CHAPTER 2

Design, synthesis and characterization of some novel neutral 2-substituted benzamidobenzene derivatives as factor Xa inhibitors

2.1 Abstract

This chapter deals with design and development of novel 2-substituted benzamidobenzene derivatives as probable factor Xa inhibitors. These derivatives were synthesized using cheap and readily available starting material like *p*-toluic acid, 2-nitrobenzene sulfonylchloride, *p*-nitro toluene and *o*-nitro toluene. All the compounds were isolated using chromatographic techniques and characterized by standard spectral and analytical analysis.

2.2 Introduction

Anticoagulants are used to treat a wide variety of thromboembolic diseases which are associated with high mortality and morbidity as discussed in chapter 1. The main side effect of anticoagulant therapy is bleeding. The current therapeutic options are limited and most of them do not meet patient's requirements. Hence still it is a topic of debate whether the anticoagulant drug under development will have better therapeutic window than existing drugs and what are the best targets for anticoagulant therapy. Before targeting factors in the coagulation cascade it is important to know that the amplification of each step in cascade is a result of sequential activation of factors by proteolytic cleavage. Also the coagulation cascade is subdivided into three pathways the extrinsic pathway, which is the primary activator of the cascade includes tissue factor and factor VIIa. The complex of tissue factor and factor VIIa can be targeted for inhibition, which initiates the coagulation cascade however this complex is essential for haemostasis and inhibition of this complex can lead to considerable bleeding.[1] The second is intrinsic pathway which amplifies the cascade includes factor XIIa, factor XIa, factor IXa and factor VIIIa and finally the common pathway contains factor Xa factor Va and thrombin. A study showed that deficiency of factors VIII, factor IX or factor XI have mild haemostatic defects in humans while that of factor XII showed normal haemostasis.[2] Therefore these factors from intrinsic pathway might be a useful target for anticoagulant therapy.[3,4] However many pharmaceutical industries have focused on inhibition of factor Xa and thrombin of common pathway due to its large impact on ongoing thrombosis as compared to that `of inhibition of the intrinsic pathway.[5,6] Thus with the unique position of fX in the coagulation cascade and the critical role of fXa in generation of thrombin, fXa has emerged as an attractive target for development of safer anticoagulant therapy. Factor Xa inhibitors are predicted to have lower risk of bleeding than heparins and warfarin, and offer even higher therapeutic ratio than direct thrombin inhibitors (DTIs). This provides a rationale to develop new and improved factor Xa inhibitors as anticoagulants.

Factor Xa was believed to be first isolated by Morawitz in 1905 when he identified thromboplastin.[7] Deficiency of a factor in patients administering coumarins was identified by Duckert in 1955 and he named the factor as FX.[8] In 1956 the

inherited FX deficiency was identified by Telfer and co-workers in a 22 year old patient Miss Prower.[9] Subsequently in 1957 Hougie et al identified the same deficiency in 36 year old man named Mr. Stuart.[10] Since then factor X was given a name as the Stuart-Prower factor derived from the name of the patients, until it was officially nomenclature as FX in 1962.

The human factor X gene (*F 10*) is located on the thirteenth chromosome at position 13q34.[11] It contains eight exons each of these encoding a specific functional domain of the protein as depicted in **Figure 2.1**. Exon 1 encodes the signal peptide, exon 2 encodes the propeptide sequence and the gamma-carboxylic acid-rich domain (Gla). Exon 3 encodes for short aromatic stack. Exons 4 and 5 encode two regions epidermal growth factor (EGF) like domains 1 and 2, exon 6 encodes the activation region, which is at the amino-terminus sequence of the heavy chain. Exons 7 and 8 encode the serine protease catalytic domain.[12]
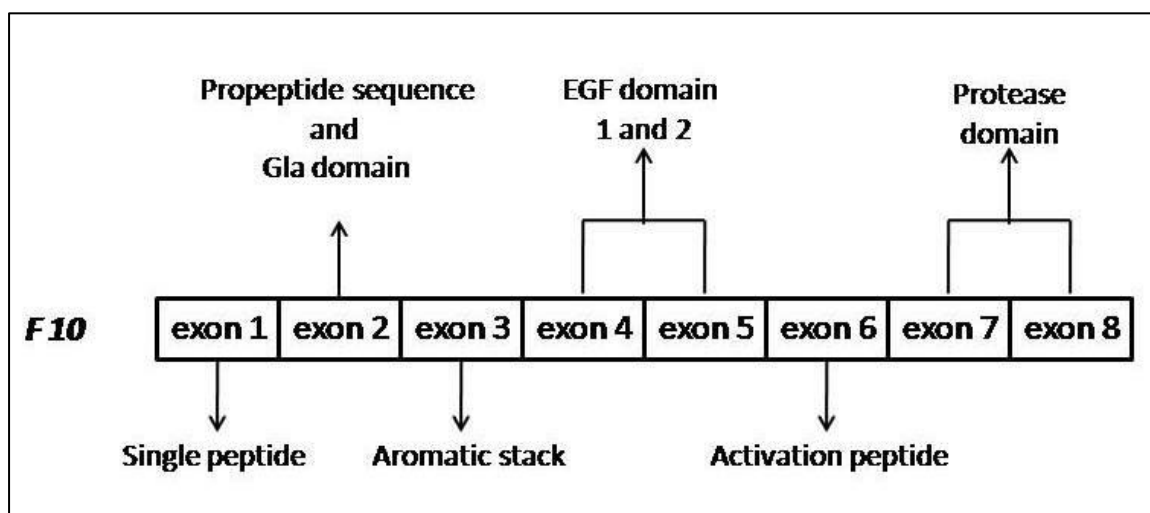

Figure 2.1 Structure of *F 10* gene

Factor X is a vitamin K-dependent serine protease (59 kDa), which is synthesized in the liver. It is secreted into blood as a zymogen and consists of two chains, which are linked by a disulfide bridge.[13] The heavy chain comprises 303 amino acids, the light chain 139. Serine proteases use a His57, Asp102, Ser195 catalytic triad which is located in the heavy chain. The activation of FX to FXa is generated by intracellular excision of the Arg194-Ile195 peptide bond in the heavy chain of the zymogen FX (**Figure 2.2**).
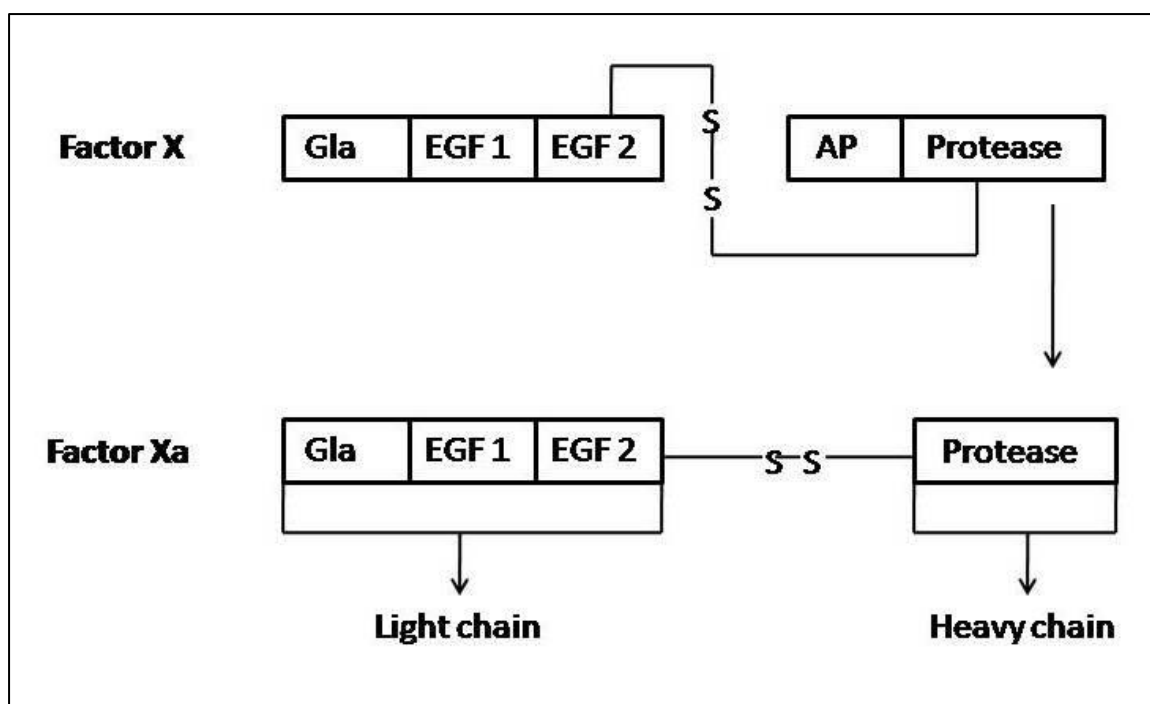
Figure 2.2 Structure of Factor X zymogene and activated Factor Xa.

The light chain of factor Xa contains a γ-carboxyglutamic acid (Gla) domain (11 Gla residues) as well as two epidermial growth factor (EGF)-like domains.[13] The vitamin K-dependent Gla domain is a post-translational modifications of many glutamate residues by vitamin K-dependent carboxylation to form gamma-carboxyglutamate.[14] This domain begins at the N-terminus of the protein and ends with a conserved aromatic residue. The Gla residues are responsible for the high-affinity binding of calcium ions. EGF-like domains have a length of approximately 40 amino acids. Factor X contains two of them located between the membrane-proximal γ-carboxyglutamic acid (Gla)- containing domain and the serine protease domain. Crystal structure suggest that the N-terminal epidermal growth factor (EGF)-like domain is flexibly, while the second EGF domain maintains contacts with the catalytic domain.[13] The heavy chain of factor Xa contains activation peptides and trypsin-like serine protease domain.

The catalytic mechanism of serine protease is shown in **scheme 2.1**. The first step is the formation of tetrahedral intermediate by the nucleophilic attack of Ser 195 on the carbonyl of the peptide bond. His57 acts as a base and initiates the reaction while Asp102 stabilizes the formed protonated His57 through hydrogen bonding. In the next

step His57 protonates the amine, endorsing formation of the acyl enzyme and release of the N-terminal portion of the substrate.

The deacylation portion repeats the same sequence. A water molecule is deprotonated by His57 and attacks the acyl enzyme, to yielding a second tetrahedral intermediate. Again, the tetrahedral intermediate is stabilized by the oxyanion hole. Upon collapse of the tetrahedral intermediate, the C-terminal portion of the protein is released.[15, 16]
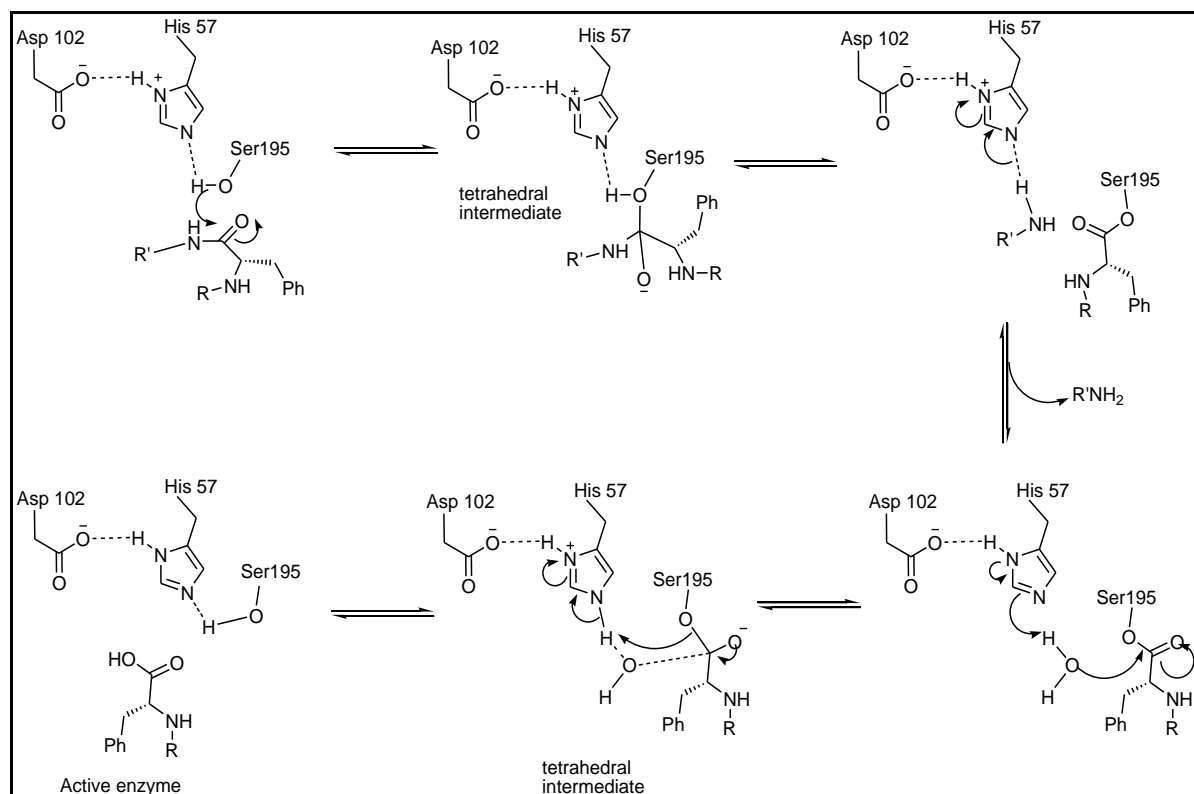
Scheme 2.1 Mechanism of action of factor Xa

The active sites of factor Xa are positioned mainly on the surface of the enzyme (**Figure 2.3**). The S1 pocket is located next to the catalytic triad and is formed by Trp215-Gly216 on one side while Ala190-Cys191-Gln192 on the other. The bottom of S1 pocket is formed of negatively charged Asp189 and the side chain of Tyr228. The natural substrate of factor Xa is prothromin which binds to S1 pocket through ionic hydrogen bonding of side chain of Arg15 with that of Asp 189. Factor Xa and thrombin feature alanine in position 190, whereas in trypsin this amino acid is replaced by Ser190, and this change in the volume and electrostatic properties of the S1 pocket can be exploited to gain selectivity.[17]
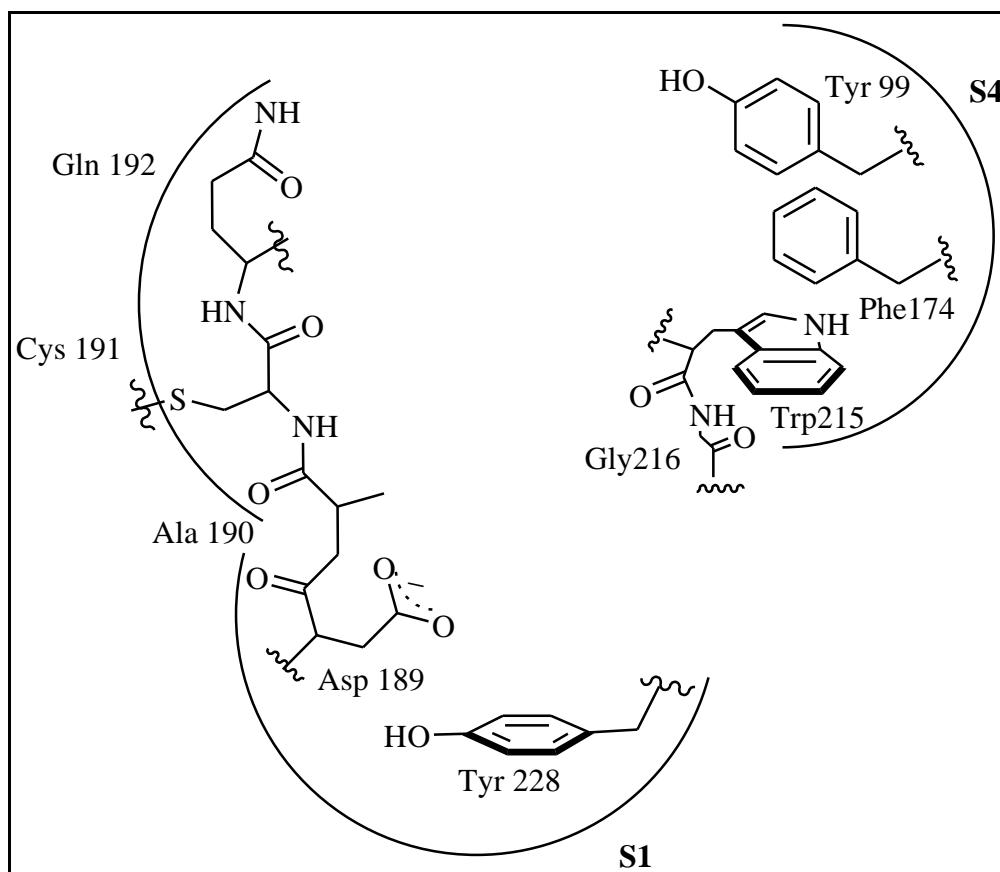
Figure 2.3 Active sites of factor Xa inhibitor

The S2 site of factor Xa is positioned adjacent to His57 it is small and shallow pocket. In contrast to other serine proteases, in factor Xa the access to the S2 pocket is blocked by Tyr99. The S3 site of factor Xa has little specificity, the side chain of Asp13 P3 residue projects out of the active site cleft.[18]

The S4 pocket is a strongly hydrophobic box located at the entrance and characterized by the side chains of Tyr99, Phe174, and Trp215 which forms deep aryl binding pocket (**Figure 2.3**). [17] Potent ligands reported in literature occupy both the S1 and S4 sites.

Factor Xa Inhibitors

Antistasin and tick anticoagulant peptide (TAP) are the first naturally occurring direct fXa inhibitors. Antistasin was discovered in 1987 by Tuszynski *et al*. is a 119 amino acids polypeptide isolated from the salivary gland of the Mexican leech *Haementeria officinalis*.[19] TAP consists of 60 amino acids was obtained from the soft tick *Ornithodoros moubata* in 1990.[20]

Fondaparinux a synthetic pentasaccharide is an indirect AT-dependent fXa inhibitor was synthesized in 1983 have a wider therapeutic window and do not trigger thrombocytopenia. The safety and efficacy of fondaparinux validated fXa as a sutible target for ACS patients. Thus Fondaparinux provided a new direction to anticoagulant research that provoked extensive research activities in developing direct fXa inhibitors as anticoagulants.[21]

DX-9065a (**Figure 2.4**), by Daiichi Sankyo was the first direct factor Xa inhibitor which contained highly basic amidine group and inhibited the enzyme with a *Ki* value of 41 nM.[22] However due to its low oral bioavailabity in humans (2-3%) DX-9065a was advanced clinically as a parenteral agent. Basic amidine group was the reason for its low oral bioavailabity.[23] A reversible fXa inhibitor by Sanofi-Aventis, Otamixaban (**Figure 2.4**), a 2,3-disubstituted *β*-aminoester derivative inhibited fXa with *Ki* value of 0.5 nM and showed good *in vitro* anticoagulant activity ($PTCT_2 = 1.1$ µM).[24] Otamixaban was administered intravenously and was found to be well tolerated in healthy human volunteers and patients with coronary artery disease in phase I/II studies.[25] Fidexaban (**Figure 2.4**), a Berlex-Pfizer product was the third parenteral agent with two amidine groups and a polar carboxylic acid advanced to human clinical trials.[26]

Clinical success of fondaparinux an indirect fXa inhibitor and the parenteral inhibitors described above motivated researchers to discover and develop safer and more effective oral factor Xa inhibitors, as parenteral inhibitors use outside hospital was problematic and required continuous monitoring of dose. Early efforts showed the discovery of small molecule inhibitors with dibasic benzamidine groups such as **4** (fXa, $Ki = 570$ nM)[27] and **5** (fXa, Ki = 610 nM)[28] set the stage for the evolution of dibasic inhibitors (**Figure 2.5**). In parallel efforts Portola Pharmaceuticals discovered compound **6** (fXa $IC_{50} = 6$ nM) and **7** (fXa $IC_{50} = 7$ nM)[29](**Figure 2.5**). Previously fXa inhibitors bearing anthranilamide[30,31] and 1, 2-dibenzamidobenzene[32,33] were reported to show good fXa inhibitory activity. However none of them were able to reach higher clinical trials due to their low oral bioavailability, short life and rapid clearance.
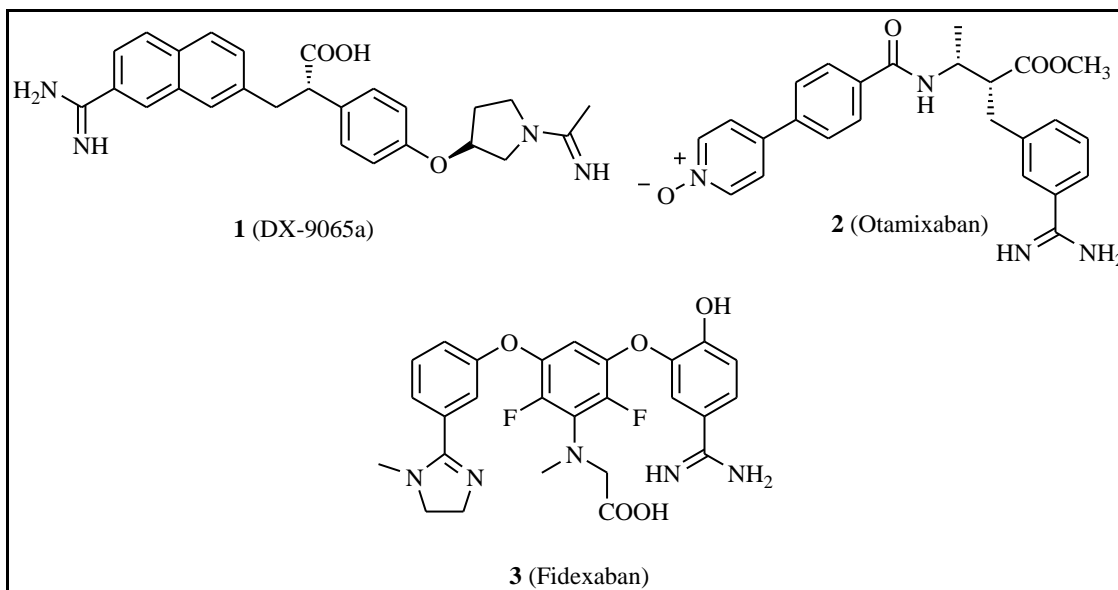
Figure 2.4 Parenteral fXa inhibitors

To improve oral bioavailability of the fXa inhibitors, several groups have come up with strategy of replacement of highly basic amidine group, traditionally used in majority of fXa inhibitors and that fits in both S1 and S4 binding pocket of fXa, with less basic group such as benzylamine.[34] Thus DPC423 (**8**, $Ki = 0.15$ nm) and razaxaban (**9**, $Ki = 0.19$ nm) was discovered, they were the first oral clinical candidate of the series which focused on lowering the pKa of the P1 ligand by replacing the amidine with less basic groups.[35,36]

Another strategy in which inhibitors bearing neutral substitutents like rivaroxaban (**10**), darexaban (**11**) edoxaban (**12**) and apixaban (**13**) were also developed. Rivaroxaban (**10, Figure 2.5**) is the first oral direct fXa inhibitor to be approved which contains neutral chloro-thiophene ring (S1 ligand) and morpholone ring (S4 ligand) as replacement of classical amidine groups. It has shown very potent fXa inhibitory activity (IC50 = 0.7 nM) and anticoagulant activity (PTCT2 = 0.23 mM using human plasma).[37] Oral bioavailability of rivaroxaban is high (80-100%) and peak plasma concentrations are reached within 3-4 hours after oral administration.[38] Rivaroxaban was first approved for marketing authorization by Health Canada and European Commission in september 2008, for the prevention of venous thromboembolism (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery. US FDA approved rivaroxaban for

prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in adults undergoing hip and knee replacement surgery in july 2011.

Apixaban (**13**) is the second compound to be approved in US and Europe in the year 2012 which contains lactam group (S4 ligand) and p-methoxyphenyl ring (S1 ligand). It has potent fXa inhibitory and anticoagulant activity (FXa, K_i = 0.08 nM, PTCT2 = 3.8 mM using human plasma).[39]

Edoxaban (**12**) is a potent inhibitor of human fXa *in vitro* (fXa, K_i = 0.56 nM), with > 10000-fold selectivity against relevant serine proteases, and demonstrated very good anticoagulant activity (PTCT2 = 0.26 μM using human plasma). It displayed *in vivo* efficacy in various animal models of thrombosis, with minimal bleeding.[40,41] It is approved in Japan for VTE prevention.

Betrixaban (**13**) has the 5-chloro-2-pyridine group as S1 ligand and possesses classical amidine group as S4 ligand. It is a potent inhibitor of fXa (K_i = 0.12 nM) and also displayed potency in a thrombin generation assay (TG2x = 0.33 μM). It is in Phase II for the treatment of DVT, PE, and prevention of stroke related to chroic AF.[42,43]
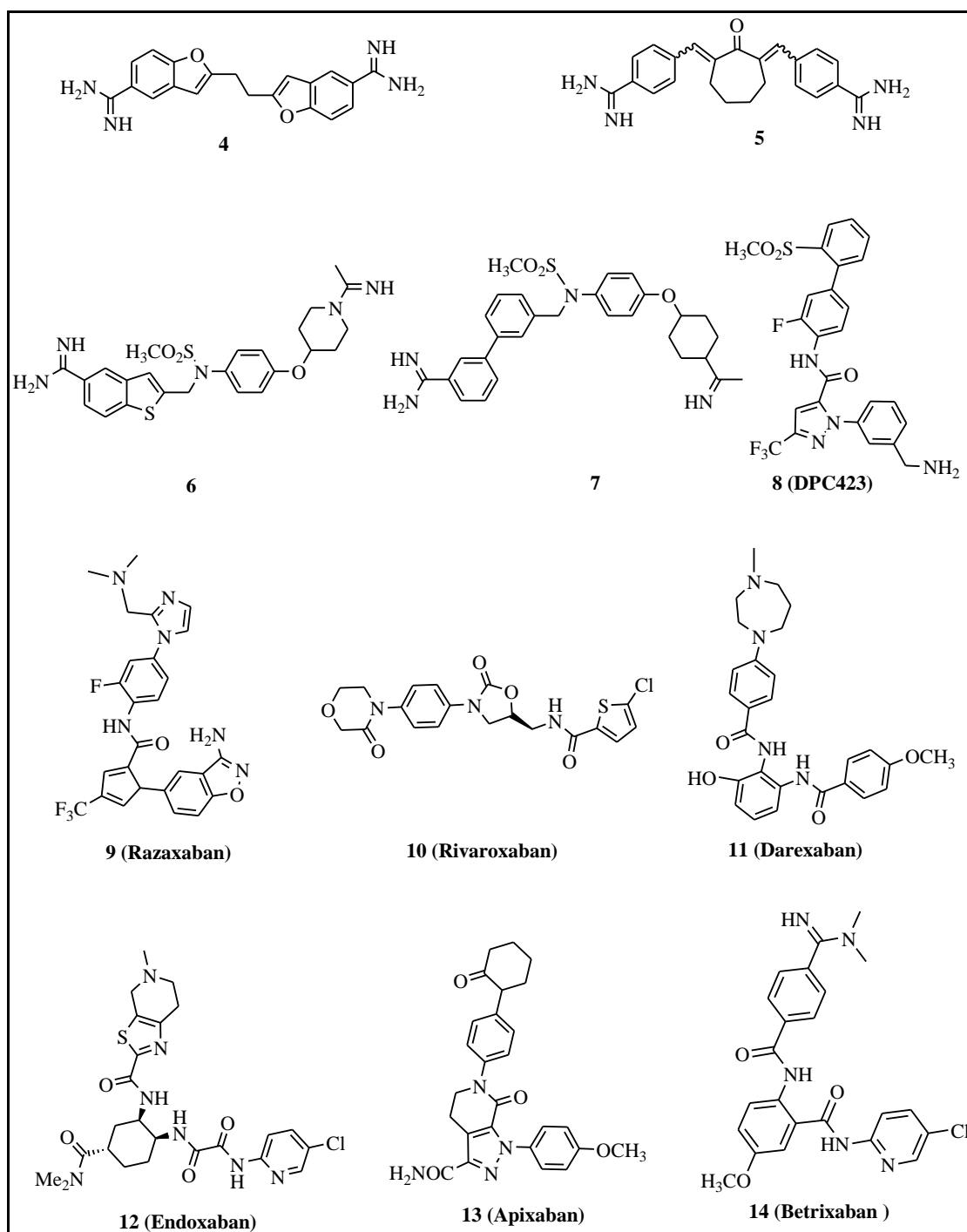
Figure 2.5 Oral factor Xa inhibitors

Table 2.1 shows few examples of novel factor Xa inhibitors approved in market for treatment of dangerous blood clots (systemic embolism) in patients with atrial fibrillation that is not caused by a heart valve problem.

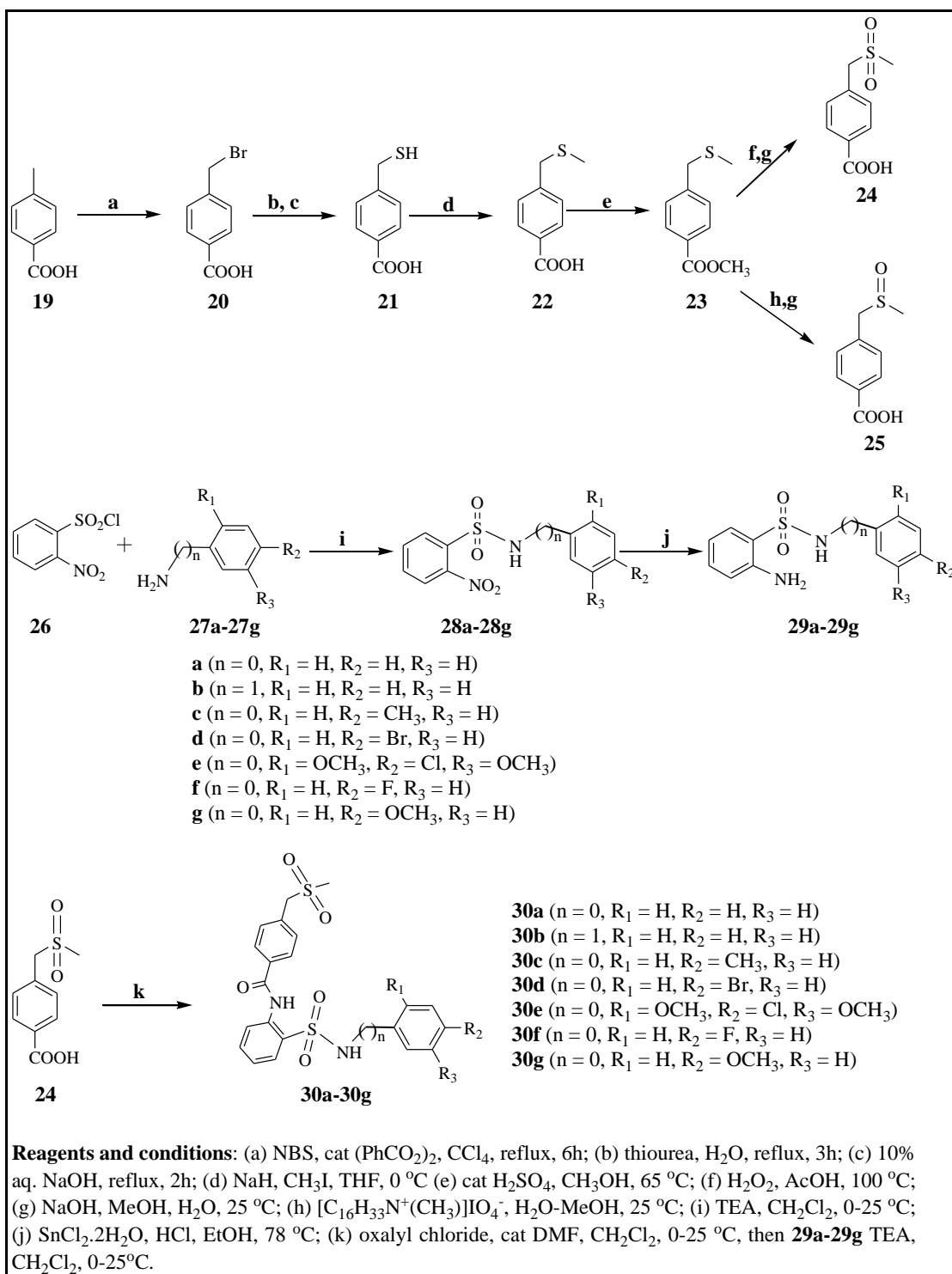**Table 2.1** Novel factor Xa inhibitors available in market

Drug	Company	Marketed Name	Current Status
Rivaroxaban	Bayer Healthcare	Xarelto®	Approved for prophylaxis of VTE (venous thromboembolism) after total hip or knee replacement, for DVT (deep vein thrombosis) and for secondary prevention of PE (pulmonary embolism) in US and European Union.
Apixaban	Bristol Myers Squibb-Pfizer	Eliquis®	Approved for prophylaxis of VTE (venous thromboembolism) after total hip or knee replacement, for DVT (deep vein thrombosis) and for secondary prevention of PE (pulmonary embolism) in US and European Union.
Edoxaban	Daiicho Sankyo	Lixiana®	Approved in Japan only for DVT (Deep vein thrombosis and PE (pulmonary embolism)

In summary, fXa inhibition is a authenticated impend to cure haemostasis and subsequent thrombosis. Many inhibitors of fXa are capable of curing various thormboembolic disorders and also approved in market (**Table 2.1**). These data thus provides a strong rationale to develop novel small molecule fXa inhibitor. In this chapter the design and synthesis of a novel neutral 2-substituted benzamidobenzene derivatives using cheap and readily available starting materials like p-toluic acid (**19**), o-nitrobenzene sulfonyl chloride(**26**), p-nitrotoluene (**31**), anthranilic acid (**36b**), o-nitroaniline (**36a**) and o-nitrotoluene (**42**), has been reported.

2.3 Results and discussion

Search for ligands providing optimal interactions within two essential sub pockets S1 and S4 of the serine protease factor Xa has been a major focus in the design of selective fXa inhibitors. Also the molecules that are able to acquire V or L-shaped conformations are reported to be able to inhibit fXa.[44] Previously fXa inhibitors bearing anthranilamide (**15**),[45] 1,2-dibenzamidobenzene (**16**),[46] sulfoamidopyrrolidin-2-one (**17**)[47] and 2-aminobenzamides (**18**)[48] were reported to show good fXa inhibitory activity (**Figure 2.6**).

Figure 2.6 Factor Xa inhibitors having anthranilamide (**15**), 1,2-dibenzamidobenzene (**16**), sulfoamidopyrrolidin-2-one (**17**), 2-aminobenzamides (**18**) derivatives.

Based on the knowledge of receptor and related reports, we designed some V shaped 2-substituted benzamidobenzene derivatives having neutral groups like sulfone, sulfide and sulfoxide and varing linkers connecting B and C rings as shown in **Figure 2.7**.

where, $X = -SO_2-$, $-SO-$, $-S-$

where,
$(Y = SO_2\ Z = NH)$
$(Y = CH_2, Z = O)$
$(Y = CH_2S, Z = CH_2)$
$(Y = CH_2, Z = S)$
$(Y = CH_2SO_2, Z = CH_2)$
$(Y = CH_2, Z = SO_2)$

where, R_1, R_2, R_3 = H, alkyl, alkoxy, halo

Figure 2.7 General structure of 2-substituted benzamidobenzene derivatives

The synthesis of first set of compounds, benzamidobenzenesulfonamide derivatives, is described in **Scheme 2.2**. The starting material used for the preparation of sulfone, sulfoxide and sulfide fragments was *p*-toluic acid (**19**). Benzylic bromination of **19** with catalytic amounts of benzoyl peroxide and NBS gave **20** which on treatment with thiourea followed by sodium hydroxide gave the corresponding thiol derivative (**21**).[49] The thiol group was then methylated using methyl iodide and a strong base like sodium hydride or sodium methoxide. Acid (**22**) thus obtained was converted into its methyl ester (**23**) which upon oxidation using hydrogen peroxide[50] and cetyltrimethyl ammonium periodate[51] gave corresponding sulfone (**24)** and sulfoxide (**25**) subsequent to alkaline hydrolysis. Condensation of 2-nitrobenzenesulfonyl chloride (**26)** with amine derivatives (**27a-27g**) gave intermediates (**28a-28g**)[52-54], which on reduction using stannous chloride[55,56] resulted into aniline derivatives (**29a-29g**). Acylation of **29a-29g** using acid chloride obtained from **24** using oxalyl chloride gave compounds (**30a-30g**).

The structures of compounds (**30a-30g)** were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS and elemental analysis. The ^{1}H NMR spectrum of **30a** displayed a singlet at δ 2.98 for methyl protons, a singlet at δ 4.65 for methylene protons, multiplets between 7.00-7.04, 7.14-7.18, 7.25-7.29, a doublet at δ 7.44, multiplet between δ 7.61-7.67, a doublet at δ 7.90, 8.35 for aromatic protons, a singlet at δ 10.13 for amide proton, and a singlet at δ 10.52 for sulfonamide proton. The ^{13}C NMR spectrum of **30a** exhibited signal at δ 40.26 for methyl carbon, peak at δ 59.45 for methylene carbon, peaks at δ 122.25, 123.58, 124.71, 125.63, 127.95, 128.20, 129.69, 131.84, 133.75, 134.38, 134.57, 136.44, 137.03 for aromatic carbon along with signal at δ 164.79 for carbonyl carbon. The structure of **30a** was further confirmed by its High Resolution Mass Spectrum which gave a molecular ion peak [M+Na]$^+$ at 467.0710. The elemental analysis was in good agreement with the required for $C_{21}H_{20}N_2O_5S_2$ it was calculated C, 56.75; H, 4.51; N, 6.08 and found: C, 56.20; H, 4.58; N, 6.01.

The ^{1}H NMR spectrum of compound **30c** exhibited a sharp singlet at δ 2.11 for methyl proton attached to aromatic ring, a singlet at δ 2.98 for methyl proton attached to sulfone group, a singlet at δ 4.65 for methylene protons, a doublet at δ
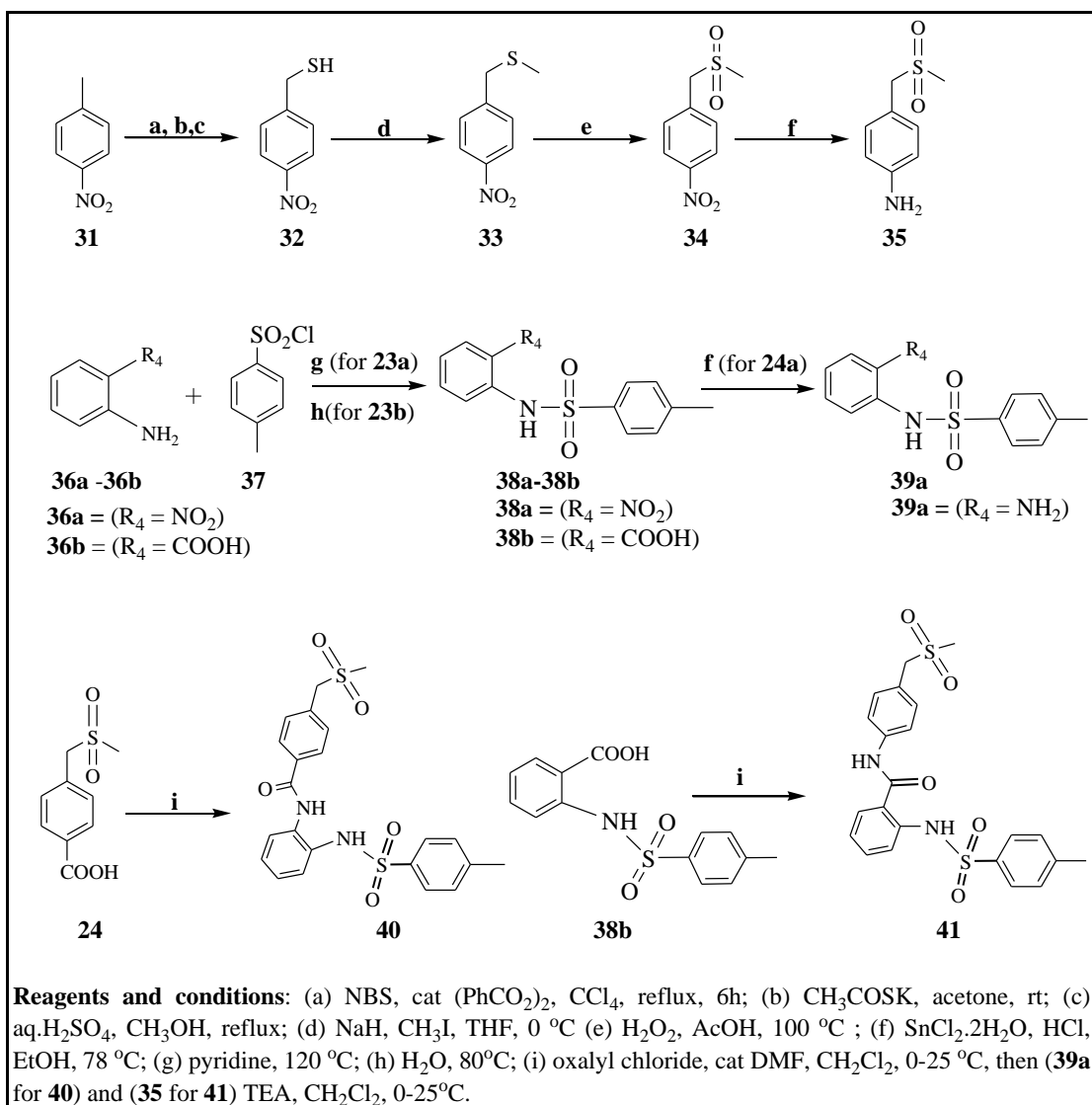
Reagents and conditions: (a) NBS, cat (PhCO$_2$)$_2$, CCl$_4$, reflux, 6h; (b) thiourea, H$_2$O, reflux, 3h; (c) 10% aq. NaOH, reflux, 2h; (d) NaH, CH$_3$I, THF, 0 ^{o}C (e) cat H$_2$SO$_4$, CH$_3$OH, 65 ^{o}C; (f) H$_2$O$_2$, AcOH, 100 ^{o}C; (g) NaOH, MeOH, H$_2$O, 25 ^{o}C; (h) [C$_{16}$H$_{33}$N$^+$(CH$_3$)]IO$_4^-$, H$_2$O-MeOH, 25 ^{o}C; (i) TEA, CH$_2$Cl$_2$, 0-25 ^{o}C; (j) SnCl$_2$.2H$_2$O, HCl, EtOH, 78 ^{o}C; (k) oxalyl chloride, cat DMF, CH$_2$Cl$_2$, 0-25 ^{o}C, then **29a-29g** TEA, CH$_2$Cl$_2$, 0-25°C.

Scheme 2.2 Synthesis of **30a-30g**

6.87, 6.93, a multiplet between δ 7.24-7.28, a doublet at δ 7.62, a multiplet between δ7.65-7.74, a doublet at δ 7.86, a multiplet between δ 8.35-8.37 for aromatic proton, singlet at δ 10.07 for a amide proton, and a singlet at δ 10.32 for sulfonamide proton. Its ^{13}C NMR spectrum displayed signal at δ 20.79 for methyl carbon, signal at δ 40.18

for methyl carbon attached to sulfone group and a signal at δ 59.46 for methylene carbon, while signals at δ 123.13, 124.57, 127.84, 127.94, 129.66, 130.13, 131.80, 133.76, 134.14, 134.38, 135.28, 136.48 for aromatic carbons and at δ 164.60 for carbonyl carbon. The structure of **30c** was further confirmed by its mass spectrum which gave a molecular ion peak 459.3. The elemental analysis was in agreement with the required for $C_{22}H_{22}N_2O_5S_2$ it was calculated C, 57.64; H, 4.80; N, 6.11and found: C, 57.33; H, 4.93; N, 6.10.

In ^{13}C NMR of **30a-30g** the peak for methyl carbon attached to the sulfone group gets merged in the solvent residual peak of DMSO-d_6 between δ 39.0-41.0, which was confirmed by HSQC spectrum of **30a** and DEPT-135 of **30c**.

Scheme 2.3 illustrates the reversal of orientation of sulfonamide linker in **40** and reversal of both amide and sulfonamide linkers in **41**. Preparation of **40** was achieved by acylation of **39a** with acid chloride obtained from **24** as discussed above. Compound (**39a**) was prepared by condensation of *o*-nitroaniline (**36a**) with *p*-toluenesulfonyl chloride (**37**) followed by reduction using stannous chloride dihydrate. Acylation of **35** with acid chloride of **38b** obtained using oxalyl chloride resulted into compound (**41**). Compound (**35**) was prepared from *p*-nitrotoluene (**31**) by treating it with NBS to obtain brominated compound which was further converted into thiol (**32**) using potassium thioacetate[57,58] followed by acidic hydrolysis. Methylation, oxidation and reduction of **32** were accomplished as discussed in **Scheme 2.2**. Treatment of anthranilic acid (**36b**) with **37** resulted into sulfonamide (**38b**). These structures were confirmed using ^1H NMR, ^{13}C NMR, HRMS and elemental analysis.

The ^1H NMR spectrum of **40** displayed a singlet at δ 2.33 for methyl protons attached to aromatic ring, a singlet at δ 3.03 for methyl protons attached to sulfone group, a singlet at δ 4.68 for methylene protons, multiplets between δ 7.16-7.32 for five aromatic protons, two doublets at δ 7.52, 7.64 for four aromatic protons, a doublet at δ 7.78 for one aromatic proton, a doublet for two aromatic protons at δ 7.88, a singlet at δ 9.59 for amide proton, and a singlet at δ 9.64 for sulfonamide proton. The ^{13}C NMR spectrum of **40** exhibited a signal at 21.42 for methyl carbon

Reagents and conditions: (a) NBS, cat (PhCO$_2$)$_2$, CCl$_4$, reflux, 6h; (b) CH$_3$COSK, acetone, rt; (c) aq.H$_2$SO$_4$, CH$_3$OH, reflux; (d) NaH, CH$_3$I, THF, 0 $^\circ$C (e) H$_2$O$_2$, AcOH, 100 $^\circ$C ; (f) SnCl$_2$.2H$_2$O, HCl, EtOH, 78 $^\circ$C; (g) pyridine, 120 $^\circ$C; (h) H$_2$O, 80°C; (i) oxalyl chloride, cat DMF, CH$_2$Cl$_2$, 0-25 $^\circ$C, then (**39a** for **40**) and (**35** for **41**) TEA, CH$_2$Cl$_2$, 0-25°C.

Scheme 2.3 Synthesis of **40** and **41**

attached to aromatic ring, singlet between δ 39.51-40.34 merged in solvent residual peak for methyl carbon attached to sulfone group, peak at δ 59.52 for methylene carbon, while peaks at δ 125.23, 125.92, 126.92, 127.15, 127.22, 128.06, 128.94, 130.12, 131.46, 133.15, 133.43, 134.40, 137.11, 143.76 for aromatic carbons, and at δ 165.11 for carbonyl carbon. The structure of **40** was further confirmed by its High Resolution Mass Spectrum which gave a molecular ion peak [M+Na]$^+$ at 481.0861. The elemental analysis was in good agreement with the required for C$_{22}$H$_{22}$N$_2$O$_5$S$_2$ it was calculated C, 57.64; H, 4.80; N, 6.11 and found: C, 57.43; H, 4.73; N, 6.14.

The methods used for the preparation of alternative linkers to sulfonamide for connecting the central 'C' ring to S1 binding elements 'B' are illustrated in **Scheme 2.4**. The starting material used was *o*-nitrotoluene (**42**) which was converted into bromide (**43**) by similar procedure as discussed above. Preparation of compounds containing ether (**44a**) or thioether (**44b-44c**) linkers, was achieved using Willamson's synthesis[59,60] by reacting **43** with appropriate phenol or thiophenols. Reduction of the nitro group using Fe/HCl resulted into intermediates **46a-46c**, while compounds having thioether linkages were oxidized using H_2O_2 followed by reduction of the nitro group to furnish other intermediates **47a-47b**. Condensation of acid chloride of **24** with appropriate intermediate **46a-46c** and **47a-47b** afforded **48a-48e**. Compounds (**49a-49c** and **50a-50c**) having sulfide and sulfoxide group at ring A have been synthesized by converting the corresponding acid (**24** and **25**) to acid chloride and reacting them with appropriate aniline intermediates (**29d** and **47a-47b**).

Reagents and conditions: (a) NBS, cat (PhCO$_2$)$_2$, CCl$_4$, reflux, 6h; (b) Ph-OH(for **44a**), PhCH$_2$-SH (for **44b**), Ph-SH (for **44c**) CH$_3$ONa, MeOH, 0 °C; (c) **44b** (for **45a**), **44c** (for **45b**) H$_2$O$_2$, AcOH, 100 °C (d) Fe, HCl, EtOH, 78 °C; (e) oxalyl chloride, cat DMF, CH$_2$Cl$_2$, 0-25 °C, then **46a-c** (for **48a-c**), **47a-b**(for **48d-e, 49a-b** and **50a-b**), and **29d** (for **49c** and **50c**), pyridine, CH$_2$Cl$_2$, 0-25°C.
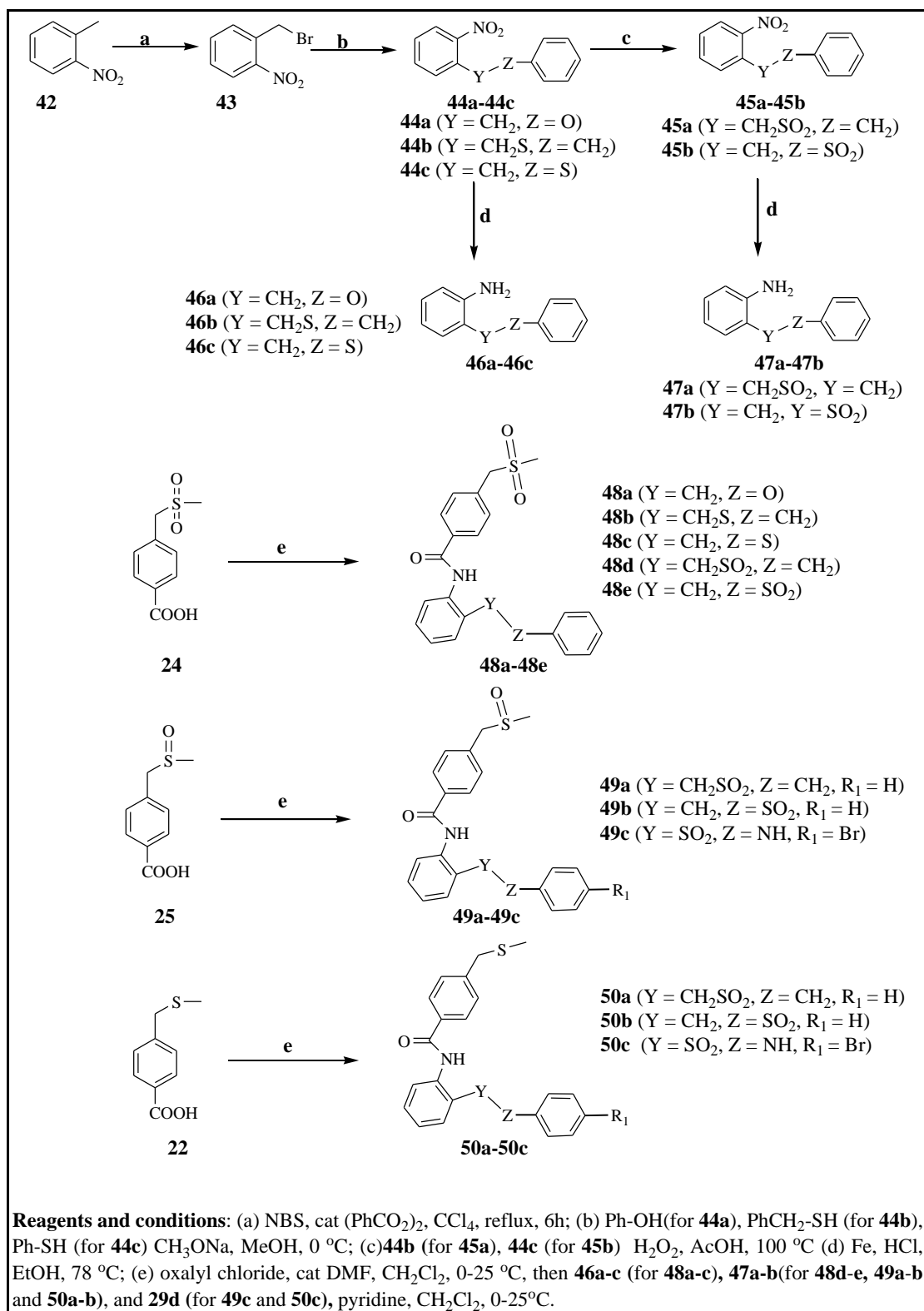
Scheme 2.4 Synthesis of **48a-48e**, **49a-49c** and **50a-50c**

2.4 Experimental

All solvents and reagents were used as such as obtained from commercial sources without purification except for anhydrous CH_2Cl_2, DMF and acetone. Thin layer chromatography (TLC) analysis was done on glass plates using silica gel G containing 13 % calcium sulphate as a binder or on silica gel Merck 60 F254 plates. Visualization of spots was achieved by exposure to iodine vapor or with ultraviolet light. Column chromatography was performed using Acme's silica gel (60-120 mesh size) and the elution was done using light petroleum (60-80) and ethyl acetate mixtures. Melting points were recorded in open capillary tubes in melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-(300/400/500) FT-NMR spectrometer (^{1}H NMR 300/400/500 MHz and ^{13}C NMR at 75/100 MHz) using $CDCl_3$ or DMSO-d_6 as solvents. The chemical shifts are reported in ppm with reference to TMS as an internal standard or relative to the residual peak of the solvent. Coupling constants (*J*) are reported in hertz and multiplicities of signals are represented by s, singlet; d, doublet; t, triplet; bs, broad singlet; m, multiplet. Yields (%) are reported based on isolation of the products from column chromatography. Mass Spectra (HRMS) are obtained on Agilent Q-Tof B.05.00 (B5042.0) higher resolution MSMS spectrometer using electrospray ionization mode. Mass spectra were recorded on a Thermo-Fischer DSQ II GCMS instrument. Elemental analyses were performed on Thermo Scientific Flash 2000 organic elemental analyzer and are within 0.4% of theoretically calculated values.

4-(Bromomethyl)benzoic acid (**20**): To a mixture of p-toluic acid (**19**) (10 g, 0.0735 mol) and N-bromosuccinimide (14.38 g, 0.0808 mol) in carbon tetrachloride (70 ml) was added a catalytic amount of benzoyl peroxide (0.74 g) under stirring and the mixture was allowed to stir under reflux for 5 h. Carbon tetrachloride was evaporated under reduced pressure, water was added to the resultant solid and was allowed to warm at 50 ^{0}C for 1 h. The contents of the flask were filtered with suction to obtain a crude dry solid which was stir in light petroleum (50 ml) for 30 min and then filtered to get white solid **20** (13.1 g, 83%): mp 226 ^{0}C[61].

4-(Mercaptomethyl)benzoic acid (**21**): A mixture of 4-(bromomethyl)benzoic acid (**20**) (10 g, 0.0465 mol) and thiourea (4.24 g, 0.0558 mol) was refluxed in water (70 ml) for 3h. The reaction mixture was cooled to room temperature after which a

solution of 10 % of aqueous NaOH (50 ml) was added and the reaction was again refluxed for 2 h (monitored on TLC). Cooling the reaction mixture to 0 ^{0}C and acidification using 2 M HCl furnished a light yellow solid which was filtered to obtain the crude thiol. Recrystallization from ethanol gave (**21**) as the pure white solid (6.64 g, 85 %); mp 186 ^{0}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.04 (t, 1H), 3.84 (d, J = 12 Hz, 2H), 7.51 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H), 12.96 (bs, 1H, exchangeable); MS m/z 168.06 (M$^+$).

4-((Methylthio)methyl)benzoic acid (**22**): To a stirred solution of **21** (5 g, 0.0297 mol) in 50 ml of dry THF at 0 ^{o}C under nitrogen atmosphere, was added NaH (2.61 g, 0.0654 mol as 60% dispersion in paraffin oil), followed by methyl iodide (5 g, 0.0357 mol). The resulting mixture was stirred at 0 ^{o}C for 1 hr, and then diluted with water (50 ml). Aqueous layer was then acidified with dilute HCl (1:1) (20 ml) and extracted with ethyl acetate (6 × 25 ml), the organic layer was dried over anhydrous sodium sulfate and evaporated to afford **22** as a pale yellow solid which was purified by column chromotagraphy (5 g, 92%); mp 148 ^{o}C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 2.00 (s, 3H) , 3.72 (s, 2H), 7.42 (d, J = 8.24 Hz, 2H), 8.07 (d, J = 8.24 Hz, 2H), MS m/z 182.06 (M$^+$).

Methyl 4-((methylthio)methyl)benzoate (**23**): The compound (**22**) (5 g, 0.0274 mol) was taken in 50 ml methanol and conc. H$_2$SO$_4$ (98 %) was added in catalytic amount and allowed to reflux for 10 h. Methanol was removed under reduced pressure, water (50 ml) was added to the reaction mixture and extracted with ethyl acetate (5 × 25 ml). Organic layer was washed with 20 % sodium bicarbonate solution (2 × 30 ml), dried over anhydrous sodium sulfate and evaporated to afford **23** as light orange liquid which was purified by column chromotagraphy (5.2 g, 96%); bp 319 ^{o}C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 1.98 (s, 3H), 3.70 (s, 2H), 3.91 (s, 3H), 7.37 (d, J = 8.24 Hz, 2H), 7.99 (d, J = 8.24 Hz, 2H); MS m/z 196.12 (M$^+$).

4-((Methylsulfonyl)methyl)benzoic acid (**24**): To a solution of **23** (2.5 g, 0.0127 mol) in glacial acetic acid (15 ml) at room temperature was added (2.1 g, 0.0638 mol) 30 % H$_2$O$_2$. The reaction mixture was allowed to reflux for 1 h, after which white precipitates formed on cooling were suction filtered and dried in hot air oven (52 ^{o}C) to give sulfone of **23** (2.5 g, 87%); mp 164 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.80 (s,

3H), 3.95 (s, 3H), 4.32 (s, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 8.11 (d, $J = 8.4$ Hz, 2H). A mixture of this sulfone (2.5 g, 0.0109 mol) prepared as above and 1 N sodium hydroxide (15 ml, 0.0438 mol) was stirred at room temperature for 3 h. The reaction mixture was diluted with water (15 ml) and pH was adjusted to 2 - 4 using 1 N HCl. The precipitate thus obtained was filtered, washed with water and dried to give **24** (1.7 g, 76%) as white solid; mp 250 $^{\circ}$C[50].

4-((Methylsulfoxy)methyl)benzoic acid (**25**): To a stirred solution of **23** (2.5 g, 0.0127 mol) in aqueous methanol (8:2) (40 ml) at room temperature was added cetyltrimethylammonium periodate (CTAPI) (2.1 g, 0.0446 mol) in portions over a period of 15 min. The mixture was then stirred for 45 min. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (6 × 25 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give sulfoxide of **23** (2.5 g, 94%); mp 68 $^{\circ}$C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.47 (s, 3H), 3.93 (s, 3H), 4.00 (d, $J = 12.8$ Hz, 1 H), 4.05 (d, $J = 12.8$ Hz, 1 H), 7.38 (d, $J = 8.2$ Hz, 2H), 8.06 (d, $J = 8.2$ Hz, 2H), MS m/z 211.99 (M^{+}). Alkaline hydrolysis of of this sulfoxide was carried out by a similar procedure as reported for **24** to obtain compound **25**; yield 74%; mp 176 $^{\circ}$C[51].

General procedure for coupling of 26 with substituted anilines (27a-27g) to yield compounds (**28a-28g**): To a mixture of amines (**27a-27g**) (0.0081 mol) and triethylamine (0.98 g, 0.0097 mol) in anhydrous CH$_2$Cl$_2$ (10 ml) at 0 $^{\circ}$C was added dropwise a solution of **26** (2 g, 0.0090 mol) in anhydrous CH$_2$Cl$_2$ (10 ml). The mixture was stirred at 0 $^{\circ}$C for 30 min and then allowed to warm to room temperature for 3 h. Then it was washed with aqueous HCl (1:1), water (20 ml), brine (10 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give crude product which was purified using column chromatography over silica gel using EtOAc/light petroleum.

N-Phenyl-2-nitrobenzenesulfonamide (**28a**): White solid; yield: 91%; mp 120 $^{\circ}$C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.07-7.13 (m, 3H), 7.25-7.29 (m, 2H), 7.78-7.86 (m, 2H), 7.95-7.98 (m, 2H), 10.75 (s, 1H, exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 120.85, 125.10, 125.16, 129.80, 130.33, 131.76, 133.01, 135.10, 137.09, 148.40.

N-(4-Bromophenyl)-2-nitrobenzenesulfonamide (28d): Pale yellow solid; yield: 78 %, mp 106 ^{o}C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.09 (d, J = 8.7 Hz, 2H), 7.30 (s, 1H, exchangeable), 7.39 (d, J = 8.7 Hz), 7.58-7.87 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 120.06, 124.79, 125.38, 131.77, 132.54, 132.71, 134.20, 134.55, 148.11.

N-(4-Chloro-2,5-dimethoxyphenyl)-2-nitrobenzenesulfonamide (28e): Pale yellow solid; yield: 88 %, mp 140 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.41 (s, 3H), 3.74 (s, 3H), 6.97 (s, 1H), 7.09 (s,1H), 7.91-8.32 (m, 4H), 10.00 (s, 1H, exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 56.68, 56.90, 112.16, 114.45, 119.69, 124.06, 124.69, 130.40, 132.72, 132.75, 134.81, 147.78, 147.90, 148.66.

General procedure for the reduction of nitro compounds to amines – Preparation of compounds (29a-29g): Reduction was carried out by addition of nitro compounds (0.0066 mol) portionwise to a heated solution (65 ^{o}C) of conc. HCl (36.5 %, 3.2 ml) and stannous chloride dihydrate (6 g, 0.0265 mol) in ethanol (20 ml). The reaction mixture was refluxed for appropriate time (TLC). After completion of the reaction ethanol was removed under reduced pressure. Ethyl acetate (20 ml) was added to the reaction mixture for removal of organic impurities and the aqueous solution was then filtered through a celite bed and the filtrate was made alkaline with 25 % of ammonia solution (10 ml) and extracted with ethyl acetate (4 × 25 ml). The combined organic extract was washed successively with water (20 ml), brine solution (10 ml) and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure furnished the crude amines, which were chromatographed using ethyl acetate/light petroleum (60-80).

N-(4-Chloro-2,5-dimethoxyphenyl)-2-aminobenzenesulfonamide (29e): Yellow solid; yield: 71%; mp 156 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.60 (s, 3H), 3.67 (s, 3H), 6.10 (bs, 2H, exchangeable), 6.50-6.54 (m, 1H), 6.74-6.76 (m, 1H), 6.89 (s, 1H), 7.20-7.24 (m, 1H), 7.45-7.47 (m, 1H), 9.57 (bs, 1H, exchangeable).

General procedure for the synthesis of compounds (30a-30g): To a stirred solution of **24** (1 g, 0.0046 mol) in anhydrous CH$_2$Cl$_2$ (10 ml) and DMF (0.02 ml) at 0-5 ^{o}C was added oxalyl chloride (0.7 g, 0.0056 mol) under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 25 ^{o}C and then concentrated under vacuum to dryness. The crude yellow acid chloride obtained was dissolved in anhydrous CH$_2$Cl$_2$ (5 ml) and then added dropwise to the solution of **29a-29g** (0.0051 mol) and

triethylamine (0.5 g, 0.0051 mol) in 5 ml anhydrous CH_2Cl_2 cooled to 0-5 ^{o}C. After complete addition of the acid chloride, the reaction mixture was stirred at 25 ^{o}C for 2 h. The mixture was then diluted with 2 N HCl (10 ml), extracted with CH_2Cl_2 (4 × 20 ml) which on drying over anhydrous sodium sufate and evaporation gave crude products. Purification by column chromatography using ethyl acetate/light petroleum (60-80) afforded **30a-30g**.

N-Phenyl-2-(4-(methylsulfonylmethyl)benzamido)benzenesulfonamide (**30a**): White solid; yield: 67 %; mp 164 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.98 (s, 3H), 4.65 (s, 2H), 7.00-7.04 (m, 3H), 7.14-7.18 (m, 2H), 7.25-7.29 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.61-7.67 (m, 3H), 7.90 (d, J = 8.4 Hz, 2H), 8.35 (d, J = 8.0 Hz, 1H), 10.13 (s, 1H), 10.52 (s,1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 39.27-40.49 (merged SO$_2$$\underline{C}H_3$), 59.45, 122.25, 123.58, 124.71, 125.63, 127.95, 128.20, 129.69, 131.84, 133.75, 134.38, 134.57, 136.44, 137.03, 164.79; HRMS (ESI) m/z [M+Na]$^+$ calculated for $C_{21}H_{20}N_2O_5S_2$: 467.0711; found: 467.0710; Anal. Calcd for $C_{21}H_{20}N_2O_5S_2$: C, 56.75; H, 4.51; N, 6.08; found: C, 56.20; H, 4.58; N, 6.01.

N-Benzyl-2-(4-(methylsulfonylmethyl)benzamido)benzenesulfonamide (**30b**): White solid; yield: 62 %; mp 180 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.95 (s, 3H), 4.04 (s, 2H), 4.63 (s, 2H), 7.24 (m, 5H), 7.34 (m, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.68 (m, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 8.46 (d, J = 7.6 Hz, 1H), 8.68 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 39.32-40.57 (merged SO$_2$$\underline{C}H_3$), 46.23, 59.43, 123.26, 124.68, 127.75, 127.88, 127.99, 128.74, 128.97, 129.55,131.89, 133.81, 134.15, 134.50, 136.10, 137.57, 164.78; HRMS (ESI) m/z [M+Na]$^+$ calculated for $C_{22}H_{22}N_2O_5S_2$: 481.0868; found; 481.0861; Anal. Calcd for $C_{22}H_{22}N_2O_5S_2$: C, 57.64; H, 4.80; N, 6.11; found: C, 57.61; H, 4.77; N, 5.96.

(N-(4-Methylphenyl)-2-(4-(methylsulfonylmethyl)benzamido))benzenesulfonamide (**30c**): White solid; yield: 59 %; mp 186 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.11 (s, 3H), 2.98 (s, 3H), 4.65 (s, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 7.24-7.28 (m, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.65-7.74 (m, 2H), 7.86 (d, J = 8.4 Hz, 2H), 8.35-8.37 (m, 1H), 10.07 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 20.79, 40.18, 59.46, 123.13, 124.57, 127.84, 127.94, 129.66, 130.13, 131.80, 133.76, 134.14, 134.38,

135.28, 136.48, 164.60; EI-MS *m/z* 459.3 [M+1]$^+$; Anal. Calcd for $C_{22}H_{22}N_2O_5S_2$: C, 57.64; H, 4.80; N, 6.11; found: C, 57.33; H, 4.93; N, 6.10.

(N-(4-Bromophenyl)-2-(4-(methylsulfonylmethyl)benzamido))benzenesulfonamide (30d): White solid; yield: 76 %; mp 198 ^{o}C; ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ: 2.98 (s, 3H), 4.65 (s, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.27-7.34 (m, 3H), 7.62-7.68 (m, 3H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 8 Hz, 2H), 8.29 (d, *J* = 8.4 Hz, 1H), 10.07 (s, 1H), 10.66 (s, 1H); ^{13}C NMR (DMSO-*d$_6$*, 100 MHz) δ: 39.32-40.57 (merged SO$_2$$\underline{C}H_3$), 59.49, 117.92, 124.00, 124.09, 124.91, 127.95, 128.23, 129.66, 131.81, 132.59, 133.81, 134.38, 134.72, 136.45, 136.54; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for $C_{21}H_{19}N_2O_5S_2Br$: 546.9780; found: 546.9784; Anal. Calcd for $C_{21}H_{19}N_2O_5S_2Br$: C, 48.19; H, 3.63; N, 5.35; found: C, 47.88; H, 3.94; N, 4.95.

(N-(2,5-Dimethoxy-4-chlorophenyl)-2-(4-(methylsulfonylmethyl)benzamido))benzenesulfonamide (30e): Pale yellow solid; yield: 72 %; mp 224 ^{o}C; ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ: 3.03 (s, 3H), 3.32 (s, 3H), 3.64 (s, 3H), 4.68 (s, 2H), 6.93 (s, 1H), 6.96 (s, 1H), 7.30 (m, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.69-7.78 (m, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 8.44 (d, *J* = 8.2 Hz, 1H), 10.09 (s, 1H), 10.17 (s, 1H); ^{13}C NMR (DMSO-*d$_6$*, 100 MHz) δ: 39.32-40.57 (SO$_2$$\underline{C}H_3$ merged), 56.47, 56.63, 59.46, 113.14, 114.21, 120.22, 122.73, 123.49, 124.24, 127.69, 128.74, 129.62, 131.69, 133.82, 134.00, 134.29, 136.46, 148.44, 148.49, 164.24; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for $C_{23}H_{23}N_2O_7S_2Cl$: 561.0553; found: 561.0553; Anal. Calcd for $C_{23}H_{23}N_2O_7S_2Cl$: C, 51.25; H, 4.27; N, 5.26; found: C, 51.04; H, 4.13; N, 5.34.

(N-(4-Fluorophenyl)-2-(4-(methylsulfonylmethyl)benzamido))benzenesulfonamide (30f): White solid; yield: 69 %; mp 200 ^{o}C; ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ: 2.98 (s, 3H), 4.64 (s, 2H), 6.99 (m, 4H), 7.28 (m, 1H), 7.68 (m, 4H), 7.88 (d, *J* = 8.4 Hz, 2H), 10.07 (s, 1H), 10.43 (s, 1H); ^{13}C NMR (DMSO-*d$_6$*, 100 MHz) δ: 39.32-40.57 (merged SO$_2$$\underline{C}H_3$), 59.47, 116.34, 116.56, 123.64, 124.75, 125.29, 127.87, 127.93, 129.68, 131.81, 133.08, 133.83, 134.33, 134.65, 136.45, 164.66; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for $C_{21}H_{19}N_2O_5S_2F$: 485.0617; found: 485.0607; Anal. Calcd for $C_{21}H_{19}N_2O_5S_2F$: C, 54.55; H, 4.11; N, 6.06; found: C, 54.36; H, 4.05; N, 6.01.

*(*N-(4-Methoxyphenyl)-2-(4-(methylsulfonylmethyl)benzamido))benzenesulfonamide** (**30g**): White solid; yield: 59 %; mp 176 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.98 (s, 3H), 3.58 (s, 3H), 4.64 (s, 2H), 6.67 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 7.24-7.28 (m, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.63-7.70 (m, 2H), 7.84 (d, J = 8.4 Hz, 2H), 8.39-8.41 (m, 1H), 10.08 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 39.25-40.37 (SO$_2$$\underline{C}H_3$ merged), 55.55, 59.48, 114.80, 122.91, 124.49, 125.95,127.70, 127.80, 129.03, 129.69, 131.78, 133.79, 134.30, 134.48, 136.52, 157.81, 164.49; EI-MS *m/z* 475.3 [M + H]$^+$; Anal. Calcd for C$_{22}$H$_{22}$N$_2$O$_6$S$_2$: C, 55.69; H, 4.64; N, 5.90; found: C, 55.61; H, 4.70; N, 5.86.

4-(Mercaptomethyl)nitrobenzene (**32**): 4-(Bromomethyl)nitrobenzene was prepared following the procedure reported for preparation of **20** (5.1.1) from **31**. This crude product was sufficiently pure (as indicated by TLC) to be used directly for the preparation of **32**. To a stirred solution of 4-(bromomethyl)nitrobenzene (5 g, 0.0231 mol) in acetone (50 ml) was added potassium thioacetate (3.9 g, 0.0347 mol), the resulting mixture was allowed to stir at room temperature for 2 h. Then acetone was removed under vacuum, water (50 ml) was added to the mixture and extracted with ethyl acetate (5 × 30 ml). The organic layer was washed with 20 % sodium bicarbonate solution (3 × 20 ml), water, brine and dried over anhydrous sodium sulfate. Solvent was evaporated *in vacuo* and the residue was taken up in methanol (50 ml). Aqueous sulfuric acid (50 %, 8.3 ml) was added and the solution was allowed to reflux for 3 h. Methanol was rotary evaporated and water (40 ml) was added to it. Extraction was carried out using ethyl acetate (5 × 20 ml) and dried over anhydrous sodium sulfate. Removal of solvent afforded **32** as light yellow solid which was chromatographed to yield pure product (2.5 g, 73 %); mp 50 ^{o}C[57,58].

4-((Methylthio)methyl)nitrobenzene (**33**): This compound was prepared from **32** by following the procedure similar to that reported for **22**. Column chromatography afforded pure **33** as colorless liquid; yield 79%; mp 68 ^{o}C. Structure was confirmed by comparing the reported data.[62]

4-((Methylsulfonyl)methyl)nitrobenzene (**34**): This compound was prepared from **33** by following the procedure similar to that reported for **24**. The solid obtained was

directly used for the next step without further purification. Yield: 85%; mp 168 ^{o}C. Structure was confirmed by comparison with reported compound. [62]

4-((Methylsulfonyl)methyl)aniline (**35**): Reduction of **34** by a procedure similar to that reported for **29a-29g** afforded a crude product, which was chromatographed to give pure **35** white solid; yield 56 %; mp 170 ^{o}C.[63]

N-(2-Nitrophenyl)-4-methylbenzenesulfonamide (**38a**): To a stirred solution of **36a** (2.0 g, 0.0144 mol) in dry pyridine (8 ml) was added **37** (2.7 g, 0.0144 mol) in portions over a period of 5 min, and the reaction was heated to 120 ^{o}C. The reaction mixture was poured into cold water (50 ml) and extracted using ethyl acetate (4 × 25 ml). The organic layer was washed with dil. HCl (1:1) (10 ml), water (20 ml) and dried over anhydrous sodium sulfate. Removal of solvent under *vacuo* afforded **38a** as yellow solid (2.3 g, 55%). Recrystallization from EtOAc gave (1.6 g) yellow crystals; mp 114 ^{o}C.[64]

N-(2-Carboxyphenyl)-4-methylbenzenesulfonamide (**38b**): p-Toluenesulfonyl chloride (**37**) (1.7 g, 0.0087 mol) was added to a stirred solution of anthranilic acid (**36b**) (1.0 g, 0.0073 mol) and sodium carbonate (1.9 g, 0.0175 mol) in water (10 ml) at 40 ^{o}C over a period of 5 min and the reaction mixture was stirred for 6 h at 80 ^{o}C. After completion of the reaction, it was cooled to room temperature and acidified with 6 N HCl (20 ml). The solid thus obtained was filtered under vacuum and washed with water (20 ml) followed by drying in hot air oven at 60 ^{o}C to afford **38b** as brownish solid (1.8 g). Recrystallization form ethanol gave (1.2 g, 57 %) pure white crystals; mp 210 ^{o}C.[65]

N-(2-aminophenyl)-4-methylbenzenesulfonamide (**39a**): It was synthesized according to the general procedure for reduction of nitro compound **28a-28g**. The crude product so obtained was purified by column chromatography to obtain white solid; yield: 83 %; mp 136 ^{o}C.[66]

4-((Methylsulfonyl)methyl)-N-2-(tosylamino)phenyl)benzamide (**40**): Synthesized according to the general procedure for synthesis of compounds (**30a-30g**). The crude product was purified by column chromatography to obtain a white solid; yield: 62 %;

mp 190 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.33 (s, 3H), 3.03 (s, 3H), 4.68 (s, 2H), 7.16-7.32 (m, 5H), 7.52 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.2 Hz, 2H), 9.59 (s, 1H), 9.64 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 21.42, 39.51-40.34 (merged SO$_2$$\underline{C}H_3$), 59.52, 125.23, 125.92, 126.92, 127.15, 127.22, 128.06, 128.94, 130.12, 131.46, 133.15, 133.43, 134.40, 137.11, 143.76, 165.11; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for C$_{22}$H$_{22}$N$_2$O$_5$S$_2$: 481.0868; found: 481.0861 ; Anal. Calcd for C$_{22}$H$_{22}$N$_2$O$_5$S$_2$: C, 57.64; H, 4.80; N, 6.11; found: C, 57.43; H, 4.73; N, 6.14.

N-(4-((Methylsulfonyl)methyl)phenyl)-2-(tosylamino)benzamide (**41**): This compound was prepared from **38b** using the procedure similar to that reported for compounds (**30a-30g**). The crude product was purified by column chromatagrophy to obtain a white solid; yield: 66 %; mp 228 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.26 (s, 3H), 2.91 (s, 3H), 4.47 (s, 2H), 7.22-7.26 (m, 3H), 7.40-7.52 (m, 4H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.77-7.74 (m, 1H), 10.42 (s, 1H), 10.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 21.42, 39.47-40.14 (merged SO$_2$$\underline{C}H_3$), 59.44, 121.29, 121.83, 124.61, 125.27, 127.30, 129.58, 130.26, 131.67, 132.88, 136.30, 137.61, 138.93, 144.20, 167.14; HRMS (ESI) *m/z* [M+H]$^+$ calculated for C$_{22}$H$_{22}$N$_2$O$_5$S$_2$: 459.0970; found: 459.0904; Anal. Calcd for C$_{22}$H$_{22}$N$_2$O$_5$S$_2$: C, 57.64; H, 4.80; N, 6.11; found: C, 57.55; H, 4.66; N, 5.98.

4-Nitro-benzylbromide (**43**): The title compound was synthesized from **42** according to the general procedure reported for the preparation of **20**. The product was obtained as lachrymatory yellow needles; yield: 48%; mp 46 °C.[59]

General procedure for the synthesis of compounds (**44a-44c**): To a stirred solution of sodium metal (0.25 g, 0.0111 mol) in methanol (20 ml) at 0 °C under nitrogen was added phenol/mercaptan (0.0093 mol). The reaction was stirred for 30 minutes at 0 °C after addition of **43** (2g, 0.0093 mol). The mixture was then warmed to room temperature and allowed to stir for 2 h. The solvent was removed *in vacuo*, and the residue was extracted with ethyl acetate (4 × 25 ml), washed with water (30 ml) and brine (25 ml) and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave the crude product which on purification by column chromatography, afforded compound (**44a-44c**).

Benzyl 2-nitrobenzyl sulfide (**44b**): Yellow liquid; yield: 78 %; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.74 (s, 2H), 4.05 (s, 2H), 7.35-8.06 (m, 9H); MS m/z 259.1 (M$^+$).

General procedure for the synthesis of 45a and **45b**: To a solution of sulfide (0.0077 mol) in glacial acetic acid (10 ml) at room temperature was added (1.3 g, 0.0385 mol) 30 % H$_2$O$_2$. The reaction mixture was heated at 100 ^{o}C for 1 h, white precipitates thus formed on cooling were suction filtered and dried in hot air oven (52 ^{o}C) to give sufficiently pure (as indicated by TLC) compounds (**45a** and **45b**) which were used as such in the next step.

General procedure for the preparation of 46a-46c, 47a and 47b: To a solution of nitro compound (**44a-44b**, **45a** and **45b**) (0.00612 mol) in ethanol was added iron powder (2 g, 0.0369 mol) followed by conc. HCl (3.0 ml) at room temperature. The resulting mixture was then allowed to reflux for 3 h. Ethyl acetate was added to the reaction mixture and was made alkaline with 25 % of ammonia solution (10 ml). The reaction mixture was filtered through celite bed and the filtrate was extracted with ethyl acetate (4 × 25 ml). The combined organic extract was washed with water (30 ml), brine (25 ml) and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was then subjected to column chromatography to obtain pure products (**46a**-**46c**, **47a** and **47b**).

2-((Benzylsulfonyl)methyl)aniline (**47a**): White solid; yield: 65 %; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 4.30 (s, 2H), 4.36 (s, 2H), 6.86-7.30 (m, 4H), 7.35 (s, 2H), 7.50-7.54 (m, 5H; MS m/z 261.1 (M$^+$).

General procedure for the synthesis of 48a-48e: These compounds were synthesized according to the general procedure reported for synthesis of **30a-30g**. Here pyridine was used instead of triethylamine.

4-((Methylsulfonyl)methyl)-N-(2-(phenoxymethyl)phenyl)benzamide (**48a**): White solid; yield: 76 %; mp 152 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.83 (s, 3H), 4.33 (s, 2H), 5.24 (s, 2H), 7.02-7.06 (m, 3H), 7.16-7.20 (m, 1H), 7.31-7.38 (m, 3H), 7.43-7.48 (m, 3H), 7.88-7.90 (m, 2H), 8.32 (d, J = 8.4 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 39.37, 60.86, 69.89, 114.93, 122.21, 122.59, 124.67, 126.00, 127.79,

129.61, 129.81, 129.92, 131.01, 131.97, 135.36, 137.62, 157.55, 164.26; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for C$_{22}$H$_{21}$NO$_4$S: 418.1089; found: 418.1088; Anal. Calcd for C$_{22}$H$_{21}$NO$_4$S: C, 66.82; H, 5.35; N, 3.54; found: C, 66.88; H, 5.09; N, 3.65.

N-(2-((Benzylthio)methyl)phenyl)-4-((methylsulfonyl)methyl)benzamide   (**48b**): White solid; yield: 74 %; mp 196 ^{o}C; ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ: 3.01 (s, 3H), 3.69 (s, 2H), 3.80 (s, 2H), 4.67 (s, 2H), 7.21-7.31 (m, 5H), 7.35-7.39 (m, 1H), 7.44-7.46 (m, 1H), 7.50-7.52 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 10.52 (s, 1H); ^{13}C NMR (DMSO-*d$_6$*, 100 MHz) δ: 33.57, 35.52, 39.45 (merged SO$_2$CH$_3$), 60.94, 123.87, 124.85, 126.83, 128.03, 128.70, 128.88, 130.99, 131.04, 131.90, 135.41, 136.64, 137.17, 164.40; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for C$_{23}$H$_{23}$NO$_3$S$_2$: 448.1017 found: 448.1013; Anal. Calcd for C$_{23}$H$_{23}$NO$_3$S$_2$: C, 64.91; H, 5.45; N, 3.29; found: C, 64.36; H, 5.05; N, 3.01.

4-((Methylsulfonyl)methyl)-N-(2-((phenylthio)methyl)phenyl)benzamide   (**48c**): White solid; yield: 69 %; mp 170 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.83 (s, 3H), 4.18 (s, 2H), 4.35 (s, 2H), 7.11-7.24 (m, 2H), 7.26-7.30 (m, 3H), 7.31-7.38 (m, 3H), 7.55 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.96 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 37.58, 39.47, 60.86, 124.09, 125.23, 127.37, 127.70, 127.99, 128.81, 129.18, 130.75, 131.09, 131.37, 132.00, 133.74, 135.27, 136.25, 164.52; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for C$_{22}$H$_{21}$NO$_3$S$_2$: 434.0860 found: 434.0859; Anal. Calcd for C$_{22}$H$_{21}$NO$_3$S$_2$: C, 64.21; H, 5.14; N, 3.40; found: C, 6.20; H, 4.88; N, 3.11.

N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methylsulfonyl)methyl)benzamide (**48d**): White solid; yield: 62 %; mp 230 ^{o}C; ^{1}H NMR (DMSO-*d$_6$*, 400 MHz) δ: 3.02 (s, 3H), 4.63 (s, 2H), 4.68 (s, 4H), 7.33-7.41 (m, 4H), 7.43-7.53 (m, 4H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 39.45, 55.22, 58.83, 60.94, 126.27, 126.84, 128.17, 129.28, 129.53, 130.40, 130.76, 130.99, 131.99, 132.82, 134.58, 136.84, 137.57, 164.90; HRMS (ESI) *m/z* [M+Na]$^+$ calculated for C$_{23}$H$_{23}$NO$_5$S$_2$: 480.0915 found: 480.0916; Anal. Calcd for C$_{23}$H$_{23}$NO$_5$S$_2$: C, 60.37; H, 5.07; N, 3.06; found: C, 59.99; H, 4.95; N, 3.15.

4-((Methylsulfonyl)methyl)-N-(2-((phenylsulfonyl)methyl)phenyl)benzamide

(**48e**): White solid; yield: 66 %; mp 194 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.58 (s, 3H), 4.36 (s, 2H), 4.44 (s, 2H), 6.65-6.67 (m, 1H), 6.98-7.02 (m, 1H), 7.39-7.43 (m, 1H), 7.50-7.54 (m, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.66-7.72 (m, 3H), 7.94 (d, J = 7.7 Hz, 1H), 8.15 (d, J = 8.3 Hz, 2H), 9.72 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 39.40, 60.28, 60.99, 120.90, 125.82, 126.46, 128.27, 128.51, 129.29, 130.10, 132.27, 132.52, 134.47, 134.68, 136.61, 137.36, 164.84; HRMS (ESI) m/z [M+Na]$^+$ calculated for C$_{22}$H$_{21}$NO$_5$S$_2$: 466.0758 found: 466.0757; Anal. Calcd for C$_{22}$H$_{21}$NO$_5$S$_2$: C, 59.57; H, 4.77; N, 3.16; found: C, 59.61; H, 4.70; N, 3.56.

General procedure for the synthesis of 49a-49c: These compounds were synthesized according to the general procedure for synthesis of **30a-30g** from acid **25** (1 g, 0.0050 mol) and amines (**47a-47b**, **29d**) (0.0050 mol) using pyridine as a base.

N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methylsulfinyl)methyl)benzamide

(**49a**): White solid; yield: 56 %; mp 224 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.52 (s, 3H), 4.04 (d, J = 12.8 Hz, 1H), 4.26 (d, J = 12.8 Hz, 1H), 4.58 (s, 2H), 4.63 (s, 2H), 7.26-7.30 (m, 1H), 7.33-7.35 (m, 3H), 7.37-7.42 (m, 2H), 7.44-7.46 (m, 4H), 7.64 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 9.86 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 37.76, 54.30, 58.38, 58.42, 122.78, 126.23, 126.73, 128.02, 128.58, 128.95, 128.99, 129.64, 130.90, 131.53, 133.42, 133.98, 135.63, 138.07, 165.38; MS m/z 441.43 (M$^+$).; Anal. Calcd for C$_{23}$H$_{23}$NO$_4$S$_2$: C, 62.58; H, 5.21; N, 3.17; found: C, 62.11; H, 5.25; N, 3.03.

4-((Methylsulfinyl)methyl)-N-(2-((phenylsulfonyl)methyl)phenyl)benzamide

(**49b**):

White solid; yield: 60 %; mp 166 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.52 (s, 3H), 4.08 (d, J = 12.8 Hz, 1H), 4.26 (d, J = 12.8 Hz, 1H), 4.89 (s, 2H), 7.09-7.11 (m, 2H), 7.35-7.39 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.53-7.57 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.68-7.71 (m, 3H), 7.92 (d, J = 8.4 Hz, 2H), 9.88 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 37.79, 58.28, 58.43, 122.86, 125.70, 126.25, 128.15, 128.32, 129.56, 129.70, 130.86, 133.39, 134.27, 134.45, 135.60, 138.02, 138.73, 165.41; MS m/z 427.83 (M$^+$).; Anal. Calcd for C$_{22}$H$_{21}$NO$_4$S$_2$: C, 61.74; H, 4.91; N, 3.27; found: C, 61.47; H, 4.87; N, 3.30.

(N-(4-Bromophenyl)-2-(4-(methylsulfinylmethyl)benzamido))benzenesulfonamide (**49c**): White solid; yield: 57 %; mp 144 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.49 (s, 3H), 3.97 (d, J = 12.8 Hz, 1H), 4.02 (d, J = 12.8 Hz, 1H), 6.88-6.91 (m, 2H), 7.13-7.21 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.56-7.61 (m, 1H), 7.71-7.73 (m, 1H), 7.88 (d, J = 8.0 Hz, 2H), 8.43 (s, 1H), 8.53 (d, J = 8.4 Hz, 2H), 10.11 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 37.50, 59.31, 119.88, 122.71, 123.98, 125.41, 129.49, 130.62, 132.36, 133.82, 134.03, 134.49, 134.91, 136.14, 164.49; HRMS (ESI) m/z [M+Na]$^+$ calculated for C$_{21}$H$_{19}$N$_2$O$_4$S$_2$Br: 530.9677 found: 530.9676; Anal. Calcd for C$_{21}$H$_{19}$N$_2$O$_4$S$_2$Br: C, 49.71; H, 3.75; N, 5.52; found: C, 49.64; H, 3.53; N, 5.29.

General procedure for the synthesis of 50a-50c: These compounds were synthesized according to the general procedure for the synthesis of **30a-30g** from the acid (**22**) (1 g, 0.0055 mol) and amines (**47a-47b**, **29d**) (0.0055 mol) using pyridine as base.

N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methylthio)methyl)benzamide (**50a**): White solid; yield: 62 %; mp 182 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.04 (s, 3H), 3.75 (s, 2H), 4.25 (s, 2H), 4.34 (s, 2H), 7.26-7.28 (m, 2H), 7.37-7.39 (m, 3H), 7.42-7.43 (m, 4H), 7.44-7.50 (m, 1H), 7.86-7.92 (m, 3H), 10.14 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 30.99, 38.04, 55.22, 58.77, 119.92, 126.08, 126.88, 126.93, 127.65, 129.24, 129.45, 130.33, 130.77, 132.46, 132.75, 137.74, 142.74, 165.44; HRMS (ESI) m/z [M+Na]$^+$ calculated for C$_{23}$H$_{23}$NO$_3$S$_2$: 448.1017 found: 448.1020; Anal. Calcd for C$_{23}$H$_{23}$NO$_3$S$_2$: C, 64.92; H, 5.41; N, 3.29; found: C, 64.91; H, 5.38; N, 3.10.

4-((Methylthio)methyl)-N-(2-((phenylsulfonyl)methyl)phenyl)benzamide (**50b**): White solid; yield: 68 %; mp 176 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.04 (s, 3H), 3.76 (s, 2H), 4.45 (s, 2H), 6.67-6.69 (m, 1H), 6.98-7.02 (m, 1H), 7.39-7.43 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.66-7.74 (m, 3H), 7.94 (m, 1H), 8.06 (d, J = 8.4 Hz, 2H), 9.60 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 30.99, 38.01, 60.22, 120.88, 125.62, 126.55, 127.70, 128.53, 129.26, 129.37, 130.04, 132.46, 132.53, 134.40, 136.40, 136.73, 137.59, 142.90, 165.43; HRMS (ESI) m/z [M+Na]$^+$ calculated for C$_{22}$H$_{21}$NO$_3$S$_2$: 434.0861 found: 434.0862; Anal. Calcd for C$_{22}$H$_{21}$NO$_3$S$_2$: C, 64.15; H, 5.10; N, 3.40; found: C, 63.88; H, 4.94; N, 3.42.

(N-(4-Bromophenyl)-2-(4-(methylthiomethyl)benzamido))benzenesulfonamide
(**50c**): Light yellow solid; yield: 66 %; mp 190 ^{o}C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ:
2.04 (s, 3H), 3.74 (s, 2H), 6.86-6.88 (m, 2H), 7.14-7.18 (m, 3H), 7.19 (s, 1H) 7.42 (d,
J = 8.4 Hz, 2H), 7.56-7.60 (m, 1H), 7.75-7.77 (m, 1H), 7.80 (d, J = 8.4 Hz, 2H), 8.44-
8.47 (m, 1H), 9.93 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 15.08, 38.03, 120.64,
123.13, 124.11, 126.01, 126.55, 127.56, 129.33, 132.04, 132.49, 134.25, 134.65,
136.36, 143.33, 164.77; HRMS (ESI) *m/z* [M+Na]$^{+}$ calculated for C$_{21}$H$_{19}$N$_2$O$_3$S$_2$Br:
514.9728 found: 514.9732; Anal. Calcd for C$_{21}$H$_{19}$N$_2$O$_3$S$_2$Br: C, 51.28; H, 3.86; N,
2.84; found: C, 50.99; H, 3.90; N, 2.62.

2.5 Conclusion

We have designed and synthesized novel 2-substituted benzamidobenzene
derivatives bearing neutral sulfone, sulfoxide and sulfide groups as S4 ligands and
varying linkers like sulfonamide, methylsulfonylmethyl and methylsulfonyl
connecting S1 ligands.

2.6 References

1. Snyder, L. A.; Rudnick, K. A.; Tawadros, R.; Volk, A.; Tam, S. H.; Anderson, G. M.; Bugelski, P. J.; Yang, J. *J. Thromb. Haemost*. **2008**, *6*, 306-314.

2. Bolton-Maggs, P.H.; Pasi, K. J. *Lancet* **2003**, *361*, 1801-1809.

3. Galiani, D.; Renne, T. *J. Thromb. Haemost*. **2007**, *5*, 1106-1112.

4. Howard, E. L.; Becker, C. D.; Rusconi, C. P.; Becker, R. C. *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 722-727.

5. Weitz, J. I.; Buller, H. R. *Circulation* **2002**, *105*, 1004-1011.

6. Turpie, A. G.; *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 1238-1247.

7. Roberts, H. R.; Bingham, M. D. Other Coagulation Factor Deficiencies. Thrombosis and Hemorrhage, *2nd edn*. Baltimore, MD: Williams & Wilkins, **1998**, 773–802.

8. Duckert F.; Fluckinger P.; Matter M.; Koller F. *Proc. Soc. Exp. Biol. Med.* **1955**, *90*, 17–22.

9. Telfer T. P.; Denson K, W.; Wright D. R. *Brit. J. Haematol*. **1956**, *2*, 308–316.

10. Hougie C.; Barrow E. M.; Graham J. B. *J. Clin. Invest.* **1957**, *36*, 485–946.

11. Miao, C.H.; Leytus, S.P.; Chung, D.W.; Davie, E. W. *J. Biol. Chem.* **1992,** *267(11)*, 7395-7401.

12. Borensztajn, K.; Spek, C. A. *Current Genomics* **2005**, *6(6)*, 383-400.

13. Padmanabhan, K.; Padmanabhan, K. P.; Tulinsky, A.; Park, C. H.; Bode, W.; Huber, R.; Blankenship, D. T.; Cardin, A. D.; Kisiel, W. *J. Mol. Biol.* **1993**, *232*, 947–966.

14. Friedman, P. A.; Przysiecki, C. T. *Int. J. Biochem.* **1987**, *19(1)*, 1-7.

15. Hedstrom, L. *Chem. Rev.* **2002**, *102(12),* 4501-4524.

16. Bugg, T. D. H. Introduction to Enzyme and Coenzyme Chemistry. In *Enzymatic Hydrolysis and Group Transfer Reactions,* 2nd ed.; Blackwell: Oxford, 2004; 84–89.

17. Maignan, S.; Mikol, V. *Curr. Top. Med. Chem.* **2001**, *1*, 161–174.

18. Rai, R.; Sprengeler, P. A.; Alrod, K. C.; Young, W. B. *Curr. Med. Chem.* **2001**, *8(2)*, 101-119.

19. Tuszynski, G. P.; Gasic, T. B.; Gasic, G. J. *J. Biol. Chem.* **1987**, *262*, 9718-9723.

20. Waxman, L.; Smith, D. E.; Arcuri, K. E.; Vlasuk, G. P. *Science* **1990**, *248*, 593-596.

21. Yusuf, S.; Mehta, S. R.; Chrolavicius, S; Afzal, R.; Pogue, J.; Granger, C. B.; Budaj, A.; Peters, R. J.; Bassand, J. P.; Wallentin, L.; Joyner, C.; Fox, K. A. *J. Am. Med. Asso.* **2006**, *295*, 1519-1530.

22. Hara, T.; Yokoyama, A.; Ishihara, H.; Yokoyama, Y.; Nagahara, T.; Iwamoto, M. *Thromb. Haemost.* **1994**, *71*, 314-319.

23. Lam, P. Y.; Clark, C. G.; Li, R.; Pinto, D. J. P; Orwat, M. J.; Galemmo, R. A.; Fevig, J. M.; Teleha, C. A.; Alexander, R. S.; Smallwood, A. M.; Rossi, K. A.; Wright, M. R.; Bai, K. H.; Luettgen, J. M.; Wong, P. C.; Knabb, R. M.;Wexler, R. R. *J. Med. Chem.* **2003**, *46*, 4405-4418.

24. Guertin, K. R.; Choi, Y. M. *Curr. Med. Chem.* **2007**, *14*, 2471-81.

25. Hinder, M.; Frick, A.; Jordaan, P.; Hesse, G.; Gebauer, A.; Maas, J.; Paccaly, A. *Clin. Pharmacol. Ther.* **2006**, *80*, 691-702.

26. Light, D. R.; Guilford, W. J. *Curr. Top. Med. Chem.* **2001**, *1*, 121-36.

27. Tidwell, R. R.; Webster, W. P.; Shaver, S. R.; Geratz, J. D. *Thromb. Res.* **1980**, *19*, 339-349.

28. Sturzebecher, O.; Markwardt, F.; Walsman, P. *Thromb. Res.* **1980**, *17*, 545-548.

29. Huang, W.; Zhang, P.; Zuckett, J. F.; Wang, L.; Woolfrey, J.; Song, Y.; Jia, Z. J.; Cizbe, L. AA.; Su, T.; Tran, K.; Huang, B.; Wong, P.; Sinha, U.: Park, G.; Reed, A.; Malinowski, J.; Hollenbach, S. J.; Scarborough, R. M.; Zhu, B. Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 561-566.

30. Mendel, D.; Marquart, A. L.; Josheph, S.; Waid, P.; Yee, Y. K.; Tebbe, A. L.; Ratz, A. M.; Herron, D. K.; Goodson, T.; Masters, J. J.; Franciskovich, J. B.; Tinsley, J. M.; Wiley, M .R.; Weir. L. C.; Kyle, J. A.; Froelich, L. L.; Buben, J.; Craft, T. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4832-4836.

31. Chou, Y. L.; Davey, V.; Eagen, K.; Griedel, B. D.; Karanjawala, R.; Phillips, G. B.; Sacchi, K. L.; Shaw, K. J.; Wu, S. C.; Lentz, D.; Liang, A. M.; Trinh, L.; Morrissey, M .M.; Kochanny, M. J. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 507–511.

32. Herron, D. K.; Goodson, T.; Wiley, M. R.; Weir, L. C.; Kyle, J. A.; Yee, Y. K.; Tebbe, A. L.; Tinsley, J. M.; Mendel, D.; Masters, J. J.; Franciskovich, J. B.; Scott Sawyer, J.; Beight, D. W.; Ratz, A. M.; Milot, G.; Hall, S. E.; Klimkowski, V. J.; Wikel, J. H.; Eastwood, B. J.; Towner, R. D.; Moore, D. S. G.; Craft, T. J.; Smith, G. F. *J. Med. Chem.* **2000**, *43*, 859–872.

33. Wiley, M. R.; Weir, L. C.; Briggs, S.; Bryan, N. A.; Buben. J.; Campbell, C.; Chirgadze, N. Y.; Conrad, R. C.; Craft, T. J.; Ficorilli, J. V.; Franciskovich, J. B.; Froelich, L. L.; Gifford-Moore, D. S.; Goodson, T.; Herron, D. K.; Klimkowski, V. J.; Kurz, K. D.; Kyle, J. A.; Masters, J. J.; Ratz, A. M.; Milot, G.; Shuman, R. T.; Smith, T.; Smith, G. F.; Tebbe, A. L.; Tinsley, J. M.; Towner, R. D.; Wilson, A.; Yee, Y. K. *J. Med. Chem*. **2000**, *43*, 883–899.

34. Pinto, D. J.; Smallheer, J. M.; Cheney, D. L.; Knabb, R. M.; Wexler, R. R. *J. Med. Chem.* **2010**, *53*, 6243-6274.

35. Pinto, D. J. P; Orwat, M. J.; Wang, S.; Fevig, J. M.; Quan, M. L.; Amparo, E.; Cacciola, J.; Rossi, K.A.; Alexander, R. S.; Smallwood, A. M.; Luettegen, J. M.; Liang, L.; Aungst, B. J.; Wright, M. R.; Knann, R. M.; Wong, p. C.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* **2001**, *44*, 566-578.

36. Quan, M. L.; Lam, P. Y. S.; Han, Q.; Pinto, D. J. P.; He, M. Y.; Li, R.; Ellis, C. D.; Clark, C. G.; Teleha, C. A.; Sun, J. H.; Alexander, R. S.; Bai, S.; Luettgen, J. M.; Knabb, R. M.; Wong, P. C.; Wexler, R. R. *J. Med. Chem.* **2005**, *48*, 1729-1744.

37. Roehrig, S.; Straub, A.; Pohlmann, J.; Lampe, T.; Pernerstorfer, J.; Schlemmer, K. H.; Reinemer, P.; Perzborn, E. *J. Med. Chem.* **2005**, *48*, 5900-5908.

38. Perzborn, E.; Roehrig, S.; Straub, A.; Kubitza, D.; Misselwitz, F. *Nat. Rev. Drug Discov.* **2011**, *10*, 61-75.

39. Pinto, D. J.; Orwat, M. J.; Koch, S.; Rossi, K. A.; Alexander, R. S.; Smallwood, A.; Wong, P. C.; Rendina, A. R.; Luettgen, J. M.; Knabb, R. M.; He, K.; Xin, B.; Wexler, R. R.; Lam, P. Y. *J. Med. Chem.* **2007**, *50*, 5339-5356.

40. Nagata, T.; Nagamochi, M.; Kobayashi, S.; Komoriya, S.; Yoshino, T.; Kanno, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4587-4592.

41. Furugohri, T.; Isobe, K.; Honda, Y.; Kamisato-Matsumoto, C.; Sugiyama, N.; Nagahara,T.; Morishima, Y.; Shibano, T. *J. Thromb. Haemost.* **2008**, *6*, 1542-1549.

42. Zhang, P.; Huang, W.; Wang, L.; Bao, L.; Jia, Z. J.; Bauer, S. M.; Goldman, E. A.; Probst, G. D.; Song, Y.; Su, T.; Fan, J.; Wu, Y.; Li, W.; Woolfrey, J.; Sinha, U.; Wong, P. W.; Edwards, S. T.; Arfsten, A. E.; Clizbe, L. A.; Kanter, J.; Pandey, A.; Park, G.; Hutchaleelaha, A.; Lambing, J. L.; Hollenbach, S. J.; Scarborough, R. M.; Zhu, B. Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2179-2185.

43. Turpie, A. G.; Bauer, K. A.; Davidson, B. L.; Fisher, W. D.; Gent, M.; Huo, M. H.; Sinha, U.; Gretler, D. D. *Thromb. Haemostasis.* **2009**, *101*, 68-76.

44. Candia, M.; Lopopolo, G.; Altomare, C. *Expert. Opin. Ther. Patents* **2009**, *19*, 1535-1580.

45. Zhang, P.; Bao, L.; Fan, J.; Jia, Z. J.; Sinha, U.; Wong, P. W.; Park. G.; Hutchaleelaha, A.; Scarborough, R. M.; Zhu, B. Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2186–2189.

46. Herron, D. K.; Goodson, T.; Wiley, M. R.; Weir, L. C.; Kyle, J. A.; Yee, Y. K.; Tebbe, A. L.; Tinsley, J. M.; Mendel, D.; Masters, J. J.; Franciskovich, J. B.; Scott, S. J.; Beight, D. W.; Ratz, A. M.; Milot, G.; Hall, S. E.; Klimkowski, V. J.; Wikel, J. H.; Eastwood, B. J.; Towner, R. D.; Moore, D. S. G.; Craft, T. J.; Smith, G. F. *J. Med. Chem.* **2000**, *43*, 859–872.

47. Young, R. J.; Borthwik, A. D.; Brown, D.; Burns-Kurtis, C. L.; Campbell, M.; Chan, C.; Charbaut, M.; Chung, C.; Convery, M. A.; Kelly, H. A.; King P.; Kleanthous, S.; Mason, A. M.; Pateman, A. J.; Patikis, A. N.; Pinto, I. L.; Pollard, D. R.; Senger, S.; Shah, G. P.; Toomey, J. R.; Watson, N. S.; Weston, H. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 23-27.

48. Verma, A.; Giridhar, R. Kanhed, A.; Sinha, A.; Modh, P.; Yadav, M. R. *ACS Med. Chem. Lett.* **2013,** *4*, 32-36.

49. Brown, T. M.; Carruthers, W.; Pellatt, M. G. *J. Chem. Soc. Perkin* I **1982**, 483.

50. Chand, P.; Babu, Y. S.; Bantia, S.; Chu, N.; Cole, L. B.; Kotian, P. L.; Laver, W. G.; Montgomery, J. A.; Pathak, V. P.; Petty, S. L.; Shrout, D. P.; Walsh, D. A.; Walsh, G. M. *J. Med. Chem.* **1997**, *40*, 4030-4052.

51. Chaudhari, U. V.; Deota, P. T. *Org. Prep. Proced. Int*. **2012**, *44*, 381-386.

52. Freeman, J. H.; Wagner, E. C. *J. Org. Chem*. **1951**, *16*, 815-837.

53. Davis, F. A.; Johnston, R. P. *J. Org. Chem*. **1972**, *37*, 854-859.

54. Davis, F. A.; Wetzel, R. B.; Devon, T. J.; Stackhouse, J. F. *J. Org. Chem*. **1971**, *36*, 799-803.

55. Saeed, A.; Rama, N. H. *J. Chem. Soc. Pak*. **1994**, *16*, 31-37.

56. Chen, H.; Nilsen, C. N; Choudhury, A.; Sorgi, K. L. *Arkivoc* **2008**, *14*, 1-6

57. Plano, D.; Baquedano, Y.; Ibáñez, E.; Jiménez, I.; Palop, J. A.; Spallholz, J. E.; Sanmartín, C. *Molecule* **2010**, *15*, 7292-7312.

58. Makhija, M. T.; Kashwal, R. T.; Kulkarni, V. M.; Neamti, N. *Bioorg. Med. Chem.* **2004**, *12*, 2317-2333.

59. Cadogan, J. I. G.; Hickson, C. L.; Husband, J. B.; McNab, H. *J. Chem. Soc. Perkin Trans I* **1985**, 1891-1895.

60. Makosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 5272-5274.

61. Tuleen, D. L.; Hess, B. A. *J. Chem. Edu*. **1971**, *48,* 476-477.

62. Russell, G. A.; Pecoraro, J. M. *J. Org. Chem*. **1979**, *44*, 3990-3991.

63. Sammond, D. M.; Nailor, K. E.; Veal, J. M.; Nolte, R. T.; Wang, L.; Knick, V. B.; Rudolph, S. K.; Truesdale, A. T.; Nartey, E. N; Stafford, J. A.; Kumar, R.; Cheung, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3519-3523.

64. Purushottamachar, P.; Khandelwal, A.; Vasaitis, T. S.; Bruno, R. D.; Gediya, L. K.; Njar, V. C. O. *Bioorg. Med. Chem*. **2006**, *16*, 3519-3523.

65. Peifer, C.; Kinkel, K.; Abadleh, M.; Schollmeyer, D.; Laufer, S. *J. Med. Chem*. **2007**, *50*, 1213-1221.

66. Rivillo, D.; Gulyas, H.; Benet-Buchholz, J.; Escudero-Adan, E. C.; Freixa, Z.; Leeuwen, P. W. N. M. V. *Angew. Chemie.* **2007**, *46*, 7247-7250.

2.7 Spectral data of compounds
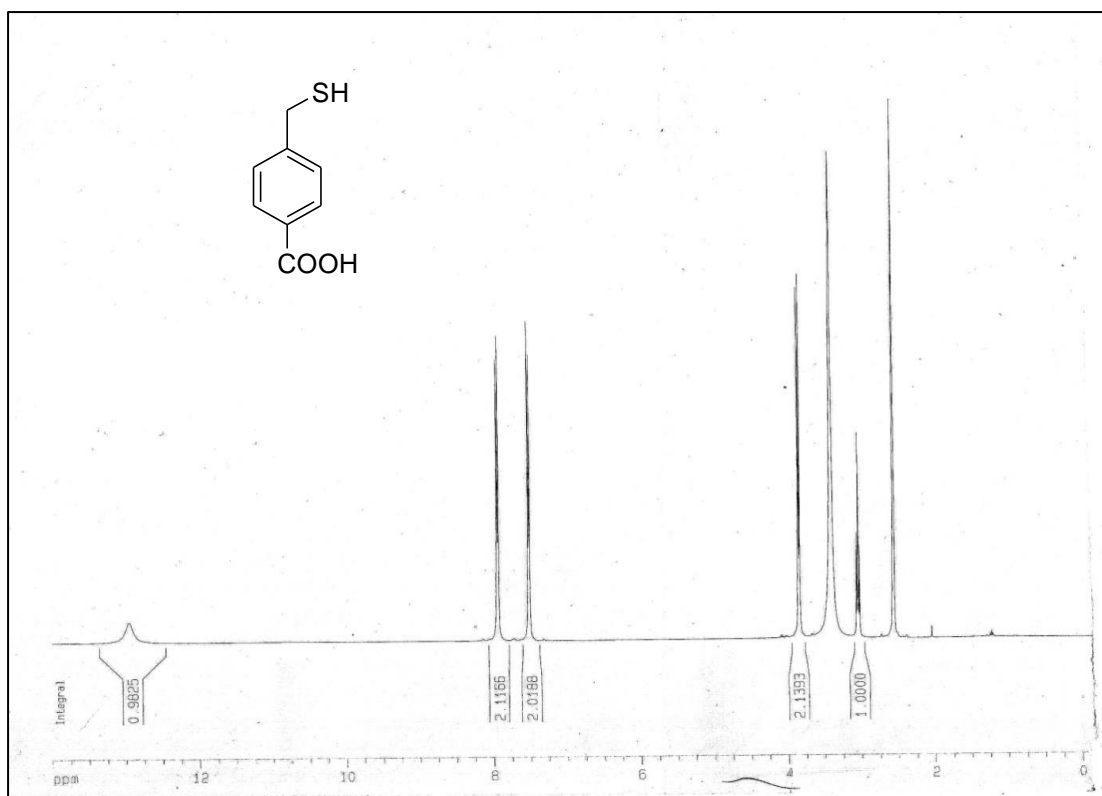
Figure 2.8 ^{1}H NMR spectrum of 4-(Mercaptomethyl)benzoic acid (**21**)
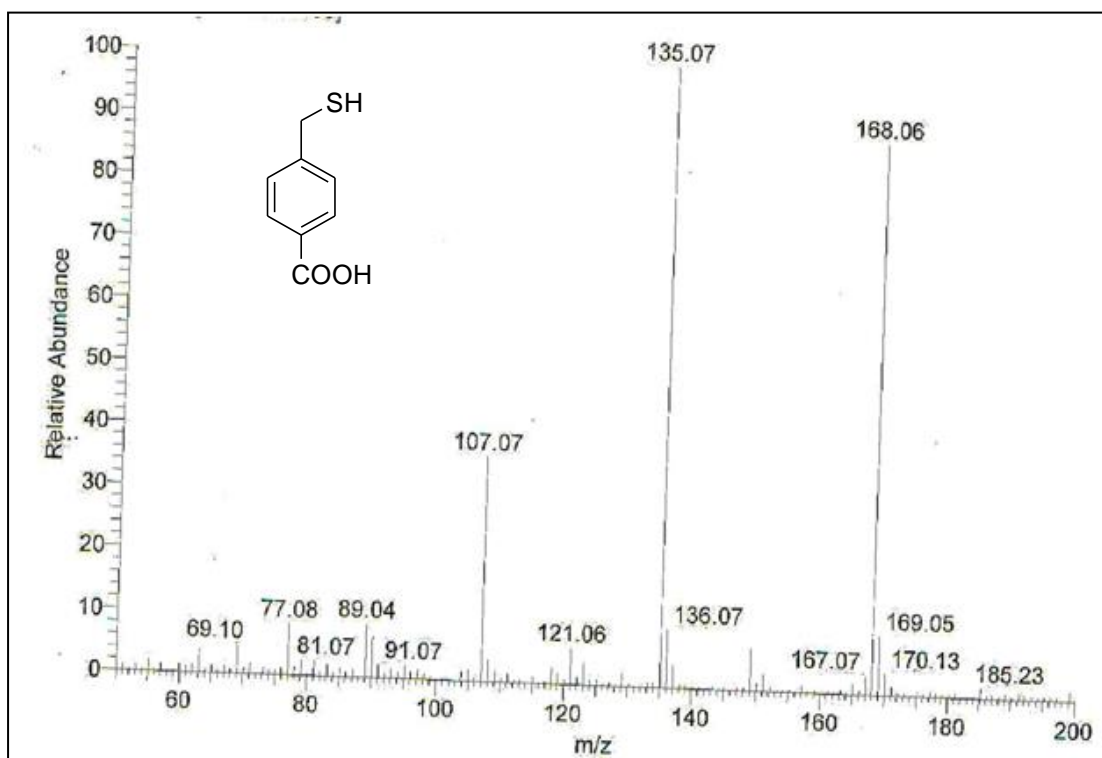
Figure 2.9 Mass specturum of 4-(Mercaptomethyl)benzoic acid (**21**)
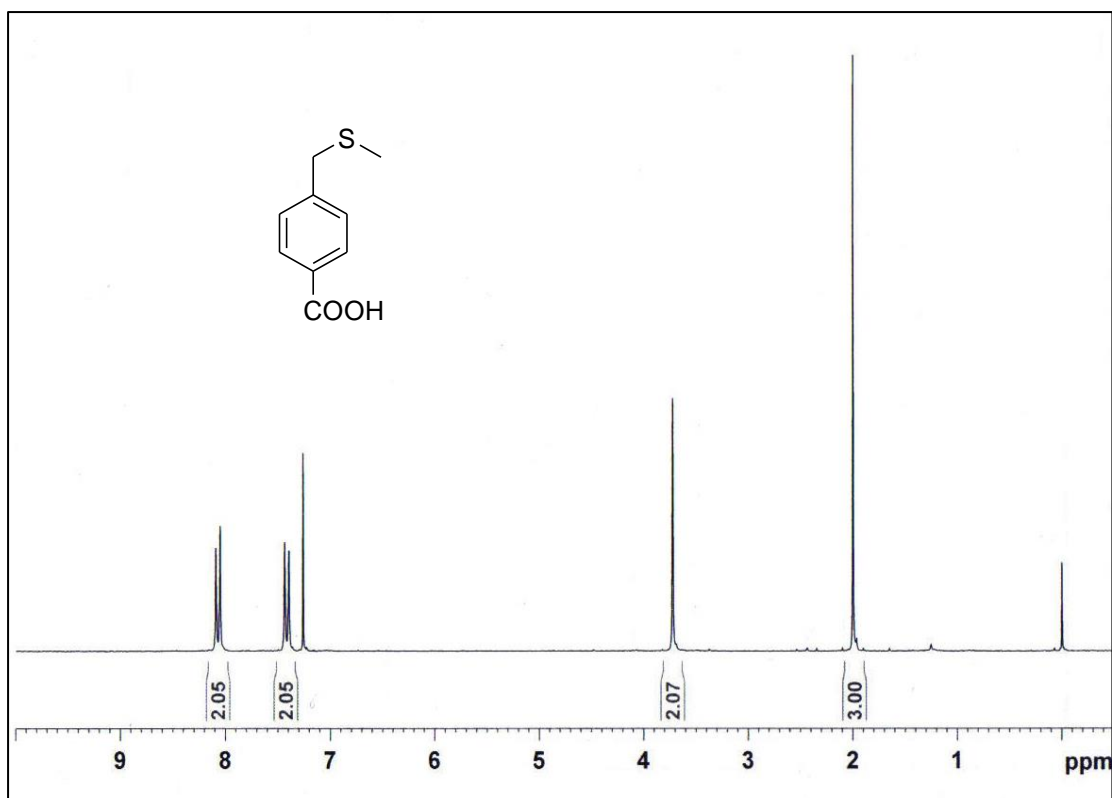
Figure 2.10 ^{1}H NMR spectrum of 4-((Methylthio)methyl)benzoic acid (**22**)
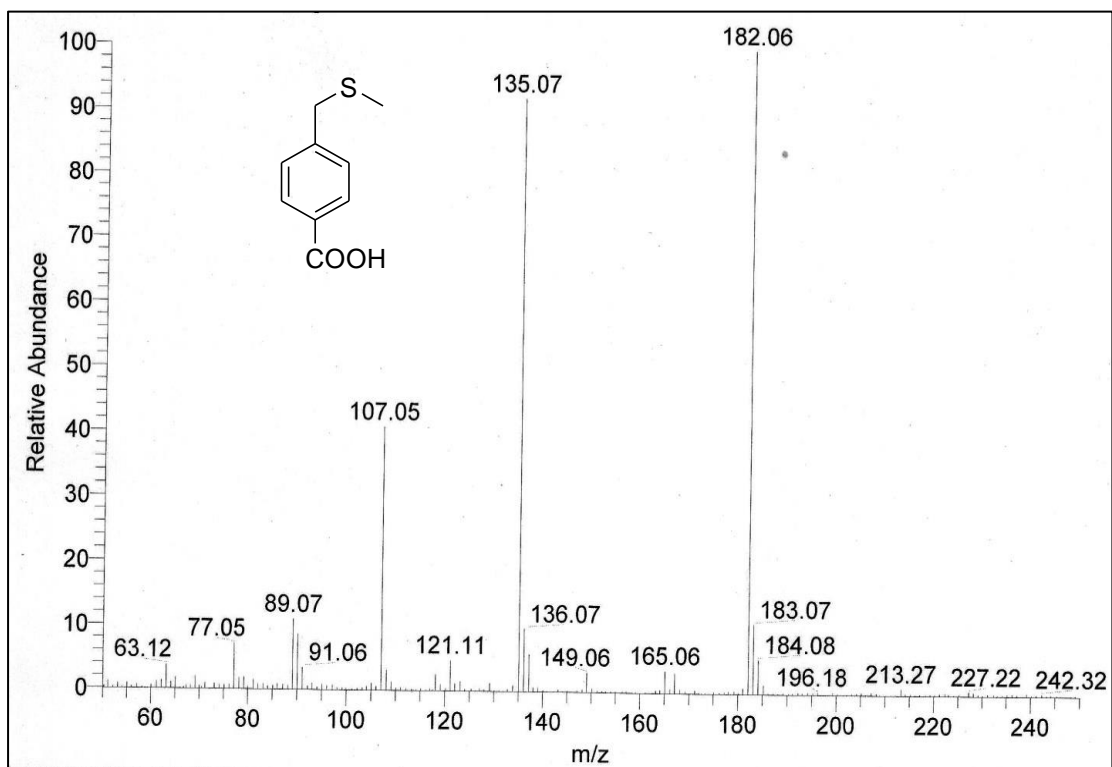
Figure 2.11 Mass specturum of 4-((Methylthio)methyl)benzoic acid (**22**)
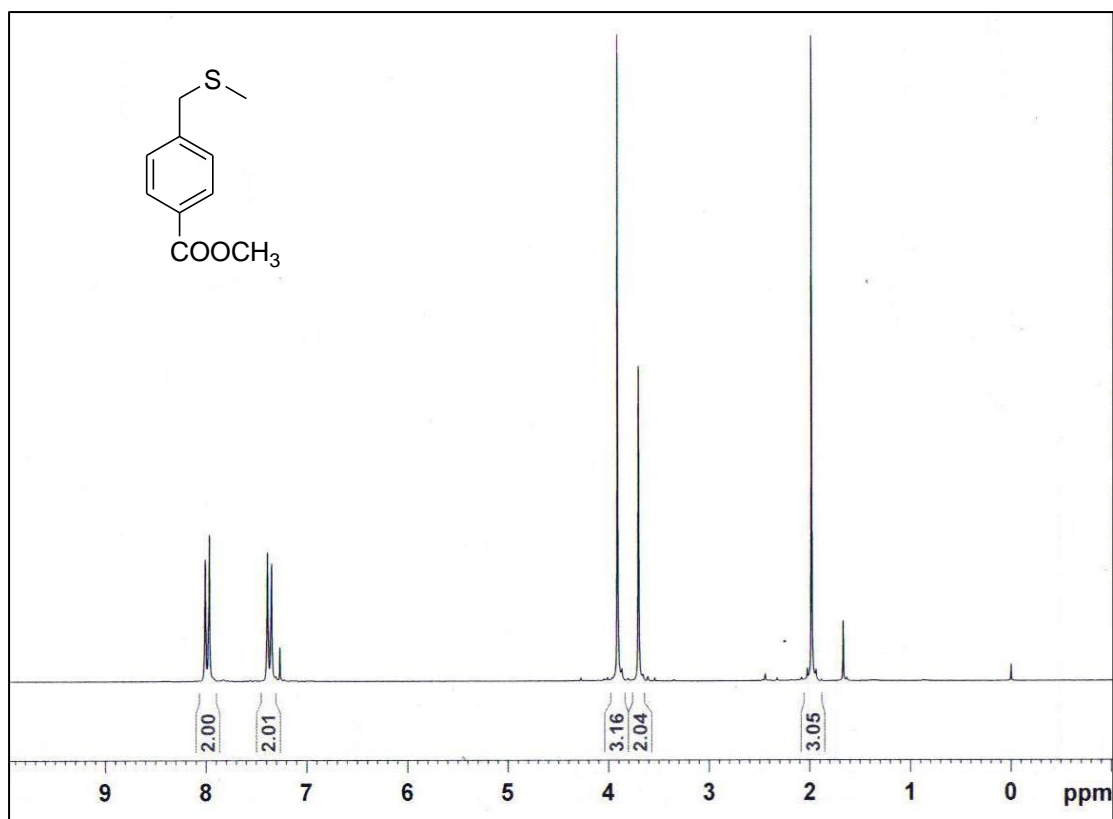
Figure 2.12 ^{1}H NMR spectrum of Methyl 4-((methylthio)methyl)benzoate (**23**)
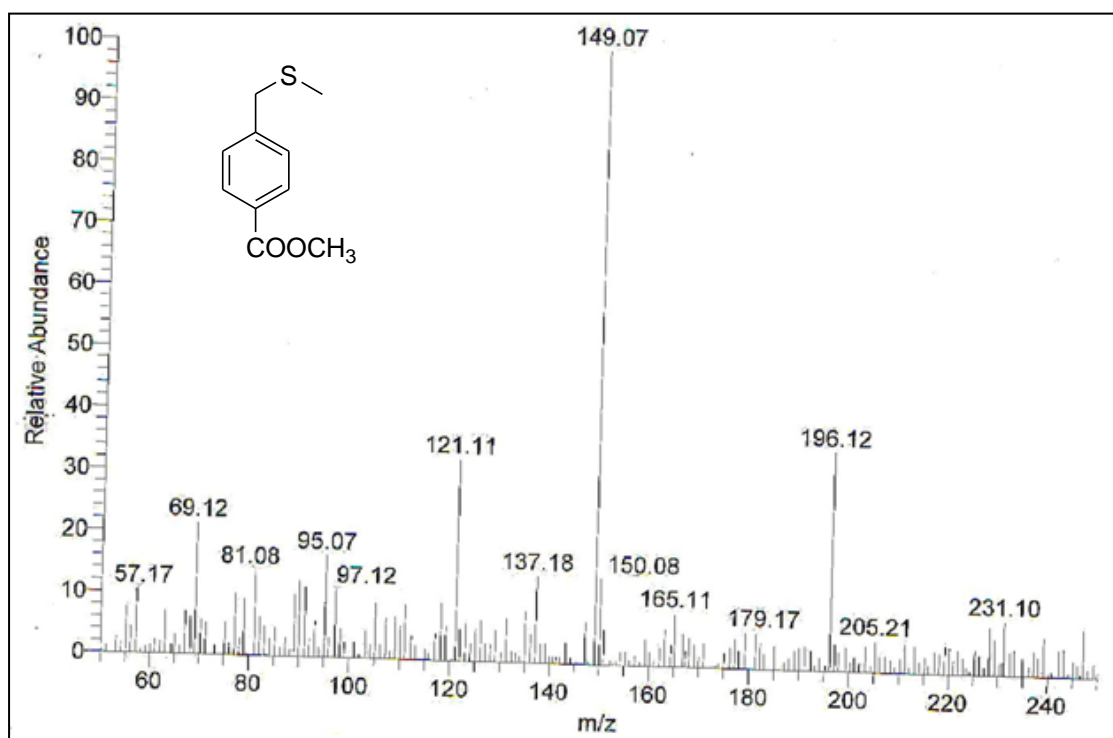
Figure 2.13 Mass spectrum of Methyl 4-((methylthio)methyl)benzoate (**23**)
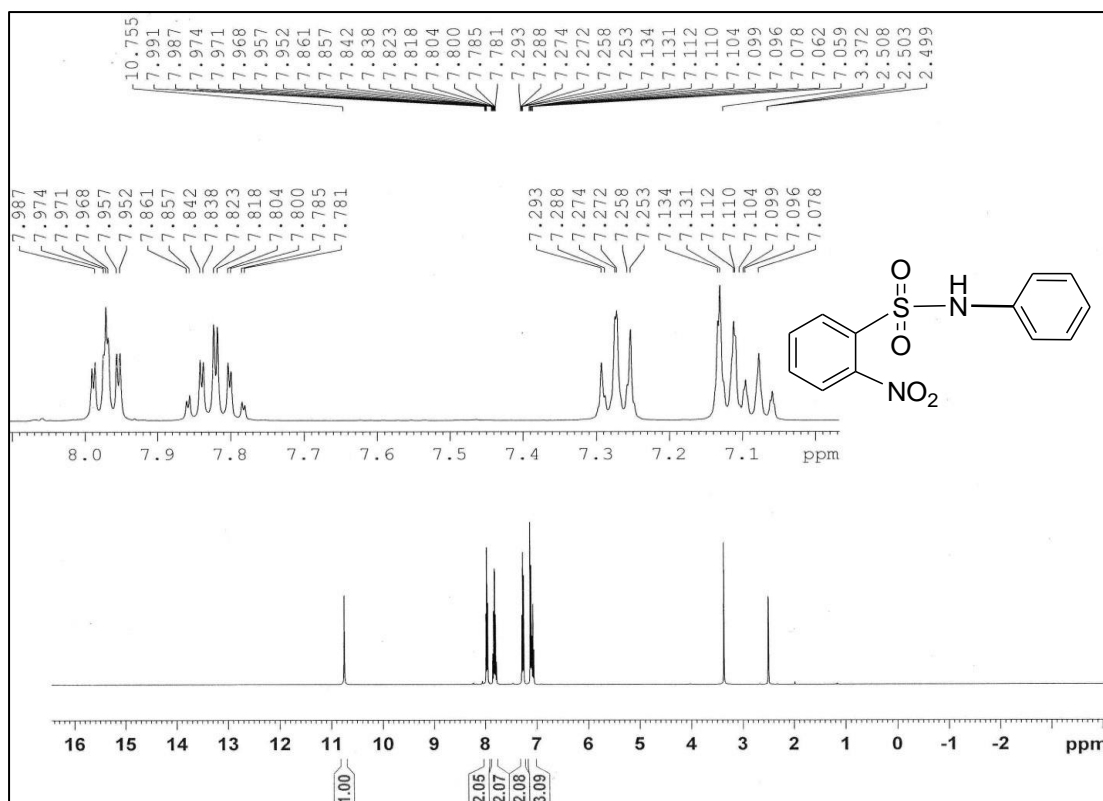
Figure 2.14 ^{1}H NMR spectrum of N-Phenyl-2-nitrobenzenesulfonamide (**28a**)
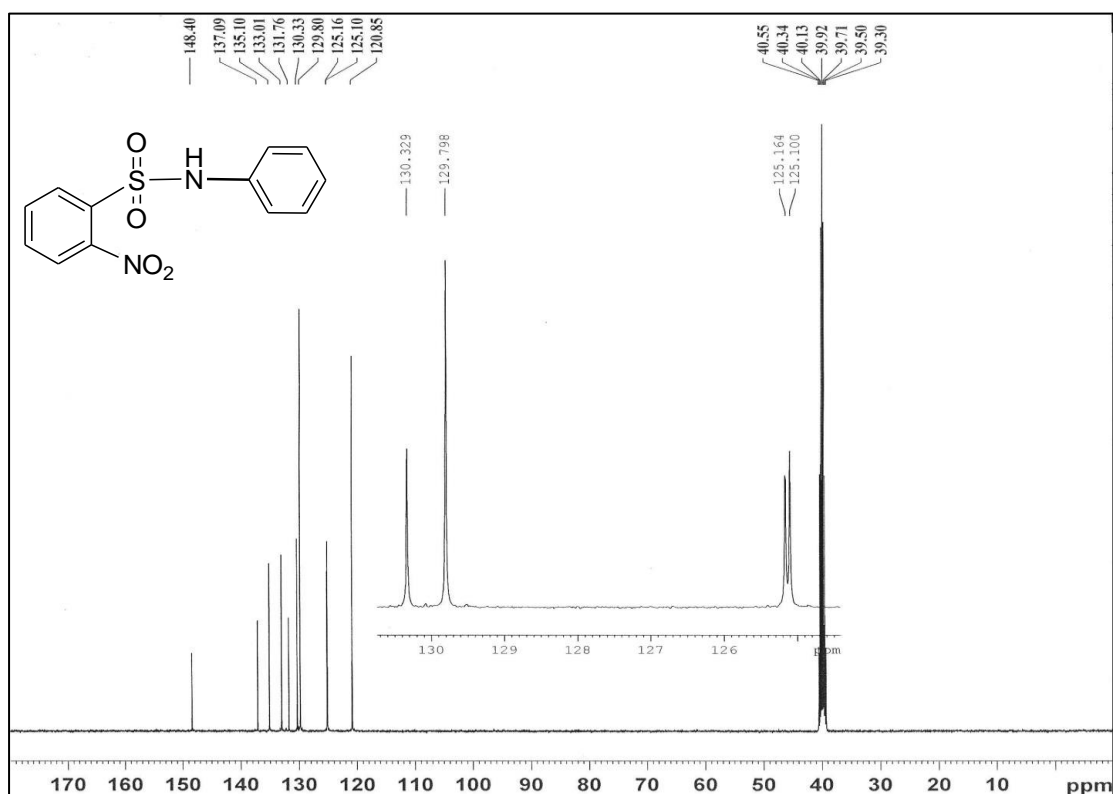
Figure 2.15 ^{13}C NMR spectrum of N-Phenyl-2-nitrobenzenesulfonamide (**28a**)
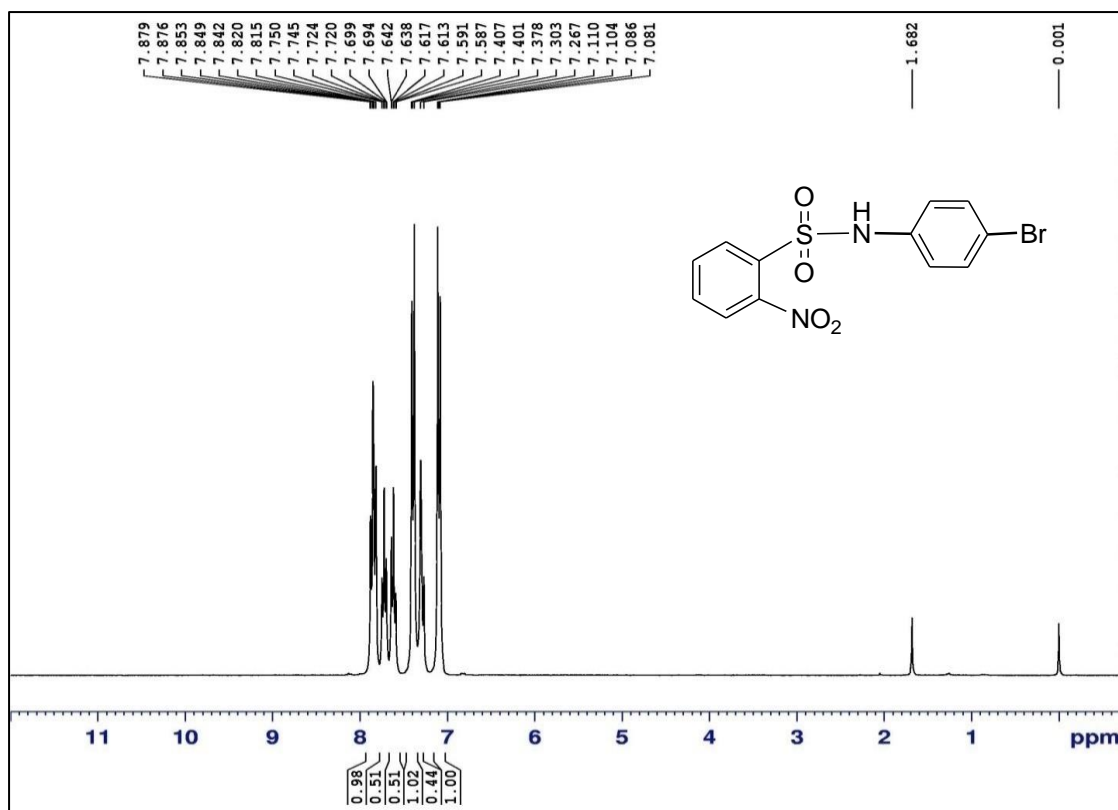
Figure 2.16 ^{1}H NMR spectrum of N-(4-Bromophenyl)-2-nitrobenzenesulfonamide (**28d**)
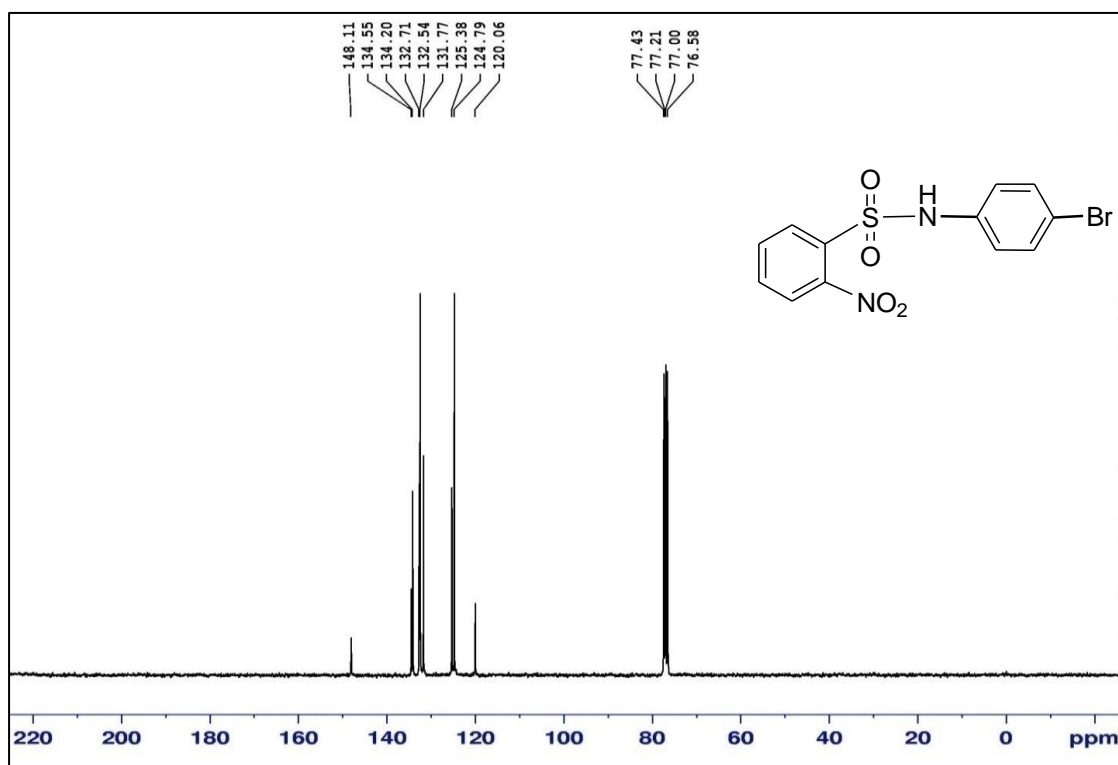
Figure 2.17 ^{13}C NMR spectrum of N-(4-Bromophenyl)-2-nitrobenzenesulfonamide (**28d**)
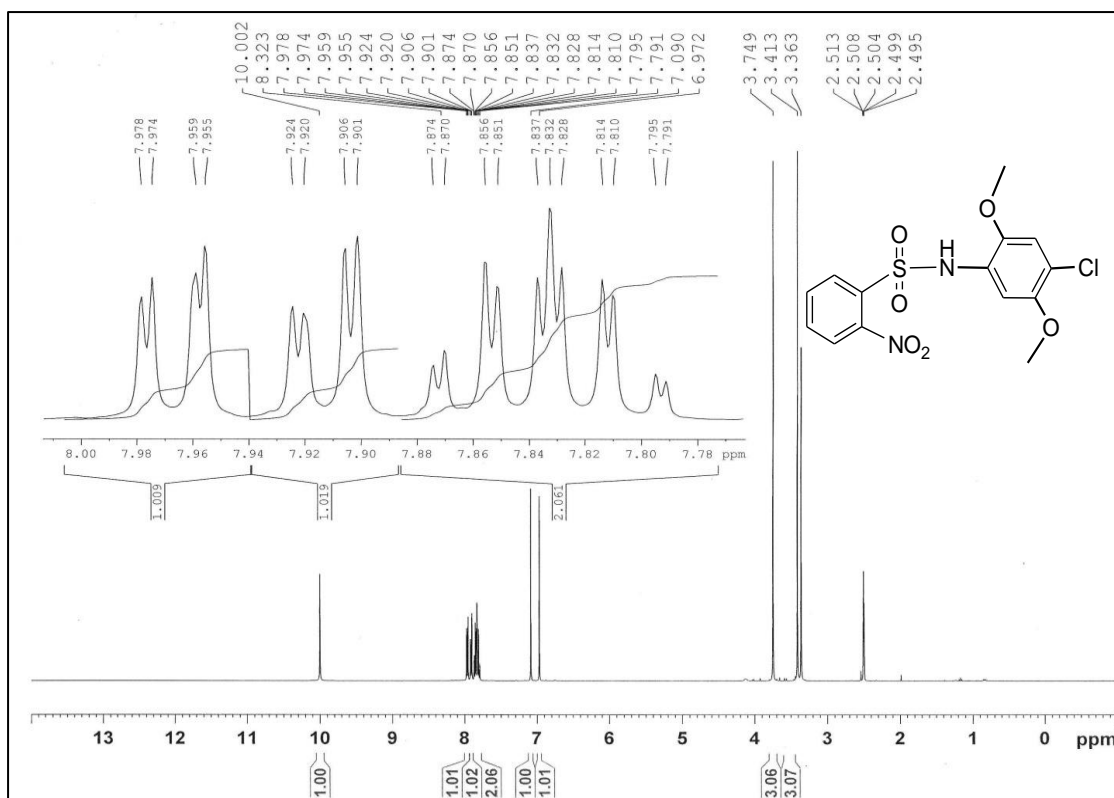
Figure 2.18 ^{1}H NMR spectrum of N-(4-Chloro-2,5-dimethoxyphenyl)-2-nitro benzenesulfonamide (**28e**)
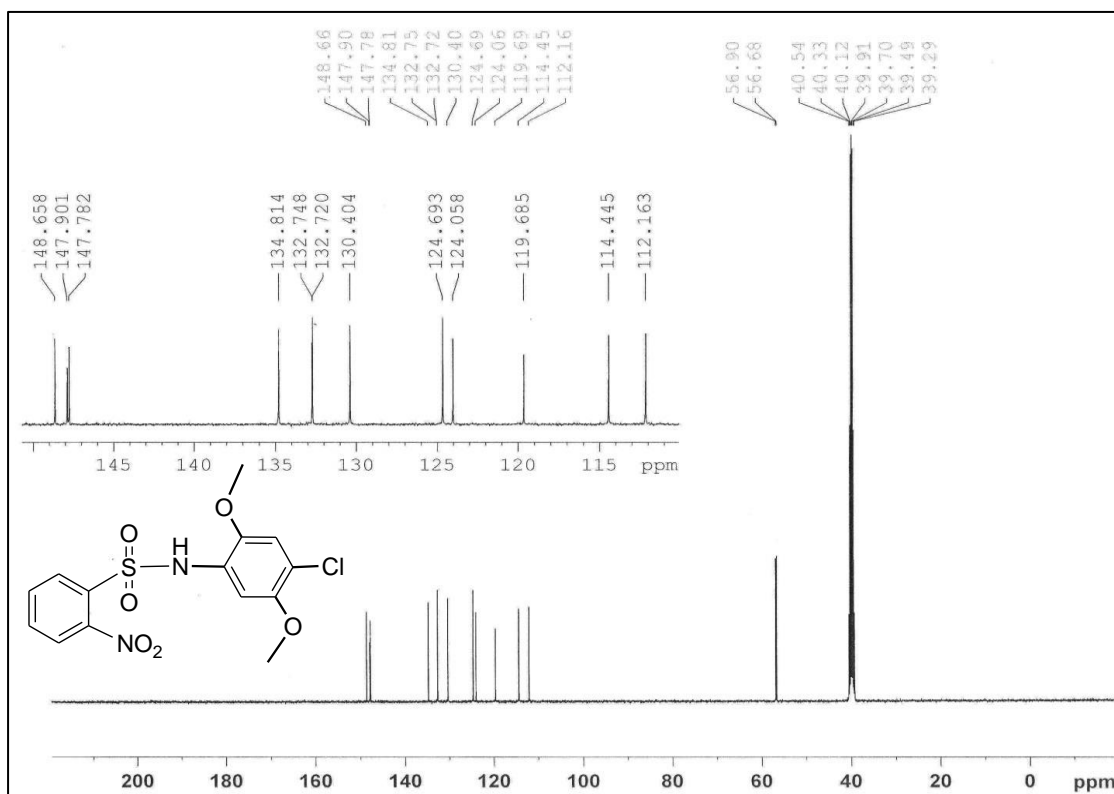
Figure 2.19 ^{13}C NMR spectrum of N-(4-Chloro-2,5-dimethoxyphenyl)-2-nitro benzenesulfonamide (**28e**)
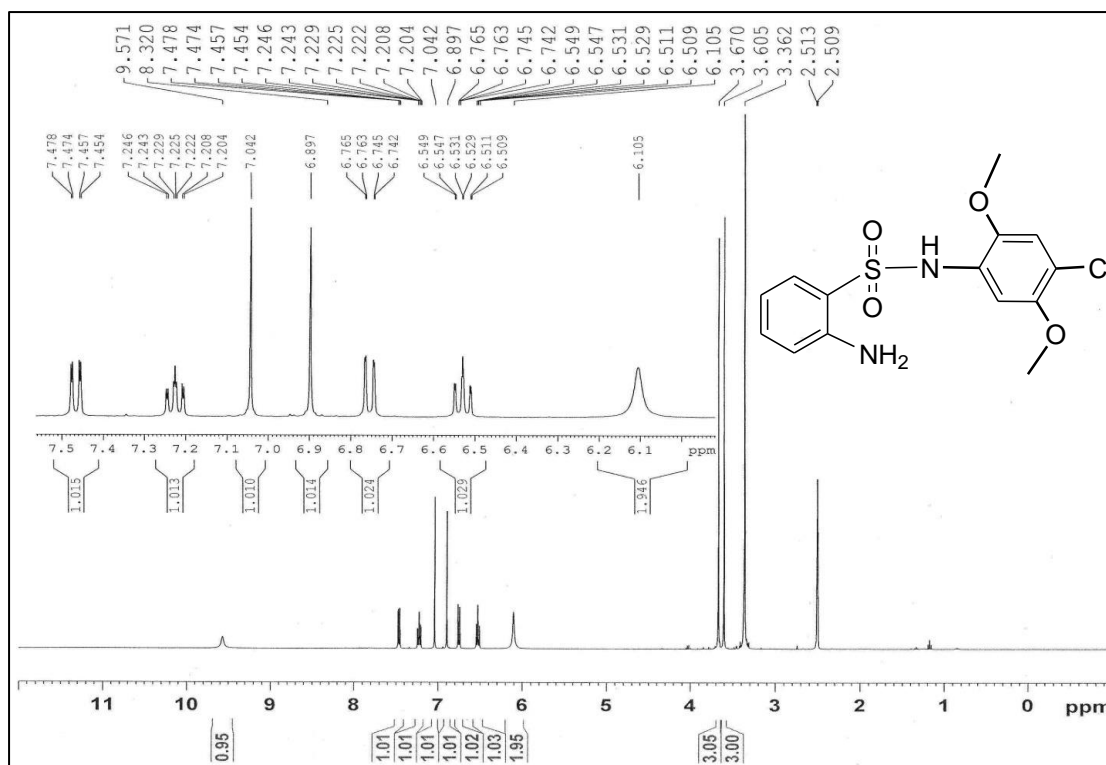
Figure 2.20 ^{1}H NMR spectrum of N-(4-Chloro-2,5-dimethoxyphenyl)-2-nitro benzenesulfonamide (**29e**)
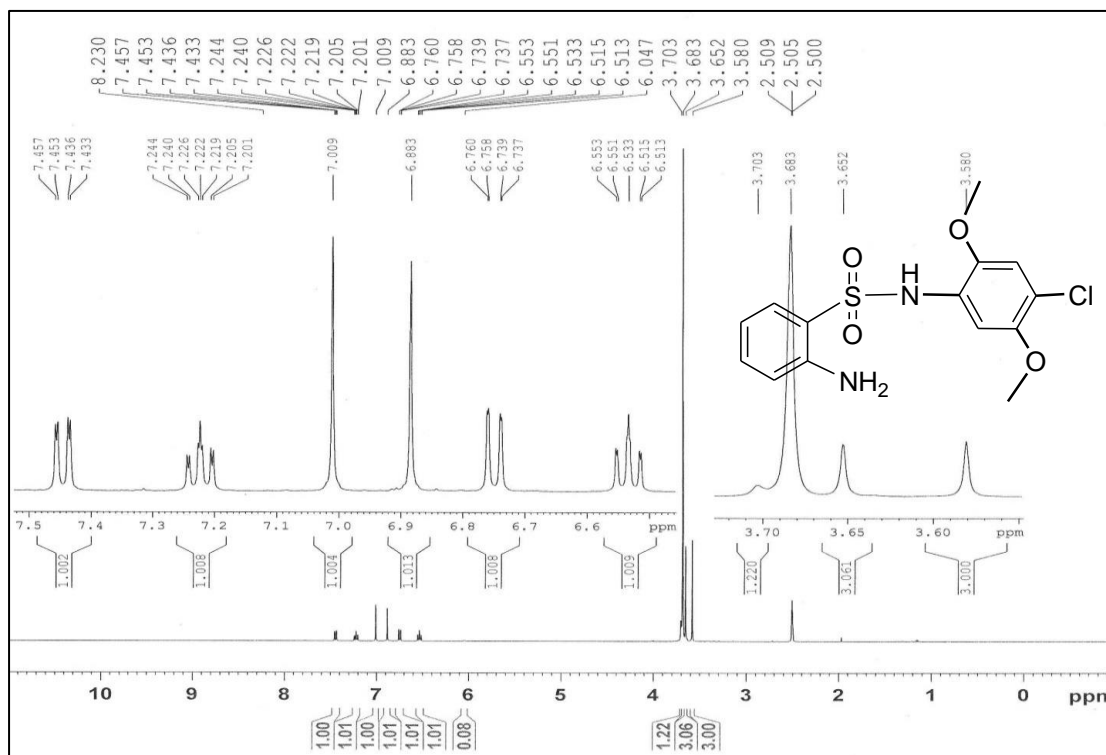
Figure 2.21 ^{1}H NMR with D_2O exchange spectrum of N-(4-Chloro-2,5-dimethoxy phenyl)-2-nitrobenzenesulfonamide (**29e**)

Figure 2.22 ^{1}H NMR spectrum of N-Phenyl-2-(4-(methylsulfonylmethyl)benzamido) benzenesulfonamide **(30a)**

Figure 2.23 ^{13}C NMR spectrum of N-Phenyl-2-(4-(methylsulfonylmethyl)benzamido) benzenesulfonamide **(30a)**
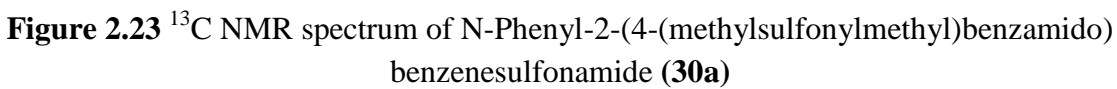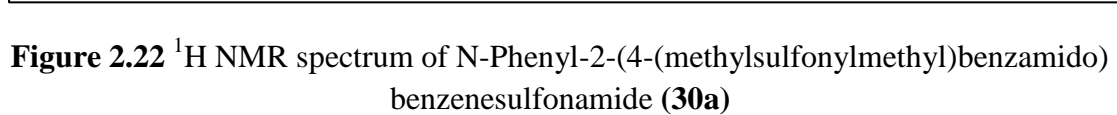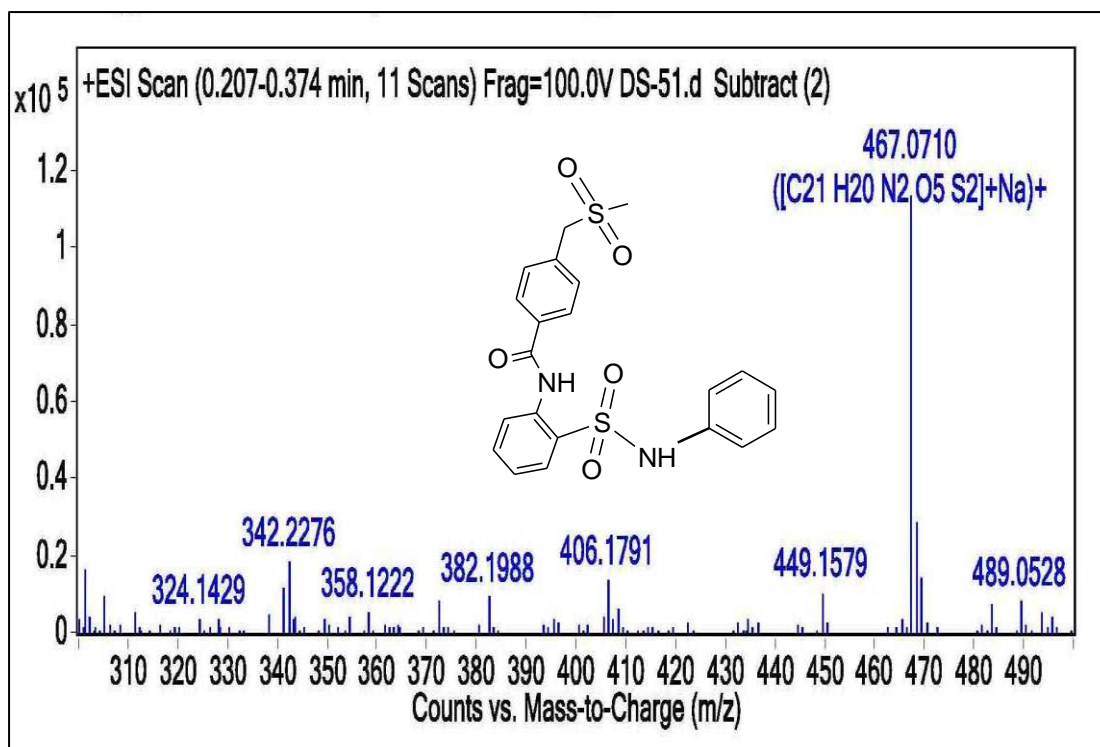
Figure 2.24 HRMS spectrum of N-Phenyl-2-(4-(methylsulfonylmethyl)benzamido)
benzenesulfonamide **(30a)**
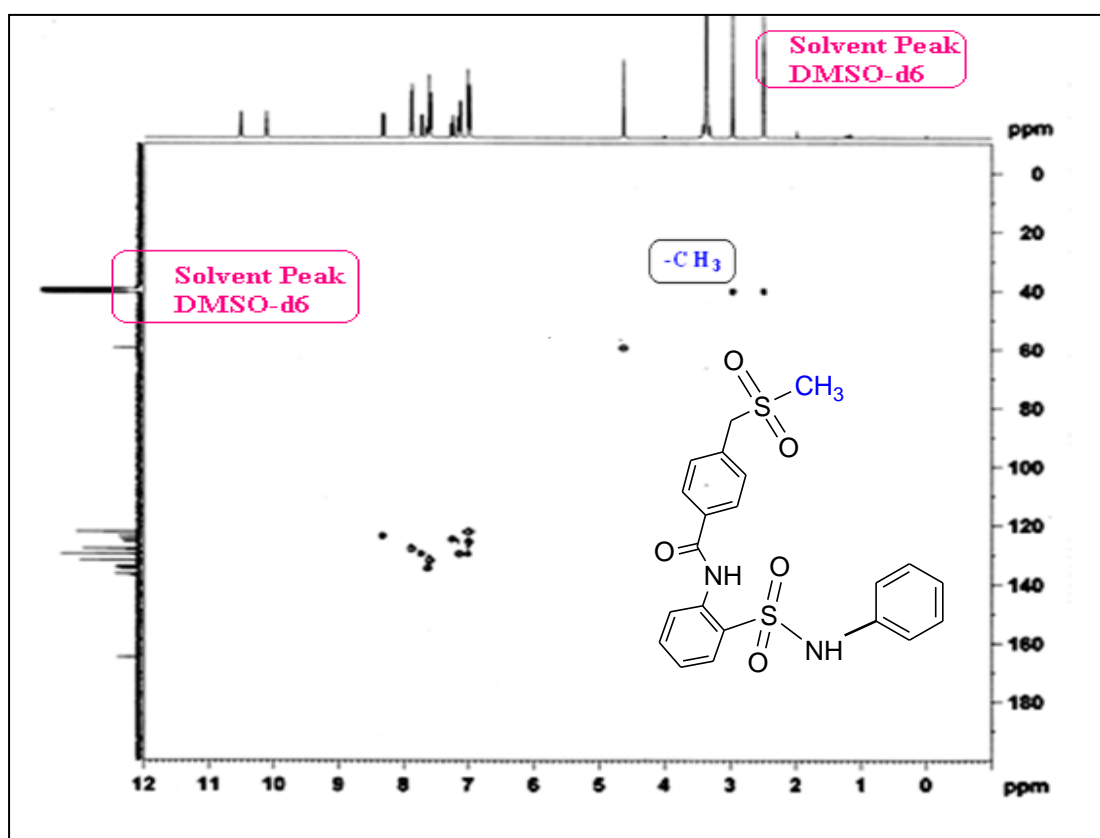
Figure 2.25 HSQC spectrum of N-Phenyl-2-(4-(methylsulfonylmethyl)benzamido)
benzenesulfonamide **(30a)**
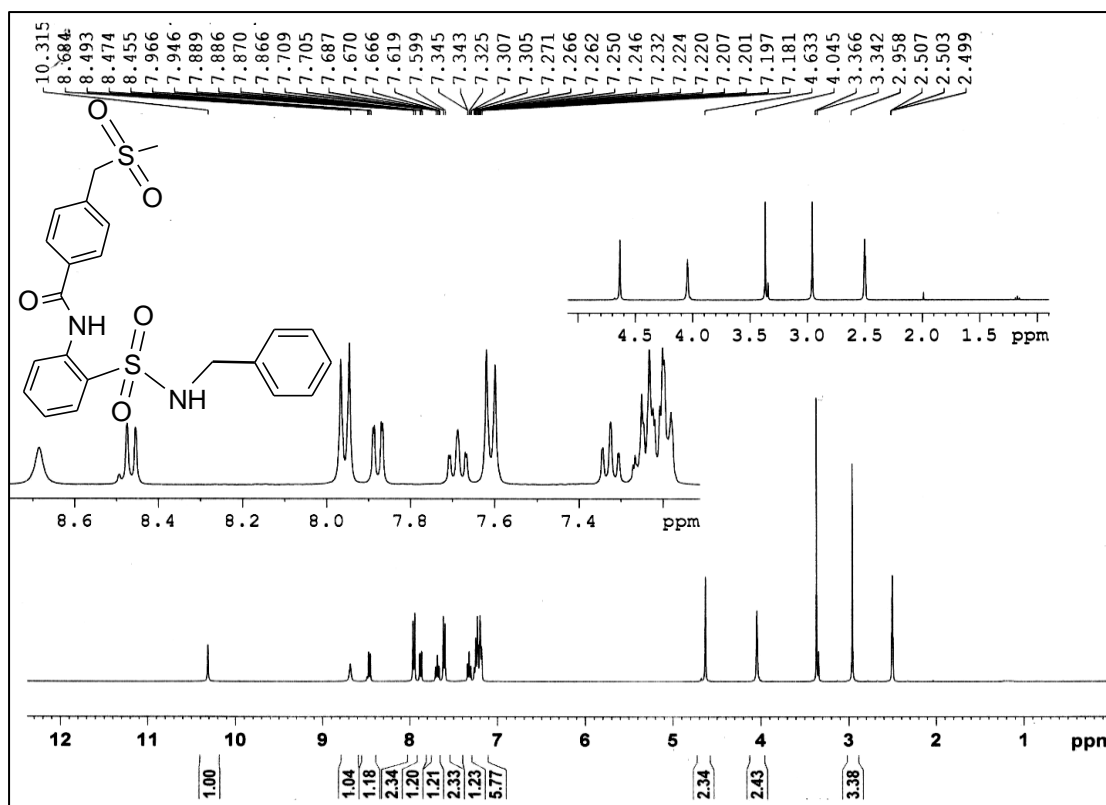
Figure 2.26 ^{1}H NMR spectrum of N-Benzyl-2-(4-(methylsulfonylmethyl)benzamido) benzenesulfonamide (**30b**)
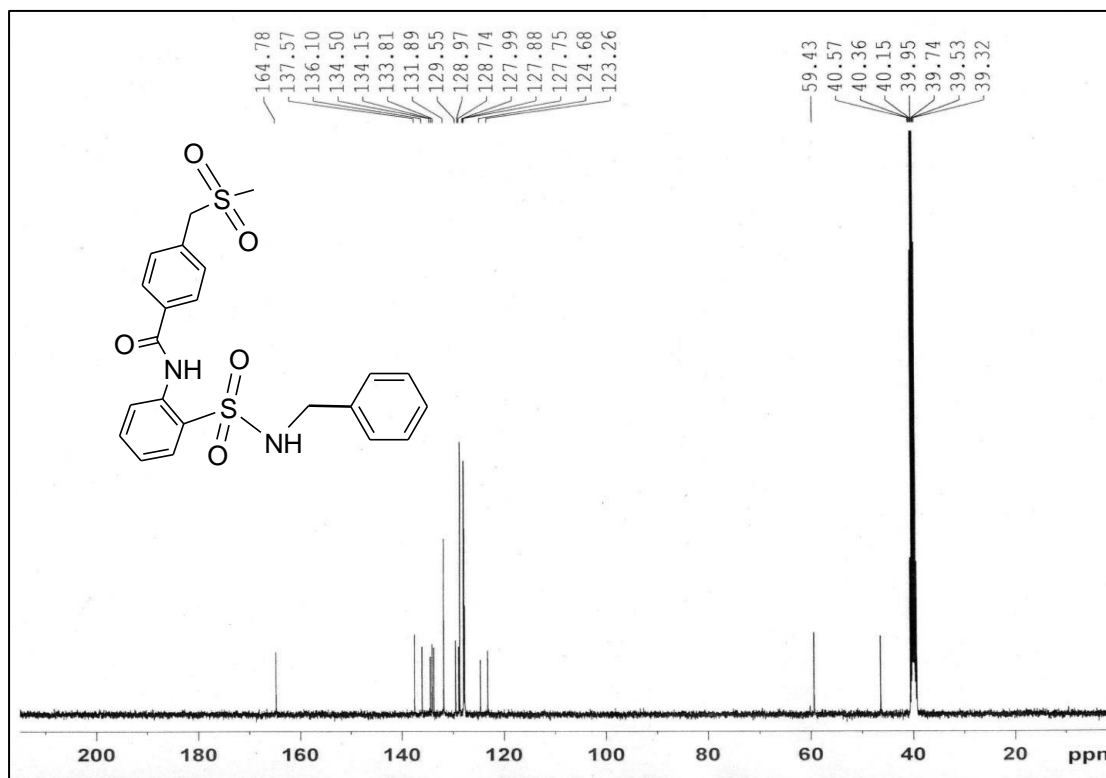
Figure 2.27 ^{13}C NMR spectrum of N-Benzyl-2-(4-(methylsulfonylmethyl) benzamido)benzenesulfonamide (**30b**)
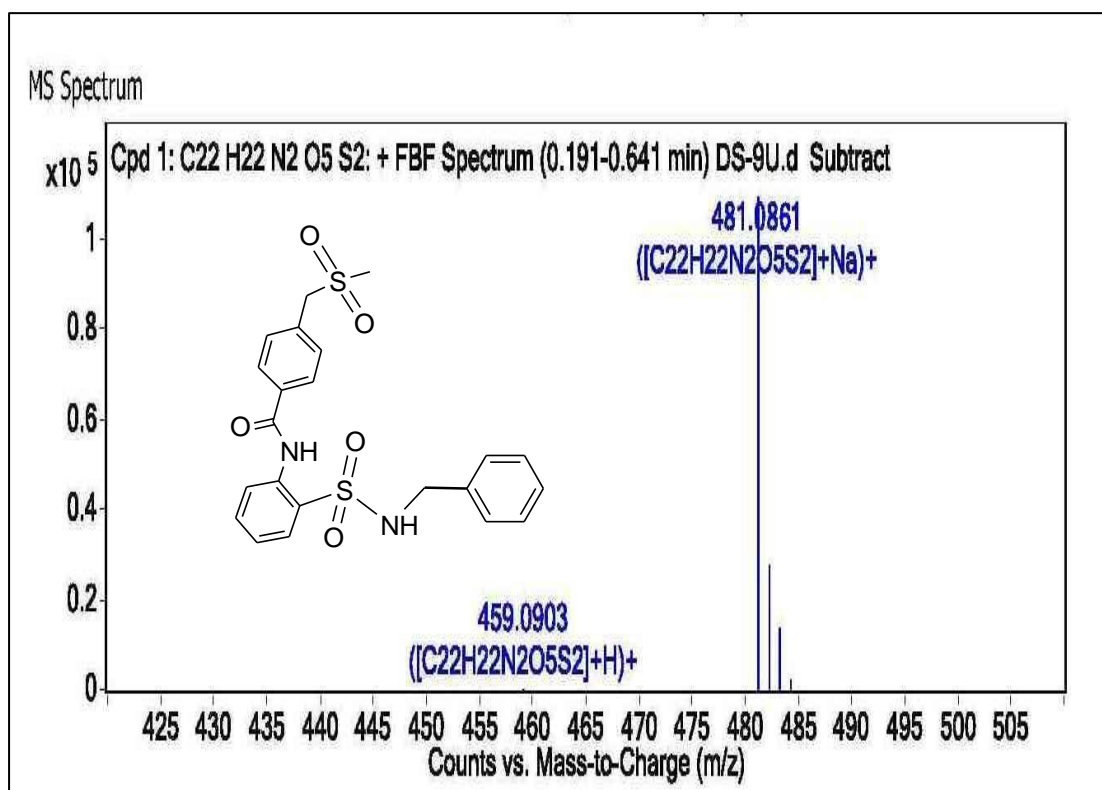
Figure 2.28 HRMS spectrum of N-Benzyl-2-(4-(methylsulfonylmethyl)benzamido) benzenesulfonamide (**30b**)
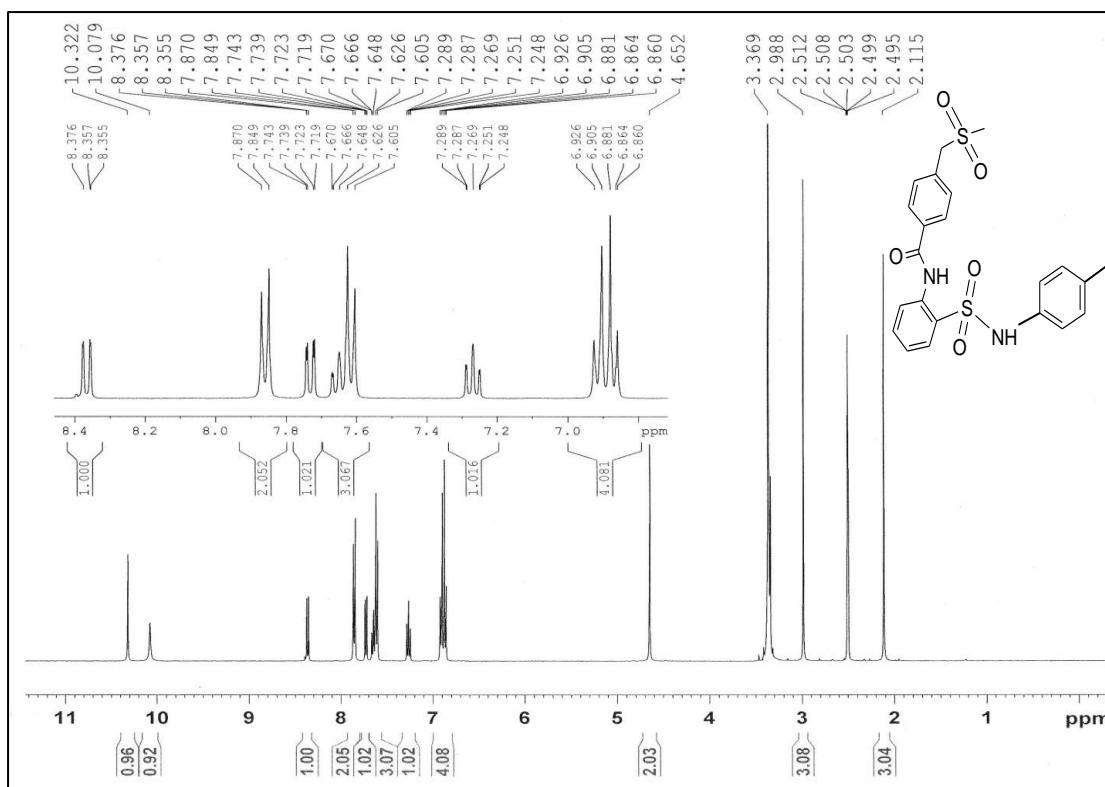
Figure 2.29 ^{1}H NMR spectrum of (N-(4-Methylphenyl)-2-(4-(methylsulfonylmethyl)benzamido))benzenesulfonamide (**30c**)
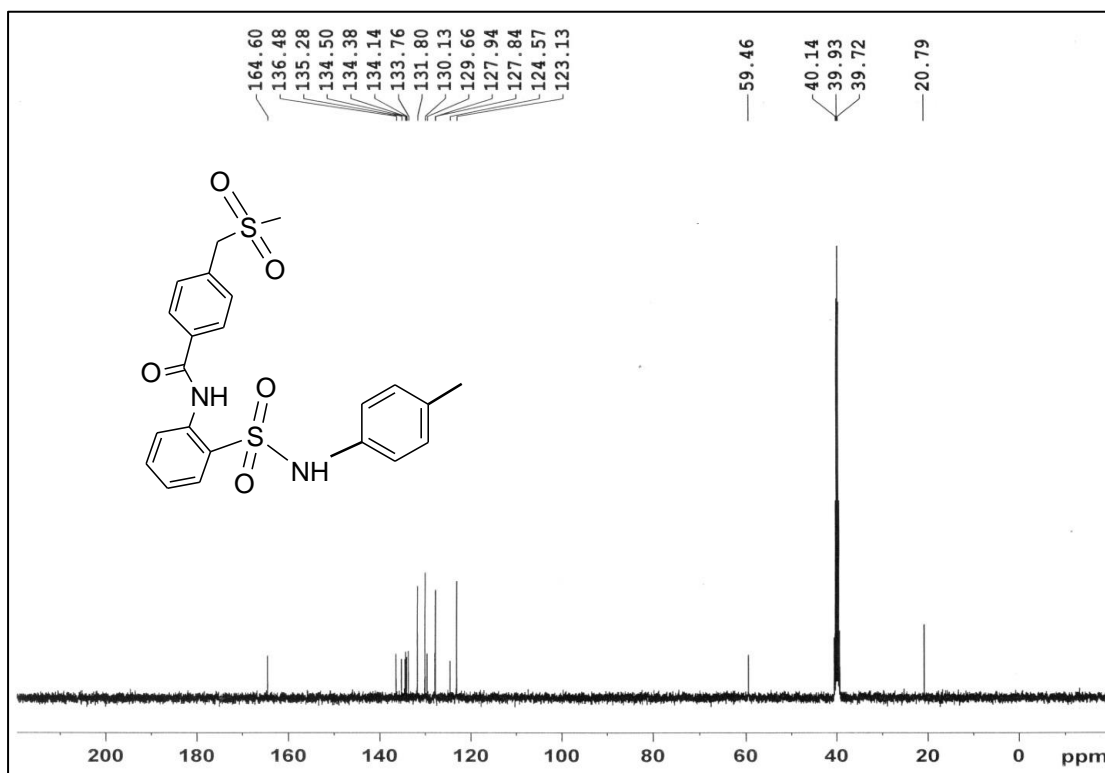
Figure 2.30 ^{13}C NMR spectrum of (N-(4-Methylphenyl)-2-(4-(methylsulfonylmethyl)benzamido))benzenesulfonamide (**30c**)
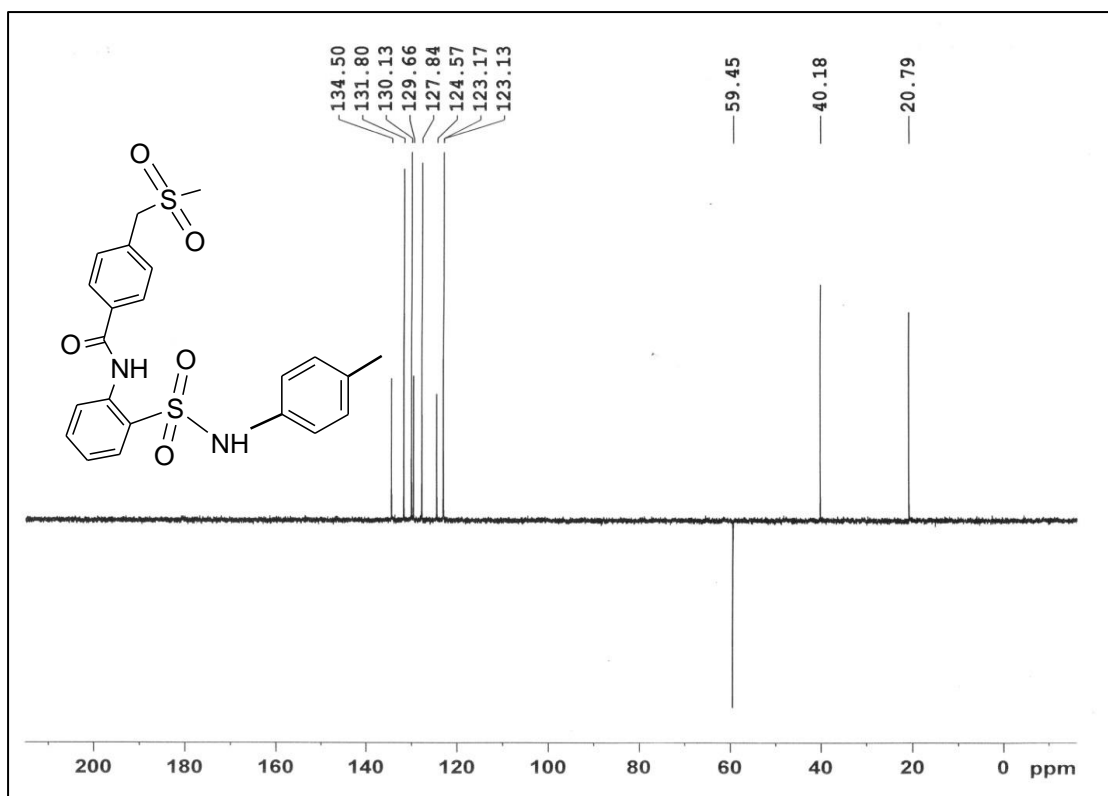
Figure 2.31 DEPT-135 spectrum of (N-(4-Methylphenyl)-2-(4-(methylsulfonyl methyl)benzamido))benzenesulfonamide (**30c**)
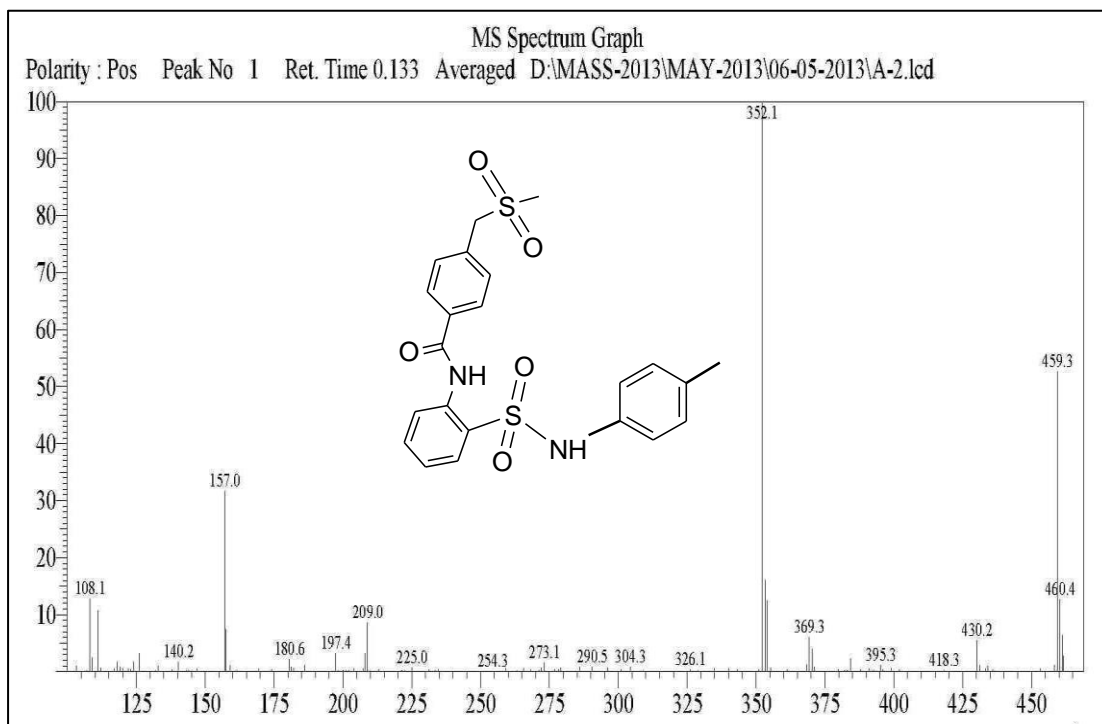
Figure 2.32 EI-MS spectrum of (N-(4-Methylphenyl)-2-(4-(methylsulfonylmethyl) benzamido))benzenesulfonamide (**30c**)
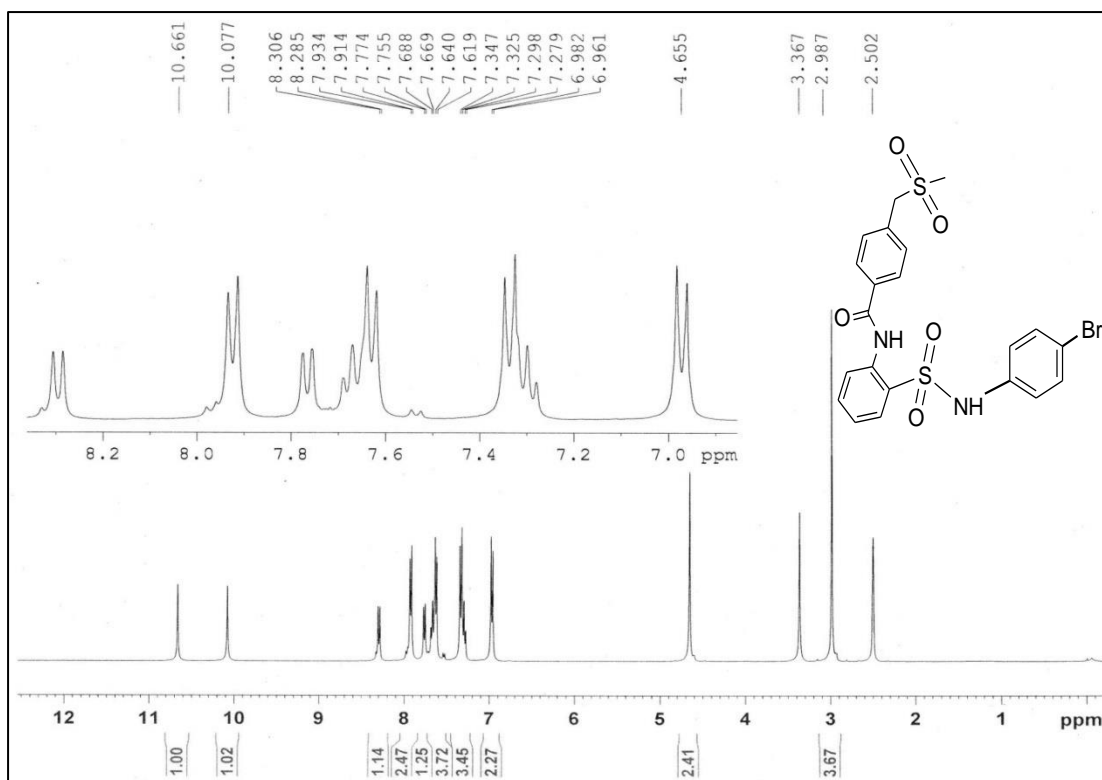
Figure 2.33 ^{1}H NMR spectrum of (N-(4-Bromophenyl)-2-(4-(methylsulfonylmethyl) benzamido))benzenesulfonamide (**30d**)
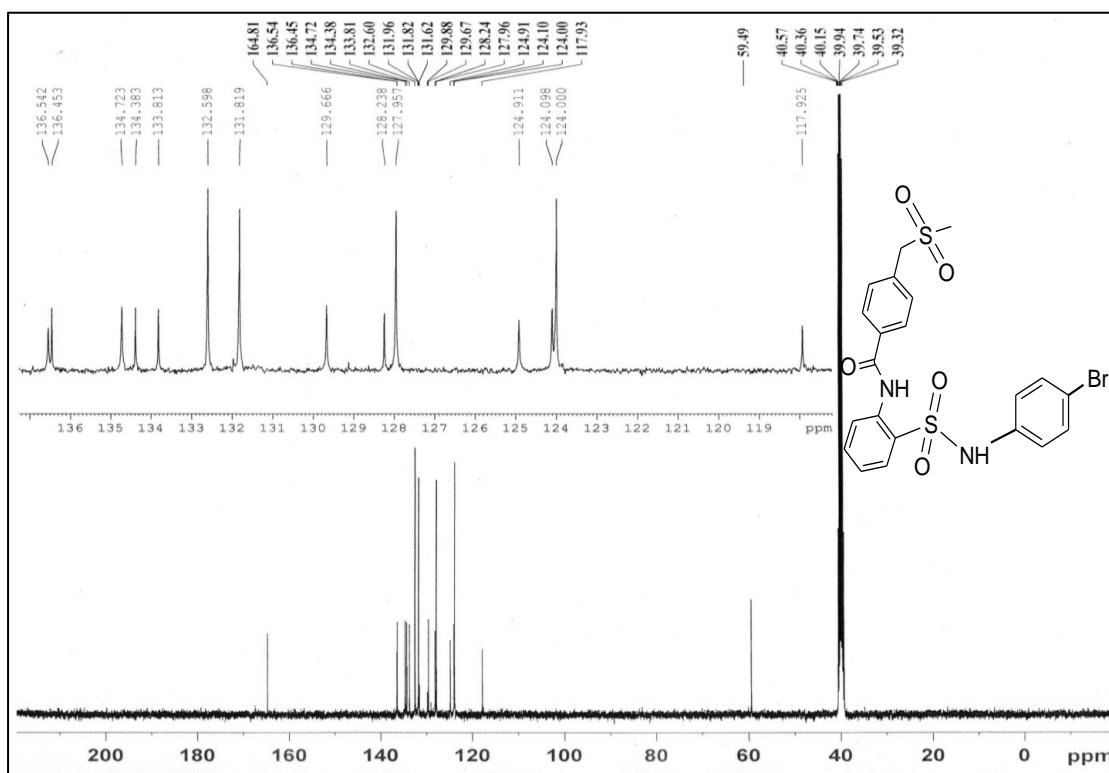
Figure 2.34 ^{13}C NMR spectrum of (N-(4-Bromophenyl)-2-(4-(methylsulfonylmethyl) benzamido))benzenesulfonamide (**30d**)
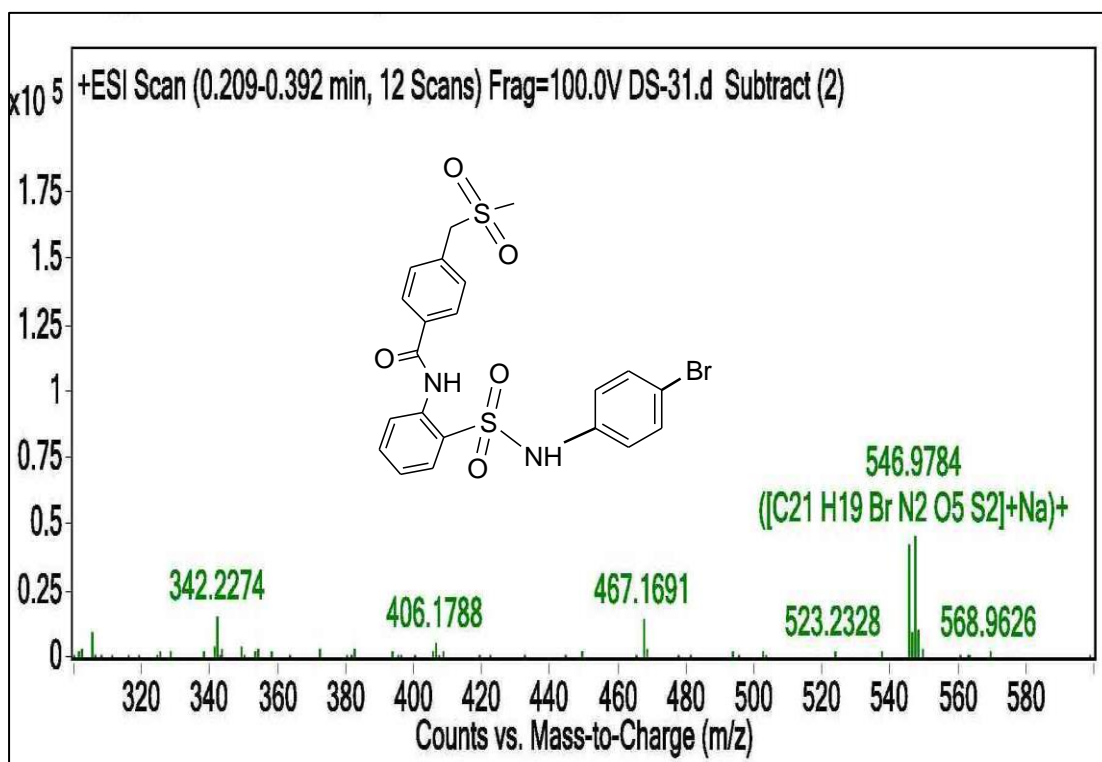
Figure 2.35 HRMS spectrum of (N-(4-Bromophenyl)-2-(4-(methylsulfonylmethyl)
benzamido))benzenesulfonamide (**30d**)
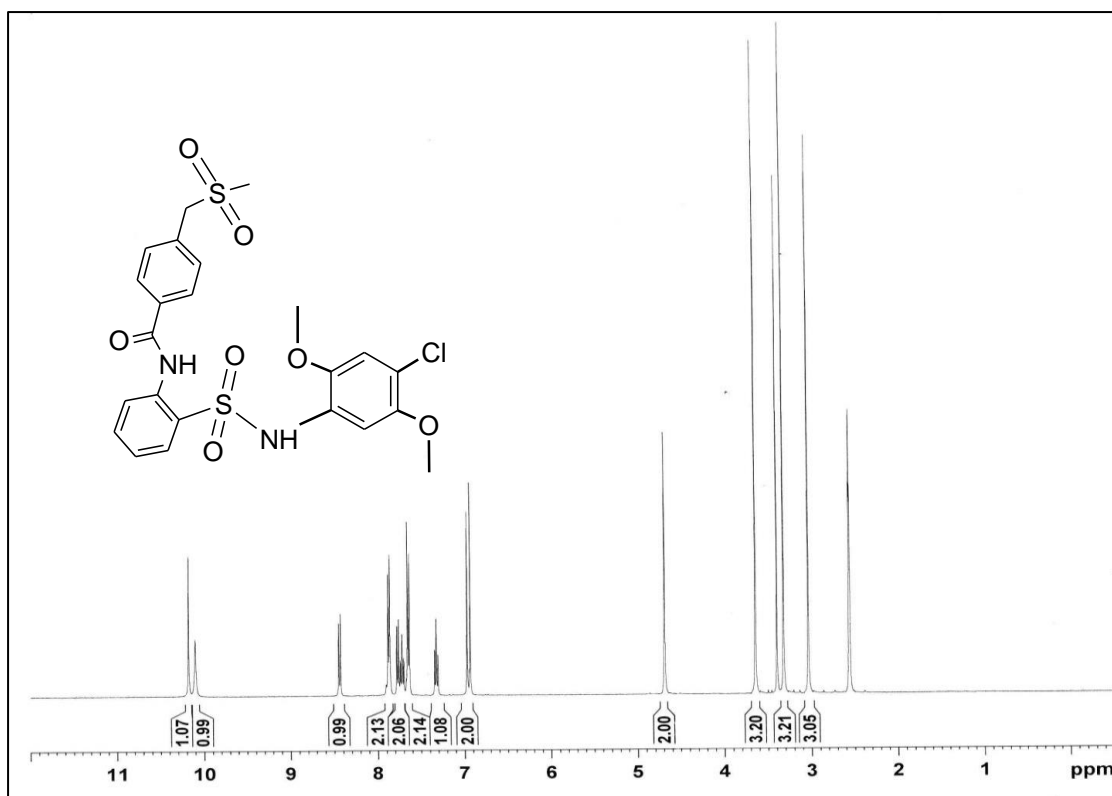
Figure 2.36 ^{1}H NMR spectrum of (N-(2,5-Dimethoxy-4-chlorophenyl)-2-(4-(methyl sulfonylmethyl)benzamido))benzenesulfonamide (**30e**)
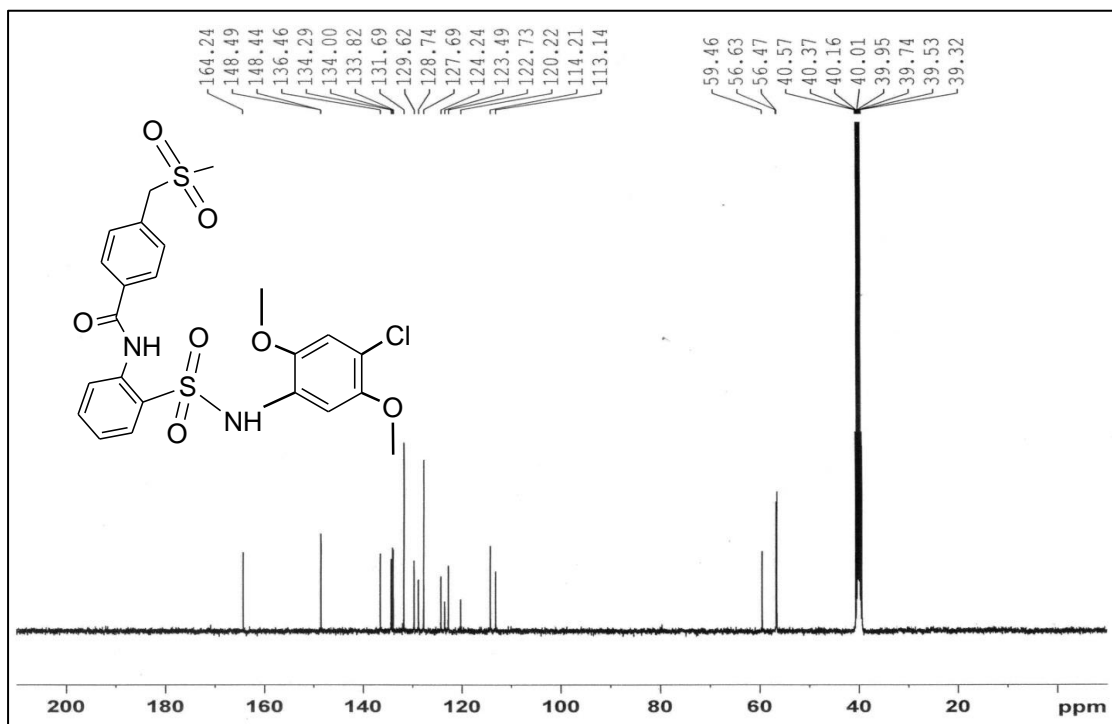
Figure 2.37 ^{13}C NMR spectrum of (N-(2,5-Dimethoxy-4-chlorophenyl)-2-(4-(methyl sulfonylmethyl)benzamido))benzenesulfonamide (**30e**)
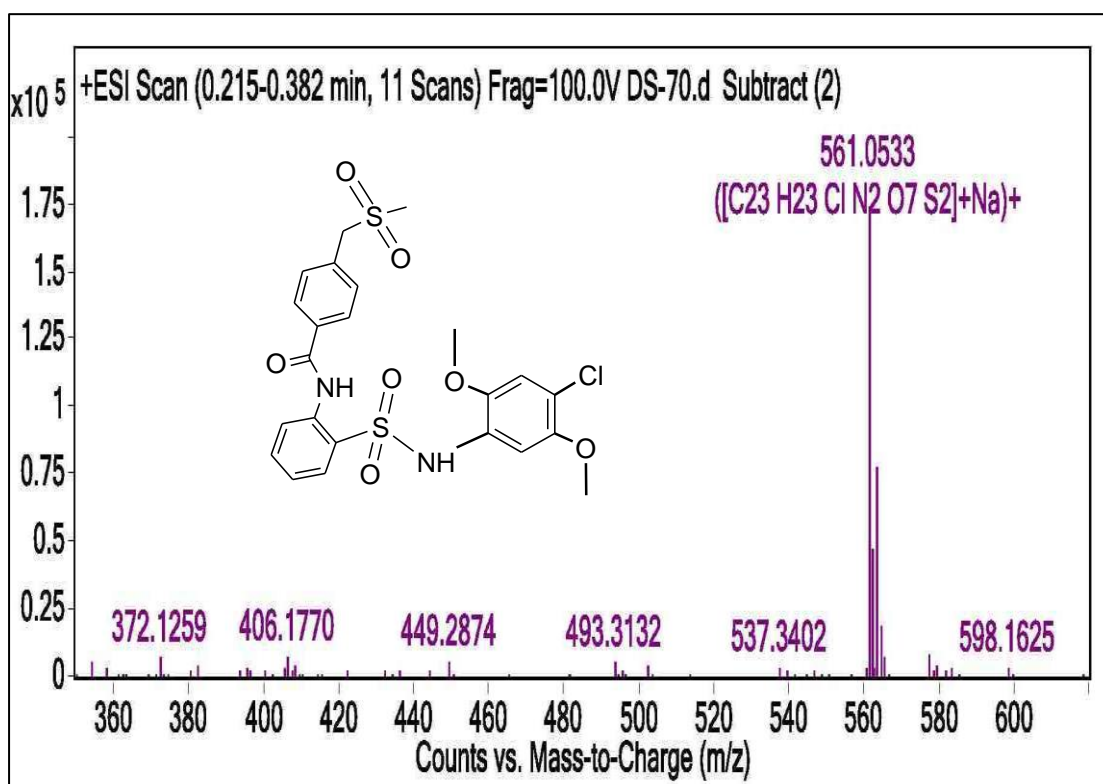
Figure 2.38 HRMS spectrum of (N-(2,5-Dimethoxy-4-chlorophenyl)-2-(4-(methyl sulfonylmethyl)benzamido))benzenesulfonamide (**30e**)
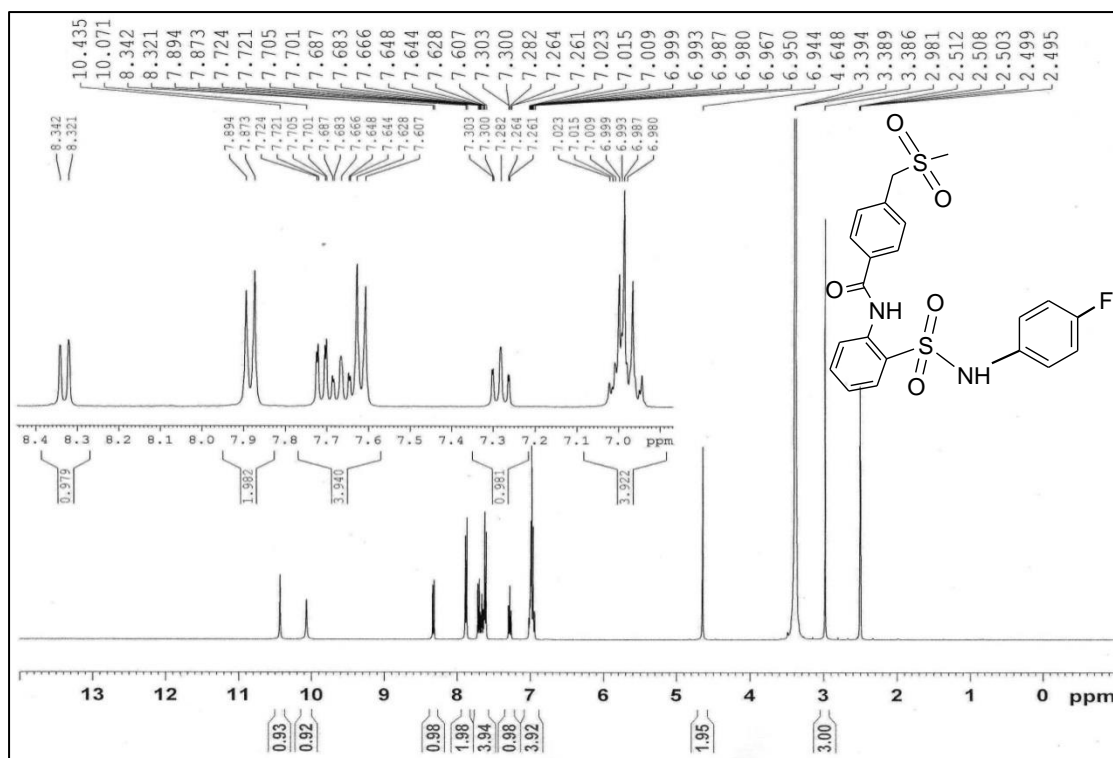
Figure 2.39 ^{1}H NMR spectrum of (N-(4-Fluorophenyl)-2-(4-(methylsulfonylmethyl) benzamido))benzenesulfonamide (**30f**)
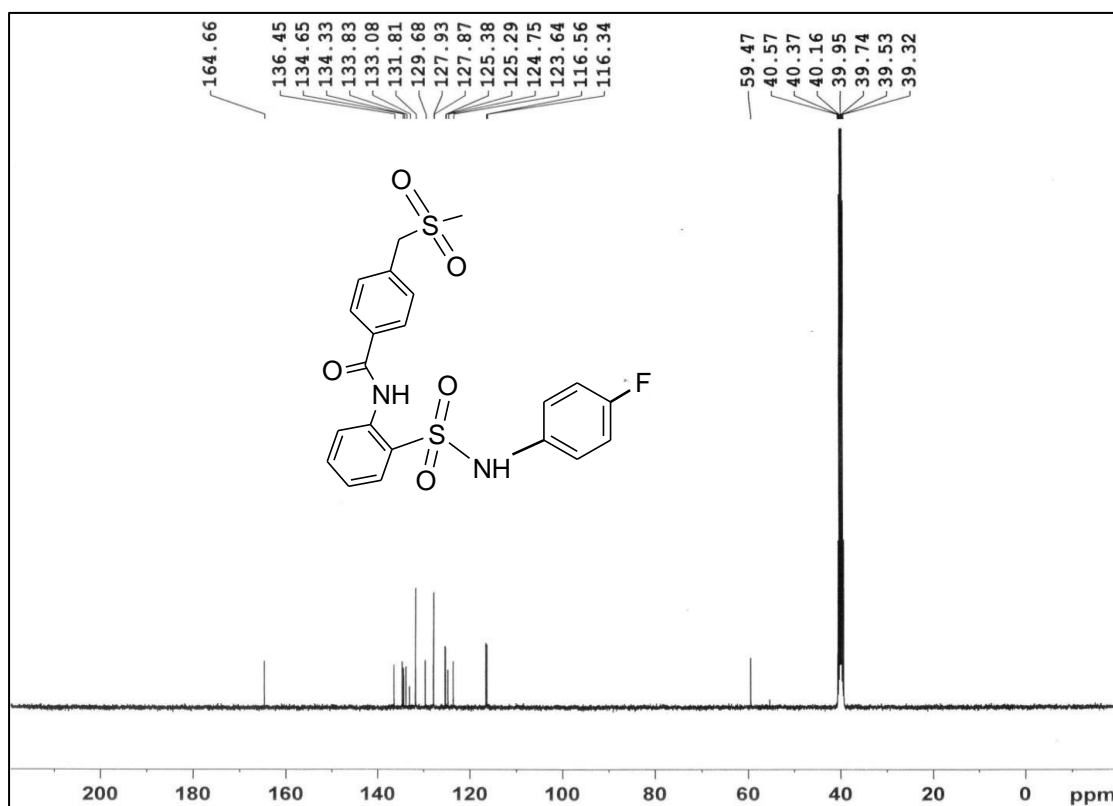
Figure 2.40 ^{13}C NMR spectrum of (N-(4-Fluorophenyl)-2-(4-(methylsulfonylmethyl) benzamido))benzenesulfonamide (**30f**)
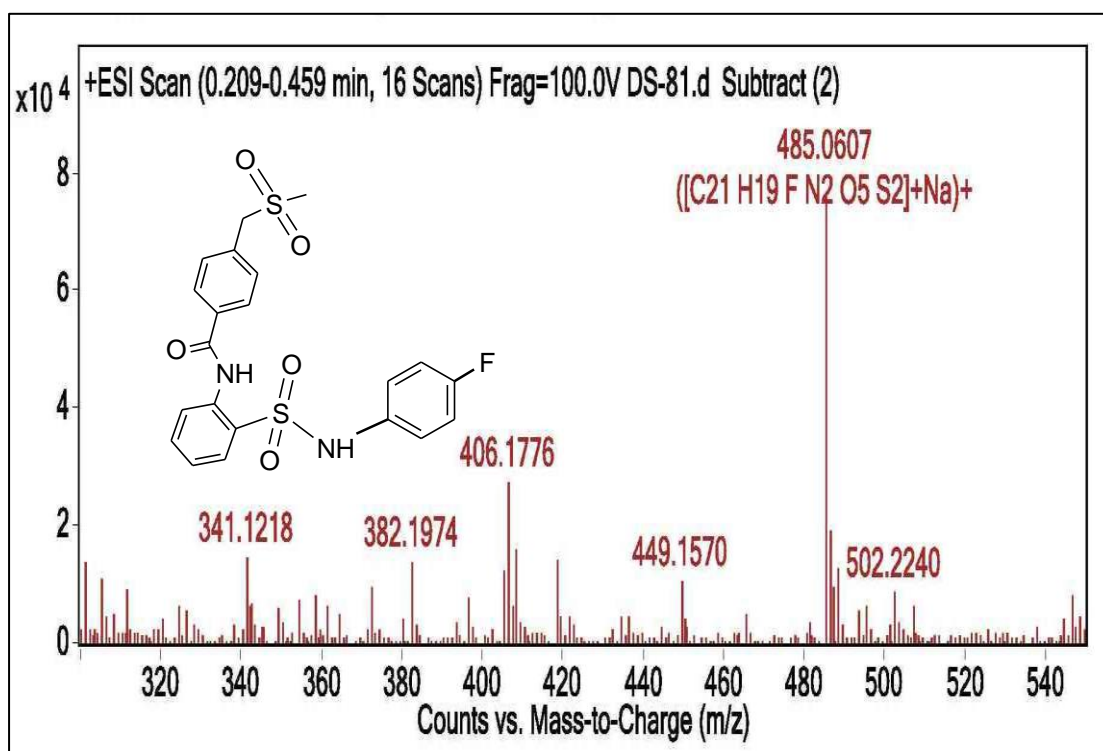
Figure 2.41 HRMS spectrum of (N-(4-Fluorophenyl)-2-(4-(methylsulfonylmethyl)
benzamido))benzenesulfonamide (**30f**)
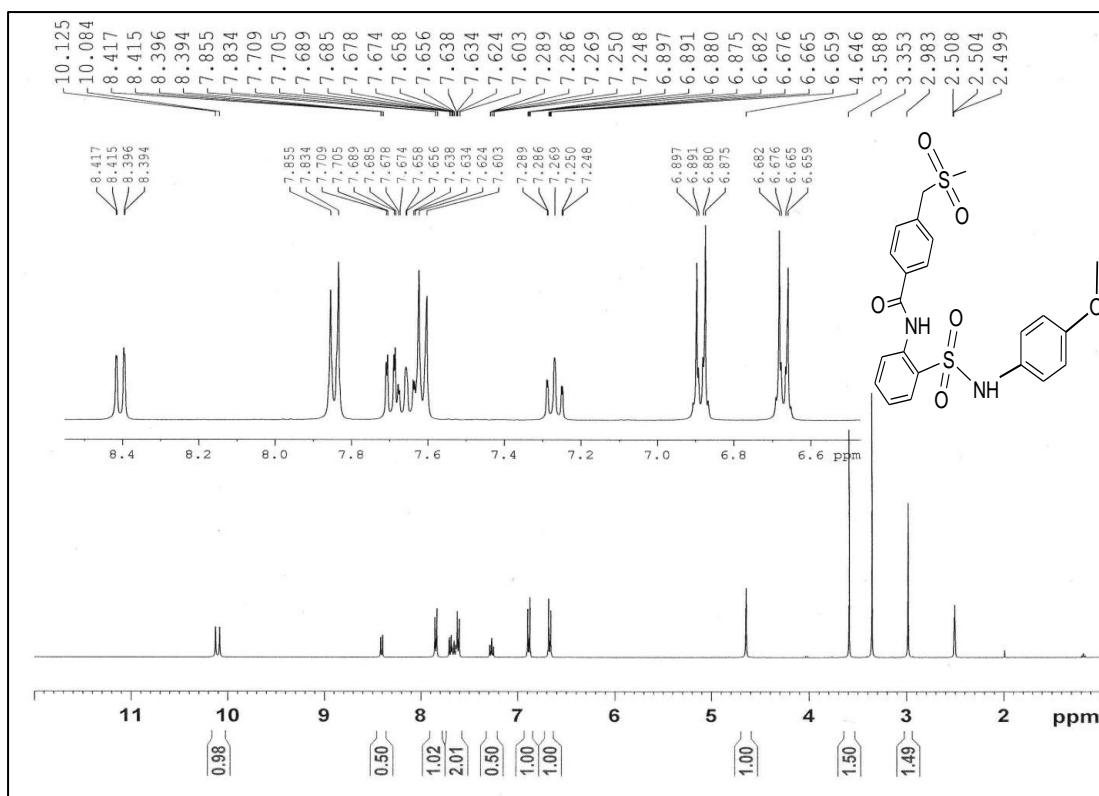
Figure 2.42 ^{1}H NMR spectrum of (N-(4-Methoxyphenyl)-2-(4-(methylsulfonyl methyl)benzamido))benzenesulfonamide (**30g**)
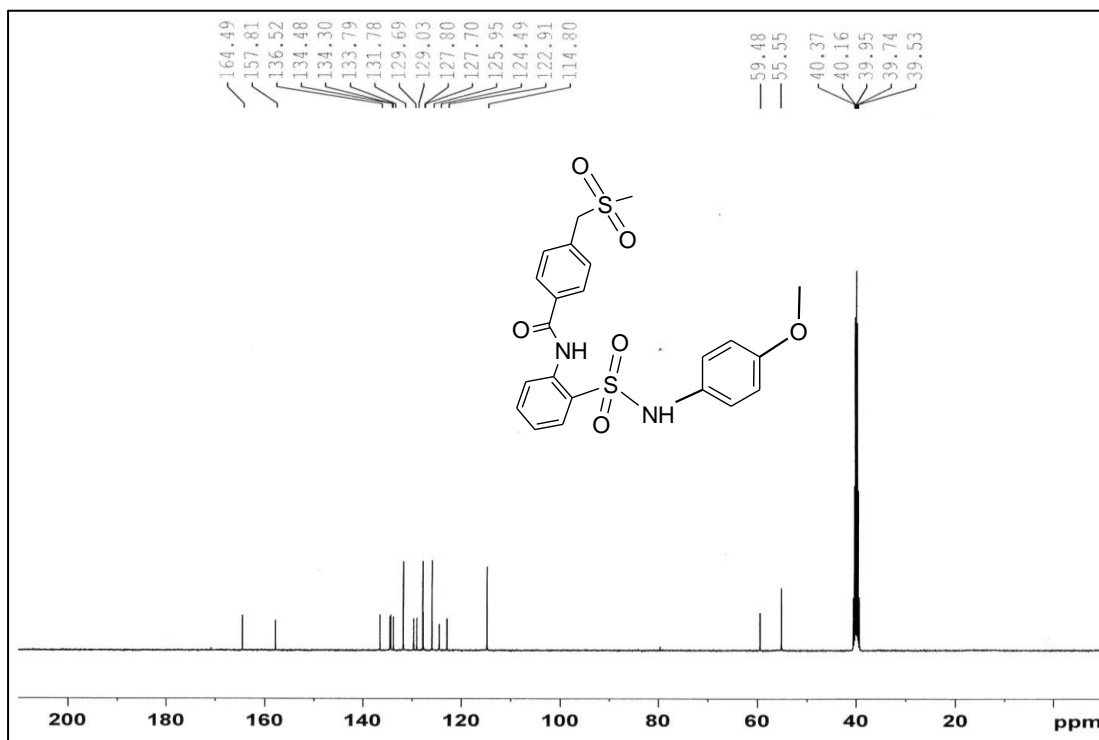
Figure 2.43 ^{13}C NMR spectrum of (N-(4-Methoxyphenyl)-2-(4-(methylsulfonyl methyl)benzamido))benzenesulfonamide (**30g**)
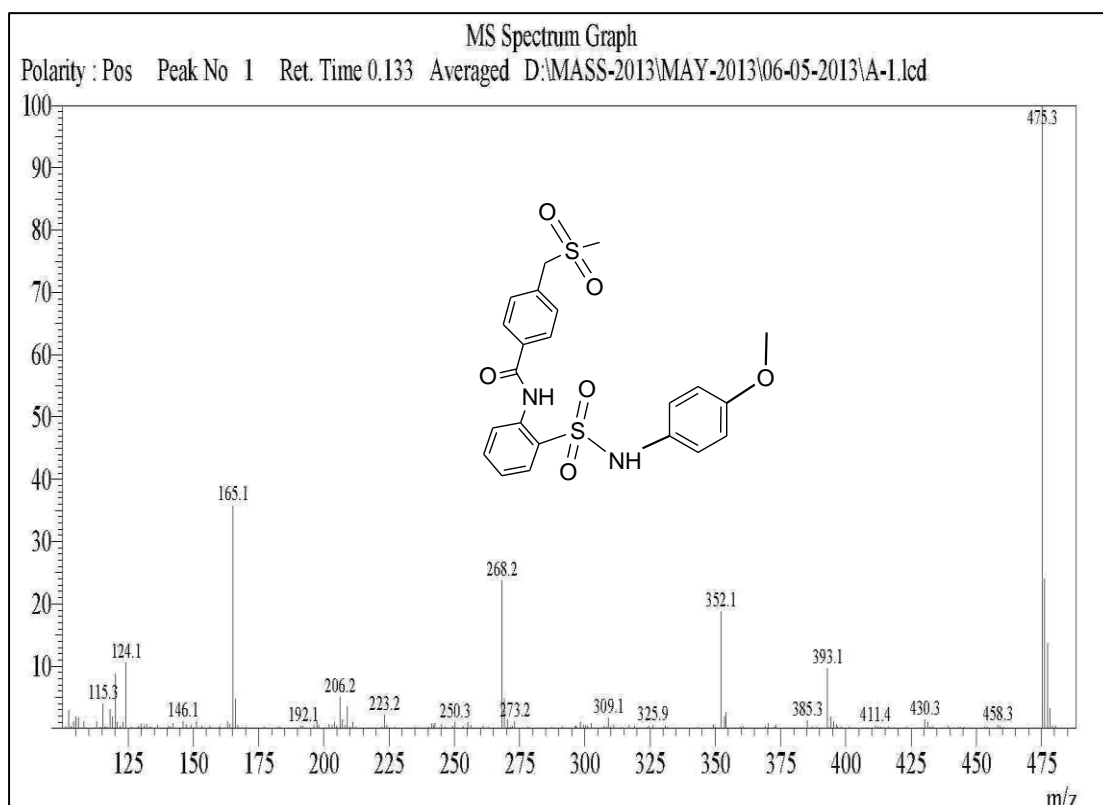
Figure 2.44 EI-MS spectrum of (N-(4-Methoxyphenyl)-2-(4-(methylsulfonylmethyl) benzamido))benzenesulfonamide (**30g**)
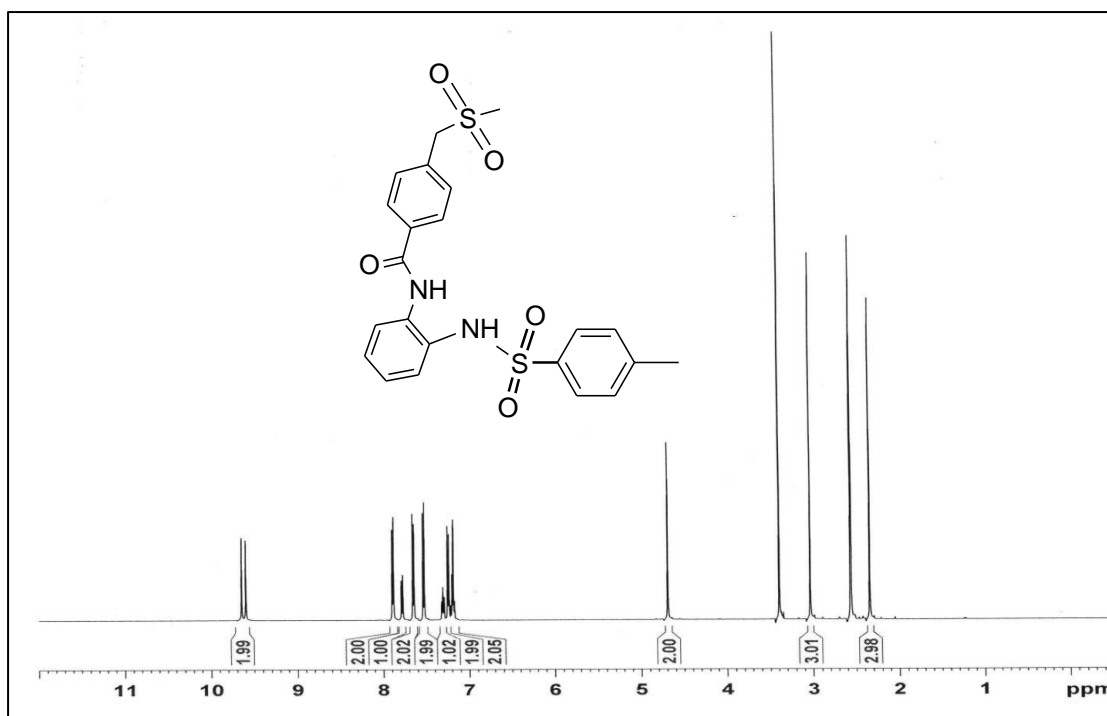
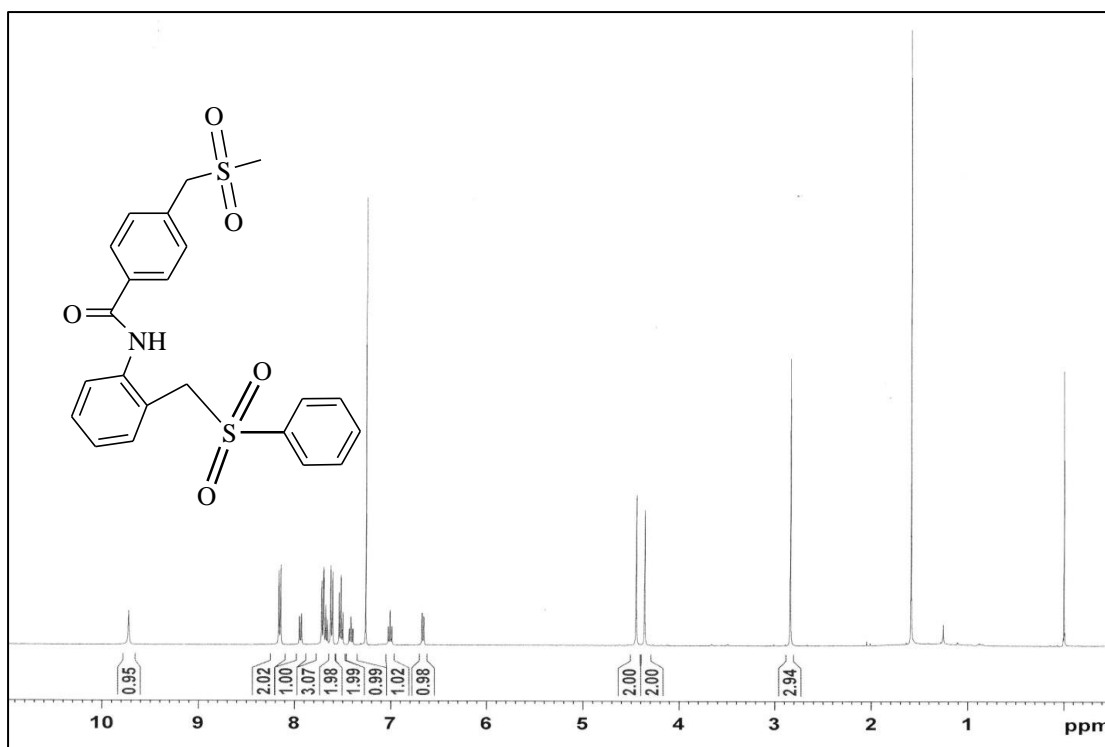**Figure 2.45** ¹H NMR spectrum of 4-((Methylsulfonyl)methyl)-N-2-(tosylamino) phenyl)benzamide (**40**)
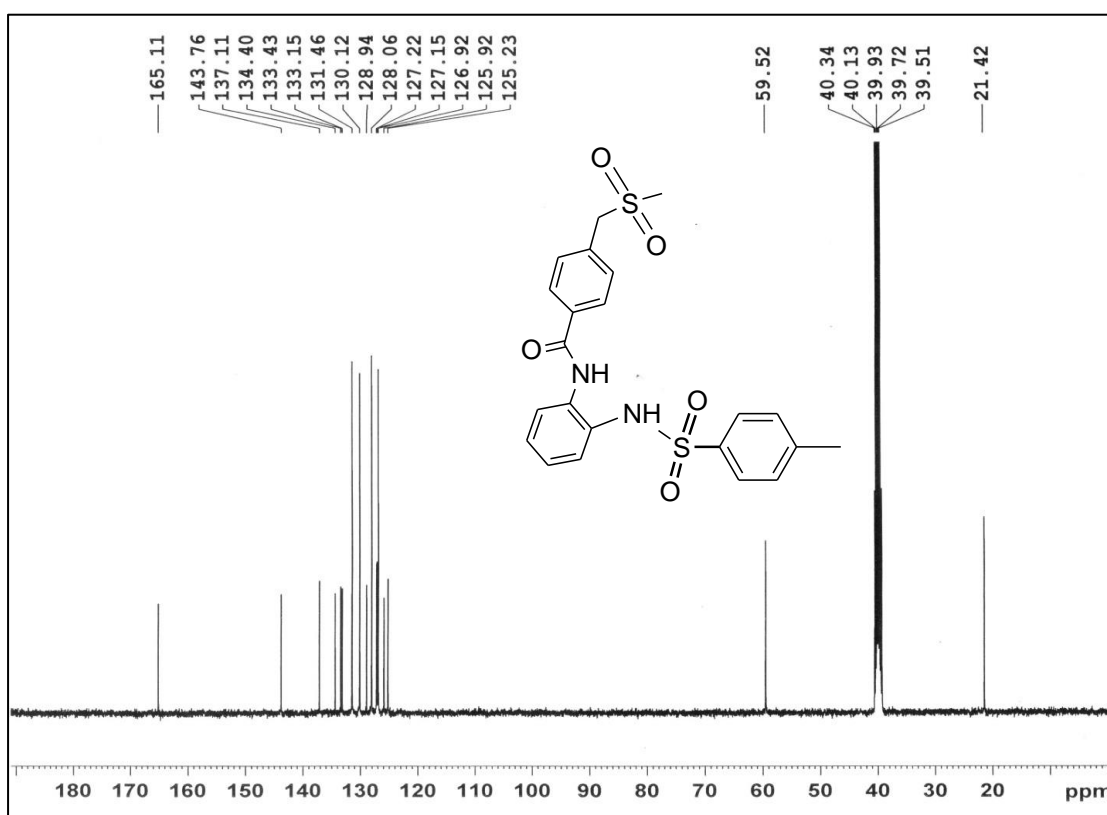
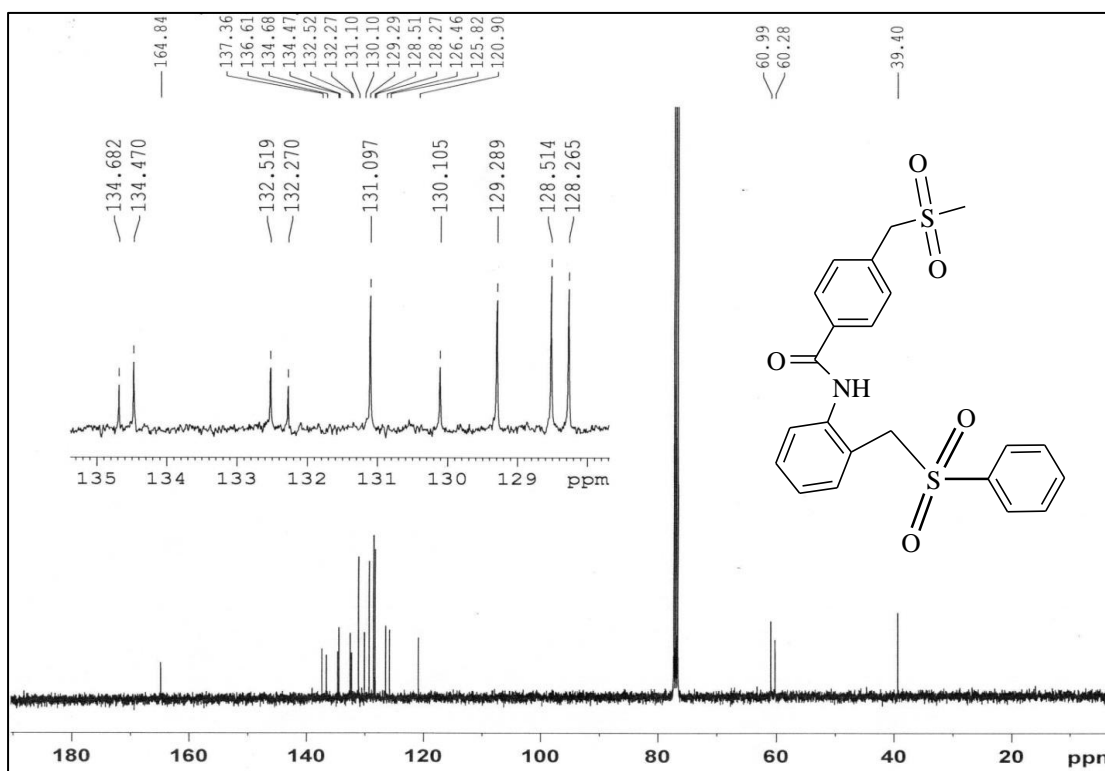**Figure 2.46** ¹³C NMR spectrum of 4-((Methylsulfonyl)methyl)-N-2-(tosylamino) phenyl)benzamide (**40**)
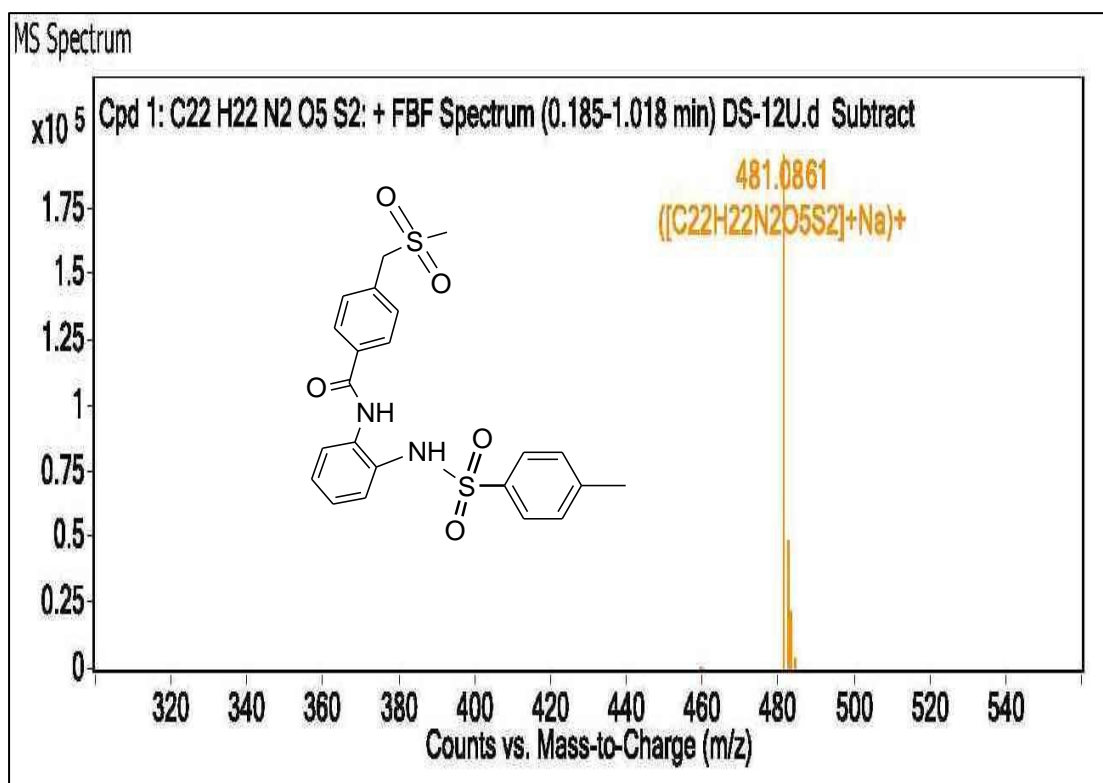
Figure 2.47 HRMS spectrum of 4-((Methylsulfonyl)methyl)-N-2-(tosylamino) phenyl)benzamide (**40**)
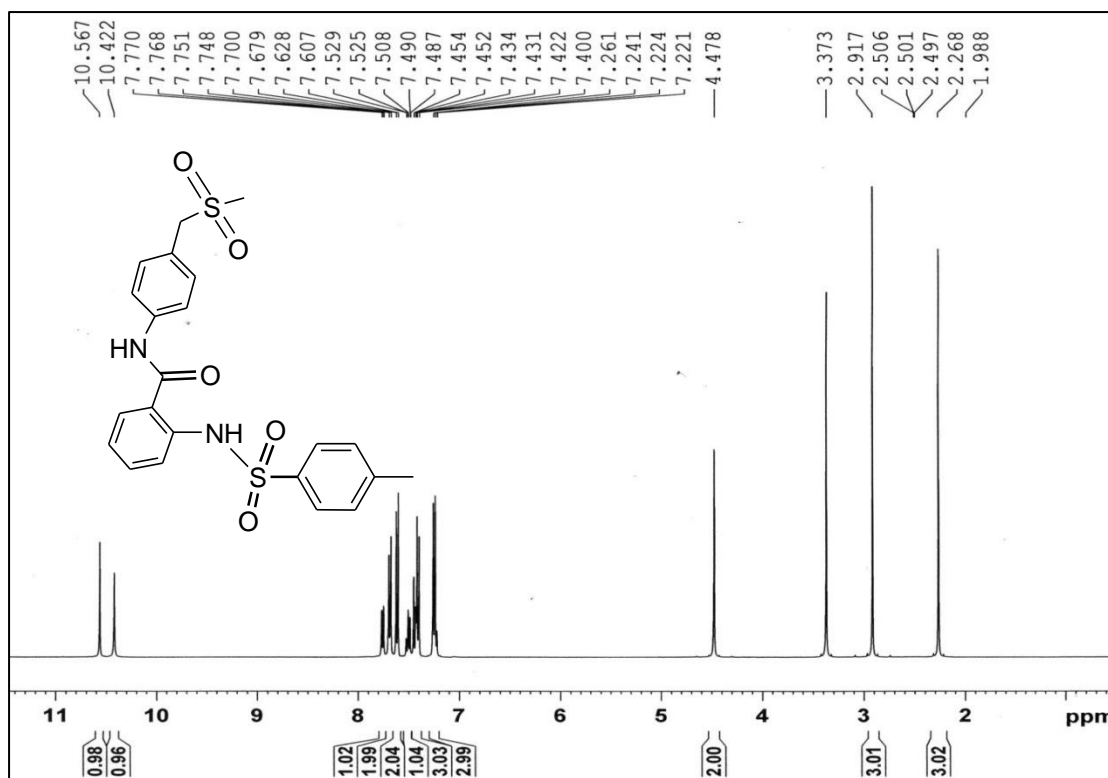
Figure 2.48 ^{1}H NMR spectrum of N-(4-((Methylsulfonyl)methyl)phenyl)-2-(tosylamino)benzamide (**41**)
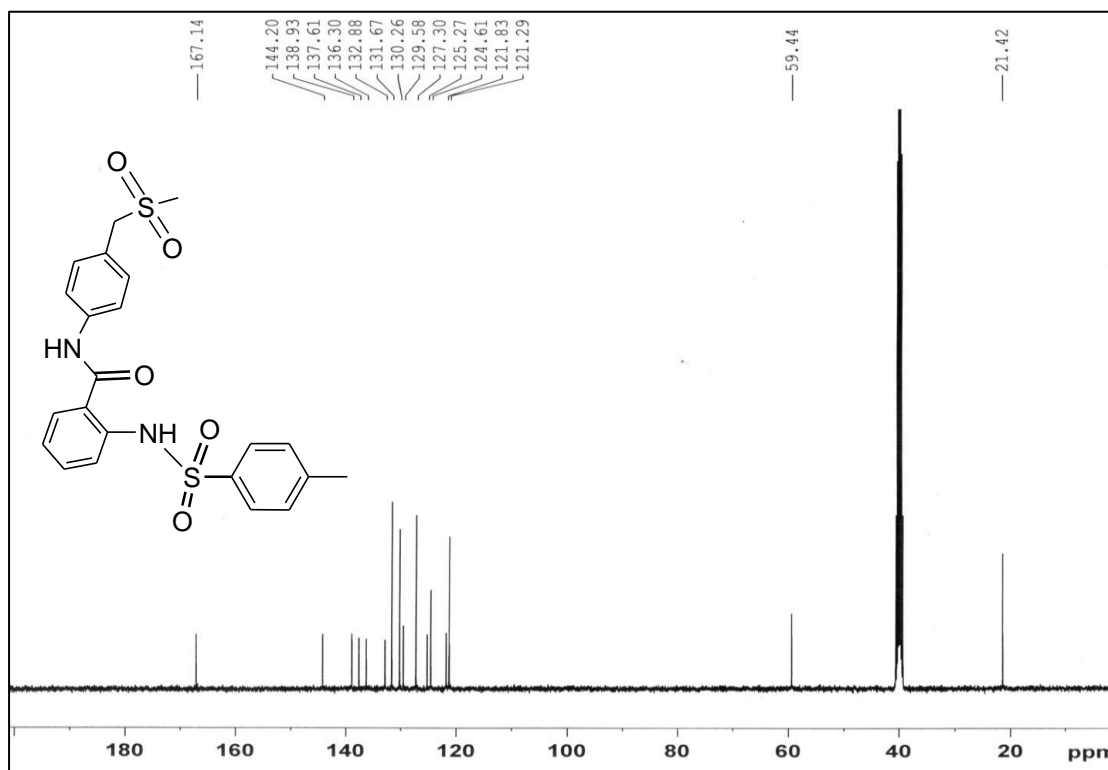
Figure 2.49 ^{13}C NMR spectrum of N-(4-((Methylsulfonyl)methyl)phenyl)-2-(tosylamino)benzamide (**41**)
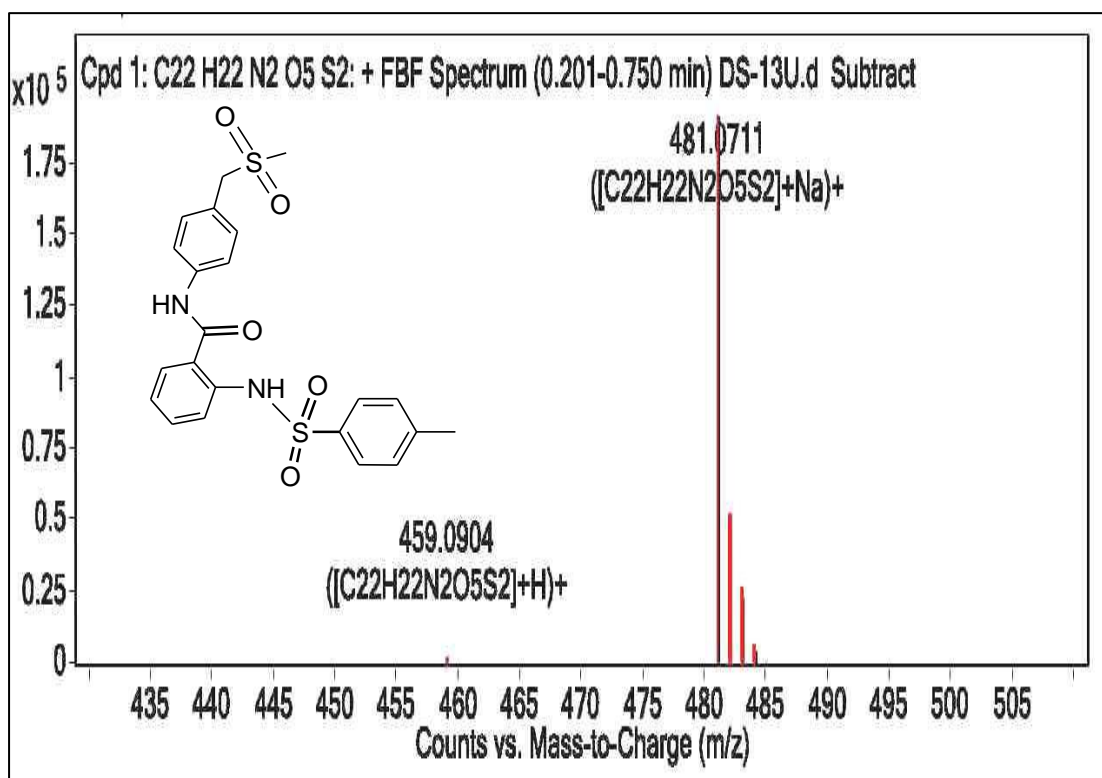
Figure 2.50 HRMS spectrum of N-(4-((Methylsulfonyl)methyl)phenyl)-2-(tosylamino) benzamide (**41**)
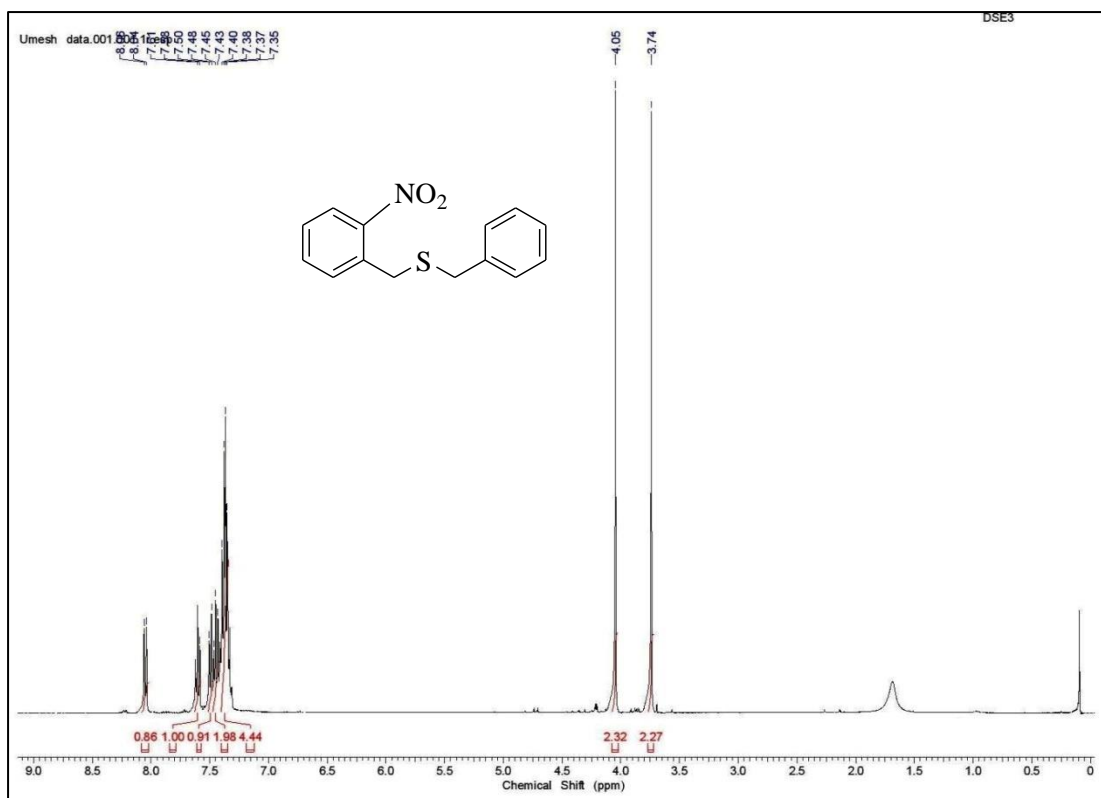
Figure 2.51 ^{1}H NMR spectrum of Benzyl 2-nitrobenzyl sulfide (**44b**)
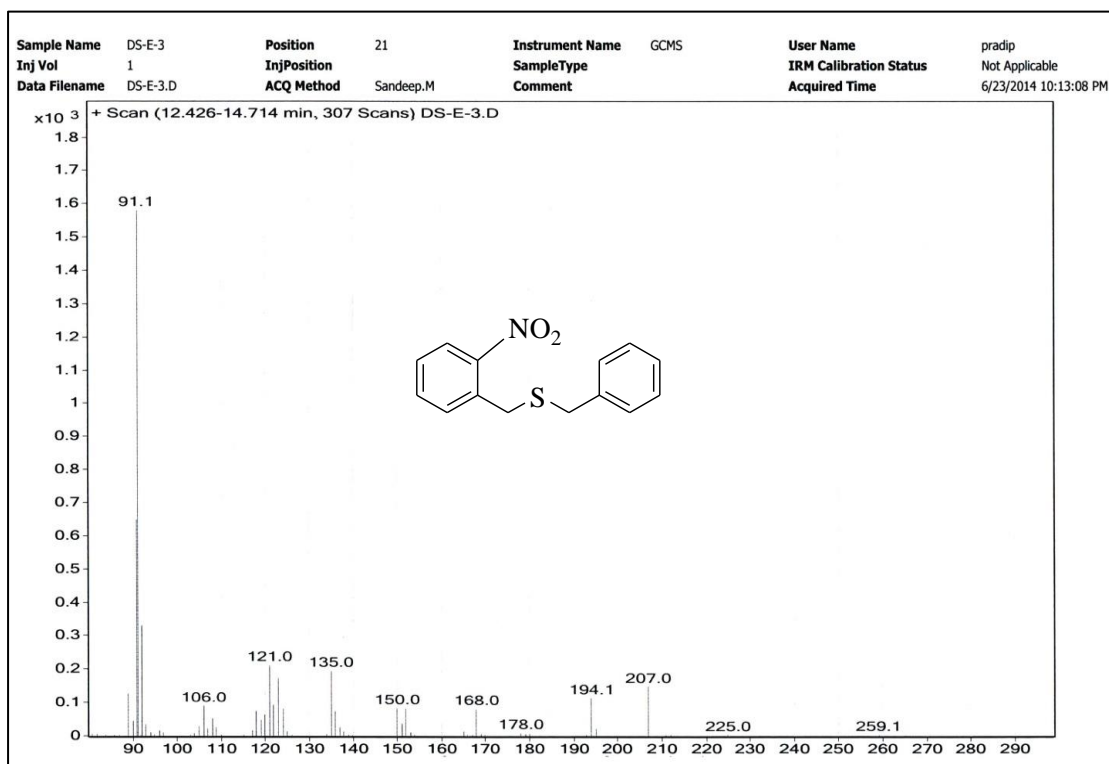
Figure 2.52 Mass spectrum of Benzyl 2-nitrobenzyl sulfide (**44b**)
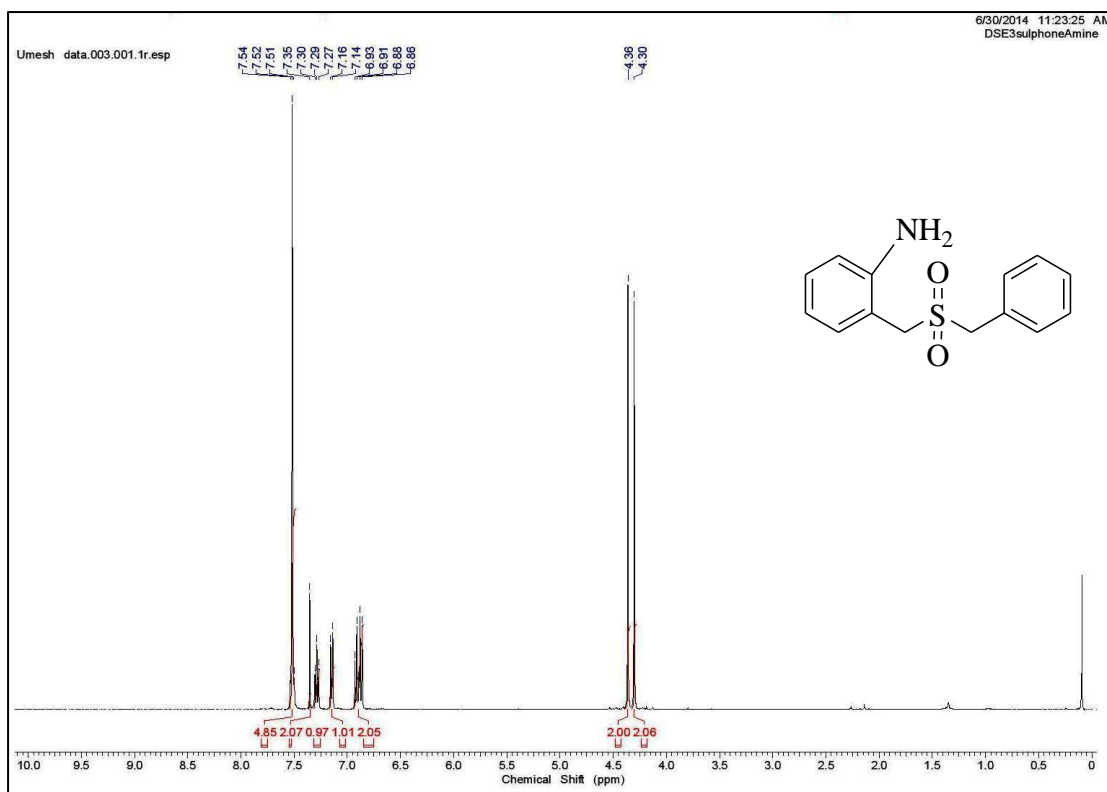
Figure 2.53 ^{1}H NMR spectrum of 2-((Benzylsulfonyl)methyl)aniline (**47a**)
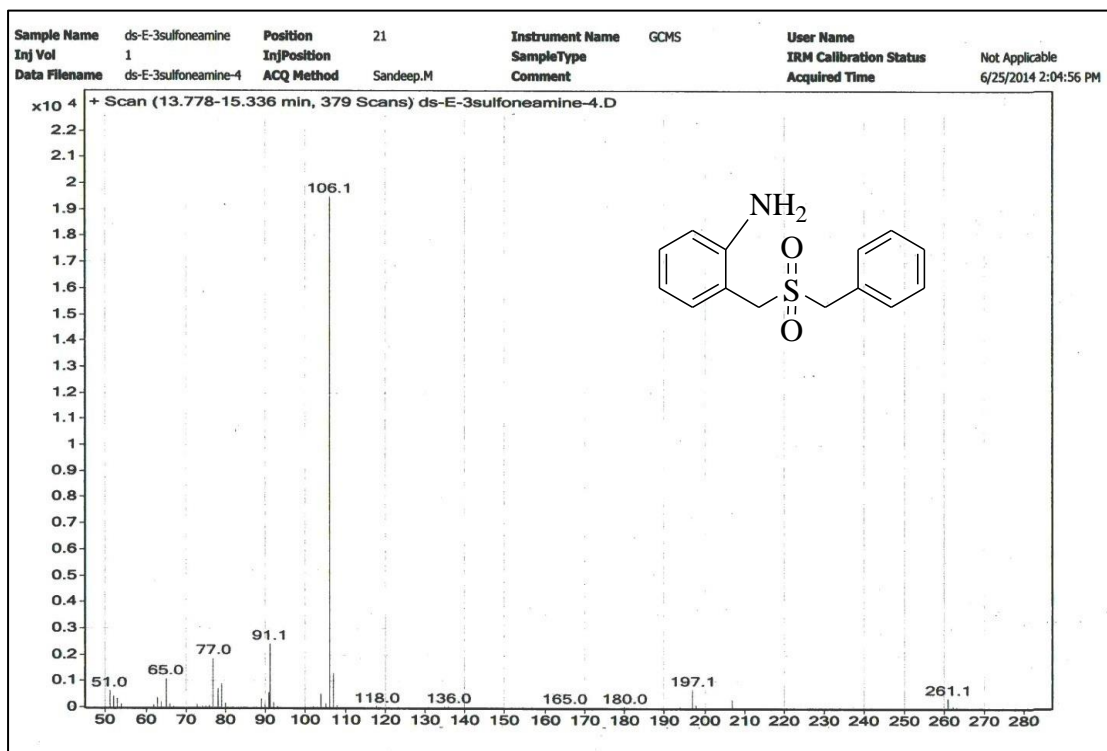
Figure 2.54 Mass spectrum of 2-((Benzylsulfonyl)methyl)aniline (**47a**)
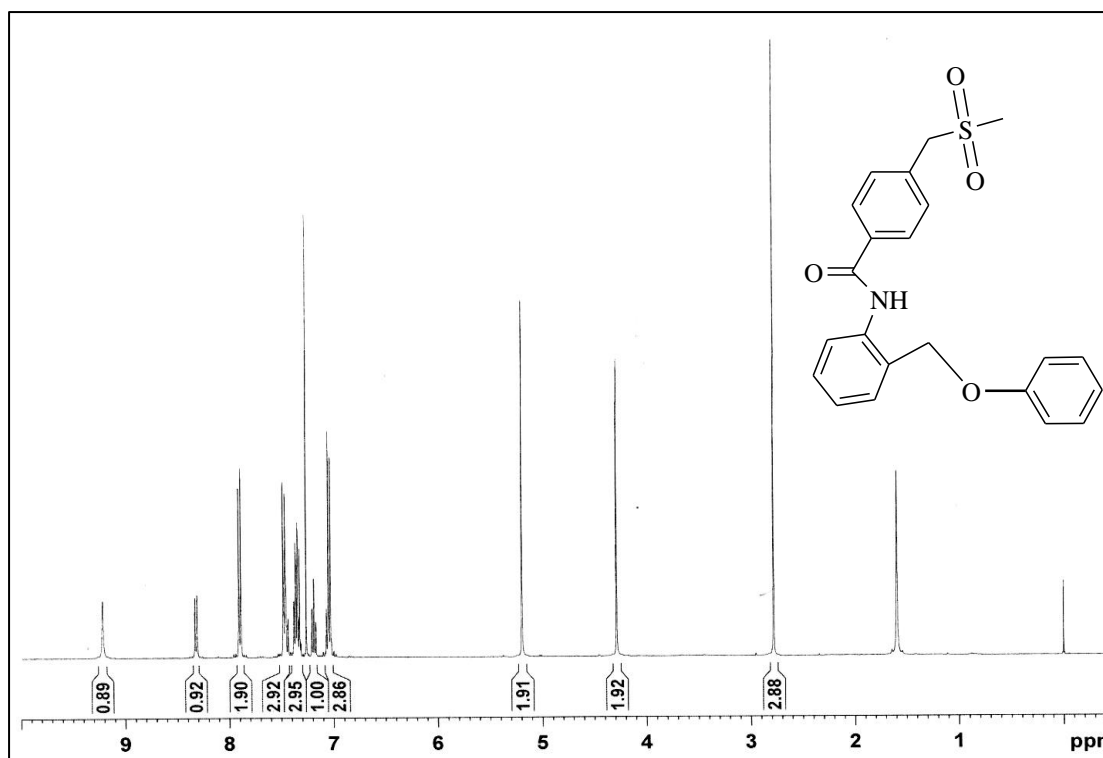
Figure 2.55 ^{1}H NMR spectrum of 4-((Methylsulfonyl)methyl)-N-(2-(phenoxymethyl) phenyl)benzamide (**48a**)
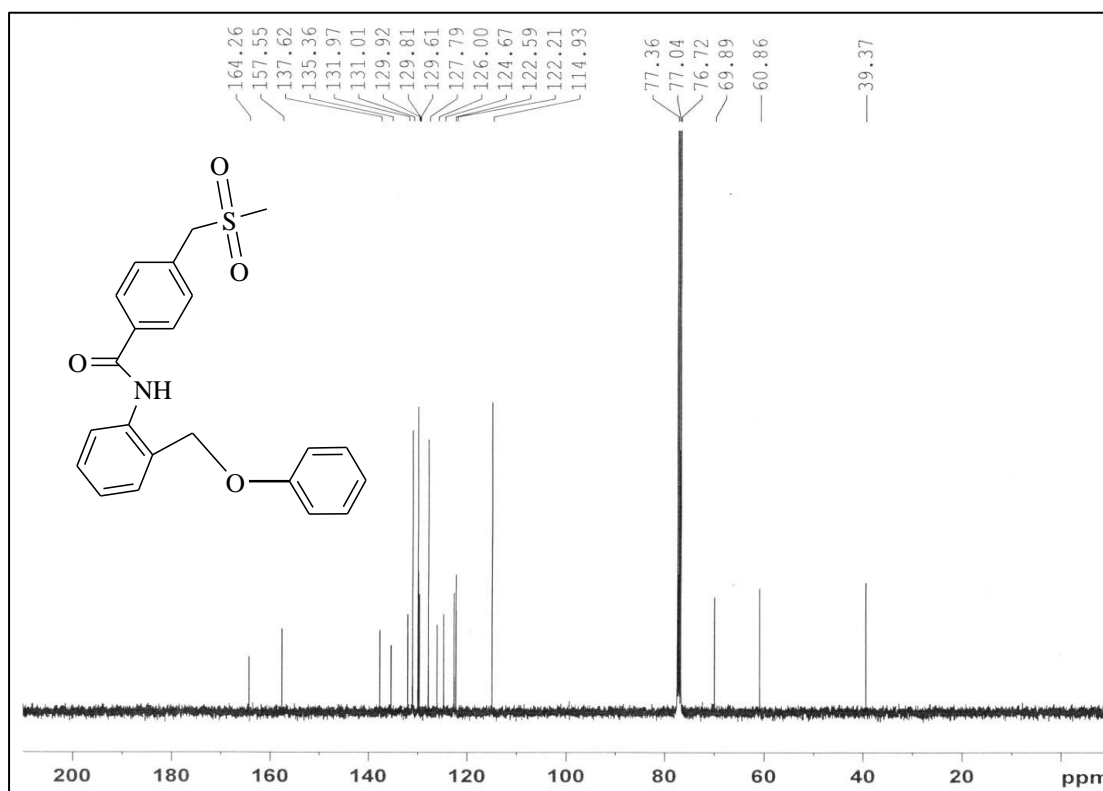
Figure 2.56 ^{13}C NMR spectrum of 4-((Methylsulfonyl)methyl)-N-(2-(phenoxy methyl)phenyl)benzamide (**48a**)
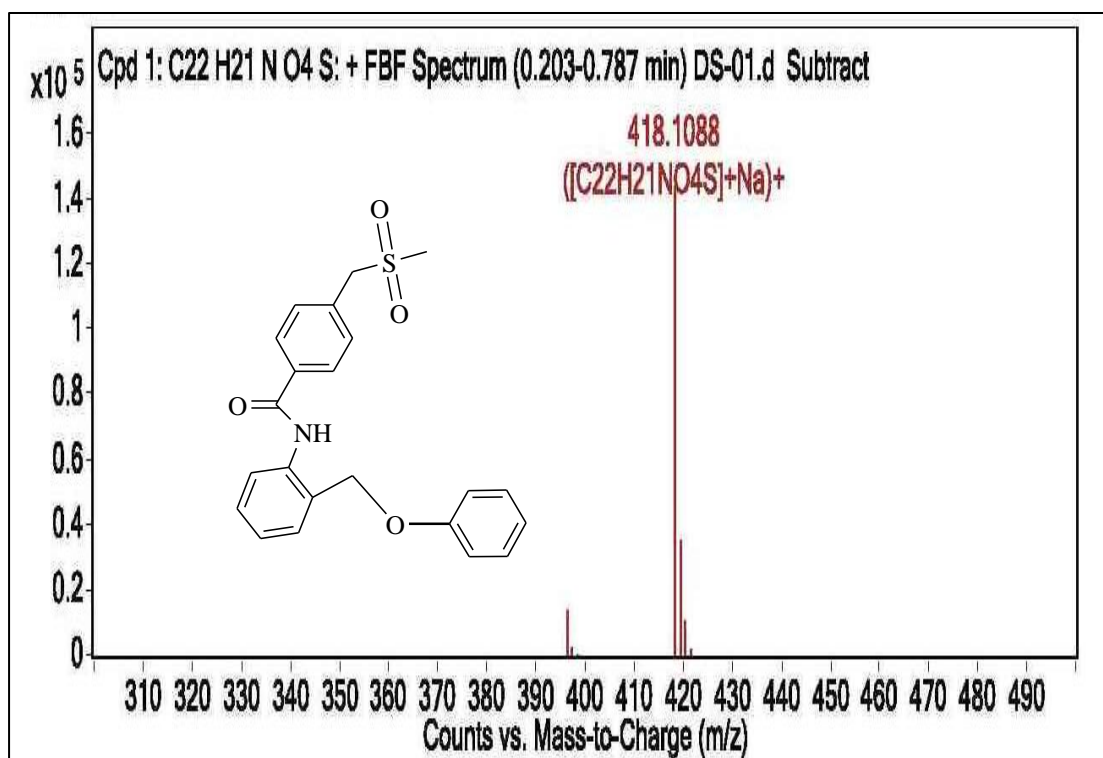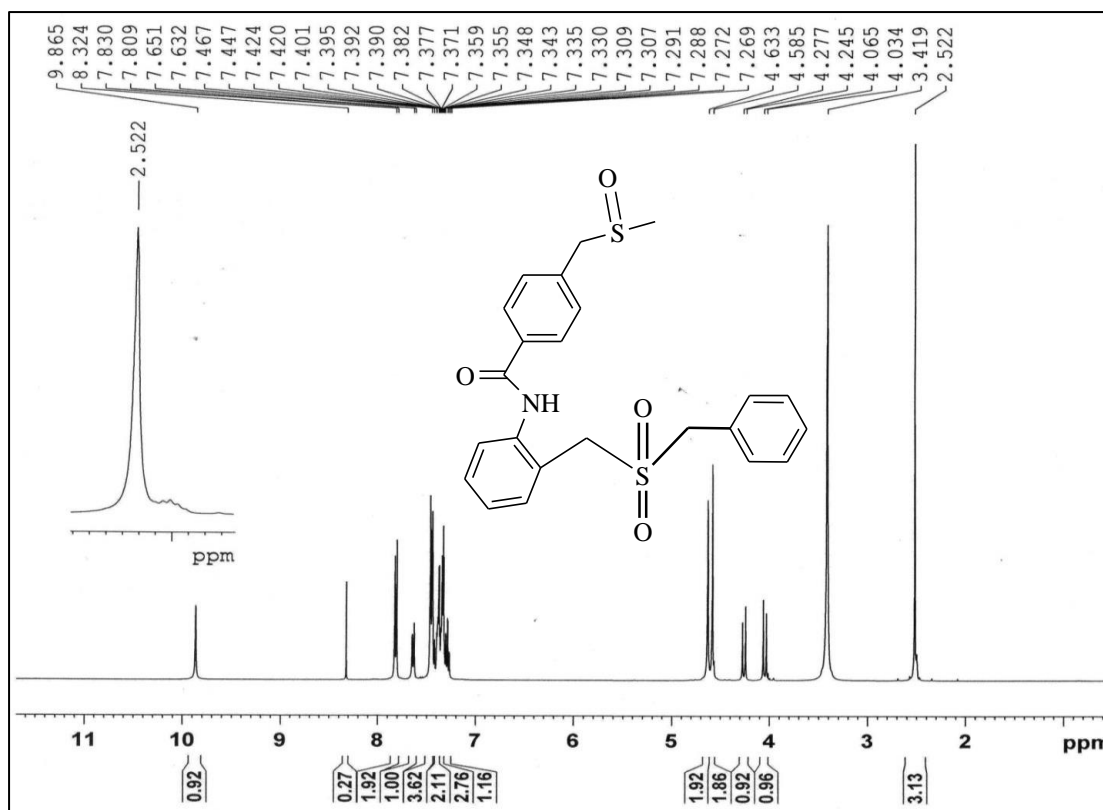
Figure 2.57 HRMS spectrum of 4-((Methylsulfonyl)methyl)-N-(2-(phenoxymethyl)
phenyl)benzamide (**48a**)
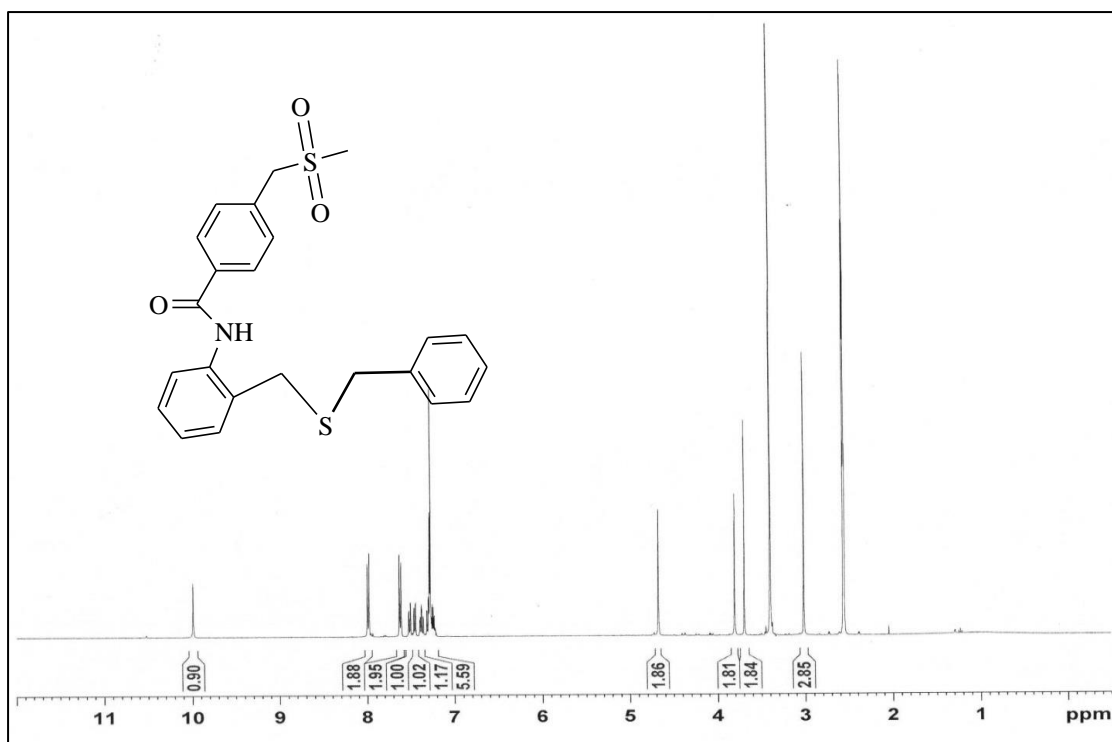
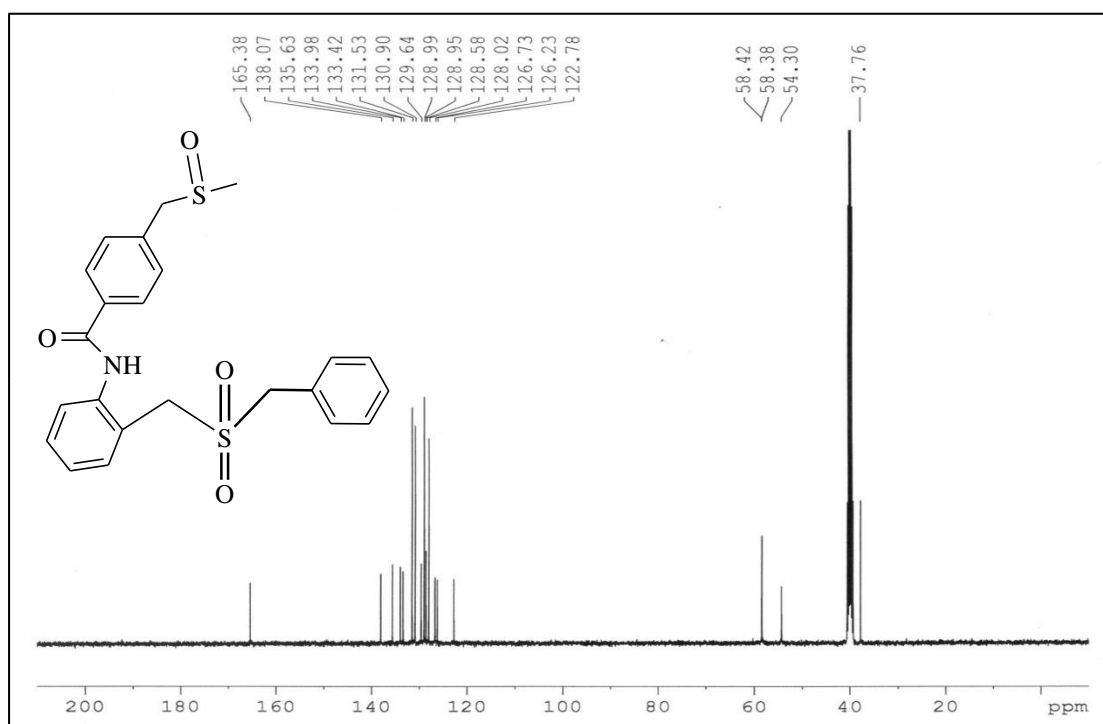**Figure 2.58** ^{1}H NMR spectrum of N-(2-((Benzylthio)methyl)phenyl)-4-((methyl sulfonyl)methyl)benzamide (**48b**)
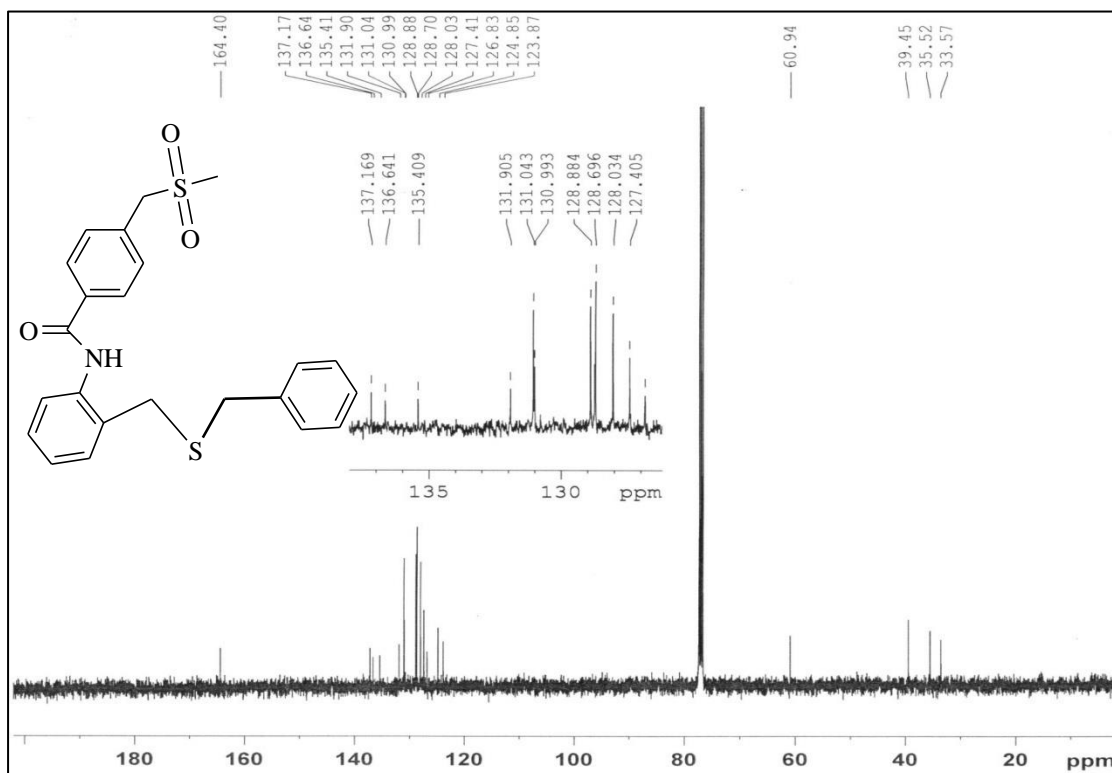
Figure 2.59 ^{13}C NMR spectrum of N-(2-((Benzylthio)methyl)phenyl)-4-((methyl sulfonyl)methyl)benzamide (**48b**)
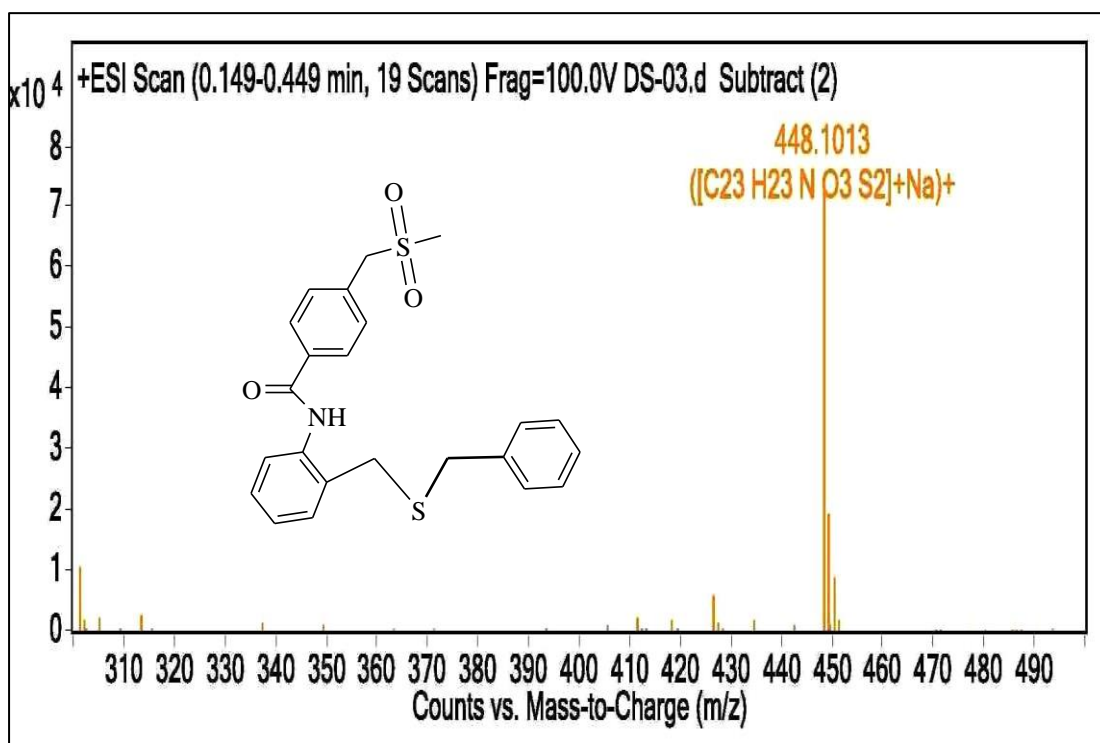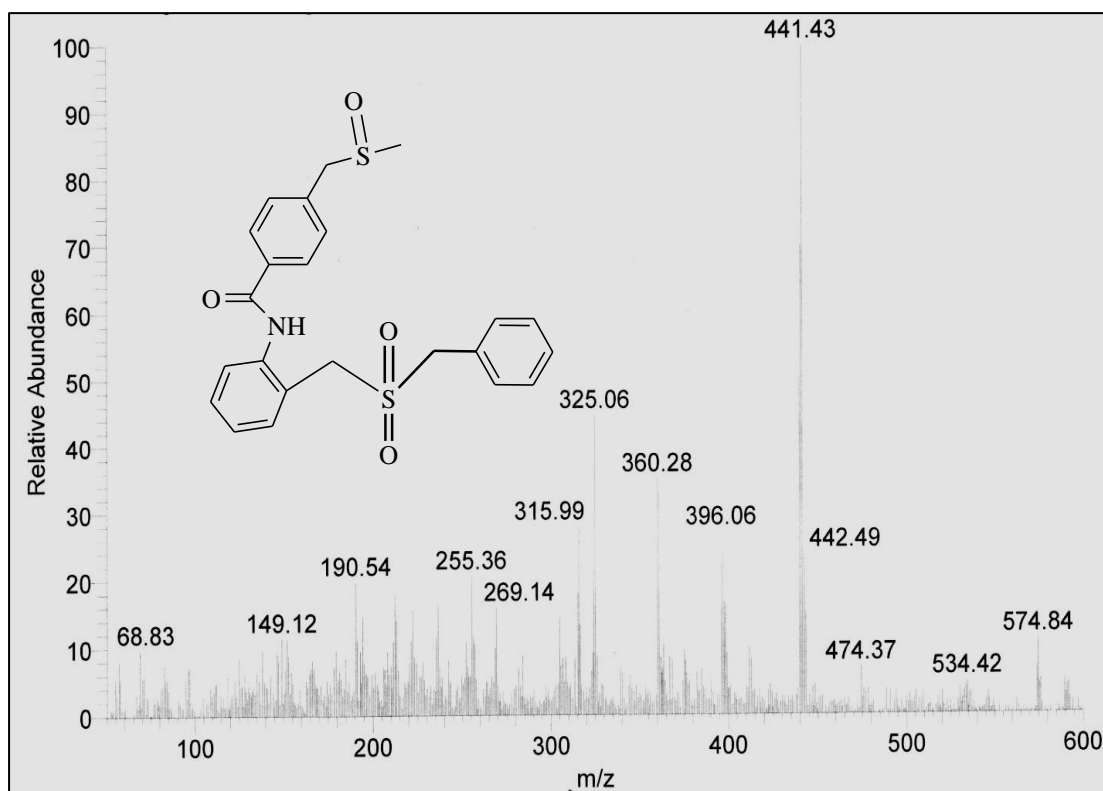
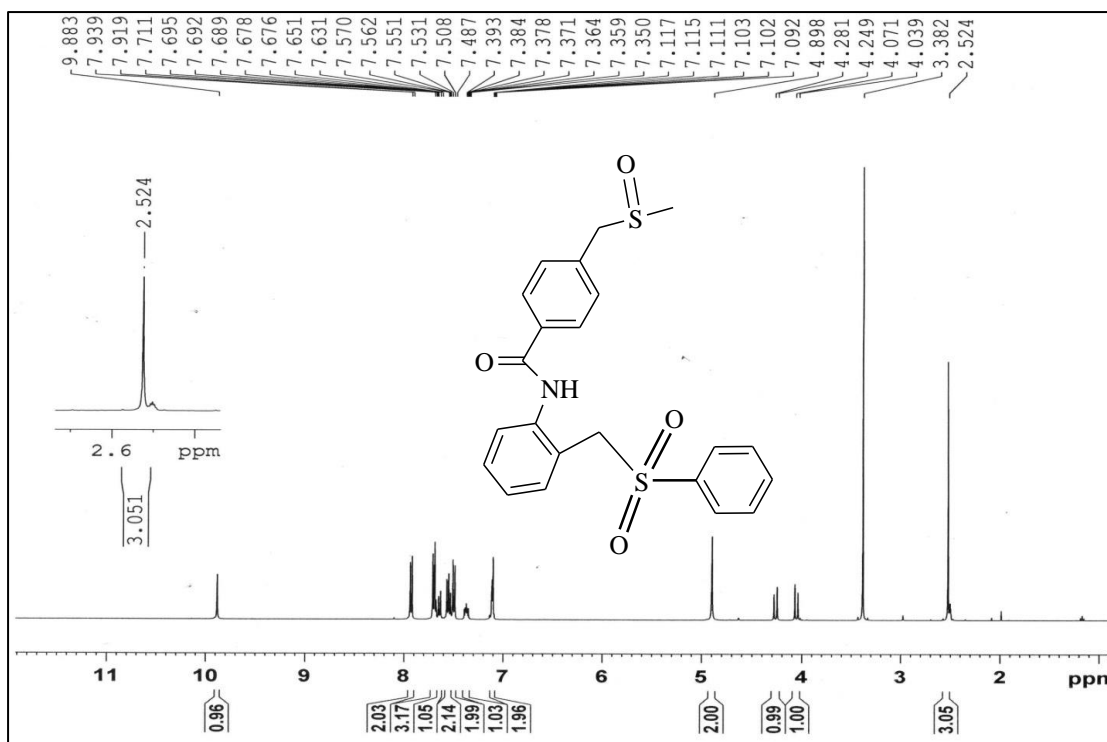**Figure 2.60** HRMS spectrum of N-(2-((Benzylthio)methyl)phenyl)-4-((methylsulfonyl) methyl)benzamide (**48b**)
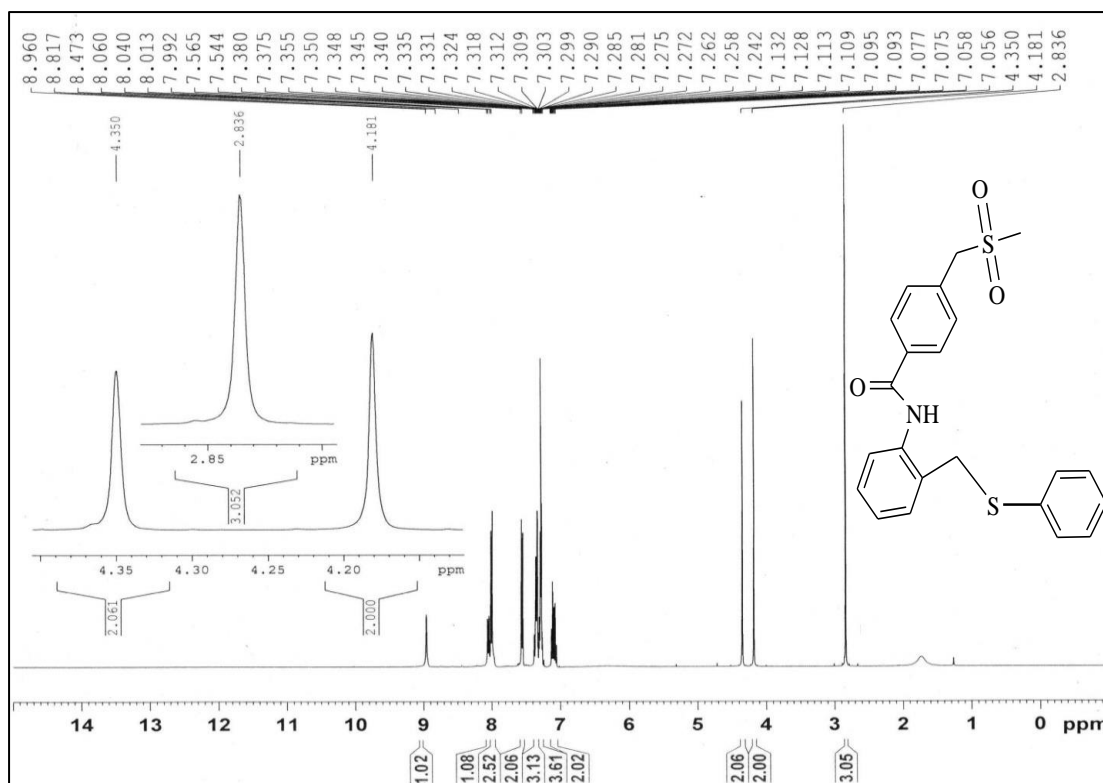
Figure 2.61 ^{1}H NMR spectrum of 4-((Methylsulfonyl)methyl)-N-(2-((phenylthio)
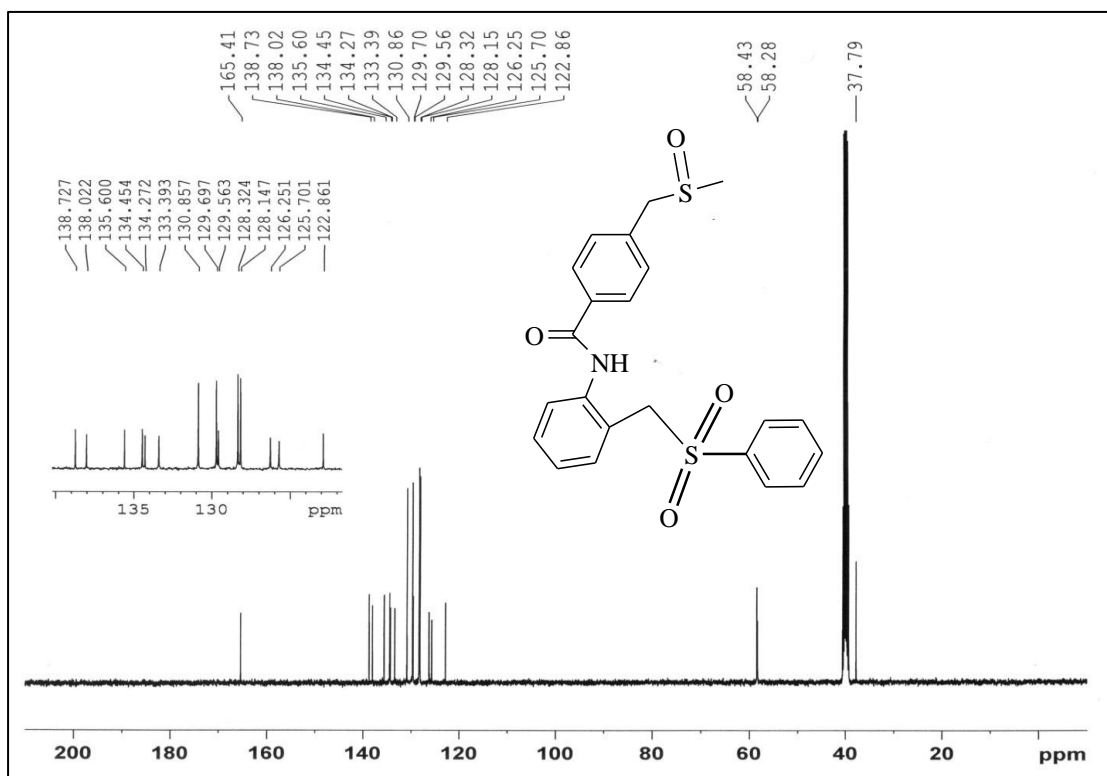methyl)phenyl)benzamide (**48c**)
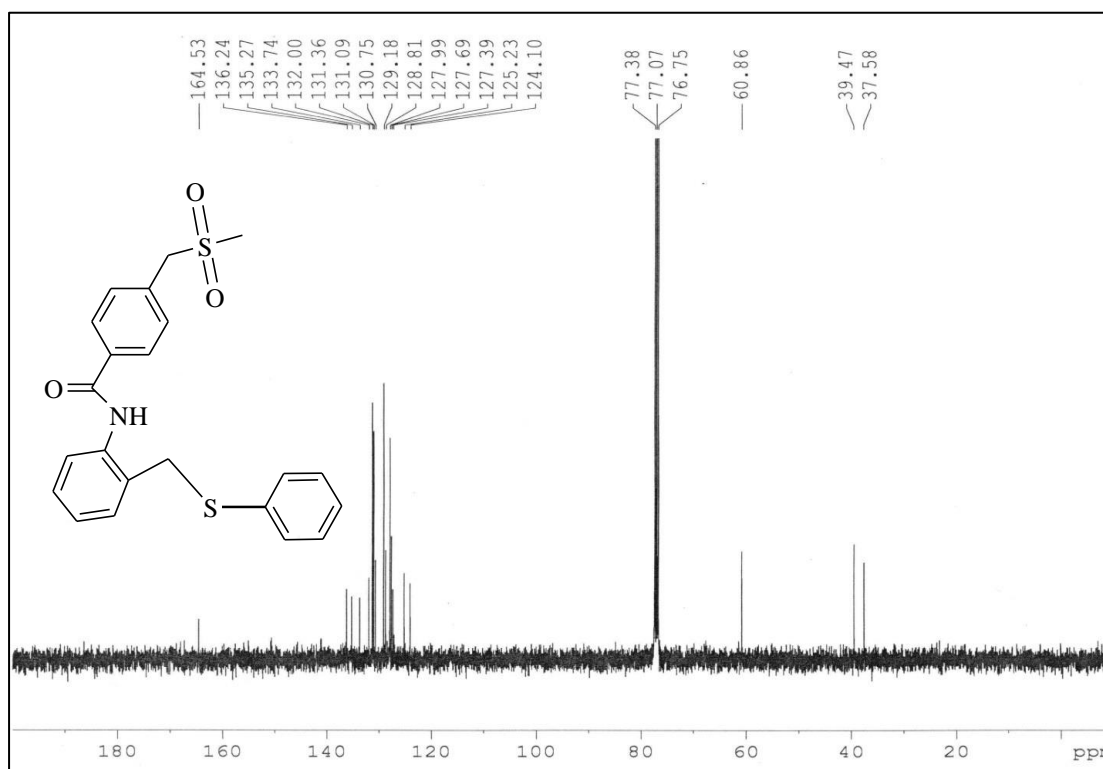
Figure 2.62 ^{13}C NMR spectrum of 4-((Methylsulfonyl)methyl)-N-(2-((phenylthio)
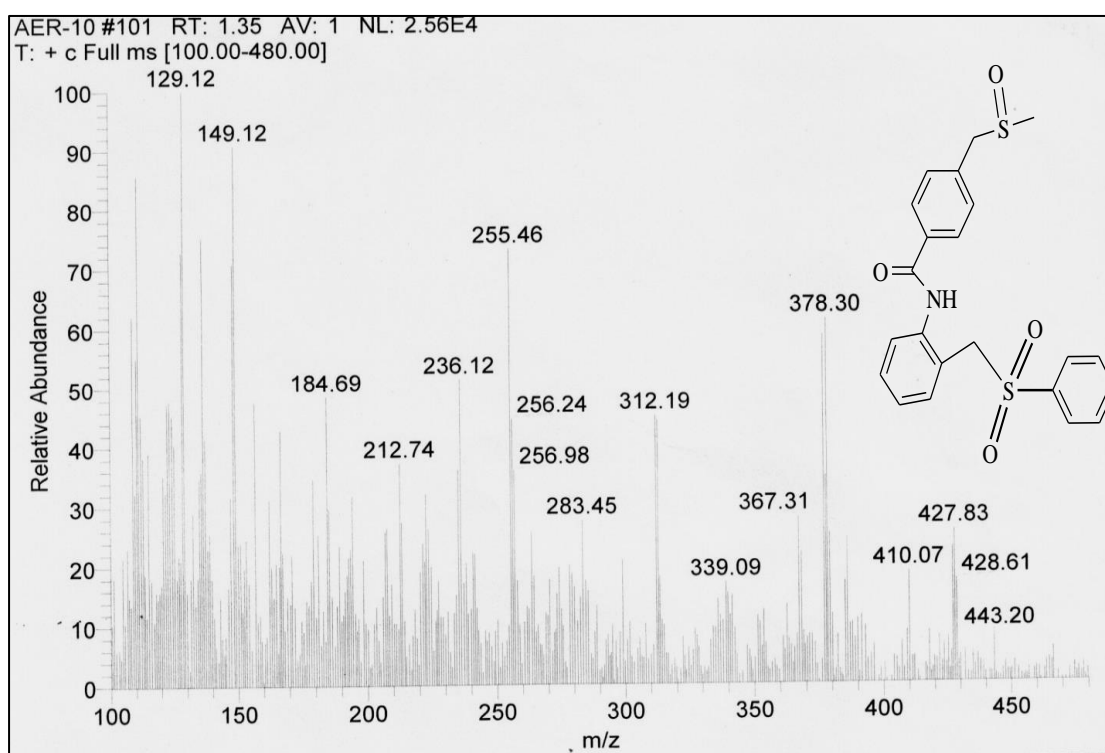methyl)phenyl)benzamide (**48c**)
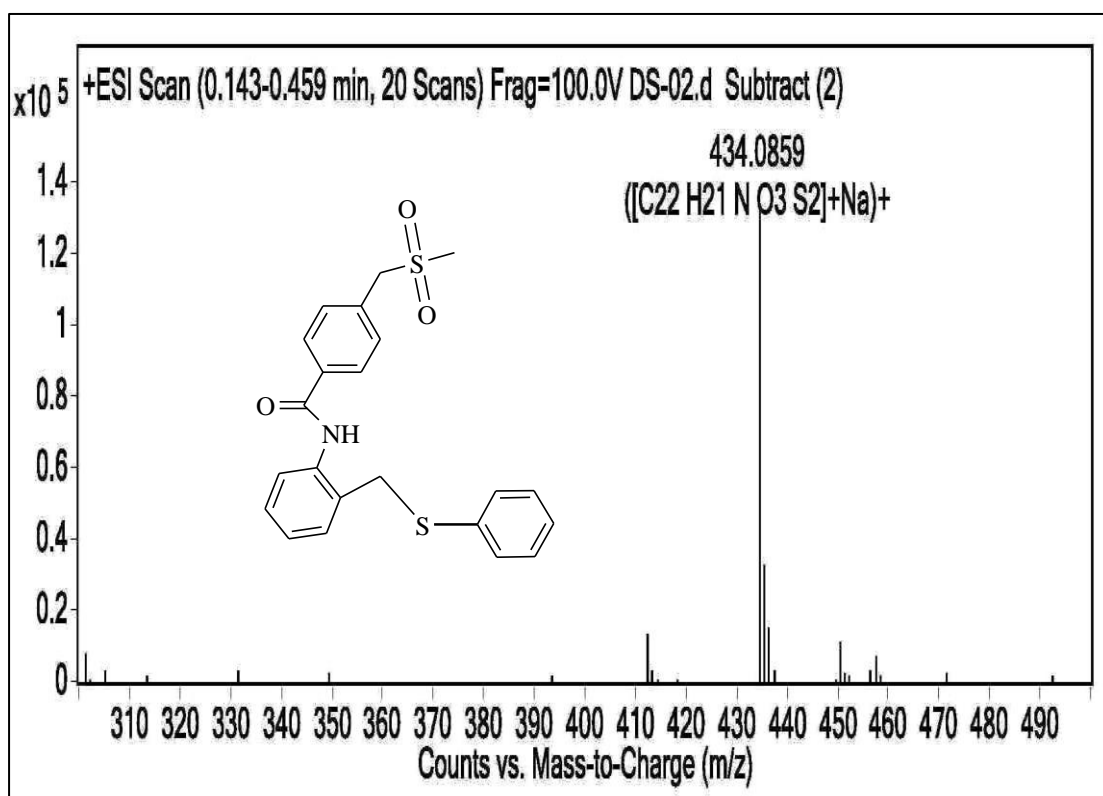
Figure 2.63 HRMS spectrum of 4-((Methylsulfonyl)methyl)-N-(2-((phenylthio)
methyl)phenyl)benzamide (**48c**)
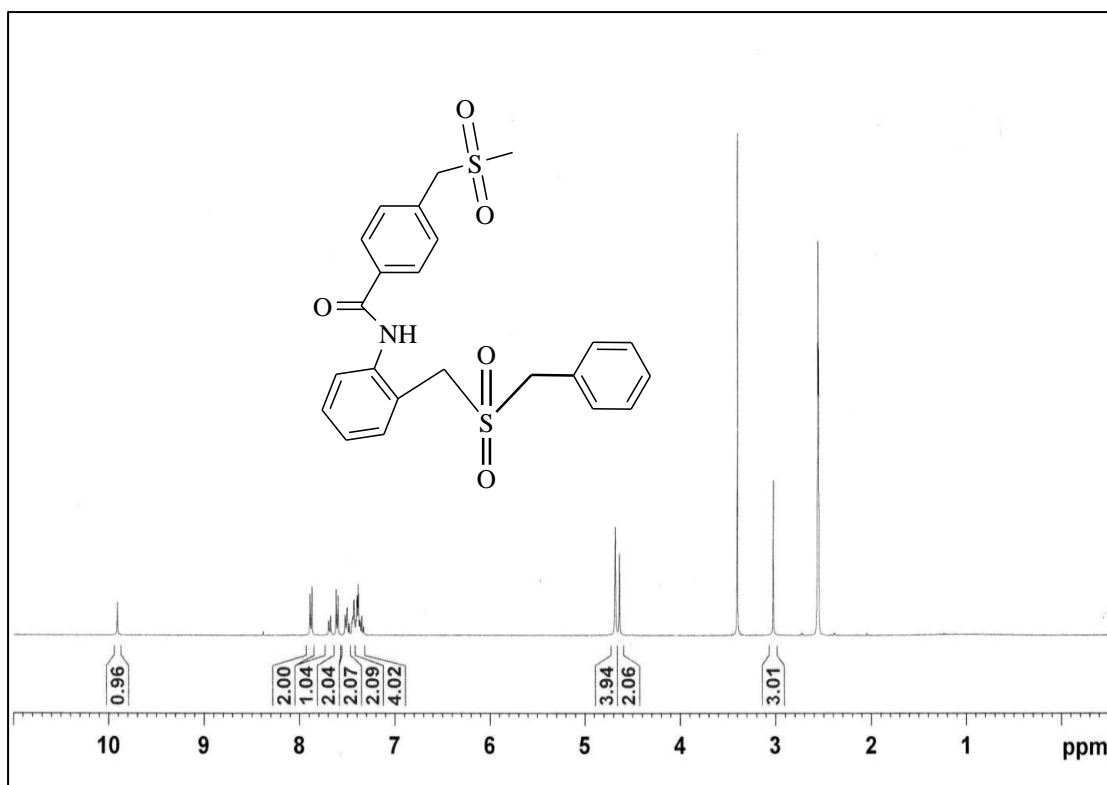
Figure 2.64 ^{1}H NMR spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl sulfonyl)methyl)benzamide (**48d**)
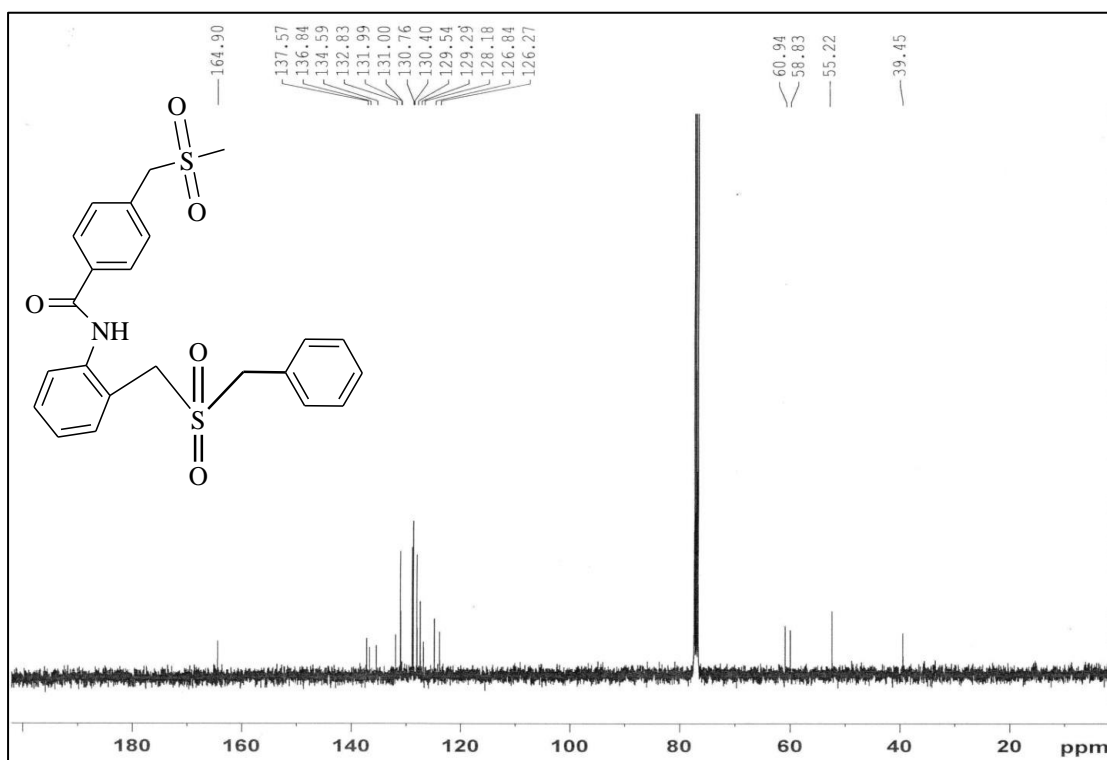
Figure 2.65 ^{13}C NMR spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl sulfonyl)methyl)benzamide (**48d**)
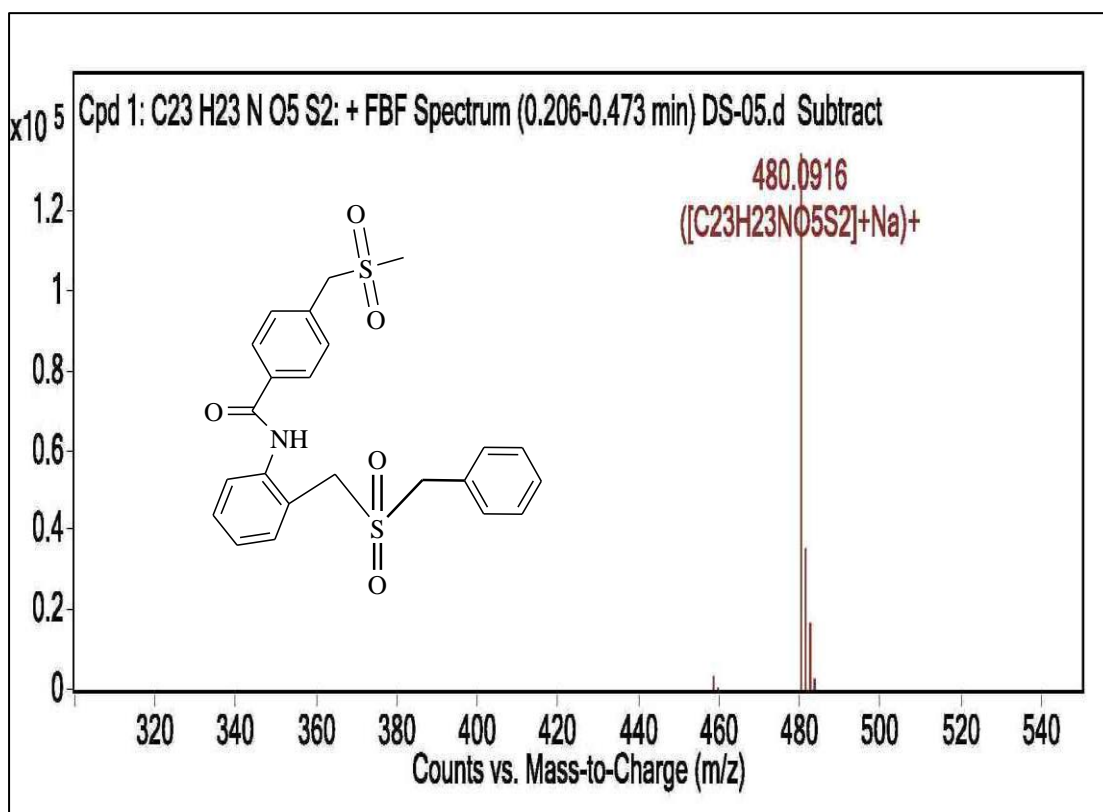
Figure 2.66 HRMS spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl sulfonyl)methyl)benzamide (**48d**)

Figure 2.67 ^{1}H NMR spectrum of 4-((Methylsulfonyl)methyl)-N-(2-((phenylsulfonyl)methyl)phenyl)benzamide (**48e**)
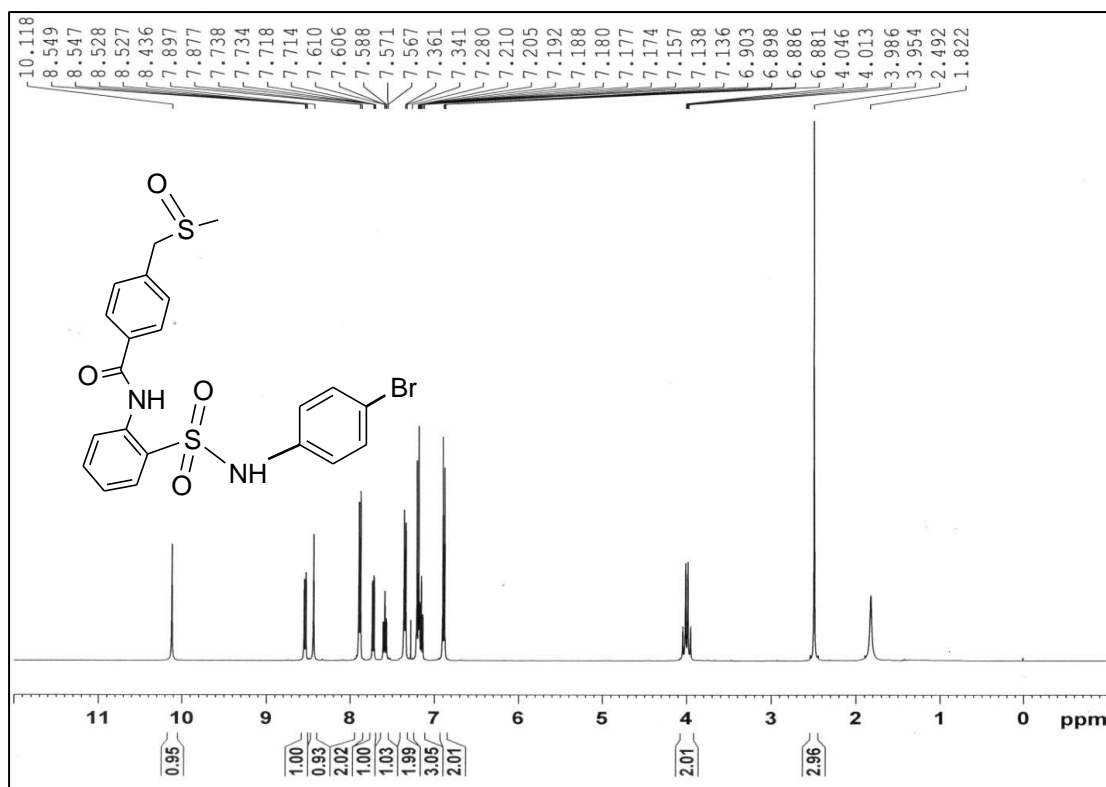

Figure 2.68 ^{13}C NMR spectrum of 4-((Methylsulfonyl)methyl)-N-(2-((phenylsulfonyl)methyl)phenyl)benzamide (**48e**)
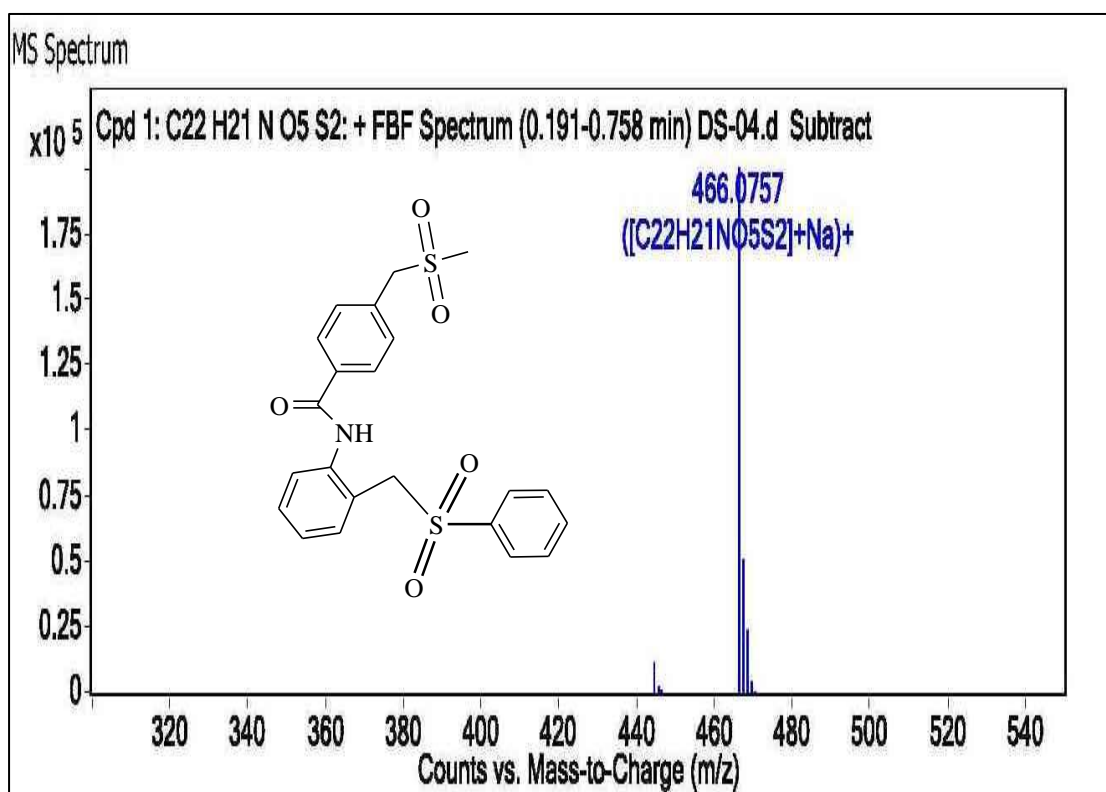
Figure 2.69 HRMS spectrum of 4-((Methylsulfonyl)methyl)-N-(2-((phenyl sulfonyl)methyl)phenyl)benzamide (**48e**)

Figure 2.70 ^{1}H NMR spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl sulfinyl)methyl)benzamide **(49a)**

Figure 2.71 ^{13}C NMR spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl sulfinyl)methyl)benzamide **(49a)**
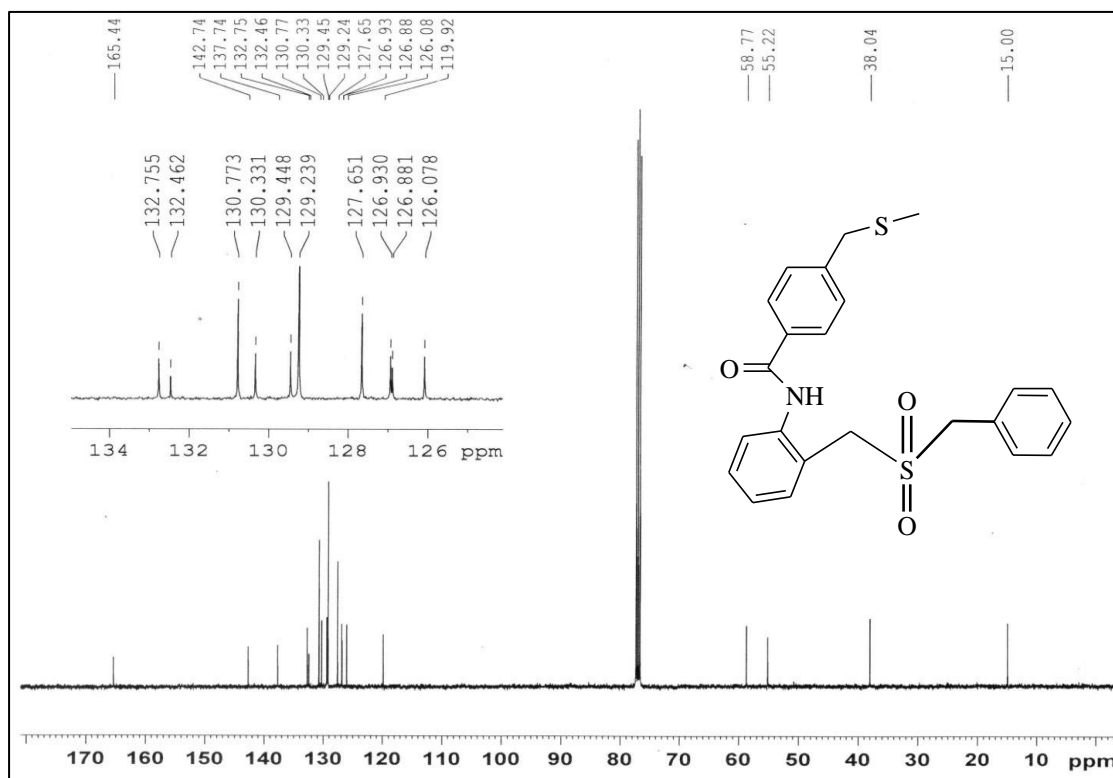
Figure 2.72 Mass spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl sulfinyl)methyl)benzamide **(49a)**

Figure 2.73 ^{1}H NMR spectrum of 4-((Methylsulfinyl)methyl)-N-(2-((phenylsulfonyl) methyl)phenyl)benzamide (**49b**)

Figure 2.74 ^{13}C NMR spectrum of 4-((Methylsulfinyl)methyl)-N-(2-((phenyl sulfonyl)methyl)phenyl)benzamide (**49b**)

Figure 2.75 Mass spectrum of 4-((Methylsulfinyl)methyl)-N-(2-((phenylsulfonyl) methyl)phenyl)benzamide (**49b**)

Figure 2.76 ^{1}H NMR spectrum of (N-(4-Bromophenyl)-2-(4-(methylsulfinylmethyl) benzamido))benzenesulfonamide (**49c**)
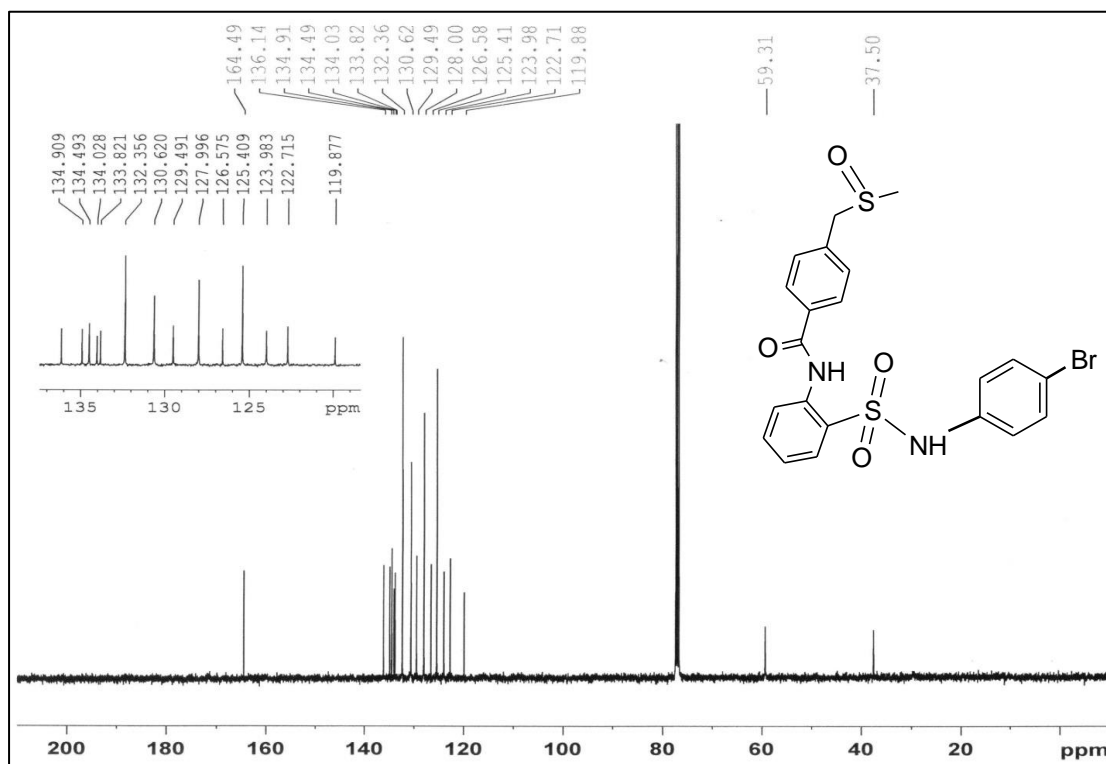
Figure 2.77 ^{13}C NMR spectrum of (N-(4-Bromophenyl)-2-(4-(methylsulfinylmethyl) benzamido))benzenesulfonamide (**49c**)
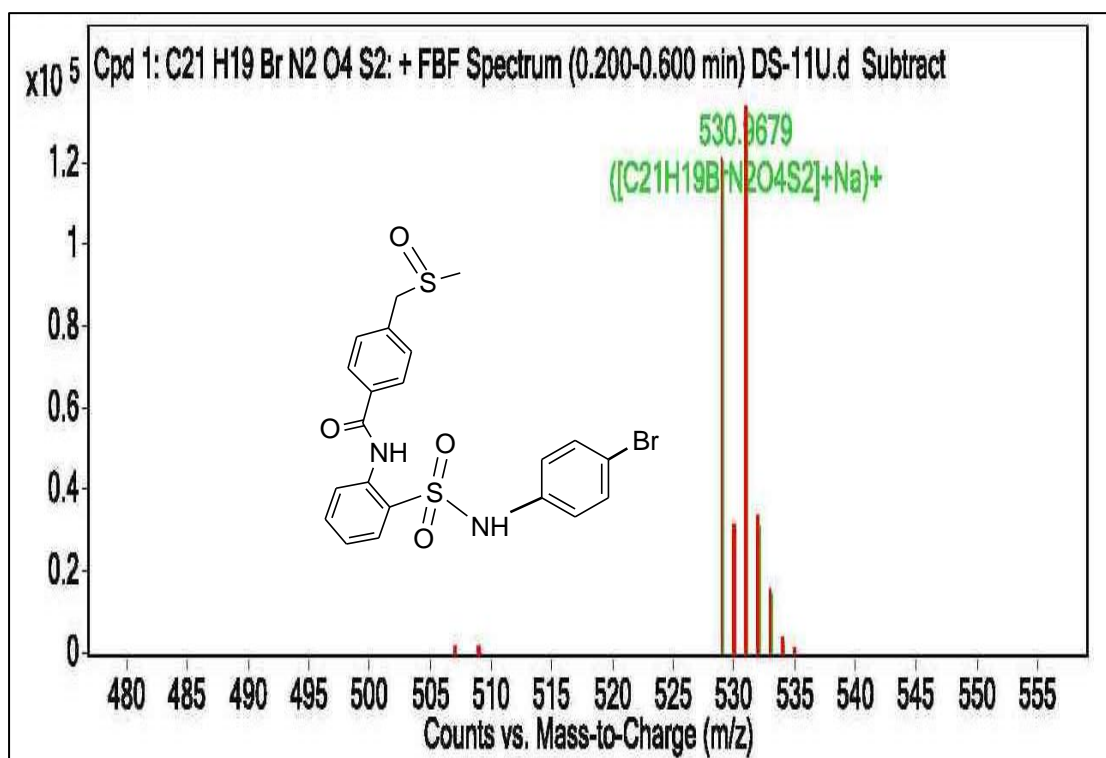
Figure 2.78 HRMS spectrum of (N-(4-Bromophenyl)-2-(4-(methylsulfinylmethyl)
benzamido))benzenesulfonamide (**49c**)
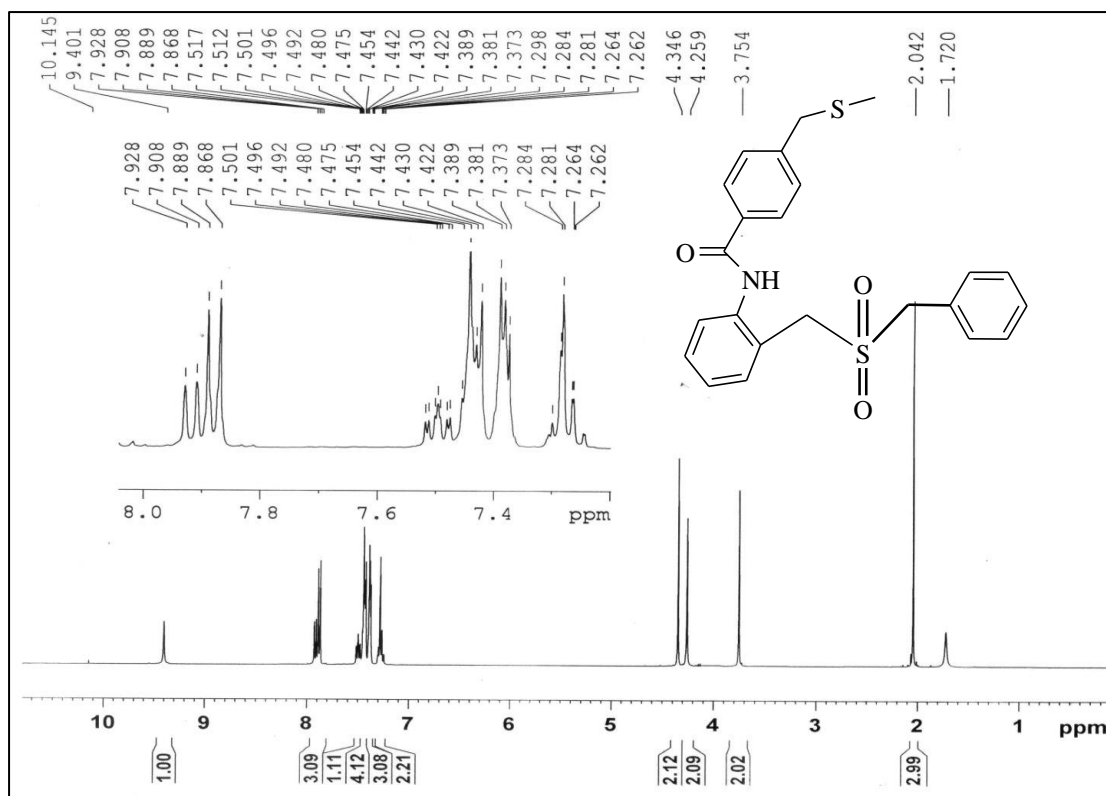
Figure 2.79 ¹H NMR spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl thio)methyl)benzamide (**50a**)

Figure 2.80 ¹³C NMR spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl thio)methyl)benzamide (**50a**)
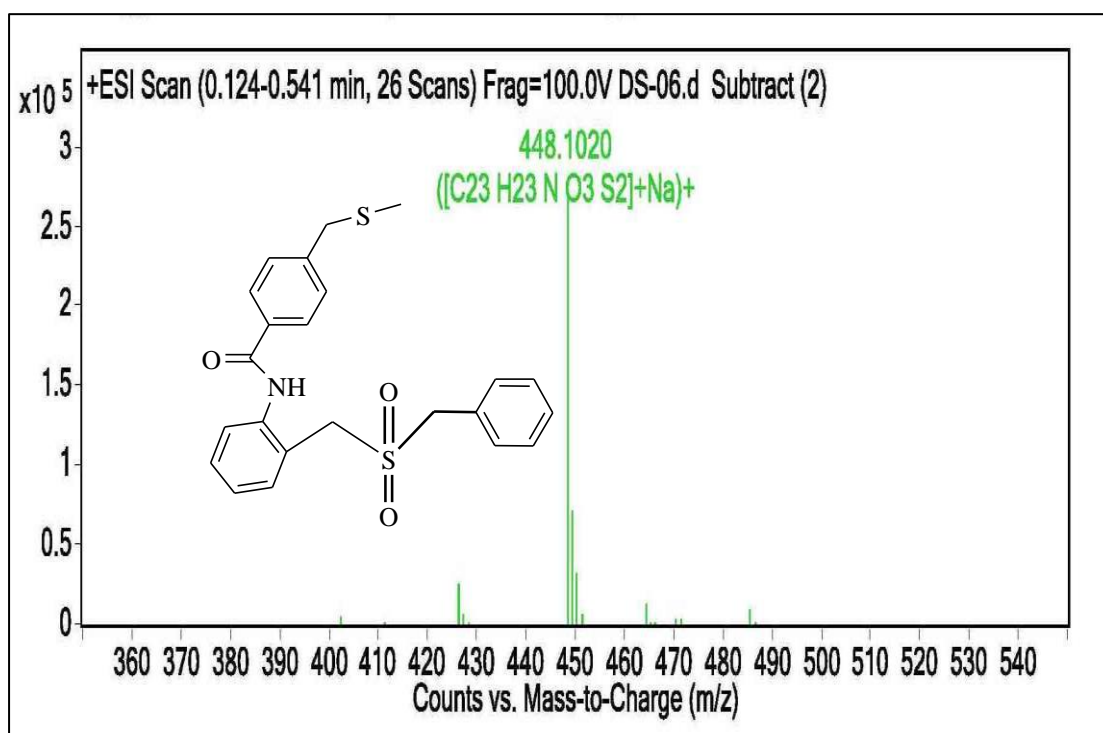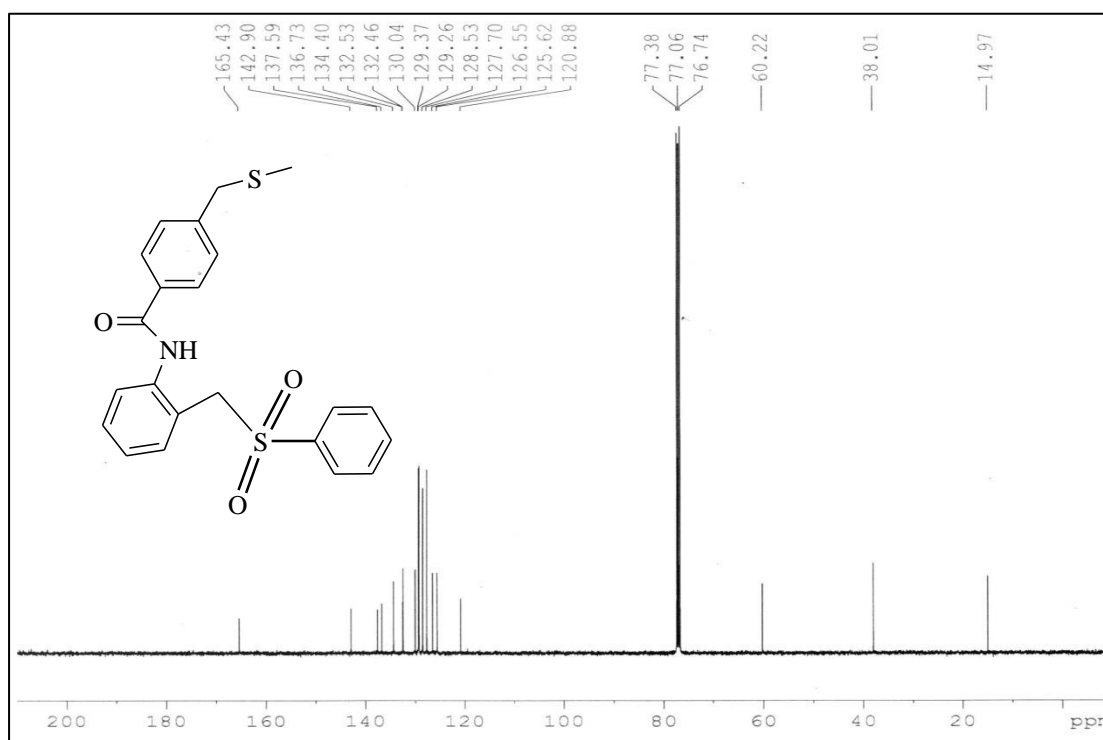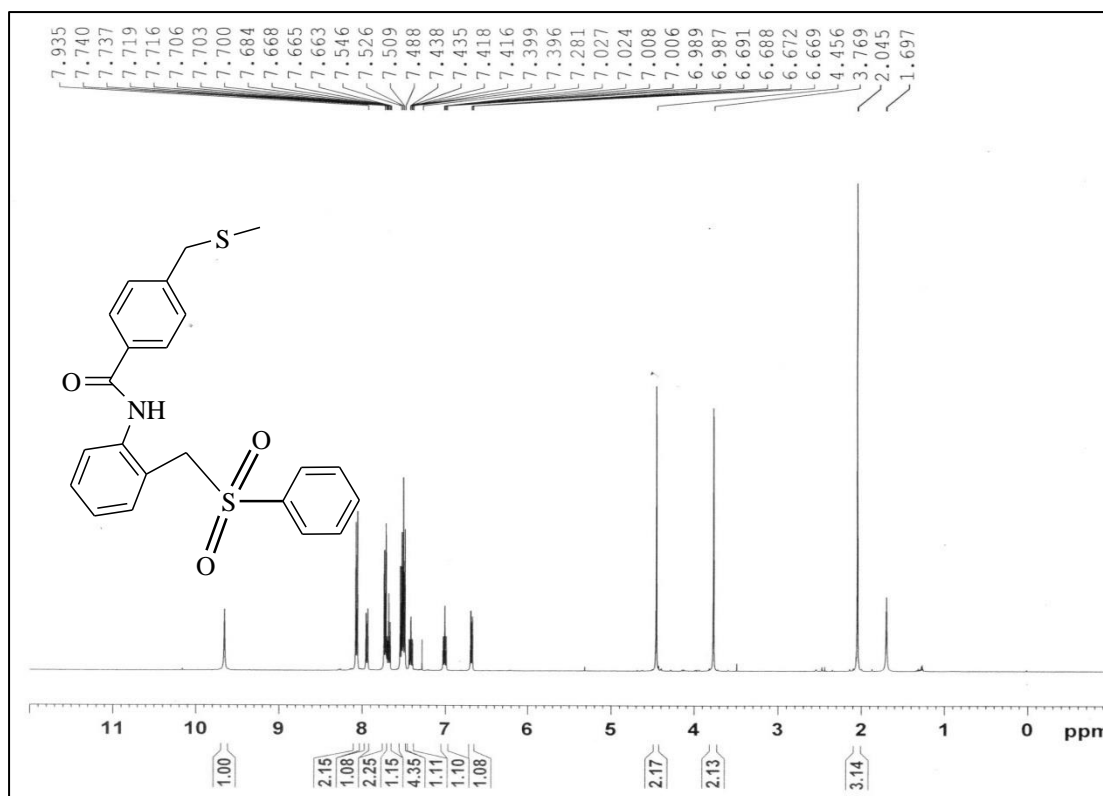
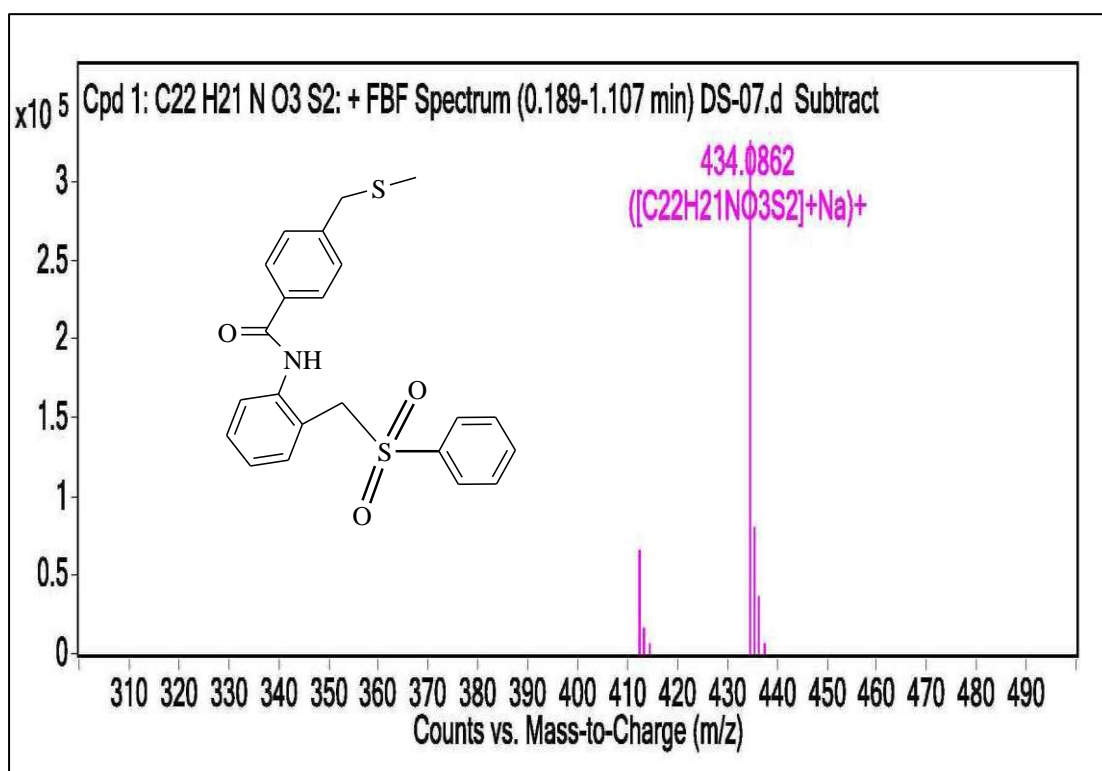**Figure 2.81** HRMS spectrum of N-(2-((Benzylsulfonyl)methyl)phenyl)-4-((methyl thio)methyl)benzamide (**50a**)

Figure 2.82 ^{1}H NMR spectrum of 4-((Methylthio)methyl)-N-(2-((phenylsulfonyl)
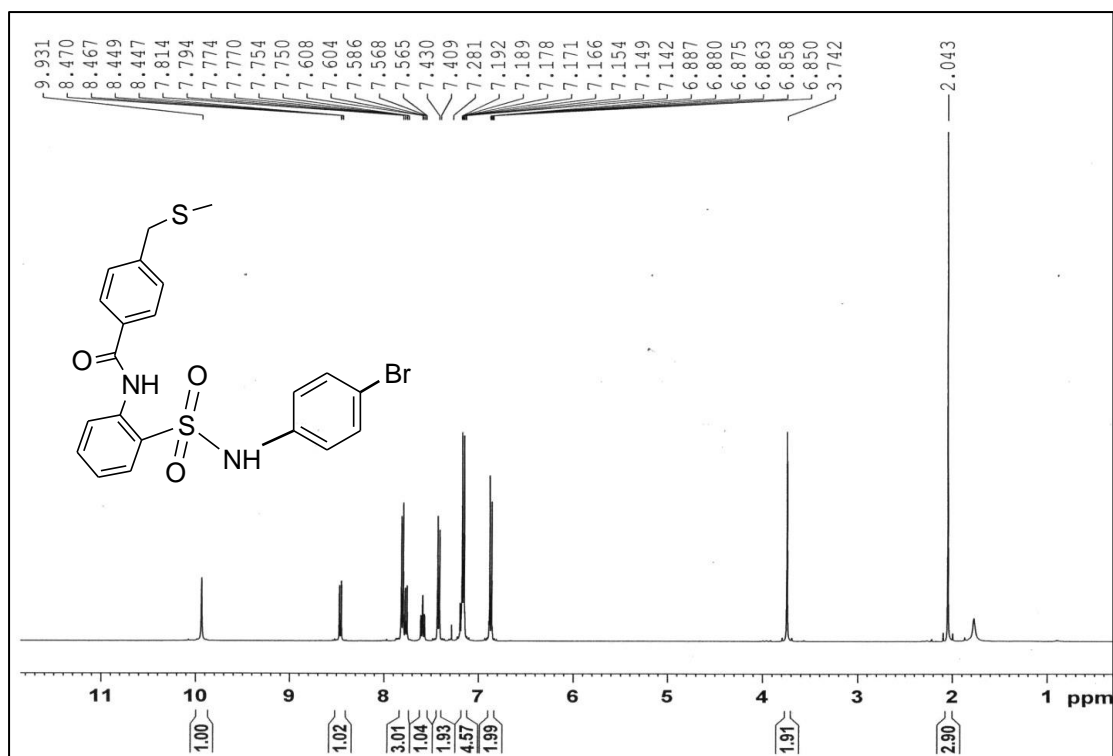methyl)phenyl)benzamide (**50b**)

Figure 2.83 ^{13}C NMR spectrum of 4-((Methylthio)methyl)-N-(2-((phenylsulfonyl)
methyl)phenyl)benzamide (**50b**)

Figure 2.84 HRMS spectrum of 4-((Methylthio)methyl)-N-(2-((phenylsulfonyl) methyl)phenyl)benzamide (**50b**)

Figure 2.85 ^{1}H NMR spectrum of (N-(4-Bromophenyl)-2-(4-(methylthiomethyl) benzamido))benzenesulfonamide (**50c**)
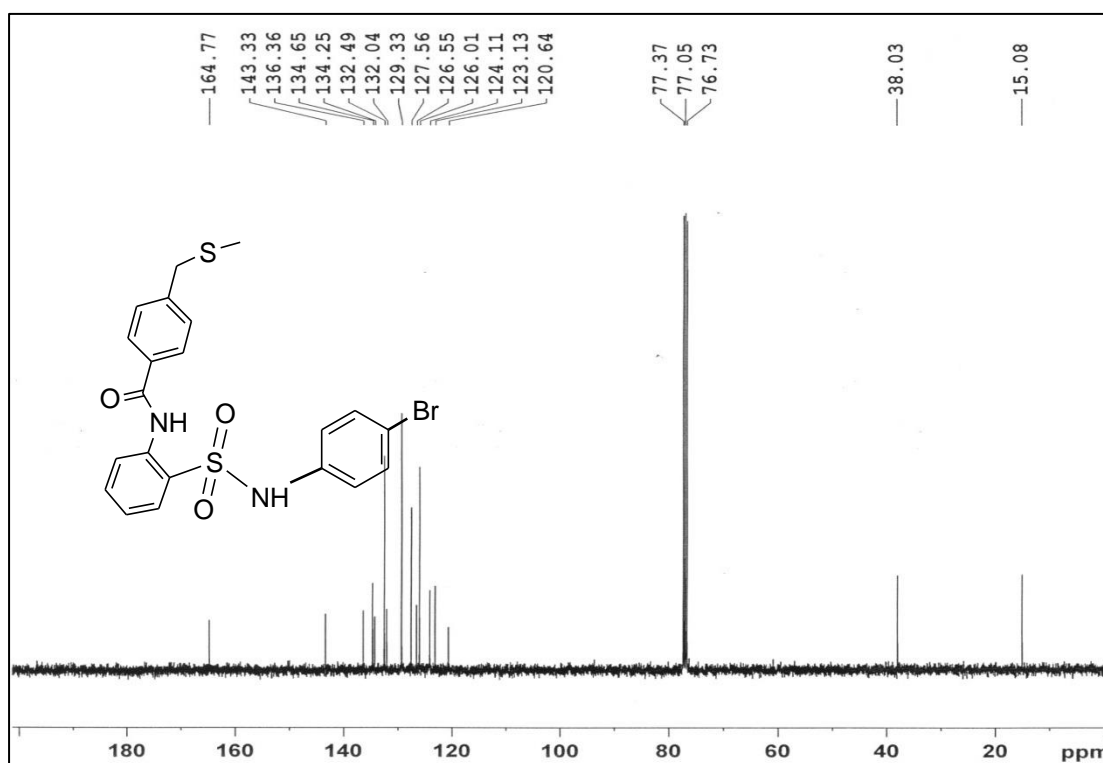

Figure 2.86 ^{13}C NMR spectrum of (N-(4-Bromophenyl)-2-(4-(methylthiomethyl) benzamido))benzenesulfonamide (**50c**)
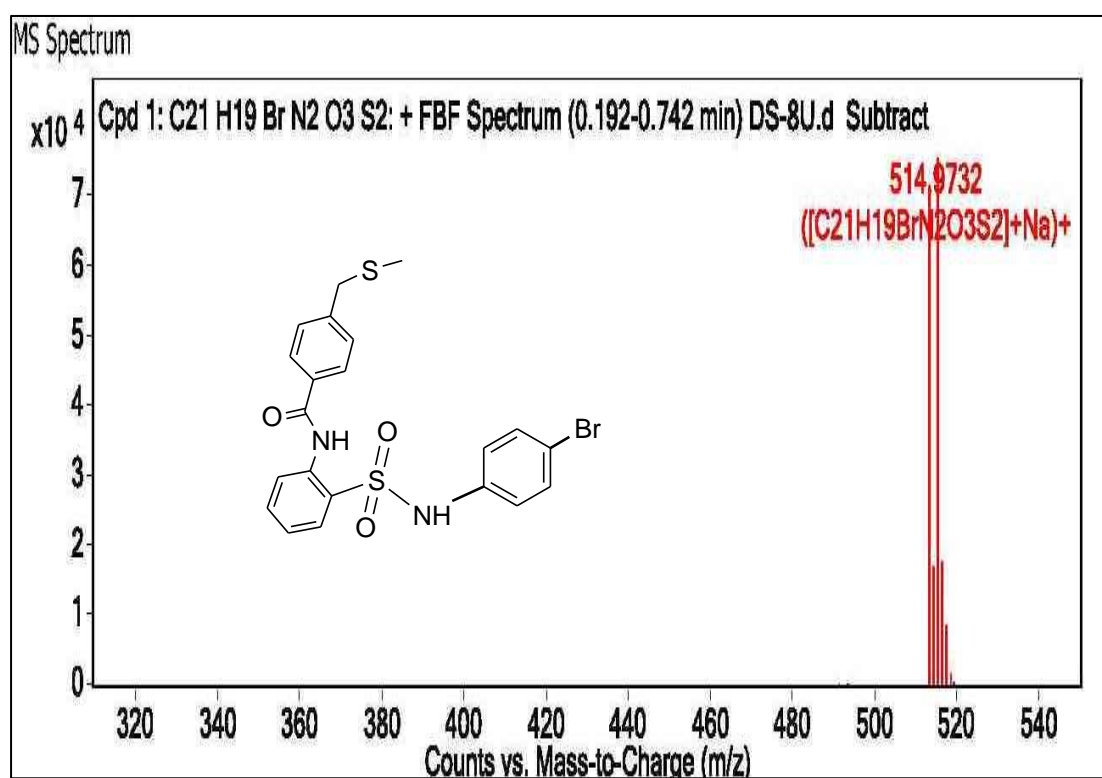
Figure 2.87 HRMS spectrum of (N-(4-Bromophenyl)-2-(4-(methylthiomethyl) benzamido))benzenesulfonamide (**50c**)