RSC Medicinal Chemistry

Supporting Information

Discovery of potent nucleotide pyrophosphatase / phosphodiesterase3 (NPP3) inhibitors with ancillary carbonic anhydrase inhibition for cancer (immuno)therapy

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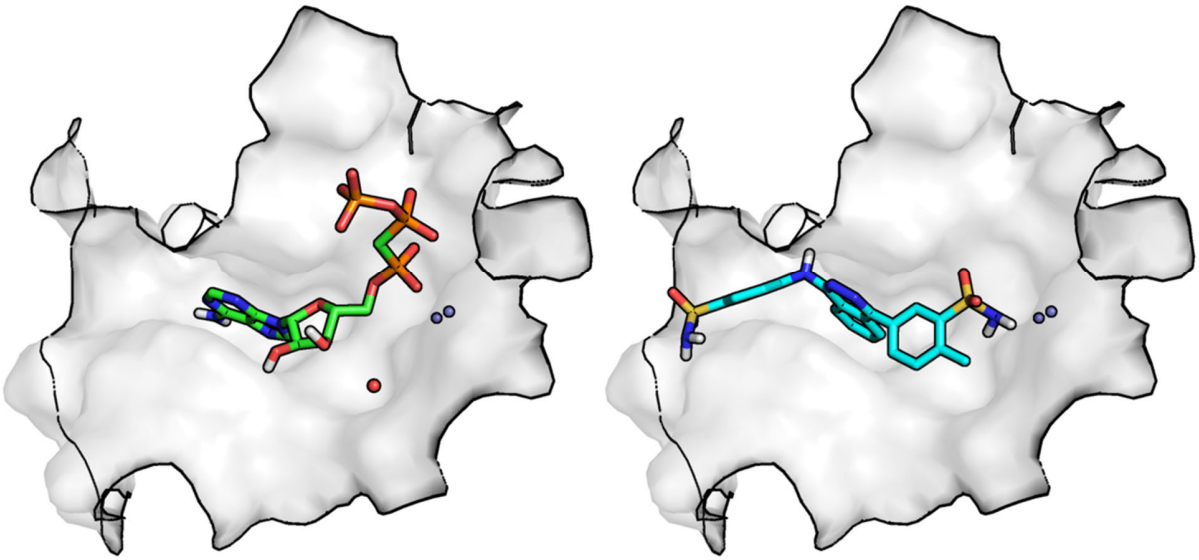

Figure S1. Comparison of binding pose of the ATP analog AMPCPP (carbon atoms colored green) and **23** (carbon atoms colored cyan) in the binding pocket of human NPP3. The two zinc ions in the substrate binding site are shown in orange. The water molecule involved in the interaction of AMPCPP and the two zinc ion is shown in red. The methyl group of the methylbenzenesulfonamide residue in compound **23** (right) is predicted to occupy the space where water molecule is located in the X-ray structure of the nucleotide-bound complex (left). The sulfonamido group likely forms strong interactions with the zinc ions.

```
SP|P22413|ENPP1_HUMAN MERDGCAGGGSRGGEGGRAPREGPAGNGRDRGRSHAAEAPGDPQAAASLLAPMDV-GEEP 59
SP|Q13822|ENPP2_HUMAN ------------------------------------------------------------
SP|O14638|ENPP3_HUMAN ----------------------------------------------MESTLTLATEQP 12

SP|P22413|ENPP1_HUMAN LEKAARARTAKDPNTYKVLSLVLSVCVLTTILGCI---------FGLK-------PSCAK 103
SP|Q13822|ENPP2_HUMAN ------MARRSSFQSCQIISLFTFAVGVNICLGFTAHRIKRAEGWEEGPPTVLSDSPWTN 54
SP|O14638|ENPP3_HUMAN VK-------KNTLKKYKIACIVLLALLVIMSLGLG---------LGLG-------LRKLE 49
                              .  :. :: .:.  .  :   **                        :

SP|P22413|ENPP1_HUMAN EVKSCKGRCFERTF---GNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKRLT 160
SP|Q13822|ENPP2_HUMAN ISGSCKGRCFELQEAGPPDCRCDNLCKSYTSCCHDFDELCLKTARGWECTKDRCGEVRNE 114
SP|O14638|ENPP3_HUMAN KQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVESTRIWMCNKFRCGETRLE 109
                         **: :**:       :****  * .  .** *::: *::  : * *.* **** *

SP|P22413|ENPP1_HUMAN RSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGF 220
SP|Q13822|ENPP2_HUMAN ENACHCSEDCLARGDCCTNYQVVCKGESHWVDDDCEEIKAAECPAGFVRPPLIIFSVDGF 174
SP|O14638|ENPP3_HUMAN ASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVILFSMDGF 169
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SP|P22413|ENPP1_HUMAN RAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMY 280
SP|Q13822|ENPP2_HUMAN RASYMKKGSKVMPNIEKLRSCGTHSPYMRPVYPTKTFPNLYTLATGLYPESHGIVGNSMY 234
SP|O14638|ENPP3_HUMAN RAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIIDNNMY 229
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SP|P22413|ENPP1_HUMAN DPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMY 340
SP|Q13822|ENPP2_HUMAN DPVFDATFHLRGREKFNHRWWGGQPLWITATKQGVKAGTFFWSV---------------- 278
SP|O14638|ENPP3_HUMAN DVNLNKNFSLSSKEQNNPAWWHGQPMWLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPY 289
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SP|P22413|ENPP1_HUMAN NGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMV 400
SP|Q13822|ENPP2_HUMAN --VIPHERRILTILQWLTLPDHERPSVYAFYSEQPDFSGHKYGPFGPEMTNPLREIDKIV 336
SP|O14638|ENPP3_HUMAN NGSVPFEERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAF 349
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SP|P22413|ENPP1_HUMAN GMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPS 460
SP|Q13822|ENPP2_HUMAN GQLMDGLKQLKLHRCVNVIFVGDHGMEDVTCDRTEFLSNYLTNVDDITLVPGTLGRIRSK 396
SP|O14638|ENPP3_HUMAN GMLMEGLKQRNLHNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAH 409
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SP|P22413|ENPP1_HUMAN DVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQL 520
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SP|P22413|ENPP1_HUMAN ALNPSE------RKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMC 574
SP|Q13822|ENPP2_HUMAN ARKPLDVYKKPSGKCFFQGDHGFDNKVNSMQTVFVGYGSTFKYKTKVPPFENIELYNVMC 514
SP|O14638|ENPP3_HUMAN V-RSKS------NTNCGGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPFENIEVYNLMC 522
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SP|P22413|ENPP1_HUMAN DLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRN-PRDNLGCSCNPSI- 632
SP|Q13822|ENPP2_HUMAN DLLGLKPAPNNGTHGSLNHLLRTNTFRPTMPEEVTRPNYPGIMYLQSDFDLGCTCDDKVE 574
SP|O14638|ENPP3_HUMAN DLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLPTESLDCFCPHLQN 582
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SP|P22413|ENPP1_HUMAN -L-PIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMP 690
SP|Q13822|ENPP2_HUMAN PKNKLDE----LNKRLHTKGSTEERHLLYGRPAVLYRTR-YDILYHTDFESGYSEIFLMP 629
SP|O14638|ENPP3_HUMAN ST-QLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMP 641
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SP|P22413|ENPP1_HUMAN LWTSYTVDRNDSF--STEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKN 748
SP|Q13822|ENPP2_HUMAN LWTSYTVSKQAEVSSVPDHLTSCVRPDVRVSPSFSQNCLAYKNDKQMSYGFLFPPYLSSS 689
SP|O14638|ENPP3_HUMAN MWSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRT 701
                       :*:**** :  .       . .*:  *.*:  *  ::*  *  :.::::*** **  . .
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SP|P22413|ENPP1_HUMAN SSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCD 808
SP|Q13822|ENPP2_HUMAN PEAKY-DAFLVTNMVPMYPAFKRVWNYFQRVLVKKYASERNGVNVISGPIFDYDYDGLHD 748
SP|O14638|ENPP3_HUMAN SDSQY-DALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFD 760
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SP|O14638|ENPP3_HUMAN APDEIT---KHLANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVES 817
                       : :::    : : . .: :***:: ::*** : ::   :* . *..  **:***  * **

SP|P22413|ENPP1_HUMAN CVHGKHDSSWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQED 925
SP|Q13822|ENPP2_HUMAN CNSSEDESKWVEELMKMHTARVRDIEHLTSLDFFRKTSRSYPEILTLKTYLHTYESEI 863
SP|O14638|ENPP3_HUMAN CPEGKPEALWVEERFTAHIARVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI 875
                       *  .: :: **** :  * **: *:* :*.*.*::.  .   :** ***:* *:.
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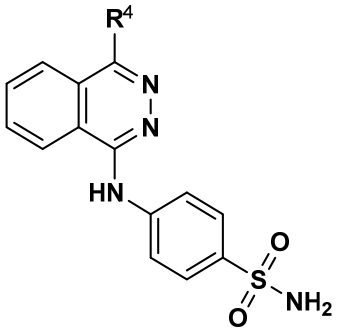
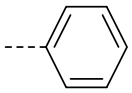
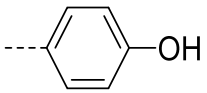
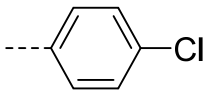
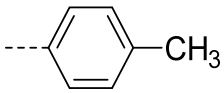
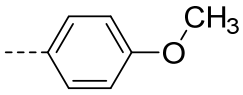
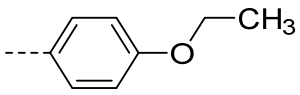
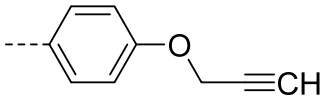
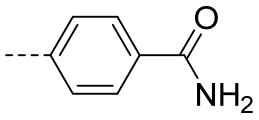
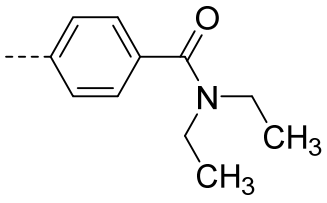
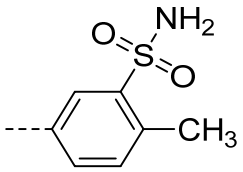
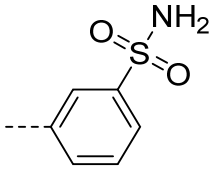
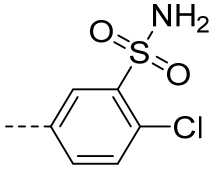
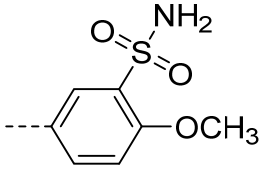
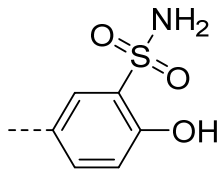
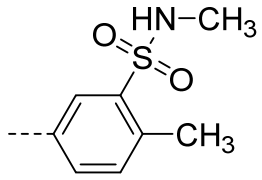
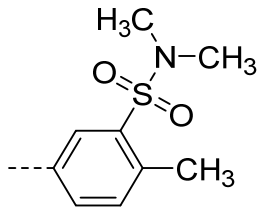
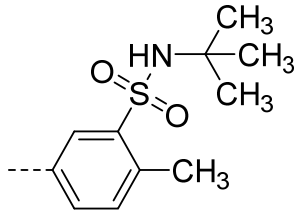
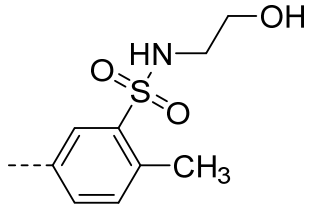
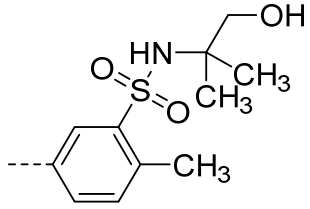
Figure S2. Sequence alignment of the human NPP subtypes NPP1, NPP2 and NPP3. For each sequence, the Uniprot accession number, the subtype and the organism name are given. Important amino acid residues in the binding pocket are highlighted in yellow.

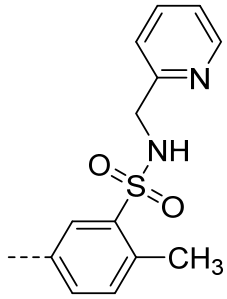
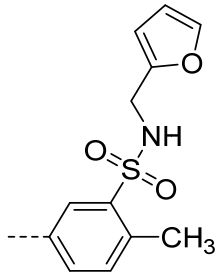
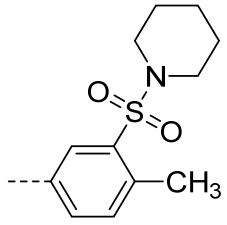
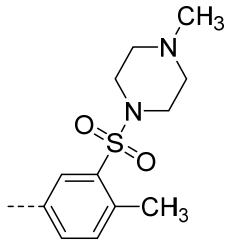
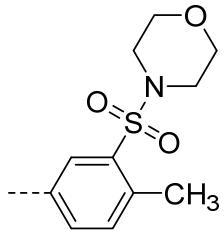
Table 1. Inhibitory activities of 4-(phthalazin-1-yl)aminobenzenesulfonamide derivatives with modification of the 4-substituent at human NPP3, CA-II and CA-IX



Compd.	R^4	K_i ± SEM (nM)		
		NPP3	*CA-II*	*CA-IX*
II	**Reactive blue 2**[1]	710 ± 30	n.d.	n.d.
1		1110 ± 40	948 ± 62	1060 ± 78
16		10300 ± 1200	208 ± 16 (>10000)[a]	932 ± 54 (>10000)[a]
17		5320 ± 120	155 ± 9	286 ± 25
6a		20100 ± 2400	2080 ± 128 (>10000)[a]	1170 ± 84 (>10000)[a]
6b		5090 ± 240	n.d.	n.d.
18		20300 ± 300	n.d.	n.d.

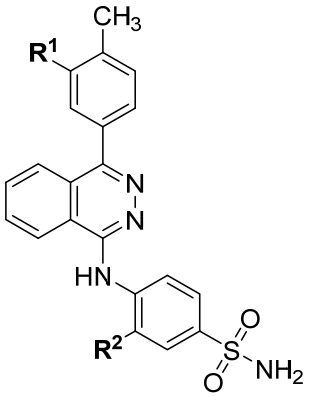
19		24700 ± 1500	285 ± 17	19.5 ± 0.70
20		30600 ± 1000	291 ± 21	22.4 ± 1.30
21		25900 ± 800	173 ± 9.6	143 ± 7.8
22		25700 ± 1400	2840 ± 157	1990 ± 155
23		53.7 ± 3.1	74.7 ± 6.1 (547 ± 25)[a]	20.3 ± 1.6 (0.48)[a]
6c		2120 ± 130	> 10000 (455 ± 3)[a]	1470 ± 115 (18.5)[a]
6d		3340 ± 650	n.d.	n.d.
6e		15600 ± 2800	n.d.	n.d.

6f		25400 ± 3800	n.d.	n.d.
24		4090 ± 140	72.7 ± 5.9	15.0 ± 0.97
25		30200 ± 700	204 ± 9	19.5 ± 1.3
26		30100 ± 1600	846 ± 49	26.2 ± 1.4
27		25400 ± 1900	139 ± 11	13.7 ± 0.65
28		23700 ± 700	72.1 ± 4.6	1120 ± 70

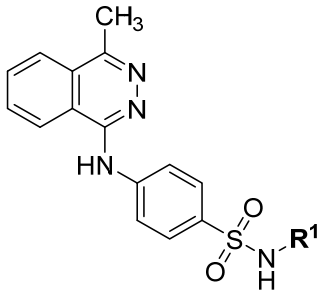
29		5570 ± 450	852 ± 49	18.9 ± 0.75
30		8880 ± 120	1730 ± 126	26.3 ± 0.9
31		50700 ± 1200	> 10000	30.7 ± 2.8
32		49800 ± 1100	941 ± 81	27.1 ± 2.0
33		45200 ± 1900	3700 ± 340	143 ± 10

[a] *IC50* values from literature[2]
n.d. = not determined

Table 2. Inhibitory activities of differently substituted 4-(phthalazin-1-yl)aminobenzenesulfonamide derivatives at human NPP3, CA-II and CA-IX



6g, **11**, and **15**



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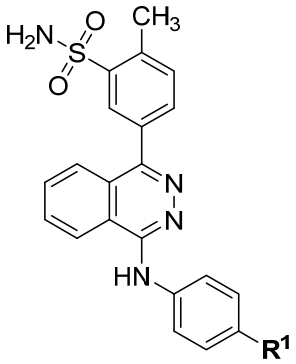
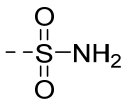
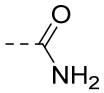
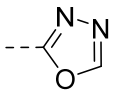
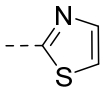
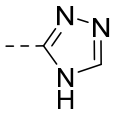
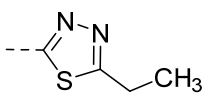


37-40

Compd.	R^1	R^2	K_i ± SEM (nM)		
			NPP3	*CA-II*	*CA-IX*
6g			29900 ± 3400	4260 ± 349	2500 ± 137
11			74200 ± 6800	> 10000	> 10000
15			80700 ± 9900	> 10000	> 10000
34			20100 ± 800	73.7 ± 6.0	19.7 ± 1.0
35			19700 ± 1100	n.d.	n.d.
36			30900 ± 1400	474 ± 38	24.5 ± 1.40

37	--CH_3	60700 ± 3500	n.d.	n.d.
38	--Cl	40200 ± 2100	n.d.	n.d.
39	---F	50900 ± 3400	n.d.	n.d.
40	--OH	35100 ± 1200	n.d.	n.d.

n.d. = not determined

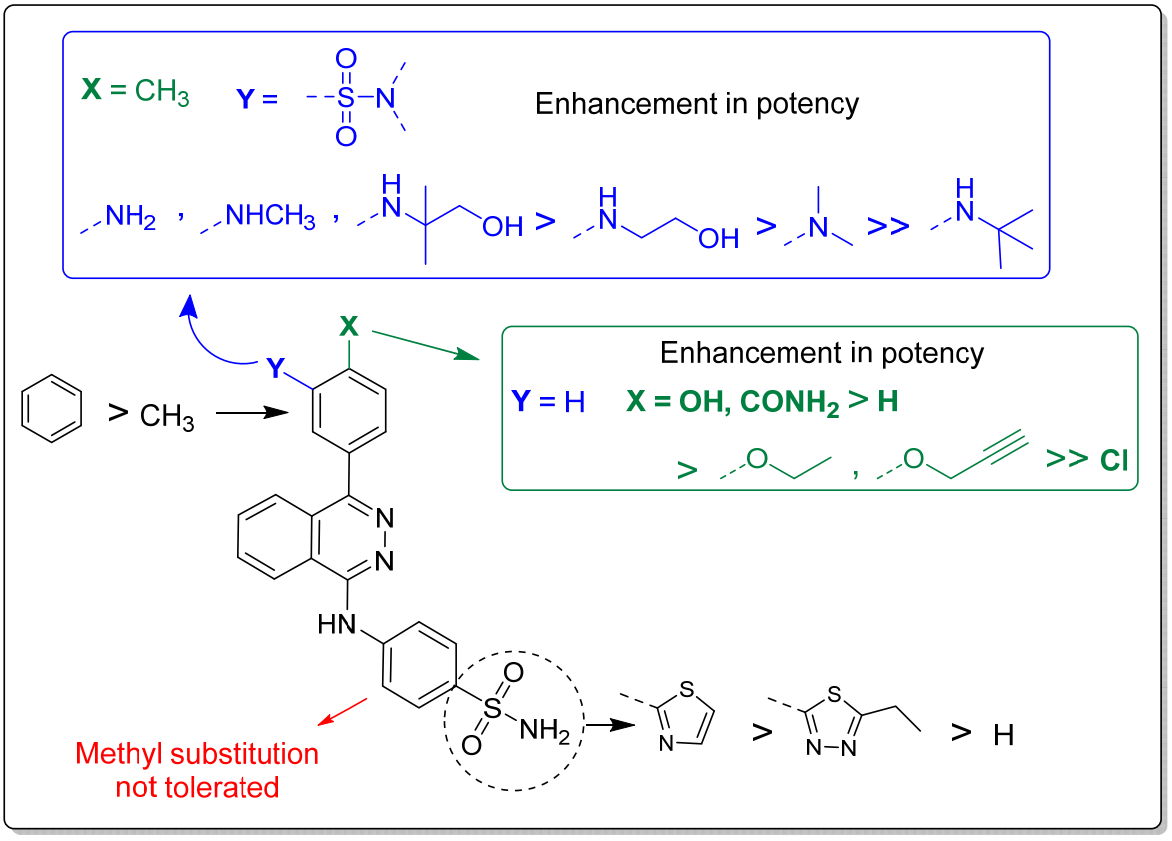


Fig. S3. Summary of the structure-activity relationships of 4-(phthalazin-1-yl)amino-benzenesulfonamide derivatives as inhibitors of CA-II.

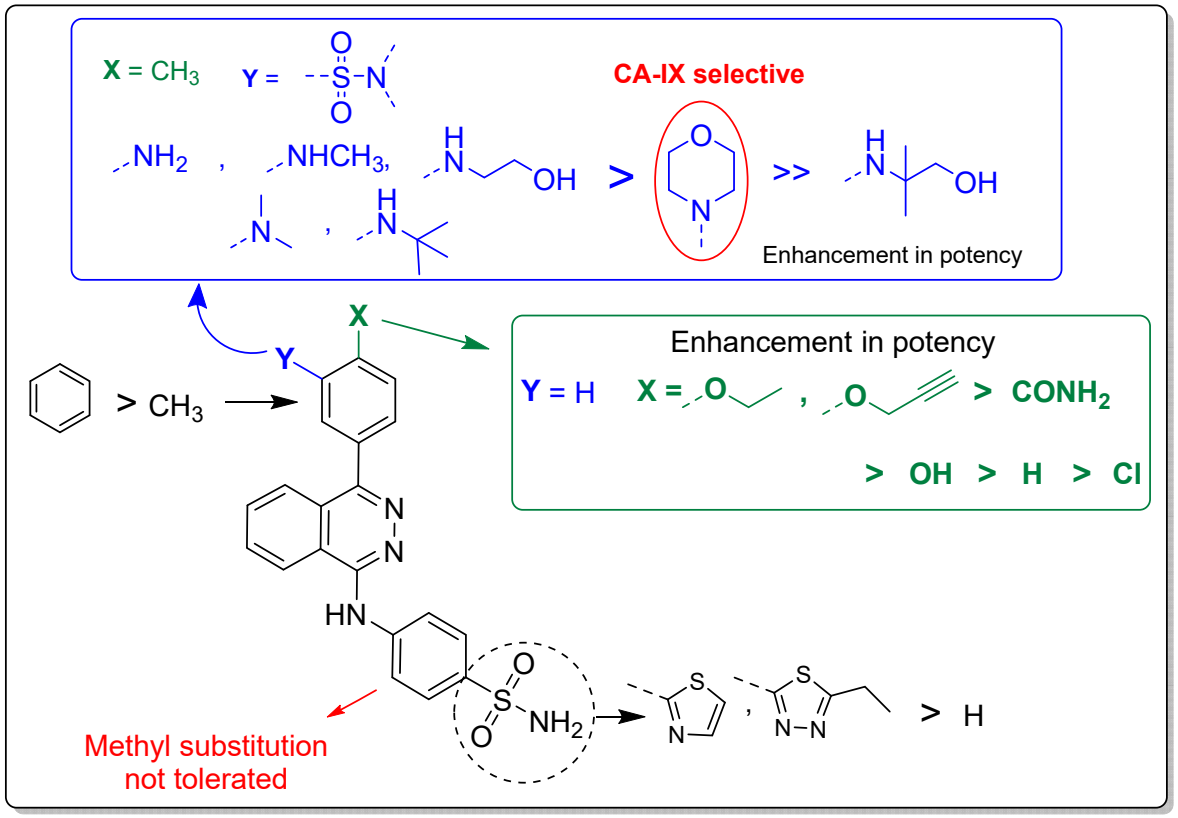


Fig. S4. Summary of the structure-activity relationships of 4-(phthalazin-1-yl)amino-benzenesulfonamide derivatives as inhibitors of CA-IX.

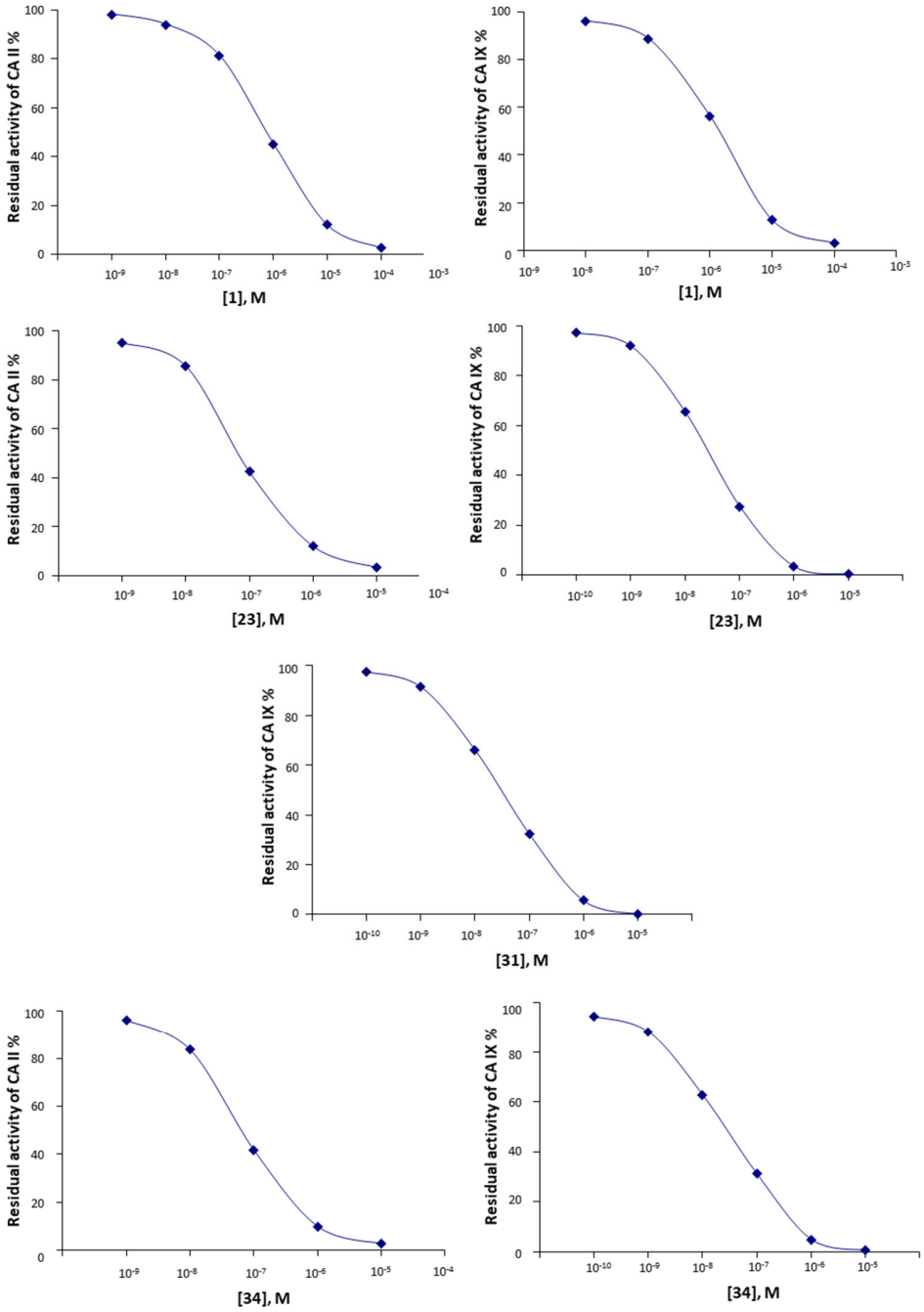
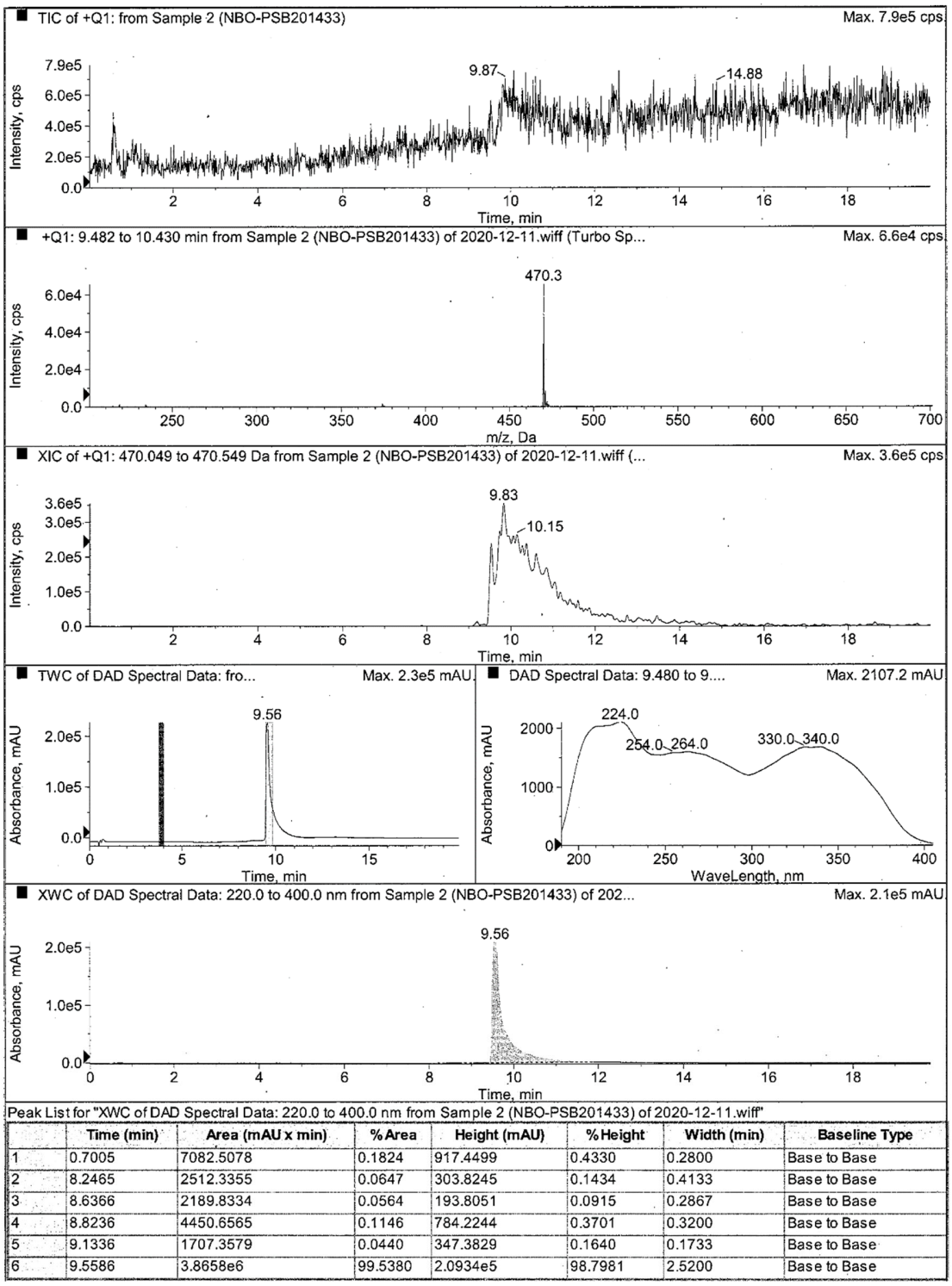


Fig. S5. Concentration-inhibition curves of **1**, **23**, **31** and **34** on CA II and CA IX, respectively.

LC-MS data for the selected compounds:

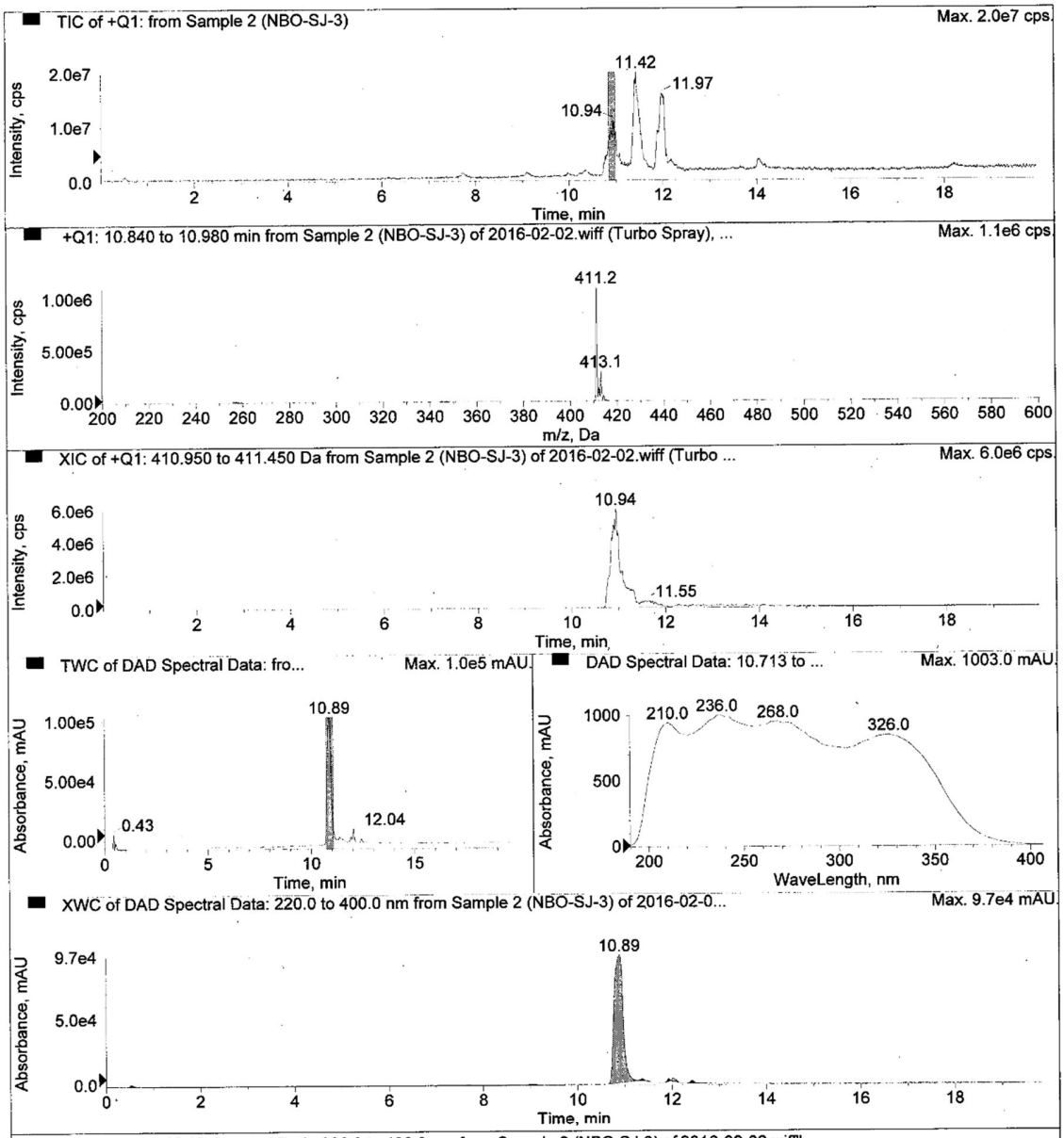
Compound 23:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 2 (NBO-PSB201433) of 2020-12-11.wiff"

	Time (min)	Area (mAU x min)	%Area	Height (mAU)	%Height	Width (min)	Baseline Type
1	0.7005	7082.5078	0.1824	917.4499	0.4330	0.2800	Base to Base
2	8.2465	2512.3355	0.0647	303.8245	0.1434	0.4133	Base to Base
3	8.6366	2189.8334	0.0564	193.8051	0.0915	0.2867	Base to Base
4	8.8236	4450.6565	0.1146	784.2244	0.3701	0.3200	Base to Base
5	9.1336	1707.3579	0.0440	347.3829	0.1640	0.1733	Base to Base
6	9.5586	3.8658e6	99.5380	2.0934e5	98.7981	2.5200	Base to Base

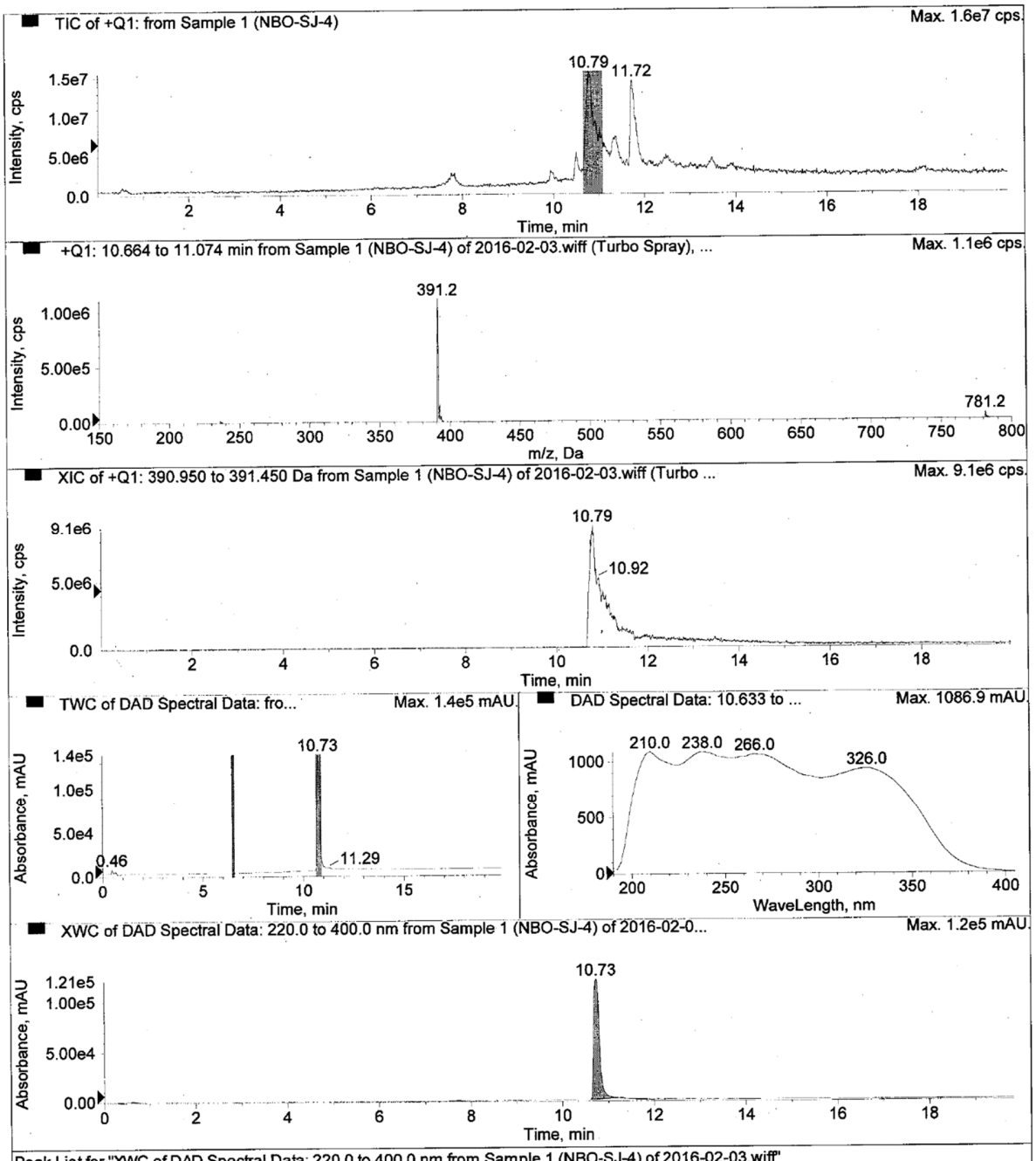
Compound 6a:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 2 (NBO-SJ-3) of 2016-02-02.wiff"

	Time (min)	Area (mAU x min)	% Area	Height (mAU)	% Height	Width (min)	Baseline Type
1	0.5276	7899.5324	0.5810	1715.4807	1.5121	0.1667	Base to Base
2	7.6708	1843.0319	0.1356	275.0121	0.2424	0.4467	Base to Base
3	9.0520	3061.5473	0.2252	388.0632	0.3420	0.6000	Base to Base
4	10.8872	1.2878e6	94.7137	9.7038e4	85.5317	0.6333	Base to Base
5	11.3621	7510.1532	0.5524	1680.2871	1.4811	0.1733	Base to Base
6	11.4653	785.3619	0.0578	173.3592	0.1528	0.1067	Base to Base
7	11.9270	8225.2013	0.6049	2441.7702	2.1522	0.1133	Base to Base
8	12.0374	3.0445e4	2.2391	7437.9789	6.5560	0.1800	Base to Base
9	12.4204	1.2107e4	0.8904	2302.7327	2.0297	0.5467	Base to Base

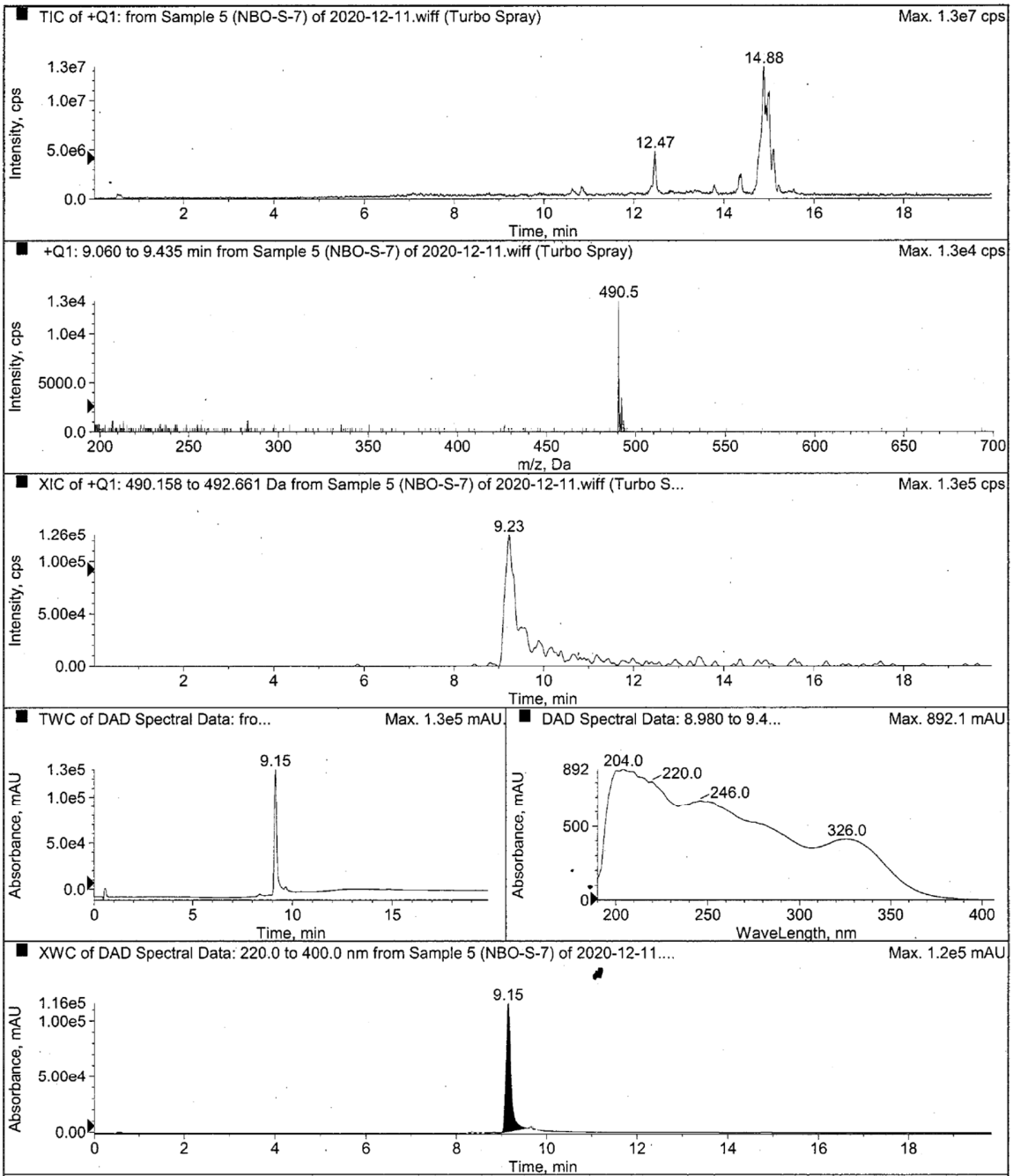
Compound 6b:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 1 (NBO-SJ-4) of 2016-02-03.wiff"

	Time (min)	Area (mAU x min)	% Area	Height (mAU)	% Height	Width (min)	Baseline Type
1	0.3971	3250.2932	0.3025	586.4970	0.4756	0.1667	Base to Base
2	0.6271	7285.7593	0.6782	1154.0557	0.9359	0.2400	Base to Base
3	7.7325	3695.2548	0.3440	405.2729	0.3287	0.5733	Base to Base
4	10.7305	1.0545e6	98.1484	1.2017e5	97.4523	0.6333	Base to Base
5	11.2914	2779.9673	0.2588	661.1599	0.5362	0.1467	Base to Base
6	11.7401	2881.7883	0.2682	334.6683	0.2714	0.3400	Base to Base

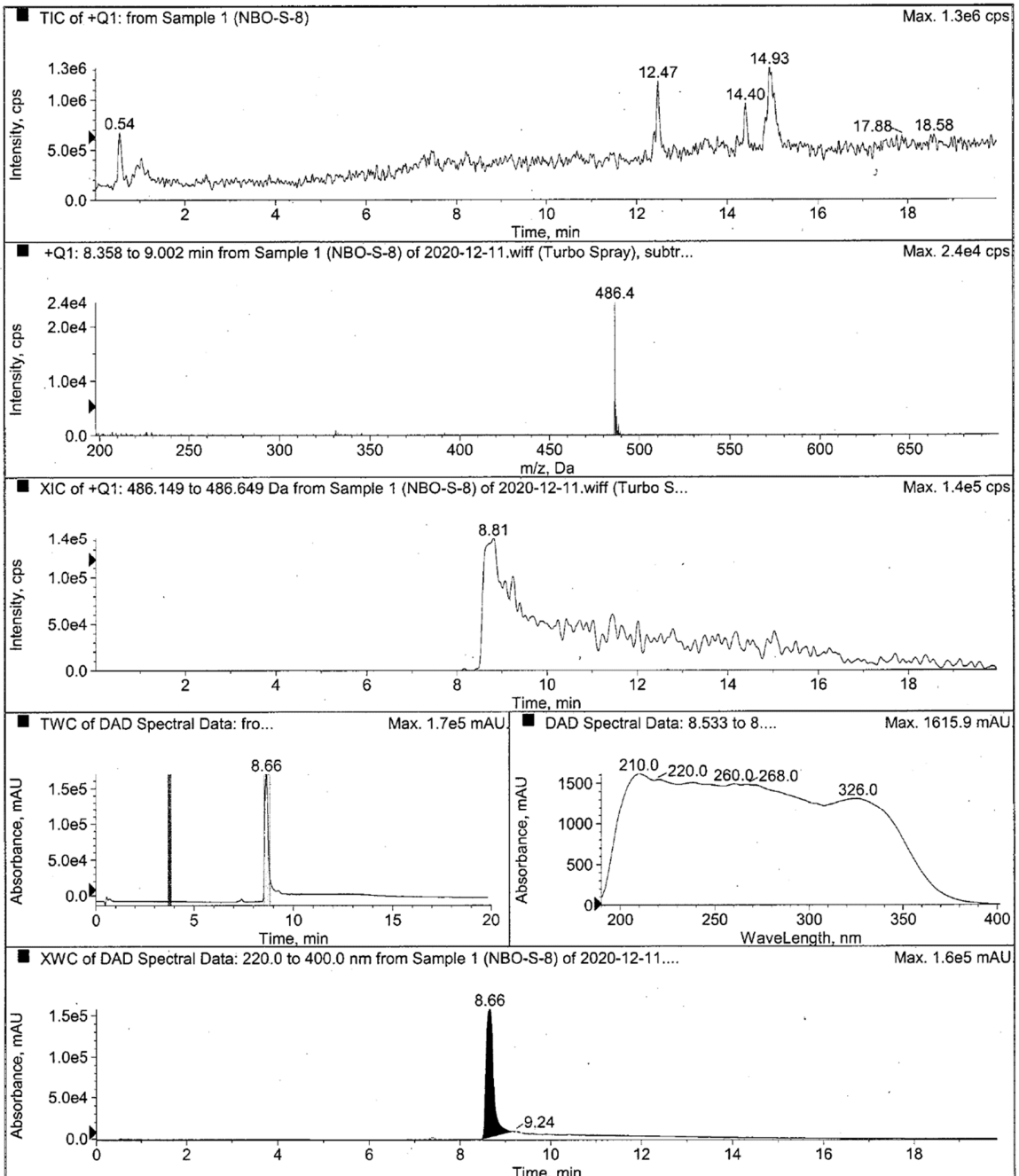
Compound 6d:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 5 (NBO-S-7) of 2020-12-11.wiff"

	Time (min)	Area (mAU x min)	% Area	Height (mAU)	% Height	Width (min)	Baseline Type
1	0.5617	1.2021e4	1.2755	1530.8984	1.2603	0.2467	Base to Base
2	8.3584	1.7622e4	1.8698	1598.4826	1.3159	0.5200	Base to Base
3	9.1498	8.9731e5	95.2114	1.1564e5	95.2006	0.5800	Base to Base
4	9.6653	1.3519e4	1.4345	2346.8687	1.9320	0.2533	Base to Base
5	10.4255	1968.2006	0.2088	353.7283	0.2912	0.2800	Base to Base

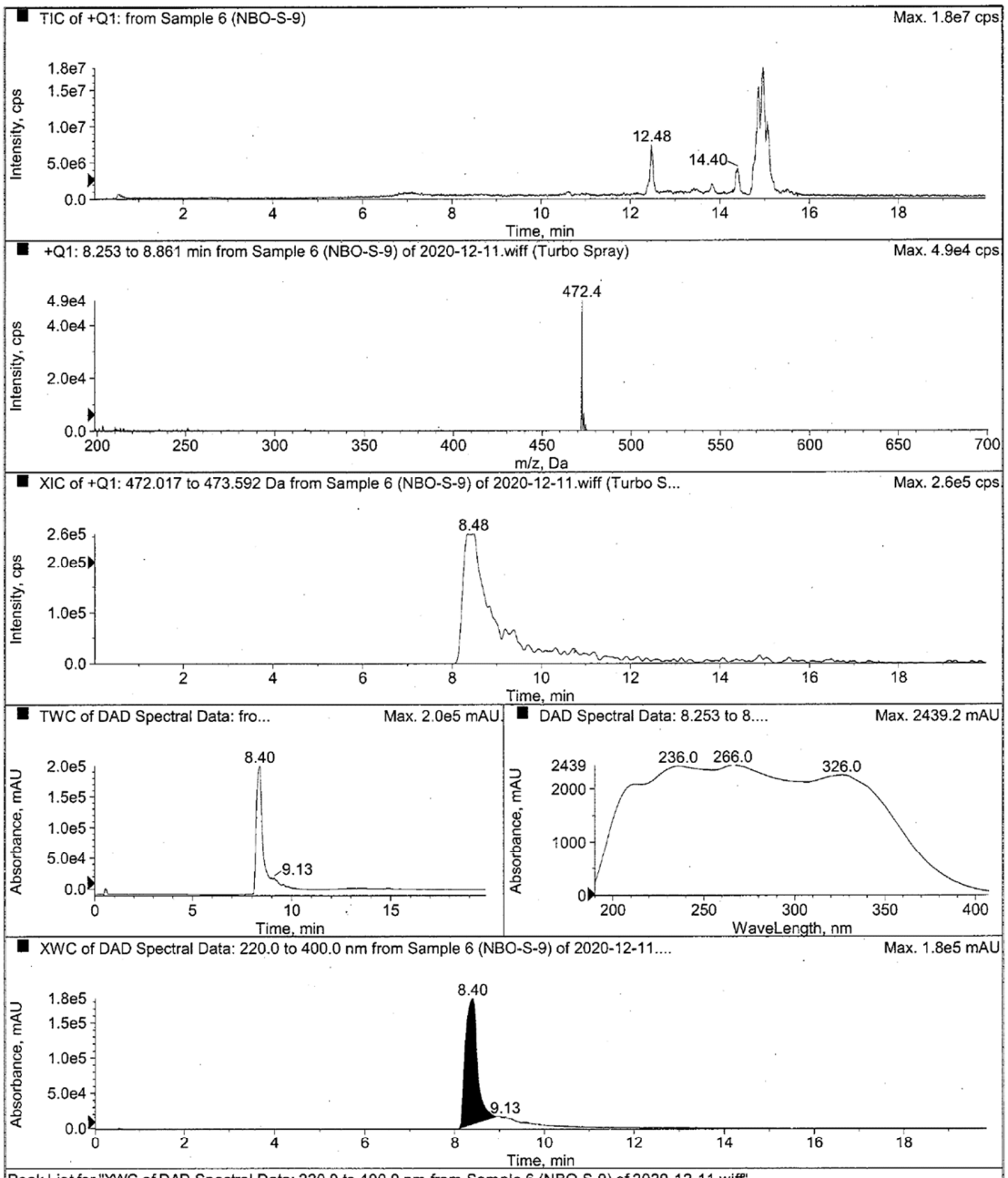
Compound 6e:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 1 (NBO-S-8) of 2020-12-11.wiff"

	Time (min)	Area (mAU x min)	%Area	Height (mAU)	%Height	Width (min)	Baseline Type
1	0.5482	5625.4944	0.3000	1037.7986	0.6418	0.1333	Base to Base
2	7.4022	2.8187e4	1.5032	2717.1583	1.6805	0.6600	Base to Base
3	8.6583	1.8285e6	97.5175	1.5583e5	96.3771	0.6800	Base to Base
4	9.2411	1.0152e4	0.5414	1532.4139	0.9477	0.2400	Base to Base
5	9.9039	2584.9724	0.1379	570.5914	0.3529	0.1733	Base to Base

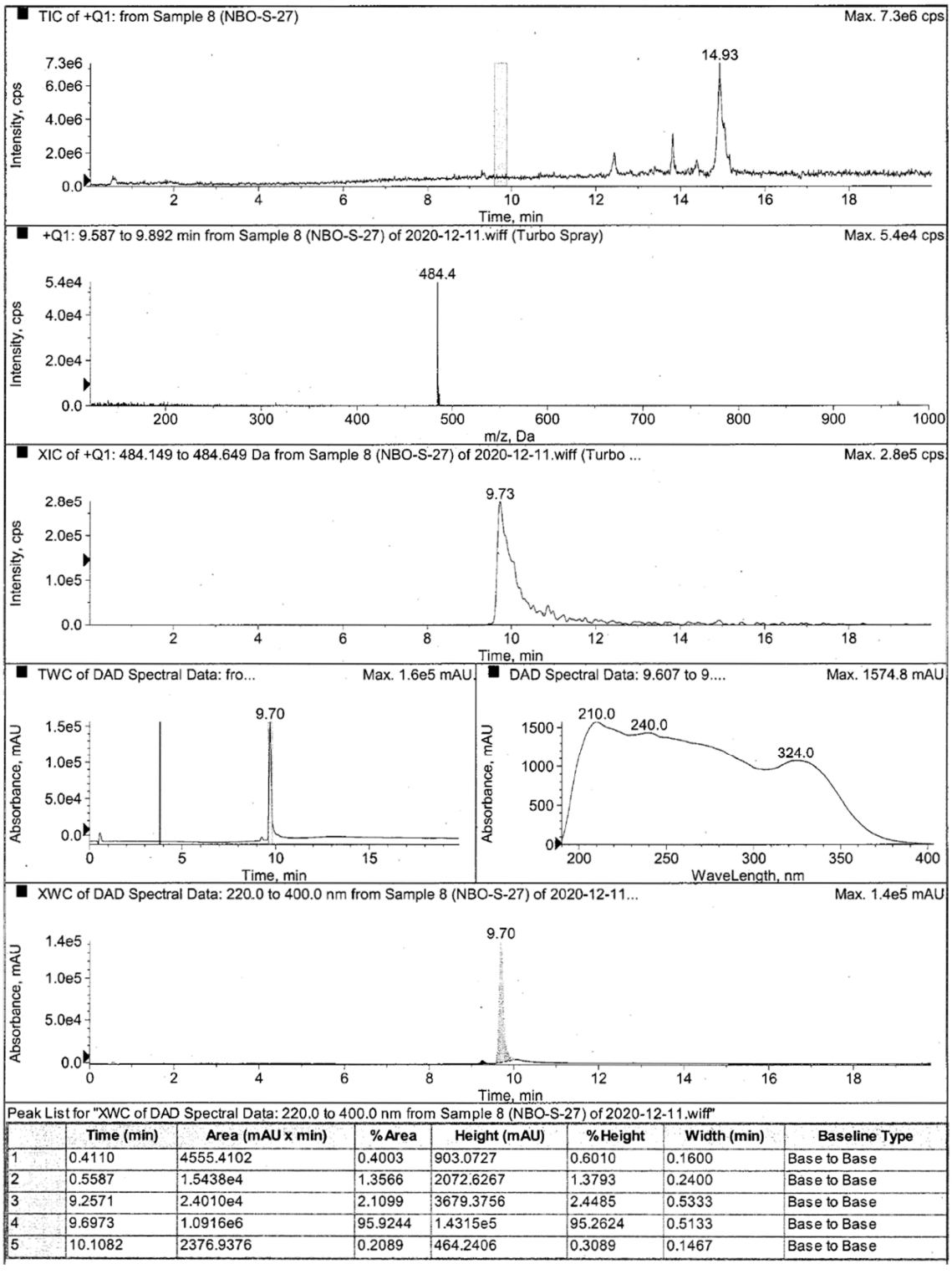
Compound 6f:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 6 (NBO-S-9) of 2020-12-11.wiff"

	Time (min)	Area (mAU x min)	% Area	Height (mAU)	% Height	Width (min)	Baseline Type
1	0.4234	2991.3537	0.0863	608.6501	0.3279	0.1800	Base to Base
2	0.5657	1.0959e4	0.3161	1442.2558	0.7770	0.2400	Base to Base
3	8.3976	3.4218e6	98.6967	1.7890e5	96.3771	0.8467	Base to Base
4	9.1305	8381.9650	0.2418	1883.1447	1.0145	0.1467	Base to Base
5	9.5705	1.0197e4	0.2941	1437.8968	0.7746	0.2333	Base to Base
6	9.8008	3194.2302	0.0921	455.5337	0.2454	0.2200	Base to Base
7	14.8608	7841.2618	0.2262	558.2882	0.3008	0.6267	Base to Base
8	15.4873	1619.7537	0.0467	339.1969	0.1827	0.1933	Base to Base

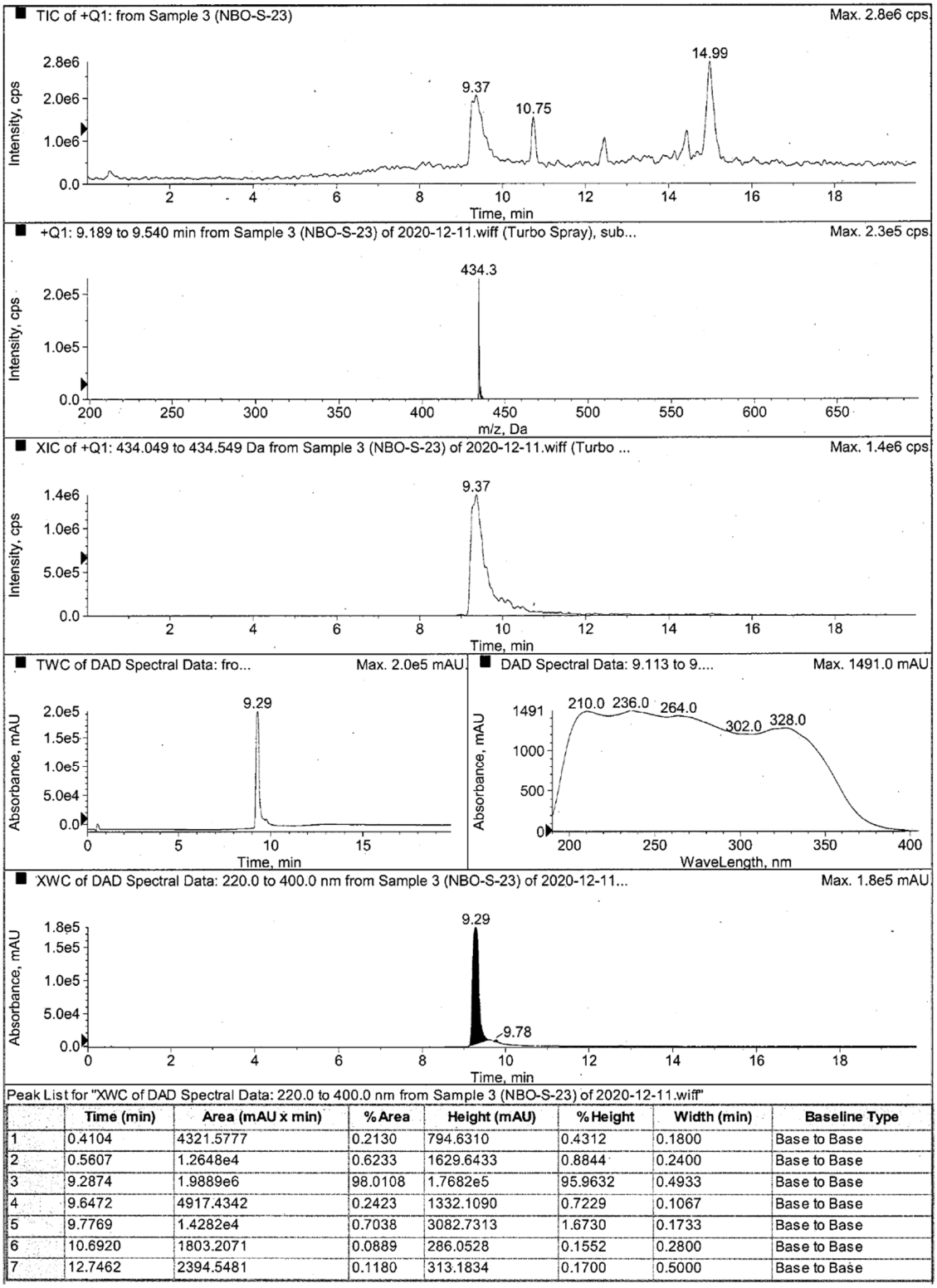
Compound 6g:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 8 (NBO-S-27) of 2020-12-11.wiff"

	Time (min)	Area (mAU x min)	%Area	Height (mAU)	%Height	Width (min)	Baseline Type
1	0.4110	4555.4102	0.4003	903.0727	0.6010	0.1600	Base to Base
2	0.5587	1.5438e4	1.3566	2072.6267	1.3793	0.2400	Base to Base
3	9.2571	2.4010e4	2.1099	3679.3756	2.4485	0.5333	Base to Base
4	9.6973	1.0916e6	95.9244	1.4315e5	95.2624	0.5133	Base to Base
5	10.1082	2376.9376	0.2089	464.2406	0.3089	0.1467	Base to Base

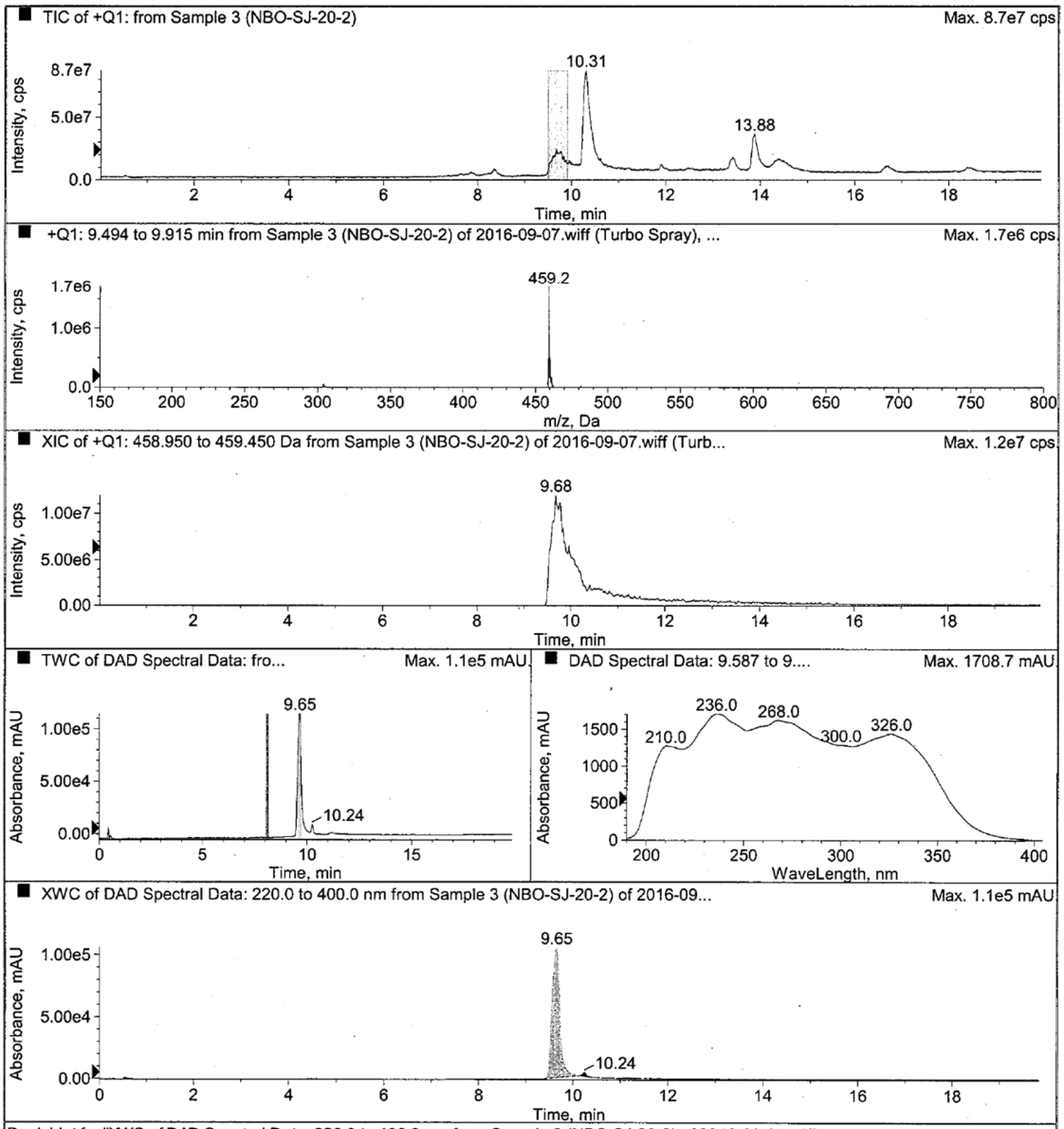
Compound 11:



Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 3 (NBO-S-23) of 2020-12-11.wiff"

	Time (min)	Area (mAU x min)	%Area	Height (mAU)	%Height	Width (min)	Baseline Type
1	0.4104	4321.5777	0.2130	794.6310	0.4312	0.1800	Base to Base
2	0.5607	1.2648e4	0.6233	1629.6433	0.8844	0.2400	Base to Base
3	9.2874	1.9889e6	98.0108	1.7682e5	95.9632	0.4933	Base to Base
4	9.6472	4917.4342	0.2423	1332.1090	0.7229	0.1067	Base to Base
5	9.7769	1.4282e4	0.7038	3082.7313	1.6730	0.1733	Base to Base
6	10.6920	1803.2071	0.0889	286.0528	0.1552	0.2800	Base to Base
7	12.7462	2394.5481	0.1180	313.1834	0.1700	0.5000	Base to Base

Compound 15:

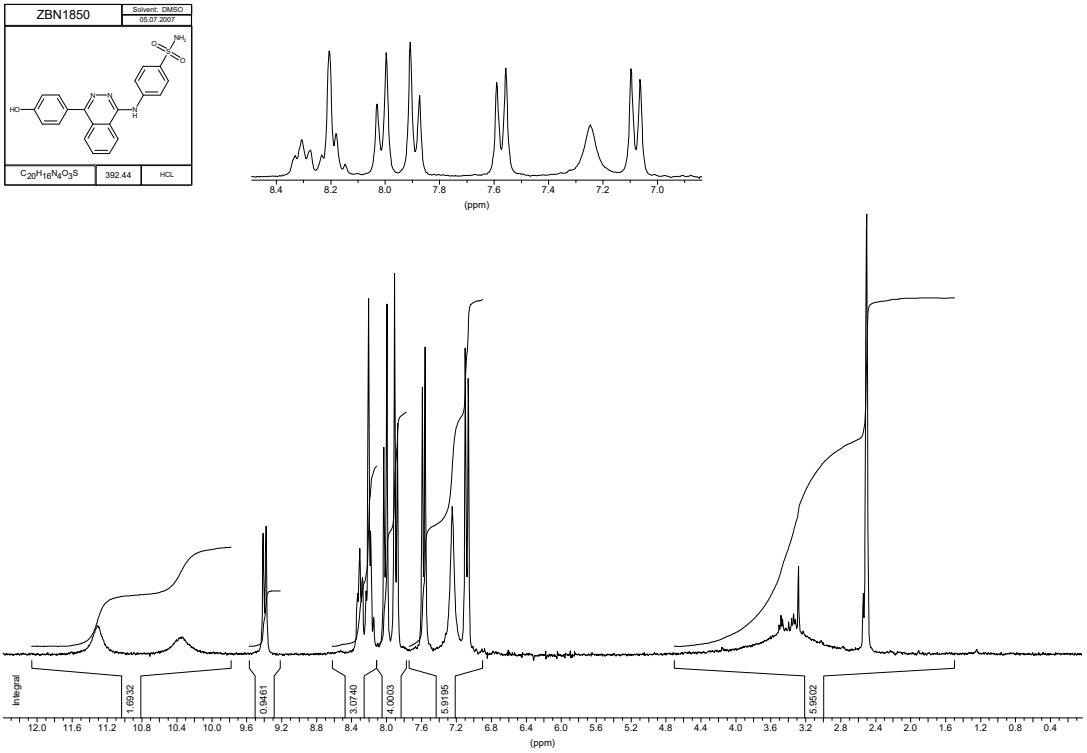


Peak List for "XWC of DAD Spectral Data: 220.0 to 400.0 nm from Sample 3 (NBO-SJ-20-2) of 2016-09-07.wiff"

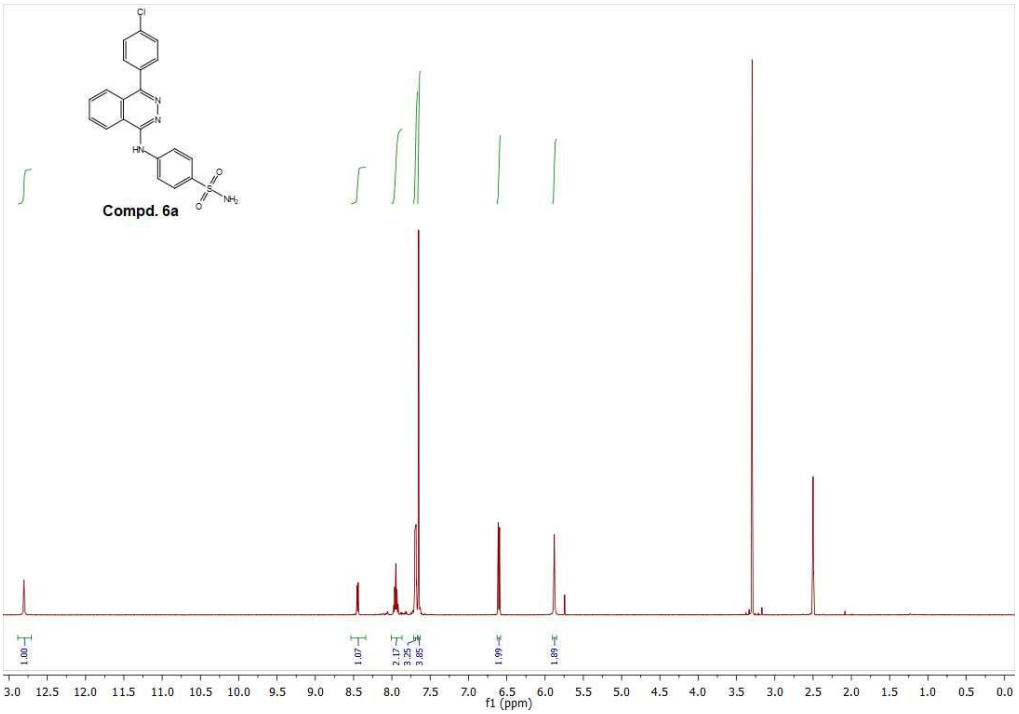
	Time (min)	Area (mAU x min)	%Area	Height (mAU)	%Height	Width (min)	Baseline Type
1	0.5392	6296.9995	0.5026	1368.3353	1.2282	0.1667	Base to Base
2	0.6954	685.0589	0.0547	145.1058	0.1302	0.1467	Base to Base
3	7.8061	1703.1722	0.1359	291.7823	0.2619	0.2400	Base to Base
4	9.6476	1.2214e6	97.4757	1.0515e5	94.3784	0.7467	Base to Base
5	10.2425	1.7779e4	1.4189	3476.4196	3.1204	0.2467	Base to Base
6	10.5468	826.7824	0.0660	188.3608	0.1691	0.1600	Base to Base
7	10.7293	447.9220	0.0357	116.5071	0.1046	0.1267	Base to Base
8	10.8795	802.9122	0.0641	171.2923	0.1538	0.1867	Base to Base
9	11.1652	1465.9325	0.1170	203.1205	0.1823	0.2733	Base to Base
10	11.4389	1104.8348	0.0882	185.6746	0.1667	0.2933	Base to Base
11	11.9566	516.7875	0.0412	116.4208	0.1045	0.2133	Base to Base

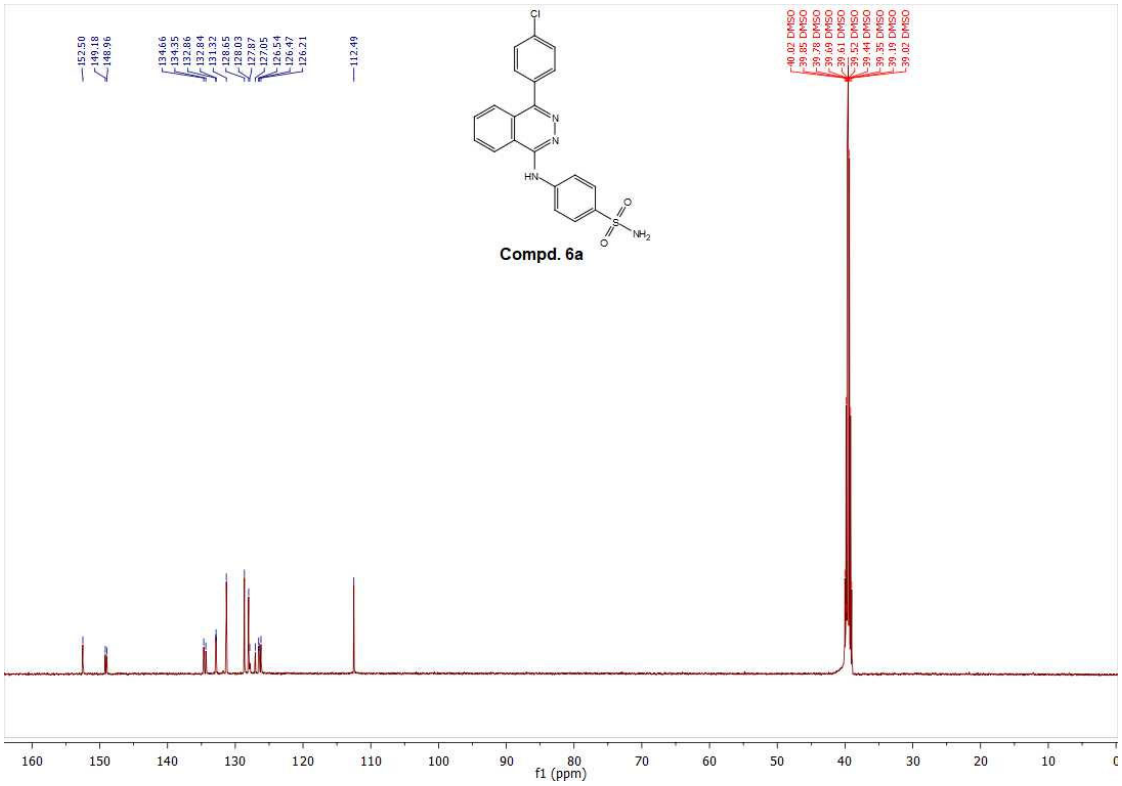
NMR data for the selected compounds

Compd. 17

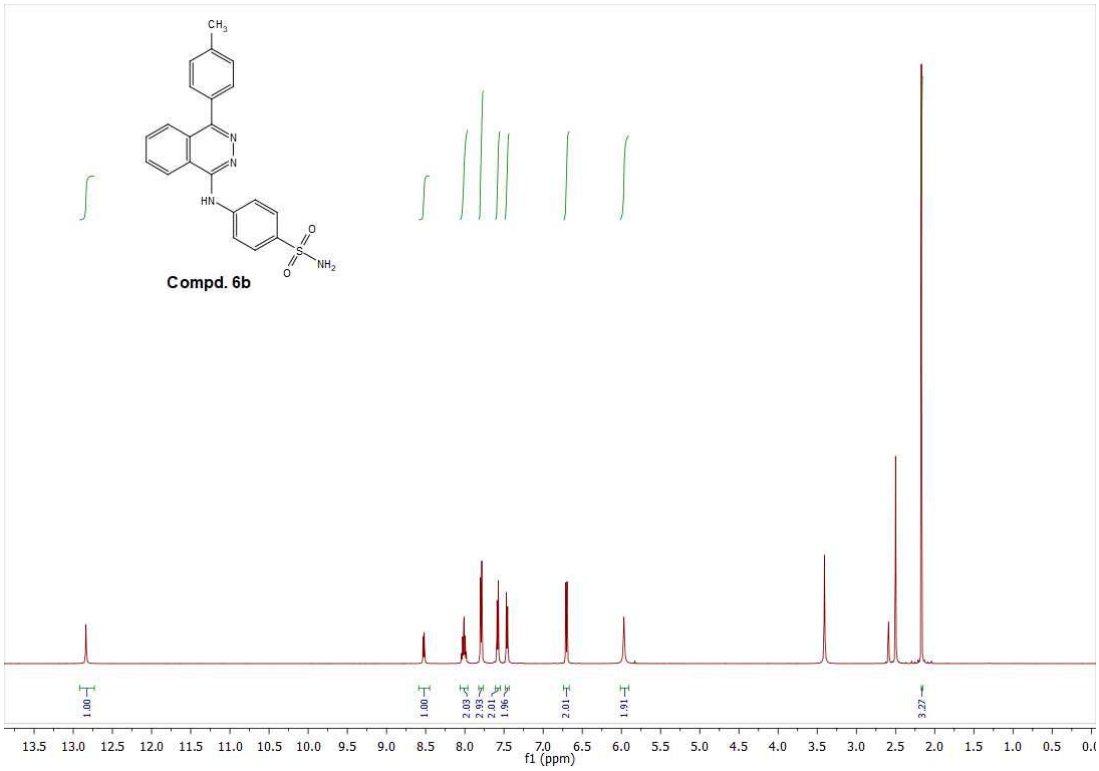


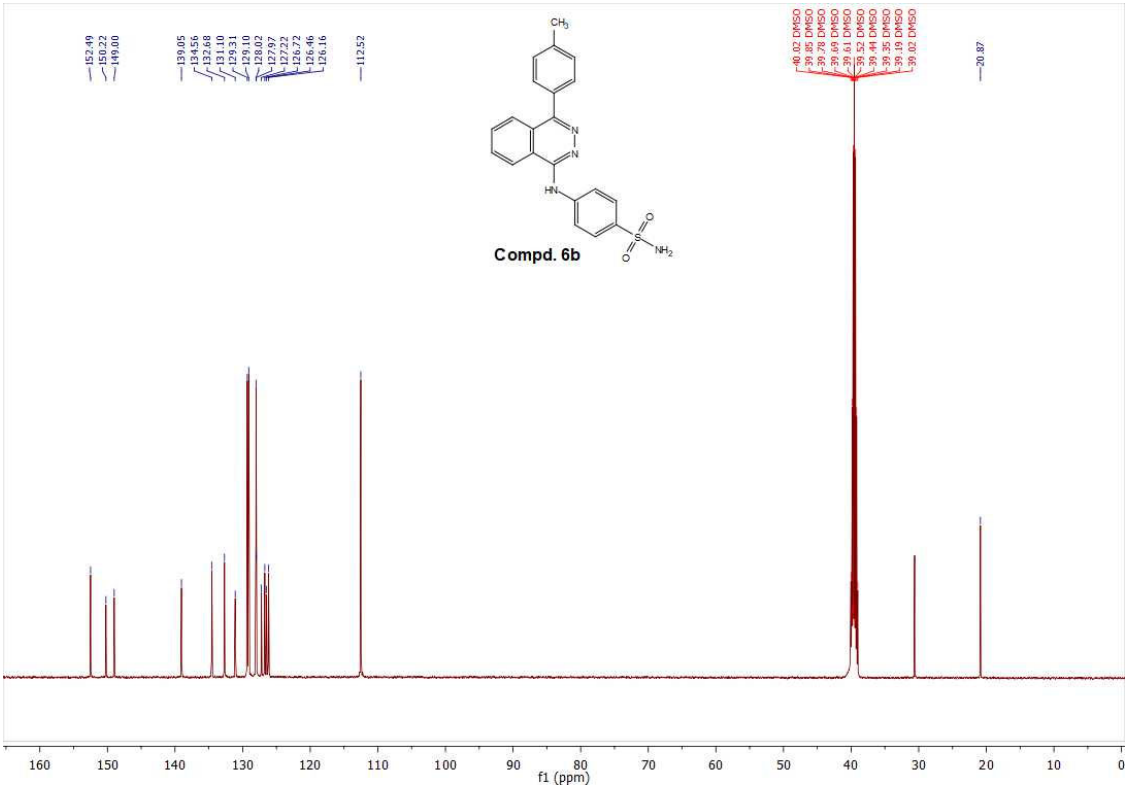
Compd. 6a



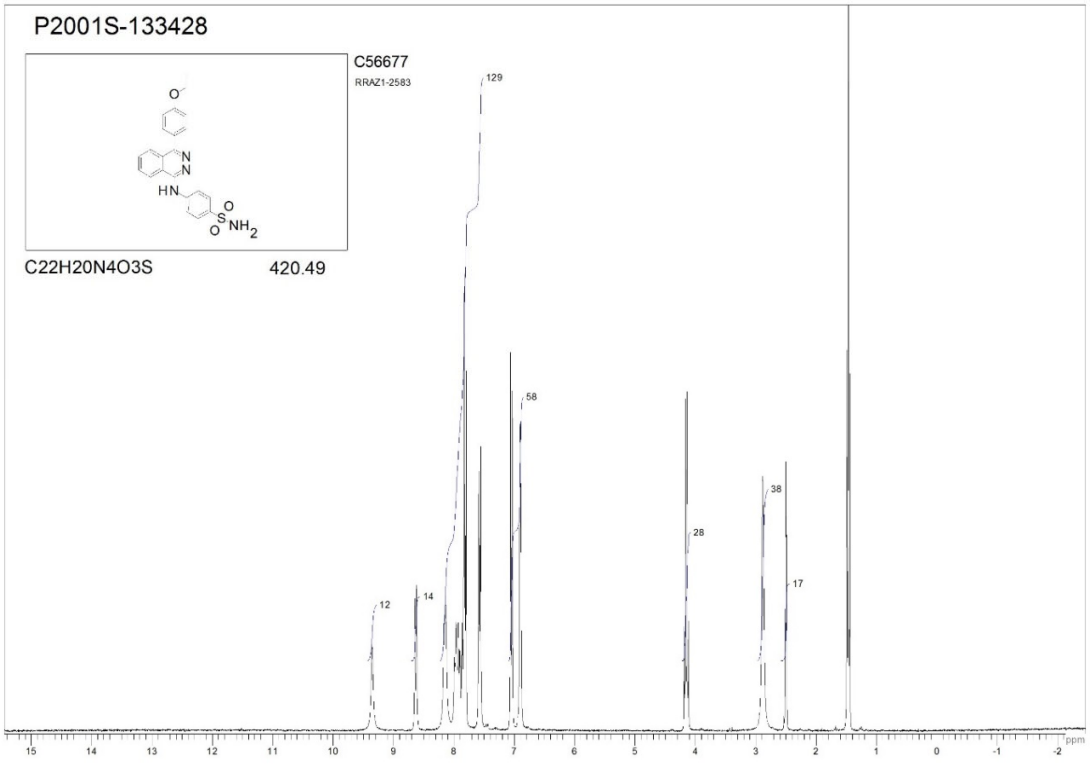


Compd. 6b

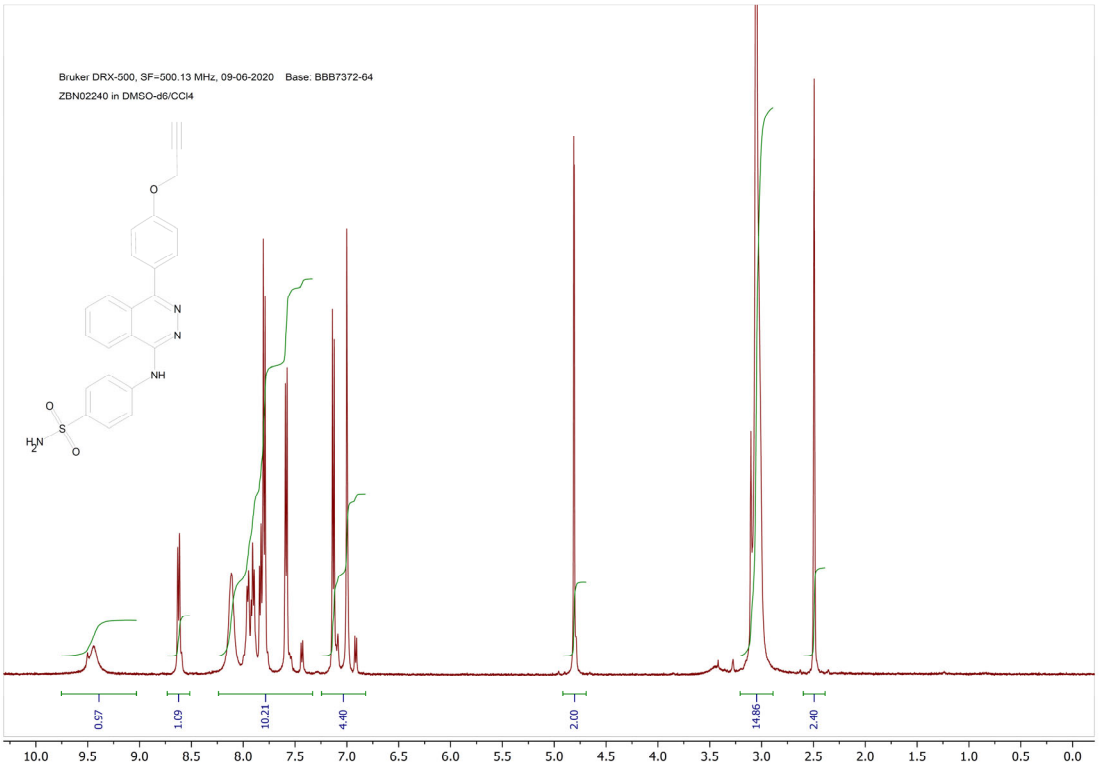



152.49
150.22
149.00
139.05
134.56
132.68
131.10
129.31
129.10
128.02
127.97
127.22
126.72
126.46
126.16
112.52
40.02 DMSO
39.85 DMSO
39.68 DMSO
39.51 DMSO
39.34 DMSO
39.17 DMSO
39.00 DMSO
20.87
Compd. 6b
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

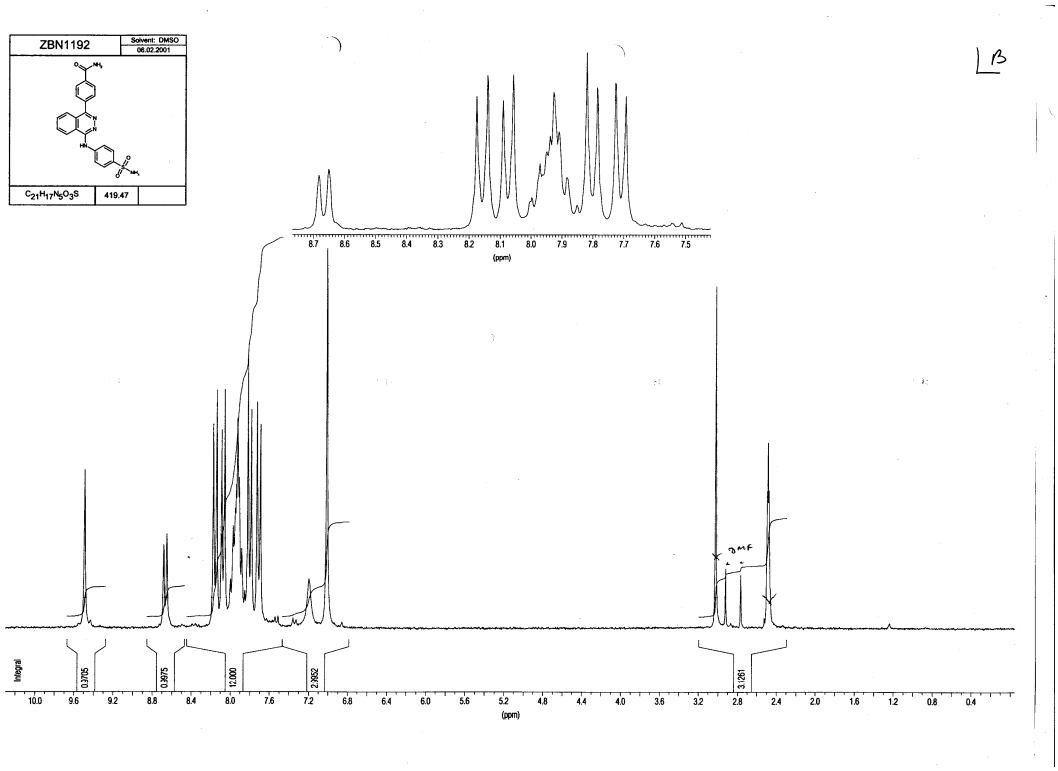
Compd. 19


P2001S-133428
C56677
RRAZ1-2583
C22H20N4O3S
420.49
129
58
38
28
17
14
12
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

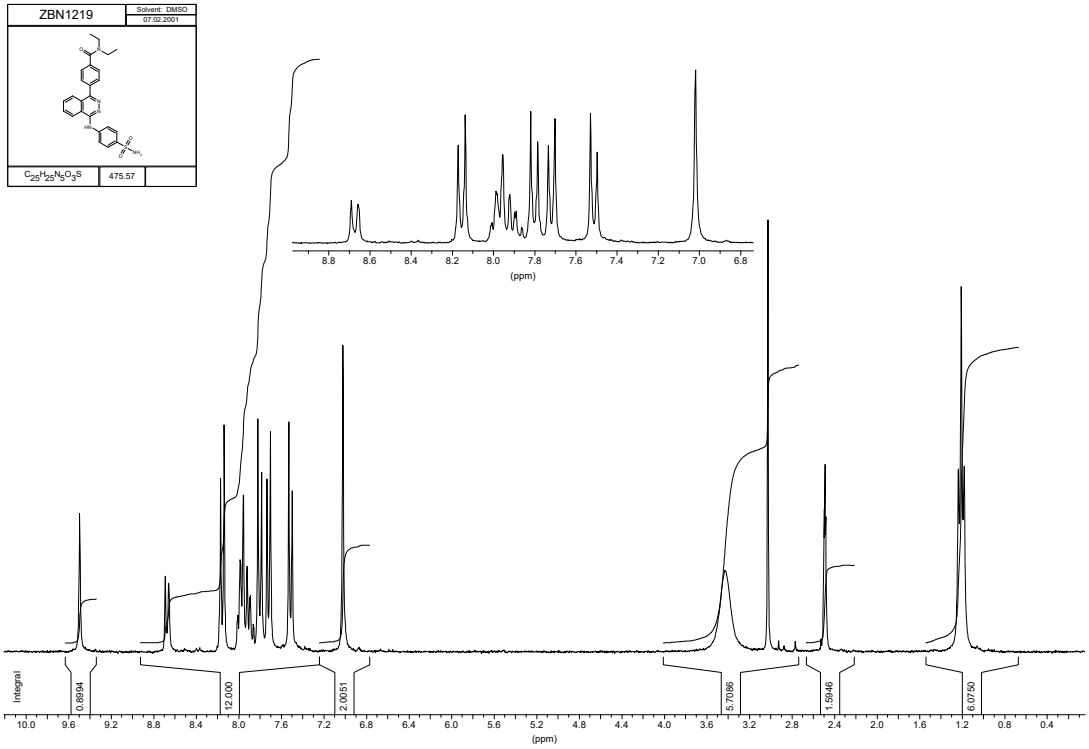
Compd. 20



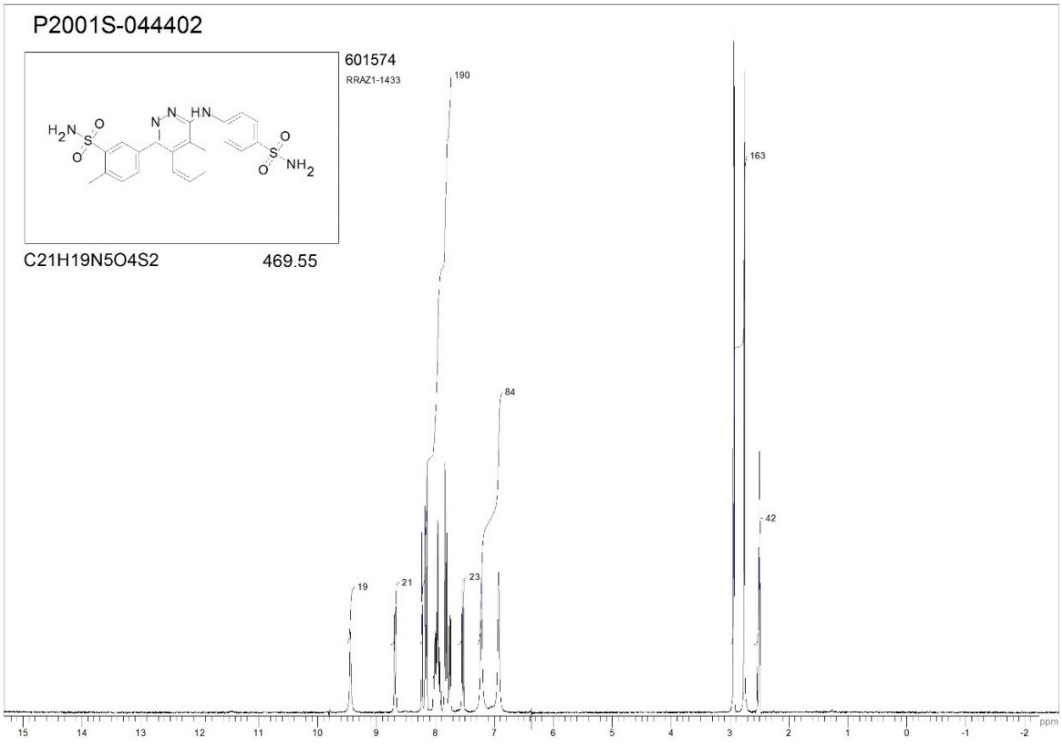
Compd. 21



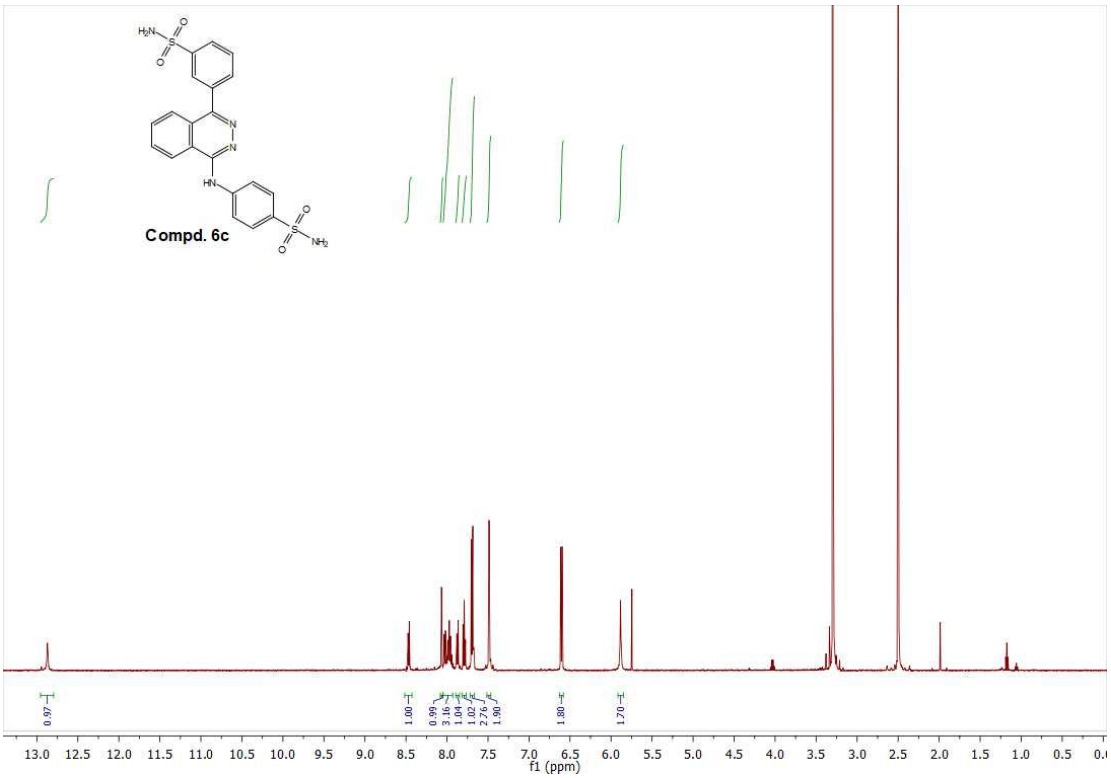
Compd. 22

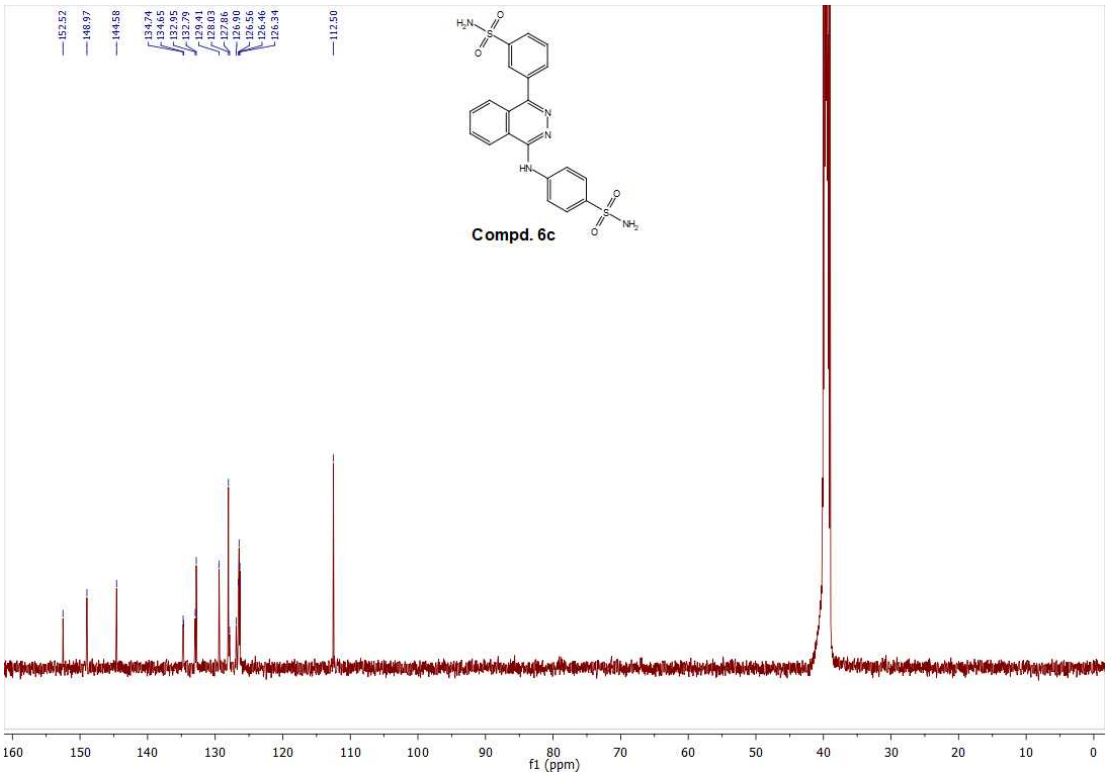


Compd. 23

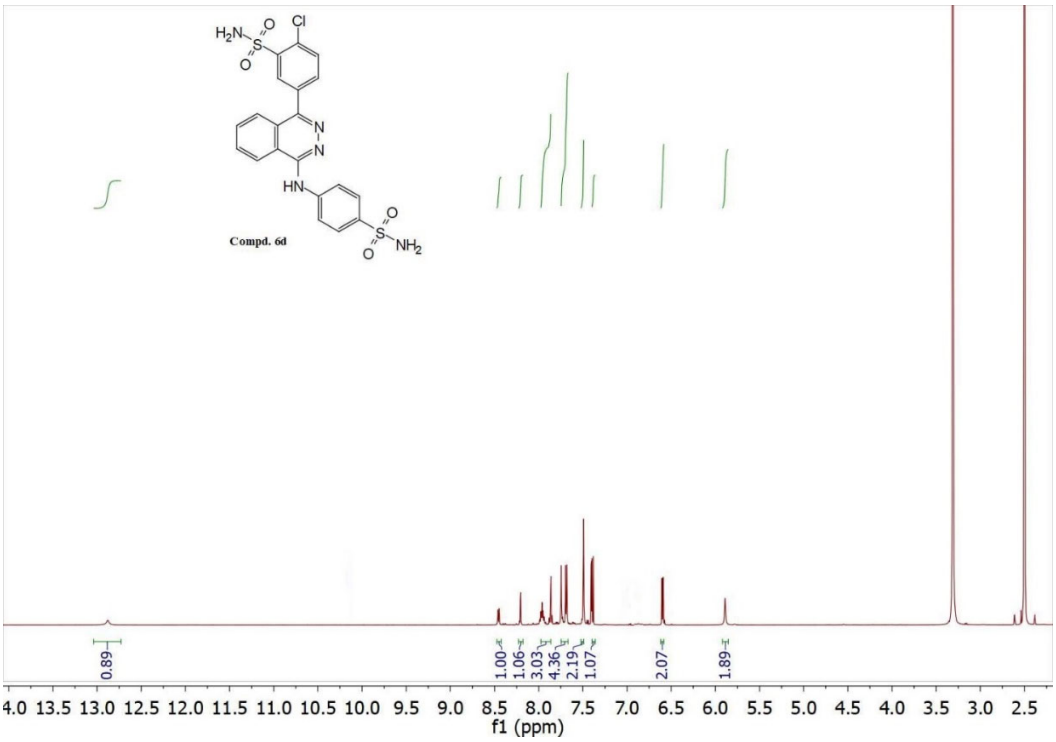


Compd. 6c

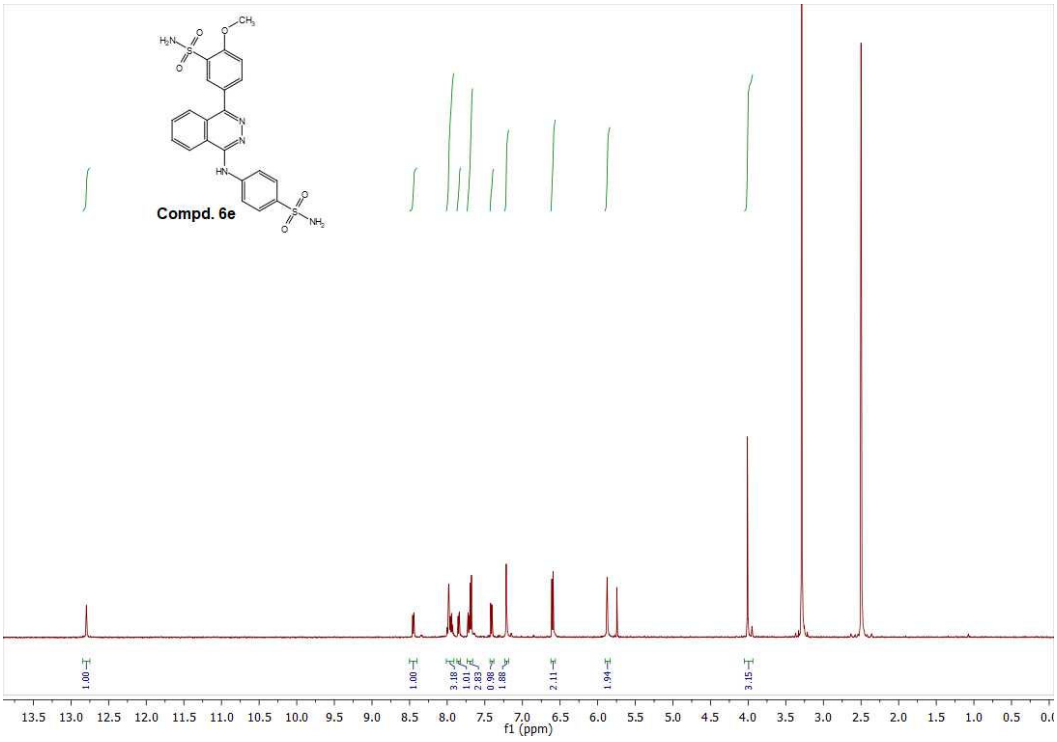

Compd. 6c
0.97
1.00
0.99
3.16
1.04
1.02
2.76
1.90
1.80
1.70
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


152.52
148.97
144.58
134.74
134.65
132.95
132.79
129.41
128.03
127.86
126.60
126.56
126.46
126.34
112.50
Compd. 6c
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

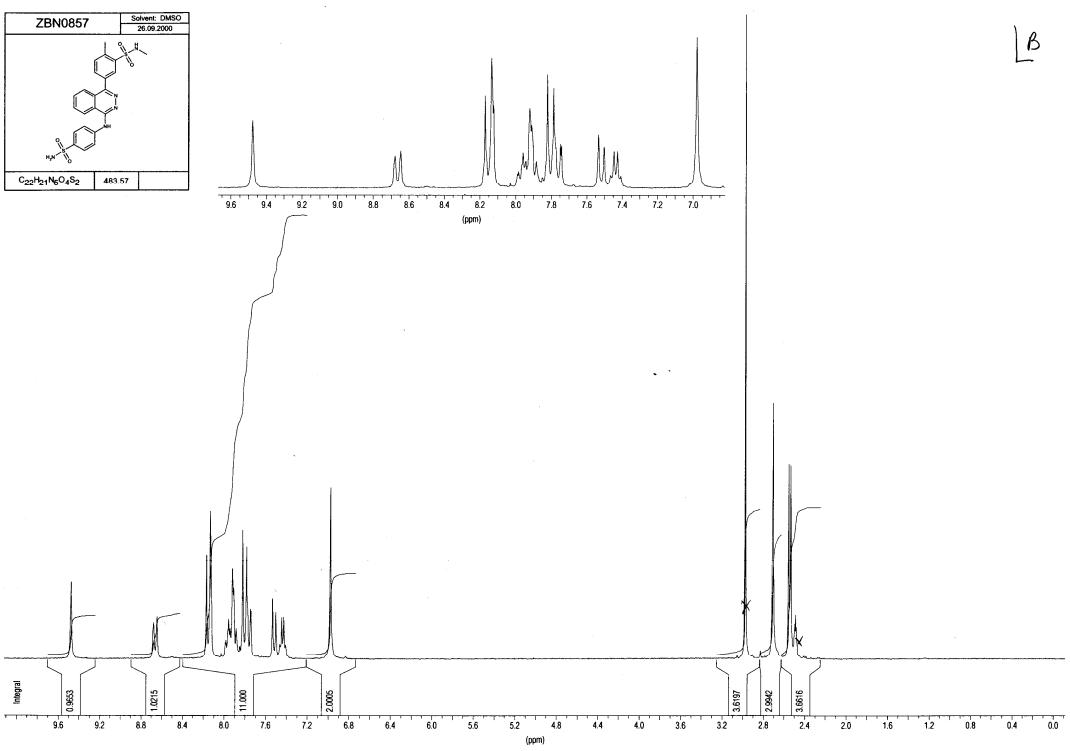
Compd. 6d



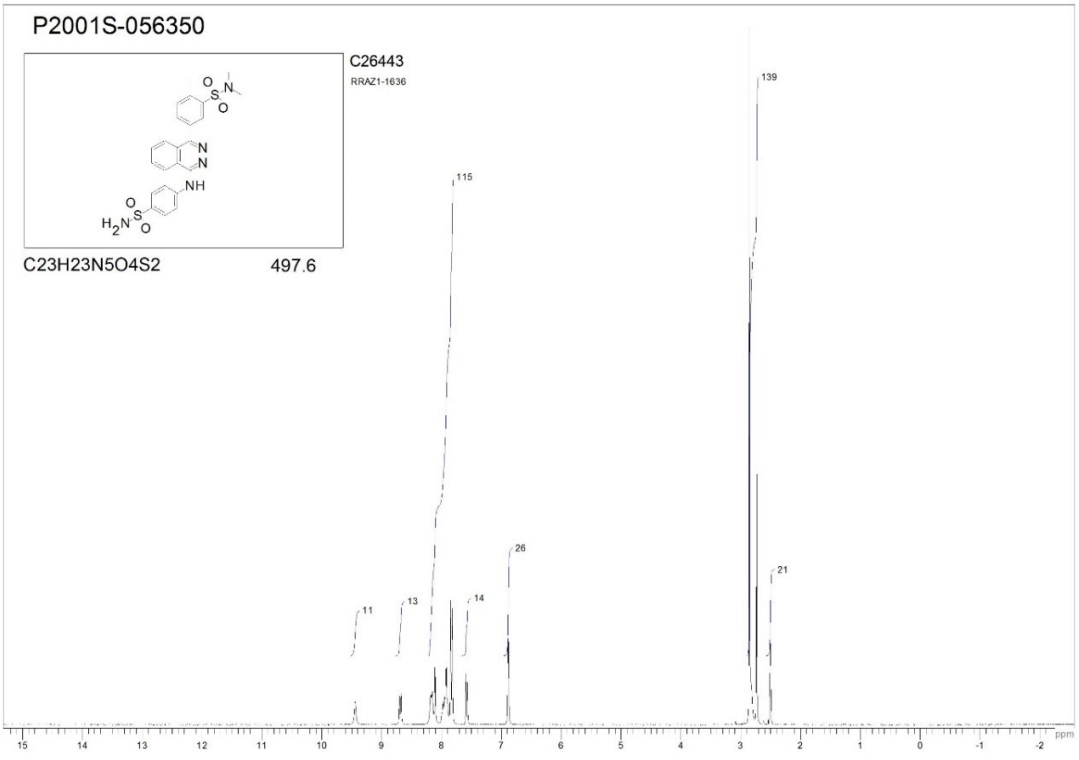
Compd. 6e



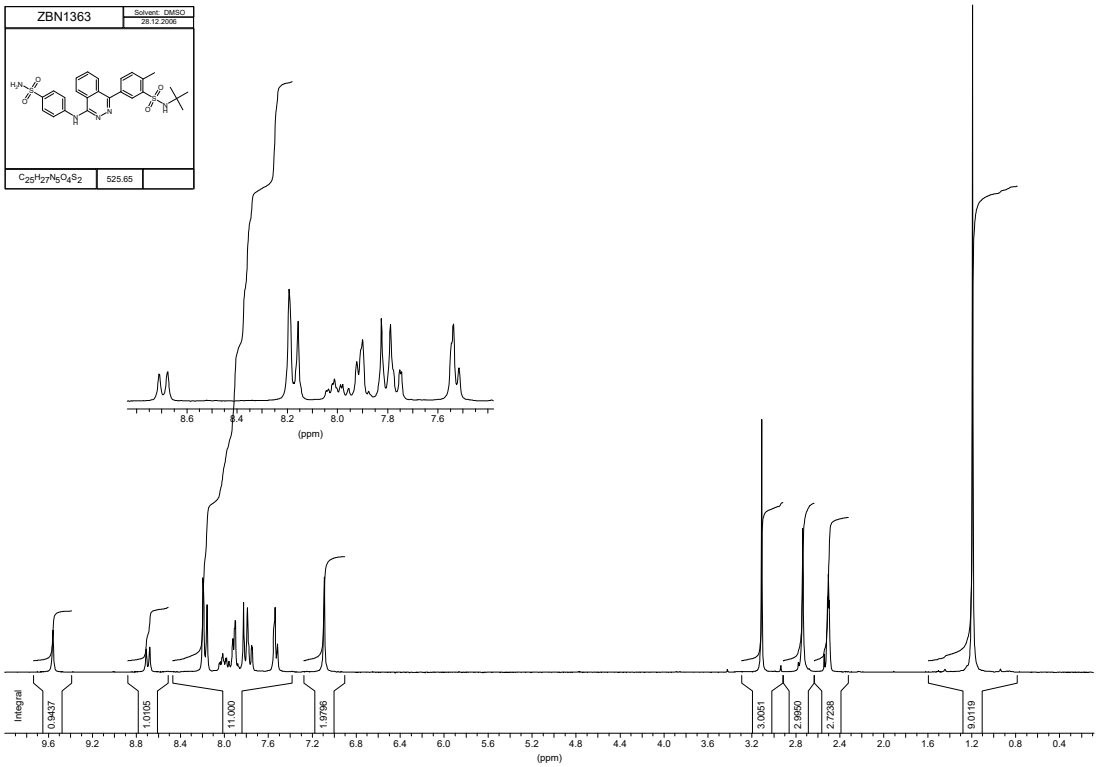
Compd. 24



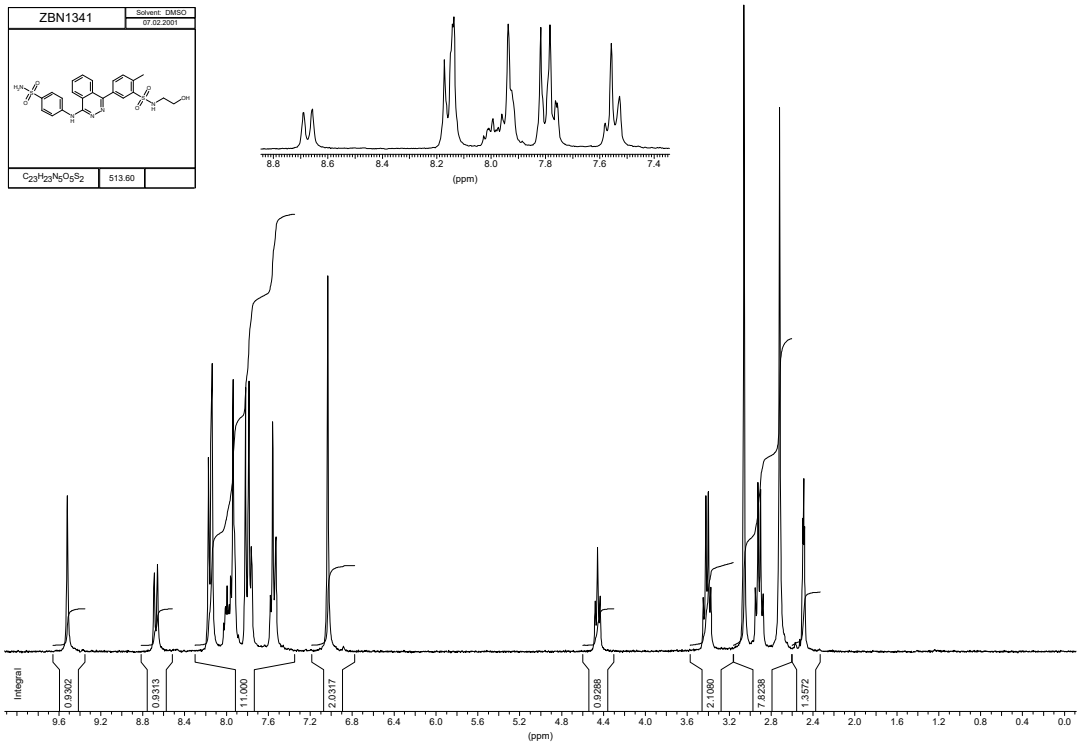
Compd. 25



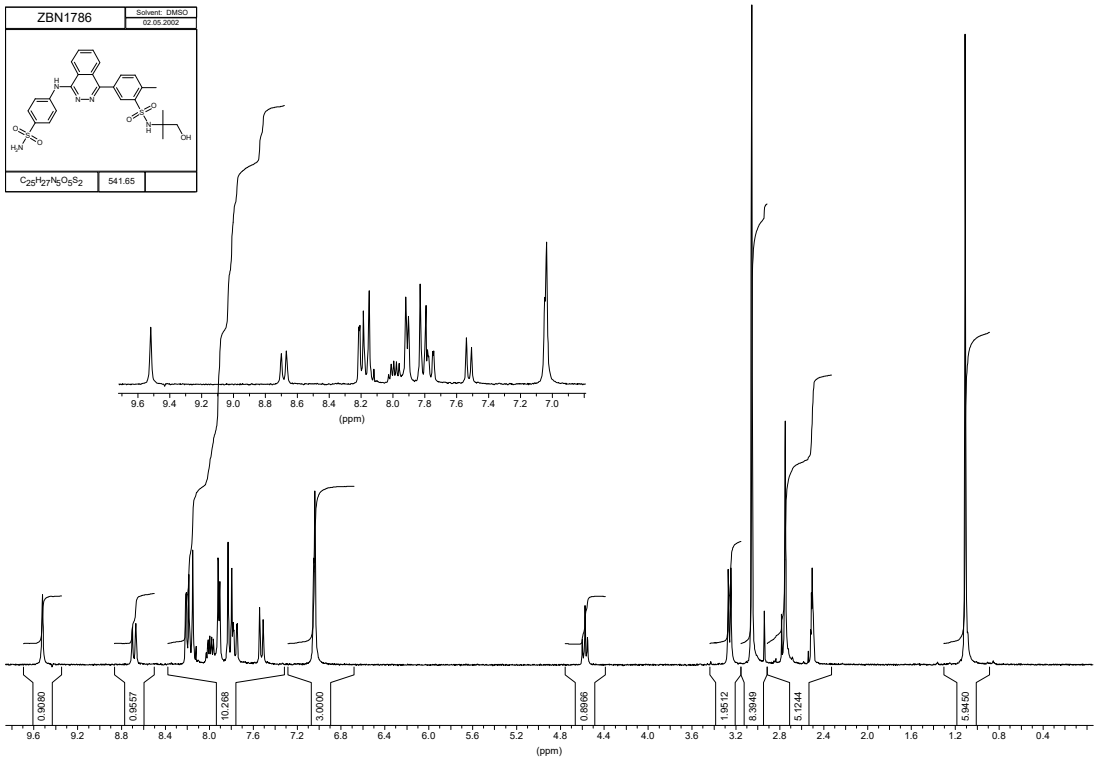
Compd. 26



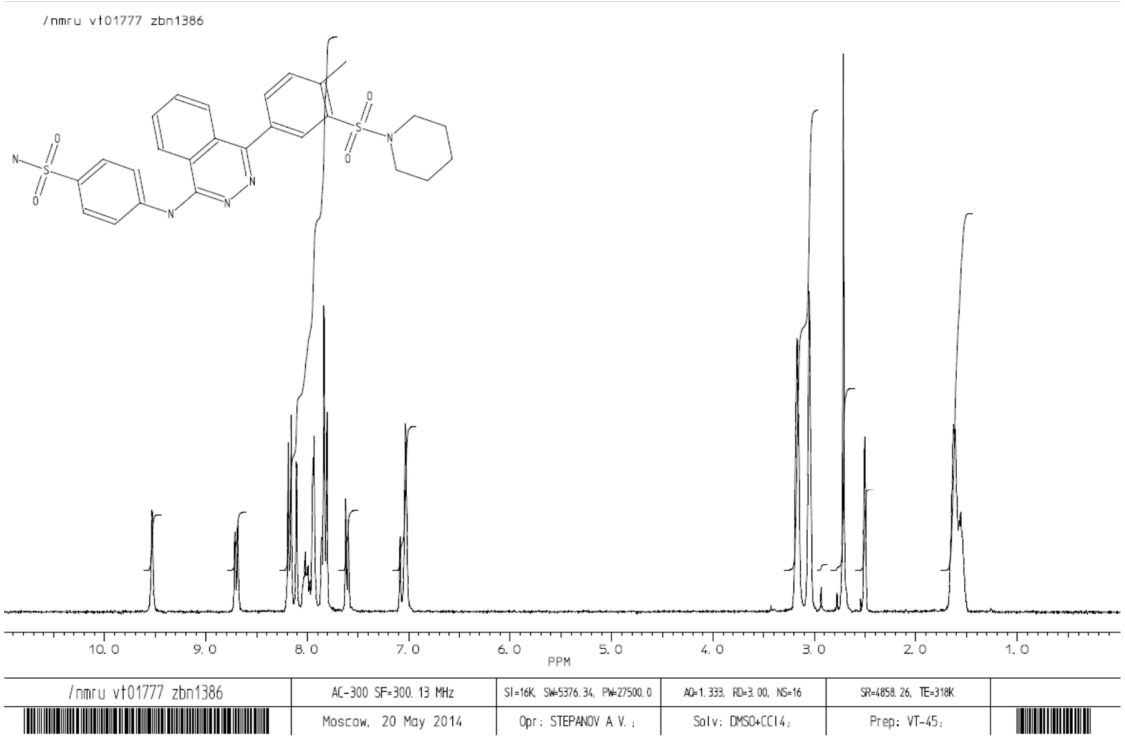
Compd. 27



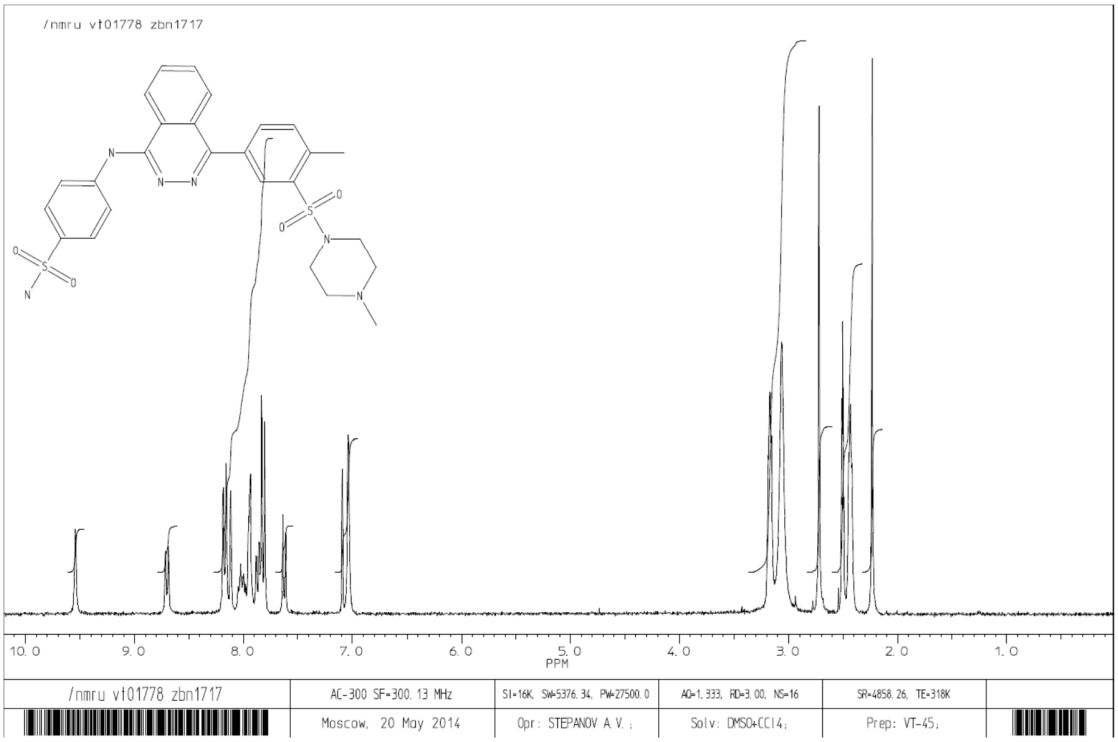
Compd. 28



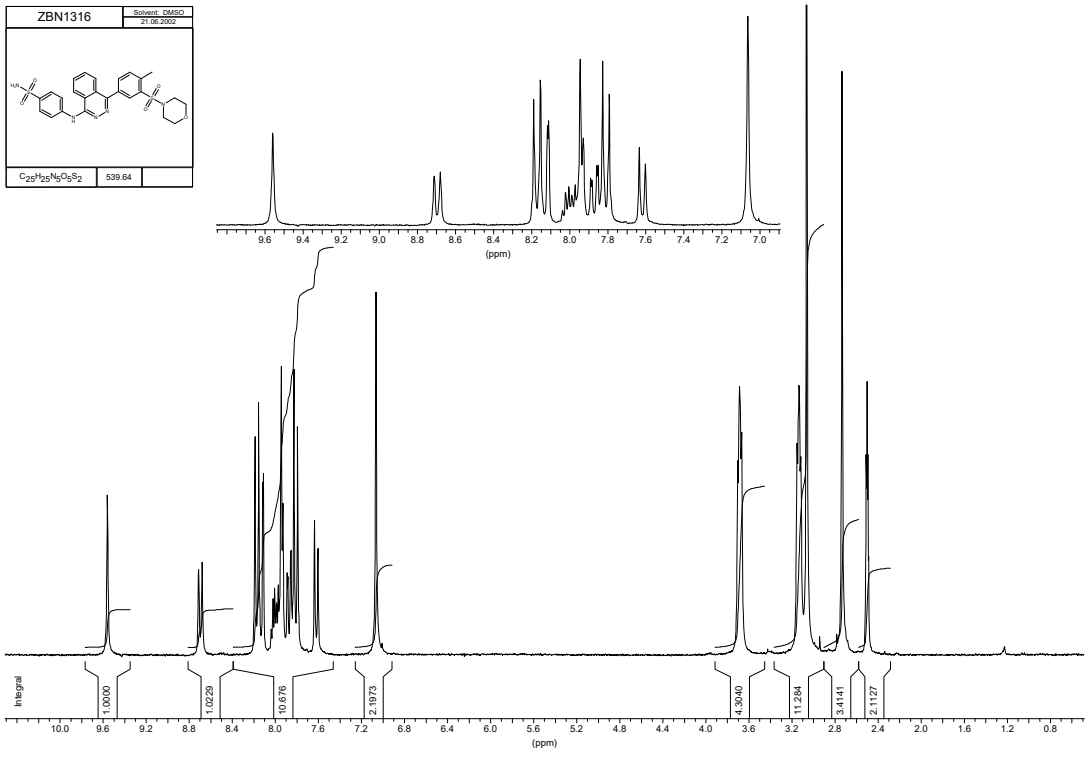
Compd. 31



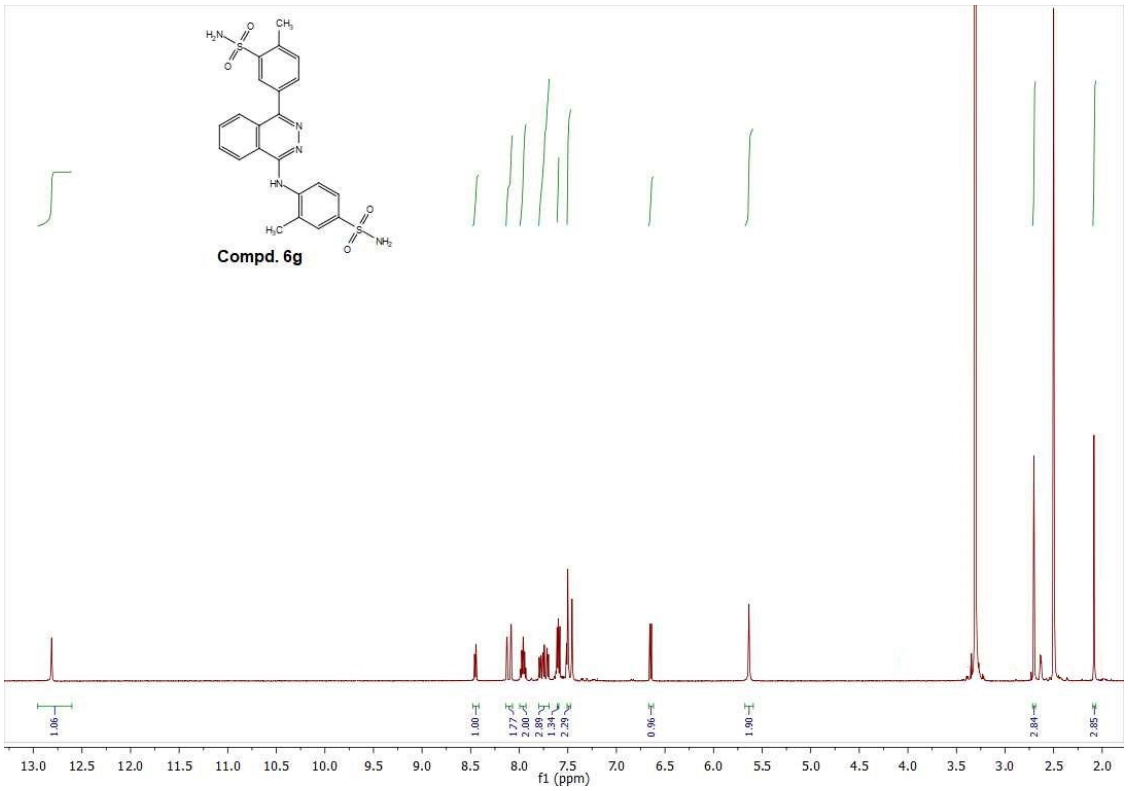
Compd. 32

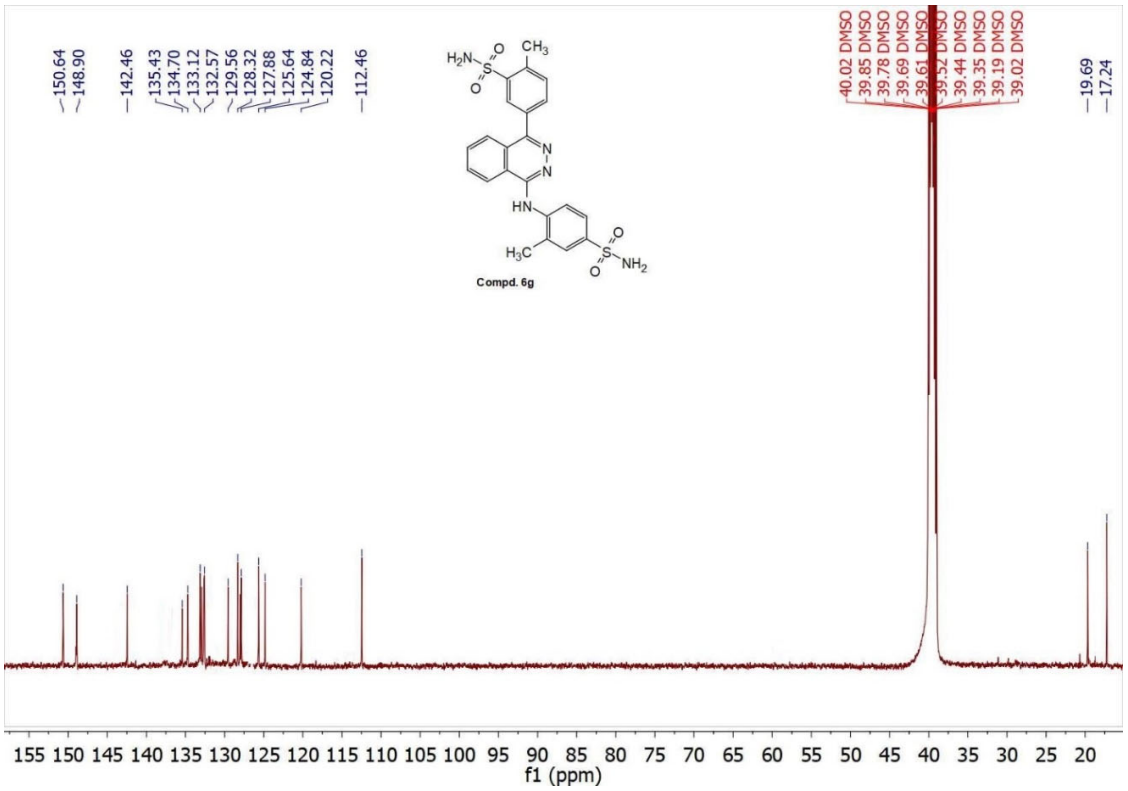


Compd. 33

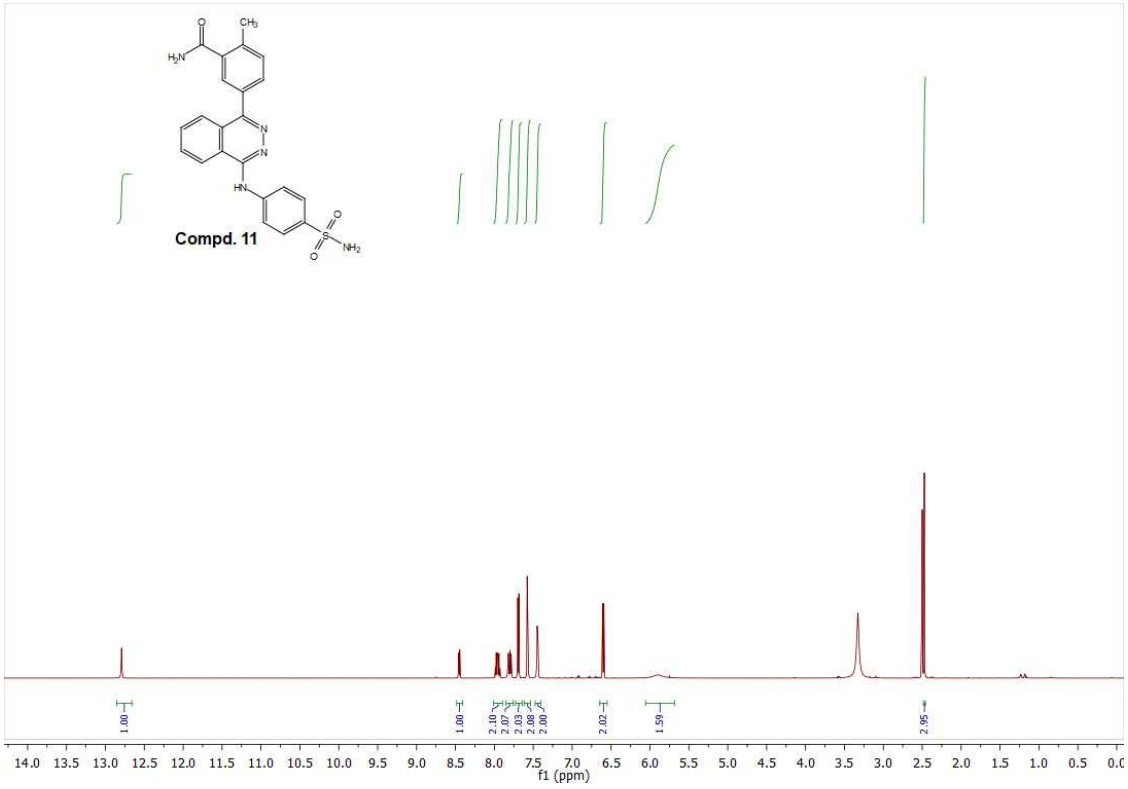


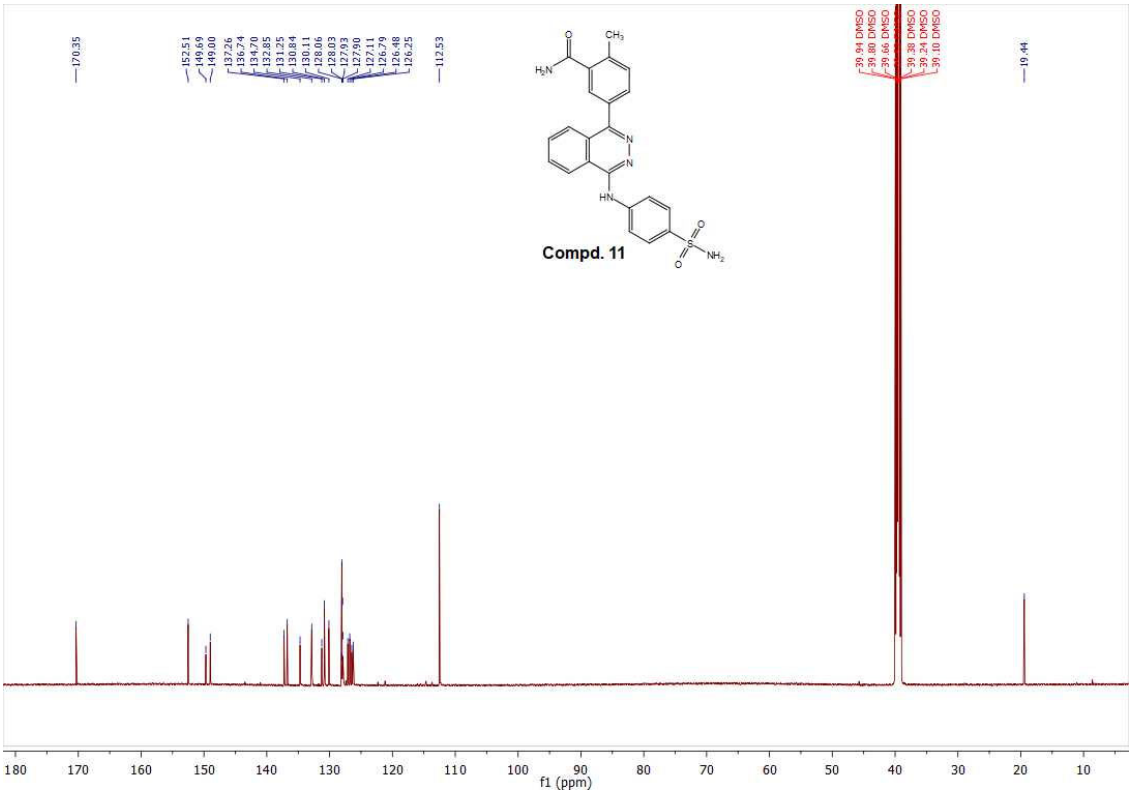
Compd. 6g


Compd. 6g
1.06
1.00
1.27
2.00
2.89
1.34
2.29
0.96
1.90
2.84
2.85
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
f1 (ppm)

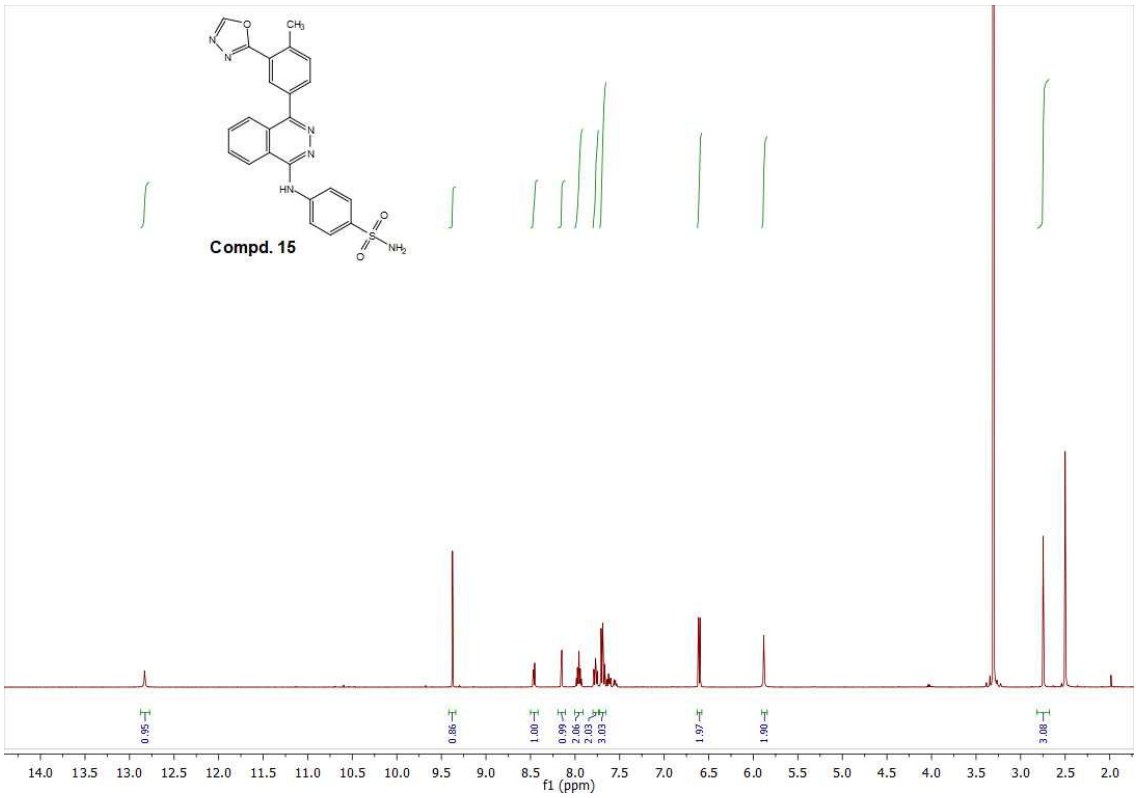

150.64
148.90
142.46
135.43
134.70
133.12
132.57
129.56
128.32
127.88
125.64
124.84
120.22
112.46
Compd. 6g
40.02 DMSO
39.85 DMSO
39.78 DMSO
39.69 DMSO
39.61 DMSO
39.52 DMSO
39.44 DMSO
39.35 DMSO
39.19 DMSO
39.02 DMSO
19.69
17.24
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

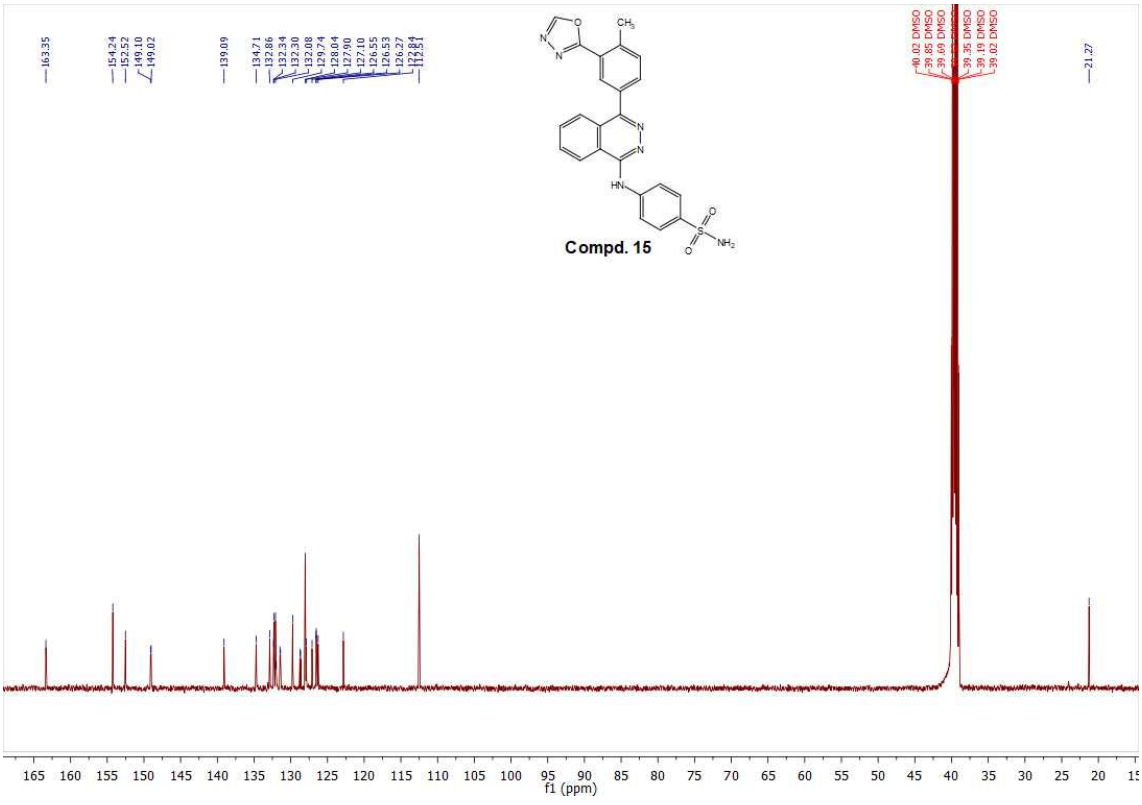
Compd. 11


Compd. 11
1.00
1.00
2.10
2.07
2.03
2.08
2.00
2.02
1.59
2.95
f1 (ppm)

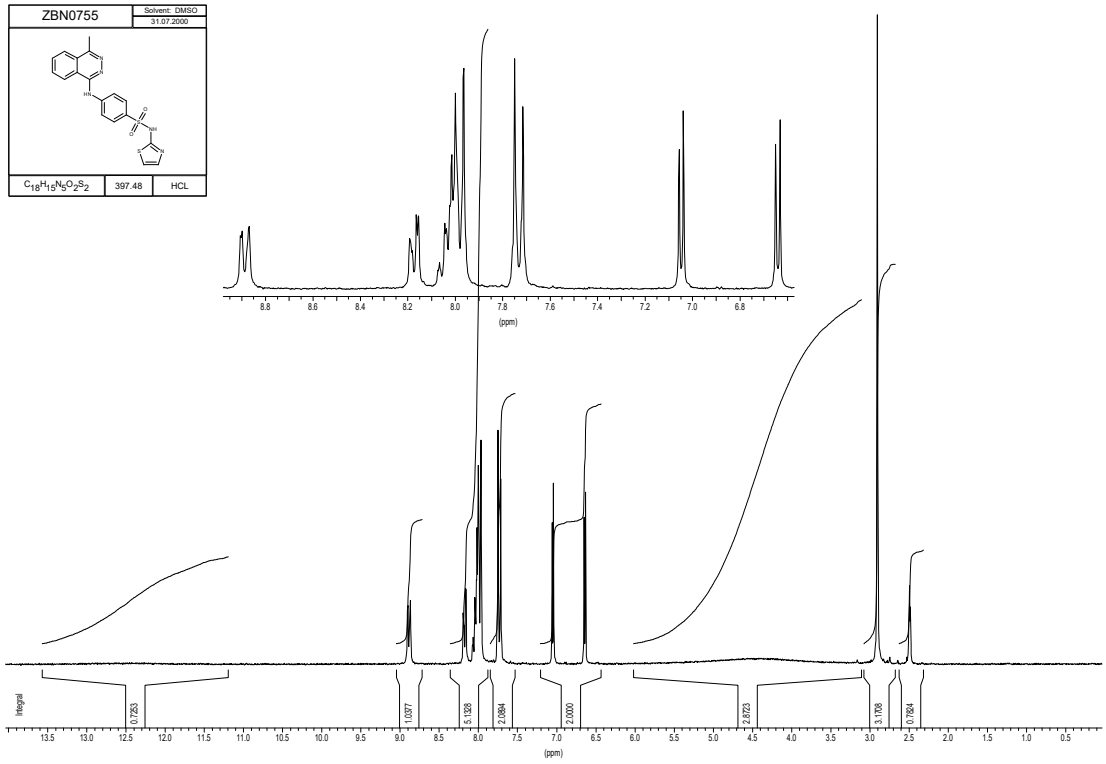

170.35
152.51
149.69
149.00
137.26
136.74
134.70
132.85
131.25
130.84
130.11
128.86
128.03
127.93
127.90
127.11
126.79
126.48
126.25
112.53
39.94 DMSO
39.80 DMSO
39.66 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
19.44
Compd. 11
f1 (ppm)

Compd. 15

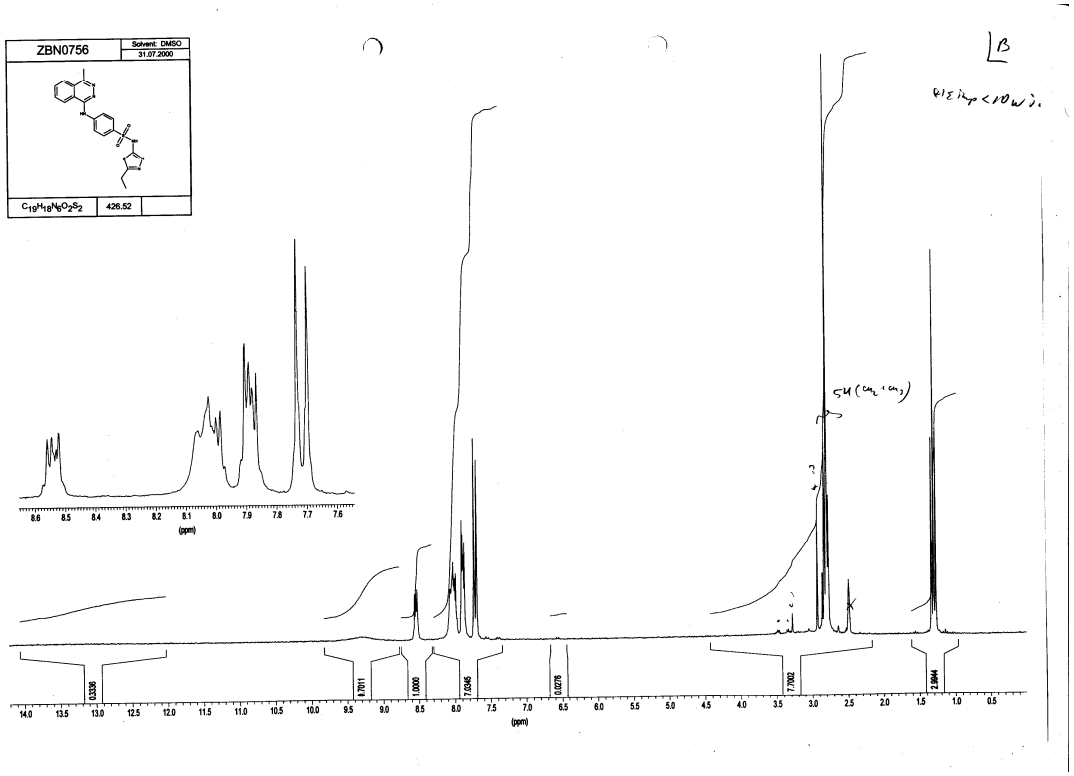

Compd. 15
0.95
0.86
1.00
0.99
2.06
2.03
3.03
1.97
1.90
3.08
f1 (ppm)


163.35
154.24
152.52
149.10
149.02
139.09
134.71
132.86
132.34
132.30
132.08
129.74
128.04
127.90
127.10
126.55
126.53
126.27
112.84
112.51
Compd. 15
40.02 DMSO
39.85 DMSO
39.69 DMSO
39.52 DMSO
39.35 DMSO
39.19 DMSO
39.02 DMSO
21.27
f1 (ppm)

Compd. 34



Compd. 36



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