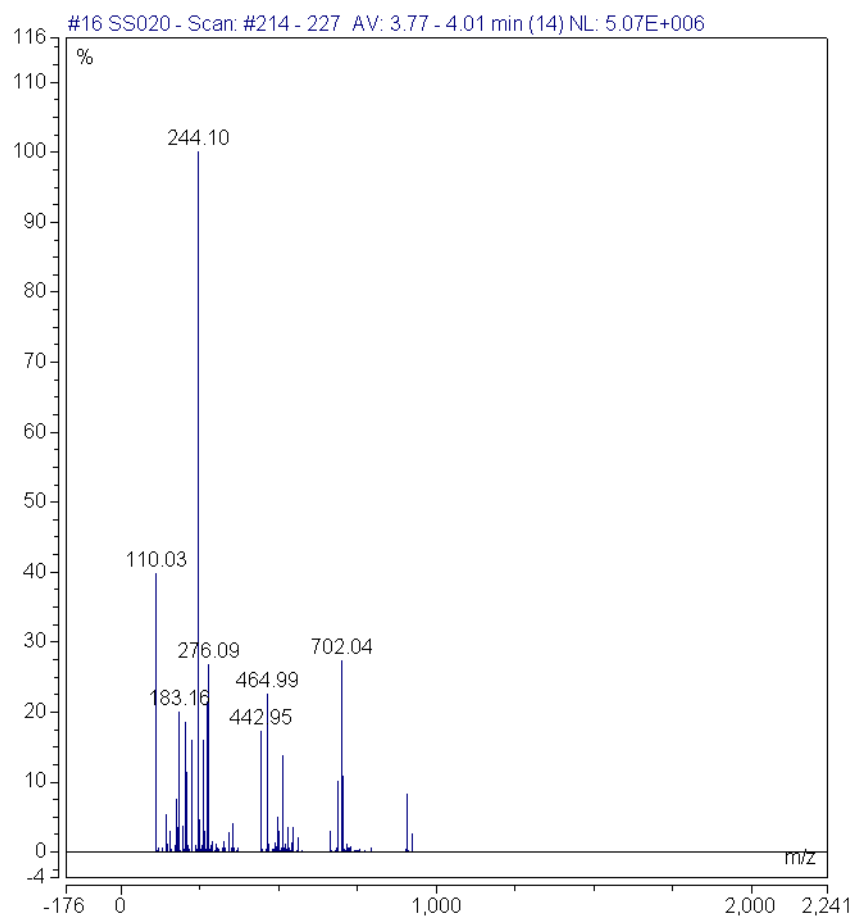
## 2. LC-MS spectra



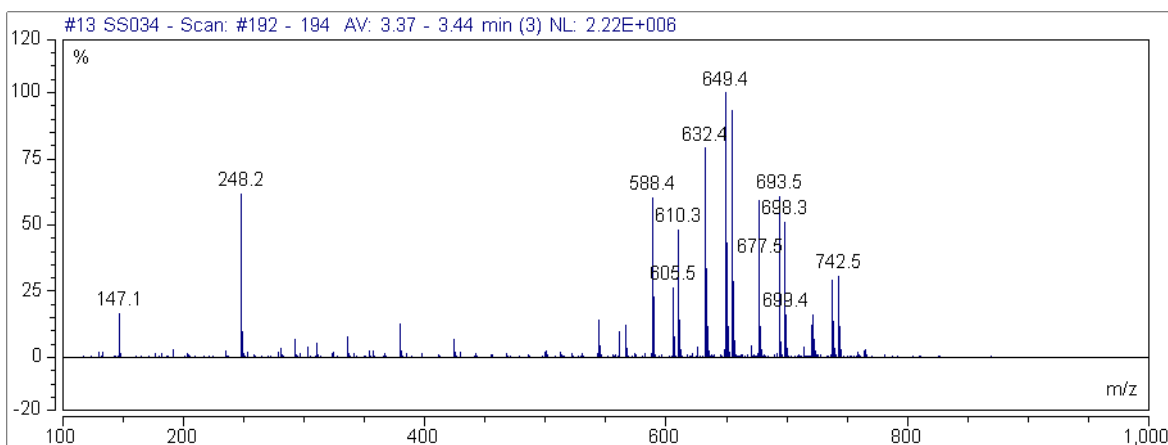
**Fig. S41.** LC-MS spectra of compound **3b**. Here are identified the  $[M+H]^+$  and  $[M+Na]^+$  values, 250.2 and 272.1 respectively.



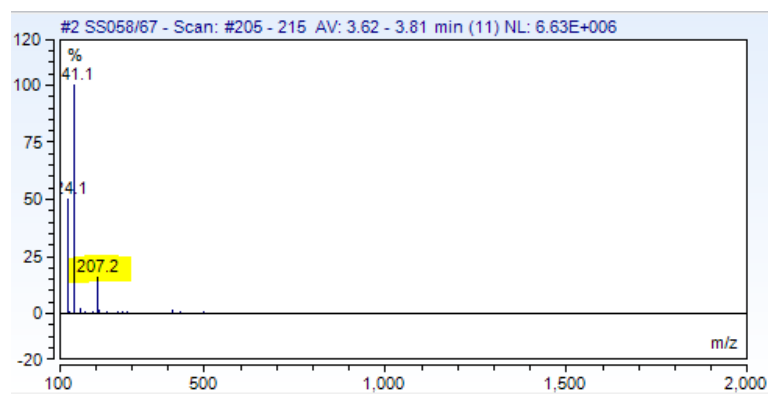
**Fig. S42.** LC-MS spectra of compound **5b**. Here the  $[M+H]^+$  value of 438.3 is identified.



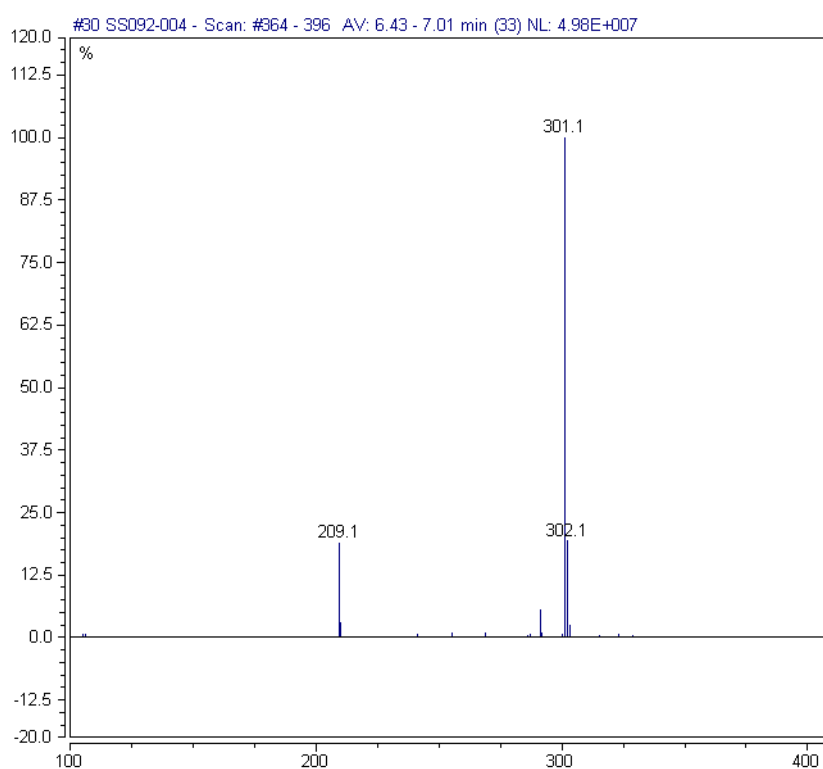
**Fig. S43.** LC-MS spectra of compound **7b**. Here the  $[M+Na]^+$  value is identified, 244.1.



**Fig. S44.** LC-MS spectra of monomer **10b**. Due to the presence of a PEG chain to the norbornene moiety, a distribution of  $m/z$  is obtained.



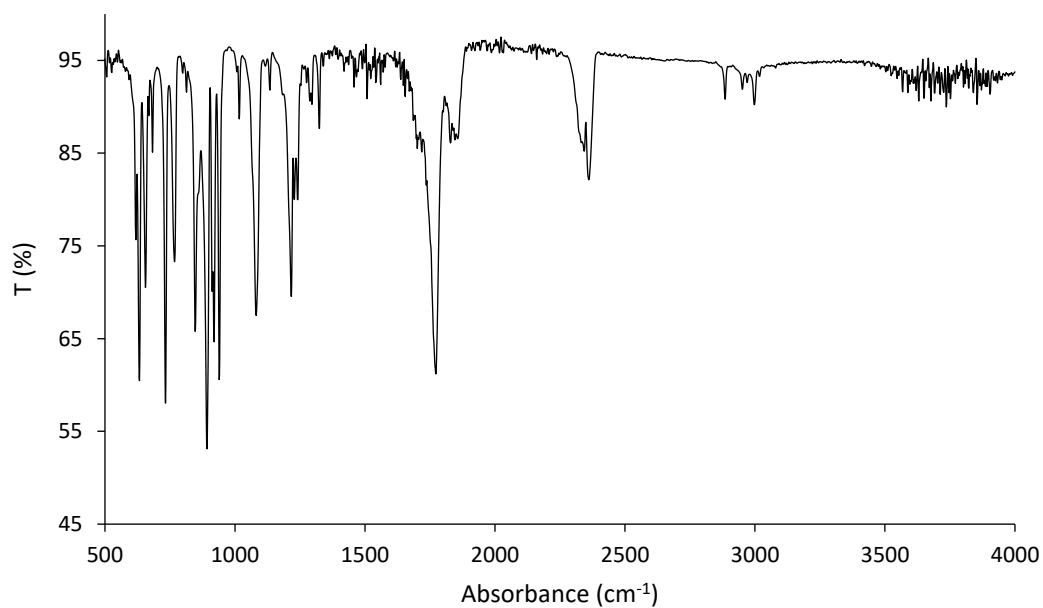
**Fig. S45.** LC-MS spectra of compound **11**. Here the  $[M+H]^+$  value is identified, 207.2.



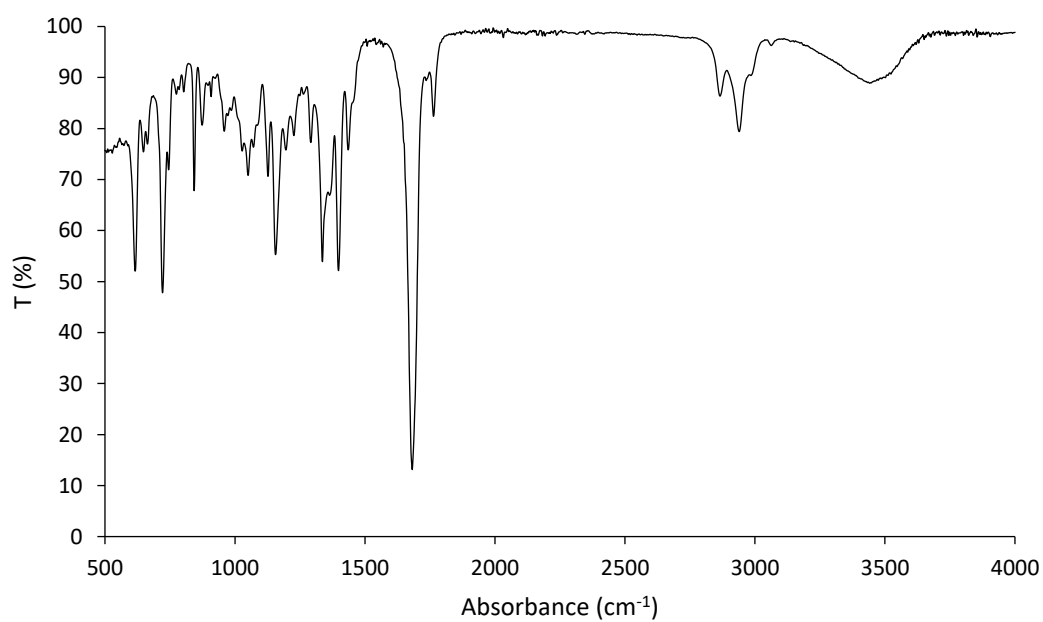
**Fig. S46.** LC-MS spectra of compound **12c**. Here the  $[M+H]^+$  value is identified, 301.1.



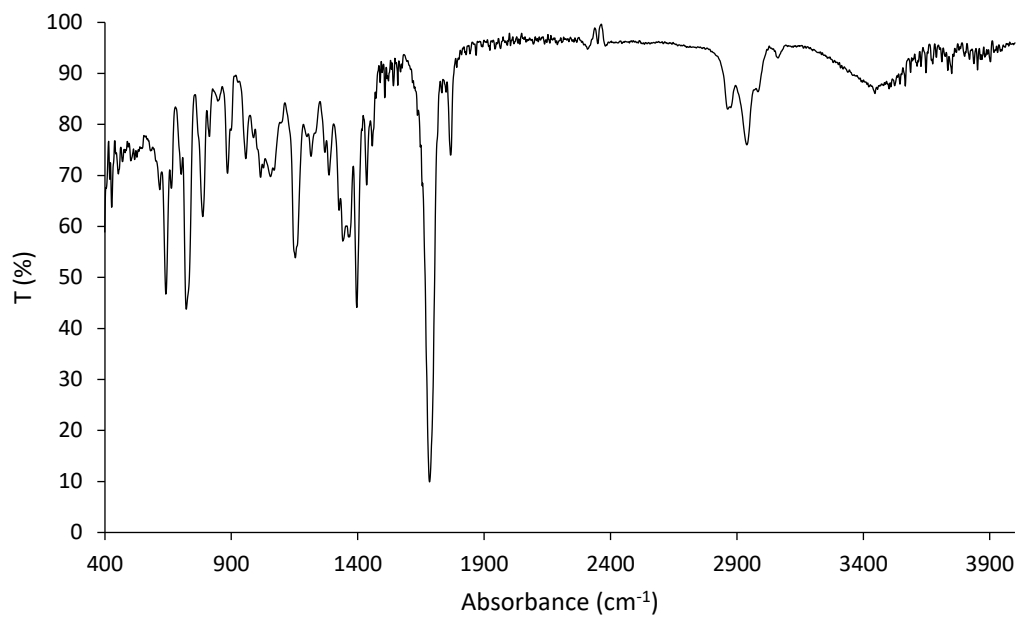
### 3. IR spectra



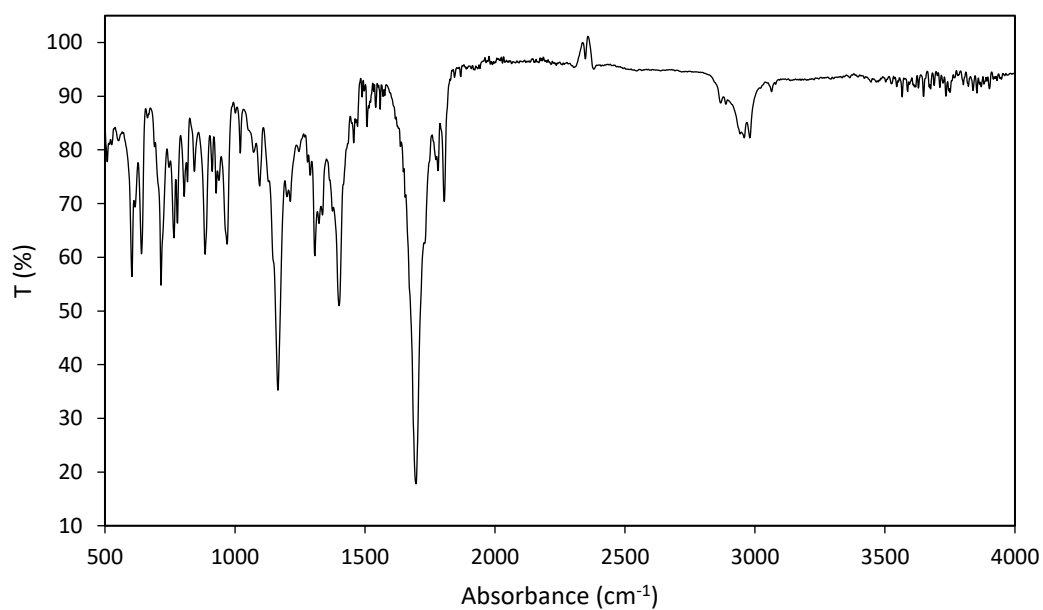
**Fig. S47.** IR spectra of *exo*-carbic anhydride, **1b**



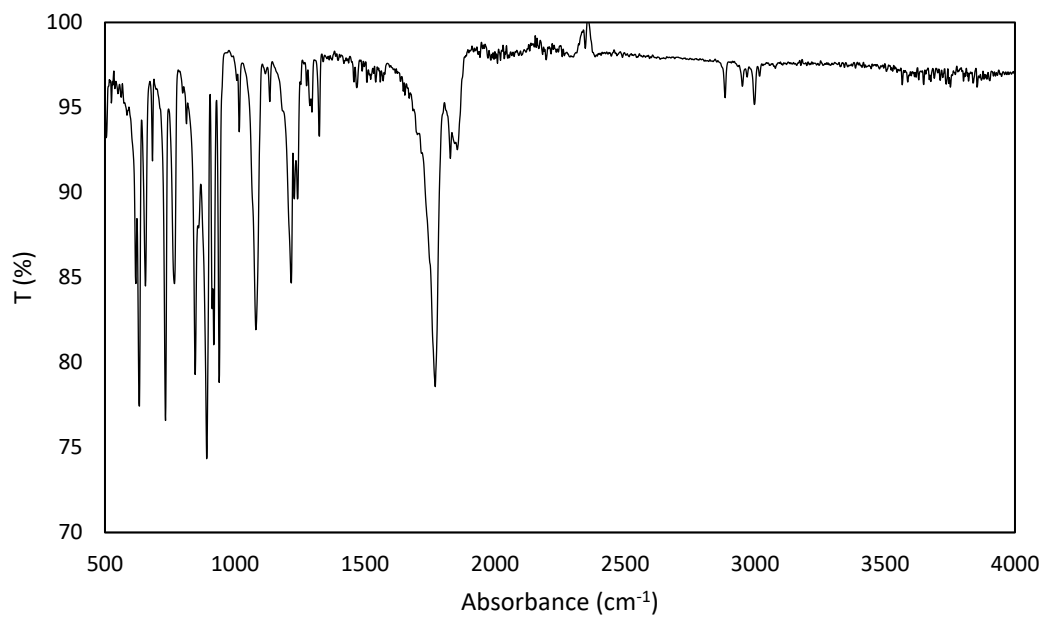
**Fig. S48.** IR spectra of *N*-(hydroxypentanyl)-*cis*-5-norbornene-*endo*-2,3-dicarboximide, **3a**



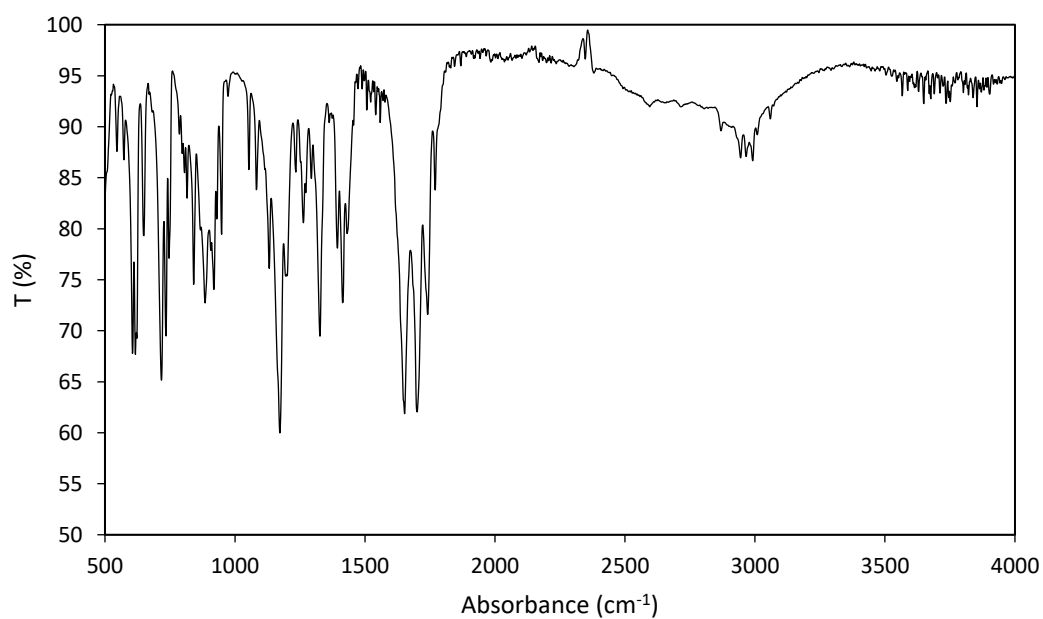
**Fig. S49.** IR spectra of *N*-(hydroxypentanyl)-*cis*-5-norbornene-*exo*-2,3-dicarboximide, **3b**



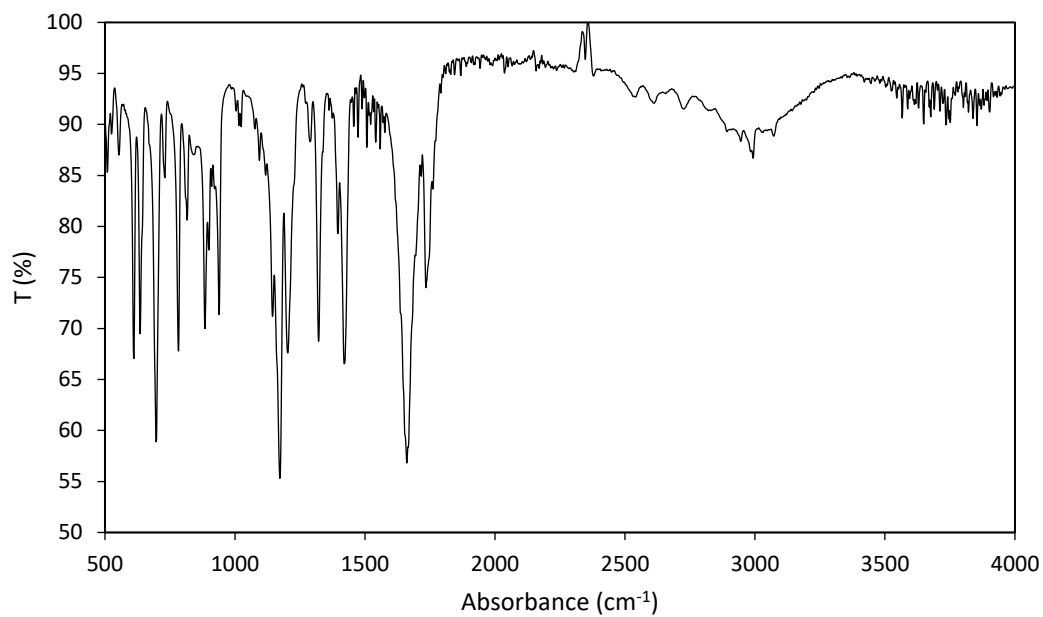
**Fig. S50.** IR spectra of *endo*-NB ibuprofen derivative, **5a**



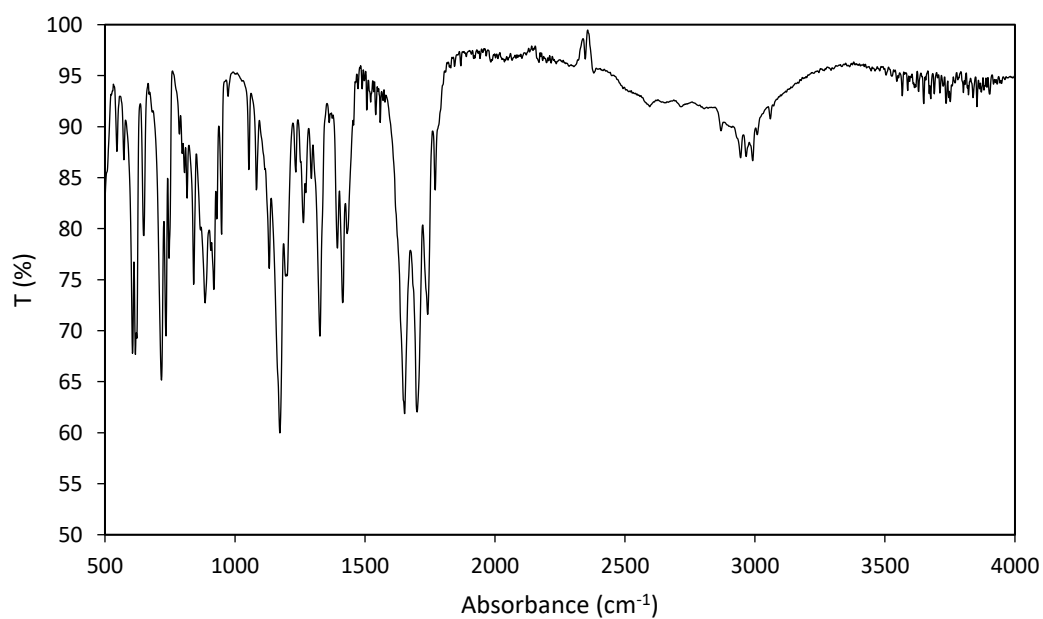
**Fig. S51.** IR spectra of NB-IBU monomer **5b**



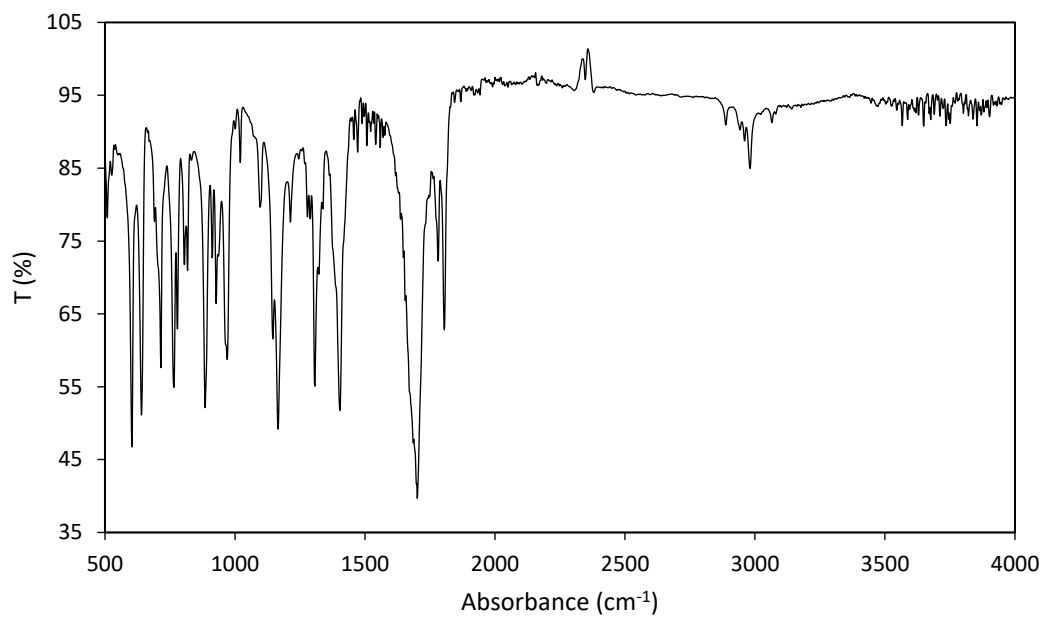
**Fig. S52.** IR spectra of *N*-(endo-himoyl)-glycine, **7a**



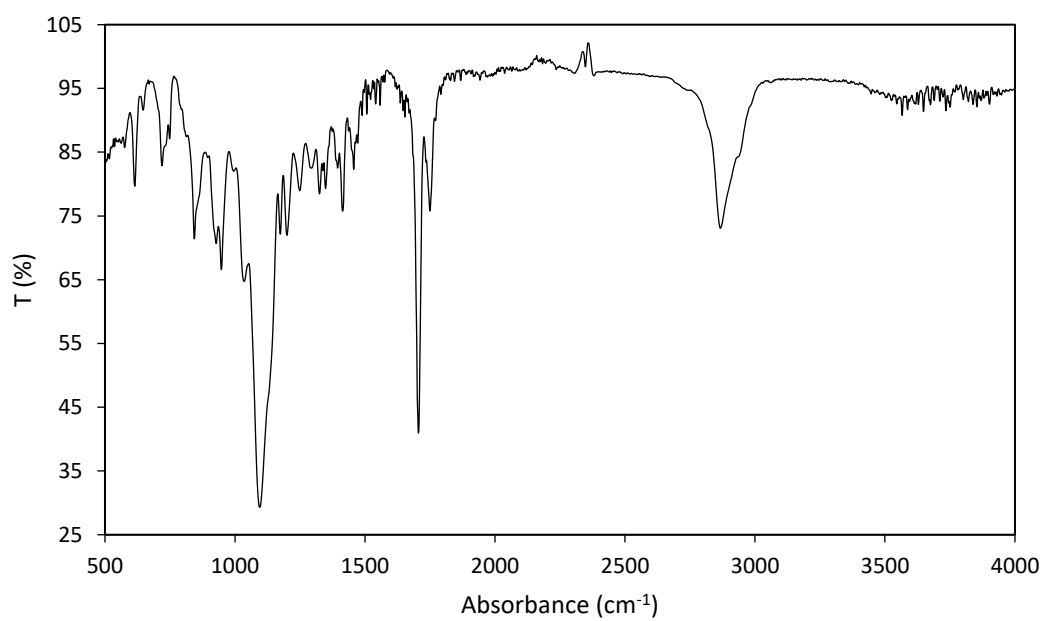
**Fig. S53.** IR spectra of *N*-(*exo*-himoyl)-glycine, **7b**



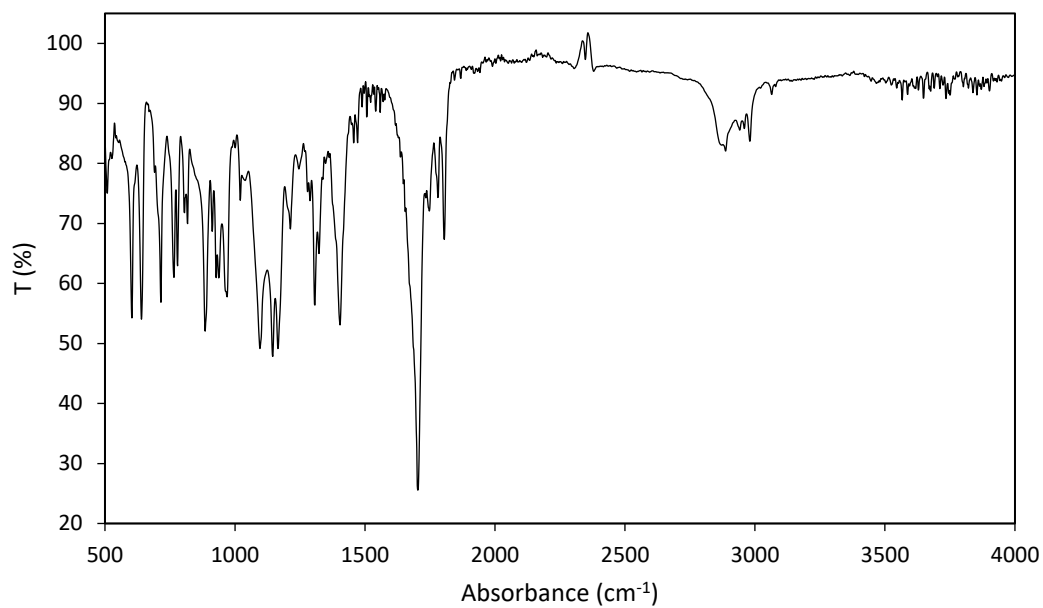
**Fig. S54.** IR spectra of *N*-(*endo*-himoyl)-glycinoyl chloride, **8a**



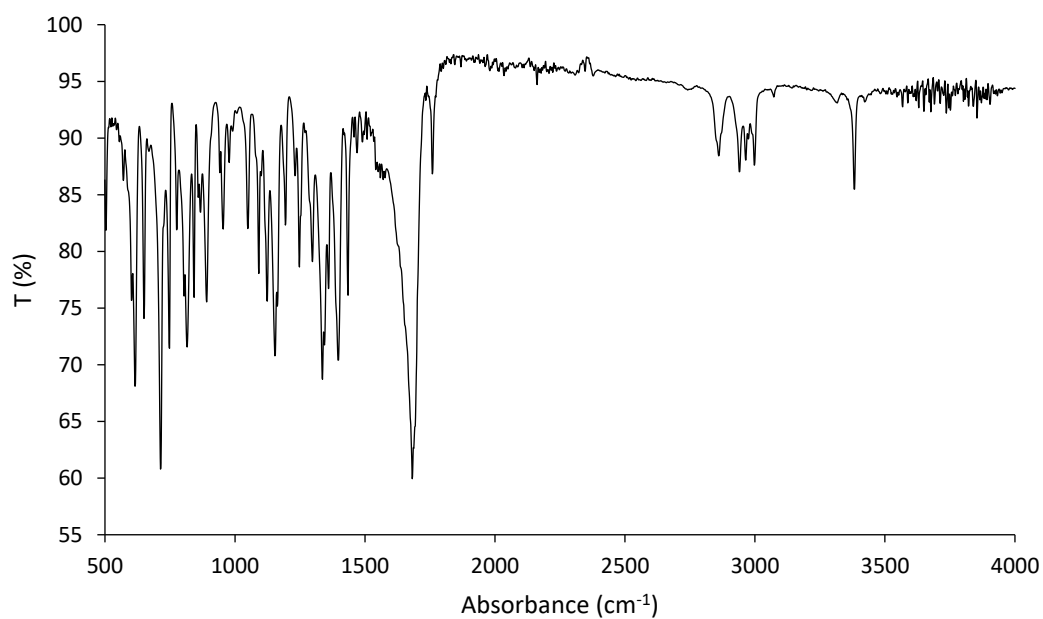
**Fig. S55.** IR spectra of *N*-(*exo*-himoyl)-glycinoyl chloride, **8b**



**Fig. S56.** IR spectra of *N*-(*endo*-himoyl)-glycine poly(ethylene glycol) ester, **10a**



**Fig. S57.** IR spectra of *N*-(*exo*-himoyl)-glycine poly(ethylene glycol) ester, NB-PEG monomer **10b**



**Fig. S58.** IR spectra of *endo*-*N*-(2-aminoethyl)-5-norbornene-2,3-dicarboximide, **11**

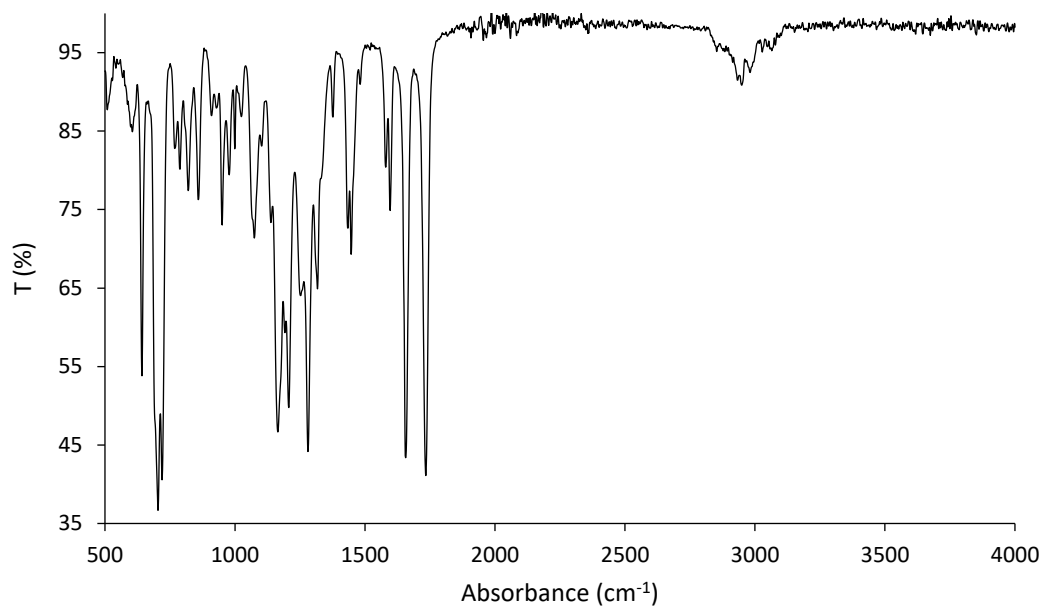


Fig. S59. IR spectra of ketoprofen ester, **12c**

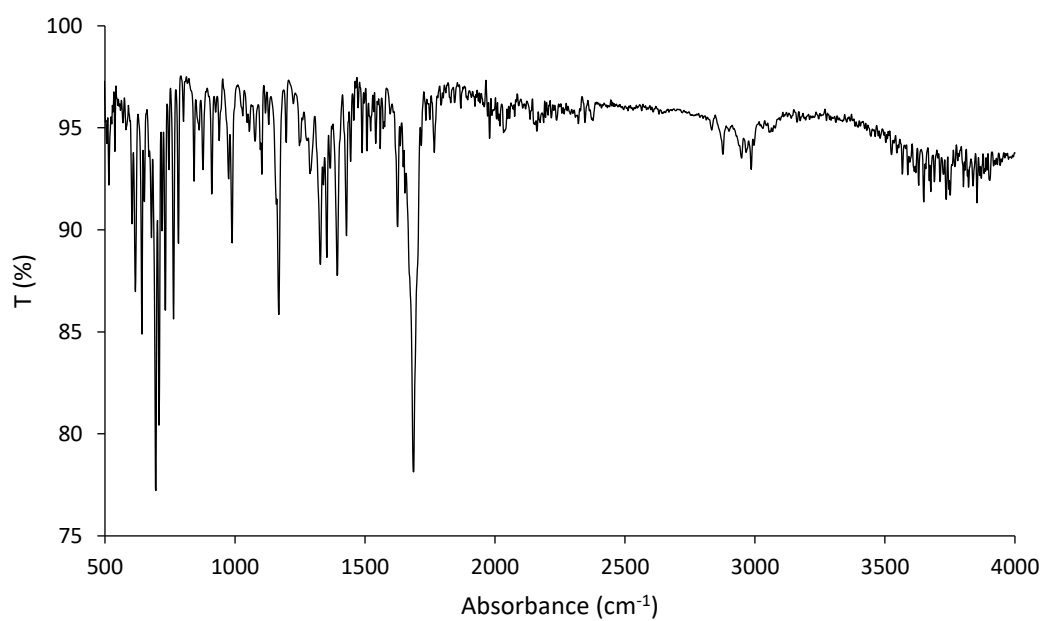
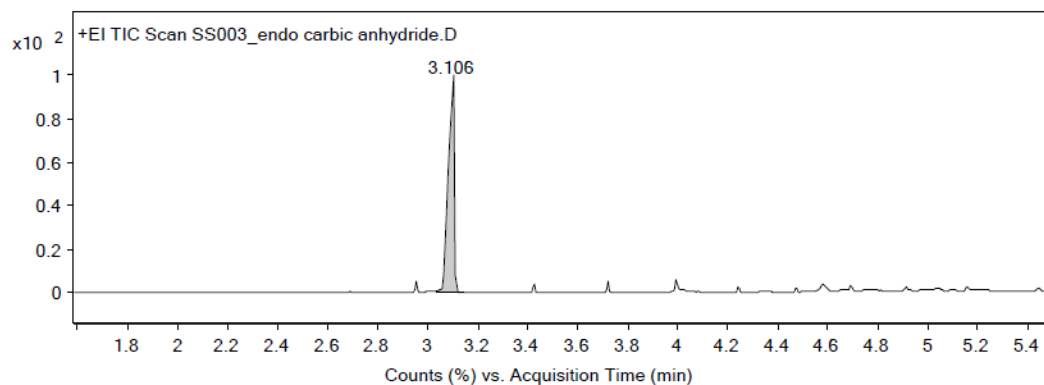


Fig. S60. IR spectra of *endo*-(2-diphenyl imine)-ethyl-5-norbornene-2,3-dicarboximide, **13a**

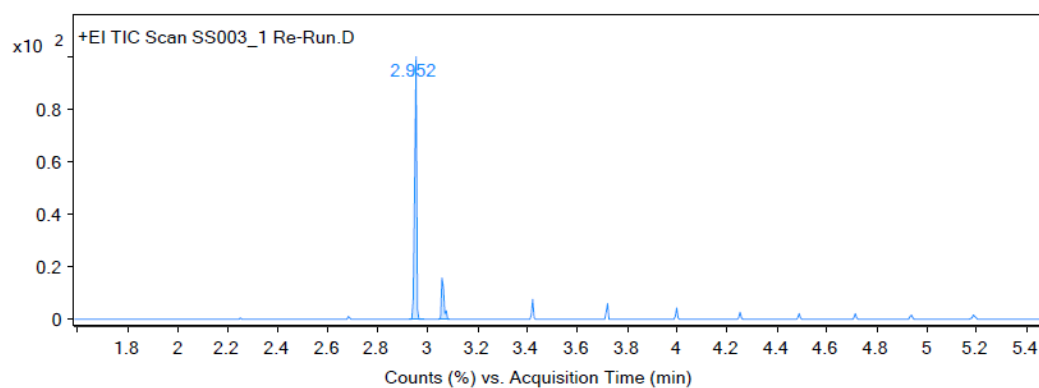
#### 4. GC chromatograms of *endo/exo* isomerisation



##### Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	3.035	3.106	3.142	1393883.18	2361026.89	100

**Fig. S61.** GC chromatogram of *endo*-carbic anhydride **1a**

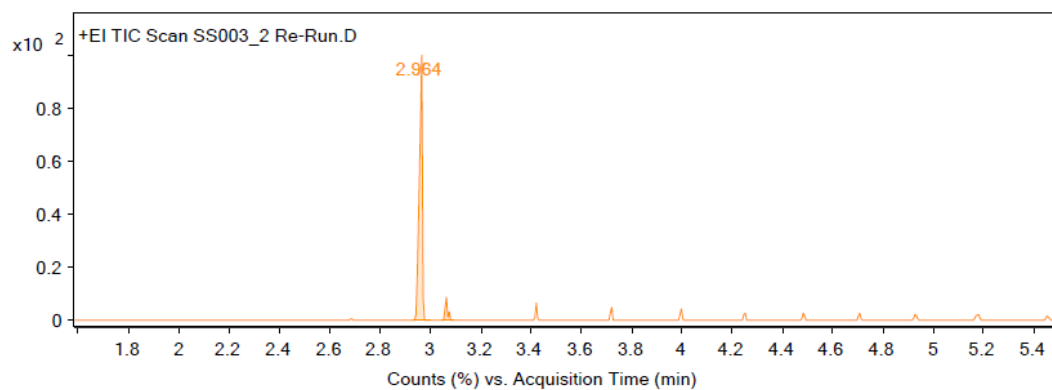


##### Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	2.925	2.952	2.982	508162.32	293324.02	100
2	3.047	3.059	3.086	80662.35	61294.99	20.9

**Fig. S62.** GC chromatogram of crude of reaction containing 83 % *exo* adduct and 17 % *endo* adduct.

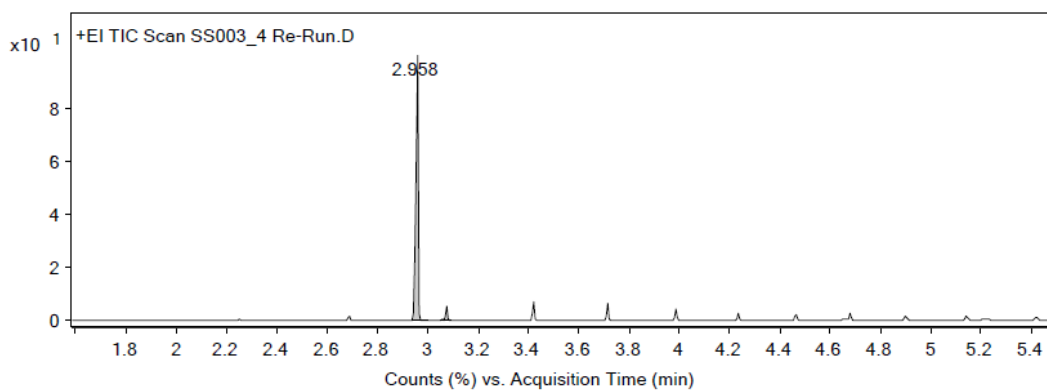




**Integration Peak List**

Peak	Start	RT	End	Height	Area	Area %
1	2.928	2.964	2.999	1103069.55	959466.49	100
2	3.048	3.065	3.092	98351.21	69425.08	7.24

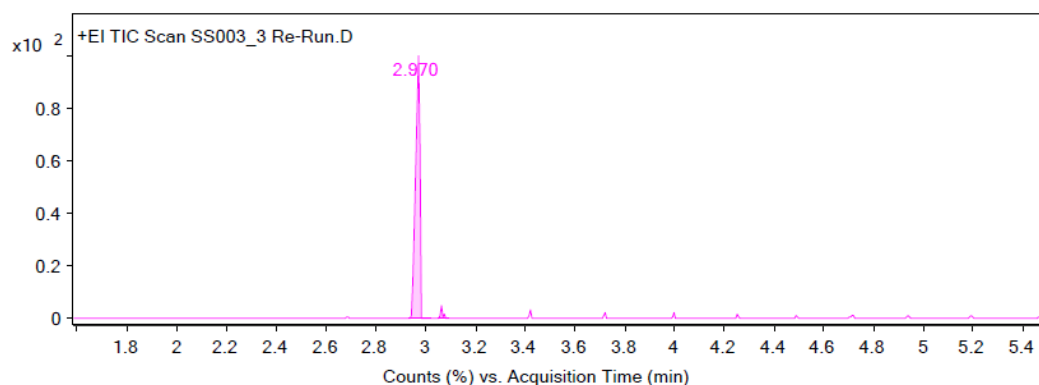
**Fig. S63.** GC chromatogram of first recrystallisation. *Exo*-carbic anhydride is 93 % pure.



**Integration Peak List**

Peak	Start	RT	End	Height	Area	Area %
1	2.934	2.958	3	754152.39	511200.7	100
2	3.053	3.077	3.092	43068.2	21683.29	4.24

**Fig. S64.** GC chromatogram of second recrystallisation. *Exo*-carbic anhydride is 96 % pure.

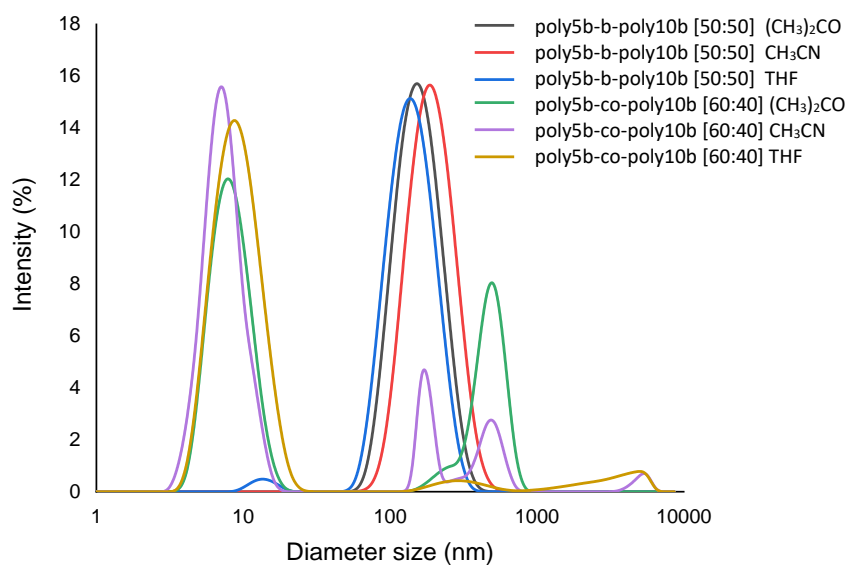


**Integration Peak List**

Peak	Start	RT	End	Height	Area	Area %
1	2.928	2.97	3.016	1364593.66	1705242.92	100
2	3.053	3.065	3.092	68029.45	42538.87	2.49

**Fig. S65.** GC chromatogram of third recrystallisation. *Exo*-carbic anhydride is 98 % pure.

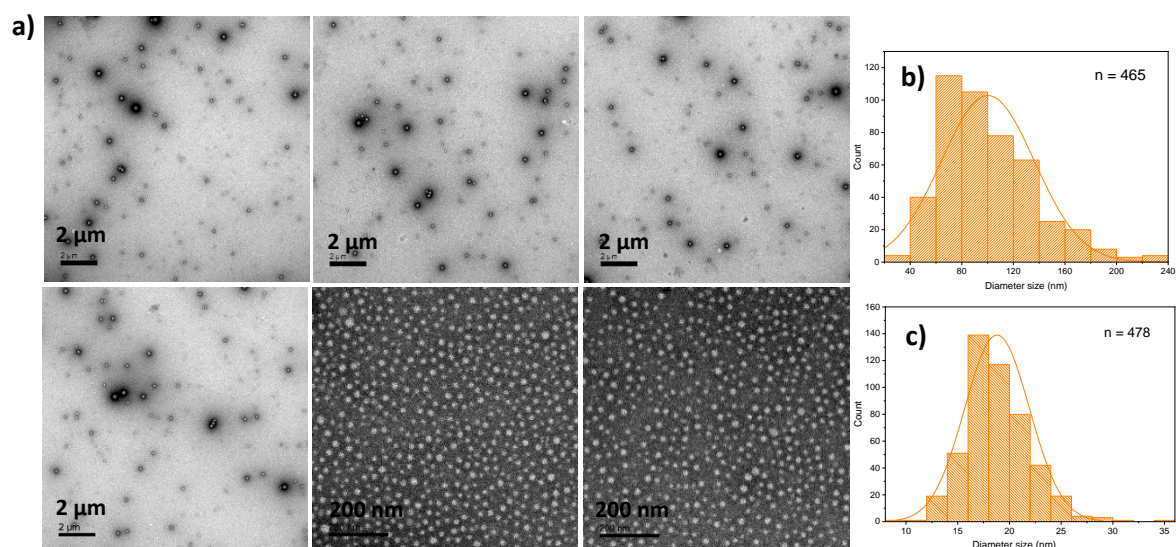
## 5. Dynamic light scattering (DLS) of block and statistical copolymers



**Fig. S66.** DLS data of **poly5b-b-poly10b [50:50]** and **poly5b-co-poly10b [60:40]** self-assembled in different organic solvents such as acetonitrile, acetone and THF.

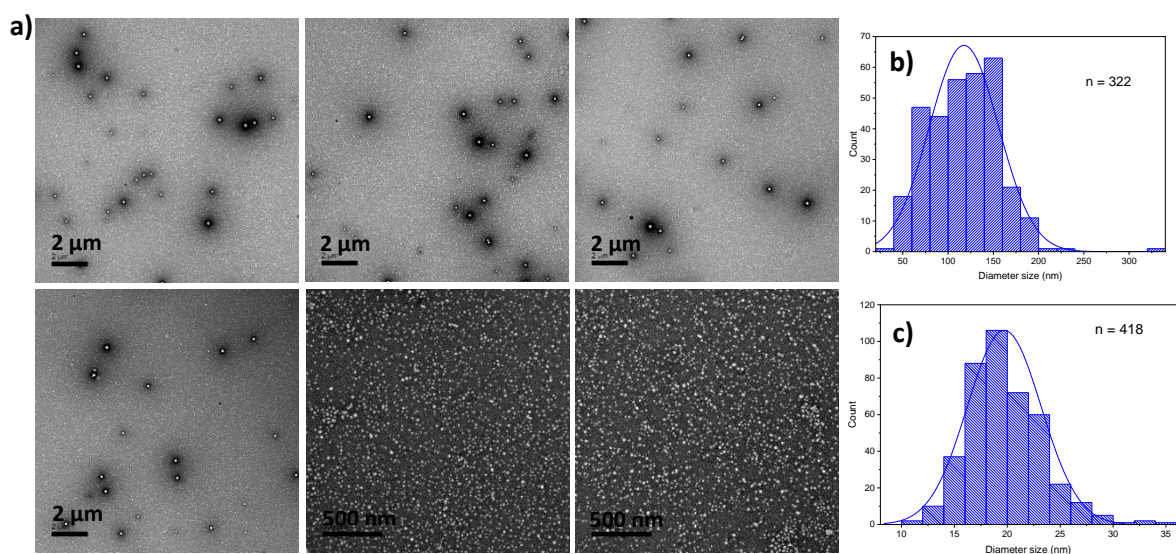
## 6. Transmission electron microscopy (TEM) images of block and statistical copolymers

### 6.1. Poly5b-b-poly10b [50:50] in acetonitrile



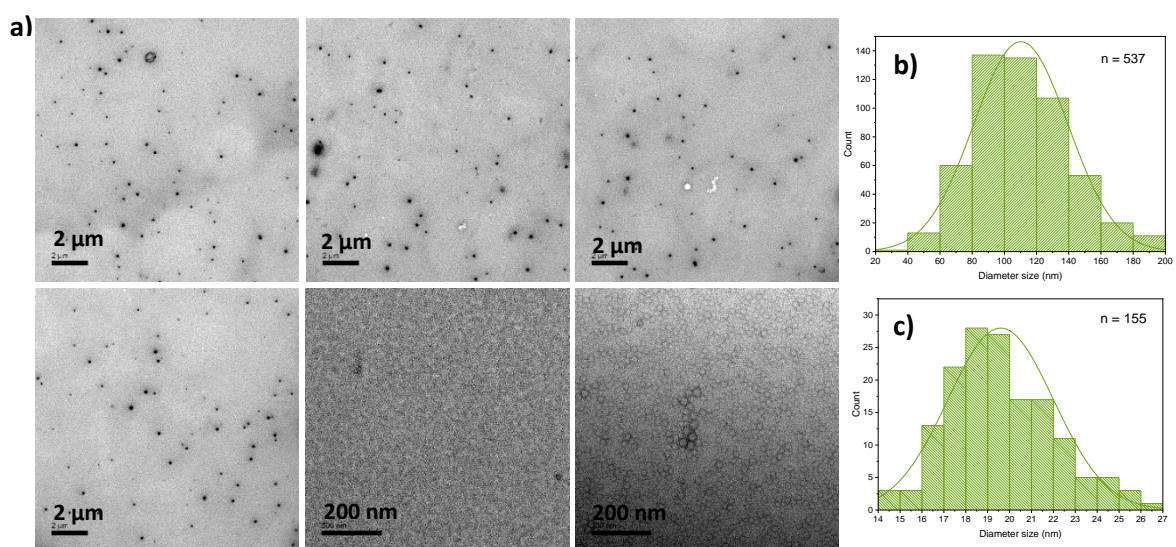
**Fig. S67.** a) TEM images of **poly5b-b-poly10b [50:50]** self-assembled in acetonitrile; b) distribution of bigger particles with average size ( $100 \pm 36$ ) nm; c) distribution of smaller particles with average size ( $19 \pm 3$ ) nm.

### 6.2. Poly5b-b-poly10b [50:50] in acetone



**Fig. S68.** a) TEM images of **poly5b-b-poly10b [50:50]** self-assembled in acetone; b) distribution of bigger particles with average size (118 ± 38) nm; c) distribution of smaller particles with average size (20 ± 3) nm.

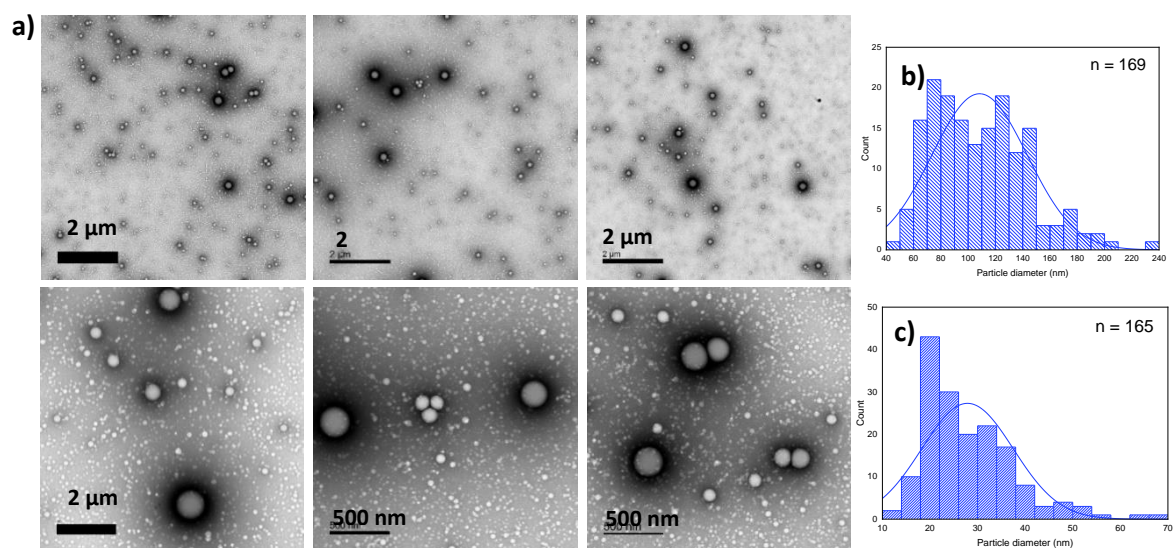
### 6.3. Poly4-b-poly2 [50:50] in tetrahydrofuran



**Fig. S69.** a) TEM images of **poly5b-b-poly10b [50:50]** self-assembled in THF; b) distribution of bigger particles with average size (110 ± 29) nm; c) distribution of smaller particles with average size (20 ± 2) nm.

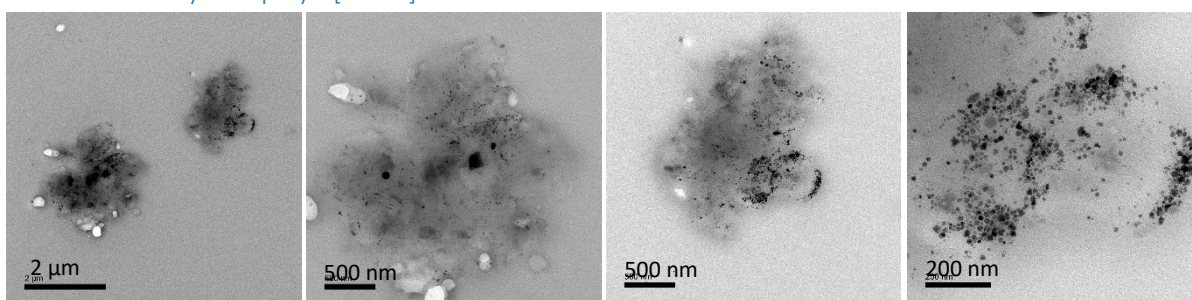


#### 6.4. Poly4-b-poly2 [64:36] in acetone



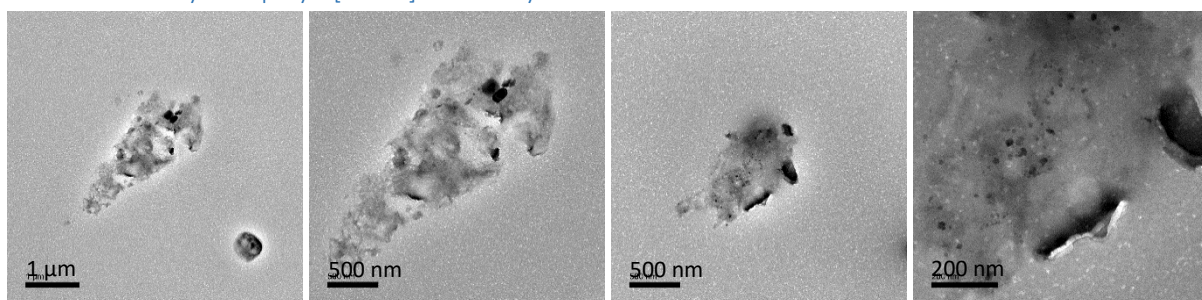
**Fig. S70.** a) TEM images of **poly5b-b-poly10b [64:36]** self-assembled in acetone; b) distribution of bigger particles with average size ( $108 \pm 35$ ) nm; c) distribution of smaller particles with average size ( $28 \pm 9$ ) nm.

#### 6.5. Poly4-co-poly2 [60:40] in acetone



**Fig. S71.** TEM images of **poly5b-co-poly10b [60:40]** self-assembled in acetone.

#### 6.6. Poly4-co-poly2 [60:40] in tetrahydrofuran



**Fig. S72.** TEM images of **poly5b-co-poly10b [60:40]** self-assembled in THF.

### 6.7. Poly4-co-poly2 [60:40] in acetonitrile

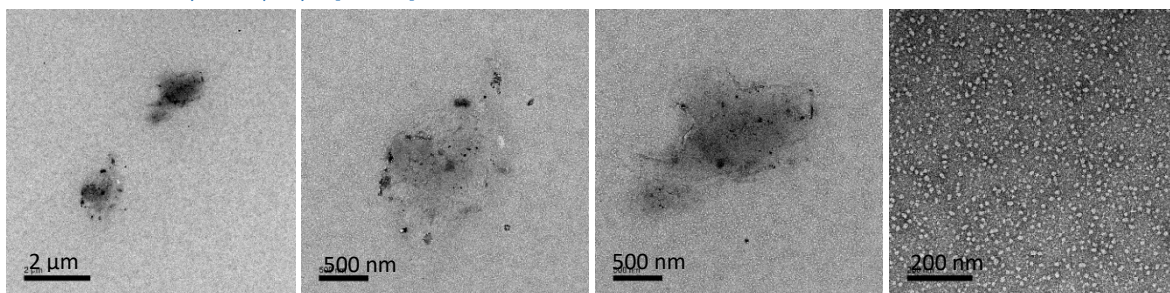


Fig. S73. TEM images of **poly5b-co-poly10b [60:40]** self-assembly in acetonitrile.

### 6.8. Poly4-co-poly2 [63:37] in acetone

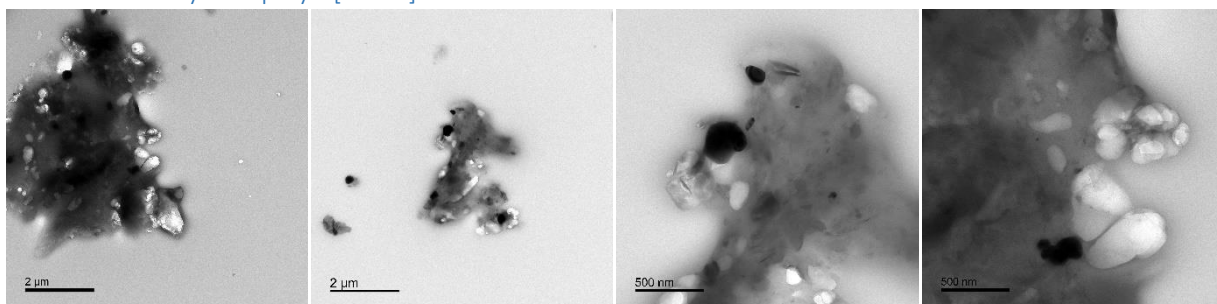


Fig. S74. TEM images of **poly5b-co-poly10b [63:37]** self-assembled in acetone.

## 7. *In vitro* release studies from polymeric nanoparticles

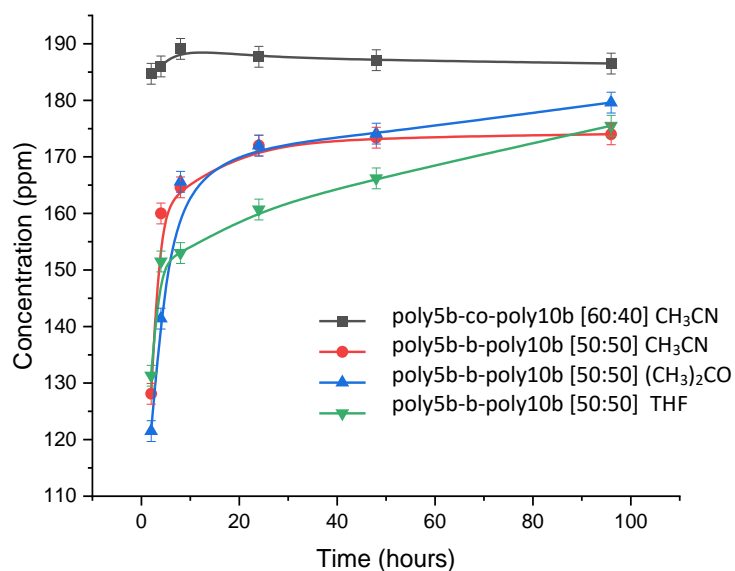
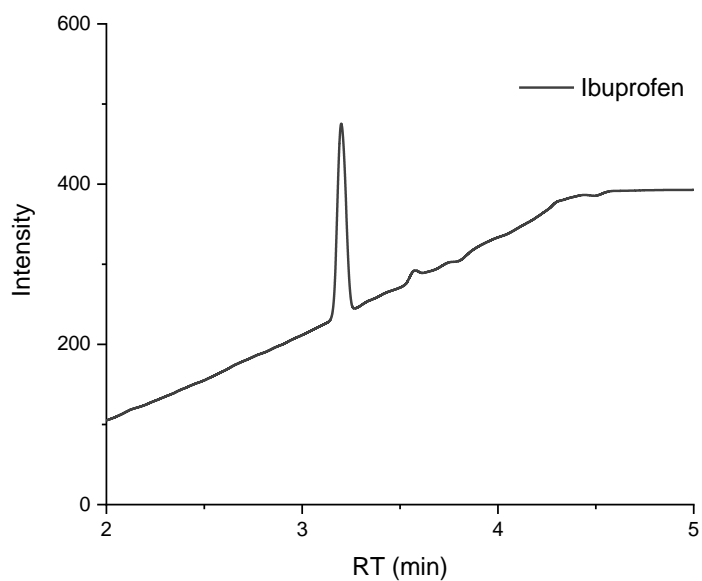
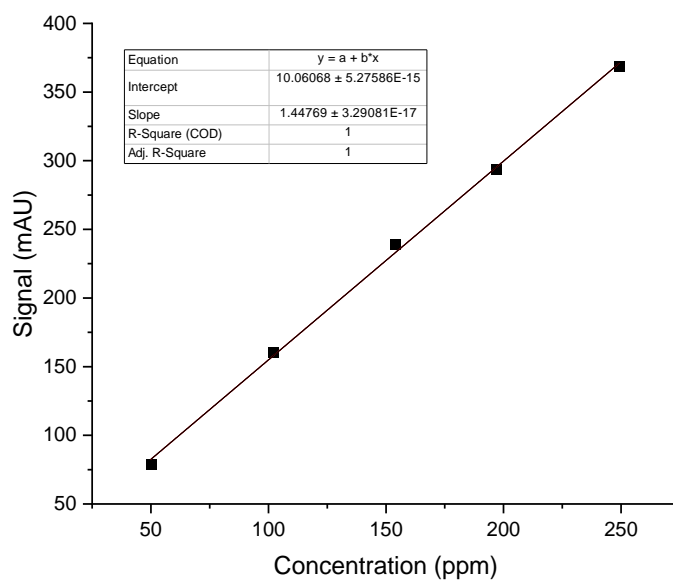


Fig. S75. Graph concentration of ibuprofen released over time in 2M NaOH. Nanoparticles have been obtained by dissolving the polymer (**poly5b-b-poly10b [50:50]** and **poly5b-co-poly10b [60:40]**) in different organic solvents such as acetonitrile, acetone and THF and then by nanoprecipitation with deionised water.



**Fig. S76.** Chromatogram showing that the ibuprofen detected after hydrolysis possesses a retention time of 3.2 minutes



**Fig. S77.** HPLC calibration curve. Standards of ibuprofen in methanol at 50, 100, 150, 200 and 250 ppm were prepared and analysed by HPLC.

## 8. References

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- 2 S. C. G. Biagini and A. L. Parry, *J. Polym. Sci. Part A Polym. Chem.*, 2007, **45**, 3178–3190.
- 3 S. C. G. Biagini, S. M. Bush, V. C. Gibson, L. Mazzariol, M. North, W. G. Teasdale, C. M. Williams, G. Zagotto and D. Zamuner, *Tetrahedron*, 1995, **51**, 7247–7262.