Supporting information

Ionic liquid promoted one-pot synthesis of thiazole-imidazo[2,1-*b*] [1,3,4]thiadiazole hybrids and their antitubercular activity

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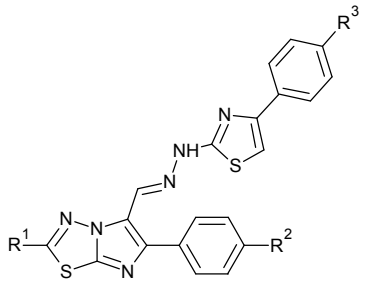
Experimental

The required solvents and raw materials were purchased from Merck, Loba Chemie Sigma Aldrich and Spectrochem Chemicals Pvt.Ltd. The progress of the reaction was monitored by TLC using pre coated aluminum sheets with 60 F254 silica gel (Merck KGaA). The Stuart SMP3 apparatus was used for recording the melting point of synthesized compounds. ^{1}H NMR spectra of the compounds were recorded using a Bruker 400 MHz NMR spectrometer using TMS as the internal standard. ^{13}C NMR spectra of the compounds were recorded using a Bruker 100 MHz NMR spectrometer. Elemental analysis was done using a Thermo electron corporation EA-112 series C, H, N, S analyzer. Mass spectra were recorded using a Waters micro mass Q-Tofmicro spectrometer with an ESI source.

Table S1. Optimization of reaction conditions for the one-pot synthesis of **5e**.

Entry	Solvent system	T (° C)	Time (h)	Isolated yield (%)
1	Ethanol	r.t.	18	-
2	Ethanol	50	18	10
3	Ethanol	80	18	15
4	[Bmim]Br and ethanol	r.t.	12	40
5	[Bmim]Br and ethanol	50	02	62
6	[Bmim]Br and ethanol	80	0.5	90

Table S2. The structural features, reaction time and yield of the target compounds (**5a-w**).



(**5a-5w**)

Entry	R^1	R^2	R^3	Time (min)	Yield (%)
5a	CH_3	CH_3	CH_3	45	85
5b	CH_3	CH_3	OCH_3	40	88
5c	CH_3	CH_3	Cl	30	90
5d	CH_3	CH_3	NO_2	30	89
5e	CH_3	CH_3	F	30	90
5f	CH_3	OCH_3	CH_3	40	84
5g	CH_3	OCH_3	OCH_3	40	80
5h	CH_3	OCH_3	Cl	30	85
5i	CH_3	OCH_3	NO_2	30	88
5j	CH_3	OCH_3	F	30	85
5k	CH_3	Cl	CH_3	30	83
5l	CH_3	Cl	OCH_3	30	87
5m	CH_3	Cl	Cl	30	94
5n	CH_3	Cl	F	30	88
5o	CF_3	OCH_3	CH_3	45	82
5p	CF_3	OCH_3	OCH_3	45	82
5q	CF_3	OCH_3	Cl	35	82
5r	CF_3	OCH_3	F	35	84
5s	CF_3	Cl	CH_3	35	88
5t	CF_3	Cl	OCH_3	35	86
5u	CF_3	Cl	Cl	30	94
5v	CF_3	Cl	NO_2	30	96
5w	CF_3	Cl	F	30	95

General procedure for the synthesis of target molecules 5a-5w

A mixture of imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde(1mmol), thiosemicarbazide (1 mmol) and the corresponding phenacyl bromide (1 mmol) was taken in ethanol (10 mL) in a dry 50 mL RBF. To this mixture ionic liquid [bmim]Br (2 mL) was added and the resulting mixture was stirred at 80 °C for 30-45 minutes. After the completion of the reaction (as monitored by TLC), water (10 mL) was added to the reaction mixture. The separated solid was filtered off and washed with water. The product was then recrystallized from ethanol.

1-((2-methyl-6-p-tolylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolylthiazol-2-yl)hydrazine (5a): Light yellow solid; m.p. 241-242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.28 (s, 1H, -NH), 8.43 (s, 1H, -CH), 8.32 – 8.24 (m, 2H, Ar-H), 8.15 – 8.07 (m, 2H, Ar-H), 7.86 – 7.79 (m, 2H, Ar-H), 7.74 (s, 1H, Ar-H), 7.33 (d, J = 7.9 Hz, 2H, Ar-H), 2.81 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.8, 161.7, 149.8, 147.3, 146.7, 145.3, 142.1, 138.0, 131.3, 131.0, 129.5, 128.4, 126.8, 123.6, 119.2, 105.3, 21.3, 21.2, 18.2; ESI-MS (*m/z*)= 445.4 (M + 1); anal. calcd (%) for $C_{23}H_{20}N_6S_2$: C, 62.14; H, 4.53; N, 18.90; S, 14.43. Found: C, 62.08; H, 4.58; N, 18.95; S, 14.38.

1-(4-(4-methoxyphenyl)thiazol-2-yl)-2-((2-methyl-6-p-tolylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)hydrazine (5b): Yellow solid; m.p. 239-240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.13 (s, 1H, -NH), 8.41 (s, 1H, -CH), 7.83-7.78 (m, 2H, Ar-H), 7.74 (s, 1H, Ar-H), 7.50-7.42 (m, 2H, Ar-H), 7.38 (d, J = 7.8Hz, 2H, Ar-H), 7.34-7.28 (m, 2H, Ar-H), 3.73 (s, 3H, OCH_3), 2.81 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 161.5, 150.2, 147.1, 145.1, 138.0, 130.2, 130.9, 129.5, 128.4, 128.1, 127.8, 119.2, 116.1, 115.8, 104.2, 55.7, 21.3, 18.2; ESI-MS (*m/z*):= 461.1 (M + 1); anal. calcd (%) for $C_{23}H_{20}N_6OS_2$: C, 59.98; H, 4.38; N, 18.25; S, 13.92. Found: C, 60.04; H, 4.36; N, 18.28; S, 13.98.

1-(4-(4-chlorophenyl)thiazol-2-yl)-2-((2-methyl-6-p-tolylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)hydrazine (5c): Light green solid; m.p. 249-250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.13 (s, 1H, -NH), 8.43 (s, 1H, -CH), 7.92 – 7.78 (m, 4H, Ar-H), 7.33 – 7.16 (m, 5H, Ar-H), 2.81 (s, 3H, CH_3), 2.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 161.5, 148.2, 146.3, 144.1, 137.0, 131.3, 130.7, 129.3, 128.5, 128.0, 127.9, 119.2, 116.0, 115.8, 103.2, 21.3, 18.2; ESI-MS (*m/z*):= 464.0 (M + 1); anal. calcd (%) for

$C_{22}H_{17}ClN_6S_2$: C, 56.83; H, 3.68; N, 18.07; S, 13.79. Found: C, 56.88; H, 3.66; N, 18.10; S, 13.78.

1-((2-methyl-6-p-tolylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-nitrophenyl) thiazol-2-yl)hydrazine (5d): Yellow solid; m.p. 257-258 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.28 (s, 1H, -NH), 8.43 (s, 1H, -CH), 8.32 – 8.24 (m, 2H, Ar-H), 8.15 – 8.07 (m, 2H, Ar-H), 7.86 – 7.79 (m, 2H, Ar-H), 7.74 (s, 1H, Ar-H), 7.33 (d, J = 7.9 Hz, 2H, Ar-H), 2.81 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.8, 161.7, 148.8, 147.3, 146.6, 145.3, 141.0, 138.0, 131.3, 131.0, 129.5, 128.4, 126.8, 124.5, 119.2, 109.3, 21.3, 18.2; ESI-MS (*m/z*):= 475.90 (M + 1); anal. calcd (%) for $C_{12}H_{17}N_7O_2S_2$: C, 55.56; H, 3.60; N, 20.62; S, 13.49. Found: C, 55.49; H, 3.58; N, 20.55; S, 13.38.

1-(4-(4-fluoro phenyl)thiazol-2-yl)-2-((2-methyl-6-p-tolyl imidazo[2,1-b][1,3,4] thiadiazol-5-yl) methylene)hydrazine (5e): Off white solid; m.p. 244-246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.14 (s, 1H, -NH), 8.41 (s, 1H, -CH), 7.93 – 7.81 (m, 4H, Ar-H), 7.31 (t, J = 3.9 Hz, 3H, Ar-H), 7.24 (t, J = 8.9 Hz, 2H, Ar-H), 2.80 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 161.7, 149.3, 147.2, 145.1, 138.0, 131.2, 130.9, 129.5, 128.4, 128.0, 128.0, 119.2, 116.0, 115.8, 104.2, 21.3, 18.2; ESI-MS (*m/z*):= 449.0 (M + 1); anal. calcd (%) for $C_{12}H_{17}FN_6S_2$: C, 58.91; H, 3.82; N, 18.74; S, 14.30. Found: C, 58.89; H, 3.78; N, 18.50; S, 14.32.

1-((6-(4-methoxyphenyl)-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolyl thiazol-2-yl)hydrazine (5f): Brown solid; m.p. 236-237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.24 (s, 1H, -NH), 8.41 (s, 1H, -CH), 7.92 – 7.79 (m, 4H, Ar-H), 7.34 – 7.18 (m, 5H, Ar-H), 3.84 (s, 3H, OCH_3), 2.80 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 161.7, 149.3, 147.2, 145.1, 138.0, 131.2, 130.9, 129.5, 128.4, 128.0, 127.9, 119.2, 116.0, 115.8, 104.2, 55.8, 21.3, 18.2; ESI-MS (*m/z*):= 461.2 (M + 1); anal. calcd (%) for $C_{23}H_{20}N_6OS_2$: C, 59.98; H, 4.38; N, 18.25; S, 13.92. Found: C, 59.91; H, 4.39; N, 18.30; S, 13.88.

1-((6-(4-methoxyphenyl)-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazine (5g): Light brown solid; m.p. 243-245 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H, -NH), 8.42 (s, 1H, -CH), 7.84 (d, J = 8.8 Hz, 2H, Ar-H), 7.78 (d, J = 7.6 Hz, 2H, Ar-H), 7.19 (s, 1H, Ar-H), 7.11 (d, J = 7.4 Hz, 2H, Ar-H), 6.97 (d, J = 9.2Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.3, 160.1, 159.3, 144.3, 149.9, 147.1, 146.7, 130.4, 130.0,

127.4, 127.3, 119.7, 118.8, 115.3, 114.6, 102.5, 55.7, 55.6, 18.2; ESI-MS (*m/z*):= 477.4 (M + 1); anal. calcd (%) for $C_{23}H_{20}N_6O_2S_2$: C, 57.97; H, 4.23; N, 17.63; S, 13.46. Found: C, 57.91; H, 4.29; N, 17.40; S, 13.58.

1-(4-(4-chlorophenyl)thiazol-2-yl)-2-((6-(4-methoxyphenyl)-2-methylimidazo[2,1-b][1,3,4] thiadiazol-5-yl)methylene)hydrazine (5h): Off white solid; m.p. 203-204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.09 (s, 1H, -NH), 8.40 (s, 1H, -CH), 7.94 – 7.80 (m, 4H, Ar-H), 7.50 – 7.42 (m, 2H, Ar-H), 7.39 (s, 1H, Ar-H), 7.10 – 7.00 (m, 2H, Ar-H), 3.82 (s, 3H, OCH_3), 2.79 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.6, 161.5, 159.7, 149.4, 147.0, 145.1, 133.8, 132.4, 131.2, 129.9, 129.0, 127.7, 126.3, 118.8, 114.3, 105.1, 55.7, 18.1; ESI-MS (*m/z*):= 481.0 (M + 1); anal. calcd (%) for $C_{22}H_{17}ClN_6OS_2$: C, 54.94; H, 3.56; N, 17.47; S, 13.33. Found: C, 54.89; H, 3.58; N, 17.50; S, 13.32.

1-((6-(4-methoxyphenyl)-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-nitro phenyl)thiazol-2-yl)hydrazine (5i): Yellow solid; m.p. 247-248 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.22 (s, 1H, -NH), 8.41 (s, 1H, -CH), 8.31 – 8.23 (m, 2H, Ar-H), 8.15 – 8.06 (m, 2H, Ar-H), 7.92 – 7.84 (m, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.11 – 7.02 (m, 2H, Ar-H), 3.83 (s, 3H, OCH_3), 2.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.8, 161.6, 159.7, 148.8, 147.1, 146.6, 145.0, 141.0, 131.3, 129.9, 126.7, 126.2, 124.5, 118.7, 114.3, 109.2, 55.7, 18.1; ESI-MS (*m/z*):= 492.2 (M + 1); anal. calcd (%) for $C_{22}H_{17}N_7O_3S_2$: C, 53.76; H, 3.49; N, 19.95; S, 13.05. Found: C, 53.80; H, 3.48; N, 19.80; S, 13.12.

1-(4-(4-fluorophenyl)thiazol-2-yl)-2-((6-(4-methoxyphenyl)-2-methylimidazo[2,1-b][1,3,4] thiadiazol-5-yl)methylene)hydrazine (5j): Green solid; m.p. 239-240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.12 (s, 1H, -NH), 8.41 (s, 1H, -CH), 7.84 – 7.70 (m, 4H, Ar-H), 7.40 – 7.32 (m, 2H, Ar-H), 7.38 (s, 1H, Ar-H), 7.10 – 7.00 (m, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 2.79 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.6, 162.5, 159.7, 149.4, 147.0, 146.1, 133.8, 132.4, 130.2, 127.9, 129.0, 127.7, 126.3, 118.8, 115.3, 105.1, 55.6, 18.1; ESI-MS (*m/z*):=465.2 (M + 1); anal. calcd (%) for $C_{22}H_{17}FN_6OS_2$: C, 56.88; H, 3.69; N, 18.09; S, 13.81. Found: C, 56.82; H, 3.68; N, 18.10; S, 13.91.

1-((6-(4-chlorophenyl)-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolylthiazol-2-yl)hydrazine (5k): Yellow solid; m.p. 249-250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.18 (s, 1H, -NH), 8.41 (s, 1H, -CH), 8.21 – 8.18 (m, 2H, Ar-H), 8.15 – 8.06 (m, 2H, Ar-H), 7.82 – 7.74 (m, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.11 – 7.02 (m, 2H, Ar-

H), 2.82 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.8, 162.6, 159.7, 148.8, 147.1, 146.6, 145.0, 141.0, 131.3, 129.9, 126.8, 126.2, 125.1, 118.7, 114.3, 109.2, 21.3, 18.1; ESI-MS (*m/z*):= 465.3 (M + 1); anal. calcd (%) for $C_{22}H_{17}ClN_6S_2$: C, 56.83; H, 3.68; N, 18.07; S, 13.79. Found: C, 56.81; H, 3.62; N, 18.12; S, 13.71.

1-((6-(4-chlorophenyl)-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazine (5l): Light yellow solid; m.p. 201-202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.22 (s, 1H, -NH), 8.41 (s, 1H, -CH), 8.31 – 8.23 (m, 2H, Ar-H), 8.10 – 8.06 (m, 2H, Ar-H), 7.82 – 7.74 (m, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.11 – 7.02 (m, 2H, Ar-H), 3.83 (s, 3H, OCH_3), 2.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.8, 161.6, 159.7, 148.8, 147.1, 146.5, 145.0, 142.0, 131.4, 129.9, 126.79, 126.2, 124.5, 118.7, 114.3, 109.2, 55.7, 18.2; ESI-MS (*m/z*):= 481.2 (M + 1); anal. calcd (%) for $C_{22}H_{17}ClN_6OS_2$: C, 54.94; H, 3.56; N, 17.47; S, 13.33. Found: C, 54.91; H, 3.52; N, 17.42; S, 13.31.

1-((6-(4-chlorophenyl)-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (5m): Orange solid; m.p. 235-236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.27 (s, 1H, -NH), 8.44 (s, 1H, -CH), 8.08 – 8.01 (m, 2H, Ar-H), 7.91 – 7.83 (m, 2H, Ar-H), 7.61 – 7.54 (m, 2H, Ar-H), 7.51 – 7.39 (m, 3H, Ar-H), 2.81 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.4, 162.2, 149.4, 147.0, 143.4, 133.8, 133.0, 132.9, 132.4, 130.8, 130.1, 129.0, 128.8, 127.7, 119.7, 105.2, 18.1; ESI-MS (*m/z*):= 484.80 (M + 1); anal. calcd (%) for $C_{21}H_{14}Cl_2N_6O_3S_2$: C, 51.96; H, 2.91; N, 17.31; S, 13.21. Found: C, 51.88; H, 2.94; N, 17.38; S, 13.22.

1-((6-(4-chlorophenyl)-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-fluorophenyl)thiazol-2-yl)hydrazine (5n): Yellow solid; m.p. 246-248 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H, -NH), 8.43 (s, 1H, -CH), 7.91– 7.82 (m, 2H, Ar-H), 7.71 – 7.63 (m, 2H, Ar-H), 7.58 – 7.54 (m, 2H, Ar-H), 7.48 – 7.39 (m, 3H, Ar-H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.3, 160.8, 148.4, 146.6, 145.2, 139.3, 133.7, 132.3, 131.5, 131.4, 129.0, 128.8, 127.7, 122.7, 122.1, 119.7, 105.3, 18.1; ESI-MS (*m/z*):= 469.2 (M +1); anal. calcd (%) for $C_{21}H_{14}ClFN_6S_2$: C, 53.78; H, 3.01; N, 17.92; S, 13.68. Found: C, 53.71; H, 3.05; N, 17.98; S, 13.62.

1-((6-(4-methoxyphenyl)-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolylthiazol-2-yl)hydrazine (5o): Light yellow solid; m.p. 238-239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.25 (s, 1H, -NH), 8.43 (s, 1H, -CH), 7.86 (d, J = 8.4 Hz,

2H, Ar-H), 7.781 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.197 (s, 1H, Ar-H), 7.11-7.10 (m, 2H, Ar-H), 6.98 (d, *J* = 9.2Hz, 2H, Ar-H), 3.84 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.3, 160.1, 159.3, 149.9, 147.1, 146.7, 143.2, 130.4, 130.0, 127.4, 127.3, 125.8, 123.5, 119.7, 114.6, 114.4, 102.5, 55.7, 21.4; ESI-MS (*m/z*):= 515.2 (M + 1); anal. calcd (%) for $C_{23}H_{17}F_3N_6OS_2$: C, 53.69; H, 3.33; N, 16.33; S, 12.46. Found: C, 53.61; H, 3.29; N, 16.38; S, 12.42.

1-((6-(4-methoxyphenyl)-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl) methylene)-2-(4-(4-methoxy phenyl) thiazol-2-yl) hydrazine (5p): Yellow solid; m.p. 232-233 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.42 (s, 1H, -CH), 7.86 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.78 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.19 (s, 1H, Ar-H), 7.11 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.97 (d, *J* = 9.2Hz, 2H, Ar-H), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.3, 160.1, 159.3, 149.9, 147.2, 146.7, 130.4, 130.0, 127.5, 127.4, 125.8, 119.7, 114.6, 114.4, 102.5, 55.7, 55.6; ESI-MS (*m/z*):= 530.90 (M + 1); anal. calcd (%) for $C_{23}H_{17}F_3N_6O_2S_2$: C, 52.07; H, 3.23; N, 15.84; S, 12.09. Found: C, 51.98; H, 3.24; N, 15.78; S, 12.12.

1-(4-(4-chlorophenyl)thiazol-2-yl)-2-((6-(4-methoxyphenyl)-2-(trifluoromethyl)imidazo [2,1-b][1,3,4]thiadiazol-5-yl)methylene)hydrazine (5q): Light brown solid; m.p. 236-237 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.25 (s, 1H, -NH), 8.43 (s, 1H, -CH), 7.91 – 7.81 (m, 4H, Ar-H), 7.52 – 7.42 (m, 3H, Ar-H), 7.16 – 7.07 (m, 2H, Ar-H), 3.85 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 160.1, 149.5, 147.1, 146.7, 133.8, 132.4, 130.2, 130.0, 129.0, 127.7, 125.8, 119.7, 114.6, 105.4, 55.7**;** ESI-MS (*m/z*):= 534.80 (M + 1); anal. calcd (%) for $C_{22}H_{14}ClF_3N_6OS_2$: C, 49.39; H, 2.64; N, 15.71; S, 11.99. Found: C, 49.40; H, 2.66; N, 15.78; S, 11.92.

1-(4-(4-fluoro phenyl) thiazol-2-yl)-2-((6-(4-methoxy phenyl)-2-(trifluoromethyl) imidazo [2,1-b][1,3,4]thiadiazol-5-yl)methylene)hydrazine (5r): Yellow solid; m.p. 267-268 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.14 (s, 1H, -NH), 8.41 (s, 1H, -CH), 7.84 (m, 2H, Ar-H), 7.61 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.52 – 7.42 (m, 2H, Ar-H), 7.35 (s, 1H, Ar-H), 7.26 – 7.18 (m, 2H, Ar-H), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.4, 159.1, 149.5, 148.1, 146.8, 133.9, 132.4, 130.3, 130.0, 129.1, 126.7, 125.8, 120.1, 114.6, 105.4, 55.7; ESI-MS (*m/z*):= 519.4 (M + 1); anal. calcd (%) for $C_{22}H_{14}F_4N_6OS_2$: C, 50.96; H, 2.72; N, 16.21; S, 12.37. Found: C, 50.90; H, 2.78; N, 16.31; S, 12.32.

1-((6-(4-chlorophenyl)-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolylthiazol-2-yl)hydrazine (5s): Yellow solid; m.p. 264-265 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H, -NH), 8.45 (s, 1H, -CH), 7.87-7.81 (m, 2H, Ar-H), 7.76 (d, J = 8.8 Hz, 2H, Ar-H), 7.61 (d, J = 8.8 Hz, 2H, Ar-H), 7.47 – 7.43 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 160.1, 149.5, 147.1, 146.7, 143.2, 133.8, 132.4, 130.2, 130.0, 129.0, 127.7, 123.4, 125.8, 119.7, 114.6, 105.4, 22.3; ESI-MS (*m/z*):= 519.3 (M + 1): anal. calcd (%) for $C_{22}H_{14}ClF_3N_6S_2$: C, 50.92; H, 2.72; N, 16.19; S, 12.36. Found: C, 50.82; H, 2.68; N, 16.18; S, 12.44.

1-((6-(4-chlorophenyl)-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl) methylene)-2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazine (5t): Yellow solid; m.p. 228-229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H, -NH), 8.45 (s, 1H, -CH), 7.97 (d, J = 8.8 Hz, 2H, Ar-H), 7.86 (d, J = 8.4 Hz, 2H, Ar-H), 7.61 (d, J = 8.4 Hz, 2H, Ar-H), 7.47 – 7.43 (m, 3H, Ar-H), 3.82(s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 160.1, 149.5, 147.1, 146.7, 144.2, 133.8, 132.4, 130.2, 130.0, 129.0, 127.7, 125.8, 123.2 119.7, 114.6, 105.4, 55.7; ESI-MS (*m/z*):= 535.20 (M + 1); anal. calcd (%) for $C_{24}H_{14}ClF_3N_6OS_2$: C, 49.39; H, 2.64; N, 15.71; S, 11.99. Found: C, 49.42; H, 2.68; N, 15.68; S, 11.94.

1-((6-(4-chlorophenyl)-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (5u): Light Yellow solid; m.p. 240-241 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H, -NH), 8.45 (s, 1H, -CH), 7.97 (d, J = 8.4Hz, 2H, Ar-H), 7.86 (d, J = 8.8 Hz, 2H, Ar-H), 7.61 (d, J =8.8Hz, 2H, Ar-H), 7.47 – 7.43 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.3, 160.8, 149.7, 146.6, 145.2, 133.7, 132.3, 131.5, 131.5, 130.2, 129.6, 129.1, 128.0, 127.9, 120.7, 116.0, 115.8, 104.5; ESI-MS (*m/z*):= 539.10 (M + 1); anal. calcd (%) for $C_{21}H_{11}Cl_2F_3N_6S_2$: C, 46.76; H, 2.06; N, 15.58; S, 11.89. Found: C, 46.66; H, 2.08; N, 15.68; S, 11.92.

1-((6-(4-chlorophenyl)-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-nitro phenyl)thiazol-2-yl)hydrazine (5v): Yellow solid; m.p. 261-262 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.30 (s, 1H, -NH), 8.46 (s, 1H, -CH), 7.96 -7.90 (m, 2H, Ar-H, Ar-H), 7.86 (d, J = 8.4 Hz, 2H, Ar-H), 7.58 (d, J =8.6 Hz, 2H, Ar-H), 7.45 – 7.41 (m, 2H, Ar-H), 7.35 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.4, 160.2, 148.4, 147.2, 146.3, 134.2, 131.4, 130.3, 130.0, 129.0, 128.2, 127.7, 124.3, 120.7, 115.8, 114.6, 105.4; ESI-MS (*m/z*):= 550.20 (M + 1); anal. calcd (%) for $C_{21}H_{11}ClF_3N_7O_2S_2$: C, 45.86; H, 2.02; N, 17.83; S, 11.66. Found: C, 45.76; H, 2.04; N, 17.85; S, 11.72.

1-((6-(4-chlorophenyl)-2-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-fluorophenyl)thiazol-2-yl)hydrazine (5w): Yellow solid; m.p. 263-264 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.24 (s, 1H, -NH), 8.45 (s, 1H), 8.01 – 7.94 (m, 2H), 7.92 – 7.84 (m, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.35 (s, 1H), 7.24 (t, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 168.3, 160.8, 149.7, 146.6, 145.2, 133.7, 132.3, 131.5, 131.5, 130.2, 129.6, 129.1, 128.0, 127.9, 120.7, 116.0, 115.8, 104.5; ESI-MS (*m/z*):= 523.10 (M + 1); anal. calcd (%) for $C_{21}H_{11}ClF_4N_6S_2$: C, 48.23; H, 2.12; N, 16.07; S, 12.26. Found: C, 48.20; H, 2.13; N, 16.10; S, 12.32.

Antitubercular studies

Two-fold serial dilutions of each test compound/drug were prepared and incorporated into Middlebrook 7H11 agar medium with oleic acid, albumin, dextrose, and catalase (OADC) growth supplement to get final concentrations of 50, 25, 12.5, 6.25, 3.13, 1.56 and 0.78 µg/mL. Inoculum of MTB H37Rv ATCC 27294/XDR-TB was prepared from fresh Middlebrook 7H11 agar slants with OADC (Difco) growth supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of ~10^7 cfu/mL. Five microliters of this bacterial suspension was spotted onto 7H11 agar tubes containing different concentrations of the drug as discussed above. The tubes were incubated at 37 °C, and final readings (as MIC in mg/mL) were determined after 28 days. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.

Anti-bacterial studies

Minimum concentration of compounds required for the inhibition of bacteria *S. aureus* (ATTC 25923), *P. aeruginosa* (ATCC 27853) and *E. coli* (ATTC 25922) was determined using compound concentration ranging from 3.125–50 µg/mL. Test compounds are dissolved in DMSO and serially diluted to 50, 25, 12.5, 6.25, 3.125 µg/mL of concentration. In a 96 well plate 50 µL of bacterial was taken and 50 µL of serially diluted above compounds were added to each well and mixed. Incubated the mixture for 12 h and observed each well for the bacterial growth. The lowest concentration at which no microbial growth found was taken as MIC. For the conformation, 10 µL of the mixture from each well was spread on a nutrient agar plate and incubated to check for any bacterial growth. Ciprofloxacin was used as standard for bacteria screening.

Cytotoxicity studies

The NIH 3T3 mouse embryonic fibroblasts cell line was procured from National Centre for Cell Sciences (NCCS), Pune, India. The cell lines were maintained in 96 wells micro titer plate containing MEM media supplemented with 10% heat inactivated fetal calf serum (FCS), containing 5% of mixture of Gentamicin (10µg), Penicillin (100 Units/ml) and Streptomycin (100µg/ml) in presence of 5% CO_2 at 37ºC for 48-72 hours. For cytotoxicity studies, each weighed test drugs were separately dissolved in distilled DMSO to obtain a stock solution of 1 mg/ml concentration and sterilized by filtration. Serial two fold dilutions were prepared from this for carrying out MTT assay. The cells were then exposed to different concentrations of drug and kept for incubation for 48 h. The control group contains only DMSO. After the incubation, stock solution of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) (20 µL, 5mg/mL in sterile PBS) was added to each well and cells were incubated for additional 2 - 3 h at 5% CO_2 atmosphere. After careful removal of incubation medium from the incubator, 100 µL of DMSO was added and the plates were gently shaken to re-suspend formed formazan and waited for few minutes to form a homogenized color. The suspension was placed on a micro vibrator for 5 minute, and absorbances of wells containing cells and blanks were recorded at 490 nm. The experiment was executed in triplicate. The mean of the absorbance of wells was calculated with the same treatment after subtracting of blank absorbance. The results were normalized by considering control wells as 100% (maximum absorbance obtained), expressing then the results as percentage of controls. Percentage of growth inhibition was calculated from below equation.

$$\% \text{ Growth Inhibition} = 100 - \left(\frac{\text{Mean OD of individual test group}}{\text{Mean OD of control group}} \text{ X } 100 \right)$$

Molecular docking studies

The crystal structure of InhA (PDB code: 1P44) and CYP121 (PDB code: 4KTF) from species of *Mycobacterium tuberculosi*s for docking explorations were taken from Protein Data Bank. The protein was initially subjected to various processes such as removal of water molecules and removal of heteroatoms etc., using the Protein Preparation Wizard of Schrödinger 2015.[1] The molecules were sketched using Maestro panel of Schrodinger[2] and were subjected for all possible conformation generation using LigPrep module.[1] These molecules were docked to the active site of protein using extra precision (XP) mode of Glide.[3]

Table S3. Docking score of the active compounds and list of interacting amino acid residues.

Compound ID	1P44		4KTF	
	Docking score (Kcal/mol)	**Interacting amino acid residues**	**Docking score (kcal/mol)**	**Interacting amino acid residues**
5d	-8.89	Phe 149, Tyr 158, Ala 157, Gly 104	-7.38	Phe 230, Trp 182, Asp 182
5e	-7.98	Glu 219, Tyr 158	-8.11	Phe 230, Trp 182
5h	-7.9	Ala 157, Gly 104, Phe 149, Tyr 158	-8.34	Val 82, Gln 385
5i	-8.11	Ala 157, Gly 104, Phe 149, Tyr 158	-8.11	Trp 182
5o	-6.71	Phe 149	-8.53	Ala 167, Trp 182
5r	-8.44	Phe 149	-8.62	Ala 167, Trp 182
5s	-7.23	Phe 149, Tyr 158	-8.27	Phe 168, Trp182, Ala 167
5t	-7.43	Phe 149	-6.46	Phe 168, Trp 182, Thr 77, Gln 385
5w	-6.28	-	-9.75	Trp 182

References

1. Schrödinger Suite 2015-1 Protein Preparation Wizard; Epik version 3.1, Schrödinger, LLC, New York, NY, 2015; Impact version 6.6, Schrödinger, LLC, New York, NY, 2015; Prime version 3.9, Schrödinger, LLC, New York, NY, 2015.
2. Maestro, version 10.1, Schrödinger, LLC, New York, NY, 2015.
3. Glide, version 6.6, Schrödinger, LLC, New York, NY, 2015.

The ^{1}H NMR, ^{13}C NMR and mass spectra of selected compounds are given below.

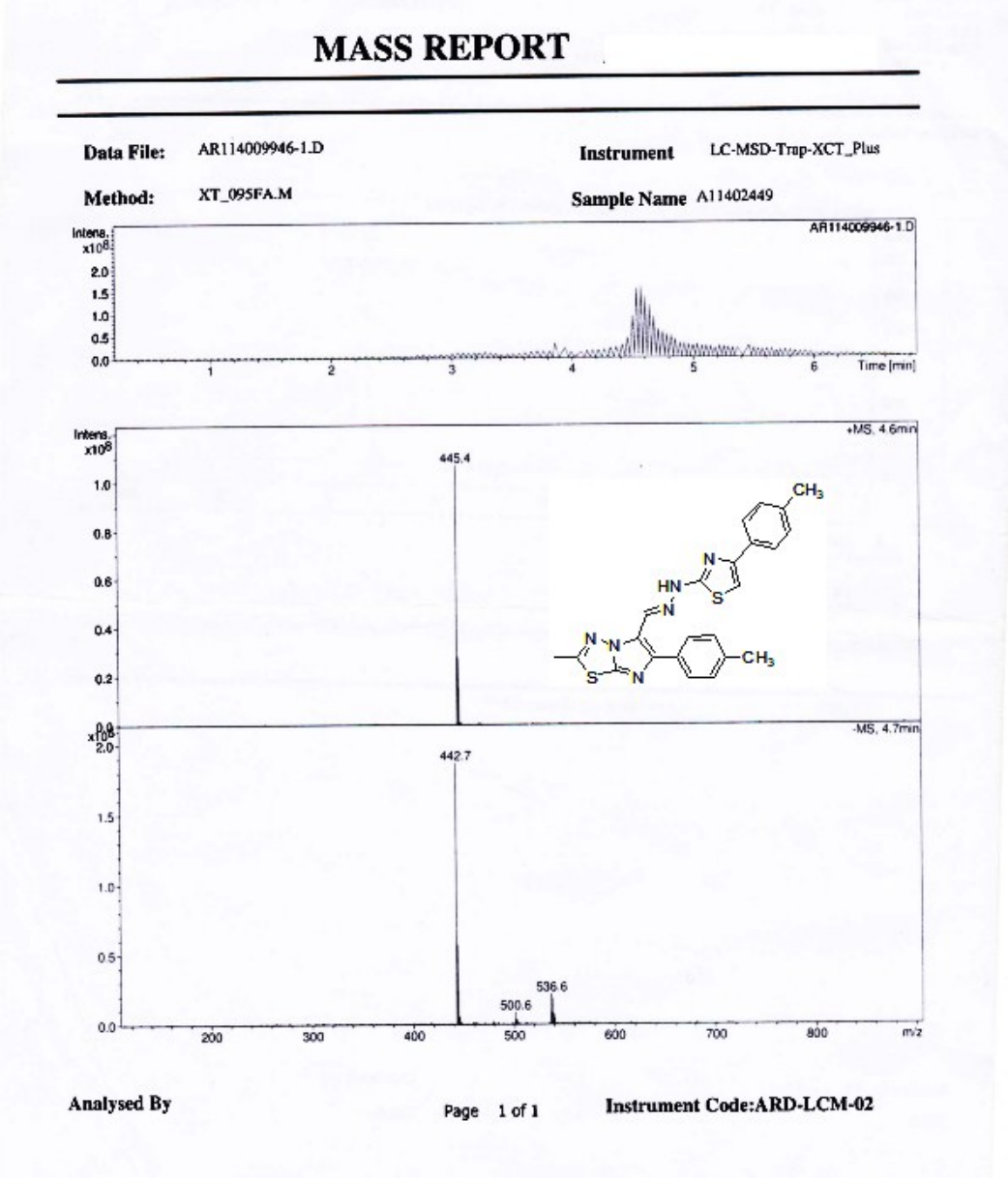


Figure S1. MS spectrum of **5a**

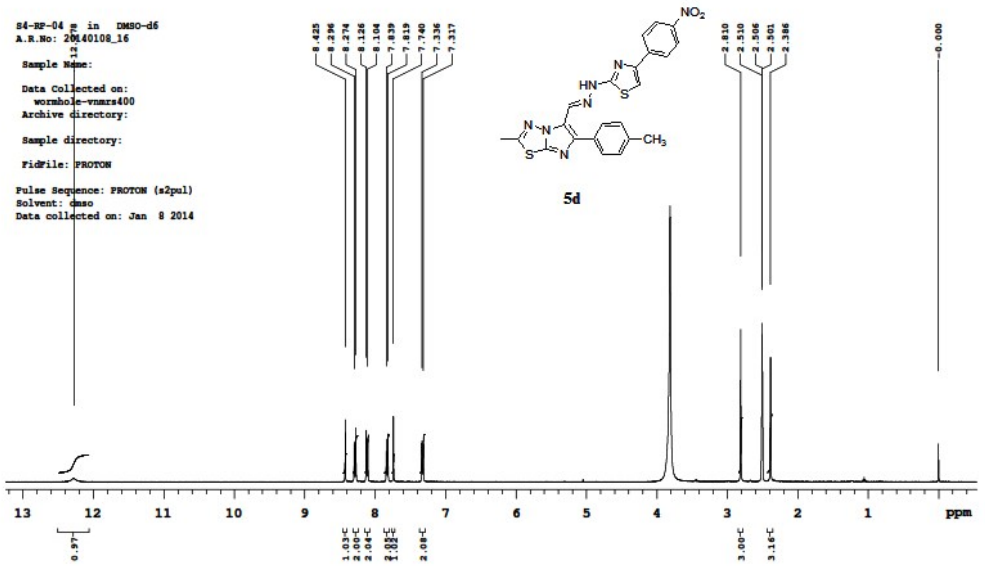


Figure S2. [1]H NMR spectrum of **5d**

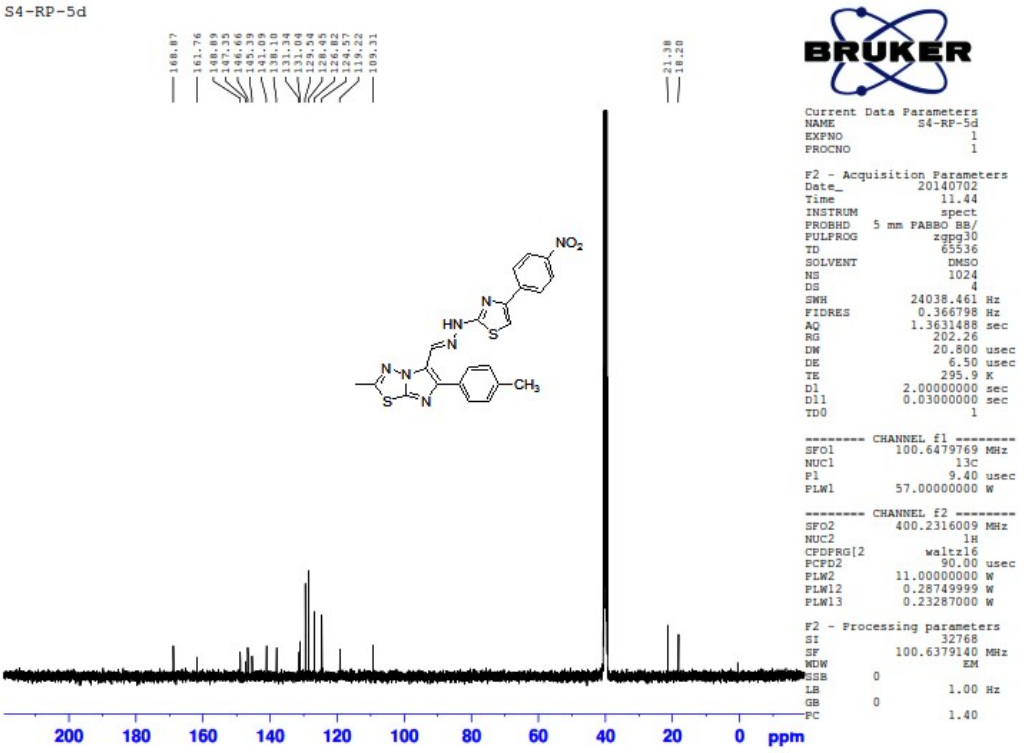


Figure S3. [13]C NMR spectrum of **5d**

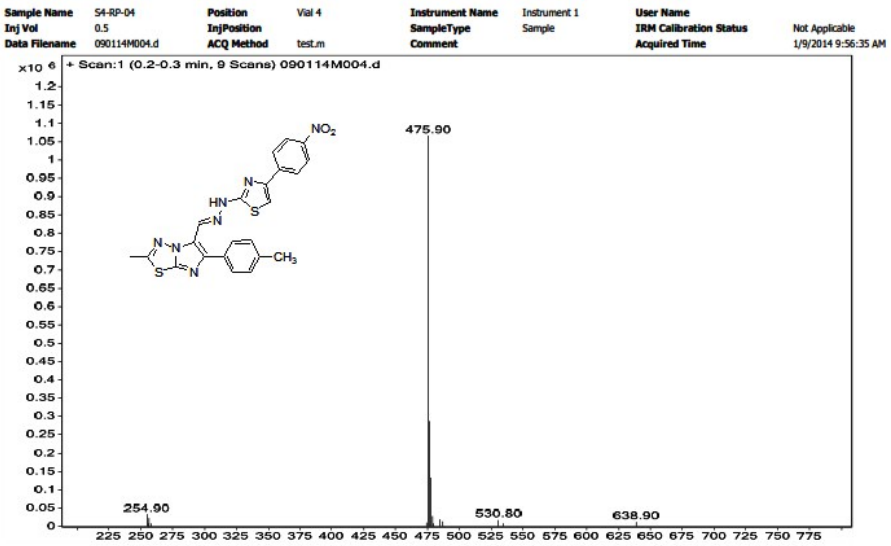


Figure S4. MS spectrum of **5d**

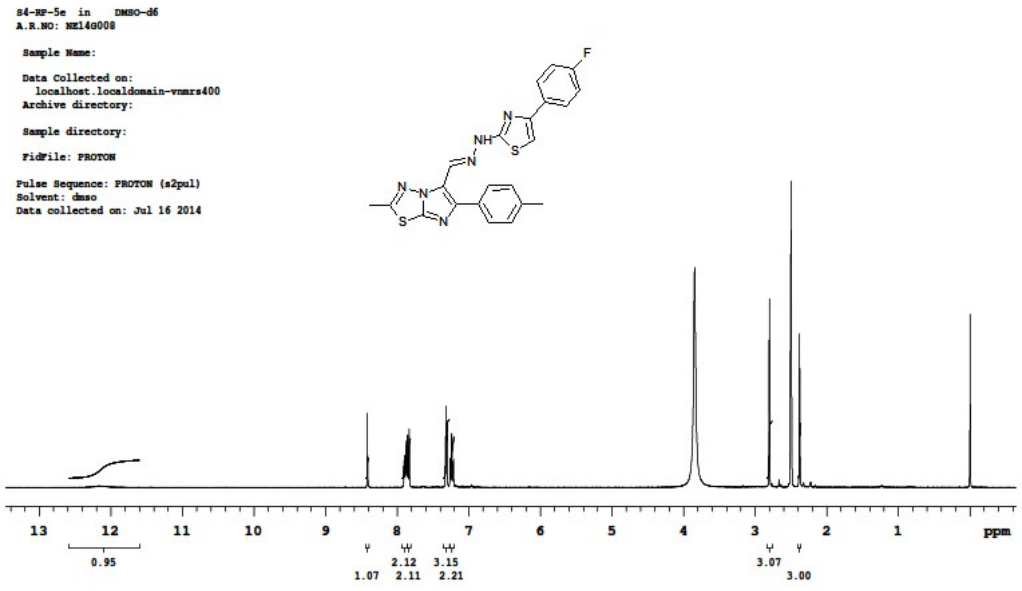


Figure S5. ^{1}H NMR spectrum of **5e**

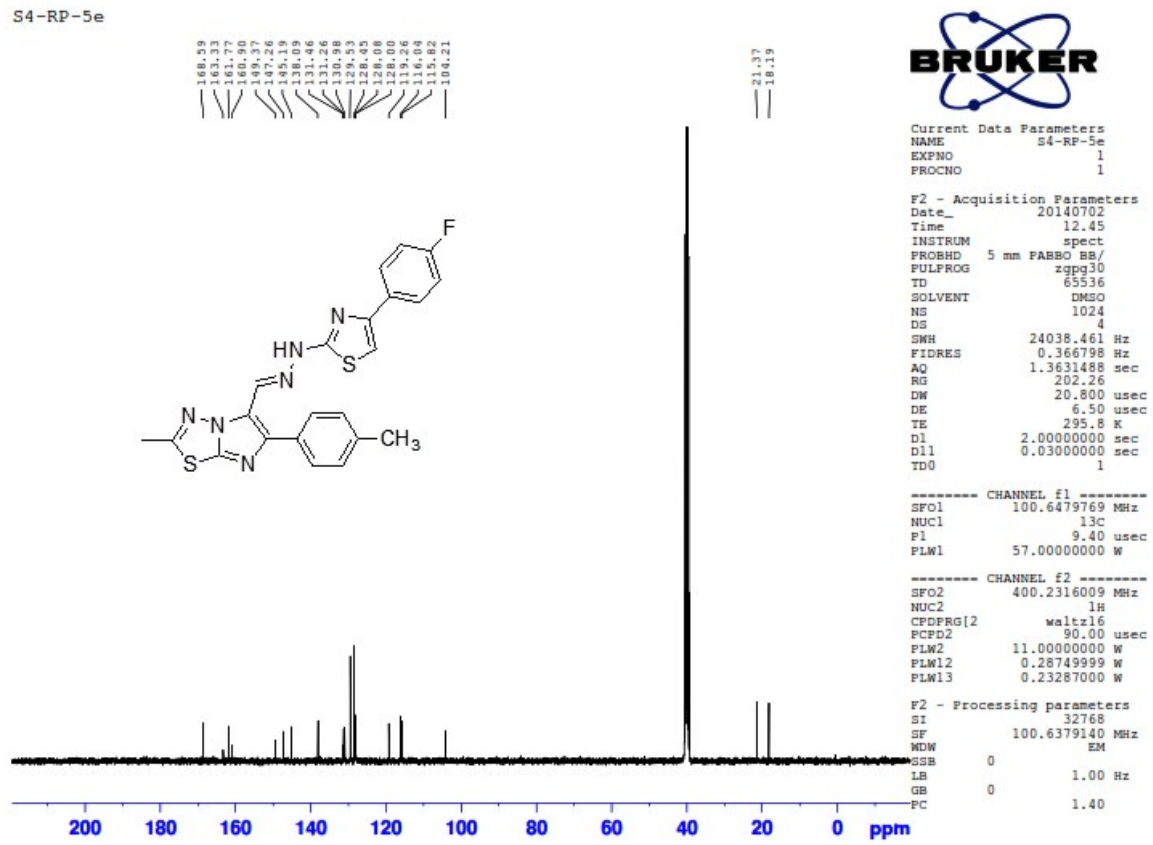


Figure S6. ^{13}C NMR spectrum of **5e**

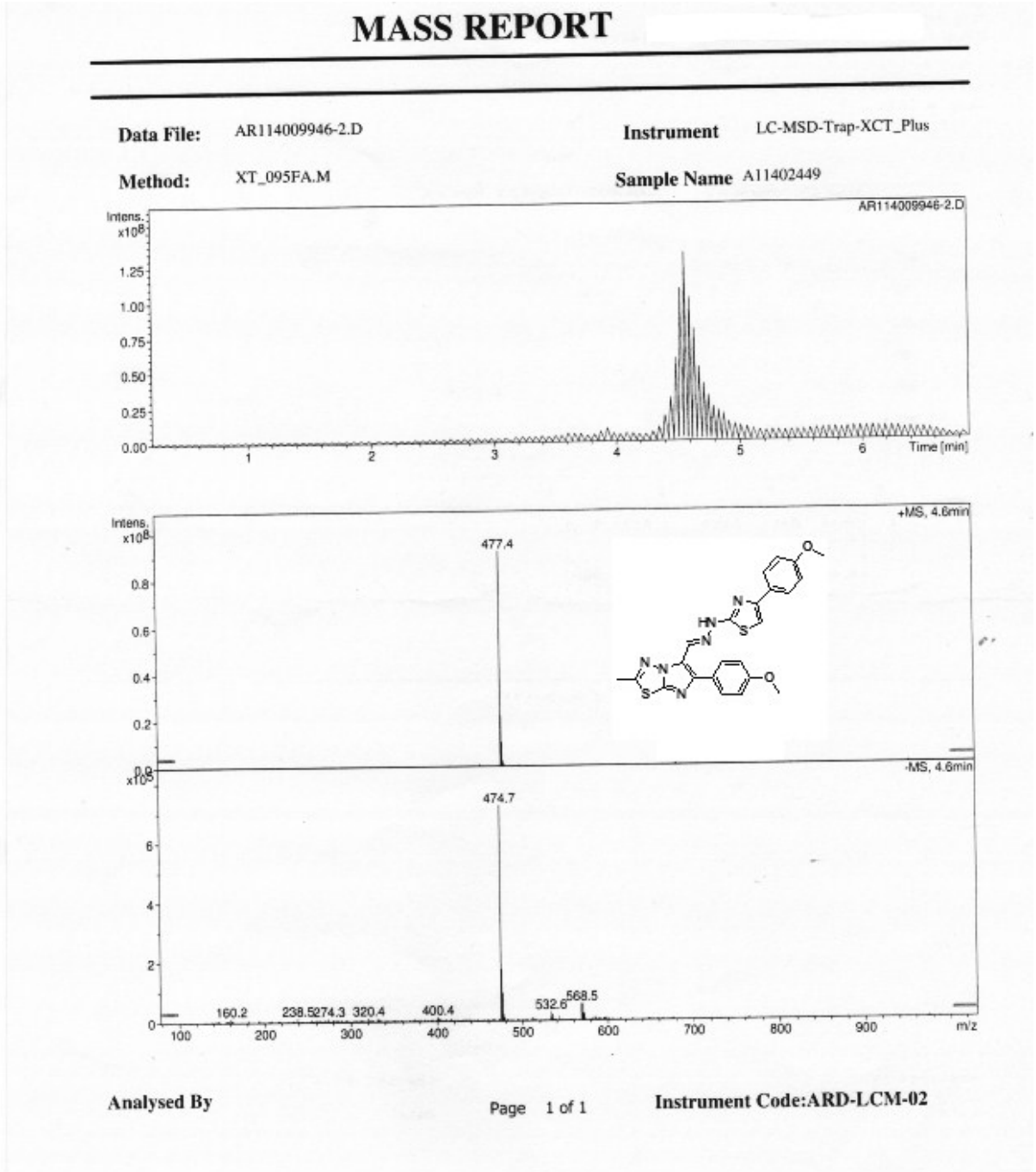


Figure S7. MS spectrum of **5g**

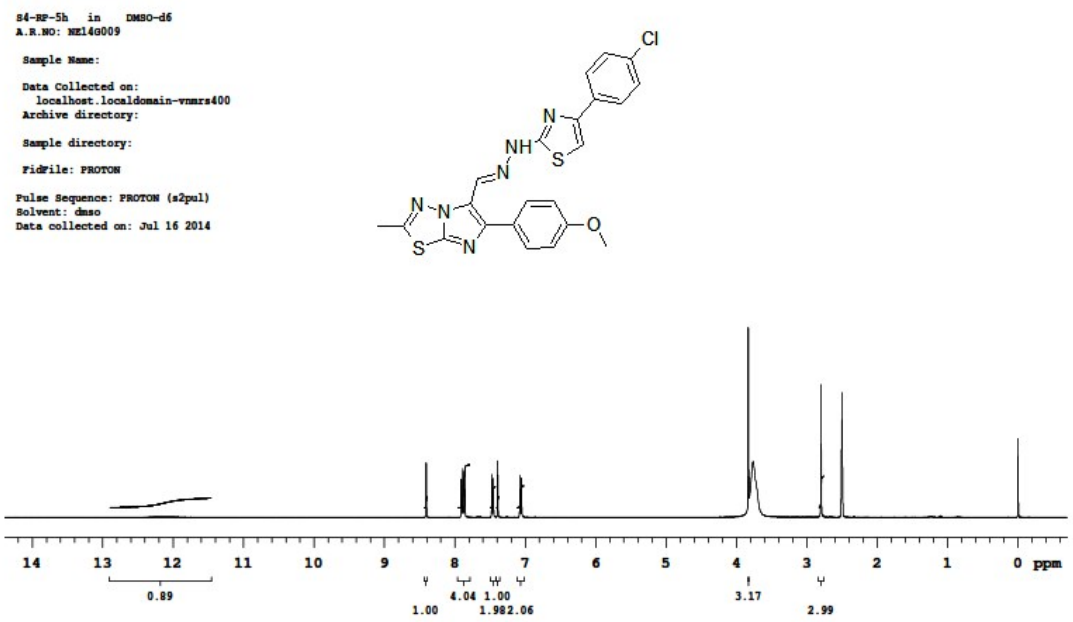


Figure S8. [1]H NMR spectrum of **5h**

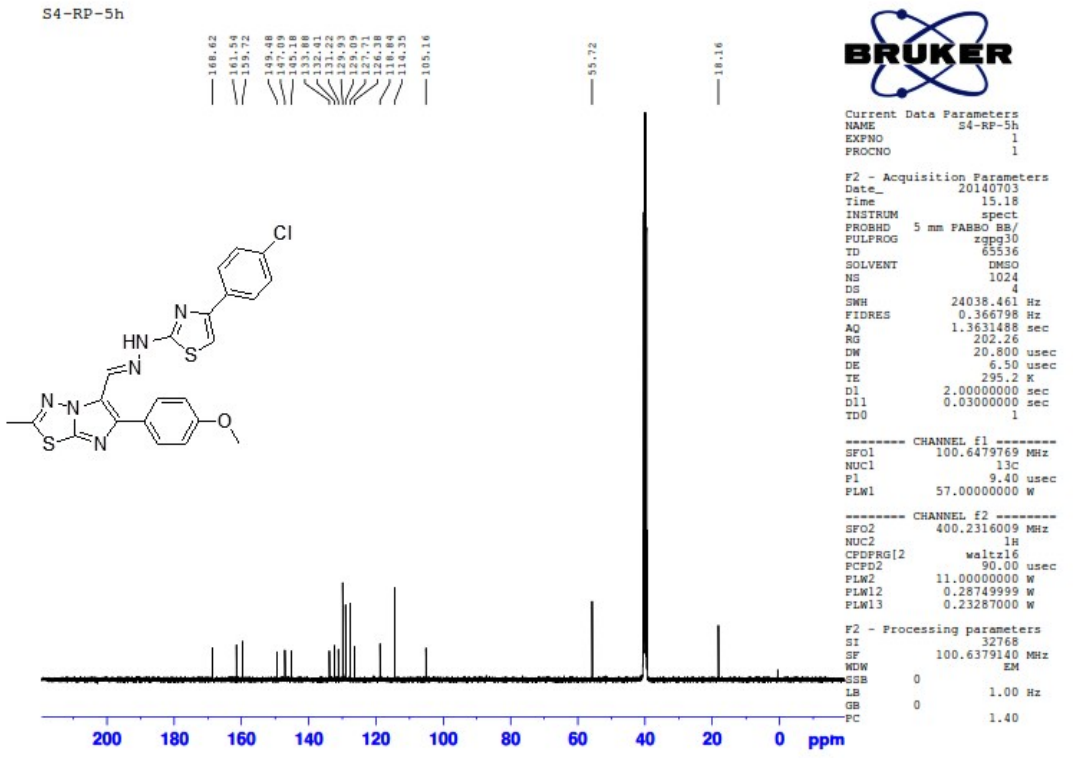


Figure S9. [13]C NMR spectrum of **5h**

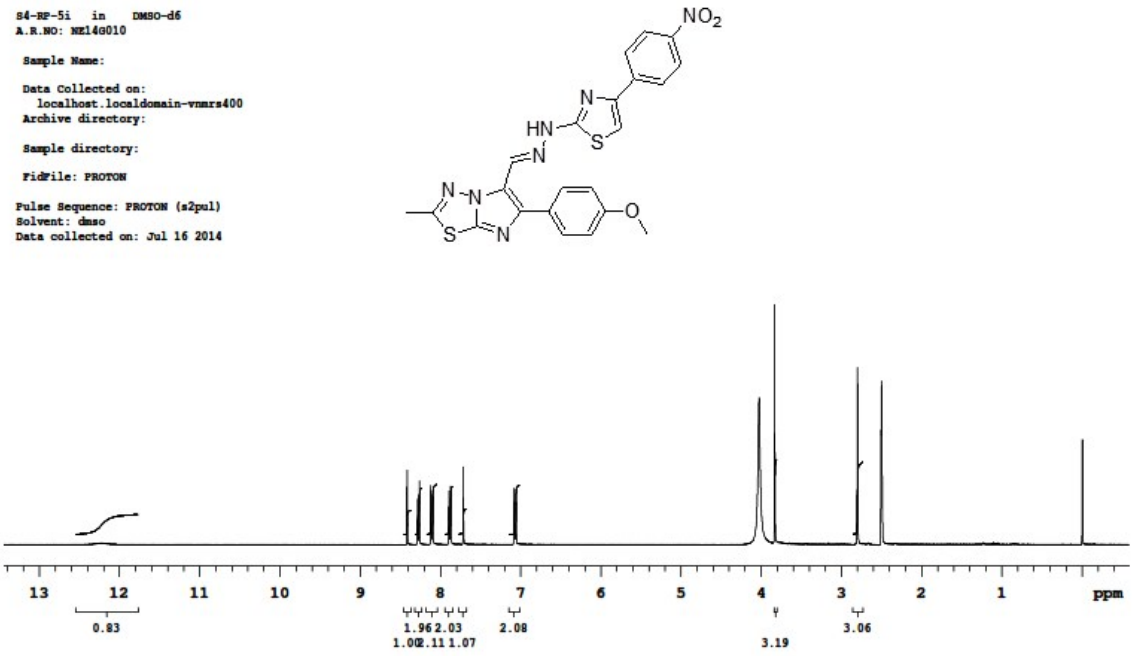


Figure S10. ^{1}H NMR spectrum of **5i**

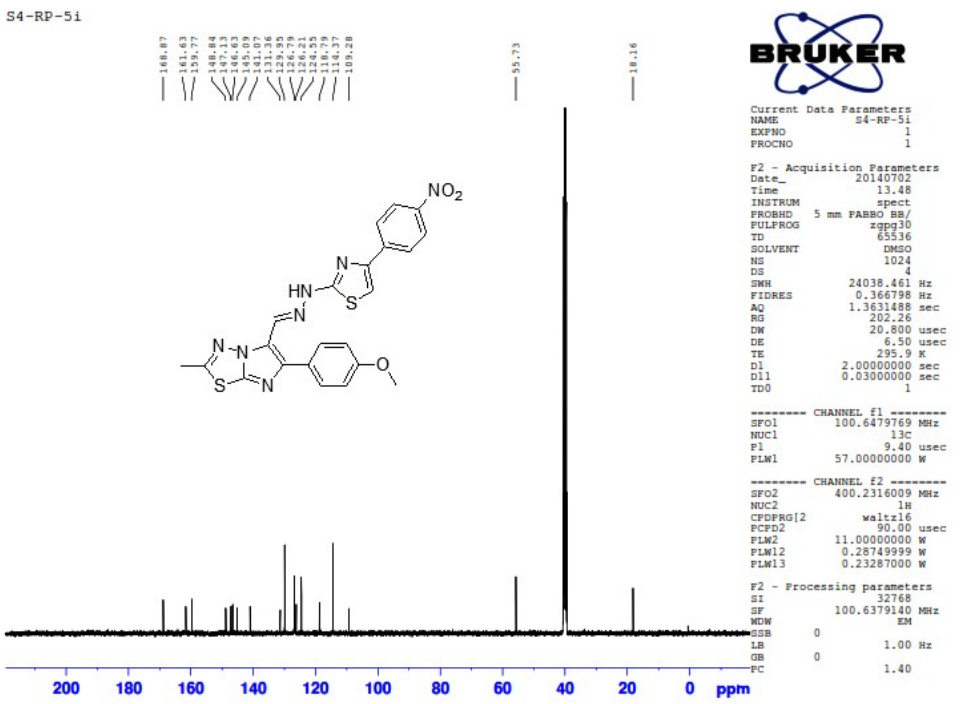


Figure S11. ^{13}C NMR spectrum of **5i**

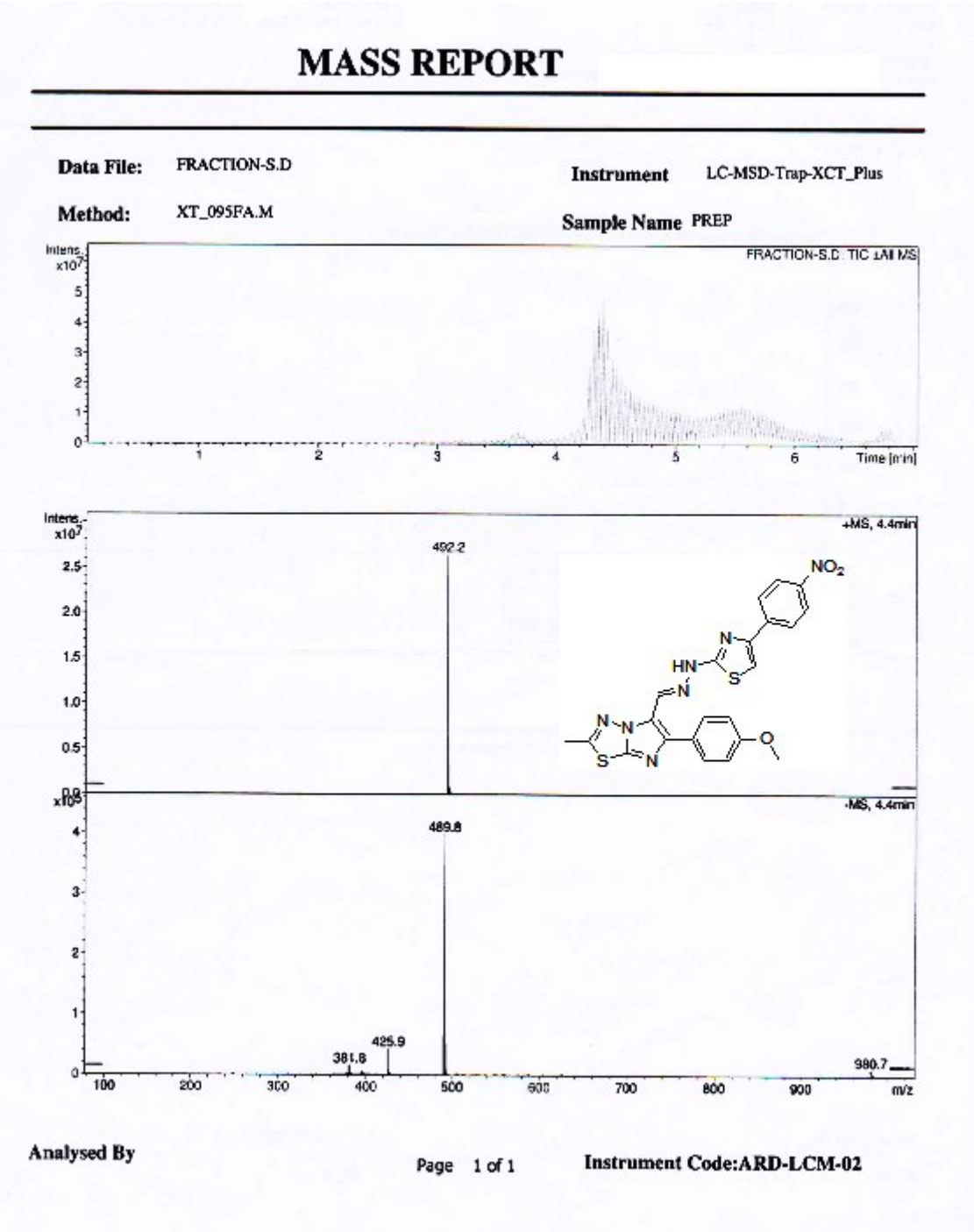


Figure S12. MS spectrum of **5i**

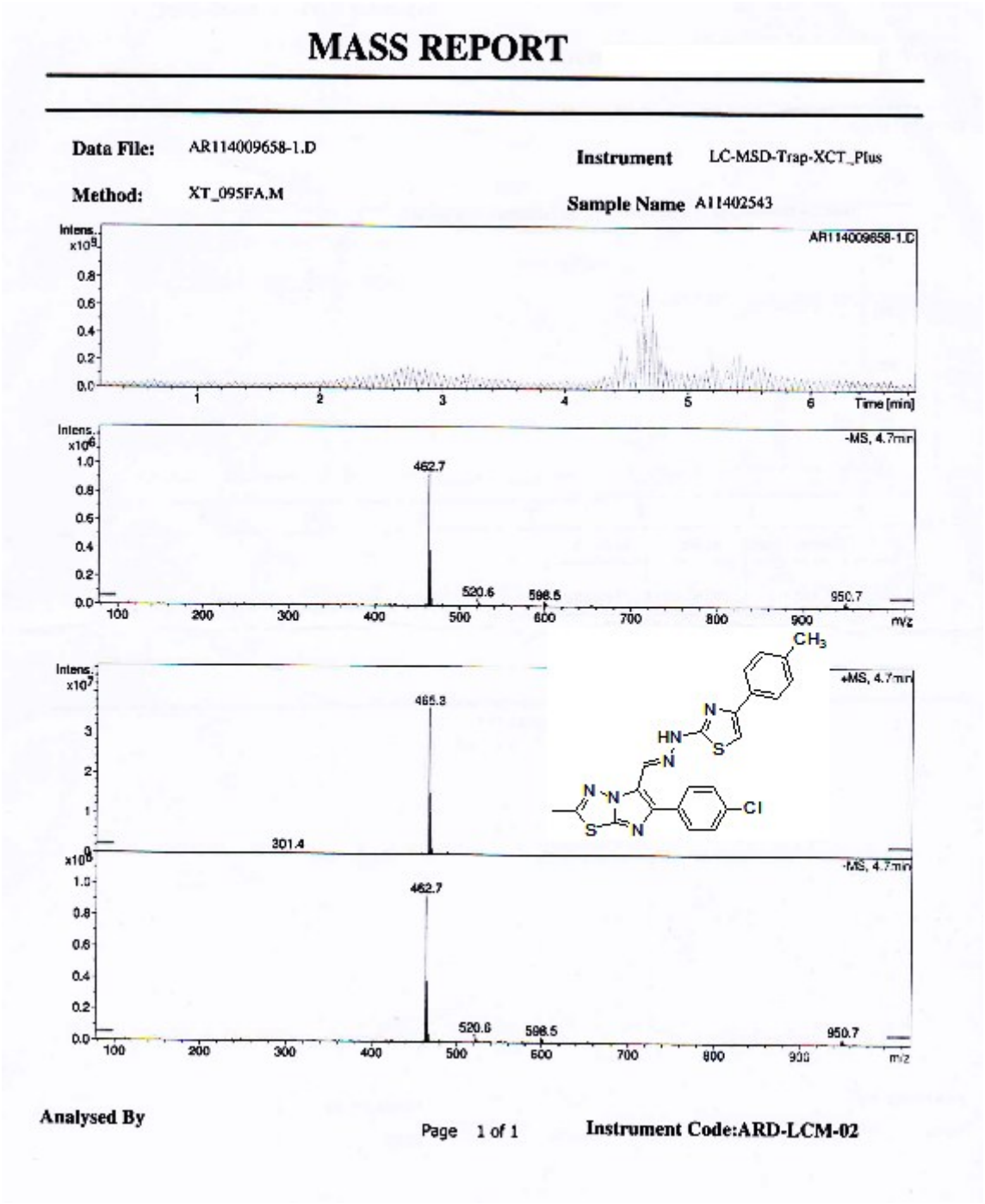


Figure S13. MS spectrum of **5k**

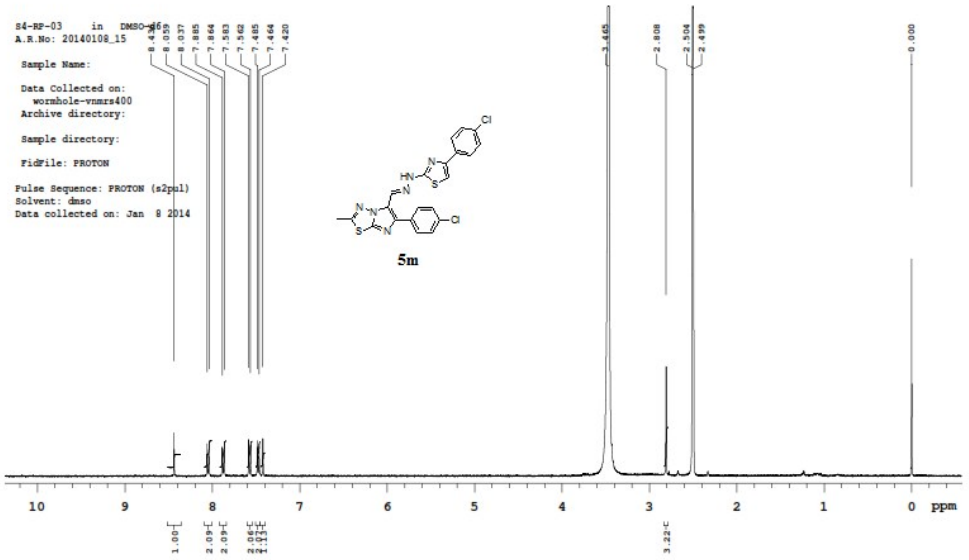


Figure S14. [1]H NMR spectrum of **5m**

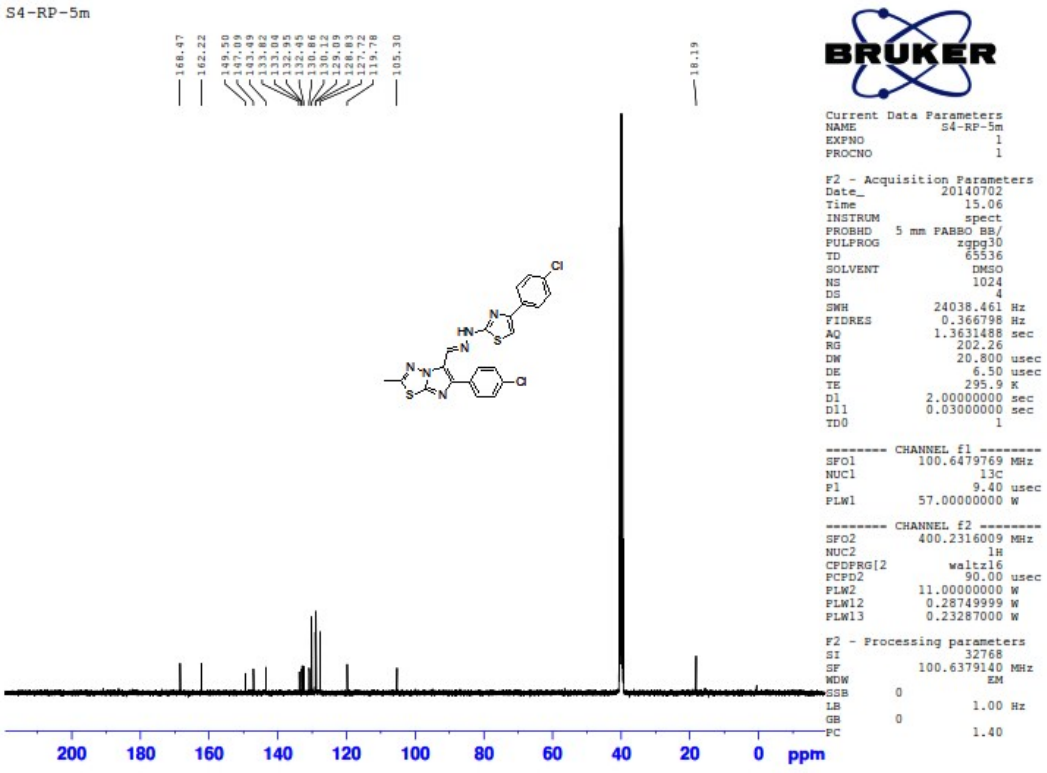


Figure S15. [13]C NMR spectrum of **5m**

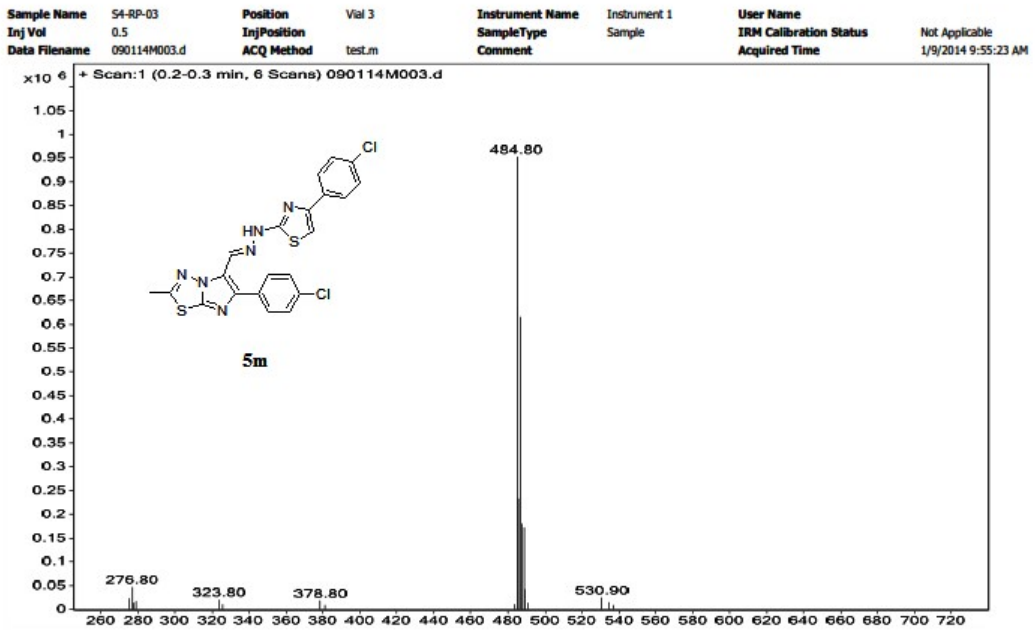


Figure S16. MS spectrum of **5m**

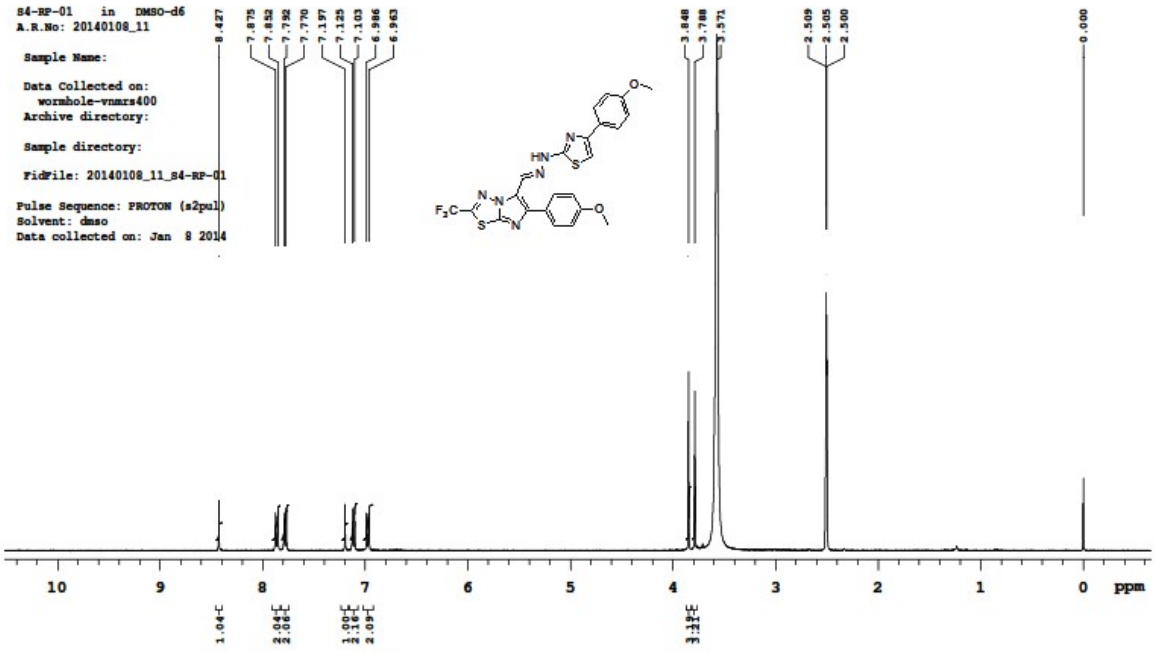


Figure S17. [1]H NMR spectrum of **5p**

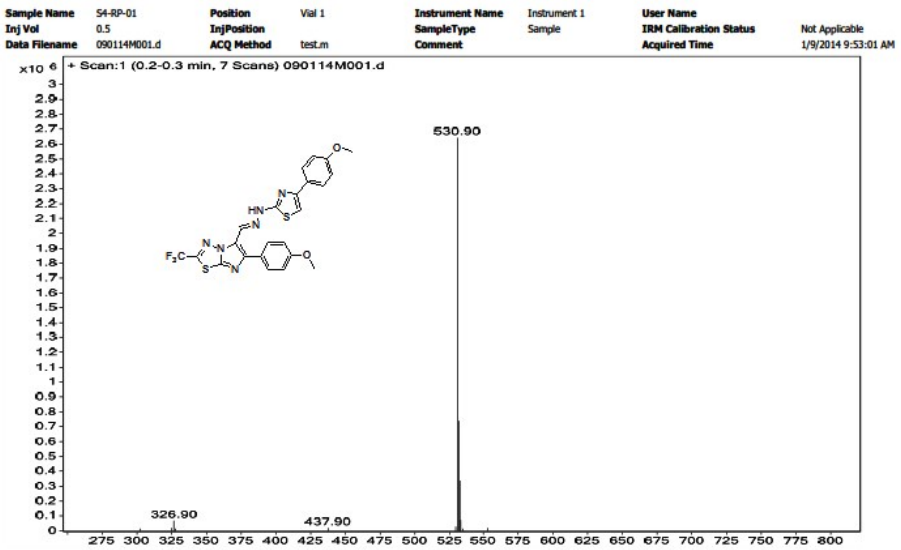


Figure S18. ^{13}C NMR spectrum of **5p**

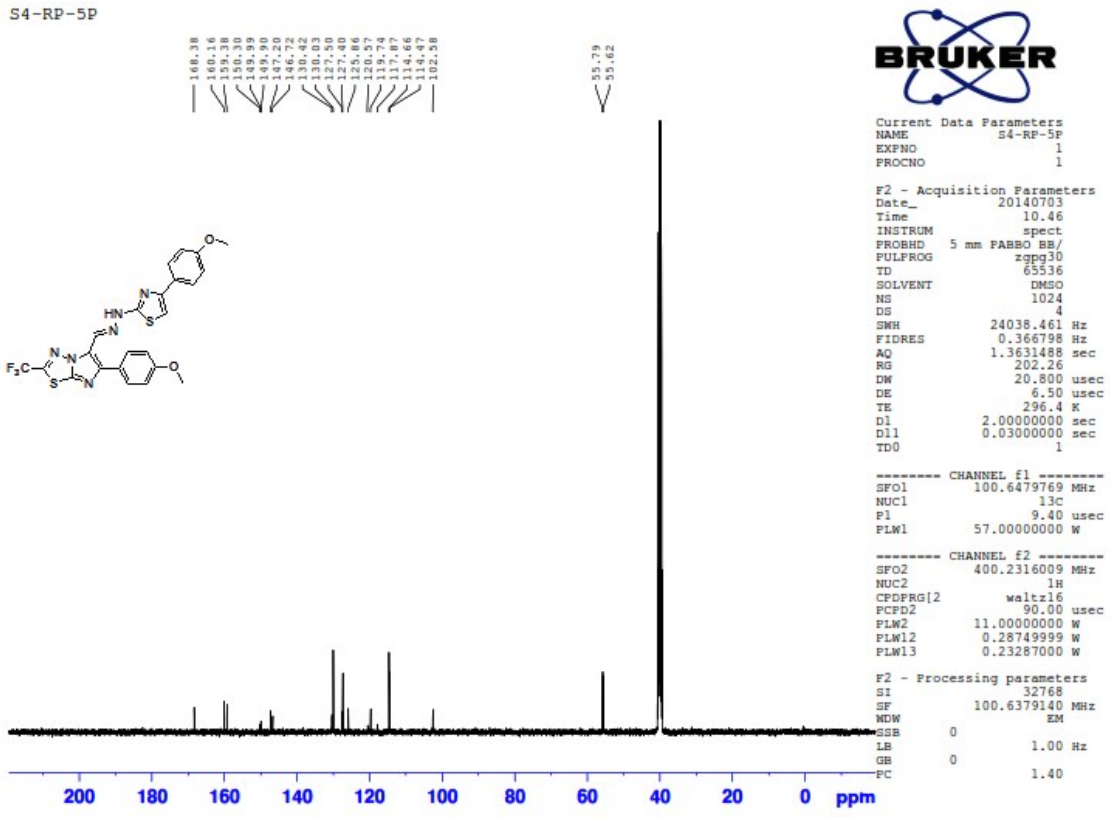


Figure S19. ^{13}C NMR spectrum of **5p**

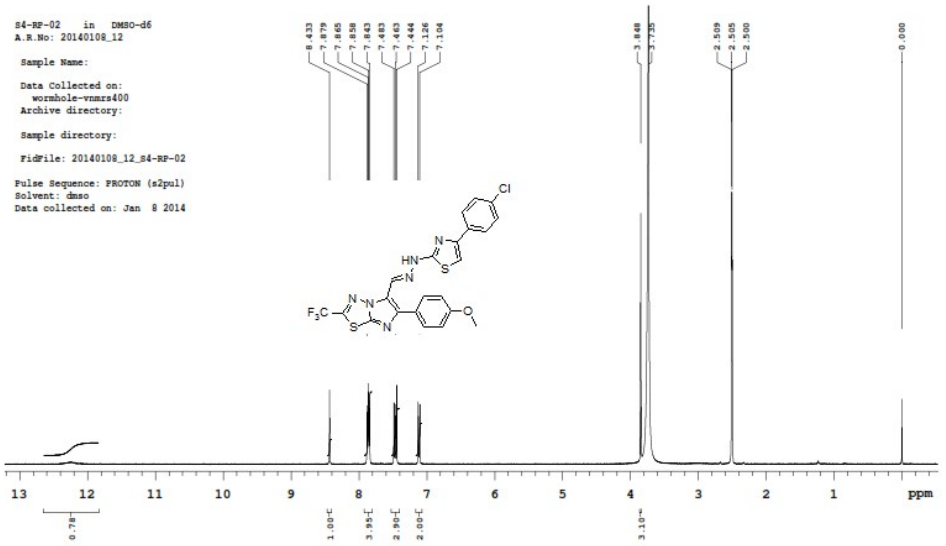


Figure S20. [1]H NMR spectrum of **5q**

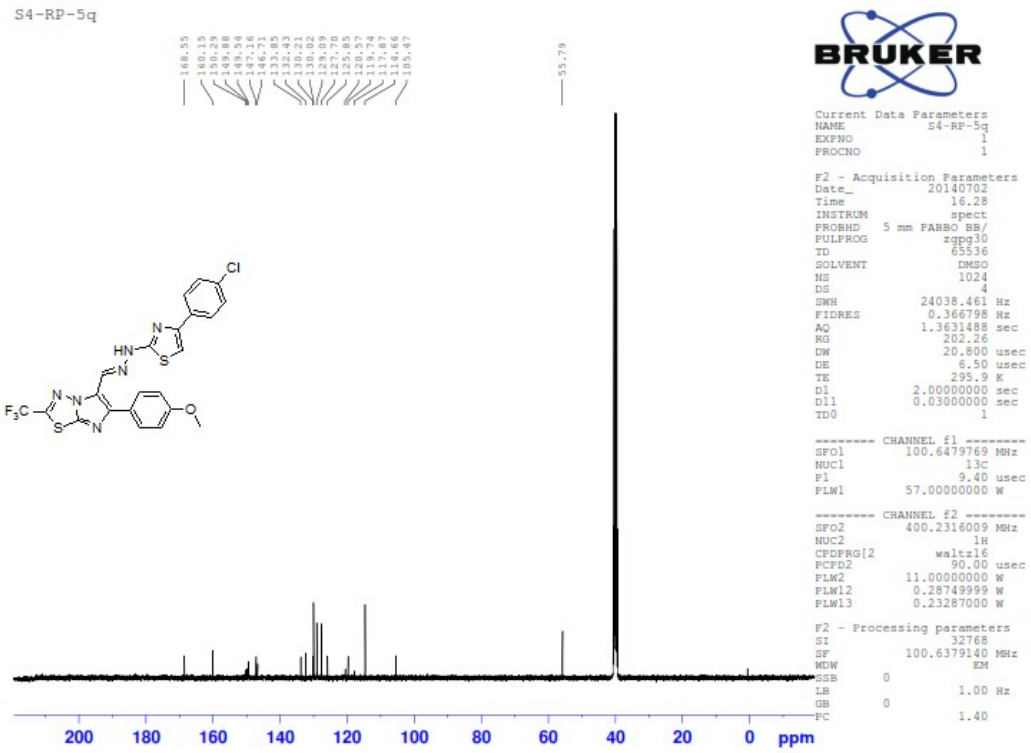


Figure S21. [13]C NMR spectrum of **5q**

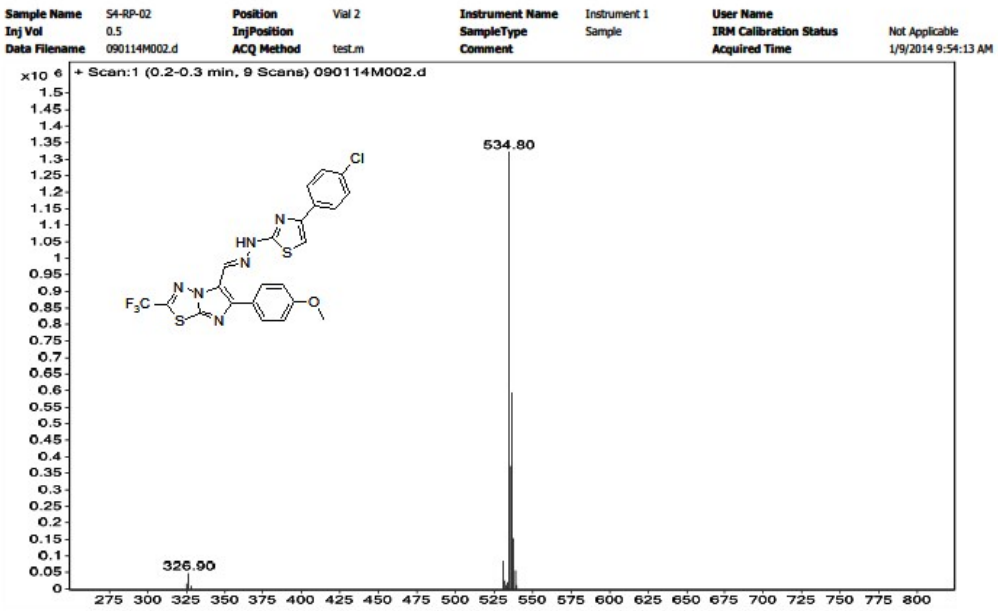


Figure S22. MS spectrum of **5q**

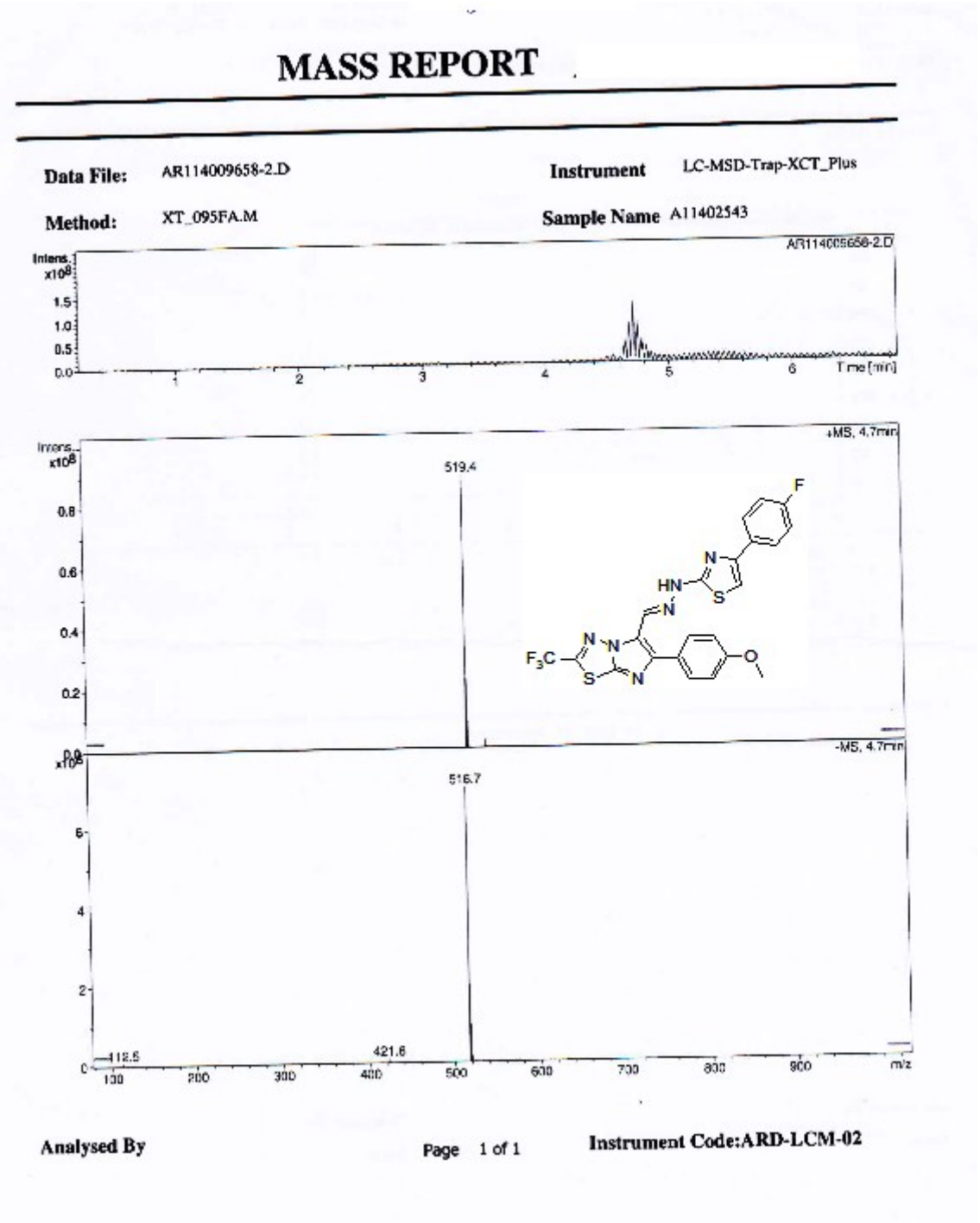


Figure S23. MS spectrum of **5r**

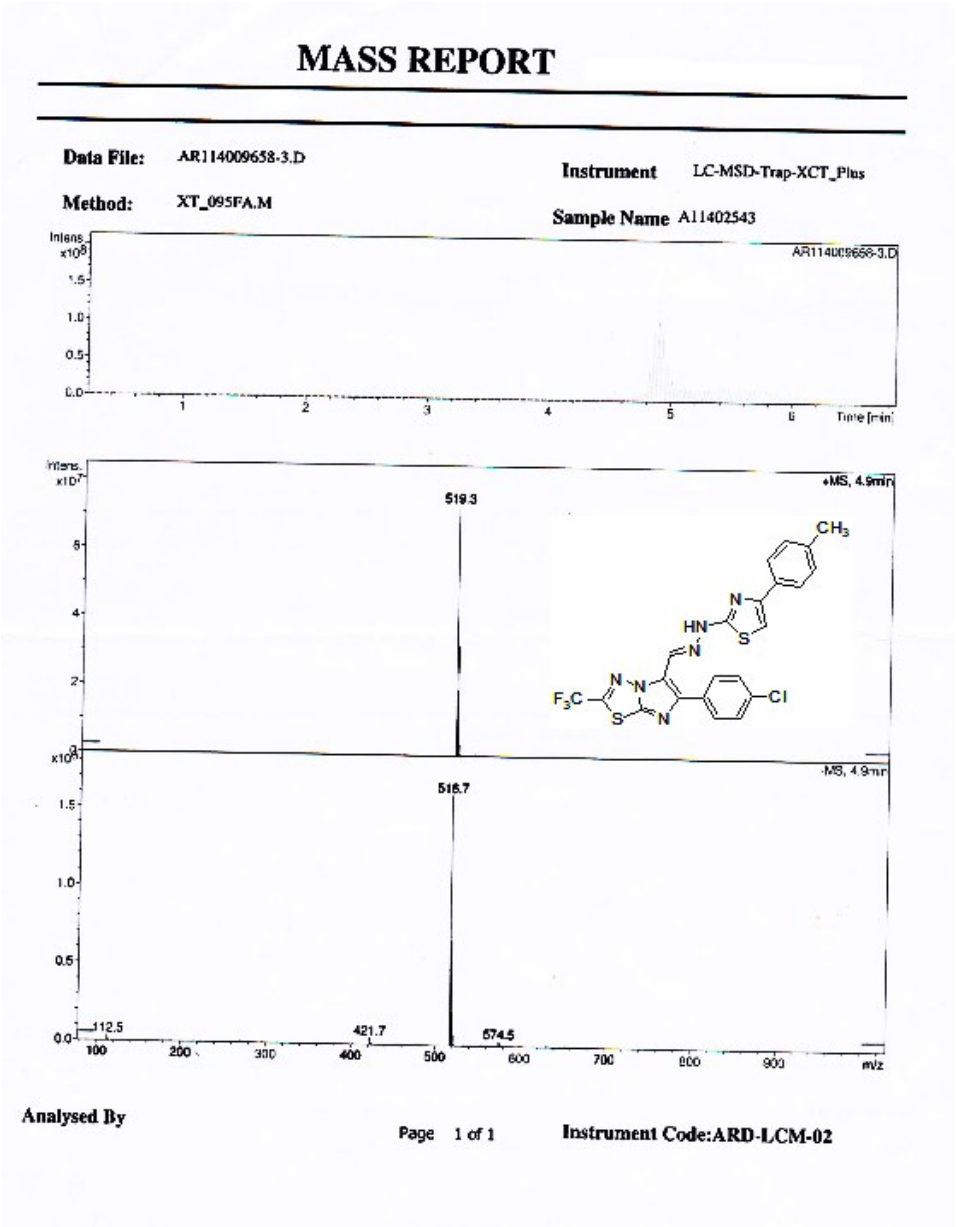


Figure S24. MS spectrum of **5s**

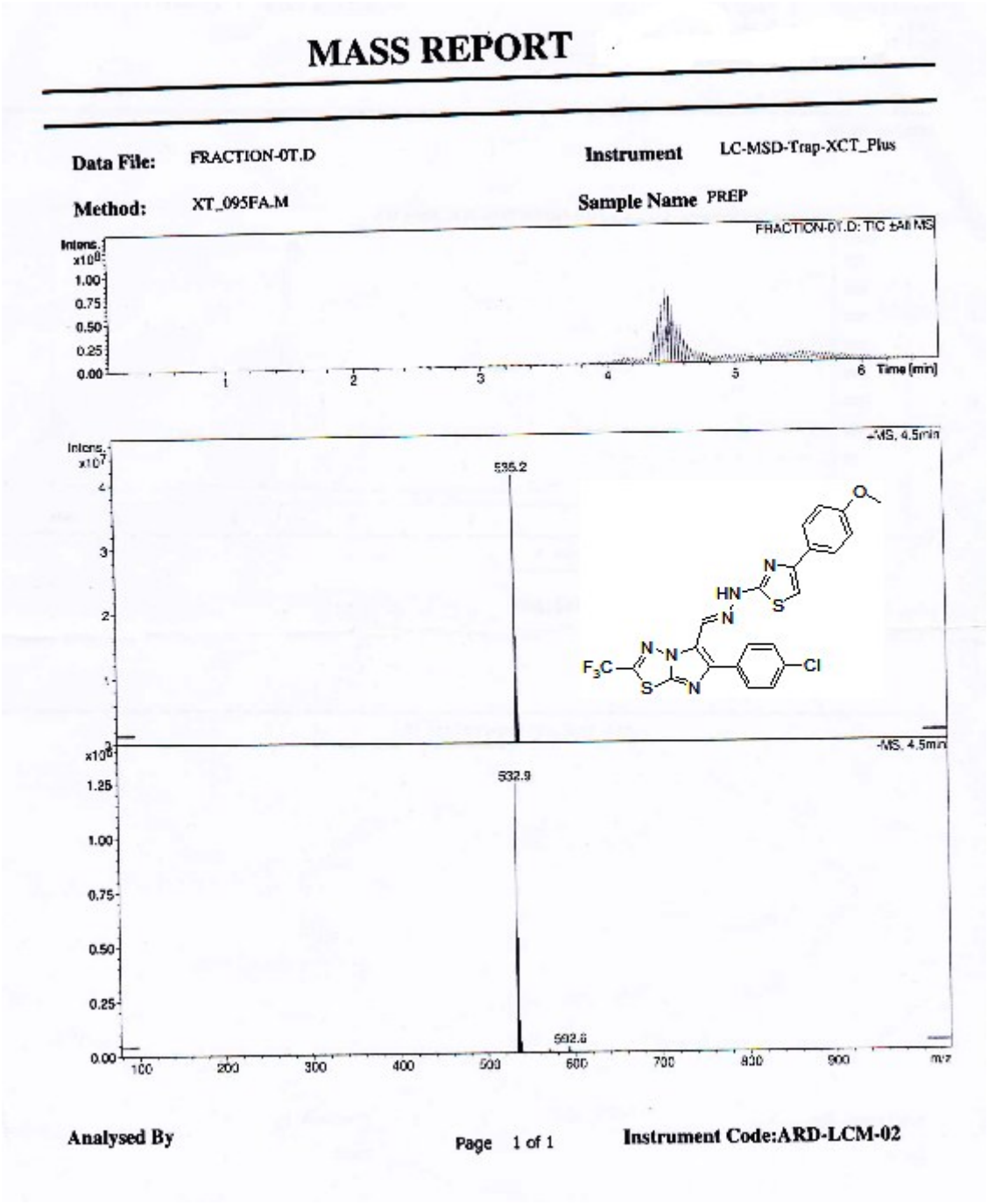


Figure S25. MS spectrum of **5t**

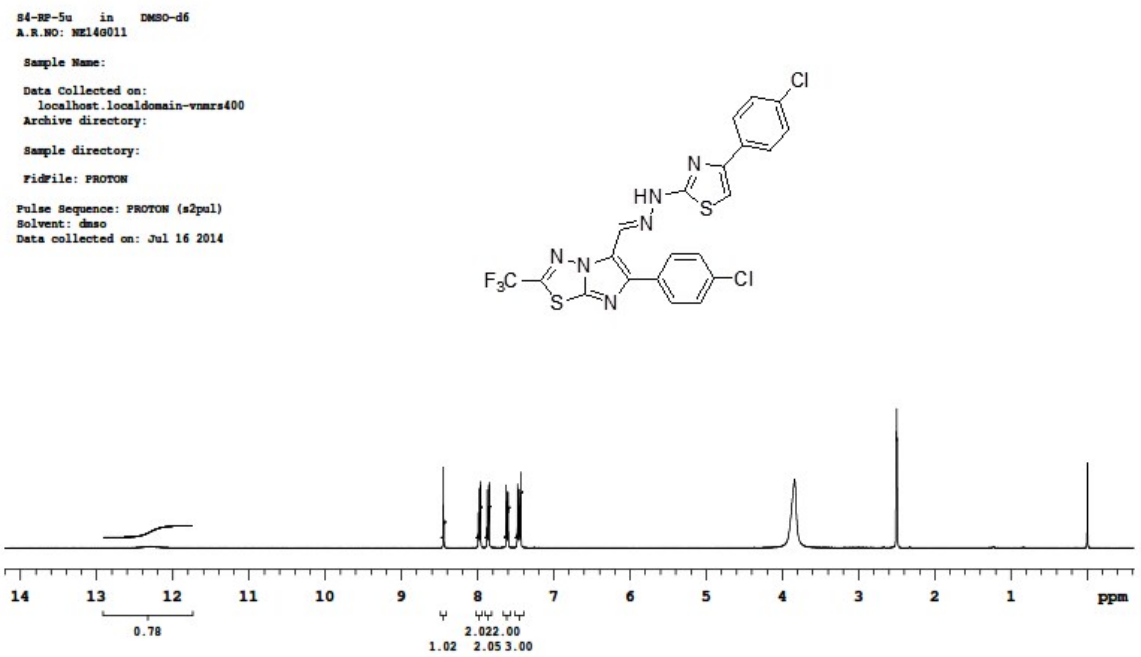


Figure S26. ^{1}H NMR spectrum of **5u**

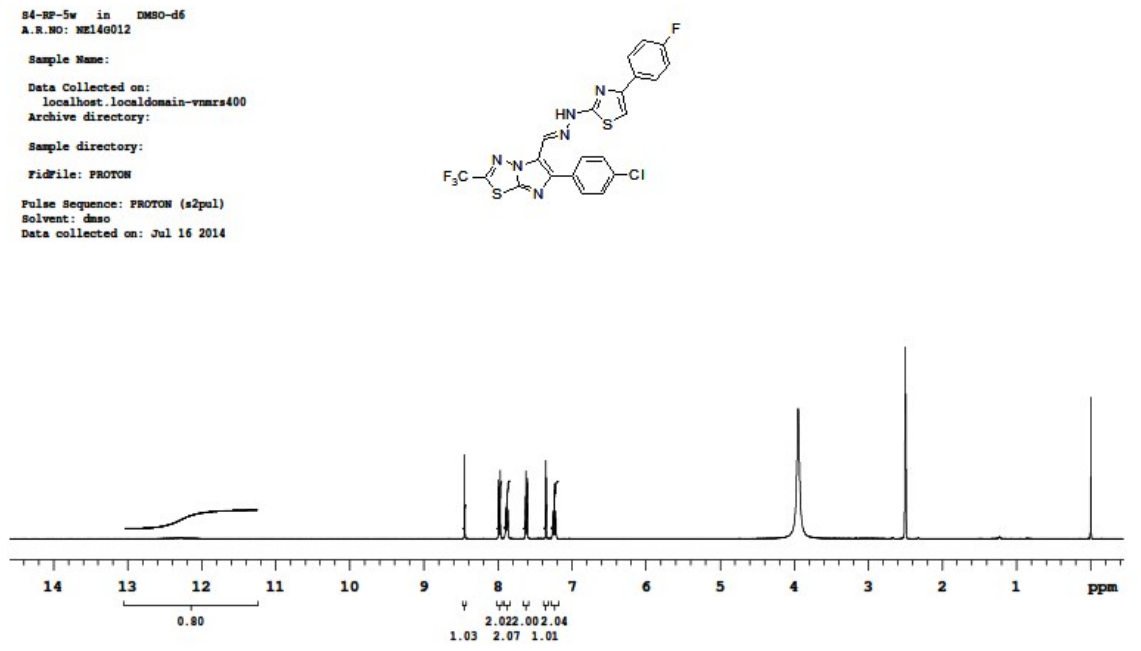


Figure S27. ^{1}H NMR of spectrum **5w**