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The Synthesis of Sulfur Model Compounds as Candidate for Carbonic Anhydrase Inhibitors and Anticancer Drugs

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ABSTRACT
Easy and effective preparation of model sulfur containing compounds were achieved with high efficiency in excellent yield via coupling of a series of amines and thiophene sulfonyl chloride under substantially mild conditions. The strategically located substituents on the newly formed sulfonamides was intended to confer a range of biological properties as inhibitors of carbonic anhydrase and cancerous diseases. Detailed spectroscopic investigations (^{1}H-NMR, MS) of the prepared compounds (10 Intermediates) were presented. The proton NMR and the Mass spectra presented were used in validating the target structures. This method is quite feasible in terms of practical and quick access to the sulfur model compounds and their derivatives over the formation of sulfonamide scaffolds.

Keywords: Sulfur, sulfonamide, carbonic anhydrase, bromothiophene, cancer.

I. INTRODUCTION

Many methods of synthesizing sulfur containing medicinally active natural products such sulfonamides, sulfamates and sulfonylcarbamates were reported in the last few decades. Among them, sulfonamides have long been explored by synthetic chemist uninterruptedly due to its diverse pharmacological and industrial applications. In 1930, Bayer chemists synthesized various azo-dyes, and the director of Bayer institute Gerhard Domagk tested these compounds effect on streptococci bacteria. These studies finally concluded as discovery of positive effect on Streptococcus and Staphylococcus bacterial infections by red azo-dye that is called prontosil. Domagk won Nobel Prize in medicine due to this discovery in 1939. Following works proved that reducing prontosil in an organism to p-aminobenzenesulfonamide was the responsible molecule to show antibacterial property (Scheme 1) (Bryant and Knights, 2011).

Scheme 1: Reduction of prontosil

After this discovery, sulfonamide derivatives have become popular in pharmaceutical area because of their diversity in biological activity like antibacterial, anticancer, antiviral, anticonvulsant, anti-inflammatory, antiviral, antitumor, HIV protease inhibitory and carbonic anhydrase inhibitors (Figure 1) (Casini et al., 2002; Supuran et al. 2003; Dai et al. 2011).

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Figure 1: Sulfonamide based well-known drugs

Moreover, sulfonamides are the most classical inhibitors of the zinc-enzymes carbonic anhydrases (CA, EC 4.2.1.1) (Supuran, 2008). Fifteen kind of carbonic anhydrase isoforms (CAs) were known that is classified as cytosolic (CAI, CAII, CAIII, CAVII), membrane-bound (CAIV, CAIX, CAXII, CAXIV). In addition to this, CAV is found in mitochondria and CAVI is located in saliva (Alterio et al., 2012). In particular, CAI and CAII are ubiquitous isoforms, targets for some diseases (such as cerebral and retinal edema, glaucoma, epilepsy, and probably altitude sickness), but often off-targets since they are the main responsible of the majority of side effects of non-selective inhibitors (Scozzafava et al., 2003). The membrane-associated isoform CA IV is a drug target for retinitis pigmentosa and stroke, in addition to glaucoma, together with CA II and XII (Datta et al., 2009; Matsui et al., 1996; Ochrietor et al., 2005). CAVII has been shown to be involved in epileptiform activity together with CA II and XIV (Hen et al., 2011). Moreover, hCA VII was recently validated as a new drug target for neuropathic pain (Supuran, 2016). The "tail approach" is the mainly applied method for the research of isoformselective sulfonamide-CAIs (Bozdag et al., 2014). Indeed, it consists in appending different tails to the aromatic/heterocyclic ring bearing the sulfonamides in order to modulate the possible interactions the ligand may establish with the middle/outer parts of the active site.The primary sulfonamide moiety is present in many clinically used drugs, such as diuretics (furosemide, indapamide, chlorthalidone, thiazides);carbonic anhydrase (CA) inhibitors (CAIs) (including acetazolamide, dichloro-phenamide, dorzolamide and brinzolamide); antiepileptics (zonisamide andsulthiame); the antipsychotic sulpiride and the cycloxygenase 2 (COX2) inhibi-tors celecoxib and valdecoxib. Recently, novel drugs have been launched, such as apricoxib and pazopanib, which also incorporate in Supuran group.

Figure 2: Some biologically active compounds containing Sulfonamides

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The sulfonamides and their structurally related derivatives such as sulfamates and sulfamides A-SO_2NHR having a general formula in which the functional group is either directly bound to an aromatic, heterocyclic, aliphatic, or sugar scaffold (of type A), or appended to such a scaffold via a heteroatom, most frequently oxygen or nitrogen (leading thus to sulfamates and sulfamides, respectively (Supuran et al., 2017; Carta et al., 2014; Scozzafava et al., 2003; Capasso et al., 2014),are used as a core structural moiety or an important fragment in many marketed drugs. Several antimicrobial drugs were prepared mainly by coupling between heterocyclic primary amines and aromatic sulfonyl chlorides e.g. sulfacetamide, sulfadiazine, sulfamethoxazole, sulfamoxole etc.The nature of the R moiety may also be quite variable, starting with hydrogen, case in which primary sulfonamides/sulfamates/sulfamides are being considered (Carta et al., 2012), and ranging to a variety of moieties incorporating heteroatoms (OH, NH_2, etc.) as well as organic scaffolds of the types mentioned above for A (Scozzafava et al., 2008-2012; Winum et al., 2006). As thus, this class of compounds may lead to a huge range of derivatives, which are generally easily available through classical synthetic route.

In this study, a number of sulfur model intermediates (**1-10**) were synthesized by adopting the method reported by Raju and colleagues (2006)**.** This convenient methodology also refers to as classical method of preparing sulfonamides included the coupling of sulfonyl chlorides with a series of amines. Specifically, in this work, halo thiophene sulfonyl chloride coupled with a wide range of aliphatic and aromatic amines (**1^{o}amines**) yielding a small library of potential Carbonic Anhydrase (CA) Sulfonamides. These 5-bromothiophene-2-sulfonamides are the major precursors for a number of bioactive agents. Thanks to previous articles, references, drugs and knowledge of computational chemistry. The development of cancer and carbonic anhydrase compounds has been yielding positive results and some of these are sulfonamide containing molecules.

EXPERIMENTALS

All the reactions were carried out under inert atmosphere in flame-dried reaction flasks and monitored with TLC precoated plates (60, F254, Merck 5735 and 5554). The products were purified by CC using silica gel 60 (Merck-109385) or neutral alumina (Merck-101077), and the eluent was the mixtures of ethyl acetate (EA) and hexanes (H). All reagents and solvents of analytical grade were purchased from commercial suppliers (Merck, Sigma-Aldrich, TCI) and used as received.

SYNTHESIS OF SULFUR MODEL INTERMEDIATES

Scheme 2: Synthesis of sulfur model compounds.

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The5-bromothiophene-2-sulfonamides were synthesized following methods reported in the literature (Raju et al., 2006), and as shown in the scheme below:

General Experimental Procedure

To a dissolved Amine**(**1.2 mmol) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride**(**1 mmol) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^{o}C. The reaction mixture was stirred for 2-5 h at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying over Na_2SO_4, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (6:1) as an eluent to afford the target intermediate.

Scheme 3: General Experimental Procedure for sulfonamide synthesis.

Sulfonamide Intermediate 1

Following the general procedure, to a solution of4-chloro-3-(trifluoromethyl) aniline**(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^{o}C. The reaction mixture was stirred for **2h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (6:1) as an eluent to afford the target intermediate, 5-bromo-N-(4-chloro-3-(trifluoromethyl)phenyl)thiophene-2-sulfonamide in 90% yield.

Sulfonamide Intermediate 2

Following the general procedure, to a solution of2-fluoro-3-(trifluoromethyl)aniline **(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^{o}C. The reaction mixture was stirred for **2.5h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (5:1) as an eluent to afford the target intermediate, 5-bromo-N-(2-fluoro-3-(trifluoromethyl)phenyl)thiophene-2-sulfonamide in 92% yield.

Sulfonamide Intermediate 3

Following the general procedure, to a solution of3-methoxyaniline**(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^{o}C. The reaction mixture was stirred for **2h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (6:1) as an eluent to afford the target intermediate, 5-bromo-N-(3-methoxyphenyl)thiophene-2-sulfonamide in 90% yield.

Sulfonamide Intermediate 4

Following the general procedure, to a solution of2,3-dihydro-1H-inden-5-amine **(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^{o}C. The reaction mixture was stirred for **2h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the

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organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (6:1) as an eluent to afford the target intermediate,5-bromo-N-(2,3-dihydro-1H-inden-5-yl)thiophene-2-sulfonamide in 79% yield.

Sulfonamide Intermediate 5

Following the general procedure, to a solution ofpyridin-3-ylmethanamine **(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^oC. The reaction mixture was stirred for 4**h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (3:1) as an eluent to afford the target intermediate, 5-bromo-N-(pyridin-3-ylmethyl)thiophene-2-sulfonamide in 85% yield.

Sulfonamide Intermediate 6

Following the general procedure, to a solution of(4-methoxyphenyl)methanamine **(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^oC. The reaction mixture was stirred for **2h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (4:1) as an eluent to afford the target intermediate, 5-bromo-N-(4-methoxybenzyl)thiophene-2-sulfonamide in 94% yield.

Sulfonamide Intermediate 7

Following the general procedure, to a solution offuran-2-ylmethanamine **(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^oC. The reaction mixture was stirred for **4h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (5:1) as an eluent to afford the target intermediate,5-bromo-N-(furan-2-ylmethyl)thiophene-2-sulfonamide in 90% yield.

Sulfonamide Intermediate 8

Following the general procedure, to a solution ofpentan-1-amine **(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^oC. The reaction mixture was stirred for **5h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (3:1) as an eluent to afford the target intermediate,5-bromo-N-pentylthiophene-2-sulfonamide in 54% yield.

Sulfonamide Intermediate 9

Following the general procedure, to a solution ofcyclopentanamine **(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^oC. The reaction mixture was stirred for **3h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M

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$NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (3:1) as an eluent to afford the target intermediate,5-bromo-N-cyclopentylthiophene-2-sulfonamide in 85% yield.

Sulfonamide Intermediate 10

Following the general procedure, to a solution oftetrahydro-2H-pyran-4-amine**(**1.2 **mmol**) in 1 mL of anhydrous pyridine was added dropwise 5-bromothiophene-2-sulfonyl chloride **(**1 **mmol**) dissolved in 1 mL of anhydrous pyridine under stirring at 0-25^{o}C. The reaction mixture was stirred for **2h** at room temperature under N_2 until TLC showed complete consumption of the limiting reagent. CH_2Cl_2 (50 mL) was added and the organic layer was contacted with 1 M HCl (5 x 50 mL), to assure transfer of the product to the aqueous phase. The aqueous layer was contacted with CH_2Cl_2 (3 x 50 mL), and the combined CH_2Cl_2 extracts were washed twice with 1 M $NaHCO_3$ and water, and were dried using Na_2SO_4. After drying, the solvent was evaporated and the residue was purified through a silica column using EtOAc: hexane (2:1) as an eluent to afford the target intermediate,5-bromo-N-(tetrahydro-2H-pyran-4-yl)thiophene-2-sulfonamidein 70% yield.

STRUCTURES OF THE SYNTHESIZED CA SULFONAMIDES

Elucidation of the Synthesized Products (Proton NMR Determination)

^{1}H-NMR spectra were recorded on NMR JEOL-ECS400 Delta NMR spectrometer (400 MHz for proton) at ambient temperature. All chemical

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shifts (δ) are reported in parts per million (ppm) downfield from TMS and J values are given in Hz. The abbreviations used for NMR signals are: s=singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, hep = heptet, m = multiplet, dd = doublet of doublets, dq = doublet of quartets, td = triplet of doublets, qd = quartet of doublets, ddd = doublet of doublet of doublets, dtd = doublet of triplet of doublets, tdt = triplet of doublet of triplets, and dddd = doublet of doublet of doublet of doublets.

Elucidation of the synthesized products (MS Determination)

Mass spectra were recorded on Agilent Technologies 2020 mass spectrometer via Electron Spray Ionization [ESI] technique. The data revealed the expected peaks at $[M+H]^+$

II. RESULTS AND DISCUSSION

The current work comprises a simple and effective synthetic route for the preparation of new sulfur model compounds as potential carbonic anhydrase inhibitors via a simple yet improved methodology. The prepared bromothiophene sulfonamideshave been synthesized over the reaction of thiophene sulfonyl chloride with a series of primary aliphatic and aromatic amines. The color of the aromatic containing intermediates ranges from green to dark green. While the intermediates with aliphatic portion **(8-10)** give brown to dark brown colors, respectively. The yield of the intermediates can also be described as good to excellent. This is not surprising in view of the results from previous and similar reports (Raju et al.,2006; Arshia et al., 2019).To illustrate, the presence of CF_3 in the intermediate 1 increases the stability of the carbocation and hence, a very high yield was obtained. The structures of CA products (sulfonamides 1-10) were fully characterized by using proton NMR and Mass spectroscopic analyses.

TABLE 1: ^{1}HNMR DATA OF THE BROMOTHIOPHENE SULFONAMIDES SOLVENT (CHLOROFORM), TMS (Internal standard), δ (ppm), J (Hz).

INTERMEDIATE 1: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.45 (d, J = 5.9 Hz, 2H), 7.30-7.32 (m, 2H), 7.12 (s, 1H), 7.04 (q, J = 2.1 Hz, 1H)

INTERMEDIATE 2: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.82 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 7.1 Hz, 1H), 7.30 (q, J = 1.7 Hz, 1H), 7.23-7.27 (m, 1H), 7.01 (q, J = 1.8 Hz, 1H), 6.92-6.99 (m, 1H)

INTERMEDIATE 3: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.25 (t, J = 3.7 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.96 (d, J = 4.1 Hz, 1H), 6.93 (s, 1H), 6.73 (t, J = 2.3 Hz, 1H), 6.69-6.71 (m, 1H), 6.67 (d, J = 7.8 Hz, 1H)

INTERMEDIATE 4: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.22 (d, J = 4.1 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.02 (s, 1H), 6.97-6.98 (m, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.73 (s, 1H), 2.84-2.87 (m, 4H), 2.03-2.10 (m, 2H)

INTERMEDIATE 5: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 8.53 (d, J = 4.6 Hz, 1H), 8.46 (s, 1H), 7.65-7.67 (m, 1H), 7.36 (dd, J = 3.7, 0.9 Hz, 1H), 7.27-7.29 (m, 1H), 7.06-7.07 (m, 1H), 5.23 (s, 1H), 4.25 (s, 2H)

INTERMEDIATE 6: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.33-7.35 (m, 1H), 7.15 (d, J = 8.2 Hz, 2H), 7.05 (t, J = 2.1 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 4.76 (t, J = 5.5 Hz, 1H), 4.15 (d, J = 5.9 Hz, 2H), 3.79 (s, 3H)

INTERMEDIATE 7: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.29-7.30 (m, 2H), 7.02 (dd, J = 4.1, 0.9 Hz, 1H), 6.26-6.27 (m, 1H), 6.16 (d, J = 3.2 Hz, 1H), 4.99 (t, J = 5.5 Hz, 1H), 4.26 (d, J = 5.9 Hz, 2H)

INTERMEDIATE 8: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.35 (d, J = 4.1 Hz, 1H), 7.06 (d, J = 4.1 Hz, 1H), 4.45 (d, J = 5.9 Hz, 1H), 3.03 (q, J = 6.9 Hz, 2H), 1.51 (t, J = 7.1 Hz, 2H), 1.26-1.30 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H)

INTERMEDIATE 9: ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.34-7.37 (m, 1H), 7.05 (t, J = 4.3 Hz, 1H), 4.60 (d, J = 6.9 Hz, 1H), 3.68 (td, J = 13.5, 6.9 Hz, 1H), 1.87 (td, J = 12.5, 7.0 Hz, 2H), 1.61-1.68 (m, 2H), 1.52-1.58 (m, 2H), 1.38-1.46 (m, 2H)

INTERMEDIATE 10: ^{1}H-NMR (400 MHz, DMSO-D6) δ 8.15 (d, J = 7.3 Hz, 1H), 7.44 (d, J = 4.1 Hz, 1H), 7.32 (d, J = 3.7 Hz, 1H), 3.73 (dt, J = 11.7, 3.3 Hz, 2H), 3.23-3.29 (m, 3H), 1.57 (dd, J = 12.8, 2.3 Hz, 2H), 1.33-1.43 (m, 2H)

In ^{1}H-NMR spectra of CA sulfonamides, the characteristic signals supporting the synthesized products were mostly the aromatic CH signals resonating at around 6.50–8.53 ppm (Table 1). Besides, olefinic CH signals of thiophene portion of the products (1-10) were resonated at around 7.05–8.15 ppm. For example, the proton NMR spectrum of sulfonamide intermediate 1 showed doublet at 7.45 ppm due to the olefinic protons on thiophene, multiplet at 7.30-7.32 ppm and quartet at 7.04 ppm representing the aromatic protons respectively. While the NH group of the sulfonamide linkage is shifted up field compared to the precursor amine.

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Table 2: Approximate calculated and measured MS values, yield (%), color of the products.

Intermediate	MS-Calculated	MS-Found	% Yield	Color
1	418.87	420	90	Dark green
2	402.90	404	92	Grey
3	346.93	348	90	Light green
4	356.95	358	79	Dark green
5	331.93	331	85%	Light green
6	360.94	361	94%	Brown
7	320.91	322	90%	Grey
8	310.96	312	54%	Brown
9	308.95	310	85%	Dark-brown
10	324.94	326	70%	Dark-brown

The formation of the intermediate 1 was confirmed by the disappearance of the NH_2 in the corresponding starting material and the appearance of new aromatic protons as contained in this report. As for the aliphatic containing sulfonamides, basic signals depicting the target product, as in for instance, Intermediate 8**,** were doublets of olefinic protons at 7.35 and 7.06 ppm. Besides, methylenic protons appeared as quartet 3.03 ppm, multiplets 1.51 ppm and (1.26-1.30) ppm, and triplet at 0.88 ppm respectively (Table 1).In mass spectra of the products, molecular ions have been found as MH^+ accurately via ESI measurements, which were in accordance with calculated accurate masses of all products (Table 2). (See supporting data in the appendix).

III. CONCLUSION

This study deals with the synthesis of bromothiophene sulfonamides (1-10), their characterization and purification. In summary, we demonstrated an efficient synthesis of new carbonic anhydrase sulfonamides in good to excellent yields via an improved existing route. The present route provides an easy, practical, and impactful access to bioactive sulfonamides bearing different aromatic, as well as aliphatic moieties. The preparation has been achieved by stirring a reaction mixture at very low degree to room temperature in the presence of pyridine acting as solvent as well as base, mostly resulting in a viscous manner within very short period of time providing the target CA sulfonamide. In addition to the potential CA activity of the newly prepared bromo thiophene sulfonamides, they have recently emerged that CAIs could have potential as novel anti-obesity, anticancer and anti-infective drugs. Therefore, our future studies will focus on exploring the bioactivities of this novel class of scaffolds including the structure–activity relationship, computational studies and the assessment of the observed biological activities. The expectation is relatively high in regard to the future studies of these molecules.

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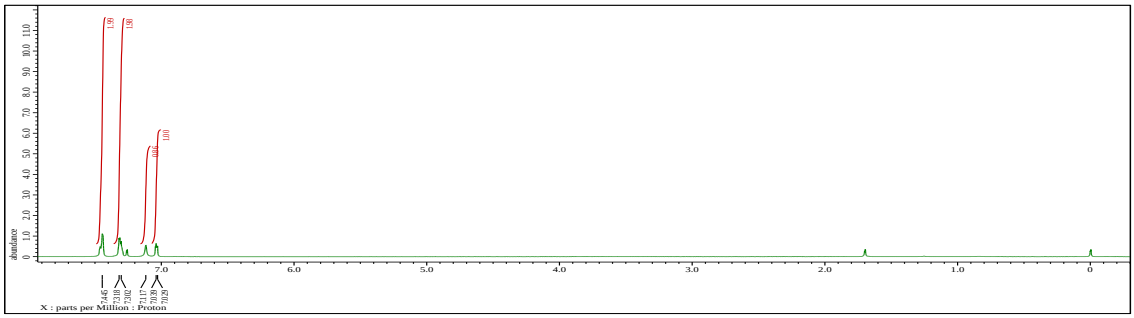
APPENDIX
PROTON NMR SPECTRA

Internediate 1



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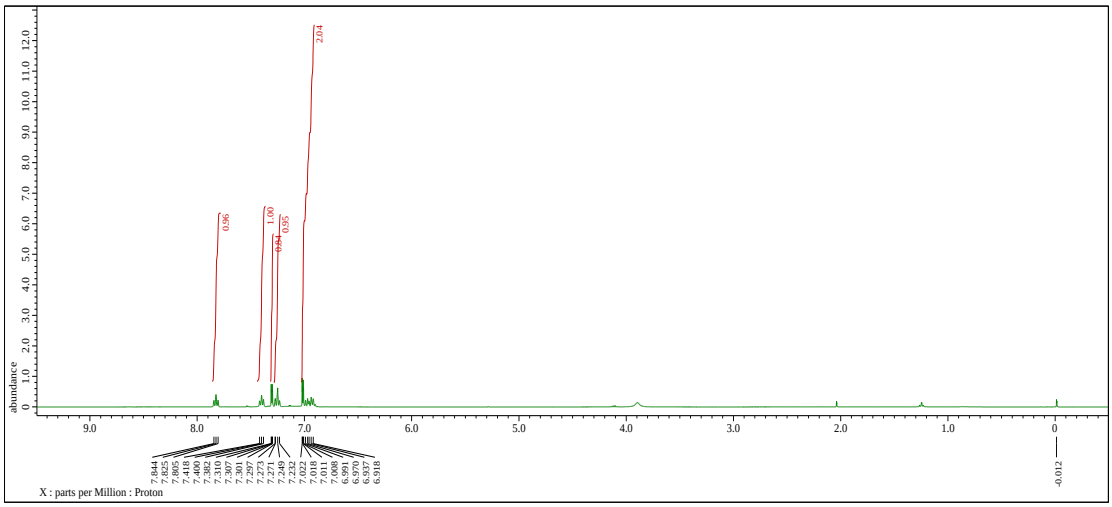
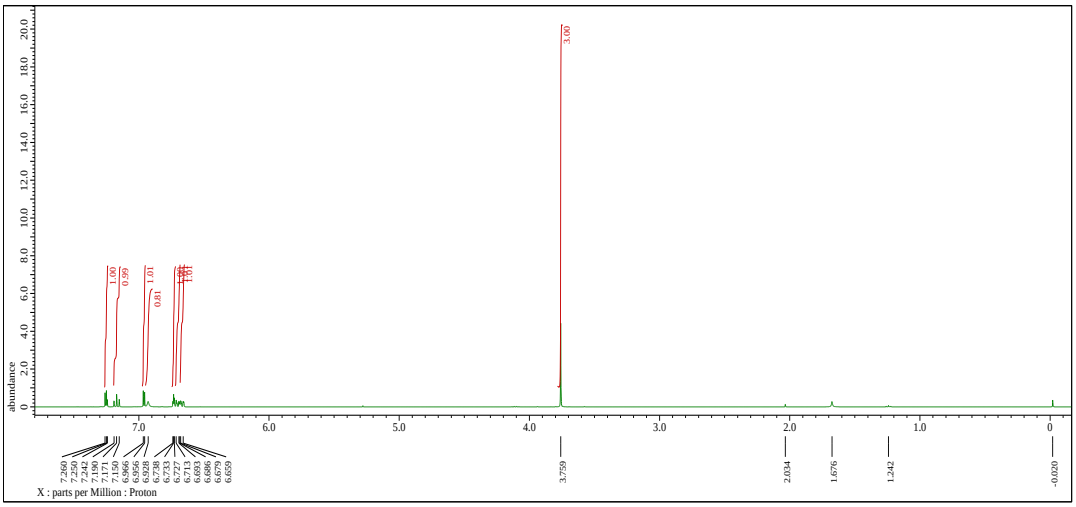
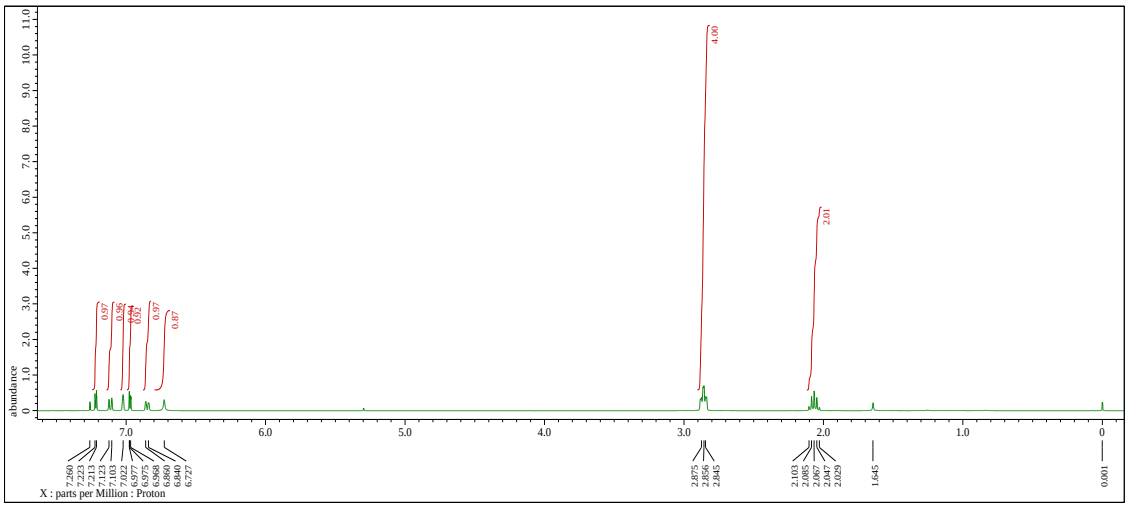
Internediate 2



Internediate 3



Intermediate 4



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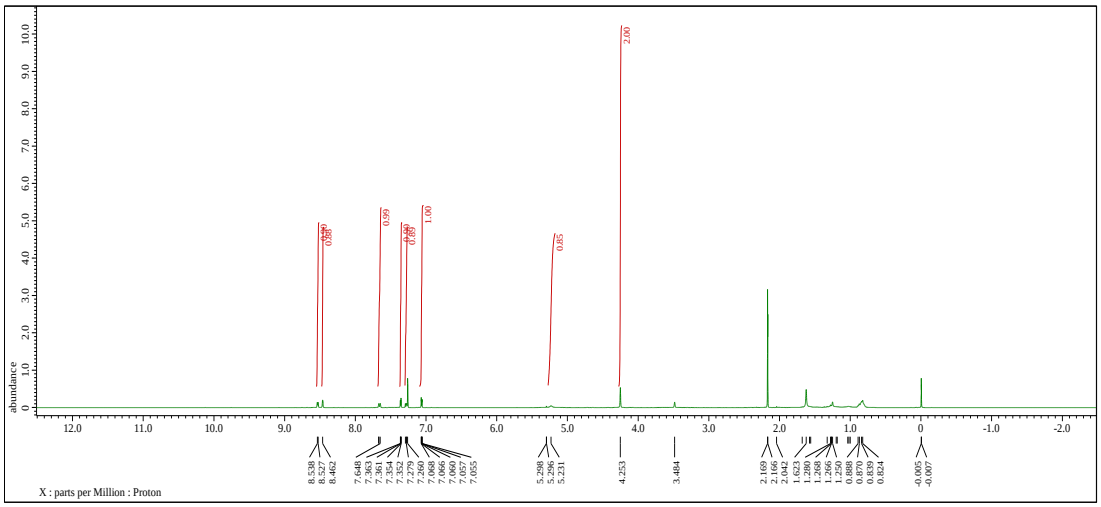
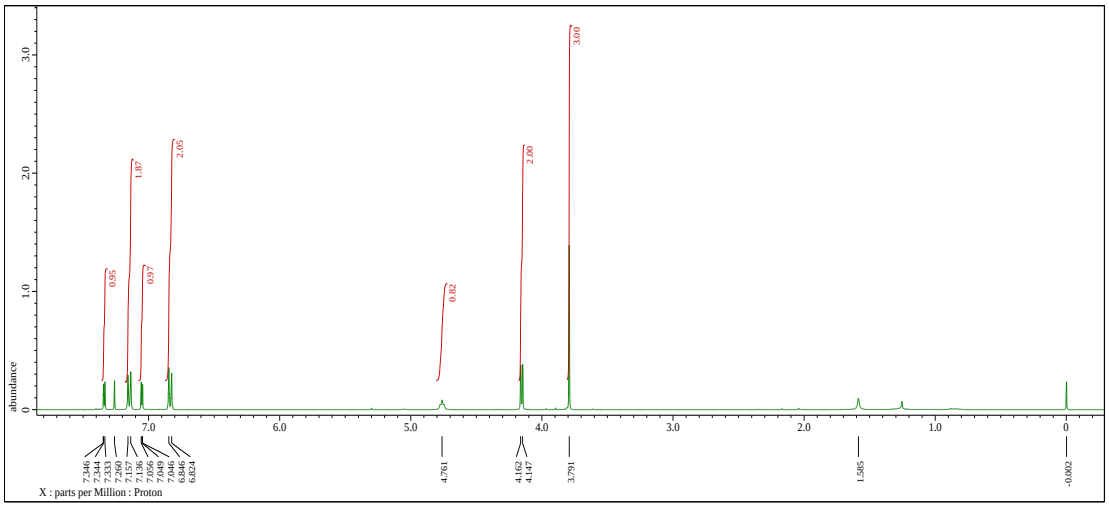
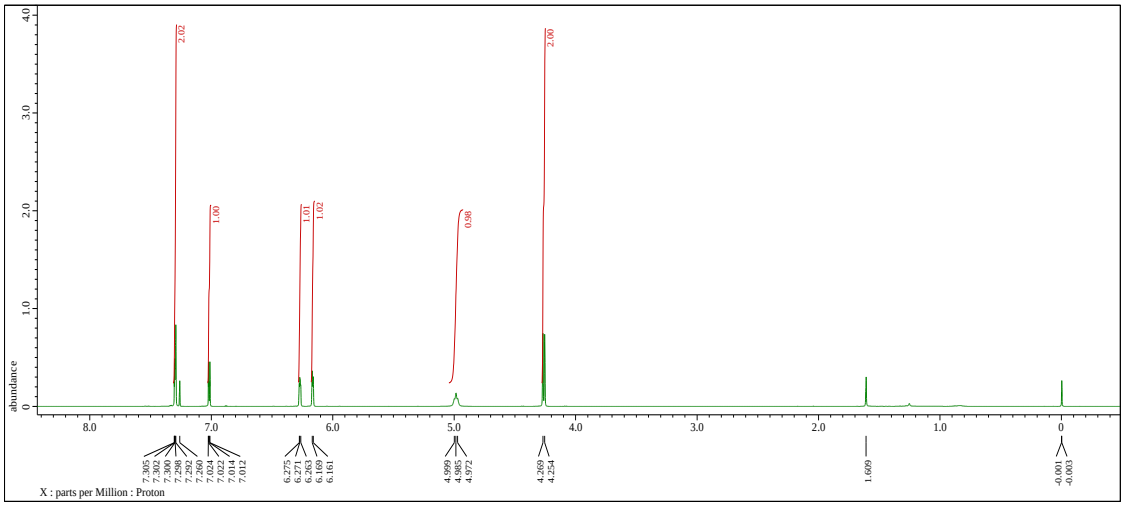
Intermediate 5



Intermediate 6



Intermediate 7



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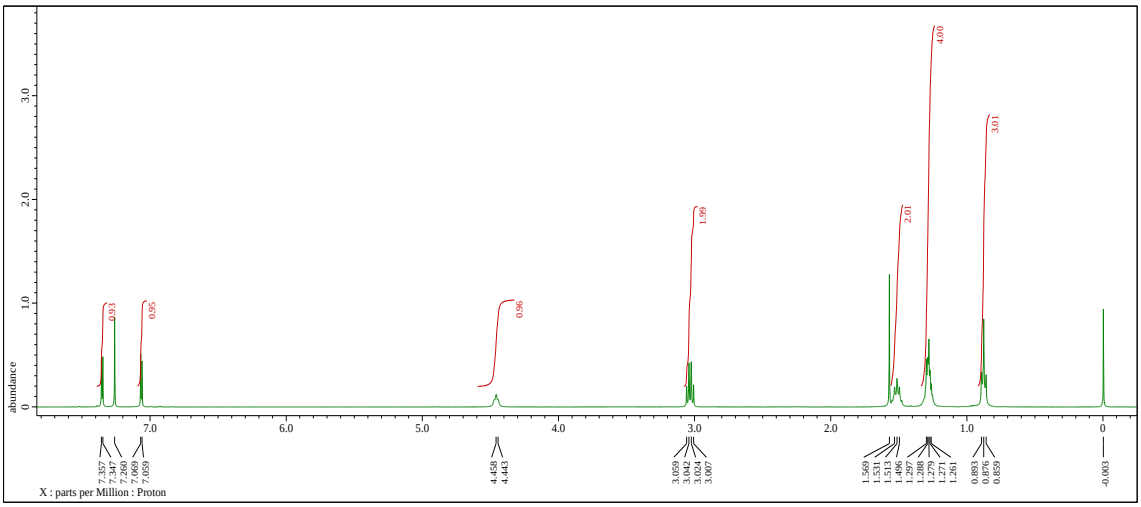
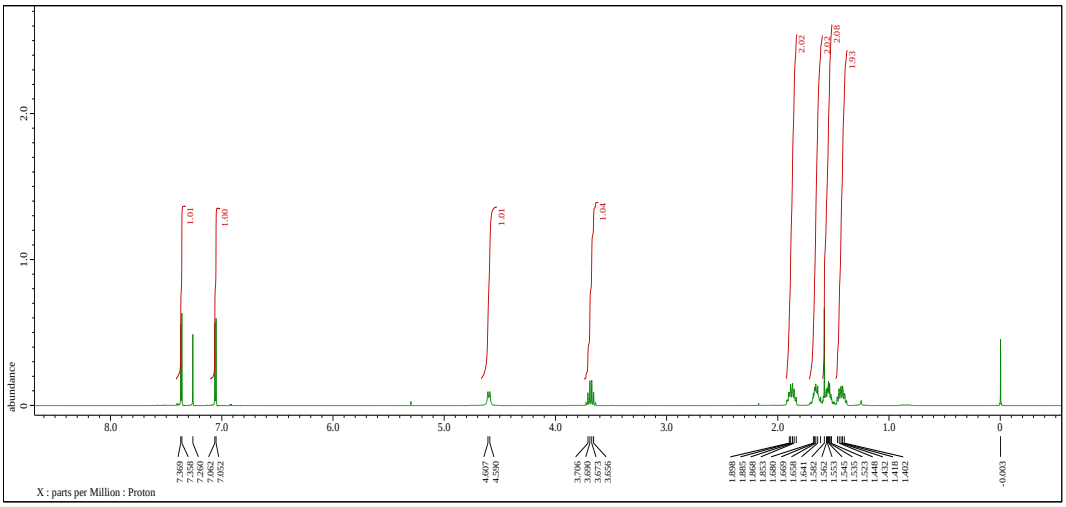
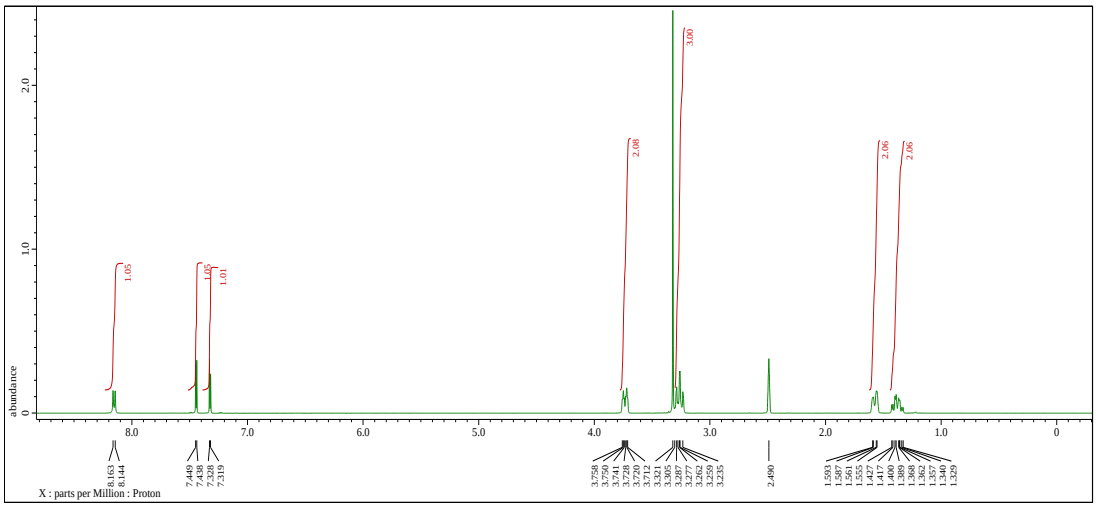
Intermediate 8



Intermediate 9



Intermediate 10



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Mass spectra of Intermediate 1-10

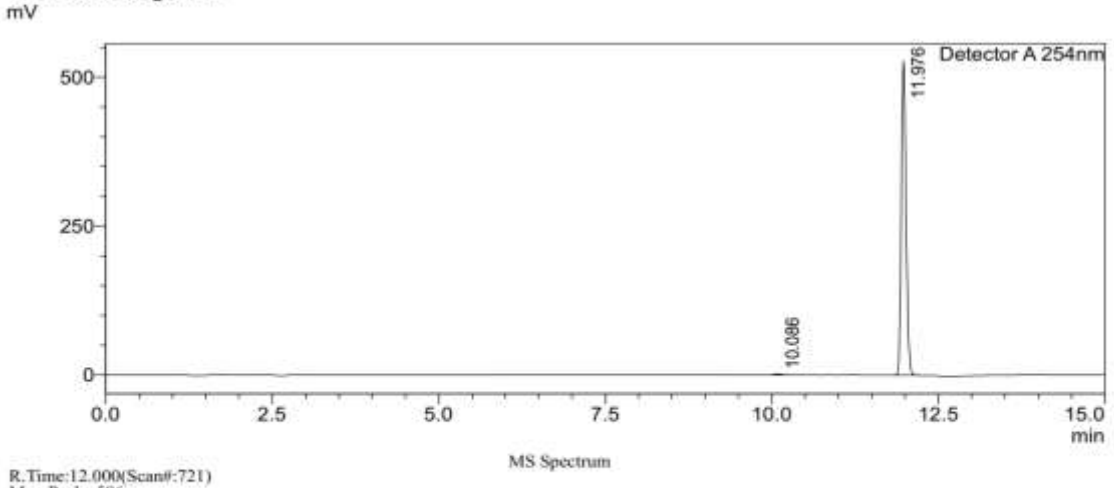
Intermediate 1

SHIMADZU LabSolutions Analysis Report

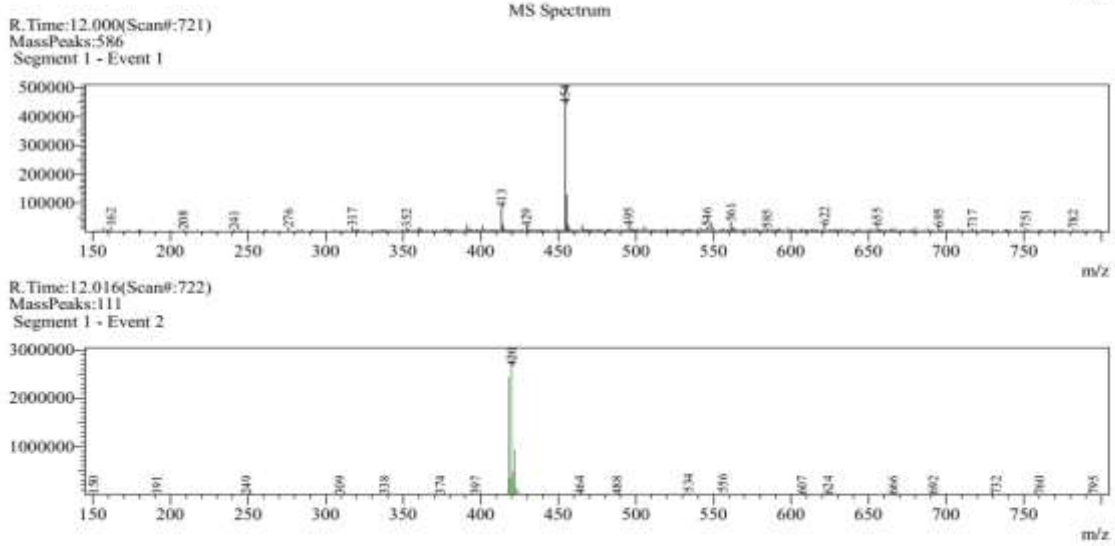
<Sample Information>

Sample Name	: GS01-57		
Sample ID	: UNK-0006		
Data Filename	: GS01-57.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-9	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

<Chromatogram>



MS Spectrum



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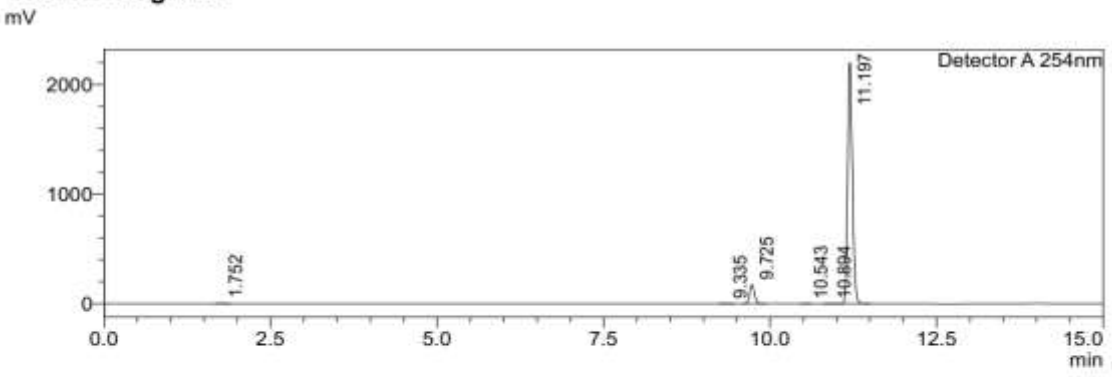
Intermediate 2

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

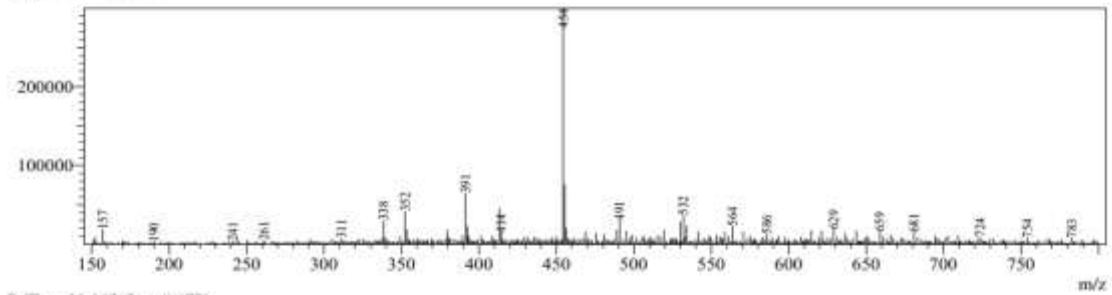
Sample Name	: GS01-58		
Sample ID	: UNK-0007		
Data Filename	: GS01-59.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-11	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

<Chromatogram>

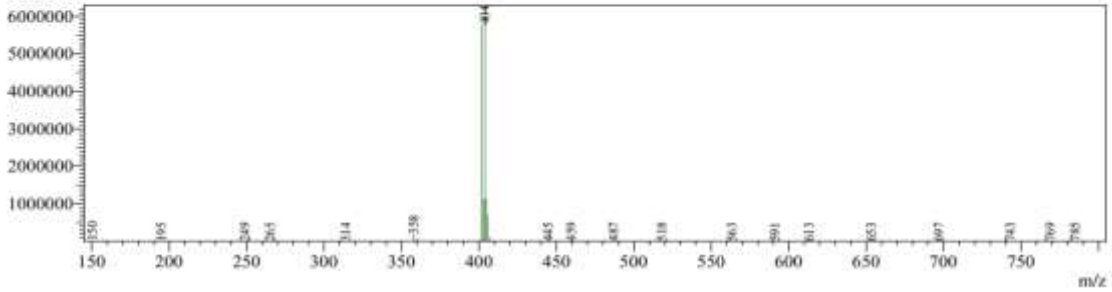


MS Spectrum

R.Time:11.167(Scan#:671)
MassPeaks:618
Segment 1 - Event 1



R.Time:11.183(Scan#:672)
MassPeaks:216
Segment 1 - Event 2



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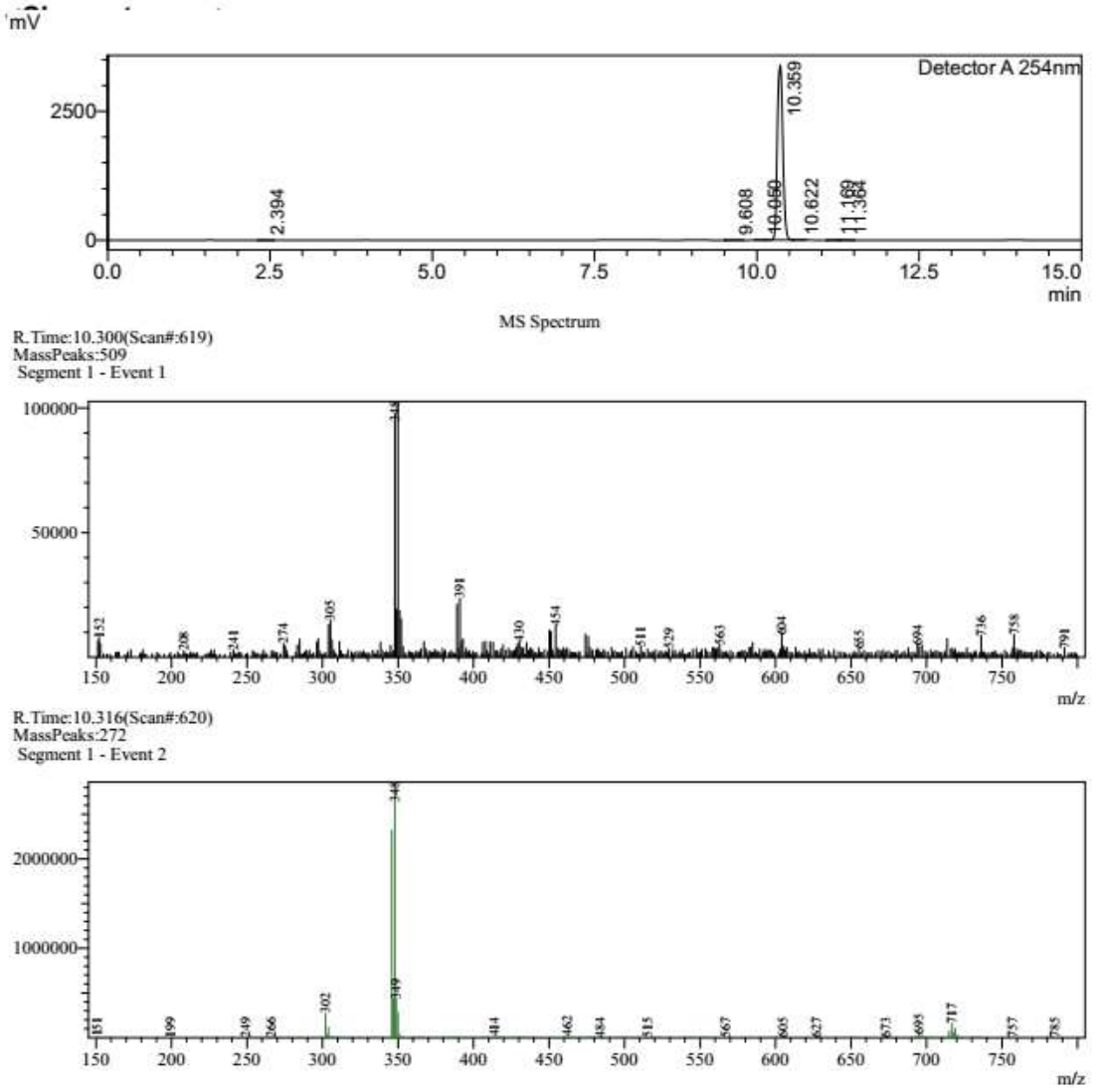
Intermediate 3

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	:		
Sample ID	: UNK-0006		
Data Filename	: GS01-71-001.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-78	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator



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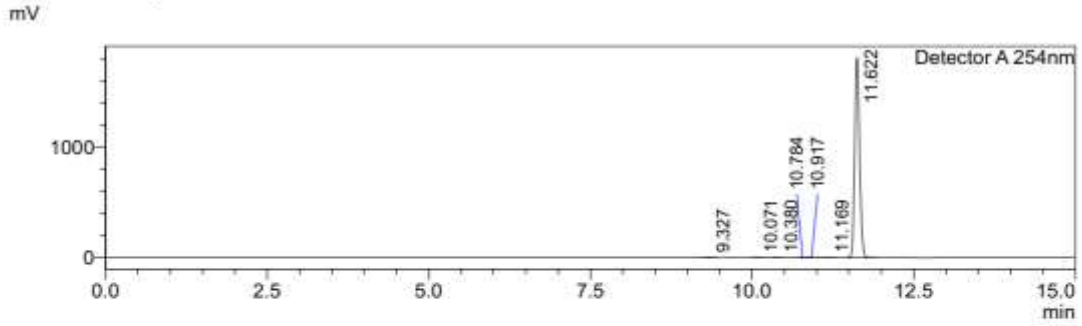
Intermediate 4

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

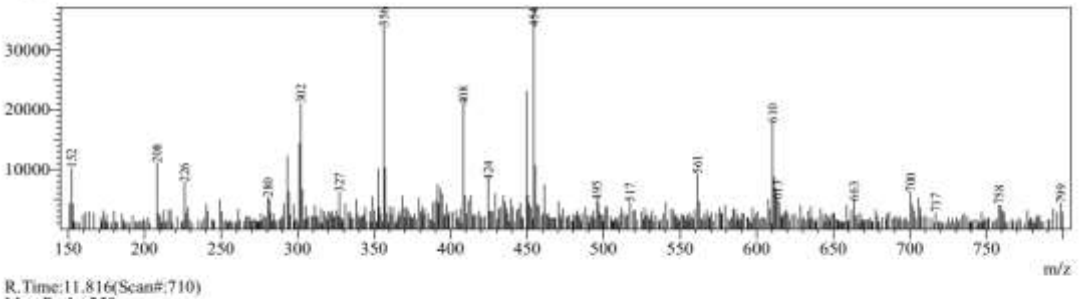
Sample Name	:			
Sample ID	: UNK-0006			
Data Filename	: GS01-72-001.lcd			
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm			
Batch Filename	: Batch 20180706.lcb			
Vial #	: 1-63		Sample Type	: Unknown
Injection Volume	: 5 uL			
Date Acquired	:	5:03:43	Acquired by	: System Administrator
Date Processed	:	5:18:45	Processed by	: System Administrator

<Chromatogram>

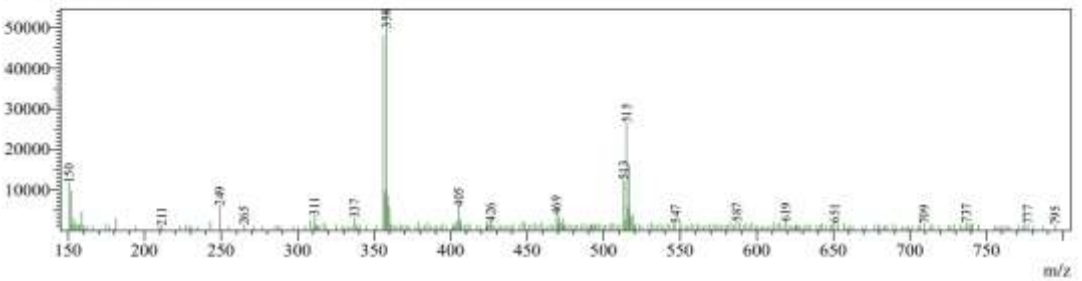


MS Spectrum

R.Time:11.800(Scan#:709)
MassPeaks:529
Segment 1 - Event 1



R.Time:11.816(Scan#:710)
MassPeaks:259
Segment 1 - Event 2



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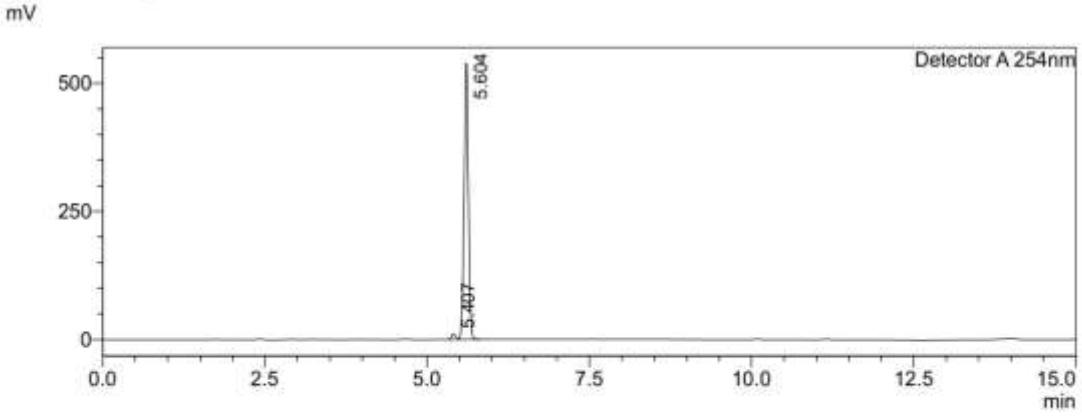
Intermediate 5

SHIMADZU LabSolutions **Analysis Report**

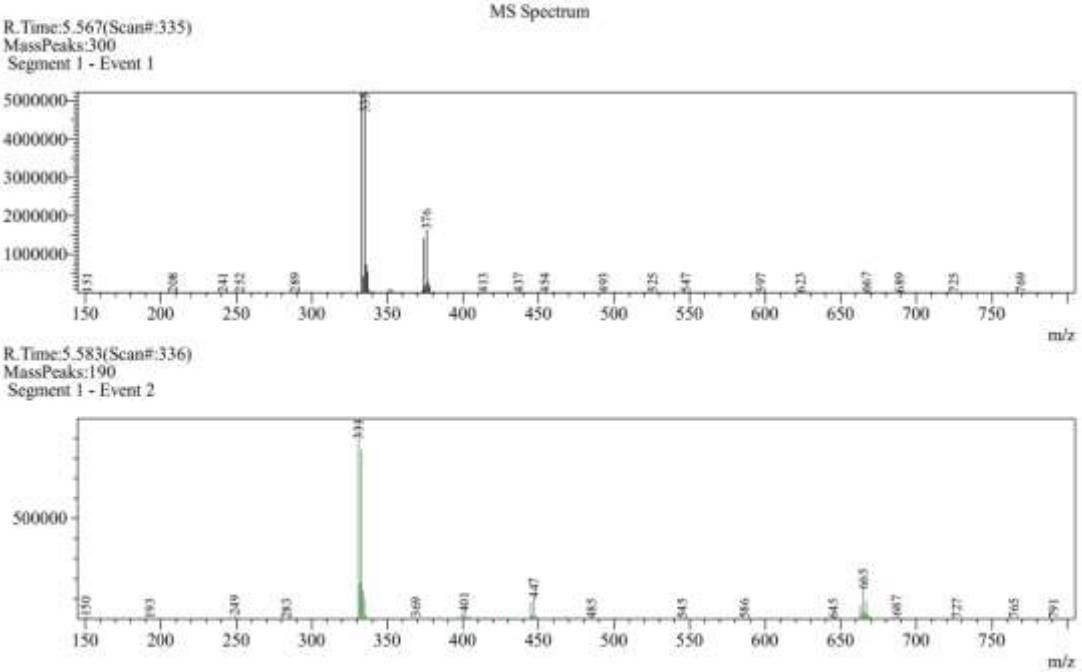
<Sample Information>

Sample Name	: GS01-85		
Sample ID	:		
Data Filename	: GS01-85.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-83	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

<Chromatogram>



MS Spectrum



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Intermediate 6

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: GS01-86		
Sample ID	:		
Data Filename	: GS01-86.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-84	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

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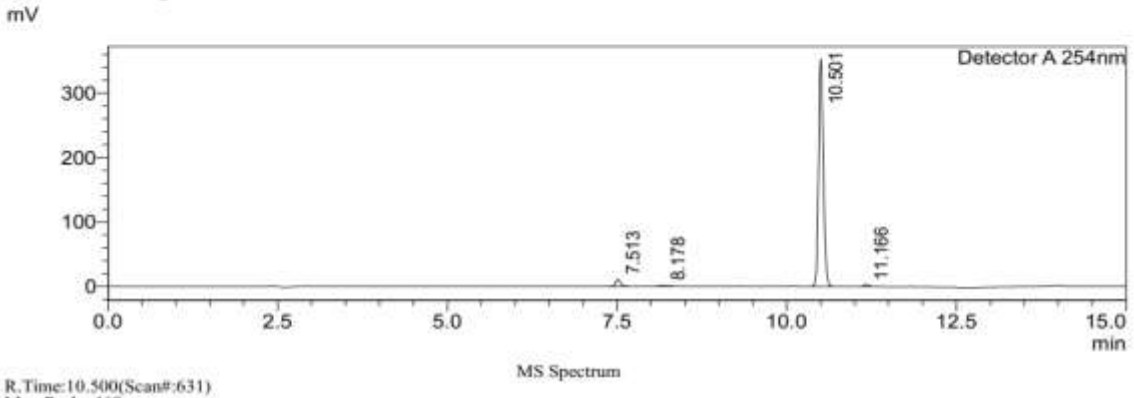
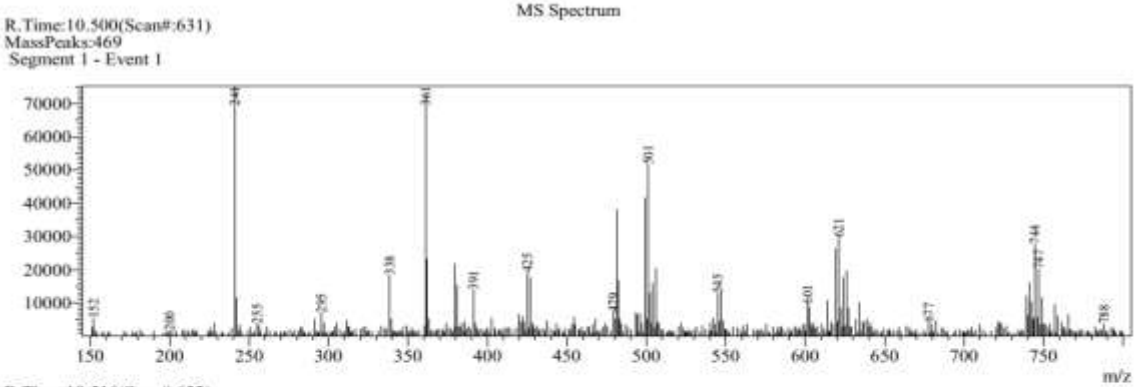
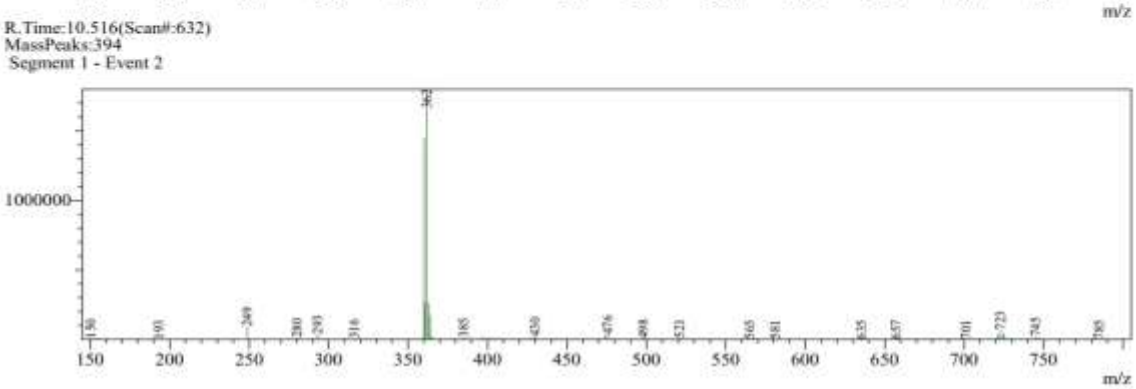


MS Spectrum





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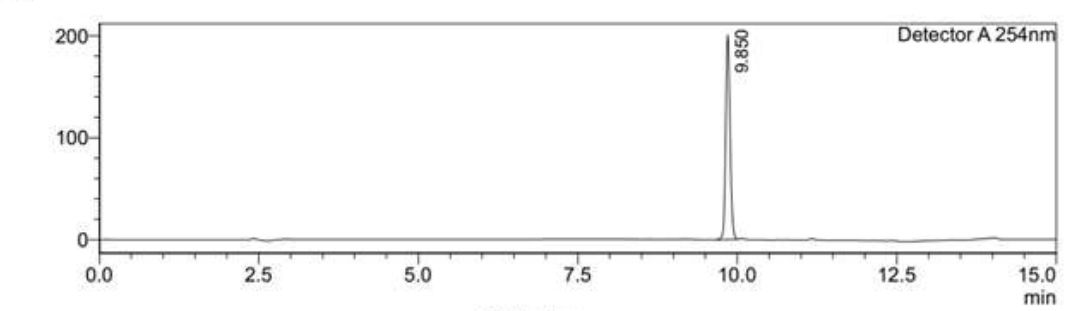
Intermediate 7

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

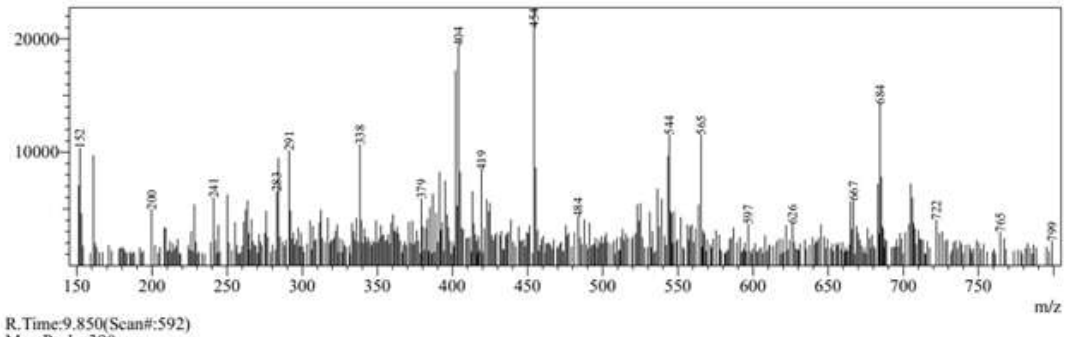
Sample Name	: GS01-87		
Sample ID	:		
Data Filename	: GS01-87.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-85	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

<Chromatogram>



MS Spectrum

R.Time:9.833(Scan#:591)
MassPeaks:505
Segment 1 - Event 1



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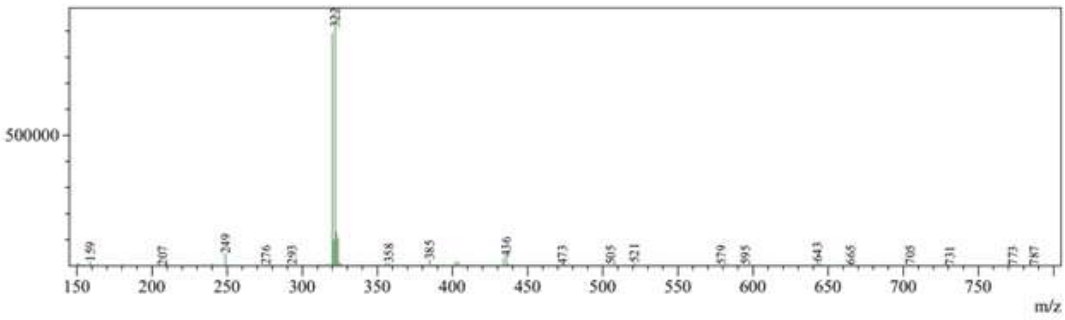
MassPeaks:390
Segment 1 - Event 2



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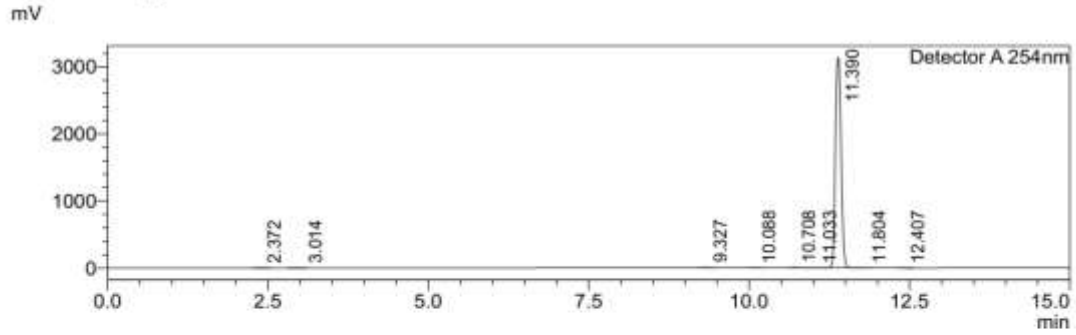
Intermediate 8

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

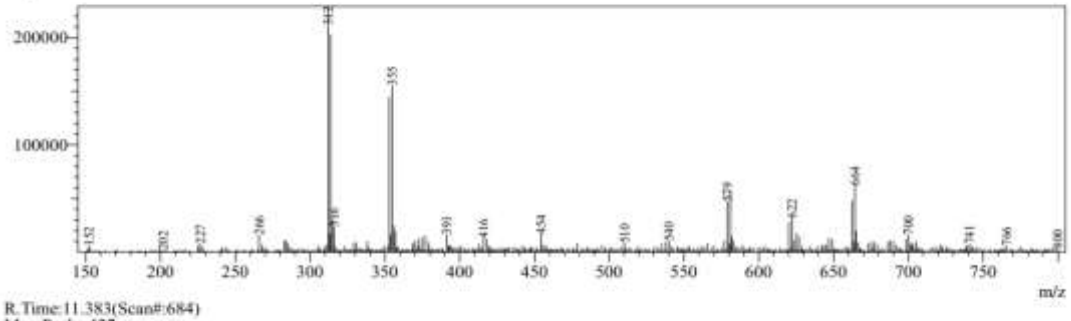
Sample Name	: Unknown Sample010		
Sample ID	: -006		
Data Filename	: GS01-89.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: [LCMS]Acridine.lcb		
Vial #	: 1-77	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

<Chromatogram>



MS Spectrum

R.Time:11.367(Scan#:683)
MassPeaks:536
Segment 1 - Event 1



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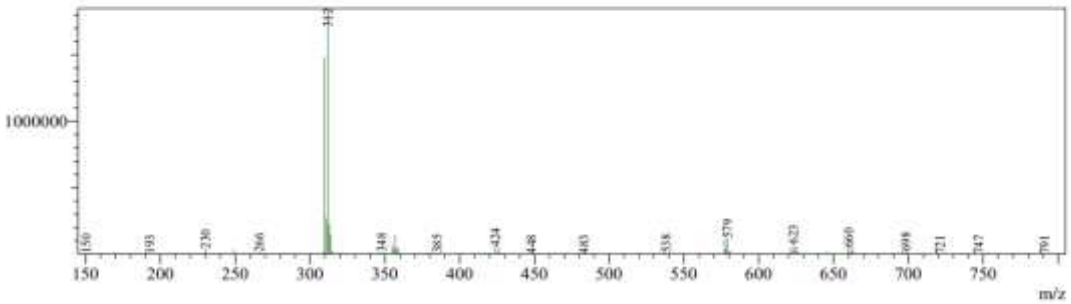
MassPeaks:427
Segment 1 - Event 2



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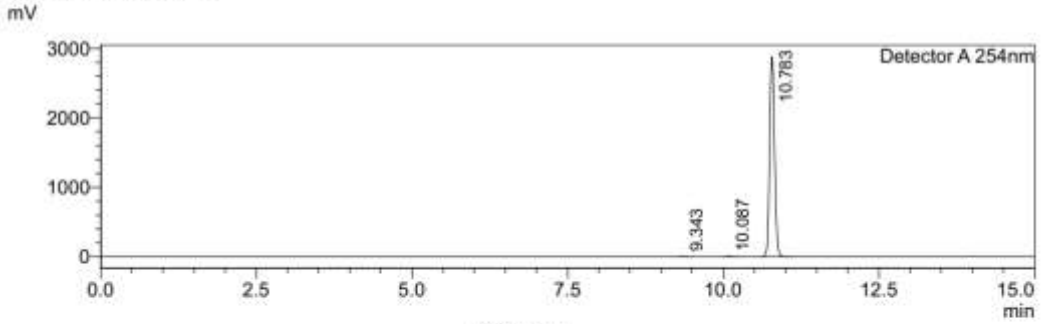
Intermediate 9

SHIMADZU LabSolutions **Analysis Report**

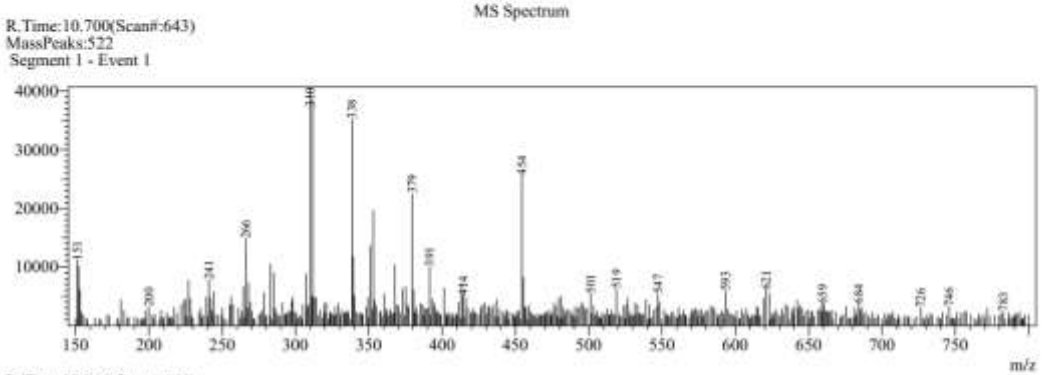
<Sample Information>

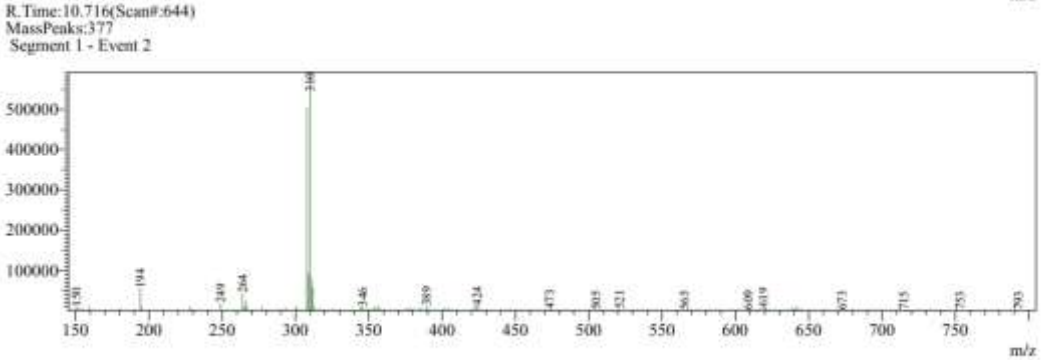
Sample Name	:		
Sample ID	:		
Data Filename	: GS01-90.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-65	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

<Chromatogram>



MS Spectrum





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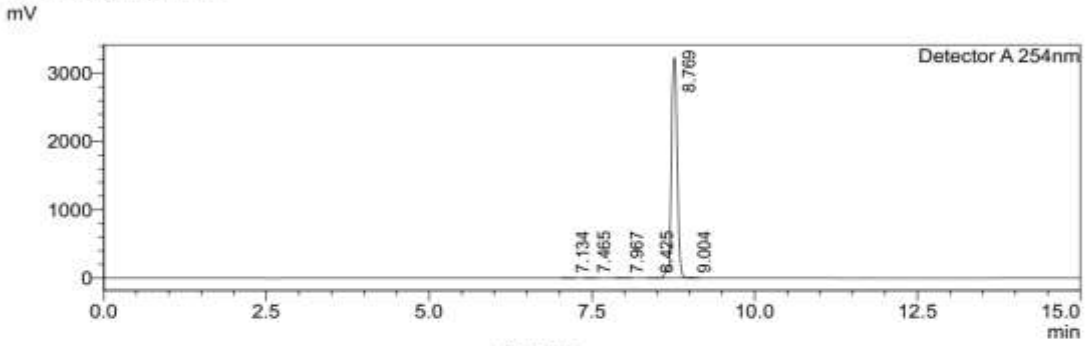
Intermediate 10

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	:		
Sample ID	:		
Data Filename	: GS01-100.lcd		
Method Filename	: 25min, 254nm(ACN 10 to 90).lcm		
Batch Filename	: Batch 20180706.lcb		
Vial #	: 1-79	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	:	Acquired by	: System Administrator
Date Processed	:	Processed by	: System Administrator

<Chromatogram>



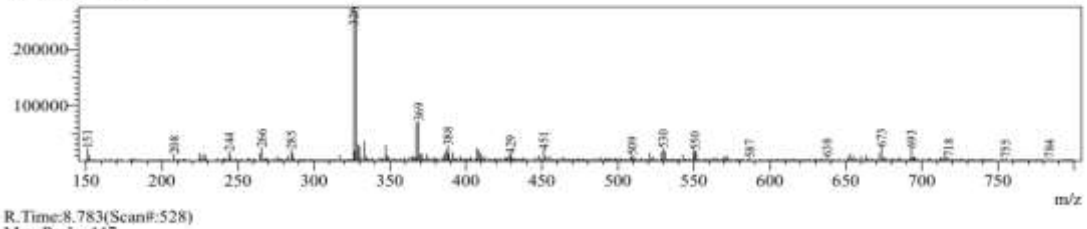
Peak Table

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7.134	20853	4414	0.104			
2	7.465	7251	1556	0.036			
3	7.967	29047	5642	0.144			
4	8.425	5385	1018	0.027			
5	8.769	20057292	3233404	99.653		SV	
6	9.004	7248	2063	0.036		T	
Total		20127076	3248097				

MS Spectrum

R.Time:8.767(Scan#:527)
MassPeaks:582
Segment 1 - Event 1



R.Time:8.783(Scan#:528)
MassPeaks:447
Segment 1 - Event 2