Supporting Information

Synthesis and Anti-tubercular Activity of New Benzo[*b*]thiophenes

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Experimental:

General procedure for the synthesis of benzo[*b*]thiophene-2-carboxylic acid (4):

To the suspension of K_2CO_3 (30 mmol) in DMF (10 mL), compound **1** (10 mmol) dissolved in DMF (20 mL) was added at room temperature, and stirred for 30 min. To this reaction mixture methyl thioglycolate (30 mmol) was added slowly, and heated at 90 °C for 1 hr (monitored by TLC). The reaction mixture was then cooled to RT and poured on crushed ice. The obtained precipitate of methyl benzo[*b*]thiophene-2-carboxylate **2** (Yellow solid, Yield: 74 %, mp = 72-74 °C) was collected, dried, and used for the next step without further purification. In the next step, a mixture of compound **3** (10 mmol) and LiOH (30 mmol) was dissolved in THF (5 mL) and water (5 mL). The mixture was stirred at RT for 30 min (monitored by TLC). Acidification with conc. HCl resulted in a white solid which was collected by filtration, then dried, and recrystallized with ethanol to afford pure product benzo[*b*]thiophene-2-carboxylic acid **4**.

White solid; Yield: 75 %; mp = 110-112 °C. ^{1}H NMR (300 MHz, DMSO, δppm): 8.10 (s, 1H, thiophene-H); 8.04-7.98 (m, 2H, ArH), 7.53-7.42 (m, 2H, ArH), 3.80 (brs, 1H, OH); ^{13}C NMR (75 MHz, DMSO, δppm): 163.5 (C=O), 141.3, 138.7, 134.9, 130.1, 126.9, 125.7, 125.0, 122.9; IR (KBr, υcm^{-1}): 3401 (OH), 3021, 2401, 1643, 1516, 1408, 1216, 1069, 923, 767, 670, 581, 468; LC-MS (ESI) *m/z*: 179.2 $(M+H)^+$; Anal. Calcd. for $C_9H_6O_2S$ (%): C, 60.66; H, 3.39. Found: C, 60.64; H, 3.40.

General procedure for the synthesis 1-(benzo[*b*]thiophen-2-yl)-3-(2-hydroxyphenyl)propane-1,3-diones (7a-g):

In the first step, phosphorus oxychloride (30 mmol) was added dropwise to a solution of the substituted *o*-hydroxyacetophenone **5a-g** (10 mmol) and benzo[*b*]thiophene-2-carboxylic acid **4** (10 mmol) in dry pyridine (20 mL), and the solution cooled in ice bath under stirring at 0 °C. The solution was stirred at room temperature for 10-15 min (monitored by TLC). After completion of the reaction, reaction mixture was poured on crushed ice, the obtained solid **6a-g** was filtered, washed with saturated solution of $NaHCO_3$, dried and used further without any purification. In the second step, compound **6a-g** (10 mmol) was dissolved in dry pyridine (10 mL) to which powdered KOH (20 mmol) was added and the reaction mixture was irradiated under ultrasound irradiation for 10-15 min (monitored by TLC). The reaction mixture was poured on crushed ice and acidified with conc. HCl. The obtained yellow solid was filtered off and crystallized from ethanol:$CHCl_3$ (8:2) to afford pure product **7a-g**.

1-(Benzo[*b*]thiophen-2-yl)-3-(2-hydroxy-5-methylphenyl)propane-1,3-dione (7c):

^{1}H NMR (300 MHz, $CDCl_3$, δppm): 15.51 (s, 1H, enolic-H), 11.76 (s, 1H, phenolic-H), 8.05 (s, 1H, thiophene-H), 7.94-7.84 (m, 2H, ArH), 7.48-7.42 (m, 2H, ArH), 7.39-7.25 (m, 1H, ArH), 6.92-6.88 (m, 1H, ArH), 6.75 (s, 1H, ArH), 4.64 (s, 1H, -CH=), 2.35 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δppm): 199.1, 195.2, 172.2, 160.5, 142.9, 141.5, 139.4, 138.6, 137.6, 131.5, 130.8, 128.2, 127.2, 125.4, 122.8, 118.8, 93.3, 20.7; IR (KBr, υcm^{-1}): 3399 (OH), 3019, 1644, 1385, 1215, 1155 (C-O), 1068, 758, 669. HRMS (ESI) *m/z*: 311.0749 $(M+H)^+$. Anal. Calcd. for $C_{18}H_{14}O_3S$ (%): C, 69.66; H, 4.55. Found: C, 69.64; H, 4.51.

General procedure for the synthesis of flavones 8a-g:

The appropriate 1-(benzo[*b*]thiophen-2-yl)-3-(2-hydroxyphenyl)propane-1,3-diones **7a-g** (10 mmol) was added in PEG-400 (10 mL) and 1-2 drops of sulphuric acid was added to this mixture. The reaction mixture was irradiated under ultrasound irradiation for 5-10 min (monitored by TLC). After completion of the reaction, reaction mixture was poured on crushed ice. The obtained solid was filtered, dried and crystallized from ethanol to afford pure flavones **8a-g**.

2-(Benzo[*b*]thiophen-2-yl)-6-methyl-4*H*-chromen-4-one (8c):

^{1}H NMR (300 MHz, $CDCl_3$, δppm): 8.00 (s, 1H, ArH), 7.96 (s, 1H, thiophene-H), 7.89-7.84 (m, 2H, ArH), 7.52-7.39 (m, 4H, ArH), 6.75 (s, 1H, chromenone-H), 2.46 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δppm): 178.1 (C=O), 158.8, 154.4, 140.9, 139.5, 135.5, 135.3, 135.0, 126.7, 125.5, 125.4, 125.3, 125.1, 123.8, 122.7, 117.9, 107.9, 21.1 (CH_3). IR (KBr, υcm^{-1}): 3019, 2400 (CH), 1637 (C=O), 1584, 1524, 1474, 1385, 1215, 1157, 1069, 758, 668. HRMS (ESI+) *m/z*: calcd: 293.0636 $(M+H)^+$, found: 293.0630. Anal. Calcd. for $C_{18}H_{12}O_2S$ (%): C, 73.95; H, 4.14. Found: C, 73.89; H, 4.12.

General procedure for the synthesis of 2-(5-(benzo[*b*]thiophen-2-yl)-1*H*-pyrazol-3-yl)phenols (9a-g):

To a stirred solution of β-diketones **7a-g** (10 mmol) in ethanol (10 mL), hydrazine monohydrate (15 mmol) was added, and the reaction mixture was irradiated under ultrasound irradiation for 10-15 min (monitored by TLC). After completion of the reaction, obtained solid was filtered, dried and crystallized with ethanol to afford pure pyrazoles **9a-g**.

2-(5-(Benzo[*b*]thiophen-2-yl)-1*H*-pyrazol-3-yl)-4-methylphenol (9c):

^{1}H NMR (300 MHz, δppm): 11.65 (s, 1H, phenolic-H), 7.86-7.77 (m, 2H, ArH), 7.53 (s, 1H, thiophene-H), 7.42-7.36 (m, 3H, ArH), 7.06-6.92 (m, 3H, ArH), 4.36 (brs, 1H, NH), 2.40 (s, 3H, CH_3). ^{13}C NMR (75 MHz, δppm): 153.5, 152.2, 140.0, 139.5, 131.3, 130.5, 128.9, 127.2, 125.4, 125.2, 124.1, 122.5, 121.4, 117.0, 115.9, 100.9, 20.7. IR (KBr, υcm^{-1}): 3852, 3749, 3398 (OH, NH), 2950 (CH), 1638, 1384, 1217, 1155, 1068, 771, 669. HRMS (ESI) *m/z*: calcd: 307.0905; found: 307.0901 $(M+H)^+$. Anal. Calcd. for $C_{18}H_{14}N_2OS$ (%): C, 70.56; H, 4.61; N, 9.14. Found: C, 70.52; H, 4.60; N, 9.20.

General procedure for the synthesis of *N*-phenylbenzo[*b*]thiophene-2-carboxamides (11a-i)

A mixture of benzo[*b*]thiophene 2-carboxylic acid **4** (10 mmol), HOBt (10 mmol) and EDC.HCl (15 mmol) was stirred in DMF (10 mL) for 10 min. at 0 °C, substituted anilines **10a-i** (10 mmol) were added and the reaction mixture was irradiated under ultrasonication for 1-2 hr (monitored by TLC). After completion of the reaction, the reaction mixture was poured on crushed ice and the obtained product was filtered, dried and recrystallized from ethanol to obtaine pure products **11a-i**.

***N*-(4-fluorophenyl)benzo[*b*]thiophene-2-carboxamide (11d):**

^{1}H NMR (300 MHz, DMSO-d_6, δppm): 10.61 (s, 1H, amide-H), 8.35 (s, 1H, thiophene-H), 8.07-7.99 (m, 2H, ArH), 7.78-7.73 (m, 2H, ArH), 7.58-7.44 (m, 4H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6, δppm): 161.7 (C-F), 160.4 (amide C=O), 140.5, 139.6, 139.0, 138.0, 131.5, 126.6, 126.0, 125.4, 125.1, 122.8, 122.1, 115.6; IR (KBr, υcm^{-1}): 3361, 3021, 1643, 1520, 1390, 1216, 1156, 1070, 871, 766, 669, 605, 504; HRMS (ESI+) *m/z*: calcd: 272.0545 $(M+H)^+$, found: 272.0547. Anal. Calcd. for $C_{15}H_{10}FNOS$ (%): C, 66.40; H, 3.72; N, 5.16. Found: C, 66.47; H, 3.70; N, 5.18.

Experimental protocols for biological activity

Chemicals, strains and media

All the chemicals such as rifampicin, DMSO, sodium salt XTT, sulfanilic acid, sodium nitrate, HCl, NEED were purchased from Sigma-Aldrich, USA. Dubos medium was purchased from DIFCO, USA. Stock solutions of the compounds were prepared in DMSO and were used for further antimycobacterial testing. Microbial strains such as *MTB H37Ra* (ATCC 25177) and *M. bovis BCG* (*ATCC* 35734) were obtained from AstraZeneca, India. The stock culture was maintained at -80 $^{\circ}$C and subcultured once in a liquid medium before inoculation into an experimental culture. Cultures were grown in Dubos media (enrichment media). For antimycobacterial assay, *M. pheli* medium (minimal essential medium) was used. It contains 0.5 g KH_2PO_4, 0.25 g trisodium citrate, 60 mg $MgSO_4$, 0.5 g aspargine and 2 ml glycerol in distilled water (100 mL) followed by pH adjustment to 6.6.

Antimycobacterium activity

All the selected compounds were screened in vitro against two *Mycobacterium* species such as *MTB H37Ra* and *M. Bovis BCG.* Both species of *Mycobacterium* were grown in *M. Pheli* medium. Screening of *MTB H37Ra* was done by using XTT reduction menadione assay (XRMA) and *M. Bovis BCG* screening was done by using NR (Nitrate reductase) assay, both of them *which* were developed earlier in our lab. Briefly, 2.5 µl of these inhibitor solutions were added in a total volume of 250 μL of *M. Pheli* medium consisting of bacilli. The incubation was terminated on the 8th day for Active and 12 days for Dormant *MTB* culture. The XRMA and NR was then carried out to estimate viable cells present in different wells of the assay plate. The optical density was read on a micro plate reader (Spectramax plus384 plate reader, Molecular Devices Inc.) at 470 nm filter for XTT and at 540 nm filter for NR against a blank prepared from

cell-free wells. Absorbance given by cells treated with the vehicle alone was taken as 100 % cell growth.

Initially primary screening was done at 30, 10 and 3 μg/mL. Those compound rich 90 percent inhibition of bacilli which were selected for further dose response curve. All experiments were performed in triplicates and the quantitative value was expressed as the average ± standard deviation. MIC and IC_{50} values of selected compound were calculated from their dose response curves by using Origin 6 software. Percent inhibition was calculated by following formula.

% Inhibition = (Cont OD)-(Test OD) / (Cont OD-Blank OD) X 100.

Blank: Cell free medium

Control: Medium contains Bacilli along with vehicle

Compound: Medium contains Bacilli along with Drug concentration

***Ex vivo* infection model assay**

The human acute monocytic cell line THP-1 was procured from the National Centre for Cell Science (NCCS), Pune, India. These cells were cultured in RPMI 1640 medium supplemented with 10% FBS, 1 mM sodium pyruvate, 1% nonessential amino acids, 1% glutamine, 50 mg/ml gentamicin and 50 mg/ml ampicillin, and incubated at 37 °C in an atmosphere of 5% CO_2. For infection model study, $3x10^5$ THP-1 cells/ml were passaged in complete RPMI having 100 nM/ml phorbol myristate acetate in 96-well microtiter plates and plated for differentiation to macrophages for 24 h. These were further infected with log phase *M. tuberculosis* at 100 multiplicity of infection (MOI) for 12 h. Plates were thoroughly washed with phosphate-buffered saline (PBS, pH 7.2) followed by addition of fresh MEM medium containing 50 mM sodium nitrate. Infected cells were then exposed to different concentrations of nanoparticles. Activity of compounds was estimated through nitrate reductase (NR) assay reading absorbance at 540 nm, at the end of incubation period for active and dormant mycobacteria.[9] The experiment was performed in triplicate. IC_{50} and MIC values were calculated from the dose-response curves plotted using OriginPro software.

Table S1. Primary antitubercular screening of compounds **4a-j**, **4**, **7a-g**, **8a-g**, **9a-g** and **11a-i** against avirulent strain of dormant MTB

Compound	% Inhibition of MTB H37Ra growth in presence of compounds			Compound	% Inhibition of *M. bovis BCG* growth in presence of compounds		
	30 μg/mL	10 μg/mL	3 μg/mL		30 μg/mL	10 μg/mL	3 μg/mL
4	5.35	-19.61	0.11	**4**	97.15	49.67	-14.66
7a	**105.87**	**97.94**	**100.16**	**7a**	**99.92**	**99.99**	**99.85**
7b	**93.91**	**98.59**	**102.47**	**7b**	**100.74**	**100.74**	**100.59**
7c	77.31	45.92	59.01	**7c**	**99.99**	**100.35**	**99.82**
7d	**98.84**	**99.21**	**99.98**	**7d**	**100.03**	**100.27**	**99.02**
7e	-3.58	26.24	4.41	**7e**	99.74	99.96	85.14
7f	**92.12**	**98.86**	**97.52**	**7f**	**97.60**	**98.60**	**97.95**
7g	52.78	24.48	23.18	**7g**	**99.45**	**100.29**	**97.45**
8a	-34.15	-6.92	-42.21	**8a**	-17.25	-47.40	18.90
8b	-27.25	-24.24	-39.14	**8b**	-5.22	13.11	14.77
8c	-2.11	13.99	-43.69	**8c**	65.29	60.42	54.52
8d	-37.21	12.71	-44.75	**8d**	0.00	80.75	82.35
8e	-21.38	-38.52	-25.76	**8e**	-18.12	0.49	6.47
8f	-1.03	23.92	-15.70	**8f**	-11.77	10.92	6.63
8g	-10.39	18.43	1.29	**8g**	-13.90	7.41	-3.12
9a	30.27	25.66	24.95	**9a**	27.73	26.89	12.17
9b	102.12	6.25	0.68	**9b**	**99.71**	**101.32**	**99.19**
9c	104.03	97.29	64.61	**9c**	**100.18**	**97.66**	**98.61**
9d	89.31	83.44	47.11	**9d**	**100.47**	**101.33**	**101.03**
9e	19.14	21.11	3.31	**9e**	-20.20	-16.98	-22.45
9f	24.66	33.07	-1.54	**9f**	30.47	27.56	22.38
9g	49.62	28.53	12.40	**9g**	95.84	88.36	56.71
11a	-11.42	18.10	-10.75	**11a**	28.45	30.38	24.85
11b	-4.55	-4.75	22.30	**11b**	49.11	48.90	36.04
11c	-3.59	27.89	6.75	**11c**	73.18	44.87	32.02
11d	-6.70	3.11	15.59	**11d**	67.45	52.50	43.58
11e	-4.35	15.41	15.49	**11e**	14.67	25.30	22.73
11f	-36.13	-34.70	-14.24	**11f**	3.99	14.51	14.40
11g	-46.31	17.24	21.09	**11g**	38.53	44.66	37.92
11h	-30.18	-24.01	-16.33	**11h**	40.36	26.11	22.15
11i	-6.49	-44.35	-28.72	**11i**	55.36	41.77	30.24

Table S2. *In Vitro* Antitubercular Activity (IC_{50}) of Compounds 7a-g, 8c and 8g against the MTB Strain *H37Ra* and *M. bovis BCG* (μg/mL)

Compd	Active *MTB H37Ra*	Dormant *MTB H37Ra*	Active *M. bovis BCG*	Dormant *M. bovis BCG*
	IC_{50}	IC_{50}	IC_{50}	IC_{50}
7a	2.15	2.13	0.73	0.66
7b	1.66	2.23	1.10	0.88
7c	15.34	17.75	1.17	0.88
7d	4.24	1.58	0.53	0.87
7e	>30	>30	2.12	1.46
7f	3.62	2.88	0.45	1.06
7g	25.65	28.54	0.26	0.37
8c	4.13	3.16	0.33	0.37
8g	21.64	22.44	0.32	0.33
RP	0.0018	0.0014	0.0022	0.0032
INH	0.0019	0.0023	0.0027	0.0039

RP; Rifampicin, INH; Isoniazid.

***In vitro* Antioxidant activity**

In the present study *in vitro* DPPH (1,1-diphenyl-2-picryl-hydrazil) radical scavenging method was used to evaluate the antioxidant potential of synthesized compounds. The interaction of all tested compounds with the stable free radical DPPH indicates their radical scavenging activity. 2 mL of solution containing 0.2 mM freshly prepared DPPH in methanol and different concentrations of synthesized compounds (10-100 μg/mL) were prepared to perform the reaction. After incubation at room temperature for 30 min, the absorbance at 517 nm was measured spectrophotometrically. Graph pad prism was used to calculate the concentration required to obtain a 50% antioxidant effect (EC_{50}) and is compared with the standard BHT, by performing experiment in triplicate. DPPH radical scavenging capacity was measured by,

% scavenging activity = $A_{control} - A_{test} / A_{control} \times 100$

Acontrol = Absorbance of the control, Atest = Absorbance of the test compounds.

Table S3. Physical data and antioxidant activity of Benzo[*b*]thiophene derivatives

Compound	R^1	R^2	R^3	Time (min)	Yield[a] (%)	M.P. (°C)	Antioxidant activity[b] (EC_{50} ± SD) (μg/mL)
7a	-H	-H	-Br	10	78	138-140	82.36 ± 1.02
7b	-H	-H	-Cl	10	81	158-160	79.32 ± 1.97
7c	-H	-H	$-CH_3$	10	80	146-148	47.32 ± 1.15
7d	-H	-H	-H	10	78	155-156	72.19 ± 0.94
7e	-Cl	-H	-Cl	15	70	102-104	38.32 ± 0.65
7f	-H	$-CH_3$	-H	10	76	96-98	**20.23 ± 1.00**
7g	-H	$-CH_3$	-Cl	10	72	170-172	87.64 ± 2.36
8a	-H	-H	-Br	10	79	225-227	-
8b	-H	-H	-Cl	5	80	170-172	-
8c	-H	-H	$-CH_3$	10	81	190-192	48.26 ± 1.39
8d	-H	-H	-H	5	82	152-154	-
8e	-Cl	-H	-Cl	5	78	126-128	-
8f	-H	$-CH_3$	-H	5	78	182-184	-
8g	-H	$-CH_3$	-Cl	10	80	210-212	64.00 ± 2.14
9a	-H	-H	-Br	10	80	194-196	-
9b	-H	-H	-Cl	10	78	168-170	-
9c	-H	-H	$-CH_3$	10	76	152-154	-
9d	-H	-H	-H	10	80	178-180	-
9e	-Cl	-H	-Cl	15	75	162-164	-
9f	-H	$-CH_3$	-H	10	76	145-147	-
9g	-H	$-CH_3$	-Cl	10	84	171-173	-
11a	-H	-H	-Br	80	76	132-134	-
11b	-H	-H	-H	65	68	103-105	-
11c	-F	-H	-H	55	72	135-137	-
11d	-H	-H	-F	65	70	120-122	-
11e	-F	-H	-F	90	72	147-149	-
11f	-H	-Br	-H	110	78	165-167	-
11g	-H	-H	-Cl	120	69	110-112	-
11h	-H	-Cl	-H	90	68	126-128	-
11i	-Cl	-H	-H	60	71	94-96	-
BHT	-	-	-	-	-	-	8.25 ± 0.34

[a]Yield after crystallization; [b]Values are expressed as mean ± standard deviation (n = 3); BHT (Butylated Hydroxy Toluene).

Cell Lines

The following cell lines were used: Panc-1 (human, pancreas epitheloid carcinoma), HeLa (human, cervix epithelial adenocarcinoma), THP-1 (human, leukemic monocyte) were obtained

from the American Type Culture Collection (ATCC). All cell lines were maintained in bottles of 25 cm^3 with Dulbecco's Modified Eagle's Medium (DMEM) for Panc-1, Minimum essential medium with Earl's salt (MEME) for HeLa with 10 % FBS and one suspended cell line THP-1 in RPMI with 5% FBS. Medium were replaced twice a week. All bottles with cell lines were maintained at 37 $^{\circ}C$, 5% CO_2 and 95% relative humidity.

Cytotoxicity by MTT assay

All the synthesized compounds were tested for their *in vitro* activity against three human cells was determined using modified MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) assay. Briefly, In 96 well plate cells were seeded as, Panc-1- 1.3×10^4, HeLa- 1.5×10^4, and THP-1- 1.3×10^4 cells/well and final volume/well made up to 100 μL with respective medium. The plates were allowed to adhere for 24 hr in CO_2 incubator at aforementioned conditions. After pre-incubation, 1μL of the Compounds were added in concentrations range of 30, 10 and 3 μg/mL to the cell lines. A control in which 1μL of DMSO was added instead of sample and a blank contains only the media without cells and sample. After addition of drugs plates were incubated for additional 72 hr for HeLa and THP-1 and 90 hr for Panc-1cell lines.

At the end of incubation time, cells were incubated for 2-4 hr by replacing the medium with 100 μL of Glucose-MTT (0.5 mg/mL)-PBS medium. In case of THP-1 cells 10 μL of Glucose-MTT (5mg/ml)-PBS medium was added without discarding the previous medium. After incubation reduced MTT or Formazan crystals were solubilized by addition of 200 μL of acidified isopropanol and plates were kept at 37 $^{\circ}C$ for complete solubilization. The optical density (OD) measured using microplate spectrophotometer system (Spectra max plus 384-Molecular Devices) at 570 nm. Each concentration was tested in triplicates in a single experiment. IC_{50} and MIC values were calculated (**Table 5**) by plotting the percentage survival versus the concentrations, using OriginPro Software. The % inhibition was determined using the following formula,

% Inhibition = (Cont OD -Test OD) / (Cont OD-Blank OD) × 100

Blank: cell free Medium

Control: Medium contains Cells along with vehicle

Compound: Medium contains cells along with Drug concentration.

Selectivity Index (SI)

The selectivity index for the selected compounds was calculated, summarized in **Table 3** for *MTB* H37Ra and *BCG*. According to drug susceptibility study of TB by Hartkoorn et al., the anti-tubercular activity considered to be specific when selectivity index is greater than 10. Percentage cytotoxicity curve plotted using Origin8 has been used for the calculation of the lowest concentration of compound killing 50% of the cells (GI_{50}- 50% Growth Inhibition Concentration). The results indicate a selective inhibition towards *MTB*. Simultaneous detection of active and dormant stage inhibitors against tubercular bacilli, XRMA assay protocol was used, which follows about similar principle of hypoxia model of dormancy. Under these conditions; the incubation was terminated on 8^{th} day and 12^{th} day respectively to identify active and dormant stage inhibitors.

Table S4. Selectivity Index (SI) of HeLa, Panc-1, andTHP-1 cell lines against Active and Dormant *MTB* H37Ra for 7a-g, 8c, and 8g

Compd	SI for *MTB* H37Ra						SI for *M. bovis* BCG					
	HeLa		Panc-1		THP-1		HeLa		Panc-1		THP-1	
	A	D	A	D	A	D	A	D	A	D	A	D
7a	2.35	2.56	6.38	6.96	-	-	5.81	3.81	15.8	10.35	-	-
7b	1.3	1.58	2.48	3.02	2.2	2.68	1.99	1.63	3.8	3.12	3.36	2.77
7c	0.23	0.23	0.52	0.52	-	-	3.74	4.74	8.33	10.55	-	-
7d	0.31	3.83	0.3	3.79	-	-	3.35	5.77	3.32	5.71	-	-
7e	-	-	0.87	0.87	-	-	-	-	9.53	10.32	-	-
7f	4.24	5.24	1.69	2.09	-	-	13.75	14.35	5.5	5.73	-	-
7g	-	-	0.67	0.67	-	-	-	-	28.67	22.62	-	-
8c	0.54	0.52	0.44	0.43	0.53	0.51	25.08	25.49	20.75	21.09	24.66	25.06
8g	0.84	0.87	-	-	37.0	34.58	37.89	35.36	-	-	37.05	34.58
INH		>1333		>1333		>1333		>2222		>2222		>2222
RP	>250	>2325	>250	>2325	>250	>2325	>6666	>2439	>6666	>2439	>6666	>2439

A-Active; D-Dormant; INH-Isoniazid; Rp-Rifampicin

Molecular docking

The crystal structure of DprE1 enzyme of *MTB* (PDB ID:4FDO) in complex with an inhibitor was obtained from the Protein Data Bank (www.rcsb.org) (**Figure 1**). The protocol adopted for docking simulation was validated by extracting the native ligand from the crystal structure and docking it into binding site of the DprE1 monitoring its ability to reproduce the experimentally observed binding mode. The root mean square deviation (RMSD) between the experimental conformation of the native ligand and that obtained from its docking into crystal structure was found to be less than 1Å, validating the reliability of the docking procedure in reproducing the experimentally observed binding mode for benzo[*b*]thiophenes investigated herein.

DprE1, an Oxidase involved in the arabinogalactan biosynthesis, has been shown to be an essential target for the survival of MTB. GLIDE searches for favorable interactions between the ligand molecules and the target protein using a filtering a approach wherein each of the ligand pose pass through a series of hierarchical filters that evaluate the ligands interaction with the receptor. Finally each of the docking solution is scored using Schrodinger's proprietary Glide score multi-ligand scoring function to rank the structures. First, the structure of the enzyme was refined for docking simulation using the *Protein Preparation Wizard* incorporated in the docking program. All the water molecules present in crystal structure were removed as none of them was found to be conserved in the interaction with the protein; the missing hydrogens/side chain atoms were added corresponding to pH 7.0 considering the appropriate ionization states for the acidic as well as basic amino acid residues; appropriate charge and protonation state were assigned and finally energy minimization with root mean square deviation (RMSD) value of 0.30Å was carried out using the Optimized Potentials for Liquid Simulations (OPLS-2005) force-field to relieve the steric clashes among the residues caused due to addition of hydrogen atoms. The three-dimensional structures of the aforementioned compounds were constructed with *build* panel in Maestro and optimized using the *ligprep* module. Partial charges were ascribed to the structures using the (OPLS-2005 force-field and were then energetically minimized until a RMSD of 0.001 Å was reached. The active site of the enzyme was defined using the *Receptor Grid Generation* panel which generates two cubical boxes having a common centroid to organize the calculations: a larger enclosing and a smaller binding box. A cubic grid box of a 12X12X12 Å dimensions centered on the centroid of the native ligand in the crystal complex was generated which was big enough to explore a larger region of the enzyme structure. Using this setup

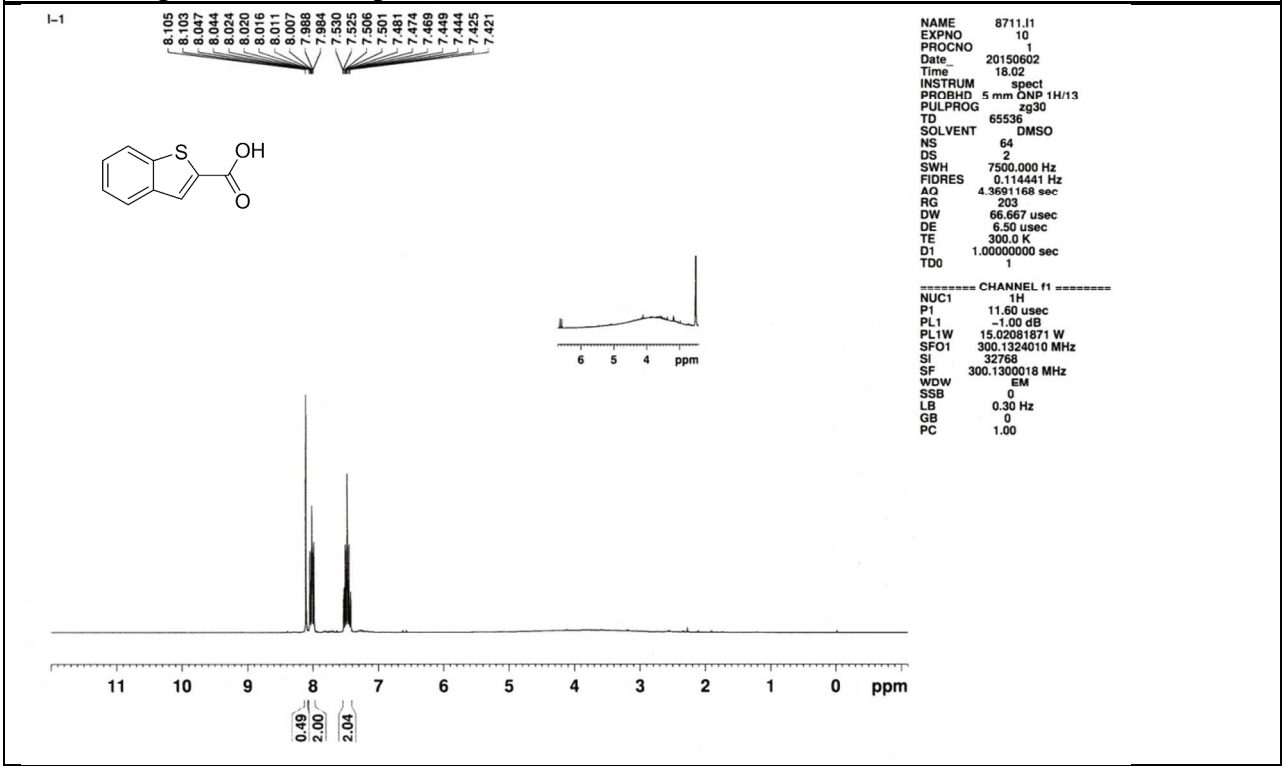
automated docking studies were carried out to evaluate the binding affinities of the aforementioned compounds within the macromolecule.

Table S5. Quantitative measure of the molecular docking study

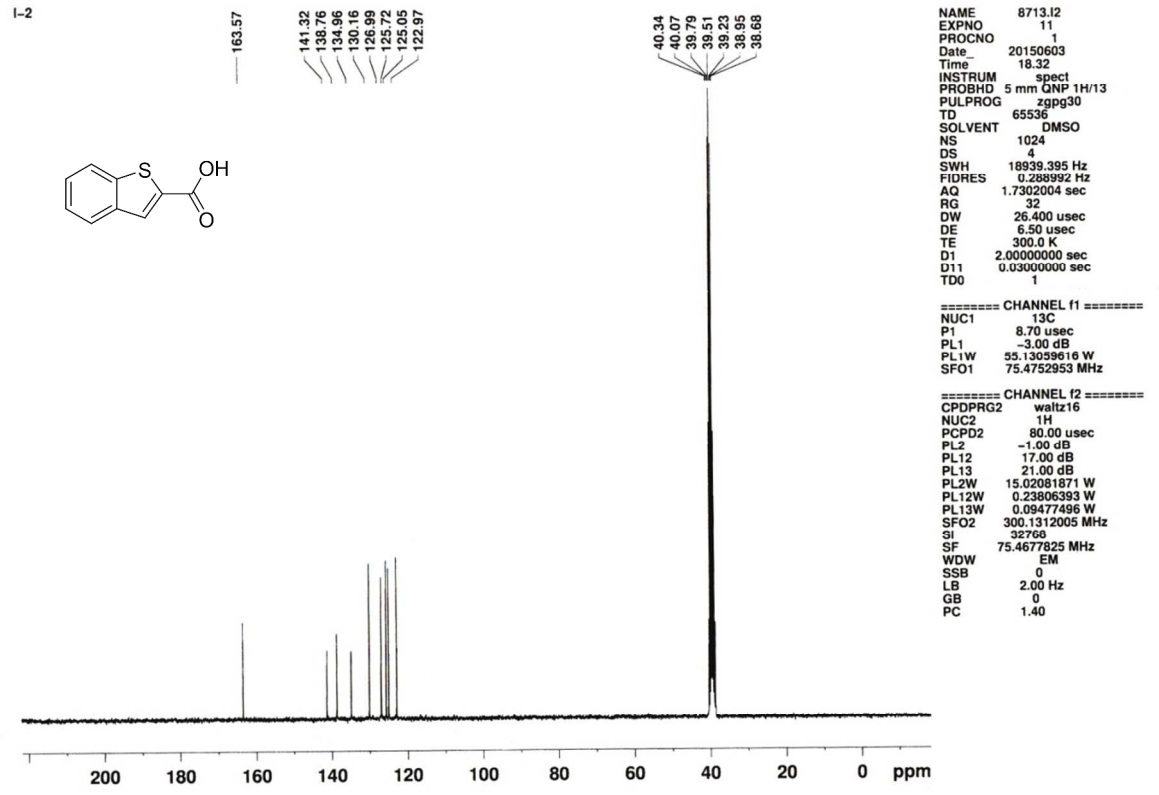
Compd	Glide score	Glide Energy (kcal/mole)	Van der Waals energy (kcal/mole)	Coulombic energy (kcal/mole)
7a	-9.198	-50.095	-45.951	-4.144
7b	-8.754	-48.395	-44.396	-3.999
7c	-7.062	-39.044	-35.538	-3.505
7d	-7.067	-41.841	-38.482	-3.359
7e	-6.995	-36.451	-33.451	-3.000
7f	-7.251	-44.176	-41.064	-3.112
7g	-7.234	-42.916	-39.159	-3.756
8c	-7.293	-47.045	-42.36	-4.685
8g	-7.495	-43.885	-40.464	-3.421

Representative Spectra:

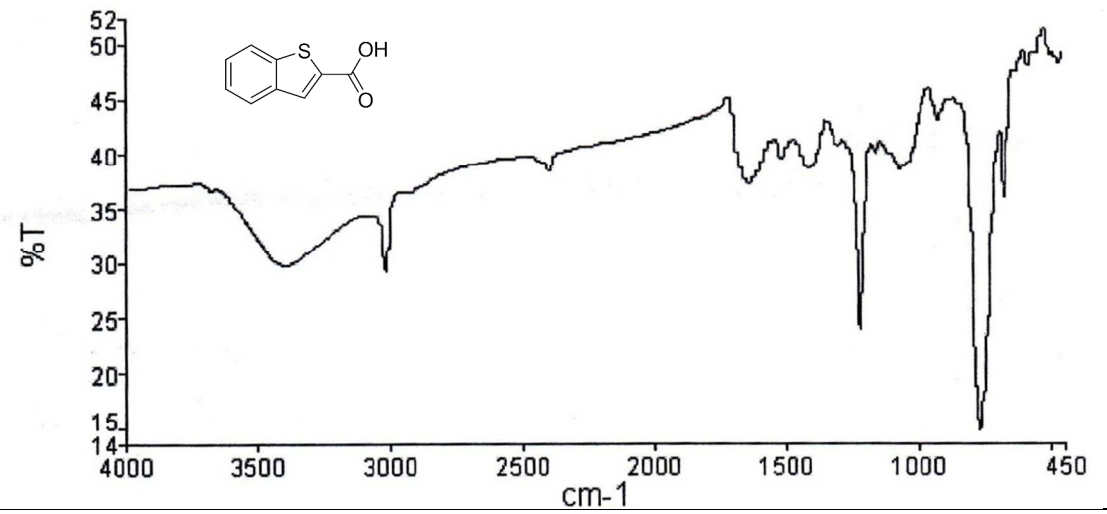
^{1}H NMR spectrum of compound 4:



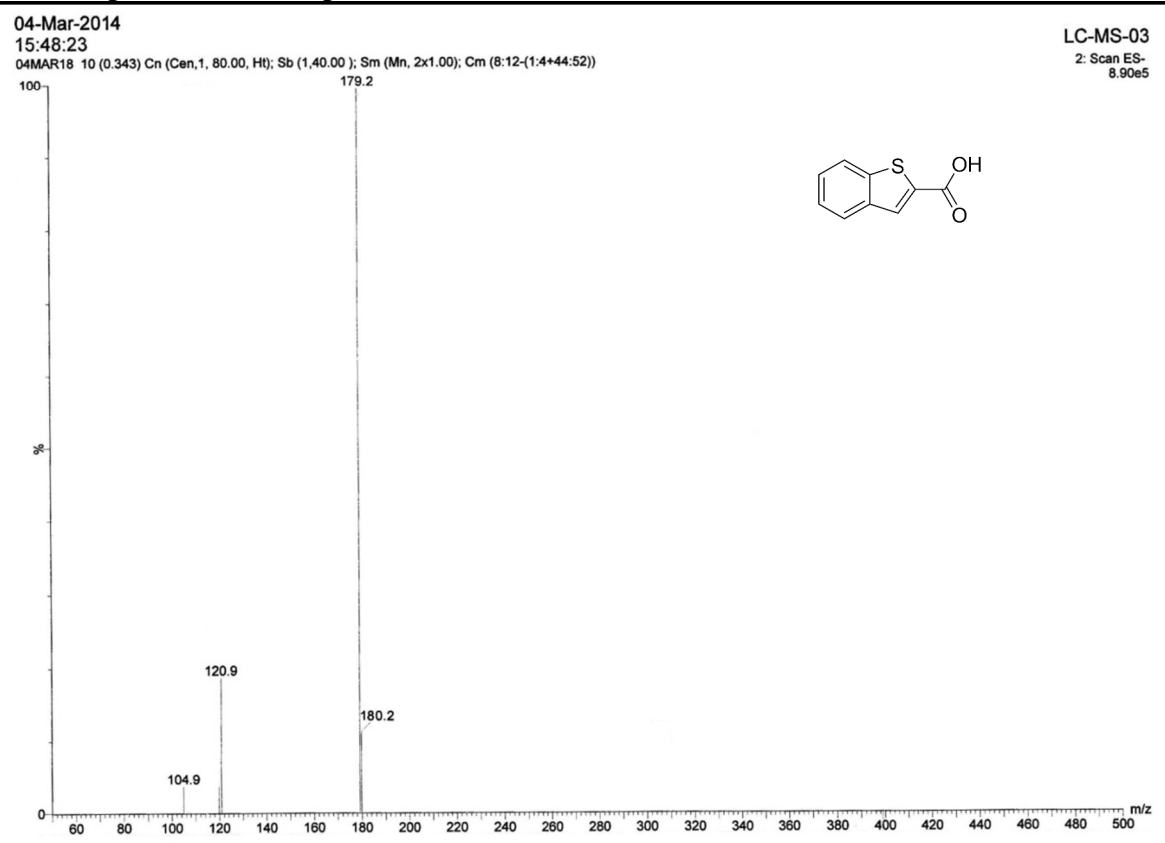
^{13}C NMR spectrum of compound 4:



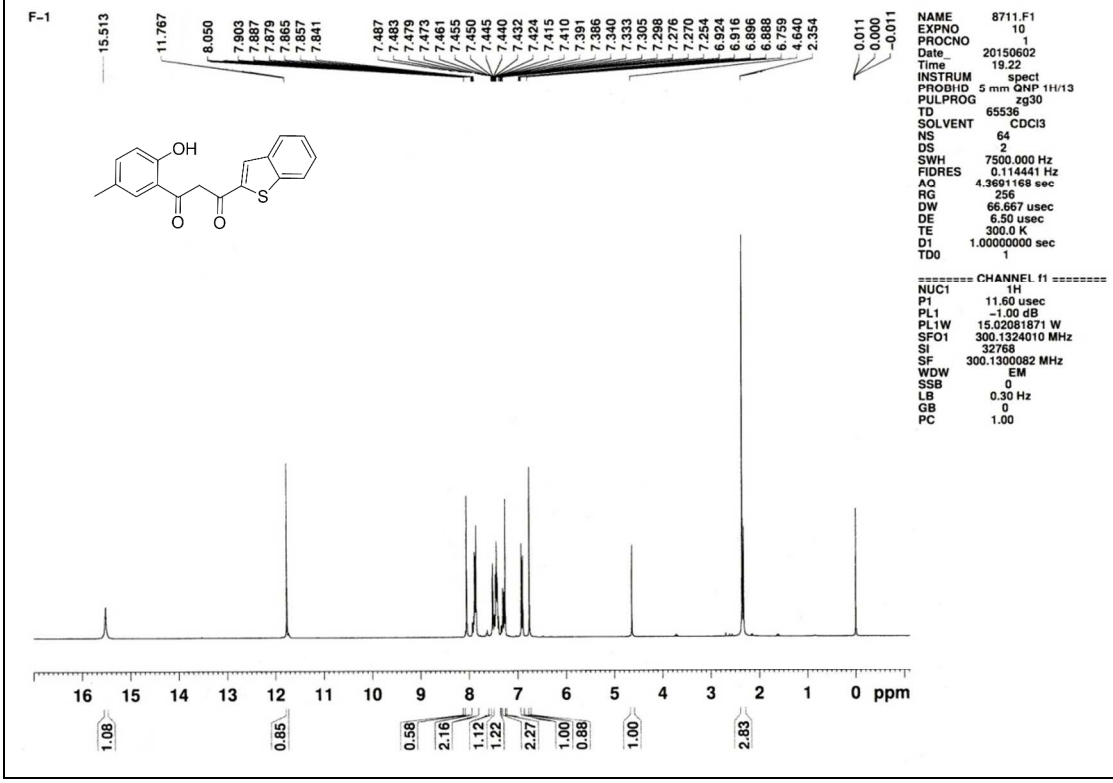
FT-IR spectrum of compound 4:



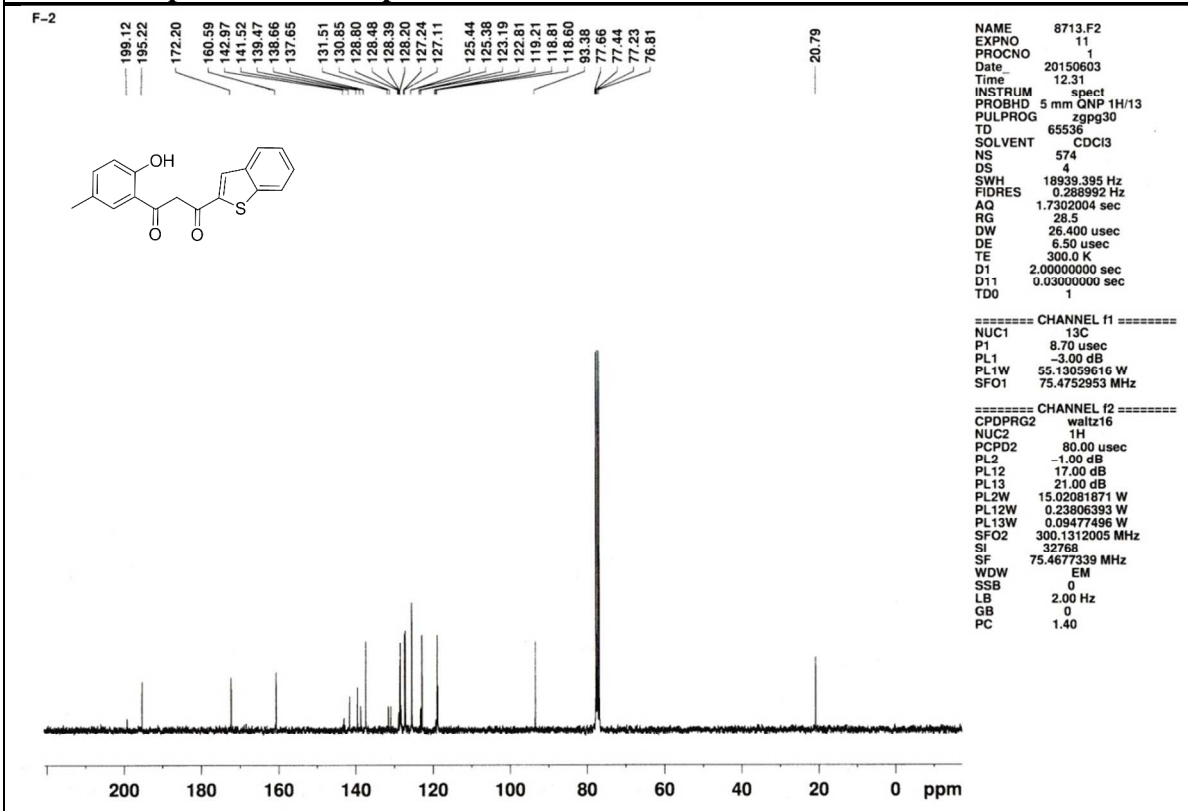
LCMS spectrum of compound 4:



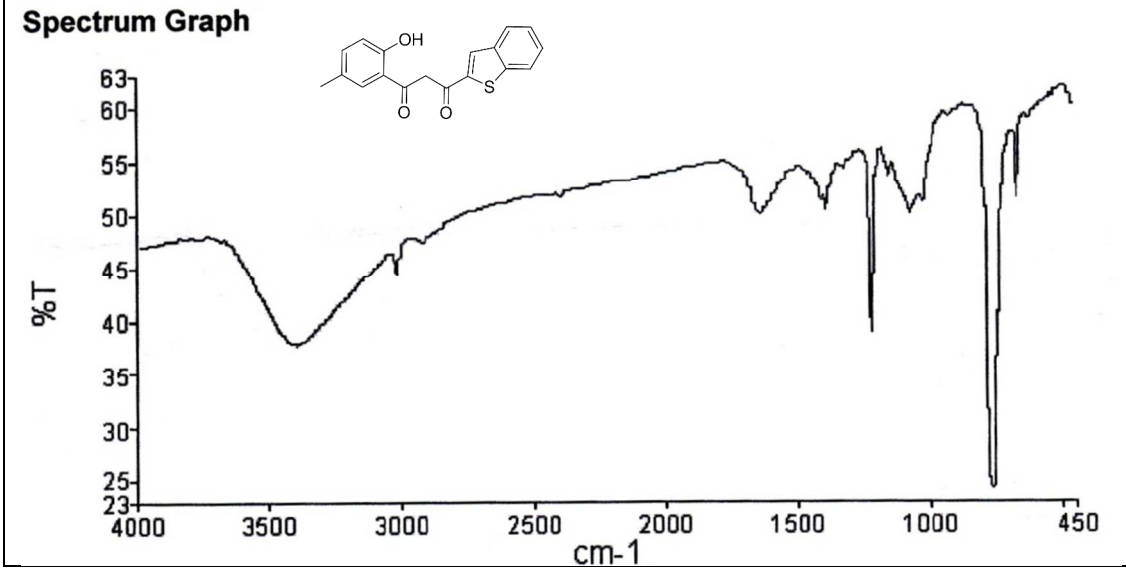
^{1}H NMR spectrum of compound 7c:



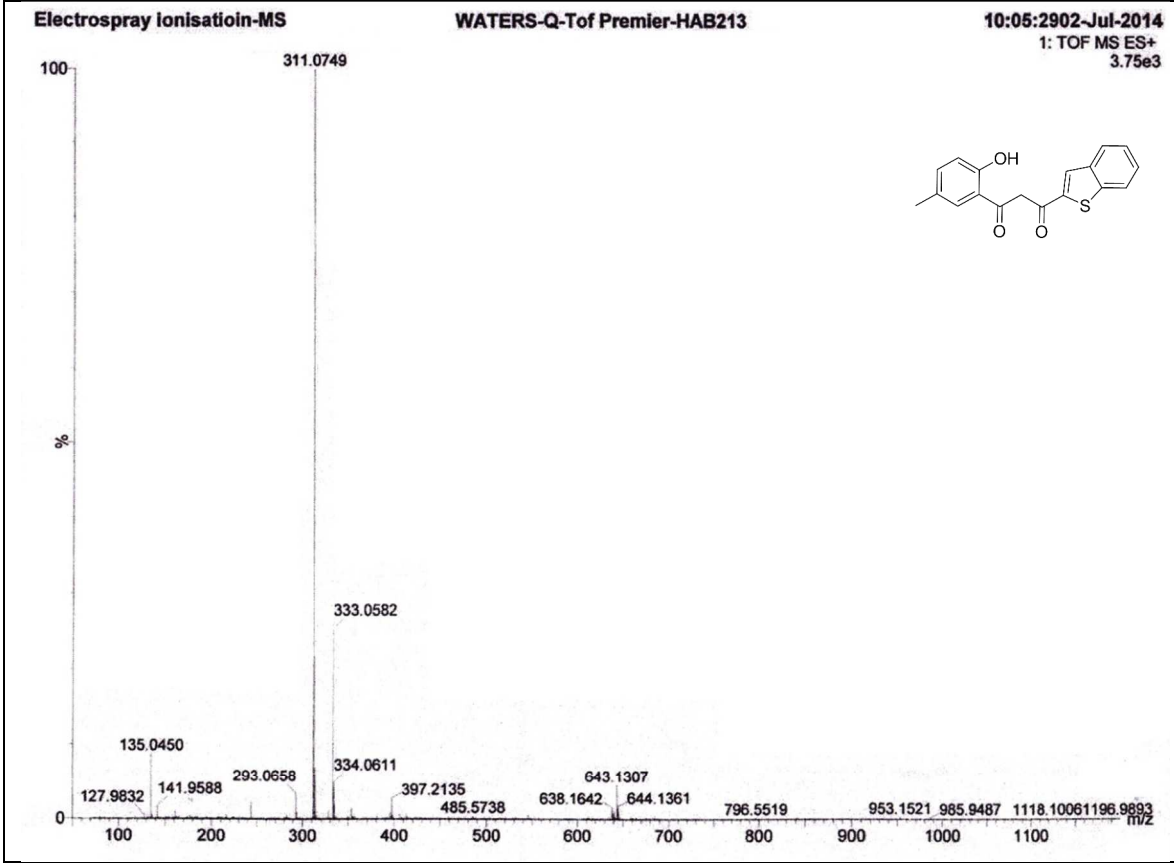
^{13}C NMR spectrum of compound 7c:



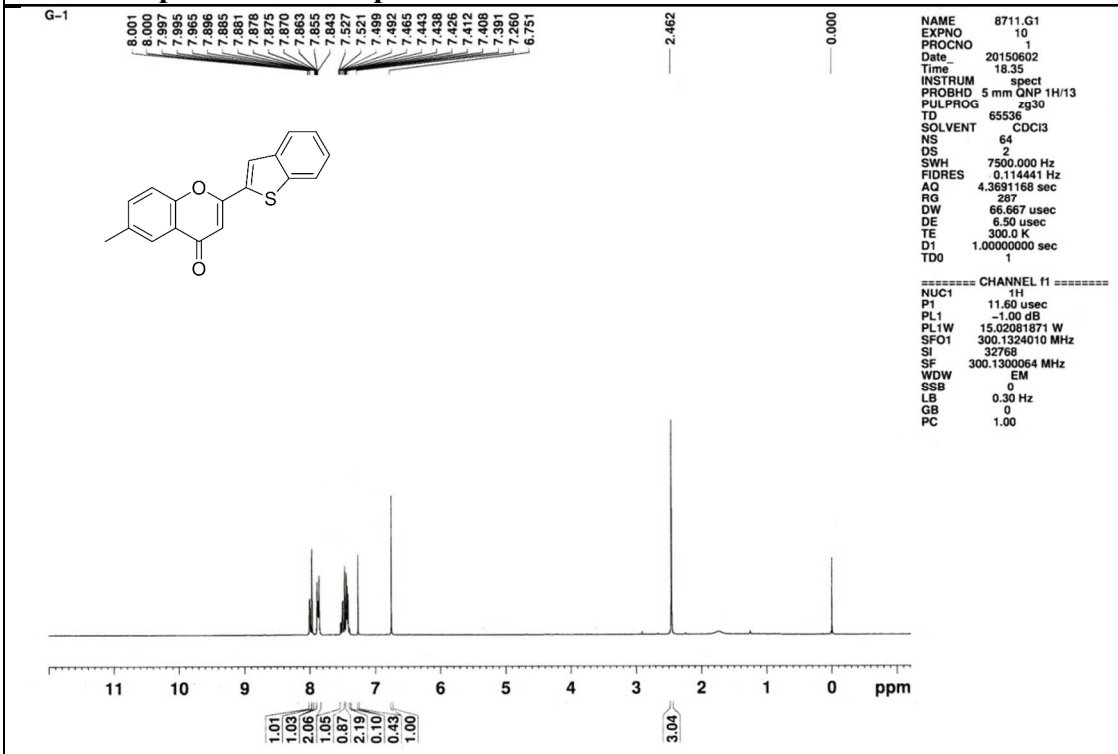
FT-IR spectrum of compound 7c:



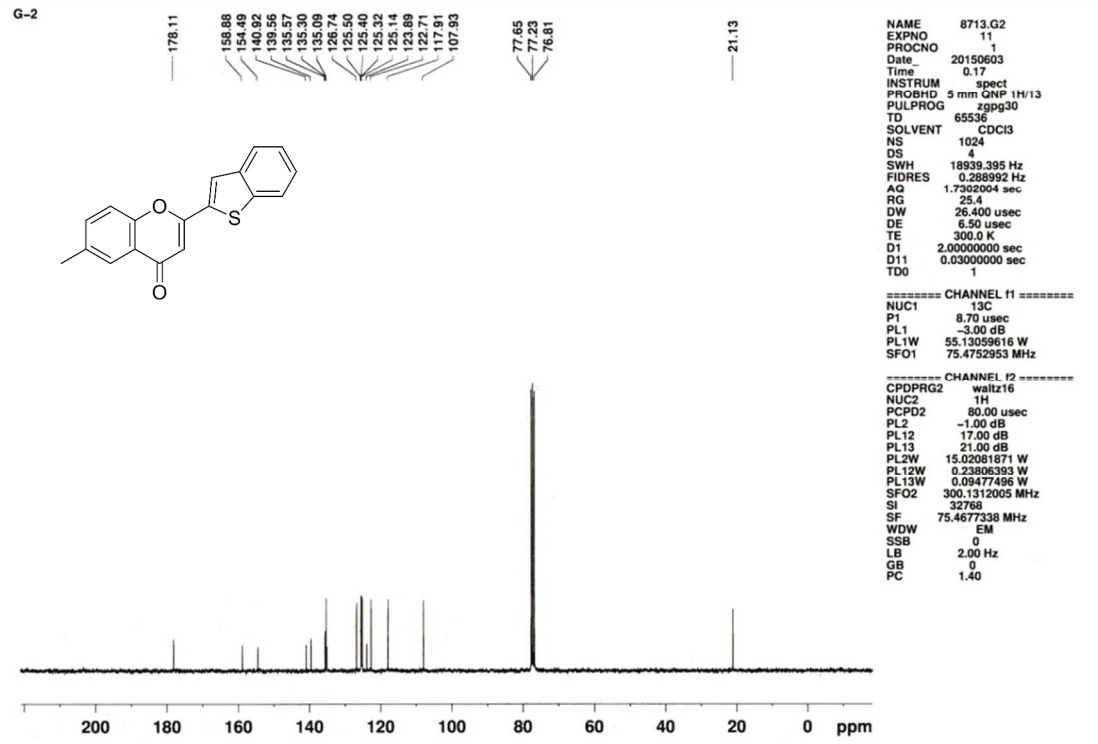
HRMS spectrum of compound 7c:



^{1}H NMR spectrum of compound 8c:



^{13}C NMR spectrum of compound 8c:



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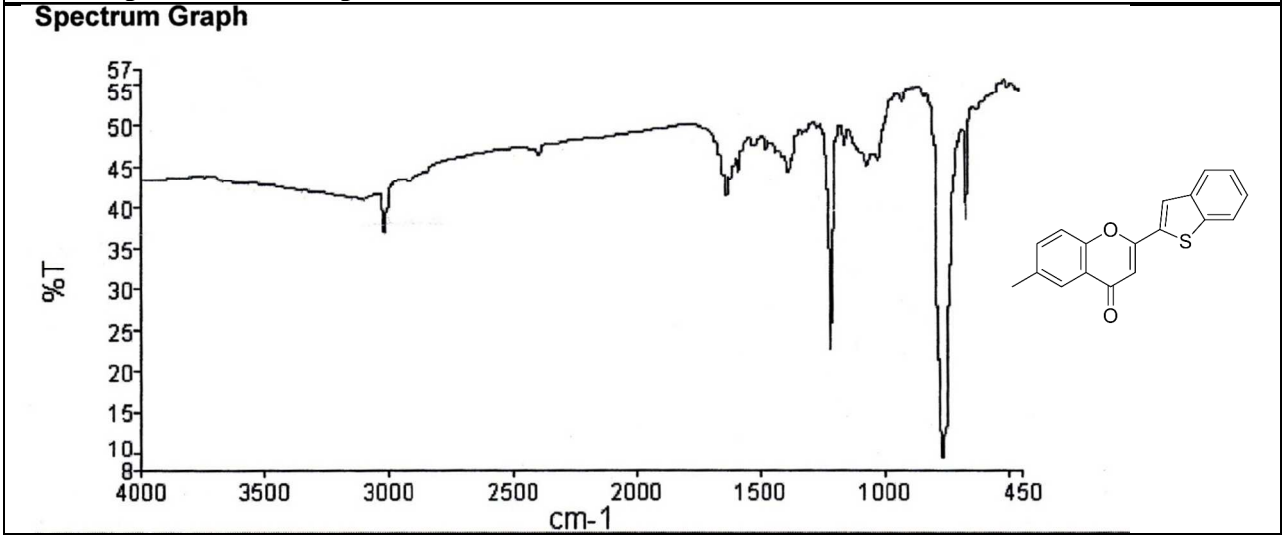

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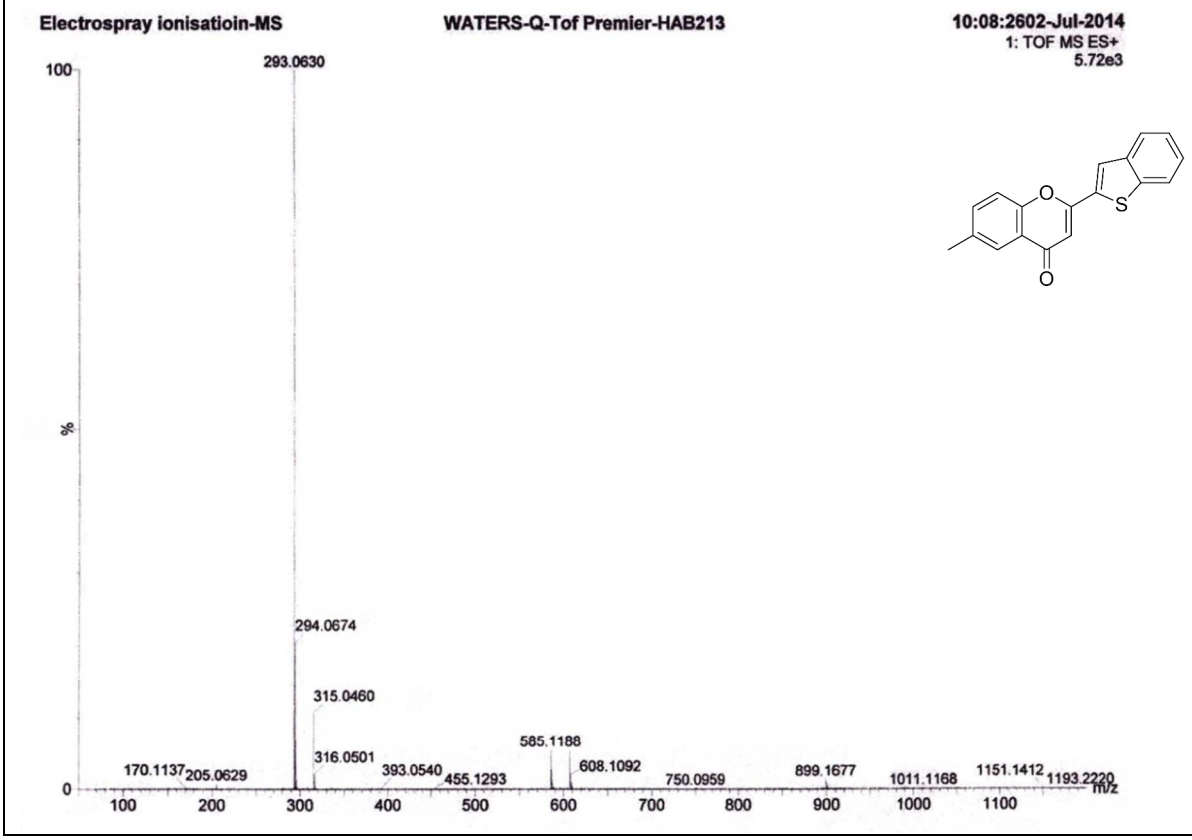
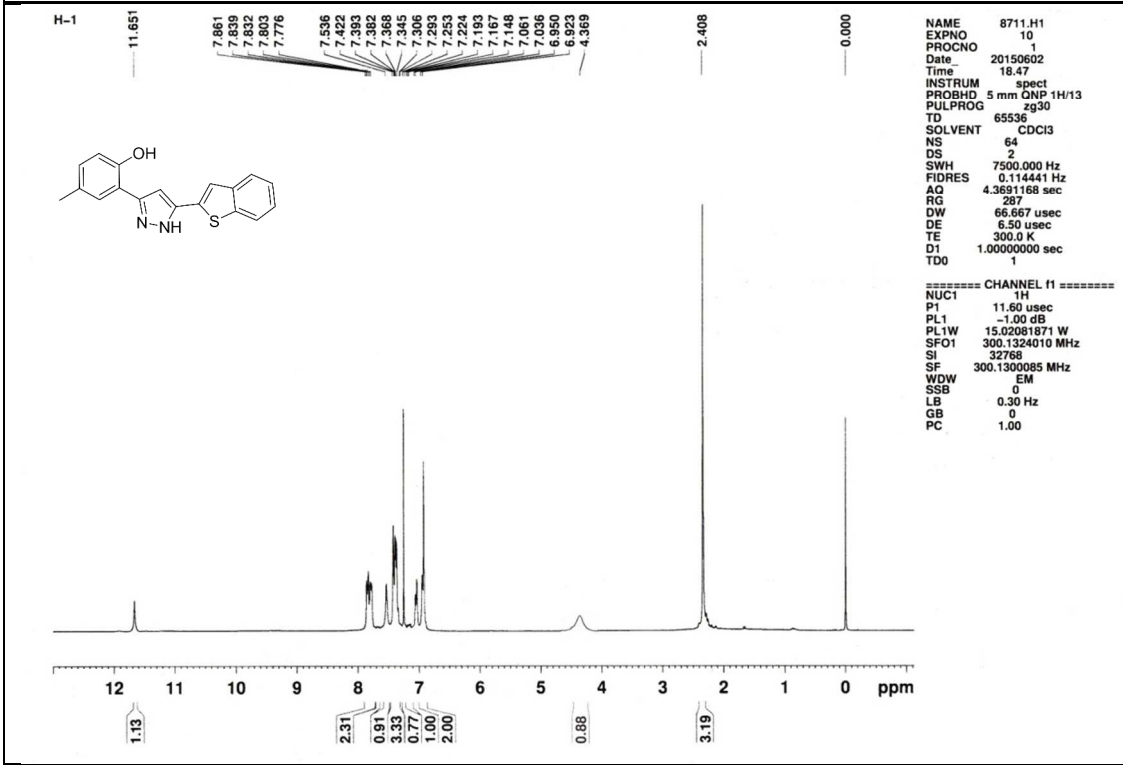
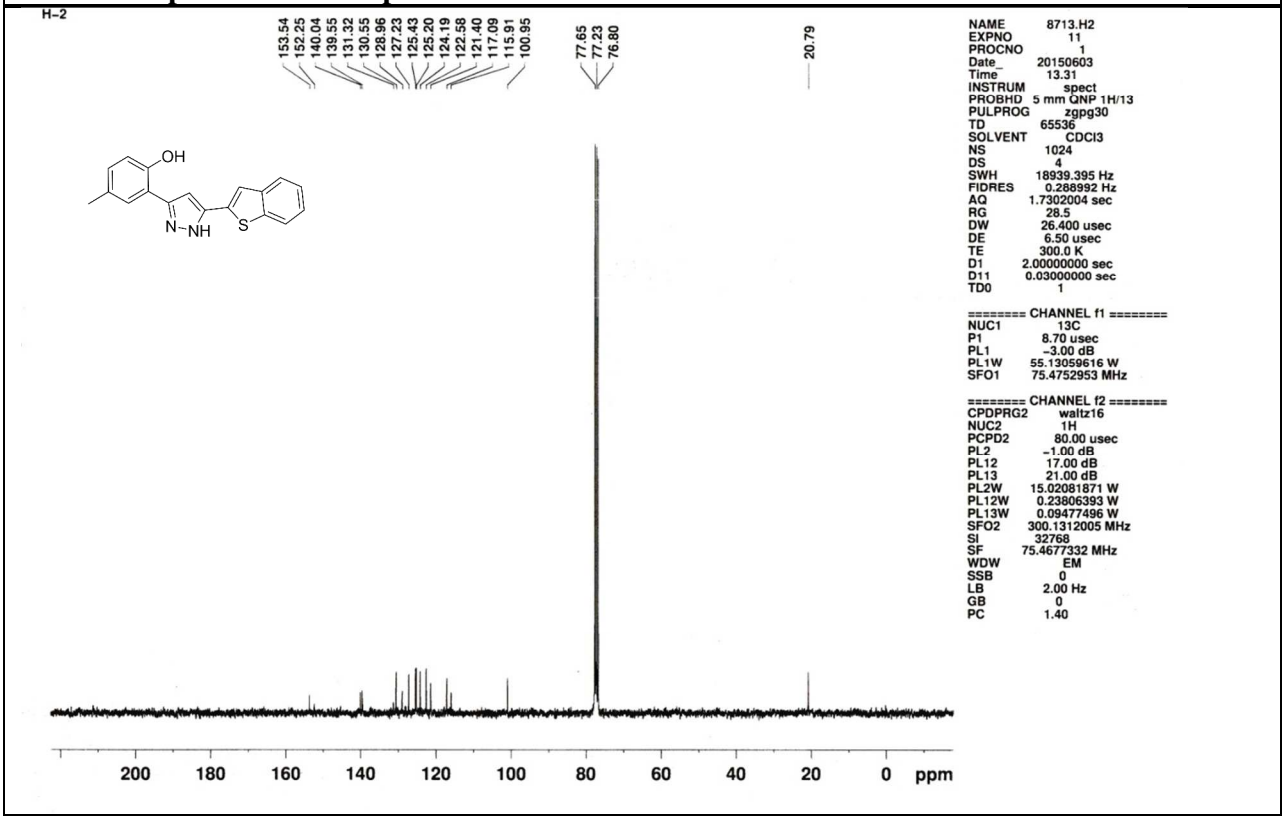


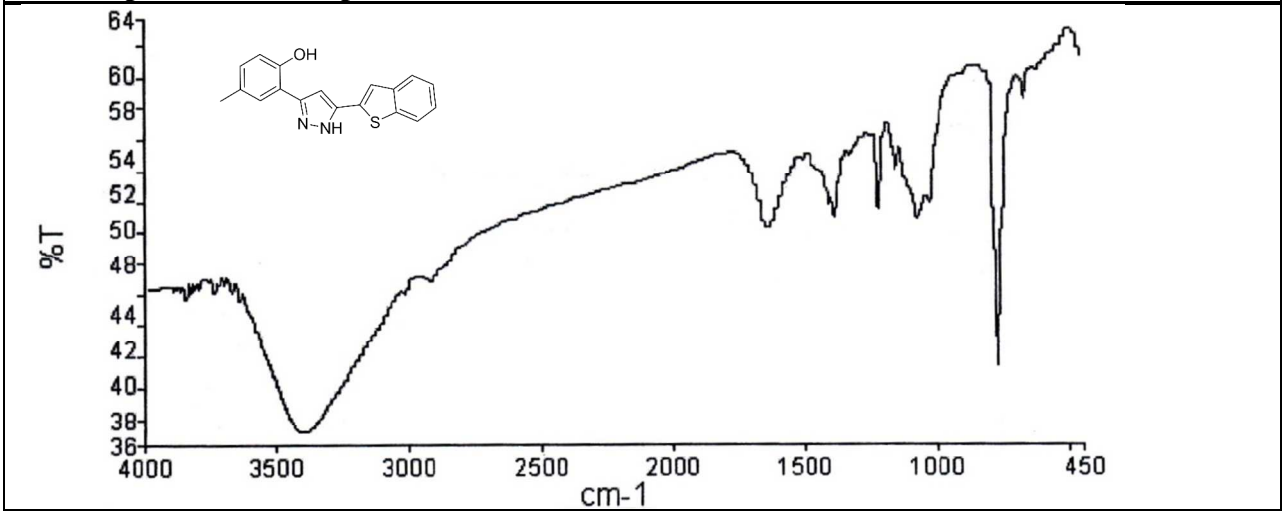
^{1}H NMR spectrum of compound 9c:



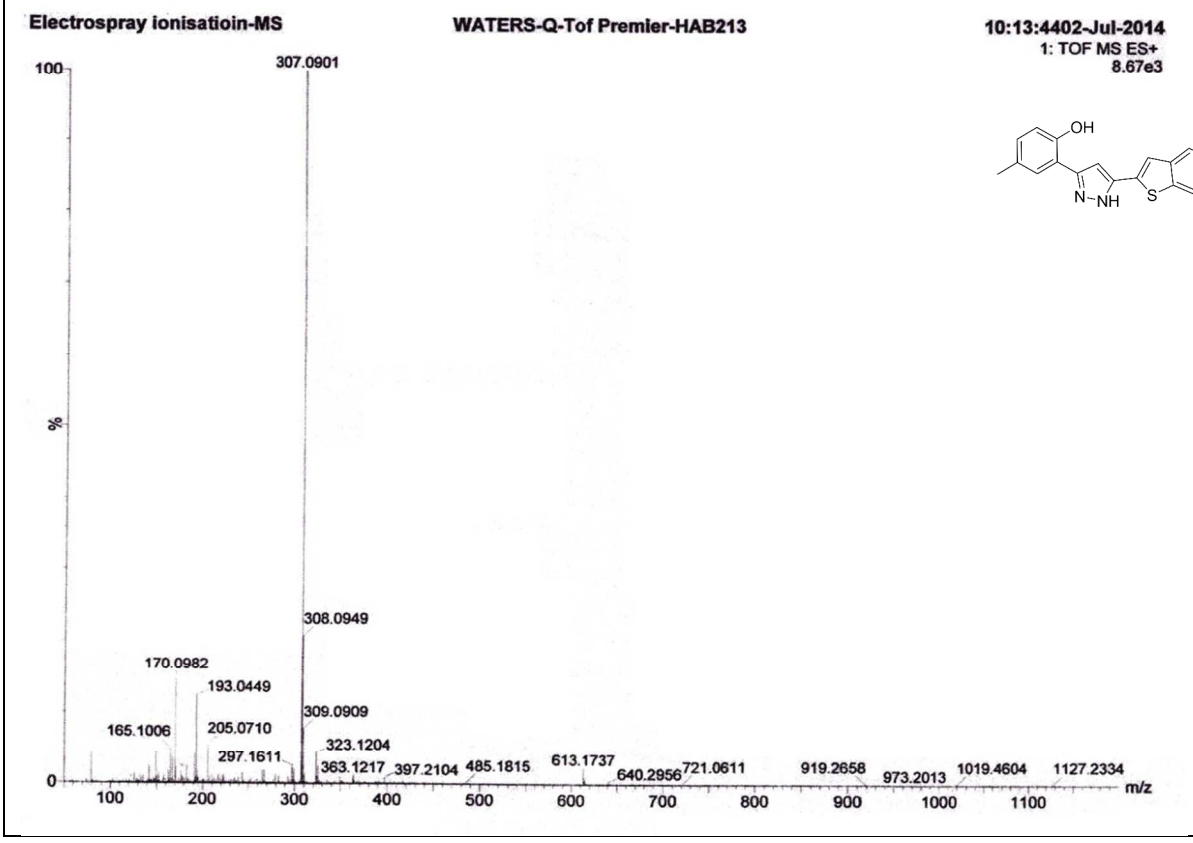
^{13}C NMR spectrum of compound 9c:



FT-IR spectrum of compound 9c:



HRMS spectrum of compound 9c:



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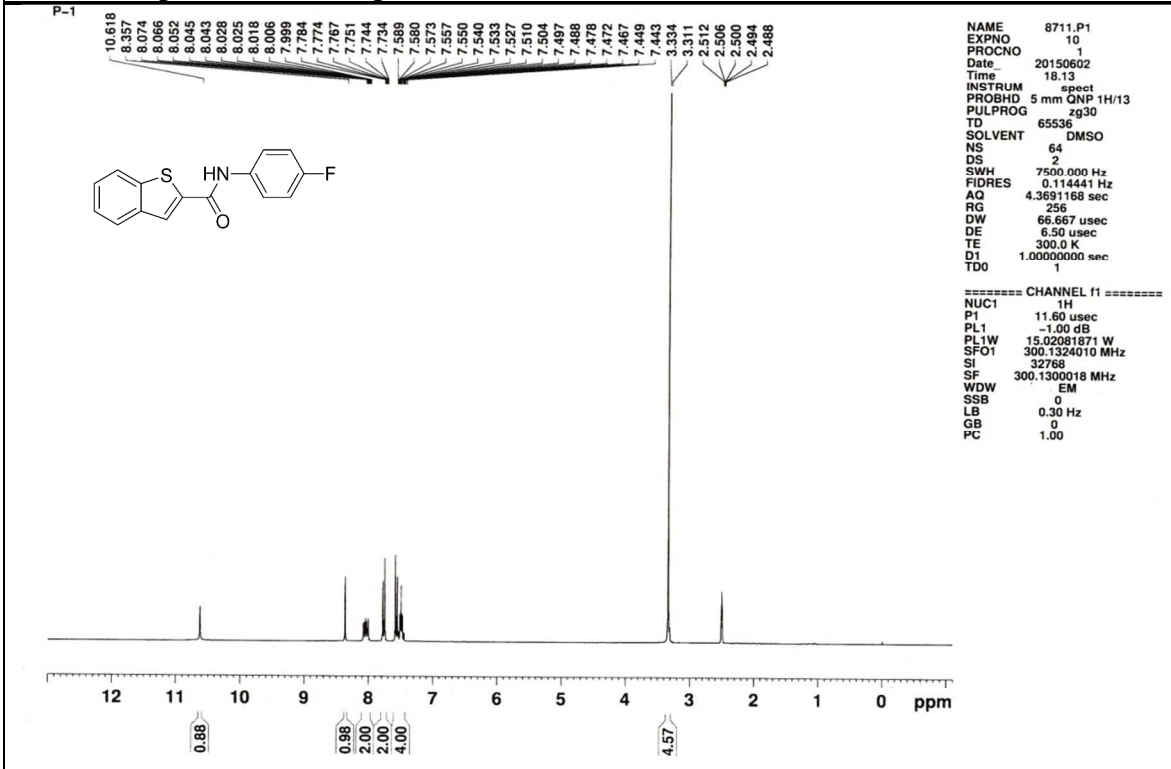
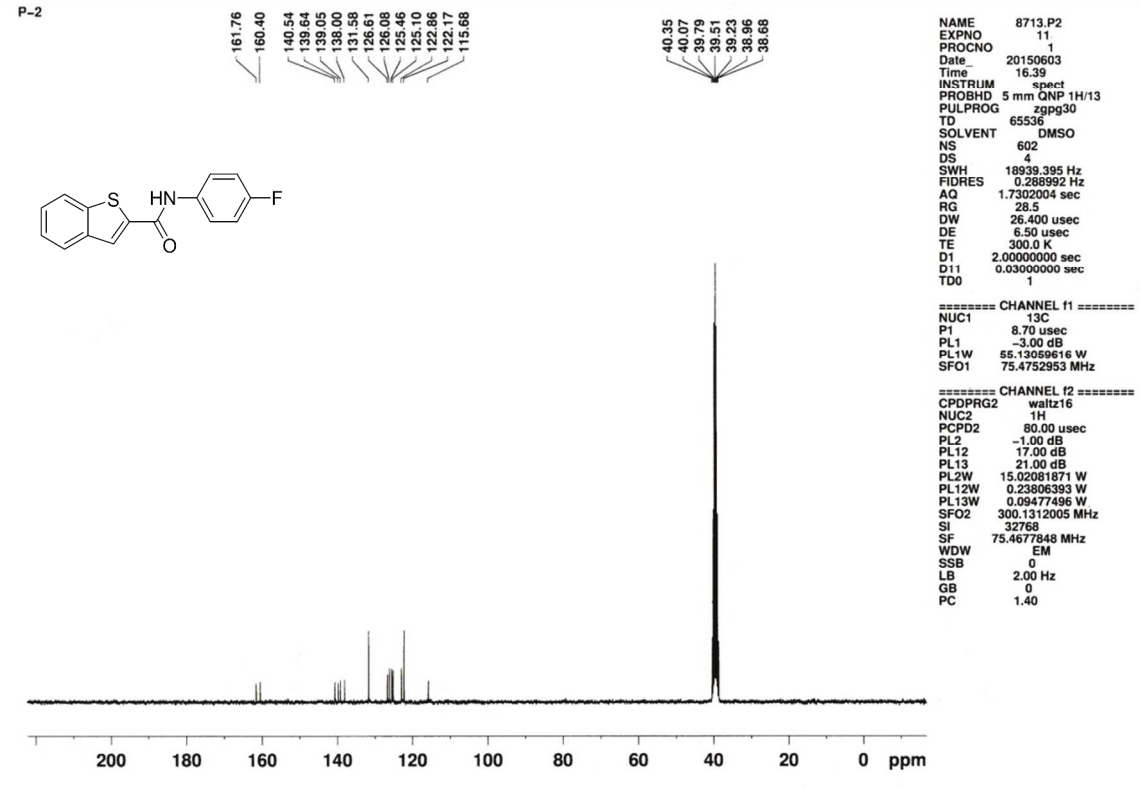
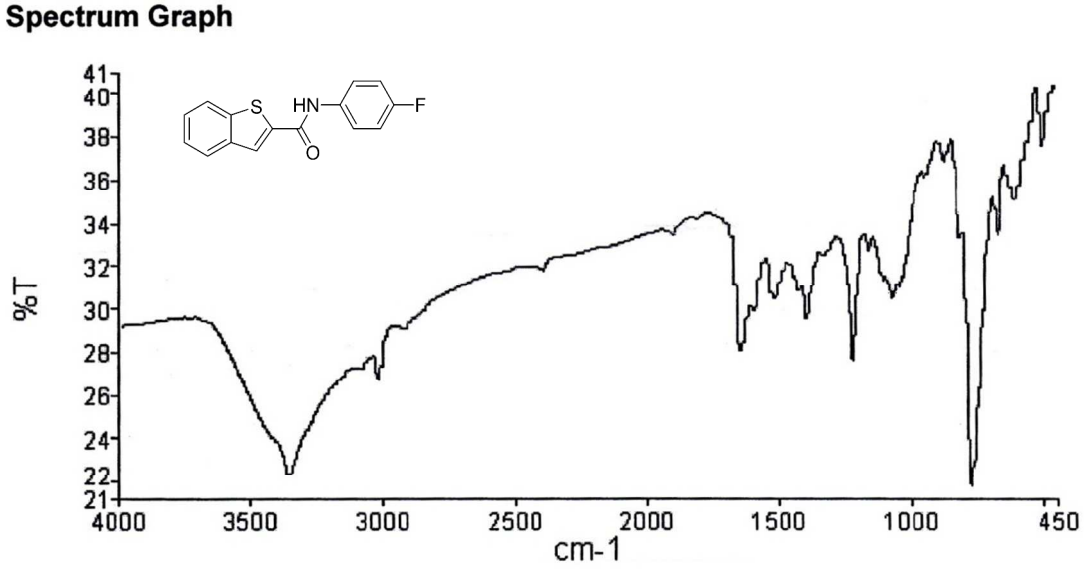


^{13}C NMR spectrum of compound 11d:



FT-IR spectrum of compound 11d:



HRMS spectrum of compound 11d: