ELECTRONIC SUPPLEMENTARY INFORMATION

Design, synthesis, and anti-bacterial activities of piperazine based phthalimide derivatives against superbug-MRSA

H. S. Nagendra Prasad [a*], A. P. Ananda [b&c], Amogh Mukarambi[a], Navyatha Prashanth Gaonkar.[a],,,S. Sumathi[d]., H. P. Spoorthy[e] and P.Mallu[a].

[a]*Department of Chemistry, Sri Jayachamarajendra College of Engineering, JSS Science and Technology University, Mysuru-570 006, Karnataka, India.*

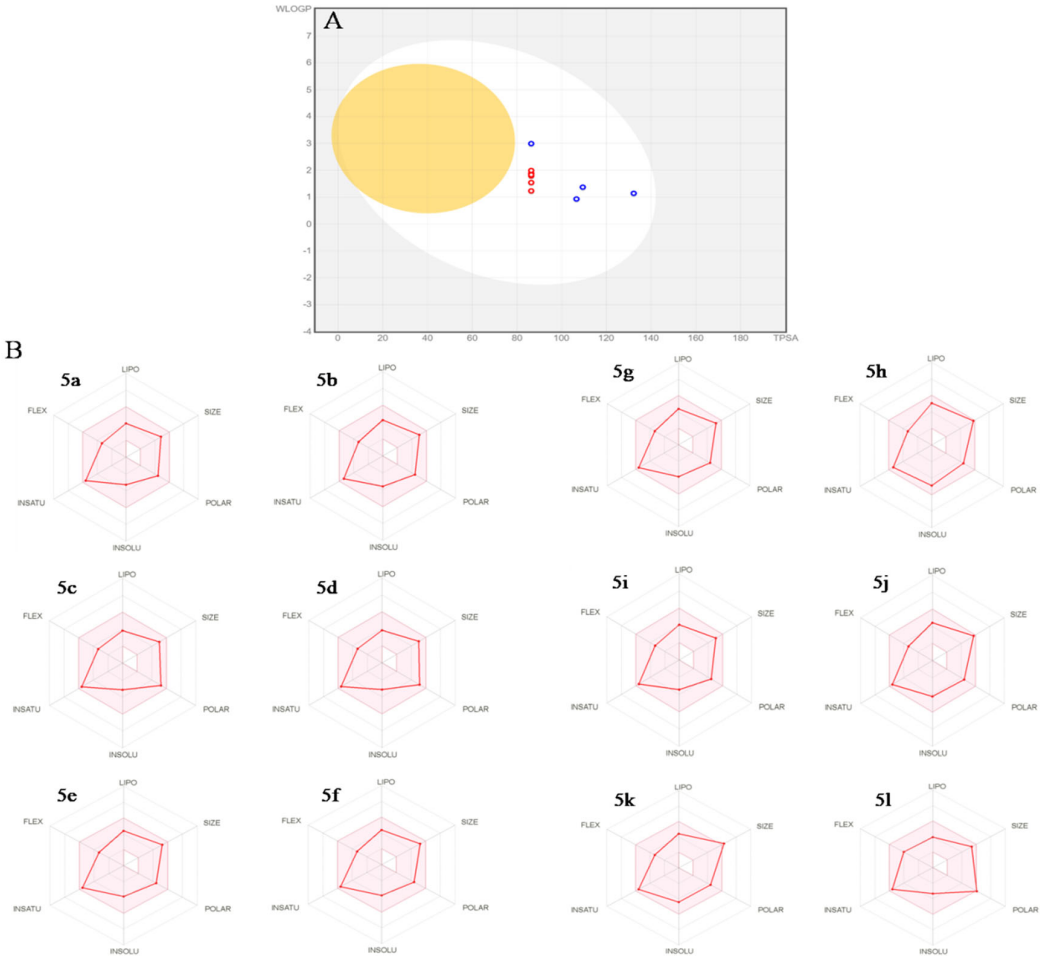
[b]*Centre for Research and Evaluation, Bharathiar University, Coimbatore, 641046, Tamil Nadu, India.*

[c]*Ganesh Consultancy and Analytical Services, Hebbal Industrial Area, Mysuru, 570016, Karnataka, India.*

[d]*Department of Biochemistry, Biotechnology and Bioinformatics, Avinashilingam institute for Homescience and higer education for Women, Coimbatore-641043.*

[e]*Department of Microbiology, JSS College of Arts, Commerce and Science (Autonomous)., Ooty Road, Mysuru-25*

*** Correspondence author: Email: nprasad@jssstuniv.in**



Supplementary Figure S1 : Bioavailability radar graph of 5(a-l) (pink area reflects the allowed values of drug likeness properties of the molecule.

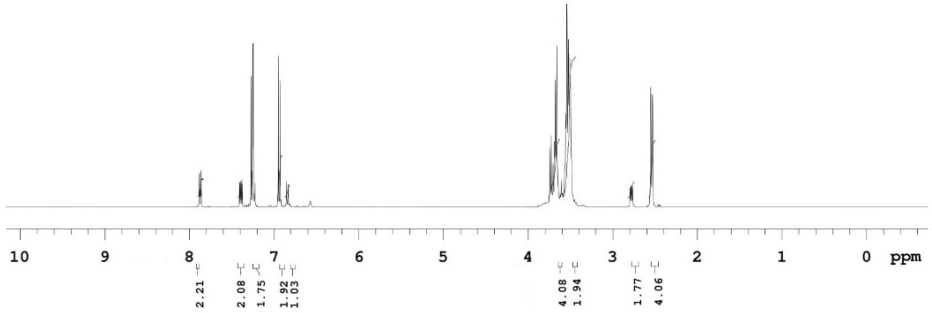
NMR and LC-MS data of new compounds

[NOTE:A. ^{1}H NMR spectra,**B.**^{13}C NMR spectra,**C.** FTIRand**D.**LC-MS]

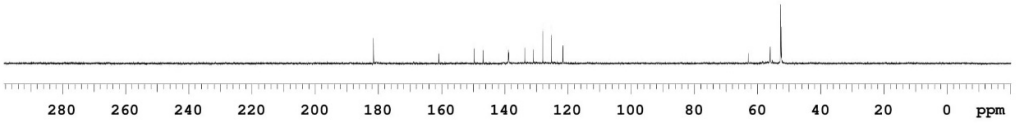
Supplementary Figure S2: Compound (5a)

2-(2-(4-(phenylsulfonyl) piperazin-1-yl) ethyl) isoindoline-1, 3-dione

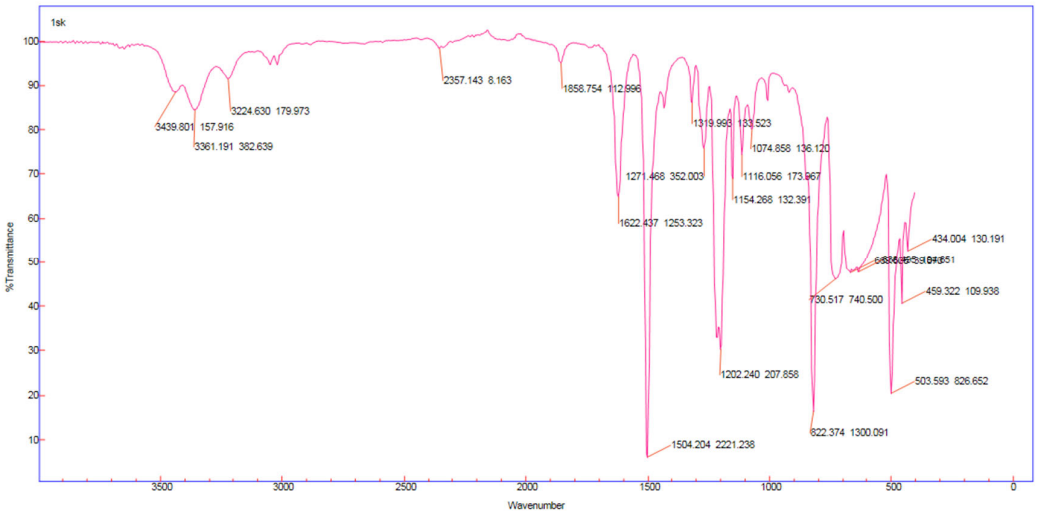
A



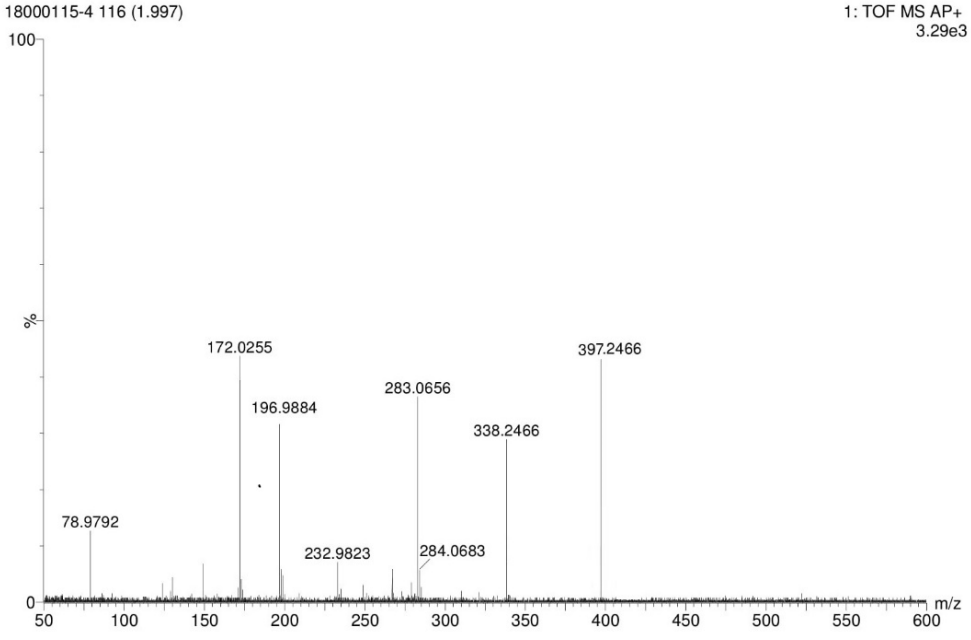
B



C


1sk
%Transmittance
Wavenumber
3439.801 157.916
3361.191 382.639
3224.630 179.973
2357.143 8.163
1858.754 112.996
1622.437 1253.323
1504.204 2221.238
1319.998 133.523
1271.468 352.003
1154.268 132.391
1116.056 173.967
1074.858 136.120
1202.240 207.858
730.517 740.500
822.374 1300.091
434.004 130.191
459.322 109.938
503.593 826.652

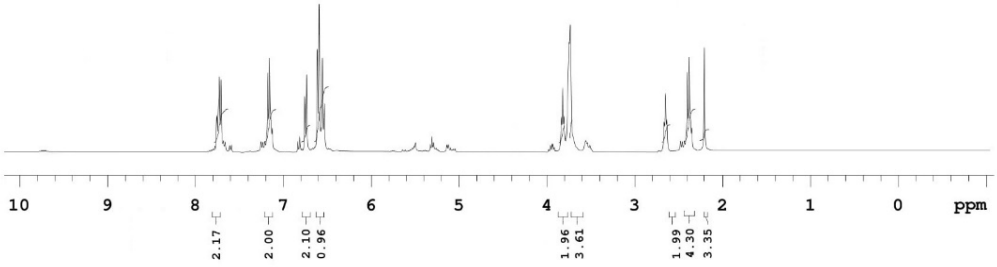
D


18000115-4 116 (1.997)
1: TOF MS AP+
3.29e3
%
m/z
172.0255
196.9884
283.0656
338.2466
397.2466
78.9792
232.9823
284.0683

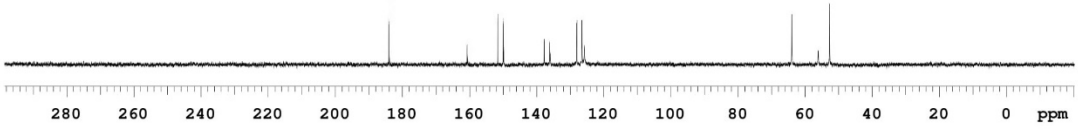
Supplementary Figure S3: Compound (5b)

(2-(2-(4-tosylpiperazin-1-yl) ethyl) isoindoline-1, 3-dione

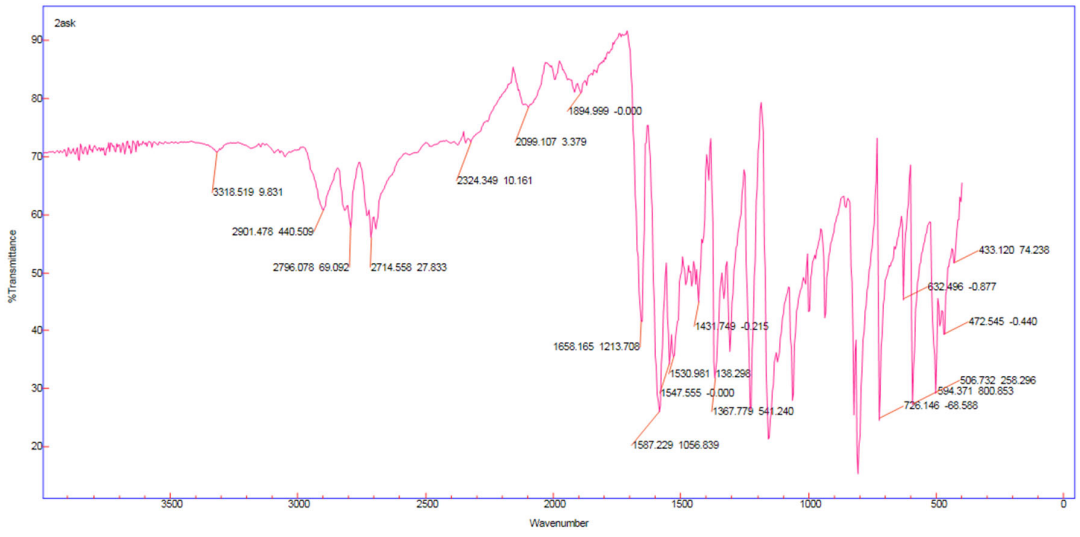
A



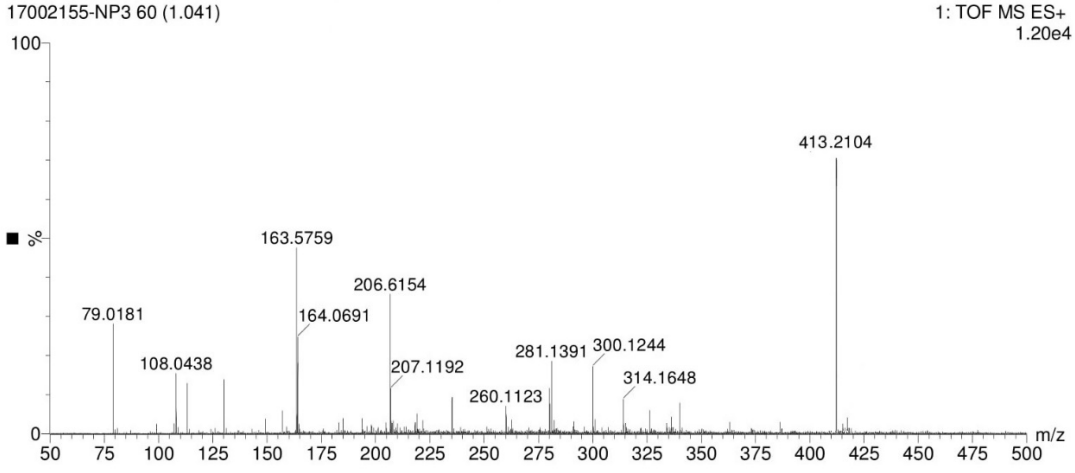
B



C


2ask
%Transmittance
Wavenumber
3318.519 9.831
2901.478 440.509
2796.078 69.092
2714.558 27.833
2324.349 10.161
2099.107 3.379
1894.999 -0.000
1658.165 1213.708
1587.229 1056.839
1530.981 138.298
1547.555 -0.000
1431.749 -0.215
1367.779 541.240
726.146 -68.568
632.496 -0.877
594.371 800.853
506.732 258.296
472.545 -0.440
433.120 74.238

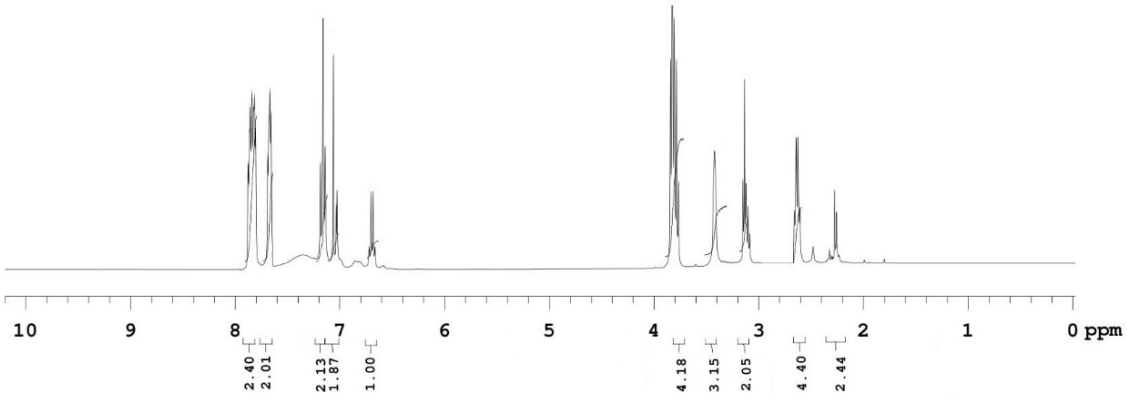
D


17002155-NP3 60 (1.041)
1: TOF MS ES+
1.20e4
100
%
0
413.2104
163.5759
206.6154
79.0181
164.0691
108.0438
207.1192
281.1391
300.1244
260.1123
314.1648
m/z
50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500

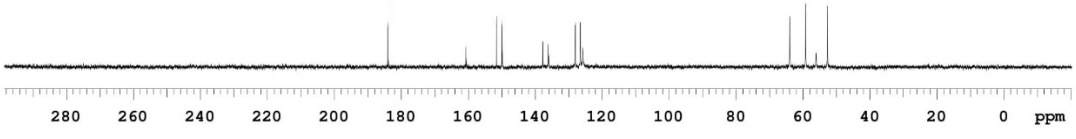
Supplementary Figure S4: Compound (5c)

2-(2-(4-((4-methoxyphenyl) sulfonyl) piperazin-1-yl) ethyl) isoindoline-1, 3-dione

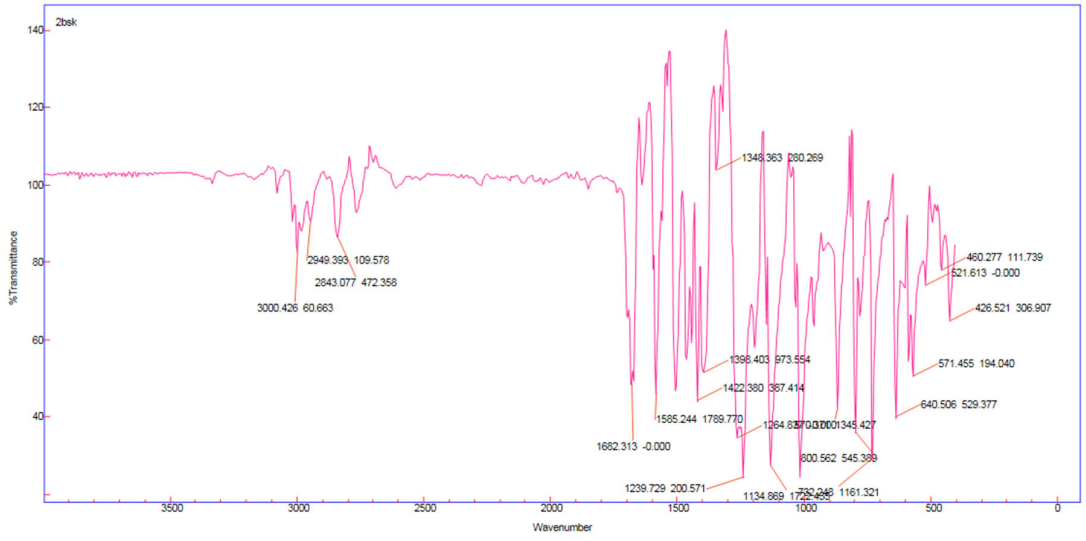
A



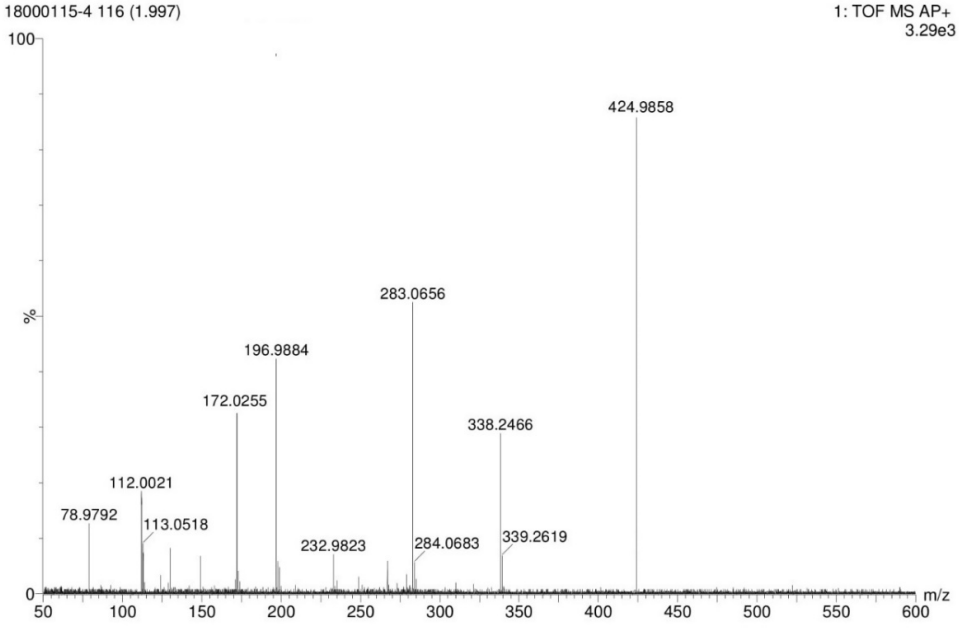
B



C


2bsk
%Transmittance
Wavenumber
3000.426 60.663
2949.393 109.578
2843.077 472.358
1682.313 -0.000
1585.244 1789.770
1398.403 973.554
1422.380 387.414
1348.363 280.269
1239.729 200.571
1134.869
1161.321
1345.427
800.562 545.389
640.506 529.377
571.455 194.040
460.277 111.739
521.613 -0.000
426.521 306.907

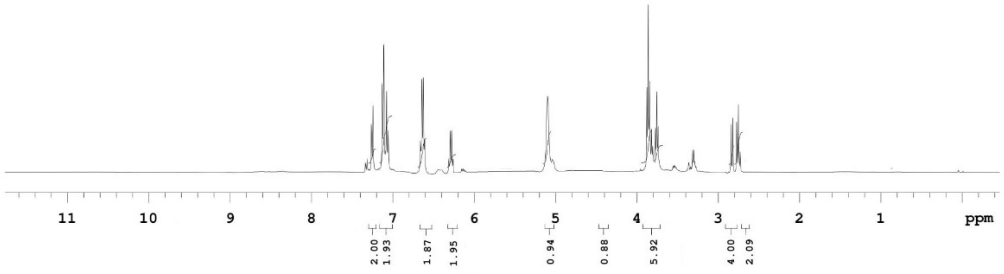
D


18000115-4 116 (1.997)
1: TOF MS AP+
3.29e3
%
m/z
424.9858
283.0656
196.9884
172.0255
338.2466
112.0021
78.9792
113.0518
232.9823
284.0683
339.2619

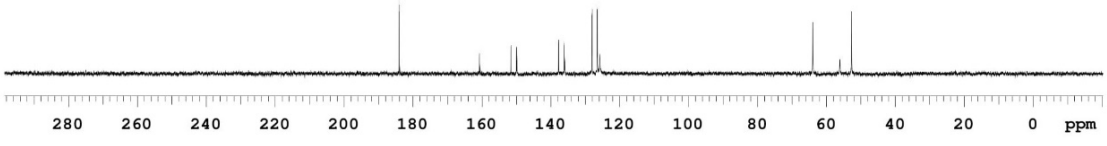
Supplementary Figure S5: Compound (5d)

2-(2-(4-((4-hydroxyphenyl) sulfonyl) piperazin-1-yl) ethyl) isoindoline-1, 3-dione

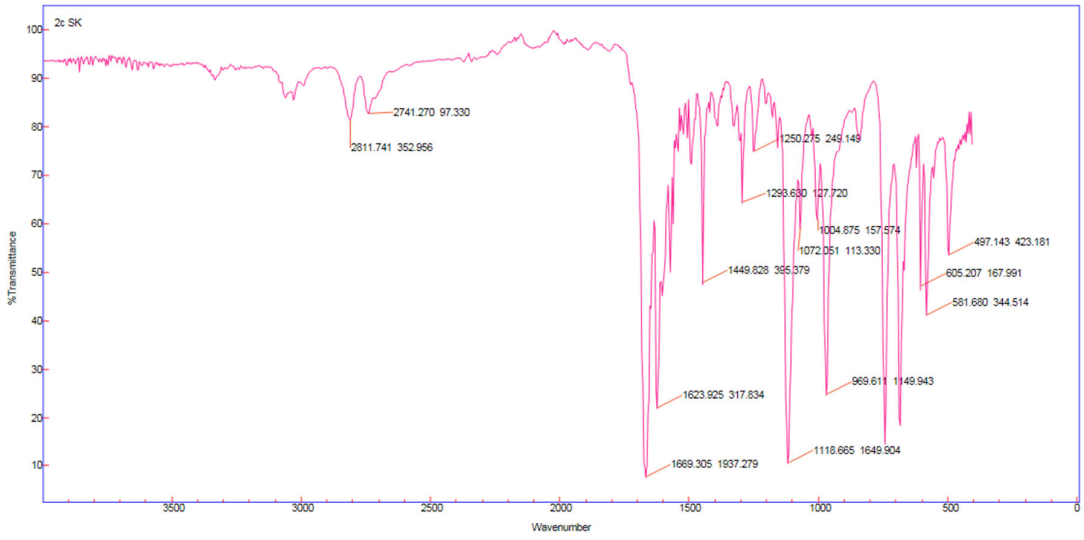
A



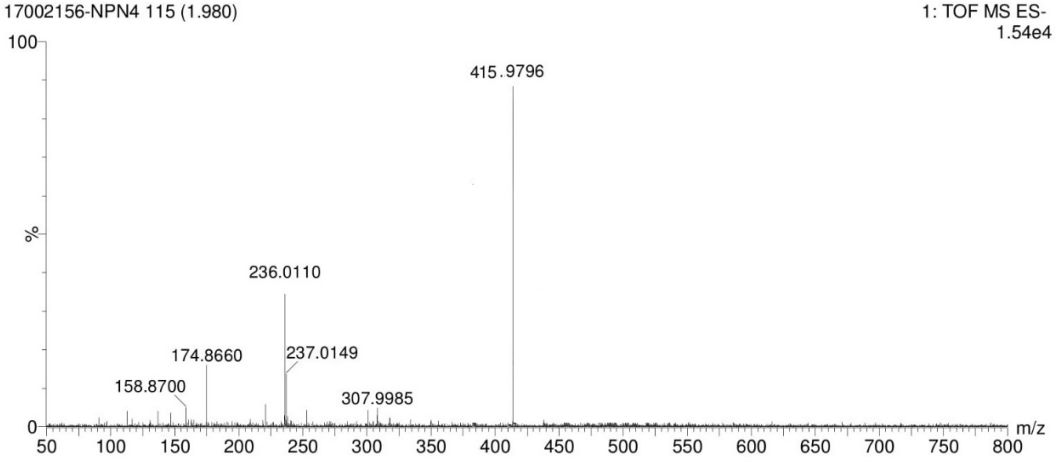
B



C


2c SK
%Transmittance
Wavenumber
2741.270 97.330
2811.741 352.956
1250.275 249.149
1293.630 127.720
1004.875 157.574
1072.051 113.330
497.143 423.181
1449.828 365.379
605.207 167.991
581.680 344.514
1623.925 317.834
969.611 1149.943
1118.665 1649.904
1669.305 1937.279

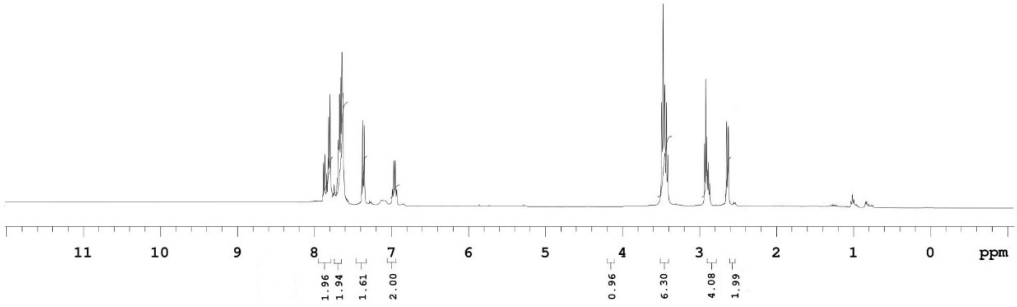
D


17002156-NPN4 115 (1.980)
1: TOF MS ES-
1.54e4
100
%
0
415.9796
236.0110
174.8660
237.0149
158.8700
307.9985
m/z
50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800

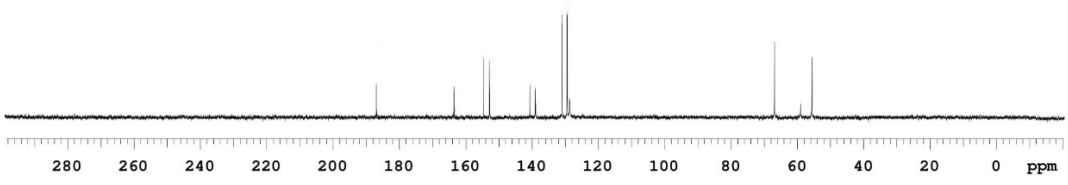
Supplementary Figure S6: Compound (5e)

2-(2-(4-((4-chlorophenyl) sulfonyl)piperazin-1-yl)ethyl)isoindoline-1,3-dione

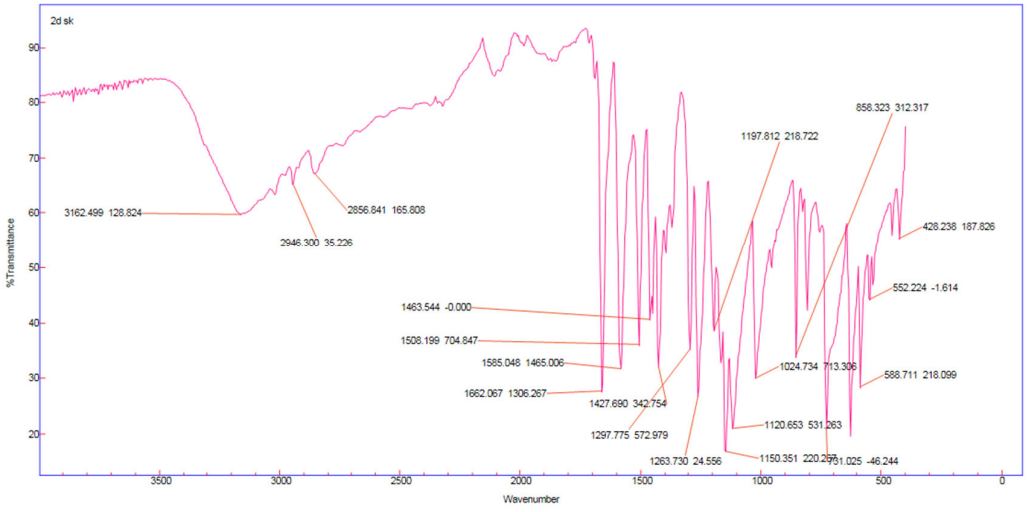
A



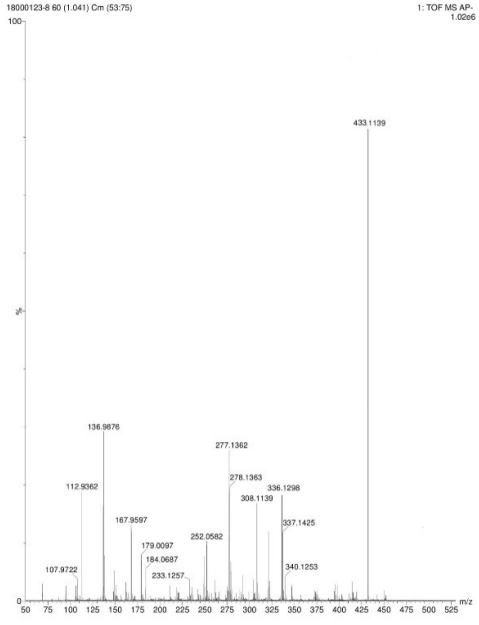
B



C


2d sk
%Transmittance
Wavenumber
3162.499 126.824
2946.300 35.226
2856.841 165.808
1463.544 -0.000
1508.199 704.847
1585.048 1465.006
1662.067 1306.267
1427.690 342.754
1297.775 572.979
1263.730 24.556
1197.812 218.722
1150.351 220.267
1120.653 531.263
1024.734 713.306
858.323 312.317
731.025 -46.244
588.711 218.099
552.224 -1.614
428.238 187.826

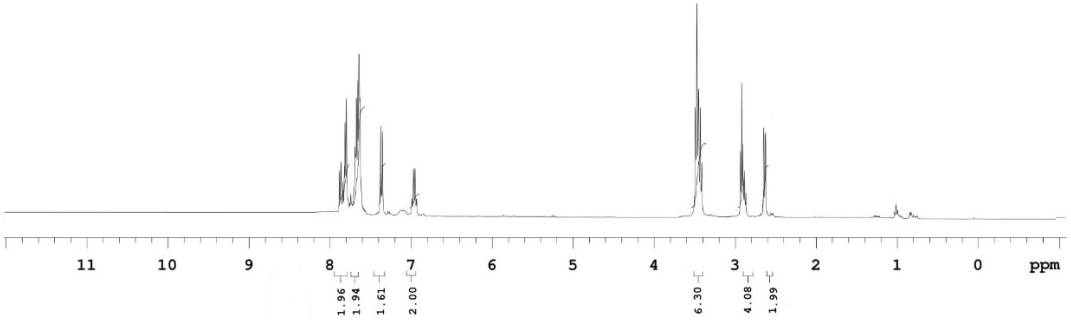
D


18000123-8 60 (1.041) Cm (53:75)
1: TOF MS AP-
1.02e6
%
m/z
433.1139
136.9876
277.1362
278.1363
336.1298
308.1139
112.9362
337.1425
167.9597
252.0582
179.0097
184.0687
107.9722
233.1257
340.1253

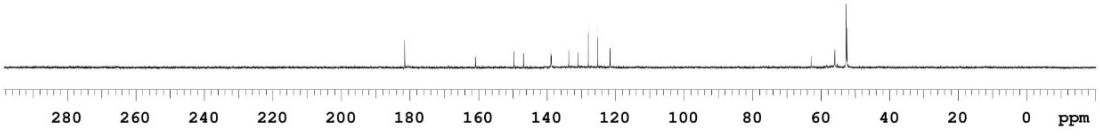
Supplementary Figure S7: Compound (5f)

2-(2-(4-((3-chlorophenyl) sulfonyl) piperazin-1-yl) ethyl) isoindoline-1, 3-dione

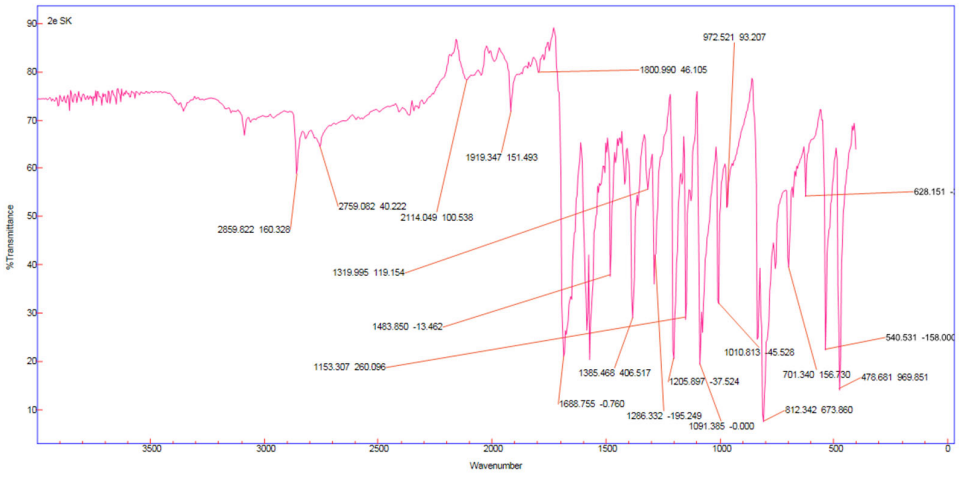
A



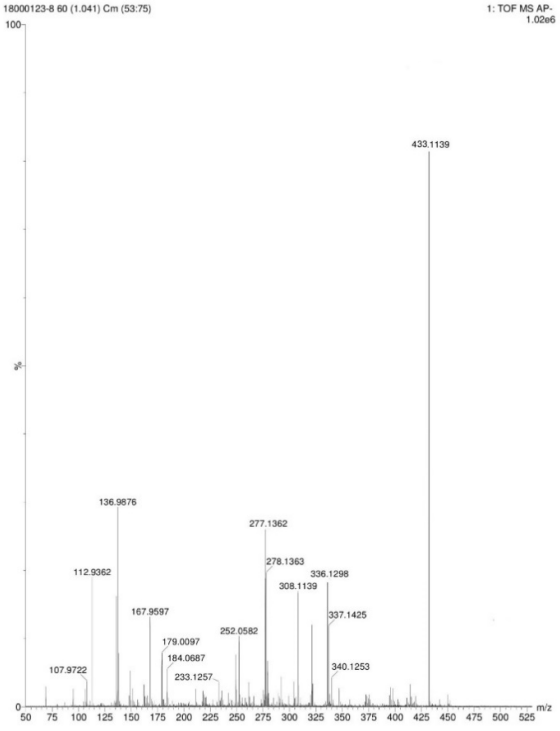
B



C


2e SK
%Transmittance
Wavenumber
972.521 93.207
1800.990 46.105
1919.347 151.493
2759.082 40.222
2114.049 100.538
2859.822 160.328
628.151
1319.995 119.154
1483.650 -13.462
1153.307 260.096
1010.813 45.526
540.531 -158.000
1385.468 406.517
1205.897 -37.524
701.340 156.730
478.681 969.851
1688.755 -0.760
1286.332 -195.249
812.342 673.860
1091.385 -0.000

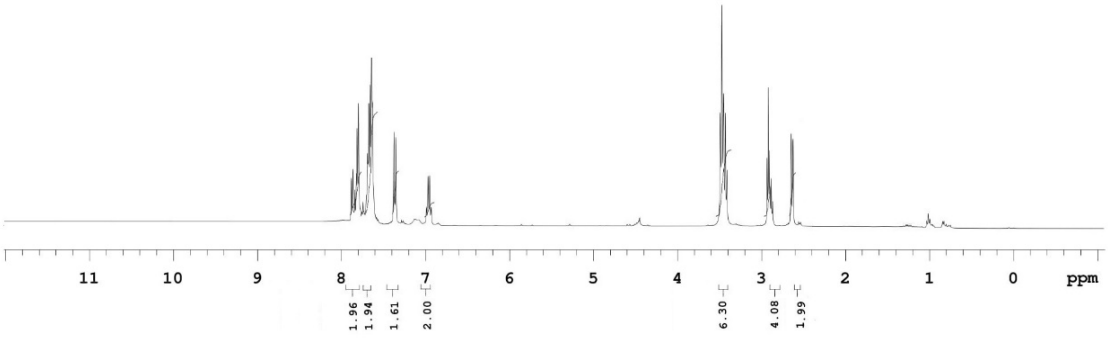
D


18000123-8 60 (1.041) Cm (53:75)
1: TOF MS AP-
1.02e6
%
m/z
433.1139
136.9876
277.1362
278.1363
112.9362
336.1298
308.1139
167.9597
337.1425
252.0582
179.0097
184.0687
107.9722
340.1253
233.1257

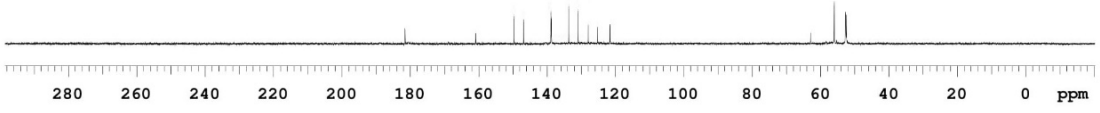
Supplementary Figure S8: Compound (5g)

2-(2-(4-((2-chlorophenyl) sulfonyl) piperazin-1-yl) ethyl) isoindoline-1,3-dione

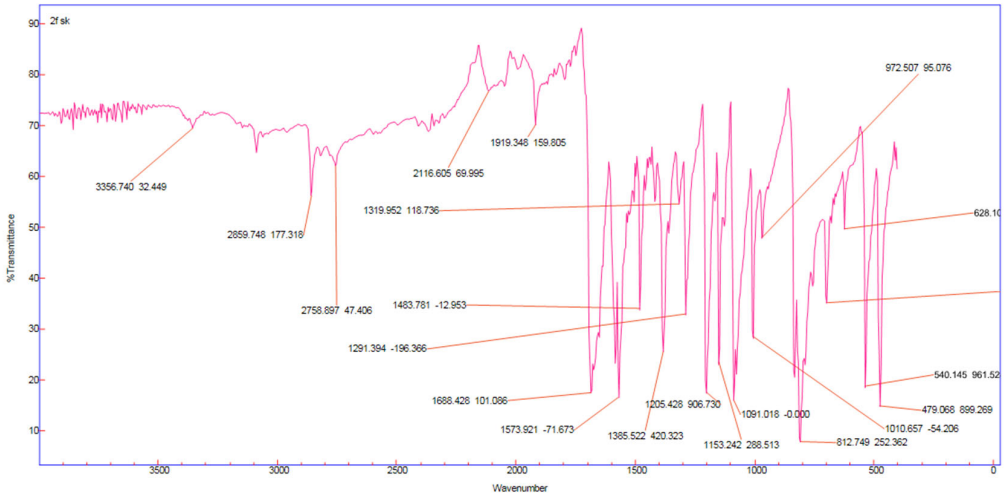
A



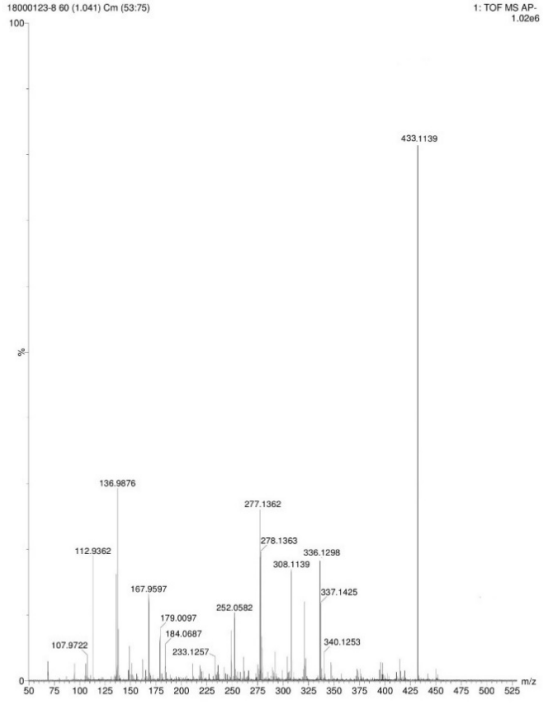
B



C


2f sk
%Transmittance
Wavenumber
3356.740 32.449
2859.748 177.318
2758.897 47.406
2116.605 69.995
1919.348 159.805
1319.952 118.736
1483.781 -12.953
1291.394 -196.366
1688.428 101.086
1573.921 -71.673
1385.522 420.323
1205.428 906.730
1153.242 288.513
1091.018 -0.000
972.507 95.076
812.749 252.362
1010.657 -54.206
479.068 899.269
540.145 961.52
628.10

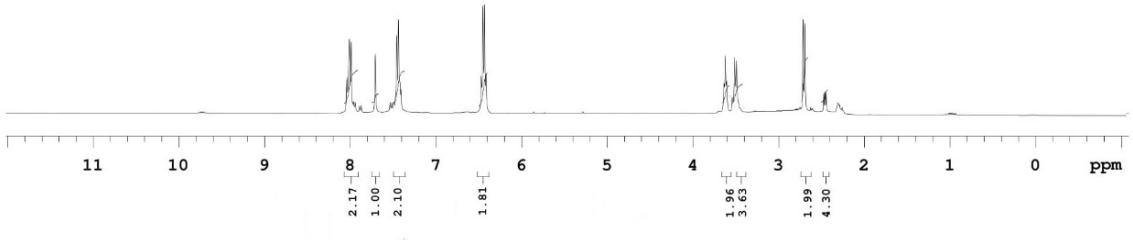
D


18000123-8 60 (1.041) Cm (53:75)
1: TOF MS AP-
1.02e6
%
m/z
433.1139
136.9876
277.1362
278.1363
112.9362
336.1298
308.1139
167.9597
337.1425
252.0582
179.0097
184.0687
107.9722
233.1257
340.1253

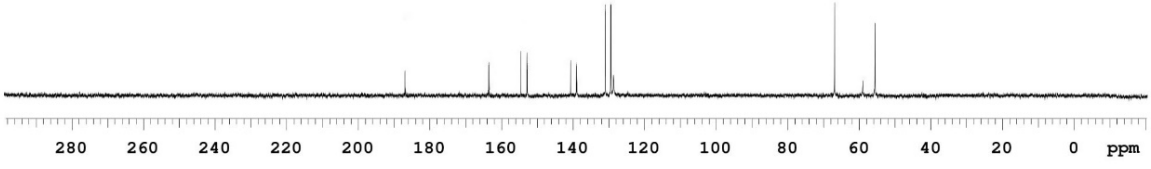
Supplementary Figure S9: Compound (5h)

22-(2-(4-((3,5-dichlorophenyl)sulfonyl)piperazin-1-yl)ethyl)isoindoline-1,3dione

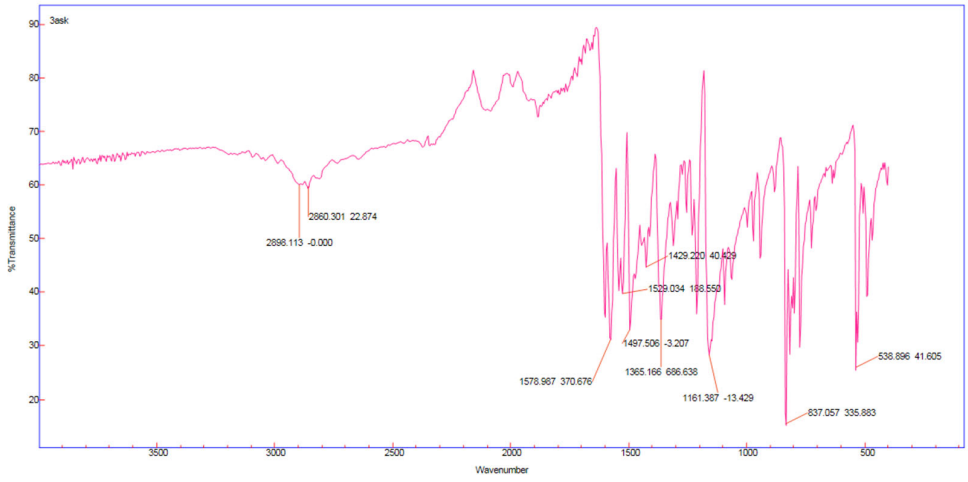
A



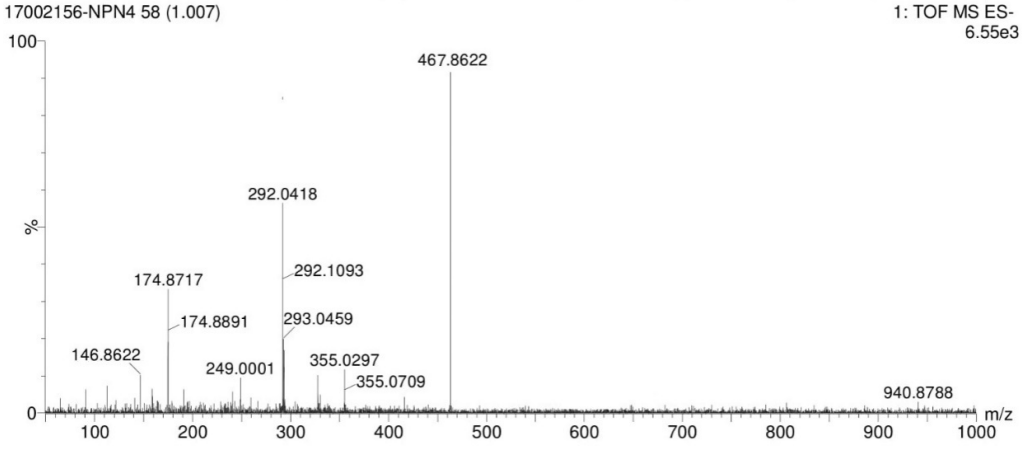
B



C


3ask
%Transmittance
Wavenumber
2860.301 22.874
2898.113 -0.000
1429.220 40.829
1529.034 188.558
1497.506 -3.207
1578.987 370.676
1365.166 686.638
1161.367 -13.429
538.896 41.605
837.057 335.883

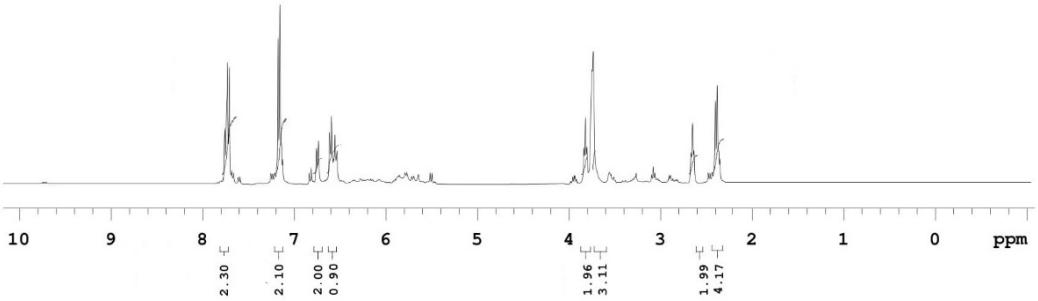
D


17002156-NPN4 58 (1.007)
1: TOF MS ES-
6.55e3
%
m/z
467.8622
292.0418
292.1093
174.8717
174.8891
293.0459
146.8622
249.0001
355.0297
355.0709
940.8788

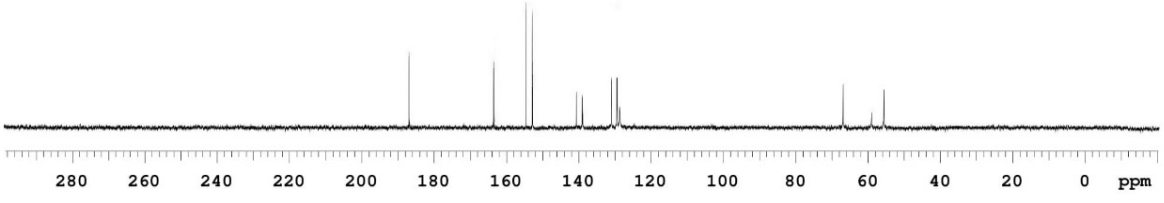
Supplementary Figure S10: Compound (5i)

2-(2-(4-((4-fluorophenyl)sulfonyl)piperazin-1-yl)ethyl)isoindoline-1,3-dione

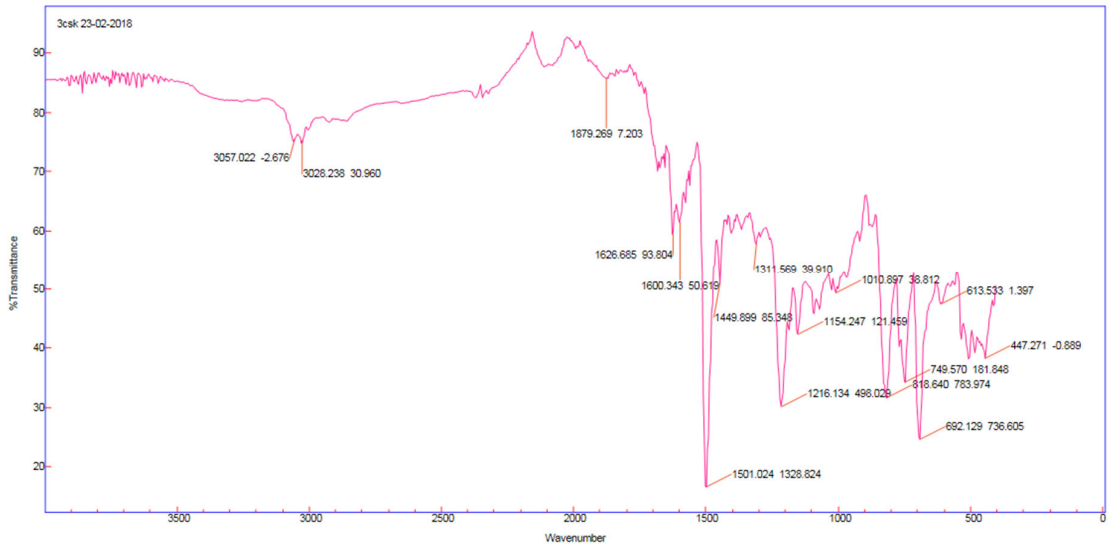
A



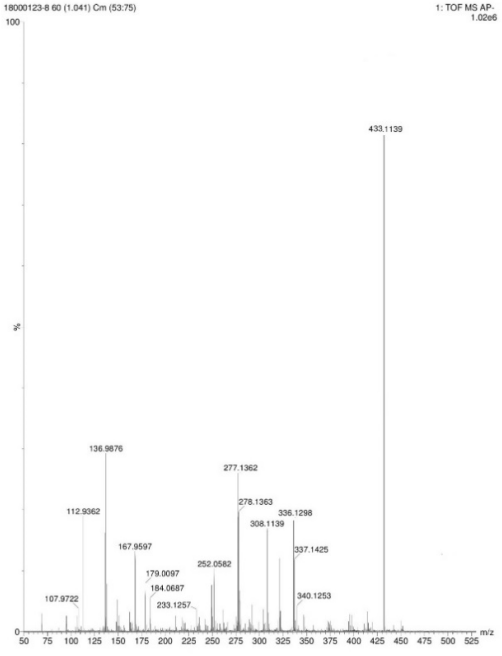
B



C


3csk 23-02-2018
%Transmittance
Wavenumber
3057.022 -2.676
3028.238 30.960
1879.269 7.203
1626.685 93.804
1600.343 50.619
1311.569 39.910
1010.897 38.812
613.533 1.397
1449.899 85.348
1154.247 121.459
447.271 -0.889
749.570 181.848
818.640 783.974
1216.134 498.028
692.129 736.605
1501.024 1328.824

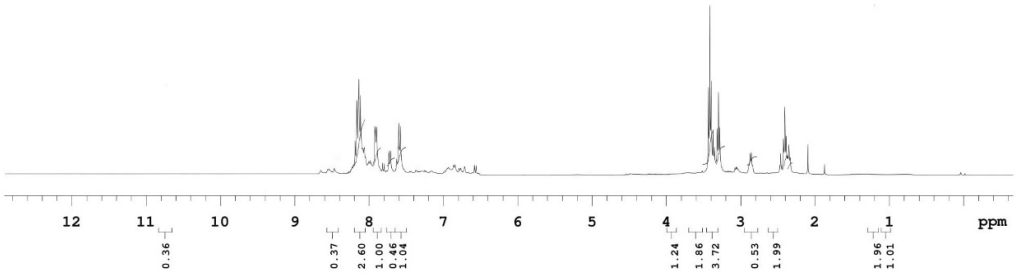
D


18000123-8 60 (1.041) Cm (53:75)
1: TOF MS AP-
1.02e6
%
m/z
433.1139
136.9876
277.1362
278.1363
112.9362
336.1298
308.1139
167.9597
337.1425
252.0582
179.0097
184.0687
340.1253
107.9722
233.1257

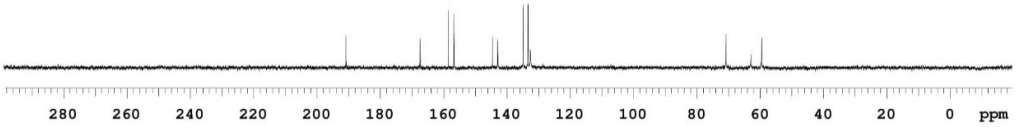
Supplementary Figure S11: Compound (5j)

2-(2-(4-((4-bromophenyl) sulfonyl) piperazin-1-yl) ethyl) isoindoline-1,3-dione

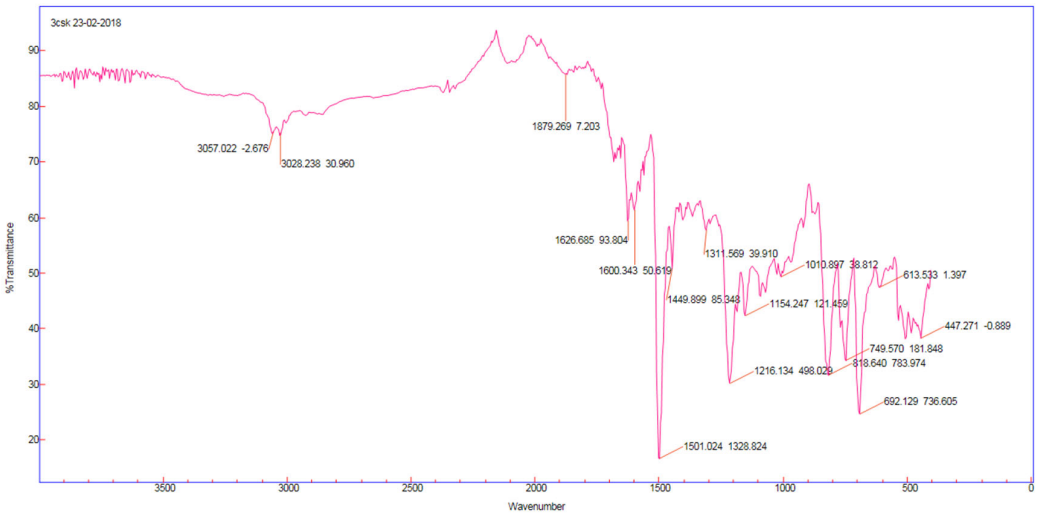
A



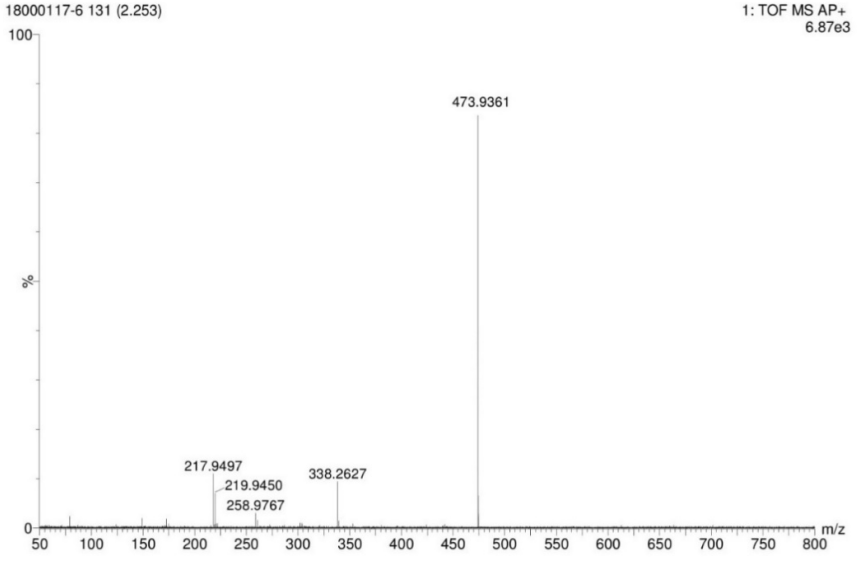
B



C


3csk 23-02-2018
%Transmittance
Wavenumber
3057.022 -2.676
3028.238 30.960
1879.269 7.203
1626.685 93.804
1600.343 50.619
1311.569 39.910
1010.897 38.812
613.533 1.397
1449.899 85.348
1154.247 121.459
447.271 -0.889
749.570 181.848
818.640 783.974
1216.134 498.029
692.129 736.605
1501.024 1328.824

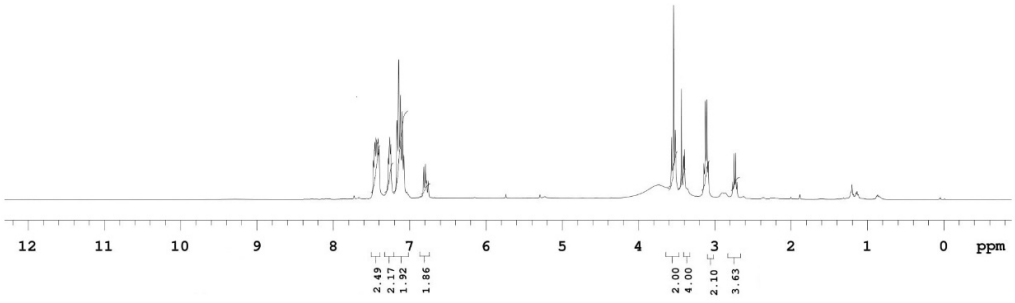
D


18000117-6 131 (2.253)
1: TOF MS AP+
6.87e3
%
m/z
473.9361
217.9497
219.9450
258.9767
338.2627

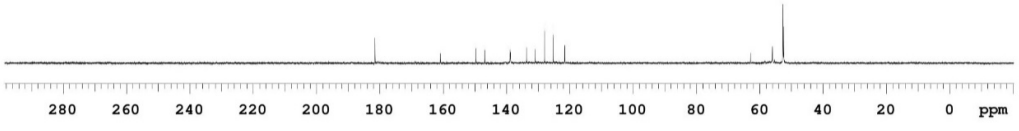
Supplementary Figure S12: Compound (5k)

2-(2-(4-((4-iodophenyl)sulfonyl)piperazin-1-yl)ethyl)isoindoline-1,3-dione

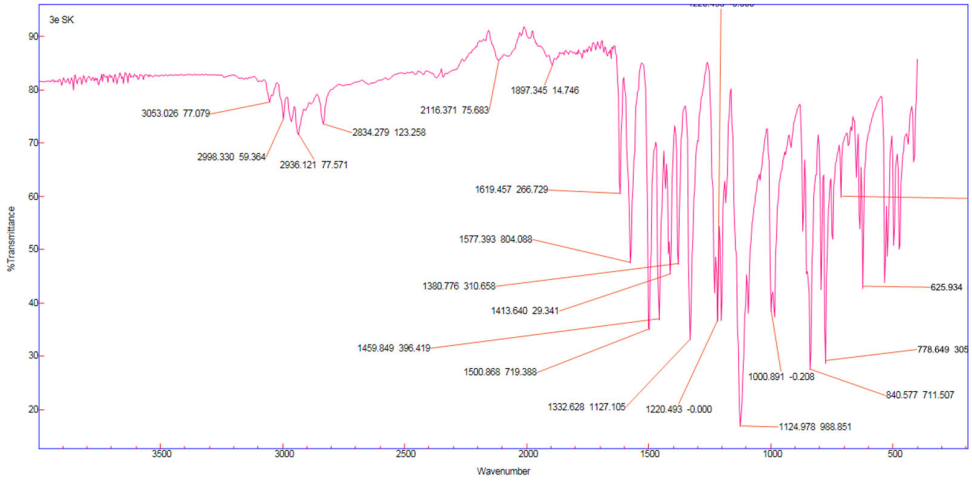
A



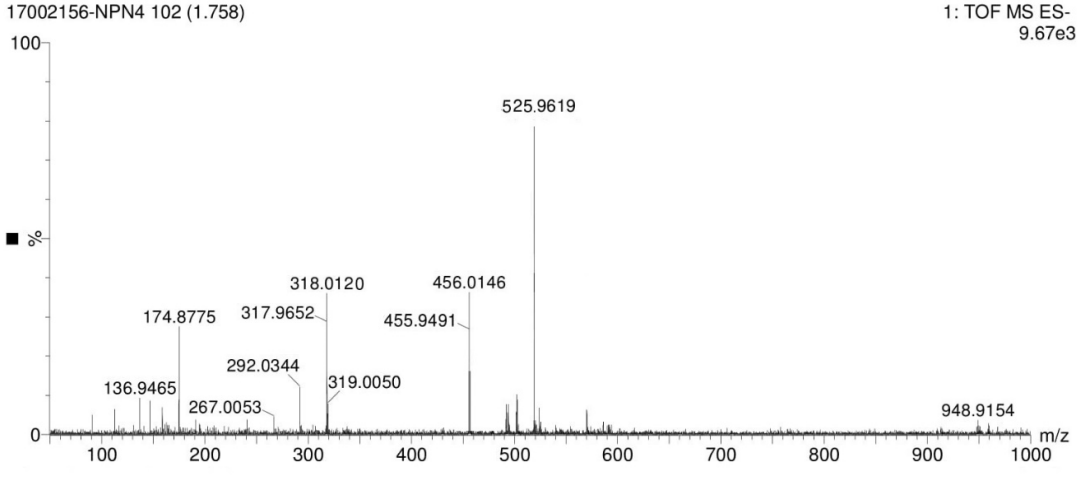
B



C


3e SK
%Transmittance
Wavenumber
3053.026 77.079
2998.330 59.364
2936.121 77.571
2834.279 123.258
2116.371 75.683
1897.345 14.746
1619.457 266.729
1577.393 804.088
1380.776 310.658
1413.640 29.341
1459.849 396.419
1500.868 719.388
1332.628 1127.105
1220.493 -0.000
1124.978 988.851
1000.891 -0.208
840.577 711.507
778.649 305
625.934

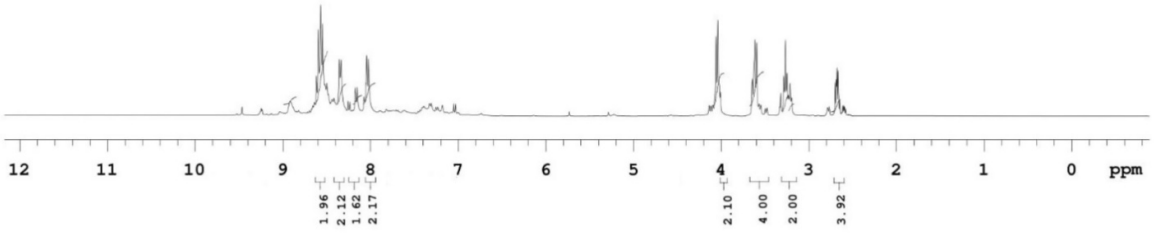
D


17002156-NPN4 102 (1.758)
1: TOF MS ES-
9.67e3
100
%
0
525.9619
318.0120
456.0146
174.8775
317.9652
455.9491
292.0344
319.0050
136.9465
267.0053
948.9154
100
200
300
400
500
600
700
800
900
1000
m/z

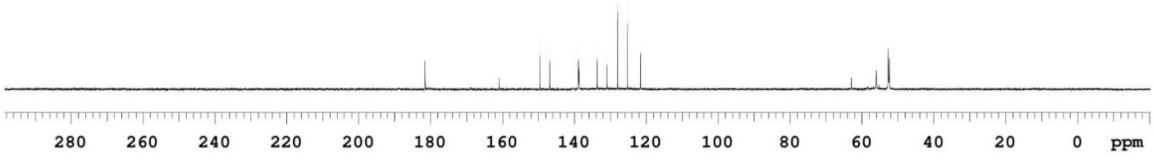
Supplementary Figure S13: Compound (5l)

2-(2-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)ethyl)isoindoline-1,3-dione

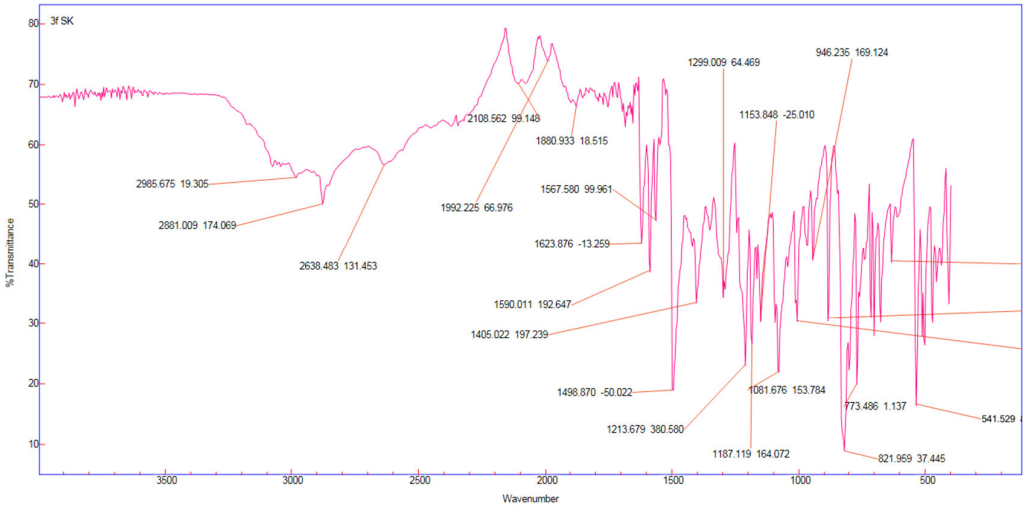
A



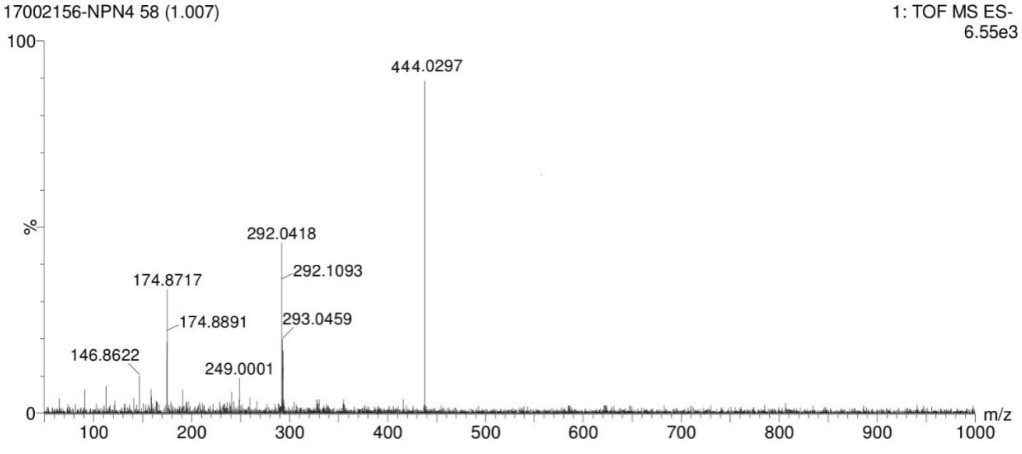
B

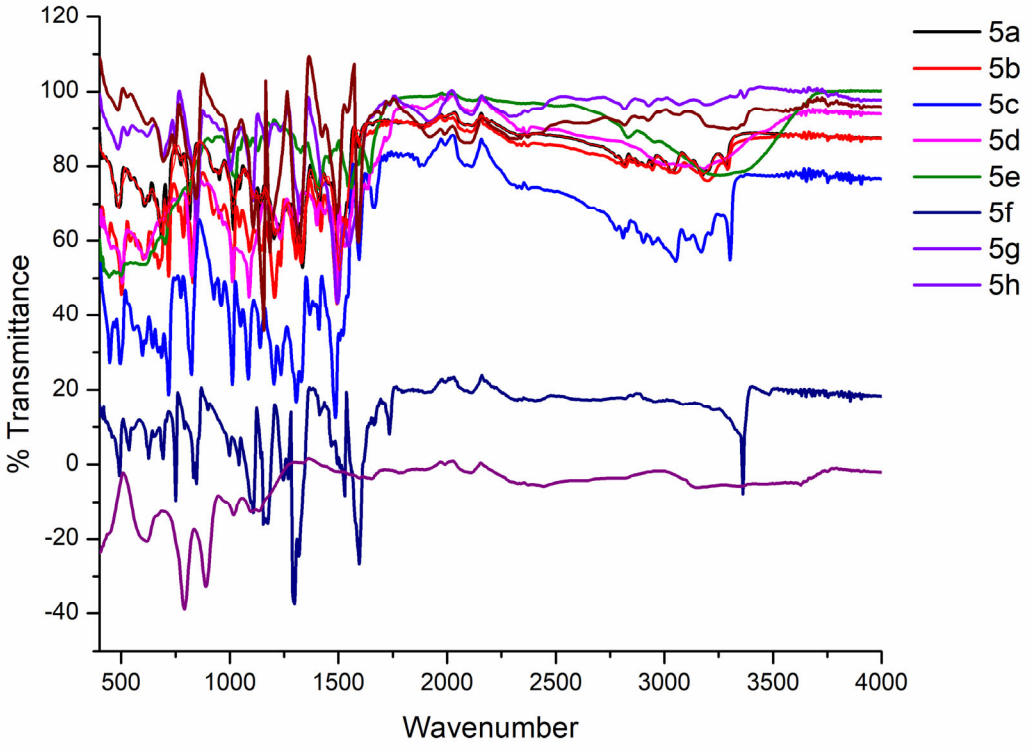


C


3f SK
%Transmittance
Wavenumber
2985.675 19.305
2881.009 174.069
2638.483 131.453
2108.562 99.148
1992.225 66.976
1880.933 18.515
1567.580 99.961
1623.876 -13.259
1590.011 192.647
1405.022 197.239
1498.870 -50.022
1213.679 380.580
1299.009 64.469
1153.848 -25.010
1081.676 153.784
1187.119 164.072
946.235 169.124
773.486 1.137
821.959 37.445
541.529

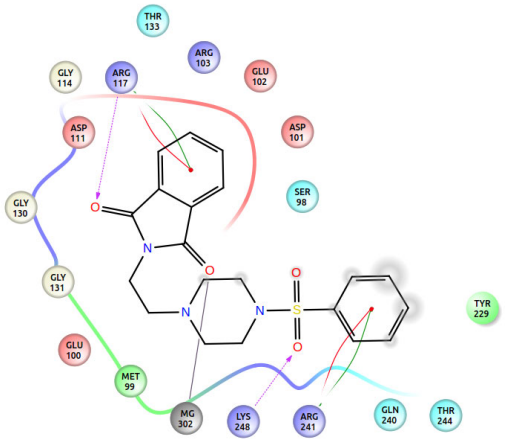
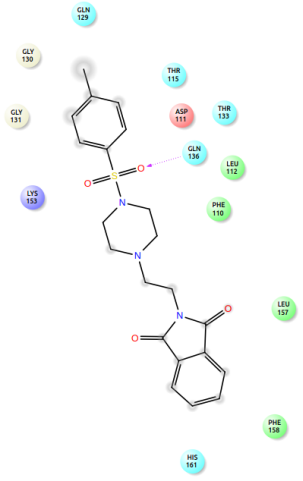
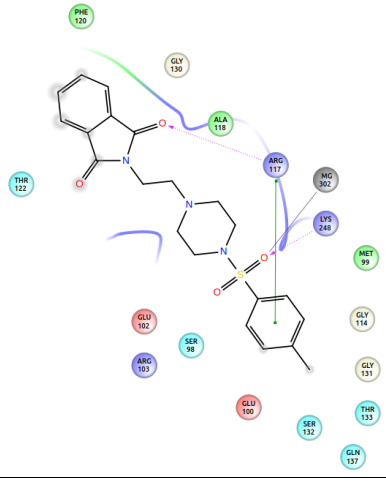
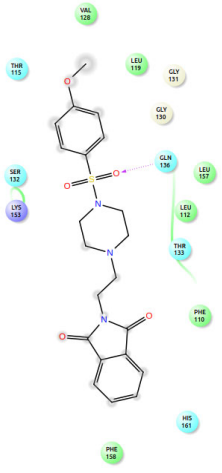
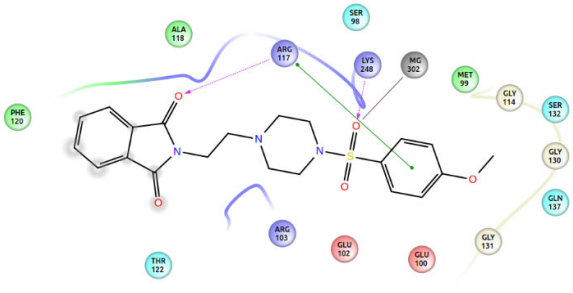
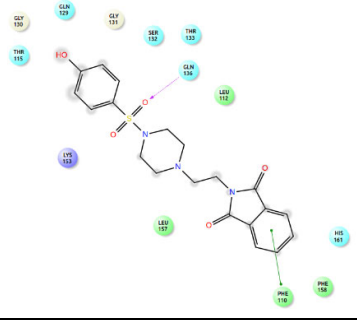
D

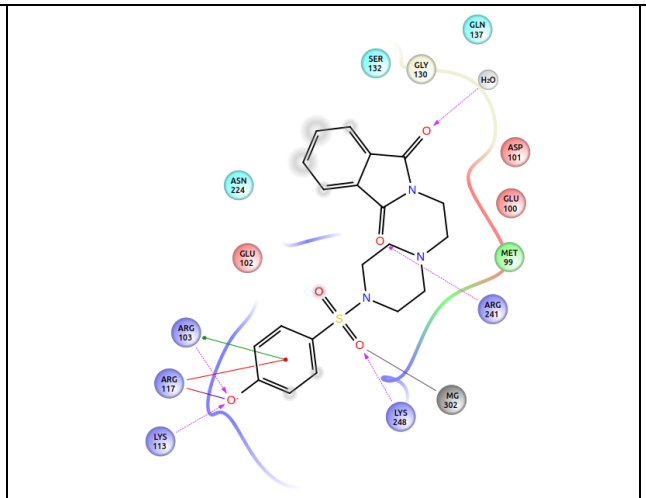
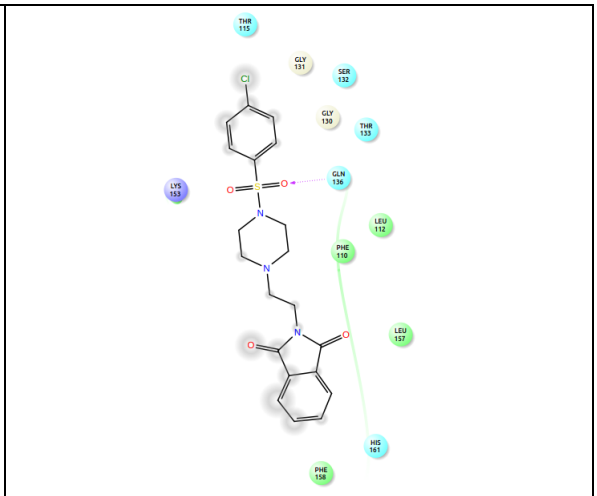
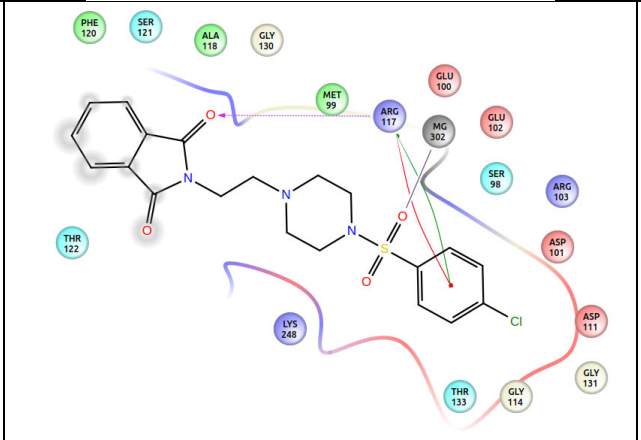
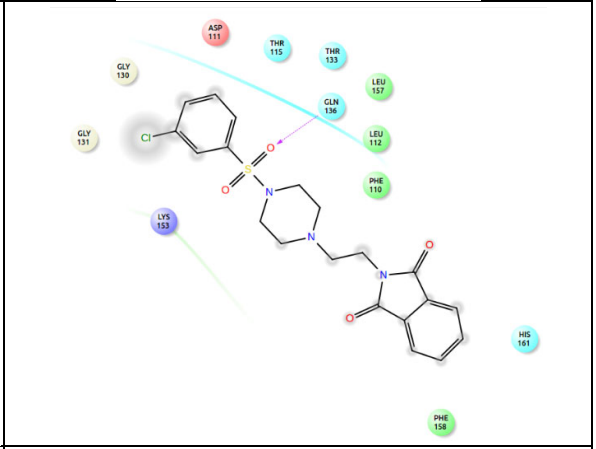
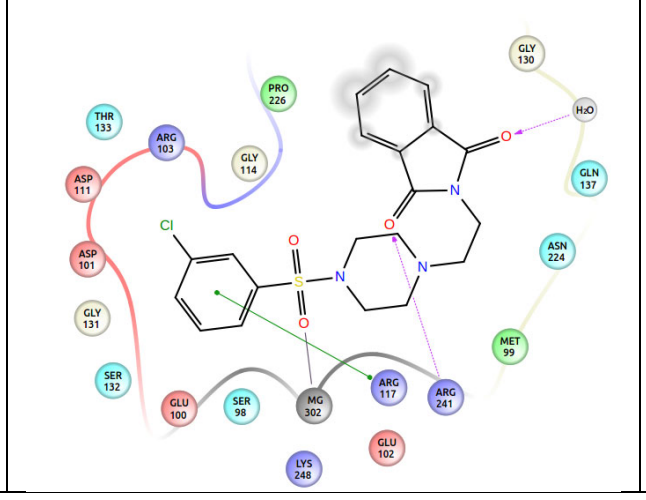
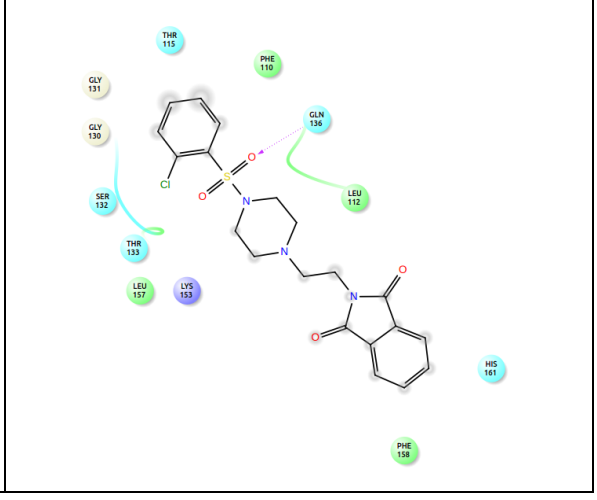

17002156-NPN4 58 (1.007)
1: TOF MS ES-
6.55e3
100
%
0
444.0297
292.0418
292.1093
174.8717
174.8891
293.0459
146.8622
249.0001
m/z
100
200
300
400
500
600
700
800
900
1000

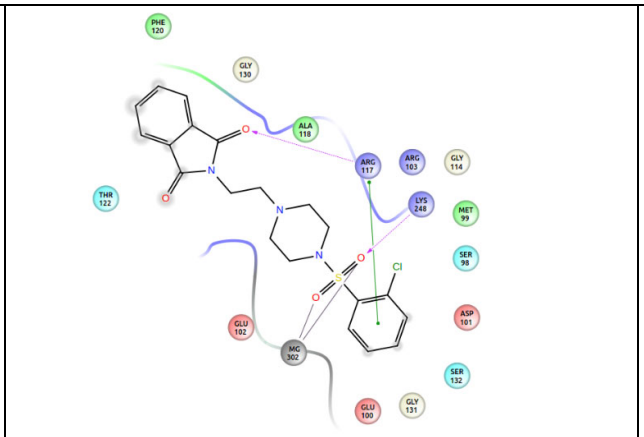
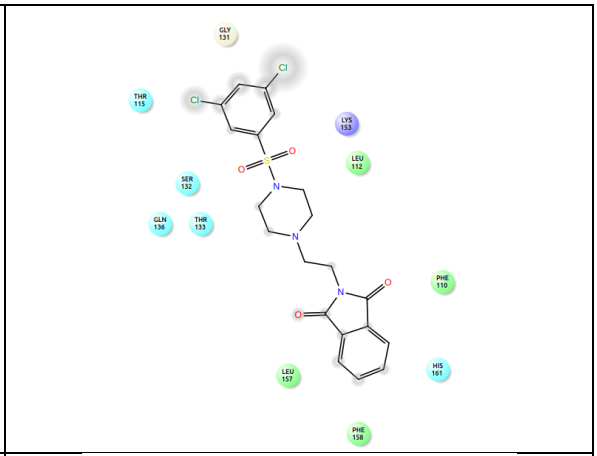
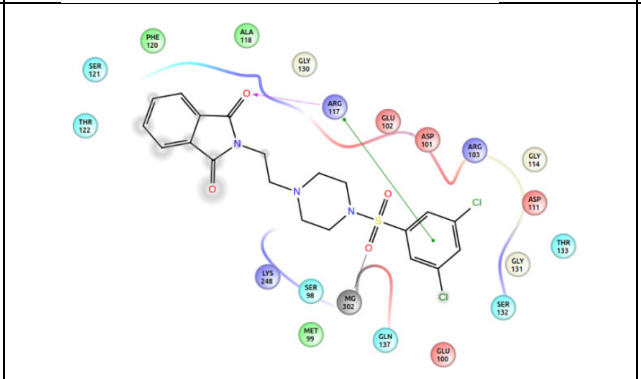
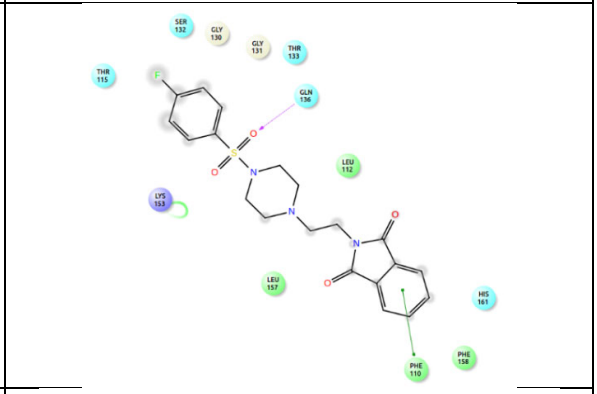
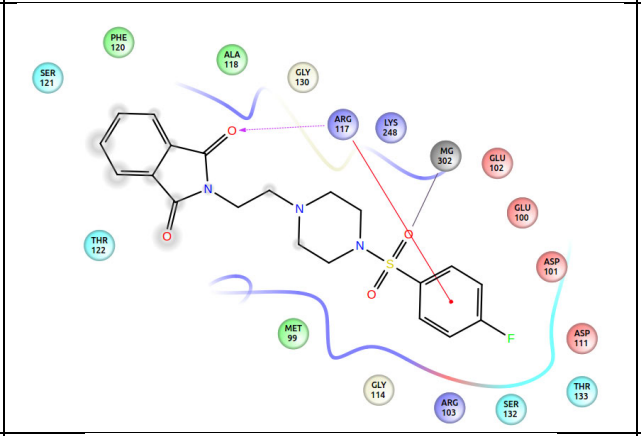
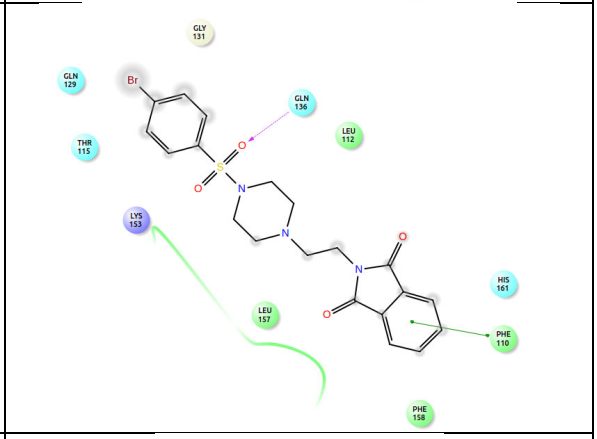
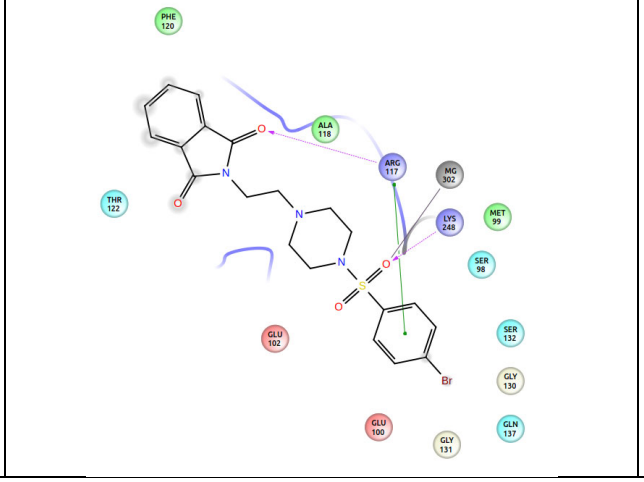
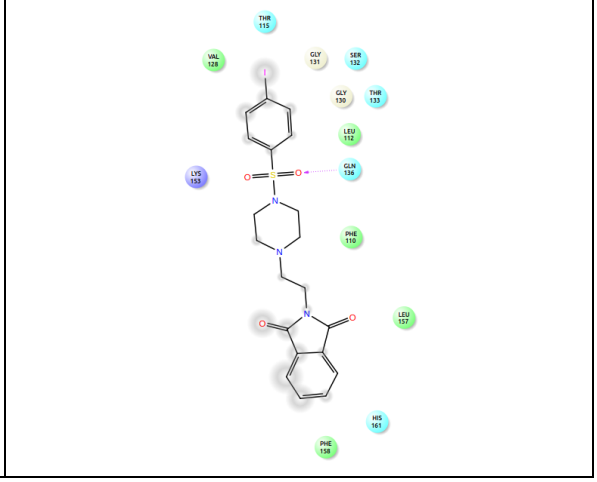


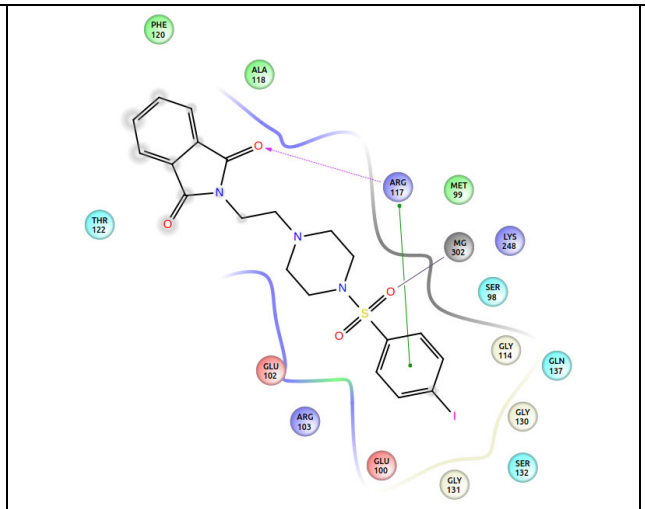
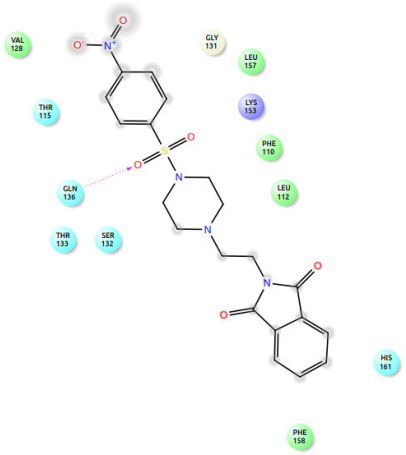
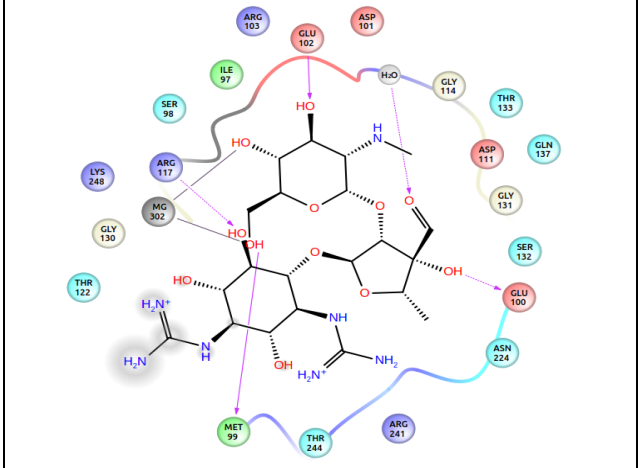
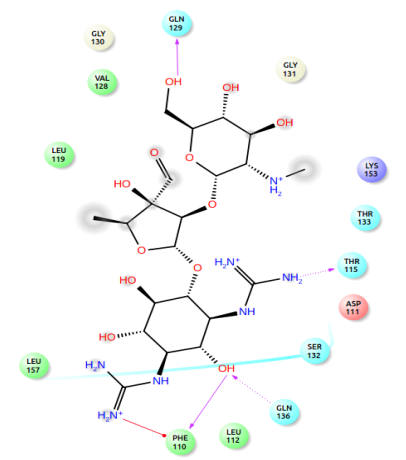
Supplementary Fig S14: FTIR spectra of synthesized compounds

Supplementary Figure. S15: Molecular docking interactive map of ligands**5(a-l)** and antibiotic streptomycin for **3VMT**and**6FTB** of binding deep inside the active site, depicting the best docking pose showing 2D respectively.

Compound name	3VMT	6FTB
5a		
5b		
5c		

5d	 GLN 137 SER 132 GLY 130 H2O ASP 101 ASN 224 GLU 100 GLU 102 MET 99 ARG 241 ARG 103 ARG 117 LYS 113 LYS 248 MG 302	 THR 115 GLY 131 SER 132 GLY 130 THR 133 LYS 153 GLN 136 LEU 112 PHE 110 LEU 157 HIS 161 PHE 158
5e	 PHE 120 SER 121 ALA 118 GLY 130 MET 99 ARG 117 GLU 100 MG 302 GLU 102 SER 98 ARG 103 THR 122 ASP 101 LYS 248 ASP 111 GLY 131 THR 133 GLY 114	 ASP 111 THR 115 THR 133 GLY 130 LEU 157 GLN 136 GLY 131 LEU 112 PHE 110 LYS 153 HIS 161 PHE 158
5f	 GLY 130 PRO 226 H2O THR 133 ARG 103 GLY 114 GLN 137 ASP 111 ASP 101 ASN 224 GLY 131 MET 99 SER 132 GLU 100 SER 98 MG 302 ARG 117 ARG 241 GLU 102 LYS 248	 THR 115 PHE 110 GLY 131 GLY 130 GLN 136 SER 132 LEU 112 THR 133 LEU 157 LYS 153 HIS 161 PHE 158

5g		
5h		
5i		
5j		

5k		
Streptomycin		

3. Supplementary table S1: Predicted biological activities of compounds 5(a-f), Pa (probability "to be active"), Pi(probability "to be inactive").

Activity	5a		5b		5c		5d		5e		5f	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Antipsychotic	0.599	0.012	0.465	0.024	0.436	0.028	0.333	0.044	0.584	0.013	0.593	0.013
Antidepressant	0.385	0.037	0.297	0.059	0.325	0.050	0.201	0.107	0.377	0.038	0.384	0.037
Antiischemic, cerebral	0.467	0.128	0.442	0.149	0.399	0.185	0.476	0.121	0.523	0.094	0.444	0.147
Antianginal	0.397	0.087	0.388	0.094	0.417	0.074	0.359	0.119	0.364	0.114	0.341	0.137
Antiprotozoal (Amoeba)	0.307	0.063	0.299	0.069	0.268	0.101	0.328	0.051	0.318	0.056	0.341	0.044
Antiadrenergic	0.191	0.033	0.124	0.052	0.191	0.033	0.129	0.050	0.143	0.045	0.124	0.052
Antieczematic atopic	0.227	0.090	0.214	0.107	0.223	0.095	0.198	0.131	0.233	0.083	0.232	0.084
Antidiuretic hormone antagonist	0.066	0.018	0.063	0.019	0.049	0.029	NE	NE	0.065	0.018	0.057	0.024
Antipyretic	0.198	0.116	0.207	0.107	0.233	0.086	0.249	0.073	0.187	0.127	0.178	0.138
Antiviral (Picornavirus)	0.331	0.181	NE	NE	NE	NE	NE	NE	0.303	0.222	0.275	0.272
Antiarthritic	0.315	0.123	0.293	0.137	0.320	0.120	0.264	0.160	0.320	0.121	0.341	0.108
Antiobesity	0.325	0.059	0.292	0.072	0.231	0.104	0.203	0.124	0.436	0.032	0.431	0.032

4. Supplementary table S1: Predicted biological activities of compounds 5(g-l), Pa (probability "to be active"), Pi(probability "to be inactive").

Activity	5g		5h		5i		5j		5k		5l	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Antipsychotic	0.596	0.012	0.616	0.011	0.655	0.009	0.503	0.020	0.397	0.033	0.314	0.048
Antidepressant	0.403	0.034	0.385	0.037	0.421	0.031	0.300	0.058	0.196	0.111	0.173	0.130
Antiischemic, cerebral	0.370	0.213	0.456	0.137	0.502	0.104	0.330	0.260	NE	NE	0.444	0.148
Antianginal	0.406	0.081	0.315	0.163	0.342	0.136	0.294	0.184	0.350	0.128	0.498	0.043
Antiprotozoal (Amoeba)	0.286	0.080	0.365	0.035	0.257	0.116	0.334	0.048	0.317	0.057	0.446	0.017
Antiadrenergic	0.121	0.053	NE	NE	0.205	0.030	0.097	0.065	0.162	0.040	0.118	0.054
Antieczematic atopic	0.263	0.052	0.225	0.093	0.263	0.052	0.218	0.101	NE	NE	0.195	0.136
Antidiuretic hormone antagonist	0.044	0.034	0.056	0.025	0.054	0.026	0.044	0.034	0.041	0.037	0.048	0.030
Antipyretic	0.169	0.150	0.166	0.155	NE	NE	0.195	0.119	0.265	0.061	0.183	0.131
Antiviral (Picornavirus)	0.285	0.253	NE	NE	NE	NE	NE	NE	0.330	0.182	0.380	0.127
Antiarthritic	0.299	0.133	0.297	0.134	0.412	0.075	NE	NE	NE	NE	NE	NE
Antiobesity	0.450	0.029	0.468	0.026	0.355	0.050	0.344	0.053	0.189	0.135	NE	NE

Table S2: Synthesized analogues 5(a-1) and their bio-activity score

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
5(a)	-0.05	-0.45	-0.28	-0.48	-0.11	-0.05
5(b)	-0.06	-0.50	-0.23	-0.51	-0.01	-0.12
5(c)	-0.03	-0.43	-0.19	-0.48	0.04	-0.07
5(d)	0.01	-0.40	-0.16	-0.37	0.05	-0.02
5(e)	-0.03	-0.44	-0.21	-0.51	0.00	-0.10
5(f)	-0.02	-0.45	-0.21	-0.50	0.00	-0.09

5(g)	-0.04	-0.45	-0.22	-0.49	-0.02	-0.09
5(h)	-0.01	-0.41	-0.19	-0.48	-0.01	-0.09
5(i)	-0.02	-0.45	-0.17	-0.47	0.01	-0.08
5(j)	-0.11	-0.50	-0.23	-0.58	-0.06	-0.13
5(k)	-0.02	-0.44	-0.18	-0.47	-0.02	-0.11
5(l)	-0.08	-0.40	-0.21	-0.46	-0.01	-0.08