Supporting Information

Design and synthesis of potent benzimidazole derivatives via scaffold hybridization and evaluating their antiproliferative and proapoptotic activity against breast and lung cancer cell lines

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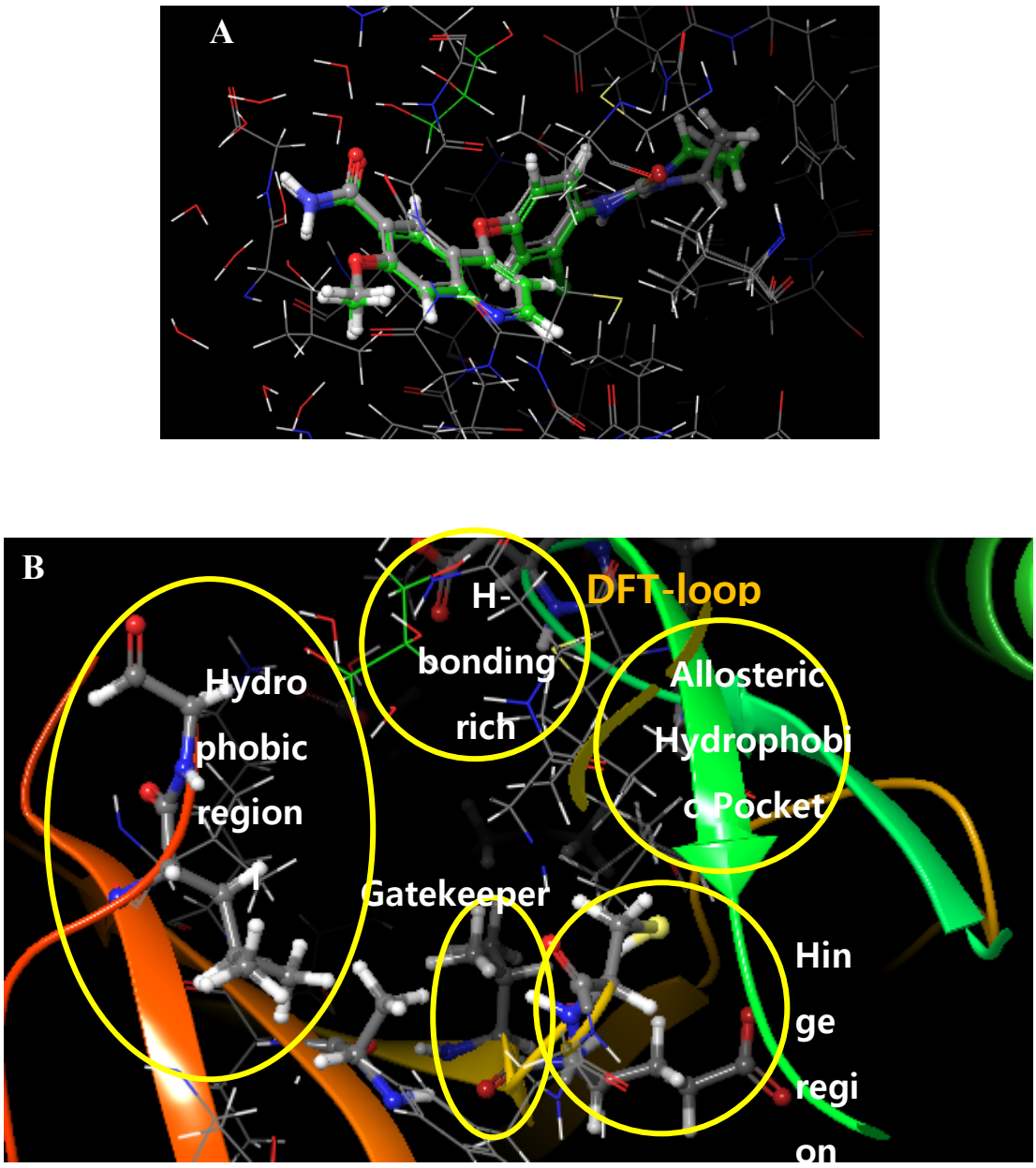


Figure S1. (A) Alignment of the crystallographic bound Lenvatinib (green) and re-docked ligand (grey), (B) the catalytic domain of VEGFR2 shown the distribution of the main regions.

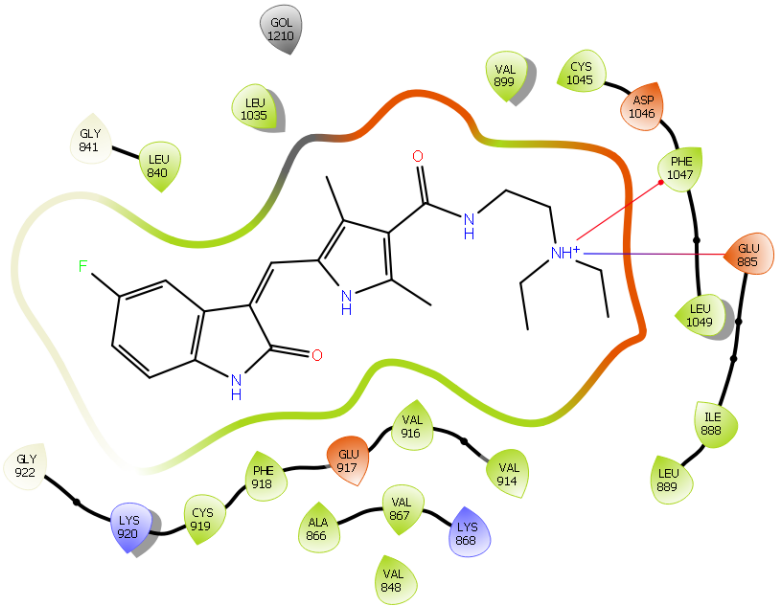
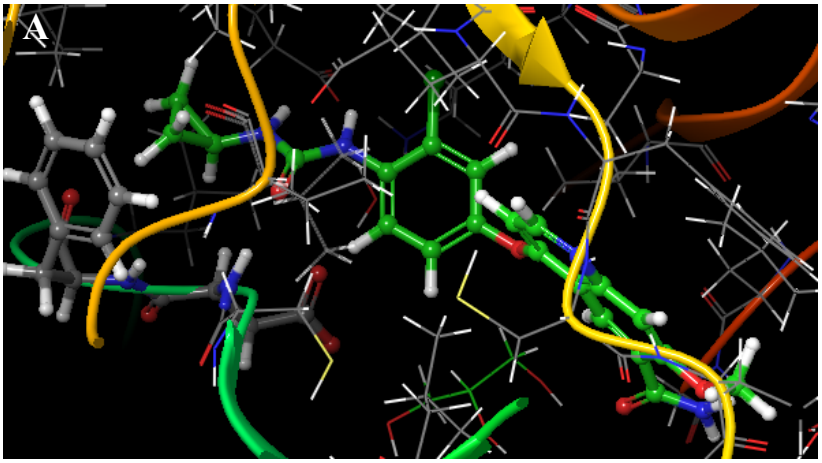
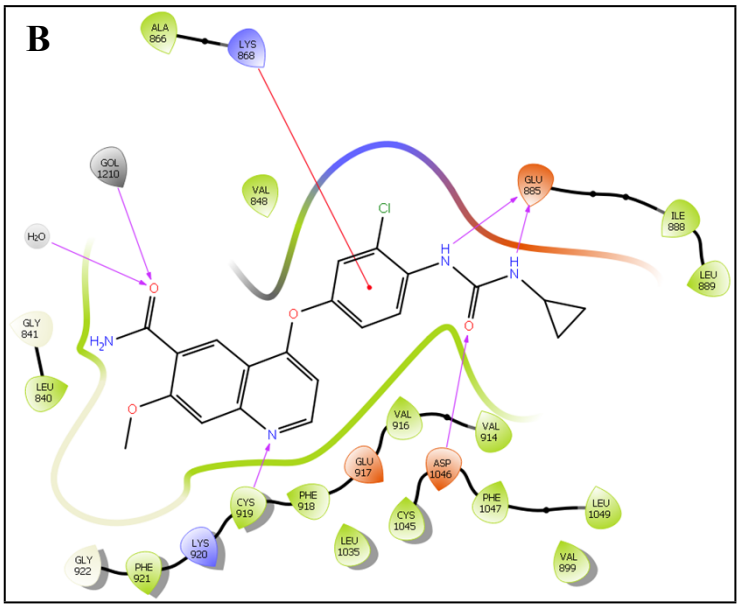
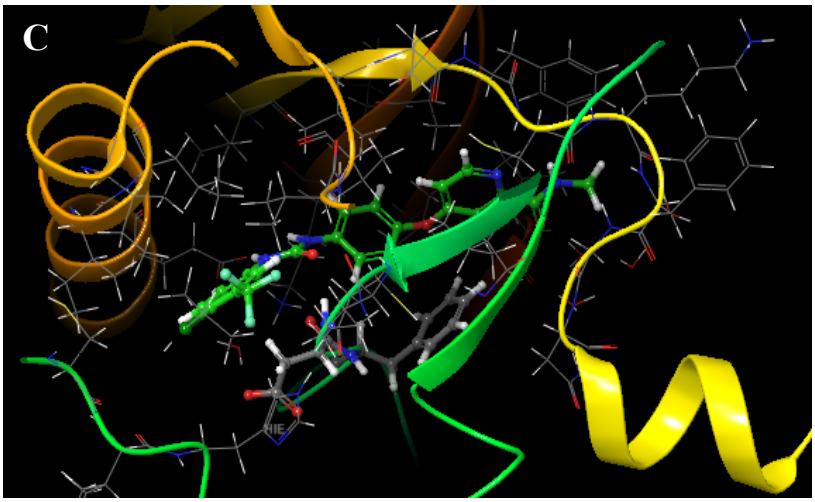


Figure S2. two-dimensional-binding modes of sunitinib in DFG-In conformation of the catalytic domain of VEGFR2 (PDB: 3WZD)







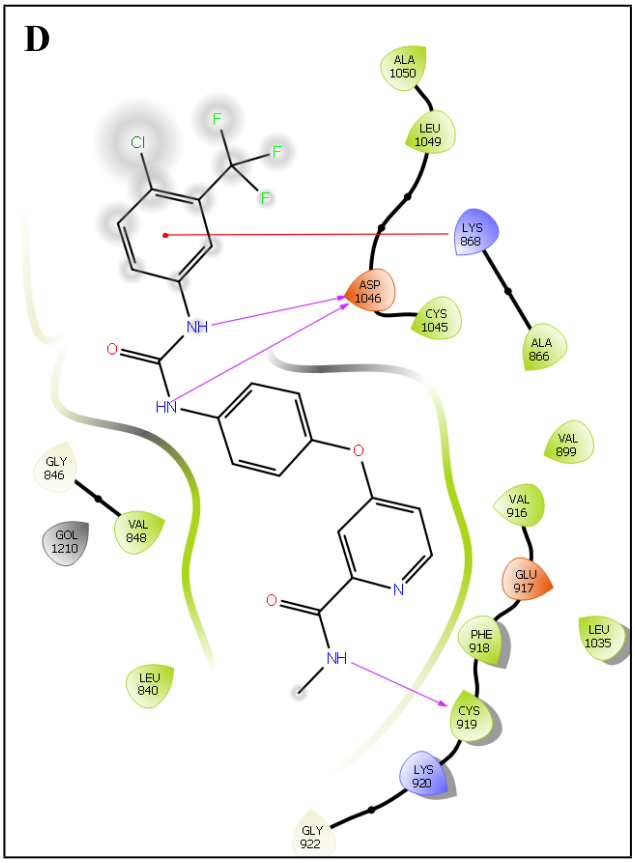


Figure S3 (**A**)Three-dimensional-binding modes of lenvatinib in DFG-In conformation of the catalytic domain of VEGFR2 (PDB 3WZD). (**B**) 2D of Lenvatinib in VEGFR2 catalytic domain, (**C**) Three-dimensional-binding modes of sorafenib in DFG-out conformation of the catalytic domain of VEGFR2 (PDB 3WZE) (**D**) 2D of sorafenib in VEGFR2 catalytic domain.

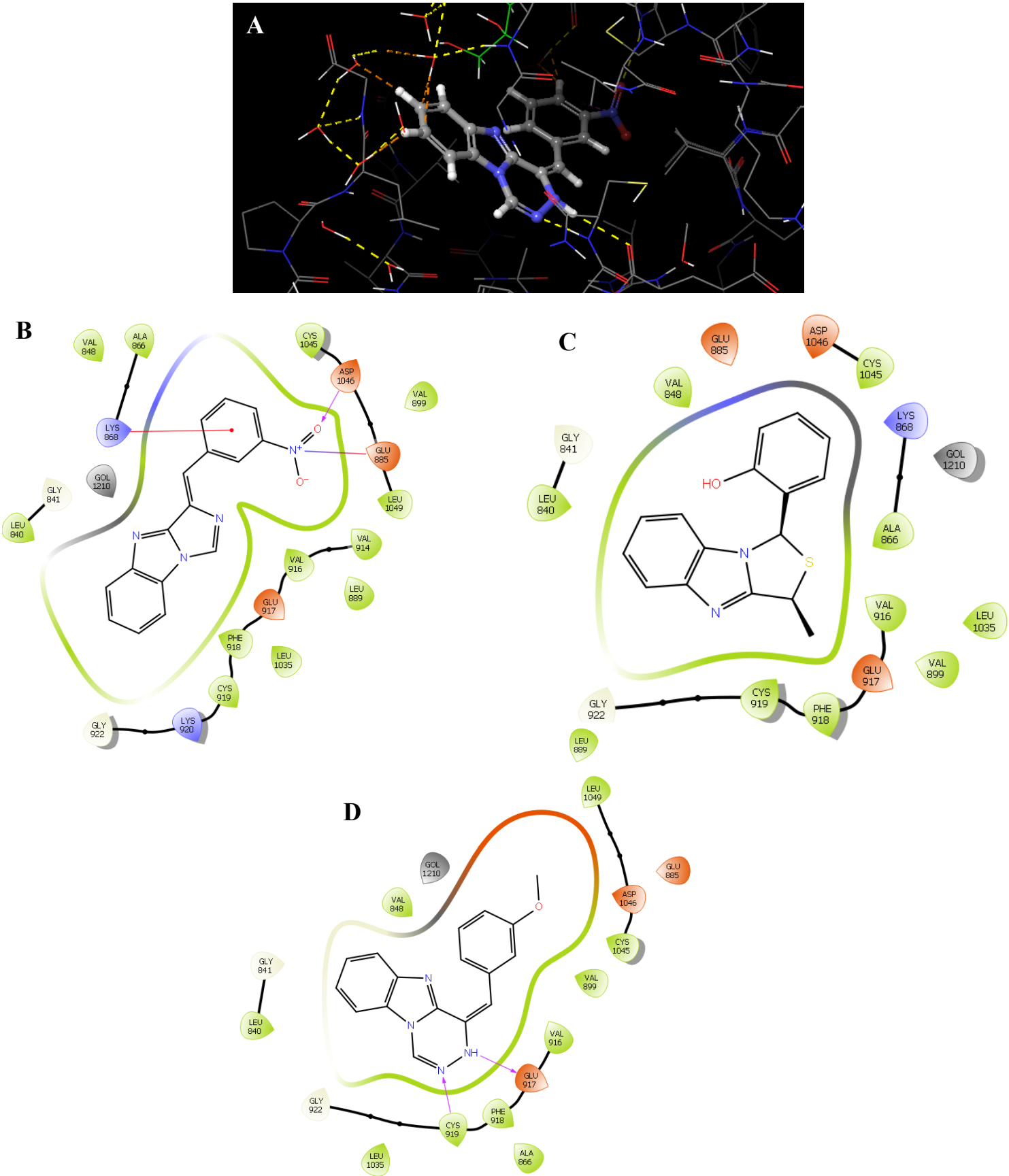


Figure S4. (A) Three-dimensional-binding modes of Compound **17** in DFG-In conformation of the catalytic domain of VEGFR2 (PDB 3WZD) shown the hydrophilic-hydrophobic interaction. **(B), (C), (D)** 2D of compounds **8**, **12**, and **19**, respectively in VEGFR2 catalytic domain.

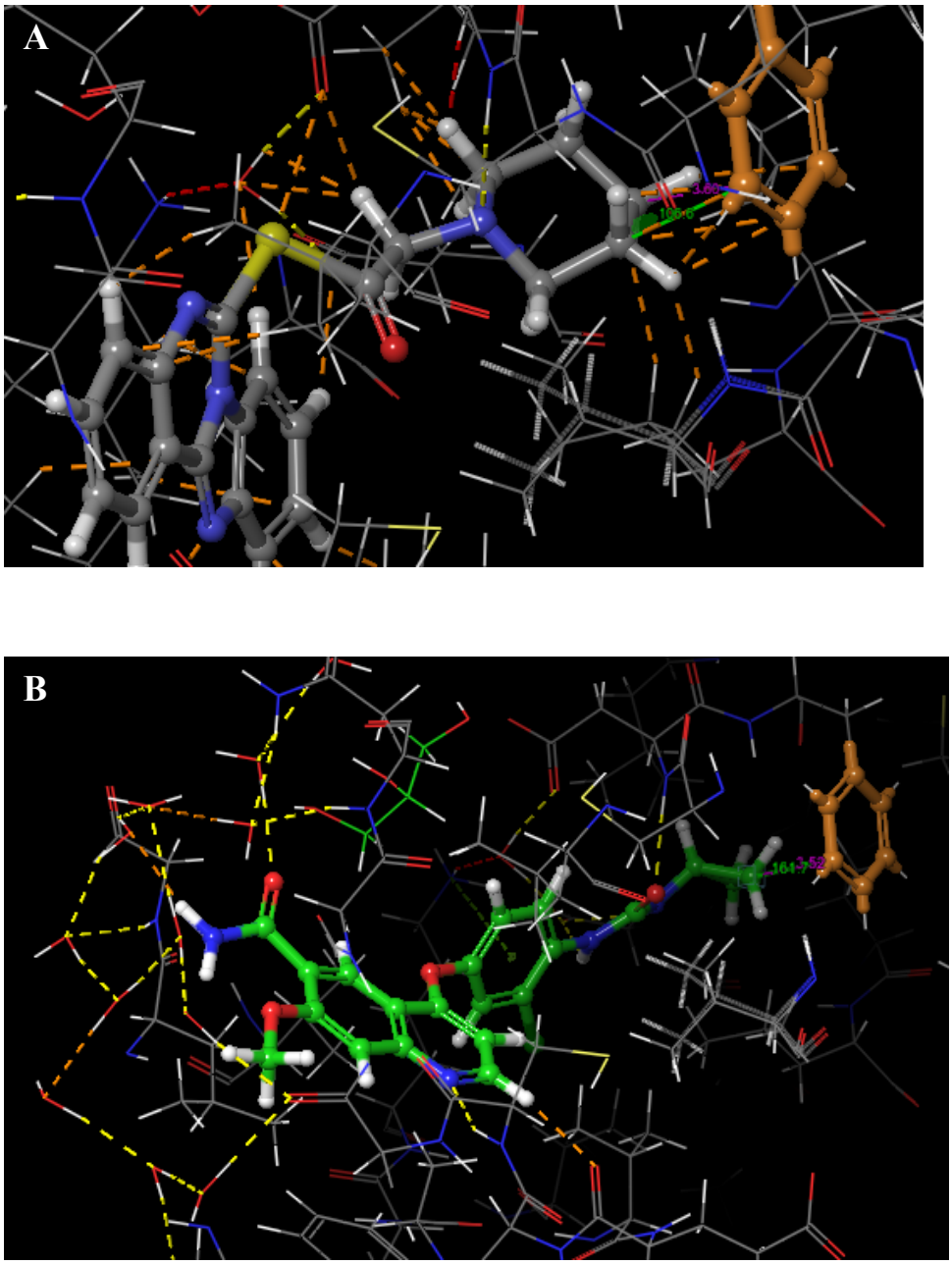
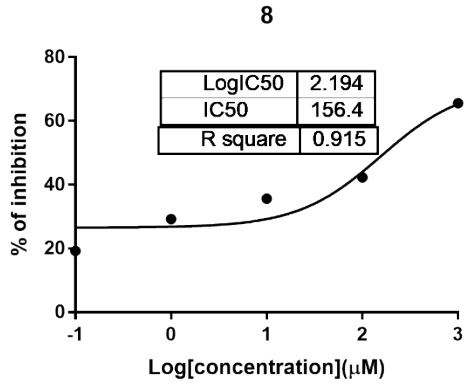
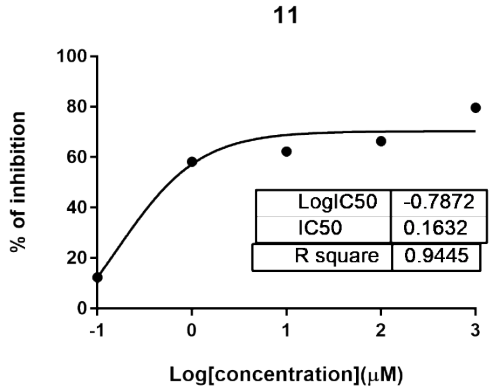
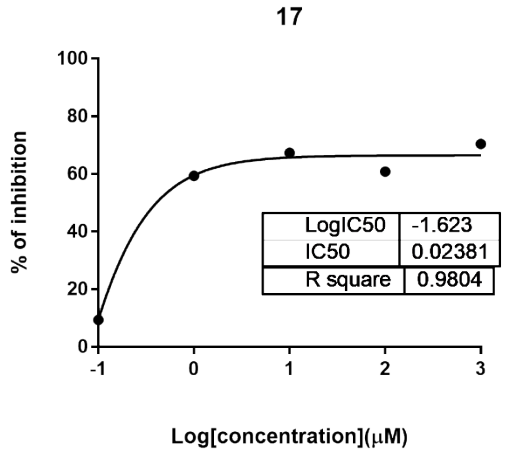


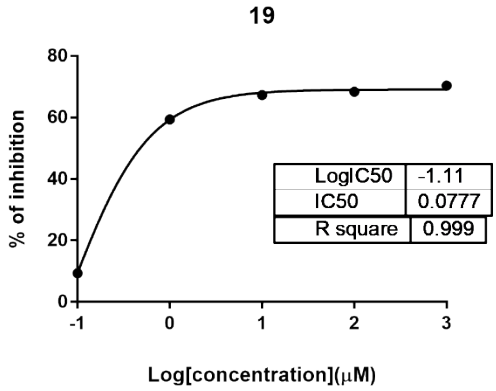
Figure S5. (A) Three-dimensional-binding modes of Compound **24** in DFG-In conformation of the catalytic domain of VEGFR2 (PDB: 3WZD) shown close-up view of piperidine ring and Phe-1047, distance and angle of interaction. (**B**)Three-dimensional-binding modes of Lenvatinib in DFG-In conformation of the catalytic domain of VEGFR2 (PDB: 3WZD) shown close-up view of cyclopropyl ring and Phe-1047, distance and angle of interaction.

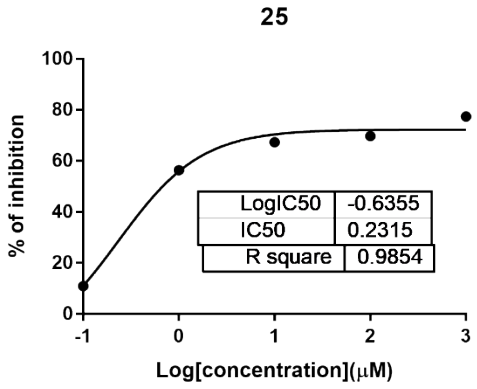
IC_{50} graph of VEGFR2 inhibitory assay





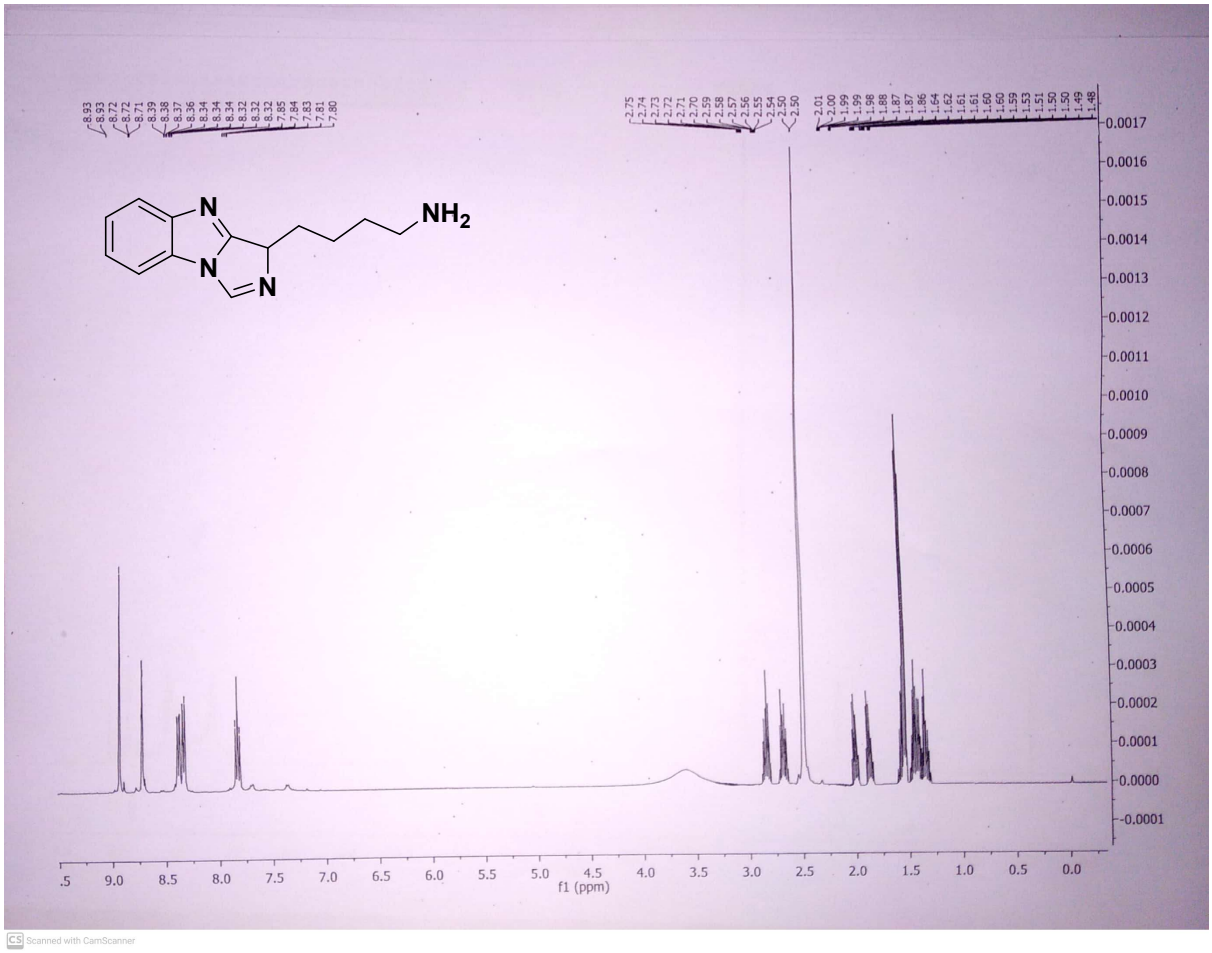


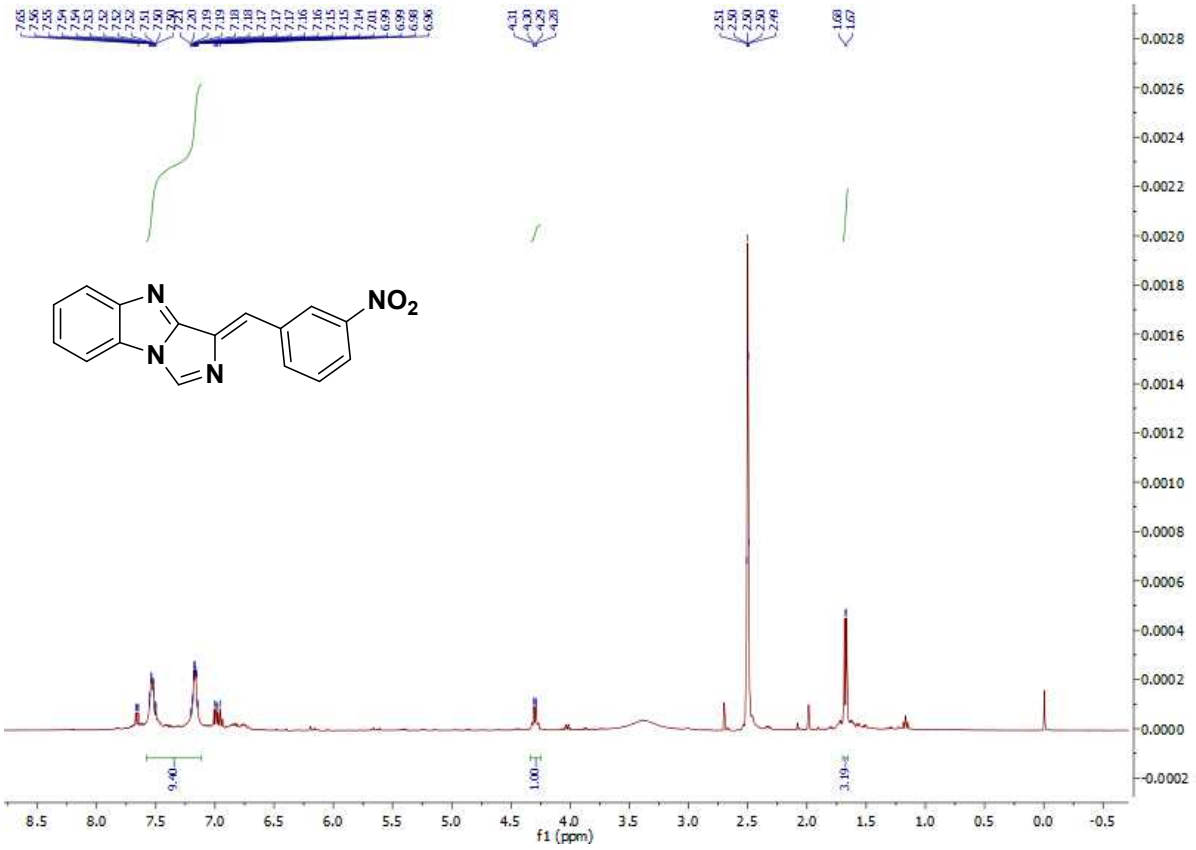




IC_{50} values were calculated according to non-linear regression curve fit of log(inhibitor) vs. response (three parameters); https://www.graphpad.com/guides/prism/7/curve-fitting/REG_DR_inhibit.htm

[1]HNMR and [13]CNMR of the designed molecules

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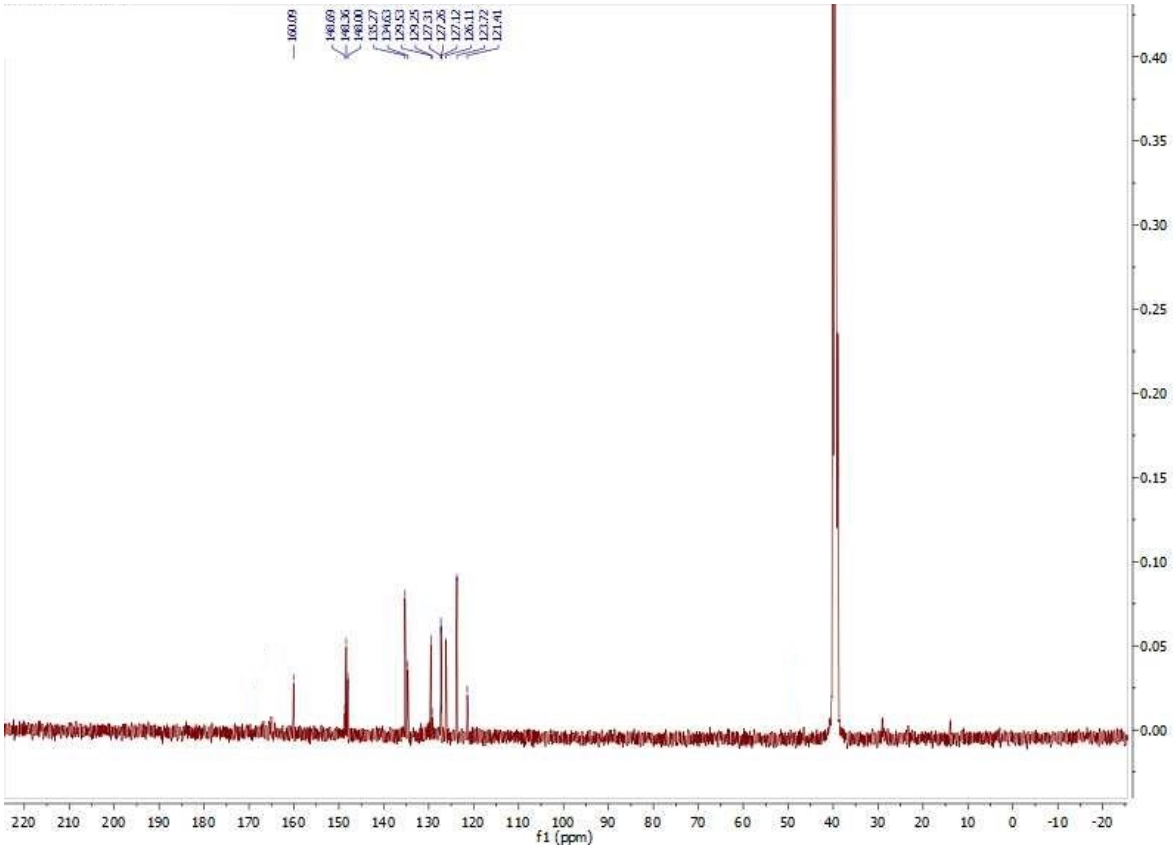
N
NO2
9.40
1.00
3.19
f1 (ppm)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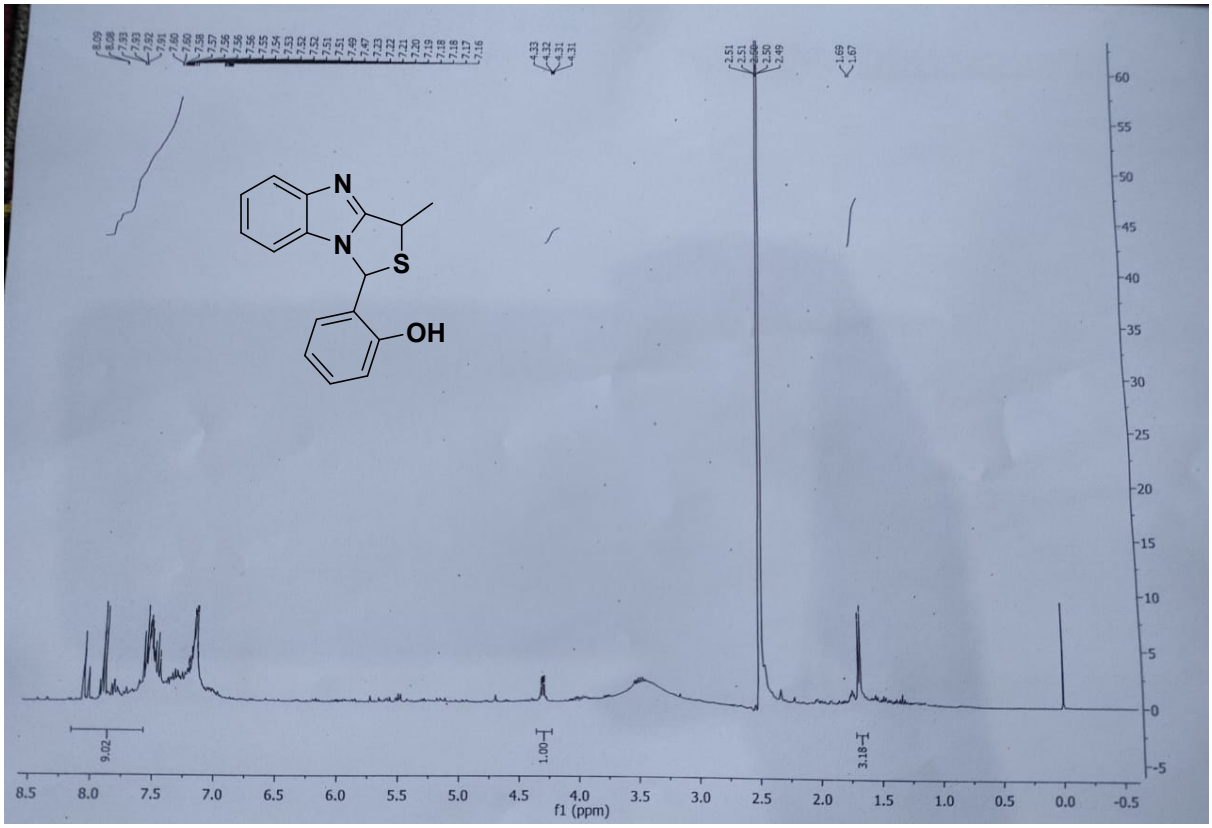
148.69
148.36
148.00
135.27
134.63
129.53
129.25
127.31
127.26
127.12
126.11
123.72
121.41
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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N
S
OH
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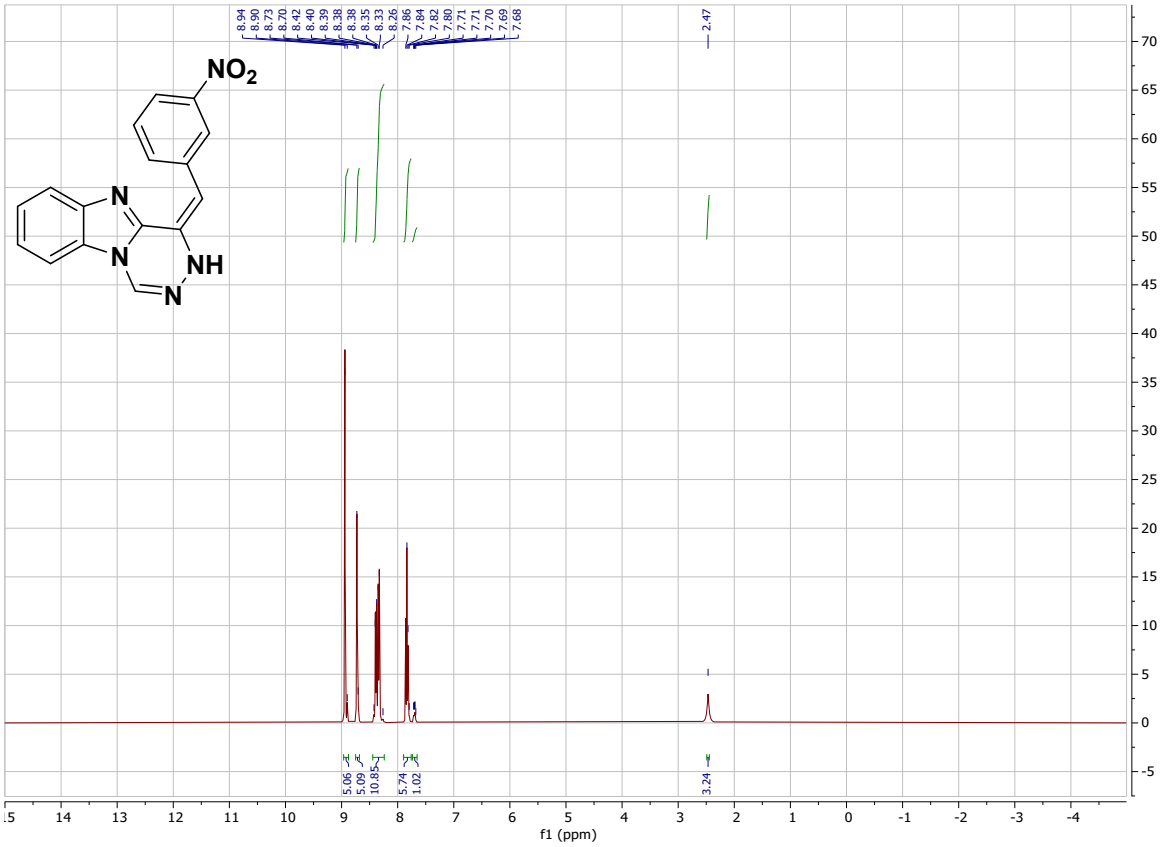
1.00
3.18
f1 (ppm)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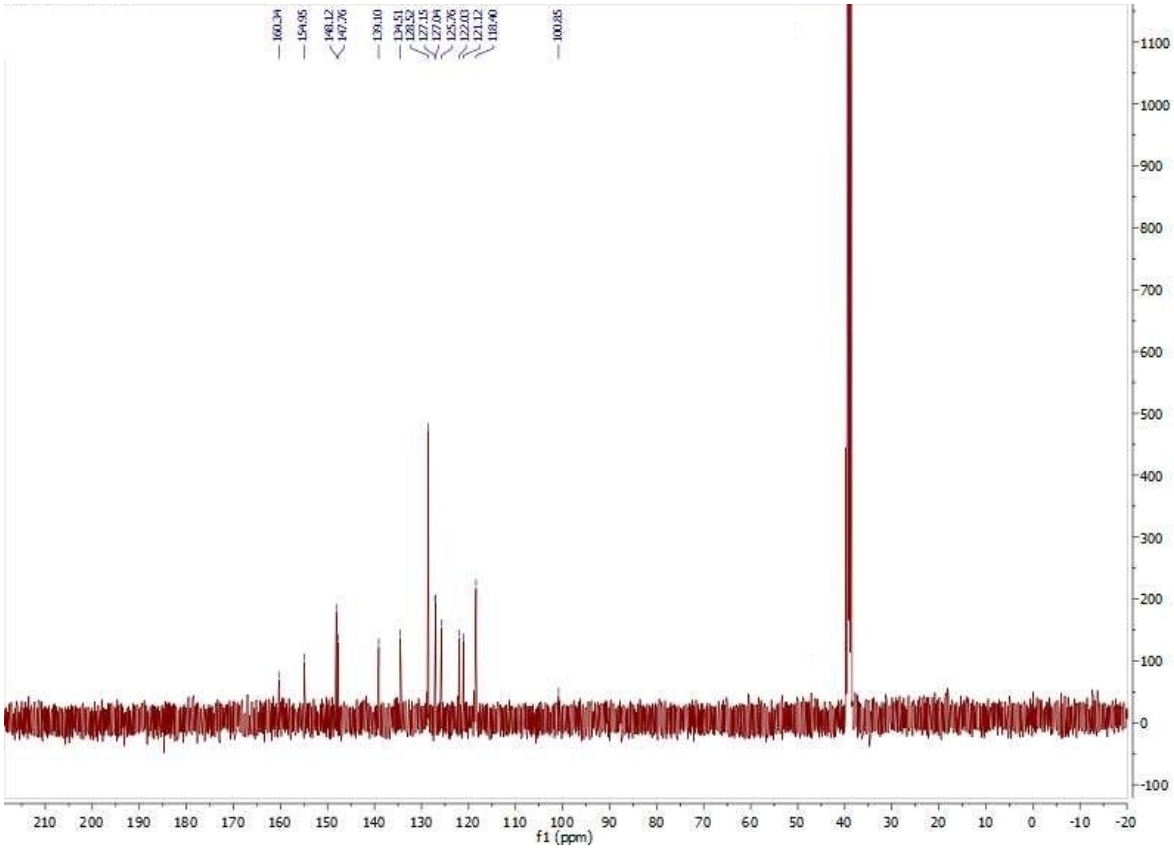
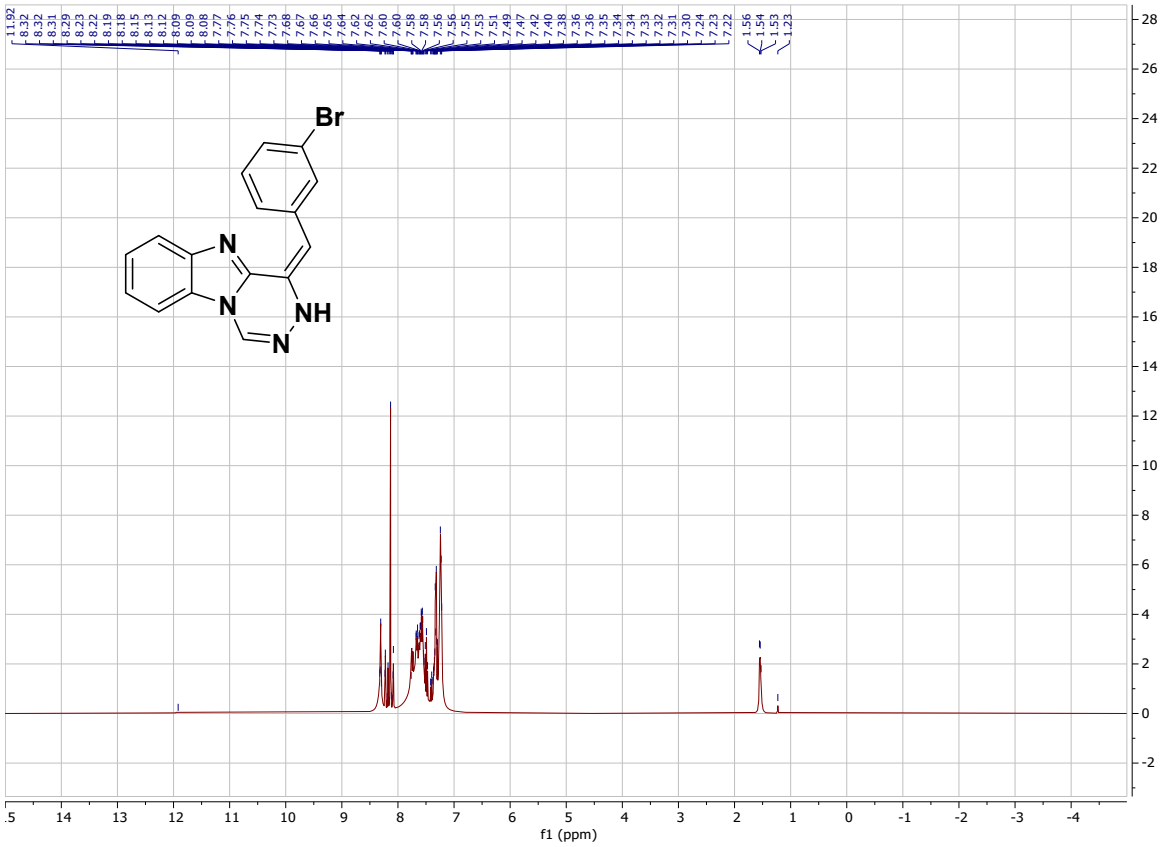
8.90
8.73
8.70
8.42
8.40
8.39
8.38
8.38
8.35
8.33
8.26
7.86
7.84
7.82
7.80
7.71
7.71
7.70
7.69
7.68
2.47
NO2
N
N
NH
N
5.06
5.09
10.85
5.74
1.02
3.24
f1 (ppm)


160.94
154.95
148.12
147.76
139.10
124.51
123.52
122.15
121.04
120.76
122.03
121.12
118.90
100.85
f1 (ppm)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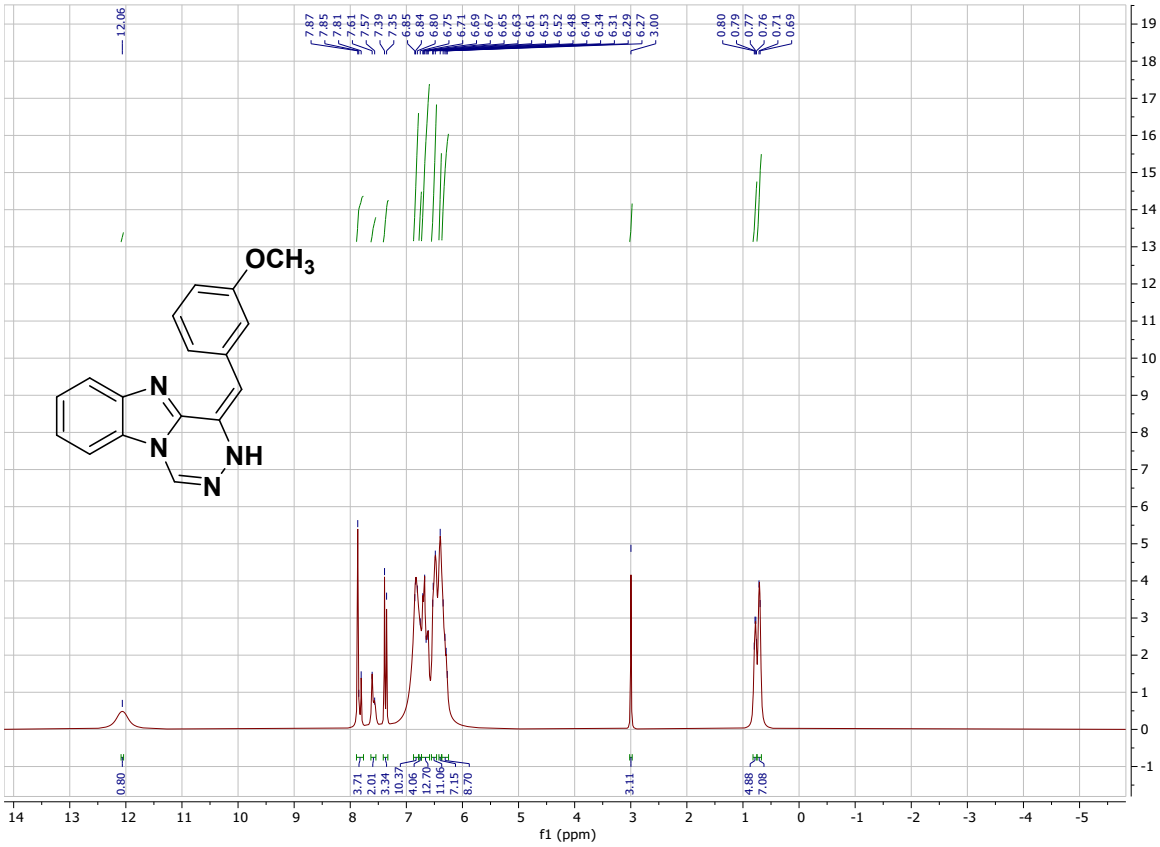
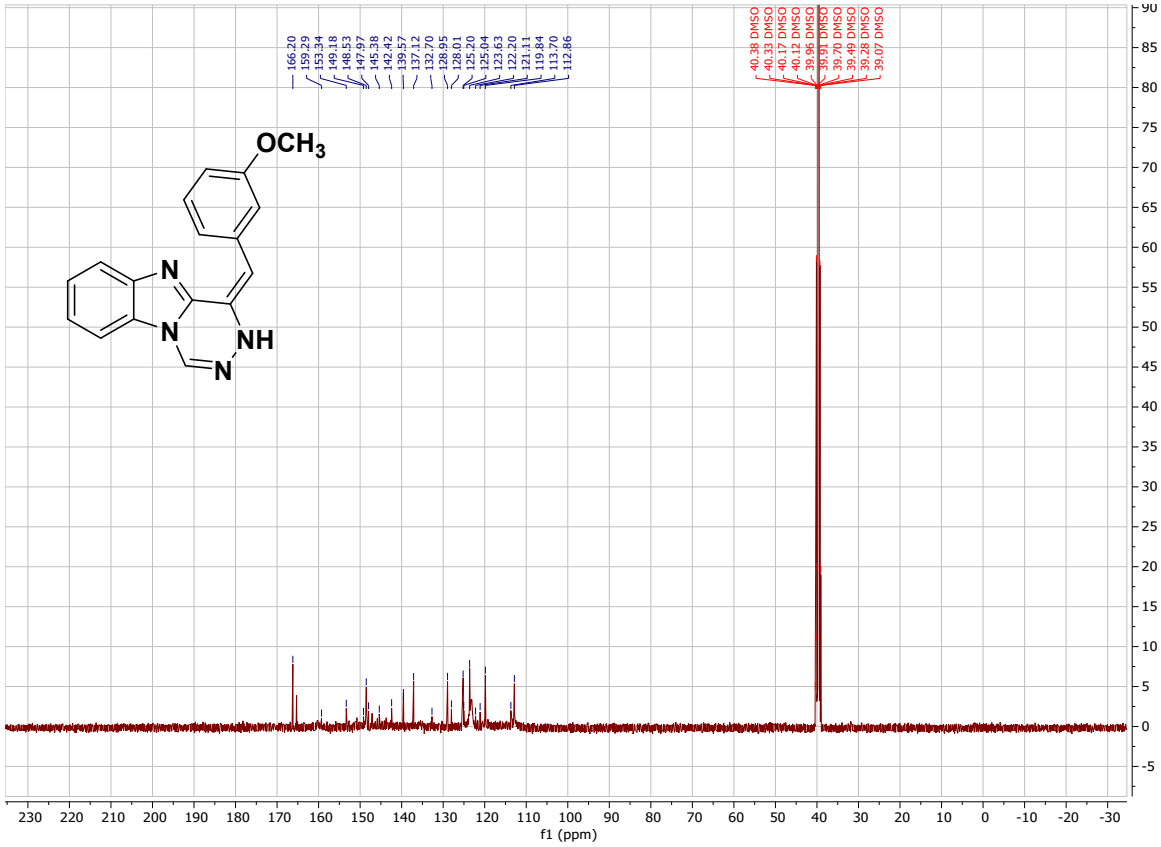
N
N
NH
N
f1 (ppm)


OCH3
N
N
NH
N
f1 (ppm)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153.34
149.18
148.53
147.97
145.38
142.42
139.57
137.12
132.70
128.95
126.01
125.04
123.63
122.20
121.11
119.84
113.70
112.86
40.38 DMSO
40.33 DMSO
40.17 DMSO
40.12 DMSO
39.96 DMSO
39.91 DMSO
39.70 DMSO
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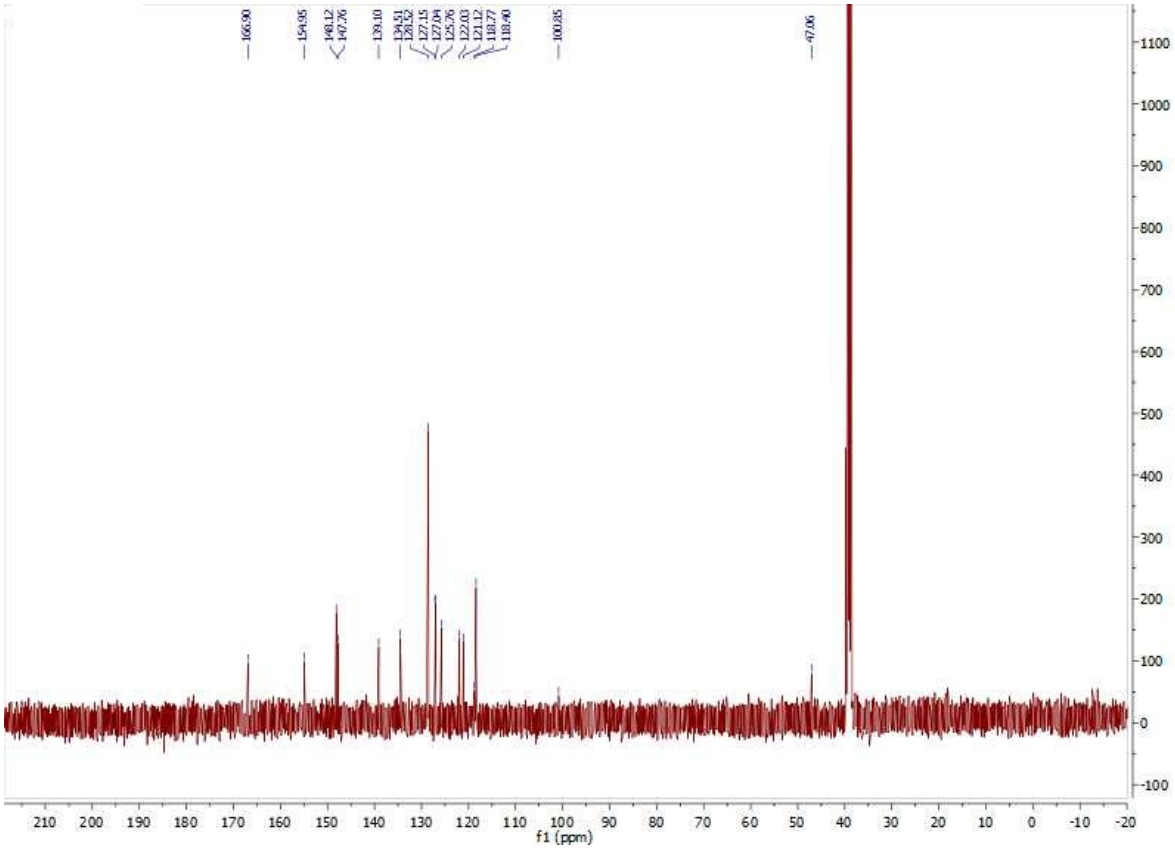
39.07 DMSO
OCH3
N
N
NH
N
f1 (ppm)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154.95
148.12
147.76
139.10
134.51
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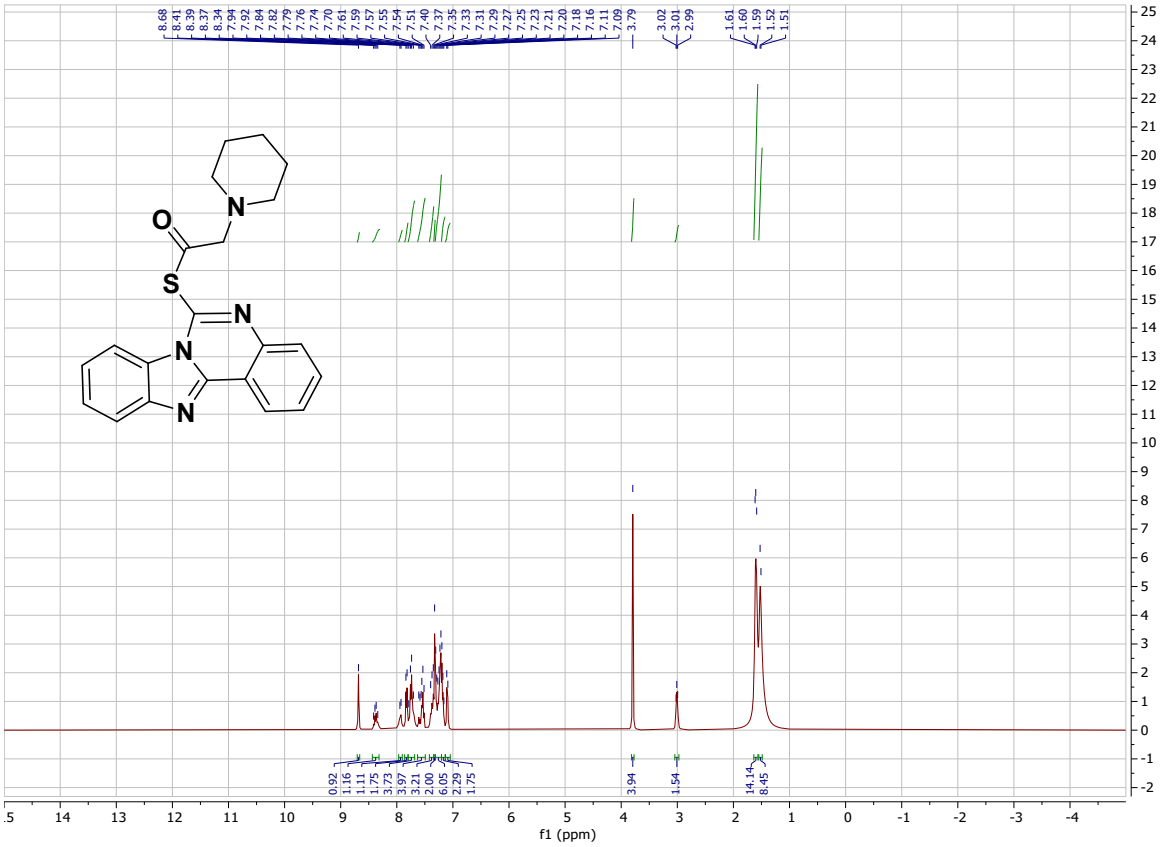
125.76
122.03
121.12
118.77
118.40
100.85
47.06
f1 (ppm)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7.84
7.82
7.79
7.76
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7.70
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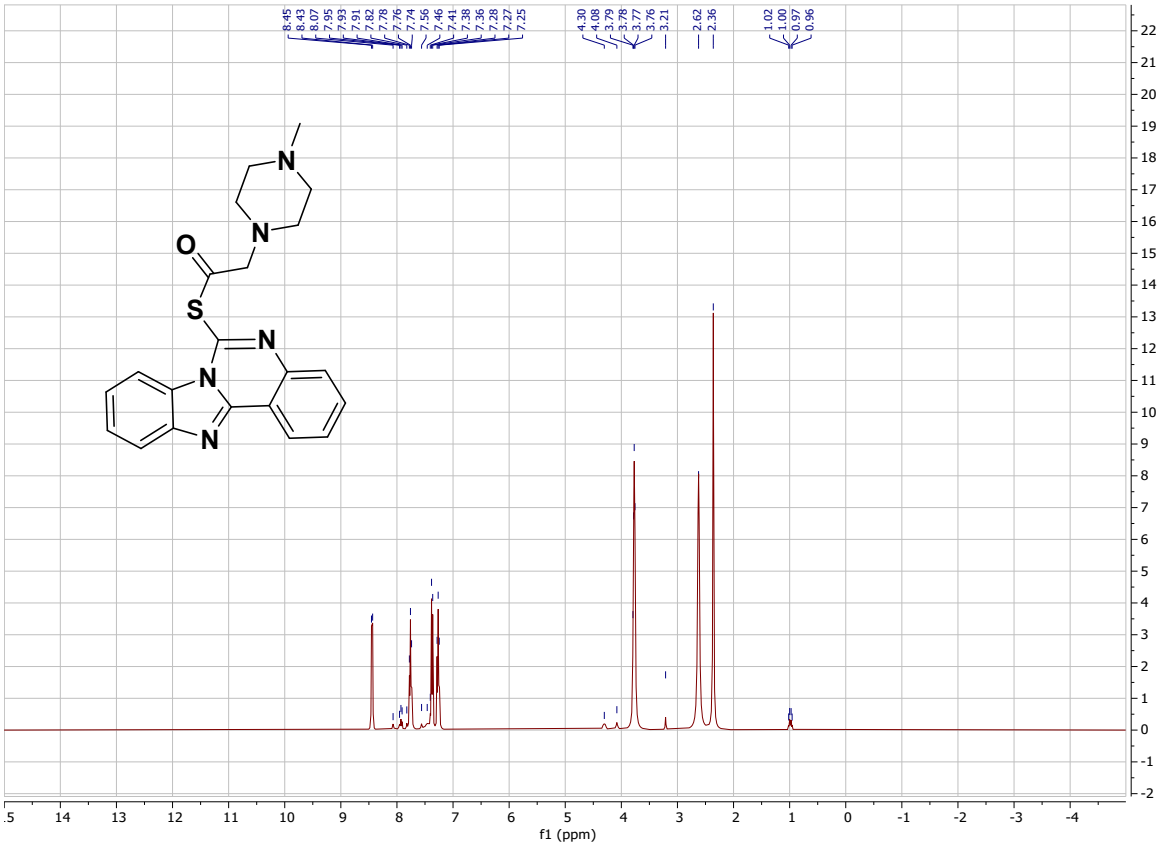
7.59
7.57
7.55
7.54
7.51
7.40
7.37
7.35
7.33
7.31
7.29
7.27
7.25
7.23
7.21
7.20
7.18
7.16
7.11
7.09
3.79
3.02
3.01
2.99
1.61
1.60
1.59
1.52
1.51
O
N
S
N
N
N
0.92
1.16
1.11
1.75
3.73
3.97
3.21
2.00
6.05
2.29
1.75
3.94
1.54
14.14
8.45
f1 (ppm)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7.36
7.28
7.27
7.25
4.30
4.08
3.79
3.78
3.77
3.76
3.21
2.62
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1.00
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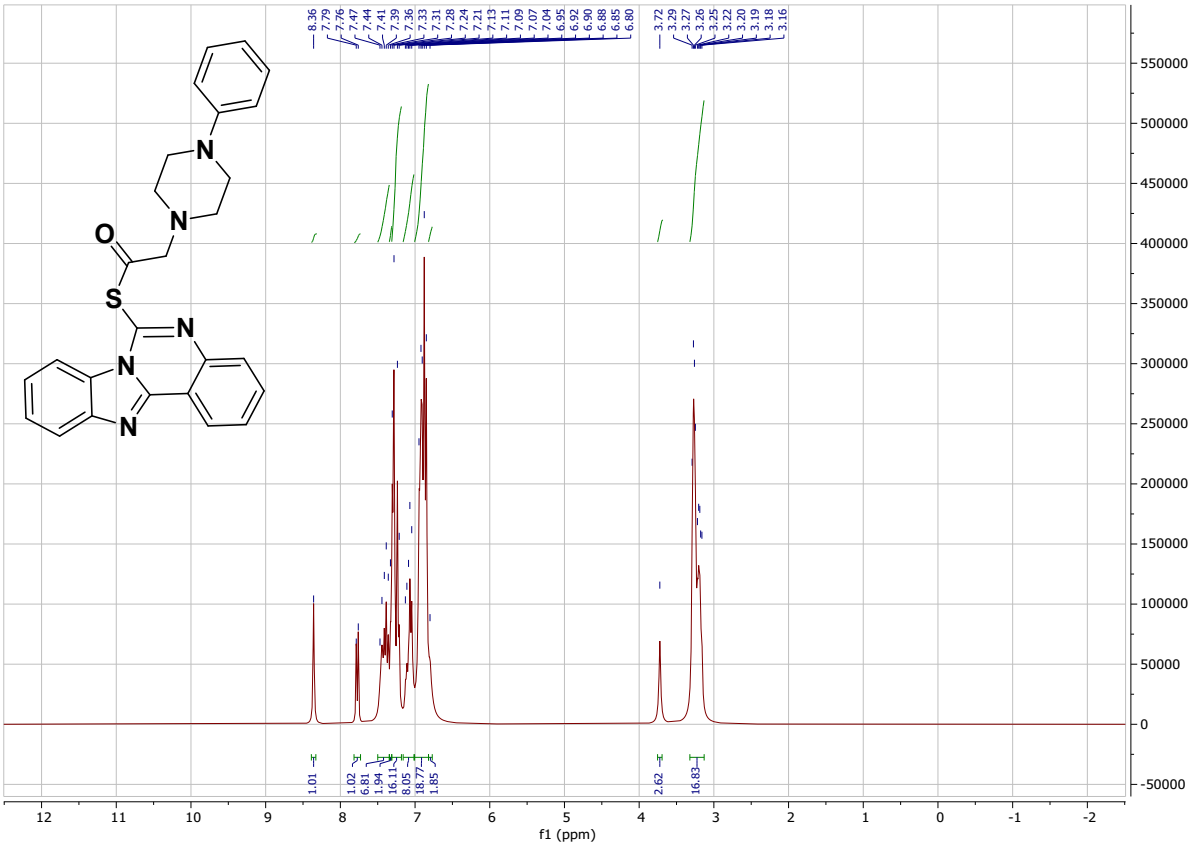
0.96
O
S
N
N
N
N
N
f1 (ppm)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7.11
7.09
7.07
7.04
6.95
6.92
6.90
6.88
6.85
6.80
3.72
3.29
3.27
3.26
3.25
3.22
3.20
3.19
3.18
3.16
1.01
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16.11
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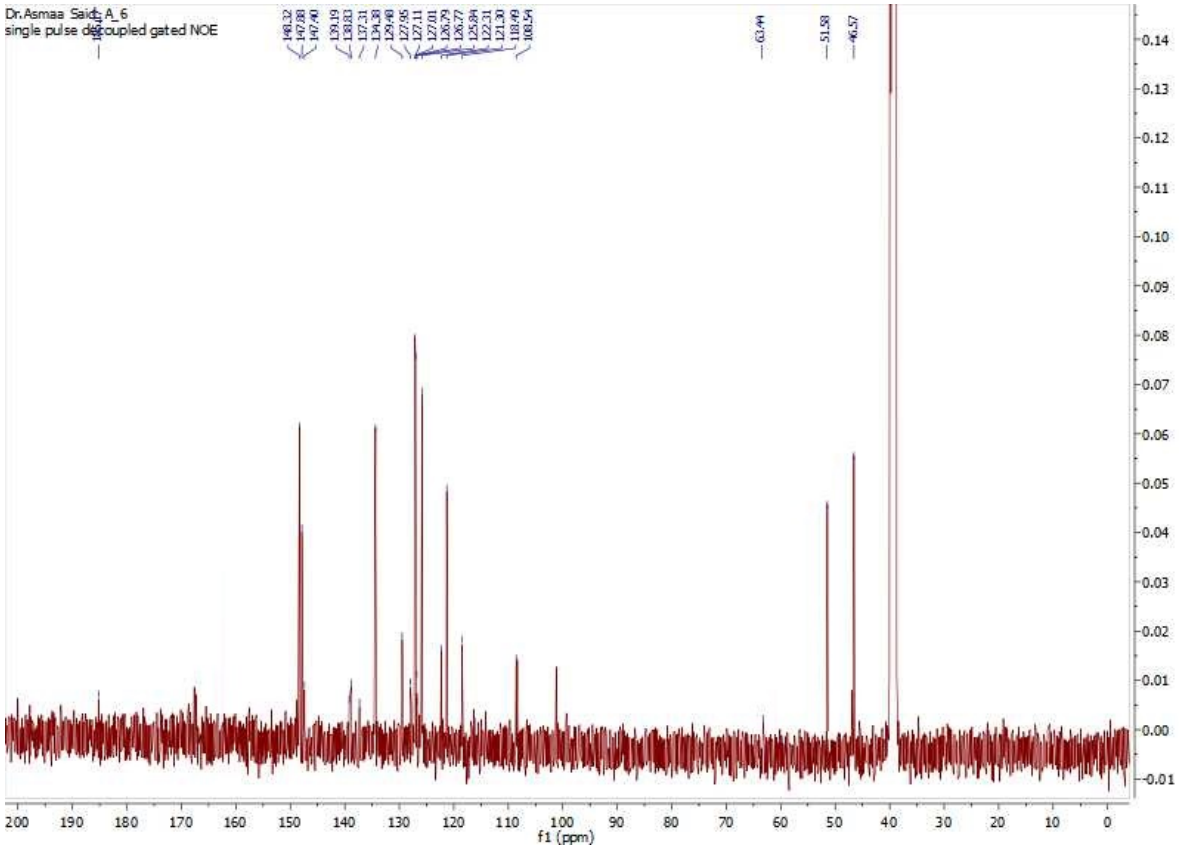
1.85
2.62
16.83
f1 (ppm)


Dr.Asmaa Said_A_6
single pulse decoupled gated NOE
148.32
147.88
147.40
139.19
138.83
137.31
134.38
129.48
127.95
127.11
127.01
126.79
126.77
125.84
122.31
121.30
118.49
108.54
63.44
51.58
46.57
f1 (ppm)

The purity of compounds (17)

The purity of the designed compounds was checked by liquid chromatography using the following condition:

HPLC separation and quantitation were made on a 150 x 4.6 mm (i.d.) Phenomenex® (5 µm particle size) reversed phase C18 analytical column. The best composition of the mobile phase through isocratic elution was prepared, the mobile phase was 0.1% orthophosphoric acid: acetonitrile: methanol in ratio 60:20:20 The flow rate was 0.2 ml min^{-1}. Quantitation was achieved with PDA detector. All determinations were performed at 25 ºC. The injection volume was 20 µl.