Synthesis of sulfonylthioureas containing two carbon linker as potential antidiabetic drugs

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Declaration

I Tiyisela Nyeleti Mbhokazi hereby declare that this dissertation titled “Synthesis of sulfonylthioureas containing two carbon linker as potential antidiabetic drugs” has been composed by myself under the supervision of **Prof. S.S Mnyakeni Moleele** and **Dr M.V Bvumbi** and that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified and it is presented for a Master of science degree in chemistry at the University of Venda.

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Abstract

Target compounds **(18a-s)** from the series (morpholine, piperidine, N-methylaniline, 2,6-dimethylaniline and diethylamine) of novel sulfonylthioureas were designed and synthesized over three reaction steps using different appropriate synthetic methods. Nucleophilic substitutions were employed in order to incorporate amines, three different carbon linkers between amines and sulfonylthioureas moiety. Furthermore, nucleophilic substitution reaction was used to incorporate appropriate substituted isothiocynates as the final main step. Compounds (**18a-s**) were obtained in good to excellent yields and were characterized using a combination of ^{1}H NMR, ^{13}C NMR, IR and HRMS analysis**.** Compounds (**18a-s**) were evaluated for their antidiabetic activity against α-glucosidase and α-amylase. The *in vitro* screening results showed that most compounds had little to moderate activity against α-amylase at the concentrations of 60μM, 120μM and 240μM. When compounds were tested against α-glucosidase, they showed little to moderate antidiabetic activity at the concentrations of 60μM and 120μM but exhibited significant anti-diabetic activities at 240μM. Compounds that have a phenyl group substituent (**18j**, **18m**, **18q**, **18r** and **18s** with inhibition 70.21±5.97, 78±3.03, 76.33±2.03, 69.55±4.11 and 84.67±3.34 respectively at 240 μM) and a methyl group substituent (**18q-s**) exhibited stronger inhibition activity.

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Abbreviations/acronyms

ATP:	Adenosine Triphosphate
α:	Alpha
ATCC:	American Type Culture Collection
β:	Beta
br s:	broad single
^{13}C NMR:	Carbon Nuclear Magnetic Resonance
$CDCl_3$:	Deuterated chloroform
DMSO-d_6:	Deuterated Dimethyl sulfoxide
DM:	Diabetes mellitus
d:	doublet
dd:	doublet of doublets
FTIR:	Fourier transform infrared spectroscopy
GDM:	Gestational Diabetes Mellitus
GPx:	Glutathione Peroxidase
Hz:	Hertz
IDF:	International Diabetes Federation
MHz:	Mega hertz
m.p:	Melting point
mL:	millilitre
mmol:	millimole
m:	multiplet
NBRC:	Nite Biological Resource Centre
ppm:	parts per million
PPAR-γ:	Peroxisome Proliferator Activated Receptor Gamma
^{1}H NMR:	Proton Nuclear Magnetic Resonance
q:	quartet
quint:	quintet
s:	singlet
SGLT1:	Sodium-glucose Co-transporter-1
SGLT2:	Sodium-glucose Co-transporter-2

SUR 1:	Sulfonylurea Receptor 1
TMS:	Tetramethylsilane
TLC:	Thin layer chromatography
t:	triplet
WHO:	World Health Organization

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CHAPTER ONE

1. INTRODUCTION AND LITERATURE REVIEW

1.1 Diabetes

Diabetes is a metabolic disease that occurs when there is a deficiency in insulin production or no insulin in the pancreas.[1] Insulin is a hormone secreted by the pancreas that allows glucose in the body to enter the body cells and is secreted from the beta cells of the pancreas.[1] The effect of insulin is on several body cells, including muscle and red blood cells, which is to absorb glucose and decrease it to the normal range.[2]

1.2 Metabolic role of insulin

Insulin is a master regulator of energy storage and metabolism and has key and complex effects on the liver, muscle, brain, and fat cells.[3] Insulin stimulates glucose uptake by muscle and adipose tissue.[4] Alternatively, another hormone called glucagon is released by alpha cells of the pancreas, as shown in **Figure 1** below. When blood glucose is low, glucagon is released by alpha cells of the pancreas, and as a result this stimulates the liver to break down glycogen in the liver so that it can be released into the blood as glucose.[5]

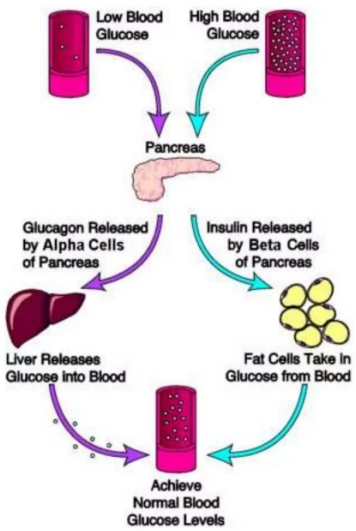


Figure 1: Insulin and glucagon action.[5]

1.3 Main types of diabetes

1.3.1 Type 1 diabetes

Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes, is characterized by insulin deficiency due to pancreatic β-cell loss.[2] In this condition, the body produces little or no insulin due to the cells in the pancreas responsible for producing insulin being destroyed. These cells can be destroyed by an autoimmune response in type 1 diabetes, where the immune system mistakenly attacks and destroys them.[6] Insulin helps keep the blood sugar level from getting too high.[7] When the insulin is not enough, glucose builds up in the bloodstream instead of going into the cells, where it is used for energy, as shown in **Figure 2** below.[8]

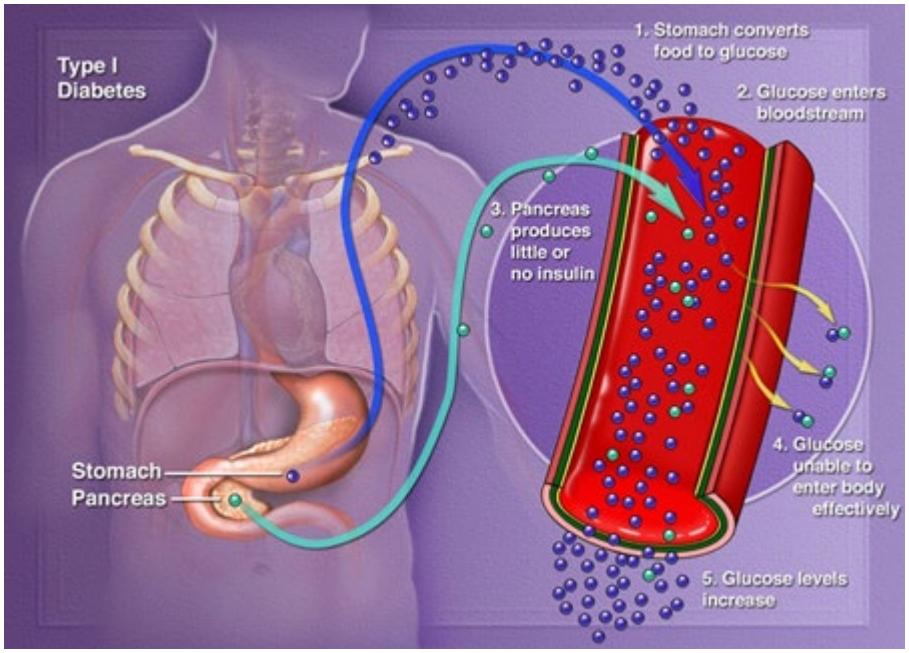


Figure 2: Type 1 diabetes.[8]

1.3.2 Type 2 diabetes

Type 2 diabetes mellitus (T2DM) is also known as insulin-independent diabetes, and occurs when the body cells are unable to use the insulin produced by the pancreas resulting in high blood glucose in the blood. (**Figure 3**).[9] Due to its insulin resistance, T2DM is considered to be a disease with a strong hereditary component.[10]

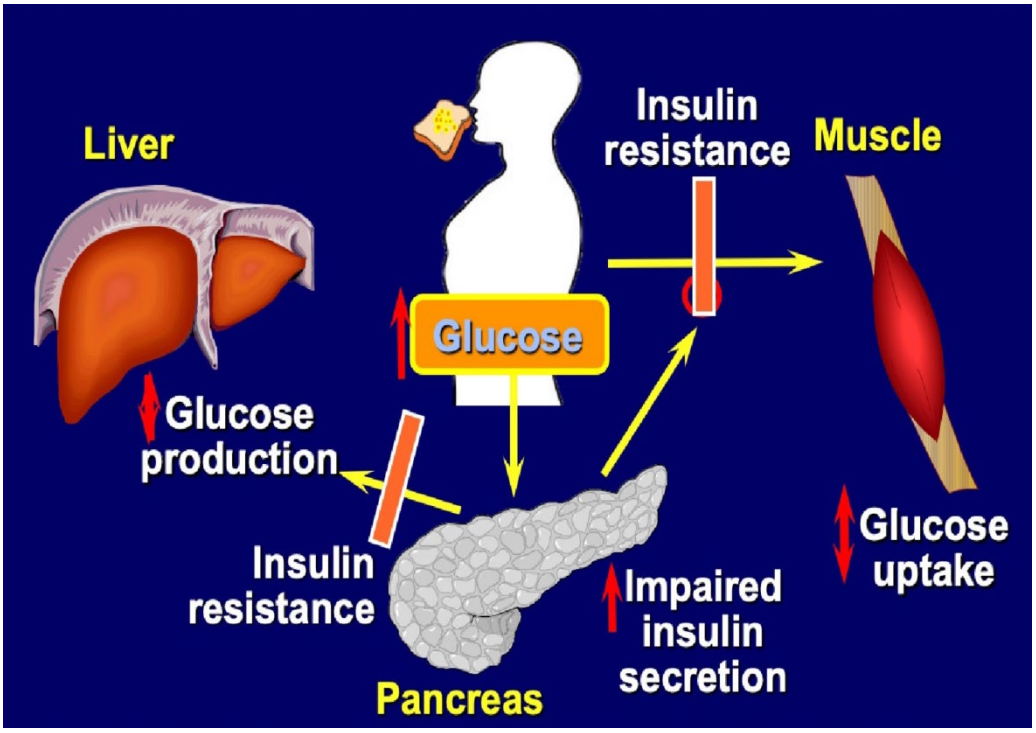


Figure 3: Type 2 diabetes.[9]

1.3.3 Gestational diabetes

Gestational diabetes is a type of diabetes that occurs during pregnancy and is diagnosed when blood glucose levels are raised above the normal ranges for pregnancy.[11] This rare type of diabetes is short-termed, but if left untreated, it can damage the health of the foetus or mother.[11] It commonly occurs between the 24th and 28th week of pregnancy and, in some cases, even earlier.[12] This form of diabetes is caused by normal pregnancy hormones released by the placenta.[12] These hormones reduce the normal function of the mother's insulin. In the presence of pregnancy hormones, normal insulin levels can no longer control blood sugar levels, which is called insulin resistance.[4]

1.4 Causes and symptoms of diabetes

In both Type 1 and 2 diabetes, glucose cannot enter the cells; hence it builds up in the blood. As a result, this causes several diabetes symptoms, such as frequent use of the lavatory, excessive thirst, weight loss, increased hunger, blurry vision, erectile dysfunction, urinary tract infections, yeast infections, and dry itchy skin.[13]

Diabetes mellitus results mainly from a deficiency or diminished effectiveness of insulin that is normally produced by the beta cells of the pancreas. It is characterized

by high blood sugar and glucose metabolism, which affects blood vessels and causes several organ damage.[14] Factors such as aging, obesity, insufficient energy consumption, smoking, and alcohol drinking play a vital role in the pathogenesis of type I or II diabetes mellitus.[15]

1.5 Diabetes in South Africa

Recent data from the International Diabetes Federation (IDF) estimates that 7% of South Africans between the ages of 21 and 79 have diabetes.[16] Diabetes has been reported as the second leading cause of death after tuberculosis (TB) and the top leading cause of death amongst women in South Africa. These statistics do not include the deaths caused by Covid-19.[17,18]

It is essential to evaluate any epidemiological or demographic transition related to diabetes for effective public health strategies, resource management, policy development, research advancement, and monitoring progress in combating diabetes.[64] In 2012, health authorities in the KwaZulu-Natal province reported that the prevalence of type 2 diabetes mellitus (T2DM) had increased from 12% to 34.1% when current comorbidities were taken into account.[19] The overall South African prevalence of diabetes has been reported to have increased rapidly from 4.5% (year 2010) to 12.7% (year 2019).[20]

1.6 Current method of treatment of diabetes.

1.6.1 Type 1 diabetes.

Individuals diagnosed with type 1 diabetes must adhere to a management plan that includes insulin administration either via needle injections or an insulin pump.[8] Other management plans may be implemented, including eating a healthy balanced diet with accurate carbohydrate counts, checking blood sugar levels as prescribed, and getting regular physical activity.[9] There has been a rapid evolution in the care and treatment for people with type 1 diabetes, such as genetically engineered insulin and glucose monitoring devices to control the blood glucose levels and to prevent or delay the diabetes-related complications.[64]

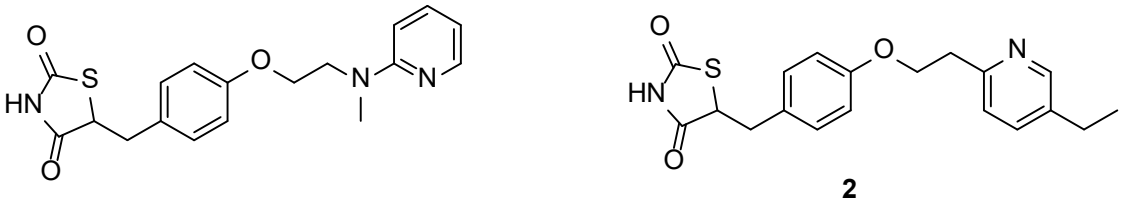
1.6.2 Type 2 diabetes.

Type 2 diabetes cannot be cured but is treated using various antidiabetic drugs. These drugs execute their effectiveness by increasing insulin levels in the body or decreasing

glucose absorption in the intestines.[21] These antidiabetic drugs and their mechanism of action are further discussed in depth below.

1.6.2.1 Thiazolidinediones

Thiazolidinedione (TZD) is a five-membered heterocyclic class of compound. It is known as an insulin sensitizer, the first drug to address the fundamental problem of insulin resistance in type 2 diabetes patients.[22] This class of oral antidiabetic agents was originally developed as antioxidants.[66] Examples of thiazolidinediones are rosiglitazone **(1)** and pioglitazone **(2)**, as shown in **figure 4** below.[22]



1 **2**

Figure 4: Examples of Thiazolidinedione drugs.

Mechanism of action

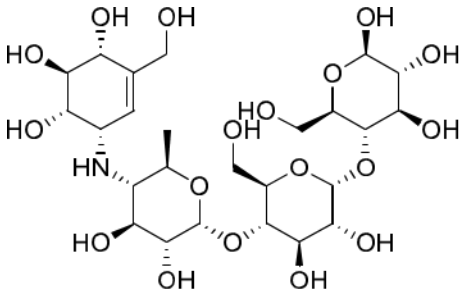
Thiazolidinediones (TZDs) aid in reducing glucose by increasing the body's sensitivity to insulin and do not cause hypoglycemia when used as single agents (or in combination with metformin). Their mechanism of action involves activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR gamma), a nuclear receptor.[22] TZDs reduce insulin resistance in adipose tissue, muscle, and the liver. However, PPAR gamma is predominantly expressed in adipose tissue.[23] Long term use of TZDs may result in several side effects such as edema, congestive heart failure, bladder cancer and increased teratogenic effects.[24]

1.6.2.2 Inhibitors of α-Glucosidases

An α-glucosidase is an enzyme that catalyzes the hydrolysis of carbohydrates and starches to produce simple sugars or glucose for intestinal absorption.[25] They coordinate this breakdown of polysaccharides to glucose by using membrane-bound intestinal enzymes such as Maltase-glucoamylase (MGAM) and Sucrase-isomaltase (SI).[26]

Inhibitors of alpha glucosidases slow the digestion of ingested carbohydrates, delay glucose absorption into the bloodstream, and decrease postprandial blood glucose

levels. [27] They are not associated with weight gain, nor do they cause hypoglycemia when used as monotherapy or in combination with metformin.[26] Examples of inhibitors of α-glucosidases are acarbose **(3)** and miglitol (**4**), as shown in **figure 5** below.



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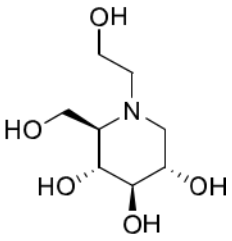

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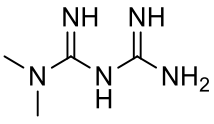
Figure 5: Examples of Inhibitors of α-Glucosidases.

Mechanism of action

Inhibitors of α-glucosidases are the only drug class not directly designed to combat a specific pathophysiologic defect of type 2 diabetes. They rather inhibit the activity of α-glucosidase, a brush-border enzyme responsible for breaking down disaccharides and polysaccharides into monosaccharides.[27] Glucose absorption is completed over an extended period, and postprandial hyperglycemia is reduced.[28] The use of inhibitors of α-glucosidases has been associated with several side effects, such as abdominal distention, flatulence, diarrhea and pneumatosis cystoid intestinalis.[29]

1.6.2.3 Biguanides

Biguanides are air-stable polynitrogenated compounds composed of two guanidine units bounded by a common nitrogen atom.[27] They are polar and hydrophilic compounds and, therefore, highly soluble in aqueous media due to their chemical structure, composed of two imino and three amino groups in tautomerism.[30] Examples of biguanides are metformin **(5)** and phenformin **(6)**, as shown in **figure 6** below.



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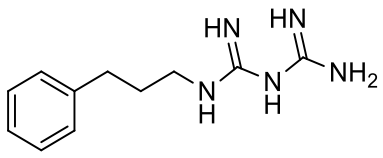

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Figure 6: Examples of Biguanides drugs.

Mechanism of action

The antidiabetic effect of the biguanides appear to be distinct from their hypoglycaemic effect.[31] Biguanides, like metformin, primarily target the liver's AMP-activated protein kinase (AMPK). By activating AMPK, metformin enhances insulin sensitivity, reduces hepatic glucose production, and improves glucose uptake in peripheral tissues.[67] Biguanides, in high doses, inhibit the oxidation of carbohydrate substrates by affecting mitochondrial function. The therapeutic use of biguanides has several side effects, including vitamin B_{12} deficiency and hemolytic anemia.[31]

1.6.2.4. Sodium-Glucose Co-transporter-2 (SGLT2) Inhibitors.

Sodium-Glucose Co-transporter-2 is a protein from the sodium-glucose co-transporter family that mediates sodium and glucose transport. This activity depends on sodium extrusion.[32] This co-transporter is mainly responsible for the reabsorption of the filtered plasma glucose in the renal tubule; as a result, there is an increase in the levels of glucose absorbed by the intestines.[33]

SGLT2 inhibitors are an insulin-independent class of oral antidiabetic medications. These inhibitors are low-capacity, high-affinity glucose transporters found exclusively in the kidney. The SGLT2 inhibitors differ primarily in their binding, affinity, and selectivity for SGLT transporters.[34] As of 2013, the Food and Drug Administration (FDA) approved the following four SGLT2 inhibitors, namely: dapagliflozin **(7)**, canagliflozin **(8)**, empagliflozin **(9)**, and ertugliflozin **(10)** represented in **figure 7** below.

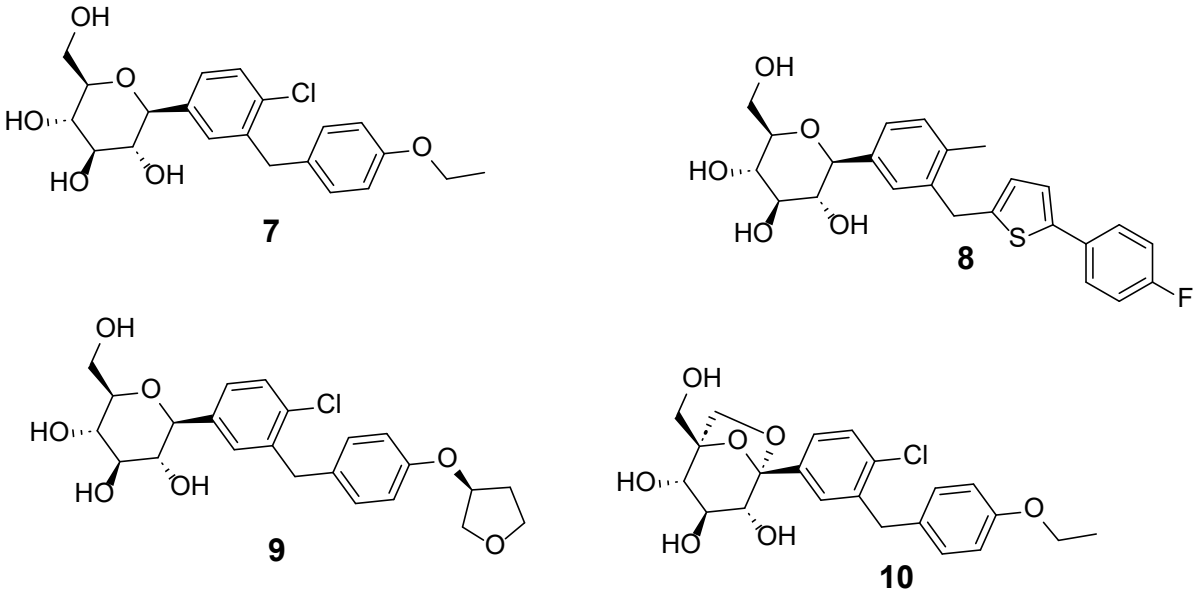


Figure 7: Examples of Sodium-glucose cotransporter-2 inhibitor drugs.

Mechanism of action.

SGLT2 inhibitors are unique compared to other antidiabetic oral agents because their mechanism of action is independent of β-cell function and insulin secretion. These inhibitors target SGLT2 proteins in the kidneys and, therefore, inhibit glucose reabsorption in the kidneys. As a result, they increase renal glucose and sodium excretion.[34] By inhibiting these transporters, which are primarily located in the proximal convoluted tubule, they prevent the reabsorption of glucose from the urine back into the bloodstream.[68] Side effects associated with SGLT2 are hypoglycaemia, hypotension, lower limb amputation, fractures, urinary infections, and diabetic ketoacidosis.[36]

1.6.2.5 Sulfonylureas.

Sulfonylureas are a class of agents that lower blood sugar levels as a result of the increasing release of insulin from the pancreas. The sulfonylureas are used for the therapy of mild-to-moderate type 2 diabetes in conjunction with diet. They can be used alone or in combination with metformin, thiazolidinediones, or other hypoglycemic agents.[37] Examples of sulfonylureas are glipizide **(11)** and tolbutamide **(12),** as shown in **figure 8** below**.**

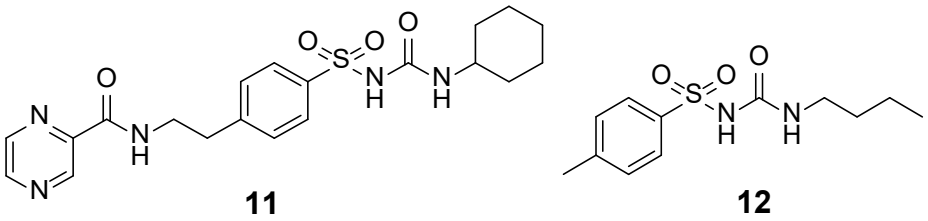


Figure 8: Examples of Sulfonylureas drugs.

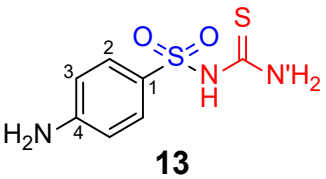
Mechanism of action

Sulfonylureas bind and inhibit the ATP-sensitive potassium channels on the pancreatic beta cells. As a result, potassium efflux decreases, and the beta-cell membrane depolarizes, thus removing the electric screen, which prevents the diffusion of calcium into the cytosol.[38] Sulfonylureas also lower blood glucose levels by increasing insulin secretion in the pancreas. Side effects associated with sulfonylureas include body weight gain, hypoglycemia, nausea, and skin reactions. [39]

1.7 The chemistry of sulfonylthioureas.

Sulfonylthiourea is a thiourea derivative bearing sulfonamide moiety that contains sulfur instead of oxygen.[40]

The structure of sulfathiourea (**13**) can be divided into four parts: the para amino group, which is essential for activity and should always be substituted on the para position of the aromatic ring, secondly the aromatic ring, which is the minimal structural requirement for activity, then the sulfonamide group whereby the sulphur atom is directly linked to the aromatic ring in a 1,4-position to the amine, and the $N'H_2$ substitution in which the sulfonamide nitrogen should be primary or secondary.[41] When the $N'H_2$ is substituted with an isothiocyanate, the compound is known as sulfonylthiourea.[40]

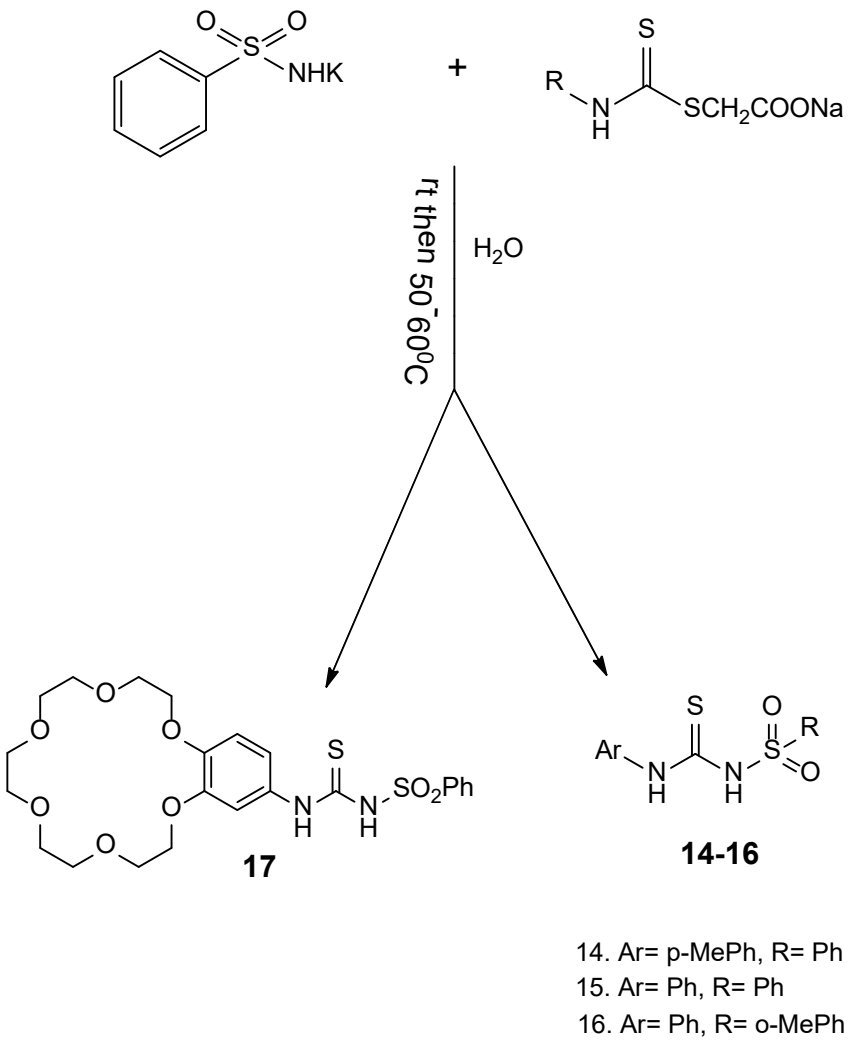


13

1.7.1 Methods of synthesis of sulfonylthioureas.

1.7.1.1 Aqueous-phase synthesis methods.

This method involves the nucleophilic substitution of potassium sulfonamides and sodium dithiocarbamate in water under mild conditions.[42] This method is advantageous due to the following: favorable reaction conditions, free organic solvent, high isolated product yields, and shorter reaction time. The synthetic route outlined in **Scheme 1** was reported [42] to have a shorter reaction time for the preparation of **17** compared to the preparation of **14-16.** These results were due to the benzo-18-crown-6 that can effectively bind K^+ from $ArSO_2NHK$.



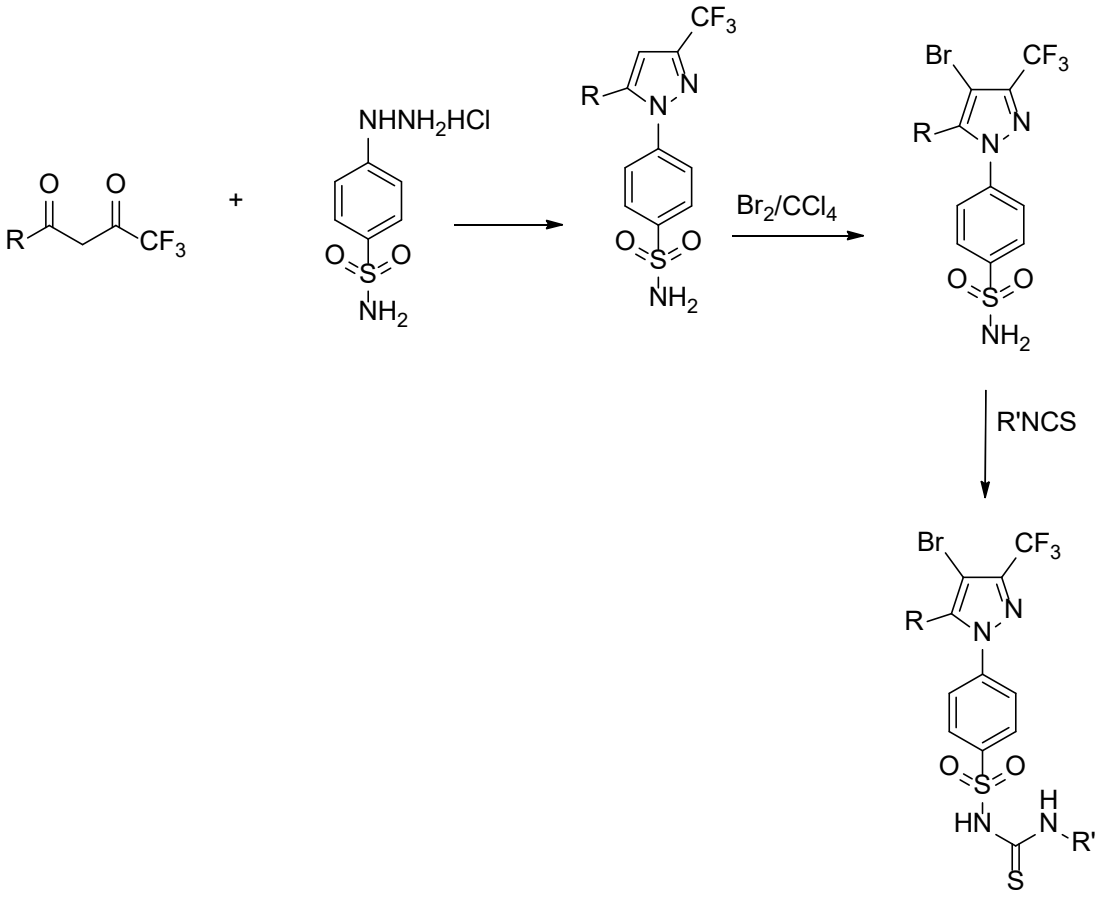
Scheme 1: Aqueous-phase synthesis of derived sulfonylthioureas.

1.8 Biological applications of sulfonylthioureas.

Sulfonylthioureas have been reported to have several biological applications, such as antimicrobial, anticancer, antifungal, antimalarial, and antidiabetic agents.

1.8.1 Antimicrobial agents.

Faidallah H.M et al have synthesized new 3-trifluoromethylpyrazolesulfonylurea and thiourea derivatives as potential antimicrobial and antidiabetic agents **(Scheme 2).**[44] Their results showed that benzoyl and p-chlorobenzene bearing 3-trifluoromethylpyrazolesulfonyl-urea derivatives showed significant activity against various strains of micro-organisms.

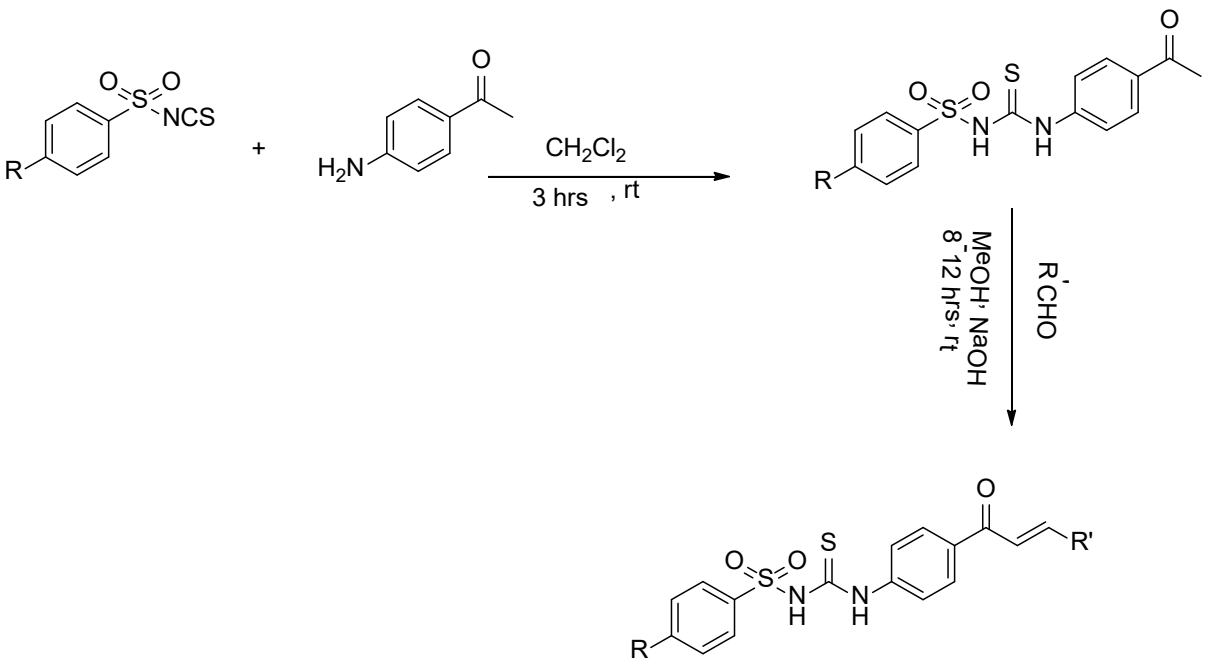


R= CH_3, Furyl
R'= Ph, cyclohexyl, naphthyl, p-C_6H_4Cl

Scheme 2: Synthesis of sulfonylthiourea derivatives with antimicrobial activity.

1.8.2 Antimalarial agents.

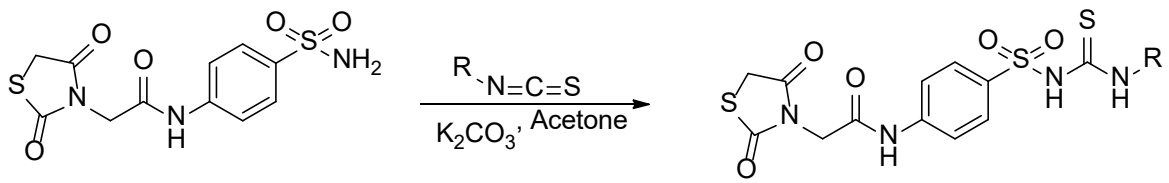
Leon C et al have successfully synthesized and evaluated sulfonylthiourea derivatives as potential antimalarial agents. **(Scheme 3)**.[45] In their study, they found that the derivatives (E)-1-(4-chlorophenylsulfonyl)-3-[4-(3-(2,4-difluorophenyl)acryloyl)phenyl]urea and (E)-1-[4-(3-(2,4-difluorophenyl)acryloyl)phenyl]-3-tosylurea showed the strongest antimalarial activity, with IC50 values of 2.1 and 1.2 mM, respectively. Furthermore, the findings indicate that fluorine substitutions in the aromatic ring of sulfonylurea derivatives may contribute to creating effective antimalarial compounds.



Scheme 3: Synthesis of sulfonylthiourea derivatives with antimalarial activity.

1.8.3 Anticancer agents.

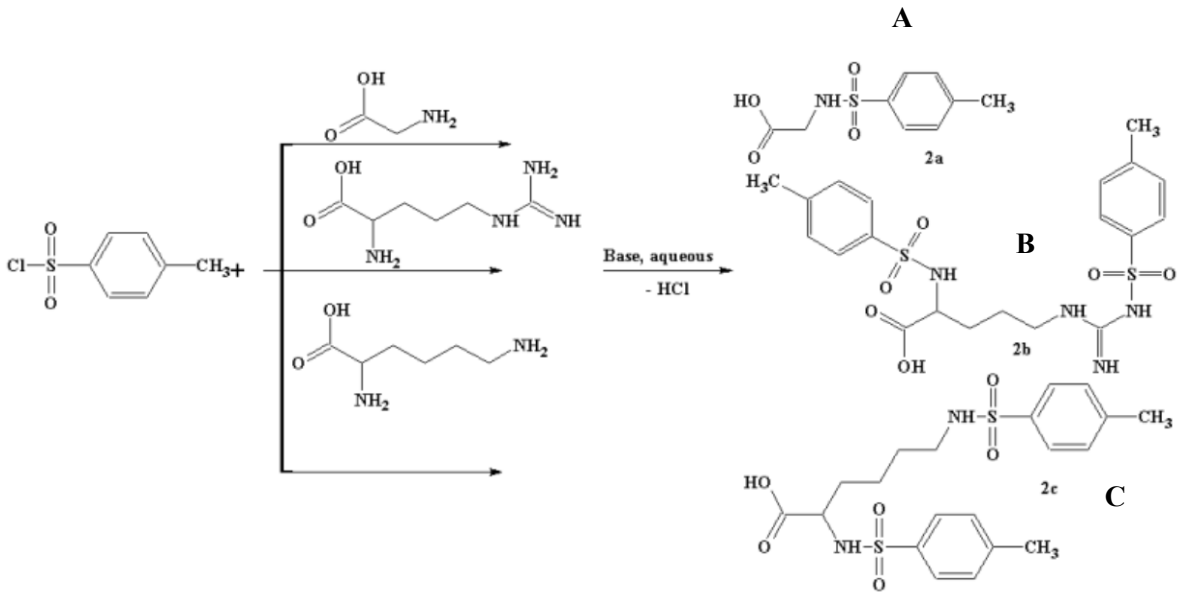
Mohamed AA et al have successfully designed, molecularly docked, and synthesized anticancer and anti-hyperglycemic assessments of thiazolidine-2,4-diones bearing sulfonylthiourea moieties as potent VEGFR-2 inhibitors and PPARγ agonists. **(Scheme 4).**[46] Their research indicated that having cyclohexyl tails linked to sulfonylthiourea linkers and benzylidene groups linked to thiazolidine-2,4-diones enhanced the affinities for the active site. Moreover, the 4-methylbenzylidene derivatives showed more significant effects compared to the unsubstituted thiazolidine-2,4-diones that lacked benzylidene groups.



Scheme 4: Synthesis of thiazolidine-2,4-diones bearing sulfonylthiourea moieties with anticancer activity.

1.8.4 Antifungal agents.

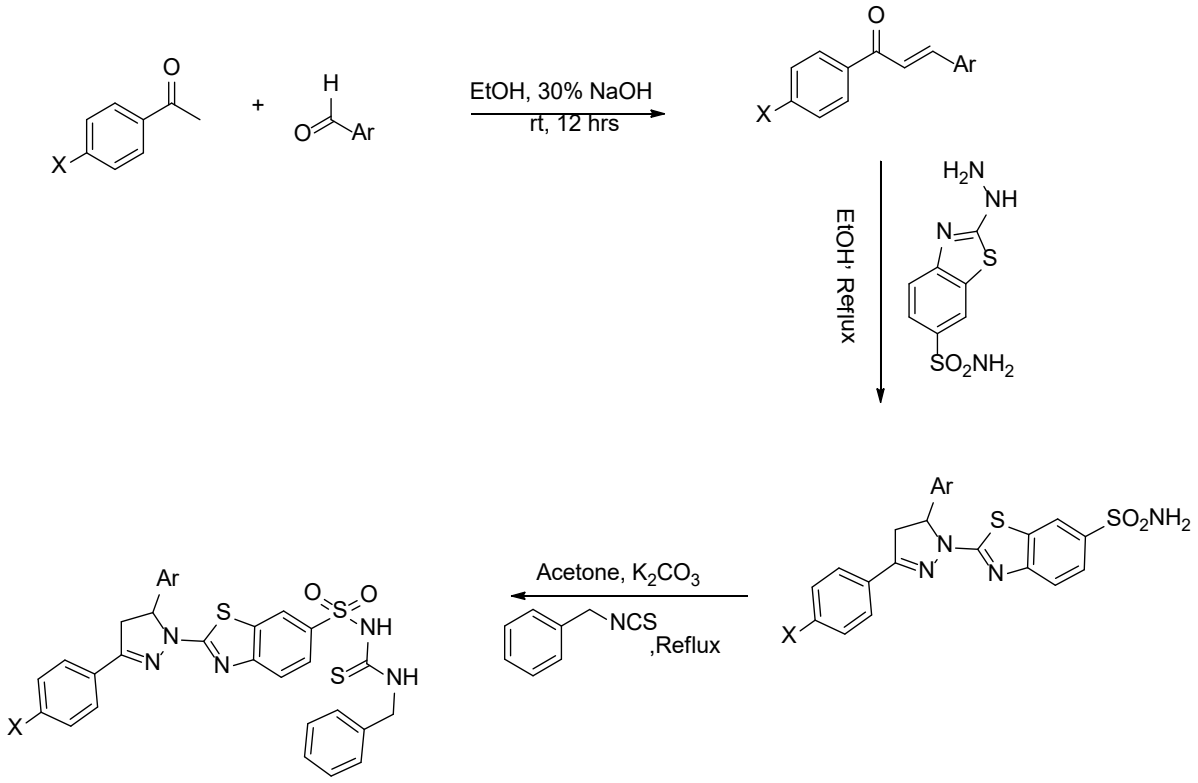
Qadir et al have successfully synthesized and evaluated antifungal properties of amino acids containing sulfonamide moieties for their antifungal activities**. (Scheme 5).**[43] In their research, they found that all synthesized sulfonamides (**A**, **B**, and **C**) demonstrated outstanding antifungal effects against the fungi tested. Furthermore, compound **B**'s derivative showed the largest zone of inhibition against the gram-positive S. aureus, which was identified as the most sensitive bacterial strain among those examined.



Scheme 5: Synthesis of antibacterial and antifungal possession of amino acids containing sulfonamide moieties.

1.8.5 Antidiabetic agents.

Kharbanda C et al have successfully synthesized benzothiazole based sulfonylthioureas as potential antidiabetic agents. **(Scheme 6).**[47] They noted that sulfonylureas made from p-chloroacetophenone are generally more biologically active than those derived from p-bromoacetophenone. Additionally, they explained that in the case of p-chloro derivatives, sulfonylureas exhibit greater activity than sulfonylthioureas, whereas the opposite is true for p-bromo derivatives, with a few exceptions.



X= Cl, Br

Scheme 6: Synthesis of sulfonylthiourea derivatives with antidiabetic activity.

1.9 Rationale of the study.

It is estimated that the number of people affected by diabetes will rise to 578 million by 2030 and 700 million by 2045, leading the World Health Organization to consider diabetes an epidemic. The prevalence of diabetes in South Africa is the highest in the African continent, reaching 11.3%.[27] Diabetes imposes a significant financial burden on the public healthcare in South Africa; as a result, it is essential to study better and more affordable antidiabetic drugs to minimize these medical costs.

1.10 Aims of the study.

This study aims at synthesizing the novel sulfonylthioureas analogues containing three different carbon linkers as potential antidiabetic drugs. The following objectives were undertaken to achieve the aim of the project.

1.10.1 Study objectives

- Synthesis and characterization of sulfonylthiourea analogues as antidiabetic drugs.

- Screening of the antidiabetic activities of synthesized sulfonylthioureas compounds against carbohydrate hydrolyzing enzymes (alpha glucosidase and alpha amylase)
- Determination of toxicity levels of the synthesized novel compounds.

CHAPTER TWO

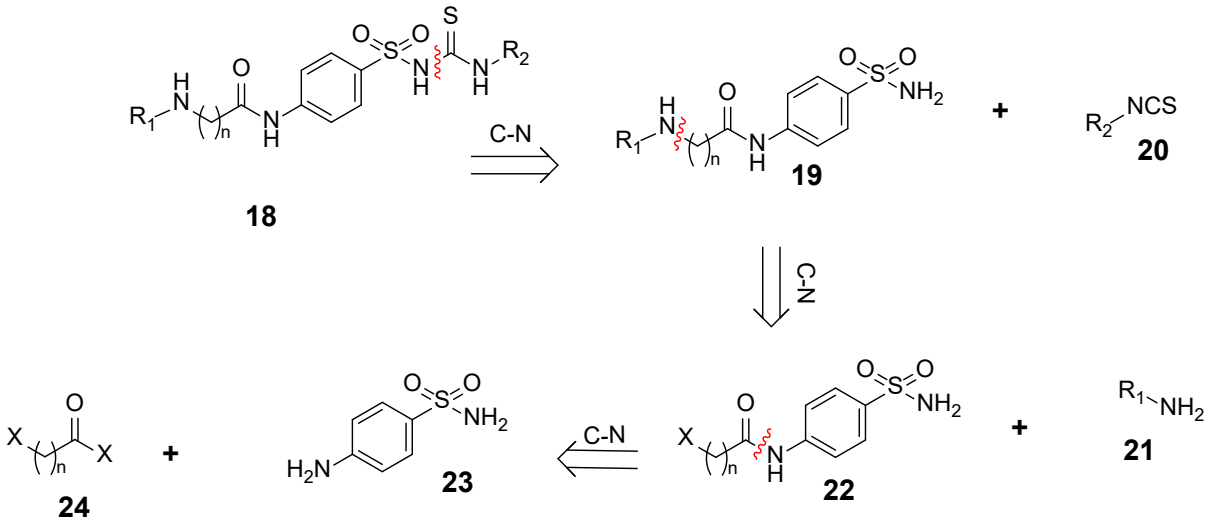
2. Results and discussion

This chapter describes the results obtained in the synthesis of sulfonylthiourea compounds. Furthermore, it also describes results obtained from different characterization techniques throughout the course of the project and the *in vitro* anti-diabetic results.

2.1 Chemistry

The general synthetic method used by Ibrahim, M.K et al [50] was adopted for the preparation of sulfonylthiourea analogues in this study.

2.1.1 Retrosynthetic analysis followed.



R_1 = Morpholine, Piperidine, N-methylaniline, 2,6-dimethylaniline, Diethylamine
R_2 = Cyclohexyl, Phenyl, Ethyl, Propyl, Butyl, Tert-butyl
X = Cl, Br
n = 1, 2

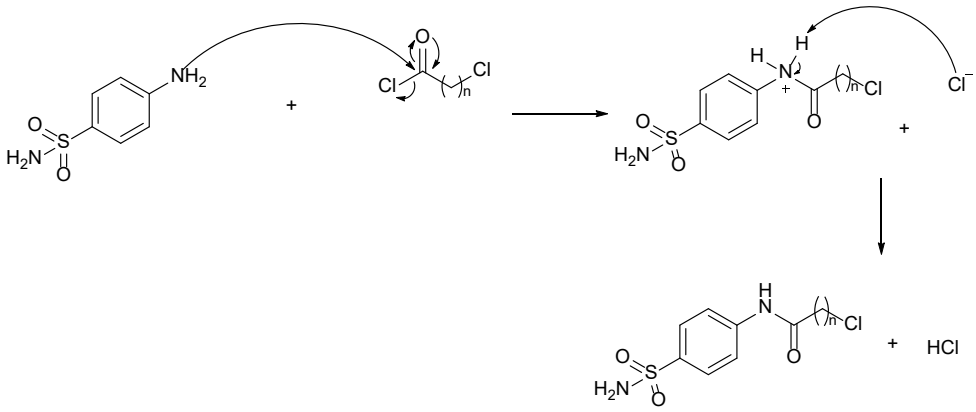
Scheme 7: Retrosynthetic analysis of the target sulfonylthiourea compounds.

Target compounds **18** could be retrosynthesized to isothiocyanates **20** and amino-*N*-(4-sulfamoylphenyl)amides **19** by cleaving the C-N bond as depicted in **scheme 7** above. Another C-N bond cleavage of compounds **19** could lead to substituted 4-aminobenzenesulfonamides **22** and amines **21**. Compounds **22** could be

retrosynthesized to the commercially available 4-aminobenzenesulfonamides **23** and (3-chloropropionyl chloride, 2-chloroacetyl chloride or 2-bromo-2-methylpropanoyl bromide) **24**.

2.1.2 N-acylation reaction.

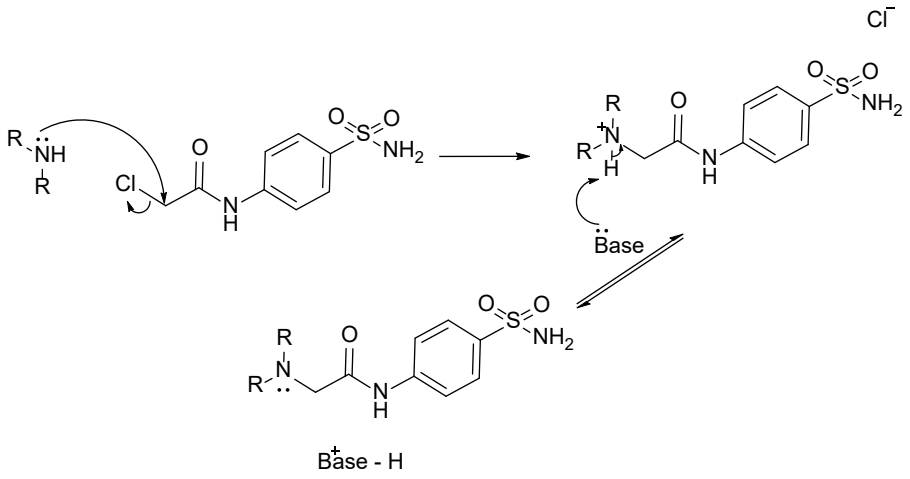
The first reaction adopted was the N-acylation reaction with acid chloride being introduced to the amine on the sulfanilamide. The nitrogen atom of the amine attacks the carbonyl carbon of the acid chloride, resulting in the formation of an N-acylated amine and HCl as a byproduct.



Scheme 8: Proposed reaction mechanism of the N-acylation with acid chloride.

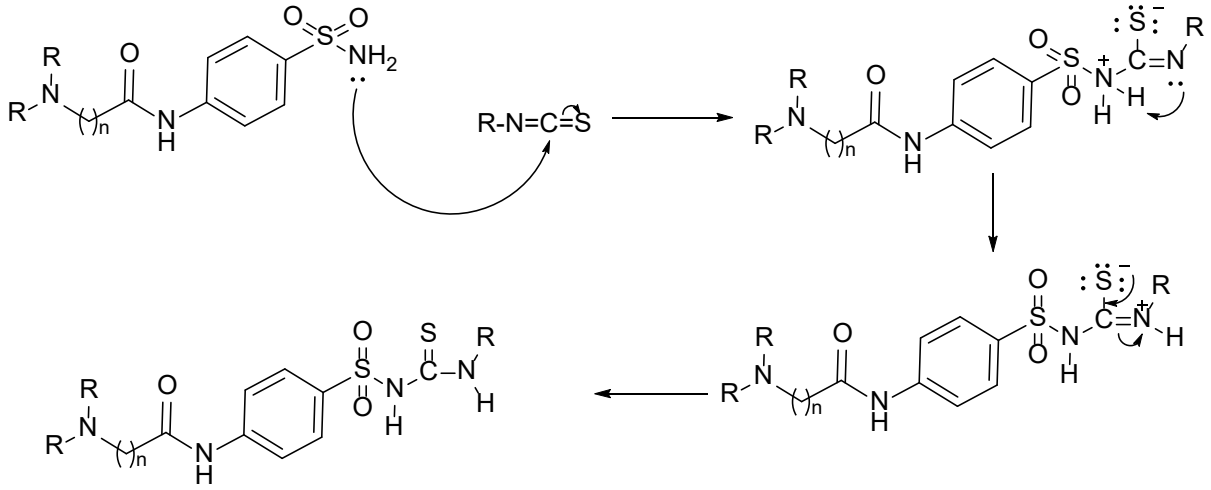
2.1.3 N-alkylation reaction.

The second reaction was the N-alkylation reaction where the amine nitrogen acts as a nucleophile, attacking the electrophilic carbon of the alkyl halide, which displaces the chloride and forms a new C-N bond. Then an acid/base reaction where the base removes a proton from the positively charged nitrogen center, resulting in the formation of the alkylation product.



Scheme 9: Proposed reaction mechanism of the N-alkylation reaction.

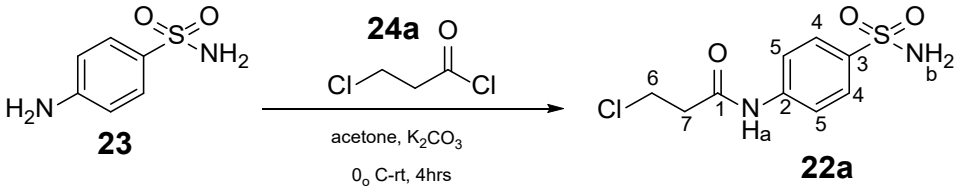
2.1.4 Amination of isothiocyanates.



Scheme 10: Proposed reaction mechanism of the amination of isothiocyanates.

2.2 Propionylamide containing sulfonylthioureas

2.2.1 Synthesis of 4-(3-chloropropionylamido)benzenesulfonamide (22a).



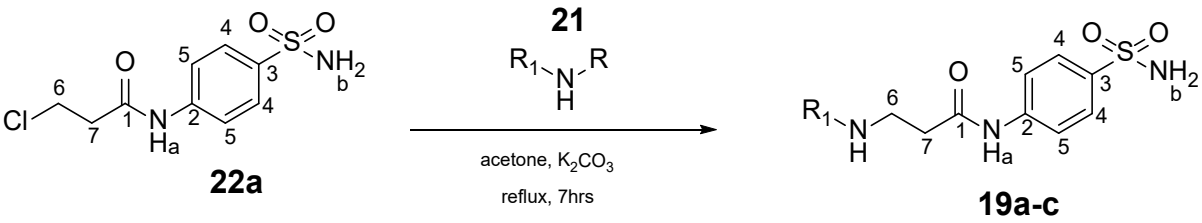
Scheme 11: Synthesis of 4-(3-chloropropionylamido)benzenesulfonamide

The first step of this project was the acylation reaction with the aim of synthesizing 4-(3-chloropropionylamido)benzenesulfonamide **(22a)** by reacting 4-aminobenzenesulfonamide **(23)** dissolved in dry acetone with anhydrous potassium carbonate and 3-chloropropionyl chloride **(24a)** from 0 ^{0}C to room temperature **(Scheme 11)**. The product was obtained as colourless needle-like crystals (10.82 g, 82.3%). Melting point = 228.9–231.2 ^{o}C, reported literature value = 227.85–229.85 ^{o}C [53]). The product was confirmed using NMR spectroscopy. ^{1}H NMR spectrum showed a total of five signals; two singlets, one accounting for one proton (Ha) and the other one accounting for two protons (Hb) at chemical shifts of 10.44 ppm and 7.29 ppm, respectively. Moreover these peaks, the ^{1}H NMR spectrum showed a multiplet at chemical shift 7.96–7.57 ppm accounting for four protons in the aromatic region,

confirming aromatic protons H-4 and H-5. Lastly, 1H NMR spectrum of compound 22a revealed two triplet signals accounting for two protons each at chemical shifts of 3.90 and 2.88 ppm; these signals were ascribed to H-6 and H-7, respectively.

^{13}C NMR spectrum of compound **22a** showed seven peaks in total; two methine carbon peaks, two methylene carbon peaks and three quaternary carbon peaks. Methine carbon peaks were observed at 127.22 ppm (C-4) and 119.12 ppm (C-5), methylene carbon peaks at 41.06 (C-6) and 39.70 (C-7), whereas quaternary carbon peaks were observed at 169.08 (C-1), 142.28 (C-2) and 138.87 (C-3).

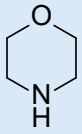
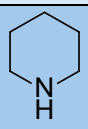
2.2.2 Synthesis of propionylamide based sulfonamides (19a-c).

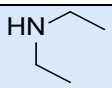


Scheme 12: Synthesis of 4-(3-aminopropionylamido)benzenesulfonamide

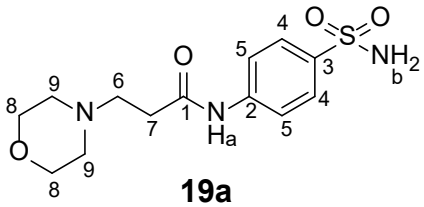
Compound **22a** was treated with secondary amines such as morpholine, piperidine and diethyl amine **21,** in the presence of anhydrous potassium carbonate, while refluxing in acetone for 7 hours **(Scheme 12)** in order to obtain the desired tertiary amines [52]**.** Compounds **19a-c** were characterized with NMR spectroscopy as discussed below. Percentage yields of compounds **19a-c** ranged from 58.11%–71.2%, as summarised in **Table 1** below.

Table 1: 4-(3-aminopropionylamido)benzenesulfonamide **19a-c** data obtained from **scheme 12**

Compound	R_1	Appearance	Melting point (°C)	Yield (%)
19a		White powder	189.3–191.2	71.20
19b		Fluffy yellow powder	192.4–194.3	60.23

19c		Yellow powder	178.6–181.4	58.11

2.2.2.1. Synthesis of 4-(3-morpholinopropionylamido)benzenesulfonamide (19a).

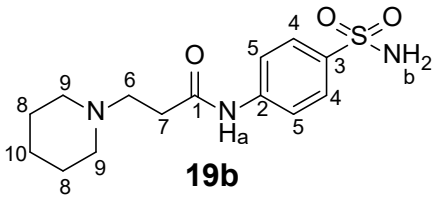


19a

^{1}H NMR spectrum of compound **19a** showed eight peaks, two singlets (one accounting for one proton (H-a) at 10.39 ppm and the other accounting for two protons (H-b) at 7.28 ppm), a multiplet in the aromatic region accounting for four protons (H-4 & H-5) at a chemical shift of 7.70–7.82 ppm, two triplets accounting for two protons each at 2.64 ppm (H-6) and 2.53 ppm (H-7) and two more new multiplets emerging after the nucleophilic substitution of morpholine to the electrophilic carbon bearing the chlorine atom in compound **22a**, accounting for four protons each at 3.58 ppm (H-8) and 2.41 ppm (H-9).

^{13}C NMR spectrum of compound **19a** showed a total of nine peaks, three quaternary carbon peaks, two methine carbon peaks and four methylene carbon peaks. The three quaternary carbon peaks were observed at 171.23 ppm, 142.54 ppm and 138.66 ppm confirming carbons 1, 2 and 3 respectively. Two methine carbon peaks were observed at 127.14 ppm and 119.01 ppm, ascribed to carbons 4 and 5, respectively. Four methylene carbon peaks were observed at 54.46 ppm (C-6), 34.38 ppm (C-7), 66.63 ppm (C-8) and 53.47 (C-9) with C-8 and C-9 having twice the intensity than that of C-6 and C-7 which indicated that there are two carbons represented.

2.2.2.2. Synthesis of 4-(3-piperidinopropionylamido)benzenesulfonamide (19b).

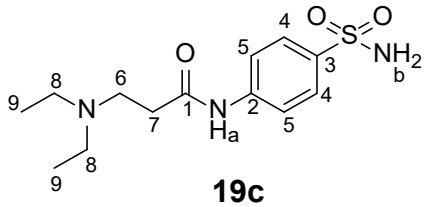


19b

^{1}H NMR spectrum of compound **19b** showed nine peaks, two singlets (one accounting for one proton (H-a) at 10.55 ppm and the other accounting for two protons (H-b) at 7.25 ppm), a multiplet on the aromatic region accounting for four protons (H-4 & H-5)at a chemical shift of 7.72–7.77 ppm, two triplets coupling each other accounting for two protons each at 2.64 ppm (H-6) and 2.53 ppm (H-7) and three more new multiplets emerging after the nucleophilic substitution of piperidine to the electrophilic carbon bearing the chlorine atom of compound **22a**, accounting for four protons at 1.57–1.44 ppm (H-8), four protons at 2.54–2.46 ppm (H-9) and two protons at 1.42–1.33 ppm (H-10).

^{13}C NMR spectrum showed a total of ten peaks, three quaternary carbon peaks, two methine carbon peaks and five methylene carbon peaks. The three quaternary carbon peaks were observed at 171.45 ppm, 142.54 ppm and 138.64 ppm confirming carbons 1, 2 and 3 respectively. Two methine carbon peaks were observed at 127.16 ppm and 118.94 ppm, ascribed to carbons 4 and 5 respectively. Five methylene carbon peaks were observed at 54.46 ppm (C-6), 34.38 ppm (C-7), 66.63 ppm (C-8), 53.47 ppm (C-9) and 24.45 ppm (C-10) with C-8 and C-9 having twice the intensity than that of C-10 which indicated that there are two carbons represented.

2.2.2.3. Synthesis of 4-(3-diethylaminopropionylamido)benzenesulfonamide (19c).



19c

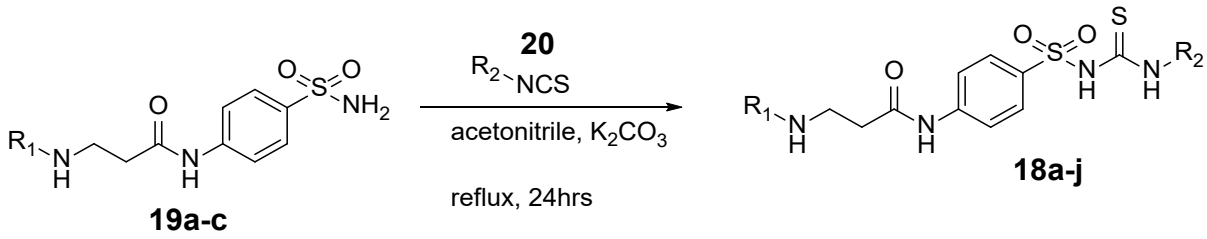
^{1}H NMR spectrum of compound **19c** showed eight peaks, two singlets (one accounting for one proton (H-a) at 10.53 ppm and the other accounting for two protons (H-b) at 6.87 ppm), two multiplets (one ascribed to the four aromatic protons at 7.70–7.96 ppm (H-4 & H-5) and the other accounting for two protons at 2.91–2.73 ppm (H-6), two triplets (one accounting for two protons (H-7) at 2.41 ppm and the other accounting for six protons (H-9) at 1.08 ppm) and a quartet accounting for four protons at 2.53 ppm (H-8).

^{13}C NMR spectrum showed a total of nine peaks, three quaternary carbon peaks, two methine carbon peaks, three methylene carbon peaks and one methyl carbon peak.

The three quaternary carbon peaks were observed at 170.15 ppm, 142.37 ppm, 138.90 ppm confirming carbons 1, 2 and 3 respectively. Two methine carbon peaks were observed at 127.06 ppm and 119.11 ppm, ascribed to carbons 4 and 5, respectively. Three methylene carbon peaks were observed at 48.64 ppm (C-6), 34.67 ppm (C-7) and 46.50 ppm (C-8). A methyl carbon peak was observed on the upfield region at 12.25 (C-9).

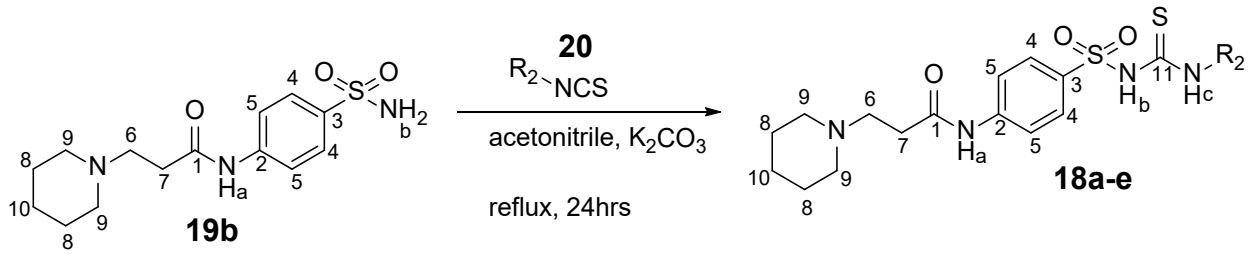
2.2.3. Synthesis of propionylamide containing target sulfonylthioureas (18a-j).

The final step involved the synthesis of target 4-(3-aminopropionylamido)-*N*-(substituted)benzenesulfonamide **18a-j** by modifying conditions outlined by Ibrahim, M.K. et al.[50] Compounds **19a-c** were subjected to nucleophilic substitution with appropriate isothiocyanates **20** namely; ethyl isothiocyanate, propyl isothiocyanate, cyclohexyl isothiocyanate, butyl isothiocyanate, tertbutyl isothiocyanate and phenyl isothiocyanate in refluxing acetonitrile in the presence of K_2CO_3 to afford the target 4-(3-aminopropionylamido)-*N*-(substituted)benzenesulfonamide **18a-j (Scheme 13).**



Scheme 13: Synthesis of 4-(3-aminopropionylamido)-*N*-(substituted)benzenesulfonamide

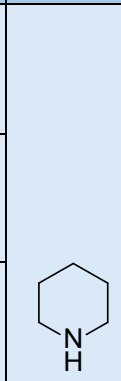
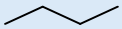
2.2.3.1. Synthesis of piperidine based propionylamide containing target sulfonylthioureas (18a-e).



Scheme 14: Synthesis of 4-(3-piperidinopropionylamido)-*N*-(substituted)benzenesulfonamide

Percentage yields of compounds **18a-e** were obtained from fair to good yields ranging from 51.84%–93.60%, as summarised in **Table 2** below.

Table 2: 4-(3-piperidinopropionylamido)-*N*-(substituted)benzenesulfonamide **18a-e** data obtained from **scheme 14**

Compound	R_1	R_2	Appearance	Melting point (°C)	Yield (%)	HRMS (m/z)
18a			Cream-white powder	214.7–217.4	86.17	found 426.1816, calcd 426.1759
18b			White powder	192.4–194.8	88.35	found 412.1618, calcd 412.1603
18c			White powder	194.3–197.6	71.91	found 398.1502, calcd 398.1446
18d			White powder	200.1–202.9	93.60	found 452.1963, calcd 452.1916
18e			White powder	242.8–245.4	51.84	found 426.1819, calcd 426.1759

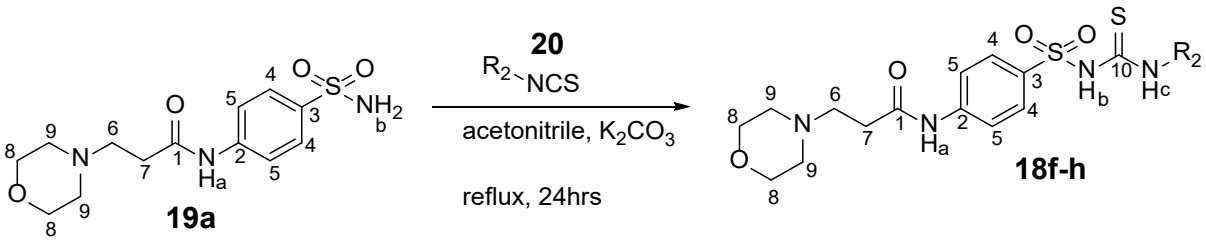
Compounds **18a-e** were confirmed using a combination of ^{1}H NMR, ^{13}C NMR as well as IR spectroscopies. ^{1}H NMR spectra of compounds **18a-e** were characterized by a total of 11–14 signals. ^{1}H NMR spectra of all five compounds (**18a-e**) showed a minimum of two singlets. These two singlets accounted for one proton each and were observed ~11 ppm (H-b, a new peak) and 10 ppm (H-a). Another new peak accounting for one proton (H-c) was observed ~8 ppm.

Nucleophilic substitution occurred at the N-H_b position that showed an integration of 2H in the starting material **19b** but upon the substitution with isothiocyanates **20** it then integrated for one proton, as a result there was a shift in the chemical shift of H-b to a more downfield region ~11 ppm. This confirmed the success of the formation of the target compounds **18a-e**. The new proton peak observed at ~ 8 ppm accounting for

H-c also confirmed the attachment of the isothiocyanates. For compounds **18a-c**, this peak appeared as a triplet due to coupling to H-12, for compound **18d** it appeared as a doublet due to coupling to H-12, whereas for compound **18e** it appeared as a singlet. Moreover these peaks, similar peaks in the ^{1}H NMR spectra of compounds **18a-e** were the two doublets accounting for two protons each depicting H-4 and H-5 observed in the aromatic region of the spectra. ^{13}C NMR spectra of compounds **18a-e** were characterized by the appearance of a new quaternary carbon peak at 177–180 ppm confirming the presence of the thiocarbonyl carbon as compared to the thiocarbonyl carbon on the isothiocyanates **20** before attachment that resonated around 129.99–140 ppm. Other similar peaks observed in the ^{13}C NMR spectra were the three quaternary carbon peaks depicting C-1, C-2 and C-3, two methine carbon peaks depicting C-4 and C-5 and lastly the two methylene carbon peaks C-6 and C-7.

The IR spectra of all final compounds **18a-e** indicated characteristic peaks for N-H stretching in the range of 3200 - 3300 cm^{-1}, C=O stretch at 1600-1790 cm^{-1}, C-H stretch at ~ 2858–3096 cm^{-1} and C=C at ~ 1501–1616 cm^{-1}. HRMS of compounds **18a-e** gave further evidence of the successful synthesis of the compounds with the molecular ion corresponding to the calculated values and the data is shown in **Table 2**.

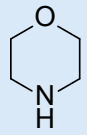
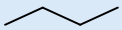
2.2.3.2. Synthesis of morpholine based propionylamide containing target sulfonylthioureas (18f-h).



Scheme 15: Synthesis of 4-(3-morpholinopropionylamido)-*N*-(substituted)benzenesulfonamide

Percentage yields of compounds **18f-h** were obtained from fair to good yields ranging from 53.22%–96.54%, as summarised in **Table 3** below.

Table 3: 4-(3-morpholinopropionylamido)-*N*-(substituted)benzenesulfonamide **18f-h** data obtained from **scheme 15**

Compound	R_1	R_2	Appearance	Melting point (°C)	Yield (%)	HRMS (m/z)
18f			White powder	222.6–225.3	96.54	found 454.1893, calcd 454.1708
18g			Yellow powder	161.4–163.7	69.48	found 428.1577, calcd 428.1552
18h		CH_3CH_2	White powder	132.7–135.3	53.22	found 400.1248, calcd 400.1239

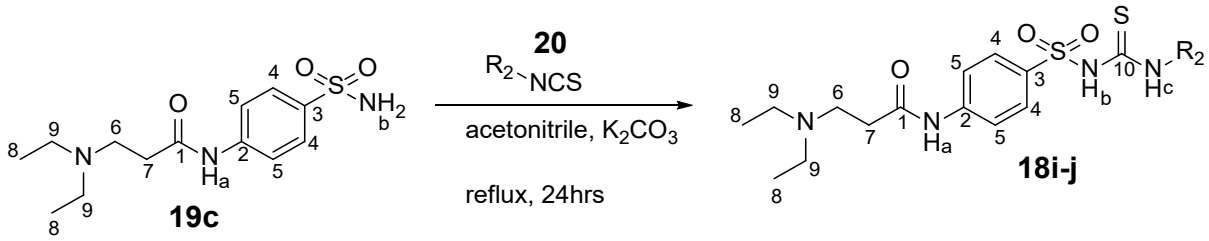
Compounds **18f-h** were confirmed using a combination of ^{1}H NMR, ^{13}C NMR as well as IR spectroscopies. ^{1}H NMR spectra of compounds **18f-h** were characterized by a total of 11–13 signals. ^{1}H NMR spectra of all three compounds (**18f-h**) showed a minimum of two singlets. These two singlets accounted for one proton each and were observed ~11 ppm (H-b, a new peak) and 10 ppm (H-a). Another new peak accounting for one proton (H-c) was observed ~8 ppm.

Nucleophilic substitution occurred at the N-H_b position that showed an integration of 2H in the starting materials **19a** but upon the substitution with isothiocyanates **20** it then integrated for one proton, as a result there was a shift in the chemical shift of H-b to a more downfield region ~11 ppm. This confirmed the success of the formation of the target compounds **18f-h**. The new proton peak observed at ~ 8 ppm accounting for H-c also confirmed the attachment of the isothiocyanates. For compound **18f**, this peak appeared as a doublet due to coupling to H-11, and for compounds **18g** and **18h** it appeared as a triplet due to coupling to H-11. Moreover these peaks, similar peaks in the ^{1}H NMR spectra of compounds **18f-h** were the two doublets accounting for two protons each depicting H-4 and H-5 observed in the aromatic region of the spectra. ^{13}C NMR spectra of compounds **18f-h** were characterized by the appearance of a new

quaternary carbon peak at 177–180 ppm confirming the presence of the thiocarbonyl carbon as compared to the thiocarbonyl carbon on the isothiocyanates **20** before attachment that resonated around 129.99 –140 ppm. Other similar peaks observed in the ^{13}C NMR spectra were the three quaternary carbon peaks depicting C-1, C-2 and C-3, two methine carbon peaks depicting C-4 and C-5 and lastly the two methylene carbon peaks C-6 and C-7.

The IR spectra of all final compounds **18f-h** indicated characteristic peaks for N-H stretching in the range of 3200 - 3300 cm^{-1}, C=O stretch at 1600-1790 cm^{-1}, C-H stretch at ~ 2858–3096 cm^{-1} and C=C at ~ 1501–1616 cm^{-1}. HRMS of compounds **18f-h** gave further evidence of the successful synthesis of the compounds with the molecular ion corresponding to the calculated values and the data is shown in **Table 3**.

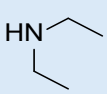
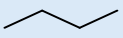
2.2.3.3 Synthesis of diethylamine based propionylamide containing target sulfonylthioureas (18i-j).



Scheme 16: Synthesis of 4-(3-diethylaminopropionylamido)-*N*-(substituted)benzenesulfonamide

Percentage yields of compounds **18i-j** were obtained from poor to good yields ranging from 33.28%–50.55%, as summarised in **Table 4** below.

Table 4: 4-(3-diethylaminopropionylamido)-*N*-(substituted)benzenesulfonamide **18i-j** data obtained from **scheme 16.**

Compound	R_1	R_2	Appearance	Melting point (°C)	Yield (%)	HRMS (m/z)
18i			Yellow-orange powder	165.9–168.6	50.55	found 414.1782, calcd 414.1759

18j			Yellow powder	270.2–273.9	33.28	found 434.1508, calcd 434.1446

Compounds **18i** and **18j** were confirmed using a combination of ^{1}H NMR, ^{13}C NMR as well as IR spectroscopies. ^{1}H NMR spectra of compounds **18i** and **18j** were characterized by a total of 12–13 signals. ^{1}H NMR spectra of the two compounds (**18i** and **18j**) showed a minimum of two singlets. These singlets accounted for one proton each and were observed ~11 ppm (H-b, a new peak) and 10 ppm (H-a). Another new peak accounting for one proton (H-c) was observed ~8 ppm. For compound **18i,** peak H-c appeared as a doublet due to its coupling to H-11 whereas for compound **18j** it appeared as a singlet.

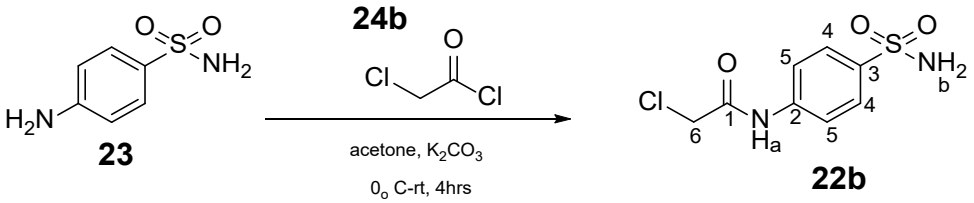
Nucleophilic substitution occurred at the N-H_b position that showed an integration of 2H in the starting materials **19c** but upon the substitution with isothiocyanates **20** it then integrated for one proton, as a result there was a shift in the chemical shift of H-b to a more downfield region ~11 ppm. This confirmed the success of the formation of the target compounds **18i** and **18j**. The new proton peak observed at ~ 8 ppm accounting for H-c also confirmed the attachment of the isothiocyanates. Moreover these peaks, similar peaks in the ^{1}H NMR spectra of compounds **18i** and **18j** were the two doublets accounting for two protons each depicting H-4 and H-5 observed in the aromatic region of the spectra. ^{13}C NMR spectra of compounds **18a** and **18j** were characterized by the appearance of a new quaternary carbon peak at 178–183 ppm confirming the presence of the thiocarbonyl carbon as compared to the thiocarbonyl carbon on the isothiocyanates **20** before attachment that resonated around 135 ppm (phenyl isothiocyanate) and 129.99 ppm (cyclohexyl isothiocyanate). Other similar peaks observed in the ^{13}C NMR spectra were the three quaternary carbon peaks depicting C-1, C-2 and C-3, two methine carbon peaks depicting C-4 and C-5 and lastly the two methylene carbon peaks C-6 and C-7.

The IR spectra of both final compounds **18i** and **18j** indicated characteristic peaks for N-H stretching in the range of 3200 - 3300 cm-^{1}, C=O stretch at 1600-1790 cm^{-1}, C-H stretch at ~ 2858–3096 cm^{-1} and C=C at ~ 1501–1616 cm^{-1}. HRMS of compounds **18i** and **18j** gave further evidence of the successful synthesis of the compounds with the

molecular ion corresponding to the calculated values and the data is shown in **Table 4**.

2.3 Acetamide containing sulfonylthioureas

2.3.1 Synthesis of 4-(2-chloroacetamido)benzenesulfonamide (22b).

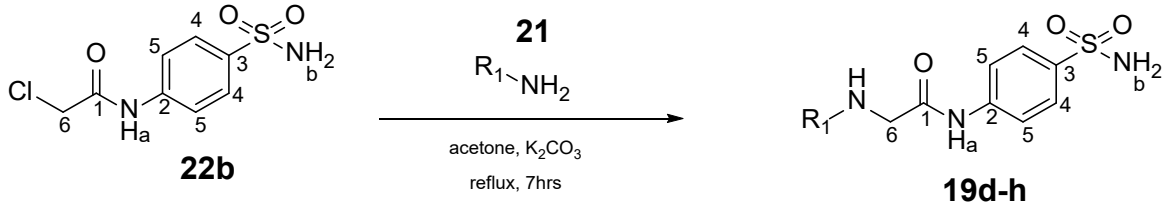


Scheme 17: Synthesis of 4-(2-chloroacetamido)benzenesulfonamide

The first step of this project was the synthesis of 4-(2-chloroacetamido)benzenesulfonamide **(22b)** by condensation of 4-aminobenzenesulfonamide **(23)** dissolved in dry acetone with anhydrous potassium carbonate and 2-chloroacetyl chloride **(24b)** from 0 ^{0}C to room temperature **(Scheme 17)**. The product was obtained as a white powder (10.95 g, 88.1%). Melting point = 230.9-233.2 ^{o}C, reported literature value = 236-238 °C [51]. The product was confirmed using NMR spectroscopy. ^{1}H NMR spectrum showed a total of five signals; three singlets, one accounting for one proton (H-a), one accounting for two protons (H-b) and the other accounting for two protons (H-6) at chemical shifts of 10.65 ppm, 7.30 ppm and 4.31 ppm respectively. Moreover these peaks, the ^{1}H NMR spectrum showed two doublets accounting for two protons each in the aromatic region confirming aromatic protons H-4 and H-5.

^{13}C NMR spectrum of compound **22b** showed six peaks in total; two methine carbon peaks, one methylene carbon peak and three quaternary carbon peaks. Methine carbon peaks were observed at 127.06 ppm (C-4) and 119.50 ppm (C-5), methylene carbon peak at 41.06 (C-6), whereas quaternary carbon peaks were observed at 165.84 (C-1), 141.71 (C-2) and 138.89 (C-3).

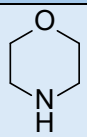
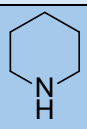
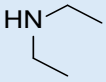
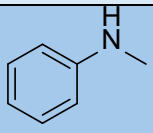
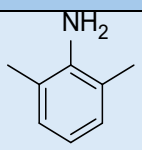
2.3.2 Synthesis of acetamide based sulfonamides (19d-h).



Scheme 18: Synthesis of 4-(2-aminoacetamido)benzenesulfonamides

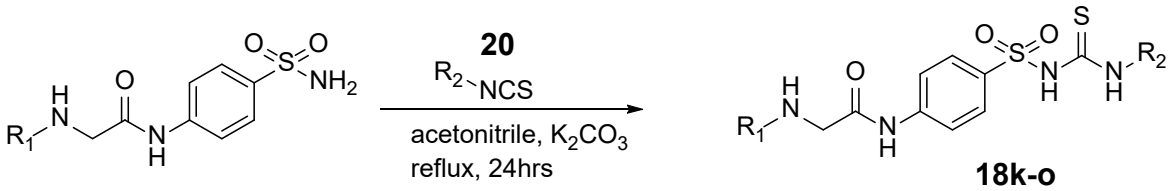
The chloro-substituted amide key intermediates **22b** were treated with amines such as morpholine, piperidine, diethyl amine, N-methylaniline and 2,6-dimethylaniline **21** in the presence of anhydrous potassium carbonate under refluxing acetone for 7 hours **(Scheme 18)** in order to obtain the desired aminoacetamido benzenesulfonamides. [52] Compounds **19d-h** yields ranged from 36.34%–89.23%, as summarised in **Table 5** below.

Table 5: 4-(2-aminoacetamido)benzenesulfonamide **19d-h** data obtained from **scheme 18**

Compound	R_1	Appearance	Melting point (°C)	Yield (%)
19d		White powder	210.9–213.0	89.03
19e		White powder	191.5–194.2	72.39
19f		Yellow powder	194.2–197.4	36.35
19g		Yellow powder	241.0–244.5	73.47
19h		Caramel-like powder	242.4–245.5	77.22

4-(2-aminoacetamido)benzenesulfonamide **19d-h** obtained from **scheme 12** were characterised using a combination of ^{1}H NMR and ^{13}C NMR. ^{1}H NMR spectra of compounds **19d-h** were characterized by a total of 7-9 signals. As a confirmation that this reaction was successful, there was the presence of new signals on the aliphatic region for compounds **19d-f**, whereas for compounds **19g-h** observed were the new aromatic signals integrating for 2H and 1H ascribed to **H-8** and **H-9** respectively. In addition, the ^{1}H NMR spectrum of compound **19h** showed the presence of a new N-H signal **(H-c)** integrating for 1H at 5.29 ppm after the substitution to compound **22b.** ^{13}C NMR spectra of compounds **19d-h** were characterized by the new aliphatic carbons and aromatic carbon signal. Compounds **19d-f** have new 2-3 carbon peaks on the upfield region, and compounds **19g-h** show new aromatic carbon peaks.

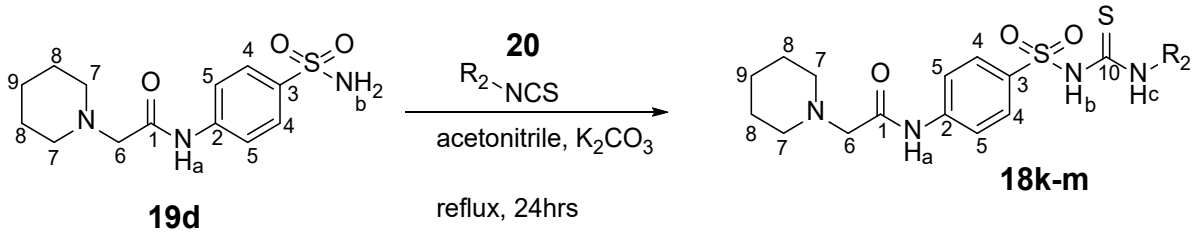
2.3.3 Synthesis of acetamide containing target sulfonylthioureas (18k-o).



Scheme 19: Synthesis of 4-(2-aminoacetamido)-*N*-(substituted)benzenesulfonamide

The final step involved the synthesis of target 4-(2-aminoacetamido)-*N*-(substituted)benzenesulfonamide **18k-o** by modifying conditions outlined by Ibrahim, M.K. et al.[50] Compounds **19d-e** were subjected into nucleophilic substitution with appropriate isothiocyanates **20** namely; propyl isothiocyanate, cyclohexyl isothiocyanate and phenyl isothiocyanate in refluxing acetonitrile in the presence of K_2CO_3 to afford the target 4-(2-aminoacetamido)-*N*-(substituted)benzenesulfonamide **18k-o (Scheme 19).**

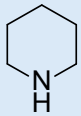
2.3.3.1 Synthesis of piperidine based acetamide containing target sulfonylthioureas (18k-m).



Scheme 20: Synthesis of 4-(2-piperidinoacetamido)-*N*-(substituted)benzenesulfonamide

Percentage yields of compounds **18k-m** were obtained from moderate to good yields ranging from 49.54%–80.75%, as summarised in **Table 6** below.

Table 6: 4-(2-piperidinoacetamido)-*N*-(substituted)benzenesulfnamide **18k-m** data obtained from **scheme 20**

Compound	R_1	R_2	Appearance	Melting point (°C)	Yield (%)	HRMS (m/z)
18k			White powder	184.8–187.6	80.75	found 438.1939, calcd 438.1759
18l			Cream-white powder	186.1–188.4	79.90	found 398.1464, calcd 398.1446
18m			Yellow powder	140.9–143.8	49.54	found 432.1328, calcd 432.1290

Compounds **18k-m** were confirmed using a combination of ^{1}H NMR, ^{13}C NMR as well as IR spectroscopies. ^{1}H NMR spectra of compounds **18k-m** were characterized by a total of 12-13 signals. ^{1}H NMR spectra of all three compounds (**18k-m**) showed a minimum of two singlets. Two of these singlets accounted for one proton each and were observed ~11 ppm (H-b, a new peak) and 10 ppm (H-a). Another new peak accounting for one proton (H-c) was observed ~8 ppm. For compound **18k,** peak H-c

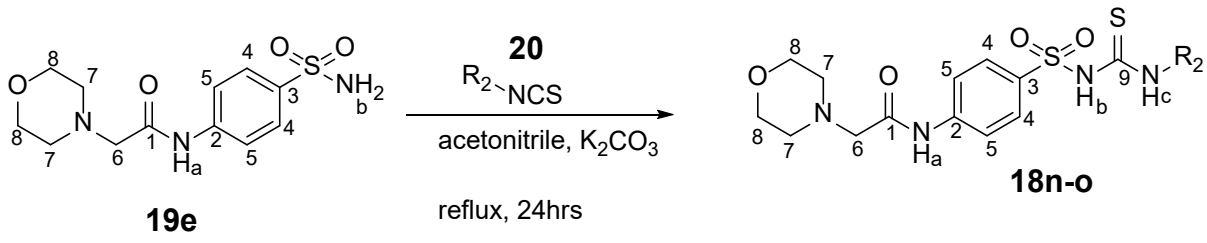
appeared as a doublet due to its coupling to H-11, for compound **18l** it appeared as a triplet due to its coupling to H-11 whereas for compound **18m** it appeared as a singlet.

Nucleophilic substitution occurred at the N-H_b position that showed an integration of 2H in the starting material **19d** but upon the substitution with isothiocyanates **20** it then integrated for one proton, as a result there was a shift in the chemical shift of H-b to a more downfield region ~11 ppm. This confirmed the success of the formation of the target compounds **18k-m**.

Moreover these peaks, similar peaks in the ^{1}H NMR spectra of compounds **18k-m** were the two doublets accounting for two protons each depicting H-4 and H-5 observed in the aromatic region of the spectra. ^{13}C NMR spectra of compounds **18k-m** were characterized by the appearance of a new quaternary carbon peak at 177 - 180 ppm confirming the presence of the thiocarbonyl carbon as compared to the thiocarbonyl carbon on the isothiocyanates **20** before attachment that resonated around 129-140 ppm. Other similar peaks observed in the ^{13}C NMR spectra were the three quaternary carbon peaks depicting C-1, C-2 and C-3, two methine carbon peaks depicting C-4 and C-5 and lastly the methylene carbon peak C-6.

The IR spectra of all three final compounds **18k-m** indicated characteristic peaks for N-H stretching in the range of 3200 - 3300 cm^{-1}, C=O stretch at 1600-1790 cm^{-1}, C-H stretch at ~ 2858 - 3096 cm^{-1} and C=C at ~ 1501 -1616 cm^{-1}. HRMS of compounds **18k-m** gave further evidence of the successful synthesis of the compounds with the molecular ion corresponding to the calculated values and the data is shown in **Table 6**.

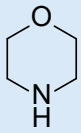
2.3.3.2 Synthesis of morpholine based acetamide containing target sulfonylthioureas (18n-o).



Scheme 21: Synthesis of 4-(2-morpholinoacetamido)-*N*-(substituted)benzenesulfonamide

Percentage yields of compounds **18n** and **18o** were obtained from moderate to good yields ranging from 51.68%–85.62%, as summarised in **Table 7** below.

Table 7: 4-(2-morpholinoacetamido)-*N*-(substituted)benzenesulfnamide **18n-o** data obtained from **scheme 21**

Compound	R_1	R_2	Appearance	Melting point (°C)	Yield (%)	HRMS (m/z)
18n			White powder	210.1–213.4	85.62	found 440.1760, calcd 440.1552
18o			Yellow-brown powder	228.2–231.7	51.68	found 434.1217, calcd 434.1180

Compounds **18n** and **18o** were confirmed using a combination of ^{1}H NMR, ^{13}C NMR as well as IR spectroscopies. ^{1}H NMR spectra of compounds **18n** and **18o** were characterized by a total of 11-12 signals. ^{1}H NMR spectra of compounds **18n** and **18o** showed a minimum of two singlets. These two singlets accounted for one proton each and were observed ~11 ppm (H-b) and 10 ppm (H-a). Another new peak accounting for one proton (H-c) was observed ~8 ppm. For compound **18n,** peak H-c appeared as a doublet due to its coupling to H-10, whereas for compound **18o** it appeared as a singlet.

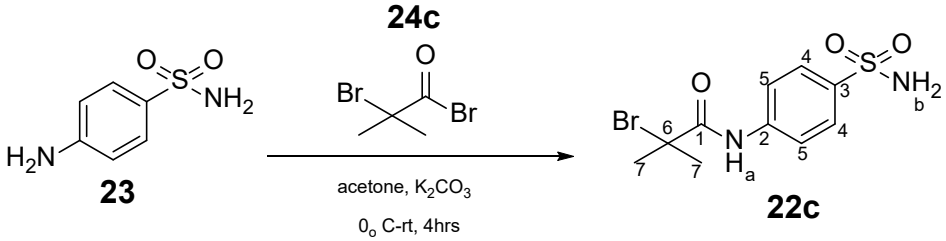
Nucleophilic substitution occurred at the N-H_b position that showed an integration of 2H in the starting material **19e** but upon the substitution with isothiocyanates **20** it then integrated for one proton, as a result there was a shift in the chemical shift of H-b to a more downfield region ~11 ppm. This confirmed the success of the formation of the target compounds **18n** and **18o**. Additionally, similar peaks in the ^{1}H NMR spectra of compounds **18n** and **18o** were the two doublets accounting for two protons each depicting H-4 and H-5 observed in the aromatic region of the spectra. ^{13}C NMR spectra of compounds **18n** and **18o** were characterized by the appearance of a new quaternary carbon peak at 177 - 180 ppm confirming the presence of the thiocarbonyl carbon. Other similar peaks observed in the ^{13}C NMR spectra were the three

quaternary carbon peaks depicting C-1, C-2 and C-3, two methine carbon peaks depicting C-4 and C-5 and lastly the methylene carbon peak C-6.

The IR spectra of both final compounds **18n** and **18o** indicated characteristic peaks for N-H stretching in the range of 3200 - 3300 cm-^{1}, C=O stretch at 1600-1790 cm^{-1}, C-H stretch at ~ 2858–3096 cm^{-1} and C=C at ~ 1501–1616 cm^{-1}. HRMS of compounds **18n** and **18o** gave further evidence of the successful synthesis of the compounds with the molecular ion corresponding to the calculated values and the data is shown in **Table 7**.

2.4 2-Methylpropanoylamide containing sulfonylthioureas

2.4.1 Synthesis of 4-(2-bromo,2,2-dimethacetamido)benzenesulfonamide (22c).



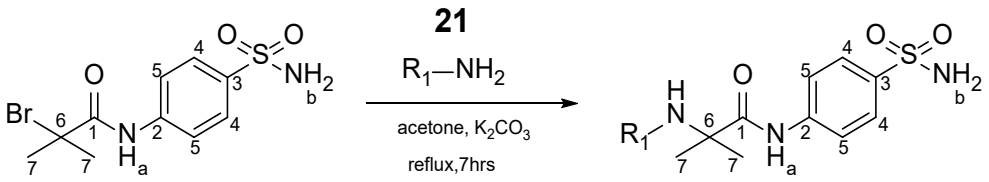
Scheme 22: Synthesis of 4-(2-bromo,2,2-dimethacetamido)benzenesulfonamide

The first step of this project was the synthesis of 4-(2-bromo,2,2-dimethacetamido)benzenesulfonamide (**22c**) by reacting 4-aminobenzenesulfonamide (**23**) dissolved in dry acetone with anhydrous potassium carbonate and 2-bromo-2-methylpropanoyl bromide (**24c**) from 0 ^{0}C to room temperature (**Scheme 22**). The product was obtained as a snow-white powder (13.2 g, 89,5%) yield. Melting point = 197.4–199.7 ^{o}C. The product was confirmed using NMR spectroscopy. ^{1}H NMR spectrum showed a total of five peaks, three singlets, one accounting for one proton (H-a), one accounting for two protons (H-b) and the third one accounting for six protons (H-7) at chemical shifts of 10.12 ppm, 7.29 ppm and 2.02 ppm, respectively. Moreover these peaks, the ^{1}H NMR spectrum showed two doublets accounting for two protons each in the aromatic region confirming aromatic protons H-4 and H-5.

^{13}C NMR spectrum of compound **22c** showed seven peaks in total, two methine carbon peaks, one methyl carbon peak and four quaternary carbon peaks. Methine

carbon peaks were observed at 126.90 ppm (C-4) and 120.54 ppm (C-5), methyl carbon peak (C-7) was observed at 31.06, whereas quaternary carbon peaks were observed at 170.27 ppm (C-1), 142.06 ppm (C-2), 139.53 ppm (C-3) and 60.87 ppm (C-6).

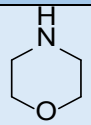
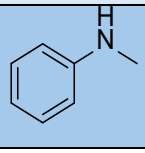
2.4.2. Synthesis of 2-methylpropanoylamide based sulfonamides (19i-l).

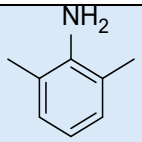
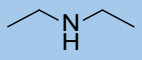


Scheme 23: Synthesis of 4-(2-amino,2,2-dimethacetamido)benzenesulfonamides

Compounds **19i-l** were synthesized by reacting amines **21** (morpholine, *N*-methylaniline, 2,6-dimethylaniline and diethylamine) with compound **22c** in the presence of anhydrous potassium carbonate under refluxing acetone for 7 hours **(Scheme 23)**. Four compounds **(19i-l)**, their percentage yields and appearances are indicated in **Table 8** below.

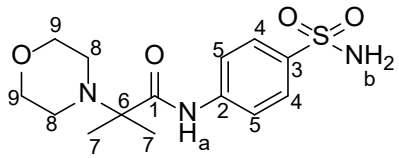
Table 8: Percentage yields and appearances of 4-(2-amino-2,2-dimethacetamido)benzenesulfonamides.

Compounds	R_1	Melting point (°C)	% Yield	Appearance
19i		233.1-236.8	69.75	Yellow powder
19j		171.4-174.8	53.37	Red powder

19k		163.1-165.9	48.50	Brown powder
19l		192.4-195.7	80.00	Orange powder

Compounds **19i-l** were characterized by NMR spectroscopy and their individual results are indicated below.

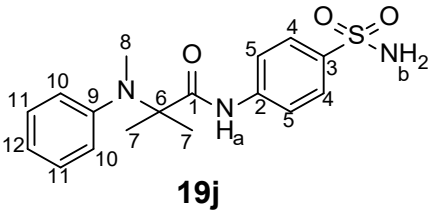
2.4.2.1. 4-(2-morpholino-2,2-dimethacetamido)benzenesulfonamide (19i).



19i

^{1}H NMR spectrum of compound **19i** showed seven peaks, three singlets (one accounting for one proton (H-a) at 9.91 ppm, another accounting for two protons (H-b) at 7.24 ppm and the third one accounting for six protons (H-7) at 1.21 ppm), two doublets accounting for two protons each at 7.85 ppm (H-4) and 7.77 ppm (H-5) and two triplets accounting for four protons each at 3.70 ppm (H-9) and 2.56 ppm (H-8). ^{13}C NMR spectrum showed a total of nine peaks, four quaternary carbon peaks, two methine carbon peaks, two methylene carbon peaks and one methyl carbon peak. The four quaternary carbon peaks were observed at 175.71 ppm, 142.13 ppm, 138.94 ppm and 66.95 ppm confirming carbons 1, 2, 3 and 6 respectively. Two methine carbons peaks were observed at 126.94 ppm and 119.70 ppm ascribed to carbons 4 and 5 respectively. Two methylene carbon peaks were observed at 64.17 ppm (C-9), 47.32 ppm (C-8) and methyl carbon peak was observed at 20.28 ppm and was ascribed to C-7.

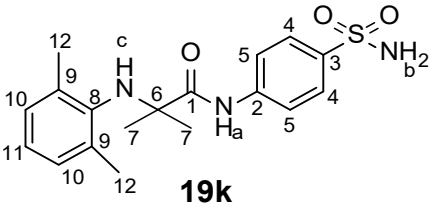
2.4.2.2. 4-(2-(N-methylanilino)-2,2-dimethacetamido)benzenesulfonamide (19j).



19j

^{1}H NMR spectrum of compound **19j** had a total of nine peaks, of which four were singlets observed at 10.04 ppm (H-a), 7.28 ppm (H-b), 2.85 ppm (H-8) and 1.35 ppm (H-7). The remaining five peaks confirmed the nine aromatic protons present in compound **19j**. These five peaks consisted of four doublets accounting for two protons each observed at 7.84 ppm (H-4), 7.77 ppm (H-5), 7.22 ppm (H-11) and 7.04 ppm (H-10). The last peak was a triplet accounting for one proton at 6.89 ppm. This peak was ascribed to H-12. ^{13}C NMR spectrum of compound **19j** showed twelve peaks, five quaternary carbon peaks (C-1, C-9, C-2, C-3 and C-6) observed at 176.11 ppm, 149.17 ppm, 142.39 ppm, 138.97 ppm and 64.08 ppm respectively, five methine carbon peaks (C-4, C-11, C-12, C-5 and C-10) observed at 128.91 ppm, 126.86 ppm, 121.30 ppm, 121,32 ppm and 120.07 ppm respectively and lastly two methyl carbon peaks (C-8 and C-7) observed at 36.02 ppm and 23.27 ppm respectively.

2.4.2.3. 4-(2-(2,6-dimethylanilino)-2,2-dimethacetamido)benzenesulfonamide (19k).

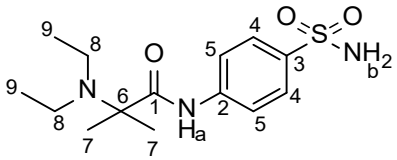


19k

^{1}H NMR spectrum of compound **19k** showed nine peaks, five singlets (two of which accounted for one proton each at 10.43 ppm and 4.01 ppm ascribed to H-a and H-b respectively, the second singlet accounted for two protons was observed at 7.30 ppm and was ascribed to H-b and the last two singlets accounted for six protons each were observed at 2.10 ppm and 1.32 ppm and were ascribed to H-12 and H-7 respectively. The other four peaks were observed in the aromatic region of the spectrum confirming the nine aromatic protons present in compound **19k**. These four peaks consisted of three doublets accounting for two protons each observed at 7.92 ppm, 7.81 ppm and 6.86 ppm and were ascribed to H-4, H-5 and H-10 respectively. The last peak was a

multiplet accounting for one proton observed between 6.19 ppm and 6,01 ppm and it ascribed to H-11. ^{13}C NMR spectrum of compound **19k** was characterized by twelve peaks, six of which were quaternary carbon peaks observed at 177.36 ppm, 143.35 ppm, 142.26 ppm, 138.87 ppm, 132.86 ppm and 59.77 ppm and ascribed to C-1, C-8, C-2, C-3, C-9 and C-6 respectively. Four of the remaining six peaks were methine carbon peaks observed at 129.03 ppm, 127.20 ppm, 123.53 ppm and 119.25 ppm and were ascribed to C-4, C-10, C-11 and C-5 respectively. The last two peaks were methyl carbon peaks observed at 27.02 ppm and 19.83 ppm and were ascribed to C-7 and C-12 respectively.

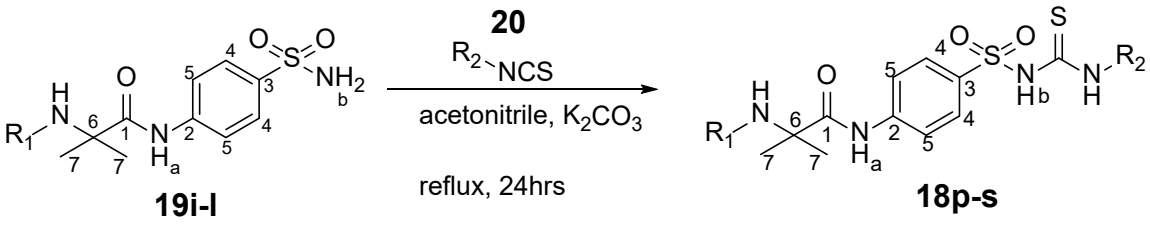
2.4.2.4. 4-(2-Diethylamino-2,2-dimethacetamido)benzenesulfonamide (19l)



19l

^{1}H NMR spectrum of compound **19l** was characterized by seven peaks. Amongst these peaks were three singlets (one accounting for one proton (H-a) observed at 9.89 ppm, the second one accounting for two protons (H-b) observed at 7.48 ppm and the last singlet accounting for six protons (H-7) observed at 1.24 ppm, two doublets accounting for two protons each observed at 7.87 ppm and 8.81 ppm. These were ascribed to H-4 and H-5 respectively. The last two peaks were a triplet accounting for six protons (H-9) observed at 1.07 ppm and a quartet accounting for four protons (H-8) observed at 2.52 ppm. ^{13}C NMR spectrum of compound **19l** showed nine peaks, four of which were quaternary carbon peaks observed at 176.84 ppm (C-1), 140.51 ppm (C-2), 138.99 ppm (C-3) and 65.61 (C-6), two methine carbon peaks observed at 127.07 (C-4) and 119.34 ppm (C-5), one methylene carbon peaks observed at 43.38 ppm (C-8) and lastly two methyl carbon peaks observed at 22.04 ppm (C-7) and 15.54 ppm (C-9).

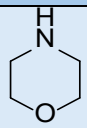
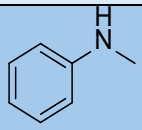
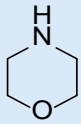
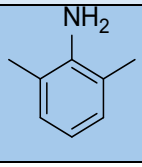
2.4.3. Synthesis of methylpropionylamide containing target sulfonylthioureas (18p-s)



Scheme 24: Synthesis of 4-(3-aminomethylpropionylamido)-*N*-(substituted)benzenesulfonamide **18p-s**

Target compounds **18p-s** were synthesized by reacting compounds **19i-l** with isothiocynates **(20)** (ethyl, cyclohexyl, phenyl) in the presence of anhydrous potassium carbonate in refluxing acetonitrile for 24 hours (**Scheme 24**). Percentage yields and appearances of compounds **18p-s** are indicated in **Table 9** below.

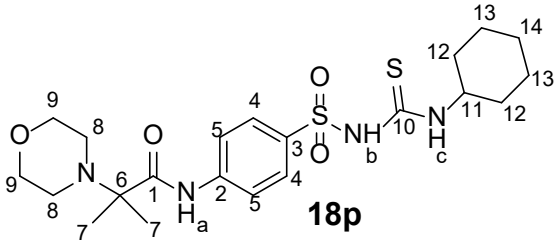
Table 9: 4-(3-aminomethylpropionylamido)-*N*-(substituted)benzenesulfonamide **18p-s** data obtained from **scheme 24**

Compounds	R_1	R_2	Appearance	Melting point (^oC)	Yield (%)	HRMS (m/z)
18p			Yellow powder	208.3–210.1	76	found 468.2048, calcd 468.1865
18q			Red crystals	198.6–201.4	60	found 488.1930, calcd 488.1916
18r			Yellow crystals	234.7–237.2	66	found 462.1454, calcd 462.1395
18s		CH_3CH_2	Brown crystals	215.8–218.6	51	found 448.1644, calcd 448.1603

Compounds **18p-s** were characterised by NMR and IR spectroscopies. IR spectra of the compounds were characterised by the presence of N-H peak observed at ~3300 cm^{-1} and C=O peak observed at ~1650 cm^{-1}. ^1H NMR spectra of all four compounds

(**18p-s**) showed a minimum of three singlets. Two of these singlets accounted for one proton each and were observed ~11 ppm (H-b, a new peak) and 10 ppm (H-a) and the third singlet accounted for six protons (H-7) and was observed ~1.2 ppm. Another new peak accounting for one proton H-c) was observed ~8 ppm. For compound **18p** this peak appeared as a doublet due to coupling to H-11, in compound **18q** it appeared as a doublet due to coupling with H-14 whereas in compound **18s** it appeared as a triplet due to coupling with H-14. In compound **18r** proton H-c appeared as a singlet. Moreover these peaks, similar peaks in the ^{1}H NMR spectra of compounds **18p-s** were the two doublets accounting for two protons each depicting H-4 and H-5 observed in the aromatic region of the spectra. ^{13}C NMR spectra of compounds **18p-s** were characterized by the appearance of a new quaternary carbon peak at ~180 ppm confirming the presence of the thiocarbonyl carbon. Other similar peaks observed in the ^{13}C NMR spectra were the three quaternary carbon peaks depicting C-1, C-2 and C-3, two methine carbon peaks depicting C-4 and C-5 and lastly the methyl carbon peak C-7. Other NMR spectroscopy peaks for compounds **18p-s** are described below for individual compounds.

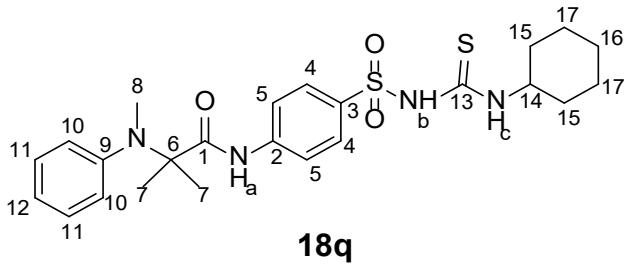
2.4.3.1 4-(2-morpholino-2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl)benzenesulfonamide (18p)



18p

^{1}H NMR spectrum of compound **18p** showed a total of twelve peaks. Moreover the six peaks (H-a, H-b, H-c, H-4, H-5 and H-7) described above, compound **18p** had seven more peaks, two triplets accounting for four protons each (H-8 and H-9) observed at 2.51 ppm and 3.70 ppm respectively. The four remaining peaks were ascribed to the cyclohexyl protons H-11, H-12, H13 and H-14. ^{13}C NMR spectrum of compound **18p** showed a total of fourteen peaks. Moreover the eight carbon peaks (C-1, C-2, C-3, C-4, C-5, C-6, C-7 and C-10) described above, two more methylene carbon peaks (C-8 and C-9) were observed at 53.29 ppm and 64.51 ppm respectively. The remaining four peaks confirmed the cyclohexyl carbons of compound **18p**.

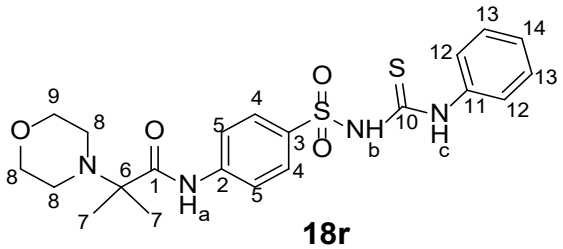
2.4.3.2 4-(2-(N-methylanilino)-2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl)benzenesulfonamide (18q)



18q

^{1}H NMR spectrum of compound **18q** had a total of thirteen peaks. Other than the six peaks (H-a, H-b, H-c, H-4, H-5 and H-7) described above, compound **18q** showed three more peaks in the aromatic region depicting protons H-10, H-11 and H-12 observed at 7.47 pp, 7.67 ppm and 7.16 ppm respectively, a singlet accounting for three protons (H-8) was observed at 3.40 ppm. The four remaining peaks confirmed the presence of the cyclohexyl protons of compound **18q**. ^{13}C NMR spectrum of compound **18q** had a total of seventeen peaks. Eight carbon peaks (C-1, C-2, C-3, C-4, C-5, C-6, C-7 and C-13) were described above. The remaining nine peaks were observed at 121.40 (C-11), 121.39 (C-12), 120.40 (C-10), 64.02 (C-14), 36.02 (C-15), 31.17 (C-8), 29.56 (C-16), 28.31 (C-17).

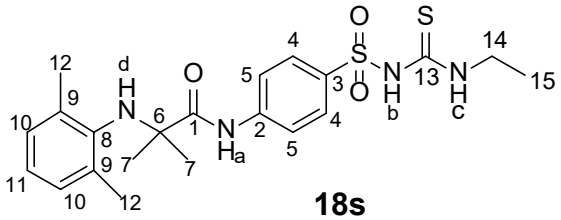
2.4.3.3. Synthesis of 4-(2-morpholino-2,2-dimethacetamido)-*N*-phenylcarbamothioyl)benzenesulfonamide (18r).



18r

^{1}H NMR spectrum of compound **18r** had a total of eleven peaks. Six of these peaks (H-a, H-b, H-c, H-4, H-5 and H-7) were described above. The remaining five peaks were observed at 7.86 ppm (H-14), 7.55 ppm (H-12), 6.96 ppm (H-13), 3.47 (H-9) and 2.51 ppm (H-8). ^{13}C NMR spectrum of compound **18r** was characterized by fourteen peaks. Eight of these carbon peaks (C-1, C-2, C-3, C-4, C-5, C-6, C-7 and C-10) were described above. The remaining six carbon peaks were observed at 139.98 ppm (C-11), 129.23 ppm (C-13), 126.93 ppm (C-14), 124.76 ppm (C-12), 64.91 ppm (C-9) and 47.75 ppm (C-8).

2.4.3.4 4-(2-(2,6-dimethylanilino)-2,2-dimethacetamido)-*N*-ethylcarbamothioyl)benzenesulfonamide (18s).



18s

^{1}H NMR spectrum of compound **18s** was characterized by twelve peaks. Six of these peaks (H-a, H-b, H-c, H-4, H-5 and H-7) were described above. The remaining six peaks were made up of a singlet accounting for six protons (H-12) observed at 2.19 ppm, a triplet accounting for three protons (H-15) observed at 0.99 ppm, a quartet accounting for two protons (H-14) observed at 1.07 ppm, a doublet accounting for two protons (H-10) observed at 6.99 ppm and lastly a triplet accounting for one proton (H-11) observed at 6.84 ppm. ^{13}C NMR spectrum of compound **18s** was characterized by fifteen peaks. Eight of these carbon peaks (C-1, C-2, C-3, C-4, C-5, C-6, C-7 and C-13) were described above. Amongst the seven remaining peaks, two are quaternary carbon (C-8 and C-9) peaks observed at 141.31 ppm and 128.97 ppm respectively, two are methine carbon (C-10 and C-11) peaks observed at 128.08 ppm and 120.43 ppm respectively, one a methylene carbon (C-14) peak observed at 31.16 ppm and the last two are methyl carbon (C-12 and C-15) peaks observed at 27.09 ppm and 14.92 ppm respectively.

CHAPTER THREE

3. Biological assays

In line with one of the main aims of this study, the sulfonylthiourea analogues **18a-s** synthesized in this project were submitted for their biological assays. The biological activity of the sulfonylthiourea analogues **18a-s** was assessed through *in vitro* enzymatic assays for the inhibition of α-glucosidase and α-amylase activity. Acarbose was used as the positive control and the results are summarized in tables 10 and 11 represent the mean ± standard deviation (SD) from three independent experiments. The target compounds were found to exert moderate to significant inhibition of these enzymes. These experiments were done in the laboratories of Dr. Ntethelelo Sibiya at Rhodes University according to the procedure described in chapter five of the experimental section.

3.1 *In vitro* α-glucosidase assay

α-Glucosidase is an enzyme found on the cell membranes at the brush border of epithelial cells within the small intestine, existing in the forms of maltase-glucoamylase (MGAM) and sucrose-isomaltase.[54] The primary role of α-glucosidase inhibitors is to

prevent the occurrence of high blood sugar levels after meals by slowing down the digestion of carbohydrates. This as a result, slows down the absorption of glucose into the bloodstream.[55] Due to their functioning in glucose control, α-glucosidase inhibitors are commonly employed as oral medications for diabetes in the initial phases of Type 2 Diabetes to combat postprandial hyperglycemia.[56]

All synthesized compounds **18a-s** were screened to evaluate their α-glucosidase inhibitory activities with standard drug acarbose at the concentration of 60, 120, and 240 μM. (Table 10).

Most of the synthesized compounds showed a concentration-dependent trend, exhibiting an increase in inhibition activity as concentration was increased from 60 μM to 120 μM and eventually to 240 μM. Set of compounds that exhibited significant inhibition against α-glucosidase are **18e**, **18i**, **18j**, **18m**, **18o**, **18q**, **18r** and **18s** with inhibition of 50±7.29, 56.16±4.24, 70.21±5.97, 78±3.03, 57±5.20, 76.33±2.03, 69.55±4.11 and 84.67±3.34 respectively at 240 μM. The compounds with the strongest inhibitory activity were analyzed and found to have a common chemical structural substituent: a phenyl group. **18j**, **18m**, **18o** and **18r** bear a phenyl group substituted at the isothiocyanate nitrogen whereas compounds **18q** and **18s** bear a phenyl group substituted at the amine. Another interesting analysis was on compound **18s** with an inhibition of 84.67±3.34 at 200 μM, which exhibited the strongest activity out of all the compounds. This compound bears both phenyl and at least three substituted methyl groups. One methyl group at the branched propanoylamide carbon and two methyl groups at the 2- and 6-positions of the arylamine.

Compounds **18d** and **18p** with inhibition of 23±11.20 and 33.25±7.34, respectively, exhibited moderate inhibition whereas the rest of the compounds exhibited little to no inhibition at all.

Moreover, activity analysis based on the three different linkers used, propionylamide, acetamide, and 2-methylpropanoylamide is discussed as follows. On the 2-methylpropanoylamide compounds **18q-s** there was a stronger α-glucosidase inhibiton greater than 60% to 80% as compared to propionylamide **18a-j** and acetamide **18k-o** compounds. Compounds **18k-o** showed moderate active compounds whereas the longer chain propionylamide compounds **18a-j** possessed more compounds with little to no inhibitory activity against alpha glucosidase. This

indicates that the lipophilic methyl group on the branched linker containing compounds **18q-s** have a more substantial inhibitory effect than the longer extended chain or linker.

Table 10: % Inhibition of α-glucosidase by **18a-s and** acarbose.

Compound	60 µM	120 µM	240 µM
18a	-28±20.52	-24±8.72	-23±8.03
18b	3.24±7.05	7.22±7.21	10.36±7.13
18c	-5.33±0,57	4.20±2.32	8.23±3.62
18d	15.59±14,01	20.28±10.66	23±11.20
18e	28,66±5,03	43±6.54	50±7.29
18f	-24±4.58	4±5.64	17±5.75
18g	-26.65±5.86	-24.40±10.61	-19.79±9.26
18h	-29.65±5,03	-32.33±7.16	-32.40±6.21
18i	42.68±3,21	48.29±3.58	56.16±4.24
18j	55.68±4,04	65.57±5.23	70.21±5.97
18k	-38.42±1.53	-33±3.42	-27±2.14
18l	-23.35±5.13	-14.22±10.78	-7±5.84
18m	63.33±4.04	70±3.06	78±3.03
18n	-7±4.58	-2.06±6.78	-1±7.23
18o	42.22±4.51	54±5.66	57±5.20
18p	23.77±9.29	29.64±8.25	33.25±7.34
18q	65.67±3.51	70.25±2.14	76.33±2.03
18r	63±3.61	65.71±4.20	69.55±4.11
18s	75.67±3.06	79.27±3.29	84.67±3.34
Acarbose	-	-	66.33±4.51

3.2 *In vitro* α-amylase assay

The enzyme alpha-amylase is a key therapeutic target that has been exploited for developing several synthetic drugs such as acarbose, voglibose, and miglitol.[57] The α-amylase mainly occurring in the saliva and pancreas [58] helps to start the chemical

process of carbohydrate breakdown by hydrolyzing the glycosidic bonds in starch and related substrate polysaccharides, transforming them into oligosaccharides and simple absorbable sugars.[59] While the salivary amylase is produced by the salivary glands and initiates carbohydrate digestion in the mouth, a large amount of pancreatic amylase is secreted by the pancreas into the duodenum to continue the digestion of incoming starch.[60] Clinically approved inhibitors of α-amylase are limited and include acarbose as well as activities of enzymes such as glucoamylase, maltase, sucrase and isomaltase.[61] Acarbose is prescribed very often but requires co-administration of carbohydrates to exert its effect and reduce the risk of hypoglycemia.[62]

All synthesized compounds **18a-s** were screened to evaluate their α-amylase inhibitory activities with standard drug acarbose at the concentration of 60, 120, and 240 µM. (Table 11).

Most of the synthesized compounds were found to show a concentration-dependent trend with a few exceptions, by exhibiting an increase in inhibition activity as concentration was increased from 60 µM to 240 µM. α-amylase percent inhibition was observed to have the highest inhibitory percent being 54,31±3,86 and 56.19±1.69 for compounds **18j** and **18s** respectively. Set of compounds **18m**, **18o**, **18p**, and **18r** with inhibition of 45.63±3.29, 48±3.74, 46.72±2.05 and 47.75±3.39 respectively at 240 µM were found to exhibit moderate inhibition against α-amylase. The rest of the compounds showed low to poor inhibitory activity. Though some compounds showed poor inhibitory activity at 120 µM, most compounds showed some improved inhibition upon increasing the concentration from 120 µM to 240 µM with the exception of compounds **18a**, **18h**, **18l** and **18n.** This set of compounds suggests that the inhibitory effect of the substance on alpha-amylase activity is weakening as more of the substance is added. This could indicate that the substance may be reaching a saturation point where further increases in concentration are not leading to increased inhibition of alpha-amylase.

Compound **18s** with an inhibition of 56.19±1.69 at 200 µM which exhibited the strongest activity out of all the compounds. This compound bears at least three substituted methyl groups. One methyl group substituted at the branched propanoylamide carbon and two methyl groups substituted at the 2- and 6-positions of the arylamine.

Table 11: % Inhibition of α-amylase by **18a-s** and acarbose**.**

Compound	60 µM	120 µM	240 µM
18a	37.56±18.82	8.34±5.03	1±15.12
18b	7.65±10.59	10±5.57	27±3.56
18c	13.67±14.98	1.33±3.06	28.33±9.46
18d	13.46±10.12	8,67±5.51	12±1.41
18e	27±5.57	29.31±5.86	33.30±834
18f	11.76±14.22	0±4.58	17.25±10.87
18g	-15±6.56	5.23±20,82	11.67±3.68
18h	11.33±11.02	28,64±13.20	7±2.94
18i	29.61±12.86	34.61±5.51	36.57±4.11
18j	41±3.61	44.56±4.93	54.31±3.86
18k	-1,57±3.06	0.33±2.52	11.69±8.22
18l	26.37±17.79	26.35±6.03	17±4.32
18m	39.30±4.51	40.29±2.08	45.63±.29
18n	27.21±15.82	25.16±8.08	24±8.64
18o	26.26±2.52	35.57±2.52	48±3.74
18p	32.13±2.08	35.68±2.08	46.72±2.05
18q	16±3.61	23.63±3.06	35.54±2.62
18r	42.16±1.53	44.26±2.31	47.75±3.39
18s	46.68±2.08	53±5.57	56.19±1.69
Acarbose	-	-	65.67±2.31

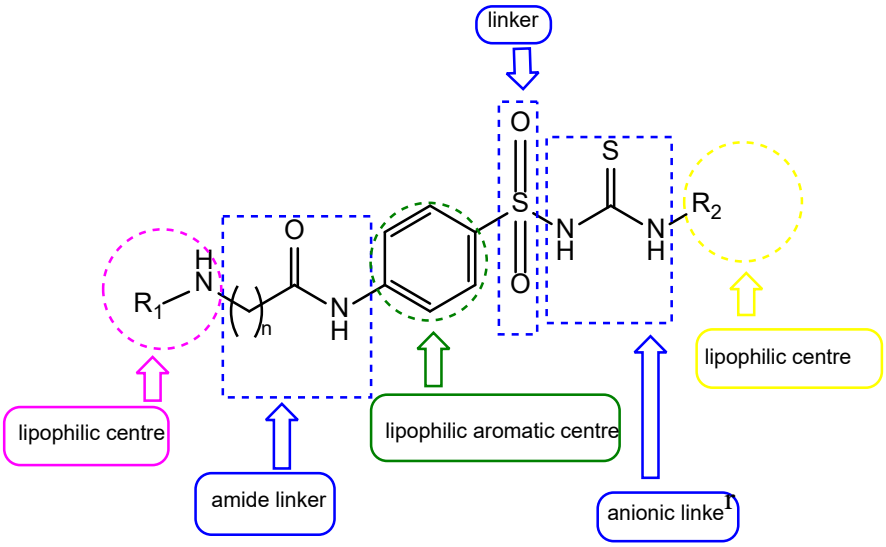


Figure 9: Agonist structural representation of the final compounds.

CHAPTER FOUR

4. Conclusion and future work

This chapter looks at the general conclusion of this study and modifications in the future to advance the study. The chemistry and biology of the target synthesized sulfonylthiourea compounds were studied extensively and gave promising % α-glucosidase and α-amylase inhibition results.

4.1 Conclusion

The first part of this study involved the synthesis of target sulfonylthiourea compounds with variations using different linkers to determine if these changes can enhance the antidiabetic activities. Known conventional methods were used to synthesize the target compounds **18a-s** over three reaction steps with fair to good percentage yields (33.28%–96.54%). All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS analysis. The second part of the study was to subject all synthesized target compounds to antidiabetic screening against the α-glucosidase and α-amylase enzymes. Most compounds showed little to no promising antidiabetic activity at the concentrations of 60μM and 120μM, but they exhibited significant anti-diabetic activities at 240μM. Activity analysis based on the three different linkers used showed that 2-methylpropanoylamide containing target compounds **18q-s** exhibited stronger enzyme inhibition of up to 84.67±3.34 at 200 μM followed by acetamide containing targets **18k-o** and lastly the propionylamide containing target compounds **18a-h** in that order.

4.2 Future work

In improvement to carbohydrate hydrolysing enzymes (glucosidase and amylase) studies that were done on this project, the future work of this study will involve exploring more targets, namely; Protein Tyrosine Phosphatase 1B (PTP1B) (a negative regulator of insulin signalling) and Glucose uptake studies in the skeletal muscle or liver cells (without targeting any enzyme). Secondly, determination of cytotoxicity levels of the synthesized compounds.

CHAPTER FIVE

5. Experimental procedure

5.1 General procedures

All reagents used in this study were analytical grade from Rochelle, Fluka and Sigma Aldrich and were used without further purification.

5.1.1. Spectroscopic techniques

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6, D_2O or $CDCl_3$ as solvents and TMS at 0.00 ppm as an internal standard. Values for the chemical shifts were expressed in parts per million (ppm), with the following abbreviations used to describe the spin multiplicities: br.s for broad singlet, s for singlet, d for doublet, dd for doublet of doublets, q for quartet, quint for quintet and m for multiplet and J as the coupling constant measured in Hertz (Hz).

The following abbreviations are used: br.s for broad singlet, s for singlet, d for doublet, dd for doublet of doublets, q for quartet, quint for quintet and m for multiplet and coupling constant (J) measured in hertz (Hz). All melting points were determined without correction on a Buchi melting point B-540 apparatus using capillary tubes.

Infrared spectra were run on a Bruker platinum 22 vector Fourier Transform spectrometer (FTIR). Mass spectra (High Resolution) were recorded on a Waters GCT using a column called the Restek Rxi Wintegra Guard (15 m, 0.25 mm ID, 0.25 µm film thickness) mass spectrometer. Samples were dissolved in a methanol and injected at a volume of 1 µl at mode of 10:1 at a temperature of 280 °C. The source temperature was 100 °C and the desolvation temperature was set at 300 °C. Helium gas was used as the carrier gas. The software used to control the hyphenated system and to do all data manipulation was Masslynx 4.1 (SCN 704).

5.1.2. Thin Layer Chromatography

Thin layer chromatography (TLC) was used to monitor the reactions using aluminium backed Macherey-Nagel ALUGRAM Sil G/UV254 plates or Aldrich or Merck TLC plates, silica gel on aluminium. The most used solvent system was a mixture of hexane and ethyl acetate. The compounds prepared during the course of this project are named in the following experimental sections according to systematic nomenclature wherever possible. The numbering system used to illustrate the diagrams of these compounds is one adopted for convenience and it is not meant to reflect the systematic numbering of these compounds.

5.1.3 Nomenclature of compounds

Compounds prepared during this project will be referred to by systematic nomenclature in the following experimental sections when applicable.

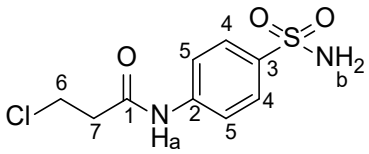
However, the numbering system used in the diagrams of these compounds is chosen for convenience and is not meant to reflect the systematic numbering of these compounds.

5.2. Synthetic procedures

5.2.1 Synthesis of substituted benzenesulfonamide by N-acylation reaction.

To a stirred mixture of sulfanilamide (50.0 mmol, 8.61 g) and anhydrous potassium carbonate (25.0 mmol, 3.46 g) in dry acetone at 0 ^{0}C was added a solution of acid chloride/bromoisobutyryl bromide (50.0 mmol, 5.68 g, 4 ml) in acetone drop-wise over 5 minutes. The reaction was allowed to warm to room temperature and stirred at this temperature for a further 4 hours. After this reaction time, the mixture was poured into ice water, and a precipitate was formed and then collected by filtration. [51,53]

5.2.1.1 Synthesis of 4-(3-chloropropionylamido)benzenesulfonamide (22a).

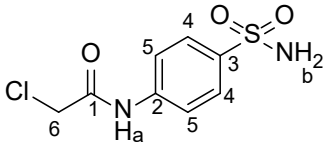


22a

The product was obtained as colourless needle-like crystals (10.82 g, 82.3 %). Melting point = 228.9–231.2 ^{0}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ (ppm), 10.44 (s, 1H, H-a), 7.96 – 7.57 (m, 4H, H-4 & H-5), 7.29 (s, 2H, H-b), 3.90 (t, *J* = 6.1 Hz, 2H, H-6), 2.88 (t, *J* = 6.1 Hz, 2H, H-7); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** (ppm), 169.08 (C-1), 142.28 (C-2), 138.87 (C-3), 127.22 (C-4), 119.12 (C-5), 41.06 (C-6), 39.70 (C-7).

5.2.1.2 Synthesis of 4-(2-chloroacetamido)benzenesulfonamide (22b).

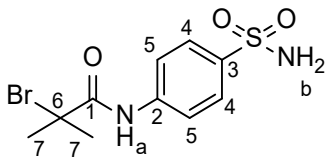


22b

The product was obtained as a white powder (10.95 g, 88.1%). Melting point = 230.9-233.2 ^{0}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ (ppm) 10.65 (s, 1H, H-a), 7.80 (d, 2H, *J* = 8.6 Hz, H-4), 7.76 (d, 2H, *J* = 8.5 Hz, H-5), 7.30 (s, 2H, H-b), 4.31 (s, 2H, H-6); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** (ppm) 165.84 (C-1), 141.71 (C-2), 138.89 (C-3), 127.06 (C-4), 119.50 (C-5), 43.26 (C-6).

5.2.1.3 Synthesis of 4-(2-bromo,2,2-dimethacetamido)benzenesulfonamide (22c).



22c

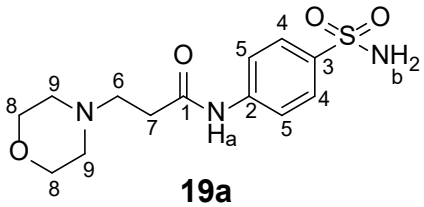
The product was obtained as a snow-white powder (13.2 g, 89%). Melting point = 197.4-199.7 ^{0}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.12 (s, 1H, H-a), 7.86 (d, *J* = 8.9 Hz, 2H, H-4), 7.80 (d, *J* = 8.9 Hz, 2H, H-5), 7.29 (s, 2H, H-b), 2.02 (s, 6H, H-7); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 170.27 (C-1), 142.06 (C-2), 139.49 (C-3), 126.91 (C-4), 120.52 (C-5), 60.86 (C-6), 31.04 (C-7).

5.2.2 General synthesis of propionylamide based sulfonamides.

Chloropropionylamido benzenesulfonamide **(22a)** was dissolved in dry acetone within a beaker. Subsequently, a reaction mixture containing suitable amines (1.0 mmol) and an equivalent quantity of potassium carbonate was subjected to reflux for one hour. Following this reflux phase, the solution of chloropropionylamido benzenesulfonamide was introduced, and the mixture was refluxed for an additional 7 hours. After being allowed to cool to room temperature, the mixture was poured into ice water and a precipitate was formed, which was collected by filtration to give the desired products.

5.2.2.1 Synthesis of 4-(3-morpholinopropionylamido)benzenesulfonamide (19a).



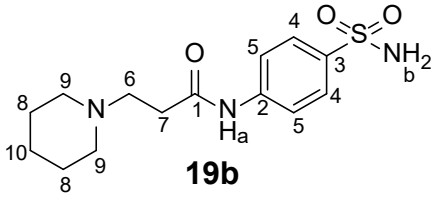
19a

A mixture of compound **22a** (22.84 mmol, 6.00 g) and anhydrous potassium carbonate (22.84 mmol, 3.15 g) in acetone (50 ml) was reacted with morpholine (22.84 mmol,

1.99g, 1.97 ml) to give the desired product **19a** as a white powder [52] (5.10 g, 71.2 %). Melting point = 189.3–191.2 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.39 (s, 1H, H-a), 7.70-7.82 (m, 4H, H-4 & H-5), 7.28 (s, 2H, H-b), 3.58 (m, 4H, H-8) 2.64 (t, *J* = 6.7 Hz, 2H, H-6), 2.53 (t, *J* = 6.4 Hz, 2H, H-7), 2.41 (m, 4H, H-9); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 171.23 (C-1), 142.54 (C-2), 138.66 (C-3), 127.14 (C-4), 119.01 (C-5), 66.63 (C-8), 54.46 (C-6), 53.47 (C-9), 34.38 (C-7).

5.2.2.2 Synthesis of 4-(3-piperidinopropionylamido)benzenesulfonamide (19b).

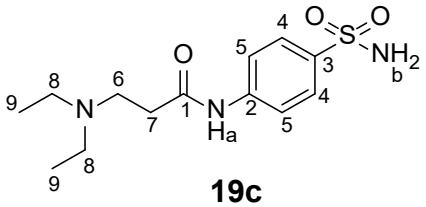


19b

A mixture of compound **22a** (29.77 mmol, 7.82 g) and anhydrous potassium carbonate (29.77 mmol, 4.12 g) in acetone (50 ml) was reacted with piperidine (29.77 mmol, 2.53 g, 2.94 ml) to give the desired product **19b** as fluffy yellow powder. (5.58 g, 60.2 %). Melting point = 192.4–194.3 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.55 (s, 1H, H-a), 7.72-7.77 (m, 4H, H-4 & H-5), 7.25 (s, 2H, H-b), 2.59 (t, *J* = 6.8 Hz, 2H, H-6), 2.54 – 2.46 (m, 4H, H-9), 2.37 (m, 2H, H-7), 1.57 – 1.44 (m, 4H, H-8), 1.39 (m, 2H, H-10); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 171.45 (C-1), 142.54 (C-2), 138.64 (C-3), 127.16 (C-4), 118.94 (C-5), 54.74 (C-6), 54.11 (C-9), 34.57 (C-7), 26.05 (C-8), 24.45 (C-10).

5.2.2.3 Synthesis of 4-(3-diethylaminopropionylamido)benzenesulfonamide (19c).



19c

A mixture of compound **22a** (30.45 mmol, 8.00 g) and anhydrous potassium carbonate (30.45 mmol, 4.20 g) in acetone (50 ml) was reacted with diethyl amine (30.45 mmol,

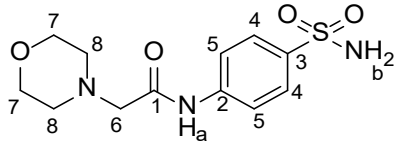
2.23 g, 3.15 ml) to give the desired product **19c** as a yellow powder (5.3 g, 58.11%). Melting point = 178.6-181.4^{o} C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.53 (s, 1H, H-a), 7.70 – 7.96 (m, 4H, H-4 & H-5), 6.87 (s, 2H, H-b), 2.91 – 2.73 (m, 2H, H-6), 2.53 (q, *J* = 6.3 Hz, 4H, H-8), 2.41 (t, *J* = 7.9 Hz, 2H, H-7), 1.08 (t, *J* = 6.3 Hz, 6H, H-9) **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**c 170.15 (C-1), 142.37 (C-2), 138.90 (C-3), 127.06 (C-4), 119.11 (C-5), 48.64 (C-6), 46.50 (C-8), 34.67 (C-7), 12.25 (C-9).

5.2.3 General synthesis of acetamide based sulfonamides.

A reaction mixture of appropriate amines (1.0 mmol) and an equivalent amount of potassium carbonate was refluxed for an hour at ambient temperatures. Meanwhile, compound **22b** was dissolved in acetone within a beaker, and this solution was subsequently added to the reaction mixture. The combined mixture was then refluxed for a duration of 5 hours. After being allowed to cool to room temperature, the mixture was poured into ice water and a precipitate was formed, which was collected by filtration to give the desired products.

5.2.3.1 Synthesis of 4-(2-morpholinoacetamido)benzenesulfonamide (19d).

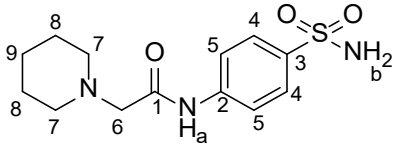


19d

A mixture of compound **22b** (24.13 mmol, 6.00 g) anhydrous potassium carbonate (24.13 mmol, 3.33 g) in acetone (50 ml) was reacted with morpholine (24.13 mmol, 2.10 g, 2.08 ml) to give the desired product **19d** as a white powder [52] (6.43 g, 89.03 %). Melting point = 210.9–213.0 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.07 (s, 1H, H-a), 7.82 (d, *J* = 8.8 Hz, 2H, H-4), 7.77 (d, *J* = 8.8 Hz, 2H, H-5), 7.26 (s, 2H, H-b), 3.72 – 3.58 (m, 4H, H-7), 3.18 (s, 2H, H-6), 2.59 – 2.44 (m, 4H, H-8); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**C 169.18 (C-1), 141.95 (C-2), 139.00 (C-3), 127.05 (C-4), 119.52 (C-5), 66.51 (C-6), 62.42 (C-7), 53.58 (C-8).

5.2.3.2 Synthesis of 4-(2-piperidinoacetamido)benzenesulfonamide (19e).

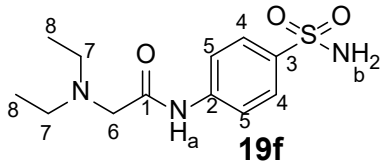


19e

A mixture of compound **22b** (25.73 mmol, 6.4 g) and anhydrous potassium carbonate (25.73 mmol, 3.55 g) in acetone (50 ml) was reacted with piperidine (25.73 mmol, 2.19 g, 2.54 ml) to give the desired product **19e** as a white powder (5.54 g, 72.39 %). Melting point = 191.5–194.2 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 9.99 (s, 1H, H-a), 7.82 (d, *J* = 8.9 Hz, 2H, H-4), 7.76 (d, *J* = 8.9 Hz, 2H, H-5), 7.26 (s, 2H, H-b), 3.11 (s, 2H, H-6), 2.49 – 2.38 (m, 4H, H-7), 1.62 – 1.52 (m, 4H, H-8), 1.45 – 1.35 (m, 2H, H-9); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C** 169.73 (C-1), 141.94 (C-2), 138.95 (C-3), 127.06 (C-4), 119.42 (C-5), 63.08 (C-6), 54.49 (C-7), 25.88 (C-8), 23.98 (C-9).

5.2.3.3 Synthesis of 4-(2-diethylaminoacetamido)benzenesulfonamide (19f).

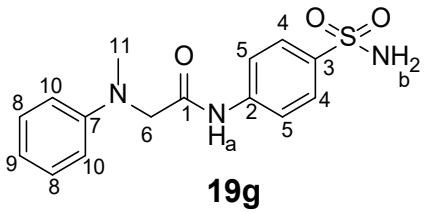


19f

A mixture of compound **22b** (32.97 mmol, 8.20 g) and anhydrous potassium carbonate (32.97 mmol, 4.55 g) in acetone (50 ml) was reacted with diethylamine (32.97 mmol, 2.41 g, 3.41 ml) to give the desired product **19f** as a yellow powder (3.42 g, 36.35%). Melting point = 194.2-197.4 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$), δ_H 10.15 (s, 1H, H-a), 7.84 (d, *J* = 8.3 Hz, 2H, H-4), 7.77 (d, *J* = 8.3 Hz, 2H, H-5), 7.25 (s, 2H, H-b), 3.19 (s, 2H, H-6), 2.62 (q, *J* = 7.0 Hz, 4H, H-7), 1.03 (t, *J* = 7.0 Hz, 6H, H-8); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C** 171.0 (C-1), 141.7 (C-2), 139.0 (C-3), 127.0 (C-4), 119.3 (C-5), 57.8 (C-6), 48.2 (C-7), 12.3 (C-8).

5.2.3.4 Synthesis of 4-(2-*N*- methylanilinoacetamido)benzenesulfonamide (19g).

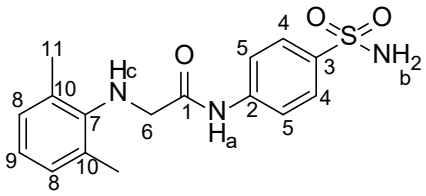


19g

A mixture of compound **22b** (12.06 mmol, 3 g) and anhydrous potassium carbonate (12.06 mmol, 1.66 g) in acetone (50 ml) was reacted with N-methylaniline (12.06 mmol, 1.29 g, 1.31 ml) to give the desired product **19g** as a yellow powder (2.83 g, 73.47 %). Melting point = 241.0–244.5 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$), δ$_H$ 9.97 (s, 1H, H-a), 8.06 (d, *J* = 7.5 Hz, 2H, H-4), 7.77 (d, *J* = 7.5 Hz, 2H, H-5), 7.31 (s, 2H, H-b), 7.08 (t, *J* = 7.5 Hz, 2H, H-8), 6.72 (dd, *J* = 7.6, 1.4 Hz, 2H, H-10), 6.68 (tt, *J* = 7.6, 1.4 Hz, 1H, H-9), 3.76 (s, 2H, H-6), 2.93 (s, 3H, H-11); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 169.51 (C-1), 149.35 (C-7), 141.81 (C-2), 138.47 (C-3), 128.58 (C-8), 126.52 (C-4), 118.56 (C-5), 116.22 (C-9), 111.88 (C-10), 56.07 (C-6), 38.88 (C-11).

5.2.3.5 Synthesis of 4-(2-(2,6-dimethylanilino)acetamido)benzenesulfonamide (19h).



19h

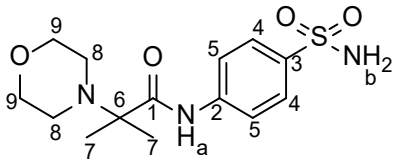
A mixture of compound **22b** (16.08 mmol, 4 g) and anhydrous potassium carbonate (16.08 mmol, 2.22 g) in acetone (50 ml) was reacted with 2,6-dimethylaniline (16.08 mmol, 1.95 g, 1.98 ml) to give the desired product **19h** as a caramel-like powder (4.14 g, 77.22 %). Melting point = 242.4–245.5 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$), δ$_H$ 9.81 (s, 1H, H-a), 8.03 (d, *J* = 7.5 Hz, 2H, H-4), 7.80 (d, *J* = 7.5 Hz, 2H, H-5), 6.97 (d, *J* = 7.5 Hz, 2H, H-8), 6.82 (s, 2H, H-b), 6.73 (t, *J* = 7.5 Hz, 1H, H-9), 5.29 (t, *J* = 8 Hz, 1H, H-c), 4.09 (s, 1H, H-6a), 4.03 (s, 1H, H-6b), 2.31 (s, 6H, H-11); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 167.96 (C-1), 151.09 (C-7), 142.71 (C-2), 139.33 (C-3), 128.89 (C-8), 128.35 (C-10), 127.89 (C-4), 120.98 (C-9), 120.35 (C-5), 45.22 (C-6), 18.23 (C-11).

5.2.4 General synthesis of 2-methylpropanoylamide based sulfonamides.

A solution of compound **22c** (1 mmol) in dry acetone was taken to 0°C before been treated with anhydrous potassium carbonate (2 mmol). This reaction mixture was treated with an amine (1 mmol) before being allowed to warm to room temperature and refluxed for 7 hrs. After being allowed to cool to room temperature, the mixture was poured into ice water and a precipitate was formed, which was collected by filtration to give the desired products.

5.2.4.1 Synthesis of 4-(2-morpholino,2,2-dimethacetamido)benzenesulfonamide (19i).

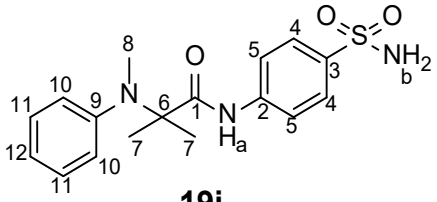


19i

A mixture of compound **22c** (12.0 mmol, 4.00 g) and anhydrous potassium carbonate (24.0 mmol, 3.37 g) in acetone (50 ml) was reacted with morpholine (12.0 mmol, 1.05 ml) to give the desired product **19i** as a yellowish solid (2.79 g, 69.75%). Melting point = 233.1-236.8 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 9.91 (s, 1H, H-a), 7.85 (d, *J* = 8.8 Hz, 2H, H-4), 7.77 (d, *J* = 8.8 Hz, 2H, H-5), 7.24 (s, 2H, H-b), 3.70 (t, 4H, *J* = 3.3 Hz, H-9), 2.56 (t, 4H, *J* = 3.2 Hz, H-8), 1.21 (s, 6H, H-7); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 175.71 (C-1), 142.13 (C-2), 138.94 (C-3), 126.94 (C-4), 119.70 (C-5), 66.95 (C-6), 64.17 (C-9), 47.32 (C-8), 20.28 (C-7).

5.2.4.2. Synthesis of 4-(2-(N-methylanilino),2,2-dimethacetamido) benzenesulfonamide (19j).



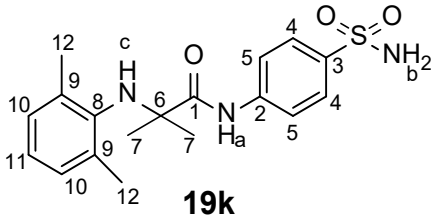
19j

A mixture of compound **22c** (9.65 mmol, 3.10 g) and anhydrous potassium carbonate (19.31 mmol, 2.66 g) in acetone (50 ml) was reacted with *N*-methylaniline (9.65 mmol,

1.05 ml) to give the desired product **19j** as a reddish solid (1.98 g, 63.87%). Melting point = 171.4-174.8 °C.

^{1}H NMR (400 MHz, DMSO-d6) δ_H, 10.04 (s, 1H, H-a), 7.84 (d, *J* = 8.6 Hz, 2H, H-4), 7.77 (d, *J* = 8.6 Hz, 2H, H-5), 7.28 (s, 2H, H-b), 7.22 (t, *J* = 7.7 Hz, 2H, H-11), 7.04 (d, *J* = 8.0 Hz, 2H, H-10), 6.88 (t, *J* = 7.2 Hz, 1H, H-12), 2.85 (s, 3H, H-8), 1.35 (s, 6H, H-7); **^{13}C NMR (100 MHz, DMSO-d6) δ_C** 176.11 (C-1), 149.17 (C-9), 142.39 (C-2), 138.97 (C-3), 128.91 (C-4), 126.86 (C-11), 121.30 (C-12), 121,32 (C-5), 120.07 (C-10), 64.08 (C-6), 36.02 (C-8), 23.27 (C-7).

5.2.4.3 Synthesis of 4-(2-(2,6-dimethylanilino),2,2-dimethacetamido) benzenesulfonamide (19k)

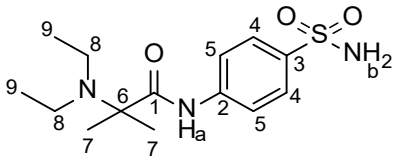


19k

A mixture of compound **22c** (6.26 mmol, 2.00 g) and anhydrous potassium carbonate (12.45 mmol, 1.72 g) in acetone (40 ml) was reacted with 2,6 dimethylaniline (6.26 mmol, 0.76 ml) to give the desired product **19k** as a brownish solid (0.97 g, 48.50%). Melting point = 163.1-165.9 °C.

^{1}H NMR (400 MHz, DMSO-d6) δ_H 10.43 (s, 1H, H-a), 7.92 (d, *J* = 8.6 Hz, 2H, H-4), 7.81 (d, *J* = 8.6 Hz, 2H, H-5), 7.30 (s, 2H, H-b), 6.86 (d, *J* = 7.4 Hz, 2H, H-10), 6.19-6,01 (m, 1H, H-11), 4.01 (s, 1H, H-c), 2.10 (s, 6H, H-12), 1.32 (s, 6H, H-7); **^{13}C NMR (100 MHz, DMSO-d6) δ_C** 177.36 (C-1), 143.35 (C-8), 142.26 (C-2), 138.87 (C-3), 132.86 (C-9), 129.03 (C-4), 127.20 (C-10), 123.53 (C-11), 119.25 (C-5), 59.77 (C-6), 27.02 (C-7), 19.83 (C-12).

5.2.4.4 Synthesis of 4-(2-diethylamino,2,2-dimethacetamido)benzenesulfonamide (19l).



19l

A mixture of compound **22c** (12.40 mmol, 2.00 g) and anhydrous potassium carbonate (24.48 mmol, 3.44 g) in acetone (40 ml) was reacted with 2,6 dimethylaniline (12.40

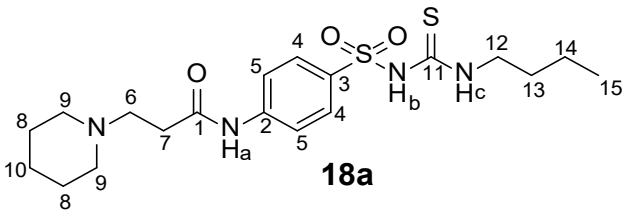
mmol, 1.02 ml) to give the desired product **19l** as an orange solid (3.2 g ,80%). Melting point = 192.4-195.7 °C.

^{1}H NMR (400 MHz, DMSO) δ_H 9.89 (s, 1H, H-a), 7.87 (d, *J* = 8.7 Hz, 2H, H-4), 7.81 (d, *J* = 8.1 Hz, 2H, H-5), 7.48 (s, 2H, H-b), 2.58-2,52 (m, 4H, H-8), 1.24 (s, 6H, H-7), 1.07 (t, *J* = 7.0 Hz, 6H, H-9); **^{13}C NMR (100 MHz, DMSO) δ_C** 176.84 (C-1), 140.51 (C-2), 138.99 (C-3), 127.07 (C-4), 119.34 (C-5), 65.61 (C-6), 43.38 (C-8), 22.04 (C-7), 15.54 (C-9).

5.2.5 General synthetic methods for propionylamide containing target sulfonylthioureas (18a-j).

A solution of compound **19a-c** (1.0 mmol) in acetonitrile was treated with anhydrous potassium carbonate (1.0 mmol) and refluxed for 1 hour thus achieving the potassium salt. Isothiocyanates (1.0 mmol) were added to this reaction mixture and further refluxed for 24 hours. After this reaction time, the excess solvent was removed using rotatory vapour and a precipitate was formed. The precipitate was then washed with acidic water and collected via filtration to obtain products which were purified by recrystallization from methanol and column chromatography.

5.2.5.1 Synthesis of 4-(3-piperidinopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18a).



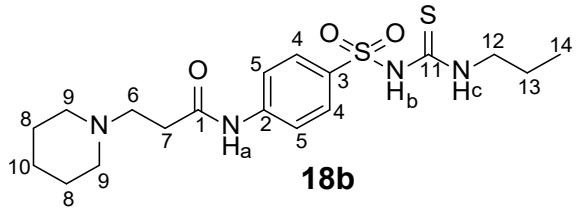
18a

A mixture of compound **19b** (3.21 mmol, 1.00 g) and potassium carbonate (3.21 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with butyl isothiocyanate (3.21 mmol, 0.4 ml). The product was obtained as a cream-white powder (1.18 g, 86.17%). Melting point = 214.7–217.4 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 10.92 (s, 1H, H-a), 10.21 (s, 1H, H-b), 8.67 (t, *J* = 5.4 Hz, 1H, H-c), 7.86 (d, *J* = 9.3 Hz, 2H, H-4), 7.83 (d, *J* = 9.4 Hz, 2H, H-5), 3.41 – 3.36 (m, 4H, H-9), 3.34 (m, 2H, H-12), 3.00 (t, *J* = 7.3 Hz, 2H, H-6), 2.96 – 2.84 (m,

2H, H-7), 1.78 (m, 4H, H-8), 1.71 (quint, *J* = 8 Hz, 2H, H-10), 1.42 (dt, *J* = 14.8, 7.3 Hz, 2H, H-13), 1.25 – 1.14 (m, 2H, H-14), 0.83 (t, J = 7.3 Hz, 3H, H-15); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ 178.46 (C-11), 169.23 (C-1), 143.79 (C-2), 133.49 (C-3), 129.19 (C-4), 119.08 (C-5), 52.66 (C-9), 51.91 (C-6), 44.47 (C-12), 31.14 (C-7), 30.18 (C-13), 22.84 (C-8), 21.70 (C-10), 19.87 (C-14), 14.05 (C-15). **IR** (KBr cm^{-1}): 3324.37 (N-H), 2987.46 (ArC-H), 1667.30 (C=O), 1589.70 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{19}H_{30}N_4O_3S_2$: 426.1759; found: 426.1816

5.2.5.2 Synthesis of 4-(3-piperidinopropionylamido)-*N*-(propylcarbamothioyl)benzenesulfonamide (18b).

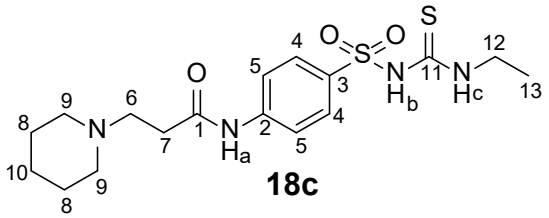


18b

A mixture of compound **19b** (3.21 mmol, 1.00 g) and potassium carbonate (3.21 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with propyl isothiocyanate (3.21 mmol, 0.3 ml). The product was obtained as a white powder (1.17 g, 88.35%). Melting point = 192.4–194.8 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.93 (s, 1H, H-a), 10.19 (s, 1H, H-b), 8.70 (t, *J* = 5.4 Hz, 1H, H-c), 7.86 (d, *J* = 9.2 Hz, 2H, H-4), 7.83 (d, *J* = 9.2 Hz, 2H, H-5), 3.41 (d, *J* = 12.4 Hz, 2H, H-12), 3.34 (dd, *J* = 12.5, 6.7 Hz, 4H, H-9), 3.00 (t, *J* = 7.2 Hz, 2H, H-6), 2.90 (m, 2H, H-7), 1.78 (m, 4H, H-8), 1.71 (quint, *J* = 8.0 Hz, 2H, H-10), 1.47 (dt, *J* = 14.5, 7.3 Hz, 2H, H-13), 0.79 (t, *J* = 7.4 Hz, 3H, H-14); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ 178.51 (C-11), 169.23 (C-1), 143.78 (C-2), 133.49 (C-3), 129.22 (C-4), 119.08 (C-5), 52.66 (C-9), 51.92 (C-6), 46.45 (C-12), 31.14 (C-7), 22.85 (C-8), 21.70 (C-10), 21.43 (C-13), 11.61 (C-14). **IR** (KBr cm^{-1}): 3321.34 (N-H), 2984.43 (ArC-H), 1663.28 (C=O), 1587.71 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{18}H_{28}N_4O_3S_2$: 412.1603; found: 412.1618

5.2.5.3 Synthesis of 4-(3-piperidinopropionylamido)-*N*-(ethylcarbamothioyl)benzenesulfonamide (18c).

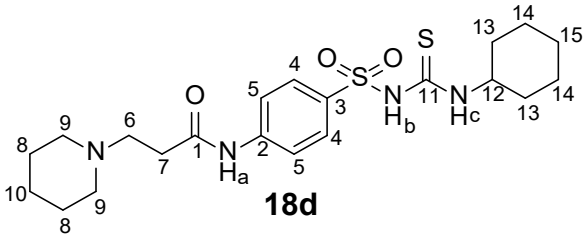


18c

A mixture of compound **19b** (3.21 mmol, 1.00 g) and potassium carbonate (3.21 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with ethyl isothiocyanate (3.21 mmol, 0.3 ml). The product was obtained as a white powder (0.92 g, 71.91%). Melting point = 194.3–197.6 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 9.92 (s, 1H, H-a), 8.72 (s, 1H, H-b), 7.86 (d, *J* = 9.2 Hz, 2H, H-4), 7.83 (d, *J* = 9.2 Hz, 2H, H-5), 7.31 (t, *J* = 5.4 Hz, 1H, H-c), 4.41 (m, 2H, H-12), 3.25 (t, *J* = 7.6 Hz, 2H, H-6), 2.58 (t, *J* = 5.3 Hz, 2H, H-9a), 2.42 (t, *J* = 7.8 Hz, 2H, H-7), 2.29 (t, *J* = 6.3, 2H, H-9b), 1.58 (m, 4H, H-8), 1.37 (quint, *J* = 7.8 Hz, 2H, H-10), 0.75 (t, *J* = 7.4 Hz, 3H, H-13); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 176.56 (C-11), 172.02 (C-1), 147.04 (C-2), 133.09 (C-3), 127.40 (C-4), 123.10 (C-5), 52.63 (C-9), 51.94 (C-6), 34.68 (C-12), 28.92 (C-7), 22.87 (C-8), 21.56 (C-10), 12.90 (C-13). **IR** (KBr cm^{-1}): 3330.26 (N-H), 2989.35 (ArC-H), 1669.19 (C=O), 1586.80 (C=C). **HRMS** (ESI-TOF): m/z [M^{+}] calcd for $C_{17}H_{26}N_4O_3S_2$: 398.1446; found: 398.1502

5.2.5.4 Synthesis of 4-(3-piperidinopropionylamido)-*N*-(cyclohexylcarbamothioyl)benzenesulfonamide (18d).

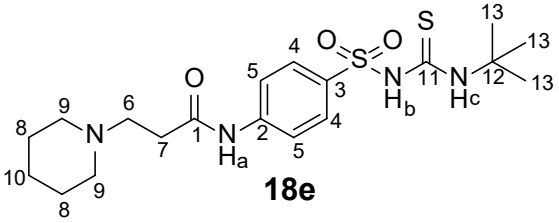


18d

A mixture of compound **19b** (3.21 mmol, 1.00 g) and potassium carbonate (3.21 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with cyclohexyl isothiocyanate (3.21 mmol, 0.5 ml). The product was obtained as a white powder (1.36 g, 93.60%). Melting point = 200.1–202.9 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 10.94 (s, 1H, H-a), 10.31 (s, 1H, H-b), 8.62 (d, *J* = 7.8 Hz, 1H, H-c), 7.84 (m, 4H, H-4 & H-5), 4.14 (quint, *J* = 7.4 Hz, 1H, H-12), 2.84 (t, *J* = 5.0 Hz, 2H, H-6), 2.47 (t, *J* = 5.4 Hz, 2H, H-9a), 2.41 (t, *J* = 5.0 Hz, 2H, H-7), 2.23 (t, *J* = 5.4 Hz, 2H, H-9b), 1.69 – 1.63 (m, 4H, H-13), 1.54 – 1.51 (m, 6H, H-8 & H-10), 1.38 – 1.32 (m, 2H, H-15), 1.29 – 1.20 (m, 4H, H-14); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C** 177.30 (C-11), 169.23 (C-1), 143.75 (C-2), 133.52 (C-3), 129.32 (C-4), 119.03 (C-5), 52.97 (C-6), 52.63 (C-9), 51.91 (C-12), 31.30 (C-13), 31.15 (C-7), 25.39 (C-15), 24.46 (C-14), 22.84 (C-8), 21.72 (C-10). **IR** (KBr cm^{-1}): 3325.46 (N-H), 2986.90 (ArC-H), 1664.89 (C=O), 1581.72 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{21}H_{32}N_4O_3S_2$: 452.1916; found: 452.1963

5.2.5.5 Synthesis of 4-(3-piperidinopropionylamido)-*N*-(tertiarybutylcarbamothioyl)benzenesulfonamide (18e).

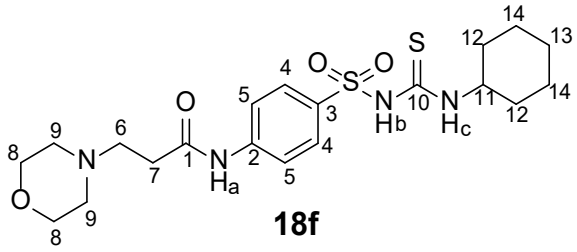


18e

A mixture of compound **19b** (3.21 mmol, 1.00 g) and potassium carbonate (3.21 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with propyl isothiocyanate (3.21 mmol, 0.3 ml). The product was obtained as a white powder (0.71 g, 51.84%). Melting point = 242.8–245.4 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 10.99 (s, 1H, H-a), 8.21 (s, 1H, H-b), 7.81 (d, *J* = 8.8 Hz, 2H, H-4), 7.76 (d, *J* = 8.8 Hz, 2H, H-5), 7.31 (s, 1H, H-c), 3.24 (t, *J* = 7.3 Hz, 2H, H-6), 3.13 – 3.03 (m, 4H, H-9), 2.97 (t, *J* = 7.5 Hz, 2H, H-7), 1.79 – 1.69 (m, 4H, H-8), 1.56 – 1.47 (m, 2H, H-10), 1.26 (s, 9H, H-13); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C** 175.01 (C-11), 169.30 (C-1), 142.38 (C-2), 138.78 (C-3), 127.09 (C-4), 119.12 (C-5), 52.70 (C-12), 52.29 (C-6), 51.45 (C-9), 31.44 (C-7), 27.53 (C-13), 23.16 (C-8), 22.04 (C-10). **IR** (KBr cm^{-1}): 3328.46 (N-H), 2987.75 (ArC-H), 1655.39 (C=O), 1580.61 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{19}H_{30}N_4O_3S_2$: 426.1759; found: 426.1819

5.2.5.6 Synthesis of 4-(3-morpholinopropionylamido)-*N*-(cyclohexylcarbamothioyl)benzenesulfonamide (18f).

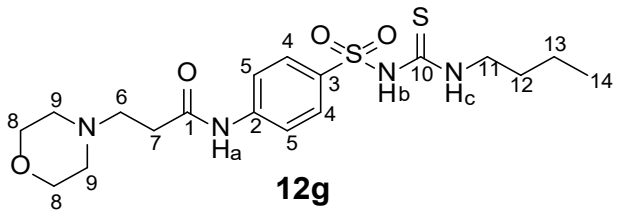


18f

A mixture of compound **19a** (3.19 mmol, 1.00 g) and potassium carbonate (3.19 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with cyclohexyl isothiocyanate (3.19 mmol, 0.5 ml). The product was obtained as a white powder (1.40 g, 96.54%). Melting point = 222.6–225.3 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.93 (s, 1H, H-a), 8.60 (d, *J* = 7.8 Hz, 1H, H-c), 7.86 – 7.82 (m, 4H, H-4 & H-5), 3.80 (m, 2H, H-6), 3.54 – 3.47 (m, 4H, H-8), 3.46 – 3.36 (m, 4H, H-9), 3.12 (m, 1H, H-11), 3.03 (t, *J* = 7.2 Hz, 2H, H-7), 1.75 (m, 2H, H-12a), 1.61 (m, 2H, H-12b), 1.49 (d, *J* = 8.5 Hz, 2H, H-13), 1.22 (dd, *J* = 17.8, 8.9 Hz, 4H, H-14); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 177.25 (C-10), 169.06 (C-1), 143.73 (C-2), 133.50 (C-3), 129.32 (C-4), 119.07 (C-5), 63.65 (C-8), 53.00 (C-11), 52.04 (C-6), 51.66 (C-9), 31.29 (C-12), 30.80 (C-7), 25.37 (C-13), 24.45 (C-14). **IR** (KBr cm^{-1}): 3324.40 (N-H), 2987.76 (ArC-H), 1667.58 (C=O), 1587.20 (C=C). **HRMS** (ESI-TOF): m/z [M^{+}] calcd for $C_{20}H_{30}N_4O_4S_2$: 454.1708; found: 454.1893

5.2.5.7 Synthesis of 4-(3-morpholinopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18g).

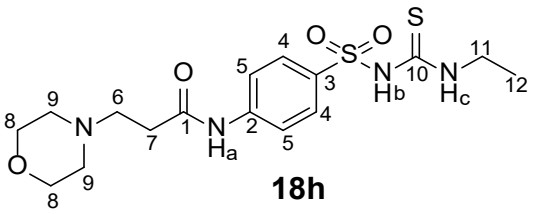


12g

A mixture of compound **19a** (3.19 mmol, 1.00 g) and potassium carbonate (3.19 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with butyl isothiocyanate (3.19 mmol, 0.4 ml). The product was obtained as a yellow powder (0.95 g, 69.48%). Melting point = 161.4–163.7 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 11.23 (s, 1H, H-a), 10.25 (s, 1H, H-b), 8.53 (t, *J* = 5.5 Hz, 1H, H-c), 7.53 (d, *J* = 8.8 Hz, 2H, H-4), 6.62 (d, *J* = 8.8 Hz, 2H, H-5), 3.77 (t, *J* = 4.7 Hz, 4H, H-9), 3.64 – 3.48 (m, 2H, H-11), 2.71 (t, *J* = 7.8 Hz, 2H), 2.66 (t, *J* = 4.7 Hz, 2H, H-9a), 2.47 – 2.39 (m, 4H, H-7 & H-9b), 1.55 – 1.44 (m, 2H, H-12), 1.41 – 1.31 (m, 2H), 0.98 (t, *J* = 6.5 Hz, 3H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 181.30 (C-10), 169.83 (C-1), 144.27 (C-2), 136.86 (C-3), 129.18 (C-4), 119.07 (C-5), 66.82 (C-8), 53.15 (C-9), 49.64 (C-6), 44.65 (C-11), 35.92 (C-7), 30.89 (C-12), 20.22 (C-13), 14.01 (C-14). **IR** (KBr cm^{-1}): 3330.46 (N-H), 2988.25 (ArC-H), 1667.88 (C=O), 1581.71 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{18}H_{28}N_4O_4S_2$: 428.1552; found: 428.1577

5.2.5.8 Synthesis of 4-(3-morpholinopropionylamido)-*N*-(ethylcarbamothioyl)benzenesulfonamide (18h).

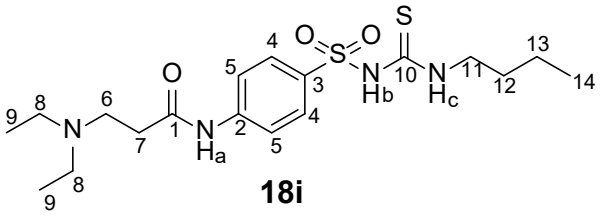


18h

A mixture of compound **19a** (3.19 mmol, 1.00 g) and potassium carbonate (3.19 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with ethyl isothiocyanate (3.19 mmol, 0.3 ml). The product was obtained as a white powder (0.68 g, 53.22%). Melting point = 132.7–135.3 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ δ 9.29 (s, 1H, H-a), 7.97 (d, *J* = 7.5 Hz, 2H, H-4), 7.74 (d, *J* = 7.5 Hz, 2H, H-5), 7.20 (t, *J* = 5.4, 1H, H-c), 4.71 (q, *J* = 6.4 Hz, 2H, H-11), 3.77 (t, *J* = 4.7 Hz, 4H, H-8), 2.71 (t, *J* = 7.8 Hz, 2H, H-6), 2.68 – 2.64 (m, 2H, H-9a), 2.48 – 2.37 (m, 4H, H-7 & H-9a), 1.21 (t, *J* = 6.3 Hz, 3H, H-12); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 178.27 (C-10), 169.10 (C-1), 154.18 (C-2), 143.78 (C-3), 129.23 (C-4), 119.12 (C-5), 63.68 (C-8), 52.07 (C-6), 51.70 (C-9), 31.16 (C-11), 30.82 (C-7), 13.71 (C-12). **IR** (KBr cm^{-1}): 3321.76 (N-H), 2984.35 (ArC-H), 1669.79 (C=O), 1586.71 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{16}H_{24}N_4O_4S_2$: 400.1239; found: 400.1248

5.2.5.9 Synthesis of 4-(3-diethylaminopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18i).

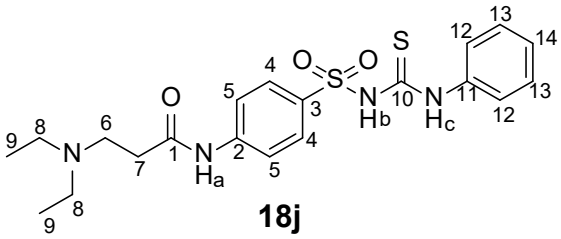


18i

A mixture of compound **19c** (3.34 mmol, 1.00 g) and potassium carbonate (3.34 mmol, 0.46 g) in acetonitrile (15 ml) was reacted with butyl isothiocyanate (3.34 mmol, 0.4 ml). The product was obtained as a yellow-orange powder (0.70 g, 50.55%). Melting point = 165.9–168.6 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 9.68 (s, 1H, H-a), 7.96 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 6.97 (t, *J* = 5.4 Hz, 1H, H-c), 3.56 (dt, *J* = 10.1, 5.1 Hz, 2H, H-11), 2.91 (t, *J* = 7.7 Hz, 2H, H-6,), 2.65 (q, *J* = 6.3 Hz, 2H, H-8a), 2.53 (q, *J* = 6.4 Hz, 2H, H-8b), 2.46 (t, *J* = 7.7 Hz, 2H, H-7), 1.59 – 1.47 (m, 2H, H-12), 1.41 – 1.30 (m, 2H, H-13), 1.07 (t, *J* = 6.3 Hz, 6H, H-9), 0.99 (t, *J* = 6.5 Hz, 3H, H-14); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 183.30 (C-10), 169.83 (C-1), 144.27 (C-2), 136.86 (C-3), 129.18 (C-4), 119.07 (C-5), 47.63 (C-8), 46.35 (C-6), 44.65 (C-11), 35.92 (C-7), 30.89 (C-12), 20.22 (C-13), 14.01 (C-14), 12.33 (C-9). **IR** (KBr cm^{-1}): 3329.50 (N-H), 2988.45 (ArC-H), 1664.59 (C=O), 1588.61 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{18}H_{30}N_4O_3S_2$: 414.1759; found: 414.1782

5.2.5.10 Synthesis of 4-(3-diethylaminopropionylamido)-*N*-(phenylcarbamothioyl)benzenesulfonamide (18j).



18j

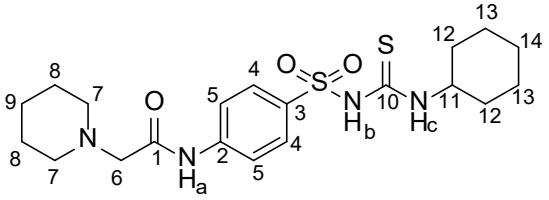
A mixture of compound **19c** (3.19 mmol, 1.00 g) and potassium carbonate (3.19 mmol, 0.44 g) in acetonitrile (15 ml) was reacted with phenyl isothiocyanate (3.19 mmol, 0.5 ml). The product was obtained as a yellow powder (0.46 g, 33.18%). Melting point = 270.2–273.9 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 9.34 (s, 1H, H-a), 9.29 (s, 1H, H-c), 7.96 (d, *J* = 7.5 Hz, 2H, H-4), 7.75 (d, *J* = 7.5 Hz, 2H, H-5), 7.36 (t, *J* = 7.5 Hz, 2H, H-13), 7.30 (dd, *J* = 7.6, 1.4 Hz, 2H, H-12), 7.21 – 7.10 (m, 1H, H-14), 2.91 (t, *J* = 7.7 Hz, 2H, H-6), 2.73 (q, *J* = 6.3 Hz, 2H, H-8a), 2.52 – 2.45 (m, 4H, H-7 & H-8b), 1.08 (t, *J* = 6.3 Hz, 6H, H-9); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 178.36 (C-10), 171.30 (C-1), 144.27 (C-2), 139.18 (C-11), 136.86 (C-3), 129.18 (C-4), 128.96 (C-13), 124.47 (C-14), 121.54 (C-12), 119.07 (C-5), 47.63 (C-8), 46.35 (C-6), 35.92 (C-7), 12.33 (C-9). **IR** (KBr cm^{-1}): 3249.30 (N-H), 2965.25 (C-H), 1686.26 (C=O), 1587.18 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{20}H_{26}N_4O_3S_2$: 434.1446; found: 434.1508

5.2.6 General synthetic methods for acetamide containing target sulfonylthioureas (18k-o).

To a solution of compound **19d-h** (1.0 mmol) in a solvent of dry acetonitrile was added anhydrous potassium carbonate (1.0 mmol). The reaction mixture was heated under reflux for 1 hour to achieve the potassium salt and then appropriate isothiocyanates (1.0 mmol) were added and the reaction mixture was further refluxed for 24 hours. After cooling, the excess solvent was removed using rotatory vapour and a slurry crude product was obtained. The crude product was stirred in acidic water until a precipitate formed. The precipitate was filtered and washed with ice-cold water to give products as solids, which were further purified using recrystallization from ethanol and column chromatography.

5.2.6.1 Synthesis of 4-(2-piperidinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (18k).

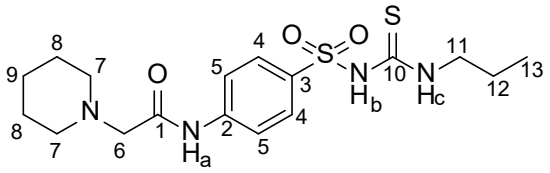


18k

A mixture of compound **19d** (3.36 mmol, 1.00 g) and potassium carbonate (3.36 mmol, 0.46 g) in acetonitrile (15 ml) was reacted with cyclohexyl isothiocyanate (3.36 mmol, 0.5 ml). The product was obtained as a white powder (1.19 g, 80.75%). Melting point = 184.8–187.6 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.94 (s, 1H, H-a), 10.31 (s, 1H, H-b), 8.62 (d, *J* = 7.8 Hz, 1H, H-c), 7.84 (m, 4H, H-4 & H-5), 4.14 (quint, *J* = 7.4 Hz, 1H, H-11), 2.84 (t, *J* = 5.0 Hz, 2H, H-6), 2.47 (t, *J* = 5.4 Hz, 2H, H-7a), 2.23 (t, *J* = 5.4 Hz, 2H, H-7b), 1.69–1.63 (m, 4H, H-12), 1.54–1.51 (m, 6H, H-8 & H-9), 1.38–1.32 (m, 2H, H-14), 1.29–1.20 (m, 4H, H-13); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 177.30 (C-10), 169.23 (C-1), 143.75 (C-2), 133.52 (C-3), 129.32 (C-4), 119.03 (C-5), 52.97 (C-6), 52.63 (C-7), 51.91 (C-11), 31.30 (C-12), 25.39 (C-14), 24.46 (C-13), 22.84 (C-8), 21.72 (C-9). **IR** (KBr cm^{-1}): 3298.86 (N-H), 2940.74 (C-H), 1695.47 (C=O), 1596.34 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{20}H_{30}N_4O_3S_2$: 438.1759; found: 438.1939

5.2.6.2 Synthesis of 4-(2-piperidinoacetamido)-*N*-(propylcarbamothioyl)-benzenesulfonamide (18l).

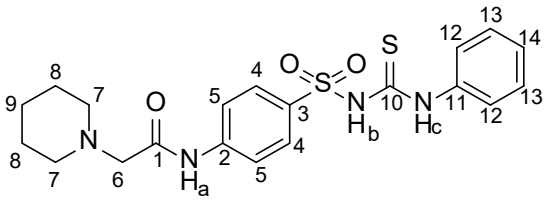


18l

A mixture of compound **19d** (3.36 mmol, 1.00 g) and potassium carbonate (3.36 mmol, 0.46 g) in acetonitrile (15 ml) was reacted with propyl isothiocyanate (3.36 mmol, 0.3 ml). The product was obtained as a cream-white powder (1.07 g, 79.90%). Melting point = 186.1–188.4 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.93 (s, 1H, H-a), 10.19 (s, 1H, H-b), 8.70 (t, *J* = 5.4 Hz, 1H, H-c), 7.86 (d, *J* = 9.2 Hz, 2H, H-4), 7.83 (d, *J* = 9.2 Hz, 2H, H-5), 3.41 (d, *J* = 12.4 Hz, 2H, H-11), 3.34 (dd, *J* = 12.5, 6.7 Hz, 4H, H-7), 3.00 (t, *J* = 7.2 Hz, 2H, H-6), 1.78 (m, 4H, H-8), 1.71 (quint, *J* = 8.0 Hz, 2H, H-9), 1.47 (dt, *J* = 14.5, 7.3 Hz, 2H, H-12), 0.79 (t, *J* = 7.4 Hz, 3H, H-13); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 178.51 (C-11), 169.23 (C-1), 143.78 (C-2), 133.49 (C-3), 129.22 (C-4), 119.08 (C-5), 52.66 (C-9), 51.92 (C-6), 46.45 (C-12), 22.85 (C-8), 21.70 (C-10), 21.43 (C-13), 11.61 (C-14). **IR** (KBr cm^{-1}): 3292.16 (N-H), 2941.75 (C-H), 1696.24 (C=O), 1597.33 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{17}H_{26}N_4O_3S_2$: 398.1446; found: 398.1464

5.2.6.3 Synthesis of 4-(2-piperidinoacetamido)-*N*-(phenylcarbamothioyl)-benzenesulfonamide (18m).

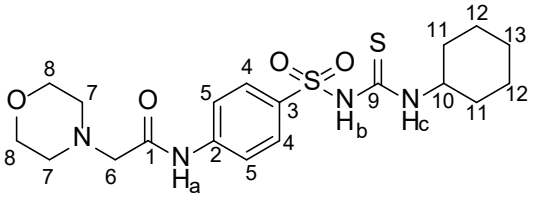


18m

A mixture of compound **19d** (3.36 mmol, 1.00 g) and potassium carbonate (3.36 mmol, 0.46 g) in acetonitrile (15 ml) was reacted with phenyl isothiocyanate (3.36 mmol, 0.5 ml). The product was obtained as a yellow powder (0.72 g, 49.54%). Melting point = 140.9–143.8 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.55 (s, 1H, H-a), 9.94 (s, 1H, H-b), 8.97 (s, 1H, H-c), 7.91 (d, *J* = 7.4 Hz, 2H, H-4), 7.72 (d, *J* = 7.5 Hz, 2H, H-5), 7.37 (t, *J* = 7.5 Hz, 2H, H-13), 7.28 (dd, *J* = 7.5, 1.5 Hz, 2H, H-12), 7.18 – 7.14 (m, 1H), 3.23 (s, 2H, H-6), 2.57 (ddd, *J* = 16.0, 6.9, 3.8 Hz, 4H), 1.68 – 1.49 (m, 6H, H-8 & H-9); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 178.36 (C-10), 167.76 (C-1), 144.27 (C-2), 139.18 (C-11), 136.86 (C-3), 129.18 (C-4), 128.96 (C-13), 124.47 (C-14), 121.54 (C-12), 119.07 (C-5), 60.23 (C-6), 54.34 (C-7), 24.60 (C-8), 23.42 (C-9). **IR** (KBr cm^{-1}): 3327.96 (N-H), 2947.65 (C-H), 1693.89 (C=O), 1598.34 (C=C). **HRMS** (ESI-TOF): m/z [M^{+}] calcd for $C_{20}H_{24}N_4O_3S_2$: 432.1290; found: 432.1328

5.2.6.4 Synthesis of 4-(2-morpholinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (18n).

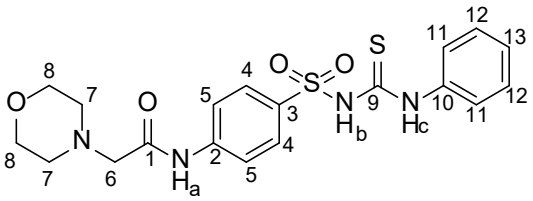


18n

A mixture of compound **19e** (3.34 mmol, 1.00 g) and potassium carbonate (3.34 mmol, 0.46 g) in acetonitrile (15 ml) was reacted with cyclohexyl isothiocyanate (3.34 mmol, 0.5 ml). The product was obtained as a white powder (1.26 g, 85.62%). Melting point = 210.1–213.4 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 11.53 (s, 1H, H-a), 8.75 (d, *J* = 7.8 Hz, 1H, H-c), 7.88 (d, *J* = 9.0 Hz, 2H, H-4), 7.85 (d, *J* = 9.1 Hz, 2H, H-5), 3.80 (m, 2H, H-6), 3.54–3.47 (m, 4H, H-8), 3.46–3.36 (m, 4H, H-7), 3.12 (m, 1H, H-10), 1.75 (m, 2H, H-11a), 1.61 (m, 2H, H-11b), 1.49 (d, *J* = 8.5 Hz, 2H, H-13), 1.22 (dd, *J* = 17.8, 8.9 Hz, 4H, H-12); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 177.25 (C-9), 169.06 (C-1), 143.73 (C-2), 133.50 (C-3), 129.32 (C-4), 119.07 (C-5), 63.65 (C-8), 53.00 (C-10), 52.04 (C-6), 51.66 (C-7), 31.29 (C-11), 25.37 (C-13), 24.45 (C-12). **IR** (KBr cm^{-1}): 3298.76 (N-H), 2947.95 (C-H), 1695.87 (C=O), 1597.78 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{19}H_{28}N_4O_4S_2$: 440.1552; found: 440.1760

5.2.6.5 Synthesis of 4-(2-morpholinoacetamido)-*N*-(phenylcarbamothioyl)-benzenesulfonamide (18o).



18o

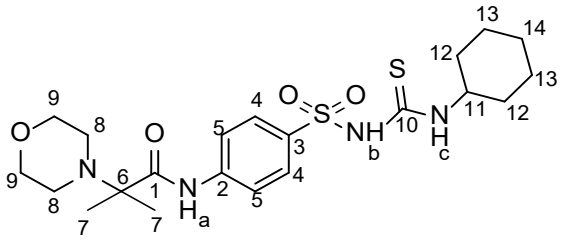
A mixture of compound **19e** (3.34 mmol, 1.00 g) and potassium carbonate (3.34 mmol, 0.46 g) in acetonitrile (15 ml) was reacted with phenyl isothiocyanate (3.34 mmol, 0.5 ml). The product was obtained as a yellow-brown powder (0.75 g, 51.68%). Melting point = 228.2–231.7 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 9.90 (s, 1H, H-a), 8.94 (s, 1H, H-c), 7.71 – 7.66 (m, 4H, H-4 & H-5), 7.63 (d, *J* = 8.7 Hz, 2H, H-11), 7.16 (t, *J* = 7.8 Hz, 2H, H-12), 6.86 (t, *J* = 7.3 Hz, 1H, H-13), 3.91 – 3.84 (m, 4H, H-8), 3.36 (s, 2H, H-6), 2.78 – 2.72 (m, 4H, H-7); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 183.68 (C-9), 169.13 (C-1), 142.50 (C-2), 141.38 (C-10), 140.67 (C-3), 128.60 (C-4), 128.37 (C-12), 121.50 (C-13), 120.39 (C-11), 118.31 (C-5), 67.01 (C-8), 63.08 (C-6), 54.12 (C-7). **IR** (KBr cm^{-1}): 3289.47 (N-H), 2941.45 (C-H), 1690.55 (C=O), 1594.32 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{19}H_{22}N_4O_4S_2$: 434.1180; found: 434.1217

5.2.7 General synthetic method for 2-methylpropanoylamide containing target sulfonylthioureas (18p-s).

A solution of compound **19i-l** (1.0 mmol) in acetonitrile was treated with anhydrous potassium carbonate (2.0 mmol). Isothiocyanates (1.0 mmol) were added neat to this reaction mixture before it was refluxed for 24 hours. After this reaction time a precipitate was formed and collected via filtration to obtain products which were purified by recrystallization from acetone.

5.2.7.1 Synthesis of 4-(2-morpholino,2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl) benzenesulfonamide (18p).

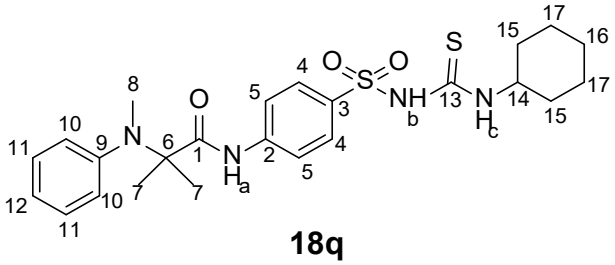


18p

Compound **19i** (3.23 mmol, 1.20 g) was reacted with anhydrous potassium carbonate (6.47 mmol, 0.20 g) and cyclohexyl isothiocynate (3.23 mmol, 0.9 ml) in 50 ml acetonitrile under reflux to give compound **18p** (0.91 g, 76%) as a yellowish solid. Melting point = 208.3–210.1 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.28 (s, 1H, H-b), 10.06 (s, 1H, H-a), 8.27 (d, *J* = 7.9 Hz, H-c), 7.93 (d, *J* = 8.8 Hz, 2H, H-4), 7.84 (d, *J* = 8.8 Hz, 2H, H-5), 3.70 (t, *J* = 8.7 4H, H-9), 2.51 (t, *J* = 6.7 Hz, 4H, H-8), 2.46-2,43 (m, 1H, H-11), 1.78 (d, *J* = 8.7 Hz, 4H, H-12), 1.62-1.58 (m, 2H, H-14), 1.51 (d, *J* = 8.7 Hz, 4H, H-13), 1.21 (s, 6H, H-7); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C** 177.24 (C-10), 175.25 (C-1), 143.74 (C-2), 133.38 (C-3), 128.94 (C-4), 119.72 (C-5), 66.84 (C-6), 64.51 (C-9), 53.29 (C-11), 47.31 (C-8), 31.20 (C-12), 25.33 (C-14), 24.53 (C-13), 20.20 (C-7); **IR** (KBr cm^{-1}): 3323.36 (N-H), 2986.45 (ArC-H), 1665.29 (C=O), 1590.71 (C=C). **HRMS** (ESI-TOF): m/z [M^{+}] calcd for $C_{21}H_{32}N_4O_4S_2$: 468.1865; found: 468.2048

5.2.7.2 Synthesis of 4-(2-(N-methylanilino),2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl) benzenesulfonamide (18q).

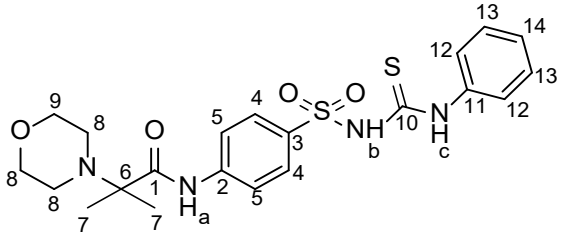


18q

Compound **19j** (1.46 mmol, 0.50 g) was reacted with anhydrous potassium carbonate (2.92 mmol, 0.20 g) and cyclohexyl isothiocynate (1.46 mmol, 0.9 ml) in 30 ml acetonitrile under reflux to give compound **18q** (0.30 g, 60%) as a reddish crystals. Melting point = 198.6–201.4 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.1 (s, 1H, H-b), 9.86 (s, 1H, H-a), 8.96 (s, 1H. H-c), 7.93 (d, *J* = 8.8 Hz, 2H, H-4), 7.84 (d, *J* = 8.8 Hz, 2H, H-5), 7.67 (d, *J* = 7.5 Hz, 2H, H-11), 7.47 – 7.24 (m, 2H, H-10), 7.16 (d, *J* = 7,6Hz, 1H, H-12), 3.40 (s, 3H, H-8), 2.84 (d, 2H, H-14), 2.51-2.34 (m, 4H, H-15), 2.09-2,05 (m, 4H, H-17), 1.34 (d, 2H, H-16) , 1.12 (s, 6H, H-7); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 182.21 (C-13), 175.71 (C-1), 140.53 (C-2), 129.15 (C-3), 129.15 (C-4), 121.40 (C-11), 121.39 (C-12), 120.40 (C-10), 118.94 (C-5), 79.97 (C-6), 64.02 (C-14), 36.02 (C-15), 31.17 (C-8), 29.56 (C-16), 28.31 (C-17), 23.33 (C-7); **IR** (KBr cm^{-1}): 3320.44 (N-H), 2925.17 (ArC-H), 1636.01 (C=O), 1589.89 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{24}H_{32}N_4O_3S_2$: 488.1916; found: 488.1930

5.2.7.3 Synthesis of 4-(2-morpholino,2,2-dimethacetamido)-*N*-phenylcarbamothioyl) benzenesulfonamide (18r).

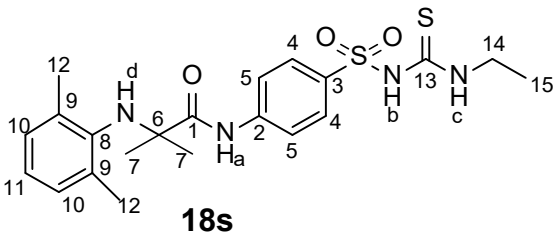


18r

Compound **19i** (3.74 mmol, 1.40 g) was reacted with anhydrous potassium carbonate (7.48 mmol, 0,52 g) and phenyl isothiocynate (3.74 mmol, 1.0 ml) in 40 ml acetonitrile under reflux to give compound **18r** (0.93 g, 66%) as a yellowish crystals. Melting point = 234.7–237.2 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.20 (s, 1H, H-b), 9.11 (s, 1H, H-a), 8.96 (s, 1H, H-c), 7.94 (d, *J* = 8.8 Hz, 2H, H-4), 7.86-7.67 (m, 1H, H-14), 7.55 (d, *J* = 8.0 Hz, 2H, H-12), 7.14 (d, 8.9 Hz, 2H, H-5), 6.96 (t, *J* = 7.3 Hz, 2H, H-13), 3.47-3.38 (m, 4H, H-9), 2.51-2.48 (m, 4H, H-8), 1.58 (s, 6H, H-7); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 179.92 (C-10), 165.01 (C-1), 140.30 (C-2), 139.98 (C-11), 138.79 (C-3), 129.98 (C-4), 129.23 (C-13), 126.93 (C-14), 124.76 (C-12), 123.85 (C-5), 76.54 (C-6), 64.91 (C-9), 47.75 (C-8), 20.03 (C-7); **IR** (KBr cm^{-1}): 3330.92 (N-H), 2954.22 (ArC-H), 1667.60 (C=O), 1587.69 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{21}H_{26}N_4O_4S_2$: 462.1395; found: 462.1454

5.2.7.4 Synthesis of 4-(2-(2,6-dimethylanilino),2,2-dimethacetamido)-*N*-ethylcarbamothioyl) benzenesulfonamide (18s).



18s

Compound **19k** (2.31 mmol, 0.80 g) was reacted with anhydrous potassium carbonate (4.62 mmol, 0.32 g) and ethyl isothiocynate (2.31 mmol, 0.8 ml) in 30 ml acetonitrile under reflux to give compound **18s** (0,41 g, 51%) as a brownish crystals. Melting point = 215.8–218.6 ^{o}C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$ 10.24 (s, 1H, H-a), 7.69 (m, 4H, H-4 & H-5), 7.50 (t, *J* = 5.2 Hz, 1H, H-c), 7.38 (s, 1H, H-d), 6.99 (d, *J* = 7.5 Hz, 2H, H-10), 6.84 (t, *J* = 7.4 Hz, 1H, H-11), 2.19 (s, 6H, H-12), 1.31 (s, 6H, H-7), 1.07-1.04 (m, 2H, H-14), 0.99 (t, *J* = 7.2 Hz, 3H, H-15); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ$_C$** 176.93 (C-13), 143.45 (C-1), 141.31 (C-8), 140.30 (C-2), 132.97 (C-3), 128.97 (C-9), 128.12 (C-4), 128.08 (C-10), 120.43 (C-11), 118.18 (C-5), 59.74 (C-6), 31.16 (C-14), 27.09 (C-12),19.91 (C-7), 14.92 (C-15); **IR** (KBr cm^{-1}): 3327.95 (N-H), 2966.07 (ArC-H), 1667.66 (C=O), 1589.80 (C=C). **HRMS** (ESI-TOF): m/z [M$^+$] calcd for $C_{21}H_{28}N_4O_3S_2$: 448.1603; found: 448.1644

5.3. Antidiabetic assays protocol

5.3.1 Alpha-amylase inhibition assay

5.3.1.1 Principle

This assay was performed using the 3,5-dinitrosalicylic acid (DNSA) method. The α-amylase activity is measured using a colorimetric method with DNSA reagent. In this method, the substrate (starch) is converted into maltose by α-amylase, and the amount of maltose released is measured by the reduction of DNSA. Maltose reduces the pale-yellow alkaline DNSA to an orange-red colour. This intensity change in colour is proportional to the concentration of maltose present in the sample, and the absorbance is measured with a spectrophotometer at a wavelength of 540 nm. The presence of an α-amylase inhibitor such as acarbose decreases the liberation of maltose, hence leading to a decrease in the reduction of DNSA and absorbance detected.

5.3.1.2 Protocol

The α-amylase inhibition assay was performed using the DNSA method with slight modifications. In a test tube, 1 mL of α-amylase (1 U/ml) in phosphate buffer solution (0.02 M with 0.006 M NaCl at pH 6.9) was mixed with 1 ML of test compound at different concentrations (60, 120 and 240 µg/mL) and preincubated at 37 °C for 10 minutes. Thereafter, 1 mL of starch solution (1% w/v) was added to each test tube and incubated for 10 minutes. The reaction was terminated by adding 1 mL DNSA reagent (12 g of sodium potassium tartrate tetrahydrate in 8.0 mL of 2 M NaOH and 20 mL of 96 mM of DNSA solution) and boiled for 5 minutes in a water bath at 85 °C. The mixture was cooled to room temperature and was diluted with 5 mL distilled water, after which the absorbance was measured with a spectrophotometer at a wavelength of 540 nm. Acarbose was used as the standard drug at concentrations of 60, 120 and 240 µg/mL. At the same time, the absolute control with 100% enzyme activity was prepared following the same procedure replacing the sulfonylthiourea derivative compounds with buffer. The assay was performed in triplicates, and the α-amylase inhibitory activity was calculated as percentage inhibition using the equation below:

$$\text{Percentage inhibition (\%)} = \left(\frac{\text{absorbance of control - absorbance of sample}}{\text{absorbance of control}}\right) \text{x } 100$$

5.3.2 Alpha- glucosidase inhibition assay

5.3.2.1 Principle

Alpha-glucosidase acts on the substrate p-nitrophenyl-α-D-glucopyranoside (pNPG) to form p-nitrophenol and α-D-glucopyranoside. The absorbance of p-nitrophenol liberated is measured with a spectrophotometer at 405 nm. A potent inhibitor such as acarbose inhibits α-glucosidase activity on the substrate, resulting in a reduction in the absorbance, which is a measure of the p-nitrophenol formed.

5.3.2.2 Protocol

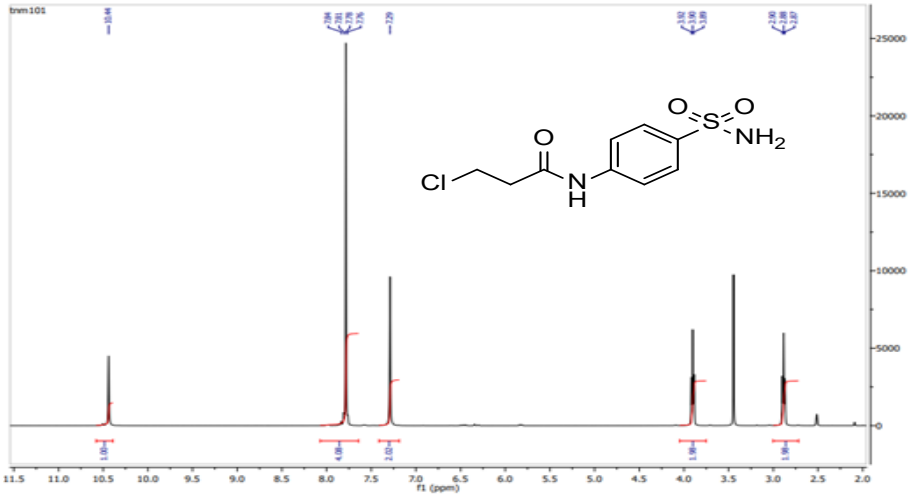
In a white 96-well plate, a reaction mixture containing 100 µL of phosphate buffer (0.1 M, pH = 6.8), 40 µL of α-glucosidase (0.1 U/ml), and 80 µL of test compounds at different concentrations (60, 120, and 240 µg/ml) were preincubated at 37°C for 10 min. The reaction was then initiated by the addition of 20 µL of *p*NPG (2mM), and the mixture was then incubated for 10 min at 37°C. The reaction was stopped by adding 100 µL of Na_2CO_3 (0.1 M), after which the absorbance of the yellow-coloured *p*-nitrophenol released from *p*NPG was measured with a spectrophotometer at a wavelength of 405 nm. Acarbose was used as the standard drug at concentrations of 60, 120 and 240 µg/mL, while the absolute control with 100% enzyme activity was prepared following the same procedure replacing the sulfonylthiourea derivative compounds with buffer. The assay was performed in triplicates and the α-glucosidase inhibitory activity was calculated as percentage inhibition using the equation below:

$$\text{Percentage inhibition } (\%) = \left(\frac{\text{absorbance of control - absorbance of sample}}{\text{absorbance of control}}\right) \text{x } 10$$

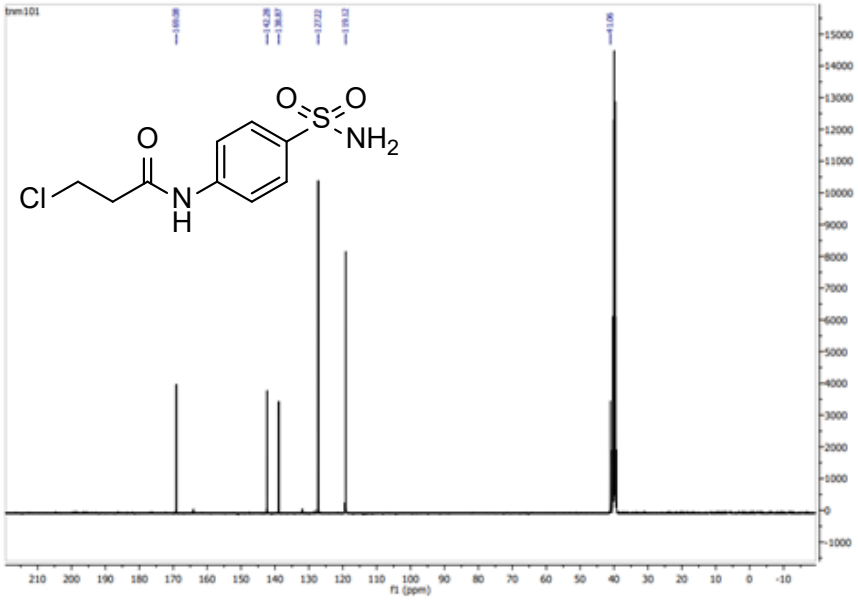
CHAPTER 6

6. Appendix

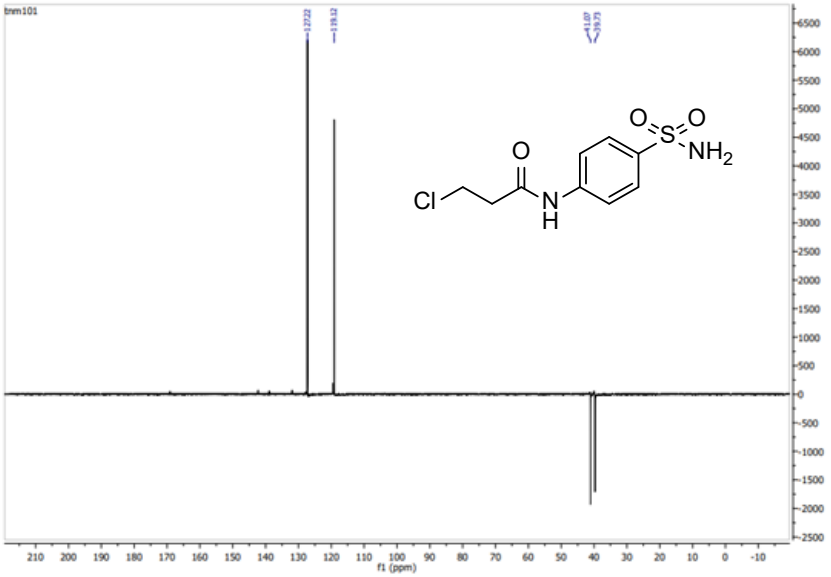
6.1 ^{1}H NMR spectrum of 4-(3-chloropropionylamido)benzenesulfonamide (22a).



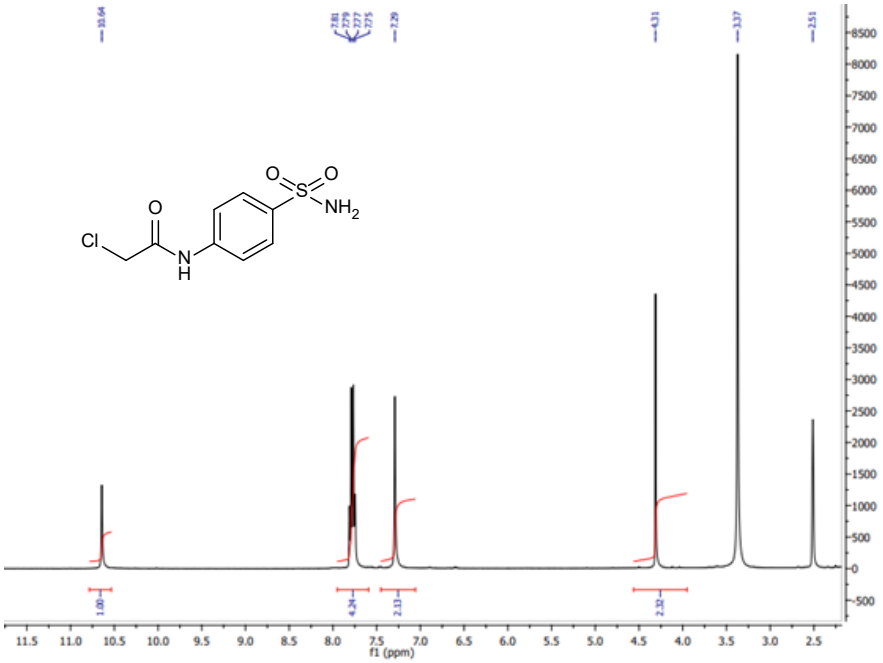
6.2 ^{13}C NMR spectrum of 4-(3-chloropropionylamido)benzenesulfonamide (22a).



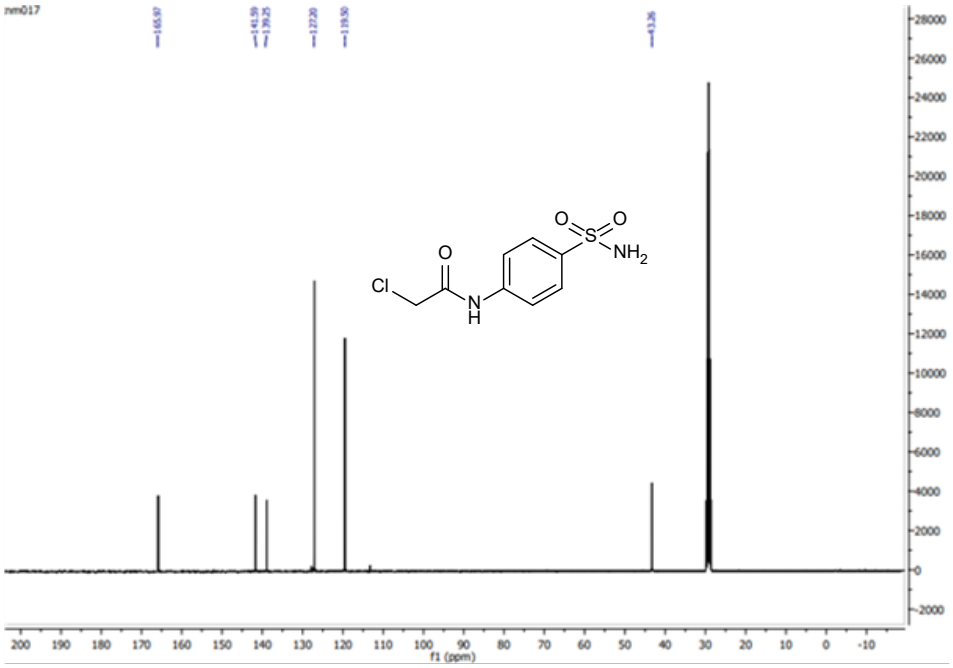
6.3 DEPT-135 NMR spectrum of 4-(3-chloropropionylamido)benzenesulfonamide (22a).



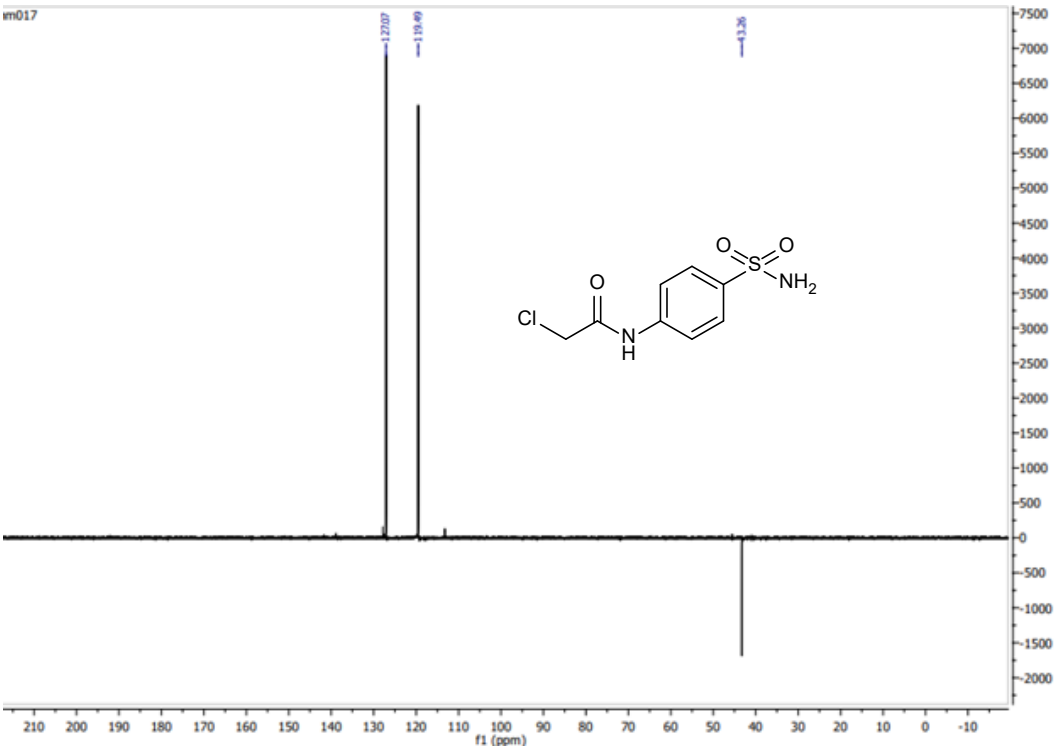
6.4 ^{1}H NMR spectrum of 4-(2-chloroacetamido)benzenesulfonamide (22b).



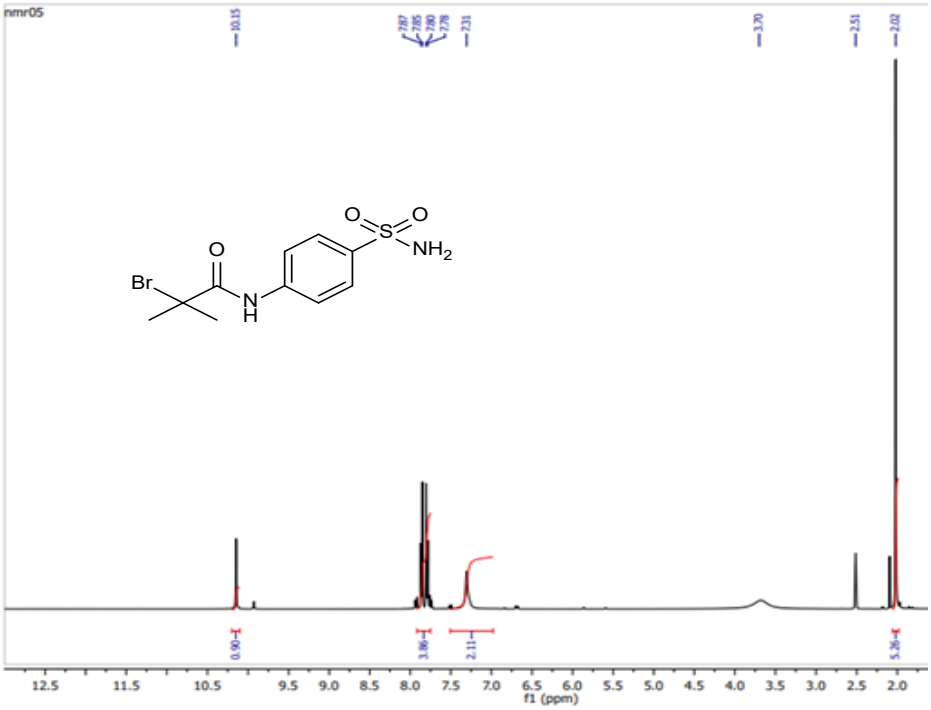
6.5 ^{13}C NMR spectrum of 4-(2-chloroacetamido)benzenesulfonamide (22b).



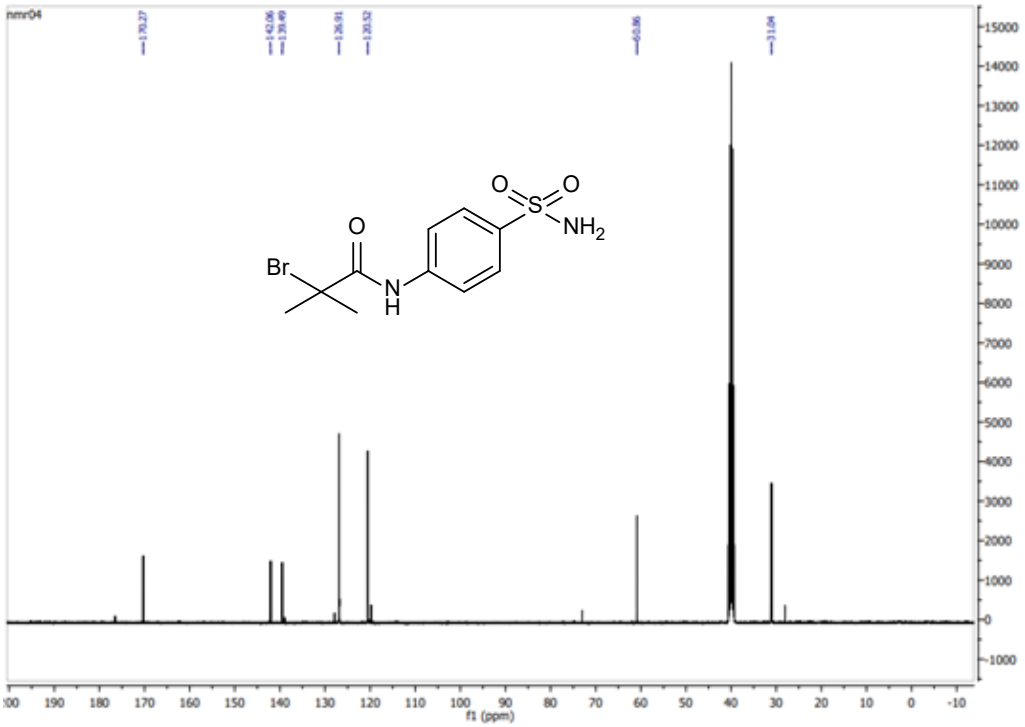
6.6 DEPT-135 NMR spectrum of 4-(2-chloroacetamido)benzenesulfonamide (22b).



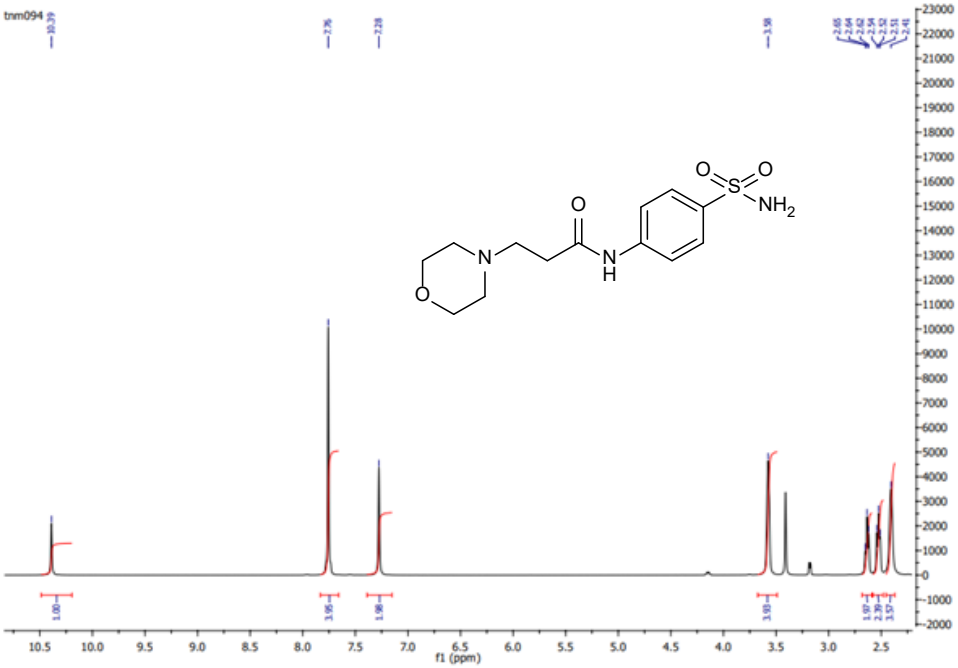
6.7 ^{1}H NMR spectrum of 4-(2-bromo,2,2-dimethacetamido)benzenesulfonamide (22c).



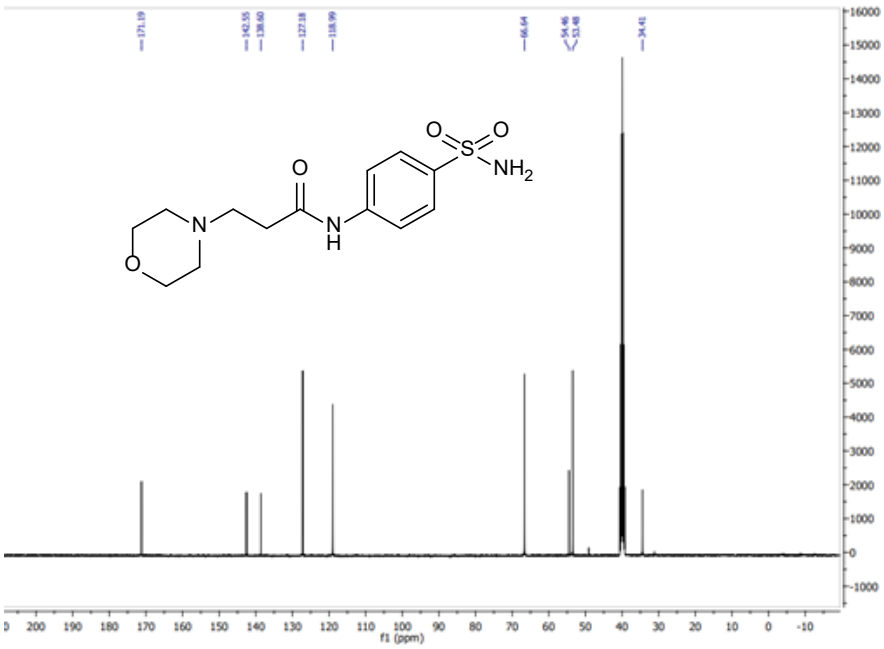
6.8 ^{13}C NMR spectrum of 4-(2-bromo,2,2-dimethacetamido)benzenesulfonamide (22c).



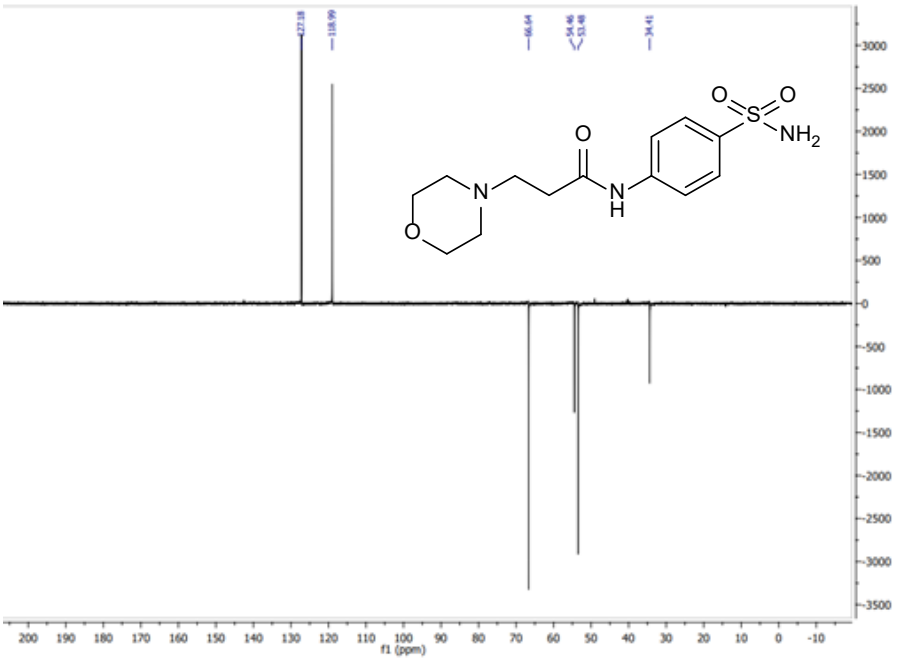
6.9 ^{1}H NMR spectrum of 4-(3-morpholinopropionylamido)benzenesulfonamide (19a)



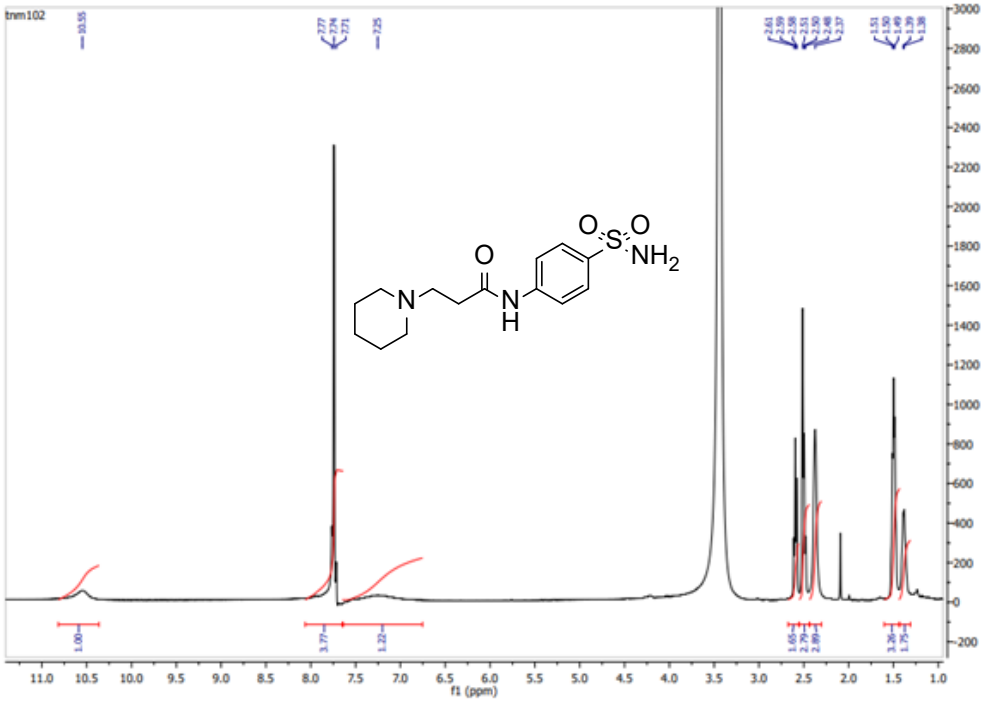
6.10 ^{13}C NMR spectrum of 4-(3-morpholinopropionylamido)benzenesulfonamide (19a)



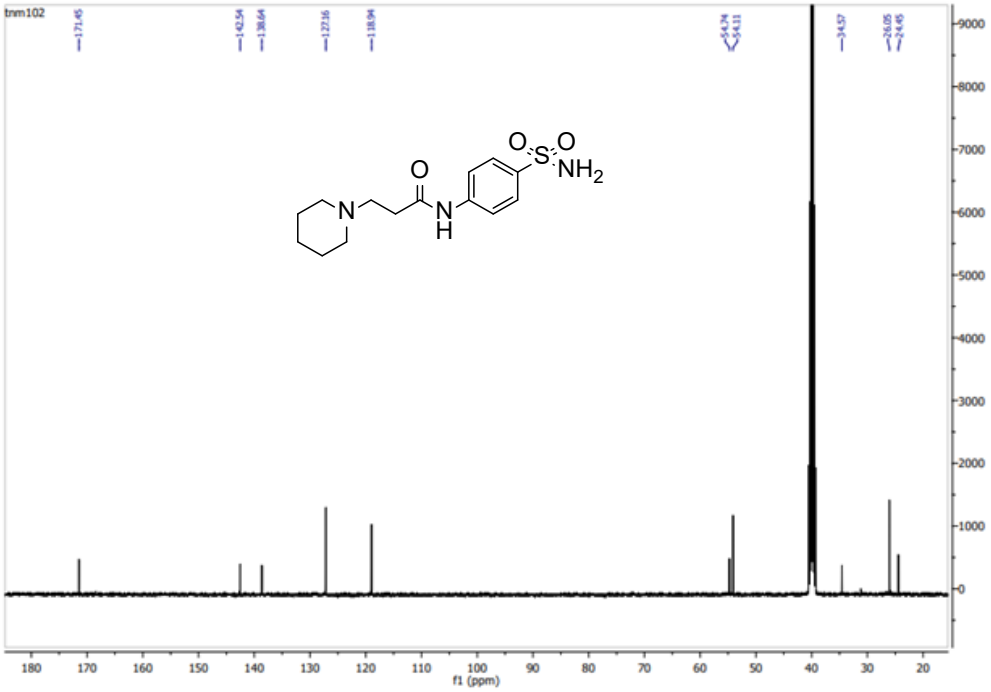
6.11 DEPT-135 NMR spectrum of4-(3-morpholinopropionylamido)benzenesulfonamide (19a)



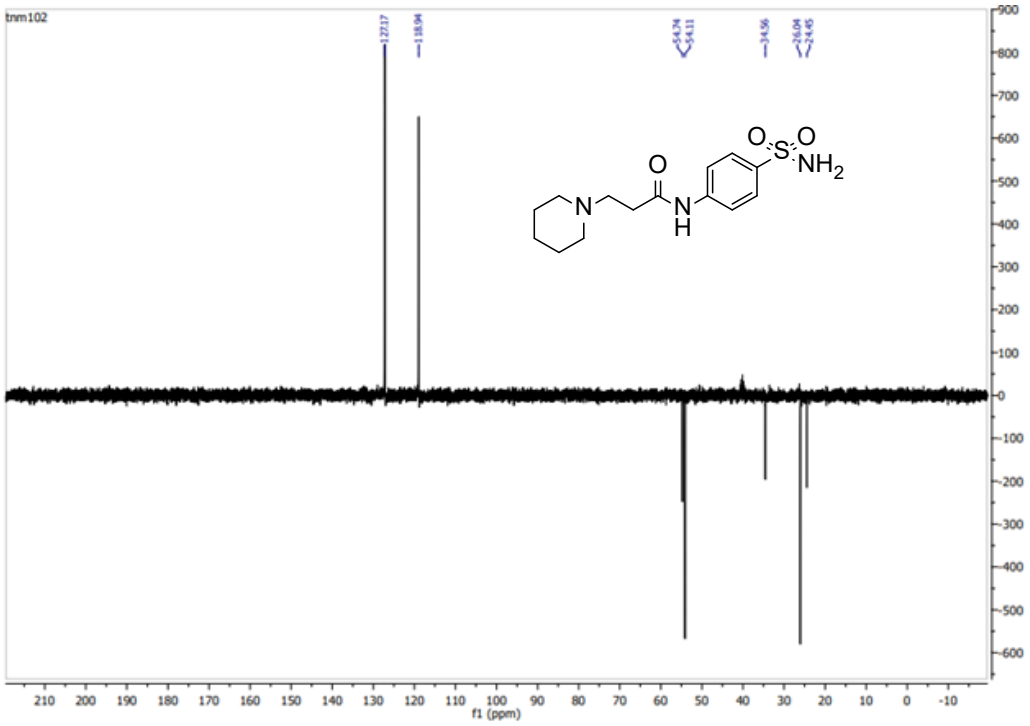
6.12 ^{1}H NMR spectrum of 4-(3-piperidinopropionylamido)benzenesulfonamide (19b).



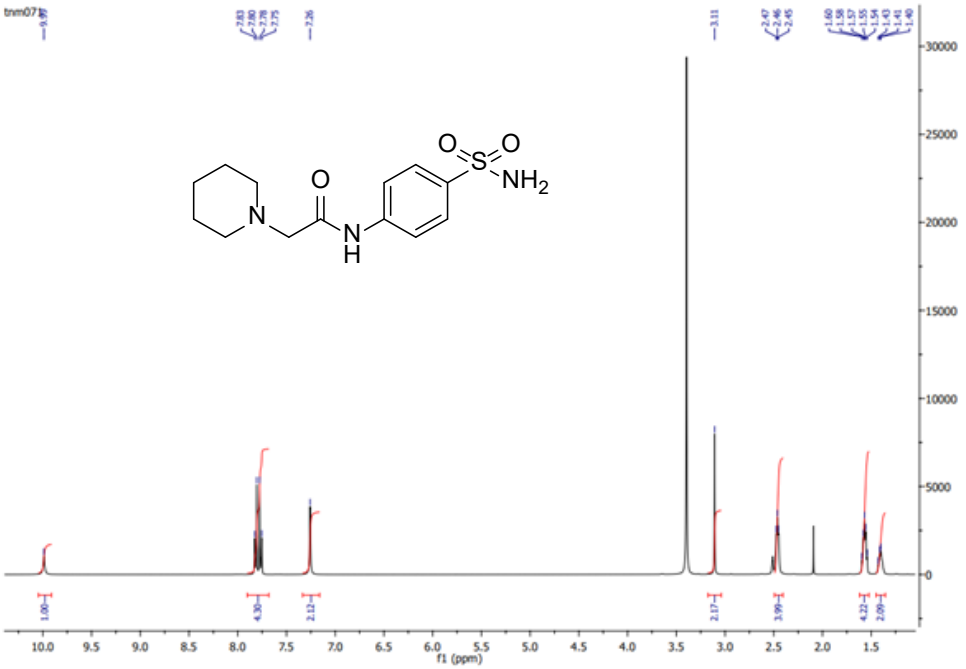
6.13 ^{13}C NMR spectrum of 4-(3-piperidinopropionylamido)benzenesulfonamide (19b).



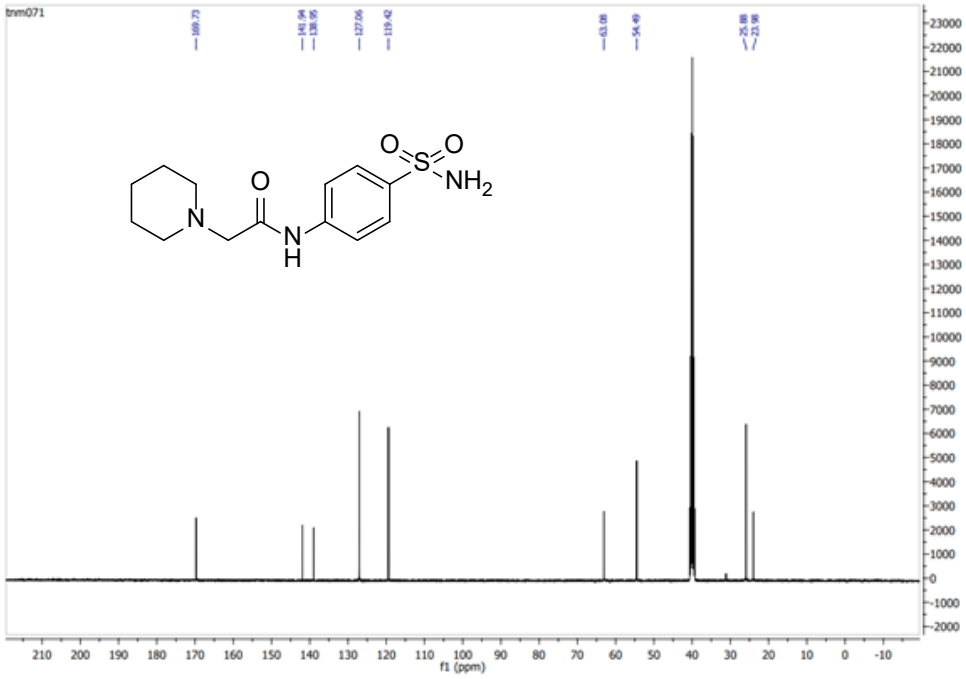
6.14 DEPT-135 NMR spectrum of4-(3-piperidinopropionylamido)benzenesulfonamide (19b).



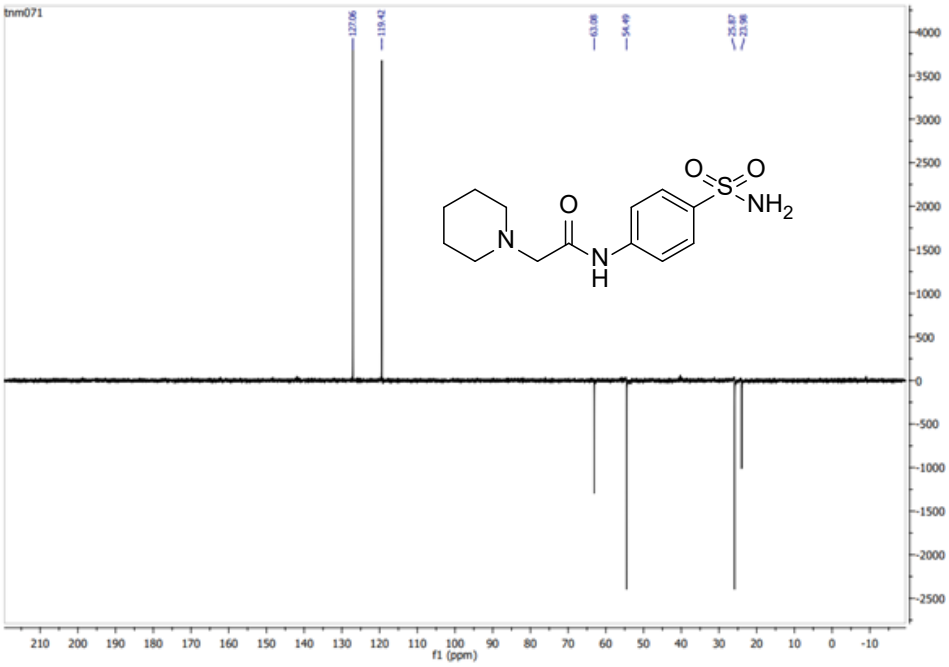
6.15 ^{1}H NMR spectrum of 4-(2-piperidinoacetamido)benzenesulfonamide (19e).



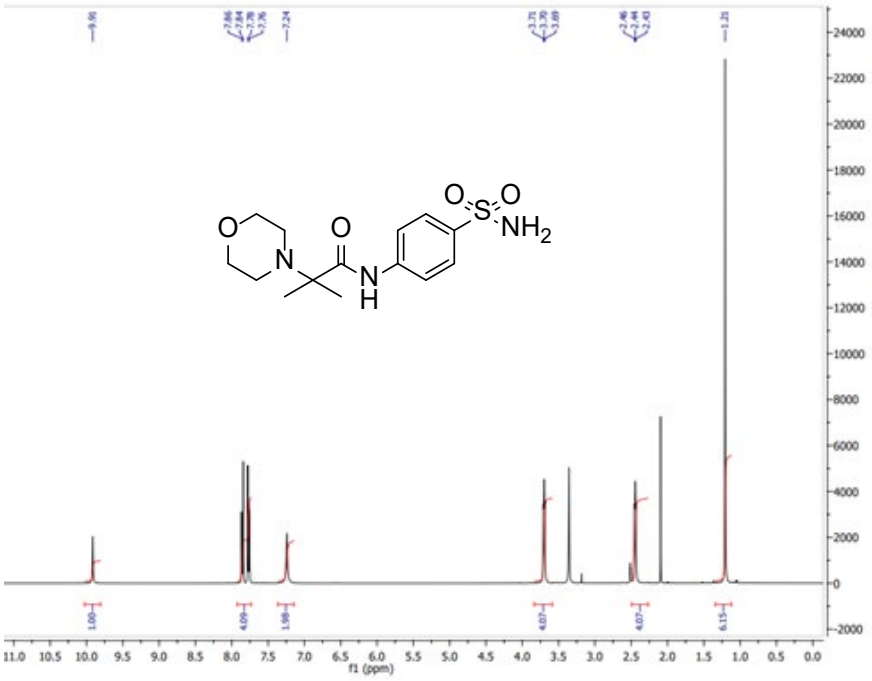
6.16 ^{13}C NMR spectrum of 4-(2-piperidinoacetamido)benzenesulfonamide (19e).



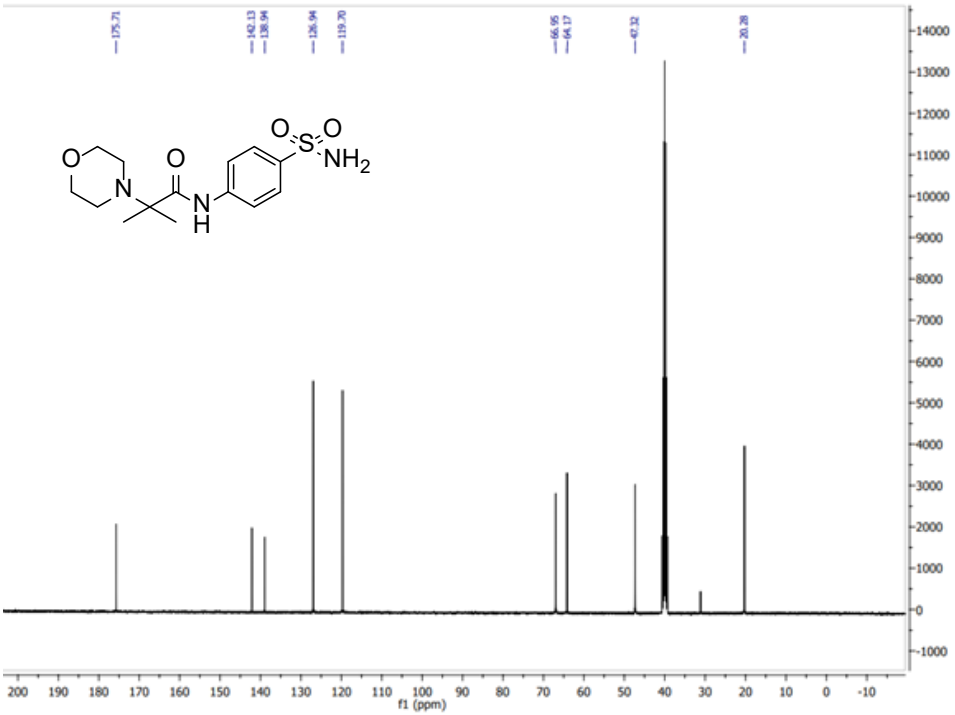
6.17 DEPT-135 NMR spectrum of4-(2-piperidinoacetamido)benzenesulfonamide (19e).



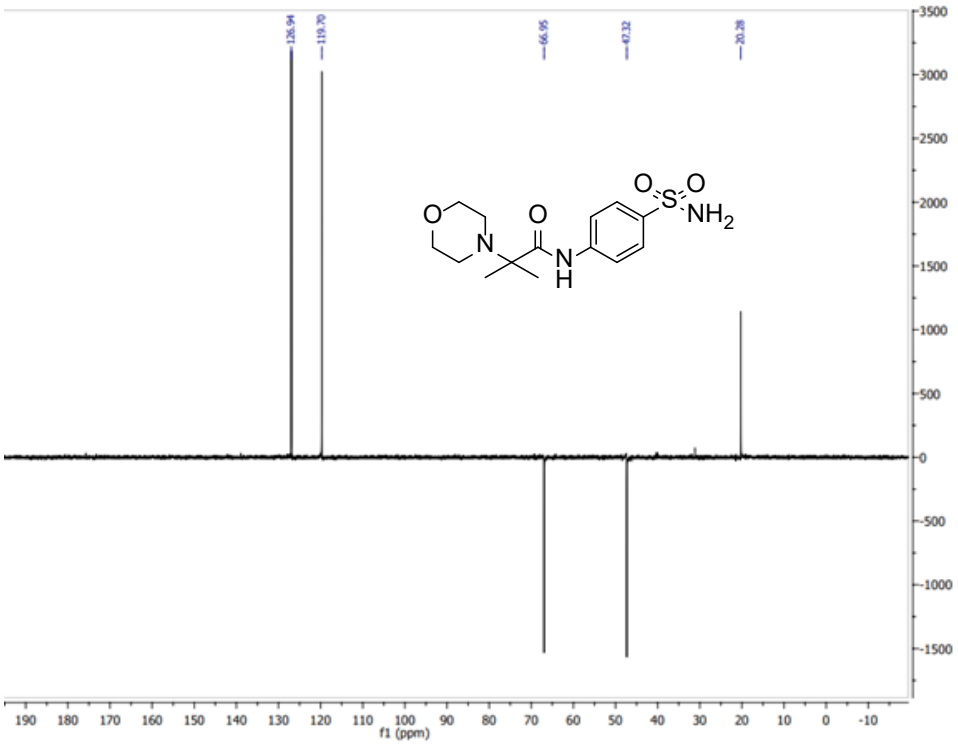
6.18 ^{1}H NMR spectrum of 4-(2-morpholino,2,2-dimethacetamido)benzenesulfonamide (19i).



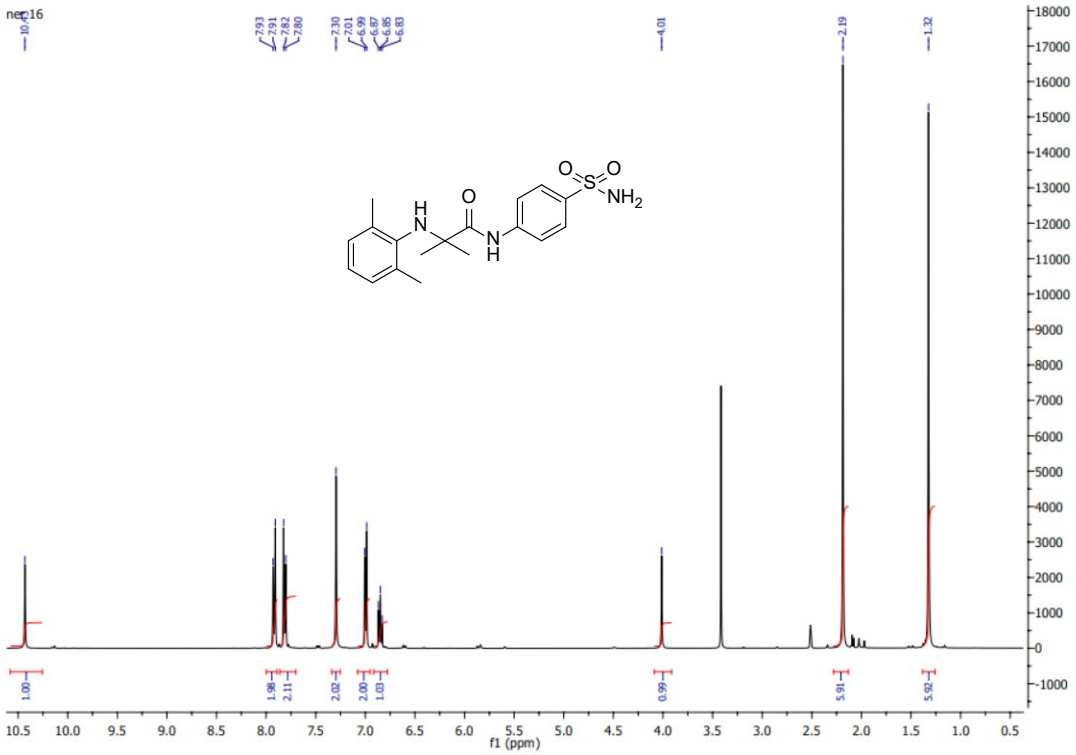
6.19 ^{13}C NMR spectrum of 4-(2-morpholino,2,2-dimethacetamido)benzenesulfonamide (19i).



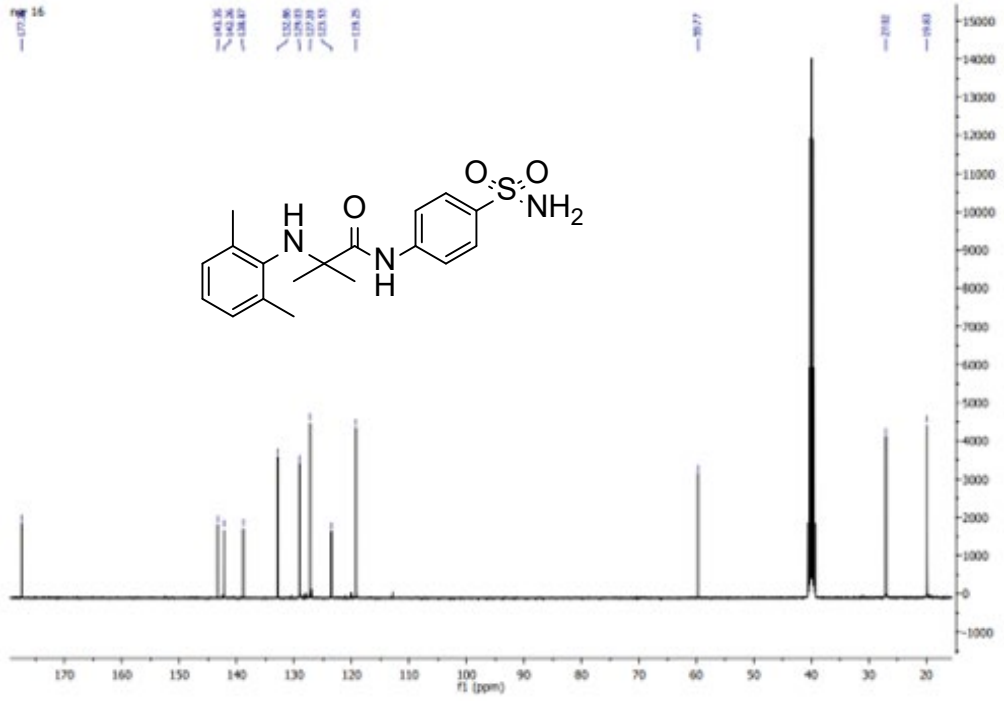
6.20 DEPT-135 spectrum of4-(2-morpholino,2,2-dimethacetamido)benzenesulfonamide (19i).



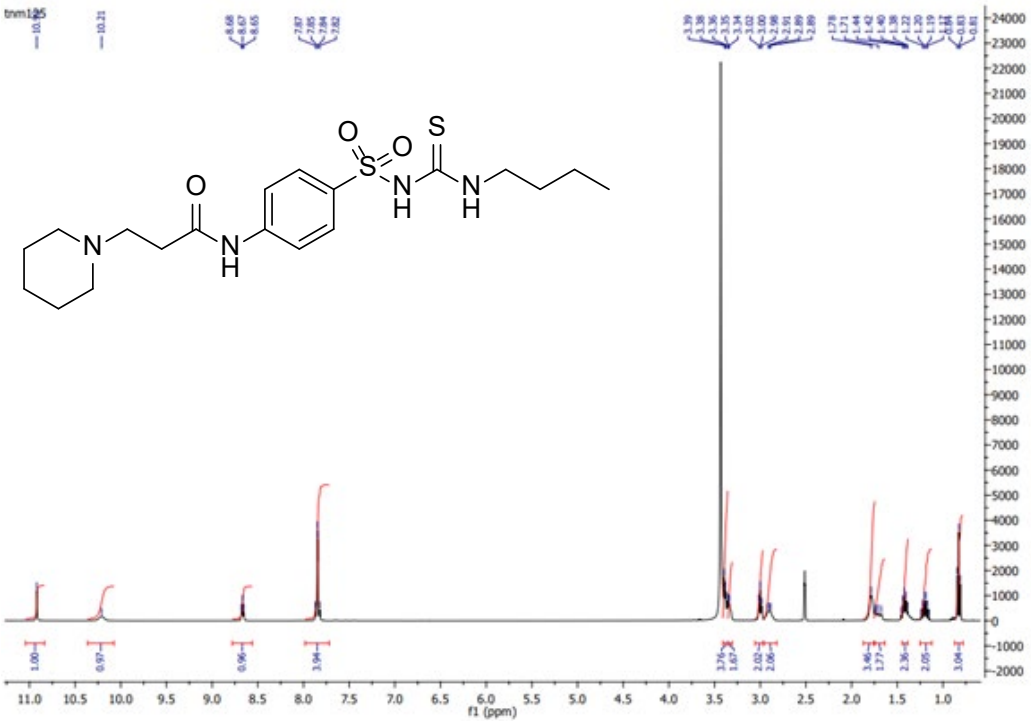
6.21 ^{1}H NMR spectrum of 4-(2-(2,6-dimethylanilino),2,2-dimethacetamido) benzenesulfonamide (19k).



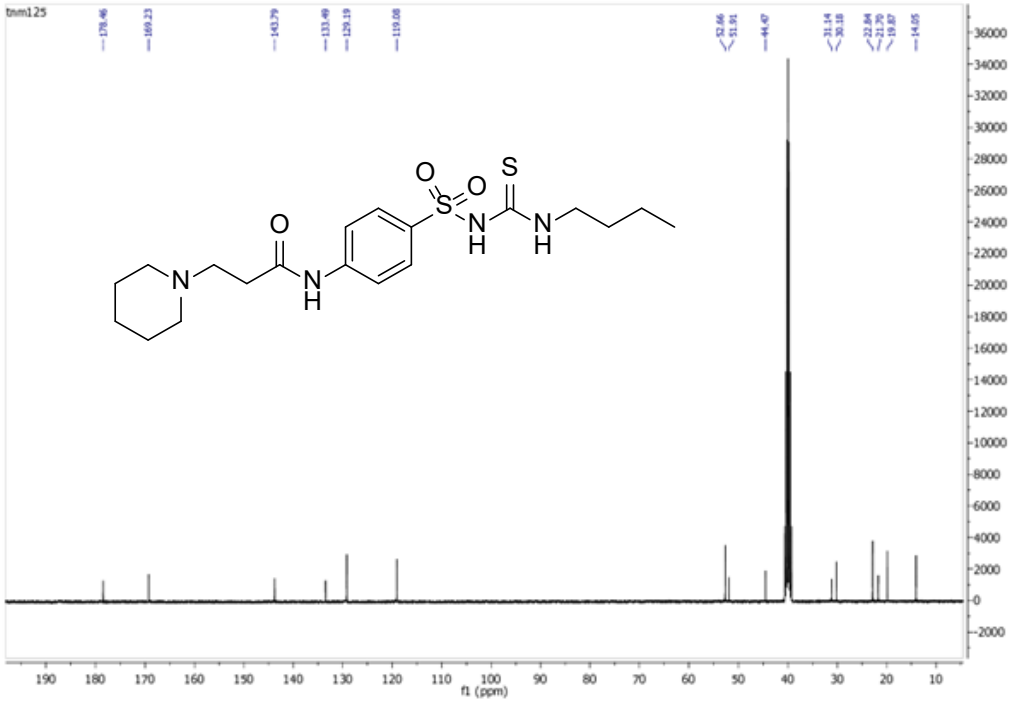
6.22 ^{13}C NMR spectrum of 4-(2-(2,6-dimethylanilino),2,2-dimethacetamido) benzenesulfonamide (19k).



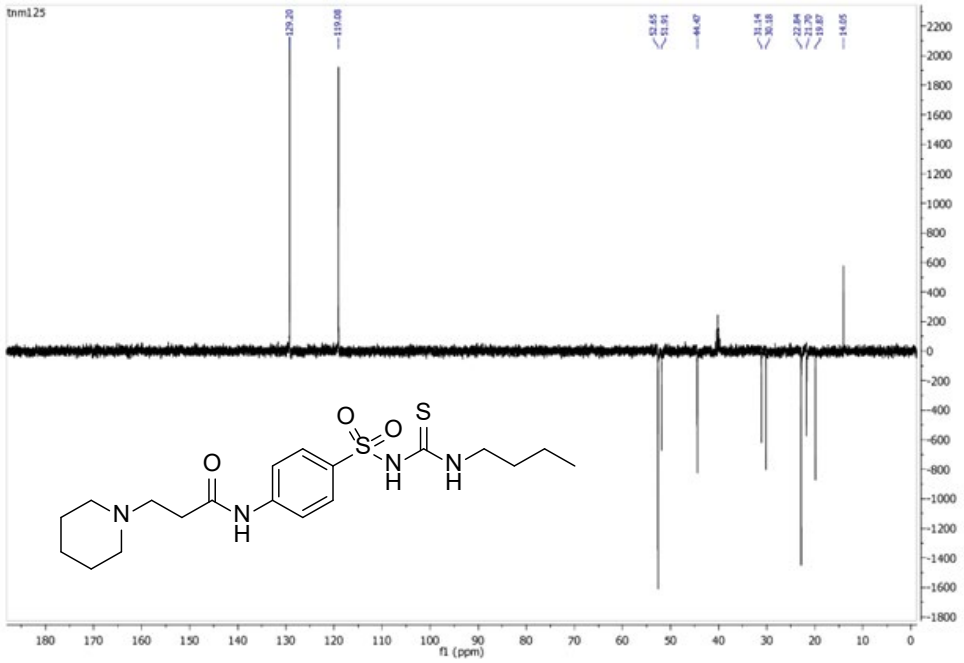
6.23 ^{1}H NMR spectrum of 4-(3-piperidinopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18a).



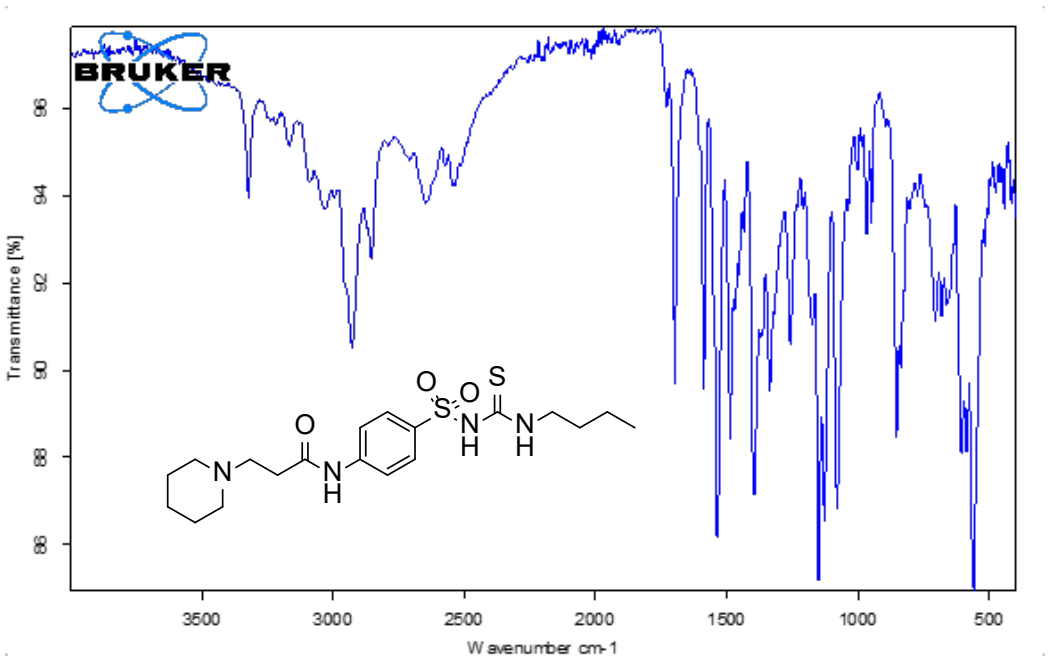
6.24 ^{13}C NMR spectrum of 4-(3-piperidinopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18a).



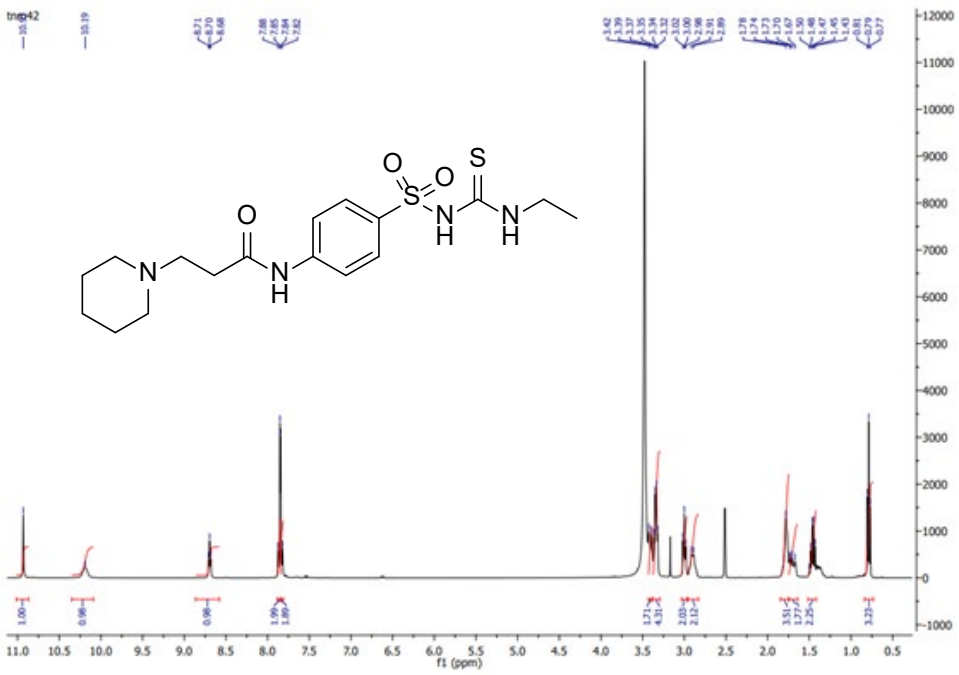
6.25 DEPT-135 NMR spectrum of4-(3-piperidinopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18a).



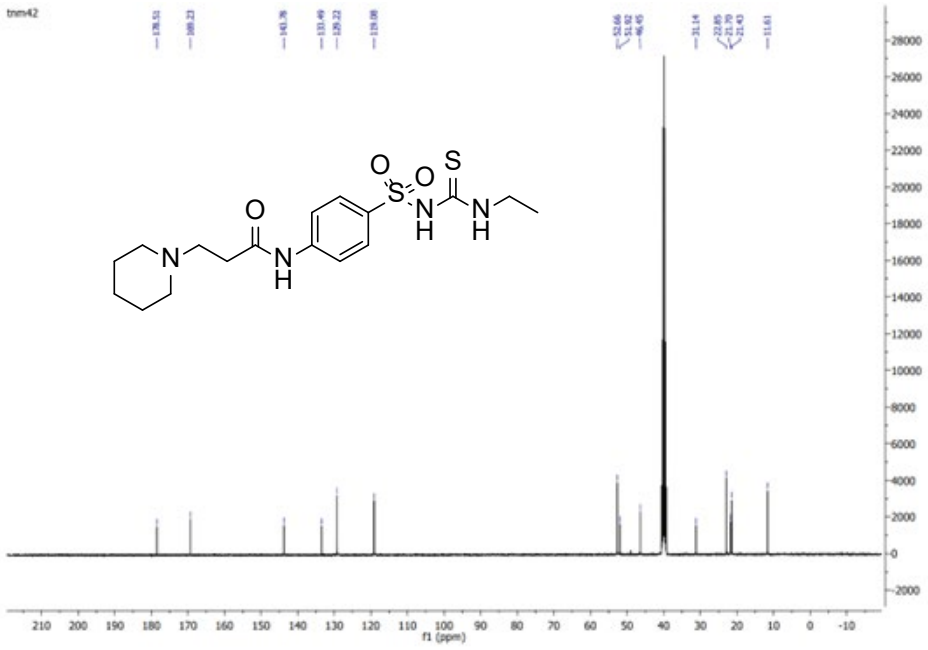
6.26 FTIR NMR spectrum of 4-(3-piperidinopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18a).



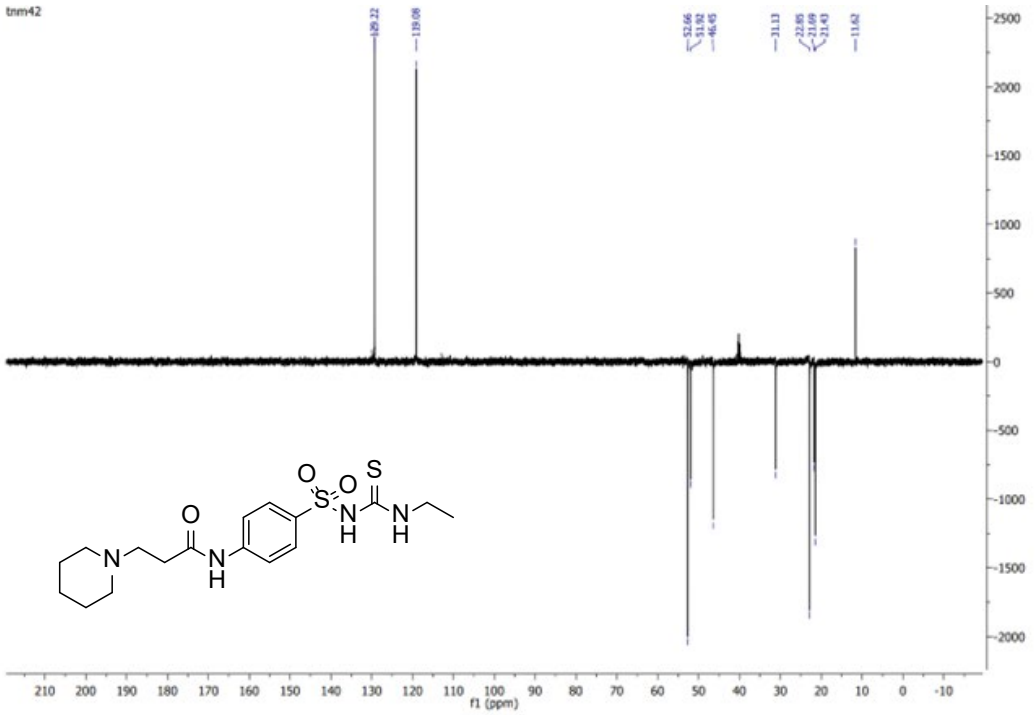
6.28 ^{1}H NMR spectrum of 4-(3-piperidinopropionylamido)-*N*-(ethylcarbamothioyl)benzenesulfonamide (18c).



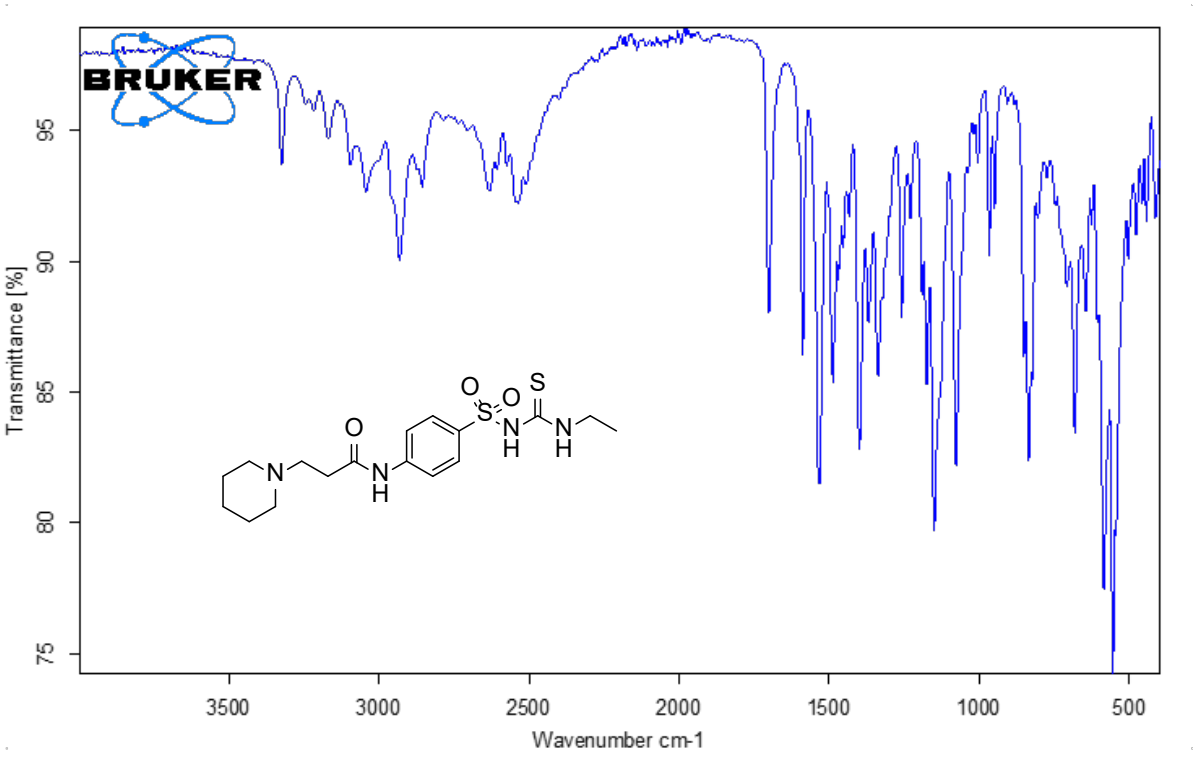
6.29 ^{13}C NMR spectrum of 4-(3-piperidinopropionylamido)-*N*-(ethylcarbamothioyl)benzenesulfonamide (18c).



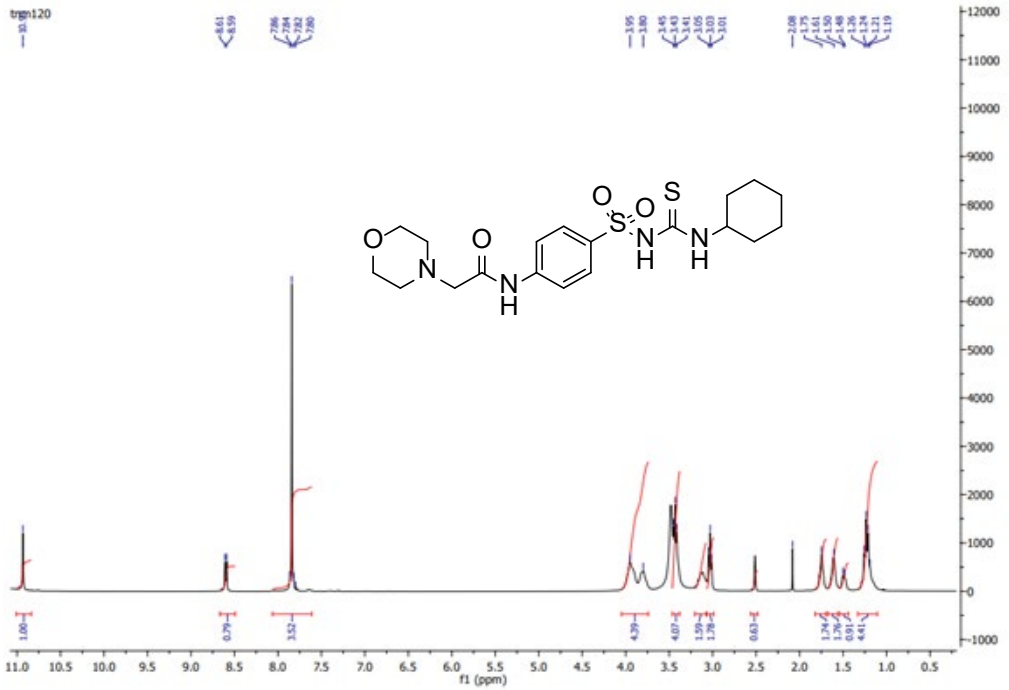
6.30 DEPT-135 spectrum of4-(3-piperidinopropionylamido)-*N*-(ethylcarbamothioyl)benzenesulfonamide (18c).



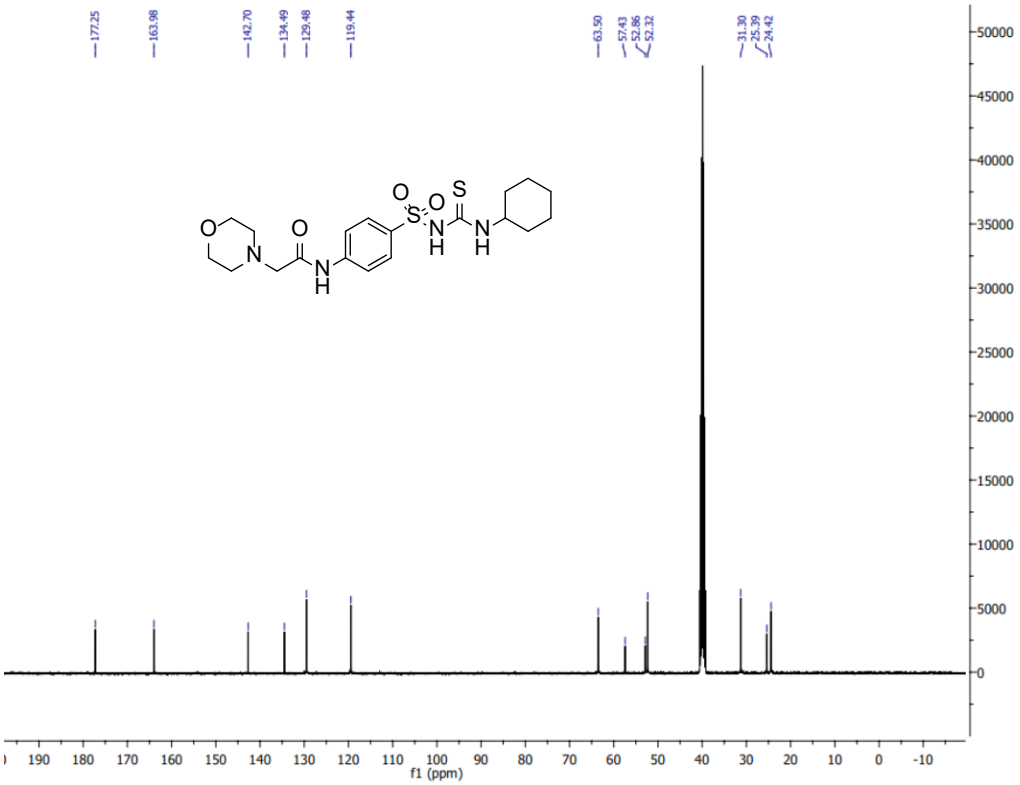
6.31 FTIR NMR spectrum of 4-(3-piperidinopropionylamido)-*N*-(ethylcarbamothioyl)benzenesulfonamide (18c).



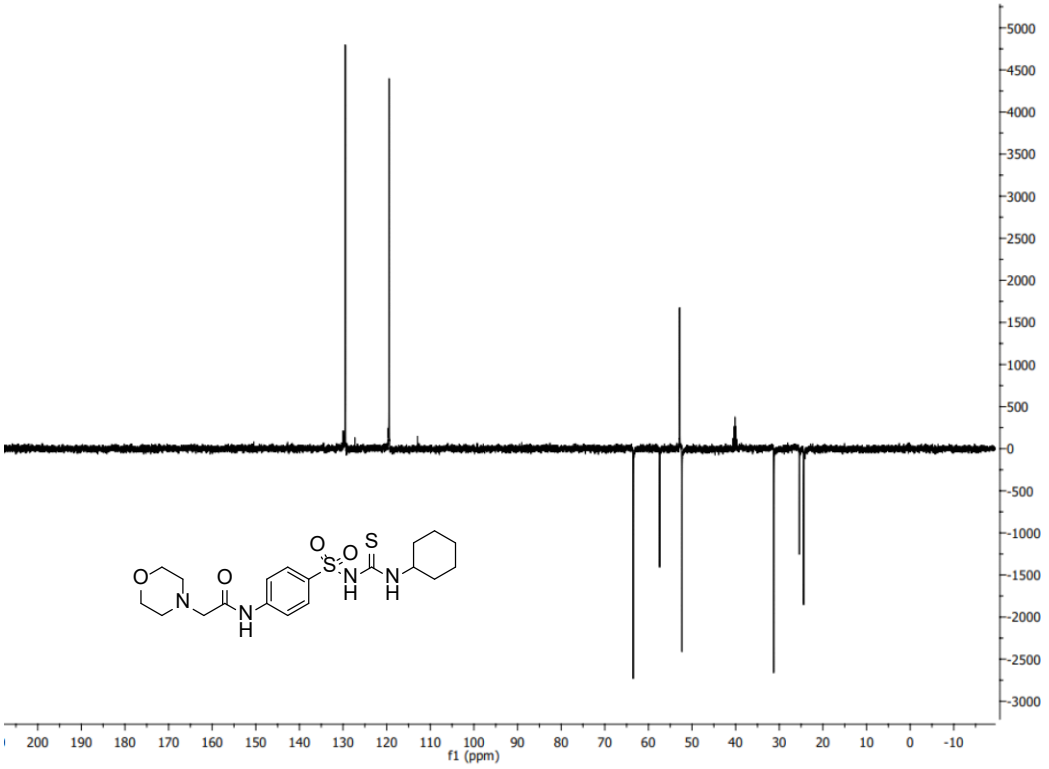
6.32 ^{1}H NMR spectrum of 4-(2-morpholinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (18f).



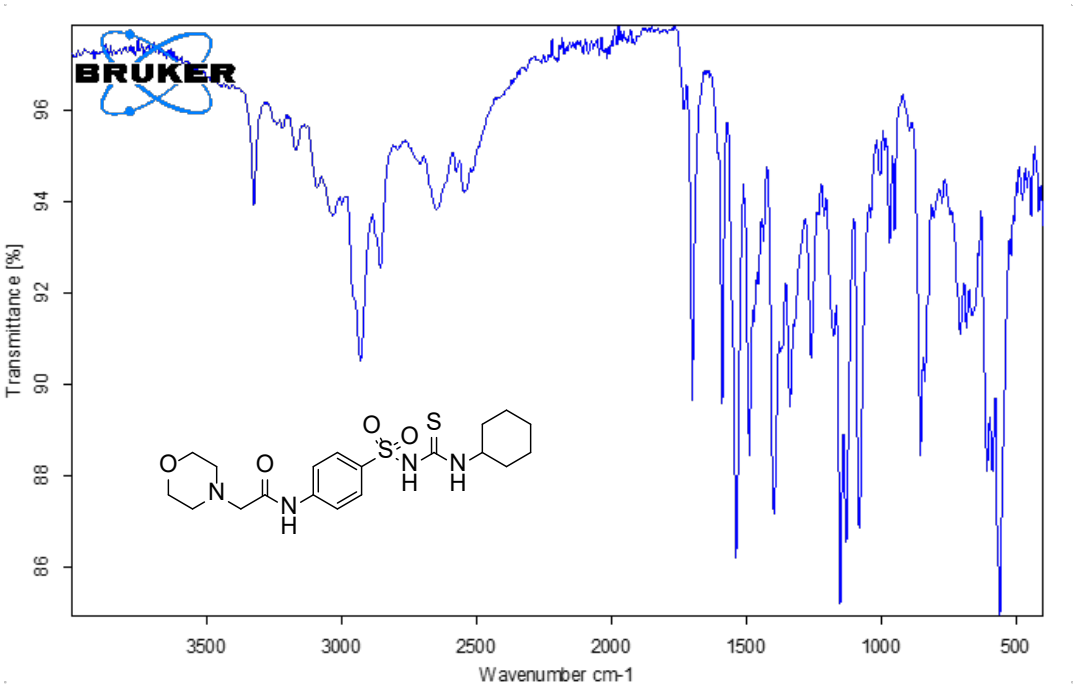
6.33 ^{13}C NMR spectrum of 4-(2-morpholinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (18f).



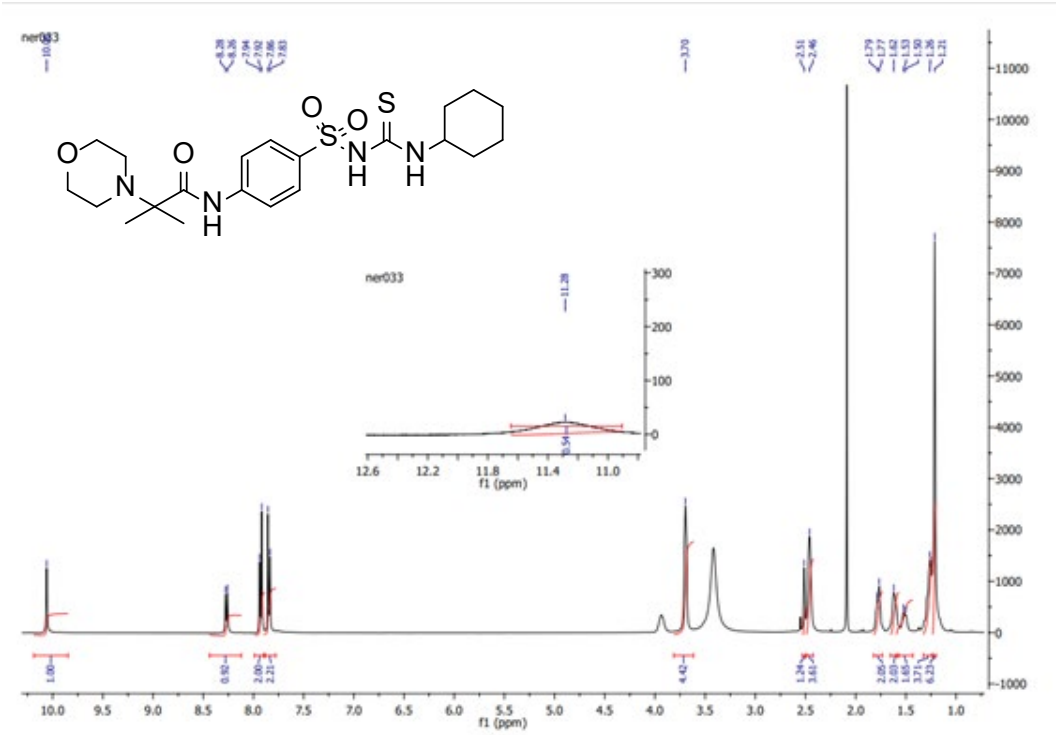
6.34 DEPT-135 spectrum of4-(2-morpholinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (18f).



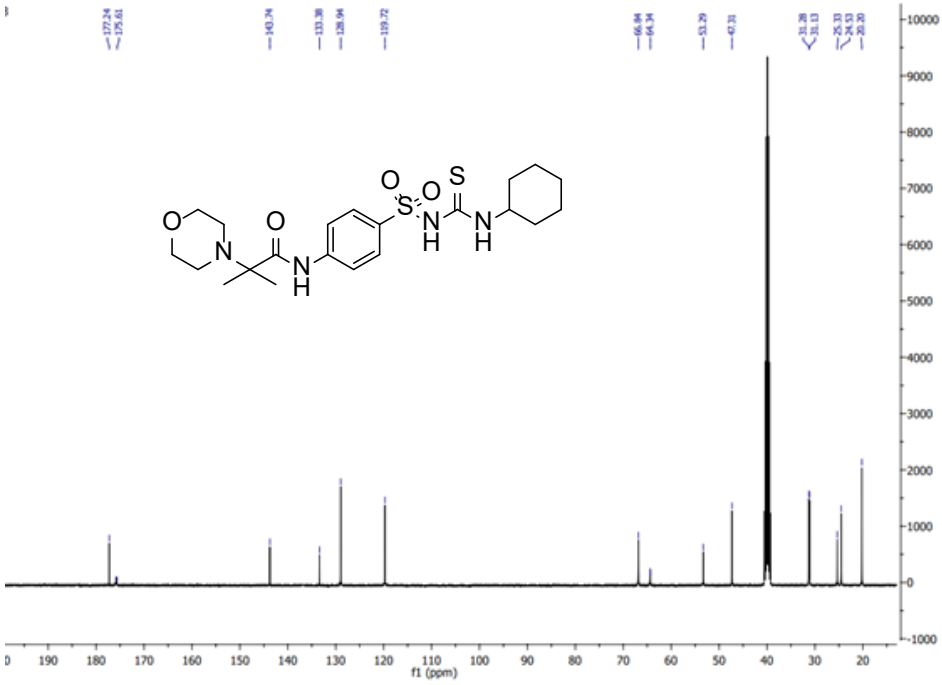
6.35 FTIR spectrum of 4-(2-morpholinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (18f).



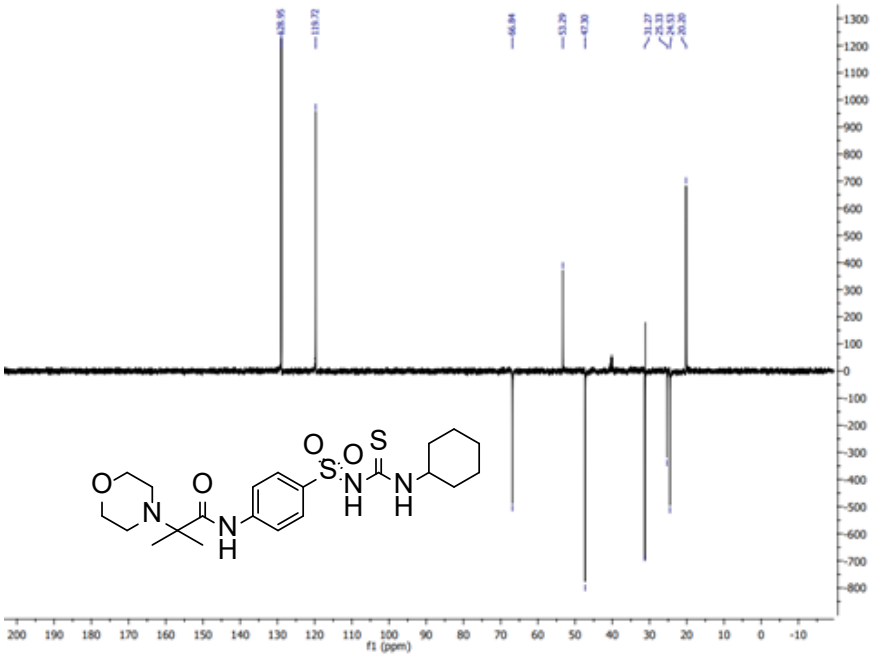
6.36 ^{1}H NMR spectrum of 4-(2-morpholino,2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl) benzenesulfonamide (18p).



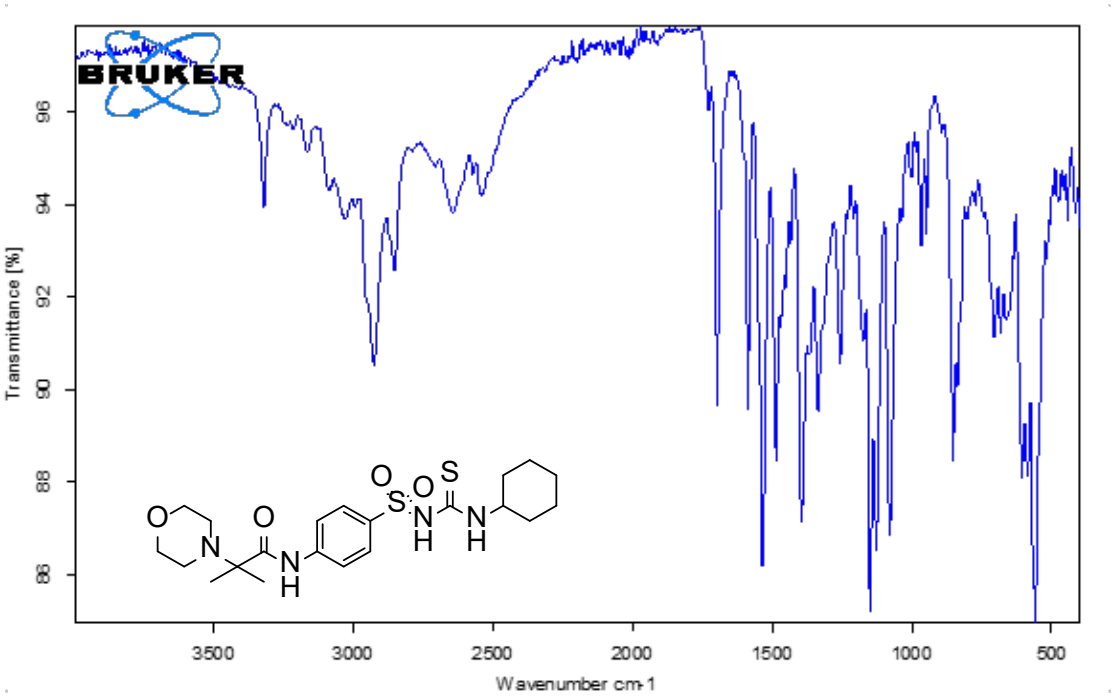
6.37 ^{13}C NMR spectrum of 4-(2-morpholino,2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl) benzenesulfonamide (18p).



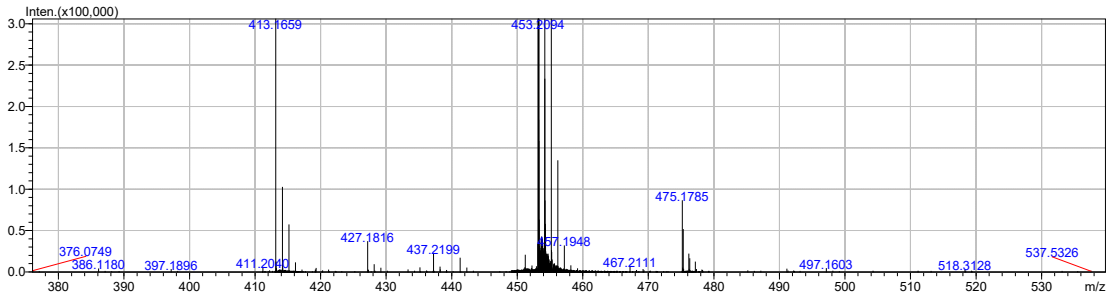
6.38 DEPT-135 spectrum of4-(2-morpholino,2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl) benzenesulfonamide (18p).



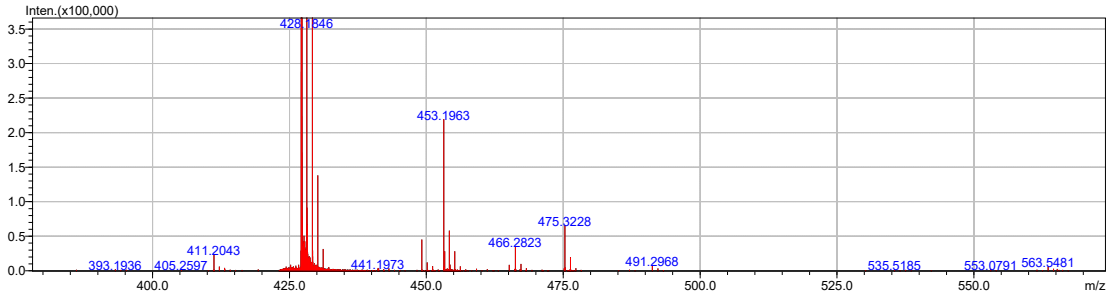
6.39 FTIR NMR spectrum of 4-(2-morpholino,2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl) benzenesulfonamide (18p).



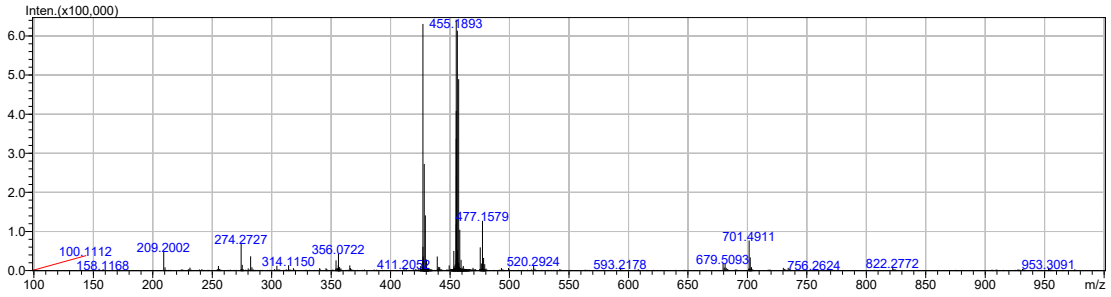
6.40 HRMS spectrum of 4-(3-piperidinopropionylamido)-*N*-(butylcarbamothioyl)benzenesulfonamide (18a).



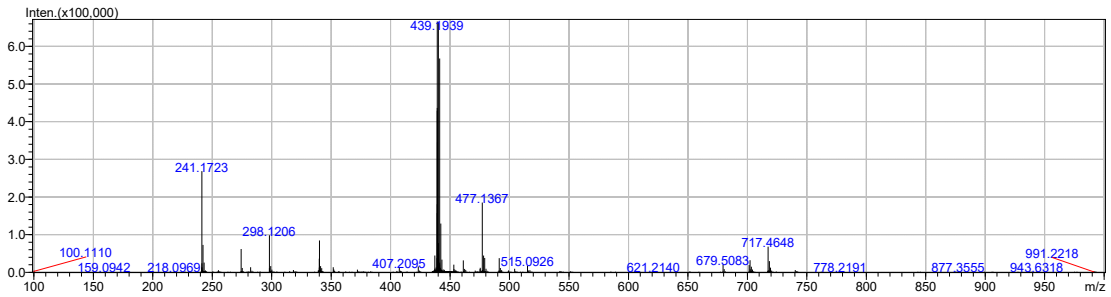
6.41 HRMS spectrum of 4-(3-piperidinopropionylamido)-*N*-(cyclohexylcarbamothioyl)benzenesulfonamide (18d).



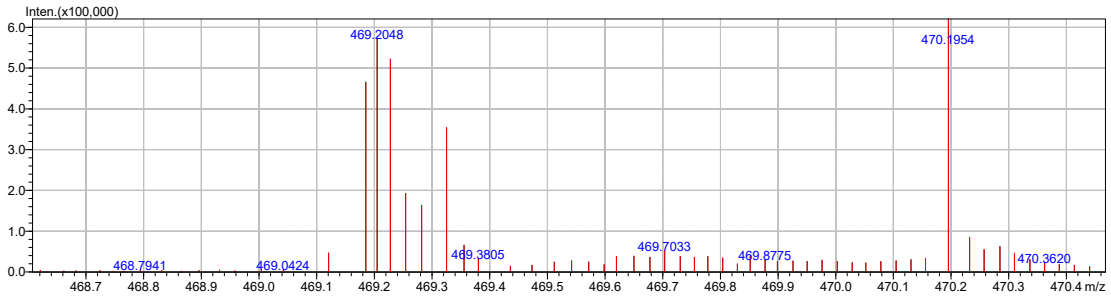
6.42 HRMS spectrum of 4-(3-morpholinopropionylamido)-*N*-(cyclohexylcarbamothioyl)benzenesulfonamide (18f).



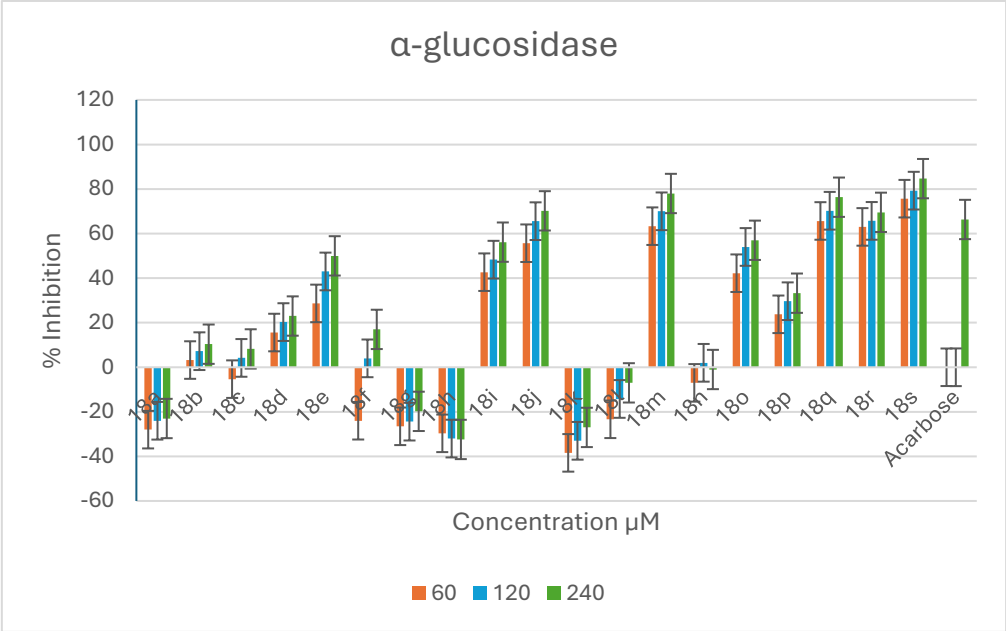
6.43 HRMS spectrum of 4-(2-piperidinoacetamido)-*N*-(cyclohexylcarbamothioyl)- benzenesulfonamide (18k).



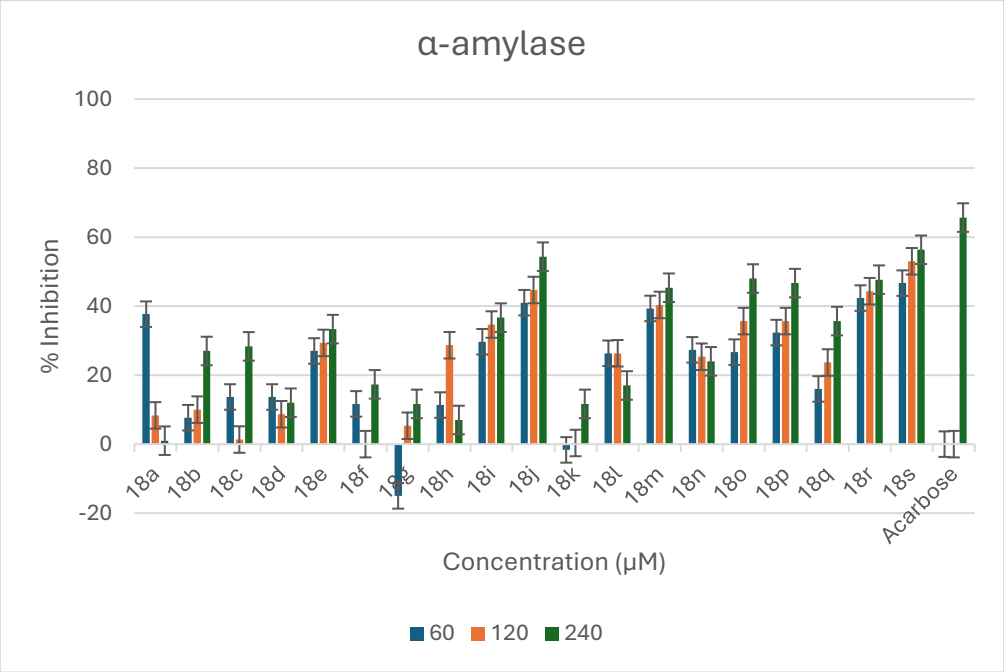
6.44 HRMS spectrum of 4-(2-morpholino,2,2-dimethacetamido)-*N*-cyclohexylcarbamothioyl) benzenesulfonamide (18p).



6.45 % α-glucosidase chart of sulfonylthiourea compounds (18a-s)



6.46 % αamylase chart of sulfonylthiourea compounds (18a-s)



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