Supplementary Information

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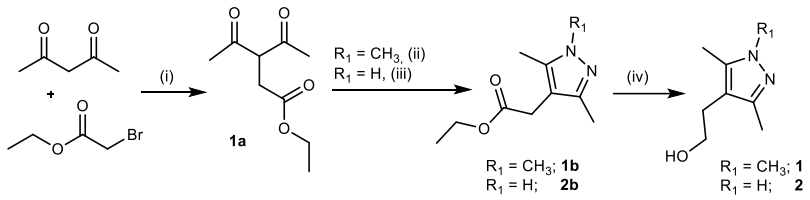
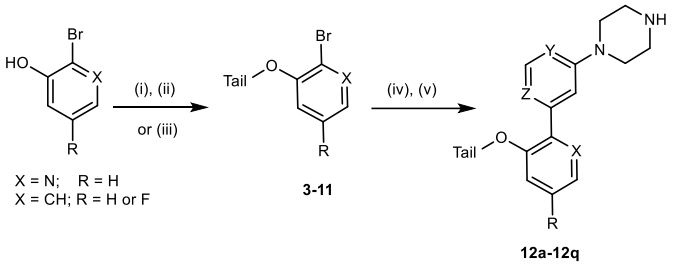
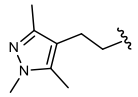
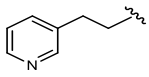
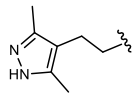
Supplementary Figures

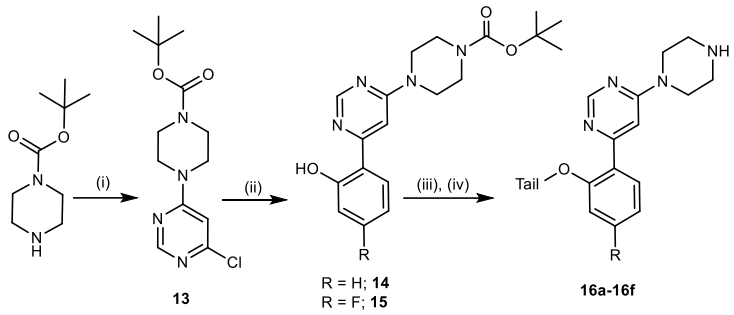


Supplementary Fig. 1. Synthesis of pyrazole moieties. Reagents and conditions: (i) NaH, THF, RT, 16 h, (85%); (ii) $MeNHNH_2$, AcOH, RT, 5 h, (89%); (iii) $NH_2NH_2.H_2O$, MeOH, RT, 5 h, (91%); (iv) LAH, N_2, THF, RT, 12 h, (65-75%).



Tail	Compound	Y	Z	X	R
	**12a**	N	CH	N	H
	12b	CH	CH	N	H
	12c	N	CH	CH	H
	12d	CH	CH	CH	H
	12e	N	CH	CH	F
	12f	CH	CH	CH	F
	**12g**	CH	CH	N	H
	12h	N	CH	N	H
	12i	CH	CH	CH	H
	12j	N	CH	CH	H
	12k	CH	CH	CH	F
	12l	N	CH	CH	F
	**12m**	CH	CH	N	H
	12n	N	CH	CH	H
	12o	N	CH	N	H
	12p	CH	CH	CH	F
	12q	N	CH	CH	F

Supplementary Fig. 2. Synthesis of compounds 12a-12q. Reagents and conditions: (i) Mesyl chloride, TEA, DCM, RT, 3 h, (80-92%); (ii) **1**, **2** or 3-(2-hydroxyethyl)pyridine, MeCN, NaOt-Bu, 140°C, 30 min, MW, (20-42%); (iii) **1**, **2** or 3-(2-hydroxyethyl)pyridine, CMBP, toluene, 100°C, 16 h, (45-60%); (iv) aryl-boronic acid, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O, N_2, 100°C, 1-3 h, (60-91%); (v) 4M HCl in dioxane, RT, 12 h, (15-95%).



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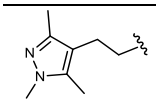
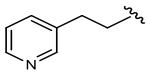
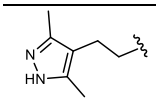
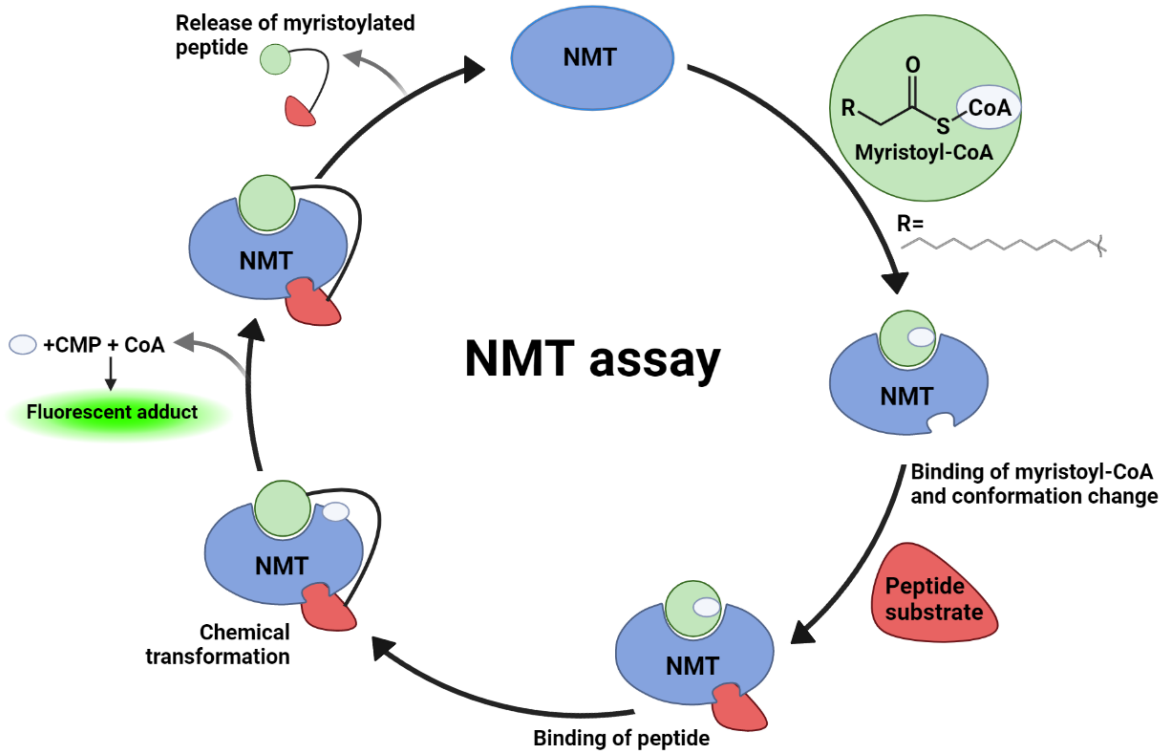
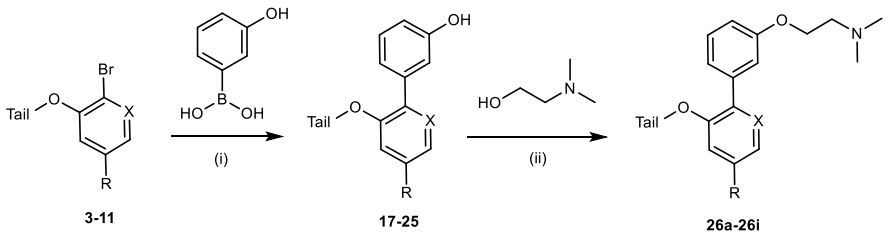
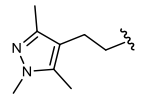
	**16a**	H
	16b	F
	**16c**	H
	16d	F
	**16e**	F
	16f	H

Supplementary Fig. 3. Synthesis of compounds 16a-16f. Reagents and conditions: (i) 2,6-dichloro-pyrimidine, DIPEA, THF, 145°C, 35 min, MW, (90%); (ii) aryl-boronic acid, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O, N_2, 100°C, 1-3 h, (60-91%); (iii) **1**, **2** or 3-(2-hydroxyethyl)pyridine, CMBP, toluene, 100°C, 16 h, (45-60%); (iv) 4M HCl in dioxane, RT, 12 h, (38-72%).



Supplementary Fig. 4. Schematic of the myristoylation assay used in this work. NMT is added to a reaction mixture of a peptide substrate along with the thiol-reactive probe CPM and CoA. This produces a fluorescent readout that is reduced when NMT activity is inhibited.



Tail	Compound	X	R
	**26a**	N	H
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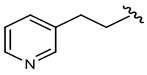
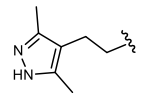
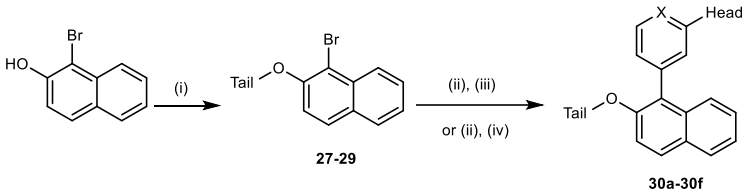
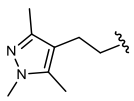
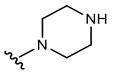
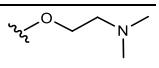
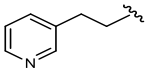
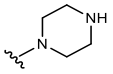
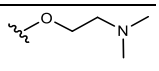
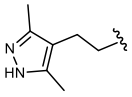
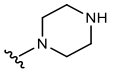
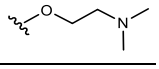
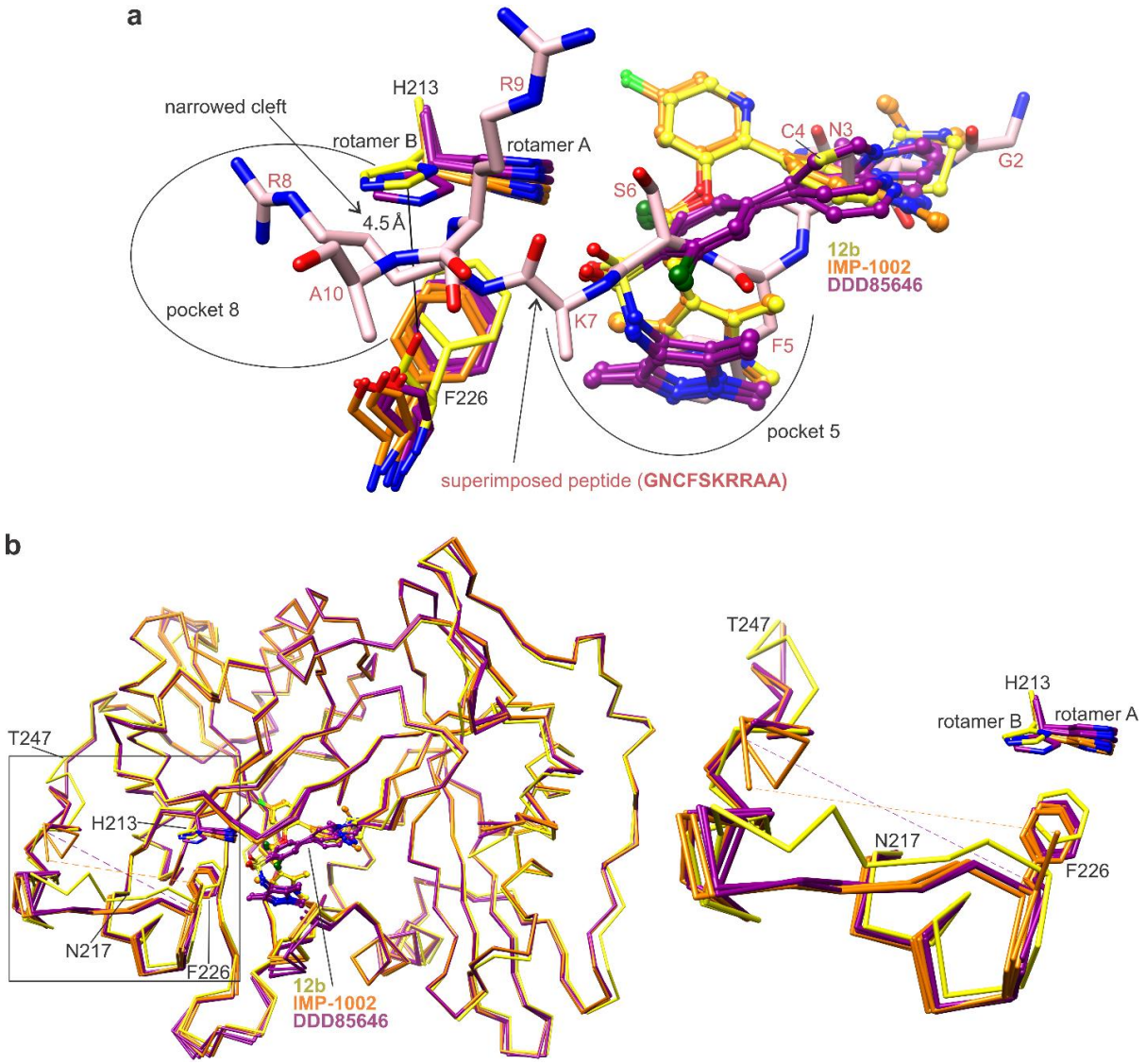
	26c	CH	F
	**26d**	N	H
	26e	CH	H
	26f	CH	F
	**26g**	N	H
	26h	CH	H
	26i	CH	F

Supplementary Fig. 5. Synthesis of compounds 26a-26i. Reagents and conditions: (i) K_3PO_4, $Pd(PPh_3)_4$, 1,4 dioxane/H_2O, N_2, 100°C, 1-3 h, (60-91%); (ii) CMBP, toluene, 100°C, 16 h (35-70%).

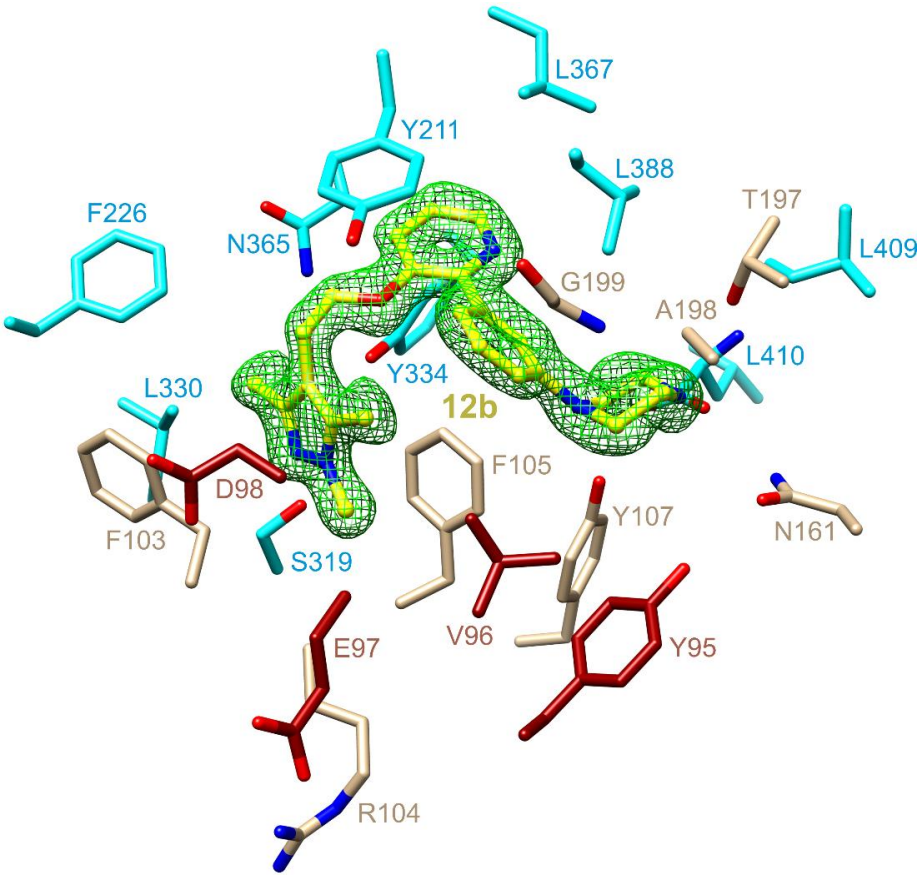


Tail	Compound	X	Head
	**30a**	N	
	30b	CH	
	**30c**	N	
	30d	CH	
	**30e**	N	
	30f	CH	

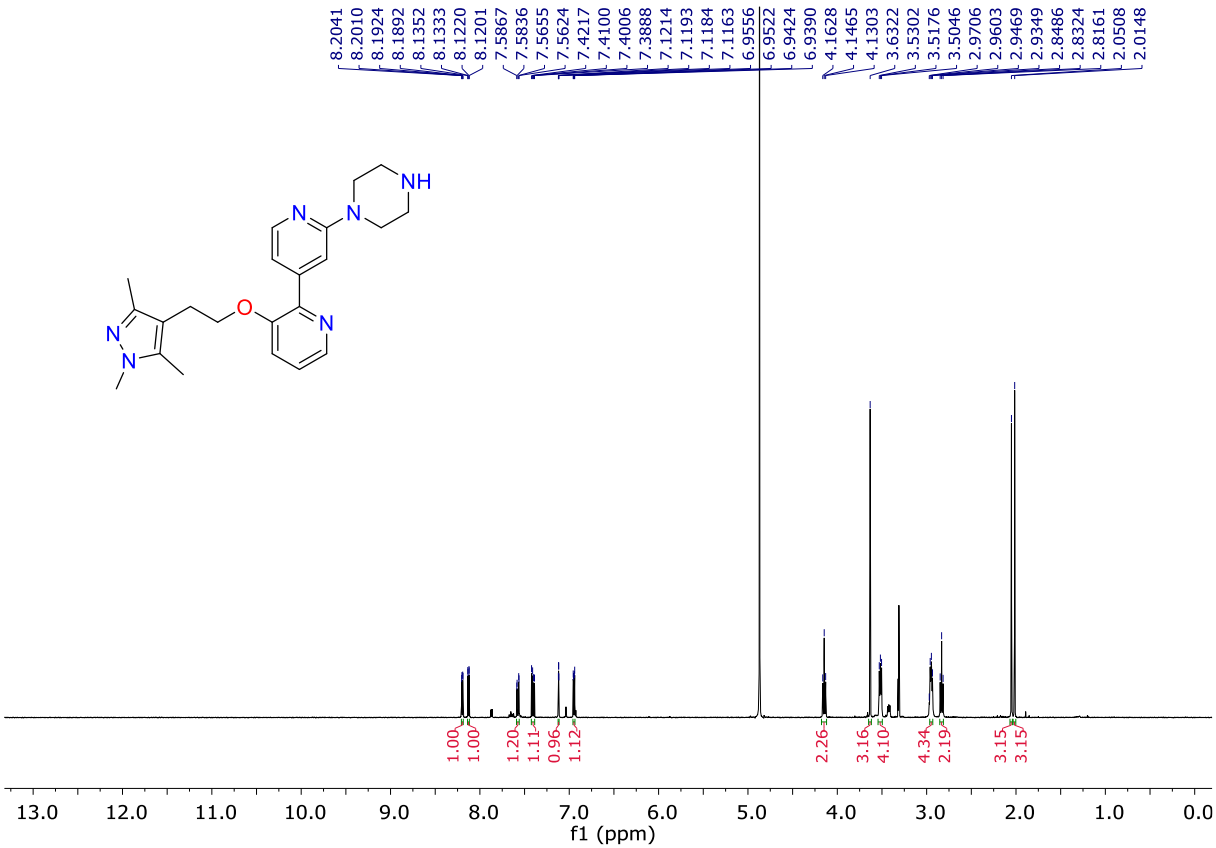
Supplementary Fig. 6. Synthesis of compounds 30a-30f. Reagents and conditions: (i) **1**, **2** or 3-(2-hydroxyethyl)pyridine, CMBP, toluene, 100°C, 16 h, (45-60%); (ii) Aryl-boronic acid, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O, N_2, 100°C, 1-3 h, (75-88%); (iii) 2-(dimethylamino)ethanol, CMBP, toluene, 100°C, 16 h, (60-80%); (iv) 4M HCl in dioxane, RT, 12 h (36-88%).



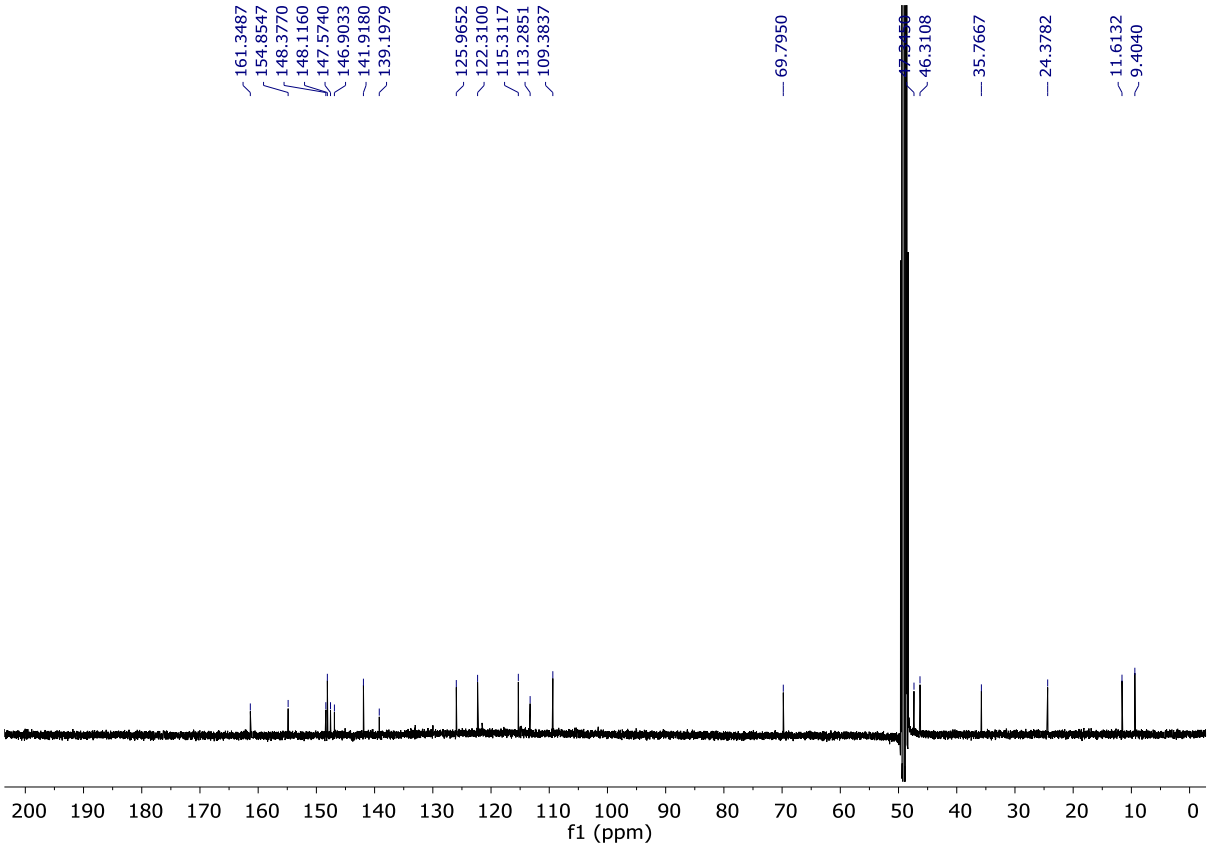
Supplementary Fig. 7. Conformational changes in pocket 8 accompanying binding to 12b. **a** Binding to **12b** induces conformational changes in Phe226 and His213 that narrow pocket 8[1] to distances incompatible with peptide binding. **b** Associated conformational change in residues 217-247, boxed in *Cα* trace (left) and enlarged (right). In panels **a** and **b**, crystal structures of IMP-1002-bound *Pv*NMT (orange, PDB entry 6MB1[2]), DDD85646-bound *Pv*NMT (dark magenta, PDB entry 2YND[3]), and peptide-bound *Hs*NMT1 (pink, PDB entry 6QRM[4]) are superimposed[5] onto that of **12b**–bound *Pv*NMT (yellow).



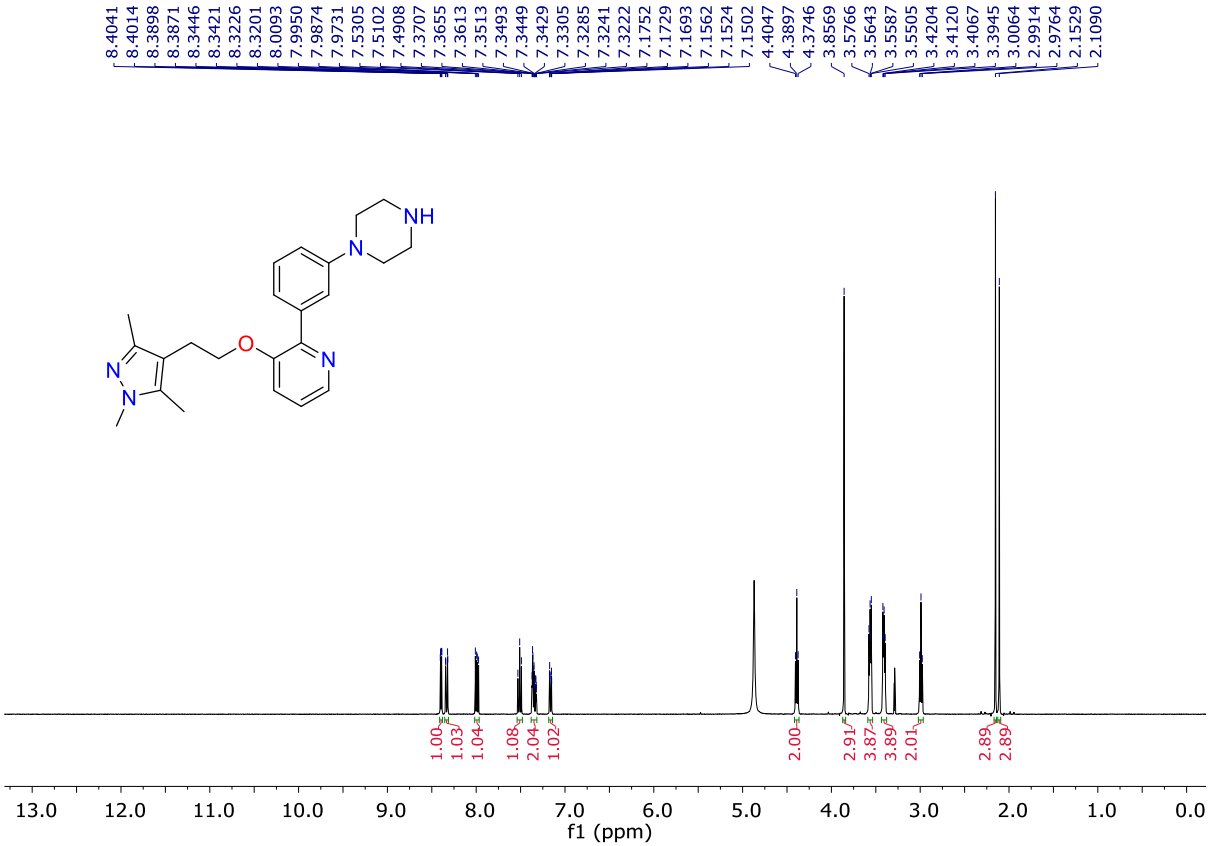
Supplementary Fig. 8. Inhibitor structure validation. A 2*Fo-Fc* simulated annealing composite omit map was computed with PHENIX using torsional angle dynamics[6,7] and was displayed around **12b** using Chimera[5] at a contour level of approximately 1.5 times the root mean square value of the map.



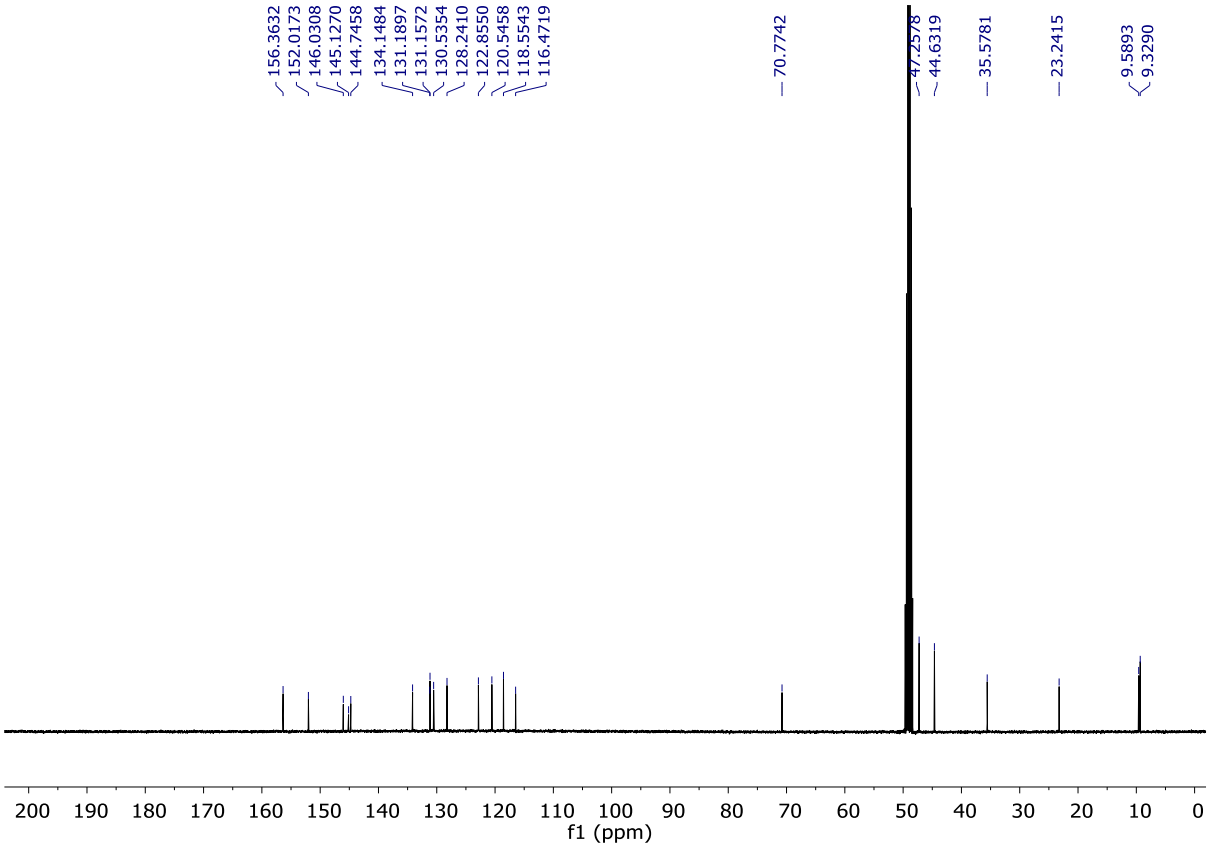
Supplementary Fig. 9. ^{1}H-NMR spectrum of compound 12a (CD_3OD, 400 MHz).



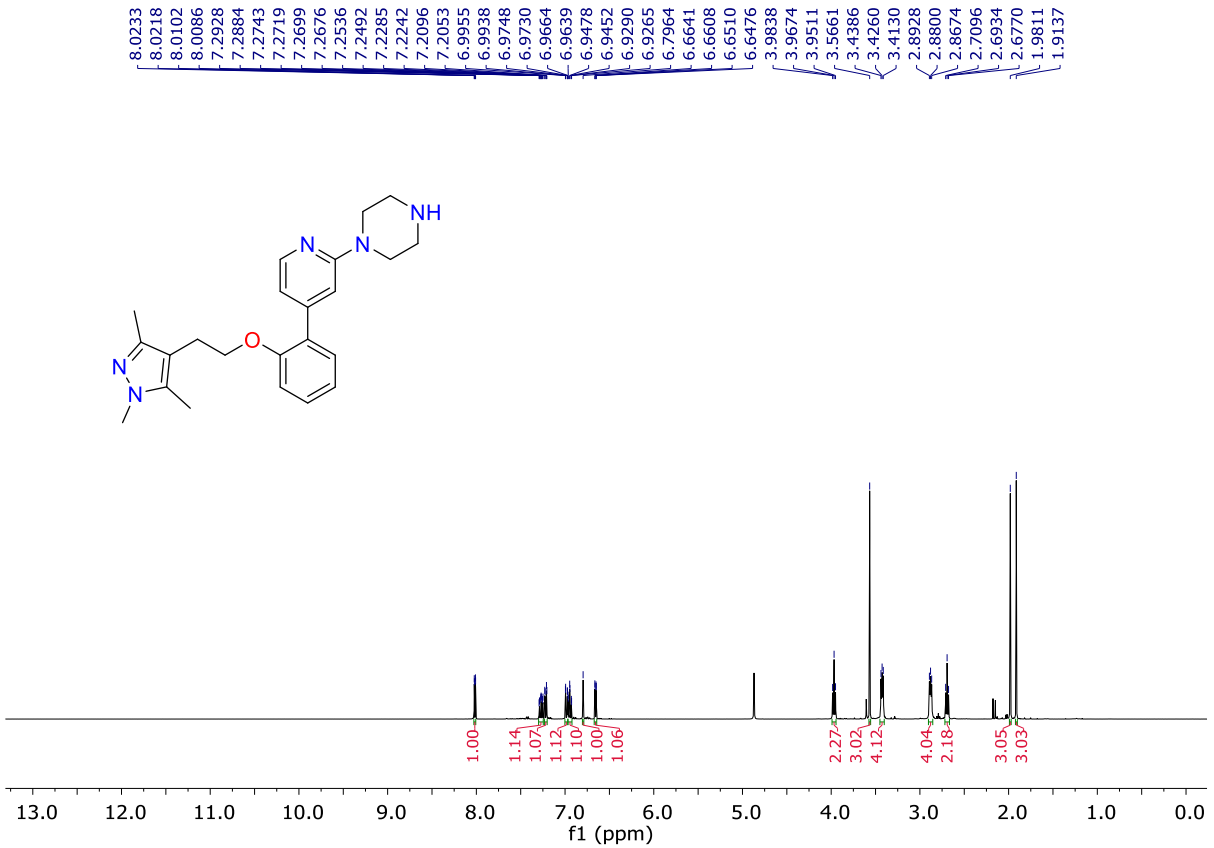
Supplementary Fig. 10. ^{13}C-NMR spectrum of compound 12a (CD_3OD, 100 MHz).



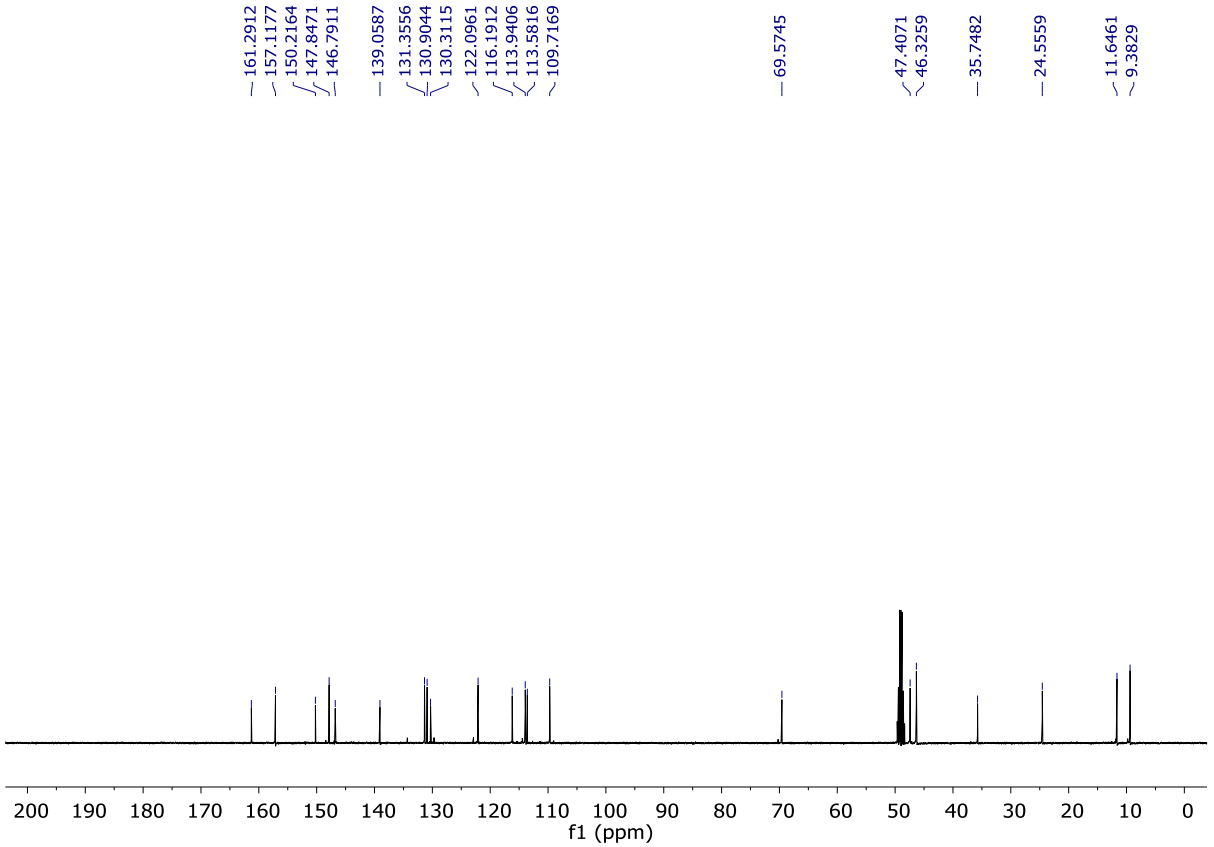
Supplementary Fig. 11. ^{1}H-NMR spectrum of compound 12b (CD_3OD, 400 MHz).



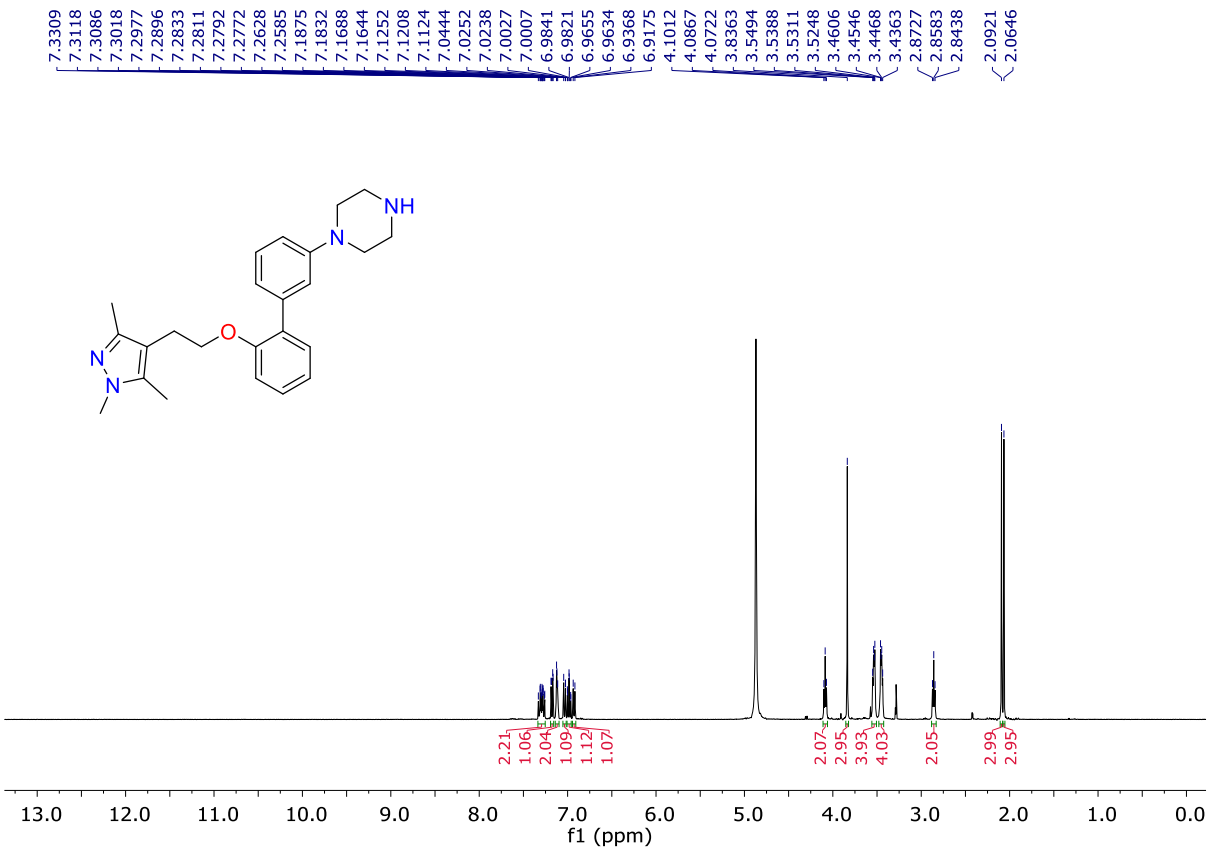
Supplementary Fig. 12. ^{13}C-NMR spectrum of compound 12b (CD_3OD, 100 MHz).



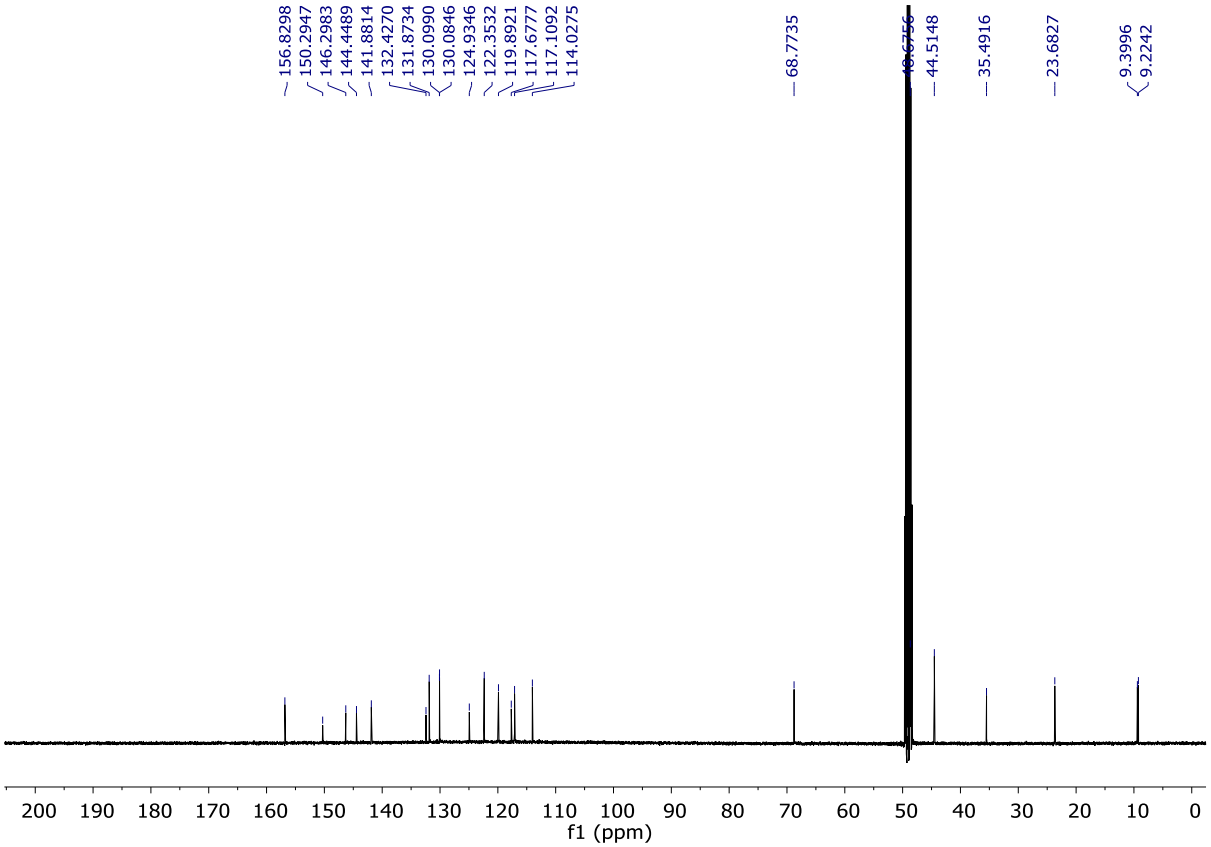
Supplementary Fig. 13. ^{1}H-NMR spectrum of compound 12c (CD_3OD, 400 MHz).



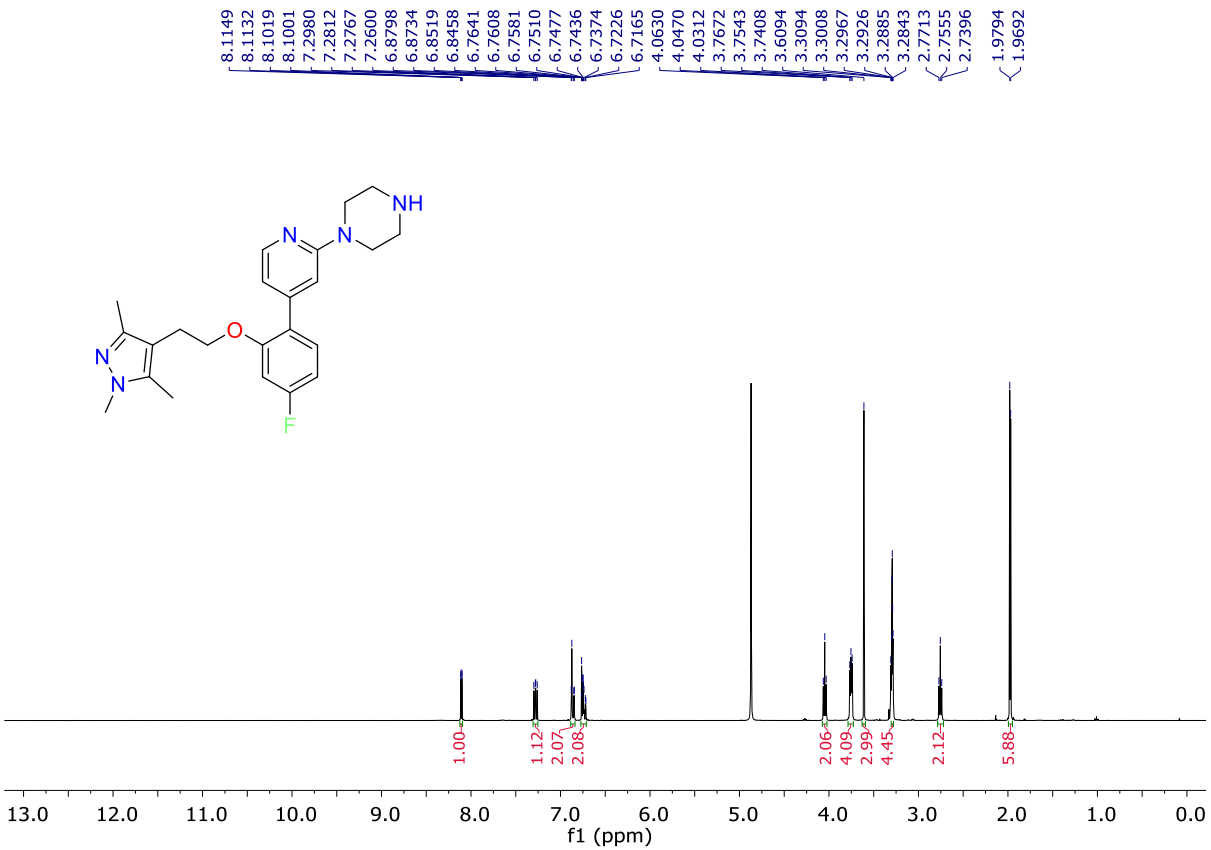
Supplementary Fig. 14. ^{13}C-NMR spectrum of compound 12c (CD_3OD, 100 MHz).



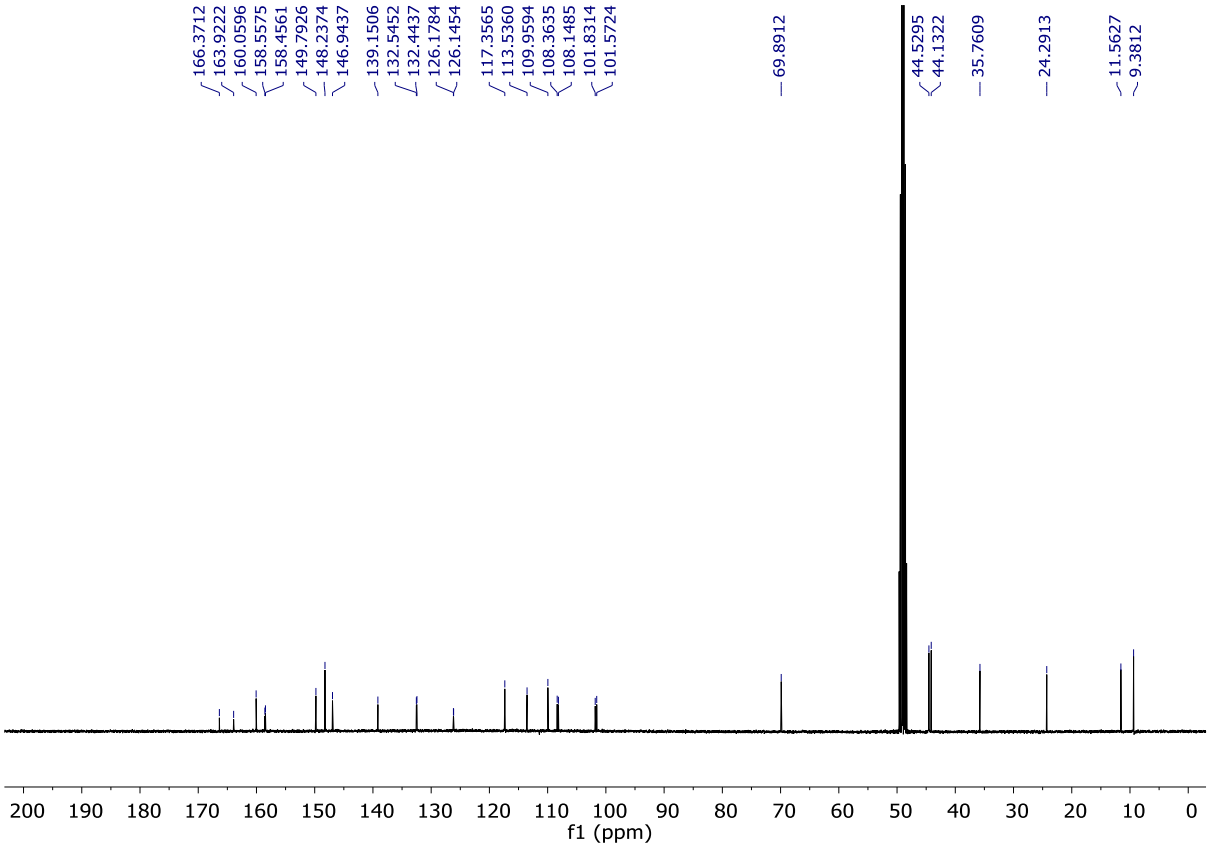
Supplementary Fig. 15. ^{1}H-NMR spectrum of compound 12d (CD_3OD, 400 MHz).



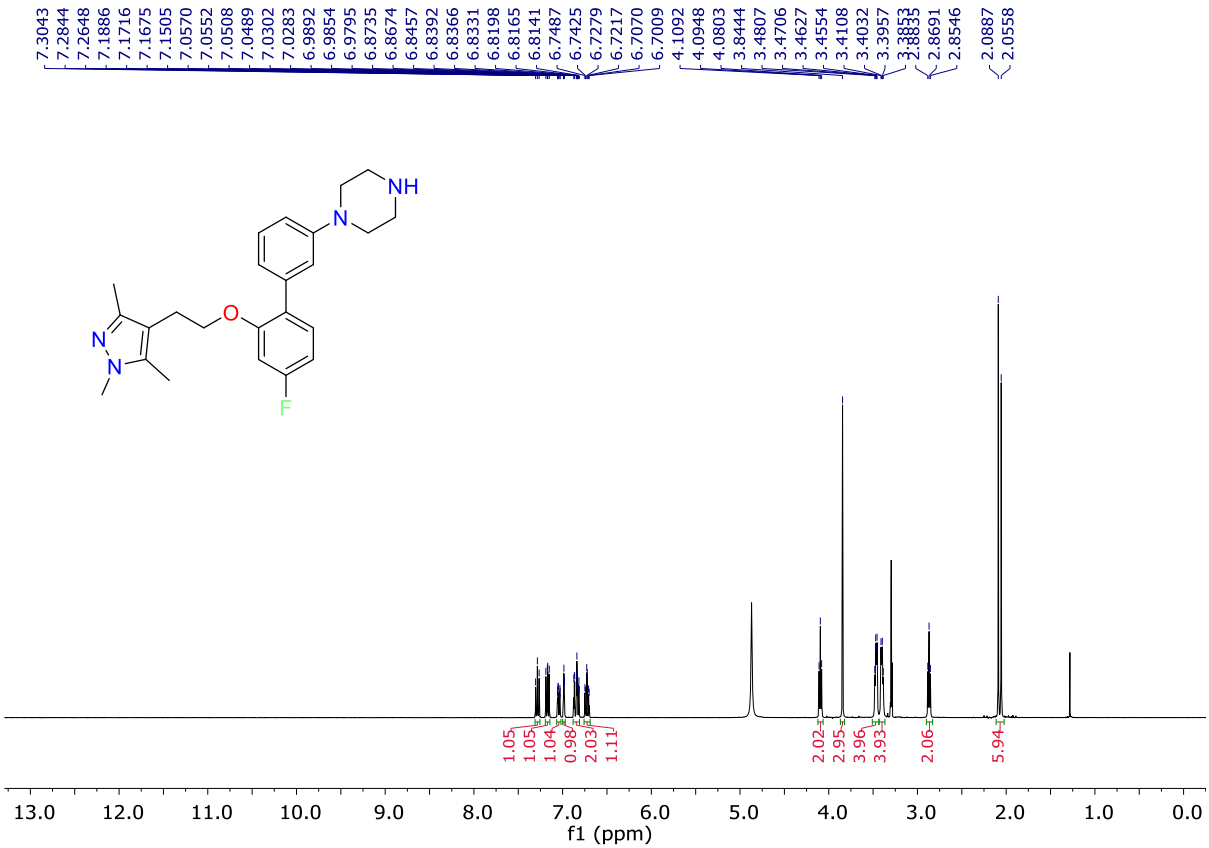
Supplementary Fig. 16. ^{13}C-NMR spectrum of compound 12d (CD_3OD, 100 MHz).



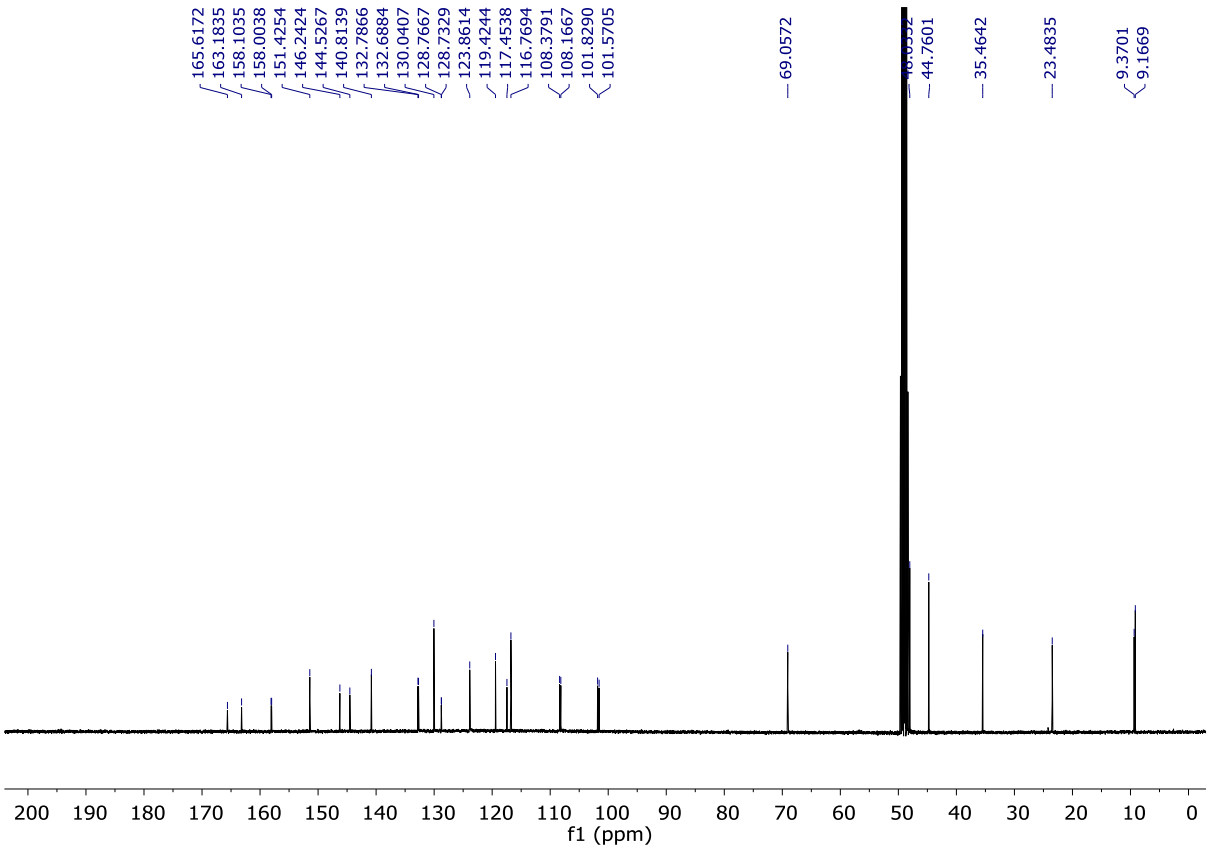
Supplementary Fig. 17. ^{1}H-NMR spectrum of compound 12e (CD_3OD, 400 MHz).



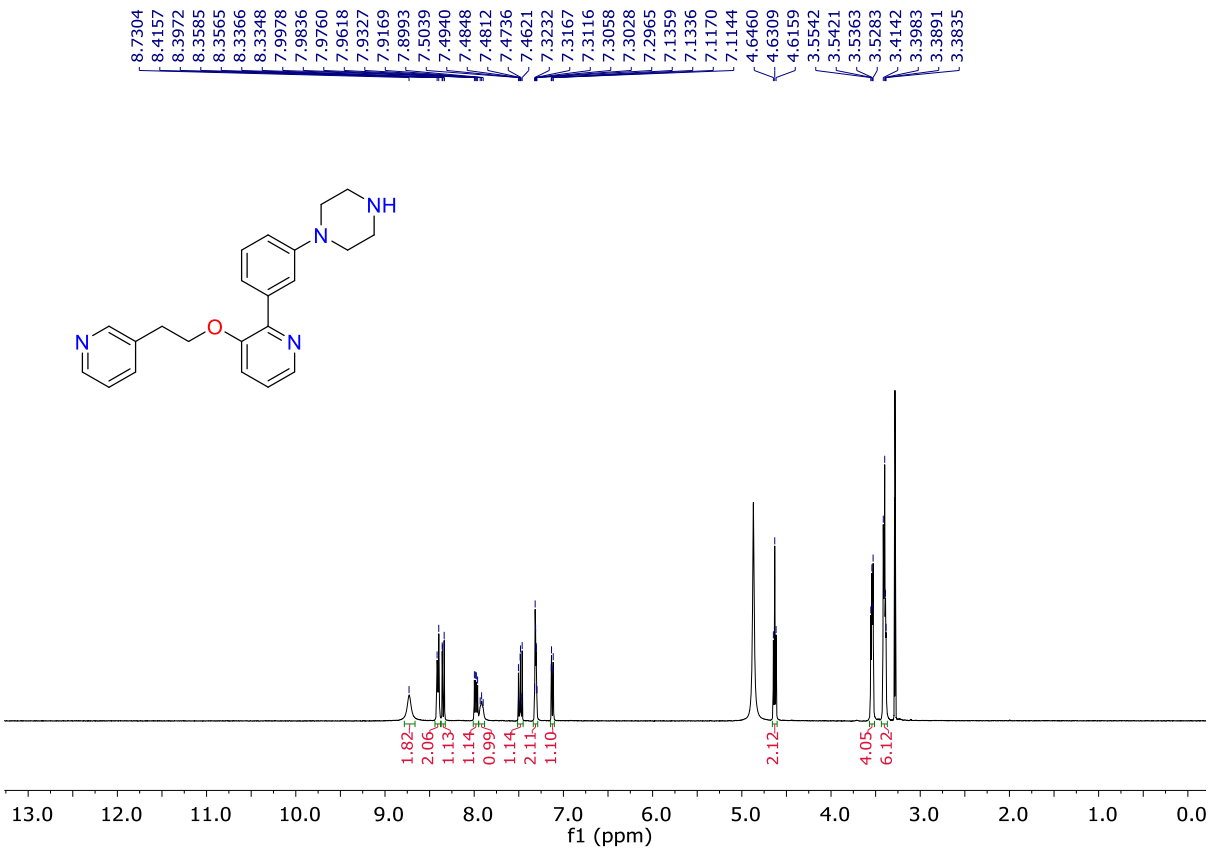
Supplementary Fig. 18. ^{13}C-NMR spectrum of compound 12e (CD_3OD, 100 MHz).



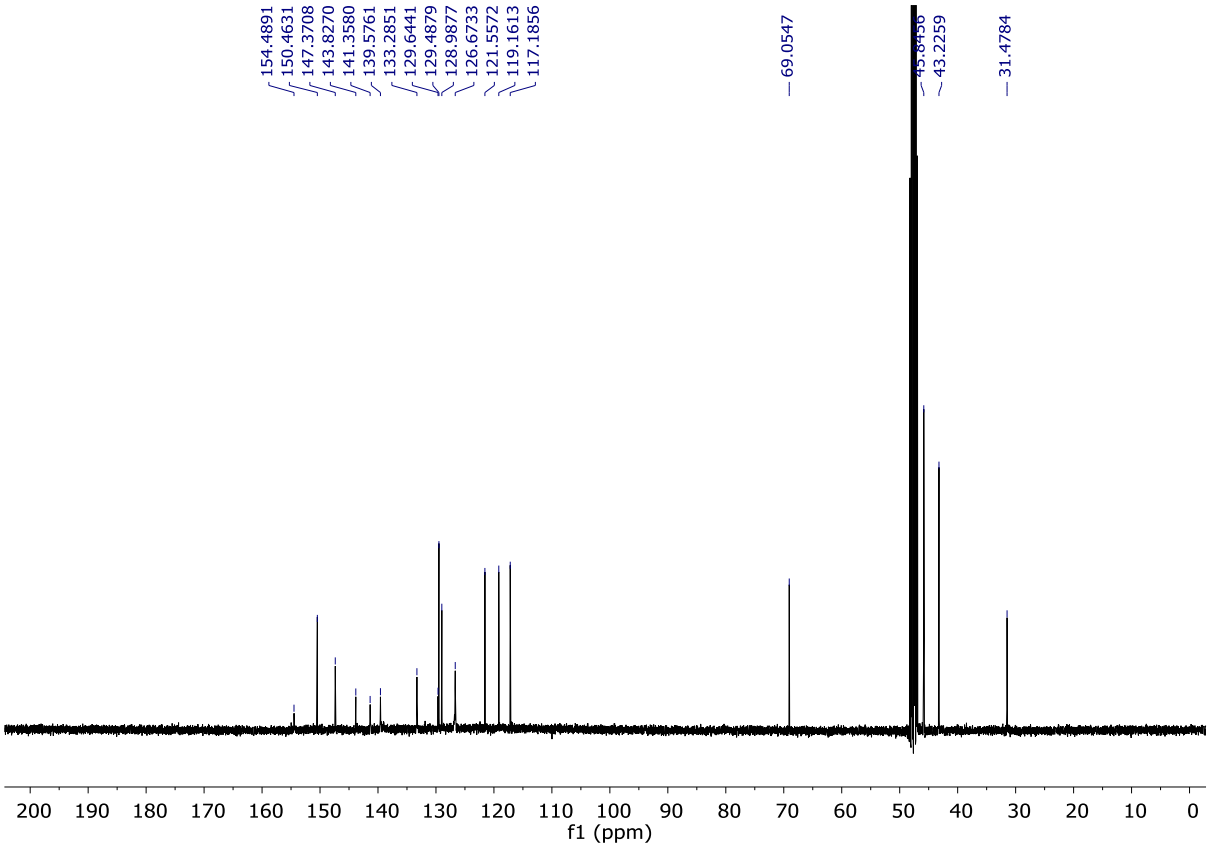
Supplementary Fig. 19. ^{1}H-NMR spectrum of compound 12f (CD_3OD, 400 MHz).



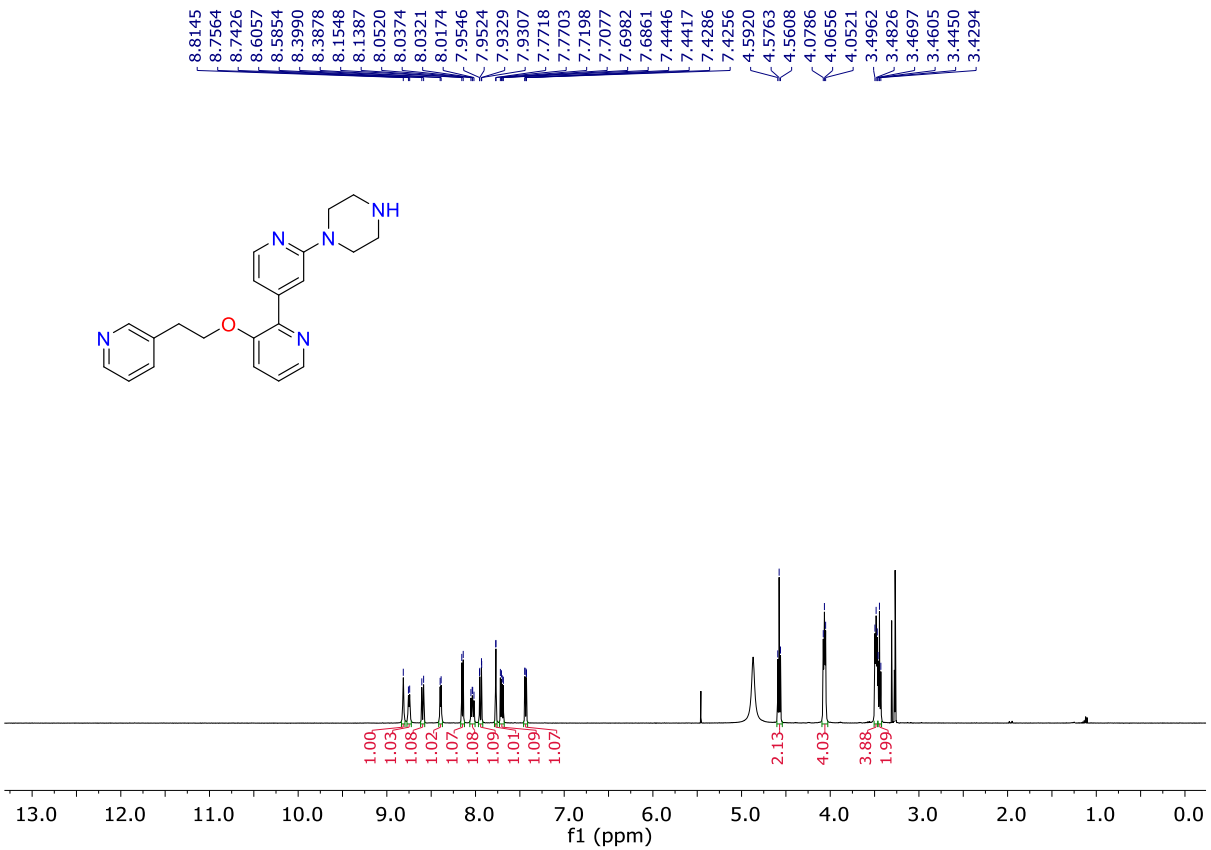
Supplementary Fig. 20. ^{13}C-NMR spectrum of compound 12f (CD_3OD, 100 MHz).



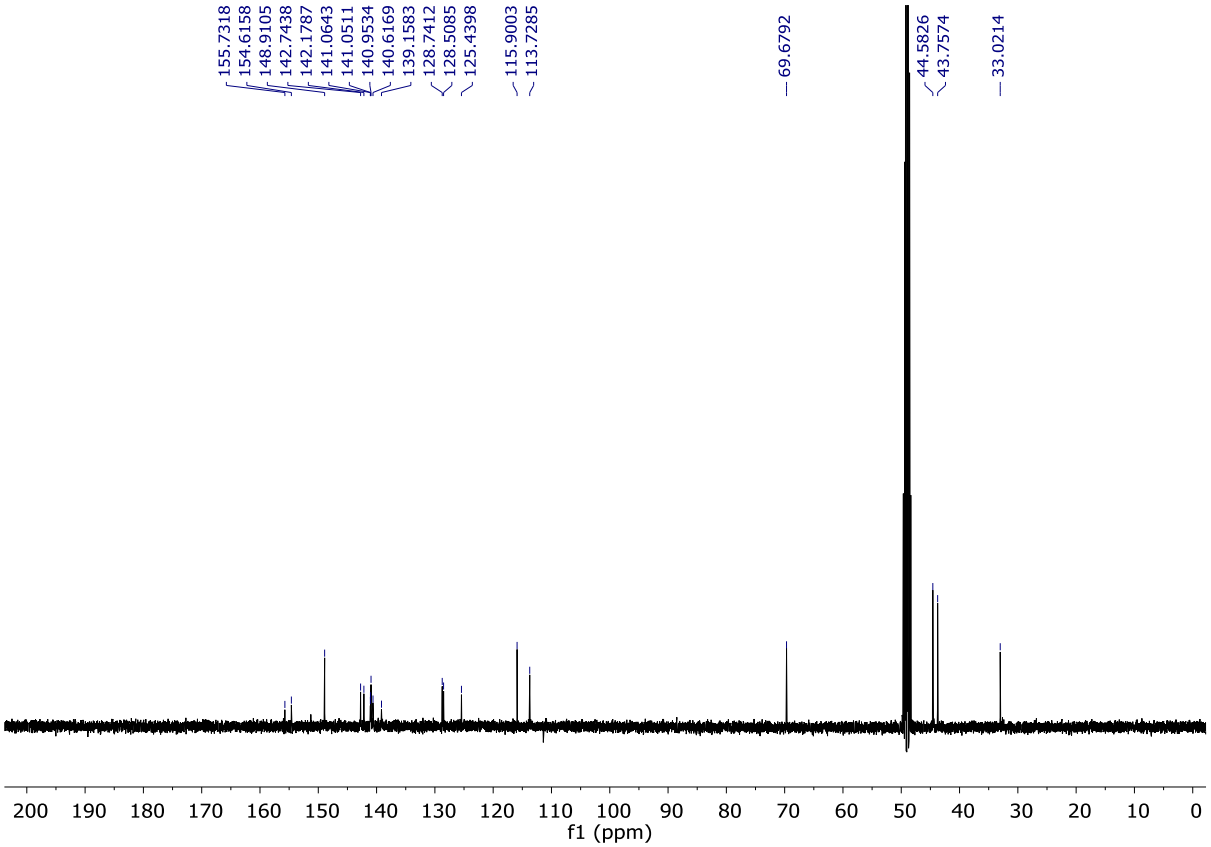
Supplementary Fig. 21. ^{1}H-NMR spectrum of compound 12g (CD_3OD, 400 MHz).



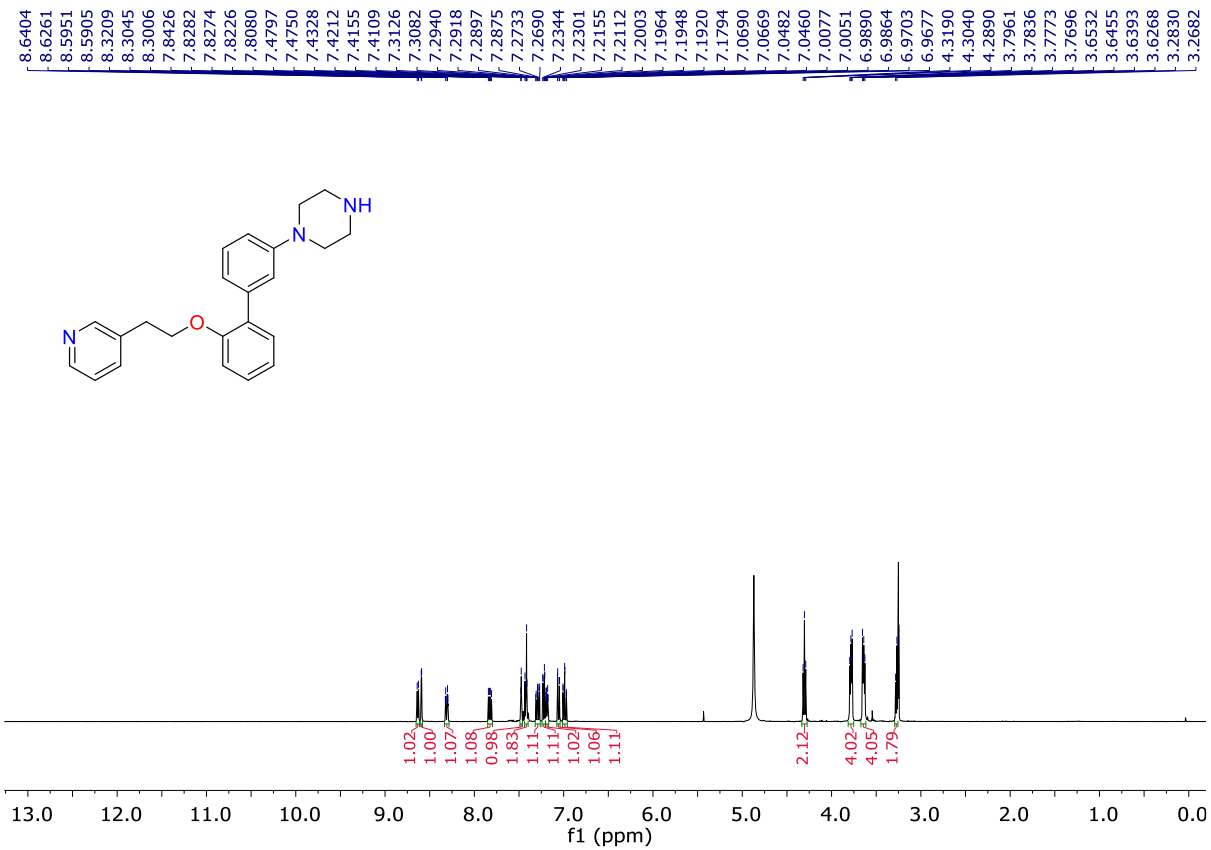
Supplementary Fig. 22. ^{13}C-NMR spectrum of compound 12g (CD_3OD, 100 MHz).



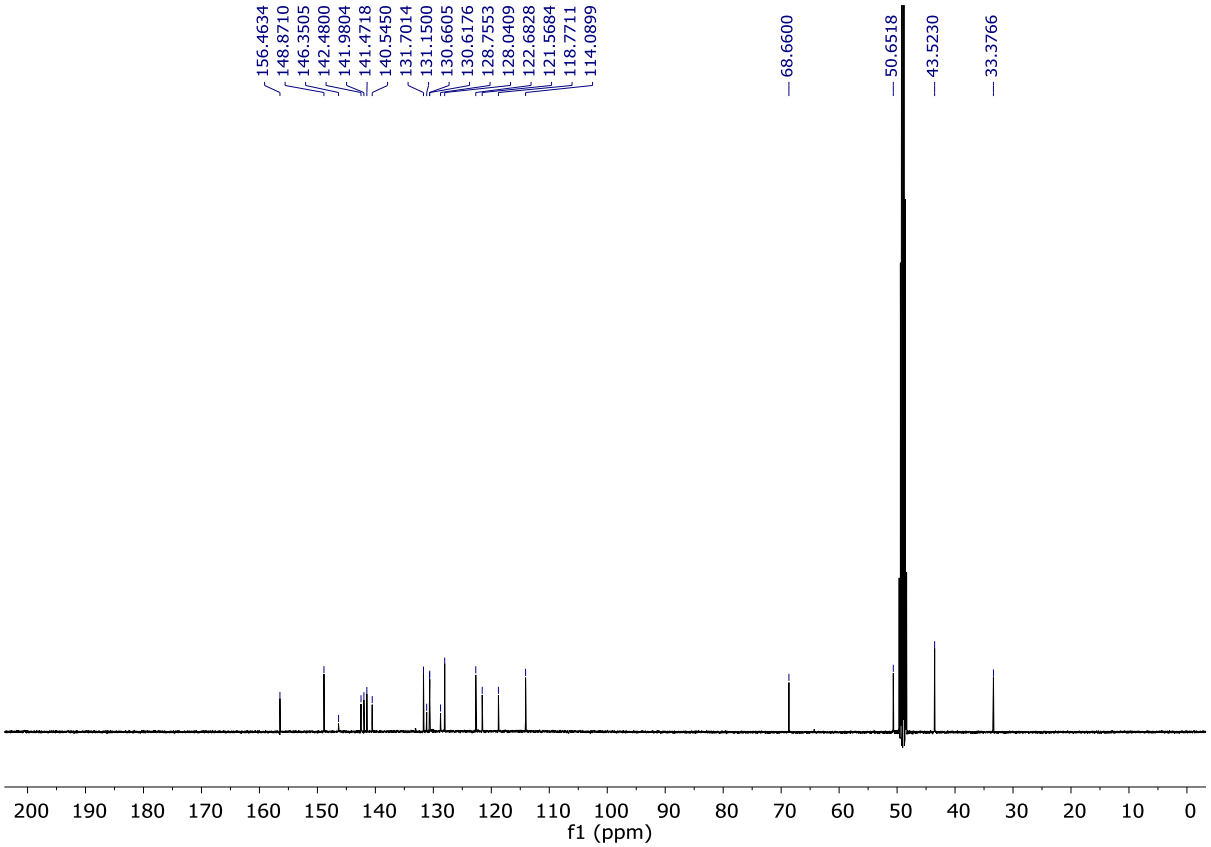
Supplementary Fig. 23. ^{1}H-NMR spectrum of compound 12h (CD_3OD, 400 MHz).



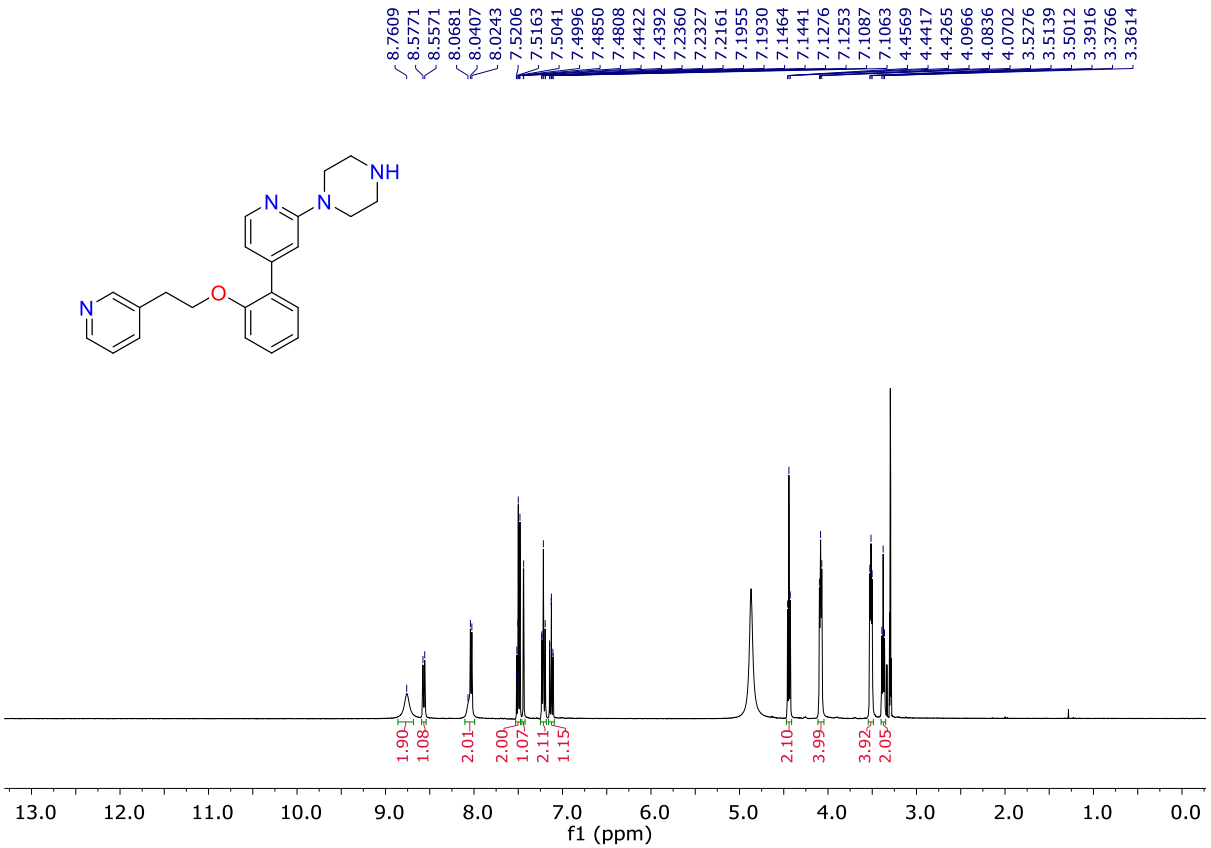
Supplementary Fig. 24. ^{13}C-NMR spectrum of compound 12h (CD_3OD, 100 MHz).



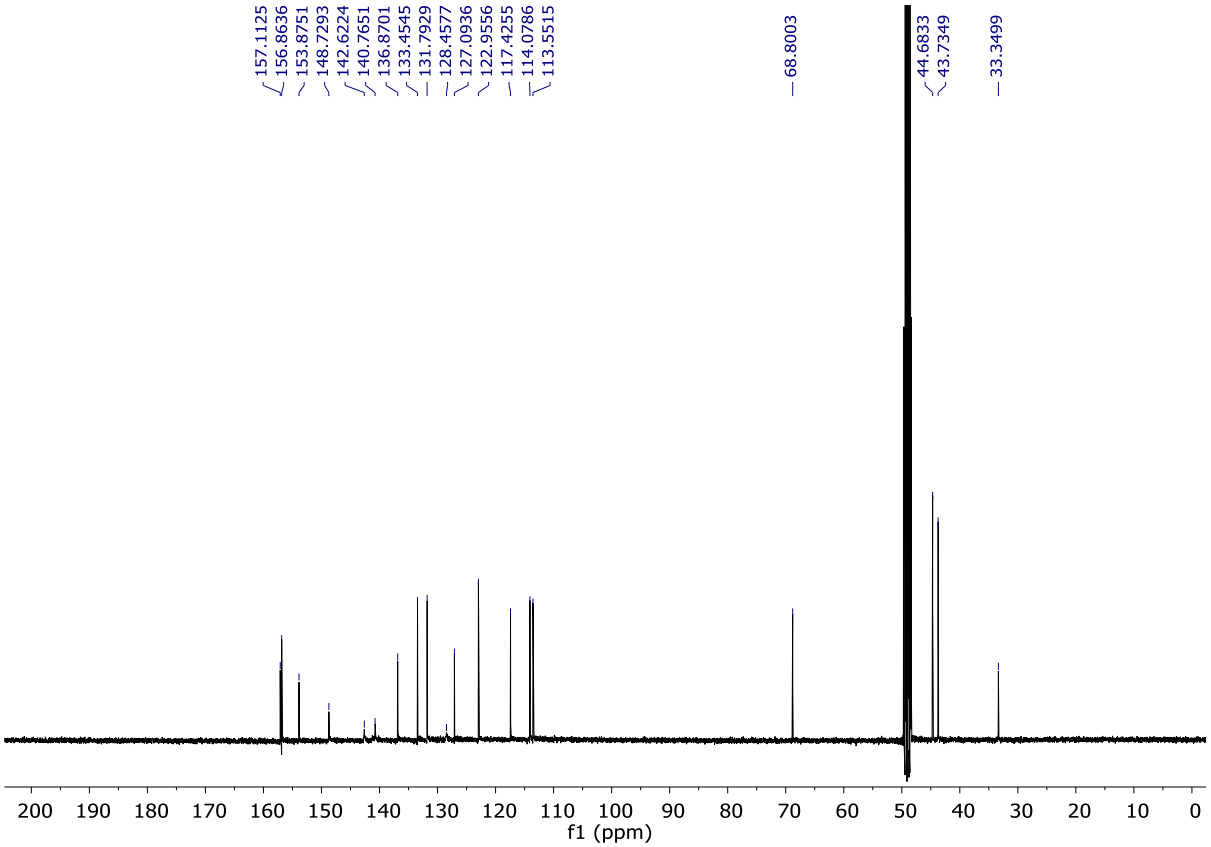
Supplementary Fig. 25. ^{1}H-NMR spectrum of compound 12i (CD_3OD, 400 MHz).



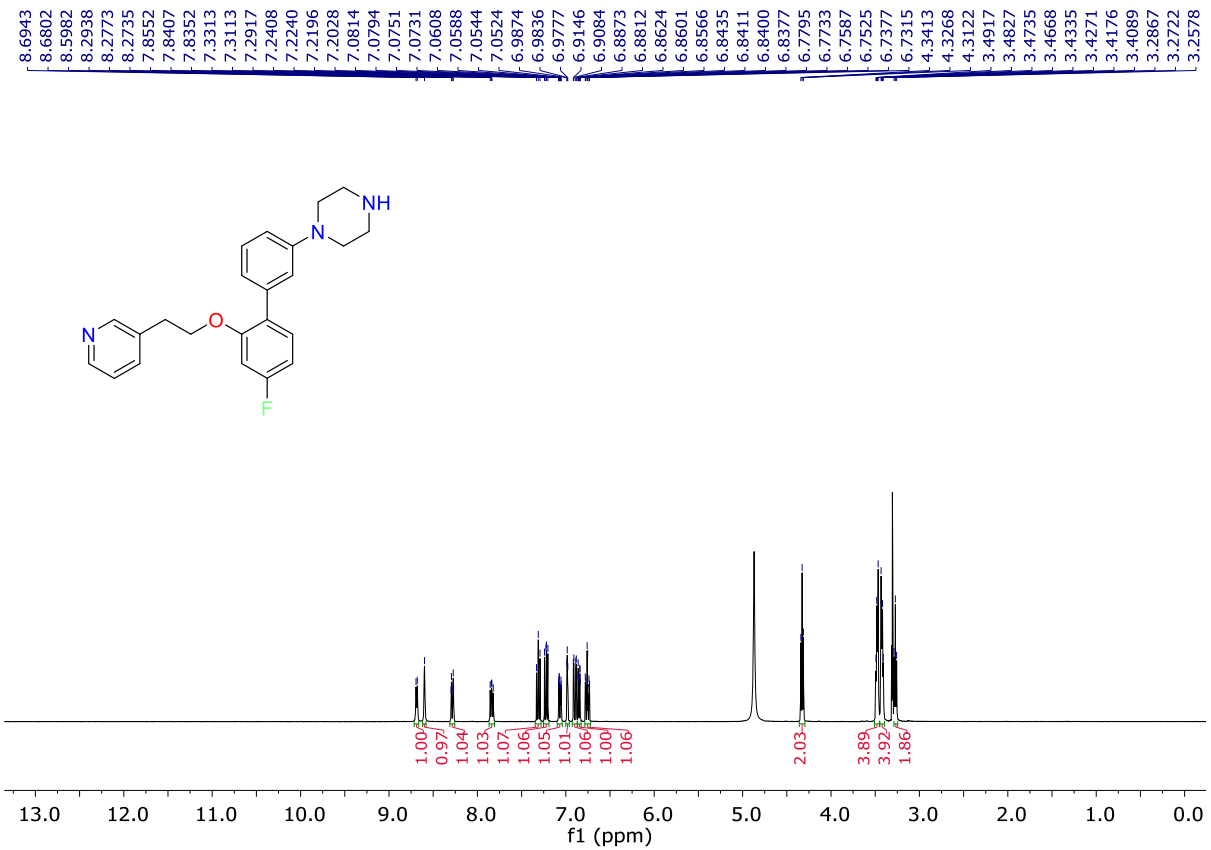
Supplementary Fig. 26. ^{13}C-NMR spectrum of compound 12i (CD_3OD, 100 MHz).



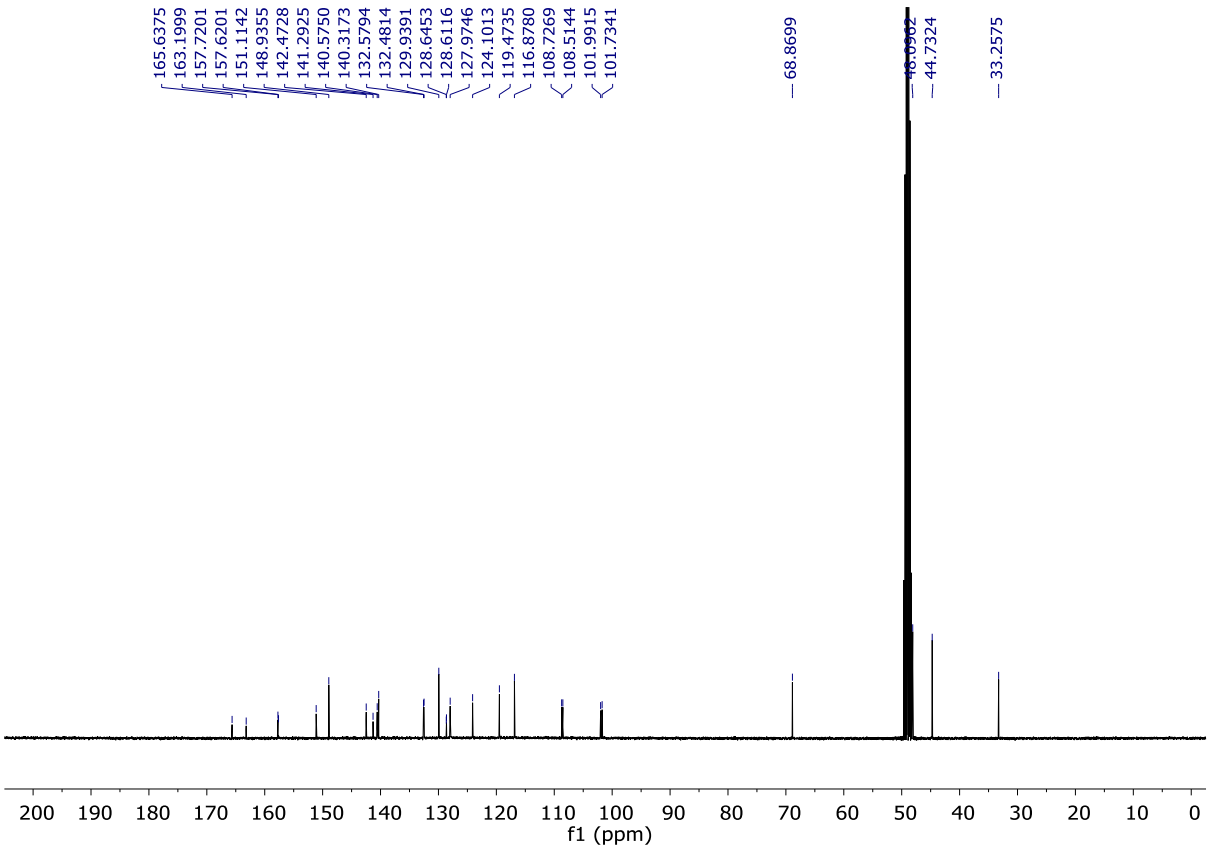
Supplementary Fig. 27. ^{1}H-NMR spectrum of compound 12j (CD_3OD, 400 MHz).



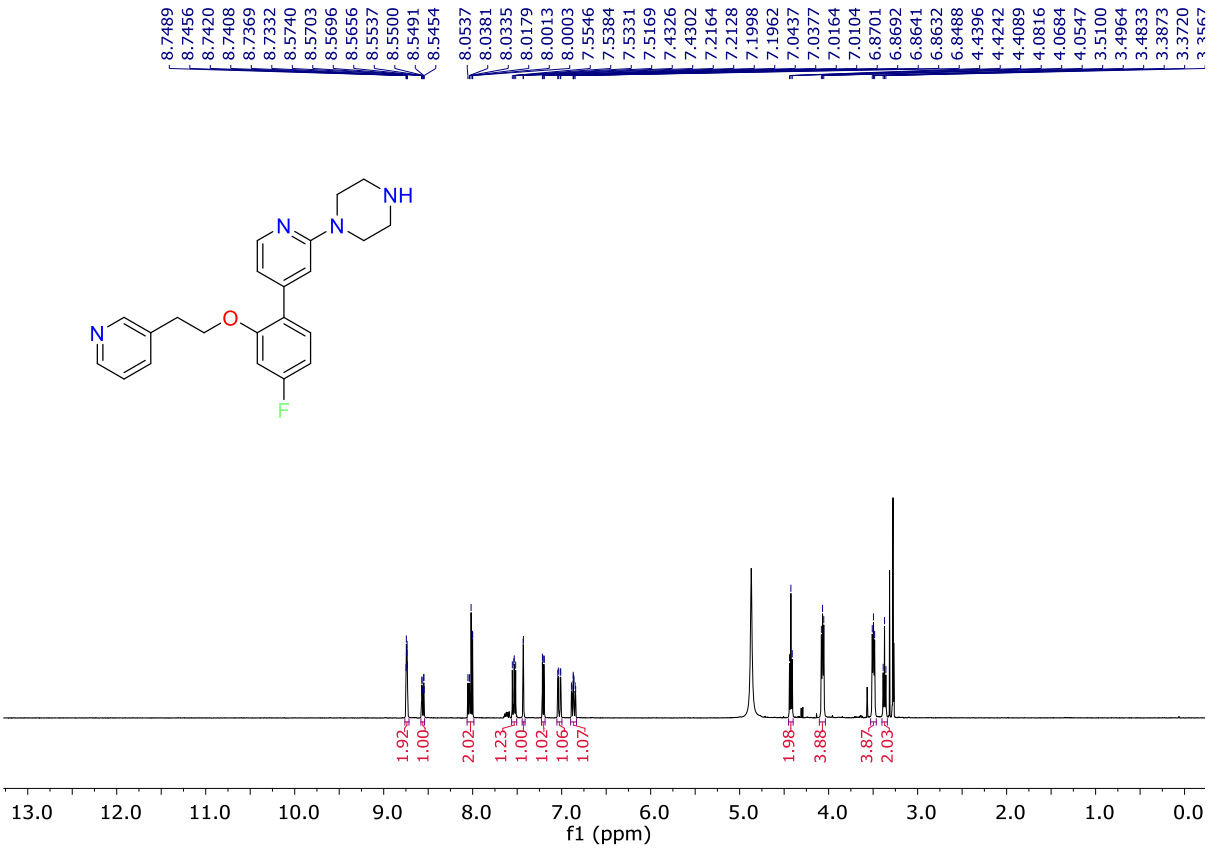
Supplementary Fig. 28. ^{13}C-NMR spectrum of compound 12j (CD_3OD, 100 MHz).



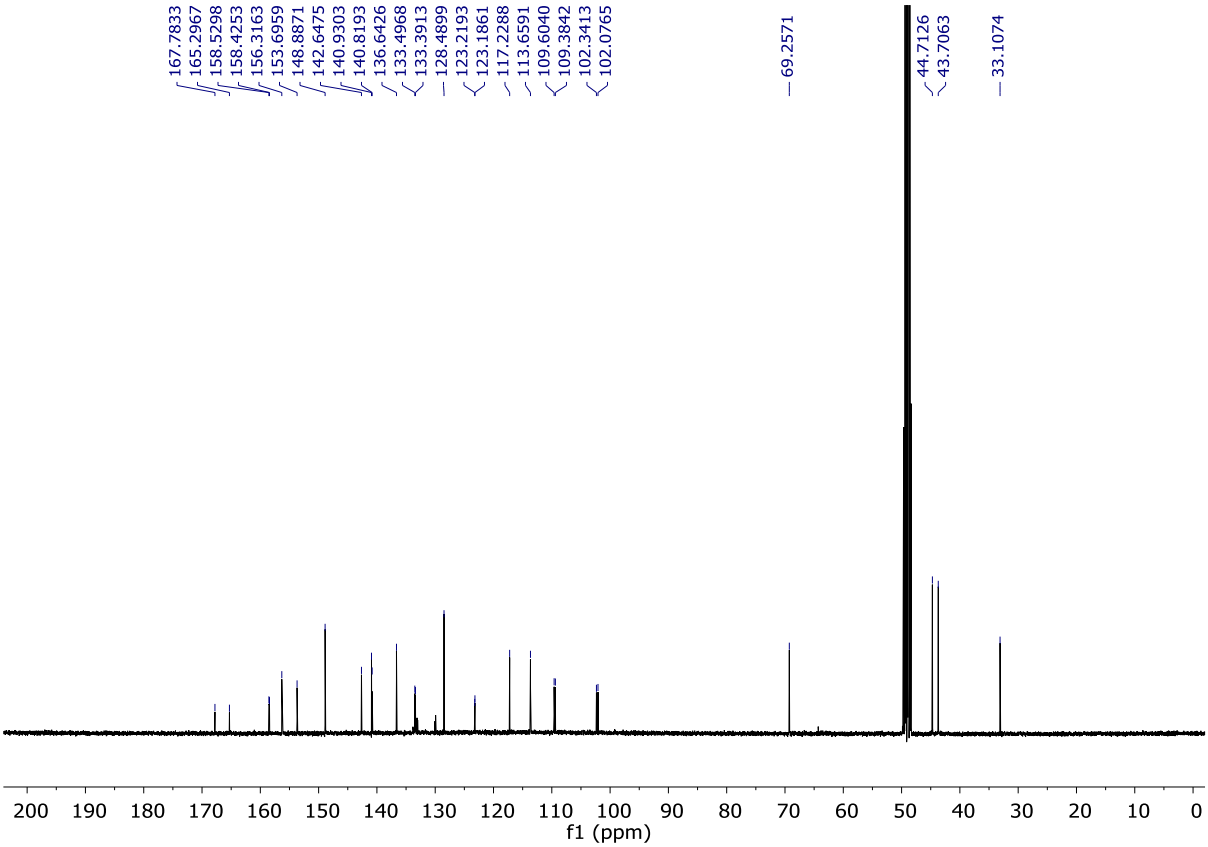
Supplementary Fig. 29. ^{1}H-NMR spectrum of compound 12k (CD_3OD, 400 MHz).



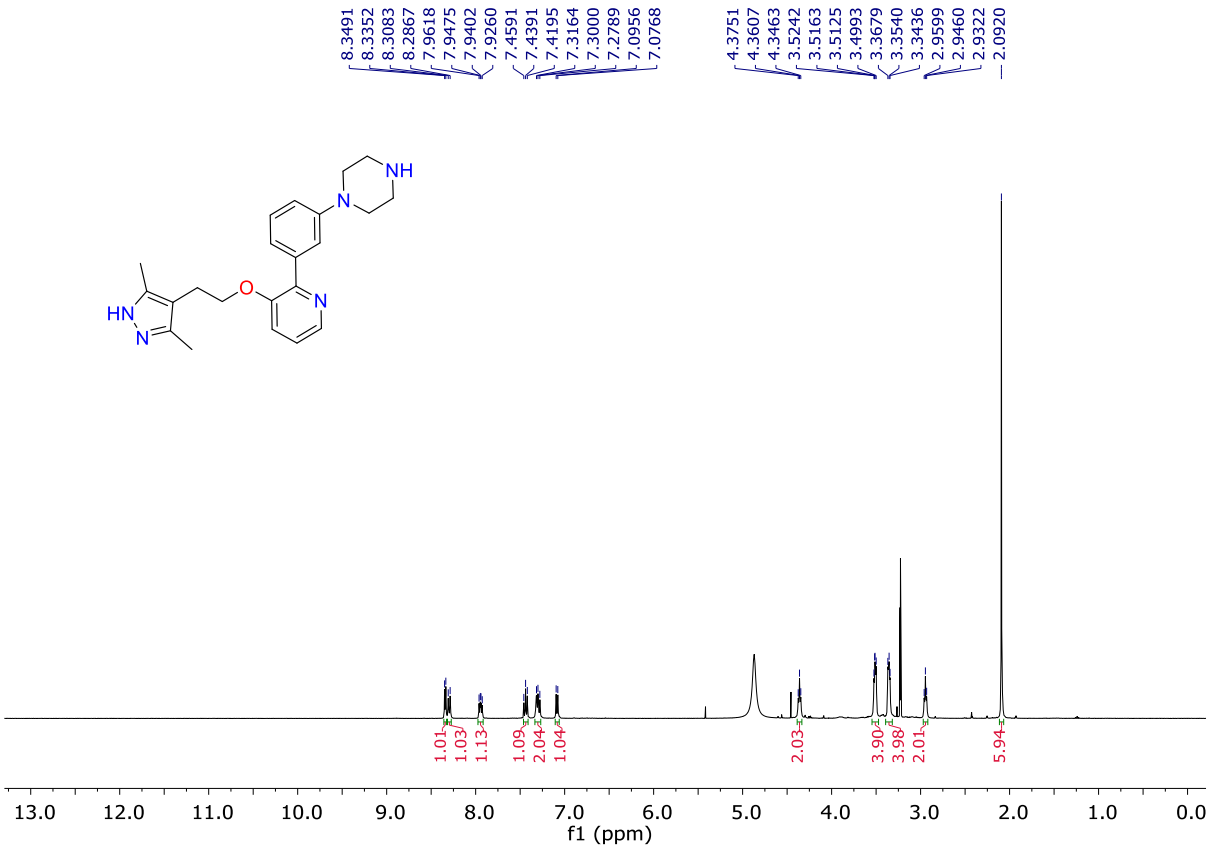
Supplementary Fig. 30. ^{13}C-NMR spectrum of compound 12k (CD_3OD, 100 MHz).



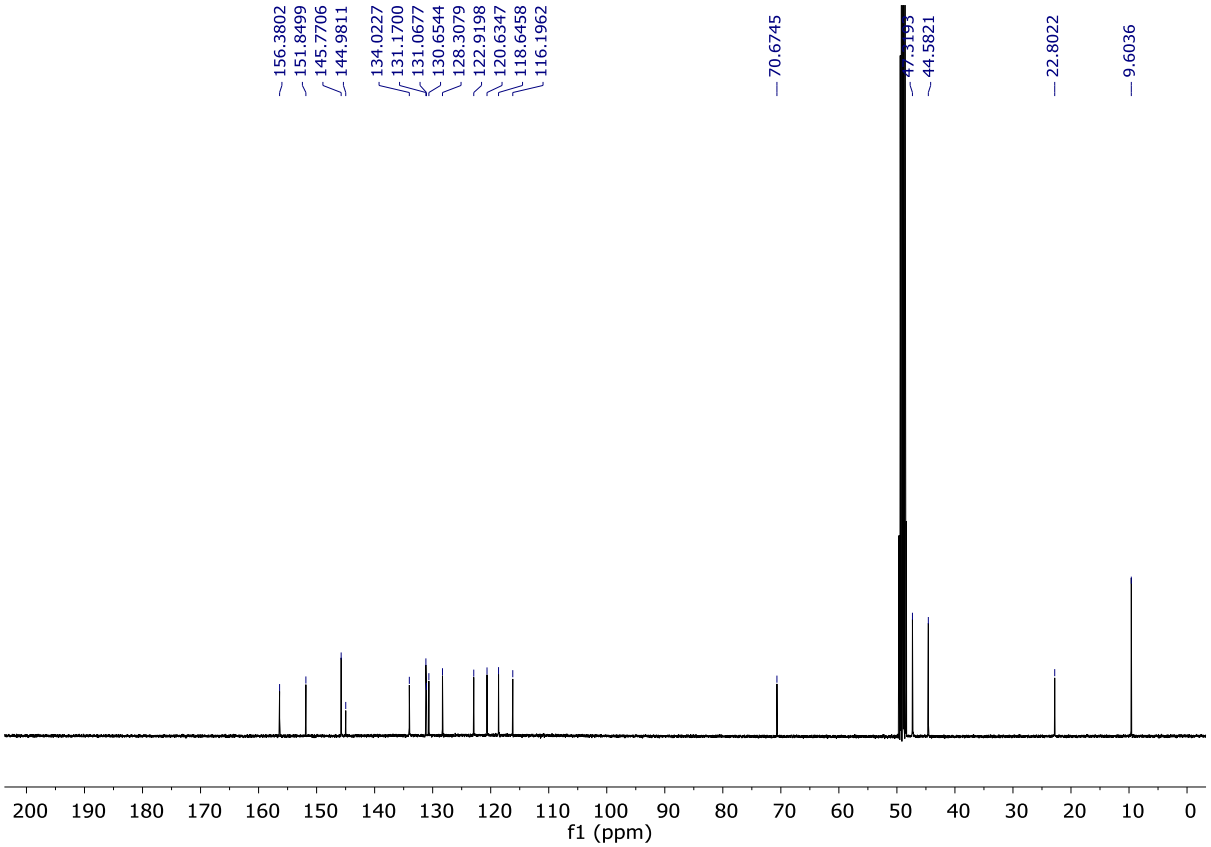
Supplementary Fig. 31. ^{1}H-NMR spectrum of compound 12l (CD_3OD, 400 MHz).



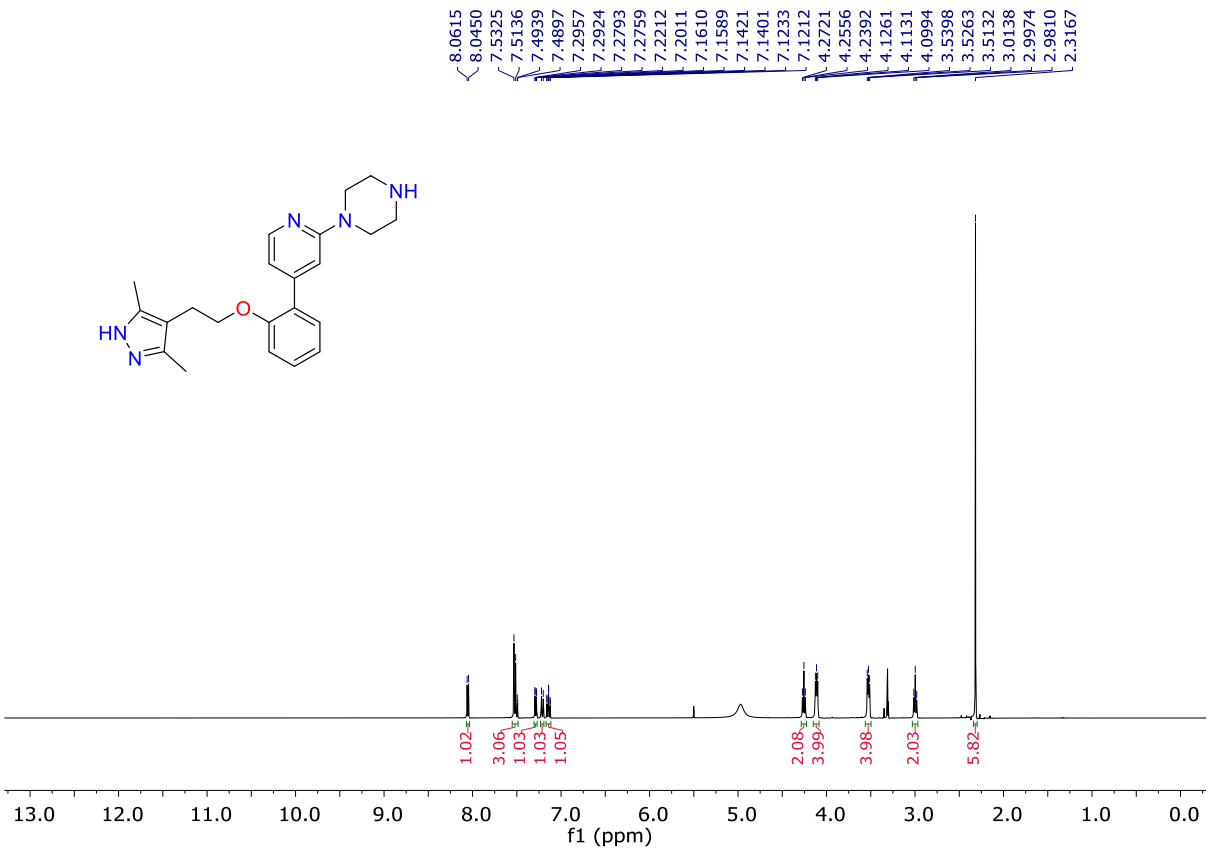
Supplementary Fig. 32. ^{13}C-NMR spectrum of compound 12l (CD_3OD, 100 MHz).



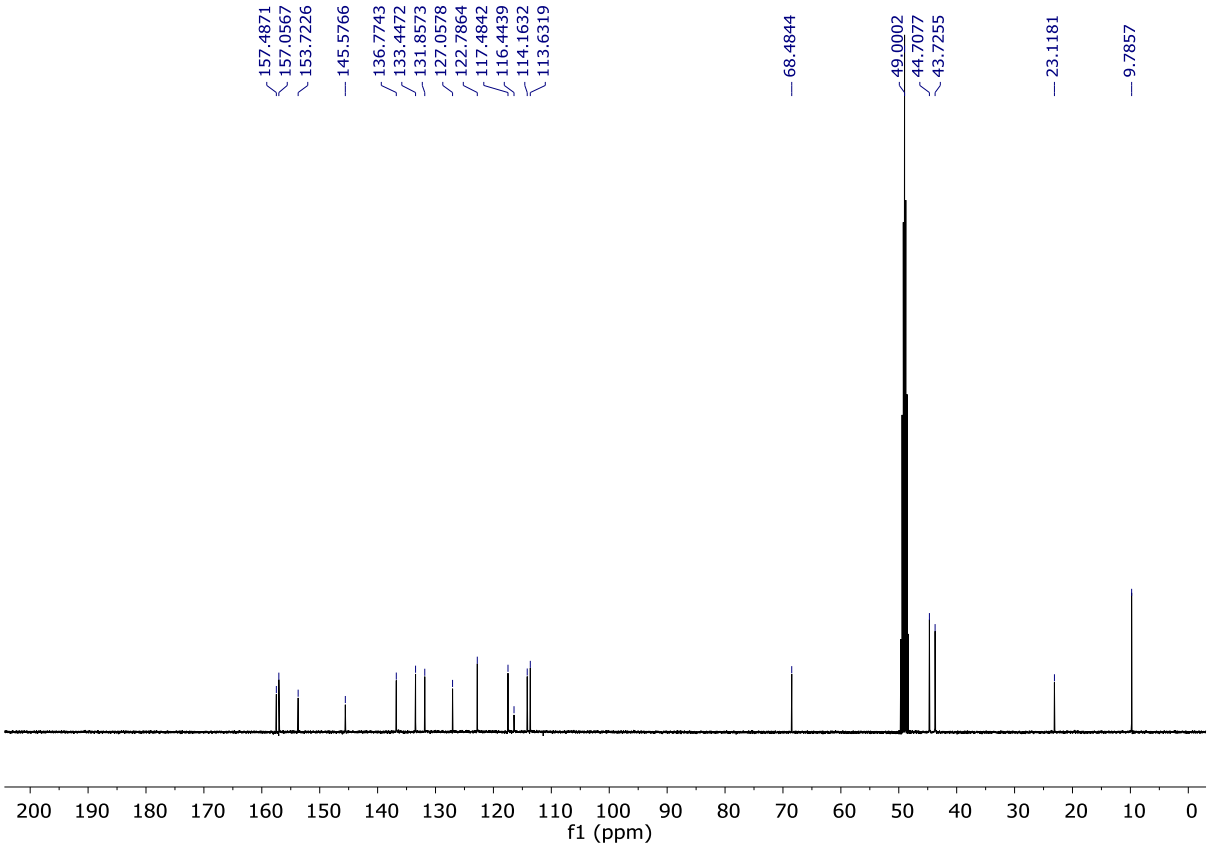
Supplementary Fig. 33. ^{1}H-NMR spectrum of compound 12m (CD_3OD, 400 MHz).



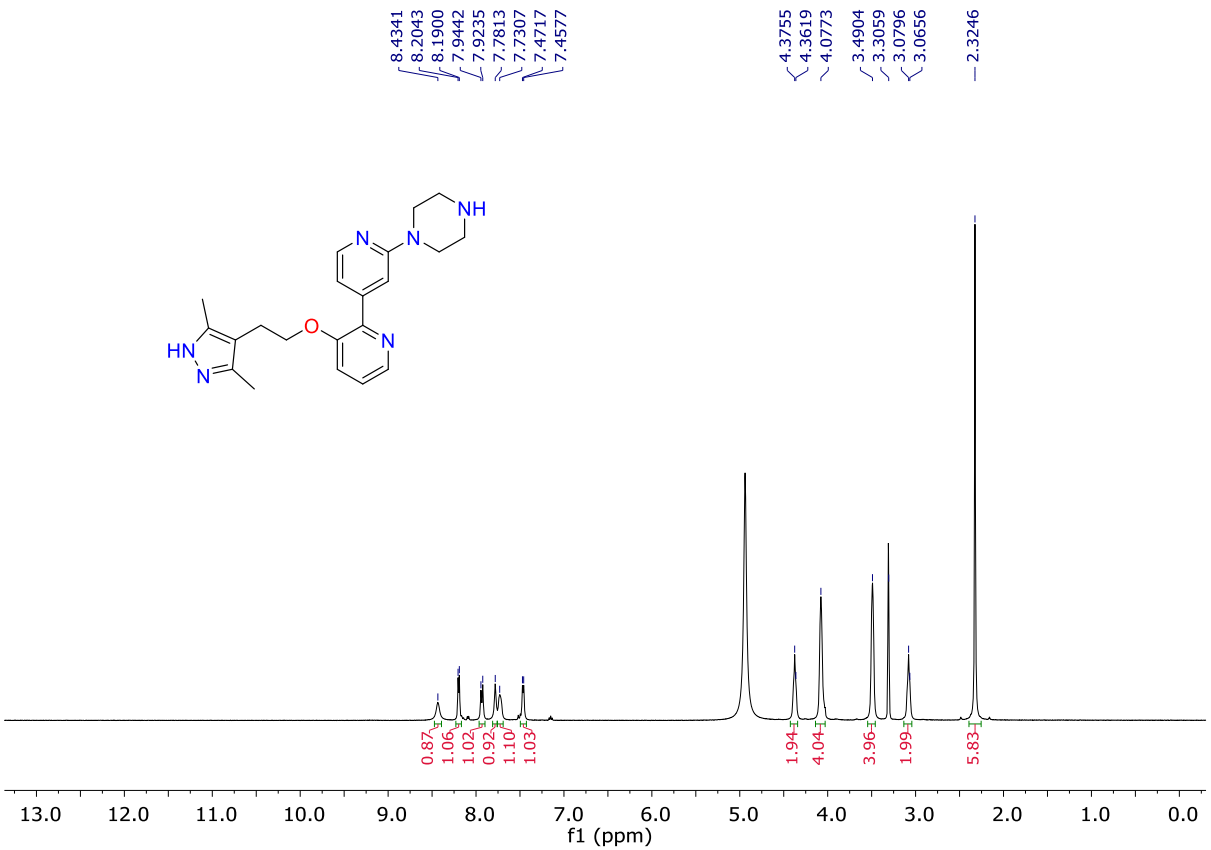
Supplementary Fig. 34. ^{13}C-NMR spectrum of compound 12m (CD_3OD, 100 MHz).



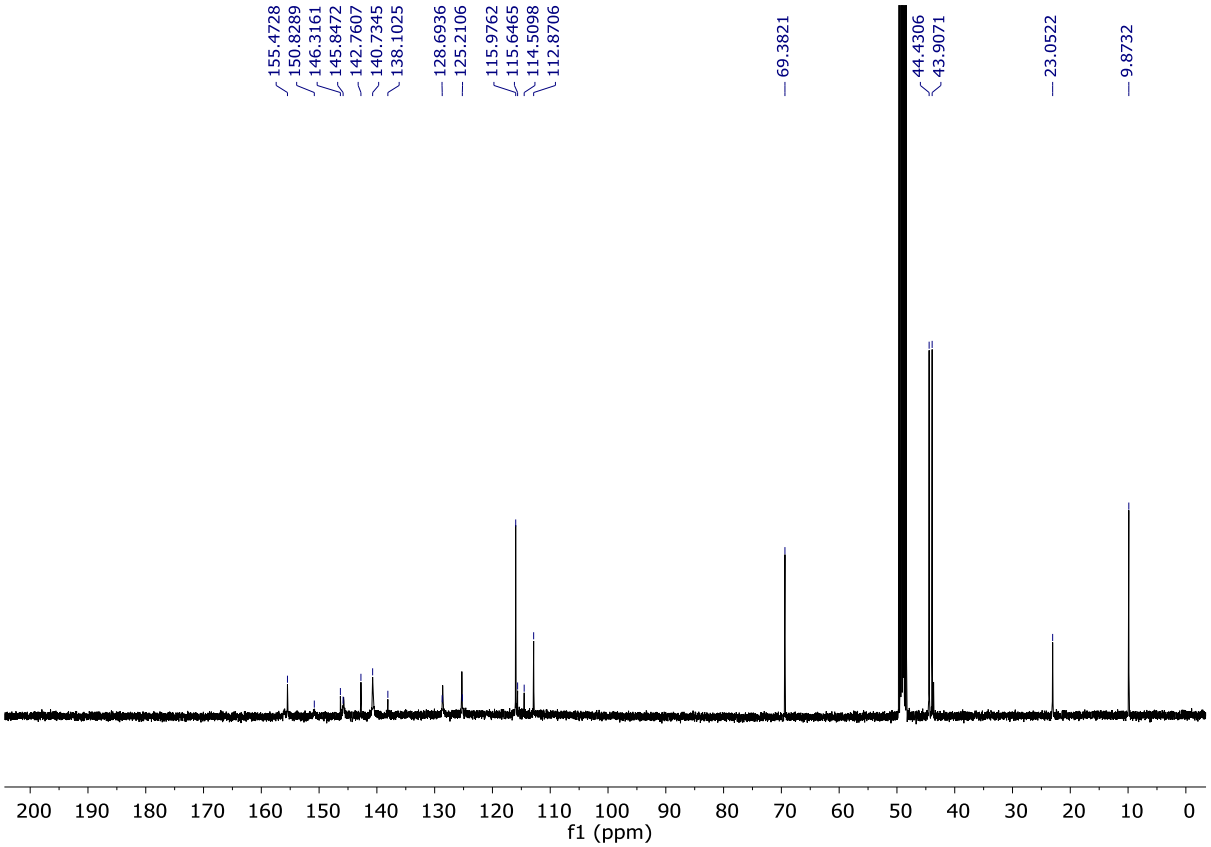
Supplementary Fig. 35. ^{1}H-NMR spectrum of compound 12n (CD_3OD, 400 MHz).



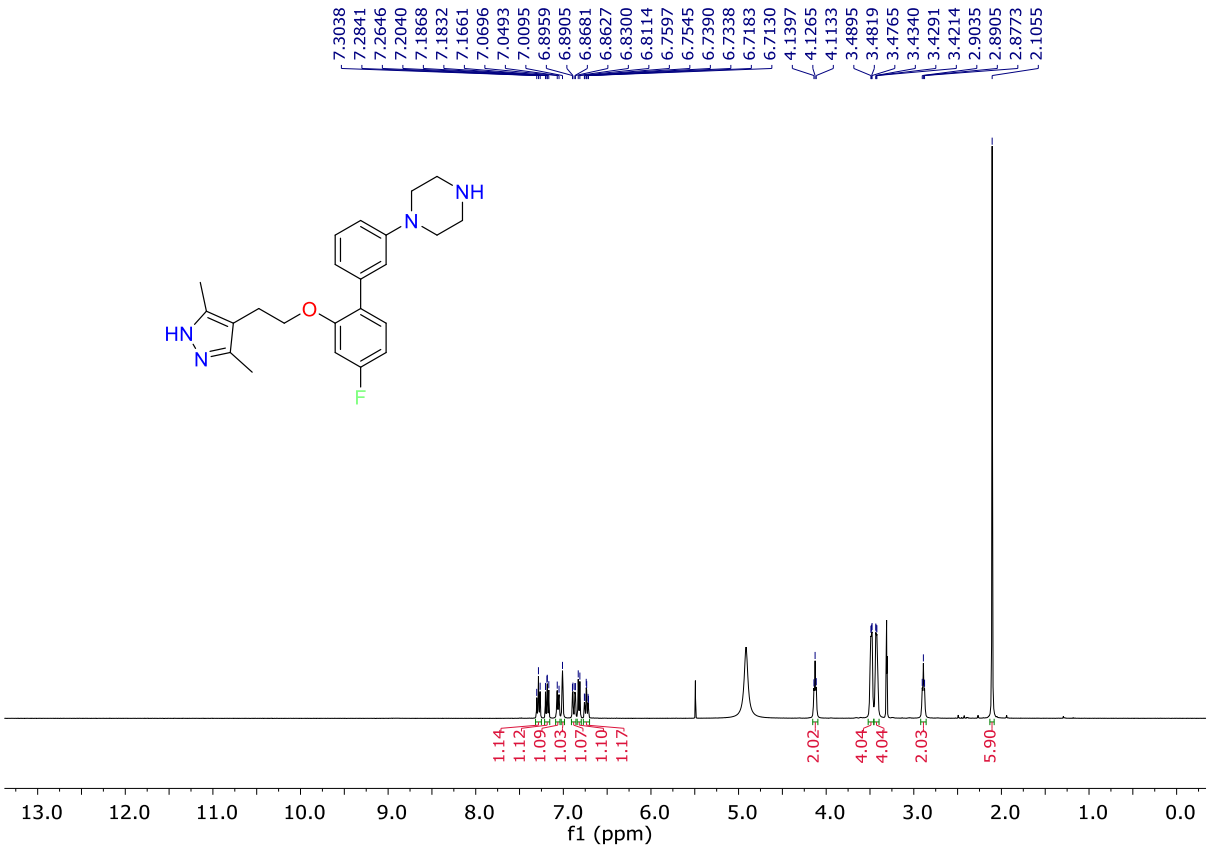
Supplementary Fig. 36. ^{13}C-NMR spectrum of compound 12n (CD_3OD, 100 MHz).



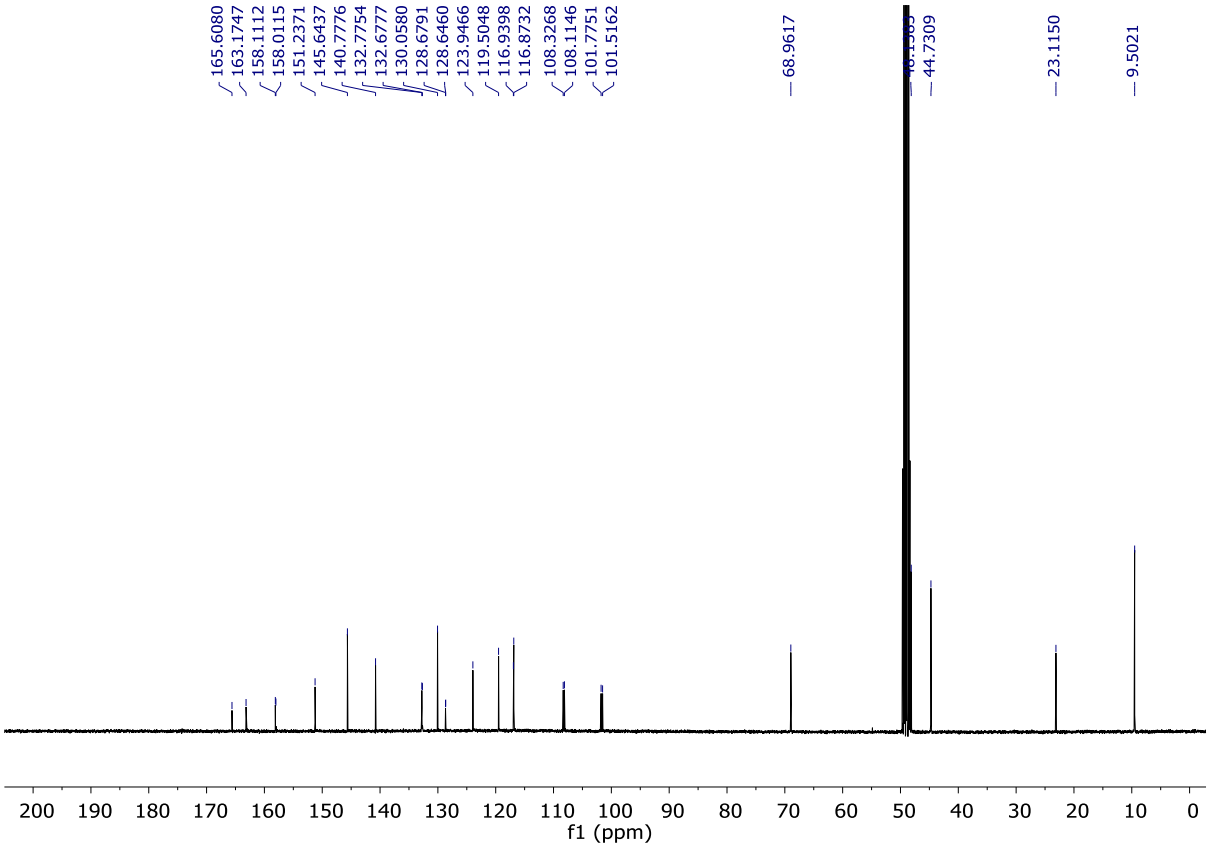
Supplementary Fig. 37. ^{1}H-NMR spectrum of compound 12o (CD_3OD, 400 MHz).



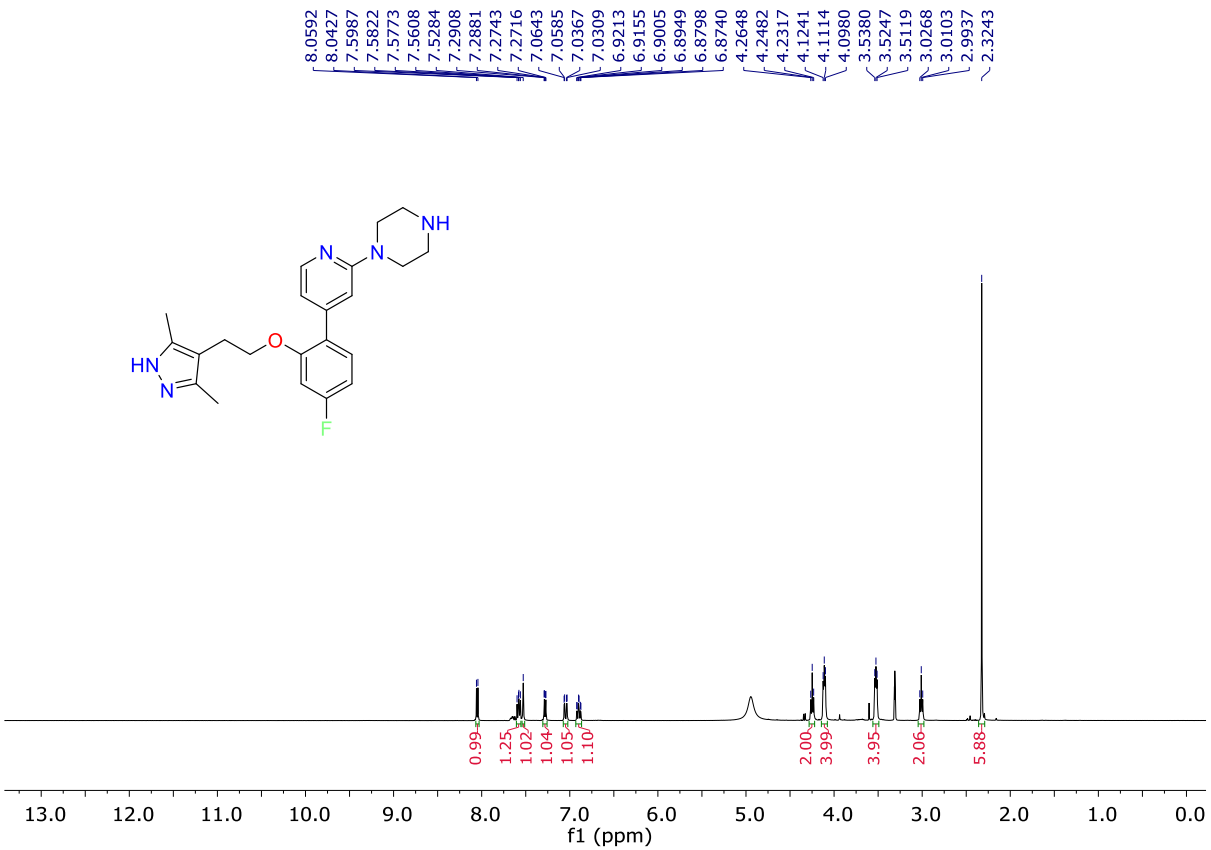
Supplementary Fig. 38. ^{13}C-NMR spectrum of compound 12o (CD_3OD, 100 MHz).



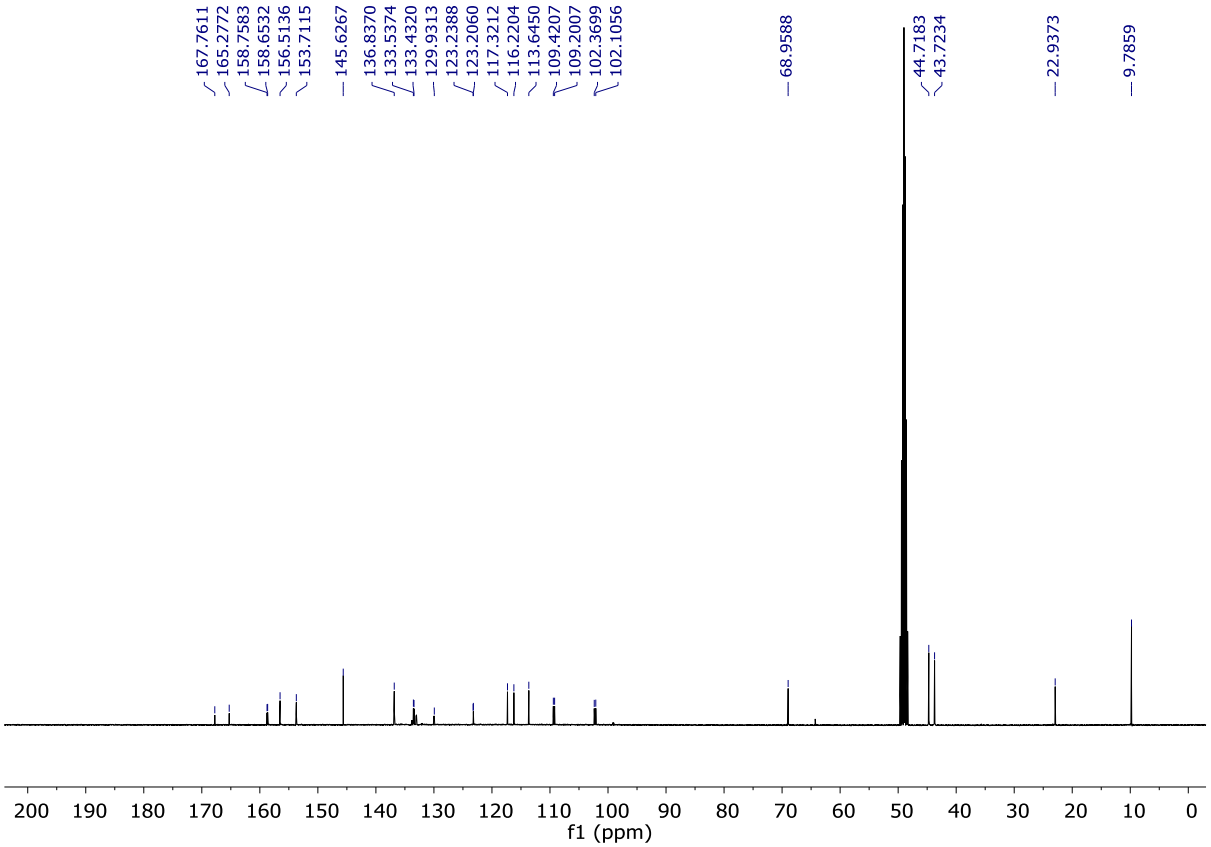
Supplementary Fig. 39. ^{1}H-NMR spectrum of compound 12p (CD_3OD, 400 MHz).



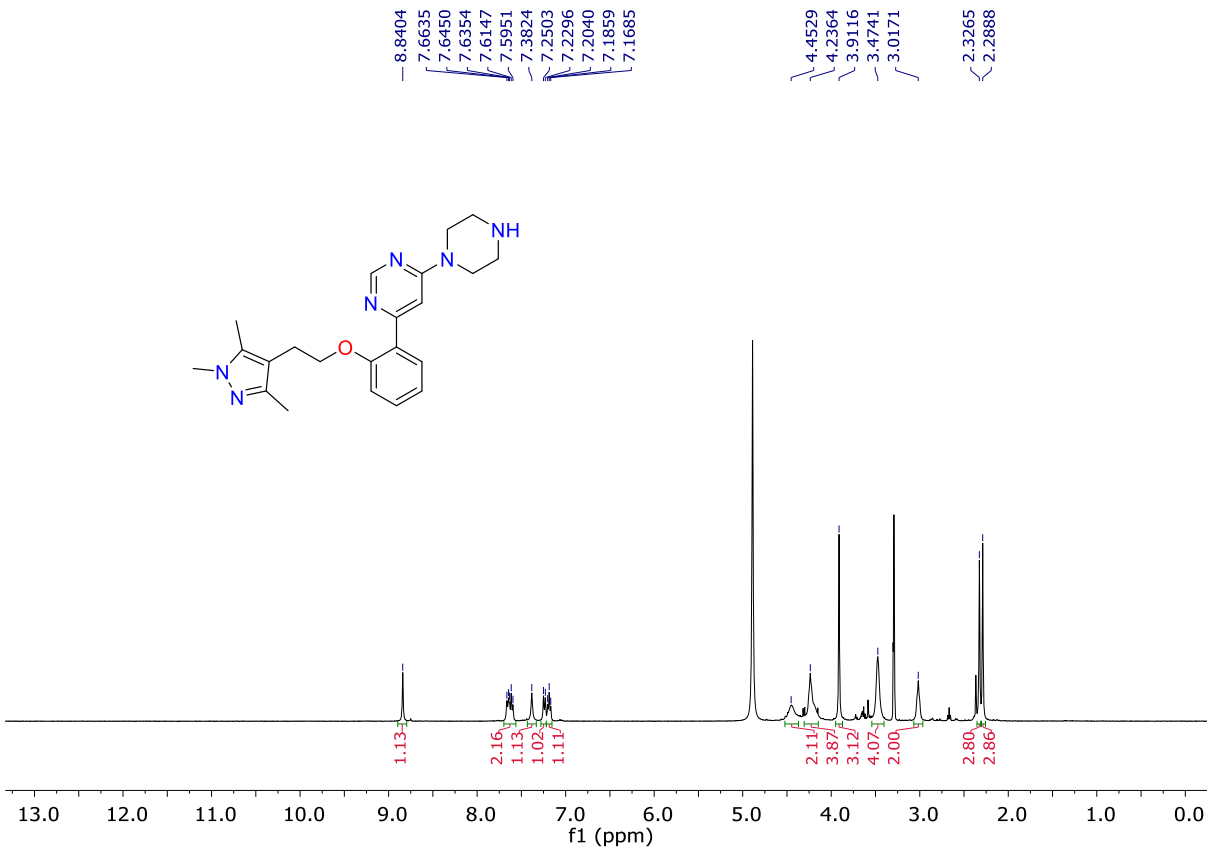
Supplementary Fig. 40. ^{13}C-NMR spectrum of compound 12p (CD_3OD, 100 MHz).



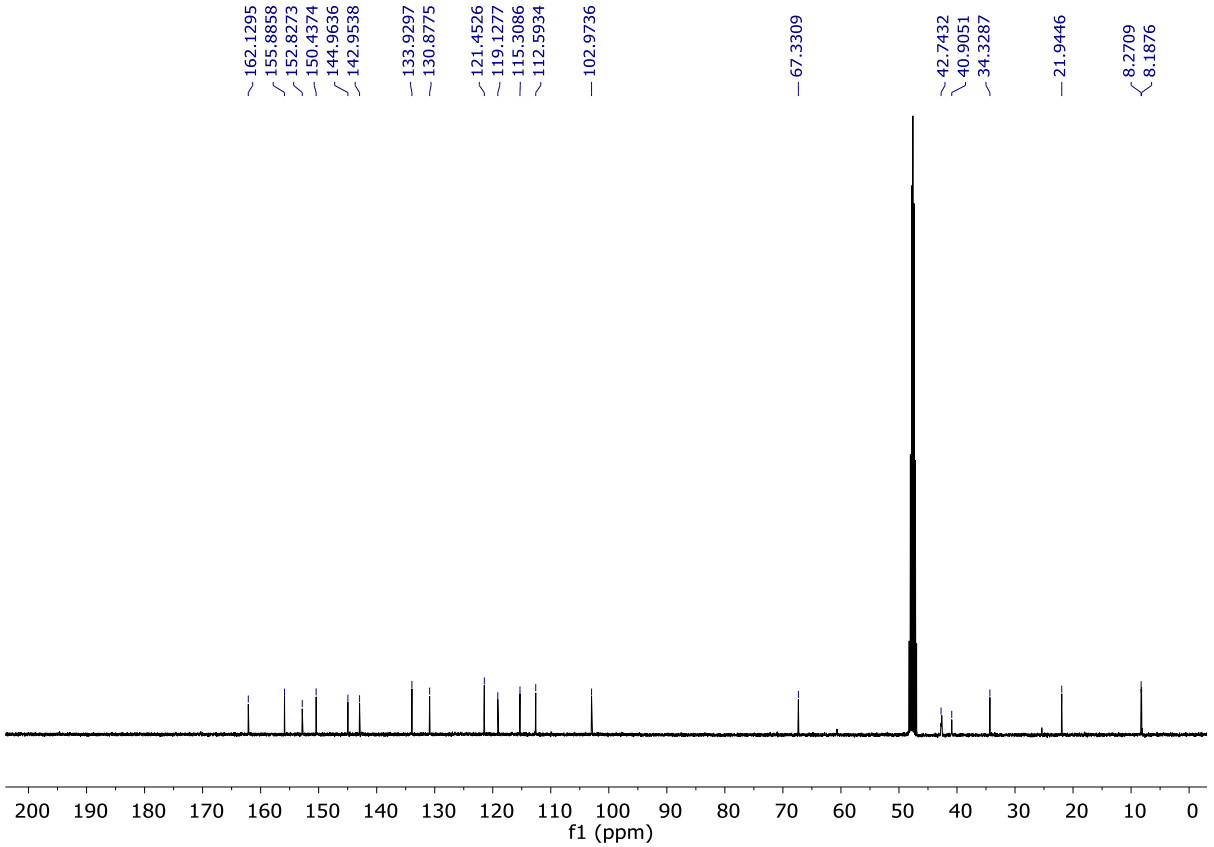
Supplementary Fig. 41. ^{1}H-NMR spectrum of compound 12q (CD_3OD, 400 MHz).



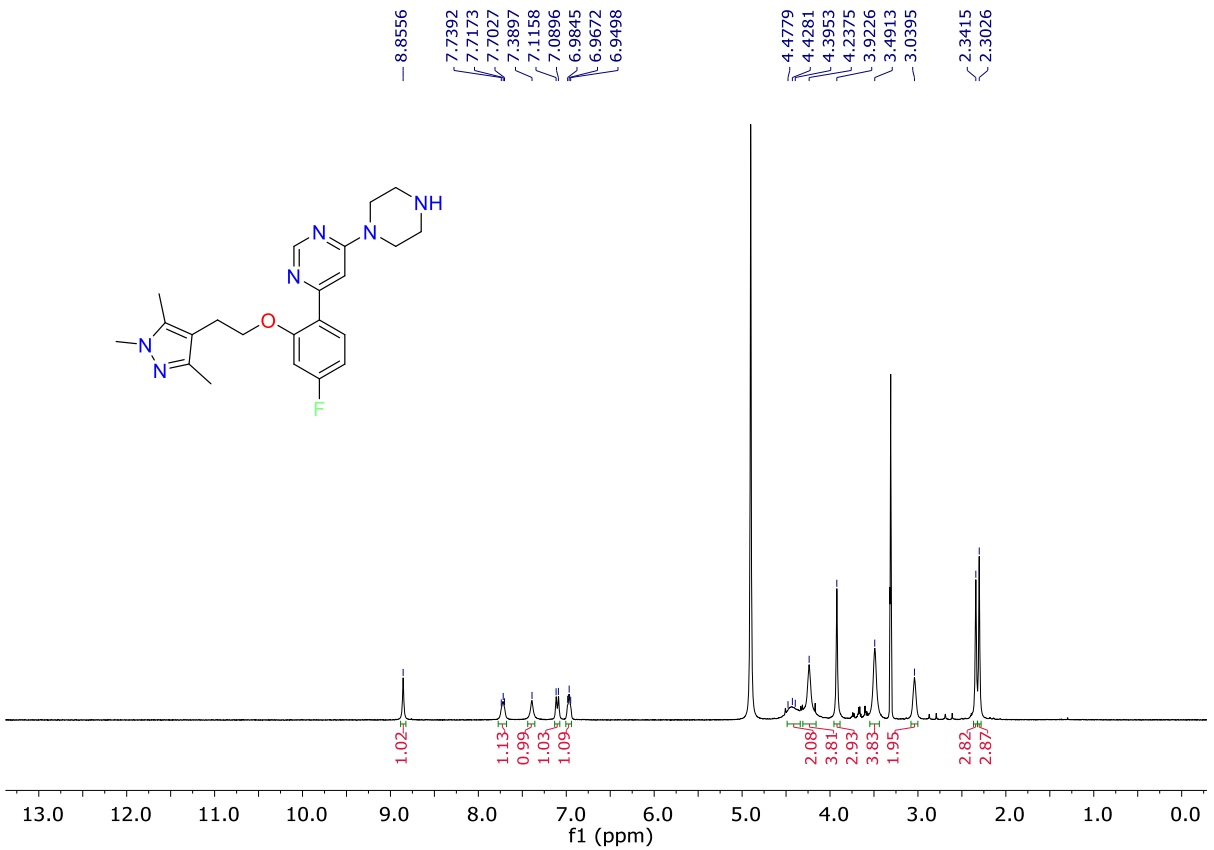
Supplementary Fig. 42. ^{13}C-NMR spectrum of compound 12q (CD_3OD, 100 MHz).



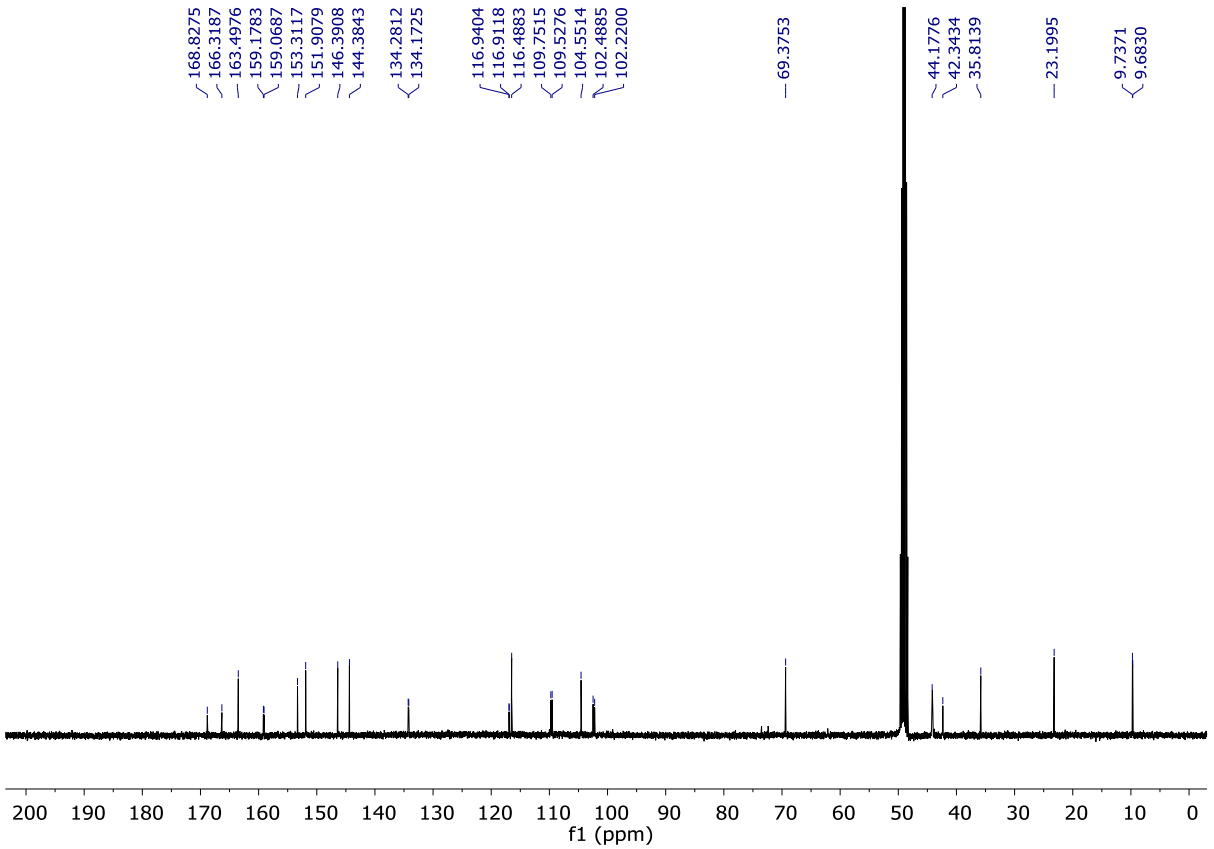
Supplementary Fig. 43. ^{1}H-NMR spectrum of compound 16a (CD_3OD, 400 MHz).



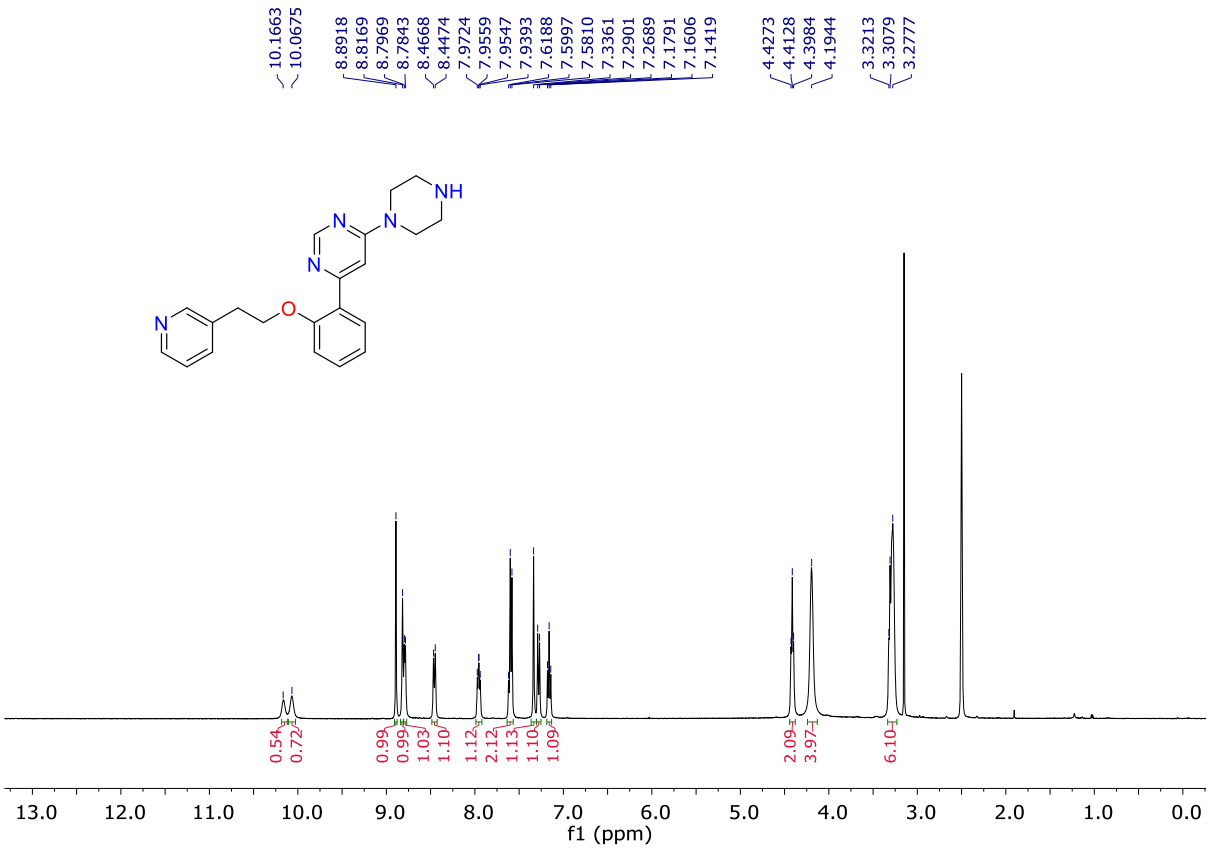
Supplementary Fig. 44. ^{13}C-NMR spectrum of compound 16a (CD_3OD, 100 MHz).



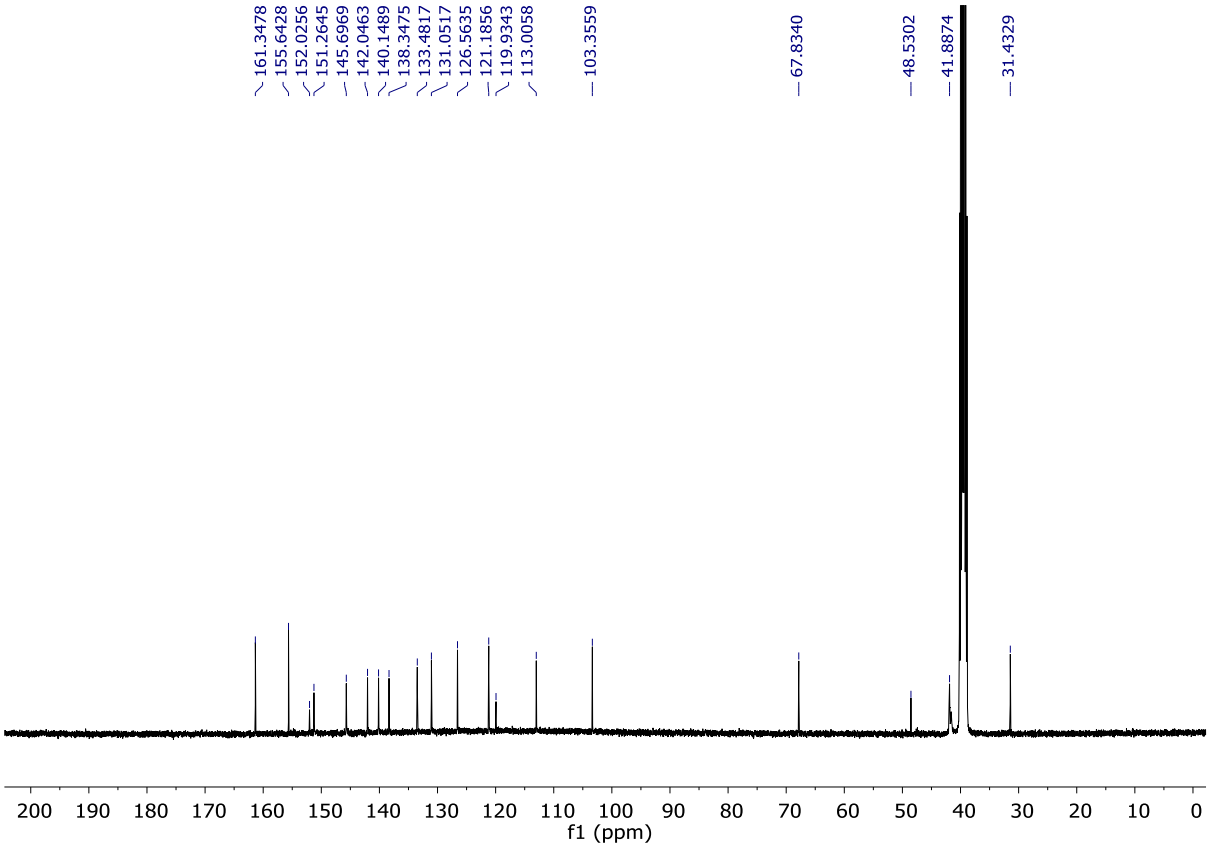
Supplementary Fig. 45. ^{1}H-NMR spectrum of compound 16b (CD_3OD, 400 MHz).



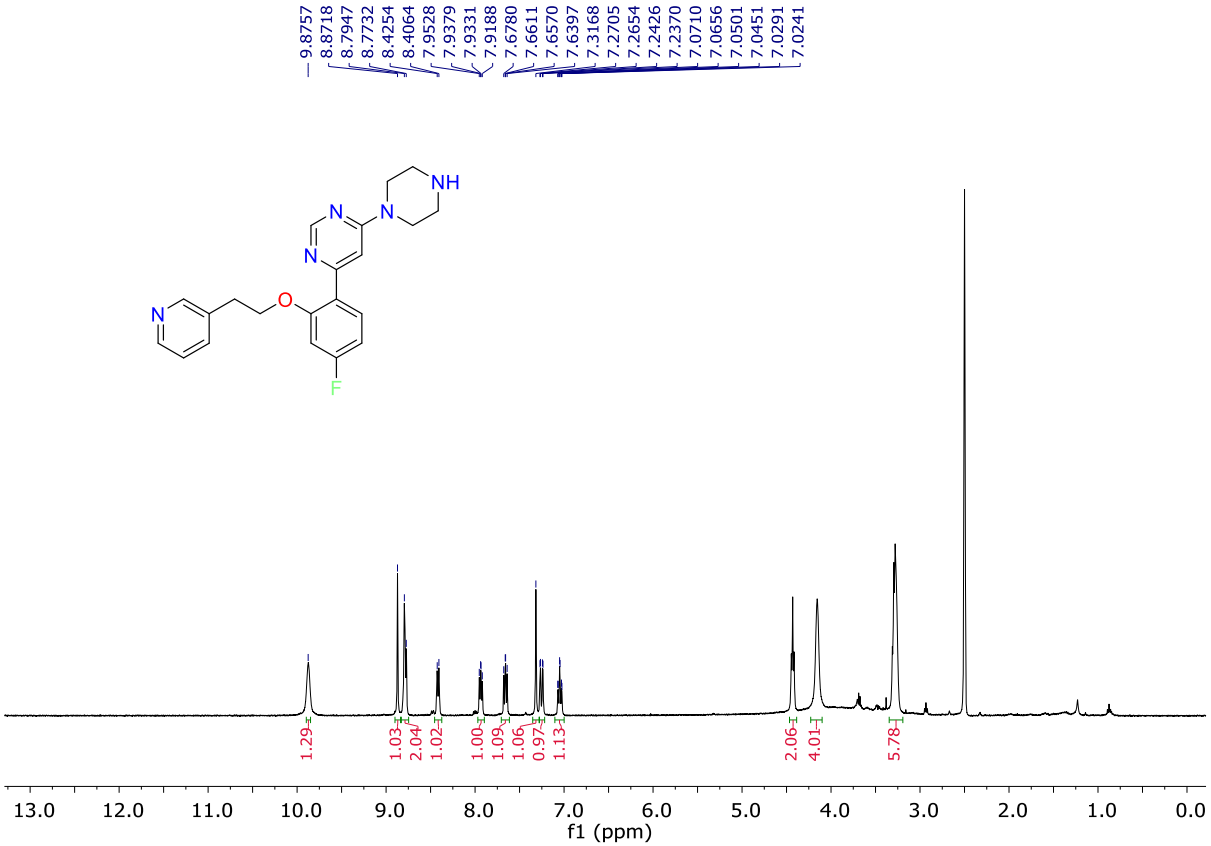
Supplementary Fig. 46. ^{13}C-NMR spectrum of compound 16b (CD_3OD, 100 MHz).



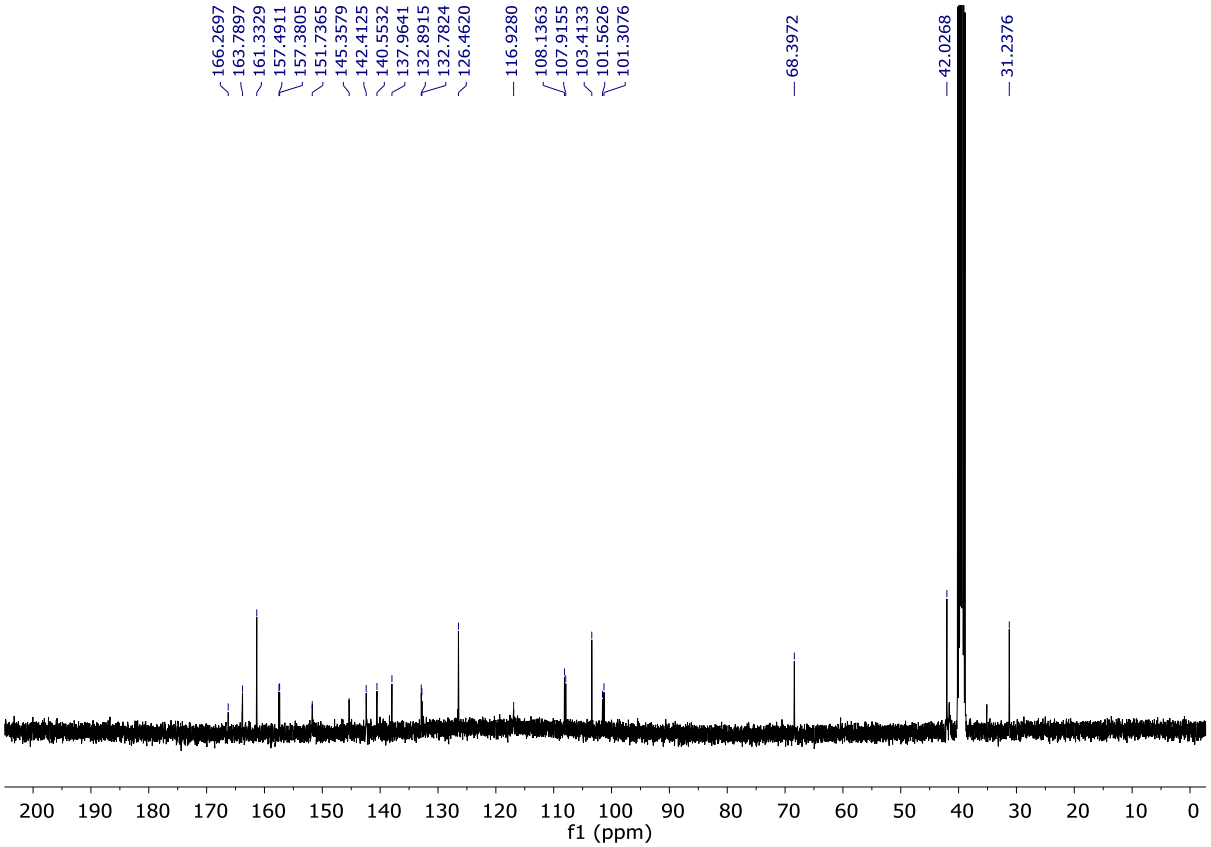
Supplementary Fig. 47. ^{1}H-NMR spectrum of compound 16c (DMSO-*d6*, 400 MHz).



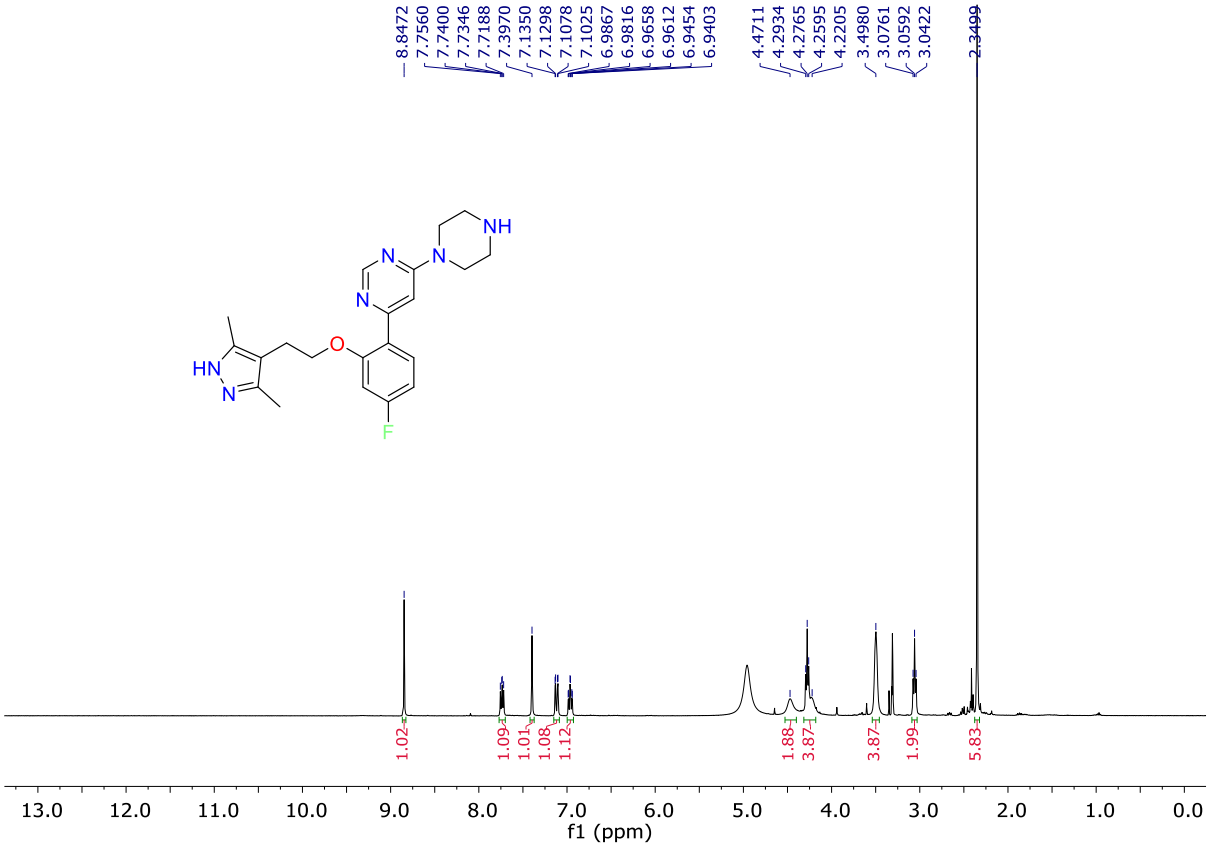
Supplementary Fig. 48. ^{13}C-NMR spectrum of compound 16c (DMSO-*d6*, 100 MHz).



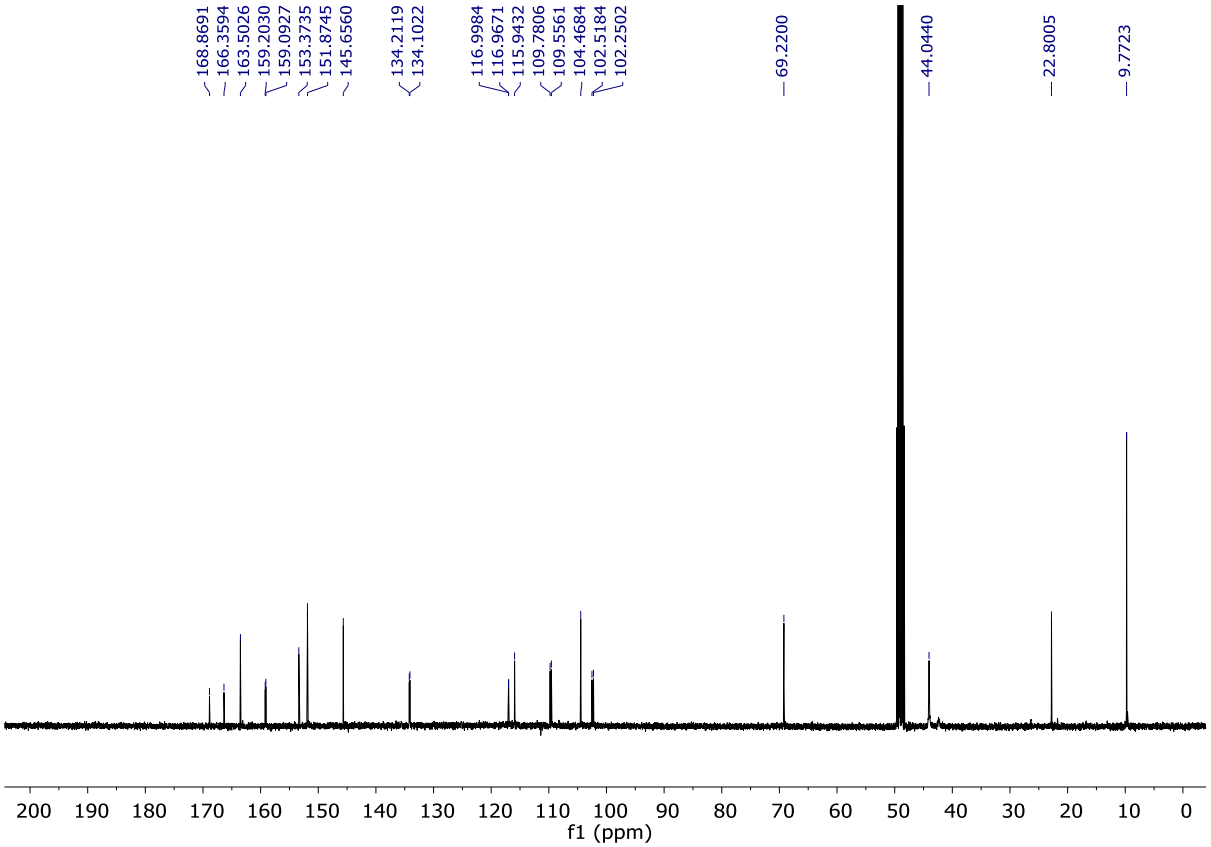
Supplementary Fig. 49. ^{1}H-NMR spectrum of compound 16d (DMSO-*d6*, 400 MHz).



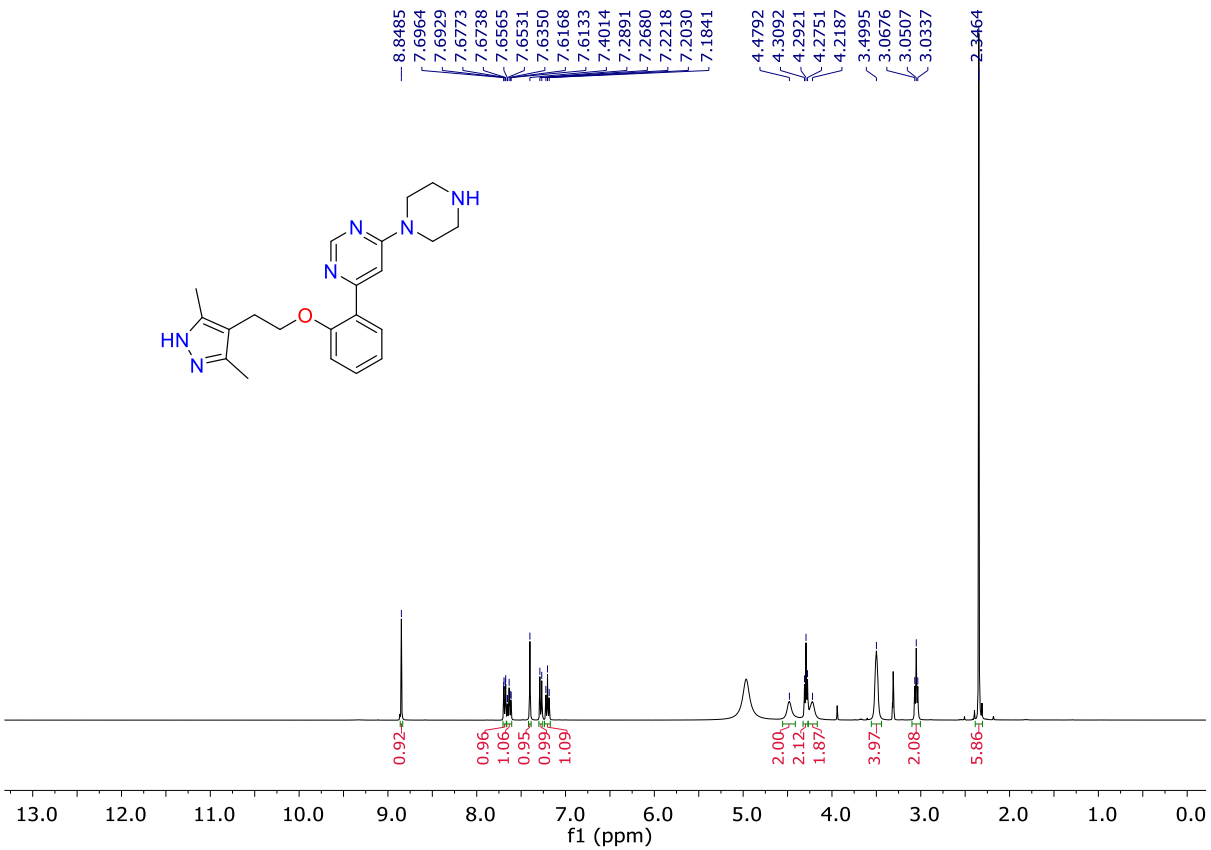
Supplementary Fig. 50. ^{13}C-NMR spectrum of compound 16d (DMSO-*d6*, 100 MHz).



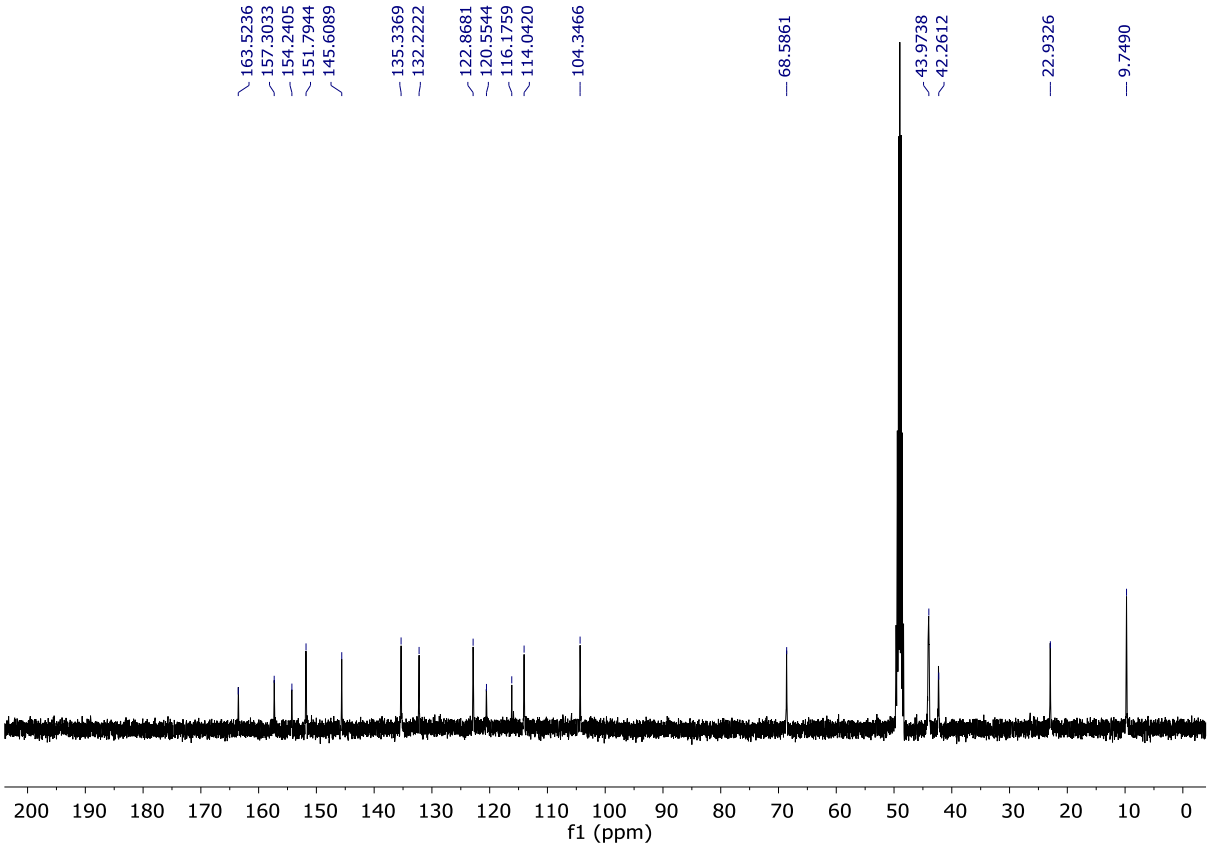
Supplementary Fig. 51. ^{1}H-NMR spectrum of compound 16e (CD_3OD, 400 MHz).



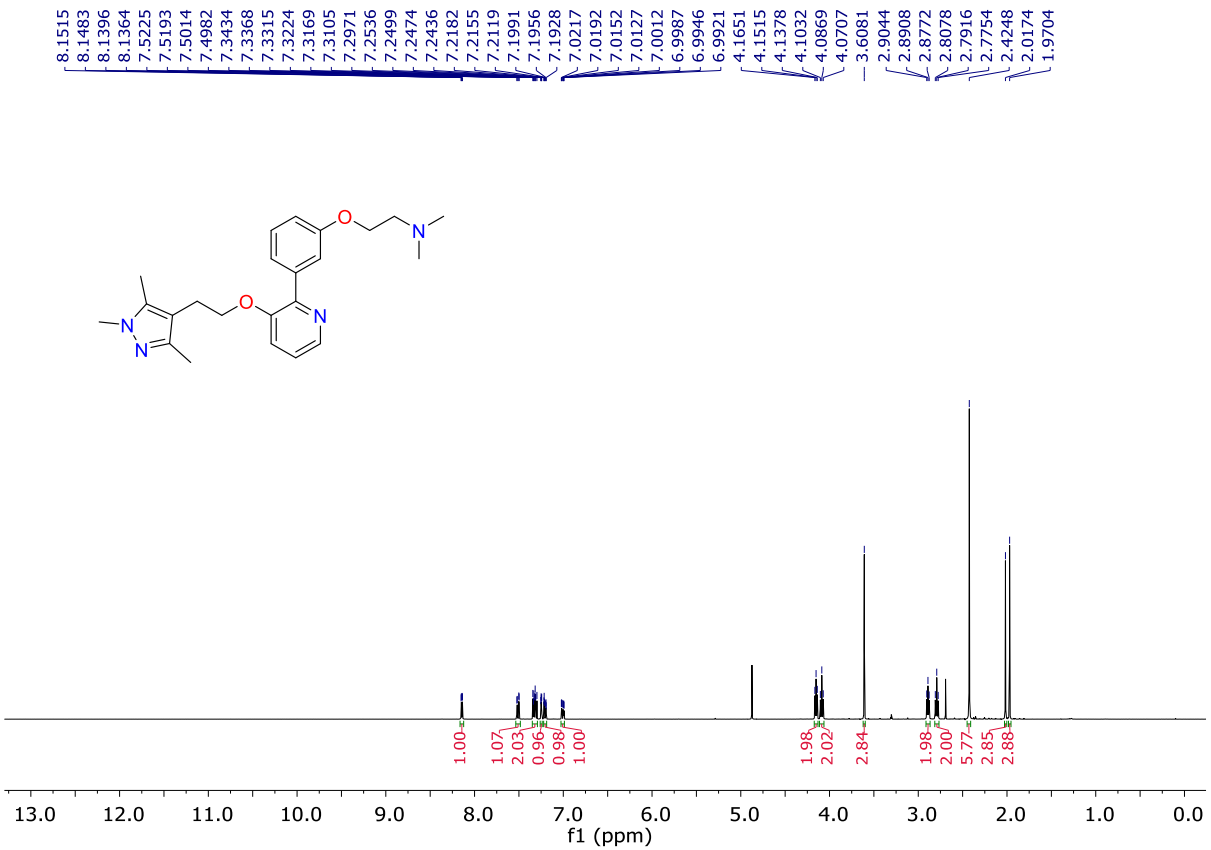
Supplementary Fig. 52. ^{13}C-NMR spectrum of compound 16e (CD_3OD, 100 MHz).



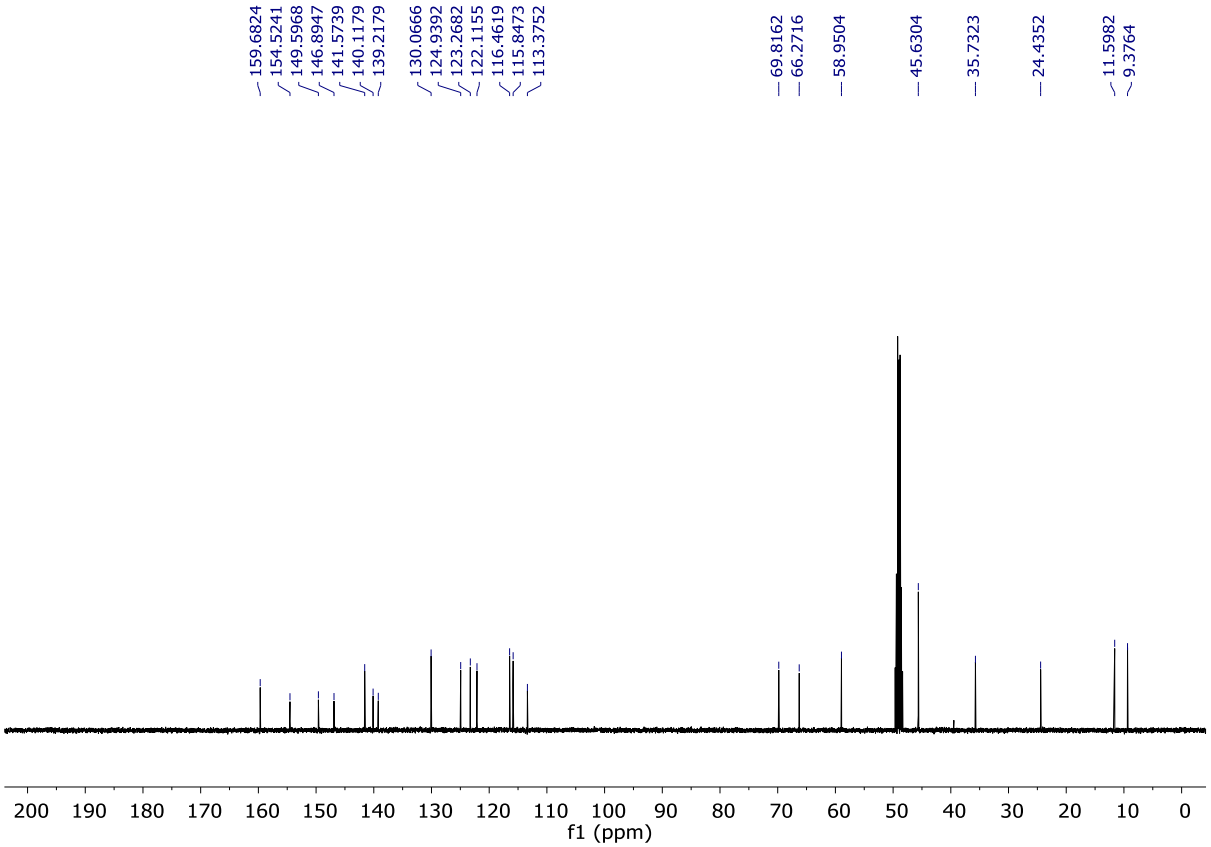
Supplementary Fig. 53. ^{1}H-NMR spectrum of compound 16f (CD_3OD, 400 MHz).



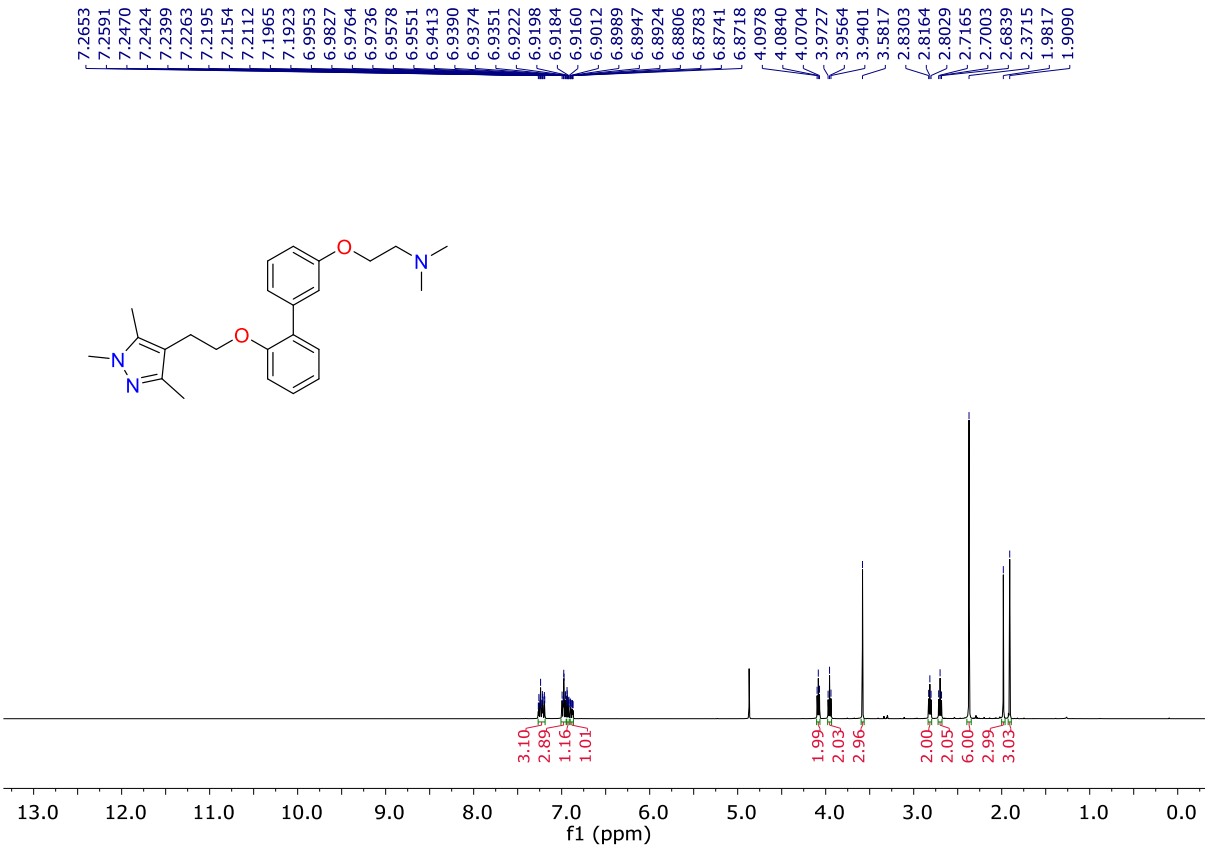
Supplementary Fig. 54. ^{13}C-NMR spectrum of compound 16f (CD_3OD, 100 MHz).



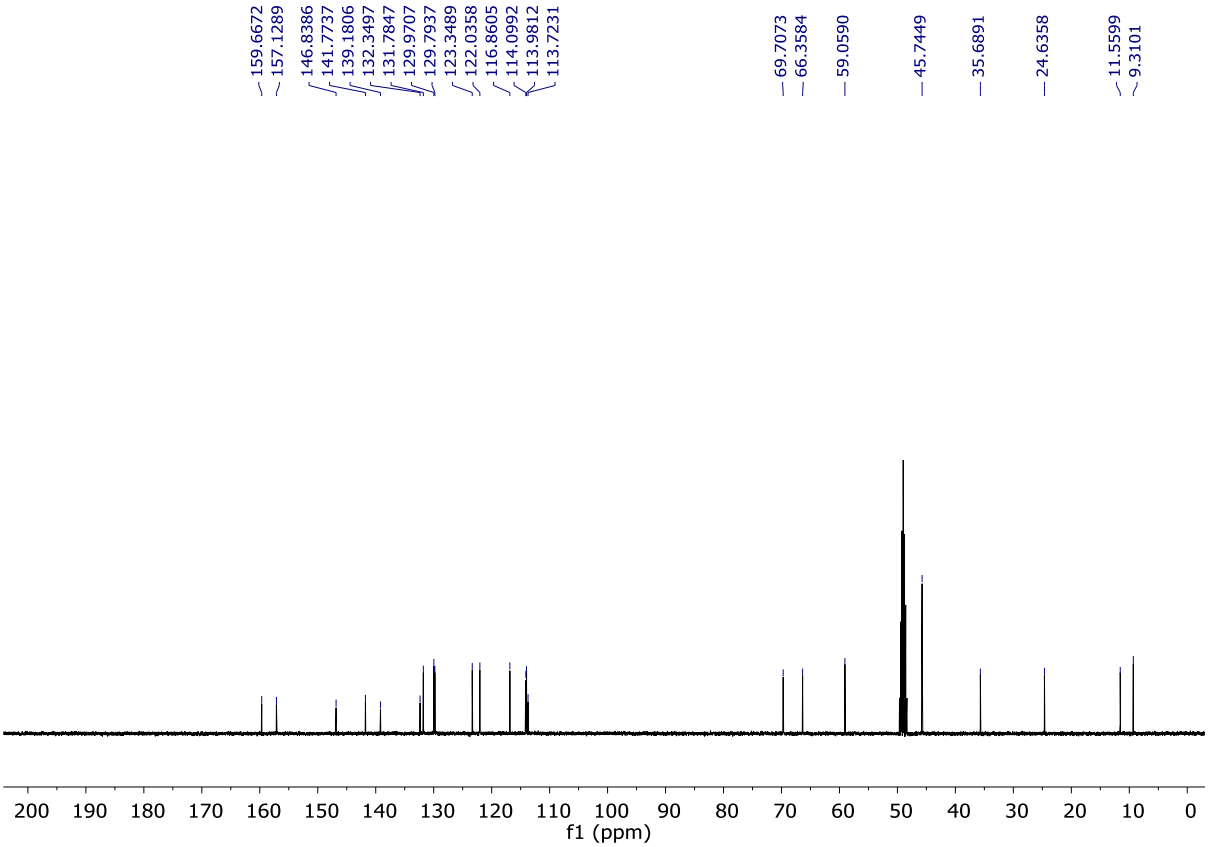
Supplementary Fig. 55. ^{1}H-NMR spectrum of compound 26a (CD_3OD, 400 MHz).



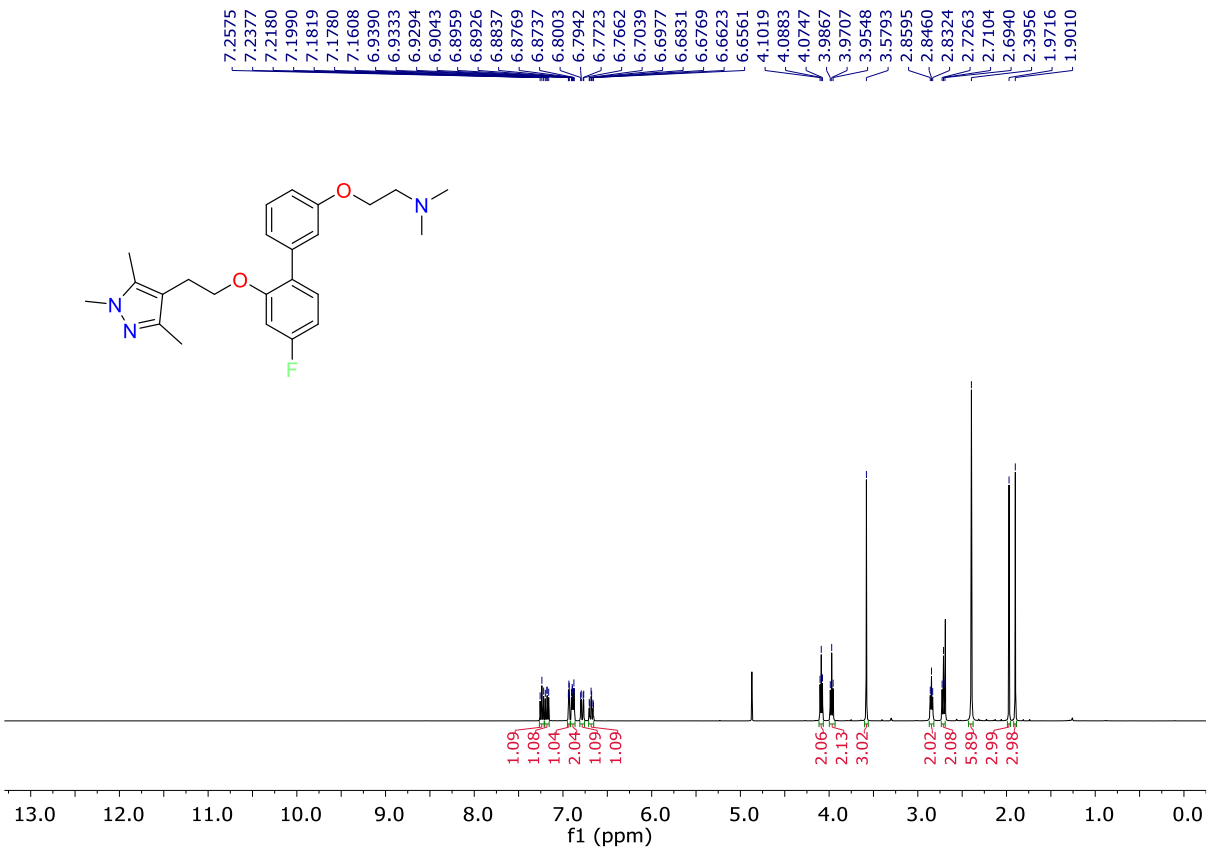
Supplementary Fig. 56. ^{13}C-NMR spectrum of compound 26a (CD_3OD, 100 MHz).



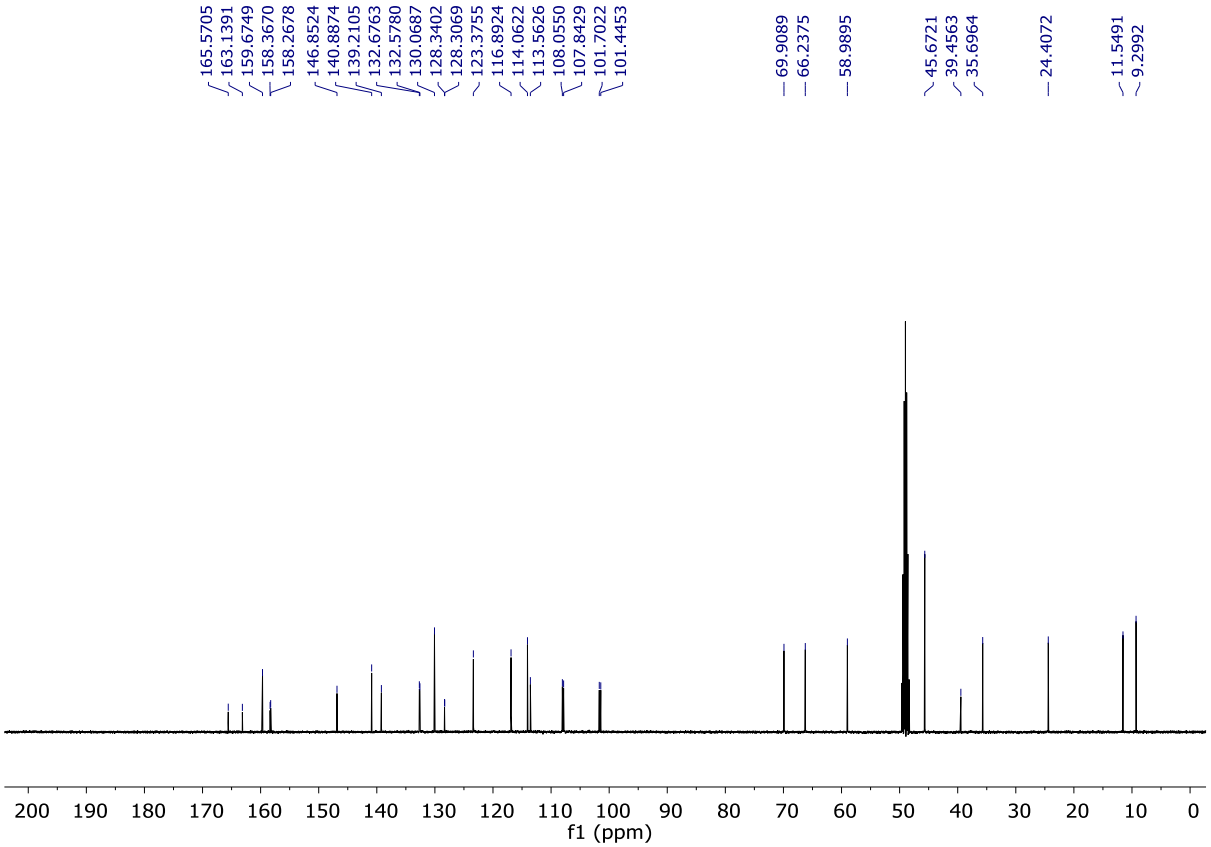
Supplementary Fig. 57. ^{1}H-NMR spectrum of compound 26b (CD_3OD, 400 MHz).



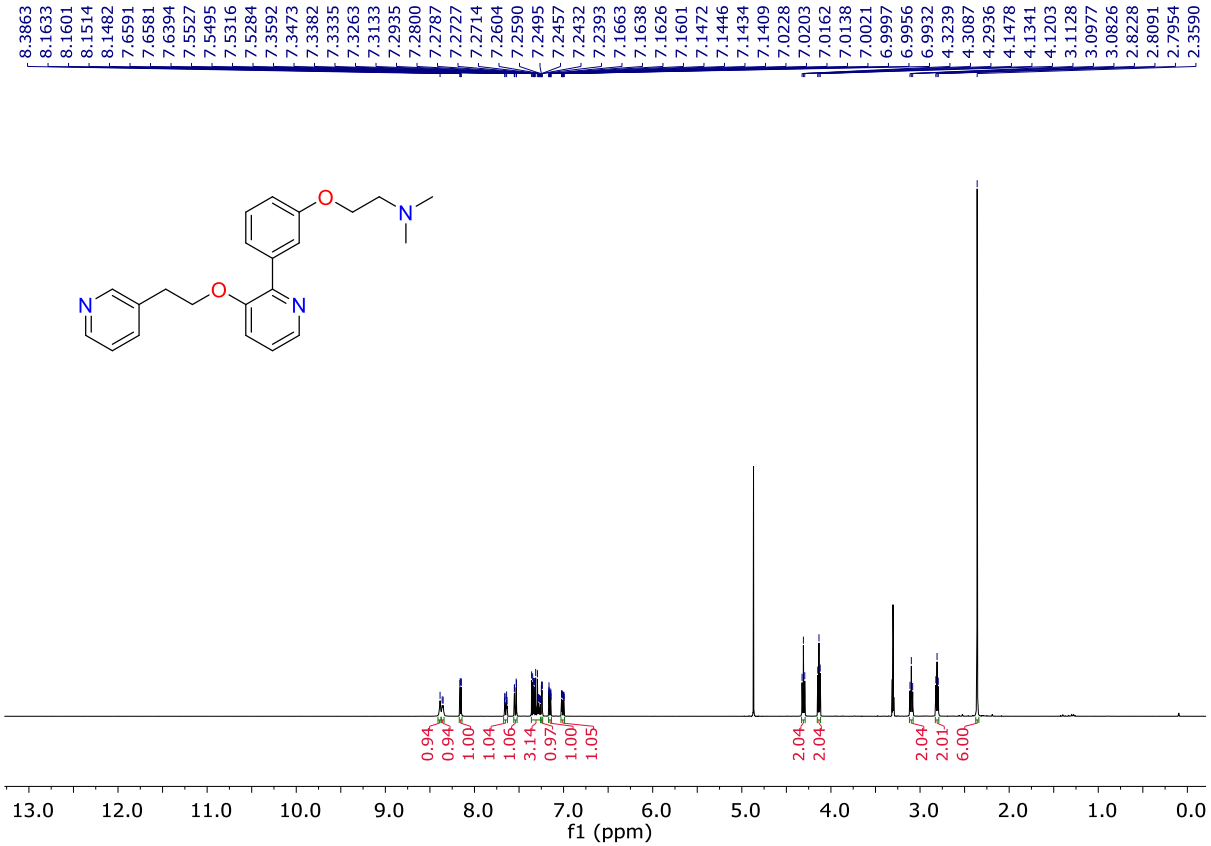
Supplementary Fig. 58. ^{13}C-NMR spectrum of compound 26b (CD_3OD, 100 MHz).



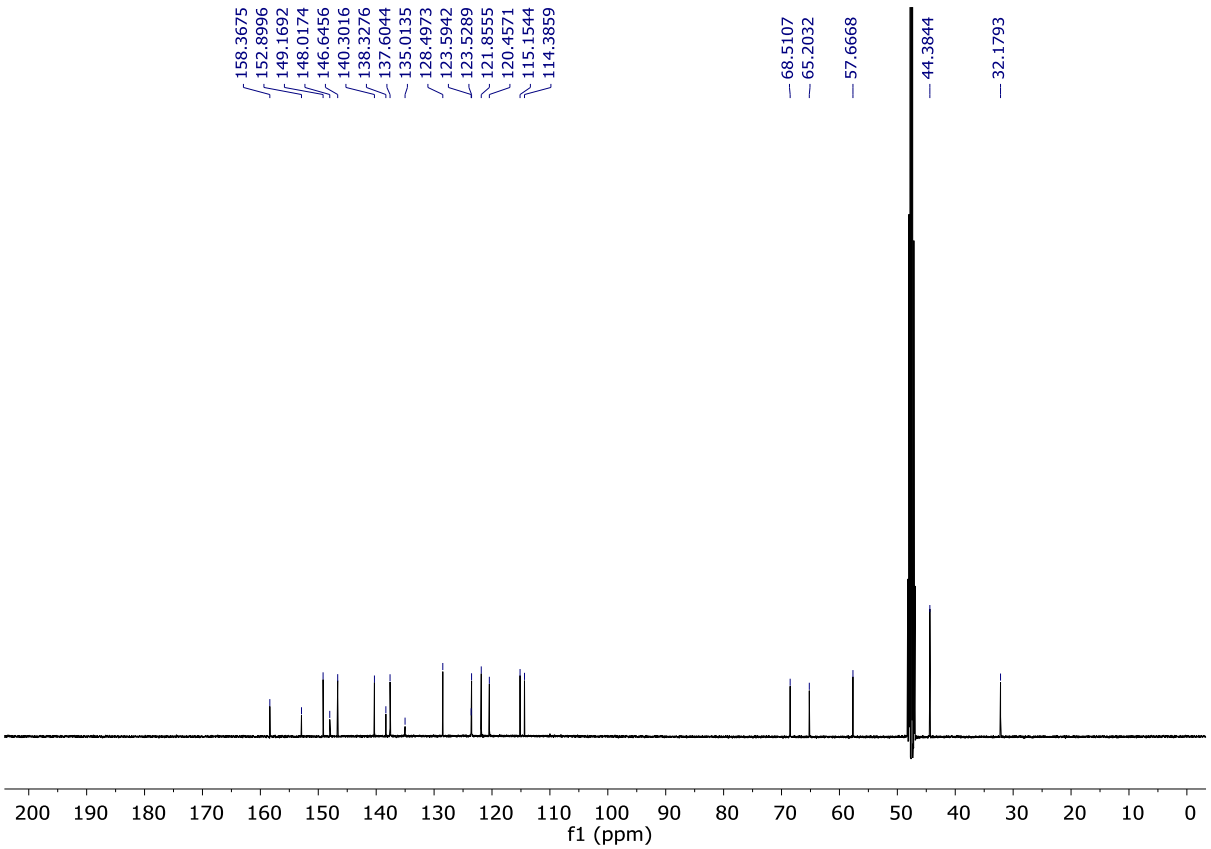
Supplementary Fig. 59. ^{1}H-NMR spectrum of compound 26c (CD_3OD, 400 MHz).



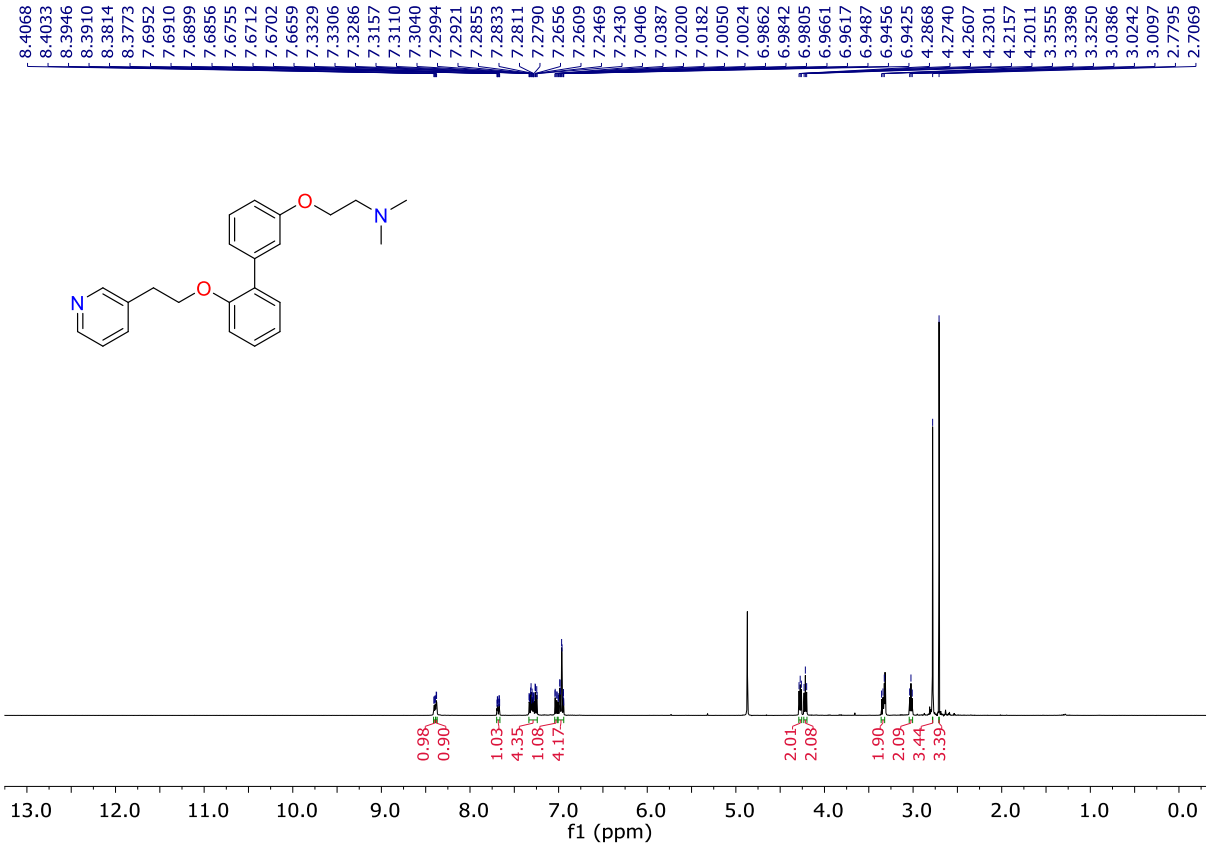
Supplementary Fig. 60. ^{13}C-NMR spectrum of compound 26c (CD_3OD, 100 MHz).



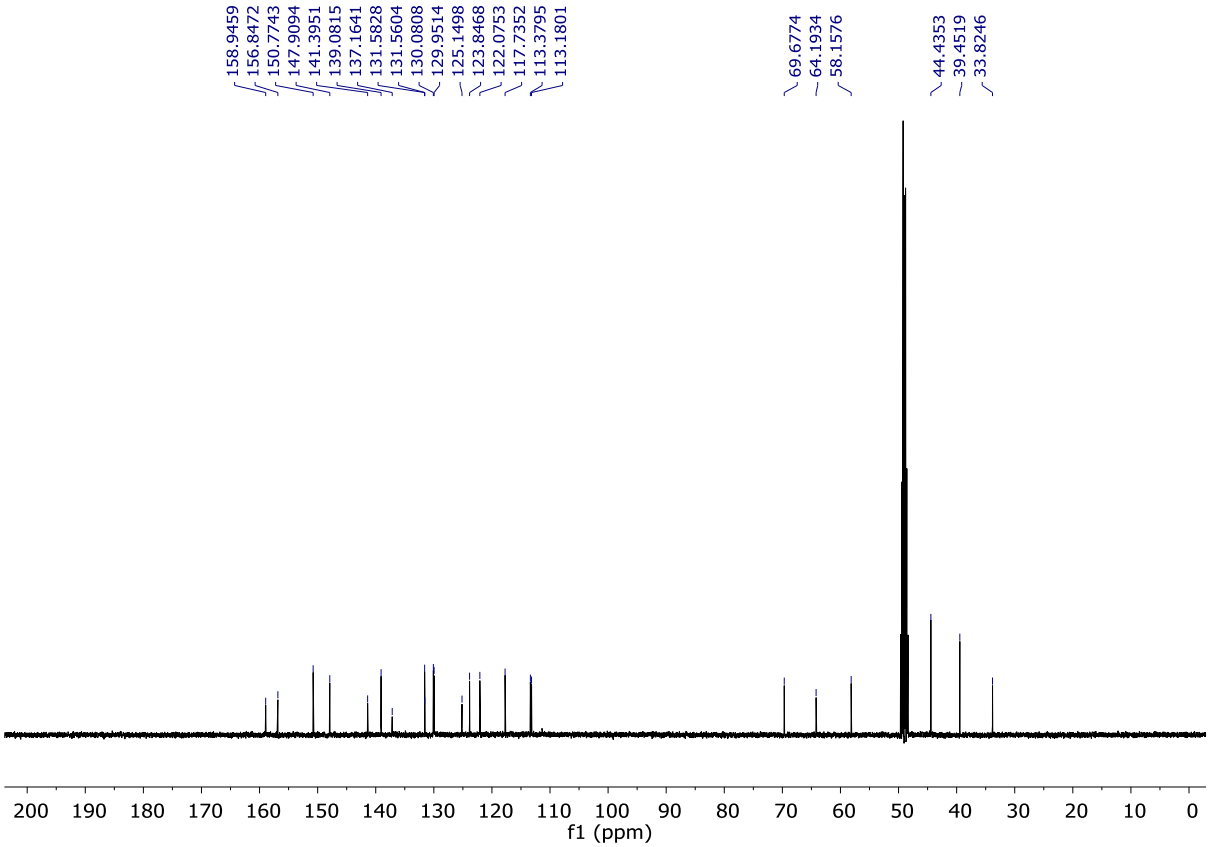
Supplementary Fig. 61. ^{1}H-NMR spectrum of compound 26d (CD_3OD, 400 MHz).



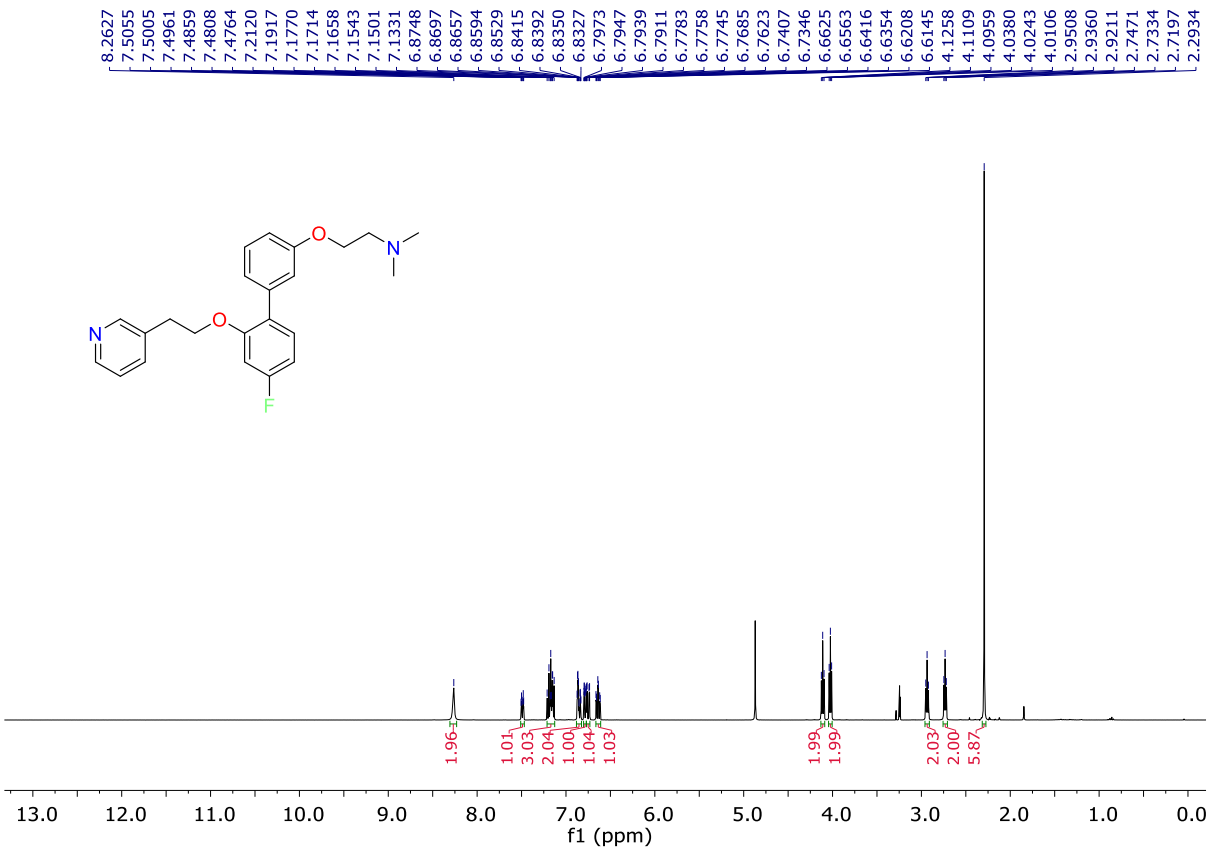
Supplementary Fig. 62. ^{13}C-NMR spectrum of compound 26d (CD_3OD, 100 MHz).



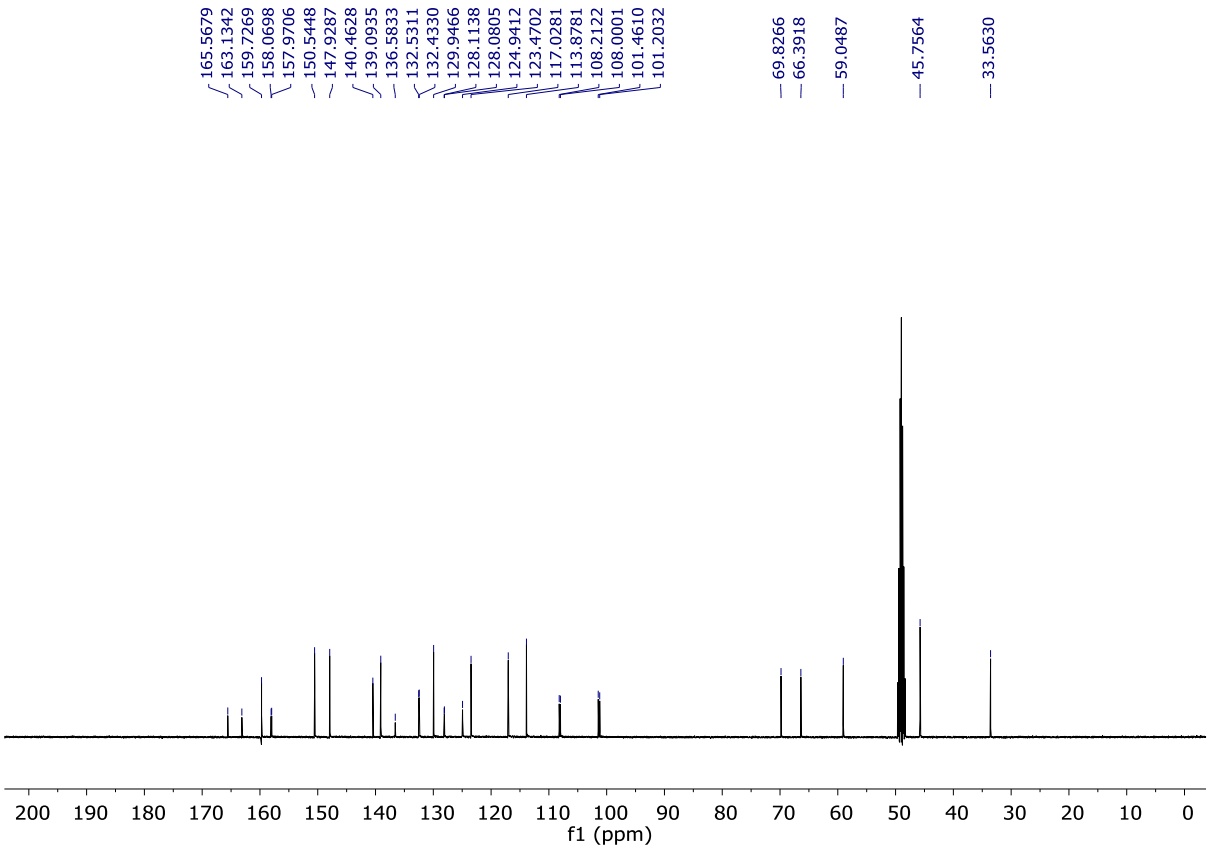
Supplementary Fig. 63. ^{1}H-NMR spectrum of compound 26e (CD_3OD, 400 MHz).



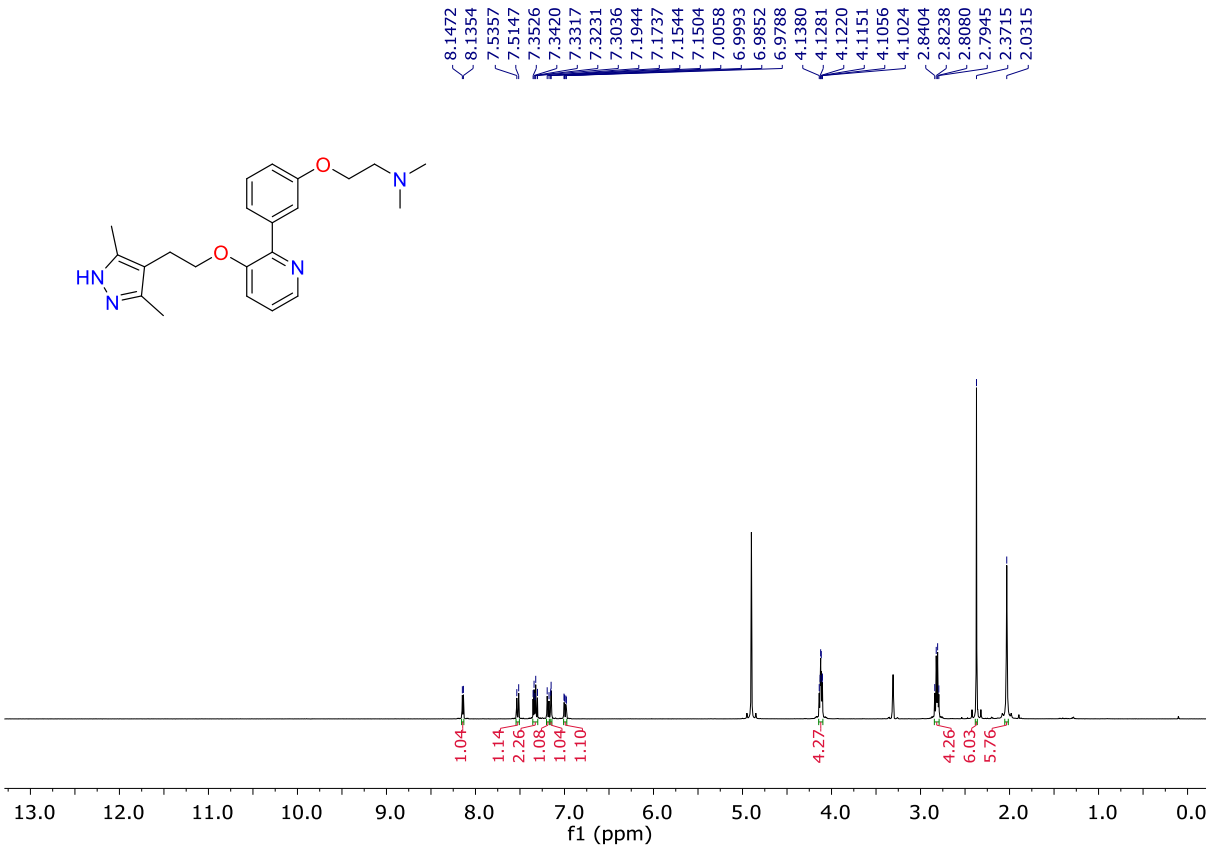
Supplementary Fig. 64. ^{13}C-NMR spectrum of compound 26e (CD_3OD, 100 MHz).



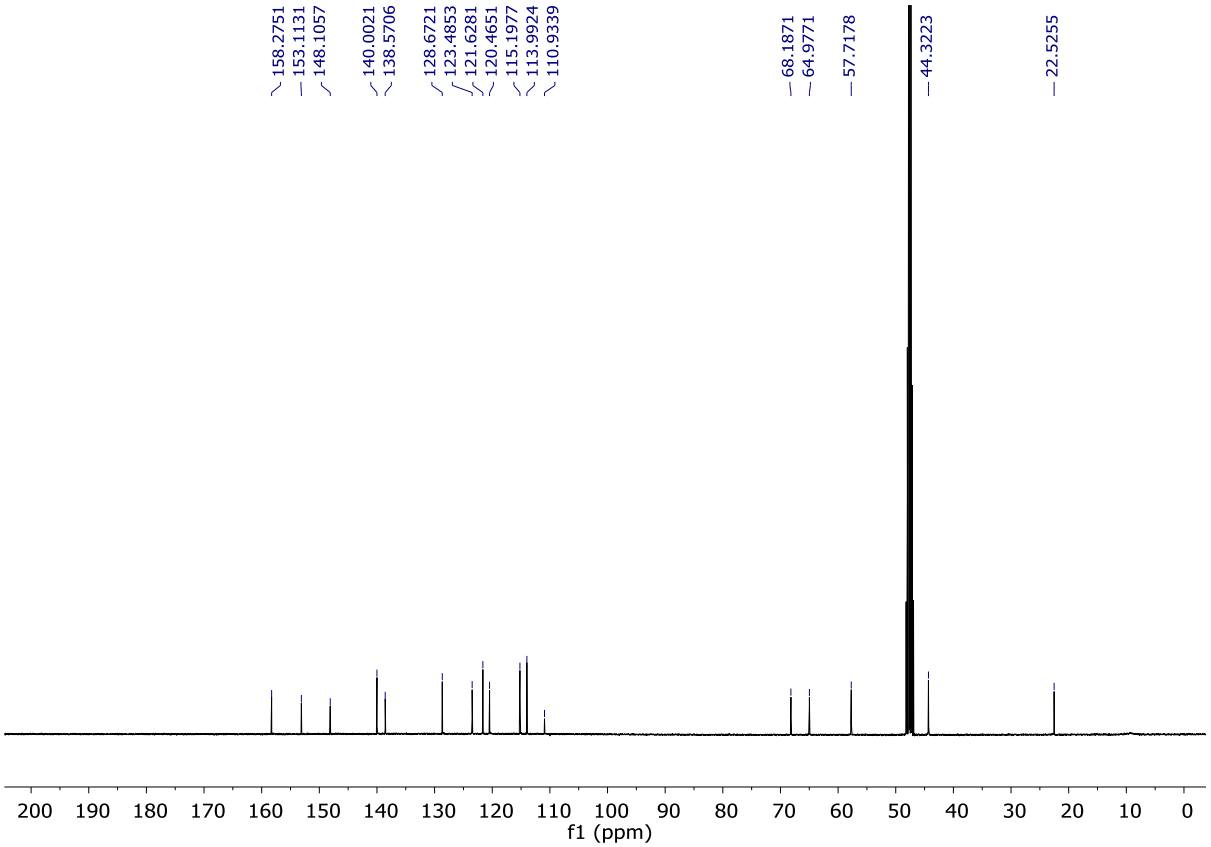
Supplementary Fig. 65. ^{1}H-NMR spectrum of compound 26f (CD_3OD, 400 MHz).



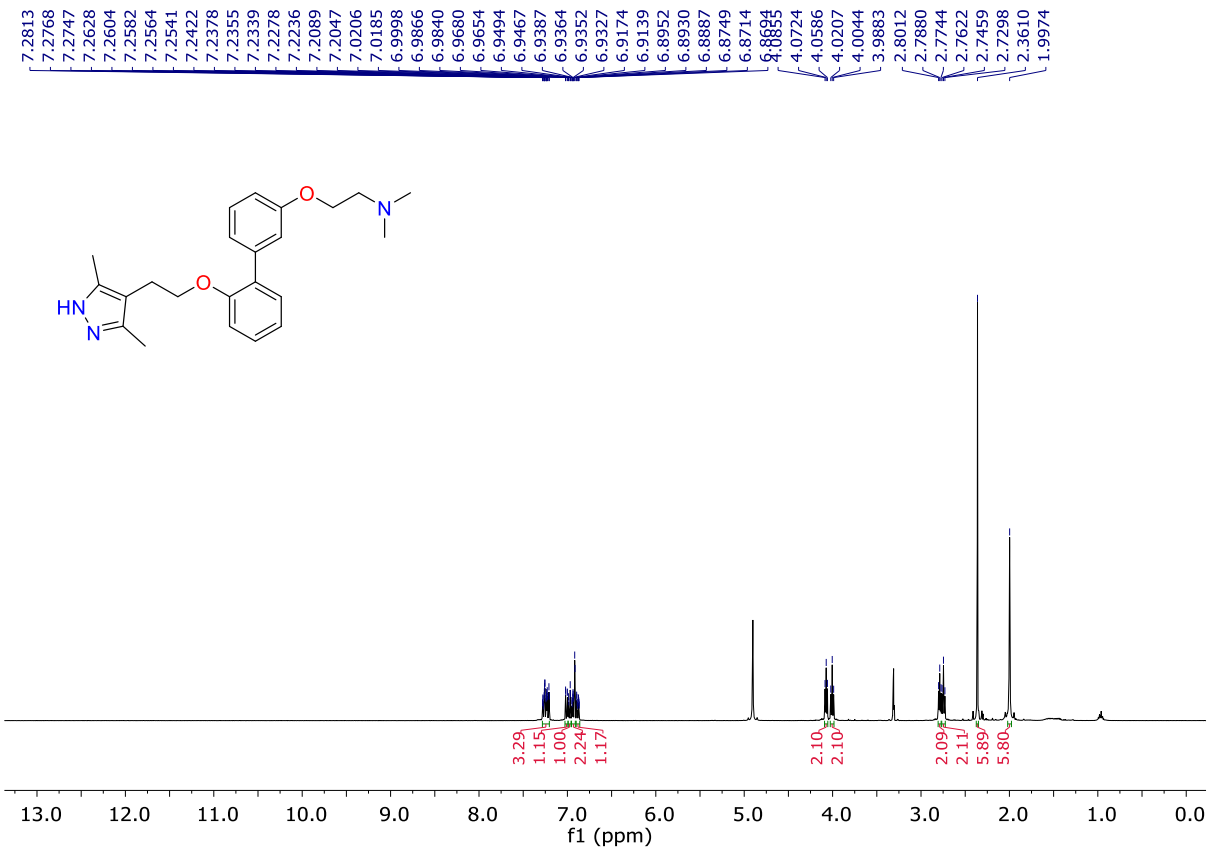
Supplementary Fig. 66. ^{13}C-NMR spectrum of compound 26f (CD_3OD, 100 MHz).



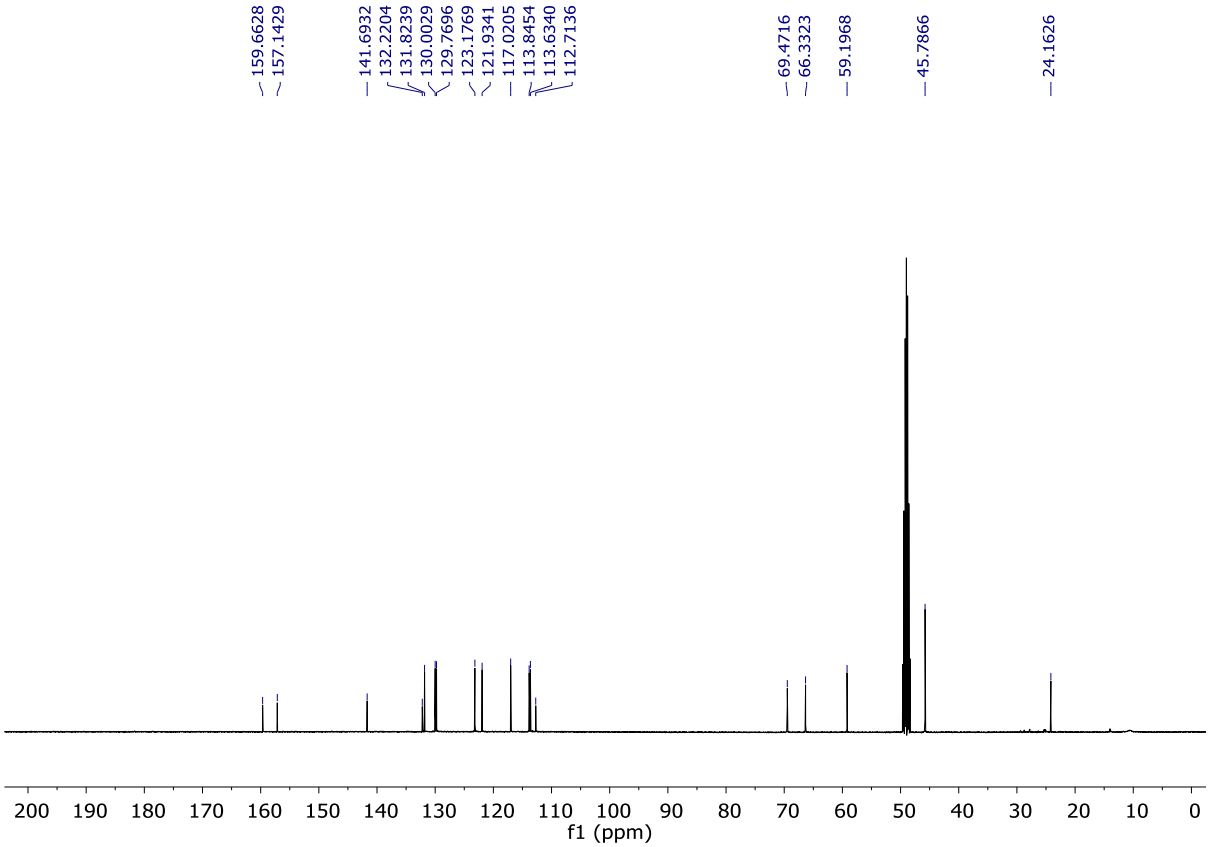
Supplementary Fig. 67. ^{1}H-NMR spectrum of compound 26g (CD_3OD, 400 MHz).



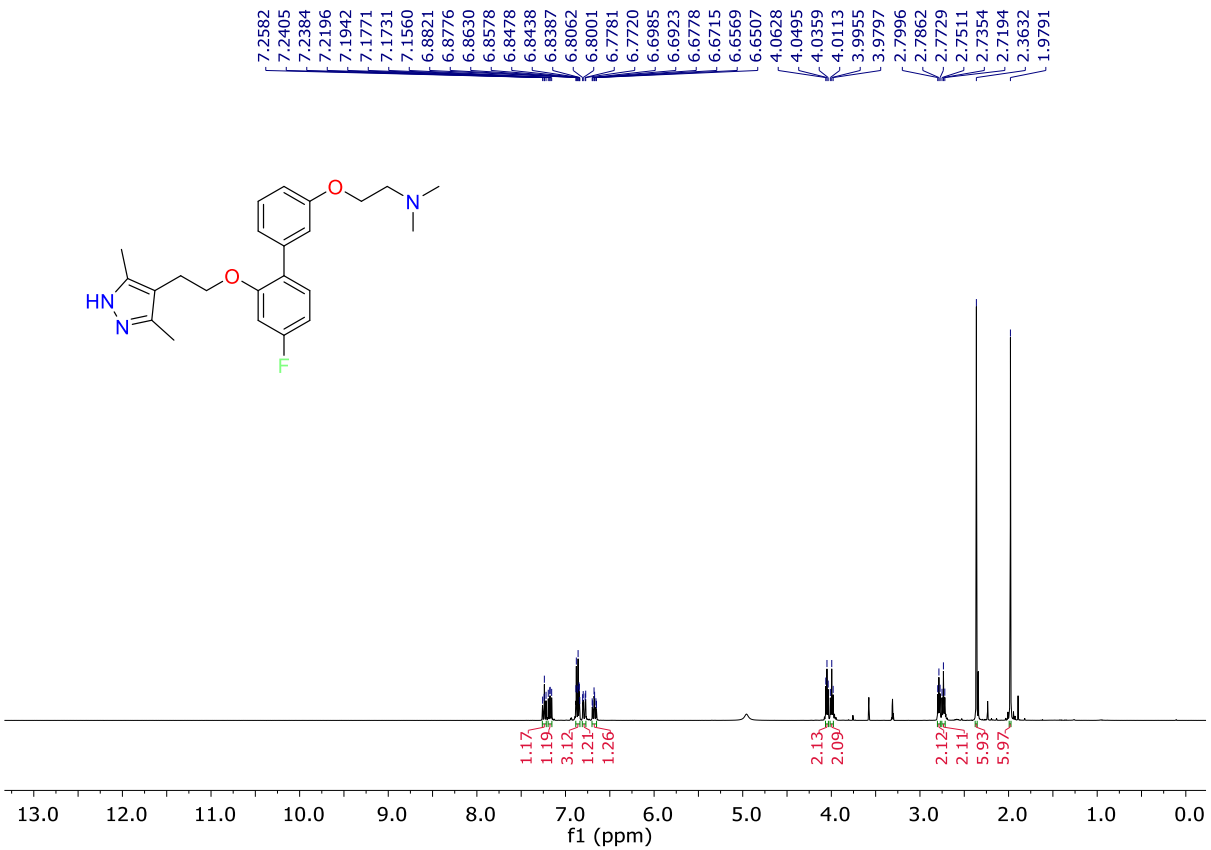
Supplementary Fig. 68. ^{13}C-NMR spectrum of compound 26g (CD_3OD, 100 MHz).



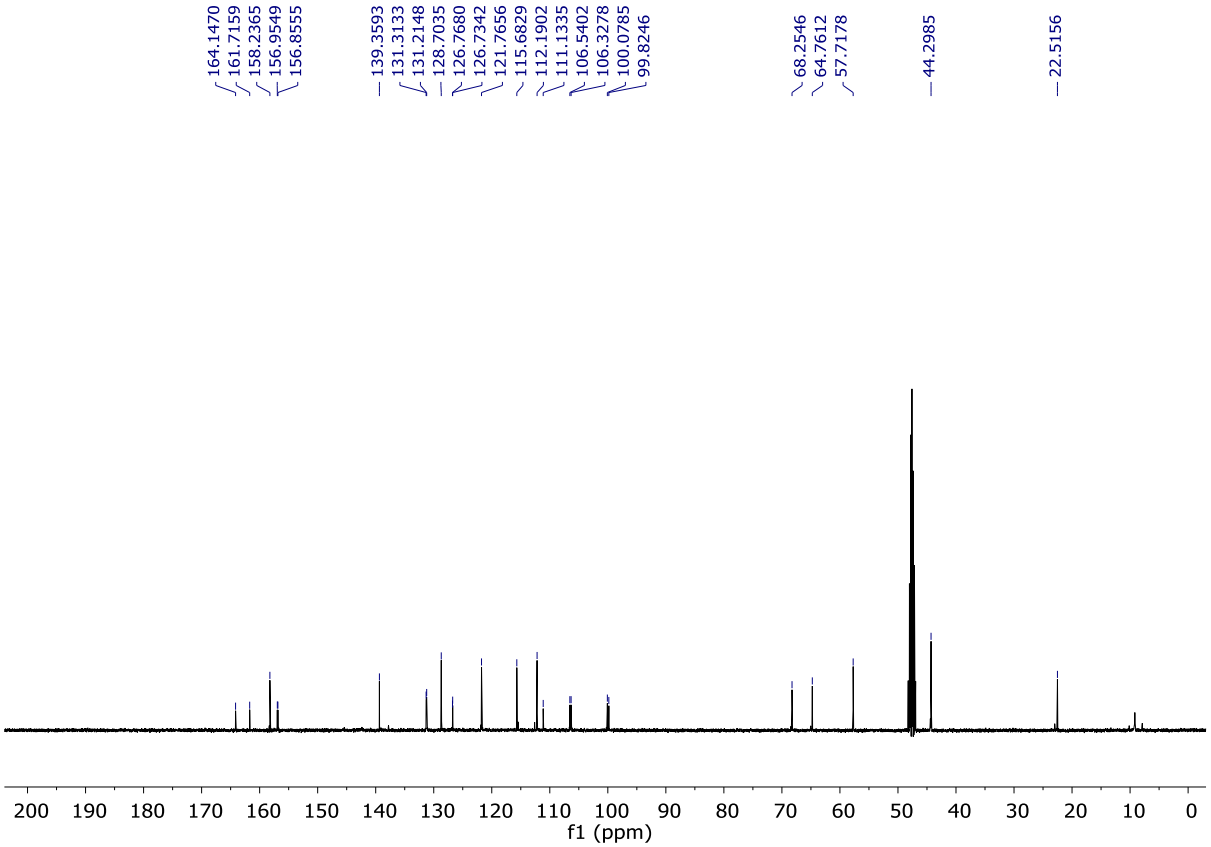
Supplementary Fig. 69. ^{1}H-NMR spectrum of compound 26h (CD_3OD, 400 MHz).



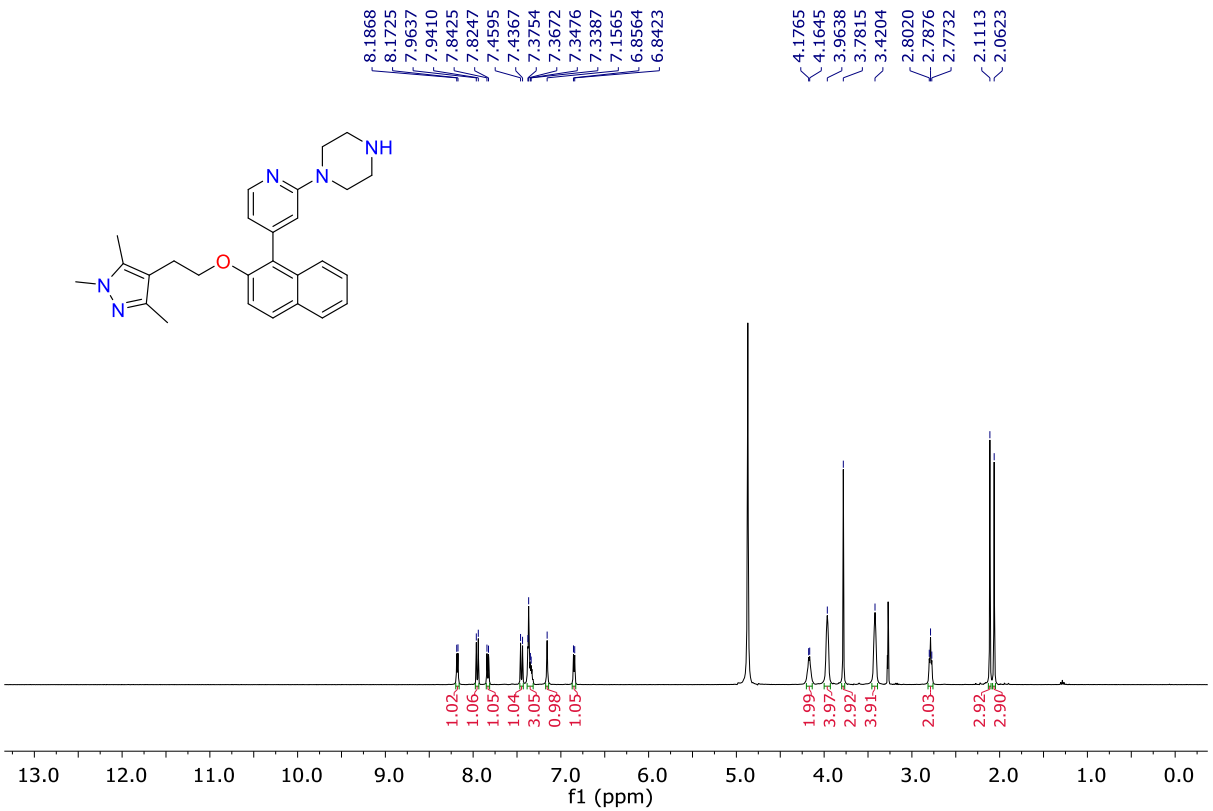
Supplementary Fig. 70. ^{13}C-NMR spectrum of compound 26h (CD_3OD, 100 MHz).



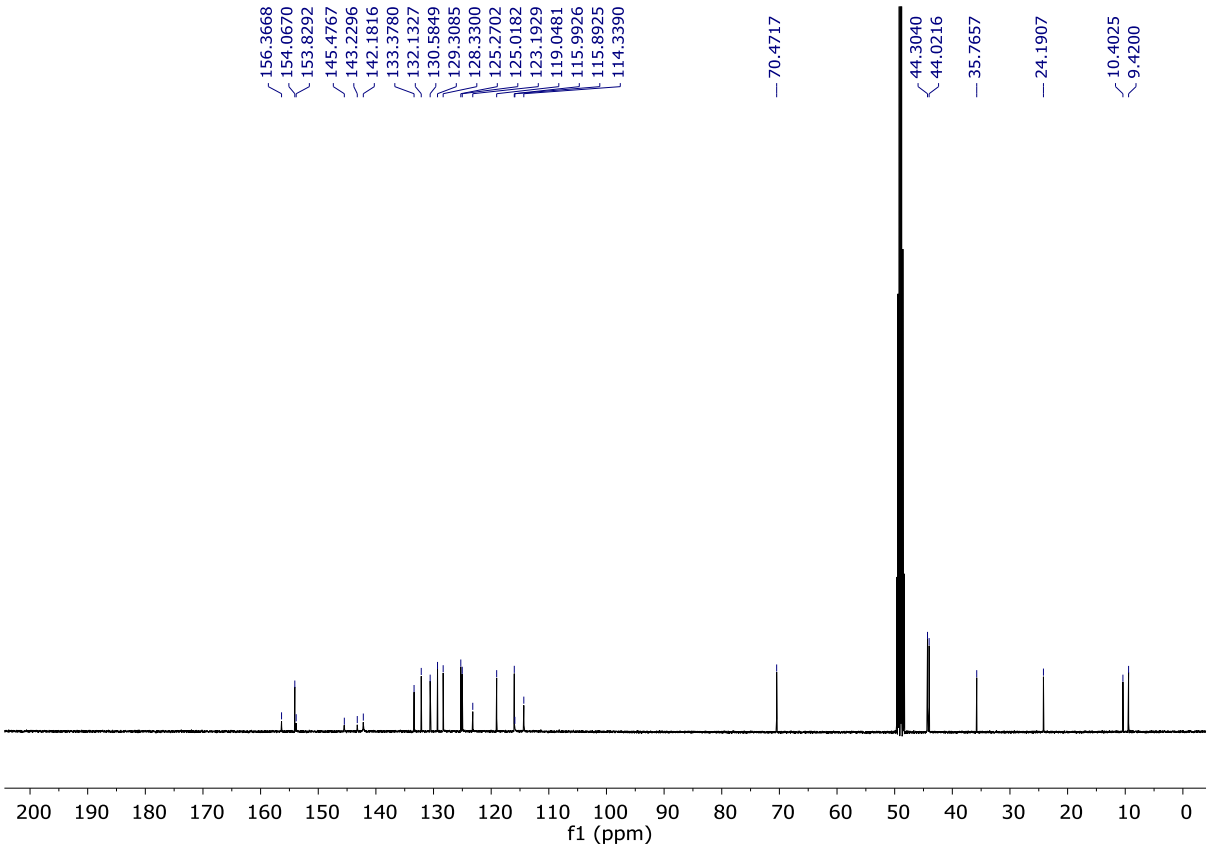
Supplementary Fig. 71. ^{1}H-NMR spectrum of compound 26i (CD_3OD, 400 MHz).



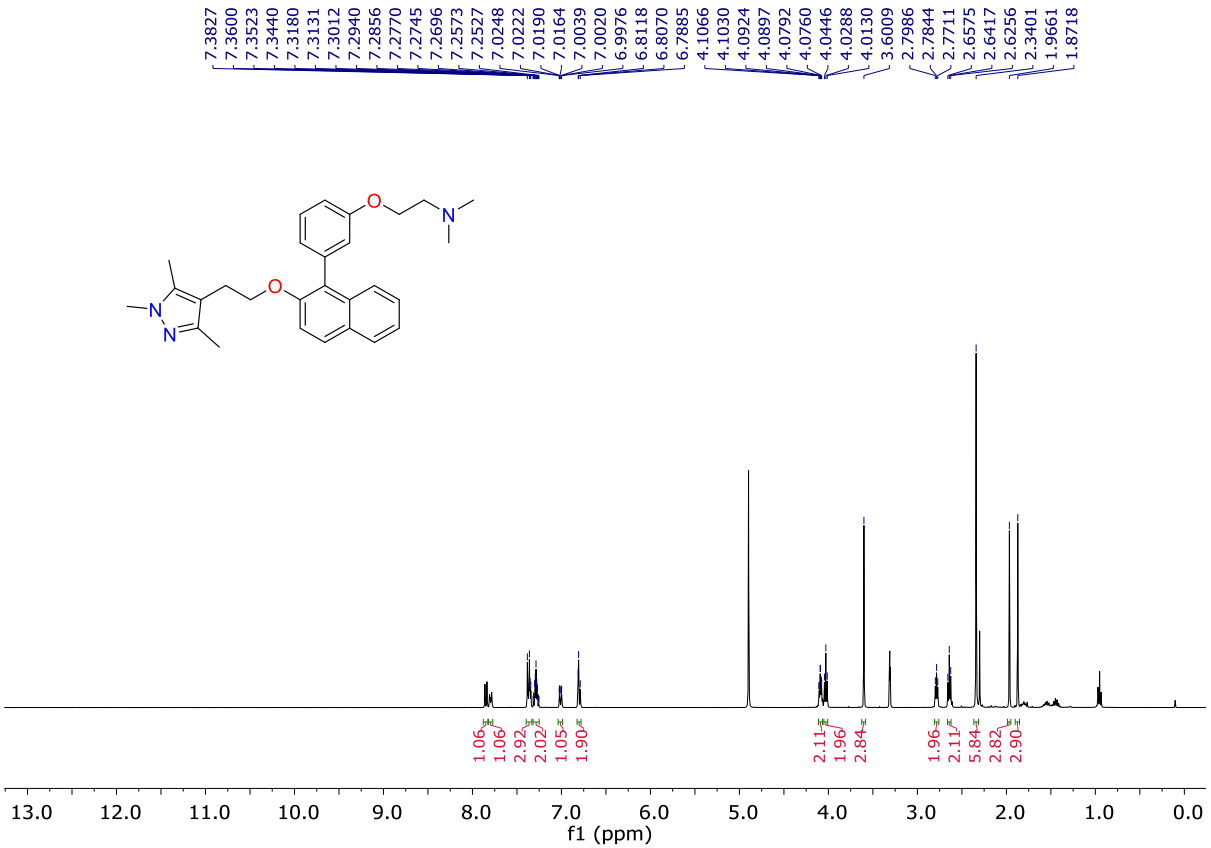
Supplementary Fig. 72. ^{13}C-NMR spectrum of compound 26i (CD_3OD, 100 MHz).



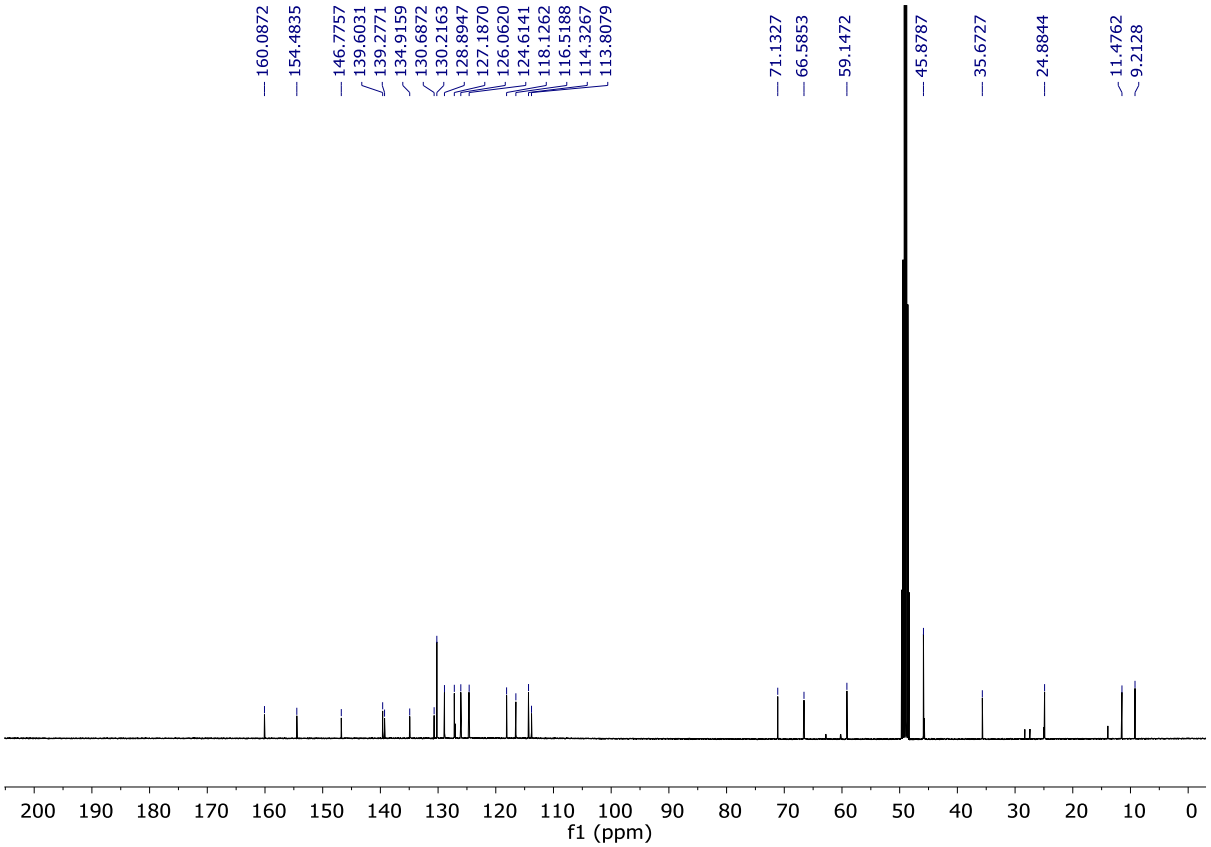
Supplementary Fig. 73. ^{1}H-NMR spectrum of compound 30a (CD_3OD, 400 MHz).



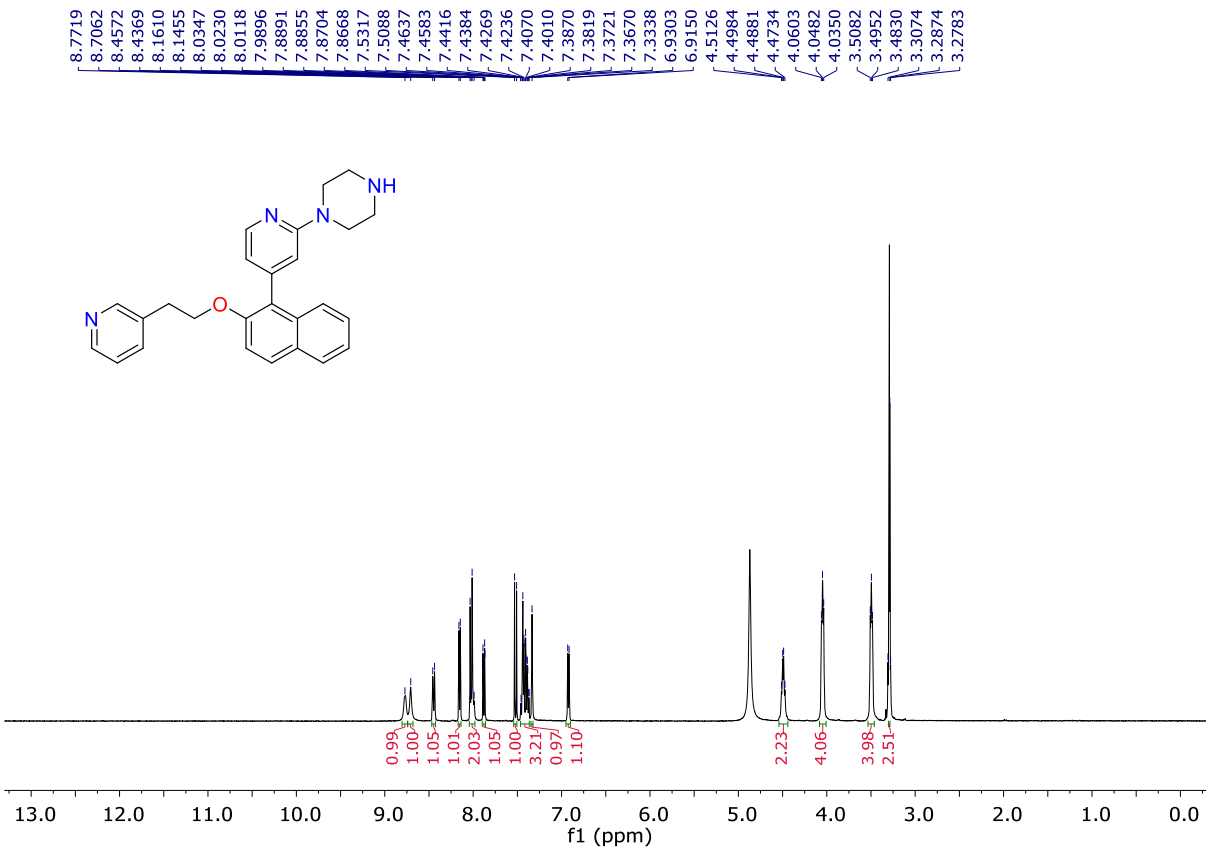
Supplementary Fig. 74. ^{13}C-NMR spectrum of compound 30a (CD_3OD, 100 MHz).



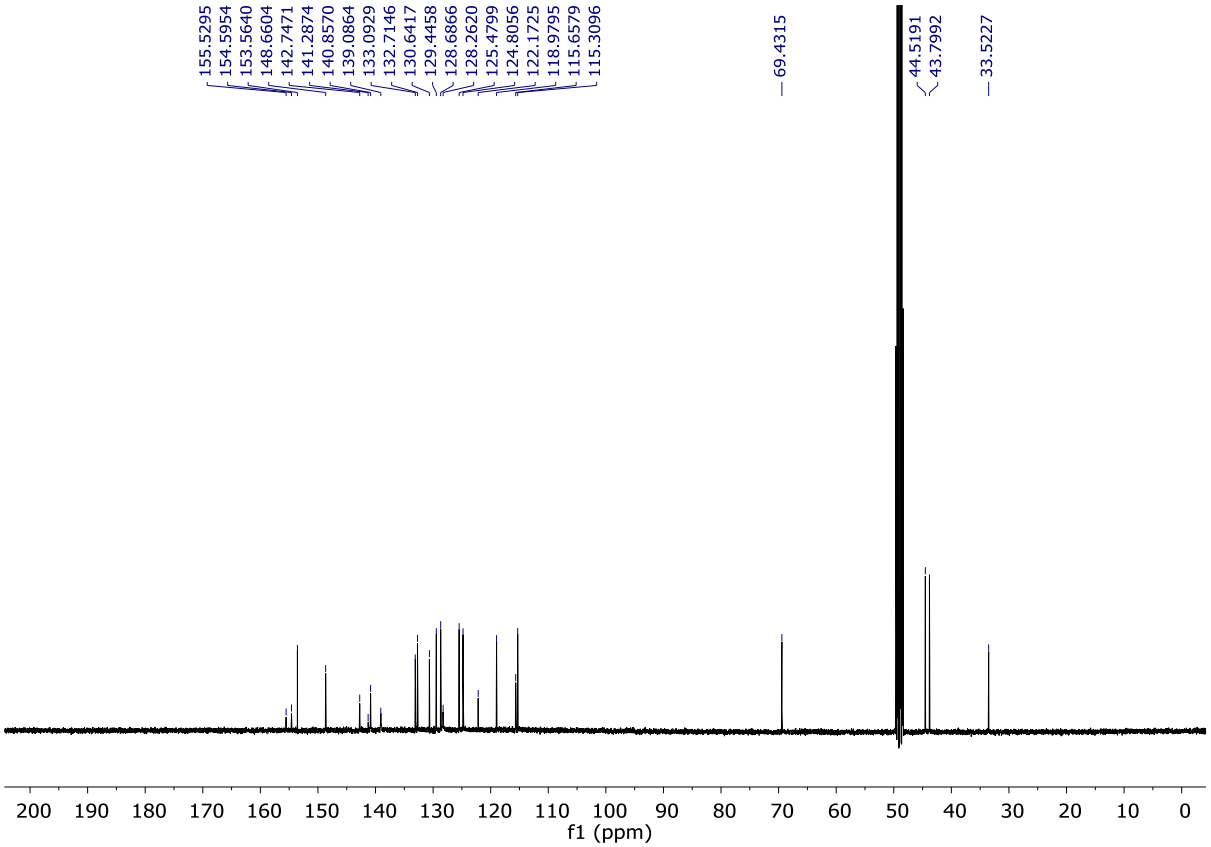
Supplementary Fig. 75. ^{1}H-NMR spectrum of compound 30b (CD_3OD, 400 MHz).



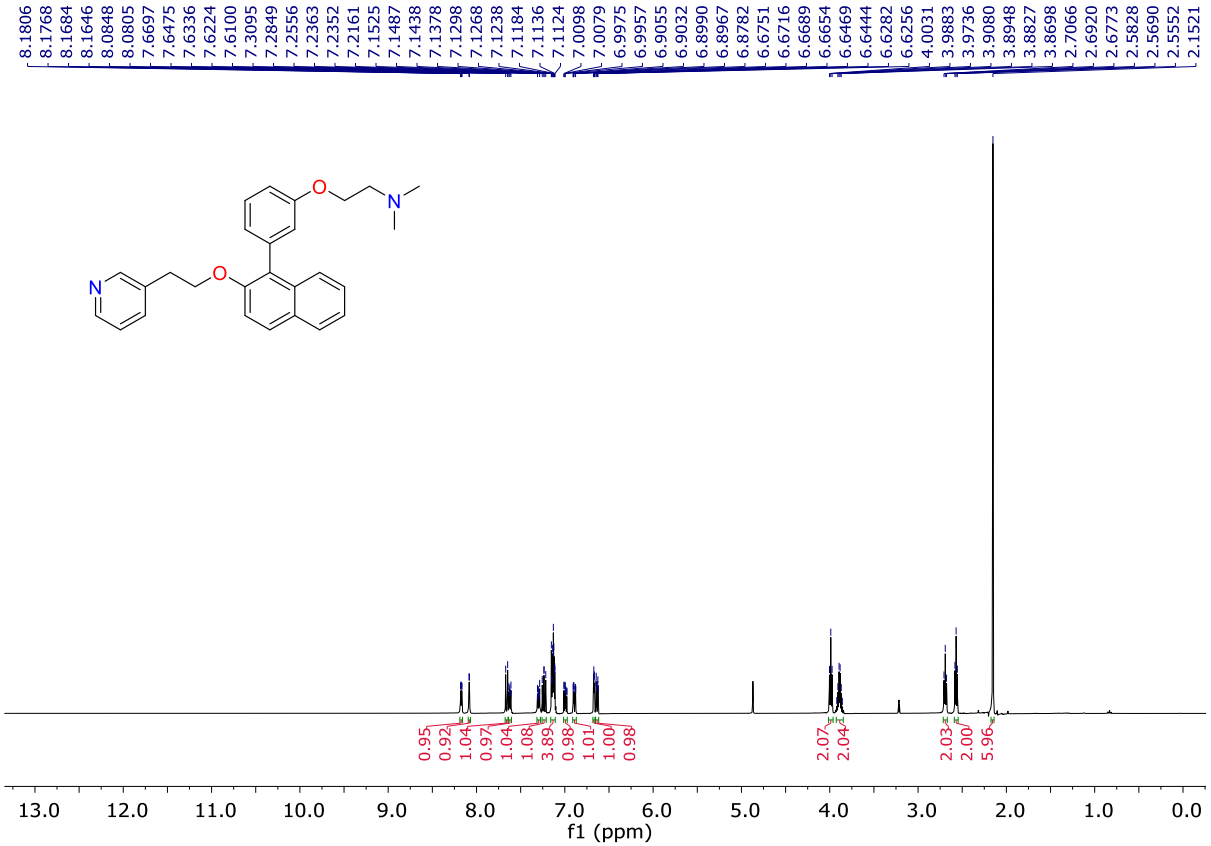
Supplementary Fig. 76. ^{13}C-NMR spectrum of compound 30b (CD_3OD, 100 MHz).



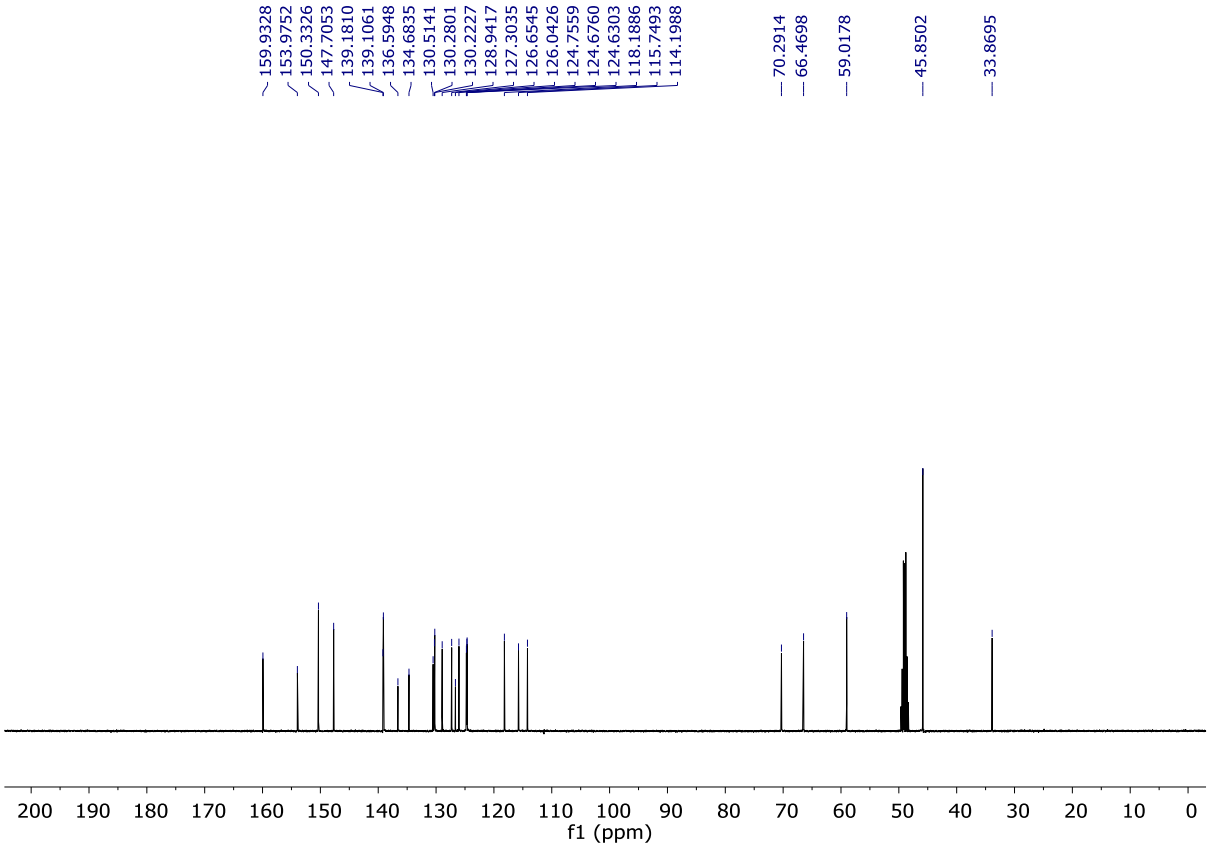
Supplementary Fig. 77. ^{1}H-NMR spectrum of compound 30c (CD_3OD, 400 MHz).



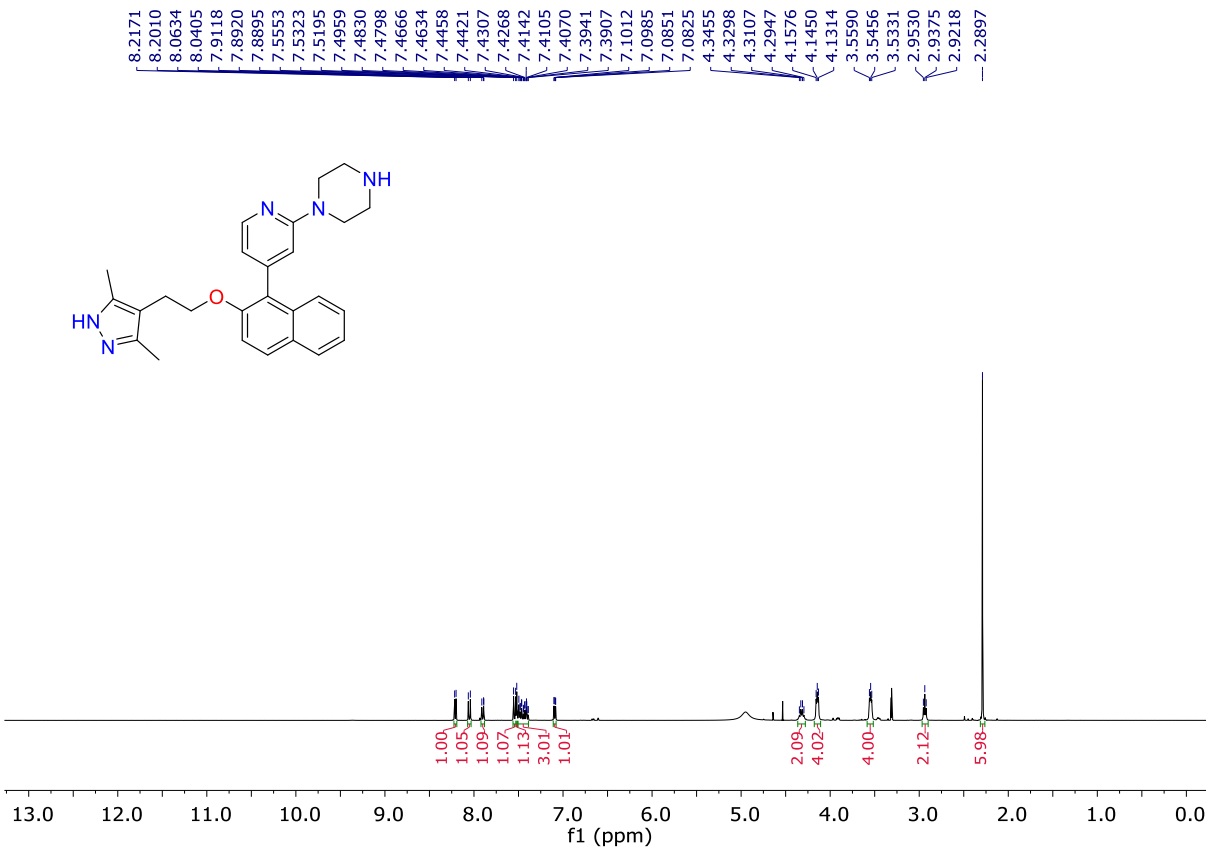
Supplementary Fig. 78. ^{13}C-NMR spectrum of compound 30c (CD_3OD, 100 MHz).



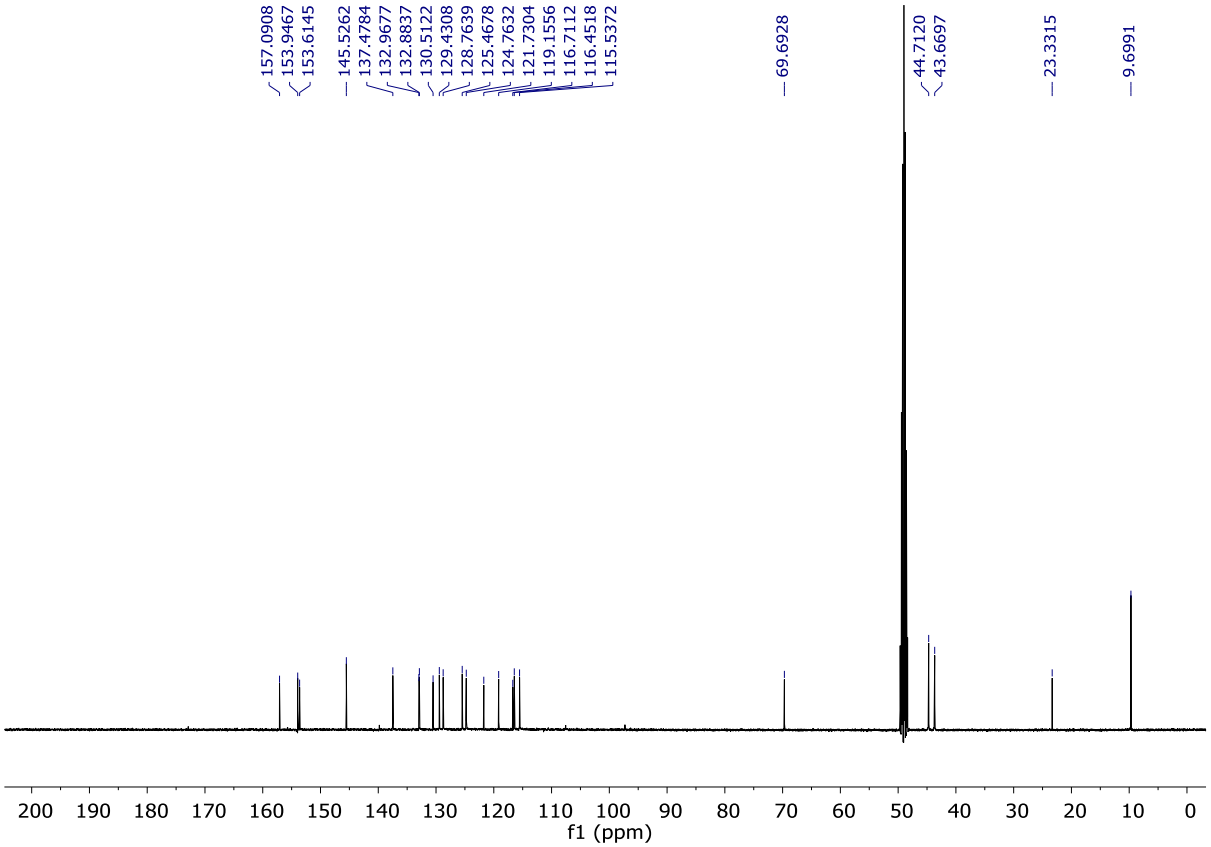
Supplementary Fig. 79. ^{1}H-NMR spectrum of compound 30d (CD_3OD, 400 MHz).



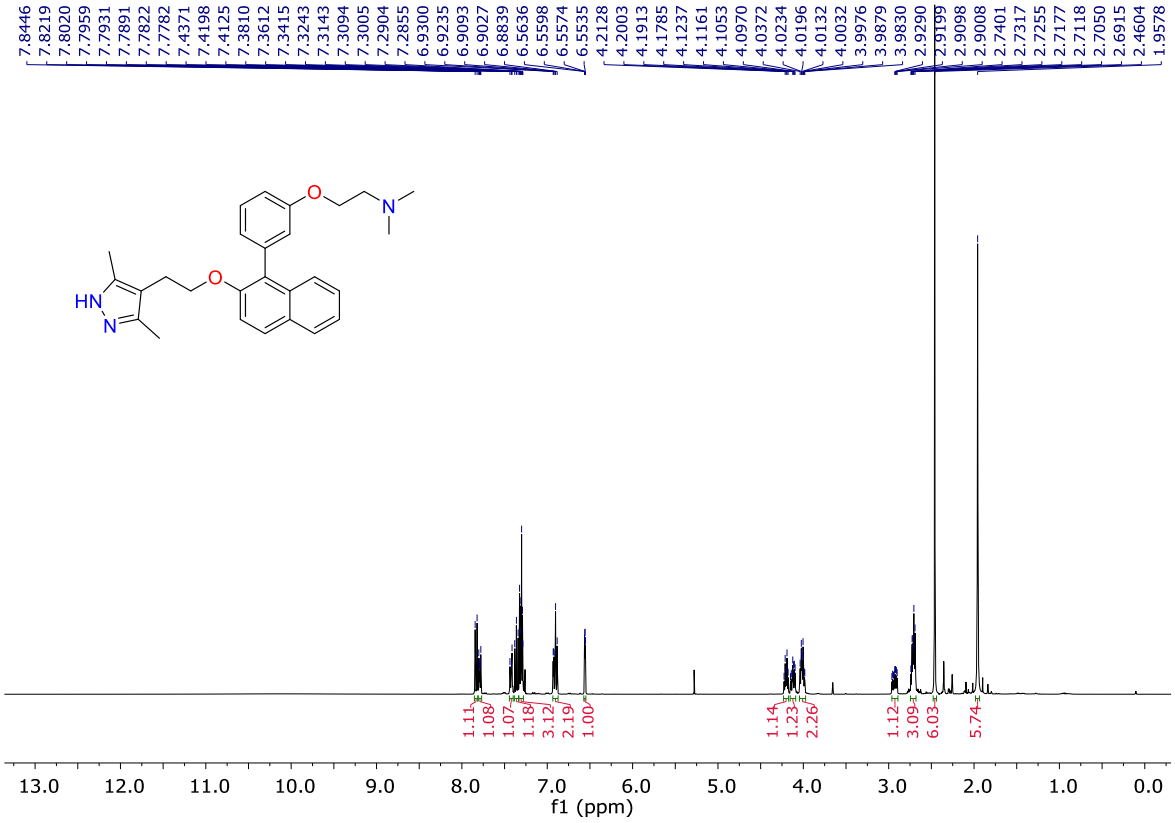
Supplementary Fig. 80. ^{13}C-NMR spectrum of compound 30d (CD_3OD, 100 MHz).



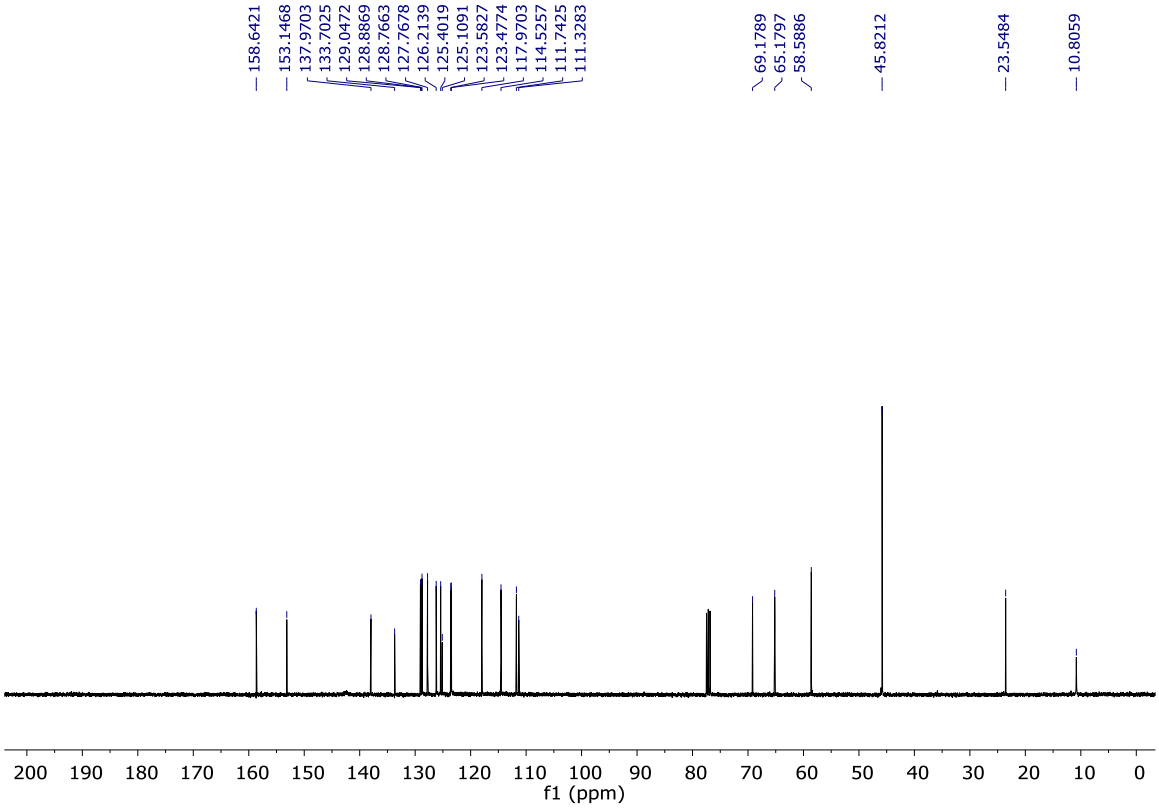
Supplementary Fig. 81. ^{1}H-NMR spectrum of compound 30e (CD_3OD, 400 MHz).



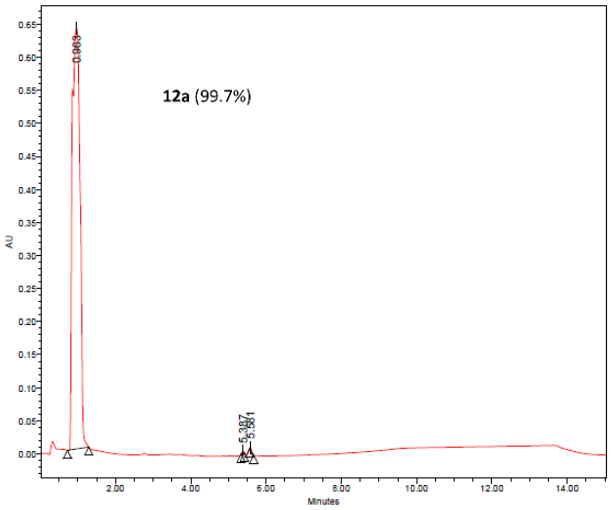
Supplementary Fig. 82. ^{13}C-NMR spectrum of compound 30e (CD_3OD, 100 MHz).



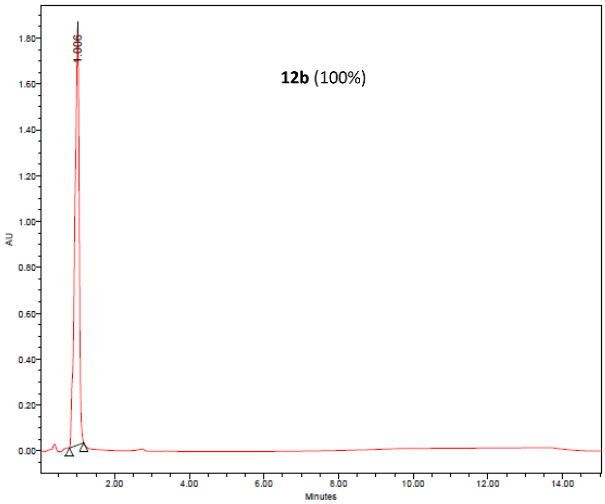
Supplementary Fig. 83. ^{1}H-NMR spectrum of compound 30f (CD_3OD, 400 MHz).



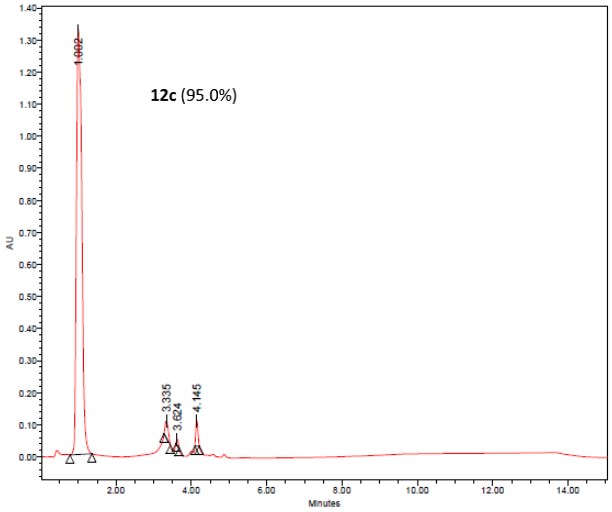
Supplementary Fig. 84. ^{13}C-NMR spectrum of compound 30f (CD_3OD, 100 MHz).



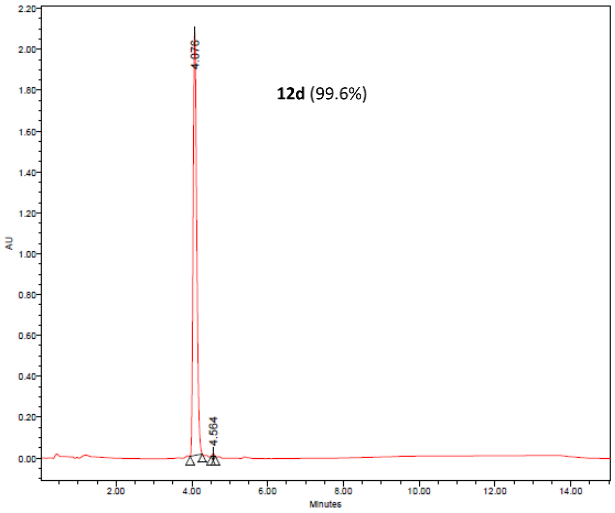
12a (99.7%)



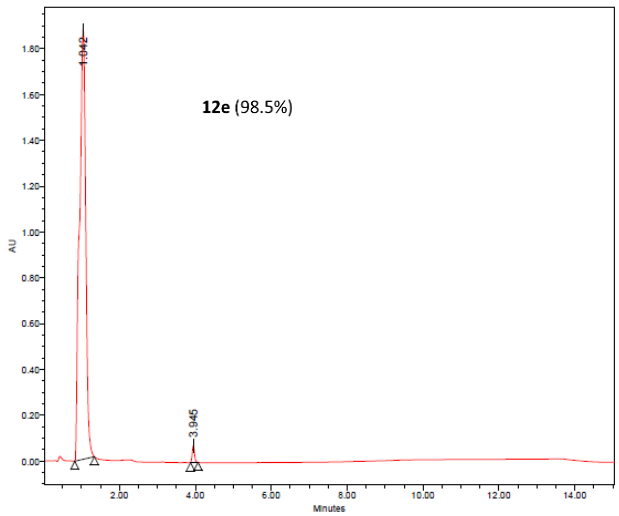
12b (100%)



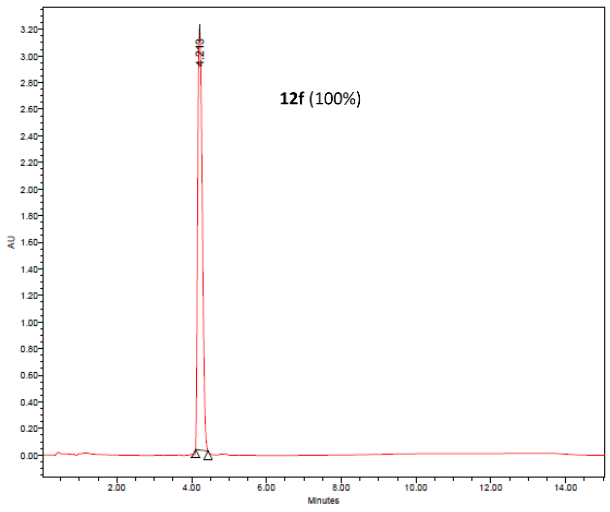
12c (95.0%)



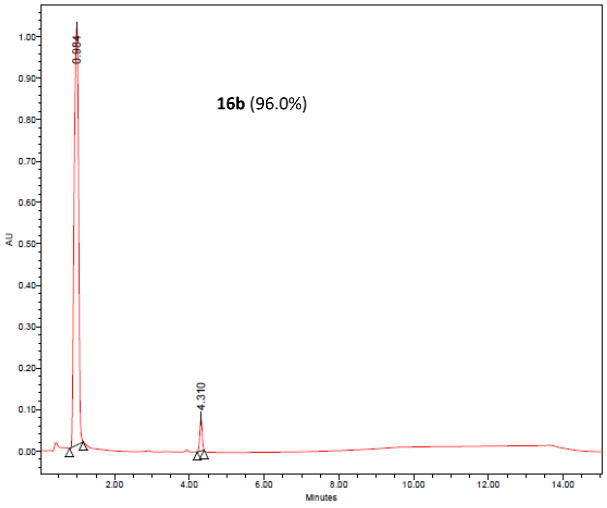
12d (99.6%)



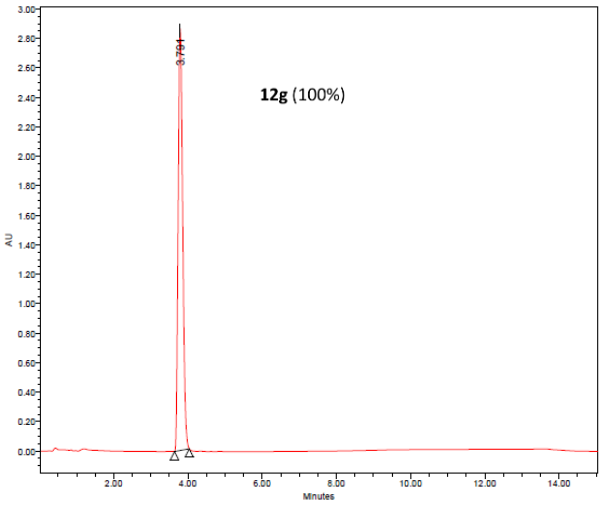
12e (98.5%)



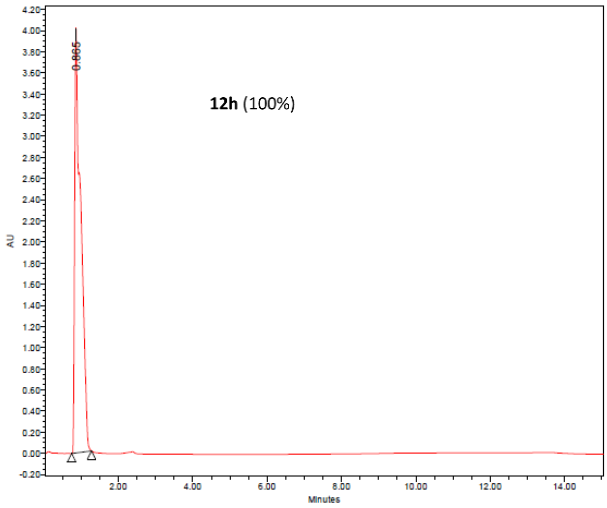
12f (100%)



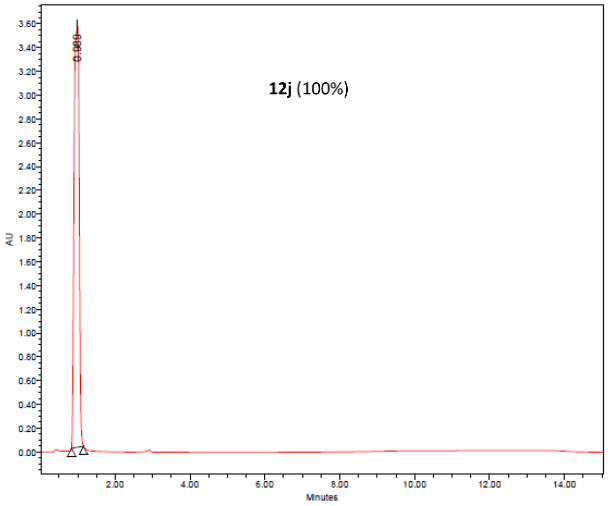
16b (96.0%)



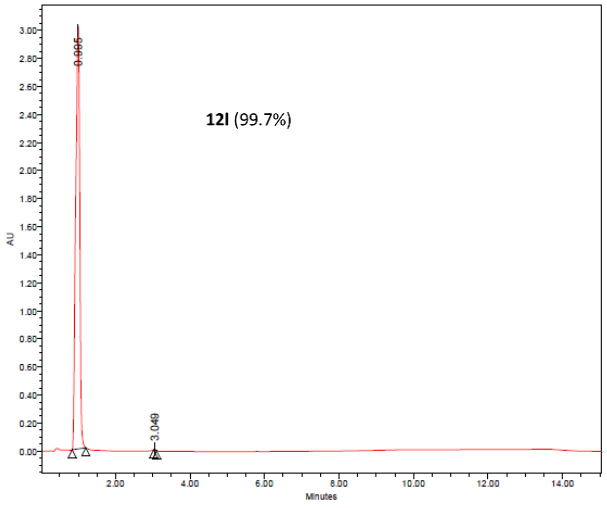
12g (100%)



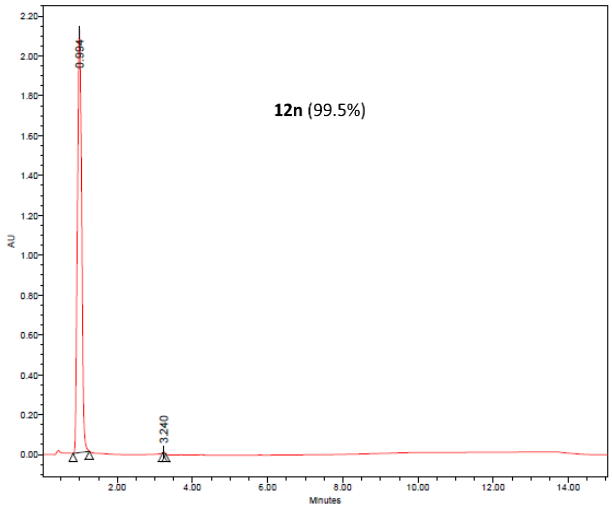
12h (100%)



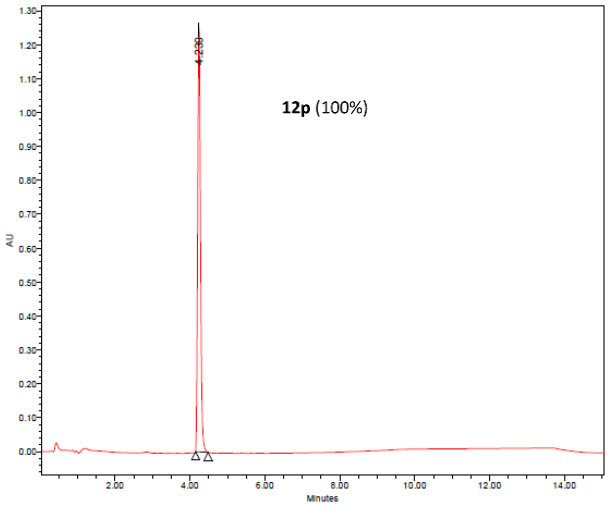
12j (100%)



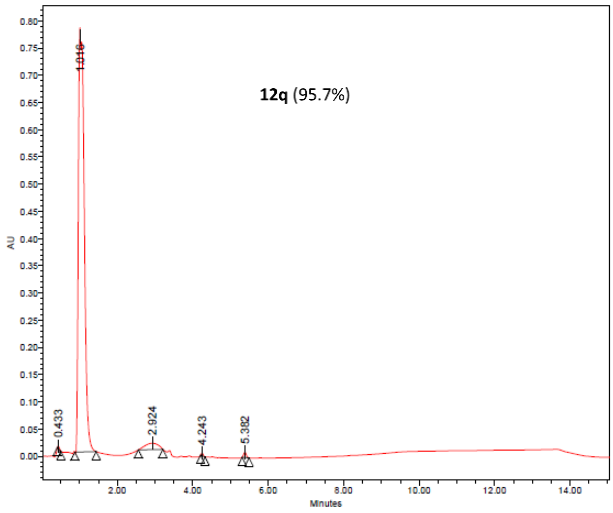
12l (99.7%)



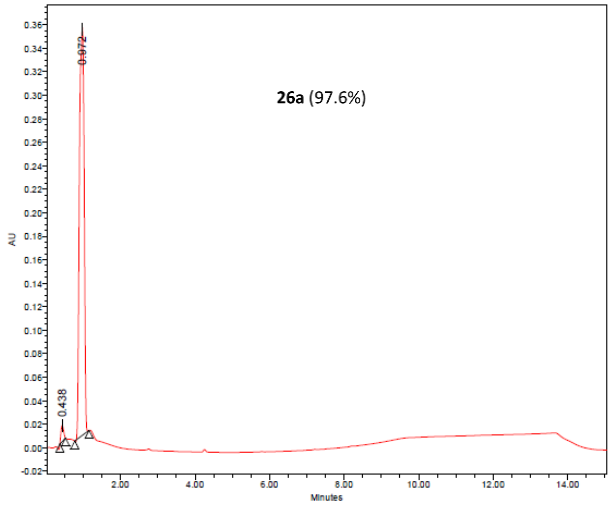
12n (99.5%)



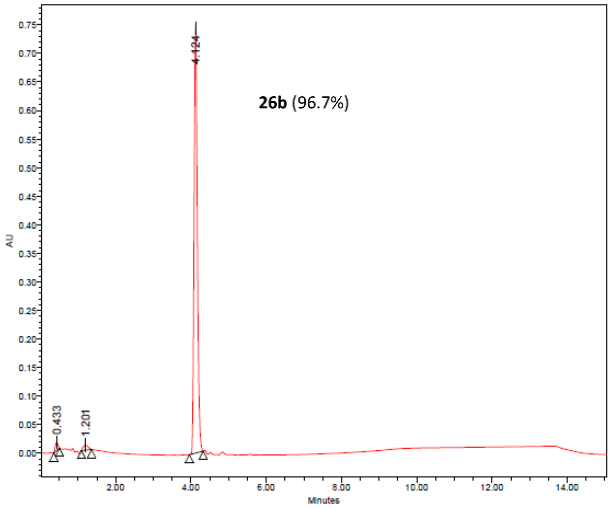
12p (100%)



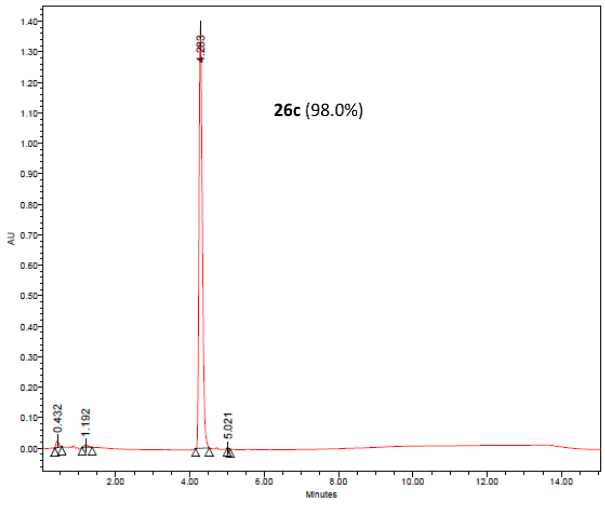
12q (95.7%)



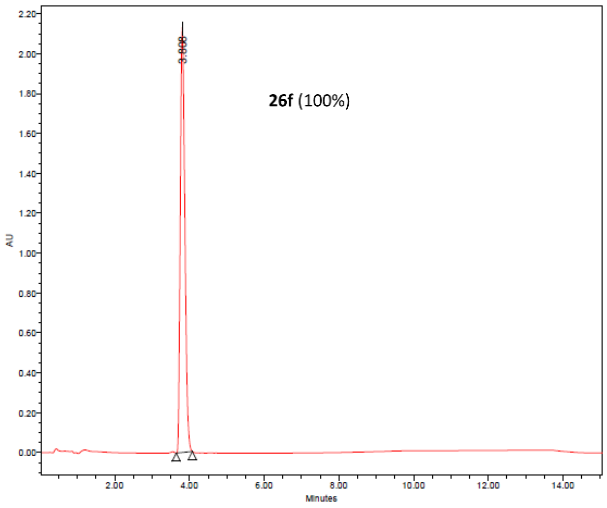
26a (97.6%)



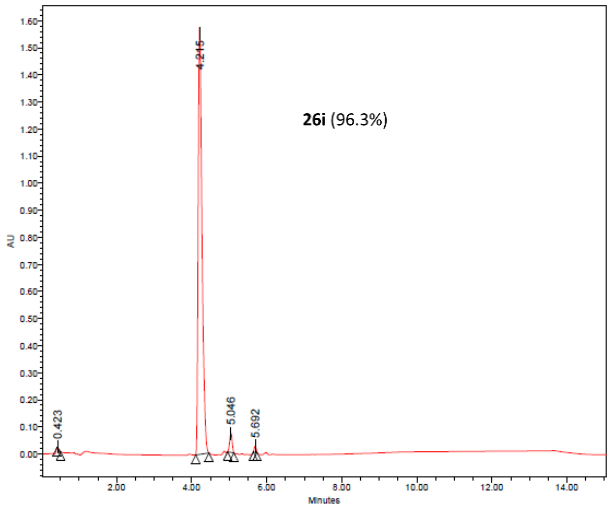
26b (96.7%)

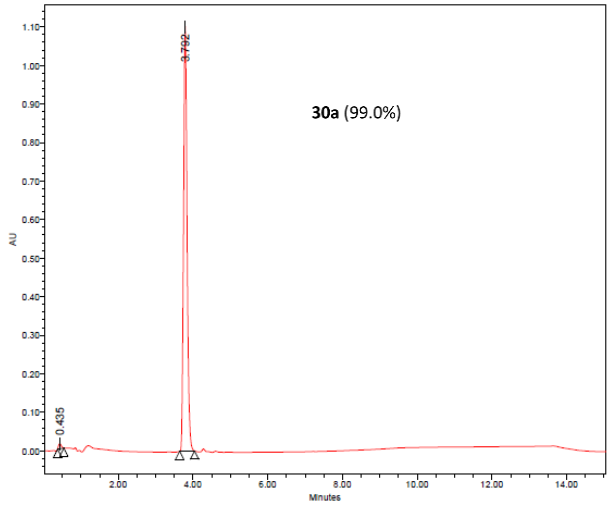


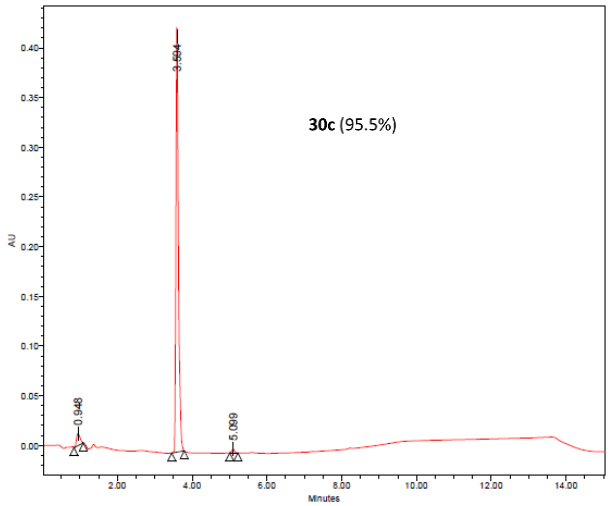
26c (98.0%)



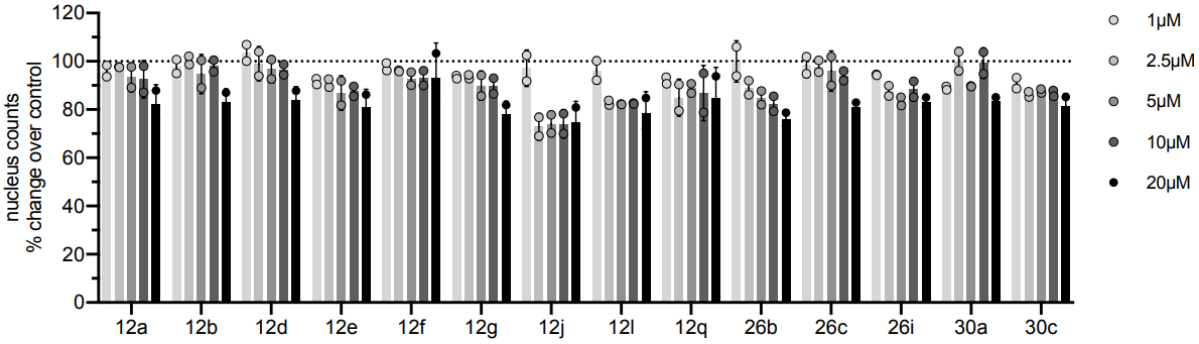
26f (100%)







Supplementary Fig. 85. HPLC chromatograms of selected compounds. AU = absorbance units



Supplementary Fig. 86. NMT inhibitors show minimal toxicity in primary hepatocytes. Nuclear counts, normalized to DMSO controls, for NMT inhibitors across a dose response. Counts were obtained using DAPI staining from the *P. vivax*-infected wells quantified in Fig. 5d. Error bars represent the standard deviation of two technical replicates.

Supplementary Tables

Supplementary Table 1. X-ray diffraction and structure refinement statistics.

	*Pv*NMT-myrCoA-**12b**
Data collection	
Space group	$P4_32_12$
Cell dimensions*	
a, *b*, *c* (Å)	91.930, 91.930, 101.286
α, β, γ (°)	90, 90, 90
Resolution (Å)	50.00–1.65 (1.68–1.65)†
R_{sym} or R_{merge}	0.116 (0.889)
avg *I*/avg σ*I*	23.7 (2.2)
Completeness (%)	100.0 (100.0)
Redundancy	14.2 (13.4)
Refinement	
Resolution (Å)	45.97–1.65
No. reflections	52,787
R_{work}/R_{free}	0.136/0.165
No. atoms	
Protein	6,928
Ligand/ion	402
Water	435
B-factors (Å^2)	
Protein	18.76
Ligand/ion	28.26
Water	32.14
R.m.s. deviations	
Bond lengths (Å)	0.010
Bond angles (°)	1.085

*The structure was determined using one crystal.
†Values in parentheses are for highest-resolution shell.

Supplementary Table 2. Effect of NMTis on *P. vivax* liver stage infection. A 2-way ANOVA with Dunnett's multiple comparisons test (unpaired) was used to compare the effect of each NMTi on schizonts and hypnozoites compared to DMSO controls and to compare the effect of each NMTi on schizonts between parasite isolates. Sidak's multiple comparisons test (paired) was used to compare the effect of each NMTi on forms within an isolate. $p < 0.05$ was used as a cutoff for statistical significance.

compound	schizonts (fold change to DMSO)						difference between isolates?	hypnozoites (fold change to DMSO)				difference between isolates?	difference between forms?
	isolate 1		isolate 2		isolate 3			isolate 1		isolate 2			
	mean diff	p-value	mean diff	p-value	mean diff	p-value		mean diff	p-value	mean diff	p-value		
12a	0.850	0.000	0.9245	<0.0001	0.7273	<0.0001	no	0.754	0.0015	0.897	<0.0001	no	no
12b	0.950	<0.0001	0.8868	<0.0001	0.8977	<0.0001	no	0.923	<0.0001	0.966	<0.0001	no	no
12d	0.967	<0.0001	0.9434	<0.0001	0.8977	<0.0001	no	0.939	<0.0001	0.862	<0.0001	no	no
12e	0.983	<0.0001	0.8302	<0.0001	0.8295	<0.0001	no	0.815	0.0005	1.000	<0.0001	no	no
12f	1.000	<0.0001	0.9811	<0.0001	0.8295	<0.0001	no	0.939	<0.0001	0.931	<0.0001	no	no
12g	1.000	<0.0001	0.7547	<0.0001	0.7955	<0.0001	no	0.785	0.0009	0.966	<0.0001	no	no
12j	0.983	<0.0001	0.9434	<0.0001	0.7614	<0.0001	no	0.985	<0.0001	0.897	<0.0001	no	no
12l	0.983	<0.0001	0.7736	<0.0001	0.6932	<0.0001	no	1.000	<0.0001	0.828	<0.0001	no	no
12q	0.983	<0.0001	0.8491	<0.0001	0.6591	<0.0001	yes	0.939	<0.0001	0.931	<0.0001	no	no
26b	0.917	<0.0001	0.8679	<0.0001	0.625	<0.0001	no	0.908	<0.0001	0.793	<0.0001	no	no
26c	1.000	<0.0001	0.9434	<0.0001	0.8977	<0.0001	no	0.923	<0.0001	0.862	<0.0001	no	no
26i	0.933	<0.0001	0.8491	<0.0001	0.8295	<0.0001	no	1.000	<0.0001	0.310	0.0429	yes	yes
30a	1.000	<0.0001	0.9245	<0.0001	0.8636	<0.0001	no	0.954	<0.0001	1.000	<0.0001	no	no
30c	0.900	0.000	0.7547	<0.0001	0.8636	<0.0001	no	0.939	<0.0001	0.690	<0.0001	no	no

Supplementary Methods

General Experimental Information for Synthesis and Compound Characterization

General reagents and solvents for synthesizing compounds were purchased from commercial sources and used as supplied unless otherwise stated.

Purification by flash column chromatography was performed on a Selekt (Biotage, U.K.) automated instrument with Sfär KP-amino D or Sfär silica D cartridges (Biotage, U.K.), mobile phase consisting of pentane (solvent A) and ethyl acetate (solvent B) or by reverse phase flash column chromatography performed on an Isolera (Biotage, U.K.) automated instrument with Sfär C18 D cartridges (Biotage, U.K.), mobile phase consisting of water (solvent A) and acetonitrile (solvent B). The standard gradient consisted of *x*% solvent B for one column volume, *x*% to *y*% B for 10 column volumes, and then *y*% B for 2 column volumes. *x* and *y* are defined in the characterization section of the compound the interest.

All NMR spectra (^{1}H and ^{13}C) were recorded on a Varian 400 MHz spectrometer at 25 °C. Samples were dissolved (0.5 mL) in deuterated chloroform, methanol, or dimethylsulfoxide ($CDCl_3$, CD_3OD, DMSO-d_6). The residual solvent peaks specific to the deuterated solvent were used as an internal reference; $CDCl_3$: 7.26 ppm (^{1}H NMR) and 77.20 ppm (^{13}C NMR); CD_3OD: 3.31 ppm (^{1}H NMR) and 49.00 ppm (^{13}C NMR); DMSO-d_6: 2.50 ppm (^{1}H NMR) and 39.52 ppm (^{13}C NMR). Data are presented as follows: chemical shift in ppm, multiplicity (br = broad, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hz and integration.

Purity determination of selected compounds was performed in analytical HPLC (Waters 2690 Separations Module; Atlantis® T3, 5 µm column, 4.6 × 250 mm; H_2O/ACN (0.1% TFA)). High-resolution mass spectra (HRMS) were recorded on an Agilent 1290 infinity LC system in tandem with an Agilent 6520 Accurate Mass Q-TOF spectrometer.

Detailed Synthetic Procedure and Characterization of Compounds

General Procedure A – Reduction of Ester to 1° Alcohol

To a solution of lithium aluminum hydride (2.5 equiv.) in anhydrous tetrahydrofuran (15 mL) was cooled to 0 °C and a solution of the selected ester (1 equiv.) in anhydrous tetrahydrofuran (25 mL) was added dropwise. The mixture was stirred at room temperature for 12 h. Then the reaction mixture was cooled to 0 °C, and 2 mL of water was slowly added. The mixture was stirred for 10 min, filtered through celite and rinsed with EtOAc (2x50 mL) before the residue was concentrated under reduced pressure to afford the desired alcohol.

General Procedure B – Mesyl transfer

The solution of the alcohol (1 equiv.) and NEt_3 (1.5 equiv.), in DCM (10 mL) was cooled to 0°-5°C and methanesulfonyl chloride (1.2 equiv.) was added dropwise. The mixture was stirred at room temperature for 3 h. The reaction was quenched with water (50 mL), and the organic compound was extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to

afford the desired phenylmethane sulfonate. The phenylmethane sulfonate (2 equiv.) was dissolved in dry acetonitrile (3 mL), in a microwave vial (2-5 mL) and a solution of the appropriate alcohol (1 equiv.) in solvent (ACN) followed by solid sodium *t*-butoxide (1.2 equiv.) were added. The vial was sealed and then heated under microwave irradiation at 140 °C for 30 min. The reaction mixture was cooled to room temperature and partitioned between EtOAc (20mL) and saturated sodium carbonate solution (10mL). The organic phase was separated, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude product was purified by flash column chromatography using a pentane/EtOAc gradient (0-60%) as eluent.

General Procedure C – Mitsunobu reaction

A solution of the alcohol (1 equiv.) in toluene (10 mL) was reacted with selected aryl or pyridine-alcohol (1.25 equiv.) and cyanomethyiene tributylphosphorane (1.5 equiv.) at 100°C for 16 h. The reaction mixture was then diluted with ethyl acetate (50 mL) and washed with water (1X25 mL) and brine (2X25 mL). The organic phase separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with a gradient of pentane/EtOAc or by reverse-phase chromatography eluting with a gradient H_2O/ACN.

General Procedure D – Suzuki cross-coupling reaction

A solution of the aryl-bromide (1 equiv.), aryl boronic acid pinacol ester (1.25 equiv.) and tetrakis(triphenylphosphine) palladium(0) (0.05 equiv.) in 1,4-dioxane (10 mL) in a microwave vial (10-20 mL) were mixed with a solution of potassium phosphate (2.7 equiv.) in water (3 mL) under N_2. The reaction mixture was heated at 100 °C for 1-3 h. The solution was cooled to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc (20 mL) and saturated sodium bicarbonate solution (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with a gradient of pentane/EtOAc or by reverse-phase chromatography eluting with a gradient of H_2O/ACN.

General Procedure E – Boc-Deprotection

The Boc-protected amine was dissolved in dioxane (1 mL) and treated with a solution of HCl in dioxane (4 M, 2mL). The reaction mixture was stirred at room temperature overnight. All volatiles were removed under reduced pressure, and the product was triturated with ether and DCM, redissolved in water, and freeze-dried to afford the desired compound.

2-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethan-1-ol (1)

Ethyl 3-acetyl-4-oxopentanoate (**1a**) and ethyl 2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)acetate (**1b**) were prepared as described previously[8]. Compound **1b** was reacted according to General Procedure A. Afforded the title compound as a colorless oil (85.1 %). ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 3.68 (3H, s), 3.63 (2H, t, J = 6.8 Hz), 2.59 (2H, t, J = 6.8 Hz), 2.16 (3H, s), 2.15 (3H, s).

2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethan-1-ol (2)

Ethyl 3-acetyl-4-oxopentanoate (**1a**) and ethyl 2-(3,5-dimethyl-1*H*-pyrazol-4-yl)acetate (**2b**) were prepared as described previously[8]. Compound **2b** was reacted according to General Procedure A. Afforded the title compound as a colorless oil (80.1 %). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 3.52 (2H, t, *J* = 7.2 Hz), 2.55 (2H, t, *J* = 7.2 Hz), 2.14 (6H, s).

4-(2-(2-Bromophenoxy)ethyl)-1,3,5-trimethyl-1*H*-pyrazole (3)

Following General Procedure B, 2-bromophenol (250 µL, 2.15 mmol) was reacted with mesyl-chloride (208 µL, 2.69 mmol) and NEt_3 (450 µL, 3.23 mmol) to afford 500 mg (92%) of 2-bromophenyl methanesulfonate. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.64 (1H, dd, *J* = 8.0, 1.6 Hz), 7.47 (1H, dd, *J* = 8.2, 1.6 Hz), 7.37 (1H, ddd, *J* = 8.2, 7.4, 1.6 Hz), 7.20 (1H, ddd, *J* = 8.0, 7.4, 1.6 Hz), 2.27 (3H, s). Next, 2-bromophenyl methanesulfonate (488 mg, 1.94 mmol) was reacted with **1** (150 mg, 0.97 mmol) to afford 122 mg (40%) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.52 (1H, dd, *J* = 7.8, 1.6 Hz), 7.22 (1H, ddd, *J* = 8.3, 7.4, 1.6 Hz), 6.85 – 6.78 (2H, m), 4.00 (2H, t, *J* = 7.0 Hz), 3.71 (3H, s), 2.89 (2H, t, *J* = 7.0 Hz), 2.23 (6H, s).

2-Bromo-3-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridine (4)

Following General Procedure C, **1** (100 mg, 0.71 mmol) was reacted with 2-bromo-3-hydroxypyridine (155 mg, 0.89 mmol). The crude was purified by flash column chromatography (gradient of pentane/EtOAc) to afford 145 mg (63%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.87 (1H, dd, *J* = 4.6, 1.6 Hz), 7.11 (1H, ddd, *J* = 8.1, 4.6, 0.9 Hz), 7.01 (1H dd, *J* = 8.1, 1.5 Hz), 3.95 (2H, t, *J* = 6.8 Hz), 3.62 (3H, s), 2.84 (2H, t, *J* = 6.6 Hz,), 2.18 (3H, s), 2.16 (3H, s).

4-(2-(2-Bromo-5-fluorophenoxy)ethyl)-1,3,5-trimethyl-1*H*-pyrazole (5)

Following General Procedure B, 2-bromo-5-fluorophenol (250 µL, 2.24 mmol) was reacted with mesyl-chloride (217 µL, 2.80 mmol) and NEt_3 (470 µL, 3.37 mmol) to afford 530 mg (87%) of 2-bromo-5-fluorophenyl methanesulfonate. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.61 (1H, dd, *J* = 8.9, 5.7 Hz), 7.25 (1H, dd, *J* = 8.7, 2.9 Hz), 6.97 (1H, ddd, *J* = 8.9, 7.6, 2.9 Hz), 3.29 (3H, s). Next, 2-bromo-5-fluorophenyl methanesulfonate (500 mg, 1.85 mmol) was reacted with **1** (143 mg, 0.92 mmol) to afford 113 mg (37%) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.49 – 7.42 (1H, m), 6.60 – 6.53 (2H, m), 3.96 (2H, t, *J* = 6.9 Hz), 3.71 (3H, s), 2.89 (2H, t, *J* = 6.9 Hz,), 2.24 (3H, s), 2.23 (3H, s).

4-(2-(2-Bromophenoxy)ethyl)-3,5-dimethyl-1*H*-pyrazole (6)

Following General Procedure C, **2** (100 mg, 0.71 mmol) was reacted with 2-bromophenol (103 µL, 0.89 mmol). The crude was purified by flash column chromatography (gradient of pentane/EtOAc) to afford 130 mg (61%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.51

(1H, dd, *J* = 7.8, 1.6 Hz), 7.21 (1H, ddd, *J* = 8.3, 7.4, 1.6 Hz), 6.84 – 6.78 (2H, m), 4.00 (2H, t, *J* = 7.1 Hz), 2.90 (2H, t, *J* = 7.1 Hz), 2.28 (6H, s).

2-Bromo-3-(2-(3,5-dimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridine (7)

Following General Procedure C, **2** (100 mg, 0.71 mmol) was reacted with 2-bromo-3-hydroxypyridine (155 mg, 0.89 mmol). The crude was purified by flash column chromatography (gradient of pentane/EtOAc) to afford 140 mg (66%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.96 (1H, dd, *J* = 4.6, 1.6 Hz), 7.18 (1H, dd, *J* = 8.1, 4.6 Hz), 7.06 (1H, dd, *J* = 8.1, 1.6 Hz), 4.03 (2H, t, *J* = 6.8 Hz), 2.93 (2H, t, *J* = 6.8 Hz,), 2.29 (s, 6H).

4-(2-(2-Bromo-5-fluorophenoxy)ethyl)-3,5-dimethyl-1*H*-pyrazole (8)

Following General Procedure C, **2** (78 mg, 0.55 mmol) was reacted with 2-bromo-5-fluorophenol (80 µL, 0.71 mmol). The crude was purified by flash column chromatography (gradient of pentane/EtOAc) to afford 120 mg (68%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.44 (1H, dd, *J* = 8.8, 6.2 Hz), 6.60 – 6.52 (2H, m), 3.98 (2H, t, *J* = 6.9 Hz), 2.91 (2H, t, *J* = 6.9 Hz), 2.30 (6H, s).

3-(2-(2-Bromophenoxy)ethyl)pyridine (9)

Following General Procedure B, 2-bromophenyl methanesulfonate (500 mg, 1.99 mmol) was reacted with 3-(2-hydroxyethyl)pyridine (112 µL, 0.99 mmol) to afford 125 mg (45%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.61 (1H, d, *J* = 2.1 Hz), 8.50 (1H, dd, *J* = 4.8, 1.6 Hz), 7.78 – 7.72 (1H, m), 7.52 (1H, dd, *J* = 7.8, 1.6 Hz), 7.27 – 7.24 (2H, m), 7.24 – 7.21 (1H, m), 6.87 – 6.79 (2H, m), 4.22 (2H, t, *J* = 6.3 Hz), 3.15 (2H, t, *J* = 6.3 Hz).

2-Bromo-3-(2-(pyridin-3-yl)ethoxy)pyridine (10)

Following General Procedure C, 3-(2-hydroxyethyl)pyridine (112 µL, 0.99 mmol) was reacted with 2-bromo-3-hydroxypyridine (138 mg, 0.79 mmol). The crude was purified by flash column chromatography (gradient of pentane/EtOAc) to afford 118 mg (69%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.61 (1H, d, *J* = 2.3 Hz), 8.52 (1H, dd, *J* = 4.8, 1.6 Hz), 7.98 (1H, dd, *J* = 4.6, 1.6 Hz), 7.76 (1H, dt, *J* = 7.8, 2.0 Hz), 7.27 (2H, dd, *J* = 7.8, 4.8 Hz), 7.18 (1H, ddd, *J* = 8.1, 4.6, 0.4 Hz), 7.08 (1H, dd, *J* = 8.1, 1.5 Hz), 4.22 (2H, t, *J* = 6.3 Hz), 3.18 (2H, t, *J* = 6.3 Hz).

3-(2-(2-Bromo-5-fluorophenoxy)ethyl)pyridine (11)

Following General Procedure C, 3-(2-hydroxyethyl)pyridine (68 µL, 0.60 mmol) was reacted with 2-bromo-5-fluorophenol (84 µL, 0.75 mmol). The crude was purified by flash column chromatography (gradient of pentane/EtOAc) to afford 130 mg (72%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.55 (1H, d, *J* = 2.2 Hz), 8.44 (1H, dd, *J* = 4.8, 1.6 Hz), 7.71 – 7.63

(1H, m), 7.37 (1H, ddd, *J* = 8.0, 6.2, 0.7 Hz), 7.18 (1H, ddd, *J* = 7.8, 4.8, 0.7 Hz), 6.55 – 6.45 (2H, m), 4.09 (2H, t, *J* = 6.2 Hz), 3.07 (2H, t, *J* = 6.2 Hz).

2'-(Piperazin-1-yl)-3-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)-2,4'-bipyridine (12a)

Following General Procedure D, **4** (35 mg, 0.11 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (51 mg, 0.14 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy colorless solid (7 mg, 16%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.20 (1H dd, *J* = 4.7, 1.3 Hz), 8.13 (1H, dd, *J* = 5.3, 0.7 Hz), 7.57 (1H, dd, *J* = 8.5, 1.3 Hz), 7.41 (1H, dd, *J* = 8.5, 4.7 Hz), 7.12 – 7.11 (1H, m), 6.95 (1H, dd, *J* = 5.3, 1.3 Hz), 4.15 (2H, t, *J* = 6.5 Hz), 3.63 (3H, s), 3.54 – 3.50 (4H, m), 2.97 – 2.93 (4H, m), 2.83 (2H, t, *J* = 6.5 Hz), 2.05 (3H, s), 2.01 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 161.35, 154.85, 148.38, 148.12, 147.57, 146.90, 141.92, 139.20, 125.97, 122.31, 115.31, 113.29, 109.38, 69.80, 47.34, 46.31, 35.77, 24.38, 11.61, 9.40. HRMS (ESI), found 393.2403 $C_{22}H_{28}N_6O$, $[M + H]^+$, requires 393.2403.

1-(3-(3-(2-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridin-2-yl)phenyl)piperazine (12b)

Following General Procedure D, **4** (100 mg, 0.32 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (123 mg, 0.40 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy yellow solid (70 mg, 83%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.40 (1H, dd, *J* = 5.7, 1.1 Hz), 8.33 (1H, dd, *J* = 8.8, 1.0 Hz), 7.99 (1H, dd, *J* = 8.8, 5.7 Hz), 7.51 (1H, t, *J* = 7.9 Hz), 7.38 – 7.32 (2H, m), 7.18 – 7.14 (1H, m), 4.39 (2H, t, *J* = 6.0 Hz), 3.86 (3H, s), 3.56 (4H, dd, *J* = 6.3, 4.1 Hz), 3.41 (4H, dd, *J* = 6.3, 4.1 Hz), 2.99 (2H, t, *J* = 6.0 Hz), 2.15 (3H, s), 2.11 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 156.36, 152.02, 146.03, 145.13, 144.75, 134.15, 131.19, 131.16, 130.54, 128.24, 122.85, 120.55, 118.55, 116.47, 70.77, 47.26, 44.63, 35.58, 23.24, 9.59, 9.33. HRMS (ESI), found 392.2454 $C_{23}H_{29}N_5O$, $[M + H]^+$, requires 392.2453.

1-(4-(2-(2-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethoxy)phenyl)pyridin-2-yl)piperazine (12c)

Following General Procedure D, **3** (100 mg, 0.32 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (154 mg, 0.40 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy pale yellow solid (65 mg, 51%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.02 (1H, dd, *J* = 5.3, 0.6 Hz), 7.27 (1H, ddd, *J* = 8.3, 7.4, 1.8 Hz), 7.22 (1H, dd, *J* = 7.6, 1.8 Hz), 7.00 – 6.97 (1H, m), 6.95 (1H, td, *J* = 7.6, 1.1 Hz), 6.80 (1H, s), 6.66 (1H, dd, *J* = 5.3, 1.1 Hz), 3.97 (2H, t, *J* = 6.5 Hz), 3.57 (3H, s), 3.45 – 3.40 (4H, m), 2.90 – 2.86 (4H, m), 2.69 (2H, t, *J* = 6.5 Hz), 1.98 (3H, s), 1.91 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ,

ppm) 161.29, 157.12, 150.22, 147.85, 146.79, 139.06, 131.36, 130.90, 130.31, 122.10, 116.19, 113.94, 113.58, 109.72, 69.57, 47.41, 46.33, 35.75, 24.56, 11.65, 9.38. HRMS (ESI), found 392.2451 $C_{23}H_{29}N_5O$, $[M + H]^+$, requires 392.2450.

1-(2'-(2-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-yl)piperazine (12d)

Following General Procedure D, **3** (100 mg, 0.32 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (123 mg, 0.40 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy brownish white solid (60 mg, 58%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 7.34 – 7.25 (2H, m), 7.18 (1H, dd, *J* = 7.5, 1.7 Hz), 7.14 – 7.10 (2H, m), 7.05 – 7.02 (1H, m), 6.98 (1H, td, *J* = 7.5, 0.8 Hz), 6.93 (1H, d, *J* = 7.7 Hz), 4.09 (2H, t, *J* = 5.8 Hz), 3.84 (3H, s), 3.54 (4H, dd, *J* = 6.4, 3.4 Hz), 3.45 (4H, dd, *J* = 6.4, 3.3 Hz), 2.86 (2H, t, *J* = 5.8 Hz), 2.09 (3H, s), 2.06 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 156.83, 150.29, 146.30, 144.45, 141.88, 132.43, 131.87, 130.10, 130.08, 124.93, 122.35, 119.89, 117.68, 117.11, 114.03, 68.77, 48.68, 44.51, 35.49, 23.68, 9.40, 9.22. HRMS (ESI), found 391.2499 $C_{24}H_{30}N_4O$, $[M + H]^+$, requires 391.2498.

1-(4-(4-Fluoro-2-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)phenyl)pyridin-2-yl)piperazine (12e)

Following General Procedure D, **5** (50 mg, 0.15 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (75 mg, 0.19 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy pale yellow solid (11 mg, 52%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.11 (1H, dd, *J* = 5.2, 0.7 Hz), 7.28 (1H, dd, *J* = 8.5, 6.7 Hz), 6.89 – 6.84 (2H, m), 6.77 – 6.71 (2H, m), 4.05 (2H, t, *J* = 6.4 Hz), 3.79 – 3.73 (4H, m), 3.31 – 3.27 (4H, m), 3.61 (3H, s), 2.76 (2H, t, *J* = 6.3 Hz), 1.97 (3H, s), 1.96 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 165.14 (d, *J* = 245 Hz), 160.06, 158.50 (d, *J* = 10.1 Hz), 149.79, 148.24, 146.94, 139.15, 132.49 (d, *J* = 10.1 Hz), 126.16 (d, *J* = 3.3 Hz), 117.36, 113.54, 109.96, 108.25 (d, *J* = 21.5 Hz), 101.70 (d, *J* = 25.90 Hz), 69.89, 44.53, 44.13, 35.76, 24.29, 11.56, 9.38. HRMS (ESI), found 410.2356 $C_{23}H_{28}FN_5O$, $[M + H]^+$, requires 410.2356.

1-(4'-Fluoro-2'-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-yl)piperazine (12f)

Following General Procedure D, **5** (100 mg, 0.30 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (121 mg, 0.39 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy brownish white solid (60 mg, 58%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 7.31 – 7.26 (1H, m), 7.17 (1H, dd, *J* = 8.4, 6.8 Hz),

7.04 (1H, ddd, *J* = 8.2, 2.5, 0.8 Hz), 7.00 – 6.97 (1H, m), 6.88 – 6.81 (2H, m), 6.72 (1H, td, *J* = 8.3, 2.5 Hz), 4.09 (2H, t, *J* = 5.8 Hz), 3.84 (3H, s), 3.47 (4H, dd, *J* = 6.7, 3.5 Hz), 3.40 (4H, dd, *J* = 6.6, 3.6 Hz), 2.87 (2H, t, *J* = 5.8 Hz), 2.08 (3H, s), 2.05 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 164.40 (d, *J* = 243.3), 158.05 (d, *J* = 9.9), 151.43, 146.24, 144.53, 140.81, 132.73 (d, *J* = 9.9), 130.04, 128.74 (d, *J* = 3.3), 123.86, 119.42, 117.45, 116.77, 108.27 (d, *J* = 21.2), 101.69 (d, *J* = 25.85), 69.06, 48.03, 44.76, 35.46, 23.48, 9.37, 9.17. HRMS (ESI), found 429.2407 $C_{24}H_{30}FN_4O$, $[M + H]^+$, requires 429.2404.

1-(3-(3-(2-(Pyridin-3-yl)ethoxy)pyridin-2-yl)phenyl)piperazine (12g)

Following General Procedure D, **10** (100 mg, 0.35 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (137 mg, 0.44 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy yellow solid (70 mg, 83%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.73 (2H, s), 8.41 (2H, d, *J* = 7.4 Hz), 8.37 – 8.32 (1H, m,), 7.98 (1H, dd, *J* = 8.7, 5.7 Hz,), 7.95 – 7.88 (1H, m), 7.51 – 7.45 (1H, m), 7.33 – 7.28 (2H, m), 7.15 – 7.10 (1H, m), 4.63 (2H, t, *J* = 6.0 Hz), 3.54 (4H, dd, *J* = 6.3, 4.0 Hz), 3.44 – 3.37 (6H, m). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 154.49, 150.46, 147.37, 143.83, 141.36, 139.58, 133.29, 129.64, 129.49, 128.99, 126.67, 121.56, 119.16, 117.19, 69.05, 45.85, 43.23, 31.48. HRMS (ESI), found 361.2029 $C_{22}H_{24}N_4O$, $[M + H]^+$, requires 361.2028.

2'-(Piperazin-1-yl)-3-(2-(pyridin-3-yl)ethoxy)-2,4'-bipyridine (12h)

Following General Procedure D, **10** (88 mg, 0.31 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (153 mg, 0.39 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy yellow solid (40 mg, 85%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.81 (1H, s), 8.75 (1H, d, *J* = 5.5 Hz), 8.60 (1H, d, *J* = 8.1 Hz), 8.39 (1H, d, *J* = 4.5 Hz), 8.15 (1H, d, *J* = 6.4 Hz), 8.03 (1H, dd, *J* = 8.0, 5.9 Hz), 7.94 (1H, dd, *J* = 8.7, 0.9 Hz), 7.79 – 7.76 (1H, m), 7.70 (1H, dd, *J* = 8.6, 4.9 Hz), 7.44 (1H, dd, *J* = 6.4, 1.2 Hz), 4.58 (2H, t, *J* = 6.2 Hz), 4.09 – 4.03 (4H, m), 3.51 – 3.46 (4H, m), 3.44 (2H, t, *J* = 6.2 Hz). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 155.73, 154.62, 148.91, 142.74, 142.18, 141.06, 141.05, 140.95, 140.62, 139.16, 128.74, 128.51, 125.44, 115.90, 113.73, 69.68, 44.58, 43.76, 33.02. HRMS (ESI), found 362.1986 $C_{21}H_{23}N_5O$, $[M + H]^+$, requires 362.1981.

1-(2'-(2-(Pyridin-3-yl)ethoxy)-[1,1'-biphenyl]-3-yl)piperazine (12i)

Following General Procedure D, **9** (100 mg, 0.36 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (137 mg, 0.44 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy off-white solid (76 mg, 74%).

^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.63 (1H, d, *J* = 5.7 Hz), 8.59 (1H, d, *J* = 1.8 Hz), 8.31 (1H, dt, *J* = 8.1, 1.6 Hz,), 7.85 – 7.80 (1H, m), 7.48 (1H, d, *J* = 1.9 Hz), 7.44 – 7.40 (2H, m), 7.29 (1H, ddd, *J* = 8.3, 7.4, 1.7 Hz), 7.22 (1H, dd, *J* = 7.6, 1.7 Hz), 7.20 – 7.17 (1H, m), 7.06 (1H, dd, *J* = 8.3, 0.9 Hz), 6.99 (1H, td, *J* = 7.5, 1.0 Hz), 4.30 (2H, t, *J* = 6.0 Hz), 3.78 (4H, dd, *J* = 6.5, 4.0 Hz), 3.64 (4H, dd, *J* = 6.5, 4.0 Hz,), 3.28 (2H, t, *J* = 6.0 Hz). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 156.46, 148.87, 146.35, 142.48, 141.98, 141.47, 140.54, 131.70, 131.15, 130.66, 130.62, 128.76, 128.04, 122.68, 121.57, 118.77, 114.09, 68.66, 50.65, 43.52, 33.38. HRMS (ESI), found 360.2077 $C_{23}H_{25}N_3O$, $[M + H]^+$, requires 360.2076.

1-(4-(2-(2-(Pyridin-3-yl)ethoxy)phenyl)pyridin-2-yl)piperazine (12j)

Following General Procedure D, **9** (100 mg, 0.35 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (174 mg, 0.45 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy pale yellow solid (70 mg, 77%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.76 (2H, s), 8.57 (1H, d, *J* = 8.0 Hz), 8.03 (2H, d, *J* = 6.6 Hz), 7.53 – 7.48 (2H, m), 7.44 (1H, d, *J* = 1.2 Hz), 7.25 – 7.18 (2H, m), 7.13 (1H, td, *J* = 7.6, 1.0 Hz), 4.44 (2H, t, *J* = 6.1 Hz), 4.11 – 4.05 (4H, m), 3.54 – 3.49 (4H, m), 3.38 (2H, t, *J* = 6.1 Hz,). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 157.11, 156.86, 153.88, 148.73, 142.62, 140.77, 136.87, 133.45, 131.79, 128.46, 127.09, 122.96, 117.43, 114.08, 113.55, 68.80, 44.68, 43.73, 33.35. HRMS (ESI), found 361.2028 $C_{22}H_{24}N_4O$, $[M + H]^+$, requires 361.2028.

1-(4'-Fluoro-2'-(2-(pyridin-3-yl)ethoxy)-[1,1'-biphenyl]-3-yl)piperazine (12k)

Following General Procedure D, **11** (100 mg, 0.33 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (129 mg, 0.42 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy yellow solid (76 mg, 74%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.69 (1H, d, *J* = 5.6 Hz), 8.60 (1H, s), 8.28 (1H, dt, *J* = 8.1, 1.6 Hz), 7.84 (1H, dd, *J* = 8.0, 5.8 Hz), 7.35 – 7.28 (1H, m), 7.22 (1H, dd, *J* = 8.5, 6.7 Hz), 7.07 (1H, ddd, *J* = 8.3, 2.5, 0.8 Hz), 7.00 – 6.96 (1H, m), 6.90 (1H, dd, *J* = 10.9, 2.5 Hz), 6.87 – 6.83 (1H, m), 6.76 (1H, td, *J* = 8.4, 2.5 Hz), 4.33 (2H, t, *J* = 5.8 Hz), 3.48 (4H, dd, *J* = 6.8, 3.1 Hz), 3.42 (4H, dd, *J* = 6.8, 3.0 Hz), 3.27 (2H, t, *J* = 5.8 Hz). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 164.41 (d, *J* = 243.7 Hz), 157.67 (d, *J* = 10 Hz), 157.62, 151.11, 148.94, 142.47, 141.29, 140.57, 140.32, 132.53 (d, *J* = 10 Hz), 129.94, 128.62 (d, *J* = 3.3 Hz), 127.97, 124.10, 119.47, 116.88, 108.62 (d, *J* = 21.2 Hz), 101.86 (d, *J* = 25.7 Hz), 68.87, 48.10, 44.73, 33.26. HRMS (ESI), found 378.1986 $C_{23}H_{24}FN_3O$, $[M + H]^+$, requires 378.1982.

1-(4-(4-Fluoro-2-(2-(pyridin-3-yl)ethoxy)phenyl)pyridin-2-yl)piperazine (12l)

Following General Procedure D, **11** (90 mg, 0.30 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (117 mg, 0.38 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy off-white solid (50 mg, 69%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.76 – 8.72 (2H, m), 8.58 – 8.54 (1H, m), 8.06 – 7.99 (2H, m), 7.54 (1H, dd, *J* = 8.6, 6.5 Hz), 7.44 – 7.41 (1H, m), 7.21 (1H, dd, *J* = 6.6, 1.5 Hz), 7.03 (1H, dd, *J* = 10.9, 2.4 Hz), 6.90 – 6.83 (1H, m), 4.42 (2H, t, *J* = 6.1 Hz), 4.10 – 4.04 (4H, m), 3.53 – 3.46 (4H, m), 3.37 (2H, t, *J* = 6.1 Hz,). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 166.54 (d, *J* = 248.6 Hz), 158.47 (d, *J* = 10.5 Hz), 156.32, 153.70, 148.89, 142.65, 140.93, 140.82, 136.64, 133.44 (d, *J* = 10.5 Hz), 128.49, 123.20 (d, *J* = 3.3 Hz), 117.23, 113.66, 109.49 (d, *J* = 21.9 Hz), 102.20 (d, *J* = 26.5 Hz), 69.26, 44.71, 43.71, 33.11. HRMS (ESI), found 379.1925 $C_{22}H_{23}FN_4O$, $[M + H]^+$, requires 379.1934.

1-(3-(3-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridin-2-yl)phenyl)piperazine (12m)

Following General Procedure D, **7** (35 mg, 0.12 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (45 mg, 0.15 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy off-white solid (12 mg, 47%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.34 (1H, d, *J* = 5.6 Hz), 8.30 (1H, d, *J* = 8.6 Hz), 7.94 (1H, dd, *J* = 8.6, 5.7 Hz), 7.44 (1H, t, *J* = 7.9 Hz), 7.33 – 7.27 (2H, m), 7.09 (1H, d, *J* = 7.5 Hz), 4.36 (2H, t, *J* = 5.8 Hz), 3.55 – 3.47 (4H, m), 3.39 – 3.32 (4H, m), 2.95 (2H, t, *J* = 5.6 Hz), 2.09 (6H, s). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 156.38, 151.85, 145.77, 144.98, 134.02, 131.17, 131.07, 130.65, 128.31, 122.92, 120.63, 118.65, 116.20, 70.67, 47.32, 44.58, 22.80, 9.60. HRMS (ESI), found 378.2294 $C_{22}H_{27}N_5O$, $[M + H]^+$, requires 378.2294.

1-(4-(2-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)phenyl)pyridin-2-yl)piperazine (12n)

Following General Procedure D, **6** (90 mg, 0.30 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (148 mg, 0.38 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy off-white solid (44 mg, 79%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.05 (1H, d, *J* = 6.6 Hz), 7.55 – 7.49 (3H, m), 7.29 (1H, dd, *J* = 6.6, 1.3 Hz), 7.21 (1H, d, *J* = 8.0 Hz), 7.14 (1H, td, *J* = 7.5, 0.8 Hz), 4.26 (2H, t, *J* = 6.6 Hz), 4.15 – 4.08 (4H, m), 3.56 – 3.50 (4H, m), 3.00 (2H, t, *J* = 6.6 Hz), 2.32 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 157.49, 157.06, 153.72, 145.58, 136.77, 133.45, 131.86, 127.06, 122.79, 117.48, 116.44, 114.16, 113.63, 68.48, 49.00, 44.71, 43.73, 23.12, 9.79. HRMS (ESI), found 378.2292 $C_{22}H_{27}N_5O$, $[M + H]^+$, requires 378.2294.

3-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy-2'-(piperazin-1-yl)-2,4'-bypyridine (12o)

Following General Procedure D, **7** (50 mg, 0.17 mmol) was reacted with 2-(4-*tert*-Butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (82 mg, 0.21 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy off-white solid (25 mg, 80%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.43 (1H, brs), 8.20 (1H, d, *J* = 5.7 Hz), 7.93 (1H, d, *J* = 8.3 Hz), 7.78 (1H, brs), 7.73 (1H, brs), 7.46 (1H, d, *J* = 5.6 Hz), 4.37 (2H, t, *J* = 5.6 Hz), 4.08 (4H, brs), 3.49 (4H, brs), 3.07 (2H, t, *J* = 5.6 Hz), 2.32 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 155.47, 150.83, 146.32, 145.85, 142.76, 140.73, 138.10, 128.69, 125.21, 115.98, 115.65, 114.51, 112.87, 69.38, 44.43, 43.91, 23.05, 9.87. HRMS (ESI), found 379.2247 $C_{21}H_{26}N_6O$, $[M + H]^+$, requires 379.2246.

3-(2'-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy-4'-fluoro-[1,1'-biphenyl]-3-yl)piperazine (12p)

Following General Procedure D, **8** (75 mg, 0.23 mmol) was reacted with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (92 mg, 0.30 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy pale yellow solid (12 mg, 47%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 7.28 (1H, t, *J* = 7.8 Hz), 7.19 (1H, dd, *J* = 8.3, 6.9 Hz), 7.06 (1H, d, *J* = 8.1 Hz), 7.01 (1H, brs), 6.88 (1H, dd, *J* = 11.1, 2.2 Hz), 6.82 (1H, d, *J* = 7.5 Hz), 6.74 (1H, td, *J* = 8.3, 2.1 Hz), 4.13 (2H, t, *J* = 5.3 Hz), 3.52 – 3.46 (4H, m), 3.45 – 3.40 (4H, m), 2.89 (2H, t, *J* = 5.2 Hz), 2.11 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 164.39 (d, *J* = 243.3 Hz), 158.06 (d, *J* = 9.9 Hz), 151.24, 145.64, 140.78, 132.72 (d, *J* = 9.8 Hz), 130.06, 128.66 (d, *J* = 3.3 Hz), 123.95, 119.50, 116.94, 116.87, 108.22 (d, *J* = 21.2 Hz), 101.64 (d, *J* = 25.9 Hz), 68.96, 48.13, 44.73, 23.11, 9.50. HRMS (ESI), found 395.2247 $C_{23}H_{27}FN_4O$, $[M + H]^+$, requires 395.2247.

1-(4-(2-(2-(3,5-Dimetyl-1H-pyrazol-4-yl)ethoxy)-4-fluorophenyl)piridin-2-yl)piperazine (12q)

Following General Procedure D, **8** (30 mg, 0.10 mmol) was reacted with 2-(4-*tert*-Butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (47 mg, 0.12 mmol), the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy off-white solid (44 mg, 79%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.05 (1H, d, *J* = 6.6 Hz), 7.58 (1H, dd, *J* = 8.5, 6.6 Hz), 7.53 (1H, s), 7.28 (1H, dd, *J* = 6.6, 1.1 Hz), 7.05 (1H, dd, *J* = 11.0, 2.3 Hz), 6.90 (1H, td, *J* = 8.3, 2.3 Hz), 4.25 (2H, t, *J* = 6.6 Hz), 4.14 – 4.08 (4H, m), 3.56 – 3.49 (4H, m), 3.01 (2H, t, *J* = 6.6 Hz), 2.32 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 166.51 (d, *J* = 248.3 Hz), 158.70 (d, *J* = 10.5 Hz), 156.51, 153.71, 145.63, 136.84, 133.48 (d, *J* = 10.5 Hz), 129.93, 123.22 (d, *J* = 3.3 Hz), 117.32, 116.22, 113.64, 109.31 (d, *J* = 22.0 Hz), 102.23 (d, *J* = 26.4 Hz), 68.96, 44.72, 43.72, 22.94, 9.79. HRMS (ESI), found 396.2201 $C_{22}H_{26}FN_5O$, $[M + H]^+$, requires 396.2200.

***tert*-Butyl 4-(6-chloropyrimidin-4-yl)piperazine-1-carboxylate (13)**

To a solution of 4,6-dichloro-pyrimidine (500 mg, 3.35 mmol) was dissolved in THF (10 mL) in a microwave vial (10-20 mL) and treated with *tert*-butyl piperazine-1-carboxylate (688 mg, 3.69 mmol) and DIPEA (0.87 mL, 5.03 mmol). The reaction mixture was heated at 145°C under microwave irradiation for 30 minutes. The resulting mixture was concentrated in a vacuum, and the residue was partitioned between DCM (50 mL) and water (50 mL). The organic fraction was washed with brine (50 mL), and the organic phase was dried over Na_2SO_4, concentrated under reduced pressure to yield the title compound (920 mg, 92%) as a light brown solid. The intermediary **13** was used without any purification in the following reactions. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) ^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm) 8.32 (1H, s), 6.93 (1H, s), 3.62 (4H, brs), 3.39 – 3.33 (4H, m), 1.38 (9H, s).

***tert*-Butyl 4-(6-(2-hydroxyphenyl)pyrimidin-4-yl)piperazine-1-carboxylate (14)**

Following General Procedure D, **13** (200 mg, 0.67 mmol) was reacted with 2-hydroxybenzeneboronic acid (115 mg, 0.83 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 130 mg (54%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.49 (1H, d, J = 1.0 Hz), 7.65 (1H, dd, J = 8.1, 1.5 Hz), 7.28 (1H, td, J = 7.9, 7.2, 1.6 Hz,), 6.94 (1H, dd, J = 8.3, 1.1 Hz,), 6.85 – 6.80 (2H, m), 3.68 (4H, d, J = 5.0 Hz), 3.55 – 3.50 (4H, m,), 1.47 (9H, s).

***tert*-Butyl 4-(6-(4-fluoro-2-hydroxyphenyl)pyrimidin-4-yl)piperazine-1-carboxylate (15)**

Following General Procedure D, **13** (90 mg, 0.25 mmol) was reacted with 4-fluoro-2-hydroxybenzene boronic acid (75 mg, 0.48 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 91 mg (63 %) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.49 (1H, d, J = 1.0 Hz), 7.64 (1H, dd, J = 9.0, 7.4 Hz), 6.75 (1H, d, J = 1.0 Hz), 6.64 (1H, dd, J = 9.1, 2.6 Hz), 6.55 (1H, ddd, J = 9.0, 7.4, 2.6 Hz), 3.75 – 3.69 (4H, m), 3.58 – 3.52 (4H, m), 1.48 (9H, s).

4-(Piperazin-1-yl)-6-(2-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)phenyl)pyrimidine (16a)

Following General Procedure C, **14** (70 mg, 0.19 mmol) was reacted with **1** (33 mg, 0.23 mmol) the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy yellow solid (8 mg 38%) ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.84 (1H, brs), 7.70 – 7.56 (2H, m), 7.38 (1H, brs), 7.24 (1H, d, J = 8.3 Hz), 7.19 (1H, t, J = 7.1 Hz), 4.45 (2H, brs), 4.24 (4H, brs), 3.91 (3H, s), 3.47 (4H, brs), 3.02 (2H, brs), 2.33 (3H, s), 2.29 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 162.13, 155.89, 152.83, 150.44, 144.96, 142.95, 133.93, 130.88, 121.45, 119.13, 115.31, 112.59, 102.97, 67.33, 42.74, 40.91, 34.33, 21.94, 8.27, 8.19. HRMS (ESI), found 393.2403 $C_{22}H_{28}N_6O$, $[M + H]^+$, requires 393.2403.

4-(4-Fluoro-2-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)phenyl)-6-(piperazin-1-yl)pyrimidine (16b)

Following General Procedure C, **15** (70 mg, 0.18 mmol) was reacted with **1** (33 mg, 0.23 mmol) the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E and afforded the title compound as a fluffy brownish white solid (8 mg 39%) ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.86 (1H, brs), 7.77 – 7.68 (1H, m), 7.39 (1H, brs), 7.10 (1H, d, *J* = 10.5 Hz), 6.97 (1H, t, *J* = 6.9 Hz), 4.49 – 4.34 (2H, m), 4.23 (4H, brs), 3.92 (3H, s), 3.49 (4H, brs), 3.04 (2H, brs), 2.34 (3H, s), 2.30 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 167.57 (d, *J* = 205.7 Hz), 163.50, 159.12 (d, *J* = 10.9 Hz), 153.31, 151.91, 146.39, 144.38, 134.22 (d, *J* = 10.9 Hz), 116.92 (d, *J* = 2.9 Hz), 116.49, 109.63 (d, *J* = 22.4 Hz), 104.55, 102.35 (d, *J* = 26.8 Hz), 69.38, 44.18, 42.34, 35.81, 23.20, 9.74, 9.68. HRMS (ESI), found 411.2309 $C_{22}H_{27}FN_6O$, $[M + H]^+$, requires 411.2309.

4-(Piperazin-1-yl)-6-(2-(2-(pyridine-3-yl)ethoxy)phenyl)pyrimidine (16c)

Following General Procedure C, **14** (66 mg, 0.18 mmol) was reacted with 3-(2-hydroxyethyl)pyridine (28 mg, 0.23 mmol) the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E and afforded the title compound as a fluffy brownish white solid (22 mg 45%) ^{1}H NMR (DMSO-d_6, 400MHz, δ, ppm) 10.16 (1H, brs), 10.06 (1H, brs), 8.89 (1H, s), 8.82 (1H, s), 8.79 (1H, d, *J* = 5.0 Hz), 8.46 (1H, d, *J* = 7.8 Hz), 7.95 (1H, brt, *J* = 6.6 Hz), 7.61 – 7.58 (2H, m), 7.34 (1H, s), 7.28 (1H, d, *J* = 8.5 Hz), 7.16 (1H, t, *J* = 7.4 Hz), 4.41 (2H, t, *J* = 5.8 Hz), 4.19 (4H, brs), 3.34 – 3.23 (6H, m). ^{13}C NMR (DMSO-d_6, 100MHz, δ, ppm) 161.35, 155.64, 152.03, 151.26, 145.70, 142.05, 140.15, 138.35, 133.48, 131.05, 126.56, 121.19, 119.93, 113.01, 103.36, 67.83, 48.53, 41.89, 31.43. HRMS (ESI), found 362.2000 $C_{21}H_{23}N_5O$, $[M + H]^+$, requires 362.1981.

4-(4-Fluoro-2-(2-(pyridine-3-yl)ethoxy)phenyl)-6-(piperazin-1-yl)pyrimidine (16d)

Following General Procedure C, **15** (88 mg, 0.23 mmol) was reacted with 3-(2-hydroxyethyl)pyridine (36 mg, 0.29 mmol) the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E and afforded the title compound as a fluffy brownish white solid (8 mg 39%) ^{1}H NMR (DMSO-d_6, 400MHz, δ, ppm) 9.88 (1H, brs), 8.87 (1H, brs), 8.78 (2H, d, *J* = 8.6 Hz), 8.42 (1H, d, *J* = 7.6 Hz), 7.97 – 7.90 (1H, m), 7.66 (1H, dd, *J* = 8.5, 6.8 Hz), 7.32 (1H, brs), 7.25 (1H, dd, *J* = 11.3, 2.1 Hz), 7.05 (1H, td, *J* = 8.4, 2.1 Hz), 4.43 (2H, t, *J* = 6.3 Hz), 4.16 (4H, brs), 3.31 – 3.26 (6H, m). ^{13}C NMR (DMSO-d_6, 100MHz, δ, ppm) 165.02 (d, *J* = 248.0 Hz), 161.33, 157.43 (d, *J* = 11.0 Hz), 151.74, 145.36, 142.41, 140.55, 137.96, 132.83 (d, *J* = 11.0 Hz), 126.46, 116.93, 108.02 (d, *J* = 22.1 Hz), 103.41, 101.43 (d, *J* = 25.5 Hz), 68.40, 42.03, 31.24. HRMS (ESI), found 380.1888 $C_{21}H_{22}FN_5O$, $[M + H]^+$, requires 380.1887.

4-(2-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)-4-fluorophenyl)-6-(piperazin-1-yl)pyrimidine (16e)

Following General Procedure C, **15** (100 mg, 0.26 mmol) was reacted with **2** (46 mg, 0.32 mmol) the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E and afforded the title as a fluffy brownish white solid (15 mg 39%) ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.85 (1H, s), 7.74 (1H, dd, *J* = 8.5, 6.4 Hz), 7.40 (1H, s), 7.12 (1H, dd, *J* = 8.5, 2.1 Hz), 6.96 (1H, td, *J* = 8.4, 2.0 Hz), 4.47 (2H brs), 4.31 – 4.17 (4H, m), 3.50 (4H, brs), 3.06 (2H, t, *J* = 6.8 Hz), 2.35 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 167.61 (d, *J* = 250.9 Hz), 163.50, 159.14 (d, *J* = 11.0 Hz), 153.37, 151.87, 145.66, 134.15 (d, *J* = 11.0 Hz), 116.98 (d, *J* = 3.1 Hz), 115.94, 109.66 (d, *J* = 22.4 Hz), 104.47, 102.38 (d, *J* = 26.8 Hz), 69.22, 44.04, 22.80, 9.77. HRMS (ESI), found 397.2154 $C_{21}H_{25}FN_6O$, $[M + H]^+$, requires 397.2152.

4-(2-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)phenyl)-6-(piperazin-1-yl)pyrimidine (16f)

Following General Procedure C, **14** (70 mg, 0.19 mmol) was reacted with **2** (34 mg, 0.24 mmol) the crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E and afforded the title compound as fluffy brownish white solid (41 mg, 72%) ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.85 (1H, brs), 7.69 (1H, dd, *J* = 7.6, 1.4 Hz), 7.66 – 7.61 (1H, m), 7.40 (1H, brs), 7.28 (1H, d, *J* = 8.4 Hz), 7.20 (1H, t, *J* = 7.5 Hz), 4.48 (2H, brs), 4.29 (2H, t, *J* = 6.8 Hz), 4.22 (2H, brs), 3.50 (4H, brs), 3.05 (2H, t, *J* = 6.8 Hz), 2.35 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 163.52, 157.30, 154.24, 151.79, 145.61, 135.34, 132.22, 122.87, 120.55, 116.18, 114.04, 104.35, 68.59, 43.97, 42.26, 22.93, 9.75. HRMS (ESI), found 379.2249 $C_{21}H_{26}N_6O$, $[M + H]^+$, requires 379.2246.

3-(3-(2-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridin-2-yl)phenol (17)

Following General Procedure D, **4** (100 mg, 0.32 mmol) was reacted with 3-hydroxyphenylboronic acid (56 mg, 0.39 mmol), the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 89 mg (74%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.79 (1H, brs), 8.24 (1H, dd, *J* = 4.6, 1.4 Hz), 7.29 (1H, dt, *J* = 7.7, 1.3 Hz), 7.24 – 7.18 (2H, m), 7.16 (1H, dd, *J* = 8.3, 4.6 Hz), 6.85 – 6.80 (2H, m), 4.01 (2H, t, *J* = 6.6 Hz), 3.68 (3H, s), 2.81 (2H, t, *J* = 6.5 Hz), 2.10 (3H, s), 2.03 (3H, s).

2'-(2-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-ol (18)

Following General Procedure D, **3** (100 mg, 0.32 mmol) was reacted with 3-hydroxyphenylboronic acid (56 mg, 0.39 mmol), the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 80 mg (76%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.28 – 7.22 (4H, m), 7.00 – 6.95 (1H, m), 6.94 – 6.89 (2H, m), 6.84 (1H, ddd, *J* =

8.1, 2.5, 1.0 Hz), 6.08 (1H, dd, *J* = 2.3, 1.6 Hz), 4.09 (2H, t, *J* = 6.2 Hz), 3.72 (3H, s), 2.82 (2H, t, *J* = 6.2 Hz), 2.08 (3H, s), 2.04 (3H, s).

4'-Fluoro-2'-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-ol (19)

Following General Procedure D, **5** (90 mg, 0.27 mmol) was reacted with 3-hydroxyphenylboronic acid (48 mg, 0.34 mmol), **and** the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 73 mg (78%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.25 – 7.17 (2H, m), 6.87 – 6.82 (2H, m), 6.70 – 6.62 (2H, m), 6.10 – 6.08 (1H, m), 4.04 (2H, t, *J* = 6.2 Hz), 3.72 (3H, s), 2.82 (2H, t, *J* = 6.2 Hz), 2.09 (3H, s), 2.02 (3H, s).

3-(3-(2-(Pyridin-3-yl)ethoxy)pyridin-2-yl)phenol (20)

Following General Procedure D, **10** (100 mg, 0.35 mmol) was reacted with 3-hydroxyphenylboronic acid (61 mg, 0.44 mmol), and the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 75 mg (71%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.57 (1H, d, *J* = 1.7 Hz), 8.47 (1H, dd, *J* = 4.9, 1.6 Hz), 8.23 (1H, dd, *J* = 3.8, 2.2 Hz), 7.60 – 7.55 (1H, m), 7.30 – 7.26 (1H, m), 7.23 (2H, dt, *J* = 7.7, 1.4 Hz), 7.16 – 7.13 (2H, m), 6.99 (1H, dd, *J* = 2.5, 1.5 Hz), 6.92 (1H, ddd, *J* = 7.8, 2.5, 1.4 Hz), 4.10 (2H, t, *J* = 5.8 Hz), 3.02 (2H, t, *J* = 5.7 Hz).

2'-(2-(Pyridin-3-yl)ethoxy)-[1,1'-biphenyl]-3-ol (21)

Following General Procedure D, **9** (100 mg, 0.36 mmol) was reacted with 3-hydroxyphenylboronic acid (62 mg, 0.45 mmol), the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 78 mg (74%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 10.03 (1H, brs), 8.53 (1H, s), 8.45 (1H, d, *J* = 3.9 Hz), 7.54 (1H, d, *J* = 7.8 Hz), 7.34 – 7.20 (4H, m), 7.02 – 6.95 (2H, m), 6.89 (3H, m), 4.08 (2H, t, *J* = 5.7 Hz), 2.96 (2H, t, *J* = 5.6 Hz).

4'-Fluoro-2'-(2-(pyridin-3-yl)ethoxy)-[1,1'-biphenyl]-3-ol (22)

Following General Procedure D, **11** (100 mg, 0.33 mmol) was reacted with 3-hydroxyphenylboronic acid (58 mg, 0.42 mmol), and the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 90 mg (86%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 9.82 (1H, s), 8.53 (1H, d, *J* = 2.0 Hz), 8.46 (1H, dd, *J* = 4.9, 1.6 Hz), 7.57 (1H, dt, *J* = 7.8, 1.9 Hz), 7.30 – 7.18 (3H, m), 6.93 (1H, ddd, *J* = 8.2, 2.5, 0.9 Hz), 6.82 (1H, dt, *J* = 7.6, 1.2 Hz), 6.71 (1H, dd, *J* = 2.4, 1.7 Hz), 6.66 (1H, td, *J* = 8.2, 2.4 Hz), 6.57 (1H, dd, *J* = 11.0, 2.4 Hz), 4.05 (2H, t, *J* = 5.6 Hz), 2.99 (2H, t, *J* = 5.6 Hz).

3-(3-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridin-2-yl)phenol (23)

Following General Procedure D, **7** (55 mg, 0.18 mmol) was reacted with 3-hydroxyphenylboronic acid (32 mg, 0.23 mmol), and the crude was purified by flash column chromatography by elution with a

gradient of pentane/EtOAc to afford 40 mg (70%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.21 (1H, d, *J* = 5.8 Hz), 7.22 – 7.11 (4H, m), 6.81 – 6.77 (2H, m), 3.98 (2H, t, *J* = 5.4 Hz), 2.75 (2H, t, *J* = 5.4 Hz), 2.00 (6H, s).

2'-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-ol (24)

Following General Procedure D, **6** (51 mg, 0.17 mmol) was reacted with 3-hydroxyphenylboronic acid (36 mg, 0.26 mmol), and the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 43 mg (80%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.26 – 7.23 (1H, m), 7.22 – 7.16 (2H, m), 6.94 (1H, td, *J* = 7.5, 1.0 Hz), 6.90 (1H, d, *J* = 8.3 Hz), 6.86 (1H, dt, *J* = 7.6, 1.2 Hz), 6.84 – 6.79 (1H, m), 6.49 – 6.46 (1H, m), 4.00 (2H, t, *J* = 6.2 Hz), 2.72 (2H, t, *J* = 6.2 Hz), 1.99 (6H, s).

2'-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)-4'-fluoro-[1,1'-biphenyl]-3-ol (25)

Following General Procedure D, **8** (100 mg, 0.31 mmol) was reacted with 3-hydroxyphenylboronic acid (55 mg, 0.40 mmol), and the crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc t to afford 71 mg (68%) of the title compound as a beige solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.21 – 7.16 (1H, m), 7.13 (1H, dd, *J* = 8.3, 6.9 Hz), 6.82 (2H, dd, *J* = 8.3, 4.2 Hz), 6.68 – 6.60 (2H, m), 6.50 – 6.46 (1H, m), 3.98 (2H, t, *J* = 6.1 Hz), 2.73 (2H, t, *J* = 6.1 Hz), 1.99 (6H, s).

***N*,*N*-Dimethyl-2-(3-(3-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridin-2-yl)phenoxy)-ethan-1-amine (26a)**

Following General Procedure C, **17** (100 mg, 0.31 mmol) was reacted with 2-(dimethylamino)ethanol (34 mg, 0.38 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 33 mg (41%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.14 (1H, dd, *J* = 4.7, 1.3 Hz), 7.51 (1H, dd, *J* = 8.4, 1.3 Hz), 7.35 – 7.29 (2H, m), 7.25 (1H, dd, *J* = 2.5, 1.5 Hz), 7.21 (1H, dt, *J* = 7.6, 1.1 Hz), 7.01 (1H, ddd, *J* = 8.2, 2.5, 1.0 Hz), 4.15 (2H, t, *J* = 5.5 Hz), 4.09 (2H, t, *J* = 6.5 Hz), 3.61 (3H, s), 2.89 (2H, t, *J* = 5.5 Hz), 2.79 (2H, t, *J* = 6.5 Hz), 2.42 (6H, s), 2.02 (3H, s), 1.97 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 159.68, 154.52, 149.60, 146.89, 141.57, 140.12, 139.22, 130.07, 124.94, 123.27, 122.12, 116.46, 115.85, 113.38, 69.82, 66.27, 58.95, 45.63, 35.73, 24.44, 11.60, 9.38. HRMS (ESI), found 395.2446 $C_{23}H_{30}N_4O_2$, $[M + H]^+$, requires 395.2447.

***N*,*N*-Dimethyl-2-((2'-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-yl)oxy)-ethan-1-amine (26b)**

Following General Procedure C, **18** (100 mg, 0.31 mmol) was reacted with 2-(dimethylamino)ethanol (34 mg, 0.38 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 36 mg (45%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD,

400MHz, δ, ppm) 7.27 – 7.19 (3H, m), 7.01 – 6.95 (3H, m), 6.93 (1H, ddd, *J* = 7.6, 1.5, 0.9 Hz), 6.89 (1H, ddd, *J* = 8.3, 2.6, 0.9 Hz), 4.08 (2H, t, *J* = 5.5 Hz), 3.96 (2H, t, *J* = 6.5 Hz), 3.58 (3H, s), 2.82 (2H, t, *J* = 5.5 Hz), 2.70 (2H, t, *J* = 6.5 Hz), 2.37 (6H, s), 1.98 (3H, s), 1.91 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 159.67, 157.13, 146.84, 141.77, 139.18, 132.35, 131.78, 129.97, 129.79, 123.35, 122.04, 116.86, 114.10, 113.98, 113.72, 69.71, 66.36, 59.06, 45.74, 35.69, 24.64, 11.56, 9.31. HRMS (ESI), found 394.2496 $C_{24}H_{31}N_3O_2$, $[M + H]^+$, requires 394.2495.

2-((4'-Fluoro-2'-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-yl)oxy)-*N*,*N*-dimethylethan-1-amine (26c)

Following General Procedure C, **19** (100 mg, 0.29 mmol) was reacted with 2-(dimethylamino)ethanol (32 mg, 0.36 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 60 mg (44%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 7.24 (1H, t, *J* = 7.9 Hz), 7.18 (1H, dd, *J* = 8.4, 6.9 Hz), 6.95 – 6.92 (1H, m), 6.89 (2H, dt, *J* = 7.5, 2.3 Hz), 6.78 (1H, dd, *J* = 11.2, 2.4 Hz), 6.68 (1H, td, *J* = 8.3, 2.5 Hz), 4.09 (2H, t, *J* = 5.4 Hz), 3.97 (2H, t, *J* = 6.4 Hz), 3.58 (3H, s), 2.85 (2H, t, *J* = 5.4 Hz), 2.71 (2H, t, *J* = 6.4 Hz), 2.40 (6H, s), 1.97 (3H, s), 1.90 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 164.35 (d, *J* = 243.1 Hz), 159.67, 158.31 (d, *J* = 9.9 Hz), 146.85, 140.89, 139.21, 132.62 (d, *J* = 9.9 Hz), 130.07, 128.32 (d, *J* = 3.3 Hz), 123.38, 116.89, 114.06, 113.56, 107.94 (d, *J* = 21.2 Hz), 101.57 (d, *J* = 25.7 Hz), 69.91, 66.24, 58.99, 45.67, 39.46, 35.70, 24.41, 11.55, 9.30. HRMS (ESI), found 412.2401 $C_{24}H_{30}FN_3O_2$, $[M + H]^+$, requires 412.2400.

***N*,*N*-Dimethyl-2-(3-(3-(2-(pyridin-3-yl)ethoxy)pyridin-2-yl)phenoxy)ethan-1-amine (26d)**

Following General Procedure C, **20** (100 mg, 0.34 mmol) was reacted with 2-(dimethylamino)ethanol (37 mg, 0.42 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 30 mg (28%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.39 (1H, s), 8.36 (1H, d, *J* = 4.2 Hz), 8.16 (1H, dd, *J* = 4.8, 1.3 Hz), 7.67 – 7.63 (1H, m), 7.54 (1H, dd, *J* = 8.4, 1.3 Hz), 7.36 – 7.26 (3H, m), 7.24 (1H, dd, *J* = 2.5, 1.5 Hz), 7.15 (1H, ddd, *J* = 7.7, 1.5, 1.0 Hz), 7.01 (1H, ddd, *J* = 8.2, 2.6, 1.0 Hz), 4.31 (2H, t, *J* = 6.1 Hz), 4.13 (2H, t, *J* = 5.5 Hz), 3.10 (2H, t, *J* = 6.0 Hz), 2.81 (2H, t, *J* = 5.5 Hz), 2.36 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 158.37, 152.90, 149.17, 148.02, 146.65, 140.30, 138.33, 137.60, 135.01, 128.50, 123.59, 123.53, 121.86, 120.46, 115.15, 114.39, 68.51, 65.20, 57.67, 44.38, 32.18. HRMS (ESI), found 364.2026 $C_{22}H_{25}N_3O_2$, $[M + H]^+$, requires 364.2025.

***N*,*N*-Dimethyl-2-((2'-(2-(pyridin-3-yl)ethoxy)-[1,1'-biphenyl]-3-yl)oxy)ethan-1-amine (26e)**

Following General Procedure C, **21** (95 mg, 0.32 mmol) was reacted with 2-(dimethylamino)ethanol (35 mg, 0.40 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 50 mg (46%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD,

400MHz, δ, ppm) 8.40 (1H, dd, *J* = 4.9, 1.4 Hz), 8.39 – 8.37 (1H, m), 7.70 – 7.66 (1H, m), 7.34 – 7.24 (4H, m), 7.04 – 7.02 (1H, m), 7.01 – 6.94 (4H, m), 4.29 – 4.26 (2H, m), 4.22 (2H, t, *J* = 5.8 Hz), 3.36 – 3.32 (2H, m), 3.02 (2H, t, *J* = 5.8 Hz), 2.78 (3H, s), 2.71 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 158.95, 156.85, 150.77, 147.91, 141.40, 139.08, 137.16, 131.58, 131.56, 130.08, 129.95, 125.15, 123.85, 122.08, 117.74, 113.38, 113.18, 69.68, 64.19, 58.16, 44.44, 39.45, 33.82. HRMS (ESI), found 363.2073 $C_{23}H_{26}N_2O_2$, $[M + H]^+$, requires 363.2073.

2-((4'-fluoro-2'-(2-(pyridin-3-yl)ethoxy)-[1,1'-biphenyl]-3-yl)oxy)-*N*,*N*-dimethylethan-1-amine (26f)

Following General Procedure C, **22** (110 mg, 0.35 mmol) was reacted with 2-(dimethylamino)ethanol (40 mg, 0.44 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 54 mg (40%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.26 (2H, brs), 7.49 (1H, dt, *J* = 7.9, 1.9 Hz), 7.21 – 7.13 (3H, m), 6.88 – 6.83 (2H, m), 6.80 – 6.77 (1H, m), 6.75 (1H, dd, *J* = 11.1, 2.5 Hz), 6.64 (1H, td, *J* = 8.3, 2.5 Hz), 4.11 (2H, t, *J* = 6.0 Hz), 4.02 (2H, t, *J* = 5.5 Hz), 2.94 (2H, t, *J* = 5.9 Hz), 2.73 (2H, t, *J* = 5.5 Hz), 2.29 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 164.35 (d, *J* = 243.3 Hz), 159.73, 158.02 (d, *J* = 9.9 Hz), 150.54, 147.93, 140.46, 139.09, 136.58, 132.48 (d, *J* = 9.9 Hz), 129.95, 128.09 (d, *J* = 3.3 Hz), 124.94, 123.47, 117.03, 113.88, 108.10 (d, *J* = 21.2 Hz), 101.33 (d, *J* = 25.8 Hz), 69.83, 66.39, 59.05, 45.76, 33.56. HRMS (ESI), found 381.1978 $C_{23}H_{25}FN_2O_2$, $[M + H]^+$, requires 381.1978.

2-(3-(3-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)pyridin-2-yl)phenoxy)-*N*,*N*-dimethylethan-1-amine (26g)

Following General Procedure C, **23** (40 mg, 0.13 mmol) was reacted with 2-(dimethylamino)ethanol (14 mg, 0.16 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 22 mg (44%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.14 (1H, d, *J* = 4.7 Hz), 7.53 (1H, d, *J* = 8.4 Hz), 7.36 – 7.30 (2H, m), 7.18 (1H, d, *J* = 8.2 Hz), 7.16 – 7.14 (1H, m), 6.99 (1H, dd, *J* = 8.2, 2.6 Hz), 4.14 – 4.10 (4H, m), 2.84 – 2.79 (4H, m), 2.37 (6H, s), 2.03 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 158.28, 153.11, 148.11, 140.00, 138.57, 128.67, 123.49, 121.63, 120.47, 115.20, 113.99, 110.93, 68.19, 64.98, 57.72, 44.32, 22.53. HRMS (ESI), found 381.2290 $C_{22}H_{28}N_4O_2$, $[M + H]^+$, requires 381.2291.

2-((2'-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)-[1,1'-biphenyl]-3-yl)oxy)-*N*,*N*-dimethylethan-1-amine (26h)

Following General Procedure C, **24** (42 mg, 0.13 mmol) was reacted with 2-(dimethylamino)ethanol (15 mg, 0.17 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 24 mg (46%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 7.28 – 7.20 (3H, m), 7.03 – 6.99 (1H, m), 6.98 (1H, dd, *J* = 7.4, 1.1 Hz), 6.95 – 6.91

(2H, m), 6.88 (1H, ddd, *J* = 8.2, 2.4, 1.1 Hz), 4.07 (2H, t, *J* = 5.4 Hz), 4.00 (2H, t, *J* = 6.5 Hz), 2.79 (2H, t, *J* = 5.4 Hz), 2.75 (2H, t, *J* = 6.5 Hz), 2.36 (6H, s), 2.00 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 159.66, 157.14, 141.69, 132.22, 131.82, 130.00, 129.77, 123.18, 121.93, 117.02, 113.85, 113.63, 112.71, 69.47, 66.33, 59.20, 45.79, 24.16. HRMS (ESI), found 380.2338 $C_{23}H_{29}N_3O_2$, $[M + H]^+$, requires 380.2338.

2-((2'-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)-4'-fluoro-[1,1'-biphenyl]-3-yl)oxy)-*N*,*N*-dimethylethan-1-amine (26i)

Following General Procedure C, **25** (90 mg, 0.27 mmol) was reacted with 2-(dimethylamino)ethanol (30 mg, 0.34 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford 40 mg (36%) of the title compound as a brown resin. ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 7.26 – 7.22 (1H, m), 7.18 (1H, dd, *J* = 8.5, 6.8 Hz), 6.88 – 6.84 (3H, m), 6.79 (1H, dd, *J* = 11.2, 2.5 Hz), 6.67 (1H, td, *J* = 8.3, 2.5 Hz), 4.05 (2H, t, *J* = 5.4 Hz), 4.00 (2H, t, *J* = 6.3 Hz), 2.79 (2H, t, *J* = 5.3 Hz), 2.74 (2H, t, *J* = 6.3 Hz), 2.36 (6H, s), 1.98 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 162.93 (d, *J* = 243.1 Hz), 158.24, 156.90 (d, *J* = 9.9 Hz), 139.36, 131.26 (d, *J* = 9.9 Hz), 128.70, 126.75 (d, *J* = 3.4 Hz), 121.77, 115.68, 112.19, 111.13, 106.43 (d, *J* = 21.2 Hz), 99.95 (d, *J* = 25.4 Hz), 68.25, 64.76, 57.72, 44.30, 22.52. HRMS (ESI), found 398.2244 $C_{22}H_{28}N_6O$, $[M + H]^+$, requires 398.2244.

1,3,5-Trimethyl-4-(2-(naphthalen-2-yloxy)ethyl)-1*H*-pyrazole (27)

Following General Procedure C, **1** (130 mg, 0.85 mmol) was reacted with 1-bromo-2-naphthol (238 mg, 1.07 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 200 mg (64%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.24 – 8.20 (1H, m), 7.78 (1H, d, *J* = 2.6 Hz), 7.77 – 7.75 (1H, m), 7.56 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz), 7.39 (1H, ddd, *J* = 8.1, 6.8, 1.1 Hz), 7.19 (1H, d, *J* = 9.0 Hz), 4.16 (2H, t, *J* = 7.2 Hz), 3.71 (3H, s), 2.94 (2H, t, *J* = 7.1 Hz), 2.25 (3H, s), 2.24 (3H, s).

3-(2-(Naphthalen-2-yloxy)ethyl)pyridine (28)

Following General Procedure C, 3-(2-hydroxyethyl)pyridine (55 mg, 0.44 mmol) was reacted with 1-bromo-2-naphthol (124 mg, 0.55 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 130 mg (89%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.61 (1H, d, *J* = 1.9 Hz), 8.47 (1H, dd, *J* = 4.8, 1.6 Hz), 8.20 – 8.16 (1H, m), 7.73 – 7.67 (3H, m), 7.51 (1H, ddd, *J* = 8.4, 6.9, 1.2 Hz), 7.34 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz), 7.22 – 7.18 (1H, m), 7.08 (1H, d, *J* = 9.0 Hz), 4.25 (2H, t, *J* = 6.4 Hz), 3.10 (2H, t, *J* = 6.3 Hz).

3,5-Dimethyl-4-(2-(naphthalen-2-yloxy)ethyl)-1*H*-pyrazole (29)

Following General Procedure C, **2** (132 mg, 0.94 mmol) was reacted with 1-bromo-2-naphthol (238 mg, 1.07 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc to afford 213 mg (65%) of the title compound as a yellow pale solid. ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 8.22 (1H, dt, *J* = 8.6, 0.9 Hz), 7.77 (2H, d, *J* = 8.9 Hz), 7.59 – 7.53 (1H, m), 7.44 – 7.36 (1H, m), 7.19 (1H, d, *J* = 9.0 Hz), 4.18 (2H, t, *J* = 7.1 Hz), 2.97 (2H, t, *J* = 7.1 Hz), 2.31 (6H, s).

1-(4-(2-(2-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)ethoxy)naphthalen-1-yl)pyridin-2-yl)piperazine (30a)

Following General Procedure D, **27** (90 mg, 0.25 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (117 mg, 0.30 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy pale yellow solid (14 mg, 36%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.18 (1H, d, *J* = 5.7 Hz), 7.95 (1H, d, *J* = 9.1 Hz), 7.83 (1H, d, *J* = 7.1 Hz), 7.45 (1H, d, *J* = 9.1 Hz), 7.38 – 7.32 (3H, m), 7.16 (1H, brs), 6.85 (1H, d, *J* = 5.6 Hz), 4.20 – 4.14 (2H, m), 3.96 (4H, brs), 3.78 (3H, s), 3.42 (4H, brs), 2.79 (2H, t, *J* = 5.8 Hz), 2.11 (3H, s), 2.06 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 156.37, 154.07, 153.83, 145.48, 143.23, 142.18, 133.38, 132.13, 130.58, 129.31, 128.33, 125.27, 125.02, 123.19, 119.05, 115.99, 115.89, 114.34, 70.47, 44.30, 44.02, 35.77, 24.19, 10.40, 9.42. HRMS (ESI), found 442.2606 $C_{27}H_{31}N_5O$, $[M + H]^+$, requires 442.2607.

***N*,*N*-Dimethyl-2-(3-(2-(2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethoxy)naphthalen-1-yl)phenoxy)ethan-1-amine (30b)**

Following General Procedure D, **27** (18 mg, 0.05 mmol) was reacted with 3-hydroxyphenylboronic acid (9 mg, 0.06 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc. The resulting residue was reacted (10 mg, 0.02 mmol) with 2-(dimethylamino)ethanol (4 mg, 0.04 mmol) according to General Procedure C. The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford the title compound as a brown resin (8 mg, 67%). 7.85 (1H, d, *J* = 9.0 Hz), 7.83 – 7.77 (1H, m), 7.40 – 7.33 (3H, m), 7.32 – 7.25 (2H, m), 7.04 – 6.99 (1H, m), 6.82 – 6.78 (2H, m), 4.09 (2H, td, *J* = 5.6, 1.4 Hz), 4.03 (2H, t, *J* = 6.3 Hz), 3.60 (3H, s), 2.78 (2H, t, *J* = 5.5 Hz), 2.64 (2H, t, *J* = 6.4 Hz), 2.34 (6H, s), 1.97 (3H, s), 1.87 (3H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 160.09, 154.48, 146.78, 139.60, 139.28, 134.92, 130.69, 130.22, 128.89, 127.19, 126.06, 124.61, 118.13, 116.52, 114.33, 113.81, 71.13, 66.59, 59.15, 45.88, 35.67, 24.88, 11.48, 9.21. HRMS (ESI), found 444.2651 $C_{28}H_{33}N_3O_2$, $[M + H]^+$, requires 444.2651.

1-(4-(2-(2-(Pyridin-3-yl)ethoxy)naphthalen-1-yl)pyridin-2-yl)piperazine (30c)

Following General Procedure D, **28** (89 mg, 0.27 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (131 mg, 0.34 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy pale yellow solid (60 mg, 88%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.77 (1H, brs), 8.71 (1H, brs), 8.45 (1H, d, *J* = 8.1 Hz), 8.15 (1H, d, *J* = 6.2 Hz), 8.04 – 7.98 (2H, m), 7.88 (1H, dd, *J* = 7.5, 1.4 Hz), 7.52 (1H, d, *J* = 9.2 Hz), 7.46 – 7.37 (3H, m), 7.33 (1H, brs), 6.92 (1H, d, *J* = 6.1 Hz), 4.49 (2H, q, *J* = 5.8 Hz), 4.08 – 4.01 (4H, m), 3.53 – 3.46 (4H, m), 3.31 – 3.27 (2H, m). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 155.53, 154.60, 153.56, 148.66, 142.75, 141.29, 140.86, 139.09, 133.09, 132.71, 130.64, 129.45, 128.69, 128.26, 125.48, 124.81, 122.17, 118.98, 115.66, 115.31, 69.43, 44.52, 43.80, 33.52. HRMS (ESI), found 411.2185 $C_{26}H_{26}N_4O$, $[M + H]^+$, requires 411.2185.

***N*,*N*-Dimethyl-2-(3-(2-(2-(pyridin-3-yl)ethoxy)naphthalen-1-yl)phenoxy)ethan-1-amine (30d)**

Following General Procedure D, **28** (100 mg, 0.30 mmol) was reacted with 3-hydroxyphenylboronic acid (52 mg, 0.38 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc. The resulting residue was reacted (90 mg, 0.26 mmol) with 2-(dimethylamino)ethanol (29 mg, 0.33 mmol) according to General Procedure C. The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford the title compound as a brown resin (85 mg, 79%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.17 (1H, dd, *J* = 4.9, 1.5 Hz), 8.08 (1H, d, *J* = 1.7 Hz), 7.66 (1H, d, *J* = 8.9 Hz), 7.64 – 7.60 (1H, m), 7.32 – 7.28 (1H, m), 7.26 – 7.21 (1H, m), 7.16 – 7.11 (4H, m), 6.99 (1H, ddd, *J* = 7.8, 4.9, 0.7 Hz), 6.89 (1H, ddd, *J* = 8.3, 2.6, 0.9 Hz), 6.67 (1H, dd, *J* = 2.5, 1.4 Hz), 6.63 (1H, dt, *J* = 7.5, 1.2 Hz), 3.99 (2H, t, *J* = 5.9 Hz), 4.00 – 3.85 (2H, m), 2.69 (2H, t, *J* = 5.8 Hz), 2.57 (2H, t, *J* = 5.5 Hz), 2.15 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 159.93, 153.98, 150.33, 147.71, 139.18, 139.11, 136.59, 134.68, 130.51, 130.28, 130.22, 128.94, 127.30, 126.65, 126.04, 124.76, 124.68, 124.63, 118.19, 115.75, 114.20, 70.29, 66.47, 59.02, 45.85, 33.87. HRMS (ESI), found 413.2229 $C_{27}H_{28}N_2O_2$, $[M + H]^+$, requires 413.2229.

1-(4-(2-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)naphthalen-1-yl)pyridin-2-yl)piperazine (30e)

Following General Procedure D, **29** (40 mg, 0.11 mmol) was reacted with 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)pyridine-4-boronic acid, pinacol ester (56 mg, 0.14 mmol). The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%). The resulting residue was reacted according to General Procedure E. Afforded the title compound as a fluffy pale yellow solid (12 mg, 50%). ^{1}H NMR (CD_3OD, 400MHz, δ, ppm) 8.21 (1H, d, *J* = 6.4 Hz), 8.05 (1H, d, *J* = 9.1 Hz), 7.92 – 7.88 (1H, m), 7.54 (1H, d, *J* = 9.2 Hz), 7.52 (1H, brs), 7.50 – 7.39 (3H, m), 7.09 (1H, dd, *J* = 6.4, 1.1 Hz), 4.32 (2H, q, *J* = 6.3 Hz), 4.18 – 4.11 (4H, m), 3.58 – 3.52 (4H, m), 2.94 (2H, t, *J* = 6.2 Hz), 2.29 (6H, s). ^{13}C NMR (CD_3OD, 100MHz, δ, ppm) 157.09, 153.95, 153.61, 145.53, 137.48, 132.97, 132.88,

130.51, 129.43, 128.76, 125.47, 124.76, 121.73, 119.16, 116.71, 116.45, 115.54, 69.69, 44.71, 43.67, 23.33, 9.70. HRMS (ESI), found 428.2450 $C_{26}H_{29}N_5O$, $[M + H]^+$, requires 428.2450.

2-(3-(2-(2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)ethoxy)naphthalen-1-yl)phenoxy)-*N*,*N*-dimethylethan-1-amine (30f)

Following General Procedure D, **29** (100 mg, 0.28 mmol) was reacted with 3-hydroxyphenylboronic acid (48 mg, 0.34 mmol). The crude was purified by flash column chromatography by elution with a gradient of pentane/EtOAc. The resulting residue was reacted (100 mg, 0.28 mmol) with 2-(dimethylamino)ethanol (30 mg, 0.33 mmol) according to General Procedure C. The crude was purified by reverse phase chromatography (6g C18 column; MeCN in water 0-100%) to afford the title compound as a brown resin (70 mg, 60%). ^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm) 7.83 (1H, d, *J* = 9.1 Hz), 7.81 – 7.77 (1H, m), 7.44 – 7.40 (1H, m), 7.39 – 7.34 (1H, m), 7.32 – 7.28 (3H, m), 6.93 – 6.87 (2H, m), 6.56 (1H, dd, *J* = 2.5, 1.5 Hz), 4.23 – 4.17 (1H m), 4.12 (1H, ddd, *J* = 10.7, 7.7, 3.3 Hz), 4.01 (2H, ddd, *J* = 8.1, 6.4, 3.7 Hz), 2.93 (1H, ddd, *J* = 13.3, 7.6, 3.6 Hz), 2.74 – 2.68 (3H, m), 2.46 (6H, s), 1.96 (6H, s). ^{13}C NMR ($CDCl_3$, 100MHz, δ, ppm) 158.64, 153.15, 137.97, 133.70, 129.05, 128.89, 128.77, 127.77, 126.21, 125.40, 125.11, 123.58, 123.48, 117.97, 114.53, 111.74, 111.33, 69.18, 65.18, 58.59, 45.82, 23.55, 10.81. HRMS (ESI), found 430.2496 $C_{27}H_{31}N_3O_2$, $[M + H]^+$, requires 430.2495.

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