

Mimicry of Sorafenib: Novel Diarylureas as VEGFR2 Inhibitors and Apoptosis Inducers in Breast Cancer

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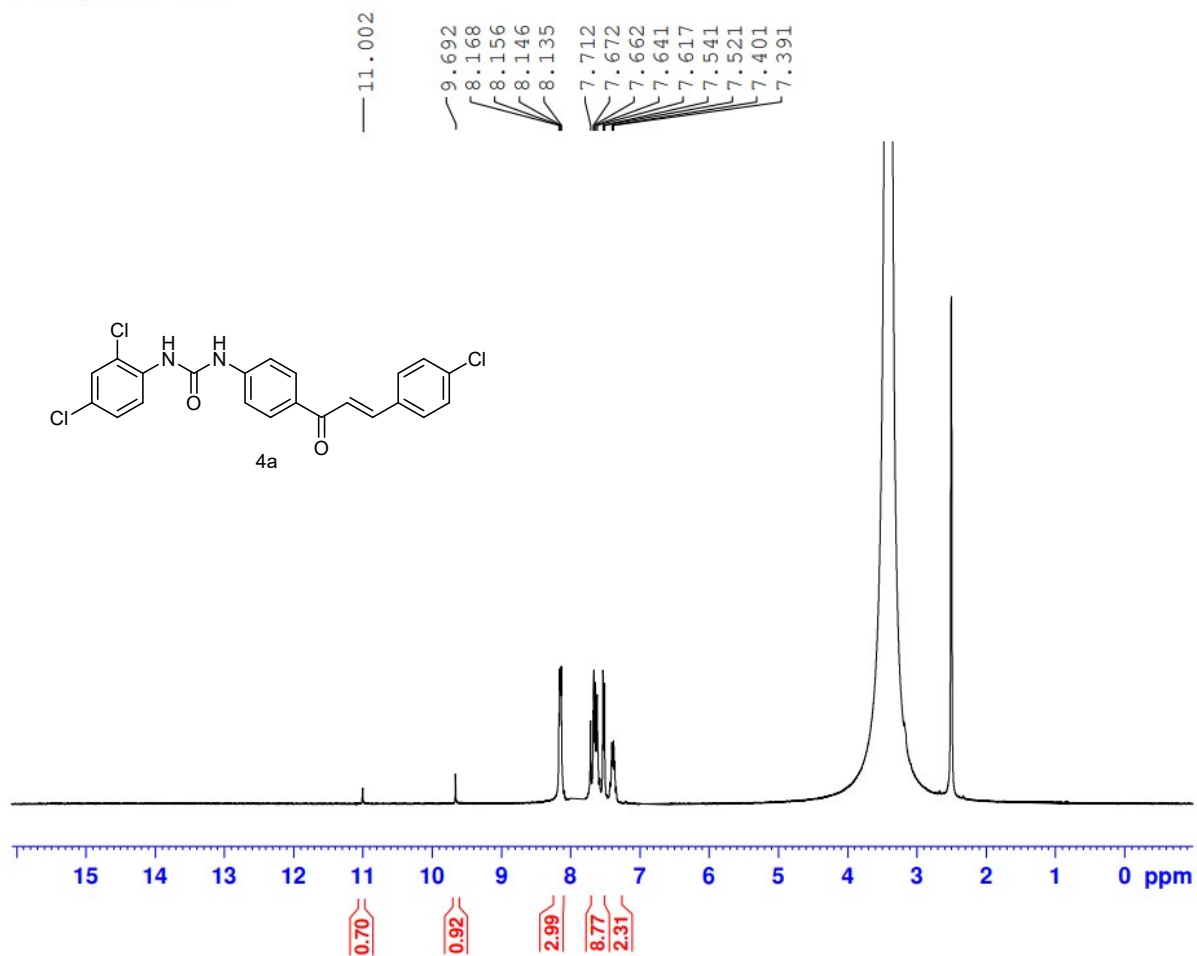
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Corresponding author:

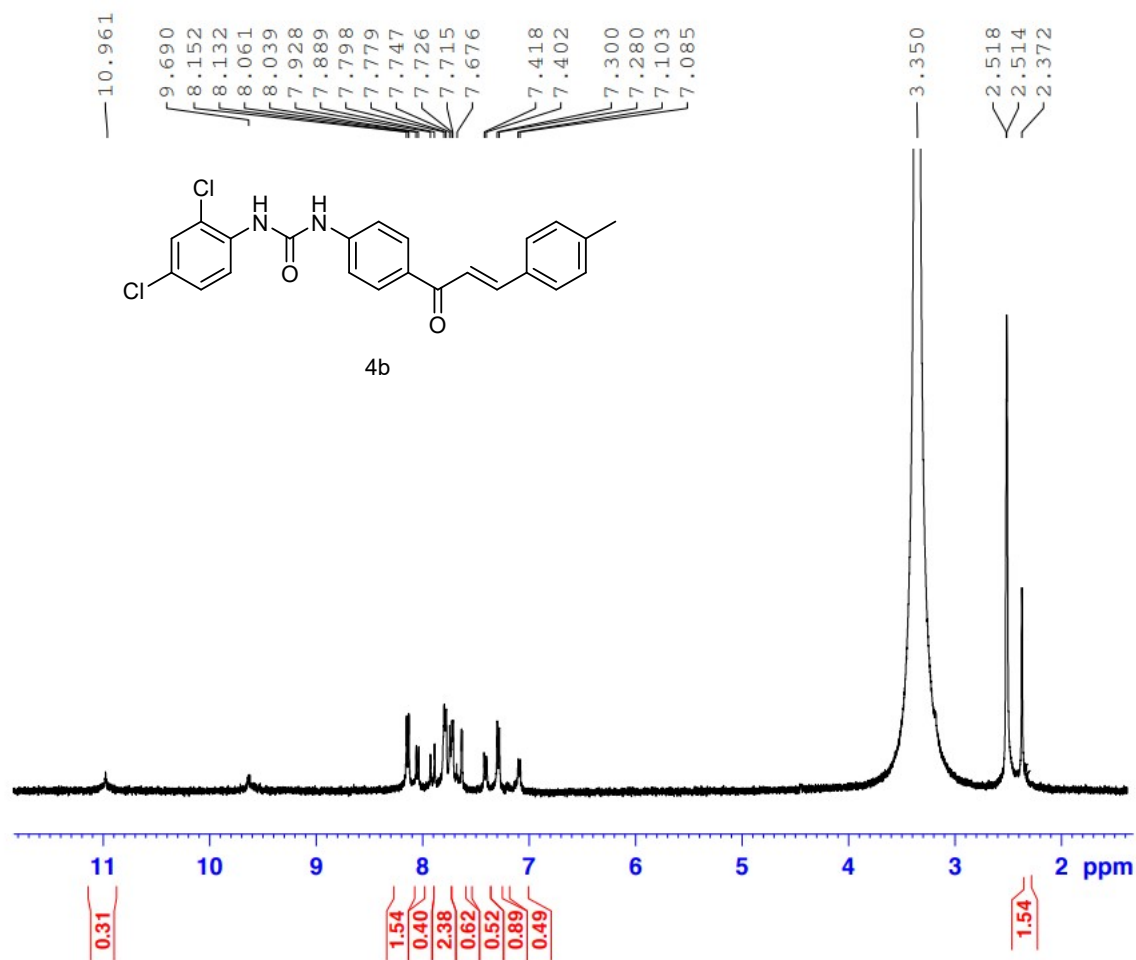
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Chemistry part data

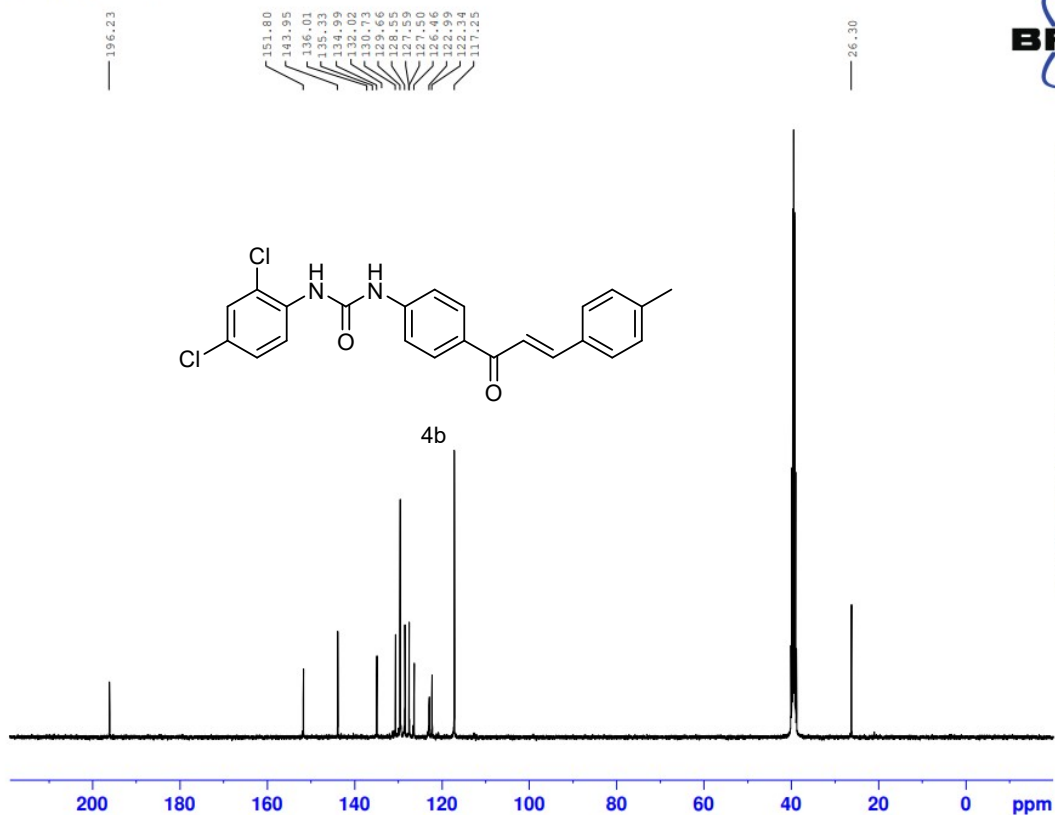
D-alsymaa-cl-1H



MONA1-B
PROTON_BSU DMSO {C:\data} abeer 10



D-monol-B-c13



```

Current Data Parameters
NAME      D-monol-B-c13
EXPNO     10
PROCNO    1

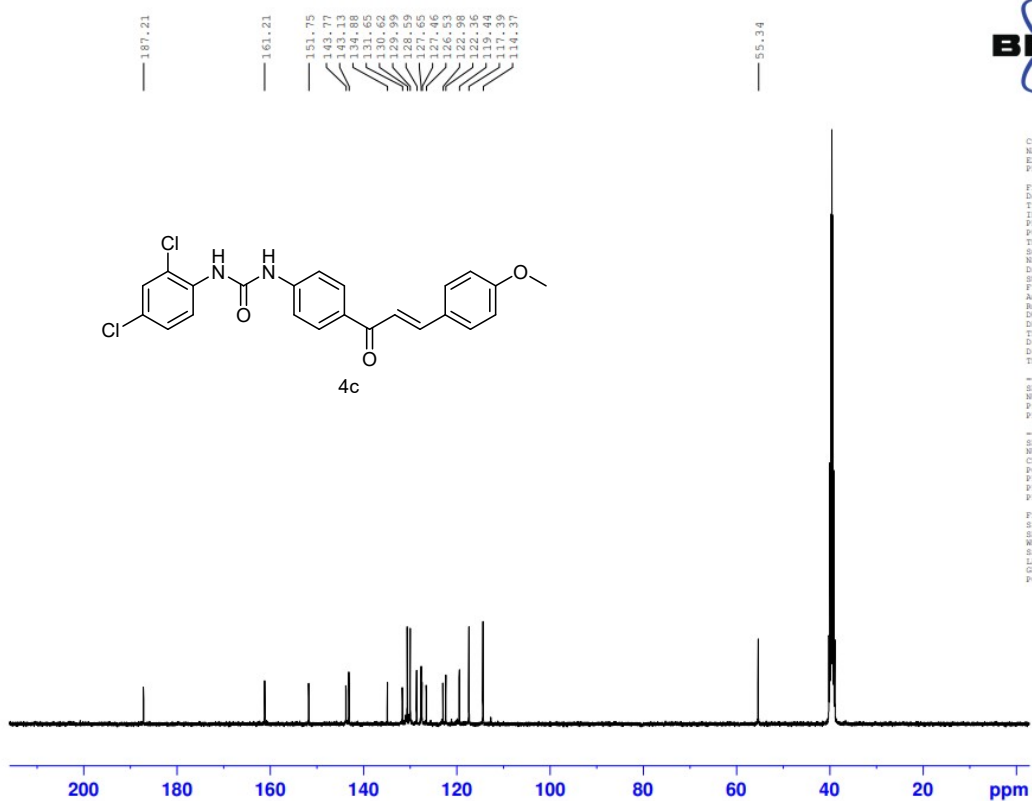
F2 - Acquisition Parameters
Date_     20220427
Time      1.21
INSTRUM   spect
PROBHD    5 mm PABBO BB/
PULPROG   zgpg30
TD         65536
SOLVENT   DMSO
NS         1024
DS         4
SWH        24038.461 Hz
FIDRES     0.366796 Hz
AQ         1.3631488 sec
RG         201.61
DW         20.800 usec
DE         6.50 usec
TE         298.2 K
D2.0000000 1 sec
D0.0300000 11 sec
T01        0

===== CHANNEL f1 =====
SFO100.6228293 1 MHz
NUC13        13C
P10.00       1 usec
PLWS0.0000000 1 W

===== CHANNEL f2 =====
SFO400.1316005 2 MHz
NUC1        13C
P20.00       2 usec
PLWS0.0000000 2 W

F2 - Processing parameters
SI          32768
SF          100.6128158 MHz
WDW         EM
SSB         0
LB          1.00 Hz
GB          0
PC          1.40
    
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D-mona-c5-c13



Current Data Parameters
NAME D-mona-c5-c13
EXPNO 10
PROCNO 1

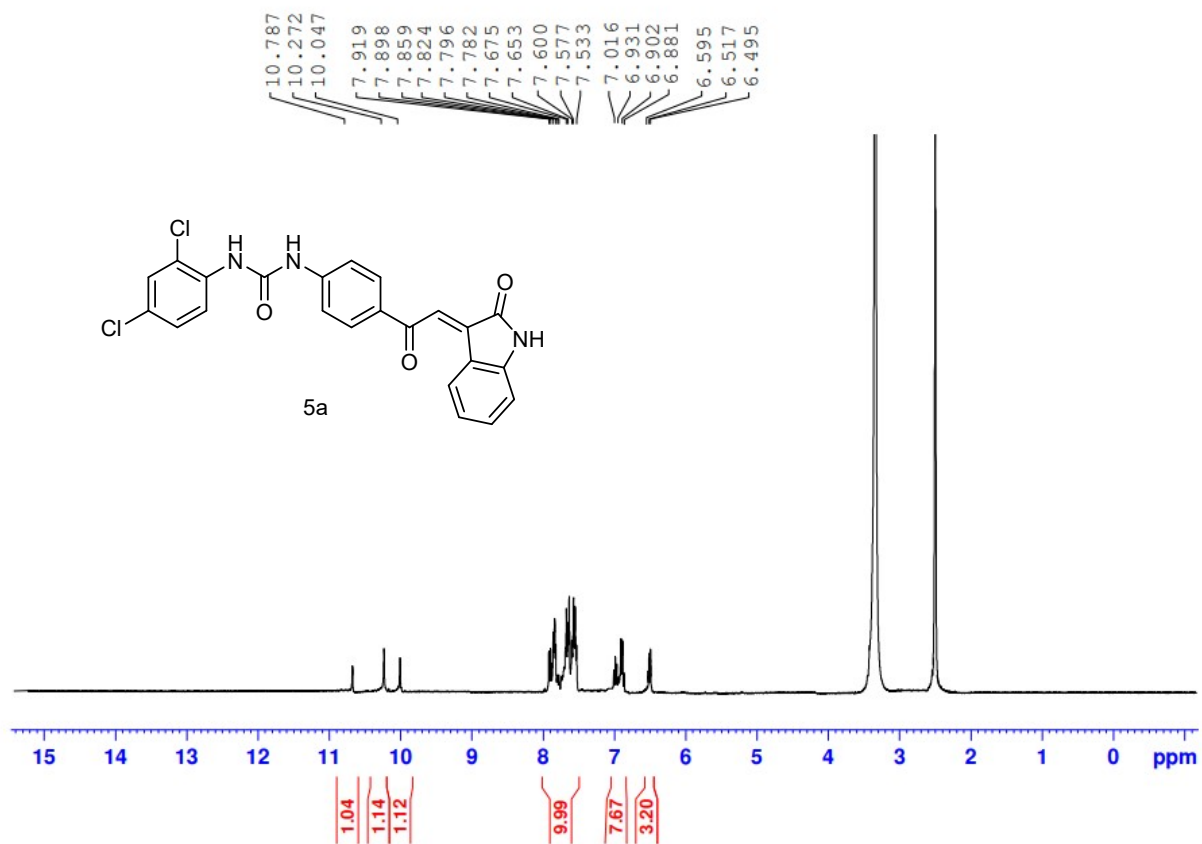
F2 - Acquisition Parameters
Date_ 20220427
Time 4.23
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 201.61
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 100.6282893 MHz
NUC1 13C
P1 10.00 usec
PLW1 50.00000000 W

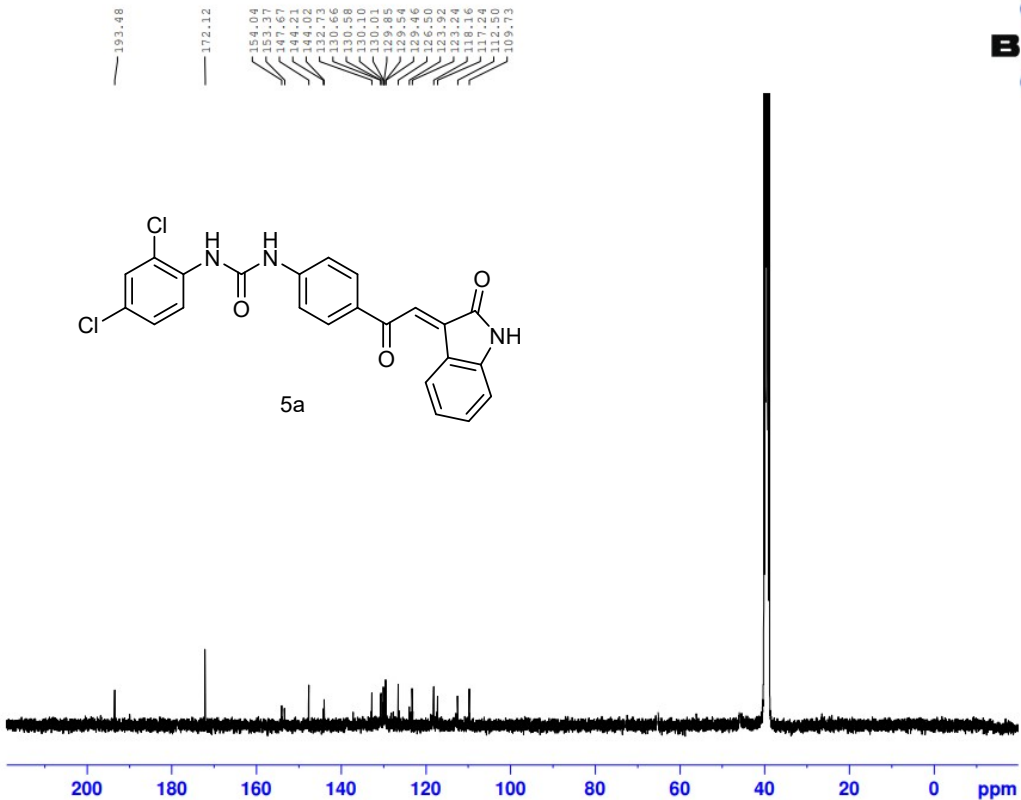
===== CHANNEL f2 =====
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG2 waltz16
DPCD2 90.00 usec
PLW2 10.39999962 W
PLW12 0.28889000 W
PLW13 0.23460000 W

F2 - Processing parameters
SI 32768
SF 100.6128171 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

D-monal-salt1-H



D-monal-salt-c13



Current Data Parameters
NAME D-monal-salt-c13
EXPNO 20
PROCNO 1

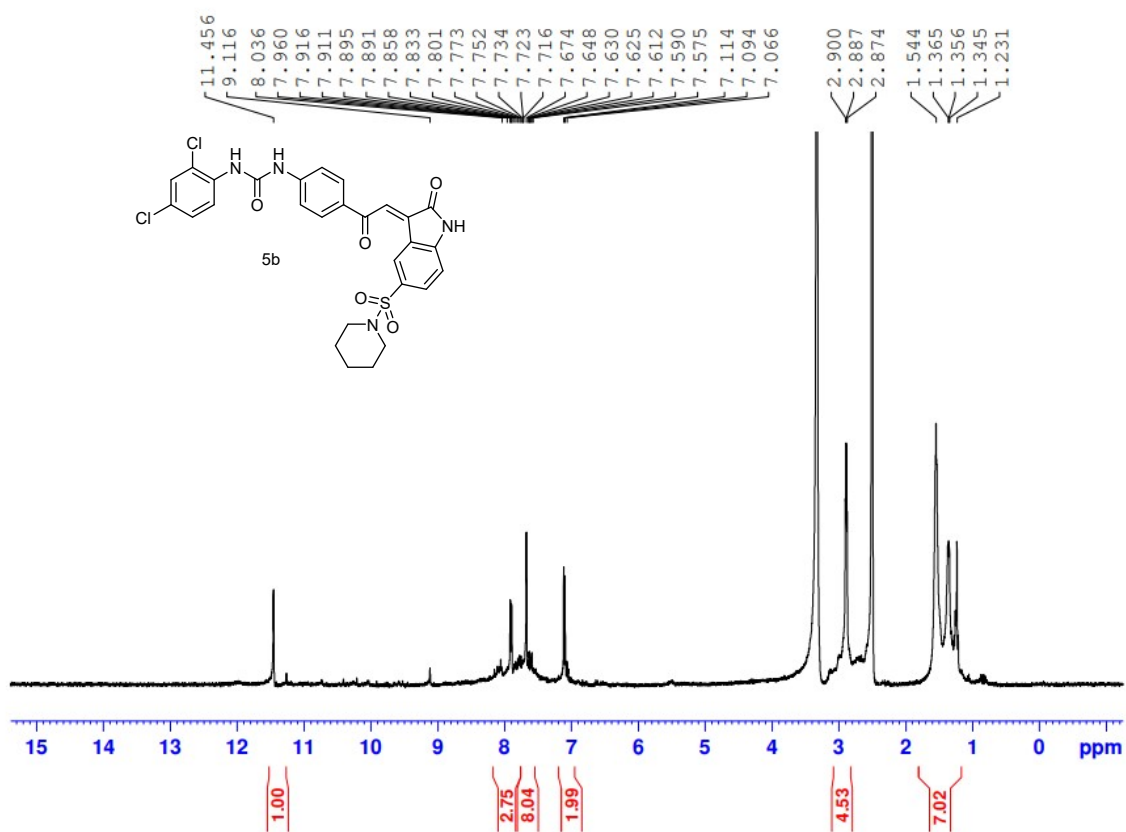
F2 - Acquisition Parameters
Date_ 20220114
Time 4.11
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 4000
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3611488 sec
RG 201.61
DM 20.800 usec
DE 6.50 usec
TE 298.2 K
DQ.00000000 1 sec
DO.03000000 11 sec
TD1 0

----- CHANNEL f1 -----
SFO100.6228293 1 MHz
NUC13 13C
P10.00 1 usec
PLM50.00000000 1 W

----- CHANNEL f2 -----
SFO400.1216005 2 MHz
NUC1 1H
CPOPRG12 waltz16
PCPD90.00 2 usec
PLM10.39999962 2 W
PLM0.28888000 12 W
PLM0.23400000 13 W

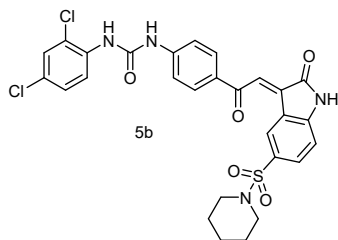
F2 - Processing parameters
SI 32768
SF 100.6128096 MHz
WDW 0 EM
GB 0 1.00 Hz
LB 0 1.40

D-mona-ISpl-H

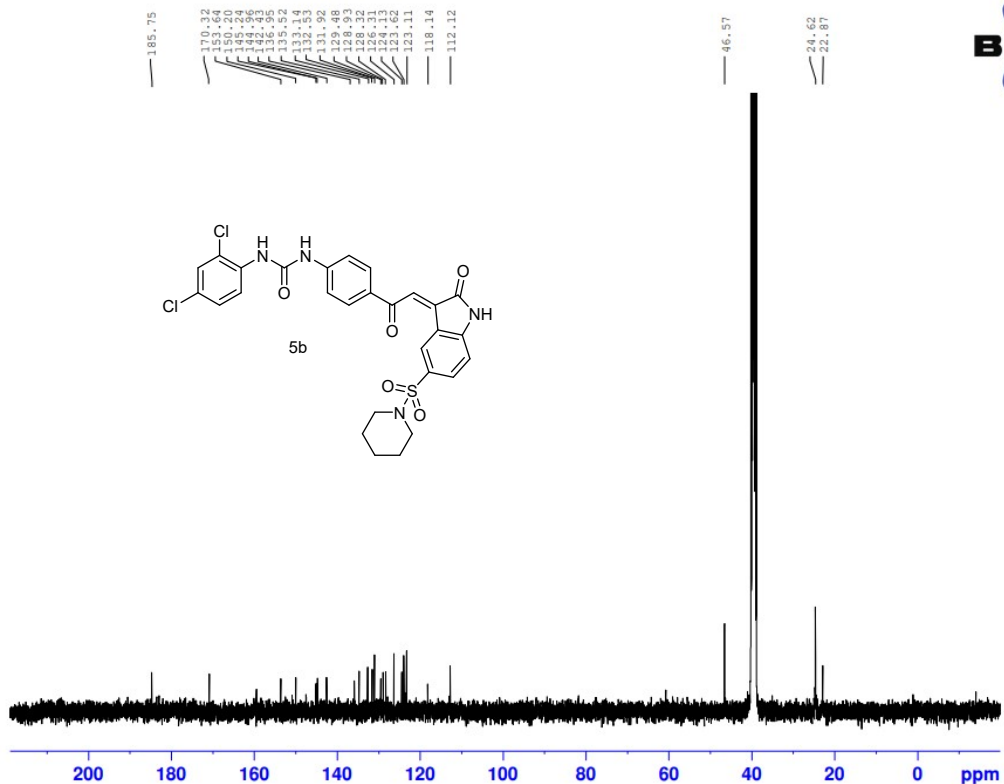


D-mona-ISP-c13

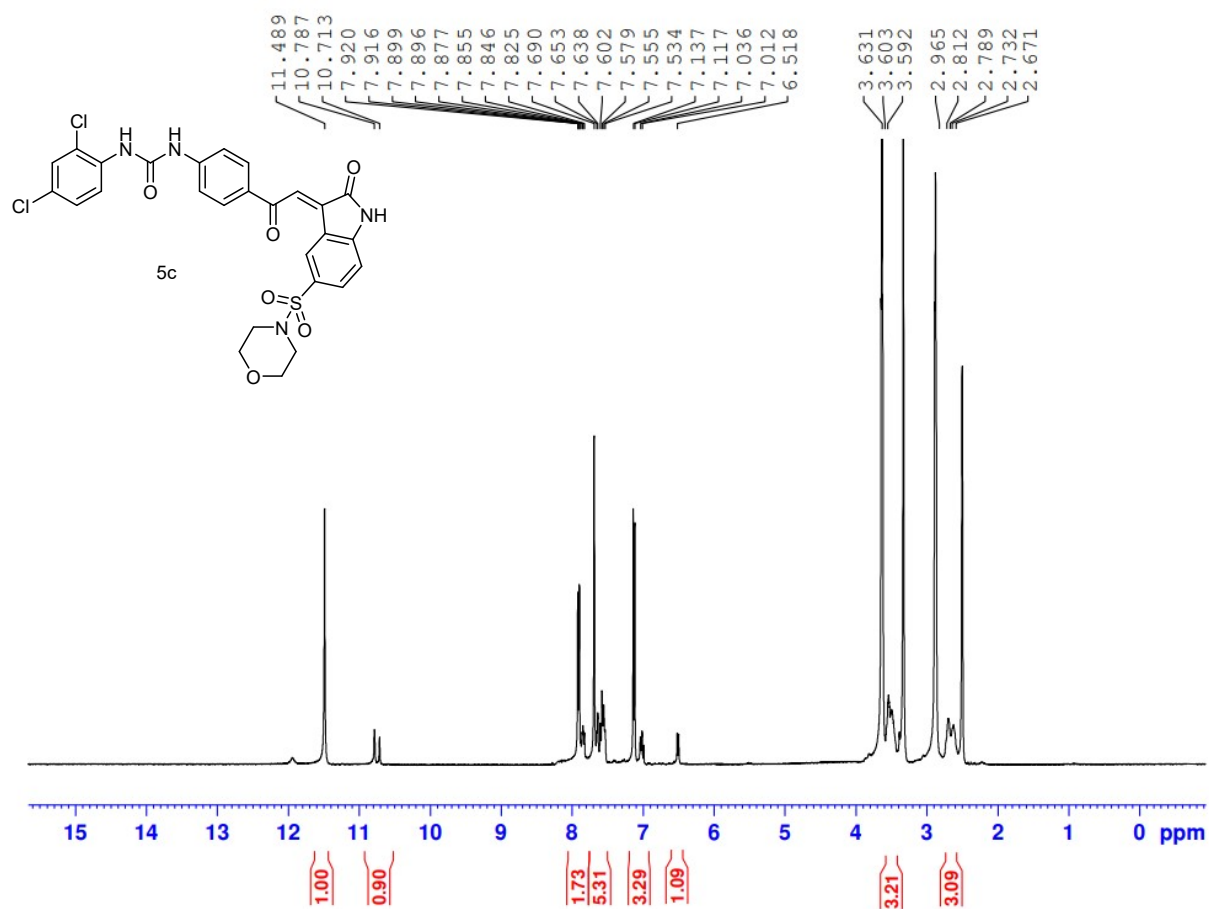
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21.40
21.00
20.60
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19.80
19.40
19.00
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17.40
17.00
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16.20
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15.40
15.00
14.60
14.20
13.80
13.40
13.00
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0.00



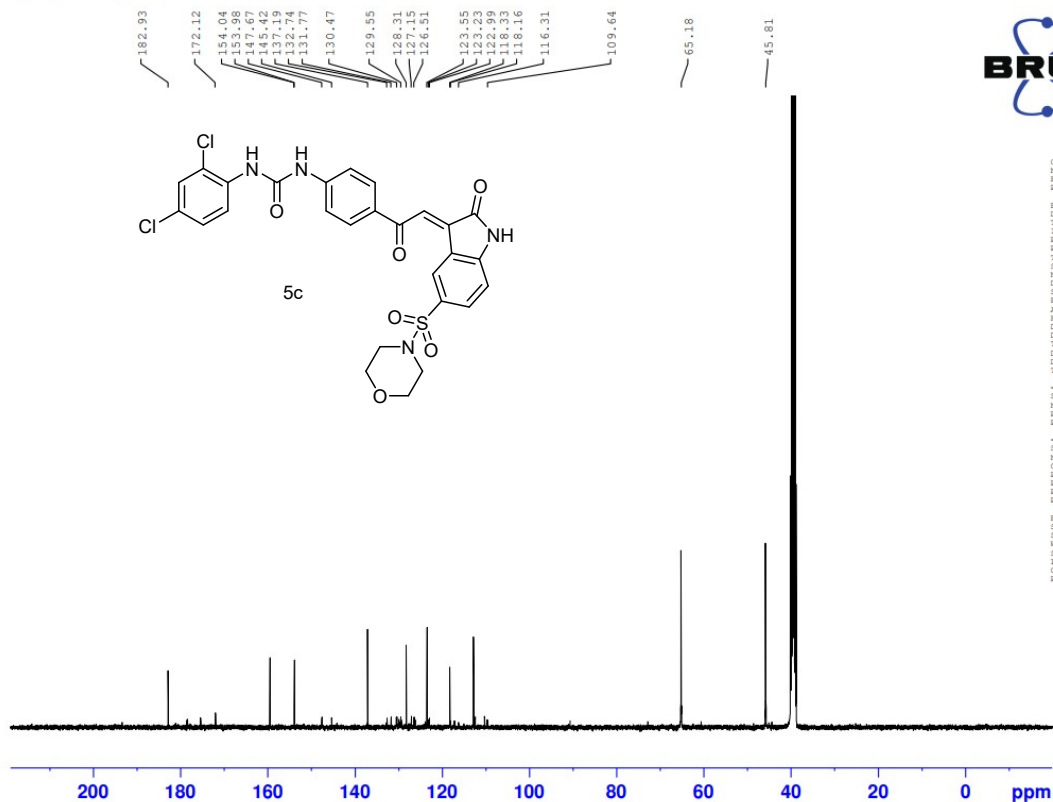
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EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220307
Time 18.48
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMF0
RG 3200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 201.61
SW 20.800 usec
DE 6.50 usec
TE 298.1 K
DZ 0.0000000
DO 0.0300000
TD1 0
----- CHANNEL f1 -----
SFO100.6228293 1 MHz
NUC13 1C
P15.00 1 usec
PLM50.0000000 1 W
----- CHANNEL f2 -----
SFO400.1316005 2 MHz
NUC1 2H
CPDPRG12 waltz16
PCPDPRG1 2 usec
PLM10.39999962 2 W
PLM0.38889000 12 W
PLM0.23400000 13 W
F2 - Processing parameters
SI 32768
SF 100.6128165 MHz
WDW 0 RM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



D-mona-ISM1-H



D-mona-ISM-c13



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Current Data Parameters
NAME      D-mona-ISM-c13
EXPNO     10
PROCNO    1

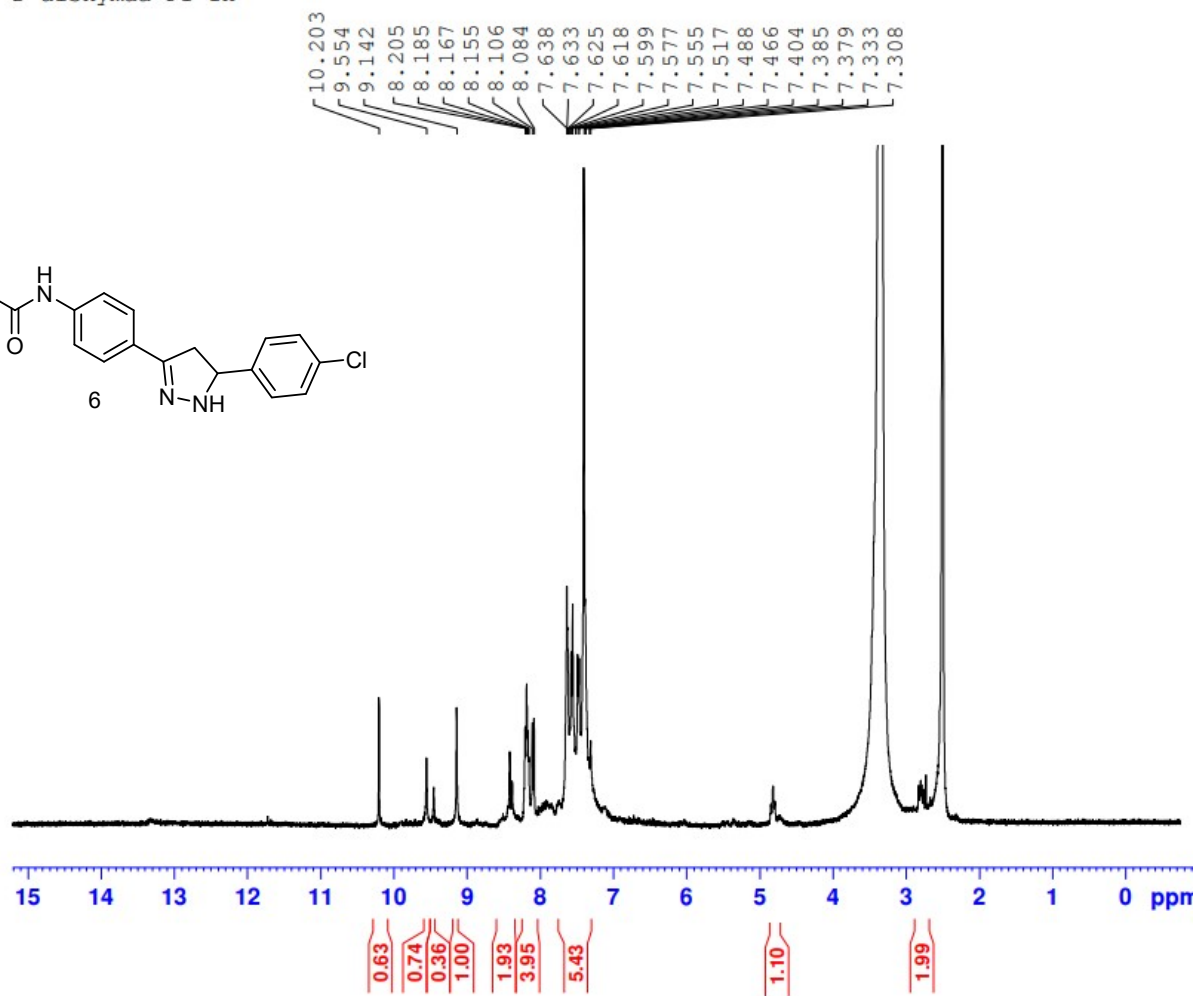
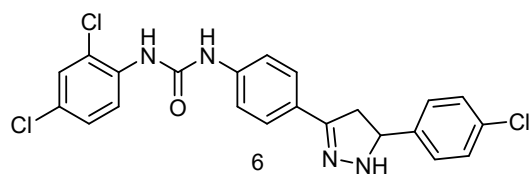
F2 - Acquisition Parameters
Date_     20220307
Time      15:53
INSTRUM   spect
PROBHD    5 mm PABBO BB/
PULPROG   zgpg30
TD         65536
SOLVENT   DMSO
RG         2000
DS         4
SHE       24038.461 Hz
FIDRES    0.364798 Hz
AQ         1.3631488 sec
RG         201.61
DN         20.800 usec
DE         6.50 usec
TE         298.1 K
DQ.00000000    1 sec
DQ.00000000    11 sec
TD1         0

===== CHANNEL f1 =====
SFO100.6228293    1 MHz
NUC13             13C
PUS.00            1 usec
PLW50.00000000    1 W

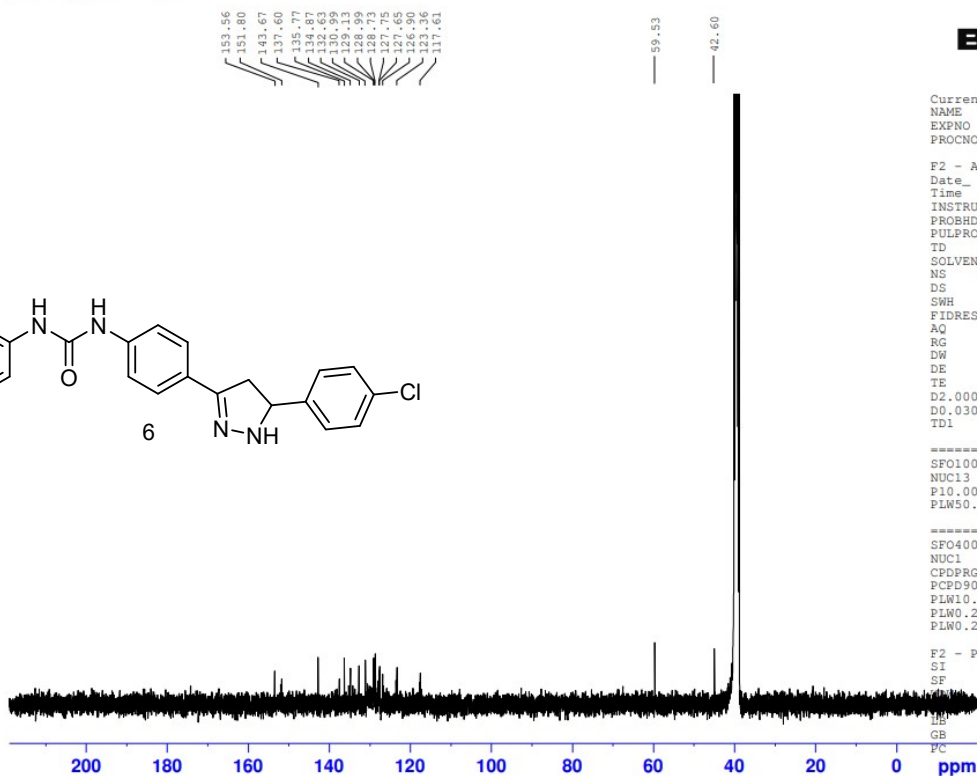
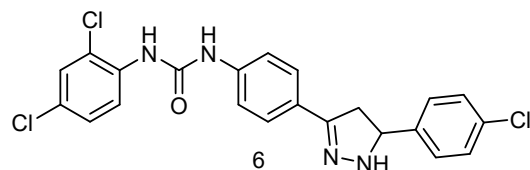
===== CHANNEL f2 =====
SFO400.1316005    2 MHz
NUC1             13C
PCPD90.00        wait10
PLW0.09999962    2 W
PLW0.23889000    12 W
PLW0.23400000    13 W

F2 - Processing parameters
SI             32768
SF            100.6128093 MHz
WDW           EM
SSB           0
GB           0
PC            1.40
  
```

D-alshymaa-F1-1H



D-alshymaa-F-1c13



Current Data Parameters
NAME D-alshymaa-F-1c13
EXPNO 1
PROCNO 1

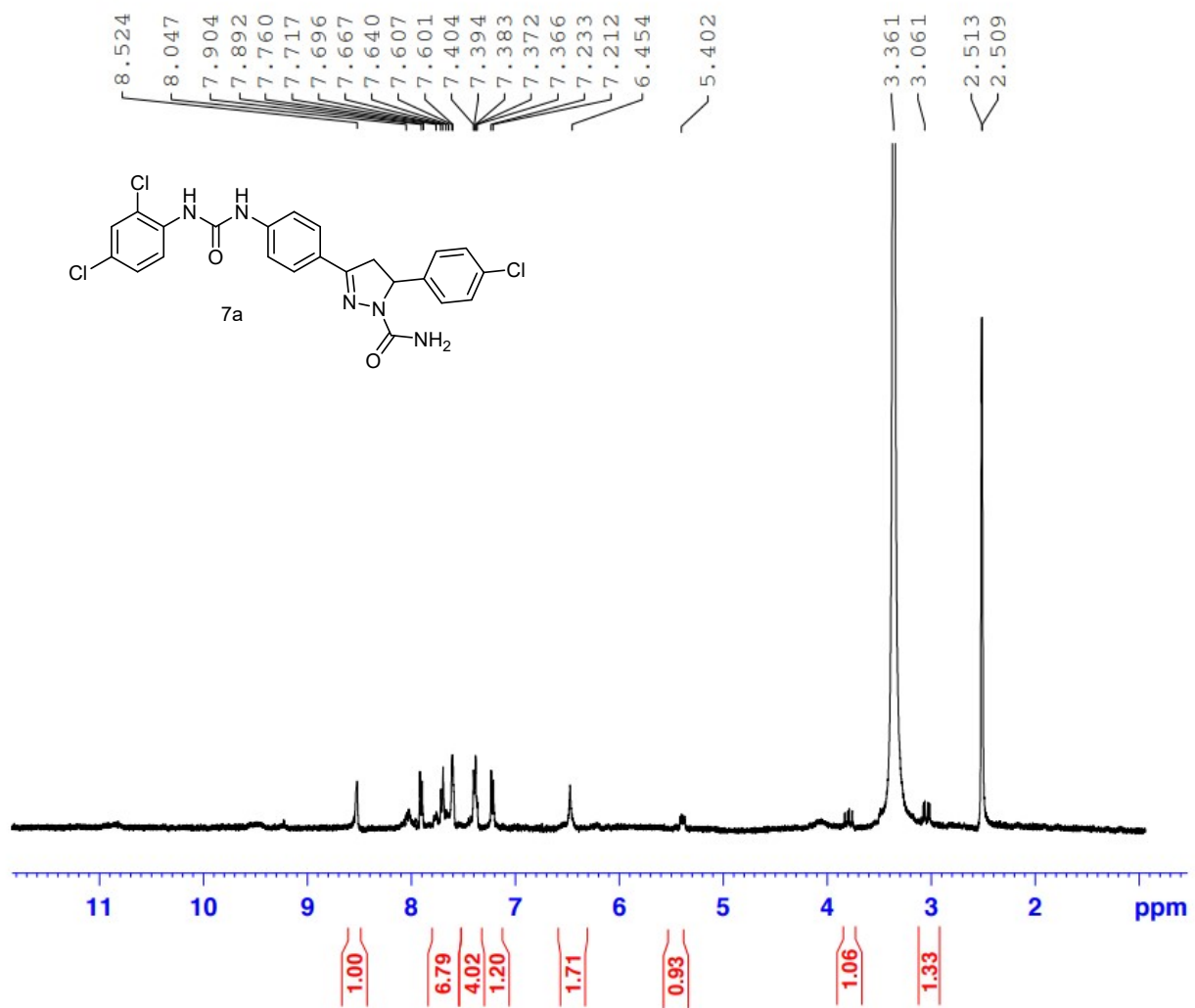
F2 - Acquisition Parameters
Date_ 20210411
Time 21.22
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 3000
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 201.61
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
D2.00000000 1 sec
D0.03000000 11 sec
TD1 0

===== CHANNEL f1 =====
SFO100.6228293 1 MHz
NUC13 1C
P10.00 1 usec
PLW50.00000000 1 W

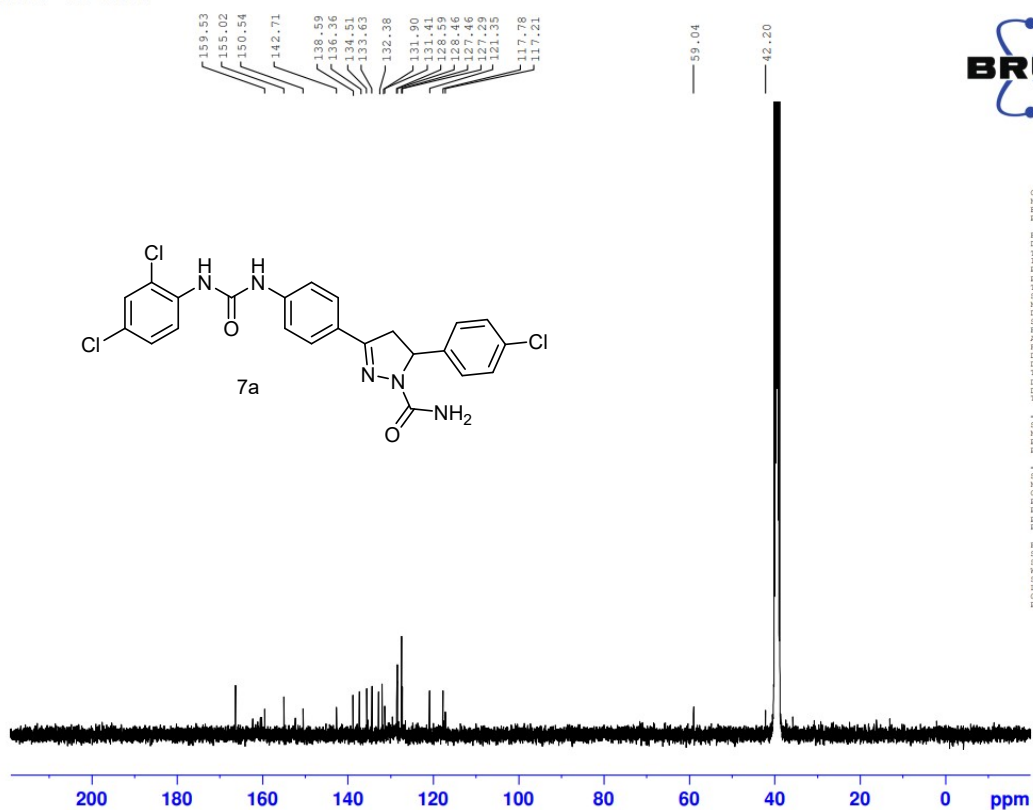
===== CHANNEL f2 =====
SFO400.1316005 2 MHz
NUC1 2H
CPDPRG2 waltz16
PCPD90.00 2 usec
PLW10.39999962 2 W
PLW0.28889000 12 W
PLW0.23400000 13 W

F2 - Processing parameters
SI 32768
SF 100.6128113 MHz
EM
GB 0 1.00 Hz
FC 0 1.40

MONA-SS1
PROTON_BSU DMSO {C:\data} abeer 9



D-mona--ss-1c13



```

Current Data Parameters
NAME      D-mona--ss-1c13
EXPNO     11
PROCNO    1

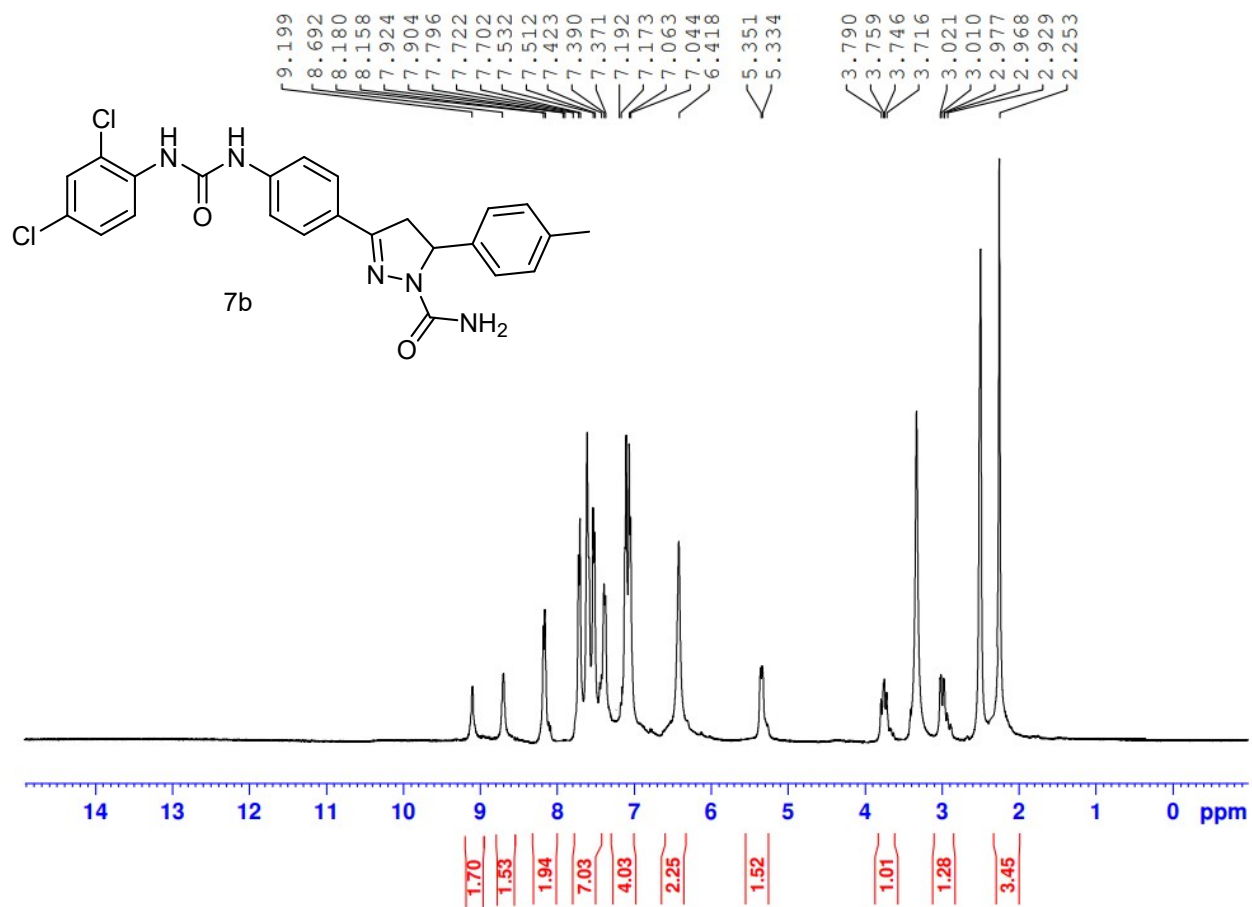
F2 - Acquisition Parameters
Date_     20220429
Time      1.07
INSTRUM   spect
PROBHD    5 mm PABBO BB/
PULPROG   zgpg30
TD        65536
SOLVENT   DMSO
NS         6000
DS         4
SWH        24039.461 Hz
FIDRES     0.364798 Hz
AQ         1.3631488 sec
RG         201.61
DW         20.800 usec
DE         6.50 usec
TE         298.2 K
DQ.00000000 1 sec
DQ.03000000 11 sec
TD1        0

===== CHANNEL f1 =====
SFO100.6228293 1 MHz
NUC13        13C
P10.00       1 usec
PLW50.00000000 1 W

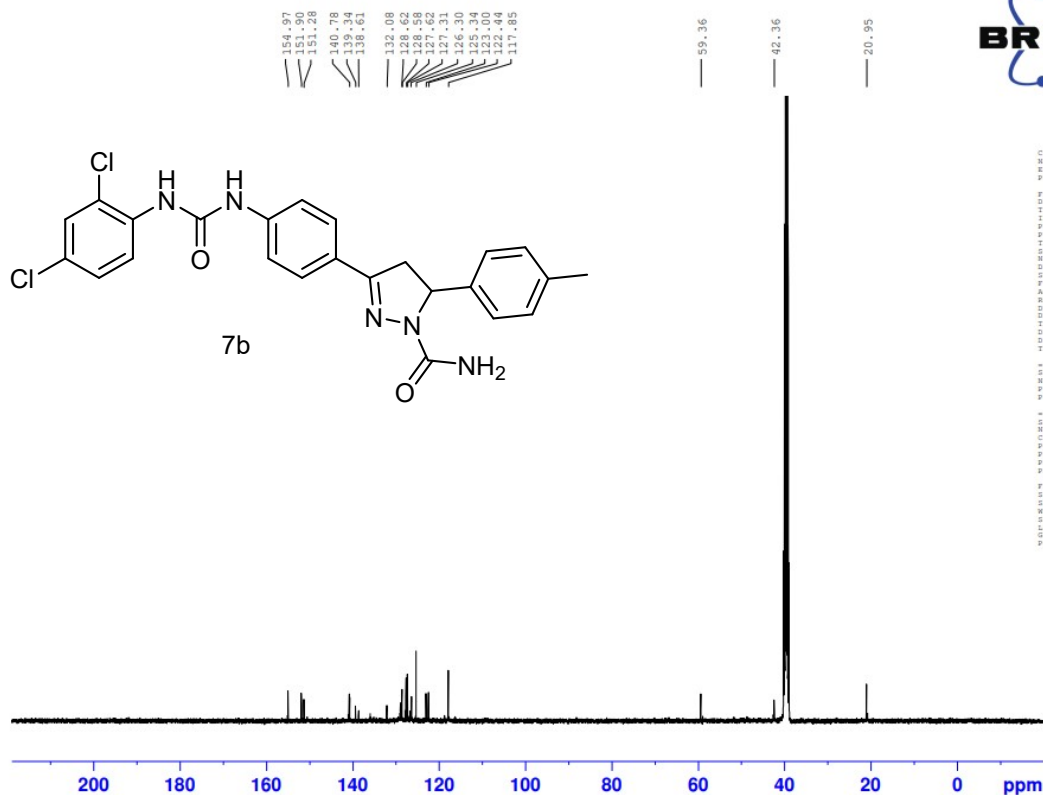
===== CHANNEL f2 =====
SFO400.1314005 2 MHz
NUC1        13C
PCPD06[2]   wait10
PCPD00.00   2 usec
PLW10.39999962 2 W
PLW0.2889000 12 W
PLW0.23400000 13 W

F2 - Processing parameters
SI          32768
SF          100.6128157 MHz
WDW         EM
SSB         0
GB          0
PC          1.40
  
```


D-mona-ss1-1H



D-mona-ss-1c13



```
Current Data Parameters
NAME      D-mona-ss-1c13
EXPNO     1
PROCNO    1

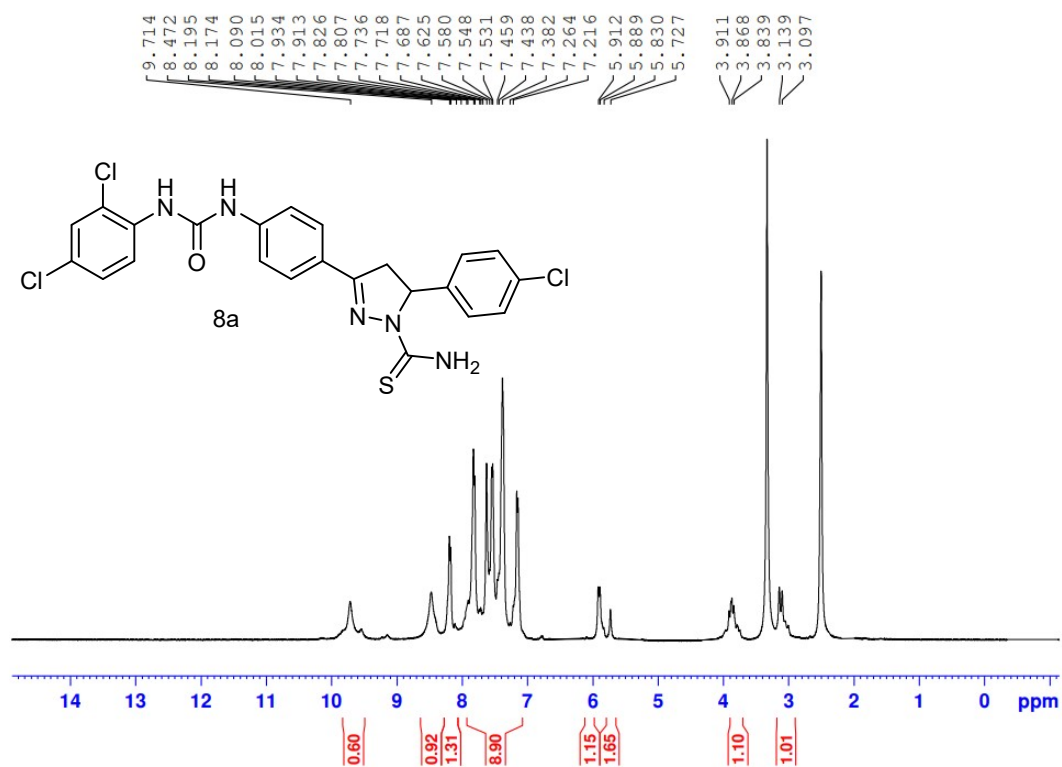
F2 - Acquisition Parameters
Date_     20220106
Time      23:06
INSTRUM   spect
PROBHD    5 mm PABBO BB/
PULPROG   zgpg30
TD        65536
SOLVENT   DMSO
NS         4
DS         4
SWH        24038.461 Hz
FIDRES     0.366798 Hz
AQ         1.3631648 sec
RG         201.61
DW         20.800 nsec
DE         6.50 nsec
TE         300.2 K
DQ         0.0000000
SFO         100.628159 MHz
TD1        0

===== CHANNEL f1 =====
NUC1       13C
P1         12.00 nsec
PL1        0.0000000
PL12       0.0000000

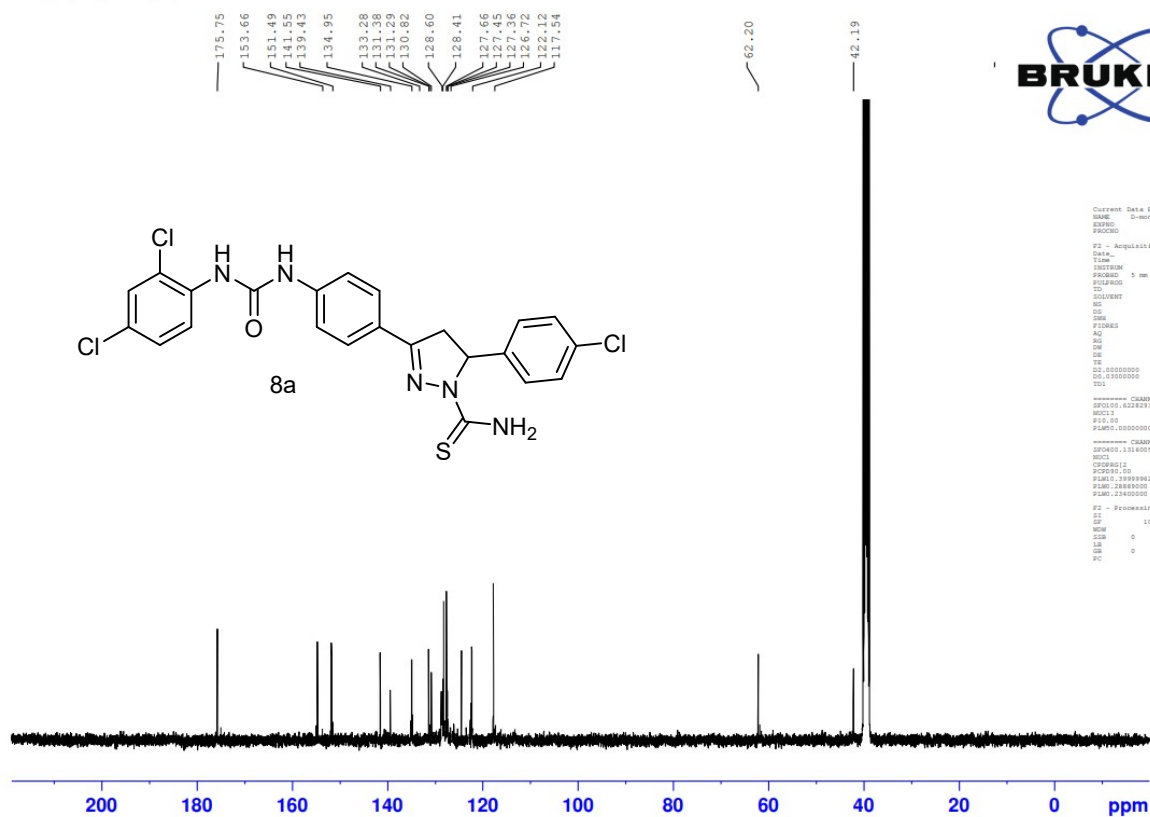
===== CHANNEL f2 =====
SFO2       400.146005 MHz
NUC2       1H
PCPD2      2.00 nsec
PL2        0.0000000
PL12       0.0000000
PL13       0.0000000
PL14       0.0000000

F2 - Processing parameters
SI         32768
SF         100.628159 MHz
WDW        EM
SSB         0
LB          1.00 Hz
GB          0
PC          1.40
```

D-mona-sth1-1H



D-mona-sth-1c13



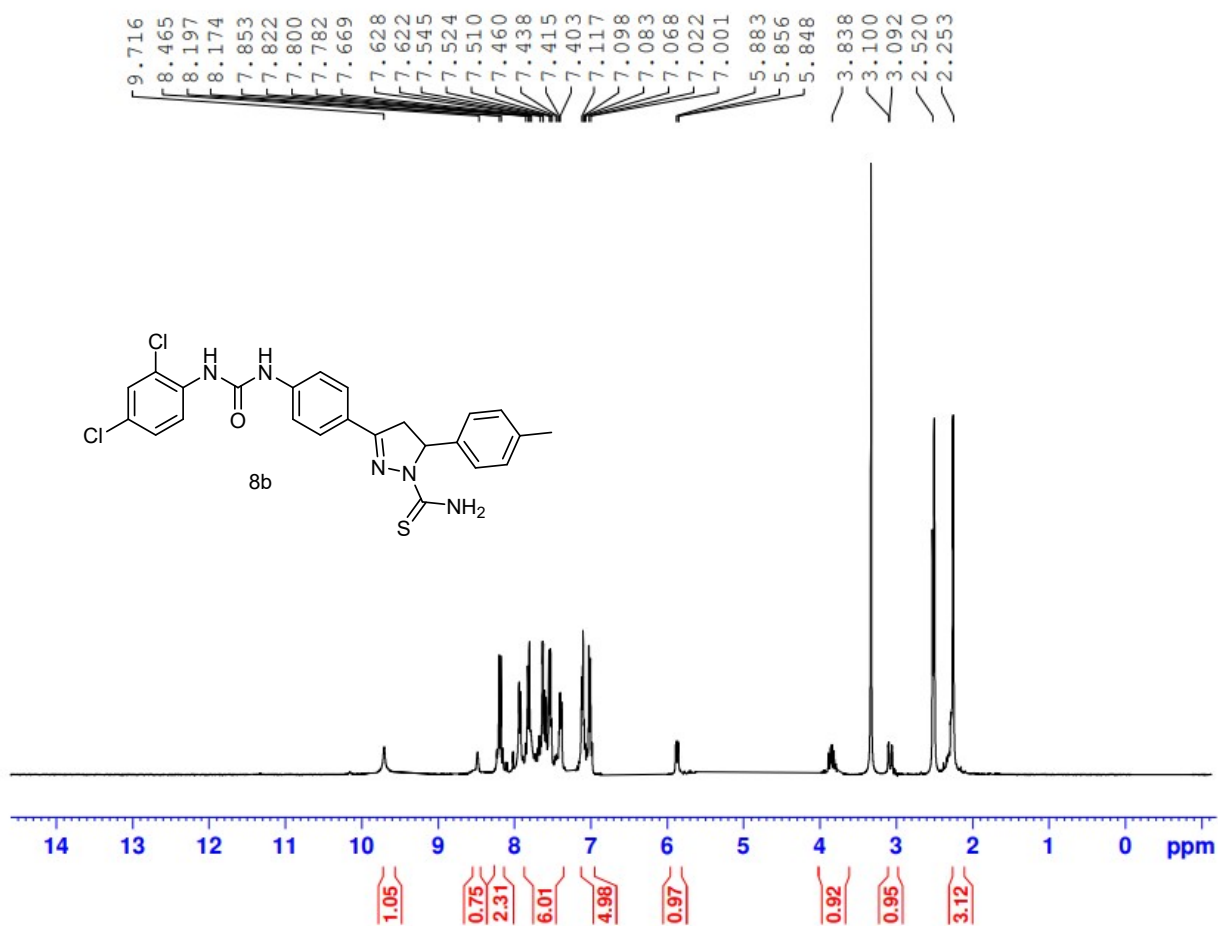
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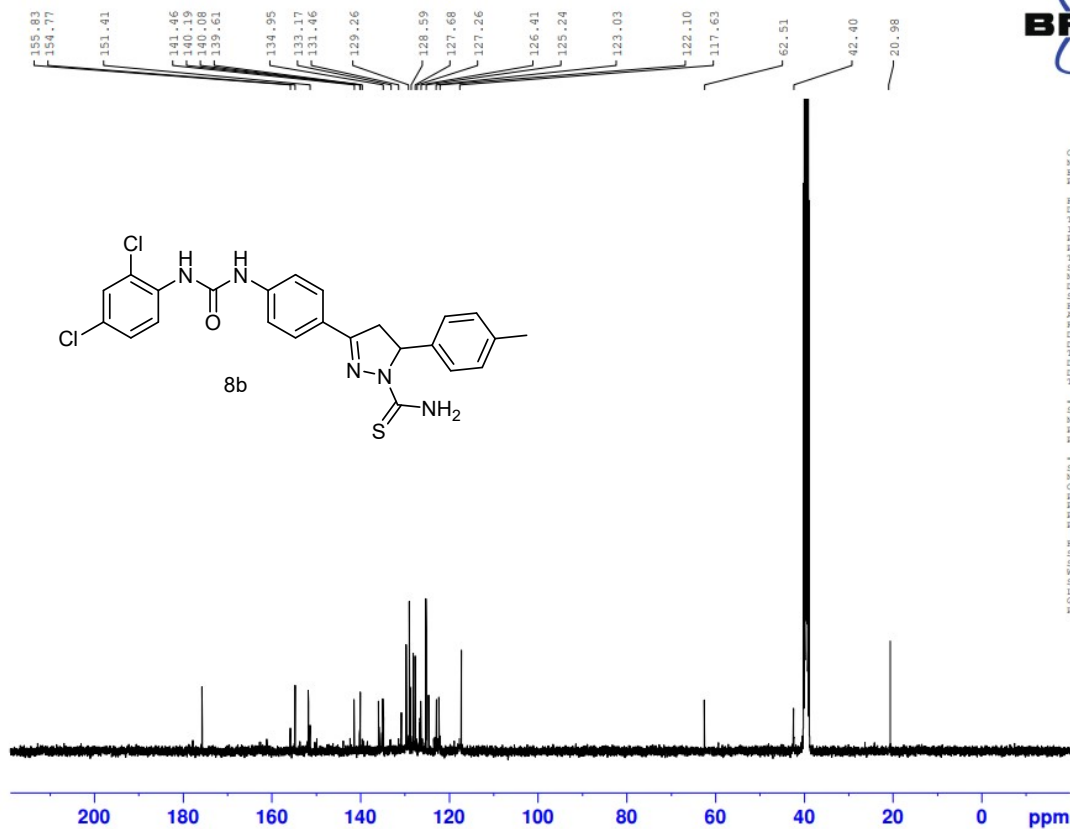
Current Data Parameters
NAME: D-mona-sth-1c13
EXPNO: 10
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20220114
Time: 0:13
INSTRUM: spect
PROBHD: 5 mm QNP1H
PULPROG: zgpg30
TD: 65536
SOLVENT: dmso
RG: 680
RG2: 4000
DS: 4
SWH: 24036.461 Hz
FIDRES: 0.38476 Hz
AQ: 1.3031489 sec
RG: 521.61
AQ2: 20.800 sec
DE: 6.30 umol
TE: 298.2 K
DQ: 0.0000000
DE: 0.0000000
DELTA: 0
===== CHANNEL F1 =====
NUC1: 13C
PULPROG: zgpg30
PL1: 1.0000000
PL12: 0.0000000
===== CHANNEL F2 =====
SFO400: 101.6005
NUC2: 13C
CPDPRG2: waltz16
NUC2F2: 101.6005
PL12: 0.0000000
PL122: 0.0000000
PL123: 0.0000000
PL124: 0.0000000
===== CHANNEL F3 =====
SFO400: 101.6005
NUC3: 13C
CPDPRG3: waltz16
NUC3F3: 101.6005
PL13: 0.0000000
PL132: 0.0000000
PL133: 0.0000000
PL134: 0.0000000
===== CHANNEL F4 =====
SFO400: 101.6005
NUC4: 13C
CPDPRG4: waltz16
NUC4F4: 101.6005
PL14: 0.0000000
PL142: 0.0000000
PL143: 0.0000000
PL144: 0.0000000

F2 - Processing parameters
SI: 32768
SF: 100.613181 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40
  
```

D-mona-sth1-2H





Current Data Parameters
NAME D-mona-sth-2013
EXPNO 11
PROCNO 1

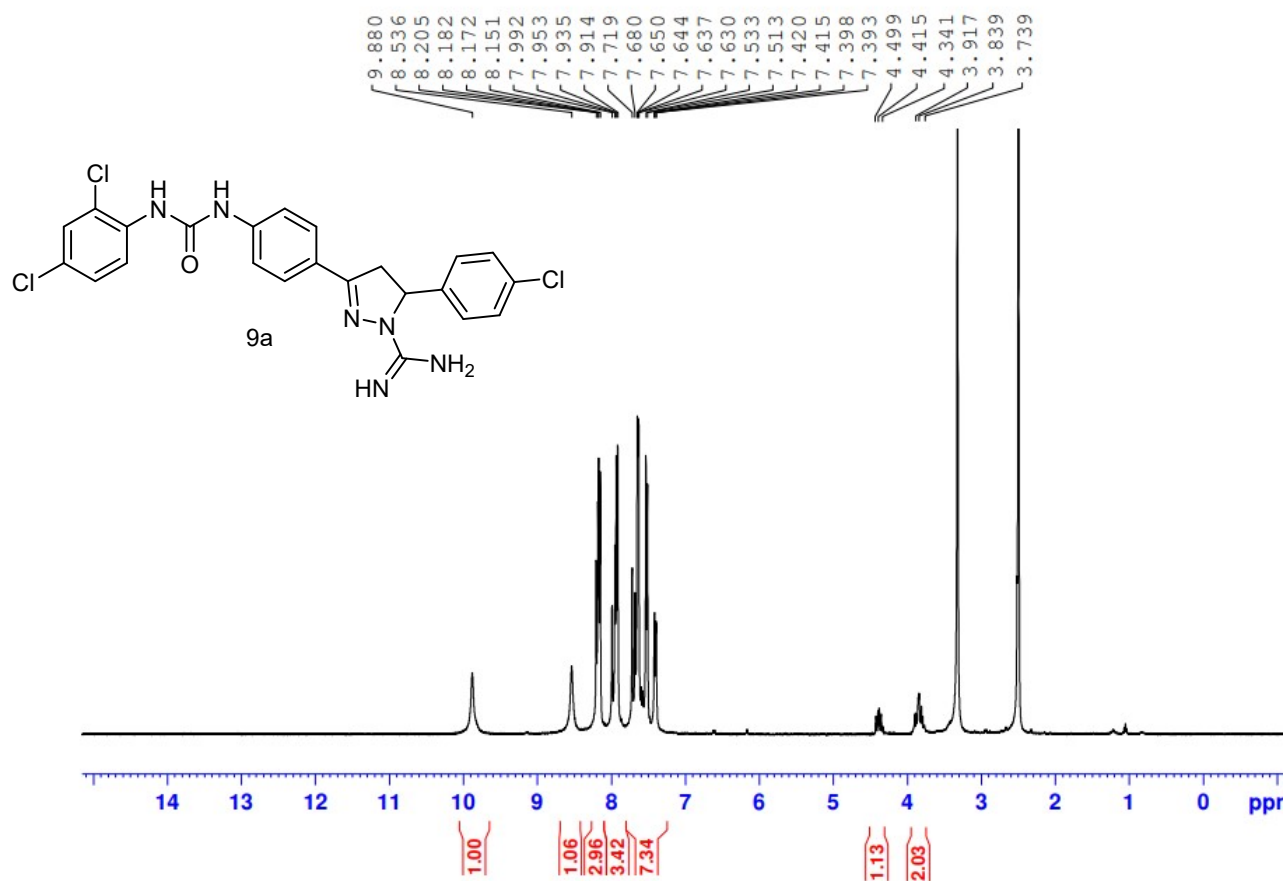
F2 - Acquisition Parameters
Date_ 20220108
Time 21.08
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 4000
DS 4
SWH 24039.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 201.61
SW 20.800 usec
DE 6.50 usec
TE 298.2 K
D2.00000000 1 sec
DQ.03000000 11 sec
TD1 0

===== CHANNEL f1 =====
SFO100.6228293 1 MHz
NUC13 13C
P10.00 1 usec
PLW50.00000000 1 W

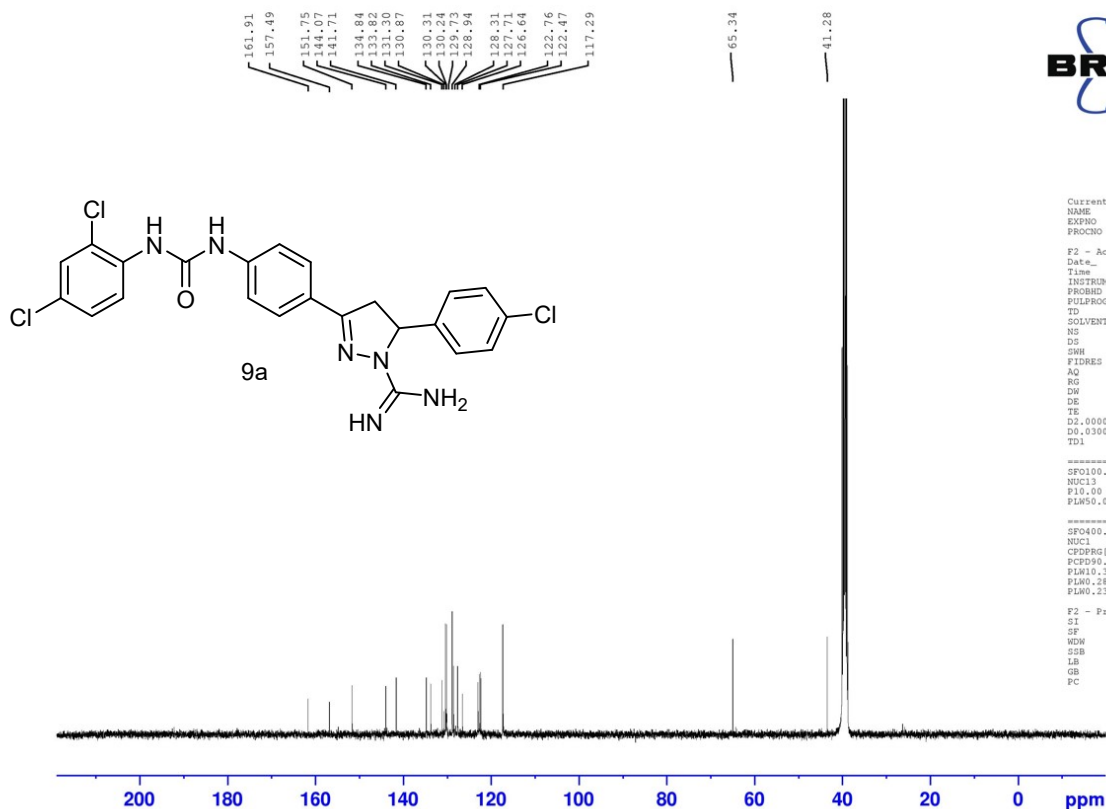
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NUC13 13C
CPDPRG2 waltz16
PCPD99.00 2 usec
PLW10.39999962 2 W
PLW0.28889000 12 W
PLW0.23400000 13 W

F2 - Processing parameters
SI 32768
SF 100.6128168 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

D-mona-G1-1H



D-mona-G-1c13



Current Data Parameters
NAME D-mona-G-1c13
EXPNO 10
PROCNO 1

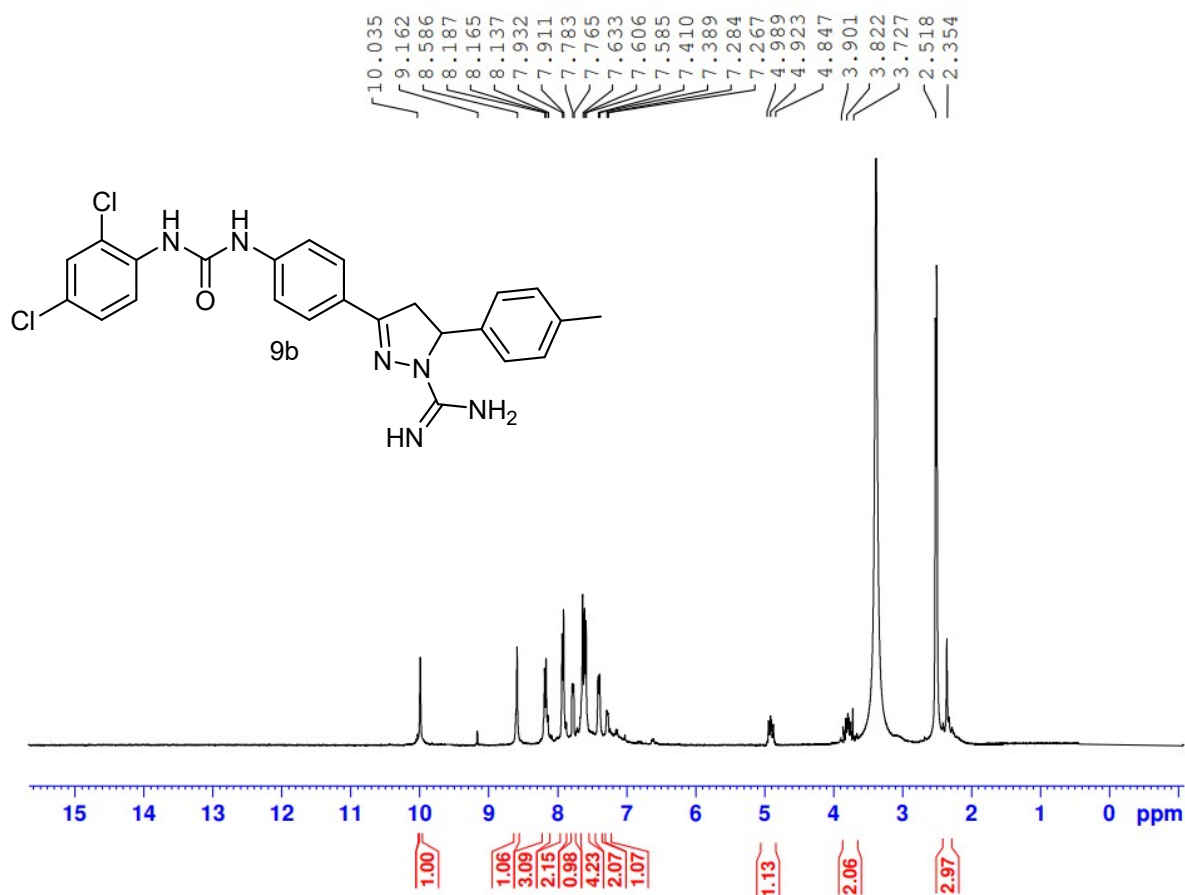
F2 - Acquisition Parameters
Date_ 20220323
Time 6.05
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 3000
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 201.61
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
D0.00000000 1 sec
D0.03000000 11 sec
TD1 0

===== CHANNEL f1 =====
SFO100.6228293 1 MHz
NUC13 13C
P10.00 1 usec
PLW50.00000000 1 W

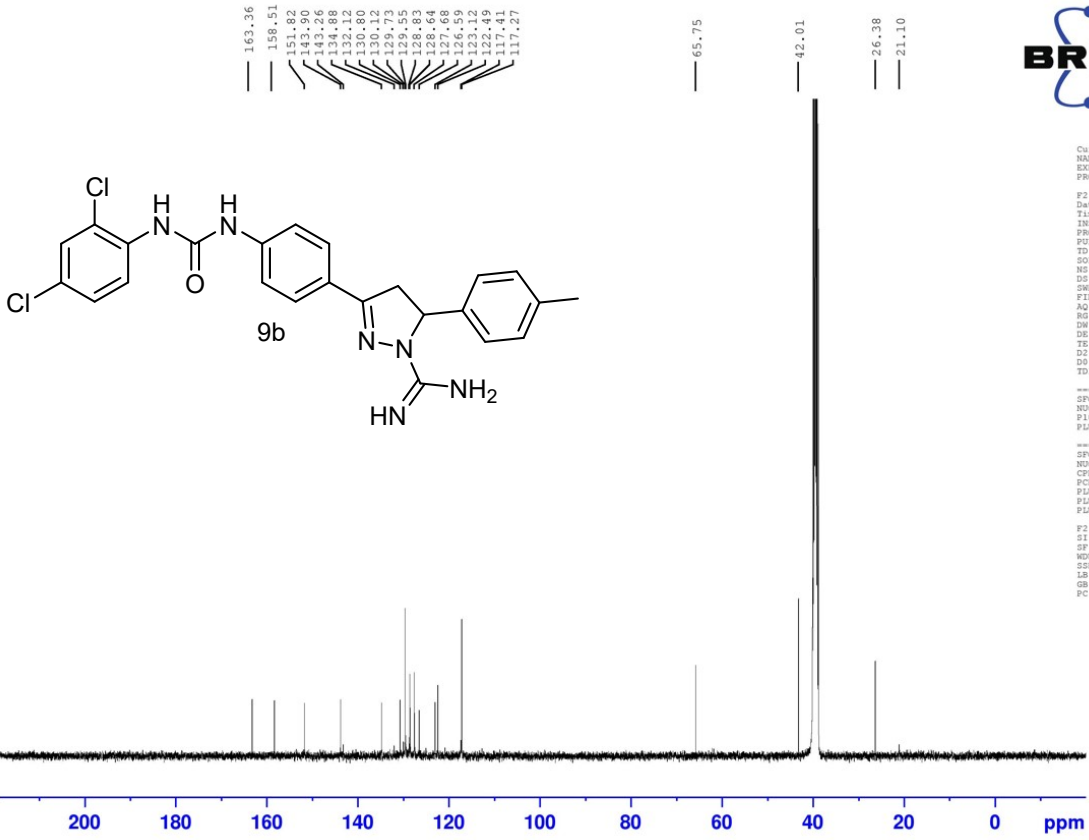
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SFO400.1316005 2 MHz
NUC1 2H
CPDPRG[2] waltz16
PCPD90.00 2 usec
PLW10.39899962 2 W
PLW0.28888000 12 W
PLW0.23400000 13 W

F2 - Processing parameters
SI 32768
SF 100.6128157 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

D-mona-G1-2H



D-mona-G-2c13



Current Data Parameters
NAME D-mona-G-2c13
EXPNO 10
PROCNO 1

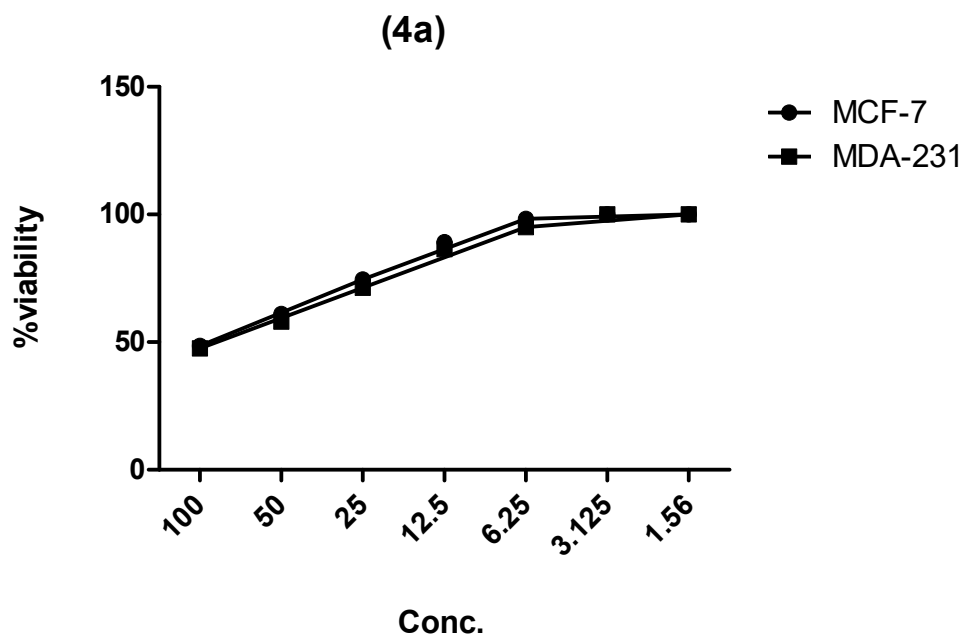
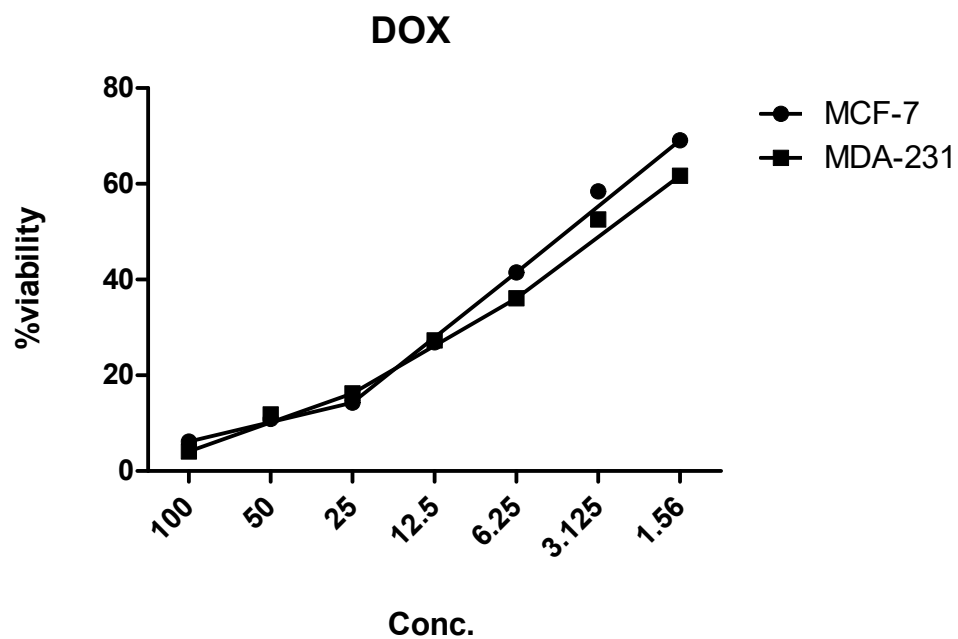
F2 - Acquisition Parameters
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Time 0.47
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PROBHD 5 mm PABBO 1H/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 3000
DS 4
SWH 24036.461 Hz
FIDRES 0.365798 Hz
AQ 1.3631488 sec
RG 201.61
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
DZ 0.0000000 1 sec
DQ 0.0000000 11 sec
TD1 0

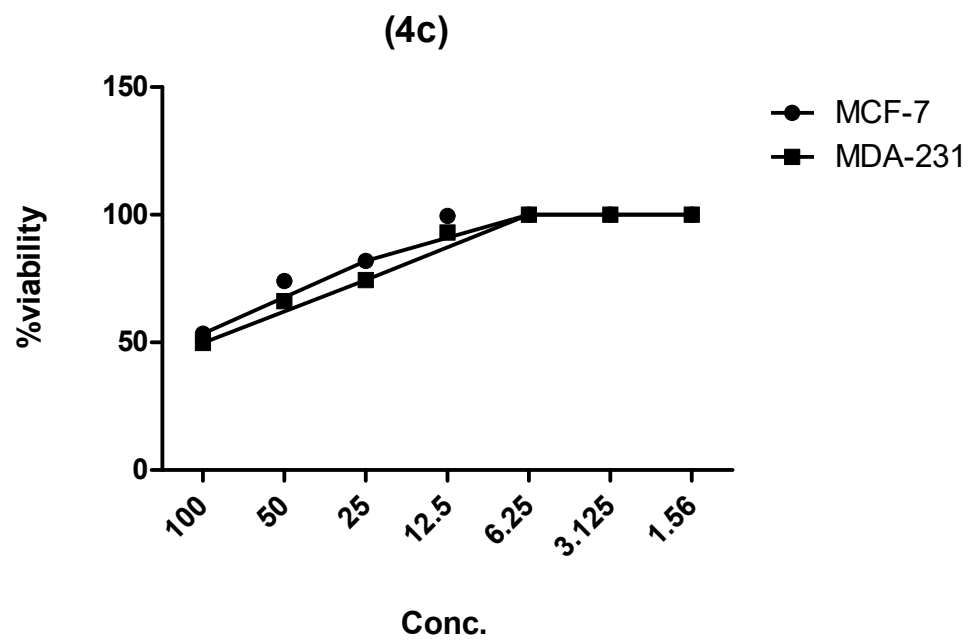
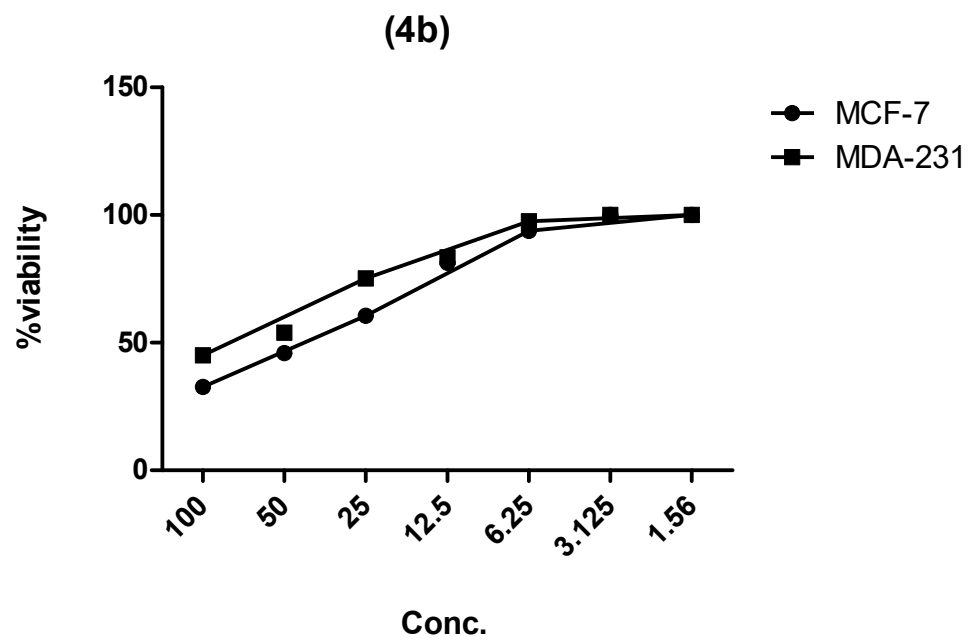
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NUC1 13C
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PL100.0000000 1 W

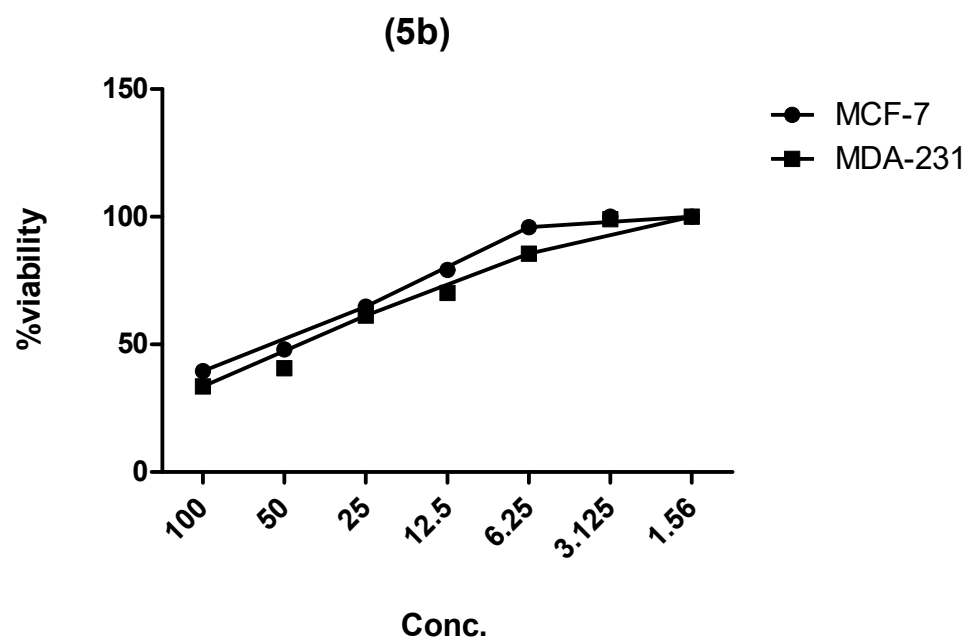
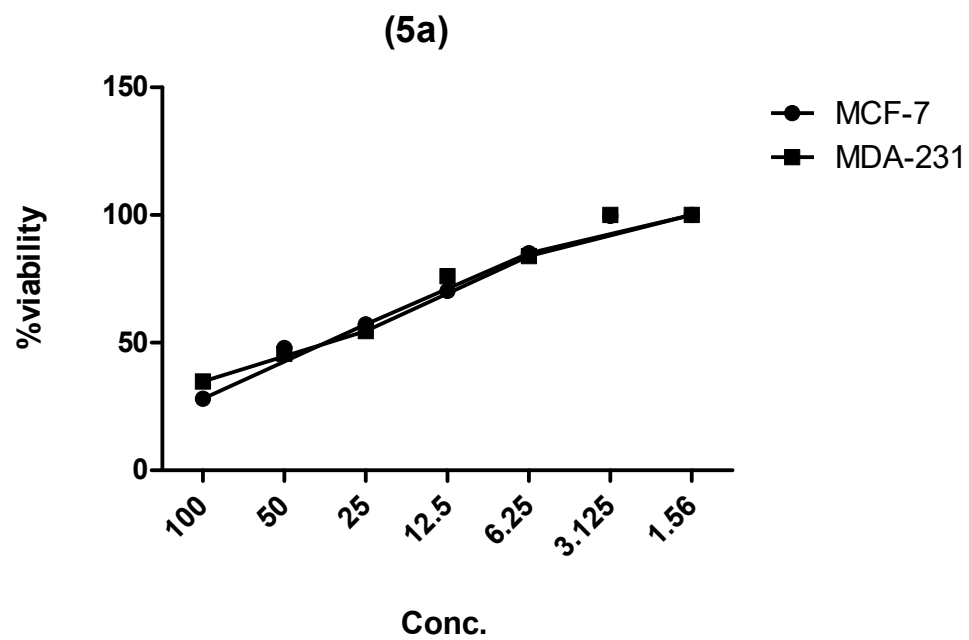
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NUC1 1H
CPCPRG12 waltz16
PCPD90.00 2 usec
PL10.39999942 2 W
PL10.28889000 12 W
PL10.23400000 13 W

F2 - Processing parameters
SI 32768
SF 100.6128147 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

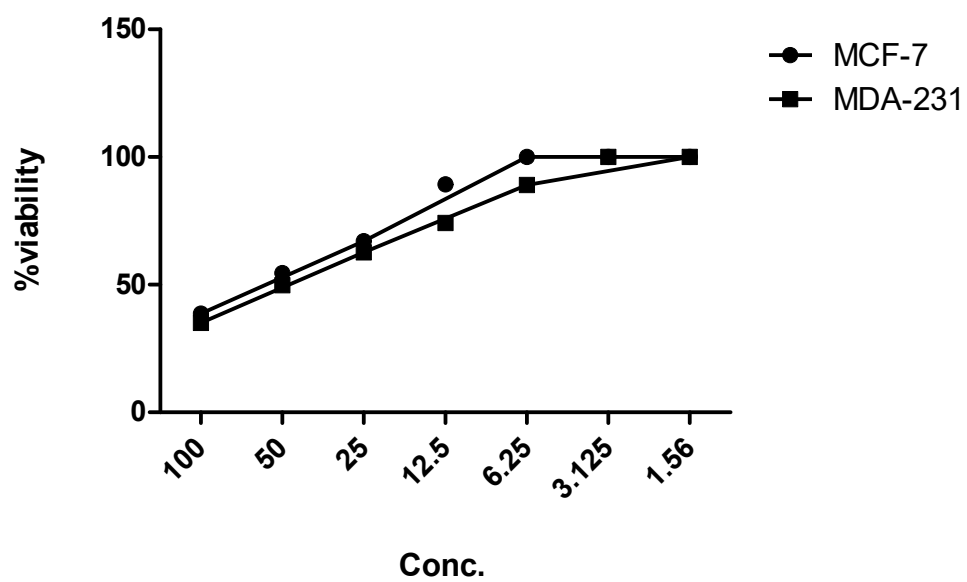
Graphical representation of cytotoxicity of the synthesized compounds against the selected breast cancer cells:



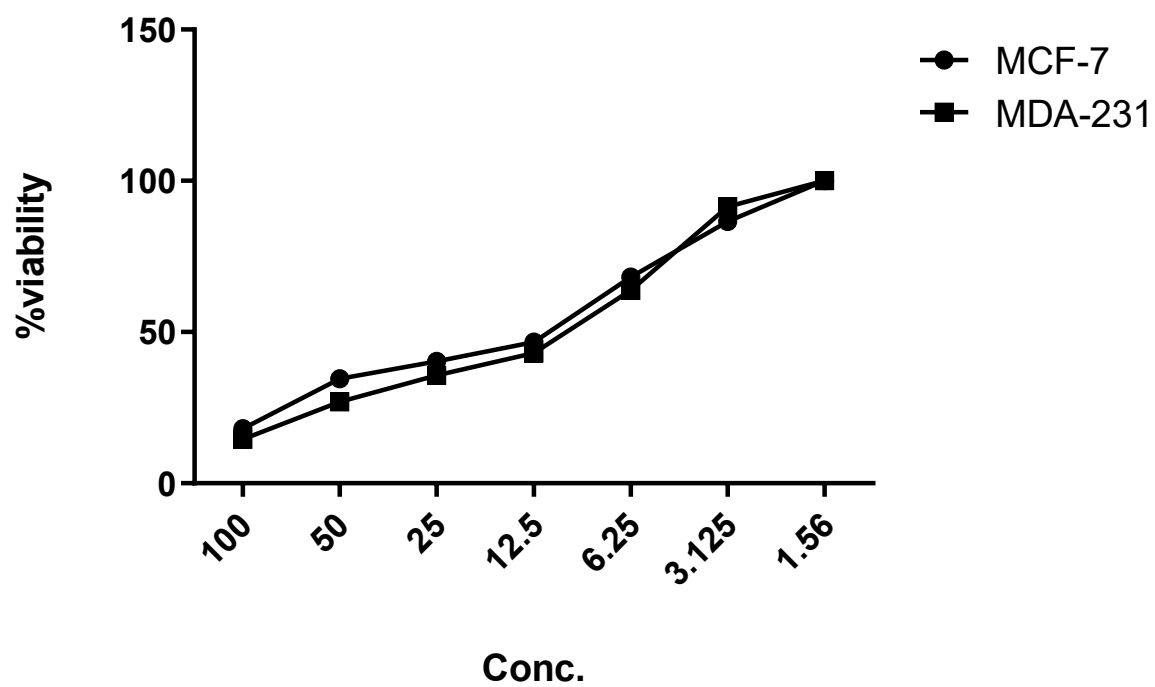




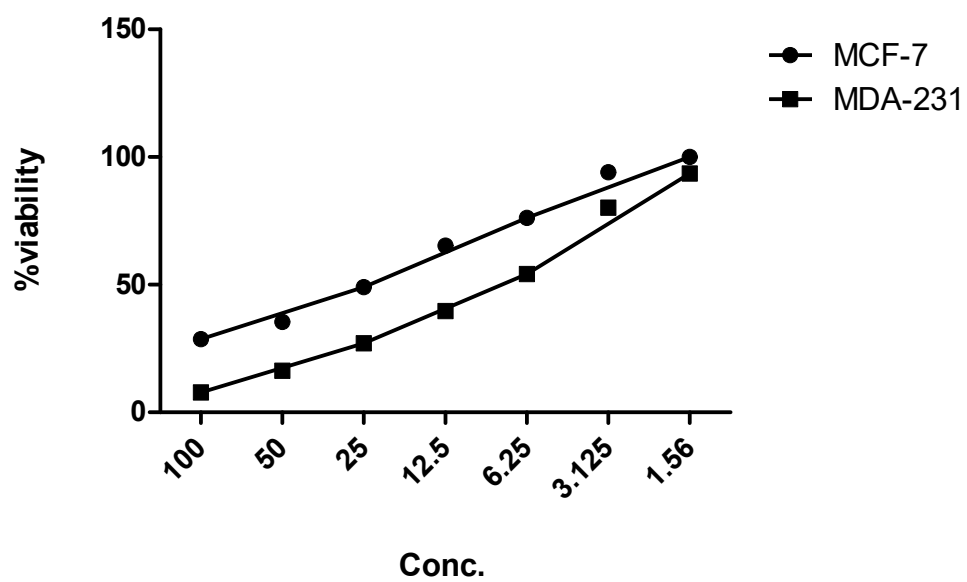
(5c)



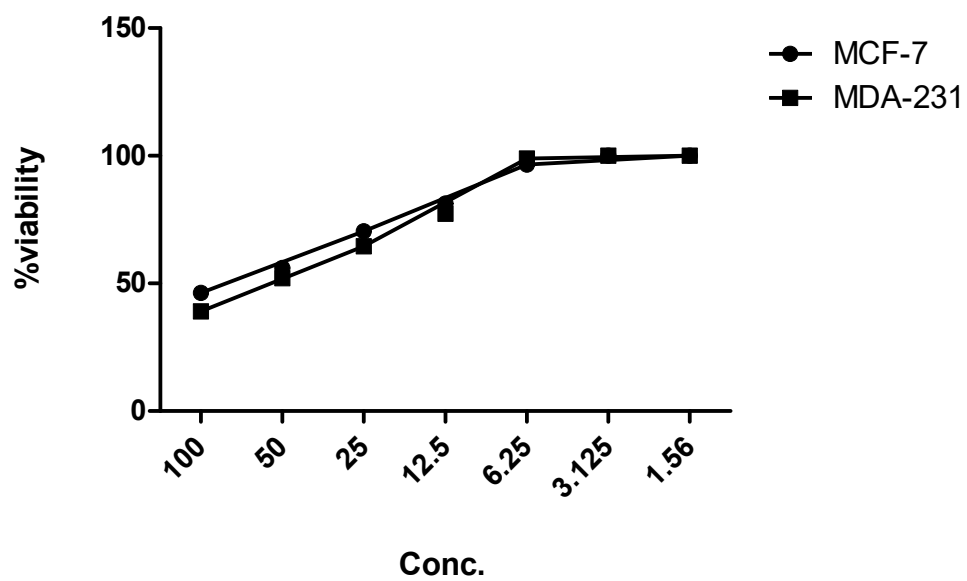
(6)

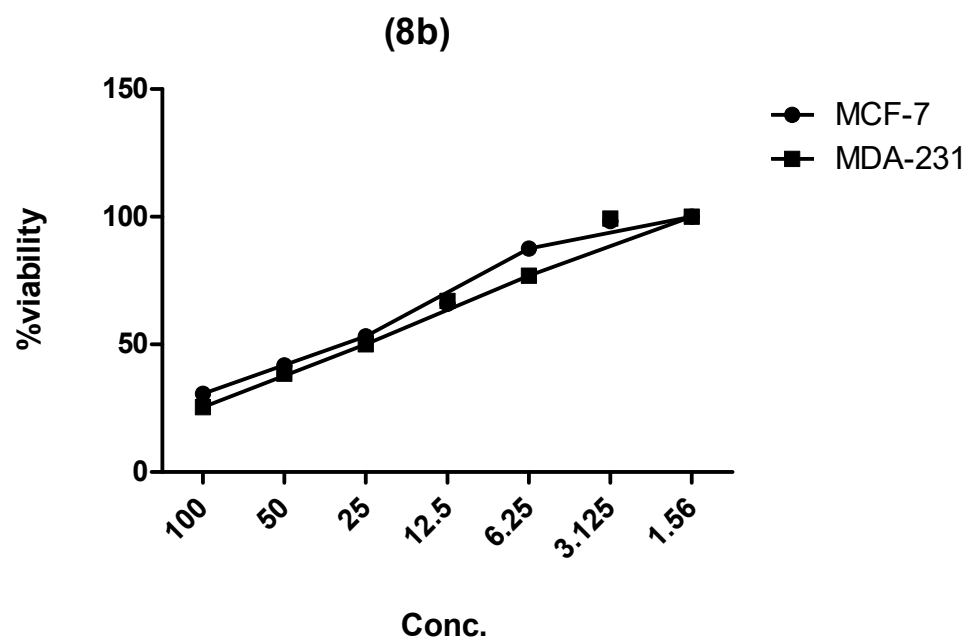
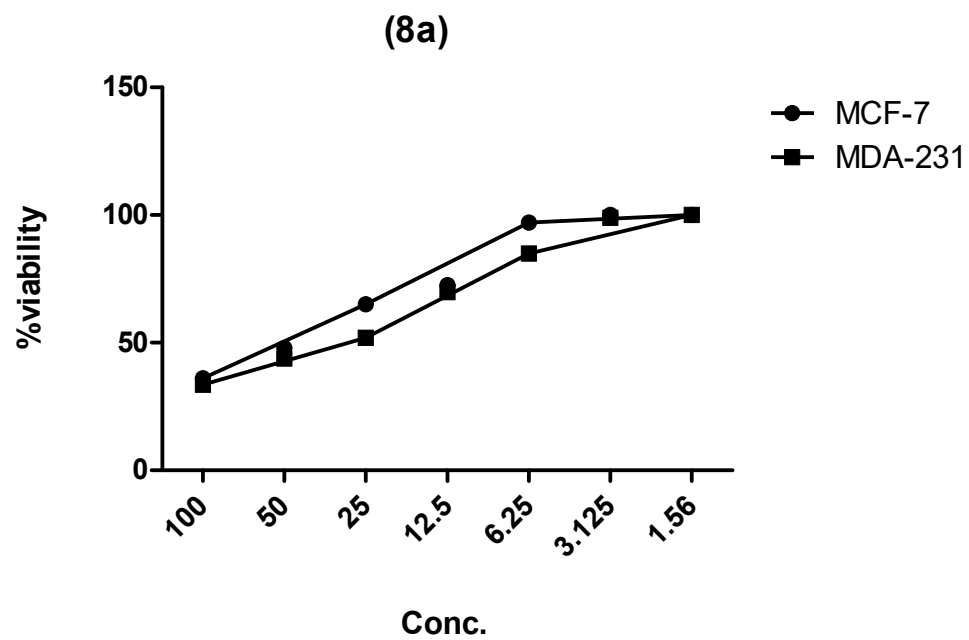


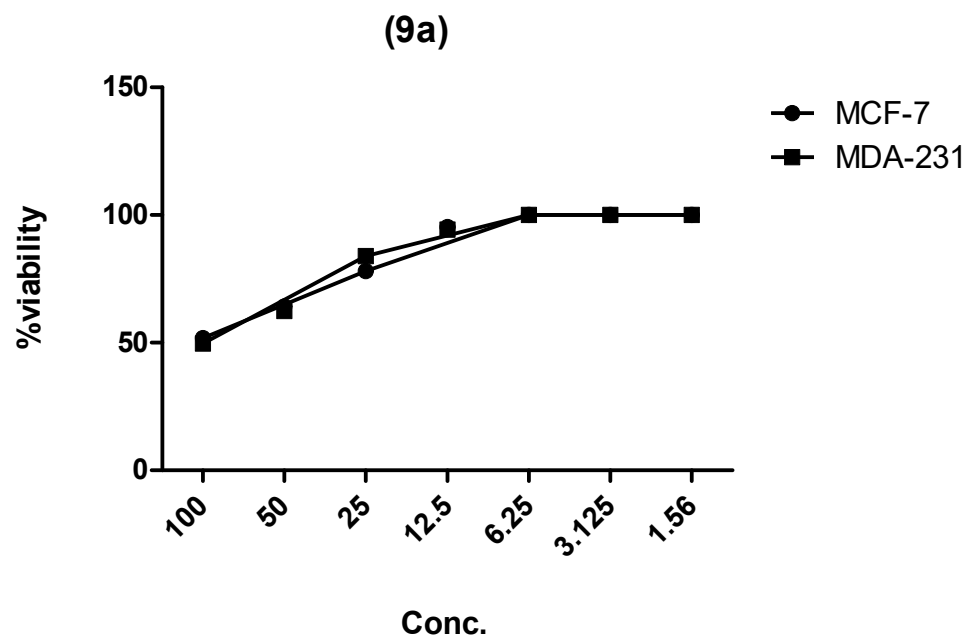
(7a)

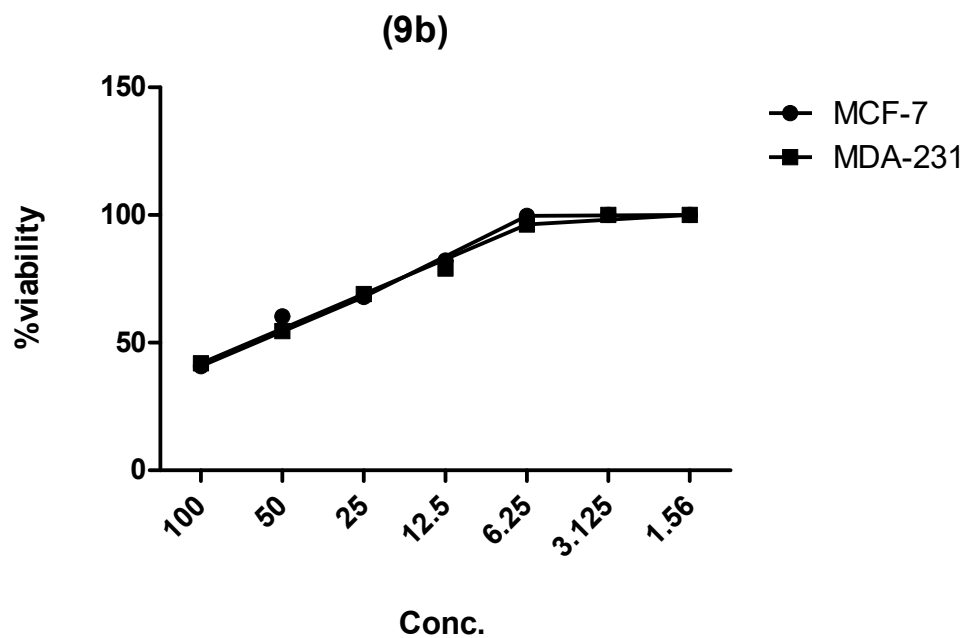


(7b)

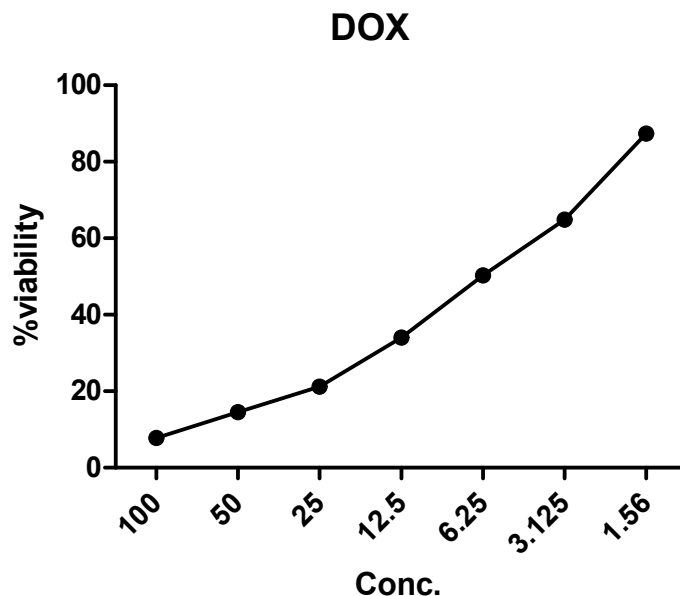






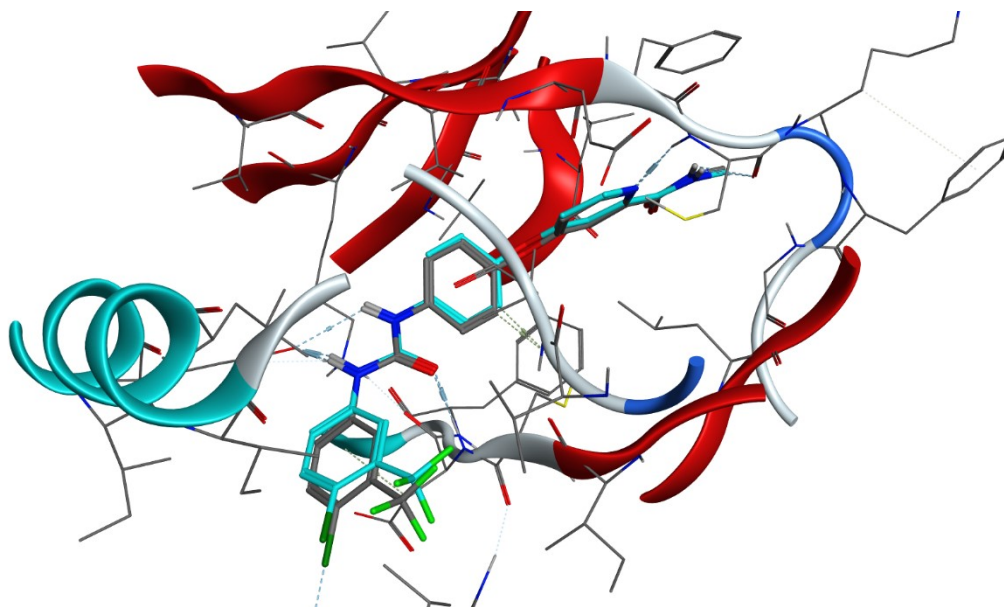


Graphical representation of the cytotoxic activity of the most active compounds against WI38 cell line



Docking study

Molecular Operating Environment (MOE-Dock 2014.09) software was used to conduct docking study. The structure of sorafenib, besides the most active derivatives **6** and **7a** were sketched via using the builder button. These compounds were then exposed to reduction of energy by the MOE program's default MMFF94x force field. Now, the 3D conformers of such compounds were gained by using the conformer search. VEGFR2 kinase enzyme was downloaded from the Protein data bank (PDB ID: 4asd) and opened in the MOE where water molecules were removed and the absent hydrogen atoms were added to obtain the appropriate ionization states of the protein structure. For the active site search in the enzyme structure, the MOE Alpha Site Finder was employed with default options. The attained alpha spheres were utilized to build the dummy atoms, which are the active site. MOE's "Docking" module was performed to achieve molecular docking. After that, the default docking procedure has been applied. The top thirty poses, which were ranked by London dG, were reserved and reduced by using MMFF94x within a rigid receptor. In order to score the generated postures, the Generalized-Born Volume Integral/Weighted Surface Area (GBVI/WSA dG) scoring function was then utilized. The selection of poses of the compounds having the top scores is done.



RMSD between the docked and co-crystallized ligands= 0.45 Å

Table S1: physicochemical properties of the test compounds

Molecule	MW	Rotatable bonds	H-bond acceptors	H-bond donors	MLOGP	Lipinski violations	Veber violations
4a	445.73	7	2	2	5.31	1	0
4b	441.31	8	3	2	4.48	0	0
4c	425.31	7	2	2	5.04	1	0
5a	452.29	6	3	3	3.61	0	0
5b	599.48	8	6	3	3.18	1	0
5c	601.46	8	7	3	2.22	1	1
6	459.76	6	2	3	4.97	0	0
7a	502.78	7	3	3	4.71	1	0
7b	482.36	7	3	3	4.44	0	0
8a	518.85	7	2	3	4.7	1	0
8b	498.43	7	2	3	4.43	0	0
9a	499.78	7	3	4	4.87	0	0
9b	479.36	7	3	4	4.61	0	0

Table S2 Pharmacokinetic properties and medicinal chemistry parameters

Compd No.	TPSA	GI absorption	BBB permeant	Pgp substrate	Bioavailability Score	PAIN S alerts	Synthetic Accessibility
4a	58.2	High	No	Yes	0.55	0	3.06
4b	67.43	High	No	No	0.55	0	3.05
4c	58.2	High	No	Yes	0.55	0	3.16
5a	87.3	High	No	No	0.55	0	3.29
5b	133.06	Low	No	No	0.55	0	4.04
5c	142.29	Low	No	No	0.55	0	4.01
6	65.52	High	No	No	0.55	0	3.65
7a	99.82	High	No	No	0.17	0	3.88
7b	99.82	High	No	No	0.55	0	3.97
8a	114.84	Low	No	No	0.17	0	3.95
8b	114.84	High	No	No	0.55	0	4.05
9a	108.82	Low	No	No	0.55	0	3.2
9b	108.82	Low	No	No	0.55	0	3.3