Supporting information

Design, Synthesis, In Silico Studies and In Vitro Evaluation of New Indole- and/or Donepezil-like Hybrids as Multitarget-Directed Agents for Alzheimer's Disease

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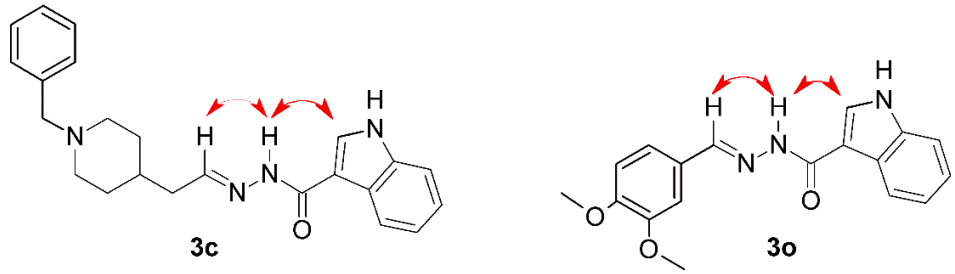
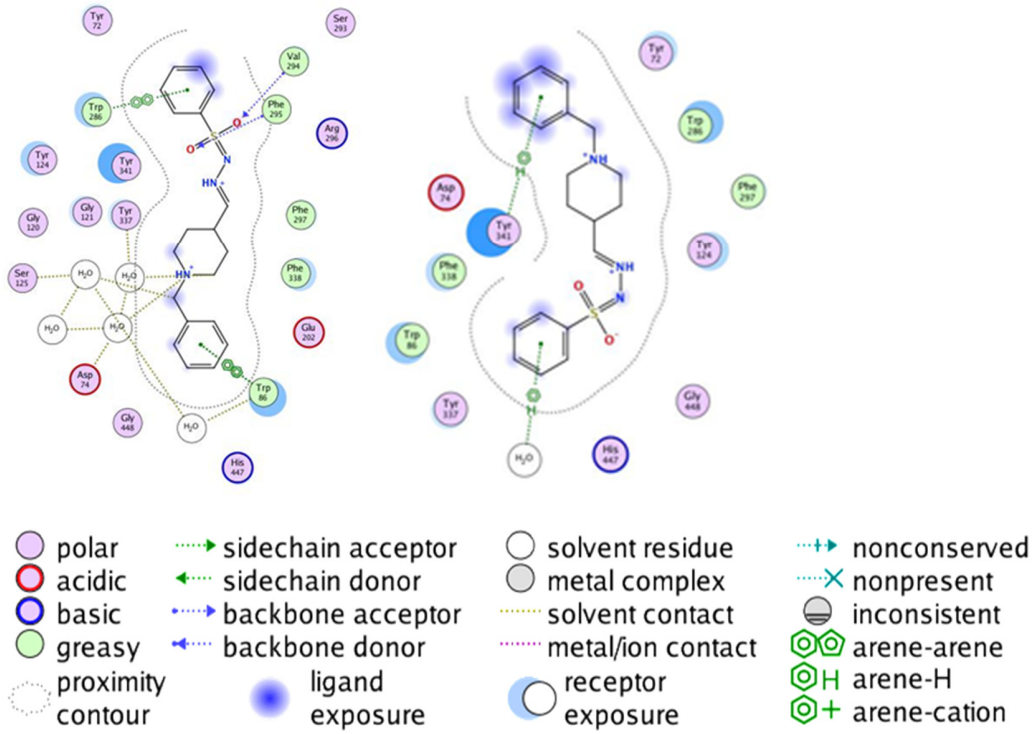


Figure S1. Key NOESY correlations of hydrazide-hydrazones **3c** and **3o**

Molecular docking of compound 5a in the active site of AChE (PDB ID 4EY7)

a)



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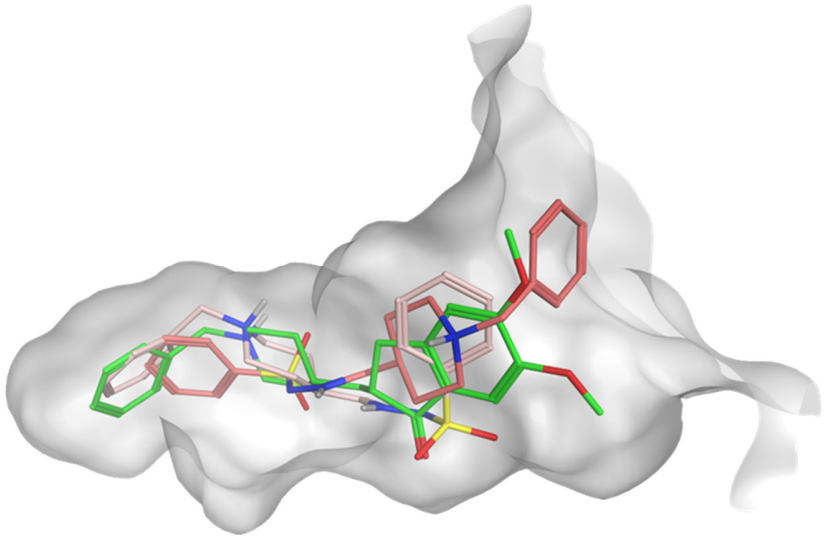


Figure S2. Docking results of compound **5a**: a) left – PLIs of the highest ranked pose; right – PLI of the second highest ranked pose; b) the best pose of donepezil (green), the highest ranked pose (light pink) and the second highest ranked pose (dark pink) in the active site of AChE (PDB ID 4EY7)

Visualization of the pocket of MT1 and MT2 receptors as well as detailed data of the docking results

Table S1. RMSD of CA of the active site residues between aligned chains of selected PDB structures for MT1 modeling

Chains	1	2	3	4	5	6	7
1:6ME2.A		0.18	0.21	0.22	1.1	1.04	0.84
2:6ME3.A	0.18		0.22	0.21	1.13	1	0.84
3:6ME4.A	0.21	0.22		0.23	1.12	1.01	0.85
4:6ME5.A	0.22	0.21	0.23		1.12	1.04	0.88
5:7DB6.D	1.1	1.13	1.12	1.12		1.4	1.23
6:7VGY.A	1.04	1	1.01	1.04	1.4		0.72
7:7VGZ.B	0.84	0.84	0.85	0.88	1.23	0.72	

Table S2. Similarity of PDB sequences of selected PDB structures for modeling MT1 receptor according to BLUSSUM62

Chains	1	2	3	4	5	6	7
1:6ME2.A		100	100	100	96.4	96.4	96.4
2:6ME3.A	100		100	100	96.4	96.4	96.4
3:6ME4.A	100	100		100	96.4	96.4	96.4
4:6ME5.A	100	100	100		96.4	96.4	96.4
5:7DB6.D	96.4	96.4	96.4	96.4		100	100
6:7VGY.A	96.4	96.4	96.4	96.4	100		100
7:7VGZ.B	96.4	96.4	96.4	96.4	100	100	

Table S3. RMSD of CA of the active site residues between aligned chains of selected PDB structures for MT2 modeling

Chains	1	2	3	4	5	6	7	8	9	10
1:6ME6.A		0.12	0.3	0.31	0.23	0.25	0.28	0.29	0.53	0.9
2:6ME6.B	0.12		0.35	0.31	0.23	0.22	0.3	0.28	0.52	0.95

3:6ME7.A	0.3	0.35		0.14	0.36	0.39	0.41	0.42	0.61	0.91
4:6ME7.B	0.31	0.31	0.14		0.36	0.36	0.42	0.41	0.61	0.96
5:6ME8.A	0.23	0.23	0.36	0.36		0.08	0.17	0.18	0.54	0.93
6:6ME8.B	0.25	0.22	0.39	0.36	0.08		0.2	0.18	0.55	0.96
7:6ME9.A	0.28	0.3	0.41	0.42	0.17	0.2		0.09	0.58	0.94
8:6ME9.B	0.29	0.28	0.42	0.41	0.18	0.18	0.09		0.58	0.96
9:6PS8.A	0.53	0.52	0.61	0.61	0.54	0.55	0.58	0.58		0.95
10:7VH0.A	0.9	0.95	0.91	0.96	0.93	0.96	0.94	0.96	0.95	

Table S4. Similarity of PDB sequences of selected PDB structures for modeling MT2 receptor according to BLUSSUM62

Chains	1	2	3	4	5	6	7	8	9	10
1:6ME6.A		98.6	99	98.3	99	98.6	98.6	97.9	81.8	96.4
2:6ME6.B	99		98.6	98.3	98.6	98.6	98.3	97.9	81.8	96.4
3:6ME7.A	98.6	97.9		98.6	98.3	97.9	97.9	97.2	81.1	96
4:6ME7.B	98.3	97.9	99		97.9	97.9	97.6	97.2	81.1	96
5:6ME8.A	99.3	98.6	99	98.3		98.6	98.6	97.9	81.8	96.4
6:6ME8.B	99	98.6	98.6	98.3	98.6		98.3	97.9	81.8	96.4
7:6ME9.A	99.3	98.6	99	98.3	99	98.6		98.6	81.8	96.4
8:6ME9.B	99	98.6	98.6	98.3	98.6	98.6	99		81.8	96.4
9:6PS8.A	81.5	81.2	81.1	80.8	81.2	81.2	81	80.7		81.3
10:7VH0.A	93.4	93.1	93.4	93	93.1	93.1	92.7	92.4	79	

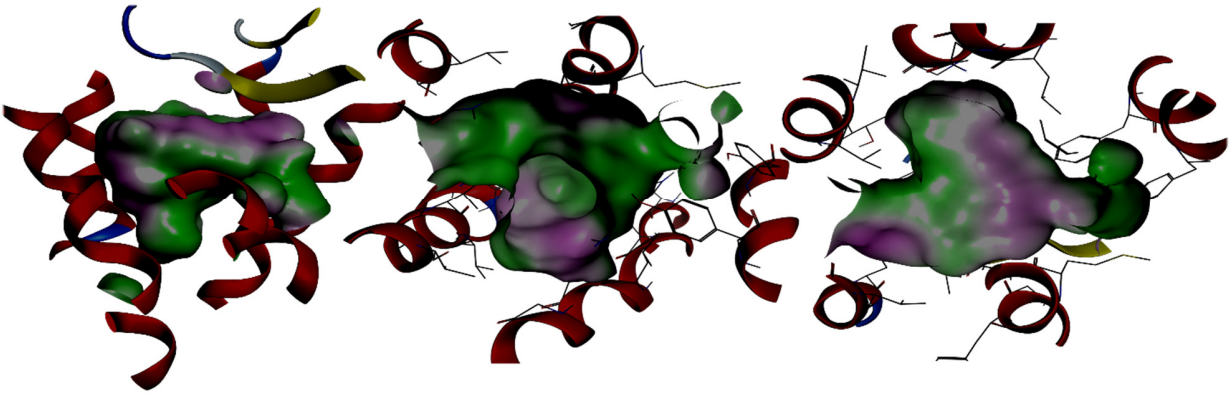
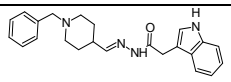
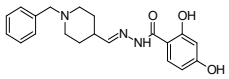
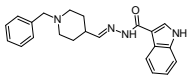
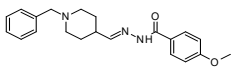
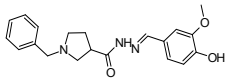
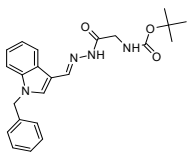
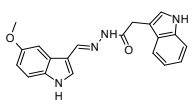
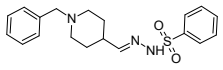
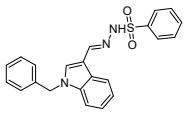
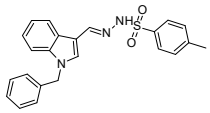
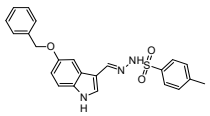


Figure S3. Side, up and down view, respectively, of the pocket that forms the active site in our model of the MT1 receptor (lipophilic parts of the pocket are in green, while hydrophilic are represented in pink)

Table S5. The best results from induced fit docking of ligands on MT1 receptor according to GBVI/WSA scoring function (kcal/mol)

Name	Formula	Score
3a		-27.1
3b		-23.0
3c		-26.7
3d		-23.0
3i		-25.8
3m		-22.4
3n		-20.1
5a		-26.0

5d		-20.8
5g		-21.8
5j		-22.9

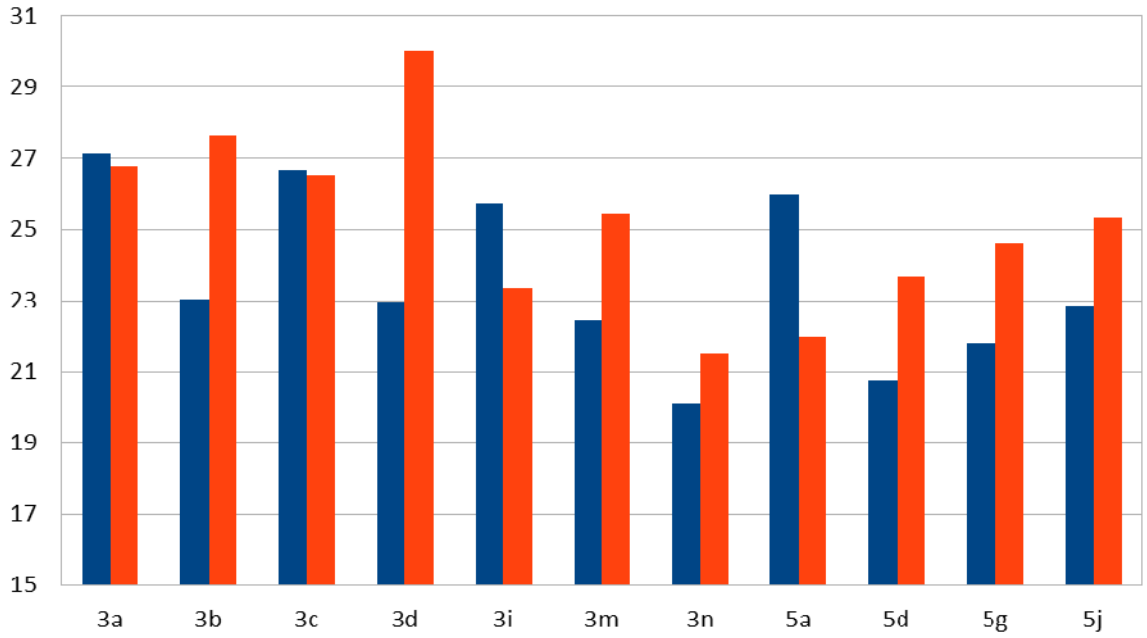


Figure S4. The best interaction energies of our ligands with the MT1 (blue) and MT2 (red) receptors according to GBVI/WSA scoring function (kcal/mol)

In order to elucidate functional groups that are essential for receptor-ligand interactions in our case a Protein Ligand Interaction Fingerprints (PLIF) analysis was performed. Being method for summarizing the interactions between ligands and receptor using a fingerprint scheme it reveals which binding site residues tends to interact with which parts of the ligands.

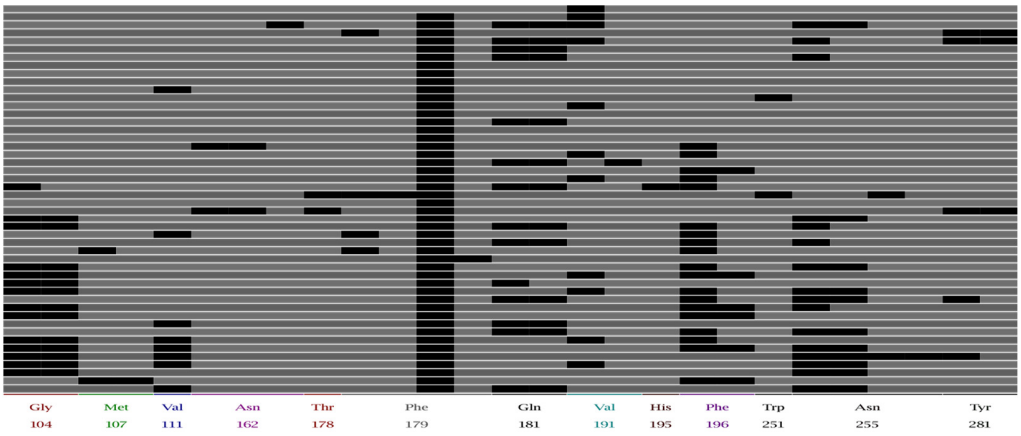


Figure S5. PLIF Barcode map of interaction between the best 50 ligands poses and amino acids of the active site cavity of the MT1 receptor.

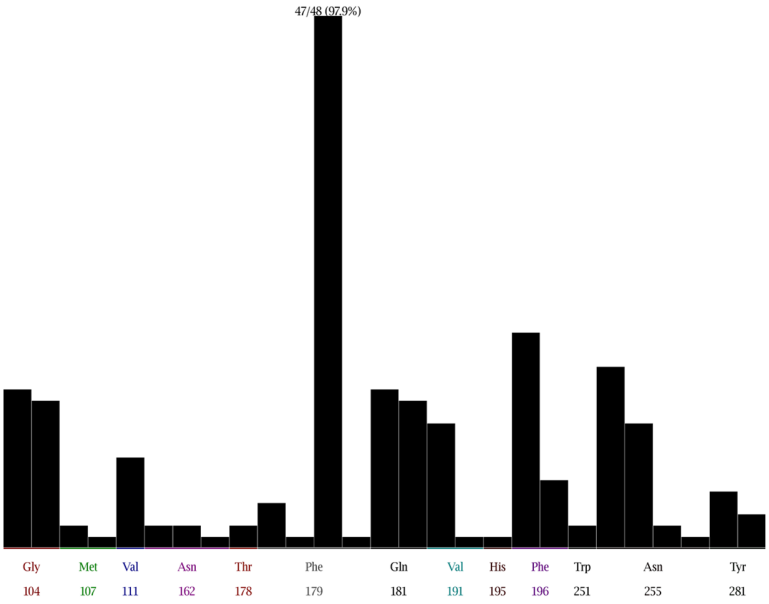


Figure S6. Population histogram of the interactions of the first 50 ligand poses with residues inside active site of the receptor according to PLIF analysis (Phe179)

MT2 receptor docking results

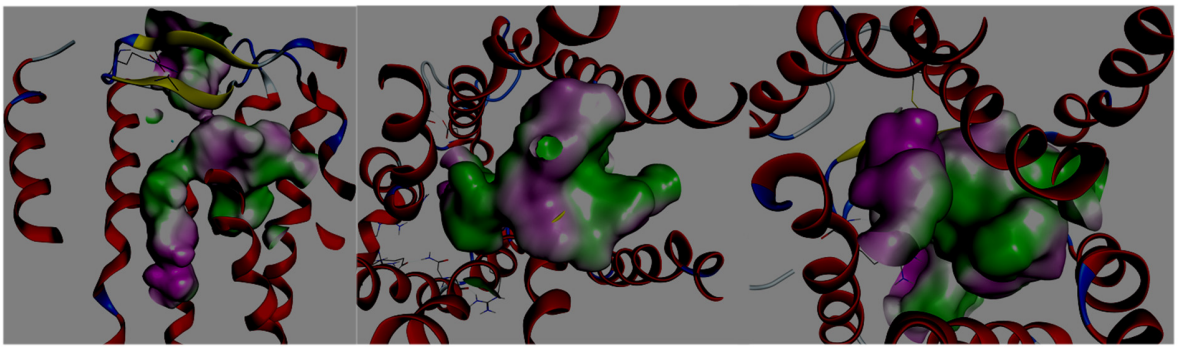


Figure S7. Side, up and down view, respectively, of the pocket that forms the active site in our model of the MT2 receptor (lipophilic parts of the pocket are in green, while hydrophilic are represented in pink)

Table S6. The best results from induced fit docking of ligands on MT2 receptor according to GBVI/WSA scoring function (kcal/mol)

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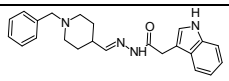
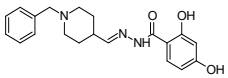
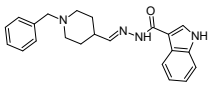
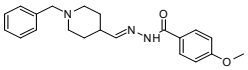
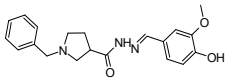
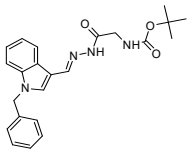
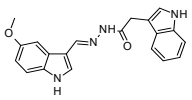
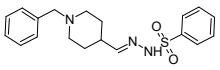
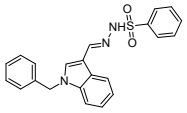
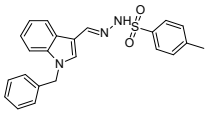
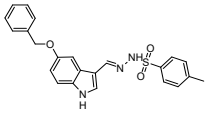
3a		-26.8
3b		-27.6
3c		-26.5
3d		-30.0
3i		-23.4
3m		-25.4
3n		-21.5

5a		-22.0
5d		-23.7
5g		-24.6
5j		-25.4

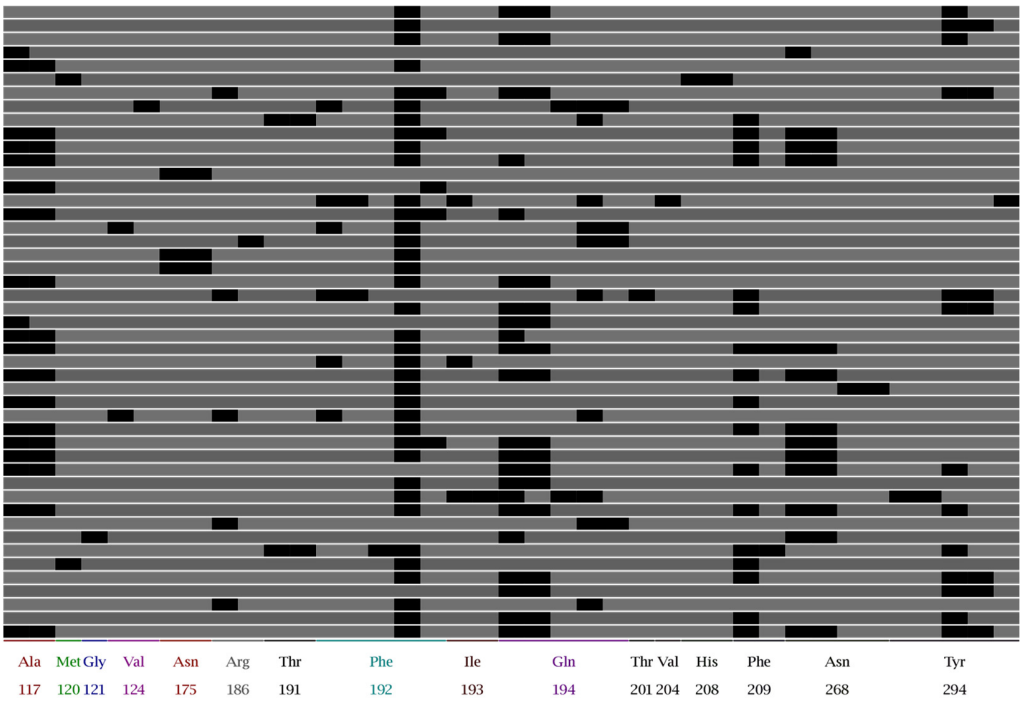


Figure S8. Barcode map of interaction between best 50 ligands poses and amino acids of the active site cavity of the MT2 receptor

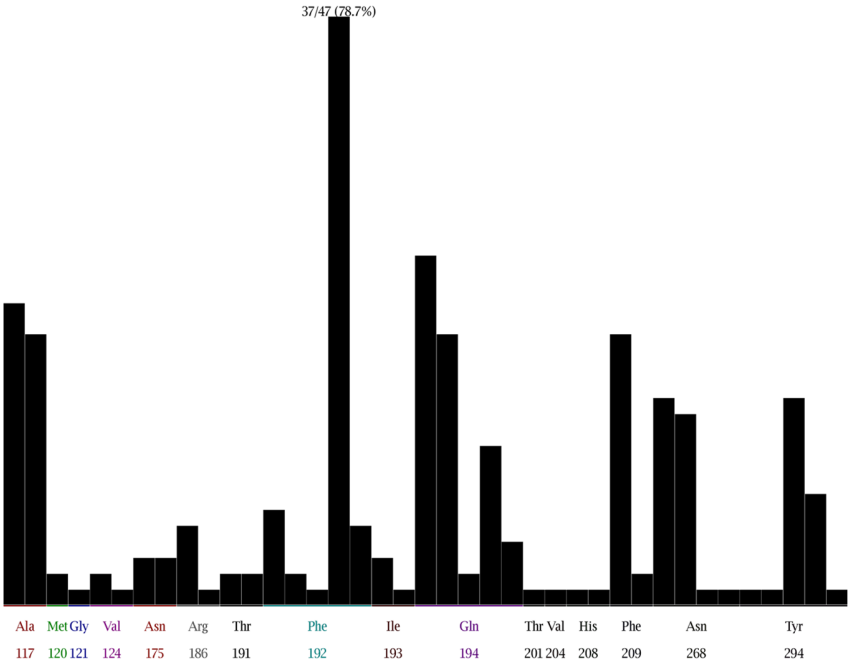


Figure S9. Population histogram of the interactions of the first 50 ligand poses with residues inside the active site of the receptor according to PLIF analysis

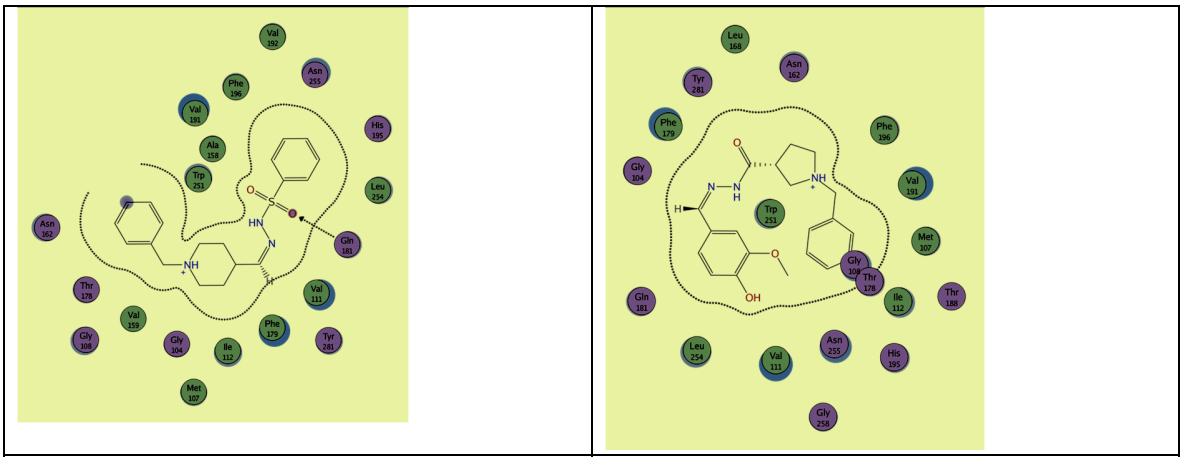


Figure S10. Interaction maps of the best poses of the third (**5a** left) and forth (**3i** right) of the best ligands for MT1 receptor

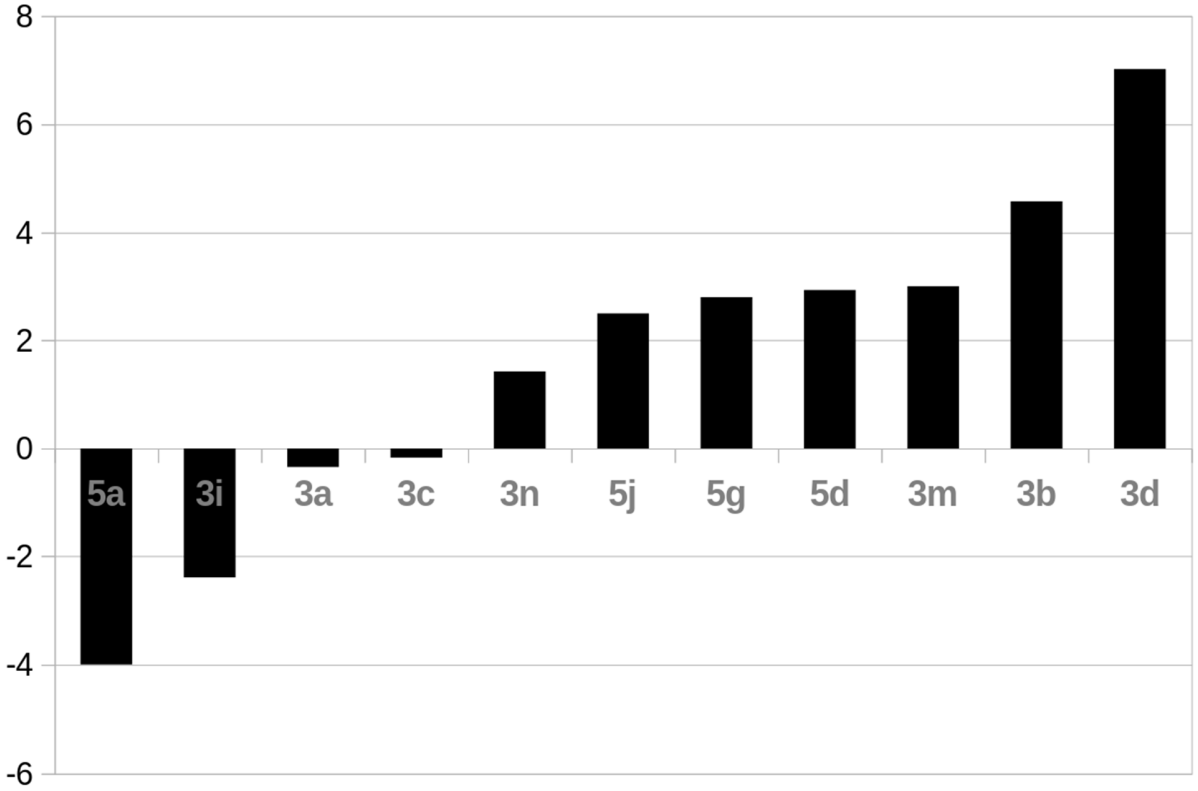


Figure S11. Difference between MT2 and MT1 receptor binding energies of our ligands (kcal/mol). Ligands with negative values prefer to bind to MT1, while ligands with positive values prefer to bind to MT2.

^{1}H NMR, ^{13}C NMR and HRMS spectra

1. ***N'-[(E)-(1-benzylpiperidin-4-yl)methylidene]-2-(1H-indol-3-yl)acetohydrazide,* 3a**

Yield: 68%; m.p. 167-168◦C. 1H NMR (400 MHz, DMSO-d6): 1:0.83 mixture of conformers; signals for major synperiplanar conformer around the amide bond: δ = 1.42-1.53 (m, 2H, CH2), 1.67-1.78 (m, 2H, CH2), 1.94-2.04 (m, 2H, CH2), 2.17-2.24 (m, 1H, H-4'), 2.77-2.82 (m, 2H, CH2), 3.46 (s, 2H, CH2), 3.90 (s, 2H, CH2), 6.98 (ddd, J=1.00, 7.0, 8.0 Hz, 1H, H-5), 7.05 (ddd, J=1.0, 7.0, 5.0 Hz, 1H, H-6), 7.17 (d, J=2.3 Hz, 1H, H-2), 7.22-7.33 (m, 10H, H-2'', H-3'', H-4'', H-5'' and H-6''), 7.35 (d, J=7.0 Hz, 1H, H-7), 7.44 (d, J=5.3 Hz, 1H, CH), 7.53 (d, J=8.2 Hz, 1H, H-4), 10.84 (s, 1H, NH), 10.85 (bs, 1H, NH); resolved signals for minor antiperiplanar conformer around the amide bond: 3.45 (s, 2H, CH2), 3.53 (s, 2H, CH2), 6.96 (ddd, J=1.0, 7.0, 8.0 Hz, 1H, H-5), 7.07 (ddd, J=1.0, 7.0, 5.0 Hz, 1H, H-6), 7.20 (d, J=2.3 Hz, 1H, H-2), 10.89 (bs, 1H, NH), 11.06 (s, 1H, NH); 13C NMR (100 MHz, DMSO-d6): signals for major synperiplanar conformer around the amide bond: δ = 28.85 (CH2), 29.06 (CH2), 38.10 (C-4'), 52.45 (CH2), 62.39 (CH2), 108.22 (C-3), 111.24 (C-7), 118.19 (C-5), 118.65 (C-4), 120.84 (C-6), 120.95 (C-5), 123.83 (C-2),

126.80 (C-4’’), 127.14 (C-4a), 127.39 (C-4a), 128.11 (C-3’’ and C-5’’), 128.73 (C-2’’ and C-6’’), 135.95 (C-7a), 138.51 (C-1’’), 149.21 (CH), 166.66 (C=0); resolved signals for minor antiperiplanar conformer around the amide bond: 152.96 (CH), 172.20 (C=O). HRMS (ESI) *m/z*: calcd: [M+H]+ 375.217938. Found: [M+H]+ 375.2178

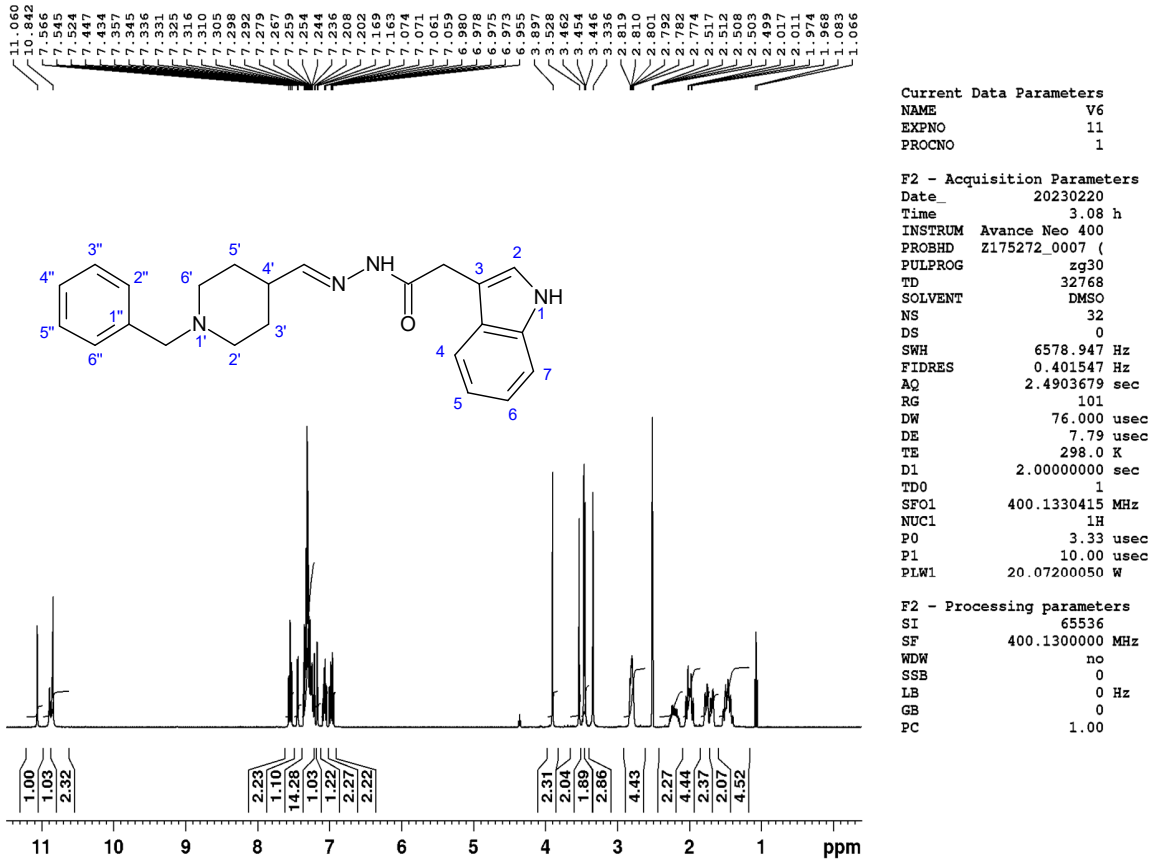
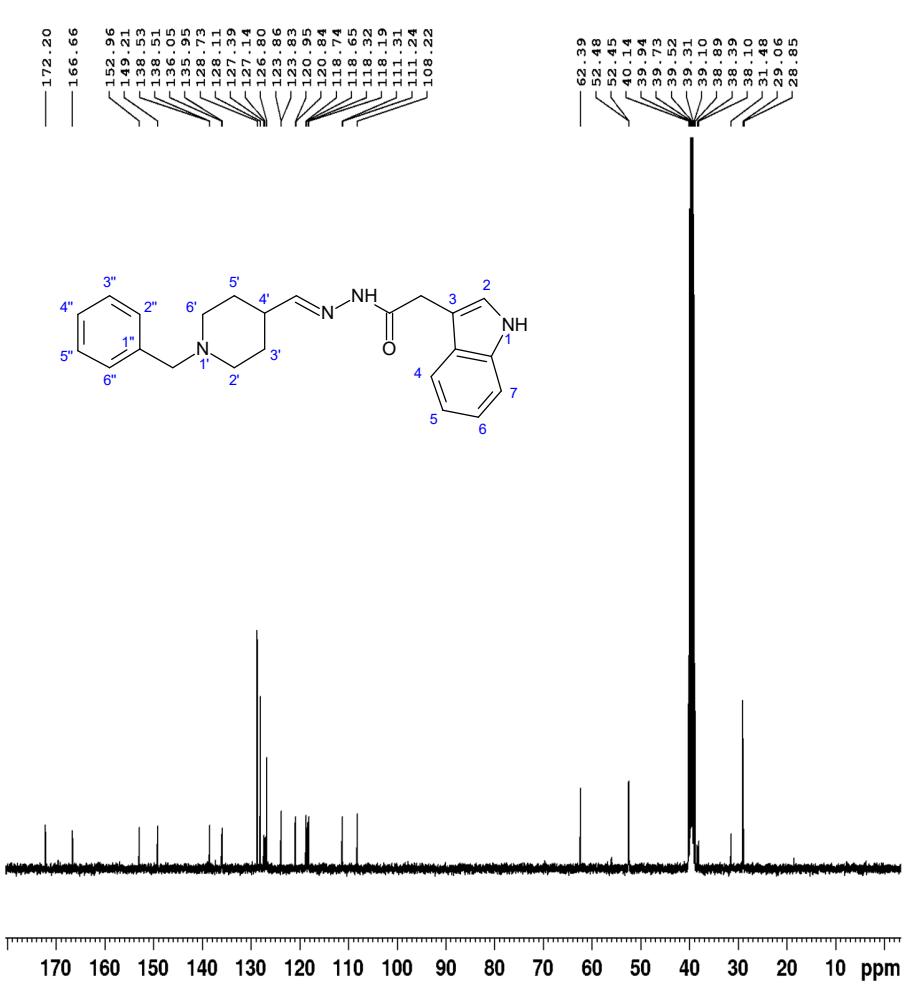


Figure S12. ^{1}H NMR spectrum of compound **3a** in DMSO-d_6

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SOLVENT             DMSO
NS                  1024
DS                     0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ              0.6881280 sec
RG                    36
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1           1.50000000 sec
D11          0.03000000 sec
TD0                    1
SF01        100.6238383 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1         58.46900177 W
SF02         400.1316008 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         20.07200050 W
PLW12         0.24781001 W

F2 - Processing parameters
SI                 65536
SF          100.6128173 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                  1.40
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Figure S13. ^{13}C NMR spectrum of compound **3a** in DMSO-d_6

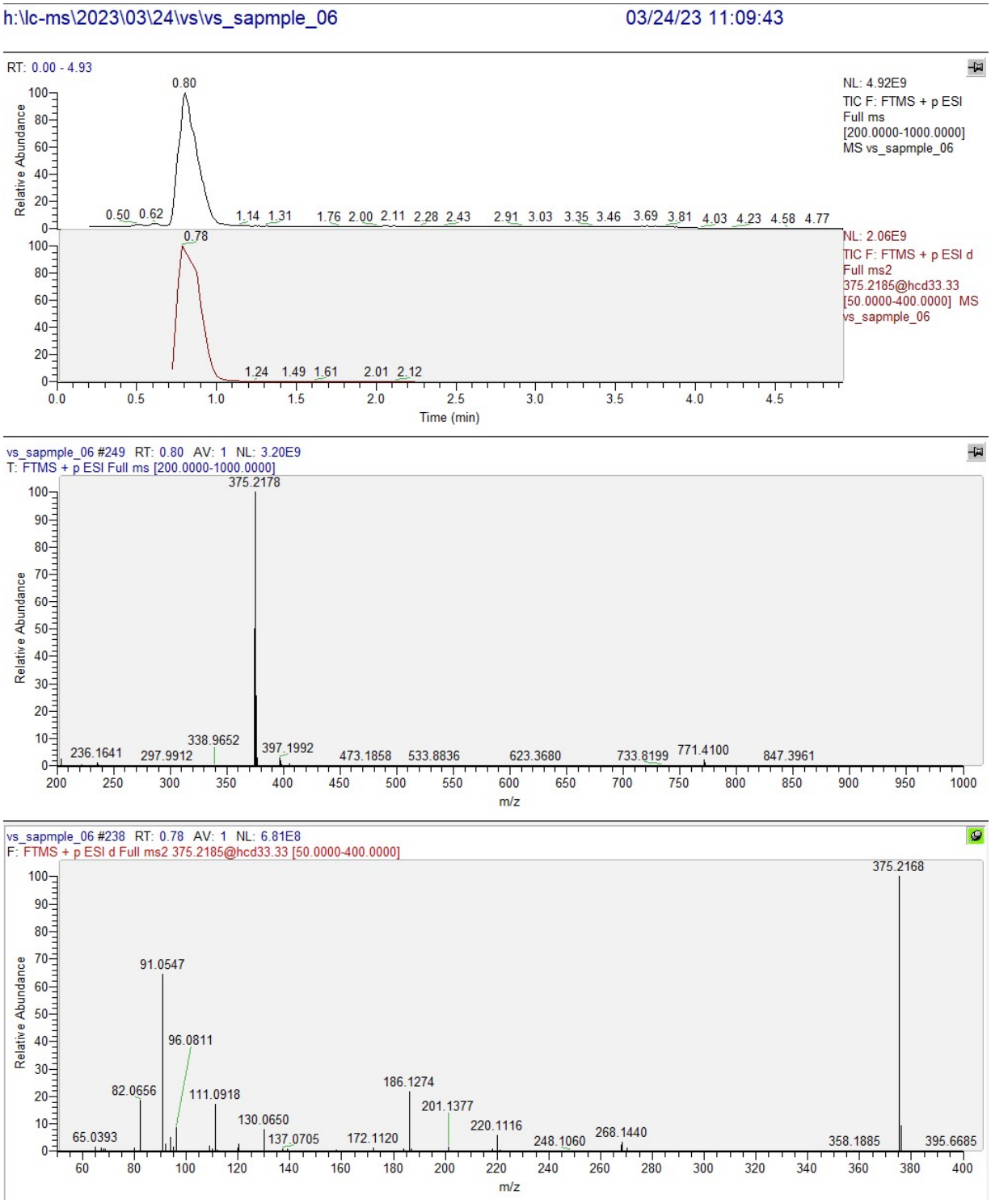
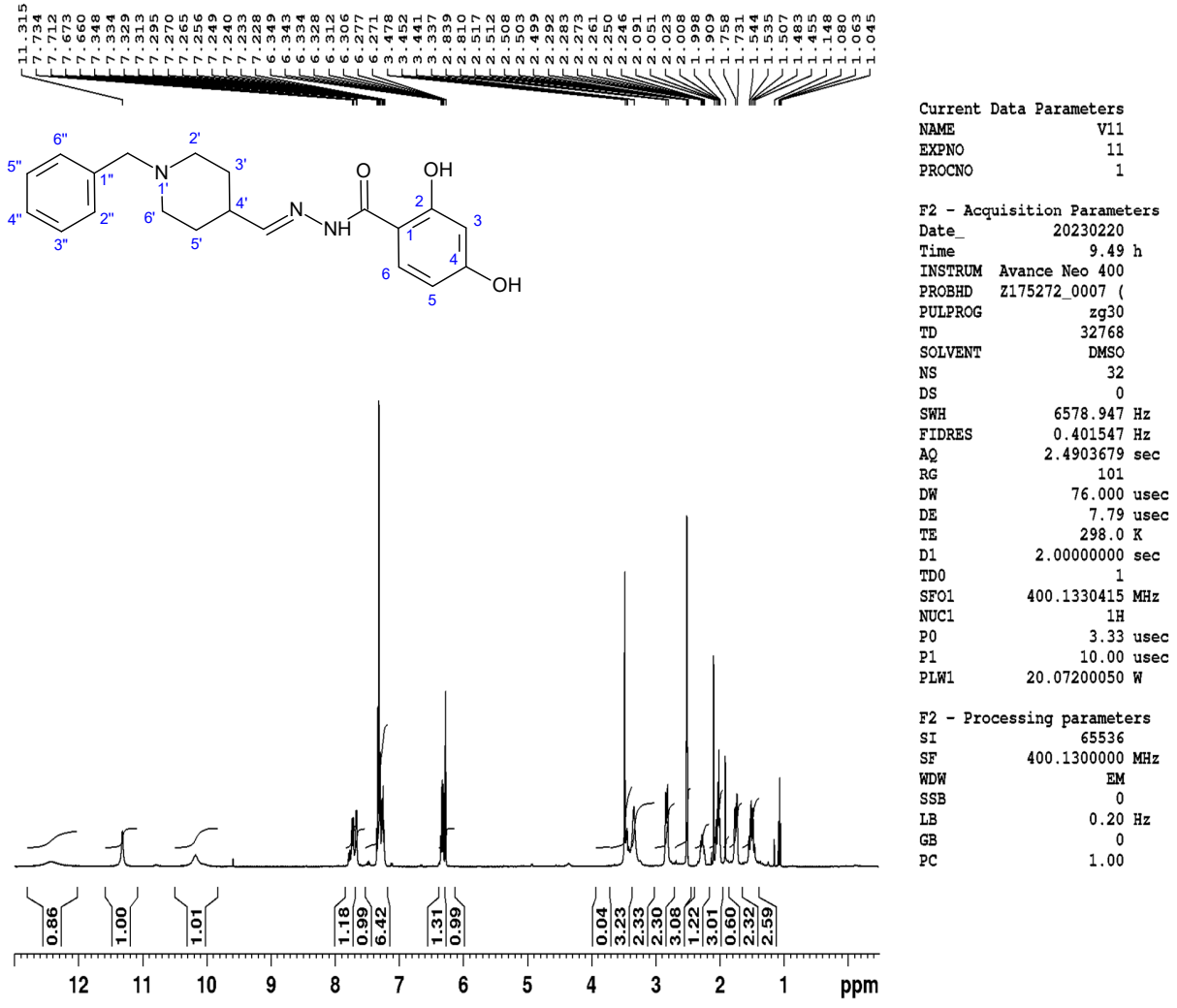


Figure S14. HRMS of compound **3a**

2. N'-[(E)-(1-benzylpiperidin-4-yl)methylidene]-2,4-dihydroxybenzohydrazide, **3b**

Yield: 59%; m.p. 201-203◦C.[1]H NMR (400 MHz, DMSO-d_6): δ = 1.46 (dd, J=3.1, 11.7, 1H) and 1.52 (dd, J=3.1, 11.7 Hz, 1H, CH_2), 1.74 (dd, J=2.7, 13.5 Hz, 2H, CH_2), 2.00-2.05 (m, 2H, CH_2), 2.22-2.34 (m, 1H, H-4'), 2.82 (d, J=11.4 Hz, 2H, CH_2), 3.48 (s, 2H, CH_2), 6.27 (d, J=2.3 Hz, 1H, H-3), 6.32 (dd, J=2.3, 8.7 Hz, 1H, H-5), 7.23-7.35 (m, 5H, Ar), 7.67 (d, J=5.0 Hz, 1H, CH), 7.72 (d, J=8.7 Hz, 1H, H-6), 10.17 (bs, 1H, OH), 11.32 (bs, 1H, NH), 12.44 (bs, 1H, OH).
[13]C NMR (100 MHz, DMSO-d_6): δ = 29.00 (C-3' and C-5'), 38.53 (C-4'), 52.42 (C-2' and C-6'), 62.36 (CH_2), 102.81 (C-3), 105.87 (C-1), 107.19 (C-5), 126.86 (C-4''), 128.13 (C-3'' and C-5''), 128.78 (C-2'' and C-6''), 129.35 (C-6), 138.41 (C-1''), 155.26 (CH), 162.49 and 162.53 (C-2 and C-4), 165.44 (C=O).
HRMS (ESI) *m/z*: calcd: [M+H]+ 354.181218. Found: [M+H]+ 354,1811



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PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
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SWH 6578.947 Hz
FIDRES 0.401547 Hz
AQ 2.4903679 sec
RG 101
DW 76.000 usec
DE 7.79 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1
SFO1 400.1330415 MHz
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P0 3.33 usec
P1 10.00 usec
PLW1 20.07200050 W

F2 - Processing parameters
SI 65536
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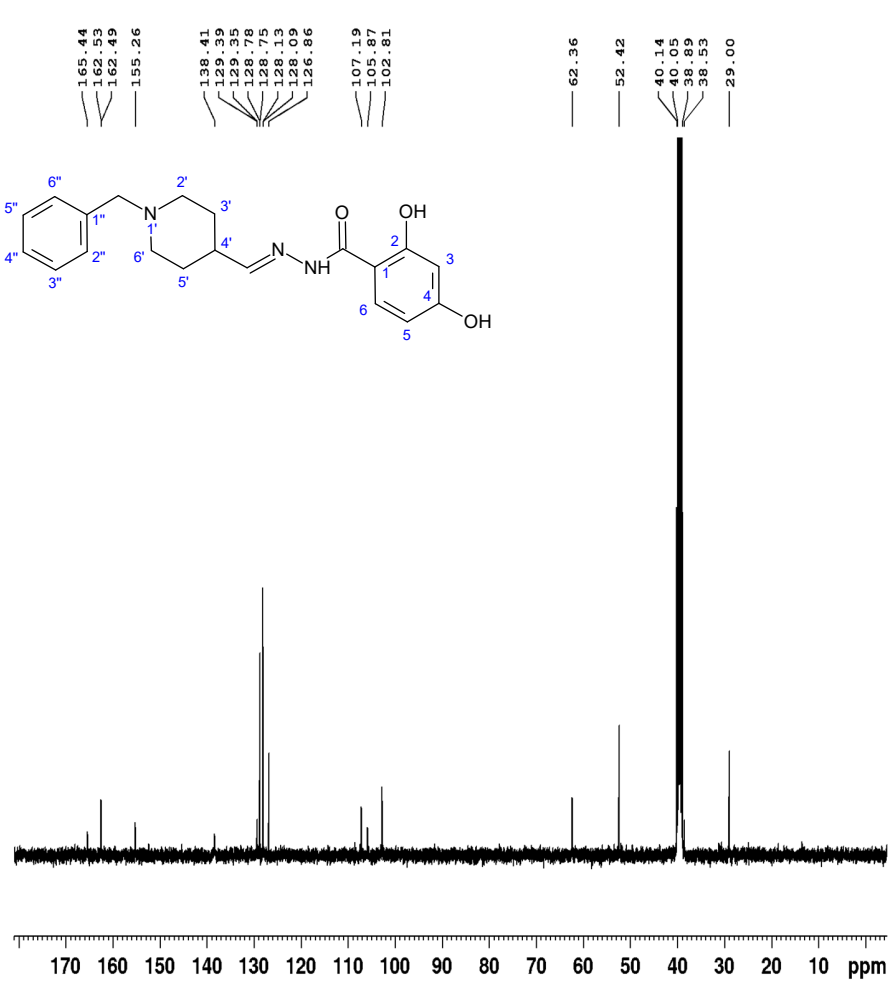
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

Figure S15. [1]H NMR spectrum of compound **3b** in DMSO-d_6

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EXPNO                   14
PROCNO                   1

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PULPROG           zgdc30
TD                 32768
SOLVENT             DMSO
NS                  1024
DS                     0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ              0.6881280 sec
RG                    36
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1           1.50000000 sec
D11          0.03000000 sec
TD0                    1
SFO1        100.6238383 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1        58.46900177 W
SFO2        400.1316008 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2              90.00 usec
PLW2        20.07200050 W
PLW12        0.24781001 W

F2 - Processing parameters
SI                 65536
SF          100.6128169 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 0.10
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Figure S16. ^{13}C NMR spectrum of compound **3b** in DMSO-d_6

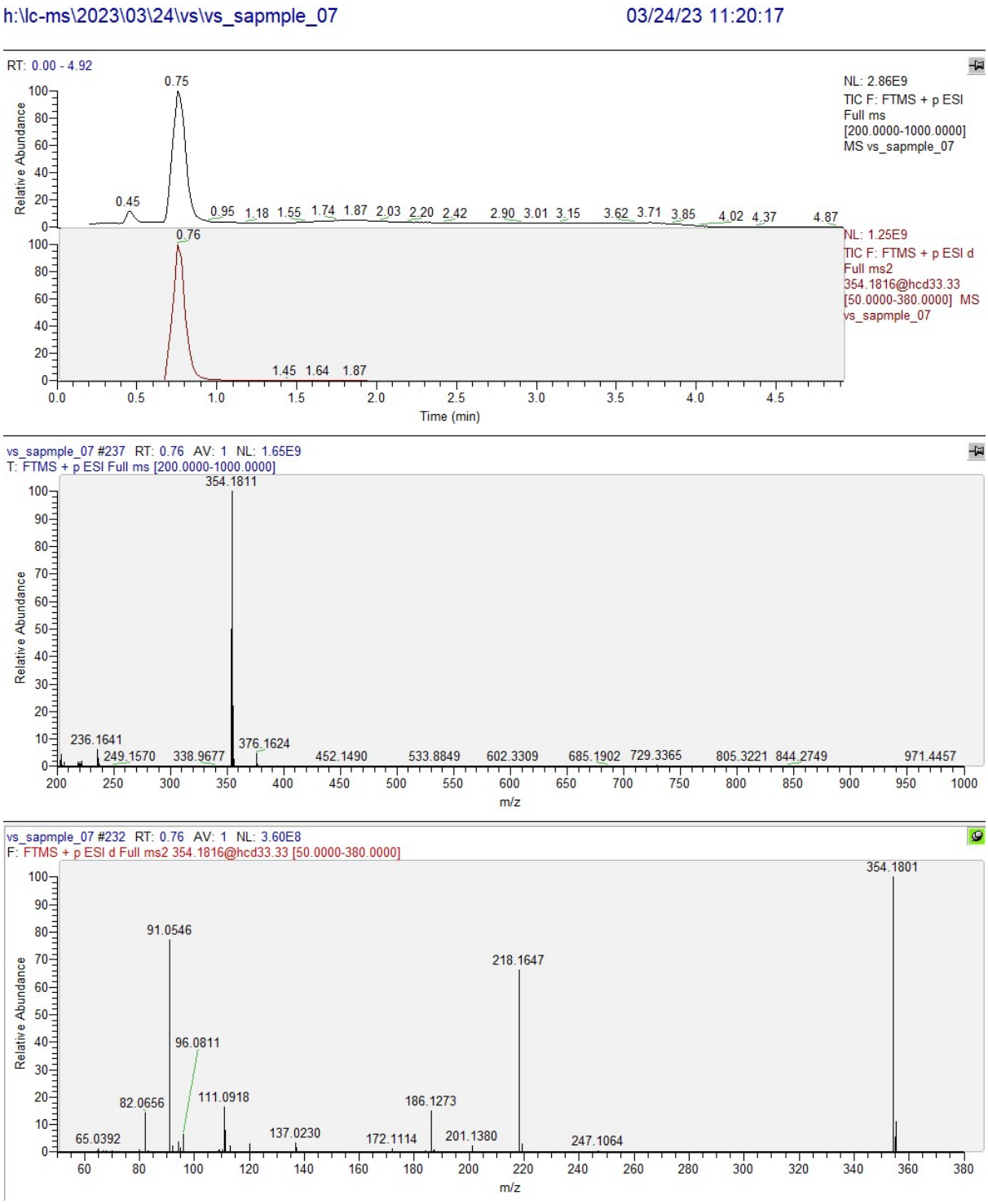
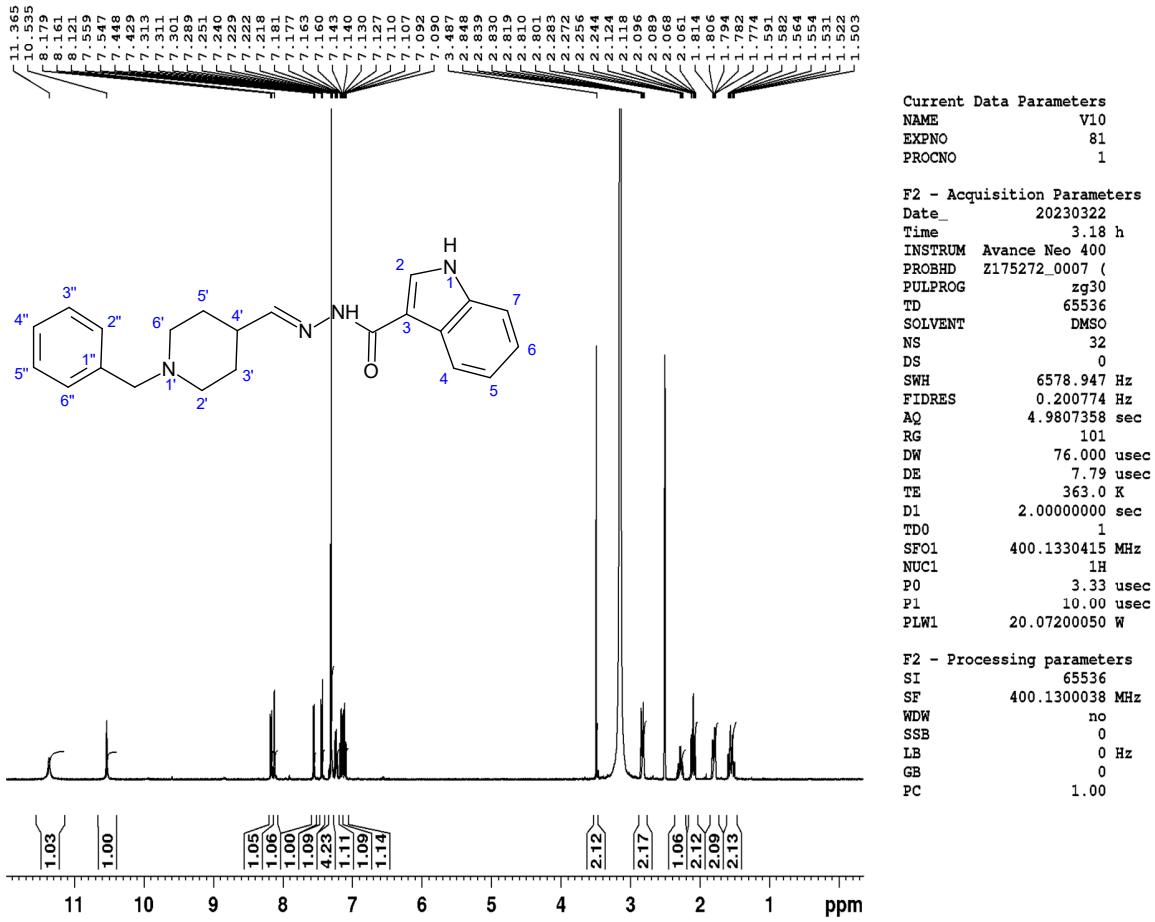


Figure S17. HRMS of compound **3b**

3. *N'-[(E)-(1-benzylpiperidin-4-yl)methylidene]-1H-indole-3-carbohydrazide,* **3c**

Yield: 72%; m.p. 249-250◦C.[1]H NMR (400 MHz, DMSO-d_6, 363K): δ = 1.51 (dd, J=3.7, 11.3 Hz, 1H, CH_2), 1.57 (dd, J=3.7, 11.1 Hz, 1H, CH_2), 1.79 (dd, J=3.4, 12.9 Hz, 2H, CH_2), 2.09 (dt, J=2.6, 11.3 Hz, 2H, CH_2), 2.23-2.32 (m, 1H, H-4'), 2.82 (td, J=3.5, 11.7 Hz, 1H, CH_2), 3.49 (s, 2H, CH_2), 7.12 (dt, J=1.2, 10.9 Hz, 1H, H-5), 7.16 (dt, J=1.4, 7.5 Hz, 1H, H-6), 7.21-7.26 (m, 1H, H-4''), 7.29-7.32 (m, 4H, C-3'', C-5'', C-2'' and C-6''), 7.44 (d, J=7.9 Hz, 1H, H-7), 7.55 (d, J=4.8 Hz, 1H, CH), 8.12 (bs, 1H, H-2), 8.17 (d, J=7.3 Hz, 1H, H-4), 10.53 (bs, 1H, NH), 11.36 (bs, 1H, NH).
[13]C NMR (100 MHz, DMSO-d_6, 363K): δ = 29.01 (C-3' and C-5'), 37.97 (C-4'), 52.19 (C-2' and C-6'), 62.11 (CH_2), 108.42 (C-3), 111.44 (C-7), 120.21 (C-5), 120.95 (C-4), 121.73 (C-6), 126.43 (C-4''), 126.63 (C-4a), 127.74 (C-3'' and C-3''), 128.44 (C-2'' and C-6''), 129.27 (C-2), 135.69 (C-7a), 138.34 (C-1''), 150.89 (CH), 162.35 (C=O). HRMS (ESI) m/z: calcd: [M+H]+ 361.202288. Found: [M+H]+ 361,2021

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PROCNO                  1

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TD                  65536
SOLVENT              DMSO
NS                     32
DS                      0
SWH             6578.947 Hz
FIDRES          0.200774 Hz
AQ              4.9807358 sec
RG                    101
DW                 76.000 usec
DE                  7.79 usec
TE                 363.0 K
D1            2.00000000 sec
TD0                     1
SFO1         400.1330415 MHz
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P1                 10.00 usec
PLW1         20.07200050 W

F2 - Processing parameters
SI                  65536
SF           400.1300038 MHz
WDW                    no
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GB                      0
PC                   1.00
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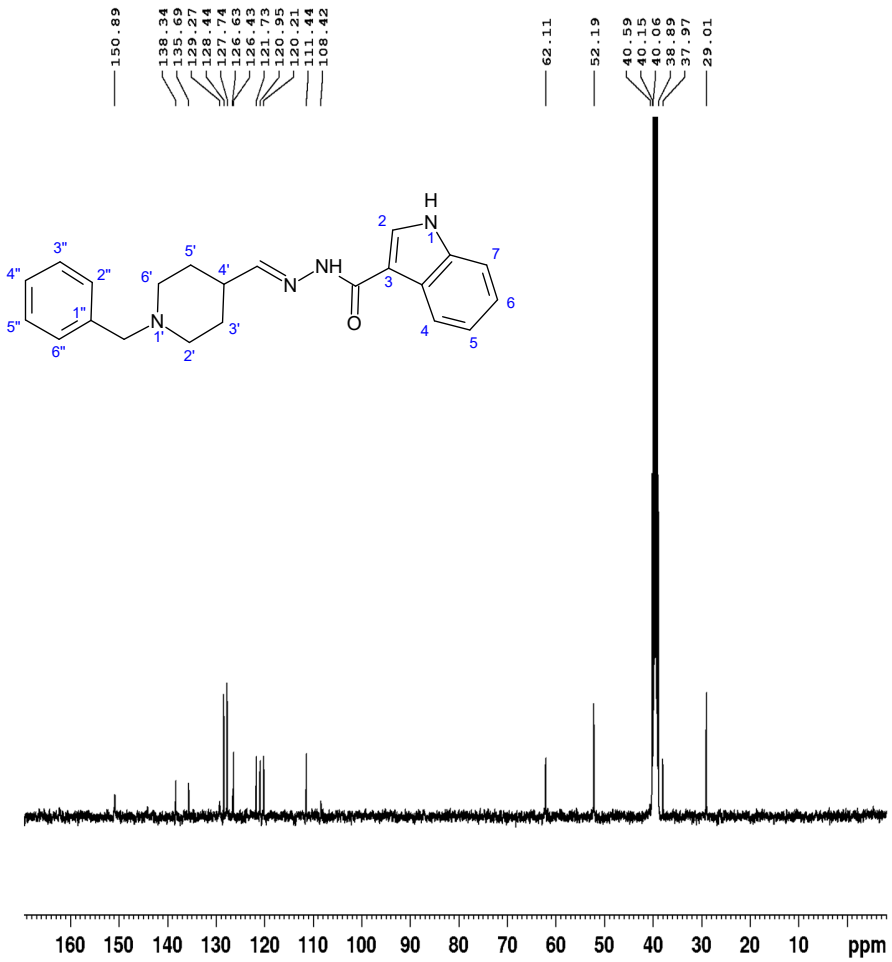
Figure S18. [1]H NMR spectrum of compound **3c** in DMSO-d_6

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PROCNO                  1

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PULPROG           zgdc30
TD                 32768
SOLVENT             DMSO
NS                  2048
DS                     0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ             0.6881280 sec
RG                    36
DW                21.000 usec
DE                 6.50 usec
TE                363.0 K
D1           1.50000000 sec
D11          0.03000000 sec
TD0                    1
SFO1         100.6238383 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1         58.46900177 W
SFO2         400.1316008 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         20.07200050 W
PLW12         0.24781001 W

F2 - Processing parameters
SI                 65536
SF           100.6128450 MHz
WDW                  EM
SSB                   0
LB                 3.00 Hz
GB                    0
PC                 0.30
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Figure S19. ^{13}C NMR spectrum of compound **3c** in DMSO-d_6

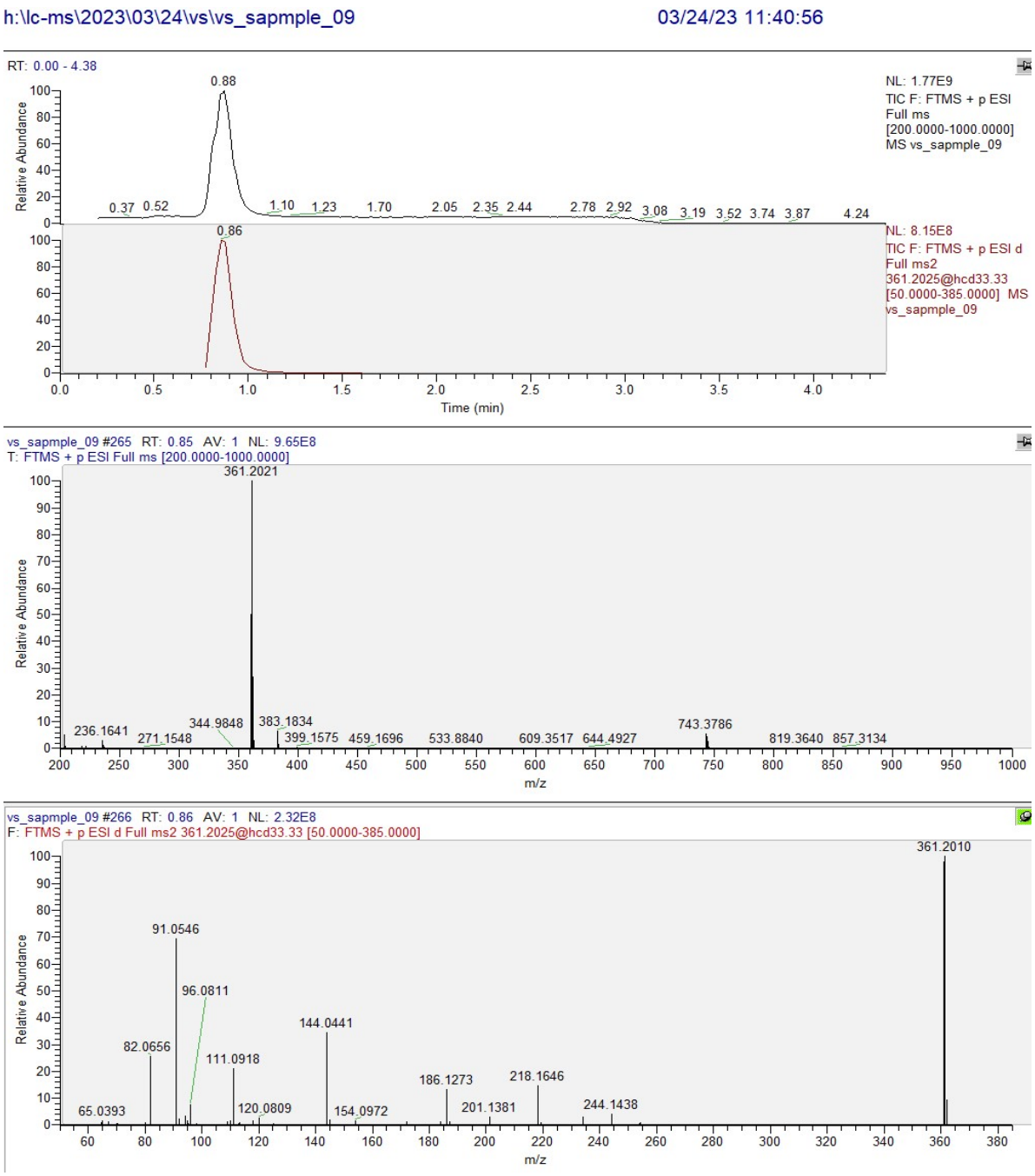
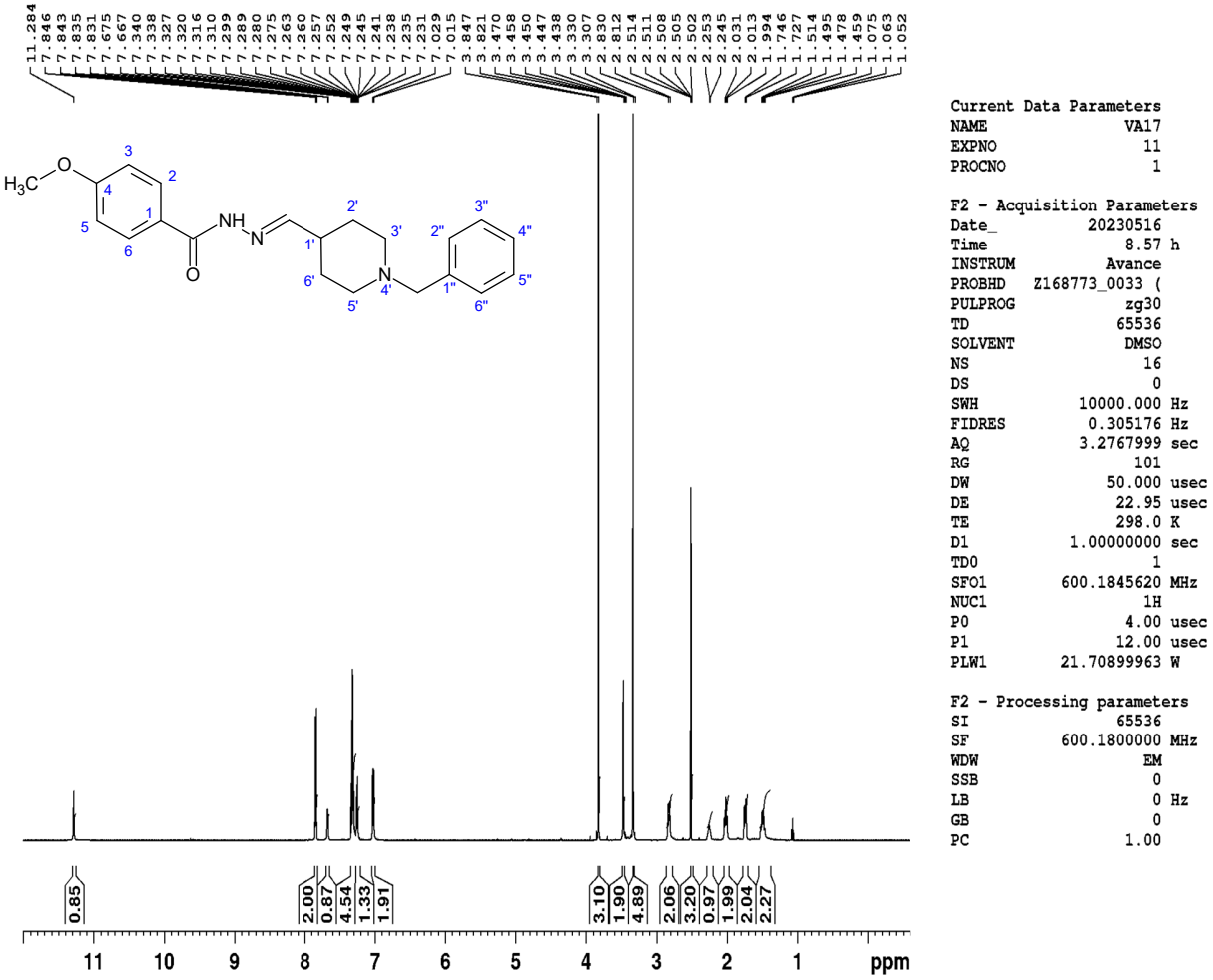


Figure S20. HRMS of compound **3c**

4. N'-[(E)-(1-benzylpiperidin-4-yl)methylidene]-4-methoxybenzohydrazide, **3d**

Yield: 82%; m.p. 138-140◦C.^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.49 (q, J=10.9 Hz, 2H) and 1.74 (d, J=11.6 Hz, 2H, H-2' and H6'), 2.01 (t, J=11.0 Hz, 2H) and 2.82 (d, J=11.2 Hz, 2H, H-3' and H-5'), 2.25 (d, J=4.7 Hz, 1H, H-1'), 3.47 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 7.02 (d, J=8.6 Hz, 2H, H-3 and H-5), 7.25 (tt, J=2.0, 6.7 Hz, 1H, H-4''), 7.30-7.34 (m, 4H, H-2'', H-3'', H-5'' and H-6''), 7.67 (d, J=5.1 Hz, 1H, CH), 7.84 (d, J=8.8 Hz, 2H, H-2 and H-6), 11.28 (s, 1H, NH).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 29.14 (C-2' and C-6'), 38.57 (C-1'), 52.48 (C-3' and C-5'), 55.37 (OCH_3), 62.42 (CH_2), 113.60 (C-3 and C-5), 125.58 (C-1), 126.82 (C-4''), 128.12 (C-3'' and C-5''), 128.76 (C-2'' and C-6''), 129.34 (C-2 and C-6), 138.51 (C-1''), 154.21 (CH), 161.80 (C-4), 162.23 (C=O). HRMS (ESI) m/z: calcd: [M+H]+ 352.201953. Found: [M+H]+ 352.20115

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PROCNO                   1

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TD                    65536
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SWH              10000.000 Hz
FIDRES               0.305176 Hz
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RG                      101
DW                   50.000 usec
DE                   22.95 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                       1
SFO1          600.1845620 MHz
NUC1                     1H
P0                   4.00 usec
P1                   12.00 usec
PLW1          21.70899963 W

F2 - Processing parameters
SI                    65536
SF            600.1800000 MHz
WDW                      EM
SSB                       0
LB                        0 Hz
GB                        0
PC                     1.00
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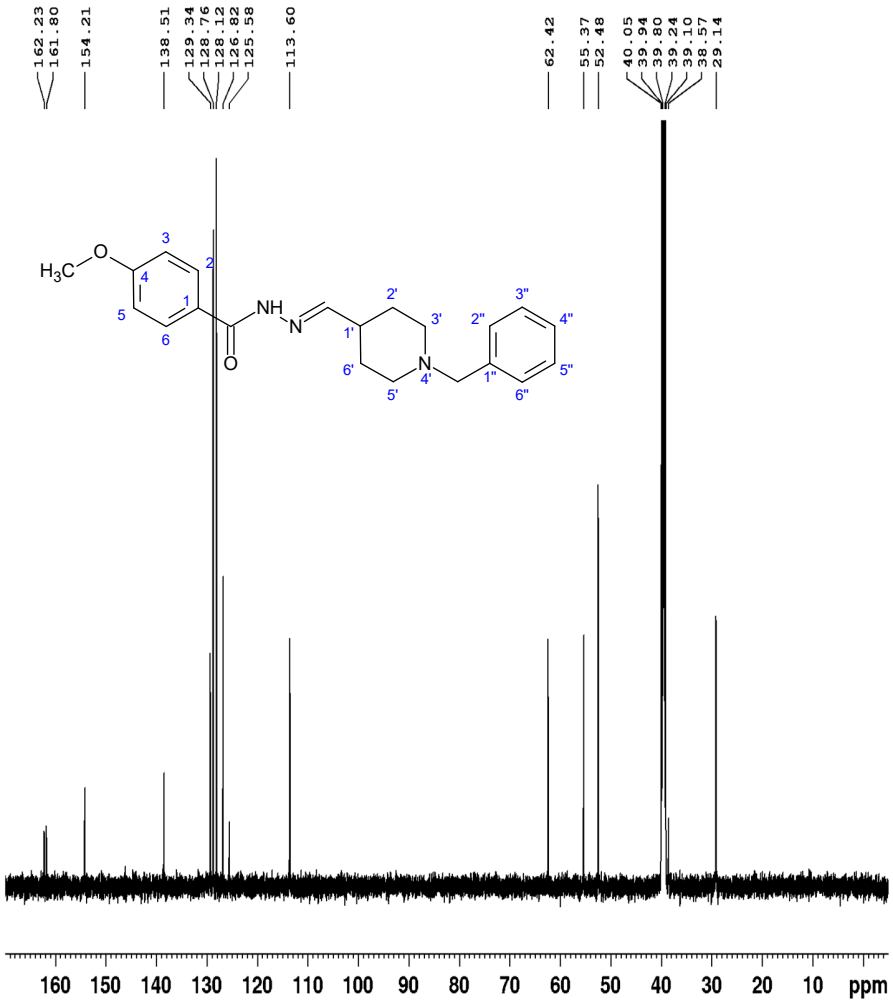
Figure S21. ^{1}H NMR spectrum of compound **3d** in DMSO-d_6

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PROCNO                   1

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PULPROG              zgdc30
TD                    32768
SOLVENT                DMSO
NS                       256
DS                         0
SWH               35714.286 Hz
FIDRES             2.179827 Hz
AQ                 0.4587520 sec
RG                       101
DW                    14.000 usec
DE                    18.00 usec
TE                    298.0 K
D1                1.50000000 sec
D11               0.03000000 sec
TD0                        1
SFO1           150.9319844 MHz
NUC1                    13C
P0                     3.33 usec
P1                    10.00 usec
PLW1           67.54000092 W
SFO2           600.1824007 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 80.00 usec
PLW2           21.72701073 W
PLW12           0.49773711 W

F2 - Processing parameters
SI                     65536
SF             150.9154541 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
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Figure S22. ^{13}C NMR spectrum of compound **3d** in DMSO-d_6

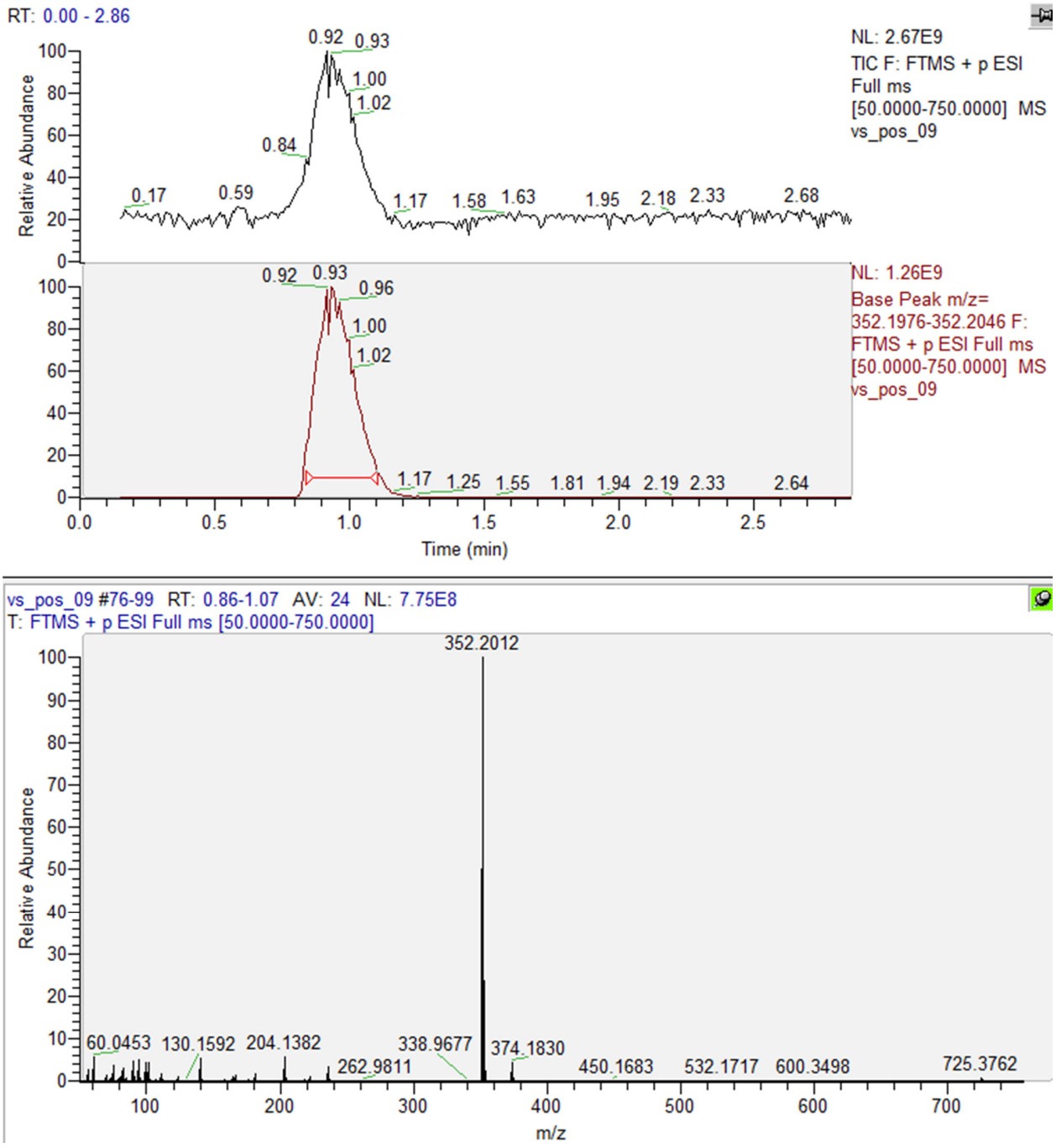
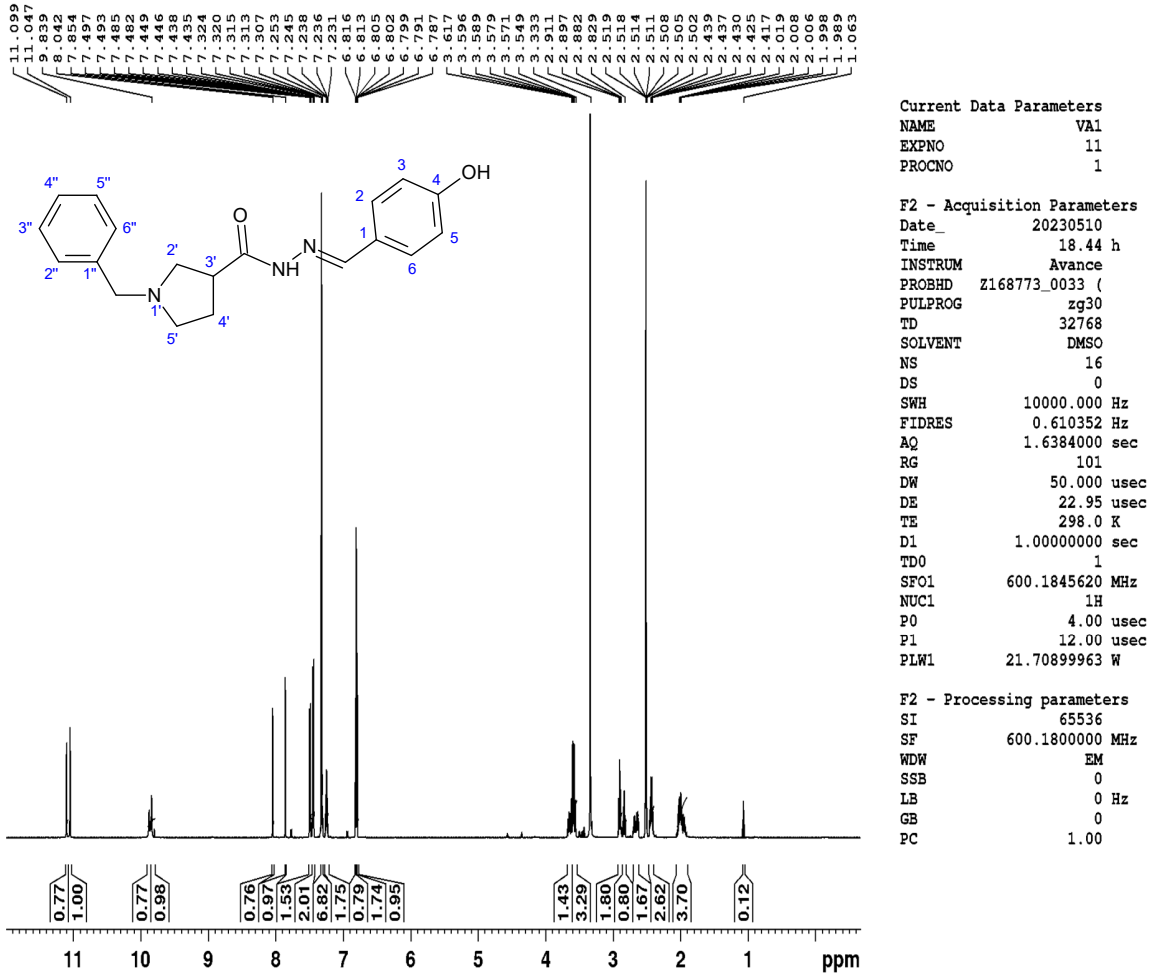


Figure S23. HRMS of compound **3d**

5. 1-benzyl-N'-[(E)-(4-hydroxyphenyl)methylidene]pyrrolidine-3-carbohydrazide, **3e**

Yield: 84%; m.p. 240-241◦C.^{1}H NMR (600 MHz, DMSO-d_6): 1:0.77 mixture of conformers; signals for major *synperiplanar* conformer around the amide bond: δ = 1.94-2.03 (m, 2H, H-4'), 2.40-2.42 (m, 2H, H-5'), 2.62-2.69 (m, 1H, 1/2H-2'), 2.88-2.91 (m, 1H, 1/2H-2'), 3.55-3.62 (m, 2H, CH_2), 3.61-3.66 (m, 1H, H-3'), 6.79 (d, J=8.6 Hz, 2H, H-3 and H-5), 7.22-7.26 (m, 1H, H-4''), 7.30-7.33 (m, 4H, H-2'', H-3'', H-5'' and H-6''), 7.44 (d, J=8.7 Hz, 2H, H-2 and H-6), 7.85 (s, 1H, CH), 9.84 (bs, 1H, OH), 11.05 (s, 1H, NH); resolved signals for minor *antiperiplanar* conformer around the amide bond: 8.04 (s, 1H, CH), 9.87 (bs, 1H, OH), 11.10 (s, 1H, NH).

^{13}C NMR (151 MHz, DMSO-d_6): signals for major *synperiplanar* conformer around the amide bond: δ = 26.95 (C-4'), 41.47 (C-3'), 53.58 (C-5'), 56.43 (C-2'), 59.30 (CH_2), 115.65 (C-3 and C-5), 125.37 (C-1), 126.75 (C-4''), 128.11 (C-2'' and C-6''), 128.28 (C-2 and C-6), 128.65 (C-3'' and C-5''), 139.16 (C-1''), 142.74 (CH), 158.99 (C-4), 175.01 (C=O); resolved signals for minor *antiperiplanar* conformer around the amide bond: 146.34 (CH), 159.22 (C-4), 169.78 (C=O). HRMS (ESI) m/z: calcd: [M+H]+ 324.170653. Found: [M+H]+ 324.1705

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PROCNO                  1

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TD                 32768
SOLVENT             DMSO
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DS                     0
SWH           10000.000 Hz
FIDRES         0.610352 Hz
AQ             1.6384000 sec
RG                   101
DW                50.000 usec
DE                22.95 usec
TE                298.0 K
D1            1.00000000 sec
TD0                    1
SFO1         600.1845620 MHz
NUC1                  1H
P0                 4.00 usec
P1                12.00 usec
PLW1         21.70899963 W

F2 - Processing parameters
SI                 65536
SF           600.1800000 MHz
WDW                   EM
SSB                    0
LB                     0 Hz
GB                     0
PC                  1.00
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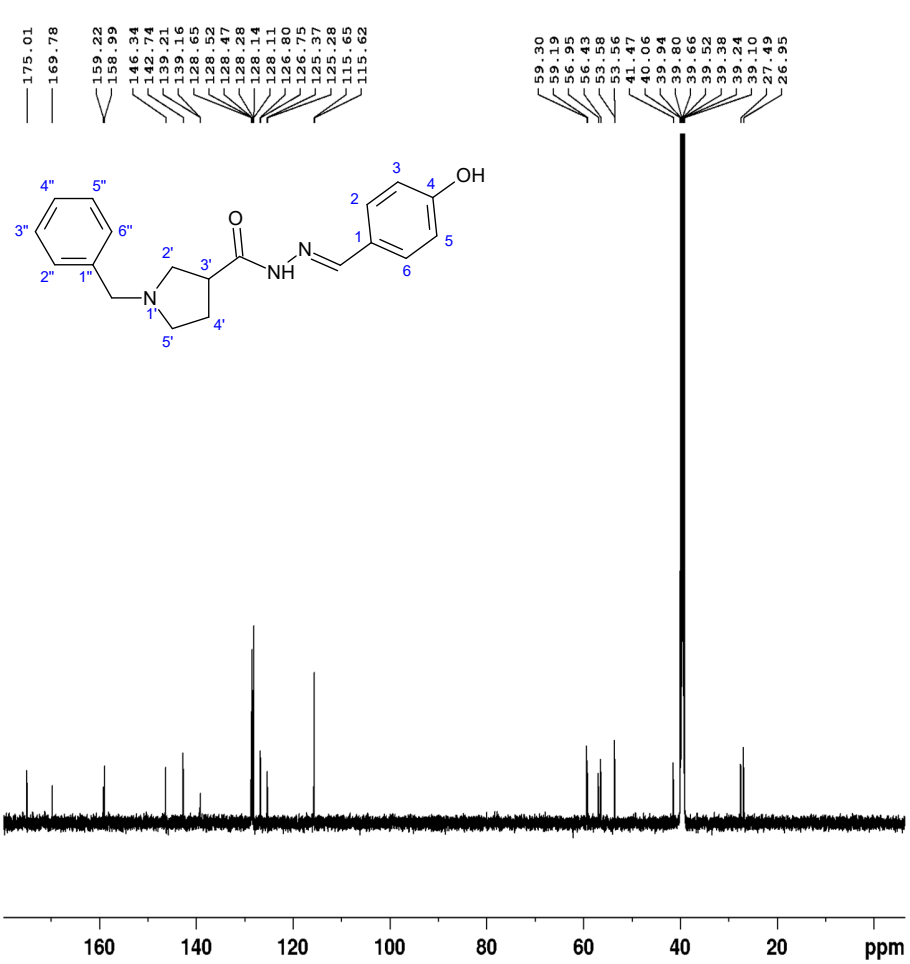
Figure S24. ^{1}H NMR spectrum of compound **3e** in DMSO-d_6

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EXPNO                  12
PROCNO                  1

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PULPROG             zgdc30
TD                   32768
SOLVENT               DMSO
NS                     256
DS                       0
SWH              35714.286 Hz
FIDRES            2.179827 Hz
AQ                0.4587520 sec
RG                     101
DW                  14.000 usec
DE                  18.00 usec
TE                  298.0 K
D1              1.50000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           150.9319844 MHz
NUC1                   13C
P0                  3.33 usec
P1                 10.00 usec
PLW1           67.54000092 W
SFO2           600.1824007 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2               80.00 usec
PLW2           21.72701073 W
PLW12           0.49773711 W

F2 - Processing parameters
SI                    65536
SF             150.9154536 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
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Figure S25. ^{13}C NMR spectrum of compound **3e** in DMSO-d_6

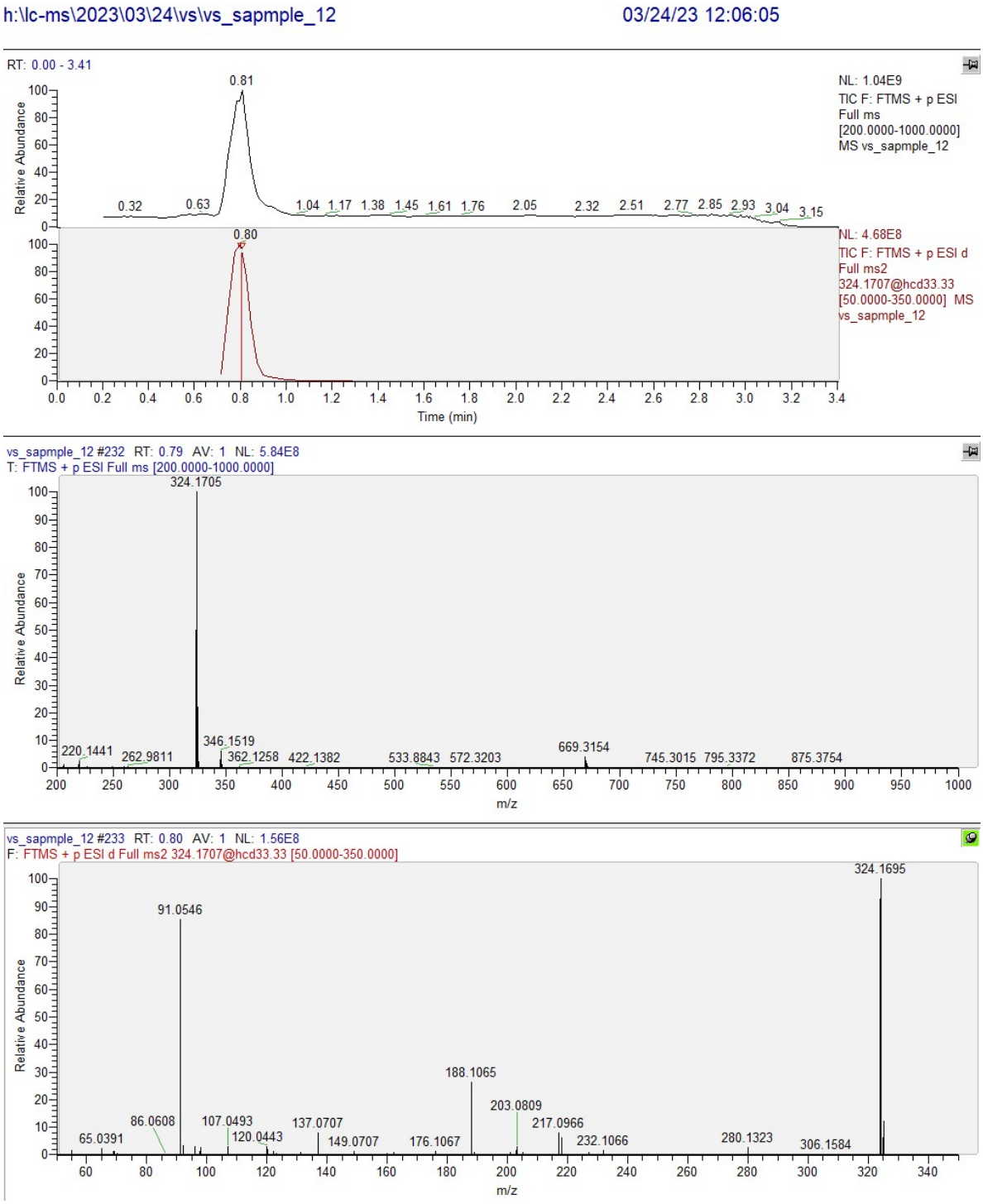


Figure S26. HRMS of compound **3e**

6. 1-benzyl-N'-[(E)-(2,4-dihydroxyphenyl)methylidene]pyrrolidine-3-carbohydrazide, **3f**

Yield: 81%; m.p. 224-225◦C.^{1}H NMR (600 MHz, DMSO-d_6): δ = 1:0.39 mixture of conformers; signals for major *synperiplanar* conformer around the amide bond: δ = 1.92-2.04 (m, 2H, H-4'), 2.41-2.48 (m, 2H, H-5'), 2.66-2.69 (m, 1H, 1/2H-2'), 2.82-2.94 (m, 1H, 1/2H-2'), 3.52-3.57 (m, 1H, H-3'), 3.57-3.61 (m, 2H, CH_2), 6.29 (d, J=2.3 Hz, 1H, H-3), 6.33 (dd, J=8.4, 2.3 Hz, 1H, H-5), 7.25 (d, J=8.5 Hz, 1H, H-6), 7.29-7.33 (m, 5H, Ar), 8.21 (s, 1H, CH), 9.91 (bs, 1H, OH), 11.32 (s, 1H, OH), 11.36 (s, 1H, NH); resolved signals for minor *antiperiplanar* conformer around the amide bond: 8.11 (s, 1H, CH), 9.79 (bs, 1H, OH), 10.11 (bs, 1H, OH), 11.04 (s, 1H, NH).

^{13}C NMR (151 MHz, DMSO-d_6): signals for major *synperiplanar* conformer around the amide bond: δ = 27.47 (C-4'), 41.23 (C-3'), 53.52 (C-5'), 56.83 (C-2'), 59.17 (CH_2), 102.58 (C-3), 107.57 (C-5), 110.41 (C-1), 126.81 (C-4''), 128.14 (C-2'' and C-6''), 128.51 (C-3'' and C-5''), 131.16 (C-6), 139.17 (C-1''), 147.58 (CH), 159.27 (C-2), 160.52 (C-4), 169.58 (C=O); resolved signals for minor *antiperiplanar* conformer around the amide bond: 141.95 (CH), 157.97 (C-2), 160.22 (C-4), 174.44 (C=O).HRMS (ESI) m/z: calcd: [M+H]+ 340.165568. Found: [M+H]+ 340.1655

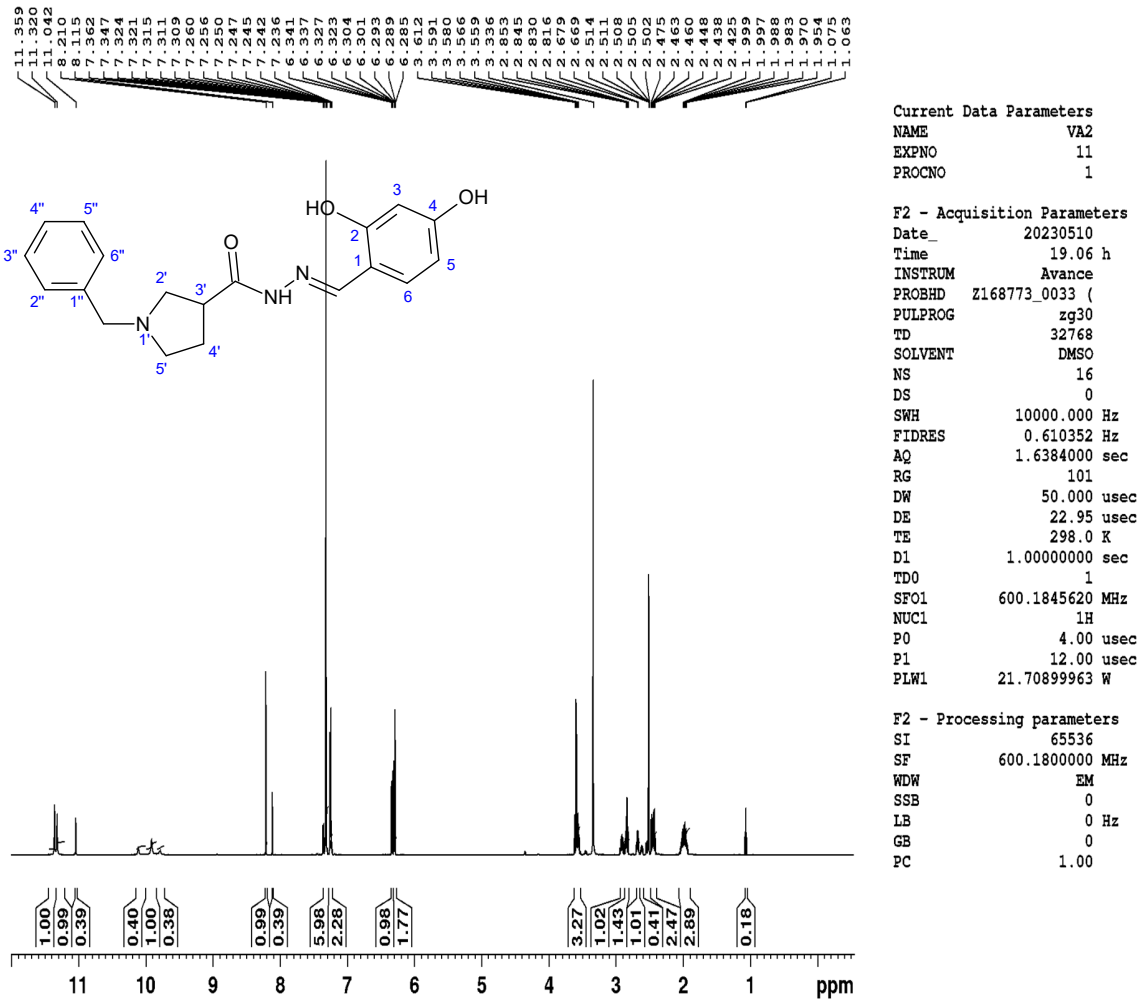
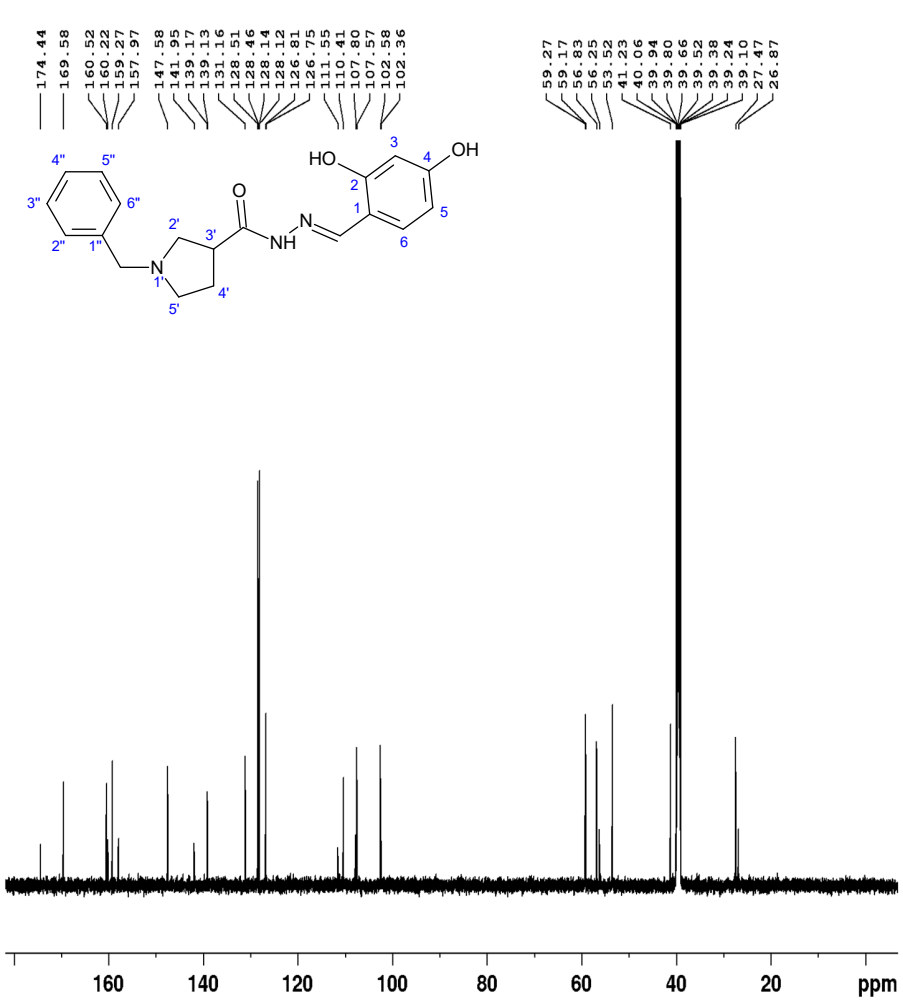


Figure S27. ^{1}H NMR spectrum of compound **3f** in DMSO-d_6

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PROCNO                   1

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TD                    32768
SOLVENT                DMSO
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FIDRES            2.179827 Hz
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RG                      101
DW                 14.000 usec
DE                 18.00 usec
TE                  298.0 K
D1              1.50000000 sec
D11             0.03000000 sec
TD0                       1
SFO1           150.9319844 MHz
NUC1                    13C
P0                  3.33 usec
P1                 10.00 usec
PLW1           67.54000092 W
SFO2           600.1824007 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2              80.00 usec
PLW2           21.72701073 W
PLW12           0.49773711 W

F2 - Processing parameters
SI                    65536
SF             150.9154535 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
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Figure S28. ^{13}C NMR spectrum of compound **3f** in DMSO-d_6

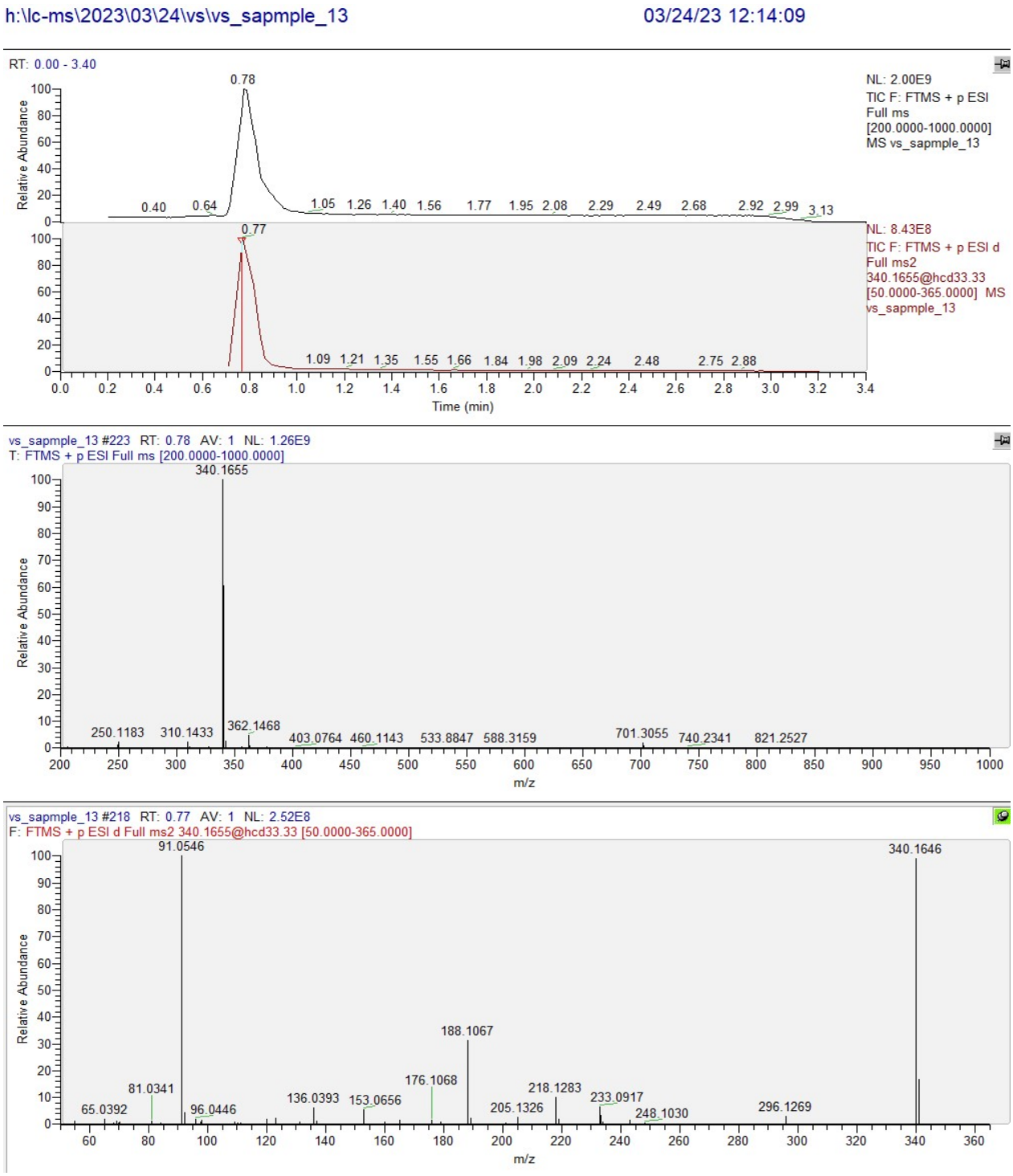
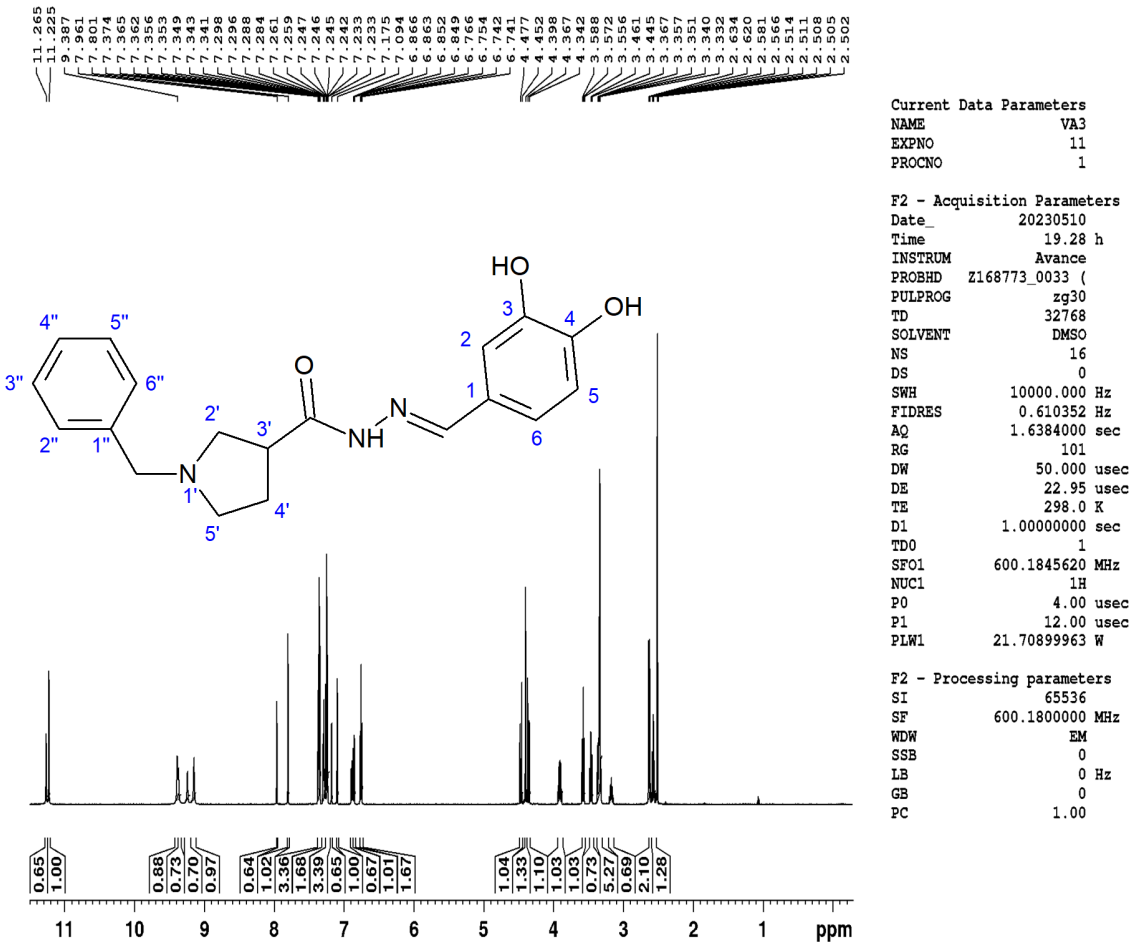


Figure S29. HRMS of compound **3f**

7. 1-benzyl-N'-[(E)-(3,4-dihydroxyphenyl)methylidene]pyrrolidine-3-carbohydrazide, **3g**

Yield: 72%; m.p. 199-201◦C.^{1}H NMR (600 MHz, DMSO-d_6): 1:0.65 mixture of conformers; signals for major *synperiplanar* conformer around the amide bond: δ = 2.57 (m, J=8.3 Hz, 2H, H-4'), 2.63 (d, J=8.45 Hz, 2H, H-5'), 3.32-3.37 (m, 1H, H-2'), 3.57 (t, J=9.5 Hz, 1H, H-2'), 3.91 (dq, J=6.2, 8.6 Hz, 1H, H-3'), 4.35 (d, J=15.0 Hz, 1H) and 4.46 (d, J=15.0 Hz, 1H, CH_2), 6.75 (dd, J=0.6, 7.7 Hz, 1H, H-5), 6.89 (dd, J=1.2, 8.3 Hz, 1H, H-6), 7.09 (s, 1H, H-2), 7.23-7.25 (m, 2H, H-2'' and H-6''), 7.27-7.30 (m, 1H, H-4''), 7.34-7.37 (m, 2H, H-3'' and H-5''), 7.80 (s, 1H, CH), 9.15 (bs, 1H, OH), 9.39 (bs, 1H, OH), 11.23 (s, 1H, NH); resolved signals for minor *antiperiplanar* conformer around the amide bond: 7.96 (s, 1H, CH), 9.24 (bs, 1H, OH), 9.37 (bs, 1H, OH), 11.26 (s, 1H, NH).
^{13}C NMR (151 MHz, DMSO-d_6): signals for major *synperiplanar* conformer around the amide bond: δ = 33.54 (C-3'), 35.41 (C-4'), 45.79 (CH_2), 48.98 (C-5'), 49.37 (C-2'), 113.21 (C-2), 116.05 (C-5), 120.37 (C-6), 126.02 (C-1), 127.73 (C-4''), 128.05 (C-2'' and C-6''), 129.06 (C-3'' and C-5''), 137.24 (C-1''), 144.49 (CH), 146.11 (C-3), 148.17 (C-4), 172.83 (C=O); resolved signals for minor *antiperiplanar* conformer around the amide bond: 147.81 (CH), 146.15 (C-3), 148.43 (C-4), 173.81 (C=O). HRMS (ESI) m/z: calcd: [M+H]+ 340.165568. Found: [M+H]+ 340.1646

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PROCNO                   1

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TD                    32768
SOLVENT                DMSO
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RG                      101
DW                   50.000 usec
DE                   22.95 usec
TE                   298.0 K
D1                1.00000000 sec
TD0                       1
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NUC1                     1H
P0                   4.00 usec
P1                   12.00 usec
PLW1          21.70899963 W

F2 - Processing parameters
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SF             600.1800000 MHz
WDW                      EM
SSB                       0
LB                        0 Hz
GB                        0
PC                     1.00
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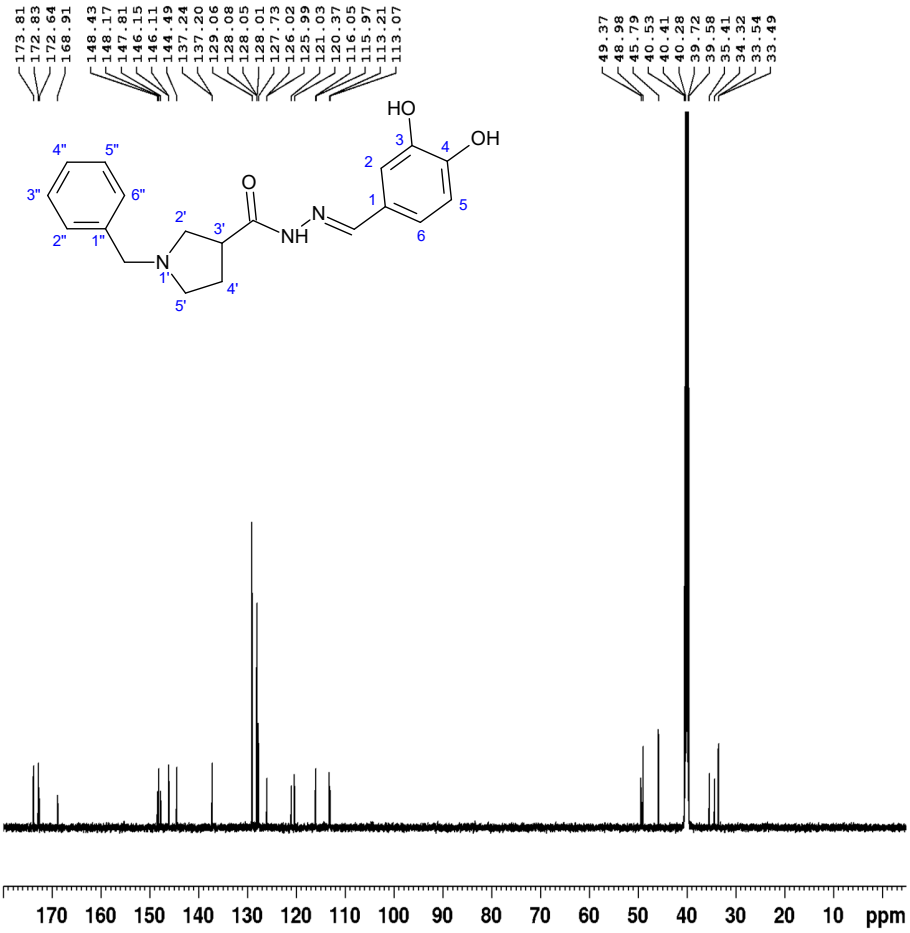
Figure S30. ^{1}H NMR spectrum of compound **3g** in DMSO-d_6

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EXPNO                  12
PROCNO                  1

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PULPROG            zgdc30
TD                  32768
SOLVENT              DMSO
NS                     256
DS                       0
SWH             35714.286 Hz
FIDRES           2.179827 Hz
AQ              0.4587520 sec
RG                     101
DW                14.000 usec
DE                 18.00 usec
TE                 298.0 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                      1
SFO1          150.9319844 MHz
NUC1                  13C
P0                  3.33 usec
P1                 10.00 usec
PLW1          67.54000092 W
SFO2          600.1824007 MHz
NUC2                   1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2          21.72701073 W
PLW12          0.49773711 W

F2 - Processing parameters
SI                  65536
SF            150.9153810 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
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Figure S31. ^{13}C NMR spectrum of compound **3g** in DMSO-d_6

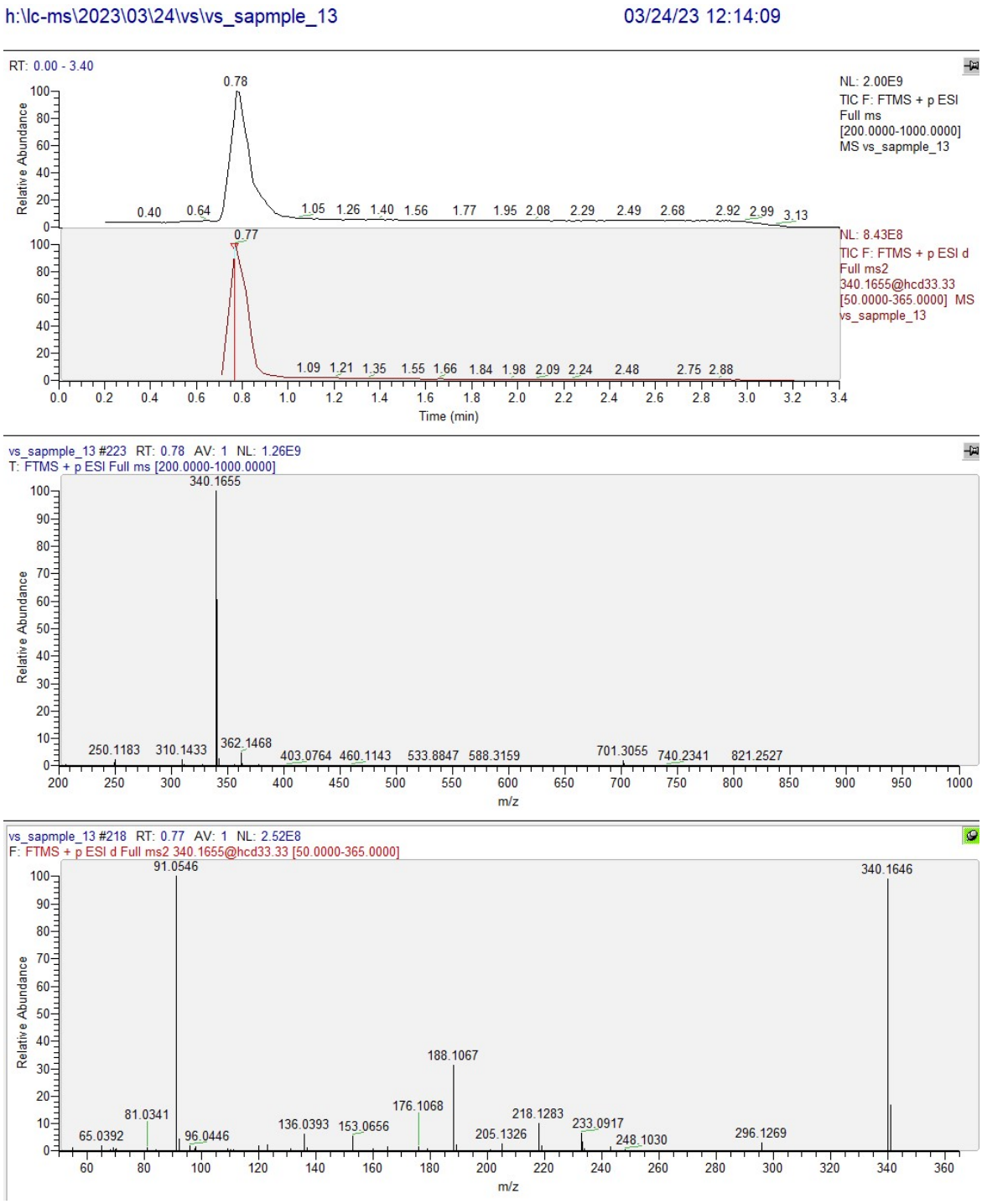


Figure S32. HRMS of compound **3g**

8. 1-benzyl-N'-[(E)-(2,4,6-trihydroxyphenyl)methylidene]pyrrolidine-3-carbohydrazide, **3h**

Yield: 65%; m.p. 215-217◦C.^{1}H NMR (600 MHz, DMSO-d_6): 1:0.19 mixture of conformers; signals for major *synperiplanar* conformer around the amide bond: δ = 1.91-2.03 (m, 2H, H-4'), 2.41-2.47 (m, 2H, H-5'), 2.66-2.69 (m, 1H, H-2'), 2.81-2.85 (m, 1H, H-2'), 2.85-2.91 (m, 1H, H-3'), 3.57 (d, J=12.8 Hz, 1H) and 3.60 (d, J=13.0 Hz, 1H, CH_2), 5.81 (s, 2H, H-3 and H-5), 7.23-7.27 (m, 1H, H-4''), 7.30-7.33 (m, 4H, H-2'', H-3'', H-5'' and H-6''), 8.49 (s, 1H, CH), 9.77 (bs, 1H, OH), 10.95 (bs, 2H, OH), 11.33 (s, 1H, NH); resolved signals for minor *antiperiplanar* conformer around the amide bond: 8.37 (s, 1H, CH), 9.80 (bs, 1H, OH), 10.51 (bs, 2H, OH), 11.12 (s, 1H, NH).

^{13}C NMR (151 MHz, DMSO-d_6): signals for major *synperiplanar* conformer around the amide bond: δ = 27.47 (C-3'), 41.19 (CH_2), 53.50 (C-4'), 56.81 (C-5'), 59.16 (C-2'), 94.29 (C-3 and C-5), 98.80 (C-1), 126.81 (C-4''), 128.14 (C-2'' and C-6''), 128.51 (C-3'' and C-5''), 139.12 (C-1''), 145.15 (CH), 159.48 (C-2 and C-6), 161.34 (C-4), 169.21 (C=O). HRMS (ESI) m/z: calcd: [M+H]+ 356.160483. Found: [M+H]+ 356.1604

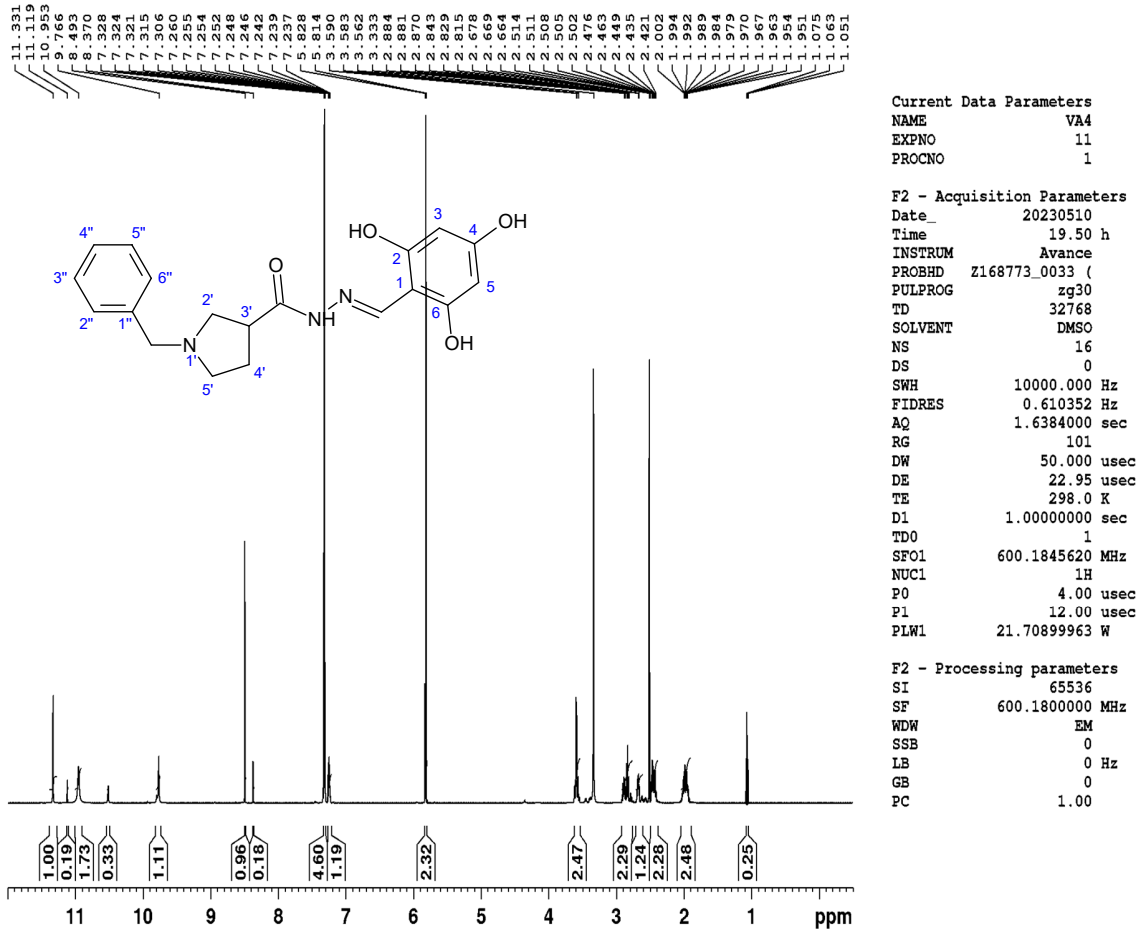


Figure S33. ^{1}H NMR spectrum of compound **3h** in DMSO-d_6

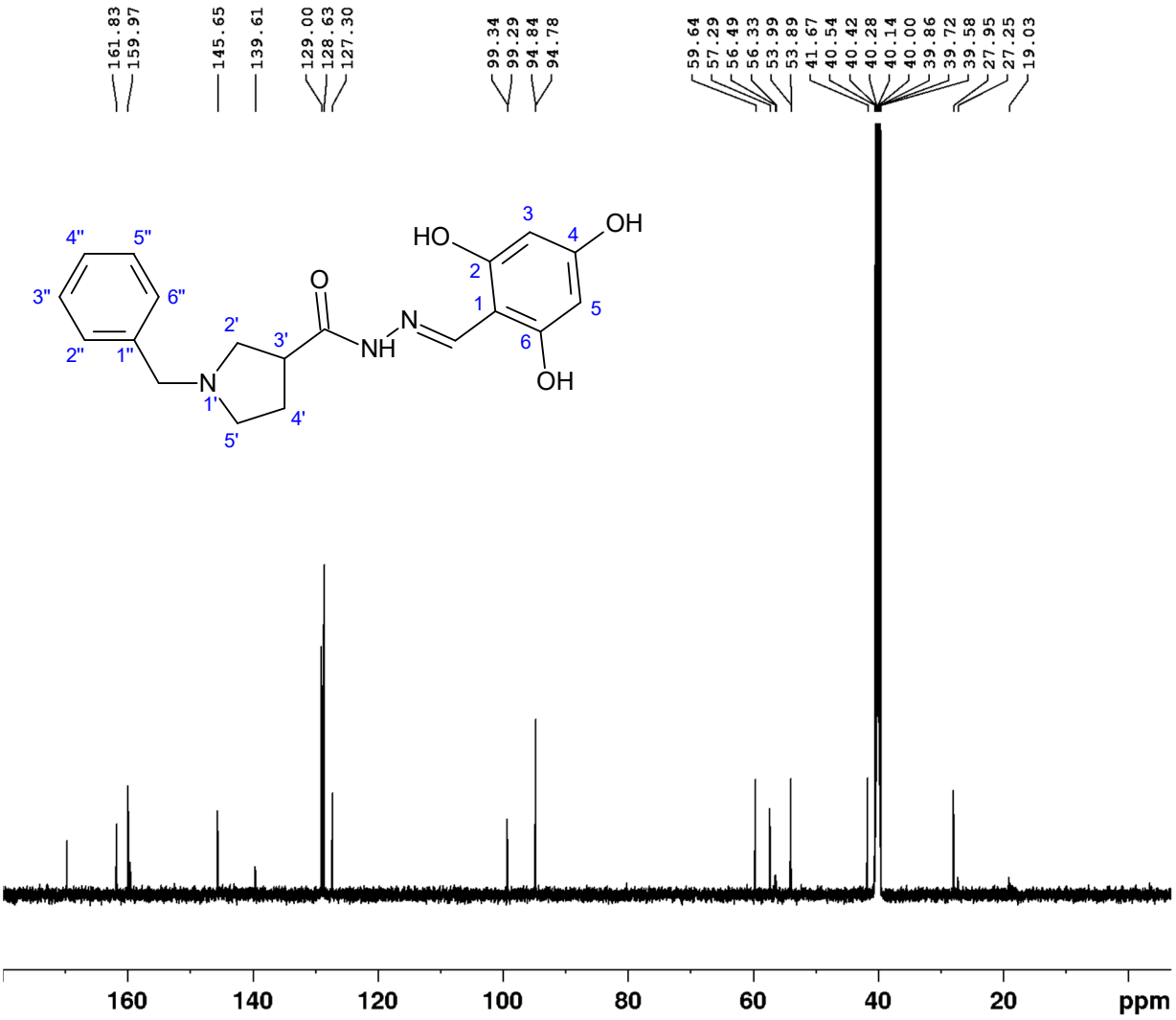


Figure S34. ^{13}C NMR spectrum of compound **3h** in DMSO-d_6

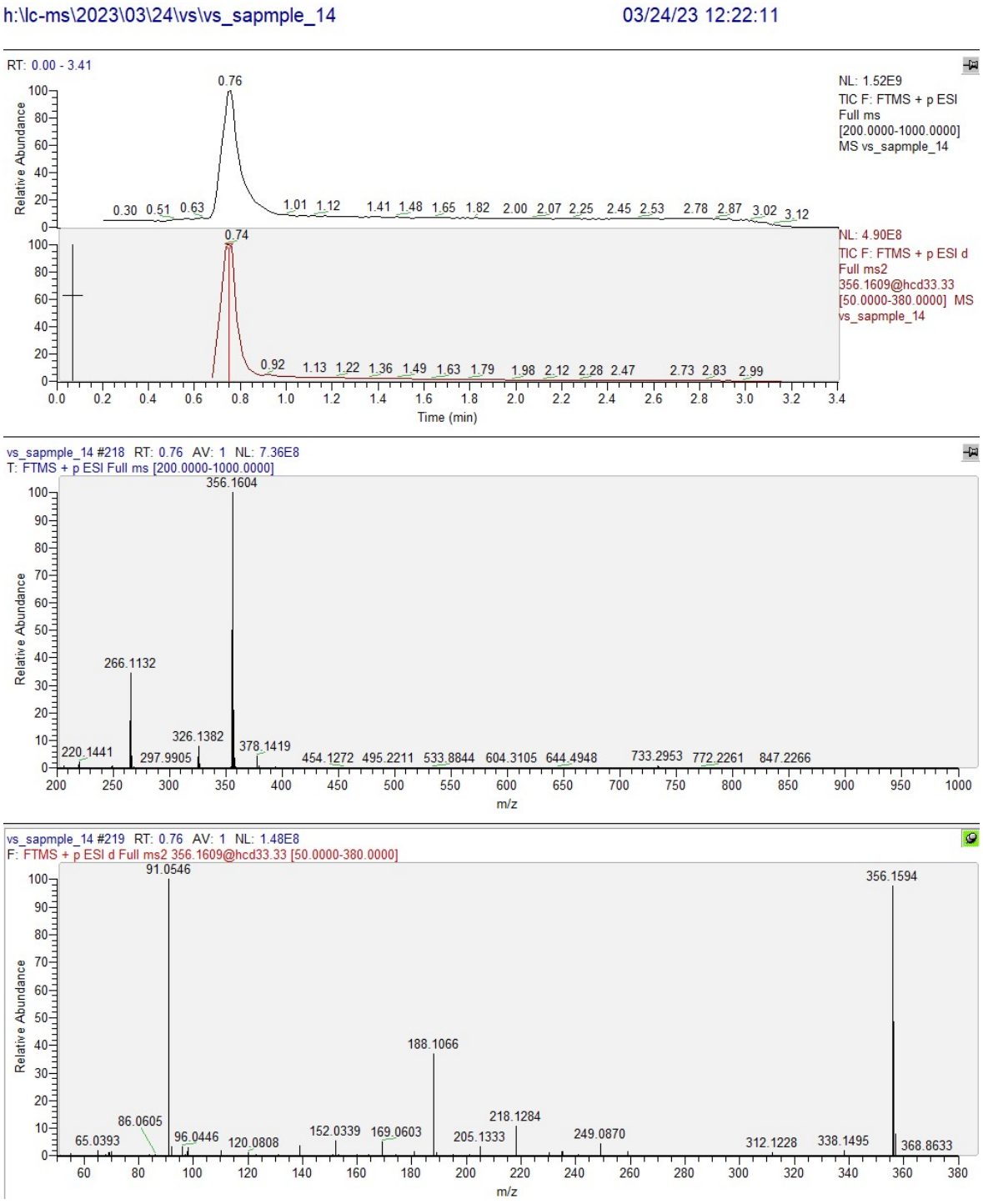


Figure S35. HRMS of compound **3h**

9. ***tert-butyl (2-{(2E)-2-[(1-benzyl-1H-indol-3-yl)methylidene]hydrazinyl}-2-oxoethyl)carbamate, 3i*** ^{1}H NMR, ^{13}C NMR and HRMS spectra of compound **3i** can be found in https://doi.org/10.1007/s00044-019-02293-w

***10. tert-butyl (2-{(2E)-2-[(5-methoxy-1-methyl-1H-indol-3-yl)methylidene]hydrazinyl}-2-oxoethyl)carbamate,* 3j**

Yield: 48%; m.p. 203-206◦C.^{1}H NMR (600 MHz, DMSO-d_6): 1:0.28 mixture of conformers; signals for major *synperiplanar* conformer around the amide bond: δ = 1.41 (s, 9H, CH_3), 3.79 (s, 3H, OCH_3), 4.16 (d, J=6.0 Hz, 2H, CH_2), 6.76 (t, J=5.9 Hz, 1H, H-4), 6.85 (dd, J=2.6, 8.8 Hz, 1H, H-6), 7.34 (d, J=8.8 Hz, 1H, H-7), 7.62 (d, J=2.4 Hz, 1H, H-4), 7.72 (d, J=2.9 Hz, 1H, C-2), 8.14 (s, 1H, CH), 11.00 (s, 1H, NH), 11.40 (bs, 1H, NH); resolved signals for minor *antiperiplanar* conformer around the amide bond: 8.35 (s, 1H, CH), 11.09 (s, 1H, NH), 11.40 (bs, 1H, NH).
^{13}C NMR (151 MHz, DMSO-d_6): signals for major *synperiplanar* conformer around the amide bond: δ = 28.22 (CH_3), 41.39 (CH_2), 55.05 (OCH_3), 77.88 (OC), 103.48 (C-4), 111.10 (C-3), 112.16 (C-7), 112.53 (C-6), 124.63 (C-3a), 130.50 (C-2), 131.93 (C-7a), 140.68 (CH), 154.37 (C-5), 155.89 (OC=O), 169.74 (C=O).HRMS (ESI) m/z: calcd: [M+H]+ 347.171382. Found: [M+H]+ 347.1712

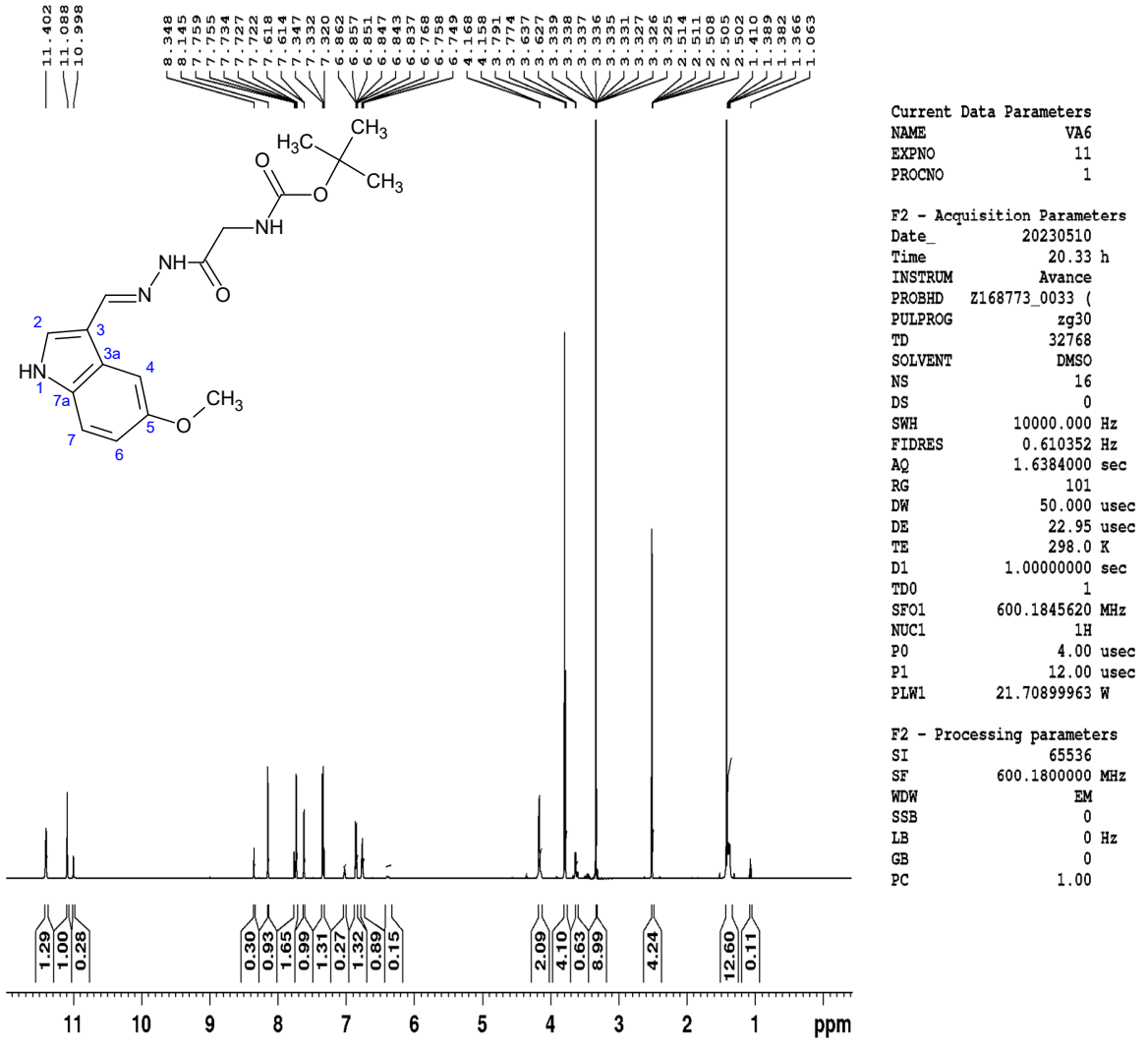
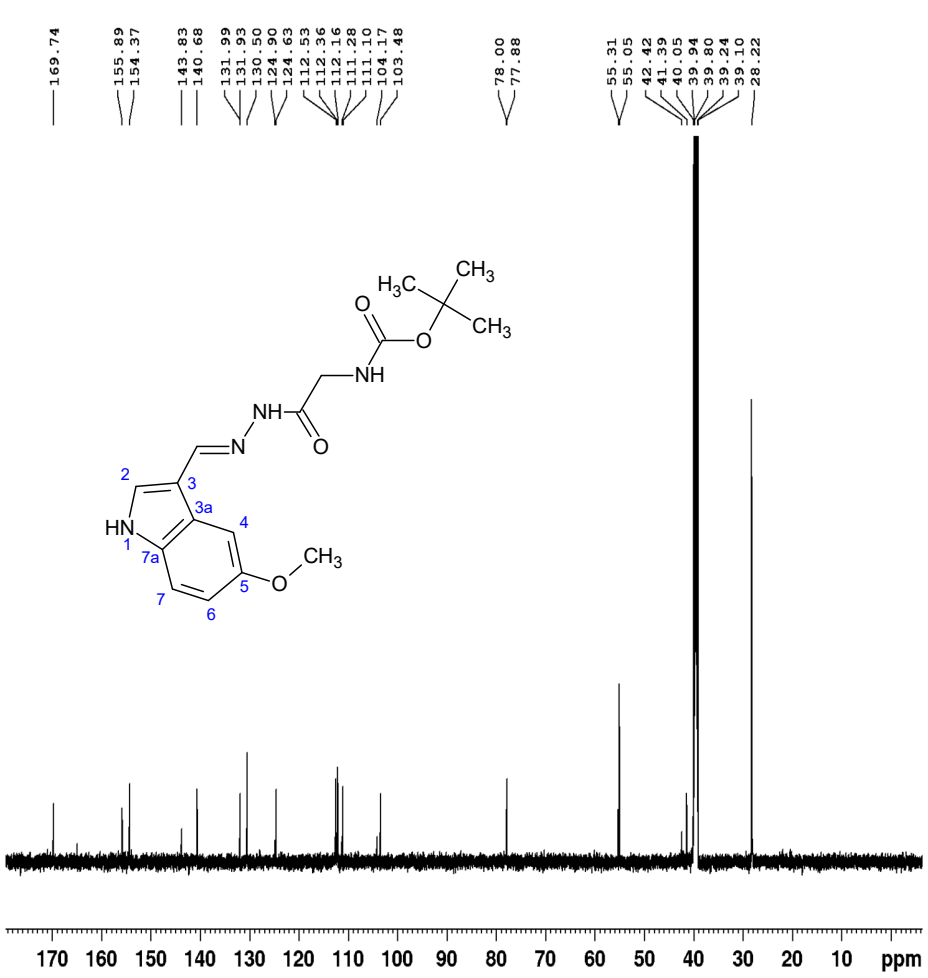


Figure S36. ^{1}H NMR spectrum of compound **3j** in DMSO-d_6

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FIDRES         2.179827 Hz
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RG                    101
DW               14.000 usec
DE               18.00 usec
TE                298.0 K
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D11          0.03000000 sec
TD0                     1
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NUC1                13C
P0               3.33 usec
P1              10.00 usec
PLW1        67.54000092 W
SFO2        600.1824007 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        21.72701073 W
PLW12        0.49773711 W

F2 - Processing parameters
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WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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Figure S37. ^{13}C NMR spectrum of compound **3j** in DMSO-*d*$_6$

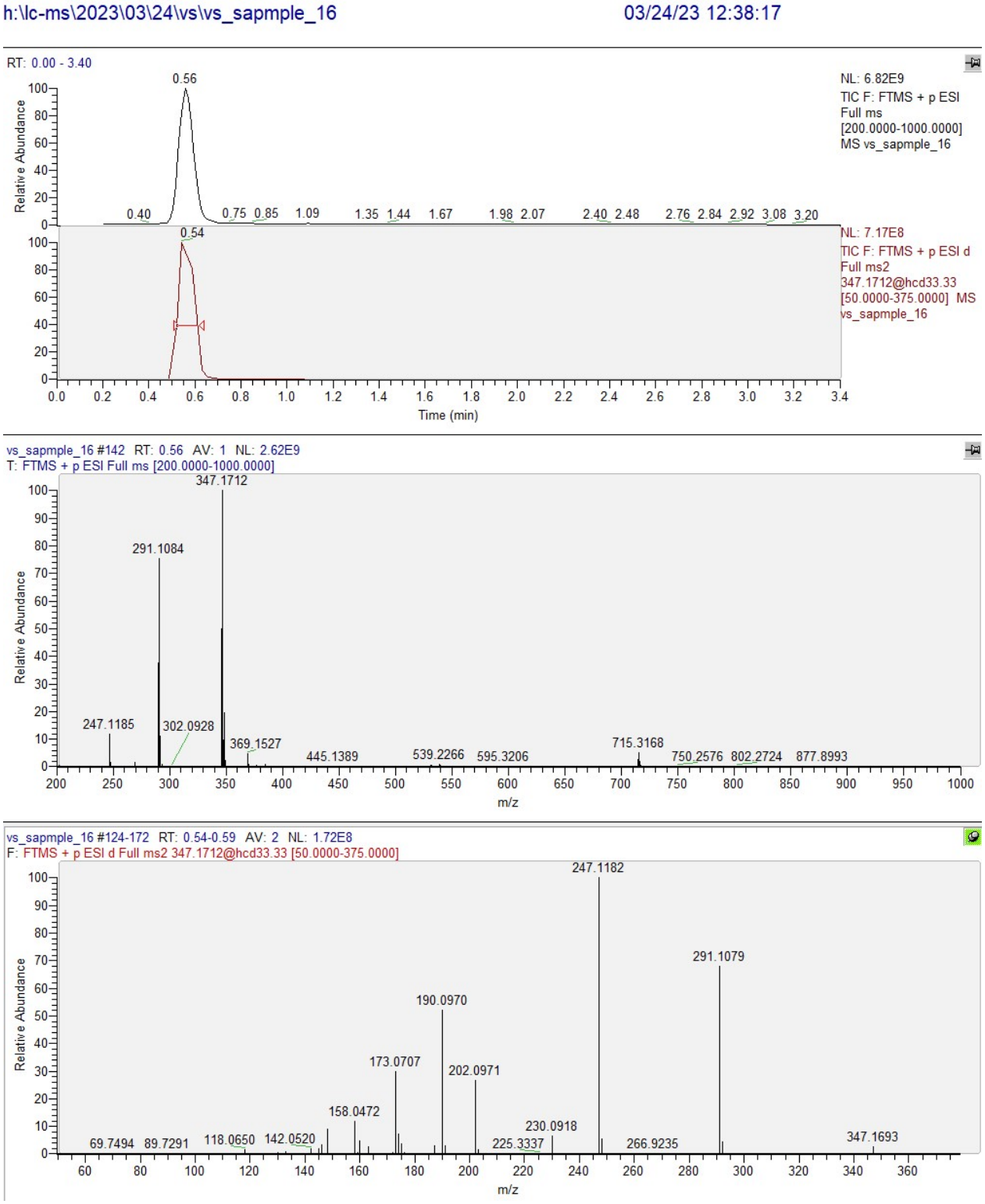


Figure S38. HRMS of compound **3j**

***11. tert-butyl (2-{(2E)-2-[(5-methoxy-1H-indol-3-yl)methylidene]hydrazinyl}-2-oxoethyl)carbamate,* 3k**

Yield: 83%; m.p. 197-199◦C.^{1}H NMR (600 MHz, DMSO-d_6): 1:0.33 mixture of conformers; signals for major *synperiplanar* conformer around the amide bond: δ = 1.41 (s, 9H, CH_3), 3.78 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 4.16 (d, J=5.9 Hz, 2H, CH_2), 6.76 (t, J=5.9 Hz, 1H, NH), 6.92 (dd, J=2.6, 8.8 Hz, 1H, H-6), 7.41 (d, J=8.8 Hz, 1H, H-7), 7.62 (d, J=2.5 Hz, 1H, H-4), 7.71 (s, 1H, C-2), 8.11 (s, 1H, CH), 11.07 (s, 1H, NH); resolved signals for minor *antiperiplanar* conformer around the amide bond: 8.32 (s, 1H, CH), 11.00 (1H, s),

^{13}C NMR (151 MHz, DMSO-d_6): signals for major *synperiplanar* conformer around the amide bond: δ = 28.01 (CH_3), 32.91 (NCH_3), 41.38 (CH_2), 55.11 (OCH_3), 77.88 (OC), 103.66 (C-4), 109.95 (C-3), 111.05 (C-7), 112.10 (C-6), 125.01 (C-3a), 132.65 (C-7a), 134.03 (C-2), 140.20 (CH), 154.65 (C-5), 155.89 (OC=O), 169.72 (C=O).HRMS (ESI) m/z: calcd: [M+H]+ 361.187032. Found: [M+H]+ 361.1869

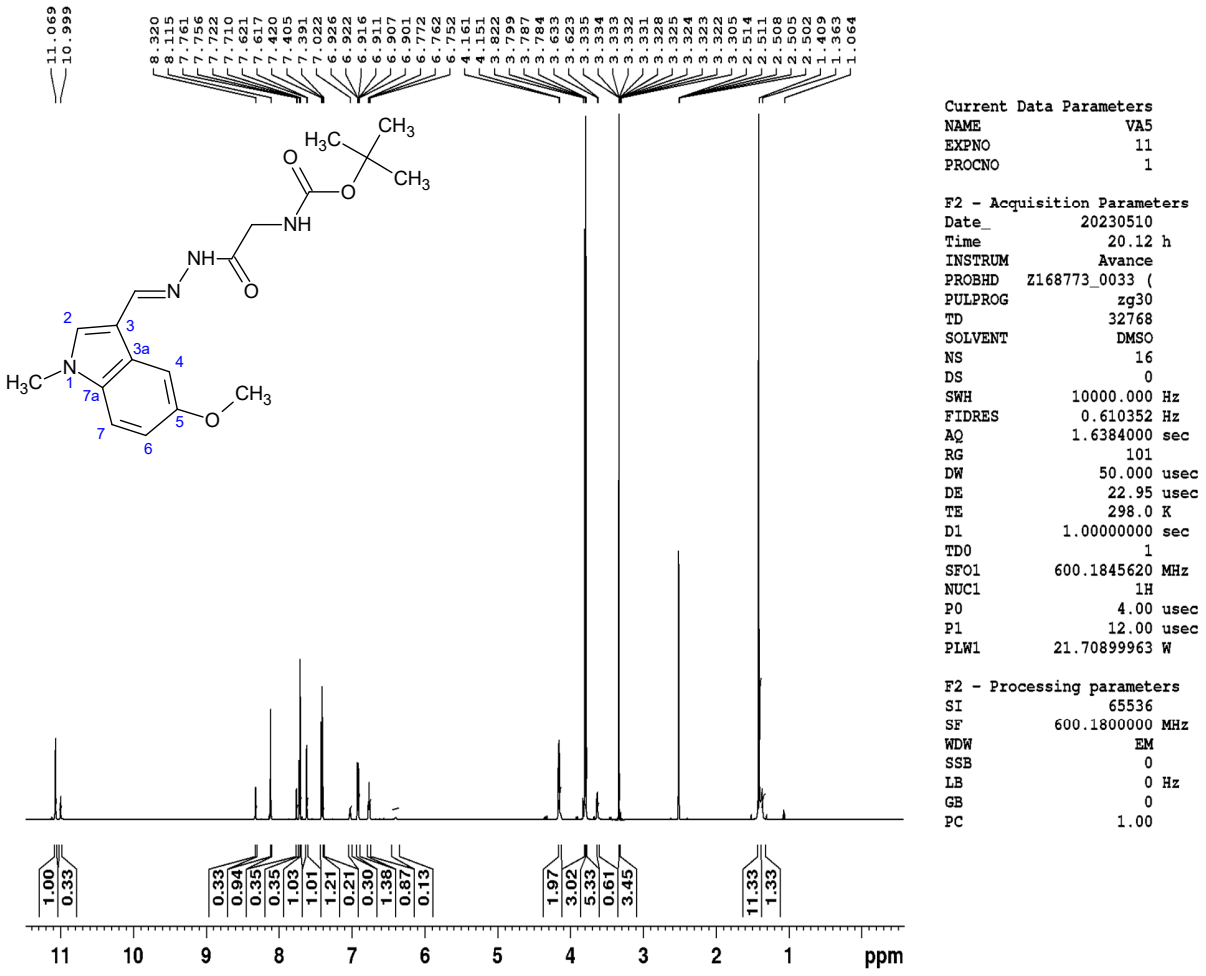
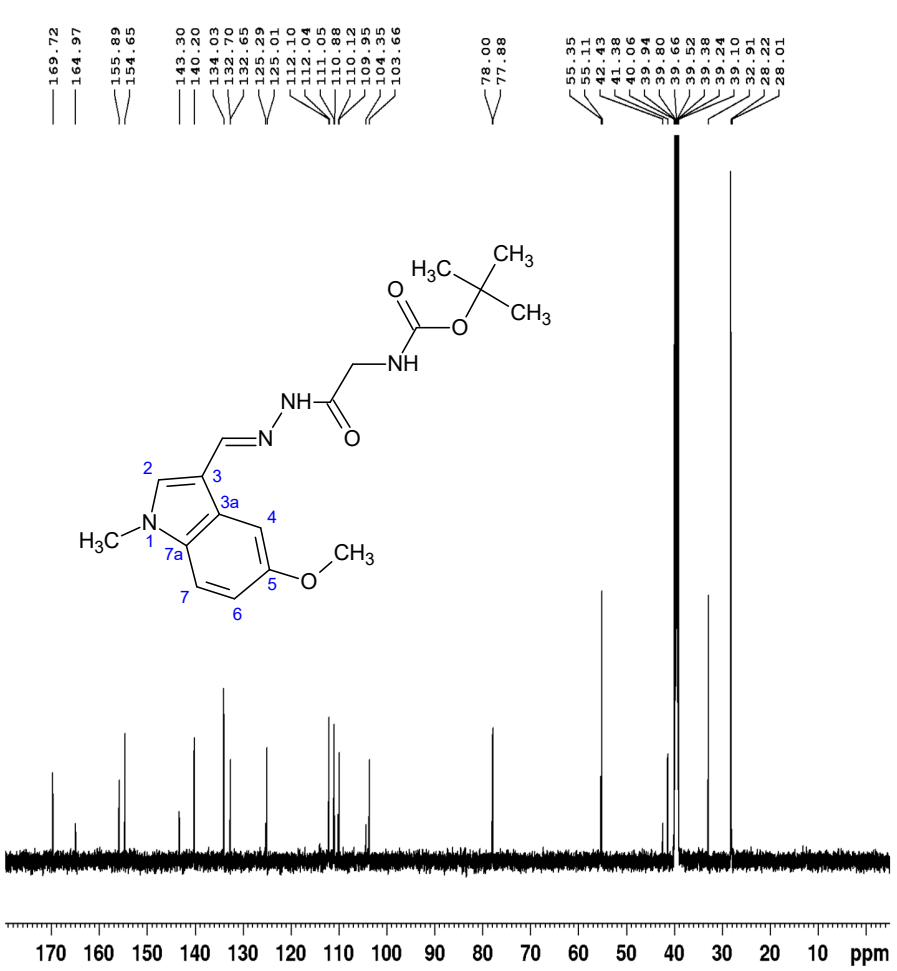


Figure S39. ^{1}H NMR spectrum of compound **3k** in DMSO-d_6

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EXPNO                  12
PROCNO                  1

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TD                32768
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FIDRES         2.179827 Hz
AQ            0.4587520 sec
RG                   101
DW                14.000 usec
DE                18.00 usec
TE                298.0 K
D1           1.50000000 sec
D11          0.03000000 sec
TD0                    1
SFO1        150.9319844 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1        67.54000092 W
SFO2        600.1824007 MHz
NUC2                1H
CPDPRG[2        waltz16
PCPD2             80.00 usec
PLW2        21.72701073 W
PLW12        0.49773711 W

F2 - Processing parameters
SI                 65536
SF          150.9154539 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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Figure S40. ^{13}C NMR spectrum of compound **3k** in DMSO-d_6

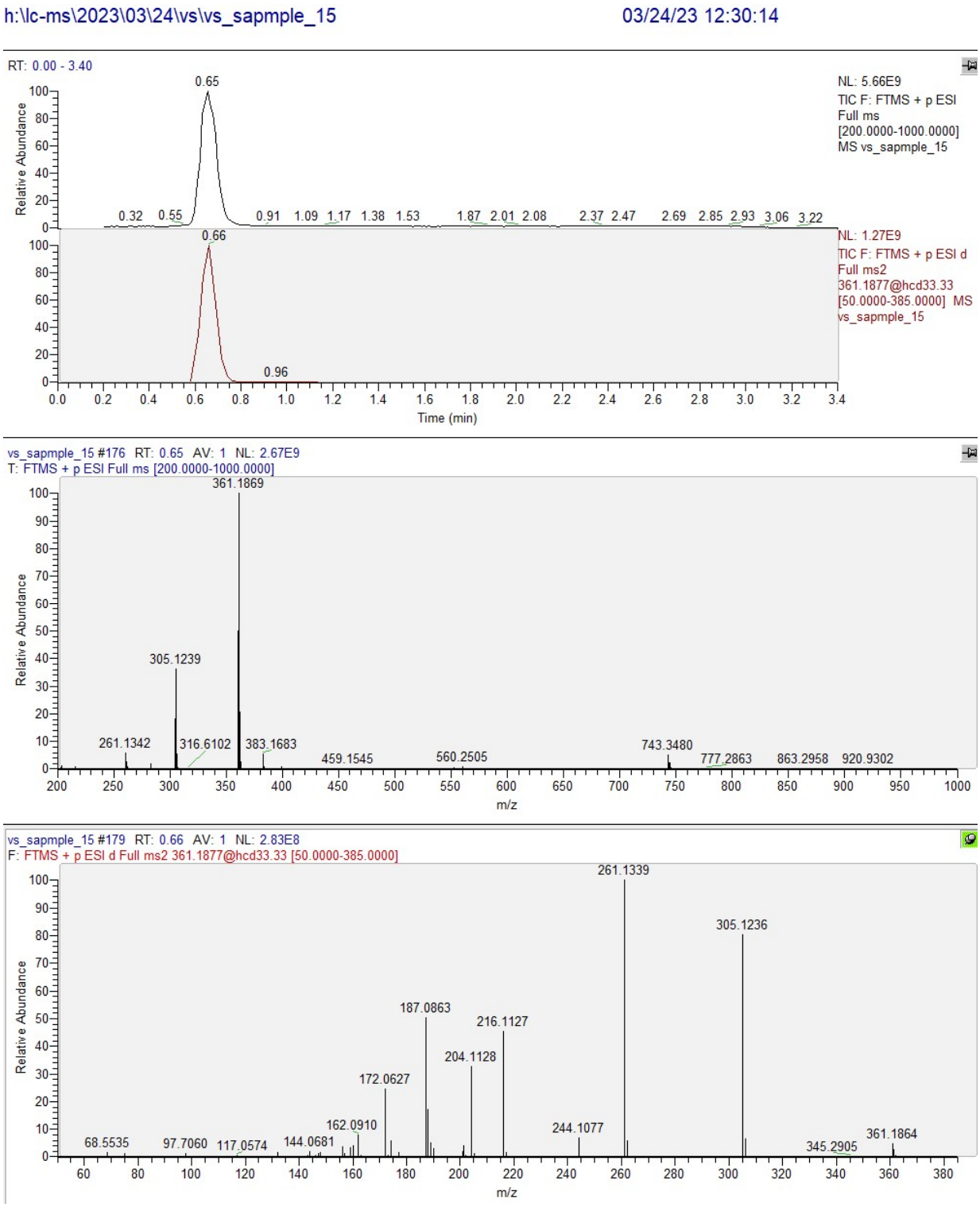


Figure S41. HRMS of compound **3k**

***12.. tert-butyl (2-{(2E)-2-[(1-methyl-1H-indol-3-yl)methylidene]hydrazinyl}-2-oxoethyl)carbamate,* 3l**

Yield: 54%; m.p. 178-179◦C.[1]H NMR (600 MHz, DMSO-d6): 1:0.40 mixture of conformers; signals for major *synperiplanar* conformer around the amide bond: δ = 1.41 (s, 9H, CH_3), 3.82 (s, 3H, NCH_3), 4.12 (d, J=6.1 Hz, 2H, CH_2), 6.83 (t, J=6.1 Hz, 1H, NH), 7.22 (ddd, J=0.7, 7.1, 7.8 Hz, 1H, H-5), 7.28 (ddd, J=1.2, 7.0, 8.2 Hz, 1H, H-6), 7.51 (d, J=7.5 Hz, 1H, H-7), 7.77 (s, 1H, C-2), 8.08 (d, J=7.8 Hz, 1H, H-4), 8.13 (s, 1H, CH), 11.06 (s, 1H, NH); resolved signals for minor *antiperiplanar* conformer around the amide bond: 8.34 (s, 1H, CH), 11.02 (s, 1H, NH).

[13]C NMR (151 MHz, DMSO-d6): signals for major *synperiplanar* conformer around the amide bond: δ = 28.24 (CH_3), 32.76 (NCH_3), 41.42 (CH_2), 77.87 (OC), 110.27 (C-7), 110.38 (C-3), 120.83 (C-5), 121.55 (C-4), 122.66 (C-6), 124.43 (C-3a), 133.90 (C-2), 137.56 (C-7a), 140.22 (CH), 155.96 (OC=O), 169.78 (C=O).HRMS (ESI) m/z: calcd: [M+H]+ 331.176467. Found: [M+H]+ 331.1764

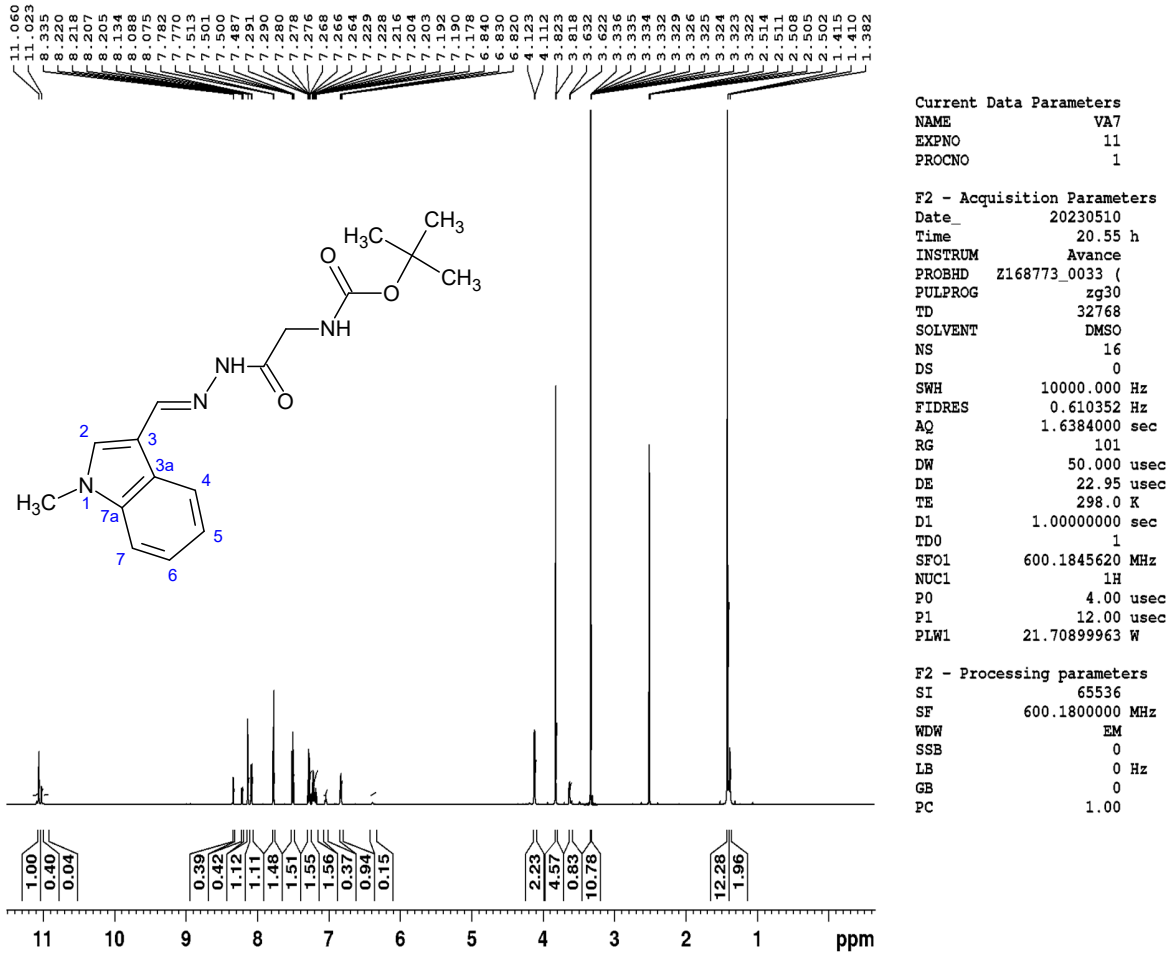
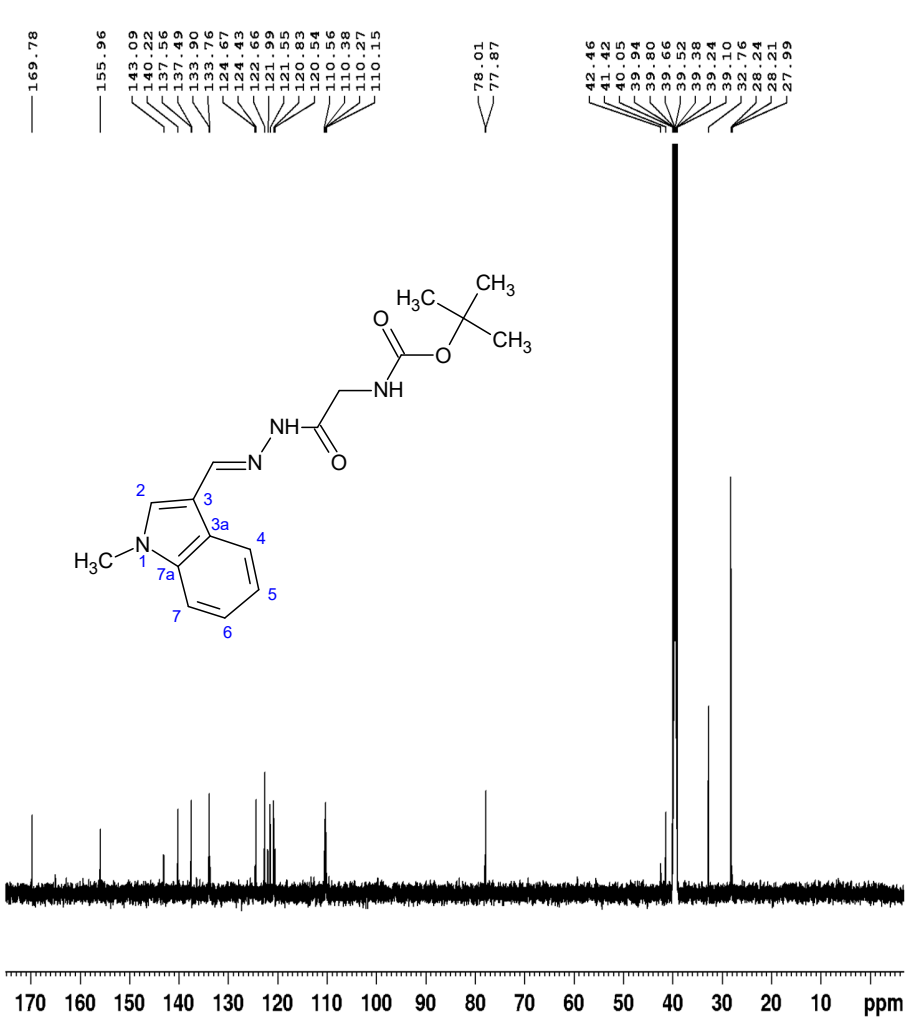


Figure S42. [1]H NMR spectrum of compound **3l** in DMSO-d_6

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EXPNO                   12
PROCNO                   1

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PULPROG           zgdc30
TD                 32768
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SWH            35714.286 Hz
FIDRES          2.179827 Hz
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RG                     101
DW                14.000 usec
DE                18.00 usec
TE                298.0 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                      1
SFO1         150.9319844 MHz
NUC1                  13C
P0                 3.33 usec
P1                10.00 usec
PLW1          67.54000092 W
SFO2         600.1824007 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2              80.00 usec
PLW2          21.72701073 W
PLW12          0.49773711 W

F2 - Processing parameters
SI                   65536
SF           150.9154538 MHz
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PC                   1.40
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Figure S43. ^{13}C NMR spectrum of compound **3l** in DMSO-d_6

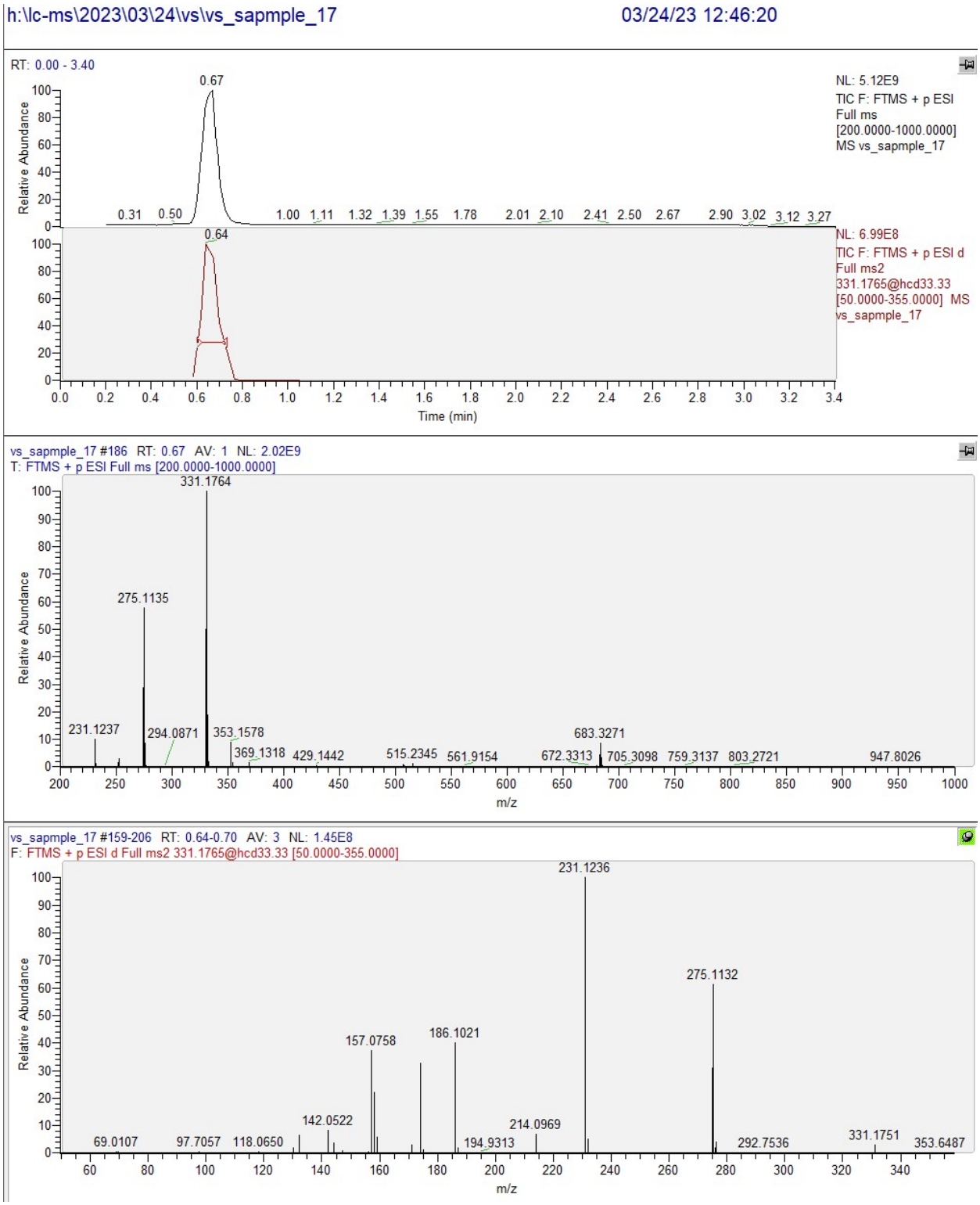
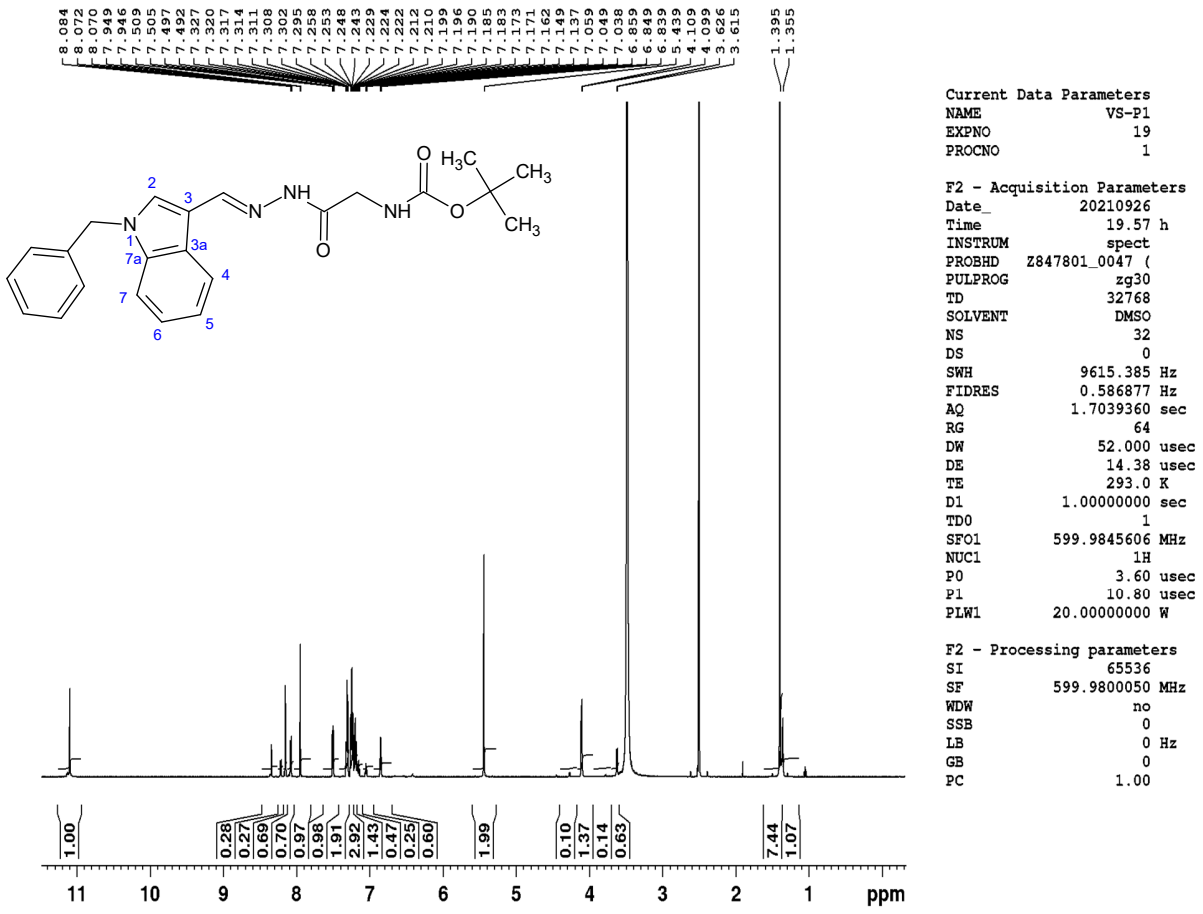


Figure S44. HRMS of compound **3l**

13. tert-butyl (2-{(2E)-2-[(1-benzyl-1H-indol-3-yl)methylidene]hydrazinyl}-2-oxoethyl)carbamate, **3m**

Yield: 90%; m.p. 207–208 ◦C.^{1}H NMR (600 MHz, DMSO-d_6): 1:0.40 mixture of conformers; signals for major *antiperiplanar* conformer around the amide bond: δ 11.10 (s, 1H, NH), 8.15 (s, 1H, CH), 8.08 (d, J = 8.3 Hz, 1H, H-4), 7.95 (s, 1H, H-2), 7.50 (d, J = 7.4 Hz, 1H, H-7), 7.30 (d, J = 7.5 Hz, 2H, o-Ph), 7.26-7.22 (m, 1H, H-6), 7.21-7.18 (m, 1H, H-5), 7.24 (t, J = 8.7 Hz, 2H, m-Ph), 7.20 (t, J = 8.0 Hz, 1H, p-Ph), 6.85 (t, J = 6.1 Hz, 1H, NH), 5.44 (s, 2H, CH_2), 4.10 (d, J = 6.1 Hz, 2H, CH_2), 1.40 (s, 9H, CH_3); resolved signals for minor *antiperiplanar* conformer around the amide bond: 7.05 (t, J = 6.0 Hz, 1H, NH), 8.21 (d, J = 7.9 Hz, 1H, H-4), 8.34 (s, 1H, CH) , 3.62 (d, J = 6.1 Hz, 2H, CH_2).
^{13}C NMR (151 MHz, DMSO-d_6): signals for major *antiperiplanar* conformer around the amide bond: δ 170.03 (C=O), 156.16 (O-C=O), 140.39 (CH), 137.68 (i-Ph), 137.02 (C-7a), 133.54 (C-2), 128.79 (C-o), 127.72 (p-Ph), 127.27 (m-Ph), 124.85 (C-3a), 123.03 (C-5), 121.87 (C-4), 121.18 (C-6), 111.15 (C-3), 110.93 (C-7), 78.12 (C), 49.45 (CH_2), 42.56 (CH_2), 28.38 (CH_3); resolved signals for minor *synperiplanar* conformer around the amide bond: 143.22 (CH), 122.29 (C-2), 78.27 (C), 41.57 (CH_2), 28.35 (CH_3). HRMS (ESI) m/z: calcd: [M+H]+ 407.207767. Found: [M+H]+ 407.2078

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PROCNO                    1

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PULPROG              zg30
TD                  32768
SOLVENT              DMSO
NS                      32
DS                       0
SWH               9615.385 Hz
FIDRES            0.586877 Hz
AQ               1.7039360 sec
RG                      64
DW                 52.000 usec
DE                 14.38 usec
TE                 293.0 K
D1              1.00000000 sec
TD0                      1
SFO1           599.9845606 MHz
NUC1                    1H
P0                 3.60 usec
P1                 10.80 usec
PLW1           20.00000000 W

F2 - Processing parameters
SI                    65536
SF             599.9800050 MHz
WDW                     no
SSB                      0
LB                       0 Hz
GB                       0
PC                    1.00
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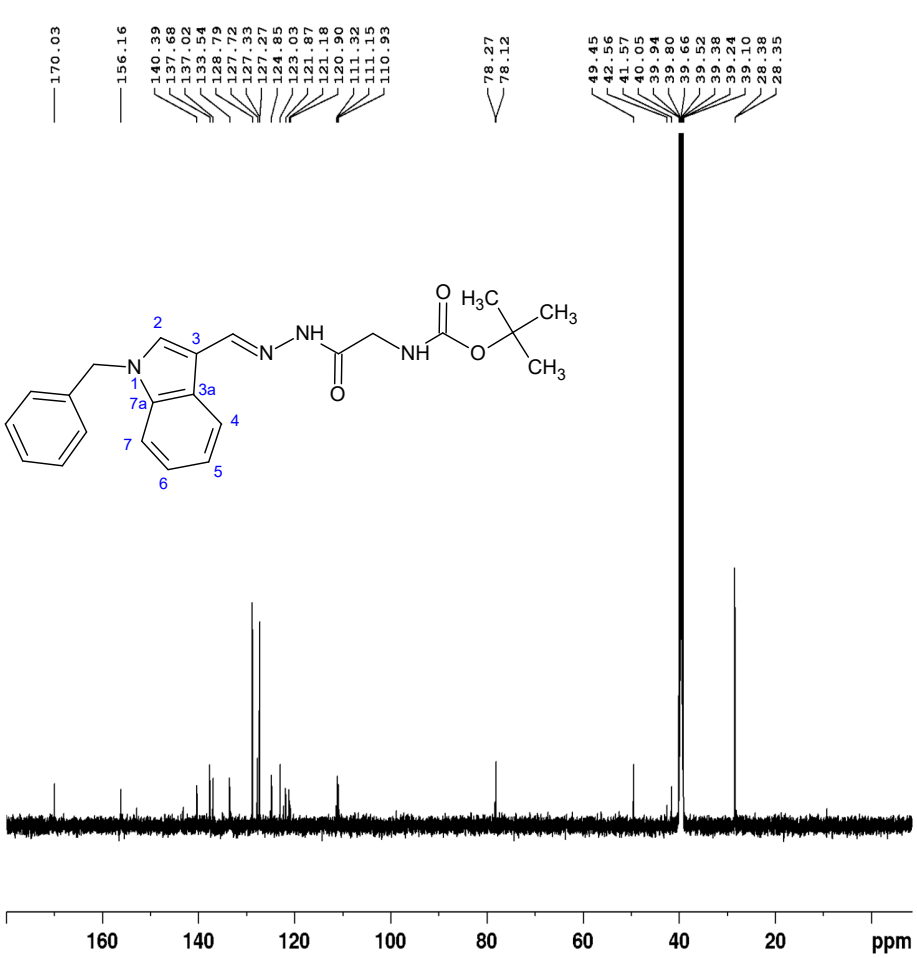
Figure S45. ^{1}H NMR spectrum of compound **3m** in DMSO-d_6

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Current Data Parameters
NAME                  VS-P1
EXPNO                    16
PROCNO                    1

F2 - Acquisition Parameters
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INSTRUM              spect
PROBHD    Z847801_0047 (
PULPROG              zgdc30
TD                   32768
SOLVENT               DMSO
NS                    1024
DS                       0
SWH              36057.691 Hz
FIDRES            2.200787 Hz
AQ                0.4543829 sec
RG                    2050
DW                  13.867 usec
DE                    6.50 usec
TE                  293.0 K
D1               1.50000000 sec
D11              0.03000000 sec
TD0                      1
SFO1           150.8816889 MHz
NUC1                   13C
P0                    3.27 usec
P1                    9.80 usec
PLW1           40.00000000 W
SFO2           599.9824003 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2                70.00 usec
PLW2           20.00000000 W
PLW12           0.53044999 W

F2 - Processing parameters
SI                    65536
SF             150.8651383 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
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Figure S46. ^{13}C NMR spectrum of compound **3m** in DMSO-d_6

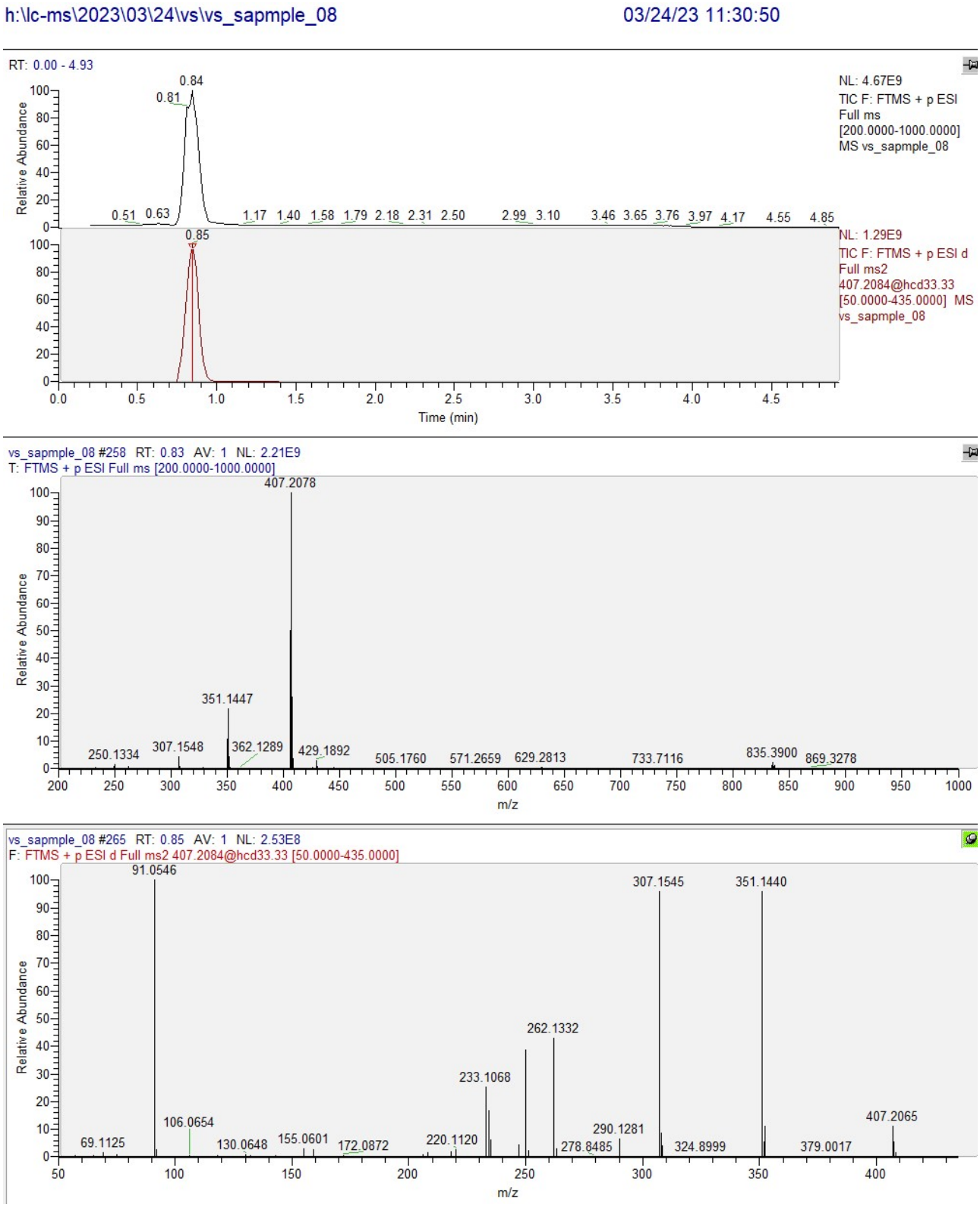


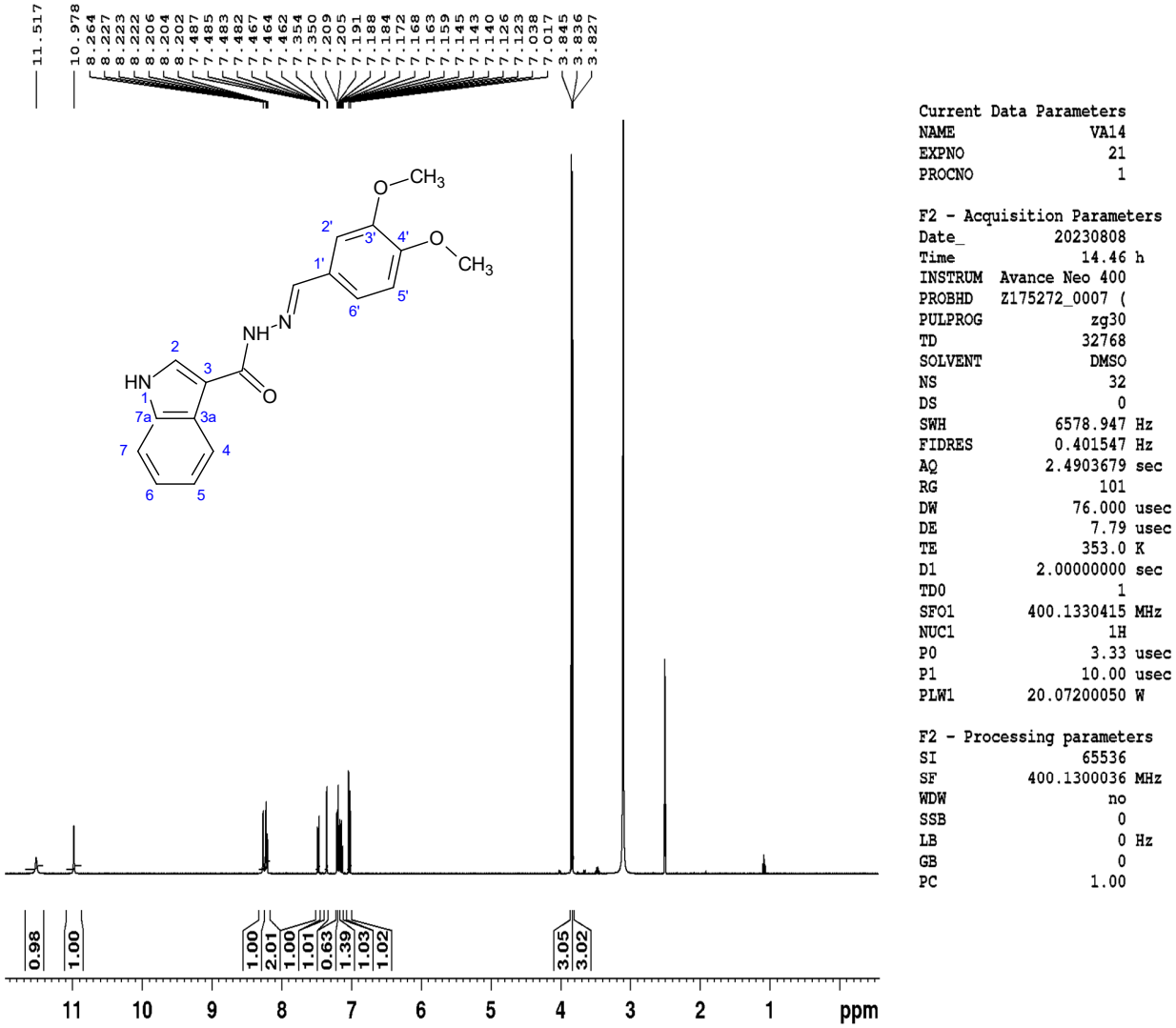
Figure S47. HRMS of compound **3m**

14. 2-(1*H*-indol-3-yl)-*N*'-[(*E*)-(5-methoxy-1*H*-indol-3-yl)methylidene]acetohydrazide, 3n [1]

^{1}H NMR, ^{13}C NMR and HRMS spectra of compound **3n** can be found in https://doi.org/10.1016/j.bmcl.2021.128516

***15. N'-[(E)-(3,4-dimethoxyphenyl)methylidene]-1H-indole-3-carbohydrazide,* 3o**

Yield: 78%; m.p. 267-270◦C. ^{1}H NMR (400 MHz, DMSO-d_6, 353K): δ = 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 7.03 (d, J=8.3 Hz, 1H, H-5'), 7.14 (ddd, J=1.3, 7.0, 7.7 Hz, 1H, H-5), 7.18 (dt, J=1.6, 6.6 Hz, 1H, H-6), 7.20 (dd, J=1.6, 7.2 Hz, 1H, H-6'), 7.35 (d, J=1.9 Hz, 1H, H-2'), 7.48 (d, J=8.0 Hz, 1H, H-7), 8.21 (d, J=7.6 Hz, 1H, H-4), 8.26 (s, 1H, CH), 10.98 (bs, 1H, NH), 11.52 (bs, 1H, NH). ^{13}C NMR (151 MHz, DMSO-d_6, 353K): δ = 55.48 (CH_3), 55.56 (CH_3), 108.45 (C-3), 109.14 (C-2'), 111.45 (C-5'), 112.05 (C-7), 120.22 (C-4), 120.74 (C-5), 120.89 (C-6'), 121.73 (C-6), 126.53 (C-1'), 127.66 (C-3a), 129.17 (C-2), 135.69 (C-7a), 144.03 (CH), 149.15 (C-3'), 150.35 (C-4'), 162.13 (C=O). HRMS (ESI) *m/z*: calcd: [M+H]+ 324.134268. Found: [M+H]+ 324.13358

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EXPNO                   21
PROCNO                   1

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PULPROG               zg30
TD                   32768
SOLVENT               DMSO
NS                      32
DS                       0
SWH               6578.947 Hz
FIDRES             0.401547 Hz
AQ                2.4903679 sec
RG                     101
DW                  76.000 usec
DE                   7.79 usec
TE                  353.0 K
D1               2.00000000 sec
TD0                      1
SFO1           400.1330415 MHz
NUC1                    1H
P0                   3.33 usec
P1                  10.00 usec
PLW1           20.07200050 W

F2 - Processing parameters
SI                   65536
SF             400.1300036 MHz
WDW                    no
SSB                     0
LB                      0 Hz
GB                      0
PC                   1.00
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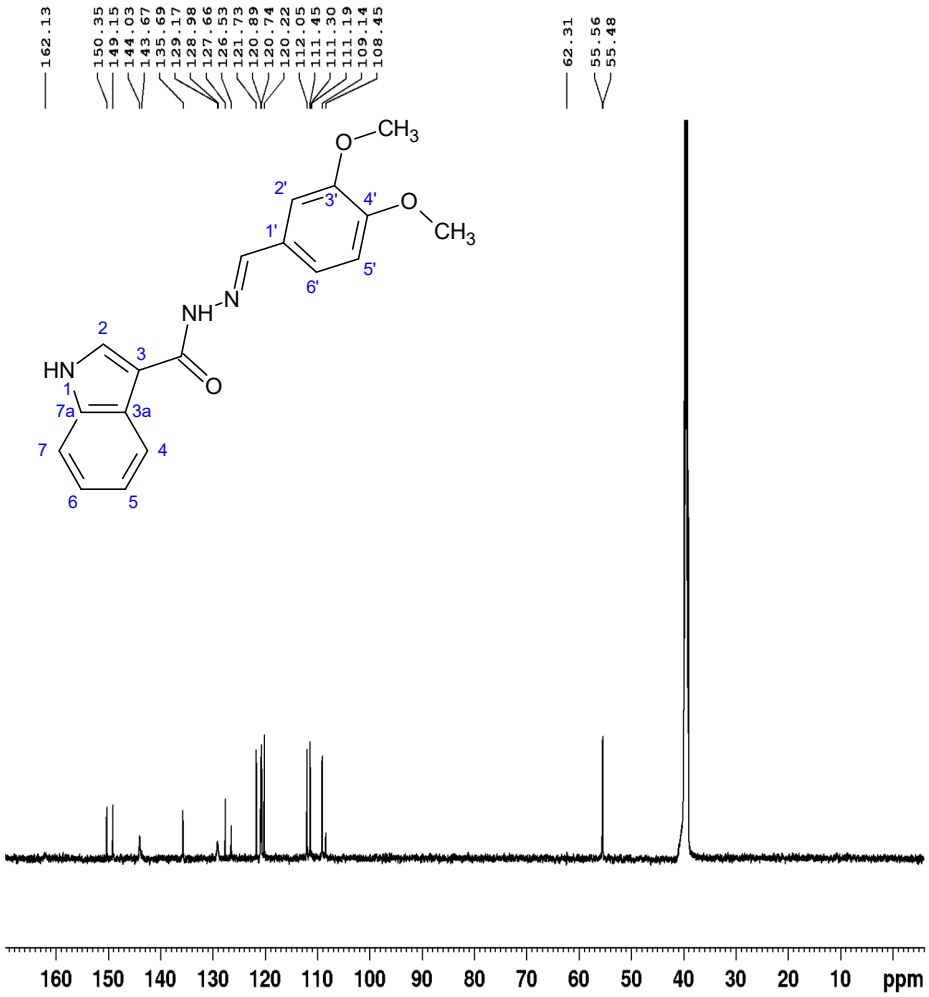
Figure S48. [1]H NMR spectrum of compound **3o** in DMSO-d_6

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EXPNO                   36
PROCNO                   1

F2 - Acquisition Parameters
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Time                 15.22 h
INSTRUM              Avance
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PULPROG              zgdc30
TD                    32768
SOLVENT                DMSO
NS                       640
DS                         0
SWH                35714.286 Hz
FIDRES             2.179827 Hz
AQ                 0.4587520 sec
RG                       101
DW                    14.000 usec
DE                    18.00 usec
TE                    353.0 K
D1                 1.50000000 sec
D11                0.03000000 sec
TD0                        1
SFO1              150.9319844 MHz
NUC1                     13C
P0                     3.33 usec
P1                    10.00 usec
PLW1              67.54000092 W
SFO2              600.1824007 MHz
NUC2                     1H
CPDPRG[2              waltz16
PCPD2                  80.00 usec
PLW2              21.72701073 W
PLW12              0.49773711 W

F2 - Processing parameters
SI                       65536
SF                150.9155076 MHz
WDW                        EM
SSB                        0
LB                     3.00 Hz
GB                         0
PC                      0.50
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Figure S49. [13]C NMR spectrum of compound **3o** in DMSO-d_6

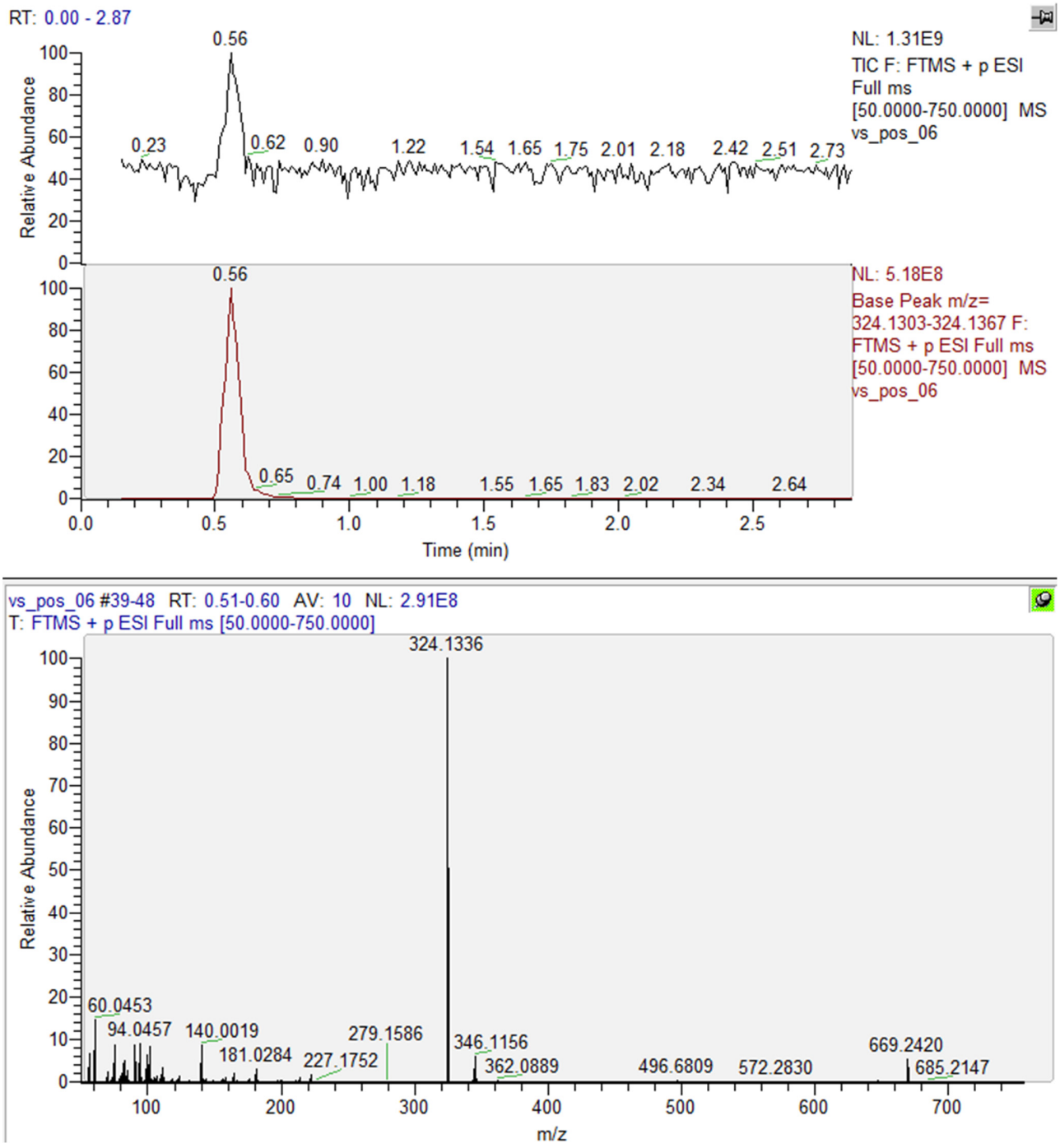
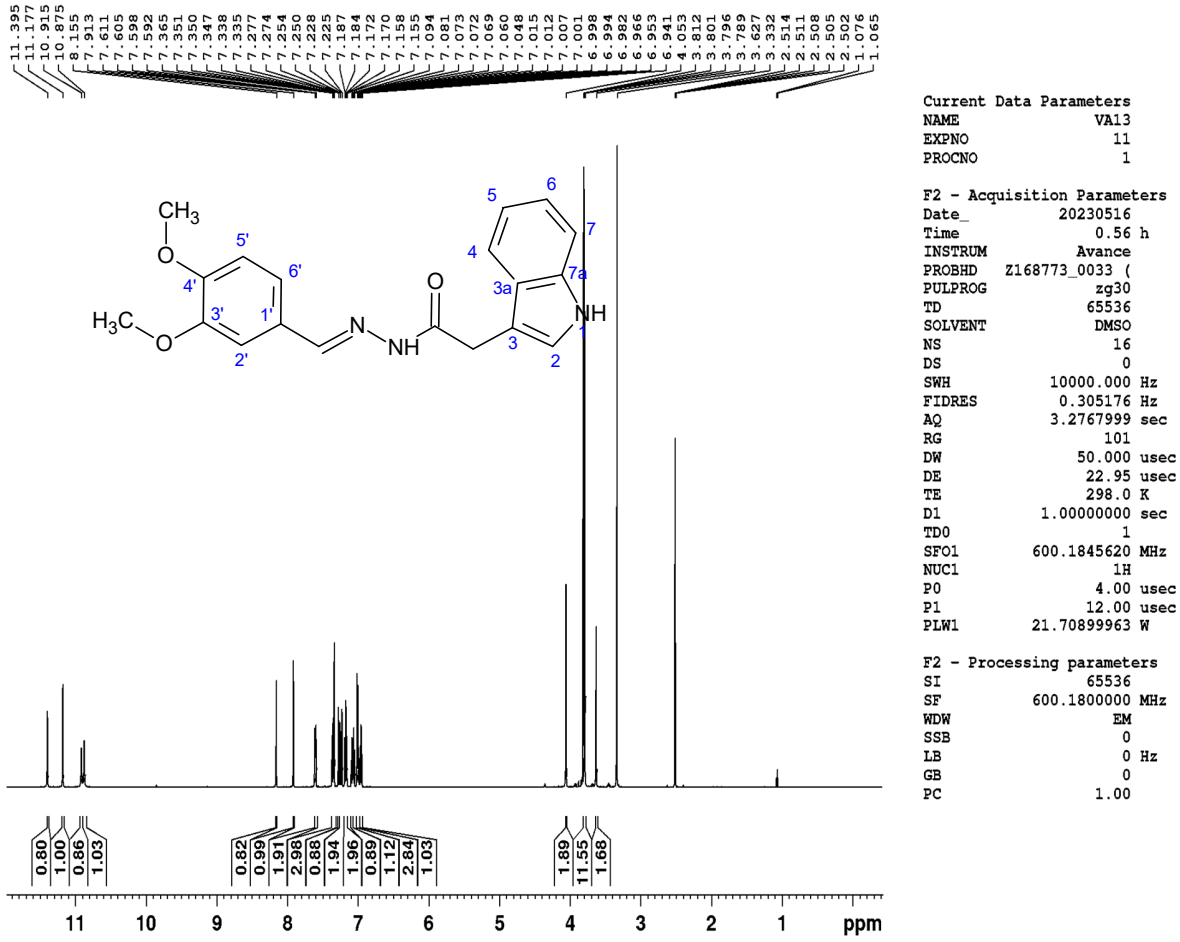


Figure S50. HRMS of compound **3o**

16. N'-[(E)-(3,4-dimethoxyphenyl)methylidene]-2-(1H-indol-3-yl)acetohydrazide, **3p**

Yield: 92%; m.p. 177-180◦C. ^{1}H NMR (600 MHz, DMSO-d_6): 1:0.80 mixture of conformers; signals for major *antiperiplanar* conformer around the amide bond: δ = 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 6.95 (t, J=7.5 Hz, 1H, H-5), 7.01 (d, 8.5 Hz, 2H, H-5'), 7.06 (t, J=7.0 Hz, 1H, H-6), 7.17 (dt, J=1.8, 8.7 Hz, 2H, H-6'), 7.28 (d, J=1.7 Hz, 1H, H-2'), 7.35 (d, J=2.42 Hz, 1H, H-2), 7.36 (d, J=9.27 Hz, 1H, H-7), 7.60 (dd, J=3.46, 7.85 Hz, 1H, H-4), 7.91 (s, 1H, CH), 10.87 (bs, 1H, NH), 11.18 (s, 1H, NH),; resolved signals for minor *antiperiplanar* conformer around the amide bond: 8.15 (s, 1H, CH), 10.91 (bs, 1H, NH), 11.40 (s, 1H, NH)

^{13}C NMR (151 MHz, DMSO-d_6): signals for major *antiperiplanar* conformer around the amide bond: δ = 29.24 (CH_2), 55.40 (OCH_3), 108.22 (C-2'), 108.25 (C-3), 111.30 (C-5'), 111.56 (C-7), 118.28 (C-4), 118.66 (C-5), 120.97 (C-6'), 121.59 (C-6), 123.86 (C-2), 127.13 (C-1'), 127.39 (C-3a), 135.98 (C-7a), 142.46 (CH), 148.99 (C-3'), 150.56 (C-4'), 172.52 (C=O). HRMS (ESI) m/z: calcd: [M+H]+ 338.149918. Found: [M+H]+ 338.14902

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PROCNO                   1

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PULPROG               zg30
TD                   65536
SOLVENT               DMSO
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FIDRES              0.305176 Hz
AQ                3.2767999 sec
RG                     101
DW                  50.000 usec
DE                  22.95 usec
TE                  298.0 K
D1               1.00000000 sec
TD0                      1
SFO1            600.1845620 MHz
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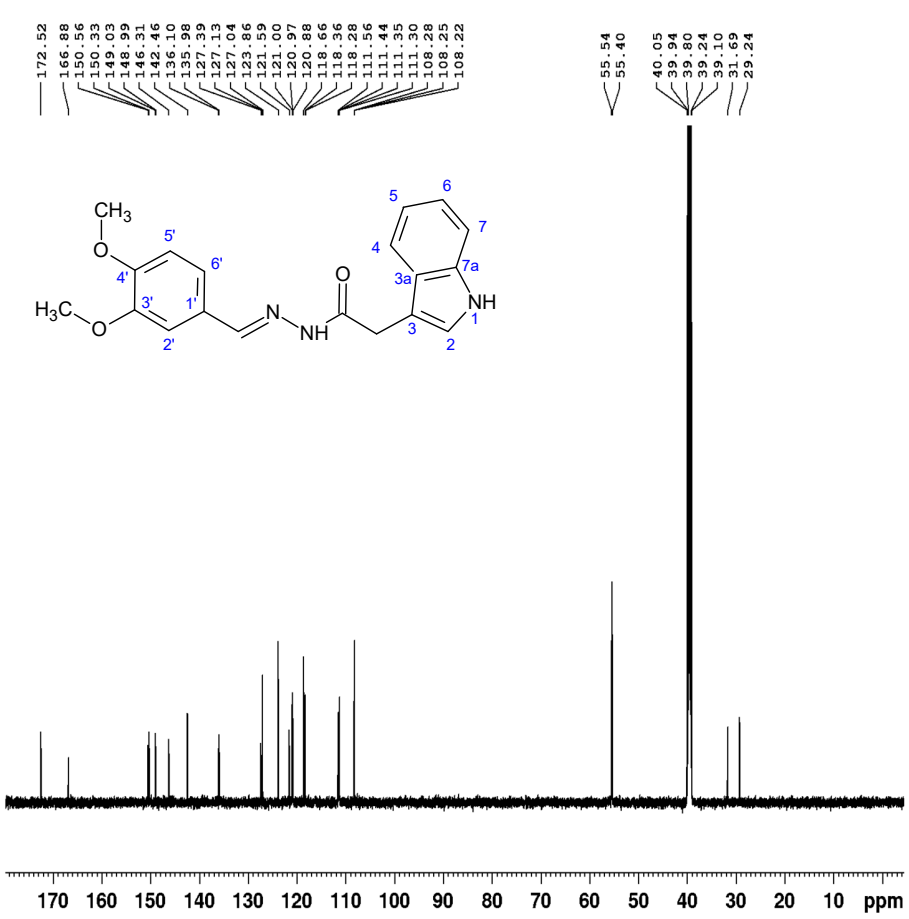
P1                  12.00 usec
PLW1            21.70899963 W

F2 - Processing parameters
SI                   65536
SF              600.1800000 MHz
WDW                     EM
SSB                      0
LB                       0 Hz
GB                       0
PC                    1.00
```

Figure S51. ^{1}H NMR spectrum of compound **3p** in DMSO-d_6

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Current Data Parameters
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EXPNO                   16
PROCNO                   1

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PULPROG             zgdc30
TD                   32768
SOLVENT                DMSO
NS                       256
DS                         0
SWH               35714.286 Hz
FIDRES             2.179827 Hz
AQ                 0.4587520 sec
RG                       101
DW                    14.000 usec
DE                    18.00 usec
TE                    298.0 K
D1                1.50000000 sec
D11               0.03000000 sec
TD0                        1
SFO1           150.9319844 MHz
NUC1                    13C
P0                     3.33 usec
P1                    10.00 usec
PLW1           67.54000092 W
SFO2           600.1824007 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                 80.00 usec
PLW2           21.72701073 W
PLW12           0.49773711 W

F2 - Processing parameters
SI                     65536
SF             150.9154538 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

Figure S52. ^{13}C NMR spectrum of compound **3p** in DMSO-d_6

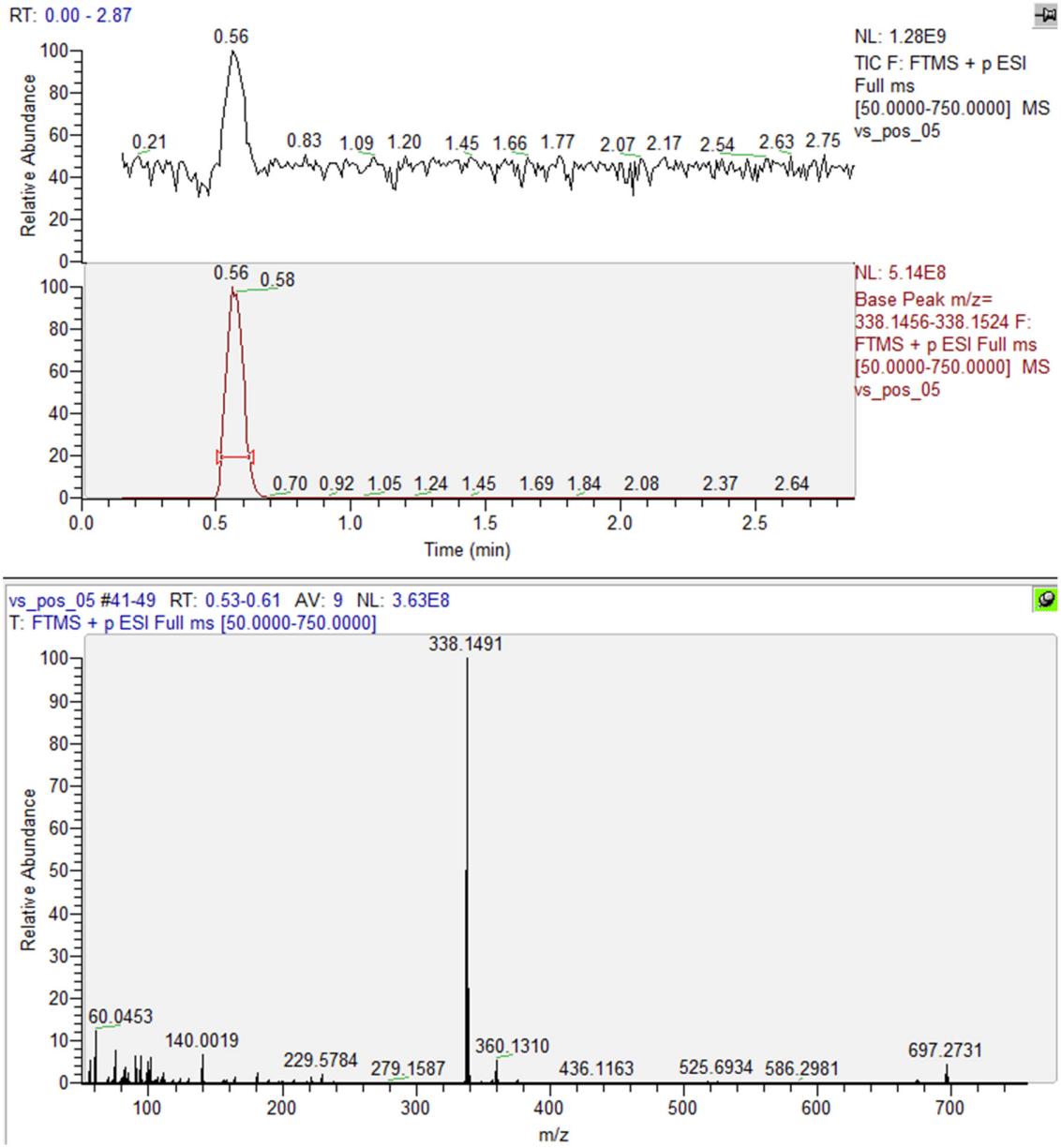


Figure S53. HRMS of compound **3p**

17. N'-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]-2-(1H-indol-3-yl)acetohydrazide, **3q**

Yield: 72%; m.p. 246-247◦C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.54 : 0.46 mixture of two conformers; signals for major conformer: δ = 3.81 (s, 3H, CH3), 4.04 (s, 2H, CH2), 6.82 (d, J=8.1 Hz, 1H, H-5'), 6.96-7.00 (m, 1H, H-5), 7.02-7.09 (m, 2H, H-6 and H-6'), 7.22 (d, J=2.3 Hz, 1H, H-2), 7.29 (d, J=1.8 Hz, 1H, H-2'), 7.33 (d, J=6.8 Hz, 1H, H-7), 7.59 (d, J=7.9 Hz, 1H, H-4), 7.87 (s, 1H, CH), 9.46 (s, 1H, OH), 10.86 (s, 1H, NH), 11.10 (s, 1H, NH); Signals for minor conformer: δ(ppm): 3.61 (s, 2H, CH2), 3.79 (s, 3H, CH3), 6.81 (d, J=8.1 Hz, 1H, H-5'), 6.93-6.97 (m, 1H, H-5), 7.02-7.09 (m, 2H, H-6 and H-6'),7.24 (d, J=1.9 Hz, 2H, H-2 and H-2'), 7.35 (d, J=7.0 Hz, 1H, H-7), 7.59 (d, J=7.9 Hz, 1H, H-4), 8.11 (s, 1H, CH), 9.48 (s, 1H, OH), 10.90 (s, 1H, NH), 11.33 (s, 1H, NH).

^{13}C-NMR (151 MHz, DMSO-d$_6$): 0.54 : 0.46 mixture of two conformers; signals for major conformer: δ = 29.20 (CH2), 55.51 (CH3), 108.33 (C-3), 109.10 (C-2'), 111.30 (C-7), 115.37 (C-5'), 118.27 (C-5), 118.68 (C-4), 120.88 (C-6'), 121.11 (C-6), 123.86 (C-2), 125.82 (C-1'), 127.42 (C-4a), 135.98 (C-7a), 142.81 (CH), 147.97 (C-3'), 148.51 (C-4'), 172.43 (C=O); Signals for minor conformer: δ(ppm): 31.69 (CH2), 55.51 (CH3), 108.31 (C-3), 108.93 (C-2'), 111.35 (C-7), 115.52 (C5'), 118.36 (C-5), 118.68 (C-4), 121.00 (C-6'), 121.87 (C-6), 123.86 (C-2), 125.73 (C-1'), 127.14 (C-4a), 136.10 (C-7a), 146.65 (CH), 147.97 (C-3'), 148.78 (C-4'), 166.79 (C=O).HRMS (ESI) m/z: calcd: [M+H]+ 324.134268. Found: [M+H]+ 324.1341

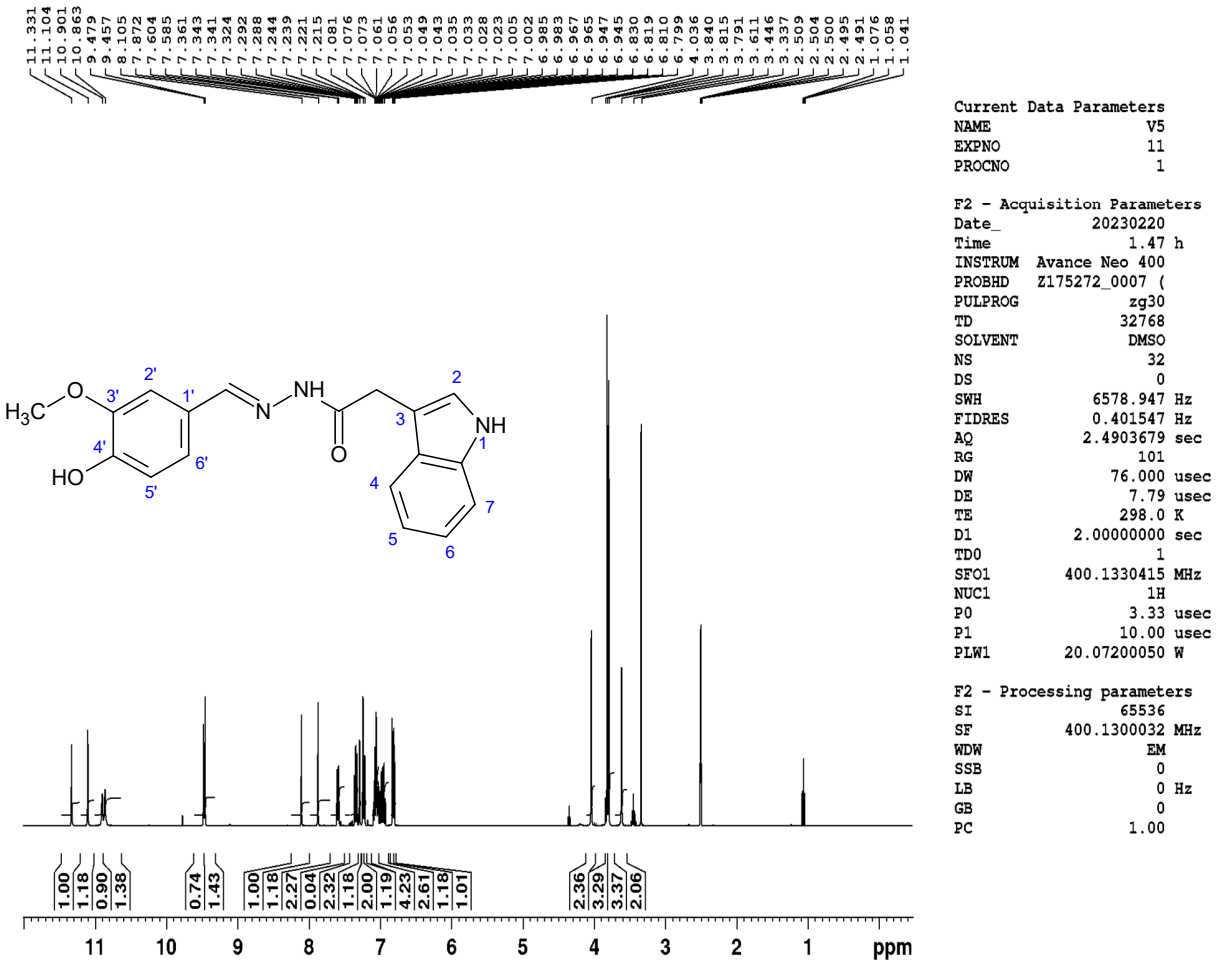
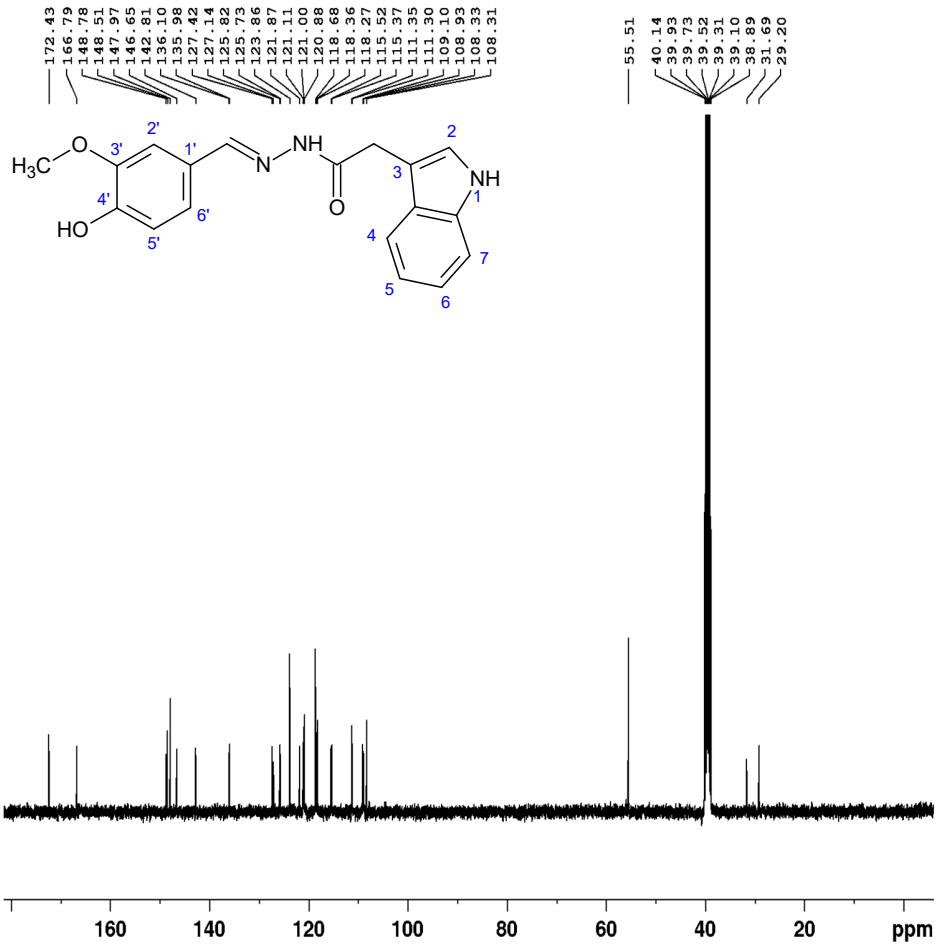


Figure S54. ^{1}H NMR spectrum of compound **3q** in DMSO-*d*$_6$

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EXPNO                  14
PROCNO                  1

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PULPROG            zgdc30
TD                  32768
SOLVENT              DMSO
NS                   1024
DS                      0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ              0.6881280 sec
RG                     36
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                     1
SFO1         100.6238383 MHz
NUC1                  13C
P0                 3.33 usec
P1                10.00 usec
PLW1         58.46900177 W
SFO2         400.1316008 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2         20.07200050 W
PLW12         0.24781001 W

F2 - Processing parameters
SI                  65536
SF           100.6128165 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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Figure S55. ^{13}C NMR spectrum of compound **3q** in DMSO-d_6

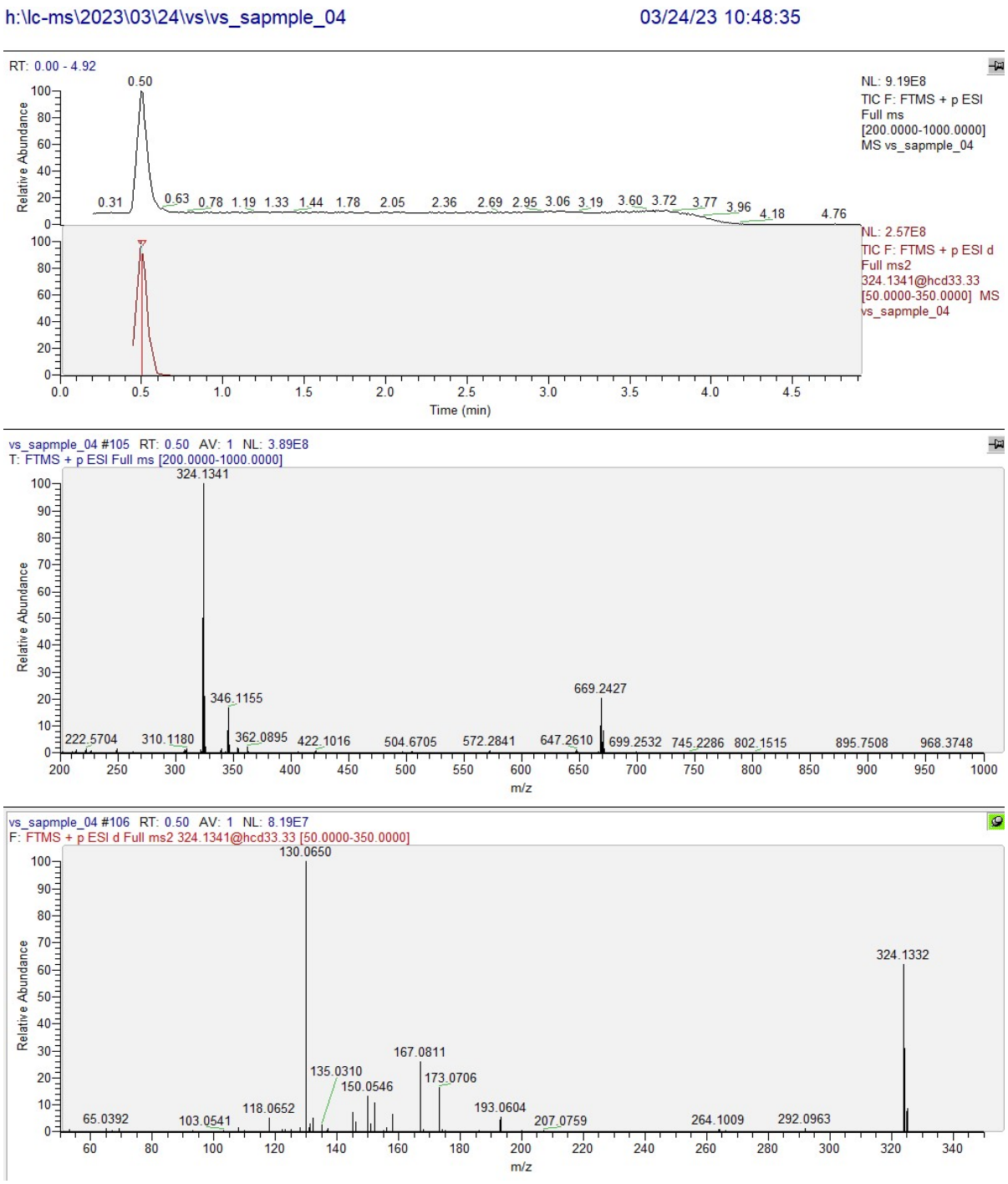


Figure S56. HRMS of compound **3q**

18. 2,4-dihydroxy-N'-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]benzohydrazide, **3r**

Yield: 76%; m.p. 242-243◦C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.36 (s, 3H, CH_3), 6.31 (d, J=2.4 Hz, 1H, H-3), 6.37 (dd, J=2.4, 8.7 Hz, 1H, H-5), 6.85 (d, J=8.1 Hz, 1H, H-6'), 7.10 (dd, J=1.8, 8.1 Hz, 1H, H-5'), 7.32 (d, J=1.8 Hz, 1H, H-2'), 7.80 (d, J=8.7 Hz, 1H, H-6), 8.33 (s, 1H, CH), 9.56 (s, 1H, OH), 10.19 (s, 1H, OH), 11.54 (s, 1H, NH), 12.45 (s, 1H, OH).
^{13}C NMR (100 MHz, DMSO-d_6): 55.55 (CH_3), 102.86 (C-3), 106.20 (C-1), 107.33 (C-5), 108.99 (C-2'), 115.45 (C-6'), 122.27 (C-5'), 125.59 (C-1'), 129.49 (C-6), 148.05 (C-4'), 148.61 (CH), 149.09 (C-3'), 162.31 (C-4), 162.57 (C-2), 165.28 (C=O).
HRMS (ESI) m/z: calcd: [M+H]+ 303.097548. Found: [M+H]+ 303.0974

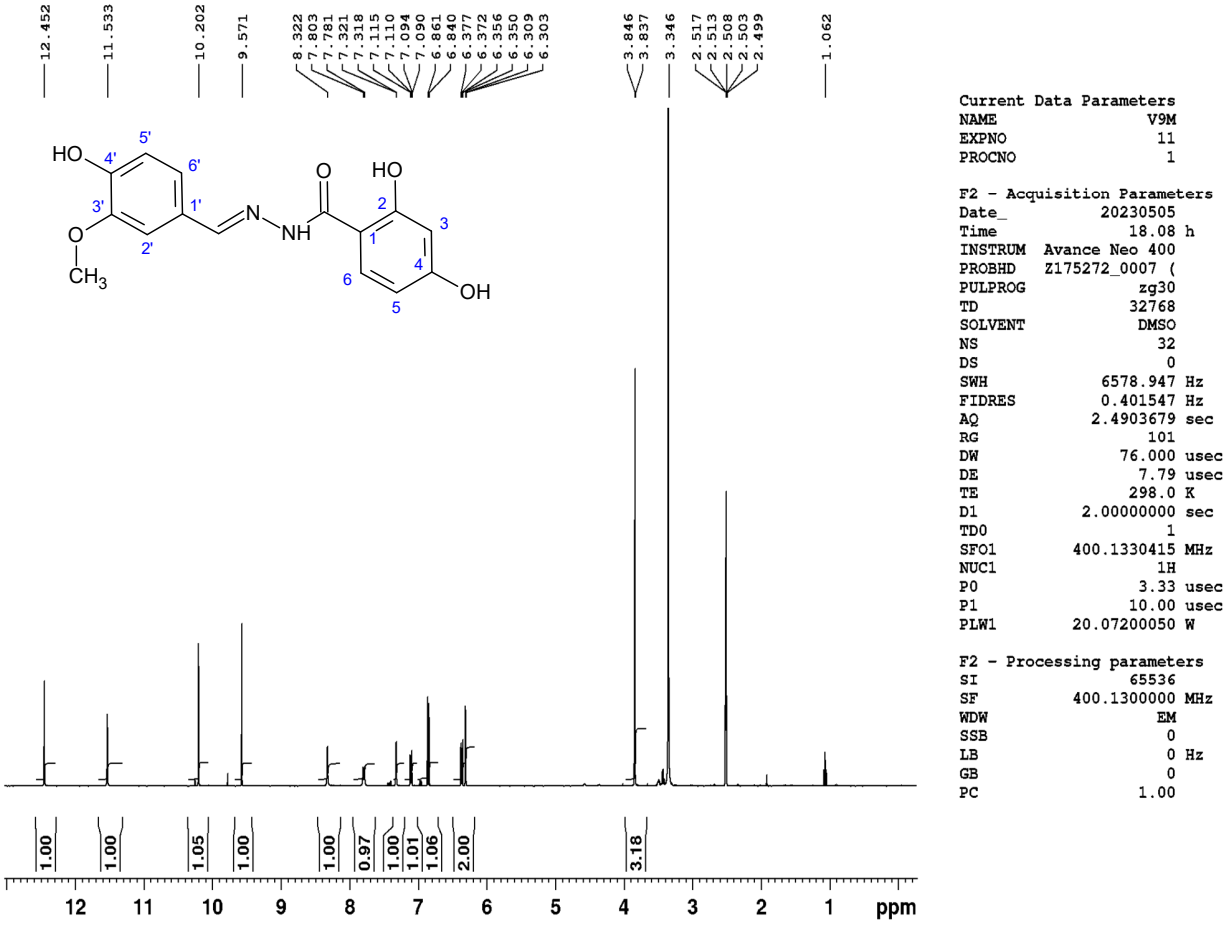
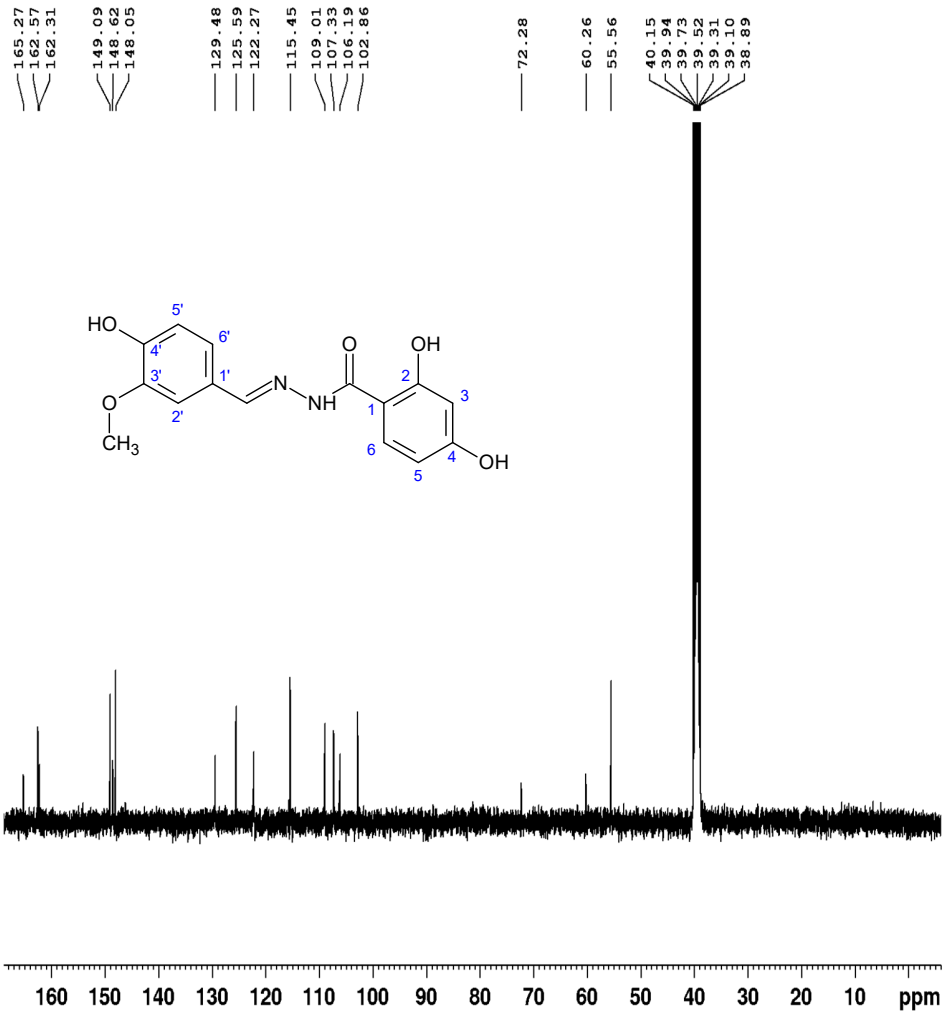


Figure S57. ^{1}H NMR spectrum of compound **3r** in DMSO-d_6

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EXPNO                  16
PROCNO                  1

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PULPROG           zgdc30
TD                 32768
SOLVENT             DMSO
NS                  4096
DS                     0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ              0.6881280 sec
RG                    32
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                    1
SFO1         100.6238383 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1         58.46900177 W
SFO2         400.1316008 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         20.07200050 W
PLW12         0.24781001 W

F2 - Processing parameters
SI                 65536
SF           100.6128150 MHz
WDW                EM
SSB                 0
LB                1.00 Hz
GB                  0
PC                1.40
```

Figure S58. ^{13}C NMR spectrum of compound **3r** in DMSO-d_6

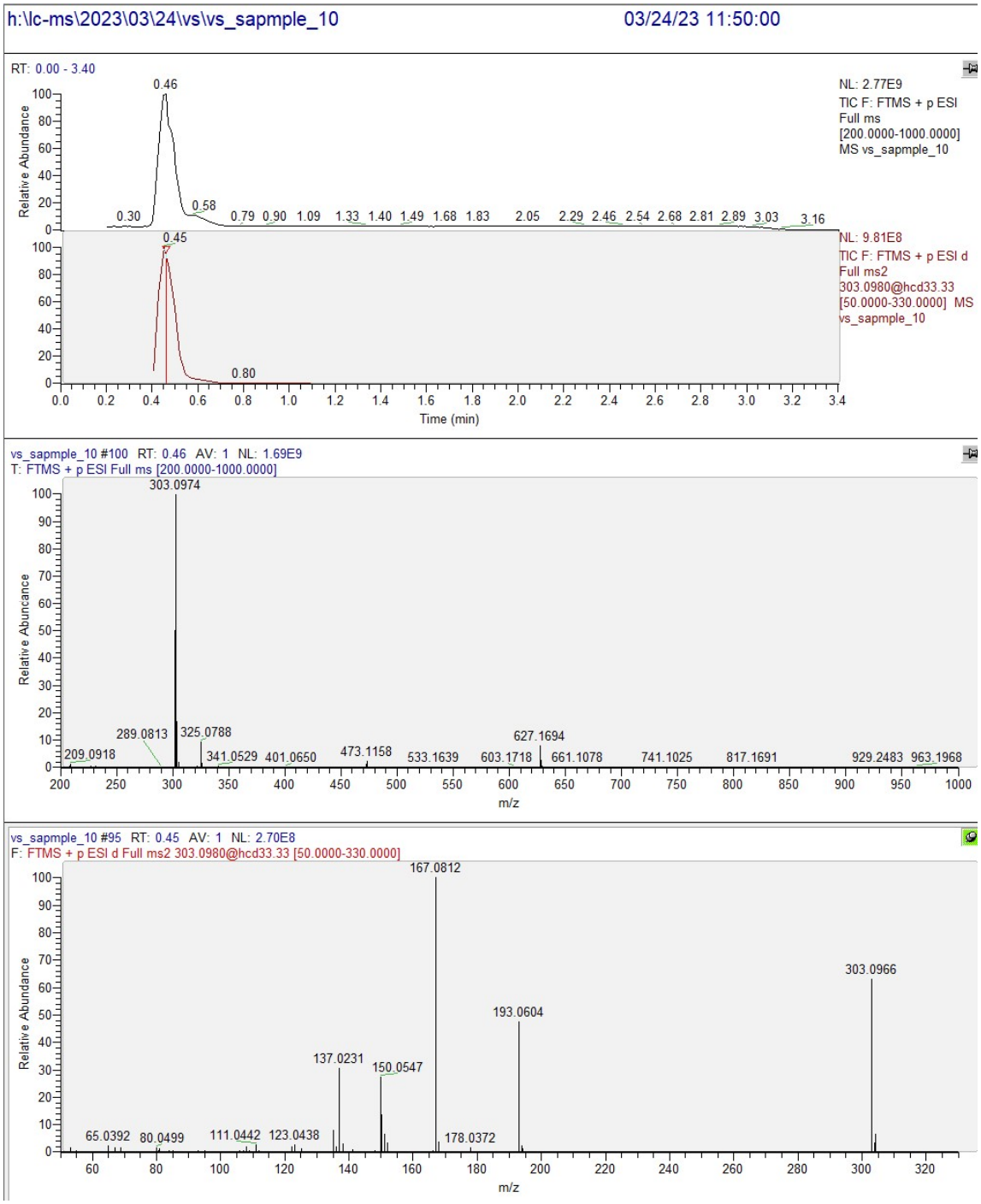


Figure S59. HRMS of compound **3r**

19. N'-[(E)-(1-benzylpiperidin-4-yl)methylidene]benzenesulfonohydrazide, **5a**

Yield: 59%; m.p. 110-111◦C.^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.26-1.36 (m, 2H, CH_2), 1.54-1.58 (m, 2H, CH_2), 1.91-1.97 (m, 2H, CH_2), 2.05-2.14 (m, 1H CH), 2.65-2.68 (m, 2H, CH_2), 3.40 (s, 2H, CH_2), 7.19 (d, J=4.8 Hz, 1H, CH), 7.21-7.27 (m, 3H, H-2'', H-4'' and H-6''), 7.29-7.33 (m, 2H, H-3'' and H-5''), 7.59-7.63 (m, 2H, H-3' and H-5'), 7.65-7.69 (m, 1H, H-4'), 7.78-7.81 (m, 2H, H-2' and H-6'), 10.93 (1H, s).

^{13}C NMR (DMSO) (100 MHz, DMSO-d_6): δ = 27.62 (CH_2), 36.94 (CH), 51.11 (CH_2), 61.25 (CH_2), 125.85 (C-4''), 126.12 (C-2' and C-6'), 127.11 (C-3'' and C-5''), 127.75 (C-2'' and C-6''), 128.07 (C-3' and C-5'), 131.86 (C-4'), 137.28 (C-1''), 137.94 (C-1'), 153.47 (CH).HRMS (ESI) m/z: calcd: [M+H]+ 358.158373. Found: [M+H]+ 358.1581

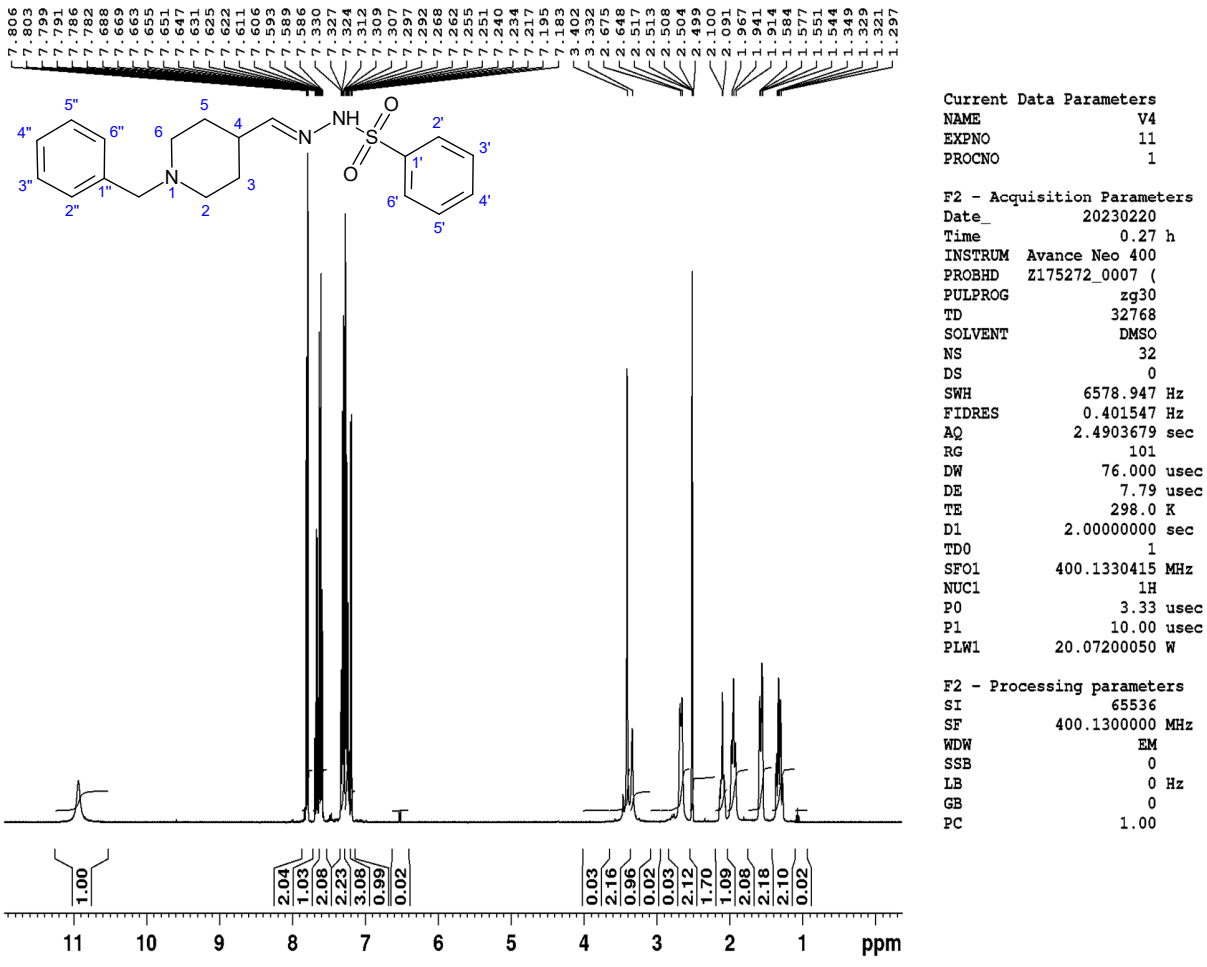
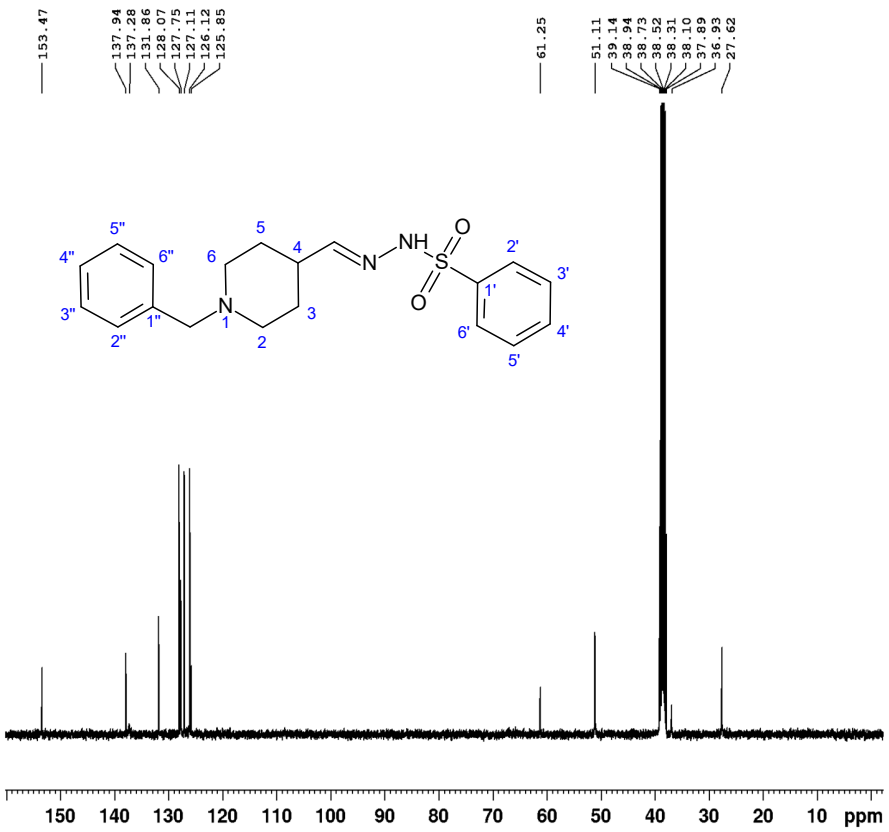


Figure S60. ^{1}H NMR spectrum of compound **5a** in DMSO-d_6

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EXPNO                  14
PROCNO                  1

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TD                32768
SOLVENT            DMSO
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DS                     0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ              0.6881280 sec
RG                    36
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                    1
SFO1         100.6238383 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1         58.46900177 W
SFO2         400.1316008 MHz
NUC2                1H
CPDPRG[2        waltz16
PCPD2             90.00 usec
PLW2         20.07200050 W
PLW12         0.24781001 W

F2 - Processing parameters
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WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
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Figure S61. ^{13}C NMR spectrum of compound **5a** in DMSO-d_6

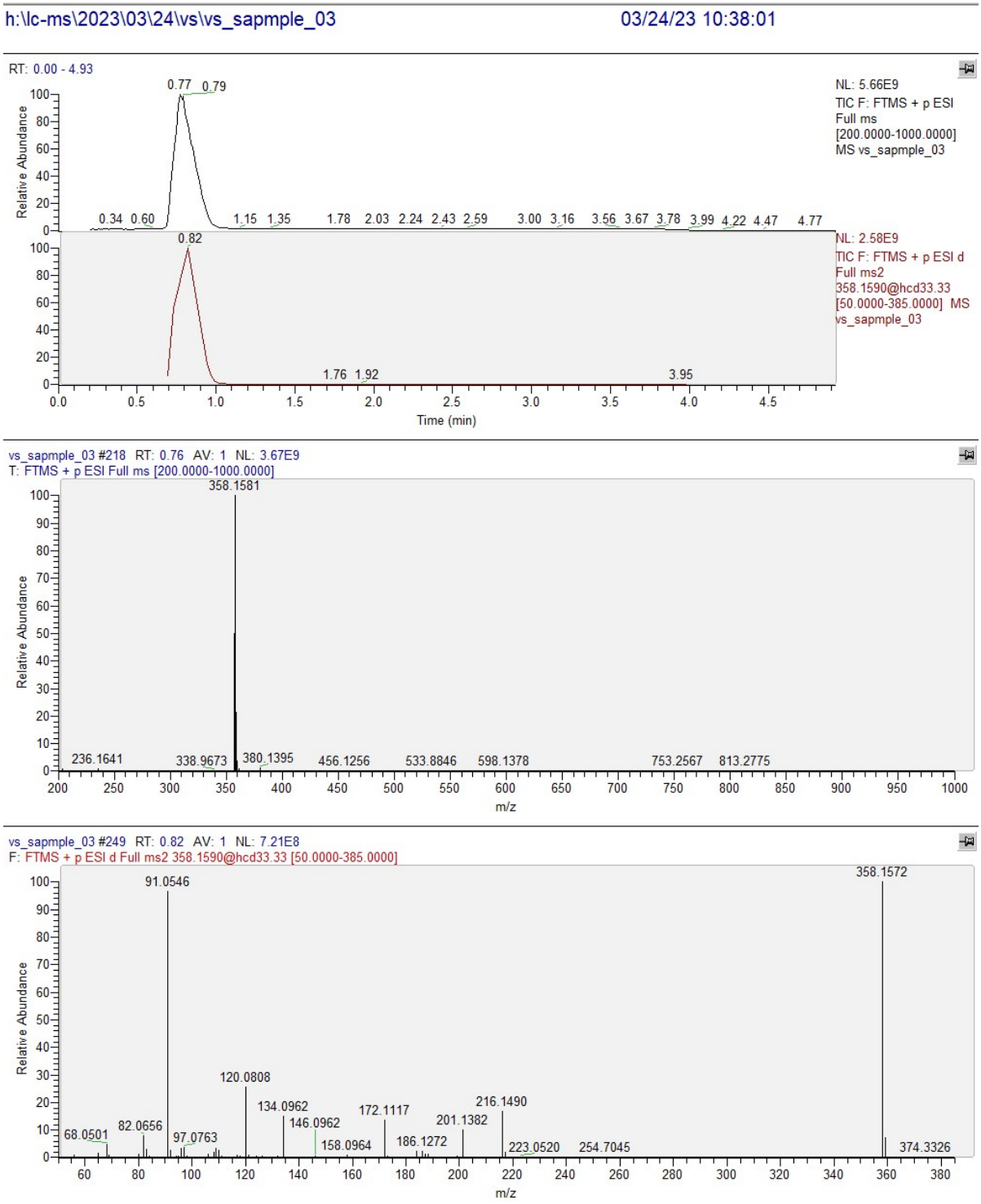
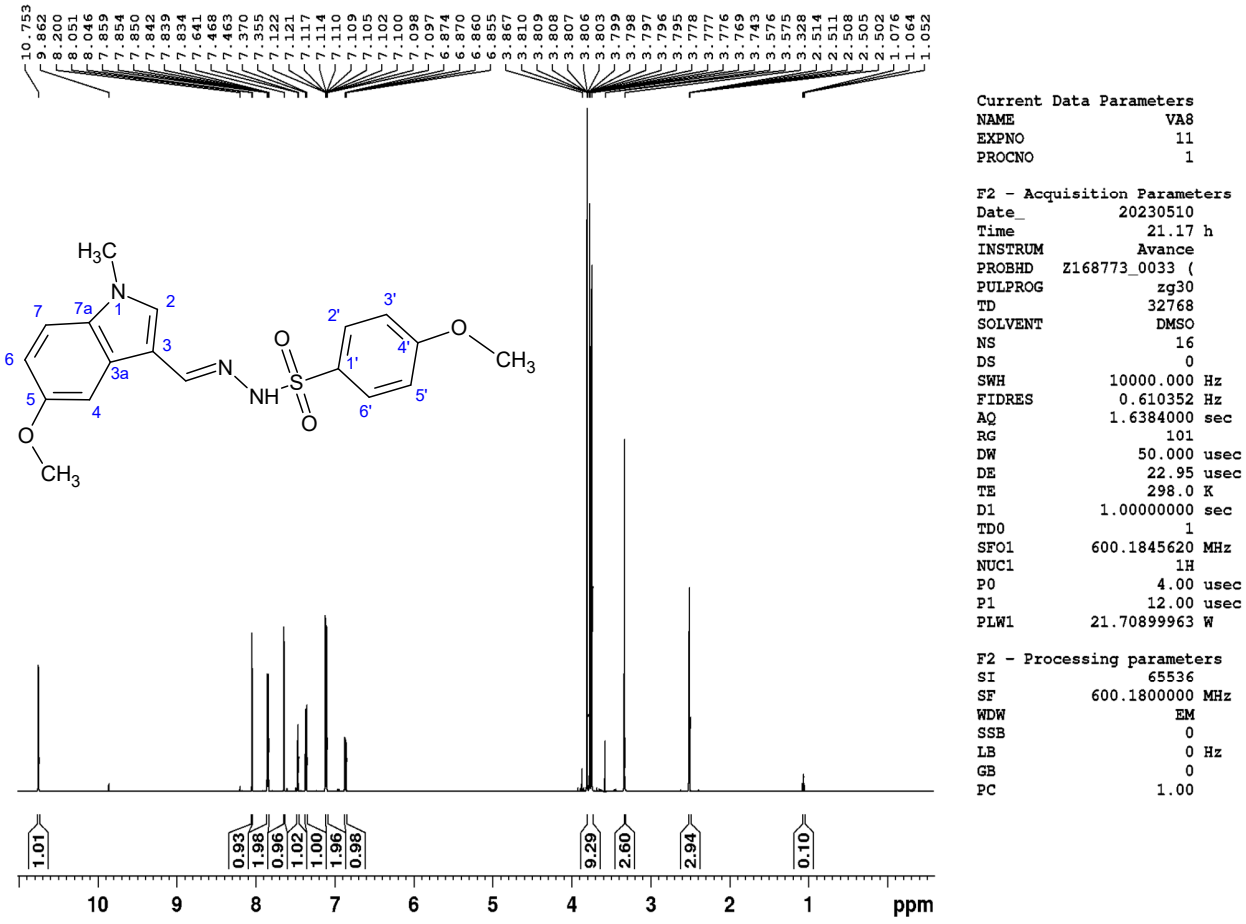


Figure S62. HRMS of **5a**

***20. 4-methoxy-N'-[(E)-(5-methoxy-1-methyl-1H-indol-3-yl)methylidene]benzenesulfonohydrazide*, 5b**

Yield: 78%; m.p. 145-146◦C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.74 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.86 (dd, J=2.6, 8.8 Hz, 1H, H-6), 7.11 (d, J=9.0 Hz, 2H, H-3' and H-5'), 7.36 (d, J=8.8 Hz, 1H, H-7), 7.47 (d, J=2.5 Hz, 1H, H-4), 7.64 (s, 1H, H-2), 7.85 (d, J=8.8 Hz, 2H, H-2' and H-6'), 8.05 (s, 1H, CH), 10.75 (s, 1H, NH).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 32.90 (NCH_3), 55.22 (OCH_3), 55.64 (OCH_3), 103.31 (C-4), 109.71 (C-3), 111.01 (C-7), 112.54 (C-6), 114.20 (C-3' and C-5'), 124.90 (C-3a), 129.49 (C-1'), 130.83 (C-2' and C-6'), 132.52 (C-7a), 134.20 (C-2), 145.01 (CH), 154.66 (C-4), 162.45 (C-4'). HRMS (ESI) m/z: calcd: [M+H]+ 374.11597. Found: [M+H]+ 374.1169

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EXPNO                  11
PROCNO                  1

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PULPROG             zg30
TD                 32768
SOLVENT             DMSO
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SWH           10000.000 Hz
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RG                   101
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DE               22.95 usec
TE               298.0 K
D1            1.00000000 sec
TD0                    1
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NUC1                  1H
P0               4.00 usec
P1              12.00 usec
PLW1         21.70899963 W

F2 - Processing parameters
SI                 65536
SF           600.1800000 MHz
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SSB                    0
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GB                     0
PC                  1.00
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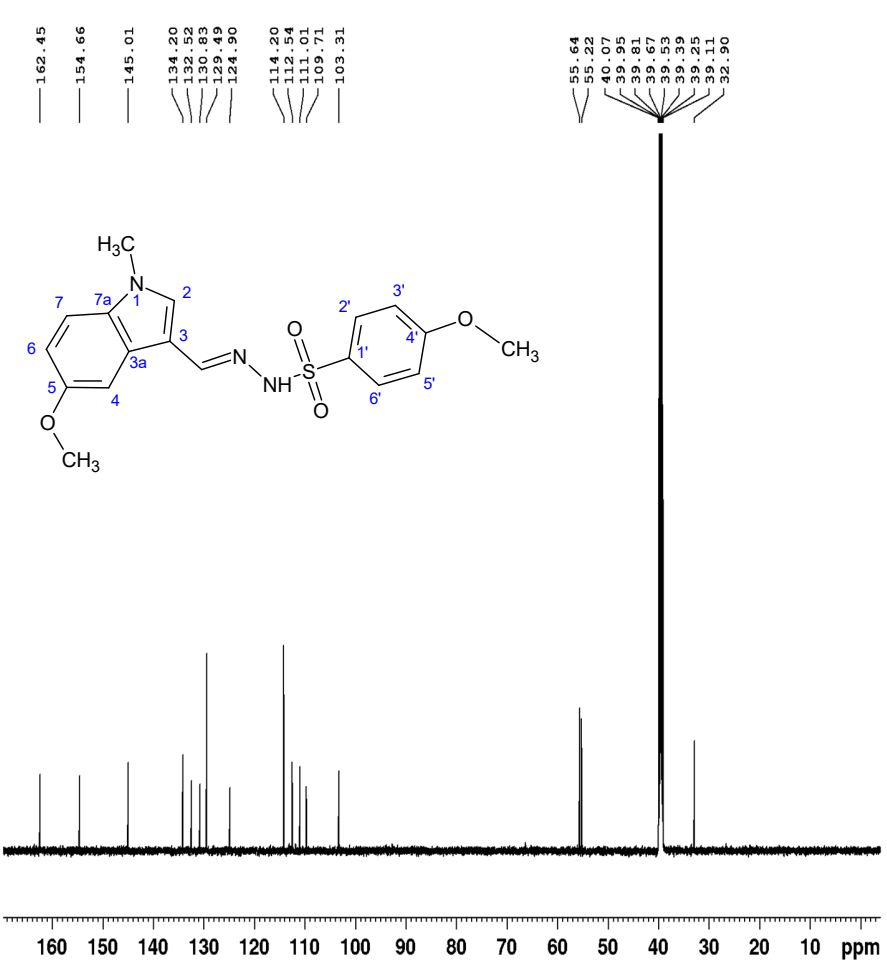
Figure S63. ^{1}H NMR spectrum of compound **5b** in DMSO-d_6

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EXPNO                  12
PROCNO                  1

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PULPROG           zgdc30
TD                 32768
SOLVENT             DMSO
NS                    256
DS                      0
SWH            35714.286 Hz
FIDRES          2.179827 Hz
AQ              0.4587520 sec
RG                    101
DW                 14.000 usec
DE                 18.00 usec
TE                 298.0 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                     1
SFO1         150.9319844 MHz
NUC1                  13C
P0                 3.33 usec
P1                10.00 usec
PLW1         67.54000092 W
SFO2         600.1824007 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         21.72701073 W
PLW12         0.49773711 W

F2 - Processing parameters
SI                 65536
SF           150.9154525 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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Figure S64. ^{13}C NMR spectrum of compound **5b** in DMSO-d_6

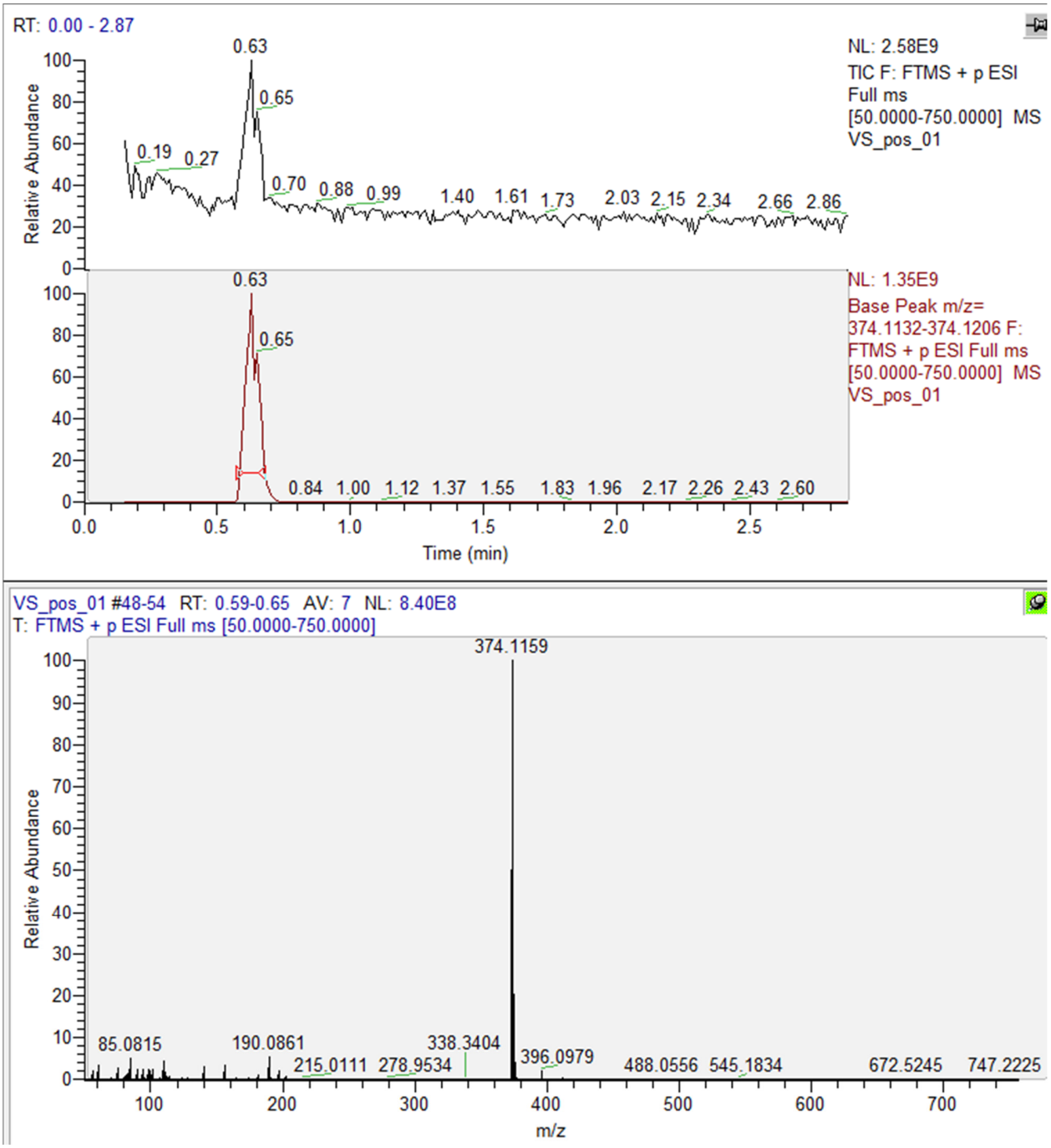


Figure S65. HRMS of compound **5b**

21. 4-methoxy-N'-[(E)-(5-methoxy-1H-indol-3-yl)methylidene]benzenesulfonohydrazide, **5c**

Yield: 53%; m.p. 159-163◦C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.80 (dd, J=2.6, 8.8 Hz, 1H, H-6), 7.11 (d, J=9.0 Hz, 2H, H-3' and H-5'), 7.29 (d, J=8.8 Hz, 1), 7.46 (d, J=2.6 Hz, 1H, H-4), 7.66 (d, J=2.8 Hz, 1H, H-2), 7.85 (d, J=9.0 Hz, 2H, H-2' and H-6'), 8.08 (s, 1H, CH), 10.76 (s, 1H, NH), 11.37 (d, J=2.2 Hz, 1H, NH).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.15 (OCH_3), 55.63 (OCH_3), 103.12 (C-4), 110.85 (C-3), 112.48 (C-7), 112.59 (C-6), 114.19 (C-3' and C-5'), 124.49 (C-3a), 129.48 (C-1'), 130.73 (C-2' and C-6'), 130.84 (C-7a), 131.78 (C-2), 145.46 (CH), 154.35 (C-4), 162.43 (C-4'). HRMS (ESI) m/z: calcd: [M+H]+ 360.10125. Found: [M+H]+ 360.10037

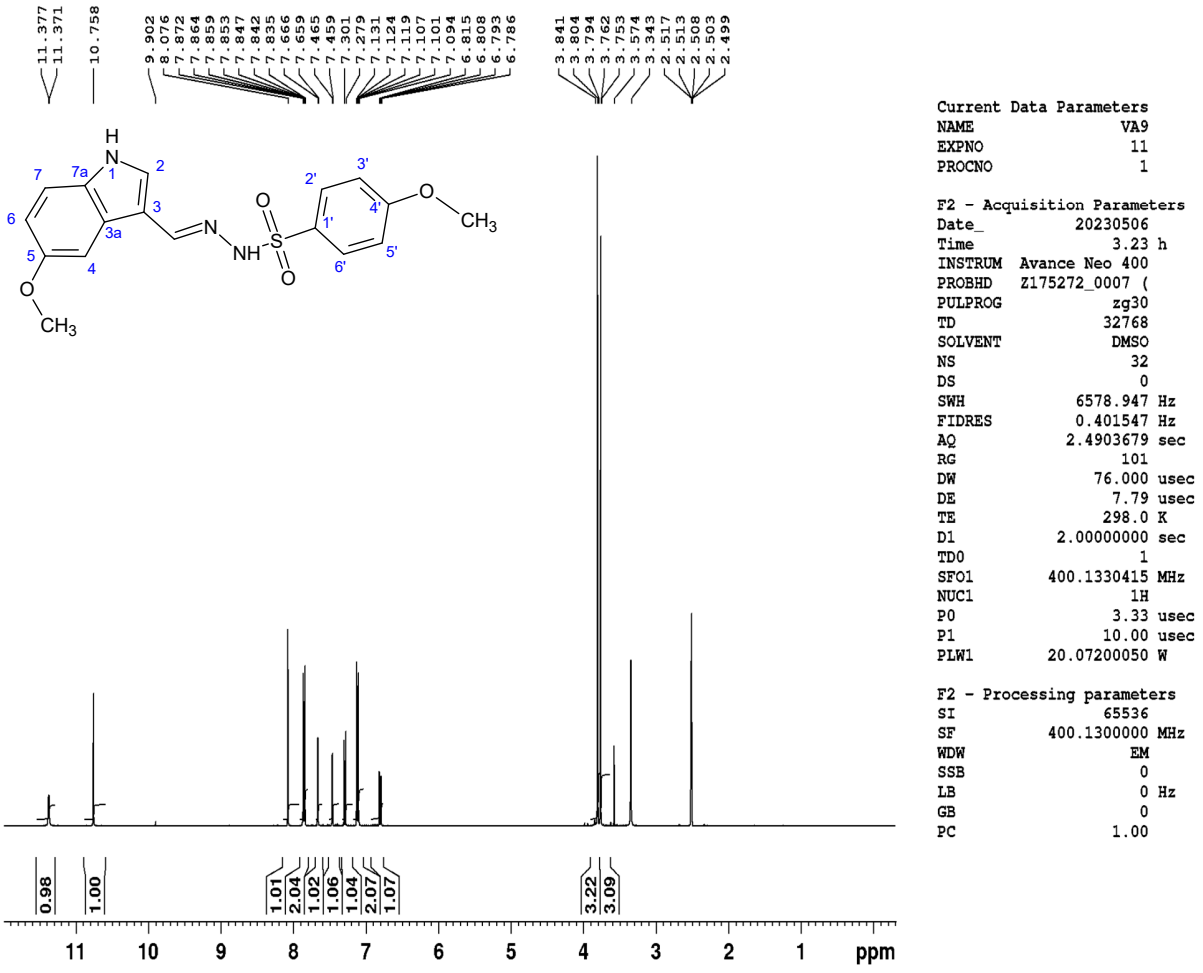
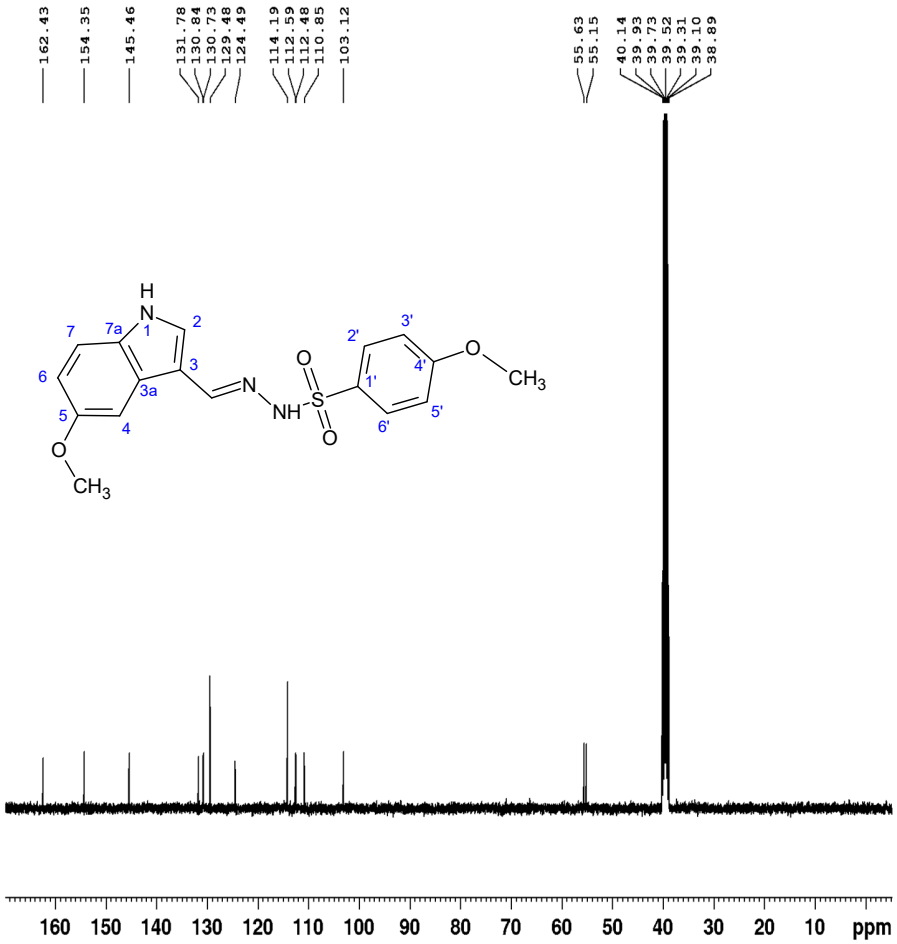


Figure S66. ^{1}H NMR spectrum of compound **5c** in DMSO-d_6

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EXPNO                   12
PROCNO                   1

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PULPROG           zgdc30
TD                 32768
SOLVENT              DMSO
NS                    1024
DS                       0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ             0.6881280 sec
RG                      32
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1            1.50000000 sec
D11           0.03000000 sec
TD0                      1
SFO1         100.6238383 MHz
NUC1                  13C
P0                 3.33 usec
P1                10.00 usec
PLW1         58.46900177 W
SFO2         400.1316008 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              90.00 usec
PLW2         20.07200050 W
PLW12         0.24781001 W

F2 - Processing parameters
SI                    65536
SF           100.6128171 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
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Figure S67. ^{13}C NMR spectrum of compound **5c** in DMSO-d_6

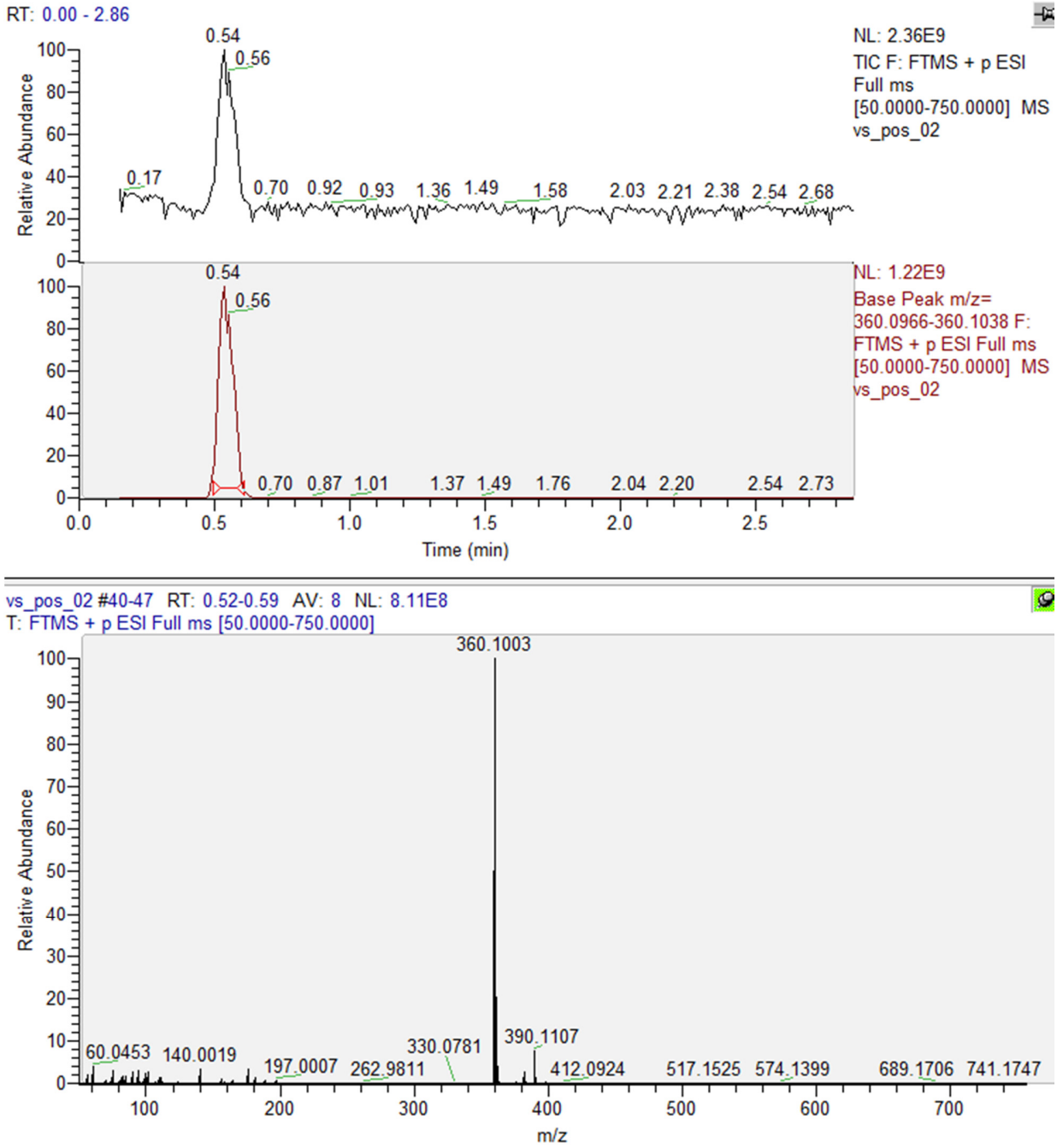
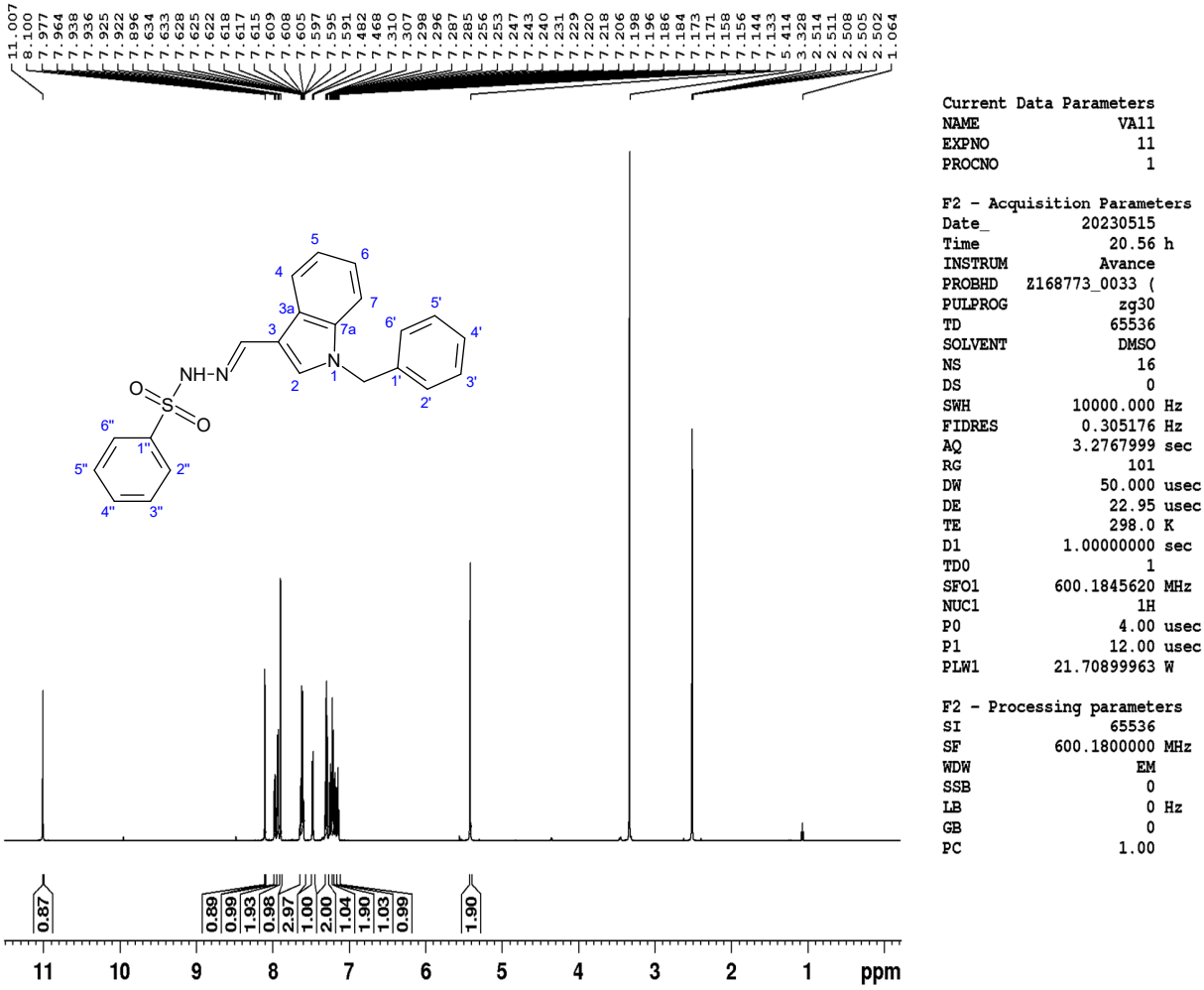


Figure S68. HRMS of compound **5c**

22. N'-[(E)-(1-benzyl-1H-indol-3-yl)methylidene]benzenesulfonohydrazide, **5d**

Yield: 89%; m.p. 146-149◦C.[1]H NMR (600 MHz, DMSO-d_6): δ = 5.41 (s, 3H, CH_2), 7.15 (t, J=7.4 Hz, 1H, H-5), 7.18 (ddd, J=1.2, 7.1, 8.2 Hz, 1H, H-6), 7.21 (d, J=7.0 Hz, 2H, H-2' and H-6'), 7.24 (t, J=7.3 Hz, 1H, H-4'), 7.30 (t, J=7.3 Hz, 2H, H-3' and H-5'), 7.48 (d, J=8.1 Hz, 1H, H-7), 7.59-7.65 (m, 3H, H-3'', H-4''and H-5''), 7.90 (s, 1H, H-2), 7.93 (dd, J=1.0, 7.6 Hz, 2H, H-2'' and H-6''), 7.97 (d, J=7.8 Hz, 1H, H-4), 8.10 (s, 1H, CH), 11.01 (s, 1H, NH).

[13]C NMR (151 MHz, DMSO-d_6): δ = 49.27 (CH_2), 110.65 (C-3), 110.67 (1C, s), 120.89 (C-5), 121.78 (C-4), 122.79 (C-6), 124.61 (C-3a), 127.09 (C-2' and C-6''), 127.28 (C-2'' and C-6''), 127.51 (C-4'), 128.59 (C-3' and C-5'), 129.05 (C-3'' and V-5''), 132.82 (C-4''), 133.50 (C-2), 136.75 (C-7a), 137.44 (C-1'), 139.13 (C-1''), 144.60 (CH). HRMS (ESI) m/z: calcd: [M+H]+ 390.127073. Found: [M+H]+ 390.12604

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PROCNO                   1

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TD                    65536
SOLVENT                DMSO
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FIDRES                0.305176 Hz
AQ                 3.2767999 sec
RG                      101
DW                   50.000 usec
DE                   22.95 usec
TE                   298.0 K
D1                1.00000000 sec
TD0                       1
SFO1           600.1845620 MHz
NUC1                    1H
P0                   4.00 usec
P1                  12.00 usec
PLW1           21.70899963 W

F2 - Processing parameters
SI                    65536
SF             600.1800000 MHz
WDW                     EM
SSB                       0
LB                        0 Hz
GB                        0
PC                     1.00
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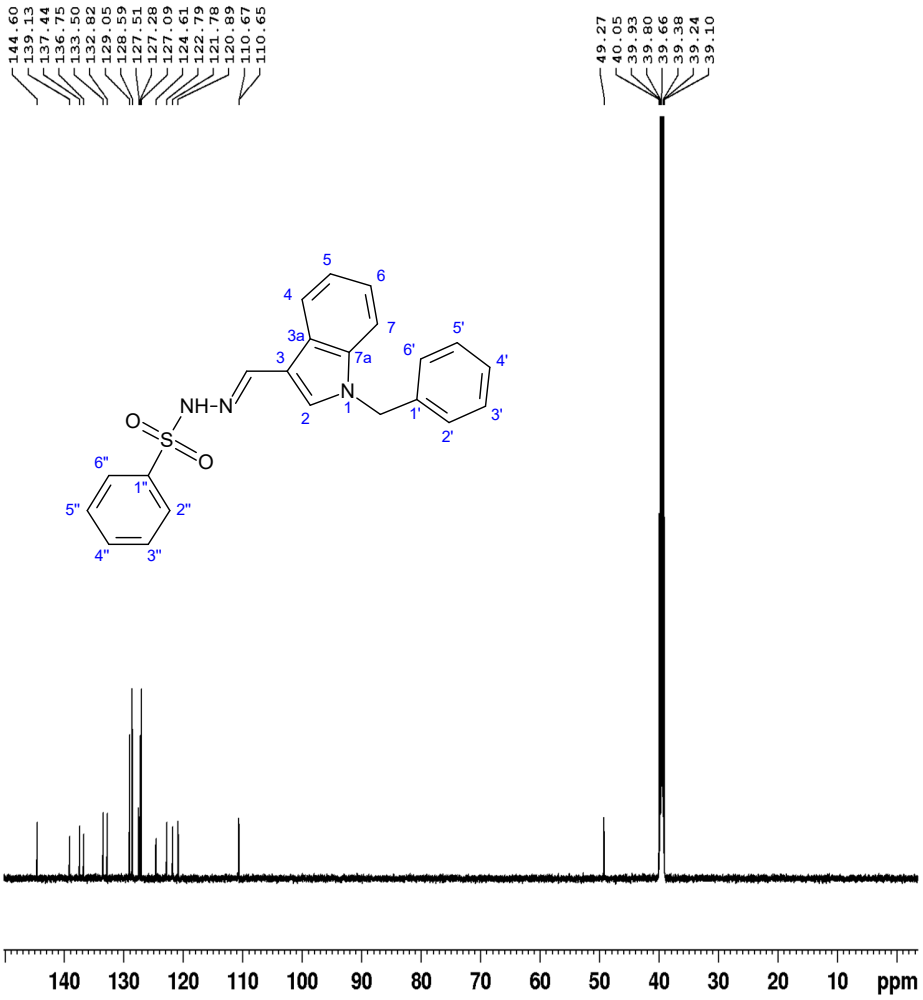
Figure S69. [1]H NMR spectrum of compound **5d** in DMSO-d_6

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EXPNO                   16
PROCNO                   1

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Time                 22.18 h
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PULPROG              zgdc30
TD                    32768
SOLVENT                DMSO
NS                      256
DS                        0
SWH               35714.286 Hz
FIDRES             2.179827 Hz
AQ                0.4587520 sec
RG                      101
DW                   14.000 usec
DE                   18.00 usec
TE                   298.0 K
D1                1.50000000 sec
D11               0.03000000 sec
TD0                       1
SFO1           150.9319844 MHz
NUC1                    13C
P0                    3.33 usec
P1                   10.00 usec
PLW1           67.54000092 W
SFO2           600.1824007 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                80.00 usec
PLW2           21.72701073 W
PLW12           0.49773711 W

F2 - Processing parameters
SI                    65536
SF             150.9154546 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
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Figure S70. ^{13}C NMR spectrum of compound **5d** in DMSO-d_6

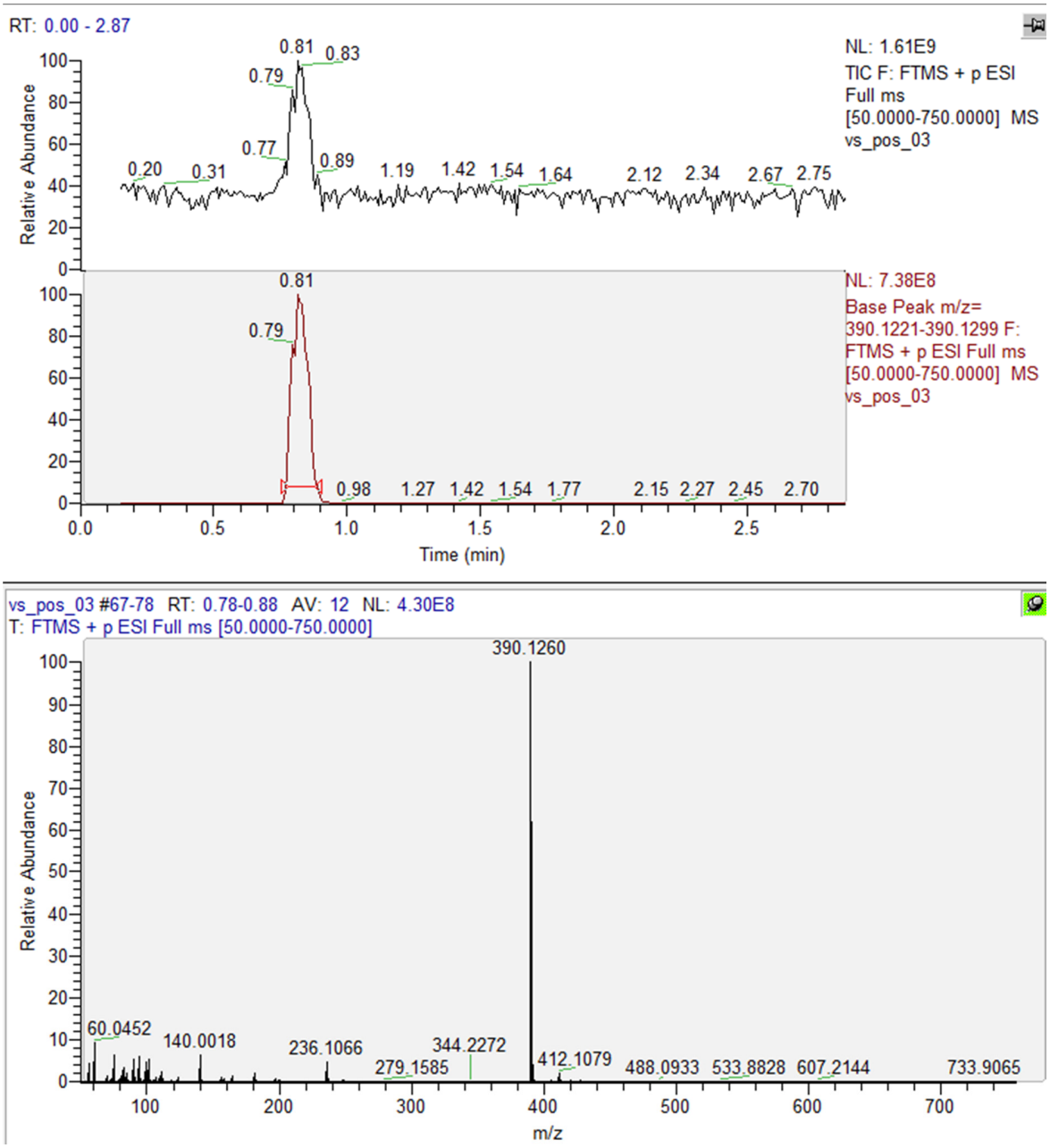


Figure S71. HRMS of compound **5d**

23. 4-methoxy-N'-[(E)-(1-methyl-1H-indol-3-yl)methylidene]benzenesulfonohydrazide, **5e**

Yield: 66%; m.p. 170-175◦C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.78 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 7.11 (d, J=9.0 Hz, 2H, H-3' and H-5'), 7.17 (t, J=7.5 Hz, 1H, H-5), 7.24 (ddd, J=1.1, 7.1, 8.1 Hz, 1H, H-6), 7.46 (d, J=8.2 Hz, 1H, H-7), 7.69 (s, 1H, H-2), 7.84 (d, J=9.0 Hz, 2H, H2' and H-6'), 7.97 (d, J=7.9 Hz, 1H, H-4), 8.05 (s, 1H, CH), 10.76 (s, 1H, NH).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 32.73 (NCH_3), 55.61 (OCH_3), 110.11 (C-3), 110.17 (C-7), 114.18 (C-3' and H-5'), 120.74 (C-5), 121.66 (C-4), 122.62 (C-6), 124.40 (C-3a), 129.48 (C-2' and C-6'), 130.81 (C-2' and C-6'), 133.89 (C-1'), 137.42 (C-7a), 144.44 (CH), 162.44 (C-4'). HRMS (ESI) m/z: calcd: [M+H]+ 344.106338. Found: [M+H]+ 344.1055

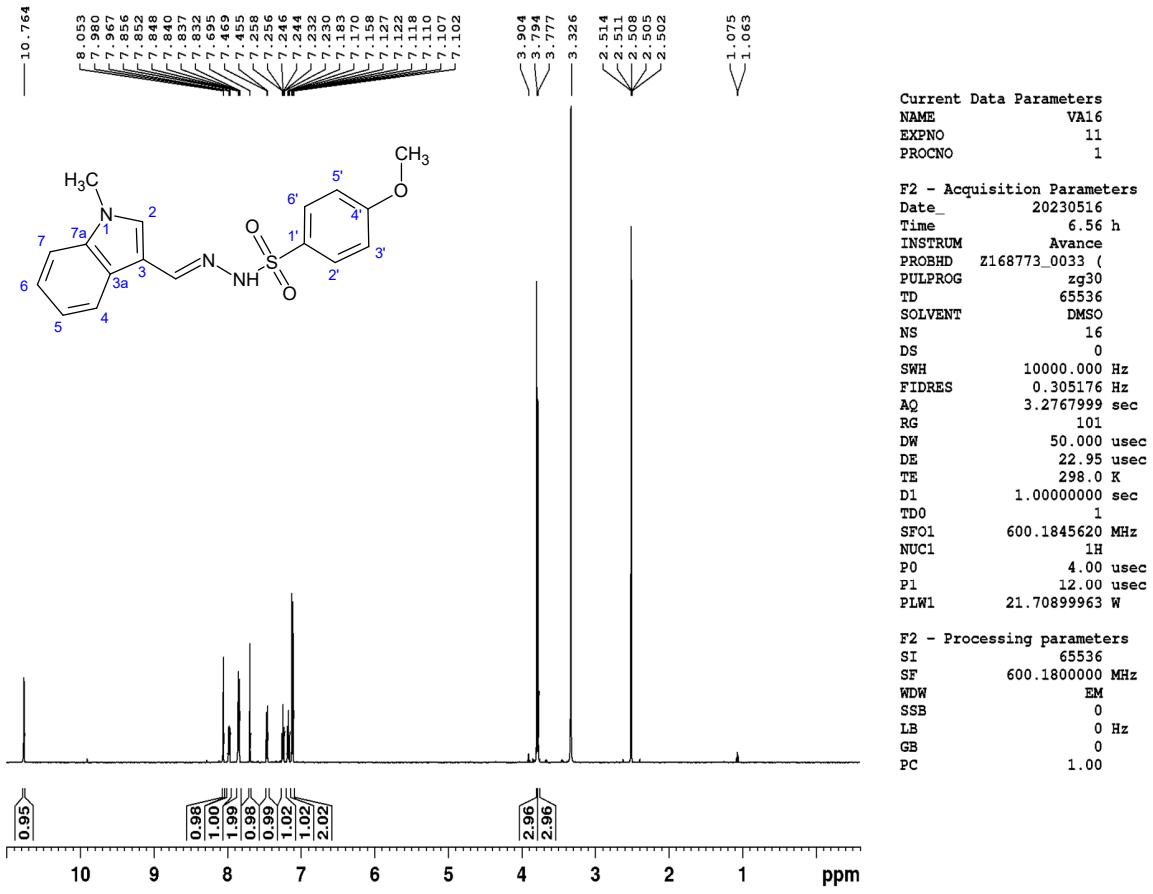
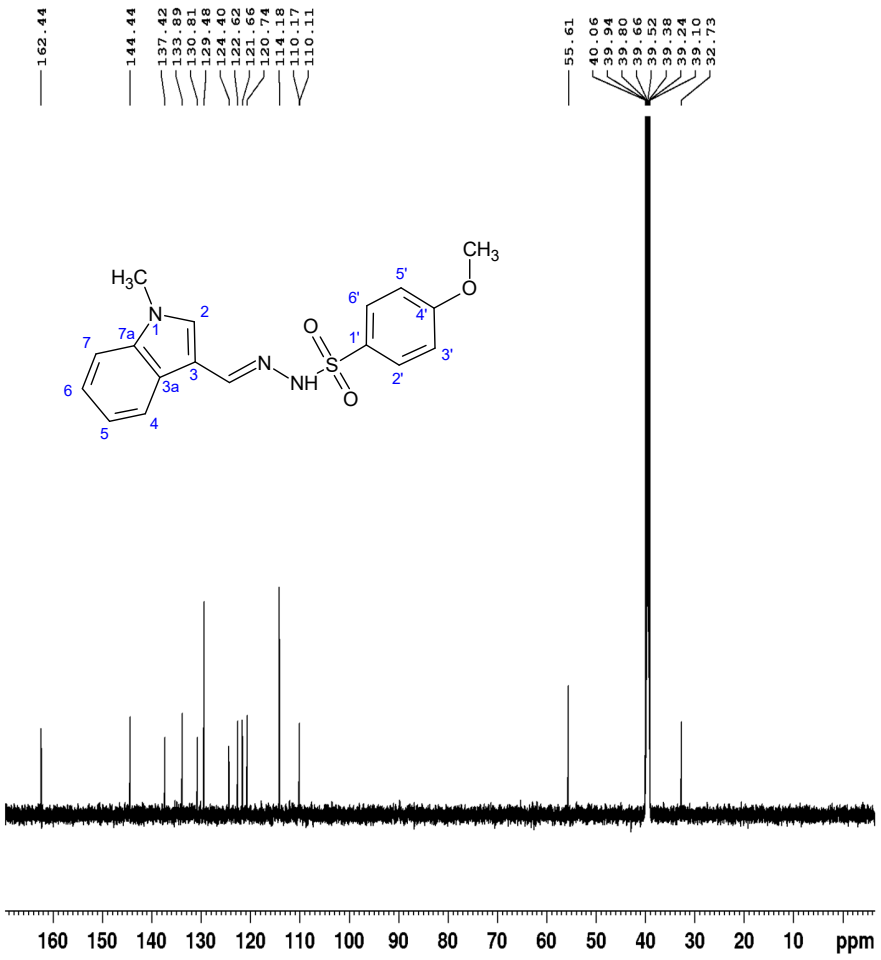


Figure S72. ^{1}H NMR spectrum of compound **5e** in DMSO-d_6

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EXPNO                   16
PROCNO                   1

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TD                   32768
SOLVENT                DMSO
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FIDRES            2.179827 Hz
AQ                0.4587520 sec
RG                       101
DW                  14.000 usec
DE                  18.00 usec
TE                  298.0 K
D1              1.50000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           150.9319844 MHz
NUC1                   13C
P0                   3.33 usec
P1                  10.00 usec
PLW1           67.54000092 W
SFO2           600.1824007 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2           21.72701073 W
PLW12           0.49773711 W

F2 - Processing parameters
SI                   65536
SF             150.9154542 MHz
WDW                    EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

Figure S73. ^{13}C NMR spectrum of compound **5e** in DMSO-d_6

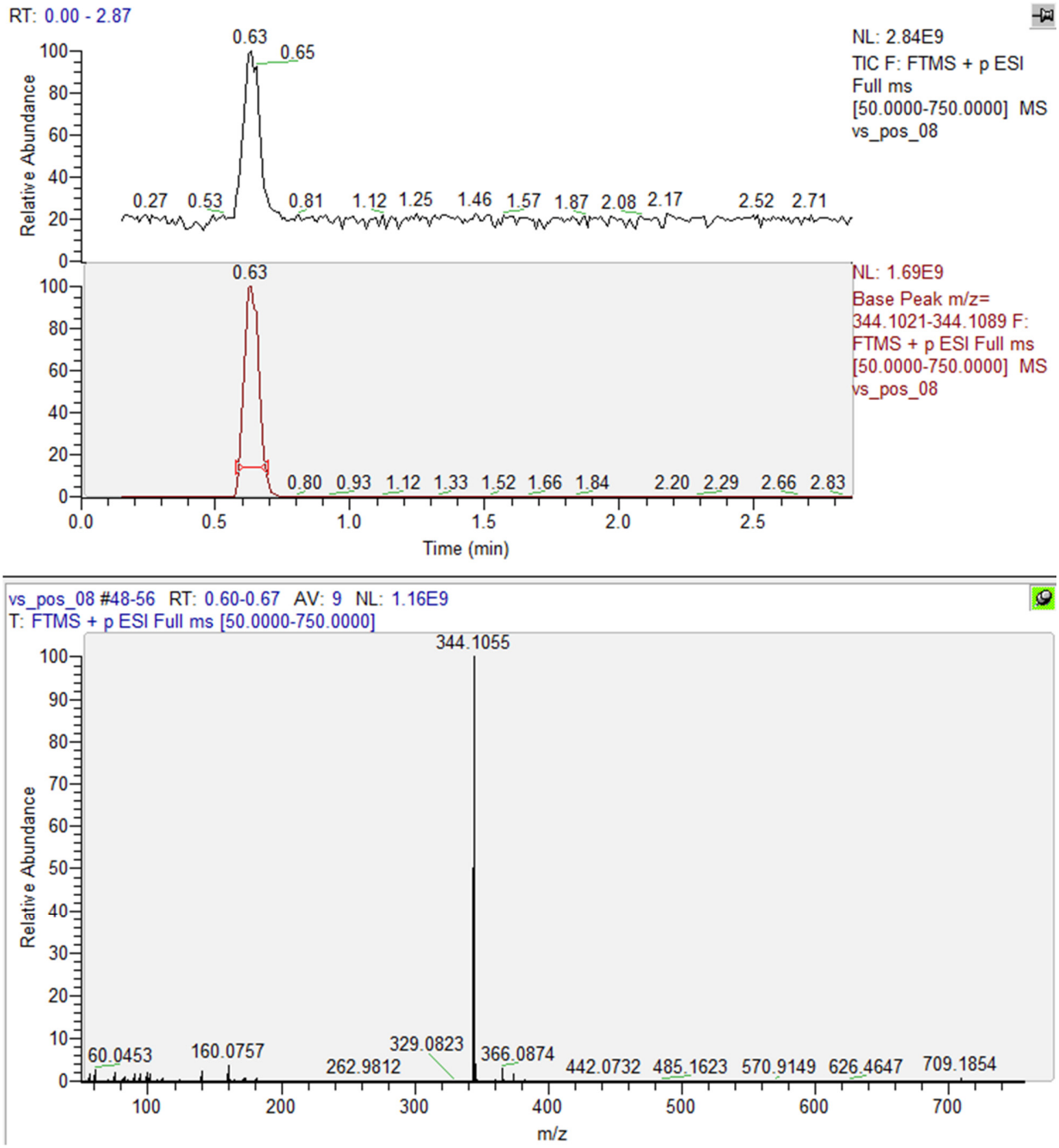


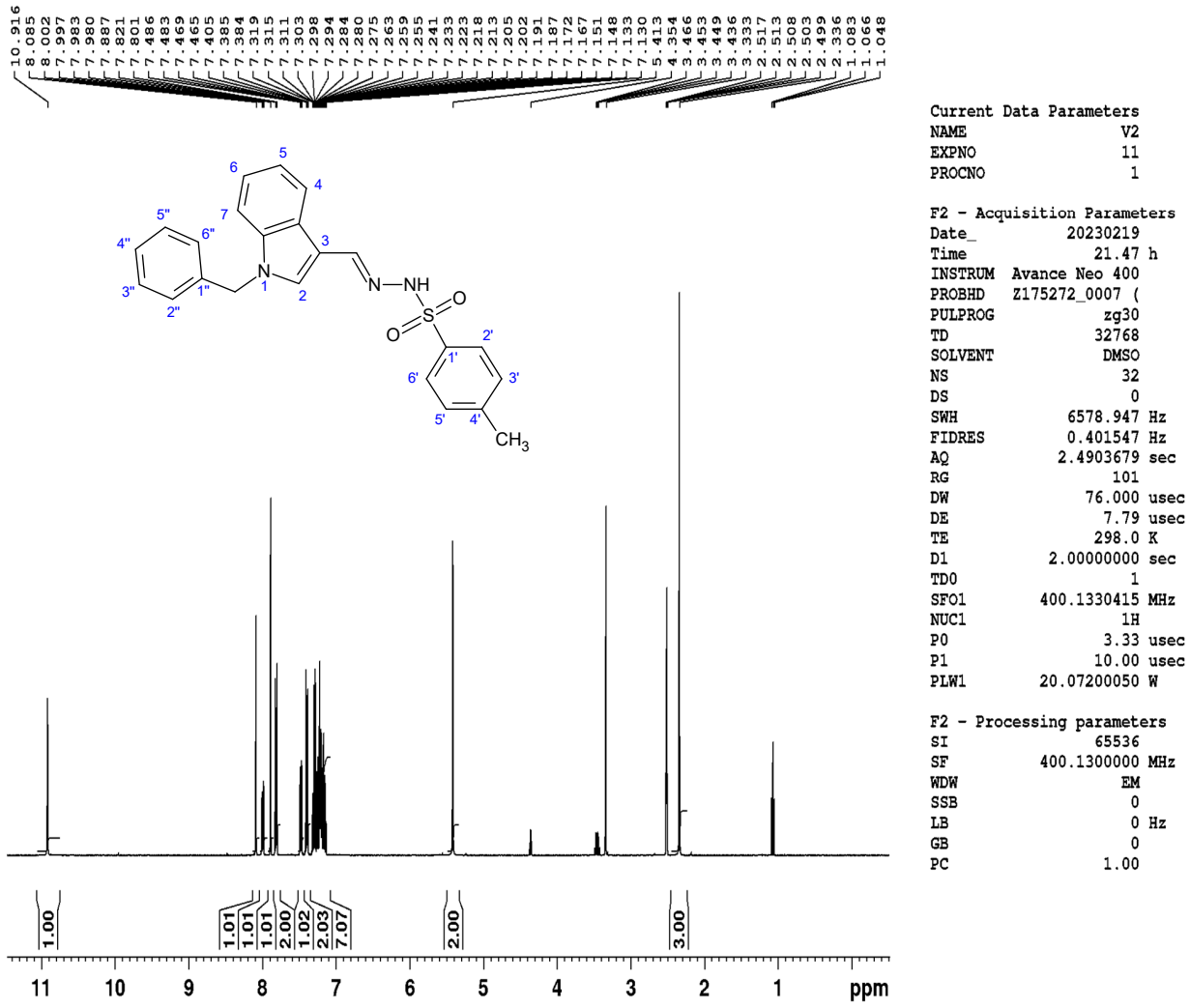
Figure S74. HRMS of compound **5e**

24. N'-[(E)-(5-methoxy-1-methyl-1H-indol-3-yl)methylidene]benzenesulfonohydrazide, 5f [2] ^{1}H NMR, ^{13}C NMR and HRMS spectra of compound 5f can be found in **https://doi.org/10.3390/molecules28052058**

25. N'-[(E)-(1-benzyl-1H-indol-3-yl)methylidene]-4-methylbenzenesulfonohydrazide, **5g**

Yield: 79%; m.p. 145-146◦C.[1]H NMR (400 MHz, DMSO-d6): δ = 2.34 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 7.13-7.32 (m, 7H, H-5, H6, H-2'', H-3'', H-4'', H-5'' and H-6''), 7.39 (d, J=7.9 Hz, 2H, H-3' and H-5'), 7.48 (dd, J=1.3, 7.1 Hz, 1H, H-7), 7.81 (d, J=8.2 Hz, 2H, H-2' and H-6'), 7.89 (s, 1H, H-2), 7.99 (d, J=7.3 Hz, 1H, H-4), 8.08 (s, 1H, CH), 10.92 (s, 1H, NH).

[13]C NMR (100 MHz, DMSO-d6): δ = 20.95 (CH_3), 49.26 (CH_2), 110.66 (C-7), 110.72 (C-3), 120.88 (C-5), 121.83 (C-4), 122.78 (C-6), 124.63 (C-4a), 127.08 (C-2'' and C-6''), 127.33 (C-2' and C-6'), 127.51 (C-4''), 128.59 (C-3'' and C-5''), 129.47 (C-3' and C-5'), 133.41 (C-2), 136.26 (C-1'), 136.74 (C-7a), 137.46 (C-1''), 143.16 (C-4'), 144.32 (C-H).HRMS (ESI) m/z: calcd: [M+H]+ 404.142723. Found: [M+H]+ 404.1425

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TD                 32768
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NS                    32
DS                     0
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FIDRES         0.401547 Hz
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DE                 7.79 usec
TE                298.0 K
D1           2.00000000 sec
TD0                    1
SFO1        400.1330415 MHz
NUC1                  1H
P0                 3.33 usec
P1                10.00 usec
PLW1        20.07200050 W

F2 - Processing parameters
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SF          400.1300000 MHz
WDW                   EM
SSB                    0
LB                     0 Hz
GB                     0
PC                  1.00
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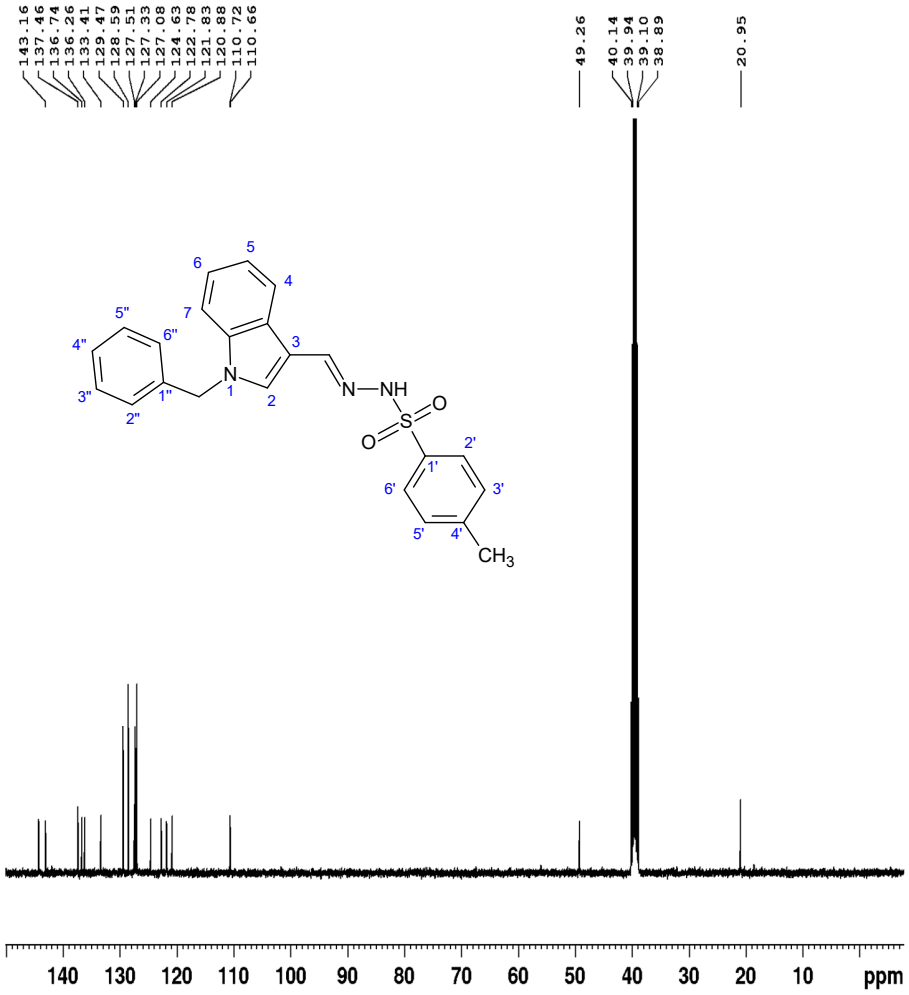
Figure S75. [1]H NMR spectrum of compound **5g** in DMSO-d_6

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AQ              0.6881280 sec
RG                     36
DW                21.000 usec
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TE                298.0 K
D1             1.50000000 sec
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TD0                     1
SFO1         100.6238383 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1          58.46900177 W
SFO2         400.1316008 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2          20.07200050 W
PLW12          0.24781001 W

F2 - Processing parameters
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SF           100.6128173 MHz
WDW                    EM
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Figure S76. ^{13}C NMR spectrum of compound **5g** in DMSO-d_6

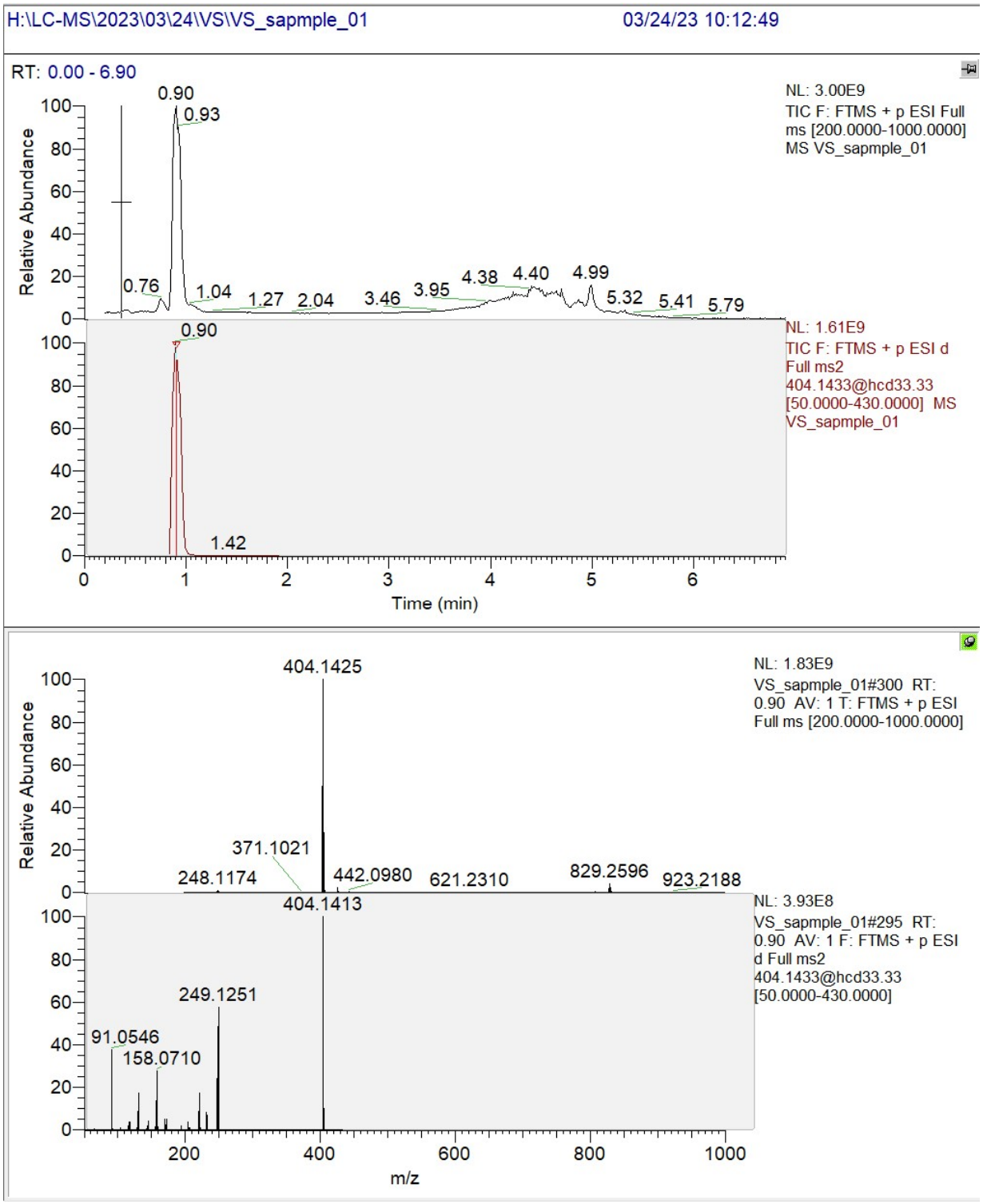


Figure S77. HRMS of compound **5g**

26. N'-[(E)-(3,4-dimethoxyphenyl)methylidene]-4-methylbenzenesulfonohydrazide, **5h** [3] ^{1}H NMR, ^{13}C NMR and HRMS spectra of compound **5h** can be found in https://doi.org/10.3390/molecules28052058

***27. N'-[(E)-(3,4-dimethoxyphenyl)methylidene]benzenesulfonohydrazide,* 5i** [2] ^{1}H NMR, ^{13}C NMR and HRMS spectra of compound **5i** can be found in https://doi.org/10.3390/molecules28052058

***28. N'-{(E)-[5-(benzyloxy)-1H-indol-3-yl]methylidene}-4-methylbenzenesulfonohydrazide,* 5j**

Yield: 67%; m.p. 222-223◦C.^{1}H NMR (400 MHz, DMSO-d6): δ = 2.28 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 6.88 (dd, J=2.5, 8.8 Hz, 1H, H-6), 7.30 (d, J=8.8 Hz, 1H, H-7), 7.34 (d, J=8.1 Hz, 2H, H-3' and H-5'), 7.36 (t, J=7.2 Hz, 1H, H-4''), 7.43 (t, J=7.4 Hz, 2H, H-3'' and H-5''), 7.53 (d, J=7.2 Hz, 2H, H-2'' and H-6''), 7.57 (d, J=2.4 Hz, 1H, H-4), 7.68 (d, J=2.8 Hz, 1H, H-2), 7.81 (d, J=8.2 Hz, 2H, H-2' and H-6'), 8.09 (s, 1H, CH), 10.84 (s, 1H, NH), 11.40 (d, J=2.0 Hz, 1H, NH).

^{13}C NMR (100 MHz, DMSO-d6): δ = 20.90 (CH_3), 69.68 (CH_2), 104.82 (C-4), 110.81 (C-3), 112.50 (C-6), 113.02 (C-7), 124.48 (C-4a), 127.37 (C-2' and C-6'), 127.84 (C-4''), 127.93 (C-2'' and C-6''), 128.46 (H-3'' and H-5''), 129.41 (C-3' and C-5'), 130.96 (C-2), 131.98 (C-7a), 136.33 (C-1'), 137.35 (C-1''), 143.08 (C-4'), 145.68 (CH), 153.38 (C-5).HRMS (ESI) m/z: calcd: [M+H]+ 404.142723. Found: [M+H]+ 420.1373

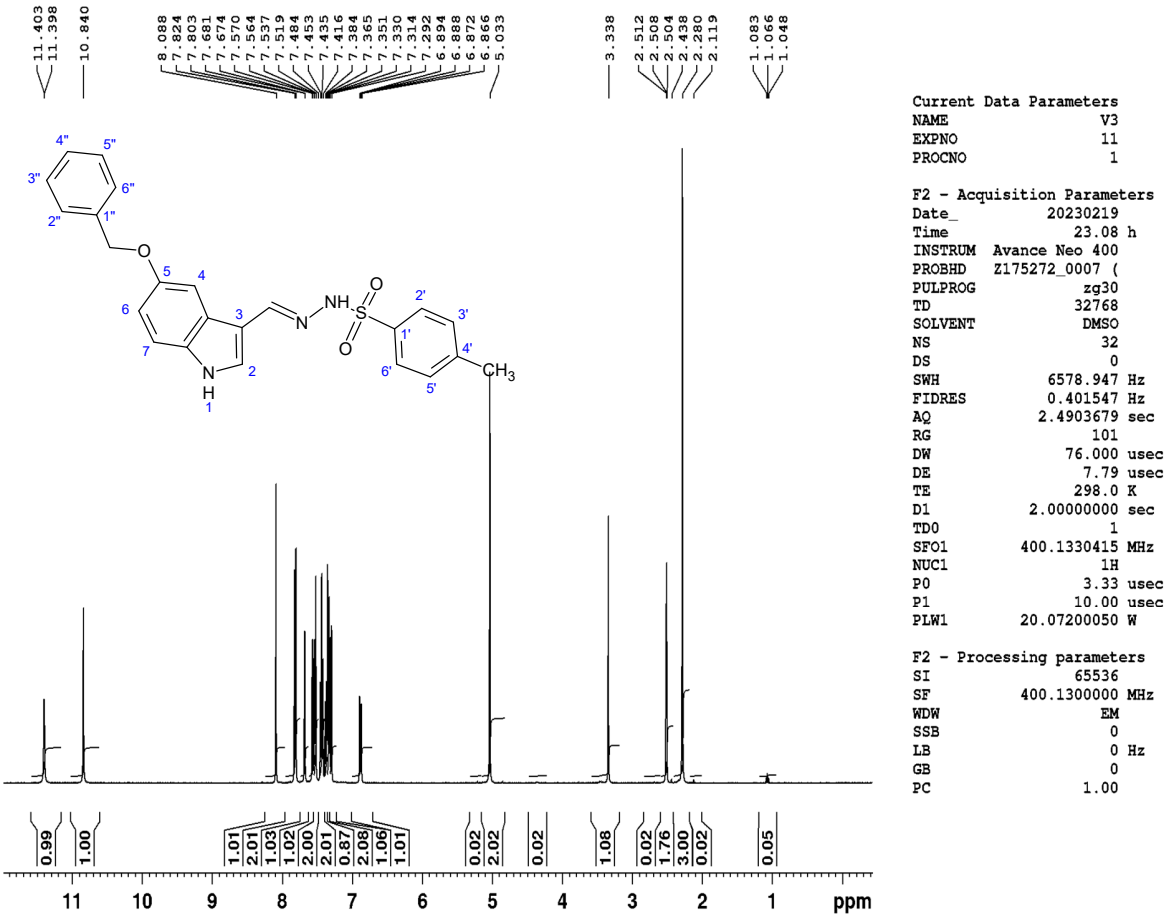
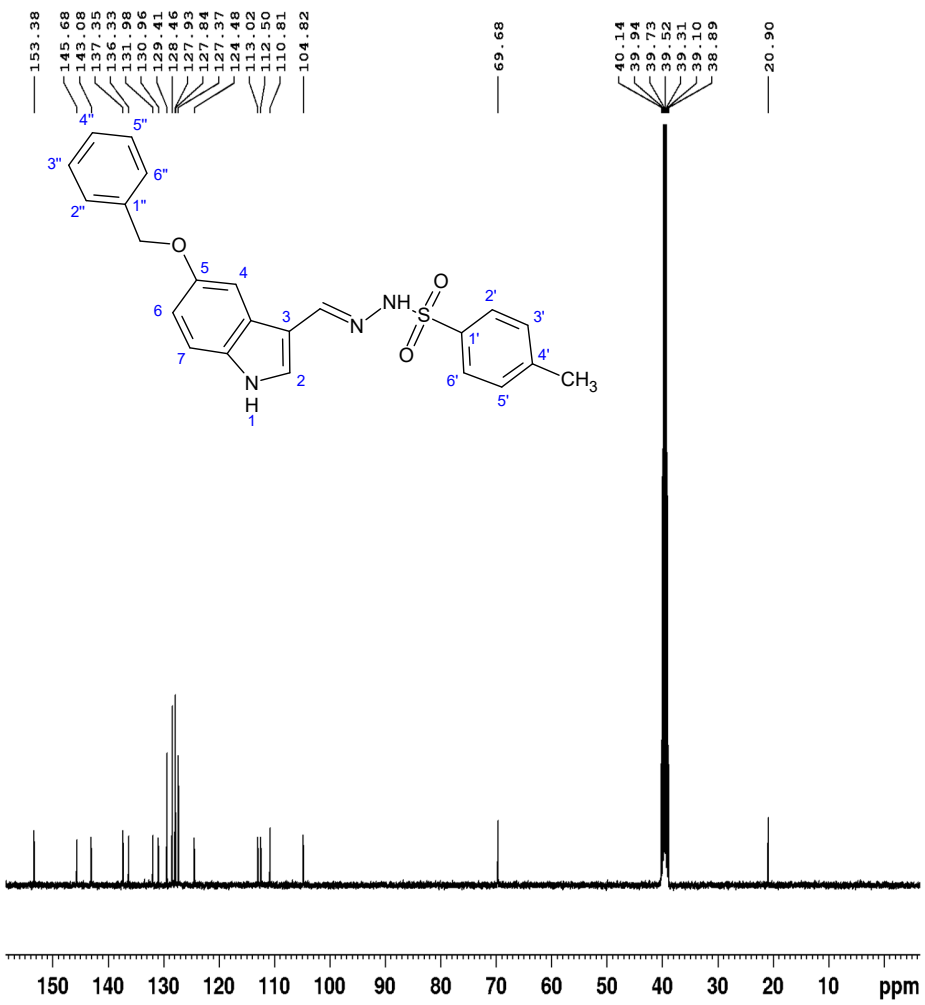


Figure S78. ^{1}H NMR spectrum of compound **5j** in DMSO-d_6

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DS                     0
SWH            23809.524 Hz
FIDRES          1.453218 Hz
AQ              0.6881280 sec
RG                    36
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                    1
SFO1         100.6238383 MHz
NUC1                13C
P0                 3.33 usec
P1                10.00 usec
PLW1         58.46900177 W
SFO2         400.1316008 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         20.07200050 W
PLW12         0.24781001 W

F2 - Processing parameters
SI                 65536
SF           100.6128171 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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Figure S79. ^{13}C NMR spectrum of compound **5j** in DMSO-d_6

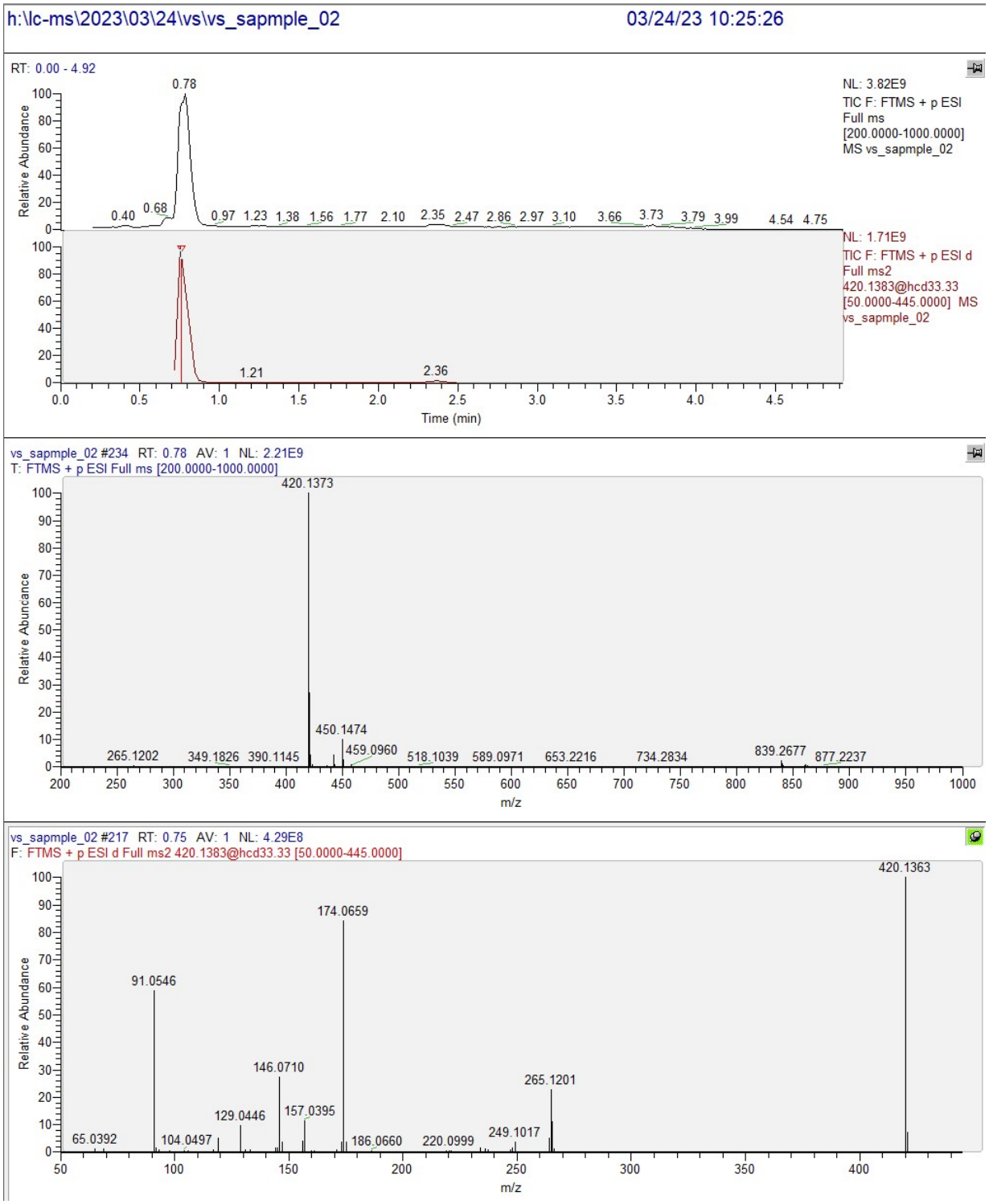

Figure S80. HRMS of compound **5j**

29. ***N'-((E)-[5-(benzyloxy)-1H-indol-3-yl]methylidenebenzenesulfonohydrazide, 5k*** [2] ^{1}H NMR, ^{13}C NMR and HRMS spectra of compound 5k can in **https://doi.org/10.3390/antibiotics11050562**

30. ***N'-[(E)-(4-chlorophenyl)methylidene]benzenesulfonohydrazide,* 5l** [2] ^{1}H NMR, ^{13}C NMR and HRMS spectra of compound 5l can be found in **https://doi.org/10.3390/molecules28052058**

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[1] V.R. Karabeliov, M.S. Kondeva-Burdina, N.G. Vassilev, K. Elena, V.T. Angelova, Neuroprotective evaluation of novel substituted 1, 3, 4-oxadiazole and aroylhydrazone derivatives, Bioorganic & Medicinal Chemistry Letters, 59 (2022) 128516.
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[3] V.T. Angelova, T. Tatarova, R. Mihaylova, N. Vassilev, B. Petrov, Z. Zhivkova, I. Doytchinova, Novel Arylsulfonylhydrazones as Breast Anticancer Agents Discovered by Quantitative Structure-Activity Relationships, Molecules, 28 (2023) 2058.