

Supporting Information for:

Synthesis, Pharmacological, and Biological Evaluation of MIF-1 Picolinoyl Peptidomimetics as Positive Allosteric Modulators of D₂R

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Supporting Information

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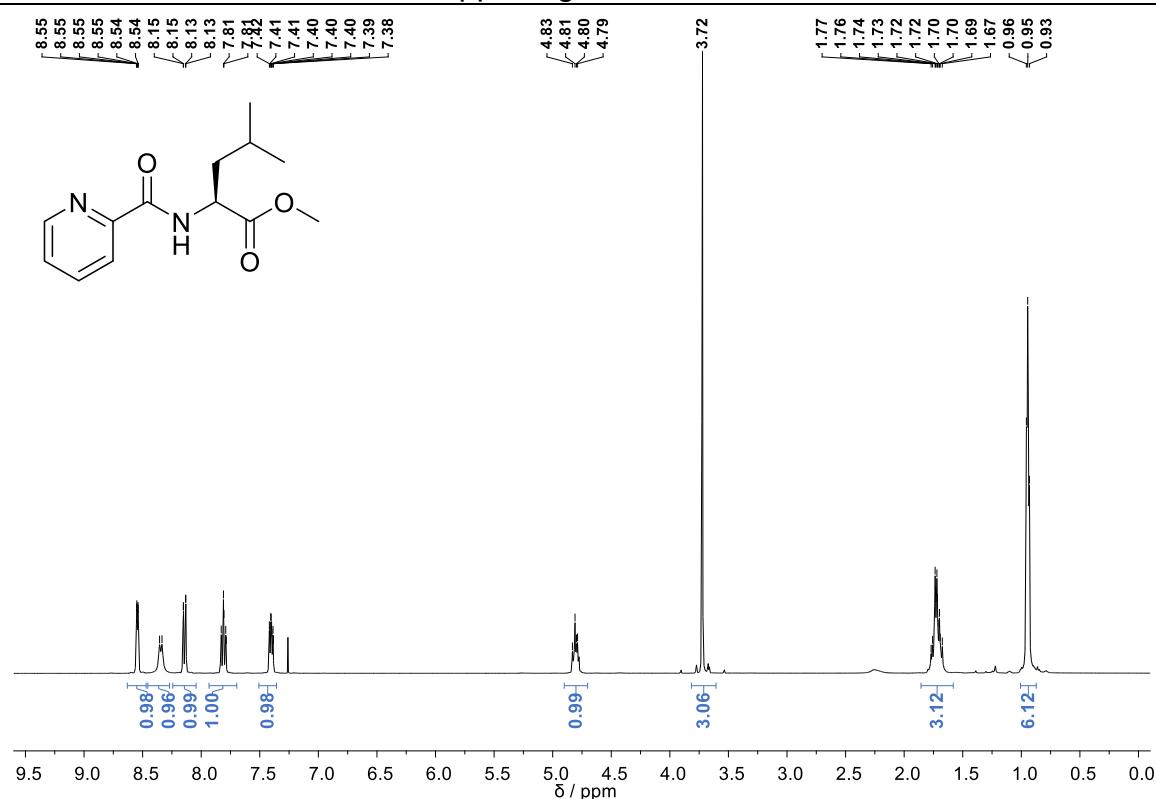


Figure S1. ¹H-NMR spectrum (CDCl_3 , 400 MHz) of **3a**.

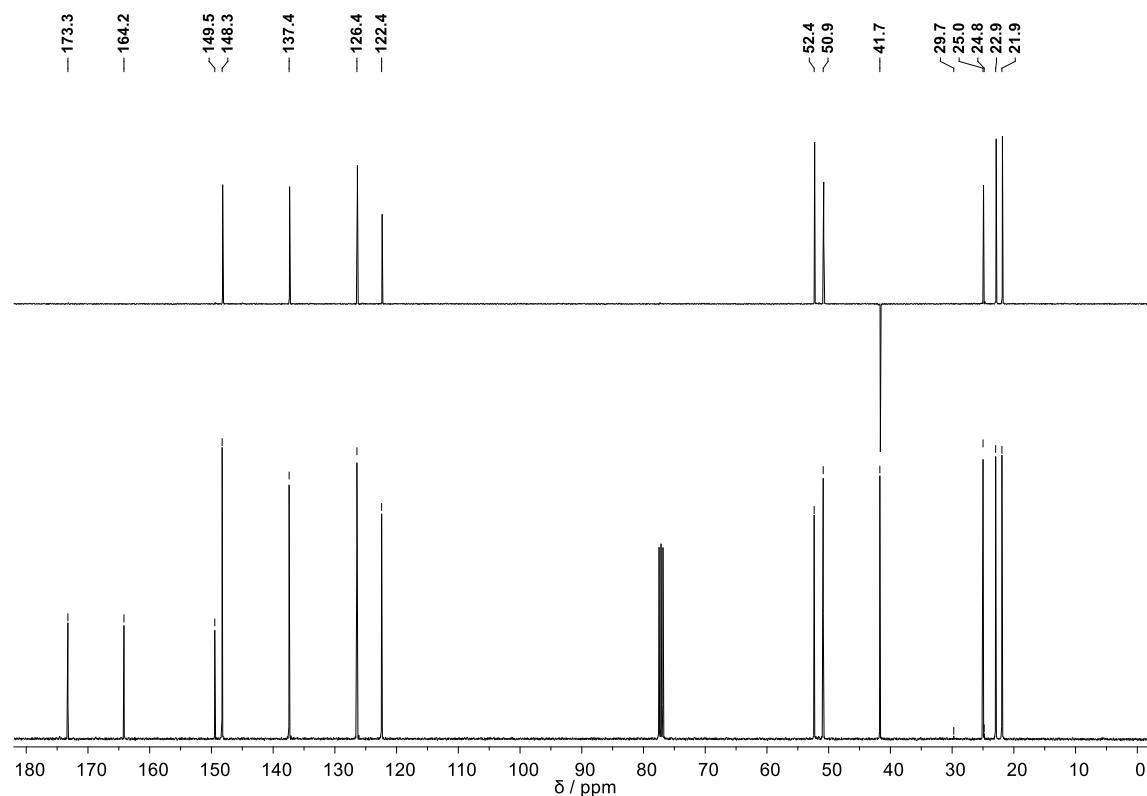


Figure S2. ¹³C-NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **3a**.

Supporting Information

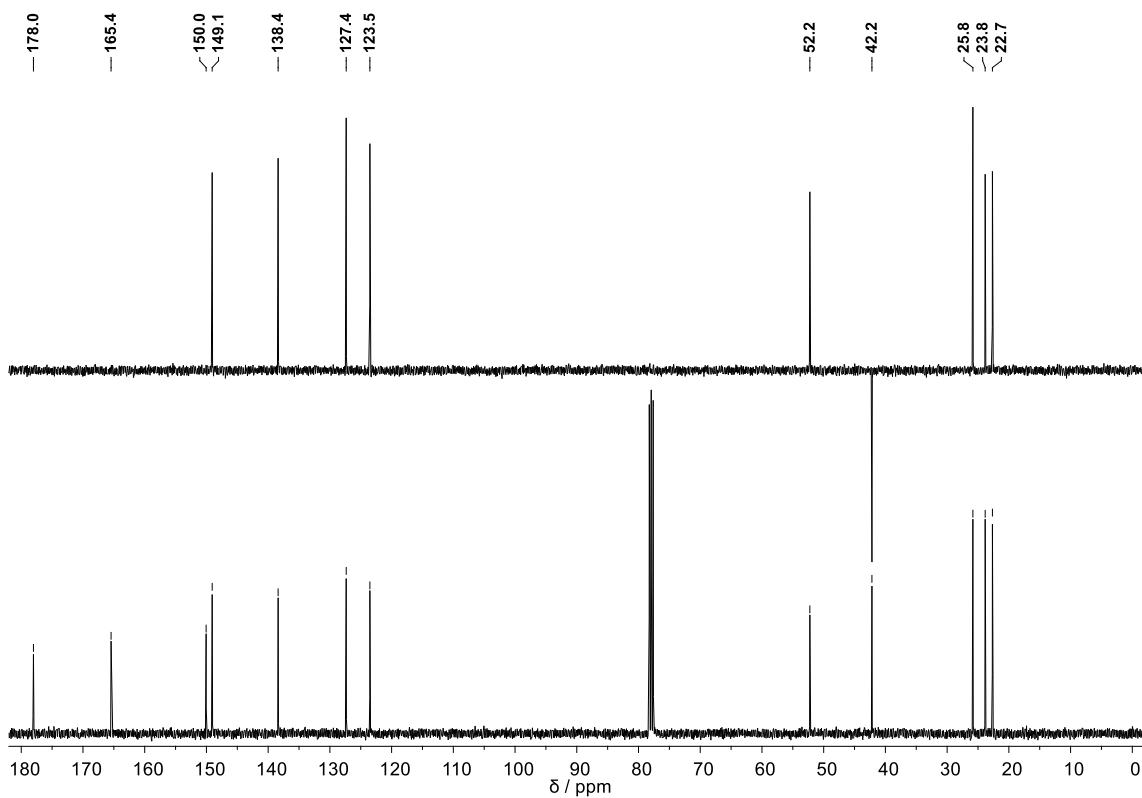
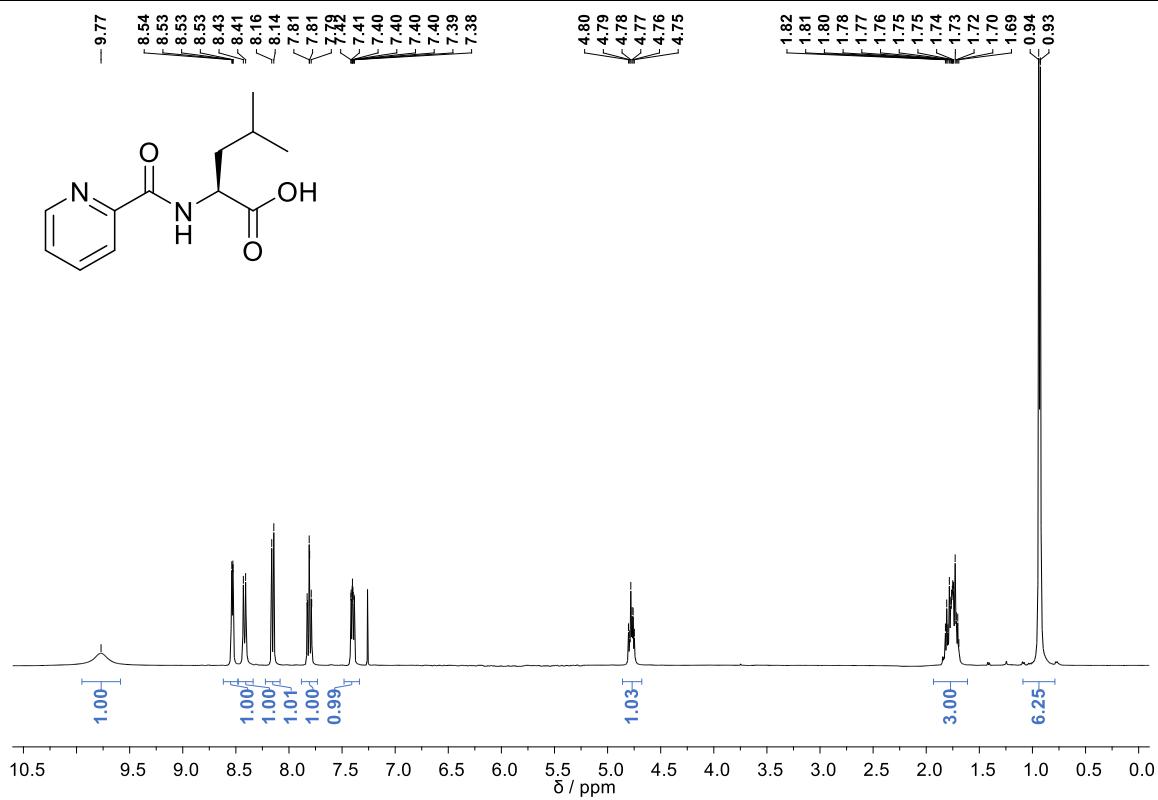


Figure S4. ^{13}C -NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **4a**.

Supporting Information

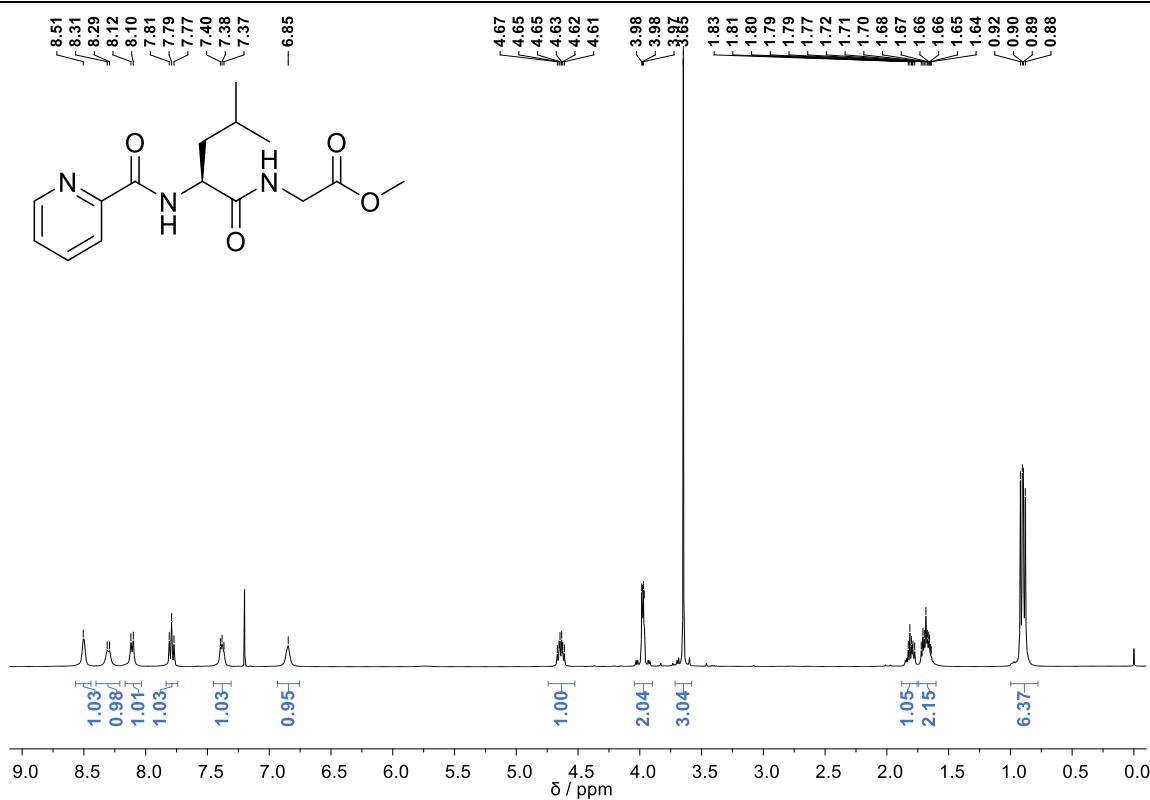


Figure S5. ^1H -NMR spectrum (CDCl_3 , 400 MHz) of **5a**.

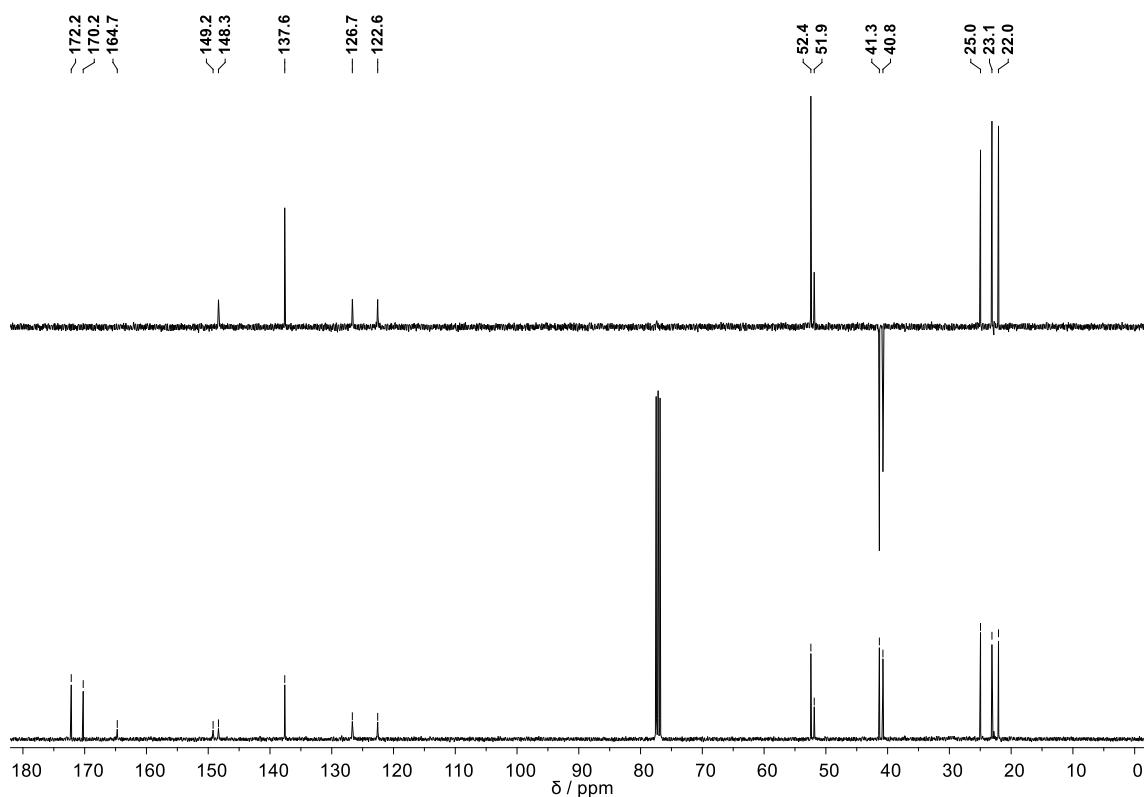


Figure S6. ^{13}C -NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **5a**.

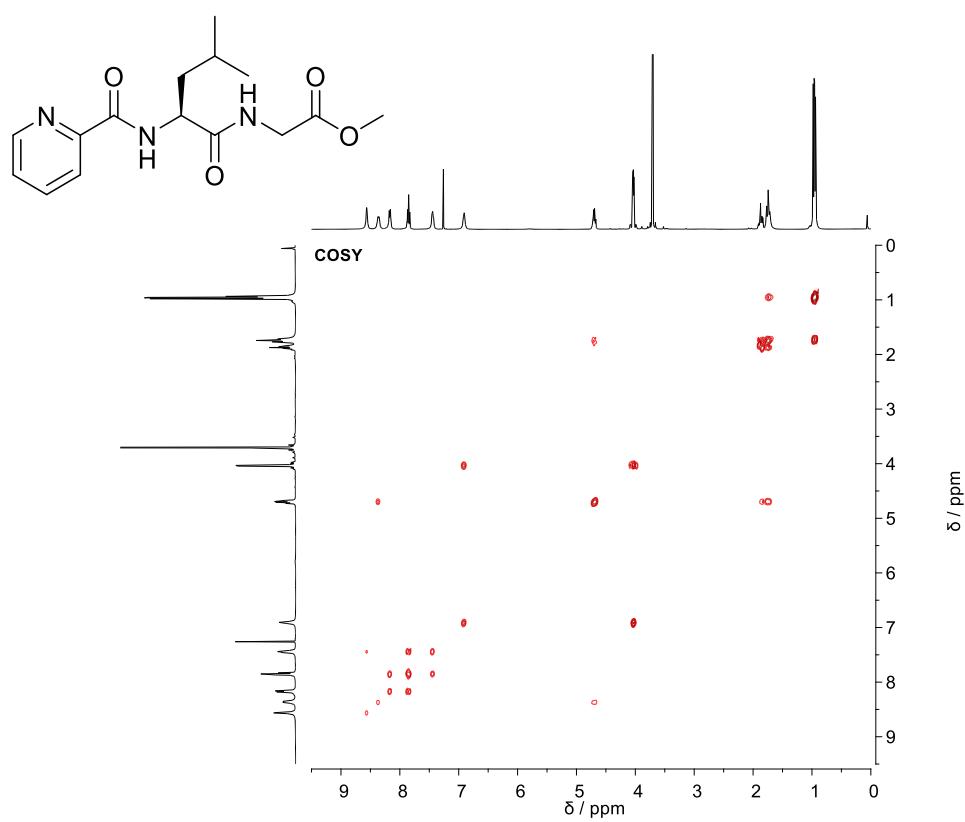


Figure S7. COSY spectrum (CDCl₃, 400 MHz) of **5a**.

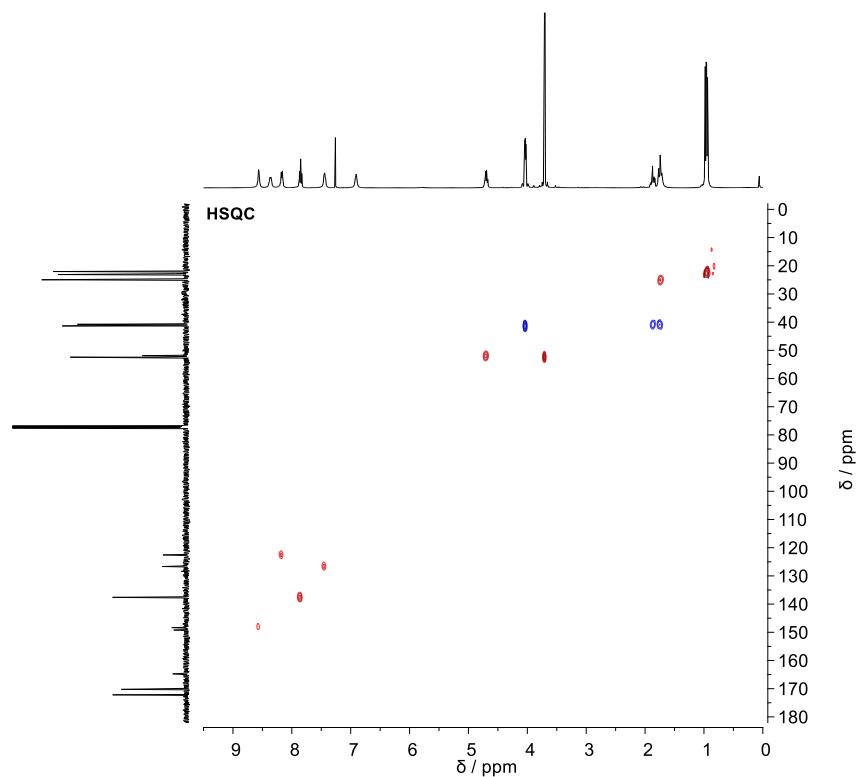


Figure S8. HSQC spectrum (CDCl₃, 400 MHz) of **5a**.

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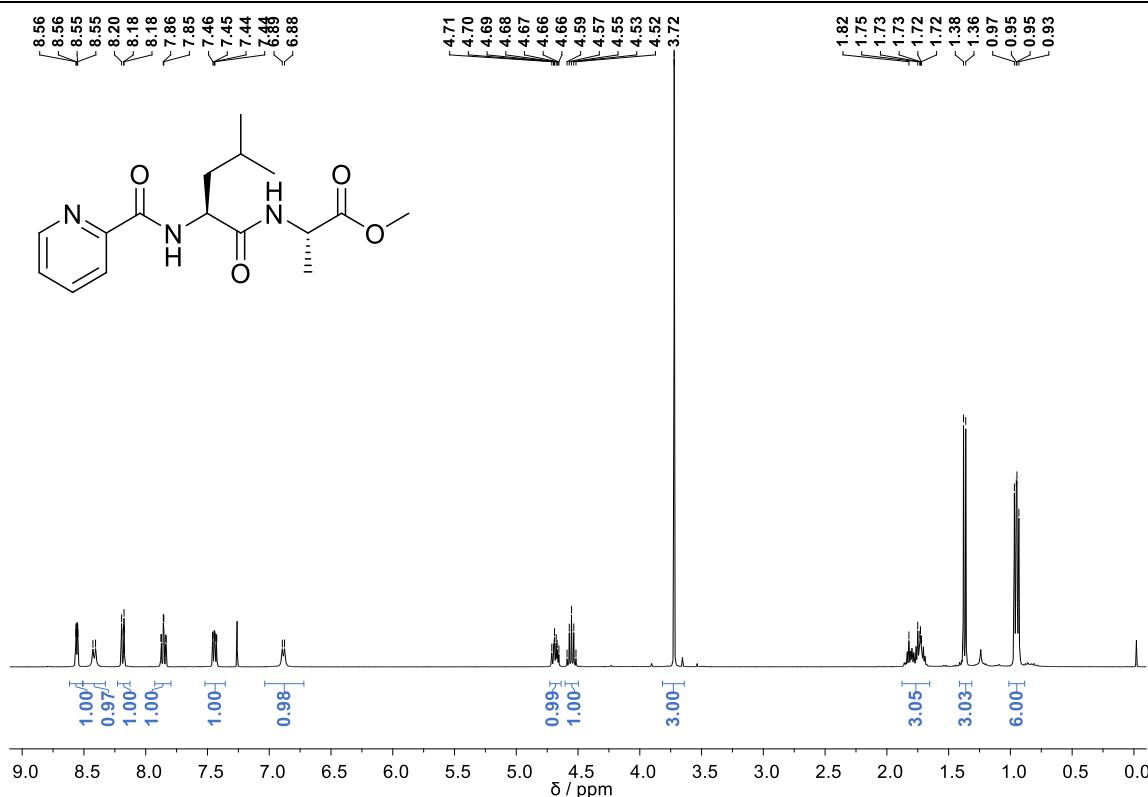


Figure S9. ^1H -NMR spectrum (CDCl_3 , 400 MHz) of **6a**.

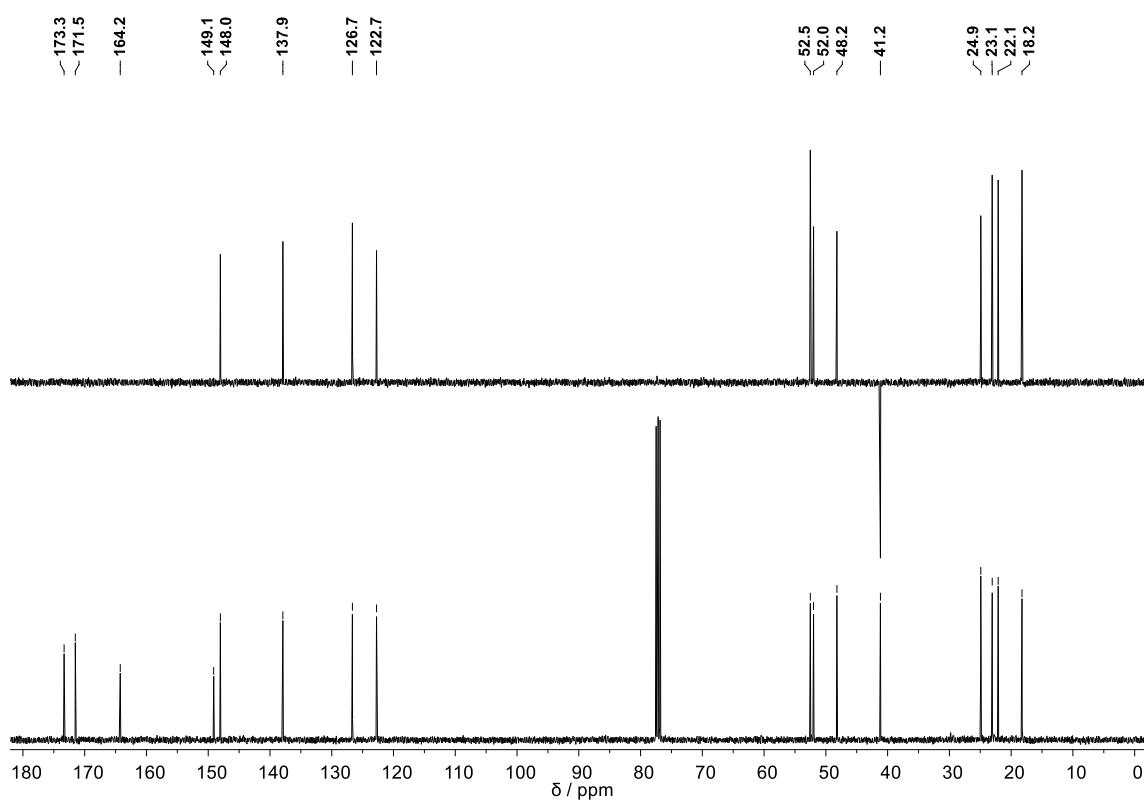


Figure S10. ^{13}C -NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **6a**.

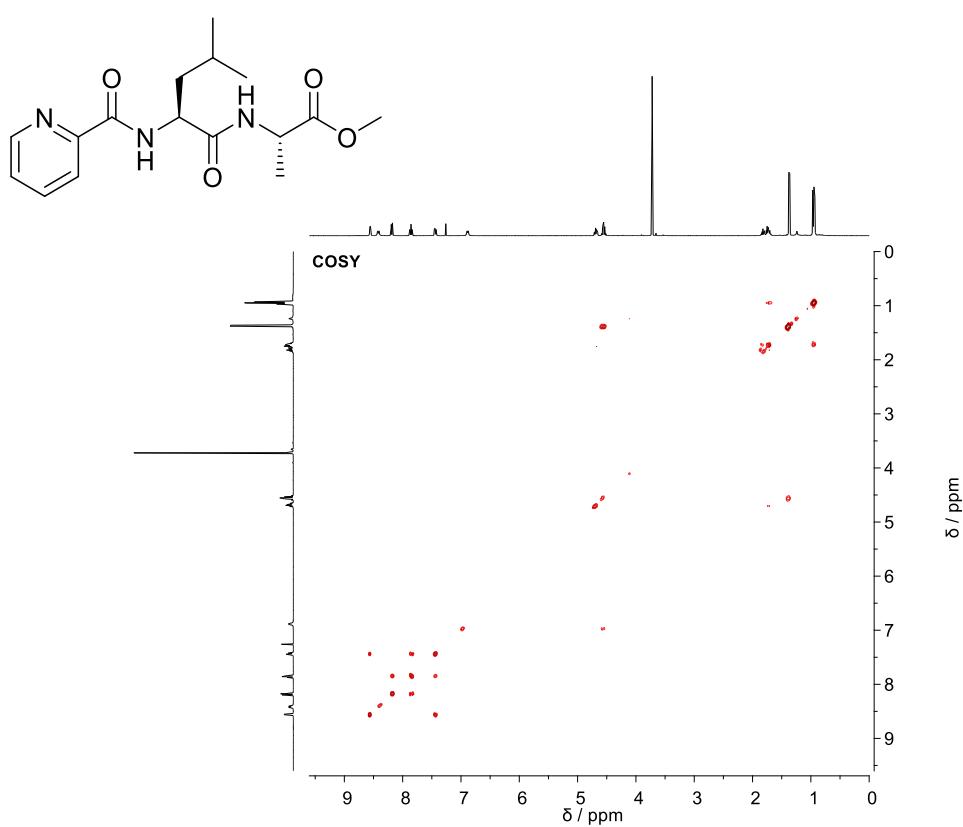


Figure S11. COSY spectrum (CDCl₃, 400 MHz) of **6a**.

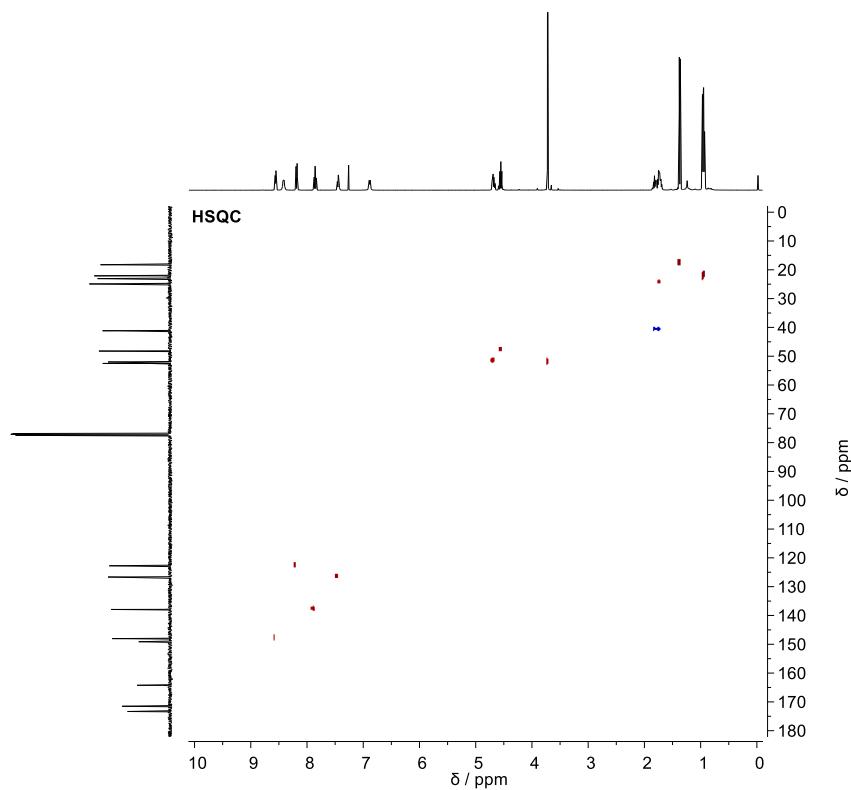


Figure S12. HSQC spectrum (CDCl₃, 400 MHz) of **6a**.

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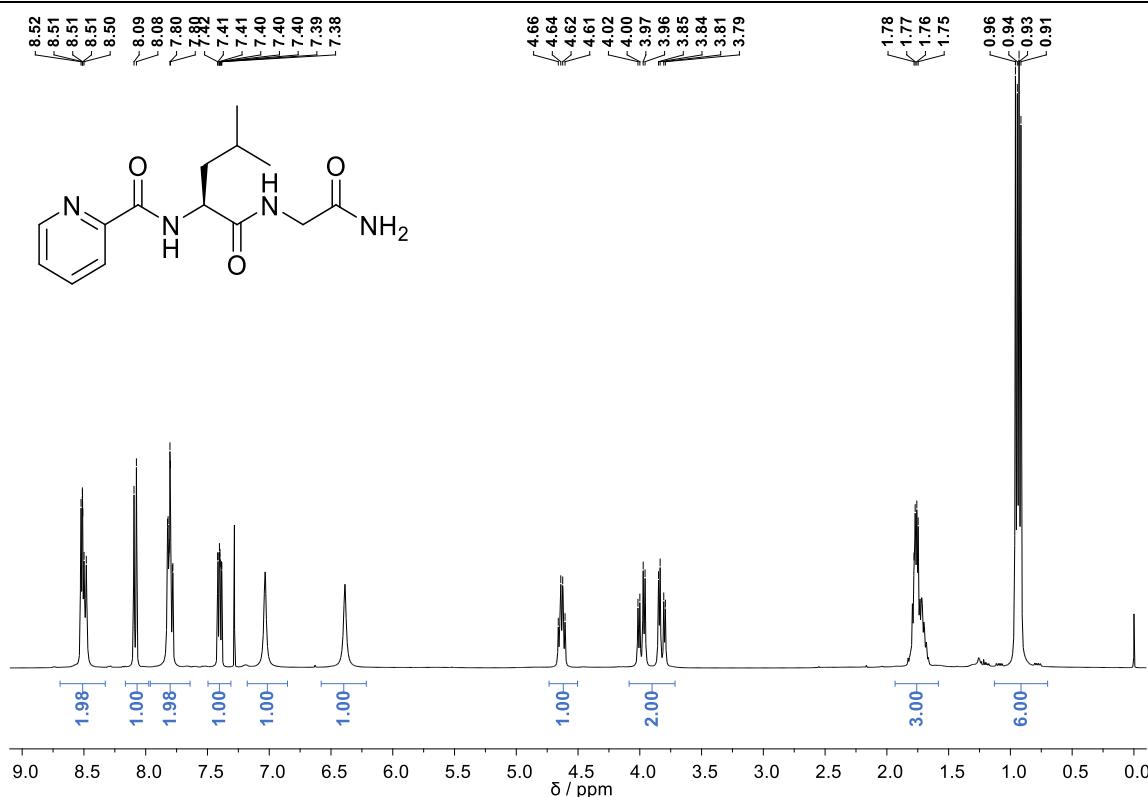


Figure S13. ^1H -NMR spectrum (CDCl_3 , 400 MHz) of **7a**.

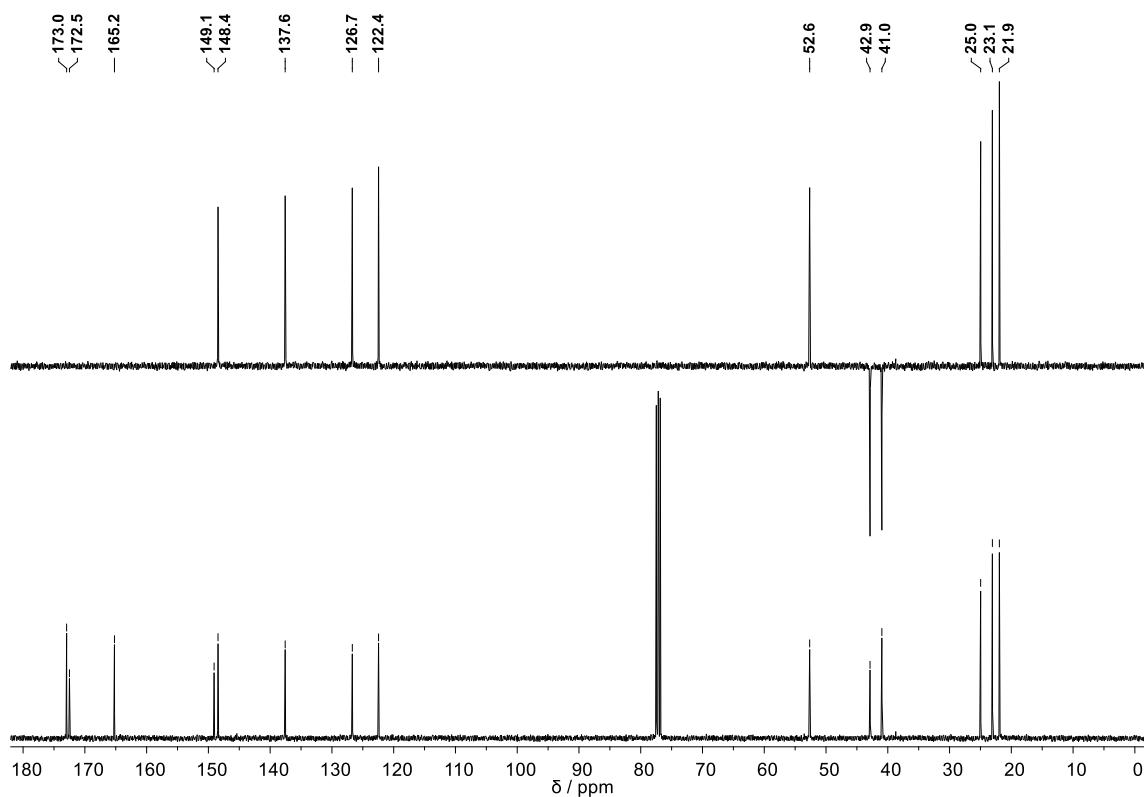


Figure S14. ^{13}C -NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **7a**.

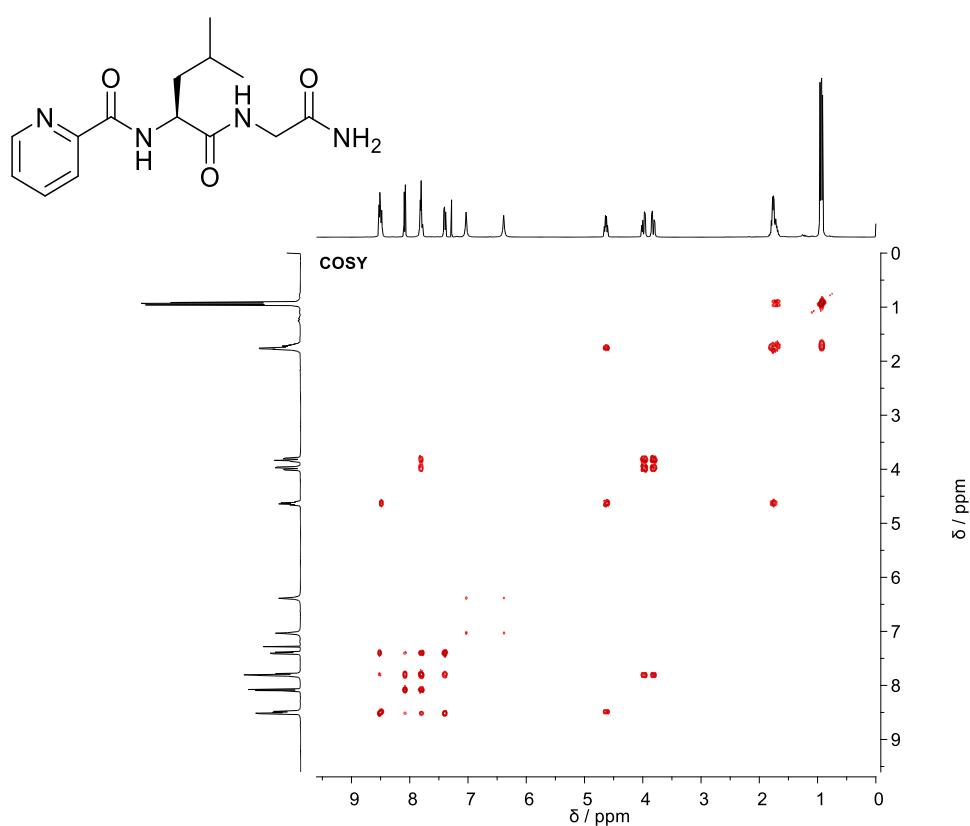


Figure S15. COSY spectrum (CDCl₃, 400 MHz) of **7a**.

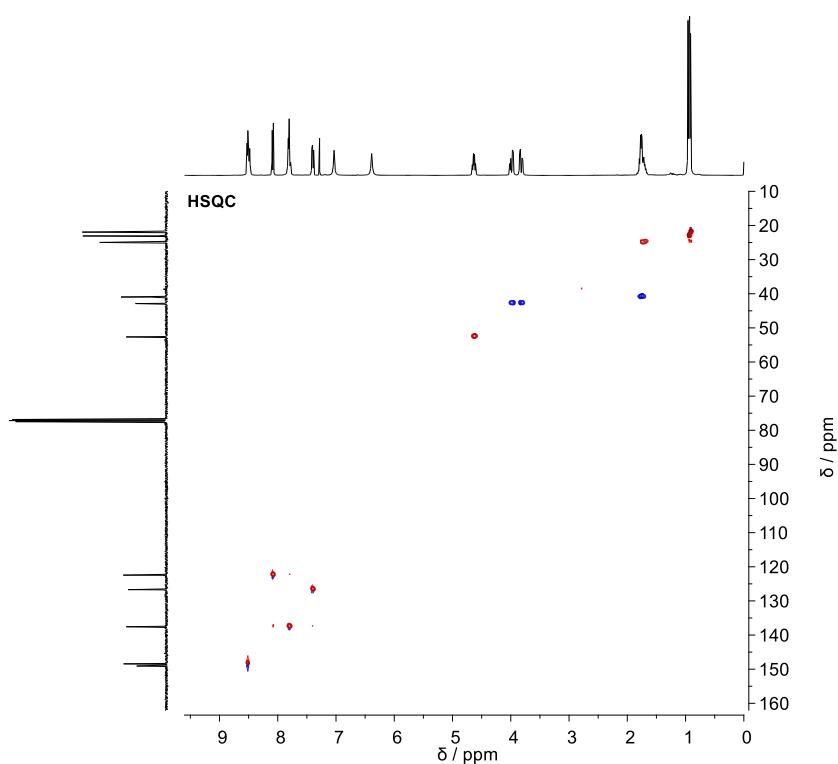


Figure S16. HSQC spectrum (CDCl₃, 400 MHz) of **7a**.

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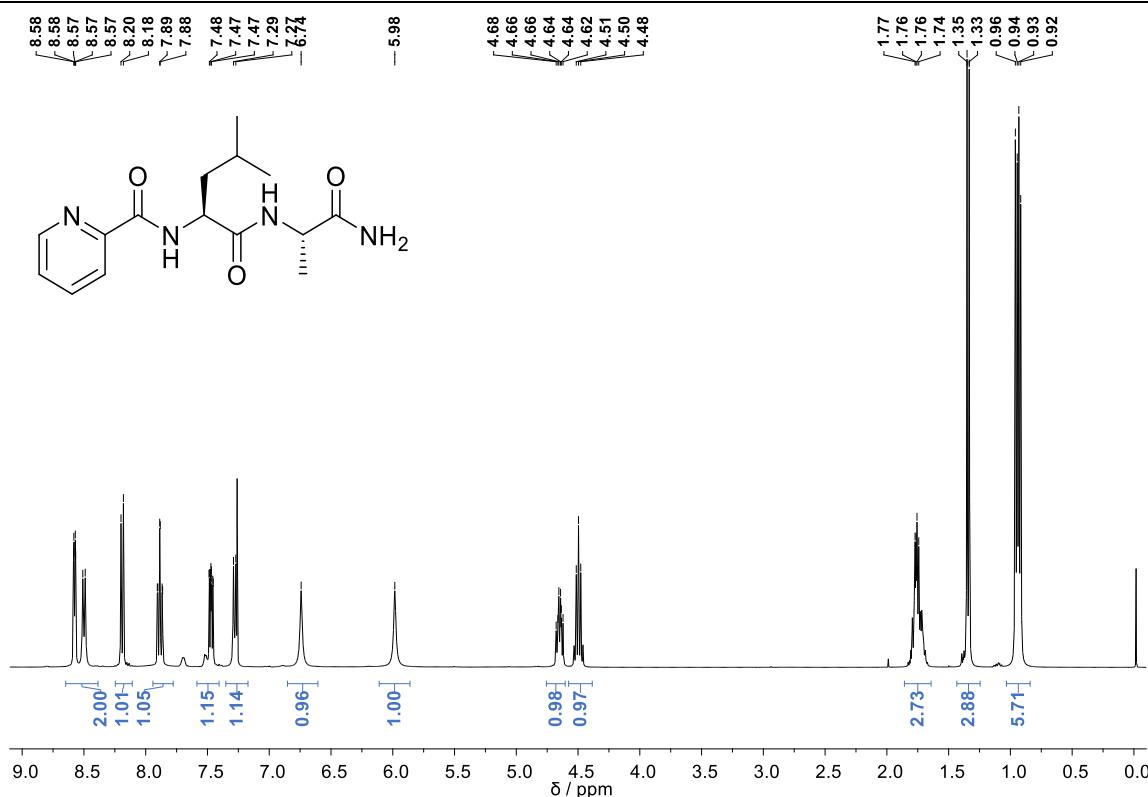


Figure S17. ^1H -NMR spectrum (CDCl_3 , 400 MHz) of **8a**.

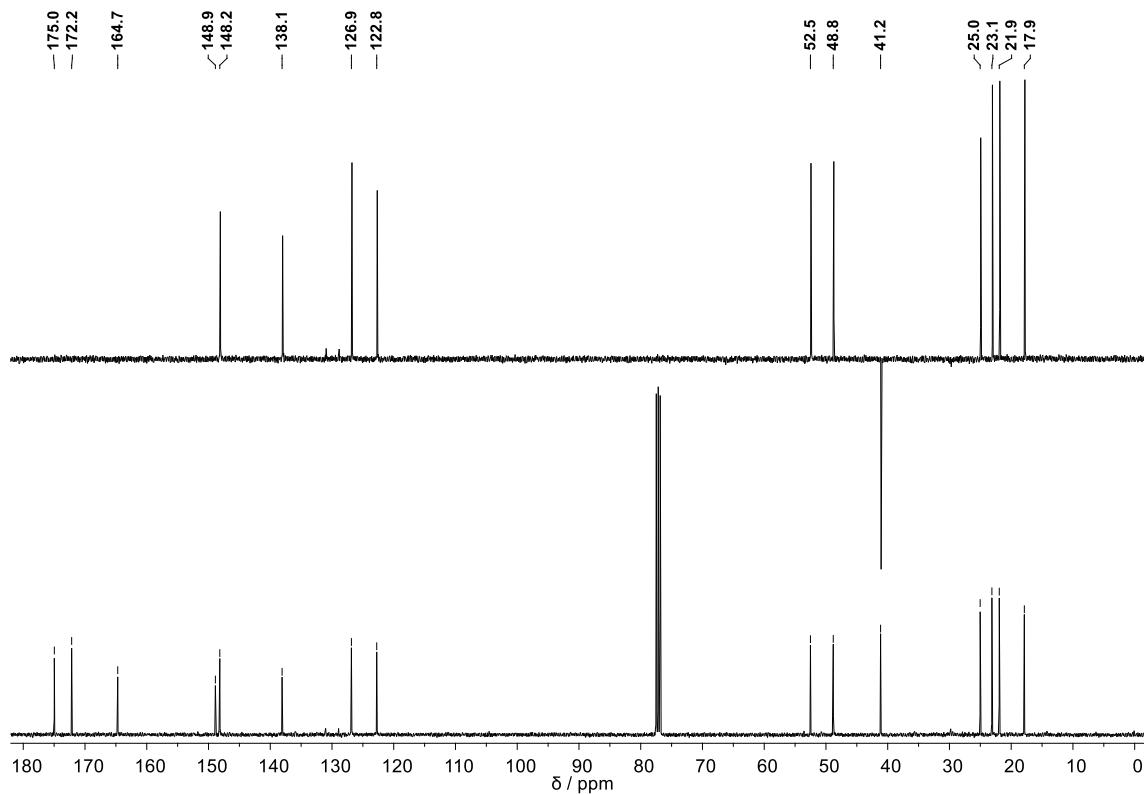


Figure S18. ^{13}C -NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **8a**.

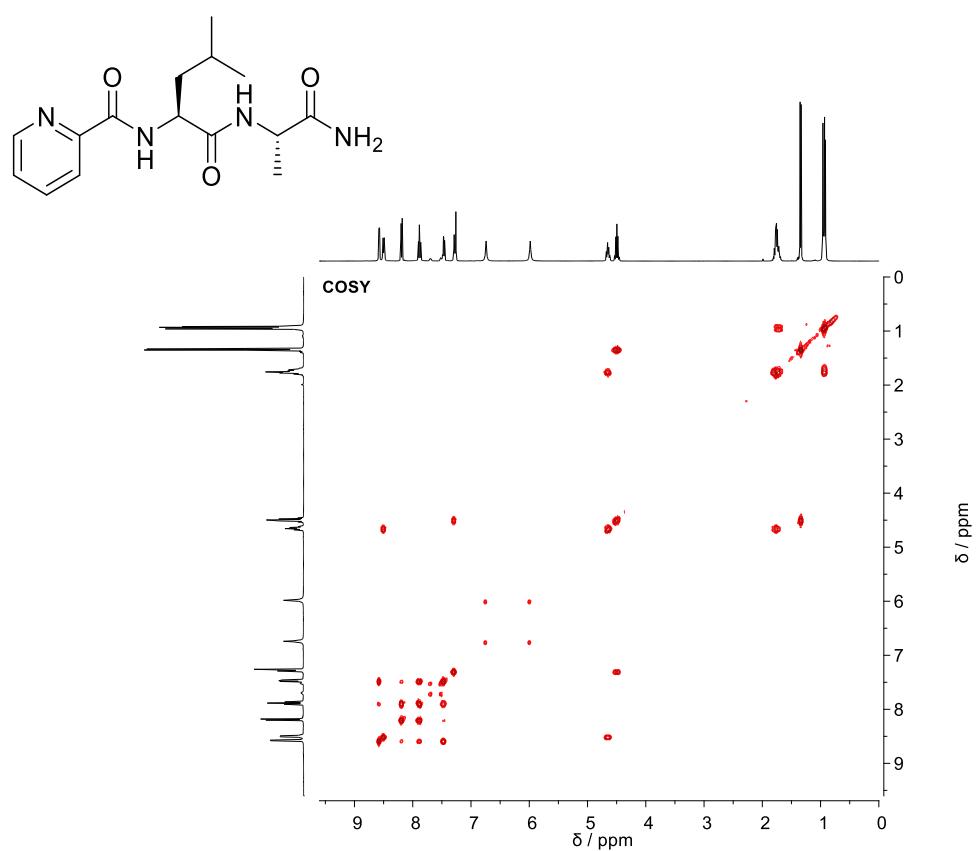


Figure S19. COSY spectrum (CDCl₃, 400 MHz) of **8a**.

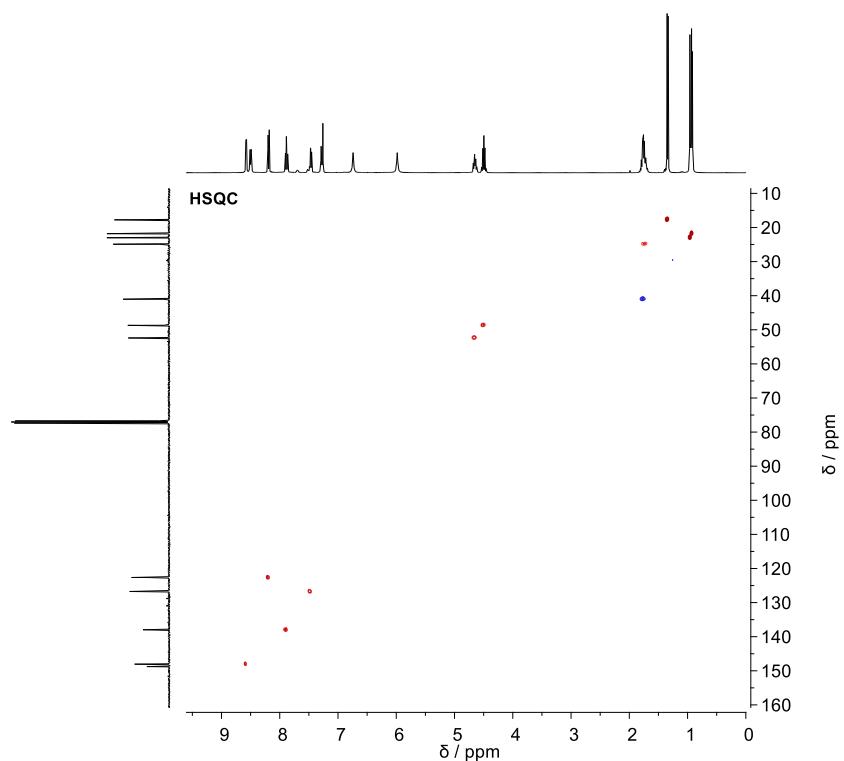


Figure S20. HSQC spectrum (CDCl₃, 400 MHz) of **8a**.

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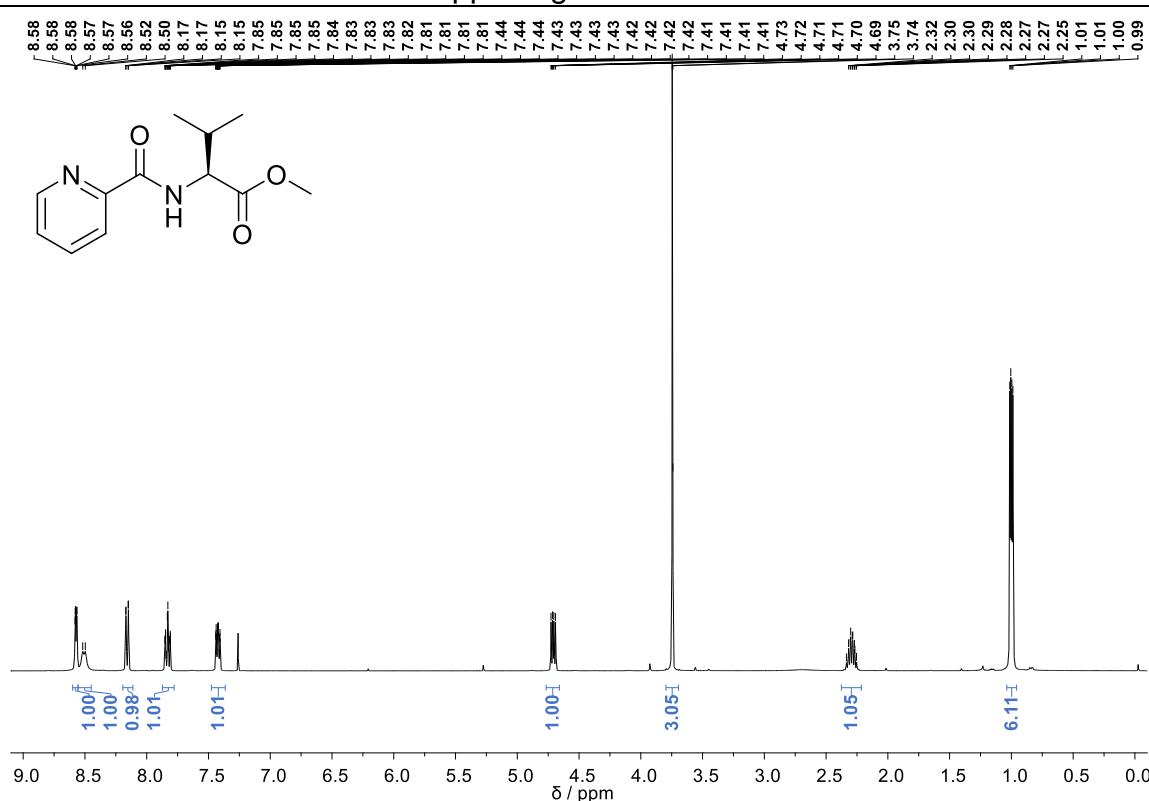


Figure S21. ¹H-NMR spectrum (CDCl₃, 400 MHz) of **3b**.

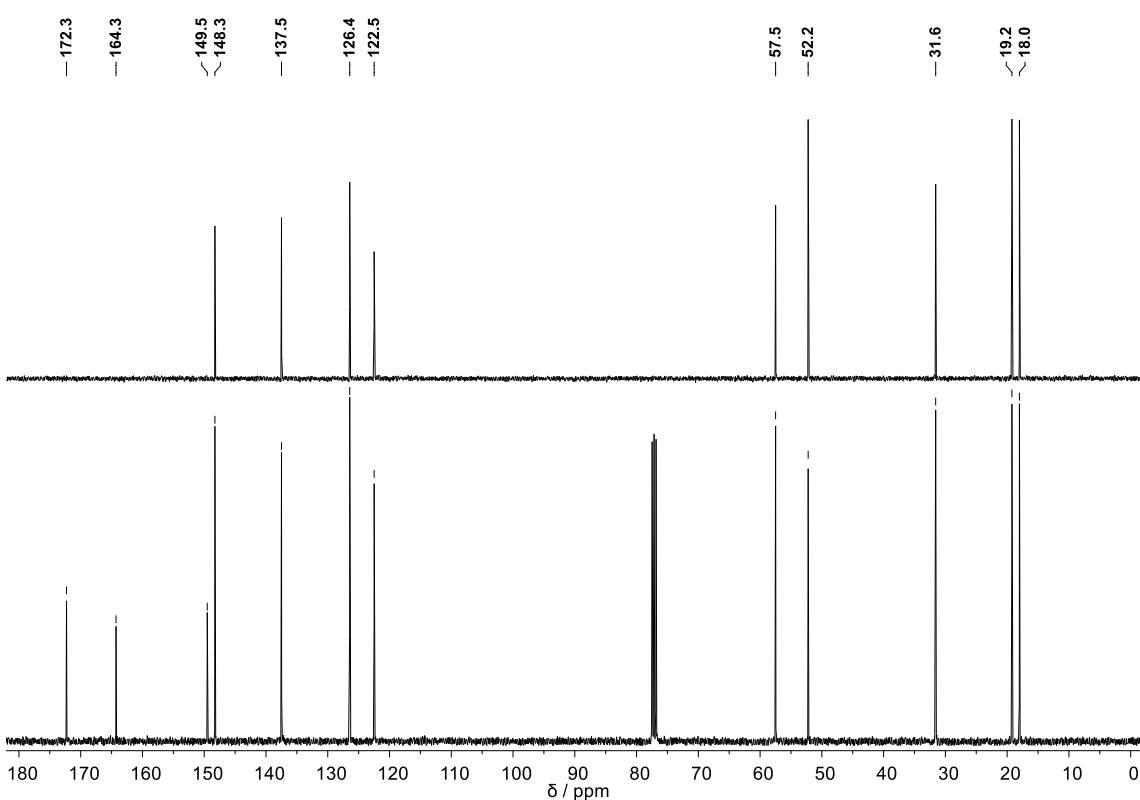


Figure S22. ¹³C-NMR and DEPT-135 spectra (CDCl₃, 100 MHz) of **3b**.

Supporting Information

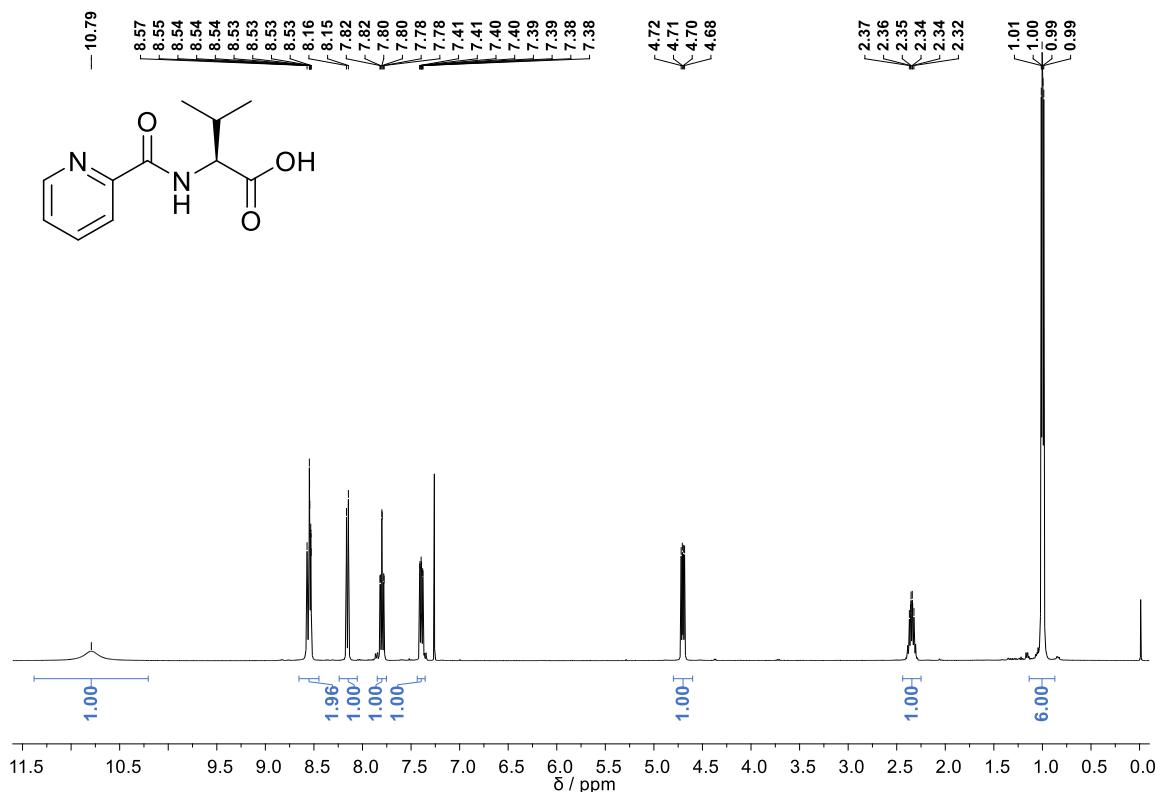


Figure S23. ¹H-NMR spectrum (CDCl_3 , 400 MHz) of **4b**.

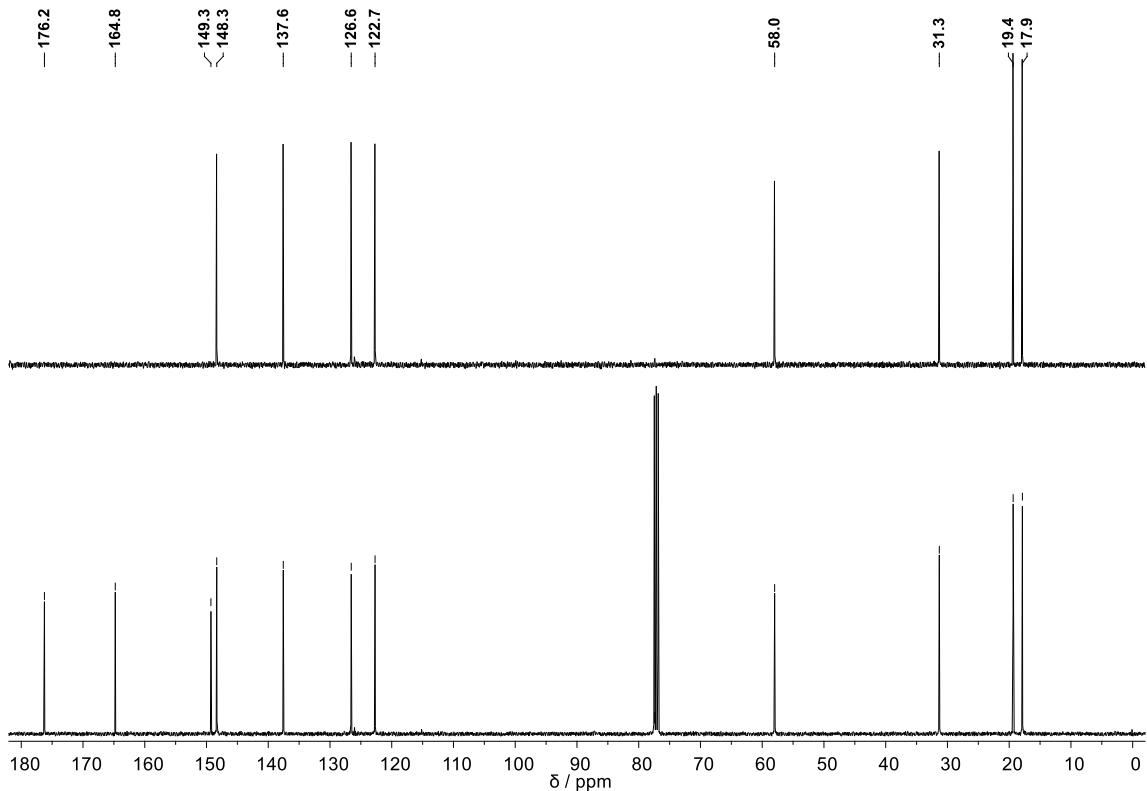


Figure S24. ¹³C-NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **4b**.

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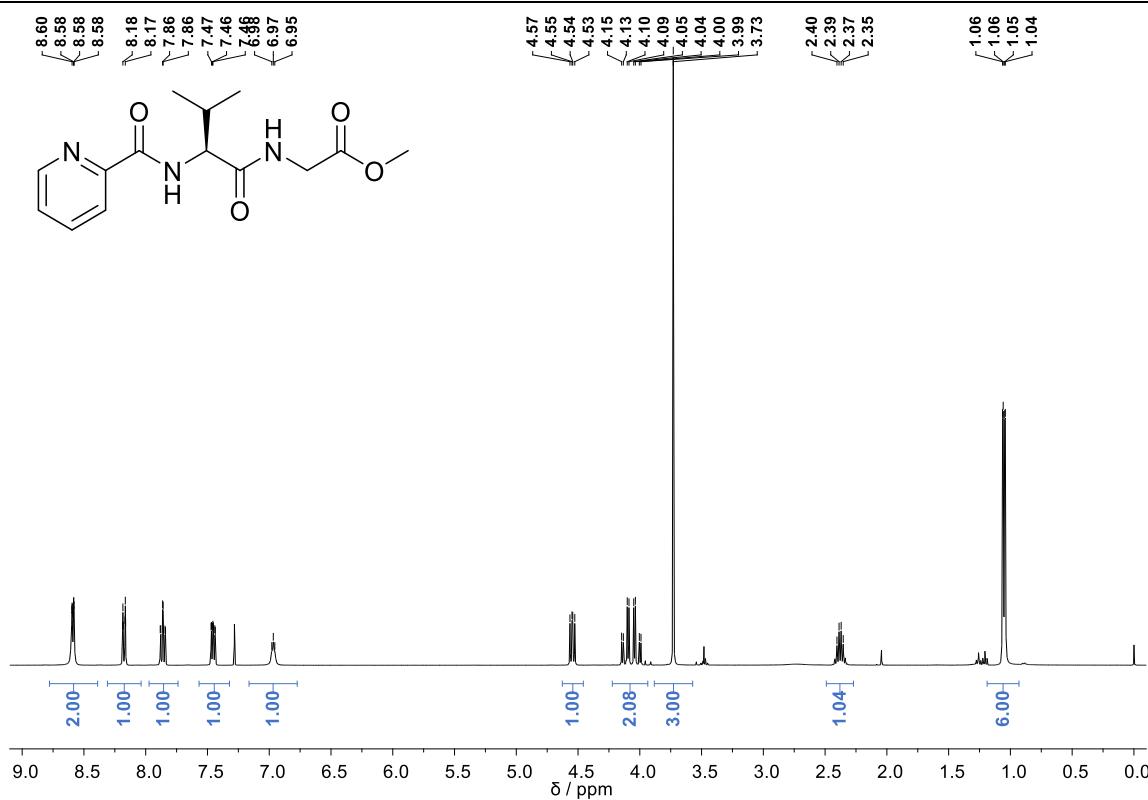


Figure S25. ^1H -NMR spectrum (CDCl_3 , 400 MHz) of **5b**.

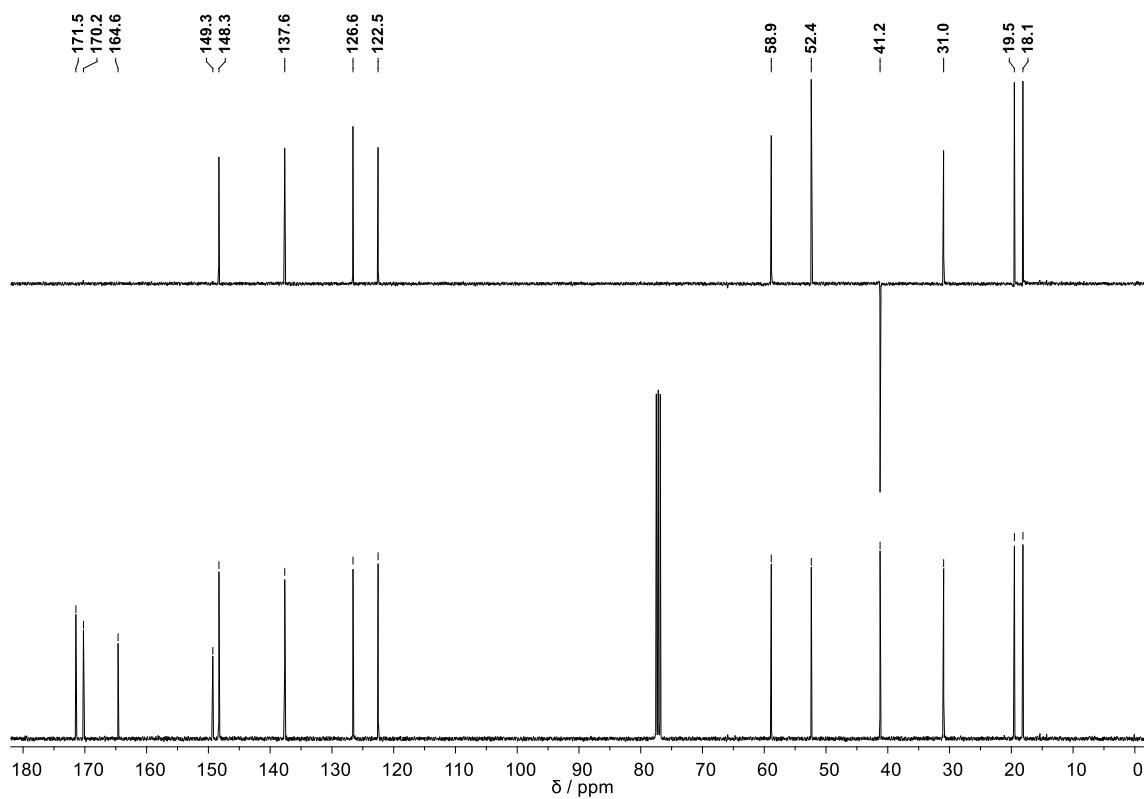


Figure S26. ^{13}C -NMR and DEPT-135 spectra (CDCl_3 , 100 MHz) of **5b**.

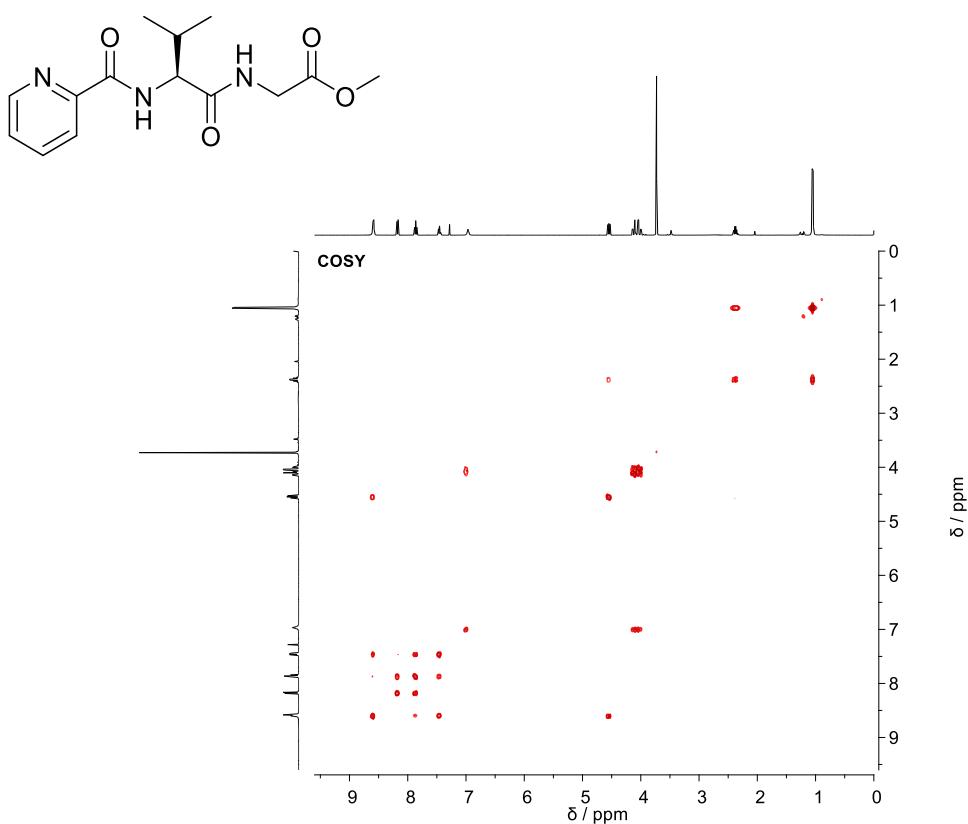


Figure S27. COSY spectrum (CDCl₃, 400 MHz) of **5b**.

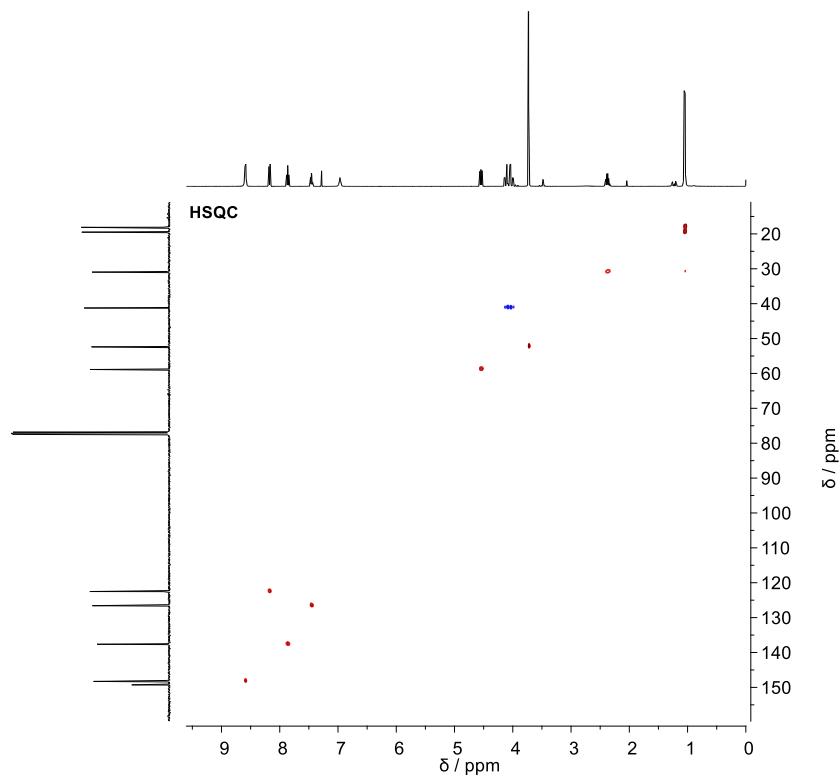


Figure S28. HSQC spectrum (CDCl₃, 400 MHz) of **5b**.

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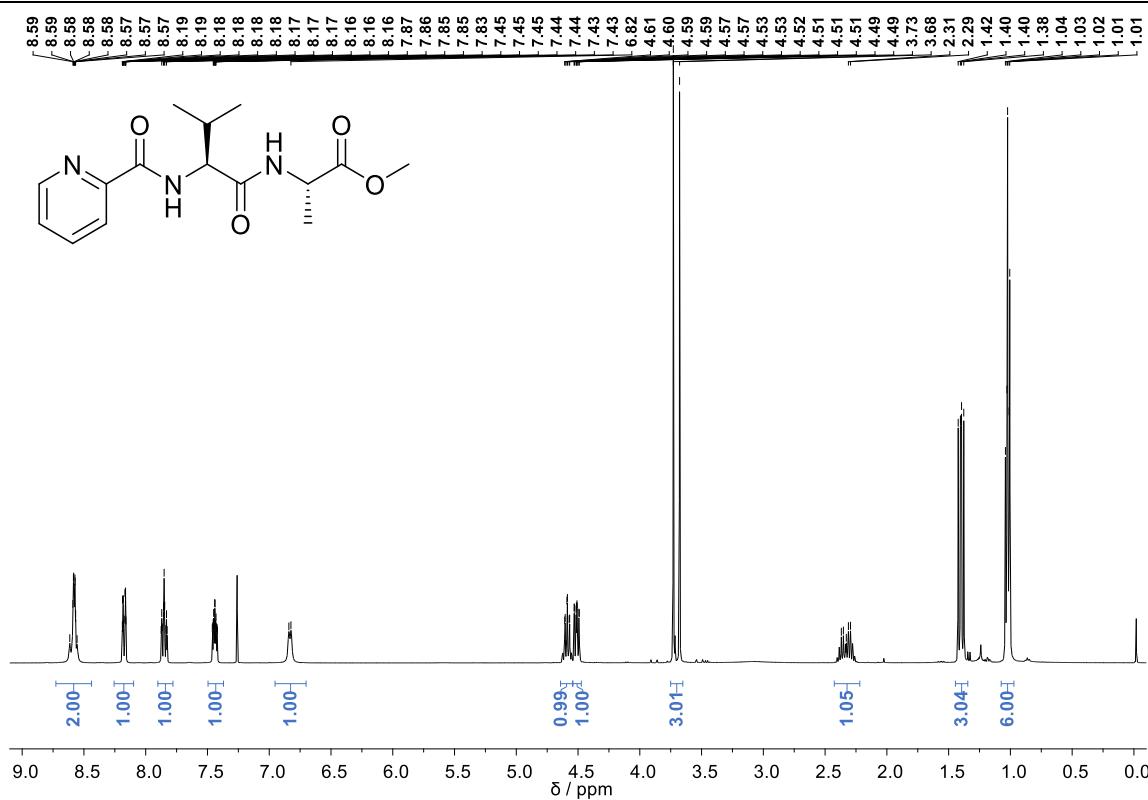


Figure S29. ¹H-NMR spectrum (CDCl₃, 400 MHz) of **6b**.

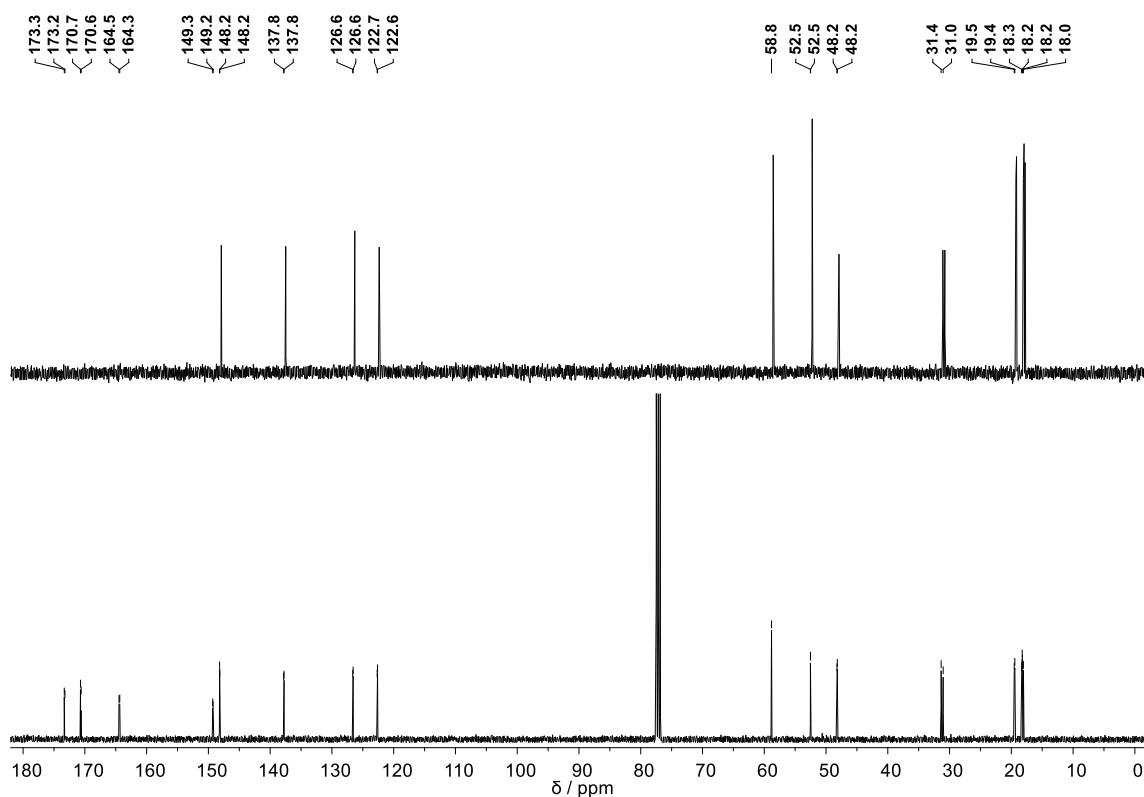


Figure S30. ¹³C-NMR and DEPT-135 spectra (CDCl₃, 100 MHz) of **6b**.

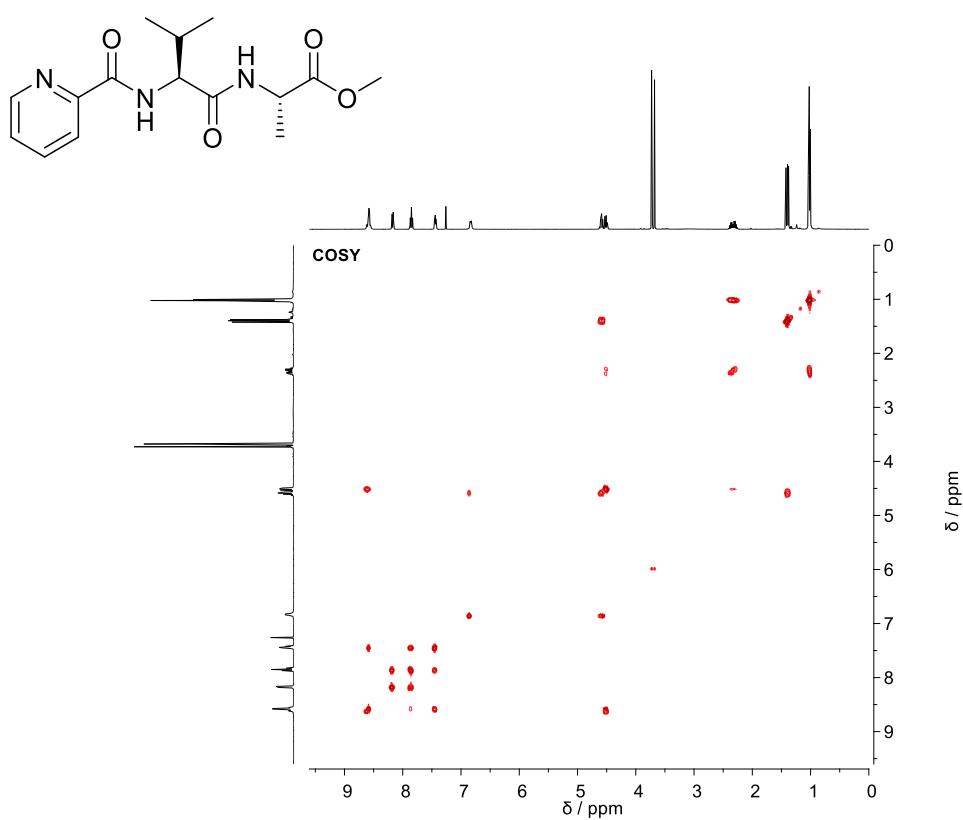


Figure S31. COSY spectrum (CDCl₃, 400 MHz) of **6b**.

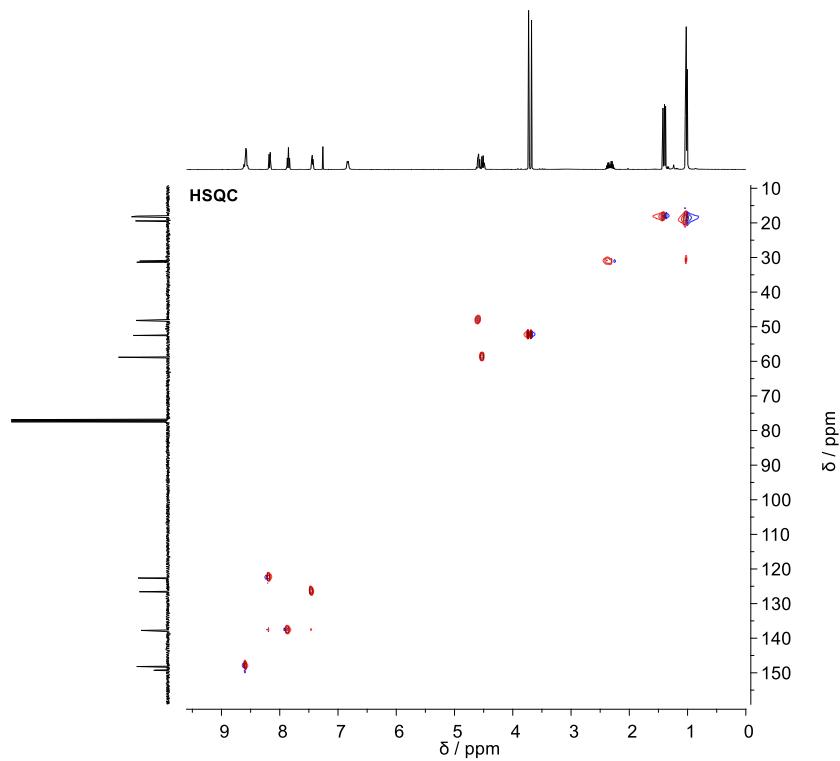


Figure S32. HSQC spectrum (CDCl₃, 400 MHz) of **6b**.

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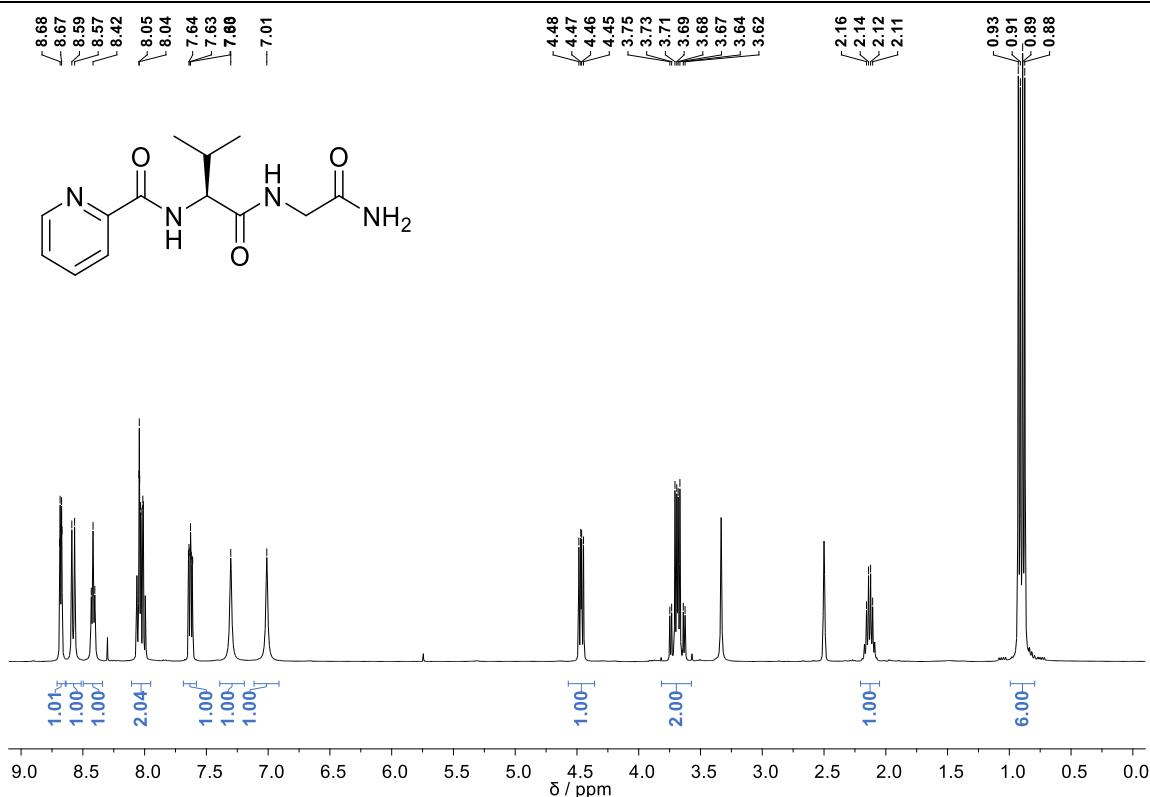


Figure S33. ¹H-NMR spectrum (DMSO-*d*₆, 400 MHz) of **7b**.

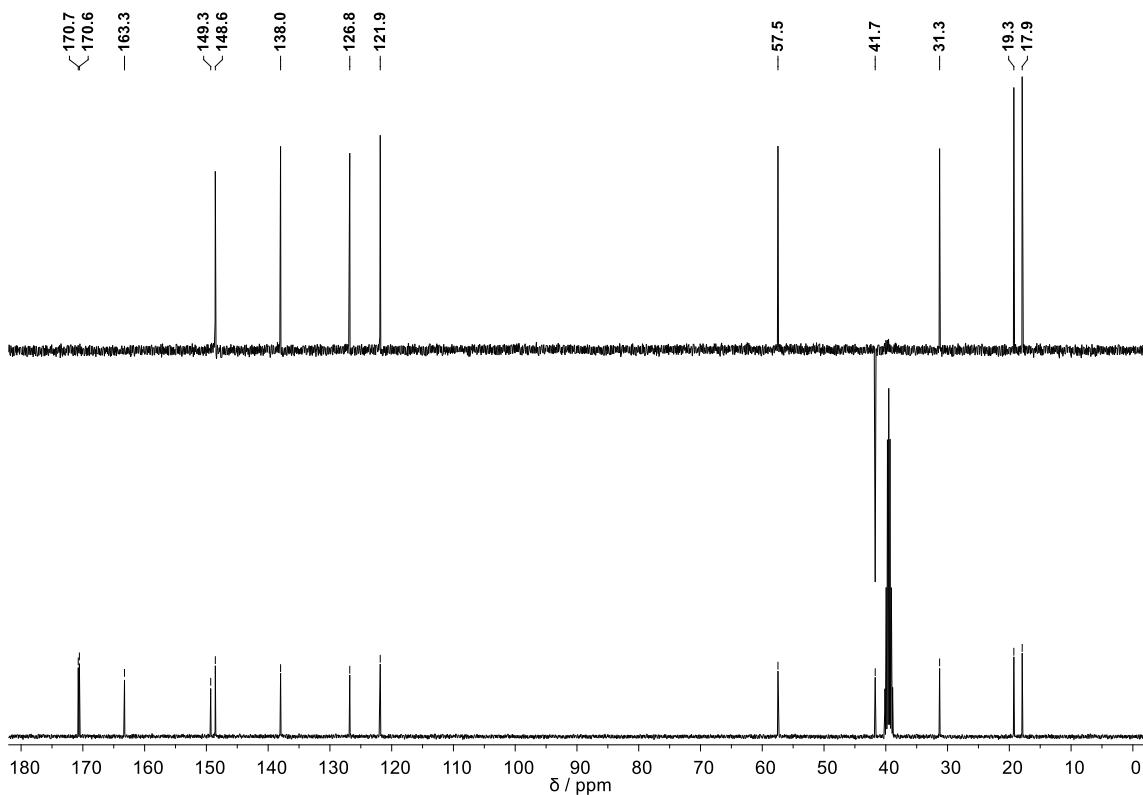


Figure S34. ¹³C-NMR and DEPT-135 spectra (DMSO-*d*₆, 100 MHz) of **7b**.

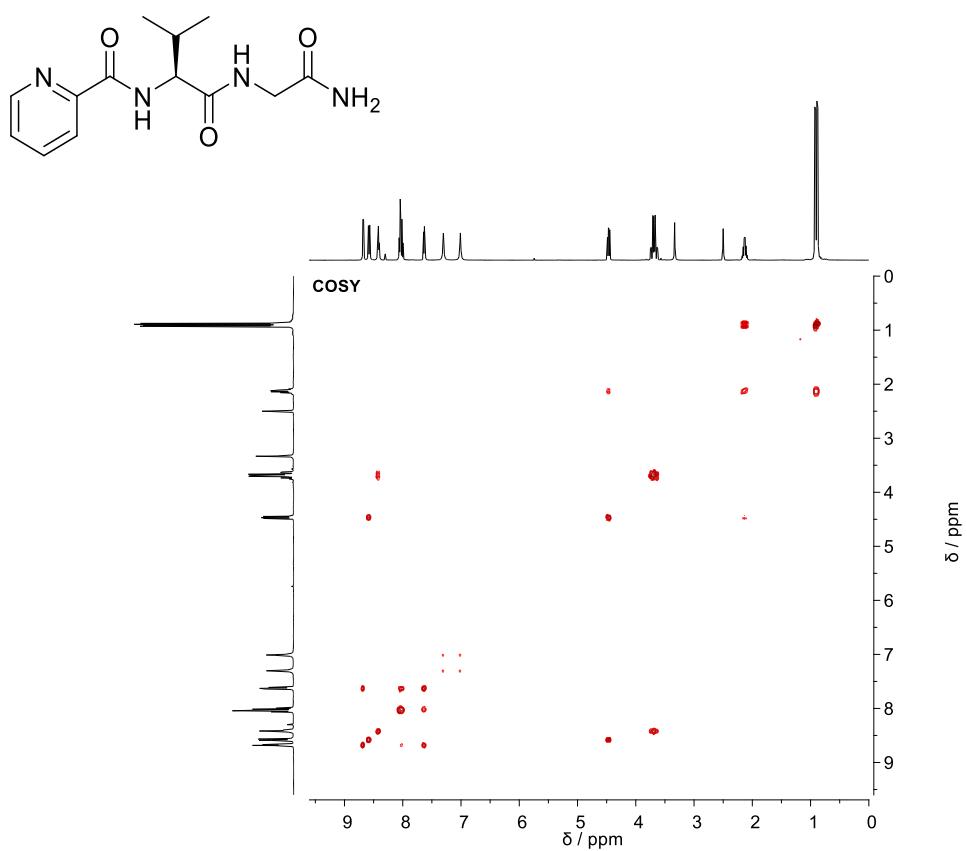


Figure S35. COSY spectrum (DMSO-*d*₆, 400 MHz) of **7b**.

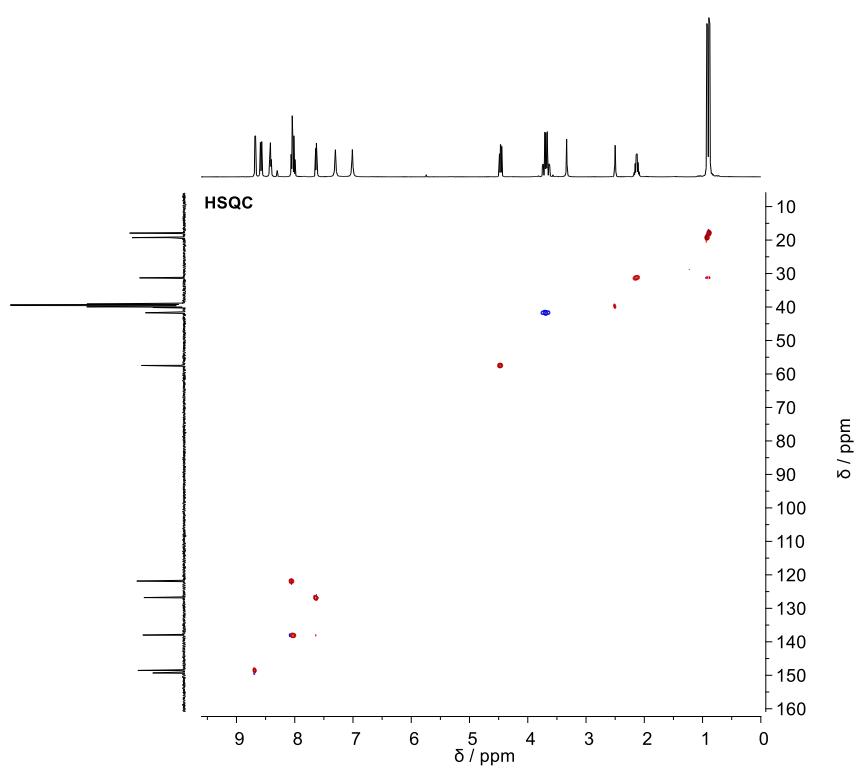


Figure S36. HSQC spectrum (DMSO-*d*₆, 400 MHz) of **7b**.

Supporting Information

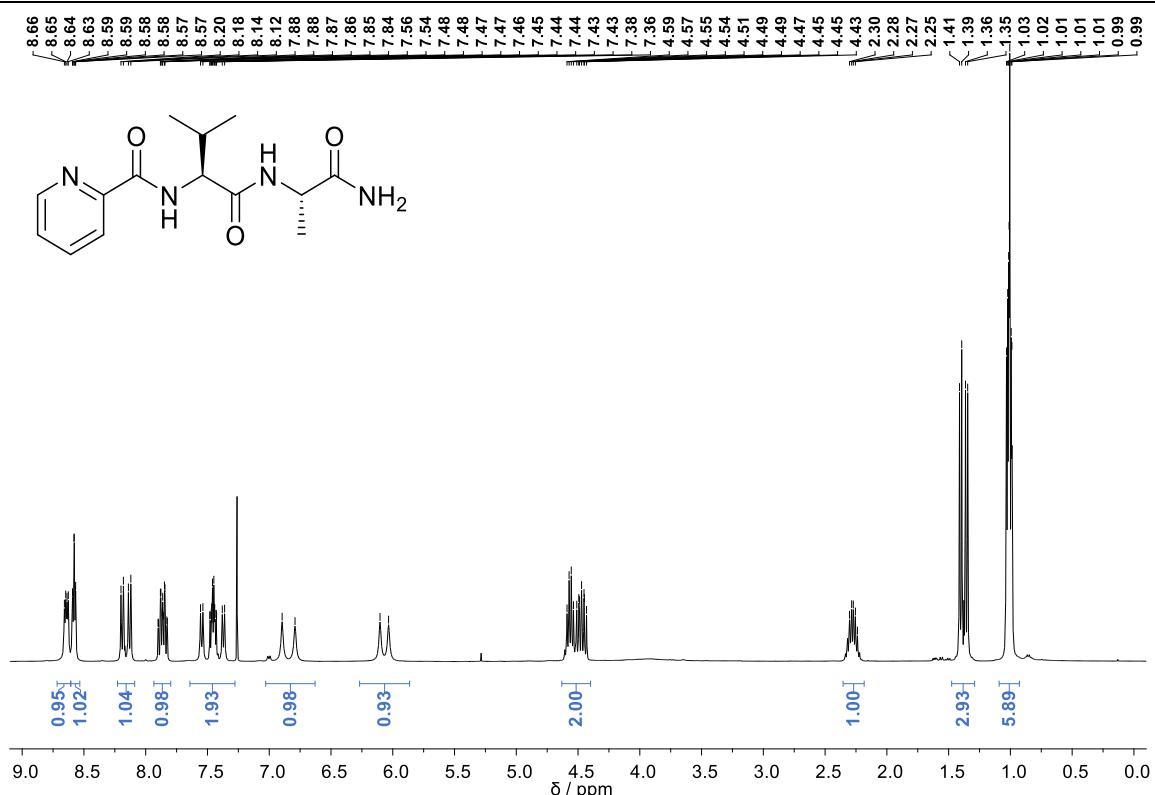


Figure S37. ¹H-NMR spectrum (CDCl₃, 400 MHz) of **8b**.

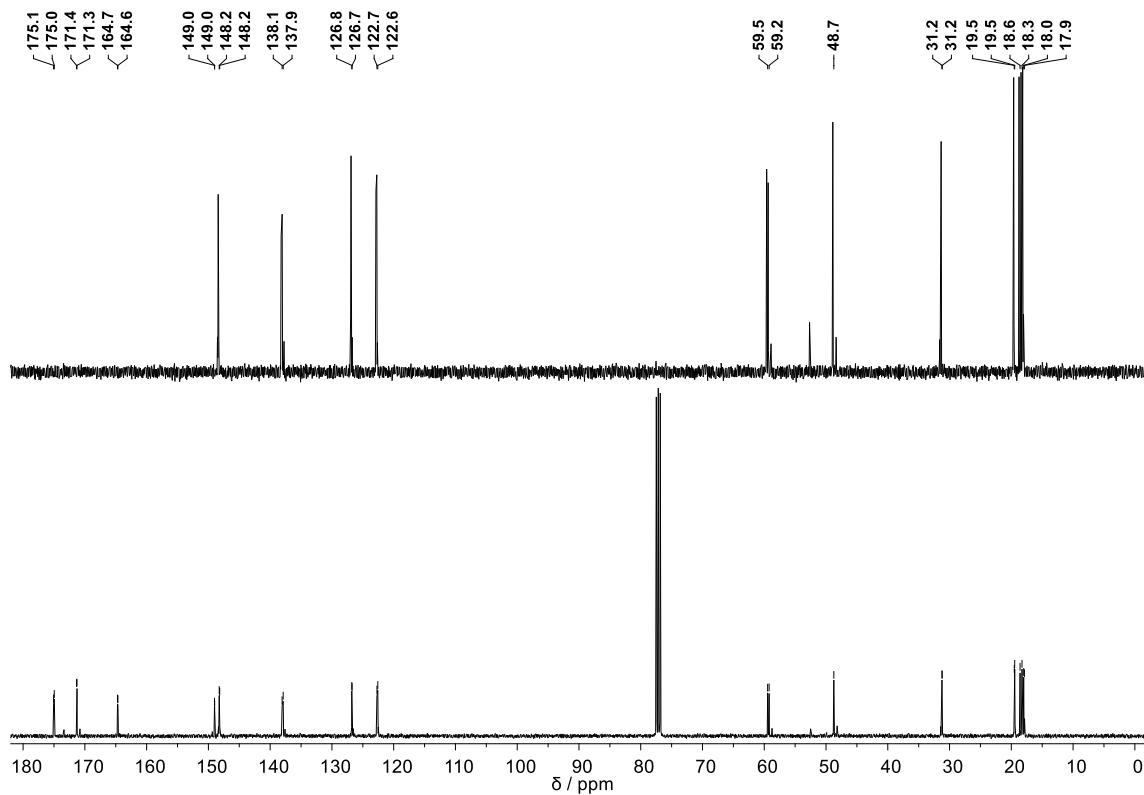


Figure S38. ¹³C-NMR and DEPT-135 spectra (CDCl₃, 100 MHz) of **8b**.

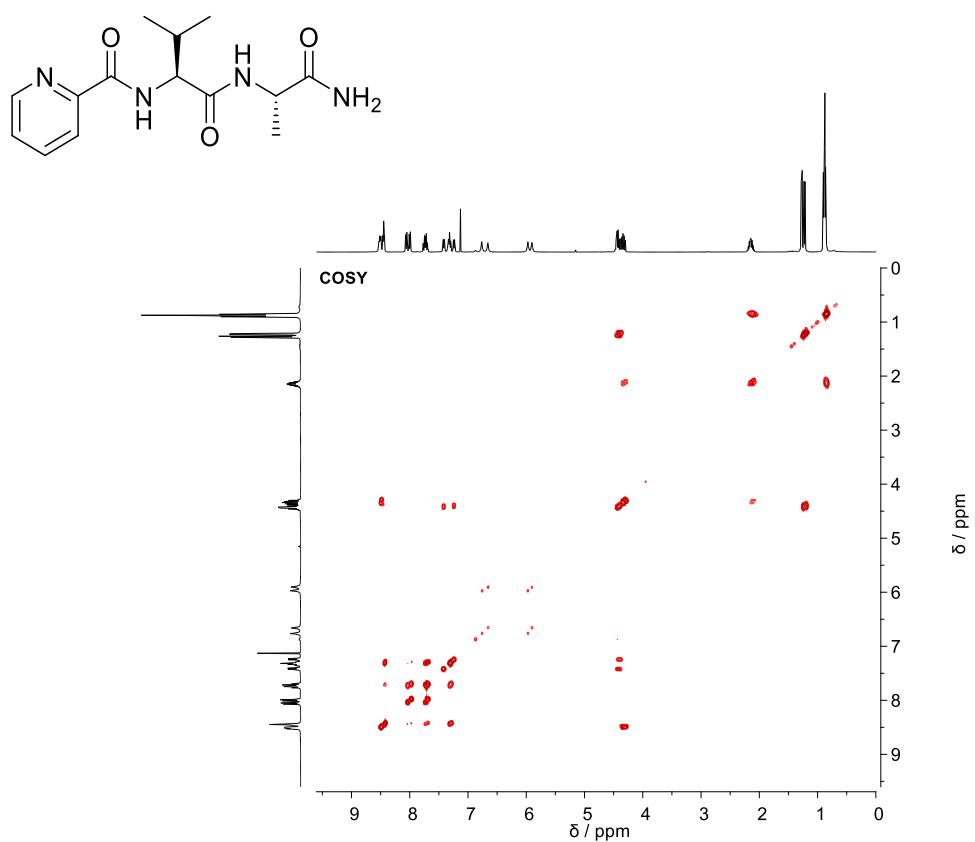


Figure S39. COSY spectrum (CDCl₃, 400 MHz) of **8b**.

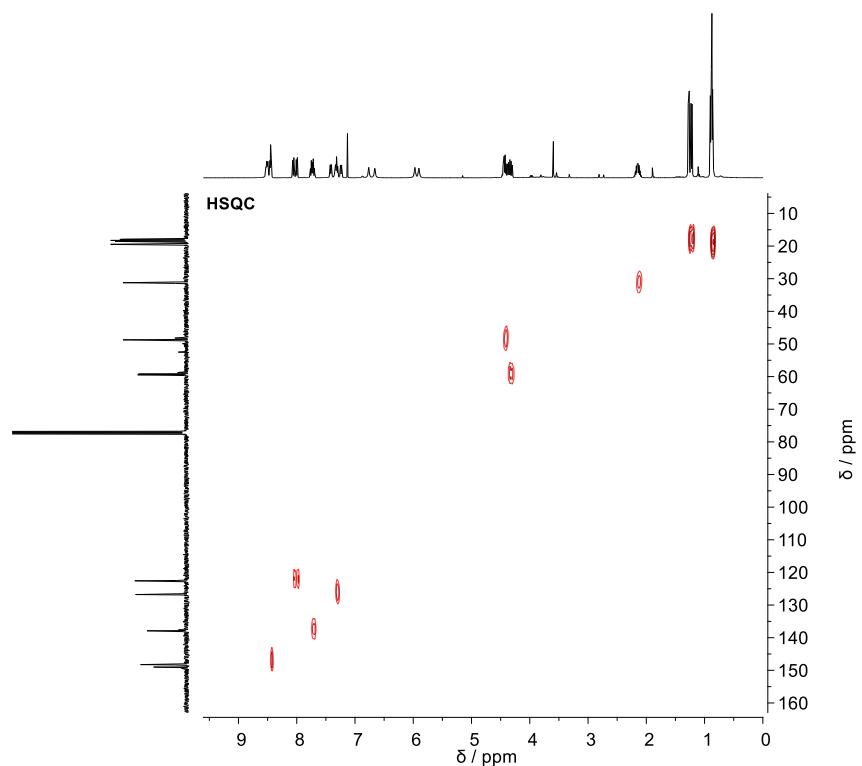


Figure S40. HSQC spectrum (CDCl₃, 400 MHz) of **8b**.

Pharmacological Assays: Specific binding of [³H]-NPA to membranes of Chinese hamster ovary (CHO) cells expressing the D₂R.

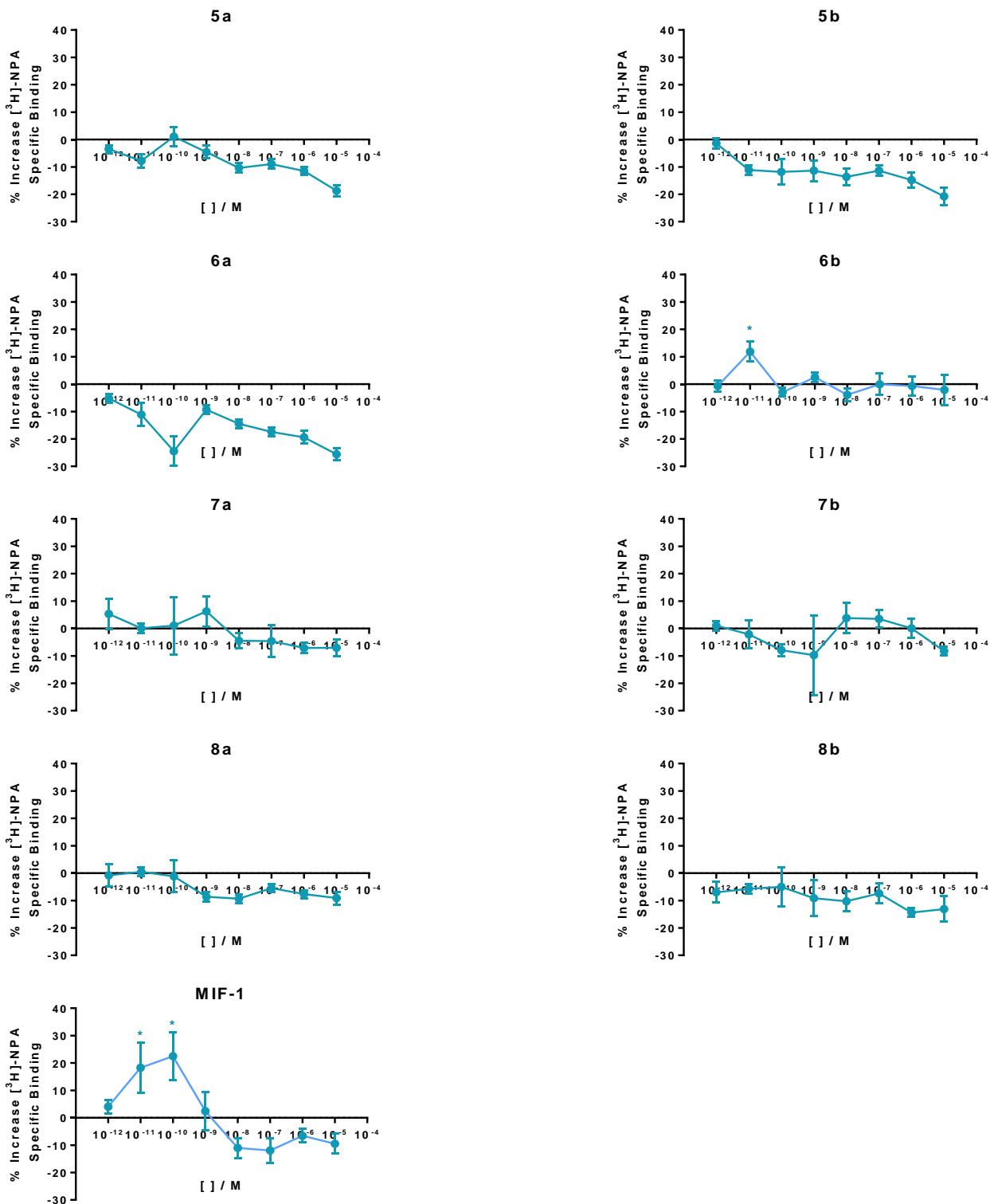


Figure S41. Modulation of [³H]-NPA binding by peptidomimetics 5-8(a,b) exerted by the different compounds at eight different concentrations. Points represent the mean \pm standard deviation (vertical bars) of three independent experiments carried out with duplicates. *P < 0.05 (ANOVA test; post-hoc Dunnett T3 test).

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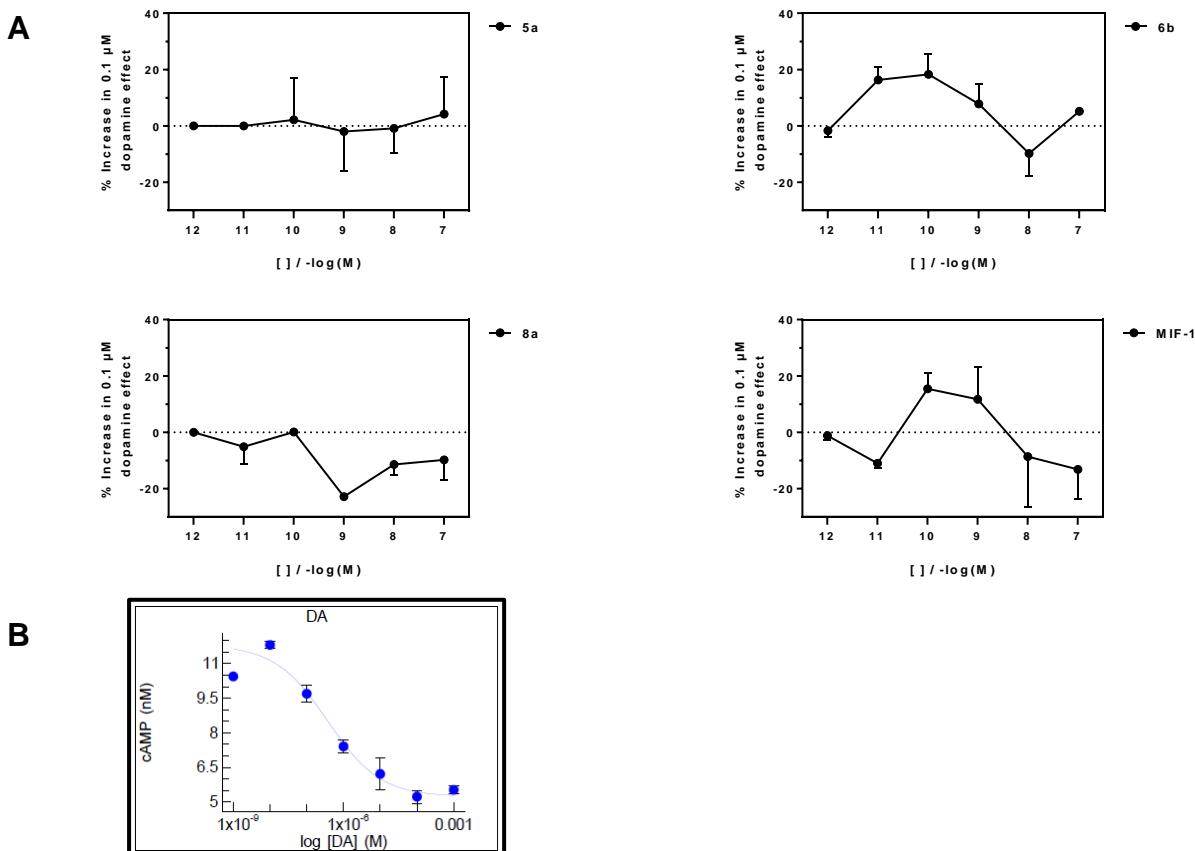


Figure S42. **A:** Increase of 0.1 μ M dopamine (DA) effect exerted by peptidomimetics **5a**, **6b**, **8a** and MIF-1 (control) at different concentrations. Data represent the mean \pm SD of 4 independent measurements. **B:** Concentration-response curves of dopamine at human D₂R. The mean \pm SEM (vertical bars) of each measure determined in duplicate.

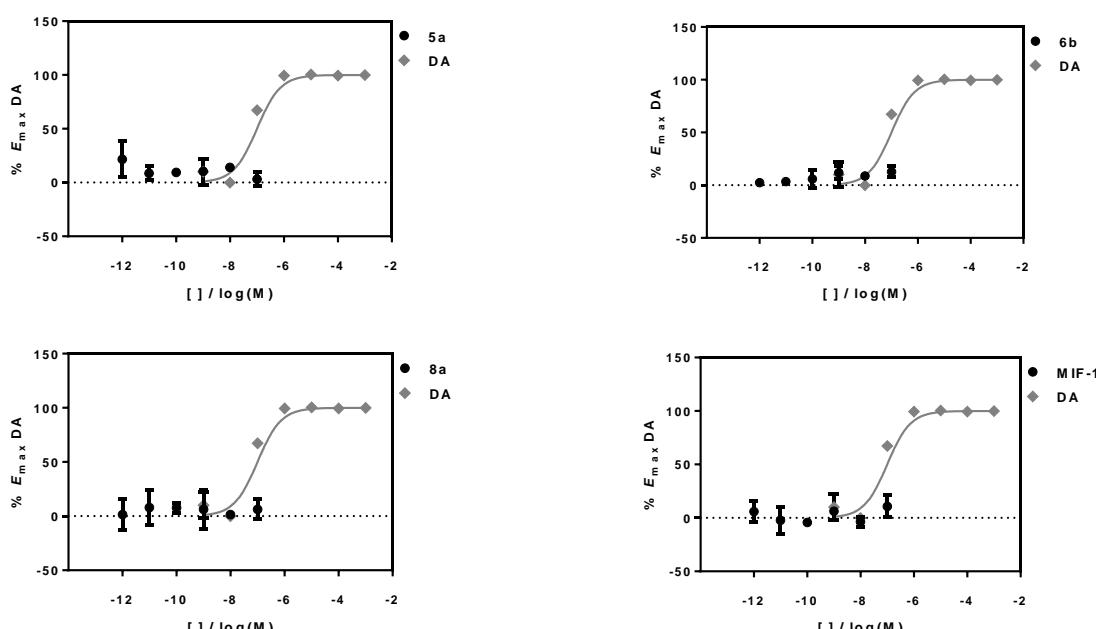


Figure S43. Concentration-response curves of peptidomimetics **5a**, **6b**, **8a** and MIF-1 (negative control) and dopamine (DA, positive control) at human D₂R. Data represent the mean \pm SD of 3 independent measurements.

Table S1. Cartesian coordinates of species **6b**, at the M06-2X level of theory, with zero imaginary frequencies and a total energy of -1048.96978121 hartree.

Atom	Cartesian coordinates		
	x	y	z
C	-8.17217	1.75879	-0.19232
C	-8.20128	0.44286	0.24304
N	-7.06057	2.37488	-0.64386
C	-5.92106	1.63833	-0.66185
C	-5.8528	0.31209	-0.24614
C	-7.02012	-0.29247	0.21162
C	-4.68649	2.34582	-1.12161
N	-3.59035	2.21106	-0.29362
O	-4.67127	3.01548	-2.1482
C	-2.37036	2.99105	-0.4871
C	-1.26011	2.27271	0.31066
N	0.01226	2.45712	-0.17154
C	1.19775	1.88649	0.46875
C	2.41694	2.69693	0.0154
O	3.55181	2.25816	0.62636
C	-2.56613	4.47456	-0.0844
H	-2.1161	2.93619	-1.55348
C	-3.08197	4.64639	1.34881
H	-4.05046	4.15399	1.48415
H	-3.22551	5.70756	1.58053
H	-2.38272	4.23452	2.08286
C	-1.30702	5.32026	-0.28641
H	-3.33453	4.89577	-0.74664
H	-1.53845	6.38414	-0.16375
H	-0.89889	5.18517	-1.29303
H	-0.52933	5.07201	0.44302
O	-1.50093	1.59405	1.30935
C	1.35774	0.41713	0.09921
H	2.2336	-0.02182	0.58835
H	1.48651	0.29493	-0.98231
H	0.48002	-0.16542	0.39738
O	2.35988	3.62671	-0.78375
C	4.73816	2.95993	0.24852
H	4.79874	3.09549	-0.83627
H	5.5985	2.36332	0.56442
H	4.77404	3.92546	0.7612
H	-3.68651	1.75257	0.60766
H	0.1709	3.05451	-0.97891
H	-9.06981	2.37113	-0.18645
H	-9.12654	0.00026	0.59621
H	-4.92222	-0.24308	-0.28935
H	-7.01049	-1.32854	0.53908
H	1.08675	2.00516	1.55242