Supporting Information

Design and Synthesis of Bicyclic Pyrimidinones as Potent and Orally Bioavailable HIV-1 Integrase Inhibitors.

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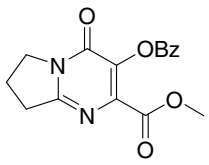
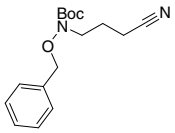
Table of Contents

Syntheses of intermediates:

Methyl 3-(benzoyloxy)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-2-carboxylate (30a).

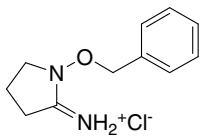


<u>Step 1.</u> tert-butyl benzyloxy(3-cyanopropyl)carbamate.



Prepared as described in literature,[1] from 4-chlorovaleronitrile. The crude oily residue obtained after workup was purified by flash column chromatography (silica gel/petroleum ether-ethyl acetate 15:1) to yield the title compound as a light yellow oil (65%). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 7.39-7-30 (m, 5H), 4.82 (s, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.90-1.82 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 156.3, 135.3, 129.5, 128.7, 128.5, 119.1, 82.0, 77.0, 48.1, 28.3, 23.5, 14.9. MS *m/z*: 313 $(M+Na)^+$, 291 $[(M-Boc)+H]^+$.

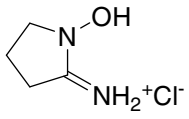
<u>Step 2.</u> 1-(benzyloxy)pyrrolidin-2-imine hydrochloride.



[1] Bergeron, R. J. and McManis, J. S. The Total Synthesis of Bisucaberin. *Tetrahedron* **1989,** *45*, 4939-4944.

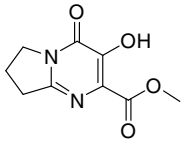
A solution of *tert*-butyl benzyloxy(3-cyanopropyl)carbamate (5.60 g, 19.31 mmol) in a 4M solution of HCl in 1,4-dioxane (200 mL) was stirred for 4 h at room temperature. The solvent was removed under reduced pressure and the solid residue was treated with diethyl ether, filtered and dried under high vacuum to give the title as white solid (4.14 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 9.76 (s, 1H), 9.23 (s, 1H), 7.59-7.53 (m, 2H), 7.45-7.40 (m, 3H), 5.07 (s, 2H), 3.77 (t, J = 7.1 Hz, 2H), 2.78 (t, J = 7.7 Hz, 2H), 2.06-1.97 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ 163.8, 133.7, 129.9, 129.3, 128.5, 75.9, 49.9, 26.8, 16.2. MS *m/z*: 191 $(M+H)^+$.

<u>Step 3.</u> 2-iminopyrrolidin-1-ol hydrochloride.



A solution of 1-(benzyloxy)pyrrolidin-2-imine hydrochloride (4.14 g, 18.3 mmol) in methanol (60 mL), containing of palladium on charcoal (10% w/w) (0.400 g) was stirred under hydrogen at atmospheric pressure for 2.5 h. The catalyst was filtered off and the solution was concentrated to dryness under reduced pressure. The residue was triturated with diethyl ether, filtered and dried under high vacuum to afford 2-iminopyrrolidin-1-ol hydrochloride (2.44 g, yield 98%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 11.89 (bs, 1H), 9.14 (s, 1H), 8.64 (s, 1H), 3.77 (t, J = 7.3 Hz, 2H), 2.79 (t, J = 7.9 Hz, 2H), 2.11-1.98 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ 161.3, 52.9, 26.8, 16.1. MS *m/z*: 101 $(M+H)^+$.

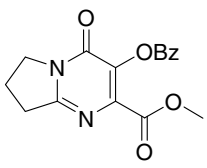
<u>Step 4.</u> Methyl 3-hydroxy-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-2-carboxylate (29a).



To a solution of 2-iminopyrrolidin-1-ol hydrochloride (0.050 g, 0.36 mmol) in chloroform (3 mL), Et_3N (54.5 g, 0.54 mmol) was added at room temperature. The mixture was then cooled to -30 °C before the addition, dropwise under stirring, of dimethylacetylenedicarboxylate (0.057 g, 0.40 mmol) in chloroform (0.5 mL). After 1h the solvent was removed under reduced pressure. To the resulting crude, anhydrous *o*-xylene (2 mL) was added and the mixture was heated under vigorous stirring at 150 °C (oil bath temperature) for 2 h, then the solvent was evaporated under reduced pressure. The residue was treated with MeOH and filtered, the filtrate was evaporated and methyl 3-hydroxy-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-2-carboxylate **29a** was isolated by preparative RP-HPLC to get (0.014 g, yield 19% from 2-iminopyrrolidin-1-ol hydrochloride). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 10.19 (s, 1H), 3.99 (t, J = 7.3 Hz, 2H), 3.80 (s, 3H), 2.92 (t, J = 7.9 Hz, 2H), 2.20-2.10 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, 300 K) δ 166.4, 157.1, 153.6, 144.6, 128.3, 52.1, 46.8, 30.9, 19.5. MS *m/z*: 211 $(M+H)^+$.

Alternatively, crude **29a** could be used in the next step, as described below.

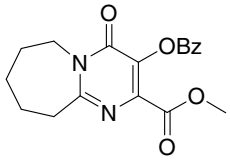
<u>Step 5.</u> Methyl 3-(benzoyloxy)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidine-2-carboxylate (30a).



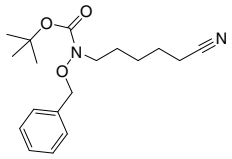
To a mixture of 2-iminopyrrolidin-1-ol hydrochloride (1.20 g, 8.80 mmol) and TEA (1.33 g, 13.2 mmol) in chloroform (60 mL) at 0 °C, a solution of dimethylacetylene dicarboxylate (1.50 g, 10.56 mmol) in chloroform (10 mL) was added dropwise. After 1h at 0 °C, the mixture was evaporated at reduced pressure. To the resulting crude, anhydrous *o*-xylene (40 mL) was added and the mixture was heated under vigorous stirring at 150 °C (oil bath temperature) for 4 h, then the solvent was evaporated under reduced pressure. Crude **29a** was taken in MeOH and the solid filtered off, the filtrate was evaporated, diluted with pyridine (40 mL) and benzoic anhydride (2.39 g, 10.56 mmol) added in one portion. The mixture was stirred at room temperature for 12 h, before being concentrated at reduced pressure. The residue was diluted with EtOAc, washed with $NaHCO_3$ aq. saturated solution, 1N HCl, brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 3:1, then AcOEt) to obtain 0.67 g a 2:1 mixture (by NMR) of desired **30a** (corresponding to a 17% yield from 2-iminopyrrolidin-1-ol hydrochloride) and 4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidin-3-yl benzoate as white solid. Crystallization of the above mixture from ethyl acetate enriched it in **30a** compound up to 6:1 (88% w/w). Analytical samples of **30a** and of 4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidin-3-yl benzoate were obtained by preparative RP-HPLC. **30a**: ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 8.67 (d, J = 7.2 Hz, 2H), 8.29 (t, J = 7.4 Hz, 1H), 8.18-8.10 (m, 2H), 4.64 (t, J = 7.4 Hz, 2H), 4.31 (s, 3H), 3.64 (t, J = 8.1 Hz, 2H), 2.87-2.78 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, 300 K) δ 163.1, 163.0, 162.8, 156.0, 142.4, 136.0, 134.4, 129.8, 129.1, 127.8, 52.7, 47.6, 31.9, 19.2. MS *m/z*: 315 $(M+H)^+$. 4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidin-3-yl benzoate: ^{1}H NMR (400 MHz, DMSO d_6, 300 K) δ 8.69 (d, J = 7.4 Hz,

2H), 8.42 (s, 1H), 8.27 (t, J = 7.4 Hz, 1H), 8.16-8.09 (m, 2H), 4.63 (t, J = 7.4 Hz, 2H), 3.61 (t, J = 8.1 Hz, 2H), 2.86-2.76 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ 163.5, 163.3, 155.5, 144.5, 136.3, 134.2, 129.8, 129.0, 128.0, 47.2, 31.8, 19.4. MS *m/z*: 257 $(M+H)^+$.

methyl 3-(benzoyloxy)-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate. (30c)

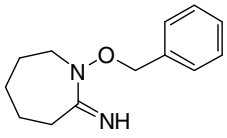


<u>Step 1.</u> *tert*-butyl (benzyloxy)(5-cyanopentyl)carbamate.



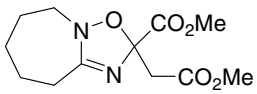
Prepared as described in literature[1] from 6-bromohexanenitrile.^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 7.39-7.32 (m, 5H), 4.78 (s, 2H), 3.39 (t, J = 6.8 Hz, 2H), 2.49 (t, J = 6.5 Hz, 2H), 1.58-1.49 (m, 4H), 1.43 (s, 9H), 1.36-1.31 (m, 2H). MS *m/z*: 319 $(M+H)^+$.

<u>Step 2.</u> 1-(Benzyloxy)azepan-2-imine.



Tert-butyl-(benzyloxy)-(5-cyanopentyl)-carbamate (12.97 g, 40.8 mmol) was dissolved in HCl in EtOH s.s (50 ml) and the mixture was stirred for 45 minutes. The excess of HCl was removed with a nitrogen stream and the solvent was removed under reduced pressure. The residue, dissolved in 1,4-dioxane (200 mL), was treated with TEA (6.2 g, 61.2 mmol) to adjust pH at 10. The mixture was stirred overnight. After solvent removal, crude 1-(benzyloxy)azepan-2-imine was used in the next step without further purification as described below. An analytical sample was purified by preparative RP-HPLC and characterized as a trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 9.39 (s, 1H), 8.81 (s, 1H), 7.61-7.52 (m, 2H), 7.48-7.38 (m, 3H), 5.03 (s, 2H), 4.02-3.93 (m, 2H), 2.70-2.59 (m, 2H), 1.69-1.54 (m, 6H). MS *m/z*: 219 $(M+H)^+$.

<u>Step 3.</u> Methyl 2-(2-methoxy-2-oxoethyl)-2,5,6,7,8,9-hexahydro[1,2,4]oxadiazolo[2,3-*a*]azepine-2-carboxylate.[2]

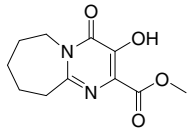


A solution of crude 1-(benzyloxy)azepan-2-imine synthesized as described above (40.8 mmol, theoretical amount) in methanol (400 ml), containing palladium on charcoal (10%, w/w) (1 g) was stirred under hydrogen at atmospheric pressure overnight. The catalyst was filtered off and the solution was concentrated to dryness under reduced pressure. The residue was triturated with HCl in diethyl ether obtaining 1-hydroxyazepan-2-iminium chloride MS *m/z*: 129 $(M+H)^+$. 1-hydroxyazepan-2-iminium chloride was dissolved in

[2] Ferrara,M.; Crescenzi,B.; Donghi,M.; Gardelli,C.; Muraglia,E.; Nizi,E.; Pesci,S.; Summa,V. Synthesis of an Hexahydropyrimido[1,2-a]azepine-2-carboxamide Derivative Useful as HIV Integrase Inhibitor. *Tetrahedron Lett.*, in press.

chloroform (100 mL) and TEA (4.1 g, 40.8 mmol) was added. The mixture was stirred for 5 min. at room temperature, then cooled to 0 °C and dimethyl acetylenedicarboxylate (5.8 g, 40.8 mmol) was added dropwise under stirring. The mixture was stirred at room temperature for 30 min, washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was filtered through silica gel, and the solvent was removed under vacuum to afford the title compound (3.6 g, 33% over three steps). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 3.68 (s, 3H), 3.58 (s, 3H), 3.43-3.38 (m, 2H), 3.24 (d, J = 15.8 Hz, 1H), 2.86 (d, J = 15.8 Hz, 1H), 2.46-240 (m, 2H), 1.69-1.52 (m, 6H).

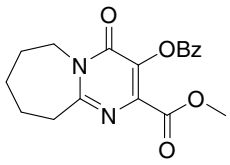
Step 4. methyl 3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate (29c).[2]



Prepared from methyl 2-(2-methoxy-2-oxoethyl)-2,5,6,7,8,9-hexahydro[1,2,4]oxadiazolo[2,3-*a*]azepine-2-carboxylate (step above) as described for **29b**[3].

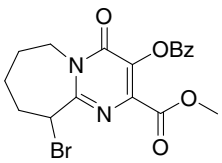
Step 5. Methyl 3-(benzoyloxy)-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate. (30c)

[3] Kinzel, O., Monteagudo, E. S., Muraglia, E., Orvieto, F., Pescatore, G., Rico Ferreira, M. D. R., Rowley, M., and Summa, V. The synthesis of tetrahydropyridopyrimidones as a new scaffold for HIV-1 integrase inhibitors. *Tetrahedron. Lett*., **2007**, *48*, 6552-6555.



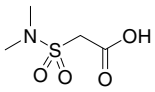
A solution of methyl 2-(2-methoxy-2-oxoethyl)-2,5,6,7,8,9-hexahydro[1,2,4]oxadiazolo[2,3-*a*]azepine-2-carboxylate (5.8 g, 21.3 mmol) in *o*-xylene (98 mL) was heated under vigorous stirring at 160 °C (oil bath temperature) for 5 h, then the solvent was evaporated under reduced pressure. The residue was diluted with pyridine (56 mL) and benzoic anhydride (6.4 g, 27.7 mmol) added in one portion. The mixture was stirred at room temperature overnight before being concentrated at reduced pressure. The residue was diluted with EtOAc, washed with $NaHCO_3$ aq. saturated solution, 1N HCl, brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 3:2) to obtain the title product **30c** in 59% yield. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 8.07 (d, J = 7.3 Hz, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 4.31-4.29 (m, 2H), 3.74 (s, 3H), 3.07-3.04 (m, 2H), 1.82-1.65 (m, 6H). ^{13}C NMR (75 MHz, DMSO-*d*6, 300 K) δ 162.8, 162.7, 162.4, 157.0, 140.3, 135.2, 134.2, 129.6, 128.9, 127.5, 52.5, 43.1, 36.1, 28.5, 26.1, 23.7. MS *m/z*: 343 $(M+H)^+$.

Methyl 3-(benzoyloxy)-10-bromo-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate (31c).



Prepared from **30c** as described for **31b**.[3] ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ 8.09-8.07 (m, 2H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 2H), 5.64 (dd, *J* = 2.2, 5.9 Hz, 1H), 4.98 (dd, *J* = 6.1, 14.3 Hz, 1H), 4.98-3.90 (m, 1H), 3.75 (s, 3H), 2.29-2.12 (m, 2H), 2.09-1.78 (m, 3H), 1.52-1.49 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, 300 K) δ 162.7, 162.1, 157.2, 157.1, 139.4, 136.6, 134.4, 129.7, 128.9, 127.4, 53.6, 52.7, 42.4, 31.5, 25.8, 24.4. MS *m/z*: 423/421 $(M+H)^+$.

[(dimethylamino)sulfonyl]acetic acid



To a solution of (chlorosulfonyl)acetyl chloride (0.100 mL, 0.94 mmol), in DCM (2 mL) was added *tert*-butanol (0.088 mL, 0.94 mmol) and TEA (0.130 mL, 0.94 mmol). The mixture was stirred for 2 h at room temperature and dimethylamine in THF (2M, 2.4 mL) was added. After 15 min the mixture was partitioned between 0.2 M HCl (50 mL) and EtOAc (50 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was dissolved in a mixture of DCM and TFA (1:1, 10 mL) and the mixture was stirred at room temperature for 3 h. The solvents were removed under vacuum and the residue was triturated with Et_2O. The residue was left under high vacuum to afford the title compound as a light brown solid (0.074 g, 48%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 13.3 (s, br, 1H), 4.10 (s, 2H), 2.79 (s, 6H).

Table 1. UPLC and HPLC data for target compounds.

compd.	retention times (min)				
	method				
	1	2	3	4	5
7a	0.89	1.31		1.89	2.99
7b	0.88	1.31		1.90	
7c	0.94	1.49	2.11	1.98	3.16
8b	0.94	1.45			
9b	0.98	1.58			
10b	0.90	1.35	2.03		3.03
10c	1.01	1.63		2.10	
11b	1.10	1.94	2.38		
11c	1.17	2.02			3.85
12a	1.28				4.16
12b	1.39				4.53
12c	1.52				4.92
13a	1.18				3.87
13b	1.21				3.97
13c	1.34				4.31
14b	1.38				4.55
15b	1.30				4.24
16b	1.20				3.92
17b	1.35				4.40
(R)-17b	1.35				4.40
(S)-17b	1.35				4.40

18b	1.24				4.08
18c	1.34				4.38
19b	1.17				3.86
20b	1.37				4.48
20c	1.45				4.75
21b	1.48				4.76
22a	1.41				4.63
22b	1.54				5.01
(S)-22b	1.54				5.00
(R)-22b	1.54				5.00
22c	1.61				5.21
23b	1.51				4.95
23c	1.56				5.10
24b	1.64				5.31
25b	1.77				5.74
26b	1.48				4.79
27b	1.00	1.68			3.33
(S)-27b	1.00	1.69			
(R)-27b	1.00	1.69			
28a	1.18, 1.21				3.86, 3.95
28b	1.23, 1.26				4.00, 4.10
(S)-28b	1.23, 1.26				4.00, 4.10
(R)-28b	1.23, 1.26				4.00, 4.09
28c	1.33, 1.38				4.26, 4.45
(S)-28c	1.33, 1.38				4.26, 4.46
(R)-28c	1.33, 1.38				4.26, 4.45

Method 1: UPLC, column: Waters Acquity UPLC BEH C18 1.7 μm, 2.1x50 mm.

Initial conditions: 10% ACN (0.1 min), then gradient to 100% ACN in 2 min.

Flow rate 0.5 ml/min.

Method 2: UPLC, column: Waters Acquity UPLC BEH C18 1.7 μm, 2.1x50 mm.

Initial conditions: 10% ACN (0.1 min), then gradient to 50% ACN in 2.3 min.

Flow rate 0.5 ml/min.

Method 3: UPLC, column: Waters Acquity UPLC BEH C18 1.7 μm, 2.1x50 mm.

Initial conditions: 0% ACN (0.5 min), then gradient to 50% ACN in 1.9 min.

Flow rate 0.5 ml/min.

Method 4: UPLC, column: Waters Aquity HSS T3 1.8 μm, 2.1x50 mm.

Initial conditions: 0% ACN (0.5 min), then gradient to 50% ACN in 1.9 min.

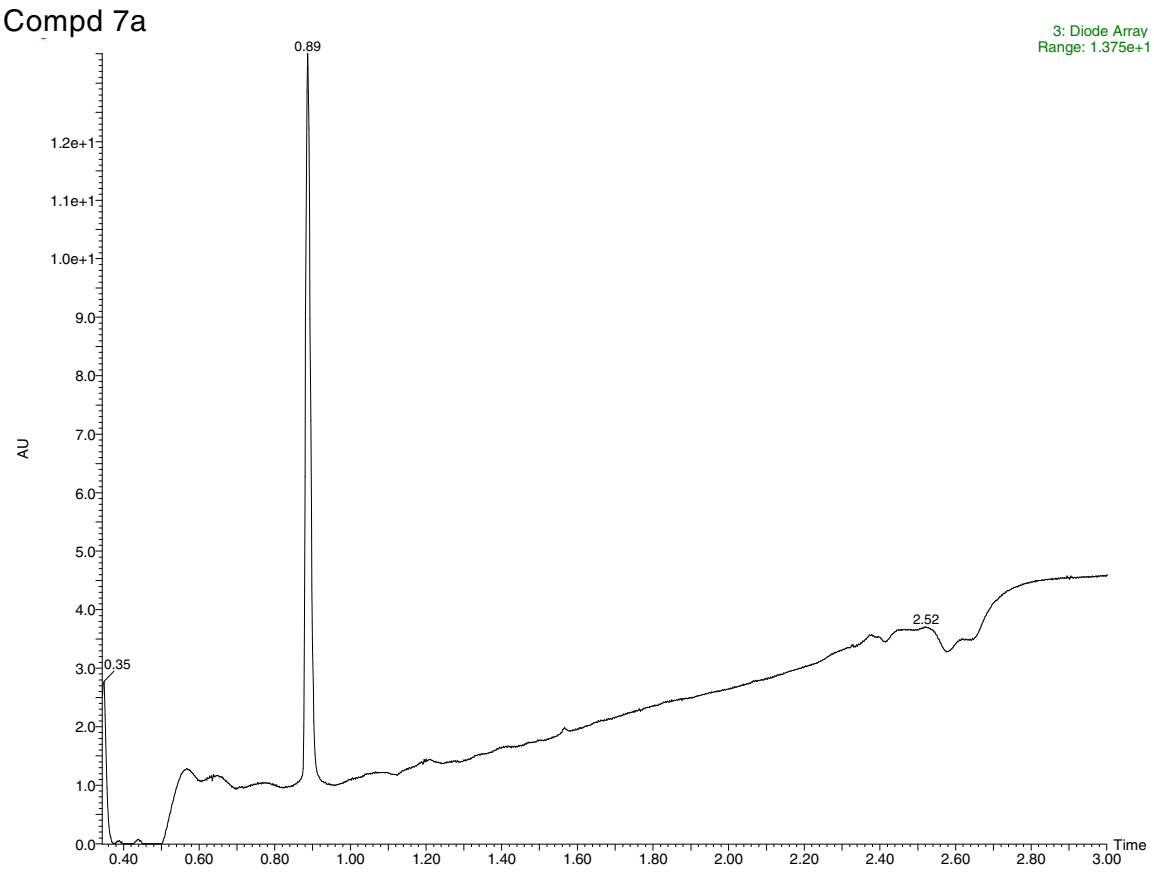
Flow rate 0.5 ml/min.

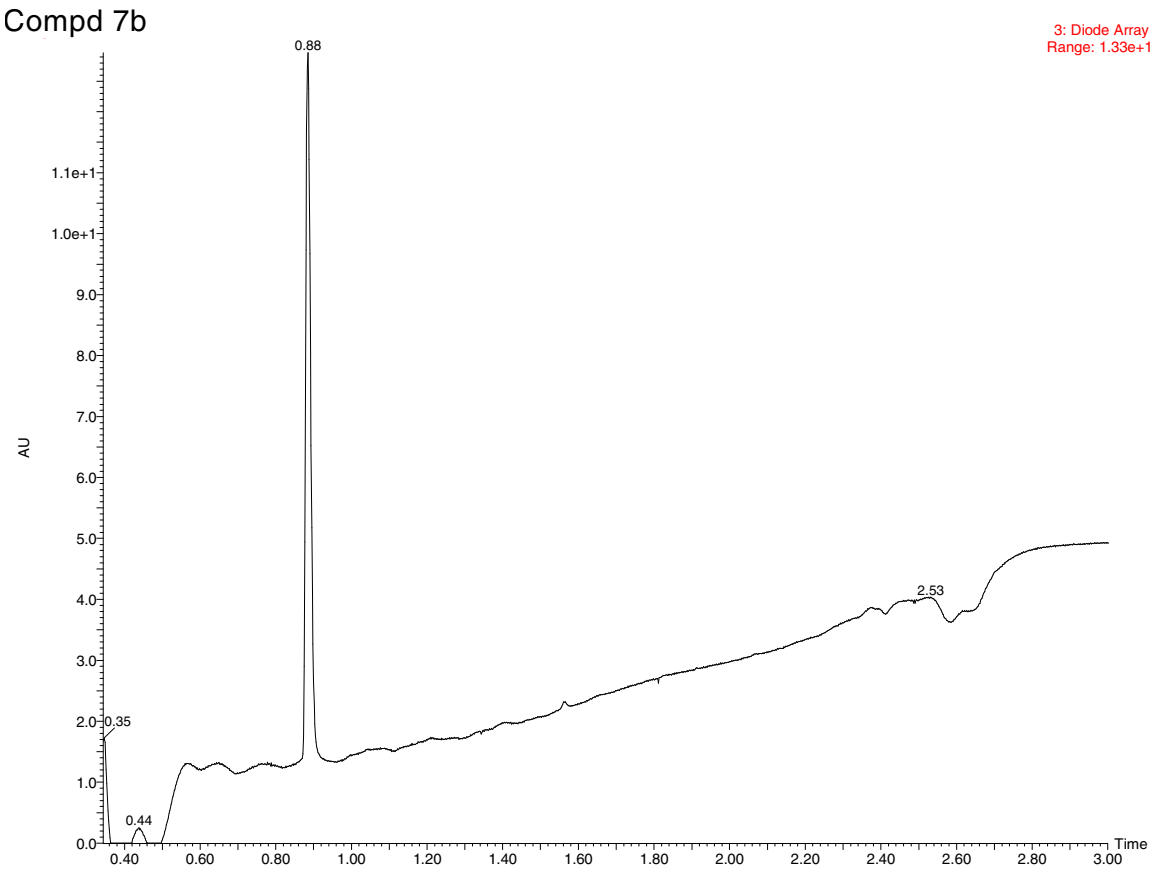
Method 5: HPLC, column: Waters XBridge C18 5 μm, 4.6x100 mm.

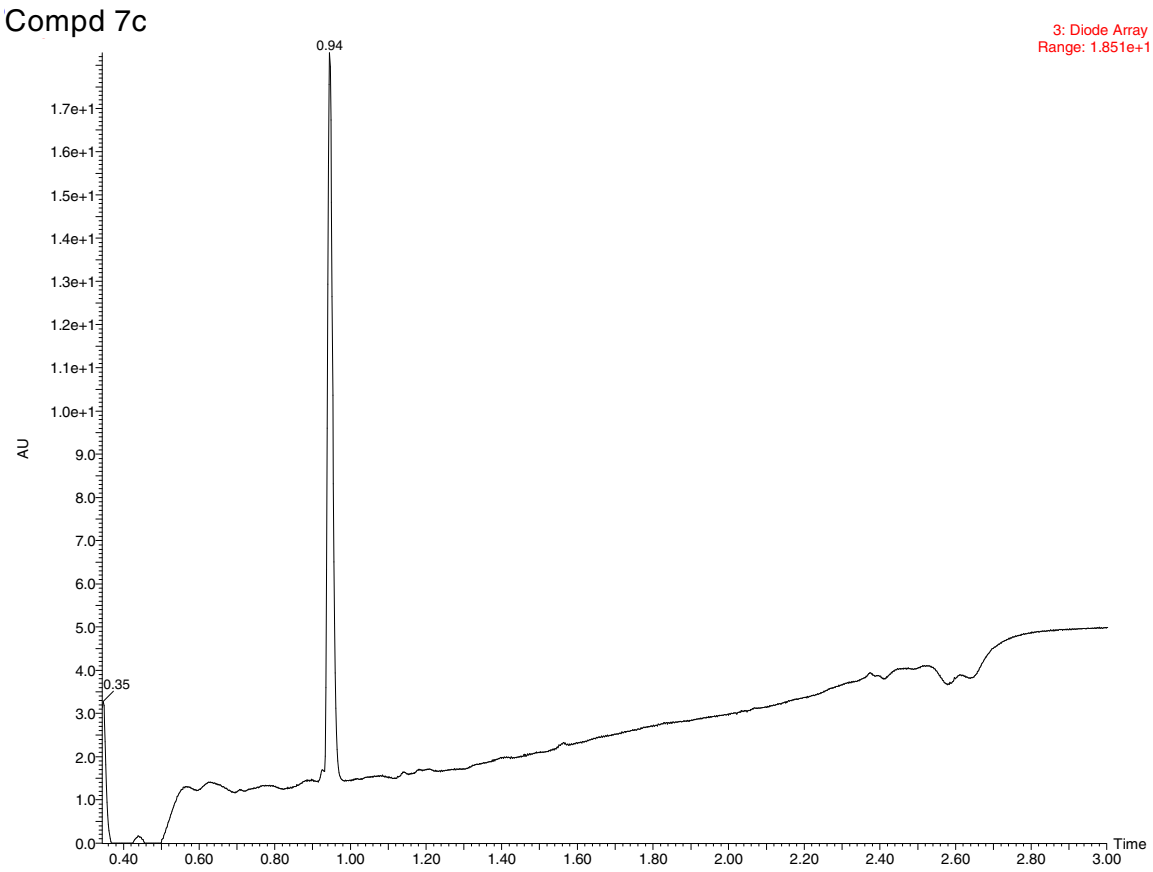
Initial conditions: 10% ACN (0.4 min), then gradient to 100% ACN in 6.4 min.

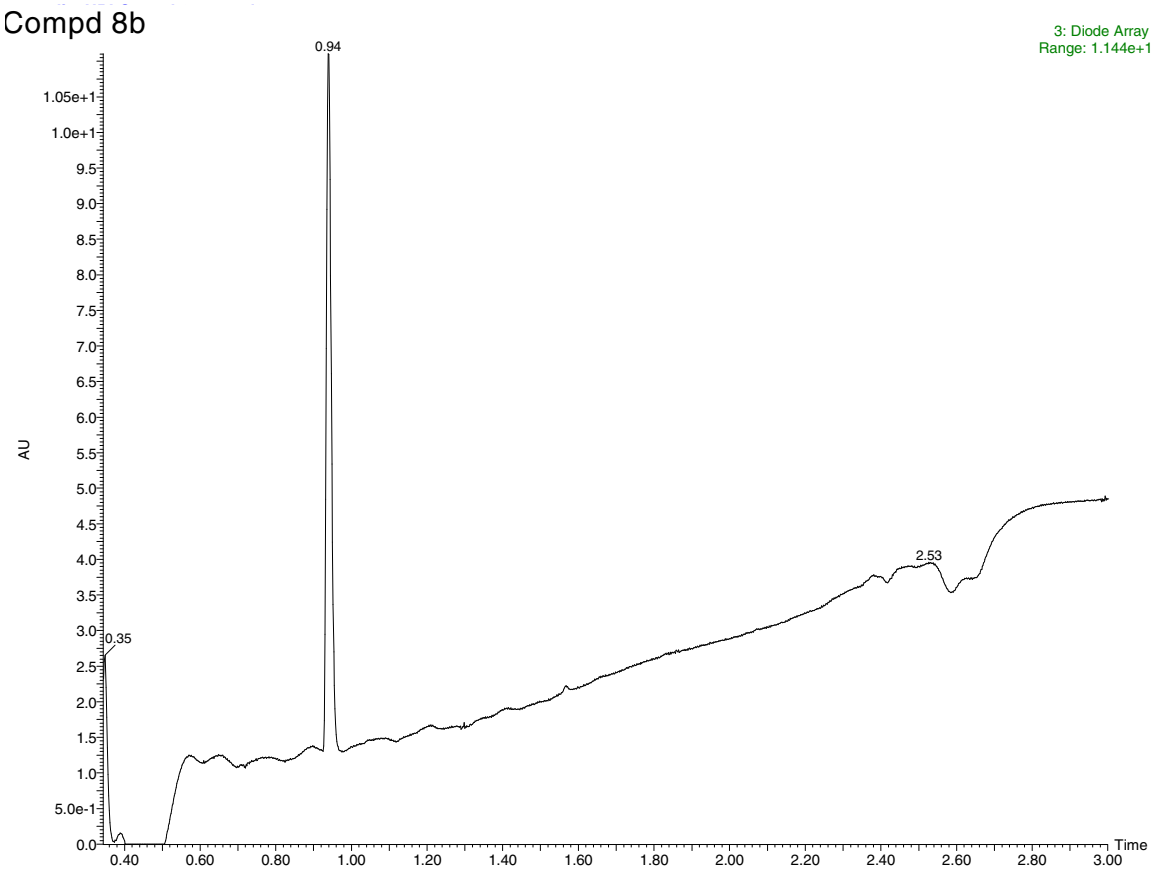
Flow rate 1 ml/min.

Fig 1. UPLC tracings (Method 1, see above).

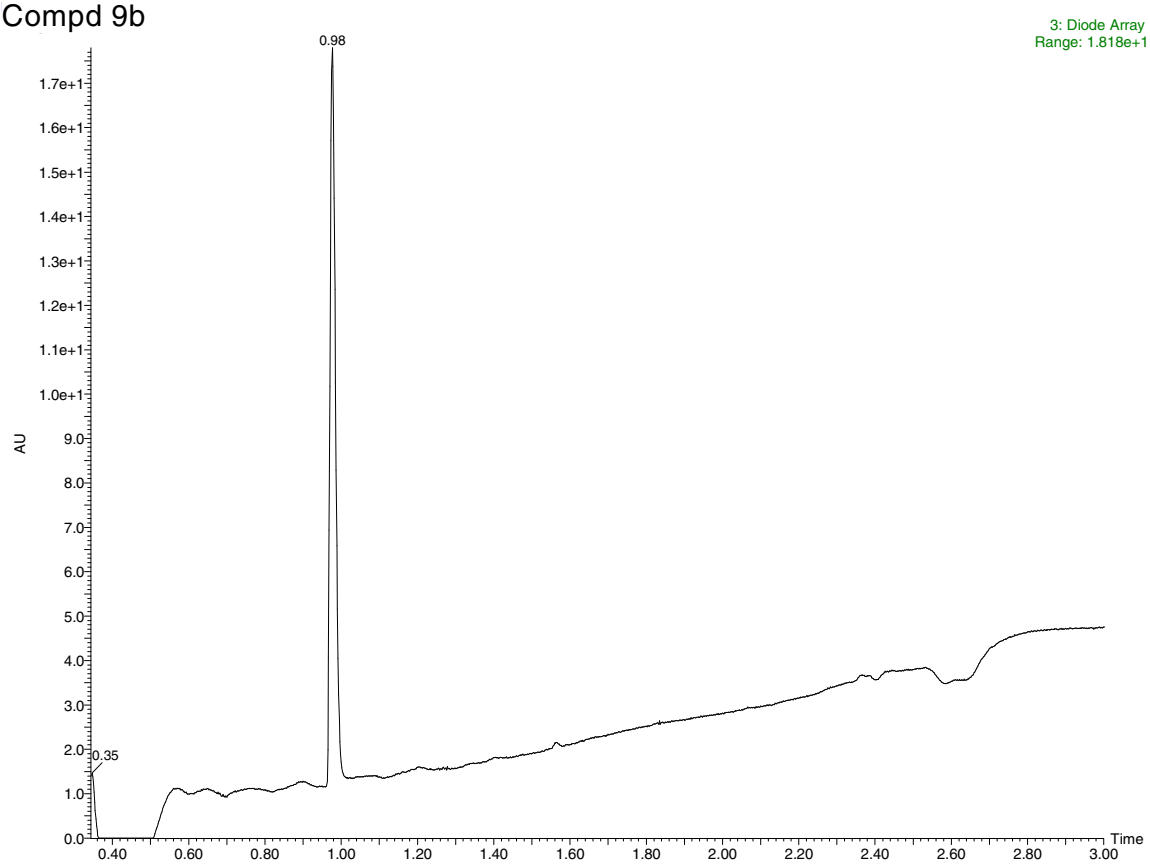


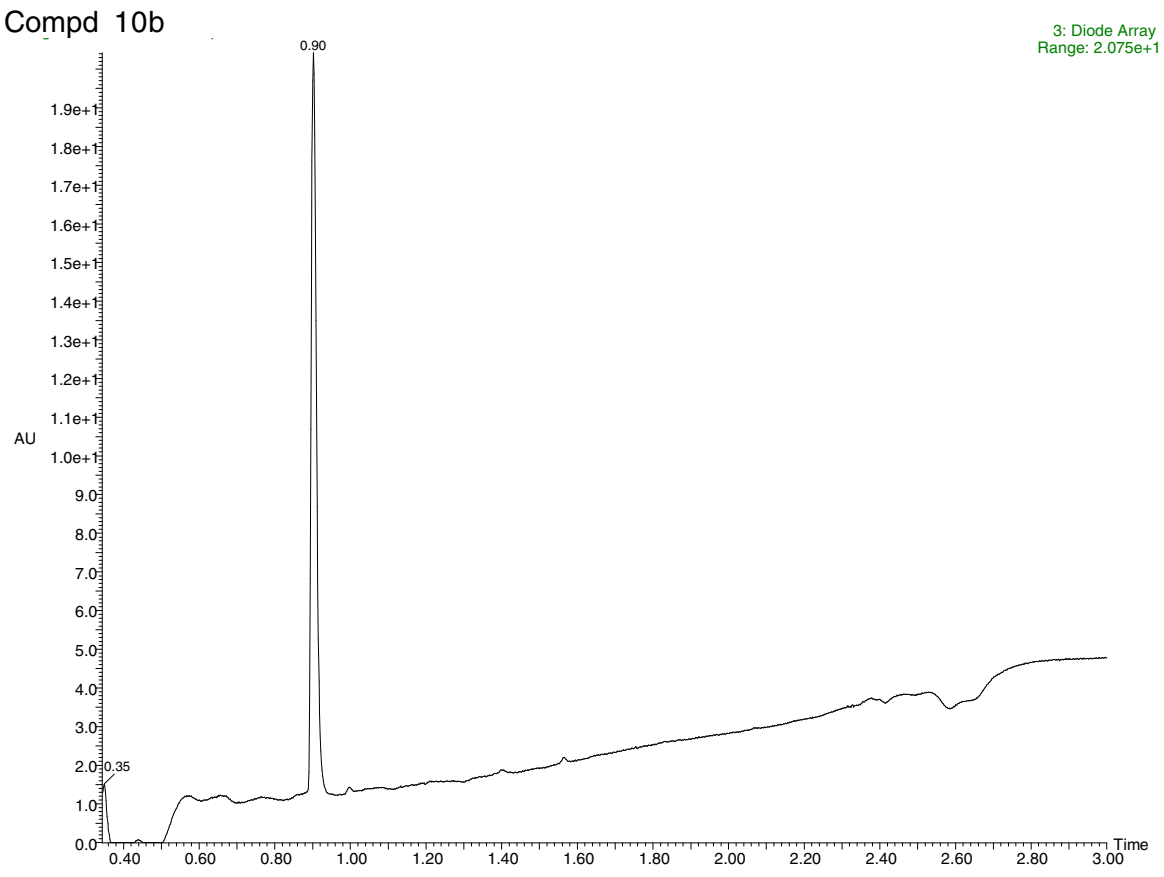

Compd 7b
3: Diode Array
Range: 1.33e+1
0.88
0.35
0.44
2.53
AU
Time
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd 7c
3: Diode Array
Range: 1.851e+1
0.94
0.35
AU
Time
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

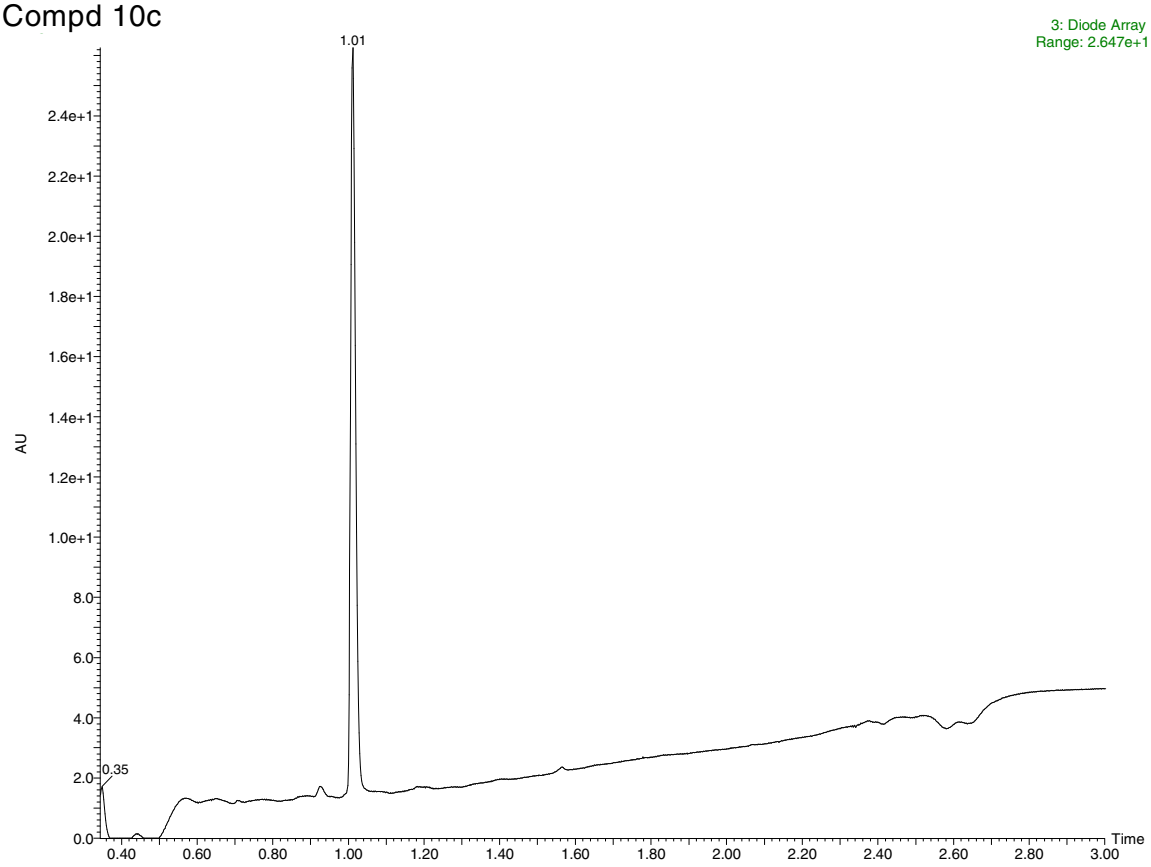

Compd 8b
3: Diode Array
Range: 1.144e+1
0.94
2.53
0.35
AU
Time
1.05e+1
1.0e+1
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
5.0e-1
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

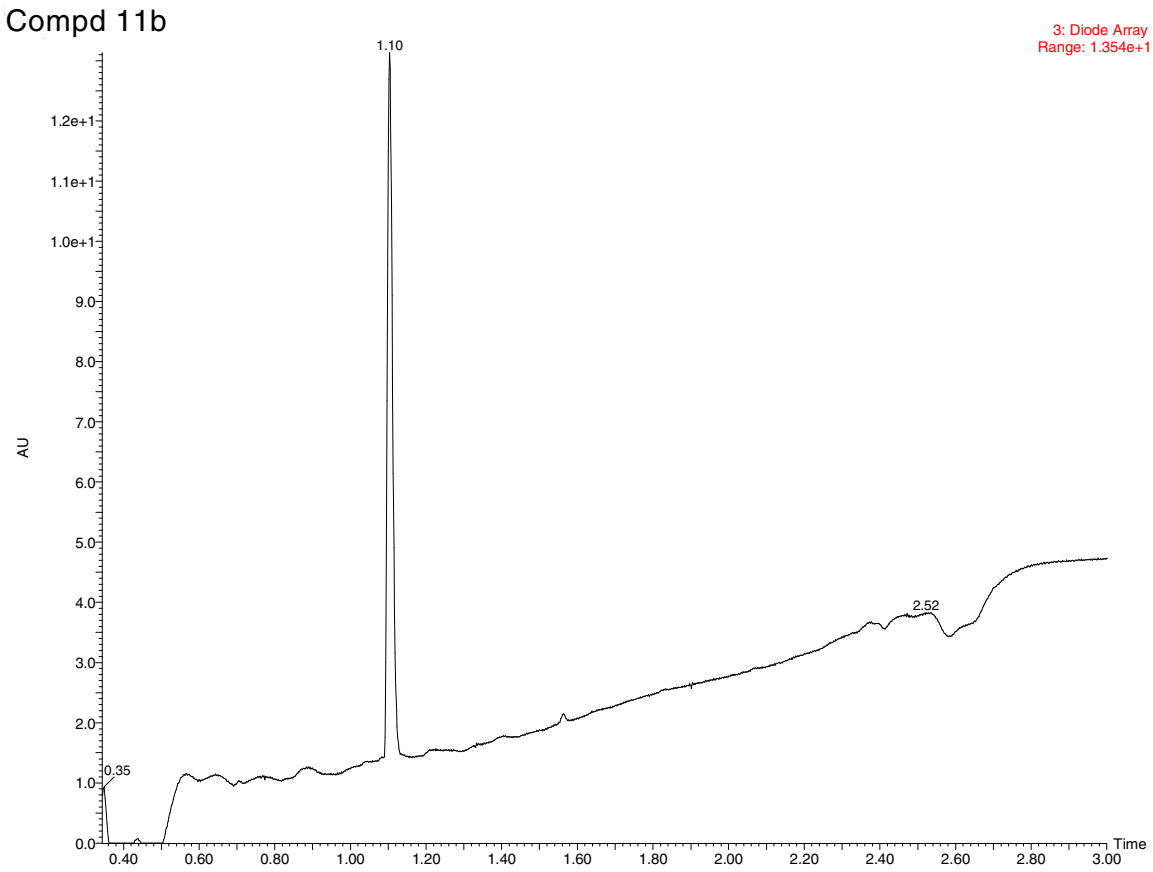
Compd 9b

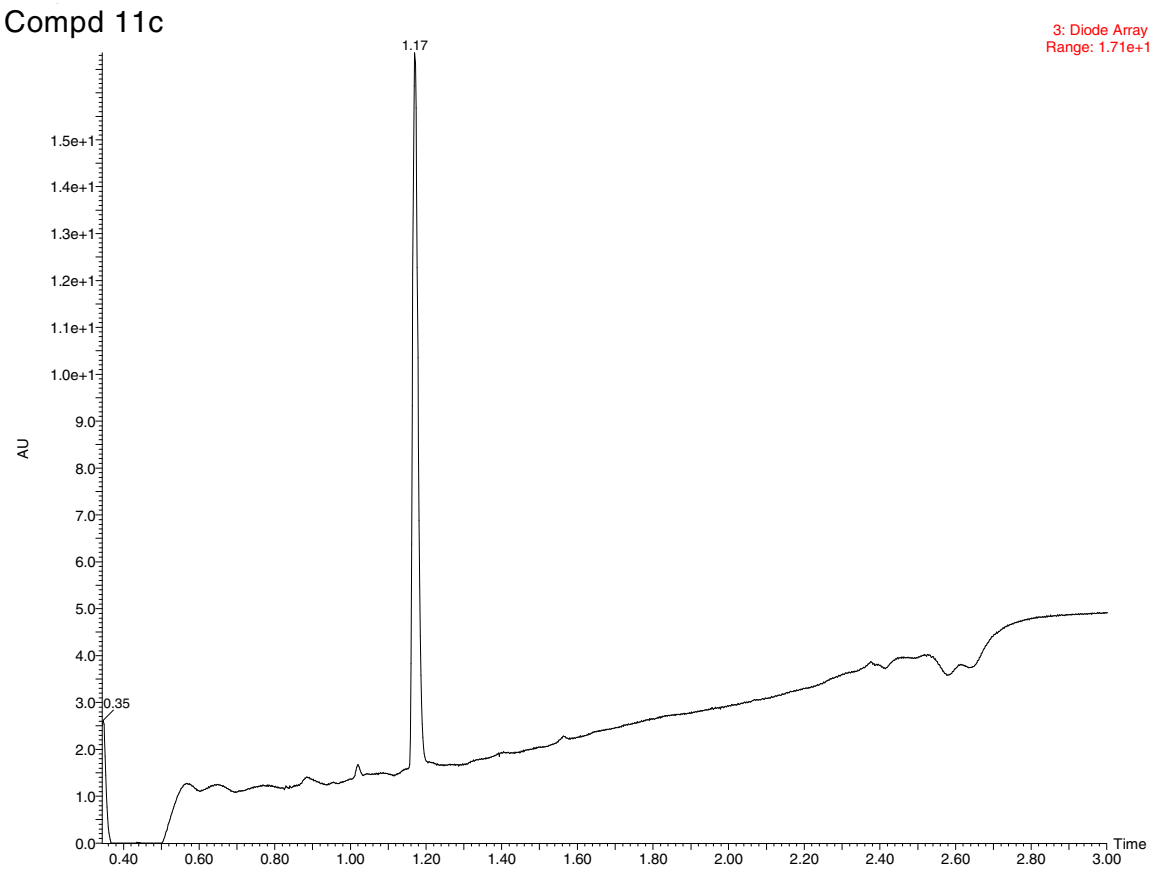

3: Diode Array
Range: 1.818e+1
0.98
0.35
AU
Time
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd 10b
3: Diode Array
Range: 2.075e+1
0.90
0.35
AU
Time
1.9e+1
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

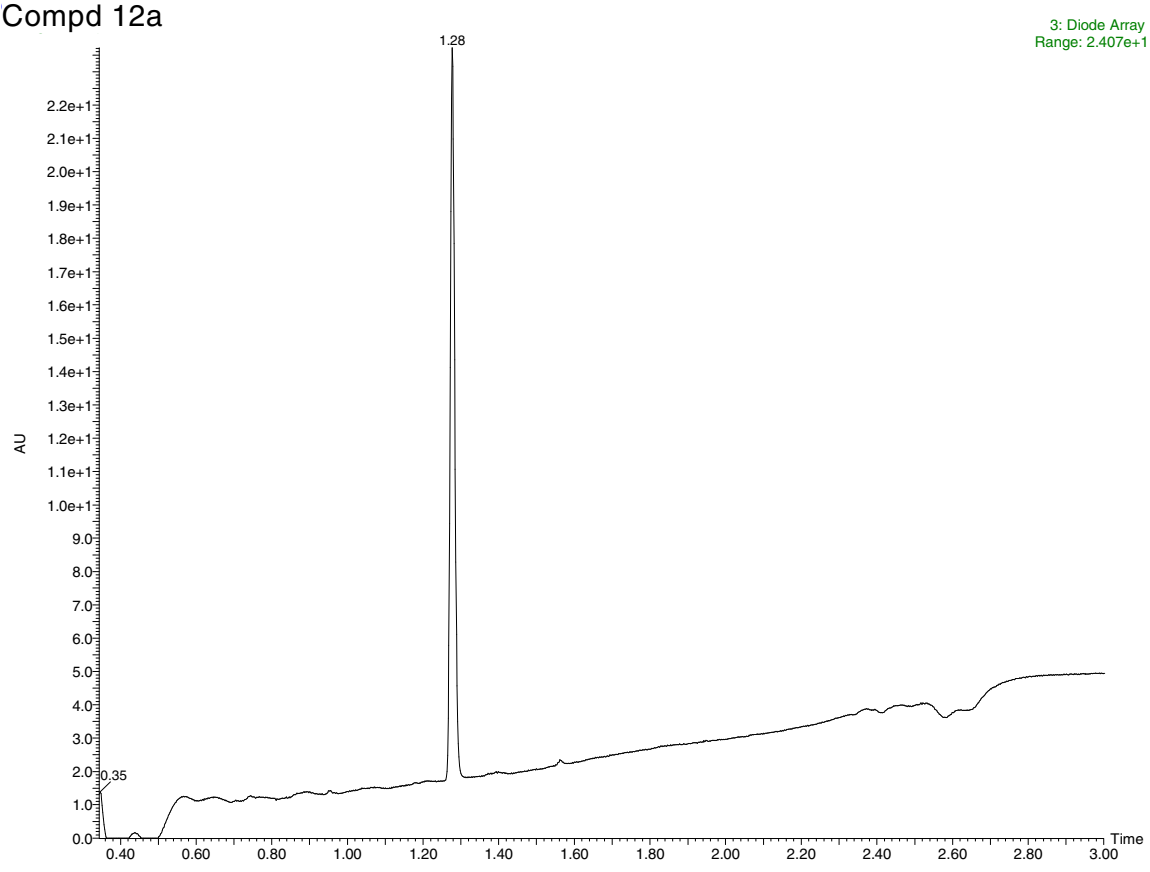
Compd 10c

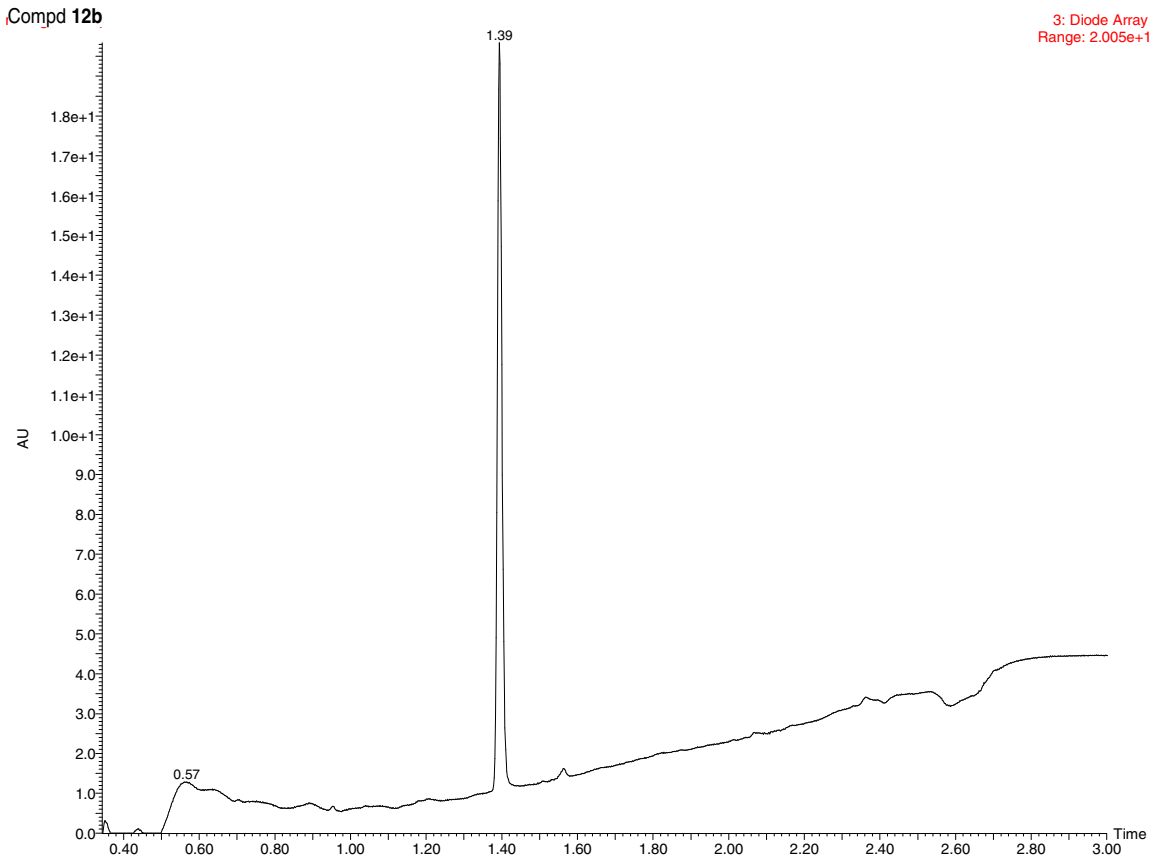

3: Diode Array
Range: 2.647e+1
1.01
0.35
AU
Time
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd 11b
3: Diode Array
Range: 1.354e+1
1.10
2.52
0.35
AU
Time
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

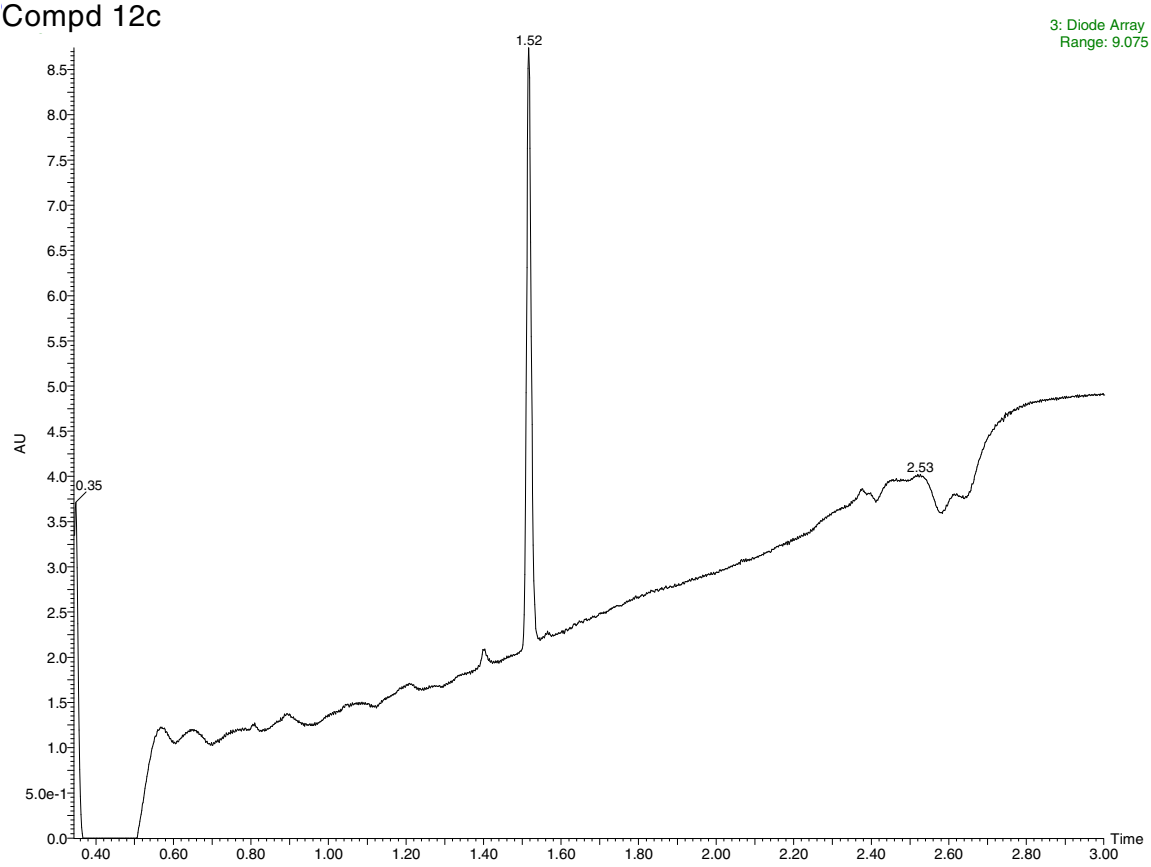

Compd 11c
3: Diode Array
Range: 1.71e+1
1.17
0.35
AU
Time
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 12a

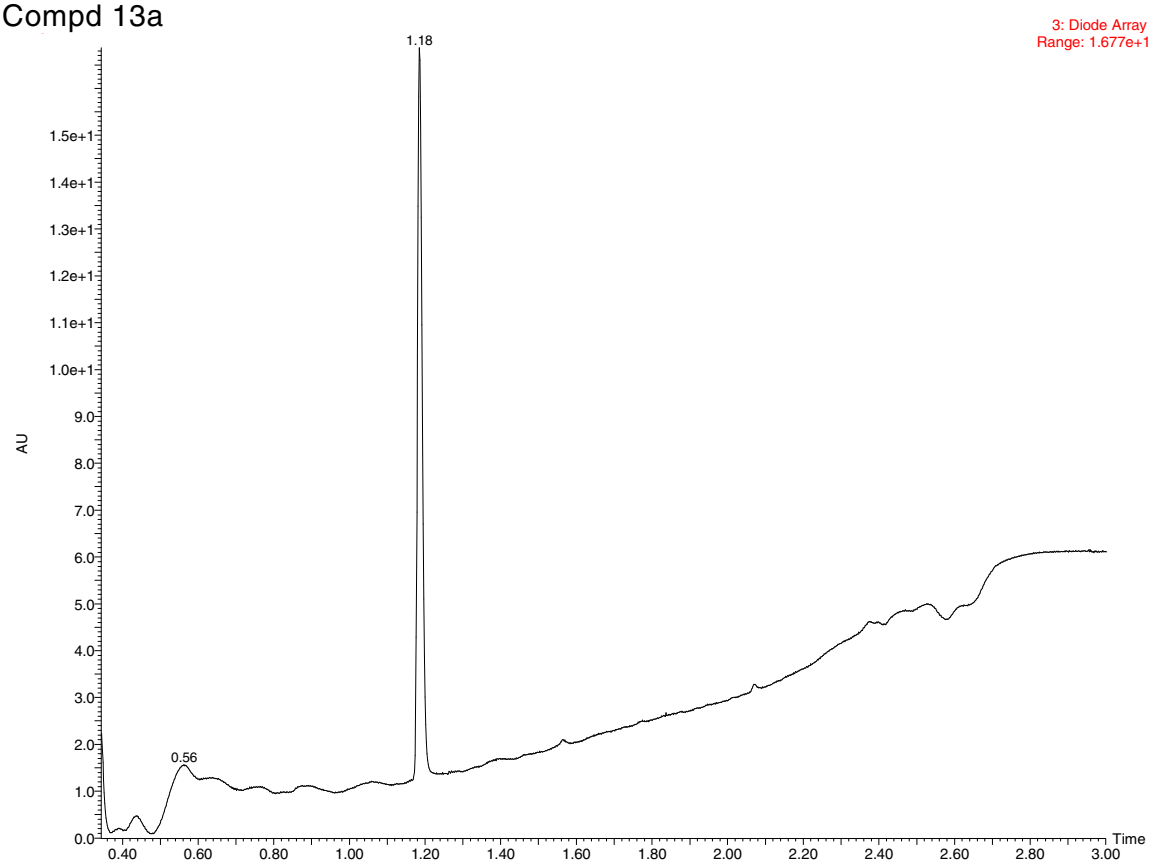

3: Diode Array
Range: 2.407e+1
1.28
0.35
AU
Time
2.2e+1
2.1e+1
2.0e+1
1.9e+1
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd 12b
3: Diode Array
Range: 2.005e+1
1.39
0.57
AU
Time
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

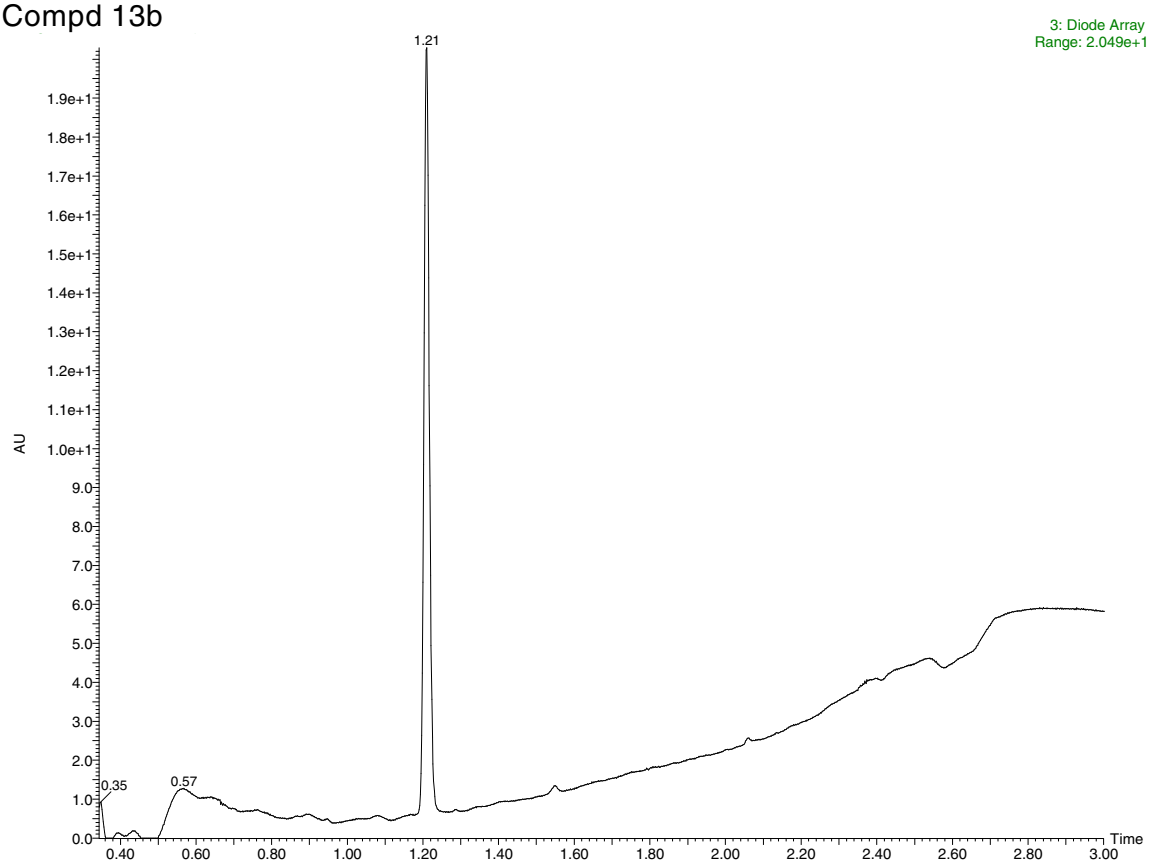
Compd 12c


3: Diode Array
Range: 9.075
1.52
0.35
2.53
AU
Time
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
5.0e-1
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

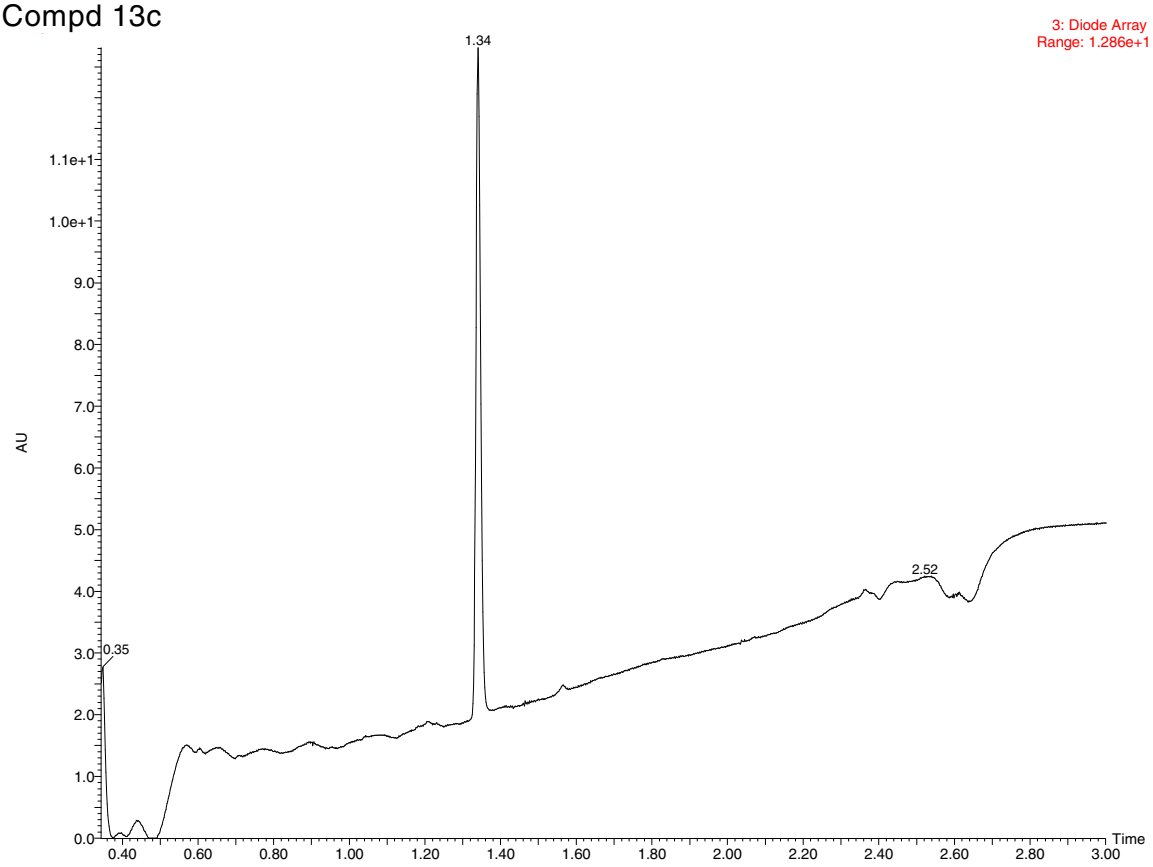
Compd 13a


3: Diode Array
Range: 1.677e+1
1.18
0.56
AU
Time
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

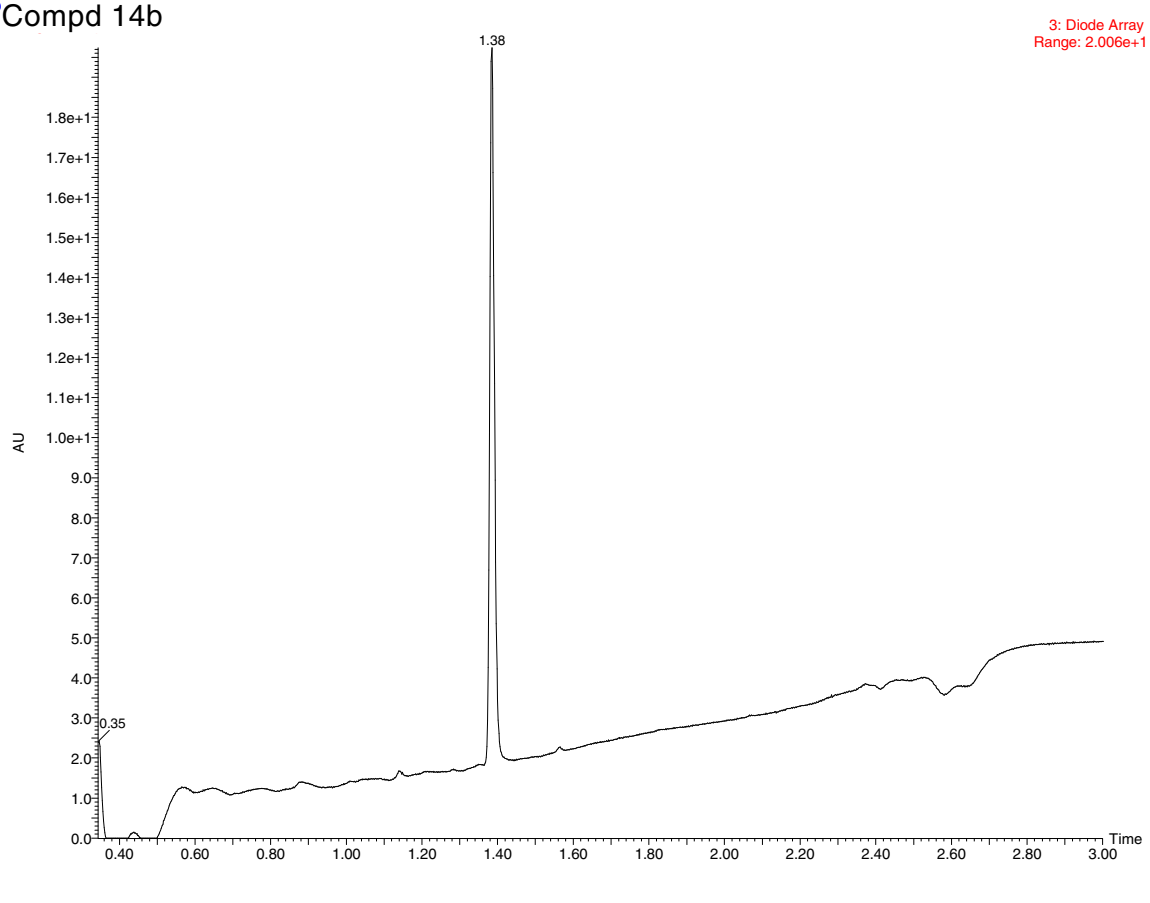
Compd 13b


3: Diode Array
Range: 2.049e+1
1.21
0.35
0.57
AU
Time
1.9e+1
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

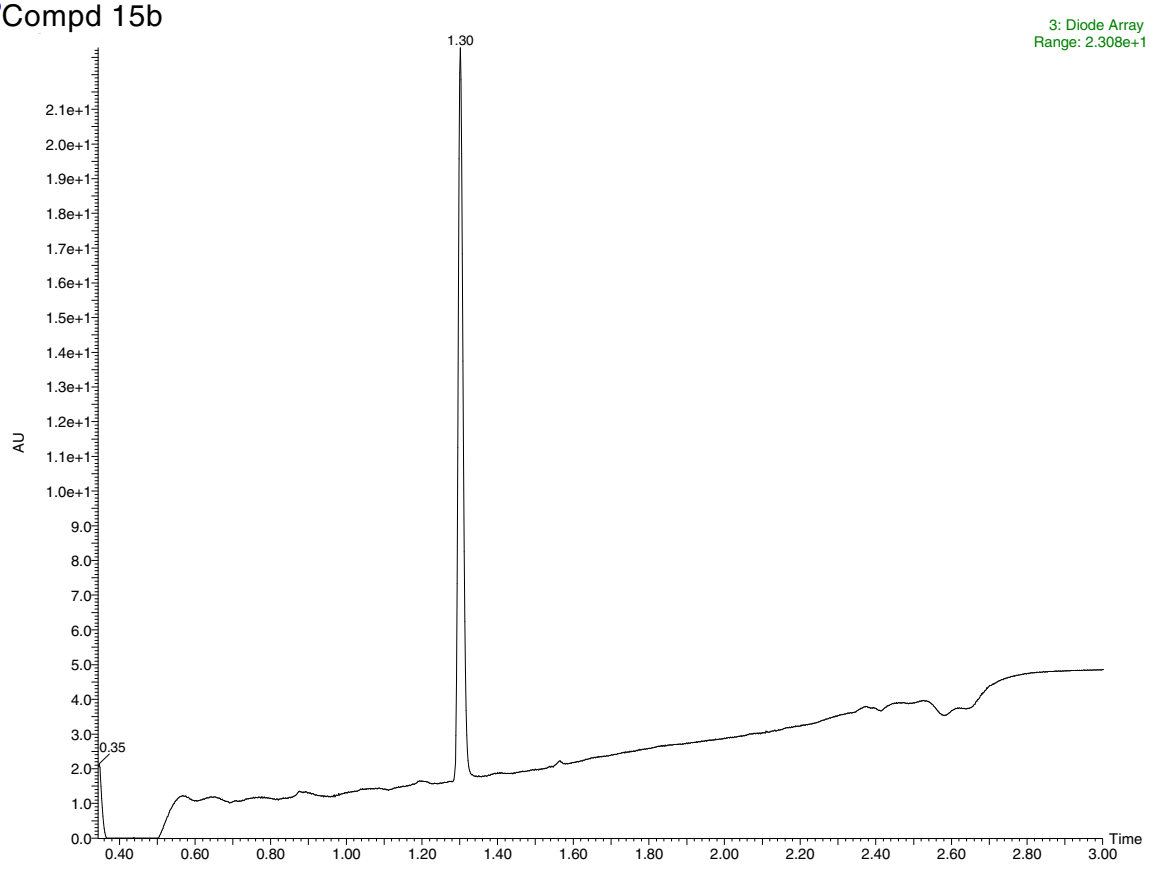
Compd 13c

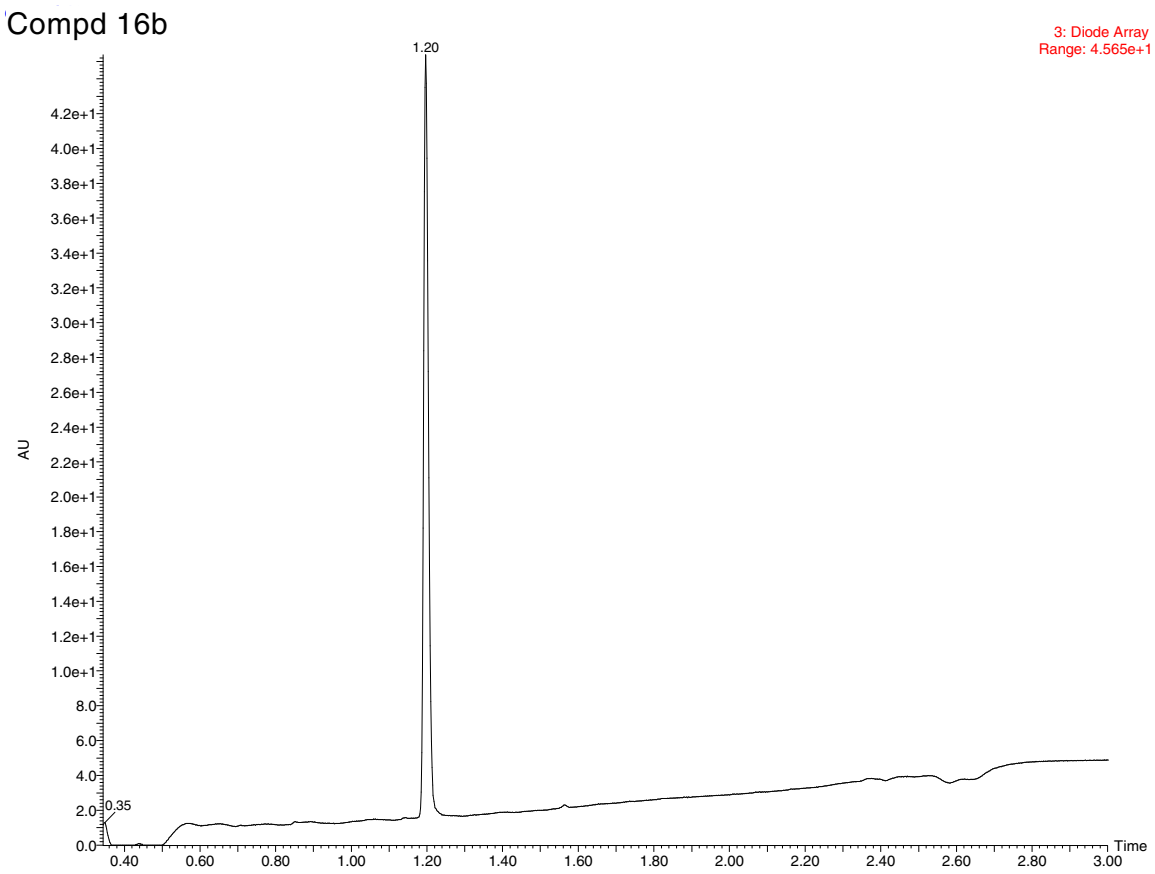

3: Diode Array
Range: 1.286e+1
1.34
2.52
0.35
AU
Time
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 14b

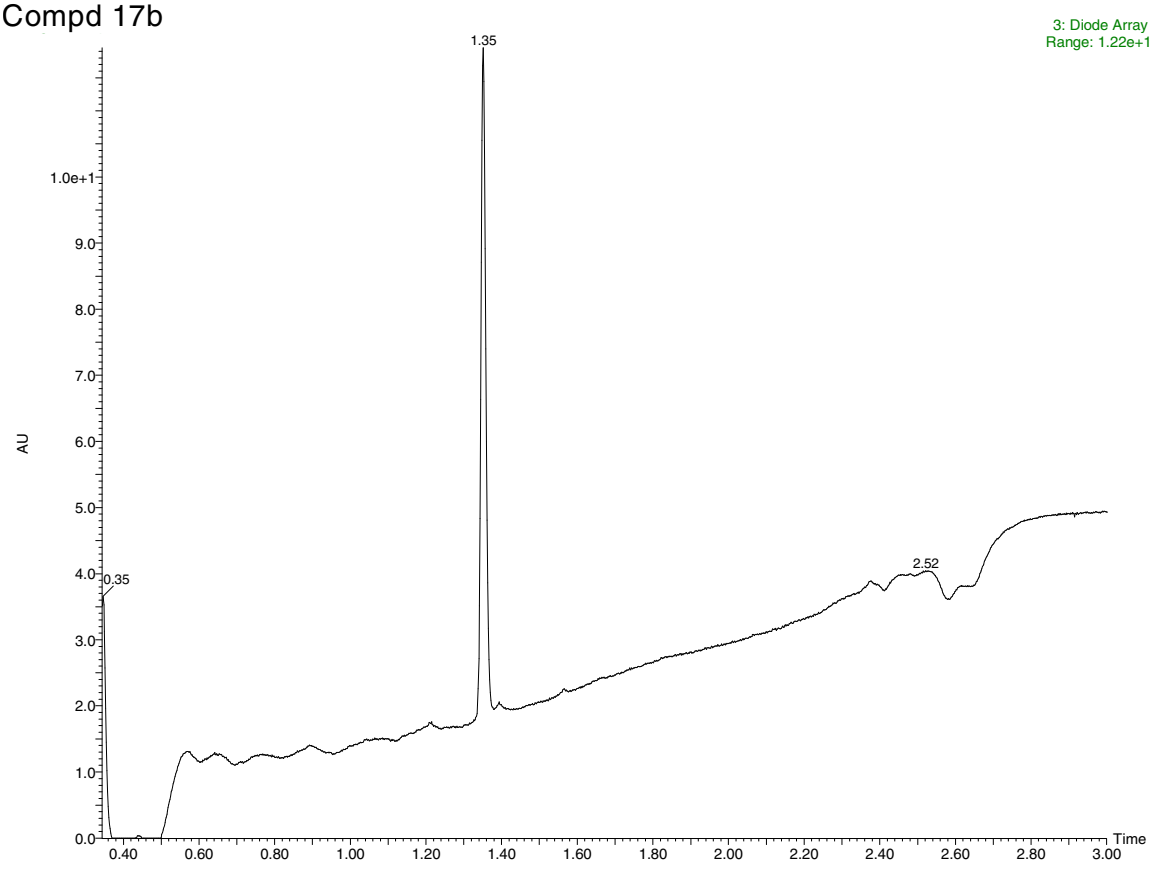

3: Diode Array
Range: 2.006e+1
1.38
0.35
AU
Time
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

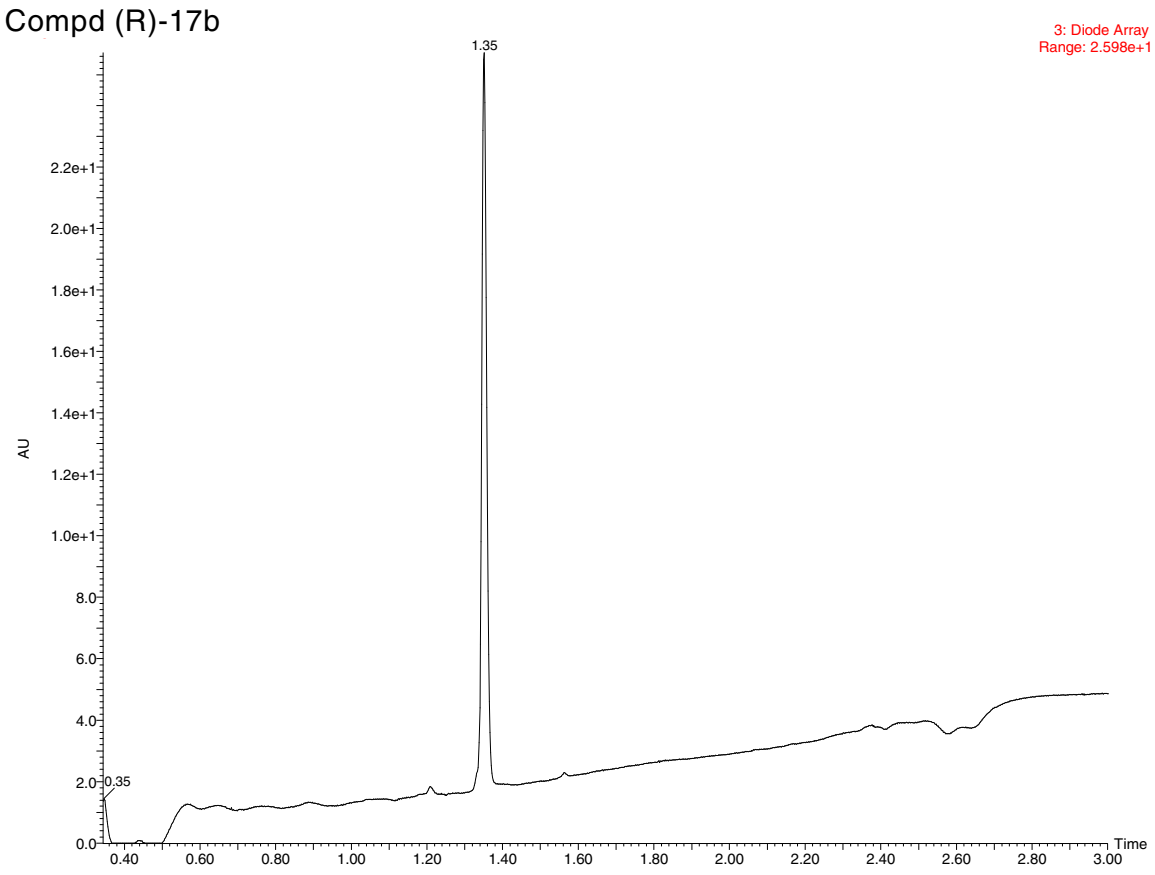
Compd 15b


3: Diode Array
Range: 2.308e+1
1.30
0.35
AU
Time
2.1e+1
2.0e+1
1.9e+1
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

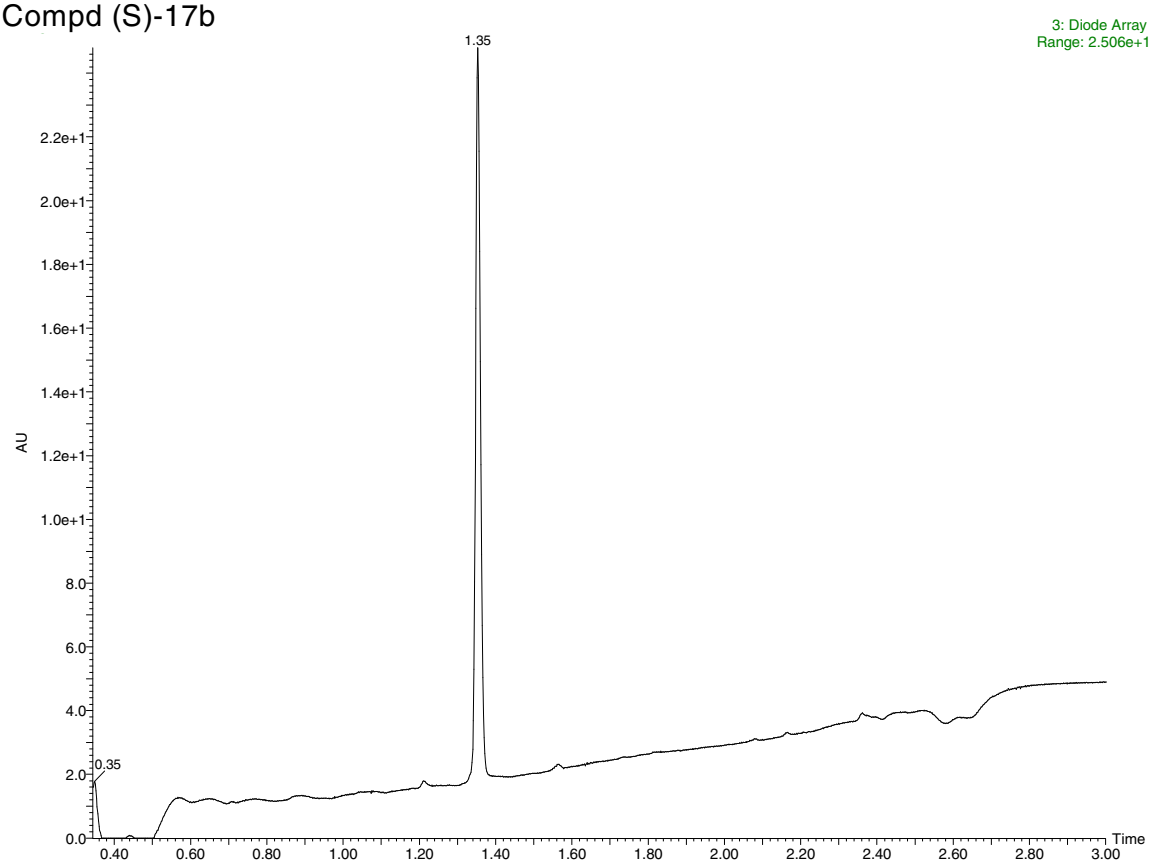

Compd 16b
3: Diode Array
Range: 4.565e+1
1.20
0.35
AU
Time
4.2e+1
4.0e+1
3.8e+1
3.6e+1
3.4e+1
3.2e+1
3.0e+1
2.8e+1
2.6e+1
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 17b

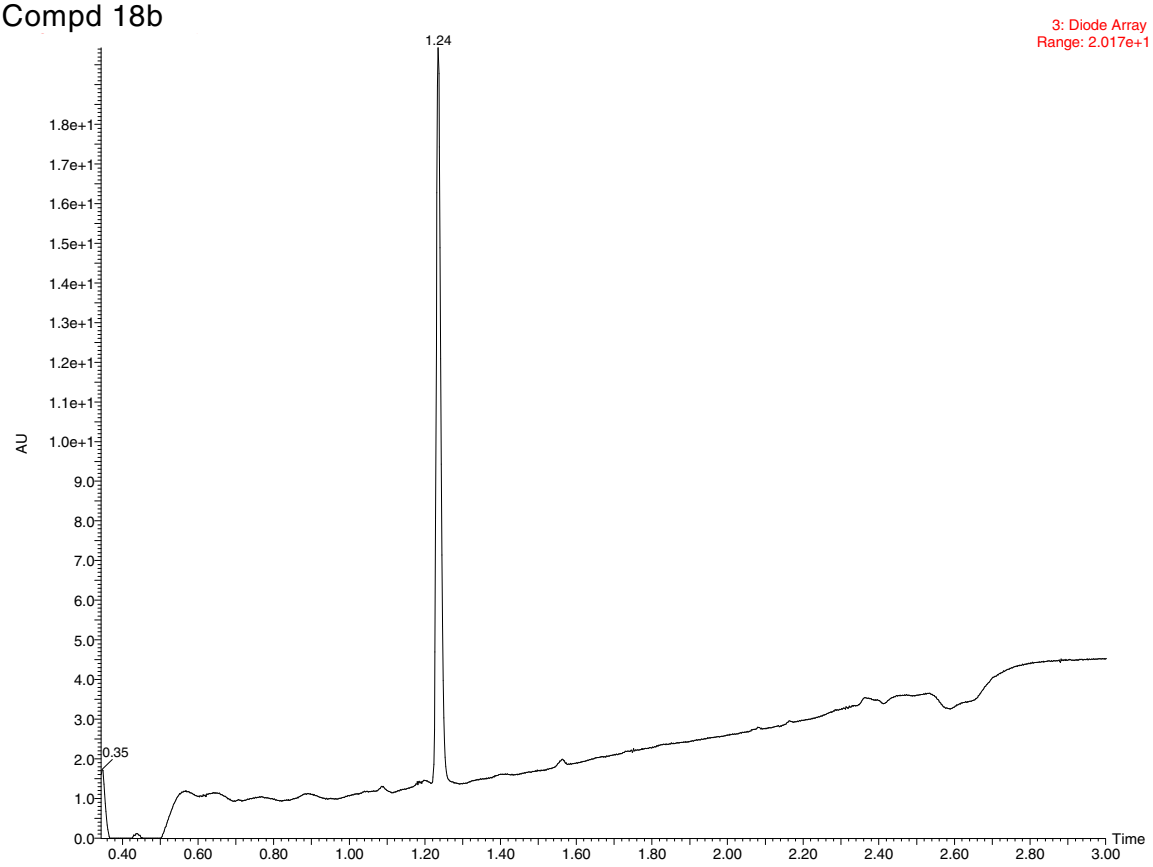

3: Diode Array
Range: 1.22e+1
1.35
2.52
0.35
AU
Time
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd (R)-17b
3: Diode Array
Range: 2.598e+1
1.35
0.35
AU
Time
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

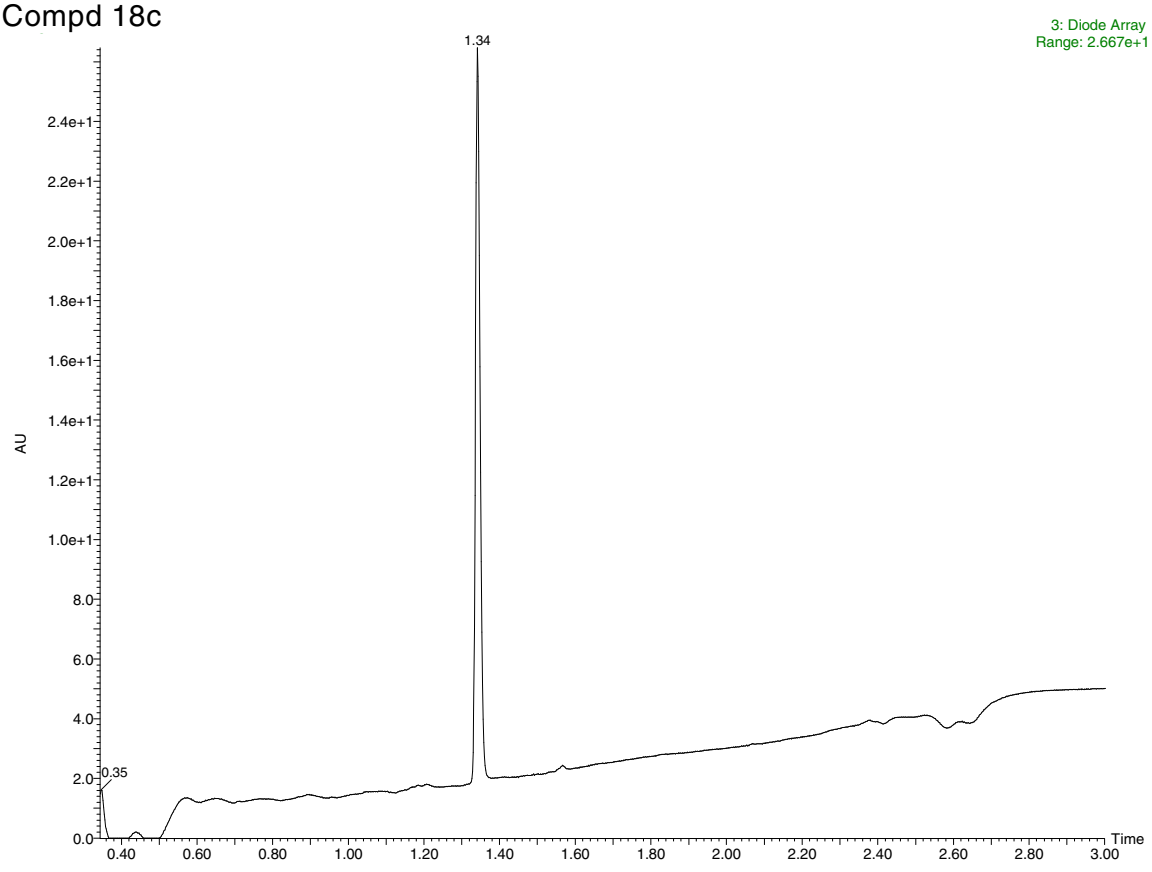
Compd (S)-17b


3: Diode Array
Range: 2.506e+1
1.35
0.35
AU
Time
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

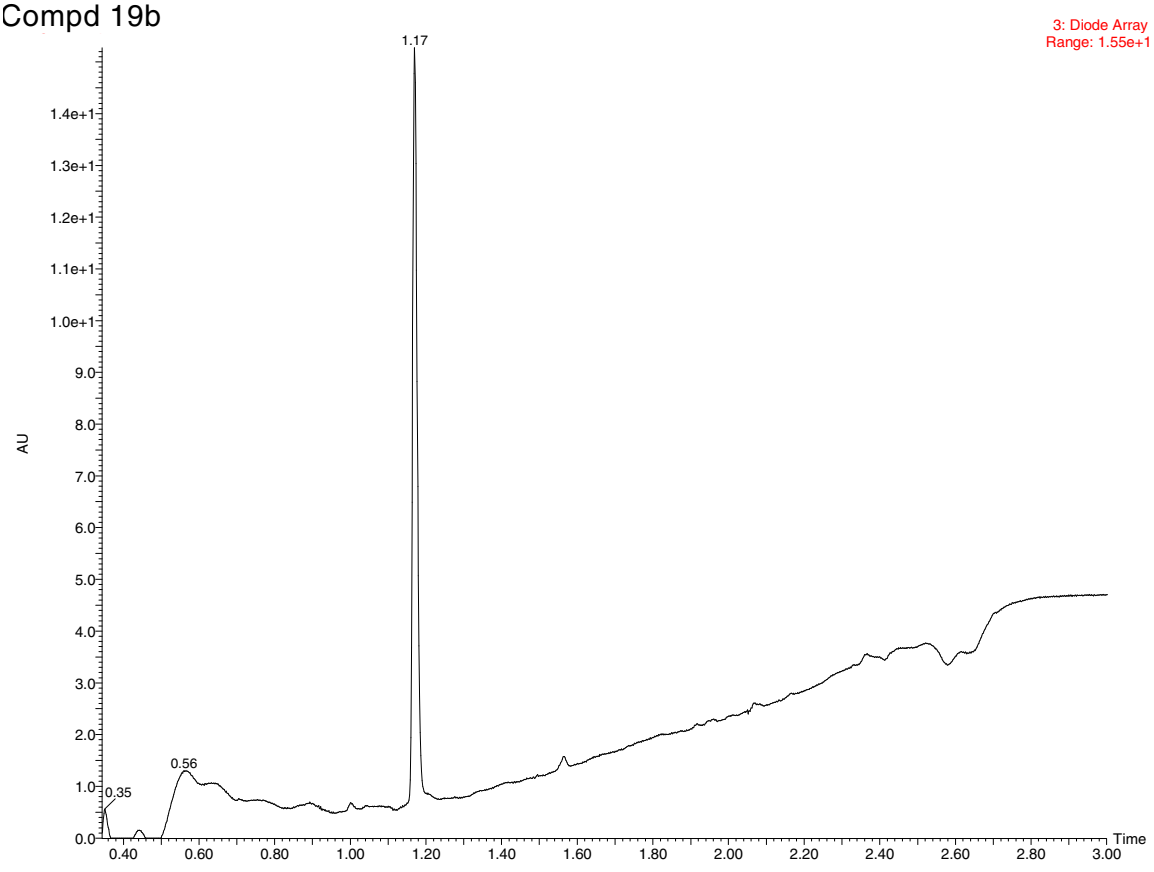
Compd 18b


3: Diode Array
Range: 2.017e+1
1.24
0.35
AU
Time
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

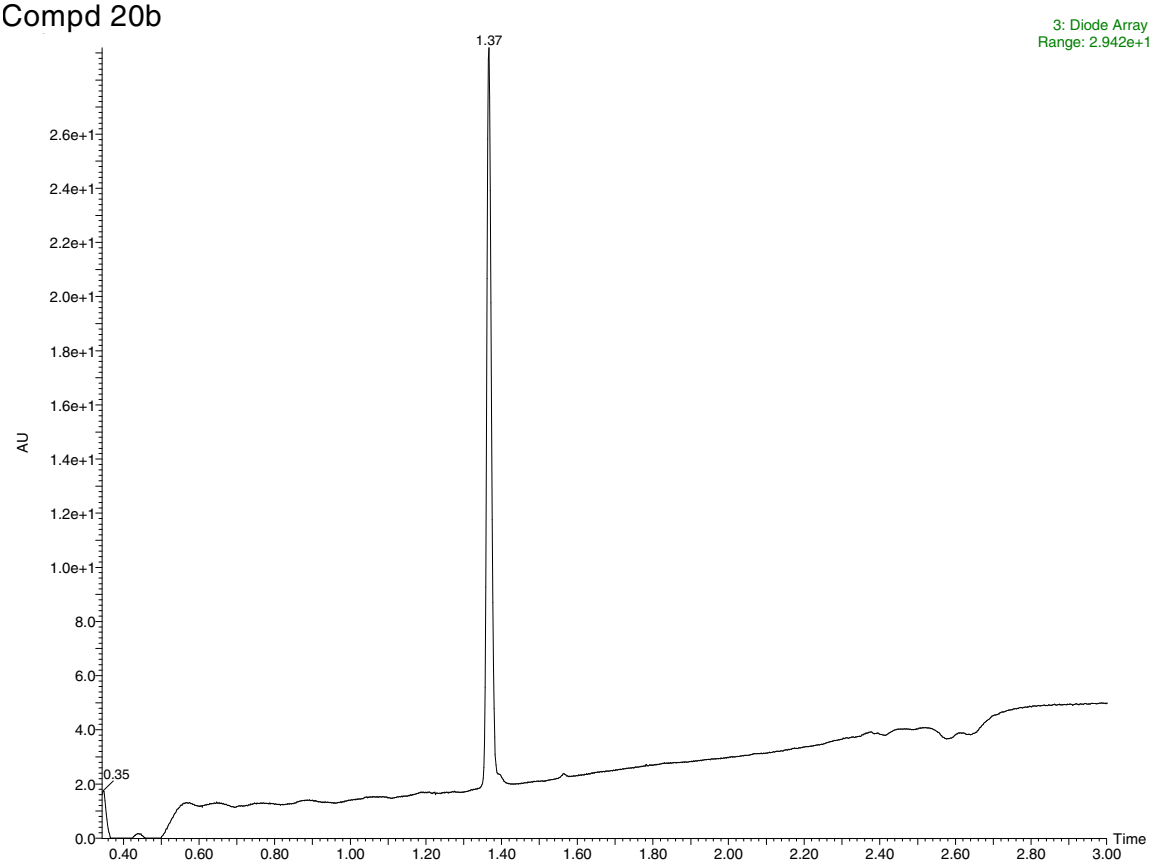
Compd 18c

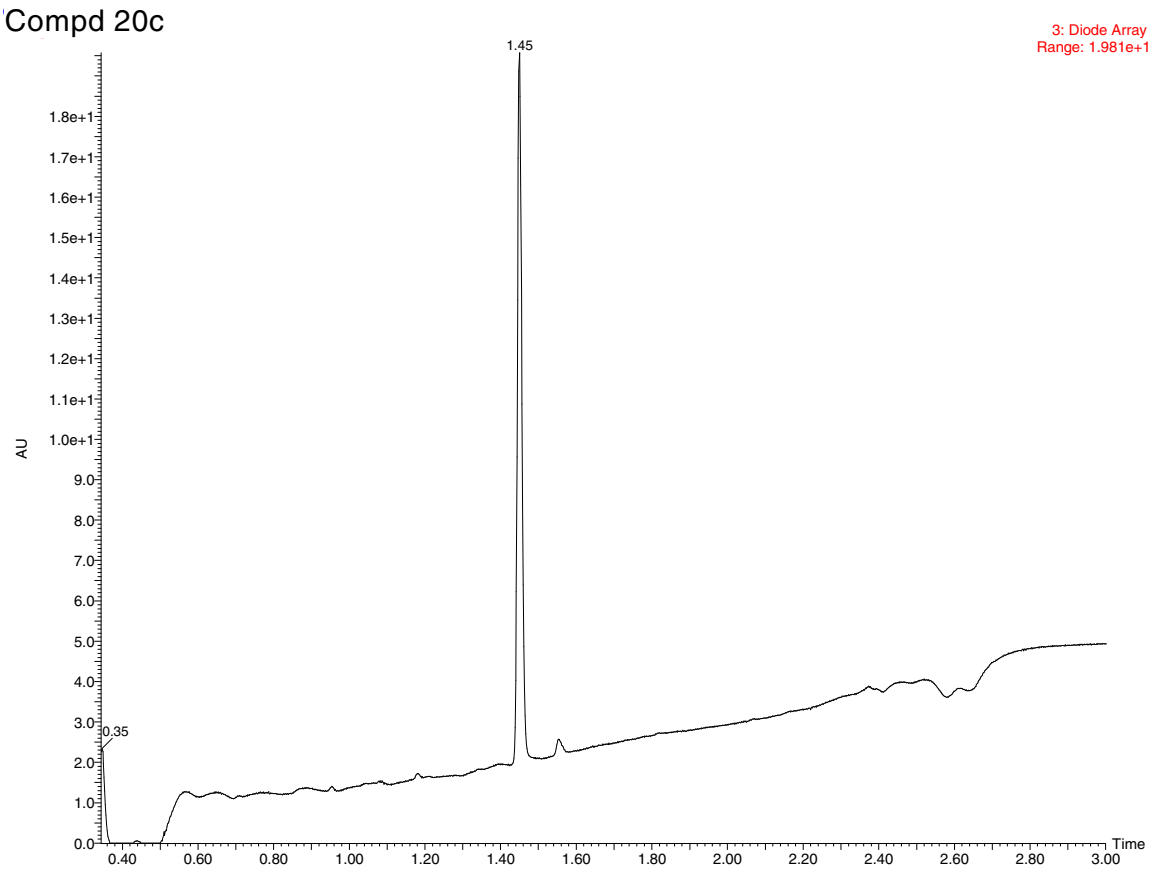

3: Diode Array
Range: 2.667e+1
1.34
0.35
AU
Time
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 19b

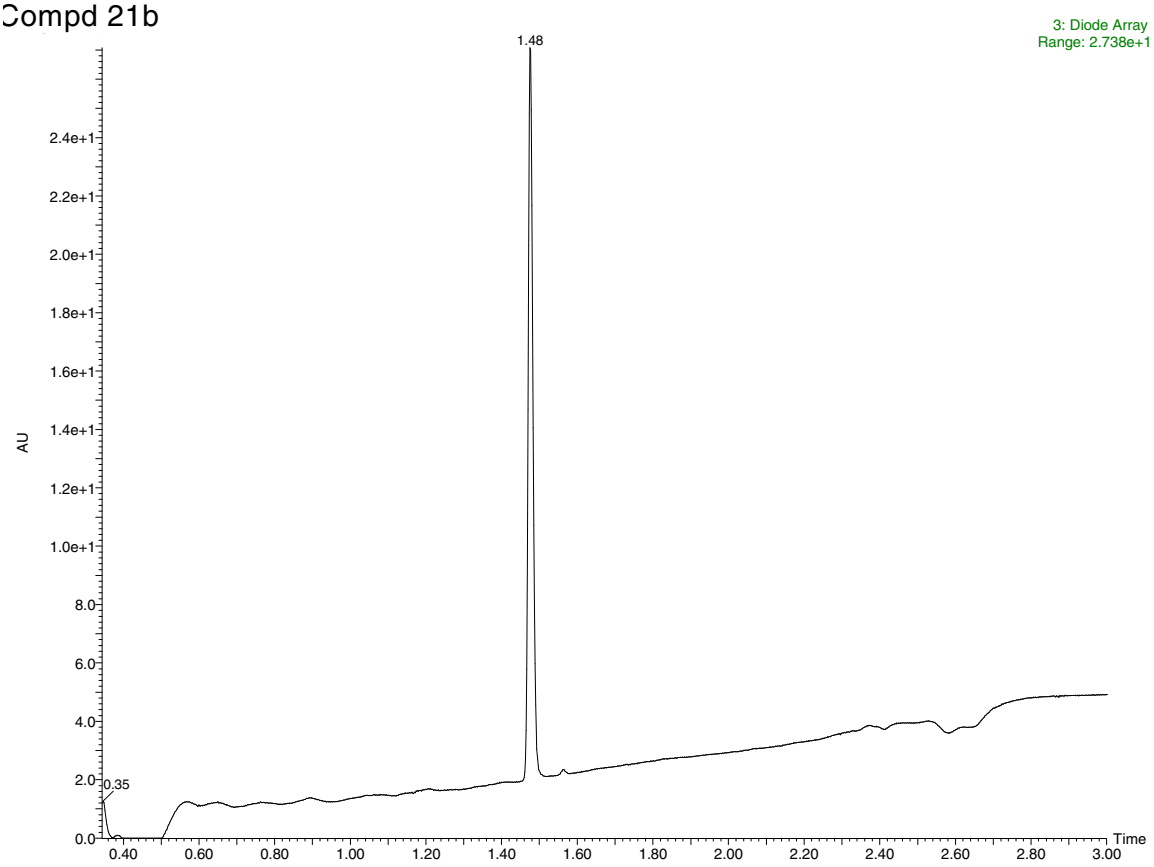

3: Diode Array
Range: 1.55e+1
1.17
0.56
0.35
AU
Time
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 20b

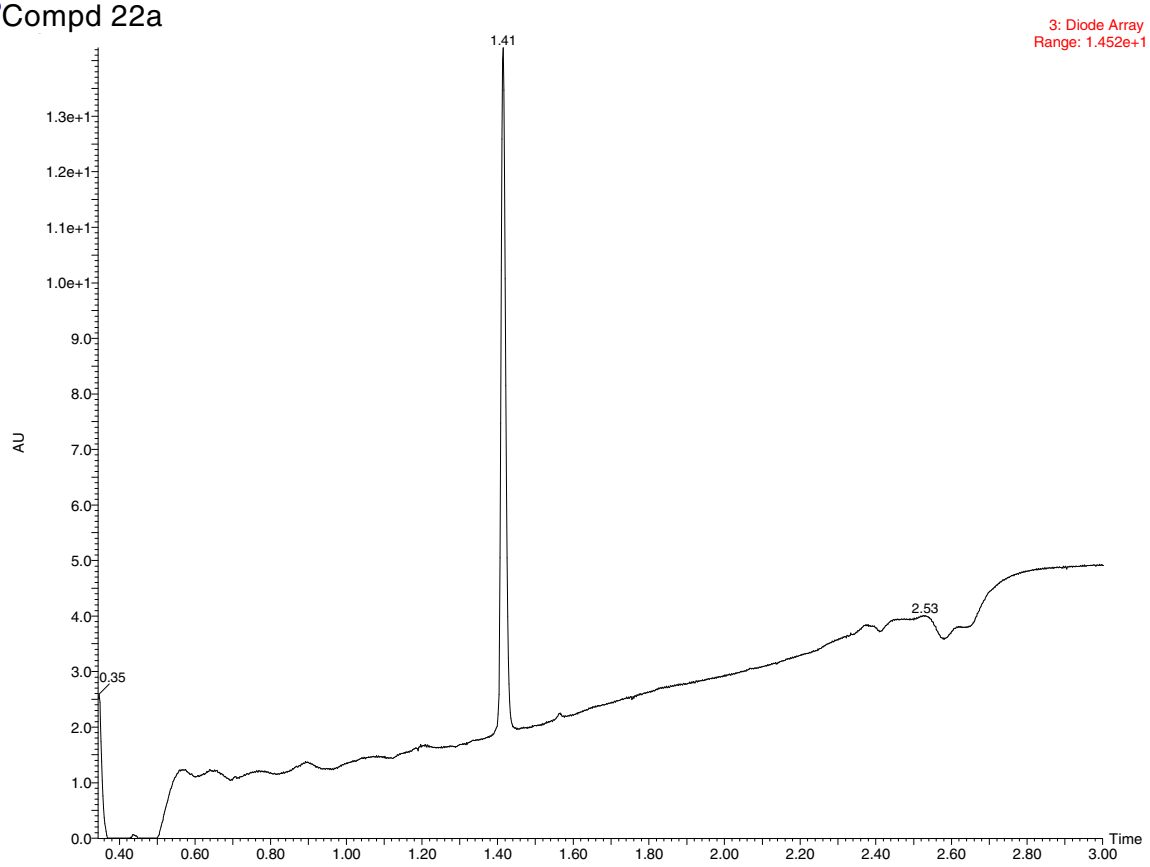

3: Diode Array
Range: 2.942e+1
1.37
0.35
AU
Time
2.6e+1
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd 20c
3: Diode Array
Range: 1.981e+1
1.45
0.35
AU
Time
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

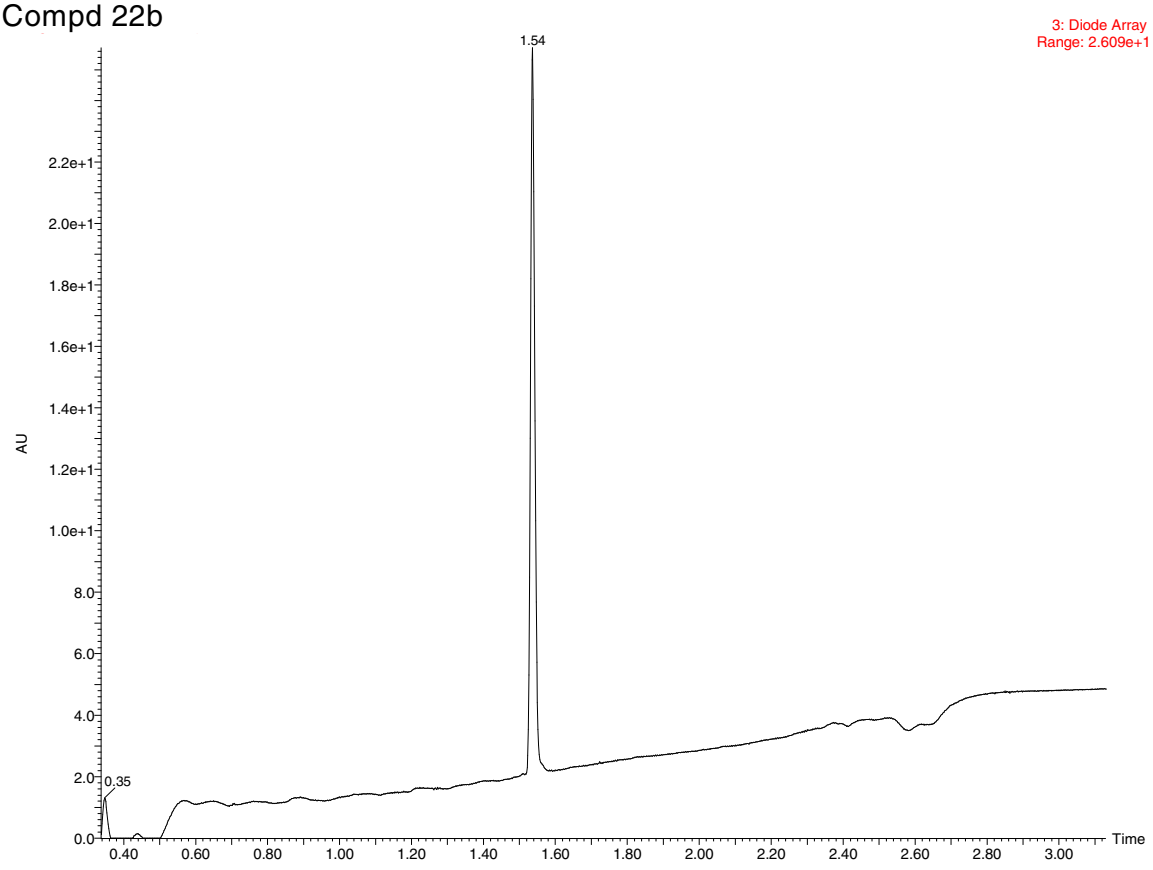
Compd 21b


3: Diode Array
Range: 2.738e+1
1.48
0.35
AU
Time
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

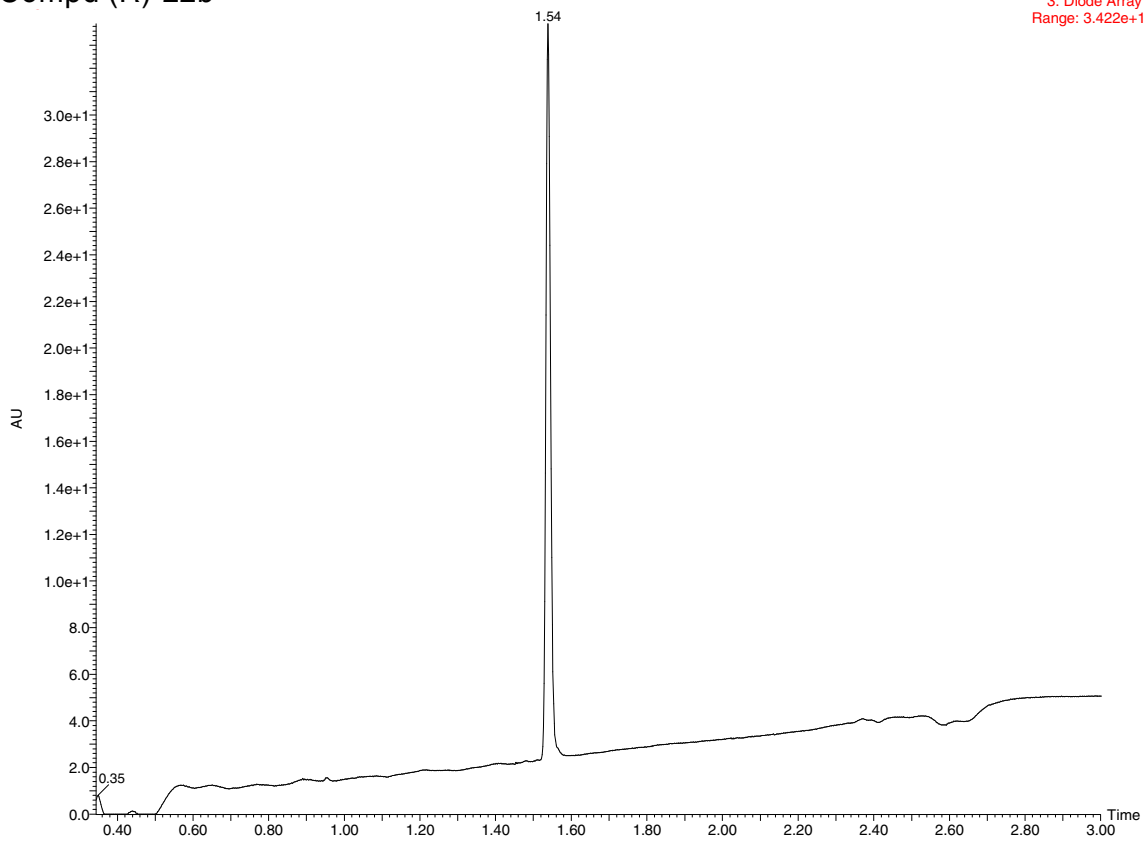
Compd 22a


3: Diode Array
Range: 1.452e+1
1.41
2.53
0.35
AU
Time
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

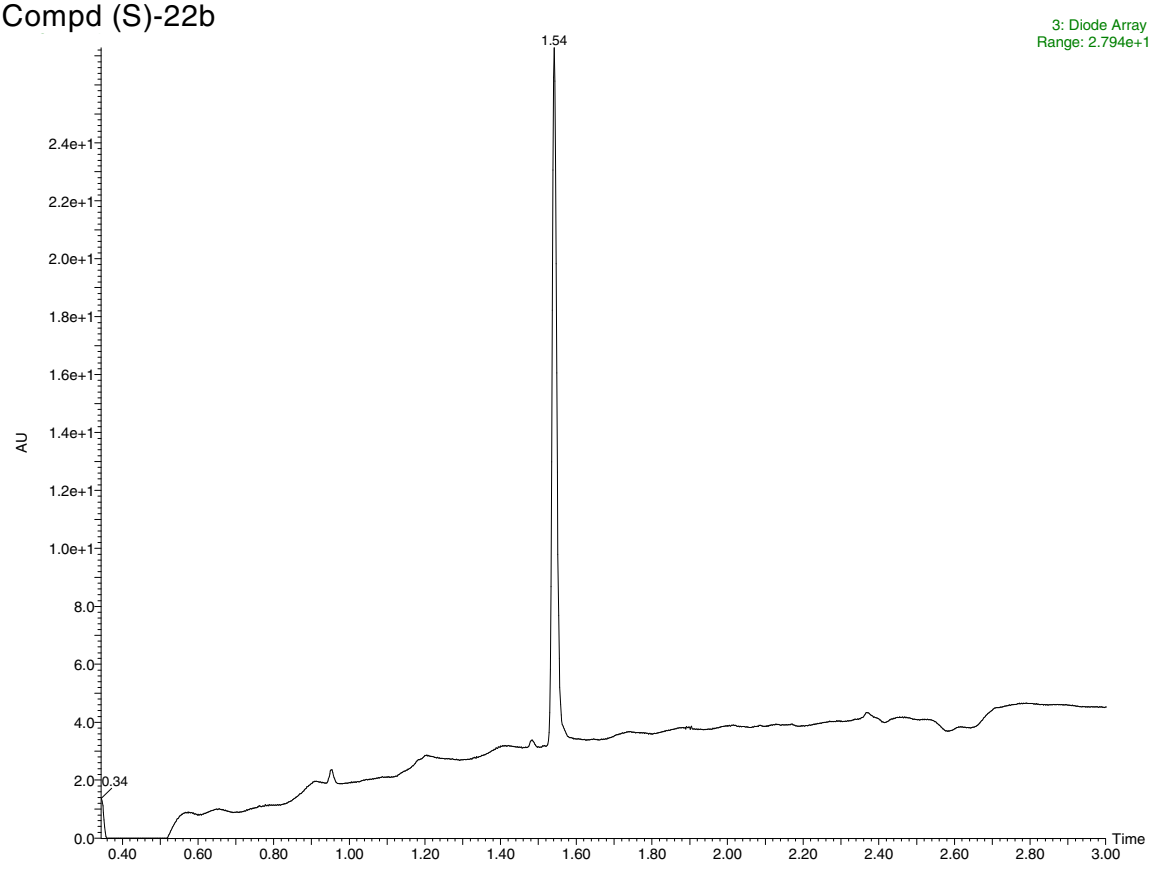
Compd 22b


3: Diode Array
Range: 2.609e+1
1.54
0.35
AU
Time
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

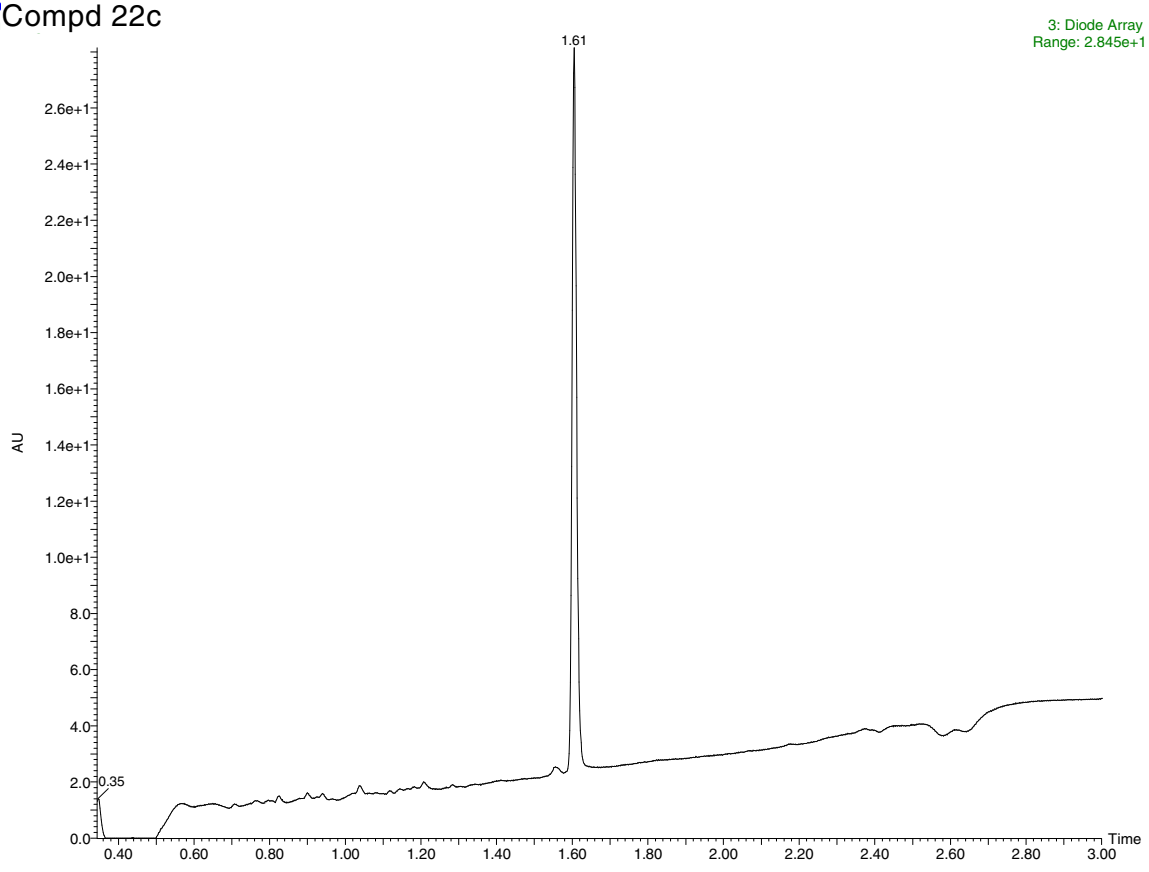
Compd (R)-22b


3: Diode Array
Range: 3.422e+1
1.54
0.35
AU
Time
3.0e+1
2.8e+1
2.6e+1
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

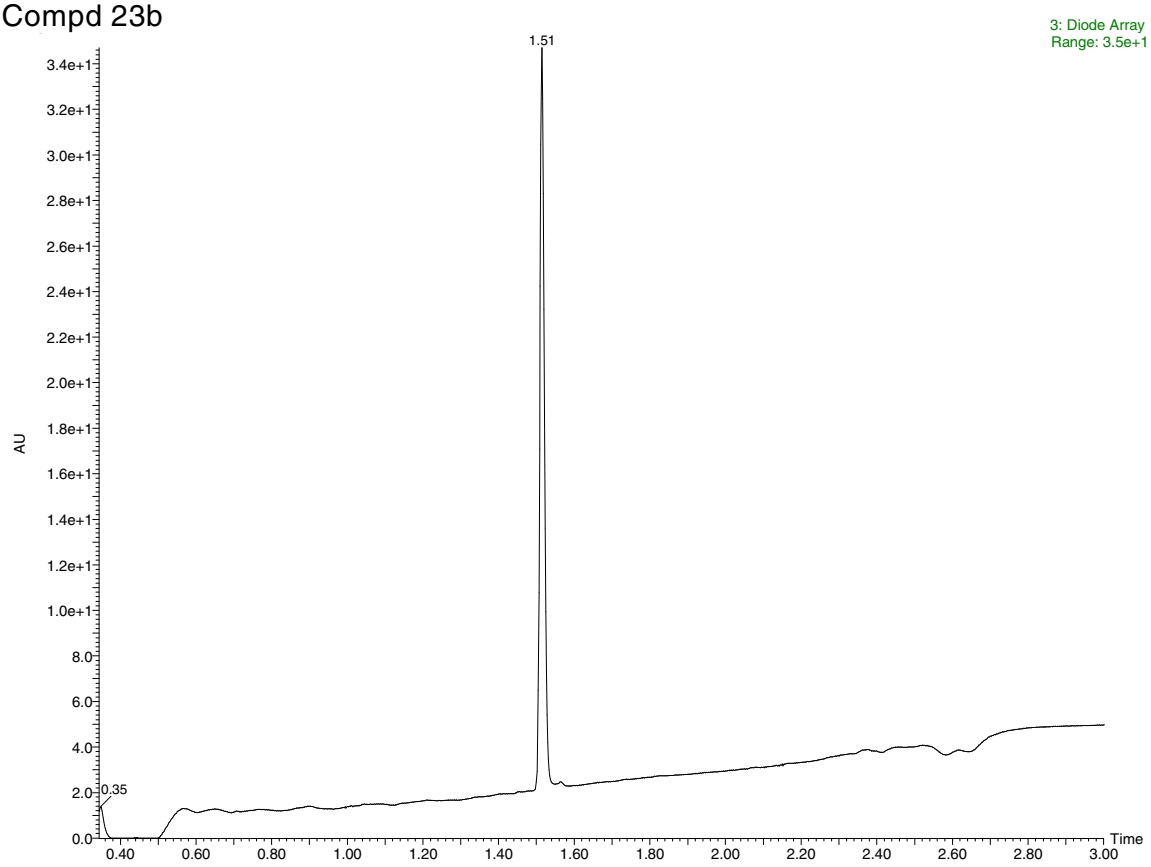
Compd (S)-22b


3: Diode Array
Range: 2.794e+1
1.54
0.34
AU
Time
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

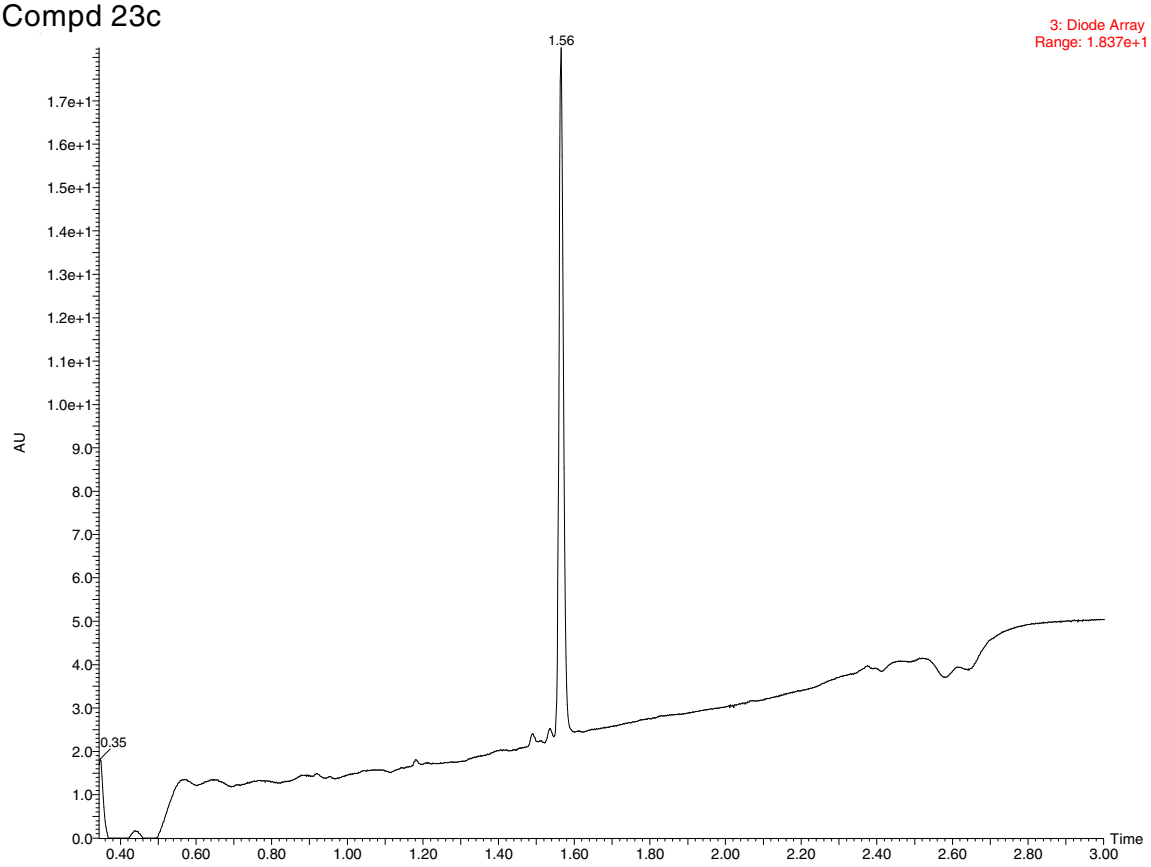
Compd 22c

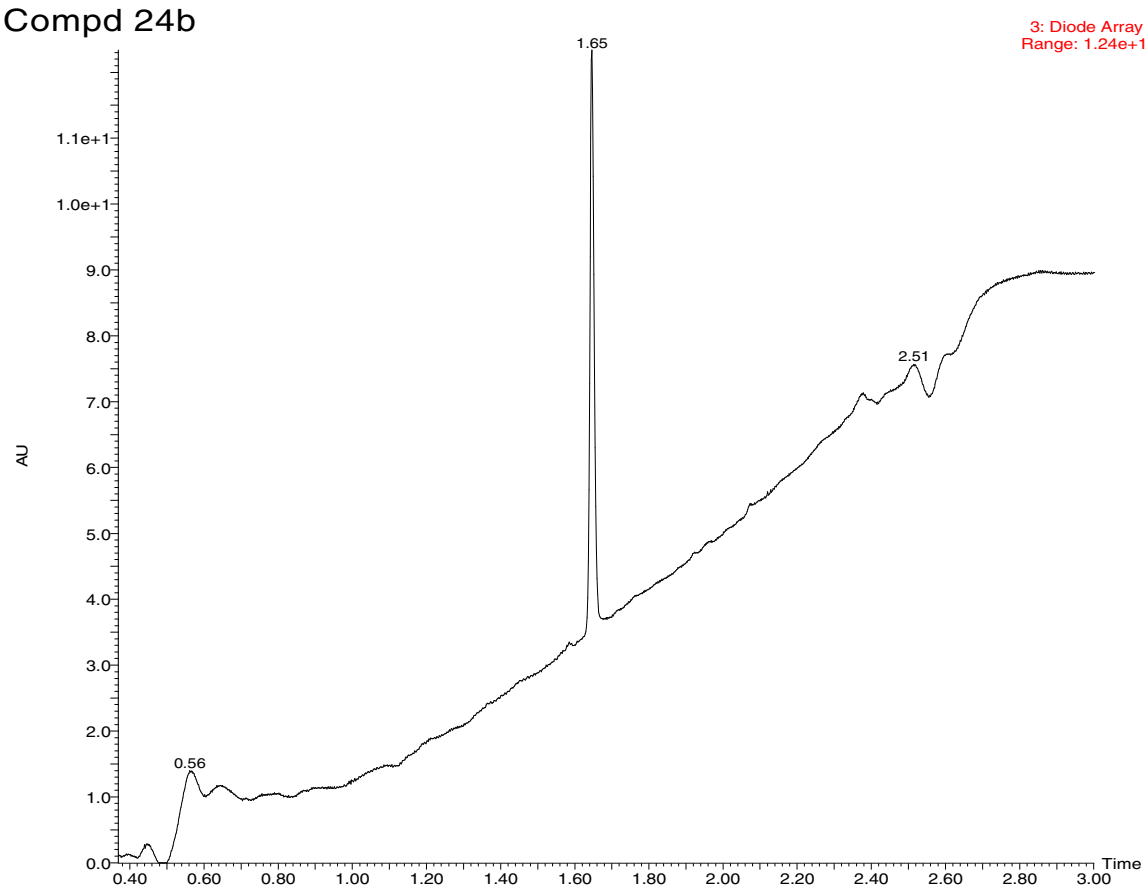

3: Diode Array
Range: 2.845e+1
1.61
0.35
AU
Time
2.6e+1
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 23b

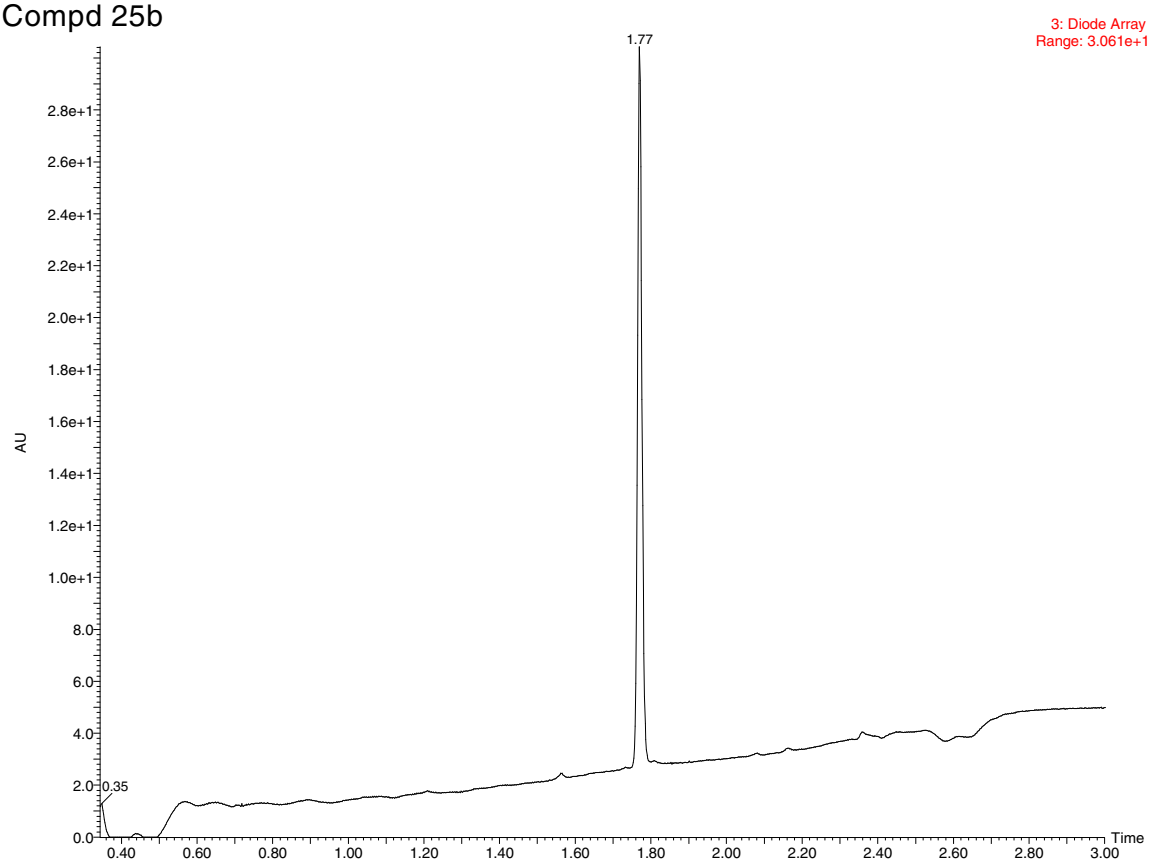

3: Diode Array
Range: 3.5e+1
1.51
0.35
AU
Time
3.4e+1
3.2e+1
3.0e+1
2.8e+1
2.6e+1
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 23c

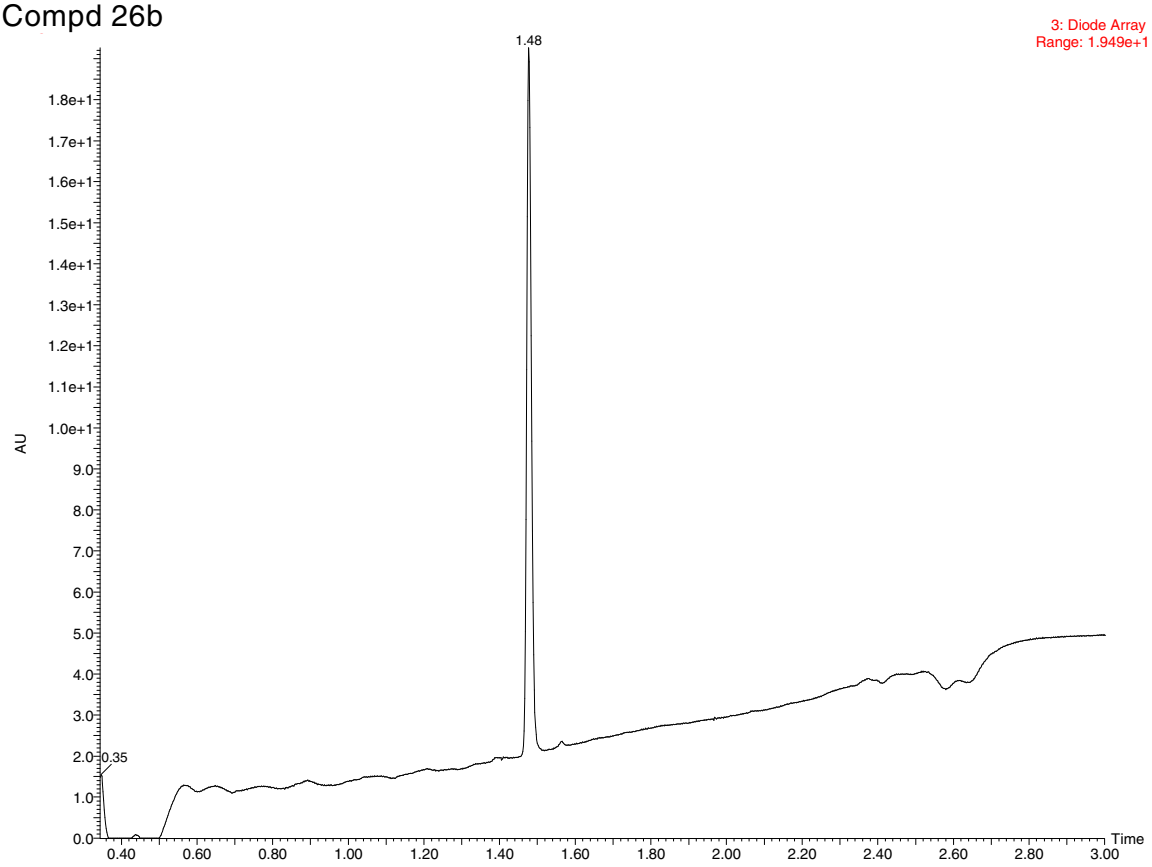

3: Diode Array
Range: 1.837e+1
1.56
0.35
AU
Time
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd 24b
3: Diode Array
Range: 1.24e+1
1.65
2.51
0.56
AU
Time
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

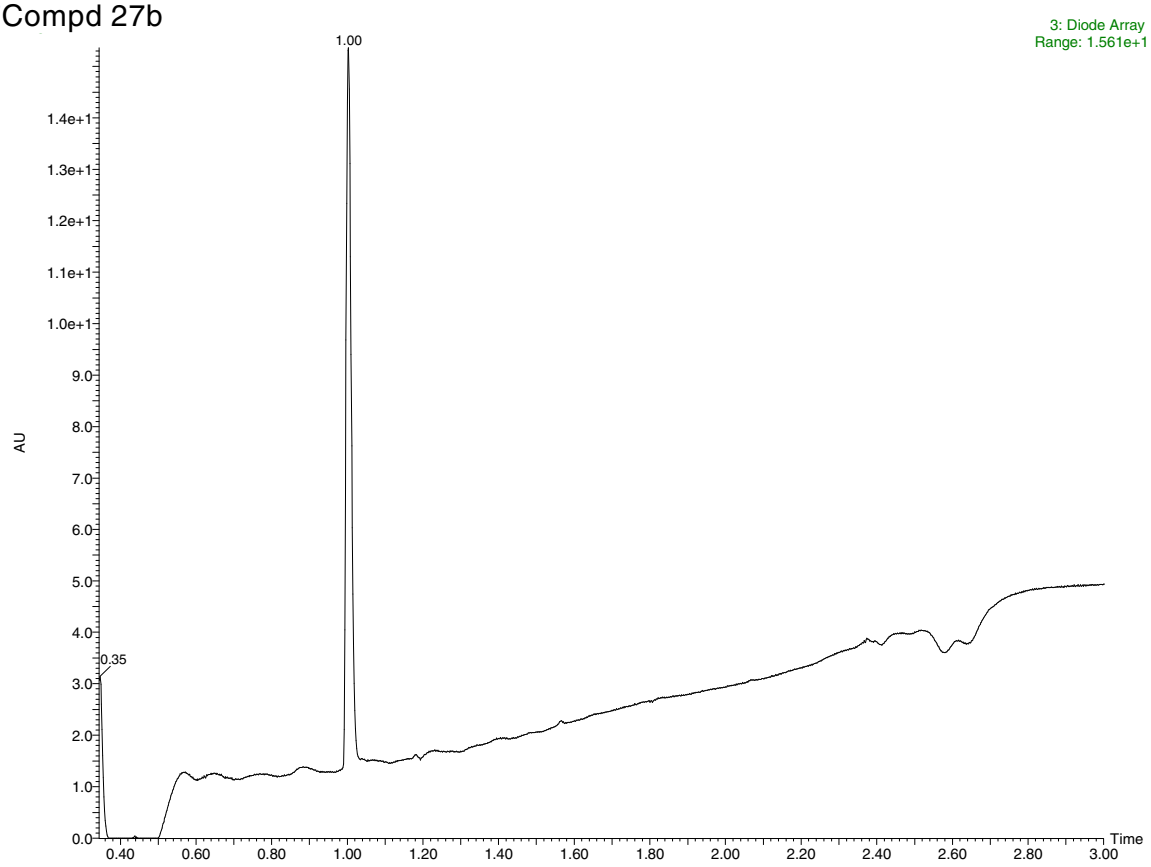
Compd 25b


3: Diode Array
Range: 3.061e+1
1.77
0.35
AU
Time
2.8e+1
2.6e+1
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

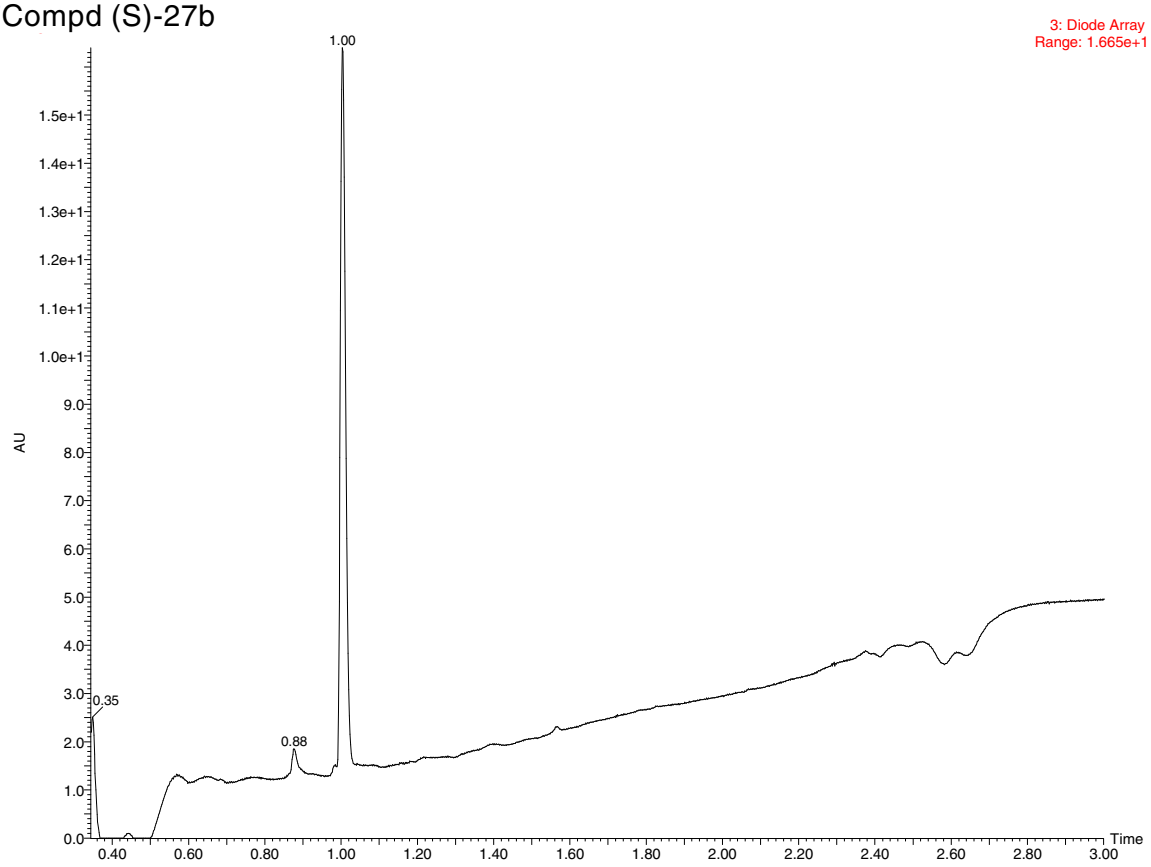
Compd 26b


3: Diode Array
Range: 1.949e+1
1.48
0.35
AU
Time
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

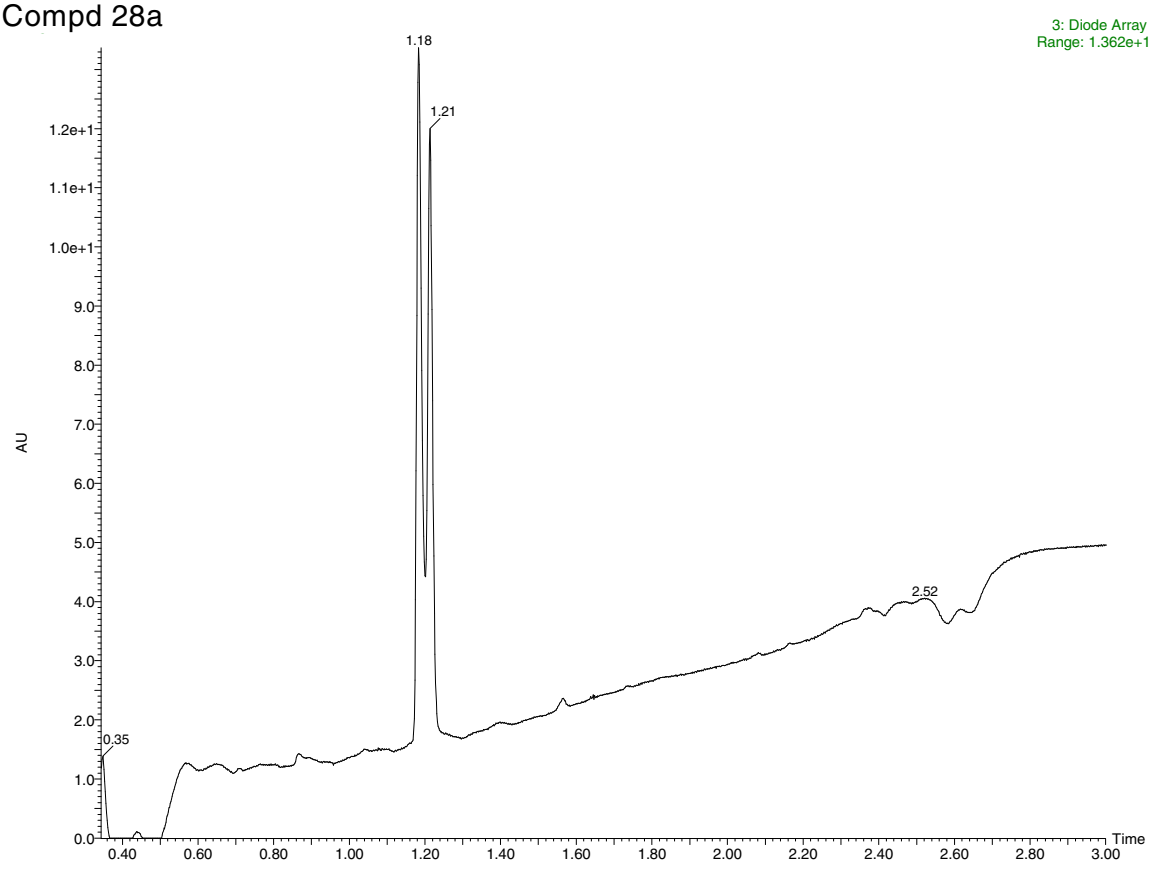
Compd 27b


3: Diode Array
Range: 1.561e+1
1.00
0.35
AU
Time
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

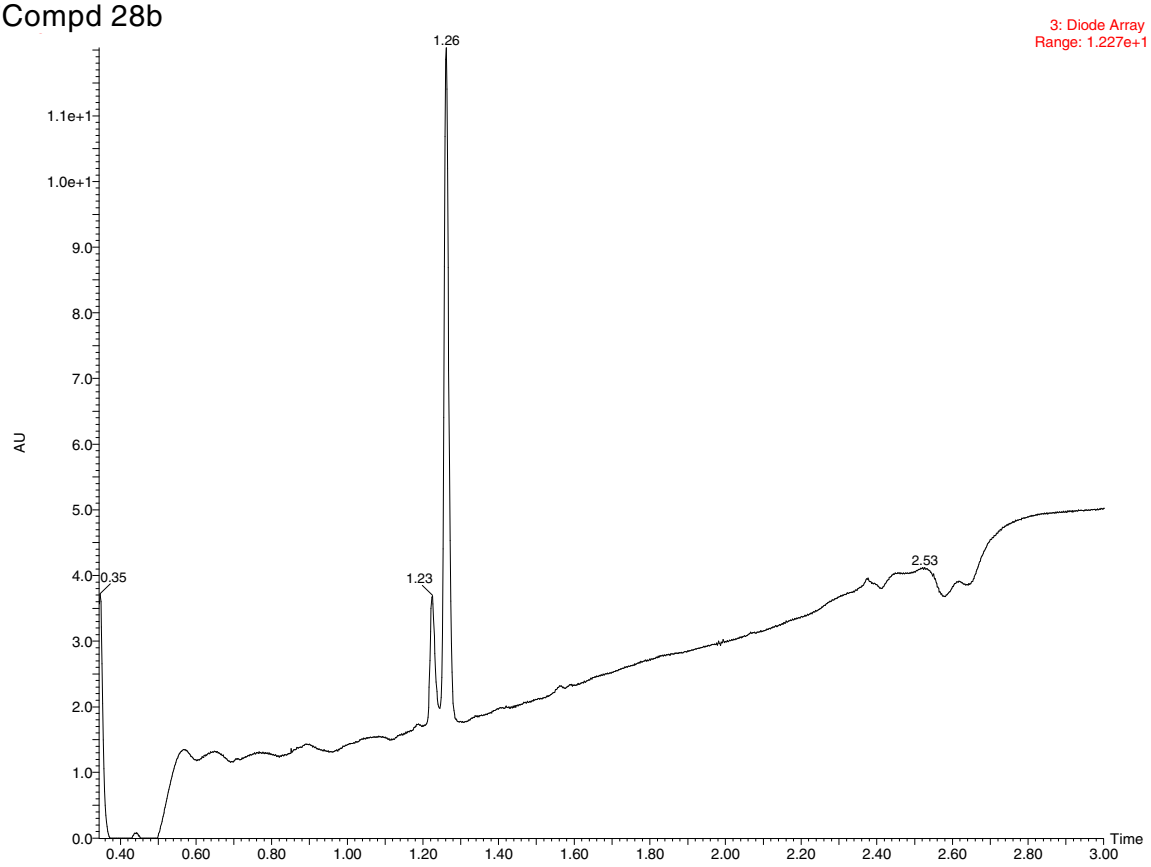
Compd (S)-27b


3: Diode Array
Range: 1.665e+1
AU
Time
1.00
0.88
0.35
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

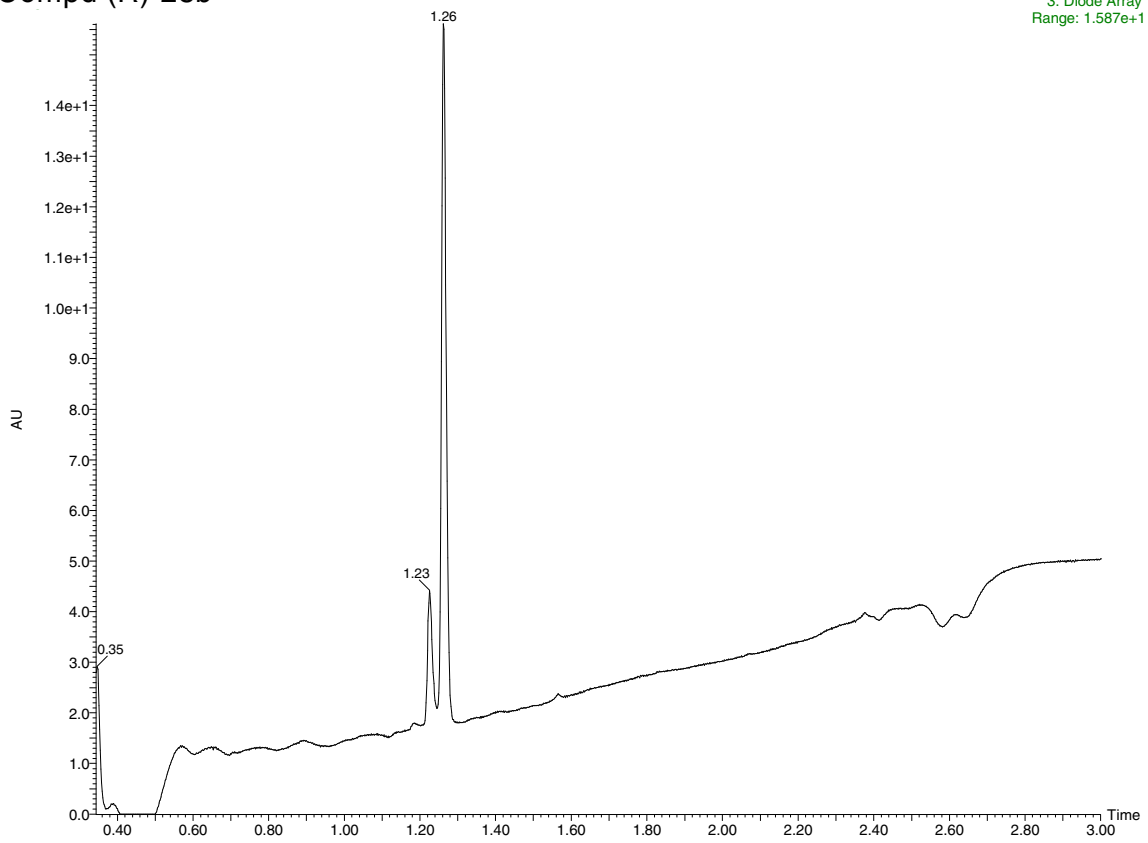
Compd 28a

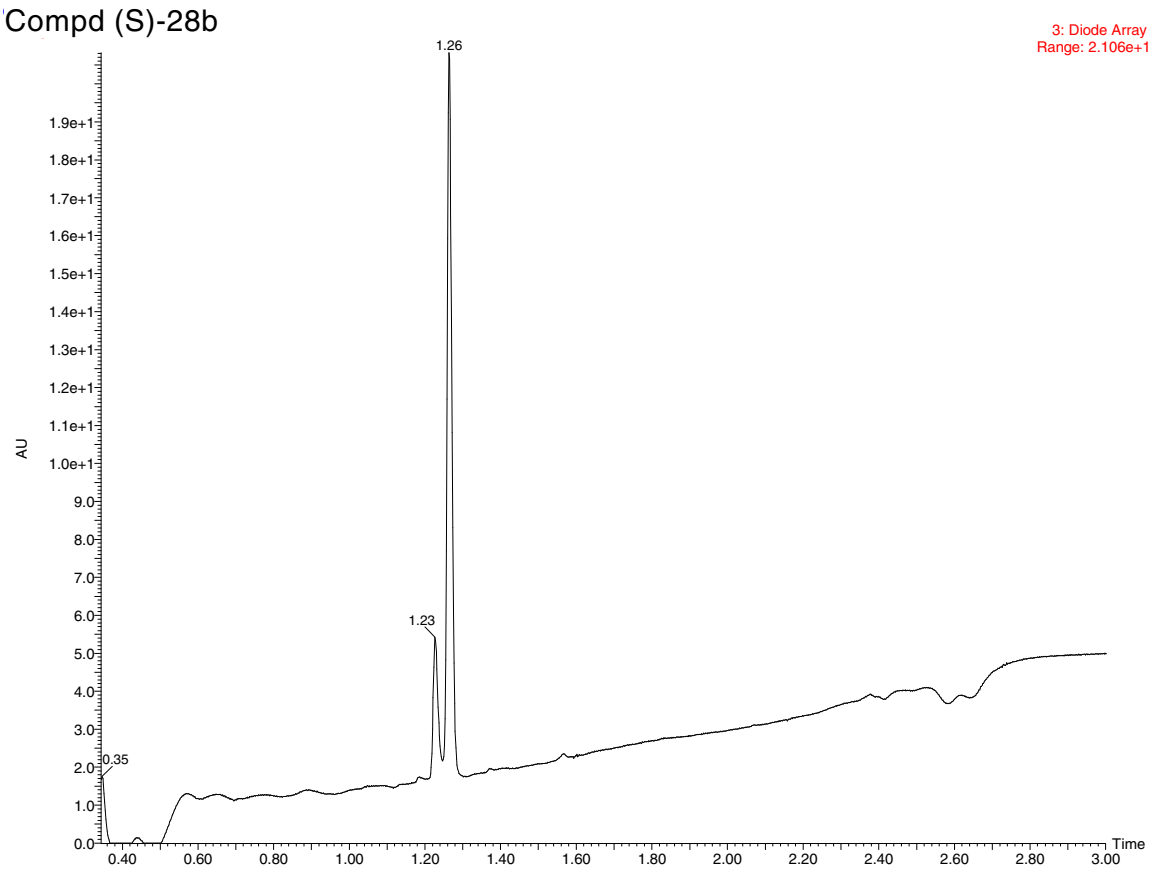

3: Diode Array
Range: 1.362e+1
1.18
1.21
2.52
0.35
AU
Time
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 28b

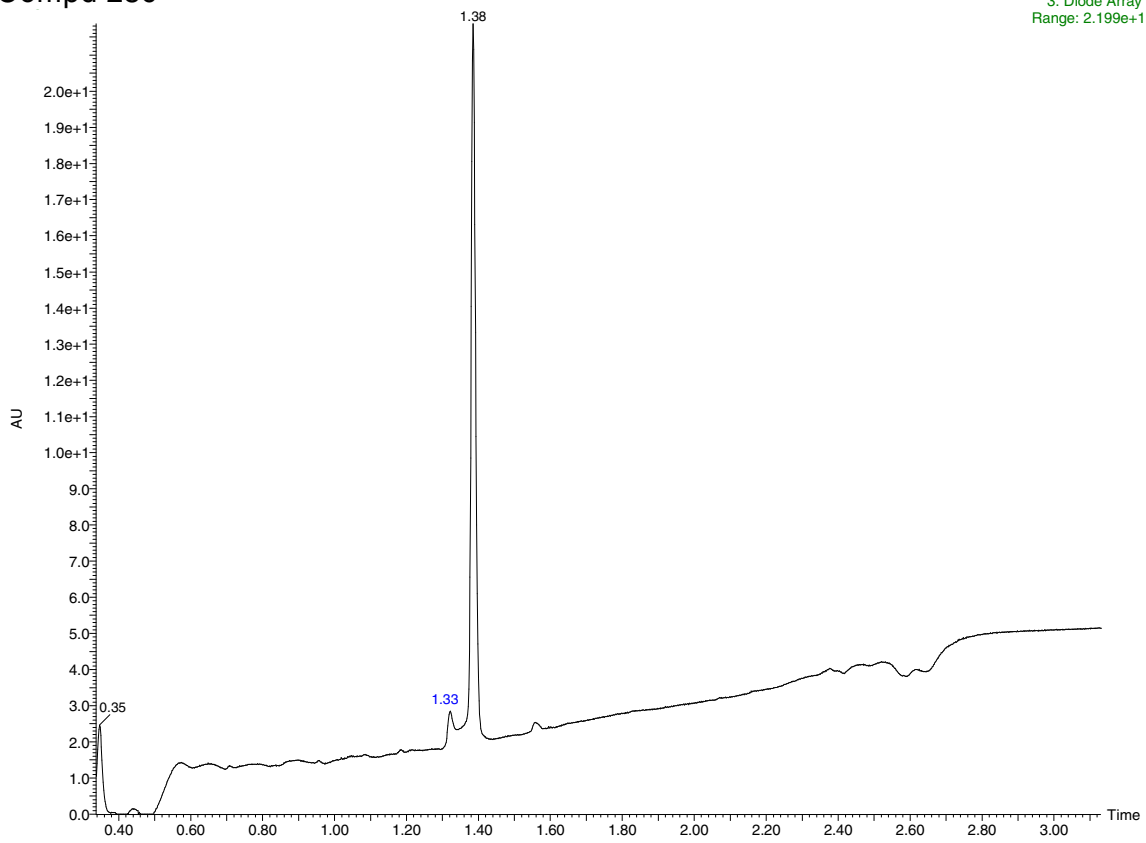

3: Diode Array
Range: 1.227e+1
AU
Time
1.26
0.35
1.23
2.53
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd (R)-28b

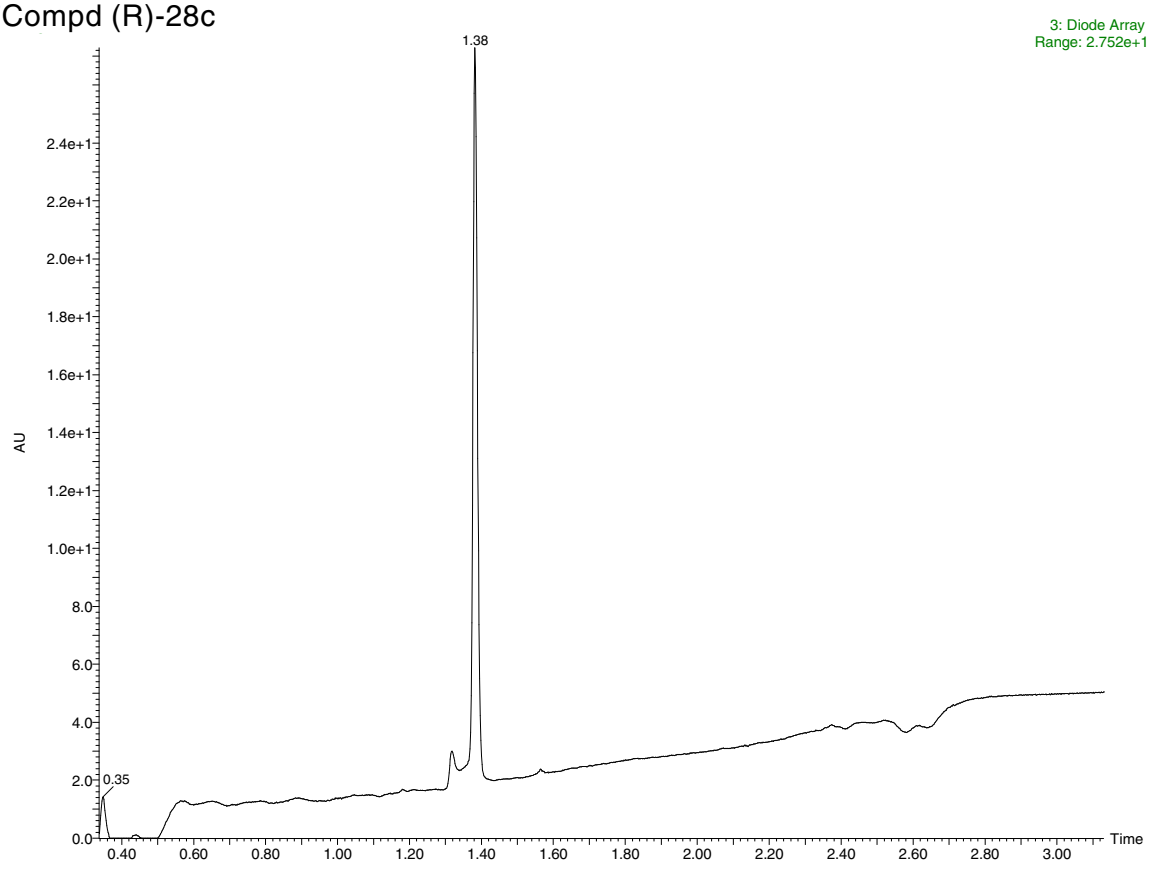

3: Diode Array
Range: 1.587e+1
1.26
1.23
0.35
AU
Time
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
1.0e+1
1.1e+1
1.2e+1
1.3e+1
1.4e+1
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00


Compd (S)-28b
3: Diode Array
Range: 2.106e+1
AU
Time
1.26
1.23
0.35
1.9e+1
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd 28c


3: Diode Array
Range: 2.199e+1
1.38
1.33
0.35
AU
Time
2.0e+1
1.9e+1
1.8e+1
1.7e+1
1.6e+1
1.5e+1
1.4e+1
1.3e+1
1.2e+1
1.1e+1
1.0e+1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd (R)-28c


3: Diode Array
Range: 2.752e+1
1.38
0.35
AU
Time
2.4e+1
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Compd (S)-28c

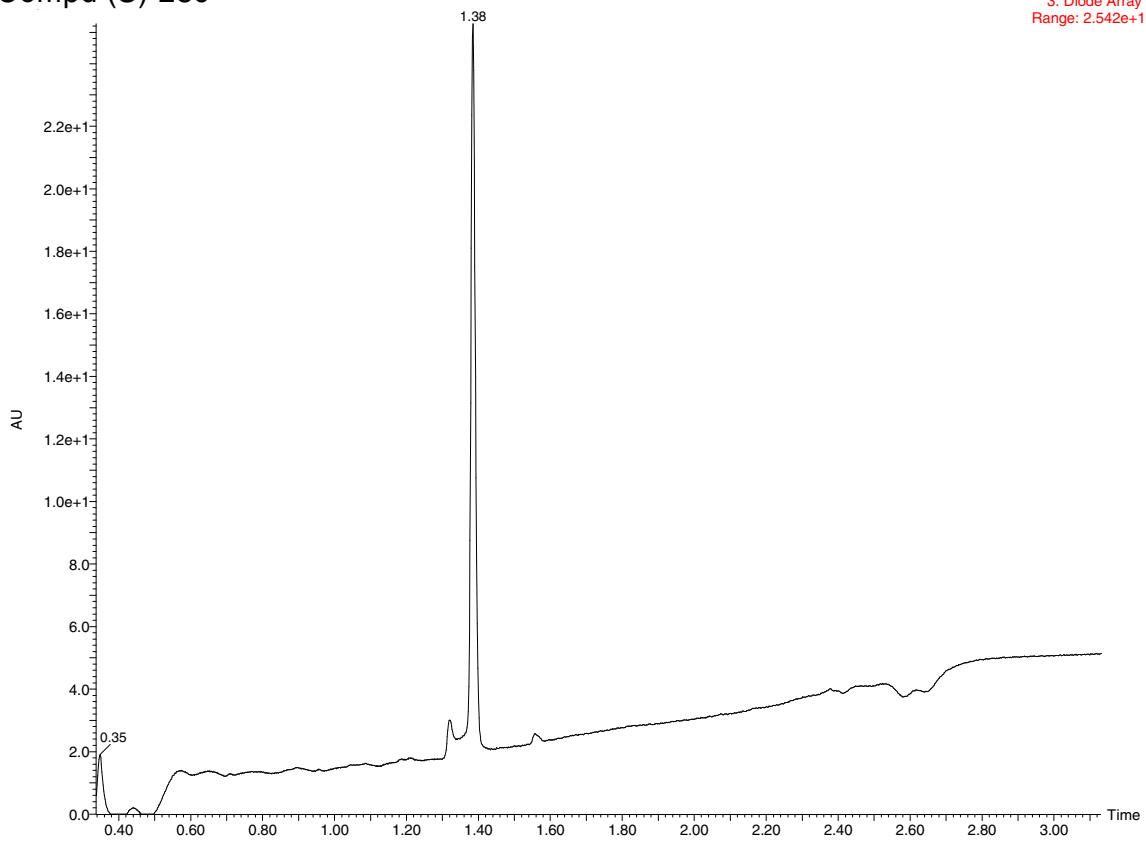

3: Diode Array
Range: 2.542e+1
1.38
0.35
AU
Time
2.2e+1
2.0e+1
1.8e+1
1.6e+1
1.4e+1
1.2e+1
1.0e+1
8.0
6.0
4.0
2.0
0.0
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00

Table 2. HRMS (high-resolution mass spectra).

compd	Elemental composition [M+H]+	Calc. for [M+H]+	Found [M+H]+	Delta (ppm)
7a	C17H20FN4O3	347.15140	347.15071	-1.98351
7b	C18H22FN4O3	361.16705	361.16786	2.24820
7c	C19H24FN4O3	375.18270	375.18298	0.76685
8b	C20H24FN4O3	387.18270	387.17947	-3.22181
9b	C21H26FN4O3	401.19835	401.19965	3.24432
10b	C20H24FN4O4	403.17761	403.17598	-1.63144
10c	C21H26FN4O4	417.19326	417.19300	-0.62961
11b	C24H26FN4O3	437.19835	437.19778	-0.56134
11c	C25H27FN4O3	451.21400	451.21304	-2.11125
12a	C15H15FN3O3	304.10920	304.10956	0.36176
12b	C16H17FN3O3	318.12485	318.12421	-2.01142
12c	C17H19FN3O3	332.14050	332.14050	0.00255
13a	C18H20FN4O4	375.14631	375.14741	2.94001
13b	C19H22FN4O4	389.16196	389.16290	2.42206
13c	C20H24FN4O4	403.17761	403.17560	-4.99084
14b	C19H20F3N4O4	425.14312	425.13974	-3.37669
15b	C22H24FN6O4	455.18376	455.18259	-1.17168
16b	C23H22FN8O4	493.17426	493.17548	2.47333
17b	C21H27FN5O6S	496.16606	496.16605	-0.02900
(R)-17b	C21H27FN5O6S	496.16606	496.16501	-2.12023
(S)-17b	C21H27FN5O6S	496.16606	496.16563	-0.87344
18b	C20H24FN4O6S	467.13951	467.13837	-2.44464
18c	C21H26FN4O6S	481.15516	481.15485	-0.65528
19b	C19H22FN4O6S	453.12386	453.12466	1.77207
20b	C18H22FN4O5S	425.12895	425.12946	1.19698

20c	C19H24FN4O5S	439.14460	439.14517	1.31016
21b	C23H28FN6O5S	519.18204	519.18182	-0.42606
22a	C18H23FN5O5S	440.13985	440.13901	-1.88948
22b	C19H25FN5O5S	454.15550	454.15324	-2.25453
(S)-22b	C19H25FN5O5S	454.15550	454.15500	-1.09442
(R)-22b	C19H25FN5O5S	454.15550	454.15430	-2.63994
22c	C20H27FN5O5S	468.17115	468.17065	-1.05003
23b	C20H25FN5O5S	466.15550	466.15551	0.02766
23c	C21H27FN5O5S	480.17115	480.17020	-1.97712
24b	C21H27FN5O5S	480.17115	480.17175	1.26422
25b	C22H29FN5O5S	494.18680	494.18573	-2.16104
26b	C21H27FN5O6S	496.16606	496.16562	-0.88096
27b	C22H30FN6O5S	509.19770	509.19674	-1.86578
(S)-27b	C22H30FN6O5S	509.19770	509.19690	-1.55535
(R)-27b	C22H30FN6O5S	509.19770	509.19690	-1.55535
28a	C20H23FN5O5	432.16777	432.16772	-0.11415
28b	C21H25FN5O5	446.18342	446.18152	-4.27059
(S)-28b	C21H25FN5O5	446.18342	446.18207	-3.02985
(R)-28b	C21H25FN5O5	446.18342	446.18344	0.02663
28c	C22H27FN5O5	460.19907	460.19944	0.78600
(S)-28c	C22H27FN5O5	460.19907	460.19943	0.77206
(R)-28c	C22H27FN5O5	460.19907	460.19880	-0.59367

High resolution mass measurements were carried out by electrospray ionization performed on a TSQ Quantum Ultra AM operating in enhanced mass resolution mode. The accurate mass measurements were carried out on a chromatographic time scale by means of flow injection of 5 µL of each working solution (20 µg/mL concentration) in acetonitrile on a Waters C_{18} Sunfire (20 x 2.1 mm, 5 µm) column using an isocratic elution (solvent A: solvent B, 50 : 50) of solvent A: water + 0.1% formic acid and solvent

B: acetonitrile + 0.1% formic acid at a flow rate of 1000 μL/min.