RESEARCH PAPER

Synthesis and Characterization of Piperazine Derivatives using Different Metal Based Ionic Liquid as a Catalyst

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ABSTRACT

The piperazine moiety, a six-membered heterocyclic molecule with two nitrogen atoms, has become crucial in drug design due to its advantageous physicochemical features, including enhanced solubility, bioavailability, and robust target binding. Piperazine and its derivatives serve as essential pharmacophores in numerous medications, encompassing anticancer, antibacterial, antibiotic, antipsychotic, and antidepressant treatments, so establishing their significance as vital scaffolds in contemporary pharmaceutical research and drug discovery. The synthetic piperazine derivatives were created using laboratory-grade chemicals and solvents obtained from Thermosil Fine Chem Industries, including tert-butyl piperazine-1-carboxylate, DMF, 1,4-dioxane, dimethoxy boronic acid, sodium carbonate, and HCl. The synthesized compounds were structurally characterized and analyzed utilizing analytical tools including NMR (Bruker), LC-MS (Shimadzu), and HPLC (Jasco). The synthetic strategy comprised a multi-step reaction sequence, commencing with a coupling reaction to produce tert-butyl 4-((5-bromothiophen-2-yl) sulfonyl) piperazine-1-carboxylate, succeeded by a palladium-catalyzed coupling (Stille reaction) to incorporate the 3,4-dimethoxyphenyl group, resulting in tert-butyl 4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine-1-carboxylate. In the concluding step, the deprotection of the tert-butyl group produced 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine, which functioned as a crucial intermediary for the synthesis of a library of piperazine derivatives. Conclusion - The synthesis of piperazine derivatives with metal-based ionic liquids as catalysts yielded encouraging results, generating compounds with diverse functional groups, including methoxy and fluoro, on phenyl and thiophene rings, with yields between 50% and 80%. The results suggest that the synthetic technique is quite efficient; nevertheless, optimizing reaction parameters, including temperature, duration, and catalyst concentration, could enhance yields. The possible reusability of metal-based ionic liquids underscores their benefits as sustainable and efficient catalysts in the synthesis process.

Keywords: Metal-based ionic liquids, Catalysis, Synthesis, Antibacterial activity, Antifungal activity, etc.

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Introduction

Cancer

Humans, undoubtedly, are the most advanced species present on the earth. Throughout their evolution journey, humans managed to overcome many obstacles such as wild animals, geographical disaster, starvation and some manmade disasters like war. But apart from all these problems, a major danger which has been with humans in their journey was in fact, inside their body which we usually call a 'disease'. A disease is an abnormal condition in the body which usually affects the body in negative way. Over the years, humans faced deadly and non-deadly diseases, in fact we can say that some of the diseases which are so common these days and are curable also used to be deadly some decades ago, like chicken pox, diphtheria and polio. But there are some fatal diseases whose cure has not been found by science despite working for so long, such as AIDS and 'Cancer'. In the above two

diseases AIDS is considered as the most lethal one as there is no cure available for it, while cancer is somehow curable scientifically, if diagnosed earlier. But what makes cancer more deadly and scary is that there are no particular causes and preventions of it. While, AIDS causes and preventions are known to all. Cancer refers to a large number of diseases that involves an abnormal cell growth with the ability to invade or spread to other parts of the body. Generally, surgeons use diagnostic test to find a cancer's stage. Cancer usually have four stages: Stage I to Stage IV. But some cancer have a Stage 0 (zero) also. **[1]**

Types of Cancer and Mechanism [2-3]

Cancer is merely the aberrant proliferation of cells. Although almost 100 forms of cancer are identified, the most prevalent include skin cancer, breast cancer, lung cancer, prostate cancer, and leukemia. We shall provide an overview of several principal kinds of cancer.

Mechanism- Even while different tumors attack different organs, such as the breast, lungs, prostate, skin, colon, or blood, their basic tactics are mostly the same. Cancer is a group of disorders that happen when unusual cells grow and spread in the body without any control. Cancer happens when normal cells have genetic changes that mess up the regular processes of cell division, growth, and programmed cell death (apoptosis). These mutations commonly affect important regulatory genes, such as oncogenes that help cells grow and tumor suppressor genes like TP53, BRCA1, BRCA2, PTEN, and APC that usually control cell division and DNA repair. Changes in these genes cause cells to lose their normal growth control, which leads to unregulated division. This can cause tumors to form or, in the case of blood cancers like leukemia, too many aberrant blood cells to build up in the bone marrow. Cigarette smoking, UV radiation, radiation exposure, pollution, poor diet, obesity, and a lack of physical activity are some of the environmental and lifestyle variables that can harm DNA and raise the risk of several problems. Hormones like estrogen, progesterone, and androgens start biological processes that help cells stay alive and grow in some cancers, which speeds up tumor growth. As time goes on, cancer cells get more genetic modifications that help them avoid being found by the immune system, resist apoptosis, and grow quickly. As the disease advances, malignant cells acquire the capacity to infiltrate neighboring tissues and spread via the bloodstream or lymphatic system to distant organs, including the brain, liver, lungs, or bones—a process known as metastasis. Cancer is a complicated and potentially fatal disease caused by the gradual accumulation of genetic mutations, environmental factors, and anomalies in molecular signaling that ultimately compromise the structure and function of normal tissues.

Introduction of Piperazine moiety and Piperazine derivatives [4-17]

The piperazine moiety denotes the structural element of a molecule comprising a piperazine ring, a six-membered heterocyclic ring featuring two nitrogen atoms situated at opposing positions (1,4-diazacyclohexane). Below is a summary of its chemical information:

The piperazine molecule is recognized as a preferred structural motif in pharmacological research. Hexahydropyrazine is a six-membered heterocyclic compound with the chemical formula C4H10N2. Hexahydropyrazine was designated as piperazine because to its structural resemblance to piperidine, a component of the piperine structure derived from the black pepper plant. It possesses two reactive secondary amine groups at the first and fourth positions. Piperazine was initially utilized in the 1800s for gout treatment, and subsequently, its derivatives were employed to address intestinal infections. During the early 20th century, many researchers created piperazine and its substituted derivatives, which emerged as significant pharmacophores in a variety of commercialized pharmaceuticals, including antibiotics, anticancer agents, antimicrobials, antipsychotics, and antidepressants. Piperazine was primarily identified in second-generation antibiotics and has been incorporated into sixth-generation antibiotics. A new statistical examination of the substructure indicates that piperazine ranks as the third most prevalent N-heterocycle in pharmaceutical small molecule medicines. A number of pharmaceuticals featuring the piperazine moiety rank among the top 100 best-selling goods.

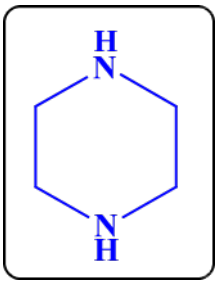


Figure 1. Structure of Piperazine Molecule

Synthesis and characterization of Piperazine Derivatives using different Metal based ionic liquid as a catalyst

Small-molecule medicines with the piperazine moiety possess substituents on one or both nitrogen atoms and are mostly utilized as linkers for various molecules/macromolecules to modify the physicochemical features of a macromolecule. Piperazine, a six-membered heterocyclic compound containing two opposing nitrogen atoms, offers a substantial polar surface area, structural rigidity, and both hydrogen-bond acceptors and donors, frequently resulting in improved target affinity, specificity, water solubility, oral bioavailability, and ADME (absorption, distribution, metabolism, and excretion) characteristics. The lack of vinyl and multifunctional groups in the piperazine molecule limits its application in polymer synthesis, although piperazine and its substituted derivatives are widely utilized as antibiotics, anticancer agents, antimicrobials, antipsychotics, and antidepressants.

1. Materials and Methods

1.1 Materials

Procurement of chemicals and solvents

The required chemicals to carryout designed synthetic schemes were procured from local chemical supplier (Thermosil Fine Chem industries). All the chemicals were of laboratory grade. The starting chemicals i.e. tert-butyl piperazine -1-carboxylate and other chemicals and solvents such as DMF, 1 ,4 dioxane, dimethoxy boronic acid , sodium carbonate, HCl were procured.

List of Instruments

Table 1- List of Instruments

Sr. no.	Name of Instrument	Make
1.	NMR	Bruker
2.	LCMS	Shimadzu
3.	HPLC	Jasco

1.2 Methods

1.2.1 General Reaction scheme- [18-23]

Synthetic strategy pertains to the formulation of the most effective reaction combinations to produce the intended final product. The synthetic method is intended to facilitate potential reactions for product generation. It entailed the subsequent steps,

- **Step-01: Synthesis of tert-butyl 4-((5 bromothiophen-2-yl) sulfonyl) piperazine-1- carboxylate.**

In this reaction step, a possible coupling will be carried out.

A coupling reaction in organic chemistry refers to a category of reactions in which two fragments are united with the assistance of a metal catalyst. In a significant reaction type, a main group organometallic compound of the form R-M (where R represents an organic fragment and M denotes the main group center) combines with an organic halide of the type R'-X, resulting in the production of a new carbon-carbon bond in the product R-R'. The predominant form of coupling reaction is cross-coupling.

- **Step-02: Synthesis of tert-butyl 4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine-1-carboxylate.**

This step involves stille reaction or coupling.

The Stille Coupling is a multifaceted C-C bond formation reaction involving stannanes and halides or pseudohalides, exhibiting little restrictions on the R-groups. Thoroughly developed procedures facilitate the synthesis of many compounds from all combinations of the halides and stannanes illustrated below. The primary disadvantage is the toxicity of the tin compounds employed, along with their low polarity, resulting in poor solubility in water. Stannanes exhibit stability; nonetheless, boronic acids and their derivatives participate in analogous chemistry in the process termed Suzuki Coupling. Advancements in the Suzuki Coupling may eventually provide comparable versatility without the disadvantages associated with tin compounds.

The Stille reaction is a chemical process extensively employed in organic synthesis. The reaction entails the coupling of two organic groups, one of which is shown as an organotin complex (sometimes referred to as organostannanes). A range of organic electrophiles serves as the alternative coupling partner. The Stille reaction is a palladium-catalyzed coupling process. The Stille reaction mechanism has been well investigated. The catalytic cycle encompasses the oxidative addition of a halide or pseudohalide (2) to a palladium catalyst (1),

transmetalation of 3 with an organotin reagent (4), and reductive elimination of 5, resulting in the coupled product (7) and the regeneration of the palladium catalyst (1).

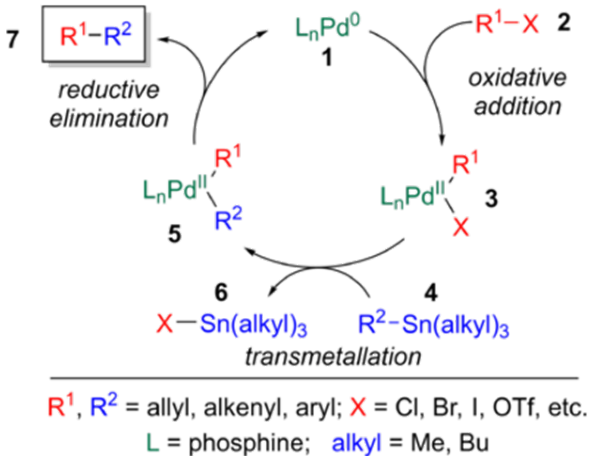


Figure 2. Stille reaction or coupling.

- **Step-03: Synthesis of 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine**
  After synthesis of 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine, it is subjected for library synthesis of different derivatives.

It involves deprotection-

In several syntheses of sensitive organic compounds, certain molecular components cannot withstand the necessary reagents or chemical conditions. Subsequently, these components or factions require safeguarding. Lithium aluminium hydride is a highly reactive yet valuable reagent that can reduce esters to alcohols. It will invariably react with carbonyl groups, and this cannot be mitigated by any means. In the reduction of an ester in the presence of a carbonyl, it is essential to inhibit the hydride's attack on the carbonyl. The carbonyl is transformed into an acetal, which is unreactive with hydrides. The acetal is then referred to as a protective group for the carbonyl. Upon completion of the hydride stage, the acetal is eliminated through reaction with an aqueous acid, restoring the original carbonyl. This process is referred to as deprotection.

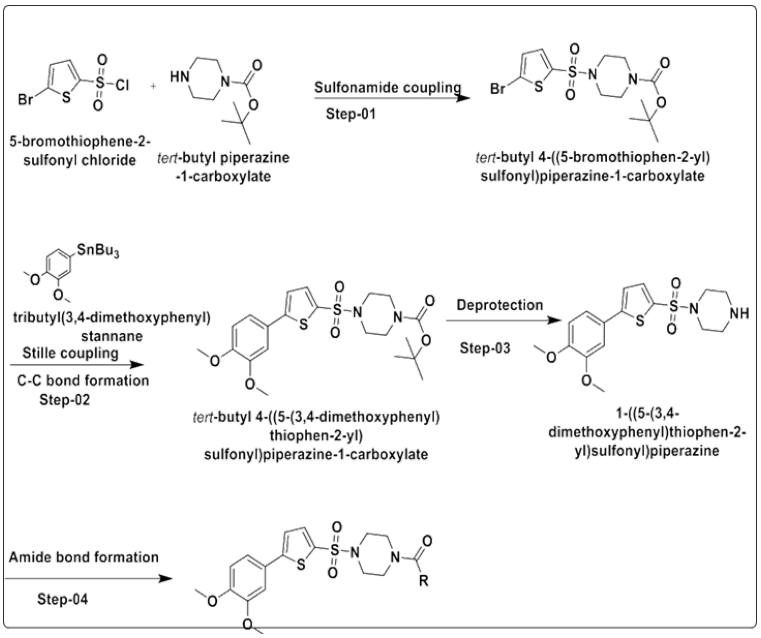
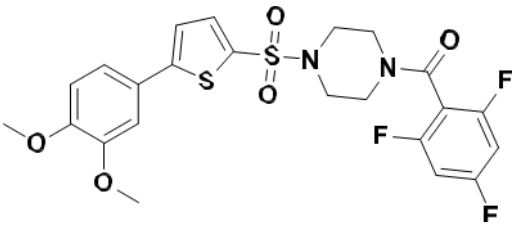


Figure 3. Plausible Synthetic scheme.

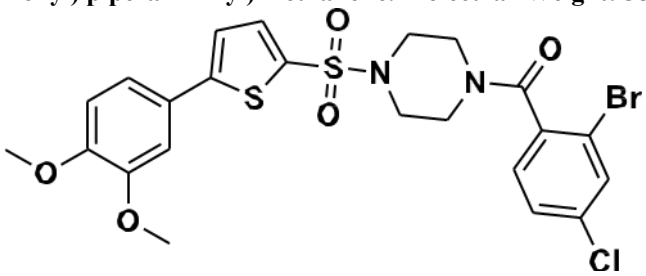
1.2.2 Library Synthesis-

2. **Step-04-T-01: Synthesis of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin- 1-yl) (2,4,6-trifluorophenyl) methanone. Molecular Weight: 526.55**



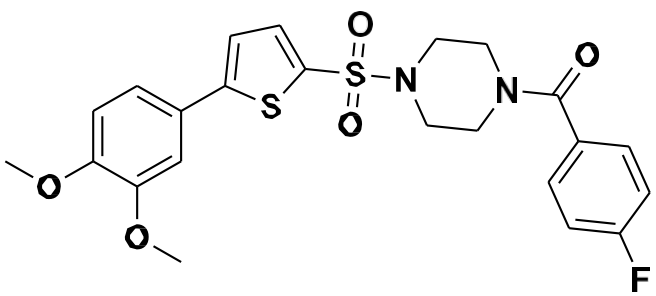
- To a stirred solution of 2,4,6-trifluorobenzoic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC.
- After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

3. **Step-04-T-02: Synthesis of (2-bromo-4-chlorophenyl) (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin-1-yl) methanone. Molecular Weight: 585.91**



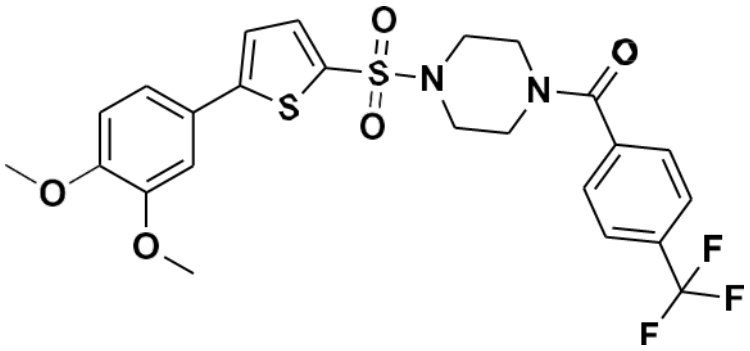
- To a stirred solution of 4-chlorobenzoic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5-(3,4-dimethoxyphenyl) thiophen- 2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC.
- After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

4. **Step-04-T-03: Synthesis of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin- 1-yl) (4-fluorophenyl) methanone. Molecular Weight: 490.56**



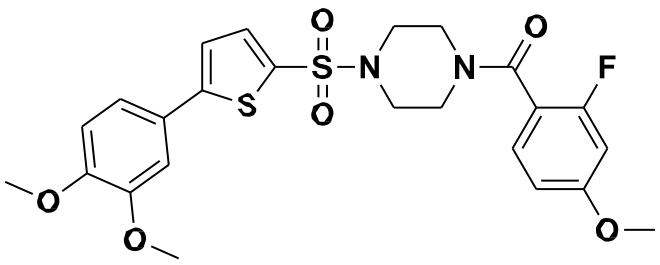
- To a stirred solution of 4-fluorobenzoic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5-(3,4-dimethoxyphenyl) thiophen- 2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC.
- After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

5. **Step-04-T-04: Synthesis of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin- 1-yl) (4-(trifluoromethyl) phenyl) methanone. Molecular Weight: 540.57**



- To a stirred solution of 4-(trifluoromethyl)benzoic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC.
- After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

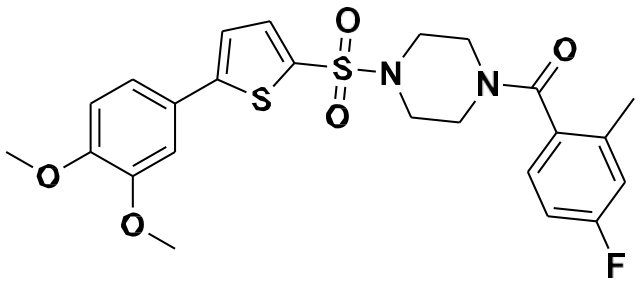
6. **Step-04-T-05: Synthesis of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin- 1-yl) (2-fluoro-4-methoxyphenyl) methanone. Molecular Weight: 520.59**



- To a stirred solution of 2-fluoro-4-methoxybenzoic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC.
- After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl

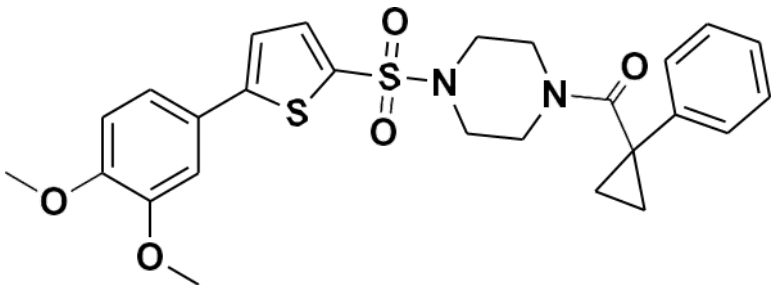
acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

7. **Step-04-T-06: Synthesis of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin- 1-yl)(4-fluoro-2-methylphenyl)methanone. Molecular Weight: 504.59**



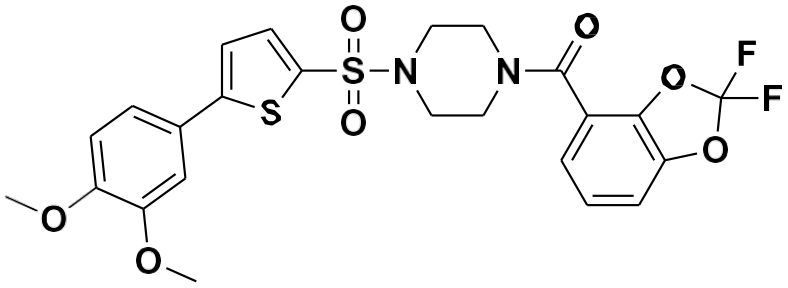
- To a stirred solution of 4-fluoro-2-methylbenzoic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC. After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

8. **Step-04-T-07: Synthesis of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin- 1-yl) (1-phenylcyclopropyl) methanone. Molecular Weight: 512.64**



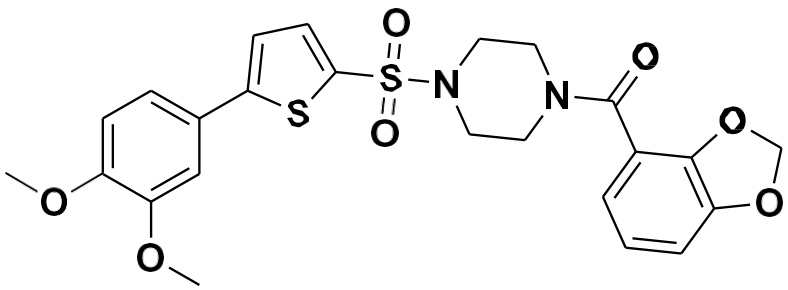
- To a stirred solution of 1-phenylcyclopropane-1-carboxylic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5-(3,4- dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC. After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

9. **Step-04-T-08: Synthesis of (2,2-difluorobenzo[d] [1,3] dioxol-4-yl) (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazin-1-yl) methanone. Molecular Weight: 552.56**



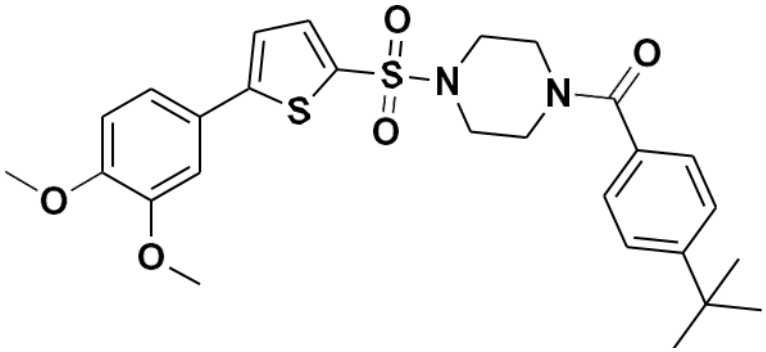
- To a stirred solution of 2,2-difluorobenzo[d][1,3]dioxole-4-carboxylic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5- (3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC.
- After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

10. Step-04-T-09: Synthesis of benzo[d][1,3] dioxol-4-yl(4-((5-(3,4-dimethoxyphenyl)thiophen-2-yl)sulfonyl)piperazin-1-yl)methanone.Molecular Weight: 516.58



- To a stirred solution of benzo[d][1,3]dioxole-4-carboxylic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of **1-((5-(3,4- dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine** (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC. After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

11. Step-04-T-10: Synthesis of (4-(tert-butyl) phenyl) (4-((5-(3,4-dimethoxyphenyl) thiophen-2- yl) sulfonyl) piperazin-1-yl) methanone. Molecular Weight: 528.68

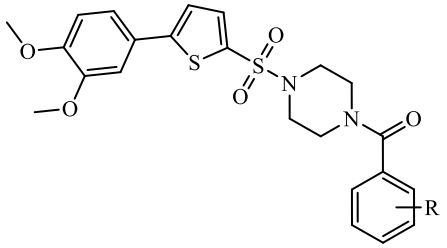


- To a stirred solution of 4-(tert-butyl)benzoic acid (1.0 eq) in DMF was added HATU (1.3 eq) DIPEA (3.0 eq) at 0°C, followed by addition of 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) sulfonyl) piperazine (1 eq).
- Then reaction mixture was stirred at rt for 16h.Progress of the reaction was monitored by TLC.
- After completion of starting material reaction mixture was poured on crushed ice and then extracted with ethyl acetate.
- The organic layer was dried over sodium sulfate and concentrated under vacuum to afford crude material which was purified by column chromatograph silica 100-200 mesh using 60 to 80% ethyl acetate in hexane as an eluent.
- Dry it and then submitted for final analysis.

3. RESULT-

3.1 Lead discovery from library

Designing Compound: The best heterocyclic compound from the literature survey



Based on a comprehensive literature survey that highlighted the pharmacological potential of piperazine and thiophene derivatives as anticancer agents, a novel compound was designed integrating both these moieties. This concept seeks to utilize the structural characteristics and biological functions of piperazine and thiophene, acknowledged for their electrical qualities and stability. The selection of substituents, especially the variable R on the benzene ring, enables the customization of the molecule's physicochemical features to improve its interaction with malignant cells. The molecule is posited to provide improved anticancer efficacy by harnessing the synergy between these two heterocycles, thereby providing a novel therapeutic strategy against diverse cancer types. This novel molecular structure highlights the significance of interdisciplinary expertise in pharmacological design, offering a focused method in cancer therapy options. All synthesized derivatives of 4-((5-(3,4-dimethoxyphenyl)thiophen-2-yl)sulfonyl)piperazin-1-yl)(substituted-phenyl)methanone, designated as Test_2 to Test_72, were deemed unique upon investigation by Scifinder.

3.2 Physiochemical Properties

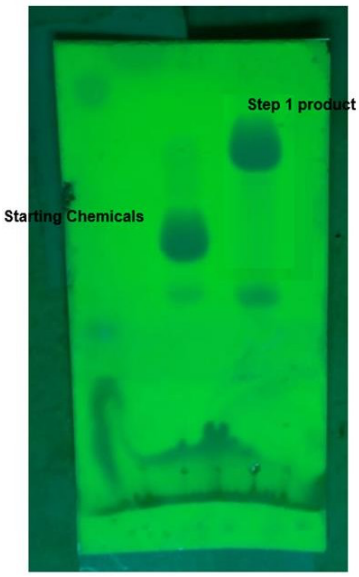


Figure 4. TLC plate showing step 1

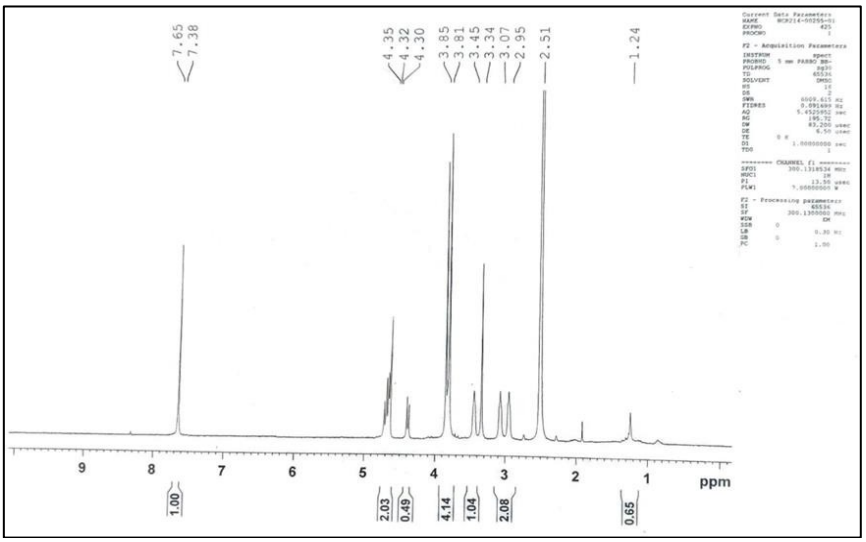


Figure 5. 1H NMR spectra of tert-butyl 4-((5-bromothiophen-2-yl) 96rapheme96) piperazine-1-carboxylate.

1H NMR: δ 1.24 (2H, ddd, J = 14.4, 6.8, 6.5 Hz), 3.11-3.31 (3H, 3.17 (dd, J = 3.5, 2.7 Hz), 3.07 (dd, J = 3.5, 2.7 Hz), 3.34 (dd, J = 3.5, 2.7 Hz)), 3.45 (dt, J = 10.2, 3.5 Hz), 3.81 (td, J = 4.6, 2.7 Hz), 3.85 (2H, d, J = 4.5 Hz), 4.30 (2H, d, J = 4.6 Hz), 4.32 (1H, d, J = 2.7 Hz), 4.35 (1H, d, J = 2.7 Hz), 6.74 (1H, dd, J = 8.4, 0.5 Hz), 7.38 (1H, dd, J = 1.8, 0.5 Hz), 7.65 (1H, dd, J = 8.4, 1.8 Hz).

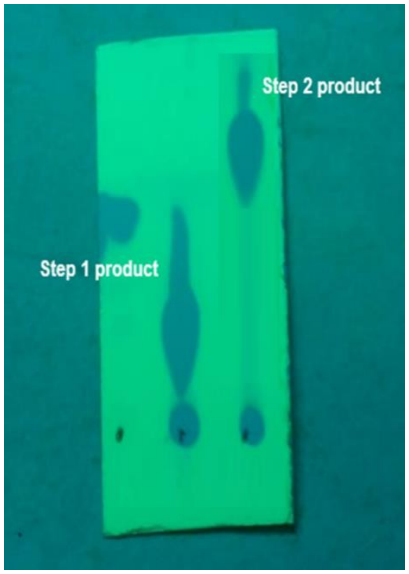


Figure 6. TLC plate showing step 2 product is formed

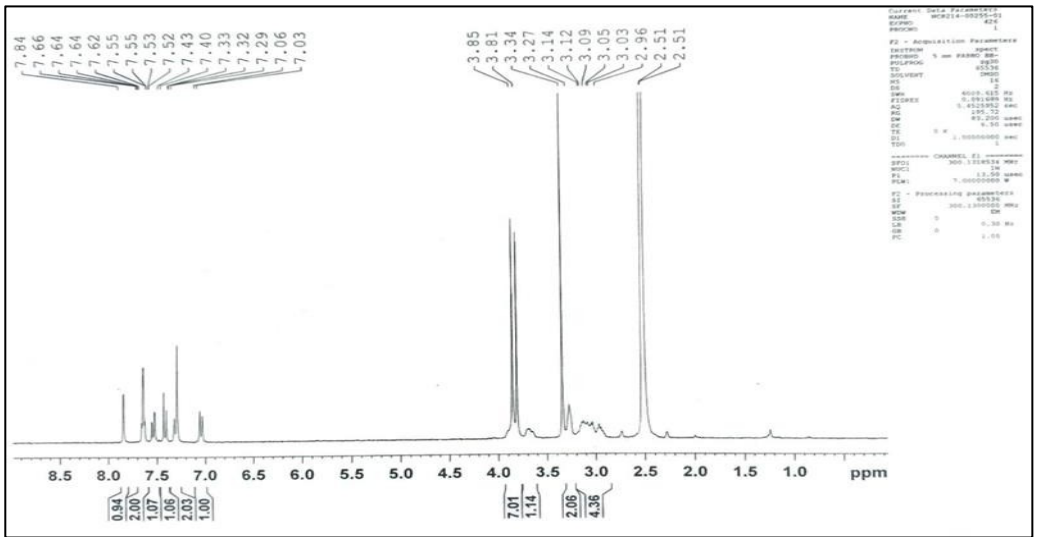


Figure 7. 1H NMR spectra of tert-butyl 4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 97rapheme97) piperazine-1-carboxylate.

1H NMR: δ 2.51 (9H, s), 3.03-3.85 (11H, 3.57 (ddd, J = 15.6, 7.0, 2.9 Hz), 3.81 (ddd, J = 14.7, 7.0, 2.9 Hz), 3.66 (s)), 3.85 (3H, s), 7.03 (1H, dd, J = 8.9, 0.5 Hz), 7.03-7.84 (3H, 7.35 (dd, J = 1.7, 0.5 Hz), 7.55 (dd, J = 8.9, 1.7 Hz), 7.62 (d, J = 8.8 Hz)), 7.64 (1H, d, J = 8.8 Hz).

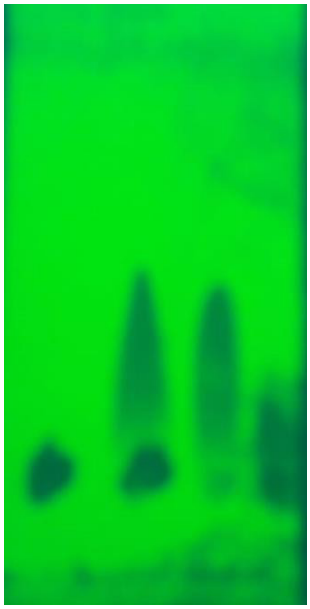


Figure 8. TLC plate indicating the step 3 product is formed.

3.3 Characterization of synthesized derivatives

Table 2- Characterization of synthesized derivatives

Compound Number	IUPAC Name	Molecular Formula	Molecular Weight	Description of compound	% yield of compound
S1	(4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 98rapheme98) 98rapheme9898-1-yl) (2,4,6-trifluorophenyl) methanone.	$C_{23}H_{21}F_3N_2O_5S_2$	527.00	colorless or pale	50% to 80%

S2	(2-bromo-4- chlorophenyl) (4-((5- (3,4 dimethoxyphenyl) thiophen-2-yl 98rapheme98) 98rapheme9898-1-yl) methanone.	$C_{23}H_{22}BrClN_2O_5S_2$	586.9	light yellow to pale brown	50% to 80%
S3	(4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 98rapheme98) 98rapheme9898-1-yl) (4-fluorophenyl) methanone	$C_{23}H_{23}FN_2O_5S_2$	491.0	light yellow or pale	50% to 80%
S4	(4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 99rapheme99) 99rapheme9999-1-yl) (4-(trifluoromethyl) phenyl) methanone	$C_{24}H_{24}F_3N_2O_5S_2$	541.0	Pale yellow	50% to 80%
S5	(4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 99rapheme99) 99rapheme9999-1-yl) (2-fluoro-4- methoxyphenyl) methanone	$C_{24}H_{25}FN_2O_6S_2$	521.0	colorless or light yellow	50% to 80%

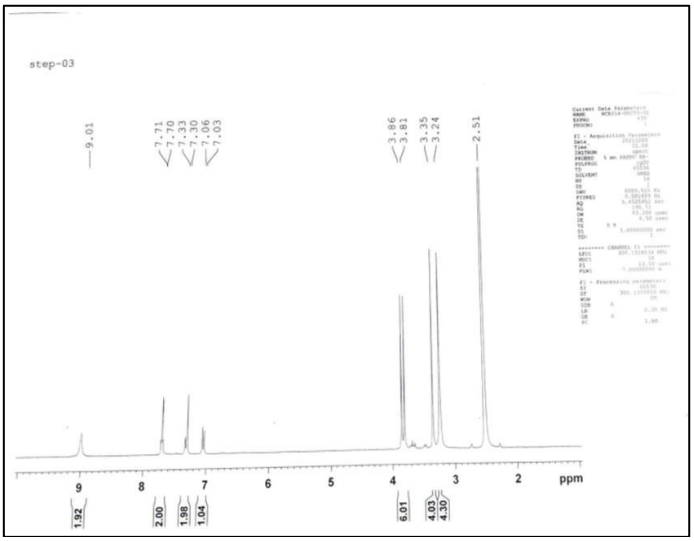


Figure 9. NMR spectrum of 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 101rapheme101) piperazine.

1H NMR: **δ** 2.51 (s, H), 3.24, 3.35 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 7.06, 7.33 (d, Ar-H), 7.71 (m, Ar-H), 9.01 (s, 1H, NH).

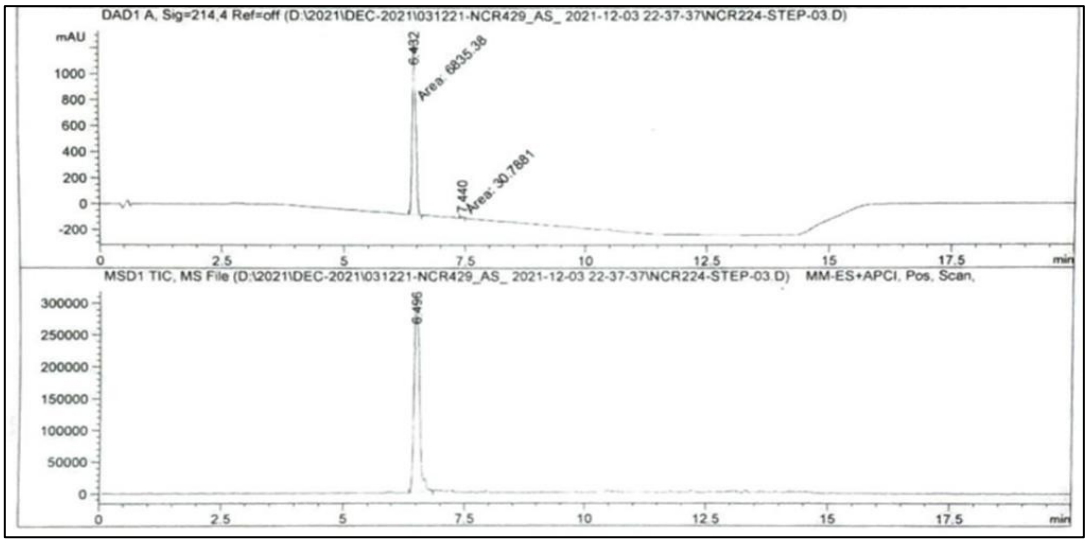
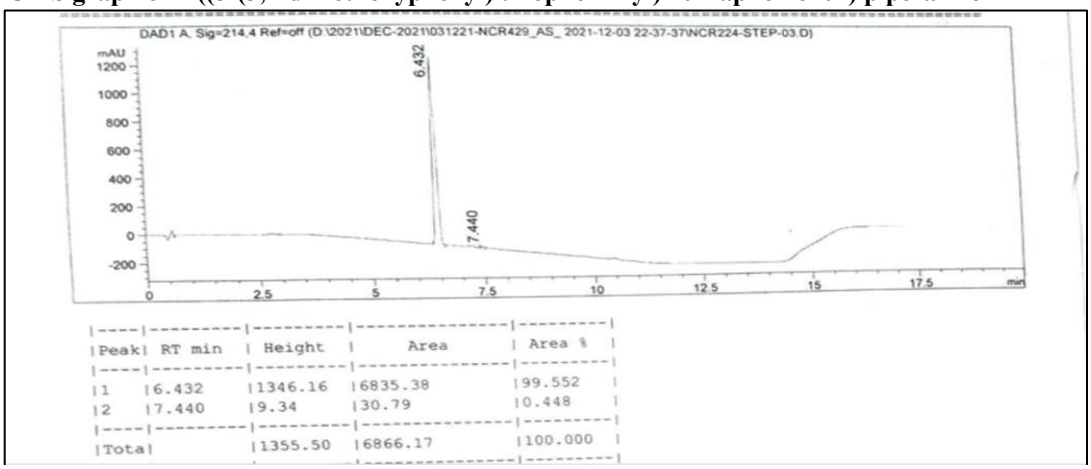


Figure 10. LCMS graph of 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 101rapheme101) piperazine



Peak	RT min	Height	Area	Area %
1	6.432	1346.16	6835.38	99.552
2	7.440	9.34	30.79	0.448
Total		1355.50	6866.17	100.000

Figure 11. HPLC graph of 1-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 102rapheme102) piperazine

3.4 NMR spectra of synthesized compound S1 to S10

- **Compound S1: 1H NMR: δ** 1. 24 (t, 5H, CH_2CH_3), 2.51, 2.95, 3.07 (s, 2H, CH_2), 3.34 (s, H), 3.45, 3.81, 3.85 (s, 2H, CH_2), 7.06, 7.32, 7.65 (d, Ar-H).

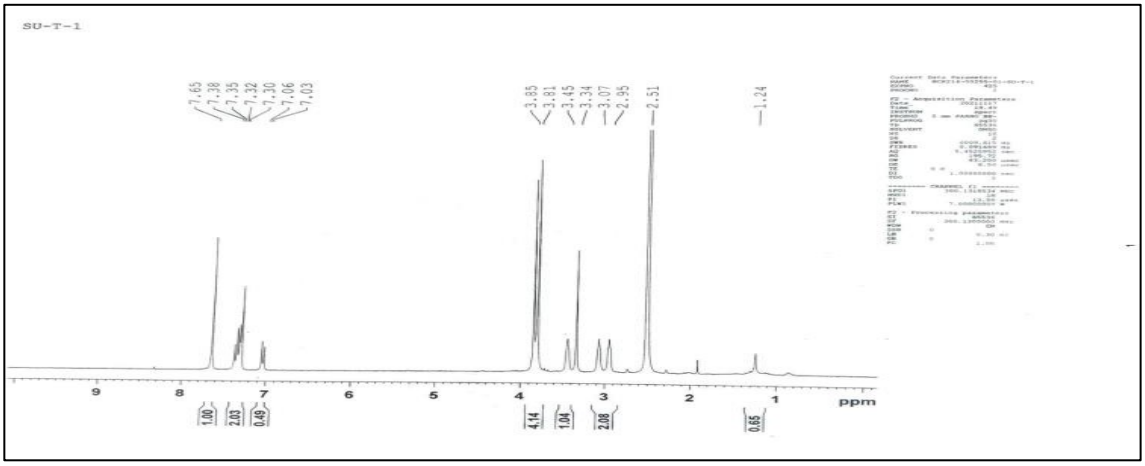


Figure 12. Graph S1. NMR spectrum of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl)102rapheme102) 102rapheme102102-1-yl) (2,4,6-trifluorophenyl) methanone.

- **Compound S2: 1H NMR: δ** 2.51, 2.96, 3.05, 3.14, 3.27, 3.34, 3.85 (s, 2H, CH2), 7.06, 7.29, 7.32, 7.43, 7.53, 7.64, 7.84 (d, Ar-H).

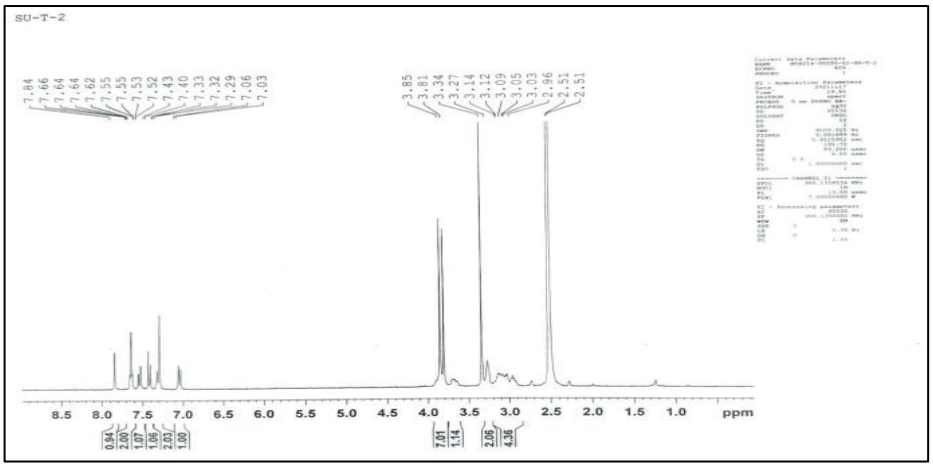


Figure 13. Graph S2. NMR spectrum of (2-bromo-4-chlorophenyl) (4-((5-(3,4- dimethoxyphenyl) thiophen-2-yl) 103rapheme103) 103rapheme103103-1-yl) methanone.

- **Compound S3: 1H NMR: δ** 2.51, 3.07, 3.35, 3.85 (s, 2H, CH_2), 7.06, 7.25, 7.32, 7.46, 7.63 (d, Ar-H).

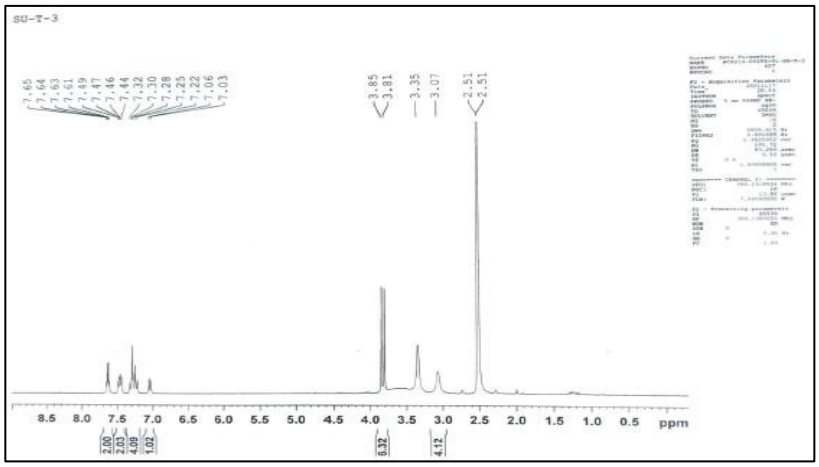


Figure 14. Graph S3. NMR spectrum of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) rapheme104) 104rapheme104104-1-yl) (4-fluorophenyl) methanone.

- **Compound S4: 1H NMR: δ** 2.51 (s, 2H, CH_2), 3.03, 3.13, 3.34, 3.42 (d, 2H, CH_2), 3.85 (s, 3H, OCH_3), 7.06, 7.32, 7.63, 7.78, 7.81 (d, Ar-H).

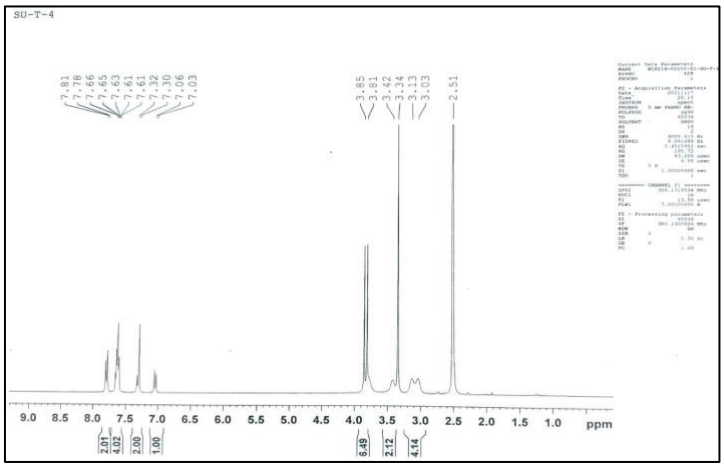


Figure 15. Graph S4. NMR spectrum of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 104rapheme104) 104rapheme104104-1-yl) (4-(trifluoromethyl) phenyl) methanone.

- **Compound S5: 1H NMR: δ** 2.51 (s, 2H, CH_2), 2.89, 2.98, 3.08, 3.28, 3.34 (d, 2H, CH_2), 3.79, 3.85 (s, 3H, OCH_3), 6.87, 7.06, 7.14 (d, Ar-H), 7.25 (m, Ar-H), 7.32, 7.64, 7.96 (d, Ar-H).

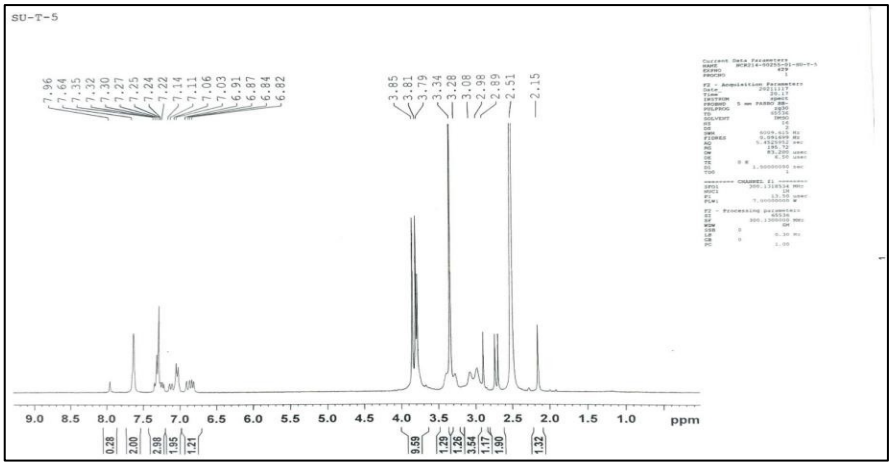


Figure 16. Graph S5. NMR spectrum of (4-((5-(3,4-dimethoxyphenyl)

thiophen-2-yl) rapheme) rapheme-1-yl) (2-fluoro-4-methoxyphenyl) methanone

- **Compound S6: 1H NMR: δ** 2.51 (s, 2H, CH_2), 2.69, 2.89, 2.98, 3.28, 3.34 (d, 2H, CH_2), 3.85 (s, 3H, OCH_3), 7.06, 7.12, 7.25, 7.32, 7.63 (d, Ar-H).

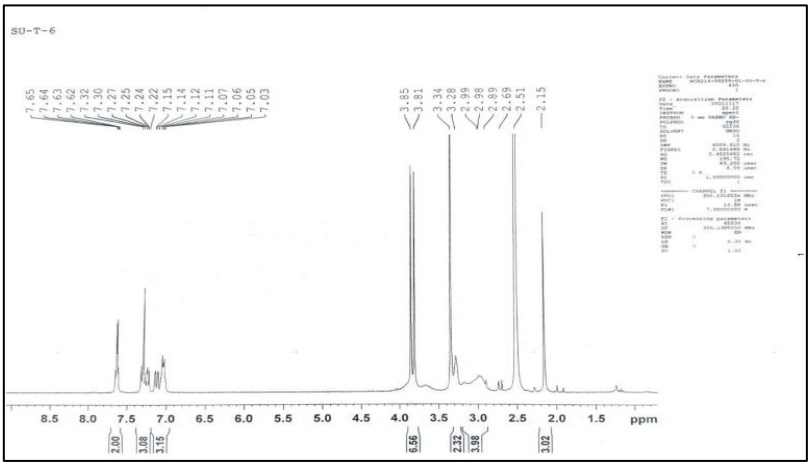


Figure 17. Graph S6. NMR spectrum of (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) rapheme) rapheme-1-yl)(4-fluoro-2 methylphenyl)methanone.

- **Compound S7: 1H NMR: δ** 1.13 (t, 3H, CH_3), 1.25 (d, 2H, CH_2), 2.51, 2.89, 3.34 (d, 2H, CH_2), 3.58, 3.87 (s, 3H, OCH_3), 7.08, 7.17, 7.20 (d, Ar-H), 7.33 (m, Ar-H), 7.53, 7.64 (d, Ar-H).

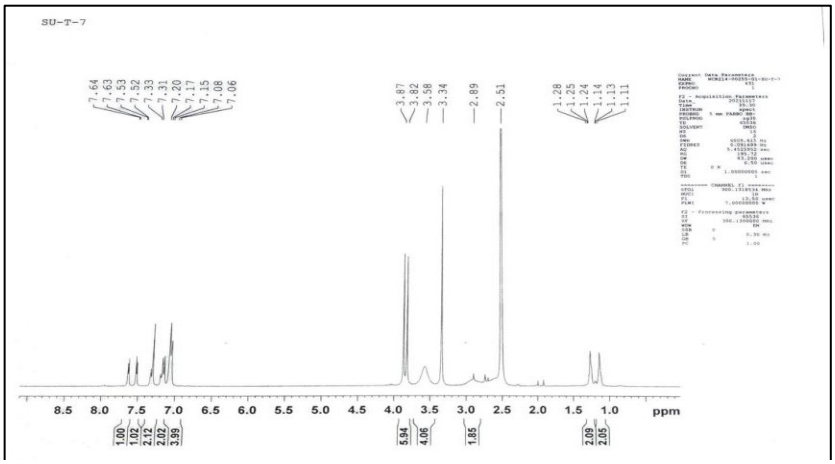


Figure 18. Graph S7. NMR spectrum of (4-((5-(3,4-dimethoxyphenyl) thiophen-2- yl) rapheme) rapheme-1-yl) (1-phenylcyclopropyl) methanone

- **Compound S8: 1H NMR: δ** 2.51 (s, 2H, CH_2), 3.03, 3.12, 3.34, 3.49 (d, 2H, CH_2), 3.81 (s, 3H, OCH_3), 7.06, 7.27, 7.31, 7.49, 7.51, 7.64 (d, Ar-H).

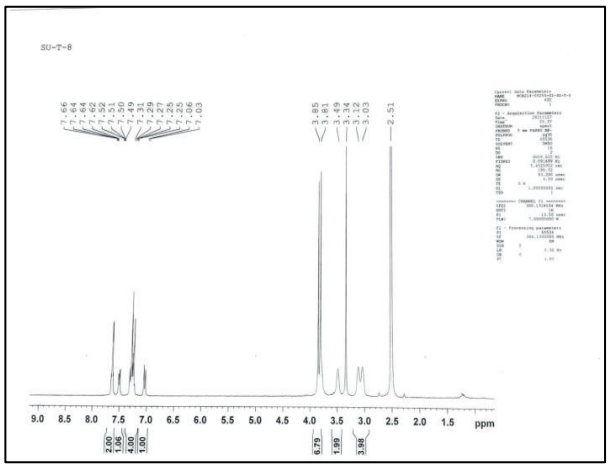


Figure 19. Graph S8. NMR spectrum of (2,2-difluorobenzo[d] [1,3] dioxol-4-yl) (4-((5-(3,4-dimethoxyphenyl) thiophen-2-yl) 106rapheme)rapheme-1-yl) methanone.

- **Compound S9: 1H NMR: δ** 1.91, 2.51 (s, 2H, CH_2), 3.03, 3.34, 3.47 (d, 2H, CH_2), 3.75, 3.85 (s, 3H, OCH_3), 6.03 (s, 1H, CH), 6.85, 6.99, 7.03, 7.32, 7.64 (d, Ar-H).

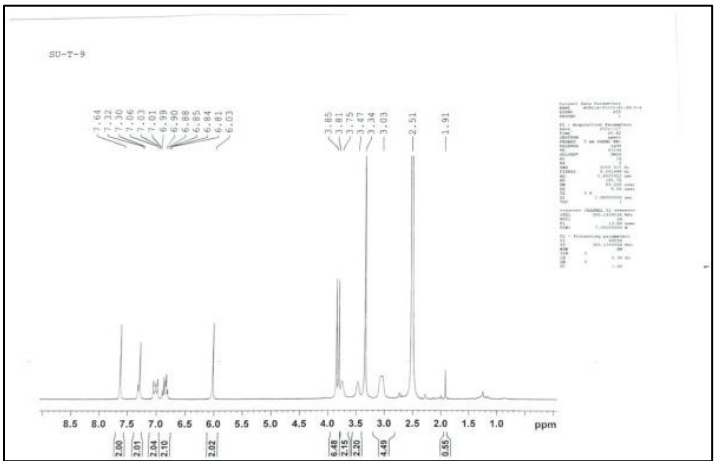


Figure 20. Graph S9. NMR spectrum of benzo[d][1,3] dioxol-4-yl(4-((5-(3,4-dimethoxyphenyl)thiophen-2-yl)rapheme)rapheme-1-yl)methanone.

- **Compound S10: 1H NMR: δ** 1.28 (t, 3H, CH_3), 2.51 (s, 2H, CH_2), 3.05, 3.34 (d, 2H, CH_2), 3.85 (s, 3H, OCH_3), 7.06, 7.33, 7.45, 7.62 (d, Ar-H).

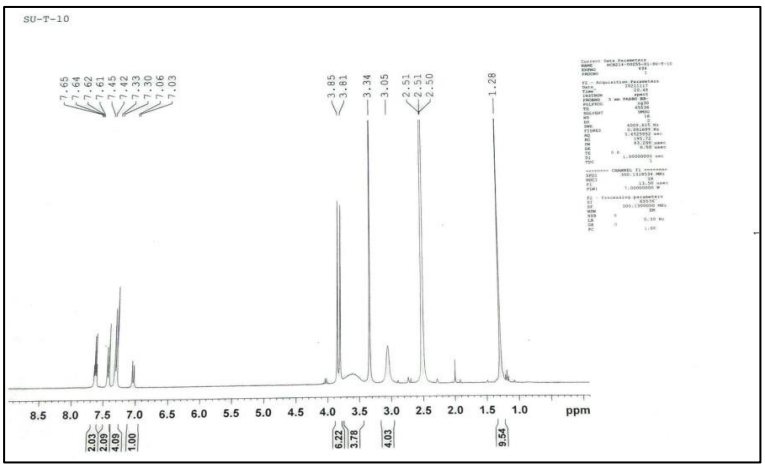
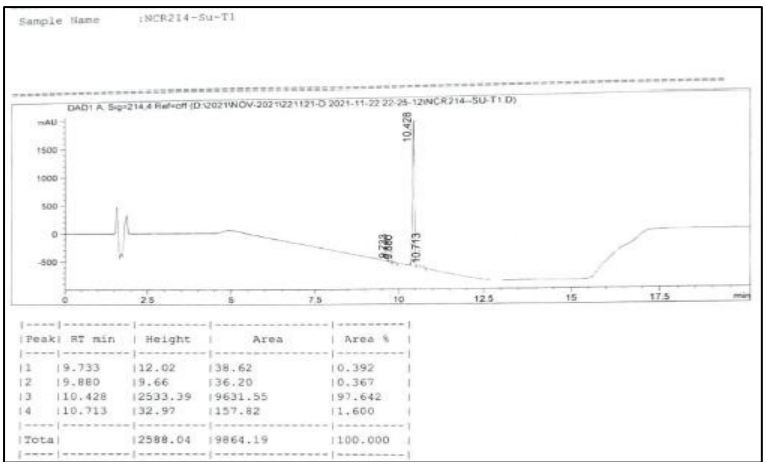


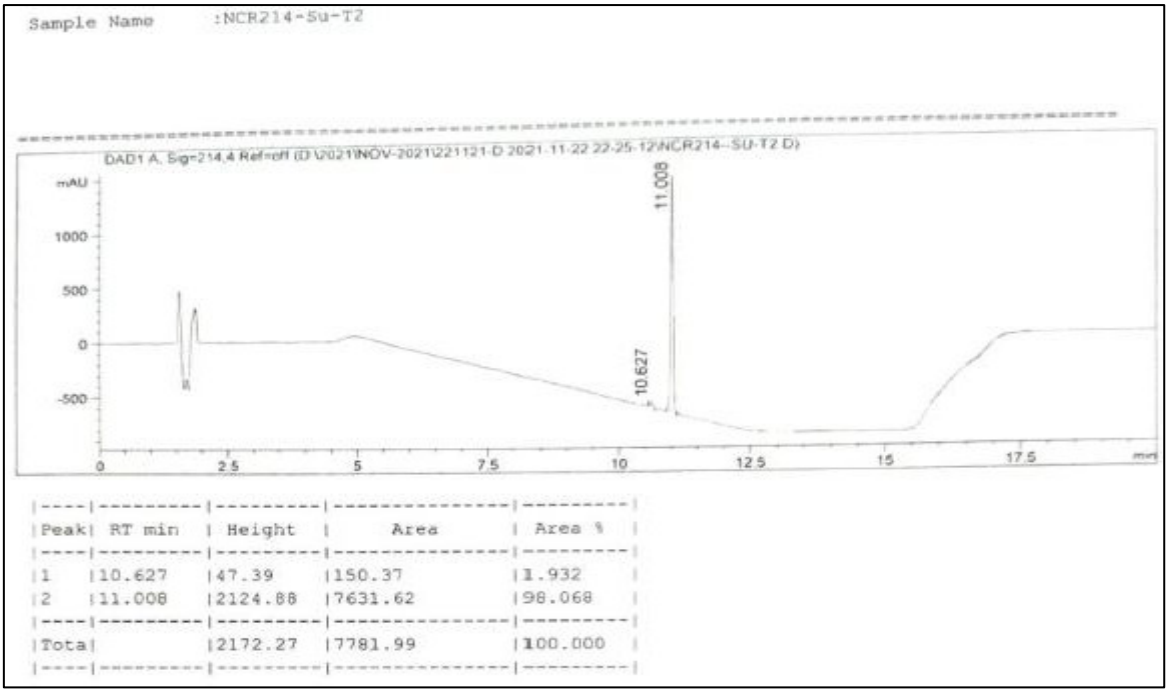
Figure 21. Graph S10. NMR spectrum of (4-(tert-butyl) phenyl) (4-((5-(3,4- dimethoxyphenyl) thiophen-2-yl) rapheme) rapheme-1-yl) methanone.

3.5 HPLC graphs of synthesized compound S1 to S10



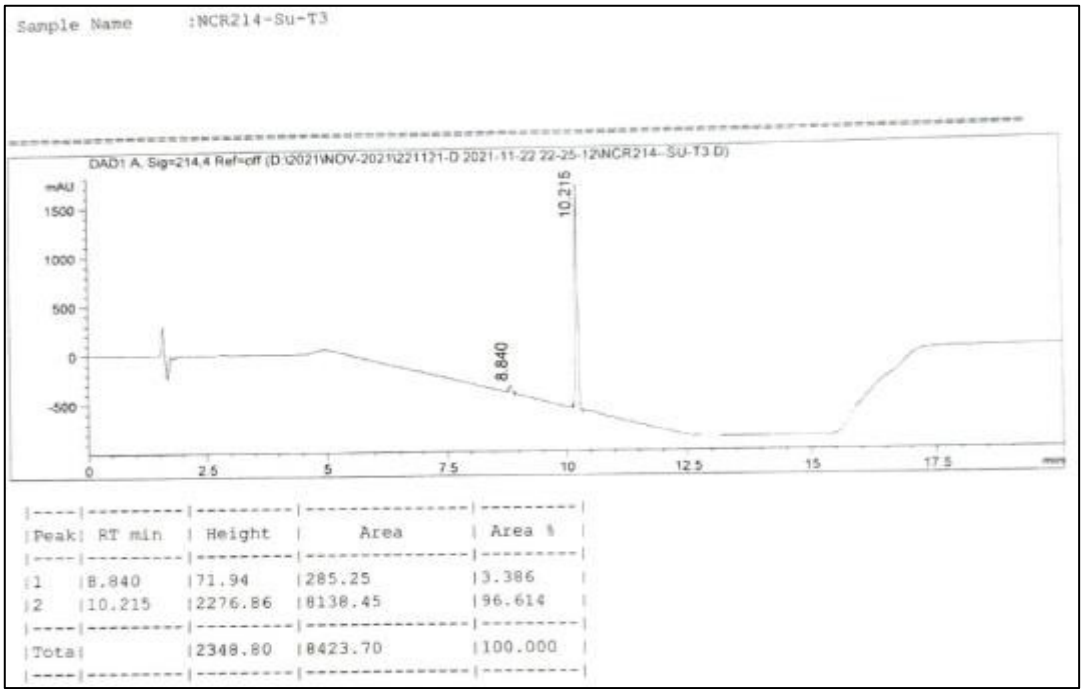
Peak	RT min	Height	Area	Area %
1	9.733	12.02	38.62	0.392
2	9.880	9.66	36.20	0.367
3	10.428	2533.39	9631.55	97.642
4	10.713	32.97	157.82	1.600
Tota		2588.04	9864.19	100.000

Figure 22. Compound S1



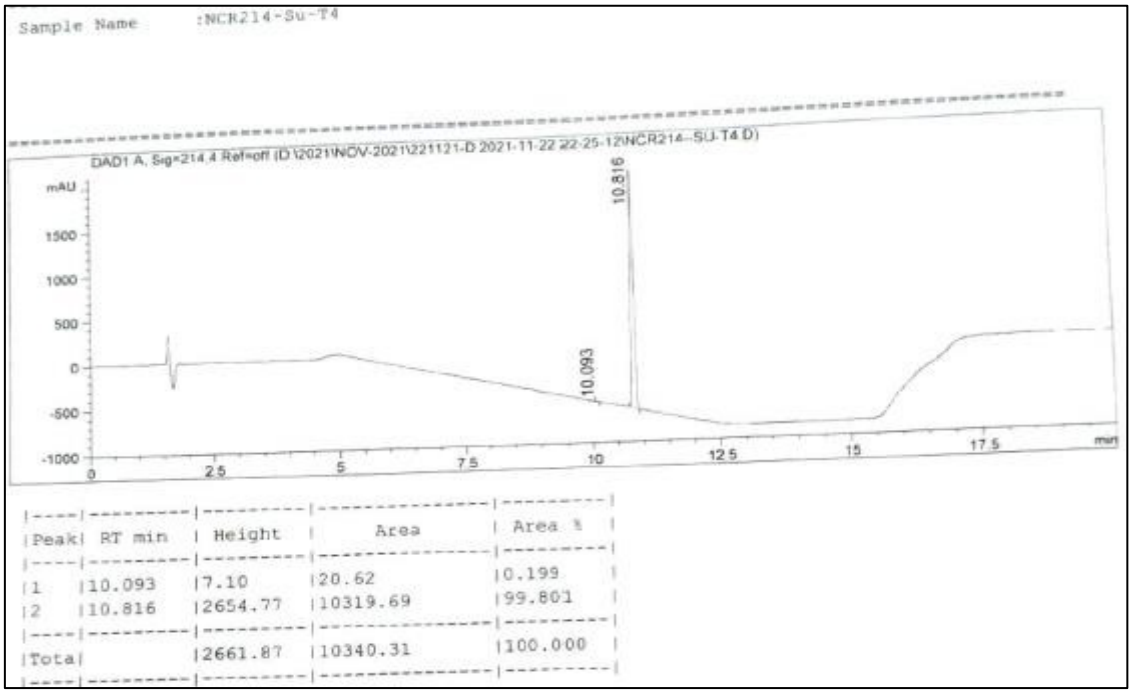
Peak	RT min	Height	Area	Area %
1	10.627	47.39	150.37	1.932
2	11.008	2124.88	7631.62	98.068
Tota		2172.27	7781.99	100.000

Figure 23. Compound S2



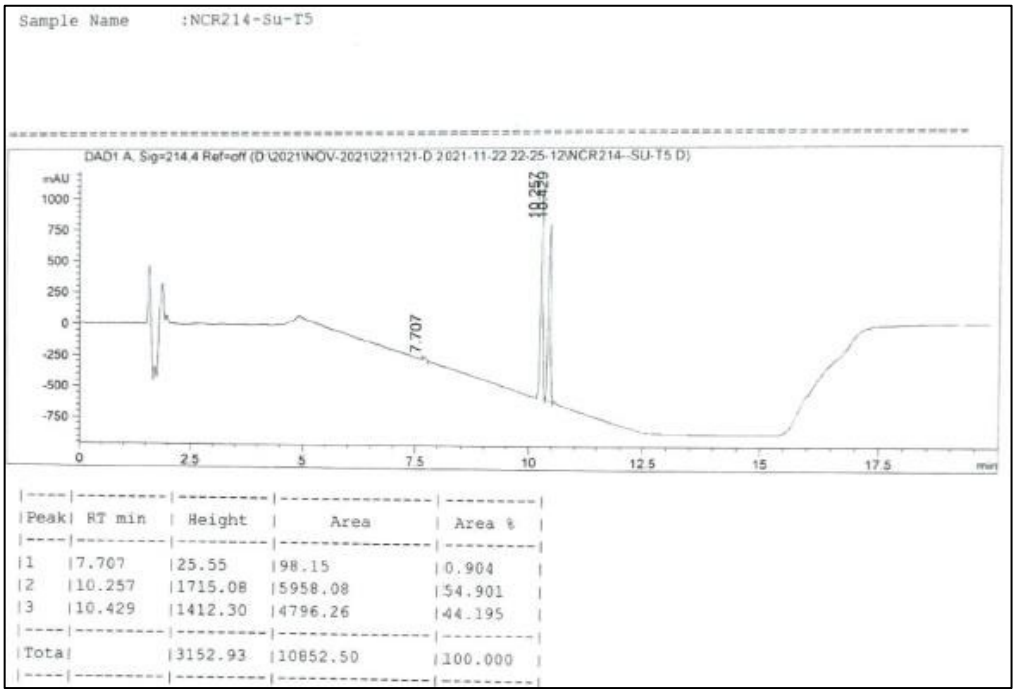
Peak	RT min	Height	Area	Area %
1	8.840	71.94	285.25	3.386
2	10.215	2276.86	8138.45	96.614
Tota		2348.80	8423.70	100.000

Figure 24. Compound S3



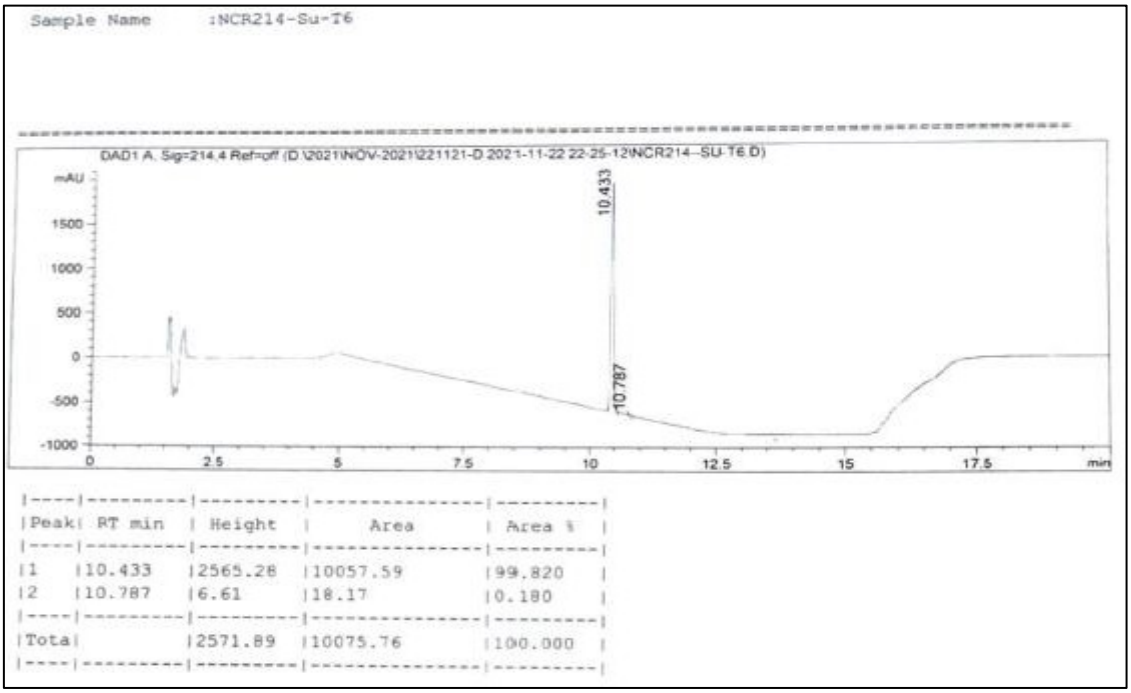
Peak	RT min	Height	Area	Area %
1	10.093	7.10	20.62	0.199
2	10.816	2654.77	10319.69	99.801
Tota		2661.87	10340.31	100.000

Figure 25. Compound S4



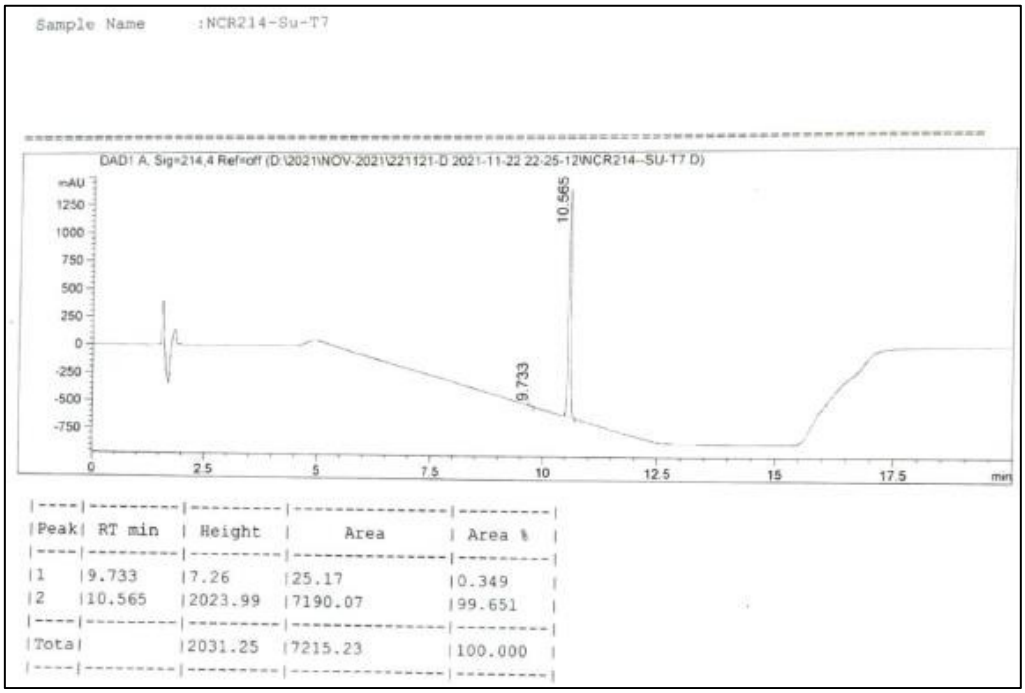
Peak	RT min	Height	Area	Area %
1	7.707	25.55	98.15	0.904
2	10.257	1715.08	5958.08	54.901
3	10.429	1412.30	4796.26	44.195
Tota		3152.93	10852.50	100.000

Figure 26. Compound S5



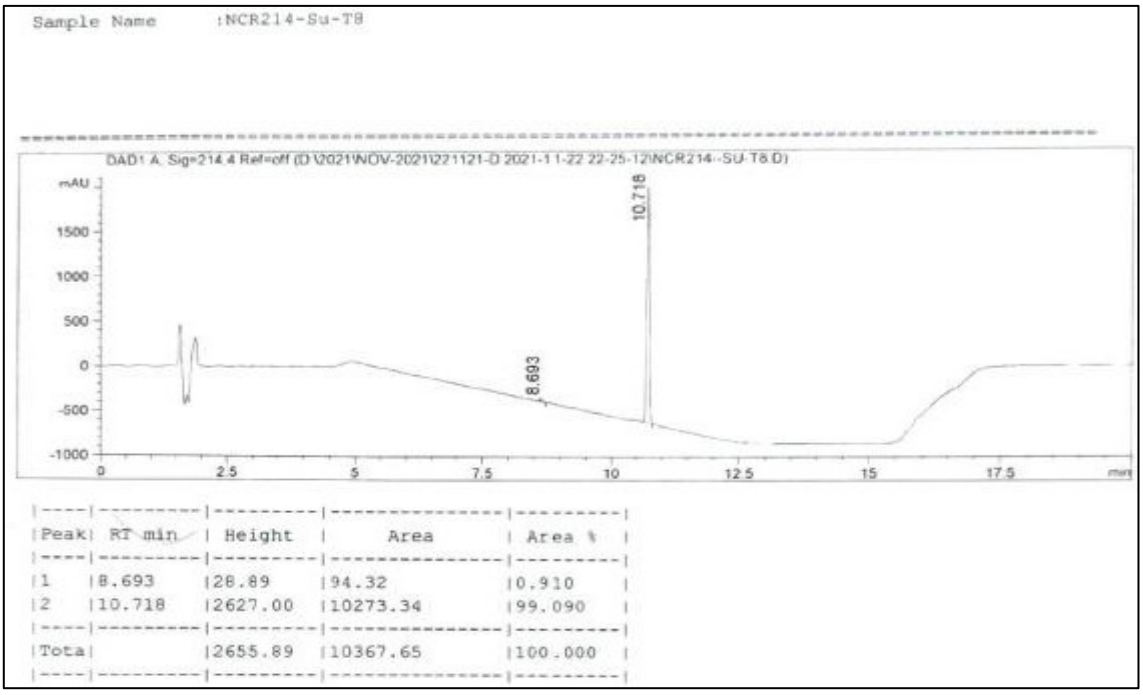
Peak	RT min	Height	Area	Area %
1	10.433	2565.28	10057.59	99.820
2	10.787	6.61	18.17	0.180
Tota		2571.89	10075.76	100.000

Figure 27. Compound S6



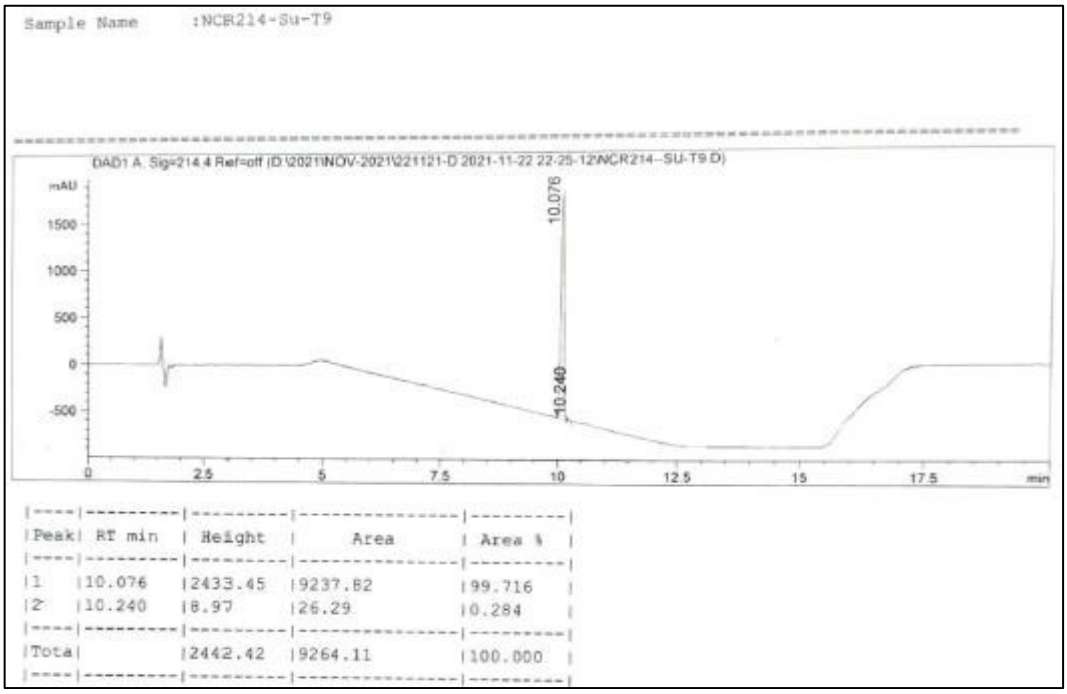
Peak	RT min	Height	Area	Area %
1	9.733	7.26	25.17	0.349
2	10.565	2023.99	7190.07	99.651
Tota		2031.25	7215.23	100.000

Figure 28. Compound S7



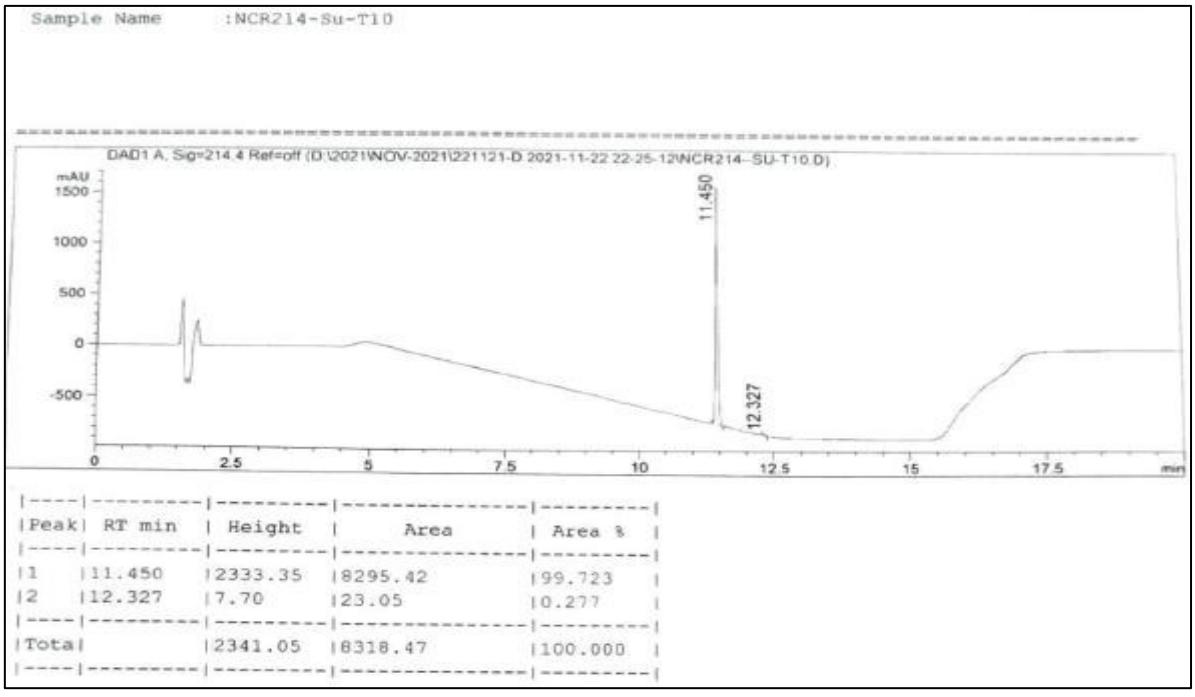
Peak	RT min	Height	Area	Area %
1	8.693	28.89	94.32	0.910
2	10.718	2627.00	10273.34	99.090
Tota		2655.89	10367.65	100.000

Figure 29. Compound S8



Peak	RT min	Height	Area	Area %
1	10.076	2433.45	9237.82	99.716
2	10.240	8.97	26.29	0.284
Tota		2442.42	9264.11	100.000

Figure 30. Compound S9



Peak	RT min	Height	Area	Area %
1	11.450	2333.35	8295.42	99.723
2	12.327	7.70	23.05	0.277
Tota		2341.05	8318.47	100.000

Figure 31. Compound S10

3.6 LCMS graphs of synthesized Compound S1 to S10

- **Compound S1:** The LC MS showed a molecular ion peak at m/z 527.00 (M] + and was in match with the proposed structure with C23H21F3N2O5S2.

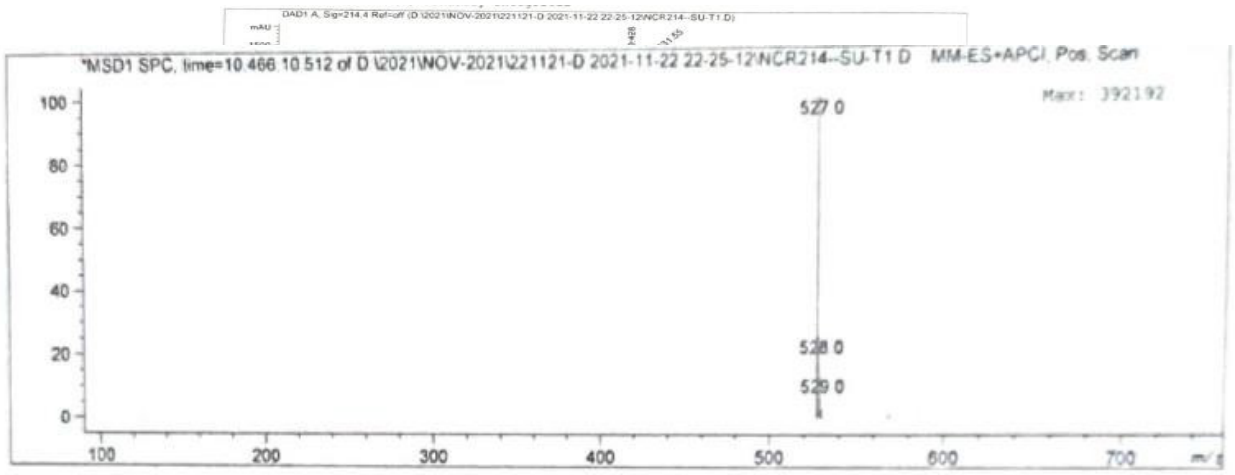
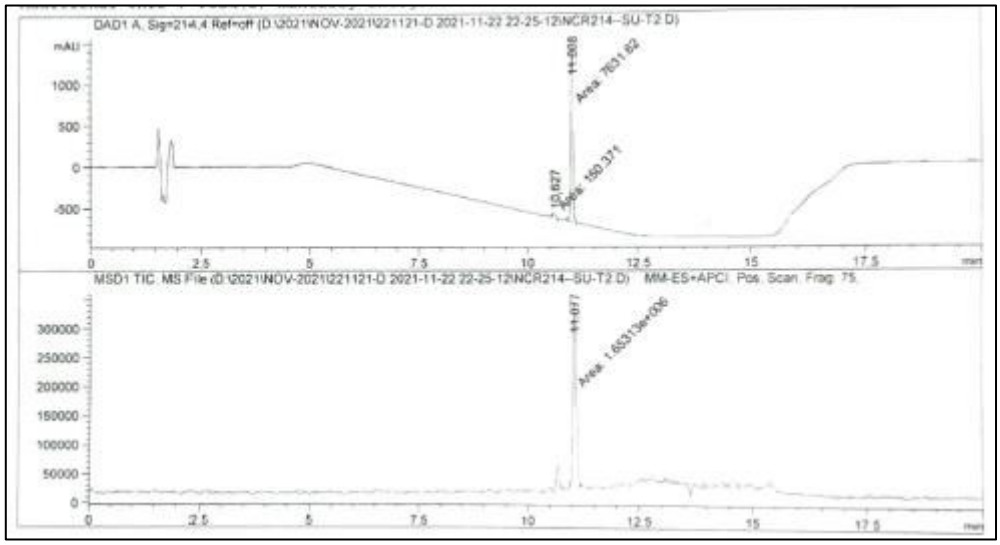


Figure 32. Compound S1

- **Compound S2:** The LC MS showed a molecular ion peak at m/z 586.9 (M] + and was in match with the proposed structure with C23H22BrClN2O5S2.



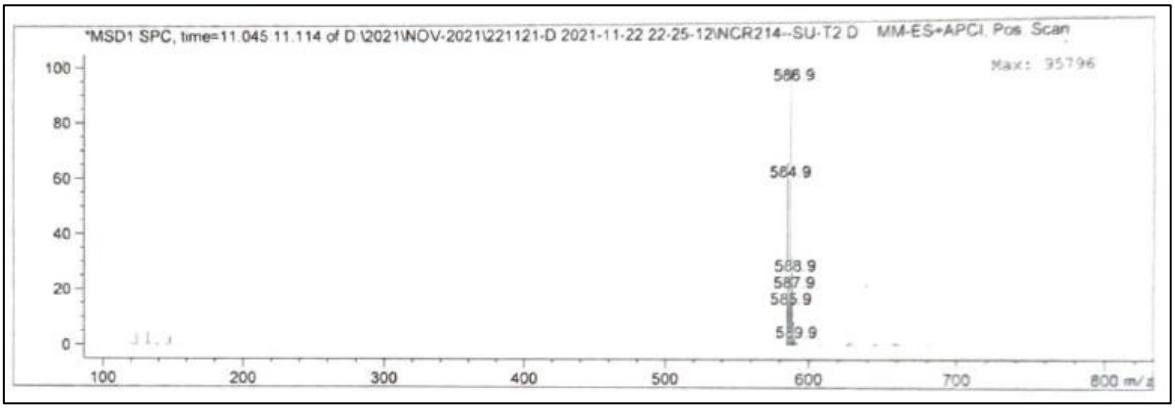
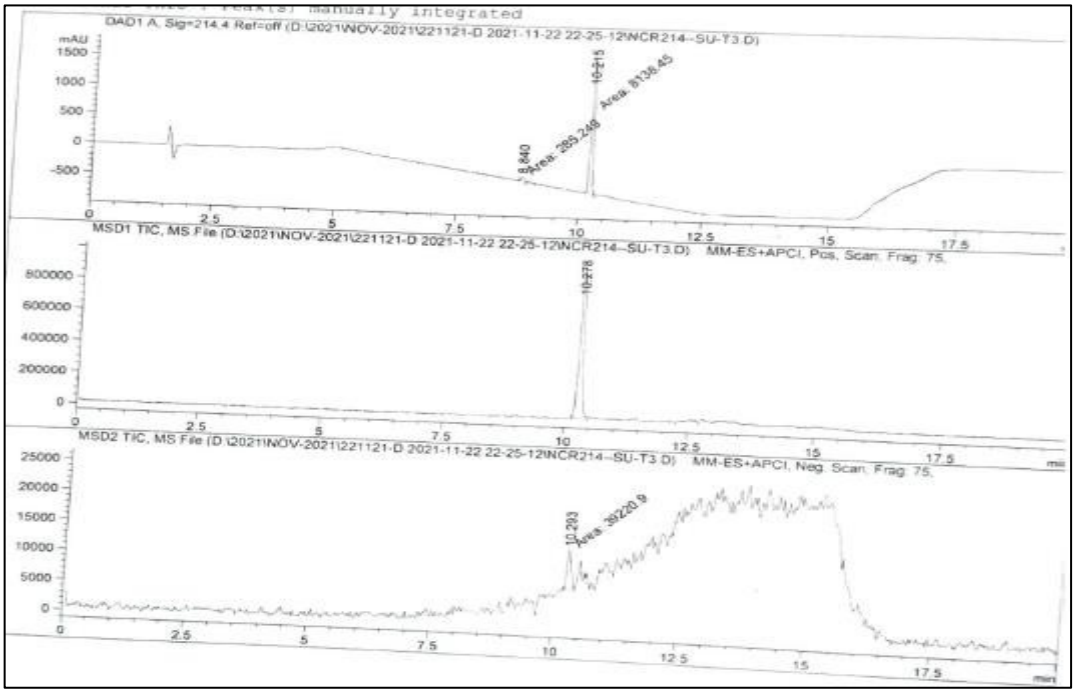


Figure 33. Compound S2

- **Compound S3:** The LC MS showed a molecular ion peak at m/z 491.0 (M] + and was in match with the proposed structure with C23H23FN2O5S2.



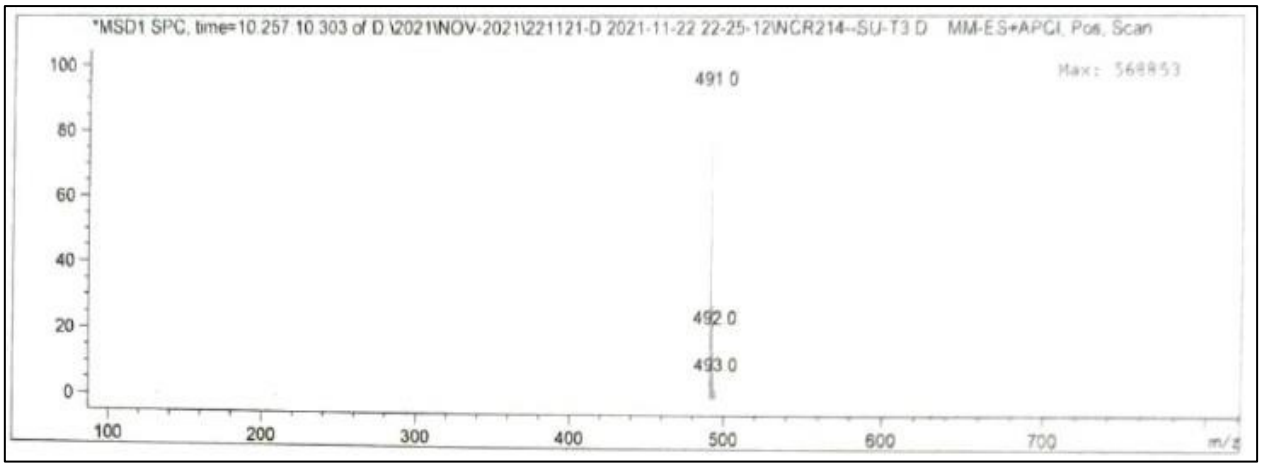
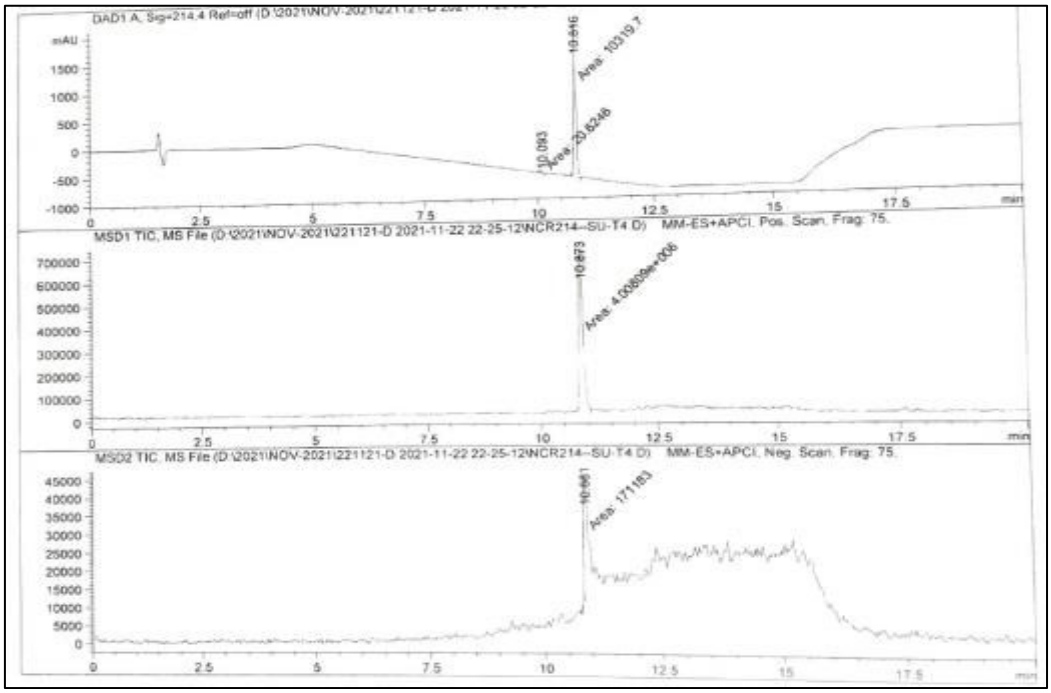


Figure 34. Compound S3

- **Compound S4:** The LC MS showed a molecular ion peak at m/z 541.0 (M] + and was in match with the proposed structure with C24H24F3N2O5S2.



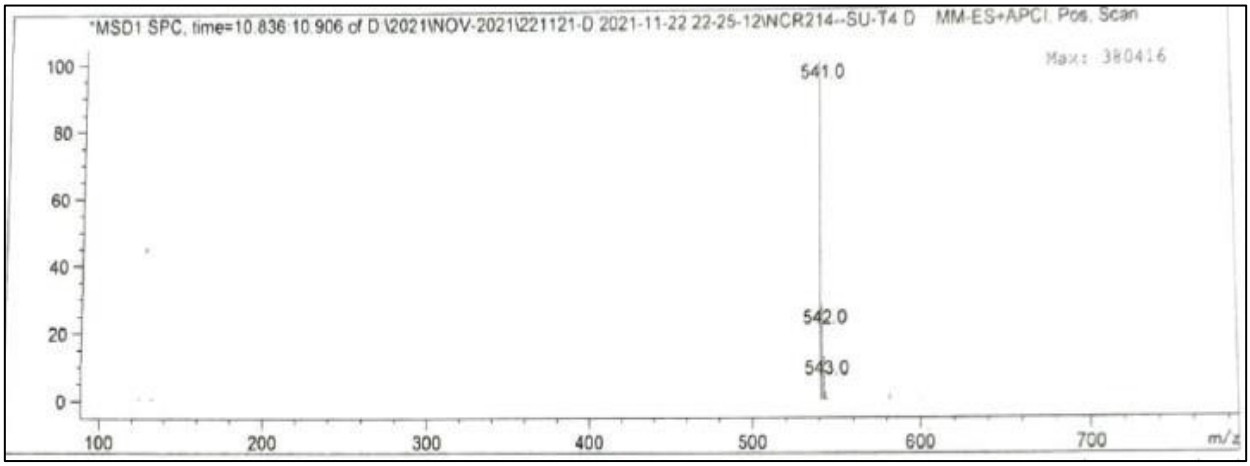
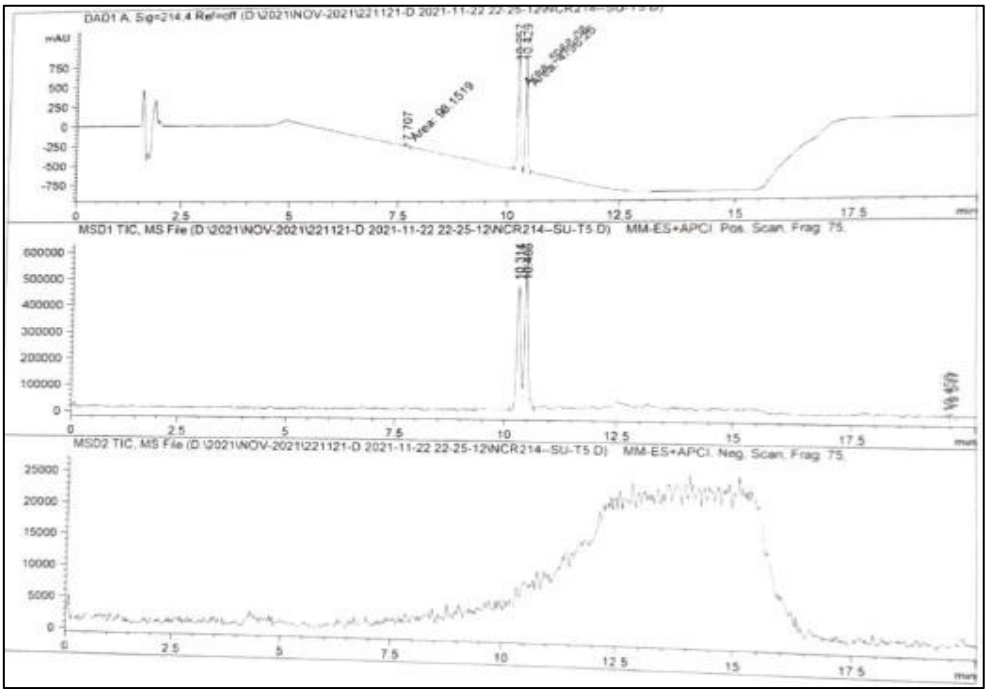


Figure 35. Compound S4

- **Compound S5:** The LC MS showed a molecular ion peak at m/z 521.0 (M] + and was in match with the proposed structure with $C_{24}H_{25}FN_2O_6S_2$.



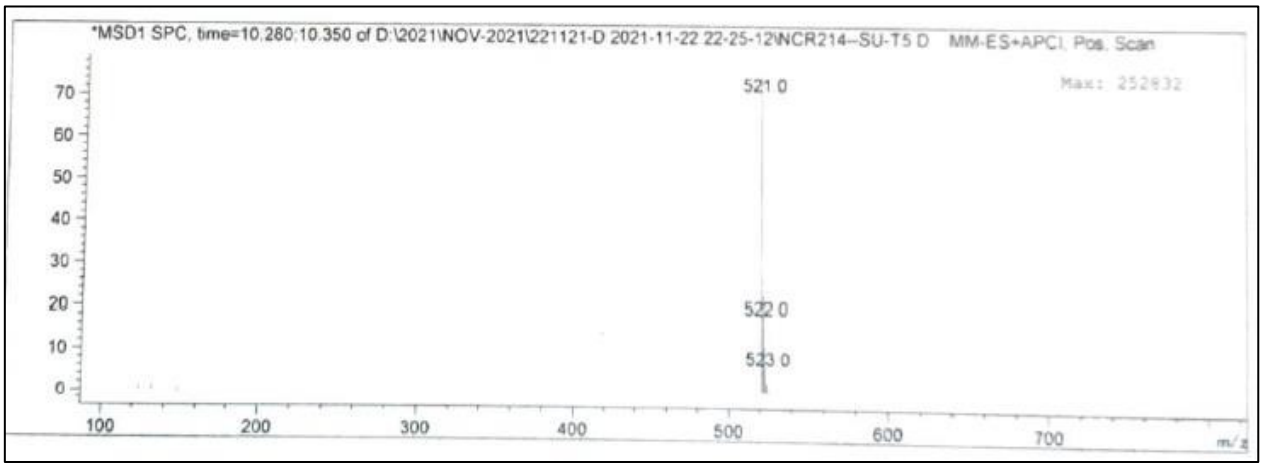


Figure 36. Compound S5

- **Compound S6:** The LC MS showed a molecular ion peak at m/z 505.0 (M] + and was in match with the proposed structure with $C_{24}H_{25}FN_2O_5S_2$.

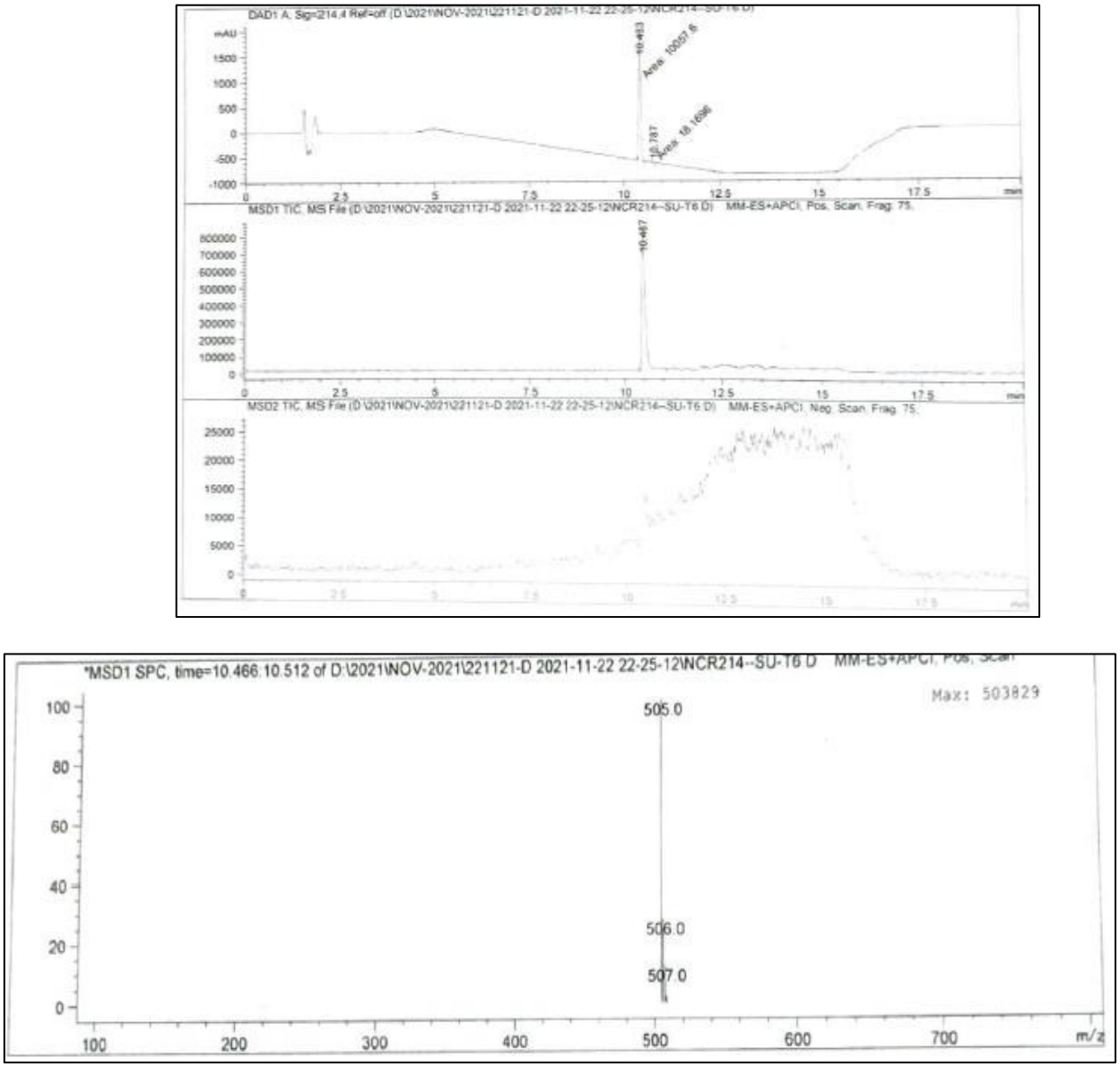
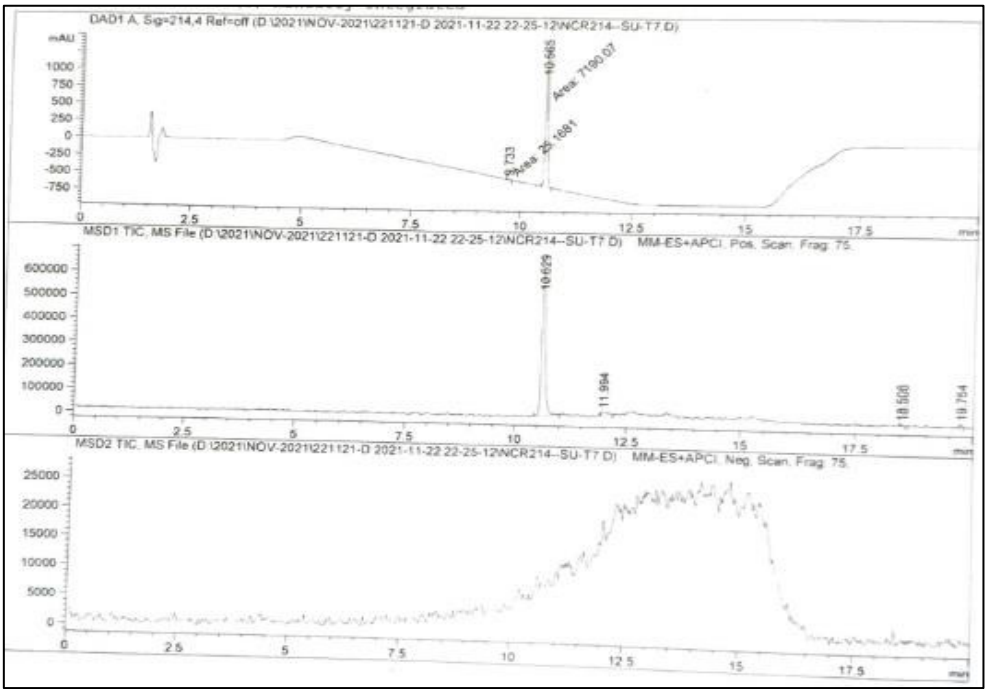


Figure 37. Compound S6

- **Compound S7:** The LC MS showed a molecular ion peak at m/z 513.0 (M] + and was in match with the proposed structure with $C_{26}H_{28}N_2O_5S_2$.



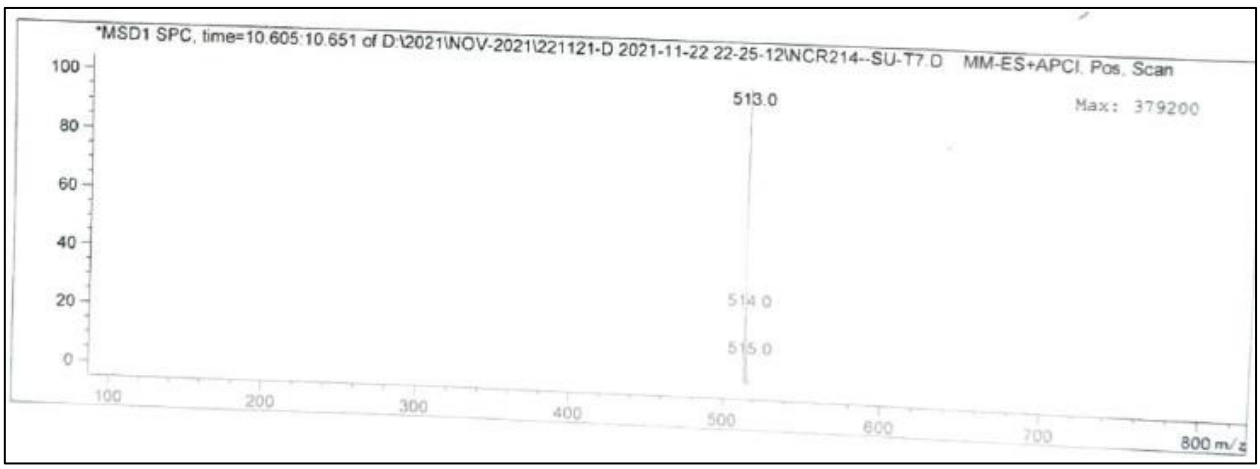
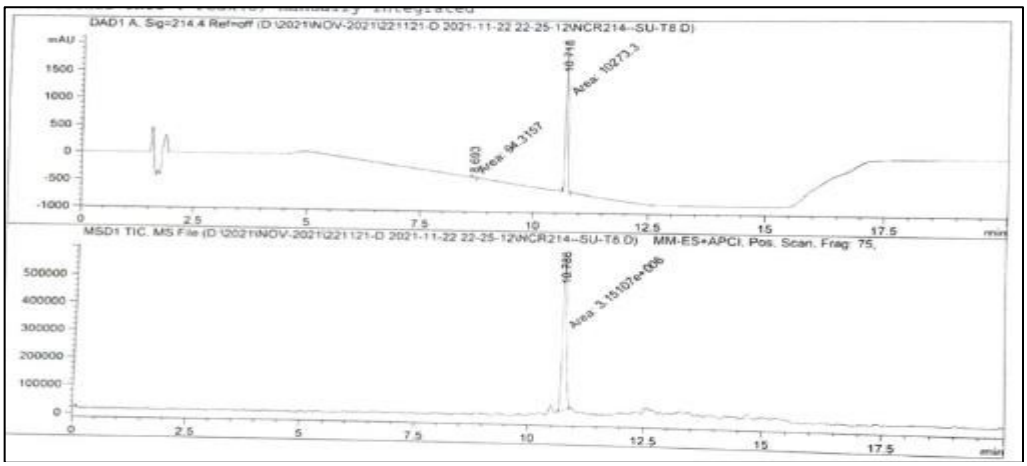


Figure 38. Compound S7

- **Compound S8:** The LC MS showed a molecular ion peak at m/z 553.0 (M] + and was in match with the proposed structure with C24H22F2N2O7S2.



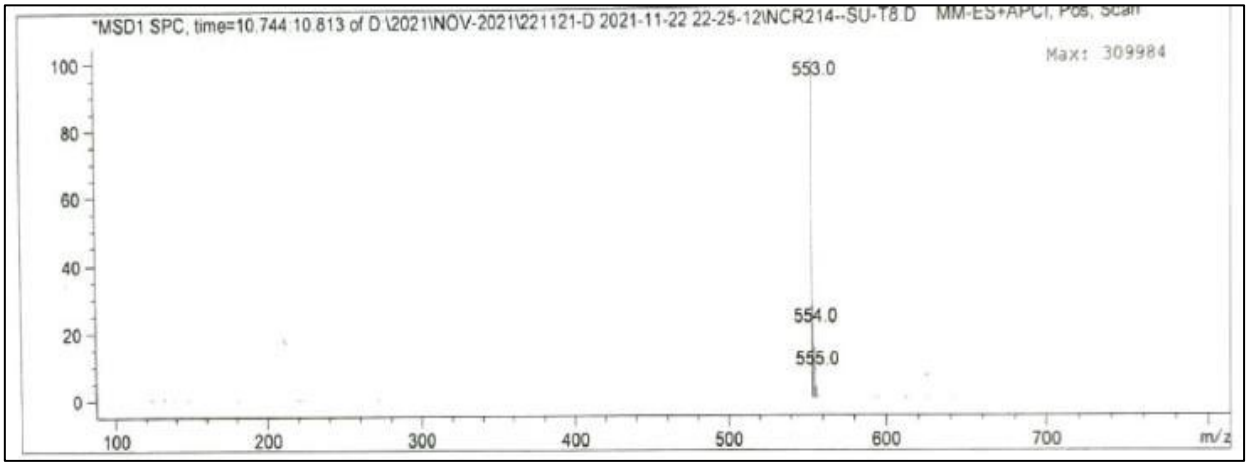
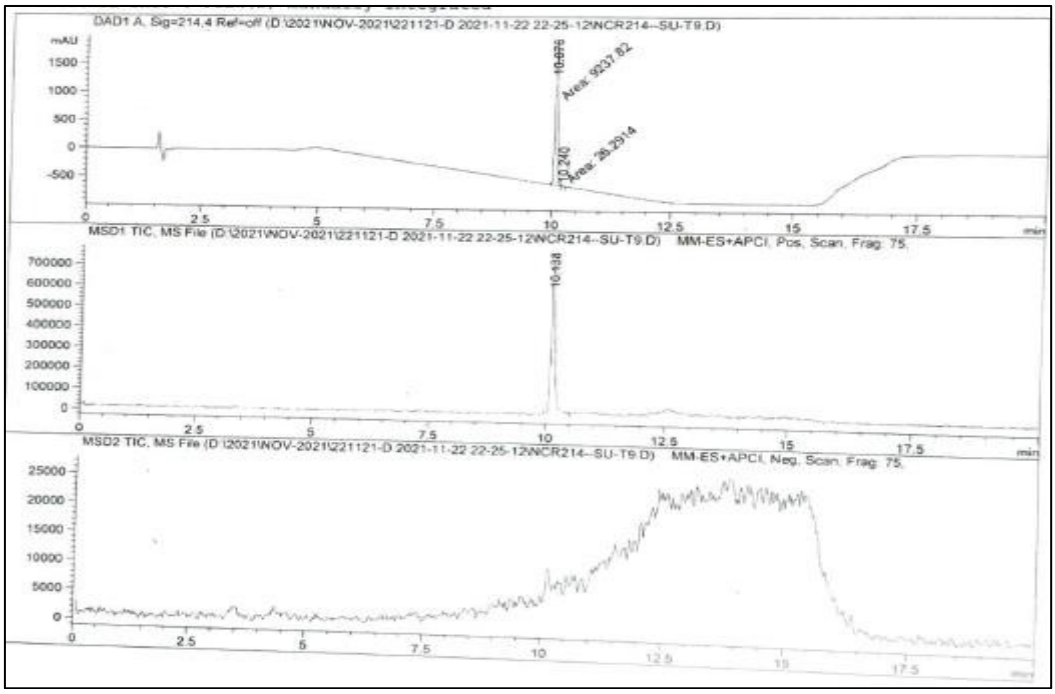


Figure 39. Compound S8

- **Compound S9:** The LC MS showed a molecular ion peak at m/z 517.0 (M] + and was in match with the proposed structure with $C_{24}H_{24}N_2O_7S_2$.



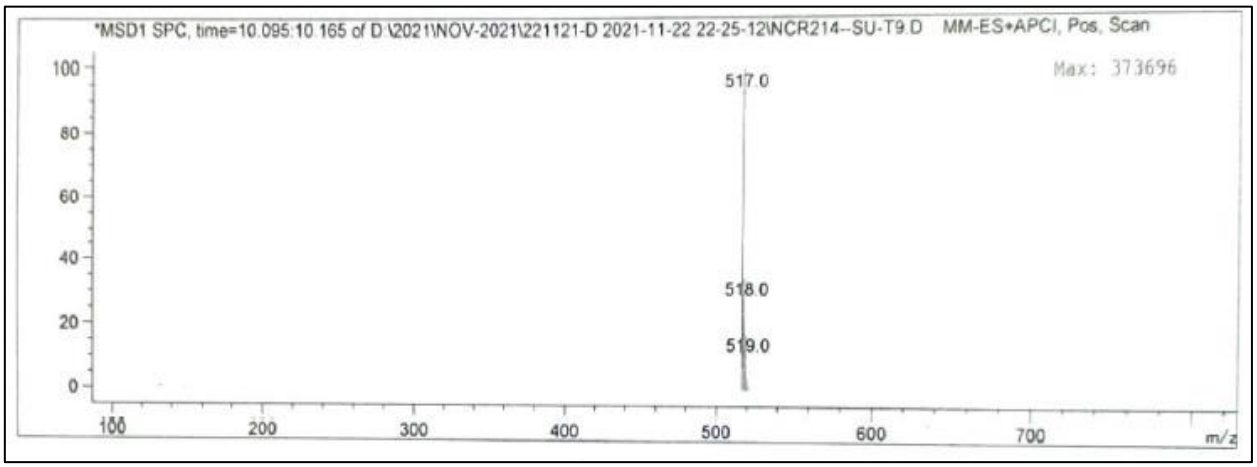
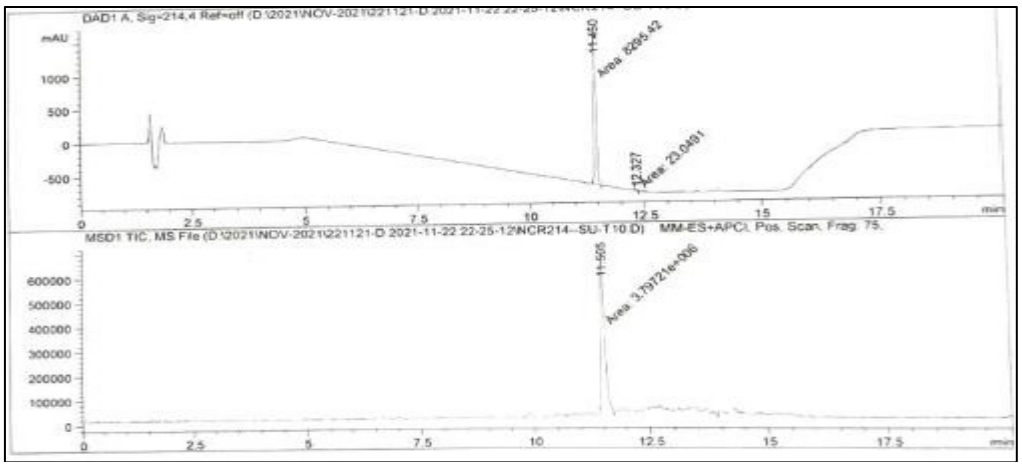


Figure 40. Compound S9

- **Compound S10:** The LC MS showed a molecular ion peak at m/z 529.1 (M] + and was in match with the proposed structure with C27H32N2O5S2.



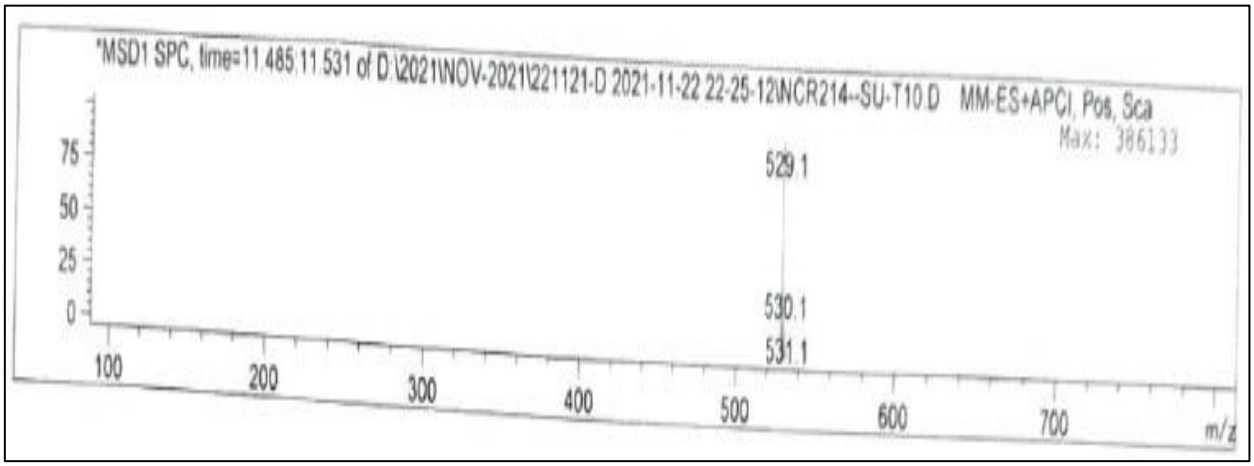


Figure 41. Compound S10

Conclusion

The production of piperazine derivatives utilizing metal-based ionic liquids as catalysts has produced encouraging outcomes. The compounds, containing diverse functional groups like methoxy, fluoro, and 129rapheme129 on the phenyl and thiophene rings, demonstrated reasonable yields between 50% and 80%. The yield range indicates that although the synthetic processes were relatively effective, there is potential for improvement to enhance the yield further. The utilization of metal-based ionic liquids as catalysts in the synthesis process is a feasible approach; however, improving reaction parameters such as temperature, duration, and catalyst concentration may enhance yields further. The reusability of these ionic liquids could improve the sustainability of the process.

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