Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Information

Halogen bonding enhances activity in a series of dual 5-HT_6/D_2 ligands designed in a hybrid bioisostere generation/virtual screening protocol

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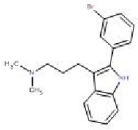
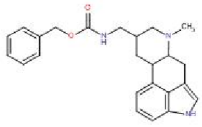
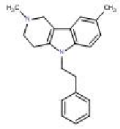
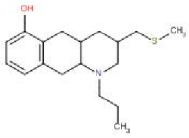
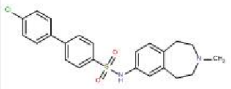
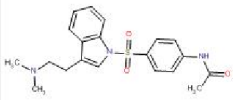
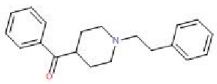
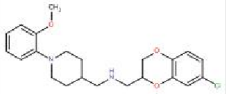
Contents

Table 1. Parent structures for 102 bioisosteres created in the vBrood program that passed all VS protocol filters. Subsequent columns show how many compounds passed each of the VS protocol filters.

Parent structure	Compound_name	Input	Veber, Lipinski filter	physiochemical filter	AMDE/Tox filter	pharmacophore mappring	docking protocol	SIFt profiling
	CMPD_13272	2628	2418	2417	2207	2093	154	0
	CMPD_13566	133	8	8	5	5	2	1
	CMPD_13596	2965	2849	2837	2506	1581	543	14
	CMPD_13884	571	411	411	348	136	0	0
	CMPD_14889	4662	4572	4562	3317	2355	933	20
	CMPD_16178	2950	2745	2738	484	403	10	0
	CMPD_16506	6323	6050	5895	5037	1551	148	4
	CMPD_17401	6555	6419	6419	5551	4840	1707	63
Total		26787	25472	25287	19455	12964	3497	102

Radioligand binding assays

Cell pellets were thawed and homogenized in 20 volumes of assay buffer using an Ultra Turrax tissue homogenizer and centrifuged twice at 35 000 g for 20 min at 4°C, with incubation for 15 min at 37°C in between the rounds of centrifugation. The composition of the assay buffers was as follows: for 5-HT_{1A}R: 50 mM Tris–HCl, 0.1 mM EDTA, 4 mM $MgCl_2$, 10 µM pargyline and 0.1% ascorbate; for 5-HT_6R: 50 mM Tris–HCl, 0.5 mM EDTA and 4 mM $MgCl_2$, for 5-HT_{7b}R: 50 mM Tris–HCl, 4 mM $MgCl_2$, 10 µM pargyline and 0.1% ascorbate; for dopamine D_{2L}R: 50 mM Tris–HCl, 1 mM EDTA, 4 mM $MgCl_2$, 120 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$ and 0.1% ascorbate.

All assays were incubated in a total volume of 200 µl in 96-well microtiter plates for 1 h at 37°C, excluding 5-HT_{1A}R, which was incubated at room temperature for 1 h. The equilibration process was terminated by rapid filtration through Unifilter plates with a 96-well cell harvester, and the radioactivity retained on the filters was quantified using a Microbeta plate reader.

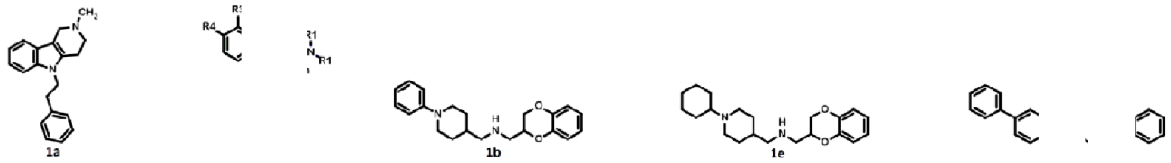
For the displacement studies, the assay samples contained the following as radioligands: 1.5 nM [^{3}H]-8-OH-DPAT (187 Ci/mmol) for 5-HT_{1A}R, 2 nM [^{3}H]-LSD (85.2 Ci/mmol for 5-HT_6R, 0.6 nM [^{3}H]-5-CT (39.2 Ci/mmol) for 5-HT_{7b}R or [^{3}H]-Raclopride (74.4 Ci/mmol) for D_2R.

Non-specific binding was defined using 10 µM of 5-HT in the 5-HT_{1A}R and 5-HT_{7b}R binding experiments, whereas 10 µM methiothepine or 1 µM (+)butaclamol was used in the 5-HT_6R and D_{2L} assays, respectively. Each compound was tested in triplicate at 7–8 concentrations (10^{-11}–10^{-4} M). The inhibition constants (K_i) were calculated using the Cheng-Prusoff equation,[1] and the results are expressed as the means of at least two independent experiments.

5-HT_6R and 5-HT_7R functional activity assay

HEK293 cells overexpressing 5-HT_6 and 5-HT_{7b} receptors (prepared using Lipofectamine 2000) were maintained at 37°C in a humidified atmosphere with 5% CO_2 and grown in Dulbecco's Modified Eagle's Medium containing 10% dialyzed foetal bovine serum and 500 mg/ml G418 sulfate. For the functional experiments, the cells were subcultured in 25-cm^2 diameter dishes, grown to 90% confluence, washed twice with phosphate-buffered saline (PBS) prewarmed to 37°C and centrifuged for 5 min (160 × g). The supernatant was aspirated, and the cell pellet was resuspended in stimulation buffer (1 × HBSS, 5 mM HEPES, 0.5 mM IBMX, 0.1% BSA). The functional properties of compounds were evaluated using their ability to inhibit cAMP production induced by agonist: the 5-CT – 100 nM for 5-HT_6R and 10 nM for 5-HT_{7b}R. Total cAMP was measured using the LANCE cAMP detection kit (PerkinElmer) according to the manufacturer's directions. To quantify the levels of cAMP, the cells (5 µl) were incubated with the test compounds and 5-CT (5 µl) for 30 min at room temperature in 384-well white opaque microtiter plate. After incubation, the reaction was stopped, and the cells were lysed by addition of 10 µl of a working solution (5 µl of Eu-cAMP and 5 µl of ULight-anti-cAMP). The assay plate was incubated for 1 h at room temperature. Time-resolved fluorescence resonance energy transfer (TR-FRET) was detected using an Infinite M1000 Pro (Tecan) with instrument settings according to the LANCE cAMP detection kit manual. K_b values were calculated using the Cheng-Prusoff equation[1] specific for the analysis of functional inhibition curves: $K_b = IC_{50}/(1 + A/EC_{50})$, where A is the agonist concentration, IC_{50} is the concentration of antagonist that produces a 50% reduction in the response to agonist, and EC_{50} is the agonist concentration that causes a half maximal response.

Table 2. Standard deviation parameters for binding affinities of synthesized compounds.



Cmpd.	Substitution					K_i *[nM]* ± S.D.				
	n	*R1*	R2	R3	R4	5-HT_6	D_2	5-HT_7	5-HT_{1A}	5-HT_{2A}
1a	-	-	-	-	-	22±6	77±12	8±2	217±41	29±5
1b	-	-	-	-	-	2280±684	210±32	430±82	10±2	n.d.
1d	1	Me	H	H	H	63±13	476±71	121±36	1682±437	233±51
1e	-	-	-	-	-	2675±749	1609±386	3428±891	22±3	n.d.
1f	-	-	-	-	-	3760±1316	110±12	857±146	101±10	n.d.
4a	1	Et	H	H	H	51±15	266±40	205±39	7614±2436	128±26
4b	2	Me	H	H	H	67±18	55±23	623±100	4486±1570	228±50
4c	1	Me	H	H	F	23±5	37±3	31±6	5707±1655	58±8
4d	1	Me	H	H	Me	25±2	33±2	10±2	482±96	70±11
4e	1	Me	H	H	CF_3	61±11	274±47	30±6	5341±1816	809±170
4f	1	Me	H	H	OMe	234±35	1147±298	141±24	n.d.	863±155
4g	1	Me	H	Me	H	264±37	n.d.	2253±721	605±127	777±163
4h	2	Me	H	H	F	38±8	80±17	38±7	8969±2691	27±6
4i	1	Me	H	F	H	64±12	594±77	748±120	n.d.	312±56
4j	1	Me	Cl	H	Cl	597±107	1176±306	387±74	n.d.	472±99
4k	1	Me	H	OMe	H	355±53	1738±504	4512±1399	n.d.	721±144
4l	2	Me	H	H	Me	83±24	108±30	24±5	2140±728	204±37
4m	1	Me	H	H	Cl	24±4	153±14	4±1	5960±1967	212±21
4n	1	Me	Me	H	H	380±49	n.d.	1040±291	n.d.	348±52
4o	1	Me	naphthyl		H	137±15	423±72	2037±550	4749±1567	621±137
4p	1	Me	H	F	F	21±1	n.d.	114±14	n.d.	79±20
4q	1	Me	H	H	Br	90±16	505±101	19±3	n.d.	295±47
4r	1	Me	H	H	I	79±7	691±111	10±1	n.d.	372±67
4s	1	Me	Me	H	Me	347±49	1751±473	597±107	n.d.	518±88
4t	1	Me	H	Cl	H	150±27	675±115	353±39	n.d.	311±31

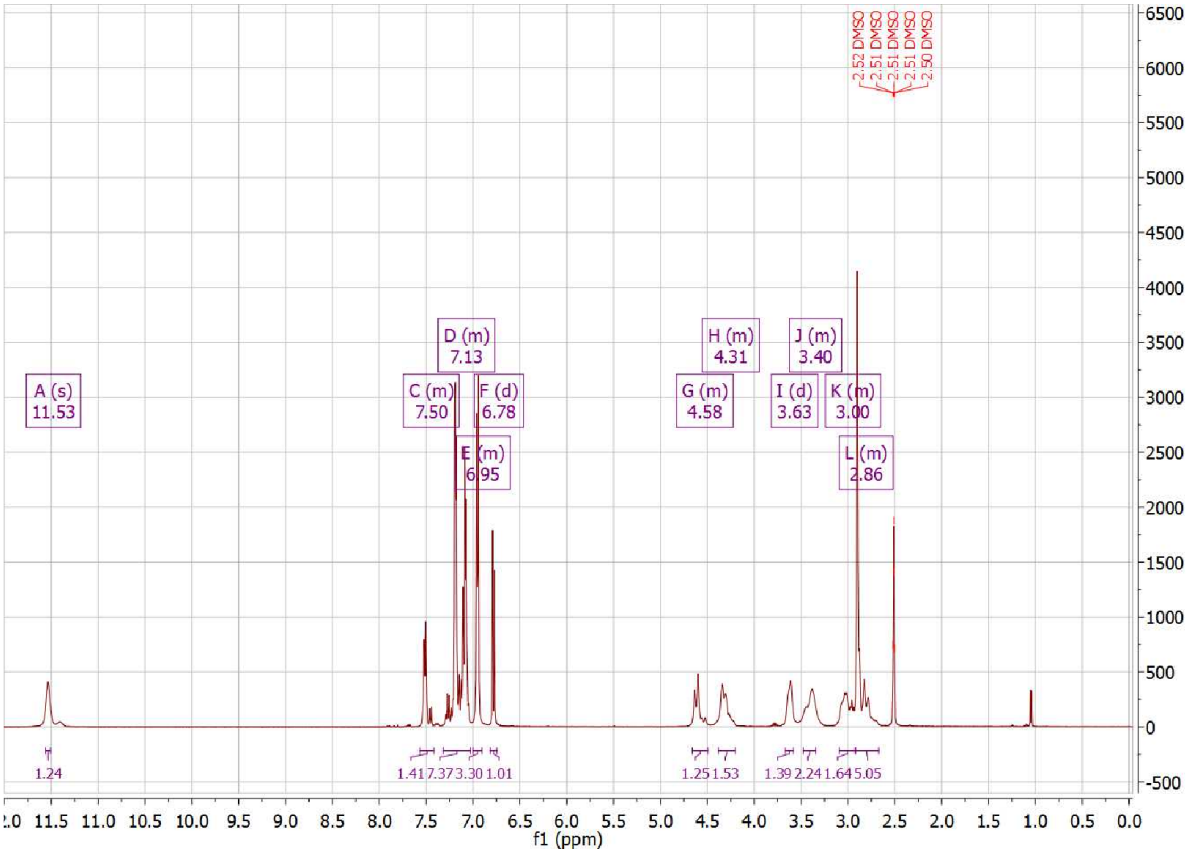
n.d. – not determined.

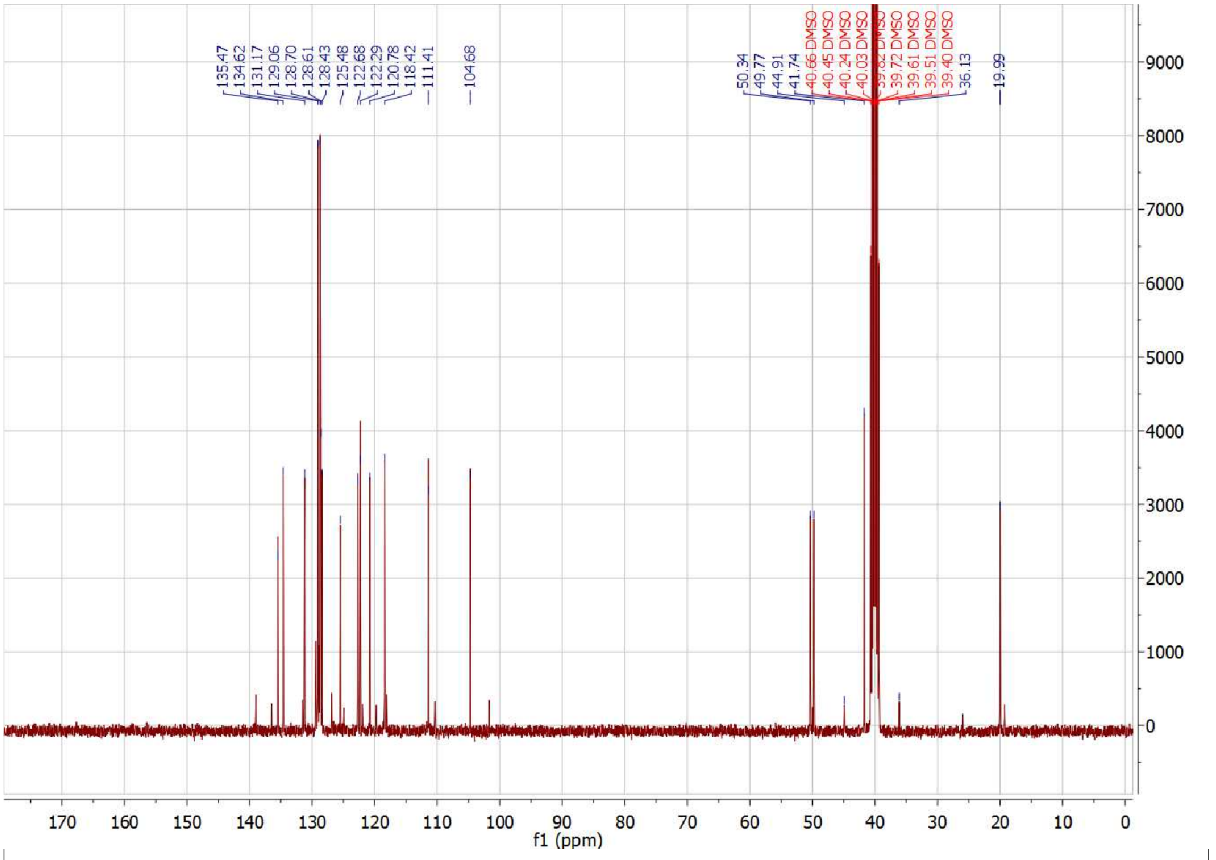
2-methyl-5-(2-phenylethyl)-1H,2H,3H,4H,5H-pyrido[4,3-b]indole (1a).

A 50-ml round bottom flask was charged with N-methyl-4-piperidone (1.04 g, 9.1 mmol), phenylhydrazine (1 g, 9.2 mmol), concentrated sulfuric acid (2.5 ml) and 1,4-dioxane (15 ml). The reaction mixture was heated to 60°C for 2 hours. After cooling to room temperature, the reaction mixture was adjusted to pH = 13 by the addition of a saturated solution of sodium bicarbonate and solid sodium hydroxide. The obtained mixture was extracted with ethyl acetate (3x 50 ml). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The product was purified using column chromatography on silica with chloroform:methanol (19:1). A brown solid of **2a** was obtained (0.86 g, 50%). LCMS [M+1] = 269.20 m/z (268.19 calc). N-methyl-2,3,4,5,tetrahydro-1H-pyrido[4,3-b]indole (**2a**) (0.68 g, 3.6 mmol) was placed in a 50-ml round bottom flask together with phenylacetylene (0.82 ml, 7.4 mmol), 60% KOH (10.28 ml), DMSO, (3.4 ml), and 50% $(Bu_4N)_2SO_4$ (0.34 ml) and sealed under argon. The reaction mixture was heated at 80°C for 20 hours. The product was extracted with dichloromethane (3x 50 ml) and purified using column chromatography on silica with chloroform:methanol (19:1). A light brown solid of **2b** was obtained (0.92 g, 89%). The 2-methyl-5-(2-phenylethynyl)-1H,2H,3H,4H,5H-pyrido[4,3-b]indole (**2b**) (0.77 g, 2.7 mmol) was placed in a pressure reactor with platinum dioxide (0.24 g) and anhydrous ethanol (100 ml). The reaction mixture was sealed and hydrogenized under 4 bar for 10 hours. After completion, the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The product was purified by column chromatography on silica with chloroform:methanol (9:1). A light brown solid of **1a** was obtained (0.5 g, 63%). LCMS [M+1] = 291.18 m/z (290.18 calc.).

^{1}H NMR (DMSO-D_6, 400.17MHz) (ppm): 2.92 – 2.67 (m, 5H), 3.09 – 2.92 (m, 2H),3.47 – 3.34 (m, 2H), 3.63 (d, J = 14.4 Hz, 1H), 4.38 – 4.20 (m, 2H), 4.66 –4.50 (m, 1H), 6.78 (d, J = 8.7 Hz, 1H), 7.00 – 6.90 (m, 2H), 7.32 – 7.02 (m,5H), 7.57 – 7.42 (m, 1H), 11.53 (s, 1H).

^{13}C NMR (DMSO-D_6, 100.04MHz) (ppm): 19.99, 36.13, 41.74, 44.91, 49.77, 50.34,104.68, 111.41, 118.42, 120.78, 122.29, 122.68, 125.48, 128.43, 128.61,128.70, 129.06, 131.17, 134.62, 135.47

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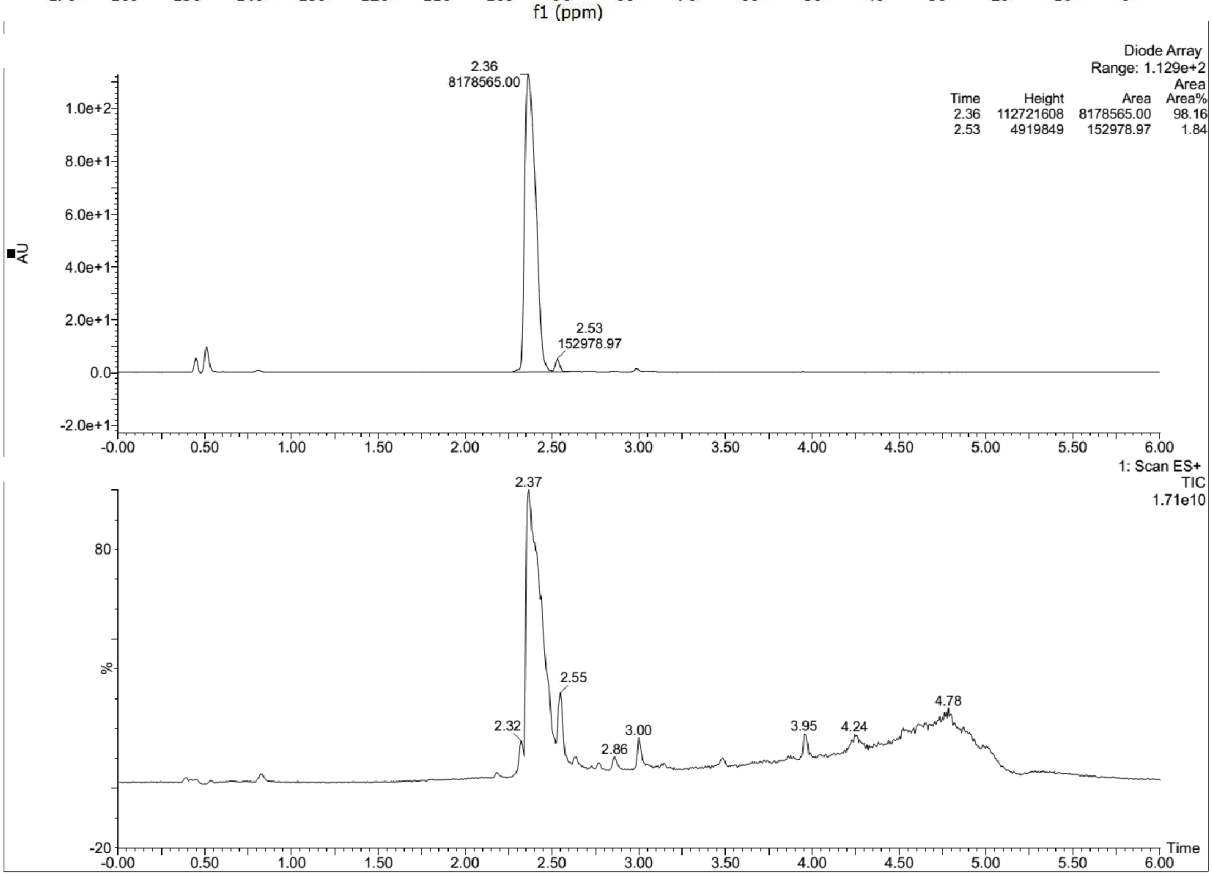
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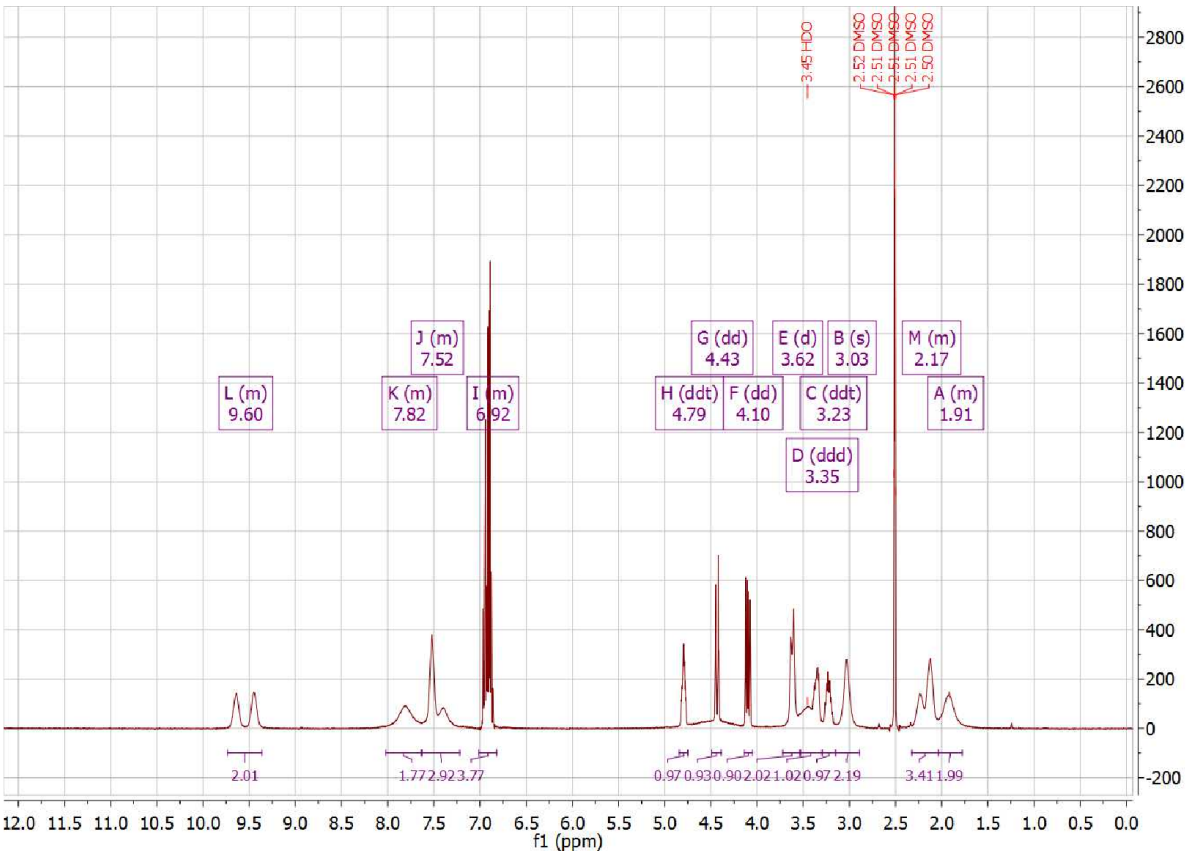
Time

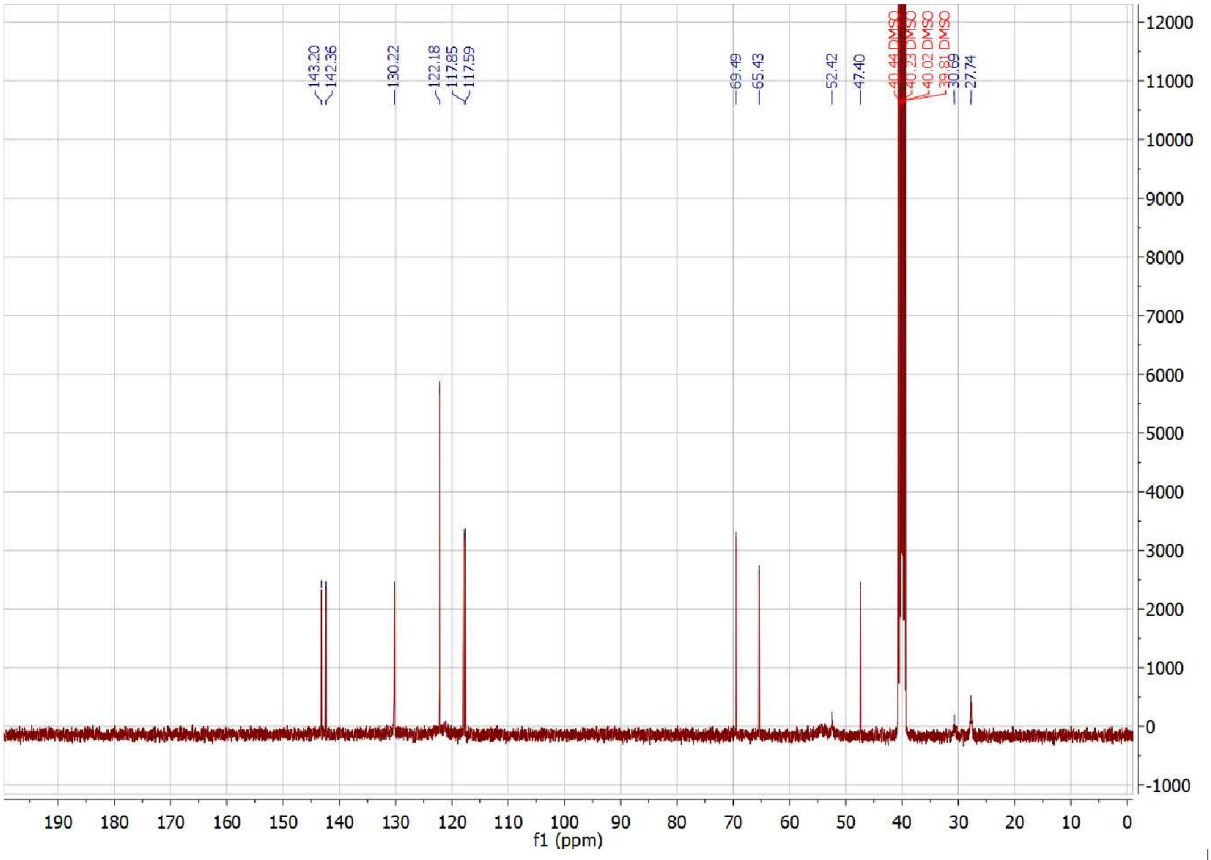
(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)[(1-phenylpiperidin-4-yl)methyl]amine (1b).

5d (0.56 g, 0.0017 mol) and **5j** (0.33 g, 1 eq.) were dissolved in acetonitrile (7 ml) with anhydrous K_2CO_3 (0.83 g) and heated in a pressure reactor in a microwave oven at 160°C for 30 min. After cooling the reaction mixture was filtered, the precipitate washed with acetonitrile (20 ml) and the combined filtrates evaporated under reduced pressure. The product was purified by column chromatography (SiO_2, $CHCl_3$:MeOH 9:1). A light brown oil of **1b** was obtained (0.424 g, 73%). LCMS [M+1] = 339.20 m/z (338.20 calc).

^{1}H NMR (DMSO-D_6, 400.17 MHz) ppm): 2.04 – 1.78 (m, 2H), 2.32 – 2.04 (m, 3H), 3.03 (s, 2H), 3.23 (ddt, J = 13.6, 8.7, 3.7 Hz, 1H), 3.35 (ddd, J = 13.8, 7.6, 3.8 Hz, 2H), 3.62 (d, J = 11.4 Hz, 3H), 4.10 (dd, J = 11.7, 6.6 Hz, 1H), 4.43 (dd, J = 11.7, 2.4 Hz, 1H), 4.79 (ddt, J = 8.4, 6.4, 3.2 Hz, 1H), 7.63 – 7.22 (m, 3H), 7.01 – 6.82 (m, 4H), 9.74 – 9.36 (m, 2H), 8.02 – 7.63 (m, 2H).

^{13}C NMR (DMSO-D_6, 100.17MHz) ppm): 7.74, 30.69, 47.40, 52.42, 65.43, 69.49, 117.59, 117.85, 122.18, 130.22, 142.36, 143.20.

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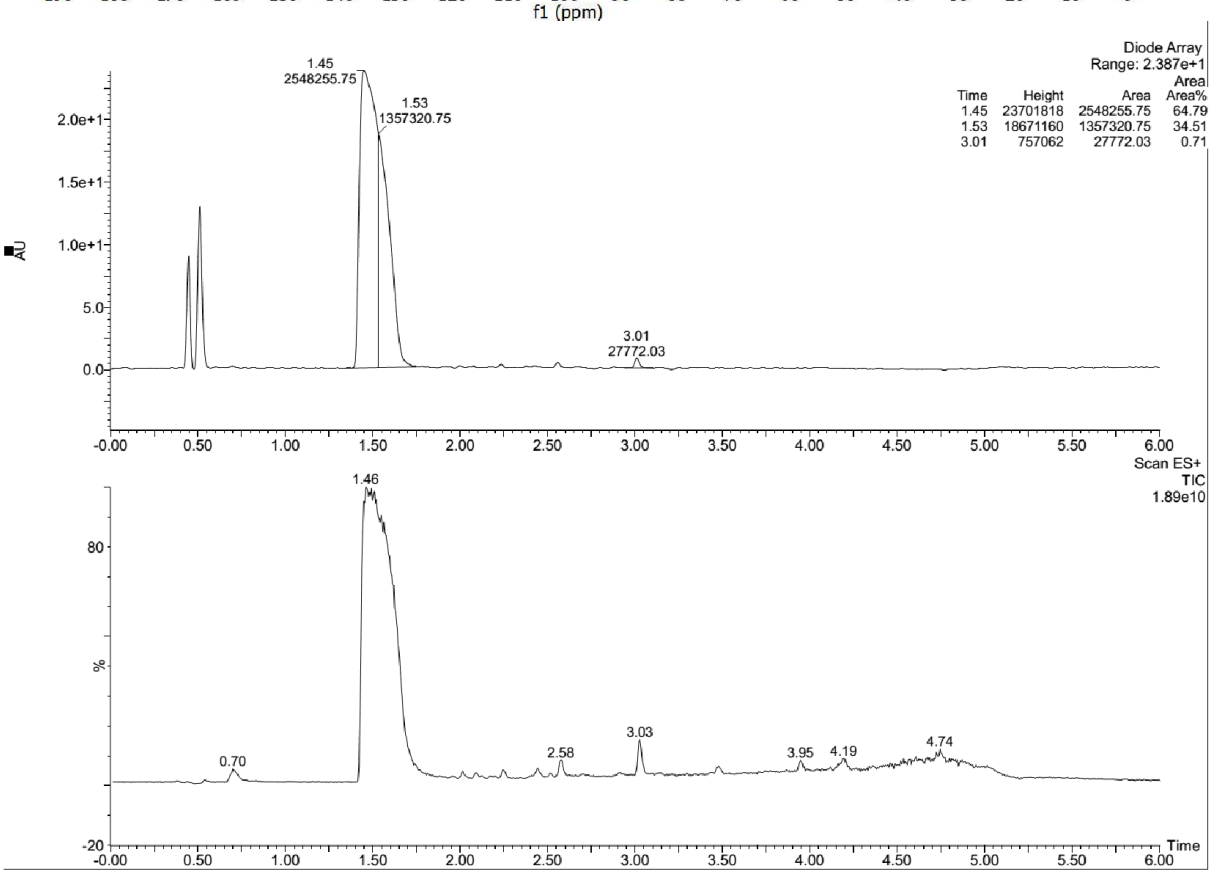
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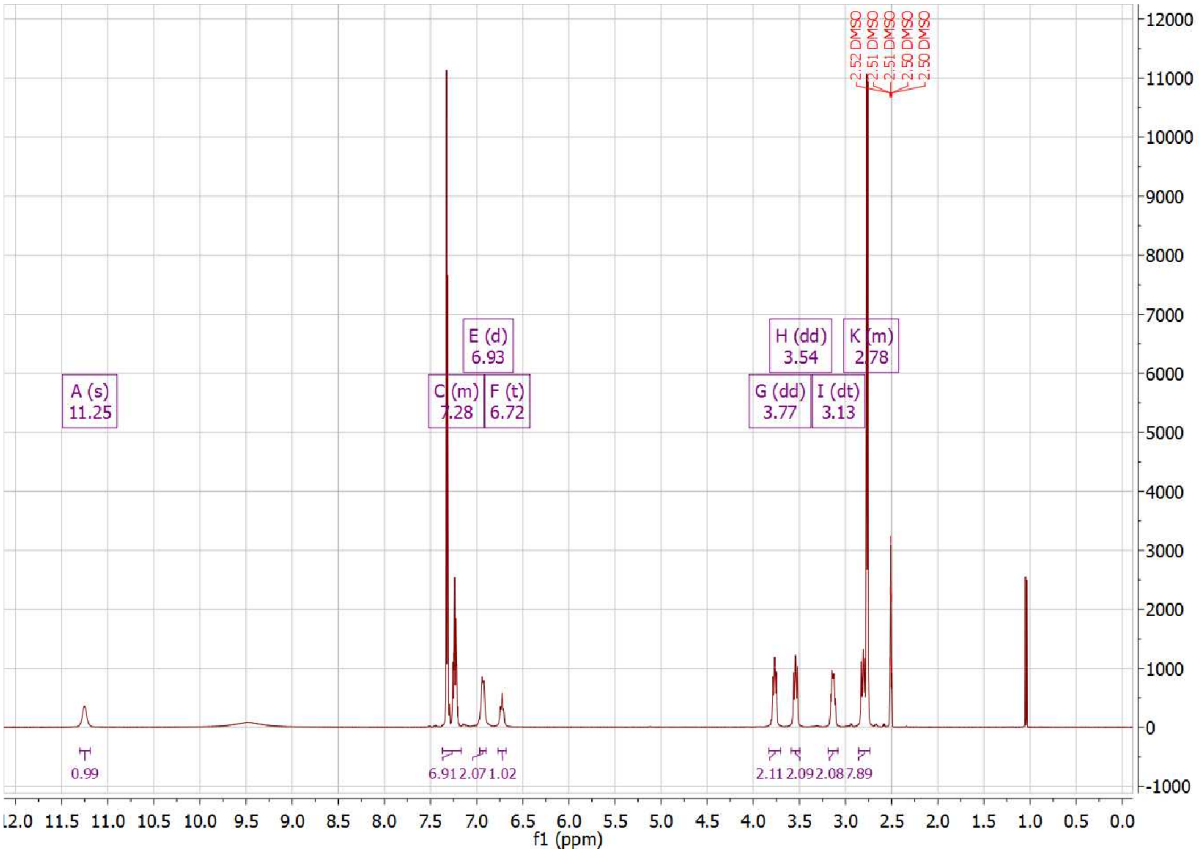
4.19
4.74
%
Time

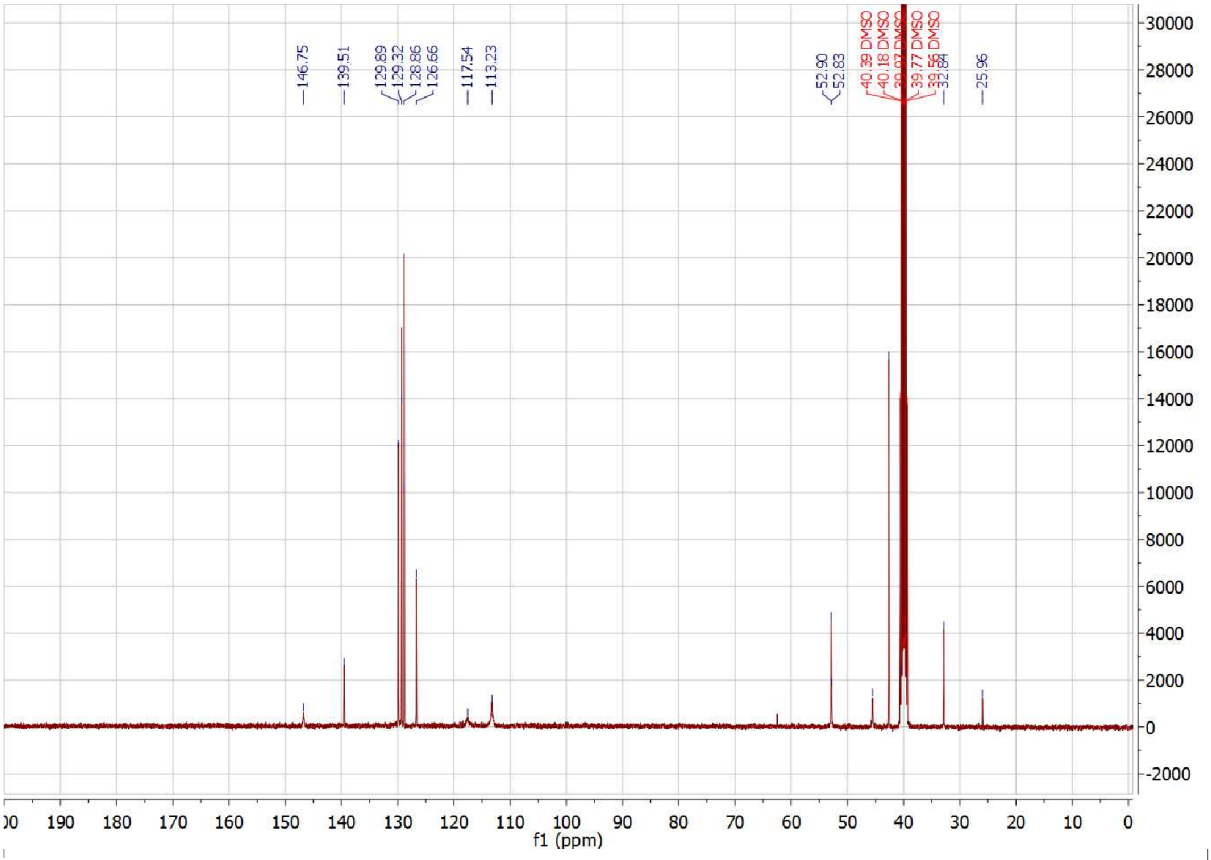
N-[2-(dimethylamino)ethyl]-N-(2-phenylethyl)aniline (1d).

3a (N-[2-(dimethylamino)ethyl]aniline) was synthesized according to general procedure 1 using aniline (5 g, 0.053 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 2.30 g), K_2CO_3 (2 eq., 14.63 g), isopropanol (100 ml). A brown oil of **3a** was obtained (2.35 g, 90%) LCMS [M+1] = 165.20 m/z (164.25 calc). **1d** was synthesized according to general procedure for 2 using 2.086 g (0.0127 mol) of **3a**, phenylacetaldehyde (1.5 eq., 2.29 g), sodium triacetoxyborohydride (2 eq., 5.38 g), dichloroethane (50 ml). A light-brown oil was obtained (0.56 g, 16%). LCMS [M+1] = 269.20m/z (268.19 calc).

^{1}H NMR (DMSO-D_6, 400.17 MHz) ppm): 2.86 – 2.73 (m, 8H), 3.13 (dt, J = 9.1, 5.7Hz, 2H), 3.54 (dd, J = 9.2, 6.8 Hz, 2H), 3.77 (dd, J = 9.5, 6.0 Hz, 2H), 6.72 (t,J = 7.3 Hz, 1H), 6.93 (d, J = 8.1 Hz, 2H), 7.37 – 7.17 (m, 7H), 11.25 (s, 1H).

^{13}C NMR (DMSO-D_6, 100.17MHz) ppm): 25.96, 32.84, 40.31, 42.65, 45.53, 52.83, 52.90, 113.23, 117.54, 126.66, 128.86, 129.32, 129.89, 139.51, 146.75

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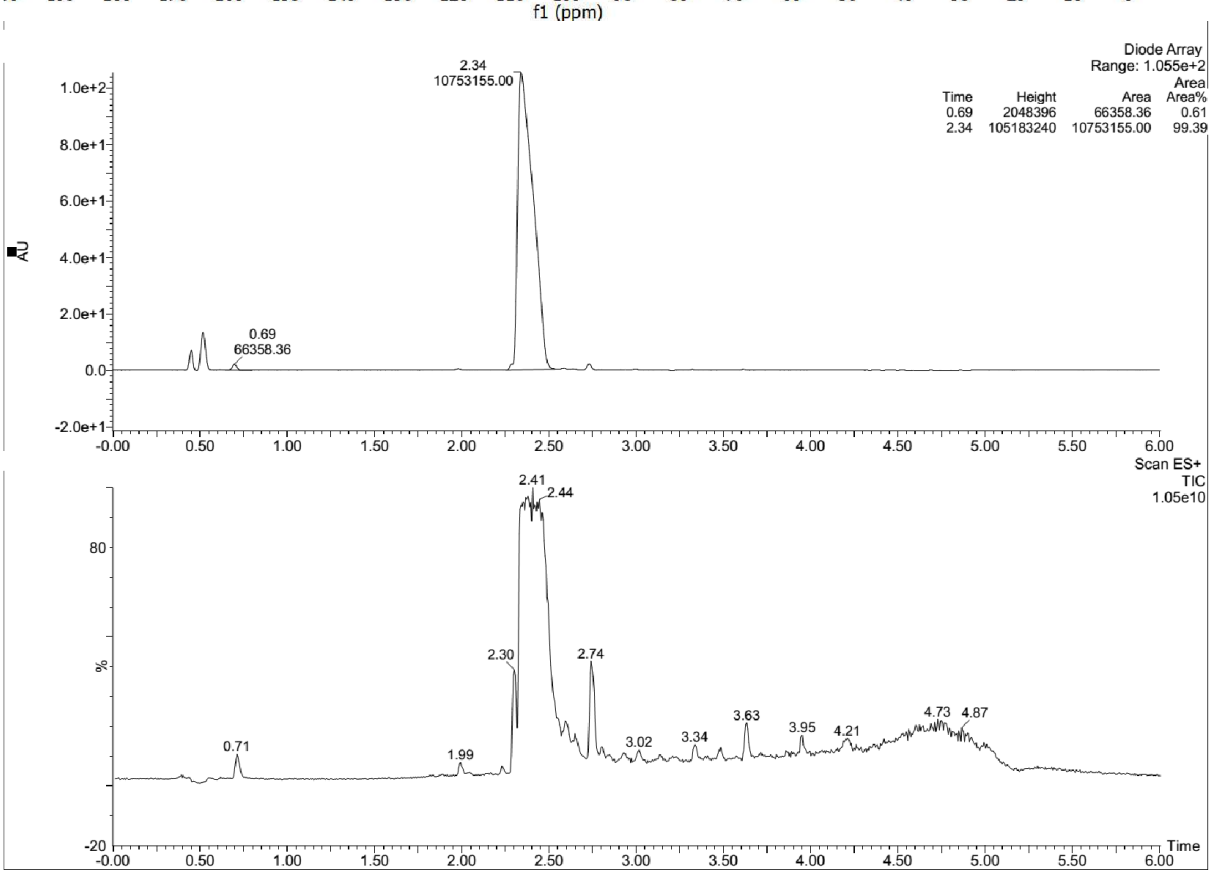
f1 (ppm)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2.30
2.74
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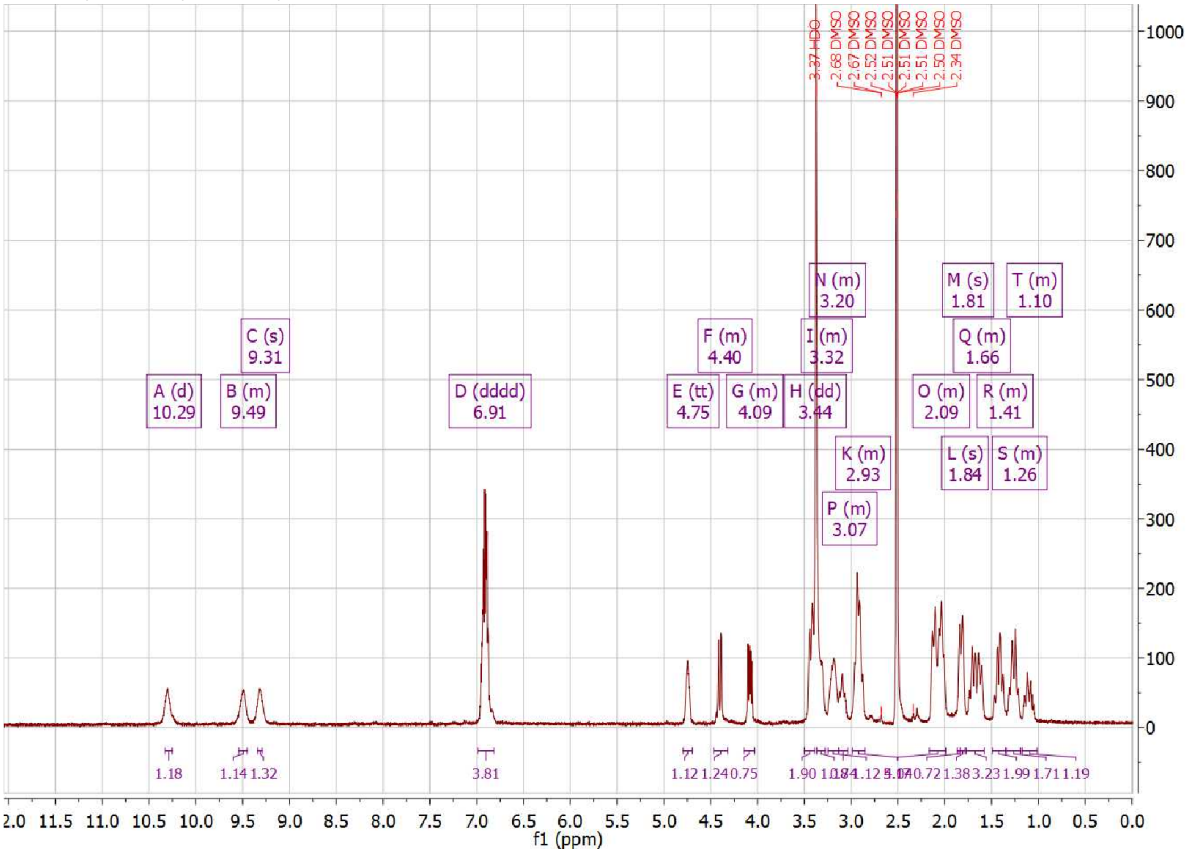
1.99
3.02
3.34
3.63
3.95
4.21
4.73
4.87
%
Time

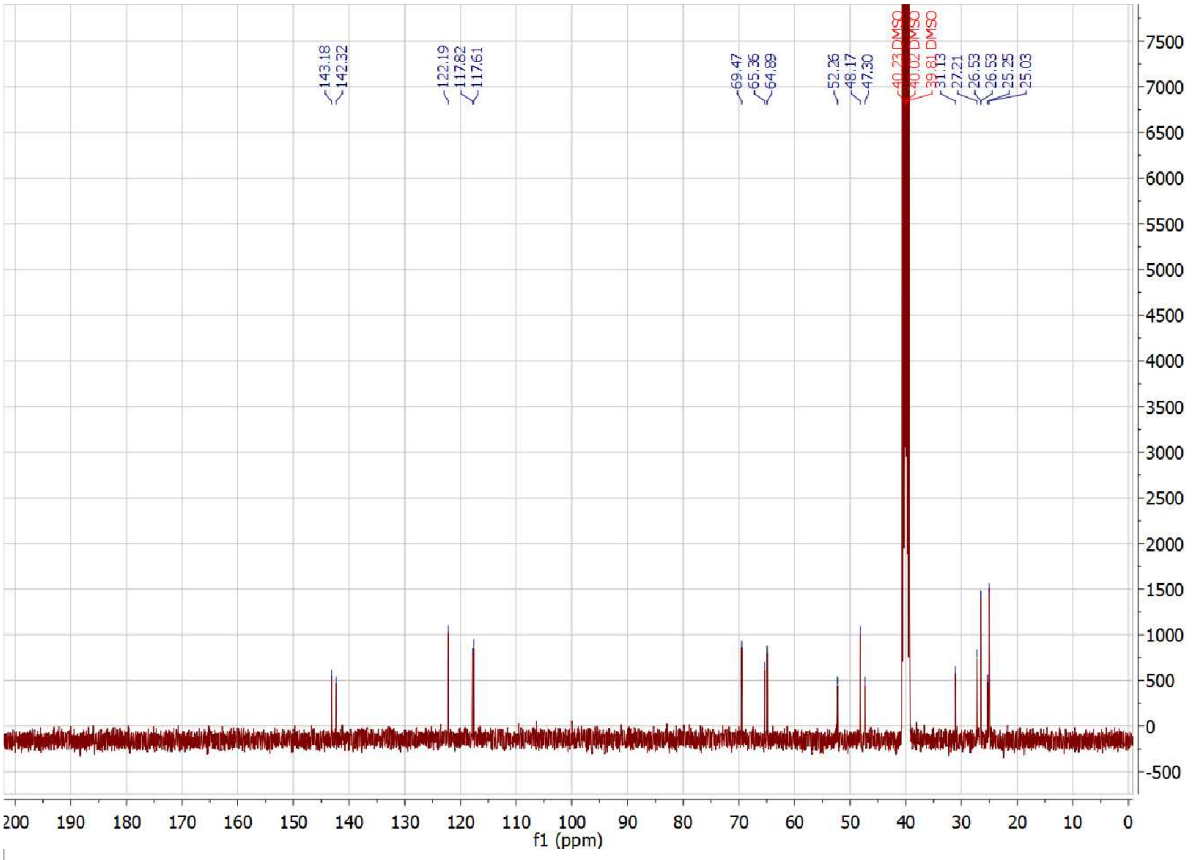
[(1-cyclohexylpiperidin-4-yl)methyl](2,3-dihydro-1,4-benzodioxin-2-ylmethyl)amine (1e).

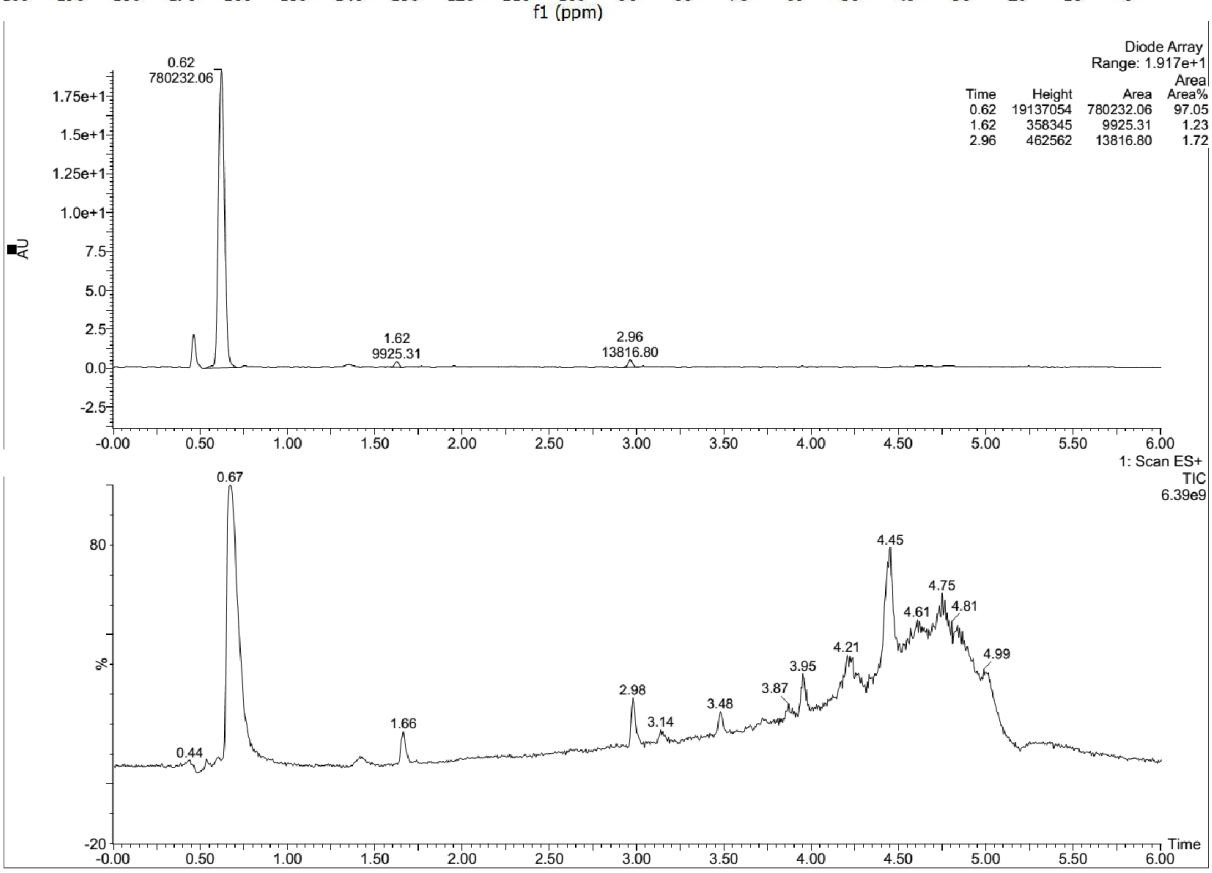
5d (0.25 g, 0.8 mmol) and **5i** (0.15 g, 1 eq.) were dissolved in acetonitrile (5 ml) with anhydrous K_2CO_3 (0.36 g) and heated in a pressure reactor in a microwave oven at 160°C for 30 min. After cooling the reaction mixture was filtered, the precipitate washed with acetonitrile (20 ml) and the combined filtrates evaporated under reduced pressure. The product was purified by column chromatography (SiO_2, $CHCl_3$:MeOH 9:1). A light brown oil of **1e** was obtained (0.24 g, 87%). LCMS [M+1] = 339.20 m/z (338.20 calc).

^{1}H NMR (DMSO-D_6, 400.17 MHz) ppm): 2.04 – 1.78 (m, 2H), 2.32 – 2.04 (m, 3H), 3.03 (s, 2H), 3.23 (ddt, J = 13.6, 8.7, 3.7 Hz, 1H), 3.35 (ddd, J = 13.8, 7.6, 3.8 Hz, 2H), 3.62 (d, J = 11.4 Hz, 3H), 4.10 (dd, J = 11.7, 6.6 Hz, 1H), 4.43 (dd, J = 11.7, 2.4 Hz, 1H), 4.79 (ddt, J = 8.4, 6.4, 3.2 Hz, 1H), 7.63 – 7.22 (m, 3H), 7.01 – 6.82 (m, 4H), 9.74 – 9.36 (m, 2H), 8.02 – 7.63 (m, 2H).

^{13}C NMR (DMSO-D_6, 100.17MHz) ppm): 7.74, 30.69, 47.40, 52.42, 65.43, 69.49, 117.59, 117.85, 122.18, 130.22, 142.36, 143.20.




143.18
142.32
122.19
117.82
117.61
69.47
65.36
64.89
52.26
48.17
47.30
40.23 DMSO
40.02 DMSO
39.81 DMSO
31.13
27.21
26.53
26.33
25.25
25.03
f1 (ppm)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Time Height Area Area%
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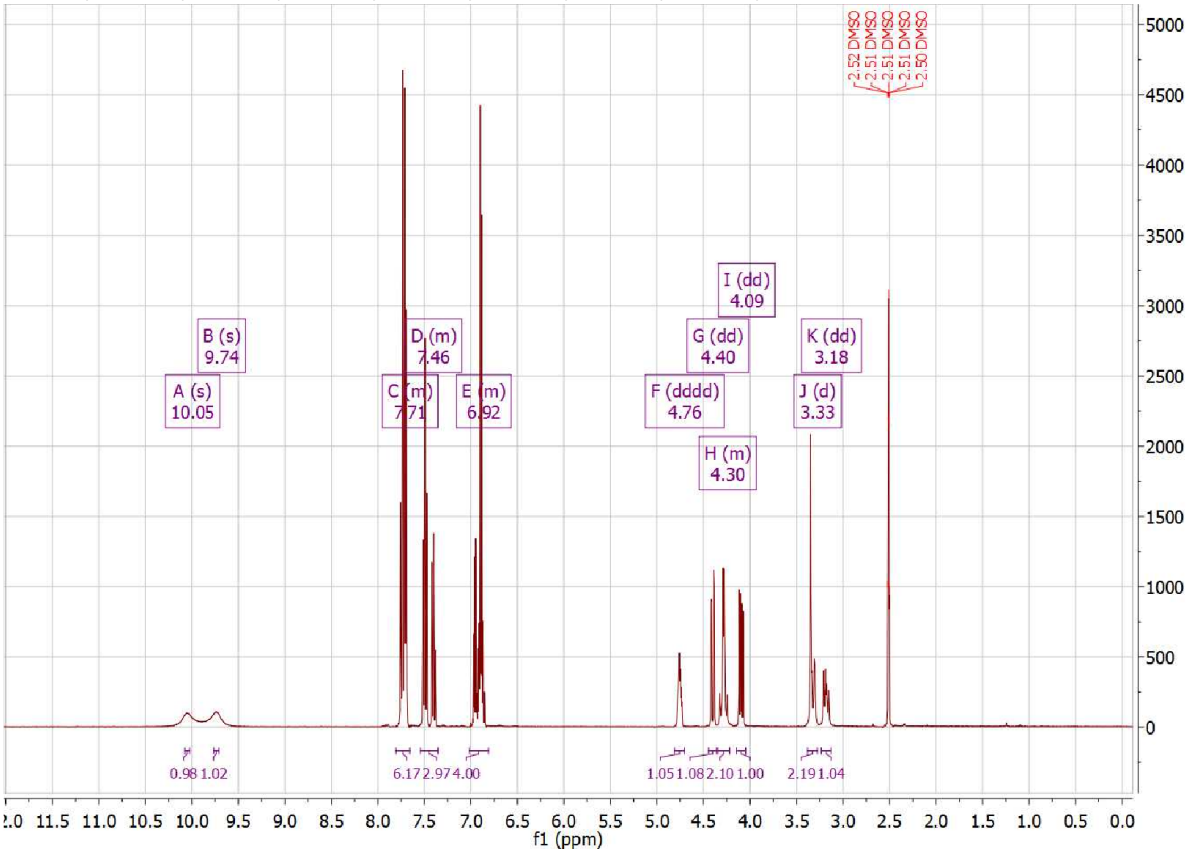
0.62
780232.06
1.62
9925.31
2.96
13816.80
AU
1: Scan ES+
TIC
6.39e9
0.67
0.44
1.66
2.98
3.14
3.48
3.87
3.95
4.21
4.45
4.61
4.75
4.81
4.99
%
Time

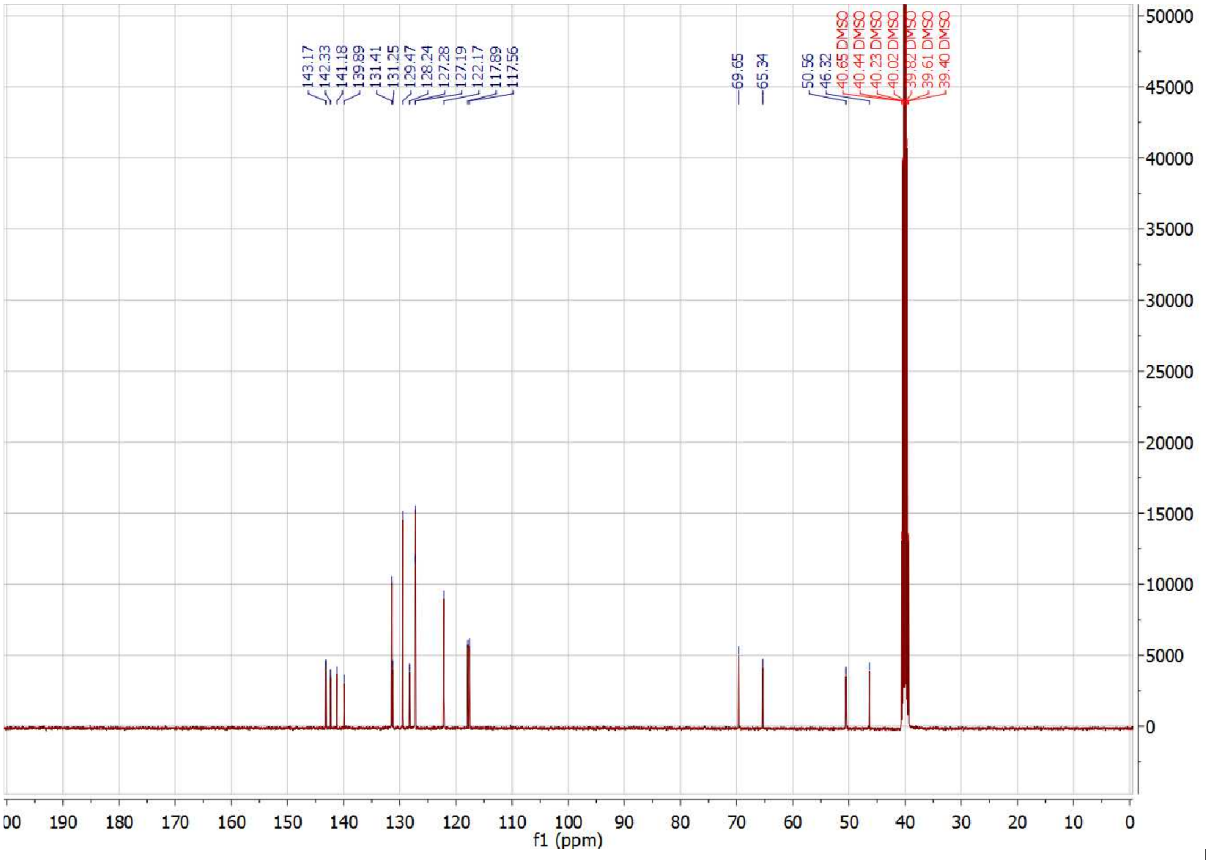
(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)[(4-phenylphenyl)methyl]amine (1f).

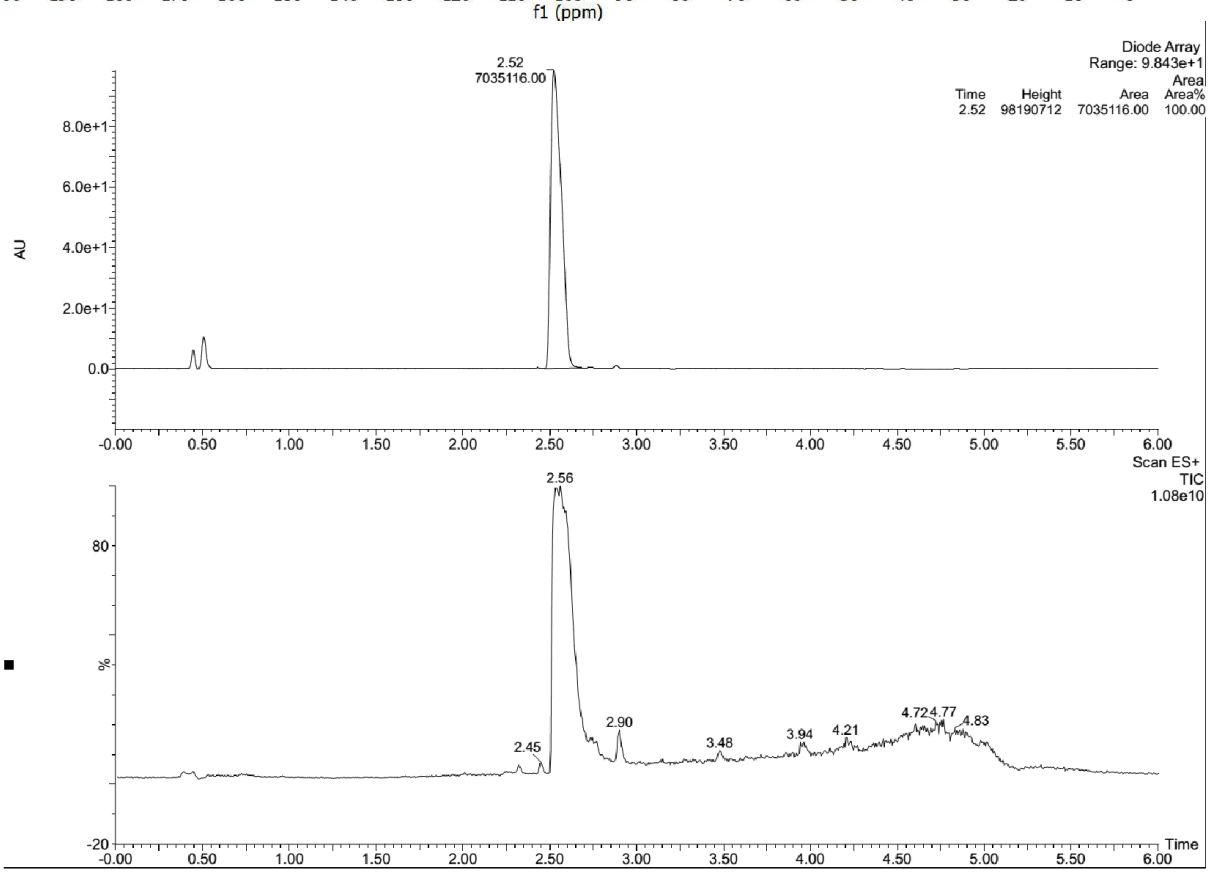
5d (0.62 g, 2 mmol) and **6b** (0.36 g, 1 eq.) were dissolved in acetonitrile (10 ml) with anhydrous K_2CO_3 (0.84 g) and heated in a pressure reactor in a microwave oven at 160°C for 30 min. After cooling the reaction mixture was filtered, the precipitate washed with acetonitrile (30 ml) and the combined filtrates evaporated under reduced pressure. The product was purified by column chromatography (SiO_2, $CHCl_3$:MeOH 9:1). A light brown oil of **1f** was obtained (0.55 g, 84%). LCMS [M+1] = 339.20 m/z (338.20 calc).

^{1}H NMR (DMSO-D_6, 400.17 MHz) ppm): 3.23 – 3.13 (m, 1H); 3.33 (d, J = 15.6 Hz, 2H); 4.09 (dd, J = 11.7, 6.6 Hz, 1H); 4.35 – 4.22 (m, 1H); 4.40 (dd, J = 11.7, 2.4 Hz, 1H); 4.40 (dd, J = 11.7, 2.4 Hz, 1H); 4.76 (dddd, J = 8.4, 6.3, 3.8, 2.4 Hz, 1H); 7.02 – 6.81 (m, 4H); 7.54 – 7.35 (m, 3H); 7.81 – 7.66 (m, 6H); 9.74 (s, 1H); 10.05 (s, 1H).

^{13}C NMR (DMSO-D_6, 100.17MHz) ppm): 46.32, 50.56, 65.34, 69.65, 117.56, 117.89, 122.17, 127.19, 127.28, 128.24, 129.47, 131.25, 131.41, 139.89, 141.18, 142.33, 143.17.




143.17
142.33
141.18
139.89
131.41
131.25
129.47
128.24
127.28
127.19
122.17
117.89
117.56
69.65
65.34
50.56
46.32
40.65 DMSO
40.44 DMSO
40.23 DMSO
40.02 DMSO
39.82 DMSO
39.61 DMSO
39.40 DMSO
f1 (ppm)


Diode Array
Range: 9.843e+1
Area
Time Height Area Area%
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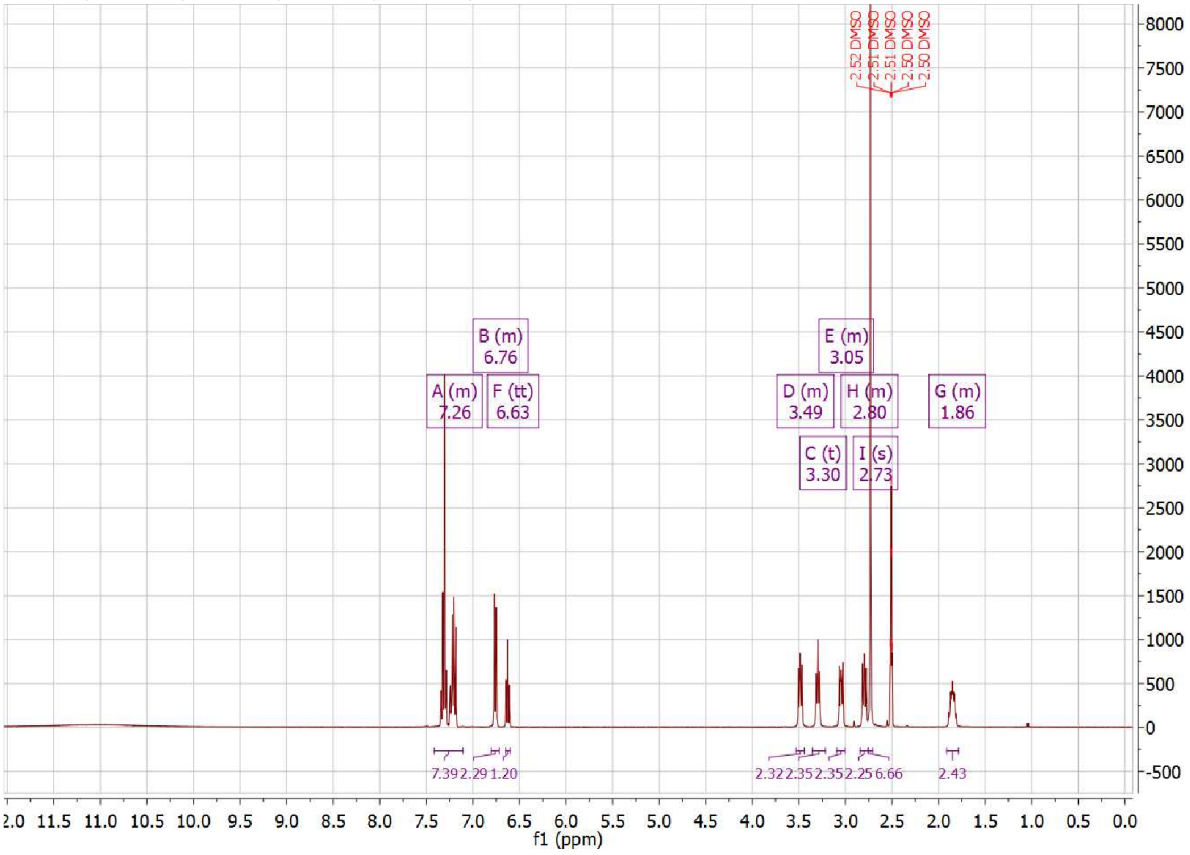
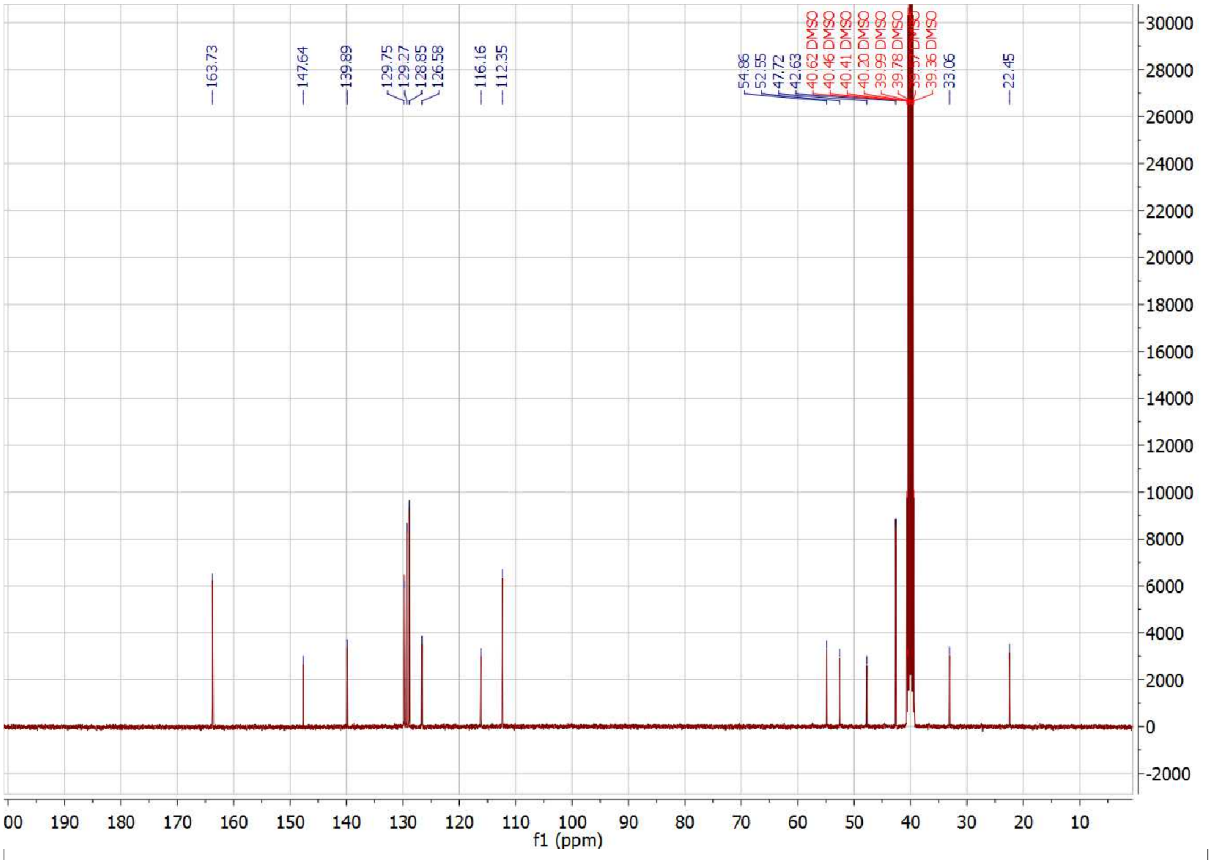
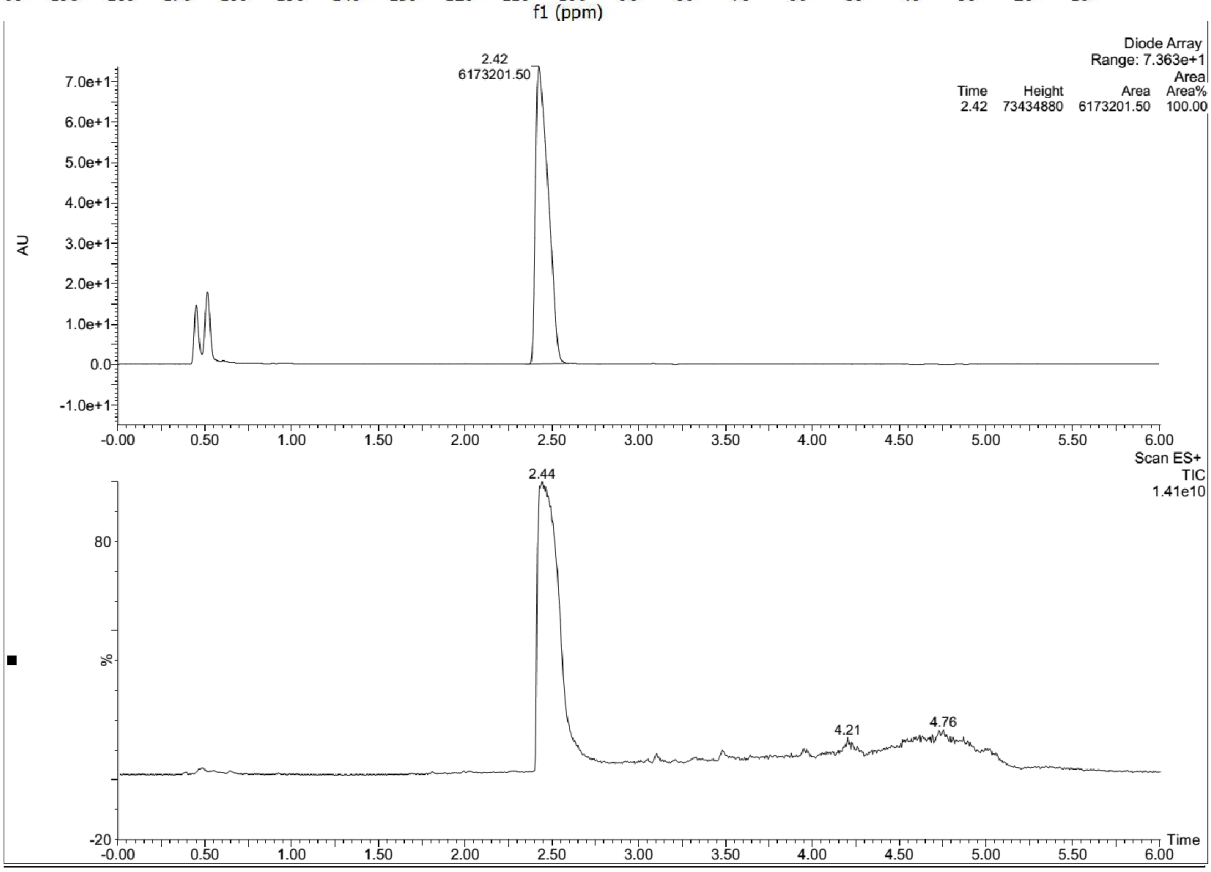
2.52
7035116.00
AU
Scan ES+
TIC
1.08e10
2.56
2.45
2.90
3.48
3.94
4.21
4.72
4.77
4.83
%
Time

N-[2-(diethylamino)ethyl]-N-(2-phenylethyl)aniline (4a).

3b (N-[2-(diethylamino)ethyl]aniline) was synthesized according to general procedure 1 using aniline (5 g, 0.054 mol) and (2-chloroethyl)diethylamine hydrochloride (0.3 eq., 2.77 g), K_2CO_3 (2eq., 14.82 g), isopropanol (100 ml). A brown oil of **3b** was obtained (1 g, 32%) LCMS [M+1] = 193.28 m/z (192.30 calc). **4a** was synthesized according to general procedure 2 using 1 g (0.0052 mol) of **3b**, phenylacetaldehyde (1.5 eq., 1.25 g), sodium triacetoxyborohydride (2 eq., 2.2 g), dichloroethane (50 ml). A brown oil of **4a** was obtained (0.3 g, 19%). LCMS [M+1] = 297.22 m/z (296.22 calc).
^{1}H NMR (DMSO-D_6, 400.17MHz) (ppm): 1.91 – 1.79 (m, 2H), 2.73 (s, 7H), 2.84 –2.75 (m, 2H), 3.09 – 3.00 (m, 3H), 3.30 (t, J = 7.4 Hz, 2H), 3.53 – 3.44 (m,2H), 6.63 (tt, J = 7.2, 0.9 Hz, 1H), 6.80 – 6.72 (m, 2H), 7.42 – 7.11 (m, 7H).
^{13}C NMR (DMSO-D_6, 100.17 MHz) ppm): 11.23, 33.50, 47.52, 50.84, 52.34, 54.09,114.38, 117.54, 126.81, 128.70, 129.15, 130.28, 139.20, 150.01.




163.73
147.64
139.89
129.75
129.27
128.85
126.58
116.16
112.35
54.86
52.55
47.72
42.63
40.62 DMSO
40.46 DMSO
40.41 DMSO
40.20 DMSO
39.99 DMSO
39.78 DMSO
39.57 DMSO
39.36 DMSO
33.06
22.45
f1 (ppm)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Time Height Area Area%
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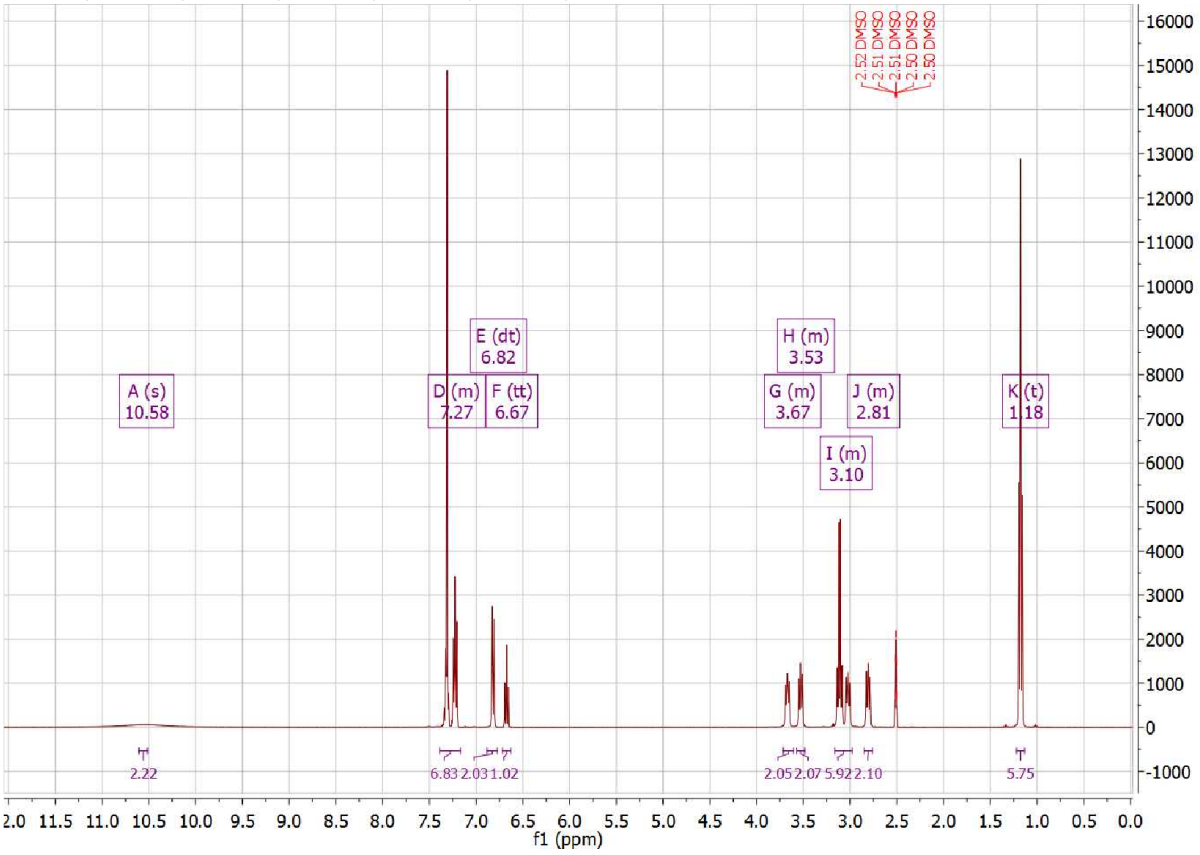
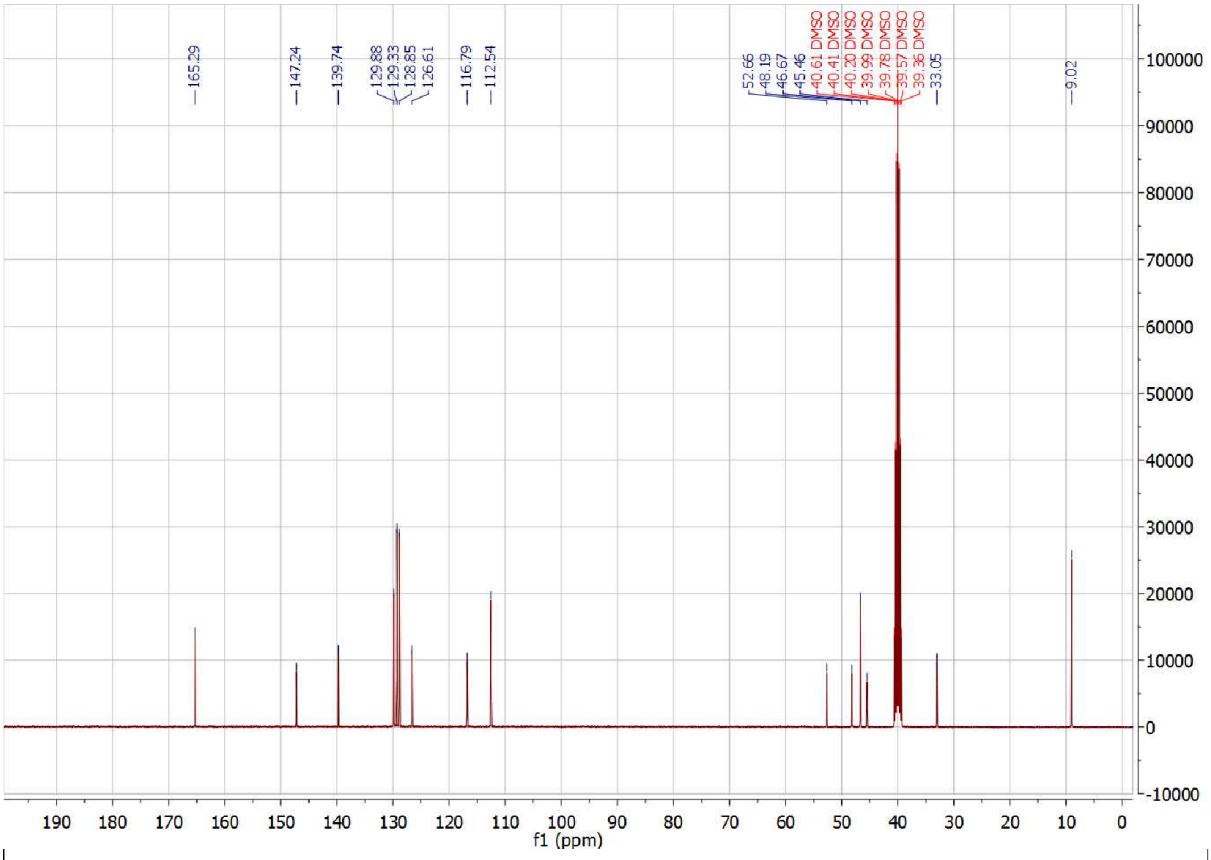
6173201.50
AU
Scan ES+
TIC
1.41e10
2.44
4.21
4.76
%
Time

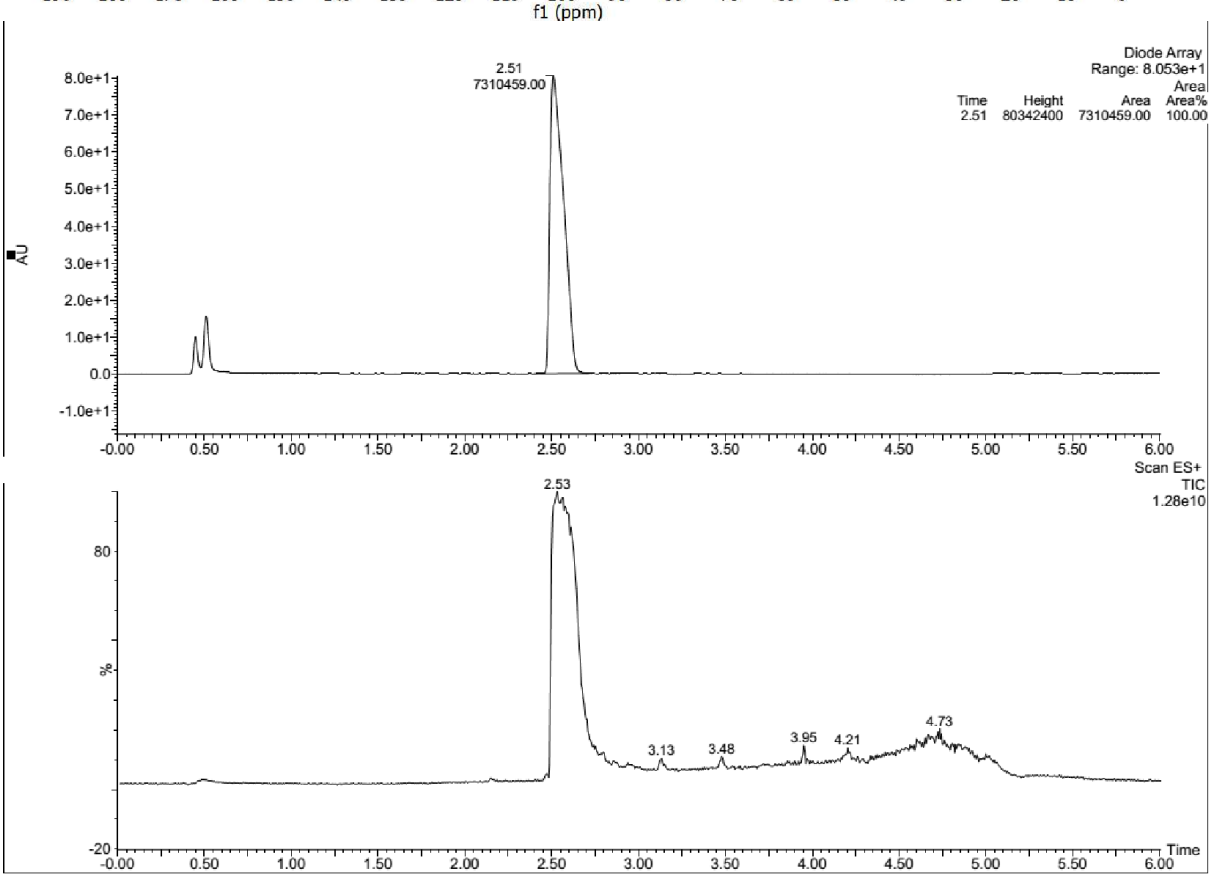
N-[3-(dimethylamino)propyl]-N-(2-phenylethyl)aniline (4b).

3c (N-[3-(dimethylamino)propyl]aniline) was synthesized according to general procedure 1 using aniline (5 g, 0.054 mol) and (3-chloropropyl)dimethylamine hydrochloride (0.3 eq., 2.55 g), K_2CO_3 (2 eq., 14.87 g), isopropanol (100 ml). A brown oil of **3c** was obtained (1.5 g, 53%) LCMS [M+1] = 179.22 m/z (178.27 calc). **4b** was synthesized according to general procedure 2 using 1 g (0.0056 mol) of **3c**, phenylacetaldehyde (1.5 eq., 0.95 ml), sodium triacetoxyborohydride (2eq., 3.57 g), dichloroethane (50 ml). A brown oil of **4b** was obtained (0.748 g, 47%). LCMS [M+1] = 283.10 m/z (282.21 calc). ^{1}H NMR (DMSO-D_6, 400.17MHz) (ppm): 1.18 (t, J = 7.2 Hz, 6H), 2.85 – 2.76 (m,2H), 3.16 – 2.98 (m, 4H), 3.57 – 3.48 (m, 2H), 3.71 – 3.61 (m, 2H), 6.67 (tt,J = 7.3, 0.9 Hz, 1H), 6.82 (dt, J = 7.8, 1.0 Hz, 2H), 7.39 – 7.17 (m, 7H)10.58(s, 2H).

^{13}C NMR (DMSO-D_6, 100.17 MHz) (ppm): 9.02, 33.05, 45.46, 46.67, 48.19, 52.66, 112.54, 116.79, 126.61, 128.85, 129.33, 129.88, 139.74, 147.24, 165.29.




165.29
147.24
139.74
129.88
129.33
128.85
126.61
116.79
112.54
52.66
48.19
46.67
45.46
40.61 DMSO
40.41 DMSO
40.20 DMSO
39.99 DMSO
39.78 DMSO
39.57 DMSO
39.36 DMSO
33.05
9.02
f1 (ppm)


Diode Array
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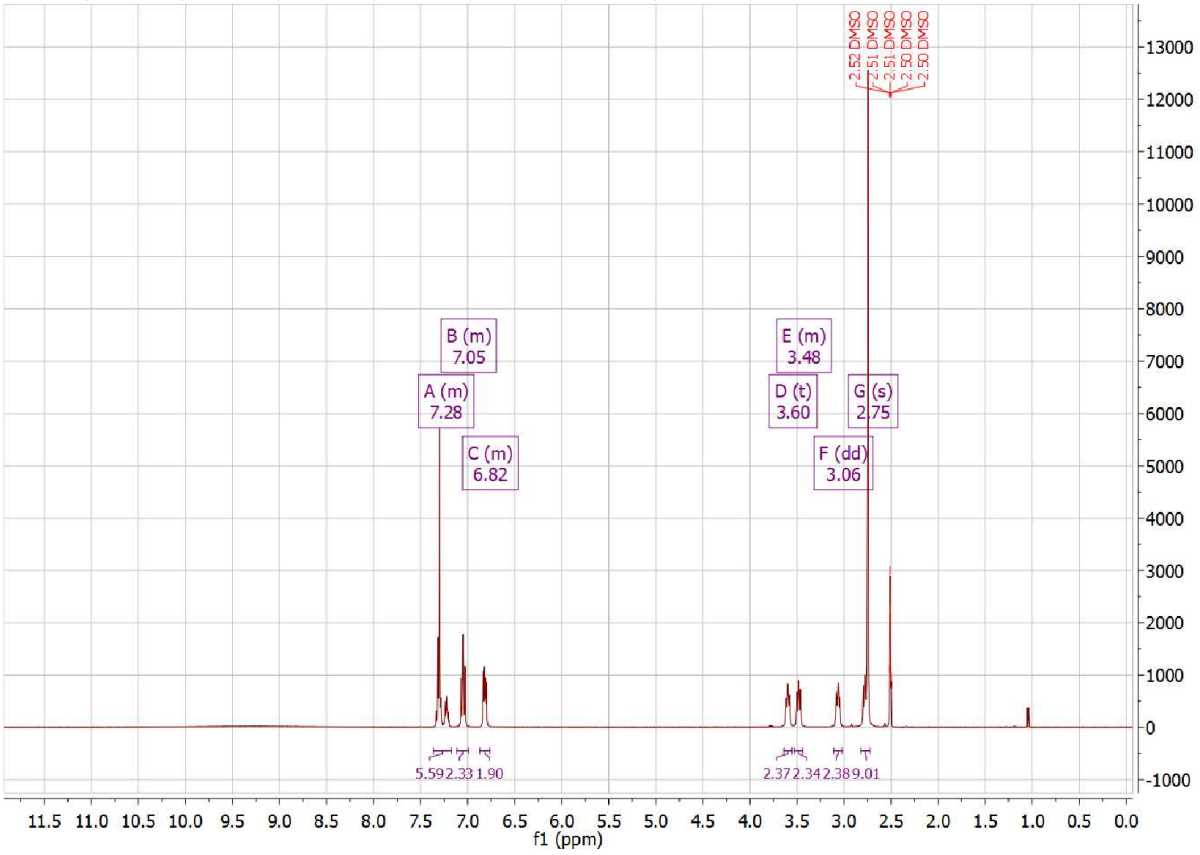
7310459.00
AU
Scan ES+
TIC
1.28e10
2.53
3.13
3.48
3.95
4.21
4.73
%
Time

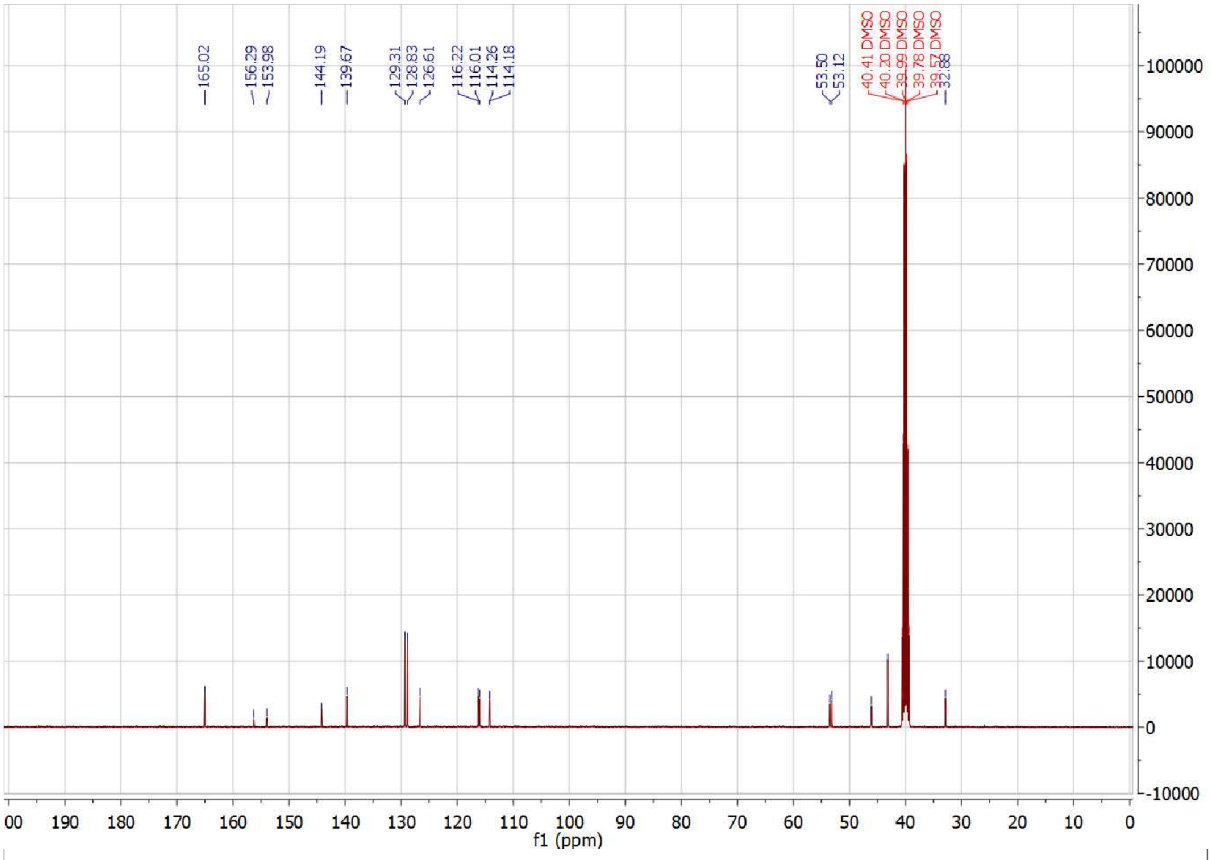
N-[2-(dimethylamino)ethyl]-4-fluoro-N-(2-phenylethyl)aniline (4c).

3d (N-[2-(dimethylamino)ethyl]-4-fluoroanilin) was synthesized according to general procedure 1 using 4-fluoroaniline (5 g, 0.045 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.95 g), K_2CO_3 (2 eq., 12.42 g), isopropanol (100 ml). A brown oil of **3d** was obtained (1 g, 40%) LCMS [M+1] = 183.19 m/z (182.24 calc). **4c** was synthesized according to general procedure 2 using 1 g (0.0055 mol) of **3d**, phenylacetaldehyde (1.5 eq., 0.93 ml), sodium triacetoxyborohydride (2 eq., 3.5 g), dichloroethane (50 ml). A brown oil of **4c** was obtained (0.071 g, 4.5%). LCMS [M+1] = 287.17 m/z (286.18 calc).

^{1}H NMR (DMSO-D_6, 400.17MHz) (ppm): 2.75 (s, 8H), 3.06 (dd, J = 8.8, 6.2 Hz,2H), 3.53 – 3.44 (m, 2H), 3.60 (t, J = 7.6 Hz, 2H), 6.87 – 6.76 (m, 2H), 7.11– 6.99 (m, 2H), 7.36 – 7.17 (m, 5H).

^{13}C NMR (DMSO-D_6, 100.17 MHz) (ppm): 32.88, 43.18, 46.08, 53.12, 53.50,114.18, 114.26, 116.01, 116.22, 126.61, 128.83, 129.31, 139.67, 144.19,153.98, 156.29, 165.02.

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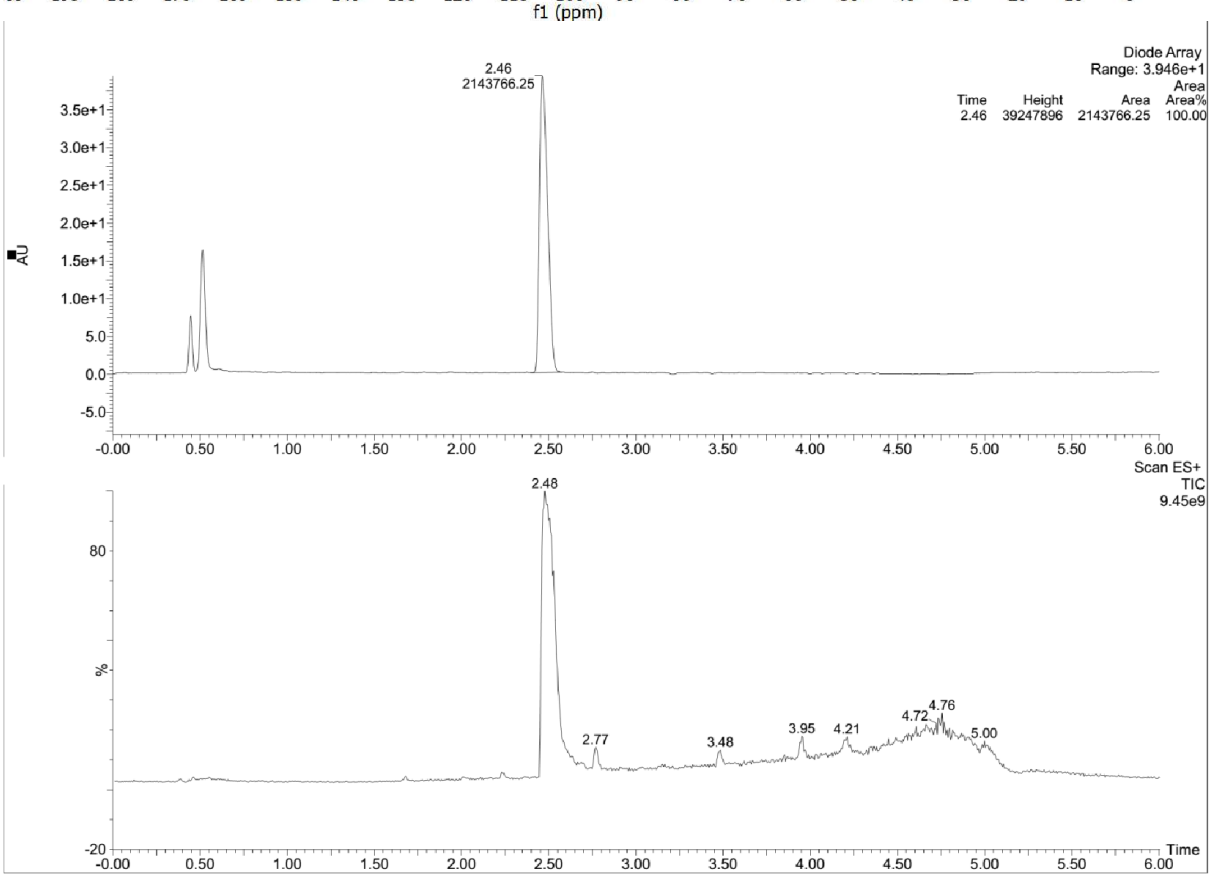
156.29
153.98
144.19
139.67
129.31
128.83
126.61
116.22
116.01
114.26
114.18
53.50
53.12
40.41 DMSO
40.30 DMSO
39.99 DMSO
39.78 DMSO
39.57 DMSO
32.88
f1 (ppm)


2.46
2143766.25
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Time Height Area Area%
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AU
Time

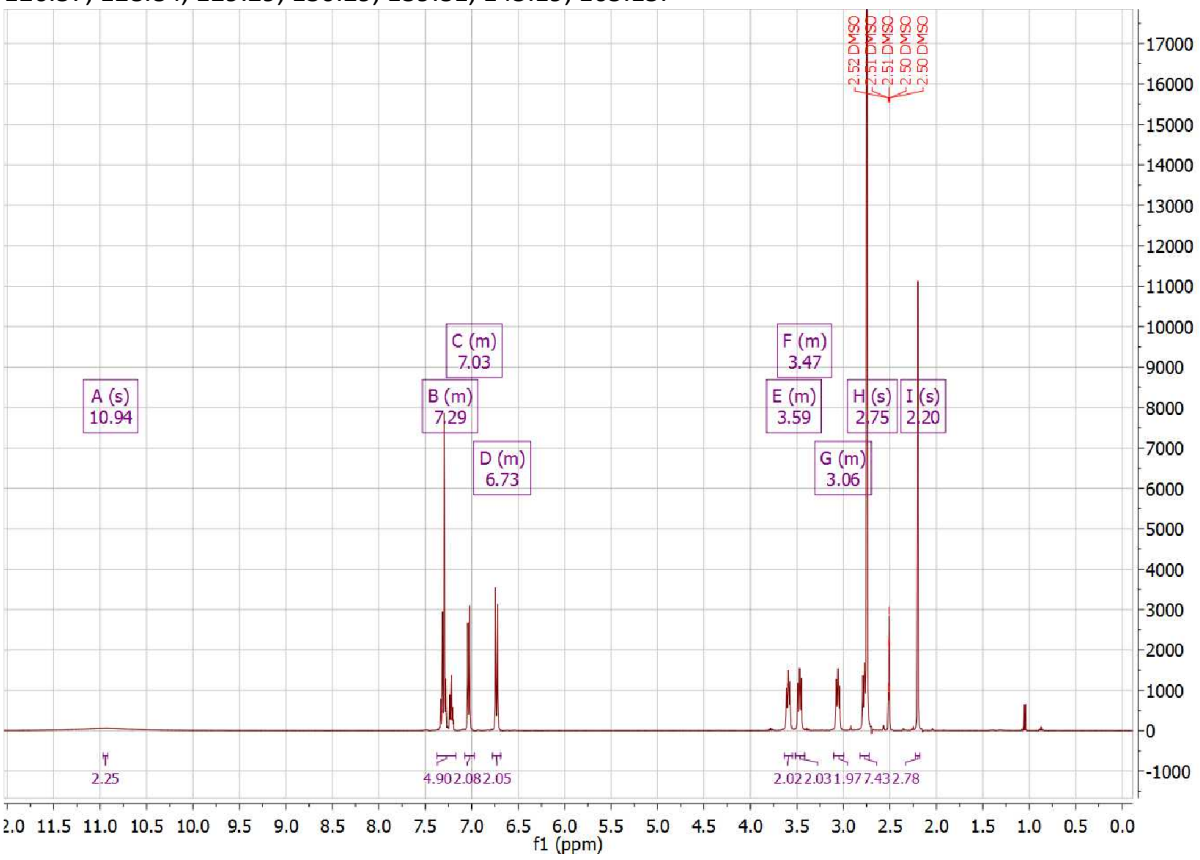
Scan ES+
TIC
9.45e9
2.48
2.77
3.48
3.95
4.21
4.72
4.76
5.00
%
Time

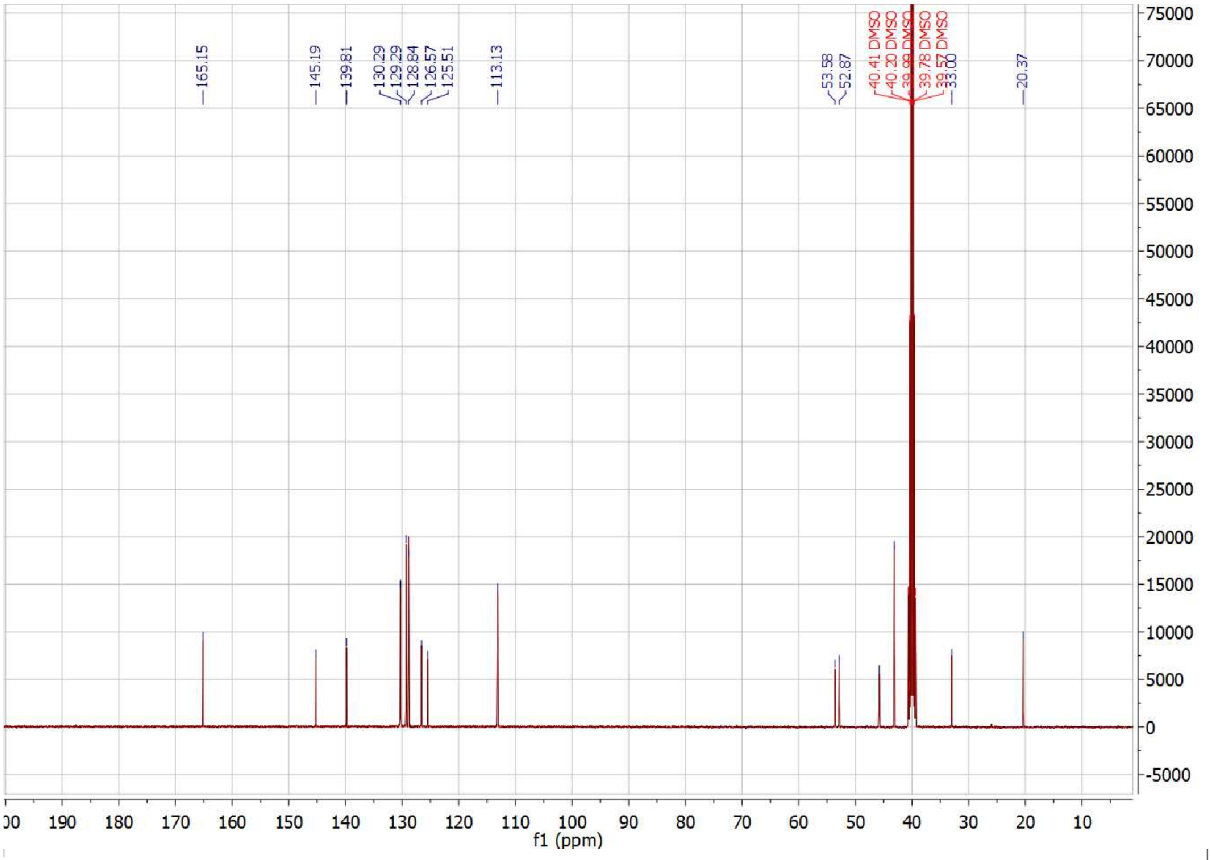
N-[2-(dimethylamino)ethyl]-4-methyl-N-(2-phenylethyl)aniline (4d).

3e (N-[2-(dimethylamino)ethyl]-4-methylaniline) was synthesized according to general procedure 1 using 4-methylaniline (5 g, 0.047 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 2.02 g), K_2CO_3 (2 eq., 12.88 g), isopropanol (100 ml). A brown oil of **3e** was obtained (1.72 g, 69%) LCMS [M+1] = 179.11 m/z (178.27 calc). **4d** was synthesized according to general procedure 2 using 1 g (0.0056 mol) of **3e**, phenylacetaldehyde (1.5 eq., 0.94 ml), sodium triacetoxyborohydride (3 eq., 3.57 g), dichloroethane (50 ml). A brown oil of **4d** was obtained (1.27 g, 80%). LCMS [M+1] = 283.20 m/z (282.21 calc).

^{1}H NMR (DMSO-D_6, 400.17MHz) (ppm): 2.20 (s, 3H), 2.75 (s, 8H), 3.10 – 3.00 (m,2H), 3.52 – 3.42 (m, 2H), 3.64 – 3.55 (m, 2H), 6.78 – 6.69 (m, 2H), 7.08 –6.97 (m, 2H), 7.37 – 7.17 (m, 5H), 10.94 (s, 2H).

^{13}C NMR (DMSO-D_6, 100.17 MHz) ppm): 20.37, 33.00, 43.13, 45.78, 52.87, 53.58, 113.13, 125.51, 126.57, 128.84, 129.29, 130.29, 139.81, 145.19, 165.15.




165.15
145.19
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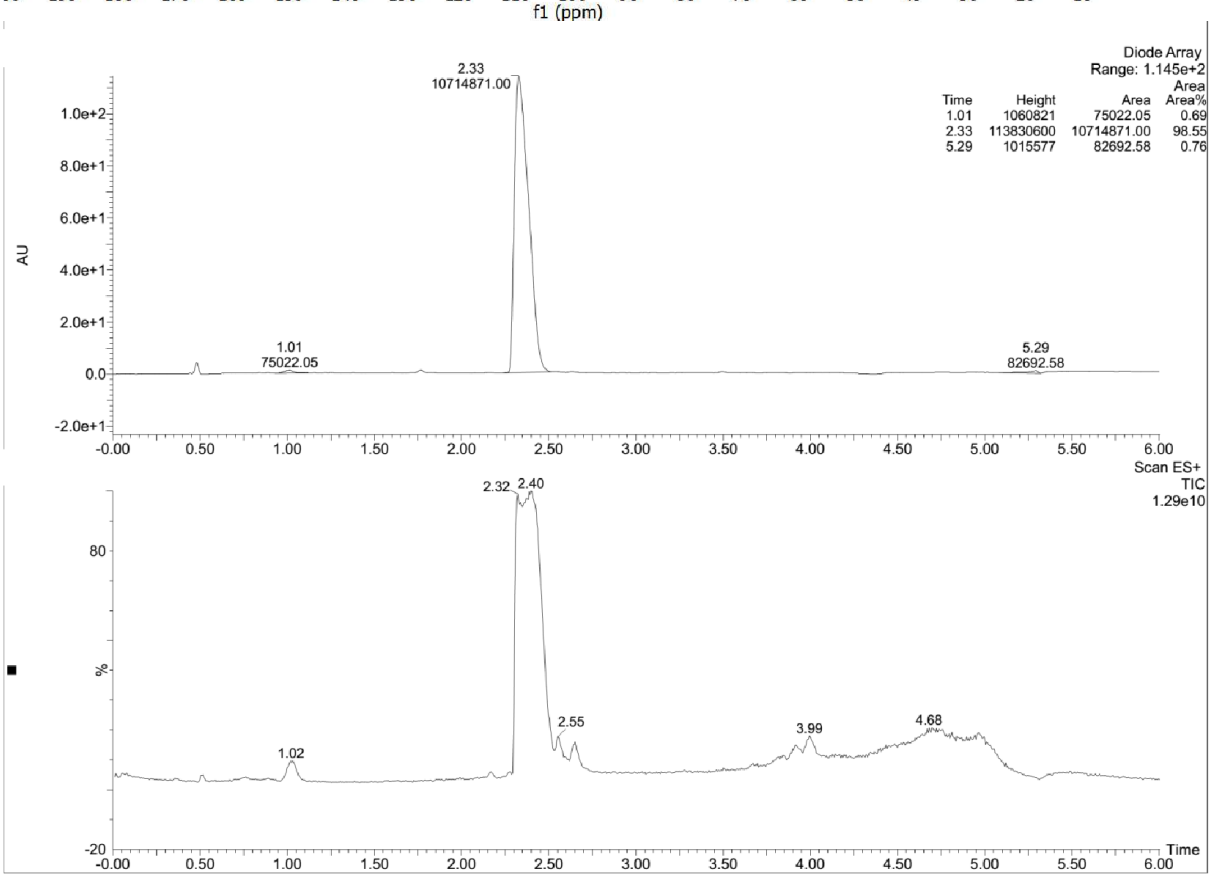
130.29
129.29
128.84
126.57
125.51
113.13
53.58
52.87
40.41 DMSO
40.20 DMSO
39.99 DMSO
39.78 DMSO
39.57 DMSO
39.36 DMSO
33.00
20.37
f1 (ppm)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10714871.00
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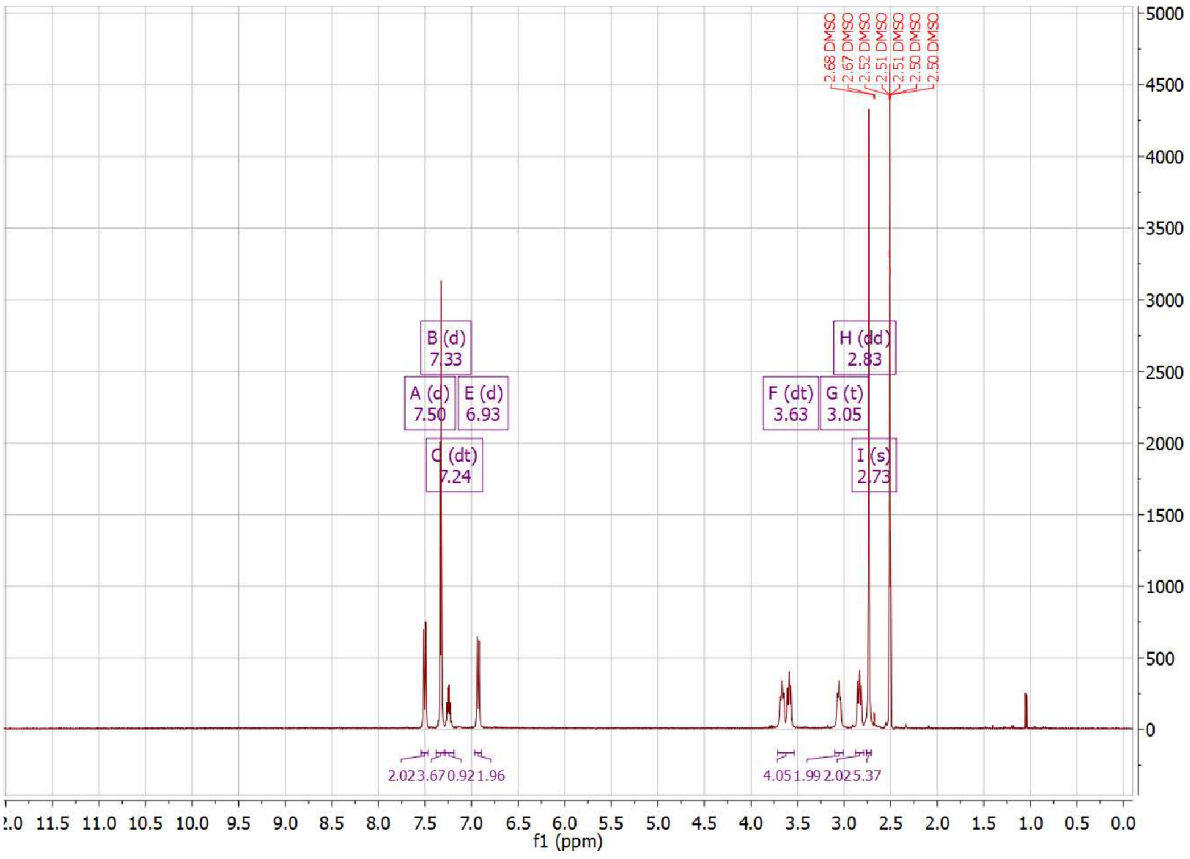
75022.05
5.29
82692.58
AU
Scan ES+
TIC
1.29e10
2.32
2.40
2.55
3.99
4.68
1.02
%
Time

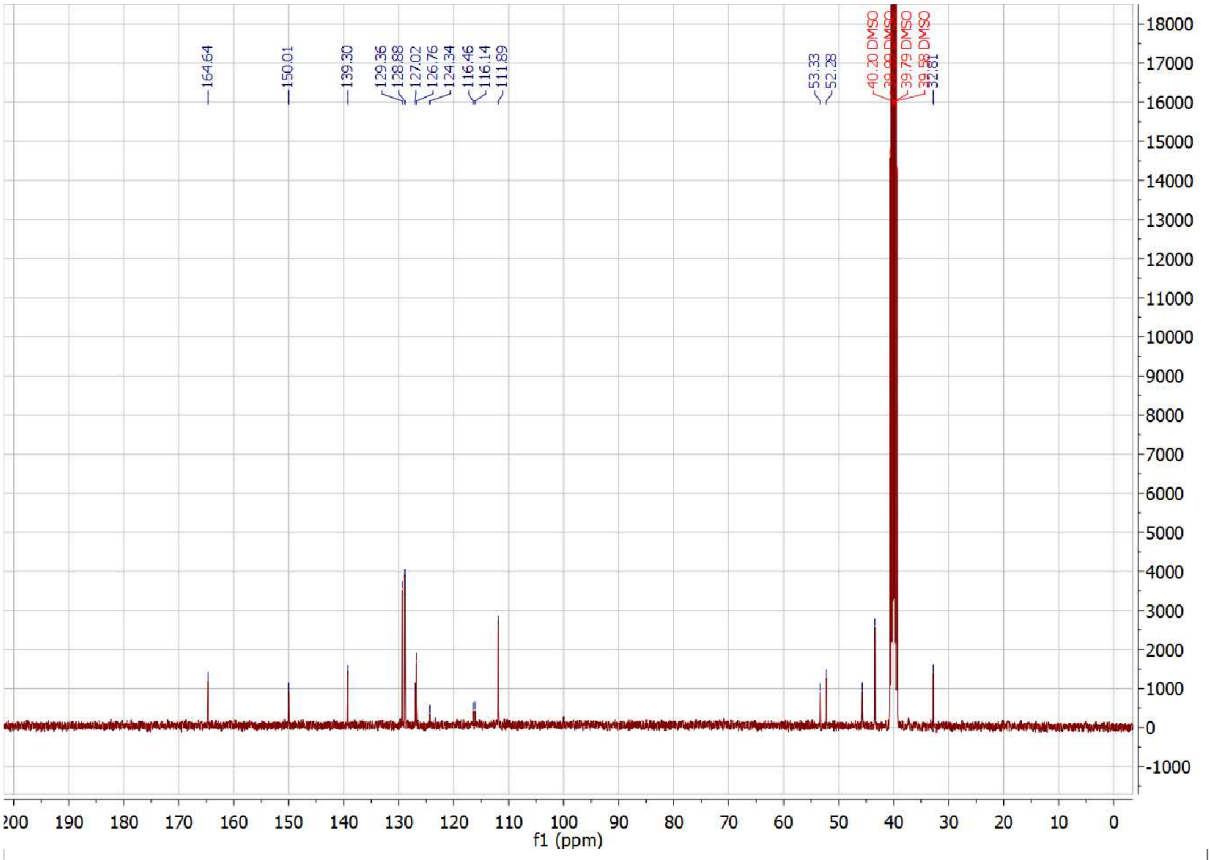
N-[2-(dimethylamino)ethyl]-N-(2-phenylethyl)-4-(trifluoromethyl)aniline (4e).

3f (N-[2-(dimethylamino)ethyl]-4-(trifluoromethyl)aniline) was synthesized according to general procedure 1 using 4-trifluoromethylaniline (5 g, 0.031 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.34 g), K_2CO_3 (2 eq.), isopropanol (100 ml). A brown oil of **3f** was obtained (0.35 g, 16%) LCMS [M+1] = 233.33 m/z (232.25 calc). **4e** was synthesized according to general procedure 2 using 0.3 g (0.0013mol) of **3f**, phenylacetaldehyde (1.5 eq., 0.22 ml), sodium triacetoxyborohydride (3 eq., 0.82 g), dichloroethane (50 ml). A violet oil of **4e** was obtained (0.029 g, 6,6%). LCMS [M+1] = 337.19 m/z (336.18 calc).

^{1}H NMR (DMSO-D_6, 400.17MHz) (ppm): 2.73 (s, 6H), 2.83 (dd, J = 8.9, 6.6 Hz,2H), 3.05 (t, J = 7.1 Hz, 2H), 3.63 (dt, J = 31.2, 7.7 Hz, 4H), 6.93 (d, J = 8.6Hz, 2H), 7.24 (dt, J = 8.6, 4.1 Hz, 1H), 7.33 (d, J = 4.4 Hz, 4H), 7.50 (d, J =8.6 Hz, 2H).

^{13}C NMR (DMSO-D_6, 100.17 MHz) ppm): 32.81, 43.42, 45.73, 52.28, 53.33, 111.89, 116.14, 116.46, 124.34, 126.76, 127.02, 128.88, 129.36, 139.30, 150.01, 164.64.




164.64
150.01
139.30
129.36
128.88
127.02
126.76
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111.89
53.33
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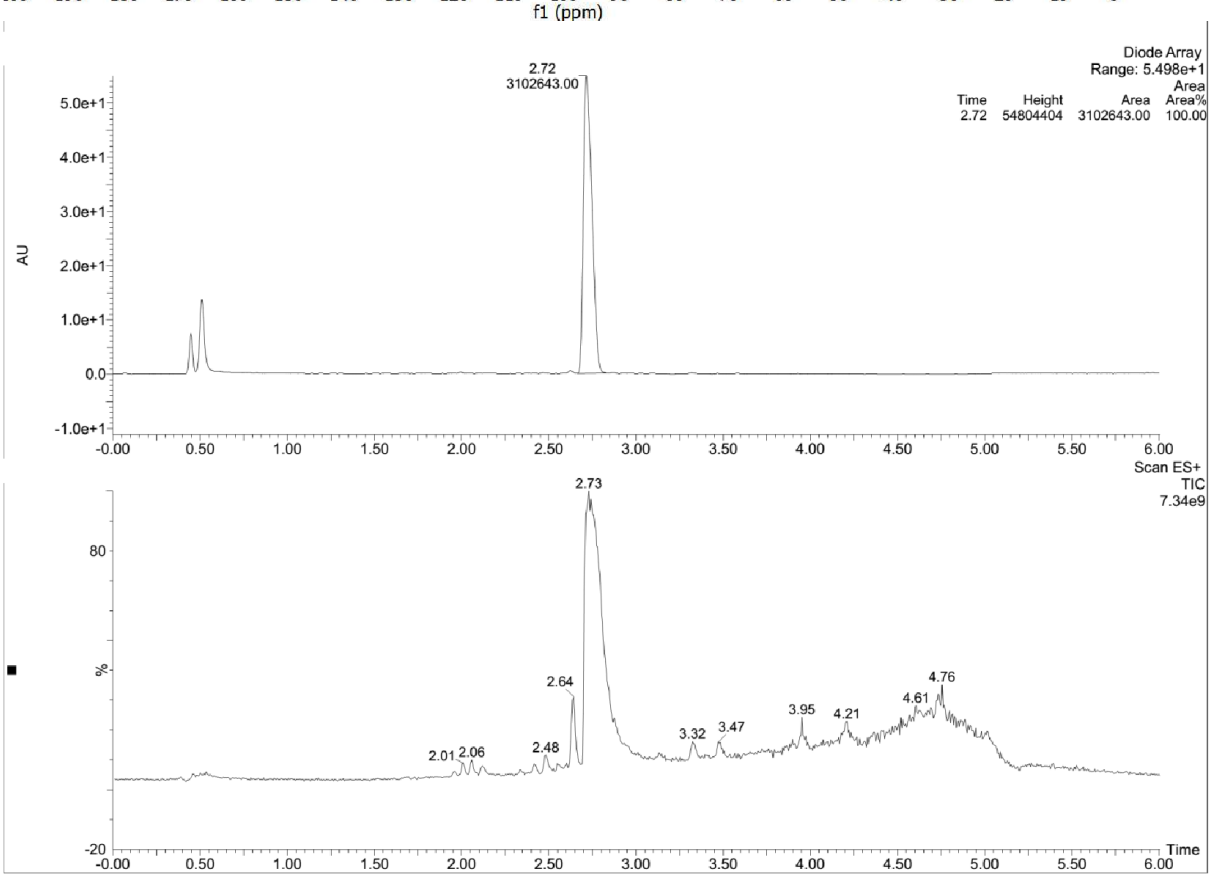
40.20 DMSO
39.79 DMSO
39.38 DMSO
32.81
f1 (ppm)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3102643.00
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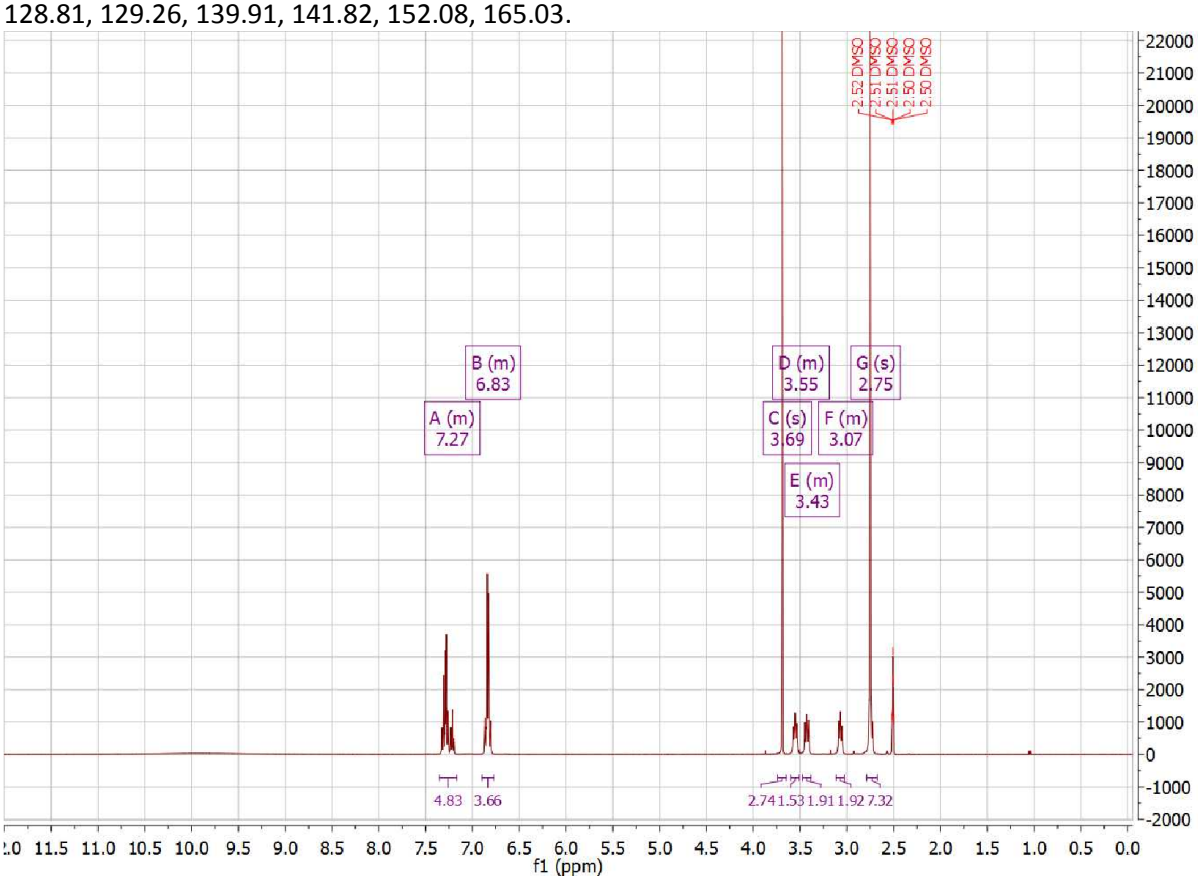
2.73
2.64
2.01
2.06
2.48
3.32
3.47
3.95
4.21
4.61
4.76
%
Time

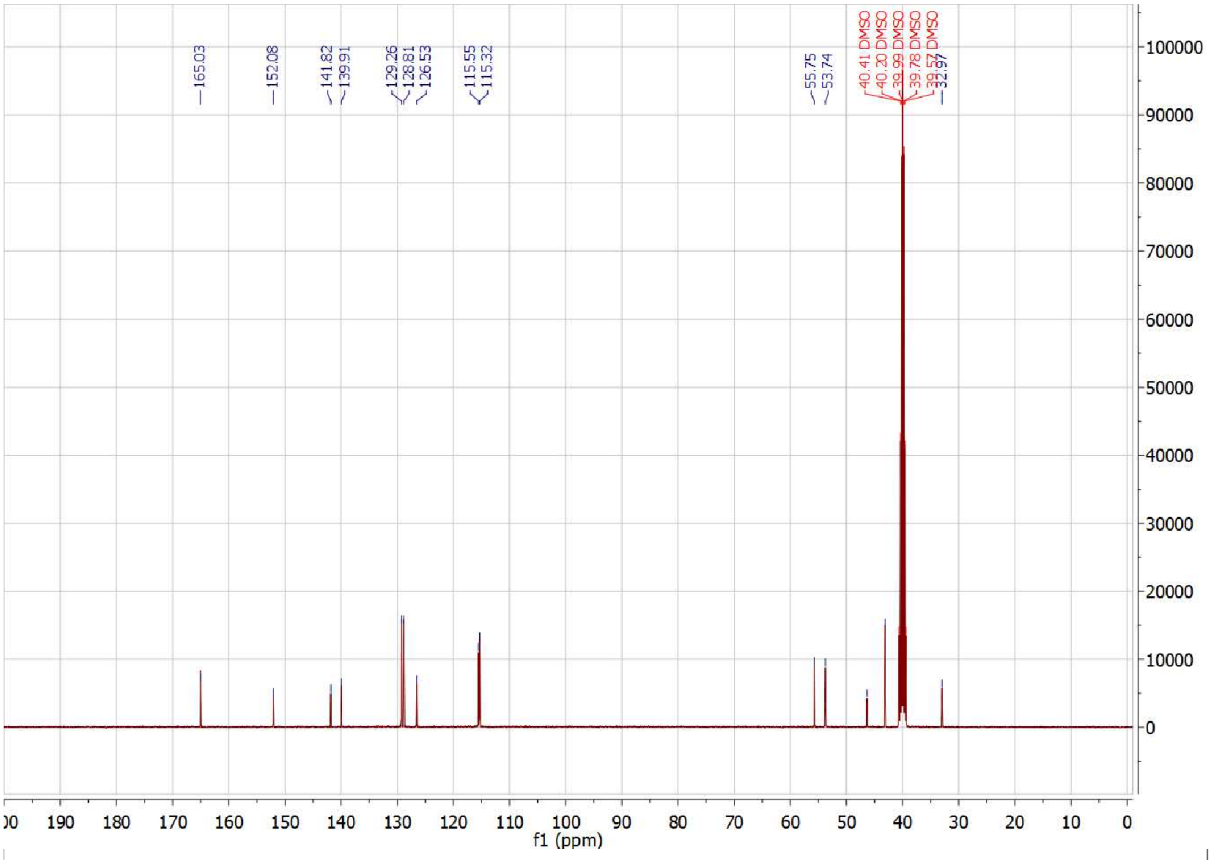
N-[2-(dimethylamino)ethyl]-4-methoxy-N-(2-phenylethyl)aniline (4f).

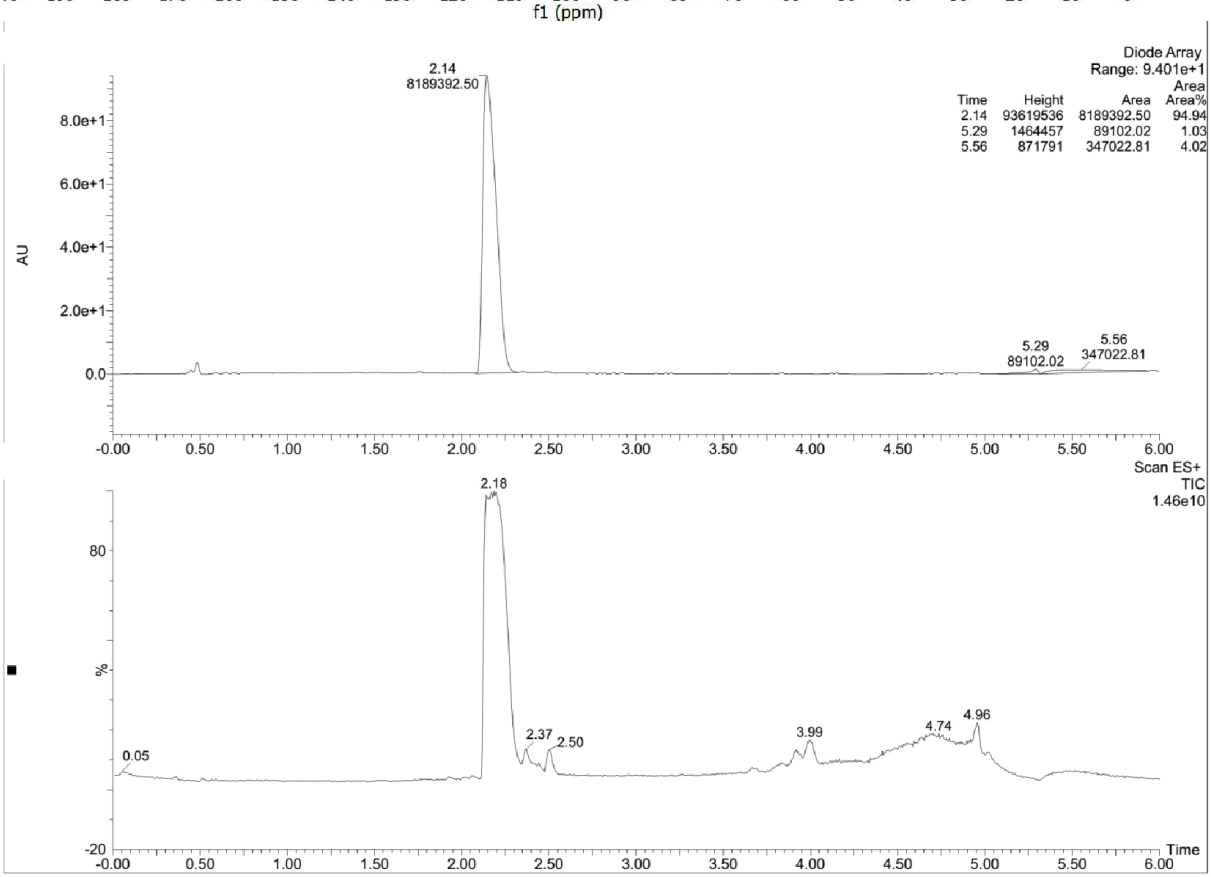
3g (N-[2-(dimethylamino)ethyl]-4-methoxyaniline) was synthesized according to general procedure 1 using 4-methoxyaniline (5 g, 0.040 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.76 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3g** was obtained (2.05 g, 79%) LCMS [M+1] = 195.17 m/z (194.27 calc). **4f** was synthesized according to general procedure 2 using 1 g (0.0051 mol) of **3g**, phenylacetaldehyde (1.5 eq., 0.86 ml), sodium triacetoxyborohydride (3 eq., 3.27 g), dichloroethane (50 ml). A brown oil of **4f** was obtained (1.314 g, 86%). LCMS [M+1] = 299,20 m/z (298,20 calc).

^{1}H NMR (DMSO-D_6 400.17MHz) (ppm): 2.75 (s, 8H), 3.11 – 3.03 (m, 2H), 3.47 –3.38 (m, 2H), 3.60 – 3.51 (m, 2H), 3.69 (s, 3H), 6.90 – 6.77 (m, 4H), 7.35 –7.17 (m, 5H).

^{13}C NMR (DMSO-D_6, 100.17 MHz) (ppm): 32.97, 43.12, 46.32, 53.74, 55.75, 115.32, 115.55, 126.53, 128.81, 129.26, 139.91, 141.82, 152.08, 165.03.




165.03
152.08
141.82
139.91
129.26
128.81
126.53
115.55
115.32
55.75
53.74
40.41 DMSO
40.20 DMSO
39.99 DMSO
39.78 DMSO
39.57 DMSO
32.97
f1 (ppm)


Diode Array
Range: 9.401e+1
Time Height Area Area%
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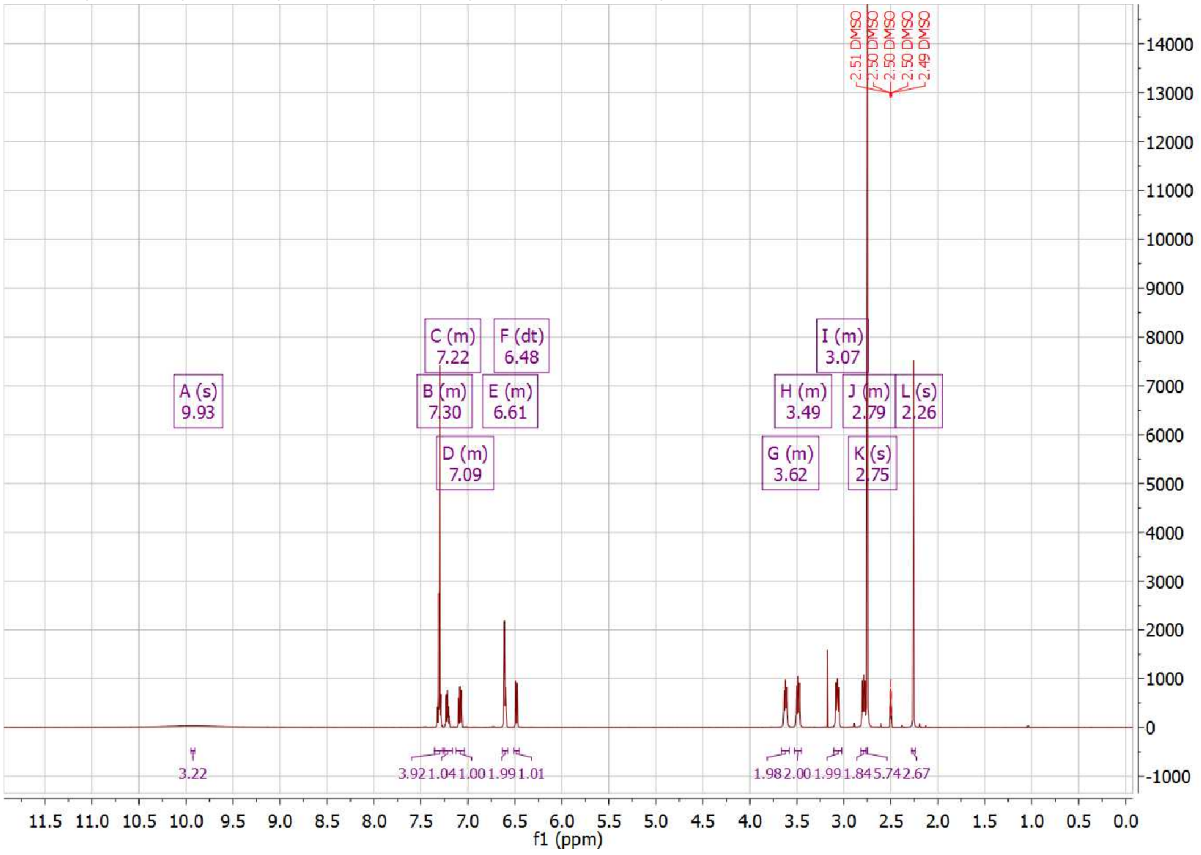
5.29 1464457 89102.02 1.03
5.56 871791 347022.81 4.02
2.14
8189392.50
5.29
89102.02
5.56
347022.81
AU
Scan ES+
TIC
1.46e10
2.18
0.05
2.37
2.50
3.99
4.74
4.96
%
Time

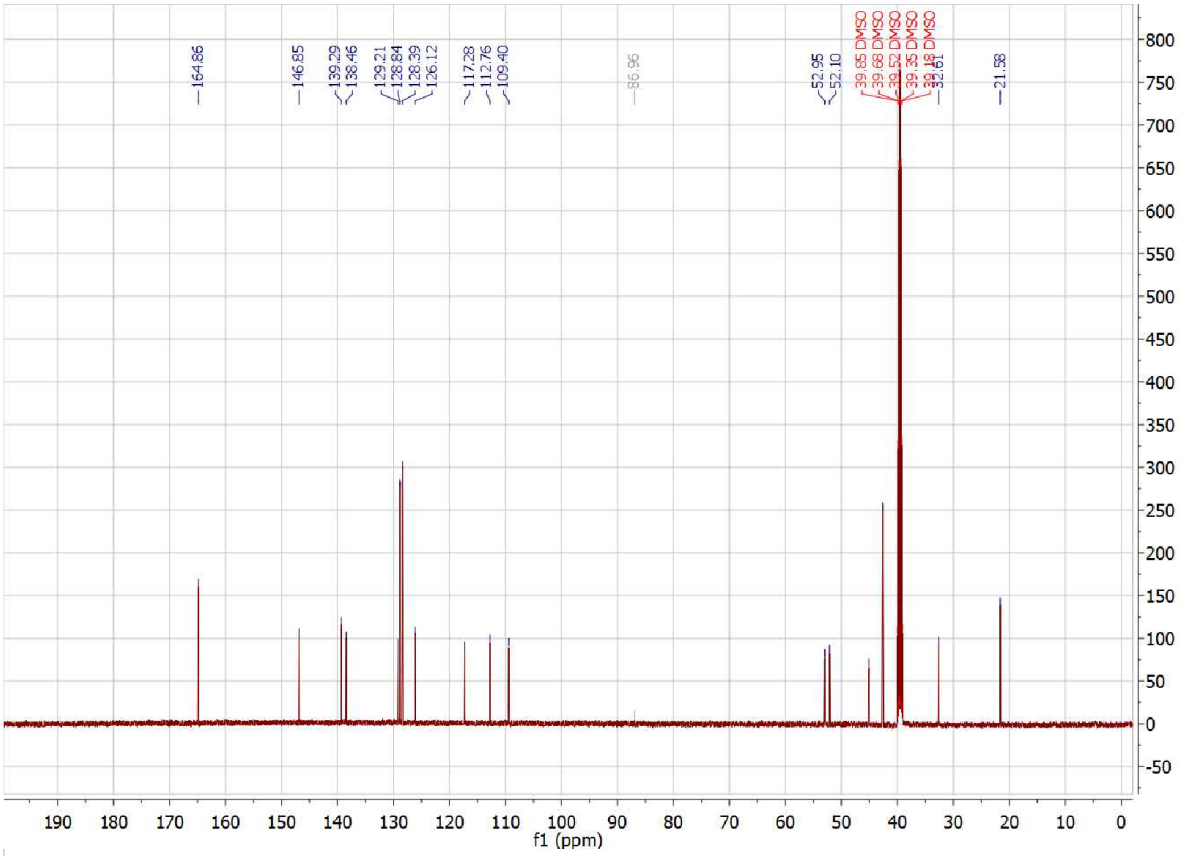
N-[2-(dimethylamino)ethyl]-3-methyl-N-(2-phenylethyl)aniline (4g).

3h (N-[2-(dimethylamino)ethyl]-3-methylaniline) was synthesized according to general procedure 1 using 3-methylaniline (5 g, 0.047 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 2.02 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3h** was obtained (0.64 g, 23%) LCMS [M+1] = 179.11 m/z (178.27 calc). **4g** was synthesized according to general procedure 2 using 0.64 g (0.0036 mol) of **3h**, phenylacetaldehyde (1.5 eq., 0,60 ml), sodium triacetoxyborohydride (3 eq., 1.14 g), dichloroethane (50 ml). A brown oil of **4g** was obtained (0.502 g, 37%). LCMS [M+1] = 283.15 m/z (282.43 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.93 (s, 2H), 7.35 – 7.25 (m, 4H), 7.27 – 7.17 (m, 1H), 7.13 – 7.04 (m, 1H), 6.63 – 6.57 (m, 2H), 6.48 (dt, *J* = 6.6, 0.9 Hz, 1H), 3.66 – 3.58 (m, 2H), 3.52 – 3.45 (m, 2H), 3.10 – 3.02 (m, 2H), 2.82 – 2.76 (m, 2H), 2.75 (s, 6H), 2.26 (s, 3H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 21.58, 32.61, 42.59, 45.07, 52.10, 52.95, 109.40, 112.76, 117.28, 126.12, 128.39, 128.84, 129.21, 138.46, 139.29, 146.85, 164.86.




164.86
146.85
139.29
138.46
129.21
128.84
128.39
126.12
117.28
112.76
109.40
86.96
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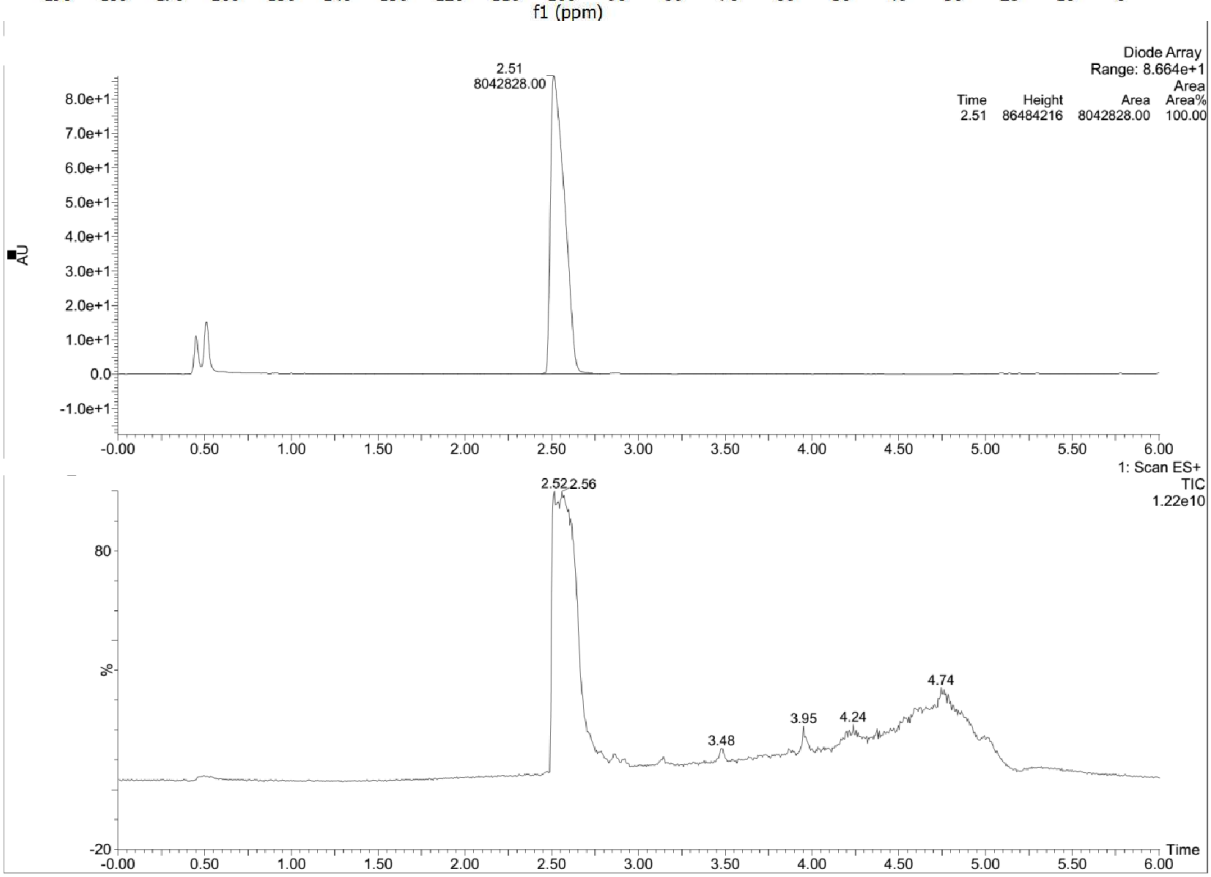
39.68 DMSO
39.52 DMSO
39.35 DMSO
39.18 DMSO
32.61
21.58
f1 (ppm)


Diode Array
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Time Height Area Area%
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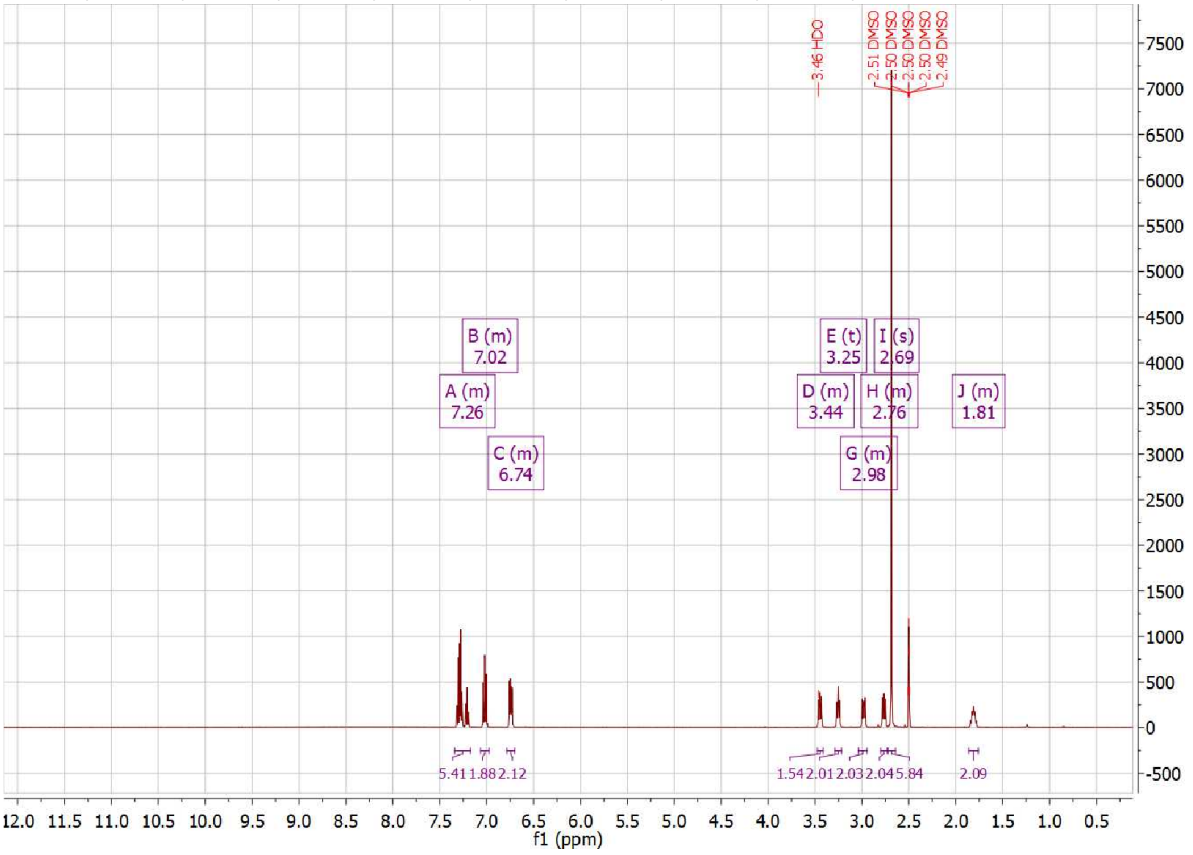
2.51
8042828.00
AU
1: Scan ES+
TIC
1.22e10
2.52 2.56
3.48
3.95
4.24
4.74
%
Time

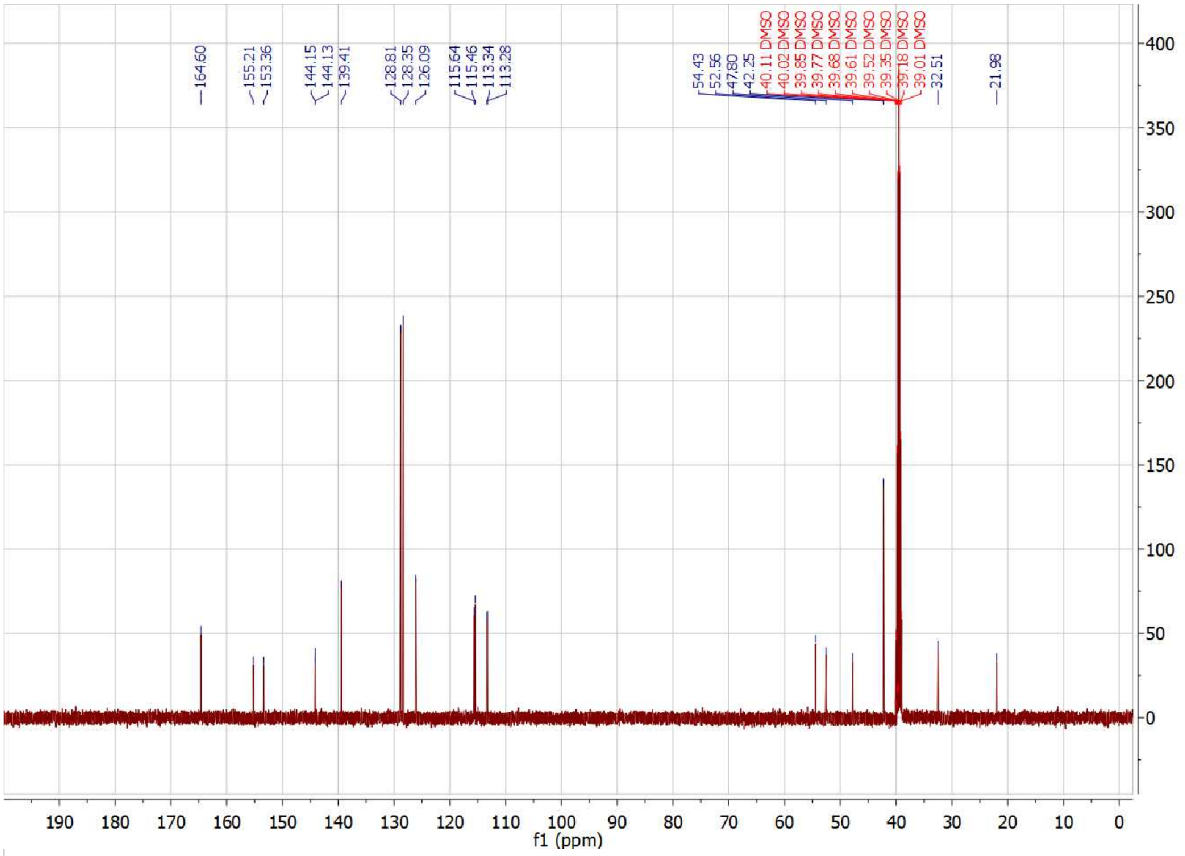
N-[3-(dimethylamino)propyl]-4-fluoro-N-(2-phenylethyl)aniline (4h).

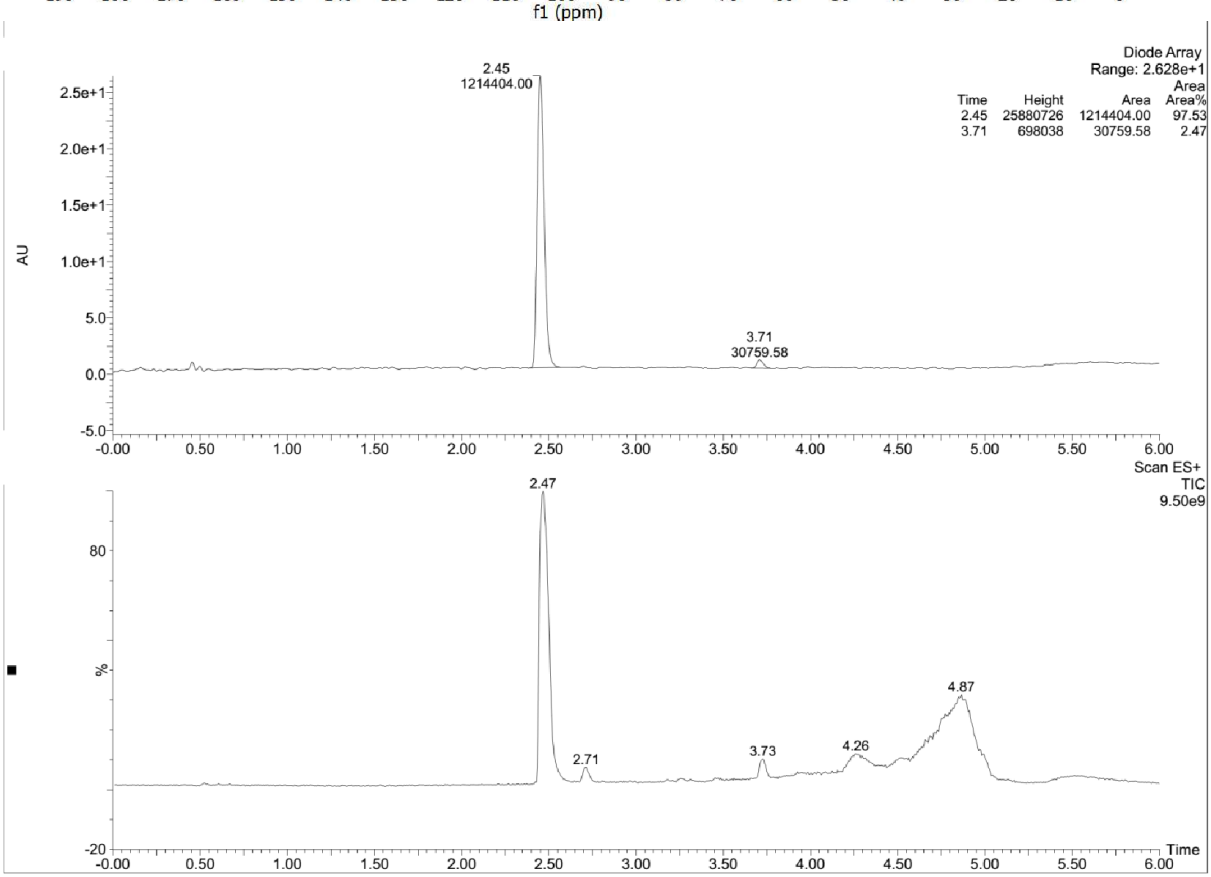
3i (N-[3-(dimethylamino)propyl]-4-fluoroaniline) was synthesized according to general procedure 1 using 4-fluoroaniline (5 g, 0.045 mol) and ((3-chloropropyl)dimethylamine hydrochloride (0.3 eq., 2.13 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3i** was obtained (1.21 g, 45%) LCMS [M+1] = 197.31 m/z (196.27 calc). **4h** was synthesized according to general procedure 2 using 0.64 g (0.0032 mol) of **3i**, phenylacetaldehyde (1.5 eq., 0.54 ml), sodium triacetoxyborohydride (3 eq., 2.03 g), dichloroethane (50 ml). A brown oil of **4h** was obtained (0.336 g, 35%). LCMS [M+1] = 301.35 m/z (300.42 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 7.34 – 7.17 (m, 5H), 7.07 – 6.97 (m, 2H), 6.78 – 6.70 (m, 2H), 3.47 – 3.41 (m, 2H), 3.25 (t, *J* = 7.4 Hz, 2H), 3.04 – 2.95 (m, 2H), 2.80 – 2.73 (m, 2H), 2.69 (s, 6H), 1.86 – 1.76 (m, 2H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 21.98, 32.51, 42.25, 47.80, 52.56, 54.43, 113.28, 113.34, 115.46, 115.64, 126.09, 128.35, 128.81, 139.41, 144.13, 144.15, 153.36, 155.21, 164.60.




164.60
155.21
153.36
144.15
144.13
139.41
128.81
128.35
126.09
115.64
115.46
113.34
113.28
54.43
52.56
47.80
42.25
40.11 DMSO
40.02 DMSO
39.85 DMSO
39.77 DMSO
39.68 DMSO
39.61 DMSO
39.52 DMSO
39.35 DMSO
39.18 DMSO
39.01 DMSO
32.51
21.98
f1 (ppm)


Diode Array
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Time Height Area Area%
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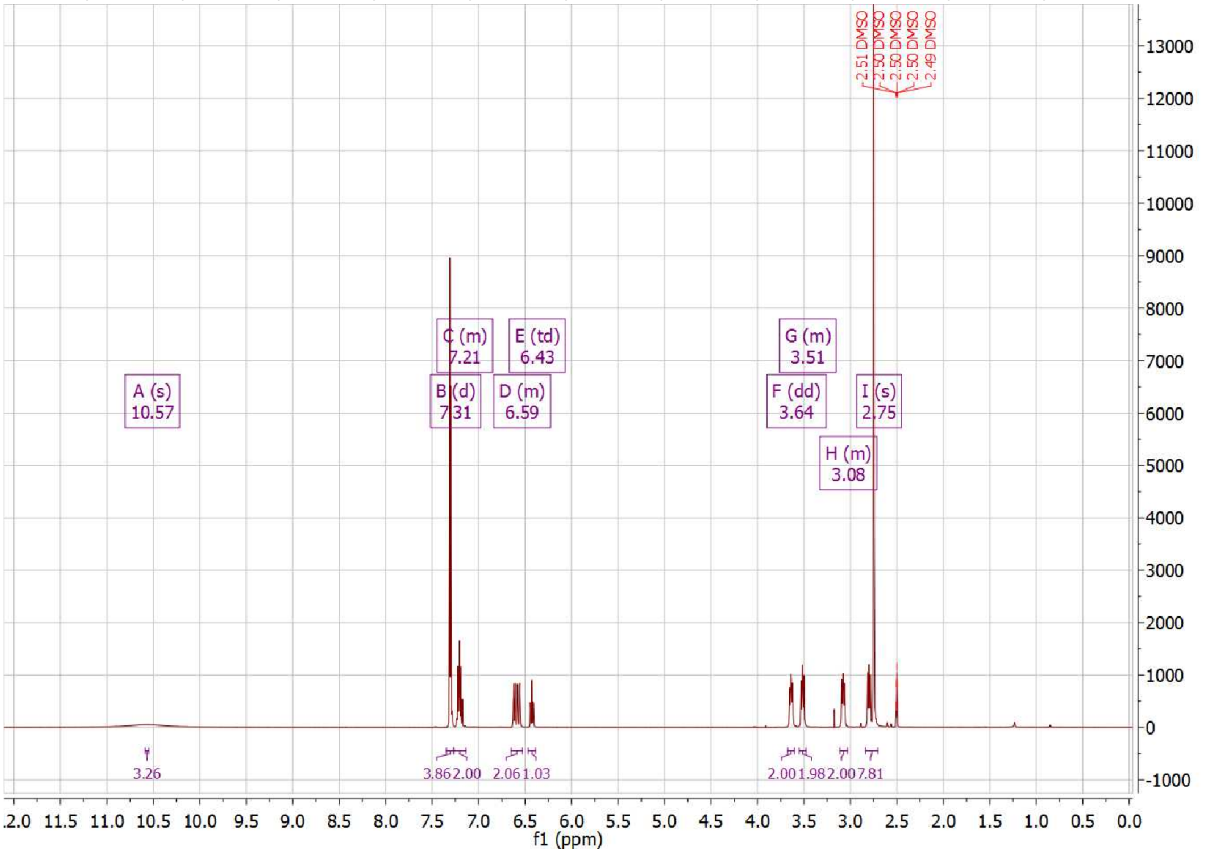
2.45
1214404.00
3.71
30759.58
AU
Scan ES+
TIC
9.50e9
2.47
2.71
3.73
4.26
4.87
%
Time

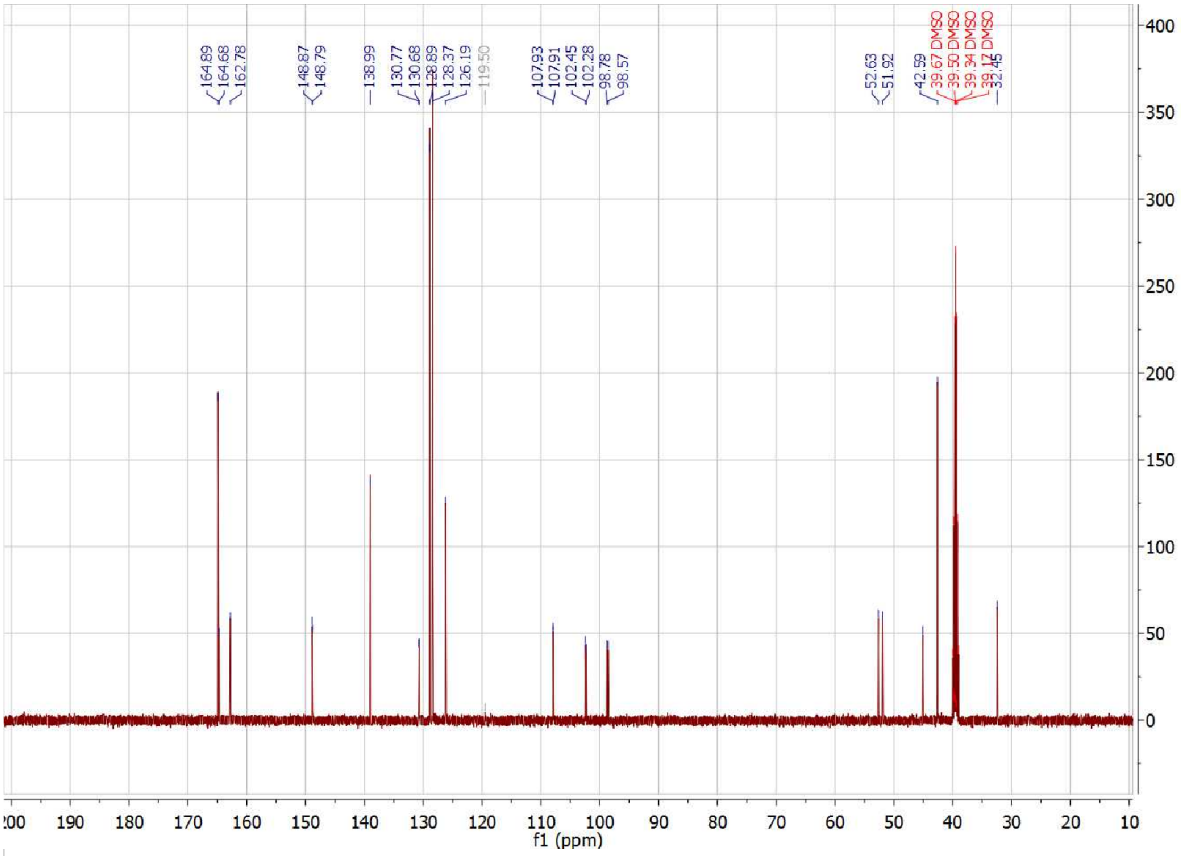
N-[2-(dimethylamino)ethyl]-3-fluoro-N-(2-phenylethyl)aniline (4i).

3j (N-[2-(dimethylamino)ethyl]-3-fluoroaniline) was synthesized according to general procedure 1 using 3-fluoroaniline (5 g, 0.045 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 2.13 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3j** was obtained (0.85 g, 34%) LCMS [M+1] = 183.18 m/z (182.24 calc). **4i** was synthesized according to general procedure 2 using 0.70 g (0.0038 mol) of **3j**, phenylacetaldehyde (1.5 eq., 0.64 ml), sodium triacetoxyborohydride (3 eq., 2.41 g), dichloroethane (50 ml). A brown oil of **4i** was obtained (0.392 g, 36%). LCMS [M+1] = 287,35 m/z (286,39 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 10.57 (s, 2H), 7.31 (d, *J* = 4.3 Hz, 4H), 7.27 – 7.14 (m, 2H), 6.65 – 6.53 (m, 2H), 6.43 (td, *J* = 8.2, 2.2 Hz, 1H), 3.64 (dd, *J* = 8.9, 6.7 Hz, 2H), 3.55 – 3.48 (m, 2H), 3.11 – 3.03 (m, 2H), 2.75 (s, 8H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 33.50, 45.57, 50.56, 54.09, 56.64, 101.36, 101.56, 106.19, 106.39, 108.19, 108.22, 126.81, 128.70, 129.15, 129.74, 129.82, 139.20, 150.42, 150.50, 163.00, 165.52.




164.89
164.68
162.78
148.87
148.79
138.99
130.77
130.68
128.89
128.37
126.19
119.50
107.93
107.91
102.45
102.28
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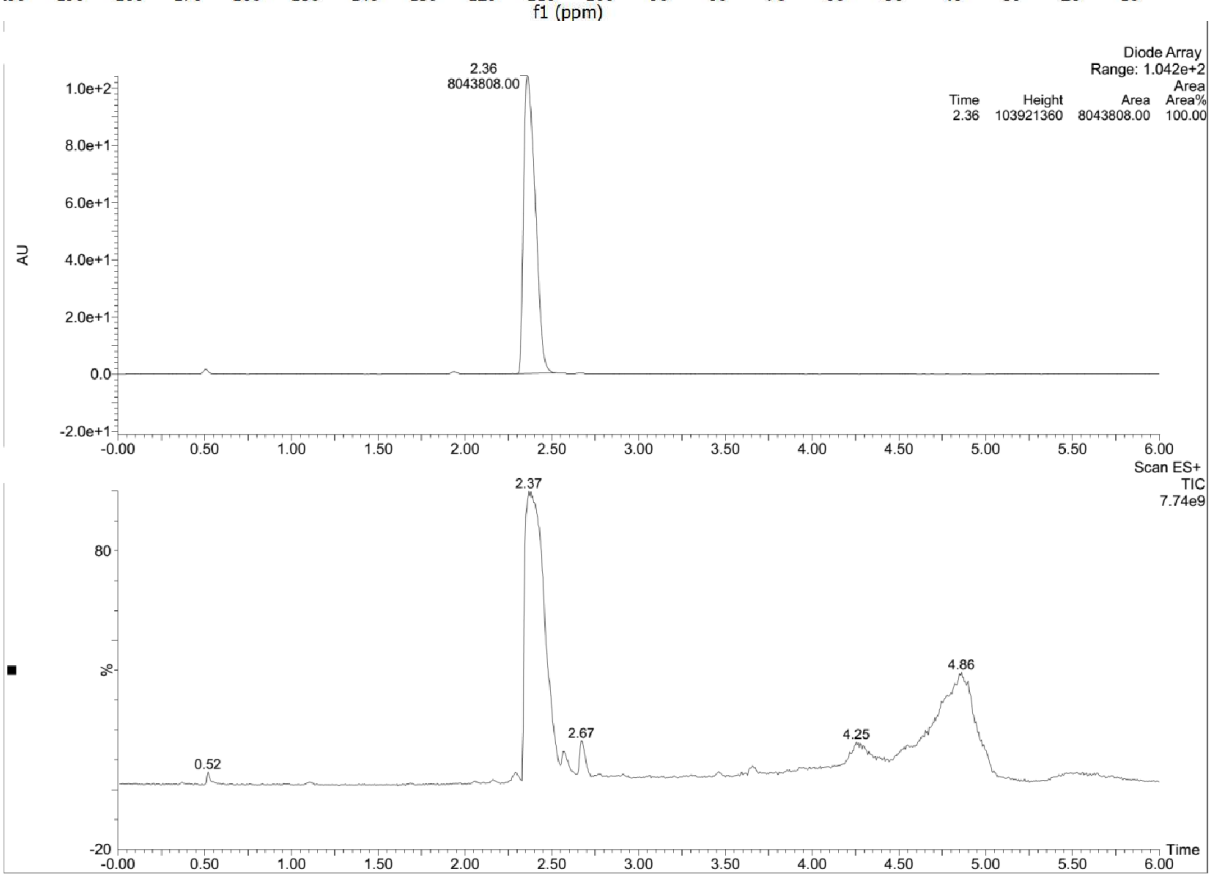
39.50 DMSO
39.34 DMSO
39.17 DMSO
32.45
f1 (ppm)


Diode Array
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Time Height Area Area%
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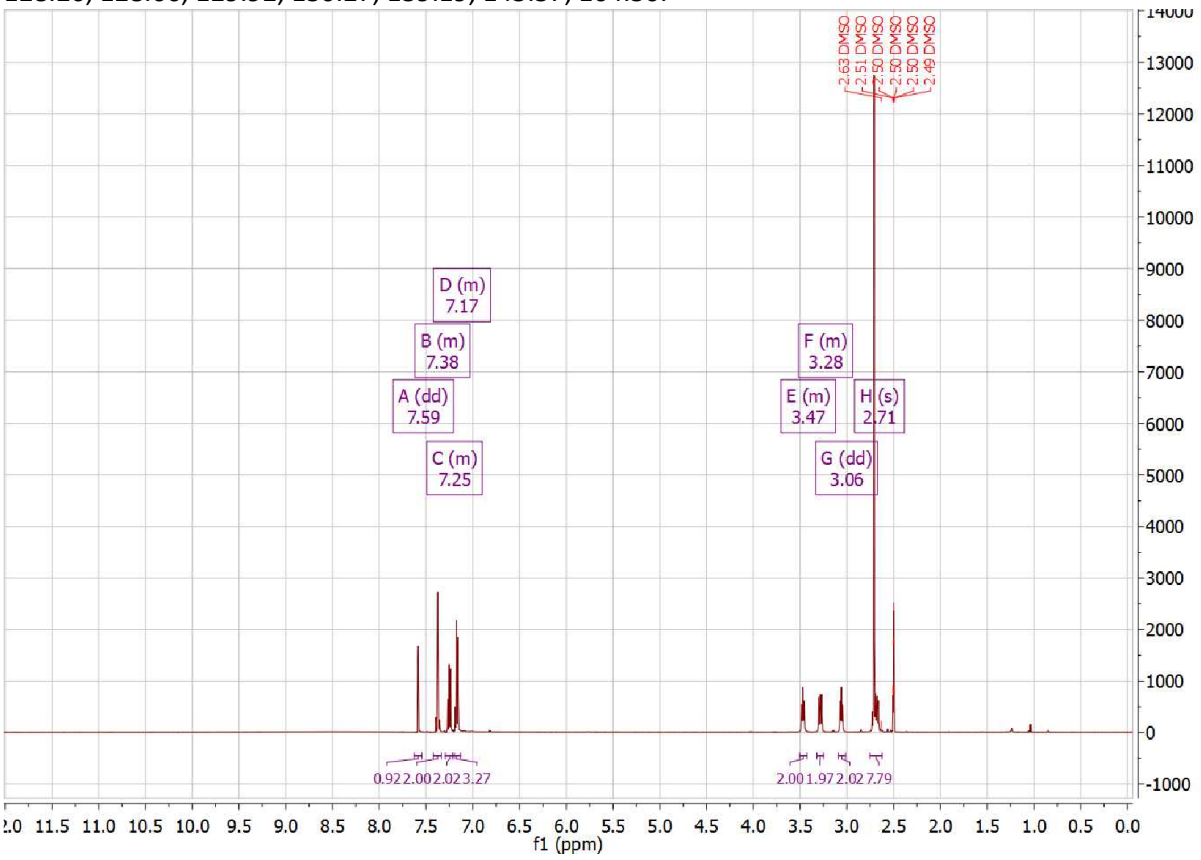
8043808.00
AU
Scan ES+
TIC
7.74e9
2.37
4.86
2.67
4.25
0.52
%
Time

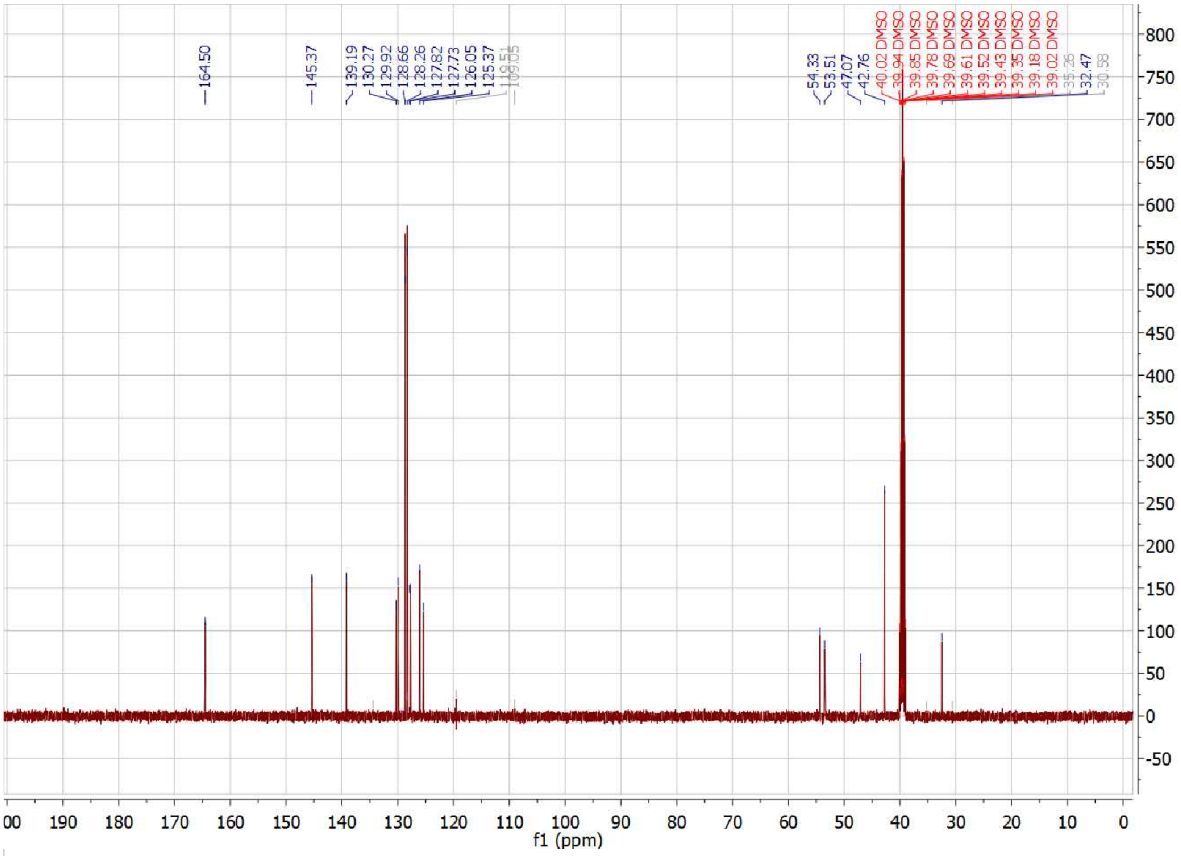
2,4-dichloro-N-[2-(dimethylamino)ethyl]-N-(2-phenylethyl)aniline (4j).

3k (2,4-dichloro-N-[2-(dimethylamino)ethyl]aniline) was synthesized according to general procedure 1 using 2,4-dichloroaniline (5 g, 0.031 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.46 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3k** was obtained (0.97 g, 40%) LCMS [M+1] = 233.07 m/z (232.05 calc). **4j** was synthesized according to general procedure 2 using 0.70 g (0.003 mol) of **3k**, phenylacetaldehyde (1.5 eq., 0.50 ml), sodium triacetoxyborohydride (3 eq., 1.9 g), dichloroethane (50 ml). A brown oil of **4j** was obtained (0.130 g, 13%). LCMS [M+1] = 337,21; 339,27 m/z (337,29 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 7.59 (dd, *J* = 2.0, 0.7 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.29 – 7.20 (m, 2H), 7.22 – 7.13 (m, 3H), 3.50 – 3.43 (m, 2H), 3.32 – 3.25 (m, 2H), 3.06 (dd, *J* = 7.7, 6.3 Hz, 2H), 2.71 (s, 8H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 32.47, 42.76, 47.07, 53.51, 54.33, 125.37, 126.05, 127.73, 127.82, 128.26, 128.66, 129.92, 130.27, 139.19, 145.37, 164.50.




164.50
145.37
139.19
130.27
129.92
128.66
128.26
127.82
127.73
126.05
125.37
54.33
53.51
47.07
42.76
40.02 DMSO
39.94 DMSO
39.85 DMSO
39.78 DMSO
39.69 DMSO
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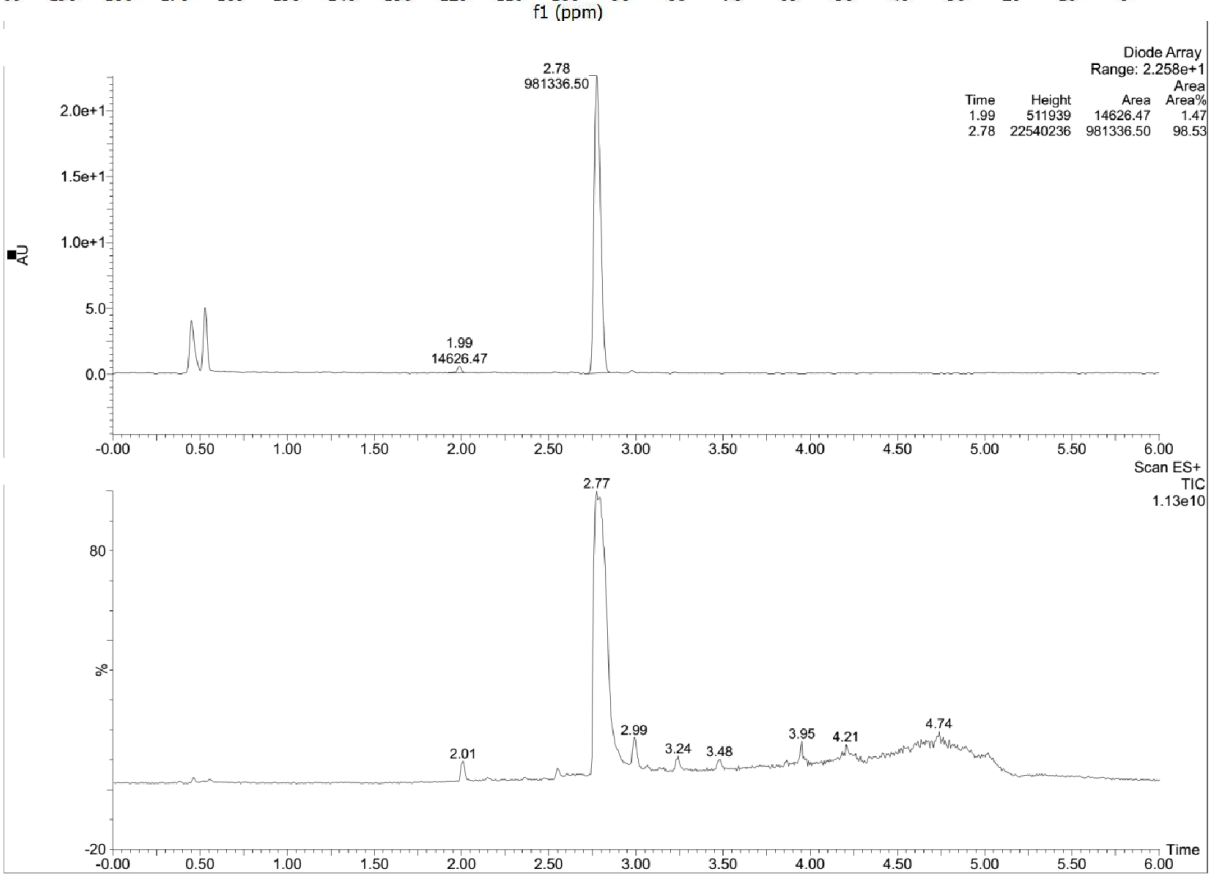
39.02 DMSO
35.26
32.47
30.58
f1 (ppm)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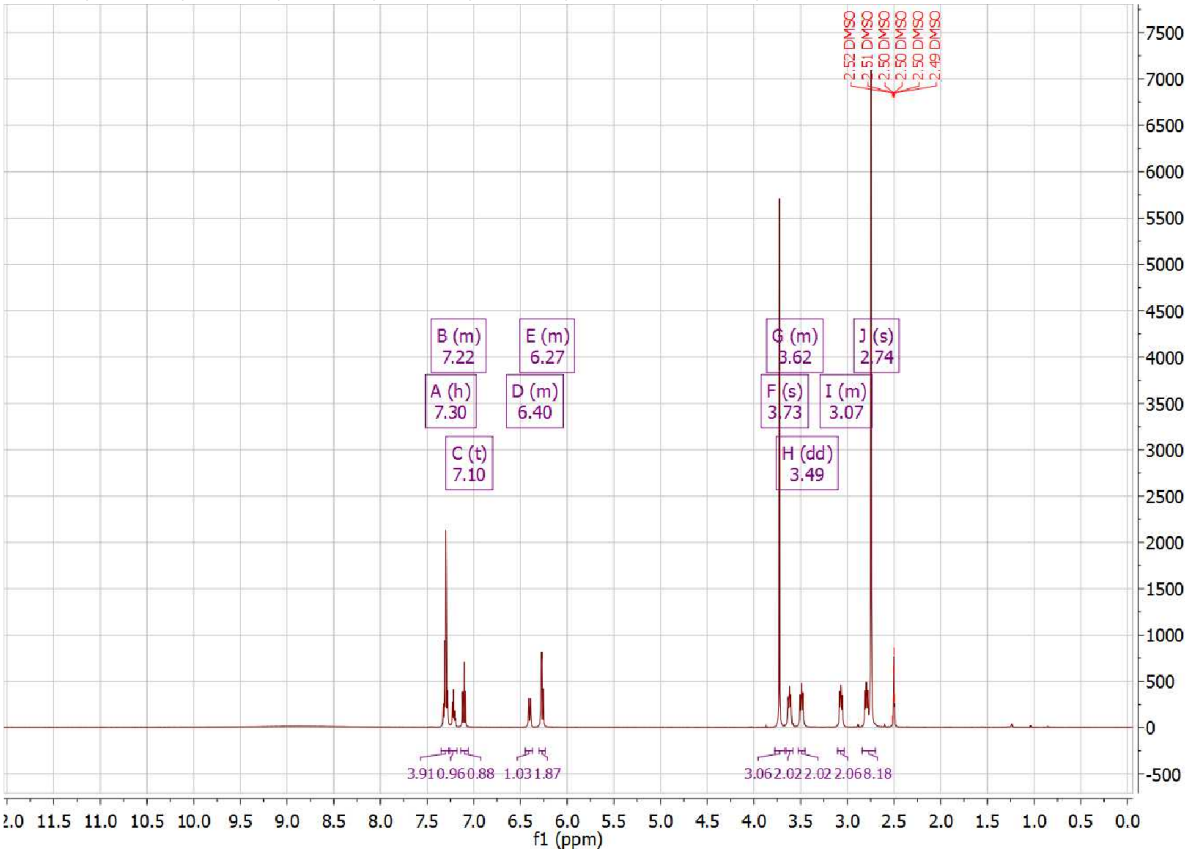
2.78
981336.50
1.99
14626.47
AU
Scan ES+
TIC
1.13e10
2.77
2.01
2.99
3.24
3.48
3.95
4.21
4.74
%
Time

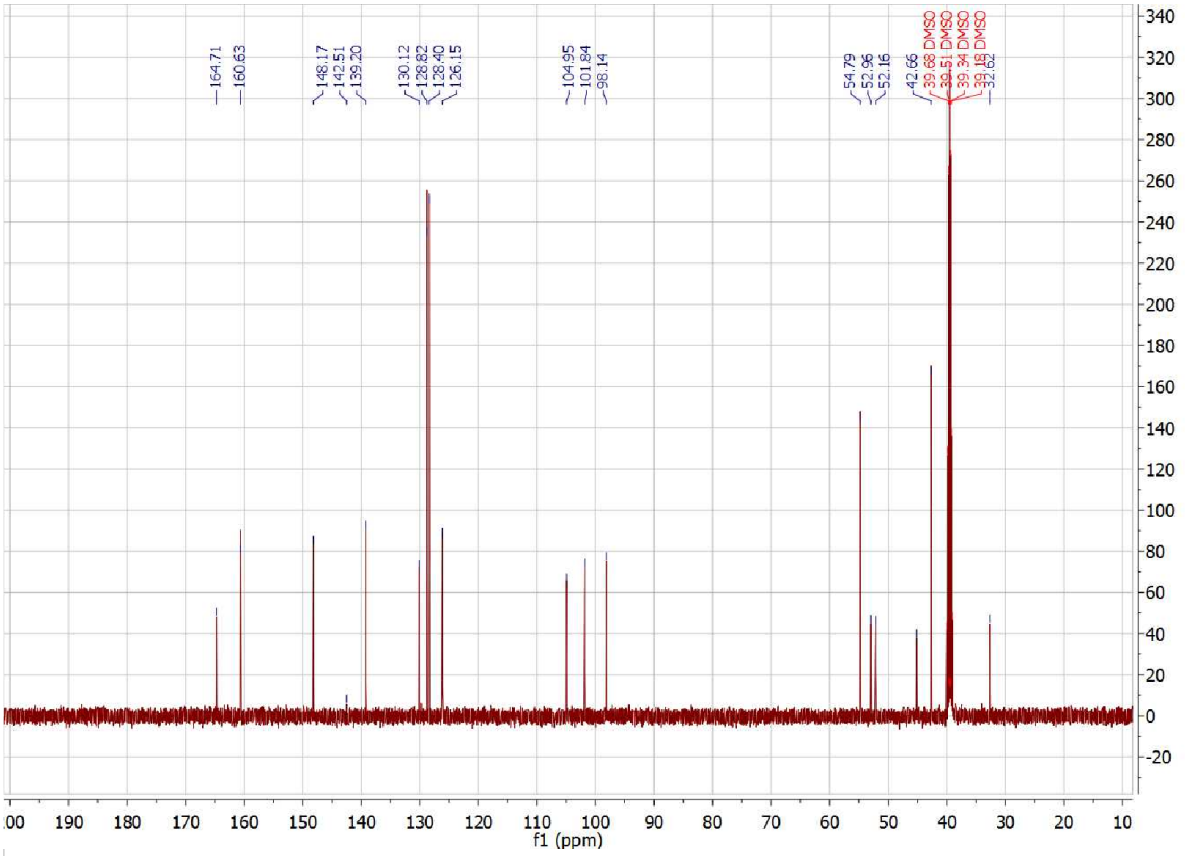
N-[2-(dimethylamino)ethyl]-3-methoxy-N-(2-phenylethyl)aniline (4k).

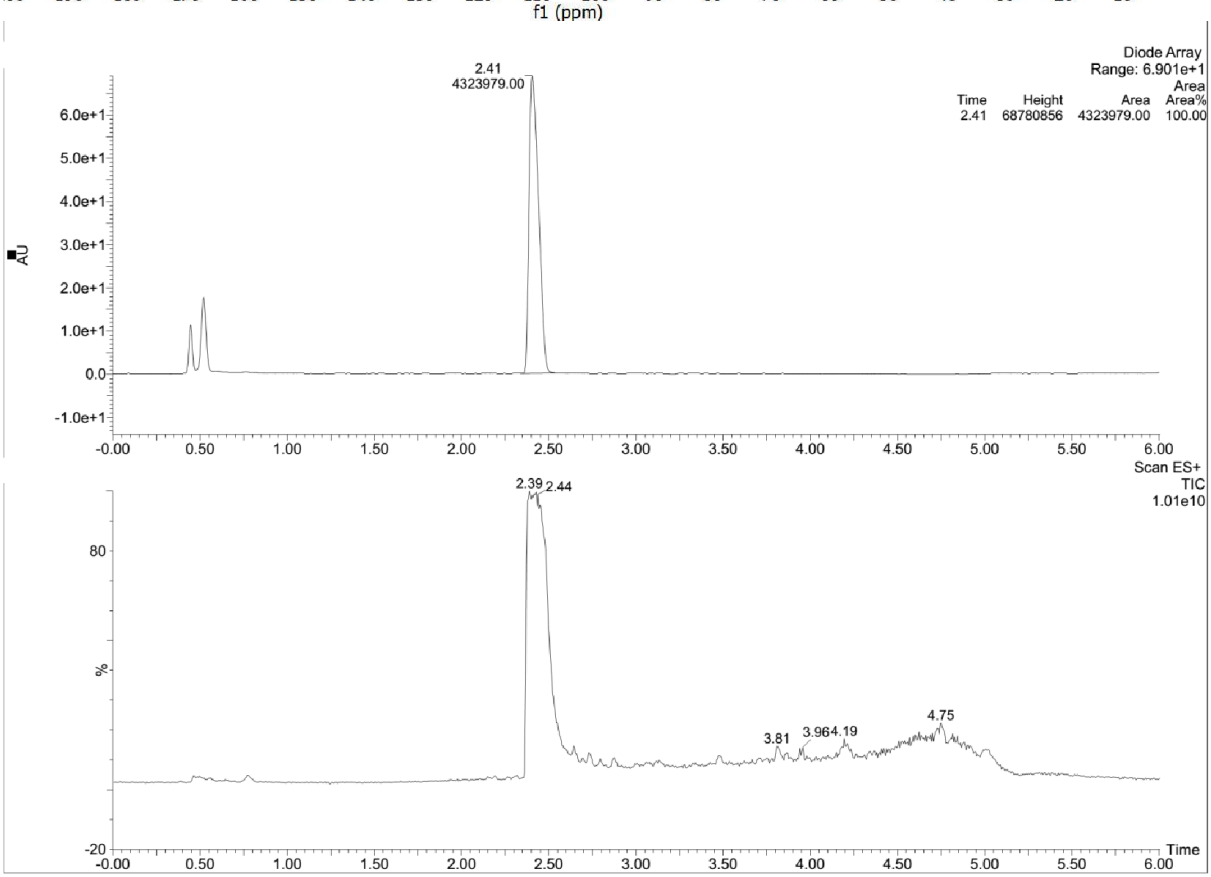
3l (N-[2-(dimethylamino)ethyl]-3-methoxyaniline) was synthesized according to general procedure 1 using 3-methoxyaniline (5 g, 0.04 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.76 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3l** was obtained (0.58 g, 24%) LCMS [M+1] = 195.24 m/z (194.28 calc). **4k** was synthesized according to general procedure 2 using 0.50 g (0.0026 mol) of **3l**, phenylacetaldehyde (1.5 eq., 0.43 ml), sodium triacetoxyborohydride (3 eq., 1.65 g), dichloroethane (50 ml). A brown oil of **4k** was obtained (0.248 g, 32%) LCMS [M+1] = 299.41 m/z (298.43 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 7.30 (h, *J* = 5.9 Hz, 4H), 7.27 – 7.18 (m, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.45 – 6.37 (m, 1H), 6.30 – 6.23 (m, 2H), 3.73 (s, 3H), 3.65 – 3.58 (m, 2H), 3.49 (dd, *J* = 9.0, 6.7 Hz, 2H), 3.10 – 3.03 (m, 2H), 2.74 (s, 8H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 32.62, 42.66, 45.13, 52.16, 52.96, 54.79, 98.14, 101.84, 104.95, 126.15, 128.40, 128.82, 130.12, 139.20, 142.51, 148.17, 160.63, 164.71.




164.71
160.63
148.17
142.51
139.20
130.12
128.82
128.40
126.15
104.95
101.84
98.14
54.79
52.96
52.16
42.66
39.68 DMSO
39.51 DMSO
39.34 DMSO
39.18 DMSO
32.62
f1 (ppm)


Diode Array
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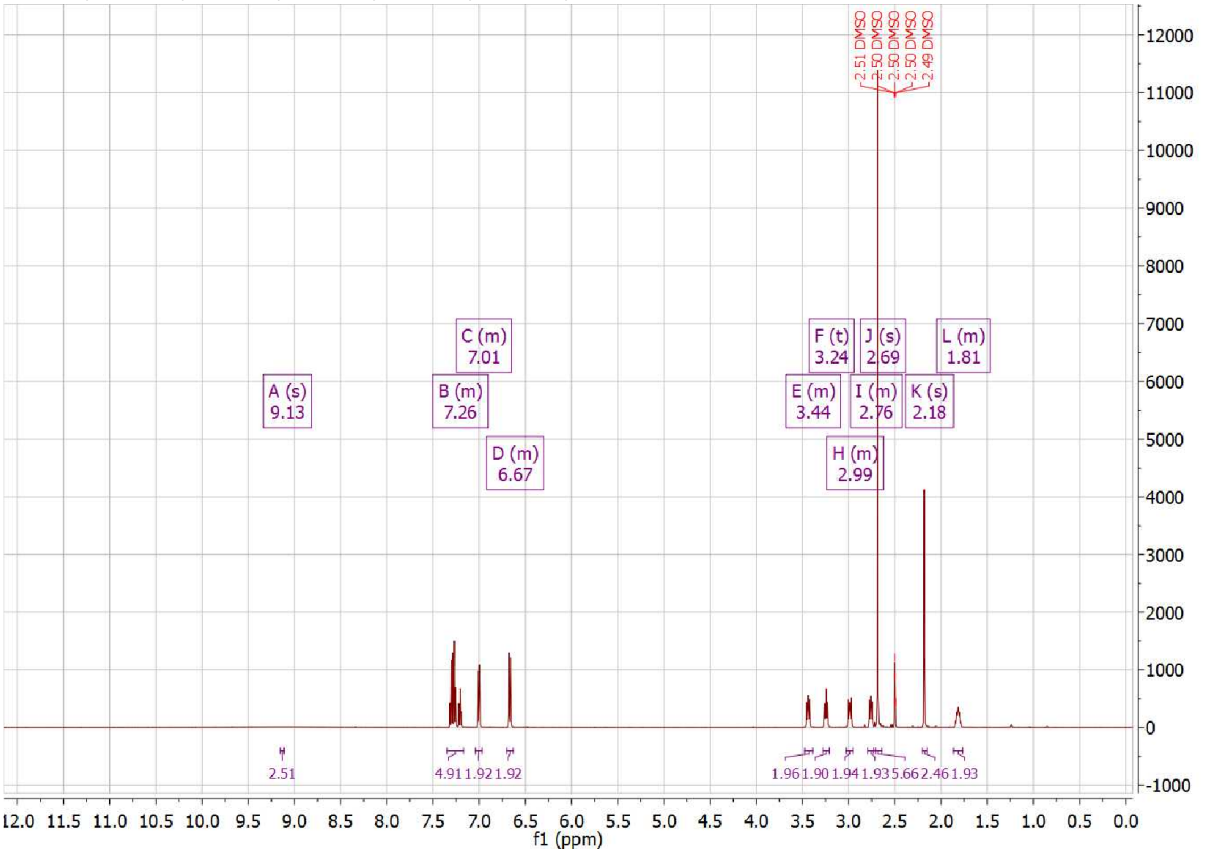
4323979.00
AU
Scan ES+
TIC
1.01e10
2.39
2.44
3.81
3.96
4.19
4.75
%
Time

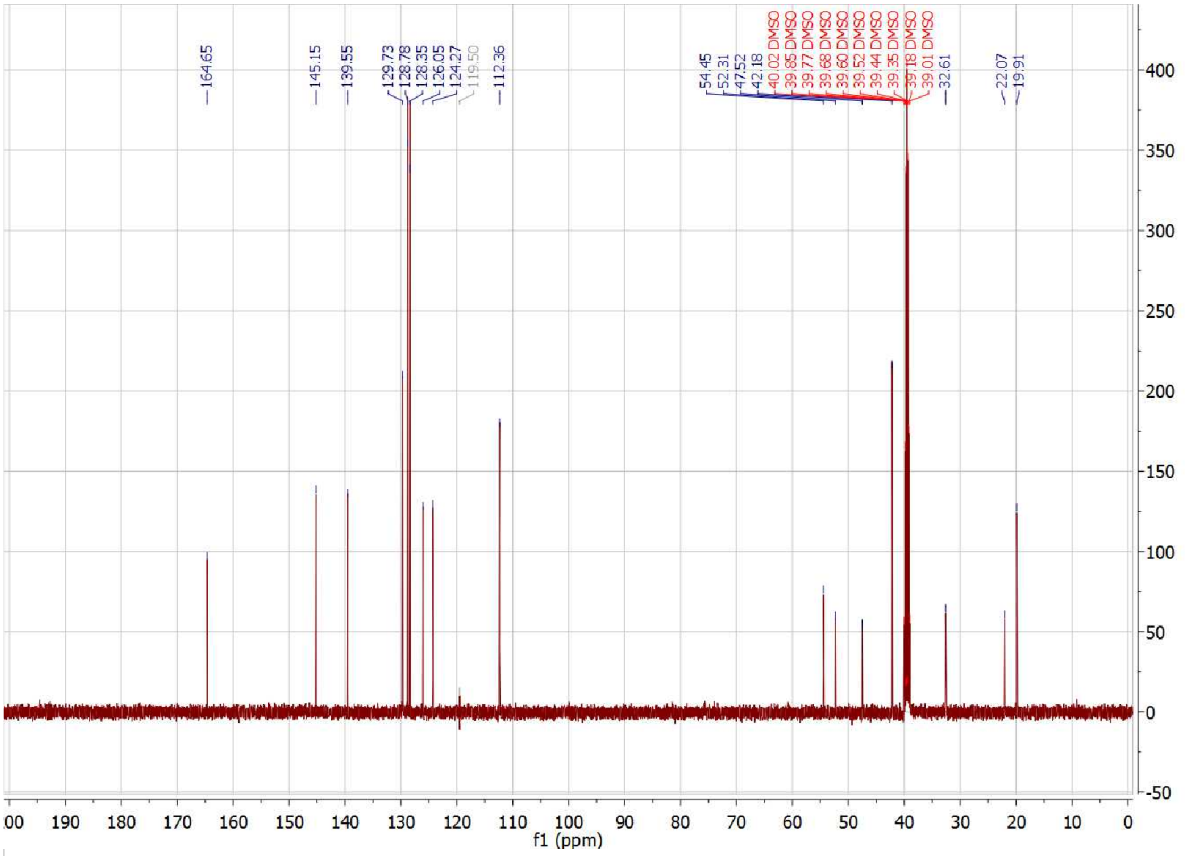
N-[3-(dimethylamino)propyl]-4-methyl-N-(2-phenylethyl)aniline (4l).

3m (N-[3-(dimethylamino)propyl]-4-methylaniline) was synthesized according to general procedure 1 using 4-methylaniline (5 g, 0.047 mol) and (3-chloropropyl)dimethylamine hydrochloride (0.3 eq., 2.21 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3m** was obtained (0.64 g, 21%) LCMS [M+1] = 193.11 m/z (192.3 calc). **4l** was synthesized according to general procedure 2 using 0.64 g (0.0033 mol) of **3m**, phenylacetaldehyde (1.5 eq., 0.56 ml), sodium triacetoxyborohydride (3 eq., 1.06 g), dichloroethane (50 ml). A brown oil of **4l** was obtained (0.361 g, 37%). LCMS [M+1] = 297.41 m/z (296.46 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.13 (s, 2H), 7.35 – 7.17 (m, 5H), 7.04 – 6.97 (m, 2H), 6.70 – 6.63 (m, 2H), 3.47 – 3.39 (m, 2H), 3.24 (t, *J* = 7.4 Hz, 2H), 3.02 – 2.95 (m, 2H), 2.79 – 2.71 (m, 2H), 2.69 (s, 6H), 2.18 (s, 3H), 1.87 – 1.76 (m, 2H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 19.91, 22.07, 32.61, 42.18, 47.52, 52.31, 54.45, 112.36, 124.27, 126.05, 128.35, 128.78, 129.73, 139.55, 145.15, 164.65.




164.65
145.15
139.55
129.73
128.78
128.35
126.05
124.27
119.50
112.36
54.45
52.31
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42.18
40.02 DMSO
39.85 DMSO
39.77 DMSO
39.68 DMSO
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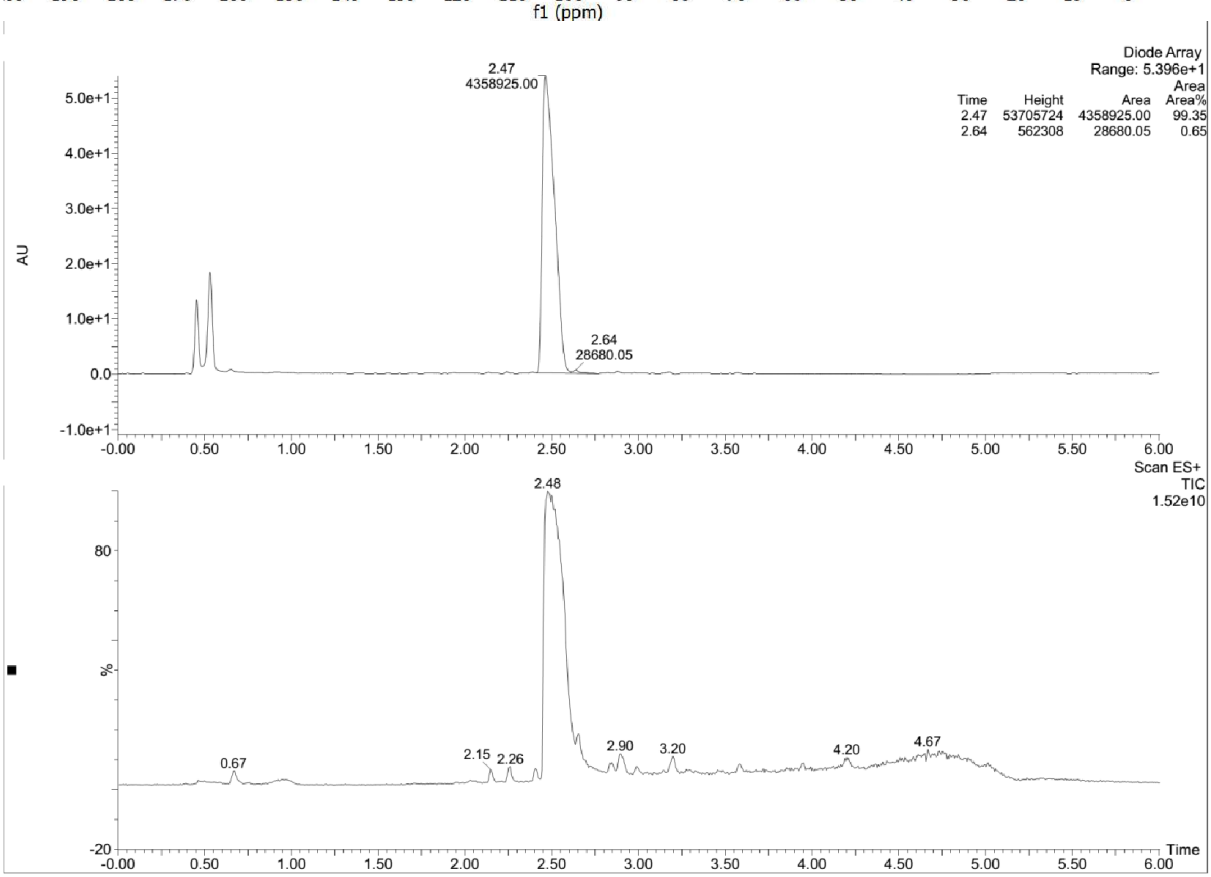
39.01 DMSO
32.61
22.07
19.91
f1 (ppm)


Diode Array
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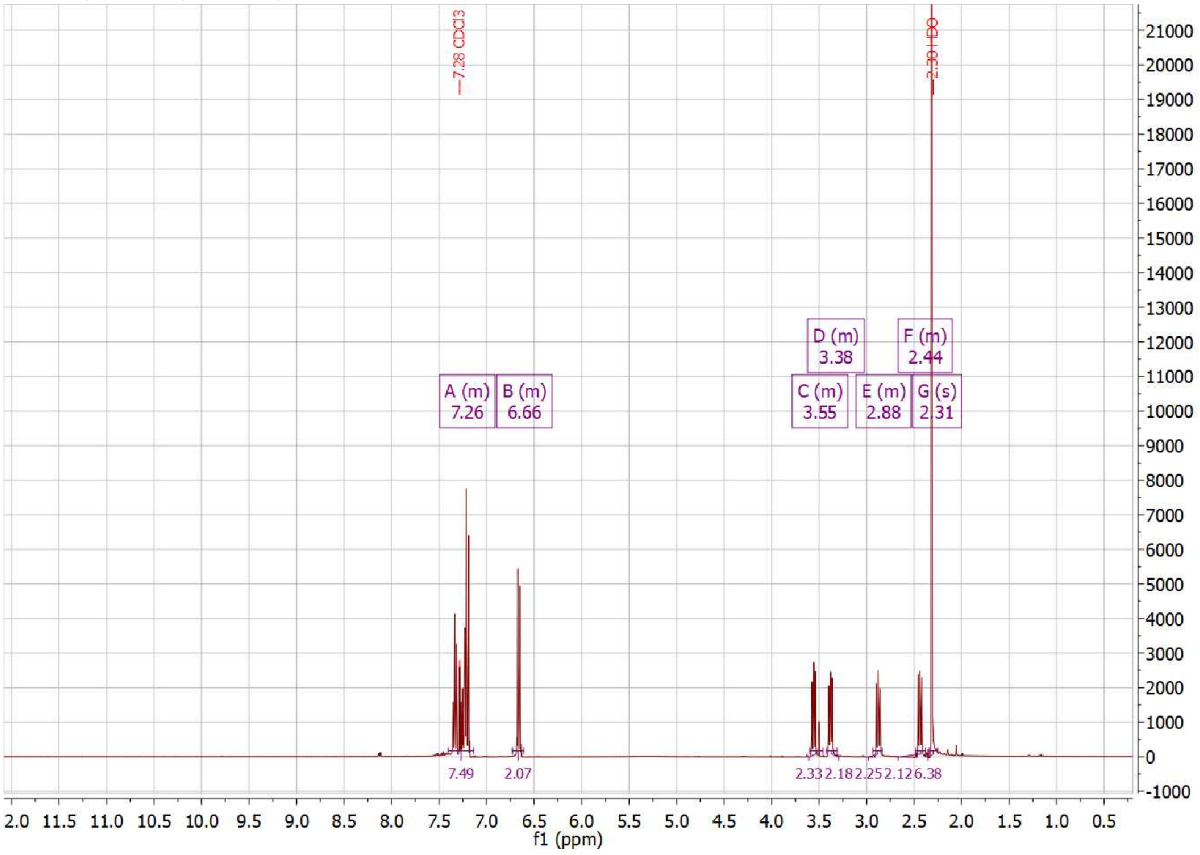
4358925.00
2.64
28680.05
AU
Scan ES+
TIC
1.52e10
2.48
0.67
2.15
2.26
2.90
3.20
4.20
4.67
%
Time

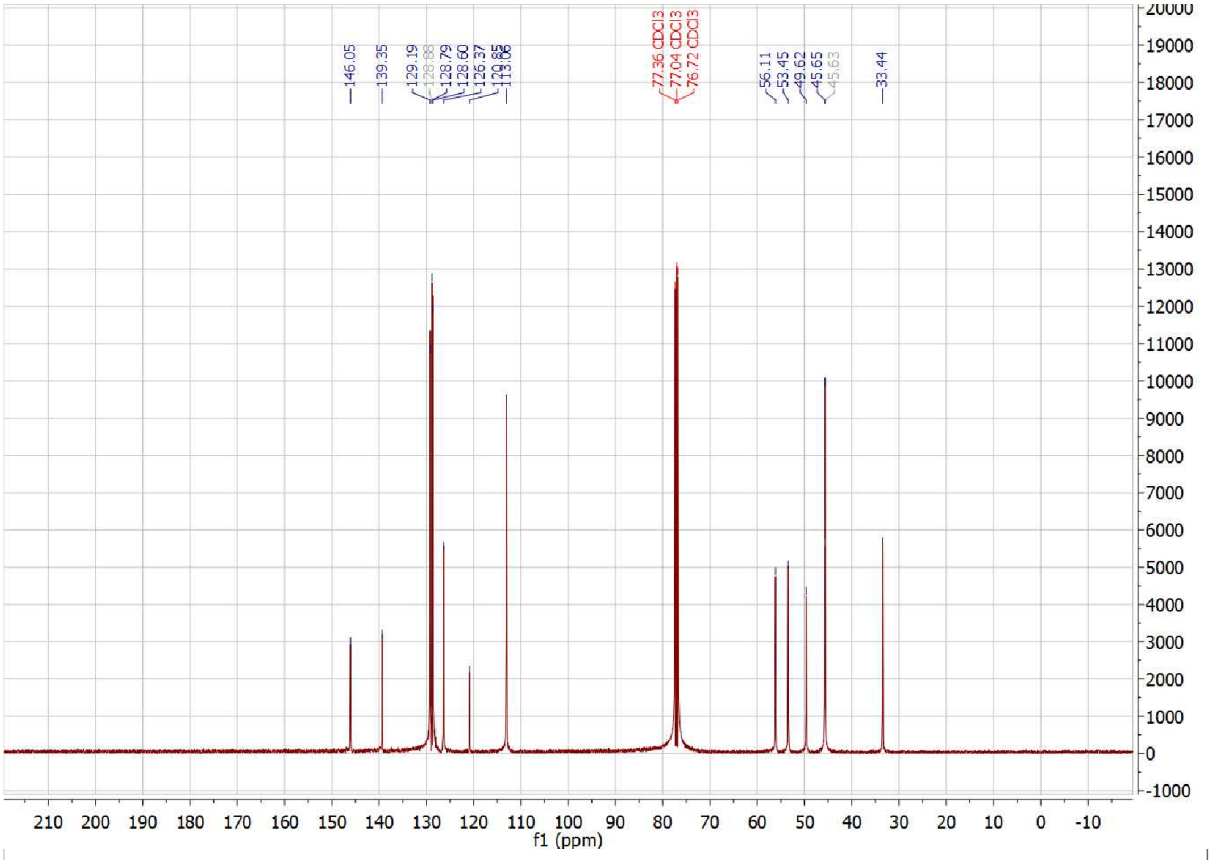
4-chloro-N-[2-(dimethylamino)ethyl]-N-(2-phenylethyl)aniline (4m).

3n (4-chloro-N-[2-(dimethylamino)ethyl]aniline) was synthesized according to general procedure 1 using 4-chloroaniline (5 g, 0.039 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.7 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3n** was obtained (0.51 g, 20%) LCMS [M+1] = 199.48 m/z (198.69 calc). **4m** was synthesized according to general procedure 2 using 0.51 g (0.0026 mol) of **3n**, phenylacetaldehyde (1.5 eq., 0.43 ml), sodium triacetoxyborohydride (3 eq., 0.82 g), dichloroethane (50 ml). A brown oil of **4m** was obtained (0.355 g, 45%). LCMS [M+1] = 303.28 m/z (302.85 calc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.14 (m, 7H), 6.73 – 6.61 (m, 2H), 3.60 – 3.46 (m, 2H), 3.42 – 3.31 (m, 2H), 2.93 – 2.83 (m, 2H), 2.48 – 2.38 (m, 2H), 2.31 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 33.44, 45.65, 49.62, 53.45, 56.11, 113.06, 120.85, 126.37, 128.60, 128.79, 129.19, 139.35, 146.05.




146.05
139.35
129.19
128.79
128.60
126.37
120.85
113.08
77.36 CDCl3
77.04 CDCl3
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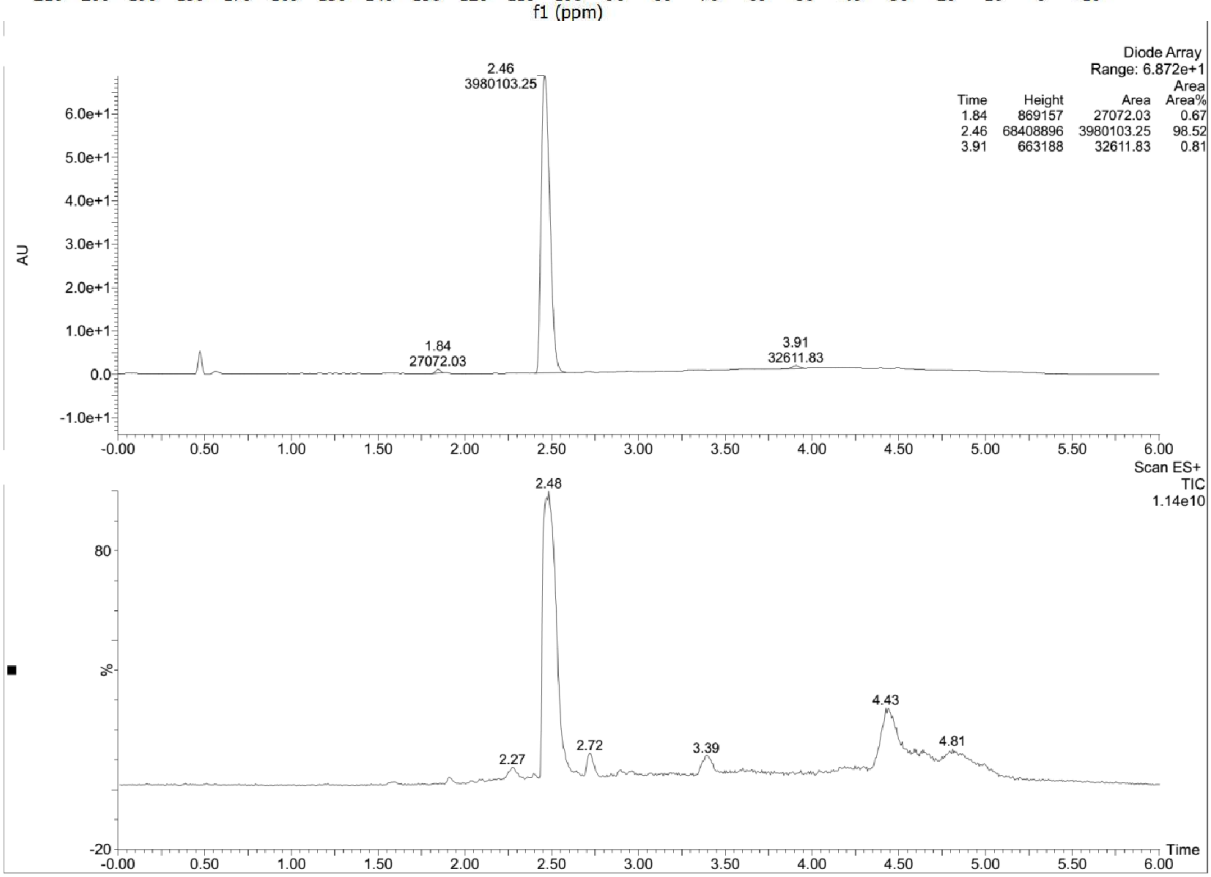
56.11
53.45
49.62
45.65
45.63
33.44
f1 (ppm)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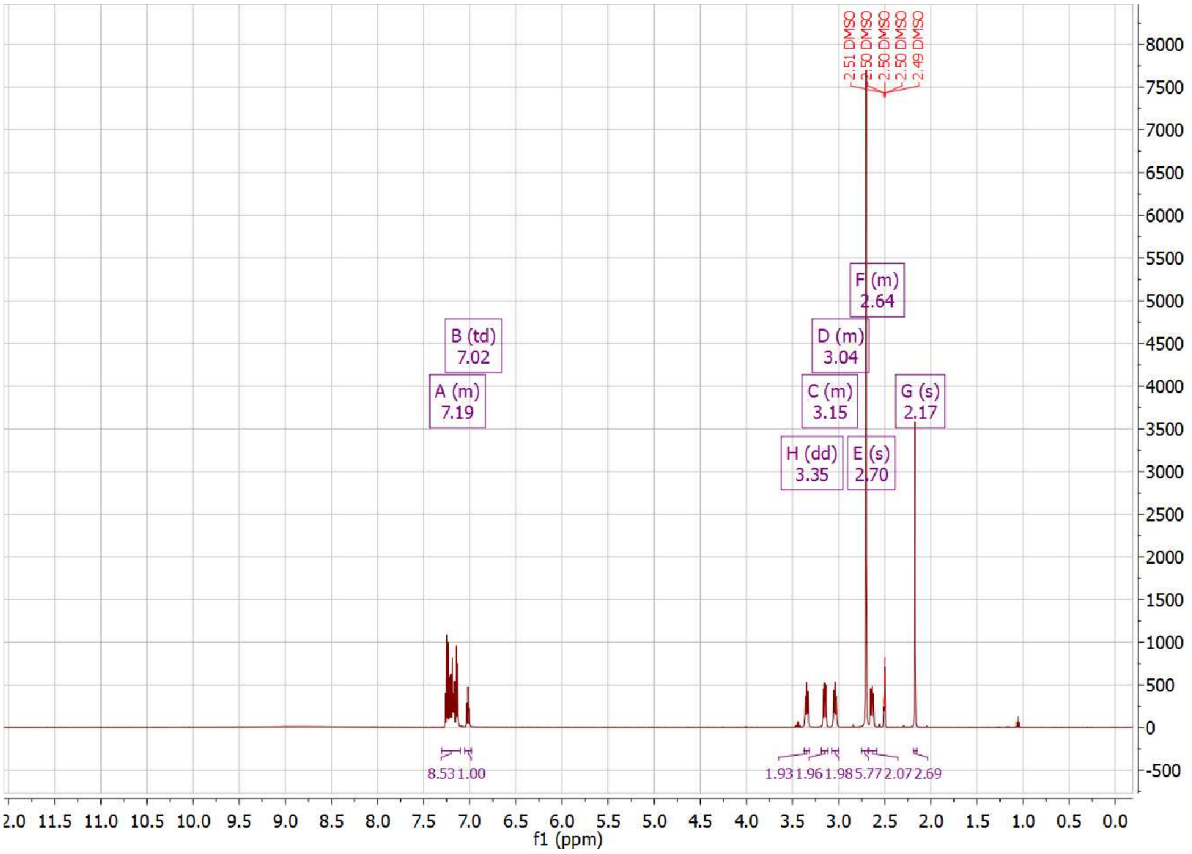
2.46
3980103.25
1.84
27072.03
3.91
32611.83
AU
Scan ES+
TIC
1.14e10
2.48
2.27
2.72
3.39
4.43
4.81
%
Time

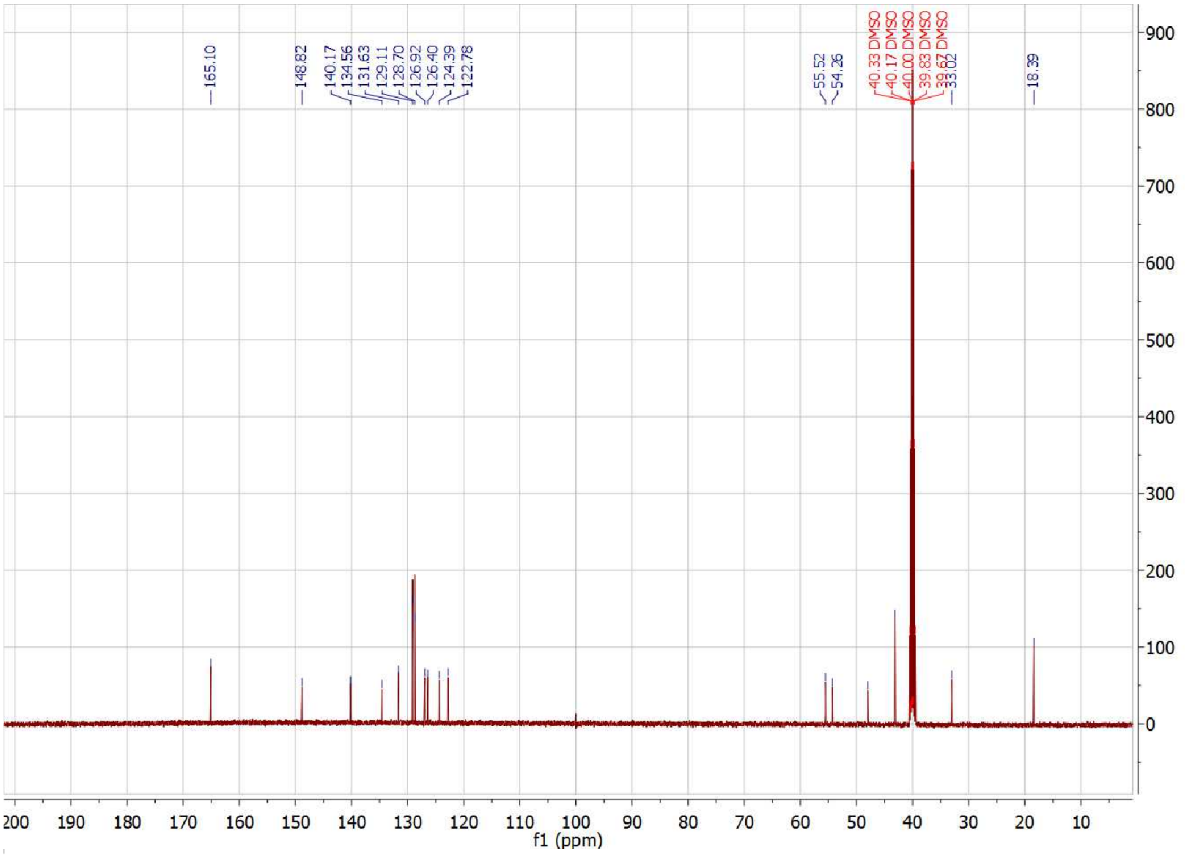
N-[2-(dimethylamino)ethyl]-2-methyl-N-(2-phenylethyl)aniline (4n).

3o (N-[2-(dimethylamino)ethyl]-2-methylaniline) was synthesized according to general procedure 1 using 2-methylaniline (5 g, 0.047 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 2.02 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3o** was obtained (0.20 g, 7%) LCMS [M+1] = 179.11 m/z (178.27 calc). **4n** was synthesized according to general procedure 2 using 0.20 g (0.0011 mol) of **3o**, phenylacetaldehyde (1.5 eq., 0.19 ml), sodium triacetoxyborohydride (3 eq., 0.36 g), dichloroethane (50 ml). A brown oil of **4n** was obtained (0.058 g, 19%). LCMS [M+1] = 283.28m/z (282.43 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 7.30 – 7.10 (m, 8H), 7.02 (td, *J* = 7.3, 1.4 Hz, 1H), 3.35 (dd, *J* = 8.3, 6.1 Hz, 2H), 3.19 – 3.12 (m, 2H), 3.07 – 3.00 (m, 2H), 2.70 (s, 6H), 2.67 – 2.59 (m, 2H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 18.39, 33.02, 43.12, 47.99, 54.26, 55.52, 122.78, 124.39, 126.40, 126.92, 128.70, 129.11, 131.63, 134.56, 140.17, 148.82, 165.10.




165.10
148.82
140.17
134.56
131.63
129.11
128.70
126.92
126.40
124.39
122.78
55.52
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40.17 DMSO
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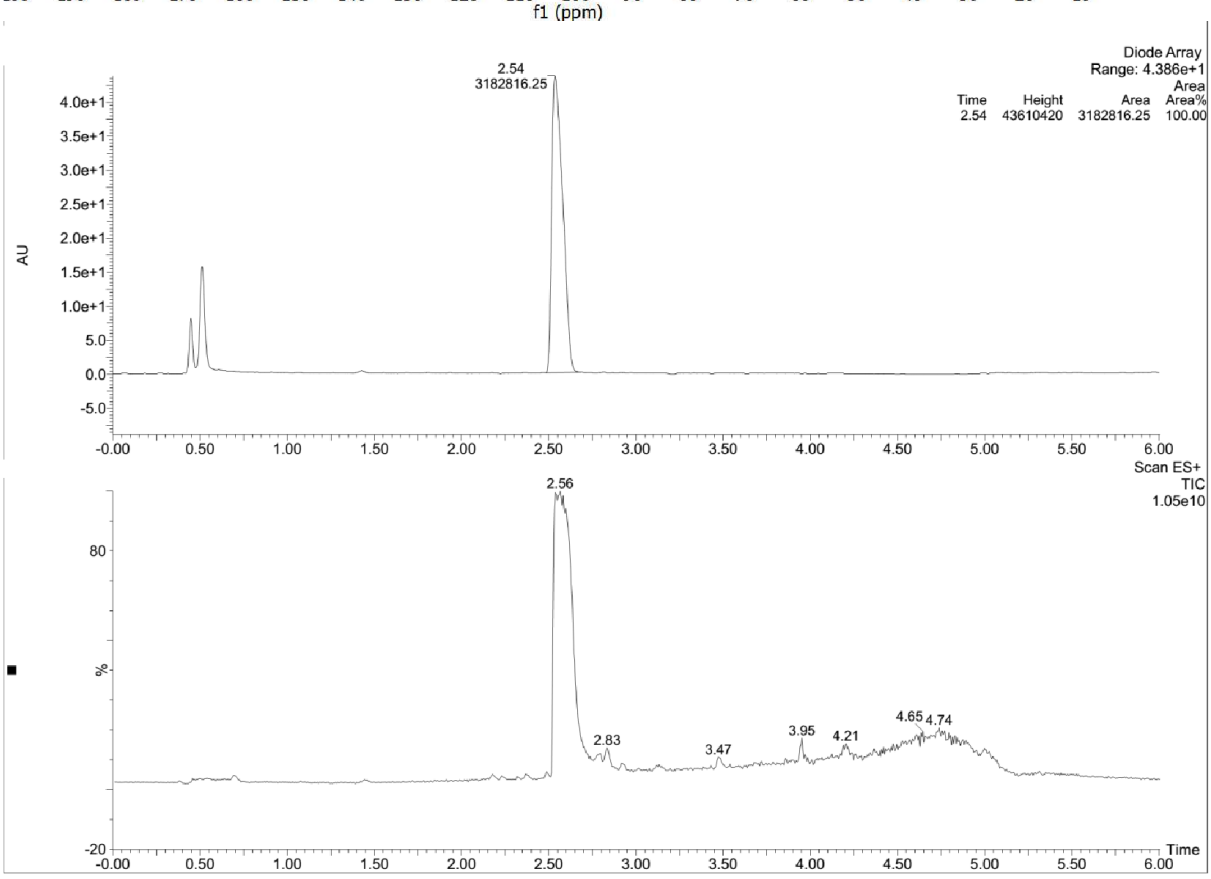
39.67 DMSO
39.50 DMSO
39.33 DMSO
18.39
f1 (ppm)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3182816.25
AU
Scan ES+
TIC
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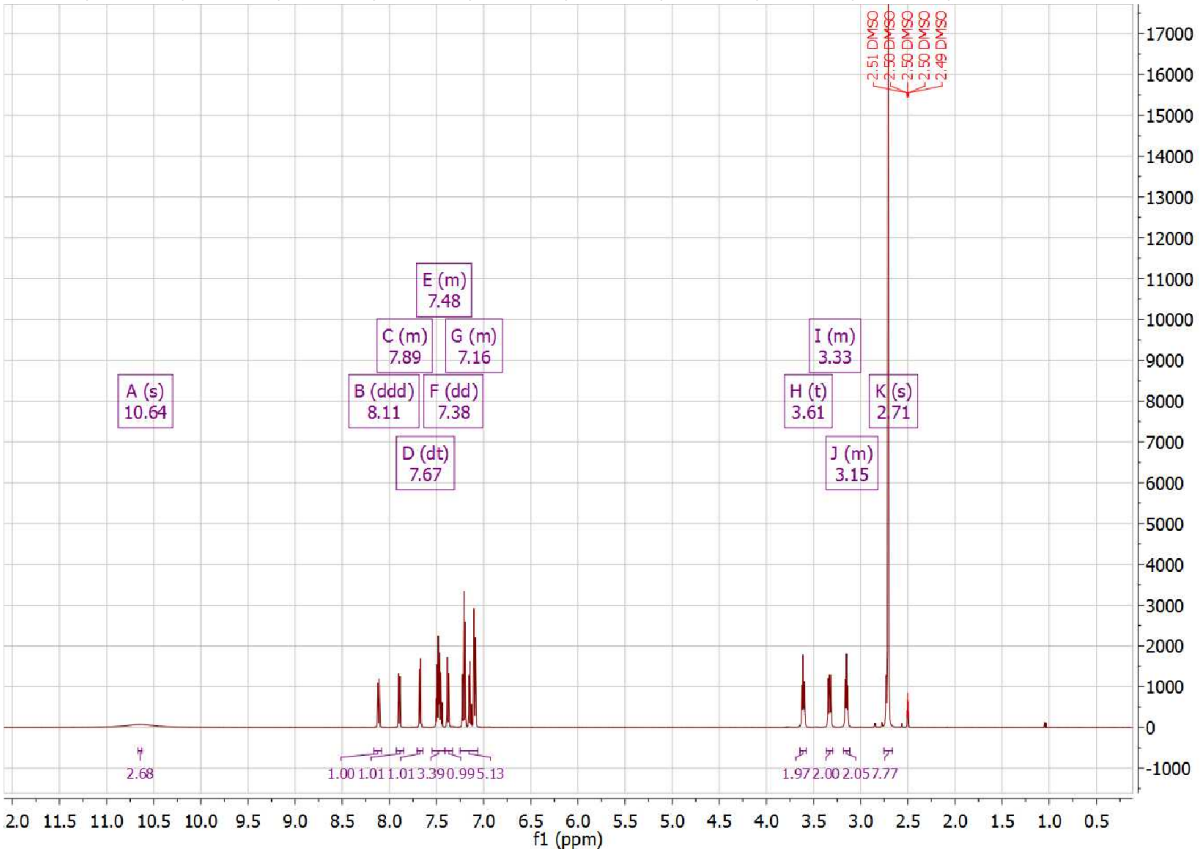
2.56
2.83
3.47
3.95
4.21
4.65
4.74
%
Time

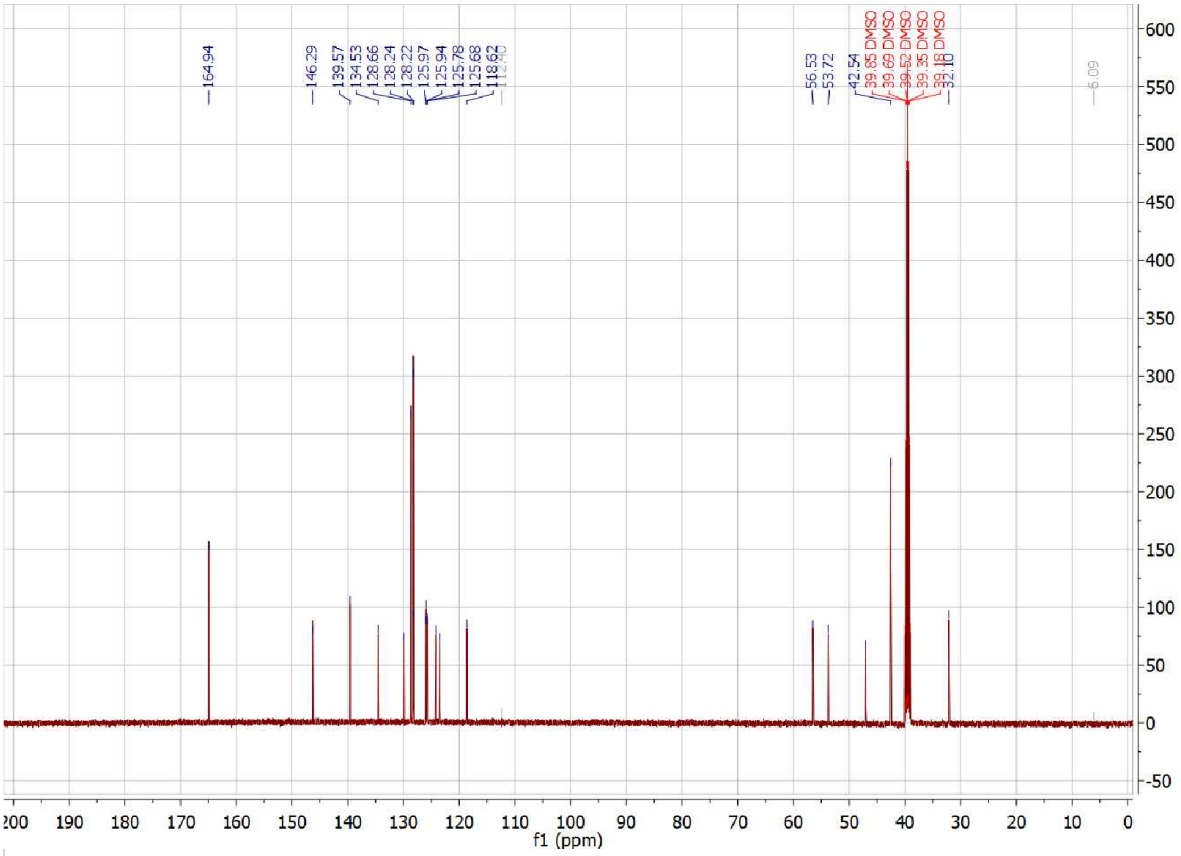
N-[2-(dimethylamino)ethyl]-N-(2-phenylethyl)naphthalen-1-amine (4o).

3p (N-[2-(dimethylamino)ethyl]naphthalen-1-amine) was synthesized according to general procedure 1 using 1-napthylamine (5 g, 0.035 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.51 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A violet oil of **3p** was obtained (1.88 g, 75%) LCMS [M+1] = 215.23 m/z (214.30 calc). **4o** was synthesized according to general procedure 2 using 1.84 g (0.0086 mol) of **3p**, phenylacetaldehyde (1.5 eq., 1.5 ml), sodium triacetoxyborohydride (2 eq., 3.64 g), dichloroethane (50 ml). A brown oil of **4o** was obtained (1,88 g, 68%). LCMS [M+1] = 319.21 m/z (318.46 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 10.64 (s, 2H), 8.11 (ddd, *J* = 8.1, 1.7, 0.8 Hz, 1H), 7.93 – 7.85 (m, 1H), 7.67 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.38 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.25 – 7.06 (m, 5H), 3.61 (t, *J* = 6.9 Hz, 2H), 3.36 – 3.29 (m, 2H), 3.18 – 3.12 (m, 2H), 2.71 (s, 8H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 32.10, 42.54, 47.03, 53.72, 56.53, 118.62, 123.49, 124.17, 125.68, 125.78, 125.94, 125.97, 128.22, 128.24, 128.66, 129.89, 134.53, 139.57, 146.29, 164.94.




164.94
146.29
139.57
134.53
128.66
128.24
128.22
125.97
125.94
125.78
125.68
118.62
56.53
53.72
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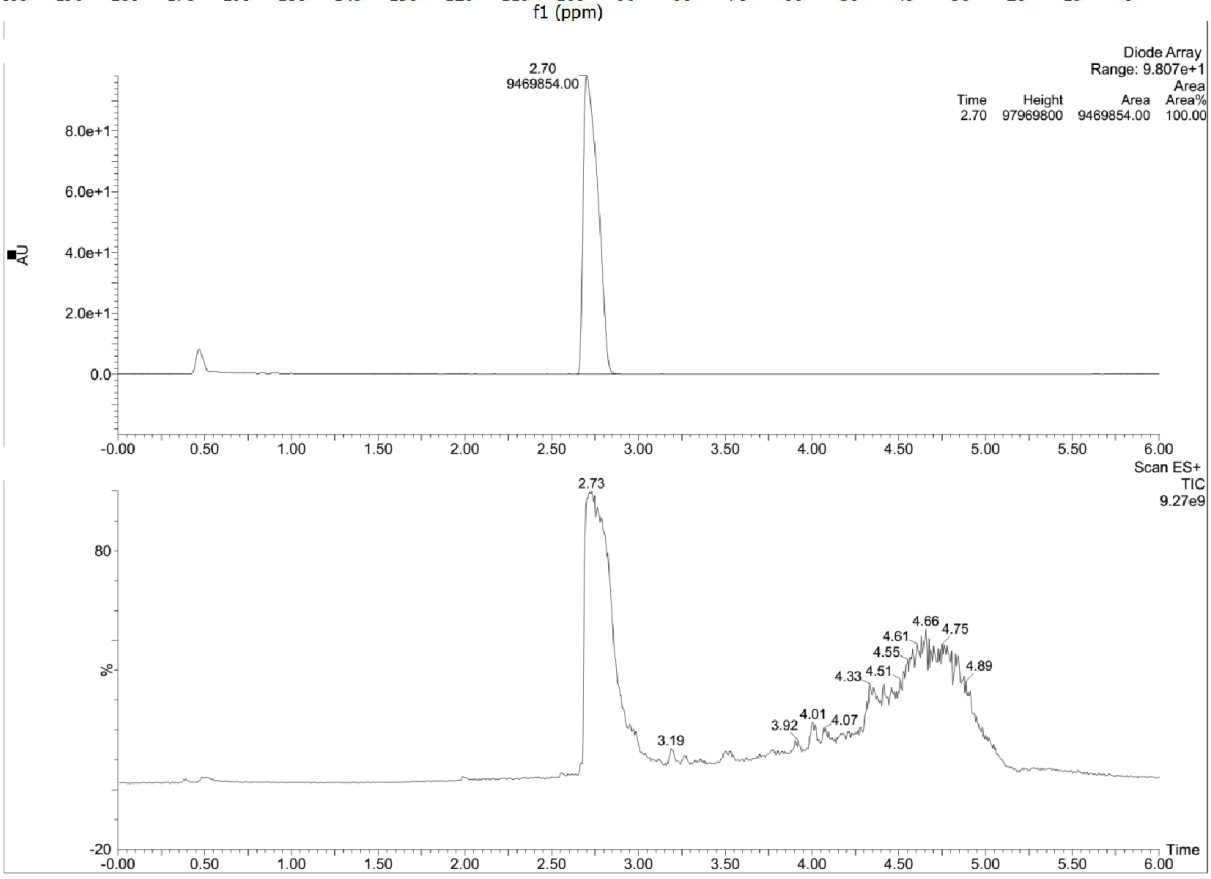
39.69 DMSO
39.52 DMSO
39.35 DMSO
39.18 DMSO
32.10
6.09
f1 (ppm)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9469854.00
AU
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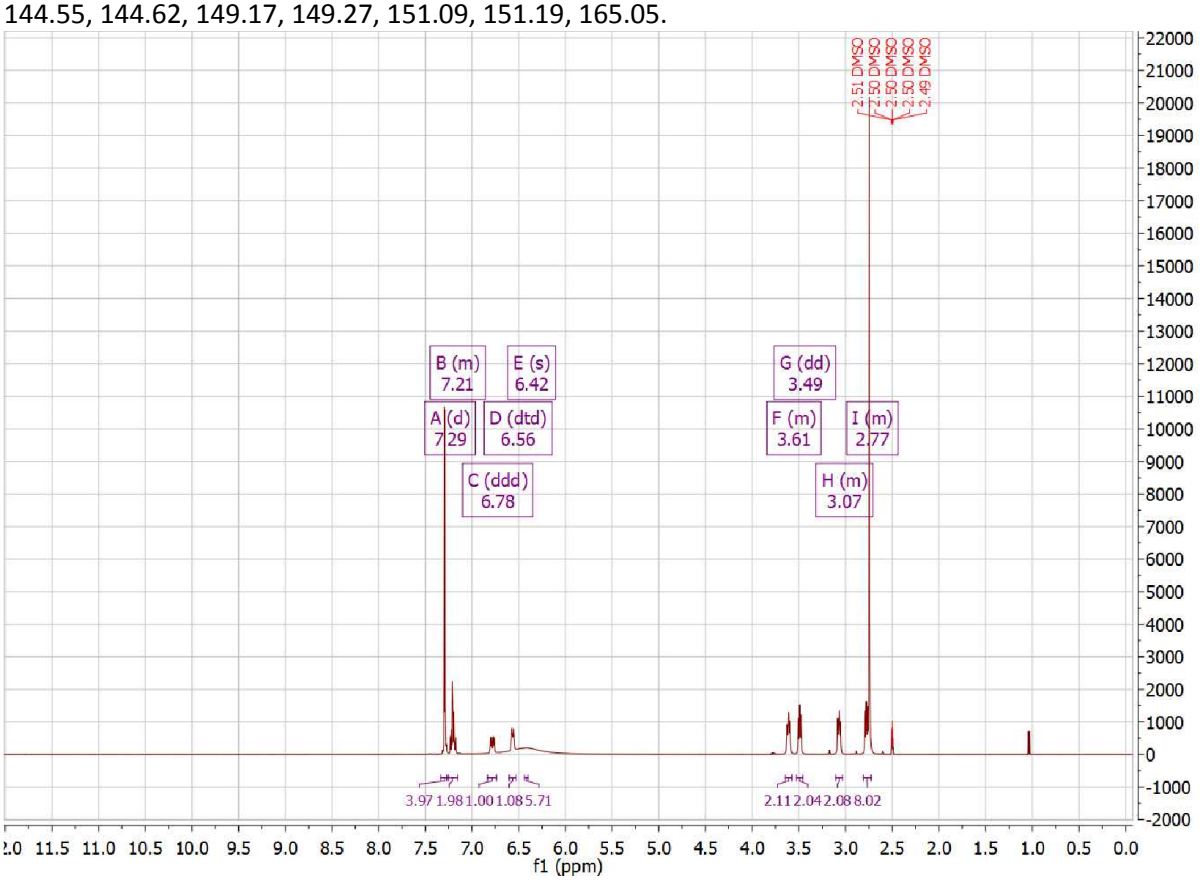
2.73
3.19
3.92
4.01
4.07
4.33
4.51
4.55
4.61
4.66
4.75
4.89
%
Time

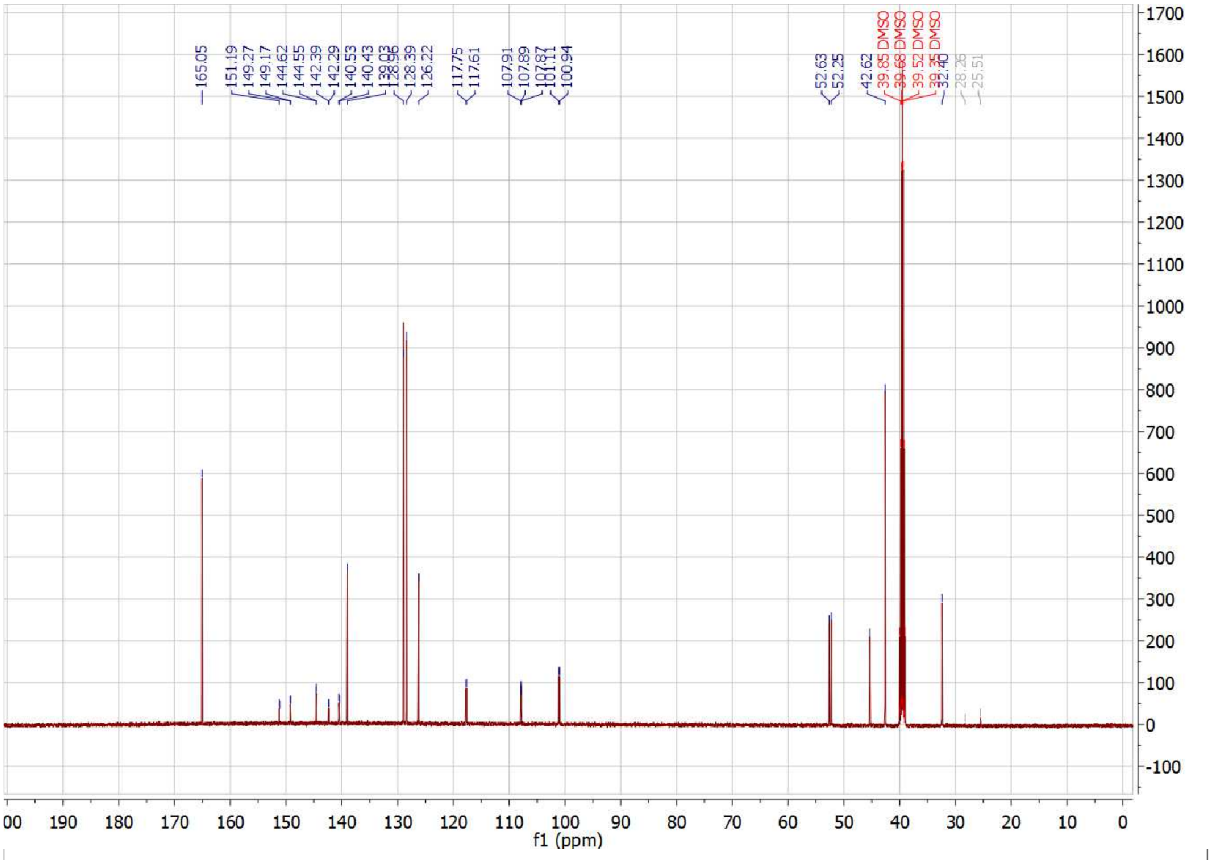
N-[2-(dimethylamino)ethyl]-3,4-difluoro-N-(2-phenylethyl)aniline (4p).

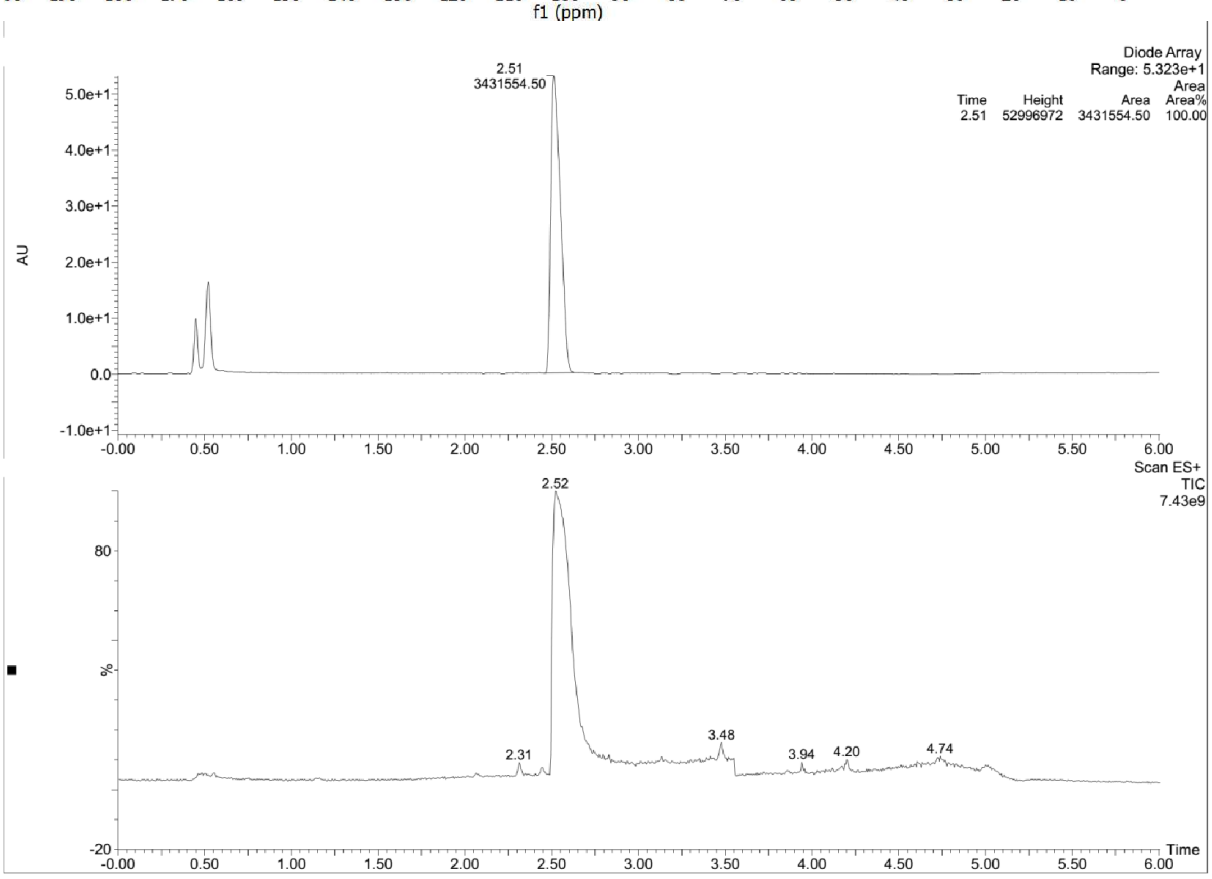
3q (N-[2-(dimethylamino)ethyl]-3,4-difluoroaniline) was synthesized according to general procedure 1 using 3,4-difluoroaniline (5 g, 0.039 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.68 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3q** was obtained (1.35 g, 52%) LCMS [M+1] = 201.11 m/z (200.23 calc). **4p** was synthesized according to general procedure 2 using 1.3 g (0.0065 mol) of **3q**, phenylacetaldehyde (1.5 eq., 1.14 ml), sodium triacetoxyborohydride (2 eq., 2.75 g), dichloroethane (50 ml). A brown oil of **4p** was obtained (1,61 g, 81%). LCMS [M+1] = 305.31 m/z (304.39 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 7.29 (d, *J* = 4.4 Hz, 4H), 7.27 – 7.15 (m, 2H), 6.78 (ddd, *J* = 14.5, 6.7, 3.0 Hz, 1H), 6.56 (dtd, *J* = 9.2, 3.1, 1.2 Hz, 1H), 6.42 (s, 2H), 3.65 – 3.57 (m, 2H), 3.49 (dd, *J* = 8.7, 6.9 Hz, 2H), 3.10 – 3.03 (m, 2H), 2.81 – 2.73 (m, 8H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 32.40, 42.62, 45.34, 52.25, 52.63, 100.94, 101.11, 107.85, 107.87, 107.89, 107.91, 117.61, 117.75, 126.22, 128.39, 128.96, 139.03, 140.43, 140.53, 142.29, 142.39, 144.55, 144.62, 149.17, 149.27, 151.09, 151.19, 165.05.




165.05
151.19
149.27
149.17
144.62
144.55
142.39
142.29
140.53
140.43
139.03
138.96
128.39
126.22
117.75
117.61
107.91
107.89
101.87
101.71
100.94
52.63
52.25
42.62
39.85 DMSO
39.68 DMSO
39.52 DMSO
39.35 DMSO
32.40
28.26
25.51
f1 (ppm)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3431554.50
AU
Scan ES+
TIC
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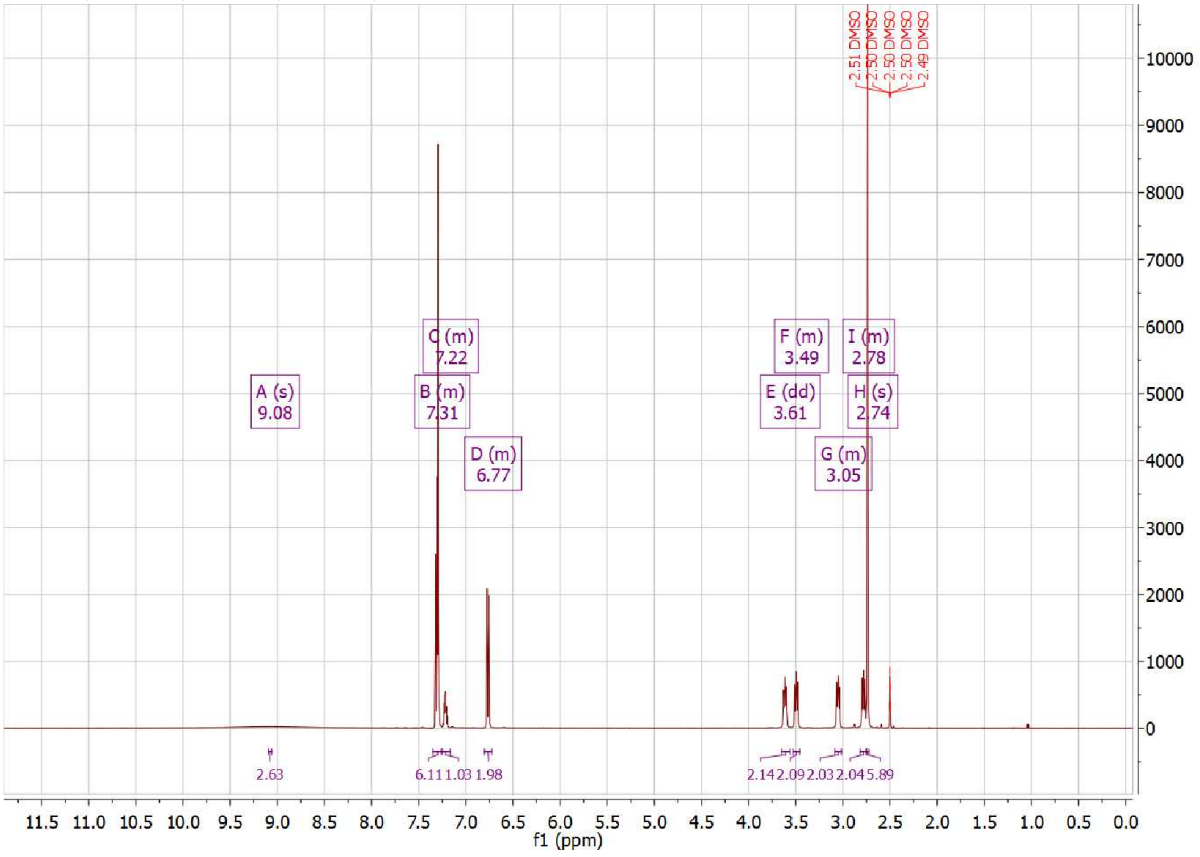
2.52
2.31
3.48
3.94
4.20
4.74
%
Time

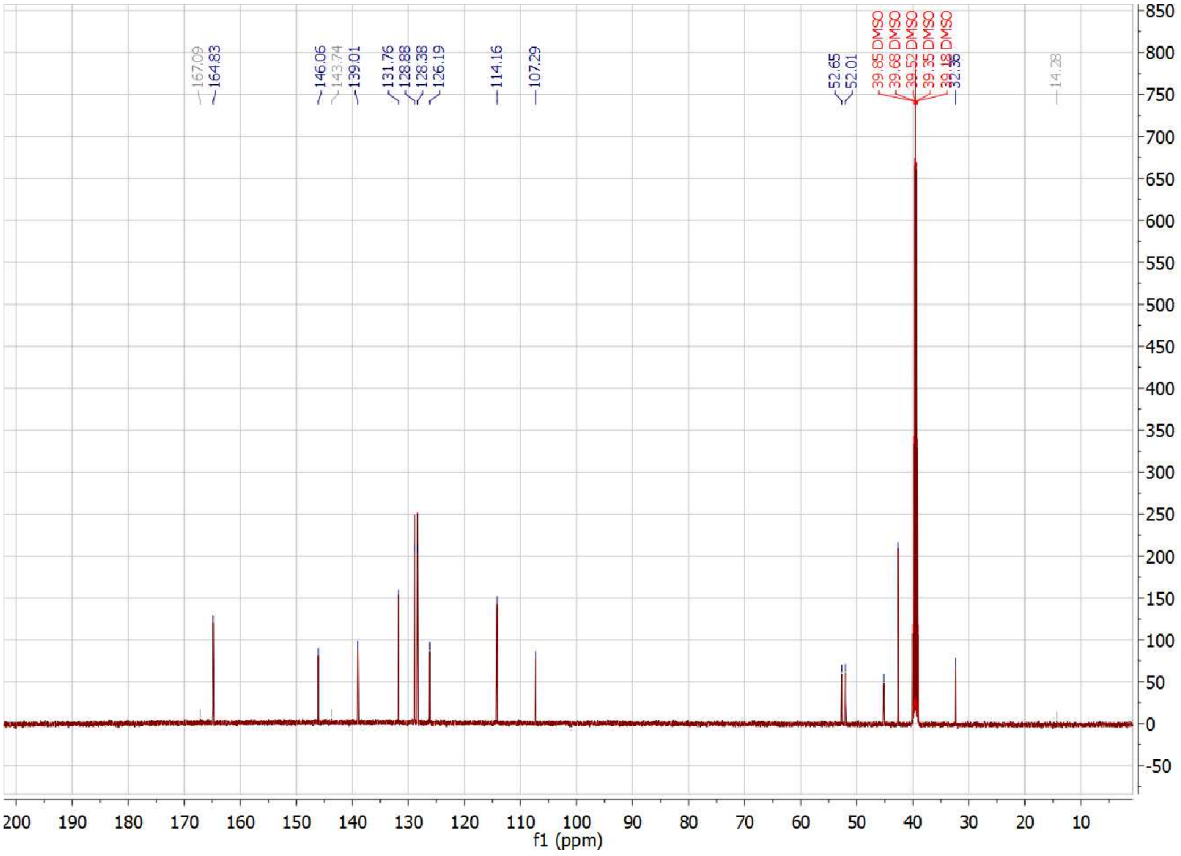
4-bromo-N-[2-(dimethylamino)ethyl]-N-(2-phenylethyl)aniline (4q).

3r (4-bromo-N-[2-(dimethylamino)ethyl]aniline) was synthesized according to general procedure 1 using 4-bromoaniline (5 g, 0.029 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.8 eq., 3.36 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3r** was obtained (1.9 g, 27%) LCMS [M+1] = 242.96; 244.89 m/z (243.14 calc). **4q** was synthesized according to general procedure 2 using 0.4 g (0.0016 mol) of **3r**, phenylacetaldehyde (1.5 eq., 0.27 ml), sodium triacetoxyborohydride (2 eq., 0.7 g), dichloroethane (20 ml). A brown oil of **4q** was obtained (0.16 g, 29%). LCMS [M+1] = 347.07; 349.14 m/z (347.30 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.08 (s, 2H), 7.35 – 7.25 (m, 6H), 7.26 – 7.17 (m, 1H), 6.80 – 6.72 (m, 2H), 3.61 (dd, *J* = 8.8, 6.7 Hz, 2H), 3.53 – 3.46 (m, 2H), 3.09 – 3.01 (m, 2H), 2.82 – 2.75 (m, 2H), 2.74 (s, 6H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 32.36, 42.61, 45.14, 52.01, 52.65, 107.29, 114.16, 126.19, 128.38, 128.88, 131.76, 139.01, 146.06, 164.83.

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143.74
139.01
131.76
128.88
128.38
126.19
114.16
107.29
52.65
52.01
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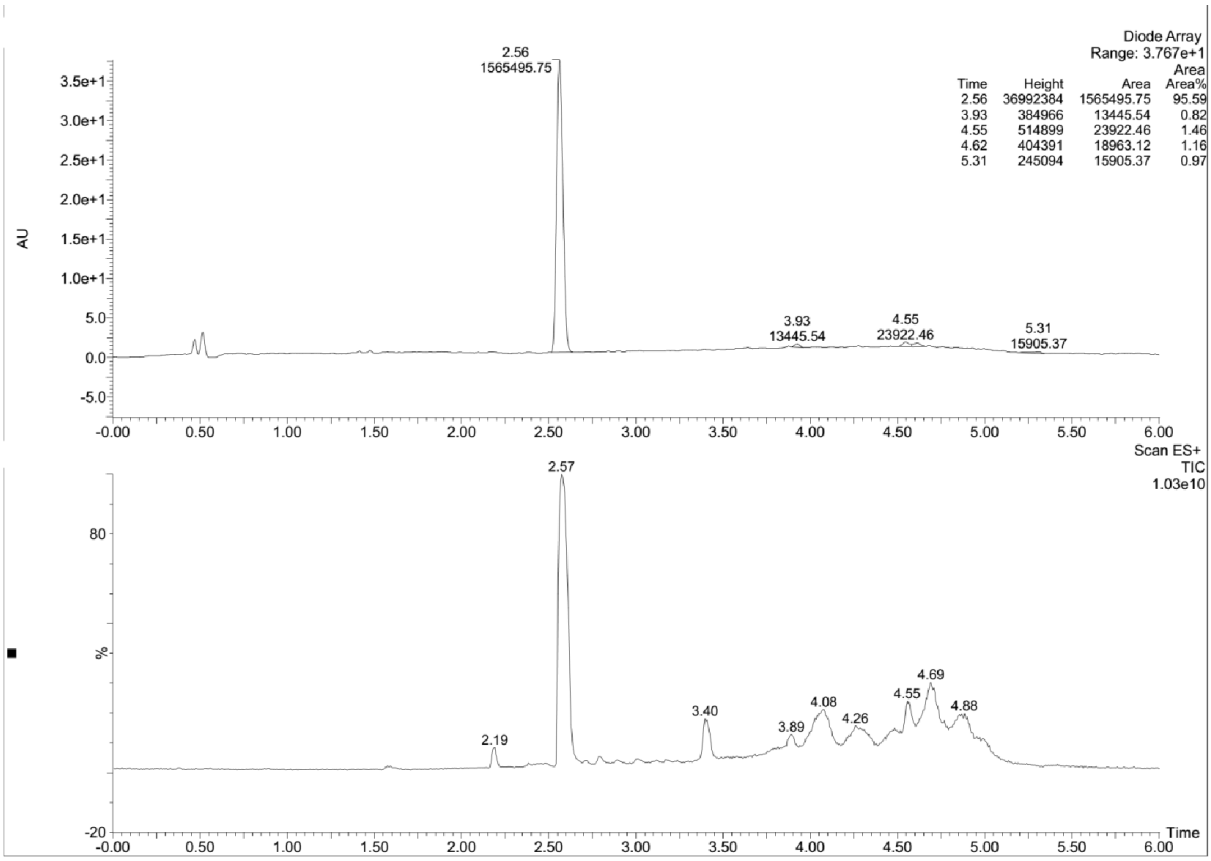
39.68 DMSO
39.52 DMSO
39.35 DMSO
39.18 DMSO
32.36
14.28
f1 (ppm)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13445.54
4.55
23922.46
5.31
15905.37
Scan ES+
TIC
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%
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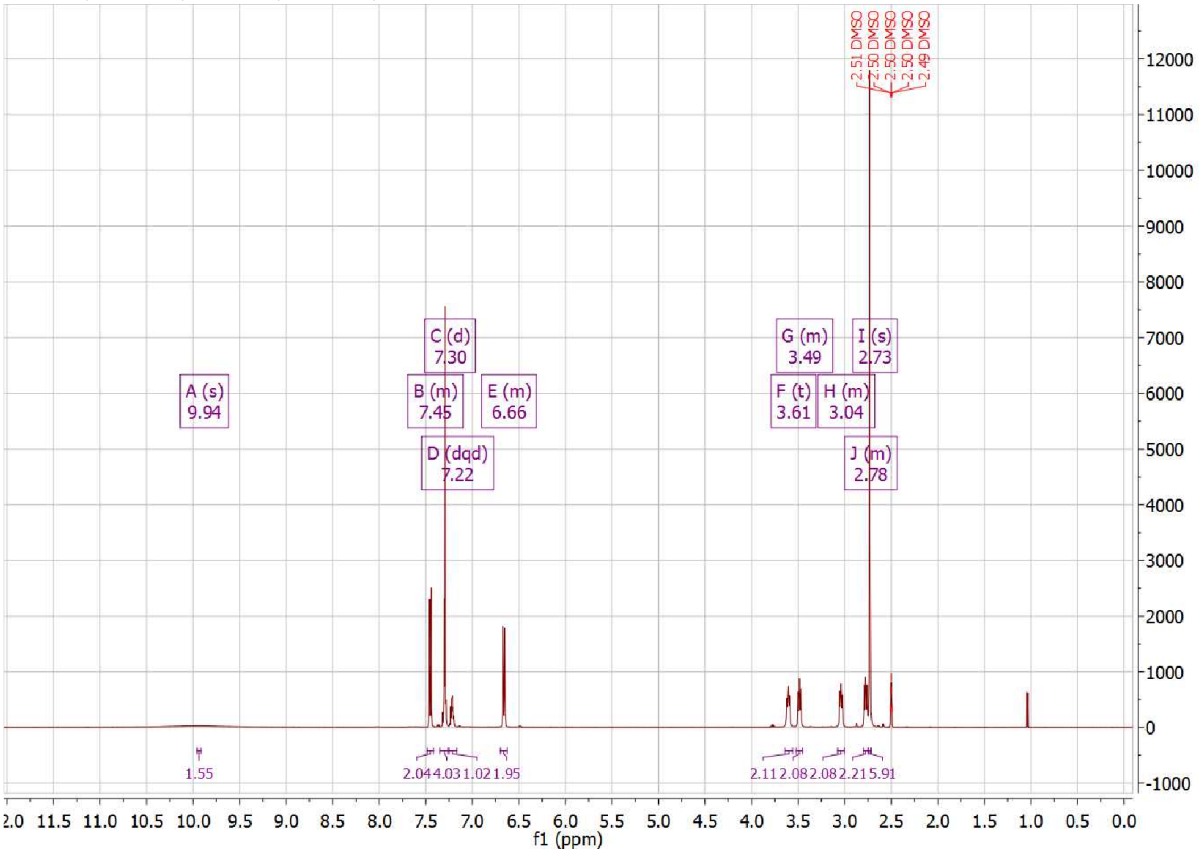
2.19
3.40
3.89
4.08
4.26
4.55
4.69
4.88
Time

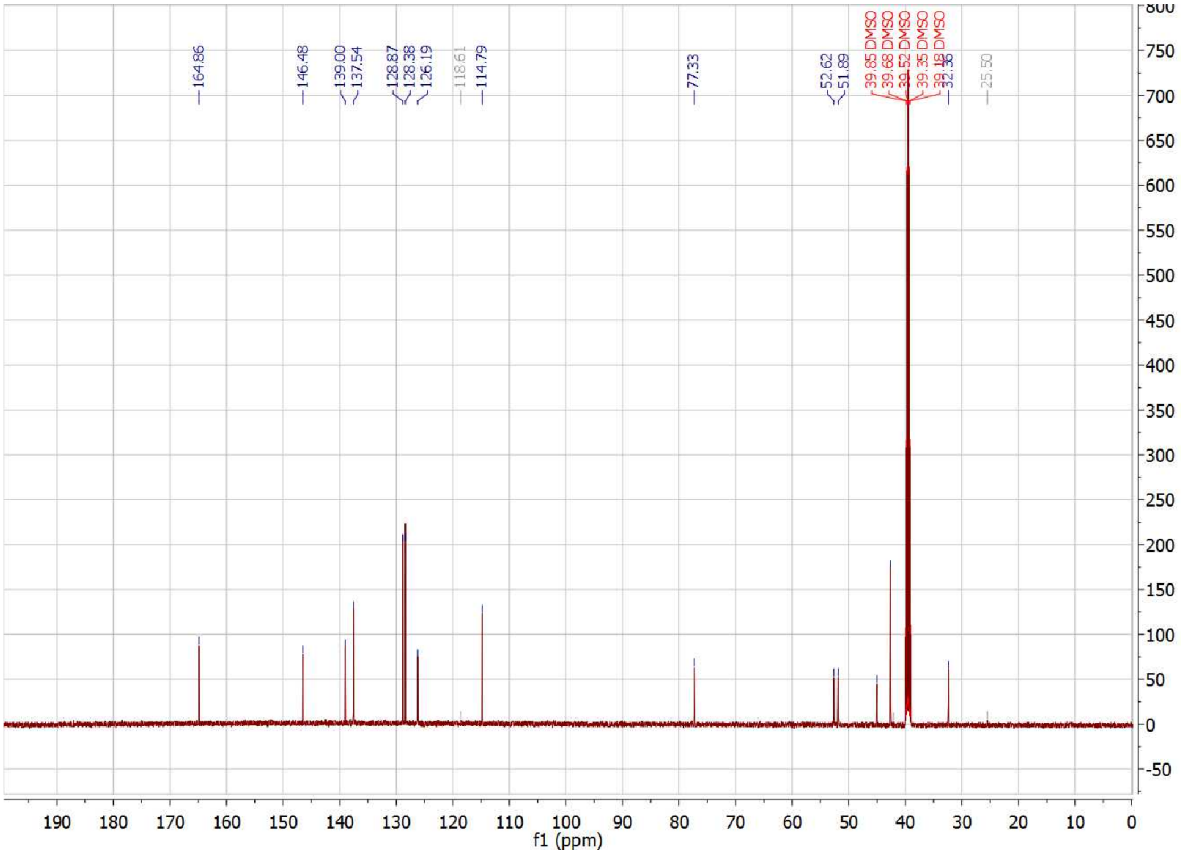
N-[2-(dimethylamino)ethyl]-4-iodo-N-(2-phenylethyl)aniline (4r).

3s (N-[2-(dimethylamino)ethyl]-4-iodoaniline) was synthesized according to general procedure 1 using 4-iodoaniline (5 g, 0.023 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.8 eq., 2.64 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3s** was obtained (1.5 g, 22%) LCMS [M+1] = 291.15 m/z (290.14 calc). **4r** was synthesized according to general procedure 2 using 0.4 g (0.0013 mol) of **3s**, phenylacetaldehyde (1.5 eq., 0.23 ml), sodium triacetoxyborohydride (2 eq., 0.58 g), dichloroethane (20 ml). A brown oil of **4r** was obtained (0.26 g, 50%). LCMS [M+1] = 395.13 m/z (394.30 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.94 (s, 2H), 7.49 – 7.42 (m, 2H), 7.30 (d, *J* = 5.7 Hz, 4H), 7.22 (dqd, *J* = 7.9, 5.3, 2.6 Hz, 1H), 6.70 – 6.63 (m, 2H), 3.61 (t, *J* = 7.7 Hz, 2H), 3.52 – 3.45 (m, 2H), 3.07 – 3.00 (m, 2H), 2.80 – 2.75 (m, 2H), 2.73 (s, 6H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 32.36, 42.61, 45.04, 51.89, 52.62, 77.33, 114.79, 126.19, 128.38, 128.87, 137.54, 139.00, 146.48, 164.86.

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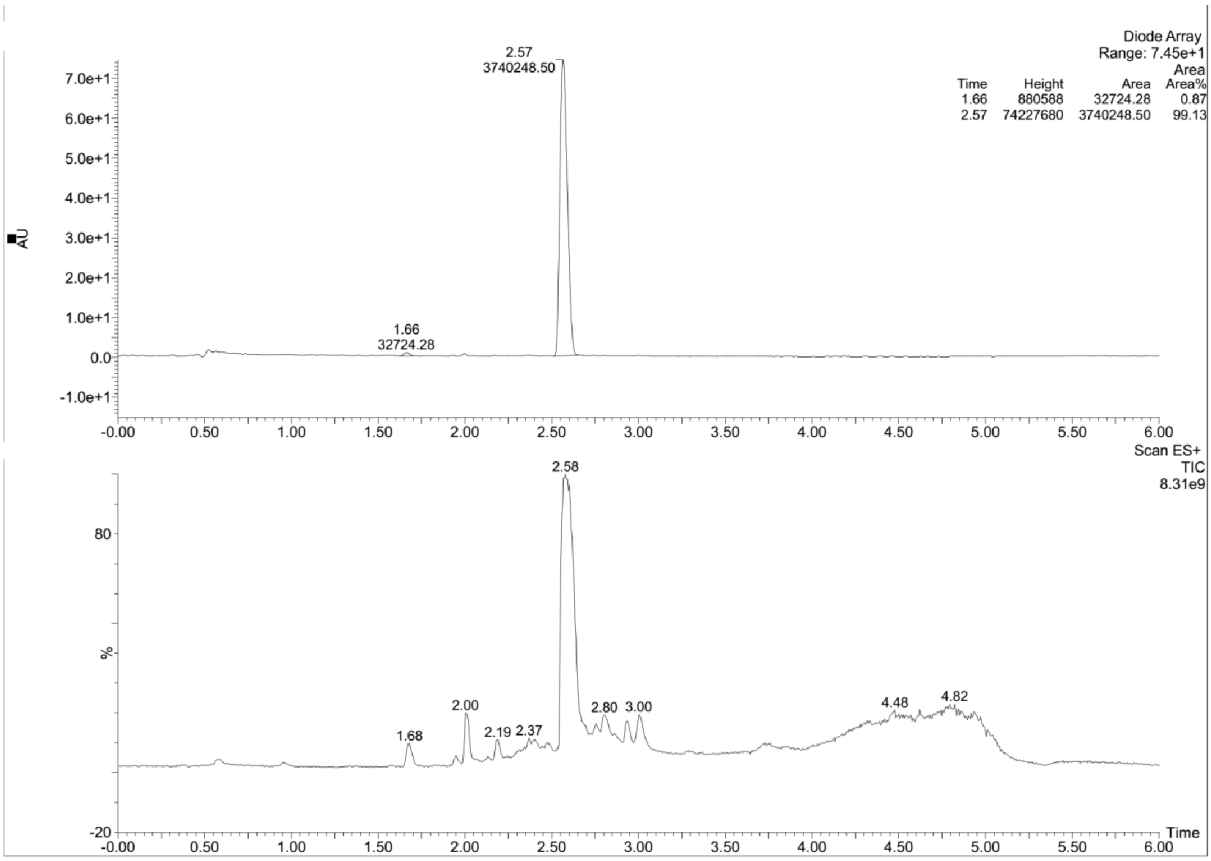
32.38
25.50
f1 (ppm)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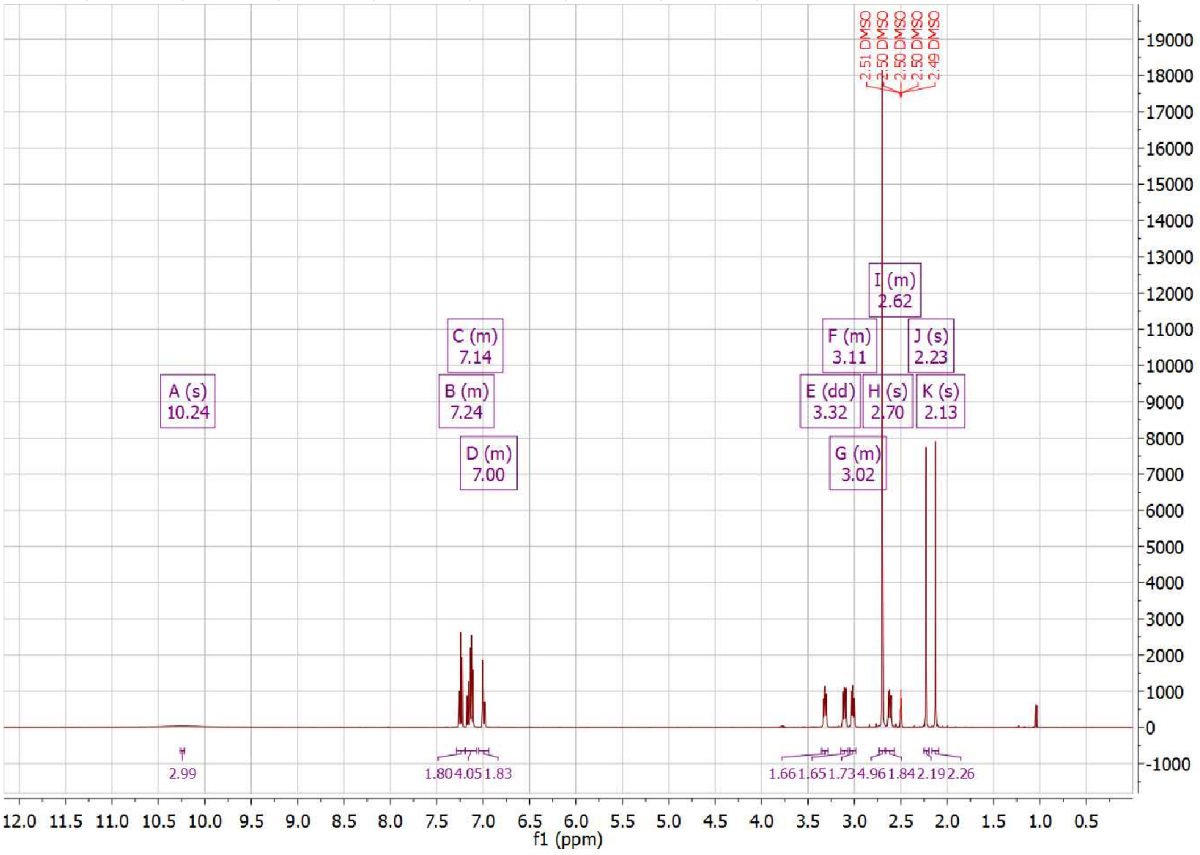
AU
Scan ES+
TIC
8.31e9
2.58
1.68
2.00
2.19
2.37
2.80
3.00
4.48
4.82
%
Time

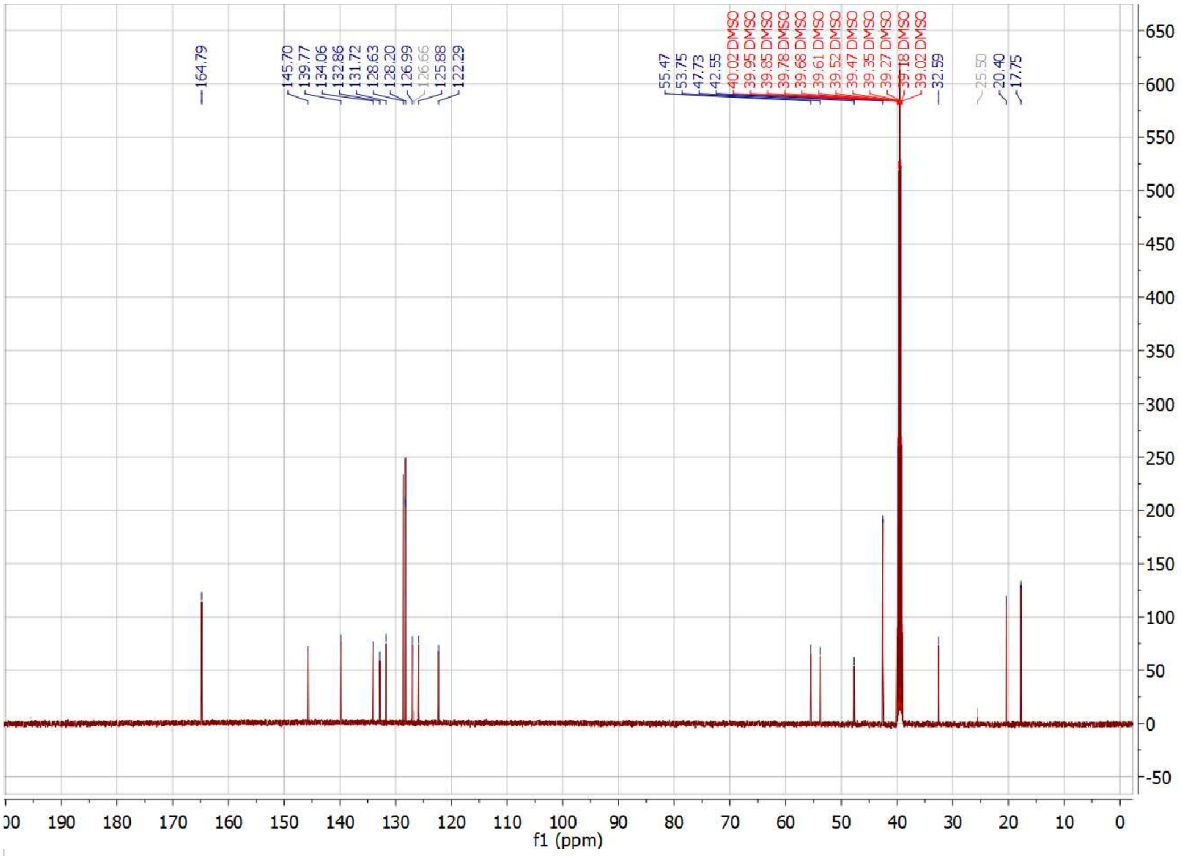
N-[2-(dimethylamino)ethyl]-2,4-dimethyl-N-(2-phenylethyl)aniline (4s).

3t (N-[2-(dimethylamino)ethyl]-2,4-dimethylaniline) was synthesized according to general procedure 1 using 2,4-dimethylaniline (5 g, 0.041 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 1.78 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3t** was obtained (1,69 g, 22%) LCMS [M+1] = 193.30 m/z (192.31 calc). **4s** was synthesized according to general procedure 2 using 0.4 g (0.0021 mol) of **3t**, phenylacetaldehyde (1.5 eq., 0.34 ml), sodium triacetoxyborohydride (2 eq., 0.88 g), dichloroethane (20 ml). A brown oil of **4s** was obtained (0,37 g, 59%). LCMS [M+1] = 297.16 m/z (296.46 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 10.24 (s, 2H), 7.29 – 7.19 (m, 2H), 7.20 – 7.07 (m, 4H), 7.05 – 6.94 (m, 2H), 3.32 (dd, *J* = 8.4, 6.0 Hz, 2H), 3.14 – 3.07 (m, 2H), 3.05 – 2.98 (m, 2H), 2.70 (s, 6H), 2.67 – 2.57 (m, 2H), 2.23 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 17.75, 20.40, 32.59, 42.55, 47.73, 53.75, 55.47, 122.29, 125.88, 126.99, 128.20, 128.63, 131.72, 132.86, 134.06, 139.77, 145.70, 164.79.

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125.88
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47.73
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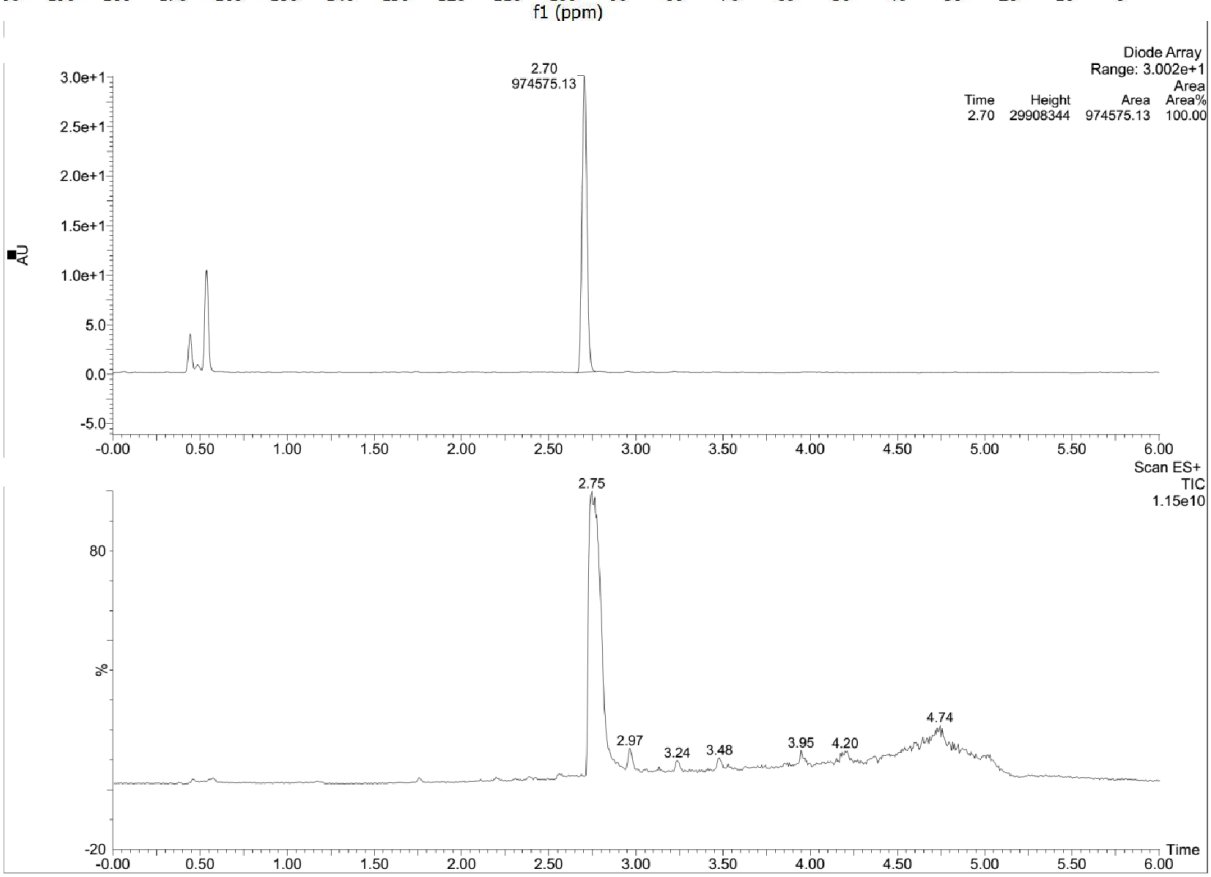
32.59
25.50
20.40
17.75
f1 (ppm)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AU
Scan ES+
TIC
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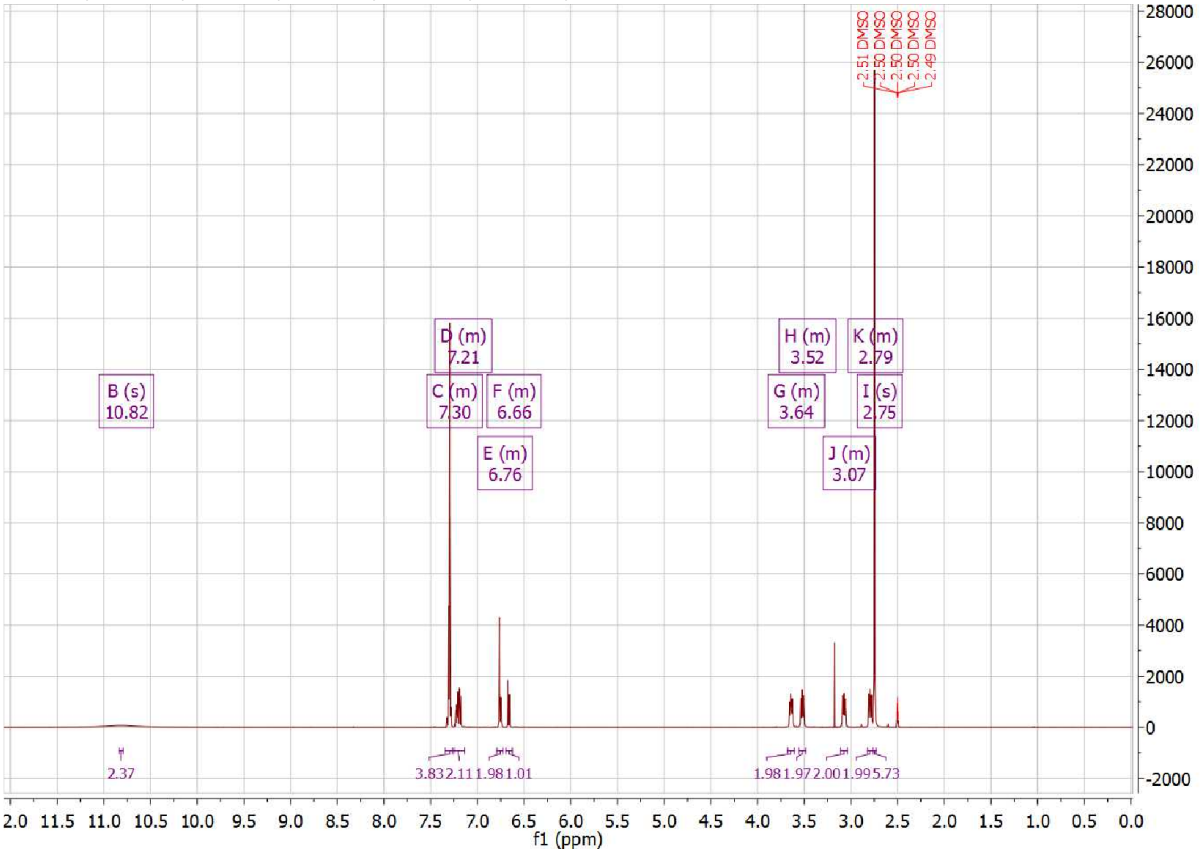
2.75
2.97
3.24
3.48
3.95
4.20
4.74
%
Time

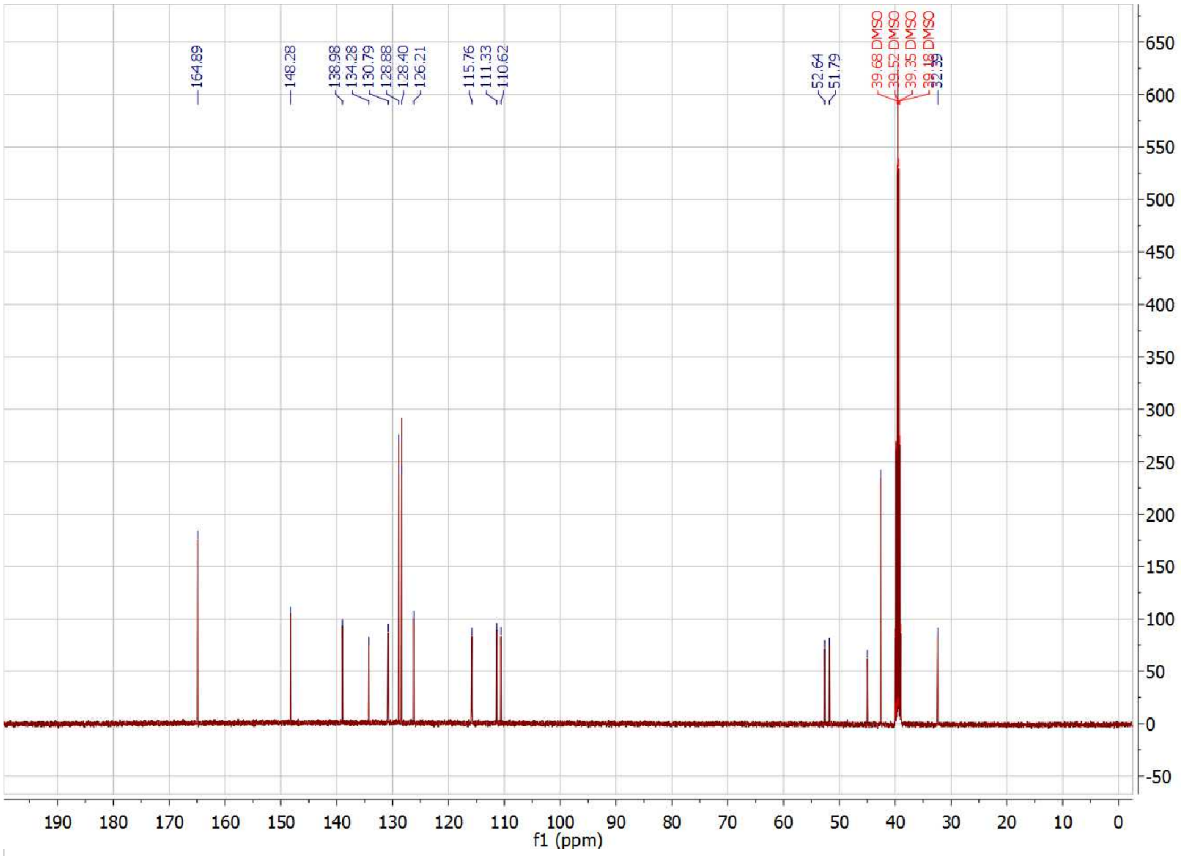
3-chloro-N-[2-(dimethylamino)ethyl]-N-(2-phenylethyl)aniline (4t).

3u (3-chloro-N-[2-(dimethylamino)ethyl]aniline) was synthesized according to general procedure 1 using 3-chloroaniline (5 g, 0.039 mol) and (2-chloroethyl)dimethylamine hydrochloride (0.3 eq., 3.96 g), K_2CO_3 (4 eq.), isopropanol (100 ml). A brown oil of **3u** was obtained (1,2 g, 46%) LCMS [M+1] = 199.21 m/z (198.69 calc). **4t** was synthesized according to general procedure 2 using 0.41 g (0.002 mol) of **3u**, phenylacetaldehyde (1.5 eq., 0.46 ml), sodium triacetoxyborohydride (2 eq., 0.85 g), dichloroethane (20 ml). A brown oil of **4t** was obtained (0.27 g, 44%). LCMS [M+1] = 303.36 m/z (302.85 calc).

^{1}H NMR (500 MHz, DMSO-D_6) δ 10.82 (s, 2H), 7.34 – 7.25 (m, 4H), 7.27 – 7.14 (m, 2H), 6.79 – 6.72 (m, 2H), 6.69 – 6.63 (m, 1H), 3.68 – 3.60 (m, 2H), 3.56 – 3.49 (m, 2H), 3.11 – 3.04 (m, 2H), 2.82 – 2.76 (m, 2H), 2.75 (s, 6H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 32.39, 42.59, 45.00, 51.79, 52.64, 110.62, 111.33, 115.76, 126.21, 128.40, 128.88, 130.79, 134.28, 138.98, 148.28, 164.89.

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110.62
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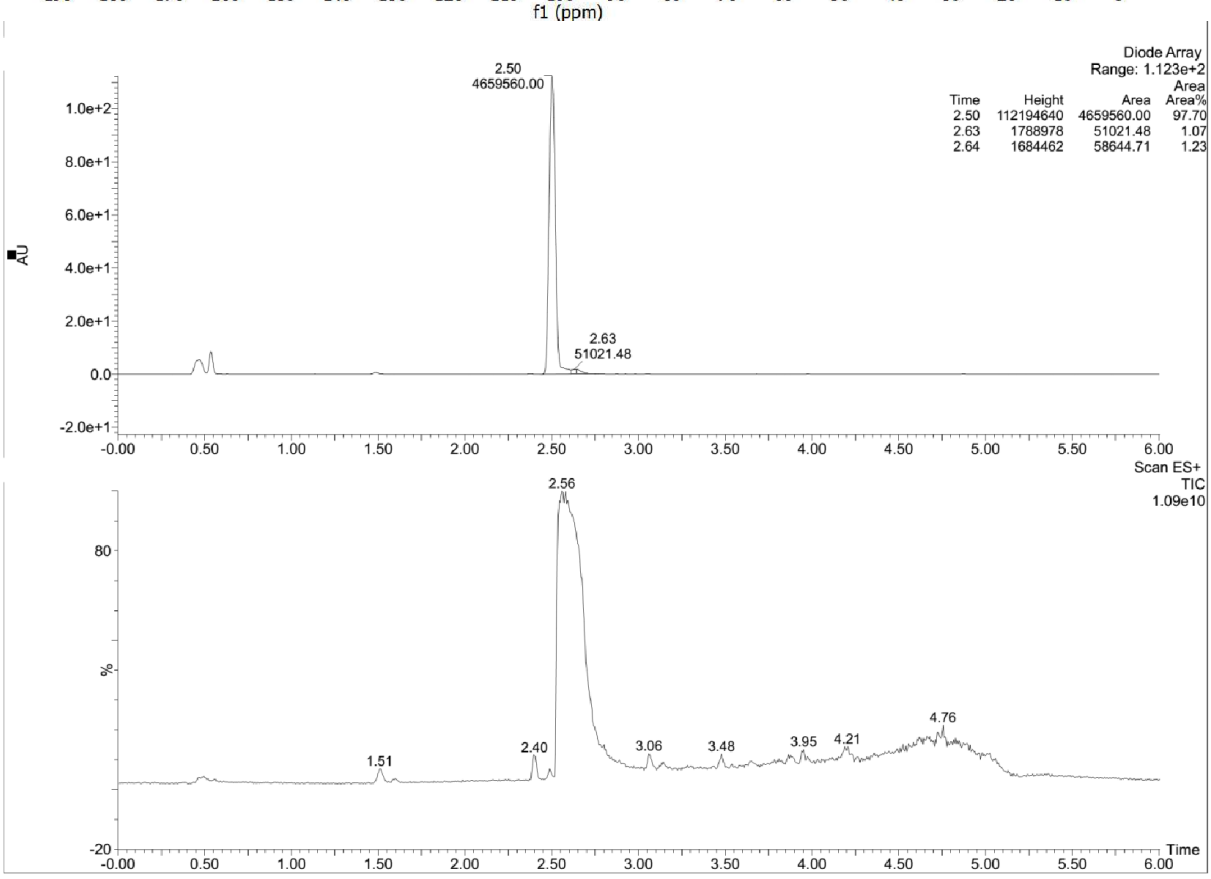
39.52 DMSO
39.35 DMSO
f1 (ppm)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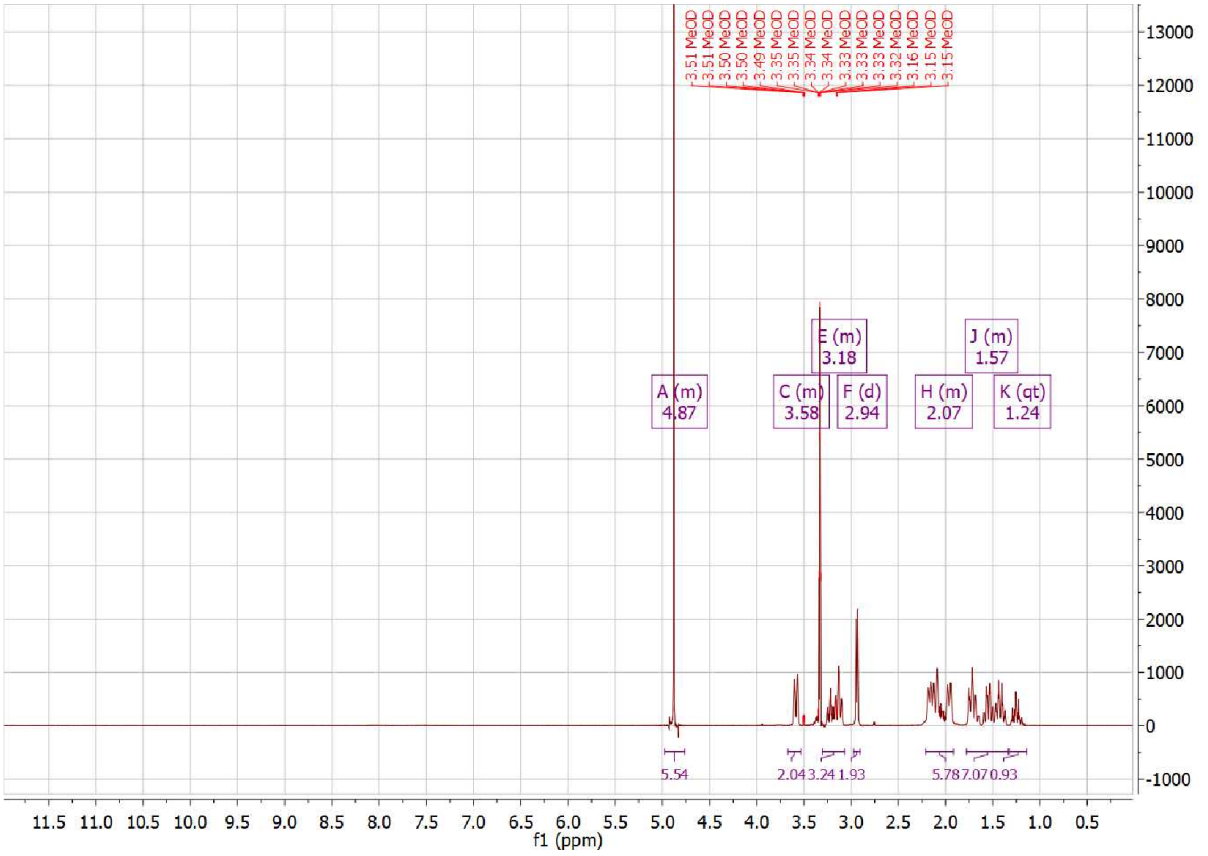
AU
Scan ES+
TIC
1.09e10
2.56
1.51
2.40
3.06
3.48
3.95
4.21
4.76
%
Time

2,3-dihydro-1,4-benzodioxin-2-ylmethyl 4-methylbenzene-1-sulfonate (5d).

Bromine (1.2 eq., 3 ml) was added dropwise to a solution of ethyl acrylate (5.16 ml, 0.048 mol) in carbon tetrachloride (10 ml) and heated at 60°C for 2 hours. After cooling to room temperature, the reaction mixture was washed with 5% sodium metabisulfate (100 ml), distilled water (100 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. A colourless liquid of **5a** (11.73 g, 94%) was obtained. The product was used in the next step without further purification. **5a** (11.73 g, 0,045 mol) was dissolved in acetone (200 ml) together with catechol (1 eq., 4.97 g), anhydrous K_2CO_3 (2 eq., 12.4 g) and heated to reflux for 5 hours. After cooling to room temperature, the reaction mixture was filtered, the precipitate was washed with acetone (100 ml) and the filtrate was evaporated under reduced pressure. The product was purified by column chromatography (SiO_2, $CHCl_3$). A colourless oil of **5b** was obtained (8.45 g, 90%) LCMS [M+1] = 209.00 m/z (208.07 calc). **5b** (8.4 g, 0.04 mol) was dissolved in anhydrous THF (100 ml) and added dropwise to a suspension of $LiAlH_4$ (2 eq., 3.06 g) in anhydrous THF (200 ml). The reaction mixture was stirred at room temperature for 30 min. After completion, distilled water (3 ml), 15% NaOH (3 ml) and distilled water again (9 ml) were added dropwise. The obtained precipitate was filtered and washed with THF (50 ml) and methanol (50 ml). The combined filtrates were evaporated under reduced pressure. The obtained residue was dissolved in dichloromethane (100 ml), washed with distilled water (50 ml) and brine (50 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The product was used in the next step without further purification. A white solid of **5c** was obtained (5.06 g, 76%) LCMS [M+1] = 167.03 m/z (166.06 calc). **5c** (4.53 g, 0.027 mol) was dissolved in pyridine (50 ml) together with tosyl chloride (1.1 eq., 5.71 g) and stirred at room temperature for 24 hours. After completion, 3 M HCl (300 ml) was added to the sample, and the product was extracted with chloroform (3x 50 ml). The combined extracts were washed with distilled water (100 ml) and brine (50 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The product was purified by column chromatography (SiO_2, $CHCl_3$). A white solid of **5d** was obtained (7.87 g, 81%) LCMS [M+1] = 321.06 m/z (320.07 calc).

(1-cyclohexylpiperidin-4-yl)methanamine (5i).

Isonicotinamide (4 g, 0.033 mol) was added to 2,4-dichloronitrobenzene (20 g, 0.099 mol) and heated at 105°C for 1.5 hours. After cooling to room temperature, the reaction mixture was dissolved in methanol (40 ml) and filtered. The obtained precipitate was crystallized from methanol. A yellow solid of **5e** was obtained (10.18 g, 95%) LCMS [M+1] = 289.52 m/z (289.06 calc). **5e** (10.18 g, 0.013 mol) was suspended in methanol (200 ml) together with aniline (7.6 g) and stirred at room temperature for 4 days, followed by heating to 55°C for 1 hour. After cooling to room temperature, the solvent was evaporated under reduced pressure. The obtained residue was ground in acetone until a white solid of **5f** was obtained (5.43 g, 33%) LCMS [M+1] = 199.02 m/z (199.08 calc). PtO_2 (0.1 g) was added to a solution of **5f** (0.52 g) in ethanol (100 ml), and the reaction mixture was hydrogenized at 7 bar for 48 hours. After completion, the reaction mixture was filtered through a pad of celite and evaporated under reduced pressure. The product was used in the next step without further purification. A white solid of **5h** was obtained (0.52 g, 98%). [M+1] = 197.13 m/z (196.19 obl.) ^{1}H NMR (DMSO-D_6, 400.17 MHz) (ppm): 1.24 (qt, J = 12.9, 3.6 Hz, 1H), 1.78 – 1.34(m, 8H), 2.21 – 1.92 (m, 6H), 2.94 (d, J = 6.8 Hz, 2H), 3.31 – 3.07 (m, 3H), 3.67 – 3.53 (m, 2H), 4.98 – 4.76 (m, 3H). ^{13}C NMR (DMSO-D_6, 100.17 MHz) (ppm): 24.69, 24.73, 26.60, 26.74, 32.12, 43.43, 48.35, 65.97.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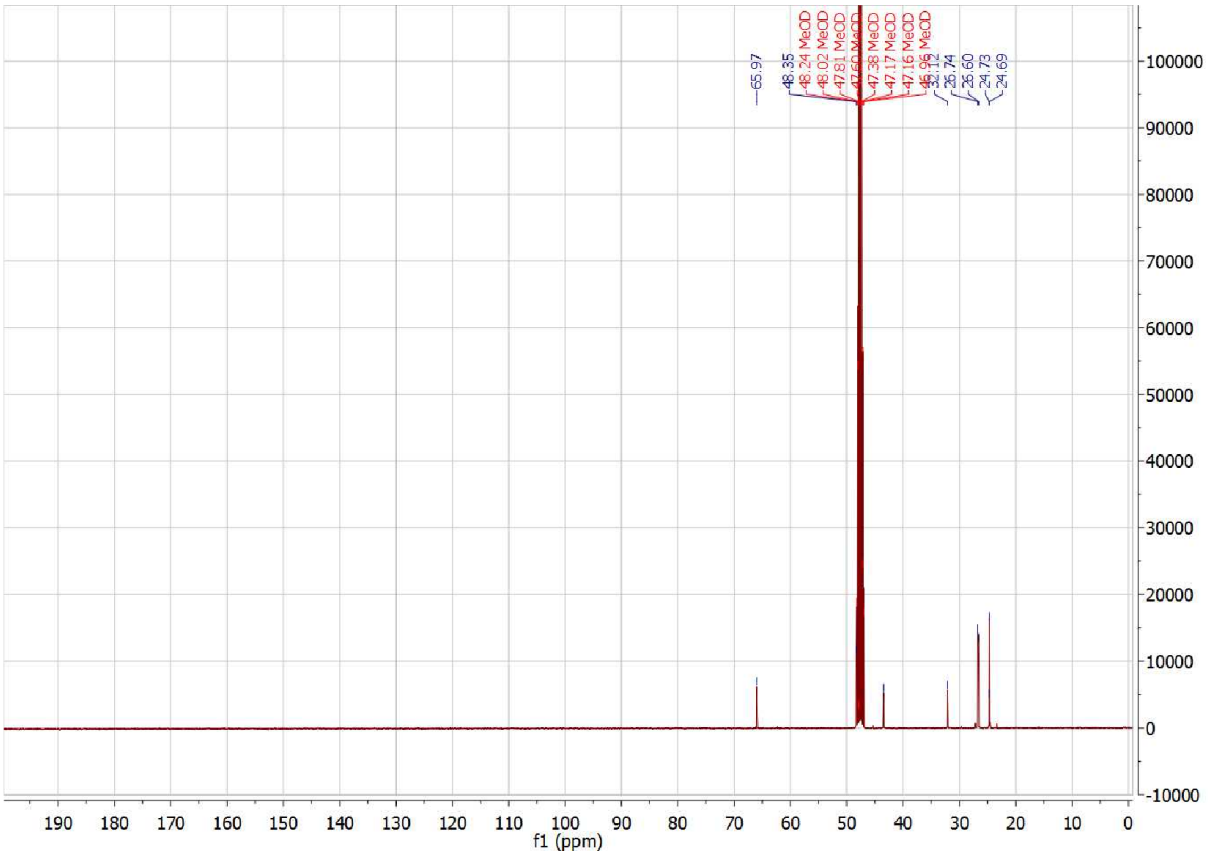
f1 (ppm)


f1 (ppm)

(1-phenylpiperidin-4-yl)methanamine (5j).

10% Pd/C (10% mass, 0.49 g) was added to a solution of **5f** (4.93 g) in ethanol (200 ml) and reaction mixture was hydrogenized at 7 bar for 3 hours. After completion, the reaction mixture was filtered through celite and evaporated under reduced pressure. The product was used for the next step without further purification. A white solid of **5g** was obtained (4.89 g, 97%) LCMS [M+1] = 205.15 m/z (204.12 calc). A solution of **5g** (4.15 g, 0.02 mol)) in anhydrous THF (50 ml) was added dropwise to a suspension of $LiAlH_4$ (1.89 g, 2.5 eq.) in anhydrous THF (150 ml). The reaction mixture was stirred at room temperature for 2 hours and then for 2 hours at reflux. After cooling to room temperature distilled water (1.89 ml), 15% NaOH (1.89 ml) and distilled water again (5.67 ml) were added. Obtained precipitate was filtered and washed with THF (100 ml) and methanol (50 ml). The combined filtrates were evaporated under reduced pressure. The obtained residue was dissolved in dichloromethane (100 ml), washed with distilled water (50 ml), brine (50 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure. A colourless oil of **5j** was obtained (3.36 g, 88%) LCMS [M+1] = 191.11 m/z (190.14 calc).

(4-phenylphenyl)methanamine (6b).

The 4-bromobenzaldehyde (1 g, 5.4 mmol) was dissolved in anhydrous ethanol (10 ml), followed by the addition of phenylboronic acid (0.72 g, 1.1 eq.), 10% Pd/C (0.28 g, 0.05 eq.) and Na_2CO_3 (1.14 g, 2 eq.). The reaction mixture was sealed under argon and stirred at room temperature for 6 hours. After completion, the precipitate was filtered and washed with dichloromethane (10 ml). Distilled water (100 ml) was added to the sample, and the product extracted with dichloromethane (3x50 ml). The combined organics were washed with brine (20 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The product was purified using column chromatography (SiO_2, $CHCl_3$). A white solid of **6a** was obtained (0.92 g, 93%) LCMS [M+1] = 182.96 m/z (182.07 calc). **6a** (0.92 g, 0.005 mol) was dissolved in ethanol (10 ml) and added to a solution of hydroxylamine hydrochloride (0.8 g, 2 eq.) and anhydrous Na_2CO_3 (0.8 g, 1.5 eq.) in distilled water (4 ml). The reaction mixture was heated to reflux for 30 min, and the solvent was evaporated under reduced pressure. The obtained residue was dissolved in methanol (40 ml), cooled on ice and $NiCl_2 \bullet 6H_2O$ (1.19 g, 1 eq.) was added followed by portion-wise addition of $NaBH_4$ (1.14 g, 6 eq.). The reaction mixture was stirred at room temperature for 15 min, followed by the addition of 1% NH_3 (100 ml). The obtained precipitate was filtered. The product was extracted with ethyl acetate (3x50 ml). The combined extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The product was purified using column chromatography (SiO_2, $CHCl_3$:MeOH:TEA 9:1:0.01). A colourless oil of **6b** was obtained (0.72 g, 78%) LCMS [M+1] = 184.08 m/z (183.10 calc).

Preparation of the ChEMBL database

Due to a large diversity of activity measures, only the compounds with defined K_i (IC50 – assumed to be 2× K_i, p K_i or pIC50 were converted to K_i), as assayed using human cloned receptors or rat cloned or native receptors, were considered in the analysis. In the case of multiple data for one ligand, the K_i and human receptors were given preference; a median value was used if numerous biological results were obtained.

Physicochemical filter

The basic p*K* was calculated using Calculator Plugins[2] implemented in IJChem Software.[3] All compounds with a basic p*K* lower than -2 were rejected.

ADME filters

The following criteria were used to filter compounds with unfavourable profiles: the number of reactive functional groups (desirable range of values: 0-2), logarithm of calculated aqueous solubility (–6.5-0.5 mole/litre), gut-blood barrier (>500 nm/s) and blood-brain barrier penetration coefficient (–3.0-1.2).

Pharmacophore filter

Pharmacophore screening was performed using Phase[4] with default settings (conformers generated during the search, 10 conformers per rotatable bond; not more than 100 conformers per structure; relative energy window between conformations – 10 kcal/mol; RMSD tolerance for the match – 2 Å).

Docking protocol

All 5-HT_6 receptors used in the virtual screening procedure were centred at D3.32 with the grid box size set to 25×25×25 Å. The docking runs were performed using Glide[5] software at the SP level under default settings (sampling nitrogen inversion, sampling ring conformations with an energy window equal to 2.5 kcal/mol, penalizing nonplanar conformation of amides up to 100 steps during energy minimization and post-docking optimization).

Evaluation and visualization of halogen bonding contribution in L-R complexes

The QM-Polarized Ligand Docking (QPLD)[6] in the Schrödinger Suit was used to re-dock all synthetized compounds to a set of 5-$HT_{6,7}$ and D_2R homology models. Next, QSite was used to perform a single-point energy calculation for each obtained L-R complex, treating the ligand with *ab initio* (B3LYP/6-31G*) and the receptor with the MM (OPLS-2005) level of theory. Partial atomic charges were calculated using the electrostatic potential fitting method. Glide was subsequently applied to re-dock the ligand using each of the ligand charge sets calculated by QSite, and the QPLD algorithm was used to return the most energetically favourable poses. For a particular ligand, the Generalized-Born/Surface Area continuum solvent model was used to estimate ΔG values to select the correct poses between possible binding conformations.
To visualize (plotting interaction spheres) the possible contribution of halogen bonding to the resulting ligand-receptor complexes, the Halogen Bonding Webserver was used (access 1.12.2015, http://www.halogenbonding.com/).

References:

(1) Y.C. Cheng and W. H. Prusoff, *Biochem. Pharmacol.*, 1973, **22**, 3099–3108.

(2) Calculator Plugins Were Used for Structure Property Prediction and Calculation, Marvin 6.2.2, 2014, ChemAxon (http://www.chemaxon.com).

(3) Instant JChem Was Used for Structure Database Management, Search and Prediction, Instant JChem 14.11.24.0, 2014, ChemAxon (http://www.chemaxon.com).

(4) Phase, Version 4.1, Schrödinger, LLC, New York, NY, 2014.

(5) Glide, Version 6.5, Schrödinger, LLC, New York, NY, 2014.

(6) Schrödinger Suite 2015-4 QM-Polarized Ligand Docking protocol; Glide version 6.9, Schrödinger, LLC, New York, NY, 2015; Jaguar version 9.0, Schrödinger, LLC, New York, NY, 2015; QSite version 6.9, Schrödinger, LLC, New York, NY, 2015