Supplementary Materials

Design, Sustainable Synthesis and Biological Evaluation of a Novel Dual α_{2A}/5-HT$_7$ Receptor Antagonist

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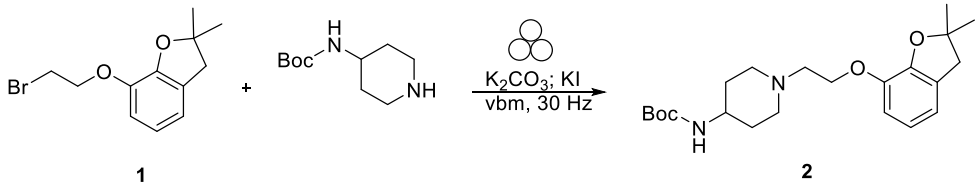
Table S1. Optimization of milling conditions for alkylation of 4-Boc-*N*-aminopiperidine.

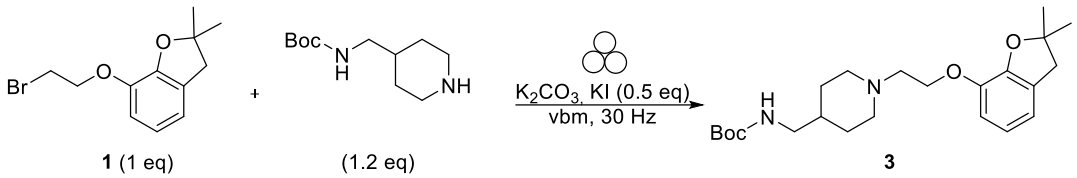


1 2

	Amine eq	K_2CO_3 eq	KI eq	Time [min]	% conversion for 2[a]
1	1	3	0.5	140	74
2	1.2	3	-	20	0
3	1.2	3	0.5	20	4
4	1.2	3	-	100	15
5	1.2	3	0.5	100	49
6	1.2	3	-	120	19
7	1.2	3	0.5	120	82
8	1.2	3	-	140	23
9	1.2	3	0.5	140	87
19	1.2	2	0.5	140	87
11	1.2	2	0.25	140	36
12[b]	1.2	2	0.5	140	36
13[b]	1.2	2	0.5	210	69
14[b]	1.2	3	0.5	140	57
15[b]	1.2	3	0.5	210	97 (84)[c]

Reaction conditions: vbm 30 Hz, ϕ_{ball} = 1.5 cm, total mass of reagents = 125 mg, milling load 15 mg/mL, 10 mL PTFE jar; [a]Conversions were determined by HPLC, [b]Reaction conditions: vbm 30 Hz, ϕ_{ball} = 1.5 cm, total mass of reagents = 500 mg, 35 mL PTFE jar, [c]Yield for isolated compound.

Table S2. Optimization of milling conditions for alkylation of 4-Boc-*N* aminomethylpiperidine.

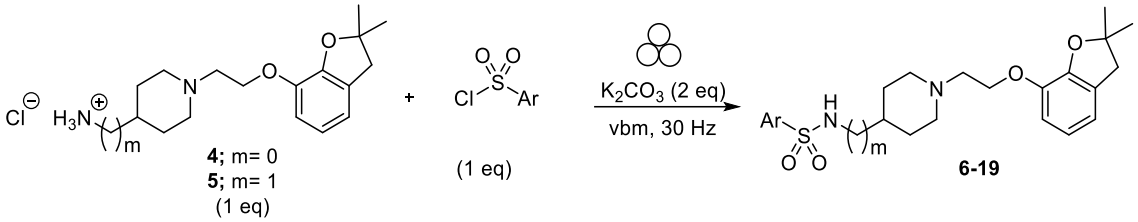


1 (1 eq) (1.2 eq) **3**

entry	base (K_2CO_3) (eq)	time [min]	% conversion for 3[a]
1	2	140	62
2	3	140	82
3	3	210	84 (81)[b]

Reaction conditions: vbm 30 Hz, ϕ_{ball} = 1.5 cm, total mass of reagents = 500 mg, milling load 15 mg/mL, 35 mL PTFE jar, [a]Conversions were determined by HPLC, [b]Yield for isolated compound

Table S3. Optimization of milling conditions for sulfonylation of primary amine.



4; m= 0
5; m= 1
(1 eq) (1 eq) **6-19**

entry	product	Ar	time [min]	% conversion[a]	% yield[b]
1	6	4-F-phenyl	1	91	89
2	7	3-Cl-phenyl	1	88	86
3	8	5-Cl,2-F-phenyl	5	69	68
4	9	5-Cl,2-MeO-phenyl	10	84	84
5	10	2,5-diMeO-phenyl	5	79	70
6	11	1-naphtyl	5	74	69
7	12	2-naphtyl	5	65	65
8	13	4-isoquinolyl	5	85	82
9	14	4-F-phenyl	1	91	90
10	15	3-Cl-phenyl	1	82	83
11	16	5-Cl,2-F-phenyl	5	70	67
12	17	5-Cl,2-MeO-phenyl	10	78	76
13	18	1-naphtyl	5	78	73
14	19	4-isoquinolyl	5	98	94

Reaction conditions: vbm 30 Hz, ϕ_{ball} = 1.5 cm, total mass of reagents = 125 mg, milling load 15 mg/mL, 10 mL PTFE jar, [a]Conversions were determined by HPLC, [b]Yield for isolated compound.

1. MS, ^{1}H-NMR and ^{13}C-NMR for intermediates and final compounds

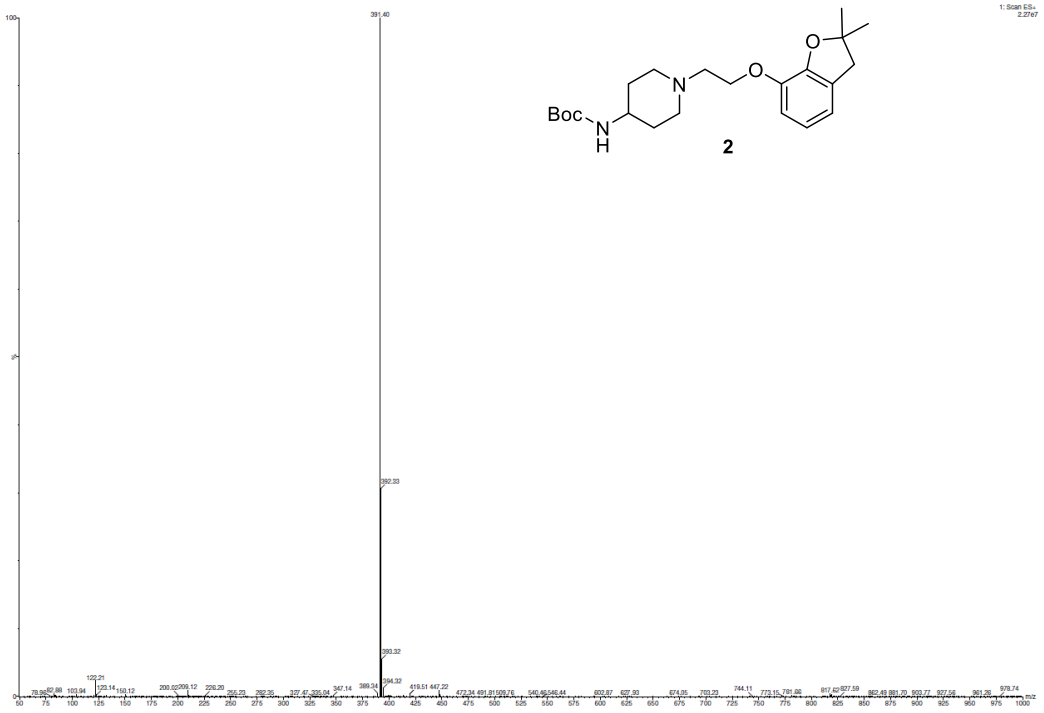


Figure S1. MS spectra for *tert*-butyl {1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}carbamate (**2**).

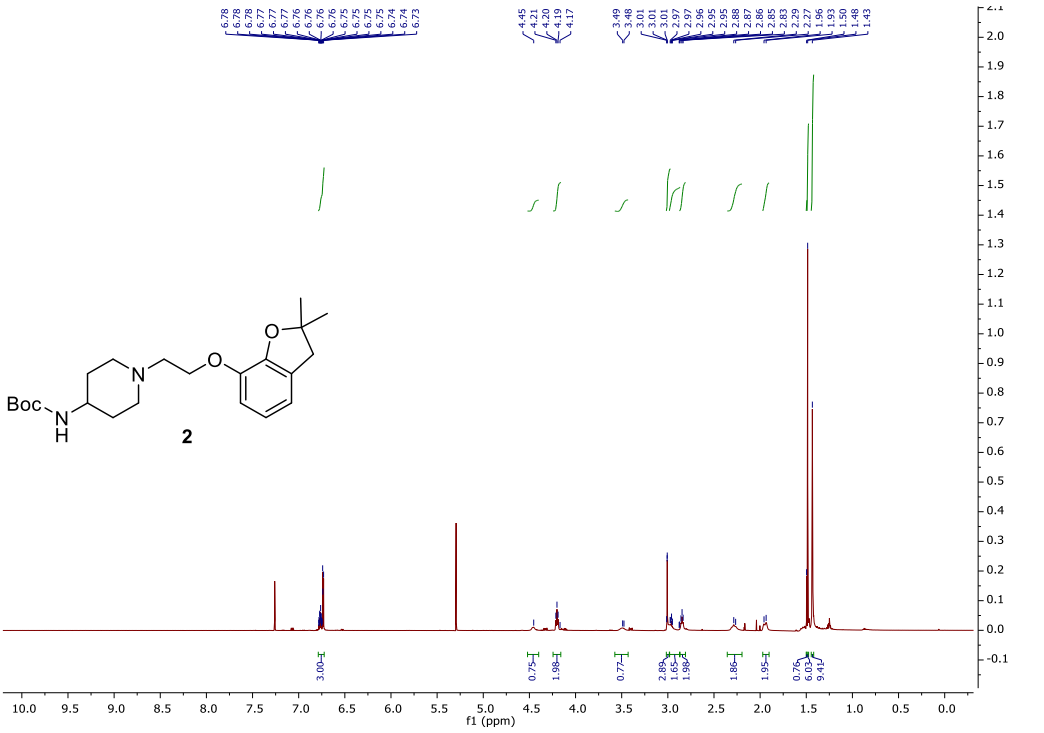


Figure S2. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for *tert*-butyl {1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}carbamate (**2**).

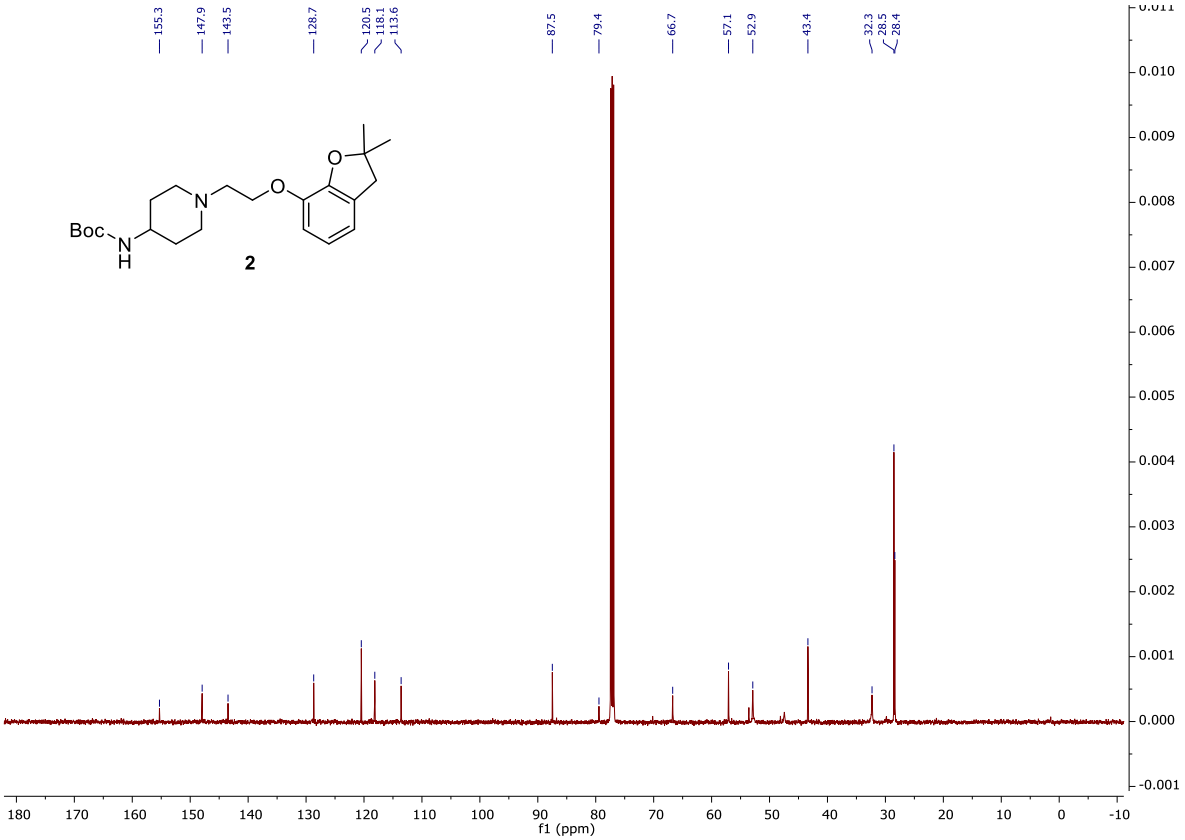


Figure S3. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for *tert*-butyl {1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}carbamate (**2**).

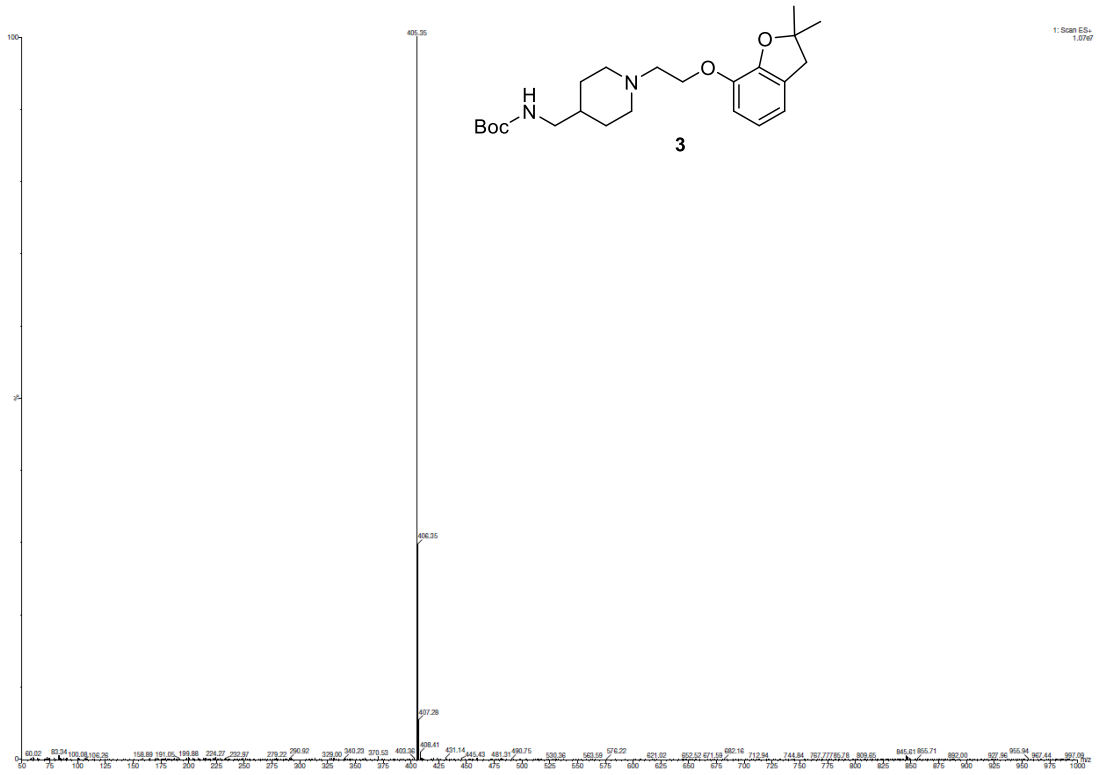


Figure S4. MS spectra for tert-butyl ({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)carbamate (**3**).

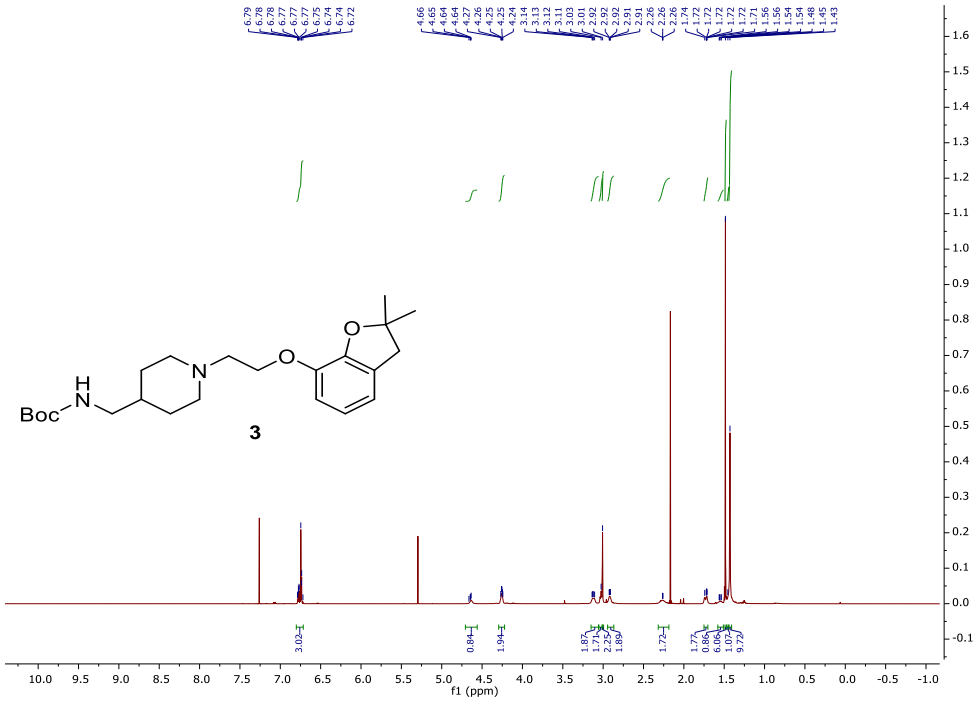


Figure S5. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for *tert*-butyl ({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)carbamate (**3**).

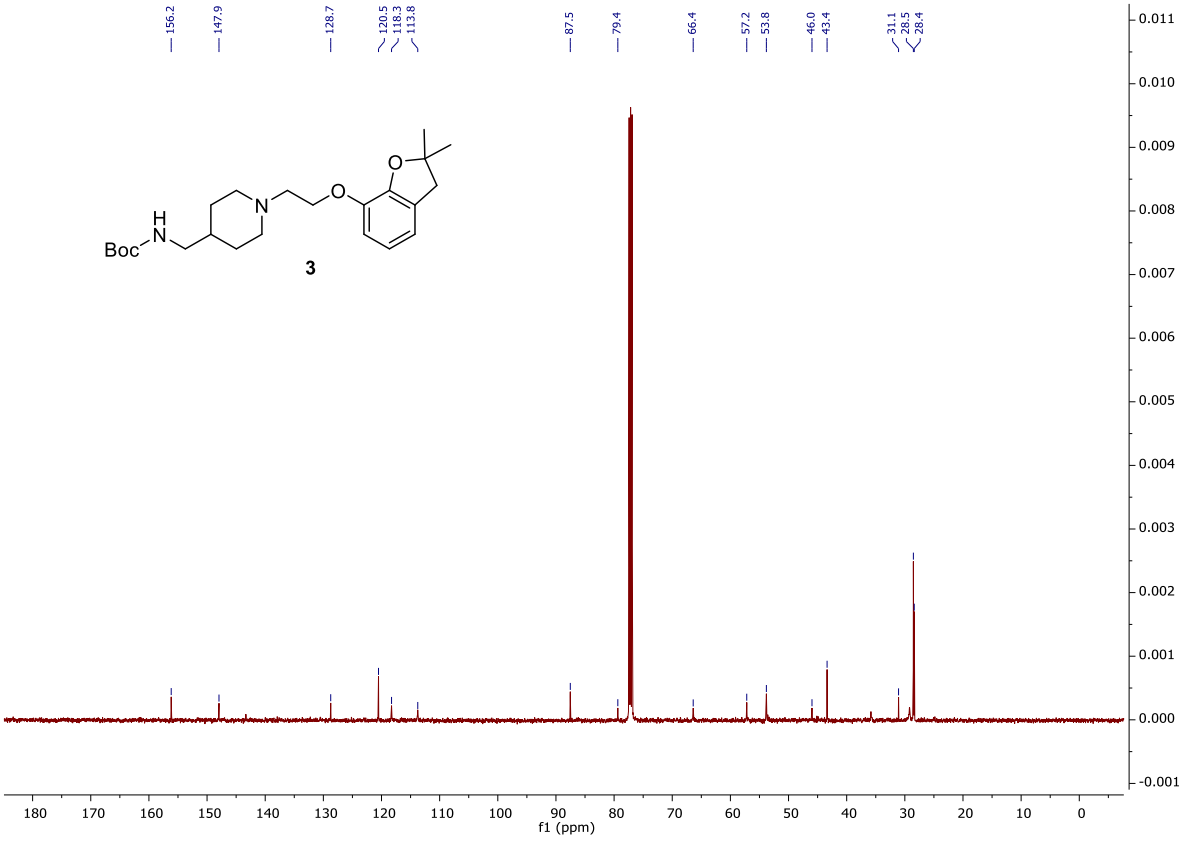


Figure S6. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for *tert*-butyl ({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)carbamate (**3**).

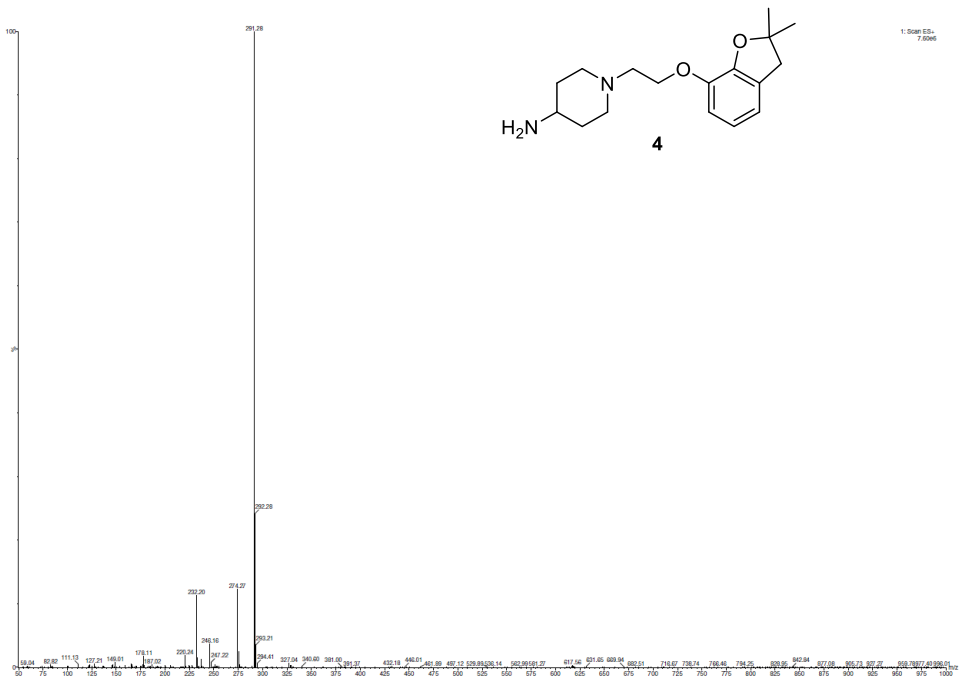


Figure S7. MS spectra for 1-{2-[(2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)oxy]ethyl}piperidin-4-amine (**4**).

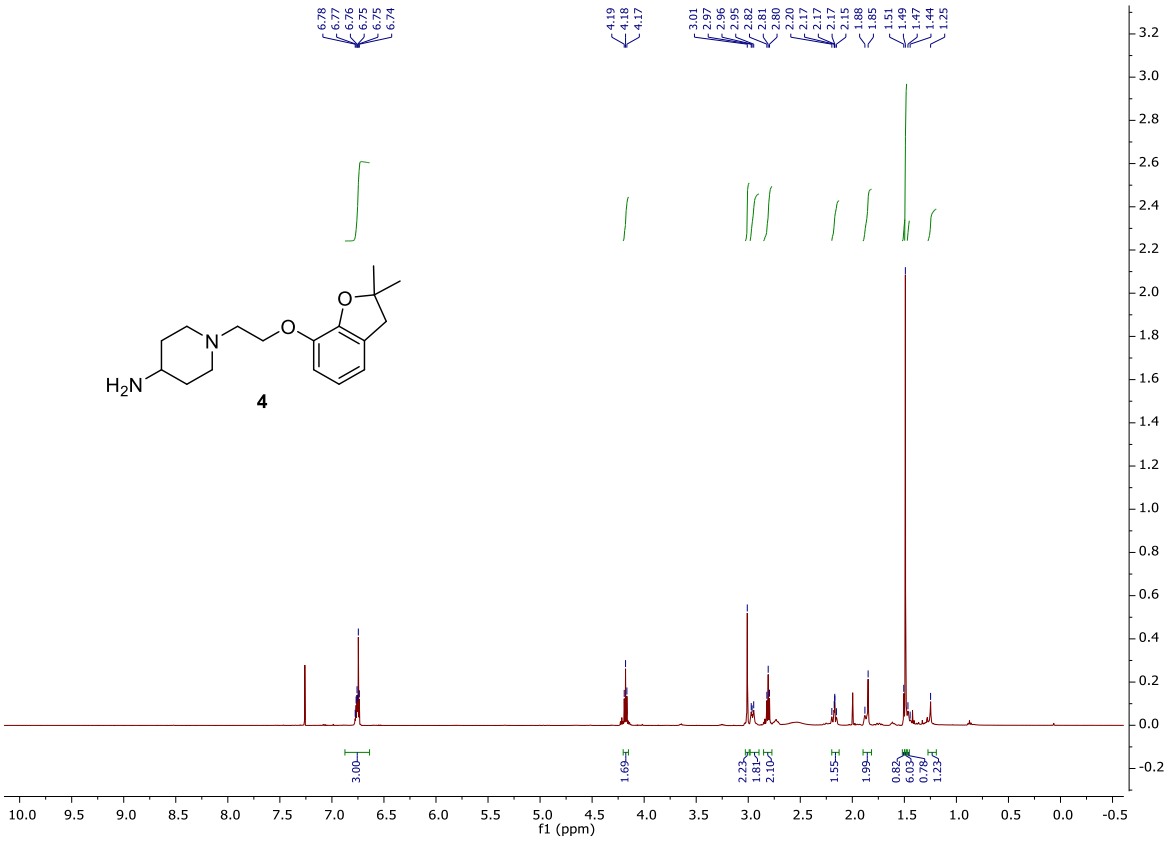


Figure S8. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 1-{2-[(2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)oxy]ethyl}piperidin-4-amine (**4**).

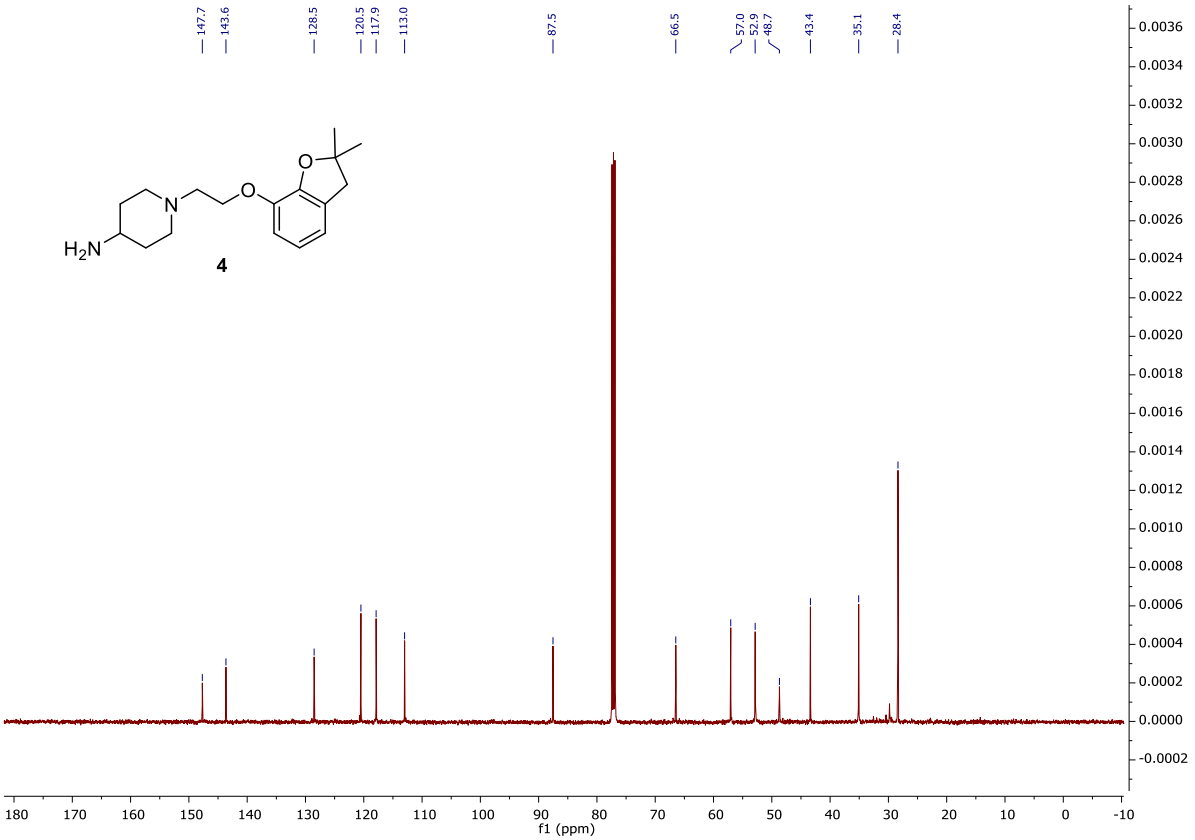


Figure S9. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 1-{2-[(2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)oxy]ethyl}piperidin-4-amine (**4**).

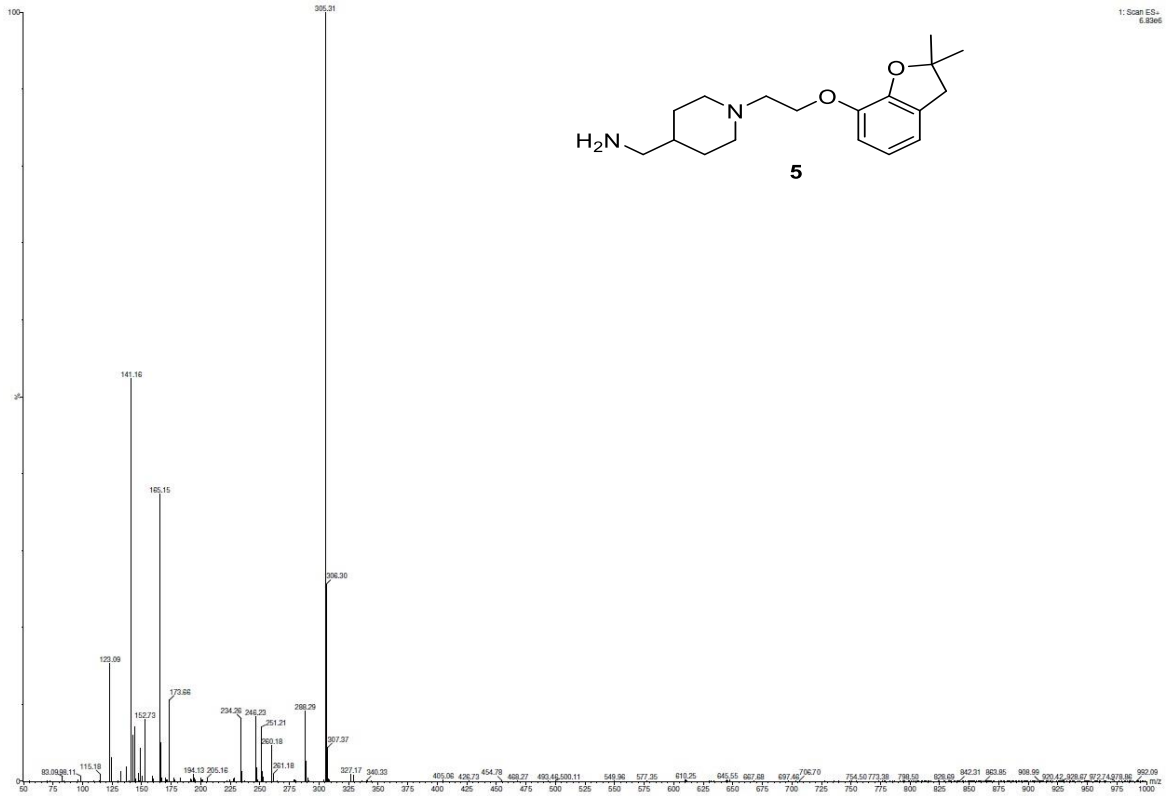


Figure S10. MS spectra for (1-{2-[(2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)oxy]ethyl)piperidin-4-yl)methanamine (**5**).

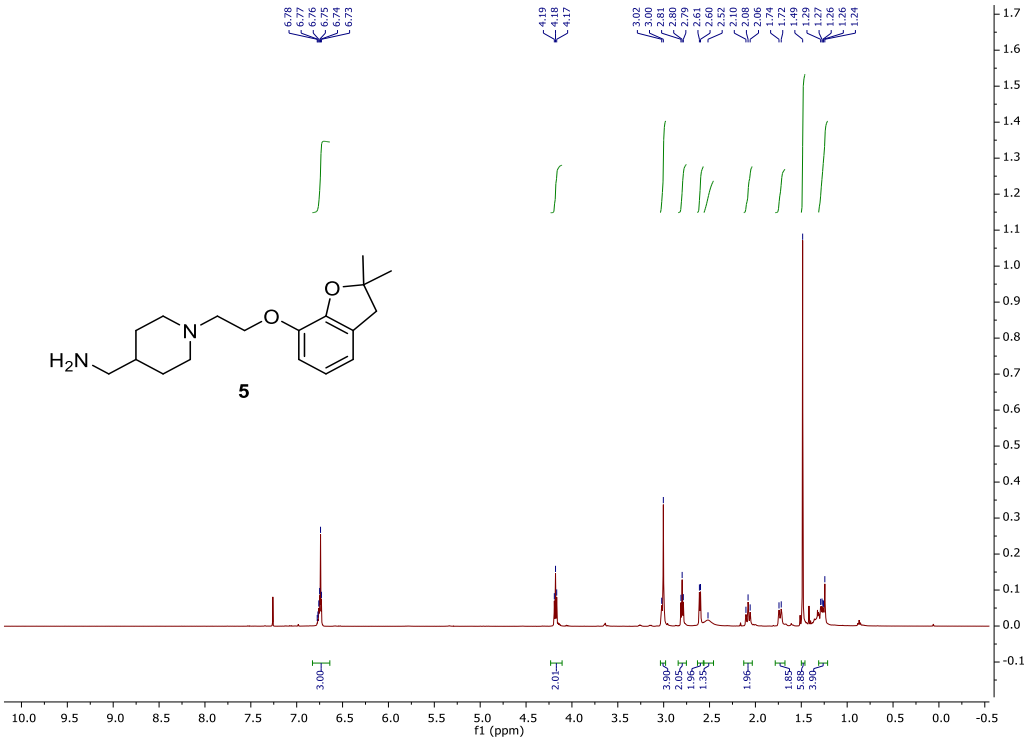


Figure S11. [1]H-NMR spectra (500 MHz, $CDCl_3$) for (1-{2-[(2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)oxy]ethyl)piperidin-4-yl)methanamine (**5**).

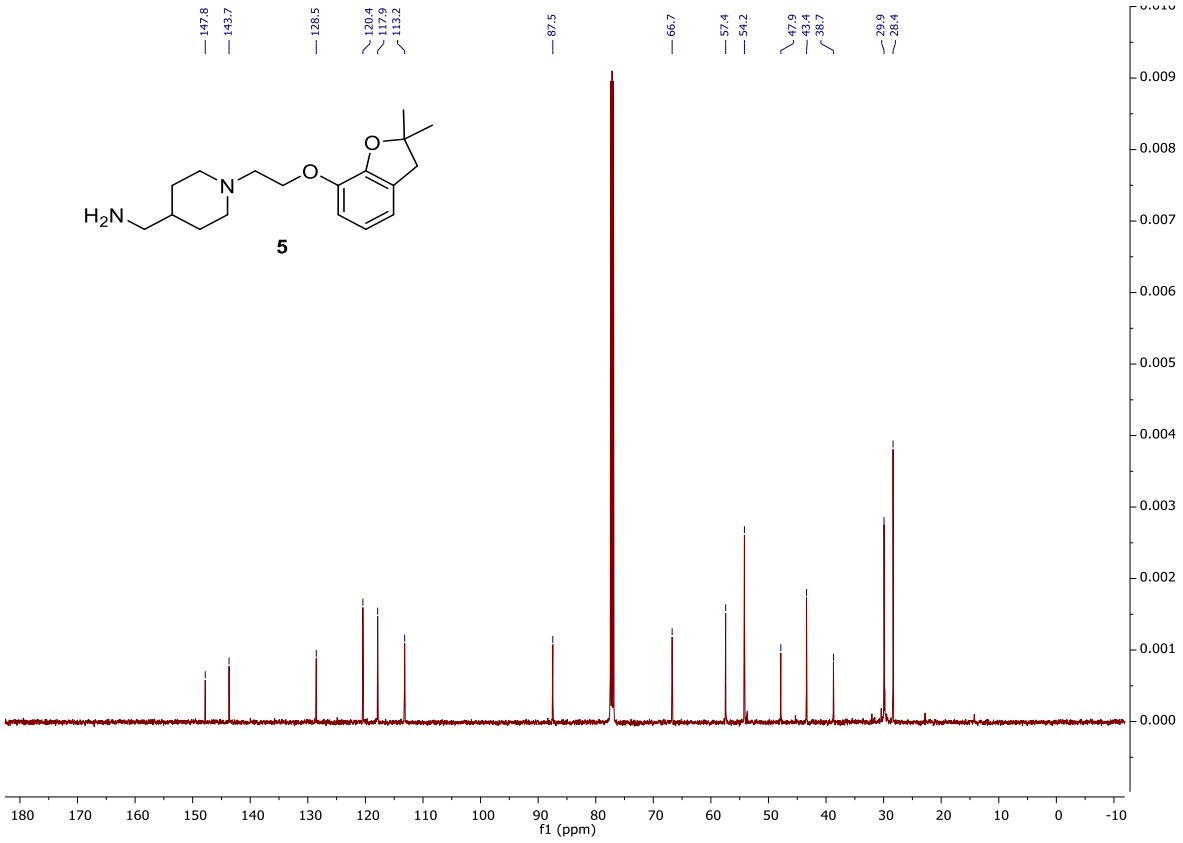


Figure S12. [13]C-NMR spectra (125 MHz, $CDCl_3$) for (1-{2-[(2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)oxy]ethyl)piperidin-4-yl)methanamine (**5**).

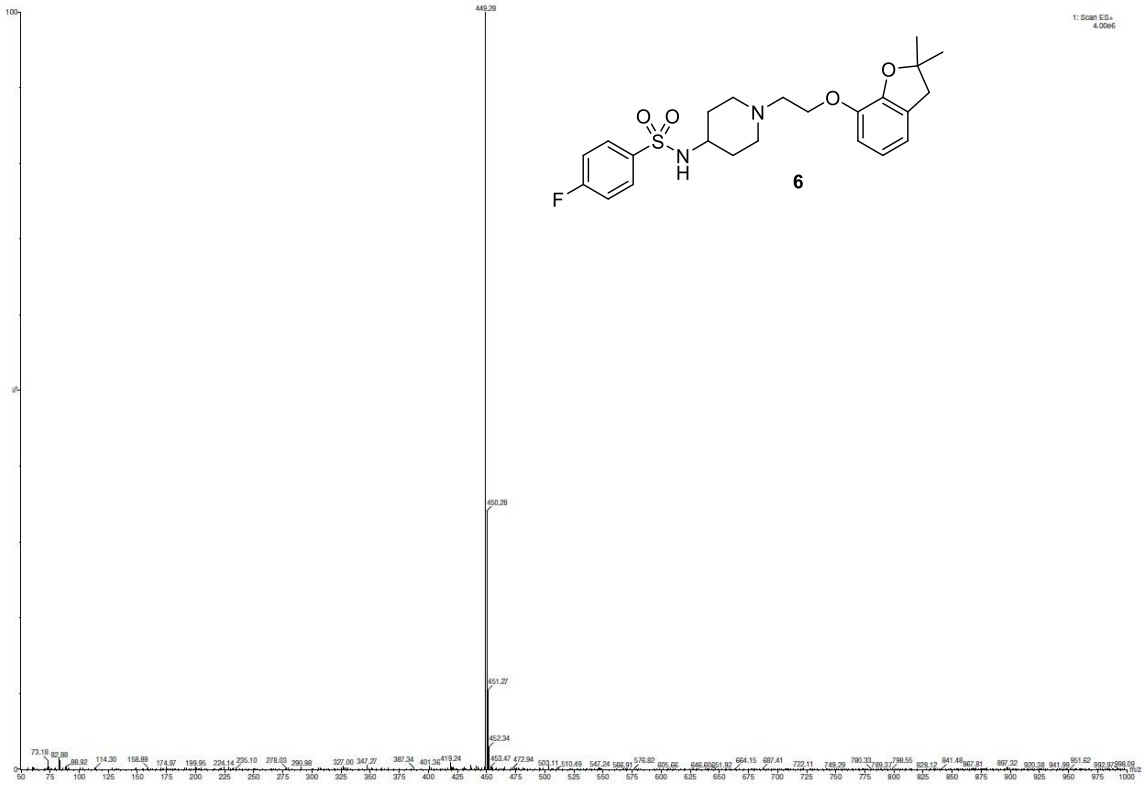


Figure S13. MS spectra for 4-fluoro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**6**).

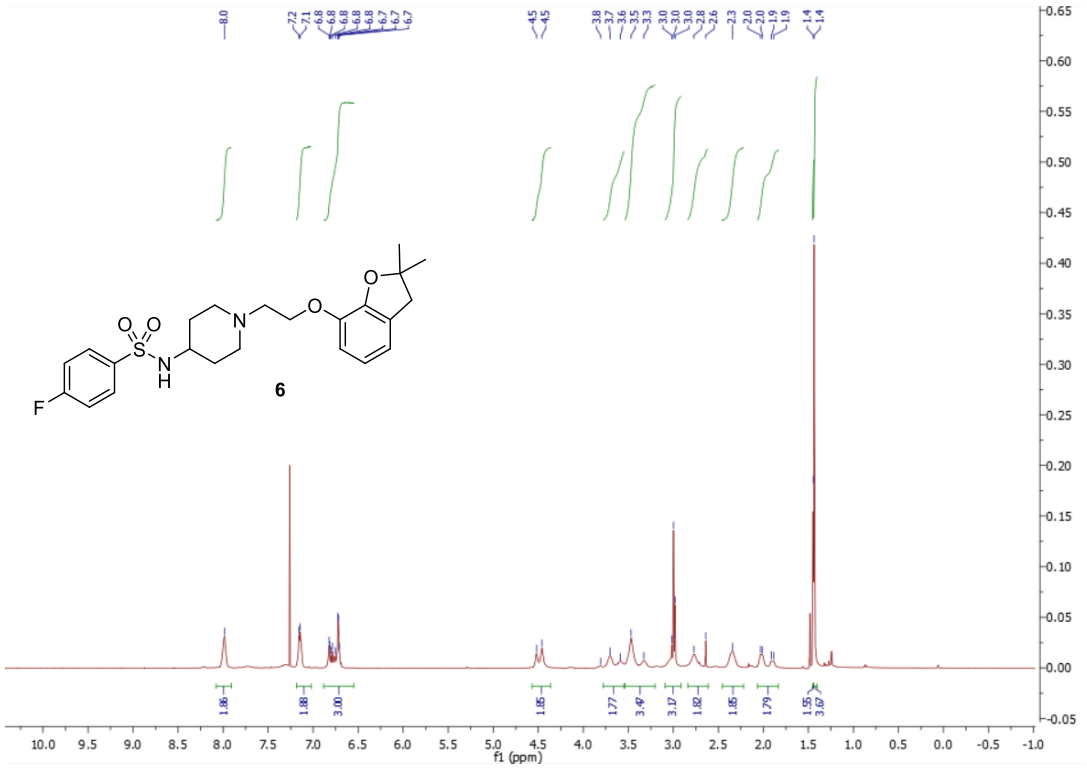


Figure S14. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 4-fluoro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**6**).

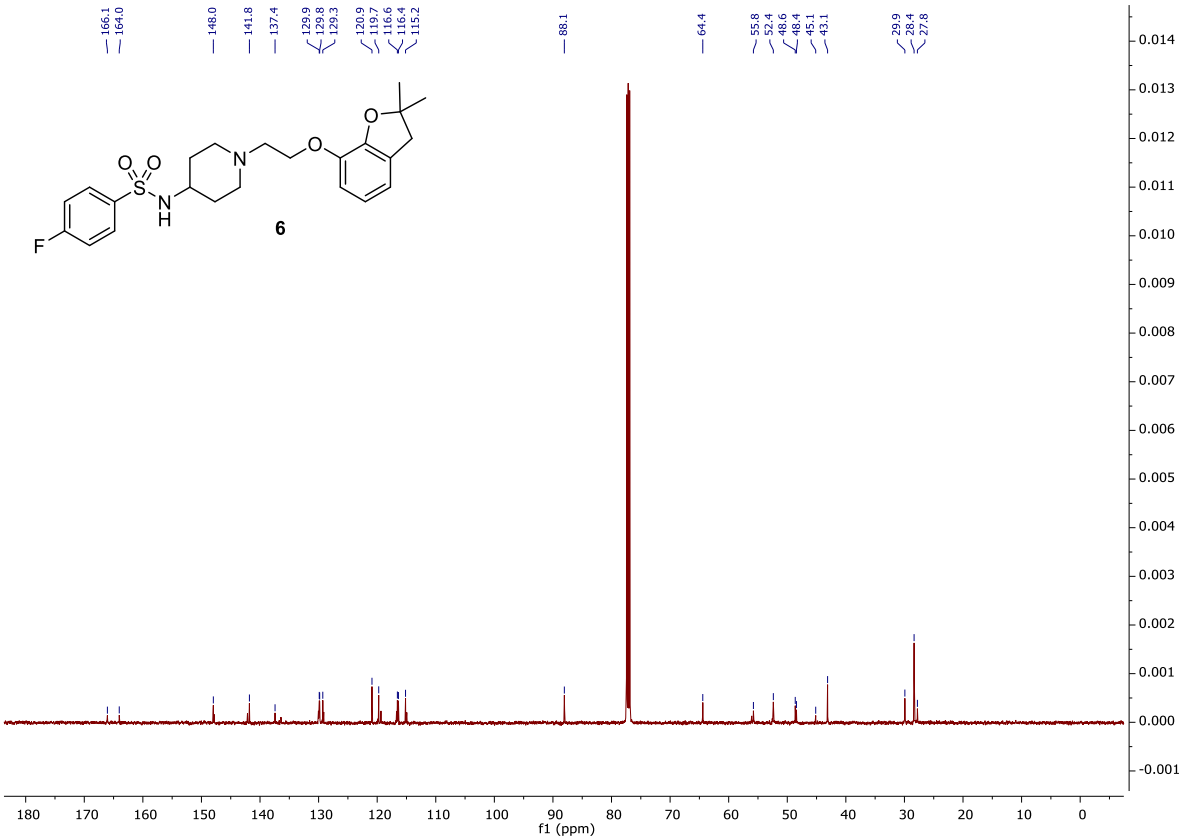


Figure S15. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 4-fluoro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**6**).

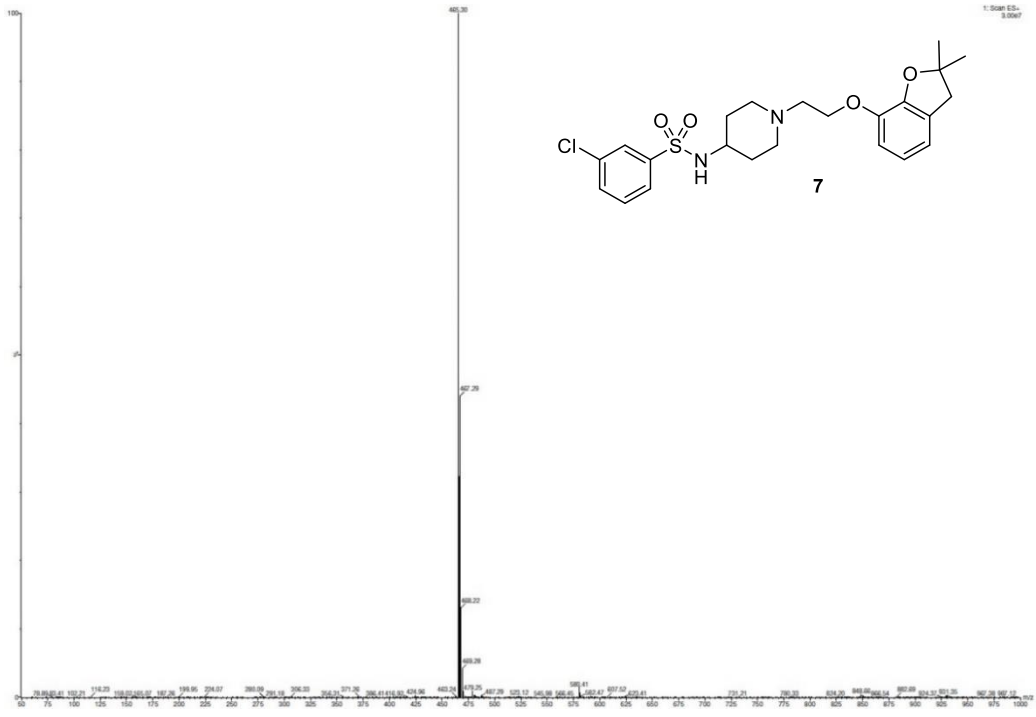


Figure S16. MS spectra for 3-chloro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl} benzenesulfonamide (**7**).

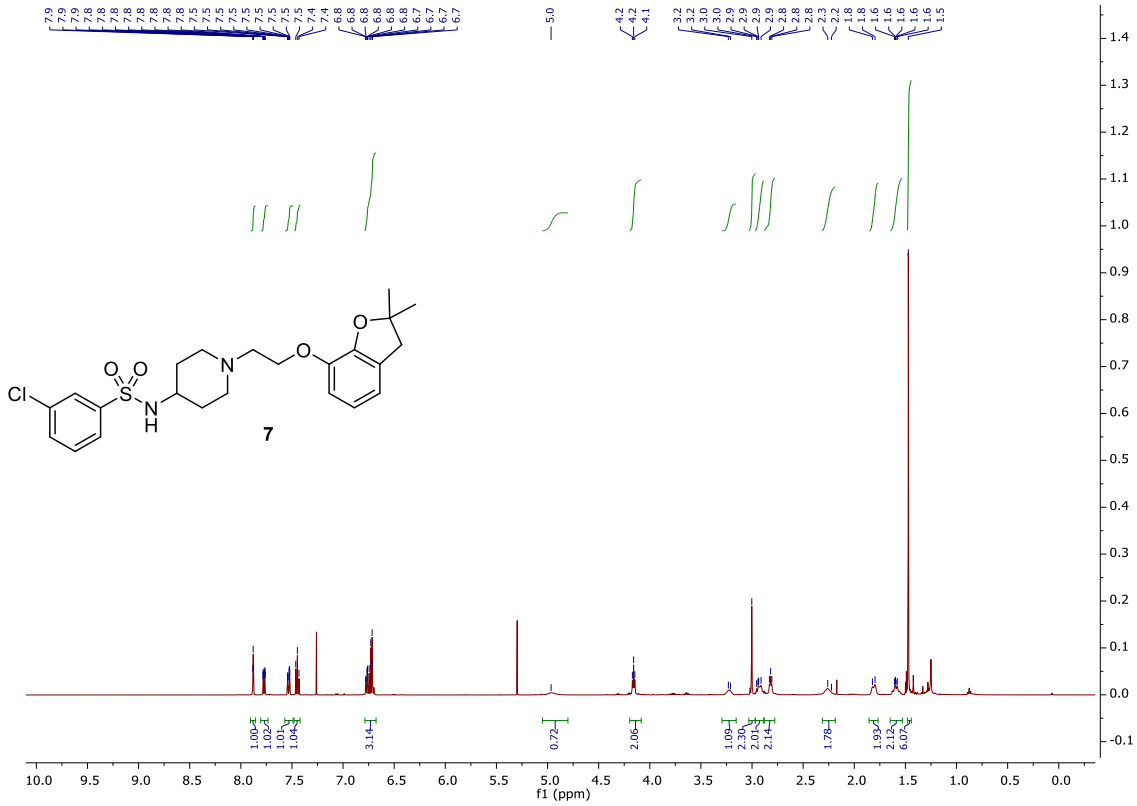


Figure S17. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 3-chloro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl} benzenesulfonamide (**7**).

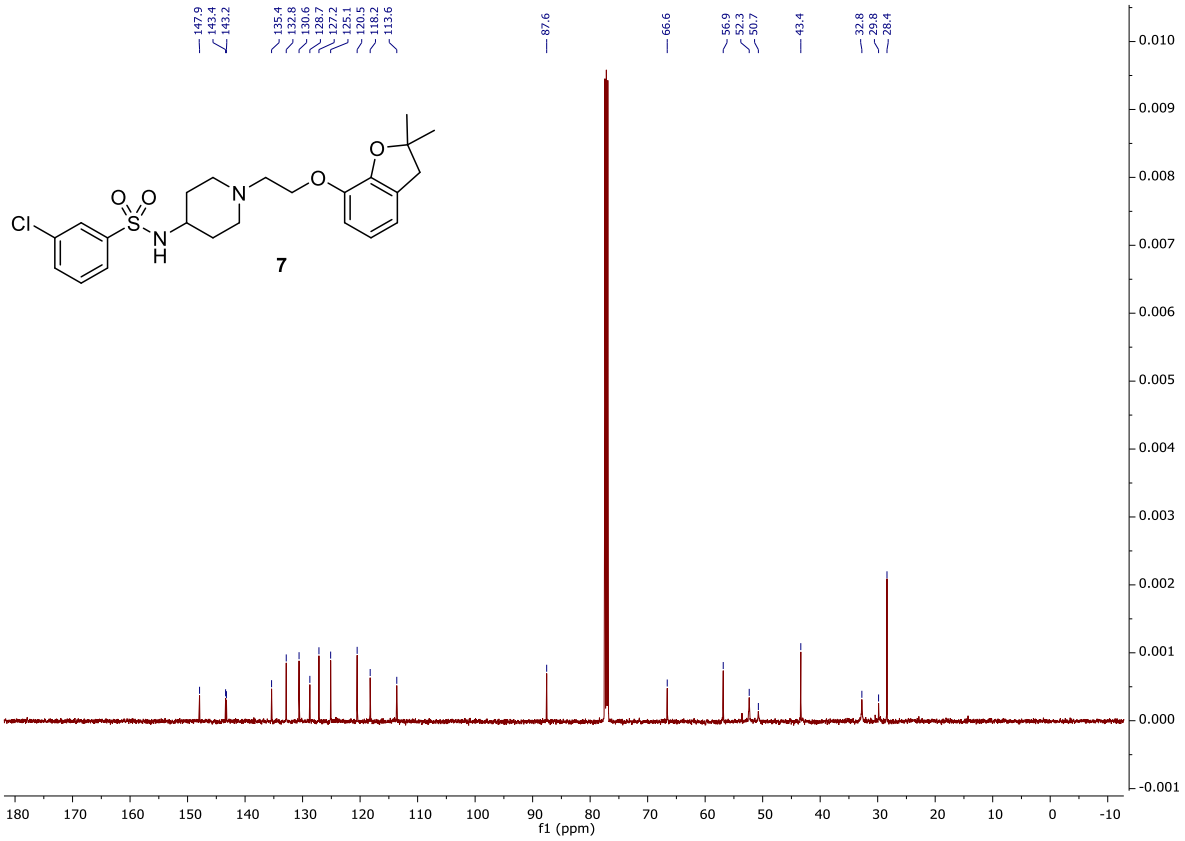


Figure S18. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 3-chloro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl} benzenesulfonamide (**7**).

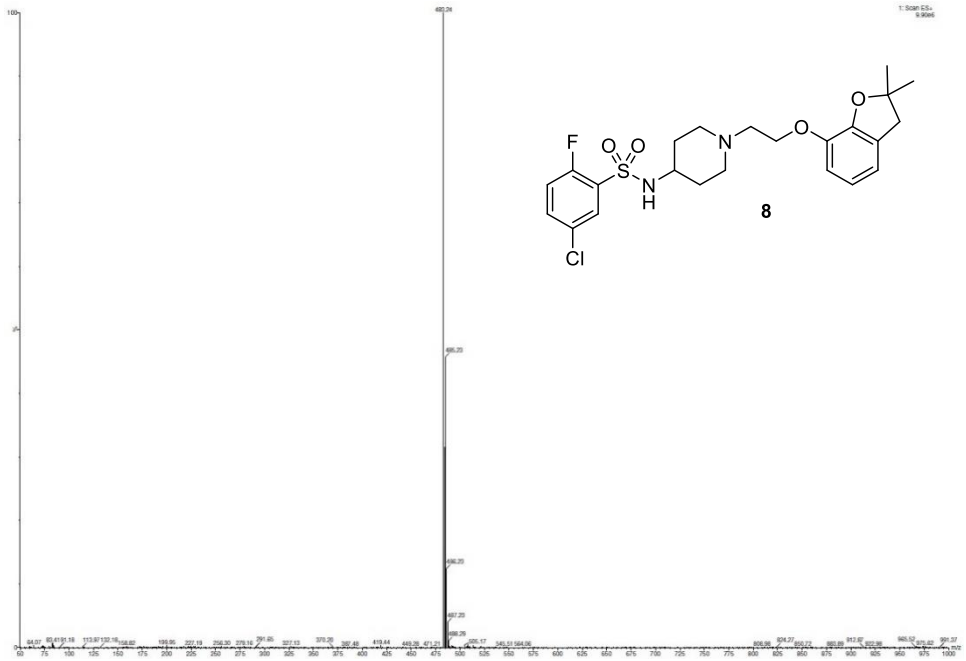


Figure S19. MS spectra for 5-chloro-2-fluoro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**8**).

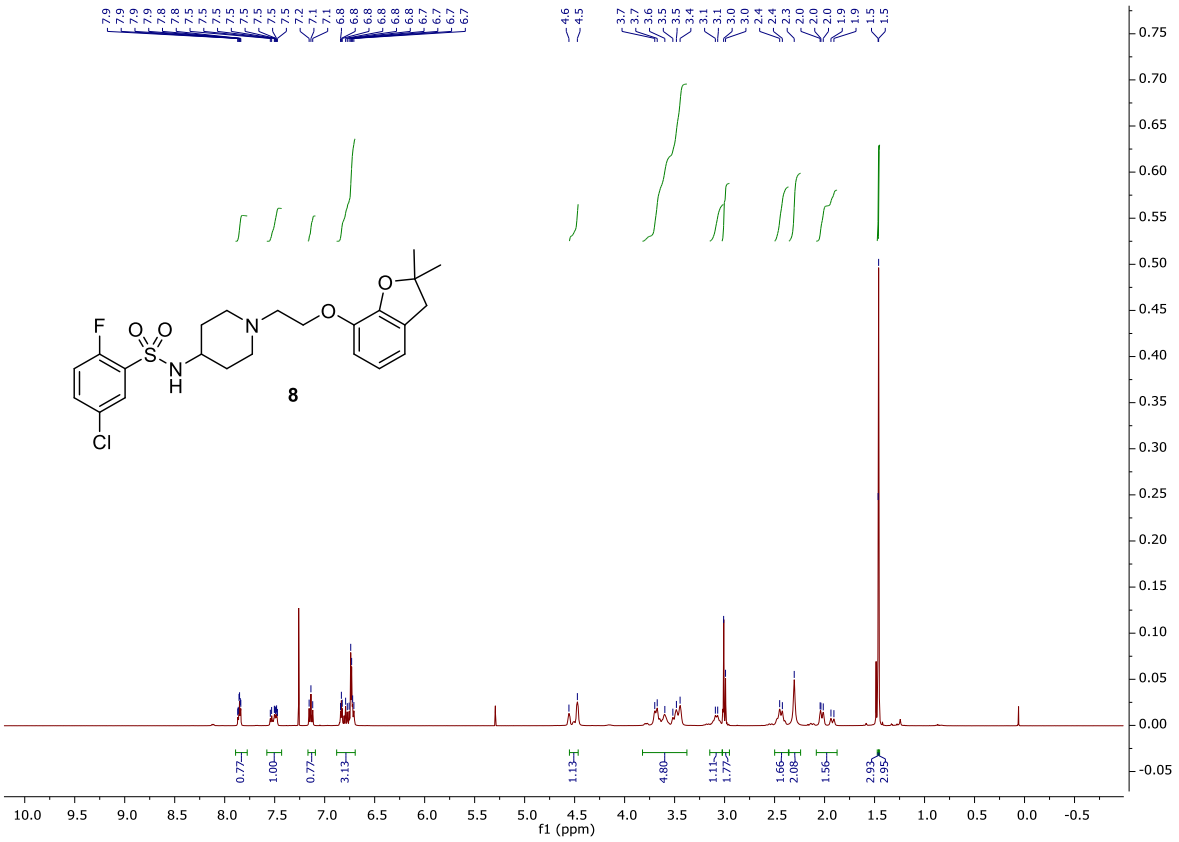


Figure S20. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 5-chloro-2-fluoro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**8**).

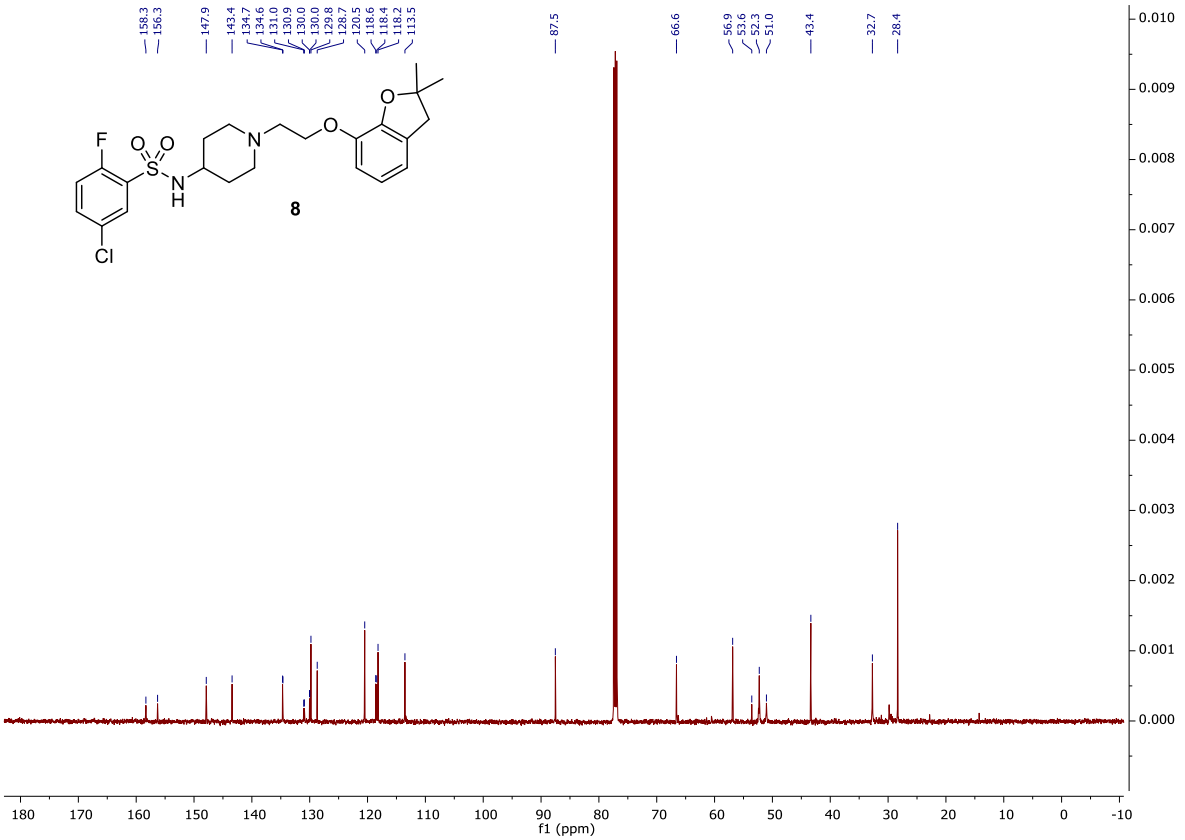


Figure S21. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 5-chloro-2-fluoro-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**8**).

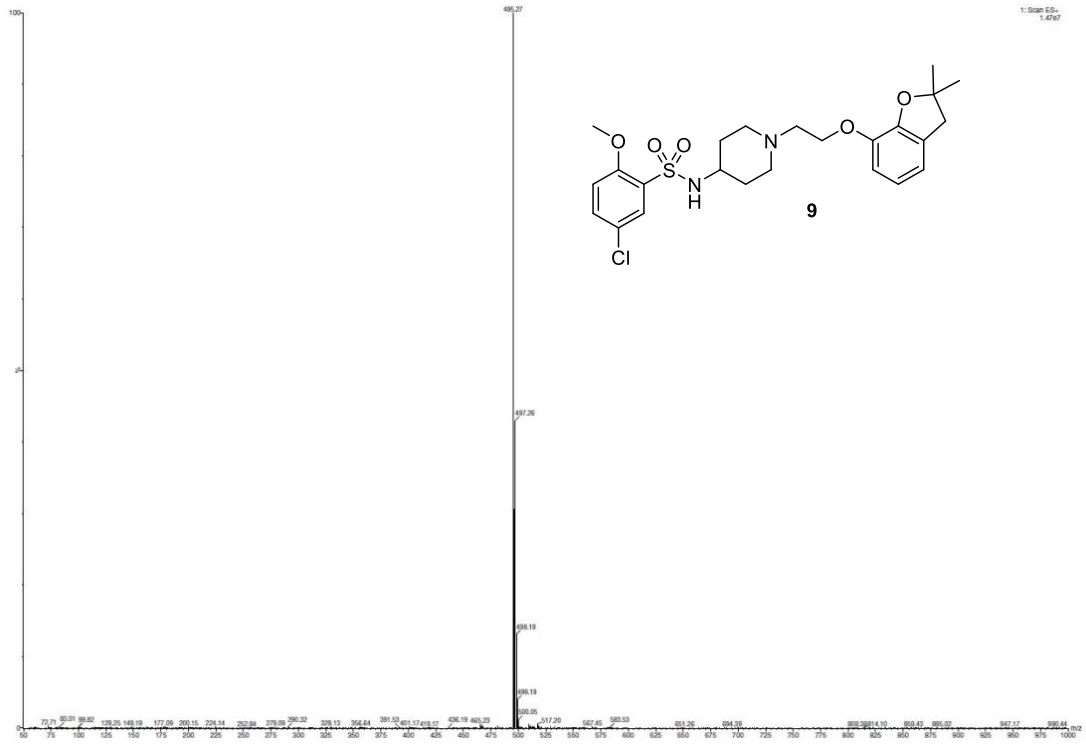


Figure S22. MS spectra for 5-chloro-2-methoxy-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl] piperidin-4-yl}benzenesulfonamide (**9**).

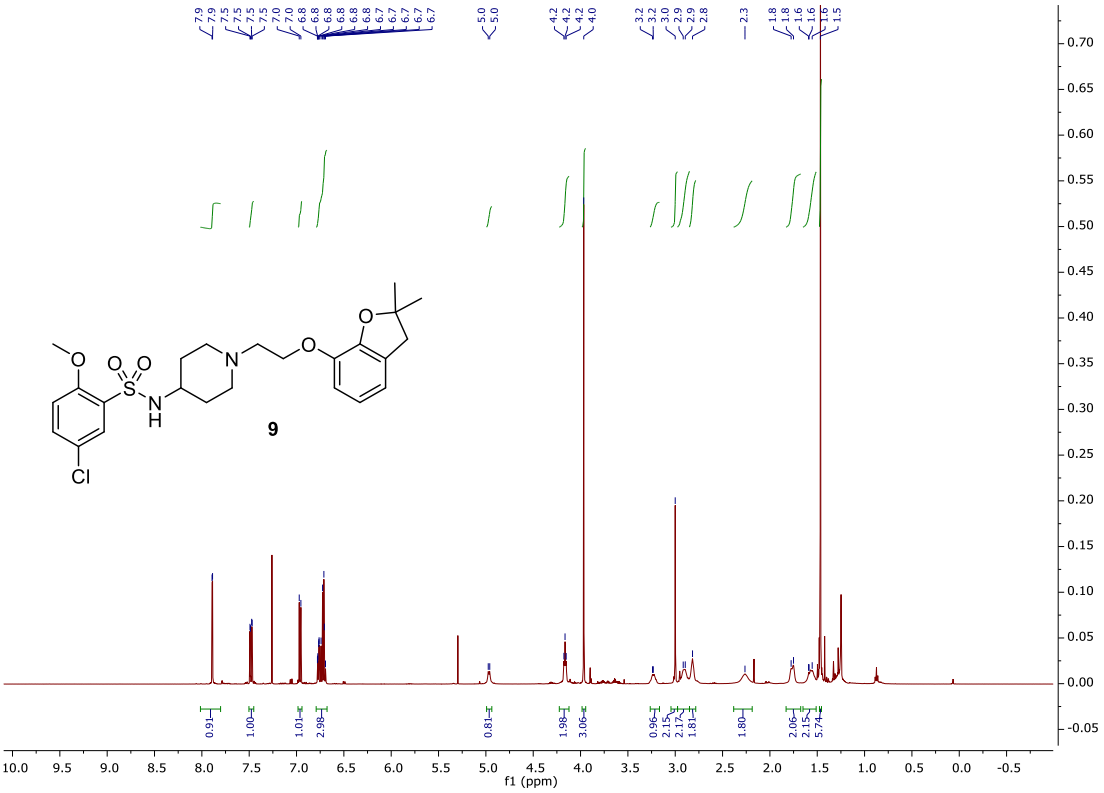


Figure S23. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 5-chloro-2-methoxy-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**9**).

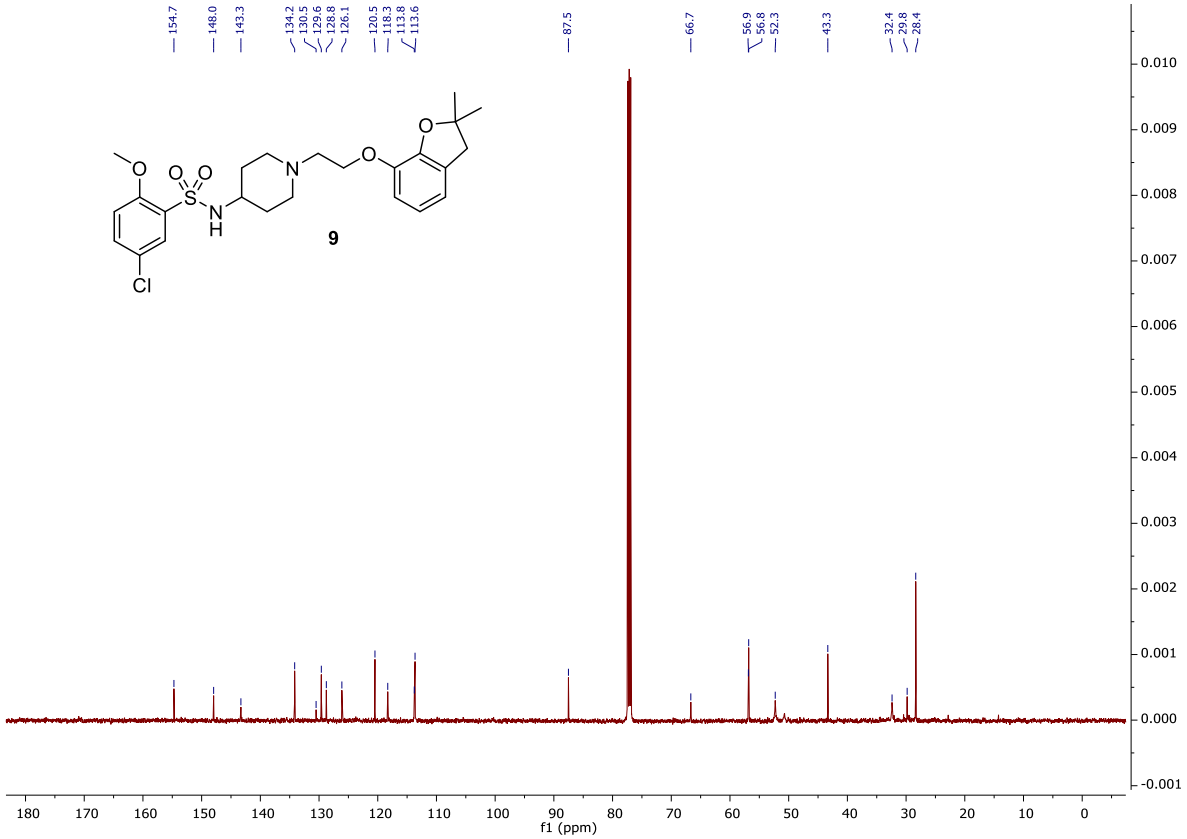


Figure S24. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 5-chloro-2-methoxy-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}benzenesulfonamide (**9**).

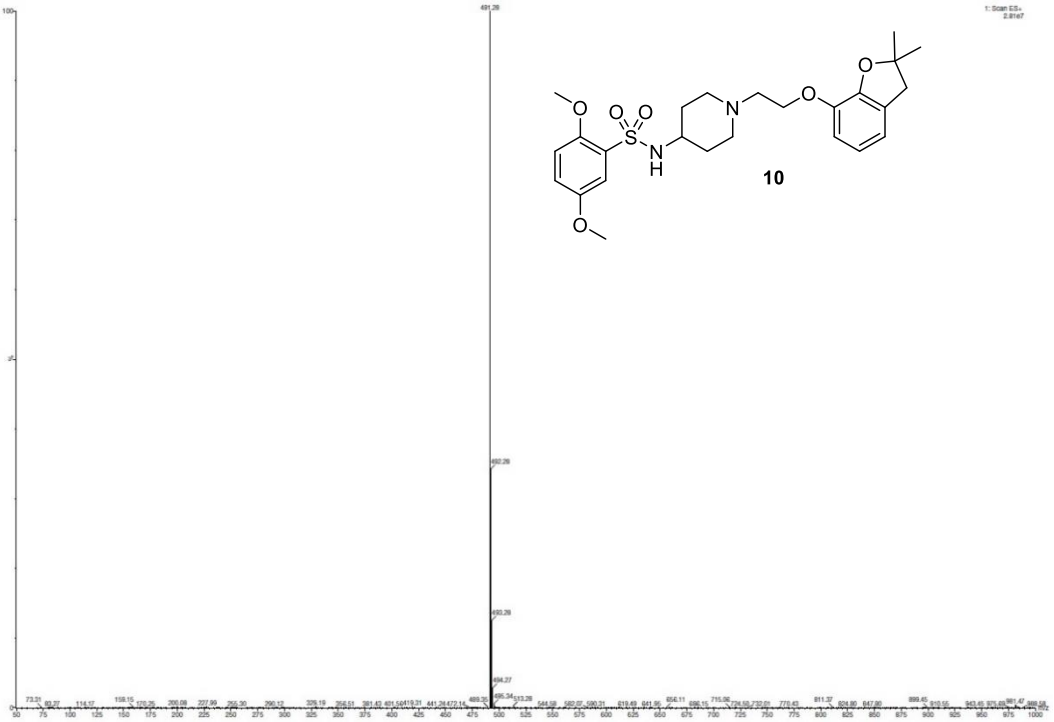


Figure S25. MS spectra for 2,4-dimethoxy-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethy]piperidin-4-yl}benzenesulfonamide (**10**).

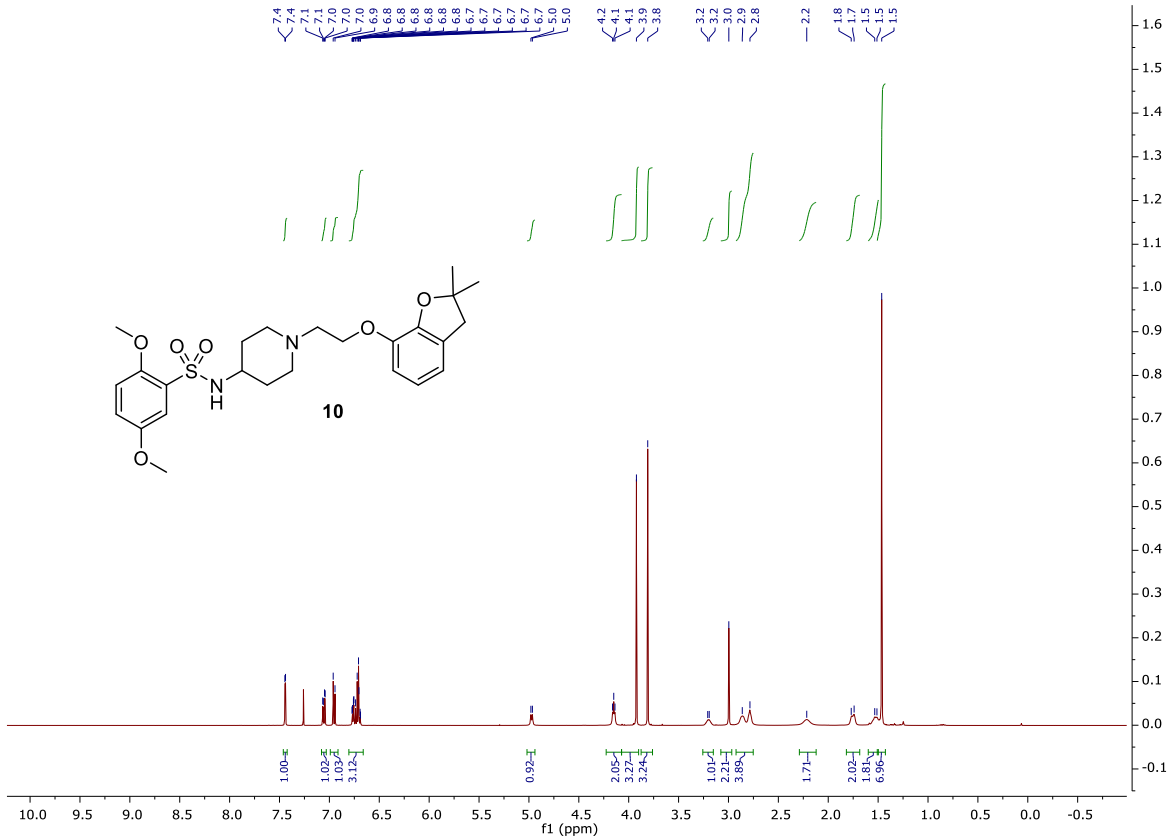


Figure S26. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 2,4-dimethoxy-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethy]piperidin-4-yl}benzenesulfonamide (**10**).

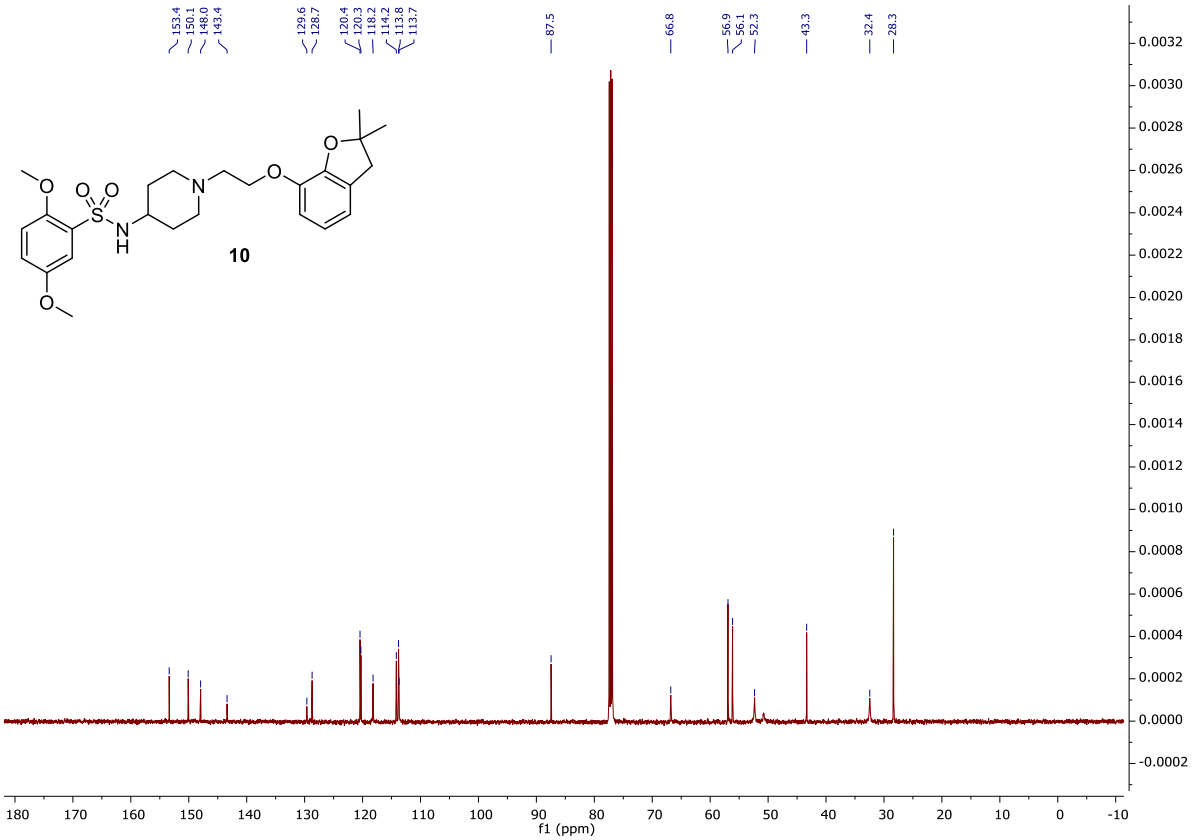


Figure S27. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 2,4-dimethoxy-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethy]piperidin-4-yl}benzenesulfonamide (**10**).

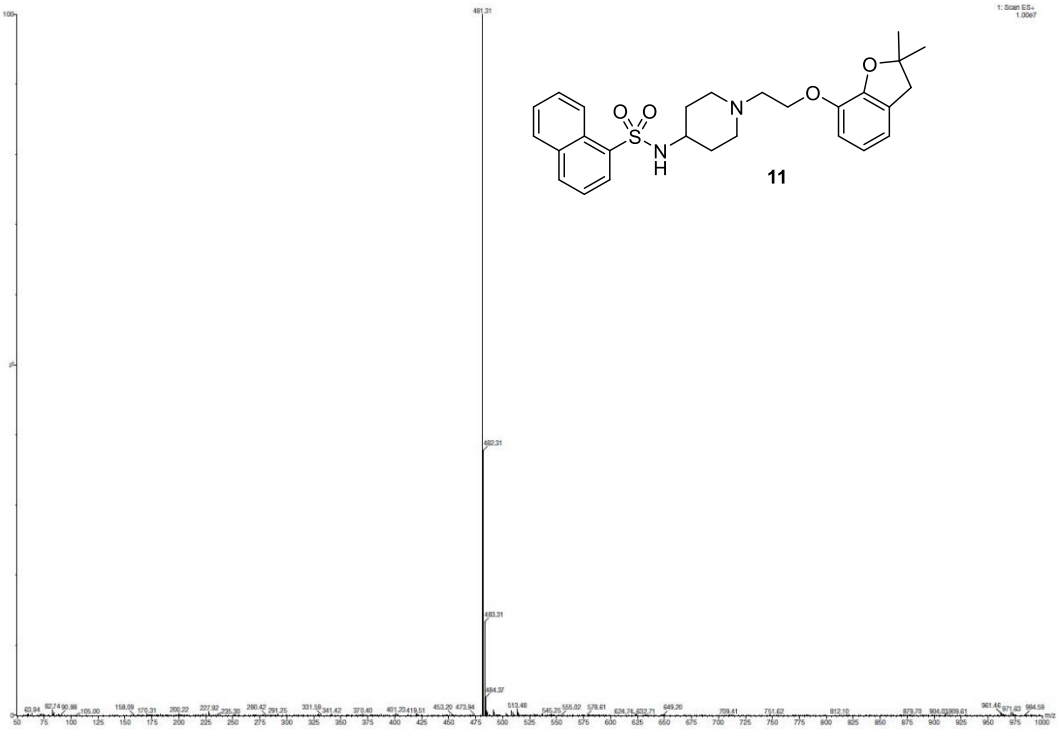


Figure S28. MS spectra for 1-naphthalene-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**11**).

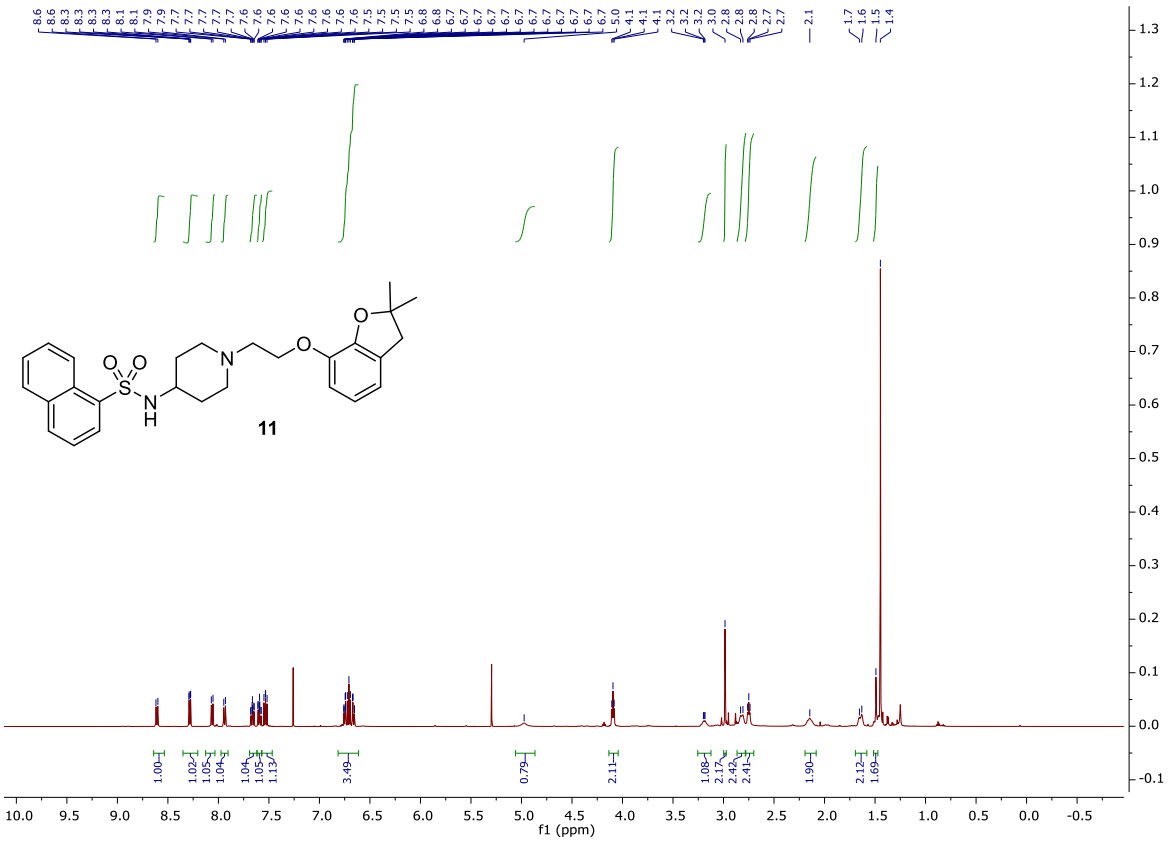


Figure S29. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 1-naphthalene-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**11**).

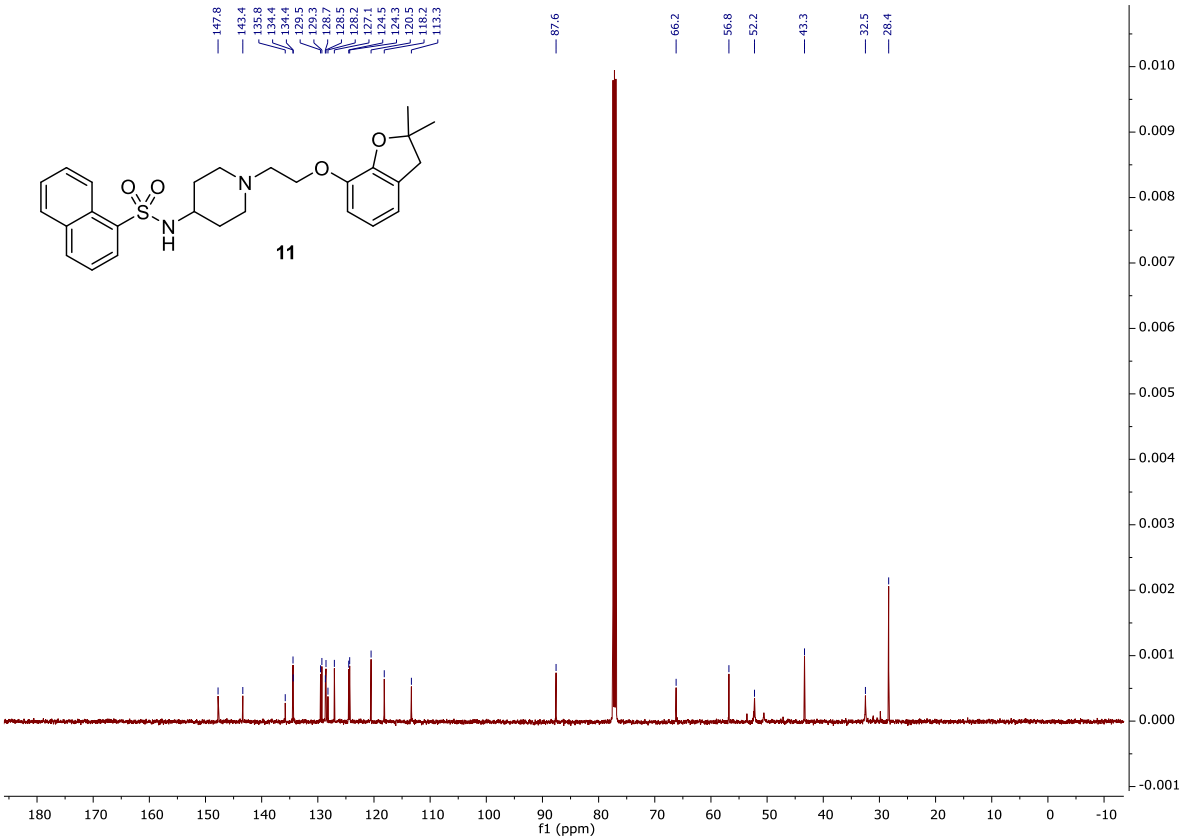


Figure S30. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 1-naphthalene-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**11**).

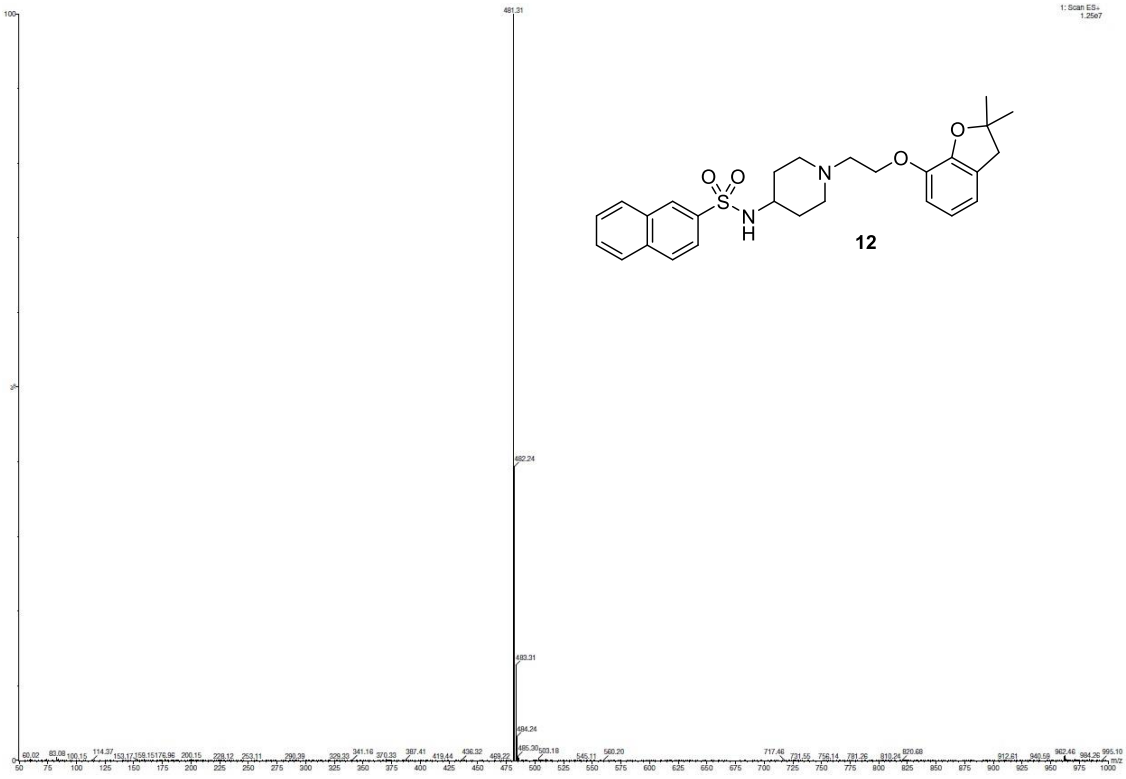


Figure S31. MS spectra for 2-naphthalene-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**12**).

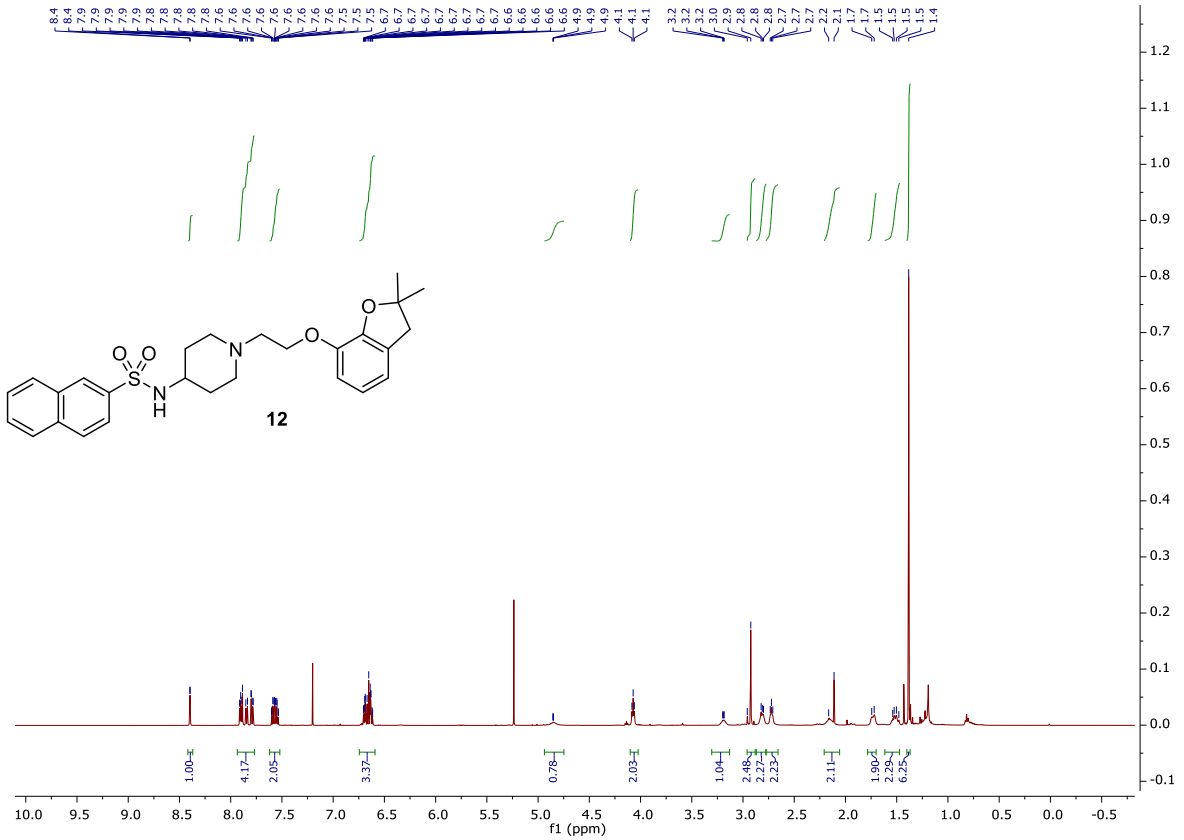


Figure S32. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 2-naphthalene-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**12**).

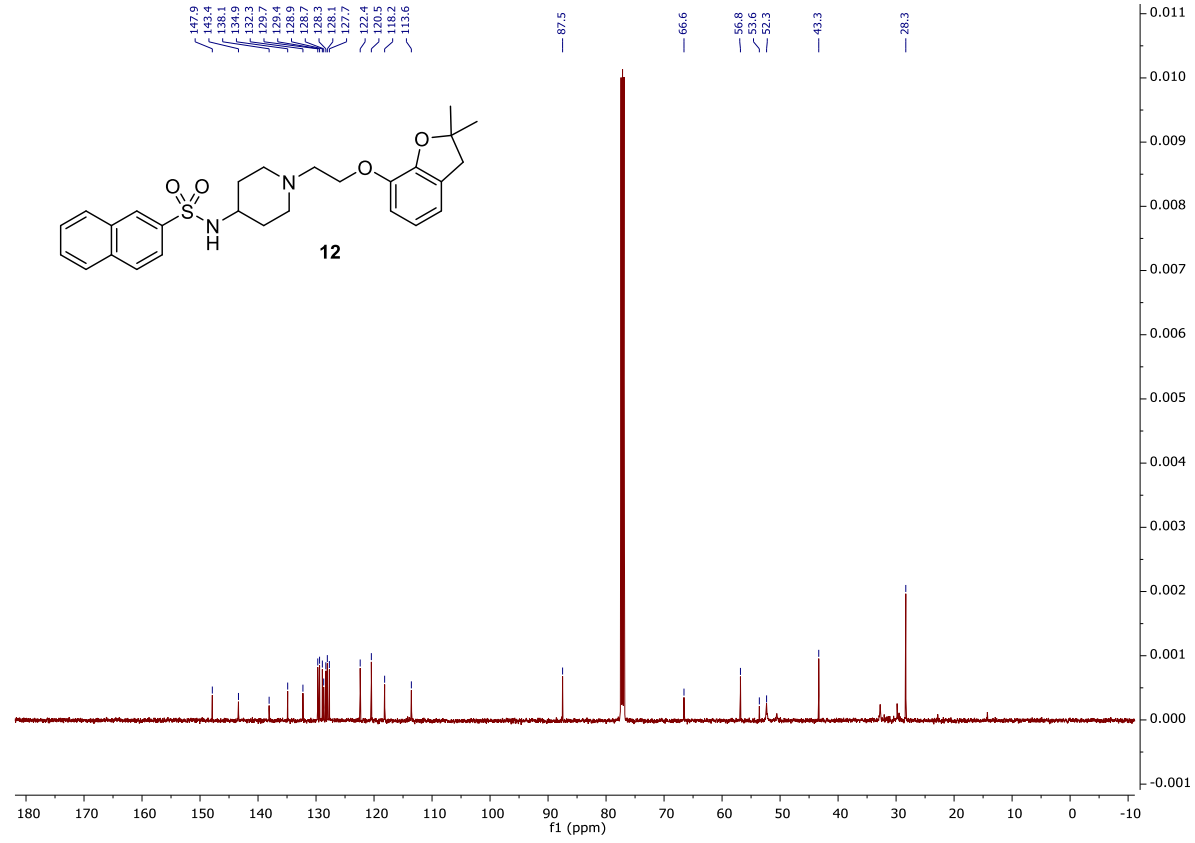


Figure S33. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 2-naphthalene-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**12**).

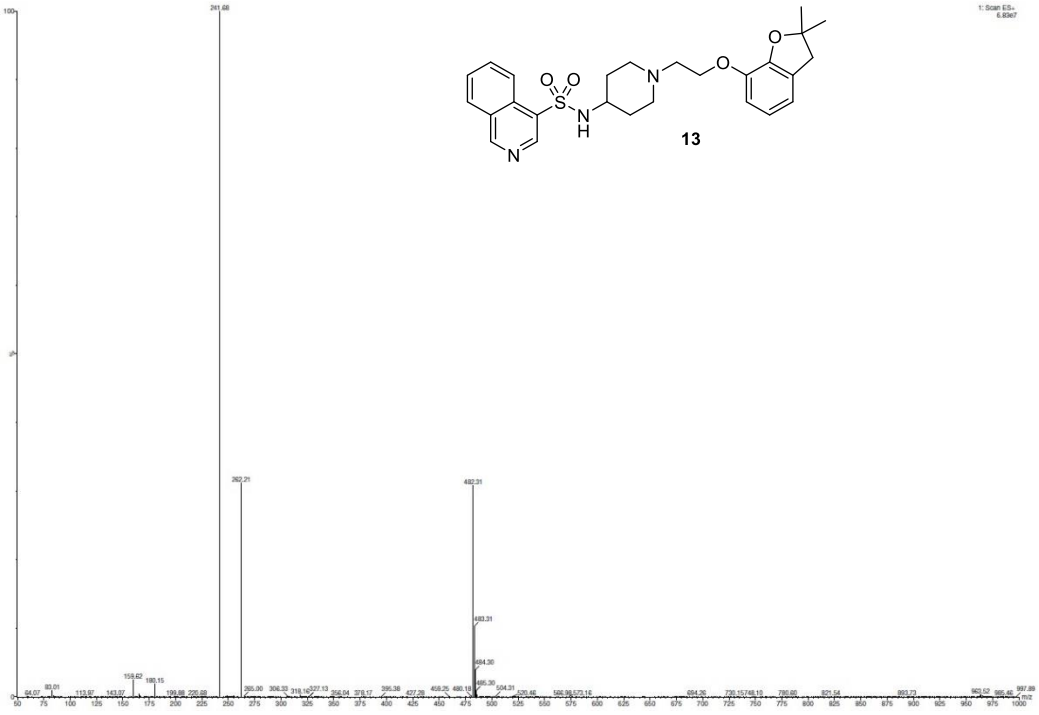


Figure S34. MS spectra for 4-isoquinoline-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (13).

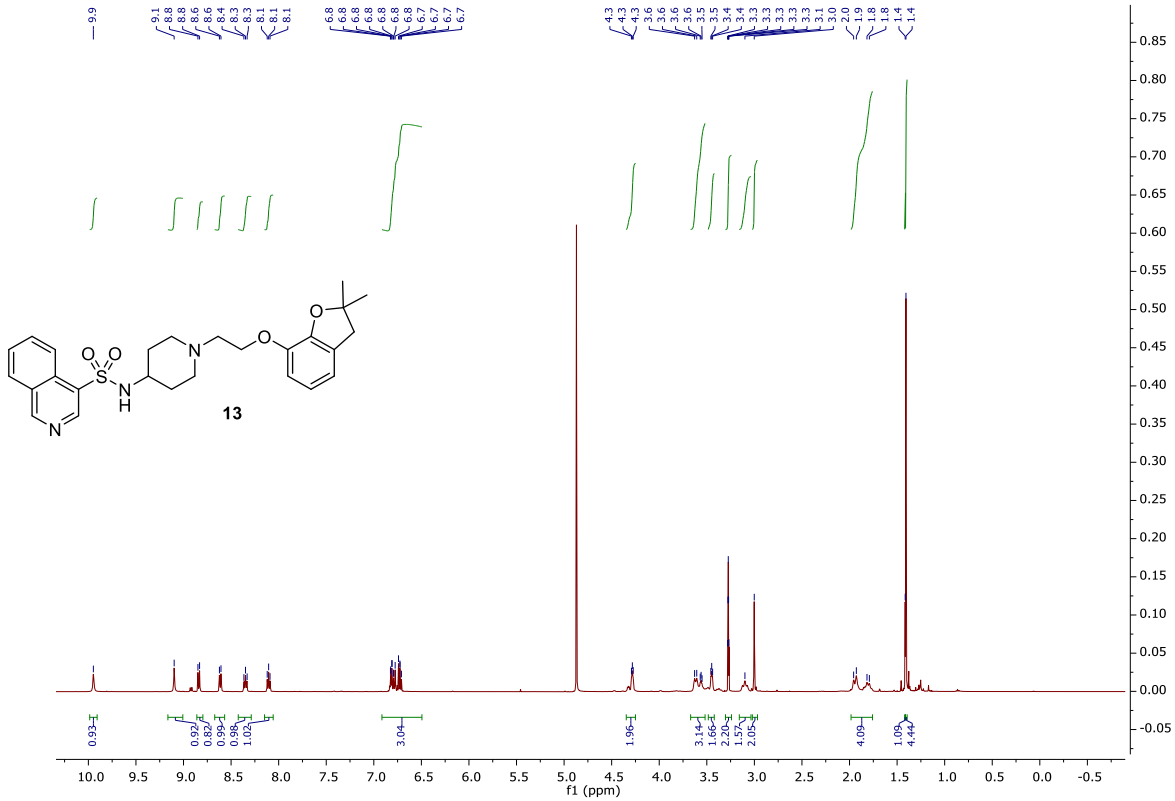


Figure S35. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 4-isoquinoline-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**13**).

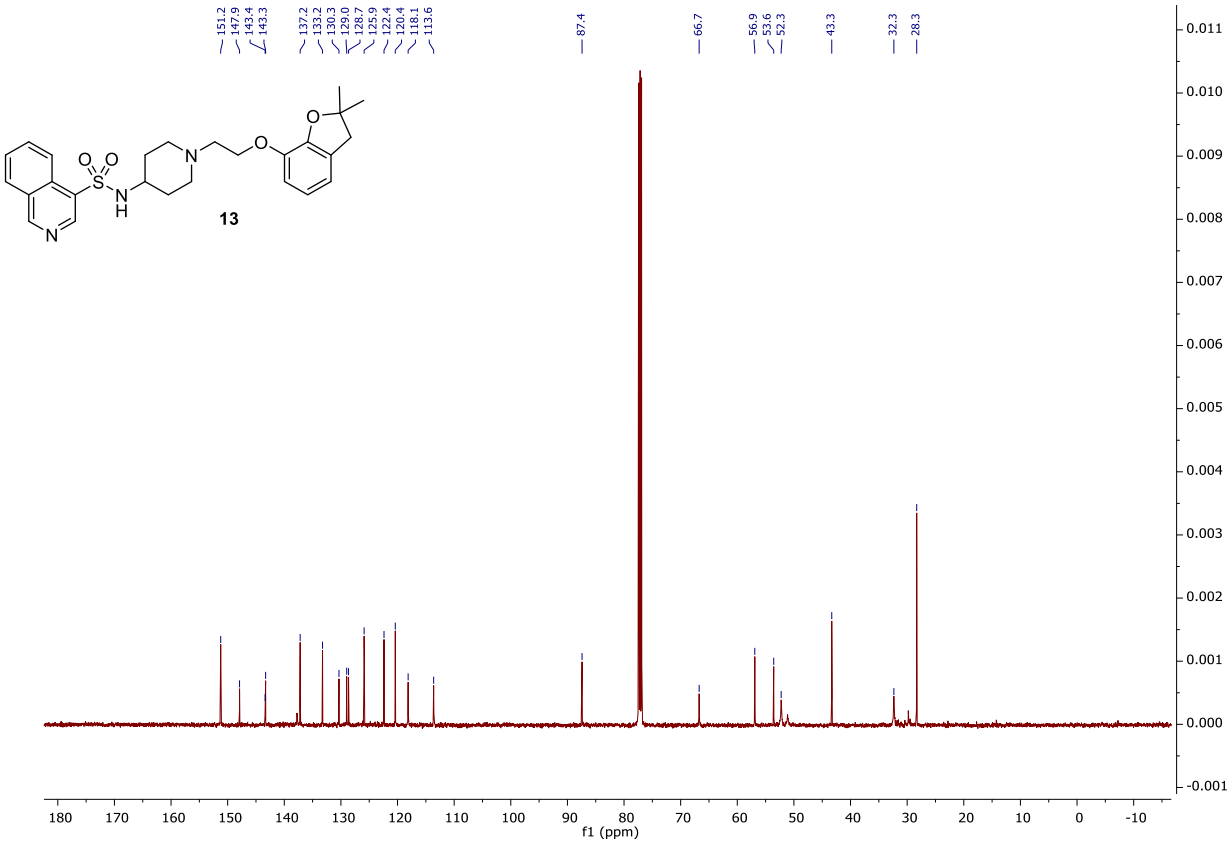


Figure S36. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 4-isoquinoline-*N*-{1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}sulfonamide (**13**).

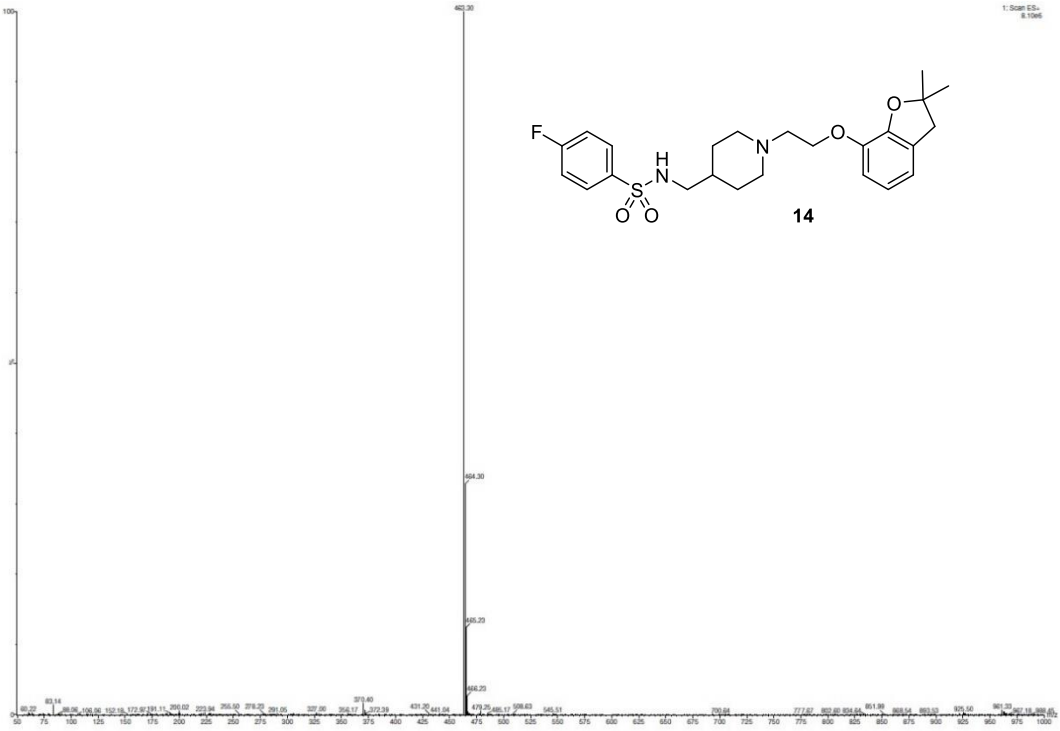


Figure S37. MS spectra for 4-fluoro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**14**).

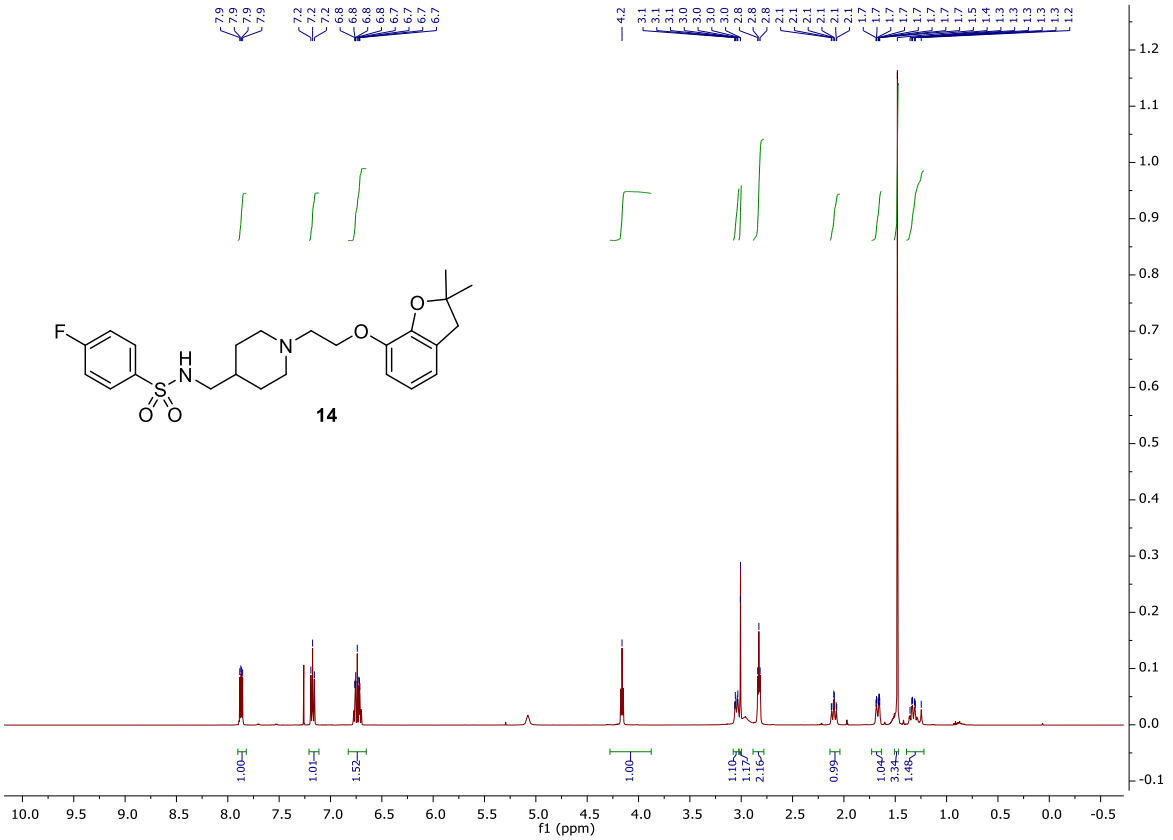


Figure S38. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 4-fluoro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**14**).

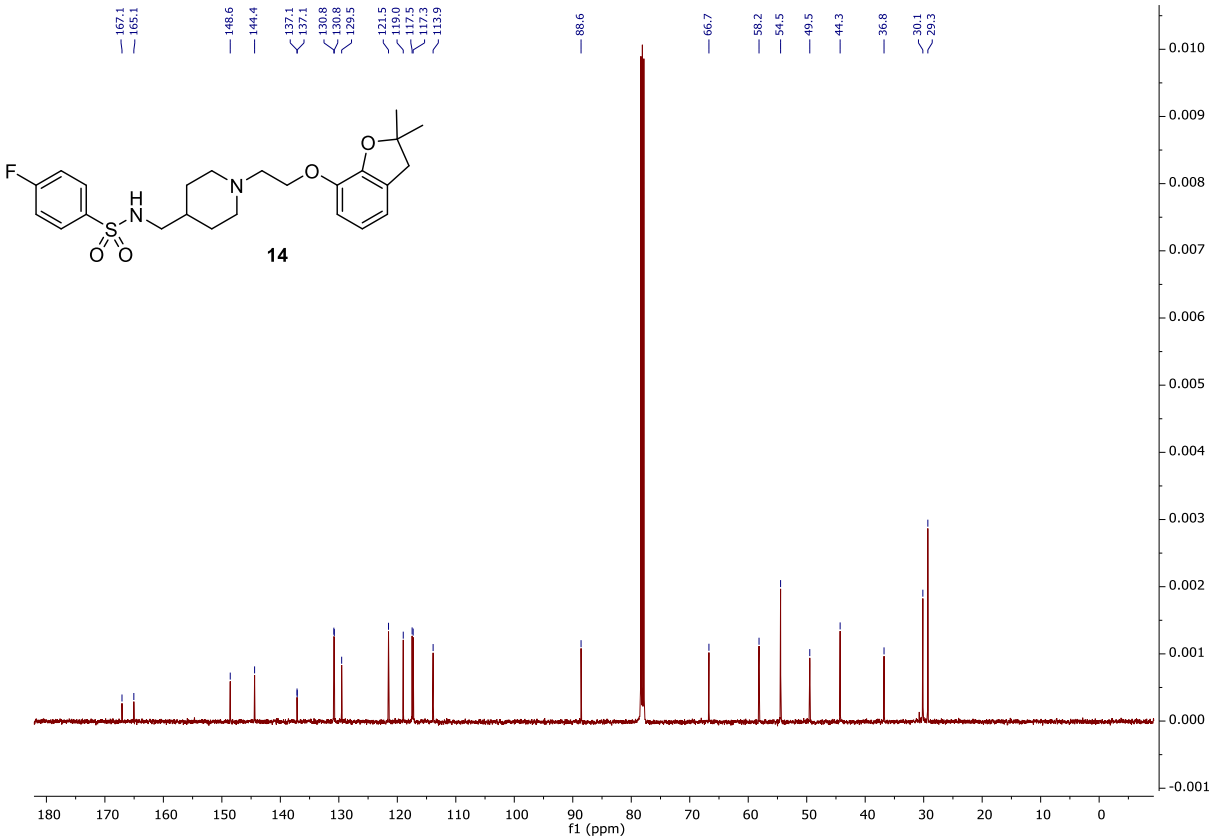


Figure S39. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 4-fluoro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**14**).

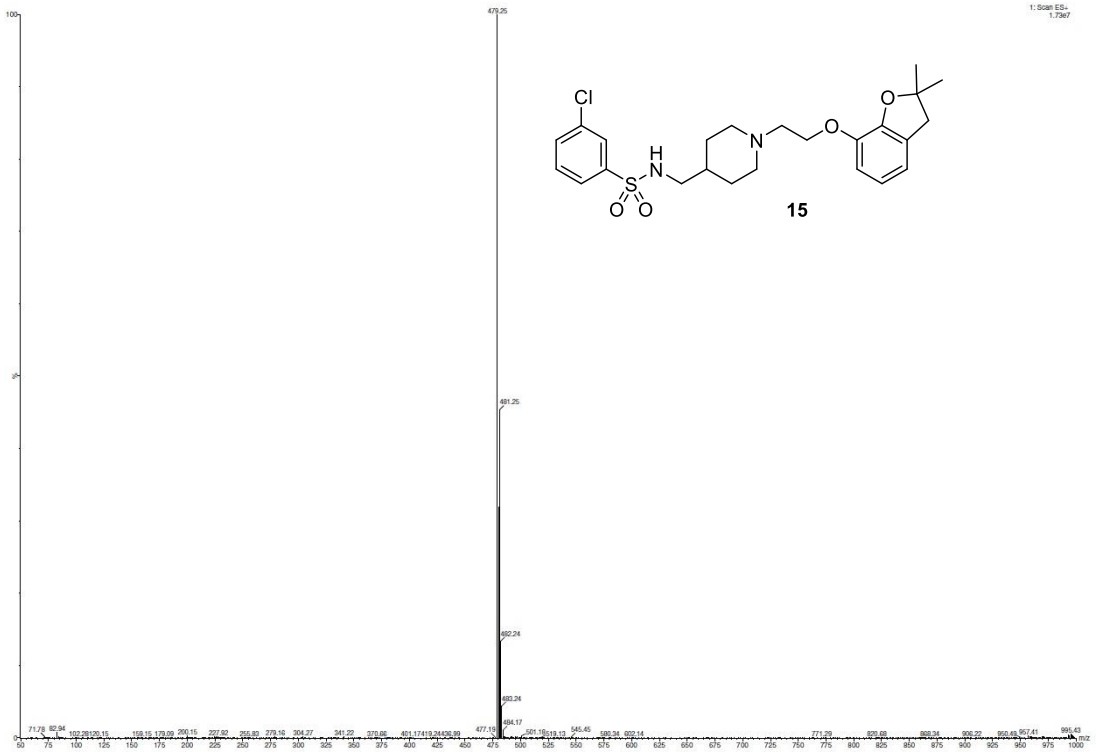


Figure S40. MS spectra for 3-chloro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (15).

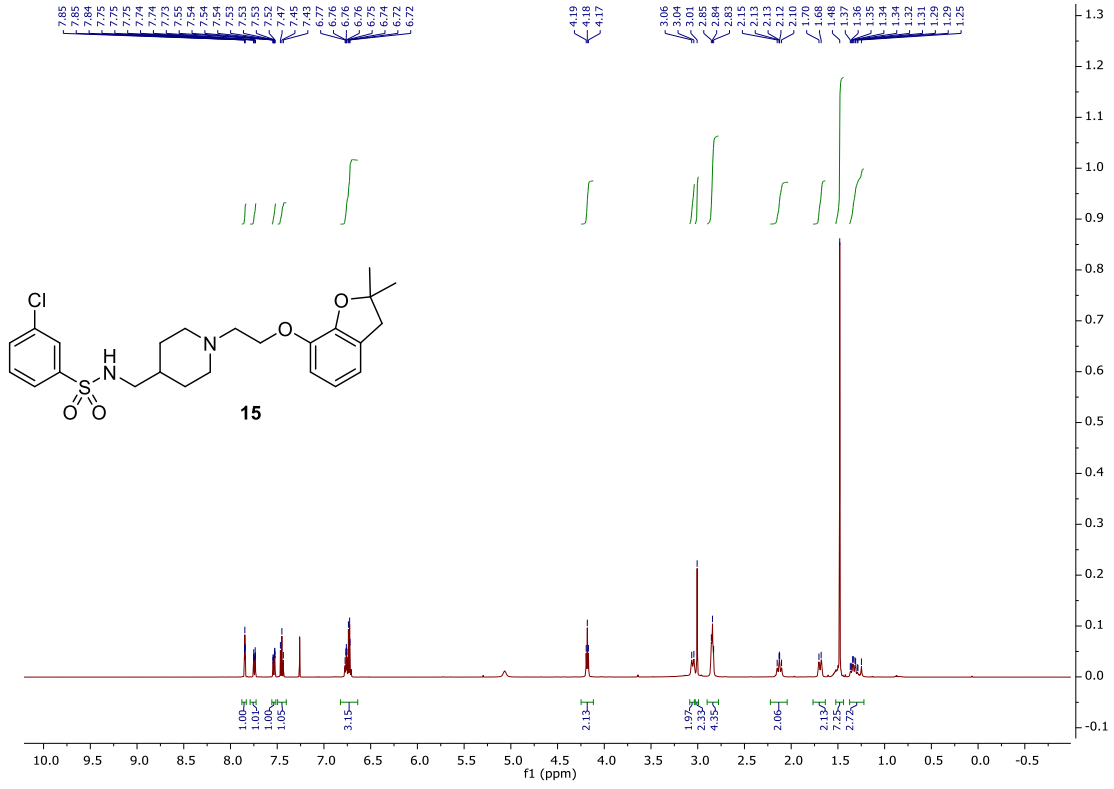


Figure S41. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 3-chloro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**15**).

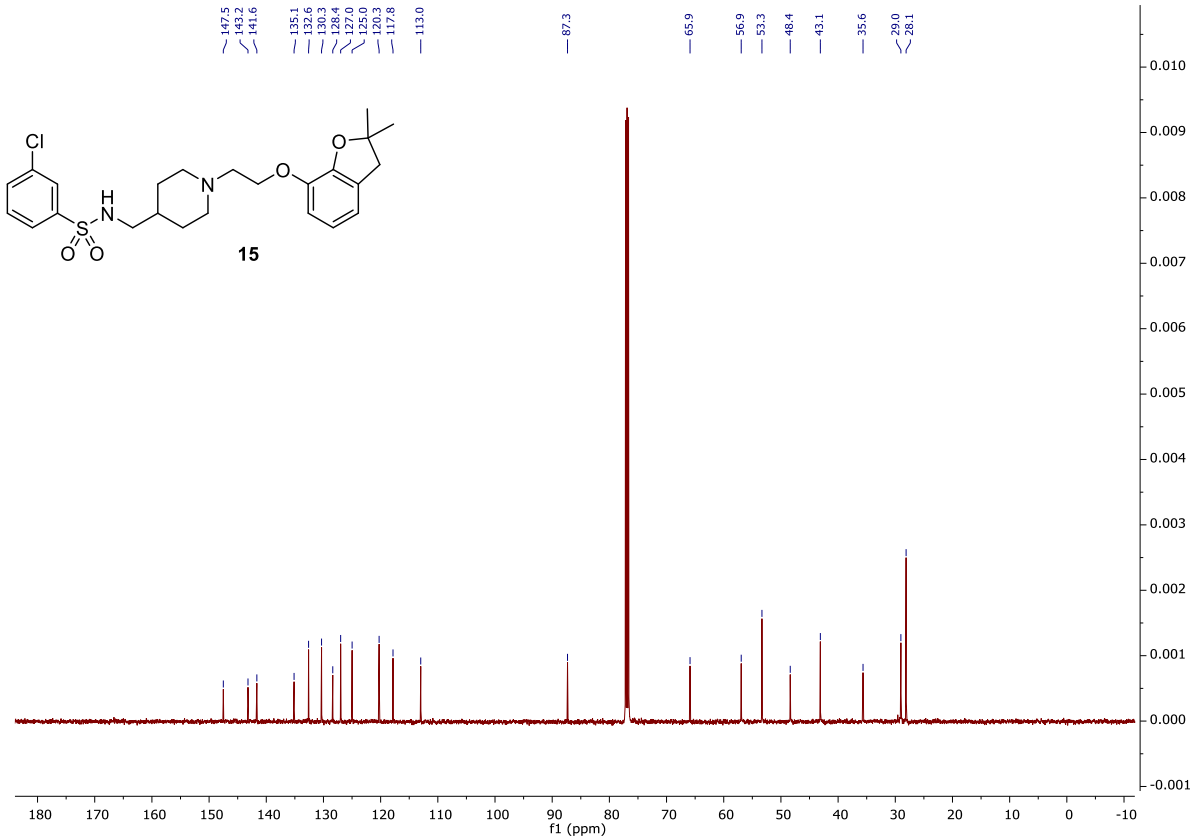


Figure S42. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 3-chloro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**15**).

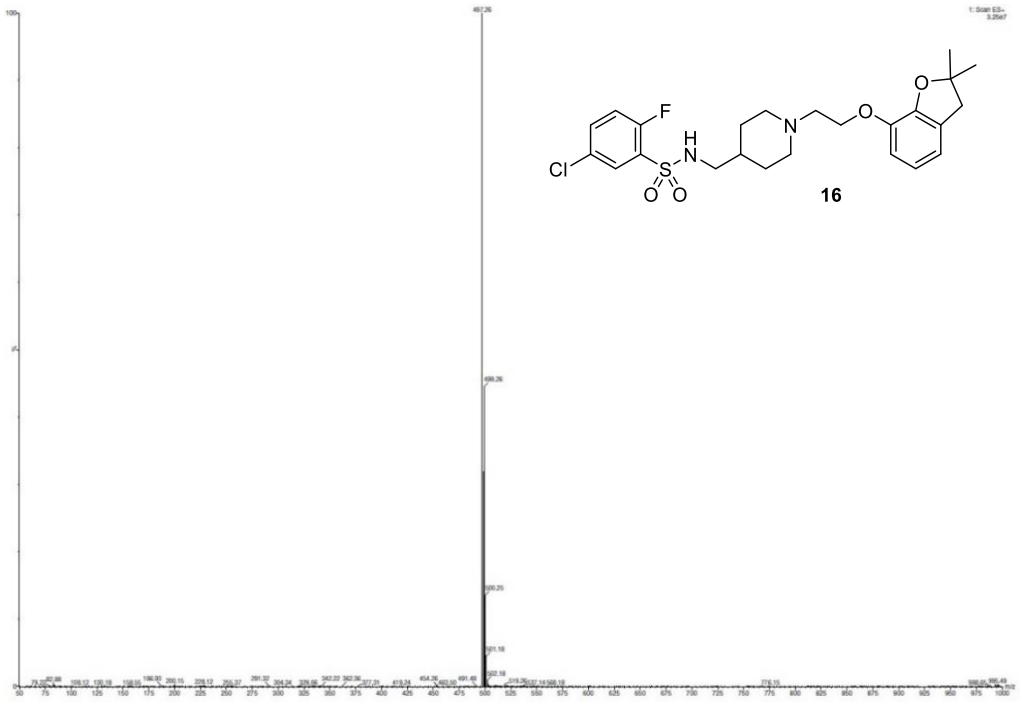


Figure S43. MS spectra for 5-chloro-2-fluoro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (16).

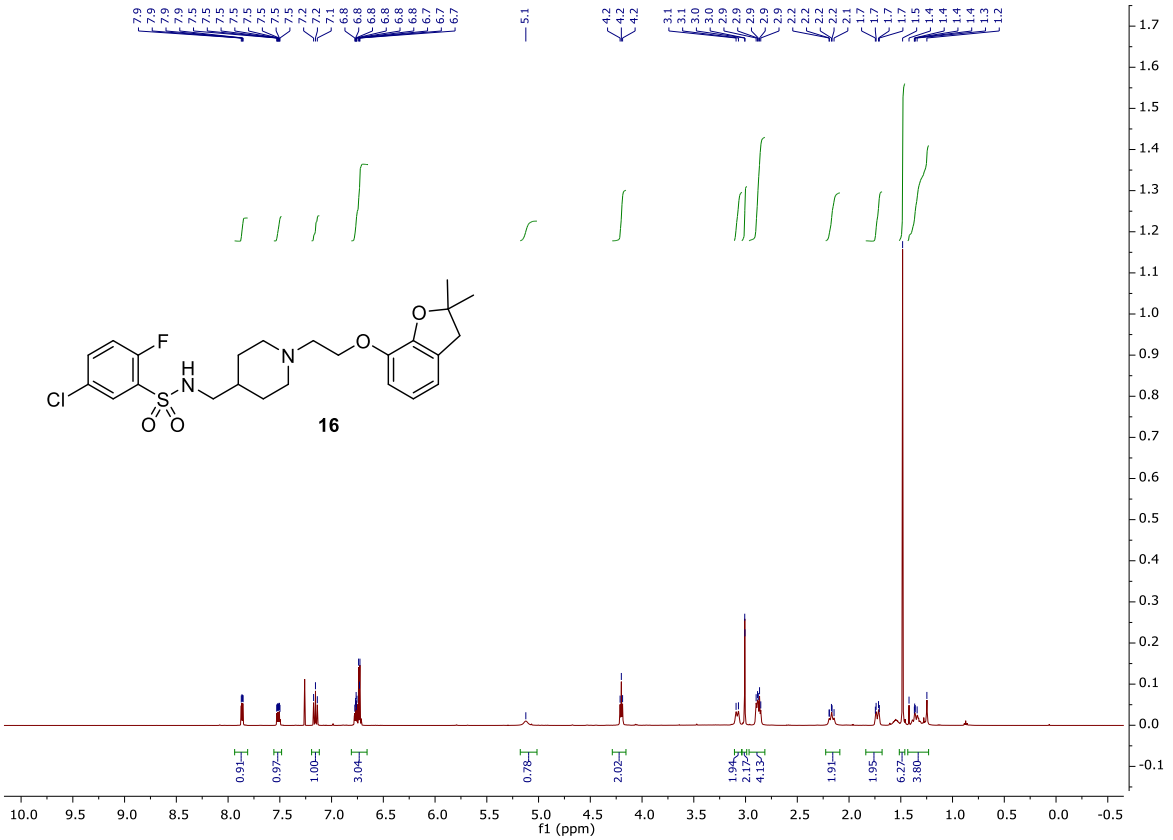


Figure S44. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 5-chloro-2-fluoro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**16**).

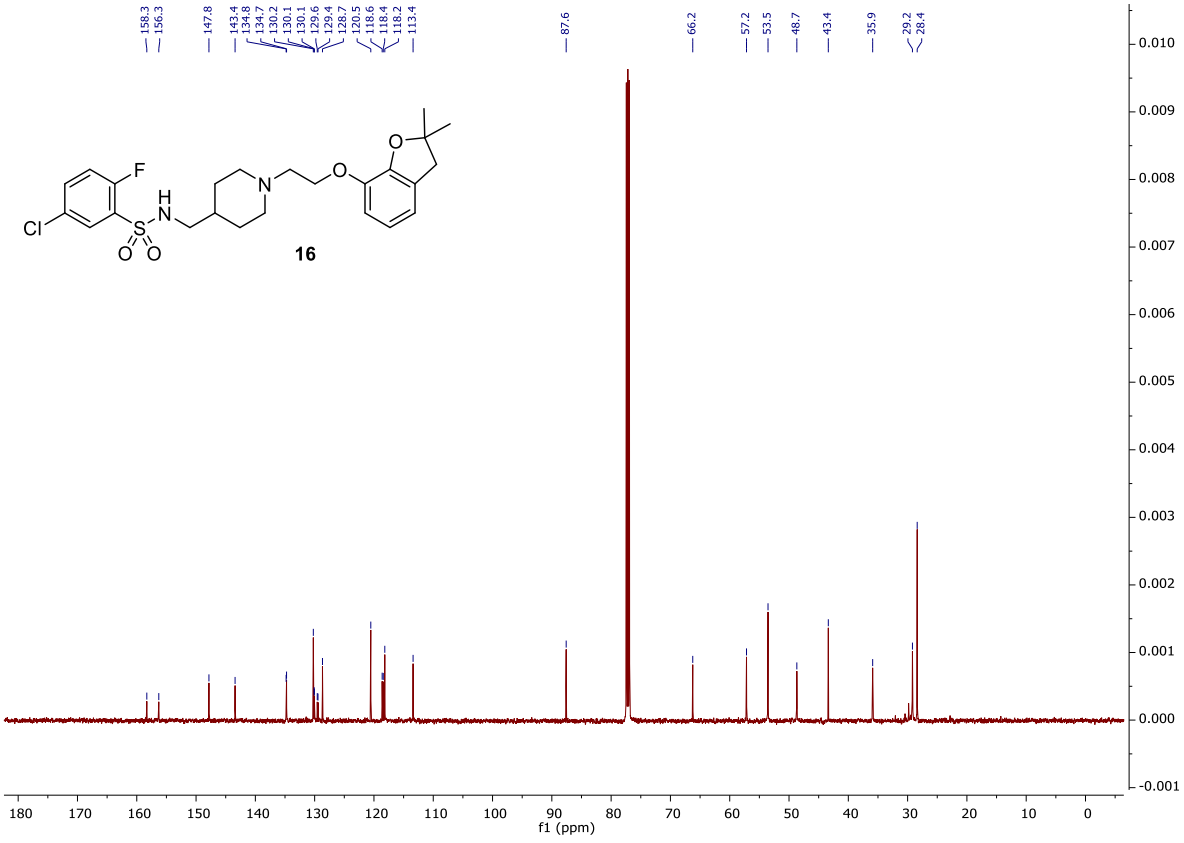


Figure S45. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 5-chloro-2-fluoro-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**16**).

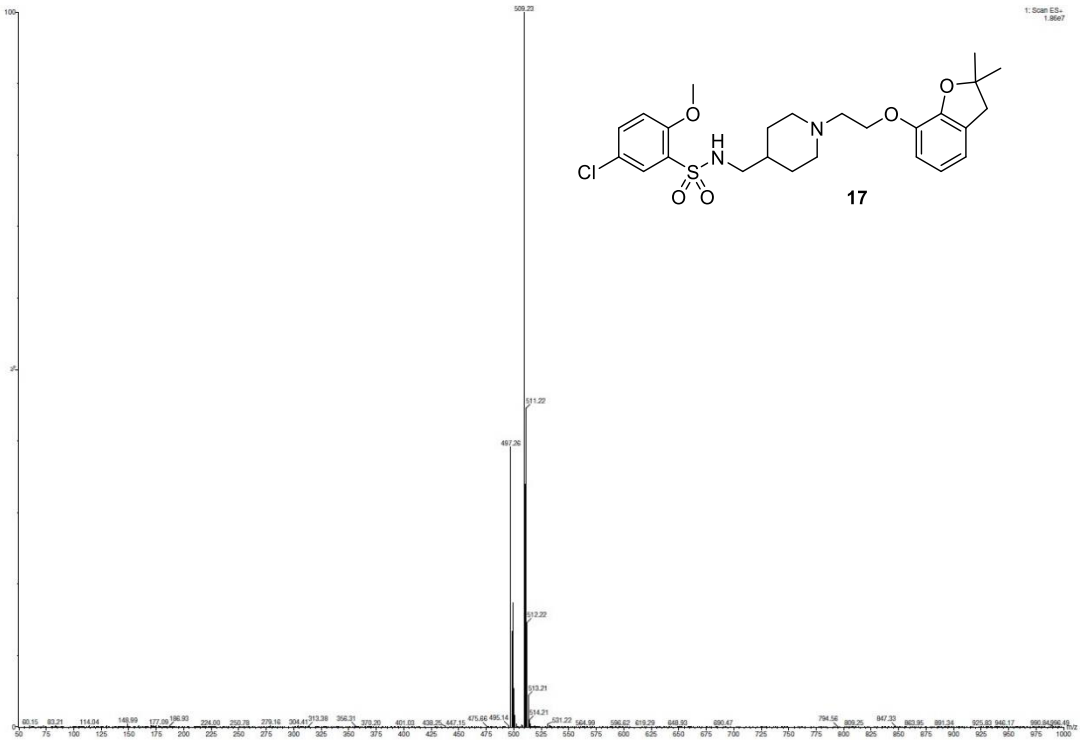


Figure S46. MS spectra for 5-chloro-2-methoxy-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**17**).

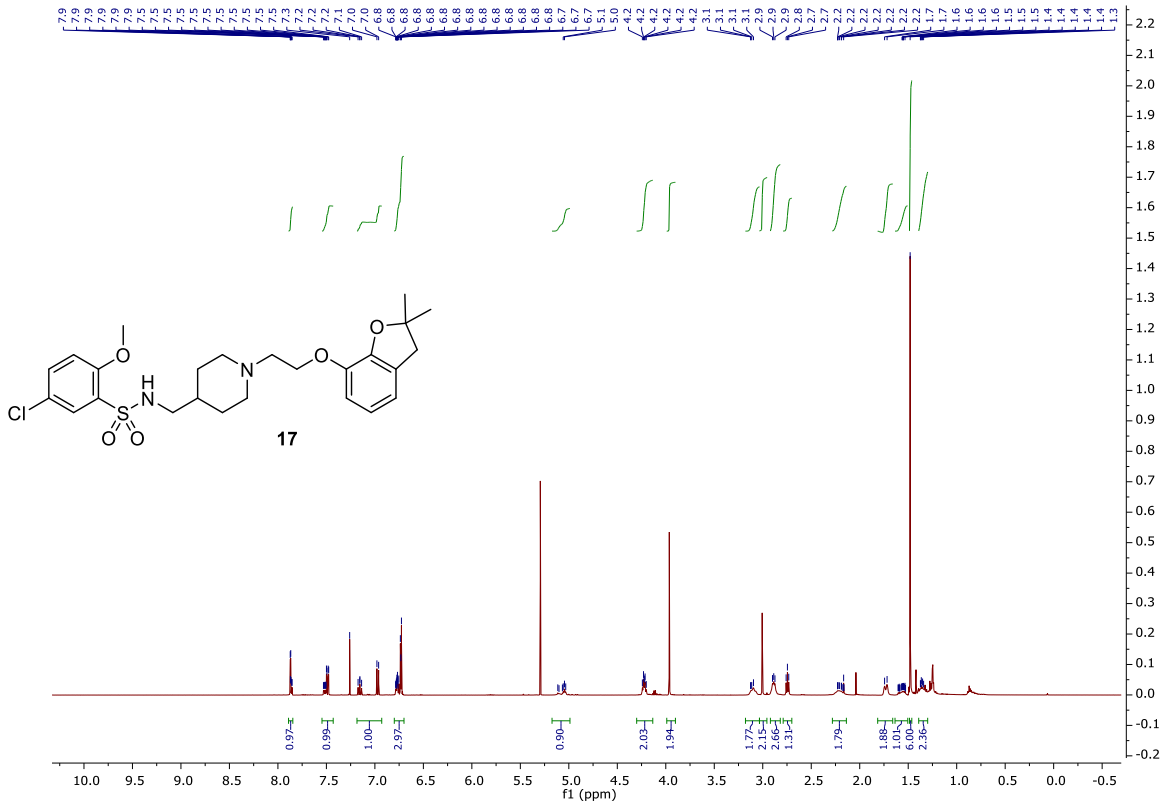


Figure S47. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 5-chloro-2-methoxy-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**17**).

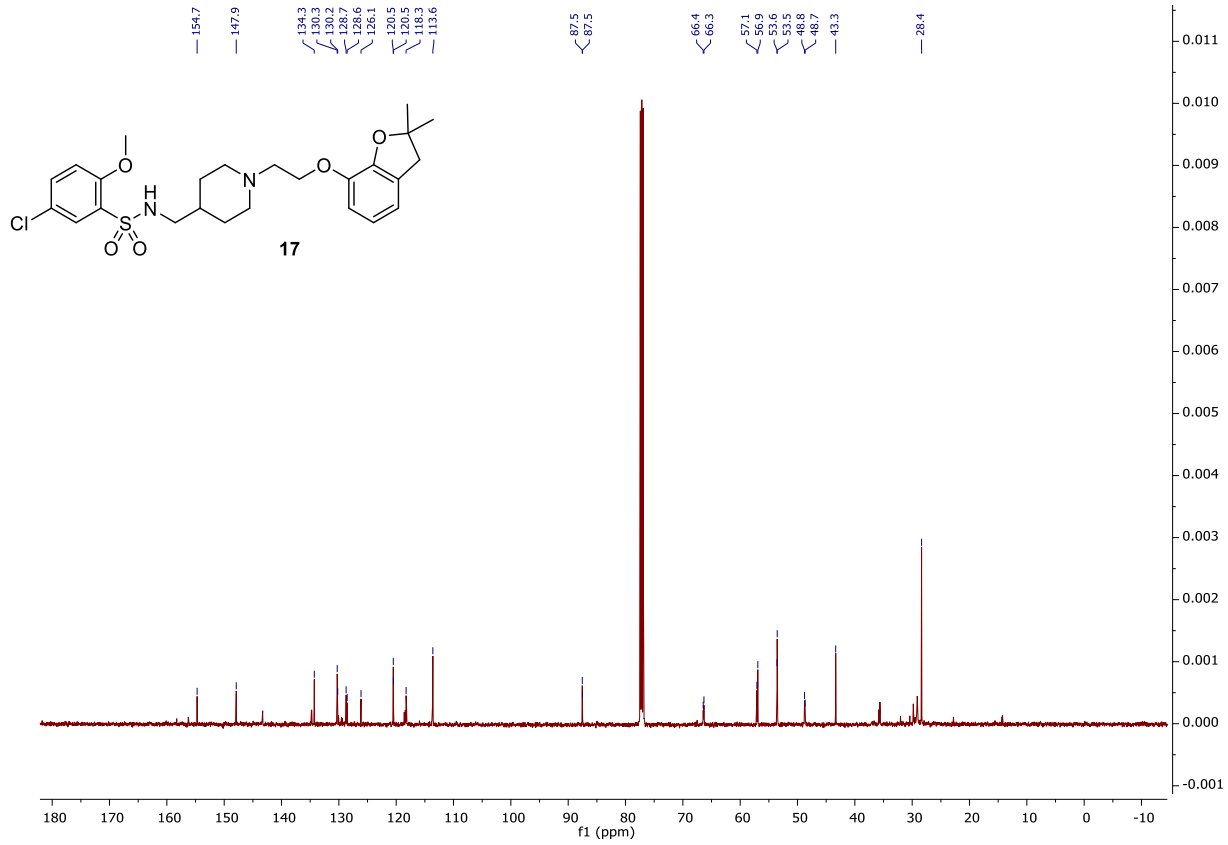


Figure S48. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 5-chloro-2-methoxy-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)benzenesulfonamide (**17**).

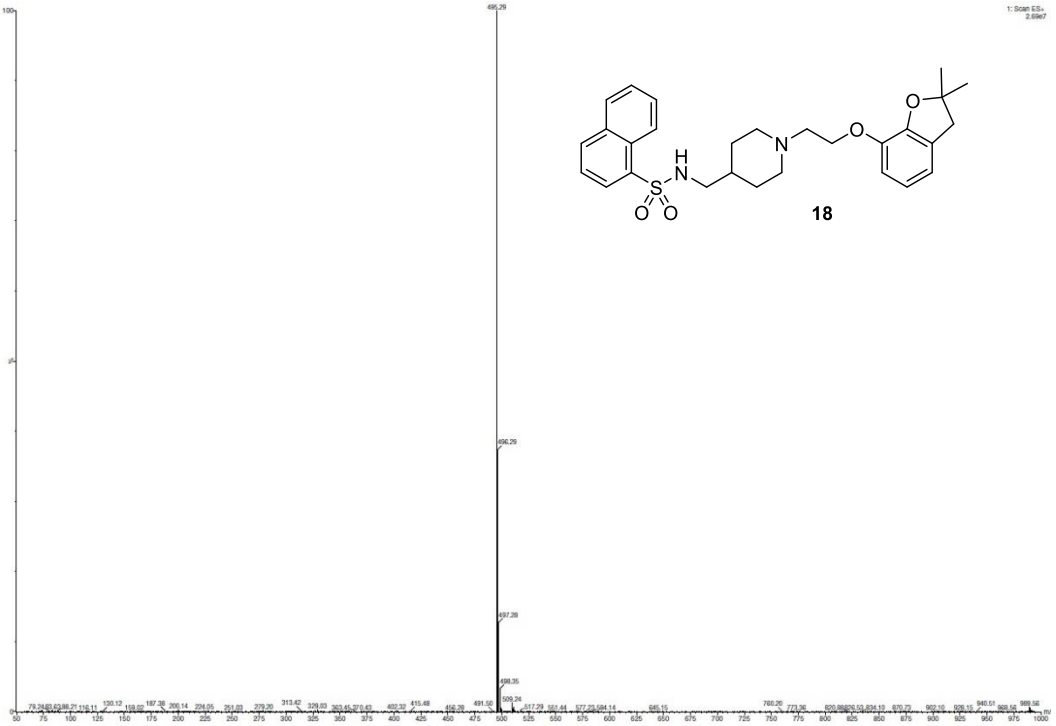


Figure S49. MS spectra for 1-naphthalene-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)sulfonamide (**18**).

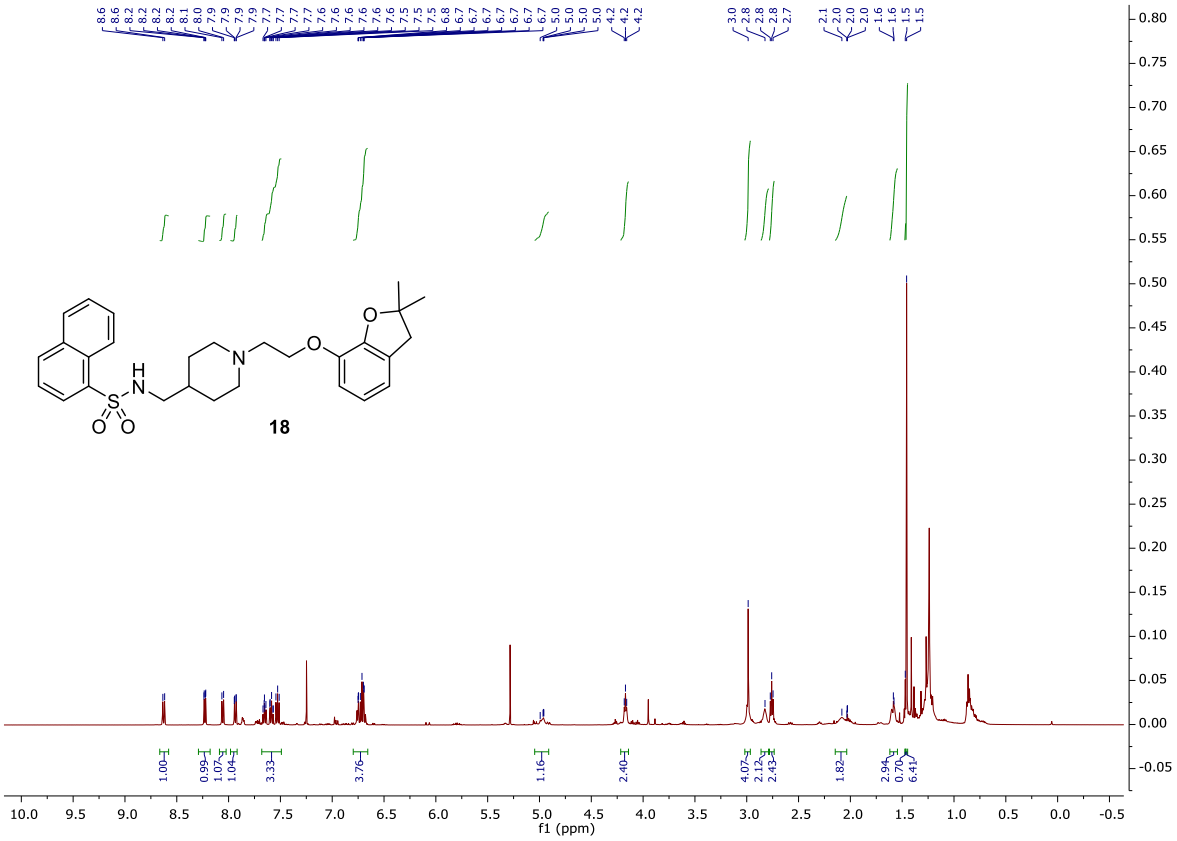


Figure S50. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 1-naphthalene-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)sulfonamide (**18**).

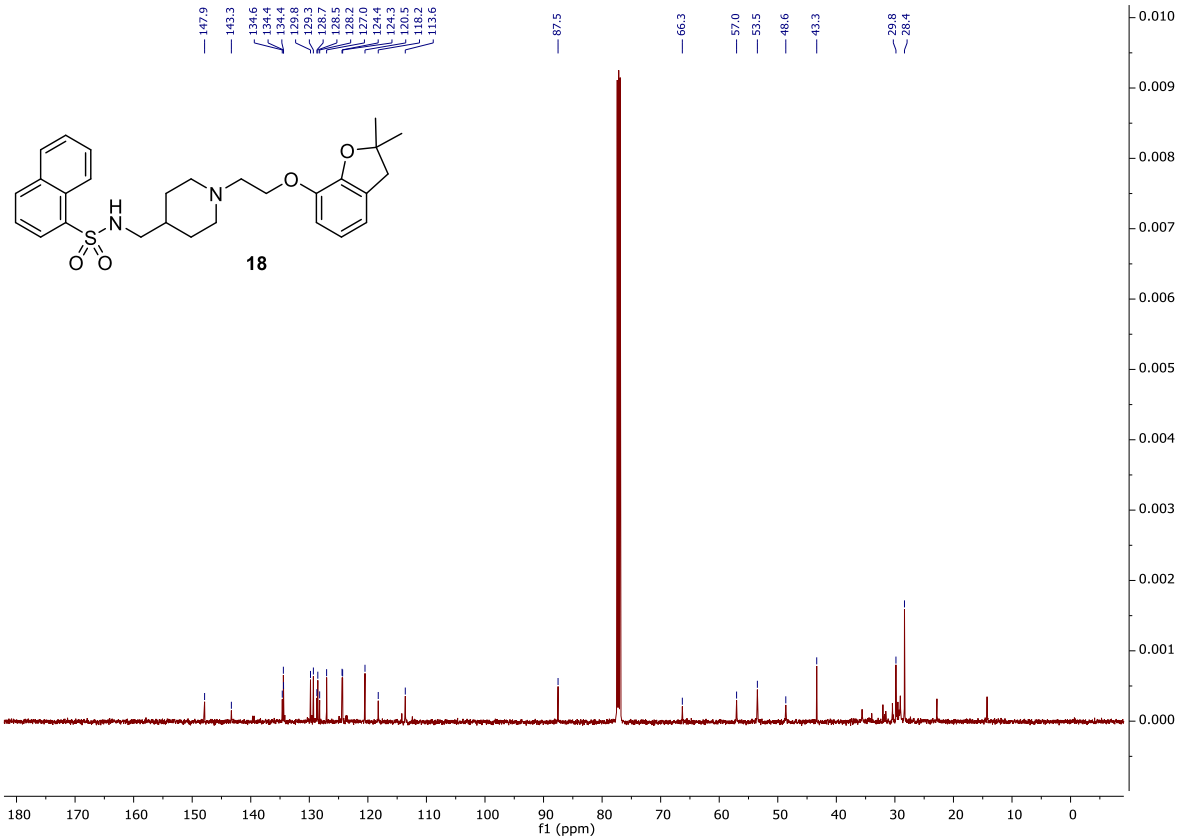


Figure S51. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 1-naphthalene-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)sulfonamide (**18**).

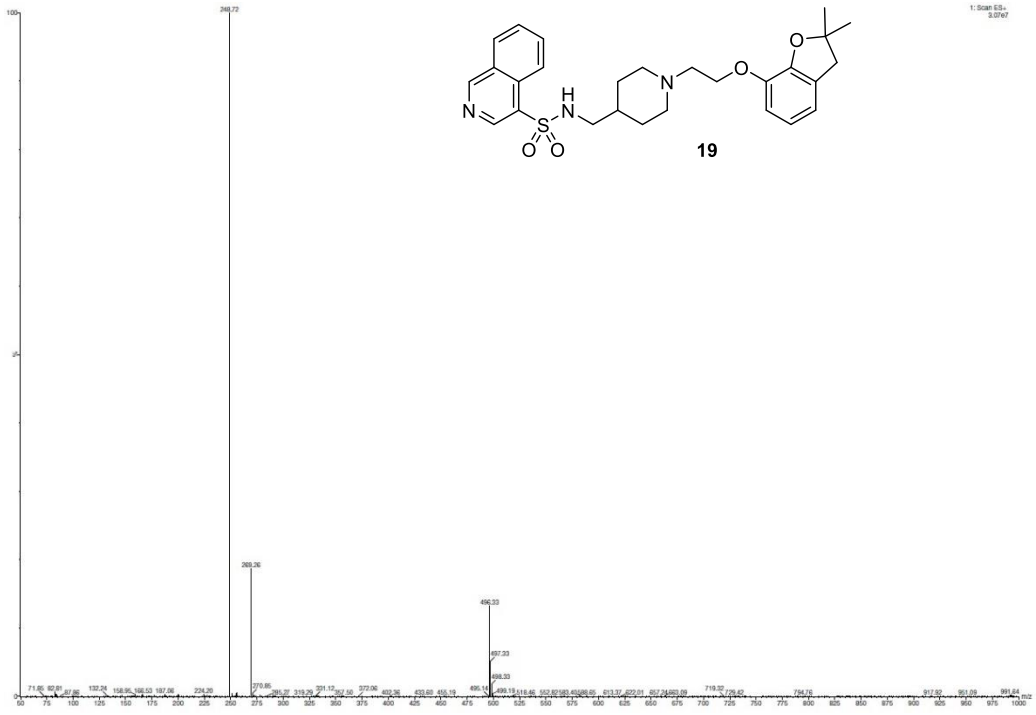


Figure S52. MS spectra for 4-isoquinoline-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)sulfonamide (**19**).

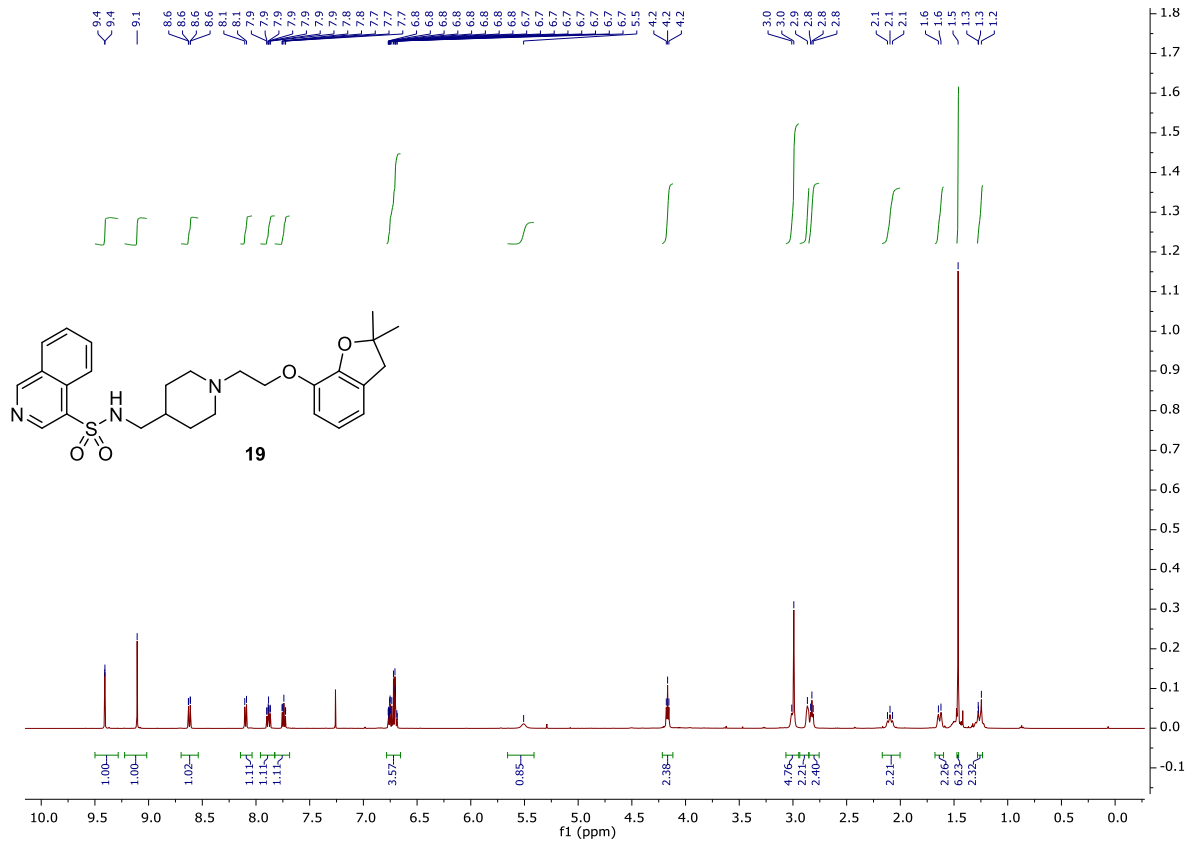


Figure S53. ^{1}H-NMR spectra (500 MHz, $CDCl_3$) for 4-isoquinoline-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)sulfonamide (**19**).

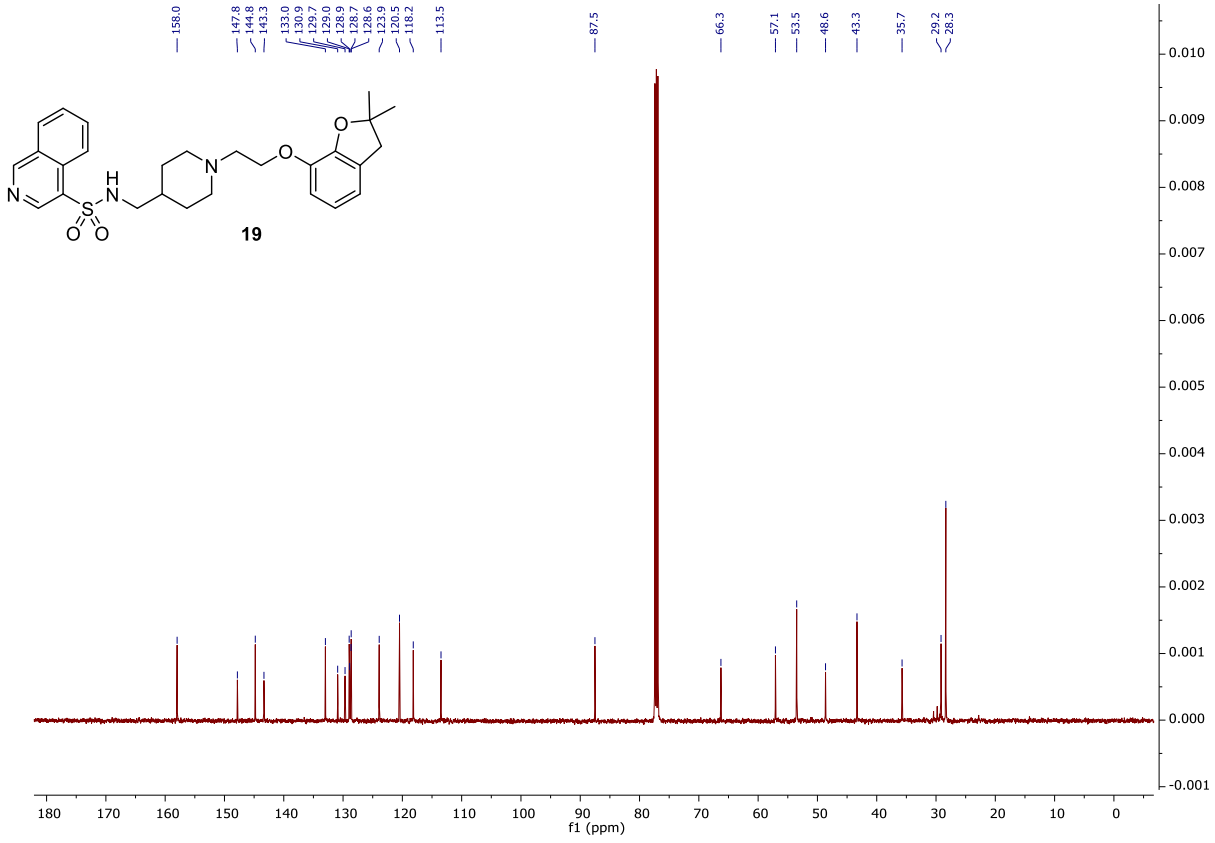


Figure S54. ^{13}C-NMR spectra (125 MHz, $CDCl_3$) for 4-isoquinoline-*N*-({1-[2-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yloxy)ethyl]piperidin-4-yl}methyl)sulfonamide (**19**).