Supporting Information

Design, synthesis and biological evaluation of novel matrix metalloproteinase inhibitors as potent antihemorrhagic agents: from hit identification to an optimized lead.

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Protocol for Prep-HPLC purification method:

The HPLC measurement was performed using Gilson 281 from 233 pump (binary), an autosampler, and a UV detector. The fractions were detected by LC-MS. The MS detector was configured with an electrospray ionization source. The source temperature was maintained at 300-350 ºC. Reverse phase HPLC was carried out on Luna C18 (100×30 mm; 4 or 5 um). Solvent A: water with 0.075% trifluoroacetic acid; Solvent B: acetonitrile with 0.075% trifluoroacetic acid. Gradient: At room temperature, 20% of B to 40% of B within 6 min at 25 mL/min; then 40% B at 25 mL/min over 2 min, UV detector.

Protocol for SFC purification method:

Analytical separation method:
Analytical separations were performed using a Thar analytical SFC with a ChiralPak AD-H column (250 x 4.6 mm). Solvent A: CO_2; Solvent B: methanol with 0.05% DEA. Mobile phase: 50% of A and 50% of B at 2.0 mL/min. Back pressure: 100 bar; and column temperature: 35 ºC. UV detector at 220 nm.

Preparative separation method:
Preparative separation was performed using a Mg II preparative SFC with a ChiralPak AD-H column (250 x 30 mm). Solvent A: CO_2; Solvent B: ethanol with 0.1% $NH_3 \cdot H_2O$. Mobile phase 50% of A and 50% of B at 40 mL/min. Back pressure: 100 bar; and column temperature: 38 ºC. UV detector at 220 nm.

Samples were prepared by dissolving in methanol to ~12 mg/ml and 2.0 mL were used per injection. After separation, the fractions were dried off via rotary evaporation (bath temperature 40 ºC) to get the desired isomers. Purity was tested via LCMS.

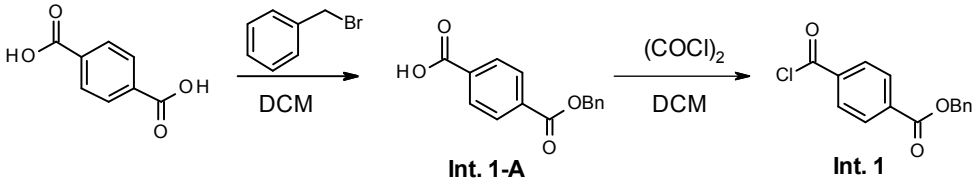
Details for Optical Rotation of compounds 5 and 22:

Optical rotation was measured with an AUTOPOL V polarimeter at room temperature and with a wavelength of 589 nm.
Compound **5**
C = 0.9762 g/100ml diluted with methanol
L = 1 dm
α_1 = + 0.163; α_2 = + 0.162; α_3 = + 0.163; $\overline{\alpha}$ = + 0.163; RSD = 0.35%;
$[\alpha]_D^{20}$ = + 16.66º ± 0.06º
Compound **22**
C = 0.9668 g/100ml diluted with methanol
L = 1 dm
α_1 = - 0.166; α_2 = - 0.165; α_3 = - 0.165; $\overline{\alpha}$ = - 0.165; RSD = 0.35%;
$[\alpha]_D^{20}$ = - 17.10º ± 0.06º

Table S1. Selectivity profile, % inhibition, at 10 μM against different MMPs

Cpd	MMP1	MMP2	MMP7	MMP8	MMP9	MMP12	MMP13	MMP14	MMP20
13	90.37	101.14	59.67	101.34	99.92	104.89	100	100.2	N/D
16	85.11	124.81	56.48	102.31	101.56	101.57	N/D	100.37	N/D
19d	86.1	100.65	65.59	99.82	102.15	99.67	N/D	92.48	N/D
19p	9	100.69	26.55	96.52	98.07	100.03	N/D	55.78	N/D
20a	N/D	100	N/D	N/D	100	N/D	100	N/D	N/D

Synthesis of benzyl 4-chlorocarbonyl benzoate (Int. 1)



To a solution of commercially available terepthalic acid (10 g, 0.06 mol) in DCM (100 mL) was added Et_3N (12.12 g, 2 eq). Then bromide (9.27 g, 0.9 eq) in DCM (20 mL) was added dropwise at room temperature. The resulting mixture was stirred at room temperature for 3 h until TLC (PE:AE=1:1) detected the most starting material was consumed, then concentrated and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude compound which was chromatographed on silica gel to give pure compound **Int.1-A** (2.2 g, 14%) as a white solid. MS *m/z* 257 $[M + H]^+$ calc. for $C_{15}H_{12}O_4$.

To the solution of **Int.1-A** (800 mg. 3.13 mmol) in DCM (20 mL) and DMF (cat.) was added oxalyl dichloride (788 mg, 2 eq) at 0-5 ^oC and the reaction was stirred at RT for 2 h. Then the mixture was concentrated to give the crude product **Int.1** (860 mg) which was used for the next step directly. MS *m/z* 275 $[M + H]^+$ calc. for $C_{15}H_{11}ClO_3$.

HPLC purities of final compounds

HPLC-analysis was performed using a Shimadzu LC-20AB or LC-20AD with a Luna-C18(2), 5um, 2.0*50mm column at 40 ºC and UV detection. Three different methods were used.

Method 1

Solvent A: water with 0.056% trifluoroacetic acid; Solvent B: acetonitrile with 0.056% trifluoroacetic acid. Gradient: After 0.1 minutes at the initial condition of 90% A and 10% B, solvent B was increased to 80% over 4 minutes, maintained at 80% for 0.9 minutes, then a linear gradient to initial conditions was applied for 0.02 minutes and maintained for 0.58 minutes to re-equilibrate the column, giving a cycle time of 5.50 minutes. Flow rate was 0.8 mL/min from 0.01 to 4.90 minutes, increased to 1.2 mL/min in 0.03 minutes and maintained until the end of the run.

Method 2
Solvent A: water with 0.056% trifluoroacetic acid; Solvent B: acetonitrile with 0.056% trifluoroacetic acid. Gradient: After 0.4 minutes at the initial condition of 100% A, solvent B was increased to 60% over 4 minutes, maintained at 60% for 0.8 minutes, then a linear gradient to initial conditions was applied for 0.02 minutes and maintained for 0.68 minutes to re-equilibrate the column, giving a cycle time of 5.90 minutes. Flow rate was 0.8 mL/min from 0.01 to 5.21 minutes, increased to 1.2 mL/min in 0.02 minutes and maintained until the end of the run.

Method 3
Solvent A: water with 0.037% trifluoroacetic acid; Solvent B: acetonitrile with 0.019% trifluoroacetic acid. Gradient: After 0.1 minutes at the initial condition of 100% A, solvent B was increased to 60% over 4 minutes, maintained at 60% for 2 minutes, then a linear gradient to initial conditions was applied for 0.01 minutes and maintained for 1.79 minutes to re-equilibrate the column, giving a cycle time of 7.80 min. Flow rate was 3 mL/min.

Method 4
Solvent A: water with 0.056% trifluoroacetic acid; Solvent B: acetonitrile with 0.019% trifluoroacetic acid. Gradient: After 0.1 minutes at the initial condition of 90% A and 10% B, solvent B was increased to 80% over 4 minutes, maintained at 80% for 2 minutes, then a linear gradient to initial conditions was applied for 0.01 minutes and maintained for 0.68 minutes to re-equilibrate the column, giving a cycle time of 7.80 minutes. Flow rate was 3 mL/ min.

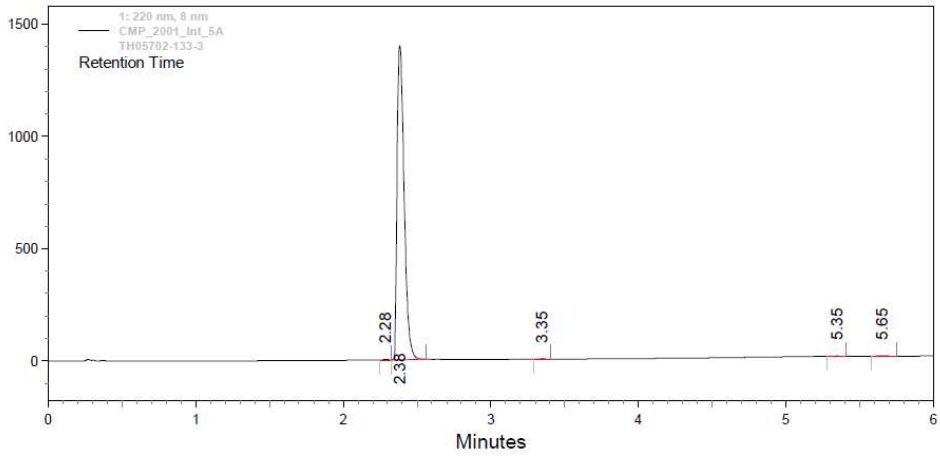
HPLC purities of final compounds

Compound	Method	Rt	Purity (%)
11	3	2.38	99.53
12	1	2.56	98.38
13	4	2.70	99.36
14	1	2.18	96.97
15	1	2.31	97.88
16	3	3.90	98.96
17	1	3.30	97.98
18	1	2.58	95.33
19a	3	3.53	97.68
19b	4	3.30	99.74
19c	1	2.37	99.38
19d	3	3.04	98.23
19e	3	3.28	95.46
19f	3	2.58	95.31
19g	3	3.23	98.50
19h	3	3.44	98.01
19i	3	3.31	98.35

19j	2	2.82	96.13
19k	2	3.41	99.63
19l	1	2.69	97.88
19m	3	3.50	98.88
19n	1	1.98	97.99
19o	3	2.50	98.14
19p	1	3.51	100
20a	4	2.66	95.45
20b	4	2.96	96.71
20c	4	3.21	99.09
21a	4	2.71	99.59
21b	2	2.79	96.16
22	1	1.61	99.46

HPLC traces for final compounds

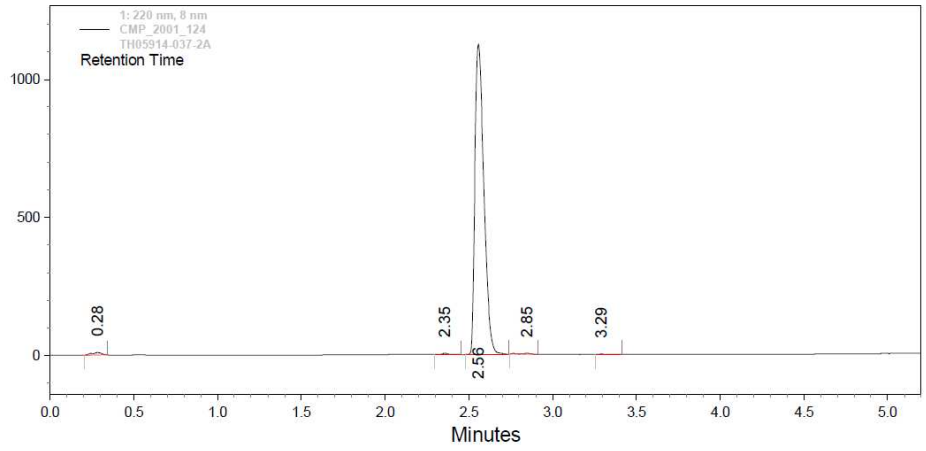
Compound 11



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.28	2151	4456	0.10
2.38	1387223	4644288	99.53
3.35	1530	5109	0.11
5.35	1497	4427	0.09
5.65	2029	7734	0.17

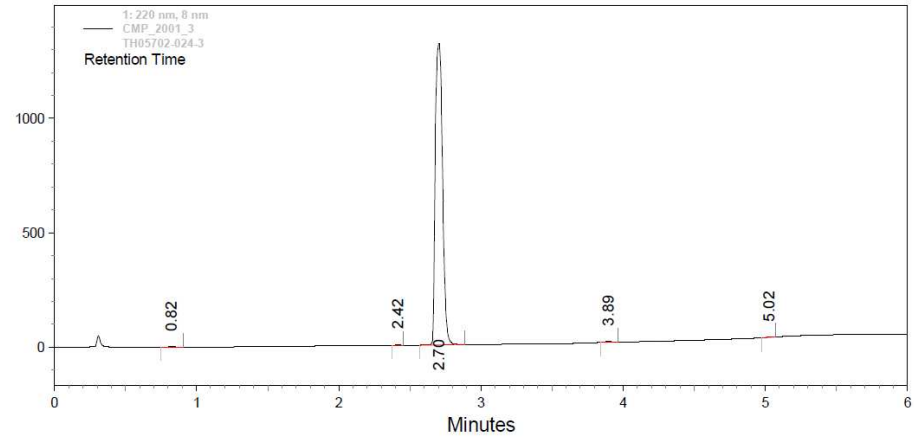
Compound 12



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.28	9036	37639	0.89
2.35	3961	11335	0.27
2.56	1119814	4183114	98.38
2.85	2747	12101	0.28
3.29	1866	7961	0.19

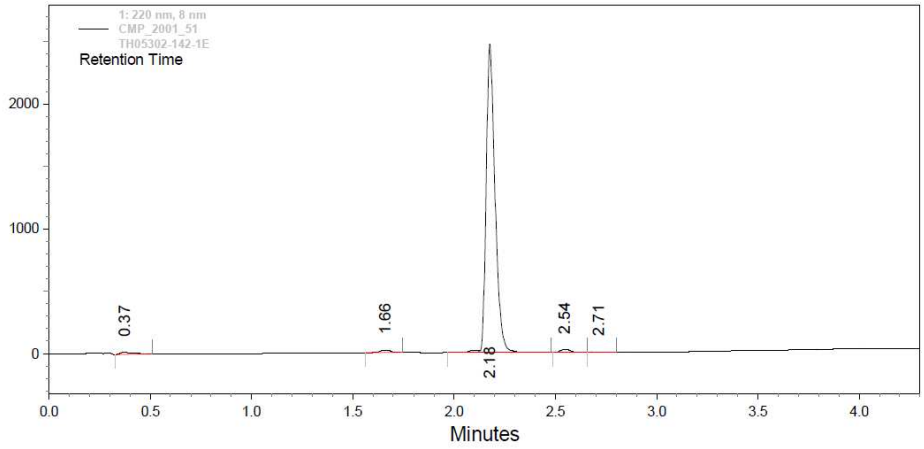
Compound 13



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.82	1772	5072	0.11
2.42	2306	4616	0.10
2.70	1311447	4653083	99.36
3.89	5885	14987	0.32
5.02	1898	5335	0.11

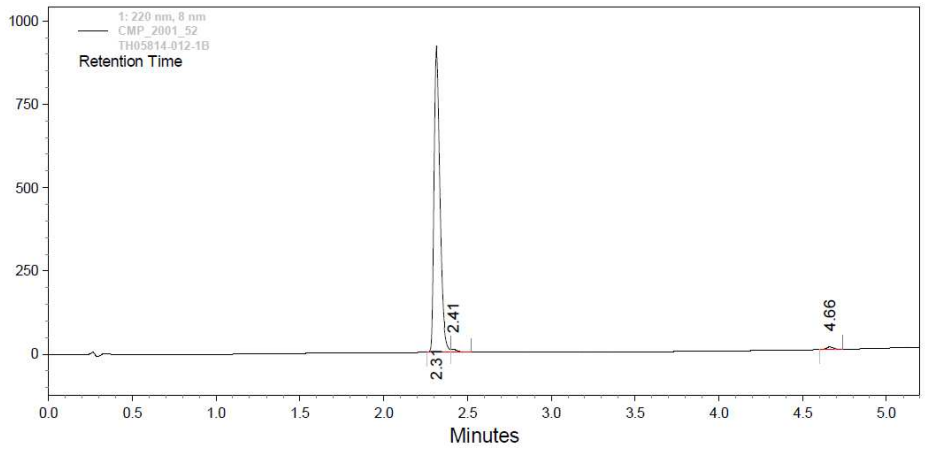
Compound 14



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.37	18071	79122	1.03
1.66	17721	61625	0.80
2.18	2416166	7474709	96.97
2.54	22829	75925	0.98
2.71	4532	16876	0.22

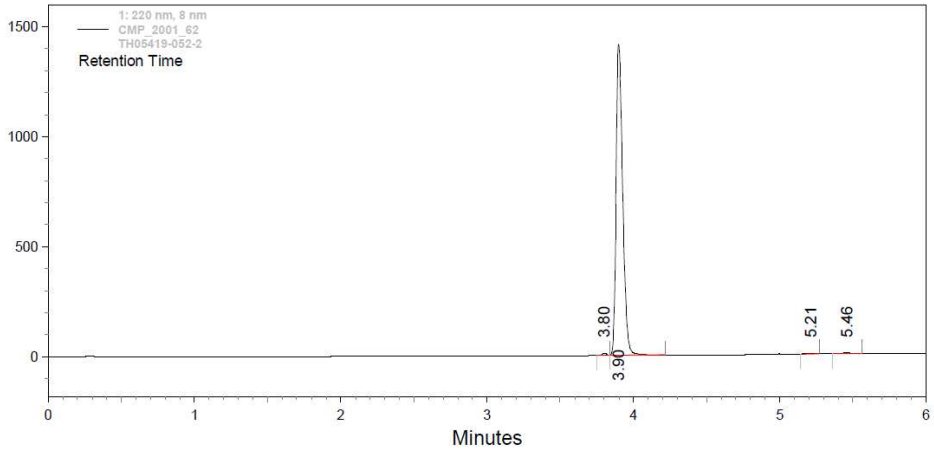
Compound 15



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.31	907927	2273490	97.88
2.41	9294	25303	1.09
4.66	8184	23962	1.03

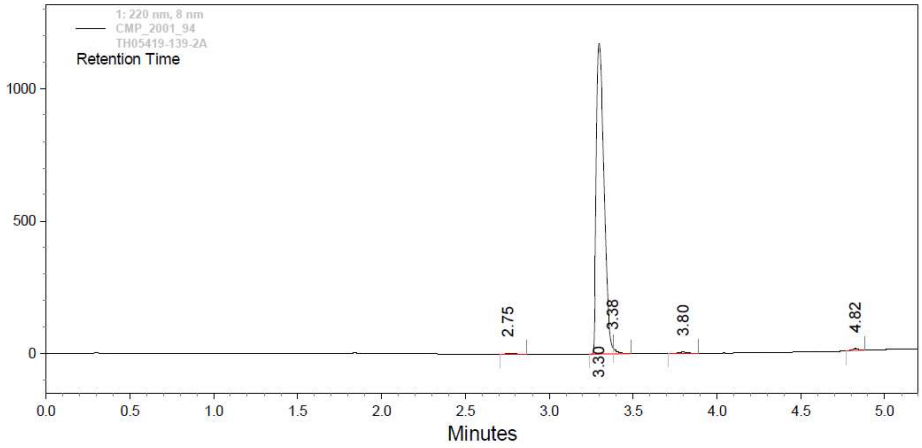
Compound 16



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
3.80	8198	21976	0.49
3.90	1397215	4438032	98.96
5.21	2179	6477	0.14
5.46	4427	18278	0.41

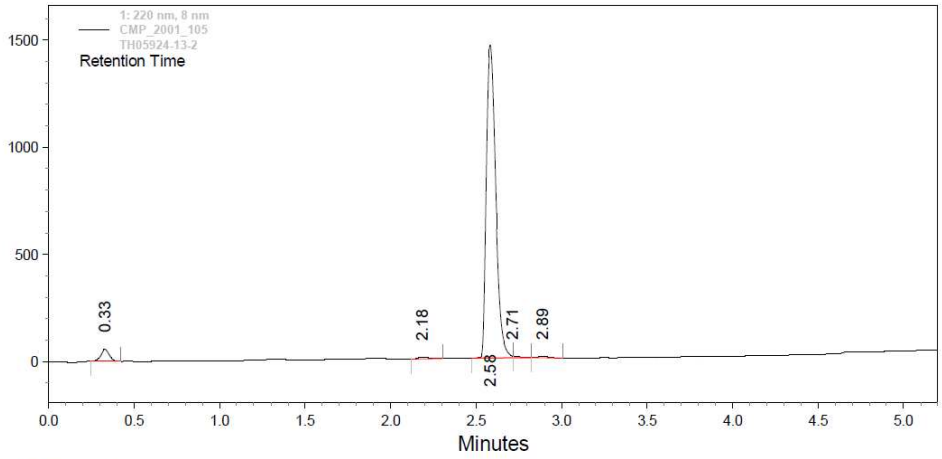
Compound 17



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.75	3993	12801	0.33
3.30	1155309	3768700	97.98
3.38	21920	28444	0.74
3.80	5390	18190	0.47
4.82	7326	18168	0.47

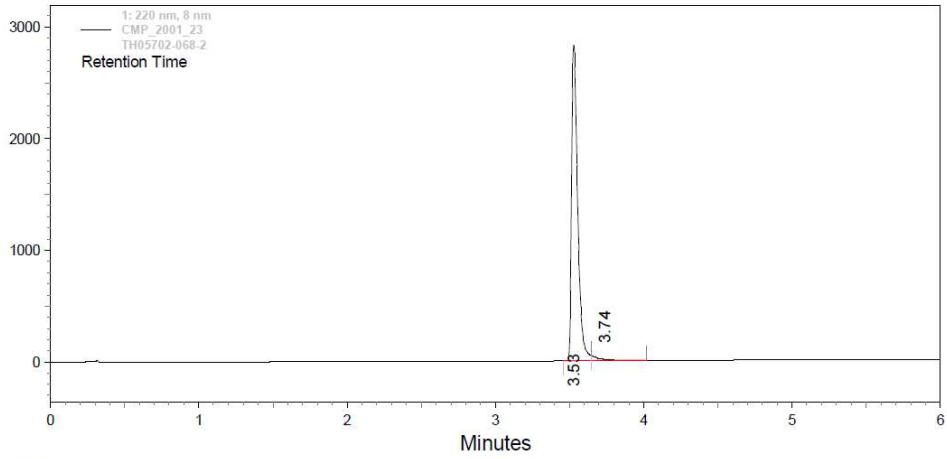
Compound 18



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.33	54806	184568	3.17
2.18	9637	37987	0.65
2.58	1423241	5553713	95.33
2.71	7322	18007	0.31
2.89	8881	31711	0.54

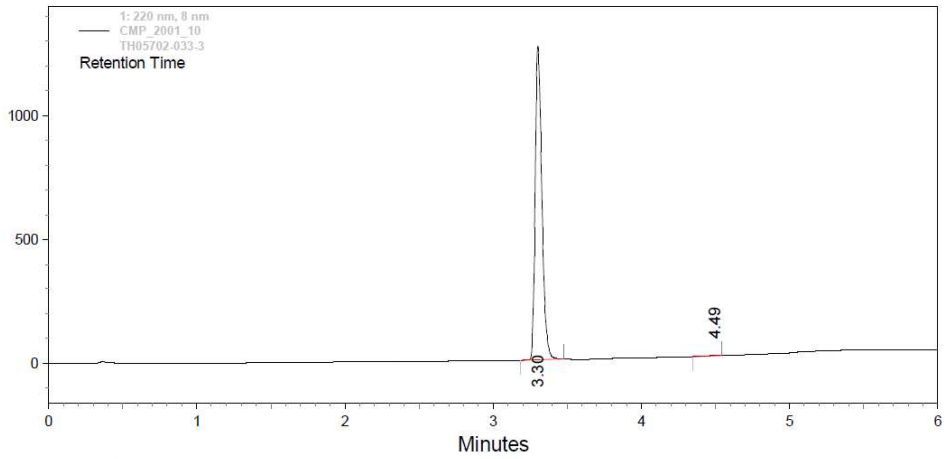
Compound 19a



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
3.53	2756139	8066475	97.68
3.74	12803	191241	2.32

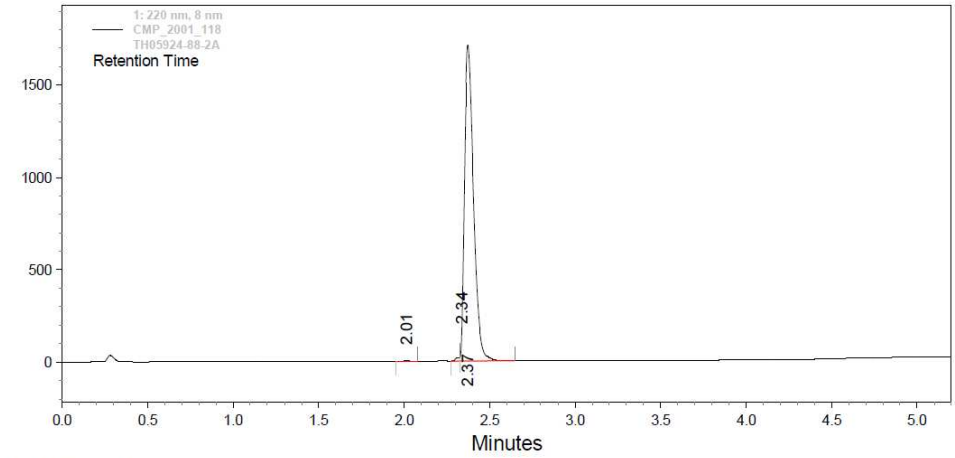
Compound 19b



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
3.30	1259450	3976292	99.74
4.49	2864	10398	0.26

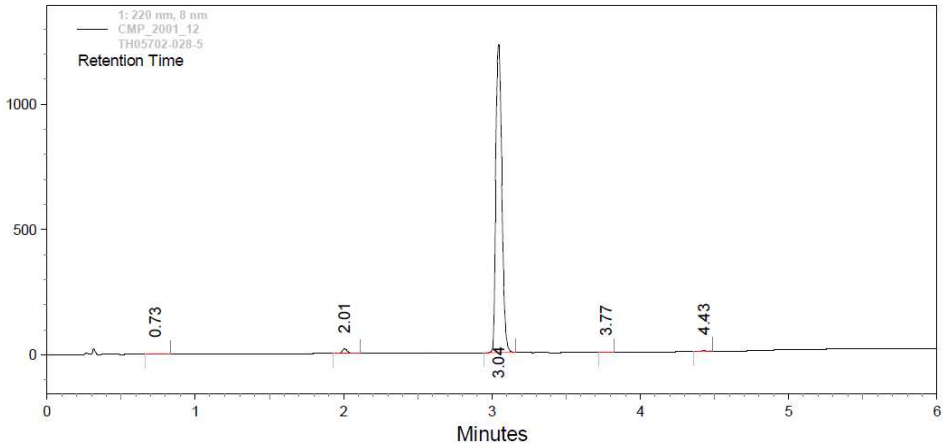
Compound 19c



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.01	2762	7111	0.11
2.34	322556	31996	0.51
2.37	1616136	6273465	99.38

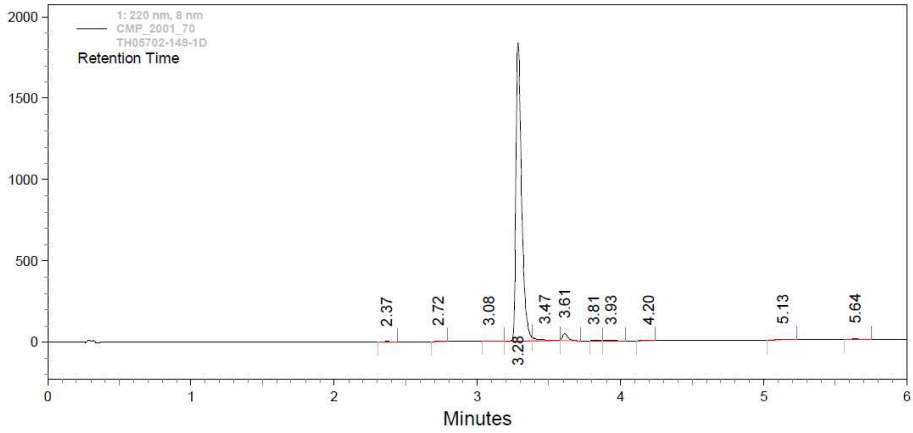
Compound 19d



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.73	2682	9227	0.26
2.01	17306	42971	1.21
3.04	1225413	3494283	98.23
3.77	1350	3700	0.10
4.43	2773	7185	0.20

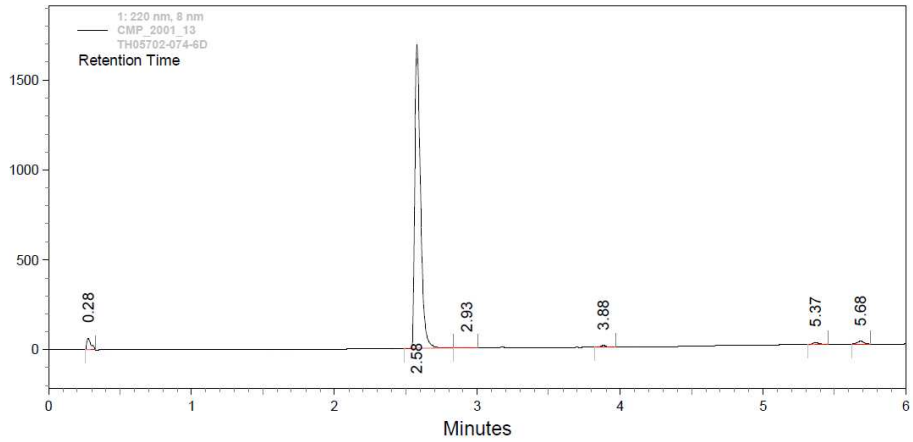
Compound 19e



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.37	2208	5532	0.11
2.72	3053	7492	0.14
3.08	2256	7608	0.14
3.28	1819825	5027596	95.46
3.47	5322	55662	1.06
3.61	39467	109407	2.08
3.81	2156	4917	0.09
3.93	3938	13075	0.25
4.20	3303	9218	0.18
5.13	2204	9773	0.19
5.64	4685	16596	0.32

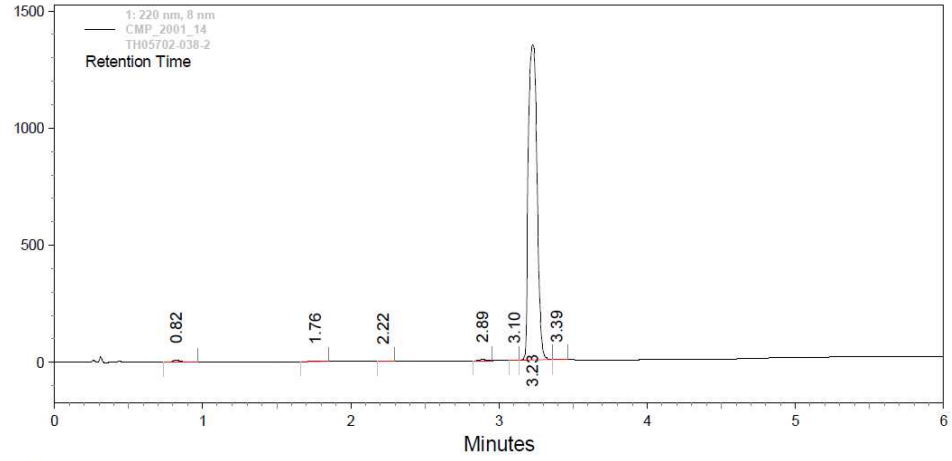
Compound 19f



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.28	50293	121354	2.43
2.58	1653786	4753557	95.31
2.93	1963	10076	0.20
3.88	7598	20438	0.41
5.37	11352	33939	0.68
5.68	14185	48035	0.96

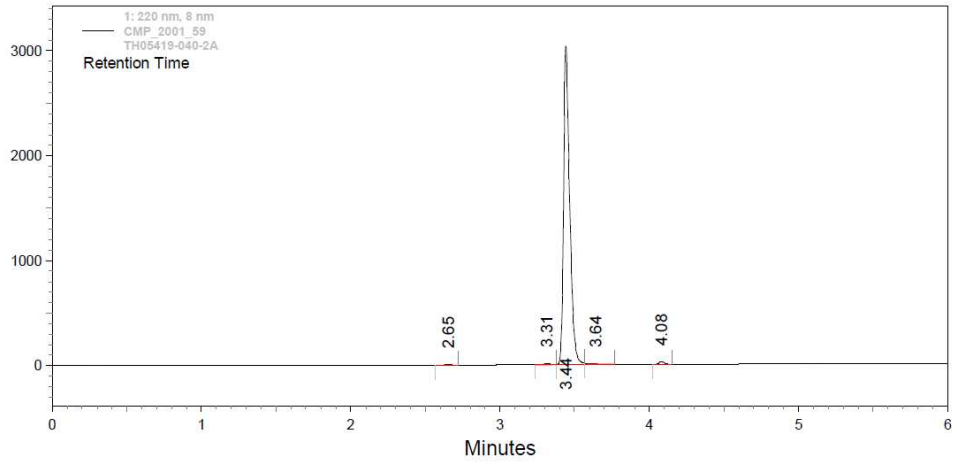
Compound 19g



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.82	11084	41576	0.76
1.76	2692	9518	0.17
2.22	2603	7098	0.13
2.89	7014	16643	0.30
3.10	815	1858	0.03
3.23	1345420	5424034	98.50
3.39	2918	5835	0.11

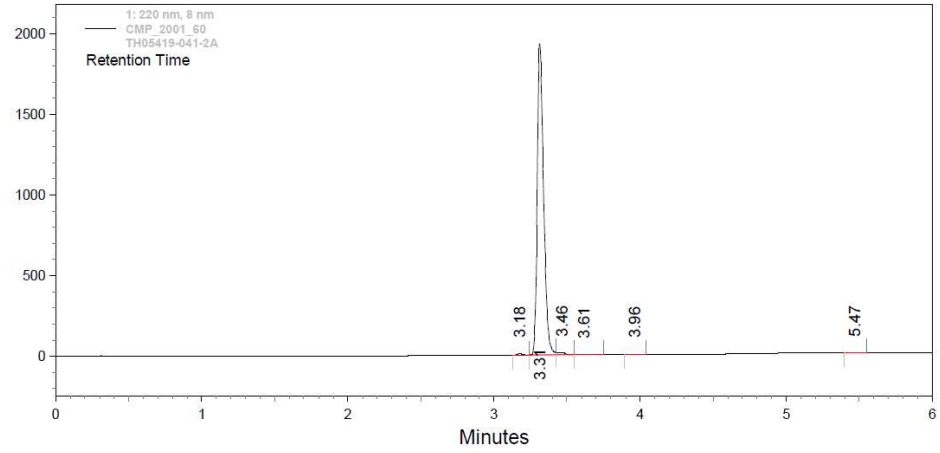
Compound 19h



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.65	4281	12457	0.14
3.31	13610	42528	0.49
3.44	2926534	8558841	98.01
3.64	5005	56175	0.64
4.08	23601	62458	0.72

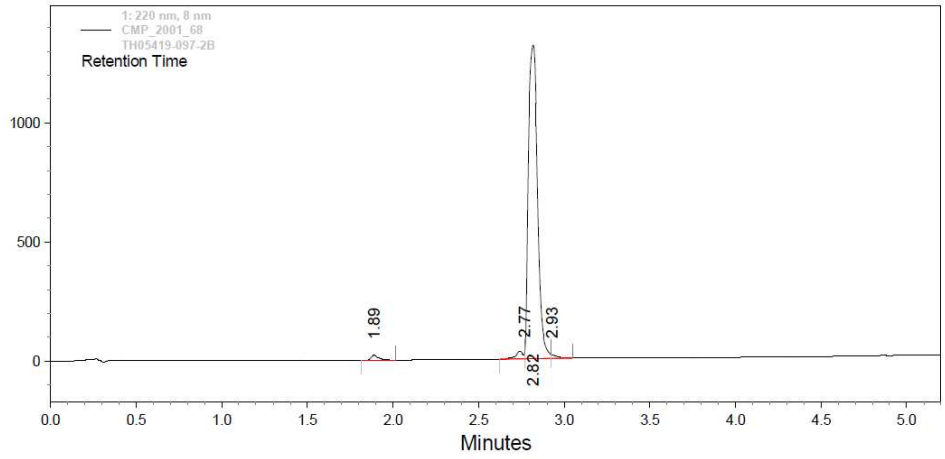
Compound 19i



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
3.18	9706	24274	0.41
3.31	1869266	5770800	98.35
3.46	12172	47956	0.82
3.61	1465	5944	0.10
3.96	4231	12703	0.22
5.47	1434	5666	0.10

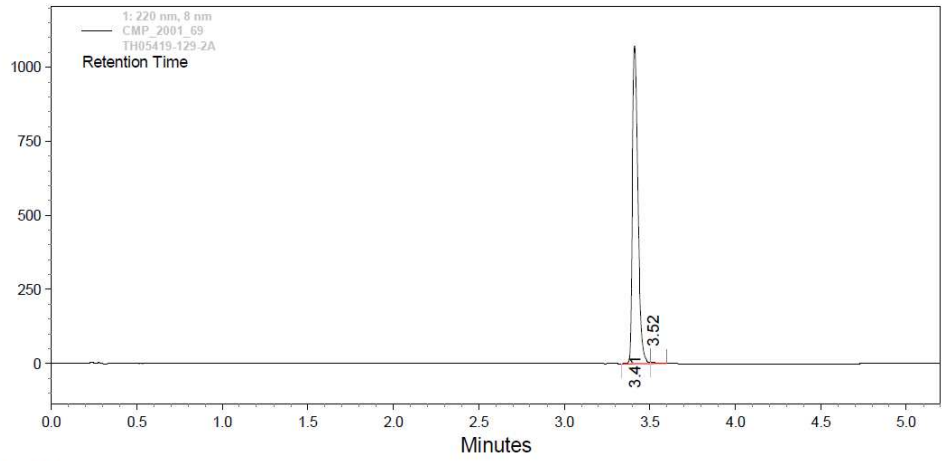
Compound 19j



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
1.89	19658	59812	1.17
2.77	72141	94405	1.84
2.82	1310362	4923237	96.13
2.93	14962	44026	0.86

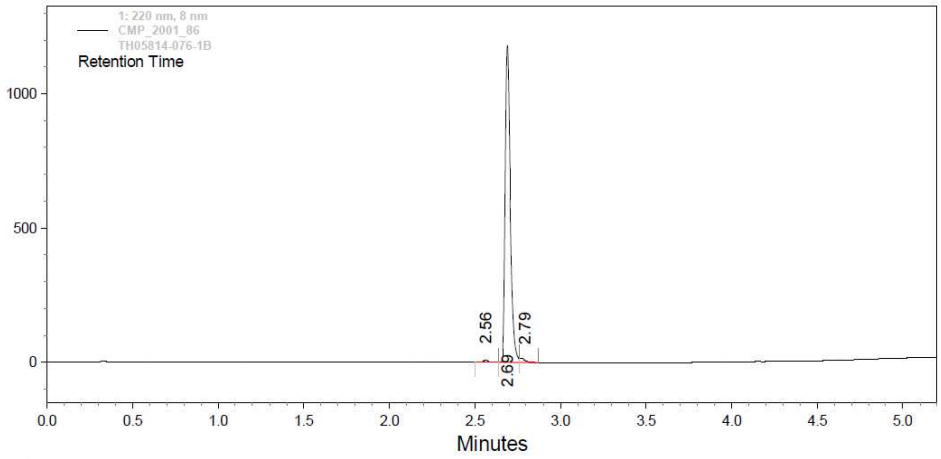
Compound 19k



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
3.41	1059247	2407045	99.63
3.52	3363	8855	0.37

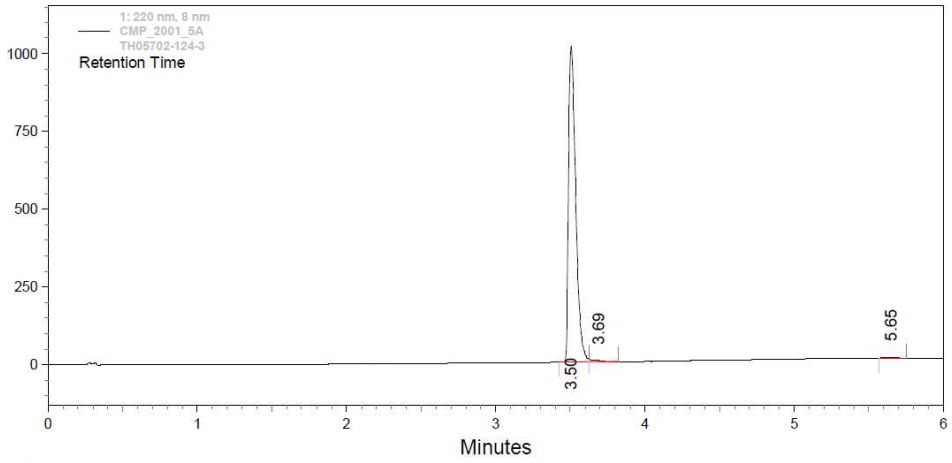
Compound 19l



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.56	7783	19130	0.77
2.69	1127819	2429308	97.88
2.79	5947	33415	1.35

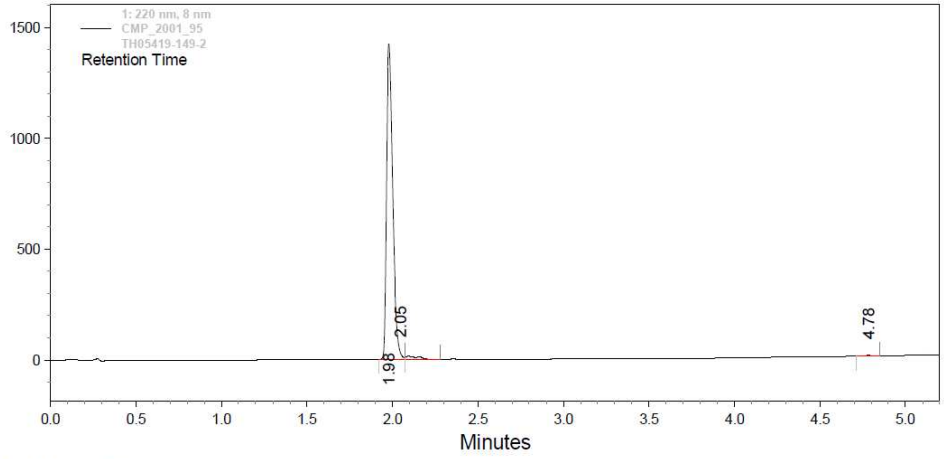
Compound 19m



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
3.50	999780	3373596	98.88
3.69	3254	27330	0.80
5.65	2930	10874	0.32

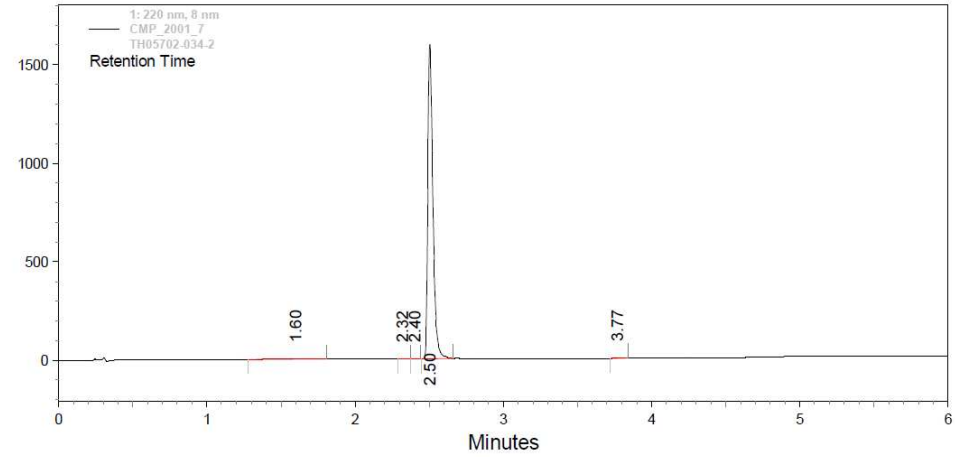
Compound 19n



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
1.98	1408143	3594339	97.99
2.05	17232	64895	1.77
4.78	3067	9007	0.25

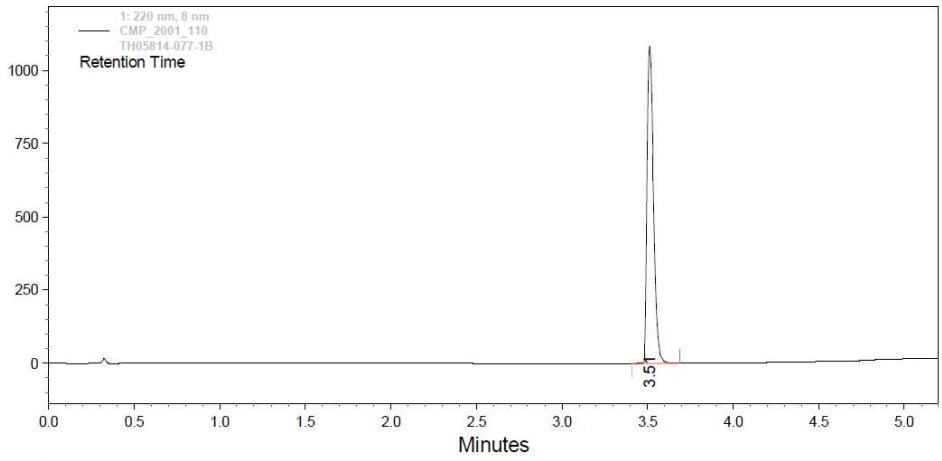
Compound 19o



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
1.60	4362	56279	1.45
2.32	909	2703	0.07
2.40	1523	2741	0.07
2.50	1555903	3805290	98.14
3.77	3900	10206	0.26

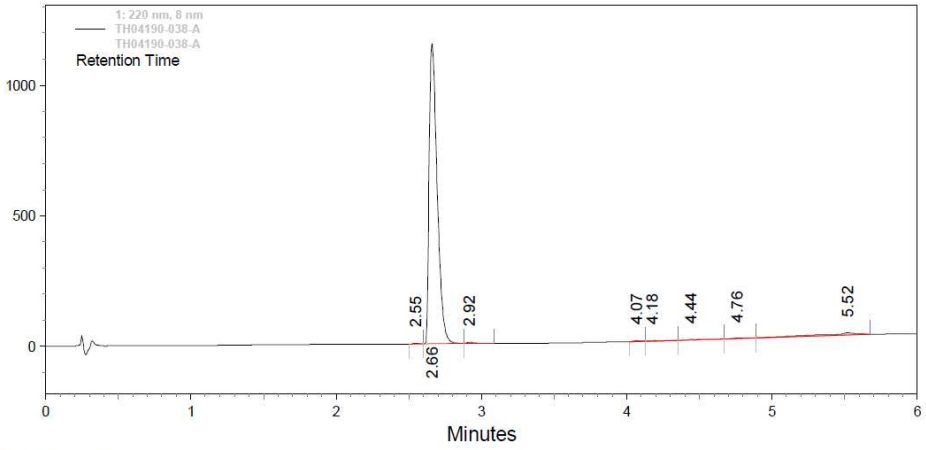
Compound 19p



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
3.51	1058522	2792921	100.00

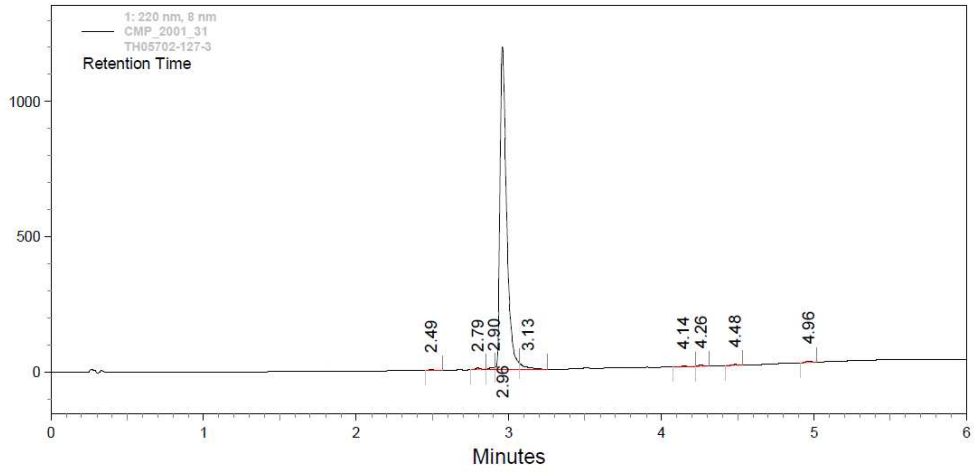
Compound 20a



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.55	3225	8529	0.18
2.66	1145745	4416883	95.45
2.92	4770	17847	0.39
4.07	3830	14497	0.31
4.18	1748	13377	0.29
4.44	1624	10097	0.22
4.76	1976	13714	0.30
5.52	7047	132430	2.86

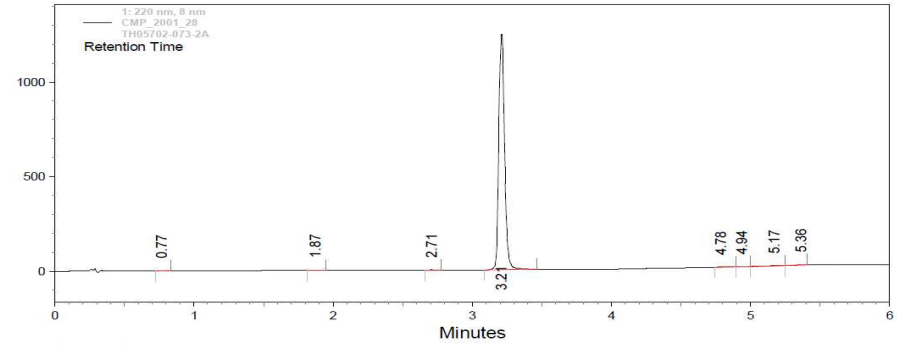
Compound 20b



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.49	3172	6850	0.18
2.79	4329	11072	0.30
2.90	5273	11743	0.32
2.96	1118856	3589961	96.71
3.13	5052	47269	1.27
4.14	2265	7259	0.20
4.26	5092	12388	0.33
4.48	3652	9455	0.25
4.96	6331	16001	0.43

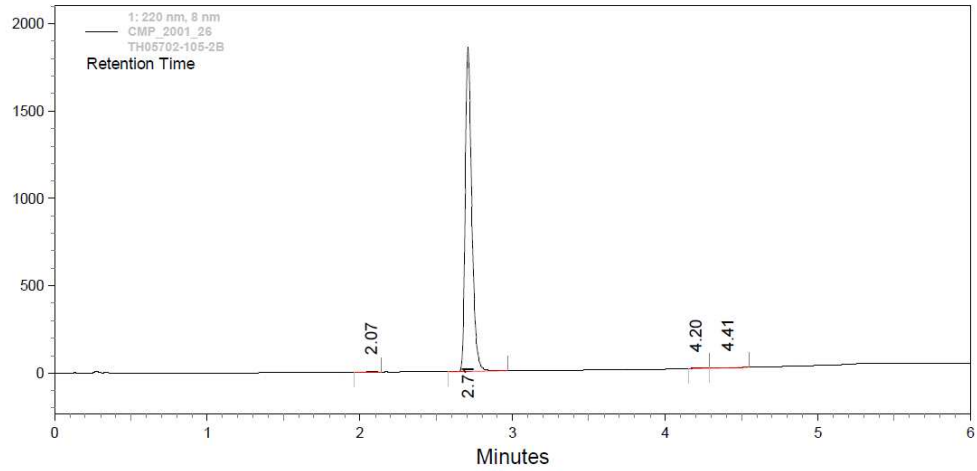
Compound 20c



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
0.77	1335	3687	0.10
1.87	1321	4007	0.11
2.71	2361	4888	0.13
3.21	1238508	3588542	99.09
4.78	771	2574	0.07
4.94	984	2847	0.08
5.17	1413	7398	0.20
5.36	1948	7641	0.21

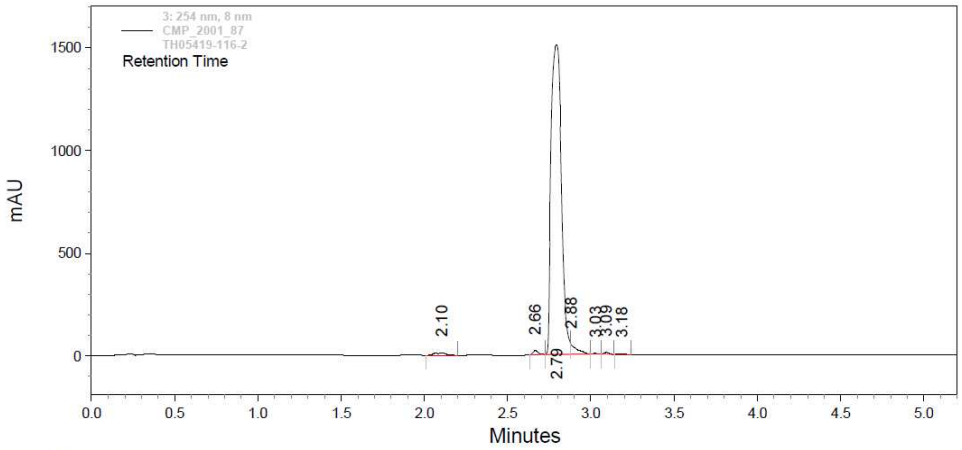
Compound 21a



1: 220 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.07	4448	15492	0.28
2.71	1839583	5539780	99.59
4.20	701	2327	0.04
4.41	1079	5133	0.09

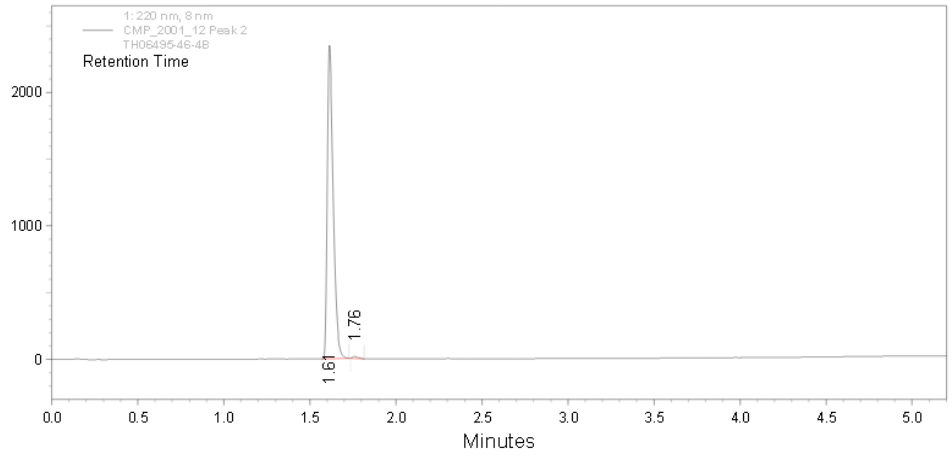
Compound 21b



3: 254 nm, 8 nm

Retention Time	*Height*	*Area*	*Area Percent*
2.10	13371	57640	0.86
2.66	19474	45756	0.68
2.79	1498949	6471428	96.16
2.88	42065	116223	1.73
3.03	4091	7877	0.12
3.09	9621	19399	0.29
3.18	4351	11663	0.17

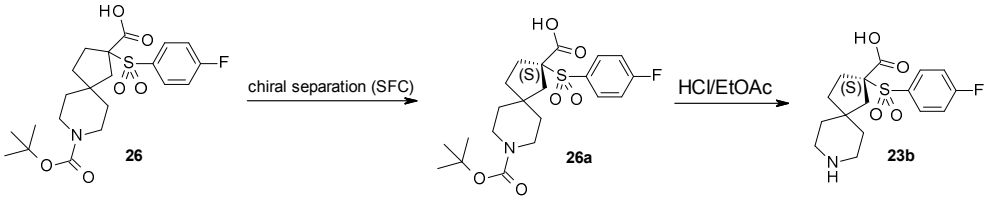
Compound 22



1: 220 nm, 8 nm

Retention Time	***Height***	***Area***	***Area Percent***
1.61	2322641	5618005	99.46
1.76	14640	30406	0.54

Synthesis of (3*S*)-3-(4-fluorophenyl)sulfonyl-8-azaspiro[4.5]decane-3-carboxylic acid (23b)



A racemic mixture of compound **26**[1] was first separated by SFC. Then, enantiomerically pure **26a** (60 mg, 0.14 mmol) was dissolved in HCl/EtOAc (2 N, 10 mL) and the mixture was stirred at RT for 1 h. Then, concentrated to give the crude product which was purified by prep-HPLC to obtained pure compound **23b** (30 mg, 59%) as a yellow oil. MS *m/z* 342 $[M + H]^+$ calc. for $C_{16}H_{20}FNO_4S$. ^1H NMR (MeOD, 400 MHz): δ 7.97-7.94 (m, 2H), 7.38-7.34 (m, 2H), 3.21-3.15 (m, 4H), 2.53-2.50 (m, 2H), 2.45-2.38 (m, 2H), 1.88-1.84 (m, 3H), 1.70-1.67 (m, 3H).

Protocol for compound 23b crystallization

We confirm the structure of compound **23b** by X-ray single crystal diffraction analysis. Compound **23b** was dissolved in a three-phase solvent system CH_2Cl_2/MeOH/THF (10:1:1) and slow evaporation at room temperature for three days led to creation of crystals which were utilized for X-ray diffraction analysis on a rigaku saturn diffractometer using graphic-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved using the SHELXS program and refined with SHELXL.

X-ray crystallographic data of compound 23b

Crystal size	0.20×0.18×0.12 mm^3
Radiation type	Mo Kα (?λ = 0.71073 Å)
Space group	Orthorhombic / P2(1)2(1)2(1)
Cell size	a = 7.2894(15) Å b = 11.834(2) Å c = 21.401(4) Å α = 90.00° β = 90.00° γ = 90.00°
Cell volume	V=1846.1(6) $Å^3$
Cell formula units	Z = 4
Crystal density	D_c = 1.359 Mg/m^3
Crystal F(000)	792.0
Absorpt coefficient mu	μ(Mo Kα)=0.348 mm^{-1}
Limiting indices	-7 ≤ h ≤ 9 -15 ≤ k ≤ 15 -24 ≤ l ≤ 28
Cell measurement temperature	T = 293(2) K.

Details for compound 23b coordinates

Table 1. Crystal data and structure refinement for **23b**

Empirical formula	C16 H21 Cl F N O4 S
Formula weight	377.85
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 7.2894(15)A alpha = 90 deg. b = 11.834(2)A beta = 90 deg. c = 21.401(4) A gamma = 90 deg.
Volume	1846.1(6) A^3
Z, Calculated density	4, 1.359 Mg/m^3
Absorption coefficient	0.348 mm^-1
F(000)	792
Crystal size	0.20 x 0.18 x 0.12 mm
Theta range for data collection	1.90 to 27.96 deg.
Limiting indices	-7<=h<=9, -15<=k<=15, -24<=l<=28

Reflections collected / unique	17535 / 4398 [R(int) = 0.0461]
Completeness to theta = 27.96	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9594 and 0.9336
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4398 / 3 / 225
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0509, wR2 = 0.1117
R indices (all data)	R1 = 0.0645, wR2 = 0.1198
Absolute structure parameter	-0.02(8)
Extinction coefficient	0.025(2)
Largest diff. peak and hole	0.273 and -0.237 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **23b**(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	9763(1)	6512(1)	1995(1)	47(1)
F(1)	4549(3)	2780(2)	1722(1)	107(1)
O(1)	12893(3)	6339(2)	668(1)	78(1)
O(2)	10158(3)	5511(2)	639(1)	67(1)
O(3)	11425(3)	6031(2)	2248(1)	58(1)
O(4)	8827(3)	7373(2)	2350(1)	65(1)
N(1)	11794(3)	11312(2)	374(1)	58(1)
C(1)	11310(4)	6296(2)	827(1)	48(1)
C(2)	10394(4)	7167(2)	1248(1)	43(1)
C(3)	8678(4)	7717(2)	937(1)	51(1)
C(4)	8854(4)	8979(2)	1064(1)	50(1)
C(5)	10943(4)	9203(2)	1051(1)	42(1)
C(6)	11693(4)	8163(2)	1415(1)	49(1)
C(7)	11526(4)	10293(2)	1377(1)	55(1)
C(8)	10994(5)	11352(2)	1014(2)	60(1)
C(9)	11698(4)	9226(2)	377(1)	47(1)
C(10)	11171(4)	10288(2)	26(1)	52(1)
C(11)	8177(4)	5398(2)	1875(1)	45(1)
C(12)	8823(5)	4301(2)	1803(1)	53(1)
C(13)	7578(5)	3406(3)	1749(2)	60(1)
C(14)	5758(5)	3654(3)	1773(2)	66(1)
C(15)	5086(5)	4719(3)	1857(2)	78(1)
C(16)	6319(4)	5619(3)	1911(2)	64(1)
Cl(1)	6149(1)	1346(1)	262(1)	55(1)

Table 3. Bond lengths [A] and angles [deg] for **23b**

S(1)-O(4)	1.443(2)
S(1)-O(3)	1.444(2)
S(1)-C(11)	1.772(3)
S(1)-C(2)	1.836(3)
F(1)-C(14)	1.364(4)
O(1)-C(1)	1.205(3)
O(2)-C(1)	1.316(3)
O(2)-H(2)	0.8200
N(1)-C(8)	1.490(4)
N(1)-C(10)	1.493(4)
N(1)-H(1A)	0.916(10)
N(1)-H(1B)	0.915(10)
C(1)-C(2)	1.522(4)
C(2)-C(6)	1.553(4)
C(2)-C(3)	1.558(4)
C(3)-C(4)	1.523(4)
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(4)-C(5)	1.546(4)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(5)-C(7)	1.528(4)
C(5)-C(9)	1.542(4)
C(5)-C(6)	1.556(4)
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-C(8)	1.524(4)
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-C(10)	1.515(4)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-H(10A)	0.9700
C(10)-H(10B)	0.9700
C(11)-C(16)	1.382(4)
C(11)-C(12)	1.390(4)
C(12)-C(13)	1.399(4)
C(12)-H(12)	0.9300
C(13)-C(14)	1.360(5)
C(13)-H(13)	0.9300
C(14)-C(15)	1.364(5)
C(15)-C(16)	1.398(5)
C(15)-H(15)	0.9300
C(16)-H(16)	0.9300
O(4)-S(1)-O(3)	118.50(14)
O(4)-S(1)-C(11)	107.06(13)
O(3)-S(1)-C(11)	107.96(13)
O(4)-S(1)-C(2)	106.22(12)
O(3)-S(1)-C(2)	106.49(12)
C(11)-S(1)-C(2)	110.55(12)
C(1)-O(2)-H(2)	109.5
C(8)-N(1)-C(10)	111.4(2)
C(8)-N(1)-H(1A)	111.3(19)
C(10)-N(1)-H(1A)	108(2)
C(8)-N(1)-H(1B)	109.3(19)

C(10)-N(1)-H(1B)	108(2)
H(1A)-N(1)-H(1B)	109.3(15)
O(1)-C(1)-O(2)	123.7(3)
O(1)-C(1)-C(2)	124.0(3)
O(2)-C(1)-C(2)	112.3(2)
C(1)-C(2)-C(6)	112.5(2)
C(1)-C(2)-C(3)	112.5(2)
C(6)-C(2)-C(3)	105.7(2)
C(1)-C(2)-S(1)	109.77(18)
C(6)-C(2)-S(1)	105.79(17)
C(3)-C(2)-S(1)	110.29(19)
C(4)-C(3)-C(2)	105.4(2)
C(4)-C(3)-H(3A)	110.7
C(2)-C(3)-H(3A)	110.7
C(4)-C(3)-H(3B)	110.7
C(2)-C(3)-H(3B)	110.7
H(3A)-C(3)-H(3B)	108.8
C(3)-C(4)-C(5)	104.3(2)
C(3)-C(4)-H(4A)	110.9
C(5)-C(4)-H(4A)	110.9
C(3)-C(4)-H(4B)	110.9
C(5)-C(4)-H(4B)	110.9
H(4A)-C(4)-H(4B)	108.9
C(7)-C(5)-C(9)	108.2(2)
C(7)-C(5)-C(4)	114.2(2)
C(9)-C(5)-C(4)	111.8(2)
C(7)-C(5)-C(6)	110.0(2)
C(9)-C(5)-C(6)	110.9(2)
C(4)-C(5)-C(6)	101.6(2)
C(2)-C(6)-C(5)	105.7(2)
C(2)-C(6)-H(6A)	110.6
C(5)-C(6)-H(6A)	110.6
C(2)-C(6)-H(6B)	110.6
C(5)-C(6)-H(6B)	110.6
H(6A)-C(6)-H(6B)	108.7
C(8)-C(7)-C(5)	113.0(2)
C(8)-C(7)-H(7A)	109.0
C(5)-C(7)-H(7A)	109.0
C(8)-C(7)-H(7B)	109.0
C(5)-C(7)-H(7B)	109.0
H(7A)-C(7)-H(7B)	107.8
N(1)-C(8)-C(7)	110.0(2)
N(1)-C(8)-H(8A)	109.7
C(7)-C(8)-H(8A)	109.7
N(1)-C(8)-H(8B)	109.7
C(7)-C(8)-H(8B)	109.7
H(8A)-C(8)-H(8B)	108.2
C(10)-C(9)-C(5)	112.9(2)
C(10)-C(9)-H(9A)	109.0
C(5)-C(9)-H(9A)	109.0
C(10)-C(9)-H(9B)	109.0
C(5)-C(9)-H(9B)	109.0
H(9A)-C(9)-H(9B)	107.8
N(1)-C(10)-C(9)	110.4(2)
N(1)-C(10)-H(10A)	109.6
C(9)-C(10)-H(10A)	109.6
N(1)-C(10)-H(10B)	109.6
C(9)-C(10)-H(10B)	109.6
H(10A)-C(10)-H(10B)	108.1
C(16)-C(11)-C(12)	121.0(3)
C(16)-C(11)-S(1)	119.4(2)

C(12)-C(11)-S(1)	119.3(2)
C(11)-C(12)-C(13)	119.8(3)
C(11)-C(12)-H(12)	120.1
C(13)-C(12)-H(12)	120.1
C(14)-C(13)-C(12)	117.8(3)
C(14)-C(13)-H(13)	121.1
C(12)-C(13)-H(13)	121.1
C(13)-C(14)-F(1)	117.6(4)
C(13)-C(14)-C(15)	123.7(3)
F(1)-C(14)-C(15)	118.7(3)
C(14)-C(15)-C(16)	118.9(3)
C(14)-C(15)-H(15)	120.5
C(16)-C(15)-H(15)	120.5
C(11)-C(16)-C(15)	118.8(3)
C(11)-C(16)-H(16)	120.6
C(15)-C(16)-H(16)	120.6

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