Supporting Information

Design and Development of Small-Molecule Arylaldoxime/5-Nitroimidazole Hybrids as Potent Inhibitors of MARK4: A Promising Approach for Target-Based Cancer Therapy

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Table of Contents

Experimental Protocols

Synthesis of Arylaldoximes (2a-h)

Sodium hydroxide 3N (75.0 mmol) was added drop wise to a stirred suspension of hydroxylamine hydrochloride (75.0 mmol) in 30 mL of water at 0 ºC. To this mixture different arylaldehydes (67.5mmol) taken in 40 mL ethanol were added dropwise and the reaction mixture was heated under reflux for 14-20 hours at 90 ºC. The mixture was cooled, poured onto ice cold water to afford the arylaldoximes (**2a, 2c, 2e, 2g** and **2h**) which were filtered and dried. However oximes (**2b**, **2d** and **2f**) were obtained by the process of extraction which was carried out with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated for the use in next step.

***N*-[(*E*)-Phenylmethylidene]hydroxylamine (2a).** Yield: 90%; C_7H_7NO; ESI-MS (m/z): [M^+ + 1] 121.13

***N*-[(*E*)-(4-Methoxyphenyl)methylidene]hydroxylamine (2b).** Yield: 85%; $C_8H_9NO_2$; ESI-MS (m/z): [M^+ + 1] 151.16

***N*-[(*E*)-(4-Methylphenyl)methylidene]hydroxylamine (2c).** Yield: 82%; C_8H_9NO; ESI-MS (m/z): [M^+ + 1] 135.16

***N*-[(*E*)-(4-Ethoxyphenyl)methylidene]hydroxylamine (2d).** Yield: 89%; $C_9H_{11}NO_2$; ESI-MS (m/z): [M^+ + 1] 165.18

***N*-[(*E*)-(4-Ethylphenyl)methylidene]hydroxylamine (2e).** Yield: 80%; $C_9H_{11}NO$; ESI-MS (m/z): [M^+ + 1] 149.18

***N*-[(*E*)-(4-Chlorophenyl)methylidene]hydroxylamine (2f).** Yield: 85%; C_7H_6ClNO; ESI-MS (m/z): [[M^+ + 1] 155.58

***N*-[(*E*)-(4-Nitrophenyl)methylidene]hydroxylamine (2g).** Yield: 84%; $C_7H_6N_2O_3$; ESI-MS (m/z): [M^+ + 1] 166.13

***N*-{(*E*)-[2-(Trifluoromethyl)phenyl]methylidene}hydroxylamine (2h).** Yield: 91%; $C_8H_6F_3NO$; ESI-MS (m/z): [M^+ + 1] 189.13

Synthesis Procedure for Carboximidoyl chlorides (3a-h)

N-Chlorosuccinimide (NCS) (43.91mmol) taken in DMF (60 ml) was added dropwise over a solution of different synthesized arylaldoximes (43.91mmol) in DMF and heated at 60 ºC for 8-12 hours. The completion of the reaction was monitored by the TLC. The reaction mixture was cooled at room temperature, poured onto ice cold water, and then extracted with tetrabutylmethyether (TBME). The organic layer was filtered and evaporated to dryness (at 30 ºC) to get the desired Carboximidoyl chlorides **3a-h.**

***N*-Hydroxybenzenecarboximidoyl chloride (3a).** Yield: 75 %; yellow solid; C_7H_6ClNO; ESI-MS (m/z): [M^+ + 1] 155.58

***N*-Hydroxy-4-methoxybenzene-1-carboximidoyl chloride (3b.** Yield: 75%; white solid; $C_8H_8ClNO_2$; ESI-MS (m/z): [M^+ + 1] 185.60

***N*-Hydroxy-4-methylbenzene-1-carboximidoyl chloride (3c).** Yield: 90%; white solid; C_8H_8ClNO; ESI-MS (m/z): [M^+ + 1] 169.60

4-Ethoxy-*N*-hydroxybenzene-1-carboximidoyl chloride (3d). Yield: 90%; white solid; $C_9H_{10}ClNO_2$; ESI-MS (m/z): [M^+ + 1] 199.63

4-Ethyl-*N*-hydroxybenzene-1-carboximidoyl chloride (3e). Yield: 73%; yellow solid; $C_9H_{10}ClNO$; ESI-MS (m/z): [M^+ + 1] 183.63

4-Chloro-*N*-hydroxybenzene-1-carboximidoyl chloride (3f). Yield: 87%; white solid; $C_7H_5Cl_2NO$; ESI-MS (m/z): [M^+ + 1] 190.02

***N*-Hydroxy-4-nitrobenzene-1-carboximidoyl chloride (3g).** Yield: 86%; white solid; $C_7H_5ClN_2O_3$; ESI-MS (m/z): [M^+ + 1] 200.57

***N*-Hydroxy-2-(trifluoromethyl)benzene-1-carboximidoyl chloride (3h).** Yield: 93%; white solid; $C_8H_5ClF_3NO$; ESI-MS (m/z): [M^+ + 1] 223.5

Molecular docking

Table S1. Molecular docking results showing the binding energy and specific interacting residues of MARK4 with each synthesized target chemotypes **4a-h**

Compound	Docking score (Kcal/mol)	Protein-ligand interactions		
		Hydrogen bonds		Other interacting residues
		Amino acid residues	Distance (Å)	
4a	-6.8	Lys85 Asp196 Asp196 Asp196	3.2 2.1 3.2 3.3	Ile62, Gly63, Lys64, Gly65, Val70, Ala83, Lys85, Val116, Asn183, Leu185, Ala195, Asp196,
4b	-6.8	Lys85 Glu182	2.4 3.2	Ile62, Gly63, Lys64, Gly65, Ala68, Lys69, Val70, Ala83, Lys85, Tyr134, Ala135, Glu182, Asn183, Leu185, Ala195, Asp196
4c	-7.1	Glu182 Asp196	2.4 2.2	Ile62, Gly63, Lys64, Gly65, Ala68, Lys69, Val70, Ala83, Lys85, Val116, Tyr134, Ala135, Glu182, Asn183, Leu185, Ala195, Asp196
4d	-7.1	Glu182 Asn183	2.2 1.8	Ile62, Gly63, Lys64, Gly65, Ala68, Lys69, Val70, Ala83, Lys85, Val116, Met132, Glu133, Glu139, Glu182, Asn183, Ala195, Asp196
4e	-7.3	Glu182 Lys64	2.5 3.2	Ile62, Gly63, Lys64, Gly65, Ala68, Lys69, Val70, Ala83, Lys85, Val116, Tyr134, Ala135, Glu182, Asn183, Leu185, Ala195, Asp196
4f	-6.9	Lys85 Glu182 Asp196	3.2 2.5 2.8	Ile62, Gly63, Lys64, Gly65, Ala68, Lys69, Val70, Ala83, Lys85, Val116, Tyr134, Ala135, Glu182, Asn183, Leu185, Ala195, Asp196
4g	-7.6	Lys85 Asn183 Asp196 Asp196	3.1 3.3 1.8 3.2	Gly63, Lys64, Ala68, Val70, Ala83, Ile84, Lys85, Val116, Leu130, Met132, Glu133, Glu182, Asn183, Ala195, Asp196
4h	-7.5	Lys85 Asn183 Asp196	3.2 3.3 3.2	Ile62, Gly63, Lys64, Ala68, Val70, Ala83, Lys85, Val116, Met132, Glu182, Asn183, Leu185, Ala195, Asp196

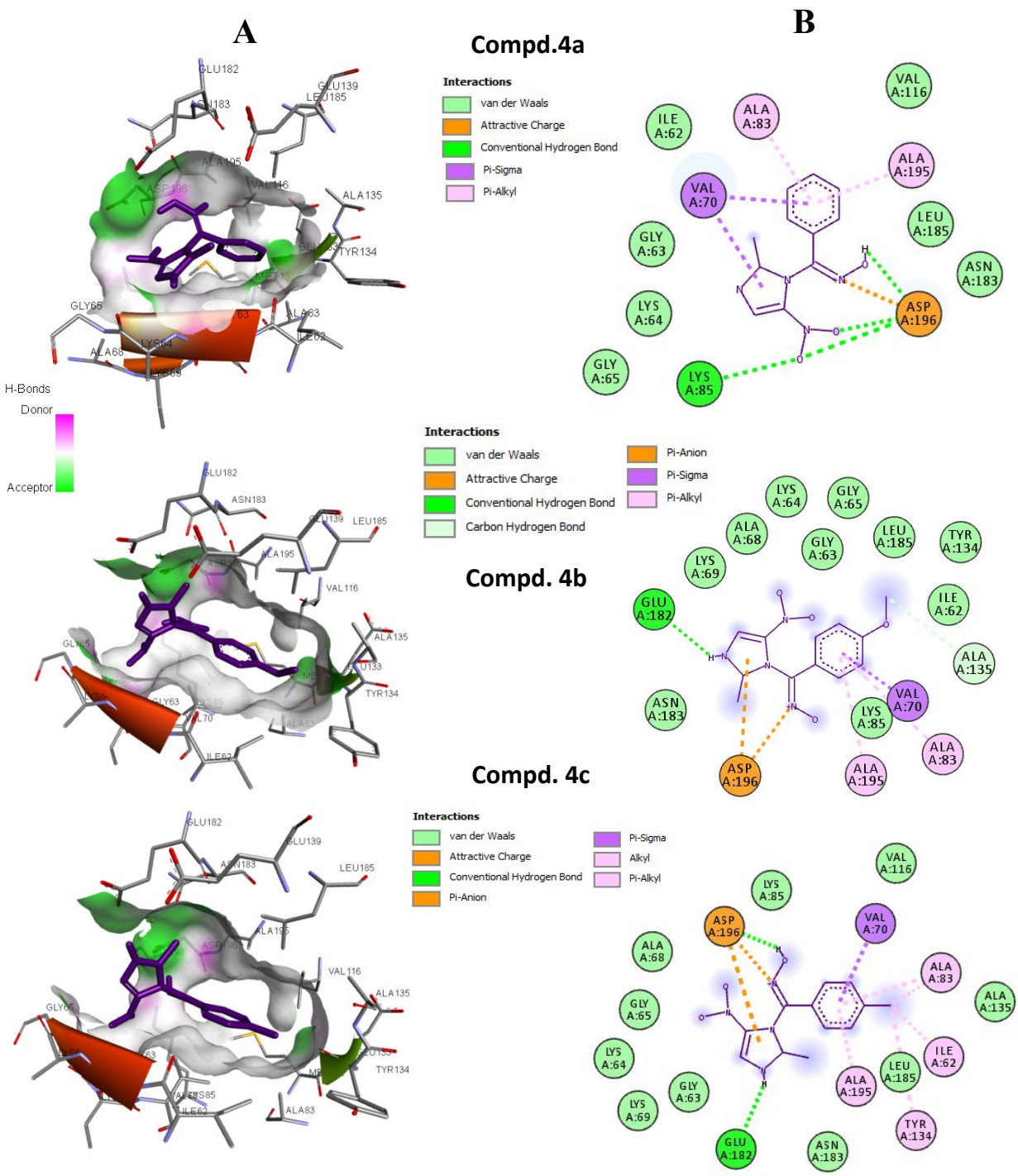


Figure S1. Molecular docking studies of synthesized compounds with MARK4: View of the catalytic pocket of MARK4 with **(A)** compound **4a**, compound **4b**, and compound **4c (B)** 2D schematic representation of the docking models of compound **4a,** compound **4b,** and compound **4c**. Dotted lines in different colours reflected various types of interaction such as hydrogen bonding, charge or polar interactions, van der Waals and π-sigma interactions

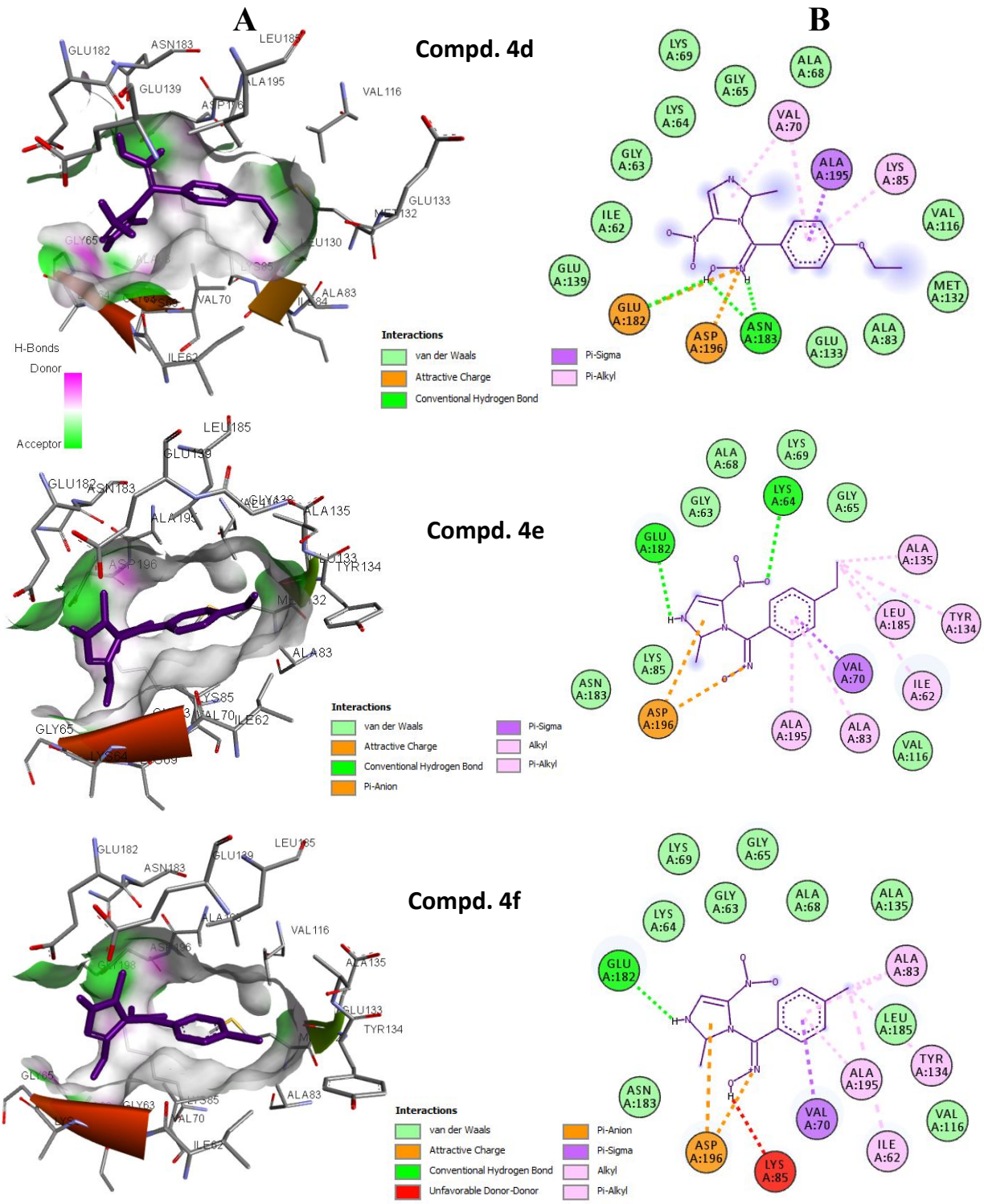


Figure S2. Molecular docking studies of synthesized compounds with MARK4: View of the catalytic pocket of MARK4 with **(A)** compound **4d**, compound **4e**, and compound **4f (B)** 2D schematic representation of the docking models of compound **4d,** compound **4e,** and compound **4f**. Dotted lines in different colours reflected various types of interaction such as hydrogen bonding, charge or polar interactions, van der Waals and π-sigma interactions

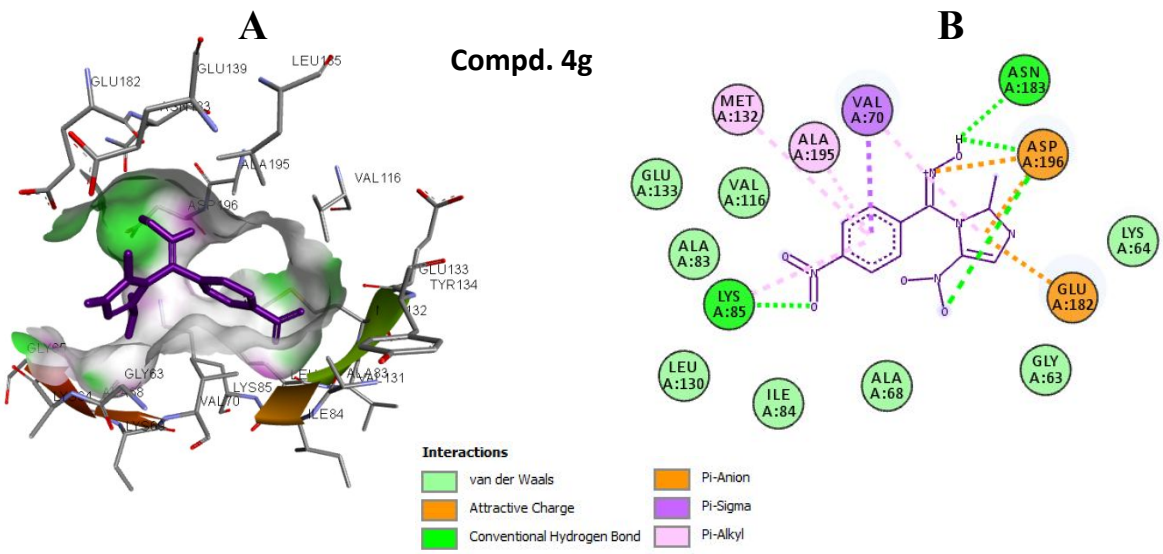


Figure S3. Molecular docking studies of synthesized compounds with MARK4: View of the catalytic pocket of MARK4 with **(A)** compound **4g**, **(B)** 2D schematic representation of the docking models of compound **4g**. Dotted lines in different colours reflected various types of interaction such as hydrogen bonding, charge or polar interactions, van der Waals and π-sigma interactions

Serine/Threonine Kinase Panel Inhibition data

Table S2. Kinase selectivity profiling of compound **4h** with 30 kinases of Ser/Thr family using kinase screening kit (Promega, Madison, USA) and malachite green assay.

S.NO.	**Kinase**	**% inhibition (at 10µM) of compound 4h**
1.	Positive control (MARK4)	**98.67**
2.	Negative control	0.38
3.	MAPKAPK2	21.44
4.	CHK1	19.25
5.	CHK2	17.15
6.	MARK1	34.24
7.	MELK	13.93
8.	PASK	11.15
9.	PIM1	8.92
10.	CAMK2 alpha	25.32
11.	CAMK2beta	13.63
12.	CAMK4	27.62
13.	CAMKI	13.26
14.	CAMKII	9.55
15.	CHKtide	15.23

16.	ZIPtide2	21.46
17.	ZIPtide	11.28
18.	AMPKA1	7.33
19.	AMPKB1	7.80
20.	MBP	16.66
21.	SAMStide	6.97
22.	S6K	11.13
23.	PKCu	7.69
24.	CREBtide	6.27
25.	MBP2	10.22
26.	HSP27tide	15.07
27.	STK33	11.45
28.	DAPK1	16.52
29.	ILK	6.24
30.	PDK3	20.29
31.	FASTK	7.77

Solubility data

Table S3. Solubility of the compounds **4a-h** (mg/mL)

Compound No.	**Aqueous Solubility (S) mg/mL**
4a	30±0.1
4b	36±0.2
4c	44±0.2
4d	34±0.5
4e	50±0.9
4f	60±1.2
4g	103±2.1
4h	90±1.5

Table S4. Bond lengths [Å] and angles [°] for the compounds **4c** and **4e**

Bond lengths	**4c**	**4e**
O(1)-N(1)	1.3839(17)	1.385(3)
N(1)-C(1)	1.279(2)	1.278(3)
C(1)-N(2)	1.4418(19)	1.449(3)
N(2)-C(9)	1.370(2)	1.368(3)
N(2)-C(10)	1.3718(19)	1.363(3)
O(2)-N(4)	1.2294(17)	1.229(3)
O(3)-N(4)	1.2309(17)	1.236(3)
Bond Angles	**4c**	**4e**
C(1)-N(1)-O(1)	113.06(13)	113.96(19)
N(1)-C(1)-N(2)	121.53(14)	121.4(2)
C(9)-N(2)-C(10)	108.25(12)	108.4(2)
C(9)-N(2)-C(1)	126.35(13)	127.6(2)
C(10)-N(2)-C(1)	125.39(13)	124.0(2)
C(10)-N(3)-C(8)	104.47(12)	104.6(2)

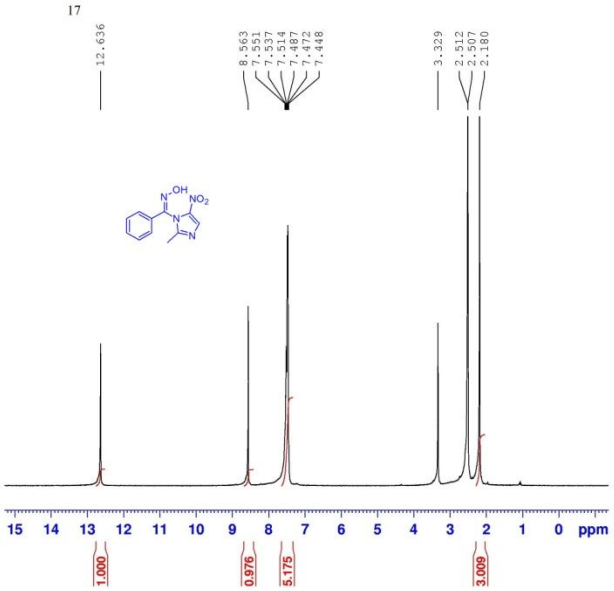
Table S5. Hydrogen bonds in the compounds **4c** and **4e**

D-H...A	**compound**	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...N(3)#1	**4c**	0.94(2)	1.82(3)	2.7589(17)	175(2)
O(1)-H(1O)...O(3)#1	**4c**	0.94(2)	2.66(2)	3.1359(16)	112.3(17)
O(1)-H(1O)...N(7)	**4e**	0.90(4)	1.89(4)	2.743(3)	160(4)
O(4)-H(4O)...N(3)#2	**4e**	1.02(4)	1.74(4)	2.747(3)	169(4)
O(4)-H(4O)...O(2)#2	**4e**	1.02(4)	2.65(4)	3.252(3)	117(3)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+1/2,z+1/2 #2 x,y,z+1 #3 x,y-1,z #4 x,y+1,z #5 -x-2,-y,-z+1 #6 -x,-y+1,-z

^{1}H NMR of Compound 4a

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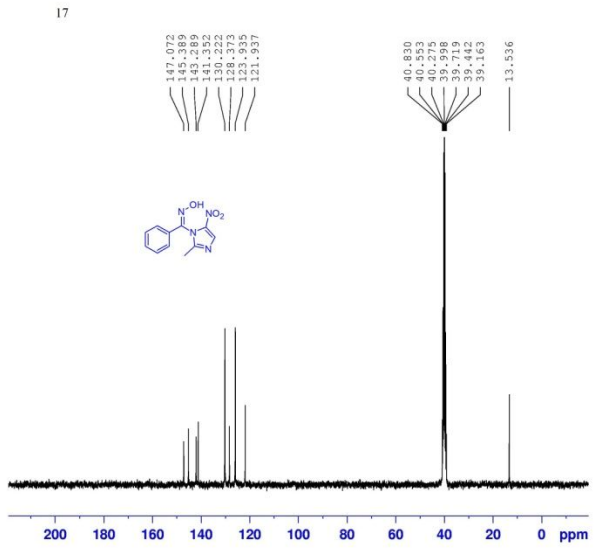


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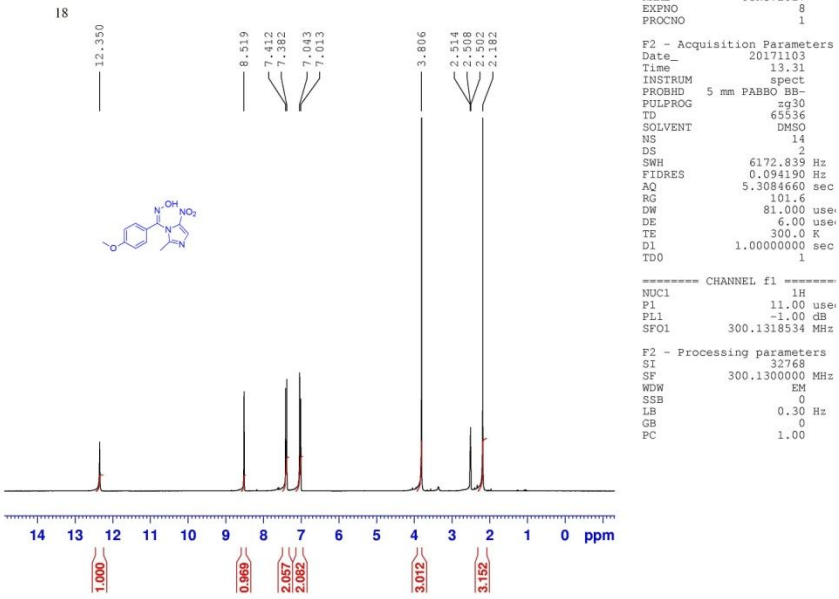


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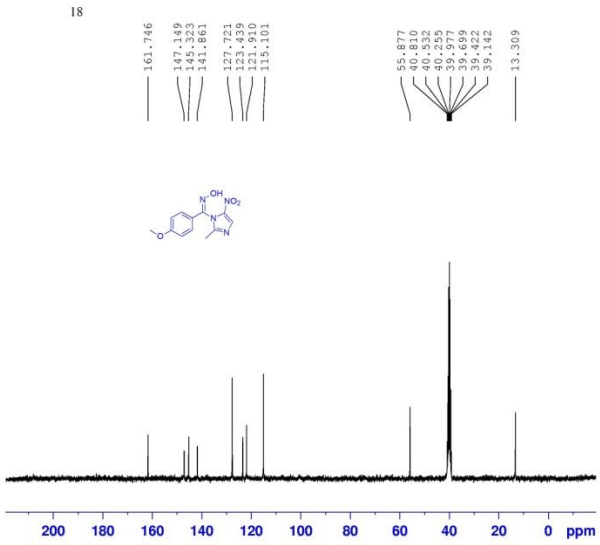


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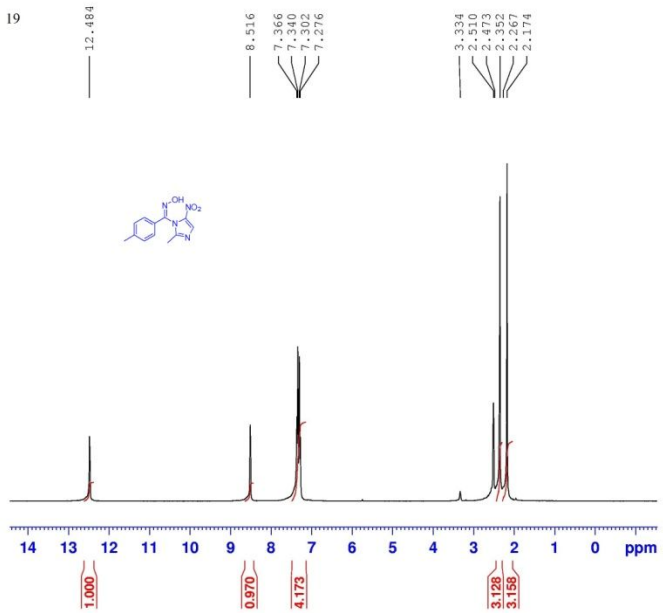


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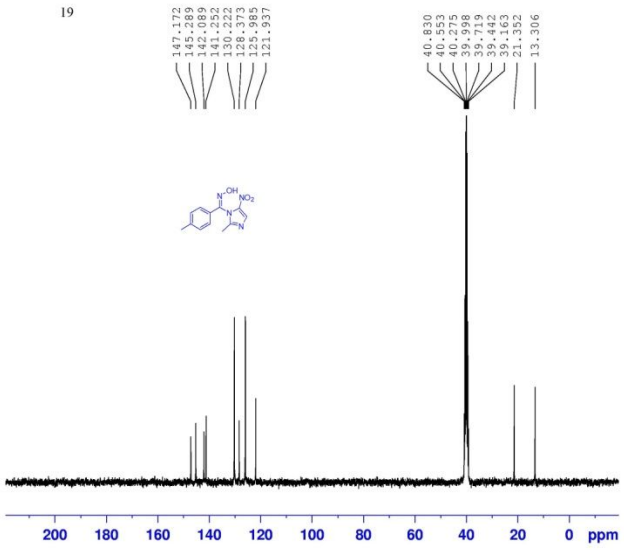


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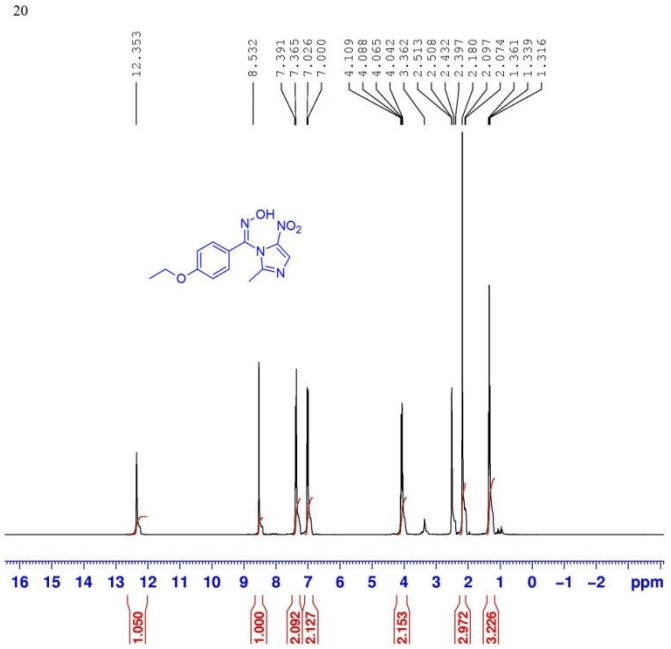


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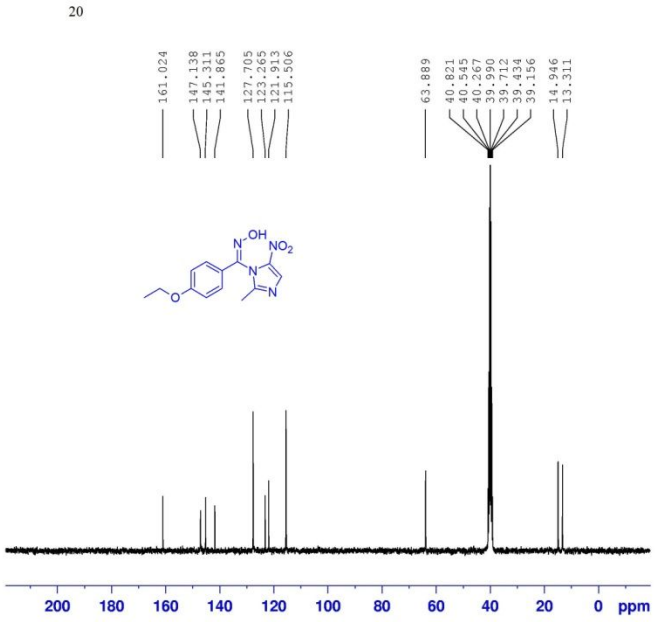


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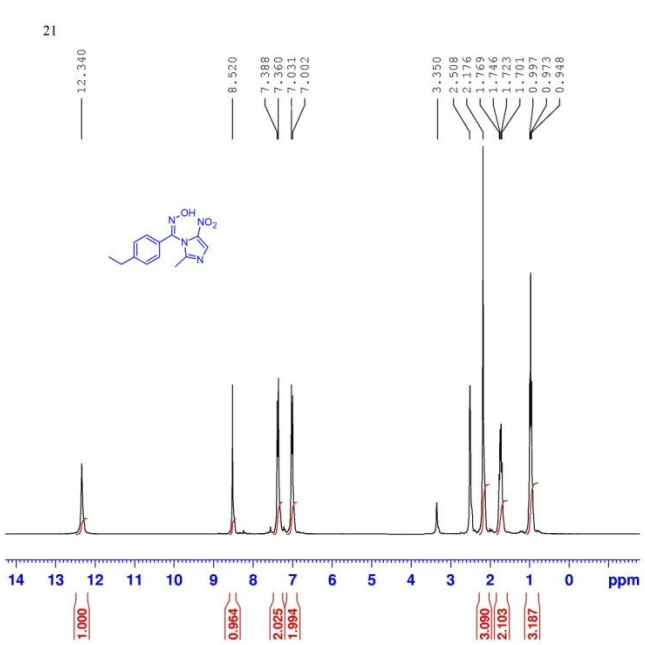
PL2                -1.00 dB
PL12               16.23 dB
PL13               20.23 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI                 32768
SF          75.4677490 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  1.40
```

^{1}H NMR of Compound 4e



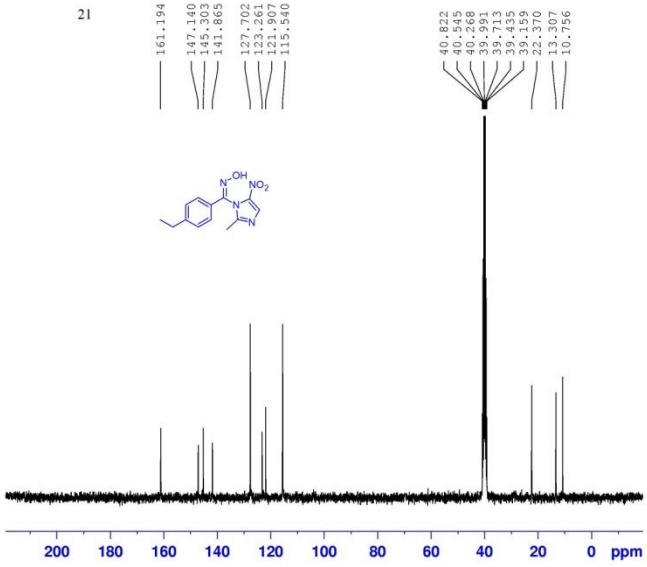

```
Current Data Parameters
NAME                  23OCTt 2017
EXPNO                          11
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20171023
Time                        13.44
INSTRUM                     spect
PROBHD    5 mm PABBO BB-
PULPROG                      zg30
TD                          65536
SOLVENT                      DMSO
NS                             16
DS                              2
SWH                    6172.839 Hz
FIDRES                 0.094190 Hz
AQ                     5.3084660 sec
RG                         101.6
DW                        81.000 use
DE                         6.00 use
TE                        300.0 K
D1                     1.00000000 sec
TD0                             1

======== CHANNEL f1 ========
NUC1                           1H
P1                          11.00 use
PL1                         -1.00 dB
SFO1                300.1318534 MHz

F2 - Processing parameters
SI                          32768
SF                    300.1300000 MHz
WDW                            EM
SSB                             0
LB                           0.30 Hz
GB                              0
PC                           1.00
```

^{13}C NMR of compound 4e




```
Current Data Parameters
NAME                  23OCTt 2017
EXPNO                          12
PROCNO                          1

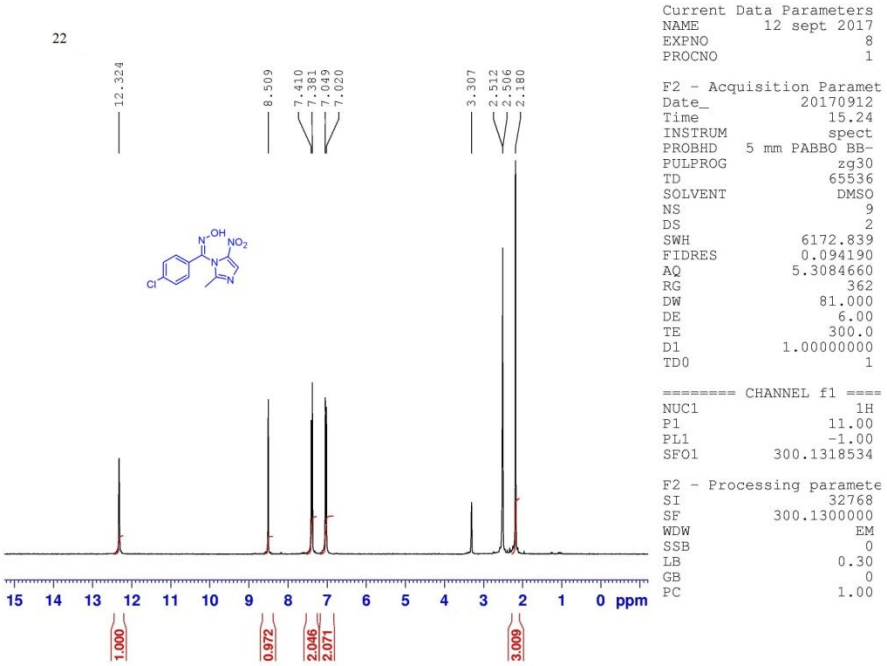
F2 - Acquisition Parameters
Date_                    20171023
Time                        13.47
INSTRUM                     spect
PROBHD    5 mm PABBO BB-
PULPROG                    zgpg30
TD                          65536
SOLVENT                      DMSO
NS                            241
DS                              4
SWH                   17985.611 Hz
FIDRES                 0.274439 Hz
AQ                     1.8219508 sec
RG                          32768
DW                         27.800 usec
DE                          6.00 usec
TE                        300.0 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                             1

======== CHANNEL f1 ========
NUC1                           13C
P1                          8.00 usec
PL1                         -3.00 dB
SFO1                75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                    waltz16
NUC2                           1H
PCPD2                      80.00 usec
PL2                         -1.00 dB
PL12                        16.23 dB
PL13                        20.23 dB
SFO2                300.1312005 MHz

F2 - Processing parameters
SI                          32768
SF                    75.4677490 MHz
WDW                            EM
SSB                             0
LB                           2.00 Hz
GB                              0
PC                           1.40
```

^{1}H NMR of Compound 4f



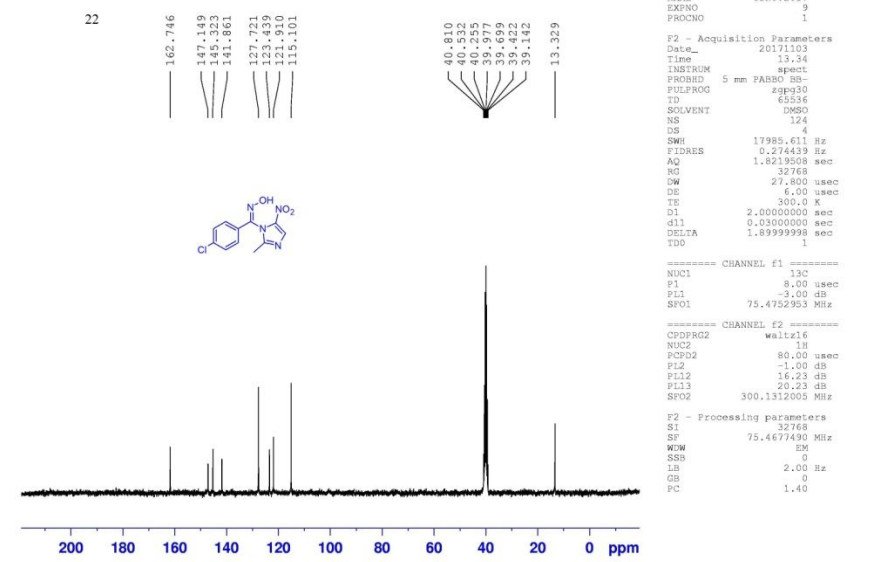

```
Current Data Parameters
NAME          12 sept 2017
EXPNO                    8
PROCNO                   1

F2 - Acquisition Paramet
Date_              20170912
Time                  15.24
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        9
DS                        2
SWH                6172.839
FIDRES            0.094190
AQ                5.3084660
RG                      362
DW                   81.000
DE                     6.00
TE                    300.0
D1               1.00000000
TD0                       1

========= CHANNEL f1 ====
NUC1                     1H
P1                    11.00
PL1                   -1.00
SFO1          300.1318534

F2 - Processing paramete
SI                    32768
SF            300.1300000
WDW                      EM
SSB                       0
LB                     0.30
GB                        0
PC                     1.00
```

^{13}C NMR of Compound 4f




```
Current Data Parameters
NAME          03NOV2017
EXPNO                 9
PROCNO                1

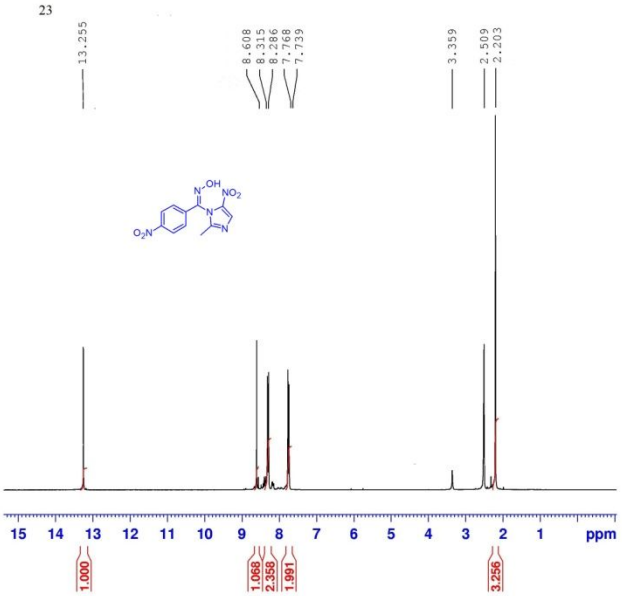
F2 - Acquisition Parameters
Date_          20171103
Time              13.34
INSTRUM           spect
PROBHD  5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                  124
DS                    4
SWH           17985.611 Hz
FIDRES            0.274439 Hz
AQ                1.8219508 sec
RG                   32768
DW                27.800 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 8.00 usec
PL1               -3.00 dB
SFO1          75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               -1.00 dB
PL12              16.23 dB
PL13              20.23 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI                   32768
SF            75.4677490 MHz
WDW                     EM
SSB                      0
LB                    2.00 Hz
GB                       0
PC                    1.40
```

^{1}H NMR of Compound 4g



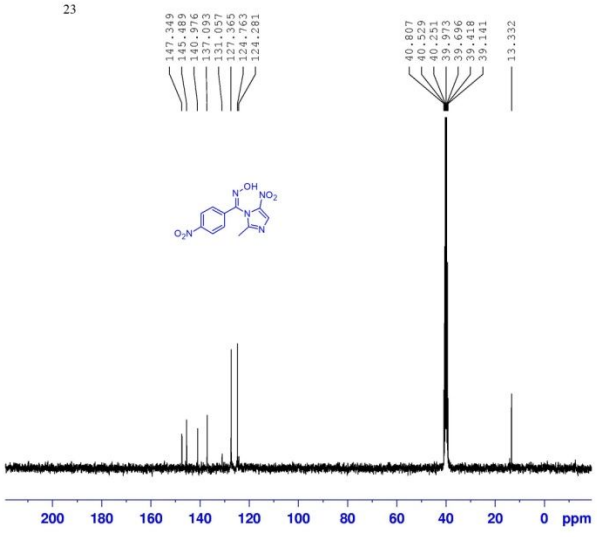

```
Current Data Parameters
NAME                  02NOV2017
EXPNO                         3
PROCNO                        1

F2 - Acquisition Parameters
Date_                20171102
Time                    13.06
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                6172.839 Hz
FIDRES             0.094190 Hz
AQ                 5.3084660 sec
RG                     161.3
DW                    81.000 use
DE                     6.00 use
TE                    300.0 K
D1                 1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        11.00 use
PL1                       -1.00 dB
SFO1               300.1318534 MHz

F2 - Processing parameters
SI                        32768
SF                 300.1300000 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

^{13}C NMR of compound 4g




```
Current Data Parameters
NAME                  03NOV2017
EXPNO                         1
PROCNO                        1

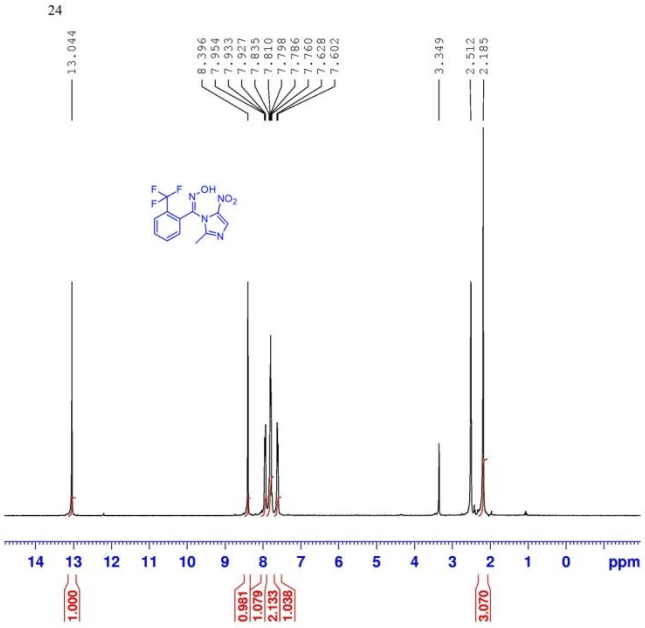
F2 - Acquisition Parameters
Date_                20171103
Time                    10.19
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                     65536
SOLVENT                 DMSO
NS                        167
DS                          4
SWH               17985.611 Hz
FIDRES             0.274439 Hz
AQ                 1.8219508 sec
RG                     32768
DW                    27.800 usec
DE                     6.00 usec
TE                    300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                        13C
P1                        8.00 usec
PL1                       -3.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                       -1.00 dB
PL12                      16.23 dB
PL13                      20.23 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
SI                        32768
SF                 75.4677490 MHz
WDW                          EM
SSB                           0
LB                         2.00 Hz
GB                            0
PC                         1.40
```

^{1}H NMR of Compound 4h



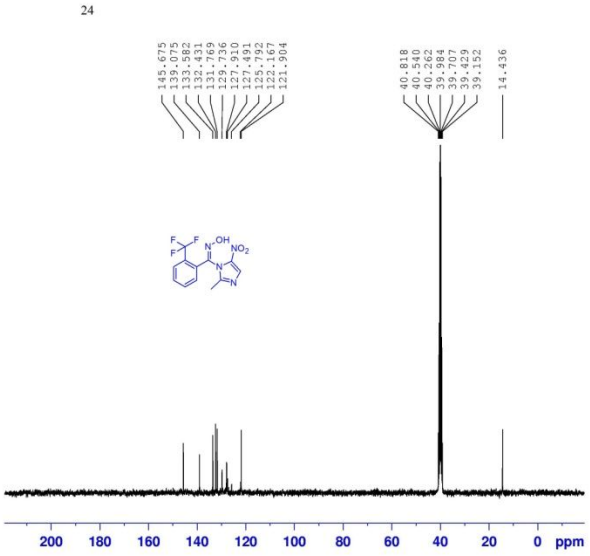

```
Current Data Parameters
NAME                  03NOV2017
EXPNO                        10
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20171103
Time                     13.44
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                   zg30
TD                       65536
SOLVENT                   DMSO
NS                          16
DS                           2
SWH                   6172.839 Hz
FIDRES                0.094190 Hz
AQ                    5.3084660 sec
RG                        228.1
DW                       81.000 use
DE                        6.00 use
TE                       300.0 K
D1                    1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                       11.00 use
PL1                      -1.00 dB
SFO1                300.1318534 MHz

F2 - Processing parameters
SI                           32768
SF                    300.1300000 MHz
WDW                             EM
SSB                              0
LB                            0.30 Hz
GB                               0
PC                            1.00
```

^{13}CNMR of Compound 4h




```
Current Data Parameters
NAME                  03NOV2017
EXPNO                        11
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20171103
Time                     13.47
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                       65536
SOLVENT                   DMSO
NS                         238
DS                           4
SWH                  17985.611 Hz
FIDRES                0.274439 Hz
AQ                    1.8219508 sec
RG                        32768
DW                       27.800 usec
DE                        6.00 usec
TE                       300.0 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         13C
P1                        8.00 usec
PL1                      -3.00 dB
SFO1                75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -1.00 dB
PL12                     16.23 dB
PL13                     20.23 dB
SFO2                300.1312005 MHz

F2 - Processing parameters
SI                           32768
SF                    75.4677490 MHz
WDW                             EM
SSB                              0
LB                            2.00 Hz
GB                               0
PC                            1.40
```