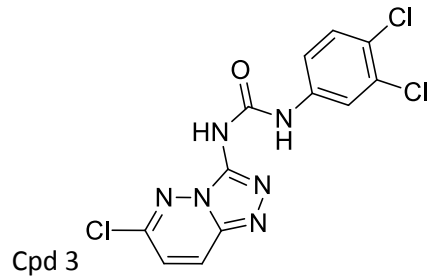
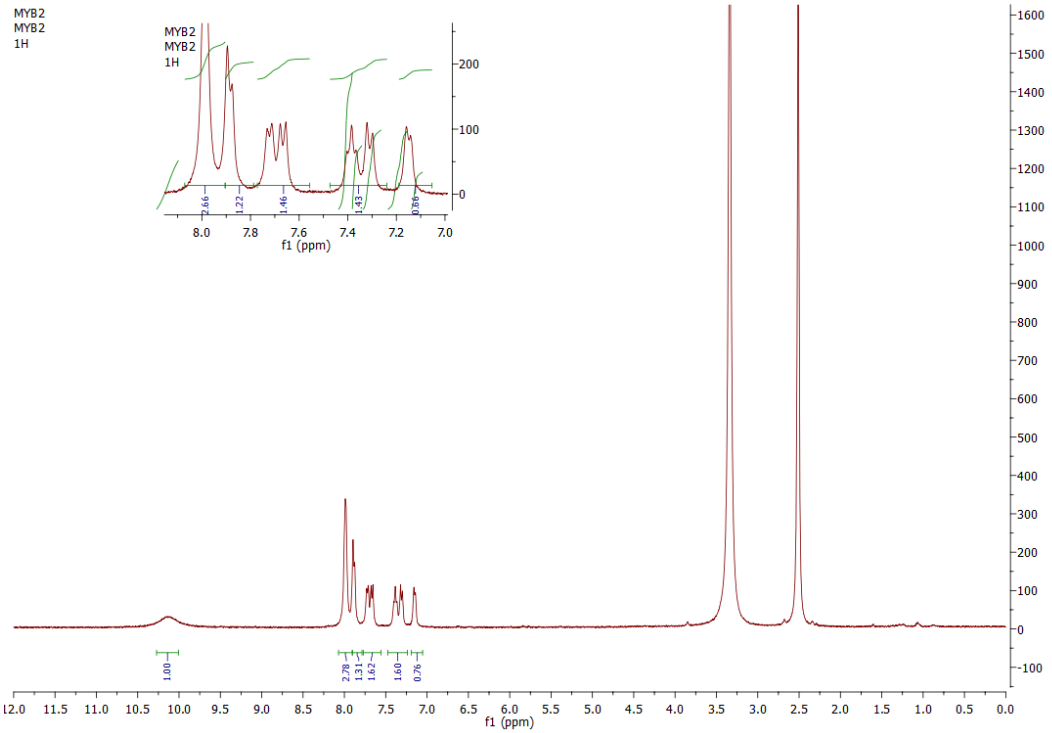
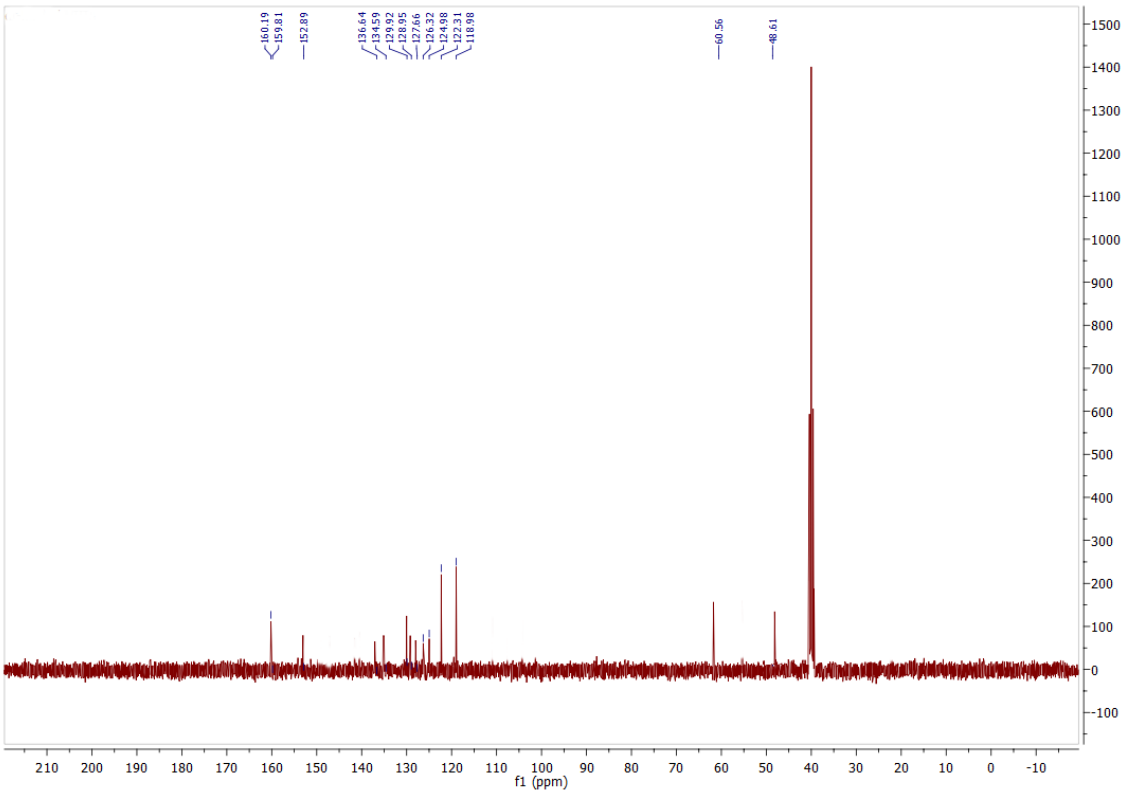
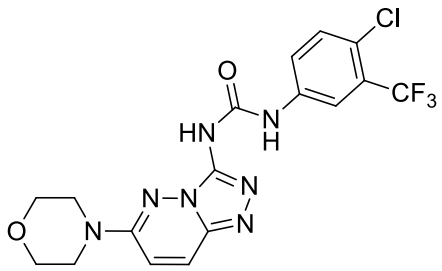


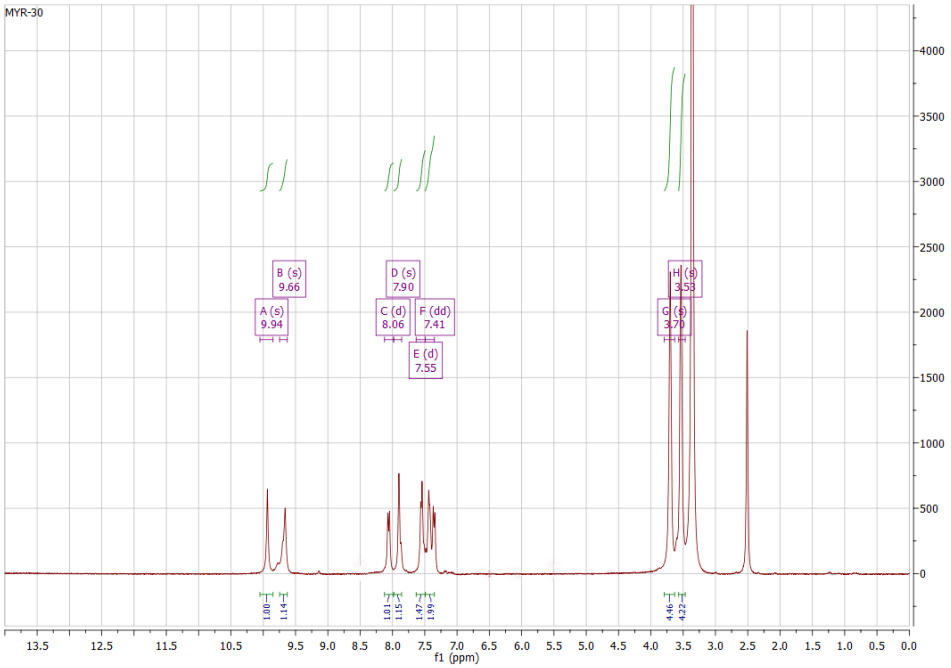
Cpd 3

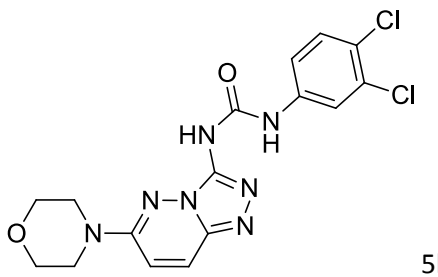



160.19
159.81
152.89
136.64
134.59
129.92
128.95
127.66
126.32
124.98
122.31
118.98
60.56
48.61
f1 (ppm)

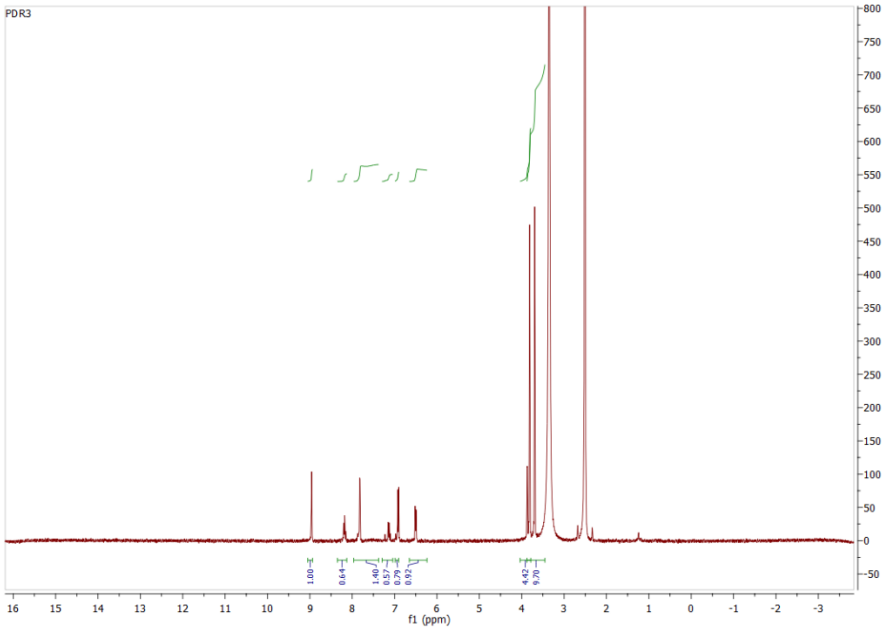

Cl
O
CF3
HN
N
H
N
N
N
O
N

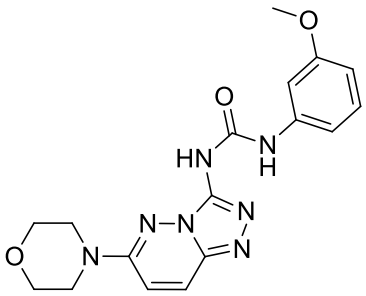
5c


MYR-30
B (s)
9.66
A (s)
9.94
D (s)
7.90
C (d)
8.06
F (dd)
7.41
E (d)
7.55
H (s)
3.53
G (s)
3.70
1.00
1.14
1.01
1.15
1.47
1.99
4.46
4.22
f1 (ppm)

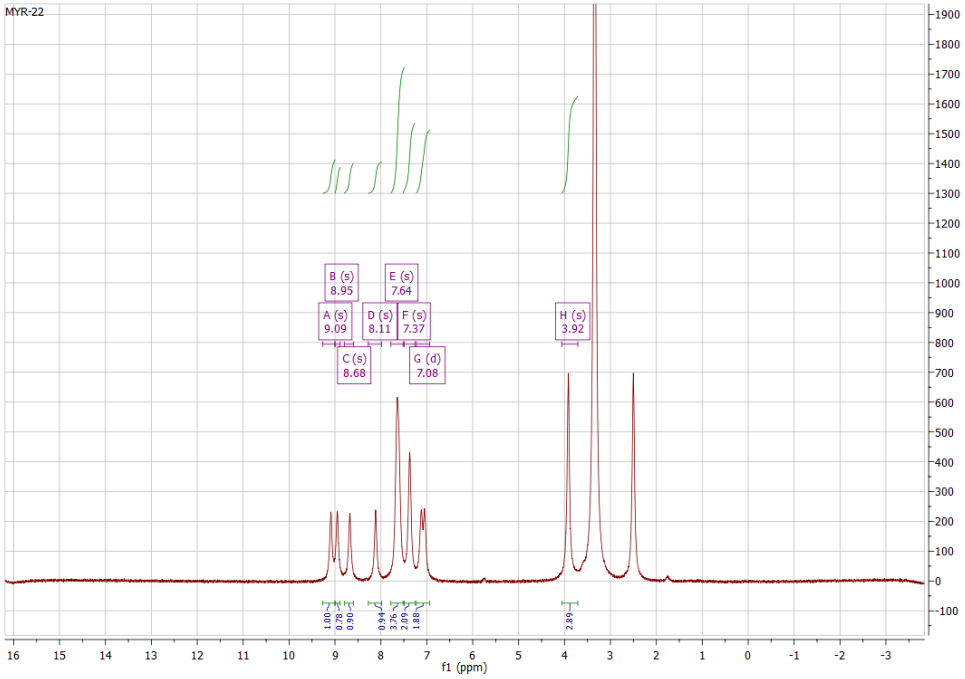


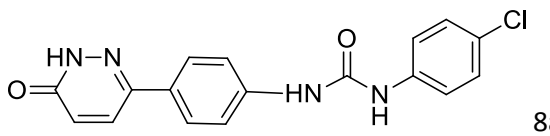
5b



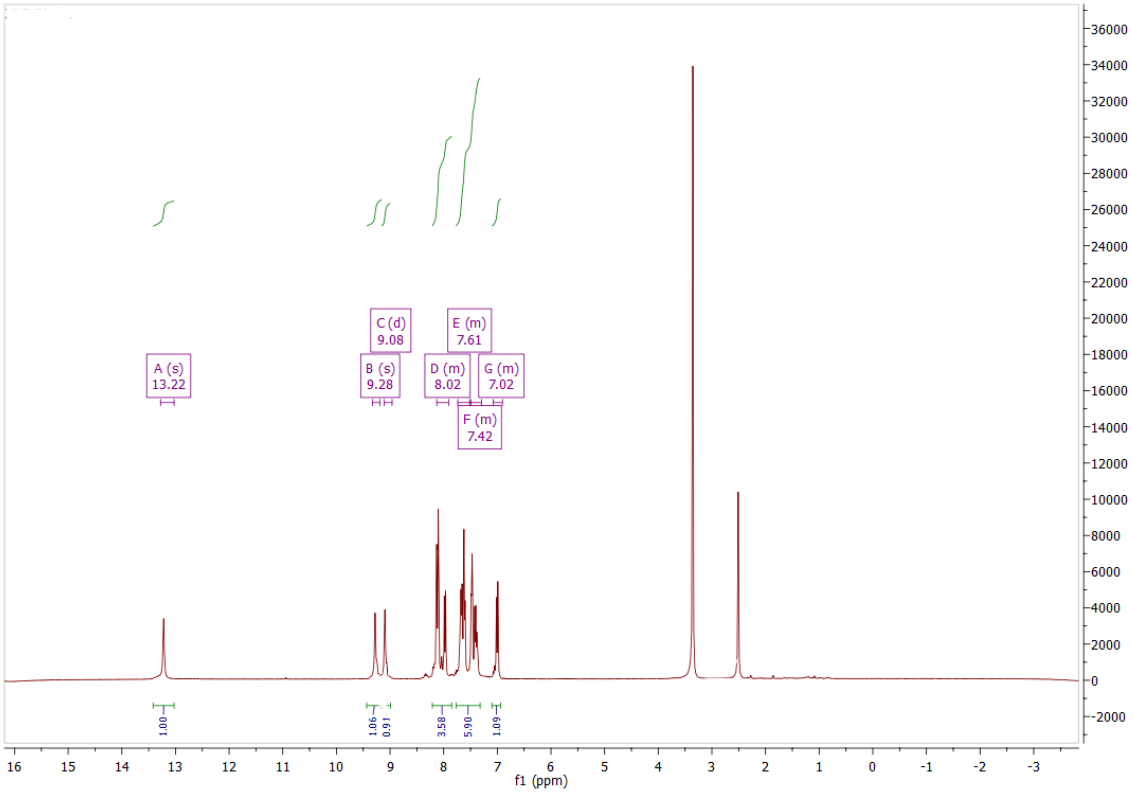

O
O
HN
N
H
N
N
N
N
O
N

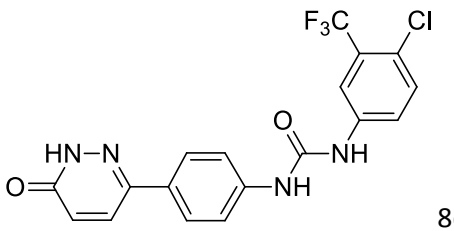
5a


MYR-22
B (s) 8.95
E (s) 7.64
A (s) 9.09
D (s) 8.11
F (s) 7.37
H (s) 3.92
C (s) 8.68
G (d) 7.08
1.00
0.78
0.90
0.94
3.76
2.09
1.88
2.89
f1 (ppm)

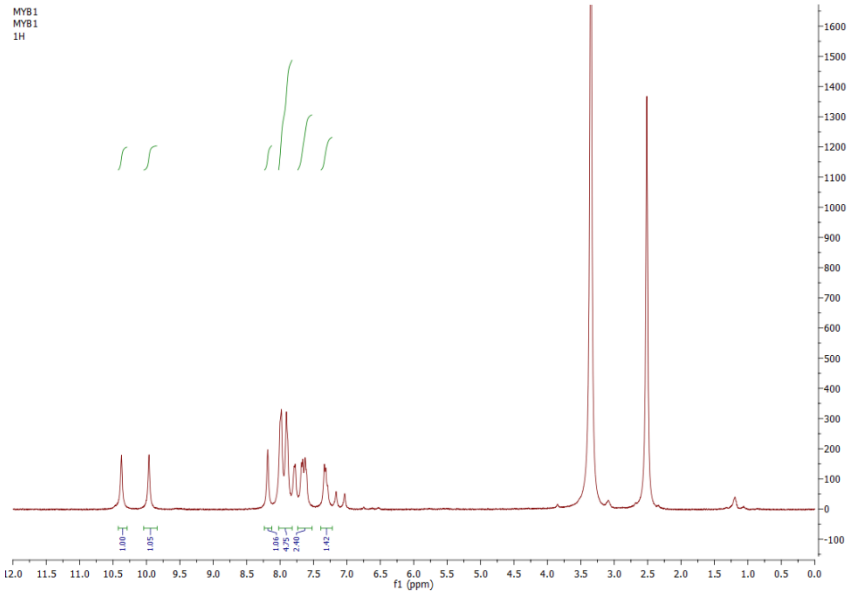

HN–N
O
HN
O
N
H
Cl

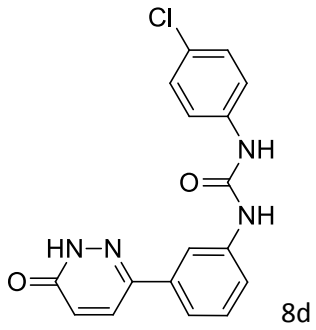
8a


A (s)
13.22
C (d)
9.08
B (s)
9.28
E (m)
7.61
D (m)
8.02
G (m)
7.02
F (m)
7.42
1.00
1.06
0.91
3.58
5.90
1.09
f1 (ppm)

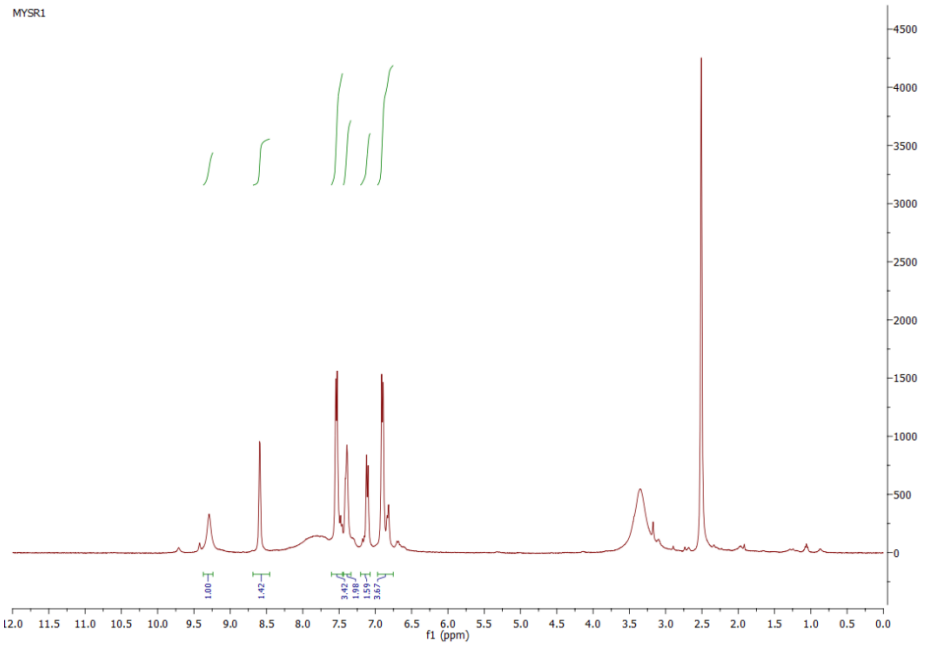


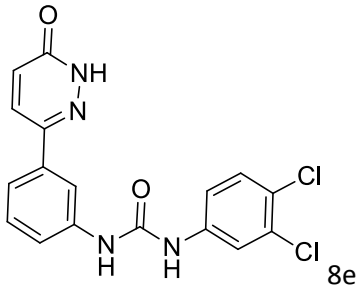
8c



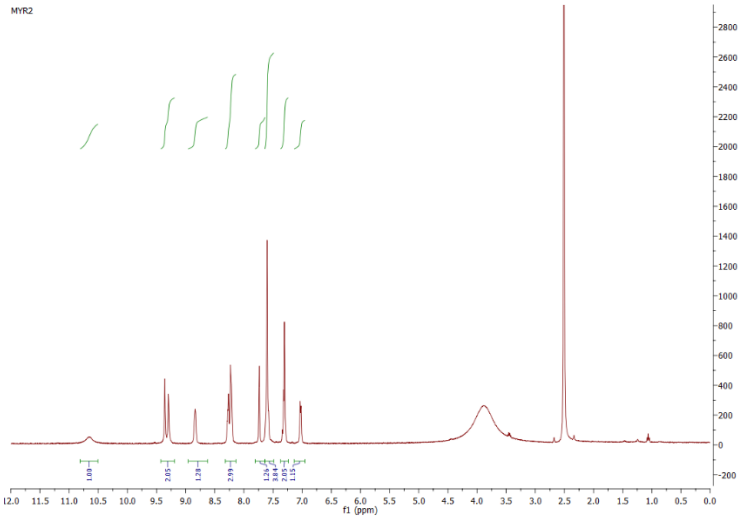

Cl
NH
O
NH
HN–N
O

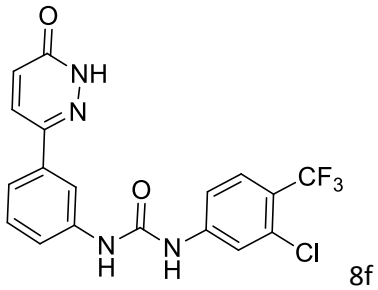
8d


MYSR1
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.00
1.42
3.42
1.98
1.57
3.57
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
0.0
f1 (ppm)

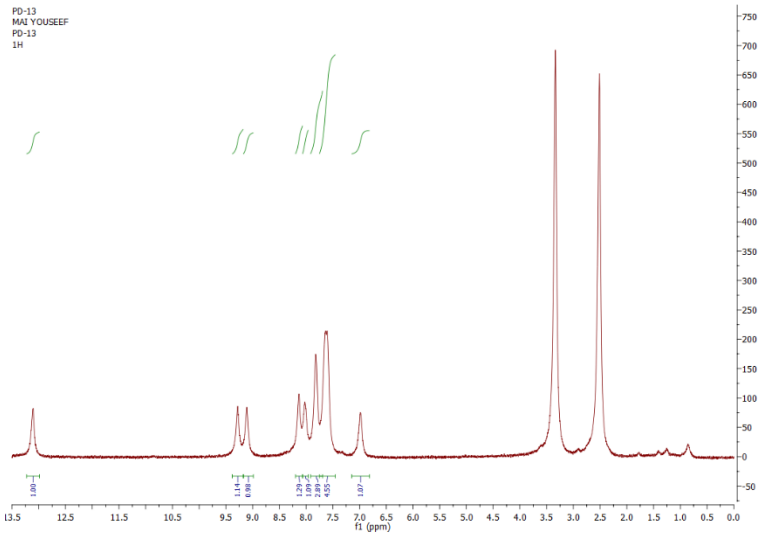


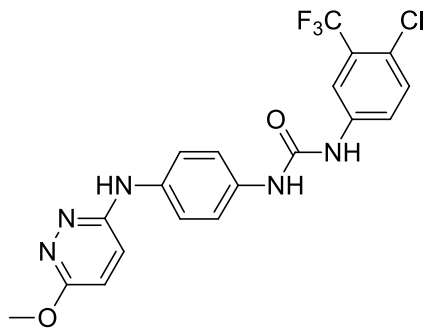
8e



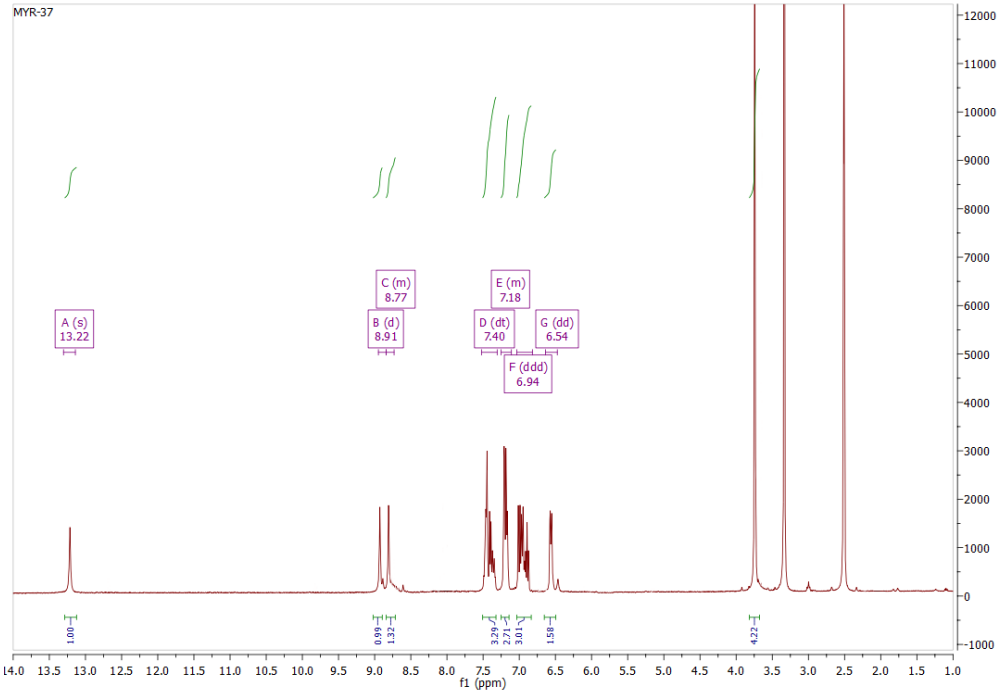


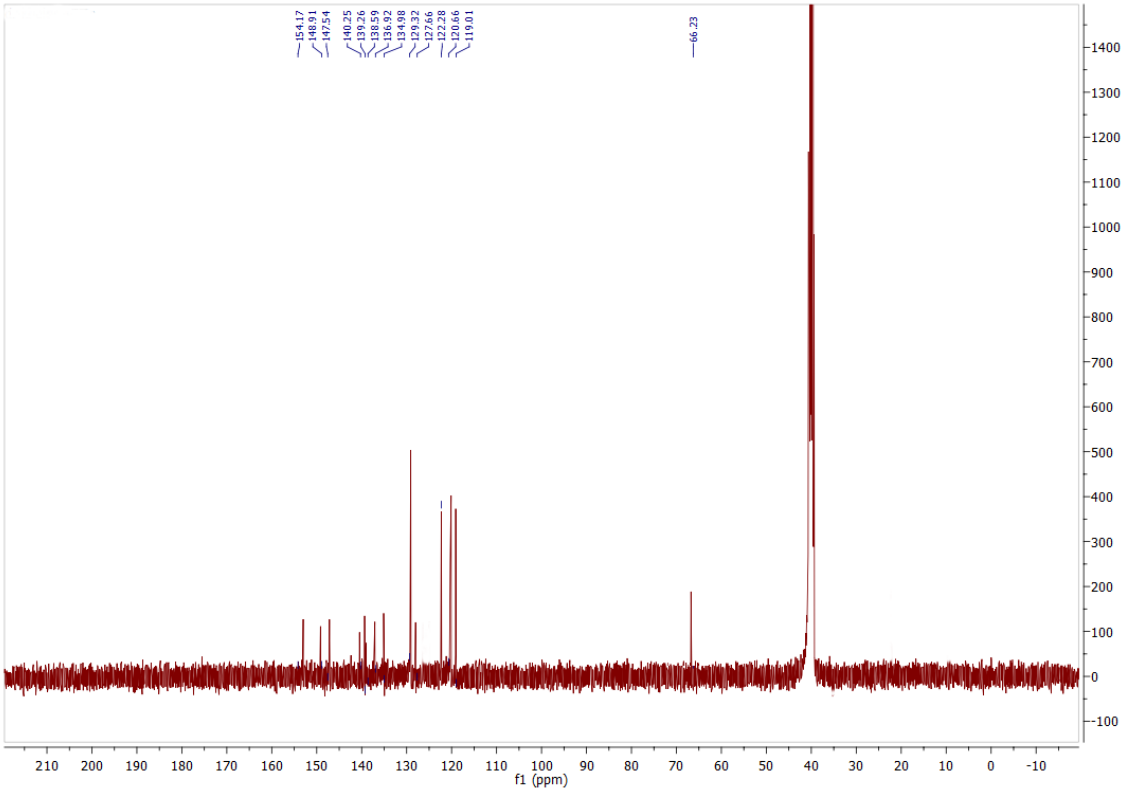
8f

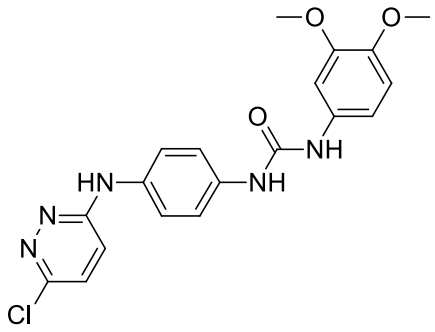



F3C
Cl
O
NH
HN
NH
N
N
O

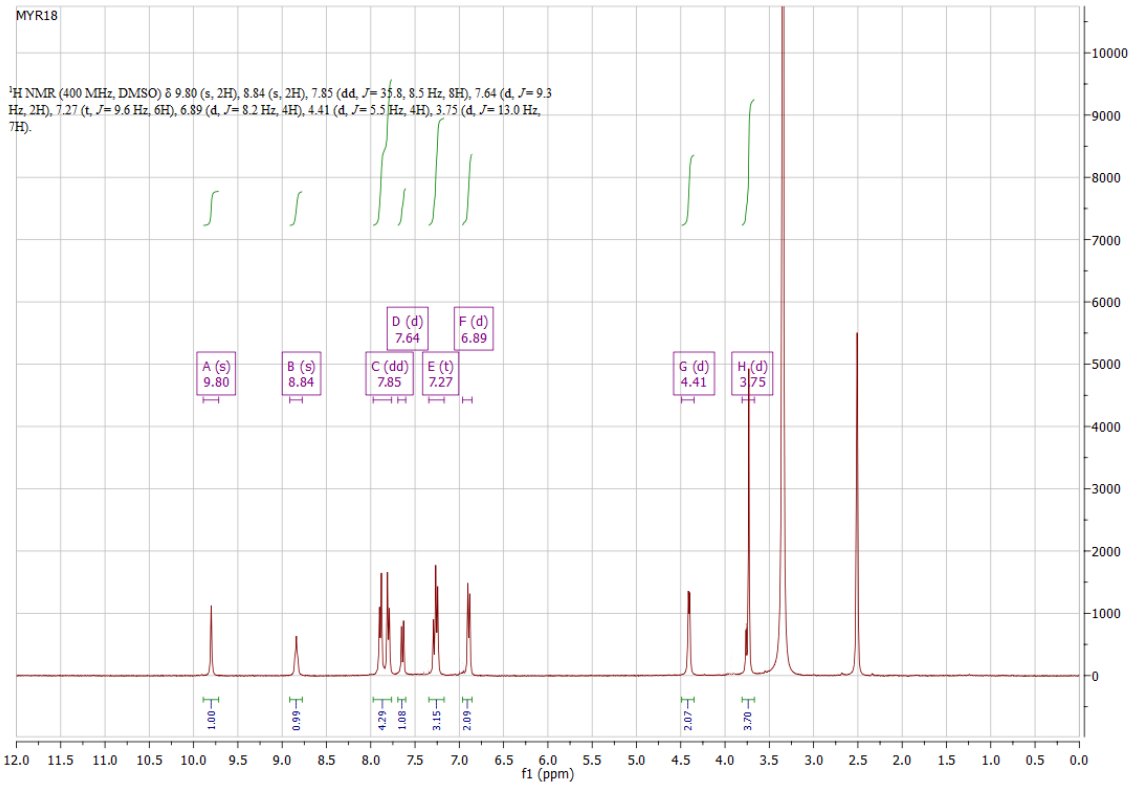
15

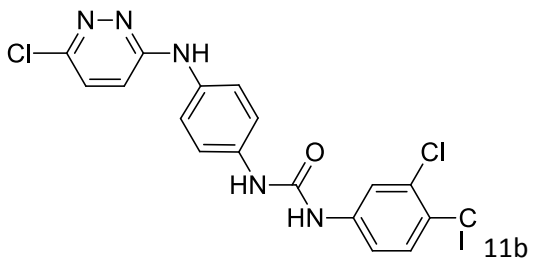

MYR-37
A (s)
13.22
C (m)
8.77
B (d)
8.91
E (m)
7.18
D (dt)
7.40
G (dd)
6.54
F (ddd)
6.94
1.00
0.99
1.32
3.29
2.71
3.01
1.58
4.22
f1 (ppm)


154.17
148.91
147.54
140.25
139.26
138.59
136.92
134.98
129.32
127.66
122.28
120.66
119.01
66.23
f1 (ppm)

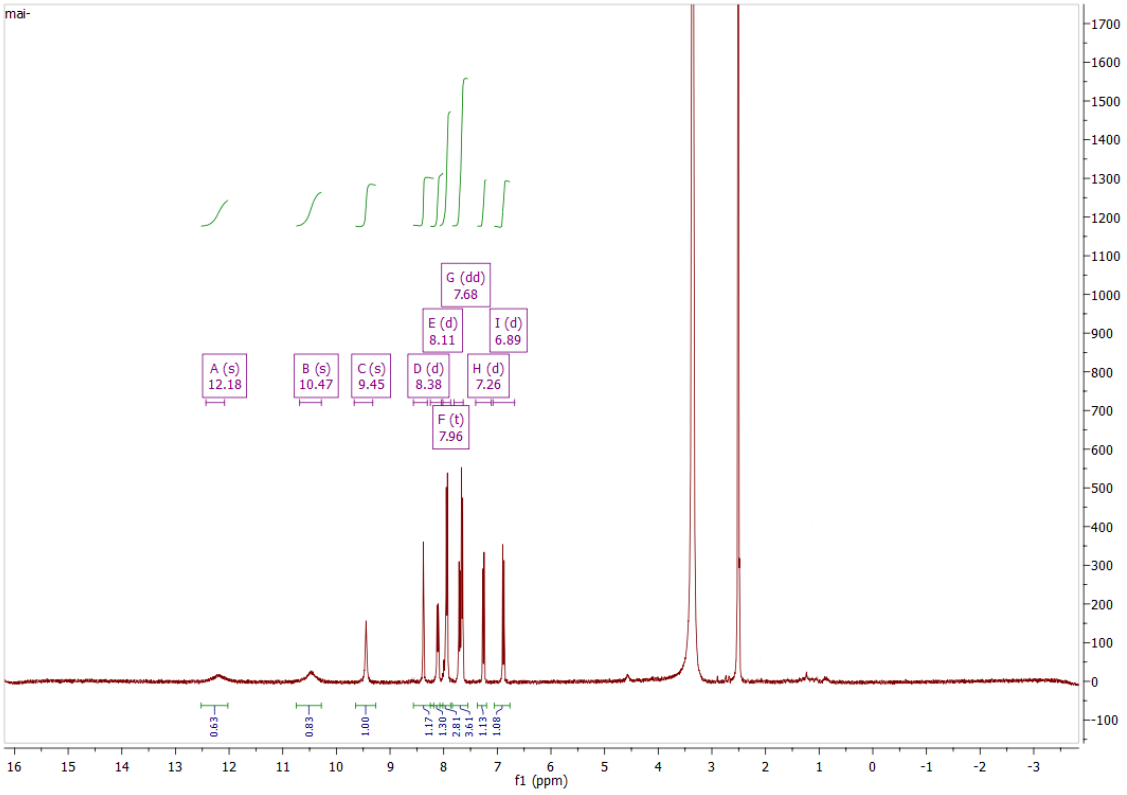

O
O
O
NH
HN
NH
N
N
Cl

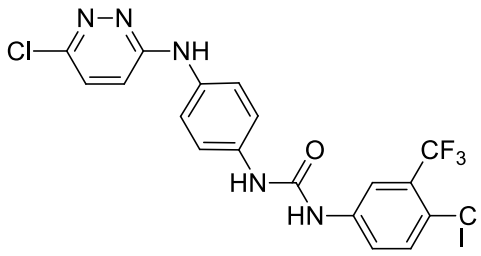
11a

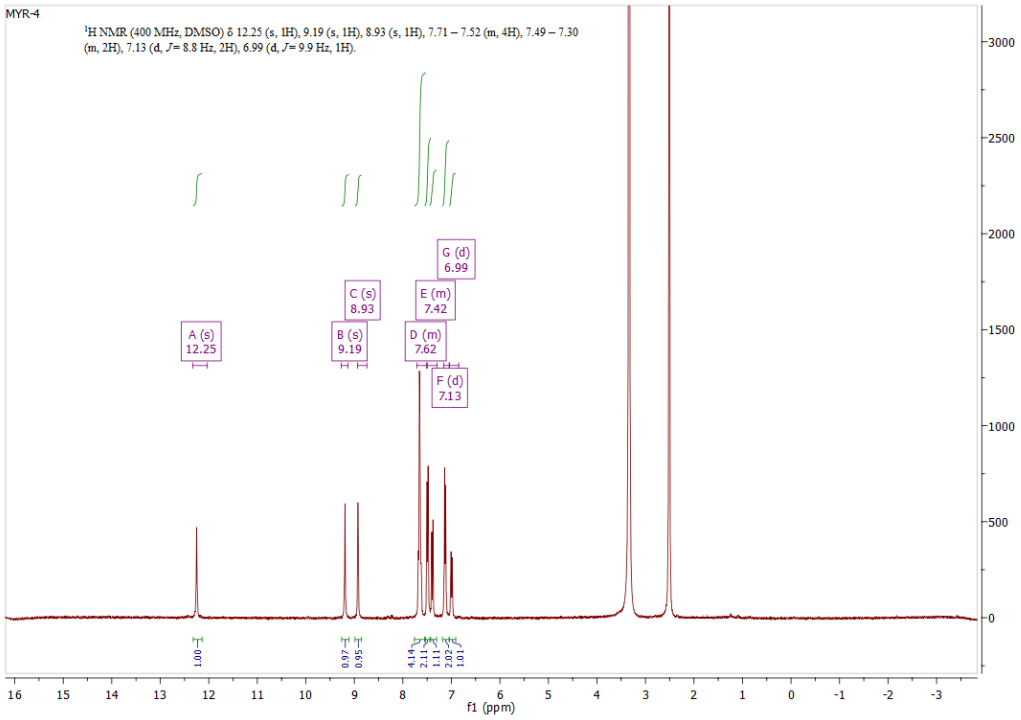

MYR18
^{1}H NMR (400 MHz, DMSO) δ 9.80 (s, 2H), 8.84 (s, 2H), 7.85 (dd, J= 35.8, 8.5 Hz, 8H), 7.64 (d, J= 9.3 Hz, 2H), 7.27 (t, J= 9.6 Hz, 6H), 6.89 (d, J= 8.2 Hz, 4H), 4.41 (d, J= 5.5 Hz, 4H), 3.75 (d, J= 13.0 Hz, 7H).
A (s) 9.80
B (s) 8.84
C (dd) 7.85
D (d) 7.64
E (t) 7.27
F (d) 6.89
G (d) 4.41
H (d) 3.75
1.00
0.99
4.29
1.08
3.15
2.09
2.07
3.70
f1 (ppm)

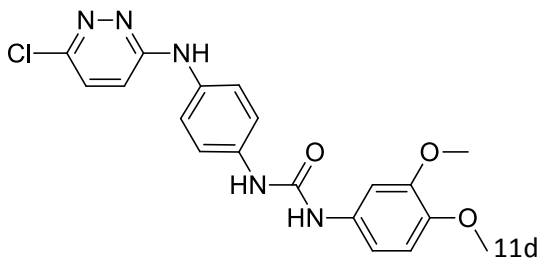

N–N
Cl
NH
HN
O
HN
Cl
Cl

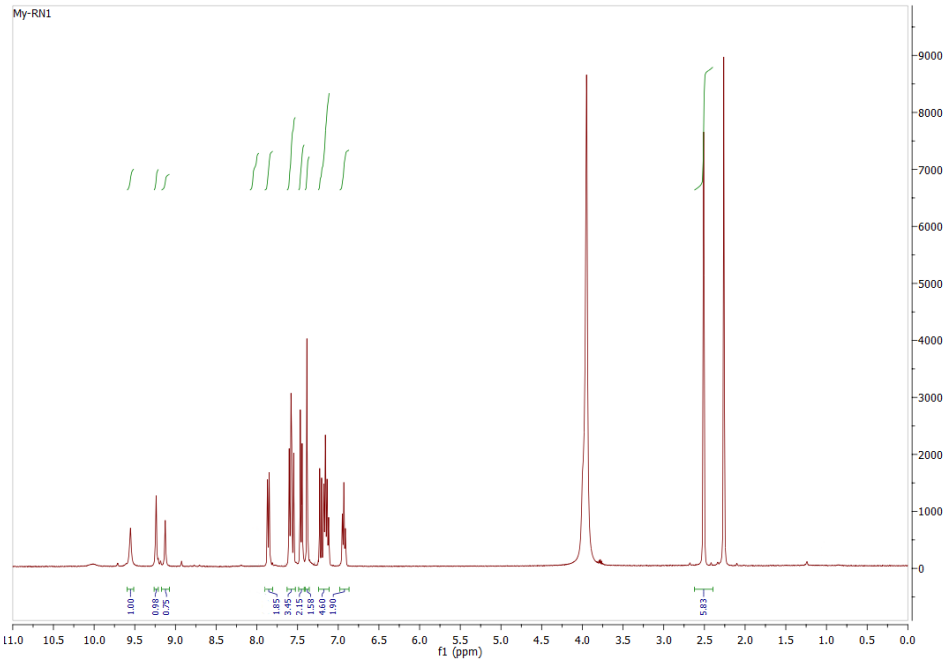
11b

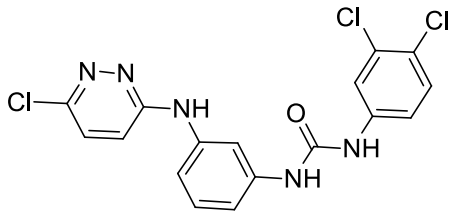

mai-
A (s) 12.18
B (s) 10.47
C (s) 9.45
D (d) 8.38
E (d) 8.11
F (t) 7.96
G (dd) 7.68
H (d) 7.26
I (d) 6.89
0.63
0.83
1.00
1.17
1.30
2.81
3.61
1.13
1.08
f1 (ppm)


N–N
Cl
NH
O
HN
HN
CF3
C
I

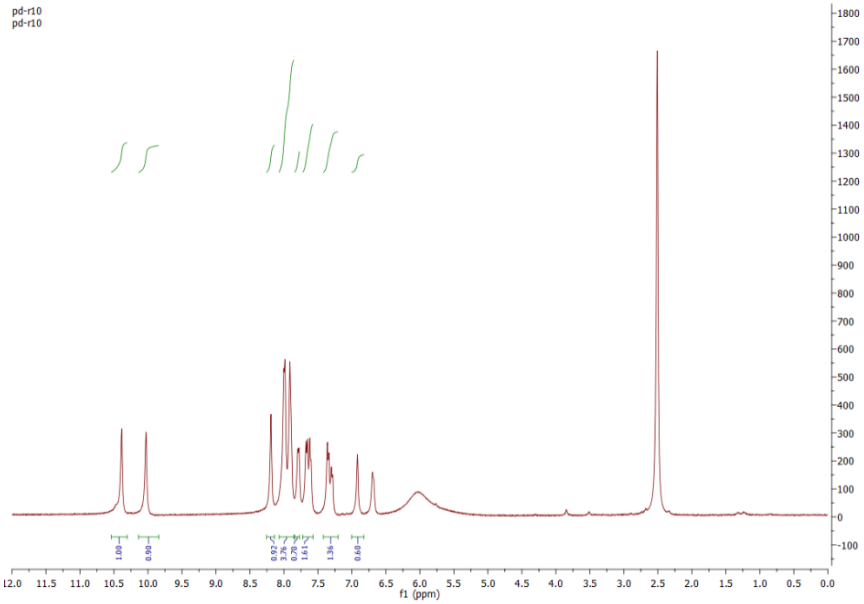

MYR-4
¹H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 9.19 (s, 1H), 8.93 (s, 1H), 7.71 – 7.52 (m, 4H), 7.49 – 7.30 (m, 2H), 7.13 (d, J= 8.8 Hz, 2H), 6.99 (d, J= 9.9 Hz, 1H).
A (s) 12.25
B (s) 9.19
C (s) 8.93
D (m) 7.62
E (m) 7.42
F (d) 7.13
G (d) 6.99
1.00
0.97
0.95
4.14
2.11
1.11
2.02
1.01
f1 (ppm)

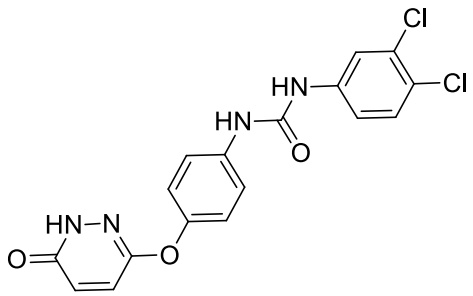

N–N
Cl
NH
HN
O
HN
O
O
11d


My-RN1
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.00
0.89
0.75
1.85
3.45
2.15
1.58
4.60
1.90
5.83
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
0.0
f1 (ppm)

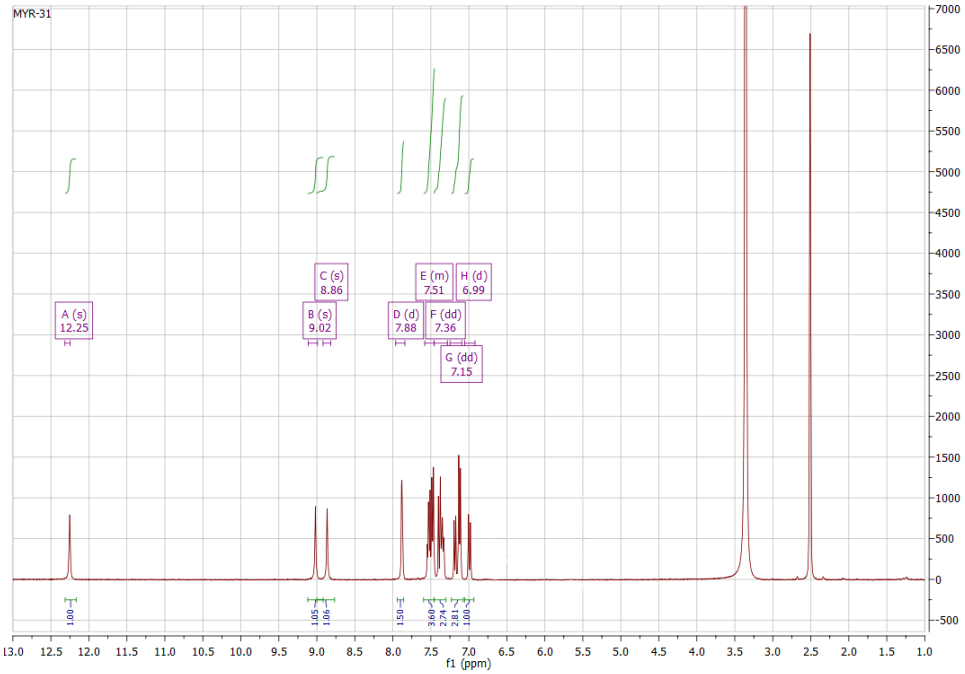


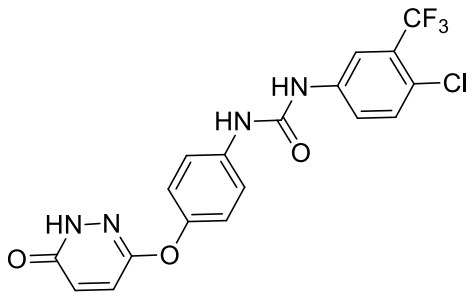
11e



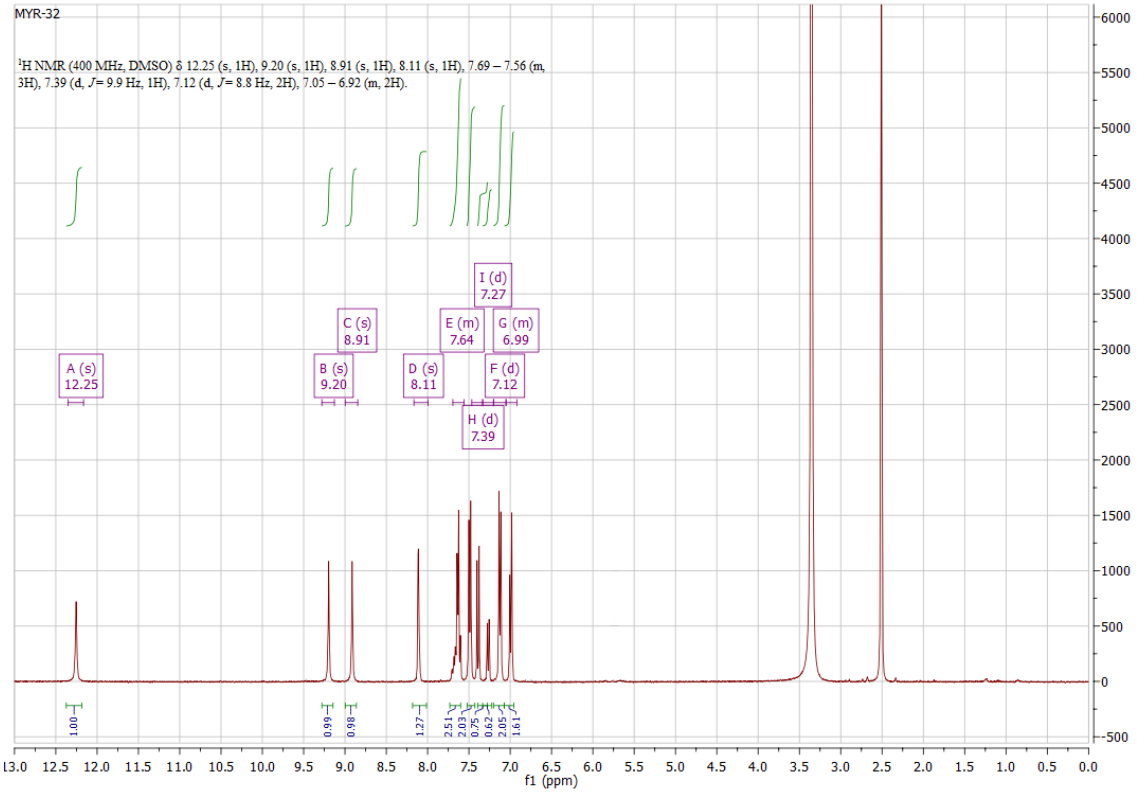

Cl
Cl
HN
HN
O
HN–N
O
O

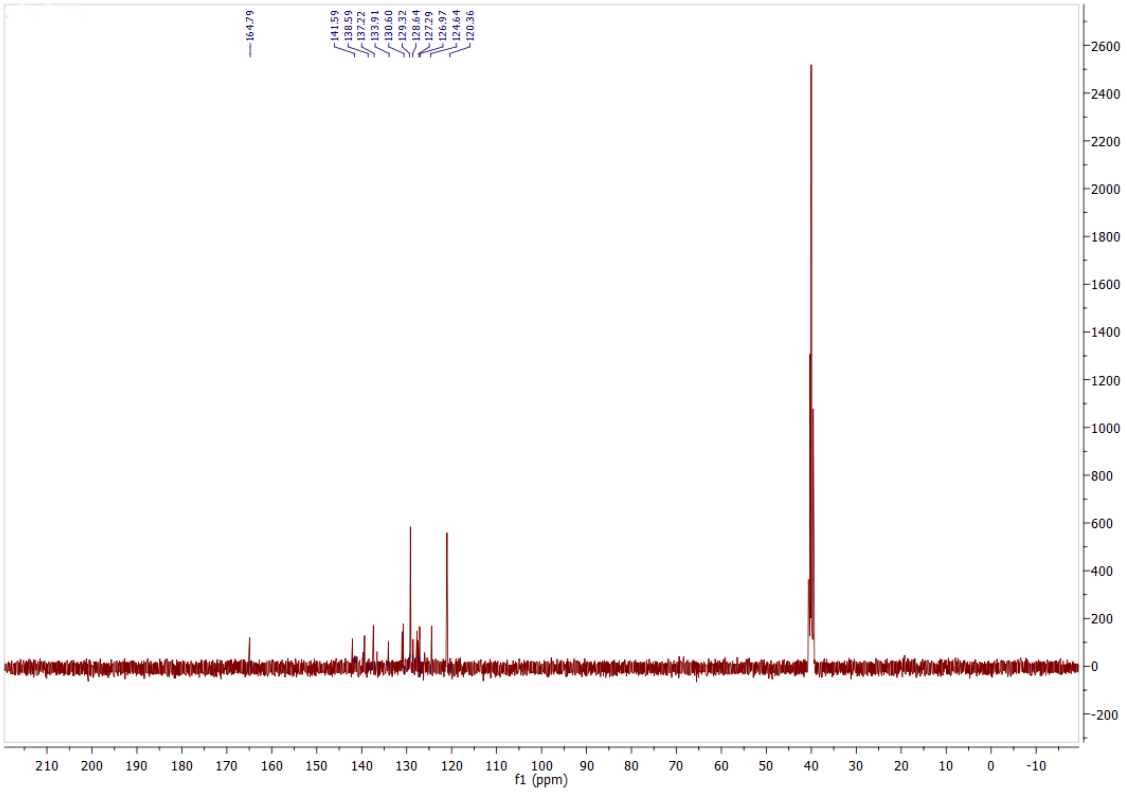
18c

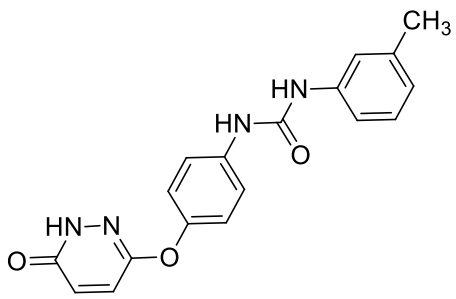

MYR-31
A (s) 12.25
C (s) 8.86
B (s) 9.02
D (d) 7.88
E (m) 7.51
F (dd) 7.36
H (d) 6.99
G (dd) 7.15
1.00
1.05
1.06
1.50
3.60
2.74
2.81
1.00
f1 (ppm)


CF3
Cl
HN
HN
O
HN–N
O
O

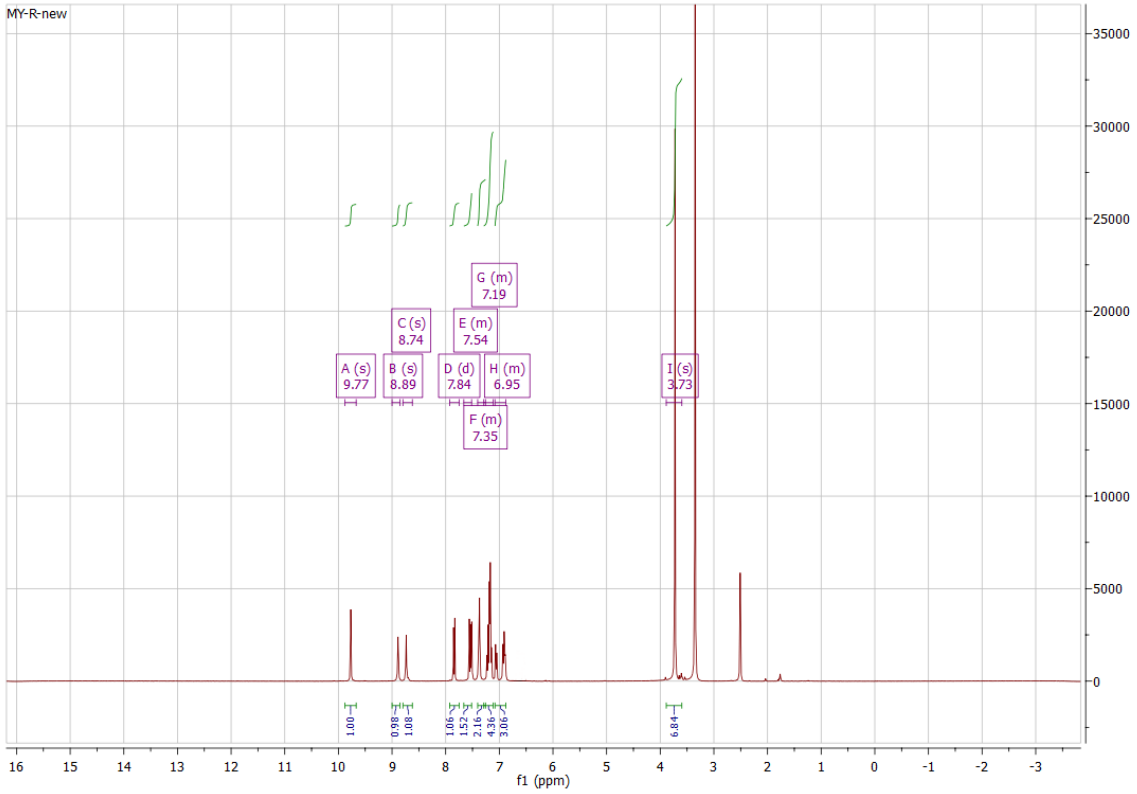
18b


MYR-32
¹H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 9.20 (s, 1H), 8.91 (s, 1H), 8.11 (s, 1H), 7.69 – 7.56 (m, 3H), 7.39 (d, J= 9.9 Hz, 1H), 7.12 (d, J= 8.8 Hz, 2H), 7.05 – 6.92 (m, 2H).
A (s) 12.25
B (s) 9.20
C (s) 8.91
D (s) 8.11
E (m) 7.64
F (d) 7.12
G (m) 6.99
H (d) 7.39
I (d) 7.27
f1 (ppm)

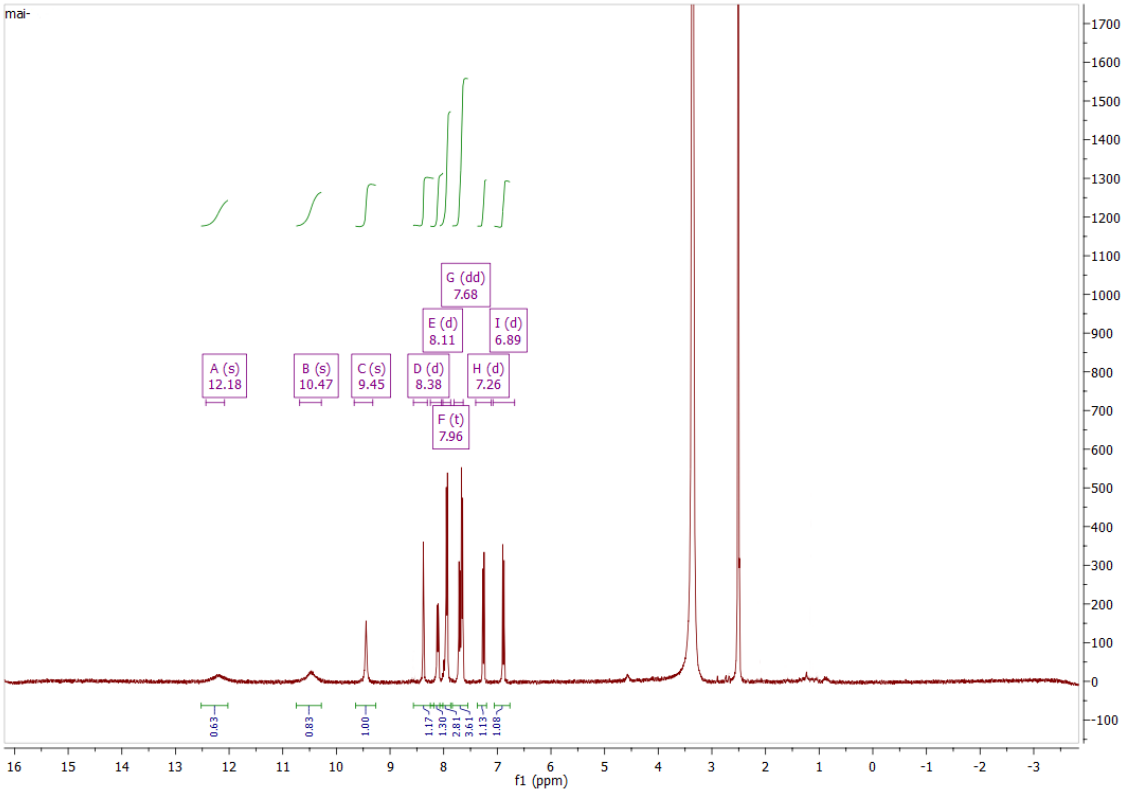

164.79
141.59
138.59
137.22
133.91
130.60
129.32
128.64
127.29
126.97
124.64
120.36
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CH3
HN
HN
O
HN–N
O
O

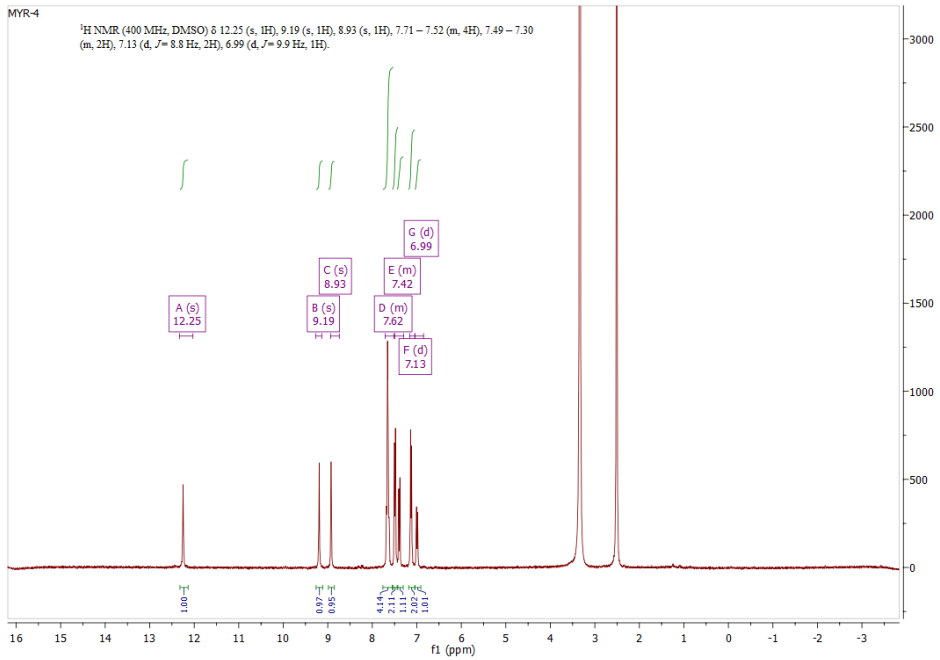
18a


MY-R-new
G (m) 7.19
C (s) 8.74
E (m) 7.54
A (s) 9.77
B (s) 8.89
D (d) 7.84
H (m) 6.95
I (s) 3.73
F (m) 7.35
1.00
0.98
1.08
1.06
1.52
2.16
4.36
3.06
6.84
f1 (ppm)

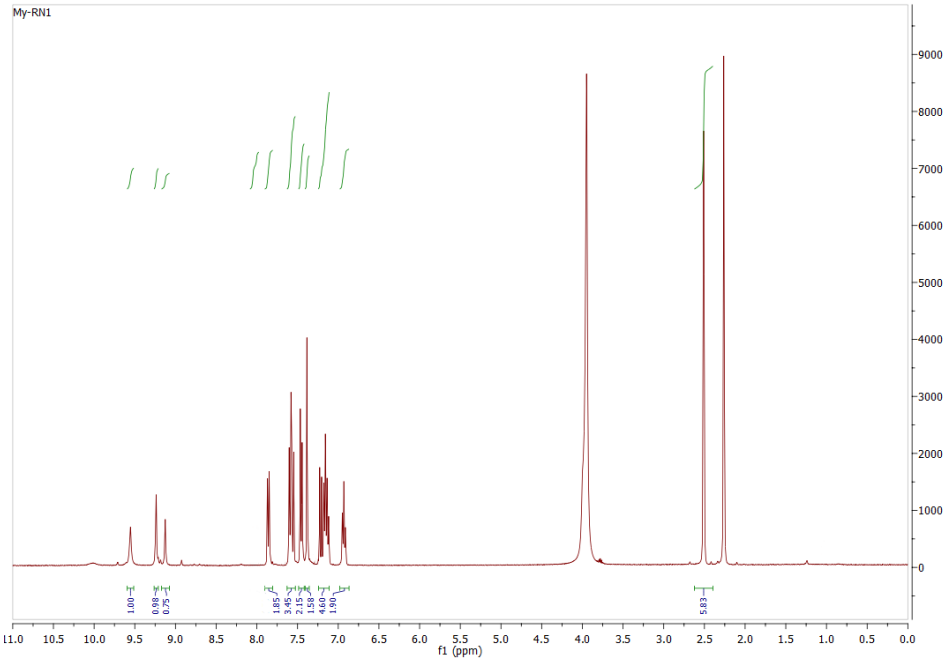
11b


mai-
A (s)
12.18
B (s)
10.47
C (s)
9.45
D (d)
8.38
E (d)
8.11
F (t)
7.96
G (dd)
7.68
H (d)
7.26
I (d)
6.89
0.63
0.83
1.00
1.17
1.30
2.81
3.61
1.13
1.08
f1 (ppm)

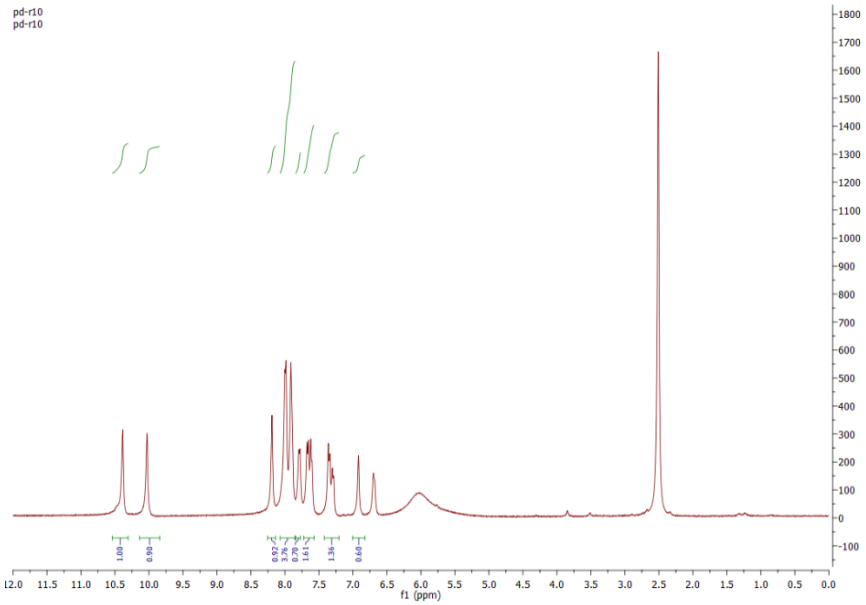
11c


MYR-4
¹H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 9.19 (s, 1H), 8.93 (s, 1H), 7.71 – 7.52 (m, 4H), 7.49 – 7.30 (m, 2H), 7.13 (d, J= 8.8 Hz, 2H), 6.99 (d, J= 9.9 Hz, 1H).
A (s) 12.25
B (s) 9.19
C (s) 8.93
D (m) 7.62
E (m) 7.42
F (d) 7.13
G (d) 6.99
f1 (ppm)

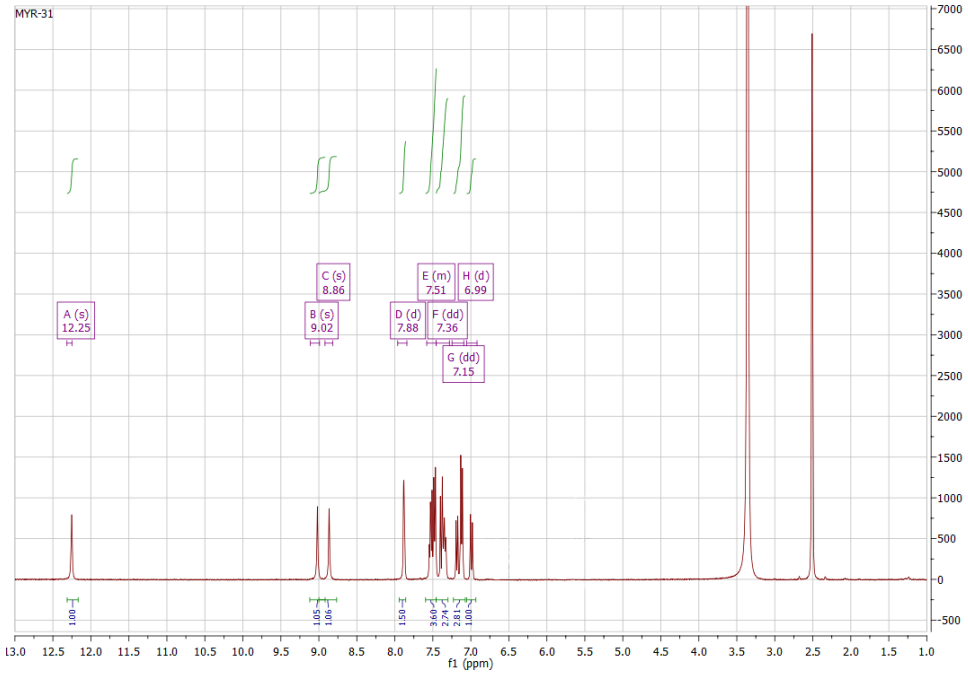
11d


My-RN1
f1 (ppm)

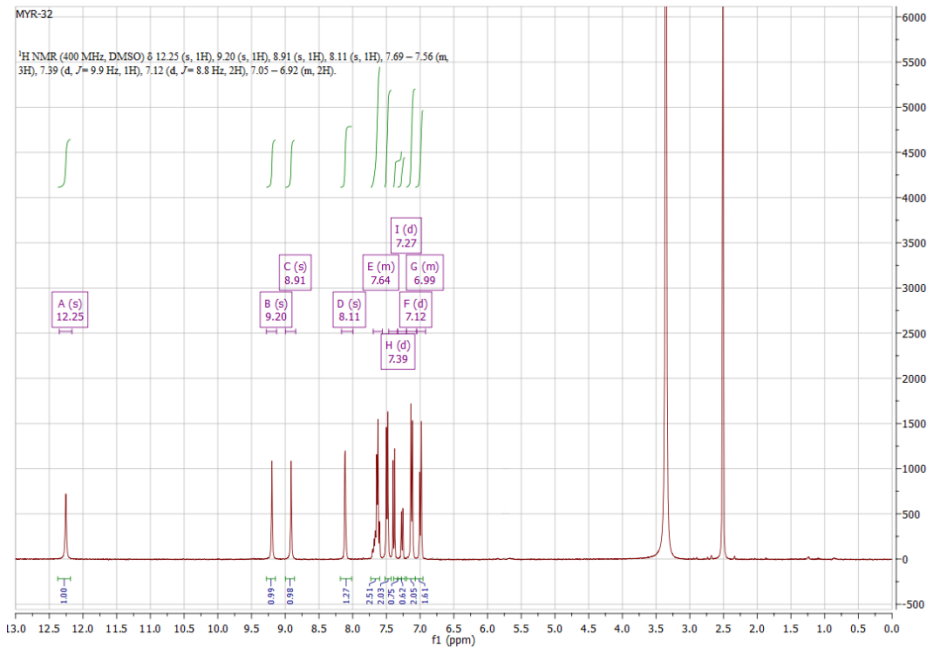
11e

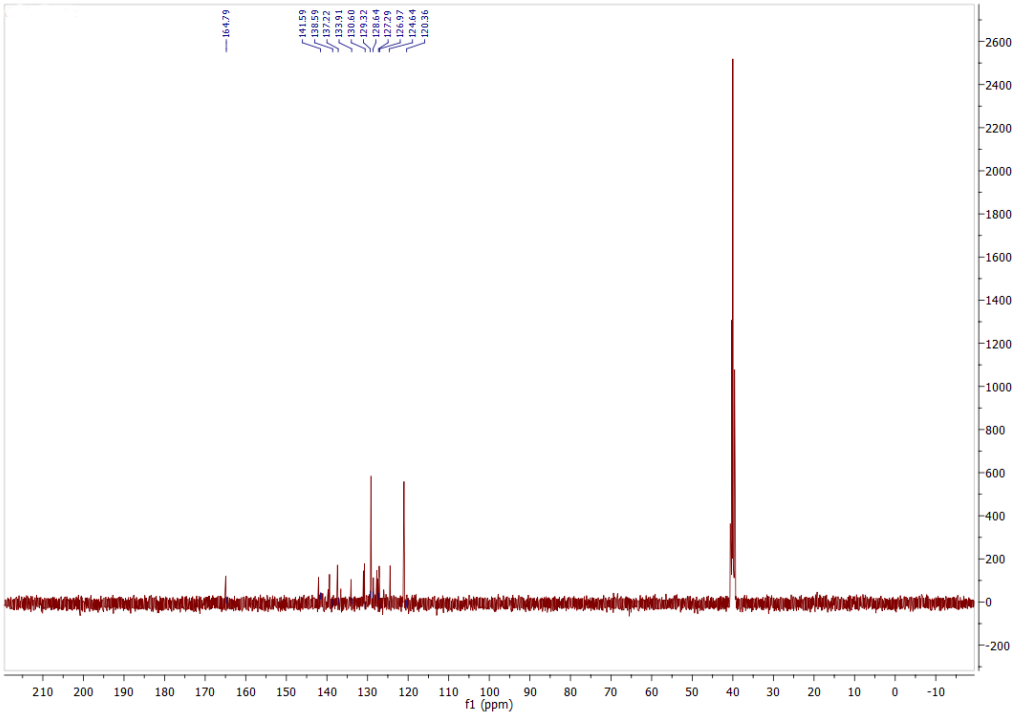

pd-r10
pd-r10
f1 (ppm)

18c

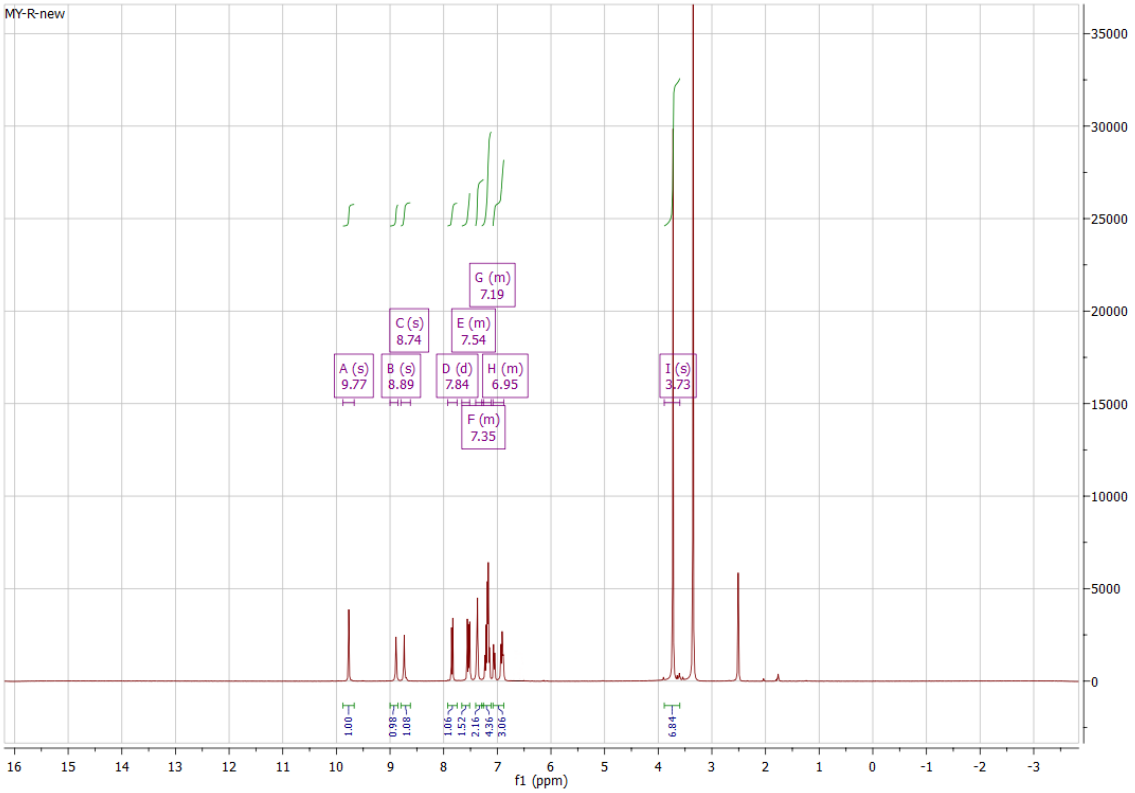

MYR-31
A (s)
12.25
B (s)
9.02
C (s)
8.86
D (d)
7.88
E (m)
7.51
F (dd)
7.36
G (dd)
7.15
H (d)
6.99
f1 (ppm)

18b


MYR-32
¹H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 9.20 (s, 1H), 8.91 (s, 1H), 8.11 (s, 1H), 7.69 – 7.56 (m, 3H), 7.39 (d, J= 9.9 Hz, 1H), 7.12 (d, J= 8.8 Hz, 2H), 7.05 – 6.92 (m, 2H).
A (s) 12.25
B (s) 9.20
C (s) 8.91
D (s) 8.11
E (m) 7.64
F (d) 7.12
G (m) 6.99
H (d) 7.39
I (d) 7.27
f1 (ppm)


164.79
141.59
139.56
137.22
133.91
130.60
129.32
128.64
127.29
126.97
124.64
120.36
f1 (ppm)

18a


MY-R-new
A (s)
9.77
B (s)
8.89
C (s)
8.74
D (d)
7.84
E (m)
7.54
F (m)
7.35
G (m)
7.19
H (m)
6.95
I (s)
3.73
1.00
0.98
1.08
1.06
1.52
2.16
4.36
3.06
6.84
f1 (ppm)

S1 Dose response curves for measurement of VEGFR-2 inhibitory activity (IC_{50}).

S2: The relaxed potential energy surface scan of the torsional angel of the selected linker for compounds SORA, 11c, 15, 18b.

S3: Calculated (a) ligands and (b) receptors RMSD graphs for SORA, 11c and 18b over the 25ns MD trajectory.

S4: The per-residue decomposed lipophilic vdW binding energy of SORA, 11c and 18b over the 25ns MD trajectory calculated using the AMBER/MM-GBSA method in AMBER.

Fig S1:

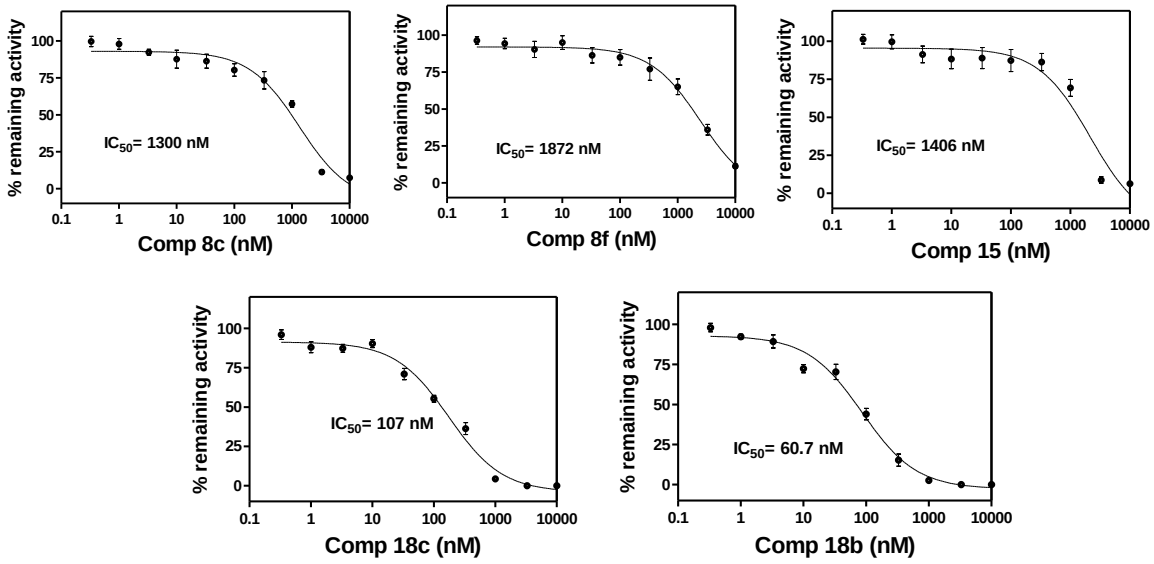


Figure S2

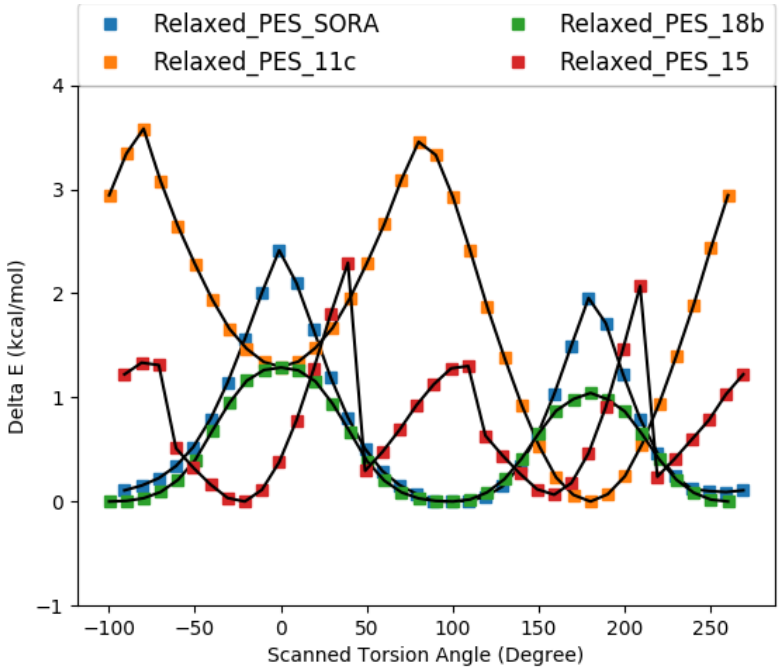

Relaxed_PES_SORA
Relaxed_PES_11c
Relaxed_PES_18b
Relaxed_PES_15
Delta E (kcal/mol)
Scanned Torsion Angle (Degree)

Figure S3:

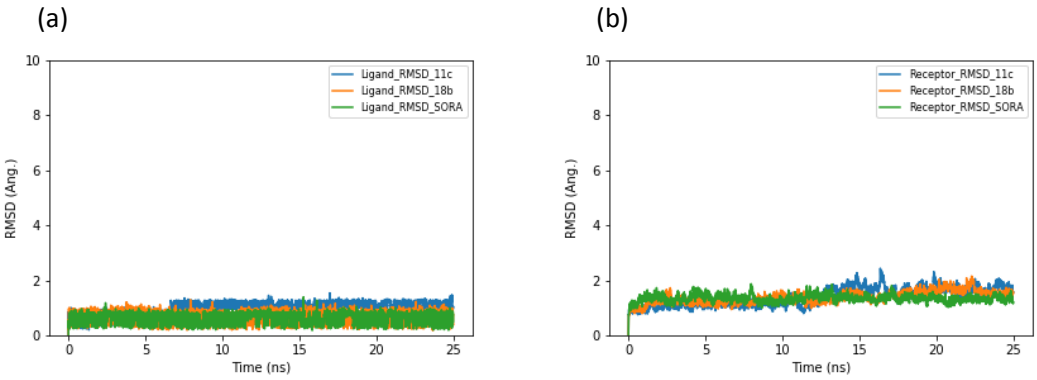

(a)
(b)
Ligand_RMSD_11c
Ligand_RMSD_18b
Ligand_RMSD_SORA
Receptor_RMSD_11c
Receptor_RMSD_18b
Receptor_RMSD_SORA
RMSD (Ang.)
Time (ns)

Figure S4

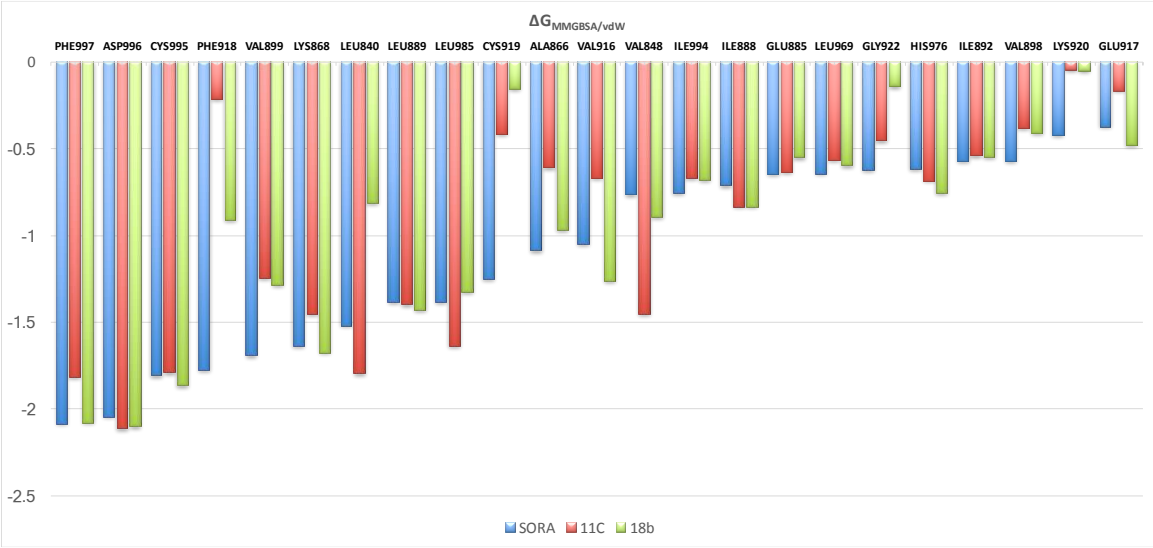


Table S1:

Selected measured and calculated activity parameters for the compounds under investigation (SORA). The AMBER/MM-GBSA scores and the H-bond occupancies are calculated over the 25ns MD simulation trajectory. Reported docking scores are for poses selected for carrying out the MD simulation. Please note that the VINA scores are reported in negative values and DLscores, NNscores and RFscores are reported in positive values.

Compound	IC50 (nm)	VINAscore	DLscore	NNscore2	RFscore	$\Delta G_{MM\text{-}GBSA}$	$\Delta G_{MM\text{-}GBSA/ELE}$	$\Delta G_{MMGBSA/vdW}$	CYS919-H-Bond Occ.	ASP996-H-Bond Occ.
SORA	90	-11.20	8.38	8.63	8.39	-46.87	-37.95	-59.72	86.34%	99.95%
11C	NA	-9.83	7.72	8.20	8.37	-36.97	-29.12	-51.84	NA	99.90%
18B	60.7	-10.79	7.61	8.38	8.28	-43.38	-39.98	-51.61	98.40%	99.90%