Dopamine-mediated vanillin multicomponent derivative synthesis via Grindstone method: Application of antioxidant, anti-tyrosinase, and cytotoxic activities

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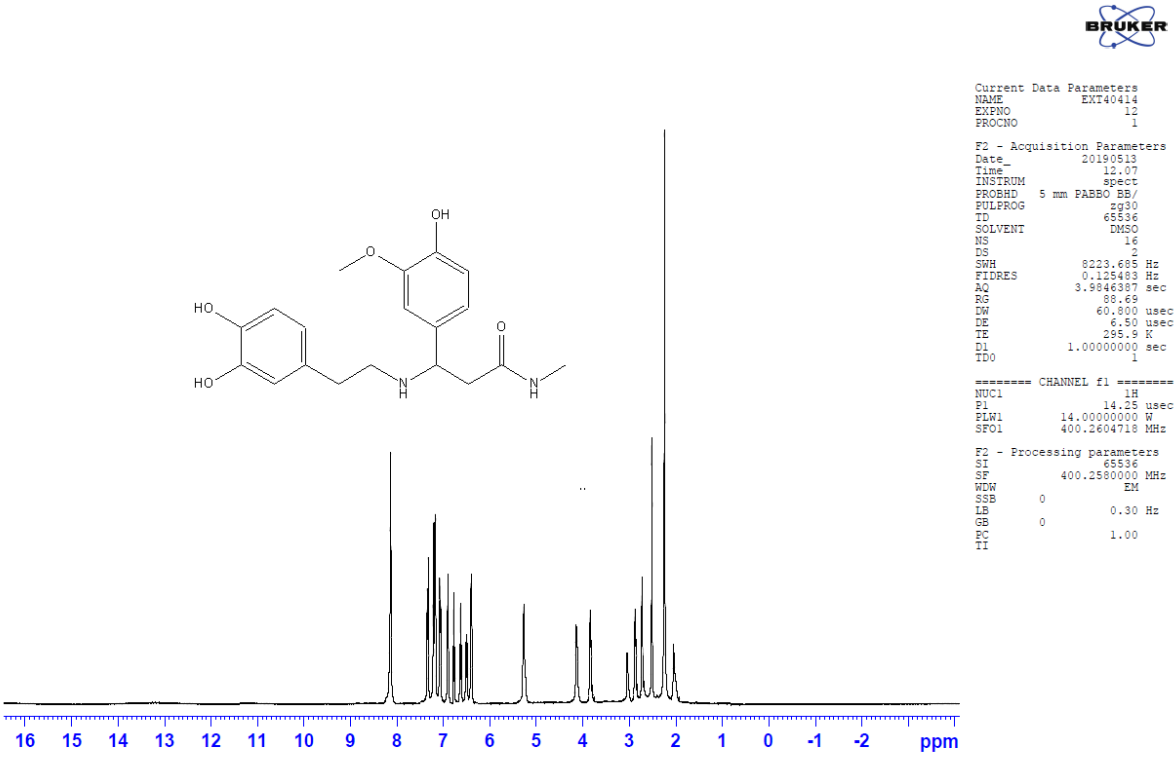


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EXPNO                       12
PROCNO                       1

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PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      88.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                  1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      14.25 usec
PLW1               14.00000000 W
SFO1              400.2604718 MHz

F2 - Processing parameters
SI                         65536
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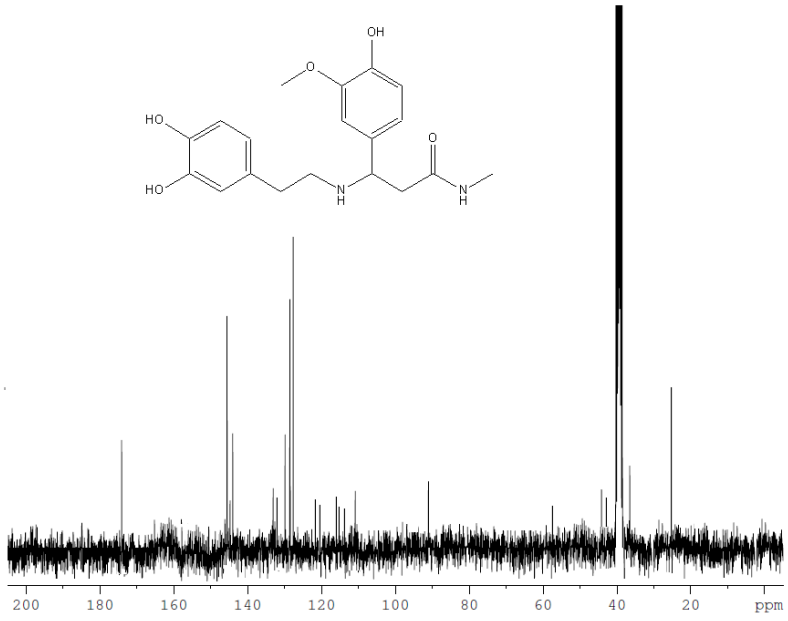
^{1}H NMR of the compound 1a

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AQ                  1.8175818 sec
RG                       287
DW                     27.733 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                      9.50 usec
PL1                     0.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    -2.00 dB
PL12                   17.37 dB
PL13                   20.00 dB
SFO2              300.1312005 MHz

F2 - Processing parameters
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SF                75.4677867 MHz
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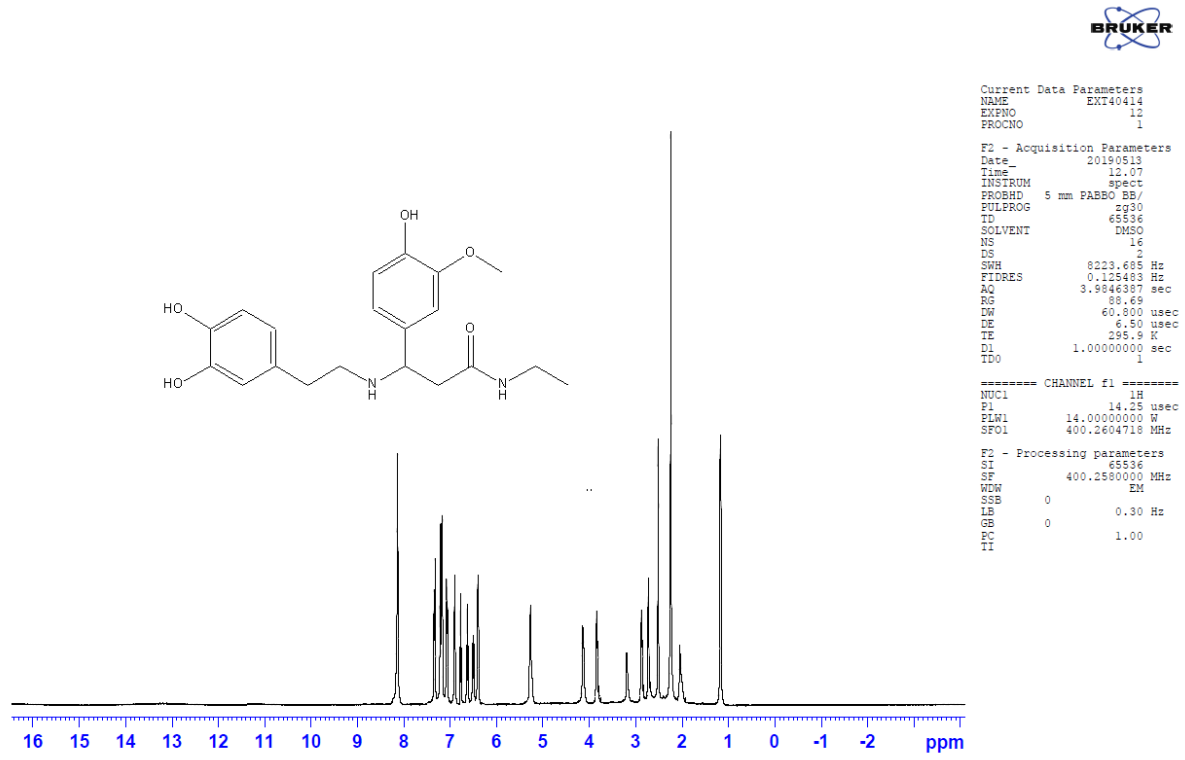
^{13}C NMR of the compound 1a

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Current Data Parameters
NAME                 EXT40414
EXPNO                      12
PROCNO                      1

F2 - Acquisition Parameters
Date_               20190513
Time                   12.07
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PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                     88.69
DW                    60.800 usec
DE                     6.50 usec
TE                    295.9 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     14.25 usec
PLW1              14.00000000 W
SFO1             400.2604718 MHz

F2 - Processing parameters
SI                    65536
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TI
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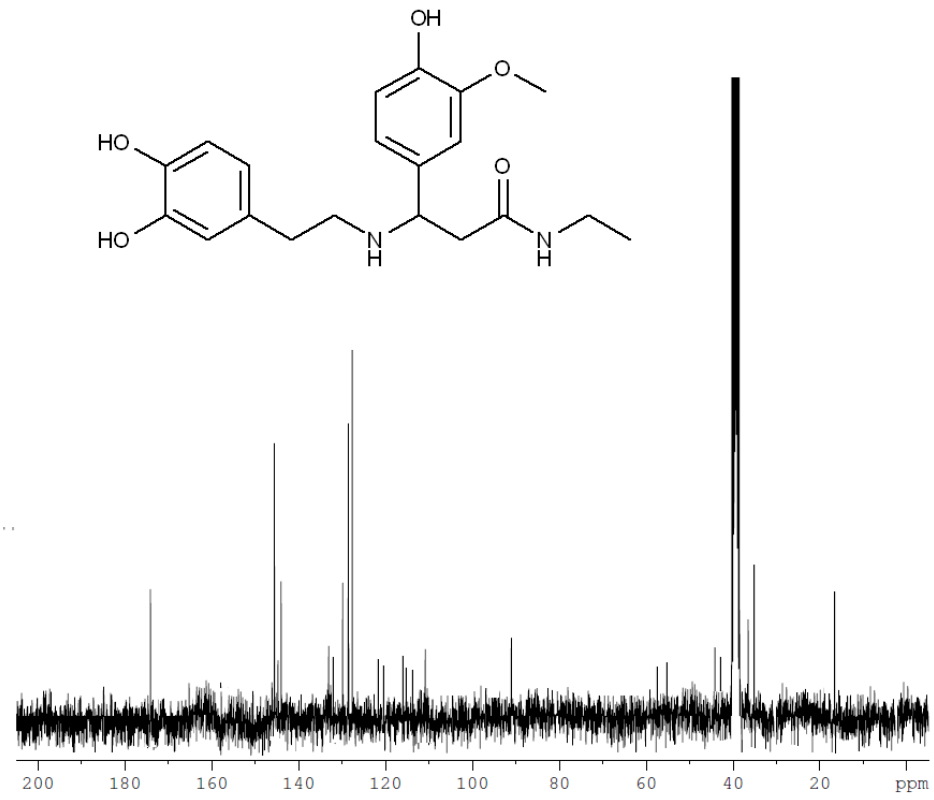
^{1}H NMR of the compound 1b

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TD                    65536
SOLVENT                DMSO
NS                     1024
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FIDRES             0.275098 Hz
AQ                 1.8175818 sec
RG                      287
DW                    27.733 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                     9.50 usec
PL1                    0.00 dB
SFO1              75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                 80.00 usec
PL2                   -2.00 dB
PL12                  17.37 dB
PL13                  20.00 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                    32768
SF               75.4677867 MHz
WDW                      EM
SSB                       0
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GB                        0
PC                     1.40
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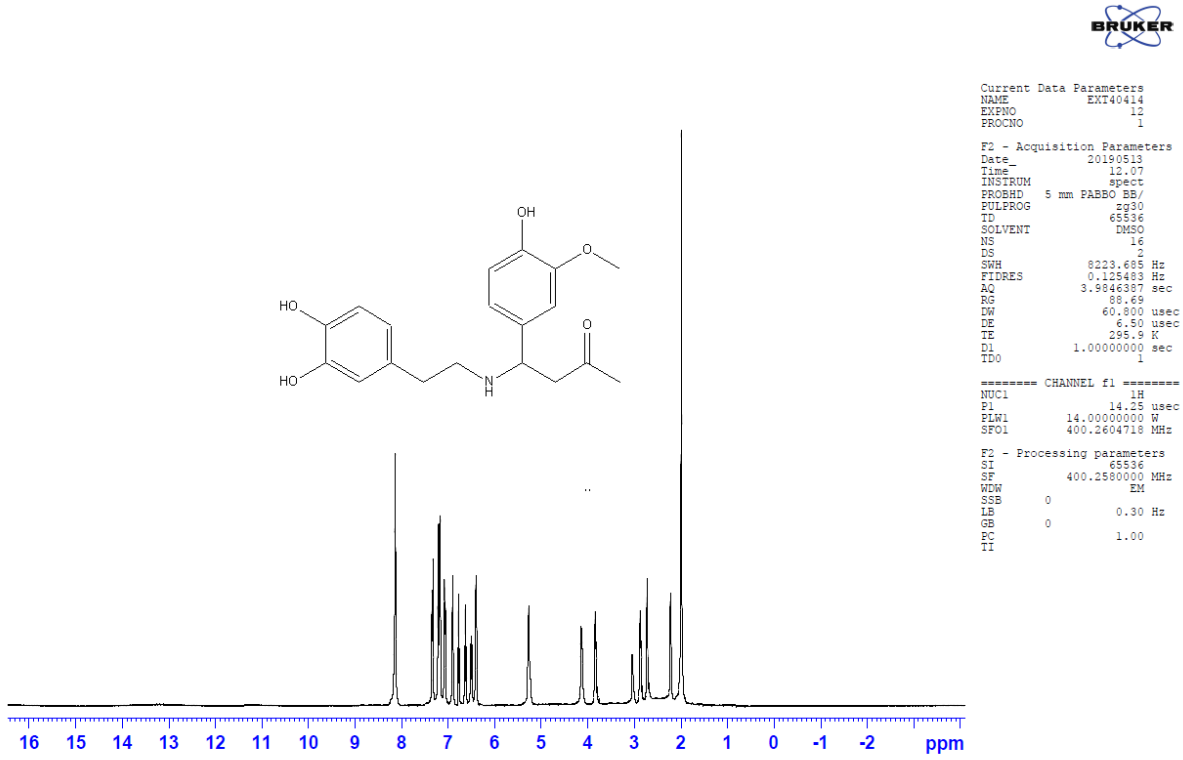
^{13}C NMR of the compound 1b

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Time                     12.07
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PROBHD    5 mm PABBO BB/
PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                         16
DS                          2
SWH                  8223.685 Hz
FIDRES               0.125483 Hz
AQ                   3.9846387 sec
RG                       88.69
DW                      60.800 usec
DE                       6.50 usec
TE                      295.5 K
D1                   1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1                14.00000000 W
SFO1               400.2604718 MHz

F2 - Processing parameters
SI                          65536
SF                 400.2580000 MHz
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SSB                 0
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GB                  0
PC                           1.00
TI
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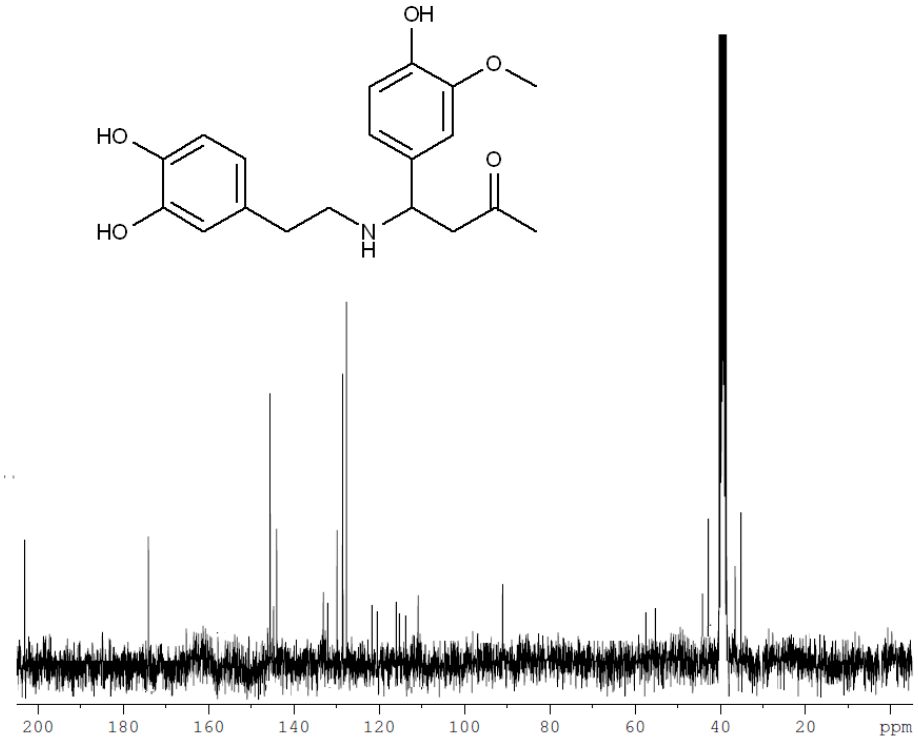
^{1}H NMR of the compound 1c

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PROCNO                    1

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TD                      65536
SOLVENT                  DMSO
NS                        1024
DS                           4
SWH                  18028.846 Hz
FIDRES               0.275098 Hz
AQ                   1.8175818 sec
RG                         287
DW                      27.733 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                        9.50 usec
PL1                       0.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                    80.00 usec
PL2                      -2.00 dB
PL12                     17.37 dB
PL13                     20.00 dB
SFO2              300.1312005 MHz

F2 - Processing parameters
SI                          32768
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PC                         1.40
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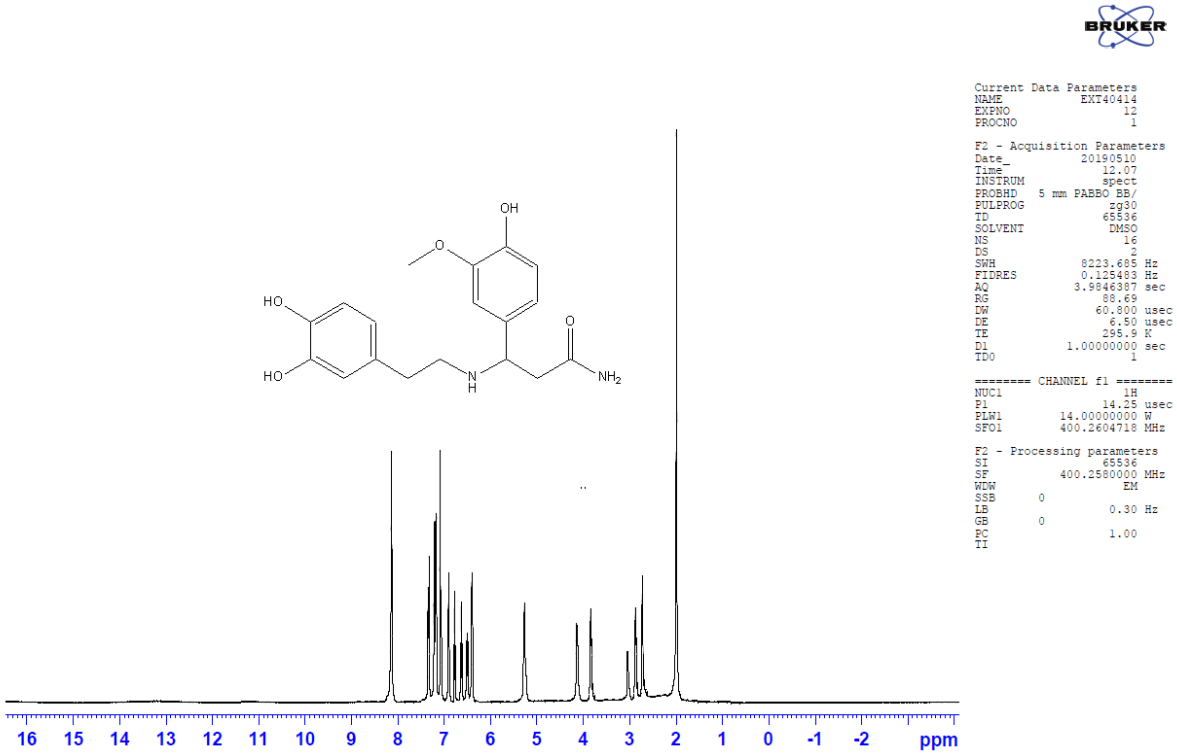
^{13}C NMR of the compound 1c

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Current Data Parameters
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EXPNO                       12
PROCNO                       1

F2 - Acquisition Parameters
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Time                    12.07
INSTRUM                 spect
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PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      88.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1               14.00000000 W
SFO1               400.2604718 MHz

F2 - Processing parameters
SI                         65536
SF                 400.2580000 MHz
WDW                           EM
SSB             0
LB                       0.30 Hz
GB              0
PC                       1.00
TI
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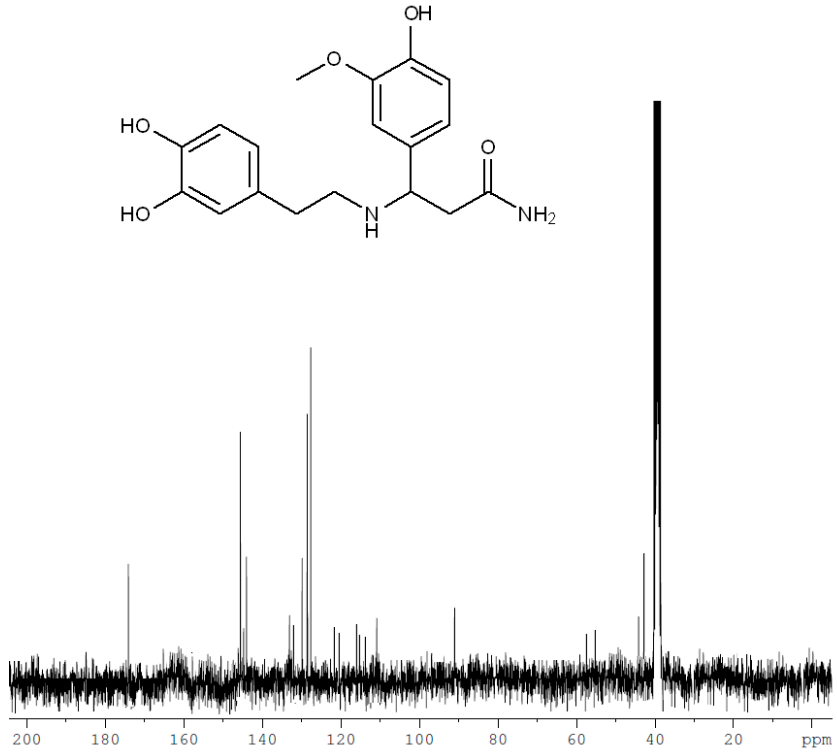
^{1}H NMR of the compound 1d

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EXPNO                     2
PROCNO                    1

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TD                     65536
SOLVENT                 DMSO
NS                      1024
DS                         4
SWH                18028.846 Hz
FIDRES              0.275098 Hz
AQ                  1.8175818 sec
RG                       287
DW                    27.733 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                       9.50 usec
PL1                      0.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                     -2.00 dB
PL12                    17.37 dB
PL13                    20.00 dB
SFO2              300.1312005 MHz

F2 - Processing parameters
SI                         32768
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SSB                            0
LB                       1.00 Hz
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PC                        1.40
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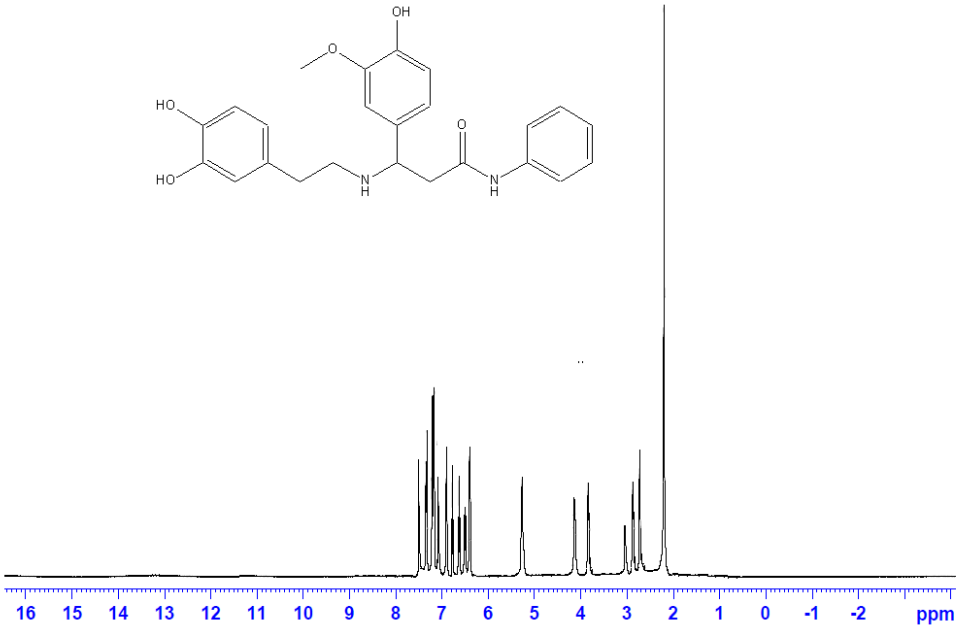
^{13}C NMR of the compound 1d

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Current Data Parameters
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PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      88.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                       1H
P1                      14.25 usec
PLW1             14.00000000 W
SFO1            400.2604718 MHz

F2 - Processing parameters
SI                        65536
SF               400.2580000 MHz
WDW                          EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
TI
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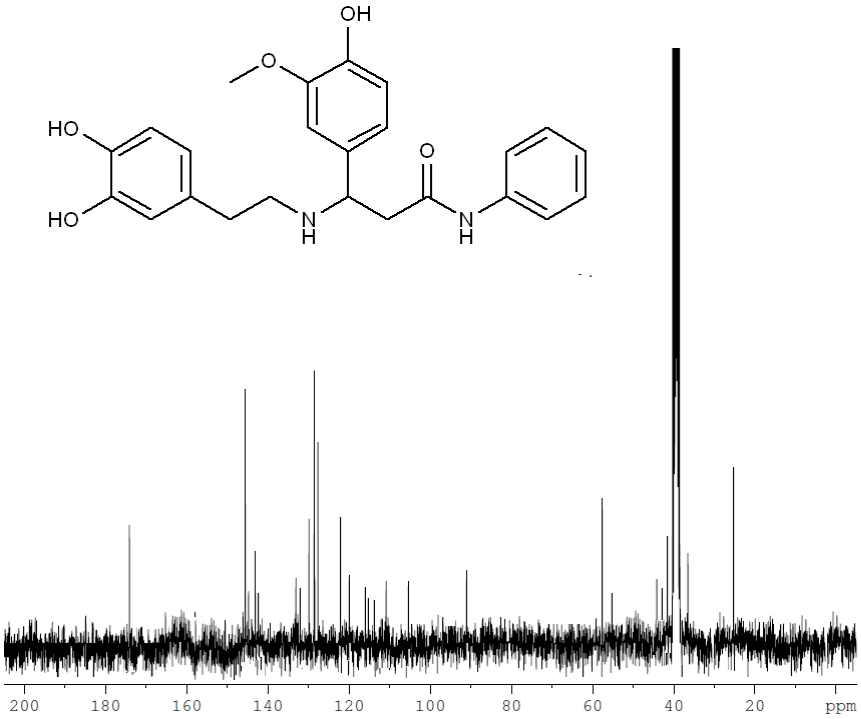
^{1}H NMR of the compound 1e

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Current Data Parameters
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EXPNO                     2
PROCNO                    1

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PROBHD   5 mm BBO BB-1H
PULPROG            zgpg30
TD                    65536
SOLVENT                DMSO
NS                      1024
DS                         4
SWH               18028.846 Hz
FIDRES             0.275098 Hz
AQ                 1.8175818 sec
RG                       287
DW                    27.733 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                     9.50 usec
PL1                    0.00 dB
SFO1           75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                80.00 usec
PL2                  -2.00 dB
PL12                 17.37 dB
PL13                 20.00 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF             75.4677867 MHz
WDW                         EM
SSB                          0
LB                      1.00 Hz
GB                           0
PC                      1.40
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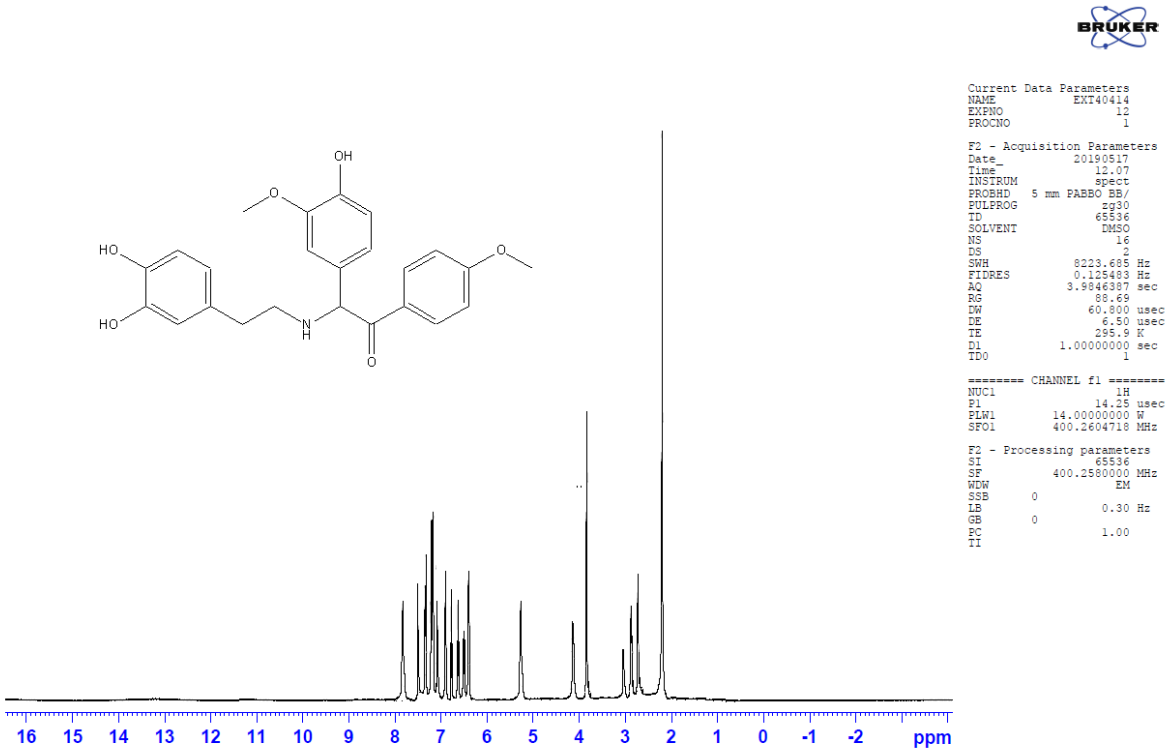
^{13}C NMR of the compound 1e

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PROCNO                       1

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PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                          16
DS                           2
SWH                   8223.685 Hz
FIDRES                0.125483 Hz
AQ                    3.9846387 sec
RG                        88.69
DW                       60.800 usec
DE                        6.50 usec
TE                       295.9 K
D1                    1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1                14.00000000 W
SFO1                400.2604718 MHz

F2 - Processing parameters
SI                          65536
SF                    400.2580000 MHz
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SSB                 0
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GB                  0
PC                           1.00
TI
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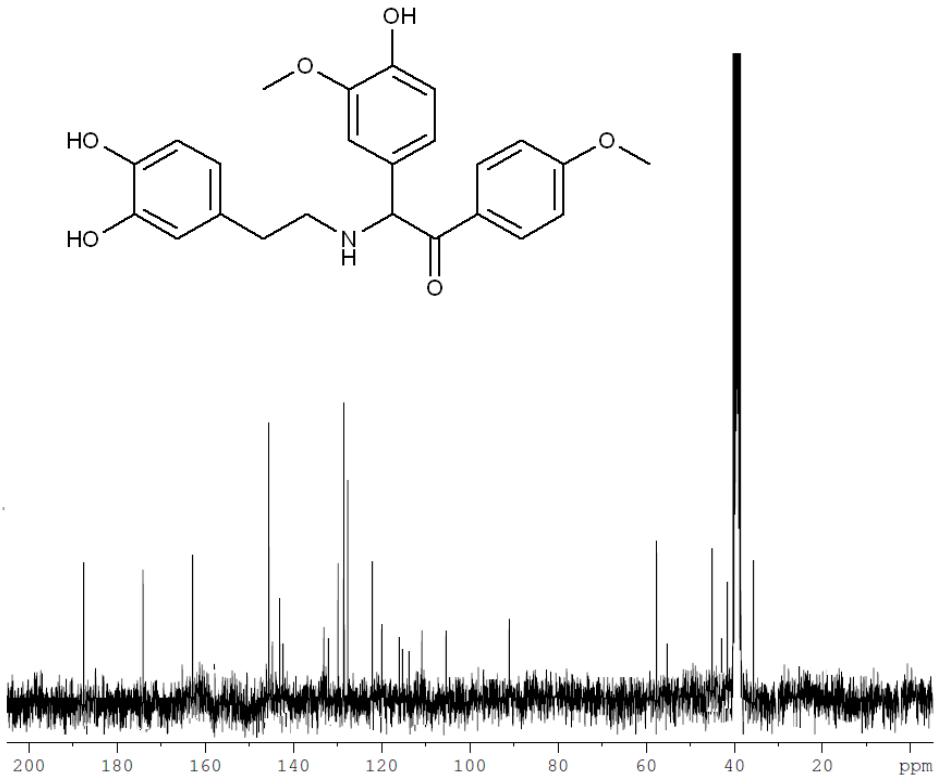
^{1}H NMR of the compound 1f

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PROCNO                    1

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PULPROG              zgpg30
TD                      65536
SOLVENT                  DMSO
NS                       1024
DS                          4
SWH                18028.846 Hz
FIDRES                0.275098 Hz
AQ                    1.8175818 sec
RG                          287
DW                       27.733 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                        9.50 usec
PL1                       0.00 dB
SFO1                75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                    80.00 usec
PL2                      -2.00 dB
PL12                     17.37 dB
PL13                     20.00 dB
SFO2                300.1312005 MHz

F2 - Processing parameters
SI                          32768
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WDW                            EM
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LB                         1.00 Hz
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PC                         1.40
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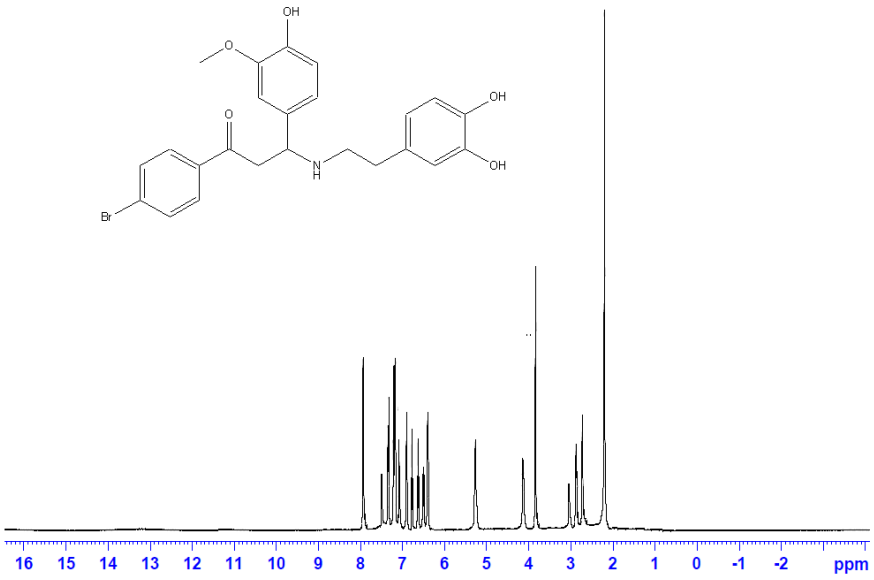
^{13}C NMR of the compound 1f

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PROCNO                      1

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PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      88.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                       1H
P1                     14.25 usec
PLW1             14.00000000 W
SFO1            400.2604718 MHz

F2 - Processing parameters
SI                        65536
SF               400.2580000 MHz
WDW                          EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
TI
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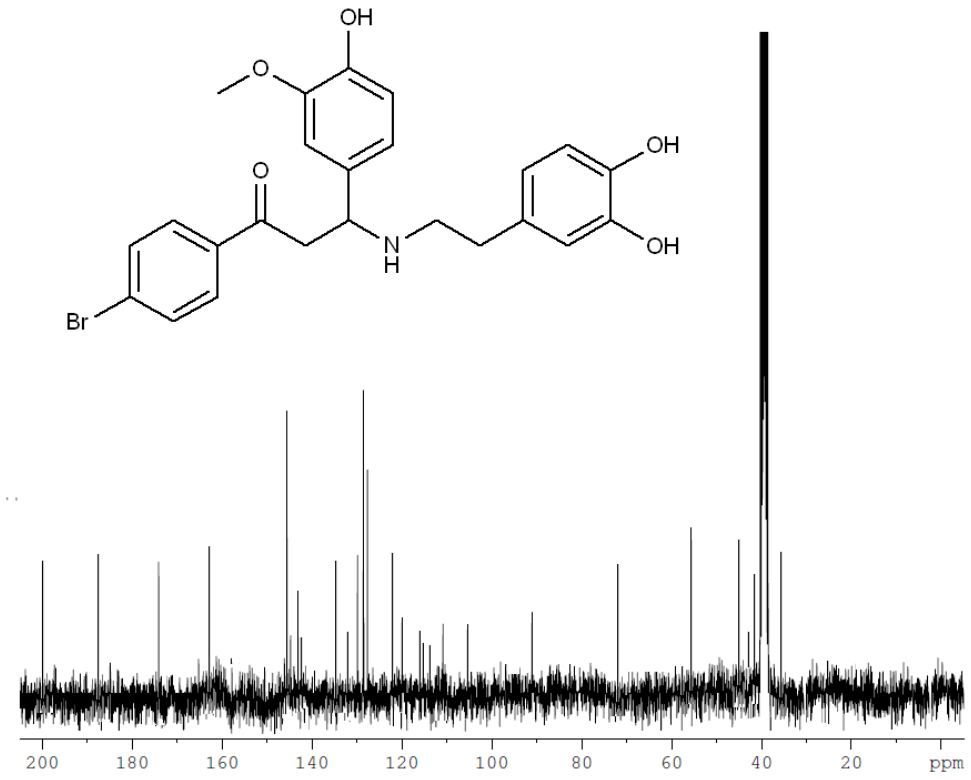
^{1}H NMR of the compound 1g

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PROCNO                    1

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PROBHD    5 mm BBO BB-1H
PULPROG            zgpg30
TD                    65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH               18028.846 Hz
FIDRES             0.275098 Hz
AQ                1.8175818 sec
RG                      287
DW                   27.733 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                    9.50 usec
PL1                   0.00 dB
SFO1           75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                80.00 usec
PL2                  -2.00 dB
PL12                 17.37 dB
PL13                 20.00 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF             75.4677867 MHz
WDW                         EM
SSB                          0
LB                    1.00 Hz
GB                           0
PC                    1.40
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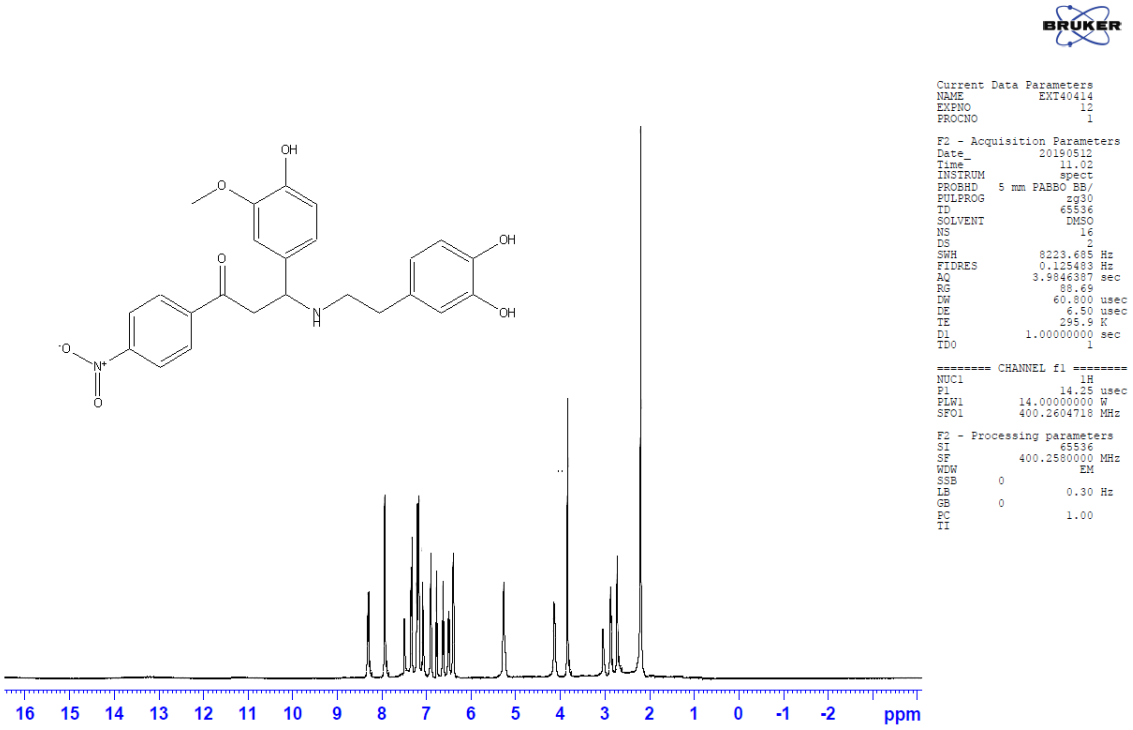
^{13}C NMR of the compound 1g

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TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      88.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1               14.00000000 W
SFO1              400.2604718 MHz

F2 - Processing parameters
SI                         65536
SF                400.2580000 MHz
WDW                           EM
SSB             0
LB                        0.30 Hz
GB              0
PC                        1.00
TI
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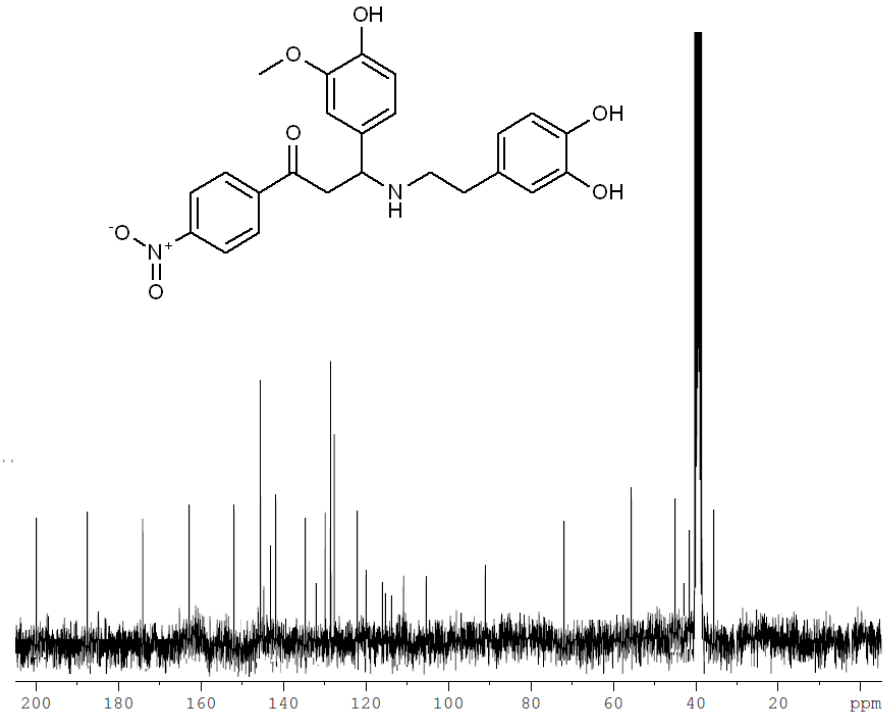
^{1}H NMR of the compound 1h

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SOLVENT                 DMSO
NS                      1024
DS                         4
SWH                18028.846 Hz
FIDRES              0.275098 Hz
AQ                  1.8175818 sec
RG                       287
DW                    27.733 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                       9.50 usec
PL1                      0.00 dB
SFO1              75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                     -2.00 dB
PL12                    17.37 dB
PL13                    20.00 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                         32768
SF                75.4677867 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                        1.40
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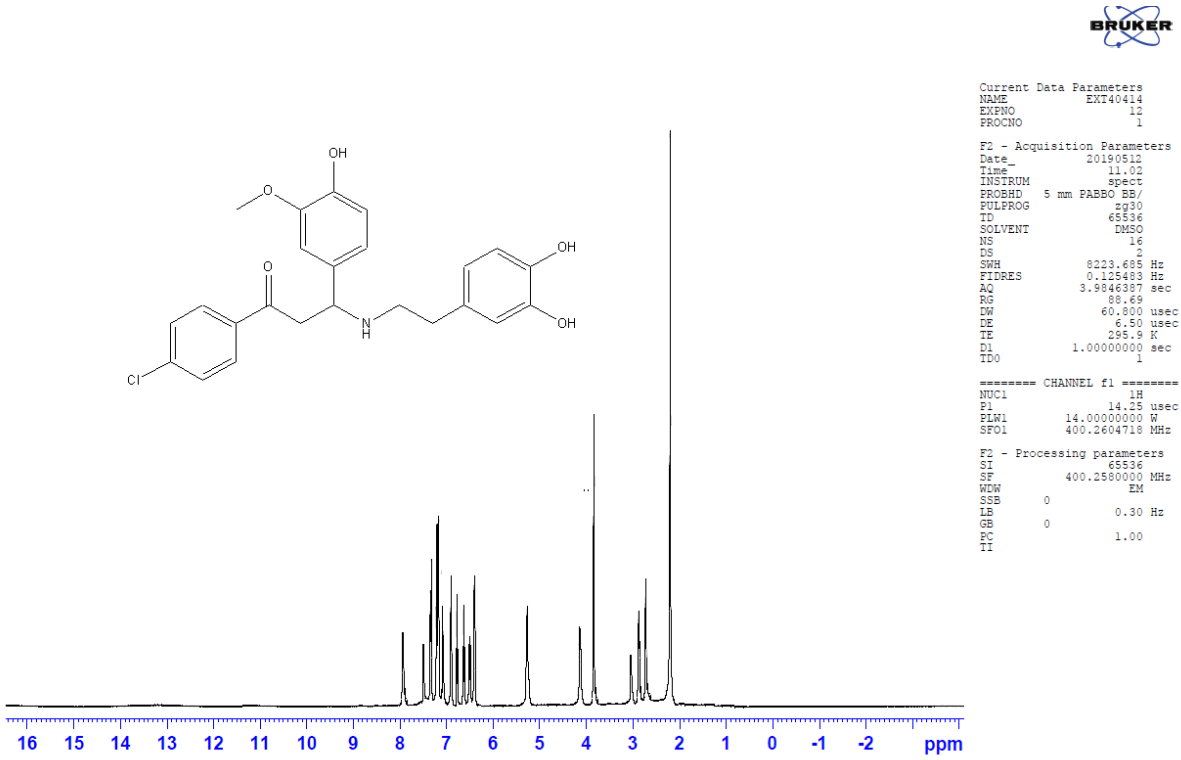
^{13}C NMR of the compound 1h

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Current Data Parameters
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EXPNO                       12
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20190512
Time                     11.02
INSTRUM                  spect
PROBHD    5 mm PABBO BB/
PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                         16
DS                          2
SWH                   8223.685 Hz
FIDRES                0.125483 Hz
AQ                    3.9846387 sec
RG                        88.69
DW                       60.800 usec
DE                        6.50 usec
TE                       295.9 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1                14.00000000 W
SFO1                400.2604718 MHz

F2 - Processing parameters
SI                      65536
SF                 400.2580000 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00
TI
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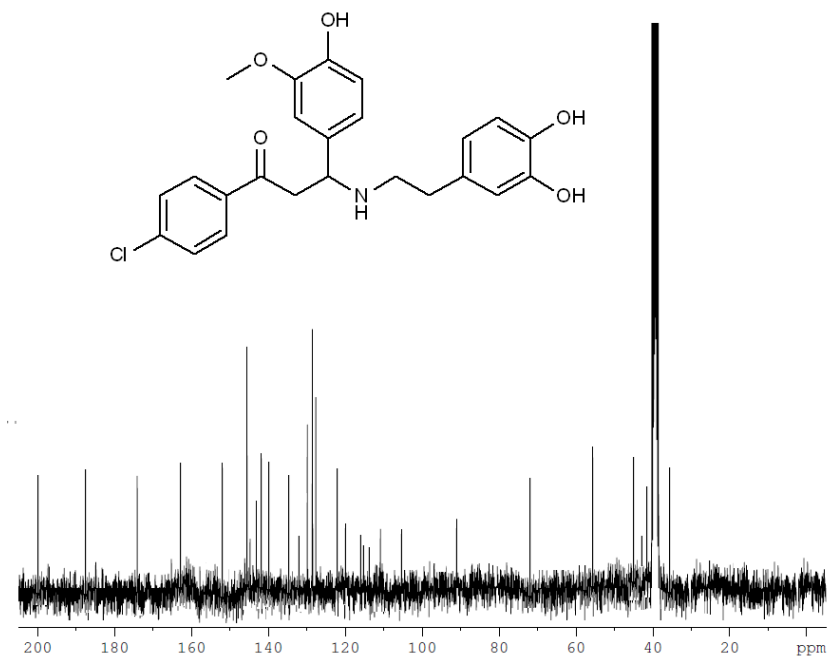
^{1}H NMR of the compound 1i

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Current Data Parameters
NAME                  1072B
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20191022
Time                  16.33
INSTRUM               spect
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PULPROG            zgpg30
TD                     65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH               18028.846 Hz
FIDRES                0.275098 Hz
AQ                1.8175818 sec
RG                      287
DW                   27.733 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                     9.50 usec
PL1                    0.00 dB
SFO1              75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                80.00 usec
PL2                  -2.00 dB
PL12                 17.37 dB
PL13                 20.00 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                    32768
SF                75.4677867 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
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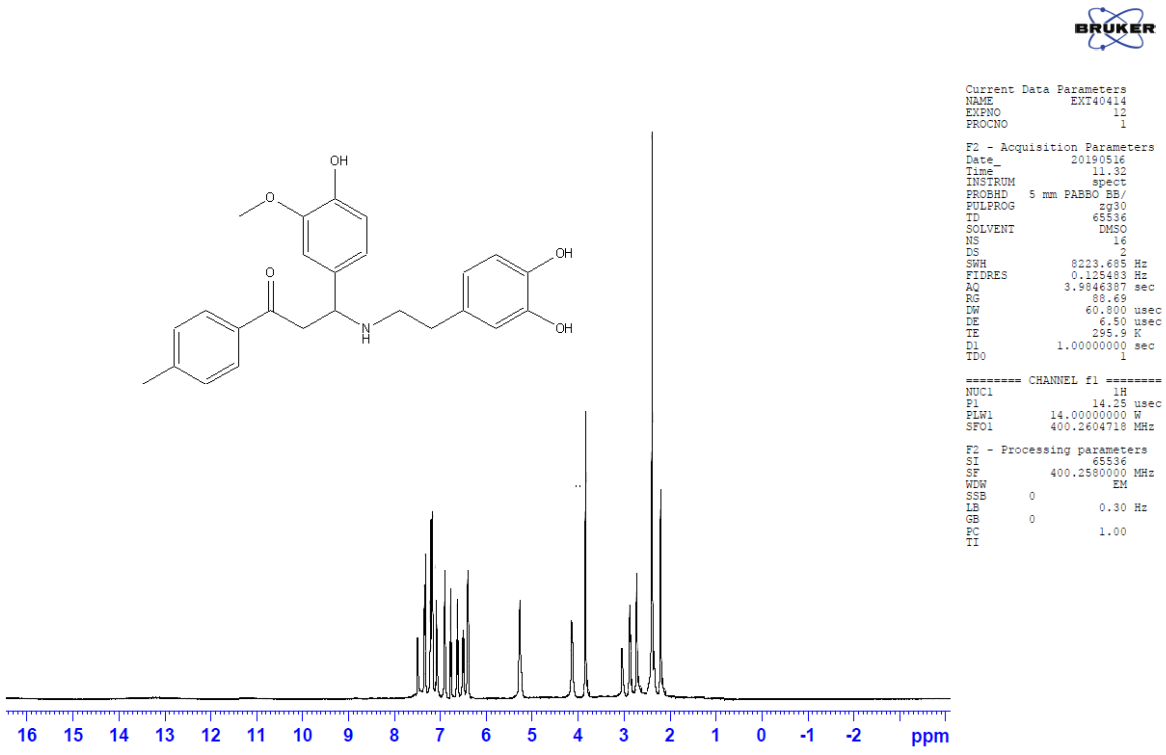
^{13}C NMR of the compound 1i

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NAME                  EXT40414
EXPNO                       12
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190516
Time                   11.32
INSTRUM                spect
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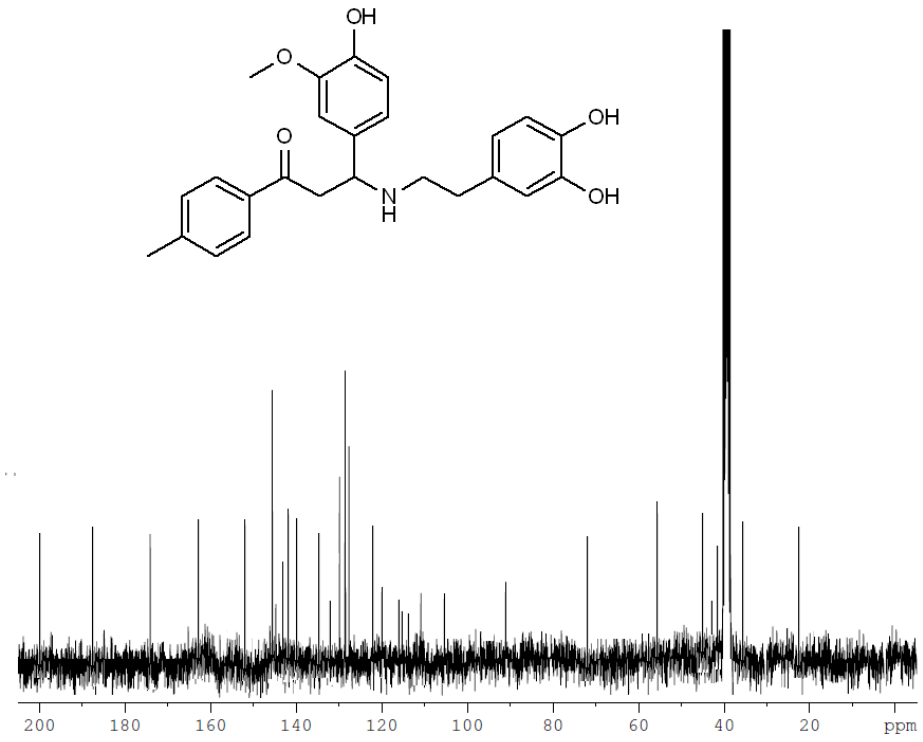
PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      68.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1             14.00000000 W
SFO1             400.2604718 MHz

F2 - Processing parameters
SI                         65536
SF                  400.2580000 MHz
WDW                           EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
TI
```

^{1}H NMR of the compound 1j

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Current Data Parameters
NAME                  1072B
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_               20191027
Time                   17.50
INSTRUM                spect
PROBHD   5 mm BBO BB-1H
PULPROG             zgpg30
TD                     65536
SOLVENT                 DMSO
NS                      1024
DS                         4
SWH                18028.846 Hz
FIDRES              0.275098 Hz
AQ                  1.8175818 sec
RG                       287
DW                     27.733 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                       9.50 usec
PL1                      0.00 dB
SFO1             75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                     -2.00 dB
PL12                    17.37 dB
PL13                    20.00 dB
SFO2            300.1312005 MHz

F2 - Processing parameters
SI                         32768
SF                  75.4677867 MHz
WDW                           EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
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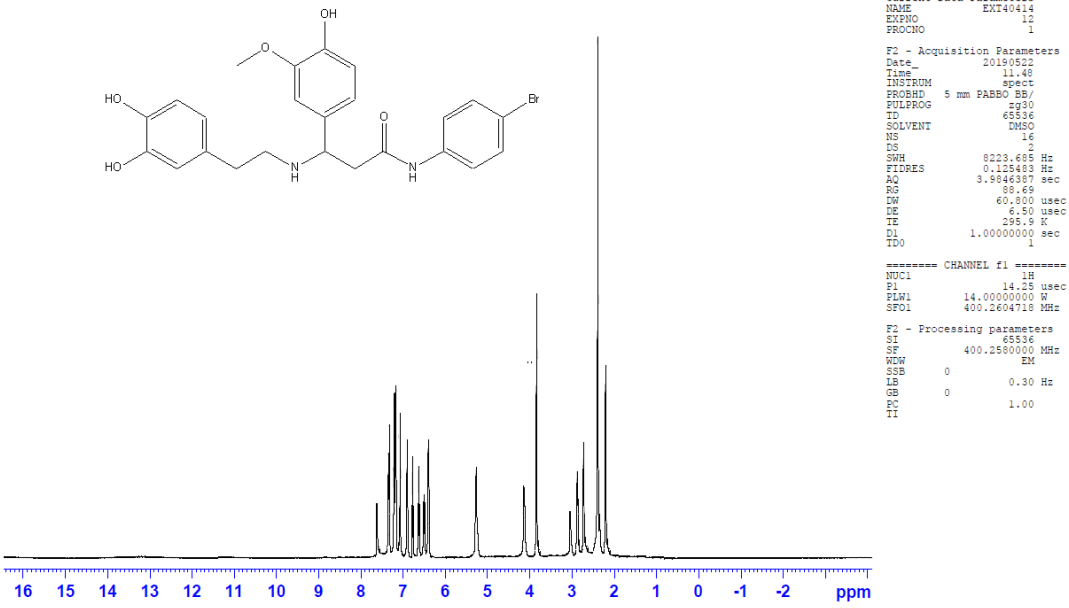
^{13}C NMR of the compound 1j

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Current Data Parameters
NAME                  EXT40414
EXPNO                       12
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190522
Time                   11.48
INSTRUM                spect
PROBHD   5 mm PABBO BB/
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      88.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1              14.00000000 W
SFO1             400.2604718 MHz

F2 - Processing parameters
SI                        65536
SF               400.2580000 MHz
WDW                          EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
TI
```
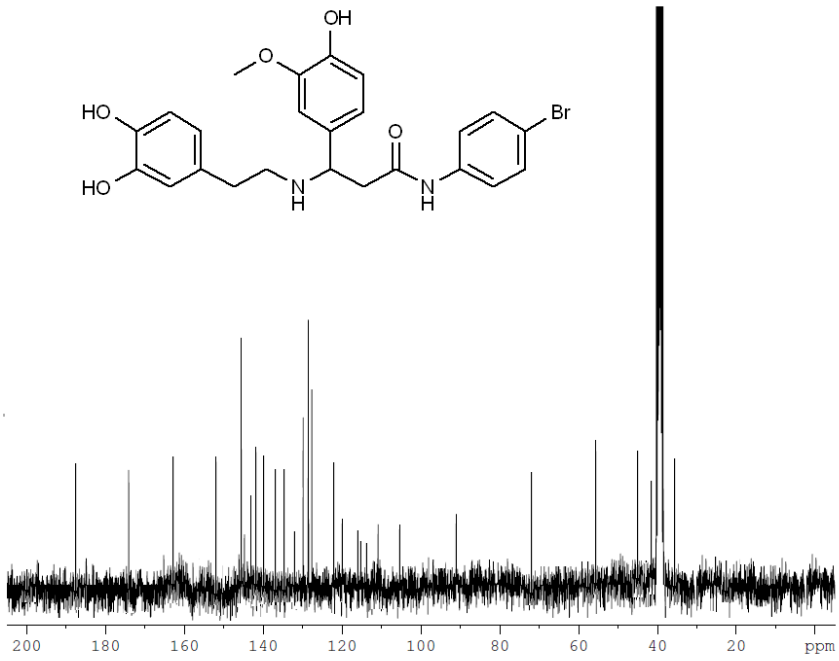

^{1}H NMR of the compound 1k

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Current Data Parameters
NAME                  1072B
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_               20191021
Time                   18.36
INSTRUM                spect
PROBHD   5 mm BBO BB-1H
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      1024
DS                         4
SWH               18028.846 Hz
FIDRES             0.275098 Hz
AQ                 1.8175818 sec
RG                       287
DW                    27.733 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                       9.50 usec
PL1                      0.00 dB
SFO1             75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                     -2.00 dB
PL12                    17.37 dB
PL13                    20.00 dB
SFO2            300.1312005 MHz

F2 - Processing parameters
SI                        32768
SF               75.4677867 MHz
WDW                          EM
SSB                           0
LB                       1.00 Hz
GB                            0
PC                       1.40
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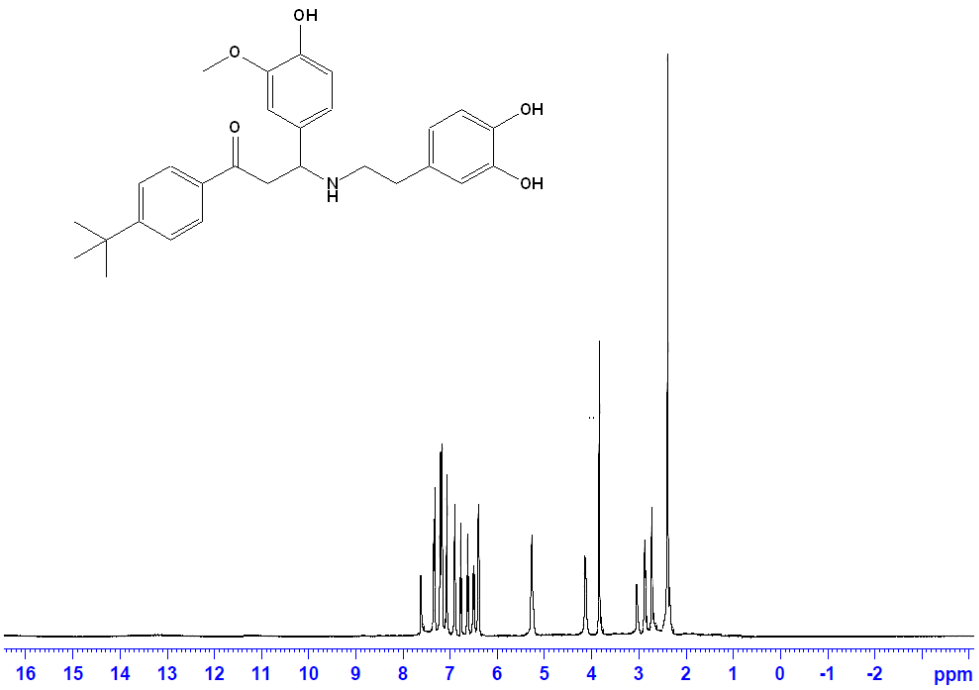
^{13}C NMR of the compound 1k

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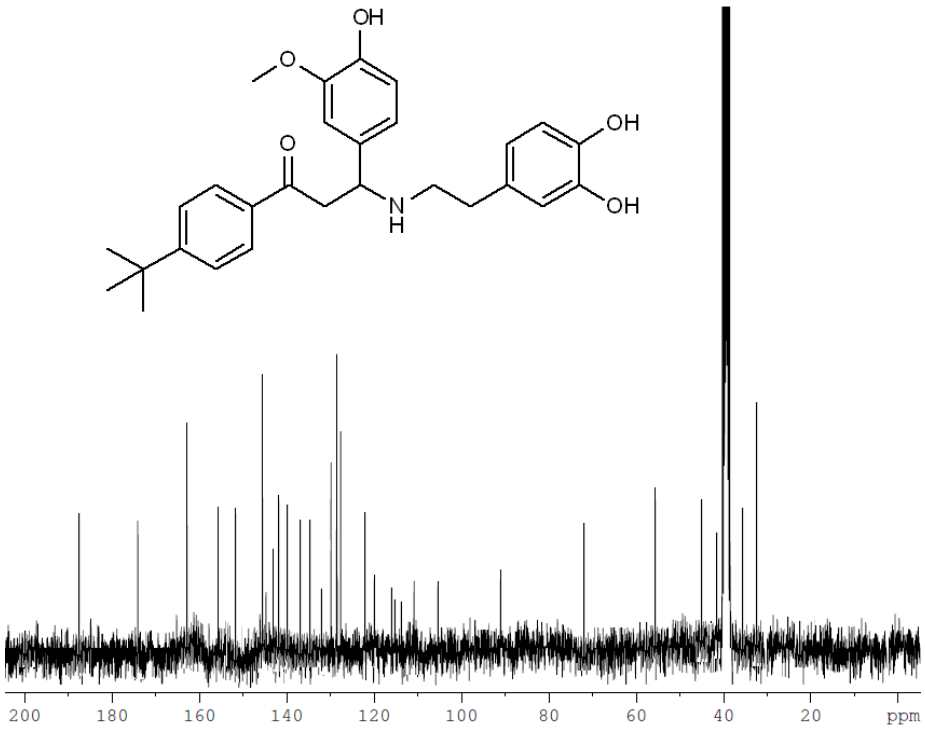
Current Data Parameters
NAME                  EXT40414
EXPNO                       12
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20190522
Time                     11.48
INSTRUM                  spect
PROBHD    5 mm PABBO BB/
PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                          16
DS                           2
SWH                 8223.685 Hz
FIDRES              0.125403 Hz
AQ                  3.9846387 sec
RG                      88.69
DW                     60.800 usec
DE                      6.50 usec
TE                     295.9 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       14.25 usec
PLW1               14.00000000 W
SFO1               400.2604718 MHz

F2 - Processing parameters
SI                          65536
SF                 400.2580000 MHz
WDW                            EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
TI
```

^{1}H NMR of the compound 1l

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Current Data Parameters
NAME                      1072B
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20191020
Time                      18.46
INSTRUM                   spect
PROBHD    5 mm BBO BB-1H
PULPROG                 zgpg30
TD                       65536
SOLVENT                   DMSO
NS                        1024
DS                           4
SWH                 18028.846 Hz
FIDRES              0.275098 Hz
AQ                  1.8175818 sec
RG                         287
DW                     27.733 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                       9.50 usec
PL1                      0.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                     -2.00 dB
PL12                    17.37 dB
PL13                    20.00 dB
SFO2              300.1312005 MHz

F2 - Processing parameters
SI                          32768
SF                 75.4677867 MHz
WDW                            EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```

^{13}C NMR of the compound 1l

Experimental for Biological activity

Antioxidant activity

DPPH method

DPPH (2,2-diphenyl-1-picrylhydrazyl) antioxidant activity was screened for all compounds (**1a-l**). DPPH antioxidant activity was screened for various concentration (10, 25, 50, and 100µg/mL) of tested compounds. Accordingly, extracts were examined for their ability to prevent the bleaching of the purple colored methanol solution of 1,1-diphenyl-1-picrylhydrazyl(DPPH). Aliquots (1.6 mL) teat sample were added to 1.6mL of 0.004% (w/v) methanol solution of DPPH at room temperature, absorbance was read against a blank at 517nm.

Percentage inhibition was calculated by.

DPPH Scavenging effect (%) = $[(A_{control} - A_{sample}) / A_{control}] \times 100$

H_2O_2 scavenging activity

Hydrogen peroxide scavenging activity was screened for all compounds (**1a-1l**). A solution of H_2O_2(40 mM) was prepared in phosphate buffer (pH 7.4). Test compound (3.4 mL) (10, 25, 50, and 100µg/mL) with phosphate buffer were added to H_2O_2solution (0.6 mL, 40 mM). Absorbance of reaction mixtures was recorded at 230 nm. Percentage inhibition of H_2O_2 scavenging was calculated by.

% Inhibition = $[(A_{control} - A_{sample}/ A_{control}) \times 100]$

NO scavenging activity

The compounds (**1a-1l**) was screened for Nitric oxide scavenging activity. Sodium nitroprusside (1 mL, 10 mM) and 1.5mL of phosphate buffer saline (0.2M, pH 7.4) were added to different concentrations (10, 25, 50, and 100µg/mL) of test sample incubated for 150 min at 25°C. Aliquots (1 mL) of reaction mixtures were then treated with 1 mL of Griess reagent (1% sulfanilamide, 2% H_3PO_4 and 0.1% naphthylethylene diamine dihydrochloride).

Percentage inhibition of H_2O_2 scavenging was calculated by.

% NO Scavenging = $[(A_{control} - A_{sample}/ A_{control}) \times 100]$

Where $A_{control}$ is the absorbance of the control reaction, and A_{sample} is the absorbance of the test compounds.

Antioxidant – ($ABTS^{\bullet+}$) scavenging activity

The compounds (1a-1l) were screened for $ABTS^{\bullet+}$ scavenging activity. The $ABTS^{\bullet+}$ radical cation was produced by the reaction of 7 mM aqueous ABTS with 2.45 mM potassium persulfate in the dark at room temperature for 12 h. Prior to the experiment, the $ABTS^{\bullet+}$ solution was diluted with phosphate buffer (0.1 M, pH 7.4) to an absorbance of 0.700 ± 0.025 at 734 nm. Subsequently, 1 mL of the diluted solution was added to 1.5-mL aliquots of ethanolic solutions of (**1a-1l**) with different concentrations (10, 25, 50,100 μg/mL). After 30 min, the percentage of inhibition at 734 nm was calculated for each concentration relative to a blank sample (ethanol).

The capability of scavenging the $ABTS^{\bullet+}$ radical was calculated using the following equation:

$$ABTS^{\bullet+} \text{ scavenging effect (\%)} = [(A_c - A_s)/A_c] \times 100\%$$

where A_c is the initial absorbance of $ABTS^{\bullet+}$, and A_s is the absorbance in presence of **2a–f** and **4a–f**.

Inhibition of AAPH assays free radical analysis

All synthesised compounds (**1a-1l**) were screened for linoleic acid peroxidation. The production of the conjugated diene hydroperoxide by oxidation of linoleic acid in an aqueous dispersion was monitored at 234 nm, with 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) used as a free radical initiator. This assay can be used to follow oxidative changes and determine the inhibition of linoleic acid peroxidation induced by each compound tested. A 1-mL aliquot of a 16 mM linoleic acid dispersion was added to a UV cuvette containing 1 mL of 0.05 M phosphate buffer, pH 7.4, thermostatted at 37 °C. The oxidation reaction was initiated at 37 °C in air by adding 1 mL of the 40 mM AAPH solution. Oxidation was carried out in the presence of 1 mL of the tested compounds (10, 25, 50, and 100μg/mL) (**1a-1l**). In the absence of antioxidants, the lipid oxidation was monitored in presence of the same amount of DMSO. The rate of oxidation at 37 °C was monitored by recording the absorption increase at 234 nm caused by the formation of a conjugated diene hydroperoxide, with the corresponding data provided in Table 3.

The percentage of linoleic acid oxidation inhibition was calculated as follows:

% Inhibition = [(1 – rate of absorbance change with test compound)/rate of absorbance change with solvent control] × 100%

Anti-tyrosinase activity

All compounds (**1a-1j**) were screened for anti-tyrosinase screening. The Mushroom tyrosinase (powder, ≥1000 unit/mg solid, EC 1.14.18.1) inhibitory activities were measured spectrophotmetrically.

Tyrosinase inhibitory activities were measured spectrophotometrically according to a modified method using Mushroom tyrosinase (EC 1.14.18.1, lyophilized powder, _1000 unit/mg solid, Sigma Chemical Co.) and L-DOPA as substrate. Briefly, a reaction mixture (3.0 mL of final volume) containing 1.5 mM L-DOPA, 0.1 mM sodium phosphate buffer (pH 6.5), 12.428 U of mushroom tyrosinase, and the test sample was incubated at 30 ºC for 2 min. The formation of dopachrome was determined spectrophotometrically by monitoring absorption at 475 nm using a lambda 850 spectrophotometer. Kojic acid was used as a positive control. Percentage tyrosinase inhibition was calculated using the

following equation:

Tyrosinase inhibitory activity (%) = [(A-B)-(C-D)]/ (A-B) × 100

Where A is the absorbance of the blank solution after incubation, B is the absorbance of the blank solution before incubation, C is the absorbance of a sample solution after incubation, and D is the absorbance of the sample solution before incubation.

Cell lines and cell culture

The cell lines, MCF-7 and normal cell lines were obtained from the American Type Cell Collection (ATCC; Manassas, VA, USA). The cells were cultured at 37ºC and 5% CO_2 environment to get 70%–80% confluence in Dulbecco's Modified Eagle's Medium (DMEM; Gibco®□, Thermo Fisher Scientific, Waltham, MA, USA) with 10% fetal bovine serum (FBS) (Gibco®□).

Cytotoxic screening

The newly synthesized compounds **(1a-11)** were screened for cytotoxic activity according to a previously described procedure. MCF-7 and Vero cell lines were treated with these compounds at one primary cytotoxic assay dose of 100µM for 48 h (MTT anticancer assay). Doxorubicin was used as a standard.

The screening results were expressed in terms of the growth inhibitor concentration (GI_{50}), total growth of inhibition (TGI), and lethal concentration (LC_{50}).

In the current protocol, all cell lines were pre-incubated on a microtiter plate. The results of each test were reported as the growth percentage of treated cells compared to untreated control cells.

Compounds reducing the growth of cell lines to approximately 32% or less were described as having cytotoxic activity. The cells lines were seeded into 96-well plates at a density of 5000 cells per well, A 0.1mL aliquot of the cell suspension and 0.1 mL of the test solution (6.25–100 µg in 1% DMSO, with the final DMSO concentration in media less than 1%) were added to the wells, with the plates kept in an incubator (5% CO_2) at 37 °C for 72 h. The blank sample contained only the cell suspension, and the control wells contained 1% DMSO and the cell suspension. After 72 h, 20 µL of MTT was added, and the plates were kept in the CO_2 incubator for 2 h, followed by the addition of propanol (100 µL). The plates were covered with aluminum foil to protect them from light and subsequently agitated in a rotary shaker for 10–20 min. Afterwards, the 96-well plates were processed on an ELISA reader to obtain absorption data at 562 nm.

The experiment was performed in triplicate. Percent proliferation inhibition was calculated using the following formula:

Viability cells inhibition (%) =100-[(At-Ab)/(Ac-Ab)]x 100%

At = absorption of test compound, Ab = absorption of blank, Ac = absorption of control.

The concentration of the synthesized compounds required to inhibit 50% of the growth of the cell lines (IC50 values) was calculated by analyzing the relationship between concentrations and percent (%) inhibitions using GraphPad Prism 7 version 7.00 forWindows, GraphPad Software, La Jolla, CA, USA, www.graphpad.com.

The NCI renamed the IC50 value, the concentration that causes 50% growth inhibition, the GI_{50} value to emphasize the correction for the cell count at time zero; thus, GI50 is the concentration of test drug where 100 × (T - T0)/(C - T0) = 50 (1, 2). The optical density of the test well after a 48-h period of exposure to test drug is T, the optical density at time zero is T0, and the control optical density is C. The “50” is called the GI50PRCNT, a T/C-like parameter that can have values from +100 to -100. The GI50 measures the growth inhibitory power of the test agent.

The TGI is the concentration of test drug where 100 × (T - T0)/(C - T0) = 0. Thus, the TGI signifies a cytostatic effect. The LC_{50}, which signifies a cytotoxic effect, is the concentration of drug where 100 × (T - T0)/T0 = -50