Supporting Information

Impairing Powerhouse in Colon Cancer Cells by Hydrazide-Hydrazone-based Small Molecule

Sohan Patil,† Meenu Mahesh Kuman,† Sandeep Palvai,† Poulomi Sengupta,Ψ Sudipta Basu,, †*

† Department of Chemistry, Indian Institute of Science Education and Research (IISER) Pune, Dr. Homi Bhabha Road, Pashan, Pune, 411008, India

Ψ Physical Chemistry Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India

*Corresponding author: Email: sudipta.basu@iiserpune.ac.in

Characterization of Intermediates:

Characterization of intermediate compounds 2a-2f and 3a-3f (Figure S1) are previously reported.[1-6]

Characterization of hydrazide-hydrazone derivatives:

All hydrzide-hydrazone derivatives were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS as follows:

N'-((5-methylfuran-2-yl) methylene)-2-phenoxybenzohydrazide (5):

^{1}H NMR (400 MHz, Chloroform-d): δ= 10.62 (s, 1H), 8.46 (s, 1H), 8.32 (dd, *J* = 7.9 Hz, 1.8, 1H), 7.46 – 7.37 (m, 3H), 7.26 – 7.20 (m, 2H), 7.10 (dt, *J* = 9.3 Hz, 2.2 Hz, 2H), 6.84 – 6.81 (m, 1H), 6.67 (d, *J* = 3.3 Hz, 1H), 6.09 – 6.07 (m, 1H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d): δ= 161.86, 155.69, 155.04, 147.93, 139.38, 133.37, 132.78, 130.46, 125.33, 123.91, 122.65, 120.15, 117.94, 115.91, 108.52, 14.03.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{19}H_{16}N_2O_3$ = 321.1239; found= 321.1357.

N'-(furan-2-ylmethylene)-2 phenoxybenzohydrazide (6):

^{1}H NMR (400 MHz, Chloroform-d): δ= 10.68 (s, 1H), 8.47 (s, 1H), 8.34-8.32 (dd, *J* = 8.3 Hz, 1H), 7.51 (d, 1H), 7.45-7.39 (m, 3H), 7.24-7.22 (m, 2H), 7.11-7.10 (d, *J* = 7 Hz, 2H), 6.84-6.82 (d, *J* = 7 Hz, 2H), 6.49-6.47(dd, *J* = 6.48 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ= 161.9, 155.6, 155.0, 149.6, 144.7, 139.1, 133.5, 132.8, 130.5, 125.4, 123.9, 122.5, 120.1, 117.9, 113.6, 112.1.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{18}H_{14}N_2O_3$= 307.1082; Found= 307.1083.

N'-((5-(4-nitrophenyl) furan-2-yl) methylene)-2-phenoxybenzohydrazide (7):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.81 (s, 1H), 8.49 (s, 1H), 8.36-8.34 (dd, *J* = 8.3 Hz, 1H), 8.27-8.23(m, 2H), 7.89-7.86 (m, 2H), 7.48-7.41(m, 2H), 7.29-7.24 (q, 2H), 7.15-7.13 (d, 2H), 6.98-6.95 (q, *J* = 7 Hz, 2H), 6.85-6.83 (d, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 162.1, 155.8, 154.9, 153.5, 151.0, 147.0, 138.3, 135.6, 133.7, 132.9, 130.57, 125.5, 124.7, 124.5, 124.0, 122.3, 120.3, 117.9, 115.7, 111.1.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{24}H_{17}N_3O_5$ = 428.1246; found = 428.1288.

N'-((5-(hydroxymethyl)furan-2-yl)methylene)-2-phenoxybenzohydrazide (8):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.73 (s, 1H), 8.37 (s, 1H), 8.30 (dd, *J* = 7.9 Hz, 1.8 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.25 – 7.20 (m, 2H), 7.12 – 7.07 (m, 2H), 6.82 (dd, *J* = 8.3 Hz, 1H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.37 (d, *J* = 3.4 Hz, 1H), 4.65 (s, 2H), 2.42 (bs, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 162.02, 157.02, 155.67, 155.02, 149.07, 138.66, 133.50, 132.77, 130.48, 125.35, 123.92, 122.50, 120.12, 117.96, 115.13, 109.76, 57.65.

HRMS (ESI-TOF): *m/z*: [M + Na] calculated for $C_{19}H_{16}N_2O_4$ = 359.1007; found = 359.1110.

N'-((5-(2,4-dichlorophenyl)furan-2-yl)methylene)-2-phenoxybenzohydrazide (9):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.75 (s, 1H), 8.44 (s, 1H), 8.35 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.49 – 7.39 (m, 4H), 7.32 – 7.26 (m, 2H), 7.26 – 7.22 (m, 2H), 7.15 – 7.11 (m, 2H), 6.94 (d, *J* = 3.7 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 161.95, 155.77, 154.97, 151.36, 149.04, 138.54, 134.03, 133.62, 132.91, 131.06, 130.55, 129.38, 127.53, 127.03, 125.49, 123.99, 122.35, 120.28, 117.90, 115.79, 113.56.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{24}H_{16}C_{l2}N_2O_{3\,=}$ 451.0616; found = 451.0621.

N'-(furan-3-ylmethylene)-2-phenoxybenzohydrazide (10):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.61 (s, 1H), 8.35 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.16 (s, 1H), 7.69 (s, 1H), 7.46 – 7.39 (m, 4H), 7.26 – 7.21 (m, 2H), 7.14 – 7.09 (m, 2H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.83 (d, *J* = 8.5, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 161.59, 155.64, 155.09, 144.73, 144.31, 141.13, 133.44, 132.93, 130.51, 125.36, 124.00, 122.55, 120.12, 117.98, 108.06.

HRMS (ESI-TOF): *m/z*: [M + Na] calculated for $C_{18}H_{14}N_2O_3$ = 329.001; found = 329.0901.

2-phenoxy-N'-(thiophen-2-ylmethylene) benzohydrazide (11):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.63 (s, 1H), 8.70 (s, 1H), 8.33 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.47 – 7.38 (m, 4H), 7.31 – 7.27 (m, 1H), 7.26 – 7.21 (m, 2H), 7.15 – 7.10 (m, 2H), 7.05 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.82 (dd, *J* = 8.3, 0.8 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 161.80, 155.72, 155.01, 144.22, 139.15, 133.46, 132.86, 130.51, 128.98, 127.53, 125.43, 123.93, 122.52, 120.29, 117.87.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{18}H_{14}N_2O_2S$ = 323.0854; found = 323.053.

N'-((1H-pyrrol-2-yl) methylene)-2-phenoxybenzohydrazide (12):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.56 (s, 1H), 9.63 (bs, 1H), 8.35 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.89 (s, 1H), 7.47 – 7.39 (m, 3H), 7.26 – 7.22 (m, 2H), 7.14 – 7.10 (m, 2H), 6.93 (q, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.3 Hz, 1H), 6.45-6.44 (m, 1H), 6.25 – 6.20 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 161.52, 155.67, 155.06, 139.63, 133.39, 132.82, 130.54, 127.08, 125.39, 124.01, 122.60, 122.39, 120.08, 118.02, 114.82, 110.05.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{18}H_{15}N_3O_2$ = 306.1242; found = 306.1238.

N'-((4-methylthiazol-5-yl) methylene)-2-phenoxybenzohydrazide (13):

^{1}H NMR (400 MHz, Acetone-d6): δ = 10.94 (s, 1H), 8.91 (s, 1H), 8.84 (s, 1H), 7.97 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.29 – 7.219 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.08-7.01 (m,1H), 6.91 (d, *J* = 8.2 Hz, 1H), 2.48 (s, 3H).

^{13}C NMR (101 MHz, Acetone-d6): δ = 162.37, 157.12, 156.07, 155.49, 154.92, 141.72, 133.77, 132.37, 131.14, 130.66, 129.02, 126.09, 125.43, 124.62, 120.55, 119.42, 15.79.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{18}H_{15}N_3O_2S$ = 338.0963; found = 338.0970.

N'-(4-bromobenzylidene)-2-phenoxybenzohydrazide (14):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.71 (s, 1H), 8.35 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.11 (s, 1H), 7.64 – 7.61 (m, 2H), 7.52 – 7.49 (m, 2H), 7.46 – 7.39 (m, 3H), 7.27-7.21 (m, 2H), 7.13 – 7.11(m, 2H), 6.82 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 161.74, 155.75, 155.06, 147.21, 133.61, 133.01, 132.90, 132.04, 130.56, 129.23, 125.45, 124.86, 124.04, 122.43, 120.18, 117.99.

HRMS (ESI-TOF): *m/z*: [M + Na] calculated for $C_{20}H_{15}BrN_2O_2$ = 417.0214; found = 417.0216.

N'-(4-methoxybenzylidene)-2-phenoxybenzohydrazide (15):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.61 (bs, 1H), 8.23 (s, 1H), 7.66 – 7.63 (m, 2H), 7.50 – 7.36 (m, 3H), 7.29 – 7.21 (m, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.06 – 7.00 (m, 3H), 6.96 – 6.93 (m, 2H), 3.80 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 161.78, 160.81, 156.45, 153.79, 153.00, 147.20, 143.23, 131.78, 129.94, 129.62, 128.64, 128.08, 127.46, 126.70, 123.64, 123.54, 123.03, 118.69, 118.09, 114.28, 55.25.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{21}H_{18}N_2O_3$ = 347.1428; found = 347.1402.

N'-(furan-2-ylmethylene)-2-methoxybenzohydrazide (16):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.82 (s, 1H), 8.62 (s, 1H), 8.28-8.26 (dd, *J* = 8.3 Hz, 1H), 7.53-7.47(m, 2H), 7.14-7.11 (t, *J* = 7 Hz, 1H), 7.02-7.00 (d, *J* = 7 Hz, 1H), 6.84-6.83 (d, *J* = 7 Hz, 1H), 6.50-6.49 (q, 1H), 4.02 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 162.56, 157.19, 149.83, 144.68, 139.05, 133.65, 132.86, 121.89, 120.52, 113.41, 112.11, 111.54, 56.26.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{13}H_{12}N_2O_3$ = 245.0926; found = 245.1017.

2-methoxy-N'-((5-(4-nitrophenyl) furan-2-yl)methylene)benzohydrazide (17):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.94 (s, 1H), 8.63 (s, 1H), 8.30 – 8.25 (m, 3H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.54 – 7.50 (m, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.98 (q, *J* = 3.7 Hz, 2H), 4.05 (s, 3H).

^{13}C NMR (100 MHz, Chloroform-d): δ = 162.66, 157.24, 153.36, 151.23, 146.98, 138.18, 135.61, 133.88, 132.93, 124.71, 124.49, 121.99, 120.29, 115.60, 111.59, 111.24, 56.32.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{19}H_{15}N_3O_5$ = 366.1090; found = 366.1151.

2-methoxy-N'-((5-methylfuran-2-yl)methylene)benzohydrazide (18):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.76 (s, 1H), 8.64 (s, 1H), 8.27 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.49 (m, 1H), 7.15 – 7.10 (m, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 3.3 Hz, 1H), 6.10 (dd, *J* = 3.2, 1H), 4.01 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, Chloroform-d): δ = 162.50, 157.15, 155.54, 148.19, 139.44, 133.51, 132.80, 121.86, 120.69, 115.70, 111.52, 108.50, 56.23, 14.06.

HRMS (ESI-TOF): *m/z*: [M + Na] calculated for $C_{14}H_{14}N_2O_3$ = 281.0901; found = 281.1031.

N'-((5-(hydroxymethyl)furan-2-yl)methylene)-2-methoxybenzohydrazide (19):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.84 (s, 1H), 8.52 (s, 1H), 8.25 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.15 – 7.09 (m, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 3.3 Hz, 1H), 6.39 (d, *J* = 3.4 Hz, 1H), 4.68 (s, 2H), 4.01 (s, 3H), 2.48 (bs, 1H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 162.60, 157.23, 156.89, 149.30, 133.69, 133.16, 132.80, 131.12, 121.87, 120.42, 116.54, 114.90, 112.44, 111.54, 110.19, 109.79, 57.67, 56.25.

HRMS (ESI-TOF): *m/z*: [M + Na] calculated for $C_{14}H_{14}N_2O_4$ = 297.0850; found = 297.0851.

N'-(furan-3-ylmethylene)-2-methoxybenzohydrazide (20):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.74 (s, 1H), 8.31 – 8.28 (m, 2H), 7.73 (s, 1H), 7.50 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.44 (t, *J* = 1.7 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 1.8 Hz, 1H), 4.03 (s, 4H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 162.19, 157.22, 144.58, 144.31, 140.98, 133.57, 132.98, 122.88, 121.94, 120.54, 111.53, 108.09, 56.27.

HRMS (ESI-TOF): *m/z*: [M + Na] calculated for $C_{13}H_{12}N_2O_3$ = 267.0745; found = 267.0751.

2-methoxy-N'-(thiophen-2-ylmethylene)benzohydrazide (21):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.76 (s, 1H), 8.85 (s, 1H), 8.27 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.49 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.40 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.32 (dd, *J* = 3.6 , 0.8 Hz, 1H), 7.15 – 7.10 (m, 1H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 162.43, 157.19, 144.23, 139.51, 133.59, 132.85, 130.29, 128.76, 127.54, 121.89, 120.60, 111.54, 56.28.

HRMS (ESI-TOF): *m/z*: [M + Na] calculated for $C_{13}H_{12}N_2O_2S$ = 283.0516; found = 283.0515.

N'-((1H-pyrrol-2-yl)methylene)-2-methoxybenzohydrazide (22):

^{1}H NMR (400 MHz, Chloroform-d): δ = 10.70 (s, 1H), 9.62 (s, 1H), 8.30 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.00 (s, 1H), 7.49 (ddd, *J* = 8.3, 7.4, 1.8, 1H), 6.27 – 6.22 (m, 1H), 7.16 – 7.09 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.94 (q, *J* = 2.5 Hz, 1H), 6.49-6.48 (m, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d): δ = 162.07, 157.25, 139.40, 133.50, 132.83, 127.27, 122.51, 121.88, 120.35, 114.54, 111.51, 109.98, 56.26.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{13}H_{13}N_3O_2$ = 244.1086; found = 244.1086.

N'-(furan-2-ylmethylene)-4-nitrobenzohydrazide (23):

^{1}H NMR (400 MHz, DMSO-d6): δ = 12.12 (s, 1H), 8.73 (s, 1H), 8.44 – 8.30 (m, 3H), 7.88-7.82 (m, 3H), 6.99 (s, 1H), 6.66 (s, 1H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 160.89, 149.21, 147.79, 145.53, 138.46, 134.69, 134.12, 130.35, 126.39, 122.27, 114.25, 112.31.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{12}H_9N_3O_4$ = 260.0678; found = 260.0685.

N'-((5-methylfuran-2-yl)methylene)-4-nitrobenzohydrazide (24):

^{1}H NMR (400 MHz, DMSO-d6): δ = 12.04 (s, 1H), 8.73 (s, 1H), 8.44 (d, *J* = 8.1 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.26 (s, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 6.87 (s, 1H), 6.29 (s, 1H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 160.76, 154.96, 147.68, 138.31, 134.77, 134.08, 130.33, 126.32, 122.24, 116.15, 108.71, 13.53.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{13}H_{11}N_3O_4$ = 274.0778; found = 274.0836.

N'-((6-bromo-1H-indol-3-yl)methylene)-4-nitrobenzohydrazide (25):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.92 (s, 1H), 11.76 (s, 1H), 8.76 (s, 1H), 8.63 (s, 1H), 8.43 (d, *J* = 8.2 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.33 (dd, *J* = 8.4, 1.7 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 160.38, 147.80, 145.37, 137.96, 135.33, 134.05, 131.73, 130.27, 126.06, 123.46, 122.19, 115.41, 114.57, 111.72.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{16}H_{11}BrN_4O_3$ = 387.0078; found = 387.0097.

N'-((4-methylthiazol-5-yl)methylene)-4-nitrobenzohydrazide (26):

^{1}H NMR (400 MHz, DMSO-d6): δ = 12.24 (s, 1H), 8.76 (s, 1H), 8.46 (s, 2H), 8.37 (d, *J* = 7.7 Hz, 1H), 7.85 (t, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 6.7 Hz, 4H).

^{13}C NMR (100 MHz, DMSO-d6): δ = 161.02, 147.77, 147.55, 134.65, 134.16, 133.36, 131.89, 130.33, 129.09, 126.42, 123.60, 122.32.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{14}H_{10}BrN_3O_3$ = 347.9984; found = 347.9988.

N'-((1H-indol-3-yl)methylene)-2,6-difluorobenzohydrazide (27):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.88 (d, *J* = 44.8 Hz, 1H), 11.58 (d, *J* = 61.5 Hz, 1H), 8.44 – 8.21 (m, 1H), 7.80 (d, *J* = 41.4 Hz, 1H), 7.67 – 7.54 (m, 1H), 7.40 (dd, *J* = 40.6, 8.0 Hz, 1H), 7.28 – 7.05 (m, 4H), 6.81 – 6.73 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 162.06, 158.30 (dd, *J* = 247.1, 8.5 Hz), 155.06, 145.54, 141.81, 137.00 (d, *J* = 15.6 Hz), 131.33-131.19 (m), 130.59, 124.08 (d, *J* = 40.4 Hz), 122.77-120.07 (m), 112.23, 111.76, 111.21.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{16}H_{11}F_2N_3O$ = 300.0948; found = 300.0950.

N'-((6-bromo-1H-indol-3-yl)methylene)-2,6-difluorobenzohydrazide (28):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.95 (d, *J* = 47.0 Hz, 1H), 11.69 (bs 1H), 8.30 (d, *J* = 70.9 Hz, 1H), 7.84 (d, *J* = 40.9 Hz, 1H), 7.67 – 7.54 (m, 2H), 7.35 – 7.21 (m, 3H), 7.00 – 6.86 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 162.16, 159.21 (d, *J* = 240.7 Hz), 158.28 (d, *J* = 247.0 Hz), 155.16, 145.03, 141.16, 137.86 (d, J = 18.5 Hz), 132.10 (d, J = 15.4 Hz), 131.41 (d, J = 18.4 Hz), 123.56 (d, J = 10.4 Hz), 123.28, 122.80 (d, J = 21.5 Hz), 115.27 (d, J = 32.6 Hz), 114.53 (d, J = 14.4 Hz), 112.12 (d, J = 24.4 Hz), 111.74 (d, J = 23.7 Hz).

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{16}H_{10}BrF_2N_3O$ = 378.0078; found = 378.0054.

N'-(4-bromobenzylidene)-2,6-difluorobenzohydrazide (29):

^{1}H NMR (400 MHz, Chloroform-d) δ 10.72 (bs, 1H), 7.92 (s, 1H), 7.66 – 7.53 (m, 1H), 7.46 – 7.43 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.00 (dd, *J* = 8.1, 3.0 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-d) δ 164.74, 160.89, 159.67 (d, *J* = 244.8 Hz), 144.77, 132.34 (d, *J* = 32.5 Hz), 132.08, 129.39, 128.84, 124.78, 111.63 (d, *J* = 25.0 Hz).

HRMS (ESI-TOF) *m/z*: [M + H] calculated for $C_{14}H_9BrF_2N_2O$ 338.994; found 338.9949.

N'-((1H-indol-3-yl)methylene)-2-fluorobenzohydrazide (30):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.64 (d, *J* = 19.9 Hz, 1H), 11.49 (d, *J* = 20.7 Hz, 1H), 8.50 (d, *J* = 13.1 Hz, 1H), 8.30 – 8.22 (m, 1H), 7.83 (d, *J* = 2.7 Hz, 1H), 7.73 – 7.43 (m, 3H), 7.33 (q, *J* = 7.8 Hz, 2H), 7.23 – 7.15 (m, 1H), 7.10 – 6.77 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 166.67, 159.78, 159.13 (d, *J* = 248.5 Hz), 158.24(d, *J* = 246.5Hz), 145.10, 141.04, 137.00 (d, *J* = 15.8 Hz), 131.83 (dd, *J* = 111.8, 8.1 Hz), 130.71, 130.18, 129.20, 125.03 (d, *J* = 17.6 Hz), 124.49-123.85 (m), 122.71-120.03 (m) , 115.72 (dd, *J* = 85.8, 21.7 Hz), 111.78 (d, *J* = 20.2 Hz), 111.53.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{16}H_{12}FN_3O$ = 282.1042; found = 282.1047.

N'-((6-bromo-1H-indol-3-yl)methylene)-2-fluorobenzohydrazide (31):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.73 (s, 1H), 11.57 (s, 1H), 8.46 (s, 1H), 8.25 – 8.14 (m, 1H), 7.81 (d, *J* = 41.4 Hz, 1H), 7.69 – 7.45 (m, 3H), 7.40 – 7.26 (m, 2H), 7.19 – 6.73 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 167.72, 160.32, 159.08 (d *J* = 248.6 Hz), 144.48, 139.10 (d, *J* = 240.9 Hz), 137.73, 131.98 (d, *J* = 8.5 Hz), 131.39(t, *J* = 18.4 Hz), 130.12 (d, *J* = 3.0 Hz), 129.08(d, *J* = 4.3 Hz), 125.59 (d, *J* = 3.4 Hz), 124.18-124.19 (m), 116.12 (d, *J* = 21.9 Hz), 115.19(d, *J* = 30.0 Hz), 114.41 (d, *J* = 18.2 Hz), 111.66.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{16}H_{11}BrFN_3O$ = 360.0148; found = 360.0151.

N'-((1H-indol-3-yl)methylene)-4-fluorobenzohydrazide (32):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.60 (s, 1H), 11.55 (s, 1H), 8.61 (s, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 8.00 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.84 (d, *J* = 2.7 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.23-7.14 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 162.67 (d, *J* = 125.9 Hz), 161.42, 145.05, 137.04, 130.39 (d, *J* = 23.7 Hz), 130.07, 124.34, 122.63, 122.02 (d, *J* = 61.1 Hz), 120.39, 115.46 (d, *J* = 21.8 Hz), 115.24 (d, *J* = 13.5 Hz), 111.82 111.68 (d, *J* = 13.5 Hz).

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{16}H_{12}FN_3O$ = 282.1043; found = 282.1049.

N'-((6-bromo-1H-indol-3-yl)methylene)-4-fluorobenzohydrazide (33):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.65 (bs, 2H), 8.59 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.99 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.87 (s, 1H), 7.64 (s, 1H), 7.40 – 7.29 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 165.17, 162.70, 161.49, 144.45, 137.94, 131.26, 130.40 (d, *J* = 3.1 Hz), 130.13 (d, *J* = 9.0 Hz), 123.66, 123.32 (d, *J* = 6.5 Hz), 115.36 (d, *J* = 21.8 Hz), 114.50, 111.84.

HRMS (ESI-TOF): *m/z*: [M + H + 2] calculated for $C_{16}H_{11}BrFN_3O$ = 362.0148; found = 362.0128.

4-fluoro-N'-((4-methylthiazol-5-yl)methylene)benzohydrazide (34):

^{1}H NMR (400 MHz, DMSO-d6): δ = 11.87 (bs, 1H), 9.05 (s, 1H), 8.72 (s, 1H), 7.95 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.35 (t, *J* = 8.8 Hz, 2H), 2.47 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d6): δ = 164.19 (d, *J* = 249.4 Hz), 161.75, 154.97, 154.21, 140.90, 130.24 (d, *J* = 9.1 Hz), 129.63 (d, *J* = 2.8 Hz), 127.59, 115.54 (d, *J* = 21.9 Hz), 15.33.

HRMS (ESI-TOF): *m/z*: [M + H] calculated for $C_{12}H_{10}FN_3OS$ = 264.0577; found = 264.0604.

Crystal data and structure refinement for compound 28 (CCDC 1559783):

Empirical formula: C16 H10 Br F2 N3 O

Formula weight: 378.17

Temperature: 100(2) K

Wavelength: 0.71073 Å

Crystal system: Monoclinic

Space group : P 21/n

Unit cell dimensions: a = 11.218(2) Å α= 90°

b = 9.7135(17) Å β= 108.759(4)°

c = 14.594(3) Å γ = 90°

Volume: 1505.8(5) $Å^3$

Z: 8

Density (calculated): 1.668 Mg/m^3

Absorption coefficient: 2.758 mm^{-1}

F(000): 752

Crystal size: 0.17 x 0.12 x 0.09 mm^3

Theta range for data collection: 2.008 to 28.402°

Index ranges: -15<=h<=15, -12<=k<=8, -19<=l<=17

Reflections collected: 7259

Independent reflections: 3760 [R(int) = 0.0273]

Completeness to theta = 25.242° 99.8 %

Absorption correction: Multi-scan

Max. and min. transmission: 0.679 and 0.780

Refinement method: Full-matrix least-squares on F2

Data / restraints / parameters: 3760 / 0 / 208

Goodness-of-fit on F2: 1.0449

Final R indices [I>2sigma(I)]: R1 = 0.0273, wR2 = 0.0675

indices (all data): R1 = 0.0369, wR2 = 0.0639

Largest diff. peak and hole : 0.370 and -0.455 e.Å-3

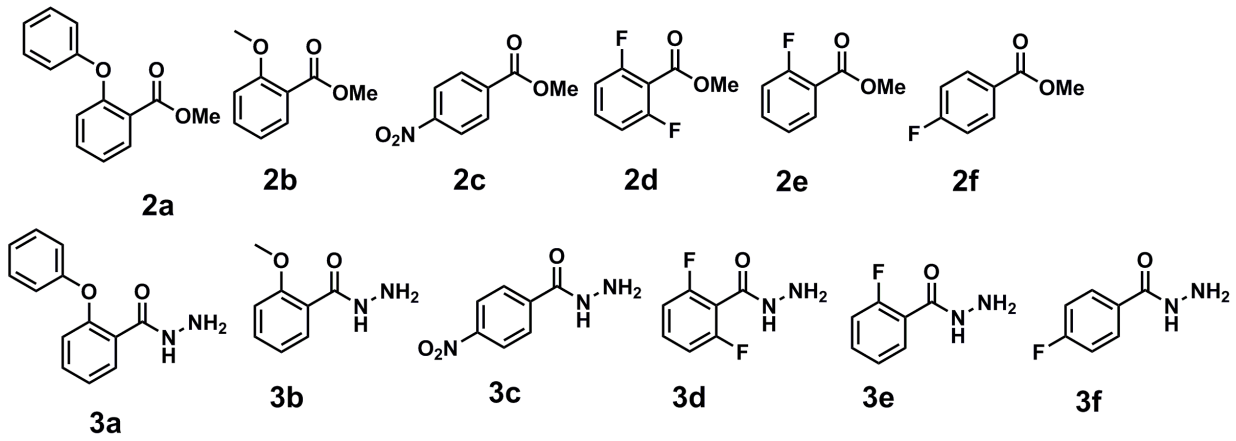


Figure S1: Chemical structures of the methyl benzoates and aromatic hydrazide intermediates.

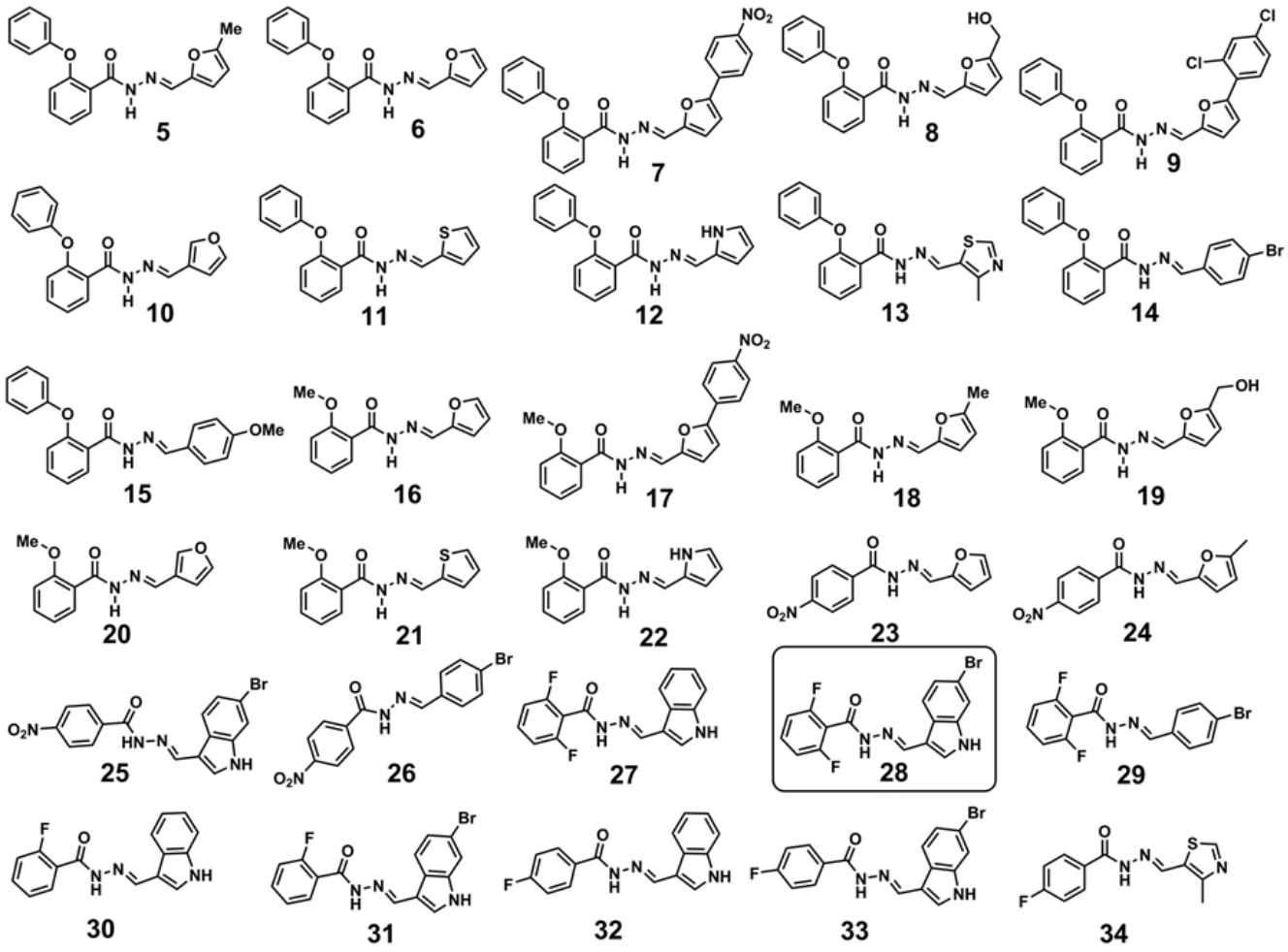


Figure S2: Chemical structures of the hydrazide-hydrazone library members.

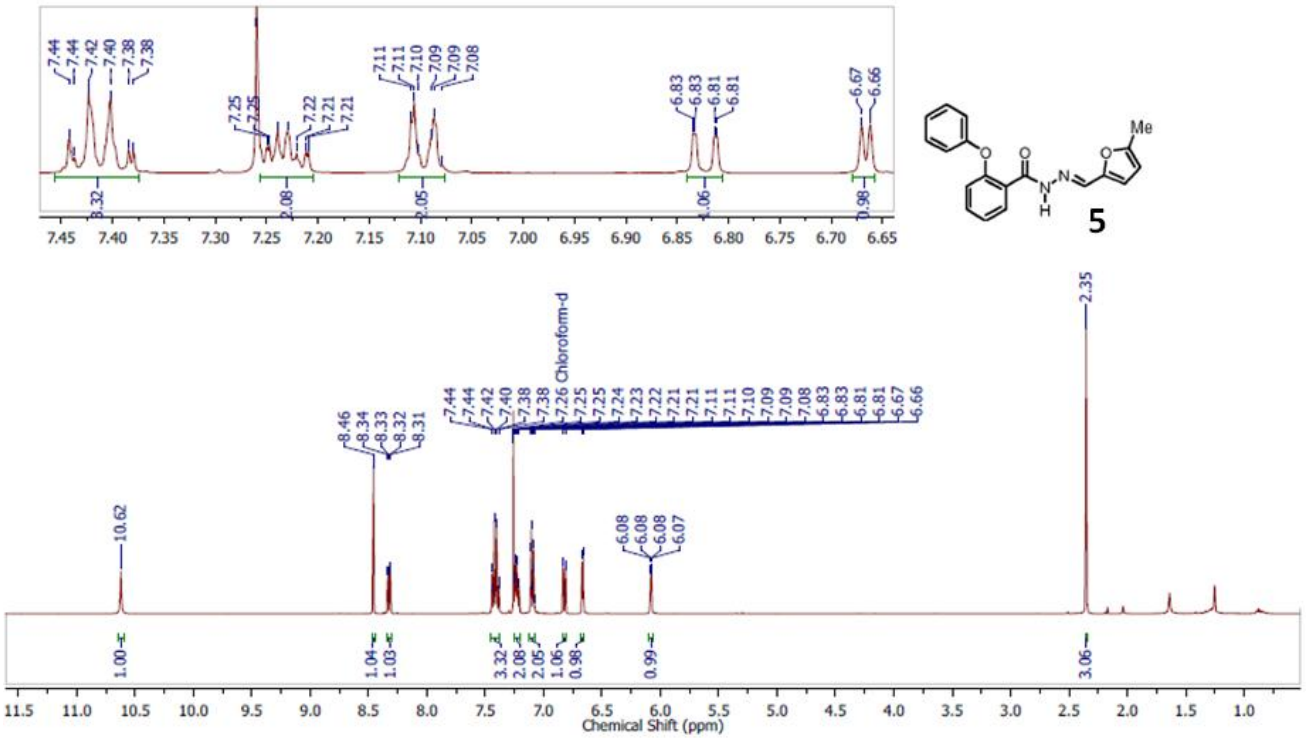


Figure S3: ^{1}H NMR spectra of compound 5.

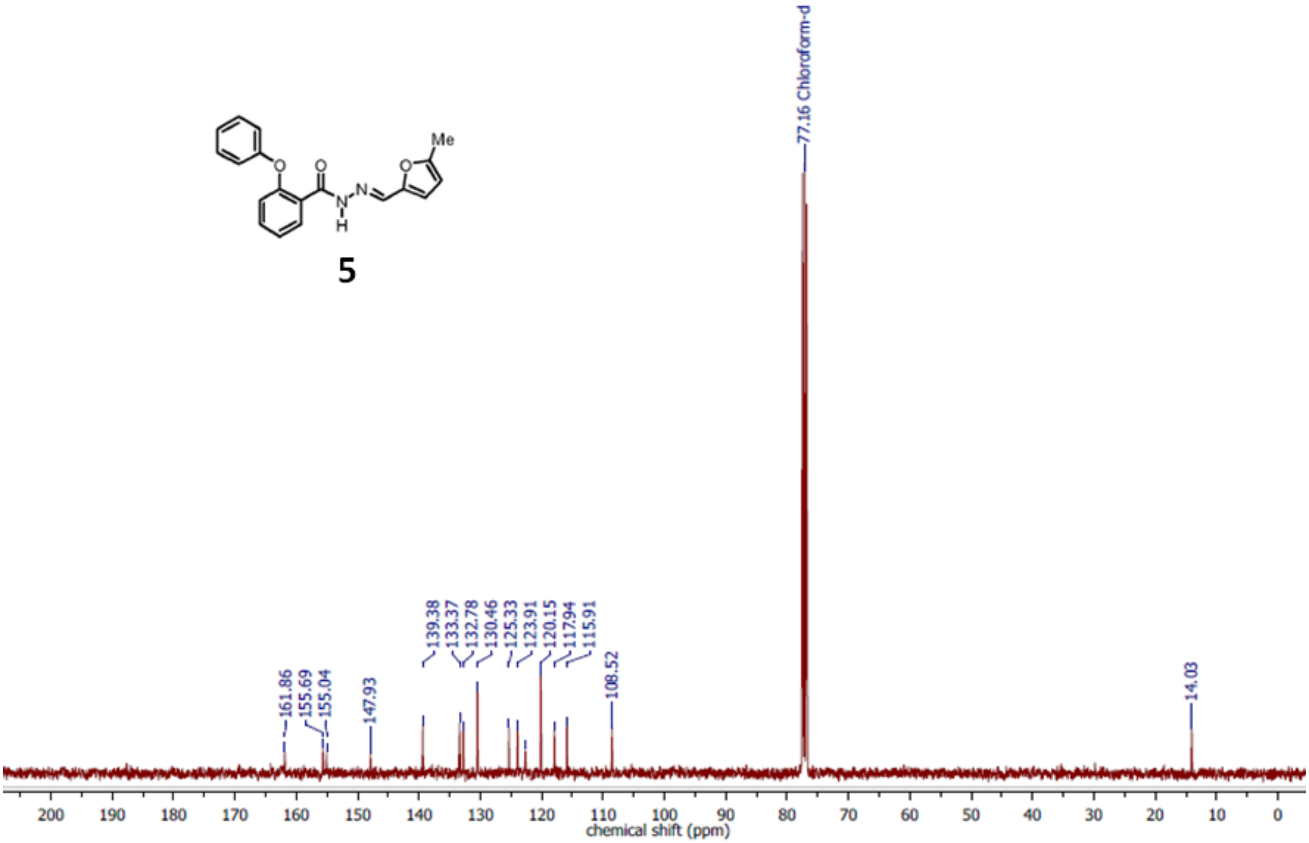


Figure S4: ^{13}C NMR spectra of compound 5.

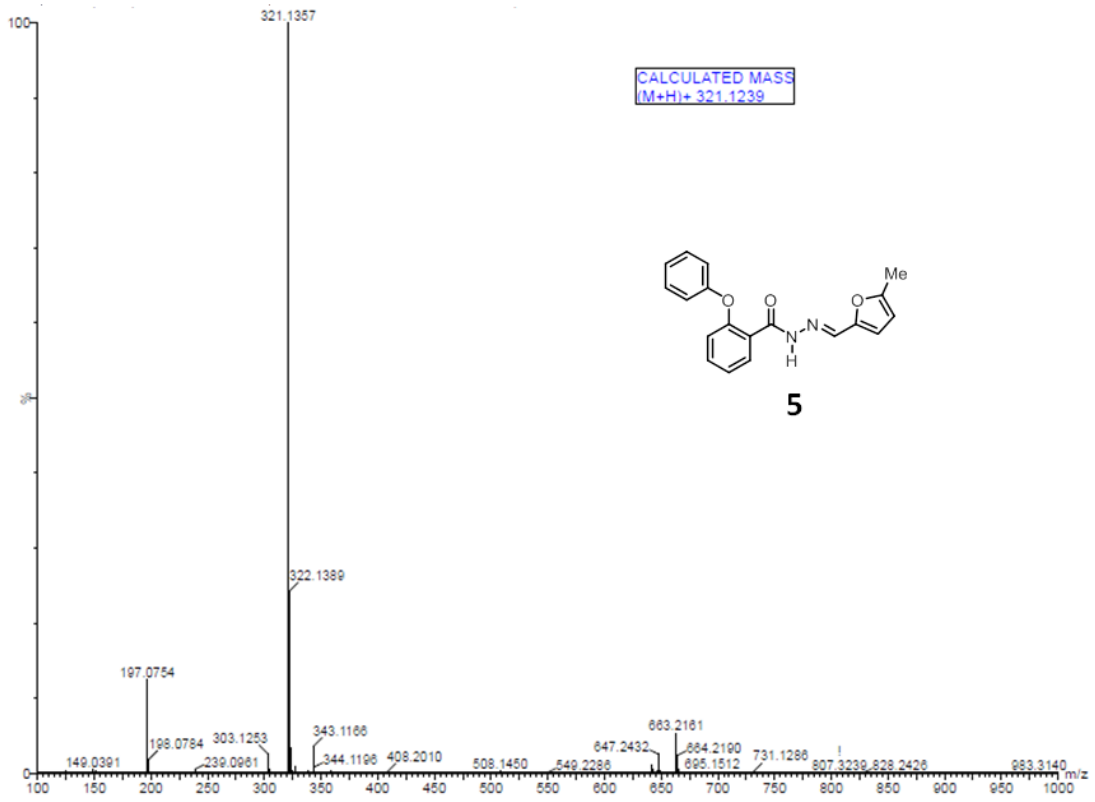


Figure S5: HR-MS spectra of compound 5.

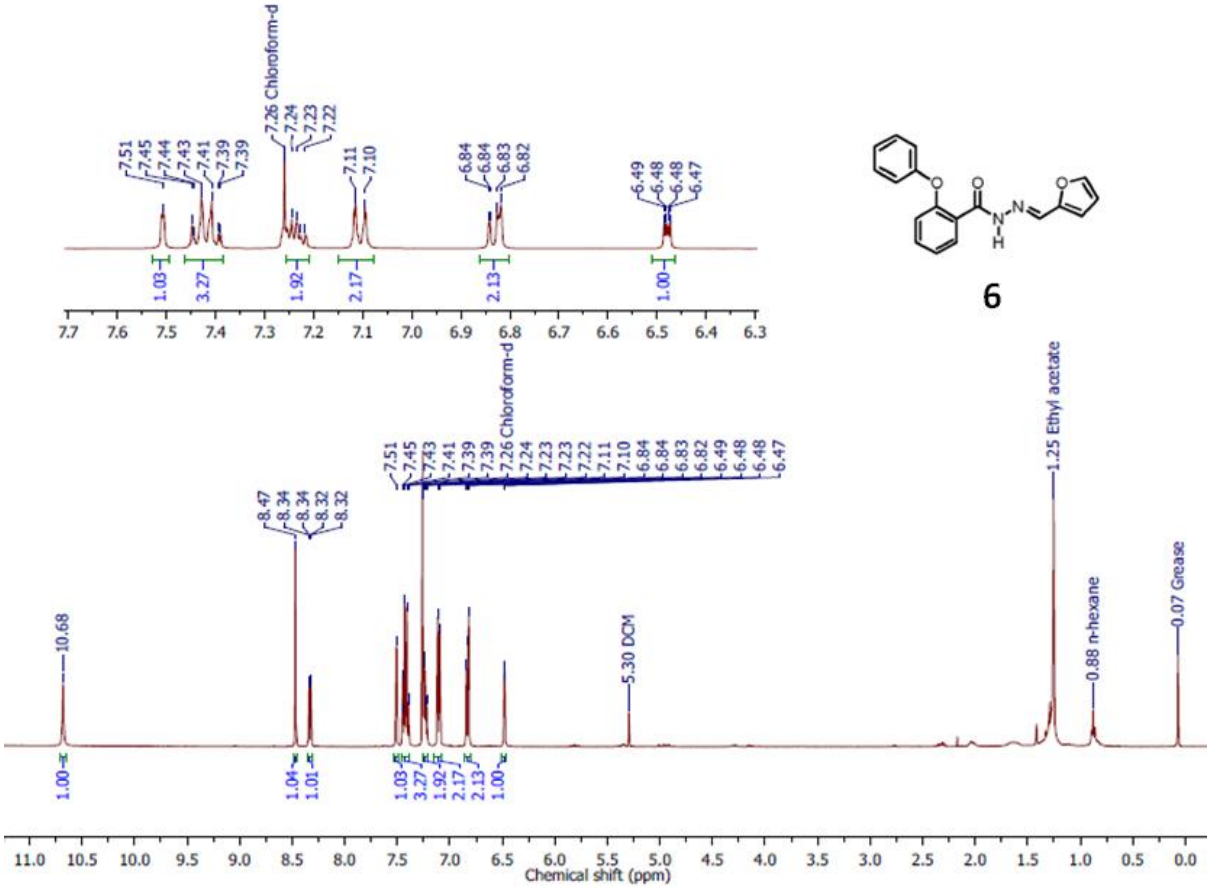


Figure S6: ^{1}H NMR spectra of compound 6.

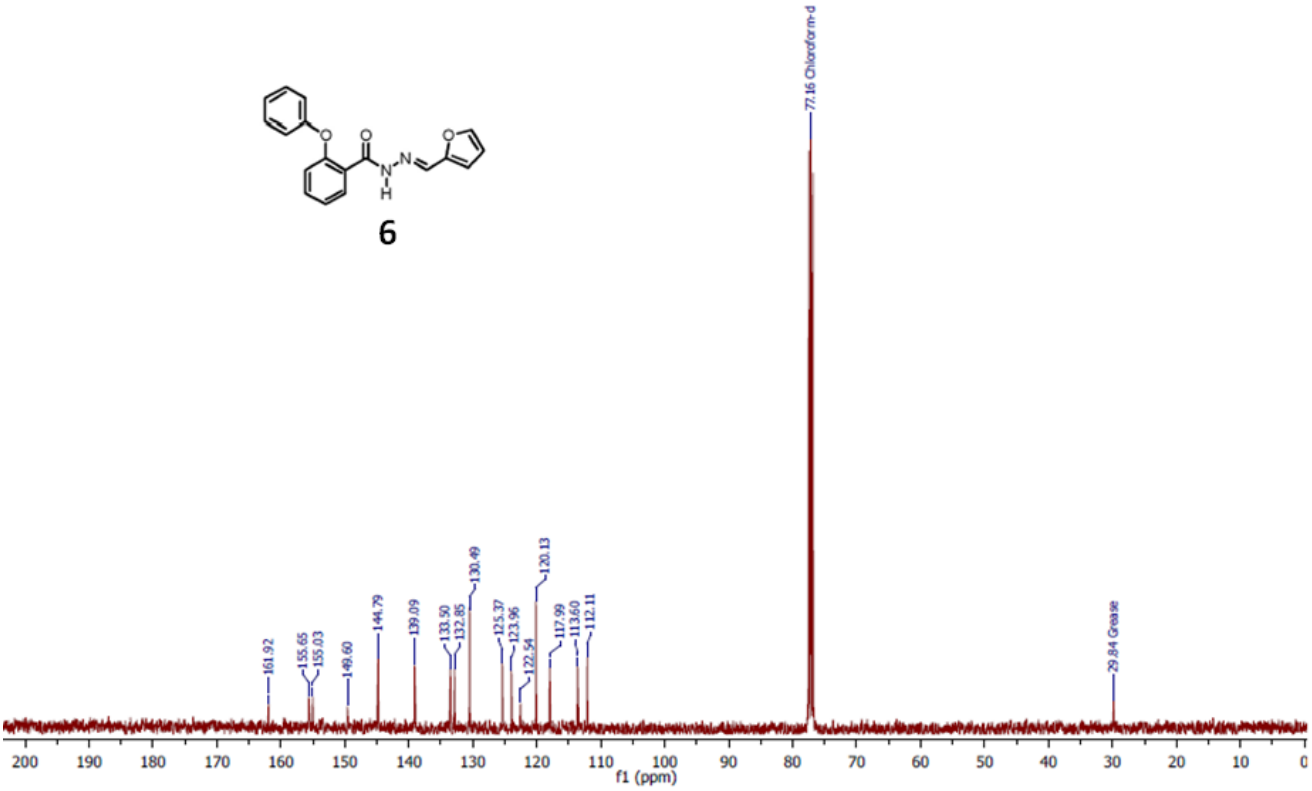


Figure S7: ^{13}C NMR spectra of compound 6.

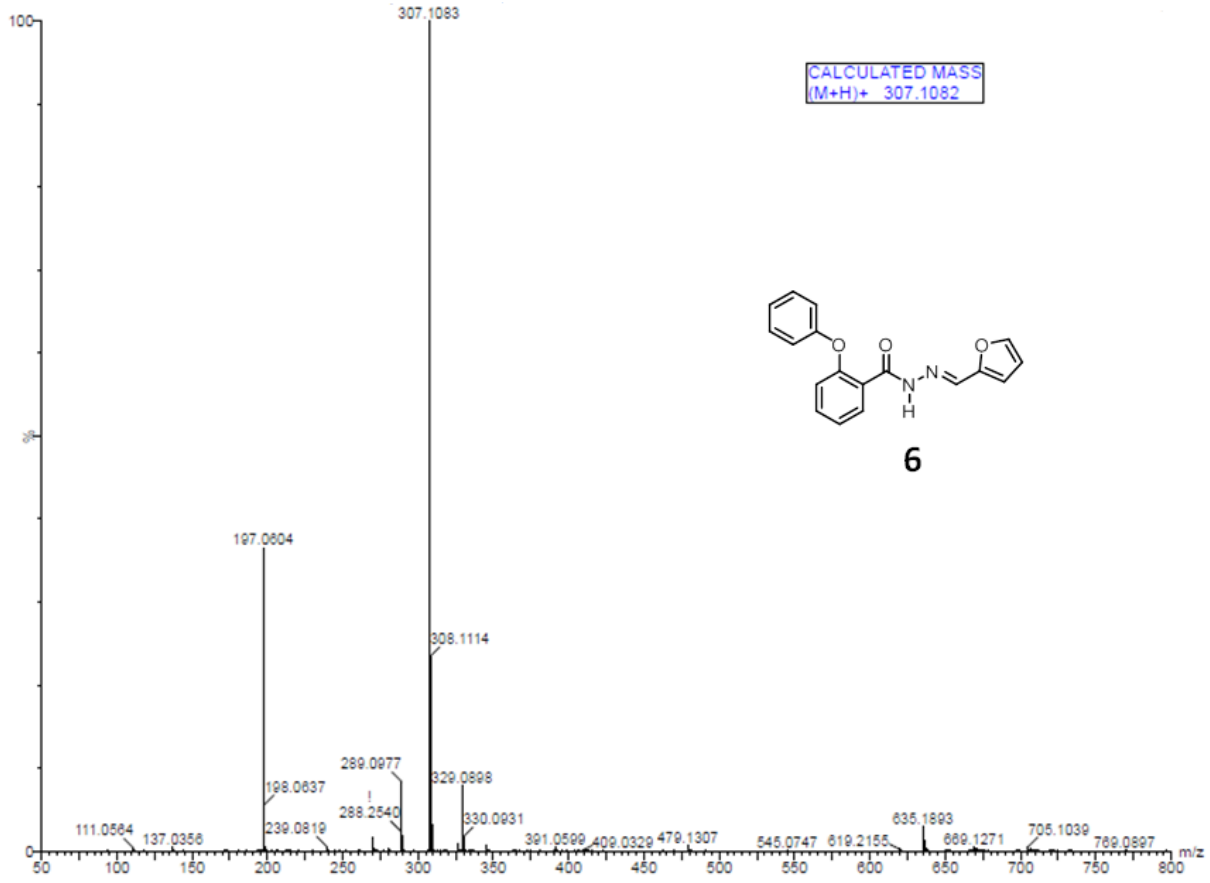


Figure S8: HR-MS spectra of compound 6.

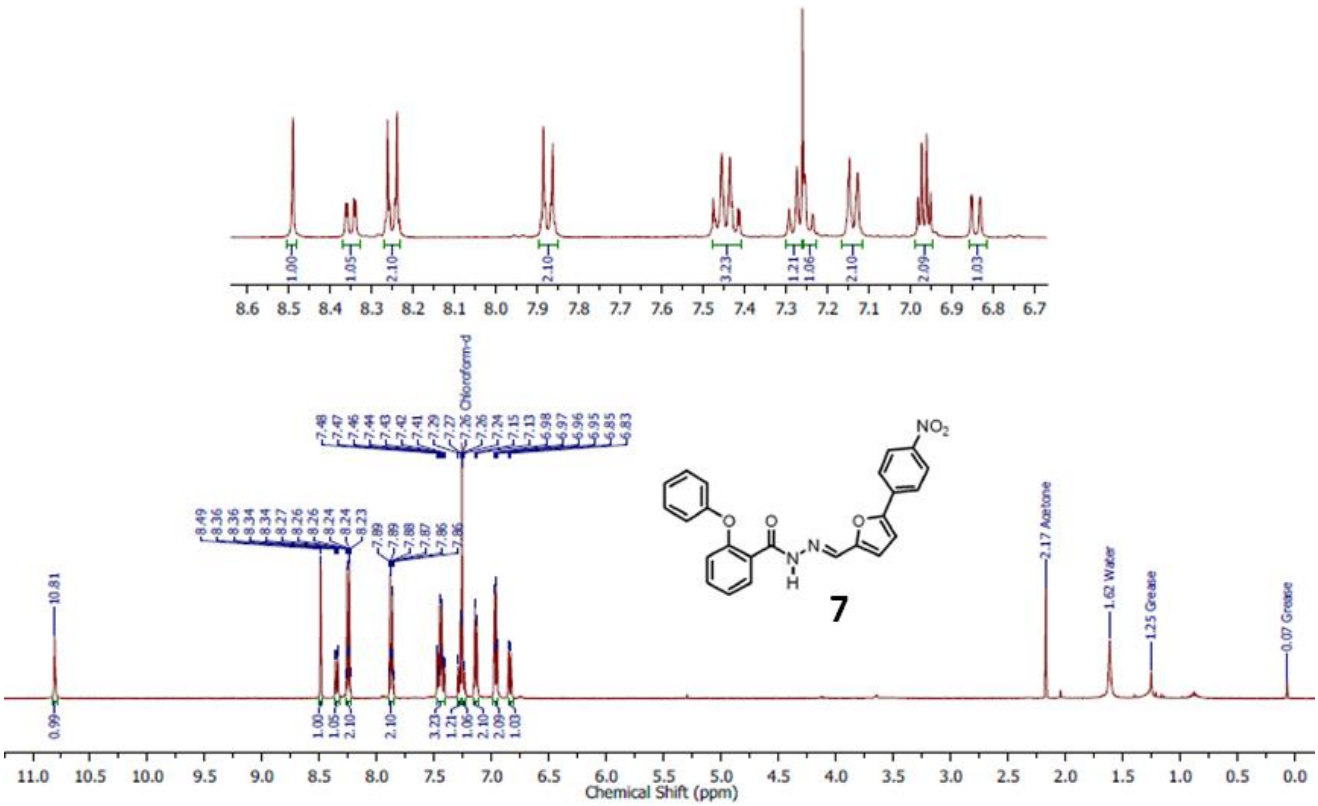


Figure S9: ^{1}H NMR spectra of compound 7.

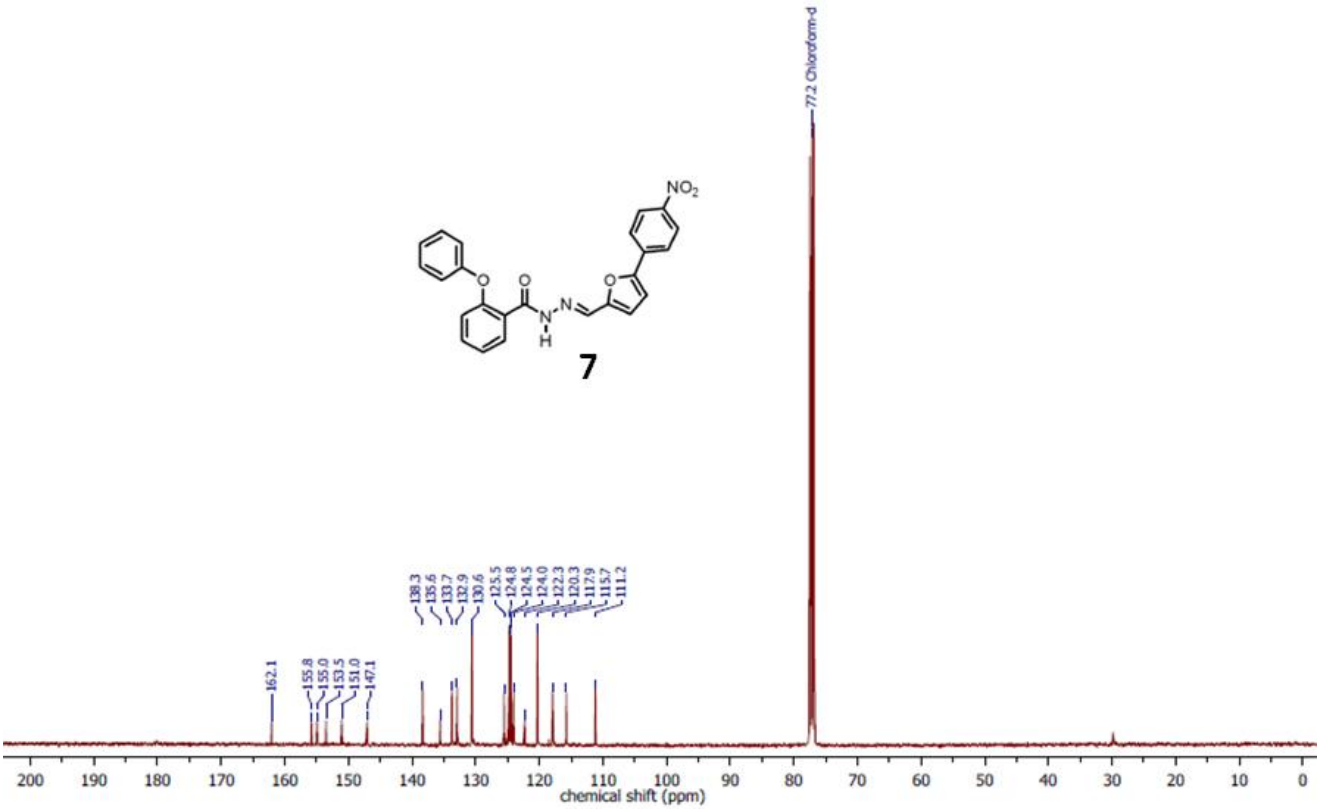


Figure S10: ^{13}C NMR spectra of compound 7.

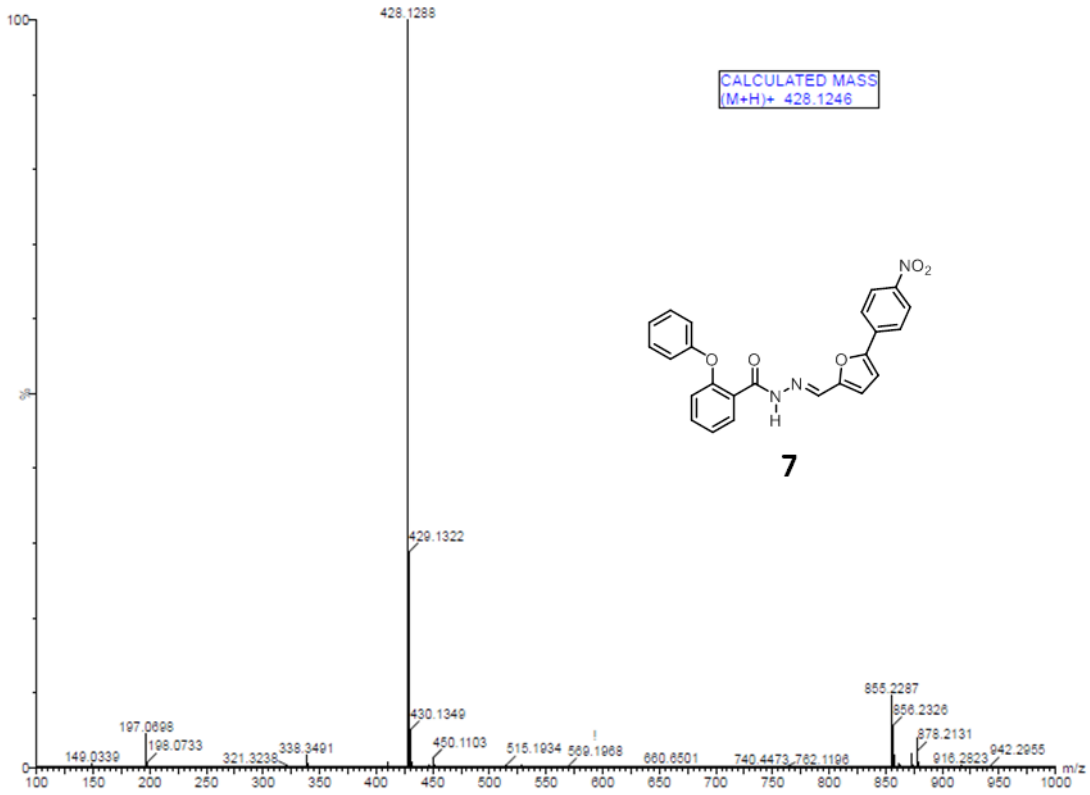


Figure S11: HR-MS spectra of compound 7.

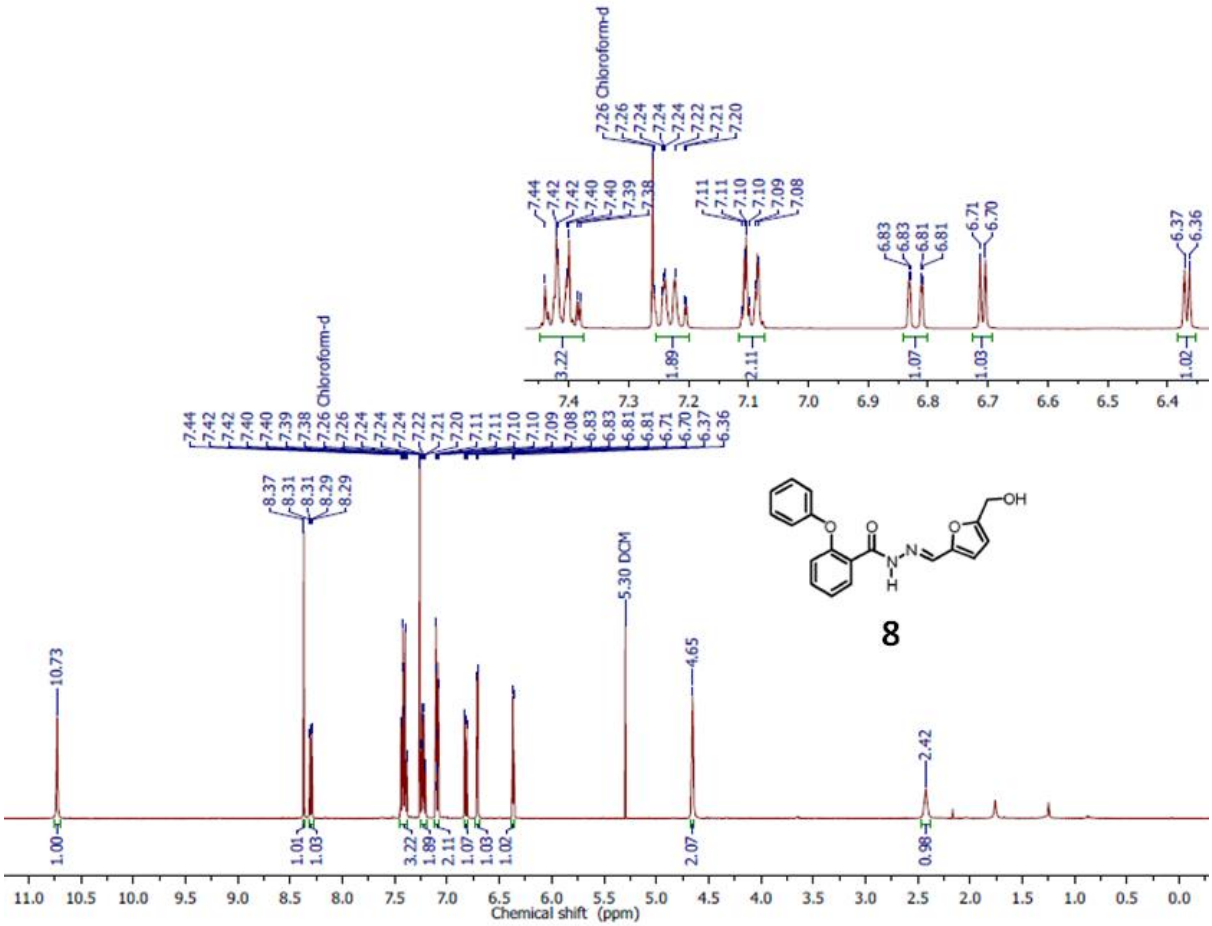


Figure S12: ^{1}H NMR spectra of compound 8.

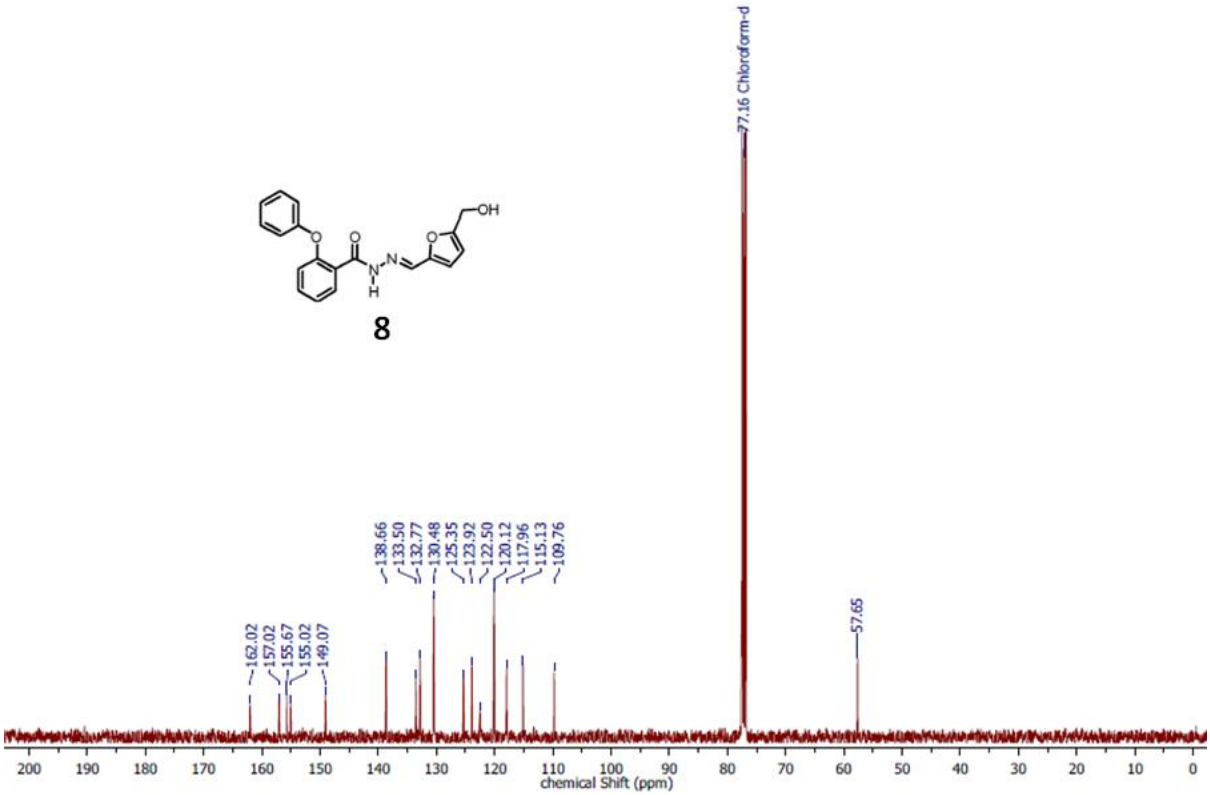


Figure S13: ^{13}C NMR spectra of compound 8.

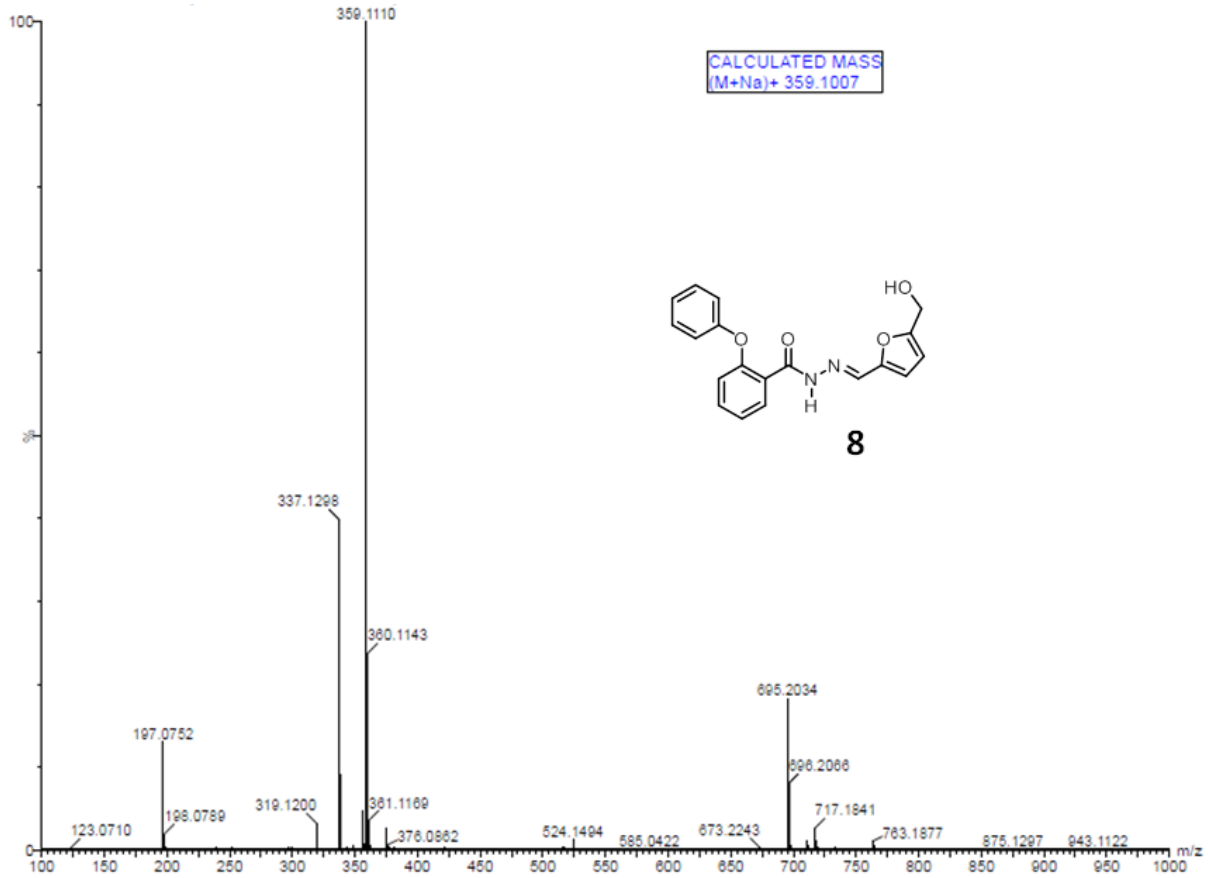


Figure S14: HR-MS spectra of compound 8.

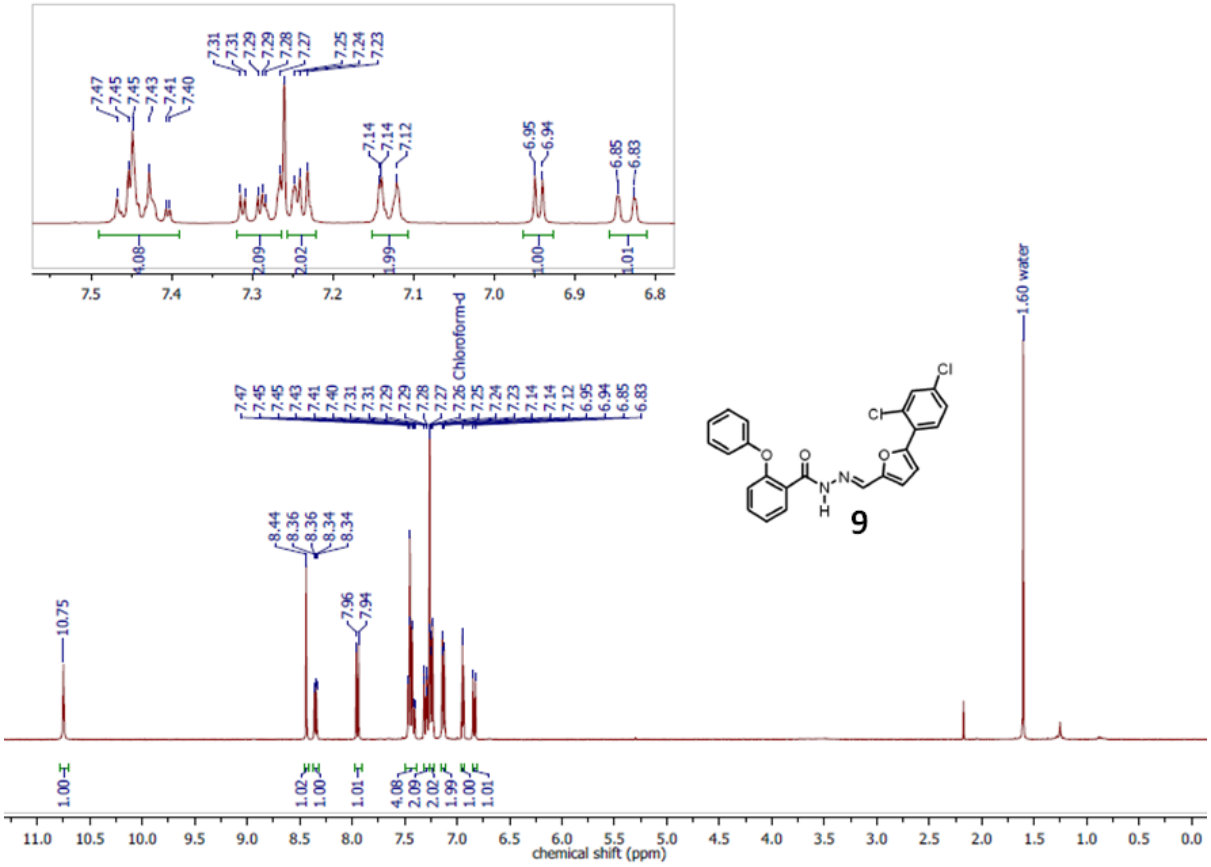


Figure S15: ^{1}H NMR spectra of compound 9.

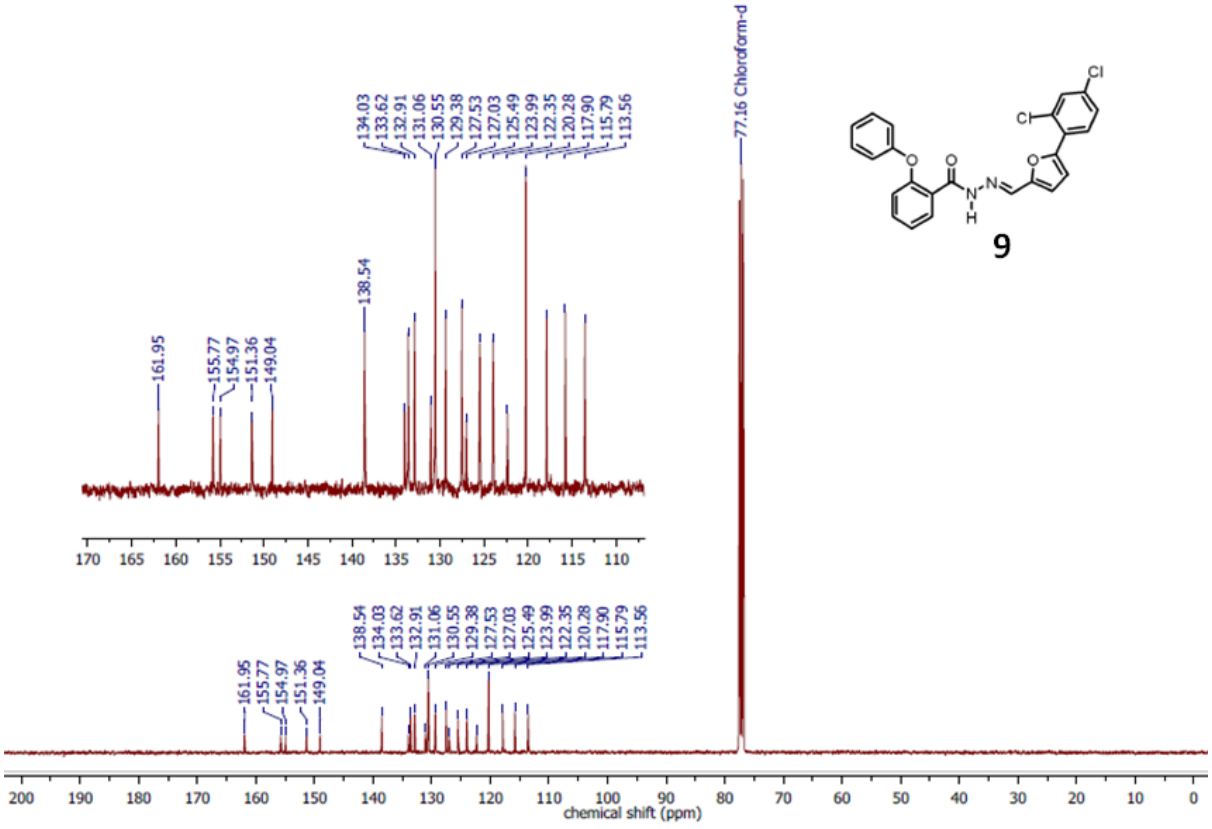


Figure S16: ^{13}C NMR spectra of compound 9.

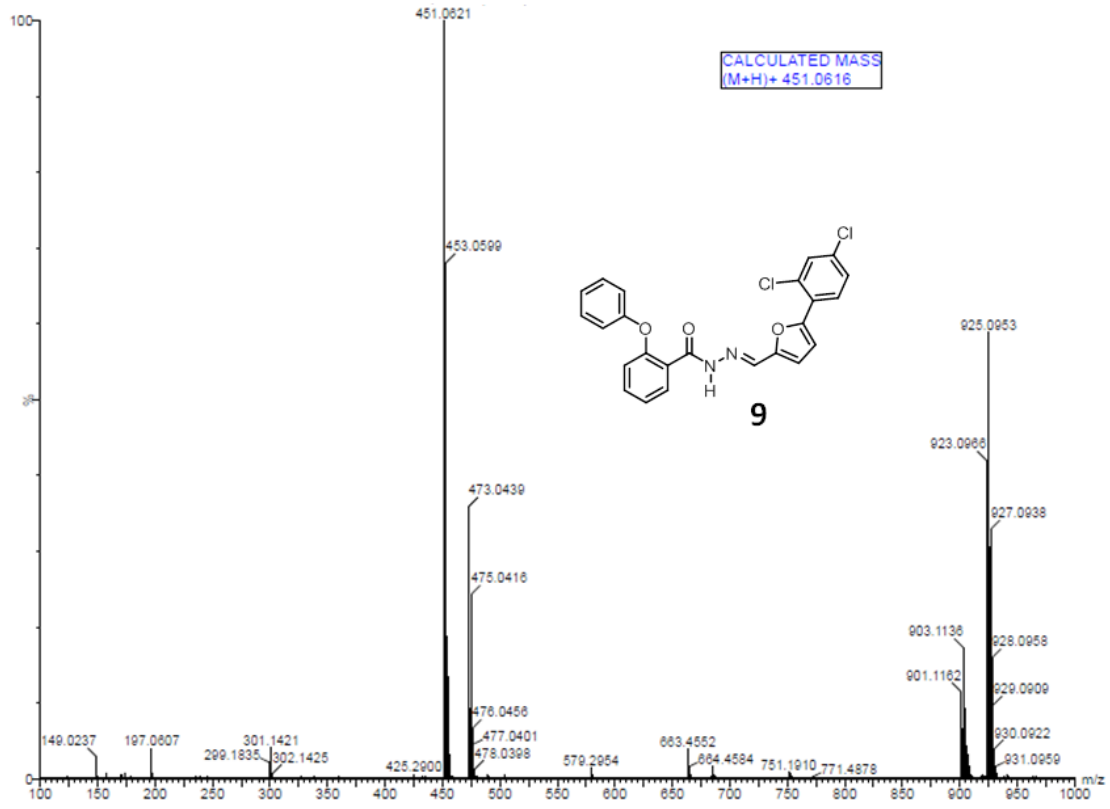


Figure S17: HR-MS spectra of compound 9.

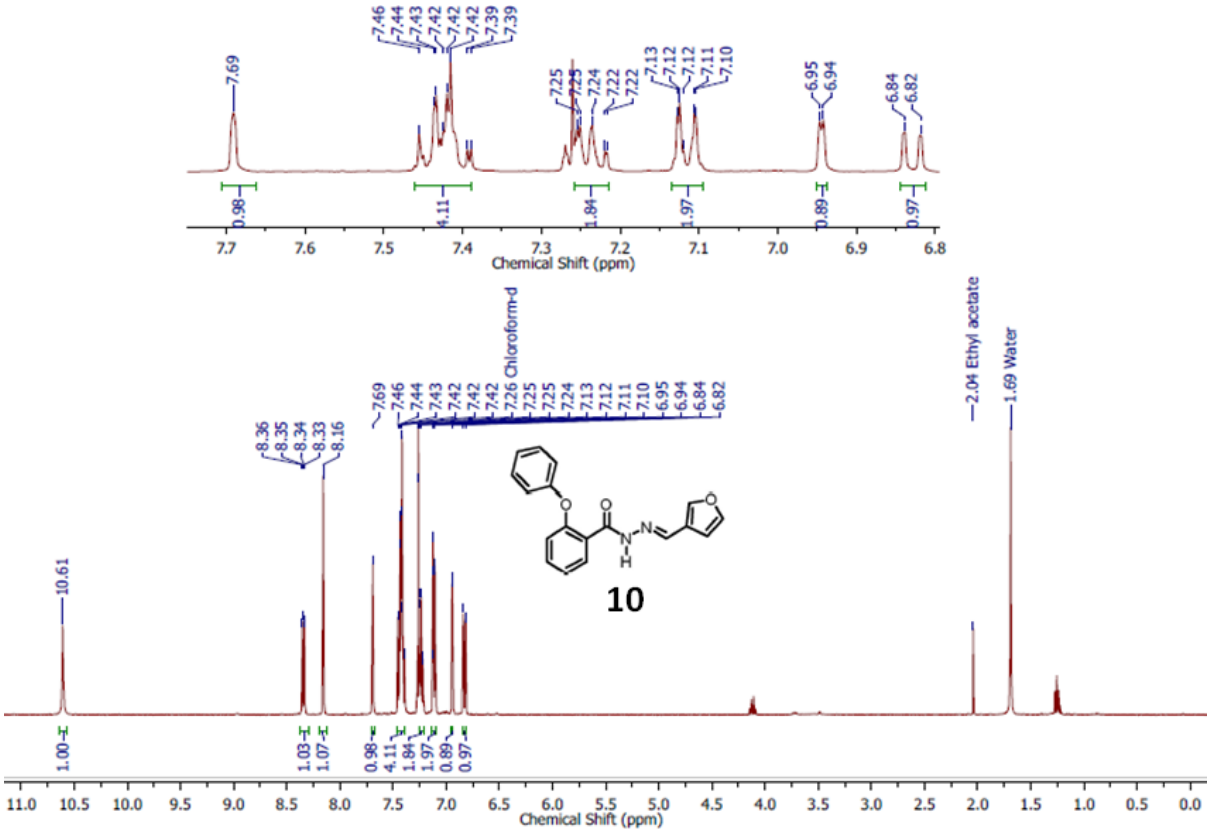


Figure S18: ^{1}H NMR spectra of compound 10.

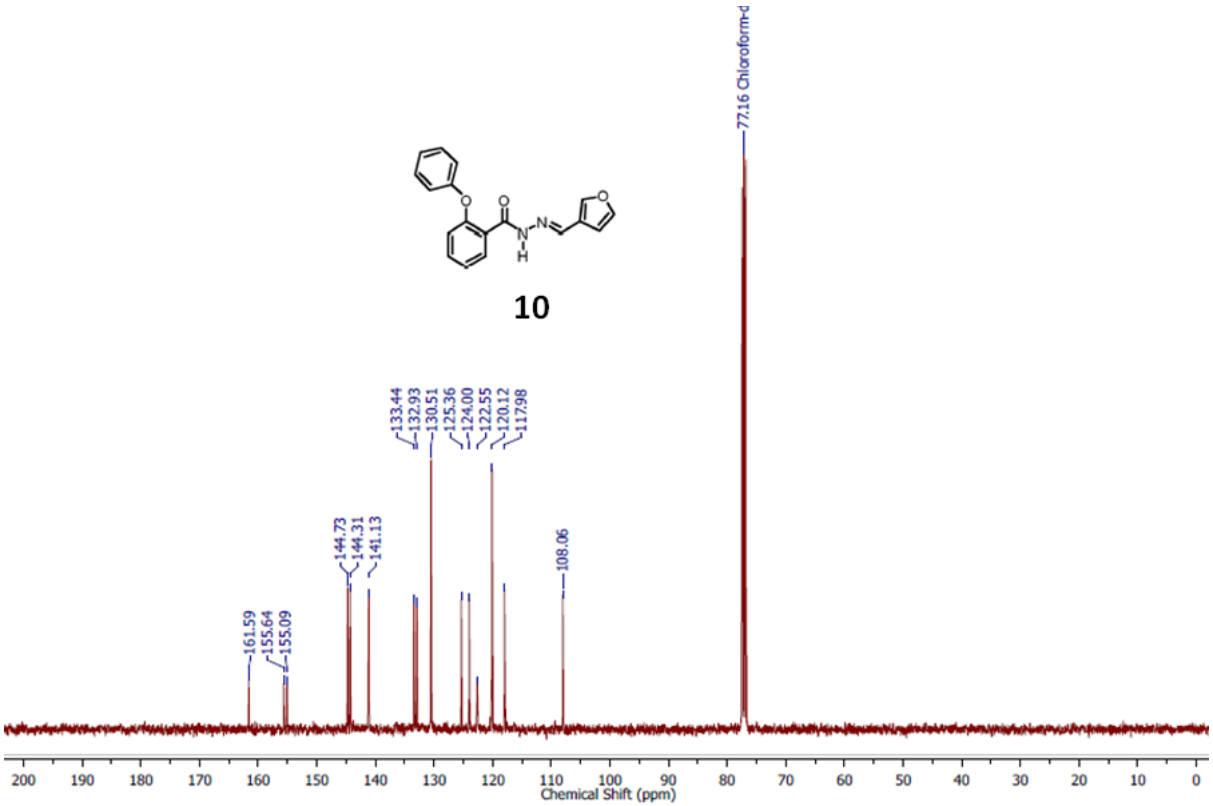


Figure S19: ^{13}C NMR spectra of compound 10.

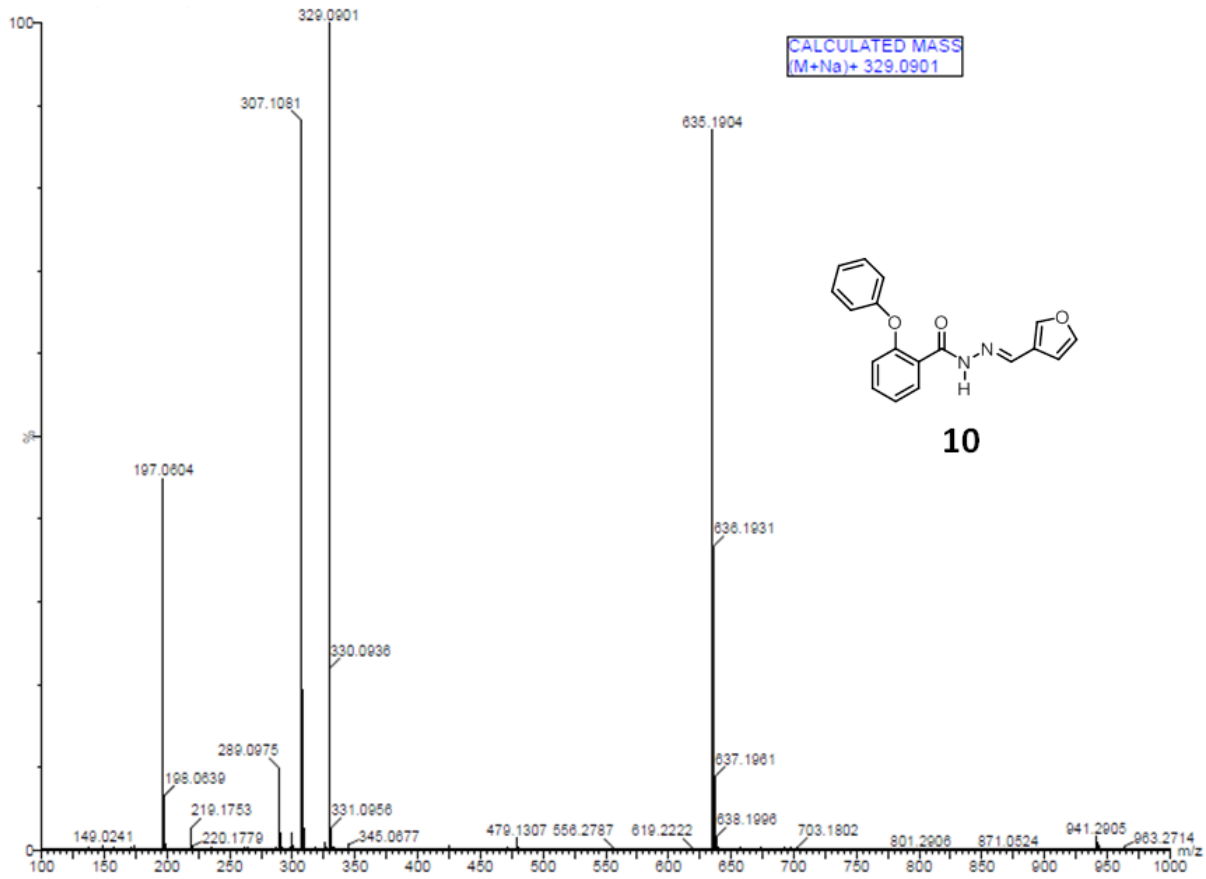


Figure S20: HR-MS spectra of compound 10.

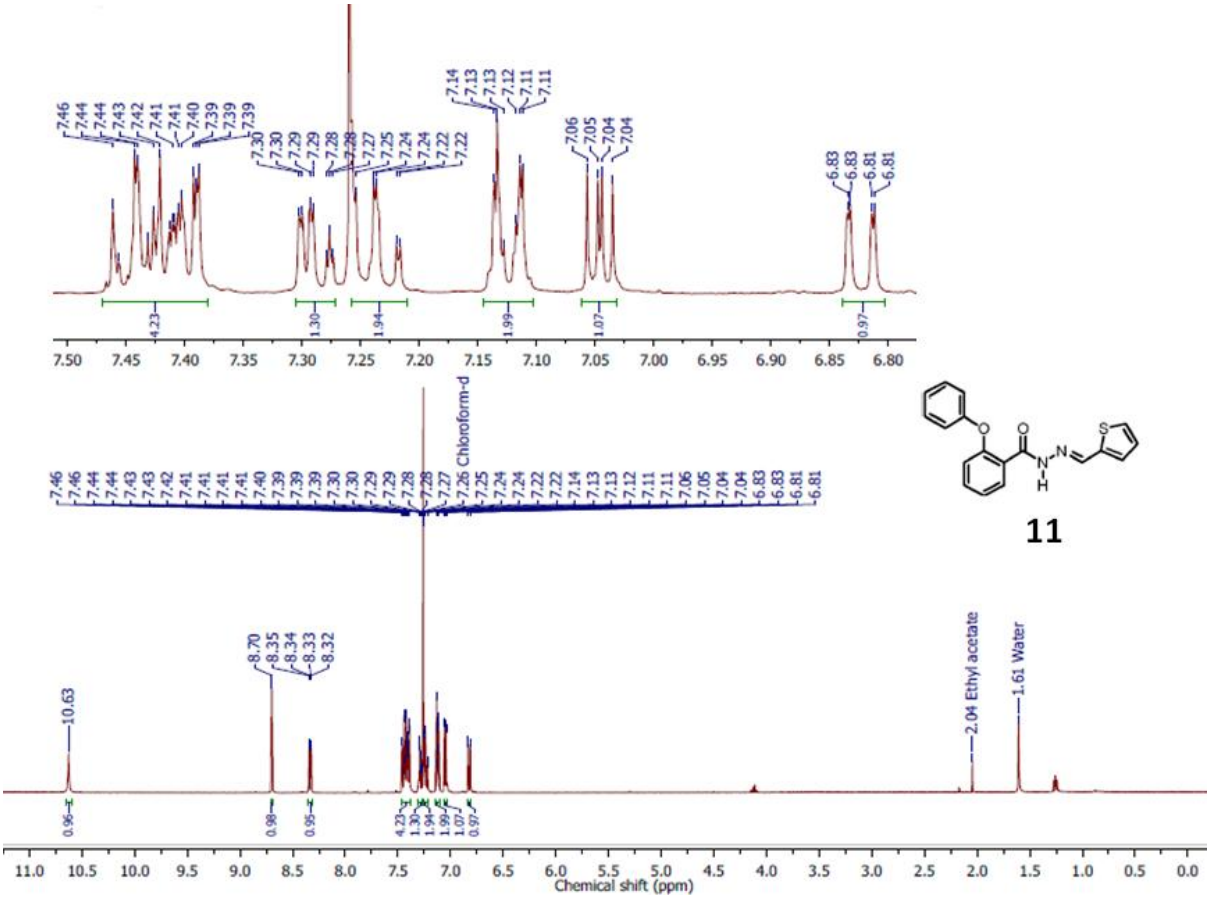


Figure S21: ^{1}H NMR spectra of compound 11.

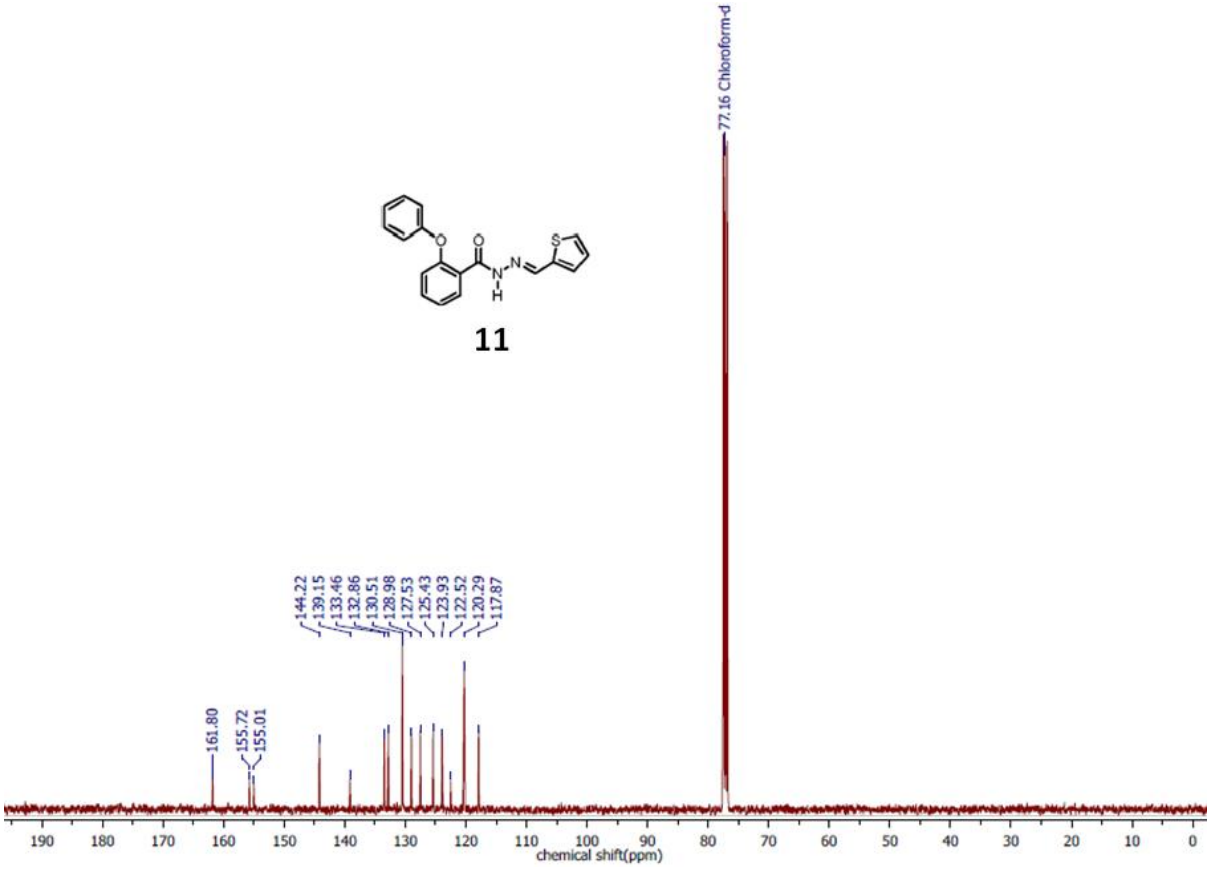


Figure S22: ^{13}C NMR spectra of compound 11.

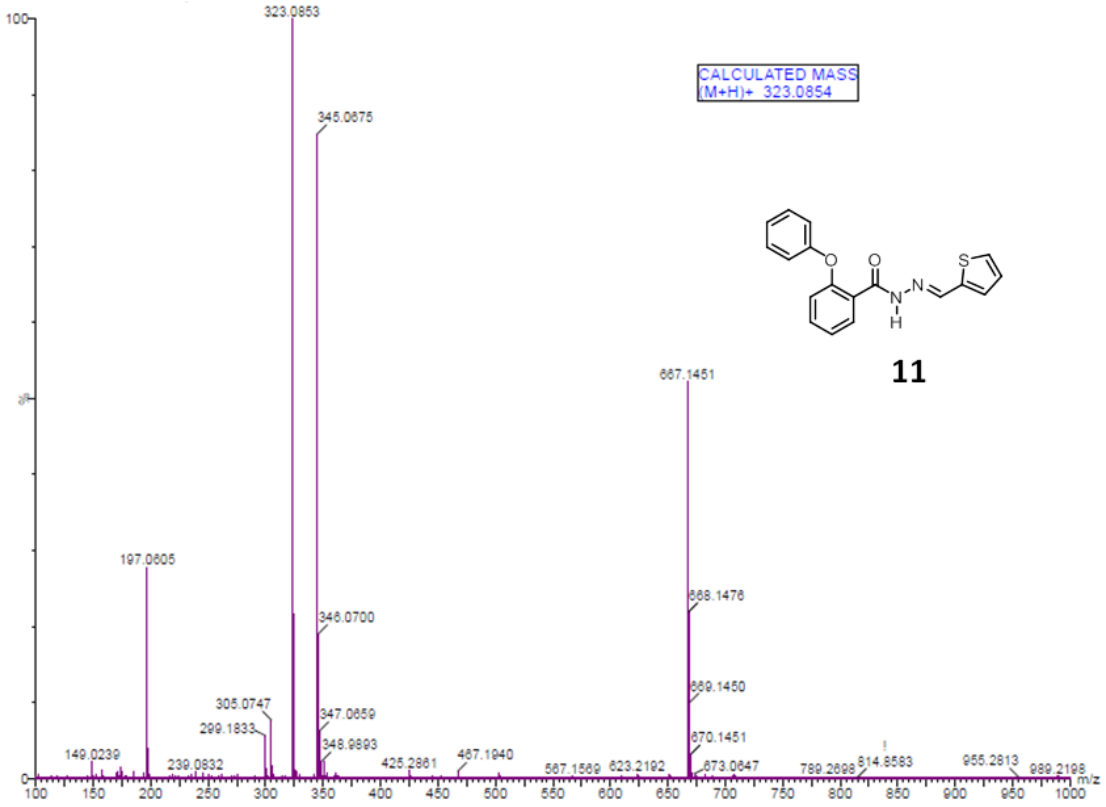


Figure S23: HR-MS spectra of compound 11.

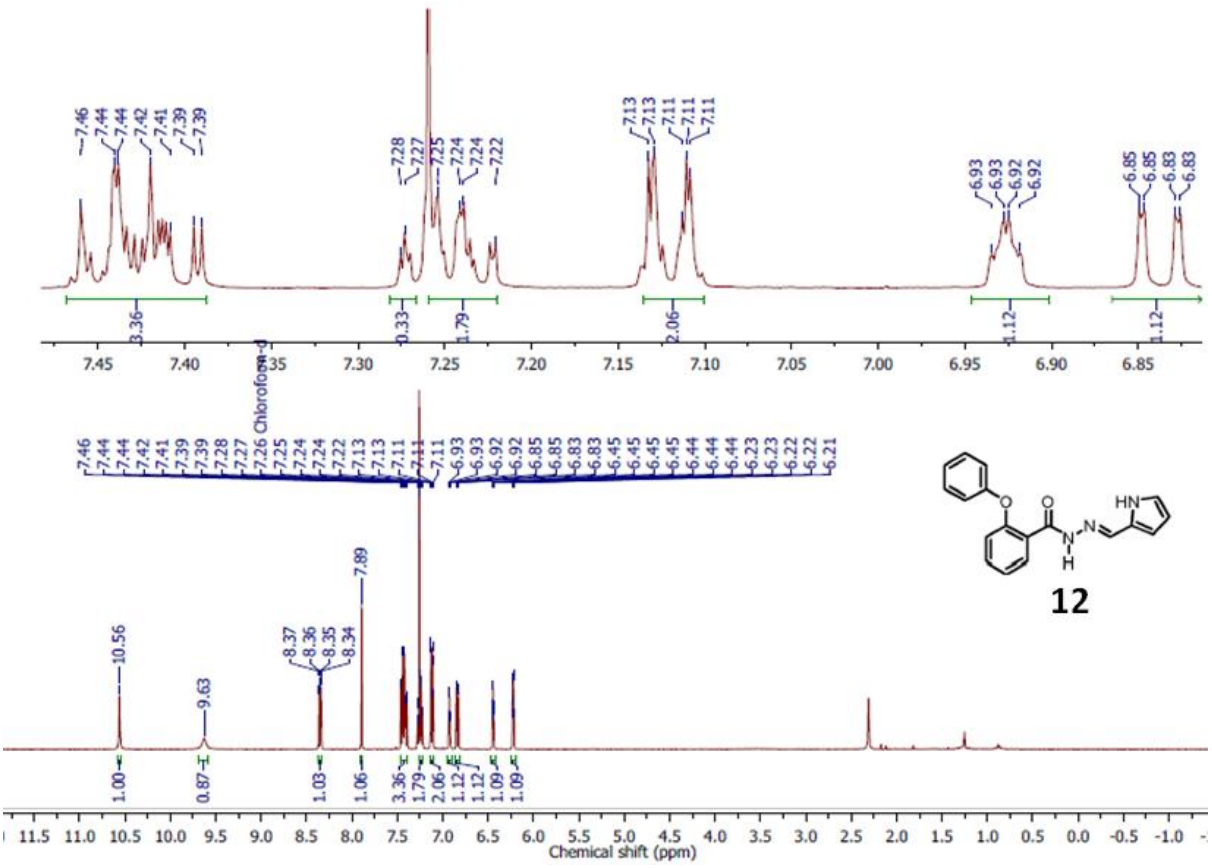


Figure S24: ^{1}H NMR spectra of compound 12.

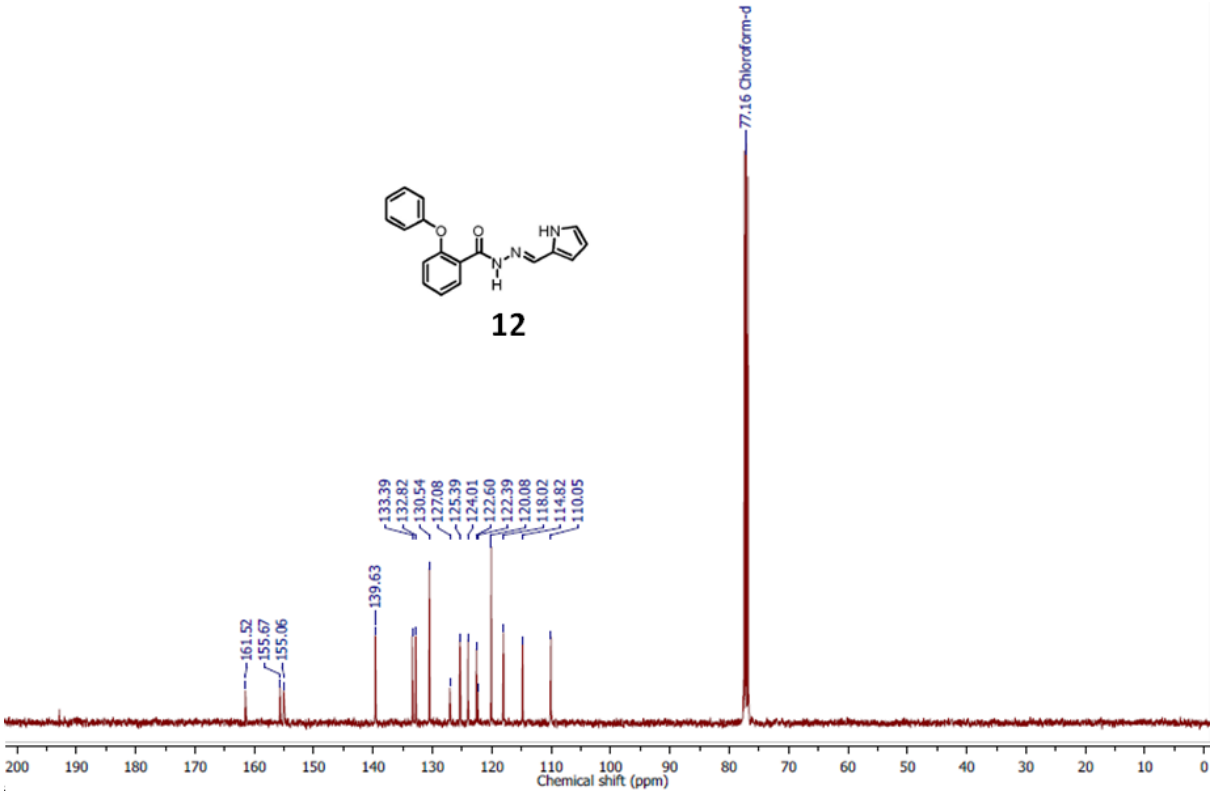


Figure S25: ^{13}C NMR spectra of compound 12.

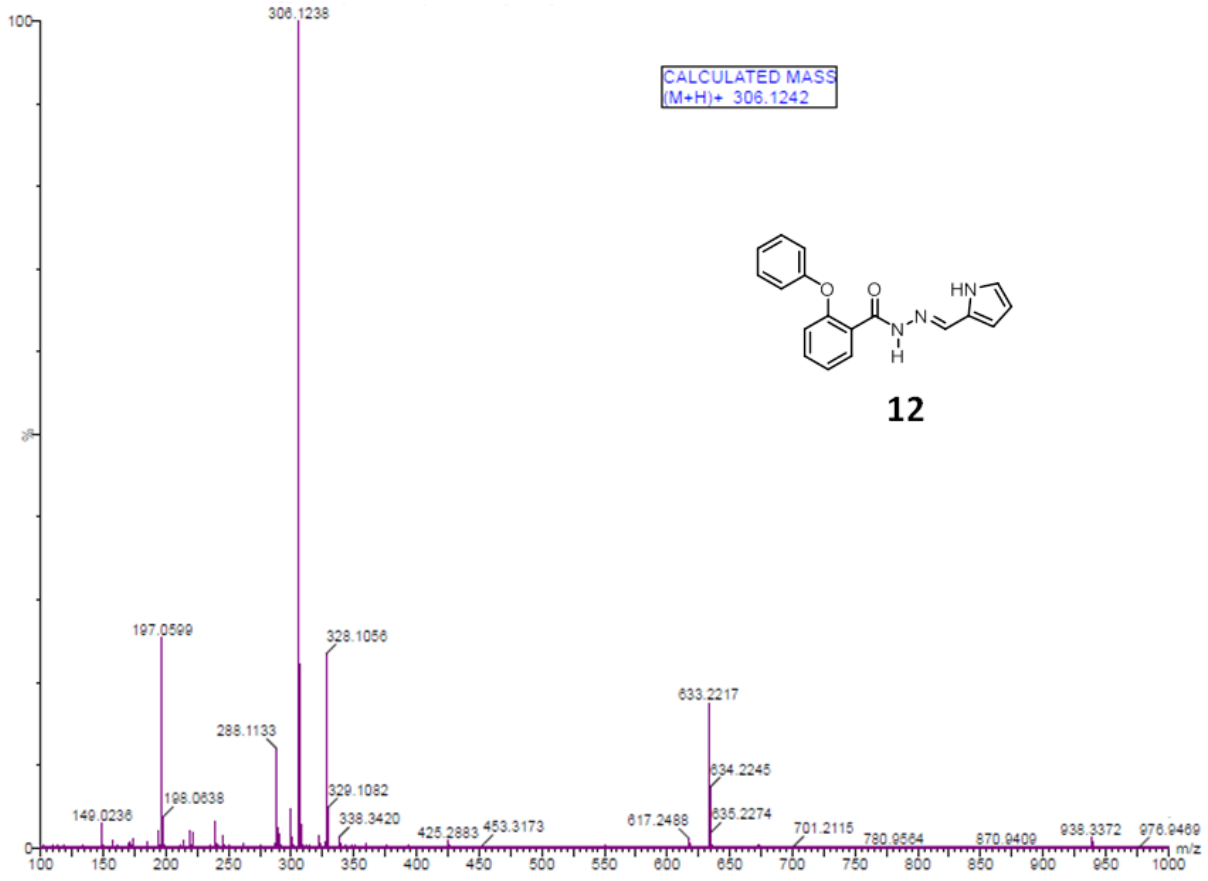


Figure S26: HR-MS spectra of compound 12.

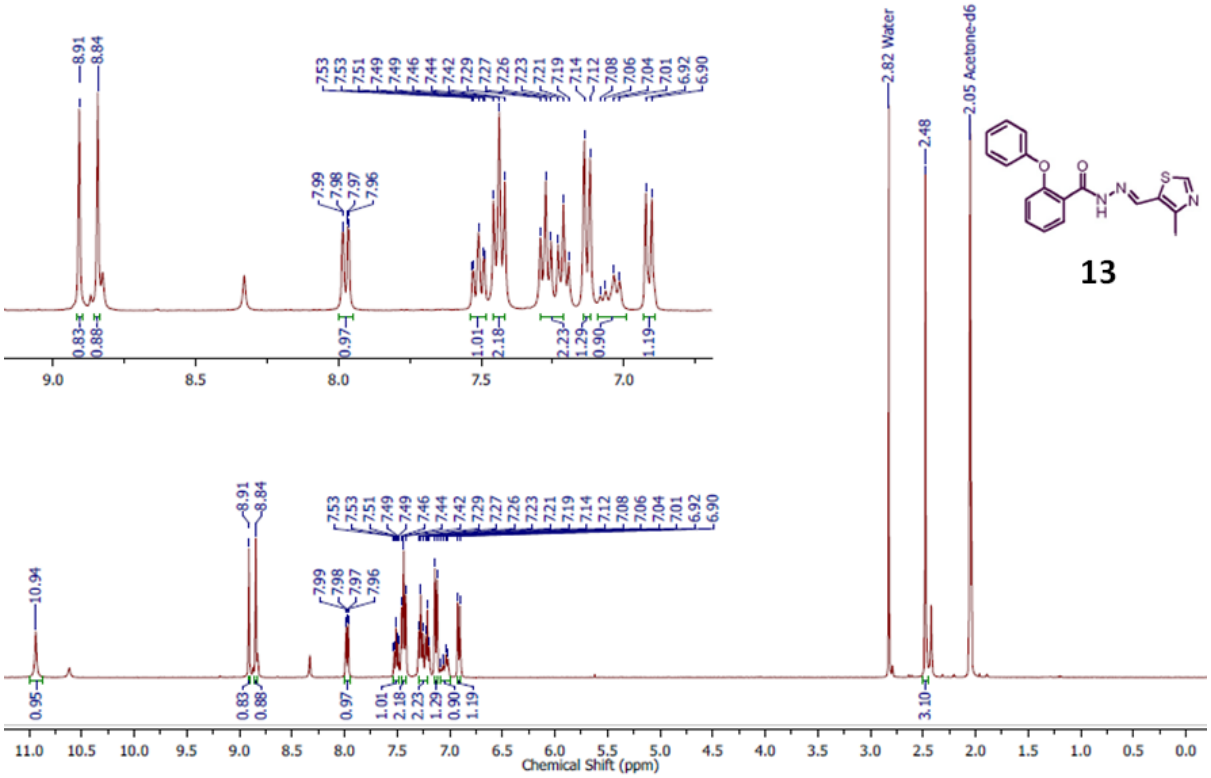


Figure S27: ^{1}H NMR spectra of compound 13.

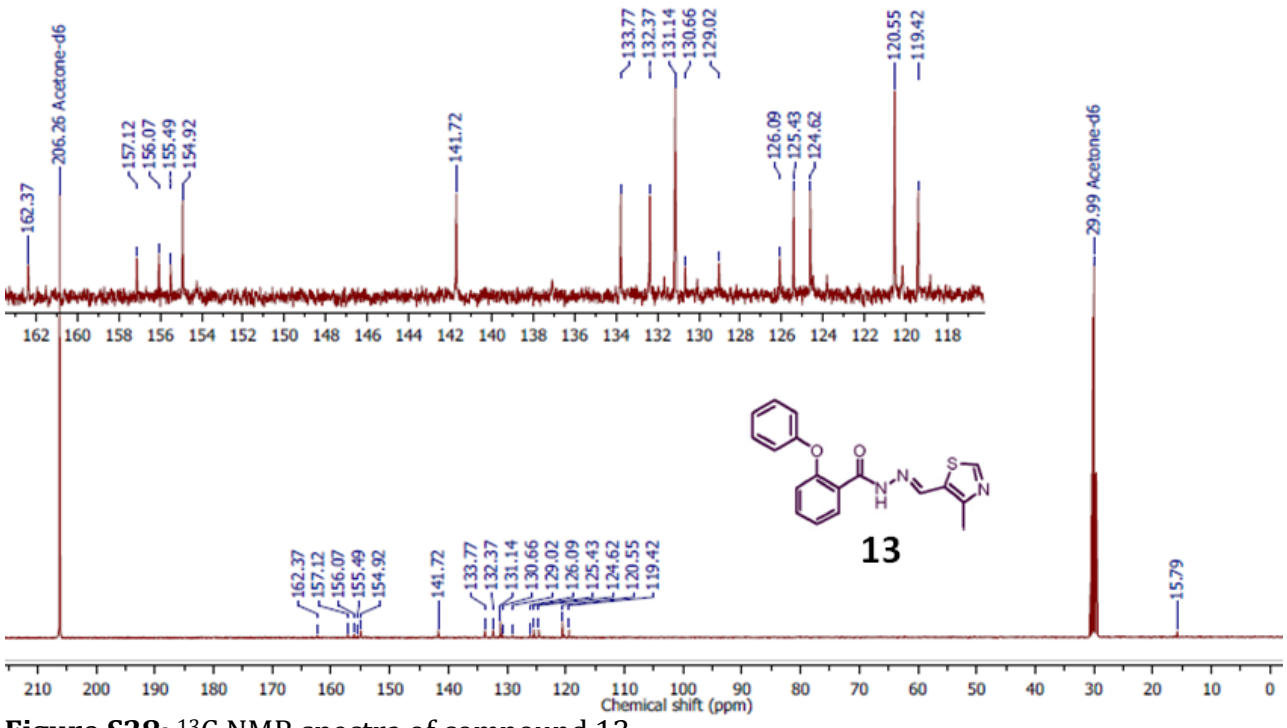


Figure S28: ^{13}C NMR spectra of compound 13.

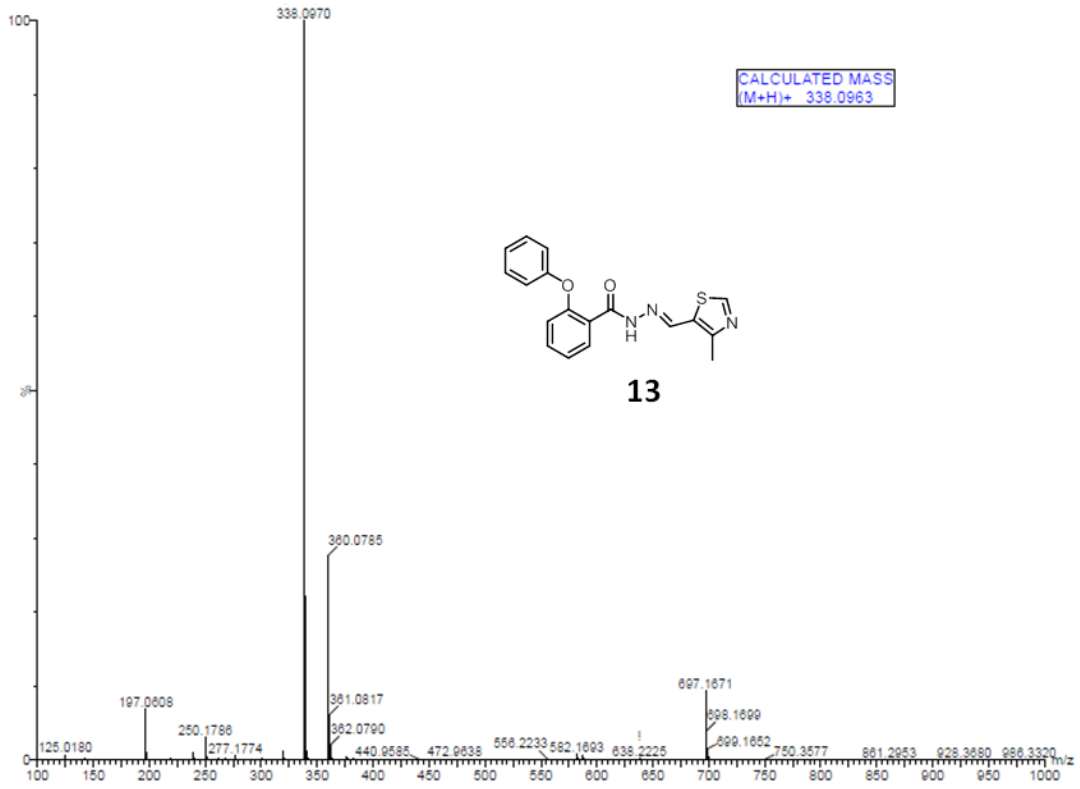


Figure S29: HR-MS spectra of compound 13.

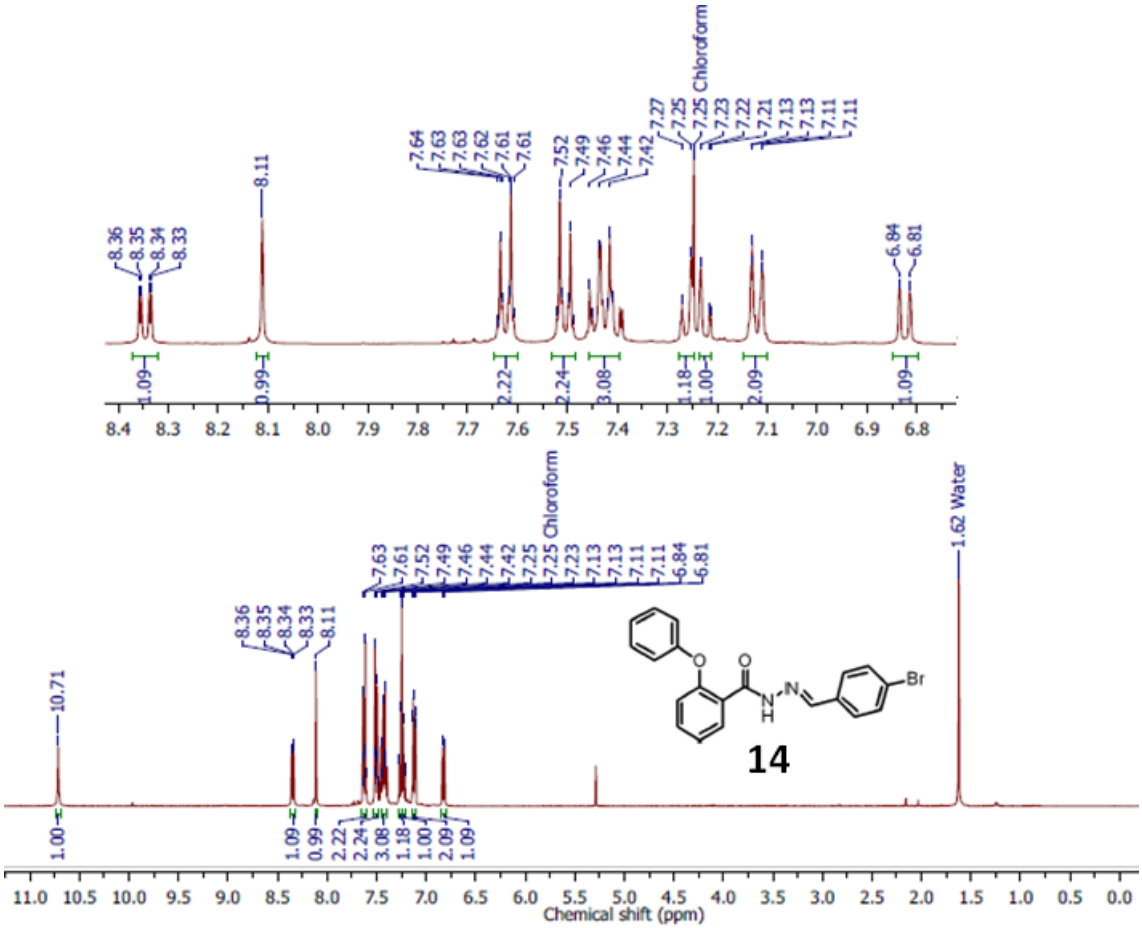


Figure S30: ^{1}H NMR spectra of compound 14.

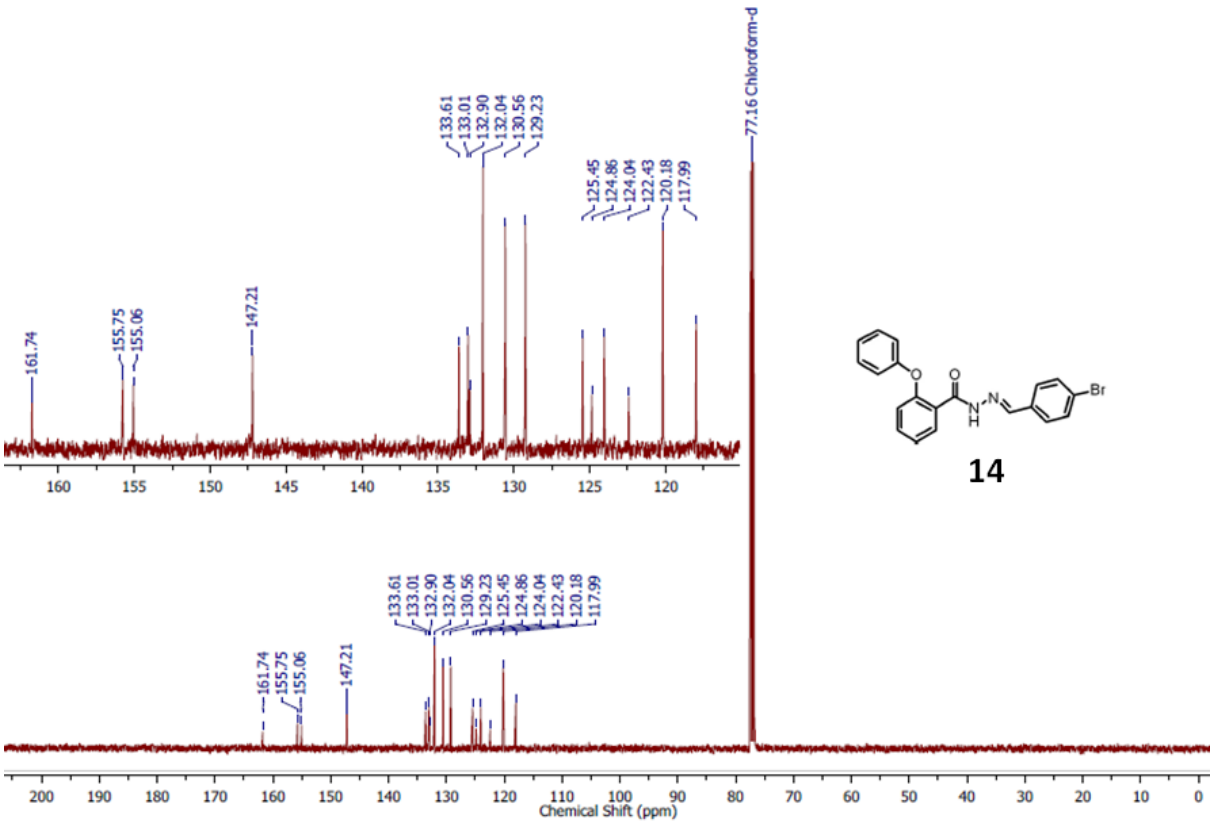


Figure S31: ^{13}C NMR spectra of compound 14.

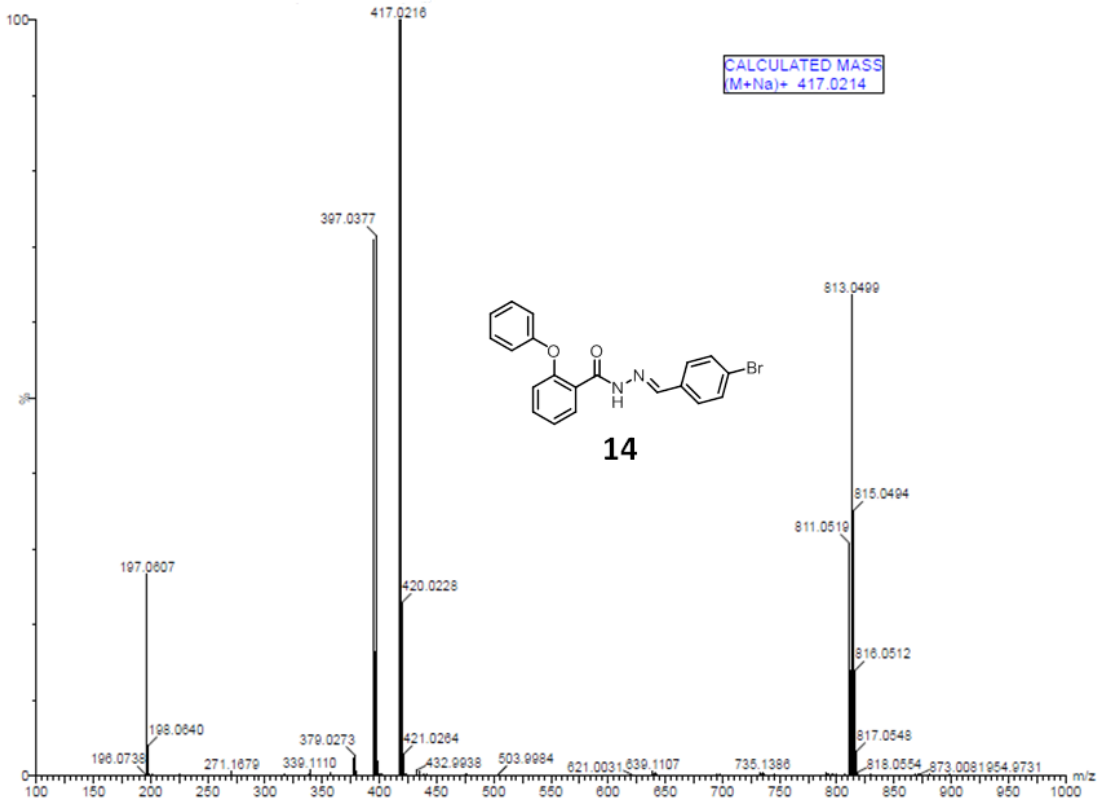


Figure S32: HR-MS spectra of compound 14.

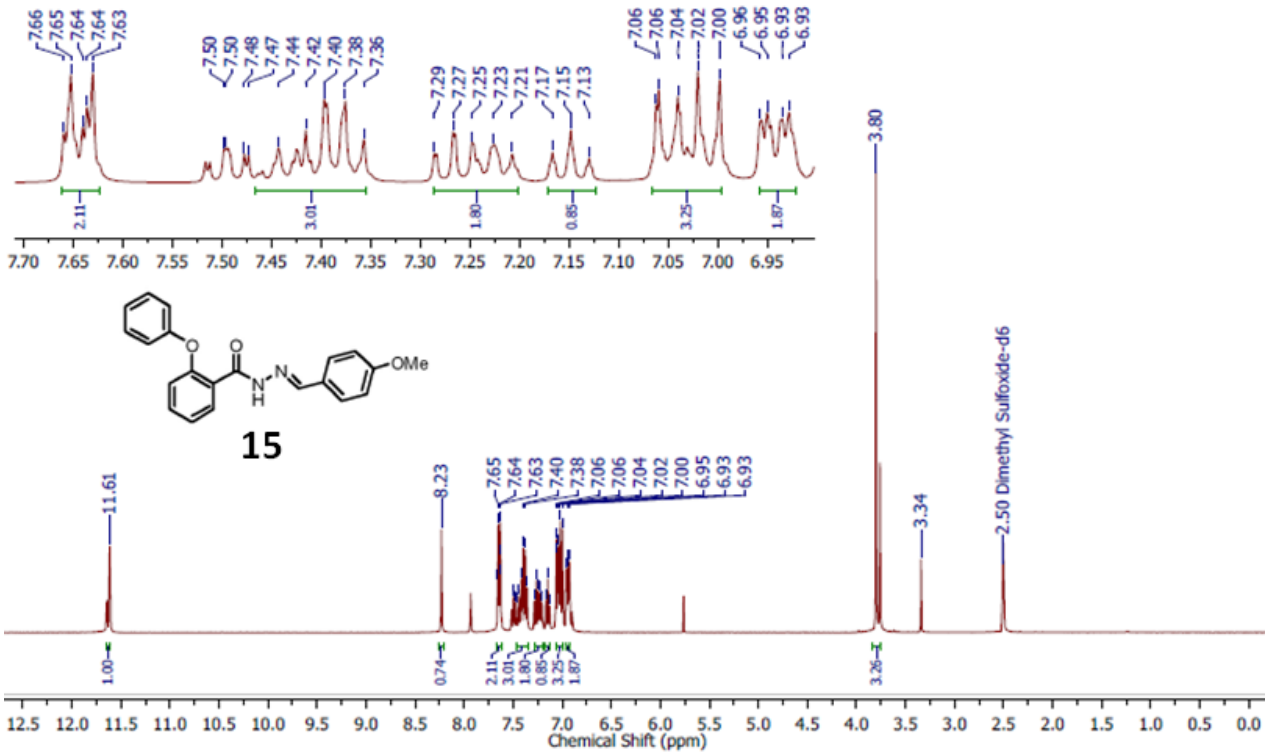


Figure S33: ^{1}H NMR spectra of compound 15.

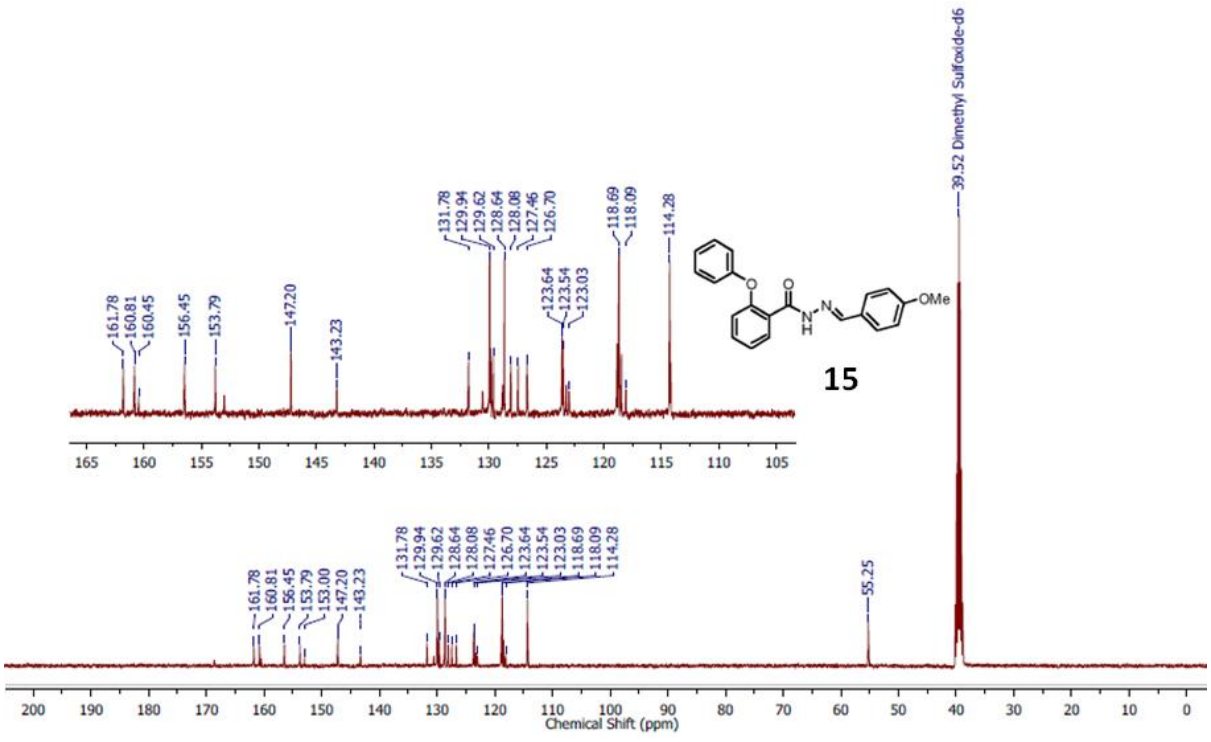


Figure S34: ^{13}C NMR spectra of compound 15.

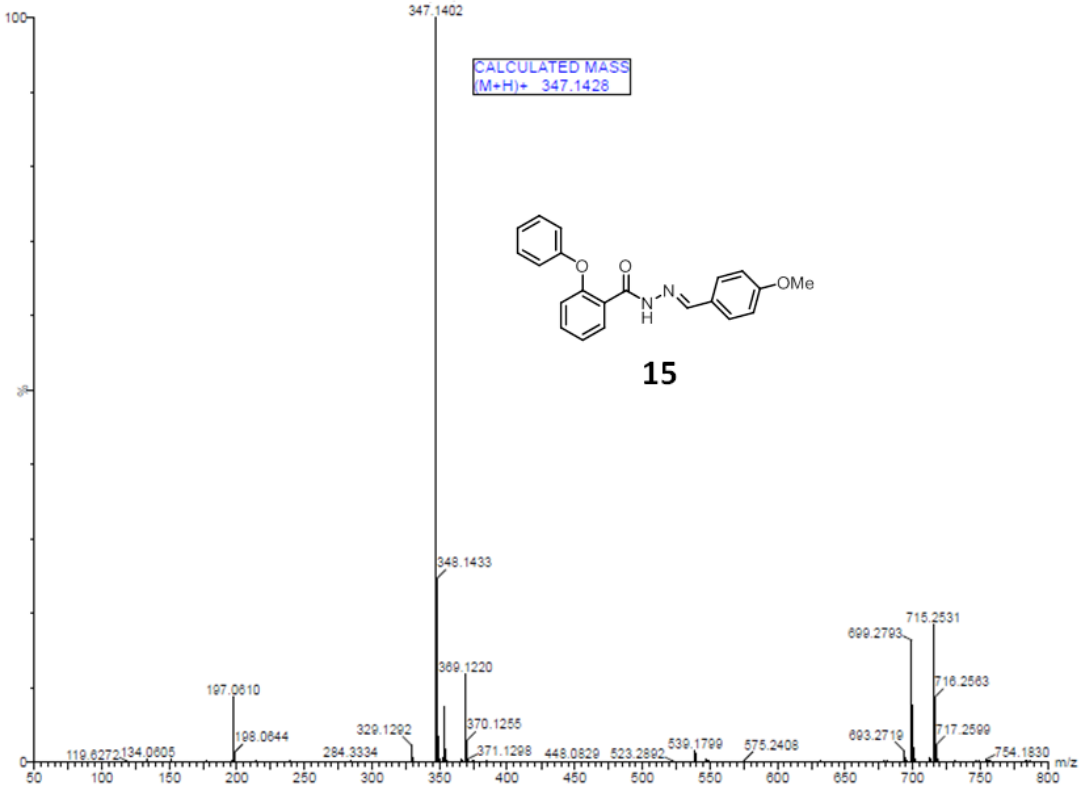


Figure S35: HR-MS spectra of compound 15.

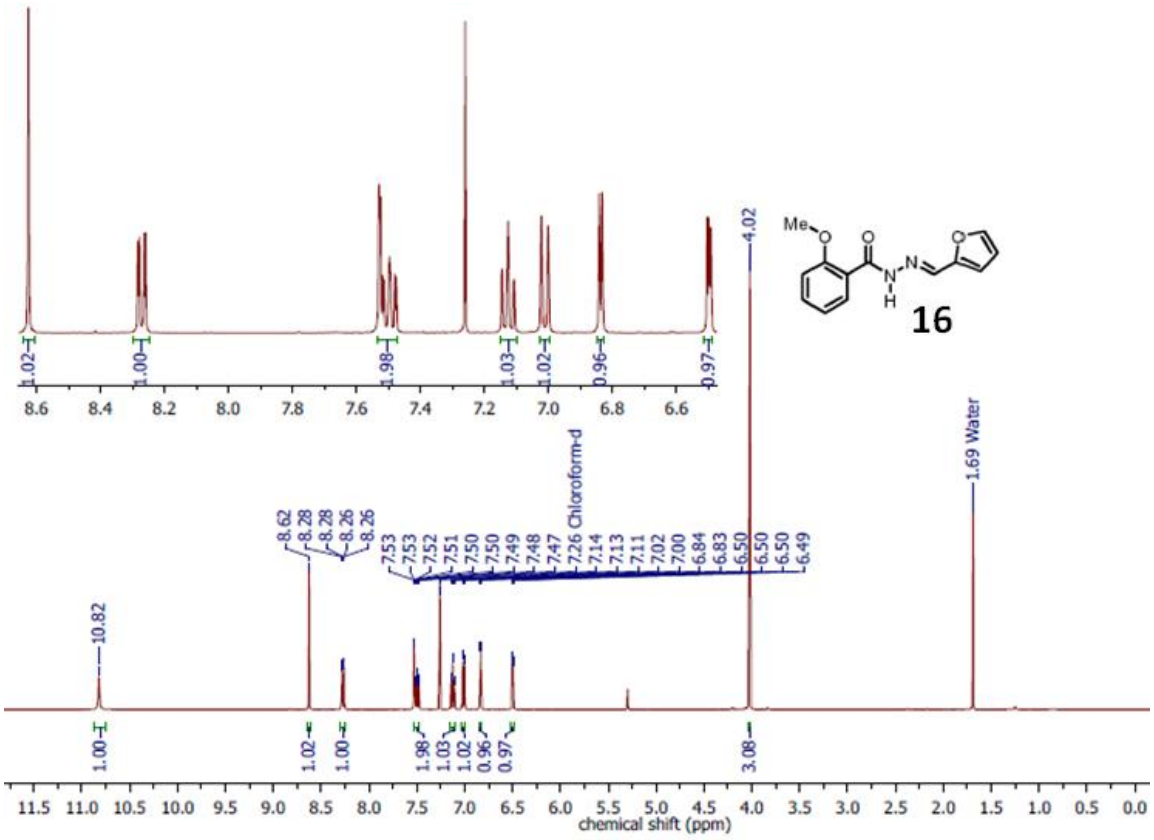


Figure S36: ^{1}H NMR spectra of compound 16.

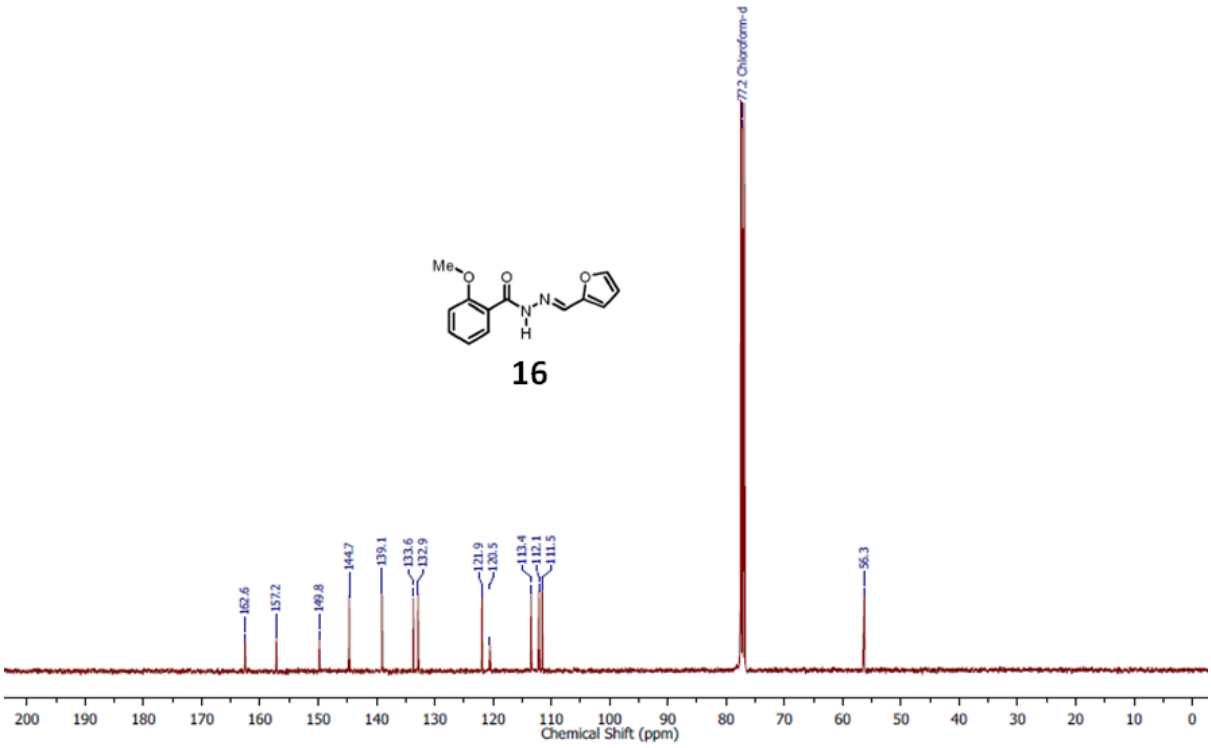


Figure S37: ^{13}C NMR spectra of compound 16.

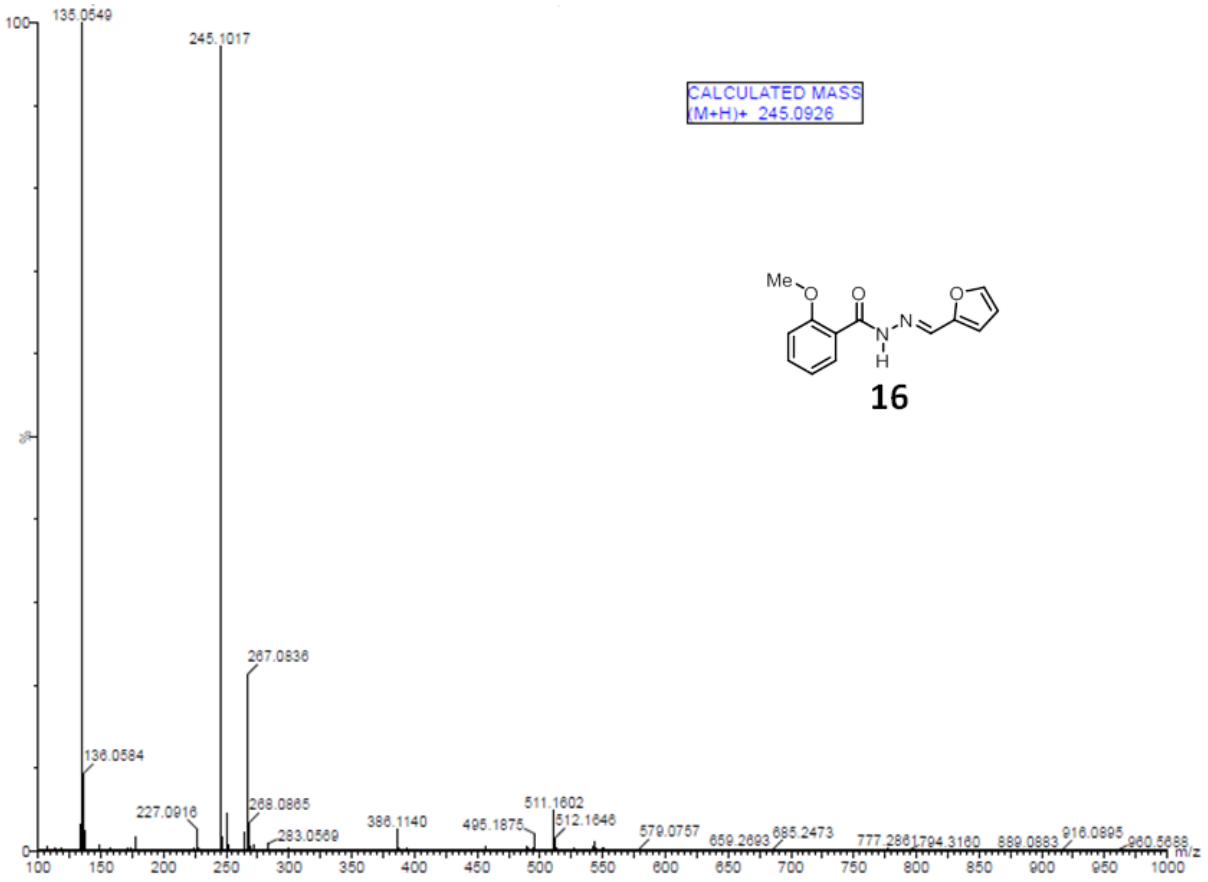


Figure S38: HR-MS spectra of compound 16.

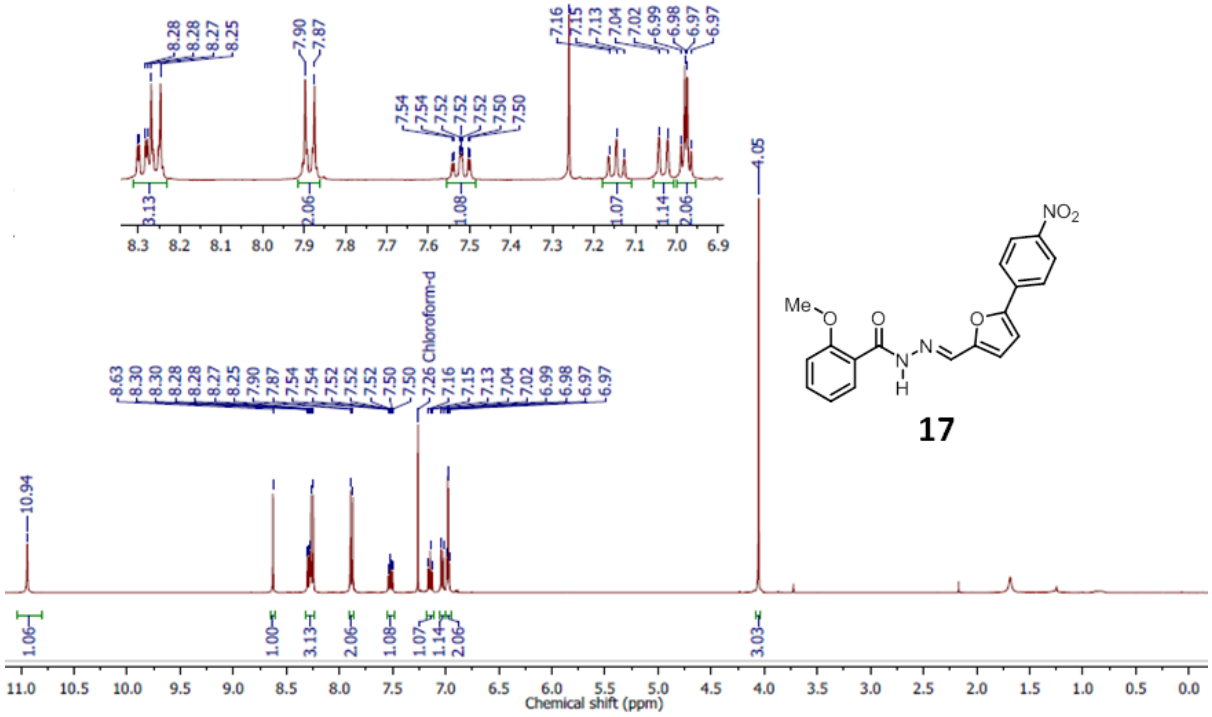


Figure S39: ^{1}H NMR spectra of compound 17.

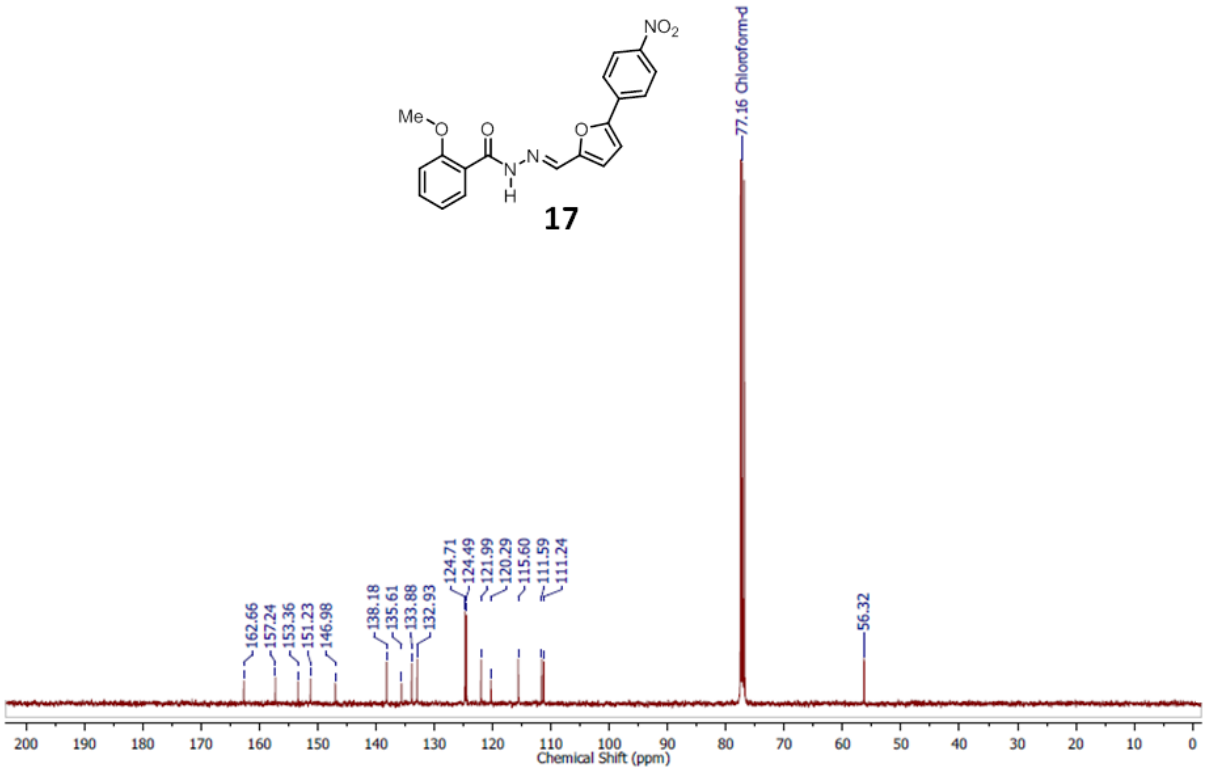


Figure S40: ^{13}C NMR spectra of compound 17.

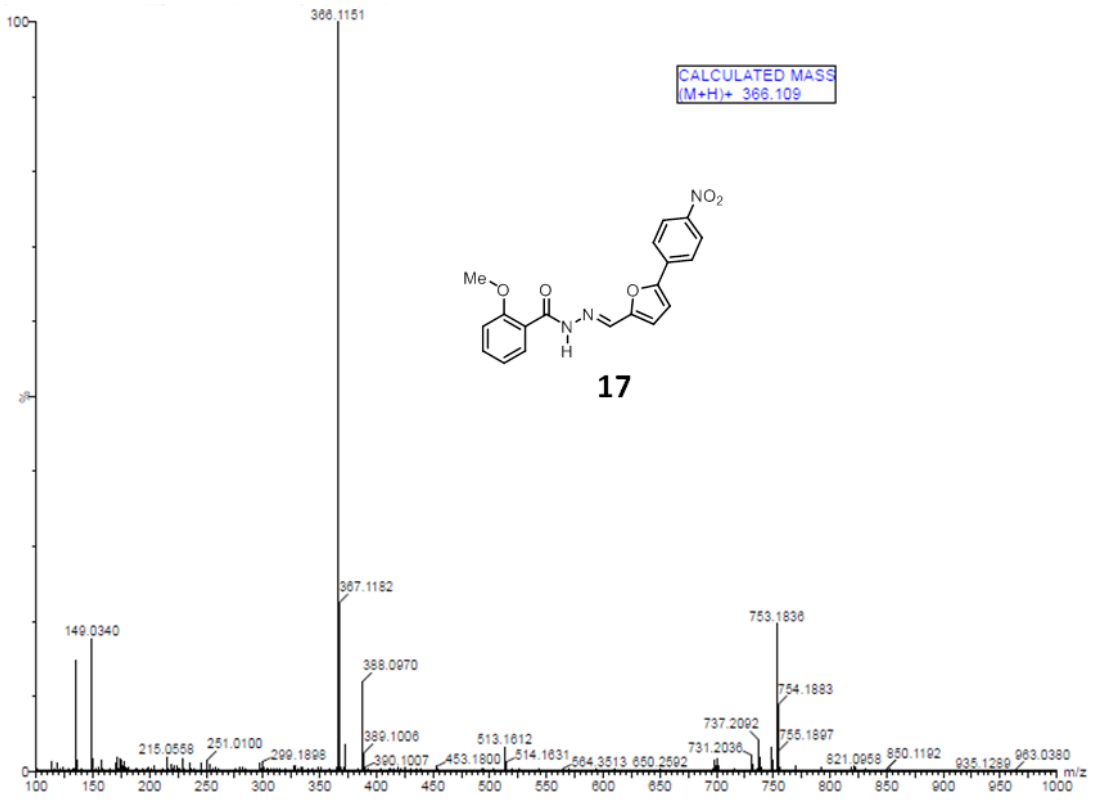


Figure S41: HR-MS spectra of compound 17.

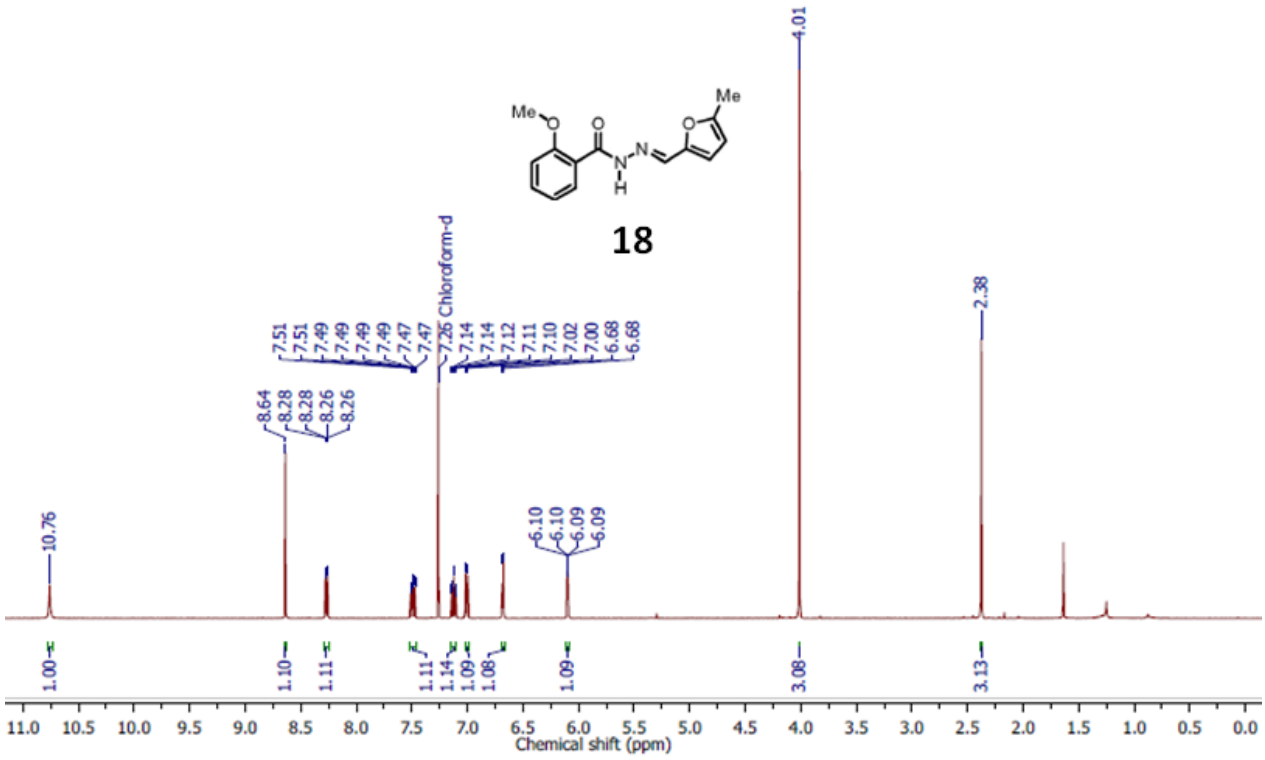


Figure S42: ^{1}H NMR spectra of compound 18.

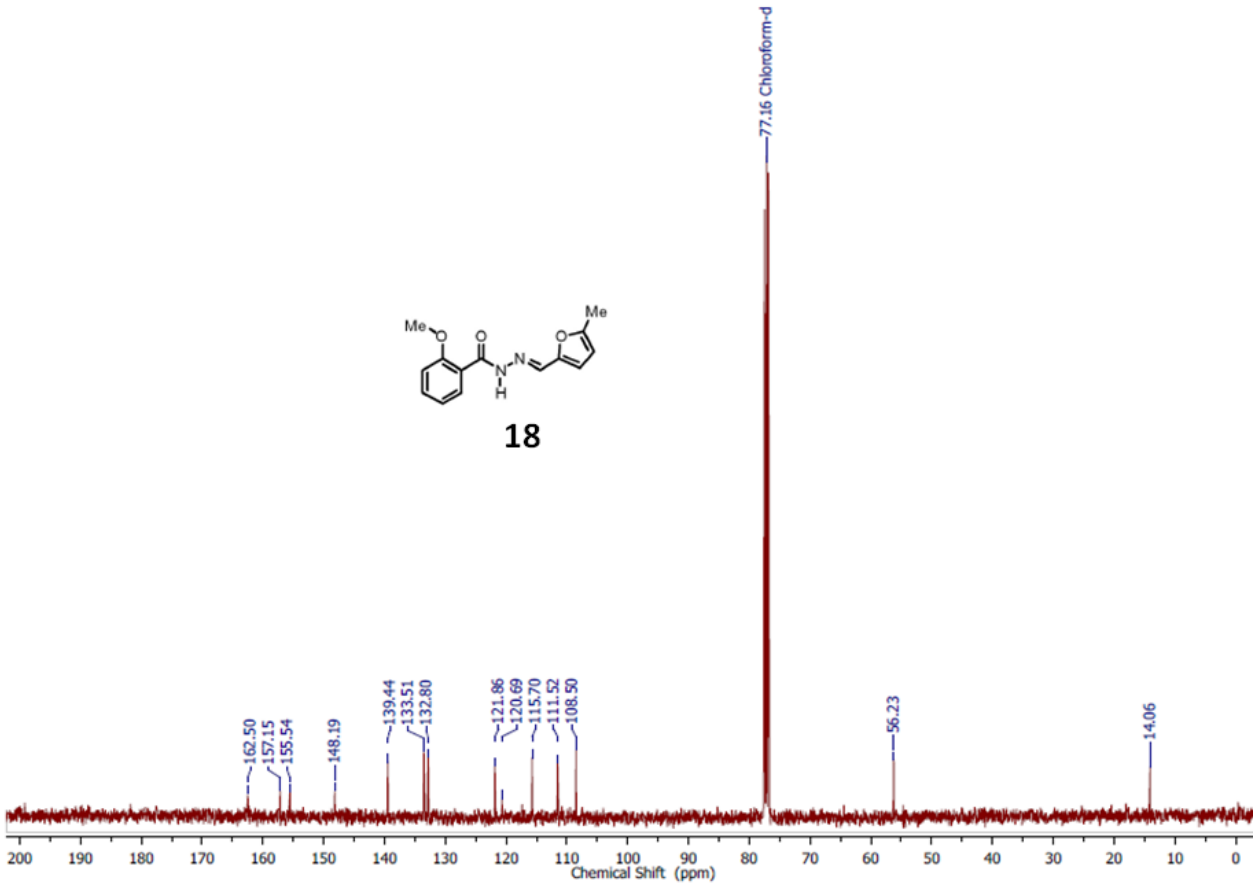


Figure S43: 13C NMR spectra of compound 18.

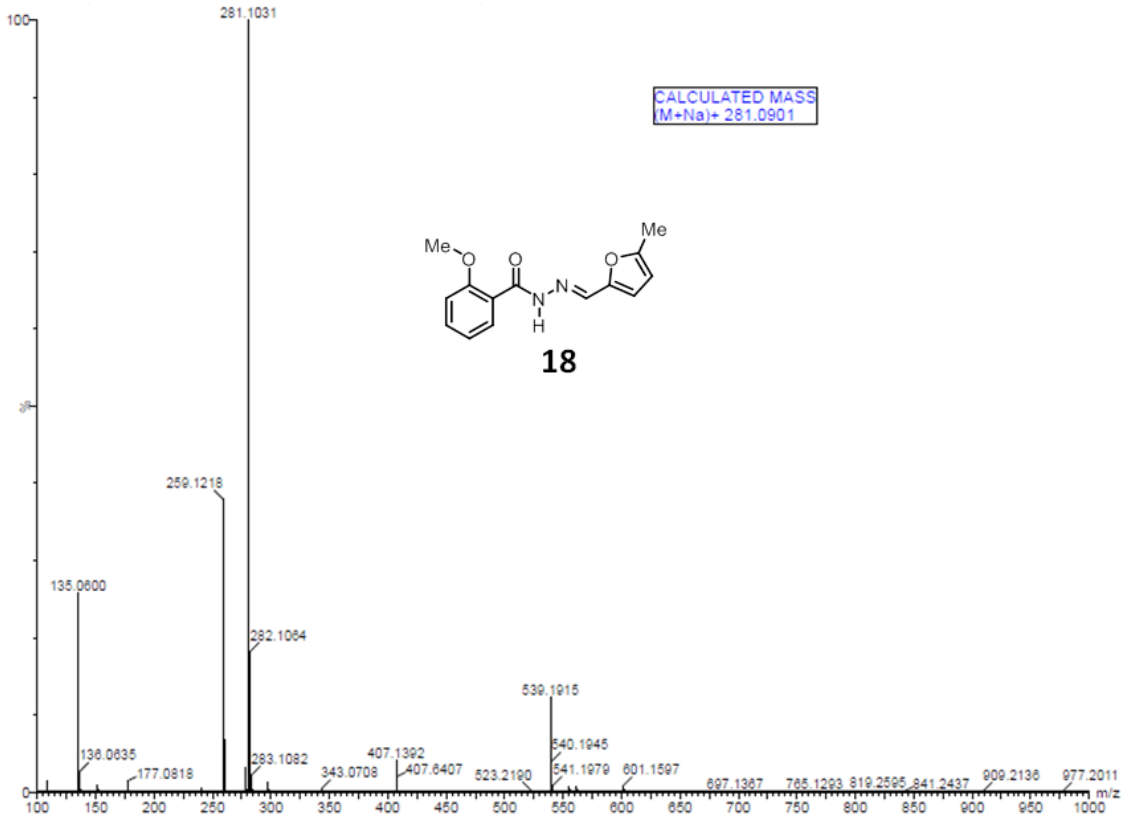


Figure S44: HR-MS spectra of compound 18.

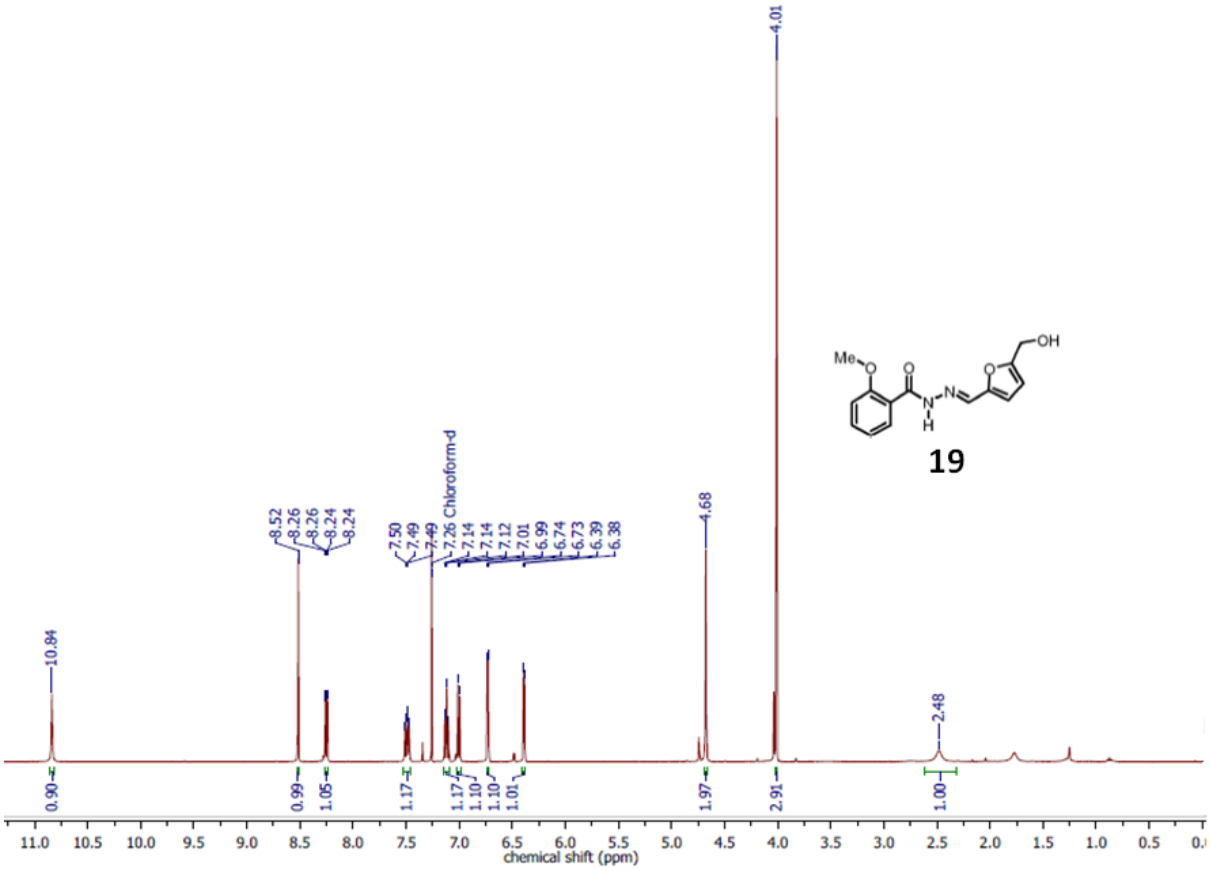


Figure S45: ^{1}H NMR spectra of compound 19.

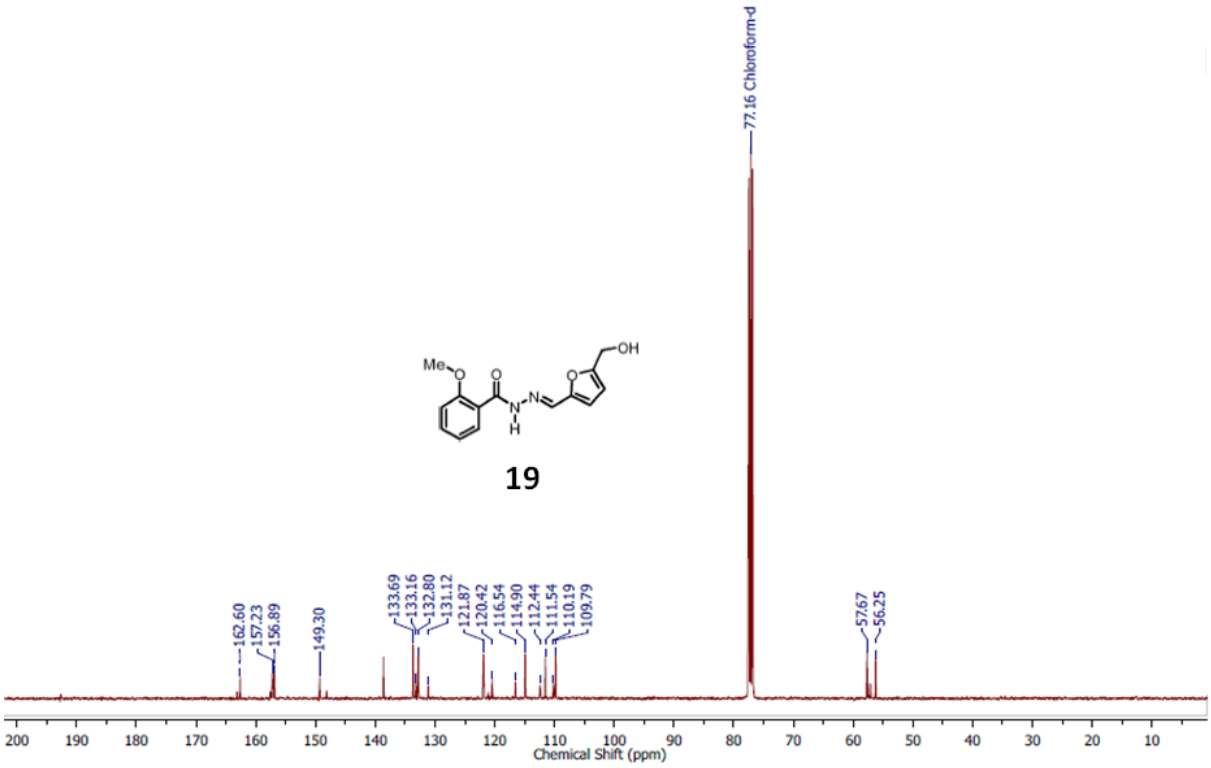


Figure S46: ^{13}C NMR spectra of compound 19.

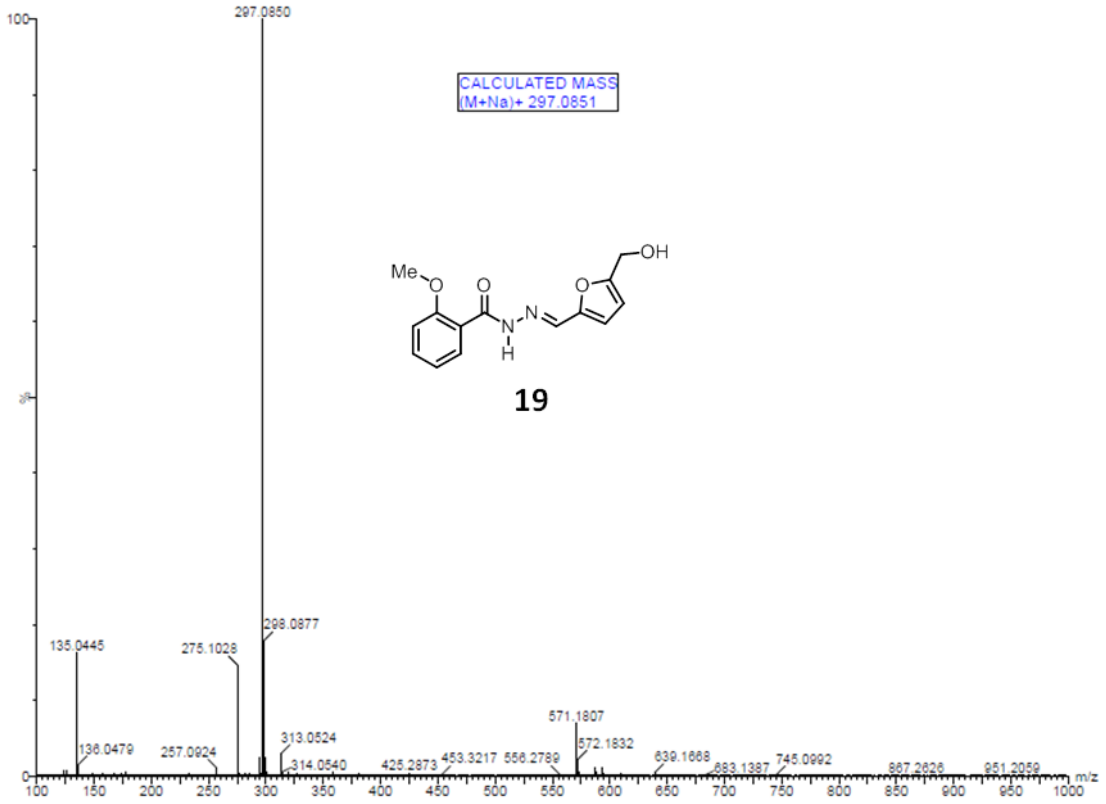


Figure S47: HR-MS spectra of compound 19.

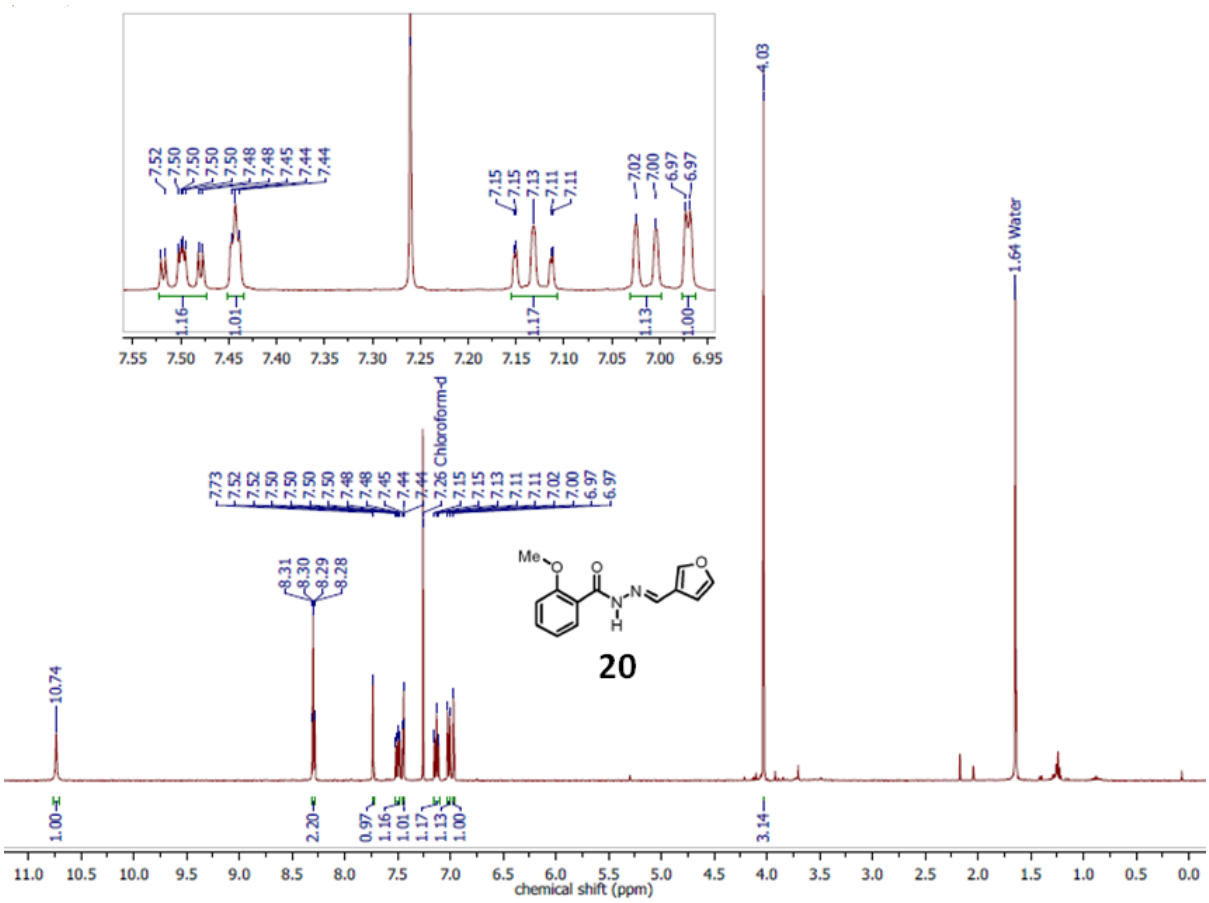


Figure S48: ^{1}H NMR spectra of compound 20.

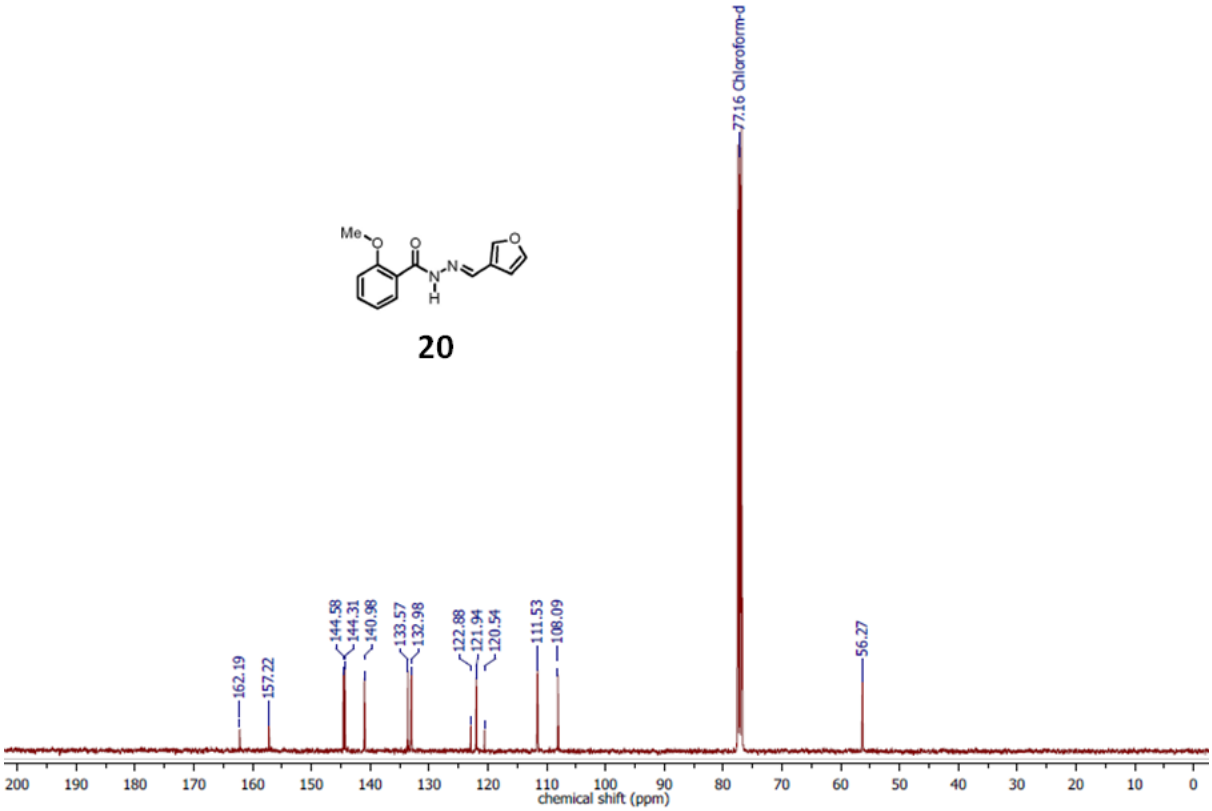


Figure S49: ^{13}C NMR spectra of compound 20.

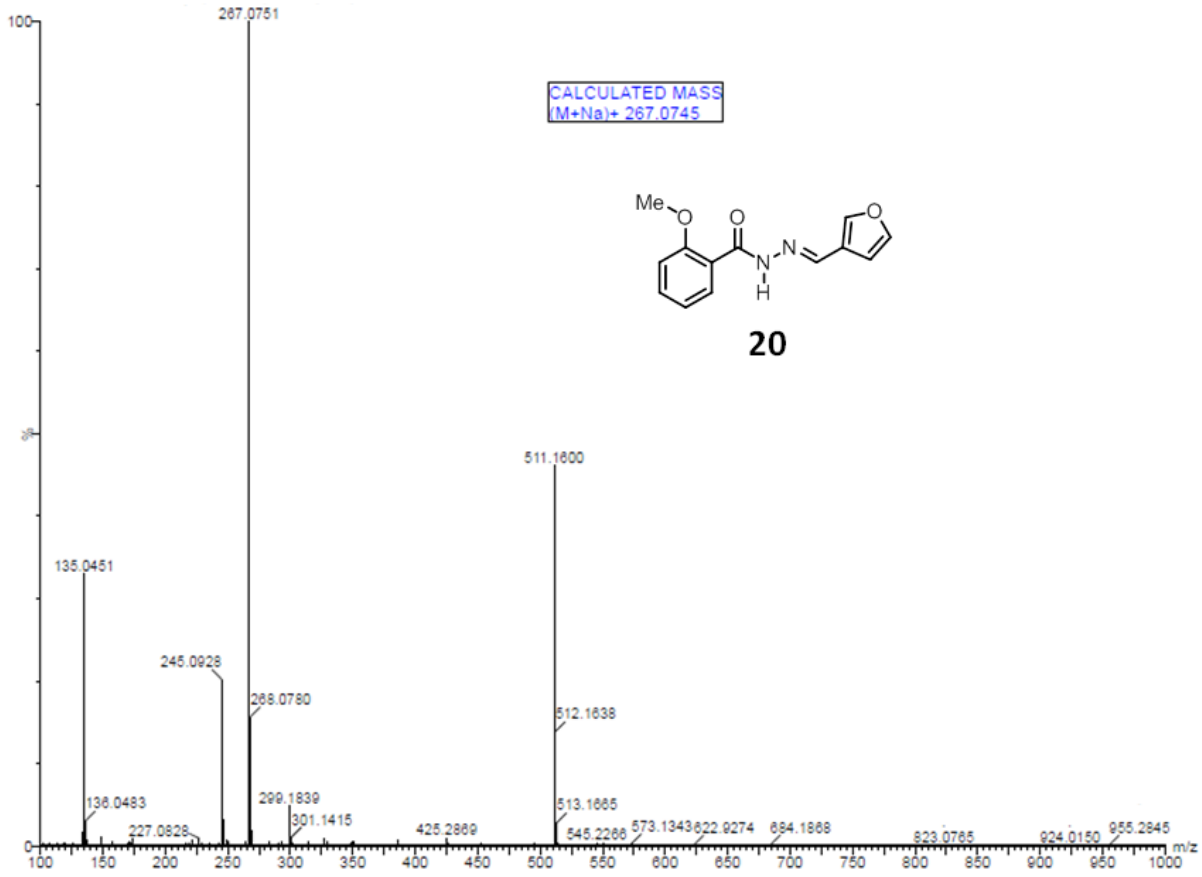


Figure S50: HR-MS spectra of compound 20.

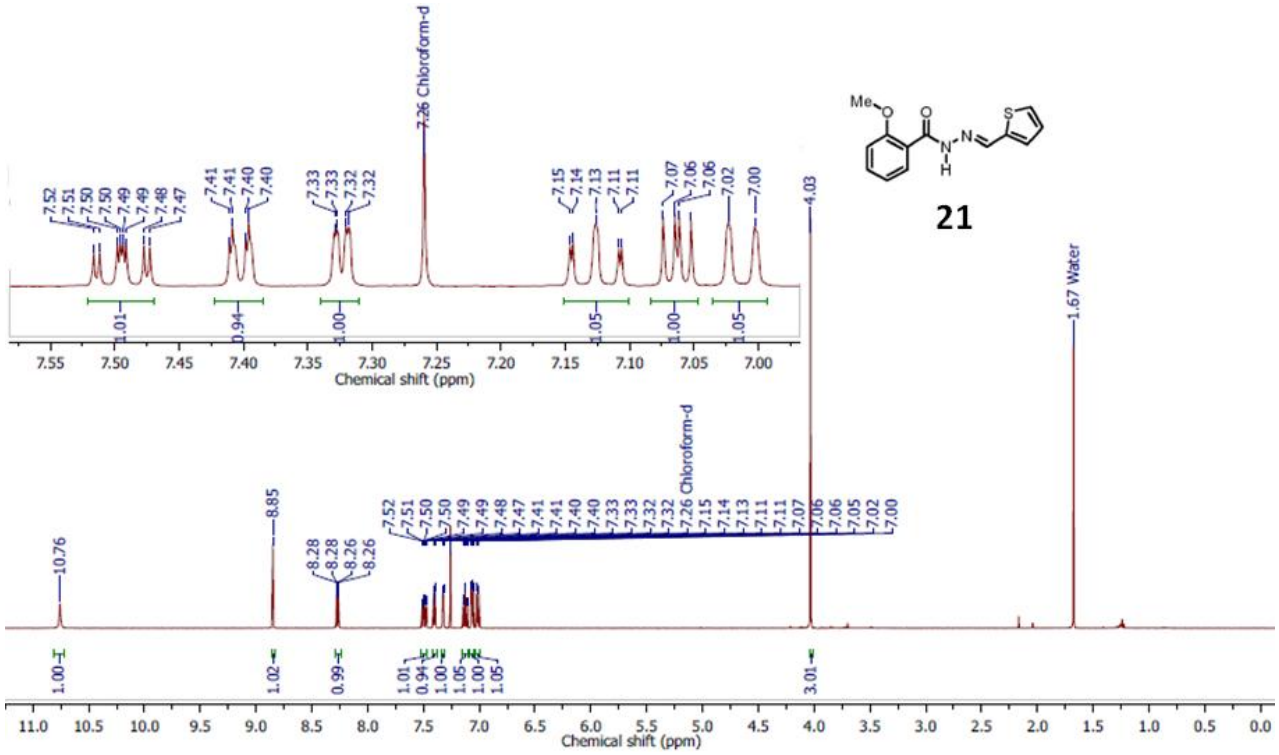


Figure S51: ^{1}H NMR spectra of compound 21.

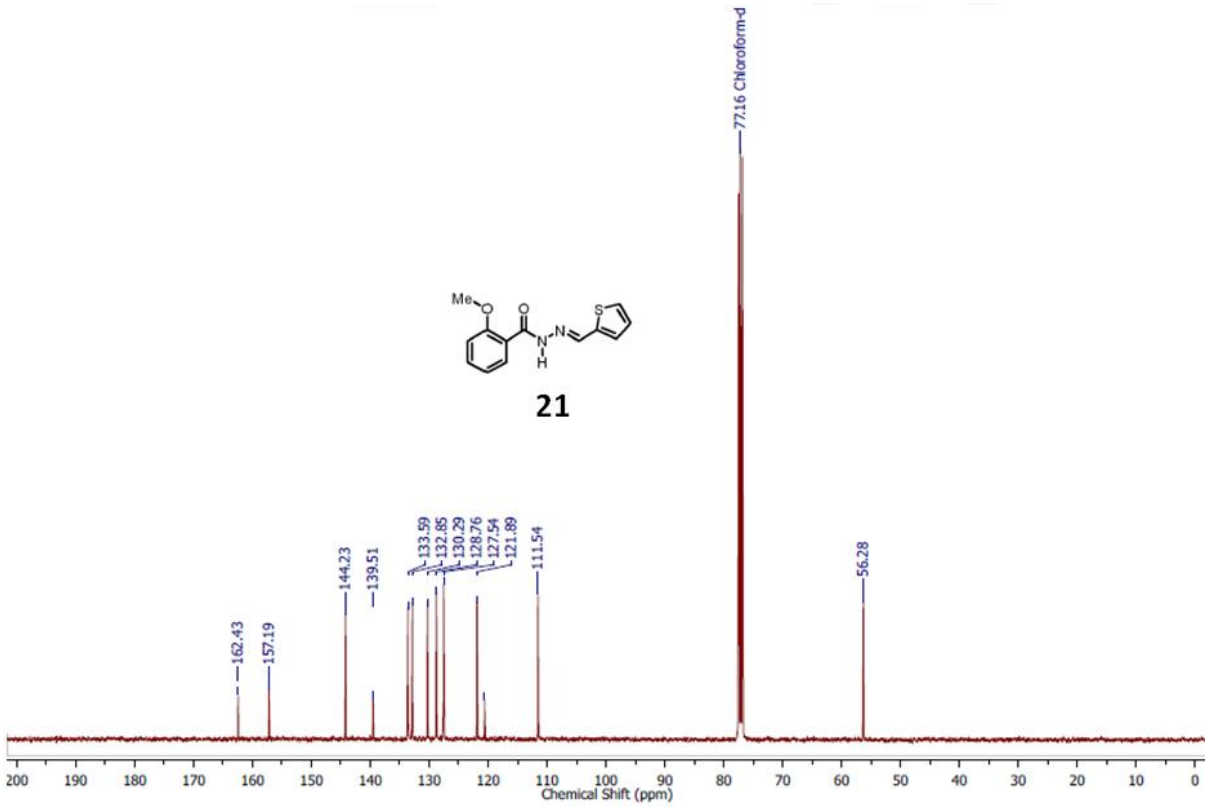


Figure S52: ^{13}C NMR spectra of compound 21.

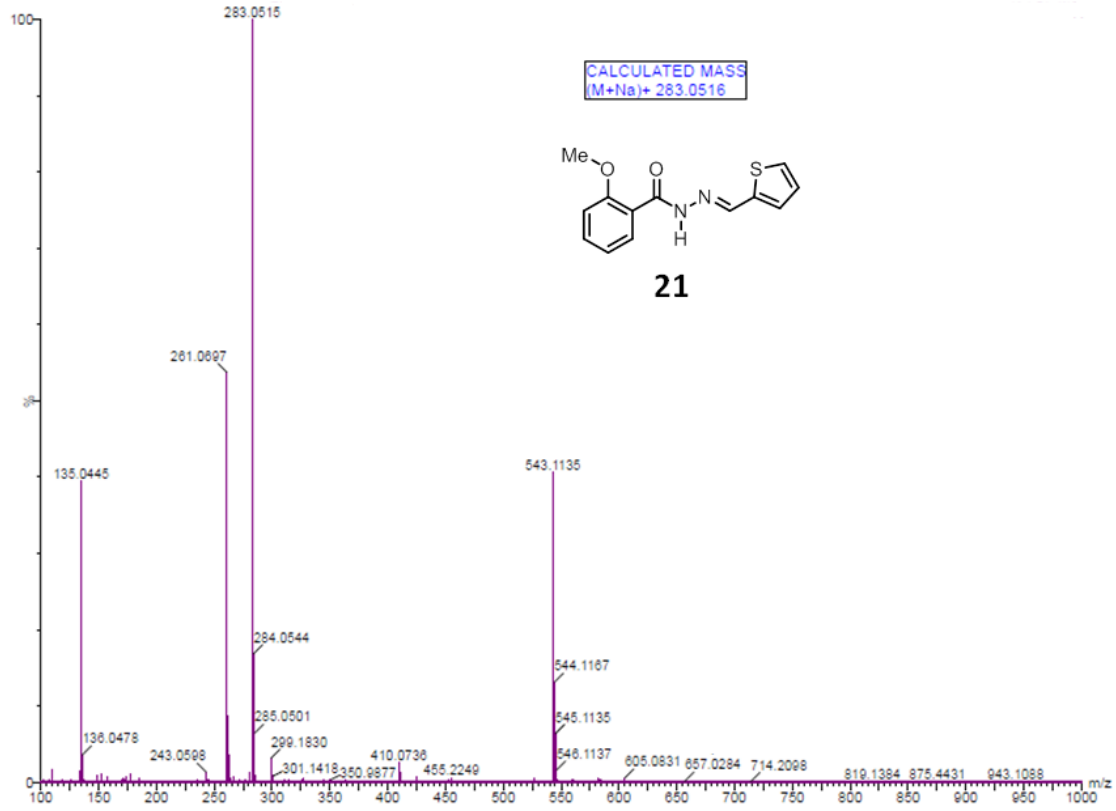


Figure S53: HR-MS spectra of compound 21.

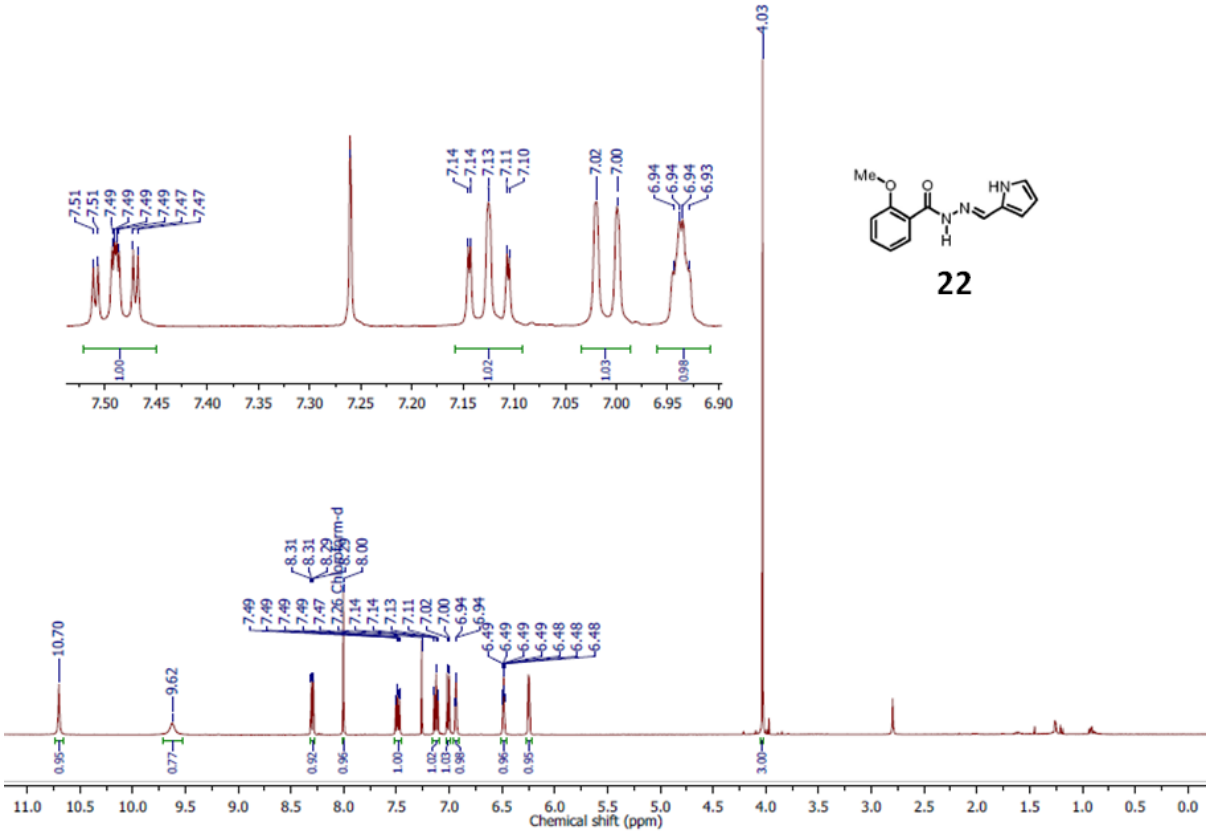


Figure S54: ^{1}H NMR spectra of compound 22.

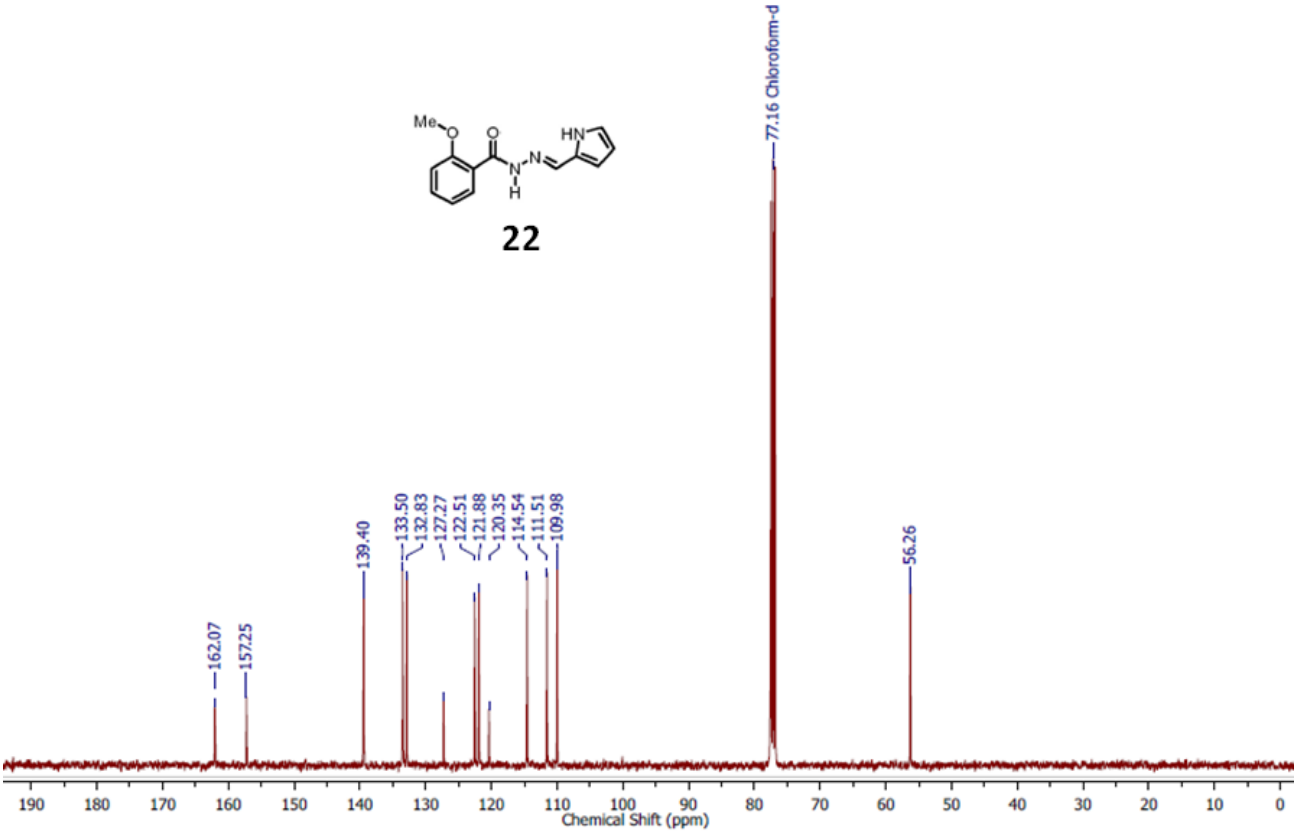


Figure S55: ^{13}C NMR spectra of compound 22.

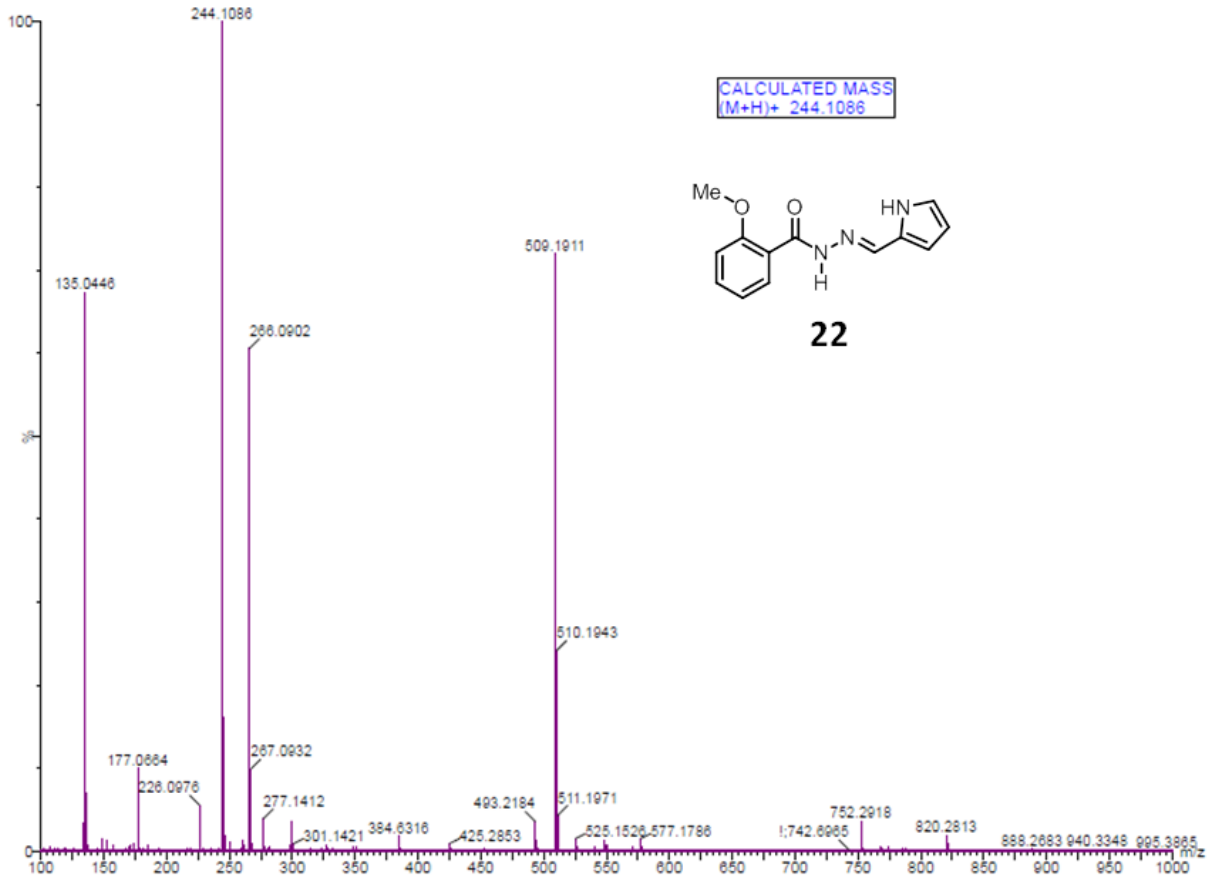


Figure S56: HR-MS spectra of compound 22.

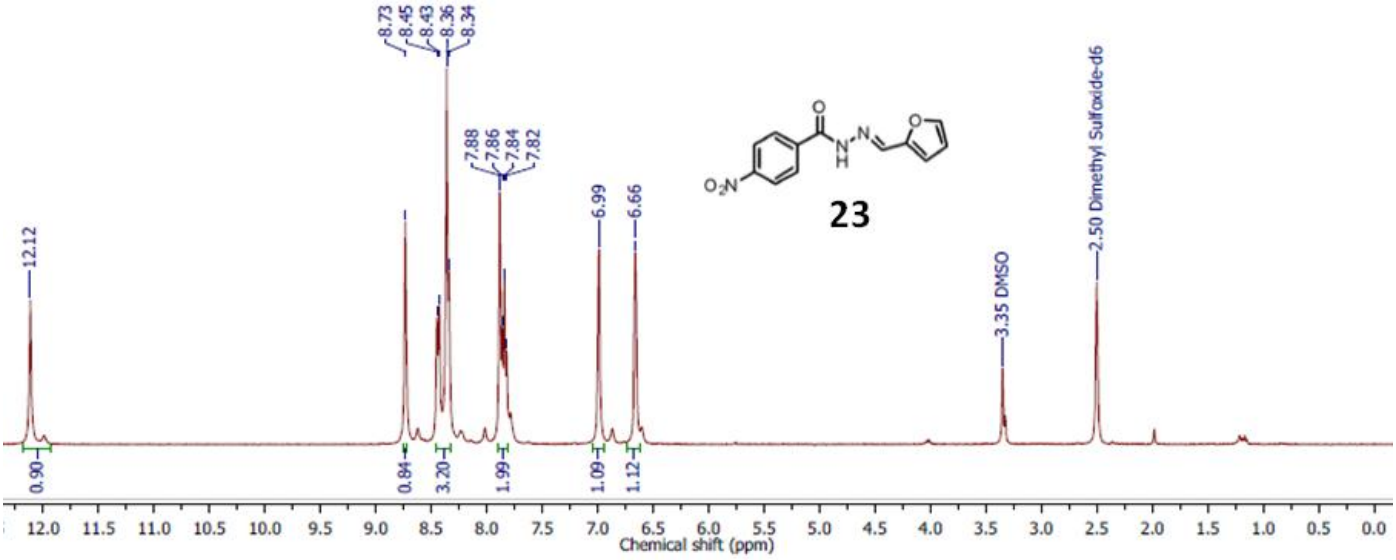


Figure S57: ^{1}H NMR spectra of compound 23.

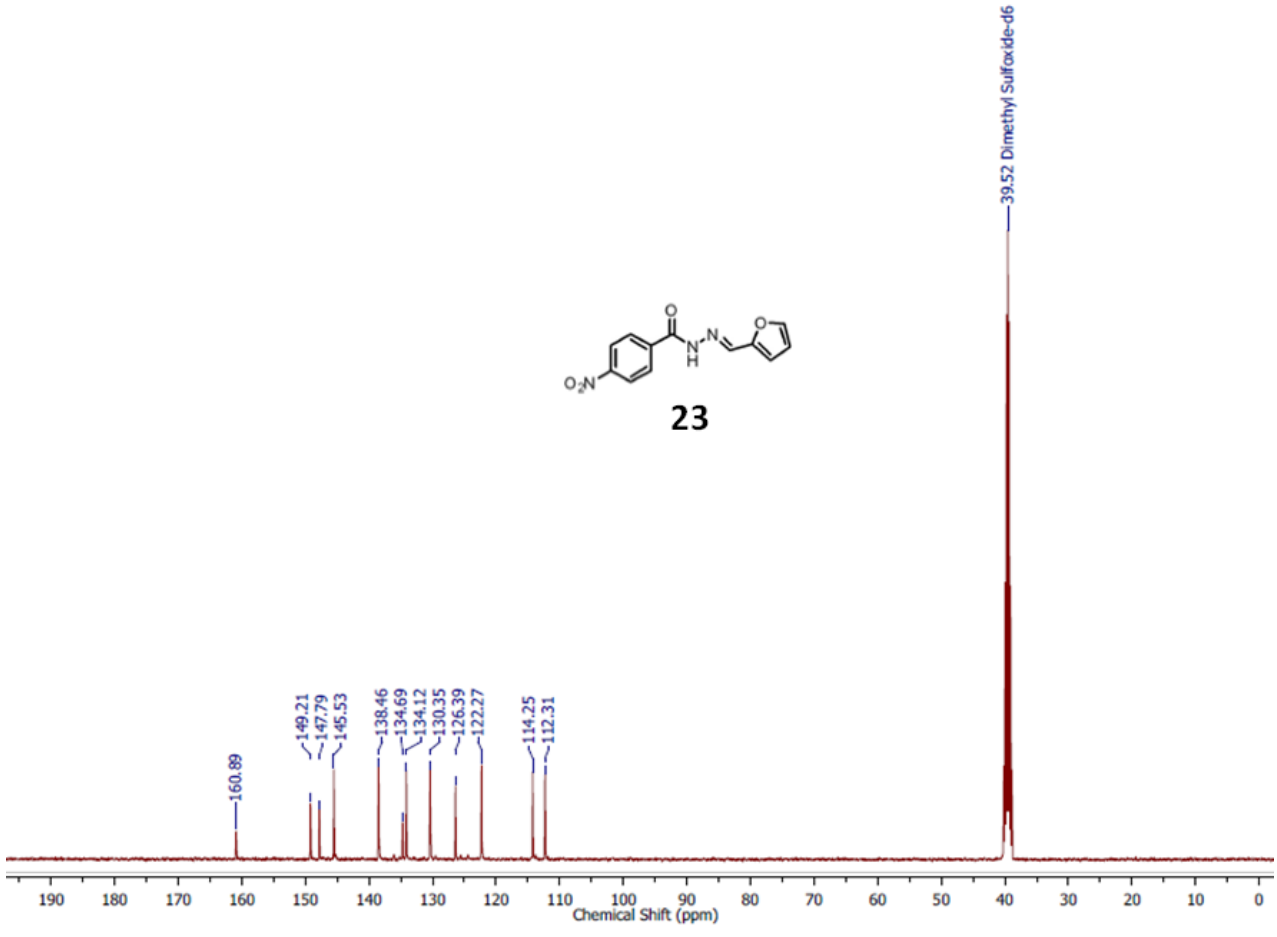


Figure S58: ^{13}C NMR spectra of compound 23.

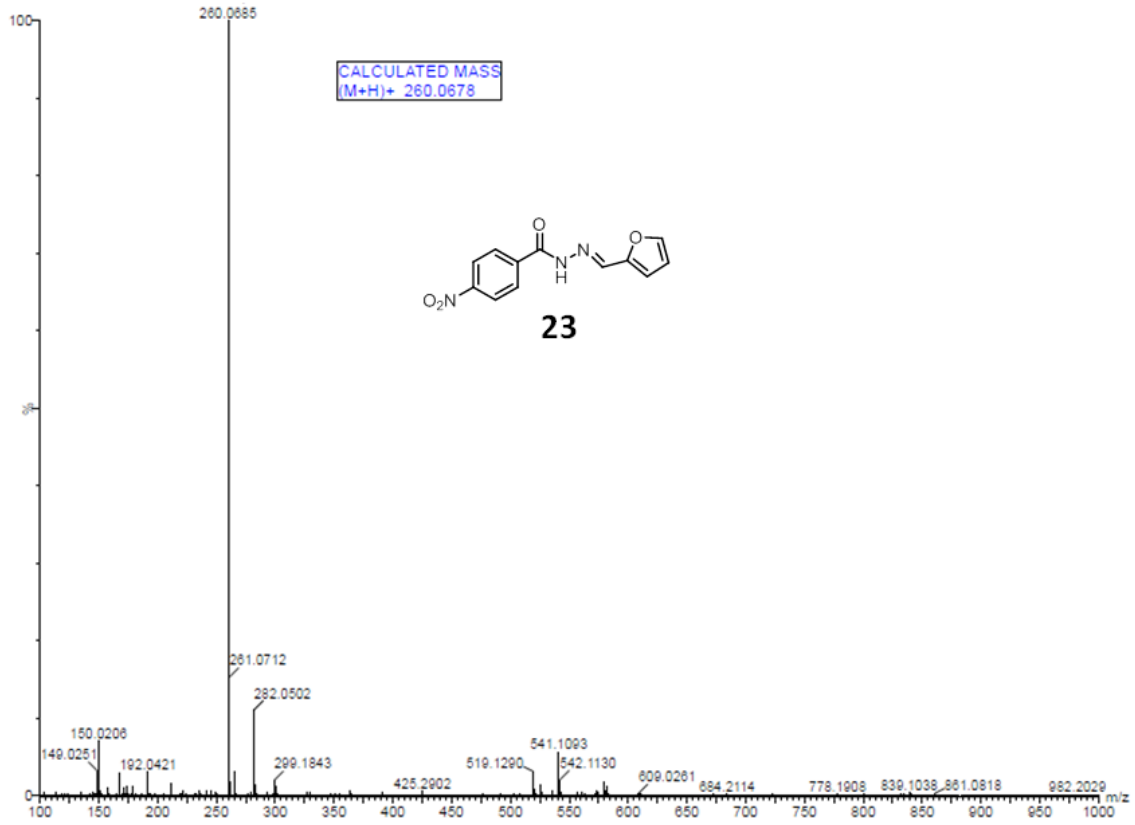


Figure S59: HR-MS spectra of compound 23.

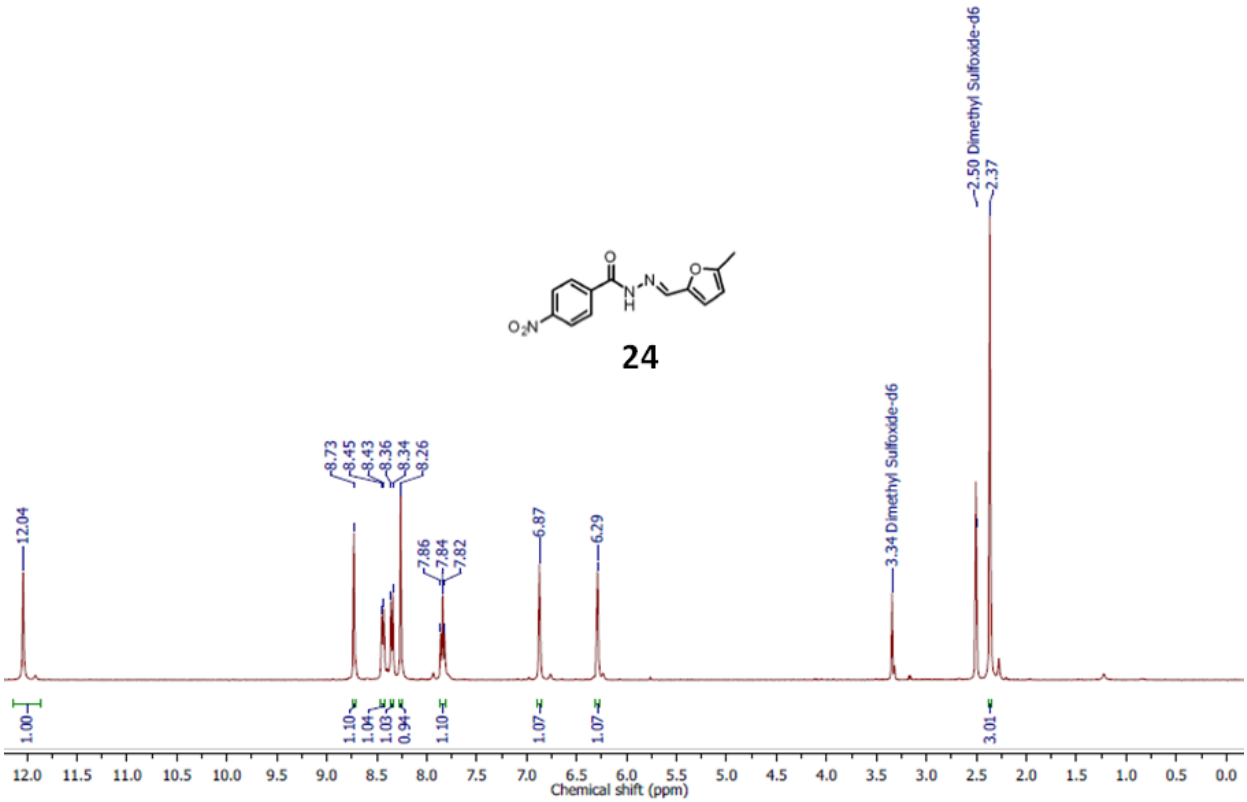


Figure S60: ^{1}H NMR spectra of compound 24.

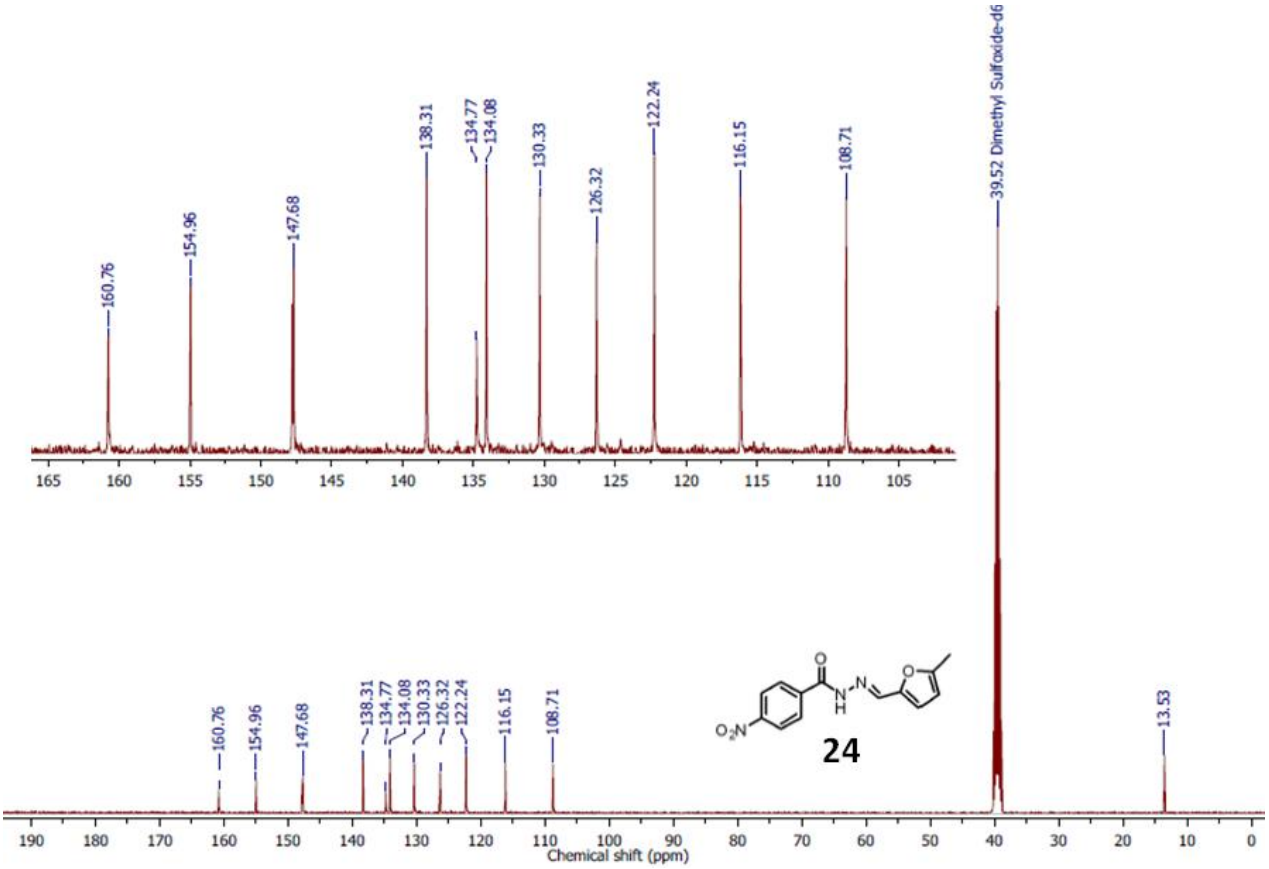


Figure S61: 13C NMR spectra of compound 24.

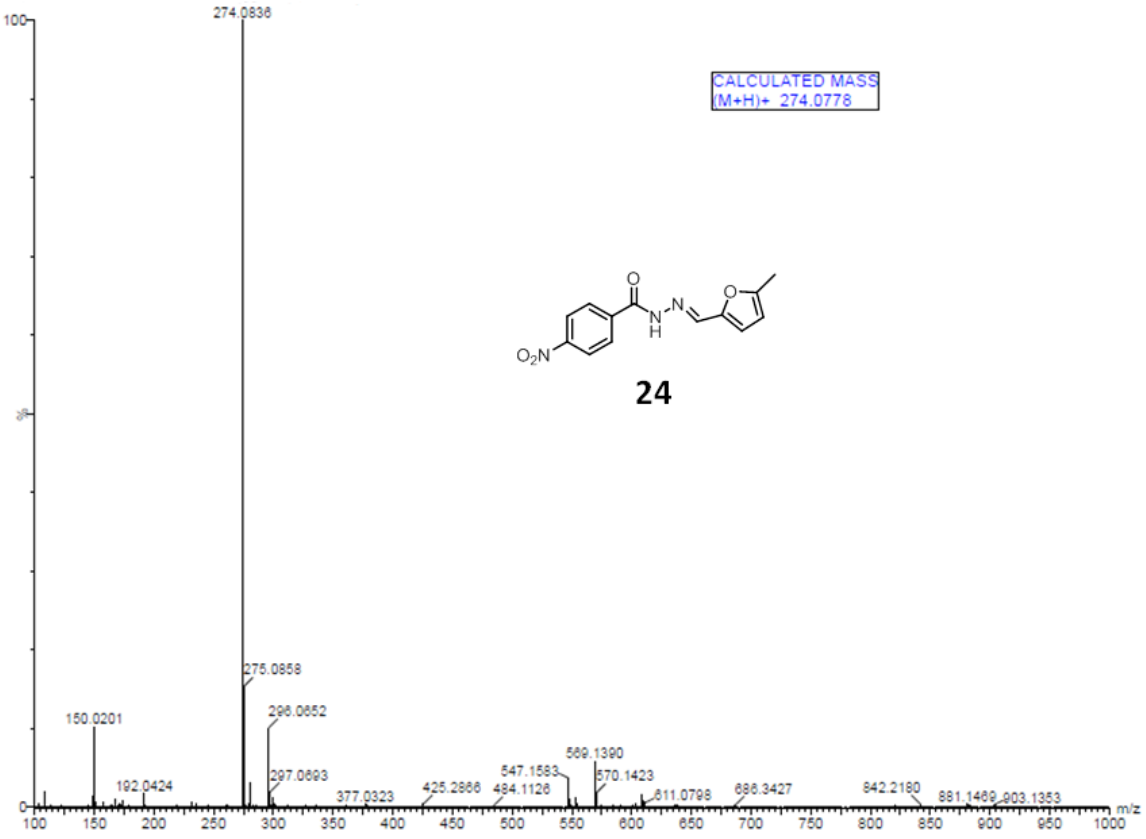


Figure S62: HR-MS spectra of compound 24.

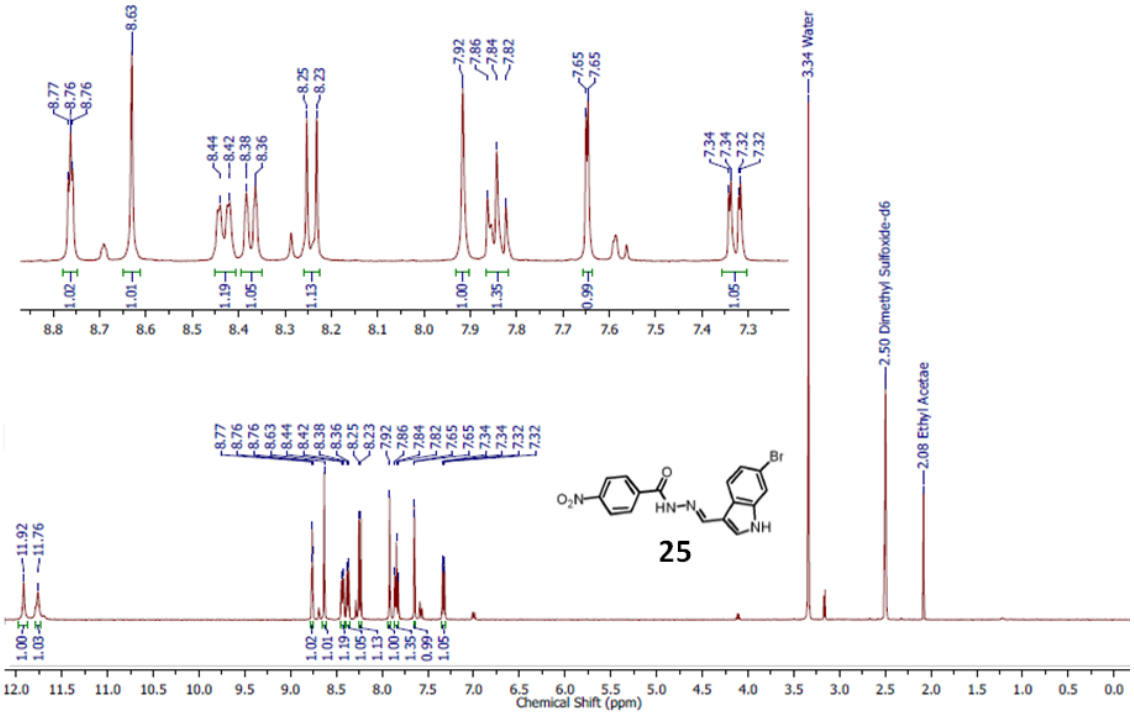


Figure S63: ^{1}H NMR spectra of compound 25.

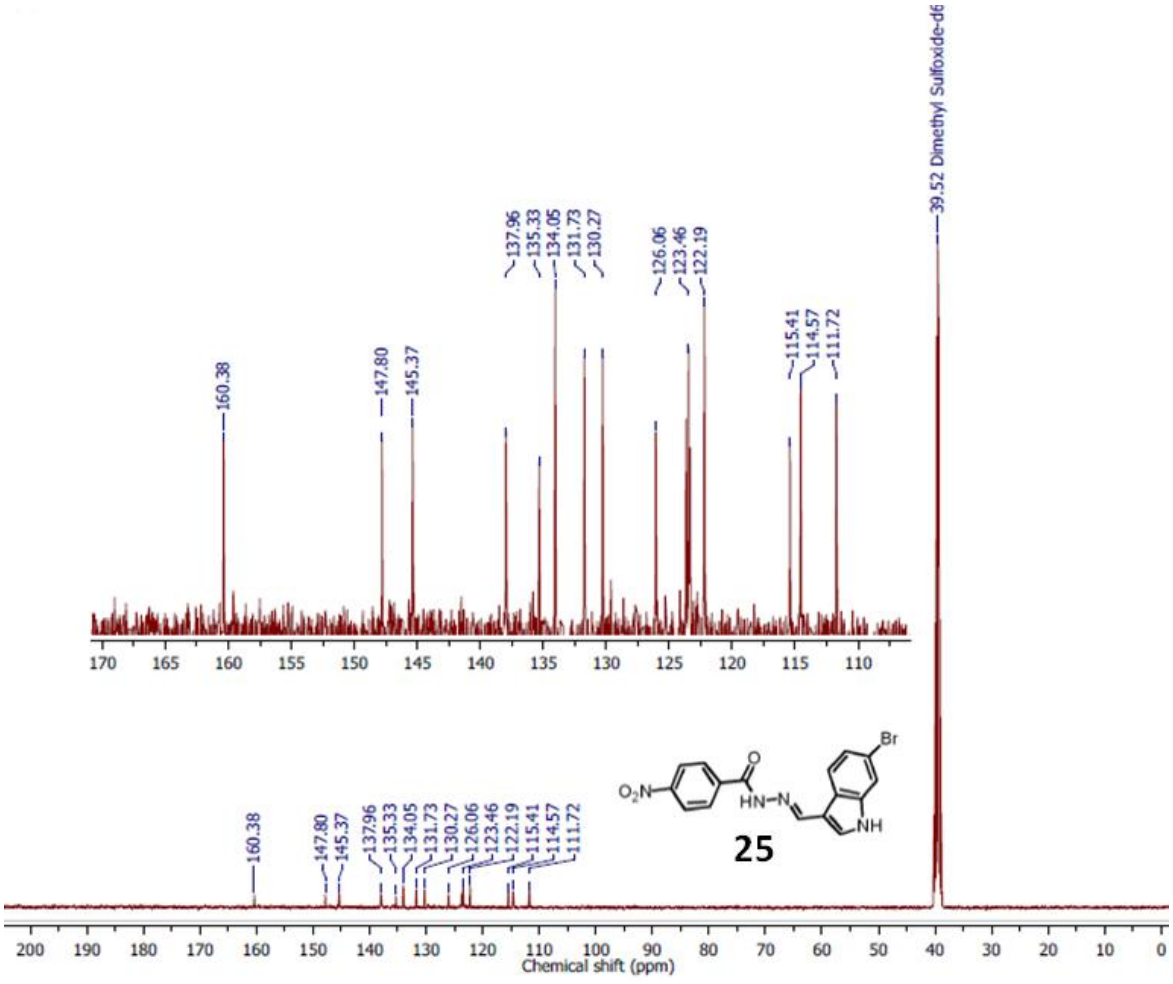


Figure S64: ^{13}C NMR spectra of compound 25.

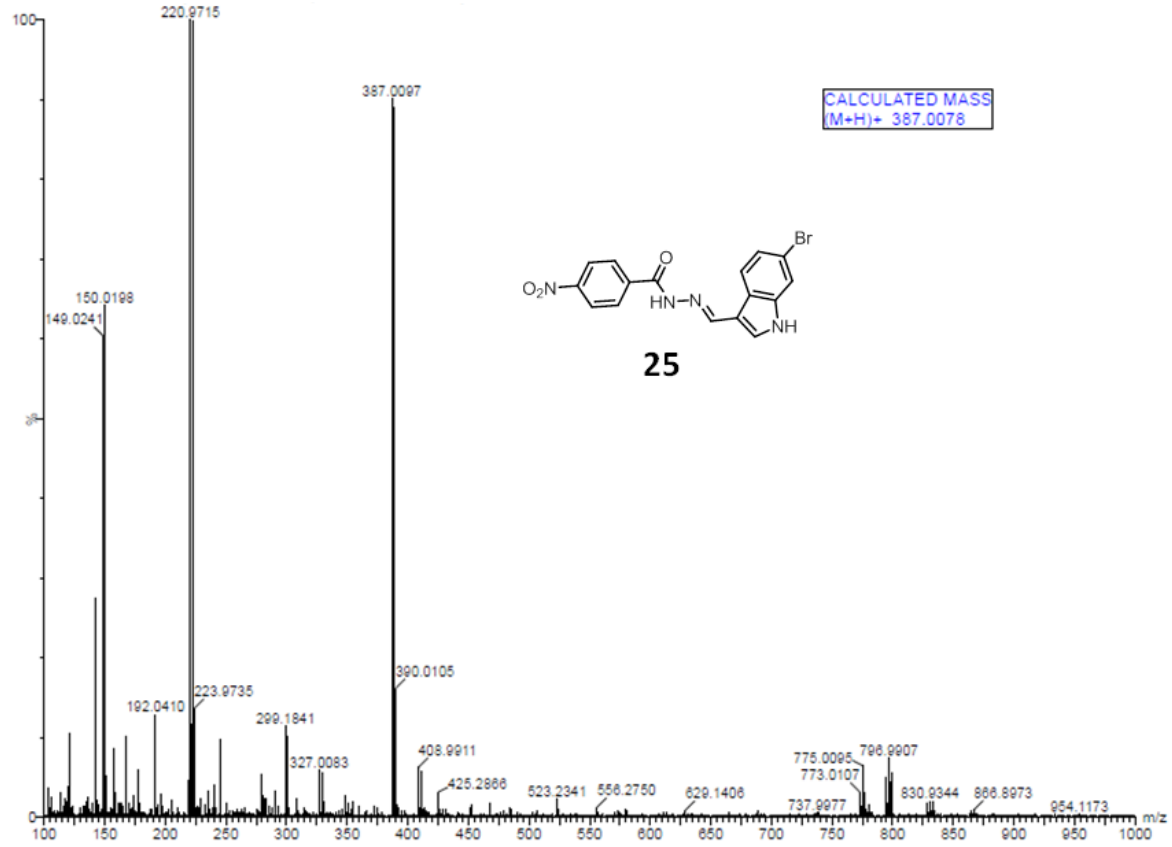


Figure S65: HR-MS spectra of compound 25.

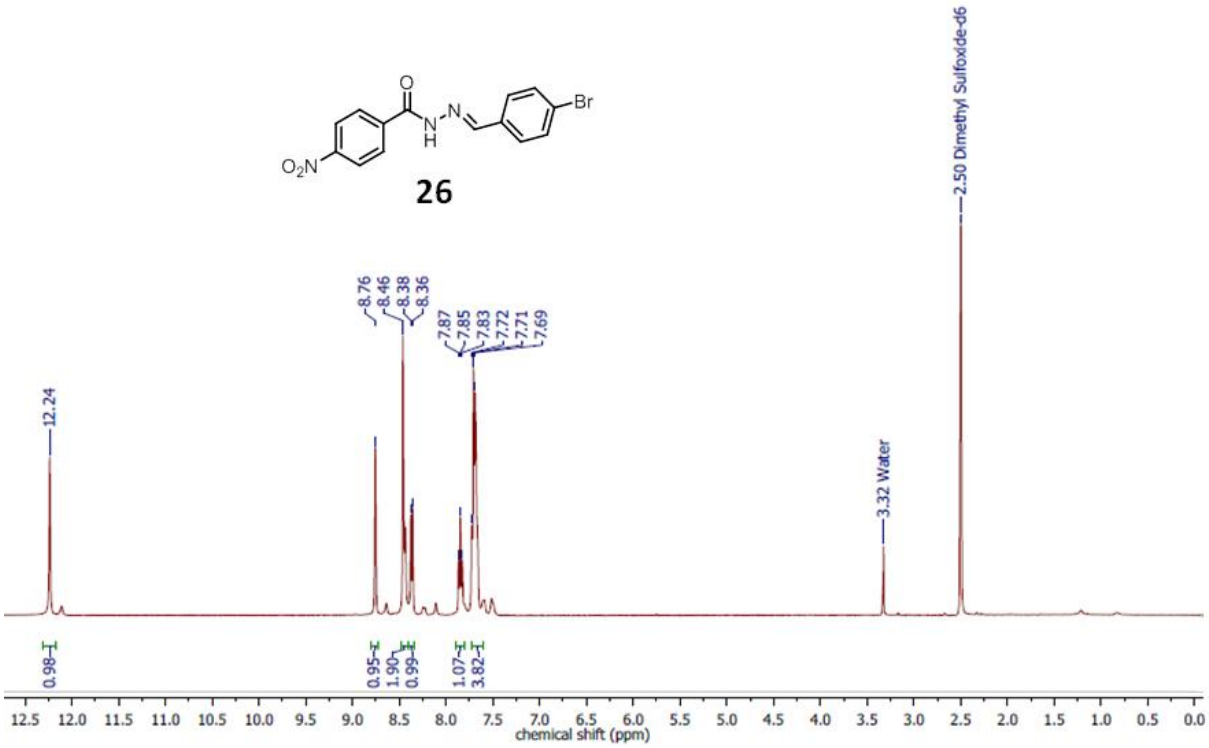


Figure S66: ^{1}H NMR spectra of compound 26.

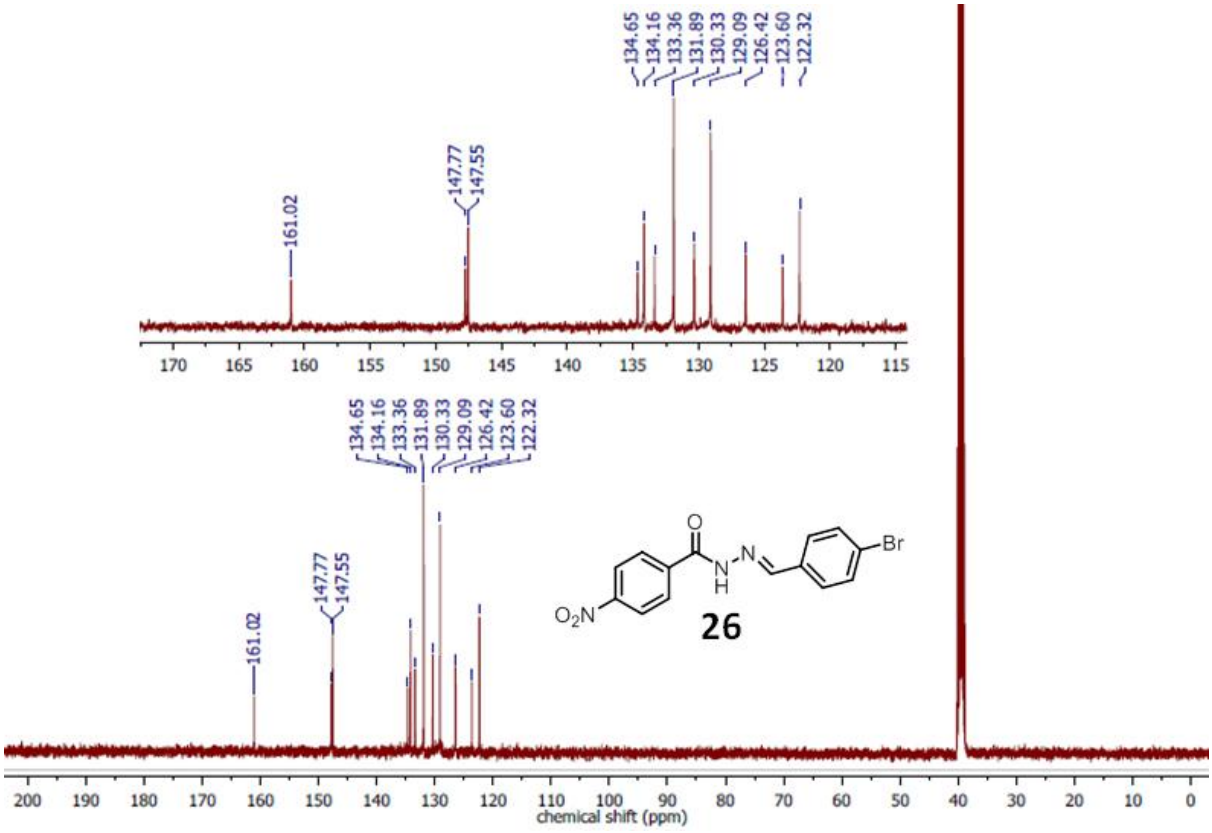


Figure S67: ^{13}C NMR spectra of compound 26.

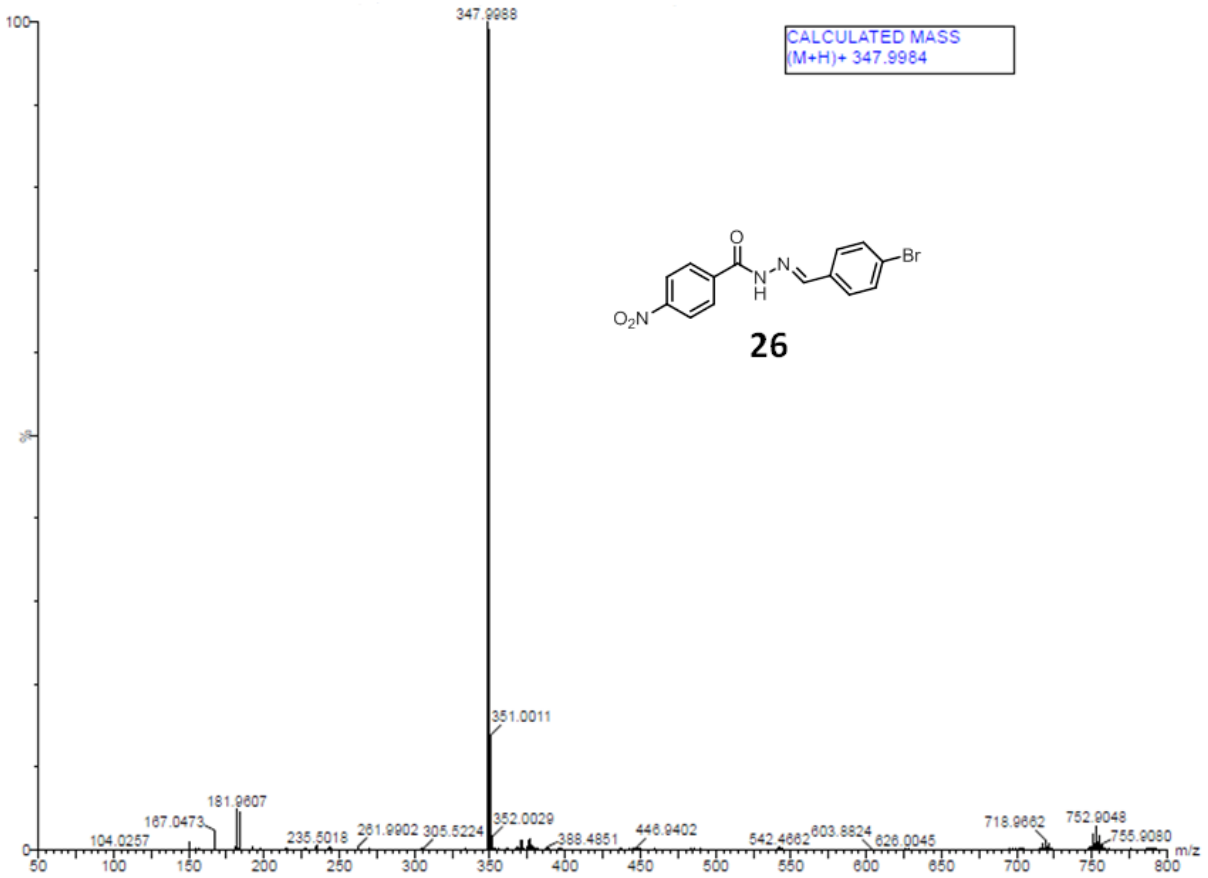


Figure S68: HR-MS spectra of compound 26.

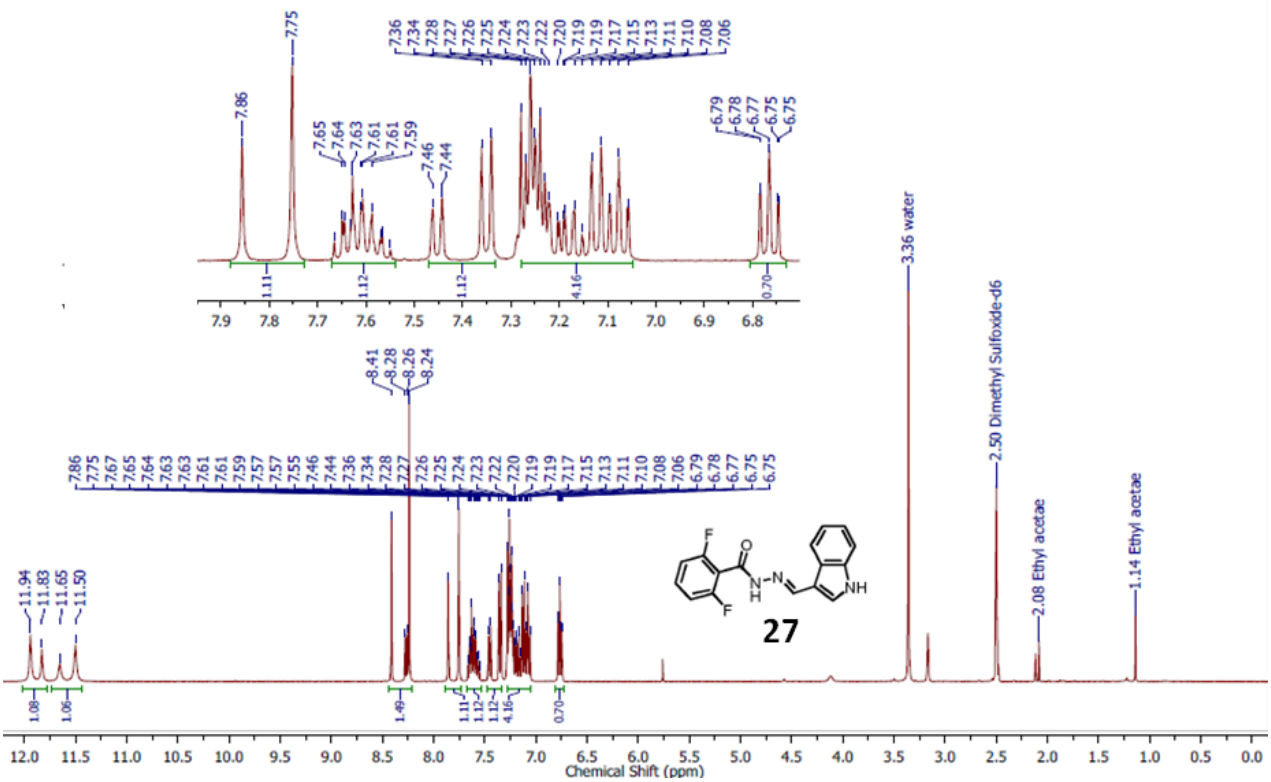


Figure S69: ^{1}H NMR spectra of compound 27.

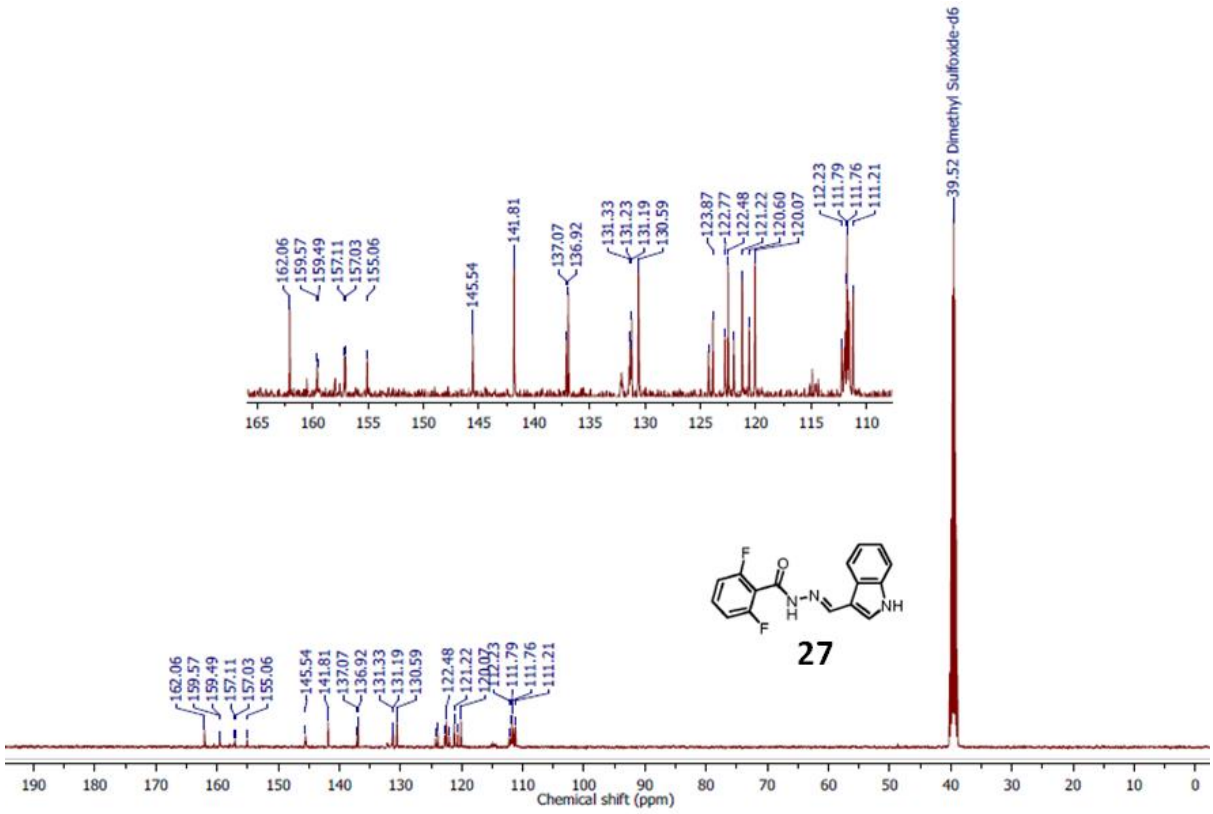


Figure S70: ^{13}C NMR spectra of compound 27.

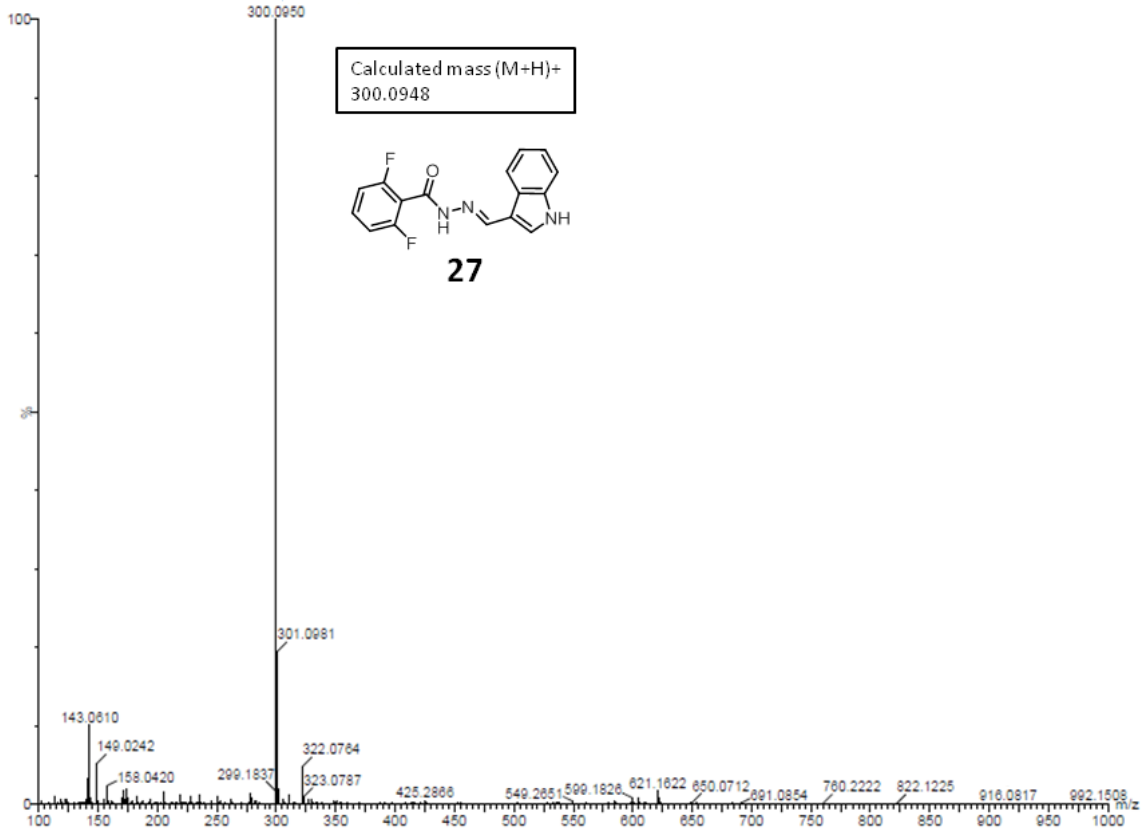


Figure S71: HR-MS spectra of compound 27.

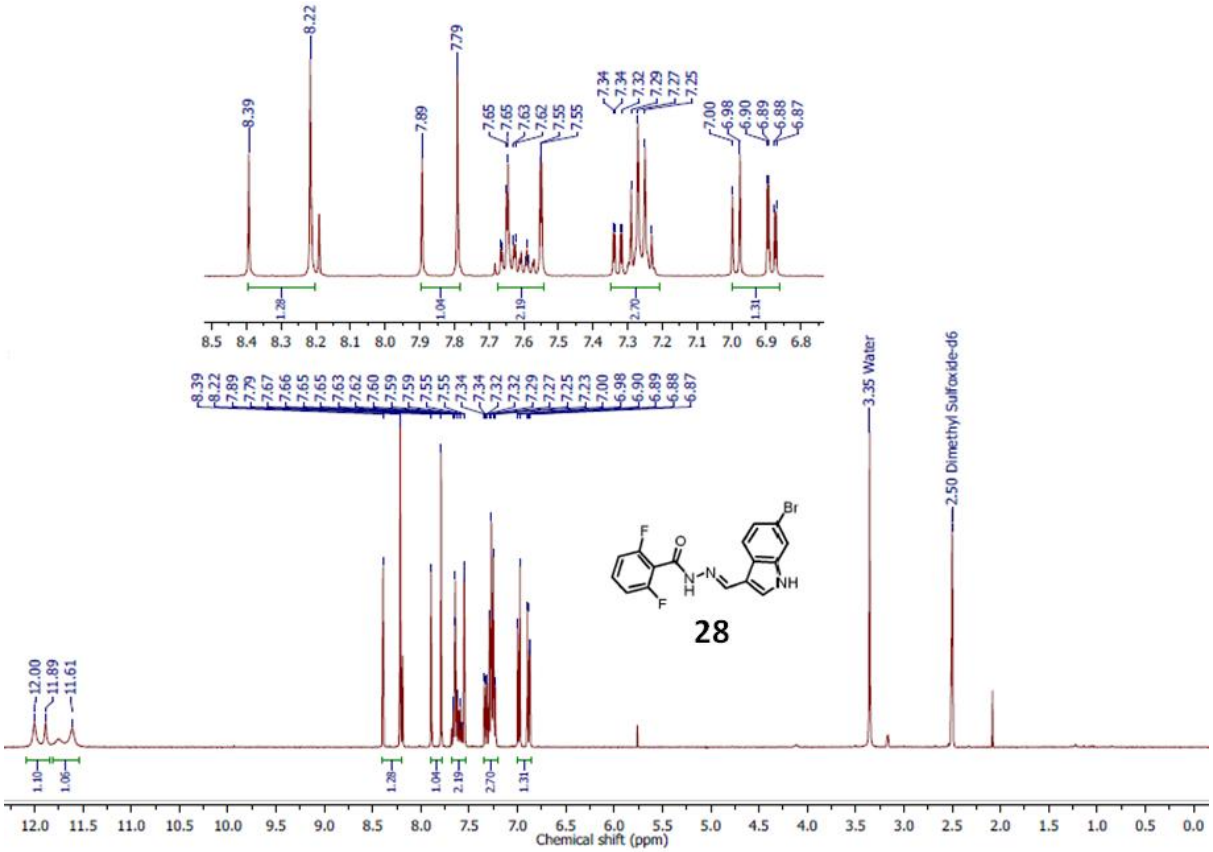


Figure S72: ^{1}H NMR spectra of compound 28.

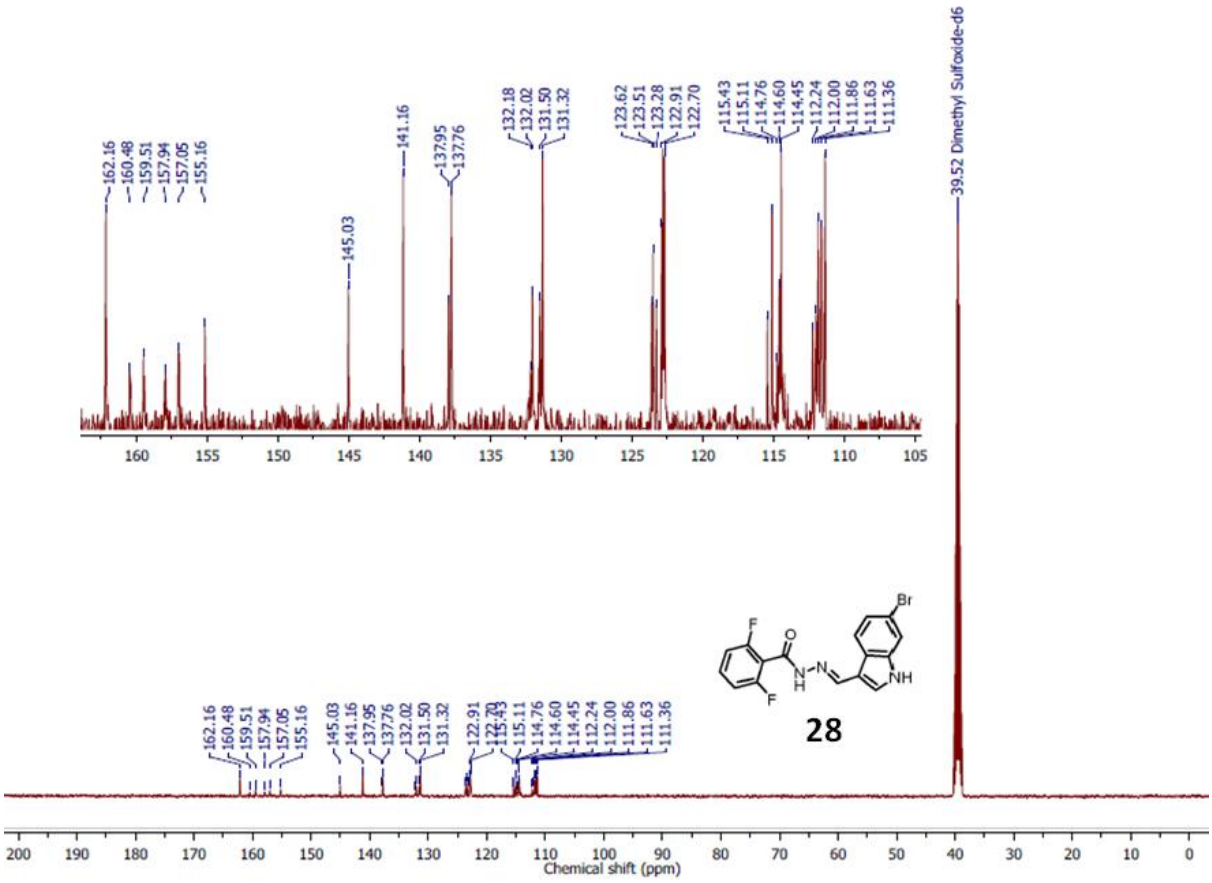


Figure S73: ^{13}C NMR spectra of compound 28.

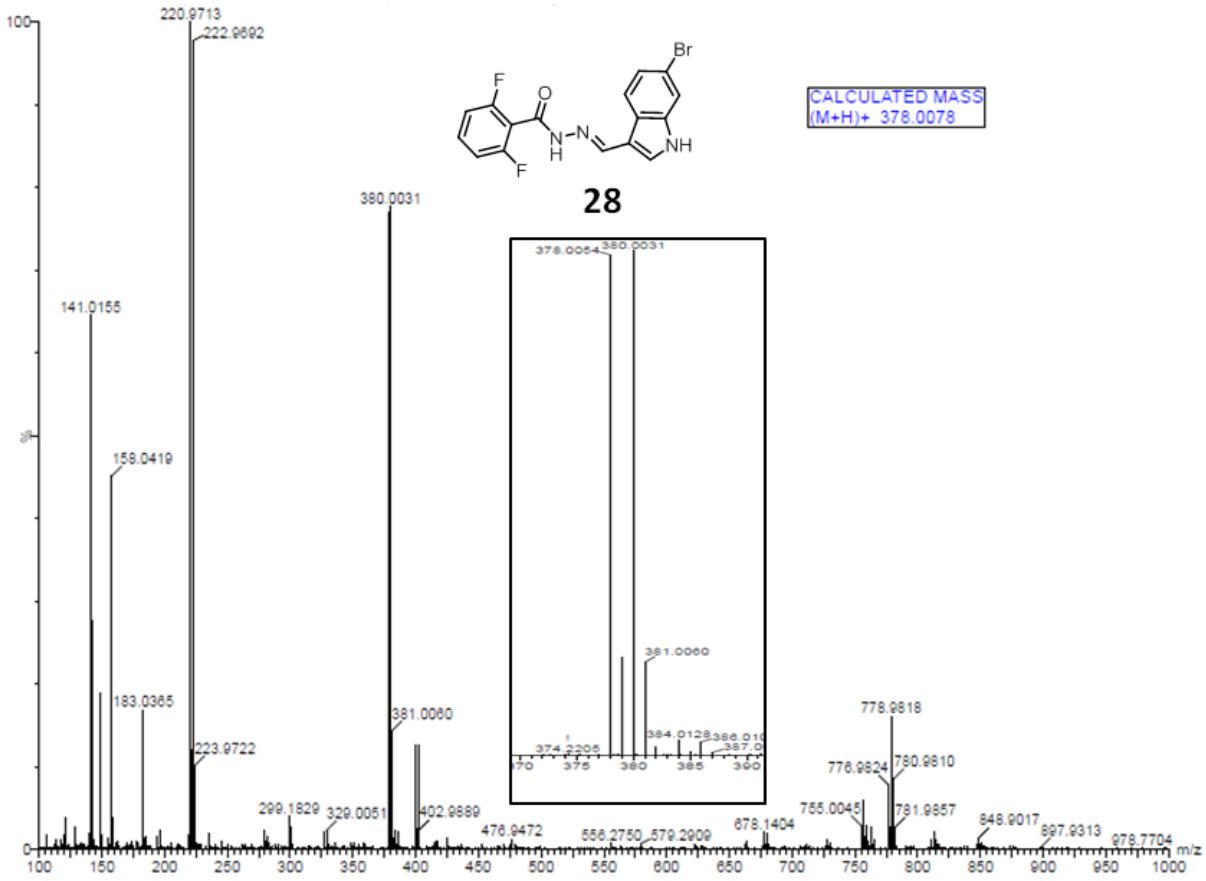


Figure S74: HR-MS spectra of compound 28.

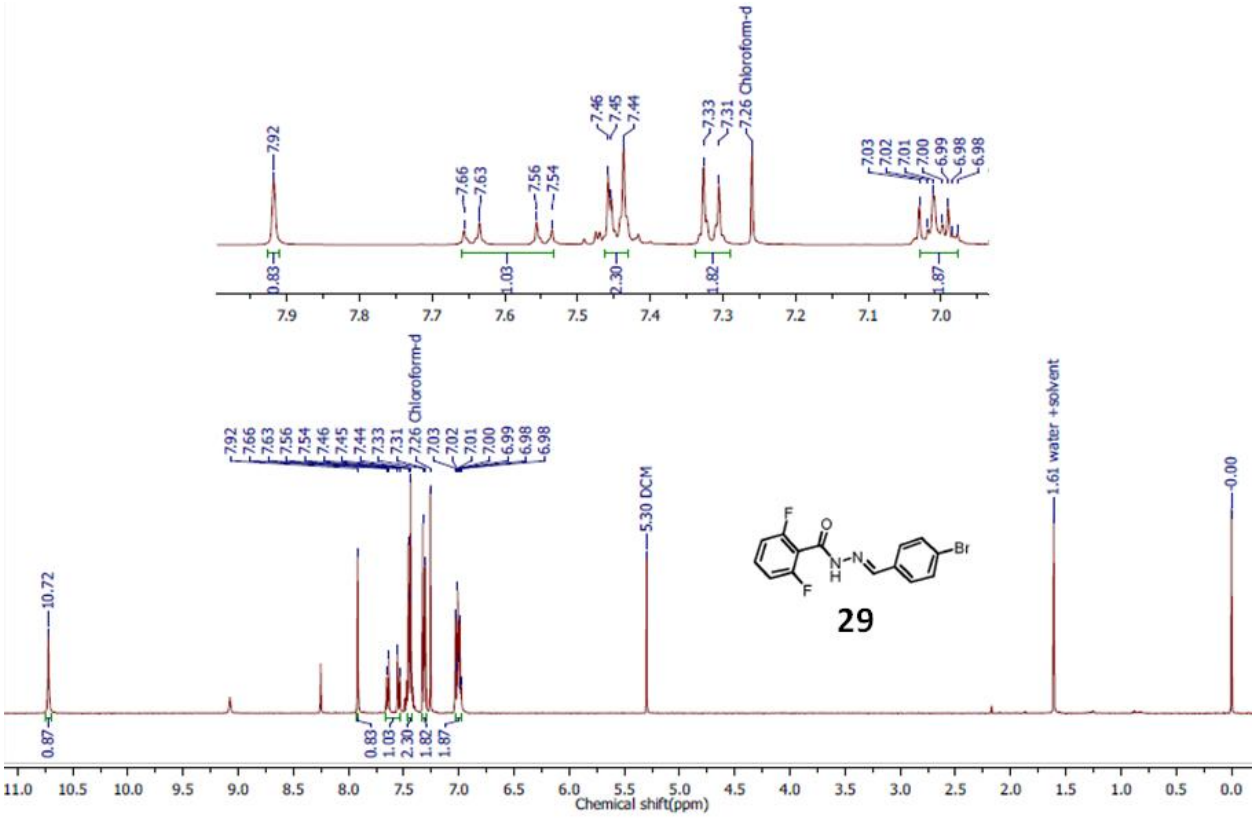


Figure S75: ^{1}H NMR spectra of compound 29.

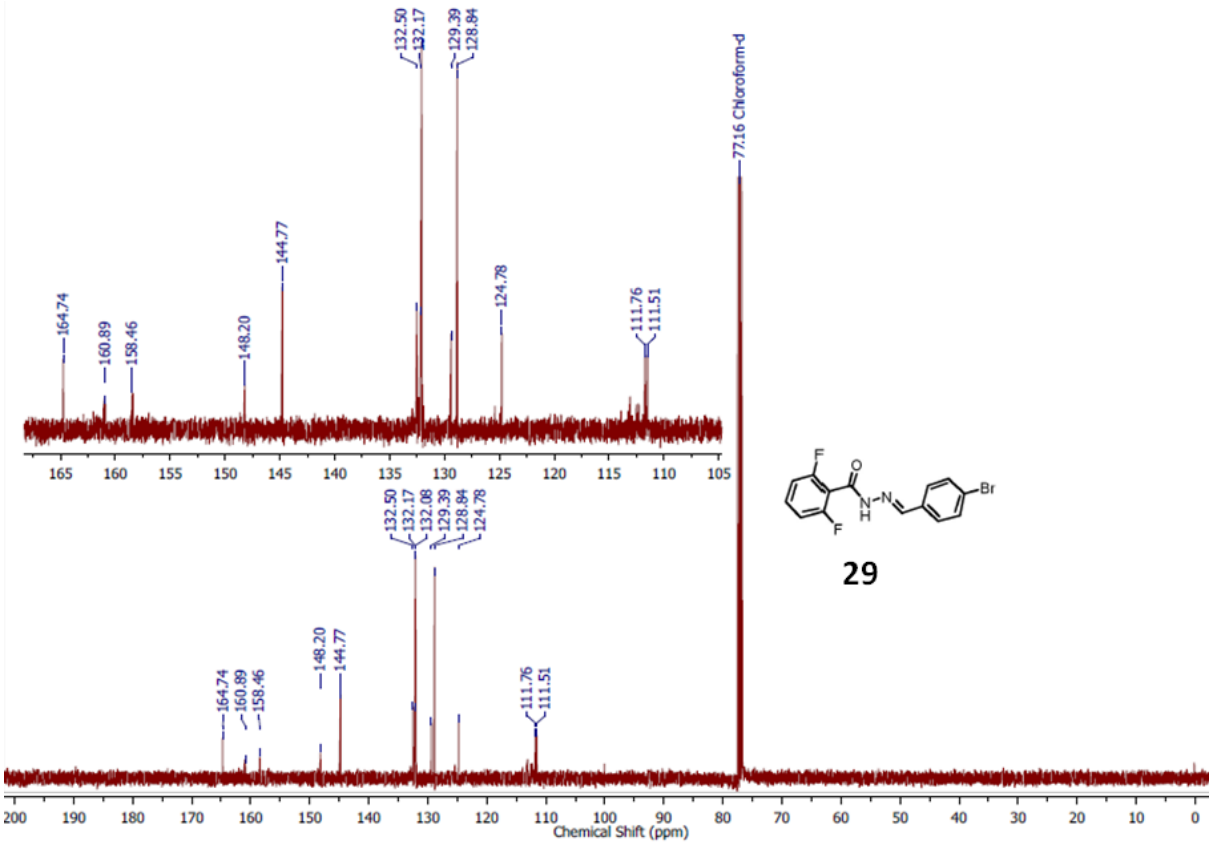


Figure S76: ^{13}C NMR spectra of compound 29.

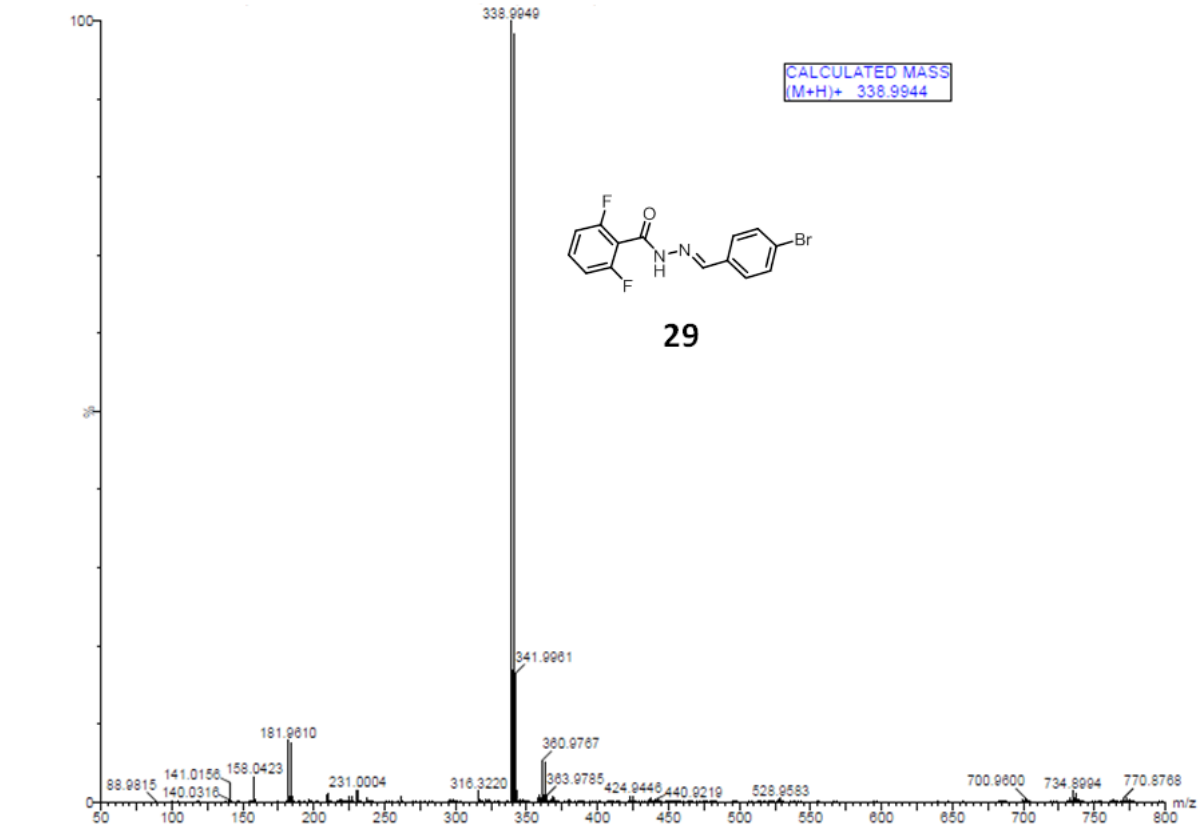


Figure S77: HR-MS spectra of compound 29.

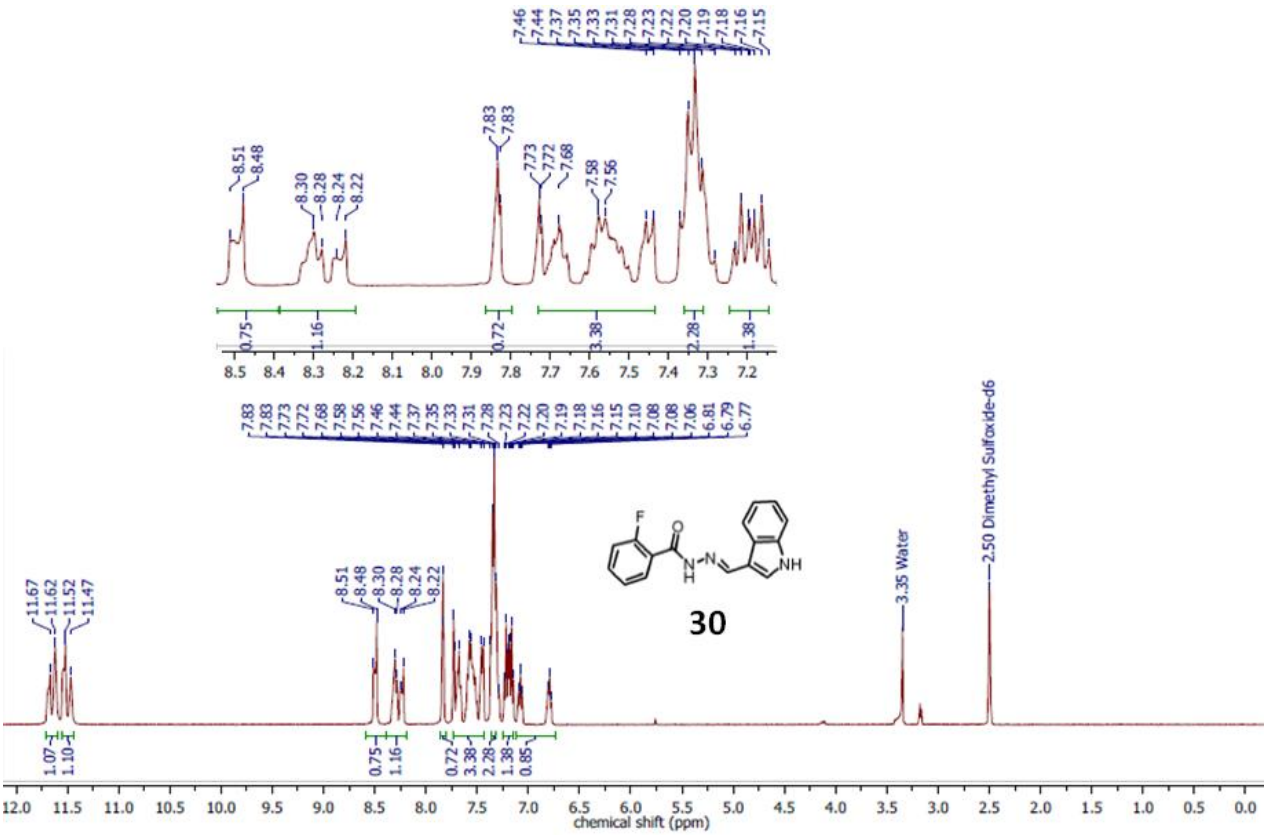


Figure S78: ^{1}H NMR spectra of compound 30.

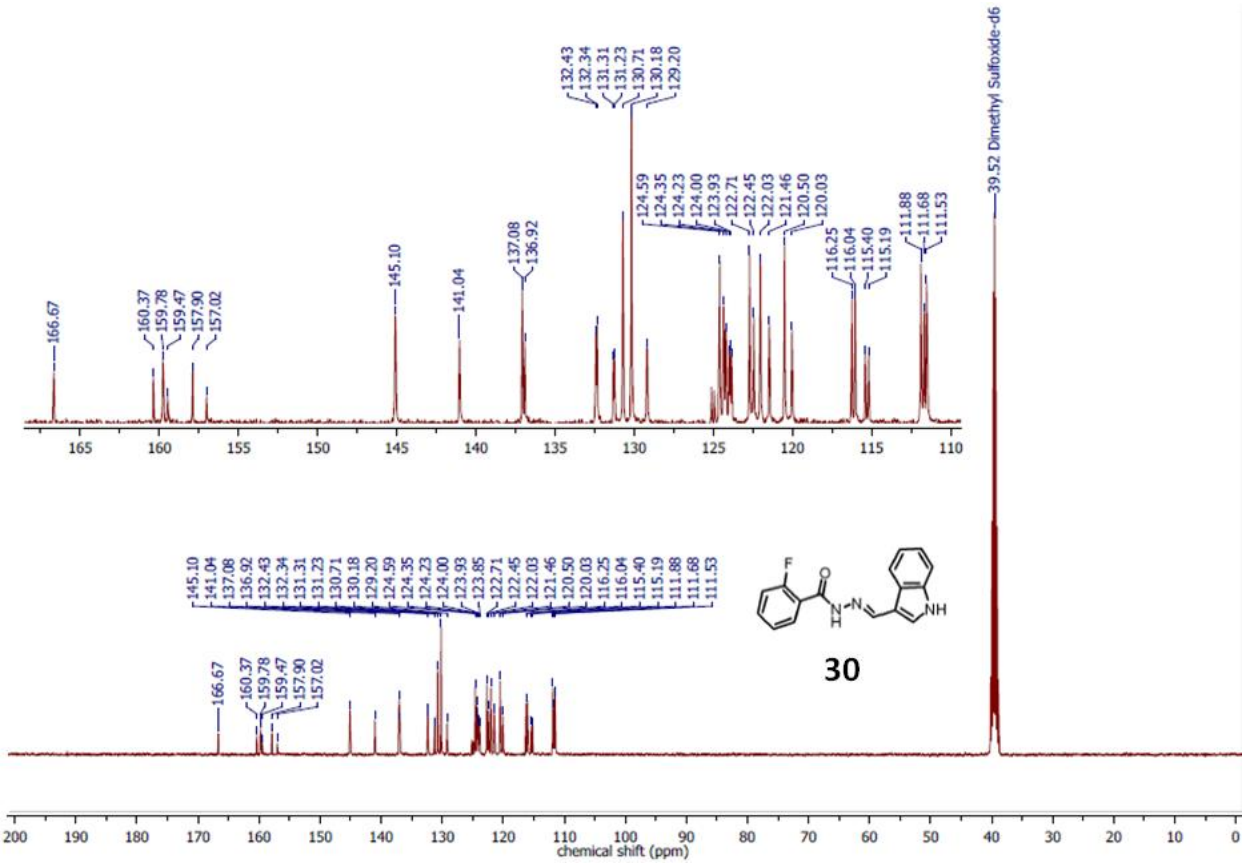


Figure S79: ^{13}C NMR spectra of compound 30.

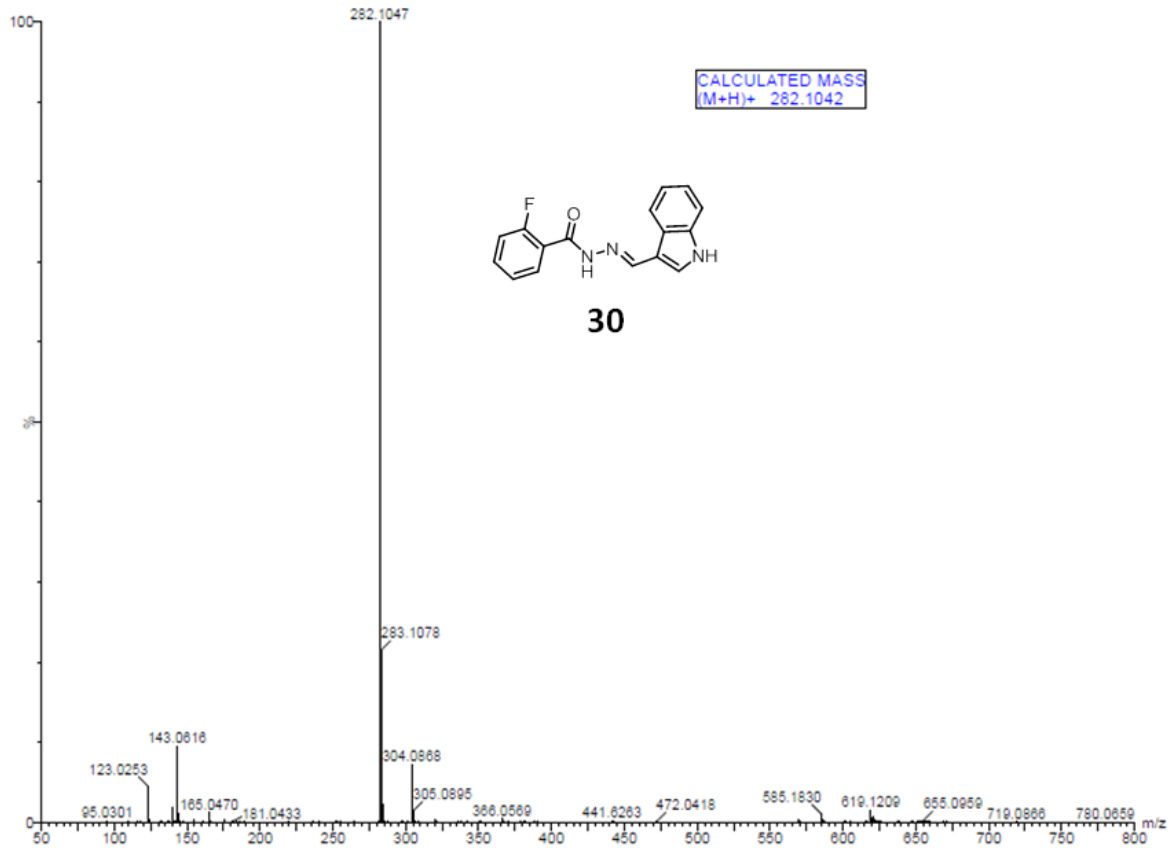


Figure S80: HR-MS spectra of compound 30.

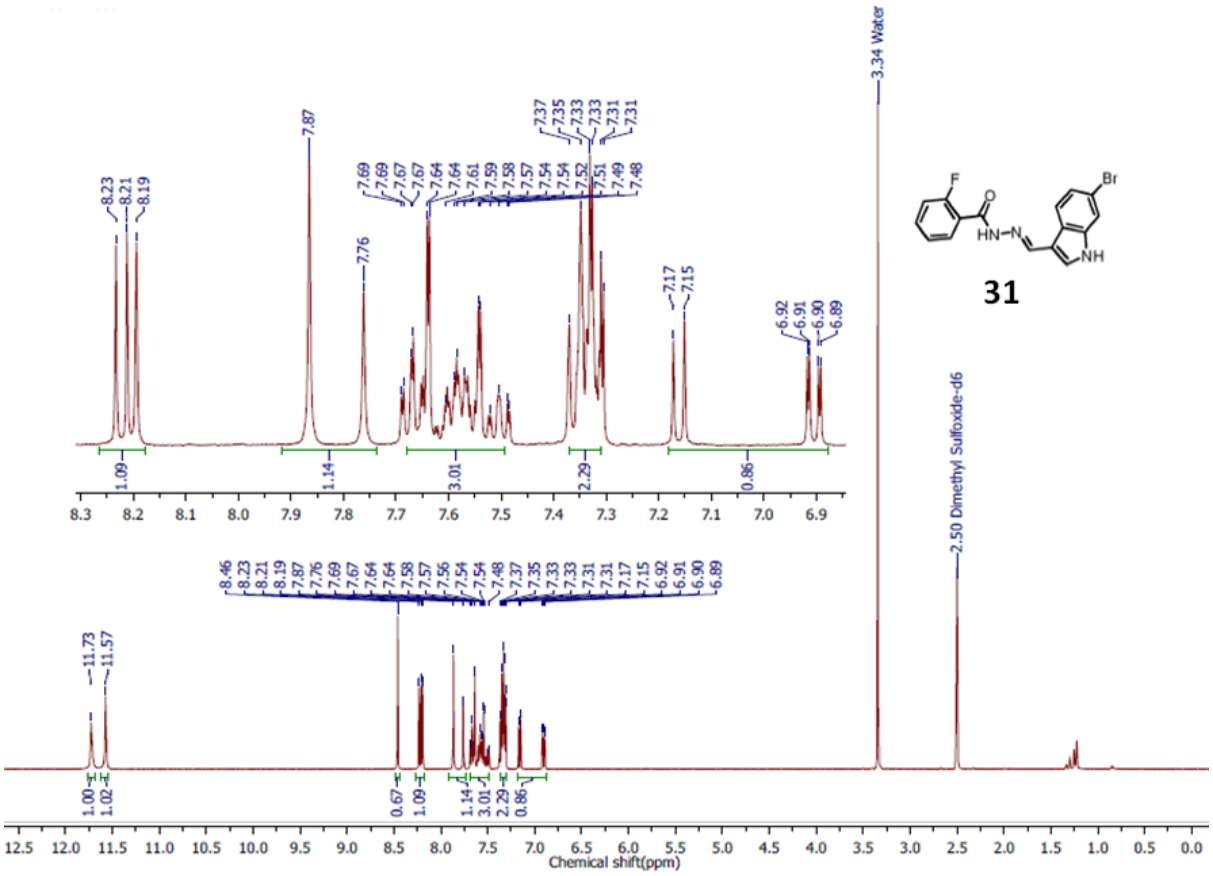


Figure S81: ^{1}H NMR spectra of compound 31.

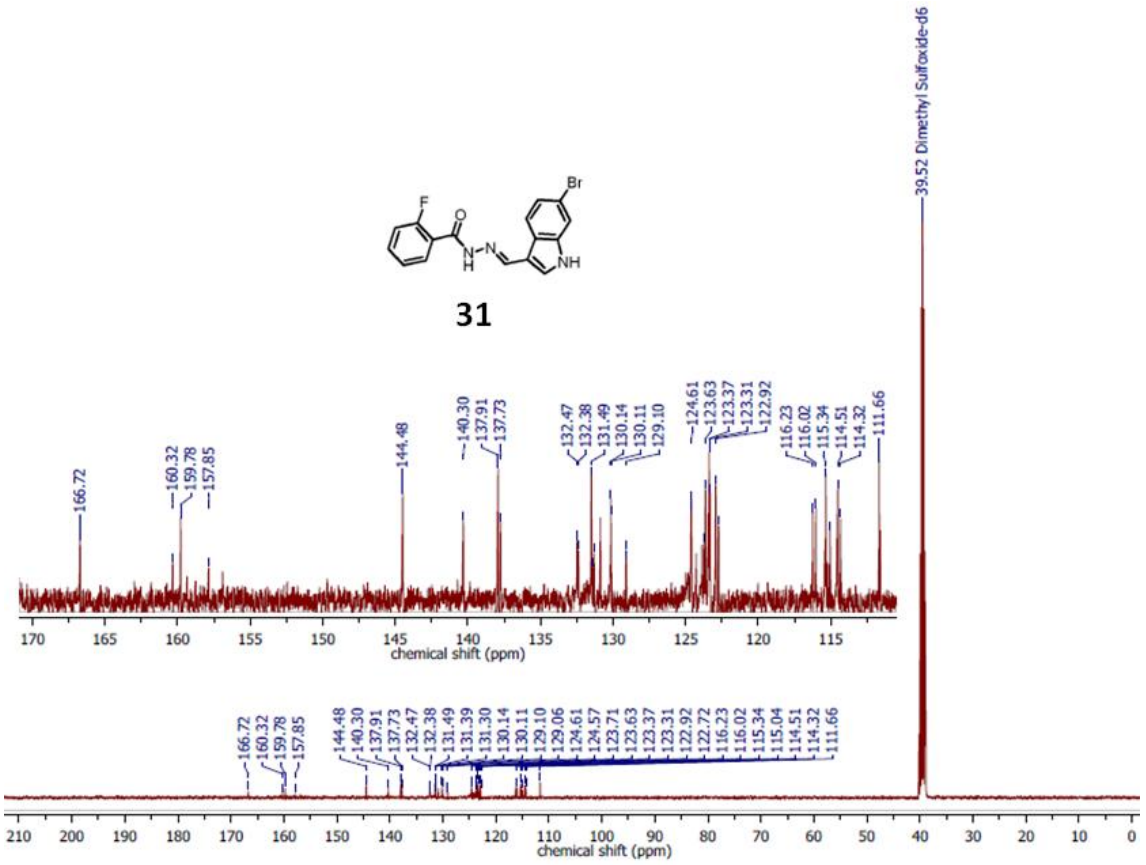


Figure S82: ^{13}C NMR spectra of compound 31.

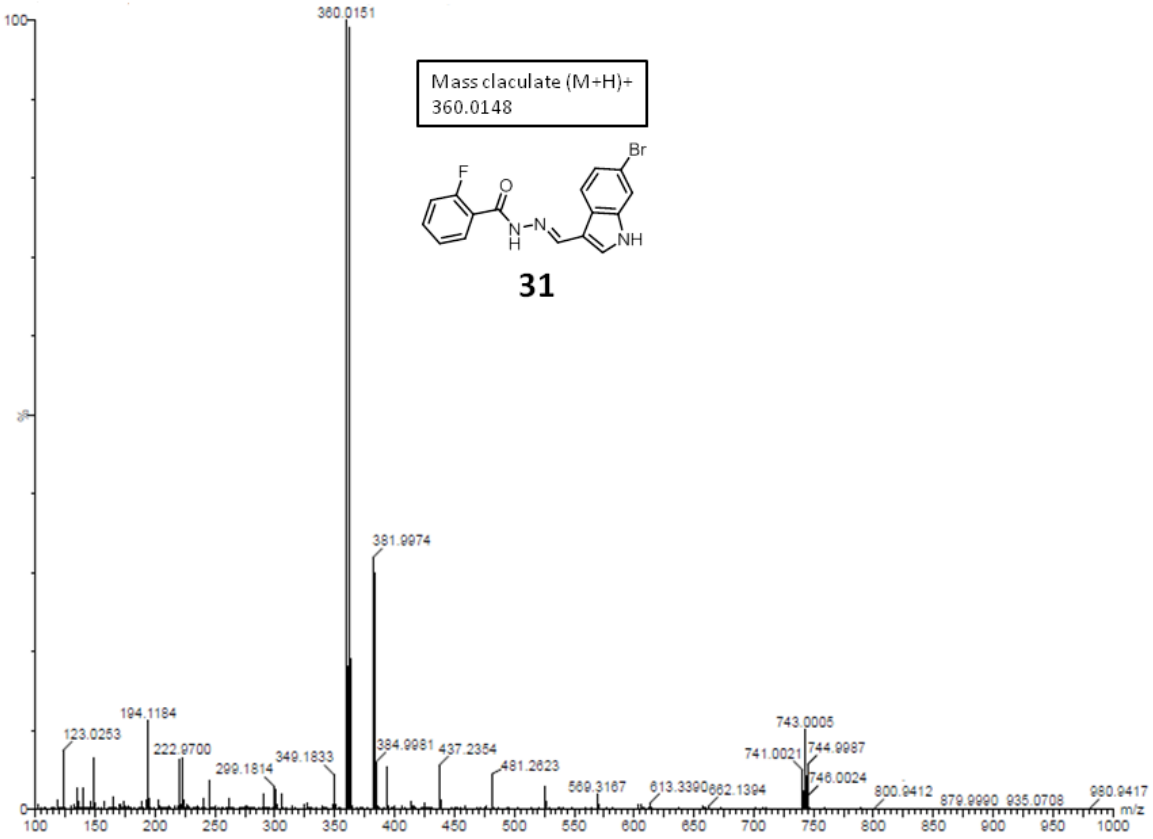


Figure S83: HR-MS spectra of compound 31.

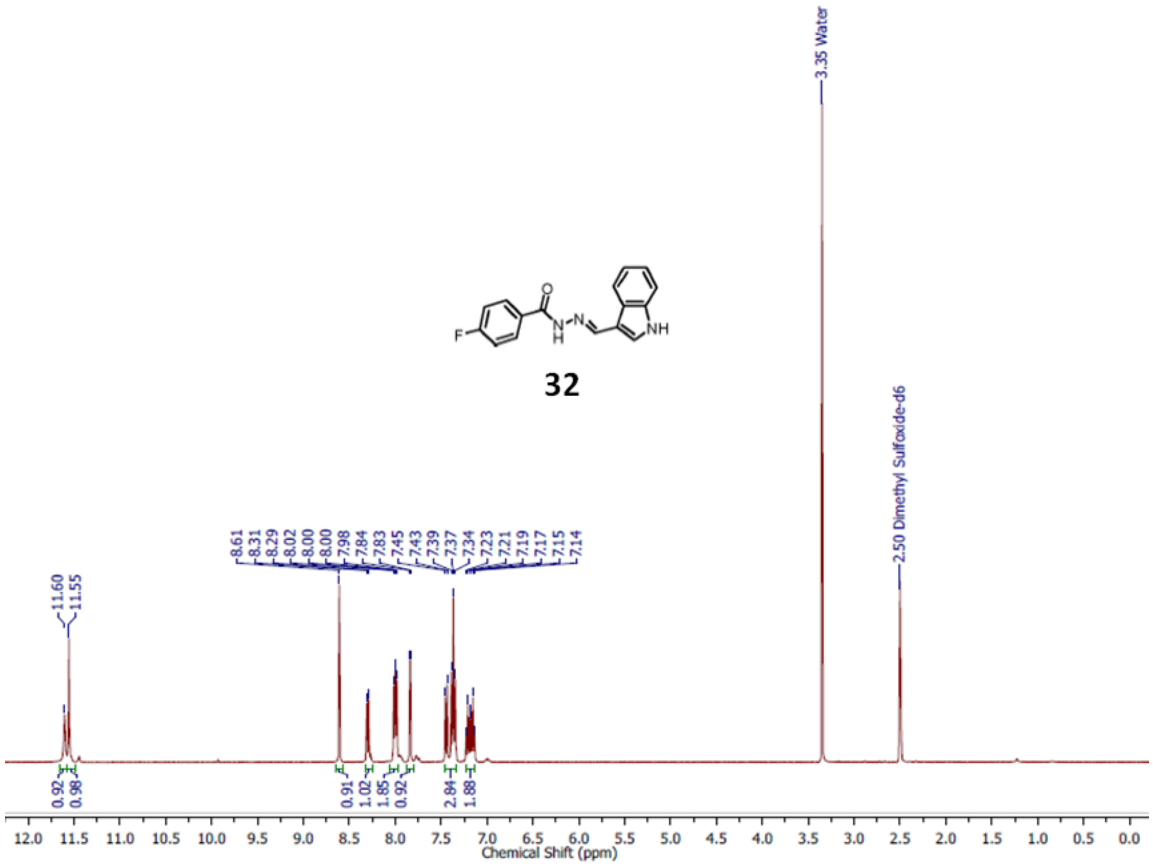


Figure S84: ^{1}H NMR spectra of compound 32.

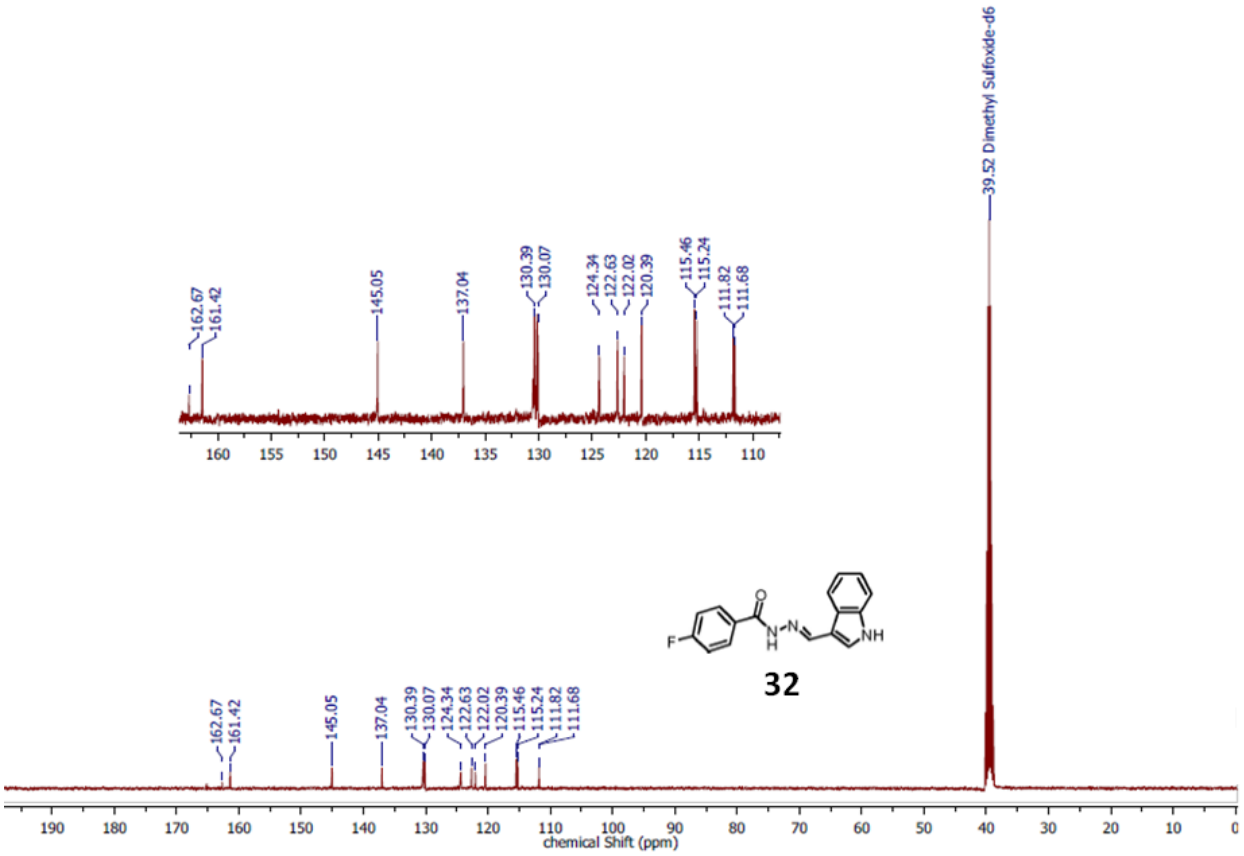


Figure S85: ^{13}C NMR spectra of compound 32.

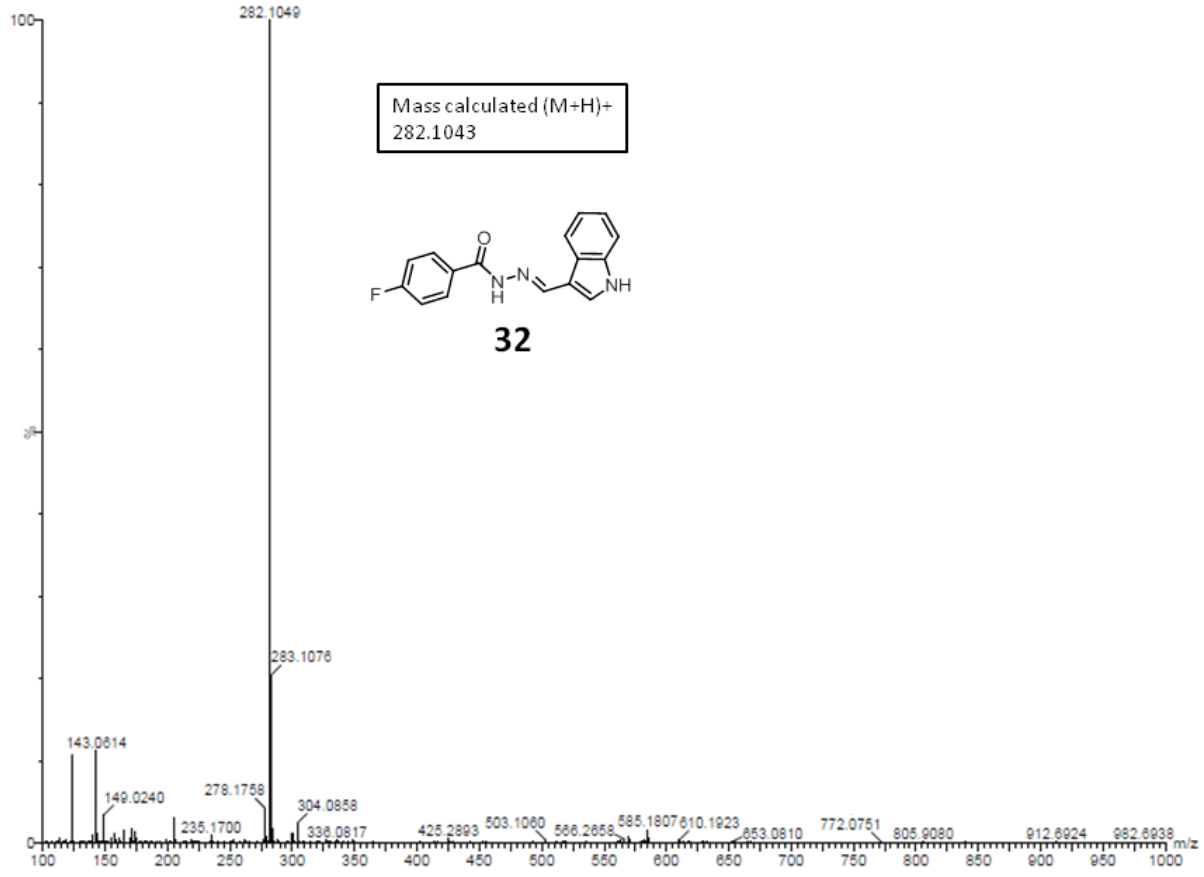


Figure S86: HR-MS spectra of compound 32.

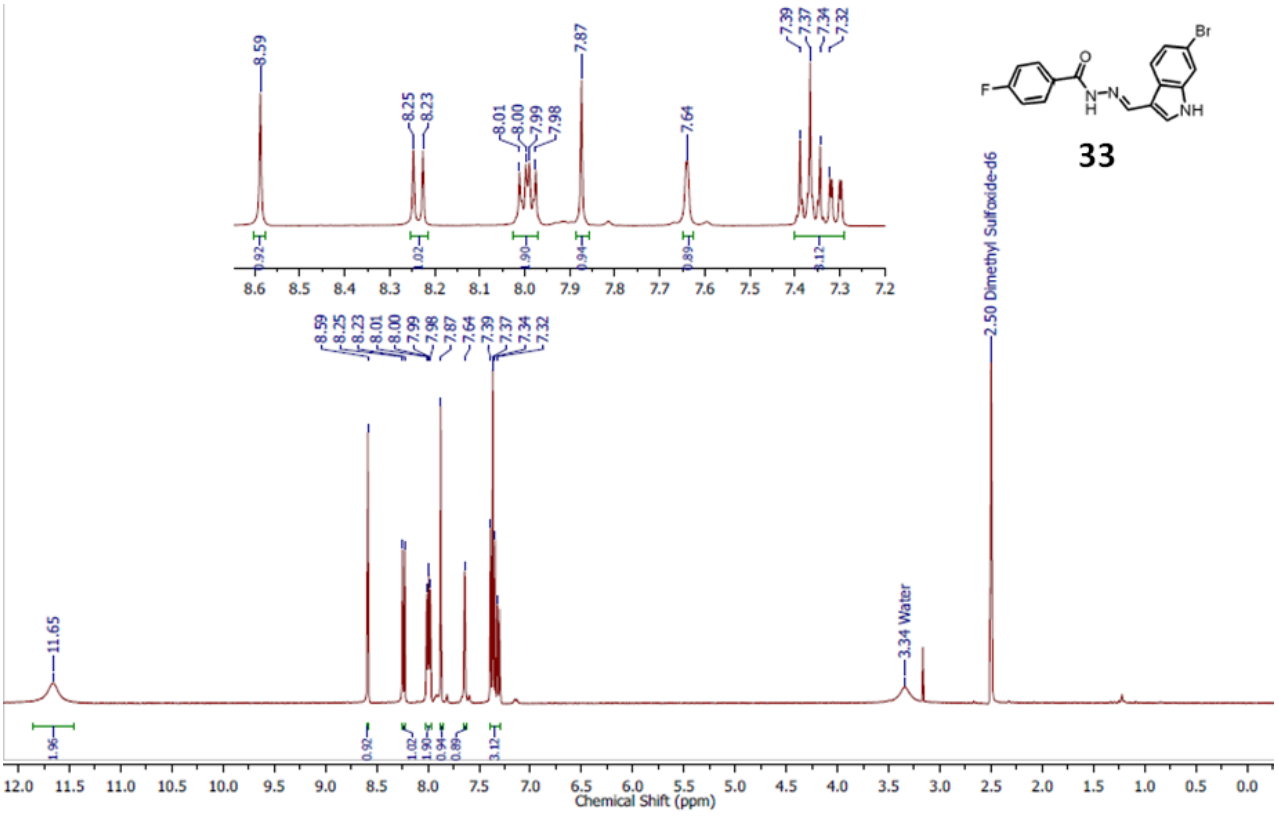


Figure S87: ^{1}H NMR spectra of compound 33.

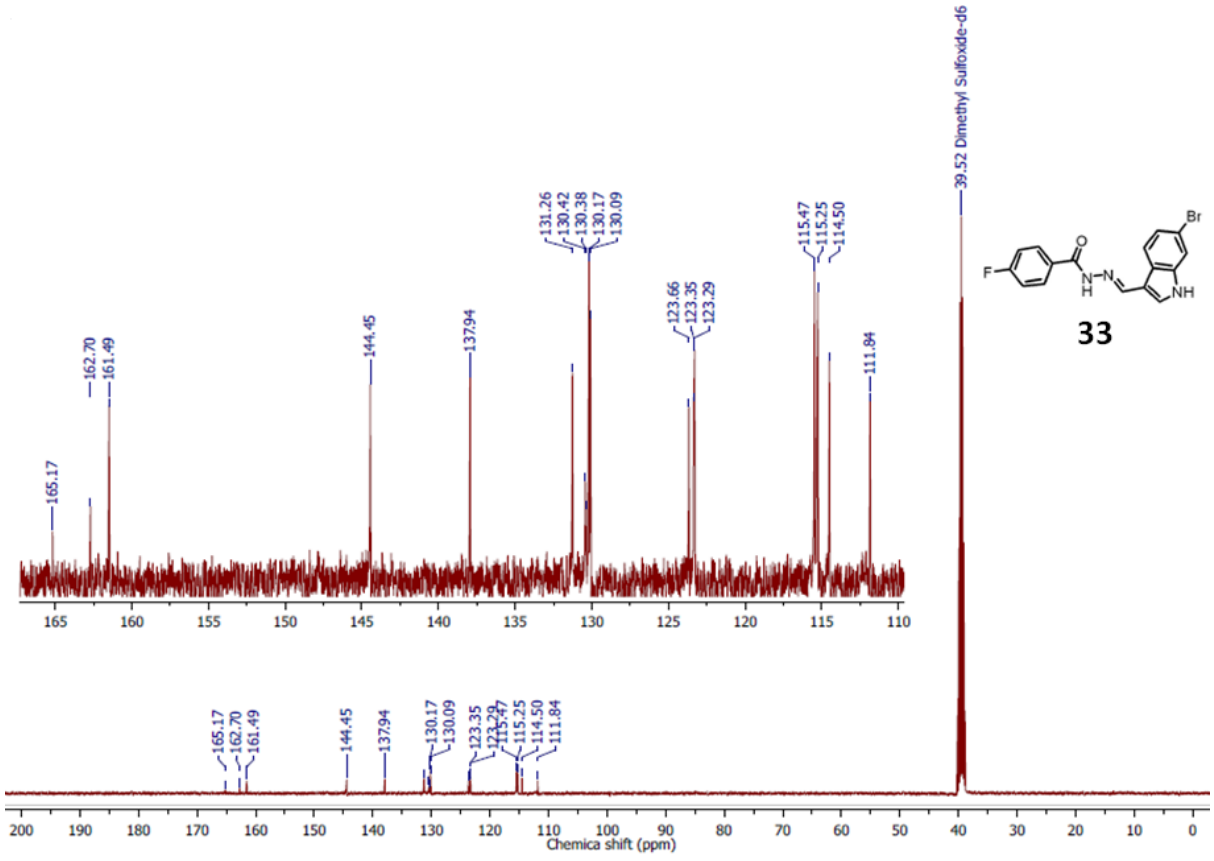


Figure S88: ^{13}C NMR spectra of compound 33.

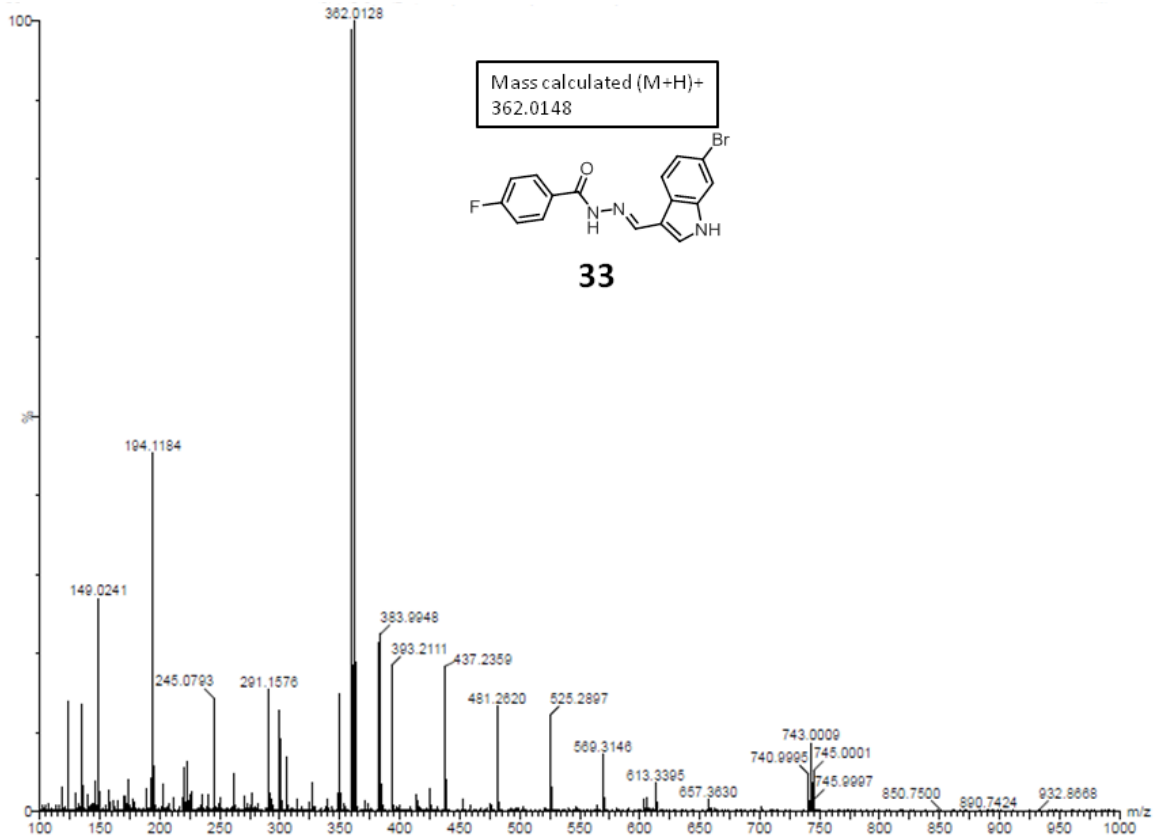


Figure S89: HR-MS spectra of compound 33.

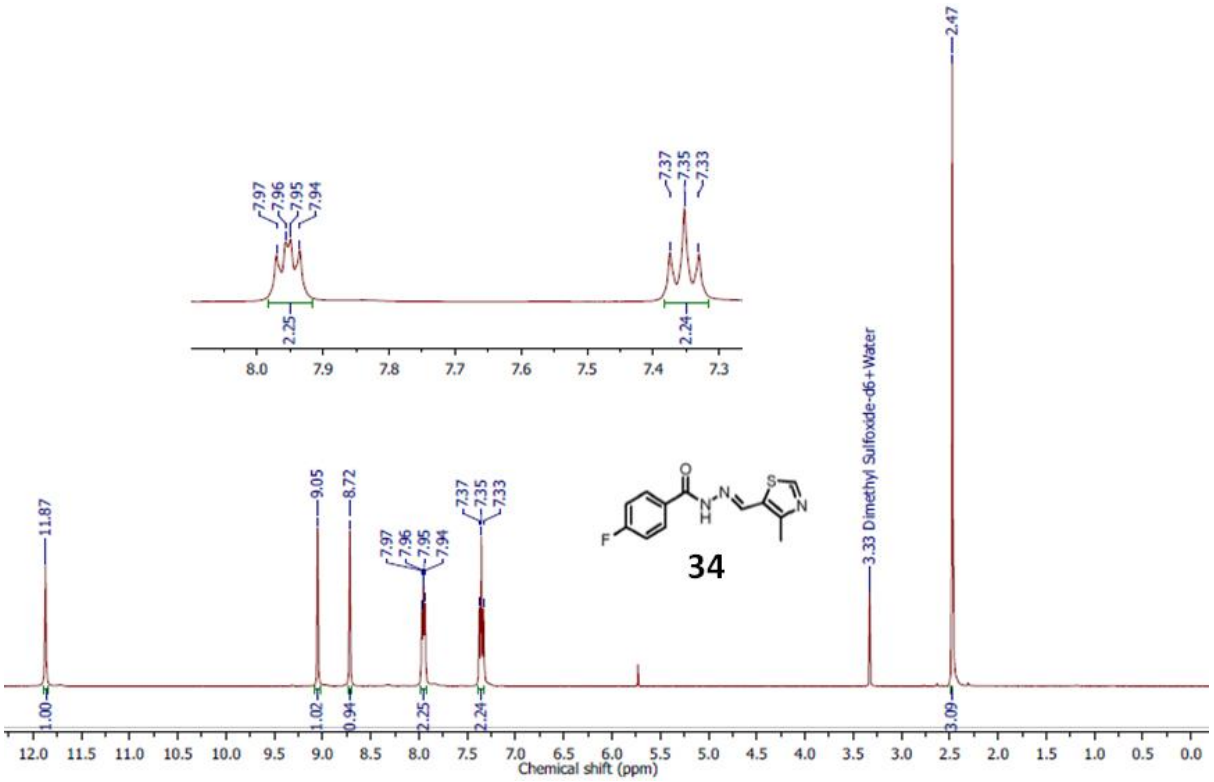


Figure S90: [1]H NMR spectra of compound 34.

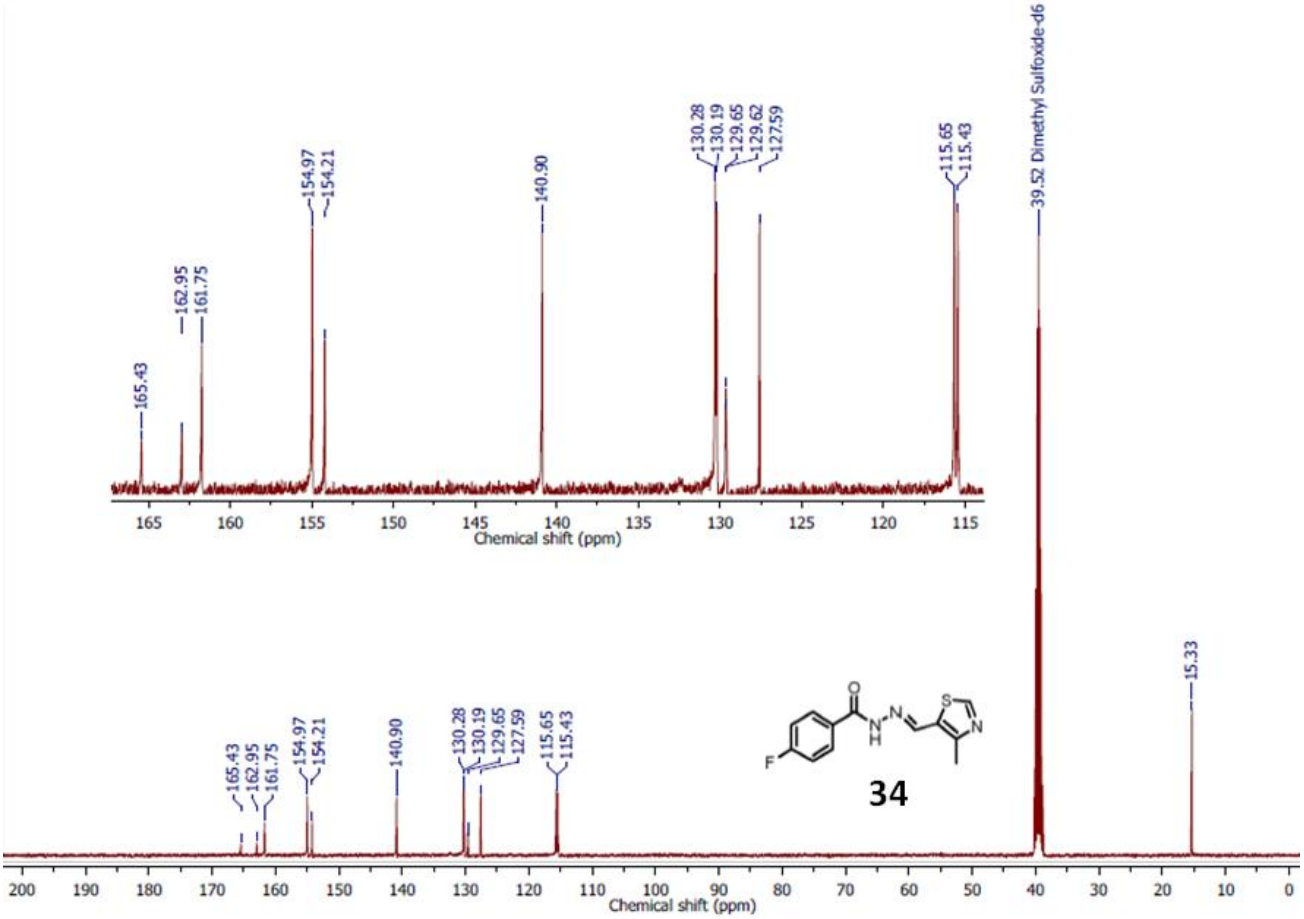


Figure S91: ^{13}C NMR spectra of compound 34.

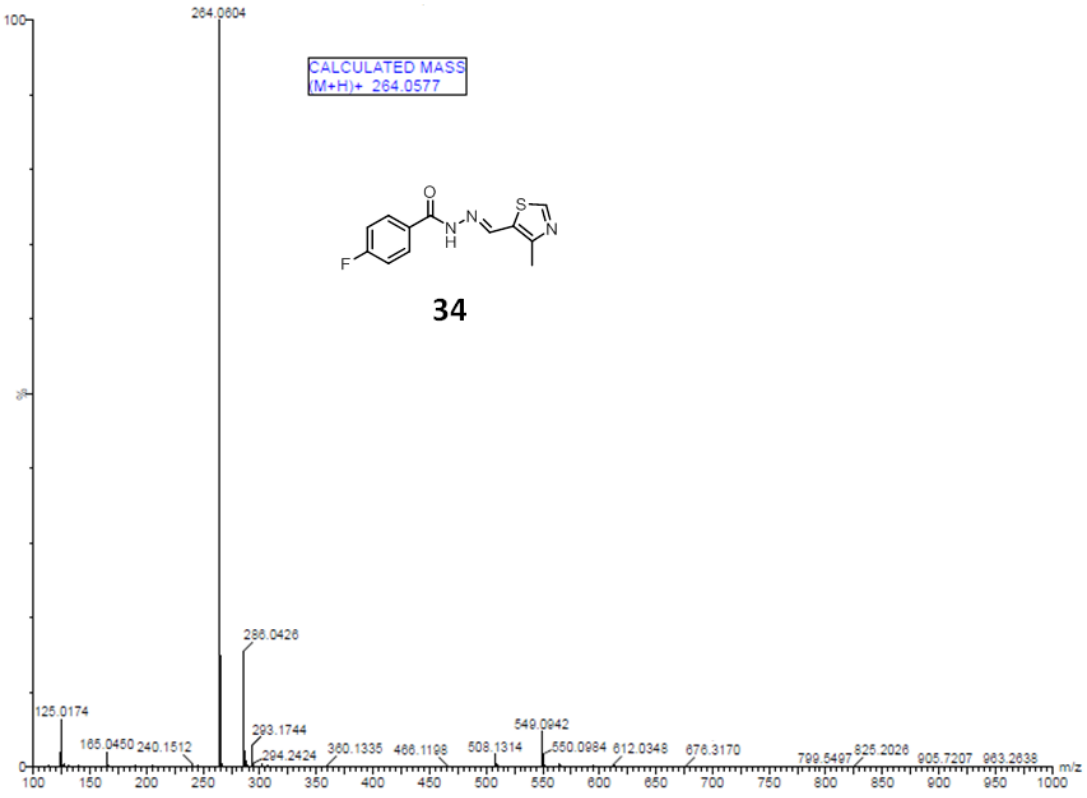


Figure S92: HR-MS spectra of compound 34.

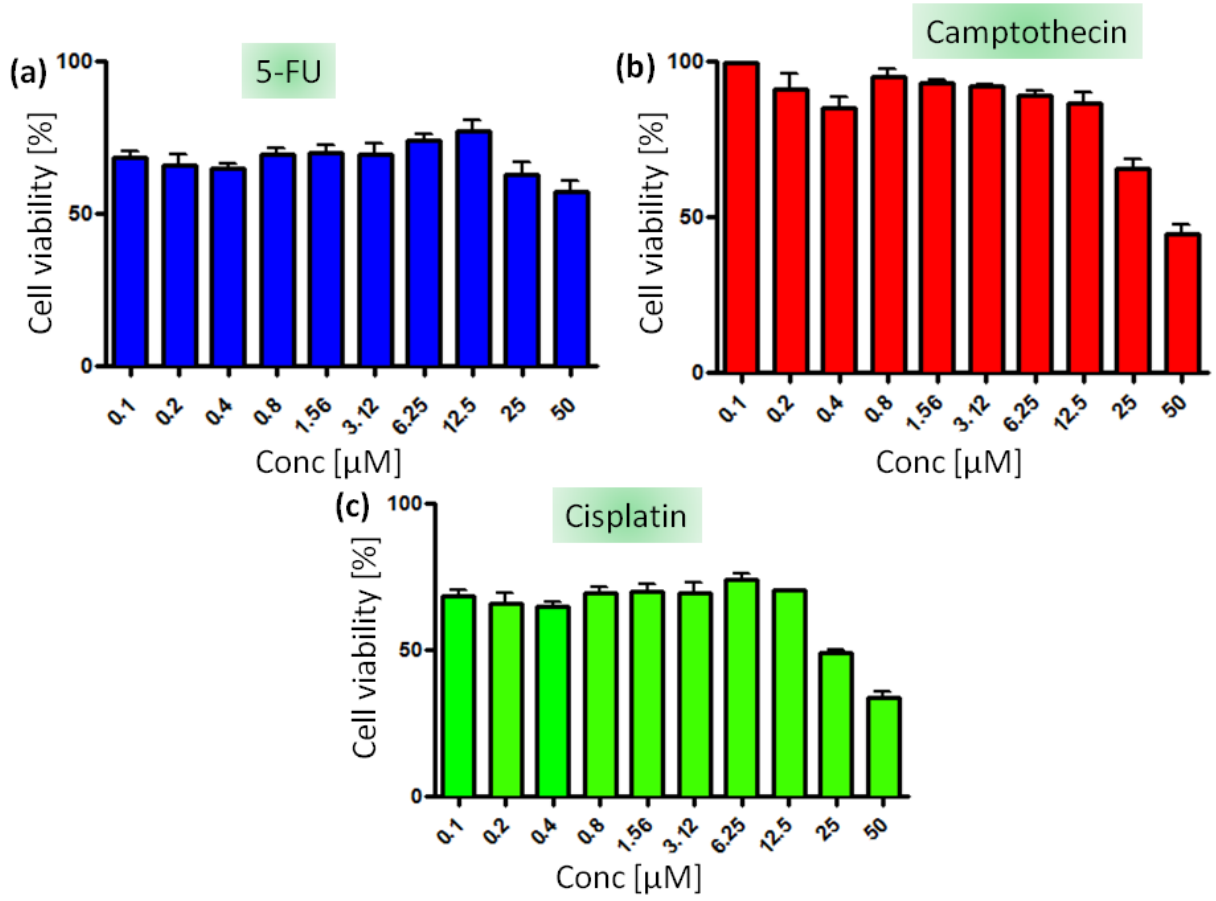


Figure S93: Concentration dependent cell viability assay of (a) 5-FU, (b) Camptothecin and (c) Cisplatin in HCT-116 cells after 24 h post incubation.

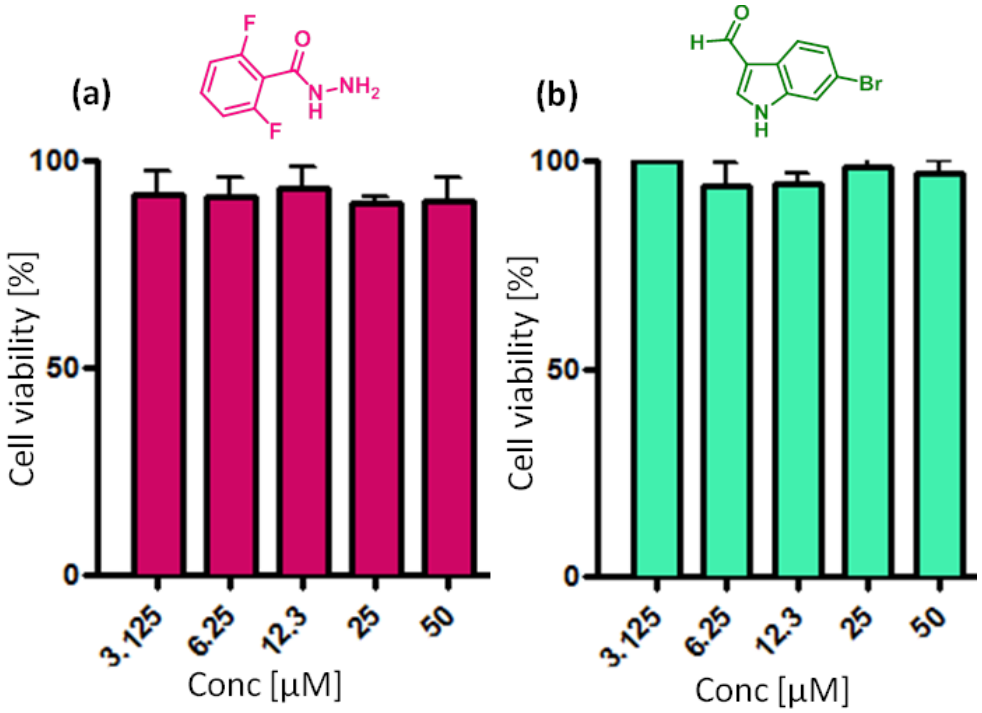


Figure S94: Concentration dependent cell viability assay of (a) 2, 6-difluorobenzohydrazide and (b) 6-bromo-1H-indole-3-carbaldehyde in HCT-116 cells at 24 h post-incubation.

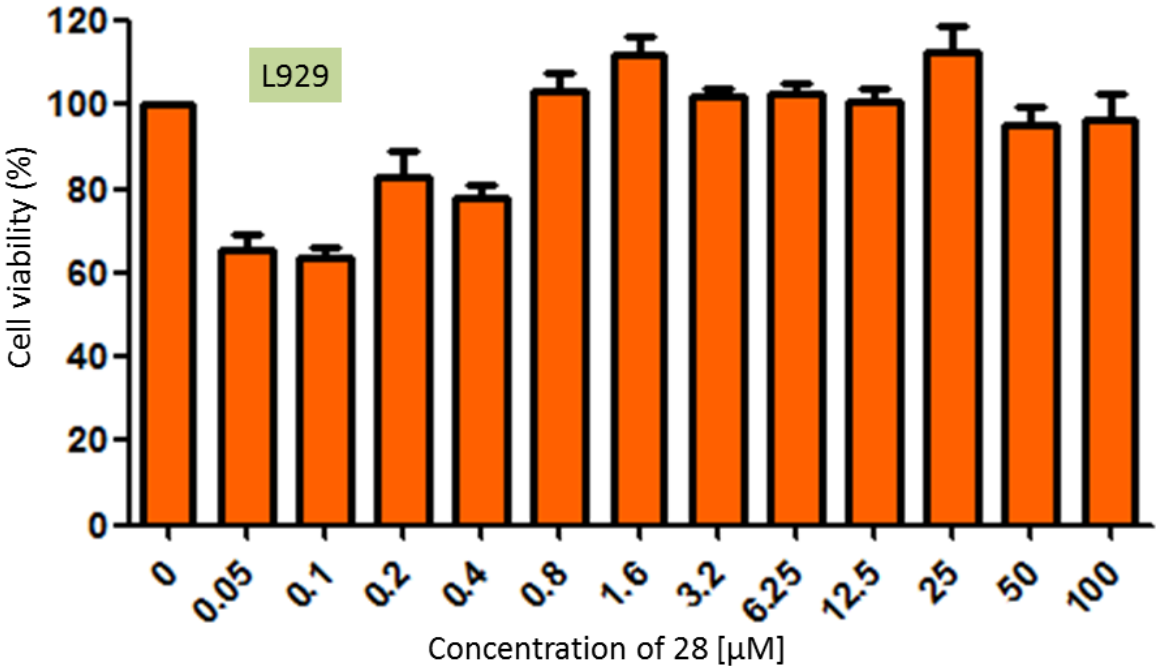


Figure S95: Concentration dependent cell viability assay of compound 28 in L929 fibroblast cells at 24 h post-incubation.

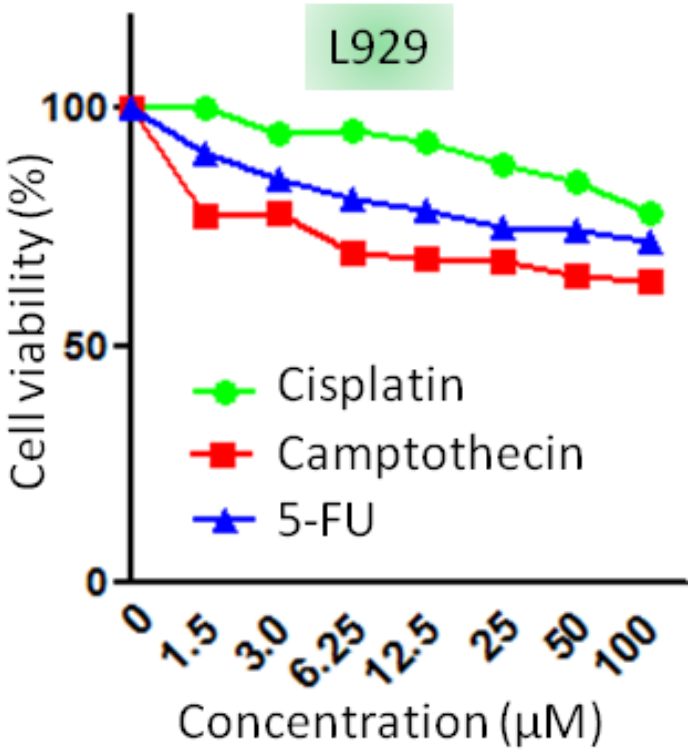
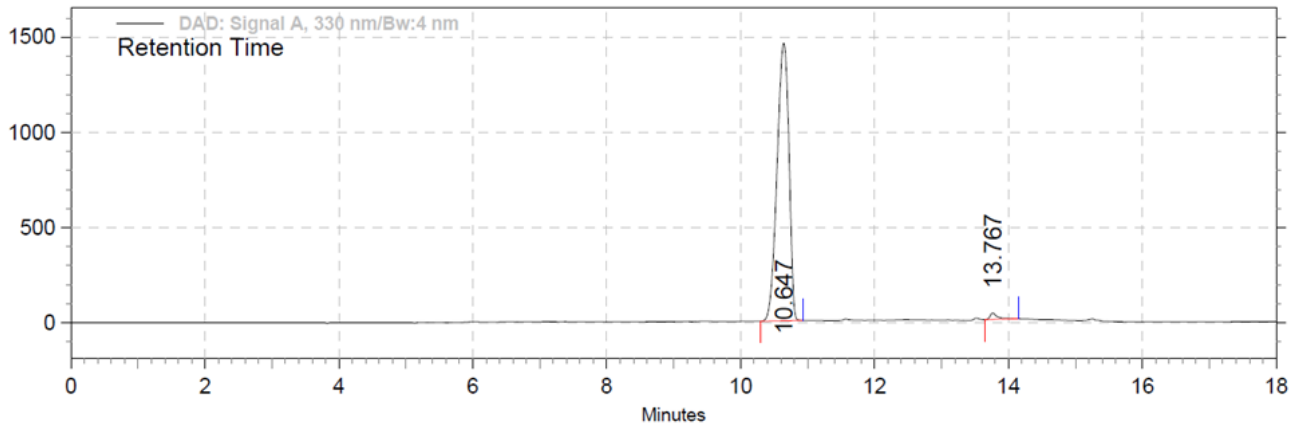


Figure S96: Concentration dependent cell viability assay of cisplatin, camptothecin and 5-FU in L929 cells at 24 h post-incubation.



Pk #	Area	Area %
1	37778053	98.59
2	540136	1.41
Totals	38318189	100.00

Figure S97: RP-HPLC traces of compound 28 after purification showing 98.6 % purity.

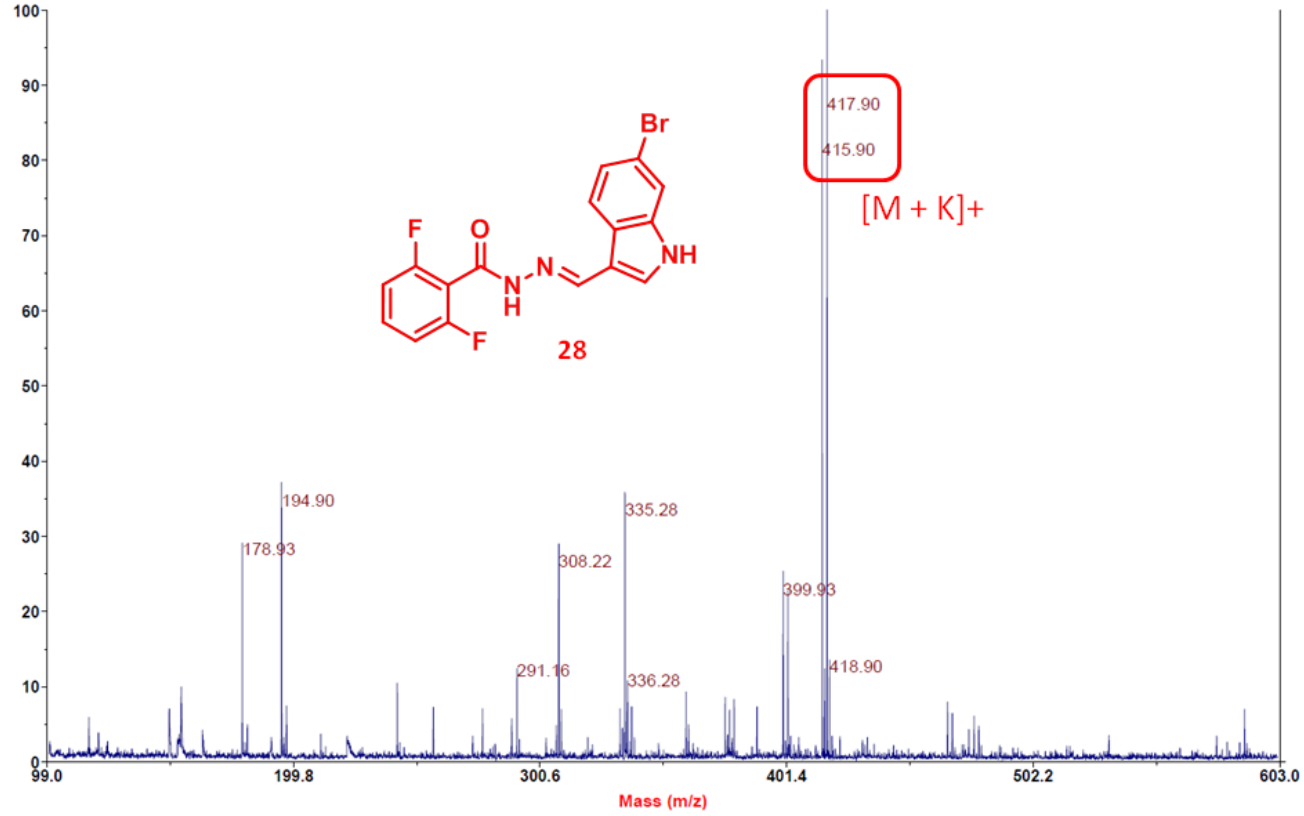


Figure S98: MALDI-TOF spectra of compound 28 after incubation at pH = 5.5 for 24 h.

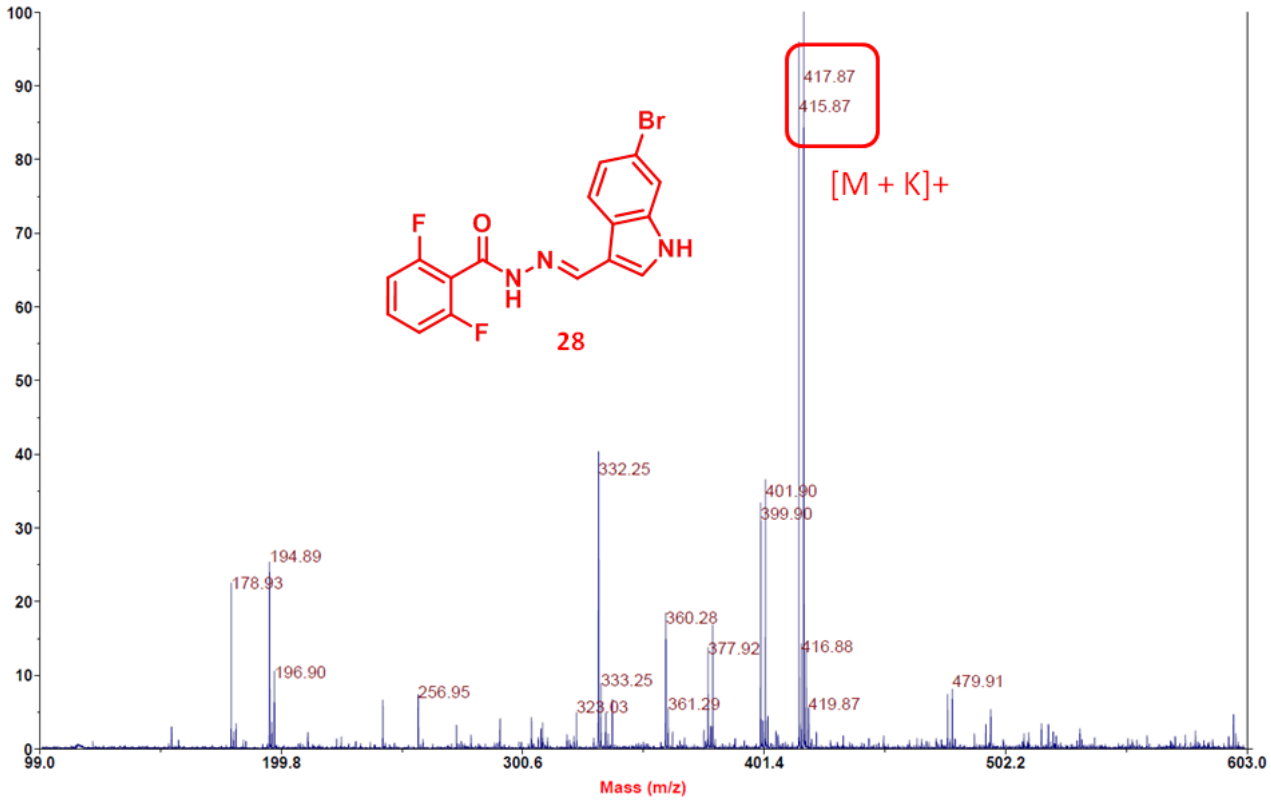


Figure S99: MALDI-TOF spectra of compound 28 after incubation at pH = 5.5 for 72 h.

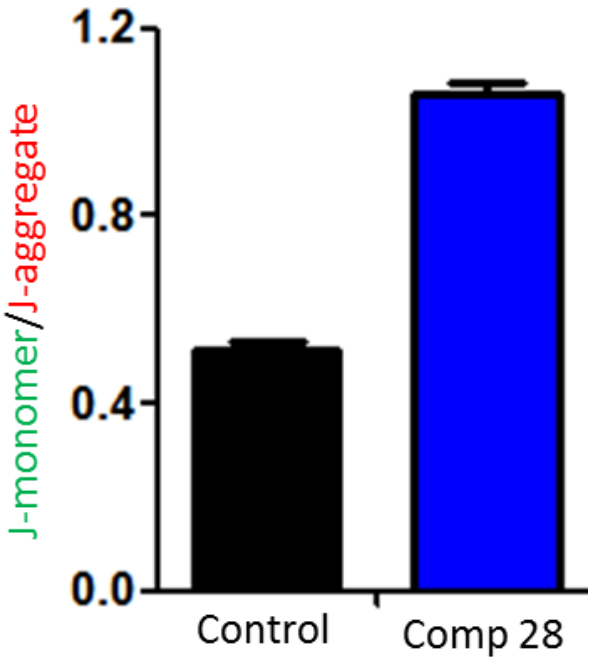


Figure S100: Quantification of J-monomer/J-aggregate from confocal laser scanning microscopy (CLSM) after treatment of HCT-116 cells with compound 28 for 24 h.

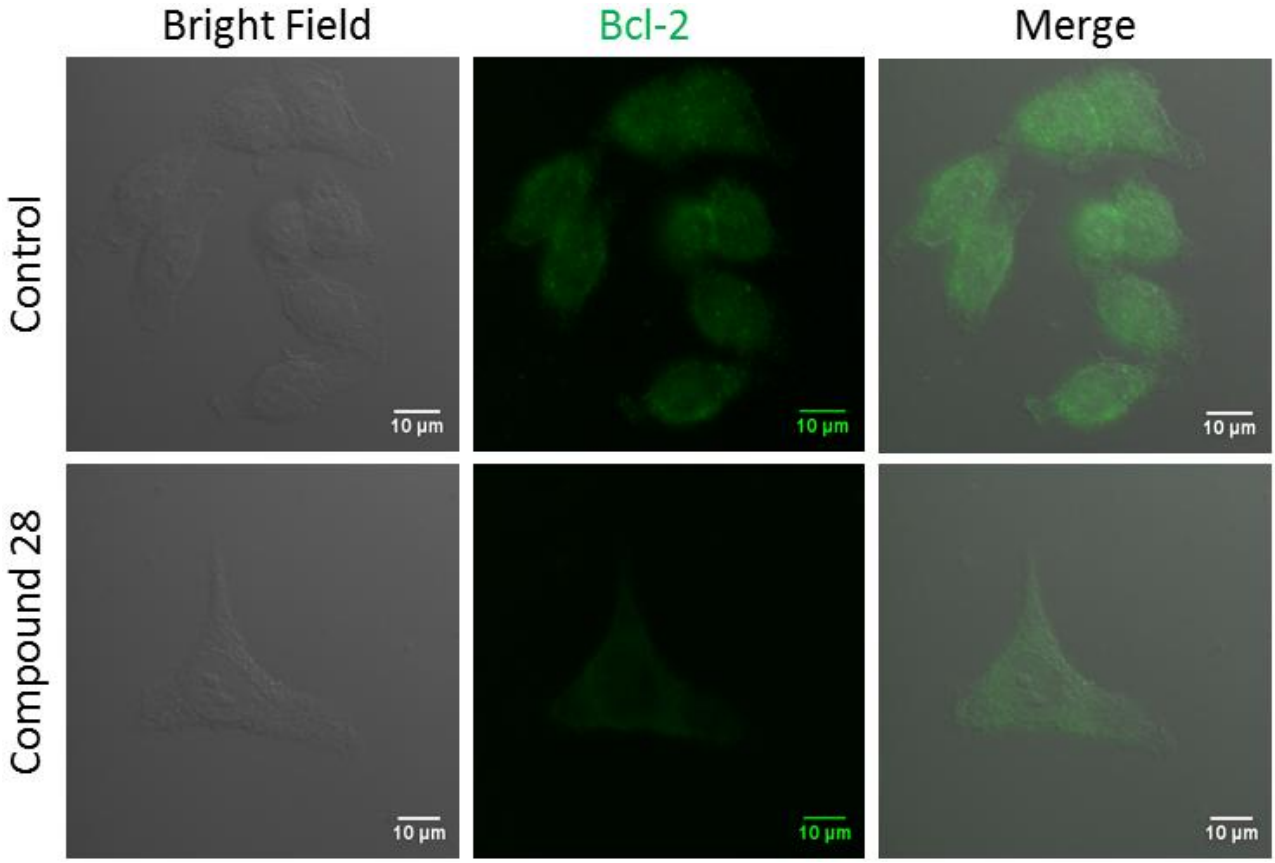


Figure S101: CLSM images of HCT-116 cells treated with compound 28 followed by stained with green fluorescent Alexa Fluor 488 labelled Bcl-2 antibody.

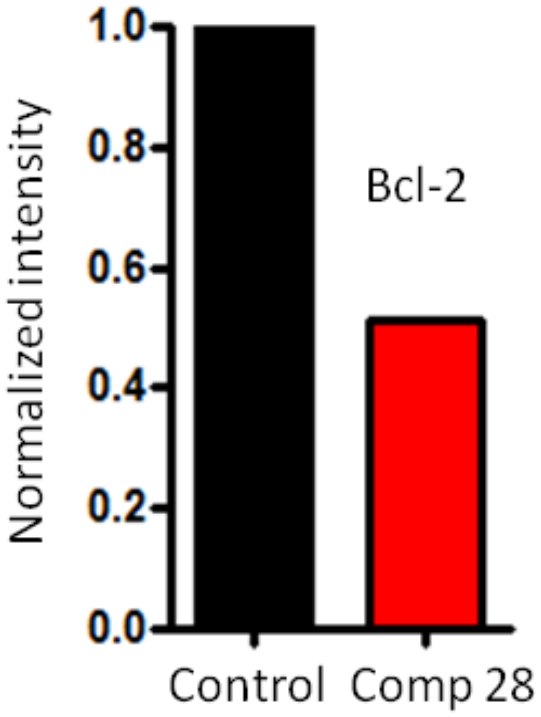


Figure S102: Quantification of Bcl-2 expression from western blot analysis after treatment with compound 28 at 24 h post-incubation.

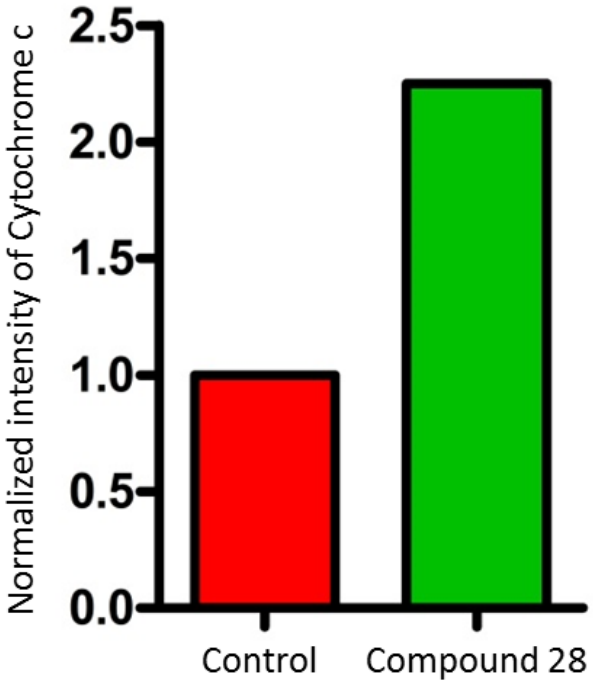


Figure S103: Quantification of cytochrome c expression from Western Blot analysis as a measure of mitochondrial damage after treatment with compound 28 at 24 h post-incubation.

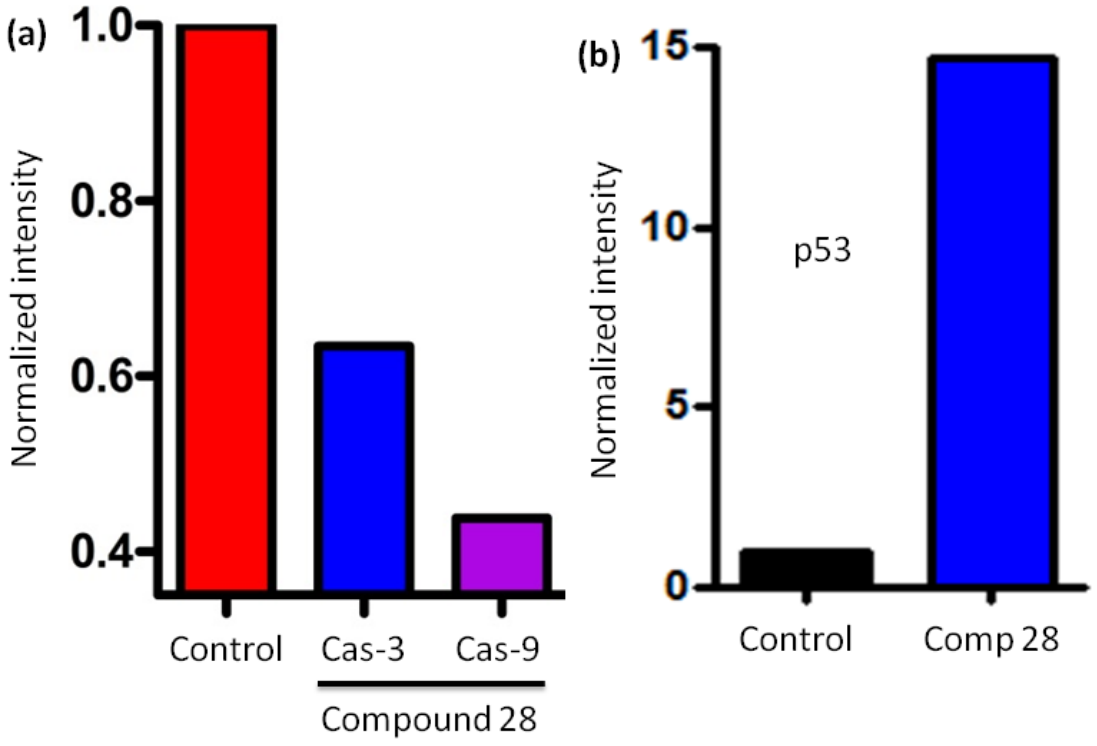


Figure S104: Quantification of (a) caspase-3, caspase-9 and (b) p53 expression from Western Blot analysis after treatment with compound 28 at 24 h post-incubation.

References:

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