Sulfonamide based pyrimidine derivatives combating *Plasmodium* parasite by inhibiting falcipains-2 and falcipains-3 as antimalarial agents

Abdur Rahman[a]*, Shazia Anjum[a]*, Jaimin D. Bhatt[b] and Bharat C. Dixit[b], Anju Singh[a], Sabiha khan[a], Sadaf Fatima[a], Tarosh S. Patel[b]**, Nasimul Hoda[a]**

[a] *Drug Design and Synthesis Lab., Department of Chemistry, Jamia Millia Islamia, New Delhi-110025, India*

[b] *Chemistry Department, V. P. & R. P. T. P Science College, Affiliated to Sardar Patel University, Vallabh Vidyanagar – 388 120, Gujarat, India.*

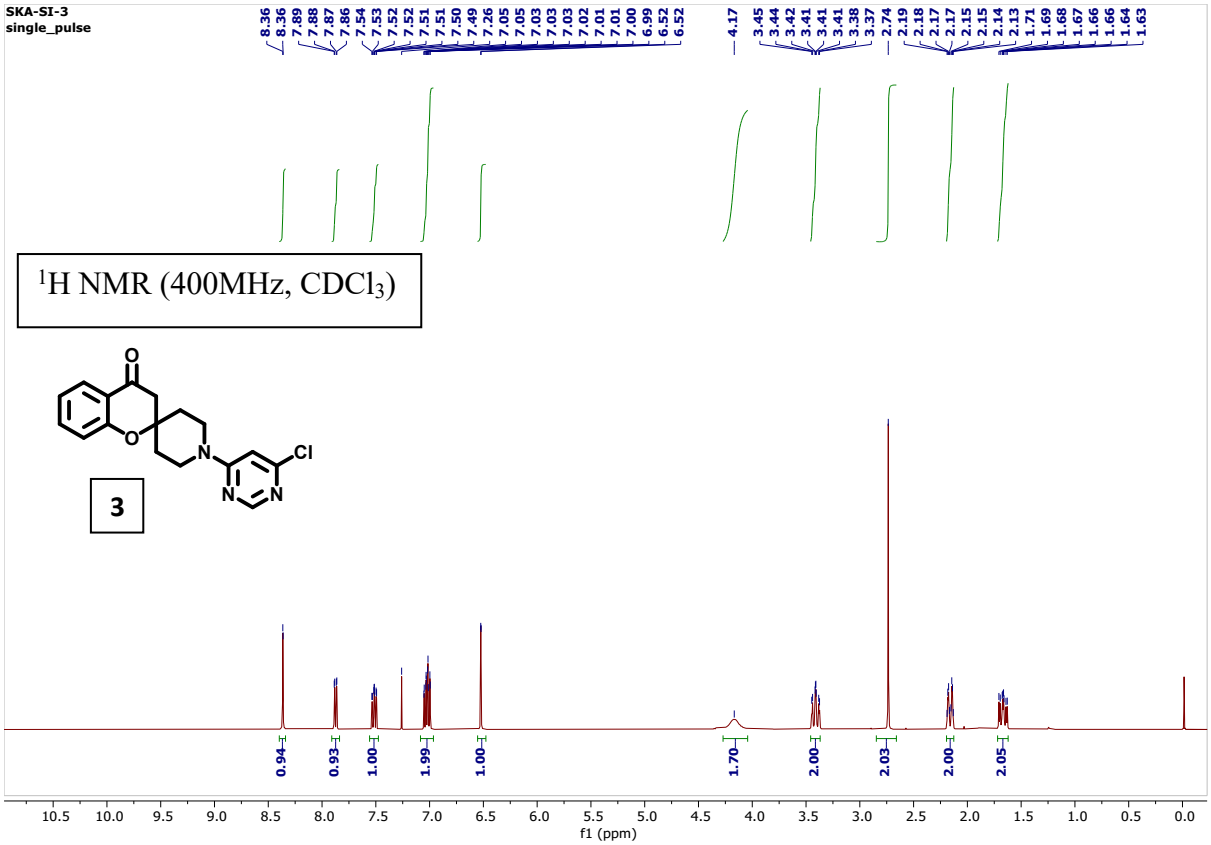
*Equal contribution

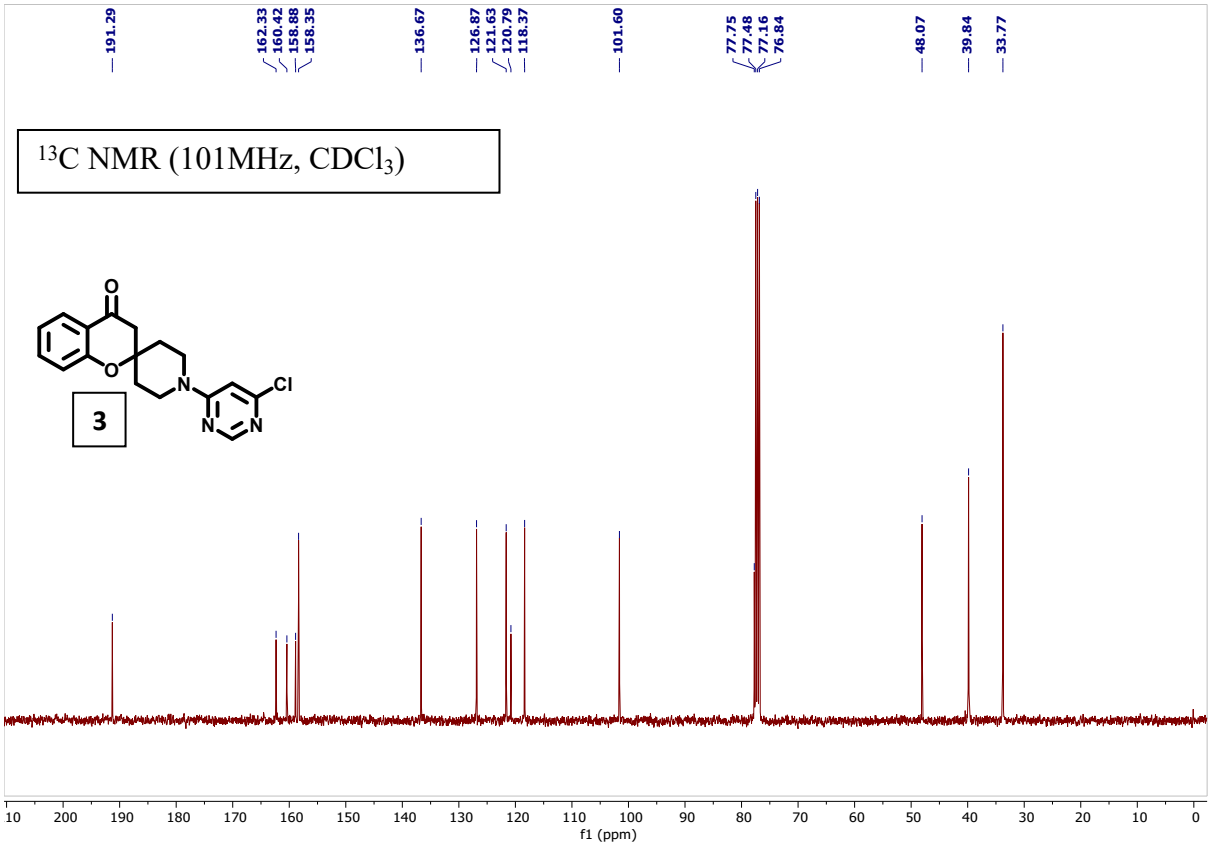
**Corresponding authors

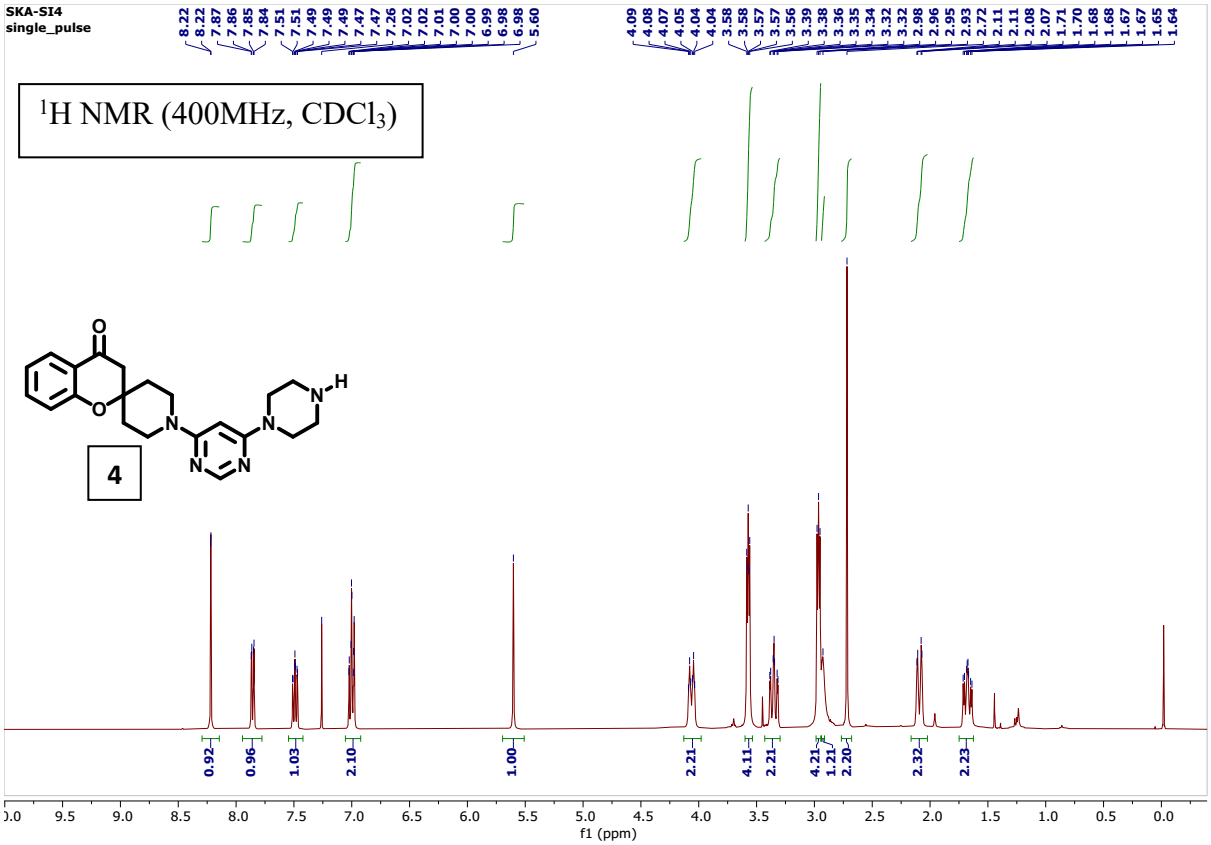
Nasimul Hoda
Professor
Department of Chemistry,
Jamia Millia Islamia,
Jamia Nagar, New Delhi-110025, India
Tel.: +0091-9910200655;
fax: +0091-11-26985507;
e-mail: nhoda@jmi.ac.in

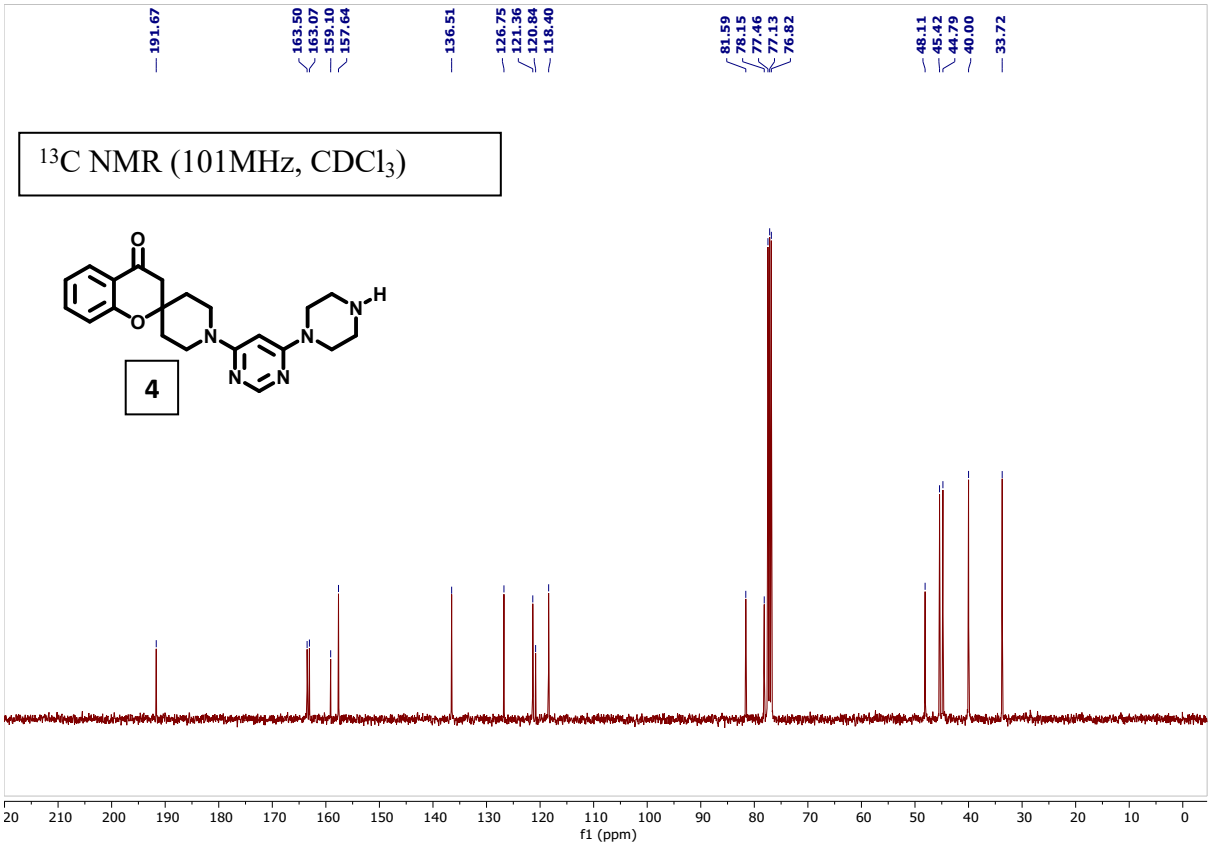
Tarosh S. Patel
Chemistry Department, V. P. & R. P. T. P
Science College, Affiliated to Sardar Patel
University
Vallabh Vidyanagar – 388 120, Gujarat, India.
Tel: +91-2692-230011#31
E-mail: tarosh_patel@yahoo.com (T.S. Patel)

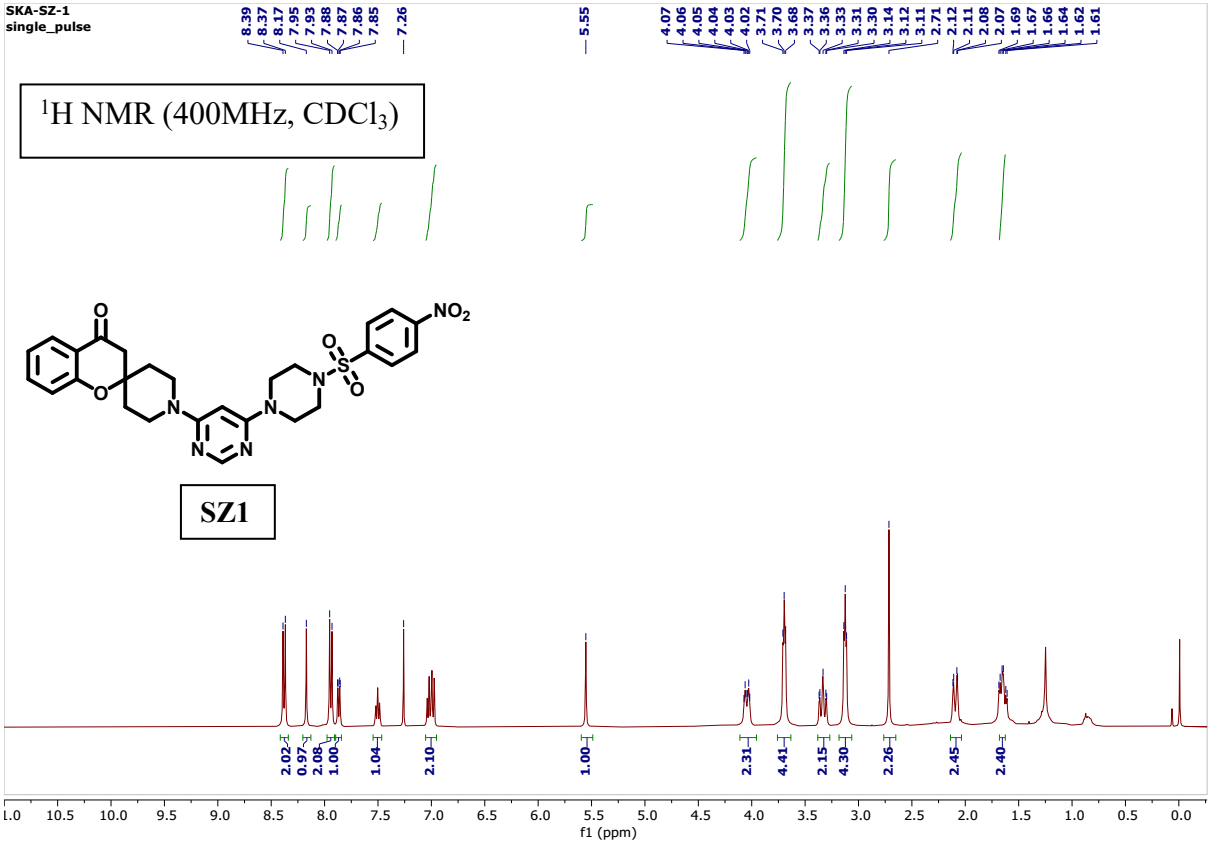
Table of content

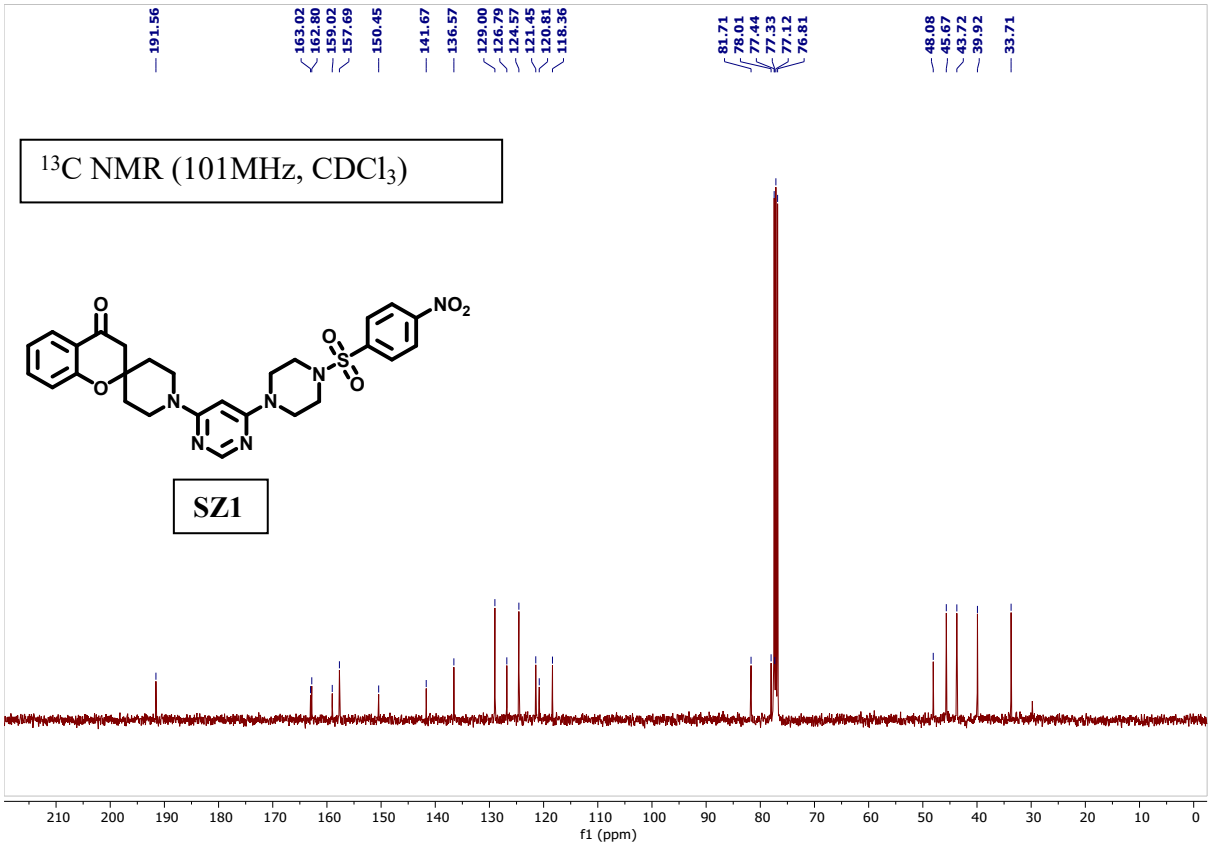

SKA-SI-3
single_pulse
^{1}H NMR (400MHz, $CDCl_3$)
3
f1 (ppm)

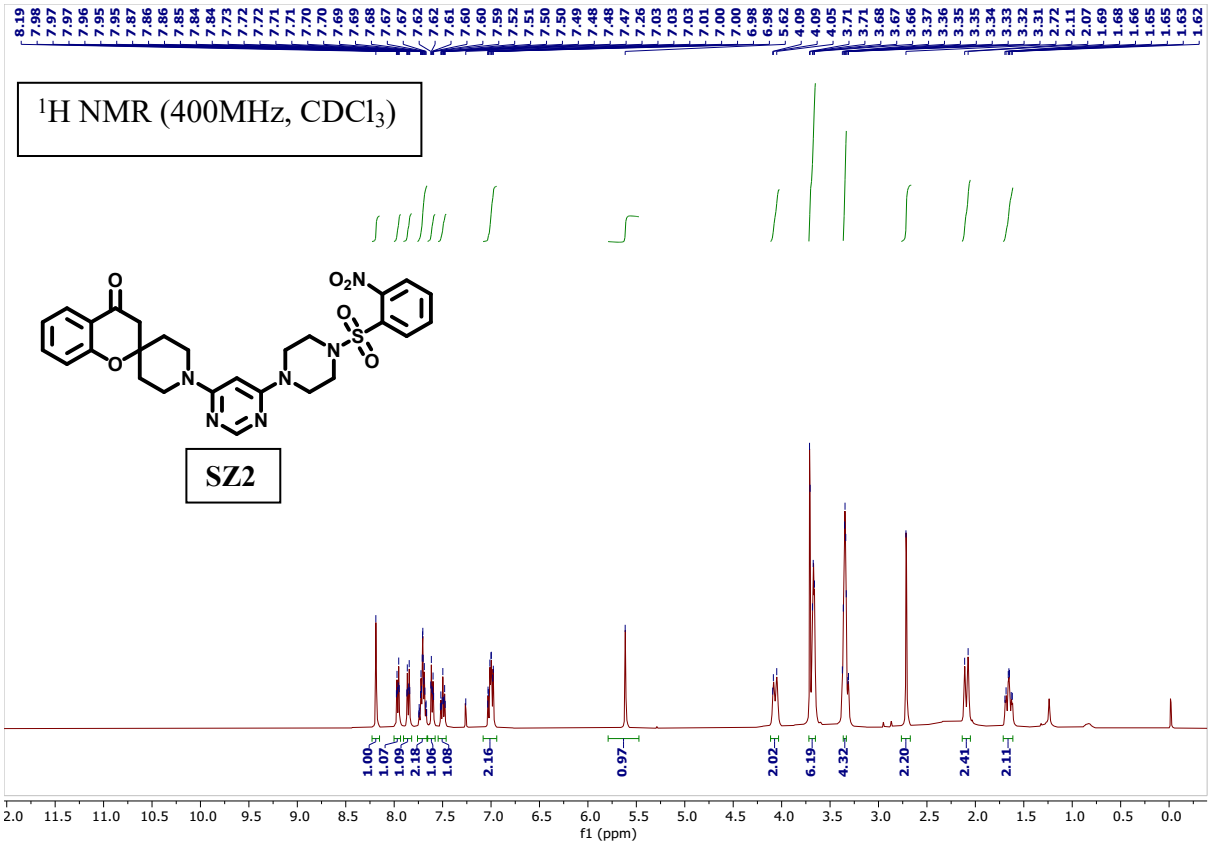

^{13}C NMR (101MHz, $CDCl_3$)
3
f1 (ppm)

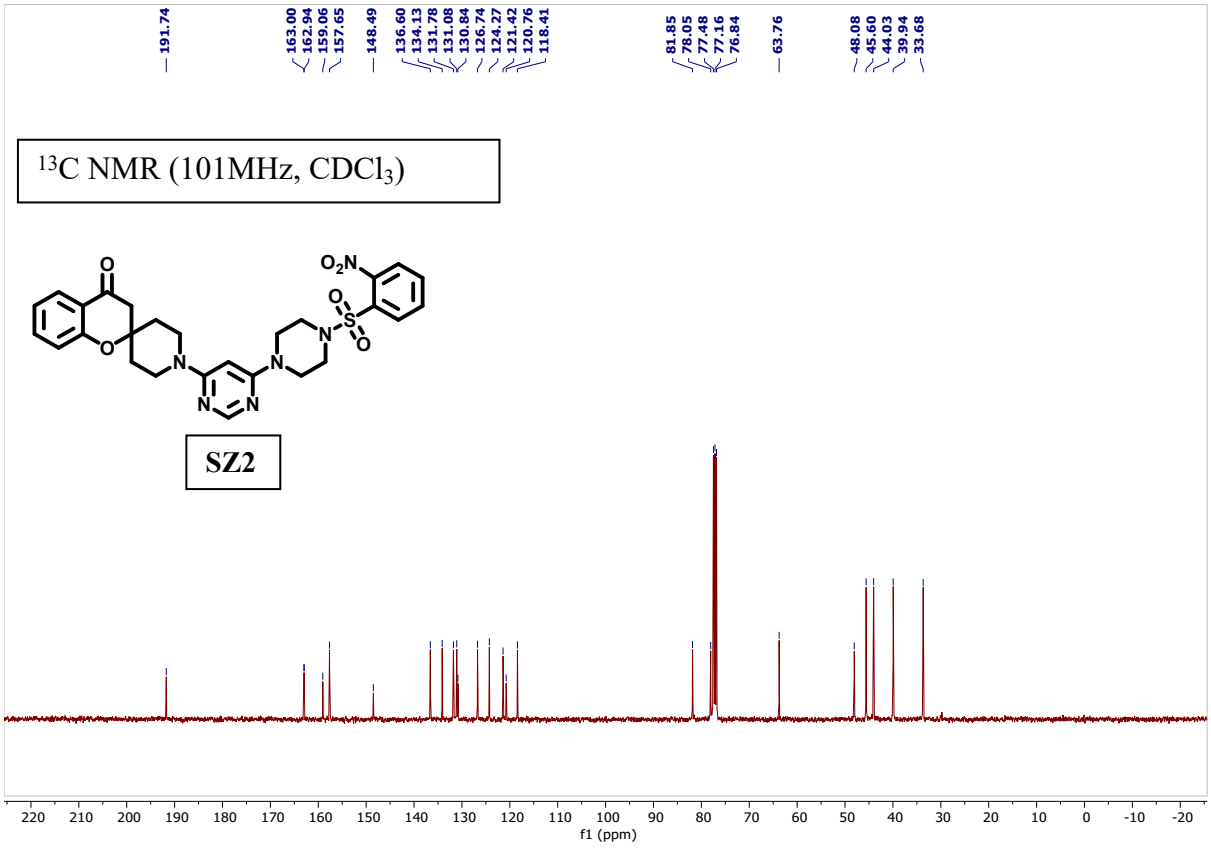

SKA-SI4
single_pulse
^{1}H NMR (400MHz, $CDCl_3$)
4
f1 (ppm)

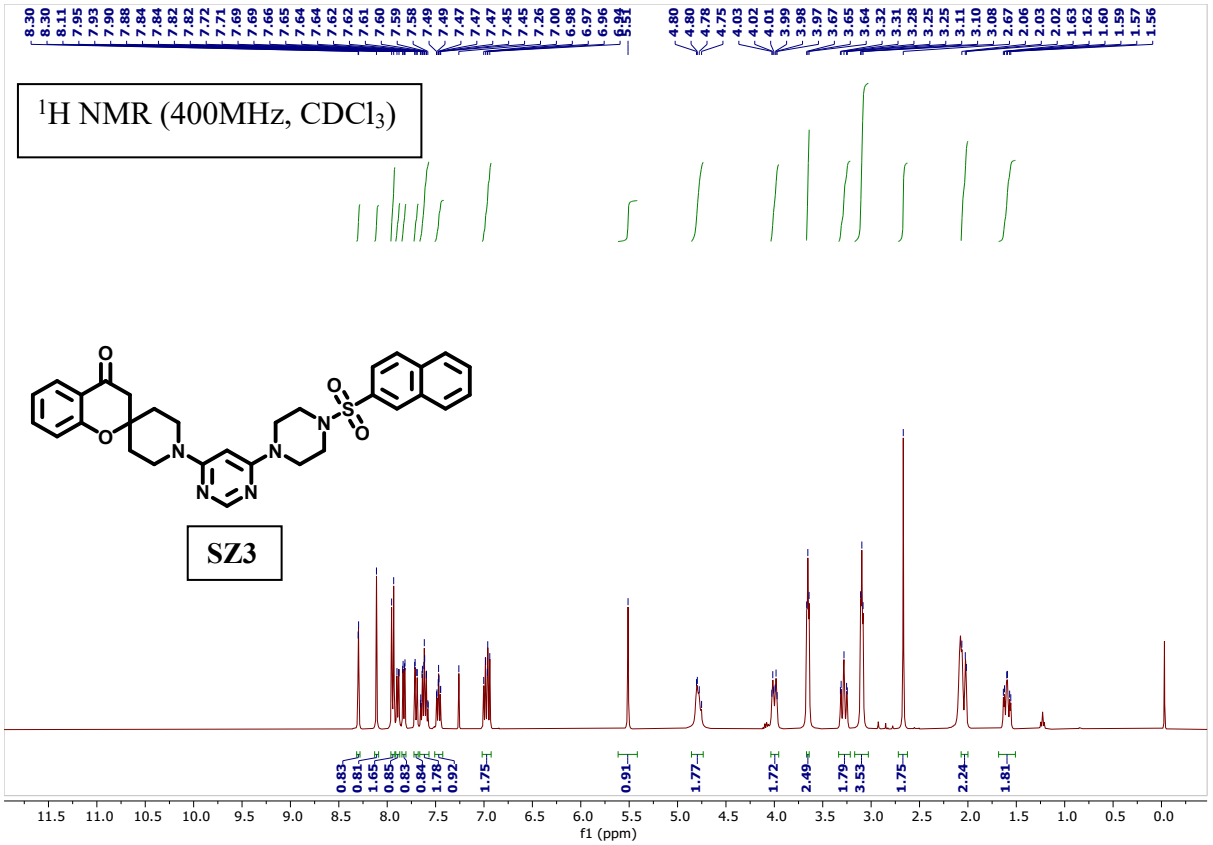

^{13}C NMR (101MHz, $CDCl_3$)
4
f1 (ppm)

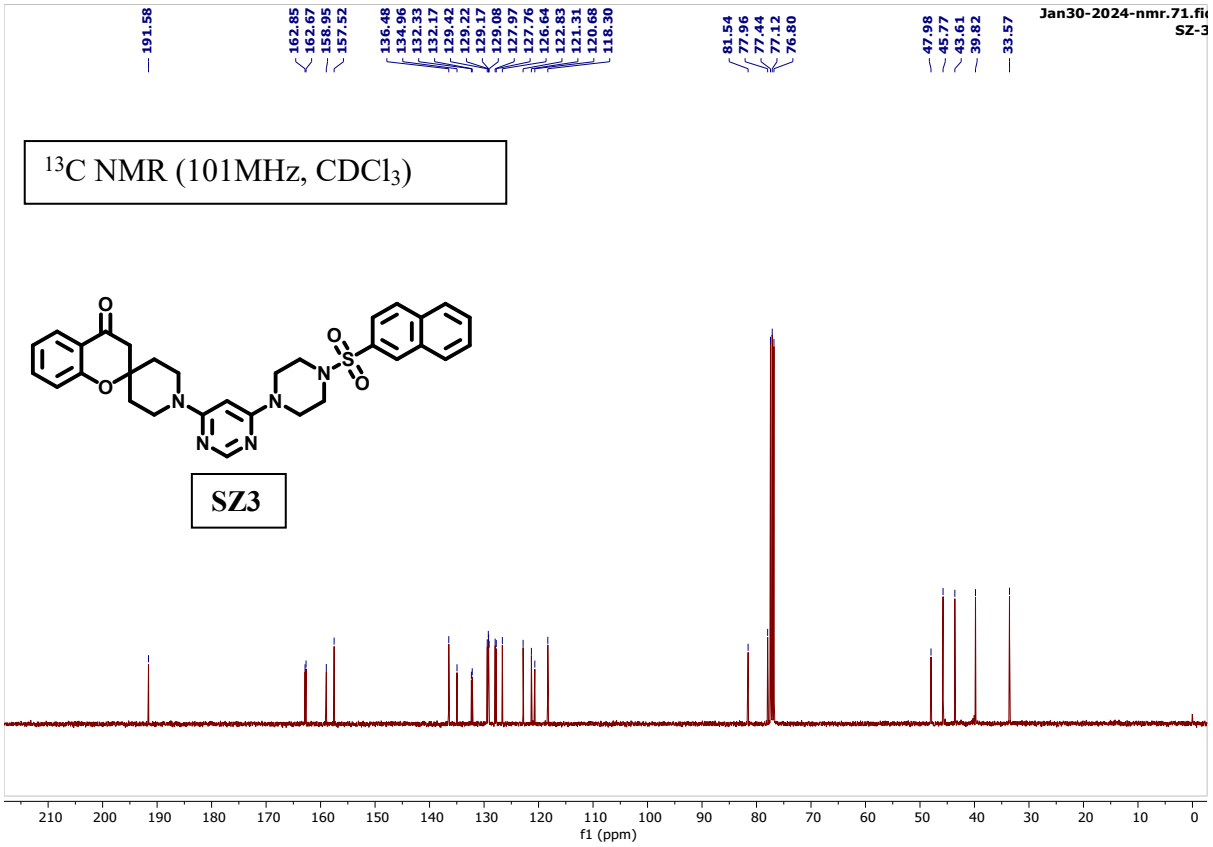

SKA-SZ-1
single_pulse
^{1}H NMR (400MHz, $CDCl_3$)
SZ1
f1 (ppm)

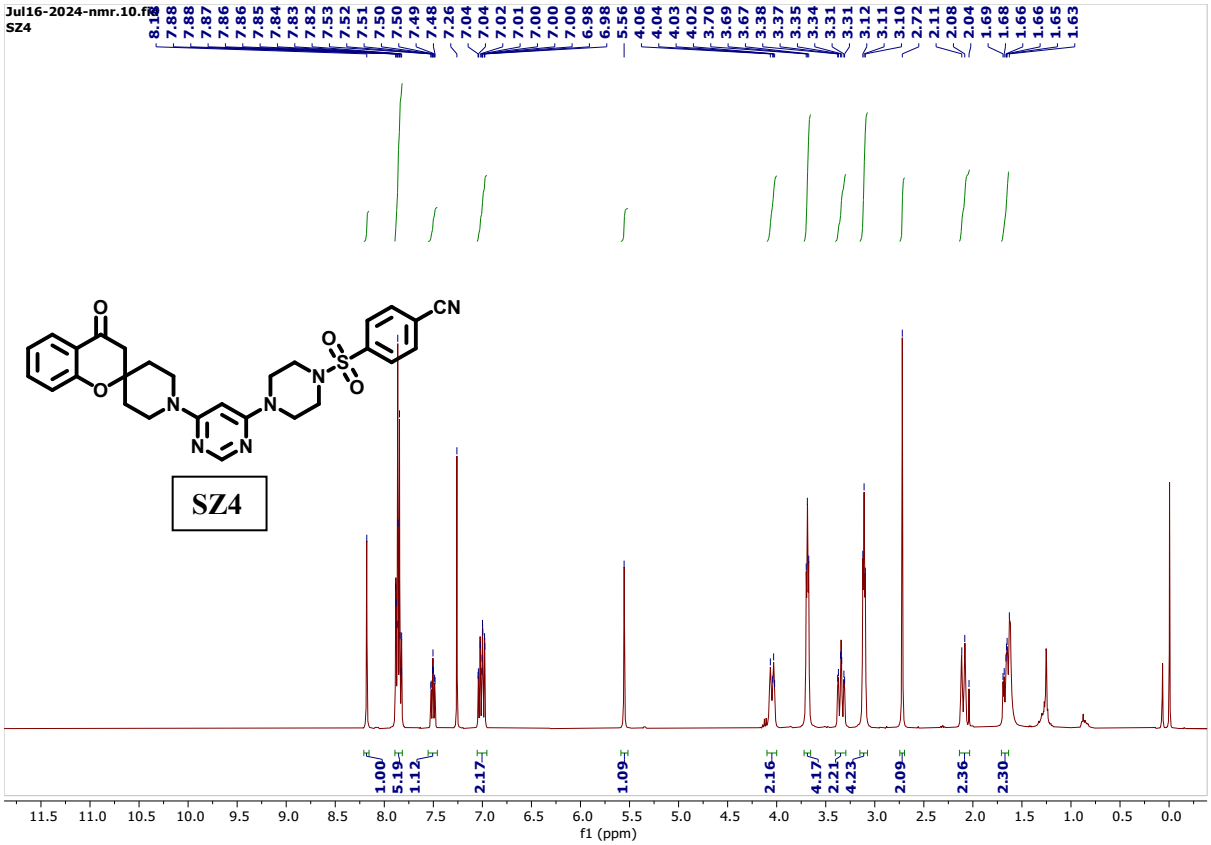

^{13}C NMR (101MHz, $CDCl_3$)
SZ1
f1 (ppm)

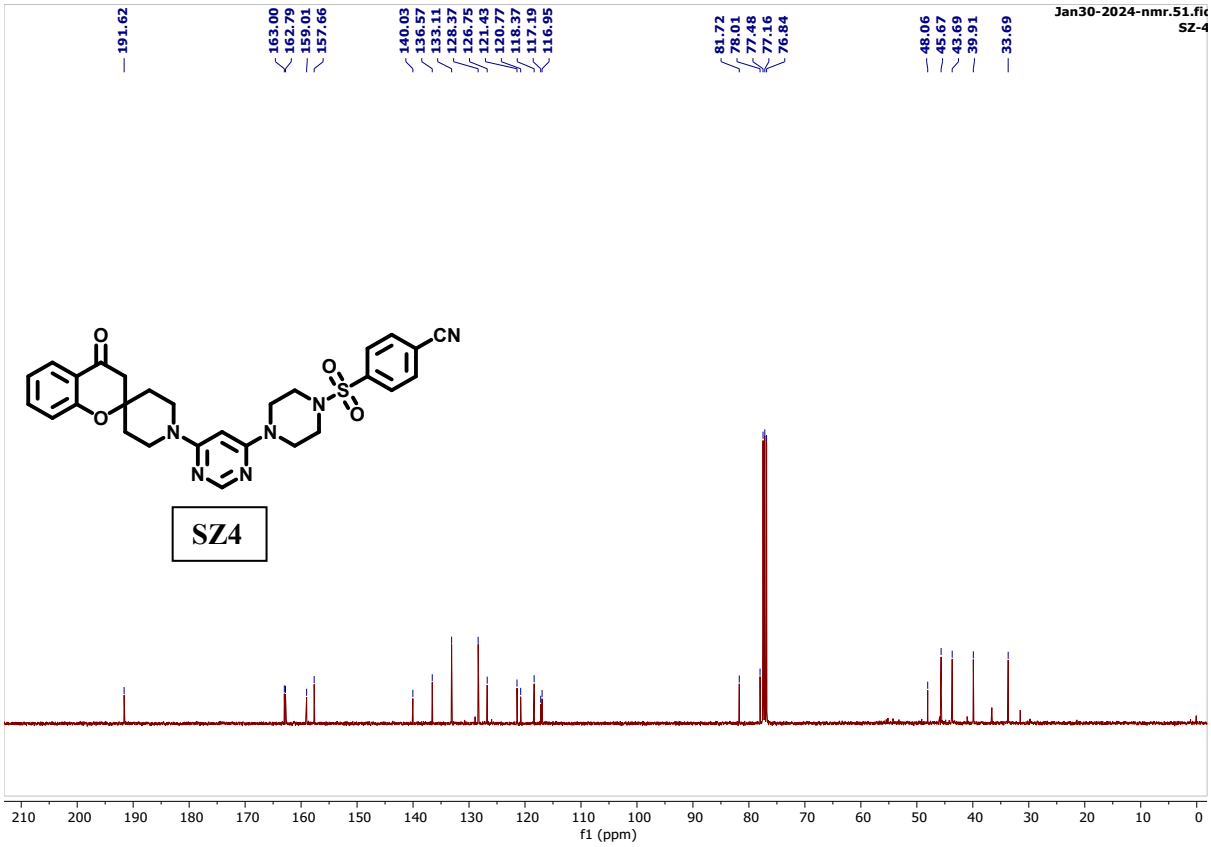

^{1}H NMR (400MHz, $CDCl_3$)
SZ2
f1 (ppm)

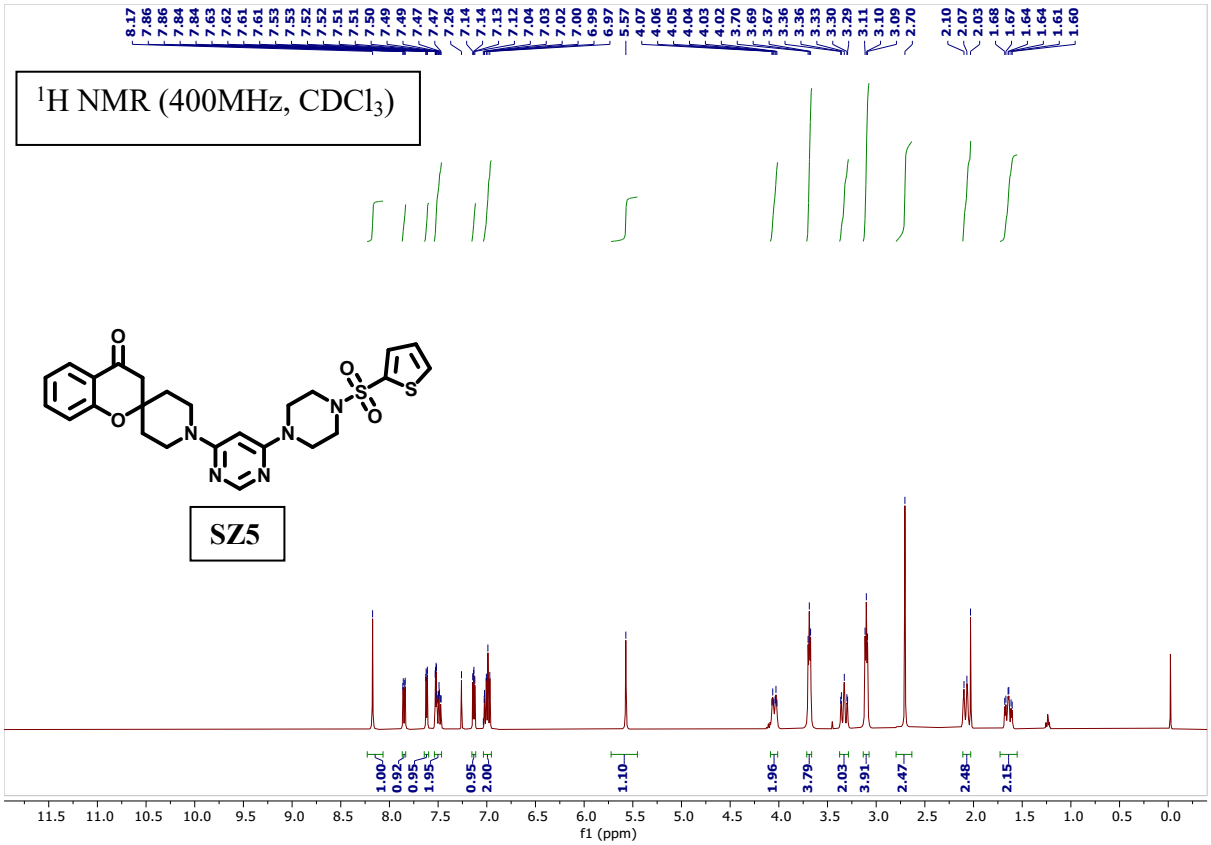

^{13}C NMR (101MHz, $CDCl_3$)
SZ2
f1 (ppm)

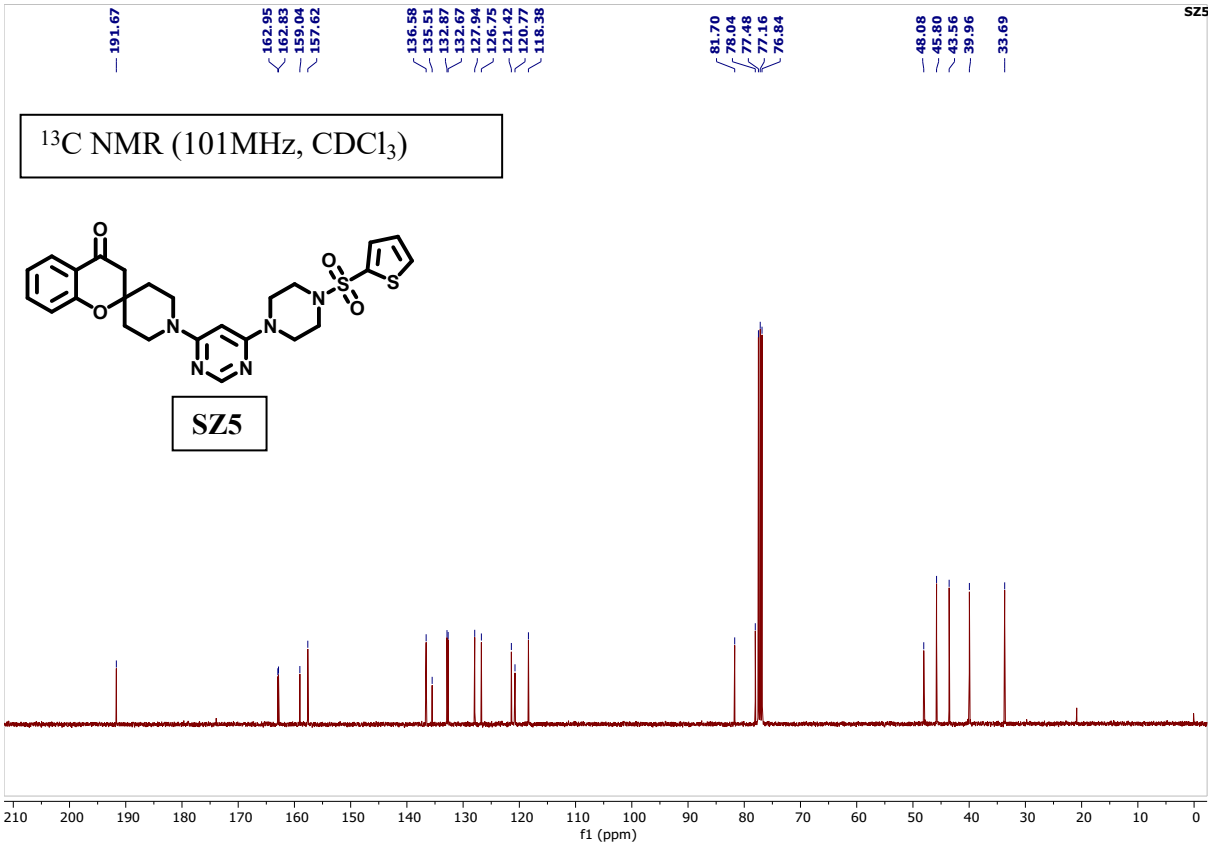

^{1}H NMR (400MHz, $CDCl_3$)
SZ3
f1 (ppm)

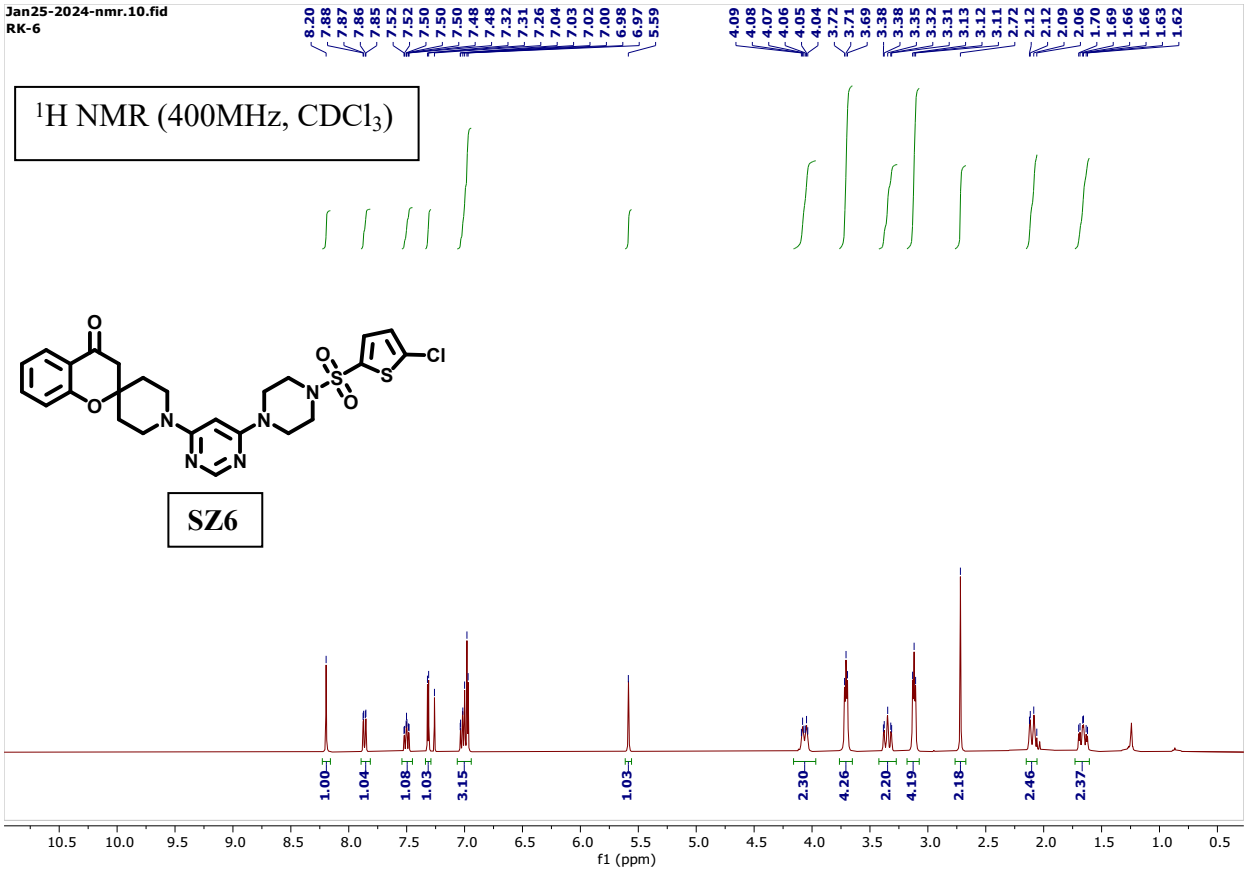

^{13}C NMR (101MHz, $CDCl_3$)
SZ3
f1 (ppm)

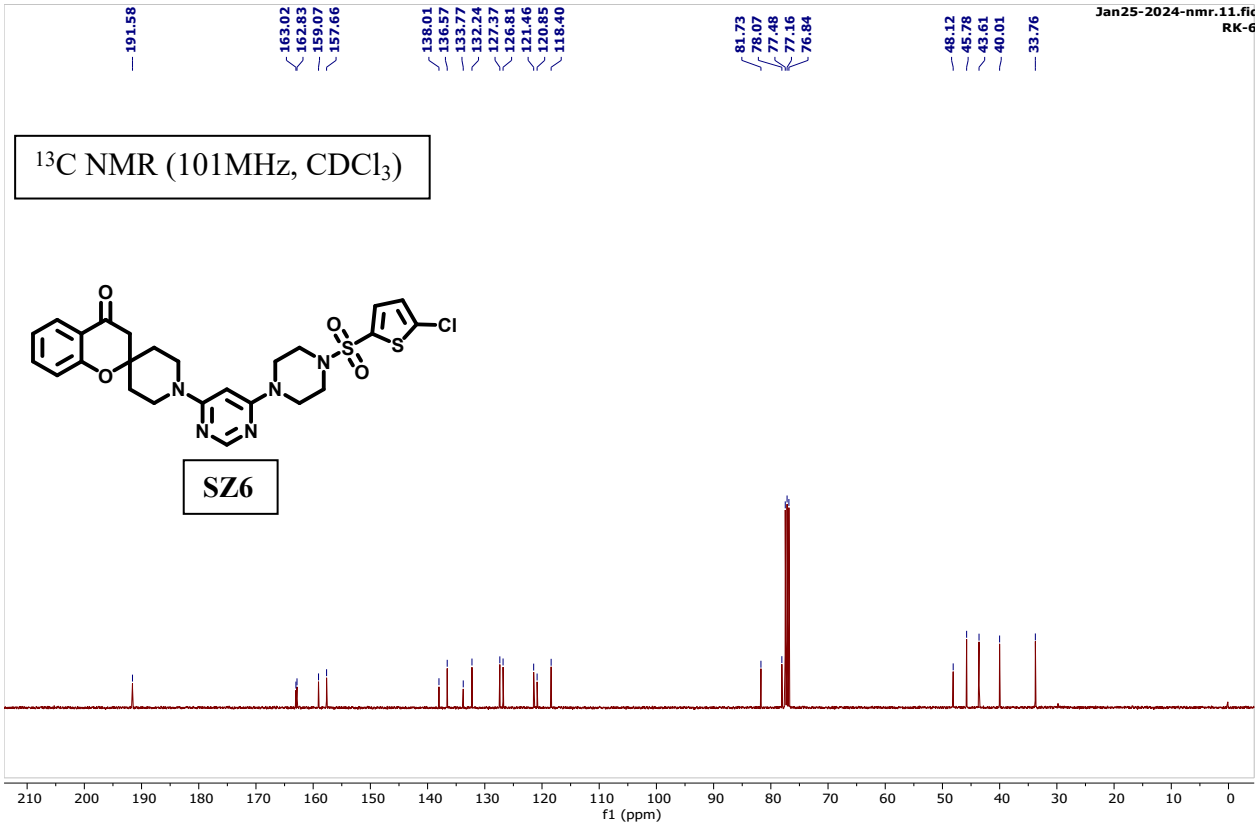

Jul16-2024-nmr.10.fid
SZ4
SZ4
f1 (ppm)

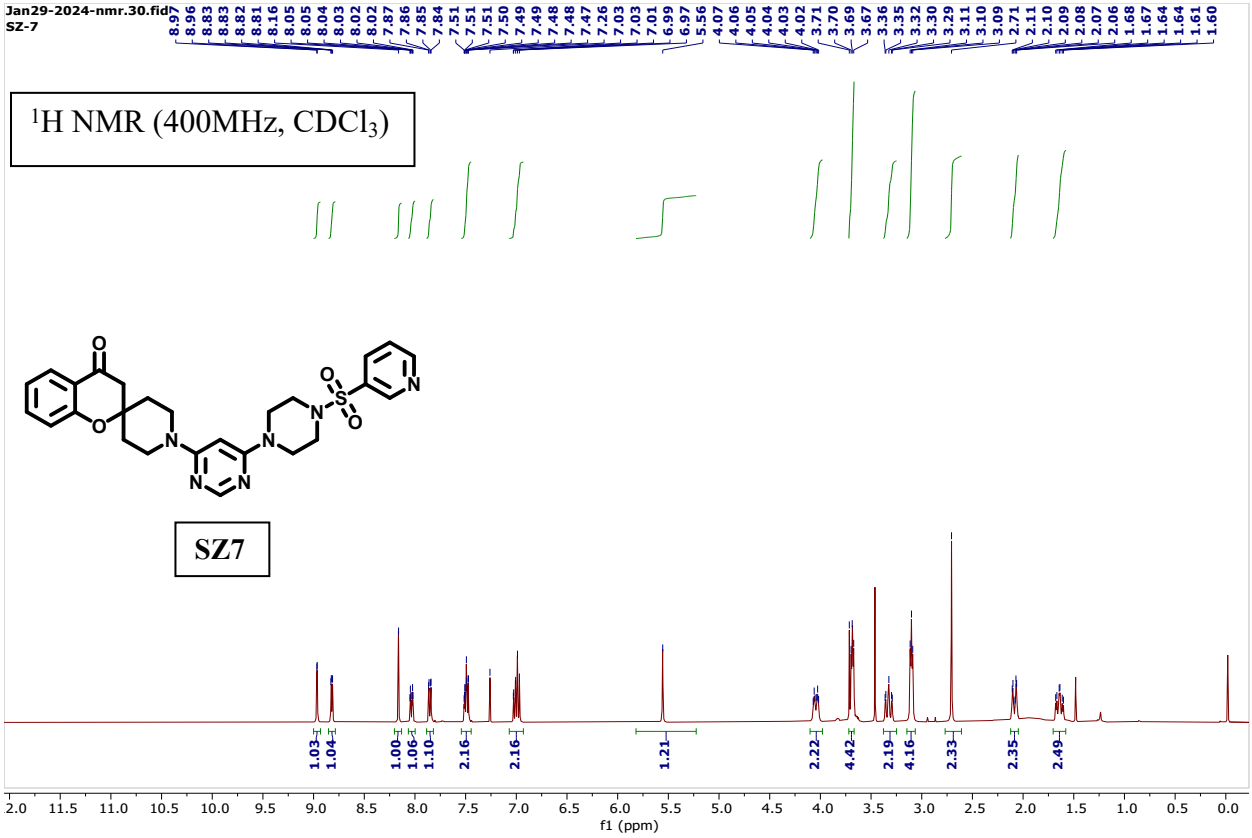

Jan30-2024-nmr.51.fid
SZ-4
SZ4
f1 (ppm)

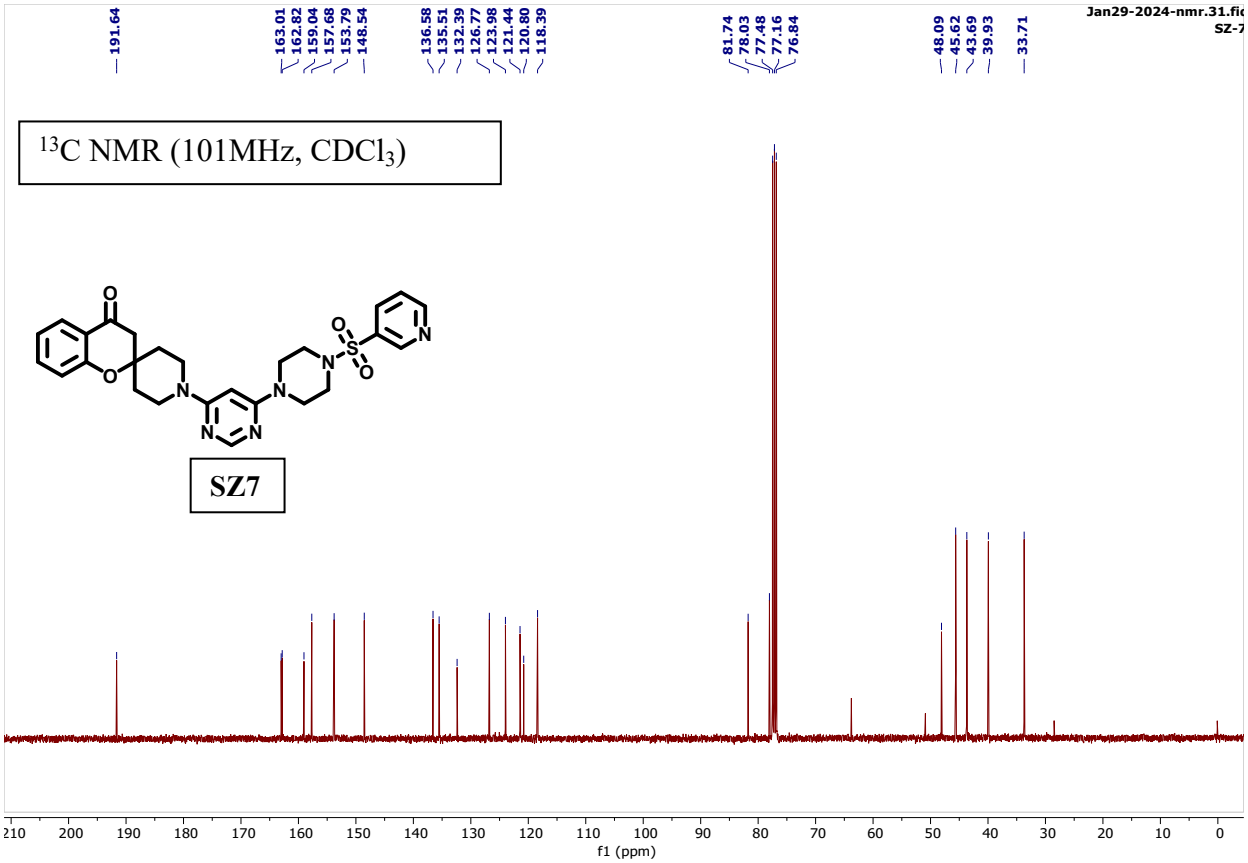

8.17 7.86 7.86 7.84 7.84 7.63 7.62 7.61 7.61 7.53 7.53 7.52 7.52 7.51 7.51 7.51 7.50 7.49 7.49 7.47 7.47 7.26 7.14 7.14 7.13 7.12 7.04 7.03 7.02 7.00 6.99 6.97 5.57 4.07 4.06 4.05 4.04 4.03 4.02 3.70 3.69 3.67 3.36 3.36 3.33 3.30 3.29 3.11 3.10 3.09 2.70 2.10 2.07 2.03 1.68 1.67 1.64 1.64 1.61 1.60
1H NMR (400MHz, CDCl3)
SZ5
1.00 0.92 0.95 1.95 0.95 2.00 1.10 1.96 3.79 2.03 3.91 2.47 2.48 2.15
f1 (ppm)

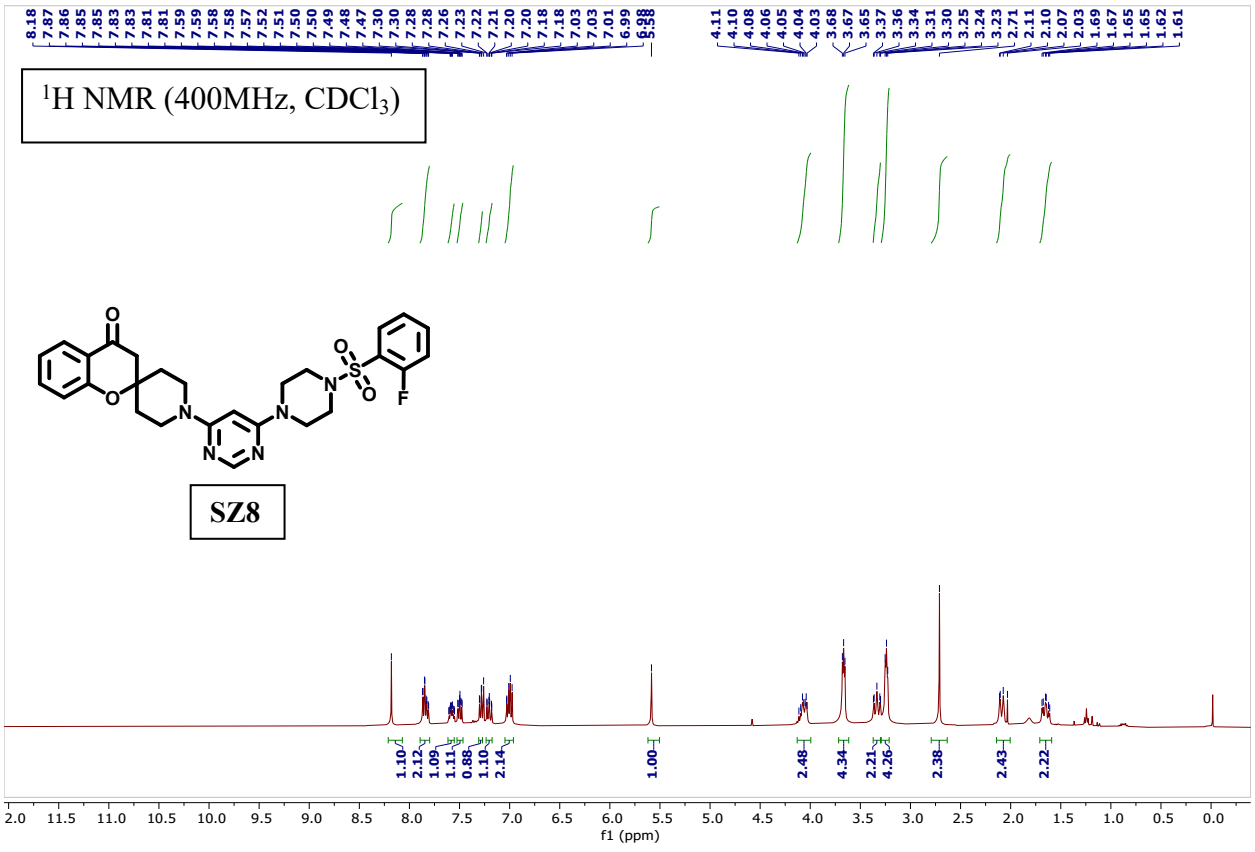

SZ5
191.67 162.95 162.83 159.04 157.62 136.58 135.51 132.87 132.67 127.94 126.75 121.42 120.77 118.38 81.70 78.04 77.48 77.16 76.84 48.08 45.80 43.56 39.96 33.69
13C NMR (101MHz, CDCl3)
SZ5
f1 (ppm)

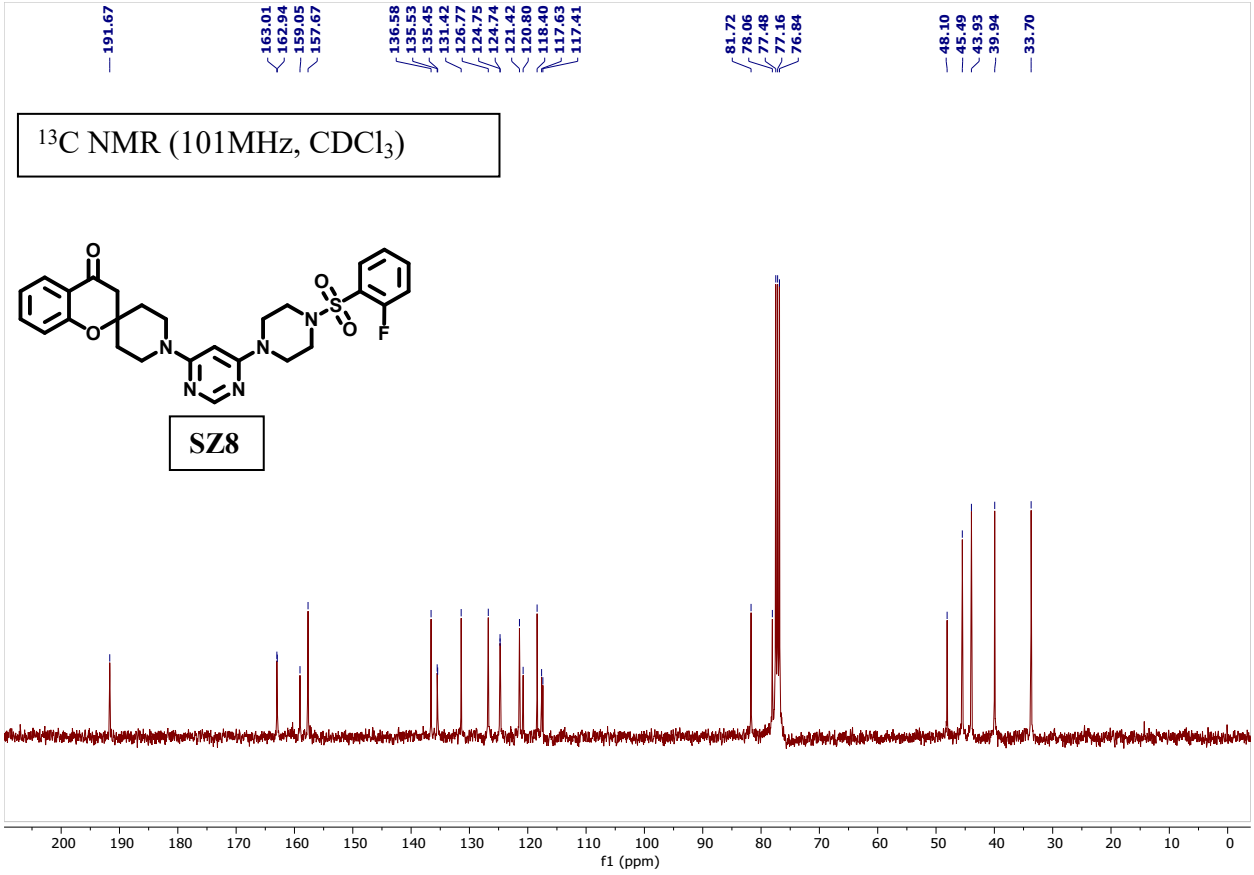

Jan25-2024-nmr.10.fid
RK-6
^{1}H NMR (400MHz, $CDCl_3$)
SZ6
f1 (ppm)

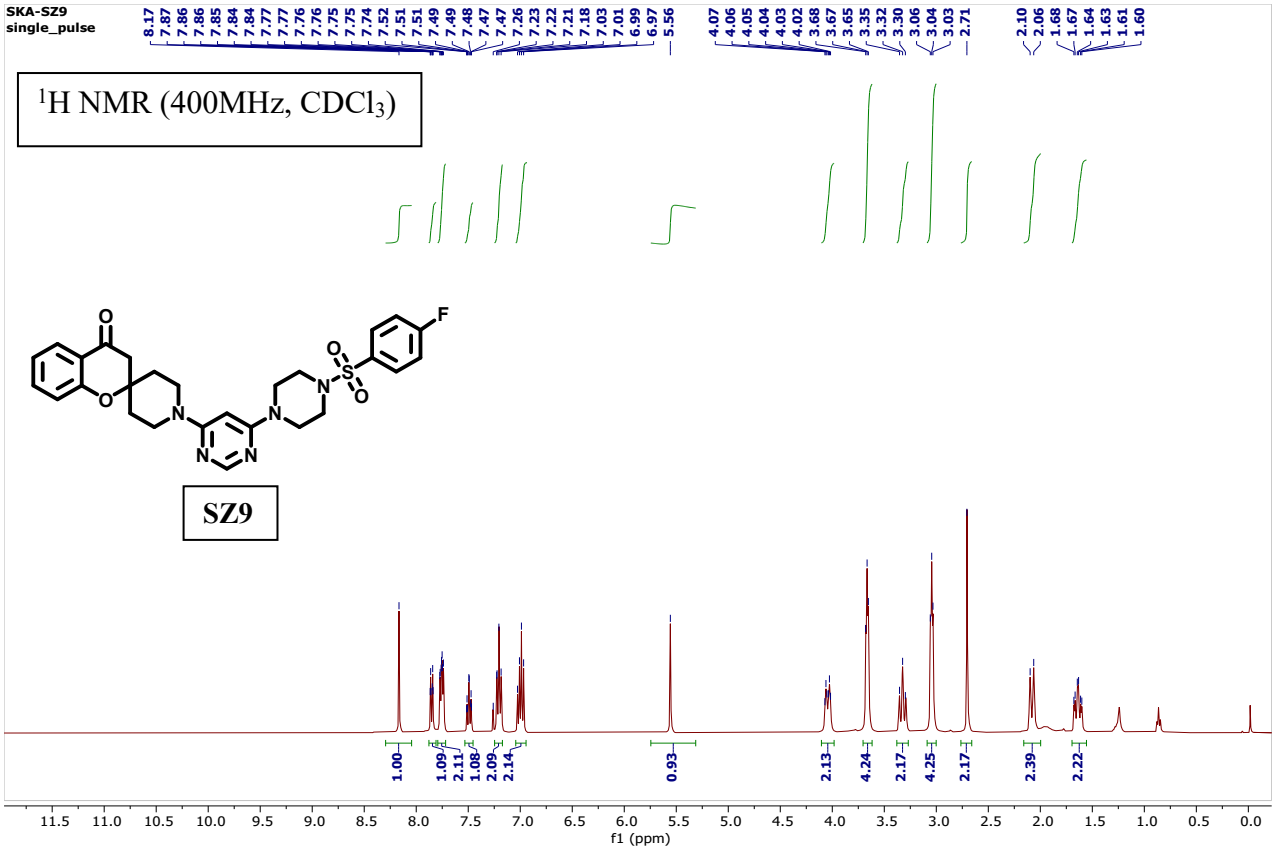

Jan25-2024-nmr.11.fid
RK-6
^{13}C NMR (101MHz, $CDCl_3$)
SZ6
f1 (ppm)

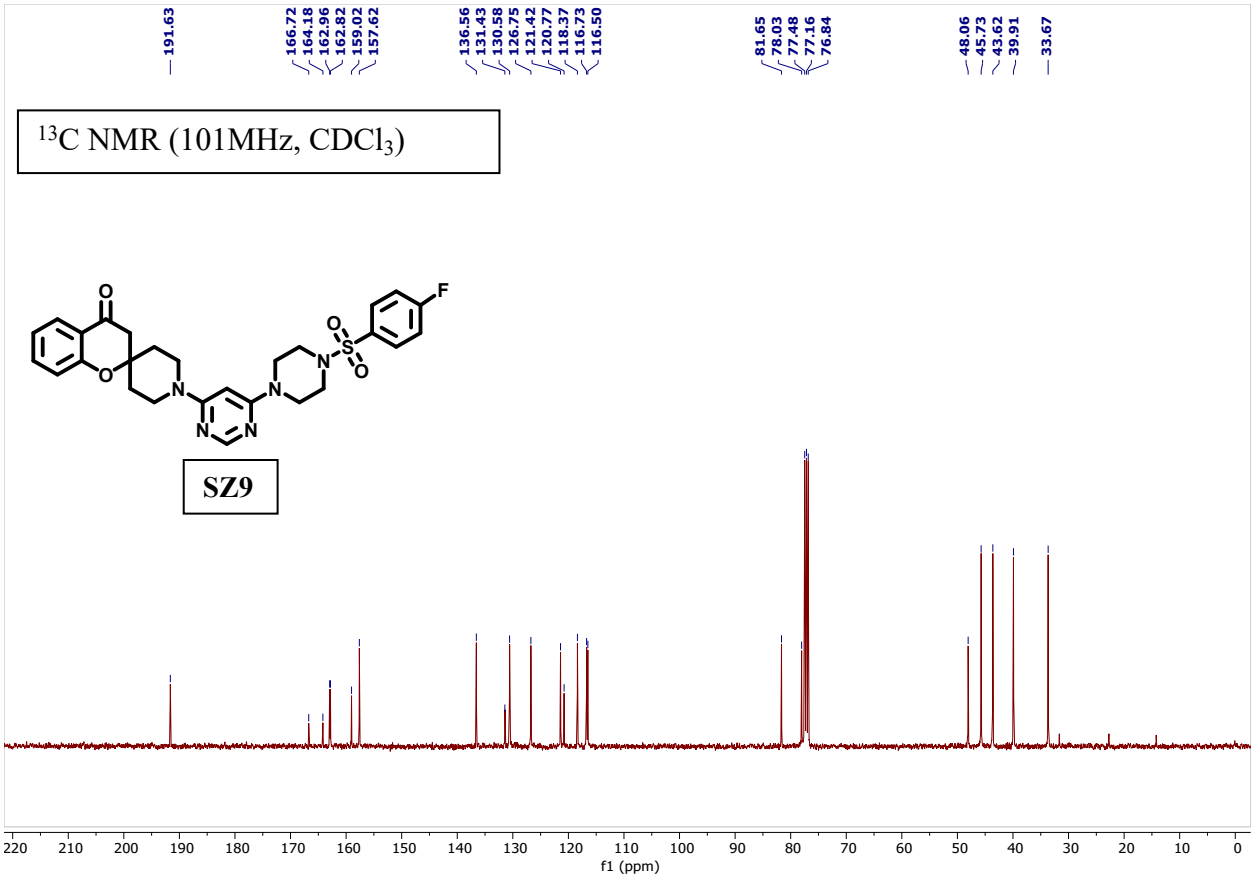

Jan29-2024-nmr.30.fid
SZ-7
^{1}H NMR (400MHz, $CDCl_3$)
SZ7
f1 (ppm)

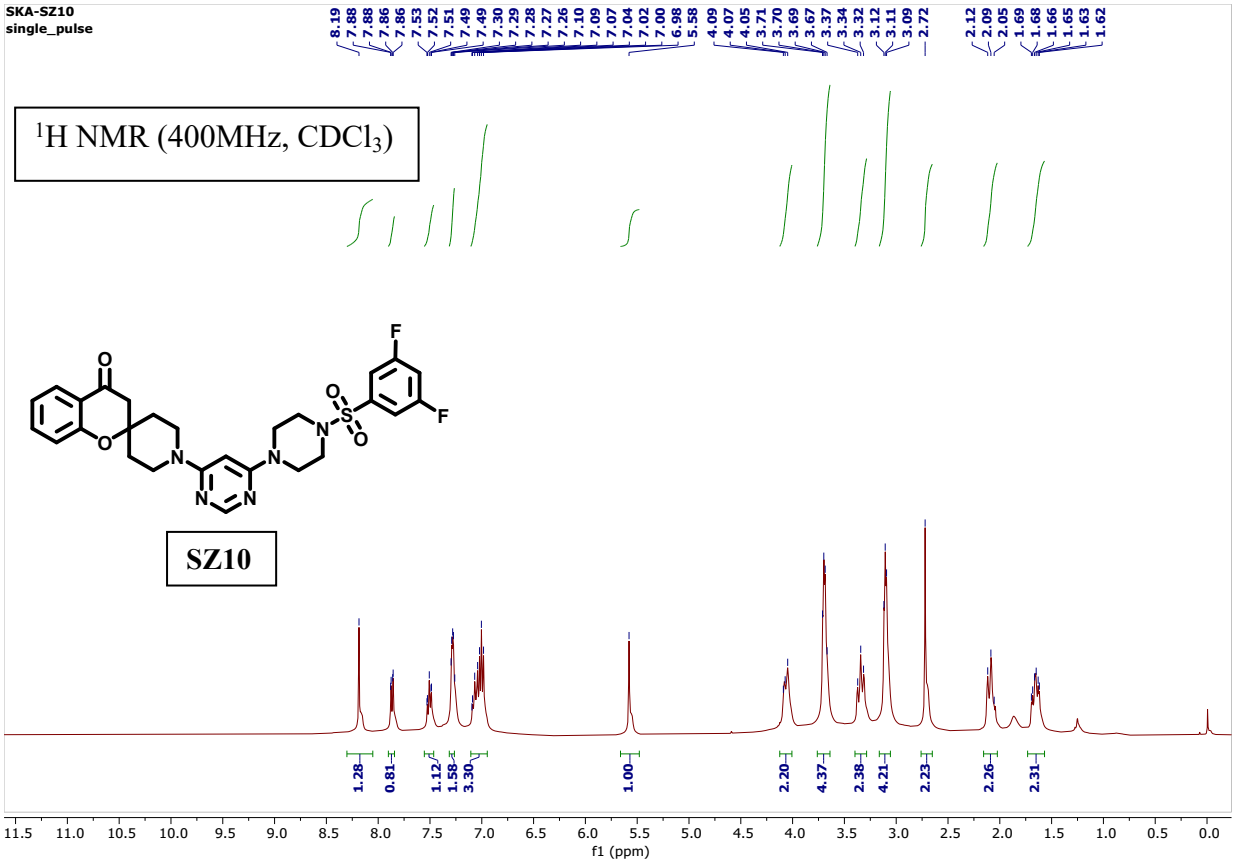

191.64
163.01
162.82
159.04
157.68
153.79
148.54
136.58
135.51
132.39
126.77
123.98
121.44
120.80
118.39
81.74
78.03
77.48
77.16
76.84
48.09
45.62
43.69
39.93
33.71
Jan29-2024-nmr.31.fi
SZ-7
13C NMR (101MHz, CDCl3)
SZ7
f1 (ppm)

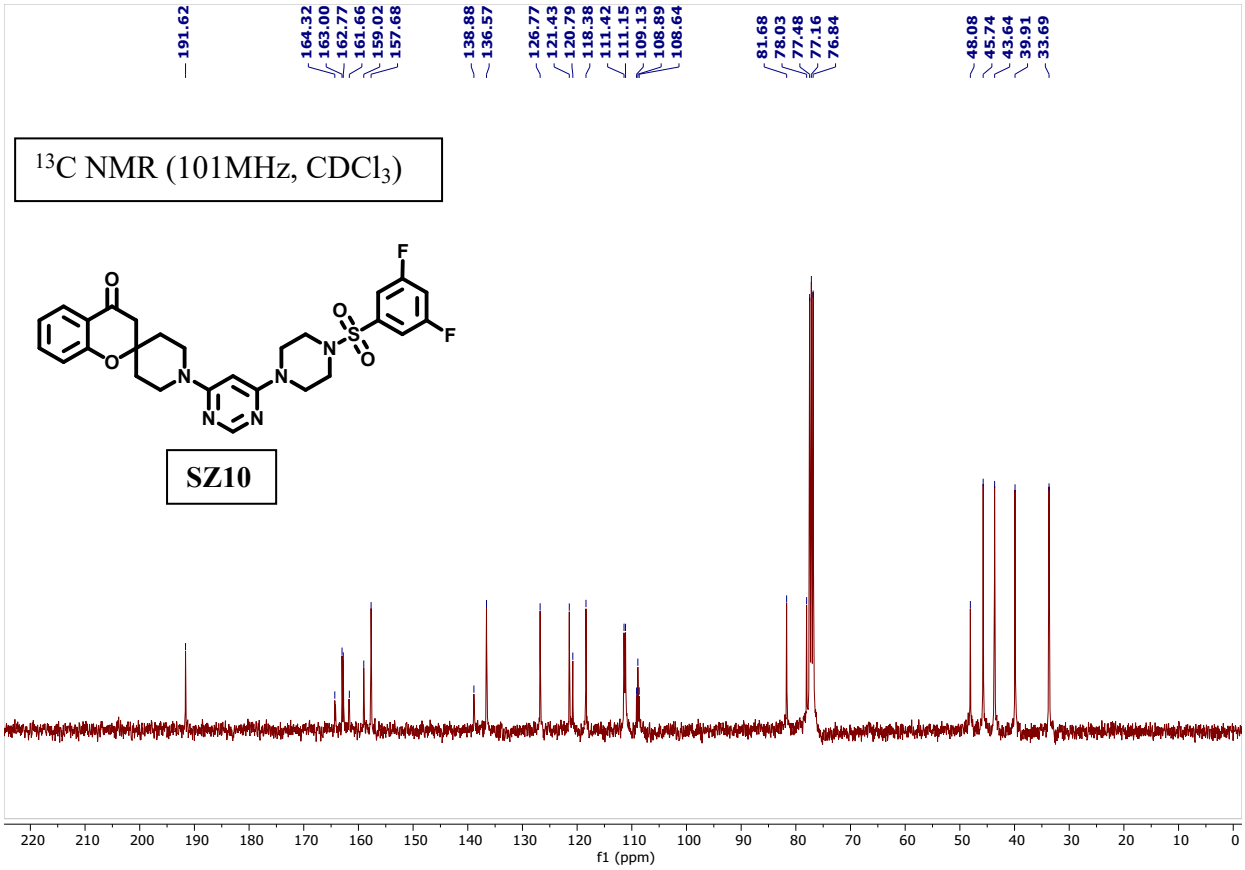

8.18
7.87
7.86
7.85
7.85
7.83
7.83
7.81
7.81
7.59
7.59
7.58
7.58
7.57
7.52
7.51
7.50
7.50
7.49
7.48
7.47
7.30
7.30
7.28
7.28
7.26
7.23
7.22
7.21
7.20
7.20
7.18
7.03
7.03
7.01
6.99
4.11
4.10
4.08
4.06
4.05
4.04
4.03
3.68
3.67
3.65
3.37
3.36
3.34
3.31
3.30
3.25
3.24
3.23
2.71
2.11
2.10
2.07
2.03
1.69
1.67
1.65
1.65
1.62
1.61
1H NMR (400MHz, CDCl3)
SZ8
1.10
2.12
1.09
1.11
0.88
1.10
2.14
1.00
2.48
4.34
2.21
4.26
2.38
2.43
2.22
f1 (ppm)

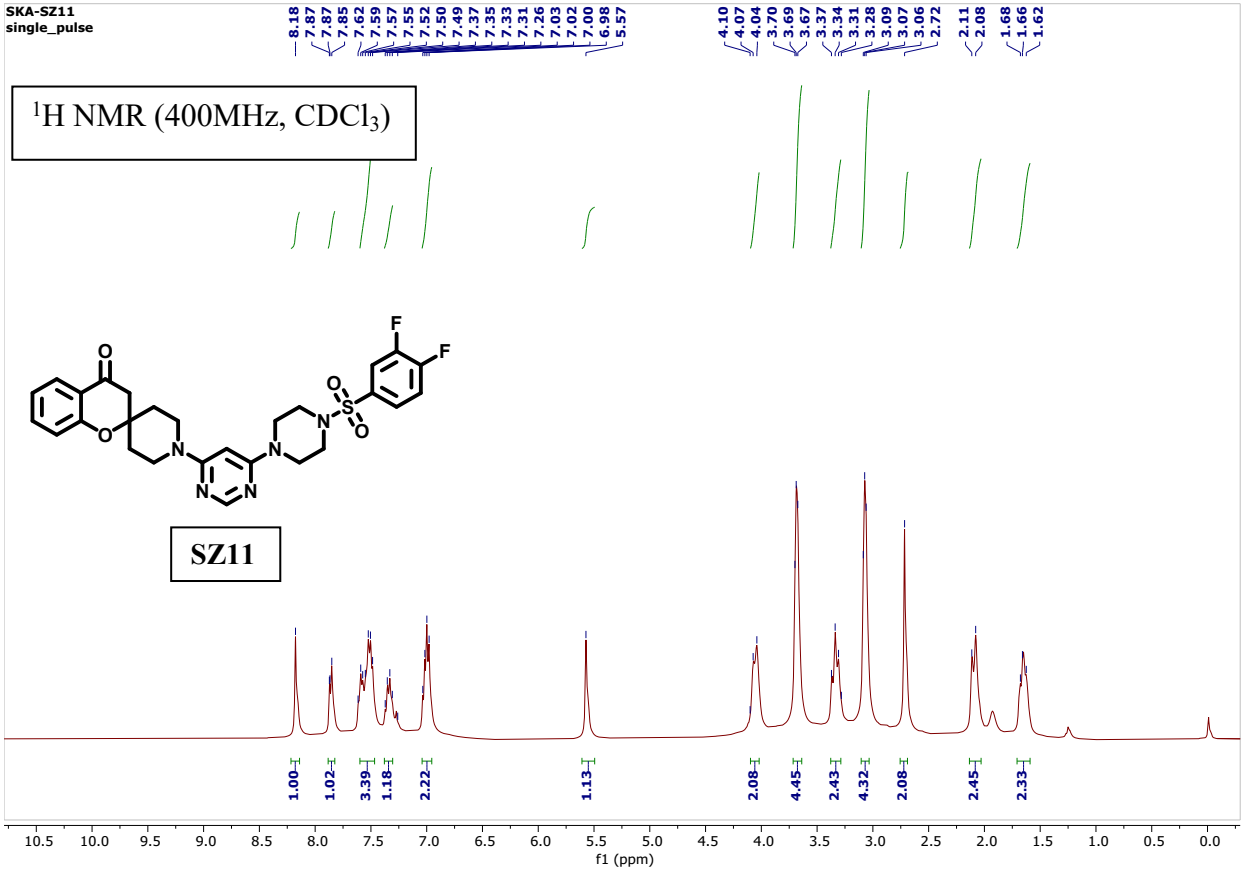

191.67
163.01
162.94
159.05
157.67
136.58
135.53
135.45
131.42
126.77
124.75
124.74
121.42
120.80
118.40
117.63
117.41
81.72
78.06
77.48
77.16
76.84
48.10
45.49
43.93
39.94
33.70
13C NMR (101MHz, CDCl3)
SZ8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

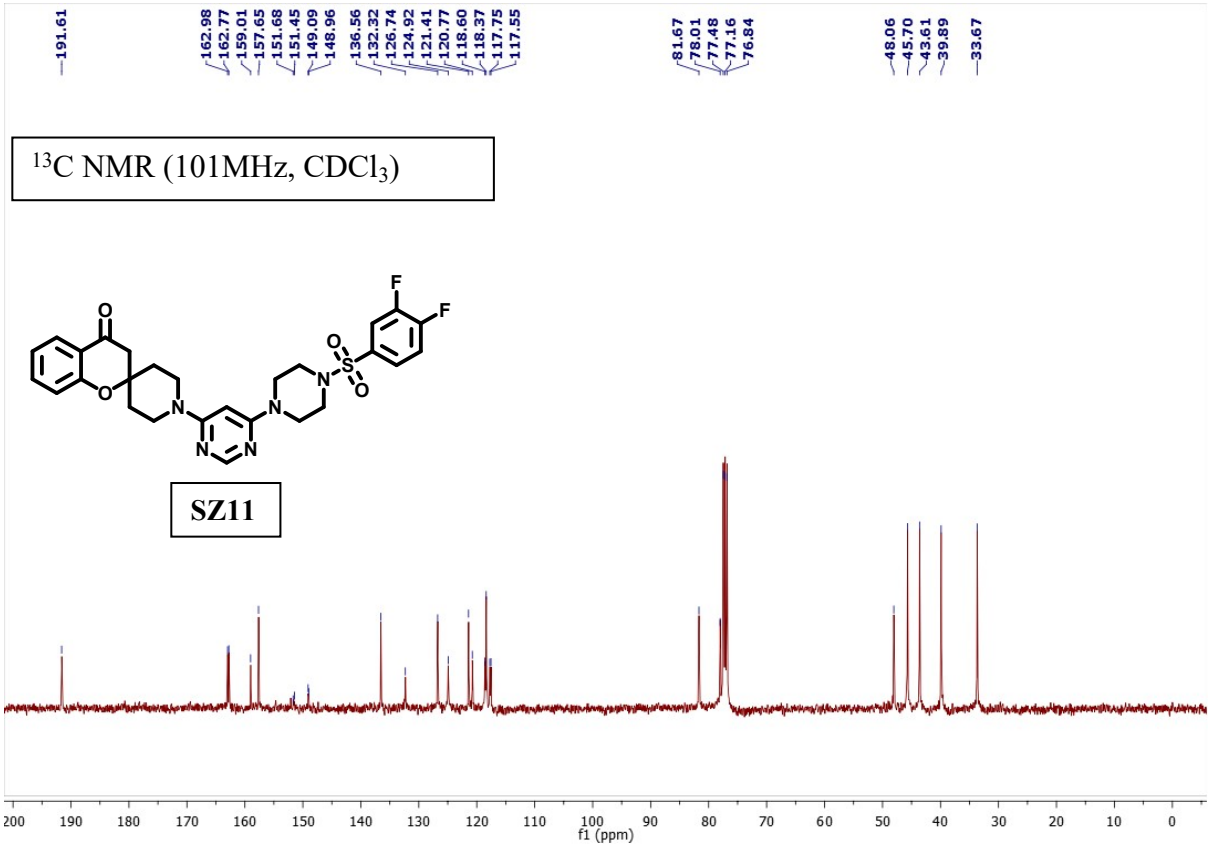

SKA-SZ9
single_pulse
^{1}H NMR (400MHz, $CDCl_3$)
SZ9
f1 (ppm)

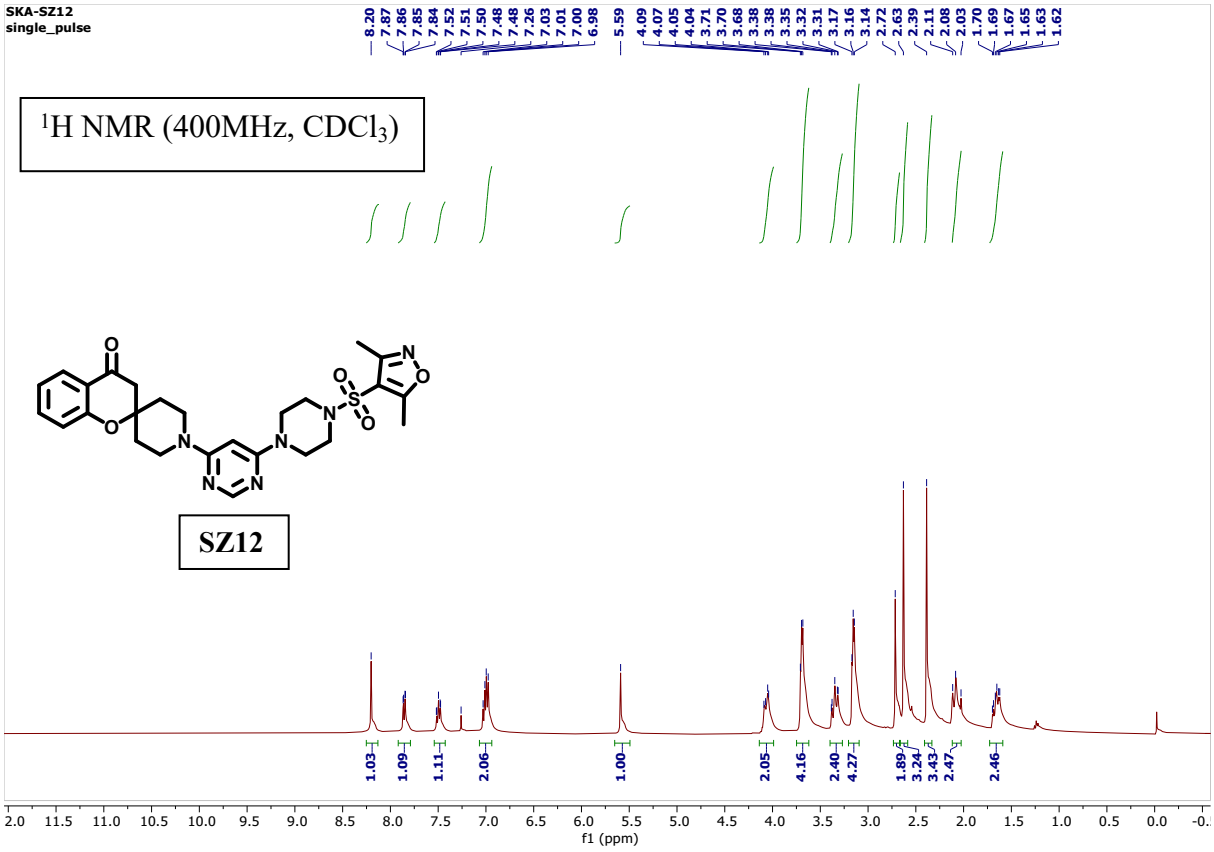

191.63
166.72
164.18
162.96
162.82
159.02
157.62
136.56
131.43
130.58
126.75
121.42
120.77
118.37
116.73
116.50
81.65
78.03
77.48
77.16
76.84
48.06
45.73
43.62
39.91
33.67
13C NMR (101MHz, CDCl3)
SZ9
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

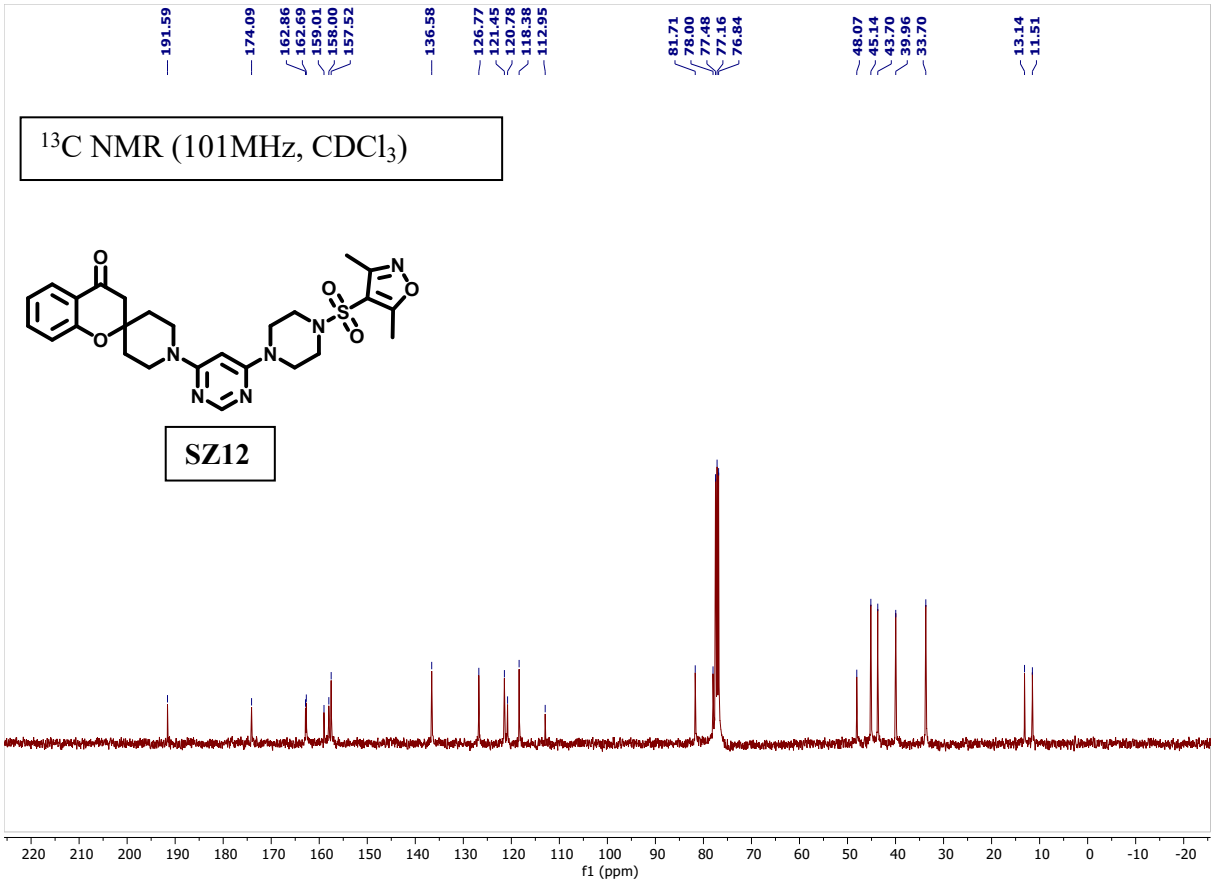

SKA-SZ10
single_pulse
^{1}H NMR (400MHz, $CDCl_3$)
SZ10
f1 (ppm)

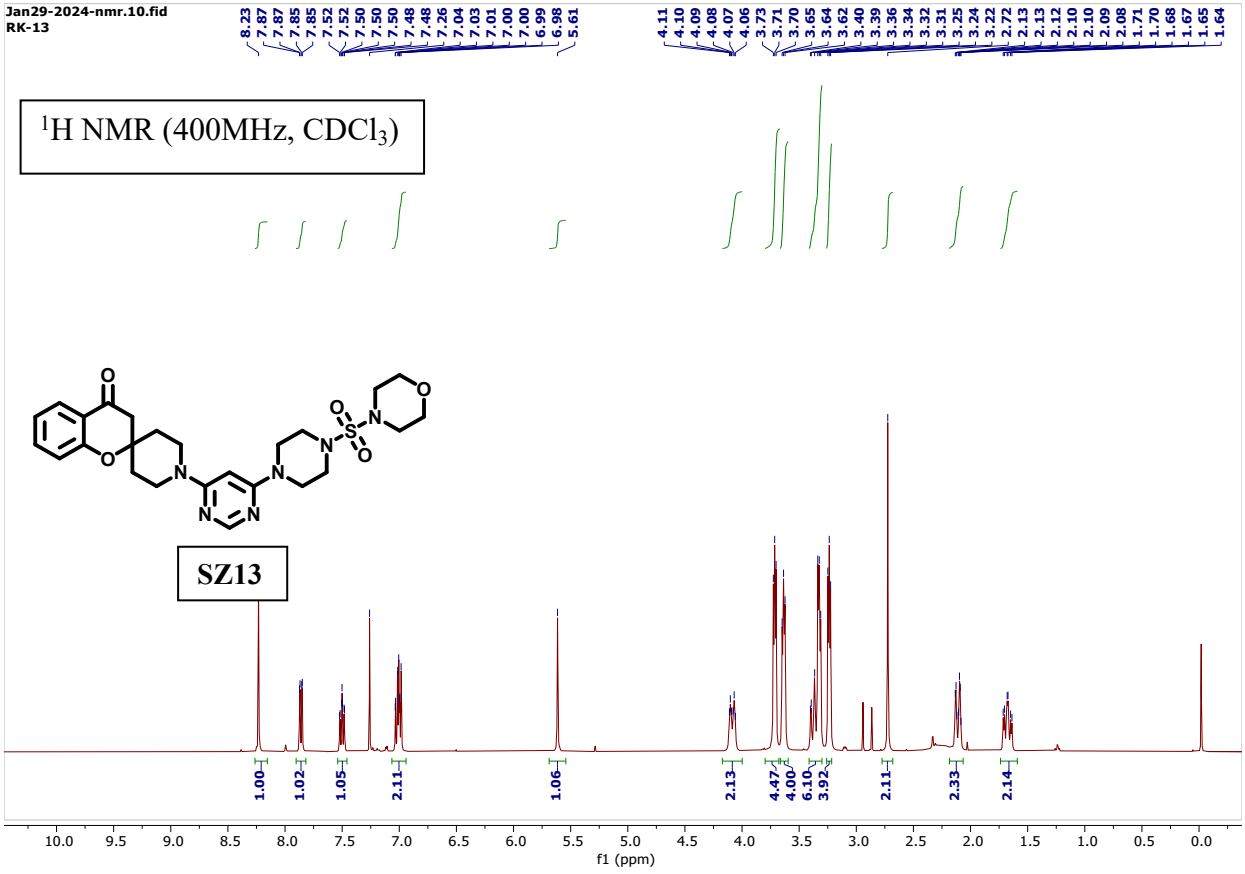

191.62
164.32
163.00
162.77
161.66
159.02
157.68
138.88
136.57
126.77
121.43
120.79
118.38
111.42
111.15
109.13
108.89
108.64
81.68
78.03
77.48
77.16
76.84
48.08
45.74
43.64
39.91
33.69
13C NMR (101MHz, CDCl3)
SZ10
f1 (ppm)

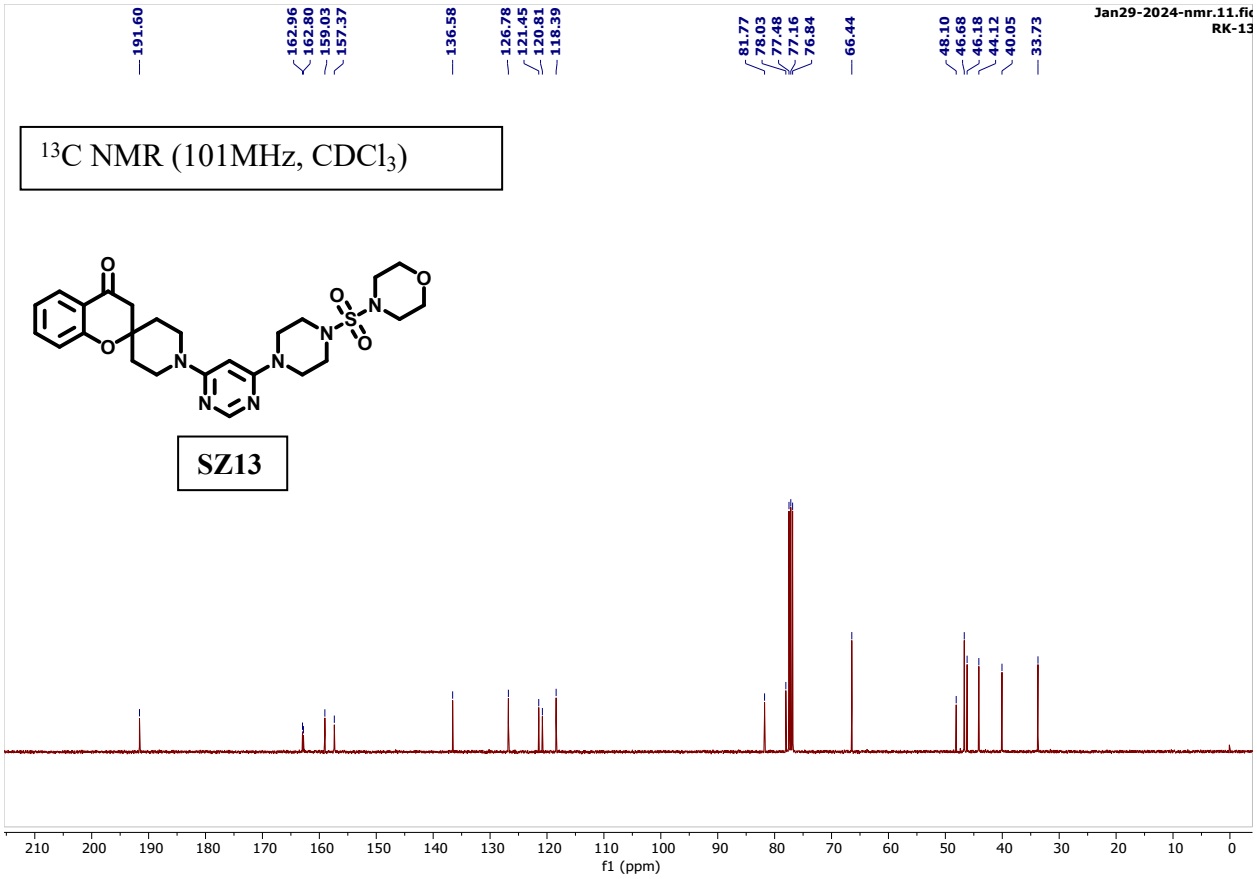

SKA-SZ11
single_pulse
8.18
7.87
7.87
7.85
7.62
7.59
7.57
7.55
7.52
7.50
7.49
7.37
7.35
7.33
7.31
7.26
7.03
7.02
7.00
6.98
5.57
4.10
4.07
4.04
3.70
3.69
3.67
3.37
3.34
3.31
3.28
3.09
3.07
3.06
2.72
2.11
2.08
1.68
1.66
1.62
1H NMR (400MHz, CDCl3)
SZ11
1.00
1.02
3.39
1.18
2.22
1.13
2.08
4.45
2.43
4.32
2.08
2.45
2.33
f1 (ppm)

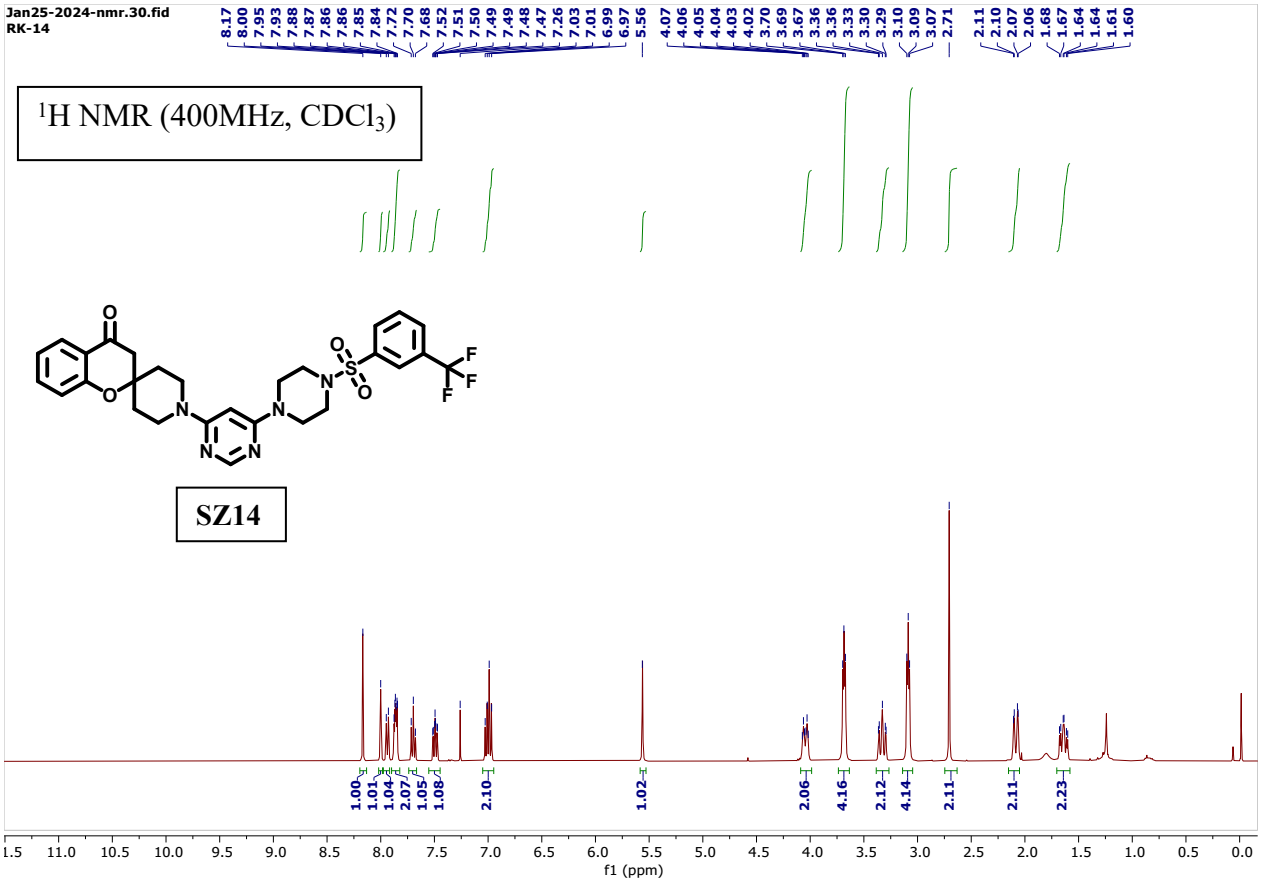

191.61
162.98
162.77
159.01
157.65
151.68
151.45
149.09
148.96
136.56
132.32
126.74
124.92
121.41
120.77
118.60
118.37
117.75
117.55
81.67
78.01
77.48
77.16
76.84
48.06
45.70
43.61
39.89
33.67
13C NMR (101MHz, CDCl3)
SZ11
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

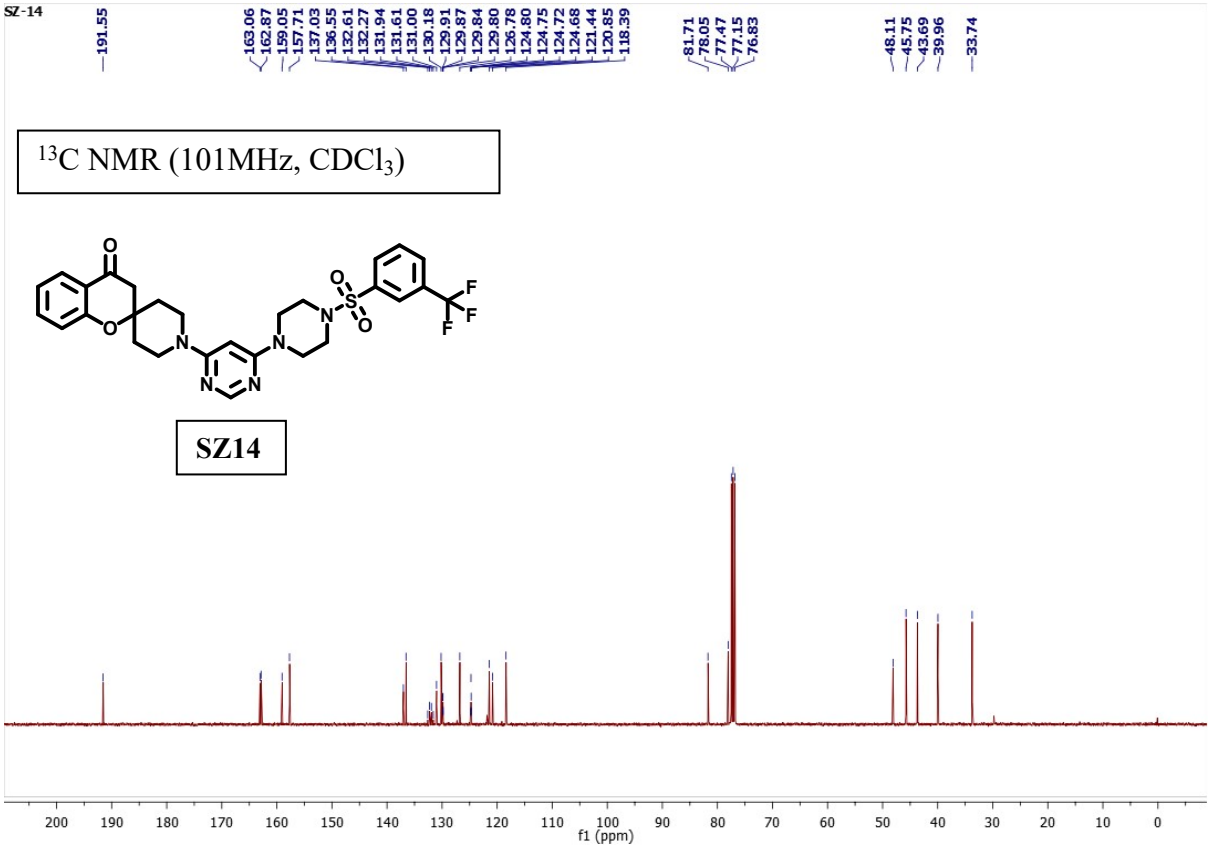

SKA-SZ12
single_pulse
8.20 7.87 7.86 7.85 7.84 7.52 7.51 7.50 7.48 7.48 7.26 7.03 7.01 7.00 6.98 5.59 4.09 4.07 4.05 4.04 3.71 3.70 3.68 3.38 3.38 3.35 3.32 3.31 3.17 3.16 3.14 2.72 2.63 2.39 2.11 2.08 2.03 1.70 1.69 1.67 1.65 1.63 1.62
1H NMR (400MHz, CDCl3)
SZ12
1.03 1.09 1.11 2.06 1.00 2.05 4.16 2.40 4.27 1.89 3.24 3.43 2.47 2.46
f1 (ppm)

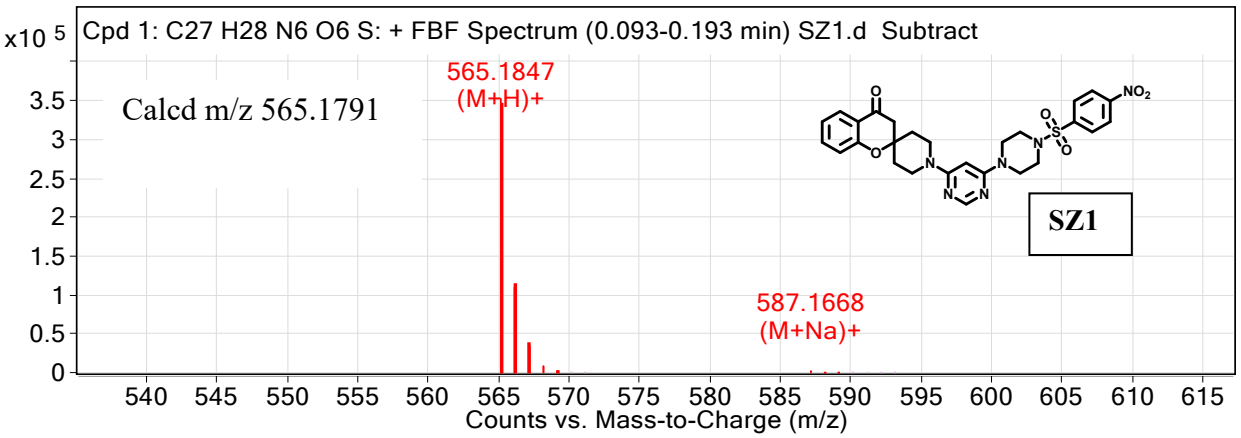

191.59
174.09
162.86
162.69
159.01
158.00
157.52
136.58
126.77
121.45
120.78
118.38
112.95
81.71
78.00
77.48
77.16
76.84
48.07
45.14
43.70
39.96
33.70
13.14
11.51
13C NMR (101MHz, CDCl3)
SZ12
f1 (ppm)

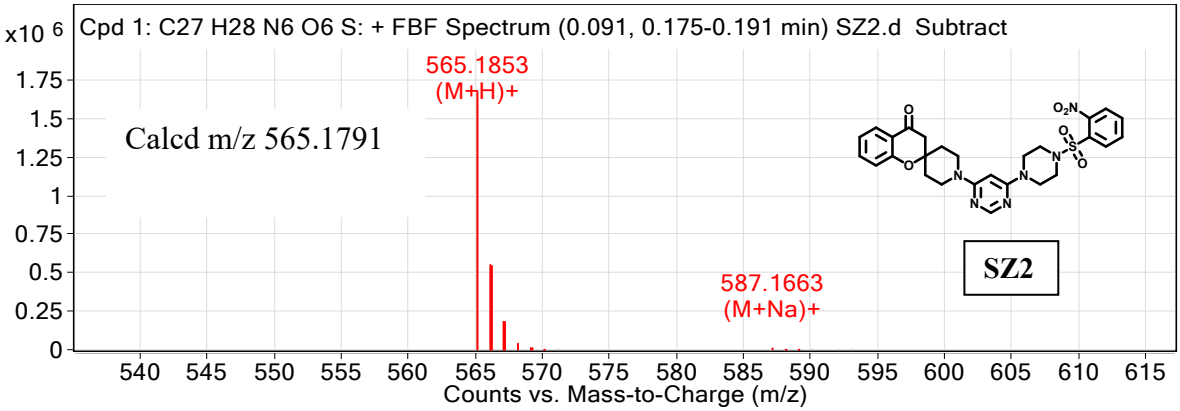

Jan29-2024-nmr.10.fid
RK-13
1H NMR (400MHz, CDCl3)
SZ13
1.00
1.02
1.05
2.11
1.06
2.13
4.47
4.00
6.10
3.92
2.11
2.33
2.14
f1 (ppm)

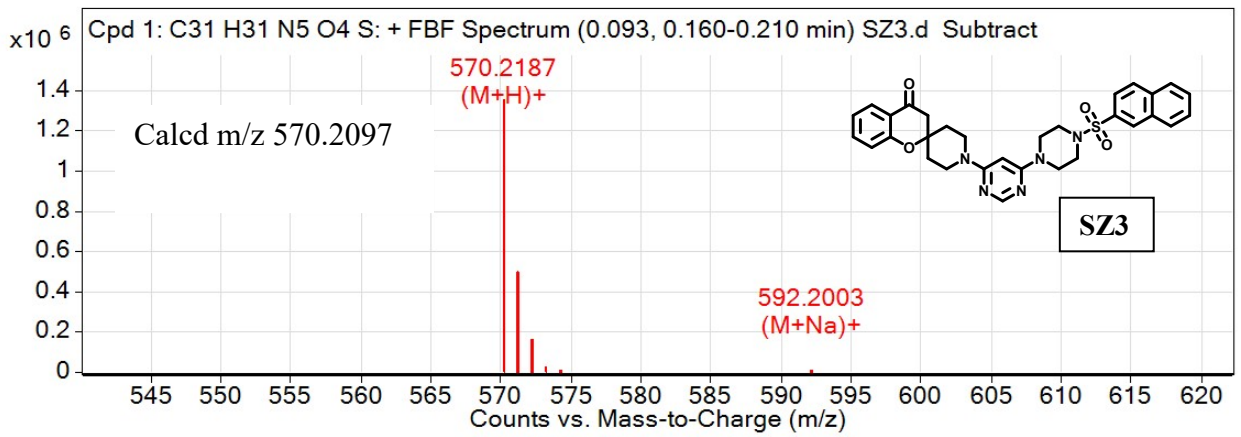

191.60
162.96
162.80
159.03
157.37
136.58
126.78
121.45
120.81
118.39
81.77
78.03
77.48
77.16
76.84
66.44
48.10
46.68
46.18
44.12
40.05
33.73
Jan29-2024-nmr.11.fi
RK-13
13C NMR (101MHz, CDCl3)
SZ13
f1 (ppm)

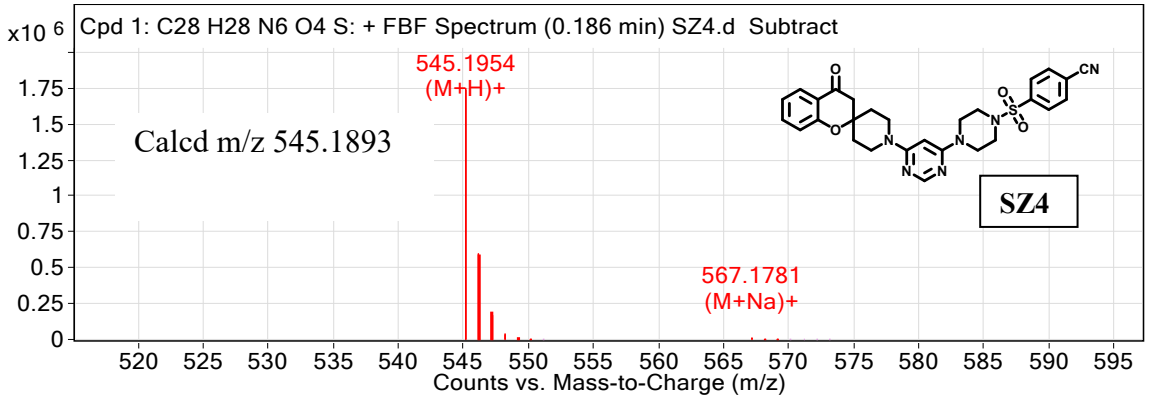

Jan25-2024-nmr.30.fid
RK-14
^{1}H NMR (400MHz, $CDCl_3$)
SZ14
f1 (ppm)

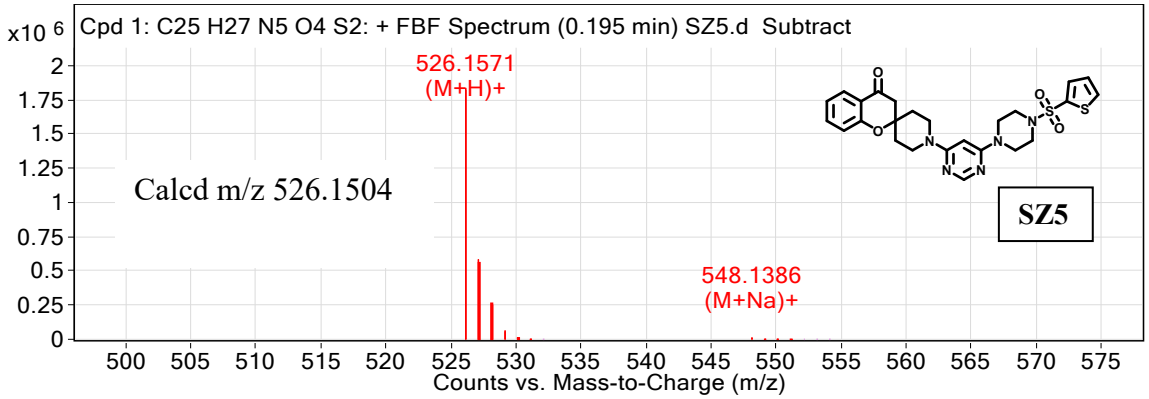

SZ-14
^{13}C NMR (101MHz, $CDCl_3$)
SZ14
f1 (ppm)

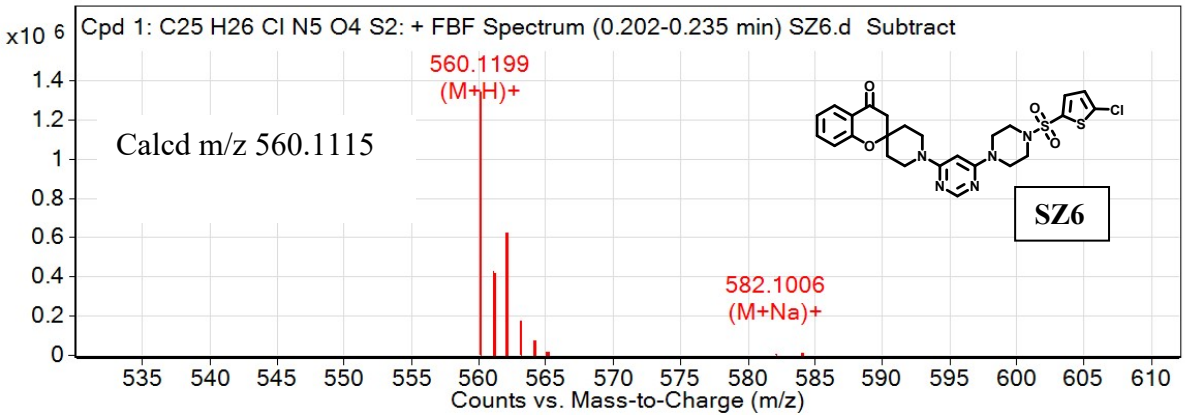

Cpd 1: C27 H28 N6 O6 S: + FBF Spectrum (0.093-0.193 min) SZ1.d Subtract
x10 5
Calcd m/z 565.1791
565.1847
(M+H)+
587.1668
(M+Na)+
SZ1
Counts vs. Mass-to-Charge (m/z)

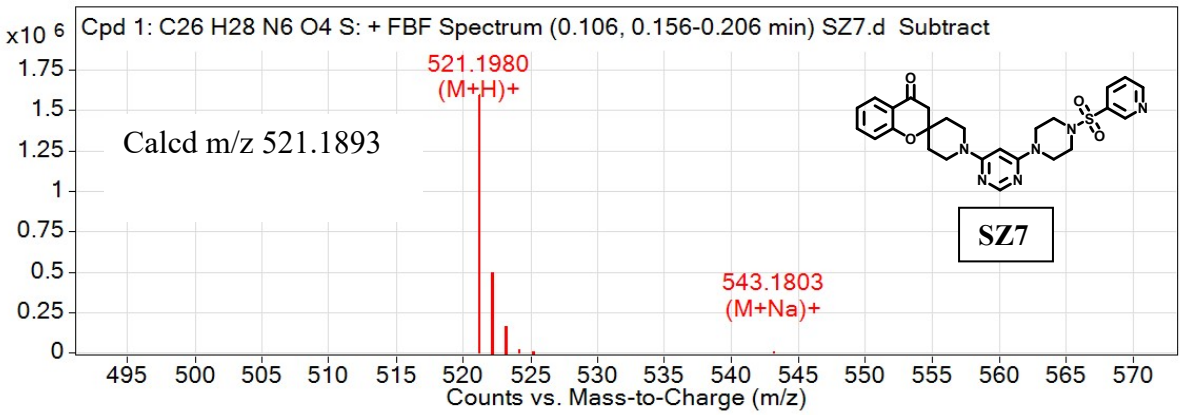

Cpd 1: C27 H28 N6 O6 S: + FBF Spectrum (0.091, 0.175-0.191 min) SZ2.d Subtract
x10 6
Calcd m/z 565.1791
565.1853
(M+H)+
587.1663
(M+Na)+
SZ2
Counts vs. Mass-to-Charge (m/z)

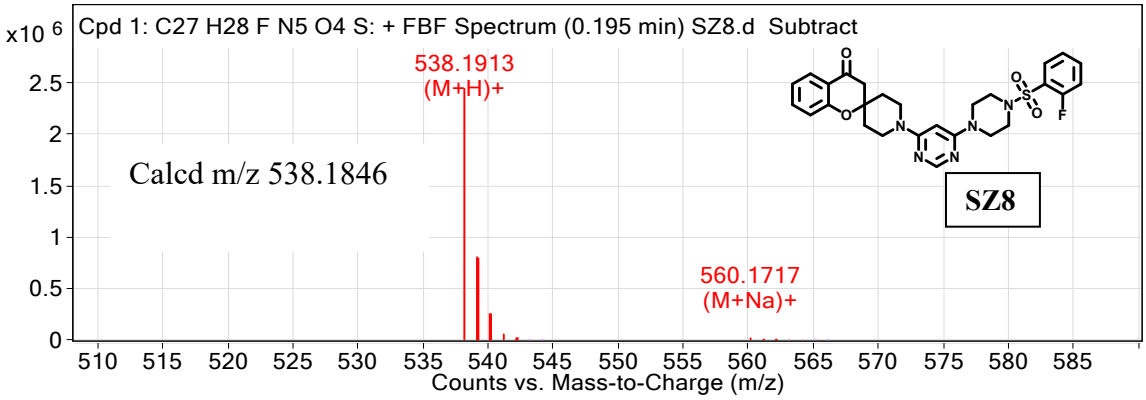

Cpd 1: C31 H31 N5 O4 S: + FBF Spectrum (0.093, 0.160-0.210 min) SZ3.d Subtract
x10 6
Calcd m/z 570.2097
570.2187
(M+H)+
592.2003
(M+Na)+
SZ3
Counts vs. Mass-to-Charge (m/z)

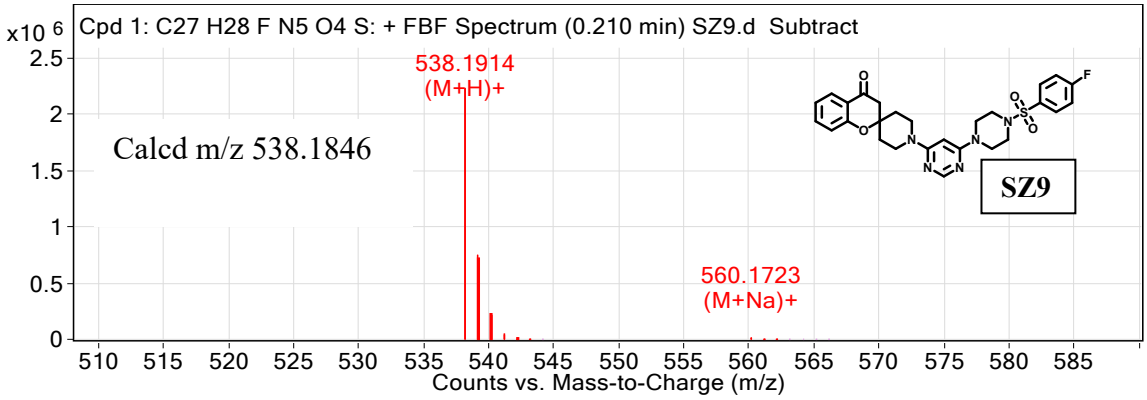

Cpd 1: C28 H28 N6 O4 S: + FBF Spectrum (0.186 min) SZ4.d Subtract
x10 6
545.1954
(M+H)+
Calcd m/z 545.1893
567.1781
(M+Na)+
SZ4
Counts vs. Mass-to-Charge (m/z)

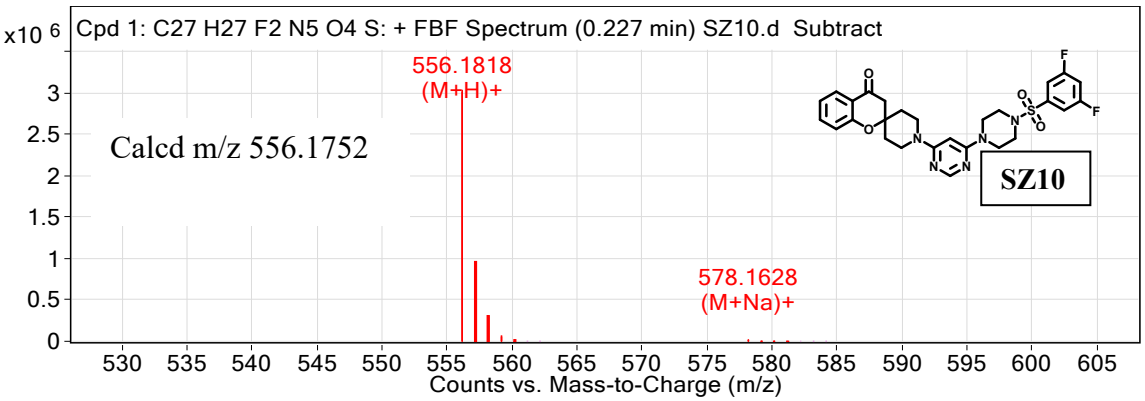

Cpd 1: C25 H27 N5 O4 S2: + FBF Spectrum (0.195 min) SZ5.d Subtract
x10 6
526.1571
(M+H)+
Calcd m/z 526.1504
548.1386
(M+Na)+
SZ5
Counts vs. Mass-to-Charge (m/z)

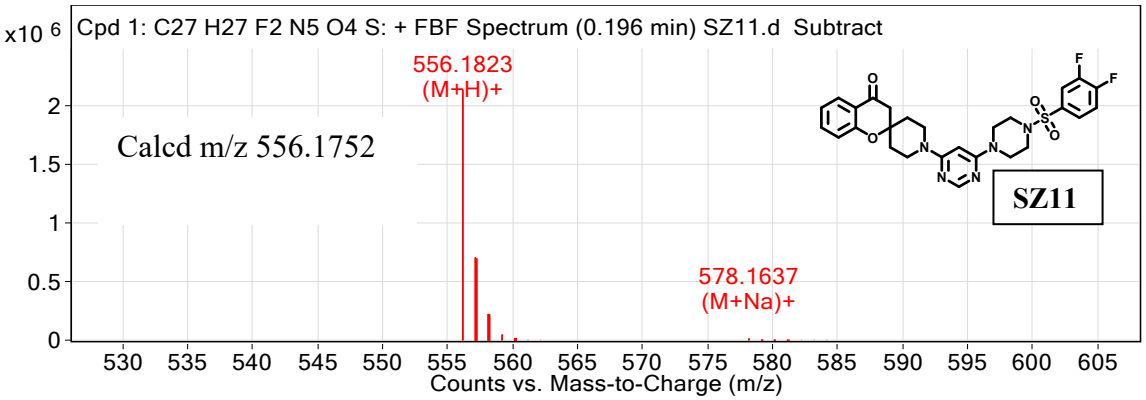

Cpd 1: C25 H26 Cl N5 O4 S2: + FBF Spectrum (0.202-0.235 min) SZ6.d Subtract
x10 6
560.1199
(M+H)+
Calcd m/z 560.1115
582.1006
(M+Na)+
SZ6
Counts vs. Mass-to-Charge (m/z)

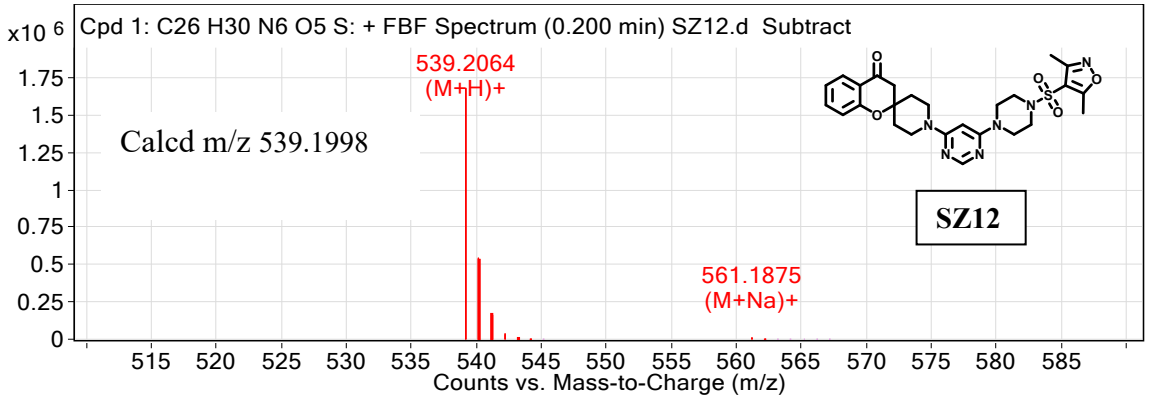

Cpd 1: C26 H28 N6 O4 S: + FBF Spectrum (0.106, 0.156-0.206 min) SZ7.d Subtract
x10 6
1.75
1.5
1.25
1
0.75
0.5
0.25
0
521.1980
(M+H)+
Calcd m/z 521.1893
543.1803
(M+Na)+
SZ7
495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570
Counts vs. Mass-to-Charge (m/z)

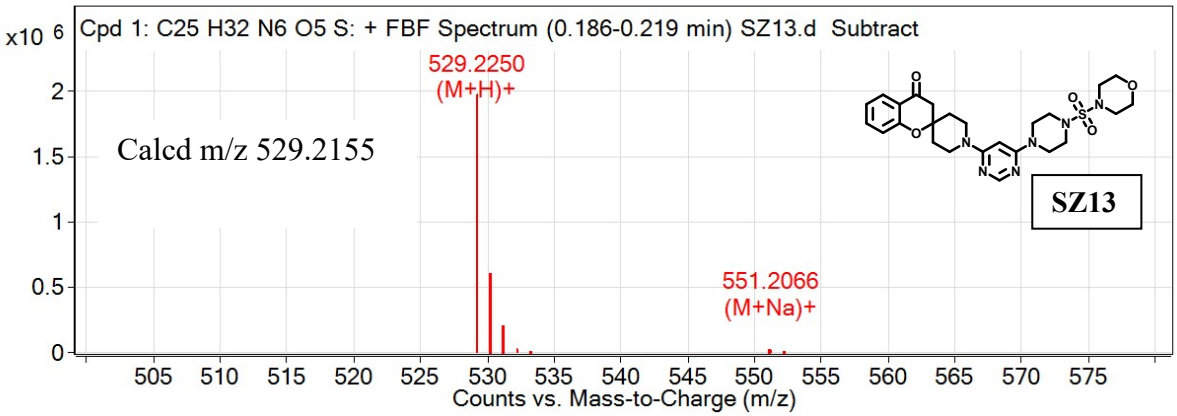

Cpd 1: C27 H28 F N5 O4 S: + FBF Spectrum (0.195 min) SZ8.d Subtract
x10 6
2.5
2
1.5
1
0.5
0
538.1913
(M+H)+
Calcd m/z 538.1846
560.1717
(M+Na)+
SZ8
510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585
Counts vs. Mass-to-Charge (m/z)

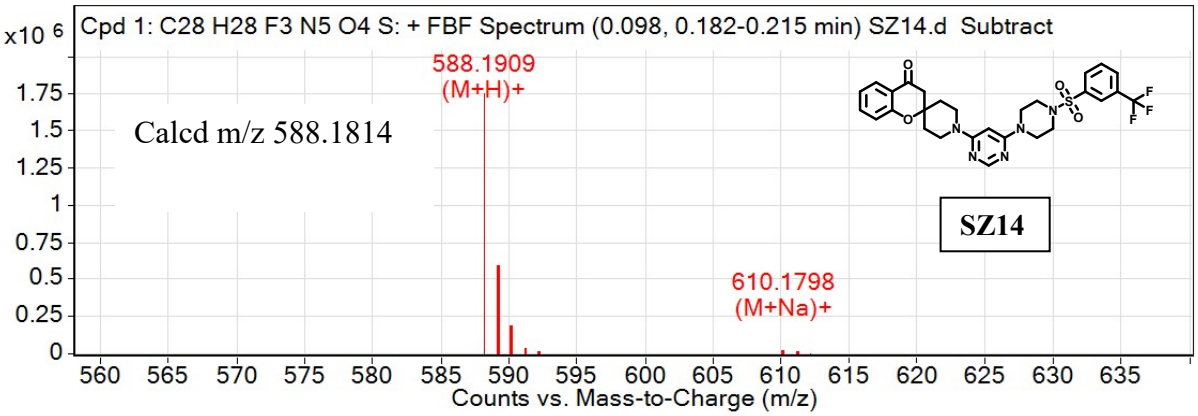

Cpd 1: C27 H28 F N5 O4 S: + FBF Spectrum (0.210 min) SZ9.d Subtract
x10 6
538.1914
(M+H)+
Calcd m/z 538.1846
560.1723
(M+Na)+
SZ9
Counts vs. Mass-to-Charge (m/z)


Cpd 1: C27 H27 F2 N5 O4 S: + FBF Spectrum (0.227 min) SZ10.d Subtract
x10 6
556.1818
(M+H)+
Calcd m/z 556.1752
578.1628
(M+Na)+
SZ10
Counts vs. Mass-to-Charge (m/z)


Cpd 1: C27 H27 F2 N5 O4 S: + FBF Spectrum (0.196 min) SZ11.d Subtract
x10 6
556.1823
(M+H)+
Calcd m/z 556.1752
578.1637
(M+Na)+
SZ11
Counts vs. Mass-to-Charge (m/z)

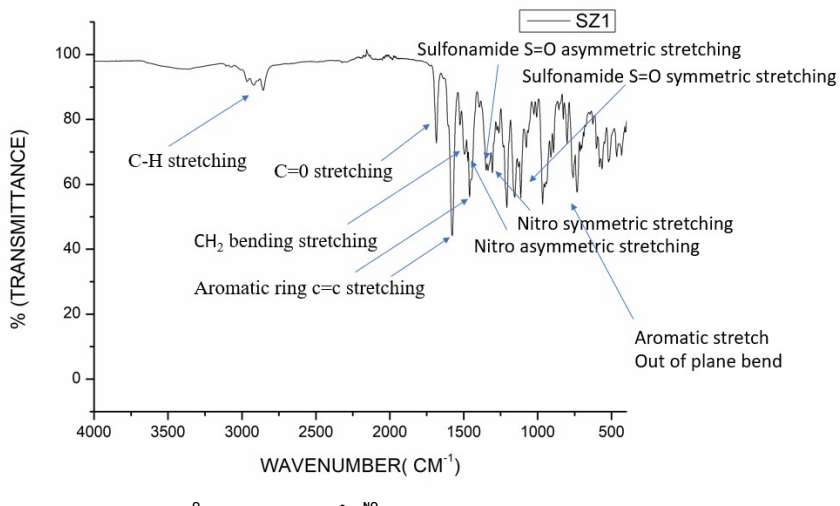

Cpd 1: C26 H30 N6 O5 S: + FBF Spectrum (0.200 min) SZ12.d Subtract
x10 6
539.2064
(M+H)+
Calcd m/z 539.1998
561.1875
(M+Na)+
SZ12
Counts vs. Mass-to-Charge (m/z)


Cpd 1: C25 H32 N6 O5 S: + FBF Spectrum (0.186-0.219 min) SZ13.d Subtract
x10 6
529.2250
(M+H)+
Calcd m/z 529.2155
551.2066
(M+Na)+
SZ13
Counts vs. Mass-to-Charge (m/z)


Cpd 1: C28 H28 F3 N5 O4 S: + FBF Spectrum (0.098, 0.182-0.215 min) SZ14.d Subtract
x10 6
588.1909
(M+H)+
Calcd m/z 588.1814
610.1798
(M+Na)+
SZ14
Counts vs. Mass-to-Charge (m/z)

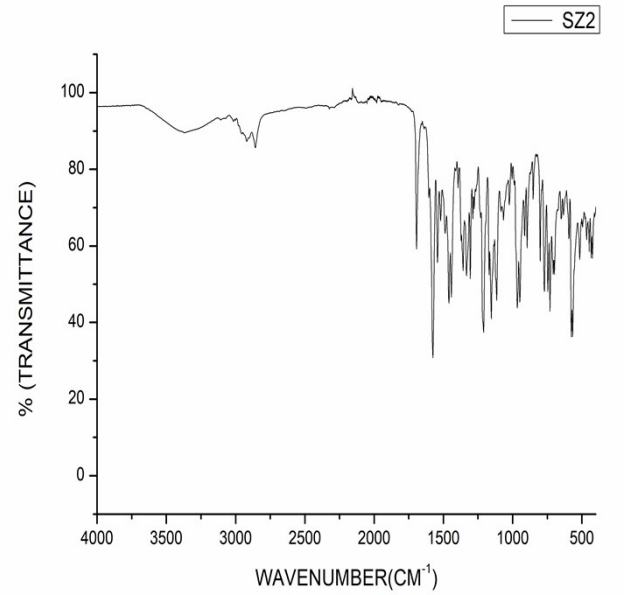
Fourier-Transform Infrared (FTIR) analysis

To analyze the functional group present in the synthesized sulfonamide-based pyrimidine derivatives (SZ1-SZ14), the Nicolet iS50 FTIR Tri-detector with gold flex spectrometer (Gold optics) bearing diamond ATR module (resolution 0.09 -1 cm) was used. The spectra of all the synthesized derivatives show all the common characteristic bands responsible for the particular functional groups. The stretching frequency of C=O conjugated with phenyl appears around 1700-1680 cm^{-1}. The peaks around 1600-1450 cm^{-1} and 1475 cm^{-1} arise due to the aromatic C=C stretching while the aromatic stretch (C=C) out of plane was found 900-960 cm-1. The common characteristic C-H stretching peak appeared around 2950-2800 cm^{-1} while C-H bending stretch was observed around 1472 cm^{-1}. The ether C-O stretching was found at 1300-1000 cm^{-1} for all the compounds. The sulfonamide S=O asymmetric stretch and symmetric frequency were observed around 1370-1335 cm^{-1} and 1116 cm^{-1} respectively. The peak around 1550-1475 cm^{-1} and 1360-1290 cm-1 were due to asymmetric stretching and symmetric stretching of

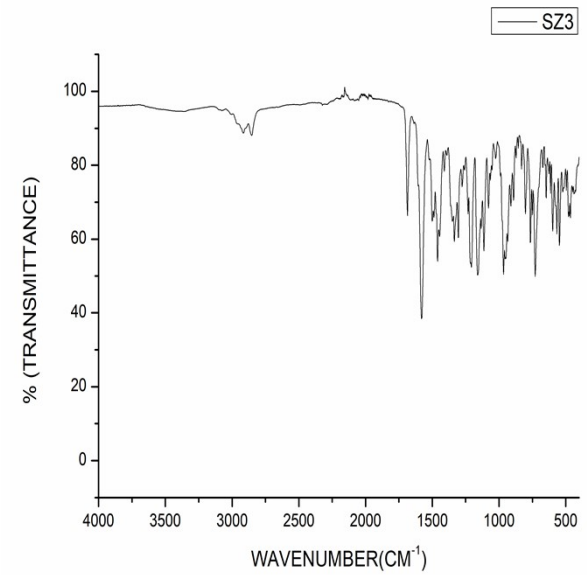


the nitro group (SZ1 and SZ2). For the cyano functional group present in the SZ4 molecule exhibited a peak at 2232 cm^{-1}. The different common characteristic functional peaks were marked in the FTIR spectrum of SZ1.

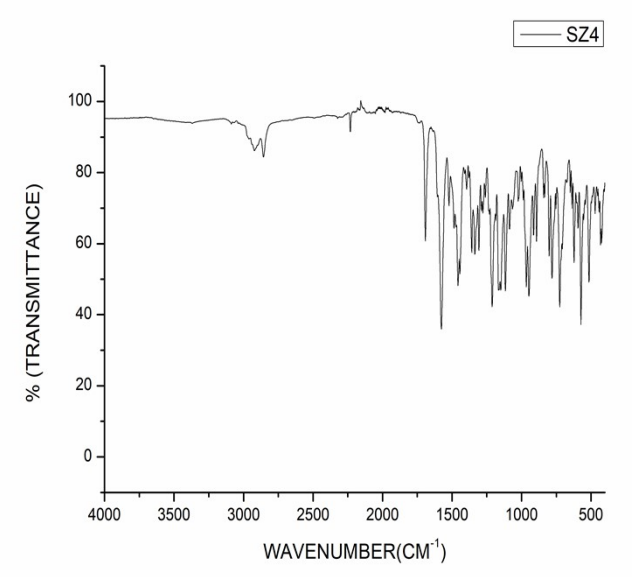
FTIR spectrum of SZ1 compound



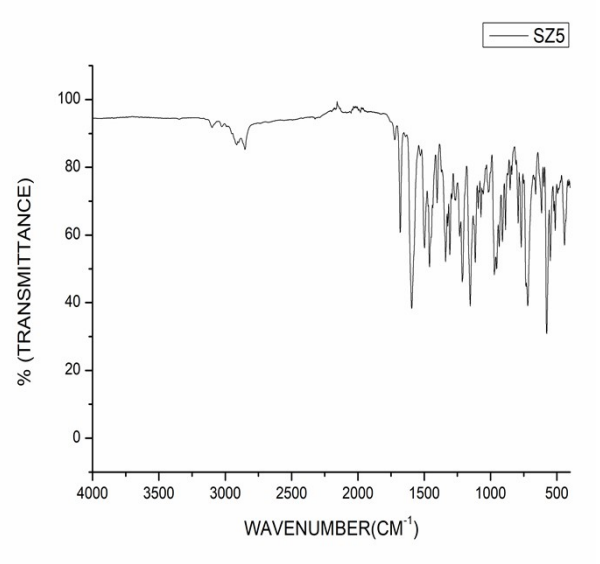
FTIR spectrum of SZ2 compound



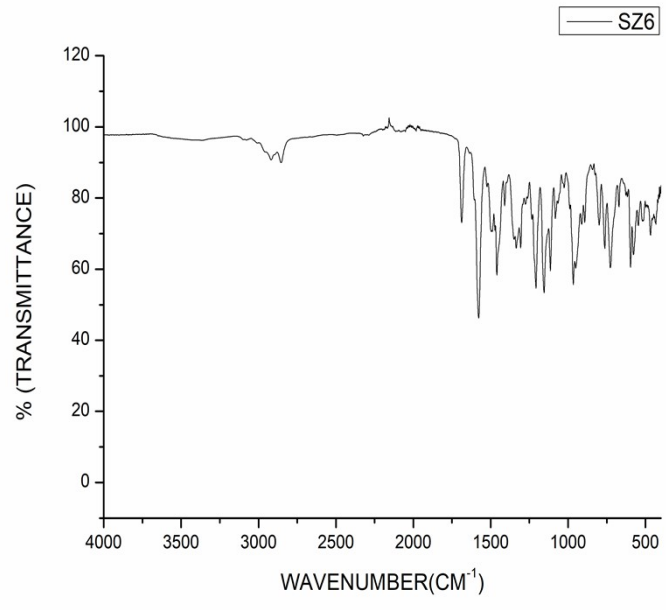
FTIR spectrum of SZ3 compound



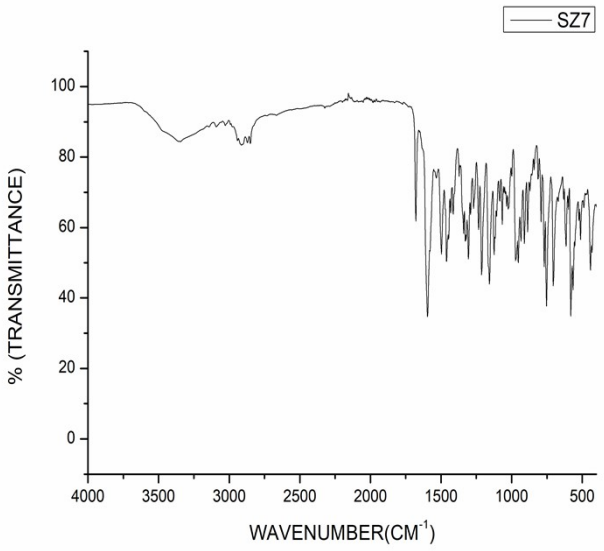
FTIR spectrum of SZ4 compound



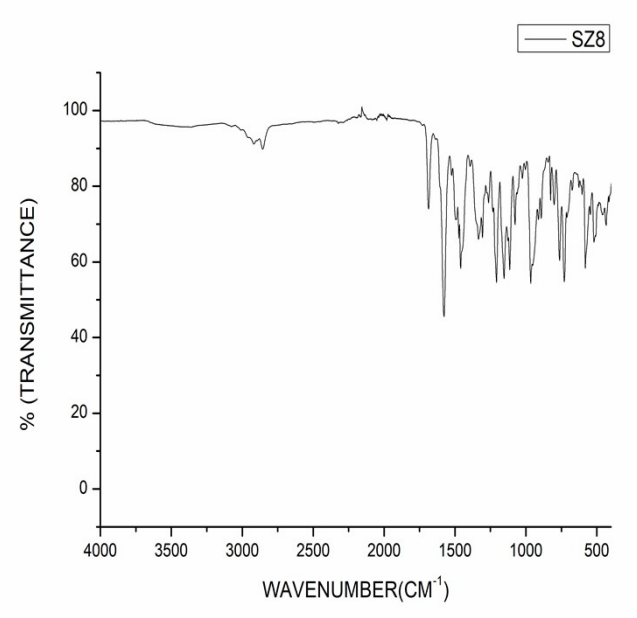
FTIR spectrum of SZ5 compound



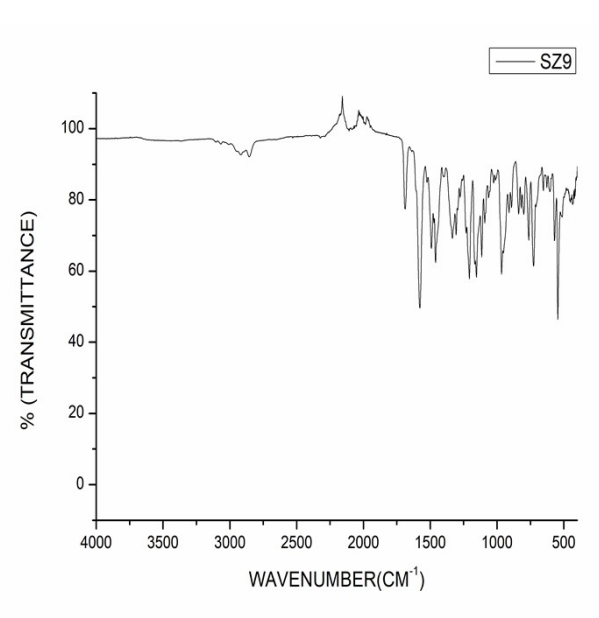
FTIR spectrum of SZ6 compound



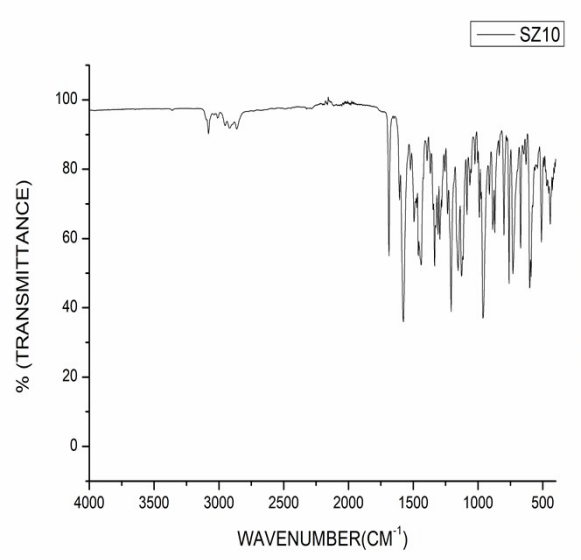
FTIR spectrum of SZ7 compound



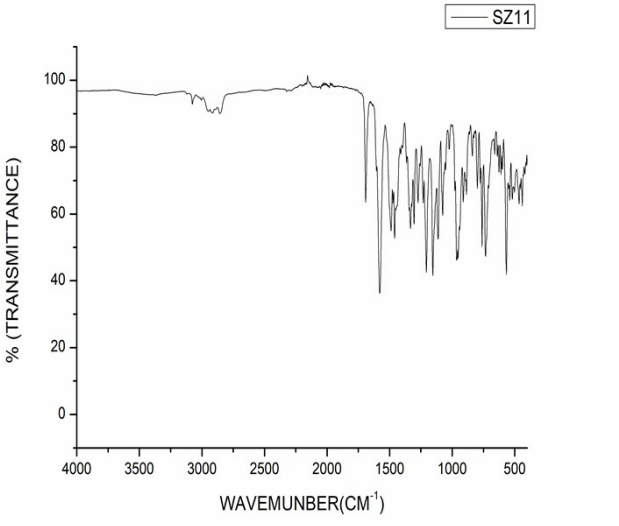
FTIR spectrum of SZ8 compound



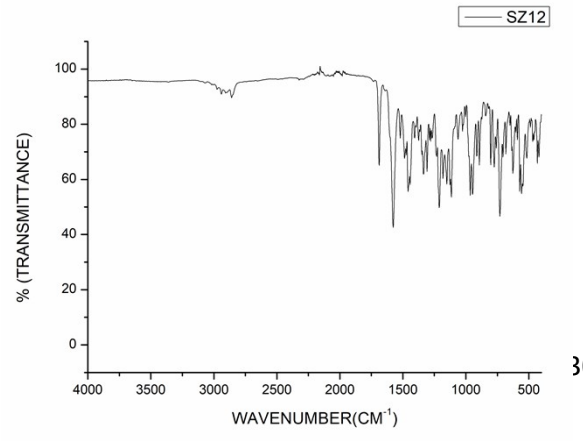
FTIR spectrum of SZ9 compound

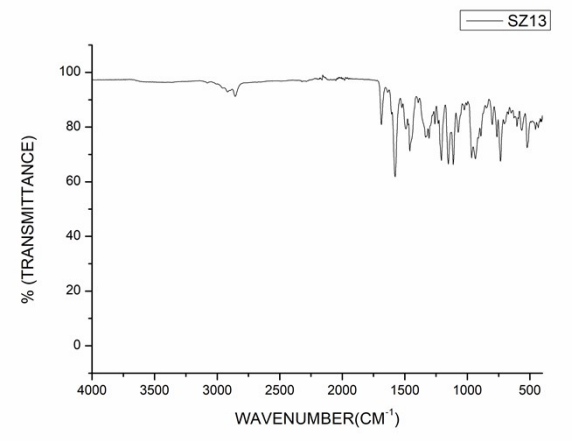


FTIR spectrum of SZ10 compound



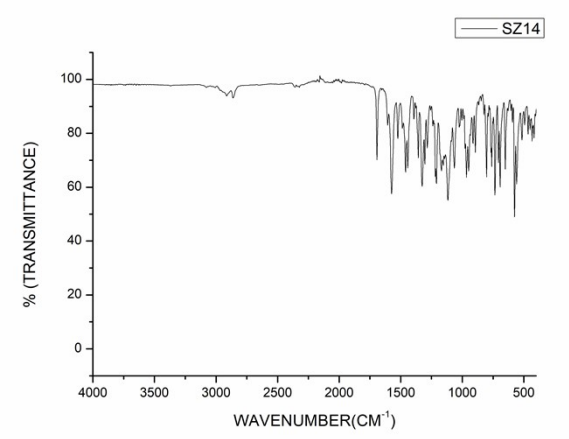
FTIR spectrum of SZ11 compound





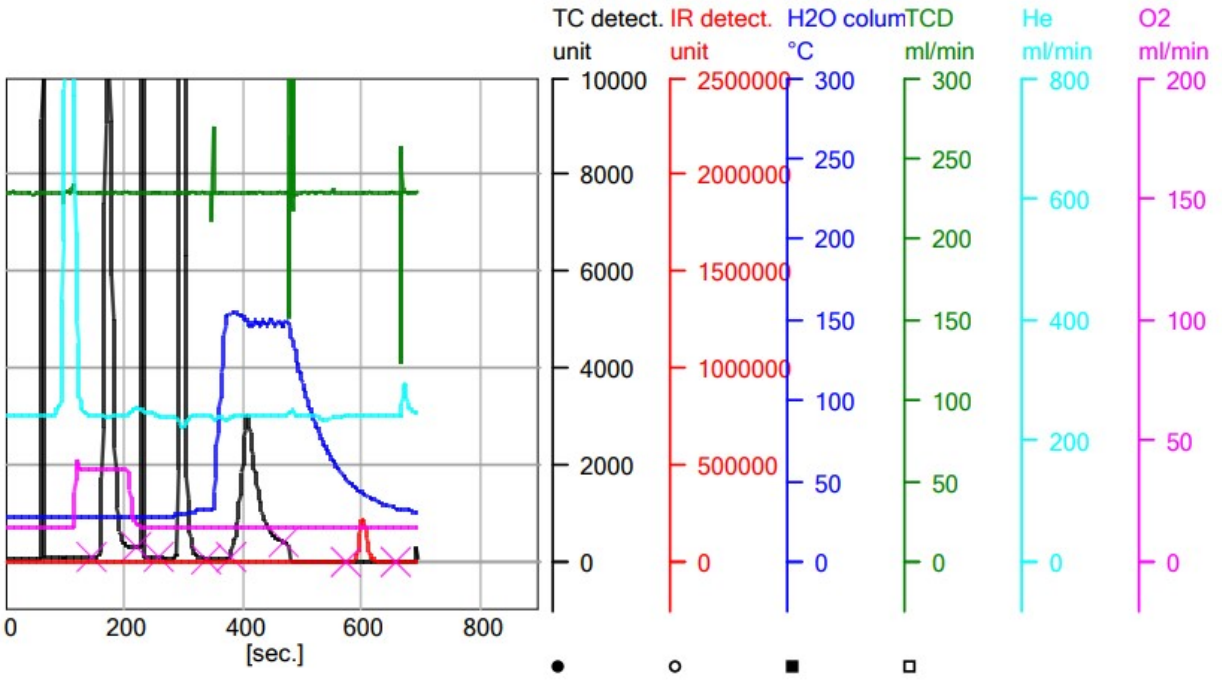
FTIR spectrum of SZ12 compound FTIR spectrum of SZ13 compound

FTIR spectrum of SZ14 compound



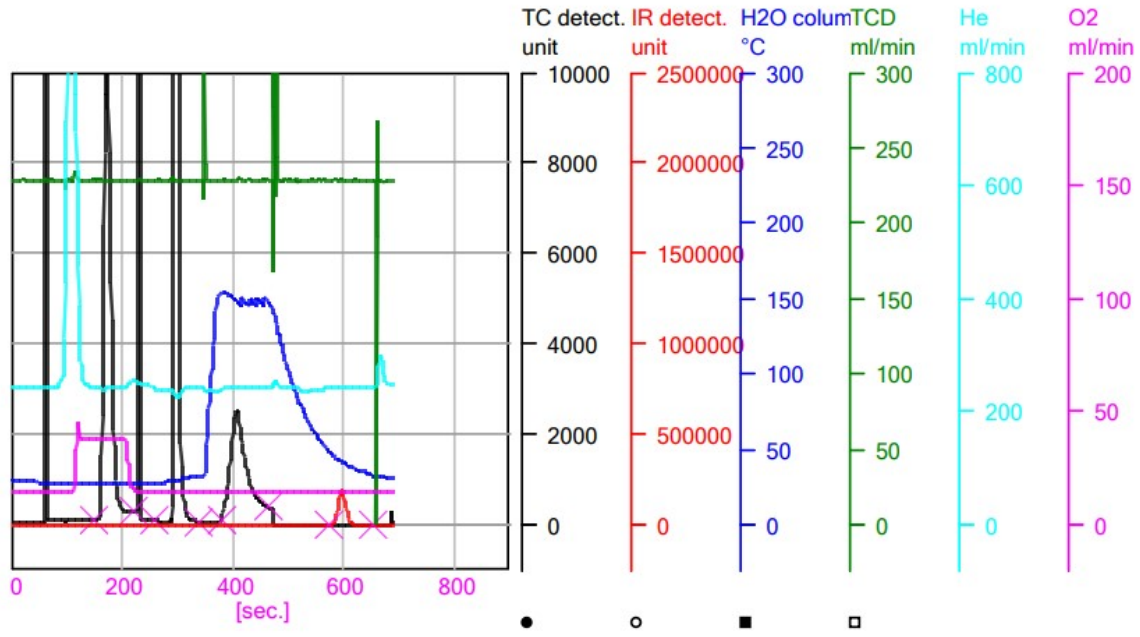
Graphic report

No.	Weight [..	Name	Method	N [%]	C [%]	H [%]	S [%]	N Area	C Area	H Area	S Area	C/N ratio	C/H ratio	Date Time
46	3.4470	SZ9	5mg90s	12.75	60.23	5.093	7.563	17 251	54 136	10 110	127 809	4.7230	11.8261	10/07/2024 21:45



CHNS analysis report of SZ9

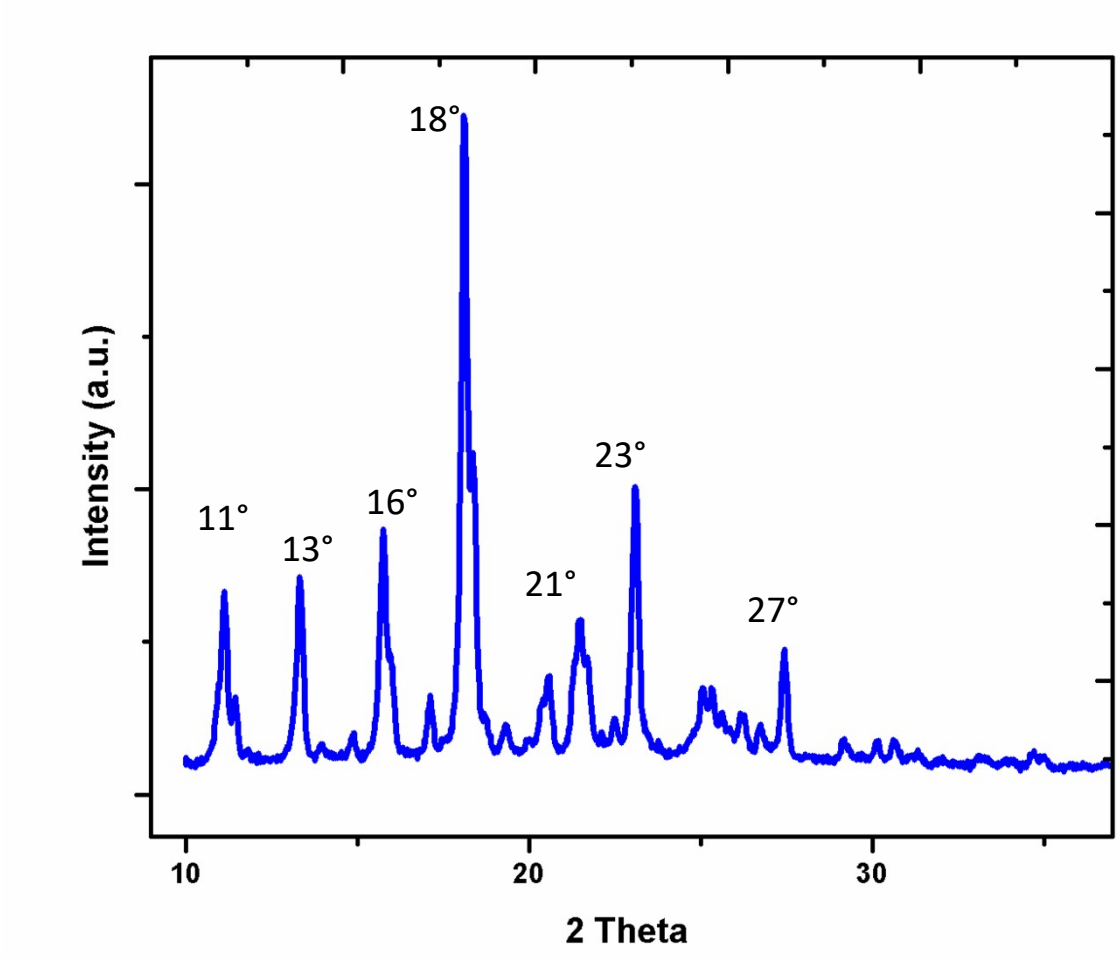
No.	Weight [..	Name	Method	N [%]	C [%]	H [%]	S [%]	N Area	C Area	H Area	S Area	C/N ratio	C/H ratio	Date Time
47	3.3970	SZ14	5mg90s	11.67	58.01	4.366	7.072	15 611	51 416	8 583	114 293	4.9712	13.2869	10/07/2024 21:57



CHNS analysis report of SZ14

Powder XRD

To determine the nature of the powder solid compound (SZ14), a Rigaku UltimaIV X-RAY diffractometer was used. The target (source) of the wave was copper (Cu) K-alpha with a wavelength of 1.5406 Angstrom. The XRD diffraction pattern of SZ14 has been shown below. The XRD pattern of the SZ14 showed crystalline structure with diffraction peaks around 11°, 13°, 16°, 18°, 21°, 23°, and 27°.



X-ray diffraction pattern of SZ14 compound