Supporting Information

Alicyclic Ring Size Variation of 4-Phenyl-2-Naphthoic Acid Derivatives as $P2Y_{14}$ Receptor Antagonists

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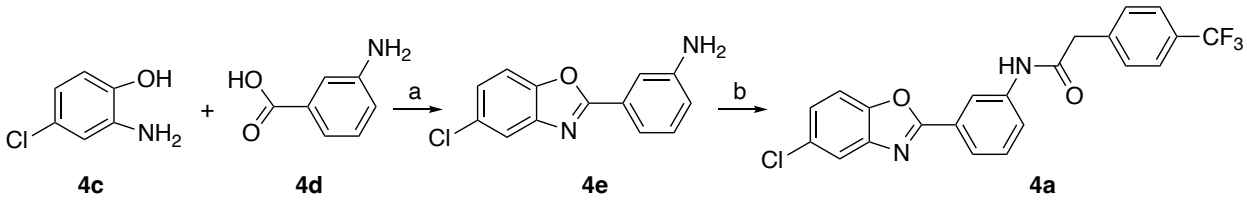
Chemical Synthesis

Compound 2-phenyl-benzoxazole acetamide (**4a**, Chart 1) was synthesized using a modified reported procedure.[1] briefly, cyclization of 2-amino-4-chlorophenol (**4c**) with *m*-aminobenzoic acid (**4d**) in polyphosphoric acid offered intermediate 3-(5-chlorobenzo[d]oxazol-2-yl)aniline (**4e**), which underwent amidation with 2-(4-(trifluoromethyl)phenyl)acetic acid (**4f**) activated with HATU in the presence of base DIPEA to provide *N*-(3-(5-chlorobenzo[d]oxazol-2-yl)phenyl)-2-(4-(trifluoromethyl)phenyl)acetamide (**4a**). Compound **4a** was confirmed with HRMS and NMR, matching the spectra reported.[1]

Scheme S1. Synthesis of new lead, benzoxazoles, as P2Y$_{14}$R antagonists.



4c **4d** **4e** **4a**

Reagents and conditions: (a). polyphosphoric acid, reflux, overnight, 99.6%; (b) 2-(4-(trifluoromethyl)phenyl)acetic acid , HATU, DIPEA, DMF, rt, overnight, 66.7%.

Synthetic procedures

3-(5-Chlorobenzo[d]oxazol-2-yl)aniline (**4e**). A solution of **4c** (287 mg, 2 mmol) and **4d** (274 mg, 2 mmol) in polyphosphoric acid (2 mL) was refluxed at 185 ºC in an oil bath overnight. The reaction mixture was neutralized with 6 N NaOH then extracted three times with EtOAc. The

combined organic layer was dried with Na_2SO_4. The volatiles were evaporated, and the residue was column chromatographed (hexane/EtOAc, 100:0→60:40) to give **4c** (488 mg, 99.6%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.1 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.32 – 7.25 (m, 2H), 6.83 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.82 (s, 2H). HRMS m/z $[M + H]^+$ for $C_{13}H_{10}{}^{35}ClN_2O$ calculated 245.0482, found 245.0483.

N-(3-(5-Chlorobenzo[d]oxazol-2-yl)phenyl)-2-(4-(trifluoromethyl)phenyl)acetamide (**4a**). Into a solution of **4e** (4.9 mg, 0.02 mmol) and 2-(4-(trifluoromethyl)phenyl)acetic acid (4.1 mg, 0.02 mmol) in DMF (0.5 mL) was added HATU (11.4 mg, 0.03 mmol) and DIPEA (10.4 μL, 7.8 mg, 0.06 mmol). The resulting solution was stirred at rt overnight. The volatiles were removed, and the residue was column chromatographed (hexane/EtOAc, 100:0→60:40). Appropriate fractions were collected and further purified by RP-HPLC (C18, A: ACN, B: H_2O, 90% → 100% A in 40 min, flow rate = 5 mL/min, t_R = 29 min) to give **4a** as a white powder (5.75 mg, 66.7%): ^{1}H NMR (400 MHz, DMSO) δ 10.59 (s, 1H), 8.62 (s, 1H), 7.93 (d, *J* = 2.1 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.45 (m, 1H), 3.83 (s, 2H). HRMS m/z $[M + H]^+$ for $C_{22}H_{15}{}^{35}ClF_3N_2O_2$ calculated 431.0774, found 431.0772.

Figure S1. Inhibition of specific hP2Y$_{14}$R binding of fluorescent antagonist **52** by selected antagonist derivatives, including 2-phenyl-benzoxazole acetamide (**4a**, Scheme S1). The ratio of total vs. nonspecific binding is ~2. Related to Figure 1.

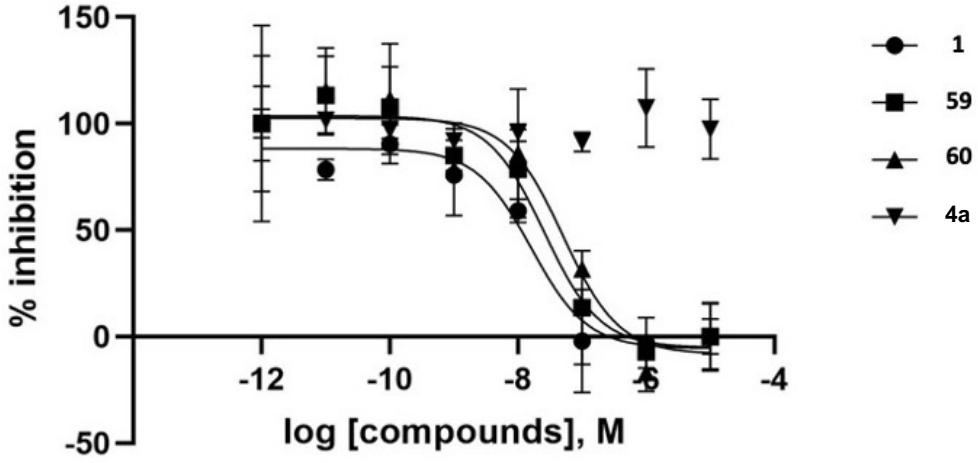
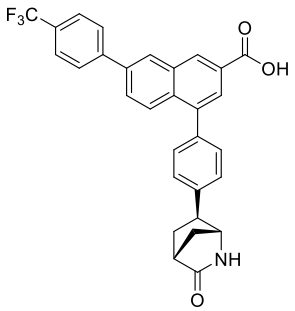


Table S1. Affinity of three previously reported P2Y$_{14}$R antagonists compared (in Figure S1 vs. Wen et al.[5]).

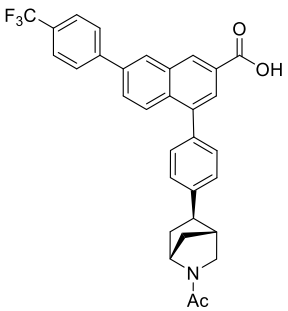
Compound	K_i (nM)	K_i (nM, Wen et al.[a], compound number)
1	7.1±1.4	4.63 (**1**)
59	14.3±6.8	21.7 (**23**)
60	16.8	37.3 (**20**)

[a] calculated from IC_{50} data in Wen et al., 2022.[5] The IC_{50} values were converted to K_i values by dividing by 1.72, based on the affinity of the fluorescent ligand **52** containing AlexaFluor488 in a binding saturation experiment of 27.8±9.3 nM (see main text). Two analogues, both related structurally to (*S*,*S*,*S*)-2-azanorbornane derivative **2b**, were reported earlier (Wen et al., 2022).[5]

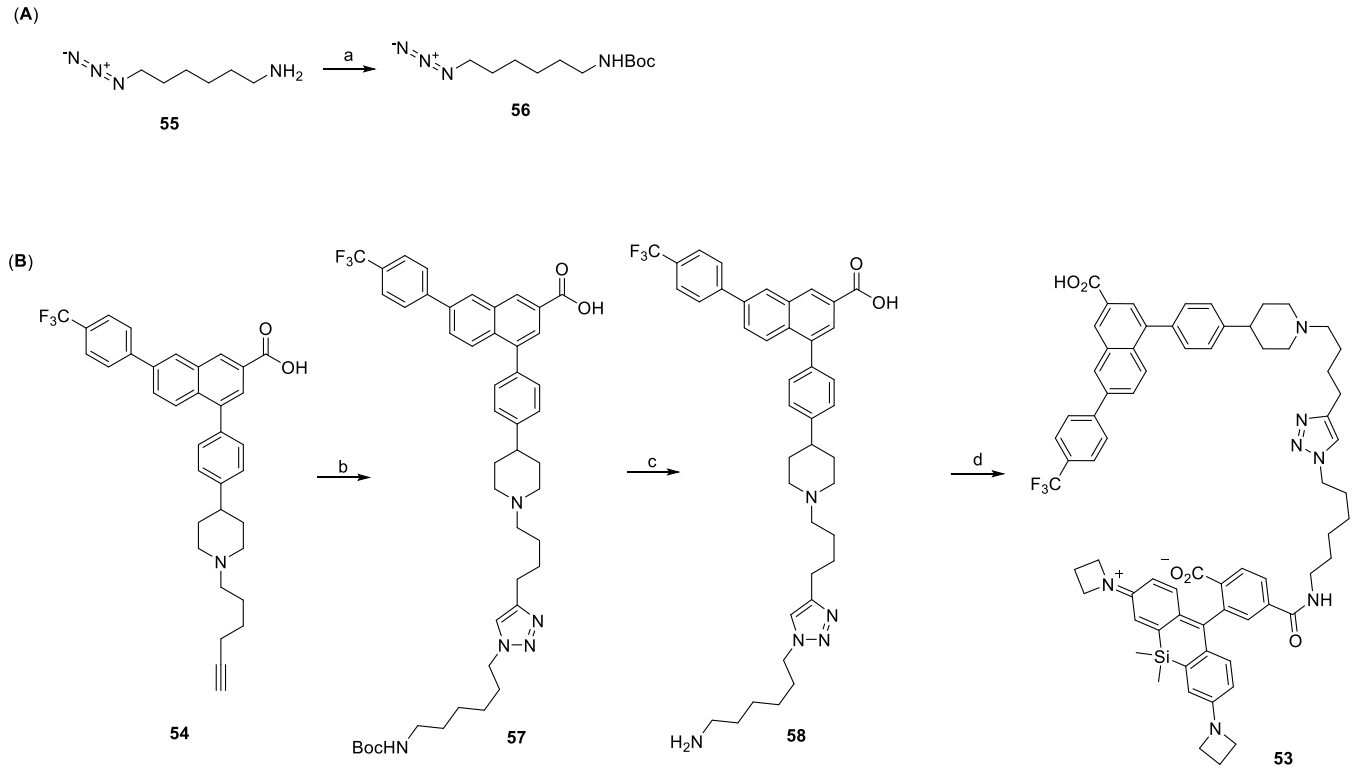
Compound 59:



Compound 60:



Scheme S2. Synthesis of novel fluorescent conjugate **53**, a JaneliaFluor646 conjugate. Related to Figure 1.



Reagents and conditions: (a) Di-*tert*-butyl dicarbonate, DMAP, THF, rt, 3 h, 95%. (b) **55**, sodium ascorbate, $CuSO_4.5H_2O$, *t*BuOH:H_2O = 4:1, rt, 12 h, 65%; (c) TFA:THF = 2:1, rt, 2 h, 76%; (d) JaneliaFluor646-NHS ester, TEA, DMSO, rt, 12 h, 70%.

tert-Butyl (6-azidohexyl)carbamate (**56**). To a solution of 6-azidohexan-1-amine (**55**, 100 mg, 0.703 mmol) in THF were added di-*tert*-butyl dicarbonate (184 mg, 0.843 mmol), and DMAP (17 mg, 0.140 mmol). The reaction mixture was stirred at room temperature for 3 h. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (dichloromethane:methanol=30:1) to afford compound **56** (162 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (t, *J* =6.90 Hz, 2H), 3.15-3.10 (m, 2H), 1.65-1.58 (m, 2H), 1.52-1.50 (m, 2H), 1.46 (s, 9H), 1.42-1.34 (m, 4H).

4-(4-(1-(4-(1-(6-((*tert*-Butoxycarbonyl)amino)hexyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperidin-4-yl)phenyl)-7-(4-(trifluoromethyl)phenyl)-2-naphthoic acid (**57**). To a mixture of compound **54** (40 mg, 0.071 mmol; synthesized according to literature procedures reported[2]) and compound **56**

(26 mg, 0.107 mmol) in *t*BuOH:H_2O (5 mL, 4:1) were added $CuSO_4 \cdot 5H_2O$ (9.0 mg, 0.035 mmol) and sodium ascorbate (21 mg, 0.107 mmol, freshly prepared 1 M aqueous solution), and then this reaction mixture was stirred at room temperature for 12 h. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (5 mL), and the aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed brine (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=10:1) to afford compound **57** (37 mg, 65%) as a white solid; HPLC purity 99% (R_t = 19.01 min); ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (s, 1H), 8.39 (s, 1H), 7.98-7.94 (m, 4H), 7.86-7.77 (m, 4H), 7.48-7.42 (m, 4H), 4.38-4.35 (m, 2H), 4.25-4.21 (m, 0.5H), 4.08-4.05 (m, 0.5H), 3.72-3.69 (m, 2H), 3.22-3.13 (m, 4H), 3.01-2.98 (m, 3H), 2.85-2.79 (m, 2H), 2.22-2.19 (m, 2H), 2.11-2.07 (m, 2H), 1.98 (s, 1H), 1.91-1.83 (m, 6H), 1.49 (s, 9H), 1.33-1.32 (m, 4H); MS (ESI, m/z) 798.4 $[M + H]^+$; ESI-HRMS calcd. m/z for $C_{46}H_{55}N_5O_4F_3$, 798.4206, found 798.4198 $[M + H]^+$.

4-(4-(1-(4-(1-(6-Aminohexyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperidin-4-yl)phenyl)-7-(4-(trifluoromethyl)phenyl)-2-naphthoic acid (**58**). A solution of compound **57** (24 mg, 0.030 mmol) in trifluoroacetic acid:tetrahydrofuran (3 mL, 2:1) was stirred at room temperature for 2 h. The solvent was evaporated with toluene under reduced pressure. The residue was purified by semipreparative HPLC (10 mM triethylammonium acetate buffer:acetonitrile = 50:50 to 20:80 in 40 min) to afford the compound **58** (37 mg, 76%) as a white solid. HPLC purity 99% (R_t = 14.85 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.45 (s, 1H), 8.04 (d, *J* =8.00 Hz, 2H), 7.96-7.82 (m, 6H), 7.42-7.37 (m, 4H), 4.27 (t, *J* =7.10 Hz, 2H), 2.92 (d, *J* =10.10 Hz, 2H), 2.72-2.68 (m, 1H), 2.60 (t, *J* =7.20 Hz, 2H), 2.29 (t, *J* =7.10 Hz, 2H), 1.98-1.93 (m, 2H), 1.89 (s, 2H), 1.79-1.73 (m, 4H), 1.70-1.66 (m, 1H), 1.61-1.57 (m, 2H), 1.49-1.43 (m, 4H), 1.34-1.29 (m, 2H), 1.25-1.20 (m, 3H); MS (ESI, m/z) 698.4 $[M + H]^+$; ESI-HRMS calcd. m/z for $C_{41}H_{47}N_5O_2F_3$ 698.3682, found 698.3674 $[M + H]^+$.

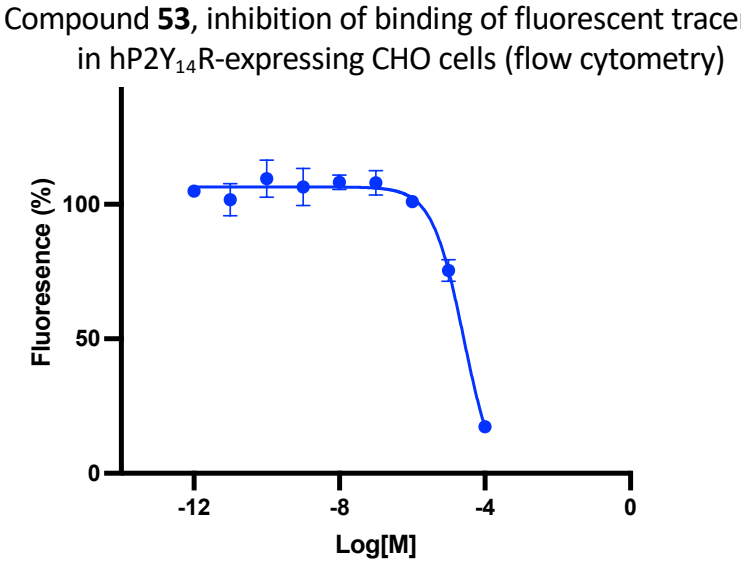
2-(3-(Azetidin-1-ium-1-ylidene)-7-(azetidin-1-yl)-5,5-dimethyl-3,5-dihydrodibenzo[b,e]silin-10-yl)-4-((6-(4-(4-(4-(4-(3-carboxy-6-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)phenyl)piperidin-1-yl)butyl)-1*H*-1,2,3-triazol-1-yl)hexyl)carbamoyl)benzoate (**53**). A mixture of compound **58** (0.88 mg, 0.001 mmol) and TEA (0.2 μL, 0.001 mmol) in anhydrous DMSO (100 μL) was added to JaneliaFluor646-NHS ester (0.5 mg, 0.842 μmol, Tocris, Bristol, UK) under nitrogen

atmosphere and stirred at room temperature for 12 h. The product was purified immediately by semipreparative HPLC (0.1% formic acid:acetonitrile = 50:50 to 20:80 in 40 min) to afford compound **53** (1.0 mg, 70%) as a blue solid. HPLC purity 99% (R_t = 15.50 min); ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (s, 1H), 8.42 (s, 1H), 8.25-8.23 (m, 1H), 8.08-8.06 (m, 1H), 7.99-7.95 (m, 4H), 7.91-7.89 (m, 1H), 7.80-7.78 (m, 4H), 7.67-7.63 (m, 1H), 7.50-7.43 (m, 4H), 6.85-6.82 (m, 3H), 6.28-6.26 (m, 2H), 4.38 (t, *J* =6.80 Hz, 2H), 4.26-4.19 (m, 6H), 3.73-3.70 (m, 2H), 3.23-3.12 (m, 4H), 3.04-2.98 (m, 2H), 2.84-2.78 (m, 2H), 2.65 (s, 2H), 2.50-2.46 (m, 4H), 2.24-2.21 (m, 2H), 2.10-2.03 (m, 3H), 1.93-1.90 (m, 2H), 1.62-1.59 (m, 3H), 1.41-1.28 (m, 7H), 0.55 (s, 3H), 0.50 (s, 3H); MS (ESI, m/z) 1176.5 $[M + H]^+$; ESI-HRMS calcd. m/z for $C_{70}H_{73}N_7O_5F_3{}^{28}Si$ 1176.5395, found 1176.5406 $[M + H]^+$.

Pharmacological characterization of JF646 conjugate 53

The fluorescent conjugate **53** (structure shown in Figure 1) did not demonstrate specific binding in whole CHO cells expressing the hP2Y$_{14}$R within a range of final concentrations of **53** of 2, 100, 500 and 20,000 nM, compared to a concentration of **52** of 20 nM. At the highest concentration used, there was no inhibition of binding by **1**.

Figure S2. Affinity measurement of JaneliaFluor646 conjugate **53** using the standard AlexFluor488 tracer **52**. At 1 µM **53** there was no inhibition of P2Y$_{14}$R binding.



The concentration range of **53** was 1 pM – 100 µM.
The IC_{50} value is 25.9 µM (n=1).

Table S2. Determination of lipophilicity by HPLC retention time. Standards with reported Log $D_{7.4}$ values for calibration of Log $D_{7.4}$ with retention factor *k*.[3] Standards related to lipophilicity data in Table 1.

Standards	Log $D_{7.4}$[a]	$k \pm$ SEM
sulpiride	-1.15	1.76 ± 0
metoprolol	-0.06	2.52 ± 0
labetolol	1.07	2.88 ± 0
diltiazem	2.7	4.00 ± 0.01
triphenylene	5.49	5.39 ± 0.01

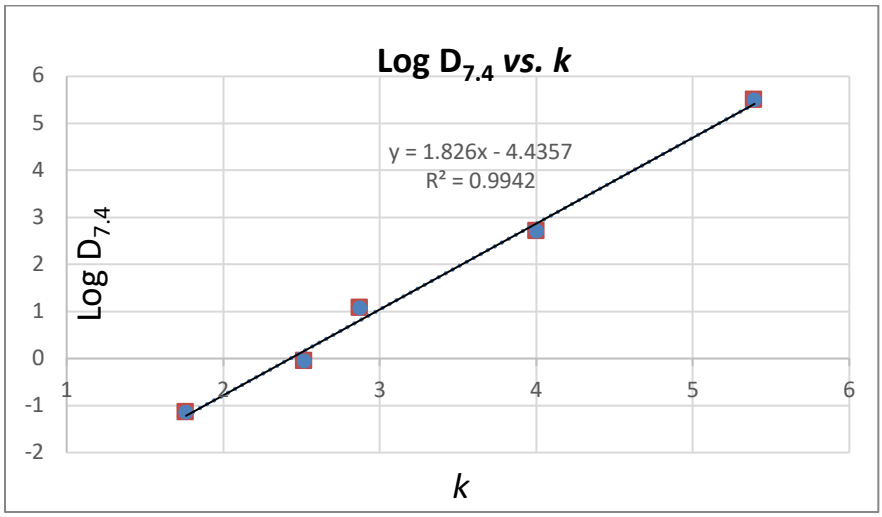


Figure S3. Calibration line Log $D_{7.4}$ *vs. k* using five standards listed in Table S2 for calculating HPLC-based Log $D_{7.4}$ of modified piperidine analogues of **1**.

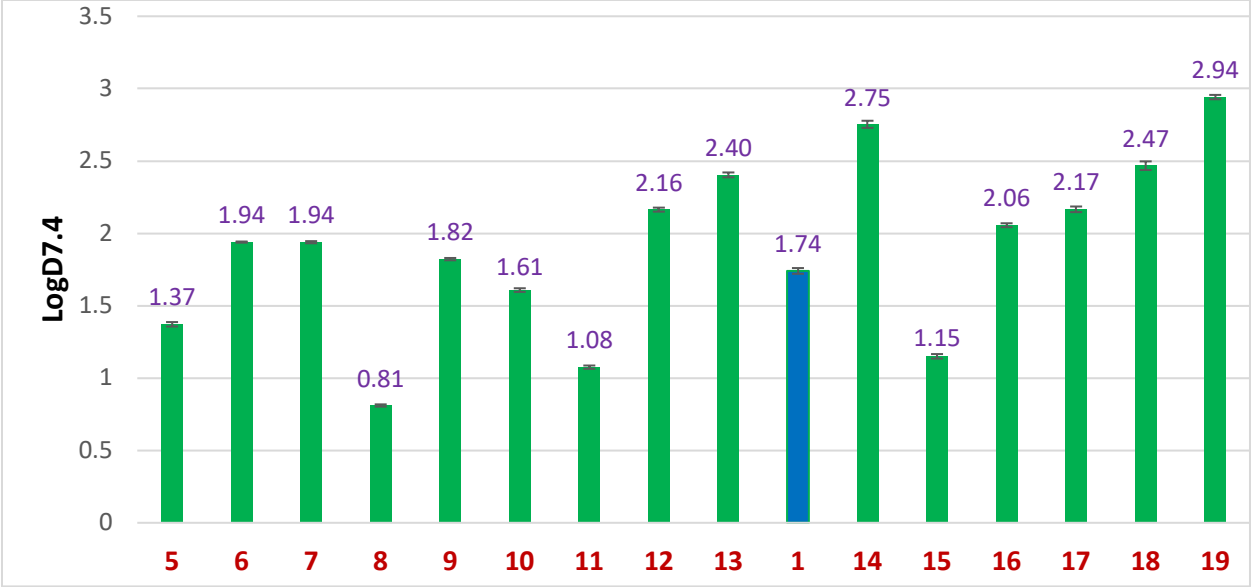


Figure S4. Lipophilicities as Log $D_{7.4}$ of modified piperidine analogues of piperidine derivative **1**, determined based on their HPLC retention time in comparison to five standard compounds (Table S2). Related to lipophilicity data in Table 1.

Binding affinities determined for off-target interactions

Determined by the the Psychoactive Drug Screening Program (PDSP)

We thank Dr. Bryan L. Roth (Univ. North Carolina at Chapel Hill) and National Institute of Mental Health's Psychoactive Drug Screening Program (Contract # HHSN-271-2008-00025-C) for screening data.[4]

Procedures: https://pdsp.unc.edu/pdspweb/content/UNC-CH%20Protocol%20Book.pdf

Unless noted in the text, no significant interactions (<50% inhibition at 10 μM) for any of the antagonists were found at the following sites (human unless noted): $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, $5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, $5HT_3$, $5HT_{5A}$, $5HT_6$, $5HT_7$, α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, β_3, BZP rat brain site, D_1, D_2, D_3, D_4, D_5, $GABA_A$, H_1, H_2, H_3, H_4, M_1, M_2, M_3, M_4, M_5, δ-opioid receptor (DOR), κ-opioid receptor (KOR), μ-opioid receptor (MOR), σ_1, σ_2, DAT, NET, SERT. K_i values in μM, or % inhibition at 10 μM, are given.

Compound, PDSP number, MRS number, K_i value, (mean±SEM, μM)

7, 60211, MRS4821: D_3, 0.50±0.02; σ_2, 2.10±0.50; M_5, 5.0; β_3, 8.3; H_1, 5.5.

11, 60212, MRS4822: α_{2A}, 5.7; $5HT_{1B}$, 5.35±1.27; $5HT_{5A}$, 2.37±0.43.

15, 60215, MRS4833: $5HT_{1B}$, 6.0±1.6; M_5, 6.0.

16, 60214, MRS4826: $5HT_{1B}$, 4.52±0.17; σ_1, 0.89±0.39; σ_2, 2.77±0.31; D_3, 0.41; M_5, 6.0; H_1, 2.84±0.32.

17, 60213, MRS4825: $5HT_{5A}$, 4.0±0.1; D_3, 1.71±0.53; KOR, 0.46±0.04; σ_1, 0.84±0.07; σ_2, 3.89±0.54; $5HT_{1B}$, 4.10±0.08; β_3, 6.6; M_5, 9.0.

Table S3A–C. ADMET properties (for procedures see refs. 5 and 6). These assays were performed by JRF (Jai Research Foundation) India of JRF Global (Gujarat, India).

Table S3A. In vivo experimental conditions for in vivo PK determination using male Wistar rats. Related to ADMET data in Table 2.

Dose (mg/kg, route)	**0.5 (i.v.)**	**1 (i.p.)**	**3 (i.p.)**	**10 (i.p.)**
Species of Strain	Rat and RccHan:WIST			
N mice	3	3	3	3
Feeding Condition	Fed	Fasting overnight, feed 4 h post-dosing		
Dose Volume (mg/kg b. wt.)	5			
Concentration (mg/mL)	0.1	0.2	0.6	2
Vehicles	DMSO: 20% HPBCD (10:90)	DMSO: Kolliphor EL: PBS (15:15:70)		
Blood Collection Site	Jugular vein through a catheter			
Anticoagulant	Heparin (20 IU/mL)			
Time Points (h)	0.083, 0.25, 0.5, 1, 2, 4, 8, 12, 24	0.25, 0.5, 1, 2, 4, 8, 12, 24		

Rats were observed daily, twice, for mortality and morbidity, and once for visible clinical signs throughout the research period. Body weight of rats was recorded on the first day of acclimatization, surgery, randomization, and treatment. Approximately 200 µL blood sample was collected from jugular vein of each rat, at every time point. Plasma was collected and frozen immediately at -70 ± 10 °C. Rats were terminally sacrificed by carbon dioxide asphyxiation after last blood collection (24h).

The plasma samples were analyzed for determination of drug concentration. The pharmacokinetic (PK) analysis of the plasma concentration vs. time was performed using the non-compartmental model of the WinNonlin® software (version 8.3).

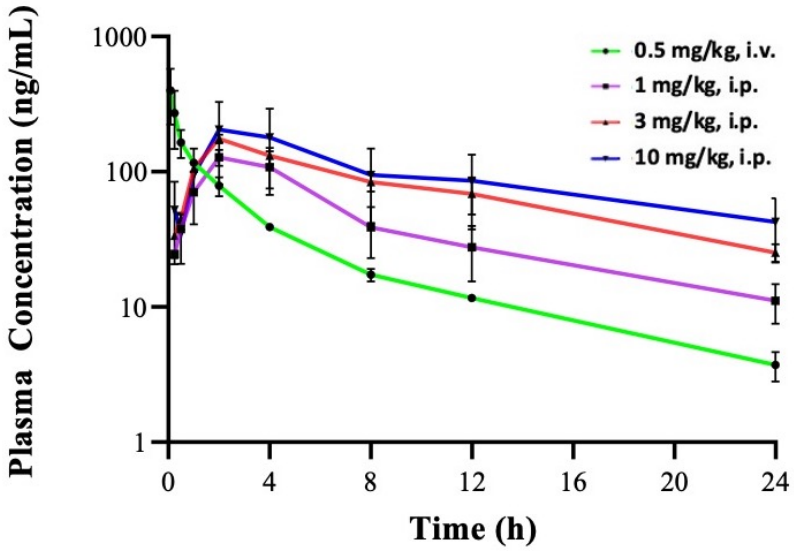
Table S3B. Caco-2 cell permeability results of compound **15**. Related to ADMET data in Table 2.

Compound Name	Average Values					
	Papp (10^6 cm/sec)		Efflux Ratio	A to B % Recovery	B to A % Recovery	Classification
	A to B	B to A				
15	0.00	0.62	NC	39.0	62.6	Low
Digoxin	0.28	14.4	51.8	84.4	84.6	Low
Propranolol	15.0	18.0	1.20	61.9	85.5	High
Atenolol	1.33	0.73	0.55	91.1	88.0	Low

hERG assay procedure. The assay used HEK-293 cells stably transfected with the hERG potassium channel. A_3AR PAM concentrations were prepared using serial half-log dilutions, starting at 30 μM. Compounds were incubated with the hERG-expressing cells for 2 h. Binding to the hERG ion channel were identified their ability to displace the tracer (Predictor™ hERG Tracer Red), resulting in a lower fluorescence polarization using a TAMRA fluorescent polarization filter. Related to ADMET data in Table 2.

Tables S3C and 3D. In vivo pharmacokinetic parameters of compounds **2b** and **15** in male Wistar rats. Related to ADMET data in Figure 2.

Table S3C. In vivo PK of compound **2b**, as reported in Wen et al.[5]



Dose (Route)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-last}}$ (h*ng/mL)	$AUC_{0\text{-}\infty}$ (h*ng/mL)	$T_{1/2}$ (h)	MRT_{last} (h)	V_d (mL/kg)	k_{el} (1/h)	F (%)	Cl (mL/h/kg)
0.5 mg/kg (i.v.)	400	0.083	696	734	7.24	4.38	7110	0.096	100	681
1 mg/kg (p.o.)	128	2.000	1030	1180	8.94	7.01	11,000	0.078	74.2	850
3 mg/kg (p.o.)	175	2.000	1800	2110	8.61	8.40	17,700	0.081	43.1	1420
10 mg/kg (p.o.)	204	2.000	2260	3080	13.3	8.94	62,300	0.052	16.1	3250

ND, not determined.

Table S3D. In vivo PK of compound **15** (a comparable graph is in the main text Figure 2).

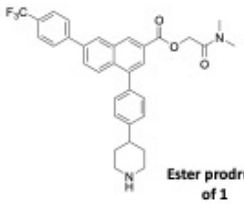
Dose (Route)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-last}}$ (h*ng/mL)	$AUC_{0\text{-}\infty}$ (h*ng/mL)	$T_{1/2}$ (h)	MRT_{last} (h)	V_d (mL/kg)	k_{el} (1/h)	F (%)	Cl (mL/h/kg)
0.5 mg/kg (i.v.)	867	0.083	631	635	2.36	0.976	2680	0.294	100	788
1 mg/kg (p.o.)	250	2.00	1490	1500	3.01	4.72	2890	0.230	118	666
3 mg/kg (p.o.)	651	2.00	4310	4380	4.32	5.54	4270	0.161	114	685
10 mg/kg (p.o.)	2020	4.00	14,400	14,600	4.15	4.97	4090	0.167	114	685

Table S4. Pharmacokinetic study of mono-ester prodrugs and active products administered subcutaneously (s.c.) in female CD1 mice. The product (active drug) derived from **63** is the 2-azanorbornyl derivative **2b**. The stability of **63** was also studied in plasma, in comparison to the corresponding mono-ester of active drug **1** was studied (structure below, obtained from Axon Medchem LLC, Reston, VA, https://www.axonmedchem.com/, product 1958). The study was performed by Paraza Pharma, Inc., 7171 Frederick Banting, Montréal, Canada H4S 1Z9 (C064-011_PS-2021-012).

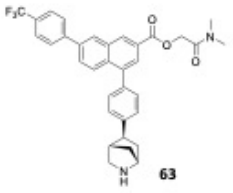
Table S4A. Calculated in vitro half-life of ester prodrug of active drug **1** and prodrug **63** (both monoesters). Monoester **63** is a prodrug of **2b**. Related to structures shown in Table 1.

Calculated half-life ($t_{1/2}$) following a 120 min incubation (controls) or 240 min (prodrugs) in human or mouse plasma

Compound	Species	$t_{1/2}$ (min)		
		Rep 1	Rep 2	Mean
Ester prodrug of 1	Human	>720.0	>720.0	**>720.0**
Compound 63		>720.0	>720.0	**>720.0**
Beclomethasone		324.1	272.4	**298.3**
Propantheline		11.8	12.8	**12.3**
Ester prodrug of 1	Mouse	1.8	1.2	**1.5**
Compound 63		2.0	1.2	**1.6**
Beclomethasone		1.3	1.5	**1.4**
Propantheline		36.7	39.8	**38.3**



Ester prodrug of 1



63

Plasma Stability Assay: Prodrugs and assay controls were incubated at 1 µM in human and mouse plasma (BioIVT, Westbury, NY, USA) at37°C for a total of 240 min for the prodrugs and 120 min for controls. The final organic percentage in each incubation was 0.5% DMSO. For controls and prodrugs, drug stability was assessed by quenching thereaction4:1withice-cold stop solution at the required 10, 30, 60 and 120-min timepoints (control compounds). For the prodrugs, the incubation time points were 10, 30, 90 and 240 min. The 0-min samples were prepared by quenching the plasma prior to spiking the test article or control drug. Resulting supernatants were further diluted 1:1 with 0.1% formic acid in water (controls) or a solution of 1:1 water/acetonitrile (prodrugs). The conversion of prodrugs to their corresponding active metabolite was assessed by quenching the plasma prior to spiking the active metabolite. The

percent of metabolite formed was determined based on the pre-quenched plasma sample spiked at a final concentration of 1µM. Samples were centrifuged and further diluted with a solution of 1:1water/acetonitrile. Samples were analyzed by LC-MS/MS, and calculations for percentage of parent remaining and % metabolite formed calculated using Excel.
Samples were analyzed by LC-MS/MS using a CTCPAL autosampler, Thermo Accela UPL Canda Thermo Quantum triple quadrupole mass spectrometer. Compounds and internal standard were monitored using positive or negative mode electrospray ionization in single reaction monitoring (SRM) mode. The analytes were injected onto a C18 column and chromatographed using a reverse phase gradient with 0.1% formic acid in water and 0.1% formic acid in methanol. Peak integrations were performed using ThermoXcalibur (v2.4) software.

Table S4B. Plasma concentrations of active drug **2b** following administration of prodrug **63**. **63** is a monoester prodrug of **2b**. Related to structures shown in Table 1.

Plasma concentration (ng/mL) of **2b** following a single SC administration of **63** at 10 mg/kg, s.c., to female CD1 mice

Time (h)	Animal ID			Mean (ng/mL)	SD (ng/mL)	%CV
	A	B	C			
0.25	120.0	301.3	189.7	203.7	91.4	0.45
0.5	312.0	695.8	360.9	456.2	208.9	0.46
1	962.5	1374.9	826.5	1054.6	285.6	0.27
2	2118.3	2277.0	1562.7	1986.0	375.1	0.19
4	2295.2	*2142.9*	*1407.6*	1948.5	474.6	0.24
8	*1035.9*	*646.6*	*403.8*	695.4	318.9	0.46
24	*37.9*	*NQ*	*NQ*	37.9	-	-
C_{max} (ng/mL)	2295.2	2277.0	1562.7	2045.0	417.8	0.20
t_{max} (h)	4.00	2.00	2.00	2.67	1.15	0.43
$t_{1/2}$ sc (h)	3.35*	2.31*	2.22*	2.63*	0.63	0.24
AUC_{last} (ng/mL*h)	21594.1	12504.7	8177.1	14092.0	6847.9	0.49
AUC_{inf} (ng/mL*h)	21777.6	14663.1	9470.6	15303.7	6178.5	0.40
% Extrapolation	0.84	14.7	13.7	9.74	7.72	0.79
MRT sc (h)	5.98	4.67	4.56	5.07	0.78	0.15

Limit of quantification (LOQ: 25.0 ng/mL)

Data points highlighted in blue were used to estimate AUC_{inf}

** Interpret $t_{1/2}$ values with caution as only 2 points could be captured in the terminal phase.*

Table S4C. Recovery of prodrug **63** and active drug **2b** in the urine. **63** is a monoester prodrug of **2b**. Related to structures shown in Table 1.

Amount of Compound **63** excreted unchanged in urine following a subcutaneous administration of **63** (10 mg/kg, s.c. in female CD1 mice)

Animal ID	Total mouse BW (kg)	Time Interval	Conc. (ng/mL)	Urine sample (mL)	Amount (ng)	Total amount (ng)	%Recovered
A,B,C	0.0681	0-8	7.43	1.283	9.5	22.5	0.003
		8-24h	9.67	1.345	13.0		

Limit of quantification (LOQ: 5.0 ng/mL)

Amount of Compound **2b** excreted unchanged in urine following a subcutaneous administration of **63** (10 mg/kg, s.c. in female CD1 mice)

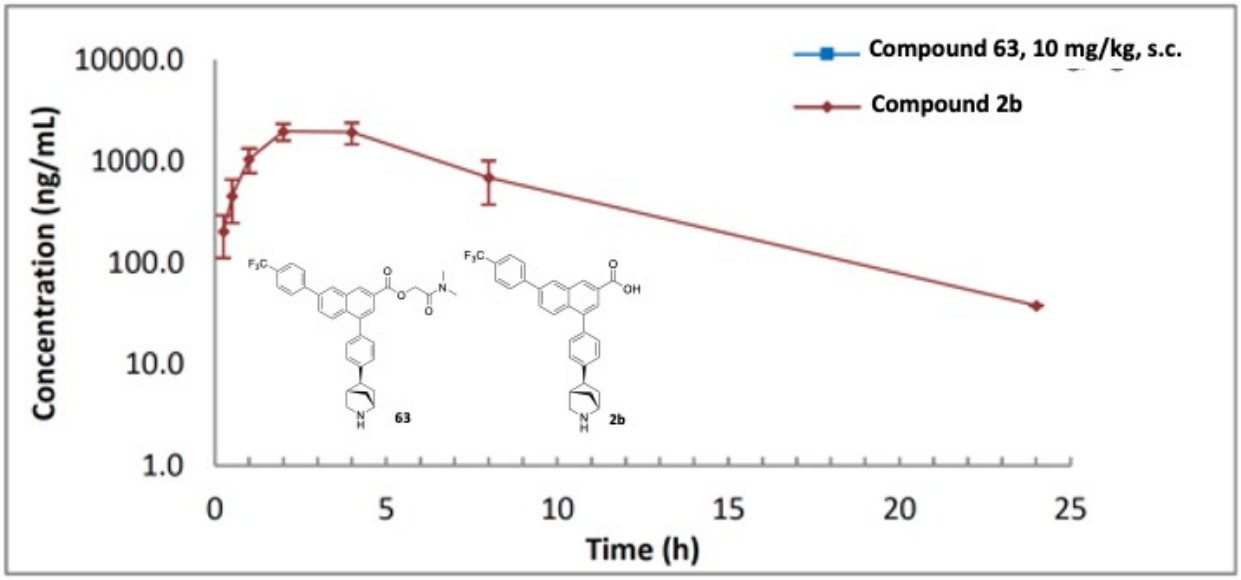
Animal ID	Total mouse BW (kg)	Time Interval	Conc. (ng/mL)	Urine sample (mL)	Amount (ng)	Total amount (ng)	CL_{renal} (mL/min/kg)
A,B,C	0.0681	0-8	137.71	1.283	176.7	1550.5	0.025
		8-24h	1021.5	1.345	1373.9		

Limit of quantification (LOQ: 5.0 ng/mL)

$CLrenal = (Total\ Amounts\ in\ ng\ /Total\ BW\ in\ Kg)/AUCinf\ ng/mL*min$

Figure S5. PK profile of active drug **2b** following prodrug **63** administration. **63** is a monoester prodrug of **2b**. Related to structures shown in Table 1.

Pharmacokinetic profile of **2b** following a single administration of **63** at 10 mg/kg, s.c. to female CD-1 mice.



*Concentration of **63** was not quantifiable. No peak observed or peak below the limit of quantification (LOQ: 2.5 ng/mL)*

Procedure for PK determination: Microsampling with heparinized capillaries was performed using the tail snip method.
A. Samples were thawed at room temperature. B. 20 µL sample + 20 µL of 0.5% formic acid in water + 200 µL internal standard working solution (0.1 µM glyburide/labetalol in methanol/ACN) were combined, followed by capping and vortexing. Then, was added: 20 µL of ACN/MeOH for the samples or 20 µL of a standard solution for the calibrant and QCs. C. Vials were vortexed and centrifuged at 10,000xg for 10 min @ 4°C. D. 150 µL of supernatant was transferred to a 0.5 mL well plate and diluted with 150 µL of 0.2% formic acid in MeOH, followed by capping and vortexing. 10 µL was injected on the LC-MS/MS. Non-compartment analysis (NCA) was performed on the composite PK profiles using WinNonlin 8.3.

Table S5. Pharmacokinetic study of double prodrug **62** (containing both ester and carbamate prodrug moieties), administered by oral gavage (p.o.) in female CD1 mice. The product (active drug) is compound **1**. The study was performed by Paraza Pharma, Inc., 7171 Frederick Banting, Montréal, Canada H4S 1Z9 (C064-011_PS-2021-012). **62** is a monoester/carbamate double prodrug of **1**. Related to structures shown in Table 1 and Scheme 4.

Table S5A. Plasma concentration of **62**.

Plasma concentration (ng/mL) of **62** following a single administration of **62** at 10 mg/kg, p.o., to female CD1 mice

Time (h)	Animal ID			Mean (ng/mL)	SD (ng/mL)	%CV
	A	B	C			
0.25	22.7	16.0	32.2	23.7	8.14	34.37
0.5	156.6	64.0	195.7	138.8	67.7	48.77
1	751.0	764.0	987.1	834.0	132.7	15.91
2	*533.6*	*474.1*	*290.9*	432.9	126.5	29.22
4	*81.5*	*194.6*	*77.3*	117.8	66.5	56.49
7	*29.0*	*70.6*	*19.2*	39.6	27.3	68.81
24	*NQ*	*NQ*	*NQ*	-	-	-
C_{max} (ng/mL)	751.0	764.0	987.1	834.0	132.7	15.91
t_{max} (h)	1.00	1.00	1.00	1.00	0.00	0.00
$t_{1/2}$ (h)	1.23	1.84	1.29	1.45	0.33	22.97
AUC_{last} (ng/mL*h)	1675.4	1904.5	1480.2	1686.7	212.3	12.59
AUC_{inf} (ng/mL*h)	1726.9	2091.4	1516.0	1778.1	291.1	16.37
% Extrapolation	2.98	8.94	2.36	4.76	3.63	76.25
%F	-	-	-	6.92		
V_z_F (L/kg)	10.3	12.7	12.3	11.7	1.3	10.93
CL_F (mL/min/kg)	96.5	79.7	109.9	95.4	15.2	15.89
$MRT_{po.inf}$ (h)	2.18	3.11	1.94	2.41	0.62	25.54

NQ: Not quantifiable. No peak or below limit of quantification (LOQ: 5.00 ng/mL)

Data points highlighted in blue were used for the half-life and AUC_{inf} estimation.

Table S5B. Plasma concentration of active drug **1** following prodrug **62** administration.

Plasma concentration (ng/mL) of **1** following a single administration of **62** at 10 mg/kg, p.o., to female CD1 mice

Time (h)	Animal ID			Mean (ng/mL)	SD (ng/mL)	%CV
	A	B	C			
0.25	*NQ*	*NQ*	*NQ*	-	-	-
0.5	*NQ*	*NQ*	*NQ*	-	-	-
1	*NQ*	*NQ*	*NQ*	-	-	-
2	5.32	8.84	5.48	6.55	1.99	30.34
4	27.0	20.9	15.2	21.1	5.88	27.93
7	***38.6***	34.5	***25.8***	33.0	6.51	19.75
24	***7.89***	*NQ*	***5.47***	6.68	1.71	25.60
C_{max} (ng/mL)	38.6	34.5	25.8	33.0	6.51	19.75
t_{max} (h)	7.00	7.00	7.00	7.00	0.00	0.00
AUC_{last} (ng/mL*h)	531.0	121.6	353.8	335.5	205.3	61.19
AUC_{inf} (ng/mL*h)	615.5	*NC*	413.8	514.6	142.6	27.72
% Extrapolation	13.7	*NC*	14.5	14.1	0.53	3.79
$MRT_{po.inf}$ (h)	12.2	*NC*	12.6	12.4	0.22	1.77

Limit of quantification (LOQ: 5.00 ng/mL)

Data points highlighted in blue were used to estimate AUC_{inf}

NC: Not calculated due to the shape of the profile

Figure S6. Plasma concentration of active drug **1** and prodrug **62**.

Pharmacokinetic profile of **62** and **1** following a single administration of **62** at 10 mg/kg, p.o. to female CD-1 mice.

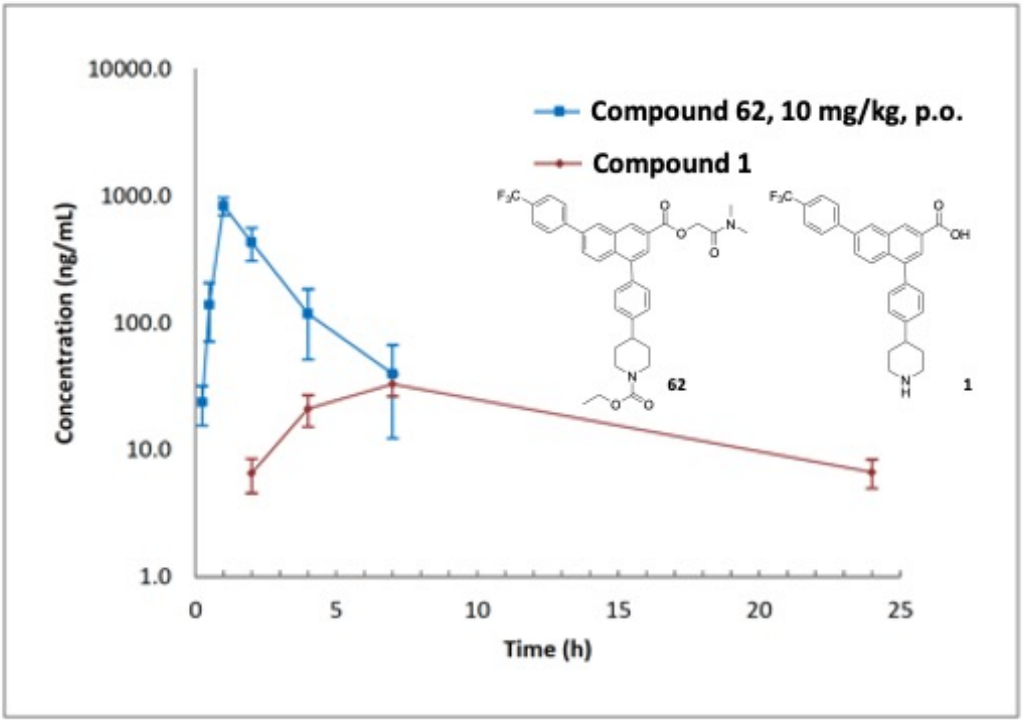


Figure S7. BAL fluid content of cells following treatment with compound **15**, its double prodrug **50** and the reference antagonist **1** in an in vivo mouse model (ovalbumin, aspergillus) of allergic asthma. See Figure 4 for content of eosinophils in the same experiment. Methods are described in Wen et al.[5] Refer to Figure 4 in the main text.

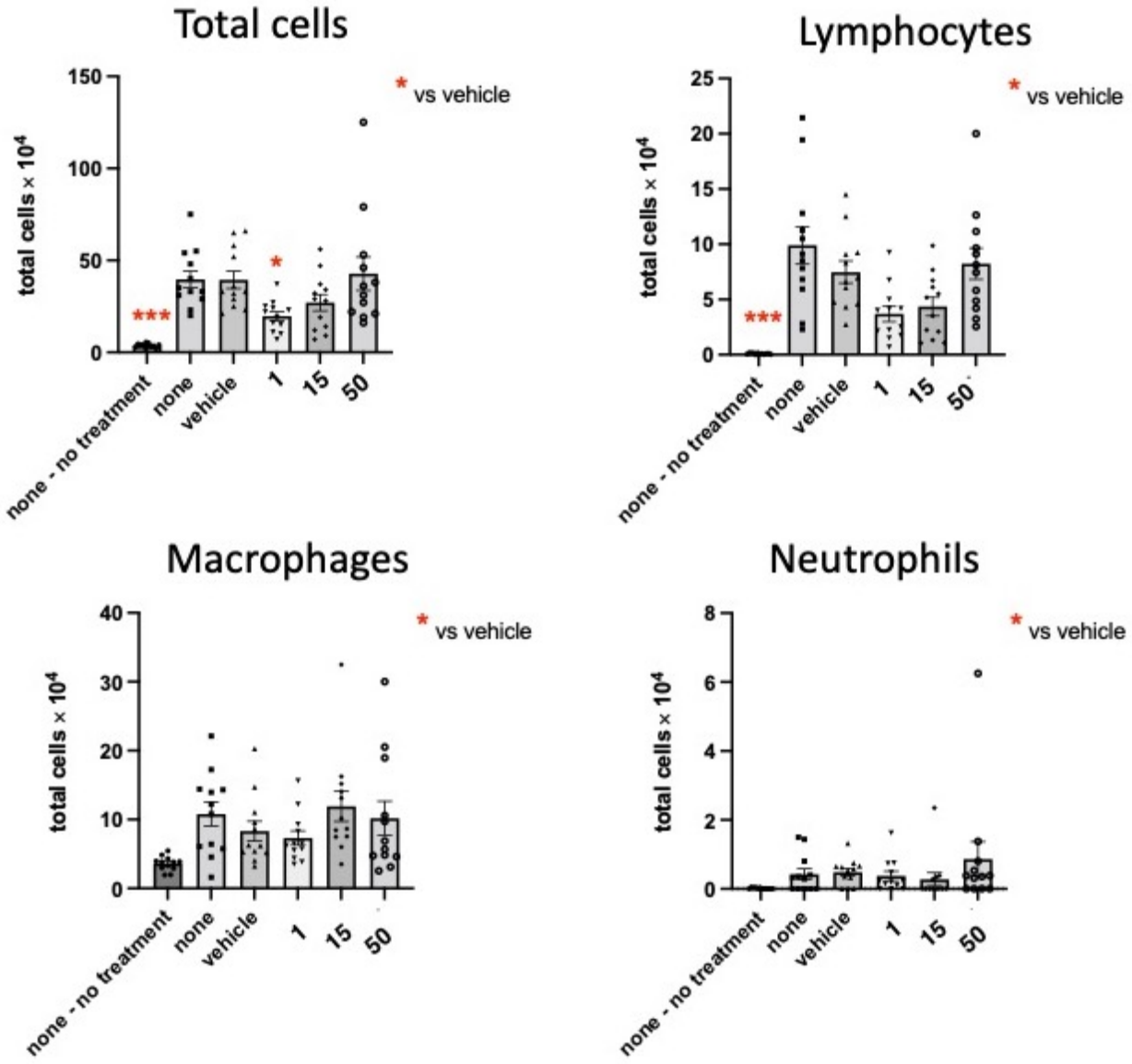


Figure S8. Additional mouse CCI chronic pain results. Refer to Figure 3 in the main text.

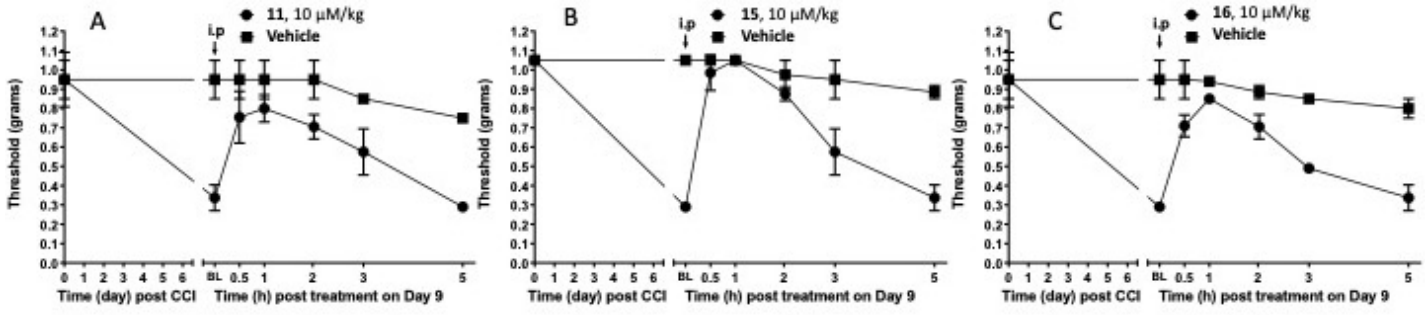


Figure S8. Representative time and dose dependence for reversal of established neuropathic pain in adult male by three $P2Y_{14}R$ antagonists. The drugs were injected 7 days post-sciatic nerve constriction. The paw withdrawal threshold was determined using von Frey filaments applied to the postsurgical hindpaw. A single injection (10 μmol/kg, i.p.) of a $P2Y_{14}R$ antagonist (**11**, **15**, and **16**) reversed the mechano-allodynia, and there was no effect of the drug injection on the contralateral hindpaw (not shown). Data represents the mean ± SD, n = 2. The vehicle used for the i.p. injection: 10% (5% Kolliphor HS-15:DMSO, 5:95 by volume) in saline (0.2 mL dose).

Figure S9. Predicted structure of compound **15** (Table 1) showing the spatial proximity of its hydroxyl group to the secondary amine, which would effectively reduce the zwitterionic character (using Chem3D, ChemDraw v. 18.2, PerkinElmer). With Chem3D, the molecule went through MM2 Minimize and MM2 Dynamics functions to achieve the most stable 3D structure. The C-O bond of the hydroxyl group rotates freely at the rigid bridging piperidine structure, and the hydroxyl group H is 2.4 – 4.1 Å away from the amine N.

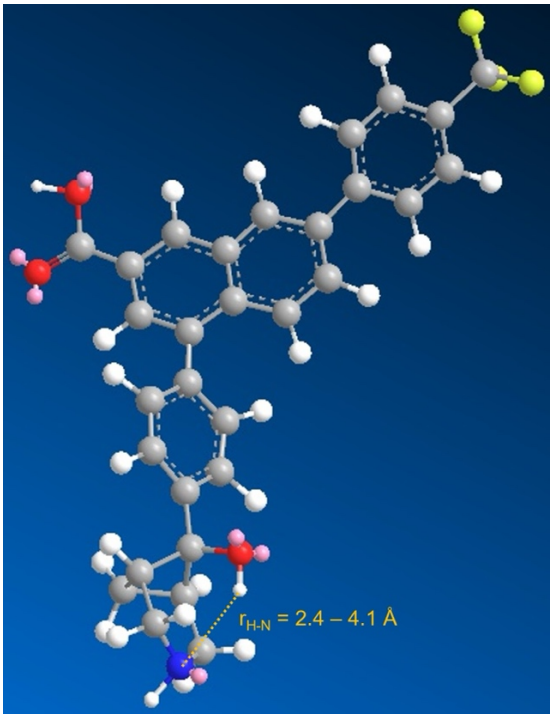
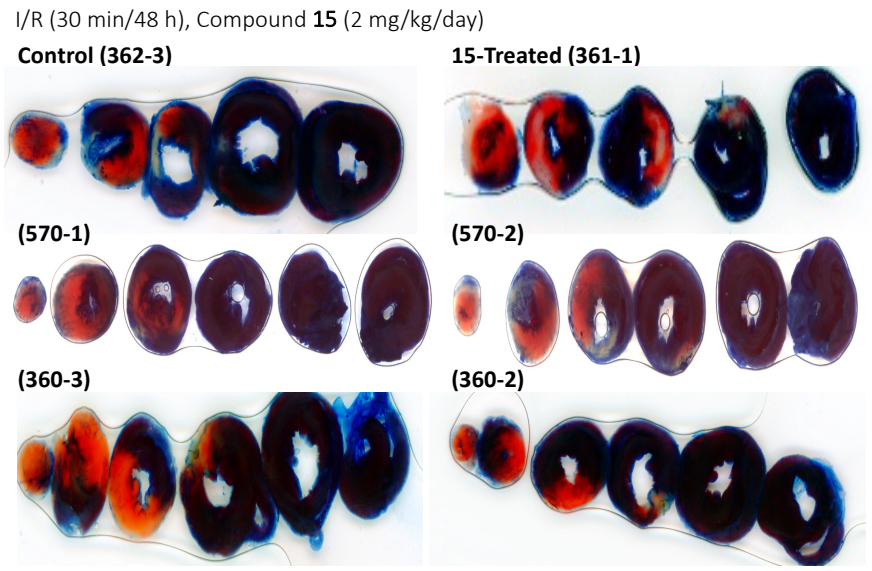


Figure S10. Mouse ischemia reperfusion results and procedures (see Legend below).

A



			SEM=SD/N^0.5					
			Incubate MP at 37C for 4 h pre-implantation. Inplant MP pre I/R					
	48 h post I/R					48 h post I/R		
1/6/23	PBS				Compound 15 ---2 day MP (use 3 day MP, 1 µL/h)			
	Mouse#	AAR/TTA %	IF/AAR %			Mouse#	AAR/TTA %	IF/AAR %
F	356-1	20.646	27.063		F	570-2	29.566	53.586
F	356-3	30.124	29.894		M	576-2	38.196	41.536
F	570-1	32.335	23.285		F	359-2	53.313	22.446
F	357-1	37.396	24.930		F	359-3	21.891	19.348
F	357-3	32.385	18.325		F	359-4	28.831	24.087
M	574-1	30.005	21.536		F	359-5	29.758	26.337
M	574-2	38.998	18.645		M	360-2	38.983	26.796
M	576-1	27.707	24.832		M	360-4	33.427	43.332
M	360-1	40.662	26.918		M	361-1	35.413	35.967
M	360-3	41.471	35.083		M	361-3	34.909	25.439
F	362-3	32.871	32.772		F	362-1	25.165	28.870
F	362-5	26.349	33.739		F	362-4	34.590	33.508
Average:		32.5791	26.4185		Average:		33.670	31.771
Standard Dev.		6.2274	5.6093		Standard Dev.		8.015	10.130
SEM		1.7977	1.6193		SEM		2.314	2.924
Ttest		0.713	0.124					
N	12	M: 5	F: 7		N	12	M: 5	F: 7

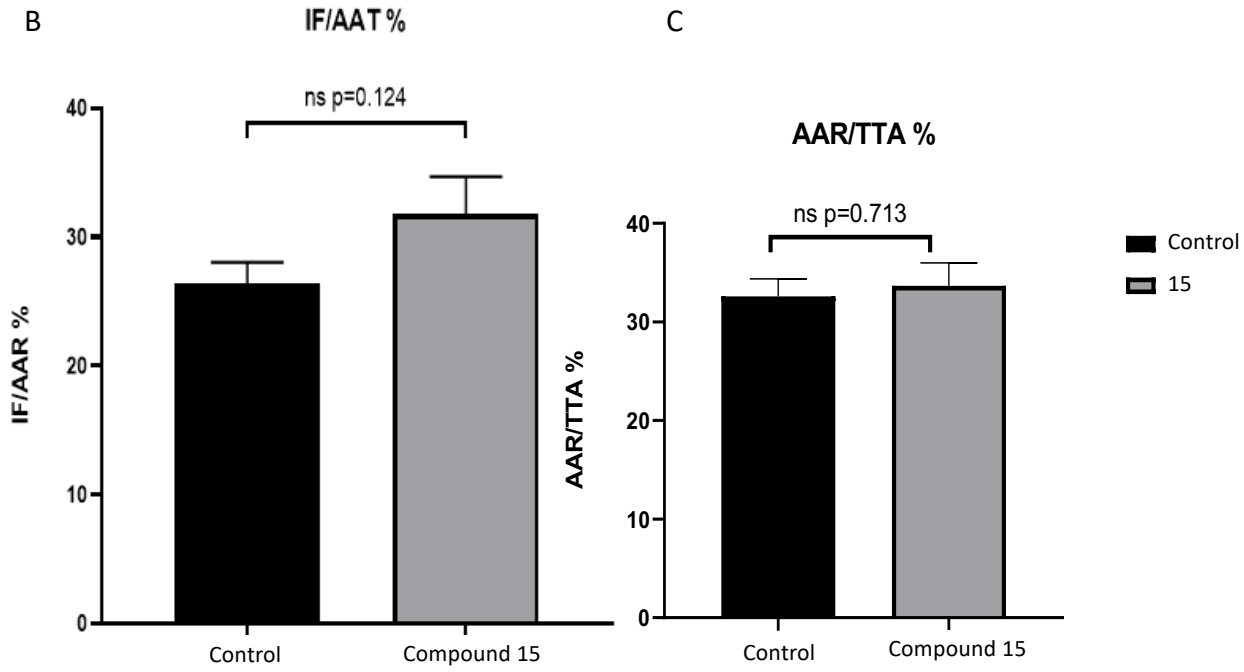


Figure S10. A. Representative images showing TTC/Evans Blue stained heart serial sections from adult WT mice subjected to 30 minutes of ischemia produced by left anterior descending artery ligation followed by 48 hours of reperfusion as described in Methods. Mice were given either the drug, Compound **15** (right images) or vehicle (left images) 30 min before ischemia. B. The infarct area (IF) as a percentage of the area at risk (AAR) was shown. Data were mean and SD. The IF/AAR was not different with P=0.124 (N=12 from drug or vehicle treated groups). C. The AAR as a percentage of total area (AAR/TTA) was also not different between the drug- and vehicle-treated mice (P=0.713, N=12 for each group). Data were mean ± SD.

Mice

C57BL/6J wild-type mice (000664; JAX) were originally obtained from the Jackson Laboratory (Farmington, CT). Mice were fed a standard rodent chow diet and were housed in microisolator cages in a pathogen-free facility at UConn Health. All experiments followed the UConn Health Institutional Animal Care and Use Committee (IACUC) guidelines with approval according to criteria outlined in the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health. Wild type male and female mice aged from 8 to 16 weeks were used.

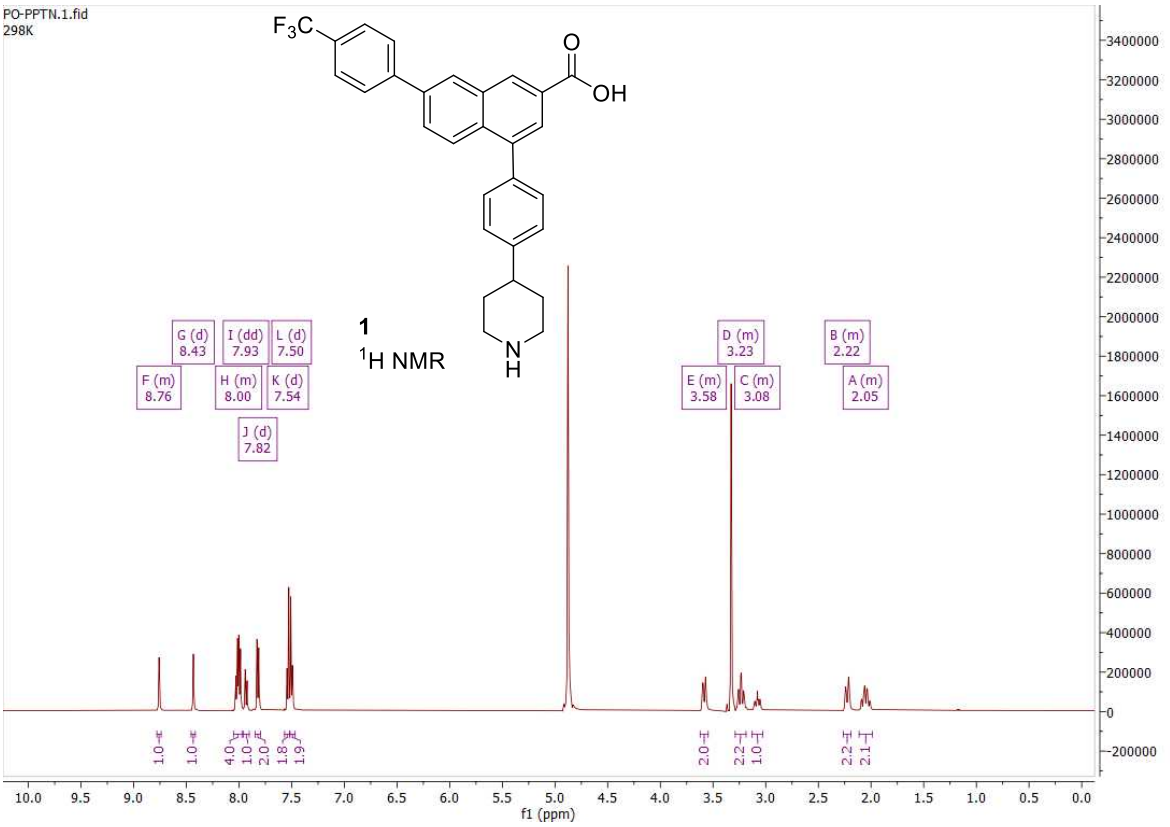
Drug delivery and cardiac ischemia-reperfusion injury

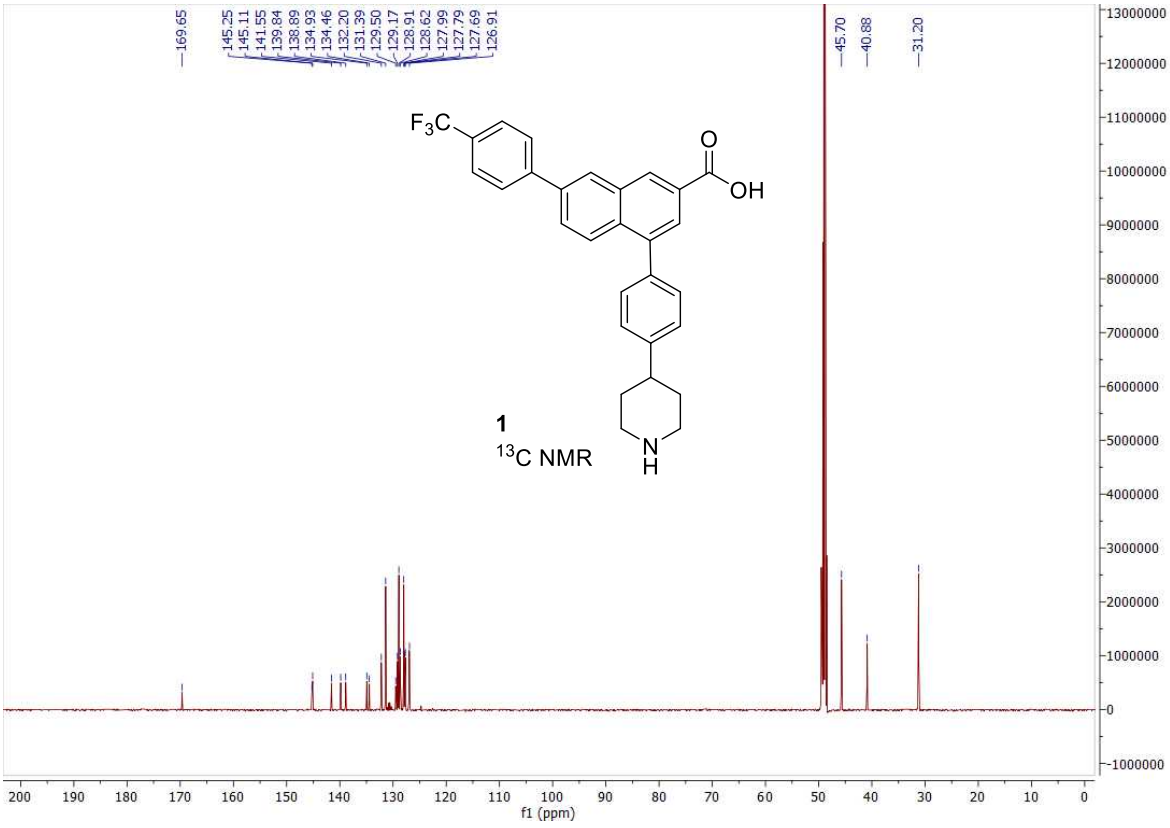
Briefly, anesthesia was induced with an intraperitoneal injection of ketamine hydrochloride (125 mg·kg^{-1}) and xylazine (12.5 mg·kg^{-1}) and then ventilated with 24G×3/4" Surflo i.v. catheter using MiniVent 845 (Harvard Apparatus, Holliston, MA). Compound **15** or vehicle was delivered via mini-

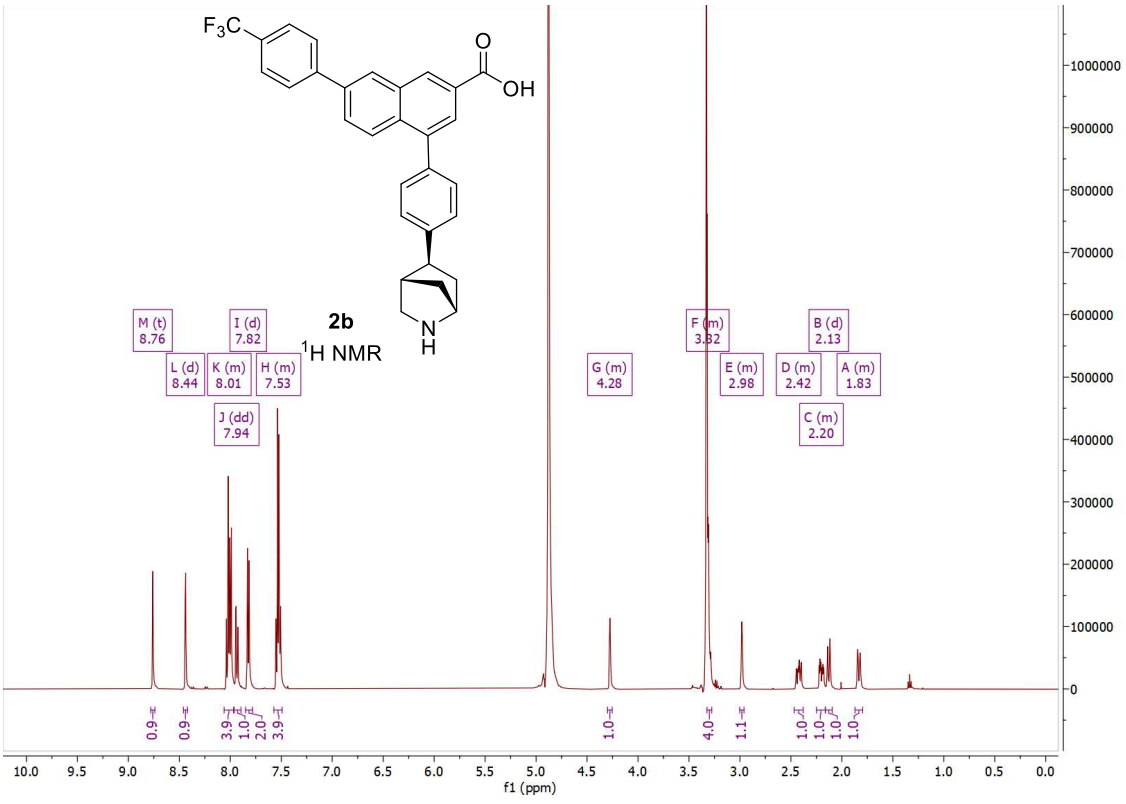
osmotic pump (model 1003D, Alzet, Cupertino, CA) implanted subcutaneously. Prior to implantation, pumps were incubated at 37°C incubator for 4 h in order to deliver at a steady 1 μL/h yielding a dosing level of 2 mg/kg/day and were then implanted 30 min before ischemia/reperfusion (I/R). **15** was first dissolved in DMSO and further diluted in 8% Kolliphor HS-15 (polyoxyethylated 12-hydroxystearic acid, Millipore Sigma, St. Louis, MO, item 42966)-PBS solution to make a working solution (DMSO-KHS-PBS) delivering at 2 mg/kg/day. Vehicle solution contained the same DMSO-KHS-PBS mixture without **15**.

Mice were subjected to 30 min of myocardial ischemia and 48 h of reperfusion.[7] In brief, surgeries were performed under a dissection microscope (Nikon). Ischemia was achieved by ligating the left anterior descending coronary artery (LAD) using a 7-0 Nylon suture (Ethilon) with a PE-10 tubing placed over the LAD as previously described.[7] Reperfusion was initiated by releasing the ligature and removing the PE-10 tubing. The chest wall was closed, animal extubated and body temperature maintained by a warm light. The loosened suture was left in place and then retied 48 h later to evaluate the ischemic area. Evans blue and TTC double staining were used to determine the area at risk and the infarct size normalized to area at risk. Viable myocardium stained red, and infarcted tissue appeared white. Images were acquired by Epson scanner V600. The infarct area or IF (white), the area at risk or AAR (red and white), and the total left ventricle area or TTA from each section were measured using ImageJ (NIH). Representative images of control (vehicle) and compound **15**-treated animals were shown in Figure S10A. Ratios of IF/AAR (Fig. S10B) and of AAR/TTA (Fig. S10C) were calculated and expressed as percentages.

^{1}H and ^{13}C NMR spectra of $P2Y_{14}R$ ligands



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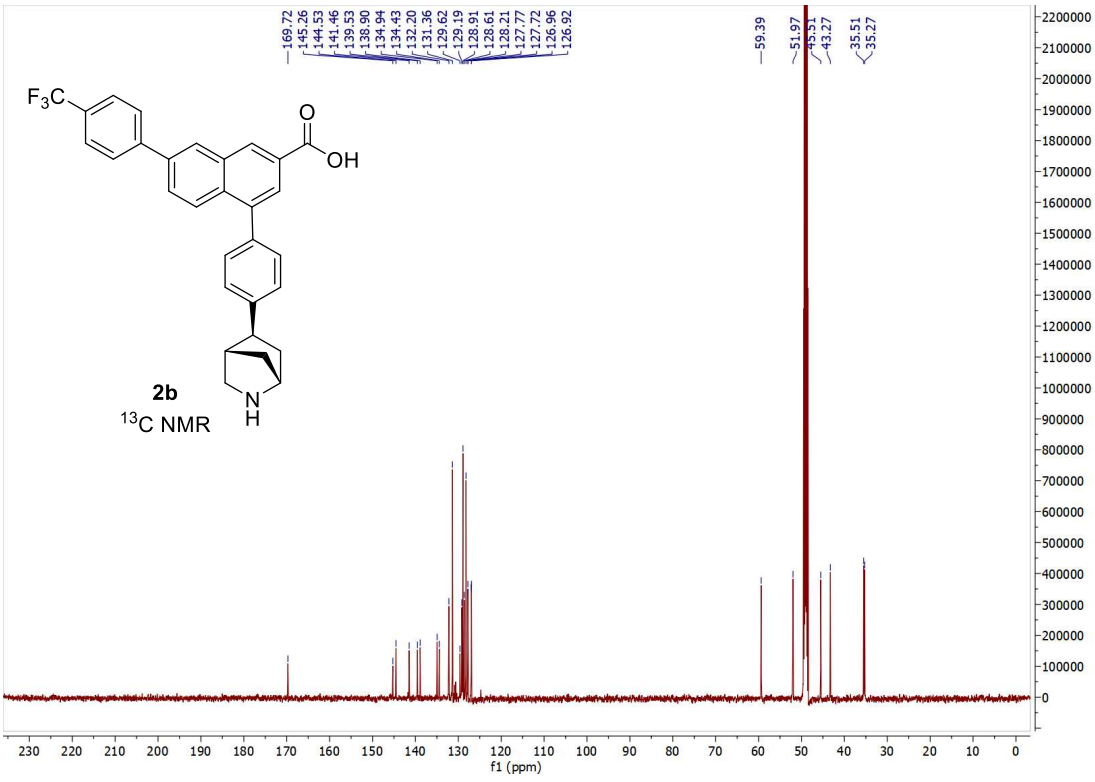
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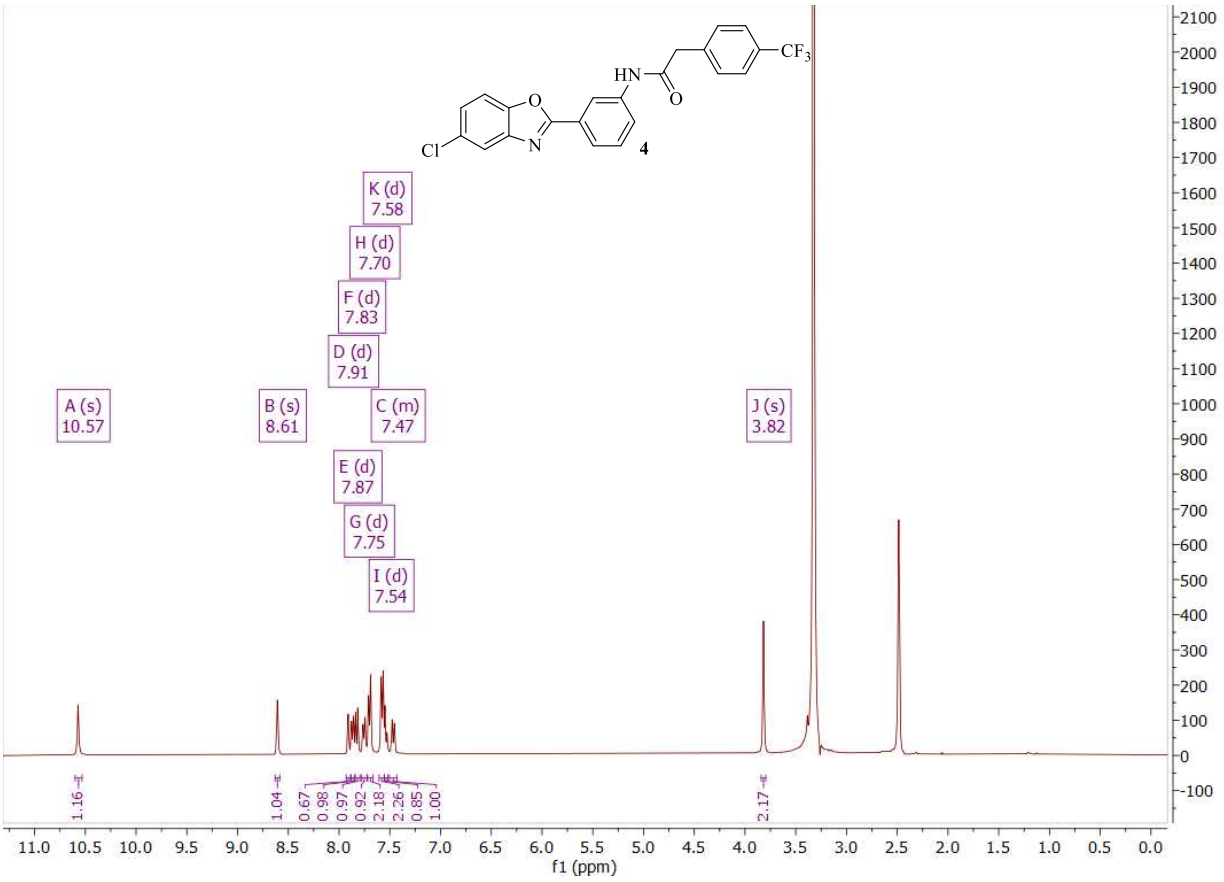
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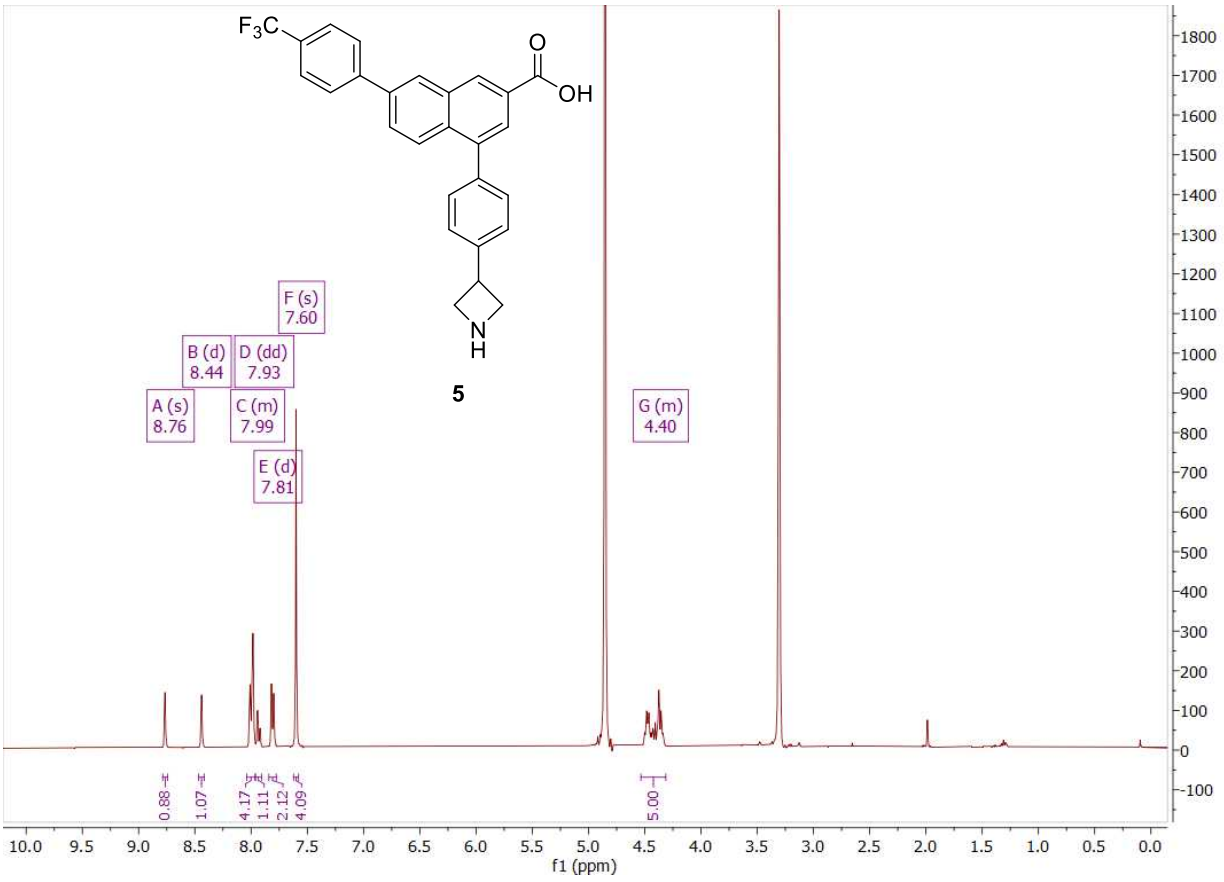
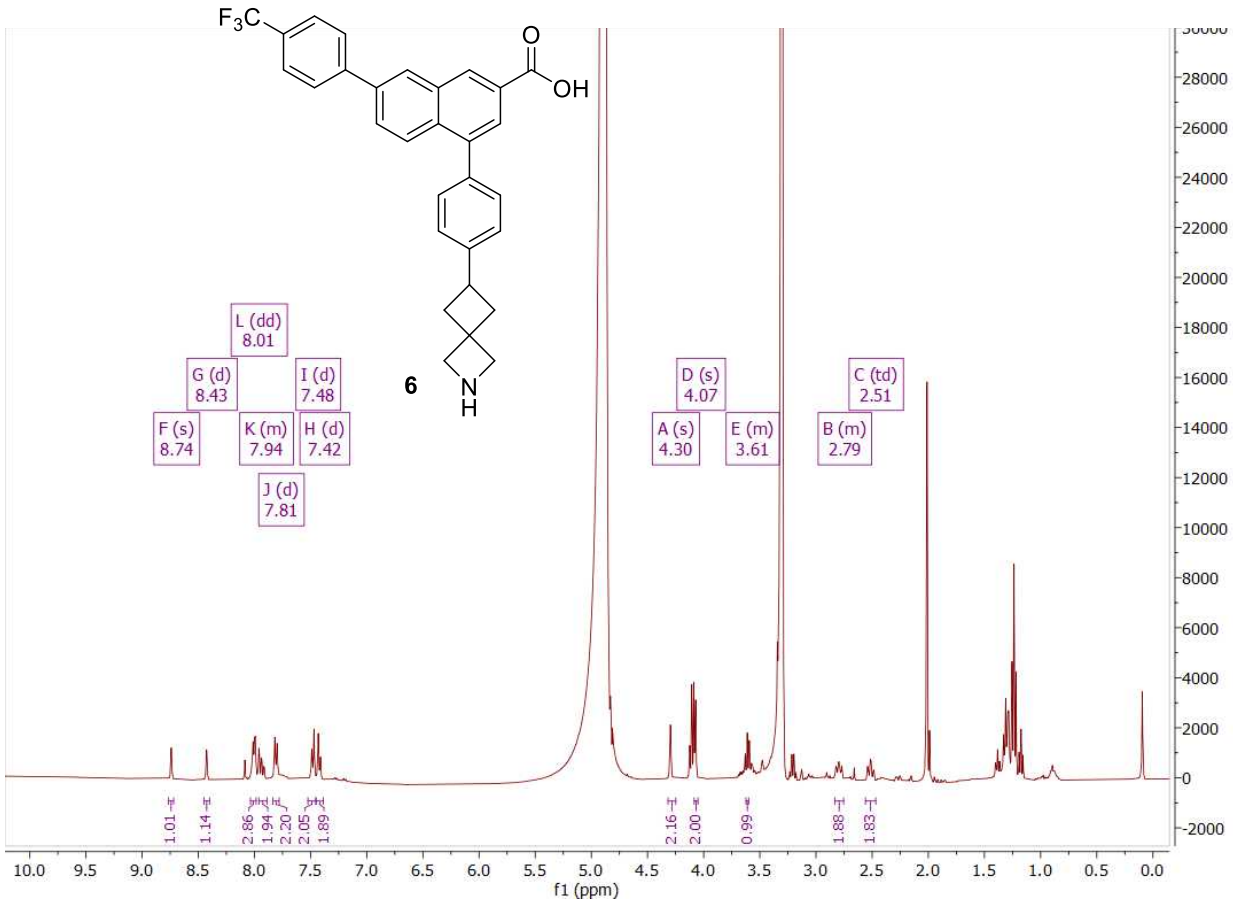
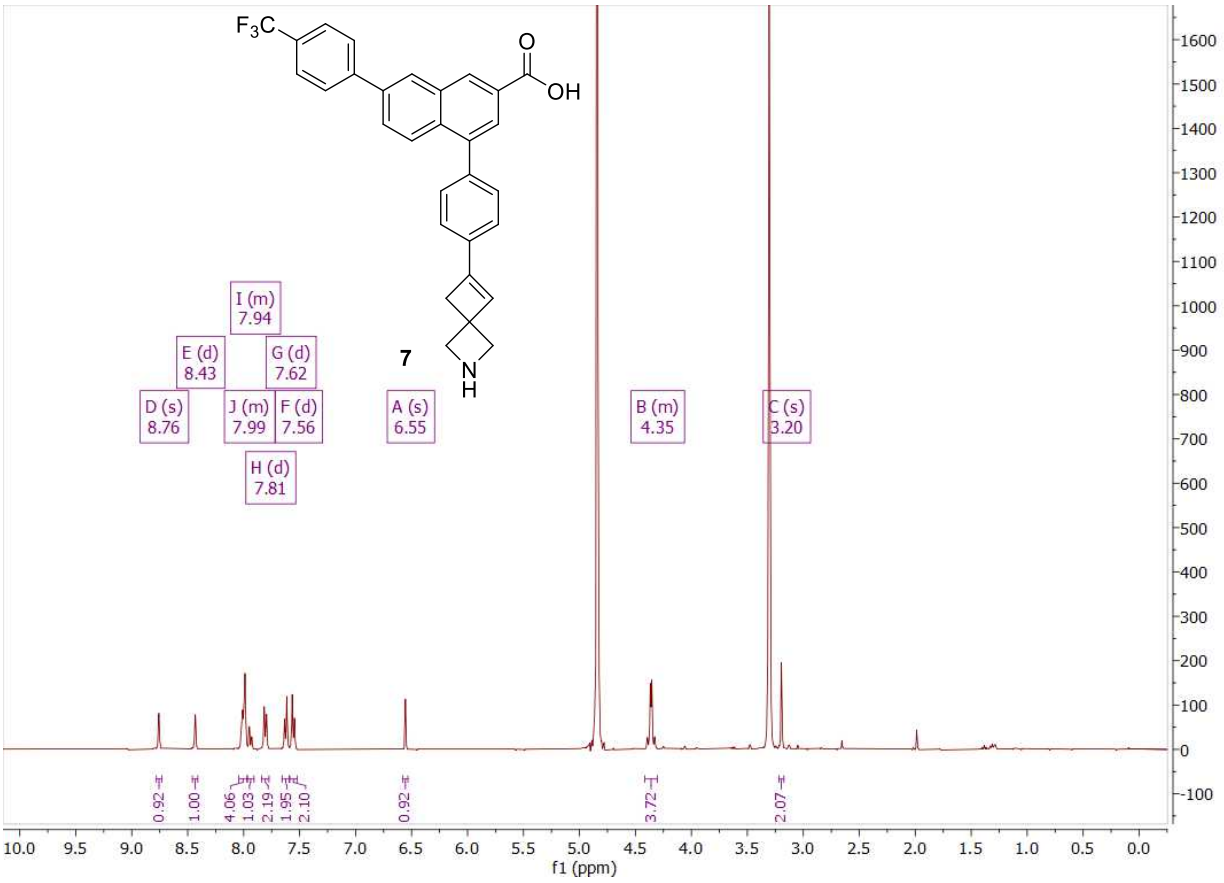
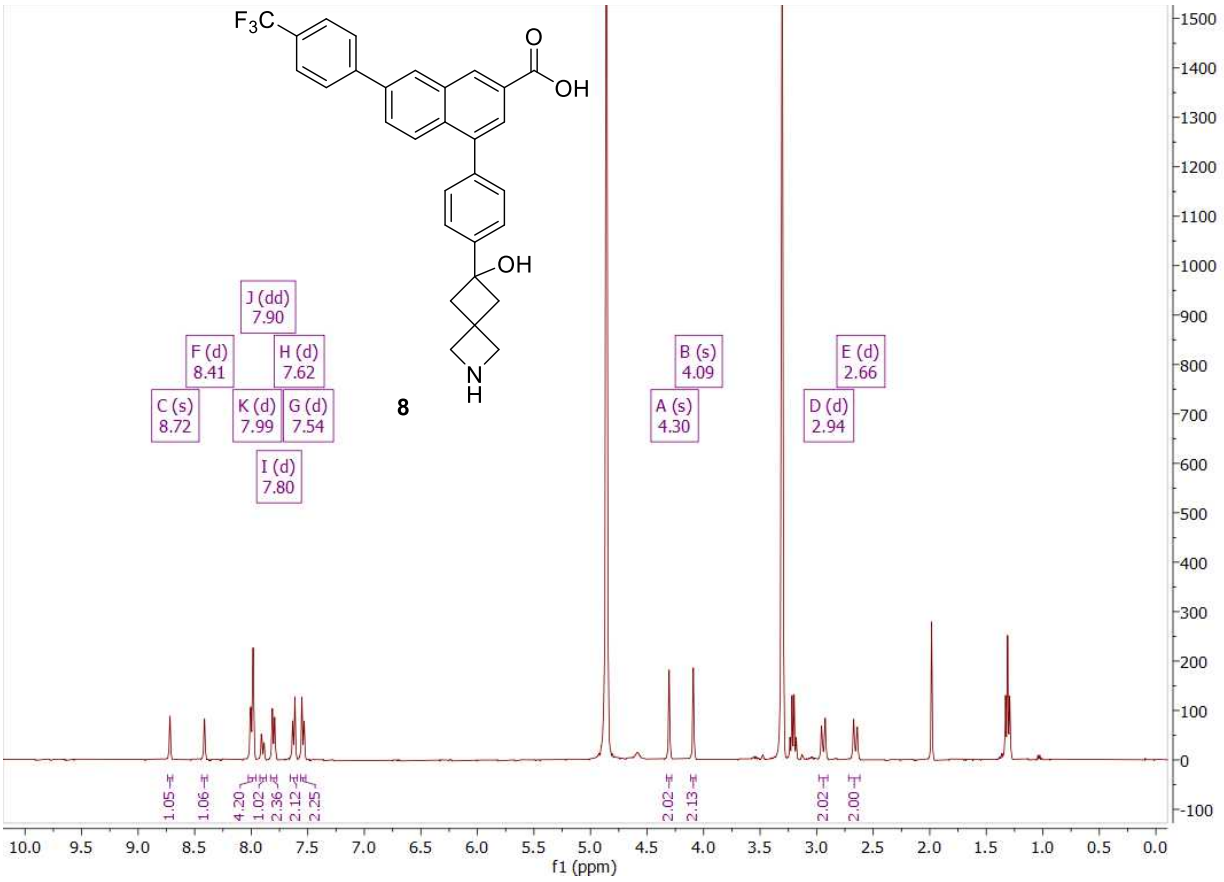
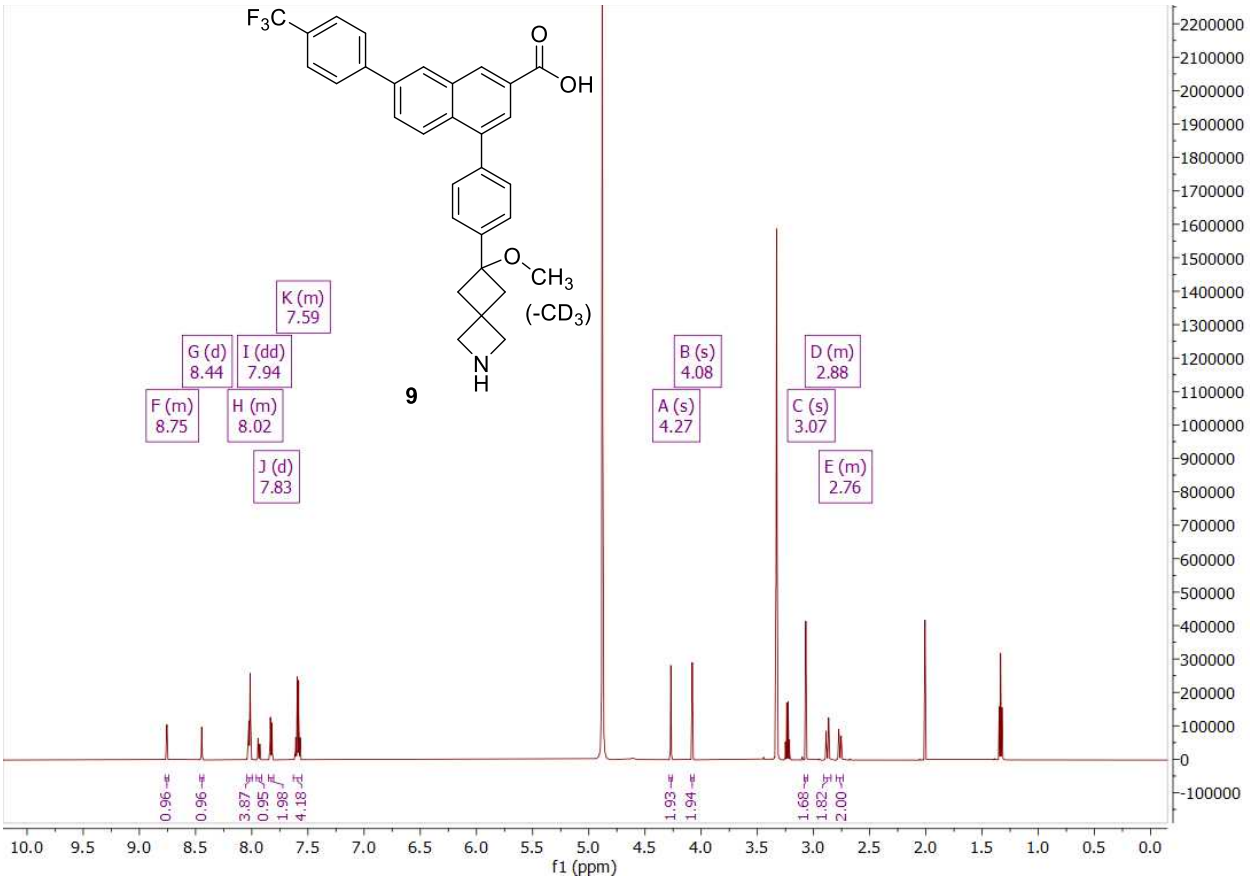
J (s) 3.82
E (d) 7.87
G (d) 7.75
I (d) 7.54
1.16
1.04
0.67
0.98
0.97
0.92
2.18
2.26
0.85
1.00
2.17
f1 (ppm)

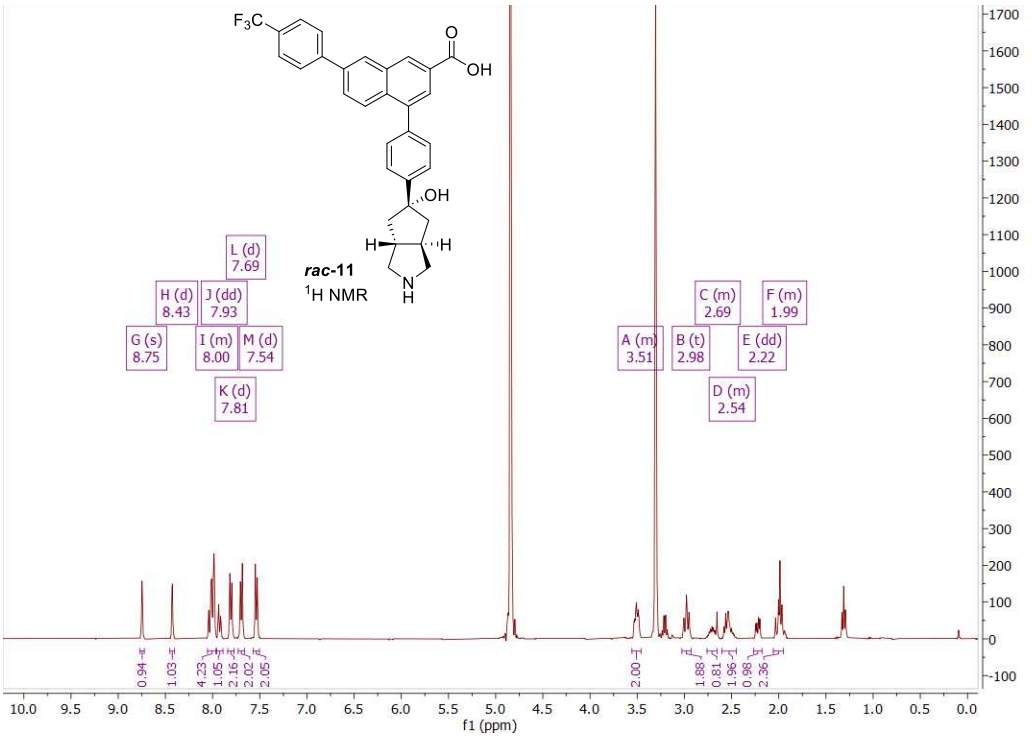

F3C
O
OH
N
H
5
A (s) 8.76
B (d) 8.44
C (m) 7.99
D (dd) 7.93
E (d) 7.81
F (s) 7.60
G (m) 4.40
0.88
1.07
4.17
1.11
2.12
4.09
5.00
f1 (ppm)

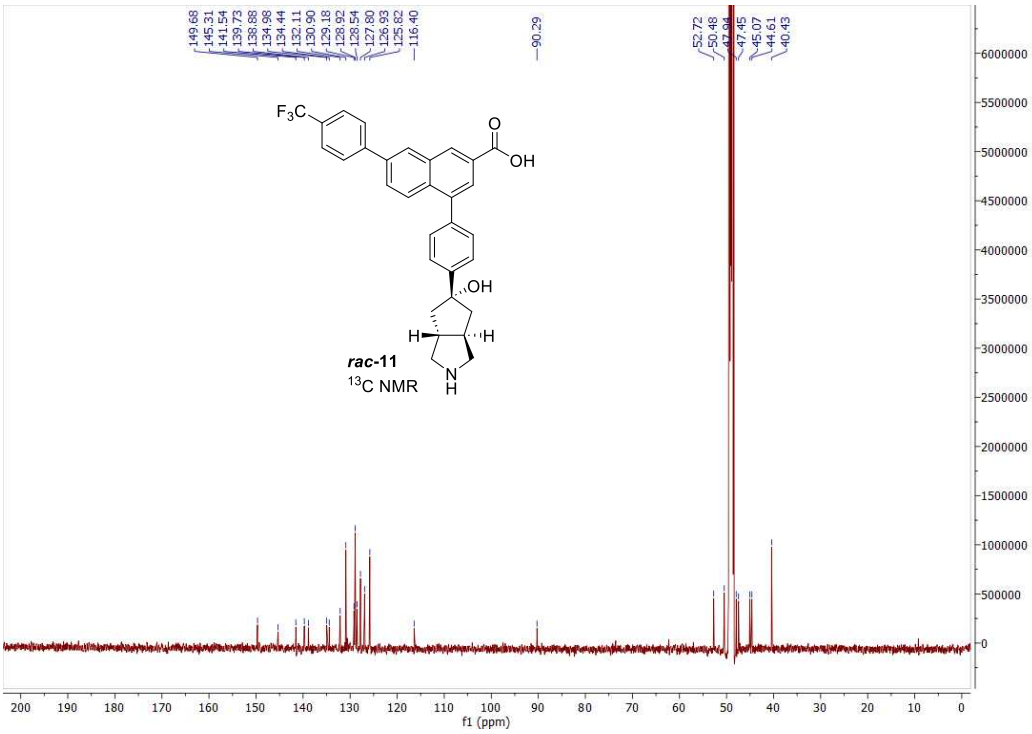

F3C
O
OH
N
H
6
L (dd)
8.01
G (d)
8.43
I (d)
7.48
F (s)
8.74
K (m)
7.94
H (d)
7.42
J (d)
7.81
D (s)
4.07
C (td)
2.51
A (s)
4.30
E (m)
3.61
B (m)
2.79
1.01
1.14
2.86
1.94
2.20
2.05
1.89
2.16
2.00
0.99
1.88
1.83
f1 (ppm)

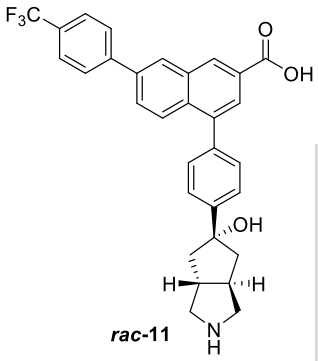

F3C
O
OH
N
H
7
I (m) 7.94
E (d) 8.43
G (d) 7.62
D (s) 8.76
J (m) 7.99
F (d) 7.56
H (d) 7.81
A (s) 6.55
B (m) 4.35
C (s) 3.20
0.92
1.00
4.06
1.03
2.19
1.95
2.10
0.92
3.72
2.07
f1 (ppm)


F3C
O
OH
OH
N
H
8
J (dd) 7.90
F (d) 8.41
H (d) 7.62
C (s) 8.72
K (d) 7.99
G (d) 7.54
I (d) 7.80
B (s) 4.09
A (s) 4.30
E (d) 2.66
D (d) 2.94
1.05
1.06
4.20
1.02
2.36
2.12
2.25
2.02
2.13
2.02
2.00
f1 (ppm)


F3C
O
OH
O
CH3
(-CD3)
N
H
9
K (m) 7.59
G (d) 8.44
I (dd) 7.94
F (m) 8.75
H (m) 8.02
J (d) 7.83
B (s) 4.08
A (s) 4.27
D (m) 2.88
C (s) 3.07
E (m) 2.76
0.96
0.96
3.87
0.95
1.98
4.18
1.93
1.94
1.68
1.82
2.00
f1 (ppm)


F3C
O
OH
OH
H
H
N
H
rac-11
1H NMR
L (d) 7.69
H (d) 8.43
J (dd) 7.93
G (s) 8.75
I (m) 8.00
M (d) 7.54
K (d) 7.81
C (m) 2.69
F (m) 1.99
A (m) 3.51
B (t) 2.98
E (dd) 2.22
D (m) 2.54
0.94
1.03
4.23
1.05
2.16
2.02
2.05
2.00
1.88
0.81
1.96
0.98
2.36
f1 (ppm)

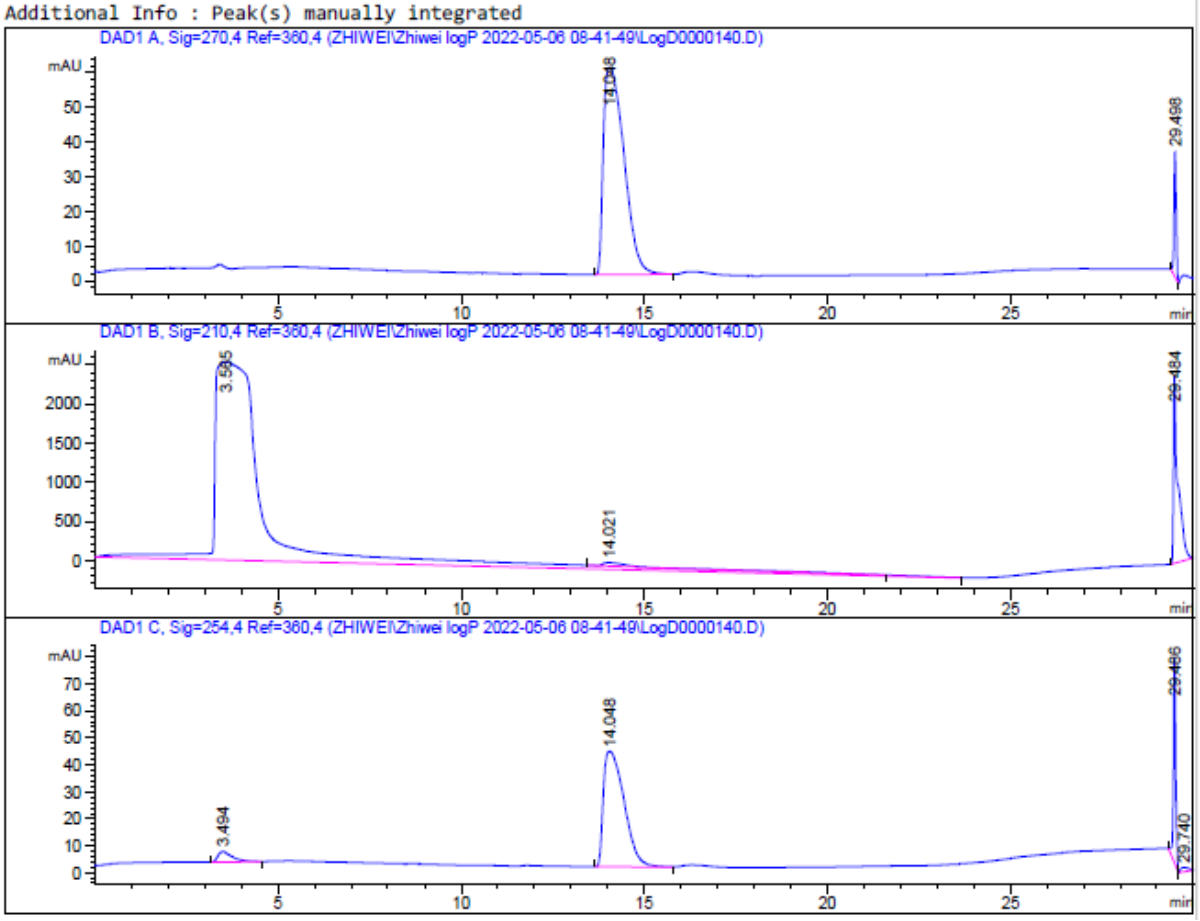

149.68
145.31
141.54
139.73
138.88
134.98
134.44
132.11
130.90
129.18
128.92
128.54
127.80
126.83
125.82
116.40
90.29
52.72
50.48
47.94
47.45
45.07
44.61
40.43
F3C
O
OH
OH
H
H
N
H
rac-11
13C NMR
f1 (ppm)



***rac*-11**

```
Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\LogD0000140.D
Sample Name: 4822

    ======================================================================
    Acq. Operator   : SYSTEM                          Seq. Line :  40
    Acq. Instrument : hplc                            Location :  37
    Injection Date  : 5/7/2022 5:02:15 AM                 Inj :  1
                                                    Inj Volume : 5.000 µl
    Different Inj Volume from Sample Entry!  Actual Inj Volume : 2.000 µl
    Method          : C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\ZW_A10-100_B_20MIN.
                      M (Sequence Method)
    Last changed    : 5/6/2022 8:41:49 AM by SYSTEM
    Additional Info : Peak(s) manually integrated
```



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=270,4 Ref=360,4

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.048	BB	0.6436	2344.19214	59.76582	94.0992
2	29.498	BB	0.0612	146.99936	36.33860	5.9008
Totals :				2491.19150	96.10442	

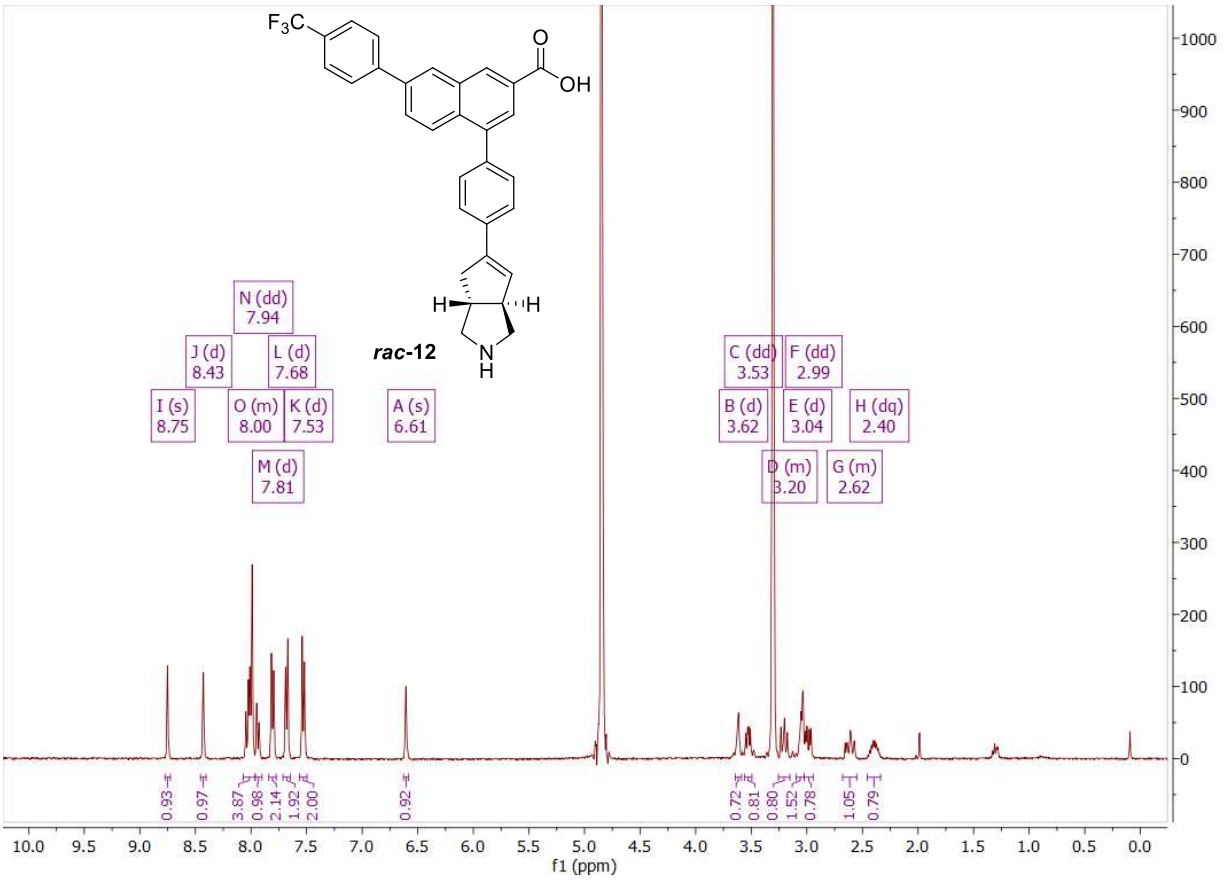
Signal 2: DAD1 B, Sig=210,4 Ref=360,4

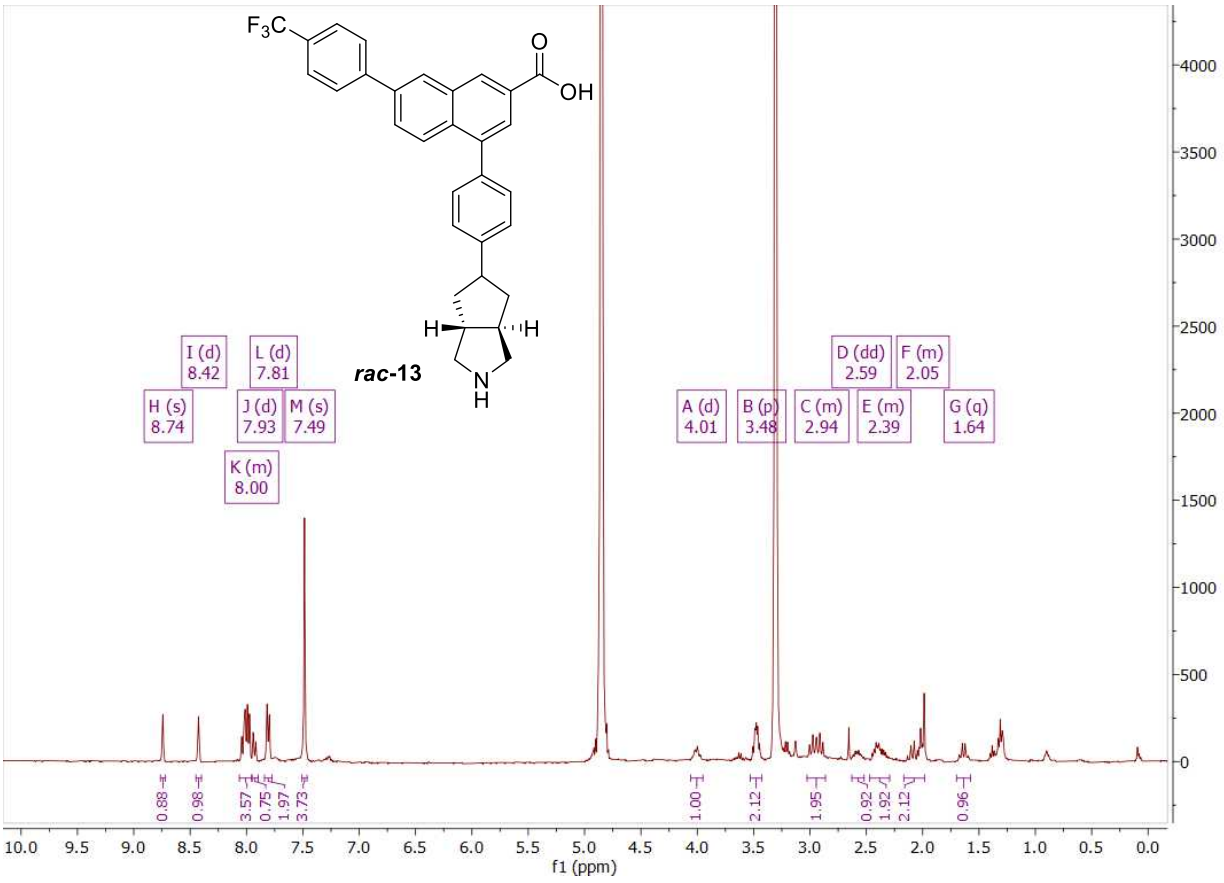
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.565	BV R	1.1132	2.39374e5	2540.63550	90.4983
2	14.021	VB E	1.2352	4197.96729	46.32541	1.5871
3	29.484	BBA	0.1196	2.09346e4	2403.77271	7.9146
Totals :				2.64507e5	4990.73361	

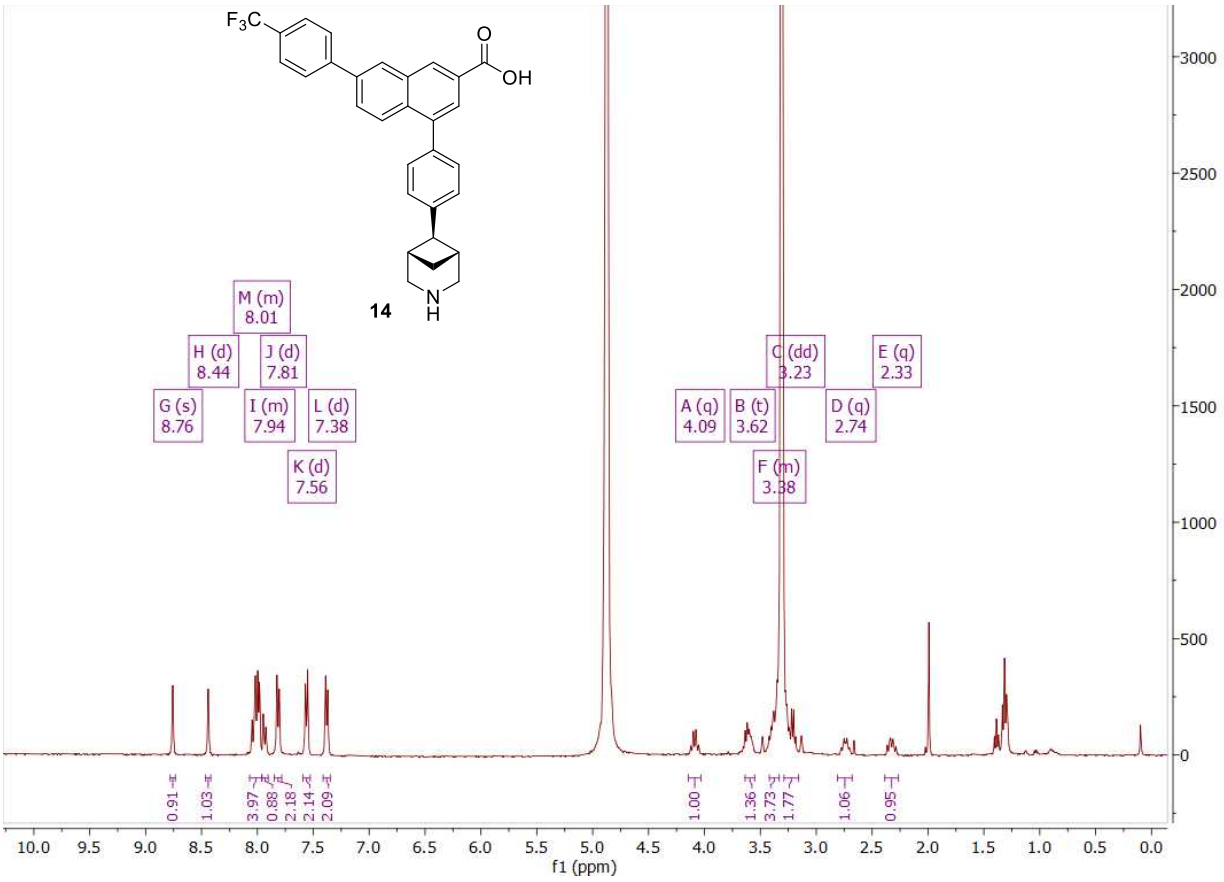
Signal 3: DAD1 C, Sig=254,4 Ref=360,4

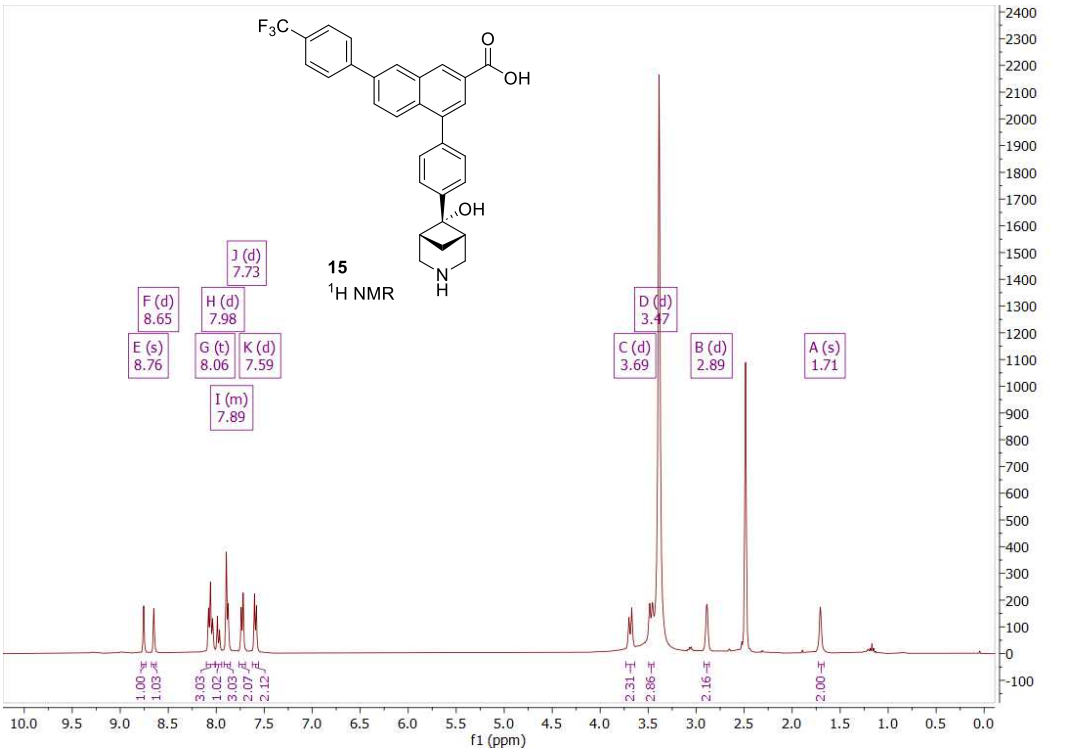
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.494	BB	0.3909	103.13339	3.77282	4.8186
2	14.048	BB	0.6434	1680.17261	42.85965	78.5016
3	29.486	BB	0.0647	333.22409	76.71456	15.5690
4	29.740	BBA	0.2178	23.77453	1.63372	1.1108
Totals :				2140.30462	124.98074	

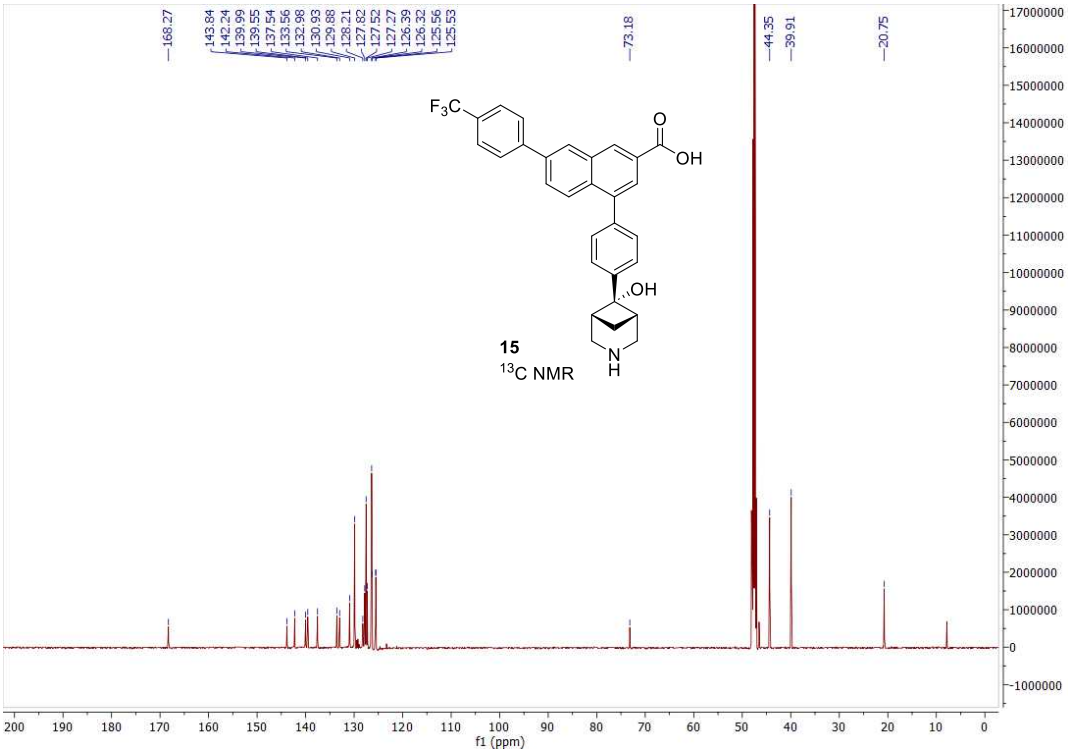
*** End of Report ***

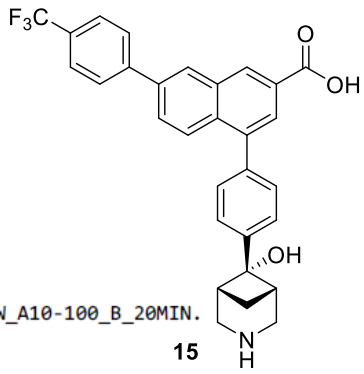

F3C
O
OH
H
H
N
H
rac-12
N (dd) 7.94
J (d) 8.43
L (d) 7.68
I (s) 8.75
O (m) 8.00
K (d) 7.53
A (s) 6.61
M (d) 7.81
C (dd) 3.53
F (dd) 2.99
B (d) 3.62
E (d) 3.04
H (dq) 2.40
D (m) 3.20
G (m) 2.62
0.93
0.97
3.87
0.98
2.14
1.92
2.00
0.92
0.72
0.81
0.80
1.52
0.78
1.05
0.79
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
1000 900 800 700 600 500 400 300 200 100 0


F3C
O
OH
H
H
N
H
rac-13
H (s) 8.74
I (d) 8.42
J (d) 7.93
K (m) 8.00
L (d) 7.81
M (s) 7.49
A (d) 4.01
B (p) 3.48
C (m) 2.94
D (dd) 2.59
E (m) 2.39
F (m) 2.05
G (q) 1.64
0.88
0.98
3.57
0.75
1.97
3.73
1.00
2.12
1.95
0.92
1.92
2.12
0.96
f1 (ppm)


F3C
O
OH
N
H
14
M (m)
8.01
H (d)
8.44
J (d)
7.81
G (s)
8.76
I (m)
7.94
L (d)
7.38
K (d)
7.56
C (dd)
3.23
E (q)
2.33
A (q)
4.09
B (t)
3.62
D (q)
2.74
F (m)
3.38
0.91
1.03
3.97
0.88
2.18
2.14
2.09
1.00
1.36
3.73
1.77
1.06
0.95
f1 (ppm)


F3C
O
OH
OH
N
H
15
1H NMR
J (d) 7.73
F (d) 8.65
H (d) 7.98
E (s) 8.76
G (t) 8.06
K (d) 7.59
I (m) 7.89
D (d) 3.47
C (d) 3.69
B (d) 2.89
A (s) 1.71
1.00
1.03
3.03
1.02
3.03
2.07
2.12
2.31
2.86
2.16
2.00
f1 (ppm)


168.27
143.84
142.24
139.99
139.55
137.54
133.56
132.98
130.93
129.88
128.21
127.82
127.52
127.27
126.39
126.32
125.56
125.53
73.18
44.35
39.91
20.75
F3C
O
OH
OH
N
H
15
13C NMR
f1 (ppm)



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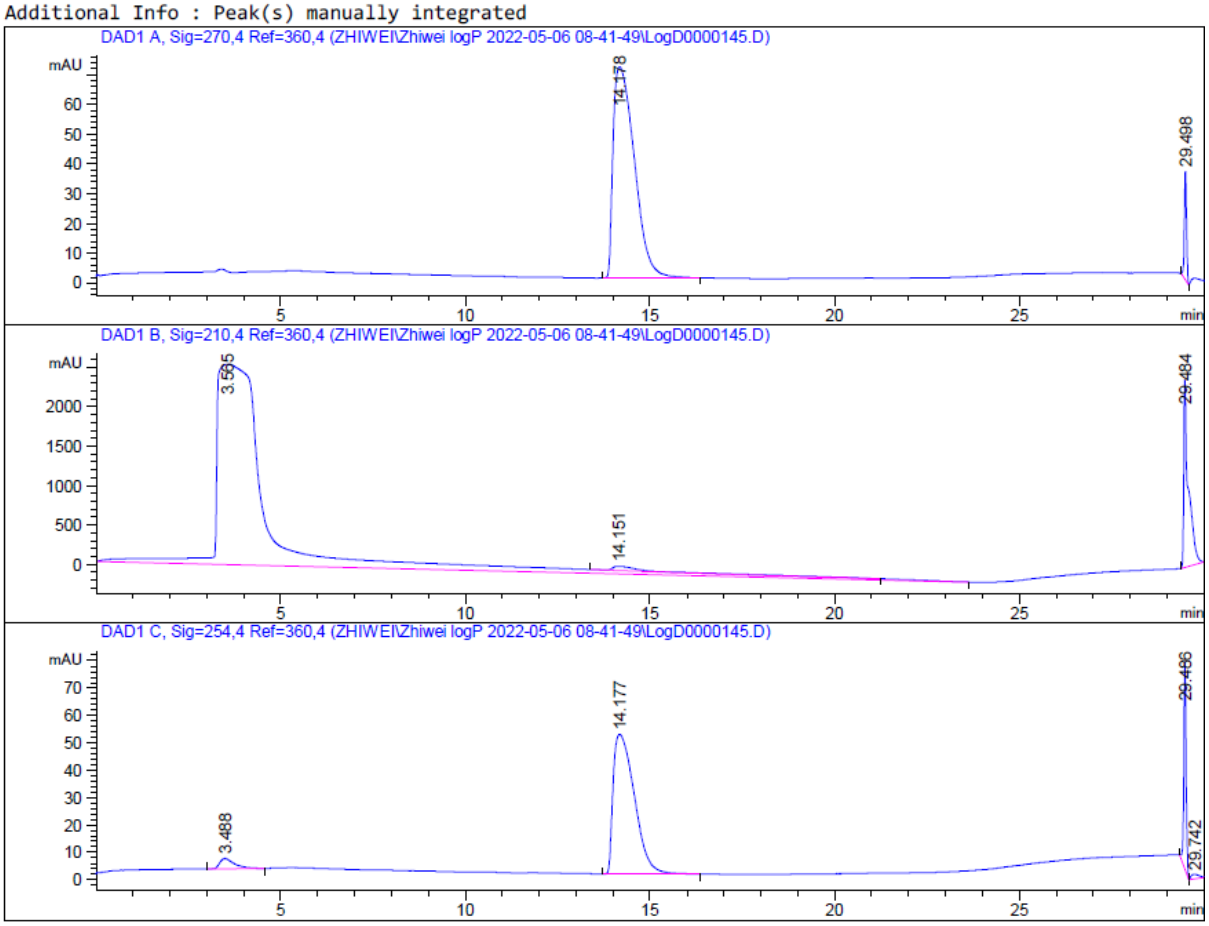
```
Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\LogD0000145.D
Sample Name: 4833

======================================================================
Acq. Operator   : SYSTEM                      Seq. Line :  45
Acq. Instrument : hplc                        Location :   42
Injection Date  : 5/7/2022 7:37:53 AM             Inj :   1
                                           Inj Volume : 5.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 2.000 µl
Method          : C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\ZW_A10-100_B_20MIN.
                  M (Sequence Method)
Last changed    : 5/6/2022 8:41:49 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```



Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\LogD0000145.D
Sample Name: 4833

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=270,4 Ref=360,4

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.178	BB	0.6516	2828.68774	70.87802	95.0269
2	29.498	BB	0.0614	148.03391	36.46857	4.9731
Totals :				2976.72165	107.34659	

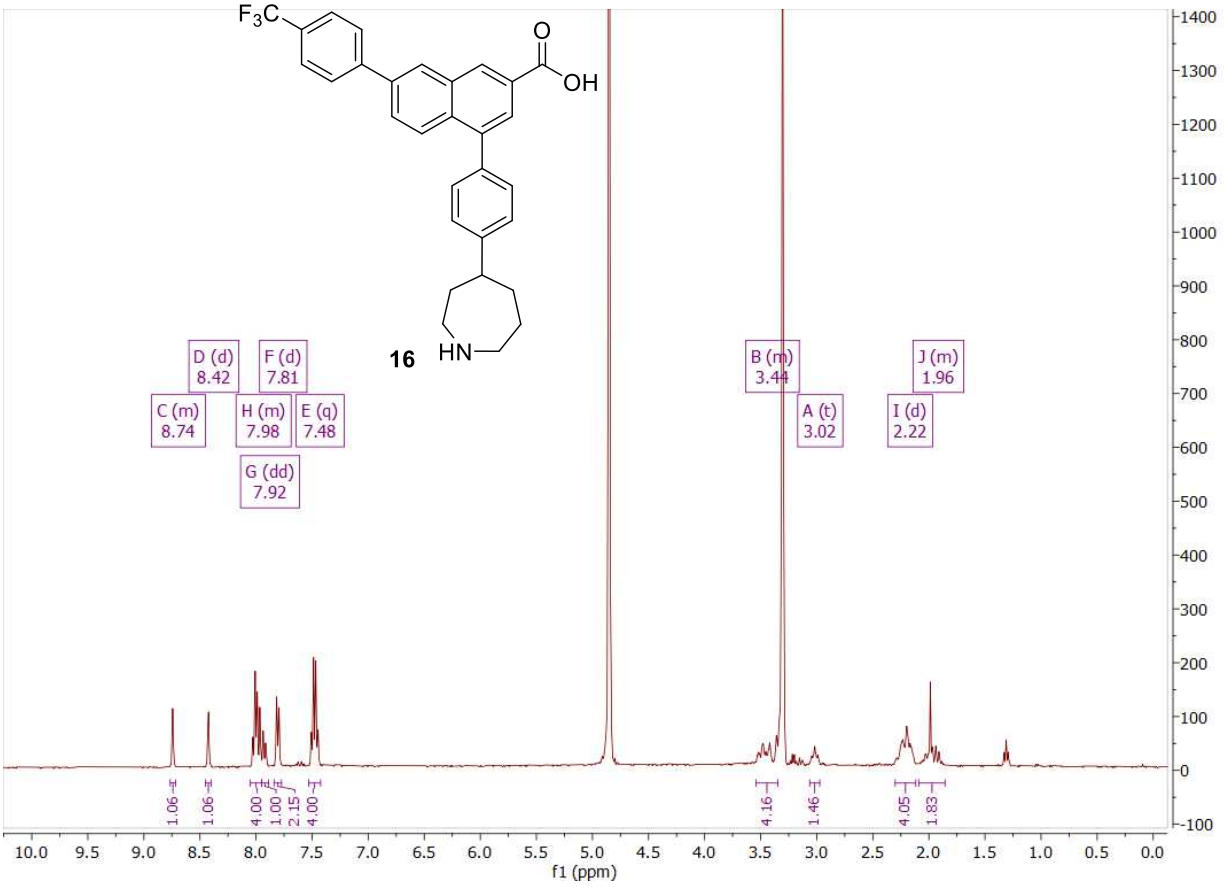
Signal 2: DAD1 B, Sig=210,4 Ref=360,4

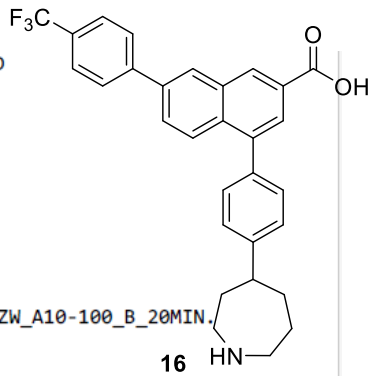
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.565	BV R	1.1306	2.42265e5	2540.45801	90.6029
2	14.151	VB E	1.1141	4250.20410	53.31234	1.5895
3	29.484	BBA	0.1198	2.08770e4	2392.57080	7.8076
Totals :				2.67392e5	4986.34115	

Signal 3: DAD1 C, Sig=254,4 Ref=360,4

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.488	BB	0.3937	100.85950	3.70393	4.0534
2	14.177	BB	0.6495	2036.60608	51.03893	81.8493
3	29.486	BB	0.0643	327.37265	75.95940	13.1568
4	29.742	BBA	0.2400	23.40212	1.60595	0.9405
Totals :				2488.24035	132.30821	

*** End of Report ***

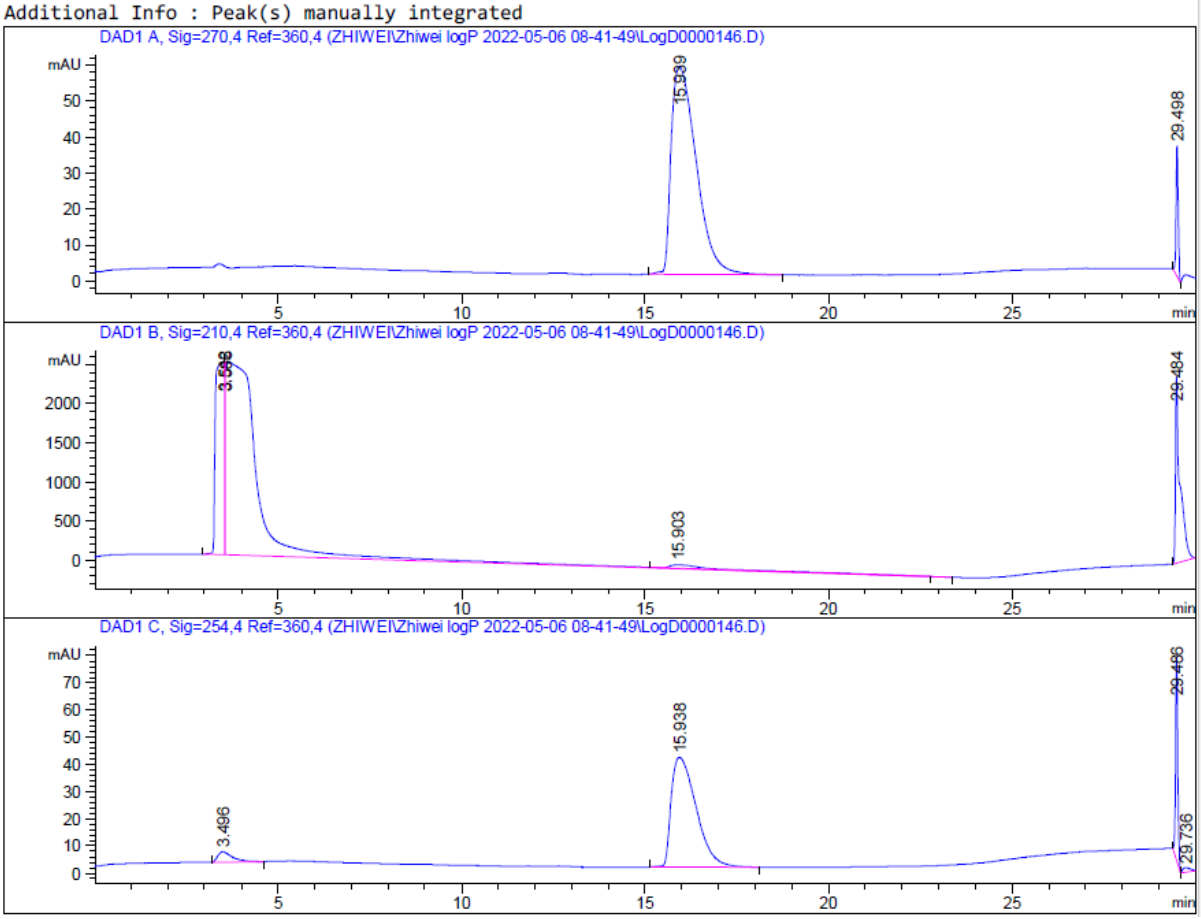

F3C
O
OH
HN
16
D (d) 8.42
F (d) 7.81
C (m) 8.74
H (m) 7.98
E (q) 7.48
G (dd) 7.92
B (m) 3.44
A (t) 3.02
J (m) 1.96
I (d) 2.22
1.06
1.06
4.00
1.00
2.15
4.00
4.16
1.46
4.05
1.83
f1 (ppm)



16

```
Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\LogD0000146.D
Sample Name: 4826

    ======================================================================
    Acq. Operator   : SYSTEM                        Seq. Line :  46
    Acq. Instrument : hplc                          Location :   43
    Injection Date  : 5/7/2022 8:08:59 AM               Inj :   1
                                                  Inj Volume : 5.000 µl
    Different Inj Volume from Sample Entry!  Actual Inj Volume : 2.000 µl
    Method          : C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\ZW_A10-100_B_20MIN.
                      M (Sequence Method)
    Last changed    : 5/6/2022 8:41:49 AM by SYSTEM
    Additional Info : Peak(s) manually integrated
```



Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-05-06 08-41-49\LogD0000146.D
Sample Name: 4826

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=270,4 Ref=360,4

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.939	BB	0.7404	2743.59302	57.73376	94.9171
2	29.498	BB	0.0611	146.92307	36.39445	5.0829
Totals :				2890.51608	94.12821	

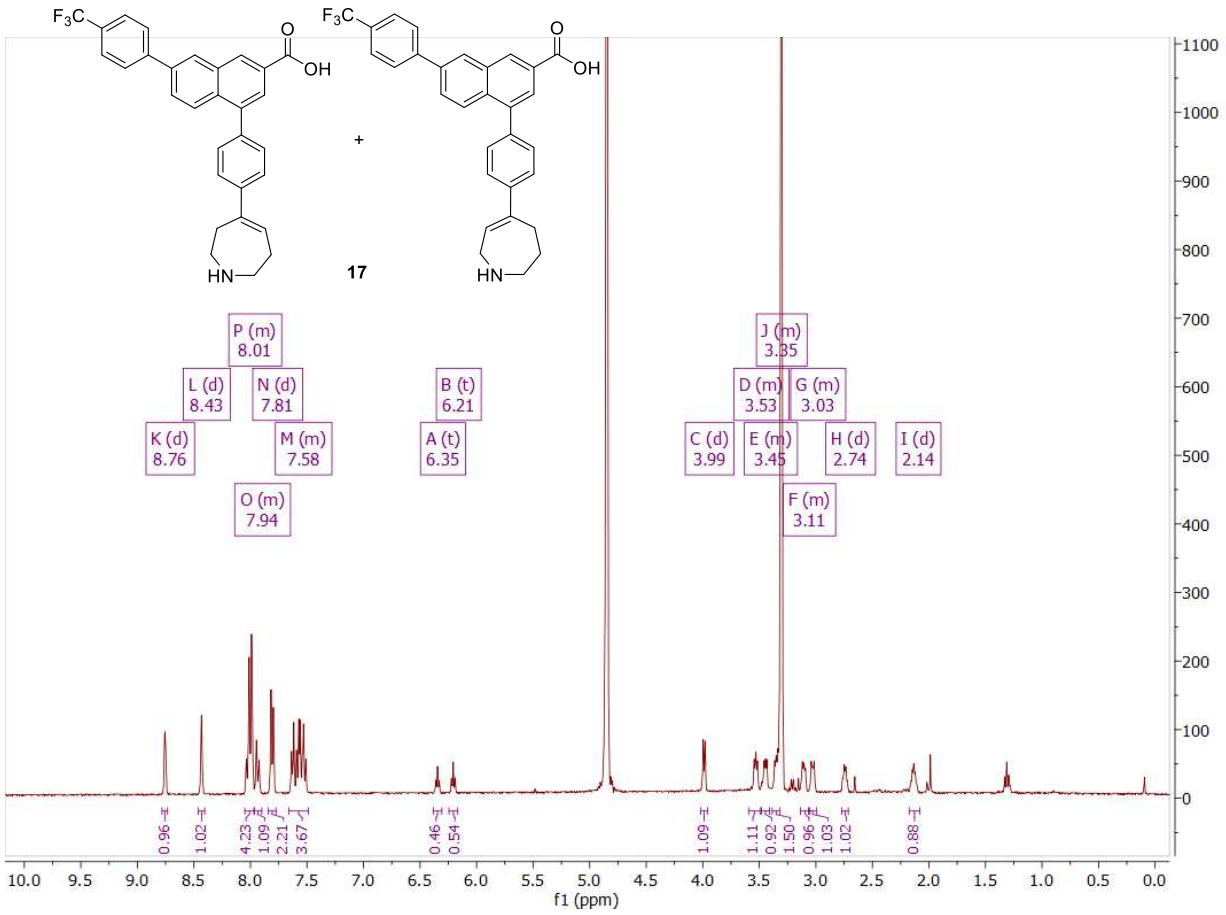
Signal 2: DAD1 B, Sig=210,4 Ref=360,4

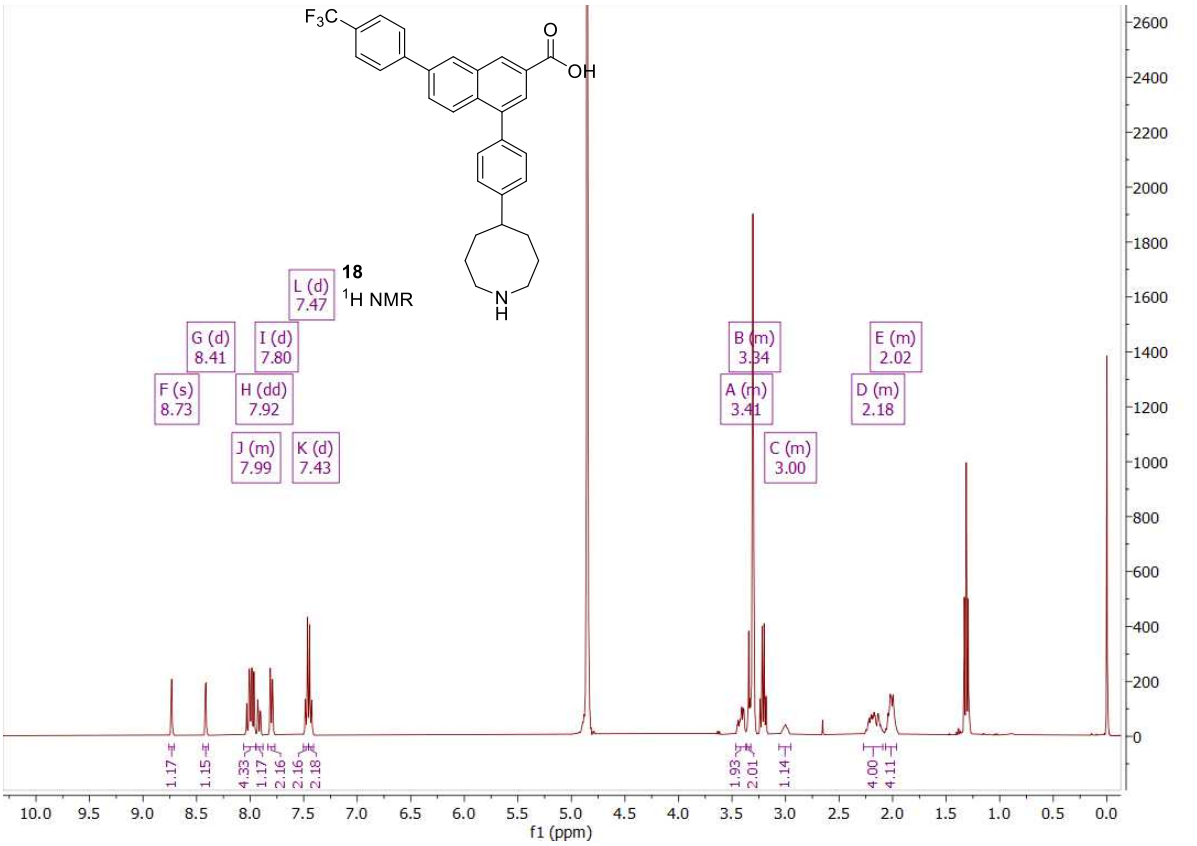
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.542	BV	0.2005	4.12259e4	2472.44702	19.3239
2	3.586	VV R	0.9928	1.47299e5	2472.89380	69.0438
3	15.903	VB E	1.2218	3955.44263	44.98698	1.8540
4	29.484	BBA	0.1178	2.08610e4	2391.48608	9.7782
Totals :				2.13341e5	7381.81388	

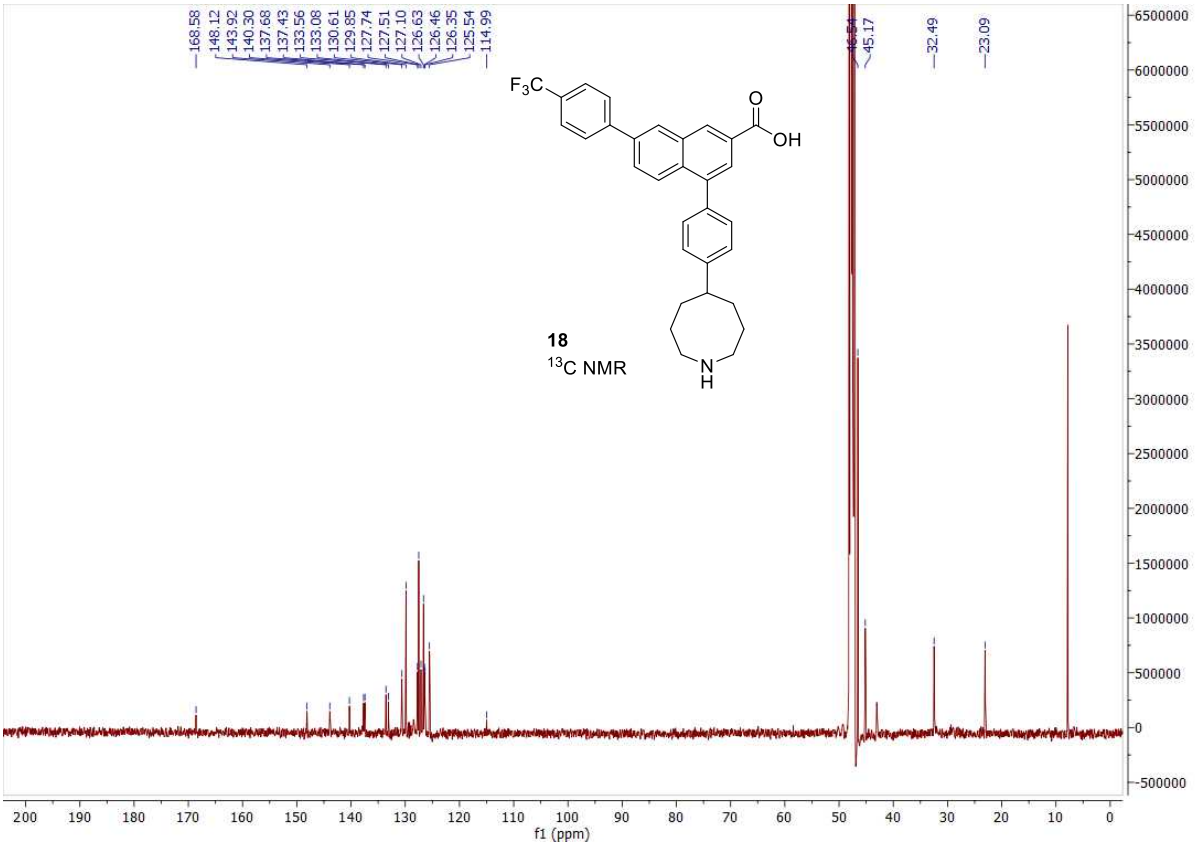
Signal 3: DAD1 C, Sig=254,4 Ref=360,4

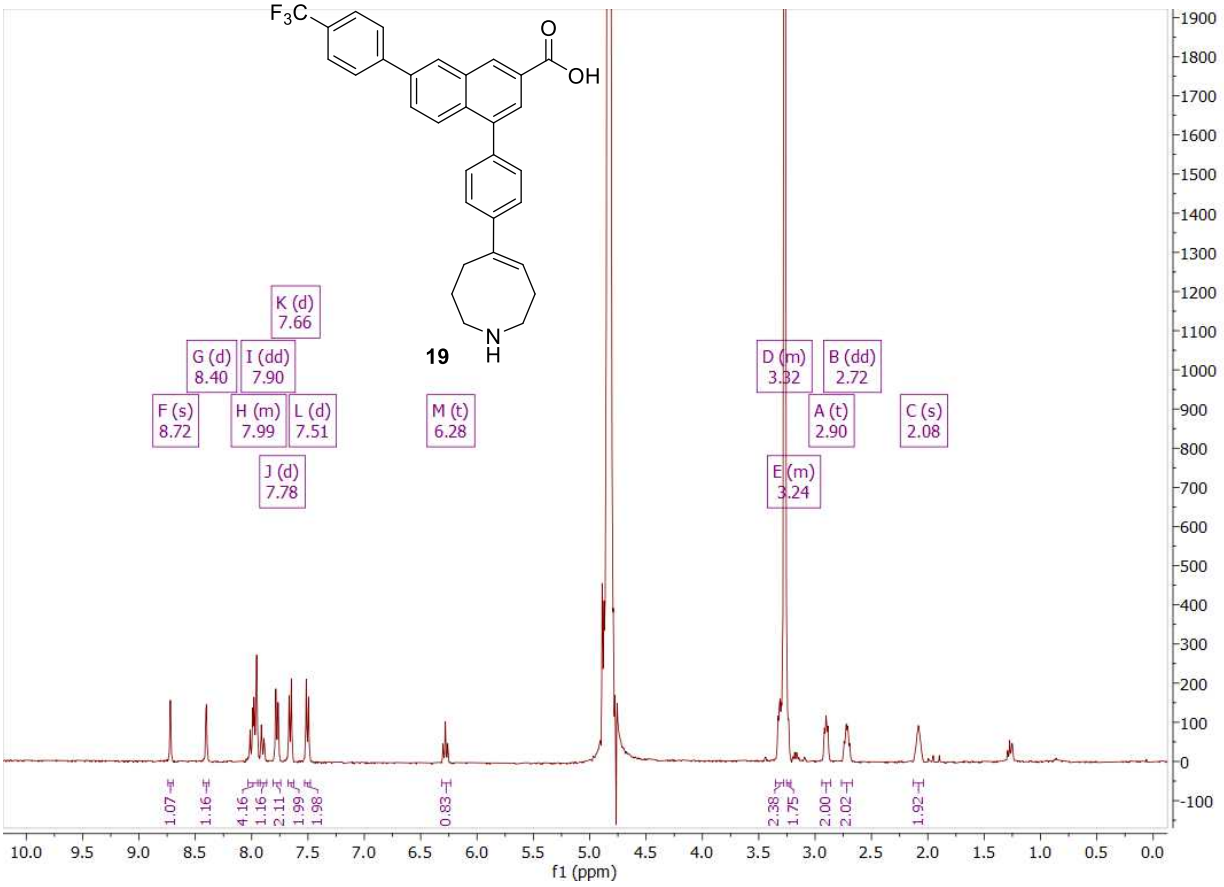
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.496	BB	0.3782	105.61524	3.80123	4.4841
2	15.938	BB	0.7370	1909.96838	40.44006	81.0910
3	29.486	BB	0.0631	316.21457	75.17724	13.4254
4	29.736	BBA	0.2144	23.54059	1.63075	0.9995
Totals :				2355.33879	121.04927	

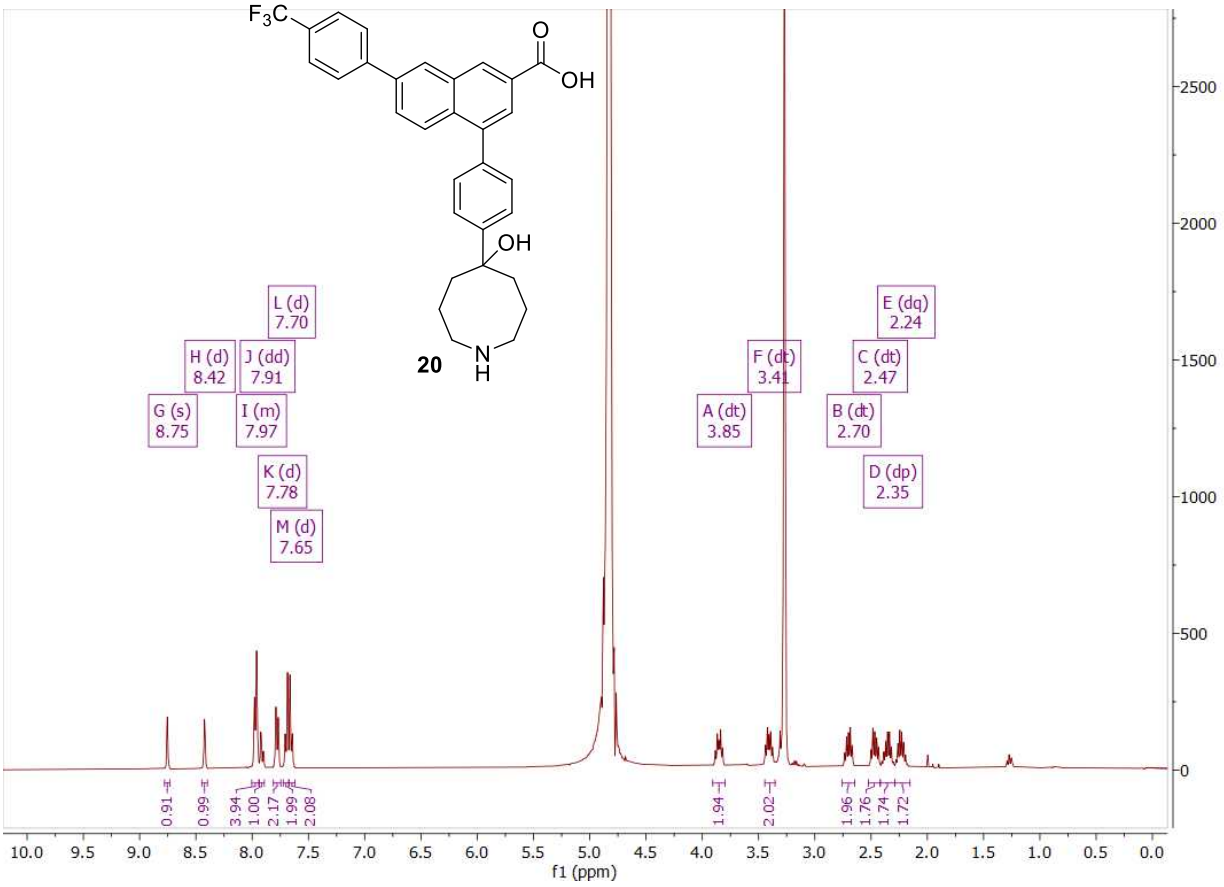
*** End of Report ***

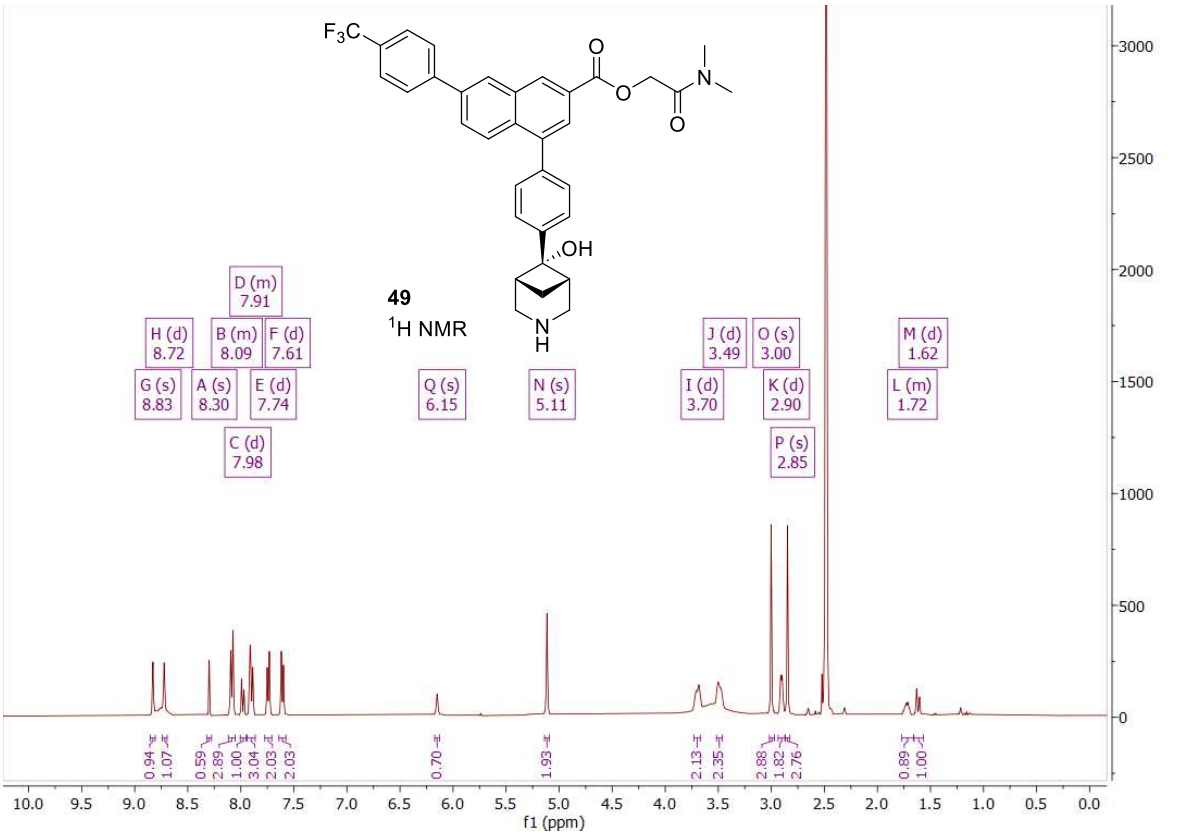

F3C
O
OH
HN
+
17
P (m) 8.01
L (d) 8.43
N (d) 7.81
K (d) 8.76
M (m) 7.58
O (m) 7.94
B (t) 6.21
A (t) 6.35
J (m) 3.35
D (m) 3.53
G (m) 3.03
C (d) 3.99
E (m) 3.45
H (d) 2.74
I (d) 2.14
F (m) 3.11
0.96 1.02 4.23 1.09 2.21 3.67 0.46 0.54 1.09 1.11 0.92 1.50 0.96 1.03 1.02 0.88
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
1100 1000 900 800 700 600 500 400 300 200 100 0

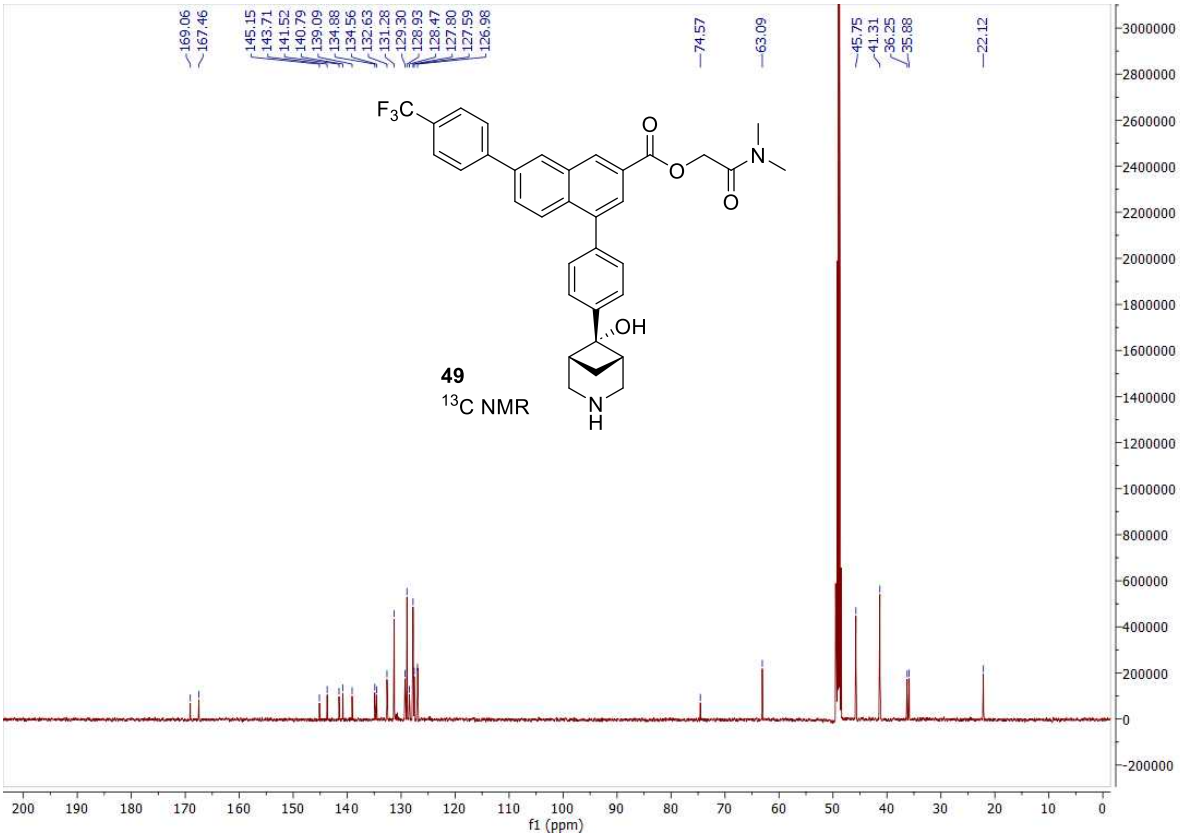

F3C
O
OH
N
H
18
1H NMR
L (d) 7.47
G (d) 8.41
I (d) 7.80
F (s) 8.73
H (dd) 7.92
J (m) 7.99
K (d) 7.43
B (m) 3.34
A (m) 3.41
C (m) 3.00
E (m) 2.02
D (m) 2.18
1.17
1.15
4.33
1.17
2.16
2.16
2.18
1.93
2.01
1.14
4.00
4.11
f1 (ppm)

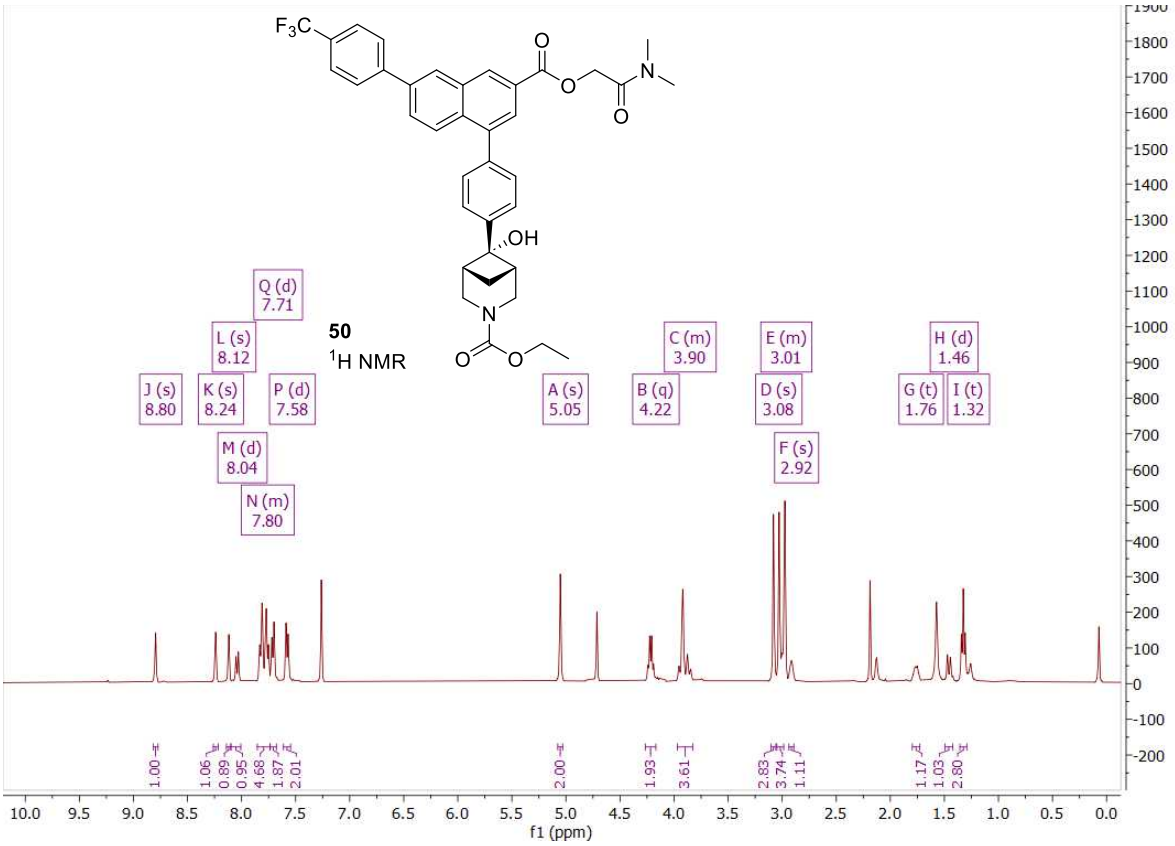

168.58
148.12
143.92
140.30
137.68
137.43
133.56
133.08
130.61
129.85
127.74
127.51
127.10
126.63
126.46
126.35
125.54
114.99
45.17
32.49
23.09
F3C
O
OH
N
H
18
13C NMR
f1 (ppm)

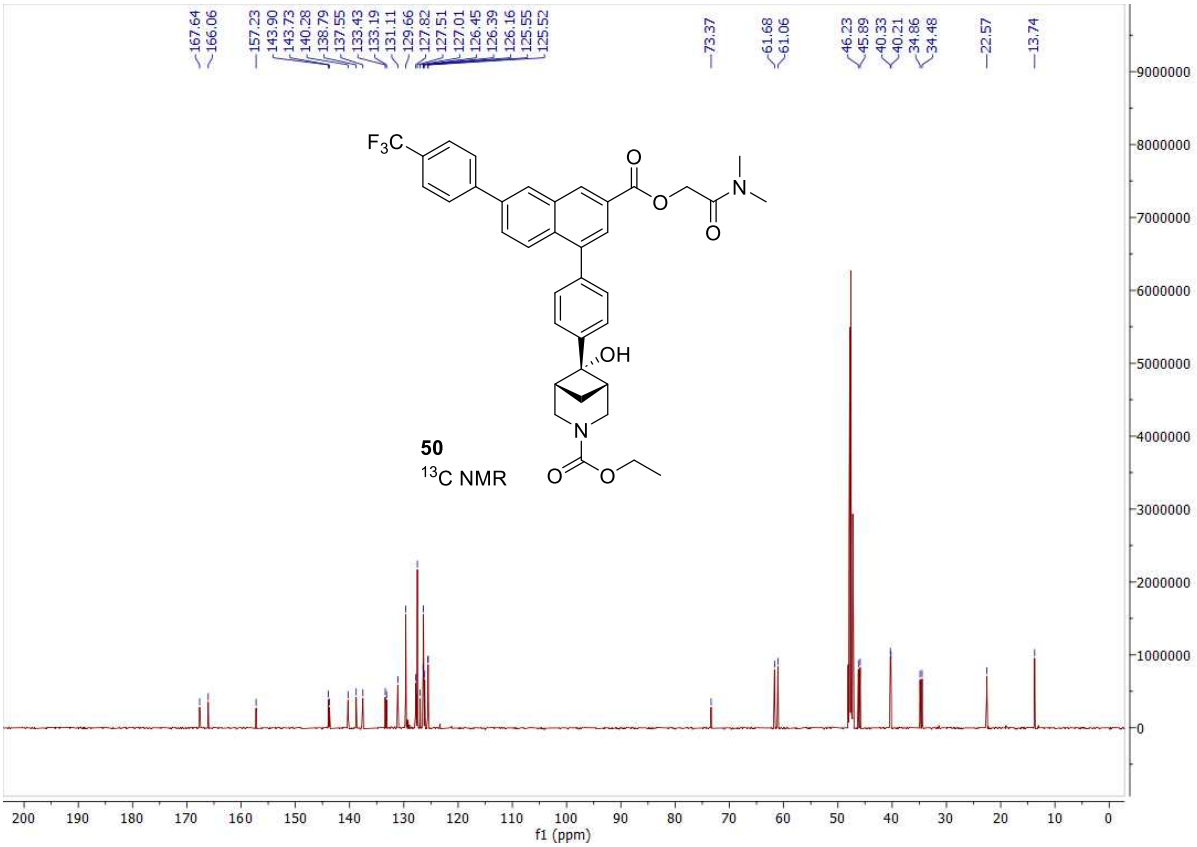

F3C
O
OH
N
H
19
K (d) 7.66
G (d) 8.40
I (dd) 7.90
F (s) 8.72
H (m) 7.99
L (d) 7.51
M (t) 6.28
J (d) 7.78
D (m) 3.32
B (dd) 2.72
A (t) 2.90
C (s) 2.08
E (m) 3.24
1.07
1.16
4.16
1.16
2.11
1.99
1.98
0.83
2.38
1.75
2.00
2.02
1.92
f1 (ppm)

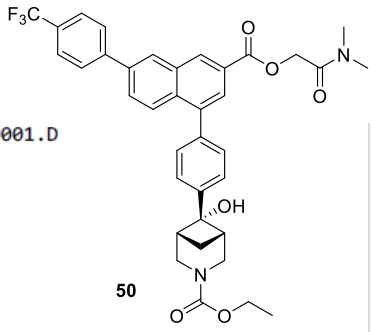

F3C
O
OH
OH
N
H
20
L (d) 7.70
H (d) 8.42
J (dd) 7.91
G (s) 8.75
I (m) 7.97
K (d) 7.78
M (d) 7.65
A (dt) 3.85
F (dt) 3.41
E (dq) 2.24
C (dt) 2.47
B (dt) 2.70
D (dp) 2.35
0.91
0.99
3.94
1.00
2.17
1.99
2.08
1.94
2.02
1.96
1.76
1.74
1.72
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


F3C
O
O
N
O
OH
N
H
49
1H NMR
D (m) 7.91
H (d) 8.72
B (m) 8.09
F (d) 7.61
G (s) 8.83
A (s) 8.30
E (d) 7.74
C (d) 7.98
Q (s) 6.15
N (s) 5.11
J (d) 3.49
O (s) 3.00
I (d) 3.70
K (d) 2.90
P (s) 2.85
M (d) 1.62
L (m) 1.72
f1 (ppm)


169.06
167.46
145.15
143.71
141.52
140.79
139.09
134.88
134.56
132.63
131.28
129.30
128.93
128.47
127.80
127.59
126.98
74.57
63.09
45.75
41.31
36.25
35.88
22.12
F3C
O
O
N
O
OH
N
H
49
13C NMR
f1 (ppm)


F3C
O
O
N
O
OH
N
O
O
50
1H NMR
Q (d) 7.71
L (s) 8.12
J (s) 8.80
K (s) 8.24
P (d) 7.58
M (d) 8.04
N (m) 7.80
A (s) 5.05
C (m) 3.90
B (q) 4.22
E (m) 3.01
D (s) 3.08
F (s) 2.92
H (d) 1.46
G (t) 1.76
I (t) 1.32
f1 (ppm)


167.64
166.06
157.23
143.90
143.73
140.28
138.79
137.55
133.43
133.19
131.11
129.66
127.82
127.51
127.01
126.45
126.39
126.16
125.55
125.52
73.37
61.68
61.06
46.23
45.89
40.33
40.21
34.86
34.48
22.57
13.74
F3C
O
O
N
O
OH
N
O
O
50
13C NMR
f1 (ppm)



50

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Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-01-24 12-54-07\MRS4855000001.D
Sample Name: MRS4855

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    Acq. Operator   : SYSTEM                          Seq. Line :   1
    Acq. Instrument : hplc                             Location :   71
    Injection Date  : 1/24/2022 12:59:10 PM               Inj :   1
                                                    Inj Volume : 5.000 µl
    Different Inj Volume from Sample Entry!  Actual Inj Volume : 10.000 µl
    Method          : C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2022-01-24 12-54-07\ZW_A10-100_B_20MIN.
                      M (Sequence Method)
    Last changed    : 1/24/2022 12:54:08 PM by SYSTEM
    Additional Info : Peak(s) manually integrated
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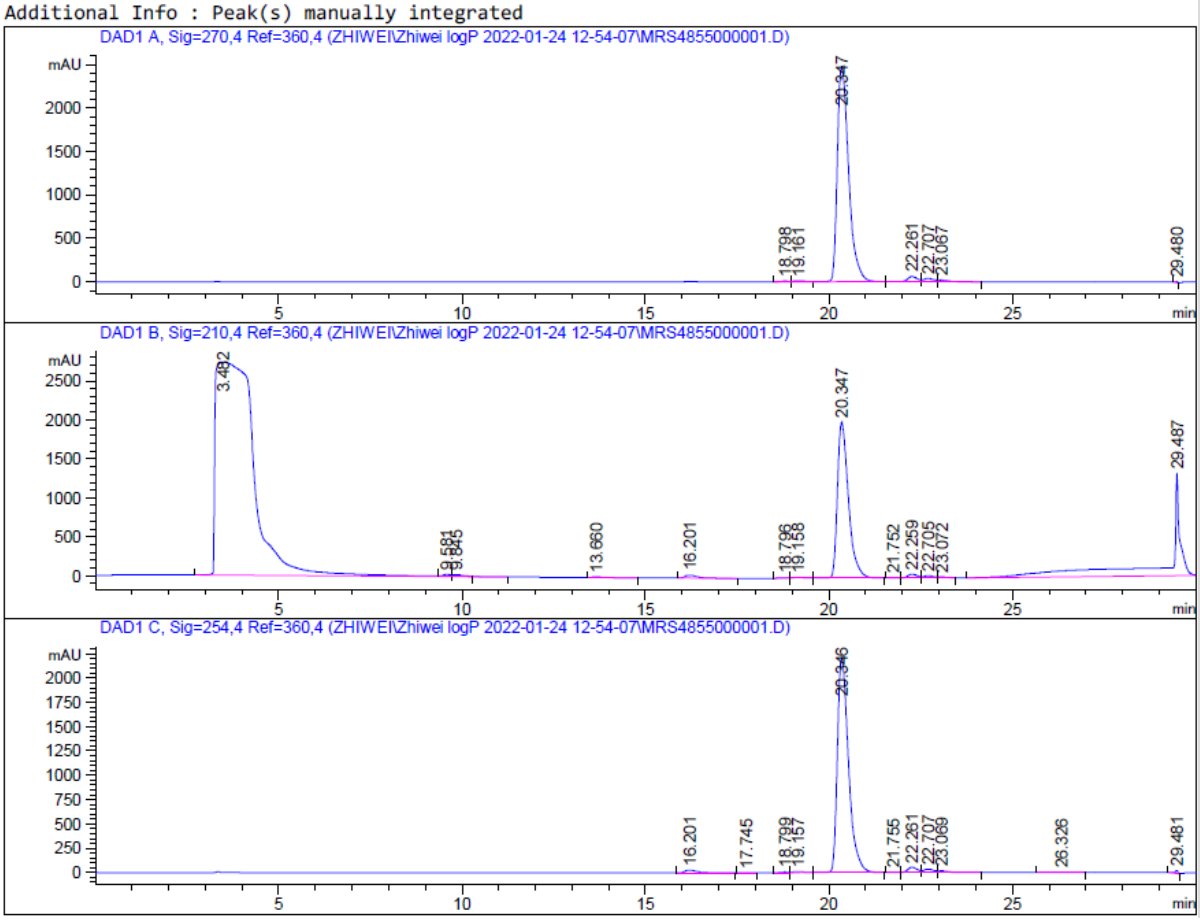


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=270,4 Ref=360,4

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.798	BV E	0.2500	130.99969	8.12964	0.2354
2	19.161	VV E	0.3147	251.59396	12.29488	0.4520
3	20.347	VB R	0.3298	5.30192e4	2476.36938	95.2546
4	22.261	BV	0.2830	1107.91040	60.10727	1.9905
5	22.707	VV	0.2845	748.83679	39.26551	1.3454
6	23.067	VB	0.2975	352.57422	17.61428	0.6334
7	29.480	BB	0.0654	49.37229	10.78990	0.0887
Totals :				5.56605e4	2624.57086	

Signal 2: DAD1 B, Sig=210,4 Ref=360,4

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.482	BV R	0.8509	1.97137e5	2734.96924	72.0487
2	9.581	VV E	0.2243	306.19781	21.48454	0.1119
3	9.845	VB E	0.2795	352.82104	19.64821	0.1289
4	13.660	BB	0.3759	211.32794	8.33208	0.0772
5	16.201	BB	0.3542	893.71490	38.30293	0.3266
6	18.796	BV	0.2453	96.13945	6.05408	0.0351
7	19.158	VV	0.3128	203.25423	9.93058	0.0743
8	20.347	VB	0.3194	4.16536e4	1996.61523	15.2234
9	21.752	BB	0.2112	16.03680	1.23777	5.861e-3
10	22.259	BV	0.2746	847.43774	48.31083	0.3097
11	22.705	VV	0.2767	524.99493	28.52562	0.1919
12	23.072	VB	0.2516	182.86534	11.25175	0.0668
13	29.487	BBA	0.2947	3.11909e4	1305.54895	11.3995
Totals :				2.73616e5	6230.21181	

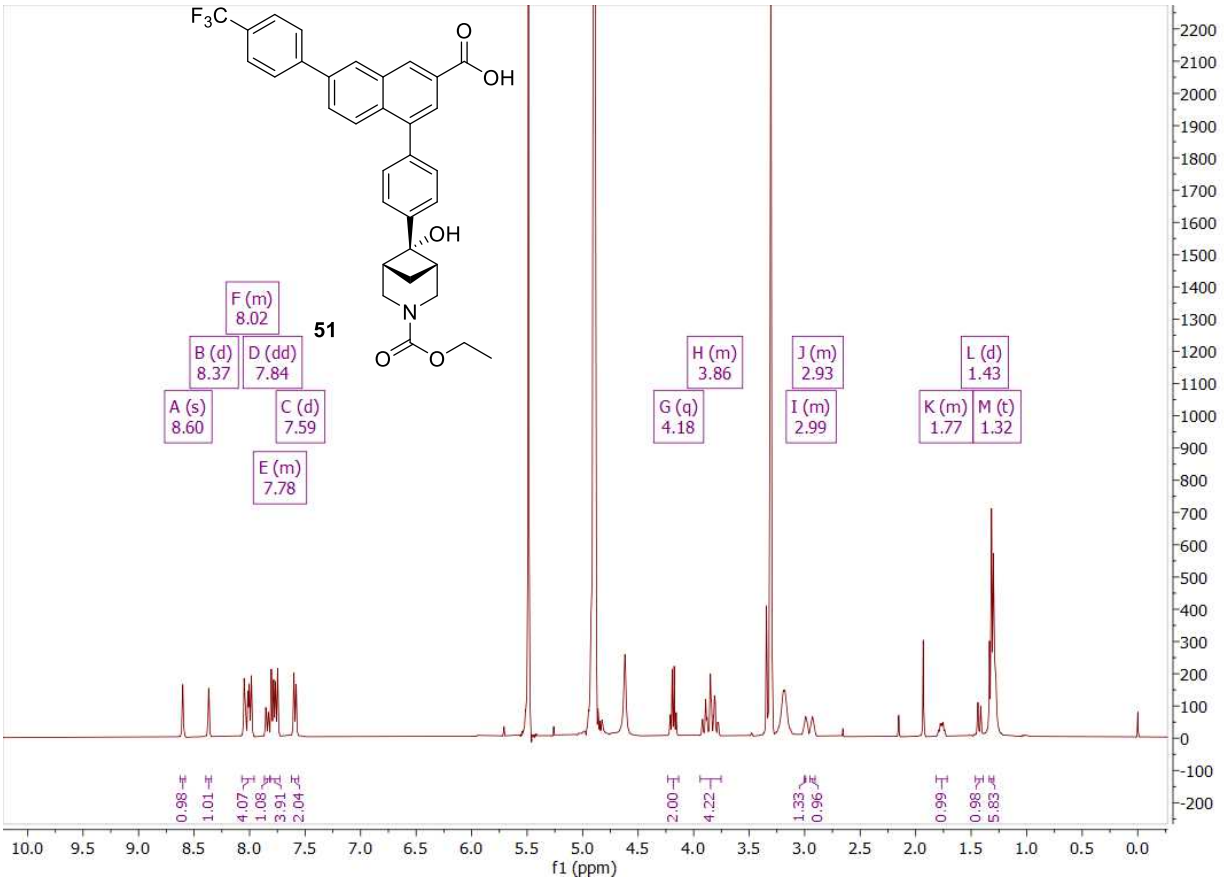
Signal 3: DAD1 C, Sig=254,4 Ref=360,4

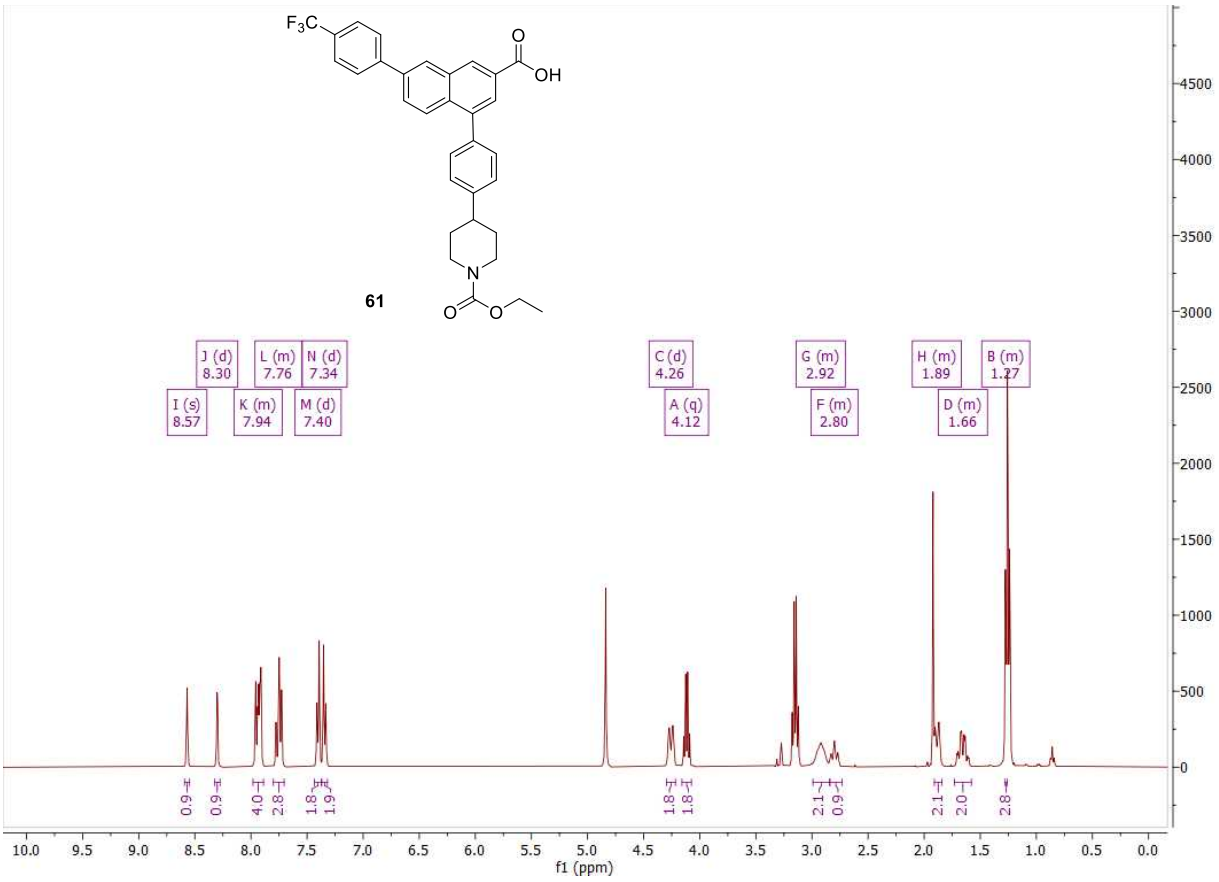
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.201	BB	0.3493	610.64655	26.85579	1.2350
2	17.745	BB	0.2606	23.68784	1.48099	0.0479

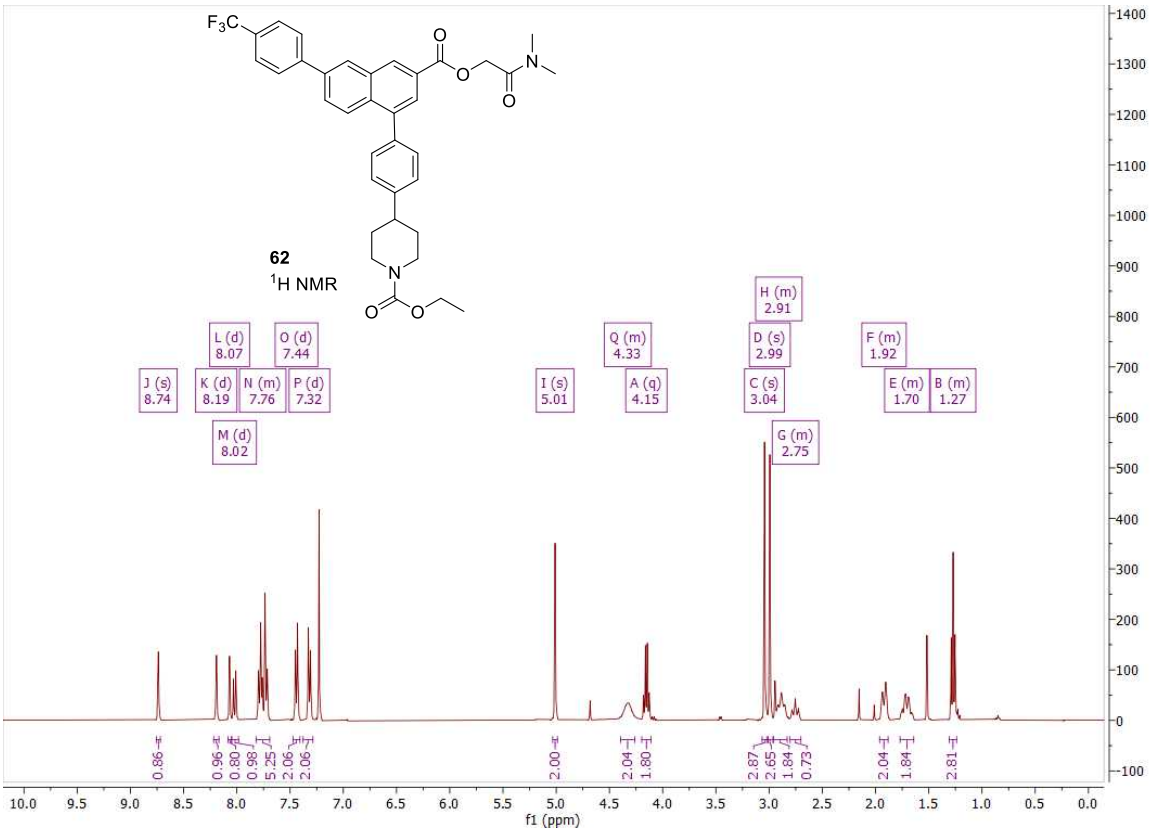
Sample Name: MRS4855

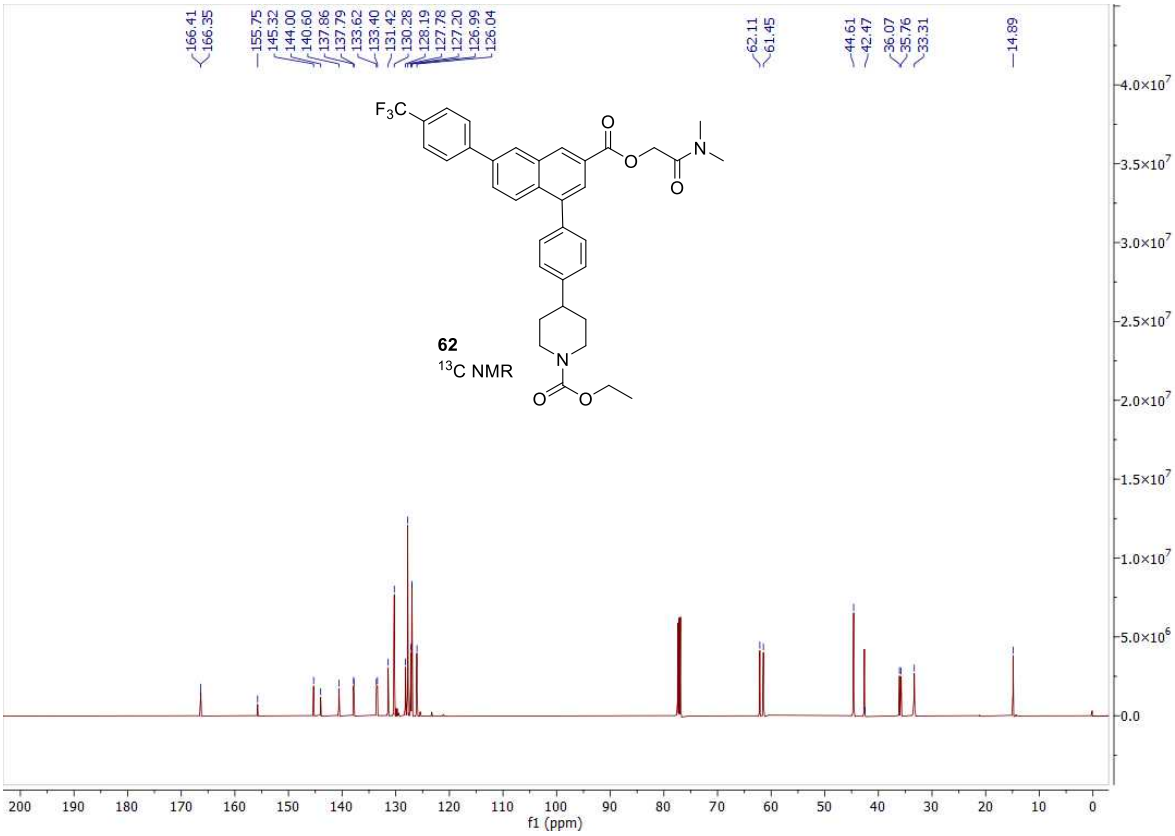
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
3	18.799	BV	0.2456	105.88486	6.72834	0.2142
4	19.157	VB	0.3066	211.09714	10.58841	0.4269
5	20.346	BB	0.3226	4.64127e4	2214.10156	93.8693
6	21.755	BB	0.2143	18.20793	1.39447	0.0368
7	22.261	BV	0.2741	909.28186	51.46049	1.8390
8	22.707	VV	0.2817	631.48682	33.52936	1.2772
9	23.069	VB	0.2831	276.31143	14.71497	0.5588
10	26.326	BB	0.3806	47.40802	1.69365	0.0959
11	29.481	BB	0.0823	197.25113	34.71066	0.3989
Totals :				4.94440e4	2397.25868	

*** End of Report ***


F3C
O
OH
OH
N
O
O
51
F (m) 8.02
B (d) 8.37
D (dd) 7.84
A (s) 8.60
C (d) 7.59
E (m) 7.78
H (m) 3.86
G (q) 4.18
J (m) 2.93
I (m) 2.99
L (d) 1.43
K (m) 1.77
M (t) 1.32
0.98
1.01
4.07
1.08
3.91
2.04
2.00
4.22
1.33
0.96
0.99
0.98
5.83
f1 (ppm)


F3C
O
OH
N
O
O
61
J (d) 8.30
L (m) 7.76
N (d) 7.34
I (s) 8.57
K (m) 7.94
M (d) 7.40
C (d) 4.26
A (q) 4.12
G (m) 2.92
F (m) 2.80
H (m) 1.89
D (m) 1.66
B (m) 1.27
0.9
0.9
4.0
2.8
1.8
1.9
1.8
1.8
2.1
0.9
2.1
2.0
2.8
f1 (ppm)


62
^{1}H NMR
J (s) 8.74
K (d) 8.19
M (d) 8.02
N (m) 7.76
L (d) 8.07
P (d) 7.32
O (d) 7.44
I (s) 5.01
Q (m) 4.33
A (q) 4.15
H (m) 2.91
D (s) 2.99
C (s) 3.04
G (m) 2.75
F (m) 1.92
E (m) 1.70
B (m) 1.27
f1 (ppm)


62
^{13}C NMR
166.41
166.35
155.75
145.32
144.00
140.60
137.86
137.79
133.62
133.40
131.42
130.28
128.19
127.78
127.20
126.99
126.04
62.11
61.45
44.61
42.47
36.07
35.76
33.31
14.89
f1 (ppm)

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Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2021-09-29 12-38-26\MRS48140000003.D
Sample Name: MRS4845

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    Acq. Instrument : hplc                          Location :   3
    Injection Date  : 9/29/2021 1:41:33 PM             Inj :   1
                                                  Inj Volume : 5.000 µl
    Method          : C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2021-09-29 12-38-26\ZW_A60-100_B_20MIN.
                      M (Sequence Method)
    Last changed    : 9/29/2021 12:38:26 PM by SYSTEM
    Additional Info : Peak(s) manually integrated
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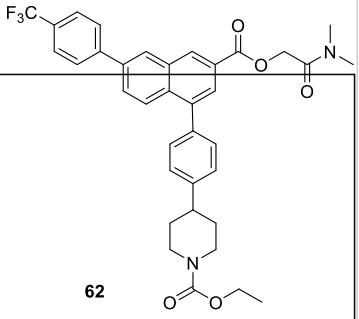


62

Data File C:\Chem32\1\Data\ZHIWEI\Zhiwei logP 2021-09-29 12-38-26\MRS48140000003.D
Sample Name: MRS4845

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=270,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.165	BB	0.4289	77.08664	2.76784	0.1615
2	15.157	BV E	0.4121	285.46634	10.60297	0.5980
3	16.206	VB R	0.4332	4.73704e4	1668.50854	99.2405
Totals :				4.77329e4	1681.87936	

Signal 2: DAD1 B, Sig=254,4 Ref=off

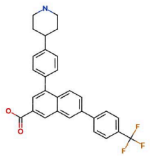
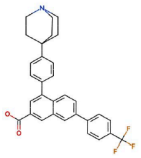
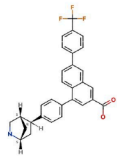
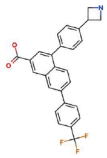
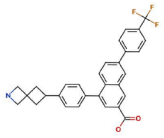
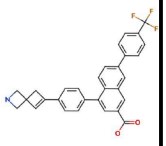
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.170	BB	0.4324	77.94099	2.80310	0.1866
2	15.157	BV	0.4047	215.17343	8.13130	0.5150
3	16.206	VB	0.4327	4.14852e4	1463.57800	99.2984
Totals :				4.17783e4	1474.51240	

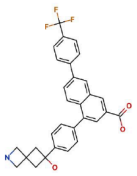
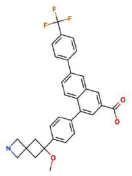
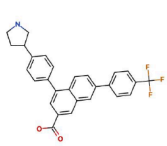
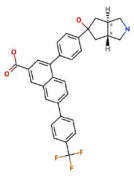
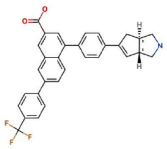
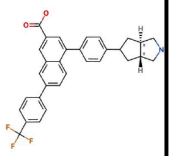
Signal 3: DAD1 C, Sig=210,4 Ref=off

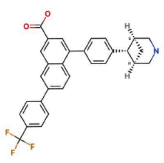
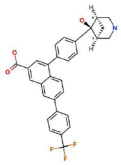
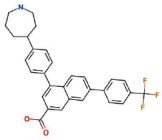
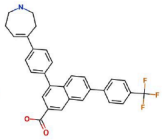
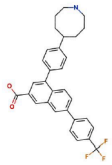
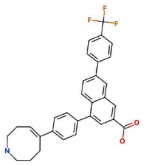
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.319	BB	0.5801	1.40381e5	2883.07837	78.4407
2	14.093	BB	0.3257	32.66845	1.55102	0.0183
3	15.151	BB	0.4345	263.81378	9.14764	0.1474
4	16.206	BB	0.4329	3.82869e4	1349.72998	21.3936
Totals :				1.78964e5	4243.50701	

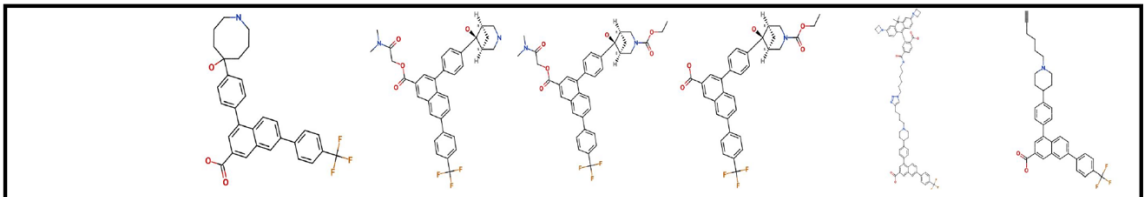
*** End of Report ***

Table S6. Calculated ADMET properties, predicted using StarDrop software (v. 7.2, https://www.optibrium.com/stardrop-installers/),[8,9] supplied by Optibrium (Cambridge, UK). Related to structures shown in Table 1.

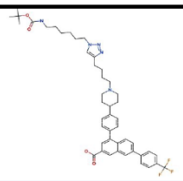
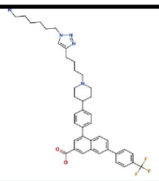
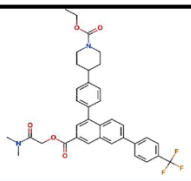
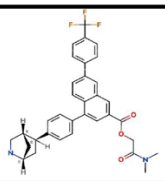
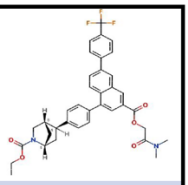
						
Compound	**1**	**2a**	**2b**	**5**	**6**	**7**
FlexX Score ORMA UNK_ _1	-	-	-	-	-	-
IC50 (nM) human P2Y14 receptor	7.96	20	3.11	65.9	46.6	9.69
pIC50, P2Y14R	8.099	7.699	8.507	7.181	7.332	8.014
Most Acidic pKa	5.7	5.6	5.8	-	6.2	6.1
Most Basic pKa	8.3	8.5	8.7	-	8.4	8.7
All pKas	Acidic pKa 1: 5.7, Basic pKa 1: 8.3	Acidic pKa 1: 5.6, Basic pKa 1: 8.5	Acidic pKa 1: 5.8, Basic pKa 1: 8.7	-	Acidic pKa 1: 6.2, Basic pKa 1: 8.4	Acidic pKa 1: 6.1, Basic pKa 1: 8.7
logS	-0.006678	-1.014	-0.3407	0.2823	-0.3099	0.0541
logS @ pH7.4	**2.391**	**1.089**	**2.265**	**2.529**	**2.165**	**2.458**
logD	2.866	3.508	2.946	2.706	3.053	2.898
2C9 pKi	5.935	6.097	6.087	5.903	6.076	5.886
hERG pIC50	5.259	6.069	5.225	4.964	5.286	5.324
BBB log([brain]:[blood])	-0.8669	-0.5774	-0.874	-0.8687	-0.7818	-0.7173
BBB category	+	+	+	+	+	+
HIA category	+	+	+	+	+	+
P-gp category	yes	yes	yes	yes	yes	yes
2D6 affinity category	medium	high	very high	medium	medium	high
PPB90 category	high	high	high	high	high	high
logP	**2.518**	**6.548**	**2.728**	**2.114**	**2.62**	**2.278**
MW	475.5	501.5	487.5	447.4	487.5	485.5
HBD	2	1	2	2	2	2
HBA	3	3	3	3	3	3
TPSA	49.33	40.54	49.33	49.33	49.33	49.33
Flexibility	0.1282	0.119	0.122	0.1351	0.122	0.122
Rotatable Bonds	5	5	5	5	5	5

						
Compound	**8**	**9**	**10**	**11**	**12**	**13**
FlexX Score ORMA UNK_ _1	-	-	-	-	-	-
IC50 (nM) human P2Y14 receptor	20.8	46.5	31.5	9.48	16.6	32
pIC50, P2Y14R	7.682	7.333	7.502	8.023	7.78	7.495
Most Acidic pKa	5.9	-	5.2	-	6.2	3.8
Most Basic pKa	8.3	-	8.8	-	8.5	9.2
All pKas	Acidic pKa 1: 5.9, Acidic pKa 2: 5.7, Basic pKa 1: 8.3	-	Acidic pKa 1: 5.2, Basic pKa 1: 8.8	-	Acidic pKa 1: 6.2, Basic pKa 1: 8.5	Acidic pKa 1: 3.8, Basic pKa 1: 9.2
logS	0.231	-0.185	0.1345	0.1514	-0.3245	-0.3706
logS @ pH7.4	**2.436**	**2.41**	**2.451**	**2.322**	**2.334**	**2.053**
logD	2.165	2.65	2.802	2.354	3.085	3.121
2C9 pKi	6.122	6.184	5.979	6.12	6.223	6.117
hERG pIC50	4.89	5.039	5.114	4.885	5.395	5.243
BBB log([brain]:[blood])	-0.9536	-0.835	-0.8689	-1.077	-0.6427	-0.8766
BBB category	-	-	+	-	+	+
HIA category	+	+	+	+	+	+
P-gp category	yes	yes	yes	yes	yes	yes
2D6 affinity category	high	high	medium	high	medium	very high
PPB90 category	high	high	high	high	high	high
logP	**1.954**	**2.396**	**2.314**	**2.174**	**2.706**	**2.852**
MW	503.5	517.5	461.5	517.5	499.5	501.5
HBD	3	2	2	3	2	2
HBA	4	4	3	4	3	3
TPSA	69.56	58.56	49.33	69.56	49.33	49.33
Flexibility	0.119	0.1395	0.1316	0.1163	0.119	0.119
Rotatable Bonds	5	6	5	5	5	5

						
Compound	**14**	**15**	**16**	**17**	**18**	**19**
FlexX Score ORMA UNK_ _1	-	-30	-	-	-	-
IC50 (nM) human P2Y14 receptor	524	5.92	9.58	11.9	18.5	58.4
pIC50, P2Y14R	6.281	8.228	8.019	7.924	7.733	7.234
Most Acidic pKa	5.1	4.6	5.7	5.9	5.7	-
Most Basic pKa	8.4	8.8	8.1	8.2	8.1	-
All pKas	Acidic pKa 1: 5.1, Basic pKa 1: 8.4	Acidic pKa 1: 4.6, Acidic pKa 2: 5.3, Basic pKa 1: 8.8	Acidic pKa 1: 5.7, Basic pKa 1: 8.1	Acidic pKa 1: 5.9, Basic pKa 1: 8.2	Acidic pKa 1: 5.7, Basic pKa 1: 8.1	-
logS	-0.2738	0.2897	-0.148	-0.07885	-0.2834	-0.2141
logS @ pH7.4	**2.116**	**2.306**	**2.291**	**2.522**	**2.201**	**2.424**
logD	3.081	2.365	2.977	2.865	3.083	2.989
2C9 pKi	6.073	6.152	6.124	6.171	5.673	6.134
hERG pIC50	5.151	4.774	5.38	5.476	5.497	5.599
BBB log([brain]:[blood])	-0.8783	-1.082	-0.8614	-0.6212	-0.854	-0.6156
BBB category	+	-	+	+	+	+
HIA category	+	+	+	+	+	+
P-gp category	yes	yes	yes	yes	yes	yes
2D6 affinity category	very high	high	medium	high	medium	high
PPB90 category	high	high	high	high	high	high
logP	**2.646**	**1.973**	**2.728**	**2.585**	**2.939**	**2.79**
MW	487.5	503.5	489.5	487.5	503.6	501.5
HBD	2	3	2	2	2	2
HBA	3	4	3	3	3	3
TPSA	49.33	69.56	49.33	49.33	49.33	49.33
Flexibility	0.122	0.119	0.125	0.125	0.122	0.122
Rotatable Bonds	5	5	5	5	5	5



Compound	20	49	50	51	53	54
FlexX Score ORMA UNK_ _1	-	-	-	-	-	-
IC50 (nM) human P2Y14 receptor	1780	4810		81.6	2.59e+04	
pIC50, P2Y14R	5.75	5.318		7.088	4.587	
Most Acidic pKa	-	-	8.4	3.5	3.8	5.7
Most Basic pKa	-	-	N/A	N/A	7.7	8
All pKas	-	-	Acidic pKa 1: 8.4	Acidic pKa 1: 3.5, Acidic pKa 2: 8.3	Acidic pKa 1: 3.8, Acidic pKa 2: 4.7, Basic pKa 1: 7.7, Basic pKa 2: 6.8, Basic pKa 2: 6.8, Basic pKa 2: 6.9	Acidic pKa 1: 5.7, Basic pKa 1: 8.0
logS	0.2738	0.7176	-0.3775	-1.346	-1.324	-1.264
logS @ pH7.4	**2.49**	**1.738**	**-0.3775**	**1.302**	**3.155**	**0.9025**
logD	2.223	3.329	5.386	3.274	3.56	4.277
2C9 pKi	5.683	6.116	5.97	6.189	5.548	5.553
hERG pIC50	5.116	6.333	6.085	5.313	6.411	6.578
BBB log([brain]:[blood])	-1.062	0.291	-0.9526	-1.235	-1.46	-0.5531
BBB category	-	-	-	-	-	+
HIA category	+	+	+	+	+	+
P-gp category	yes	yes	yes	yes	yes	yes
2D6 affinity category	high	high	high	high	high	medium
PPB90 category	high	high	high	high	high	high
logP	**2.273**	**4.879**	**5.386**	**6.037**	**3.325**	**8.324**
MW	519.6	588.6	660.7	575.6	1178	555.6
HBD	3	2	1	2	4	1
HBA	4	6	8	6	12	3
TPSA	69.56	78.87	96.38	87.07	140.9	40.54
Flexibility	0.119	0.1875	0.2264	0.1702	0.2268	0.2222
Rotatable Bonds	5	9	12	8	22	10

					
Compound	**57**	**58**	**62**	**63**	**64**
FlexX Score ORMA UNK_ _1	-	-	-	-	-
IC50 (nM) human P2Y14 receptor	424	67.4	-	-	-
pIC50, P2Y14R	6.373	7.171			
Most Acidic pKa	2.5	-	N/A	N/A	-
Most Basic pKa	8	-	N/A	9.2	-
All pKas	Acidic pKa 1: 2.5, Basic pKa 1: 8.0, Basic pKa 2: 5.6, Basic pKa 2: 7.2	-	N/A	Basic pKa 1: 9.2	-
logS	-1.174	-0.2279	-0.7504	0.1255	-1.003
logS @ pH7.4	**1.313**	**1.65**	**-0.7504**	**1.675**	**-1.003**
logD	4.301	3.661	6.407	3.996	6.531
2C9 pKi	5.441	5.495	5.966	6.098	5.923
hERG pIC50	7.269	6.889	6.65	6.8	6.56
BBB log([brain]:[blood])	-1.06	-1.08	-0.595	0.5016	-0.6635
BBB category	-	-	-	-	-
HIA category	+	+	+	+	+
P-gp category	yes	yes	yes	yes	yes
2D6 affinity category	high	high	medium	very high	very high
PPB90 category	high	high	high	high	high
logP	**8.505**	**5.815**	**6.407**	**6.004**	**6.531**
MW	797.9	697.8	632.7	572.6	644.7
HBD	2	2	0	1	0
HBA	9	7	7	5	7
TPSA	109.6	97.27	76.15	58.64	76.15
Flexibility	0.3175	0.2857	0.24	0.1915	0.2308
Rotatable Bonds	20	16	12	9	12

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