Mikrovalovima potpomognuta sinteza 1,3 - tiazola in situ počevši od primarnih alkohola

Šegedin, Adriana

UNIVERSITY OF SPLIT

FACULTY OF CHEMISTRY AND TECHNOLOGY

MICROWAVE-ASSISTED ONE-POT SYNTHESIS OF 1,3-THIAZOLES STARTING FROM PRIMARY ALCOHOLS

MASTER THESIS

ADRIANA ŠEGEDIN

Parent number: 337

Split, June 2023.

UNIVERSITY OF SPLIT

FACULTY OF CHEMISTRY AND TECHNOLOGY

MASTER STUDY OF CHEMISTRY

ORGANIC CHEMISTRY AND BIOCHEMISTRY

MICROWAVE-ASSISTED ONE-POT SYNTHESIS OF 1,3-THIAZOLES STARTING FROM PRIMARY ALCOHOLS

MASTER THESIS

ADRIANA ŠEGEDIN

Parent number: 337

Split, June 2023.

SVEUČILIŠTE U SPLITU

KEMIJSKO-TEHNOLOŠKI FAKULTET

DIPLOMSKI STUDIJ KEMIJE

ORGANSKA KEMIJA I BIOKEMIJA

MIKROVALOVIMA POTPOMOGNUTA SINTEZA 1,3-TIAZOLA *IN SITU* POČEVŠI OD PRIMARNIH ALKOHOLA

DIPLOMSKI RAD

ADRIANA ŠEGEDIN

Matični broj: 337

Split, lipanj 2023.

BASIC DOCUMENTATION CARD

MASTER THESIS

University of Split
Faculty of Chemistry and Technology
Master study of Chemistry

Scientific area: Natural sciences
Scientific field: Chemistry
Supervisor: Ivica Blažević, PhD, Full Prof.
Co-supervisor: Francisco Guerra Martínez, PhD, Assoc. Prof.

MICROWAVE-ASSISTED ONE-POT SYNTHESIS OF 1,3-THIAZOLES STARTING FROM PRIMARY ALCOHOLS

Adriana Šegedin, 337

Abstract: Thiazole is a five-membered moiety composed of nitrogen and sulfur atoms at positions 1 and 3, respectively. It has received significant attention in the fields of organic and medicinal chemistry due to its remarkable biological and pharmacological properties. Thiazole-based compounds have demonstrated a wide range of biological activities, including antimicrobial, antitumor, anti-inflammatory, and antioxidant activities, among others. The extensive exploration of thiazole derivatives has resulted in the development of numerous commercially marketed drugs that contain the thiazole ring system. Examples of these drugs include ritonavir, sulfathiazole, bleomycin, pramipexole, febuxostat, vitamin B_1 and many more. These pharmaceuticals highlight the diverse therapeutic potential of thiazole-based compounds. The main objective of this study was to develop a convenient and efficient one-pot synthesis method for 1,3-thiazoles. The primary aim was to discover novel synthetic routes for obtaining thiazoles utilizing more simple and available starting materials. This methodology was achieved by integrating the Hantzsch reaction with microwave irradiation. Initially, alcohols were utilized and transformed into *α*-halocarbonyl compounds through oxidation and chlorination. For oxidation, 2,2,6,6-tetramethylpiperidin-1-yl oxyl radical (TEMPO) was employed as the oxidant, while trichloroisocyanuric acid (TCCA) served as a chlorine source. Subsequently, the Hantzsch synthetic process proceeded, leading to the formation of 1,3-thiazoles. The utilization of microwave irradiation resulted in accelerated reaction rates, improved yields of pure products, and simplified workup procedures. This study demonstrated the numerous advantages of microwave irradiation over conventional heating methods.

Keywords: thiazole, biological activity, Hantzsch reaction, microwave irradiation

Thesis contains: 46 pages, 36 figures, 13 schemes, 10 tables, 14 supplements, 26 references
Original in: English

Defence committee for evaluation and defense of diploma thesis:

1. Franko Burčul, PhD, Assoc. Prof.	chair person
2. Azra Đulović, PhD, Research Assist.	member
3. Ivica Blažević, PhD, Full Prof.	supervisor

Defence date: June 29th, 2023

Printed and electronic (PDF) form of thesis is deposed in Library of Faculty of Chemistry and Technology in Split, Ruđera Boškovića 35, in the public library database of the University of Split Library and in the digital academic archives and repositories of the National and University Library.

TEMELJNA DOKUMENTACIJSKA KARTICA

DIPLOMSKI RAD

Sveučilište u Splitu
Kemijsko-tehnološki fakultet u Splitu
Diplomski studij Kemija

Znanstveno područje: Prirodne znanosti
Znanstveno polje: Kemija
Mentor: prof. dr.sc. Ivica Blažević
Komentor: izv. prof. dr. sc. Francisco Guerra Martínez

MIKROVALOVIMA POTPOMOGNUTA SINTEZA 1,3-TIAZOLA *IN SITU* POČEVŠI OD PRIMARNIH ALKOHOLA

Adriana Šegedin, 337

Sažetak: Tiazol je peteročlani prsten koji sadrži atome dušika i sumpora na položajima 1 i 3. Tiazol je dobio značajnu pozornost u područjima organske i medicinske kemije zbog svojih izvanrednih bioloških i farmakoloških svojstava. Spojevi na bazi tiazola pokazaju širok spektar bioloških aktivnosti, uključujući antimikrobna, antitumorska, protuupalna i antioksidacijska djelovanja. Istraživanje derivata tiazola rezultiralo je razvojem brojnih komercijalno dostupnih lijekova koji sadrže tiazolski prstenasti sustav. Primjeri ovih lijekova uključuju ritonavir, sulfatiazol, bleomicin, pramipeksol, febuksostat, vitamin B_1 i mnoge druge. Ovi farmaceutski proizvodi ističu raznoliki terapijski potencijal spojeva na bazi tiazola. Glavni zadatak ovog rada bio je razviti praktičnu i učinkovitu metodu sinteze 1,3-tiazola *in situ*. Primarni cilj bio je otkriti nove sintetske puteve za dobivanje tiazola koristeći jednostavnije i dostupnije početne materijale. Ova metodologija je izvedena integracijom Hantzschove reakcije s mikrovalnim zračenjem. U početku su se koristili alkoholi koji su se pretvarali u *α*-halokarbonilne spojeve putem oksidacije i kloriranja. Za oksidaciju je korišten 2,2,6,6-tetrametilpiperidin-1-il-oksi radikal (TEMPO), dok je trikloroizocijanurna kiselina (TCCA) služila kao izvor klora. Nakon toga, proces Hantzschove sinteze je nastavljen, što je dovelo do formiranja 1,3-tiazola. Upotreba mikrovalnog zračenja rezultirala je bržom reakcijom, poboljšanim prinosima čistih produkata i pojednostavljenim postupcima obrade. Ovo istraživanje je pokazalo brojne prednosti mikrovalnog zračenja u odnosu na konvencionalne metode zagrijavanja.

Ključne riječi: tiazol, biološka aktivnost, Hantzschova reakcija, mikrovalno zračenje

Rad sadrži: 46 stranica, 36 slika, 13 shema, 10 tablica, 14 priloga, 26 literaturnih referenci
Jezik izvornika: engleski

Sastav Povjerenstva za ocjenu i obranu diplomskog rada:

1. izv. prof. dr. sc. Franko Burčul	predsjednik
2. dr. sc. Azra Đulović, znanstv. sur.	član
3. prof. dr. sc. Ivica Blažević	član-mentor

Datum obrane: 29. lipnja 2023**.**

Rad je u tiskanom i elektroničkom (PDF) obliku pohranjen u Knjižnici Kemijsko-tehnološkog fakulteta u Splitu, Ruđera Boškovića 35, u javnoj internetskoj bazi Sveučilišne knjižnice u Splitu te u javnoj internetskoj bazi diplomskih radova Nacionalne i sveučilišne knjižnice.

Diploma thesis was made in Department of Organic Chemistry, Faculty of Science, University of Cadiz, under the mentorship of Professor Francisco Guerra Martínez, from March until July 2022.

I would like to extend my heartfelt gratitude to my mentor at the University of Cádiz, Professor Francisco Guerra Martínez for his unwavering patience, kindness, and invaluable feedback throughout my master thesis research.

I would also like to express my appreciation to Professor Ivica Blažević, my mentor at the Faculty of Chemistry and Technology in Split, and dr.sc. Azra Đulović for their support and guidance during the entire process.

I am immensely grateful to the Organic Chemistry Department at the Faculty of Science, University of Cadiz, for providing me with the opportunity to conduct my research and for the resources and support they have generously offered.

Furthermore, I would like to thank my colleagues at the Organic Chemistry Department for being an exceptional group of individuals, both within and outside the laboratory and for their time and willingness to share experiences. In particular, I would like to express my gratitude to Pablo Macías-Benítez for his friendship and guidance throughout the entire experience.

Lastly, I am deeply thankful to my family and friends for their unwavering love, continuous support, and understanding throughout my studies.

DIPLOMA THESIS TASK

- Develop a methodology for the formation of thiazole rings from alcohols using an oxidant species and a chlorinating agent.

- Study the feasibility of using the 2,2,6,6-tetramethylpiperidin-1-yl oxyl radical (TEMPO) as the oxidant species and trichloroisocyanuric acid (TCCA) as the chlorinating agent under various reaction conditions.

- Investigate the viability of employing microwave irradiation as a means of energy supply to shorten reaction times and reduce energy costs.

- Explore the scope of the reaction by using different alcohols and thioureas.

ABSTRACT

Thiazole is a five-membered moiety composed of nitrogen and sulfur atoms at positions 1 and 3, respectively. It has received significant attention in the fields of organic and medicinal chemistry due to its remarkable biological and pharmacological properties. Thiazole-based compounds have demonstrated a wide range of biological activities, including antimicrobial, antitumor, anti-inflammatory, and antioxidant activities, among others. The extensive exploration of thiazole derivatives has resulted in the development of numerous commercially marketed drugs that contain the thiazole ring system. Examples of these drugs include ritonavir, sulfathiazole, bleomycin, pramipexole, febuxostat, vitamin B_1 and many more. These pharmaceuticals highlight the diverse therapeutic potential of thiazole-based compounds.

The main objective of this study was to develop a convenient and efficient one-pot synthesis method for 1,3-thiazoles. The primary aim was to discover novel synthetic routes for obtaining thiazoles utilizing more simple and available starting materials. This methodology was achieved by integrating the Hantzsch reaction with microwave irradiation. Initially, alcohols were utilized and transformed into *α*-halocarbonyl compounds through oxidation and chlorination. For oxidation, 2,2,6,6-tetramethylpiperidin-1-yl oxyl radical (TEMPO) was employed as the oxidant, while trichloroisocyanuric acid (TCCA) served as a chlorine source. Subsequently, the Hantzsch synthetic process proceeded, leading to the formation of 1,3-thiazoles. The utilization of microwave irradiation resulted in accelerated reaction rates, improved yields of pure products, and simplified workup procedures.

This study demonstrated the numerous advantages of microwave irradiation over conventional heating methods.

Keywords: thiazole, biological activity, Hantzsch reaction, microwave irradiation

SAŽETAK

Tiazol je peteročlani prsten koji sadrži atome dušika i sumpora na položajima 1 i 3. Tiazol je dobio značajnu pozornost u područjima organske i medicinske kemije zbog svojih izvanrednih bioloških i farmakoloških svojstava. Spojevi na bazi tiazola pokazaju širok spektar bioloških aktivnosti, uključujući antimikrobna, antitumorska, protuupalna i antioksidacijska djelovanja. Istraživanje derivata tiazola rezultiralo je razvojem brojnih komercijalno dostupnih lijekova koji sadrže tiazolski prstenasti sustav. Primjeri ovih lijekova uključuju ritonavir, sulfatiazol, bleomicin, pramipeksol, febuksostat, vitamin B_1 i mnoge druge. Ovi farmaceutski proizvodi ističu raznoliki terapijski potencijal spojeva na bazi tiazola.

Glavni zadatak ovog rada bio je razviti praktičnu i učinkovitu metodu sinteze 1,3-tiazola *in situ*. Primarni cilj bio je otkriti nove sintetske puteve za dobivanje tiazola koristeći jednostavnije i dostupnije početne materijale. Ova metodologija je izvedena integracijom Hantzschove reakcije s mikrovalnim zračenjem. U početku su se koristili alkoholi koji su se pretvarali u *α*-halokarbonilne spojeve putem oksidacije i kloriranja. Za oksidaciju je korišten 2,2,6,6-tetrametilpiperidin-1-il-oksi radikal (TEMPO), dok je trikloroizocijanurna kiselina (TCCA) služila kao izvor klora. Nakon toga, proces Hantzschove sinteze je nastavljen, što je dovelo do formiranja 1,3-tiazola. Upotreba mikrovalnog zračenja rezultirala je bržom reakcijom, poboljšanim prinosima čistih produkata i pojednostavljenim postupcima obrade.

Ovo istraživanje je pokazalo brojne prednosti mikrovalnog zračenja u odnosu na konvencionalne metode zagrijavanja.

Ključne riječi: tiazol, biološka aktivnost, Hantzschova reakcija, mikrovalno zračenje

CONTENTS

INTRODUCTION 1

1. GENERAL PART 2

1.1. CHEMISTRY OF THIAZOLE 2

1.2. SYNTHESIS OF THIAZOLES 4

1.3. BIOLOGICAL ACTIVITIES OF THIAZOLE 11

1.4. GREEN CHEMISTRY-BASED SYNTHESIS OF THIAZOLE DERIVATIVES 17

1.4.1. MICROWAVE-ASSISTED ORGANIC SYNTHESIS 20

2. EXPERIMENTAL SECTION 23

2.1. MATERIALS AND METHODS 23

2.1.1. Instrumental Techniques 23

2.1.2. Solvents and Reagents 26

2.2. DESCRIPTION OF REACTIONS AND PRODUCTS 27

2.2.1. General procedure for the synthesis of thiazoles 27

3. RESULTS AND DISCUSSION 30

3.1. FUSION OF MICROWAVE IRRADIATION AND THE HANTZSCH REACTION 30

3.2. OPTIMIZATION OF REACTION CONDITIONS 32

3.3. SCOPE OF THE REACTION 35

4. CONCLUSIONS 47

5. ABBREVIATIONS 48

6. BIBLIOGRAPHY 50

7. SUPPLEMENTARY 53

INTRODUCTION

The investigation of novel compounds exhibiting multifunctional biological properties is a highly relevant and significant research field. Researchers have focused on synthesizing various inorganic, polymer, and organic compounds, as well as isolating natural products, to explore their potential biological activities.

Organic compounds have gained significant attention in the biological field due to their easily accessible synthesis methods and high yield percentages. Among the various organic compounds, heterocyclic compounds have emerged as a prominent research area in organic chemistry. Heterocyclic compounds, cyclic molecules with at least two distinct atoms acting as ring members, have numerous uses in biological and medical applications.

In recent years, extensive research efforts have been dedicated to the study of nitrogen and sulfur-containing heterocyclic compounds, with particular emphasis on thiazole, due to their wide range of applications in both synthetic and biological fields. The nitrogen and sulfur atoms in thiazole are placed at positions 1 and 3, respectively, in its five-membered ring structure. The investigation of thiazole derivatives as active chemicals has mostly concentrated on the replacement of desirable functional groups for the hydrogen atoms at positions 2, 4, and 5. These derivatives have demonstrated beneficial biological activities, such as anti-inflammation, anti-fungal, anti-cancer, antibacterial, anticonvulsant, and antitumor effects. In response to the present environmental regulations, there is consequently an increasing interest in the synthesis of novel thiazole derivatives that adhere to the principles of green chemistry. These derivatives hold great potential as drug candidates for various therapeutic applications.[1]

1. GENERAL PART

1.1. CHEMISTRY OF THIAZOLE

Thiazole (Figure 1) or 1,3-thiazole is a five-membered heteroaromatic compound.[2] The stability of thiazole as a heterocyclic compound is attributed to the presence of both an electron-donating group (-S-) and an electron-accepting group (C=N) within its structure.[1] The general formula is C_3H_3NS. Thiazoles were first described in 1887 by Hantzsch and Weber.[3] The thiazole compound is isomeric with azole compounds like isothiazole, which also consist of nitrogen and sulfur atoms but in different positions.[1]

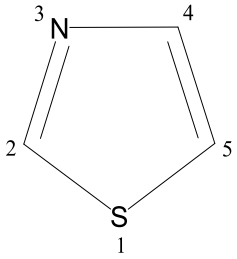


Figure 1. *Thiazole ring*

The thiazole ring meets all four requirements for aromaticity; it is cyclic, planar, conjugated, and also complies with Huckel's rule. The chemical shift values of each proton within the thiazole ring (ranging from 7.27 to 8.77 ppm) provide a basis for predicting the aromaticity of the ring. Figure 2 depicts the resonance structures associated with the thiazole ring.[2,4]

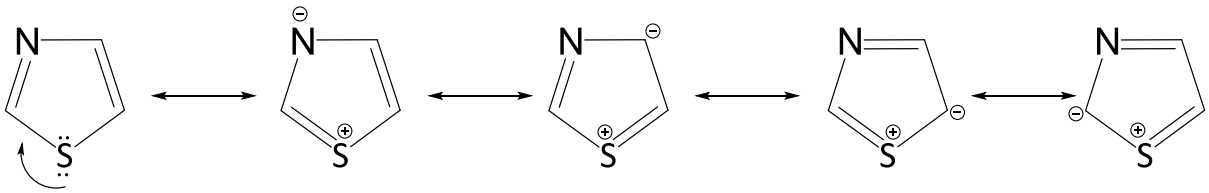


Figure 2. *Thiazole's resonance structures*

Based on the calculated π-electron density, it is evident that electrophilic substitution is predominantly favored at the C-5 position, followed by the C-4

position. On the other hand, nucleophilic substitution occurs primarily at the C-2 position, as depicted in Figure 3.[4]

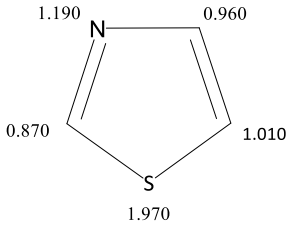


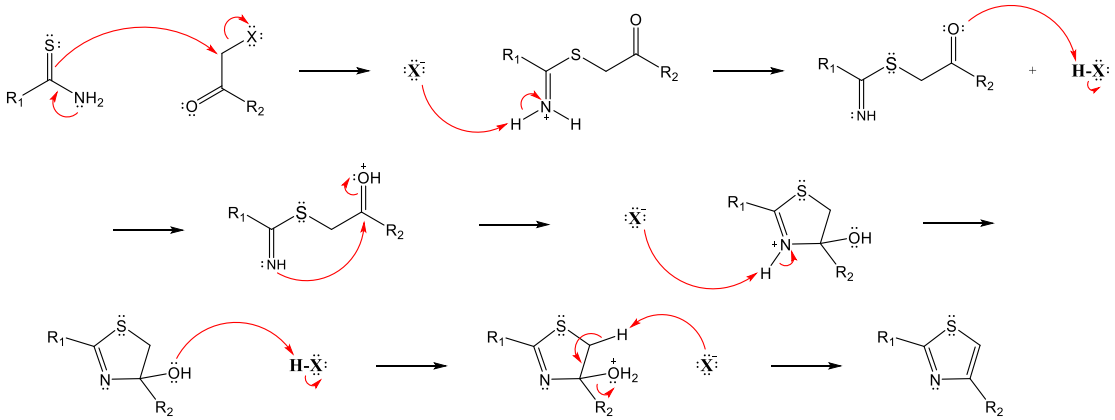
Figure 3. *Calculated π-electron density of thiazole*

Free thiazole is a volatile, light-yellow liquid that is flammable. It exhibits an odor reminiscent of pyridine and has a boiling point within the range of 116 to 118°C. Thiazole is fairly soluble in alcohol and ether, slightly soluble in water, and in small quantities soluble in organic solvents and dyes. The acidity of the three hydrogen atoms present in the thiazole ring decreases in the order H2 >> H5 >> H4.[2,4]

1.2. SYNTHESIS OF THIAZOLES

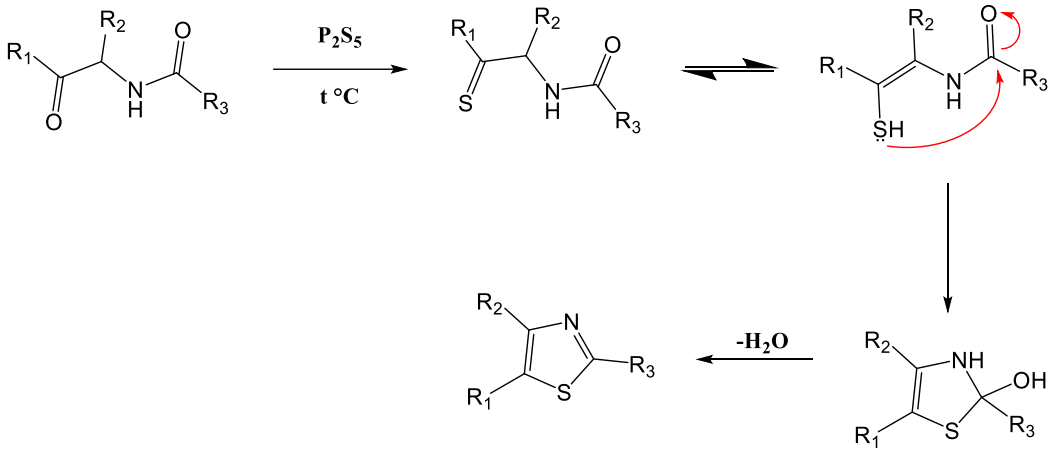
The oldest and most established method to synthesis a thiazole ring is the Hantzsch synthesis. The reaction involves a [3 + 2] atom cyclization between *α*-halocarbonyl compounds and numerous reactants containing the N-C-S structural unit, such as thiourea, thioamides, thiosemicarbazones, and thiosemicarbazides. The α-halocarbonyl component is often represented by α-haloketones and α-haloesters. Through this reaction various thiazoles with alkyl, aryl, or heteroaryl substituents at positions 2, 4, or 5 can be synthesized. The reaction occurs because of the strong nucleophilicity of the sulfur atom in reactants containing the N-C-S structural unit.[4]

The reaction mechanism proceeds with a S_N2 nucleophilic attack of the sulfur atom in reactants containing the N-C-S structural unit on the α-carbon atom bearing the halogen, leading to the formation of an intermediate compound. At this point, through several steps, the nitrogen proceeds to undertake an intramolecular condensation eliminating water and eventually hydrogen halide to furnish the final product in excellent yields. Scheme 1 depicts the reaction mechanism of Hantzsch thiazole synthesis.



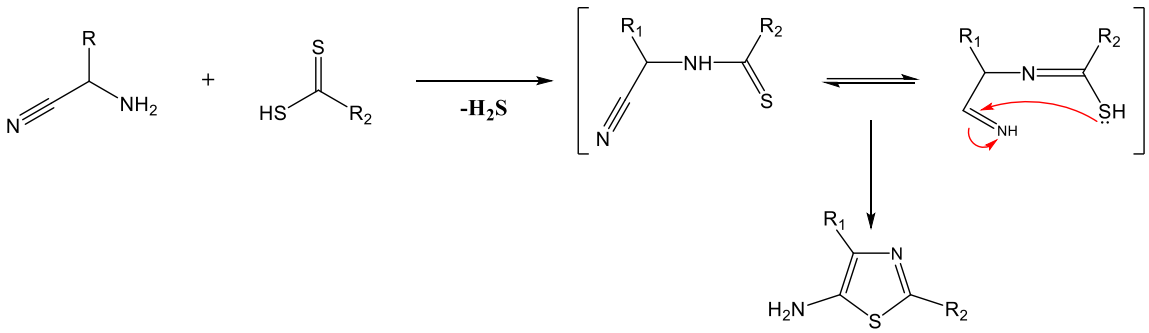
Scheme 1. *Mechanism of the Hantzsch thiazole synthesis reaction*

Gabriel synthesis is a method, reported in 1910, that involves the cyclization reaction of acyl-amino-carbonyl compounds with an equimolar amount of phosphorus pentasulfide at 170°C, resulting in the formation of thiazoles. This process is illustrated in Scheme 2.[3,5]

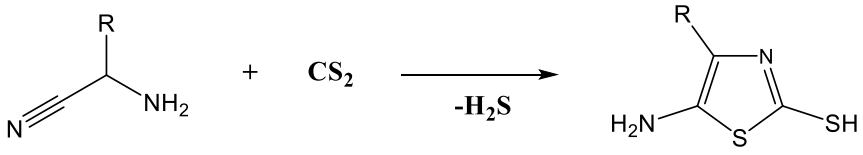


Scheme 2. *Gabriel synthesis of thiazole*

The Cook–Heilbron synthesis, initially discovered in 1947, is a method that leads to the formation of 2,4-disubstituted 5-aminothiazole derivatives. In this synthesis, an α-aminonitrile is reacted under mild reaction conditions with dithioacids or their esters, carbon disulfide, carbon oxysulfide, or isothiocyanates. The process is depicted in Scheme 3. Additionally, when carbon disulfide is utilized in the reaction, it results in the formation of 5-amino-2-mercaptothiazole compounds, as shown in Scheme 4.[1,4]



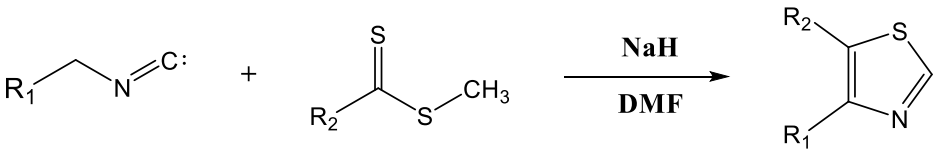
Scheme 3. *Cook–Heilbron synthesis of 5-aminothiazoles*



Scheme 4. *Cook–Heilbron synthesis of 5-amino-2-mercaptothiazoles*

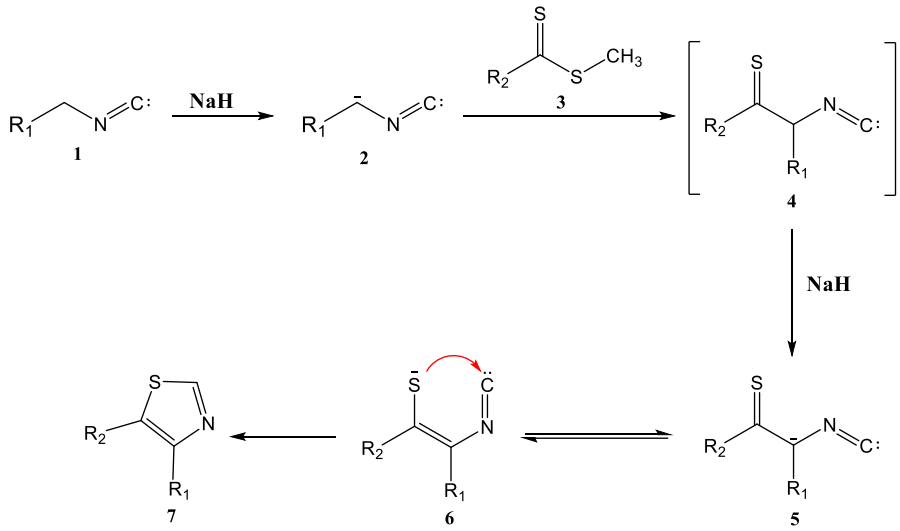
In 2012, Lingaraju et al. devised a method to synthesize a range of 4,5-disubstituted thiazole derivatives utilizing active methylene isocyanides and methyl carbodithioates. Sodium hydride was employed as a strong base, and dimethylformamide (DMF) served as the reaction solvent, as depicted in Scheme

5. The method offered notable advantages, including a short reaction time of 10 to 30 minutes and the achievement of high yields of pure end products.[6]



Scheme 5. *Synthesis of thiazoles from isocyanide derivatives and carboxymethyl dithioates*

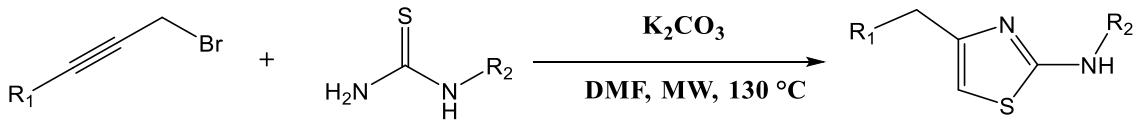
Scheme 6 presents a proposed mechanism for the reaction. Initially, compound 1 reacts with sodium hydride, resulting in the formation of carbanion 2 through deprotonation of the active methylene group. The obtained carbanion 2 subsequently attacks dithioester 3, leading to the formation of an unstable intermediate 4. Carbanion 5 is generated in the presence of sodium hydride, and it exists in equilibrium with the enethiolate anion 6. Finally, the thiazole nucleus 7 is formed through the intramolecular cyclization of compound 6.



Scheme 6. *The proposed mechanism for the synthesis of 4,5-disubtituted thiazole derivatives*

In 2009, Castagnolo et al. synthesized 2-aminothiazoles following an alkylation cyclization reaction. The synthesis involves starting with various substituted propargyl bromides and thiourea derivatives. The reaction is carried out under microwave irradiation at a temperature of 130°C for 10 minutes, divided into two

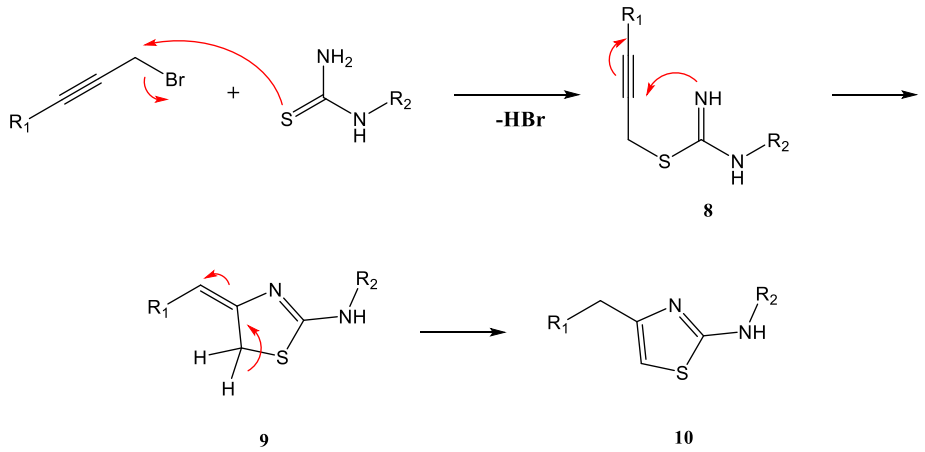
cycles of 5 minutes each. Potassium carbonate is used as a stoichiometric reagent, and DMF serves as the solvent. The reaction is depicted in Scheme 7.[7]



Scheme 7. *Synthesis of 2-aminothiazoles from substituted propargyl bromide and thioureas*

A notable advantage of this method, when compared to the Hantzsch synthesis, is the abundant availability of alkynes. Alkynes serve as a significant alternative to α-haloketones in the synthesis process.

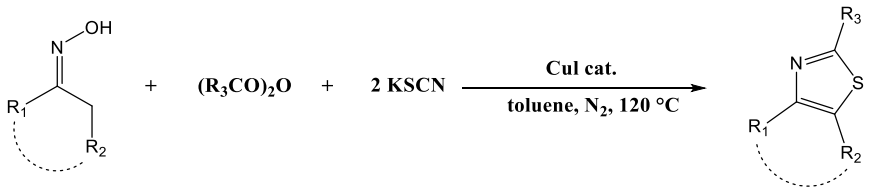
Scheme 8 illustrates the suggested reaction mechanism of this method. The generation of intermediate 8 is achieved in the first stage through the alkylation of thiourea or substituted thioureas. Finally, intermediate 9 undergoes an isomerization reaction, ultimately producing the desired product of this reaction, 2-aminothiazole 10.



Scheme 8. *The proposed mechanism for the synthesis of 2-aminothiazole derivatives*

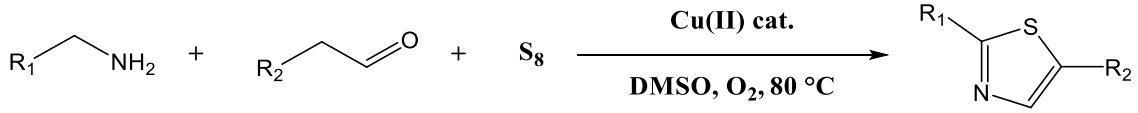
In 2016, Tang et al.'s approach to synthesize thiazoles includes a copper-catalyzed cyclization reaction starting from anhydrides, oximes, and potassium thiocyanate (Scheme 9). The reaction was performed under various conditions to optimize the yields, employing several different solvents such as 1,4-dioxane, 1,2-dichloroethane, toluene and acetonitrile. Additionally, different copper salts

(CuI, CuCl, CuBr, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$), as well as other metal salts ($Fe(OAc)_2$, $FeBr_2$, $FeBr_3$, $FeCl_3$, $PdCl_2$, and AgCl) were explored. Various sulfur sources including NaSCN, KSCN, Na_2S, S and NH_4SCN were also tested. The highest yields, reaching up to 85%, were achieved when toluene was used as the solvent, CuI as the catalyst, and two equivalents of KSCN as the sulfur source. The reaction was conducted under a nitrogen atmosphere at a temperature of 120°C for 24 h. The synthetic procedure is depicted in Scheme 9.[8]



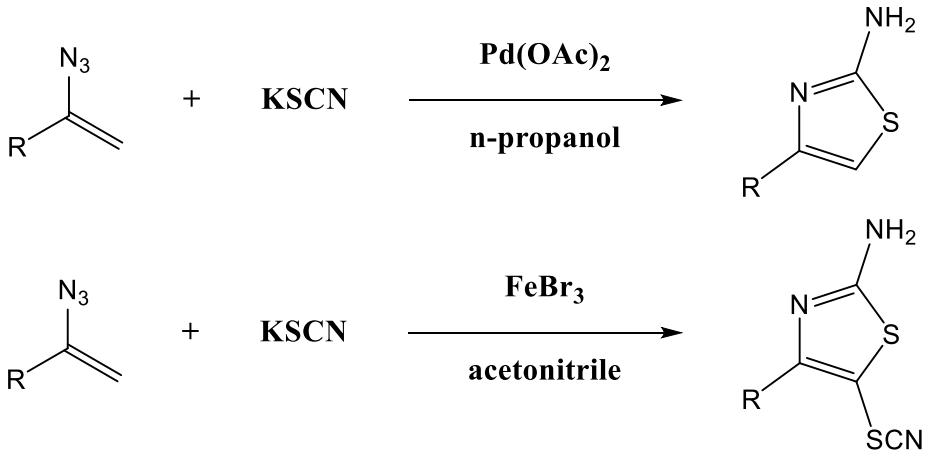
*S**cheme 9.** Synthesis of thiazoles from oximes, anhydrides, and KSCN*

In 2018, in the presence of molecular oxygen, Wang et al. were able to synthesize a number of thiazole derivatives by an oxidation reaction sped up by copper salts. The reaction begins with amines, aldehydes, and element sulfur as the starting materials, as shown in Scheme 10. This method offers several notable advantages, including the use of a low-cost catalyst, the high availability of starting materials, and the utilization of a green oxidant.[9]



***Scheme 10.** Synthesis of thiazoles from aldehydes, amines, and element sulfur*

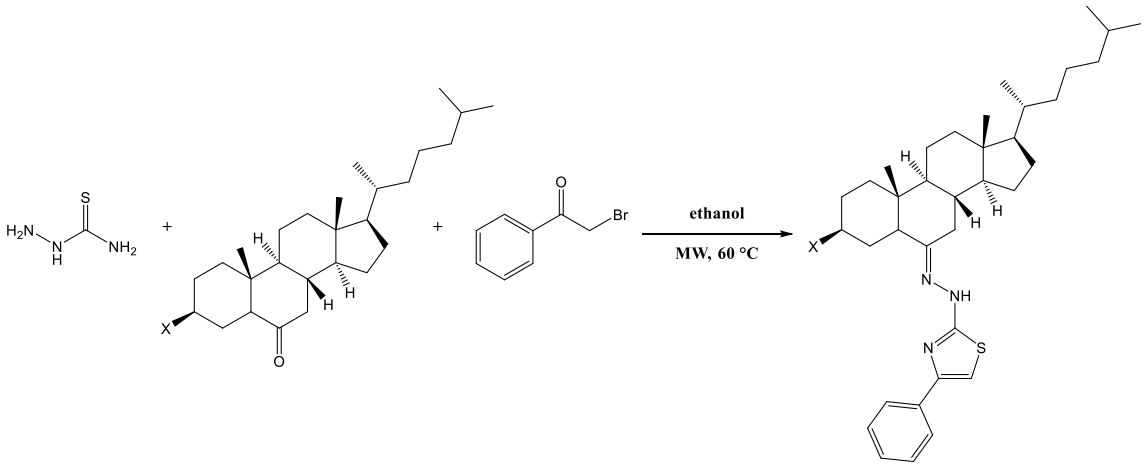
By adjusting the reaction conditions and beginning with substituted vinyl azides and potassium thiocyanate, in 2015, Chen et al. successfully synthesised 4-substituted 2-aminothiazoles and 4-substituted 5-thiocyano-2-aminothiazoles. One of the final products of this method, 4-substituted 2-aminothiazoles were formed by employing n-propanol as a solvent and palladium(II) acetate as a catalyst. The reaction was conducted at a temperature of 80°C for a duration of 12 hours. 4-substituted 5-thiocyano-2-aminothiazoles were synthesized using acetonitrile as a solvent and iron(III) bromide as a catalyst. The reaction conditions, as depicted in Scheme 11, led to the formation of the desired product.[10]



Scheme 11. *Synthesis of thiazoles from vinyl azides and potassium thiocyanate using different reaction conditions*

Microwave-assisted synthesis has proven highly effective in achieving various heterocyclic compounds containing the thiazole ring with exceptional yields.

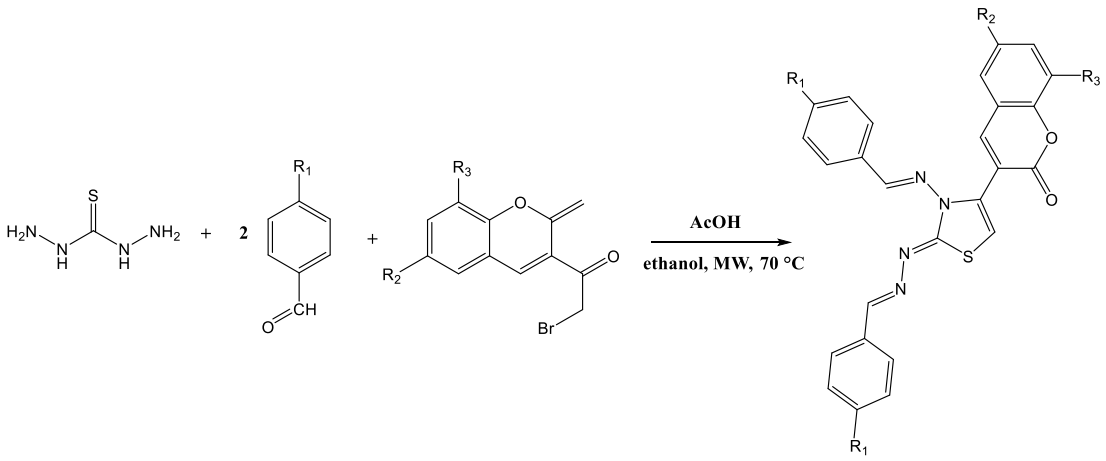
In 2017, Asif et al. developed an effortless, one-pot synthesis method for synthesizing uncommon steroidal thiazole derivatives under microwave conditions. The synthesis involves a condensation reaction between thiosemicarbazide, 2-bromoacetophenone, and steroidal carbonyl compounds, as illustrated in Scheme 12. The reaction is conducted under microwave heating at a temperature of 60°C in ethanol for 35-45 minutes, resulting in the desired compounds with yields ranging from 80% to 85%.[11]



Scheme 12. *Synthesis of thiazoles from thiosemicarbazide, ketones, and 2-bromoacetophenone using microwave irradiation*

In 2021, Mamidala et al. presented another noteworthy method for synthesizing coumarin-based thiazole derivatives under microwave heating. Thiocarbohydrazide, aldehydes, and α-halocarbonyl coumarins were used in a 1:2:1 molar ratio for the reaction during the synthesis, as depicted in Scheme 13. To optimize the reaction conditions in terms of time and yield, different solvents and catalysts were employed.

The study concluded that the use of ethanol as the solvent and a catalytic amount of acetic acid under microwave irradiation at 70°C resulted in remarkably short reaction times of 5 to 8 minutes and high yields ranging from 88% to 93%.[12]



Scheme 13. *Synthesis of thiazoles from thiocarbohydrazide, aldehydes, and α-bromoketones using microwave irradiation*

1.3. BIOLOGICAL ACTIVITIES OF THIAZOLE

Many natural and synthetic compounds include the thiazole nucleus, which has a wide range of pharmacological effects, including anticancer, antifungal, antiviral, antidiabetic, antibacterial, antiparkinsonian, anticonvulsant, and anti-inflammatory activities. There is a large number of commercially marketed drugs containing compounds with this function group such as ritonavir, vitamin-B_1, sulfathiazole, sulfazole, penicillin-G, tiazofurin, bleomycin, abafungin, febuxostat, pramipexole, and many more.[13,14] The majority of compounds are 2,4-disubstituted thiazole derivatives, with only a small number of 2,5-disubstituted or 2,4,5-trisubstituted thiazole derivatives.[4]

During the initial phase of the COVID-19 pandemic, the antiviral drug **ritonavir** was employed in combating the coronavirus COVID-19. **Sulfathiazole** is an organosulfur compound with antibacterial properties, while **abafungin** acts as an antifungal agent. **Febuxostat** found its application in treating gout caused by high levels of uric acid. **Tiazofurin** serves as an antitumor medication, whereas **pramipexole** and **talipexole**, classified as dopamine agonists, are marketed as treatments for Parkinson's disease. **Nitridazole** finds application as an antischistosomal drug, and **amiphenazole** acts as a respiratory stimulant, functioning as an antidote for barbiturate or opiate overdose. **Thiamine**, also known as vitamin B_1, plays a significant role in the release of energy from carbohydrates. Additionally, **alizatidine** is employed as an anti-ulcer agent, and **riluzole** is utilized as an anticonvulsant.[14,15] Figure 4 depicts the structures of various commercially marketed drugs containing the thiazole nucleus.

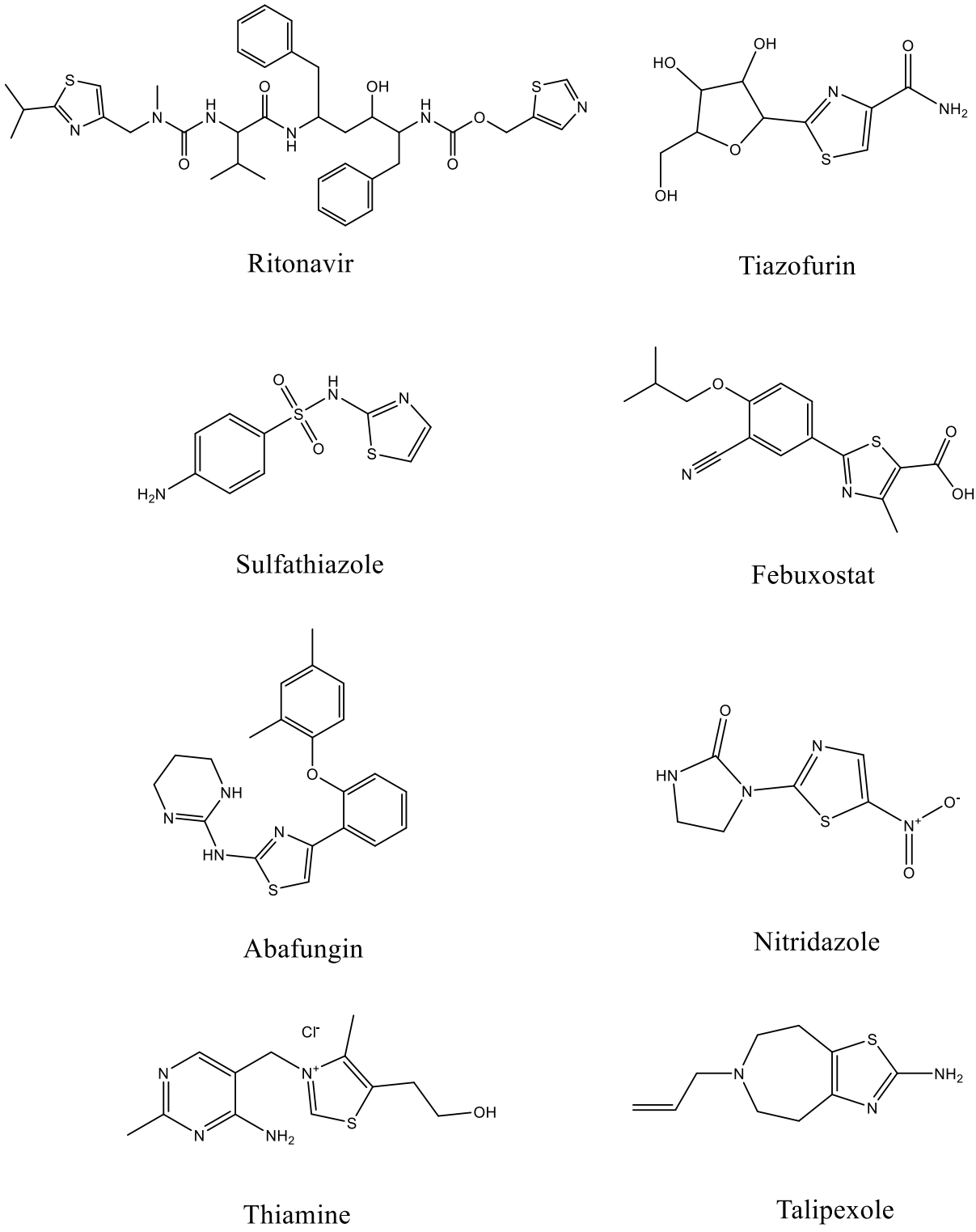


Figure 4. *Structures of some commercially marketed thiazole drugs*

Regarding the occurrence of thiazoles in natural products, the thiazole nucleus serves as a subunit in numerous terrestrial and marine products that display noteworthy biological activities.[13] These natural products are secondary

metabolites and possess notable biological effects against bacteria, fungi and viruses.[16] As a result, there has been a significant focus on natural product-inspired drug discovery and development in recent years. Countless examples exist of biologically active natural products that incorporate thiazole motifs.

- Bleomycin (Figure 5), derived from the microorganism *Streptomyces verticillus*, belongs to a group of glycopeptide antibiotics. It serves as the primary component in the anticancer medication known as Blenoxane (trade name for bleomycin). Blenoxane has been successfully employed in combination chemotherapy to treat Hodgkin's lymphoma, testicular cancers, as well as skin, head, and neck carcinomas.[16]

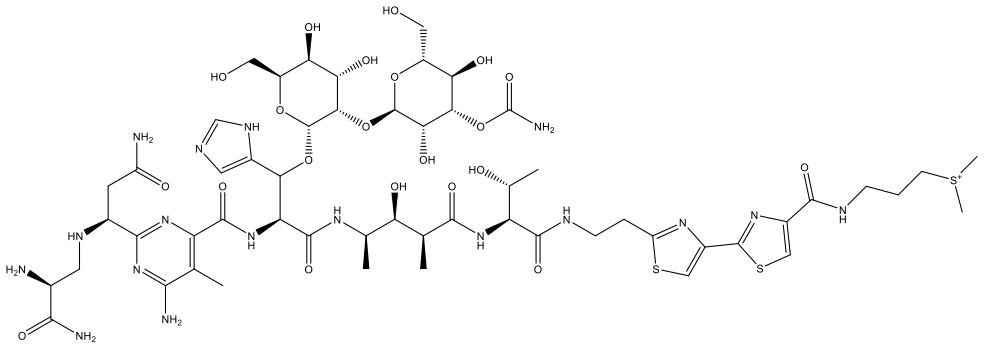


Figure 5. *Bleomycin*

- In 1998, a substance called cystothiazole A (Figure 6) was discovered in the culture broth of a bacterium called *Cystobacter fuscus*. Cystothiazole A has the ability to kill fungi and is also cytotoxic.[13,16]

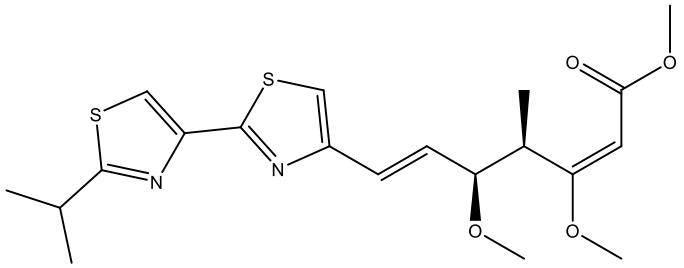


Figure 6. *Cystothiazole A*

- Mycothiazole (Figure 7), is a natural compound derived from the Indo-Pacific sponge *Spongia mycofijiensis*. It was initially discovered in 1988 and later found in a marine sponge of the *Dactylospongia* genus in

2001. Mycothiazole has been found to exhibit anthelminthic activity, meaning it can combat parasitic worms. Additionally, it has also shown to be an anticancer agent against lung cancer cells.[13]

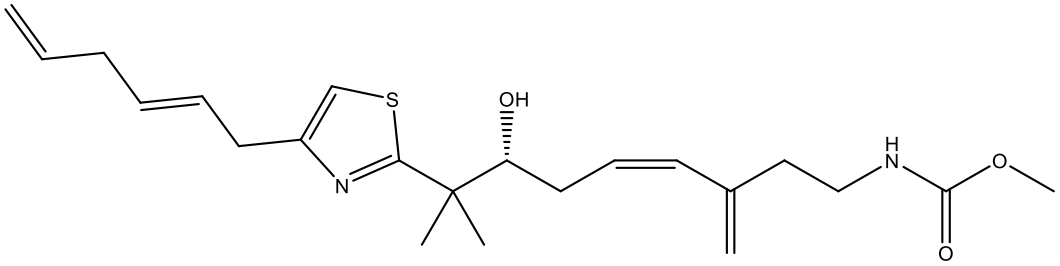


Figure 7. *Mycothiazole*

- Bistratamide C (Figure 8) belongs to a family of macrolactams derived from *Lissoclinum bistratum*, a marine organism found in the southern Philippines. This compound has been identified to possess anti-neoplastic and cytotoxic activities.[13,17]

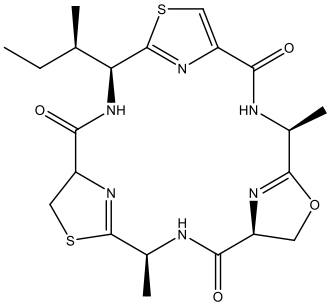


Figure 8. *Bistratamide C*

- Hectochlorin (Figure 9) is a natural fungicide found in the marine environment. It is derived from the cyanobacterium *Lynbya majuscula*, collected in Hector Bay, Jamaica.[13,16,17]

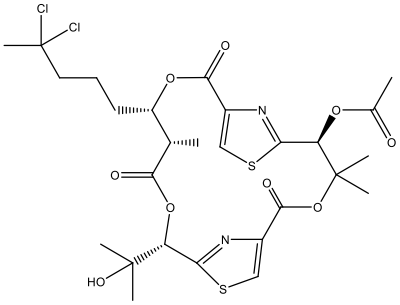


Figure 9. *Hectochlorin*

- Leinamycin (Figure 10) is a naturally occurring antibiotic isolated from *Streptomyces bacteria*. This compound has demonstrated strong antitumor activity.[13]

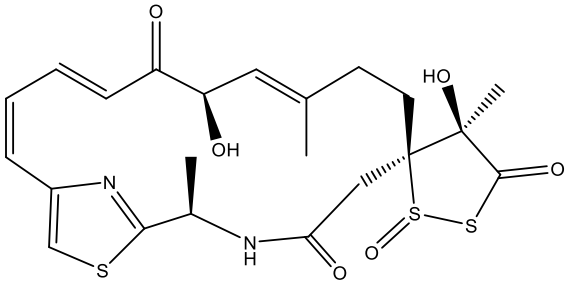


Figure 10. *Leinamycin*

- Pateamine A (Figure 11) was first isolated from the marine sponge *Mycale* sp. in New Zealand in 1991. This natural product exhibits potent cytotoxin activity. Additionally, Pateamine A has been found to possess strong immunosuppressive activity.[13]

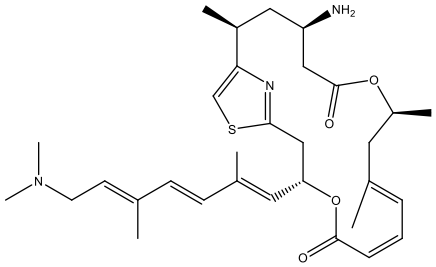


Figure 11. *Pateamine A*

- Urukthapelstatin A (Figure 12) is a thiopeptide antibiotic obtained from the culture of *Mechercharimyces asporophorigenens*, a bacterium belonging to the Thermoactinomycetaceae family. This compound has demonstrated cytotoxic activity.[16,17]

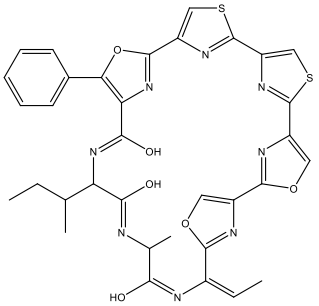


Figure 12. *Urukthapelstatin A*

These are merely a handful of examples that highlight the presence of thiazole rings in natural products, which serve as a rich source of compounds with diverse biological activities. These compounds hold great potential in the development of new drugs for treating various human diseases.

The thiazole ring also finds use in other fields, such as polymers, photonucleases, fluorescent dyes, liquid crystals, insecticides and antioxidant (Figure 13).[13]

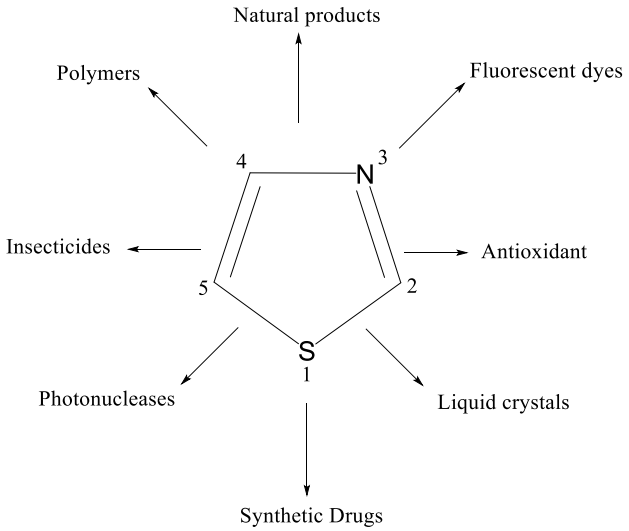


Figure 13. *Wide range application of the thiazole ring*

1.4. GREEN CHEMISTRY-BASED SYNTHESIS OF THIAZOLE DERIVATIVES

Green chemistry, sometimes referred to as sustainable chemistry or green product design, is an emerging field that represents an alternative approach in synthetic chemistry with the attempt to replace non-sustainable conventional methods with high chemical risks. The aim is to synthesize products in ways that minimize environmental impacts by preventing the formation of hazardous by-products or waste, thus diminishing the impact of hazardous substances on human health and the enviroment.[18,19]

Heterocycles containing nitrogen and sulfur are frequently present in biologically active natural products and synthetic compounds.[20] For example, the thiazole framework is present in over 18 FDA-approved drugs and numerous experimental formulations. One such example is alpelisib (Figure 14), a thiazole-derived drug marketed as Pigray®. It received approval in 2019 for the treatment of breast cancer. Most traditional approaches for synthesizing thiazole derivates depend on the use of thermal heating, high boiling solvents, toxic or expensive catalysts and reagents and longer reaction times. Due to the importance of these heterocyclic compounds, more sustainable and environmentally friendly strategies for their synthesis are being successfully applied under green chemistry principles (Figure 15). Green strategies offer a sustainable approach that focuses on achieving product yield while minimizing detrimental environmental effects. They offer several advantages, such as easy work-up, improved selectivity, reduced production of by-products with minimum steps involved in synthetic schemes.[18]

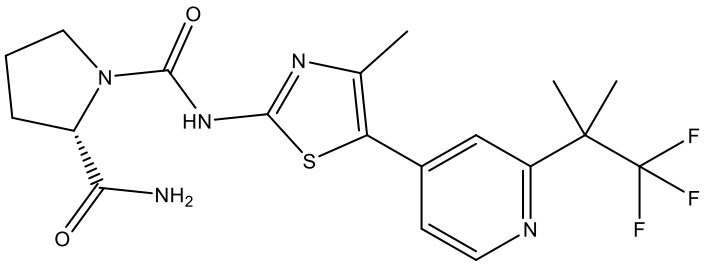


Figure 14. *Alpelisib*

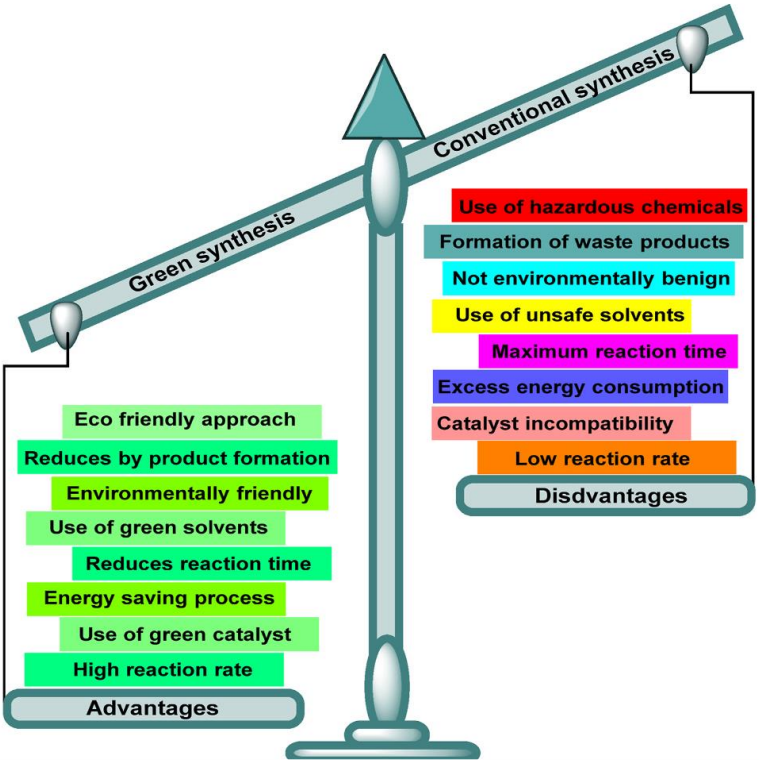


Figure 15. *Benefits of green synthetic methods over conventional synthetic methods*[18]

Green chemistry is generally described by the 12 principles defined by Paul Anastas and his team in 1998 (Figure 16). The fundamental aim of the principles include the prevention of waste, using more renewable feedstocks, maximizing the inclusion of all materials used in the synthesis of the final product, using less hazardous reactants and solvents and decreasing energy consumption.[18,19]

Based on these principles, green chemistry-based synthetic methods like one-pot-multi-component reaction (MCR), microwave-assisted synthesis, ultrasound-mediated synthesis, nanoparticle-catalysed synthesis, ionic liquid supported synthesis, water-based synthesis, solvent-free synthesis have been developed for the formation of thiazole derivatives. The one-pot-multi-component reaction (MCR) is one of the most common methods for obtaining thiazoles. This approach involves three or more reactants in a single reaction operation producing the desired product, incorporating all the reactants into the product.

Figure 16. *The 12 Principals of Green Chemistry*[18]

The benefits of this method are that it excludes the need for multiple steps and the formation of intermediates, which decreases the reaction time and increases the overrall yield. The use of bio-based starting materials, such as alcohols, sugars and amino acids, add another environmentally friendly aspect to the production process. The use of metal-impregnated nanoparticles in nanoparticle-catalyzed synthesis offers benefits such recyclability of catalysts, short reaction times, and high yields.

Another green chemistry-based approach is water-based synthesis. Water is a non-toxic and renewable solvent, offering a environmentally friendly and sustainable alternative to conventional organic solvents. Ionic liquids can be used as catalysts or solvents, which is another strategy that adheres to the green chemistry criteria. Ionic liquids are salts that at room temperature exist in a liquid state and have specific properties, such as high thermal stability, non-flammability and low volatility. The use of ionic liquids in chemical reactions improve the efficiency and selectivity, while reducing the overall environmental impact of the process. Conventional synthesis methods often use large quantities of organic solvents, which are harmful to the environment and human health. For a more environmentally friendly approach solvent-free or solvent-minimized

reactions are being achieved by using alternative reaction conditions, such as grinding or heating under reduced pressure.[18,20]

1.4.1. MICROWAVE-ASSISTED ORGANIC SYNTHESIS

Microwave (MW) radiation has become a widely employed non-conventional energy source in chemistry due to the ability of certain compounds, whether solids or liquids, to convert electromagnetic energy into heat.[19,21] The technique replaces traditional methods such as oil baths and hot plates for providing the necessary heat energy to finalize reactions.[22] MW radiation has revolutionized chemical synthesis, due to its significant benefits and advancements in the field.[22]

The MW radiation region, which covers wavelengths from 1 mm to 1 m and frequencies between 0.3 and 300 GHz, is located between radio-waves and infrared radiation on the electromagnetic spectrum.[19] This energy is utilized to break chemical bonds and further the reaction. Household microwave ovens and specialized microwave reactors for chemical synthesis both operate at frequencies of 2.45 GHz, which corresponds to a wavelength of 12.24 cm, to avoid any potential interference with radio and radar frequencies.[23]

It has been demonstrated that microwave-assisted organic synthesis (MAOS) improves yields, purity, and reaction time rates. [23] It provides uniform and selective heating with lower energy usage, promoting greater reproducibility of reactions and promoting the development of convenient and environmentally friendly synthetic pathways.[19]

Microwave-assisted organic synthesis offers several advantages, including:

- **Enhanced reaction speed:** Experimental data has proven that microwave-assisted chemical reactions can transpire at a faster rate compared to conventional heating methods. The ability of microwaves to utilize higher temperatures allows reactions to be completed in a matter of minutes instead of hours, significantly reducing reaction times.[22]
- **Improved yield and increased purity:** Microwave irradiation leads to a reduction in the formation of side products during reactions, resulting in a

higher yield of the desired product. As a result, the subsequent purification process becomes faster and easier.[24]

- **Energy efficiency:** Microwave-induced heating is highly efficient, leading to significant energy savings. This is primarily due to the fact that microwaves selectively heat only the sample rather than the entire apparatus, resulting in reduced energy consumption.[24]
- **Uniform and selective heating:** When using conventional heating methods, the walls of an oil bath are heated first, followed by the solvent, resulting often in a temperature difference between the walls and the solvent. In the case of microwave heating, only the solvent and the solute particles are excited, which results in uniform heating of the solvent. Selective heating is based on the principle that different materials respond differently to microwaves, with some being transparent while others absorb microwaves.[25]
- **Environmentally friendly synthesis:** Microwave-assisted reactions offer a greener approach compared to conventional heating methods. By directly heating the compounds, microwaves enable a reduction or elimination of solvents in chemical reactions and result in the reduction of energy consumption.[24] Additionally, the use of microwaves can also reduce the amount of purification required for end products in reactions involving toxic reagents, further contributing to a more sustainable process.[22]
- **Reproducibility:** Microwave-assisted reactions are more reproducible compared to conventional heating methods. This is due to uniform heating and allowing for a more strict control of temperature, pressure, and irradiation conditions.[19]

In summary, microwave irradiation has proven to have several advantages over conventional heating methods. Absorption and transmission of microwave energy is significantly different from conventional heating (Figure 17). Conventional heating is a superficial and inefficient heating process which relies on surface-based heat transfer through convection and conduction.[21] This requires longer heating times, tedious apparatus setup, increased process costs, and excessive use of solvents/reagents.[19] In contrast, microwave irradiation makes efficient

internal heating possible by a direct interaction of microwave energy with the reaction mixture.[21] This leads to more homogeneous and rapid heating, resulting in accelerated reaction rates, higher yields, and reduced formation of side-products.[23] Furthermore, microwave synthesis enables greater flexibility and creativity in exploring new reactions and conditions that are not easily achievable using conventional heating methods.[19]

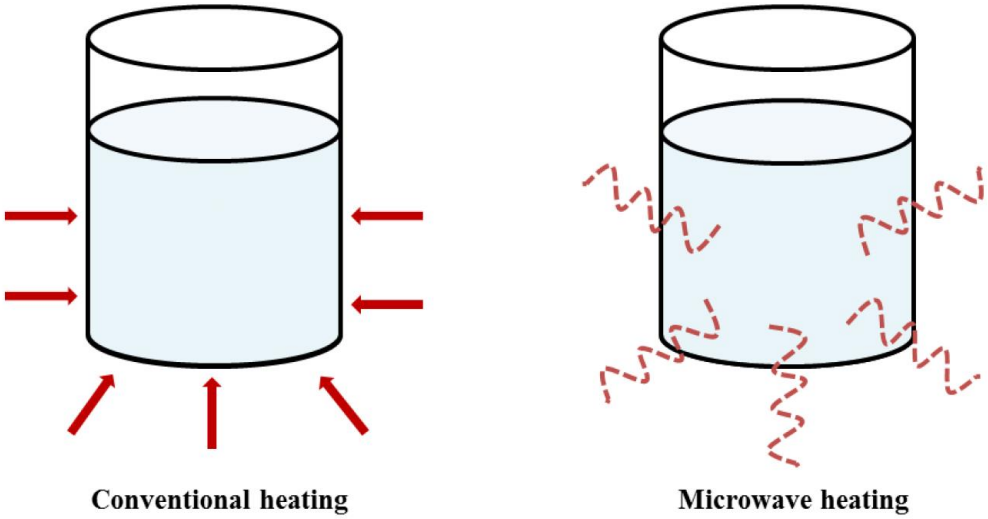


Figure 17. *Comparison of microwave heating with conventional heating*[19]

2. EXPERIMENTAL SECTION

2.1. MATERIALS AND METHODS

2.1.1. Instrumental Techniques

Nuclear Magnetic Resonance (NMR)

^{1}H-NMR and ^{13}C-NMR, spectra were recorded on a Bruker Avance Neo 400 instrument and calibrated using residual undeuterated solvent as an internal reference for ^{1}H NMR and to the central peak of $CDCl_3$ for ^{13}C NMR. Chemical shifts are expressed on the δ scale in parts per million (ppm) and coupling constants (J) in hertz (Hz). The δ values are referenced to the residual peak of chloroform at 7.26 ppm for 1H. The following abbreviations are used to denote the multiplicity of signals: a (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), etc. Multiplets are defined by the δ value at their midpoint.

Chromatographic Techniques

Thin-Layer Chromatography (TLC)

TLC experiments were performed on silica gel plates, specifically Merck Kieselgel 60 F254 plates, with a thickness of 0.25 mm and a fluorescent indicator. The elution of compounds on the plates was visualized either by exposure to UV light (254 nm and 360 nm) or by using a chemical staining reagent.

The chemical staining reagent used was a solution of anisaldehyde (25 mL), ethanol (75 mL), concentrated sulfuric acid (1 mL), and acetic acid (5 mL) (anisaldehyde).

In all cases, the plate was subsequently heated at 100 ºC for a few minutes. The eluent ratios are expressed as percentages of the most polar component.

Gas Chromatography (GC)

A Perkin-Elmer Clarus GC400 gas chromatograph with a Perkin Elmer Elite-5 column was used. The column had dimensions of 30 m in length and 0.25 mm in width, with a particle size of 0.25 µm. Sample preparation involved passing an aliquot, extracted from each reaction, through a small silica gel column with dimensions of 0.6 × 7 cm to remove metallic species and suspended solids. Injection and detection temperatures, as well as heating ramps, were adjusted according to the different compounds.

Table 1. *Column oven conditions*

Temperature injector: 250 ºC

Column oven Temperature (ºC)	Rate (ºC/min)	Hold (min)	Total (min)
50.0		4	4
200	20	0	11.5
300	25	6	21.5

Column Chromatography

For atmospheric pressure columns, Merck silica gel with a grain size of 60-200 microns was used. The mixtures to be separated were introduced dissolved in the same eluent or pre-adsorbed onto silica gel. For pressure columns, silica gel with the same characteristics was used in an Armen Spot apparatus with UV absorption detection.

When necessary to prevent decomposition of the products, deactivated silica gel was employed. This was achieved by adding distilled water to the silica gel, manually stirring it, and heating it to 30°C for a sufficient time to loosen the silica gel.

High Performance Liquid Chromatography (HPLC)

Merck-Hitachi L-6270 and L-7100 chromatographs equipped with a refractive index detector were used. Separations were carried out on a LiChrospher Si-60 silica gel column with 10 µm, 1 × 25 cm packing (semi-preparative). Sample preparation involved passing through a small silica gel column with dimensions of

0.6 × 7 cm to eliminate the baseline and subsequent filtration through 0.45 µm pore size nylon filters from Teknokroma. The eluents used were hexane, ethyl acetate, and mixtures thereof, previously distilled and filtered using 0.45 µm pore size Millipore filters.

Microwave reactor

A SynthWave MA167 reactor pressurized with nitrogen to a maximum pressure of 45 bars was used to conduct microwave-promoted reactions. The reactions were carried out in 50 mL glass vials, placed in a Teflon container with 200 mL of deionized water as the charging solvent, arranged on a rod that allows for up to five simultaneous reactions with magnetic stirring (Figure 18). These reactions were irradiated using different methods in which the pressure, temperature, and irradiation times were controlled.

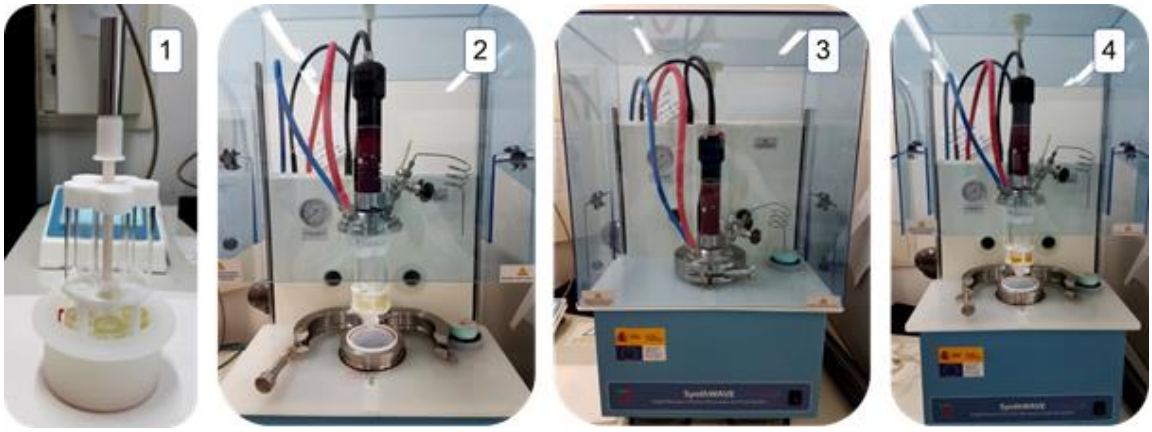


Figure 18. *Image of the microwave-assisted organic reactions setup*

2.1.2. Solvents and Reagents

Solvents for Chromatography

Technical-grade solvents were used for chromatography and were distilled. As previously mentioned, solvents for HPLC were also filtered.

Reagents

Reagents were obtained from various commercial suppliers and used without further purification.

2.2. DESCRIPTION OF REACTIONS AND PRODUCTS

2.2.1. General procedure for the synthesis of thiazoles

Preparation of Thiazoles from Primary Alcohols:

The synthesis of thiazoles from primary alcohols involved two steps. In the first step, TCCA (1 equivalent) and TEMPO (6 mol%) were weighed and dissolved in 4 mL of DCM. Then, the primary alcohol (1 mmol) was added to the mixture. The reaction mixture was subjected to microwave irradiation at 60 °C for 10 minutes, under an initial nitrogen pressure of 35 bar.

In the second step, 8 mL of t-BuOH and thiourea (1.3 equivalents) were directly added to the reaction mixture without isolating the chlorinated aldehyde intermediate. The irradiation method for the second step involved heating the mixture at 100 °C for 5 minutes, maintaining the same initial nitrogen pressure as in the first step.

Following the reduced pressure evaporation of the solvent, 15 mL of a saturated solution of $NaHCO_3$ was added. The resulting crude mixture was extracted three times with DCM (3 × 25 mL), and the organic phase was evaporated to obtain the crude thiazole product. Column chromatography using silica gel was employed for further purification, utilizing a gradient of acetyl acetate and petroleum ether as eluents (ranging from 1:4 to 4:1).

- **5-butylthiazol-2-amine, 3.**

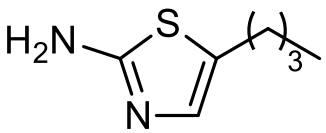


Figure 19. *5-butylthiazol-2-amine,* ***3****.*

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 2.65 (t, *J* = 2,65 Hz, 2H), 1.62 – 1.53 (m, 4H), 1.39 (dq, *J* = 14.5, 7.3 Hz, 4H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 134.1, 129.7, 33.4, 26.8, 22.0, 13.8.

- **5-pentylthiazol-2-amine, 4.**

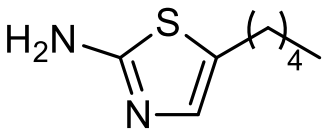


Figure 20. 5-pentylthiazol-2-amine, **4**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 2.55 (t, *J* = 7.1 Hz, 2H), 1.61 – 1.39 (m, 2H), 1.33 – 1.14 (m, 4H), 0.82 (t, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.3, 129.8, 31.1, 31.0, 27.1, 22.4, 14.00.

- **5-hexylthiazol-2-amine, 2.**

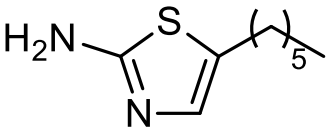


Figure 21. 5-hexylthiazol-2-amine, **2**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 2.60 (td, *J* = 7.3, 1.0 Hz, 4H), 1.65 – 1.49 (m, 5H), 1.42 – 1.15 (m, 6H), 0.87 (t, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.2, 129.6, 31.5, 31.2, 28.6, 27.0, 22.5, 14.0.

- **5-decylthiazol-2-amine, 5.**

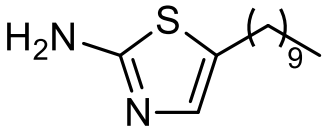


Figure 22. 5-decylthiazol-2-amine, **5**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 2.66 – 2.44 (m, 3H), 1.59 – 1.41 (m, 3H), 1.21 (d, *J* = 15.8 Hz, 20H), 0,81 (t, *J* = 6.6 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 134.2, 129.7, 31.9, 31.3, 29.6, 29.6, 29.3, 29.0, 27.1, 22.7, 14.1.

- **5-hexyl-*N*-phenylthiazol-2-amine, 6.**

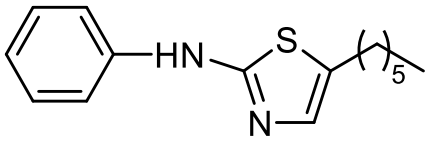


Figure 23. 5-hexyl-*N*-phenylthiazol-2-amine, **6**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 4H), 7.13 – 7.01 (m, 1H), 6.96 (t, *J* = 1.1 Hz, 1H), 2.71 (td, *J* = 7.5, 1.1 Hz, 2H), 1.71 – 1.50 (m, 2H), 1.44 – 1.20 (m, 6H), 0.91 (t, *J* = 6.5 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7, 140.7, 134.3, 129.4, 128.4, 122.5, 117.8, 31.5, 31.3, 28.7, 27.0, 22.6, 14.1.

- ***N*-benzyl-5-hexylthiazol-2-amine, 7.**

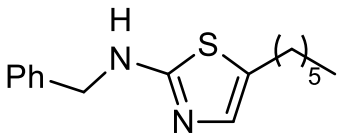


Figure 24. *N*-benzyl-5-hexylthiazol-2-amine, **7**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.10 (m, 5H), 6.77 (s, 1H), 4.46 (s, 2H), 2,63 (t, *J* = 7.6, 2H), 1.58 (m, 2H), 1.47 – 1.18 (m, 7H), 0.91 (t, *J* = 6.6, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 137.9, 134.5, 128.9, 128.7, 127.6, 127.6, 127.5, 49.7, 31.5, 31.2, 28.6, 27.1, 22.6, 14.1.

- ***N*-benzyl-5-phenylthiazol-2-amine, 8.**

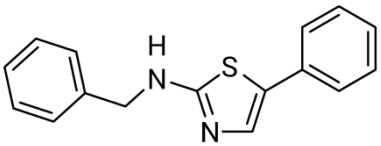


Figure 25. N-benzyl-5-phenylthiazol-2-amine, **8**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 9H), 7.15 – 7.08 (m, 1H), 7.07 (s, 1H), 4.40 (s, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 137.5, 134.5, 132. 4, 128.9, 128.8, 127.9, 127.8, 126.7, 126.6, 125.3, 50.0

3. RESULTS AND DISCUSSION

3.1. FUSION OF MICROWAVE IRRADIATION AND THE HANTZSCH REACTION

The investigation of the Hantzsch reaction reveals a mechanistic pathway involving a double nucleophilic attack between thiourea and phenacyl halide. Thiourea possesses two nucleophilic positions, while the *α*-haloaldehyde or *α*-haloketone possesses two electrophilic positions. The combined attack of both positions facilitates the formation of a cyclic compound (Figure 26). Additionally, the electrophile could be generated and subsequently trapped *in situ*. Moreover, the utilization of microwave irradiation could potentially enable the rapid synthesis of intricate heterocyclic structures within a matter of minutes.

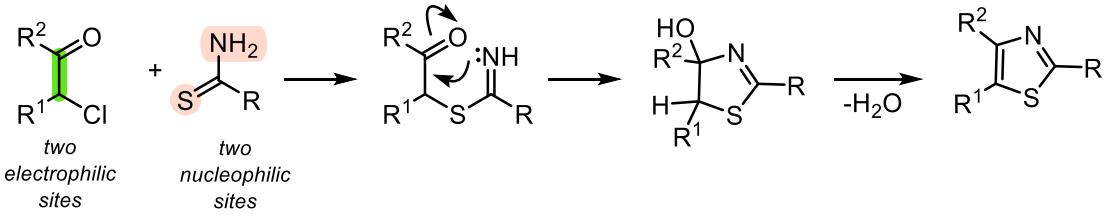


Figure 26. *The Hantzsch reaction between an α-chlorocarbonyl compound and a thiourea/thioamide.*

Upon conducting an extensive literature review, an intriguing article by Studer et al. in 2014 was discovered. The article demonstrated the conversion of primary and secondary alcohols into α-chloroaldehydes and α-chloroketones, respectively, using trichloroisocyanuric acid (TCCA). This discovery presents an appealing hypothesis due to the extensive availability of commercial alcohols, offering a wide range of potential heterocycles.[26]

Motivated by the significant findings presented in the literature, the objective of our research is to investigate the application of the Studer methodology, incorporating microwave irradiation, to achieve the *in situ* generation of α-chloroaldehydes or α-chloroketones, which will subsequently react with thiourea to yield the desired thiazole derivatives. This approach offers several notable

advantages, including the utilization of energy-efficient microwave technology and the adoption of TCCA as a cost-effective and highly efficient commercial reagent, which serves as both an oxidant and a chlorine source with three chlorine atoms per molecule. Furthermore, this methodology significantly reduces the required reaction time, thereby enhancing overall efficiency.

3.2. OPTIMIZATION OF REACTION CONDITIONS

To commence the investigation, the task of establishing appropriate reaction conditions was tackled by focusing on a chosen benchmark reaction. Preliminary experiments were conducted, and subsequently, octanol **1** was selected as the test substrate for further investigation. However, solubility challenges were encountered during the course the study. As a result, a range of solvents and solvent mixtures were explored to overcome these solubility issues, while also examining the effects of different oxidizing and chlorinating agents. Furthermore, we explored two distinct approaches to elucidate their impact on the reaction outcome. The first approach involved a one-pot reaction, which consisted of two sequential steps. In contrast, the second approach involved the separate addition of thiourea after the formation of the α-chloroaldehyde, without isolating the intermediate compound. A comprehensive summary of the obtained results is provided in Table 2, encompassing the yields achieved under each experimental condition.

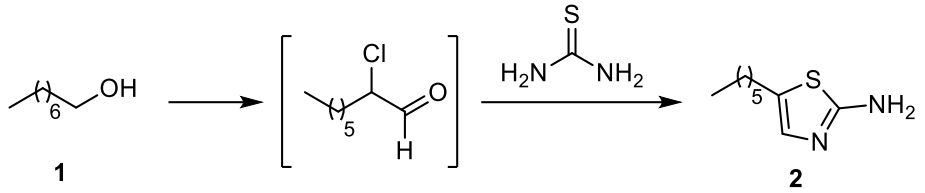
The experimental results were quite interesting and provided valuable information about the behavior of the oxidizing system. Among the "One-Pot Two-Step" entries, it was observed that entry 3, utilizing TCCA as the chlorinating agent, TEMPO as the oxidant, and a solvent mixture of DCM and DCM:t-BuOH (1:2), achieved the highest yield of 95%. This indicates the significance of optimizing both the chlorinating agent and solvent composition to maximize the conversion of **1** to the desired product. Notably, the use of water as a solvent in entry 1 yielded no detectable product, suggesting that organic solvents are crucial for this oxidation reaction.

Comparatively, the "One-Pot One-Step" entries displayed lower overall yields. Entry 10, employing DCM and t-BuOH (1:2) as the solvent, exhibited the highest yield of 47%. However, the yields obtained in this approach were generally lower than those achieved in the "One-Pot Two-Step" method. This suggests that the two-step approach allows for better control of reaction conditions, leading to higher yields.

The choice of chlorinating agent and oxidant also influenced the reaction outcome. Entries 5, 6, and 7, which employed different chlorinating agents with CH_3CN as the solvent, did not yield detectable product. This indicates that the selection of a suitable chlorinating agent is crucial for the successful execution of the oxidation reaction.

Overall, the results demonstrate the importance of optimizing the solvent composition, as well as the choice of chlorinating agent and oxidant, in achieving high yields of the desired product. Entry 3 in the "One-Pot Two-Step" approach, utilizing TCCA, TEMPO, and a DCM:DCM:t-BuOH (1:2) solvent mixture, emerged as the most promising condition, yielding 95%.

Table 2. *Screening of conditions using octanol as a starting material.*



1 **2**

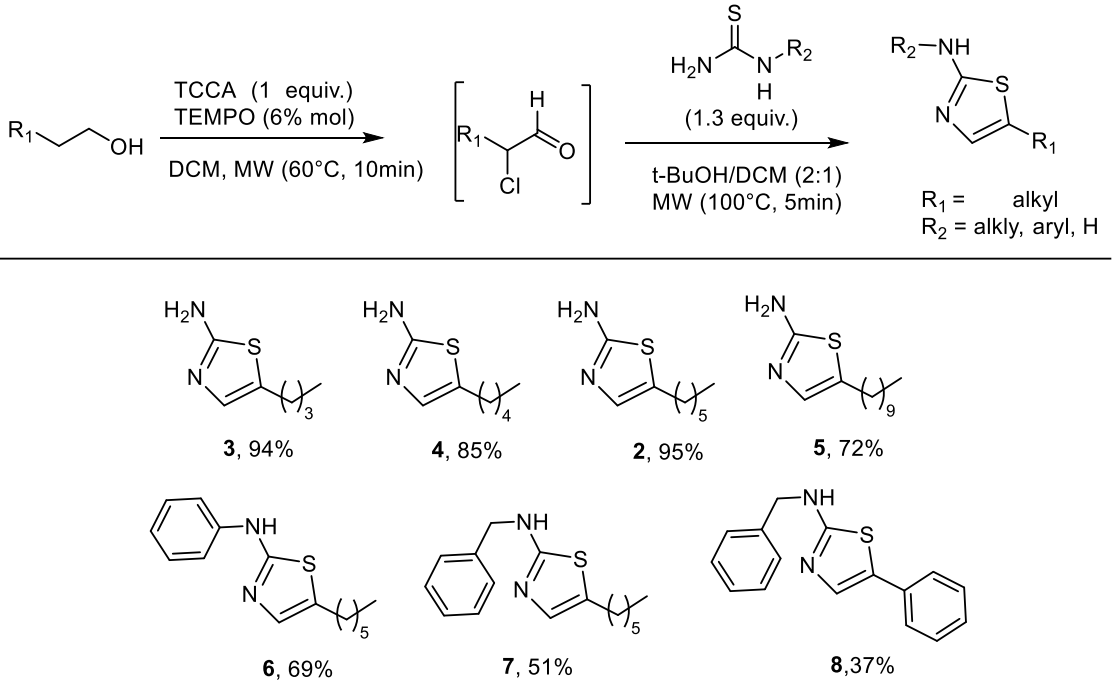
Entry	Chlorinating agent (equiv.)	Oxidant (equiv.)	Solvent	Yield (%)
One-Pot Two-Step				
1	TCCA (1)	TEMPO (1)	H_2O	NR
2	TCCA (1)	TEMPO (1)	DCM/DCM: EtOH (1:2)	40
3	TCCA (1)	TEMPO (0.06)	DCM/DCM: *t*-BuOH (1:2)	95
4	TCCA (1)	TEMPO (0.06)	CH_3CN	70
5	TsCl (1)	TEMPO (0.06)	CH_3CN	NR
6	$Ca(OCl)_2$ (3)	TEMPO (0.06)	CH_3CN	NR
7	NaOCl (6)	TEMPO (0.06)	CH_3CN	NR
One-Pot One-Step				
8	TCCA (1)	TEMPO (0.06)	DCM	10
9	TCCA (1)	TEMPO (0.06)	t-BuOH	31
10	TCCA (1)	TEMPO (0.06)	DCM/*t*-BuOH (1:2)	47

Reaction conditions. Irradiation method for entries 1-7: 60 ºC, 10 min (step 1); 100 ºC, 5 min (step 2). Irradiation method for entries 8-10: 60 ºC, 10 min, then 100 ºC, 5 min. NR, no reaction.

3.3. SCOPE OF THE REACTION

Next, a scope study of the reaction was conducted, aiming to explore its applicability and evaluate the yields across a range of alcohols. A selected series of alcohols and thioureas was employed as substrates to assess their reactivity and ascertain the performance of the reaction. The obtained results are summarized in Table 3, presenting the yields achieved for each alcohol substrate.

Table 3. *Scope of alcohols and thioureas in the microwave-promoted synthesis of thiazoles.*



Synthesis and characterization of 5-butylthiazol-2-amine, 3.

A reaction mixture comprising hexanol, TCCA at a molar equivalent of 1, and TEMPO at a loading of 6 mol% was subjected to microwave irradiation. The reaction was conducted under a nitrogen atmosphere with a pressure of 20 atm at a temperature of 60 ºC for a duration of 10 minutes. Following the initial 10-minute period, thiourea (1.3 equiv.) was added to the reaction mixture and the mixture was subjected to further irradiation at 100 ºC for an additional 5 minutes. Upon completion of the reaction, the work-up procedures outlined in the

experimental section were carried out, leading to the isolation of thiazole **3** as a yellow oil in an excellent yield of 94%.

The ^{1}H-NMR spectrum of the compound shows a singlet at δ 6.74 (1H), which is assigned to the thiazole proton H-4. The methylene group protons closer to the thiazole ring in the side chain (2H-6) show a triplet at δ 2.65 (2H). The remaining signals of the chain can be found as a multiplet at 1.62-1.53 and as dq at 1.39. Finally, the terminal methyl group (3 H-9) is present as a triplet at δ 0.94.

Table 4. ^{1}H-NMR spectrum data *of thiazole* ***3.***

Chemical Shift (ppm)	Multiplicity	Coupling Constant (Hz)
6.74	s	-
2.65	td	7.8, 1.2
1.62 – 1.53	m	-
1.39	dq	14.5, 7.3
0.94	t	7.4

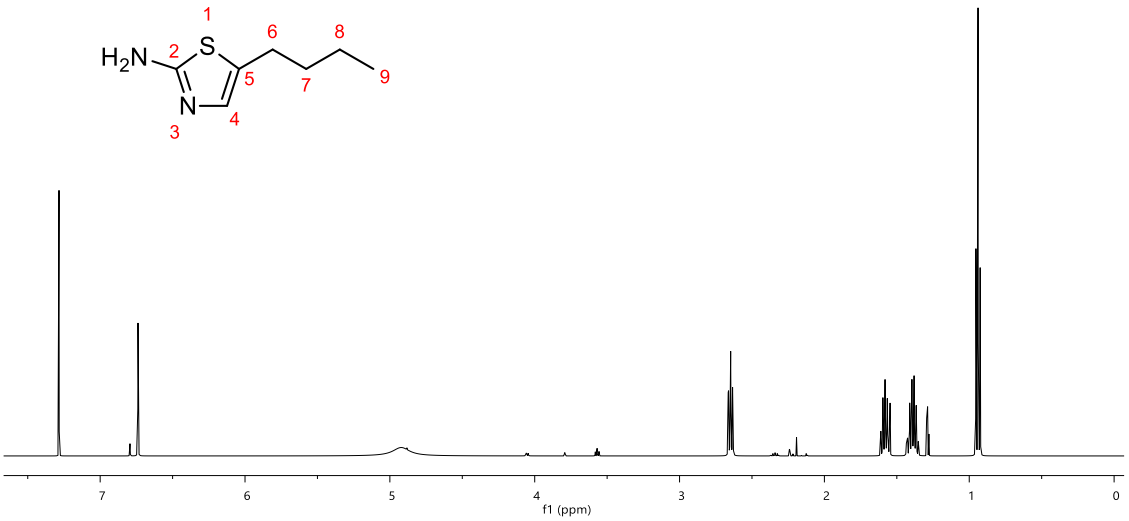


Figure 27. *^{1}H-NMR spectrum of thiazole* ***3.***

The ^{13}C-NMR spectrum of the compound shows two sets of signals corresponding to the aromatic ring and the side chain. The C-2 signal at δ 166.4 is assigned to the carbon atom in the thiazole ring. The C-4 and C-5 signals can be found at δ 134.1 and 129.7, respectively. Signals ranging from δ 33.4 to 13.8 are attributed to the carbon atoms in the terminal methyl group and the side chain's methylene groups.

Although the spectrum initially appeared straightforward, a detailed investigation was carried out using various spectroscopic techniques. The primary focus was on the COSY spectrum, as depicted in Figure 28. The interpretation of the obtained data was found to be relatively straightforward, enabling the easy assignment of hydrogen atoms in the side chain. The assignment process commenced with the methyl group H-9, displaying a triplet at δ 0.94, which exhibited a correlation with a double quartet at 1.39, identified as the two protons, 2 H-8. Furthermore, these protons displayed coupling with a multiplet signal ranging from 1.62 to 1.53, which were confirmed to be the two protons, H-7. Finally, by establishing a correlation between these two protons and a triplet of doublets located at 2.65, the identification of the latter as the two protons, H-6, closest to the thiazole ring was achieved.

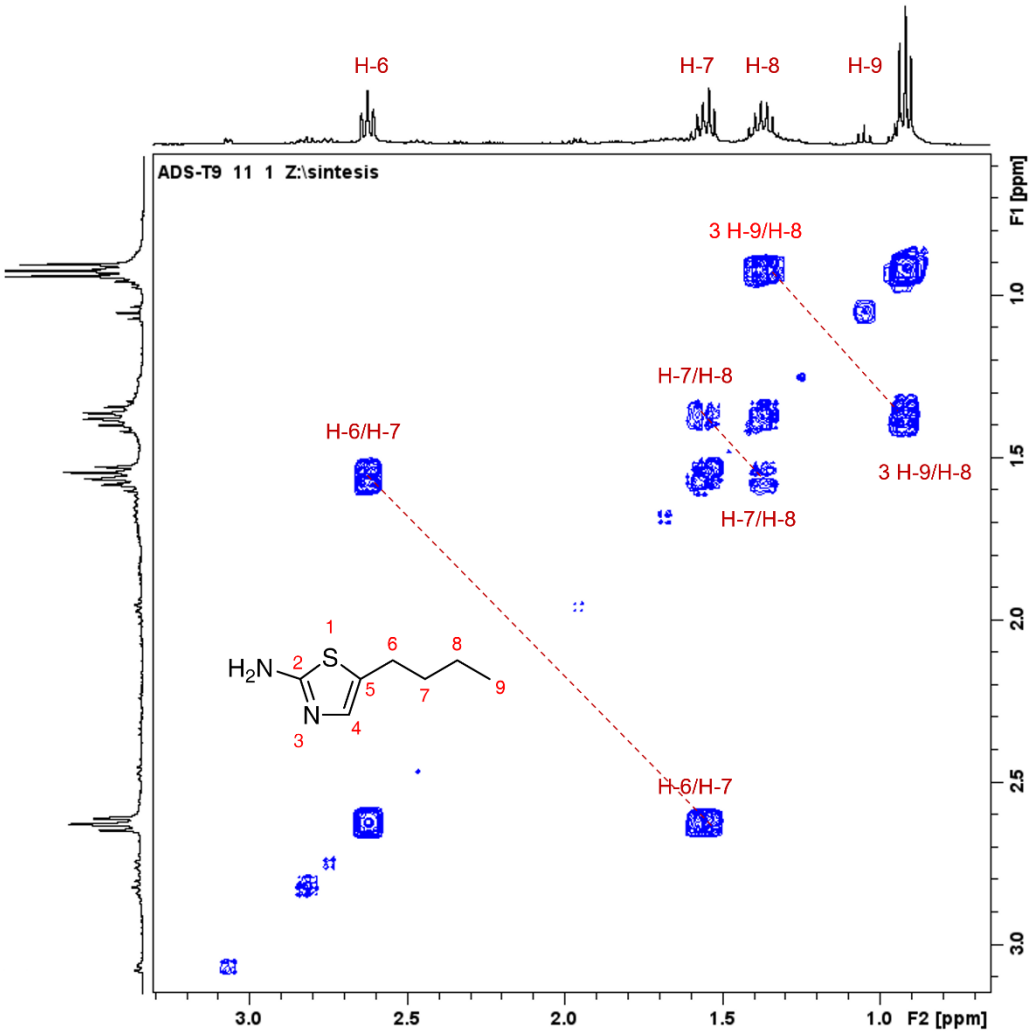


Figure 28. *^{1}H ^{1}H COSY spectrum of thiazole* ***3.***

The carbon atom assignment process was carried out using a HSQC experiment, which illustrates the correlations between proton and carbon signals. Building upon the proton assignment achieved through COSY spectroscopy, the identification of corresponding carbons was straightforward. The three protons of the terminal methyl group, 3-H-9, exhibited a correlation with a carbon atom at δ 13.7. The two protons of the methylene group, 2H-8, displayed coupling with the carbon at δ 22.0, while the methylene group's 2H-6 protons showed coupling with the carbon at δ 26.8. The two H-6 protons facilitated the identification of the C-6 carbon at 33.4 ppm. Additionally, the characteristic signals of the thiazole ring were observed at 166.4 (C-2), 134.15 (C-4), and 129.7 (C-5) ppm.

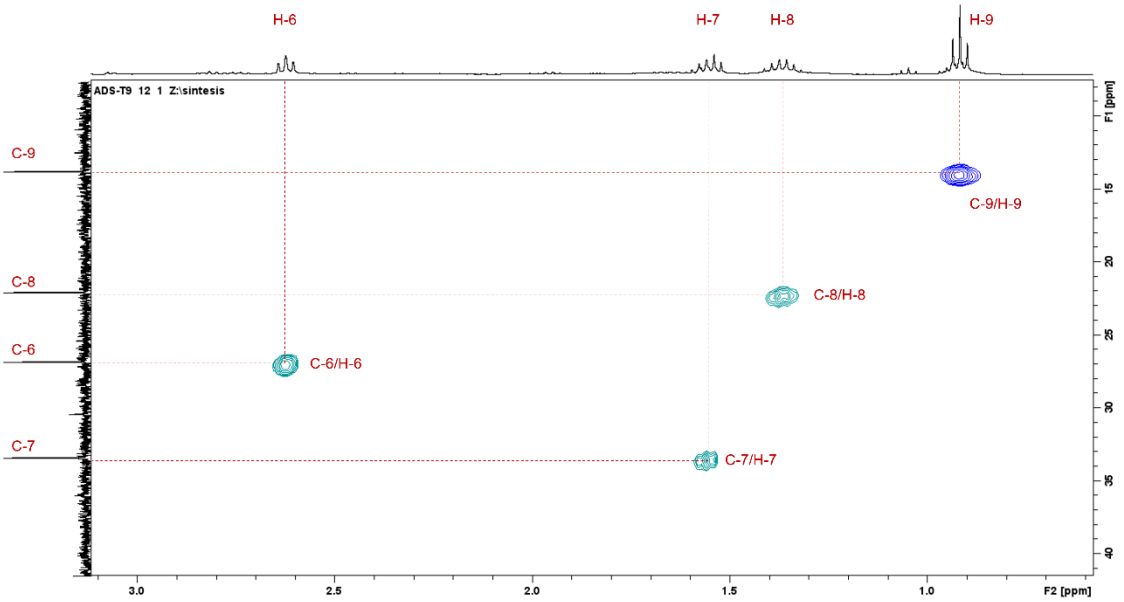


Figure 29. *HSQC spectrum of thiazole* ***3.***

The mass spectrum of the compound (Figure 30) exhibited characteristic peaks consistent with the proposed structure. Notably, the molecular ion peak corresponding to the intact compound appeared at m/z 156.3. This finding confirms the presence of the molecular ion and supports the proposed molecular formula.

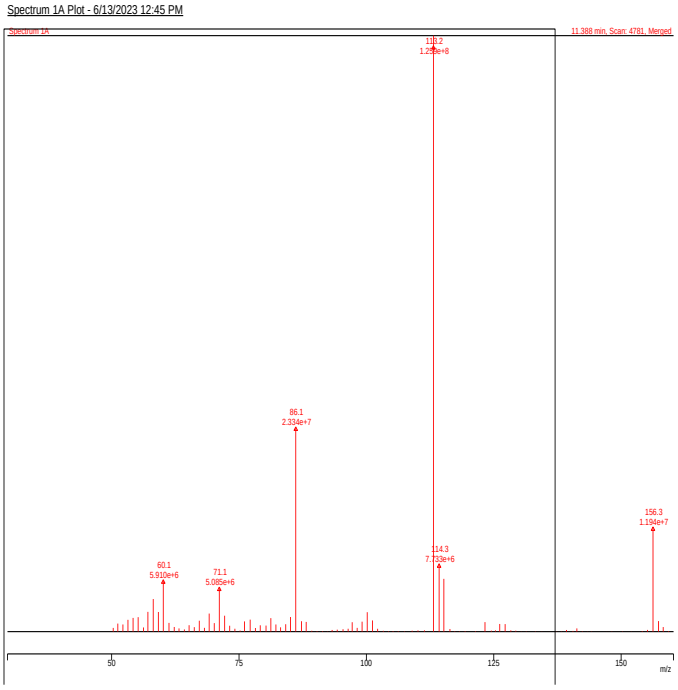


Figure 30. *Mass spectrum of thiazole* ***3.***

Furthermore, the base peak observed in the spectrum corresponded to the fragment [M-C_3H_7] at m/z 113. This peak indicates the loss of a propyl group (C_3H_7) from the side chain of the compound. The fragment ion at m/z 113 provides additional evidence for the proposed structure, as it is consistent with the expected fragmentation pattern resulting from the cleavage of a propyl group.

Synthesis and characterization of 5-pentylthiazol-2-amine, 4

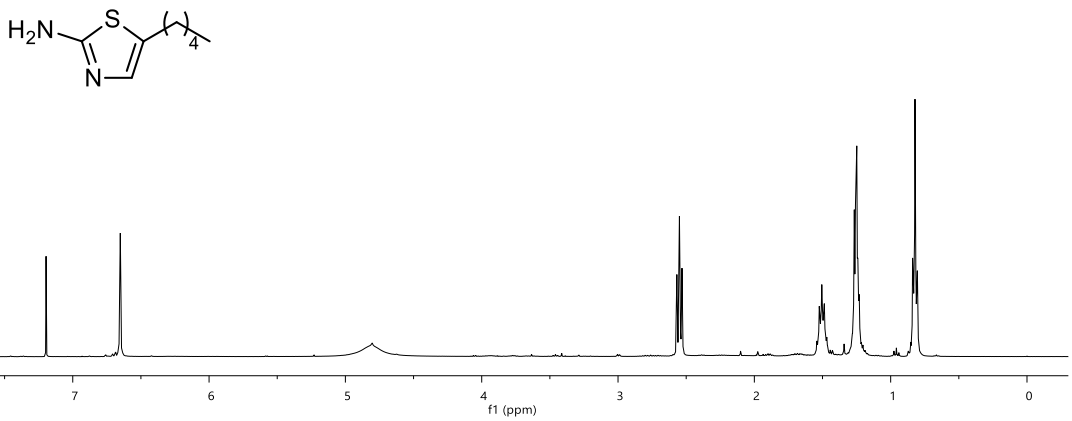


Figure 31. *^{1}H-NMR spectrum of thiazole* ***4.***

Table 5. ^{1}H-NMR spectrum data *of thiazole* ***4.***

Chemical Shift (ppm)	Multiplicity	Coupling Constants (Hz)
6.65	s	-
2.55	t	7.1
1.61 - 1.39	m	-
1.33 - 1.14	m	-
0.82	t	6.7

Treatment of heptanol under conditions similar to those described above resulted in the formation of thiazole **4** with a yield of 85%.

The ^{1}H-NMR spectrum of 5-pentylthiazol-2-amine **4** closely resembles that of compound **3**, indicating similar structural characteristics. Notably, the resonance at δ 6.65 corresponds to the aromatic proton H-4 within the thiazole ring. Furthermore, the CH_2 group directly attached to the thiazole ring is distinguished by its triplet signal at δ 2.55, indicative of coupling with two neighboring protons. The side chain exhibits two distinct sets of multiplets, spanning the ranges of 1.6-1.39 and 1.33-1.14, assigned to the methylene groups. Finally, the terminal methyl group appears as a triplet at δ 0.82.

Two sets of signals are once again observed in the ^{13}C-NMR spectrum. The signals at δ 166.4, 134.3, and 129.8 (C-2, C-4, and C-5, respectively) exhibit the characteristic pattern of a 5-substituted 2-aminothiazole ring, while the remaining signals falling between δ 31.1 and 14.0 can be attributed to the side chain.

Synthesis and characterization of 5-hexylthiazol-2-amine, 2

As it has been previously mentioned, thiazole **2** was obtained in a 95% yield when octanol was treated under conditions similar to those described before.

The ^{1}H-NMR spectrum is consistent with the proposed structure. The H-4 proton is discernible at 6.70 ppm, indicating its distinct chemical environment. Furthermore, the CH_2 moiety directly attached to the thiazole ring resonates at 2.60 ppm, presenting itself as a triplet of doublets. In addition, the remaining methylene groups within the side chain display two multiplets, with one ranging from 1.65 to 1.49 ppm and the other spanning 1.42 to 1.15 ppm. Finally, the terminal methyl group exhibits a signal at 0.87 ppm, manifesting as a triplet.

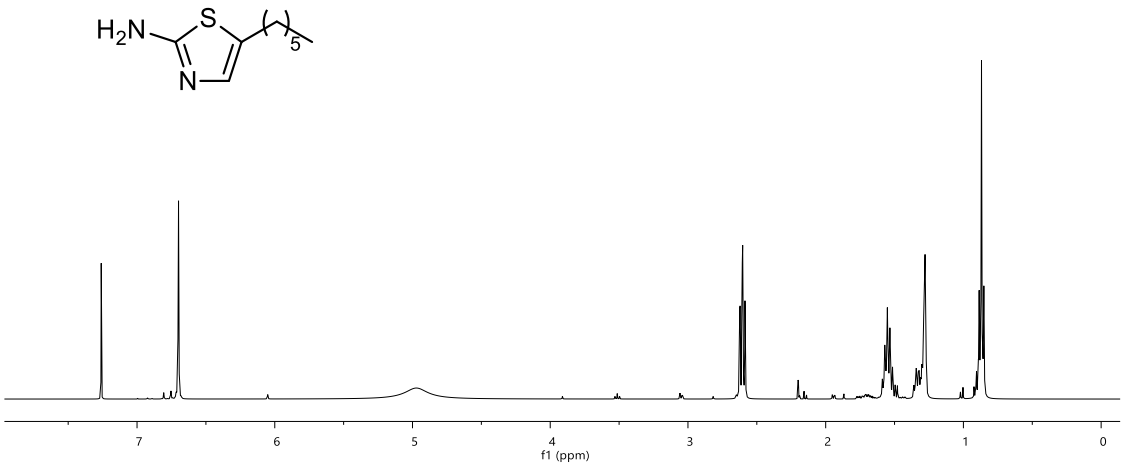


Figure 32. *[1]H-NMR spectrum of thiazole* ***2.***

Table 6. [1]H-NMR spectrum data *of thiazole* ***2.***

Chemical Shift (ppm)	Multiplicity	Coupling Constants (Hz)
6.70	s	-
2.60	td	7.3, 1.0
1.65 - 1.49	m	-
1.42 - 1.15	m	-
0.87	t	6.7

In the aromatic region of the compound's [13]C-NMR spectrum, three distinctive signals are observed. C-2 is assigned a signal at δ 166.4, C-4 exhibits a signal at δ 134.2, and C-5 is characterized by a signal at δ 129.6. The remaining signals falling within the range of 31.5-14.0 are attributed to the side chain.

Synthesis and characterization of 5-decylthiazol-2-amine, 5

The preparation of thiazol **5** was carried out in a similar manner as described above with a yield of 72%. The [1]H-NMR closely resembles that of those previously described . We can observe a distinct signal for H-4 at 6.65 ppm. The CH_2 group attached to the thiazole ring appears as a triplet at 2.55 ppm. The remaining side chain protons are grouped into two sets of signals for the methylene groups, with one set ranging from 1.59 to 1.41 ppm and the other from 1.31 to 1.11 ppm. Finally, the terminal methyl group is seen as a triplet at 0.81 ppm.

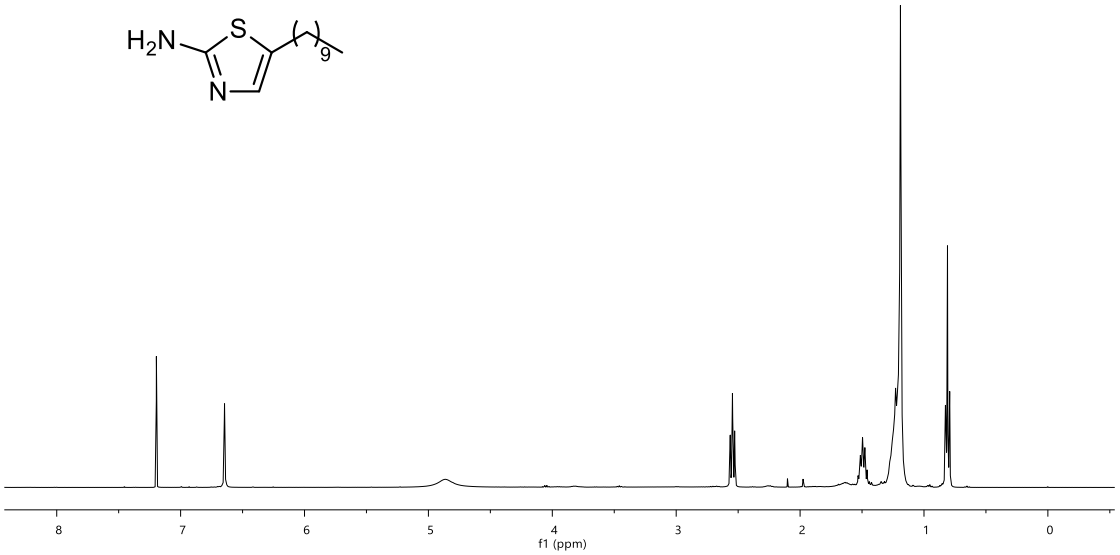


Figure 33. *[1]H-NMR spectrum of thiazole* ***5.***

Table 7. [1]H-NMR spectrum data *of thiazole* ***5.***

Chemical Shift (ppm)	Multiplicity	Coupling Constants (Hz)
6.65	s	-
2.55	t	7.2
1.59 - 1.41	m	-
1.31-1.11	m	-
0.81	t	6.6

In its [13]C-NMR spectrum, the aromatic region reveals the presence of three notable signals. C-2 resonates at δ 166.5, C-4 showcases a signal at δ 134.2, and C-5 is distinguished by a peak at δ 129.7. Additionally, the remaining signals observed in the range of 31.9-14.1 are ascribed to the side chain.

Synthesis and characterization of 5-hexyl-*N*-phenylthiazol-2-amine, 6

At this stage, the effectiveness of other substituted thioureas as the electrophilic partner was decided to be verified. Phenylthiourea was tested for this purpose. The reaction yielded *N*-substituted thiazole **6** with a yield of 69%. This result demonstrates the potential of different thioureas in the formation of desired compounds and expands the scope of the study.

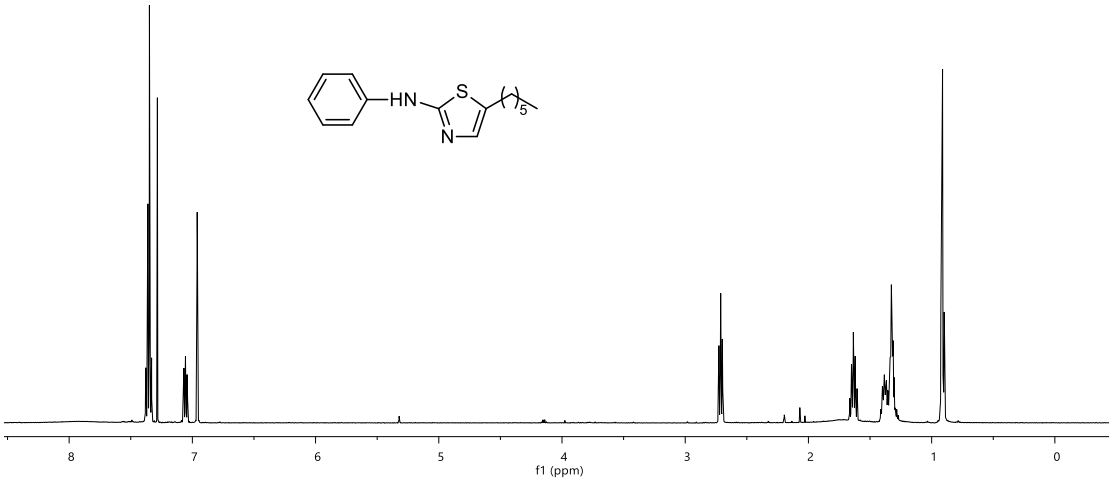


Figure 34. *[1]H-NMR spectrum of thiazole* ***6.***

Table 8. [1]H-NMR spectrum data *of thiazole* ***6.***

Chemical Shift (ppm)	Multiplicity	Coupling Constants (Hz)
7.41 - 7.30	m	-
7.13 - 7.01	m	-
6.96	s	1.1
2.71	td	7.5, 1.1
1.71 - 1.50	m	-
1.44 - 1.20	m	-
0.91	t	6.9

Its [1]H-NMR analysis agrees with the proposed structure. The aromatic signals of the phenyl group display two distinct multiplets, observed within the ranges of 7.41 - 7.30 and 7.13-7.01. The sole thiazole proton H-4 is detected as a singlet at 6.96 ppm. Additionally, the signals corresponding to the side chain are clearly discernible. The methylene group closest to the heterocyclic ring appears as a triplet of doublets at 2.71 ppm. Furthermore, two distinct ranges are observed for the remaining methylenes, with one ranging from 1.71 to 1.50 ppm and the other spanning from 1.44 to 1.20 ppm. Lastly, the distinctive methyl group manifests as a triplet at 0.91 ppm.

The [13]C-NMR analysis reveals distinct carbon resonances within the compound. C-2 exhibits a signal at 163.7 ppm, while C-4 resonates at 134.3 ppm and C-5 at 129.4 ppm. Additionally, the monosubstituted phenyl group displays other aromatic carbons with resonances observed at 140.7, 128.4, 122.5, and 117.8

ppm. Furthermore, the side chain demonstrates a range of carbon signals spanning from 31.5 ppm to 14.1 ppm.

Synthesis and characterization of *N*-benzyl-5-hexylthiazol-2-amine, 7

Like in the previous case, benzylthiourea also successfully gave the corresponding thiazole **7** when the corresponding haloaldehyde from octanol was treated. Thiazole **7** was obtained in this way with a yield of 51%.

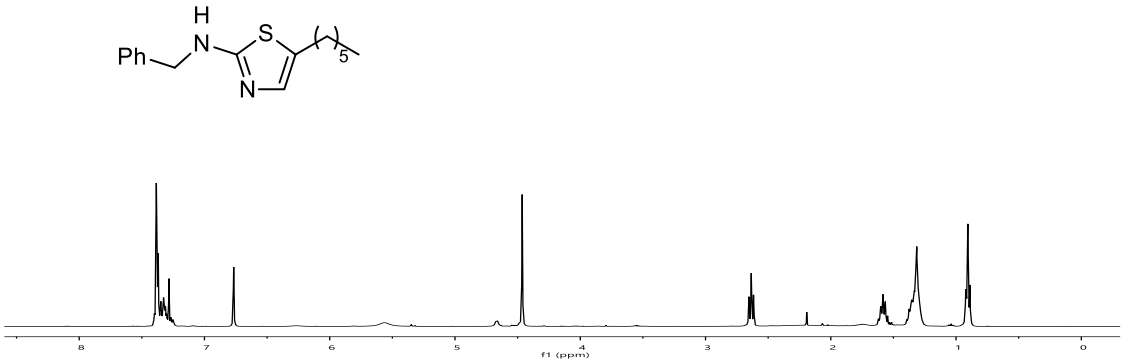


Figure 35. *[1]H-NMR spectrum of thiazole* ***7.***

Table 9. [1]H-NMR spectrum data *of thiazole* ***7.***

Chemical Shift (ppm)	Multiplicity	Coupling Constants (Hz)
7.75-7.10	m	-
6.77	s	-
4.46	s	-
2,63	t	7.6
1.58	m	-
1.47-1.18	m	-
0.91	t	6.8

The [1]H-NMR spectrum of the compound shows a range of signals in the aromatic ring region, from 7.75 to 7.10 ppm. These signals correspond to the five aromatic hydrogen atoms. The signal for the thiazole proton H-4 is observed as a singlet at 6.77 ppm, which is consistent with its expected chemical shift. The methylene protons of the benzyl group exhibit a signal at 4.46 ppm, indicating the presence of two hydrogen atoms. The first methylene of the side chain manifests as a triplet at 2.63 ppm. The remaining signals from the chain are observed as two multiplets, with one at 1.58 ppm and the other spanning a range of 1.47 to 1.18

ppm. Finally, the methyl group located at the end of the chain is observed as a triplet at 0.91 ppm.

The ^{13}C-NMR analysis displays typical carbon resonances. C-2 showcases a signal at 168.5 ppm, while C-4 resonates at 134.5 ppm and C-5 at 128.9 ppm. Moreover, the benzyl group exhibits additional aromatic carbons with resonances observed at 137.9, 128.7, 127.6 (×2), and 127.5 ppm. In addition, the side chain reveals a range of carbon signals spanning from 31.5 ppm to 14.1 ppm.

Synthesis and characterization of *N*-benzyl-5-phenylthiazol-2-amine, 8

Thiazole **8** was obtained with a yield of 37% in an interesting assay where a secondary alcohol, 1-phenylethanol, was used instead of a long-chain alcohol.

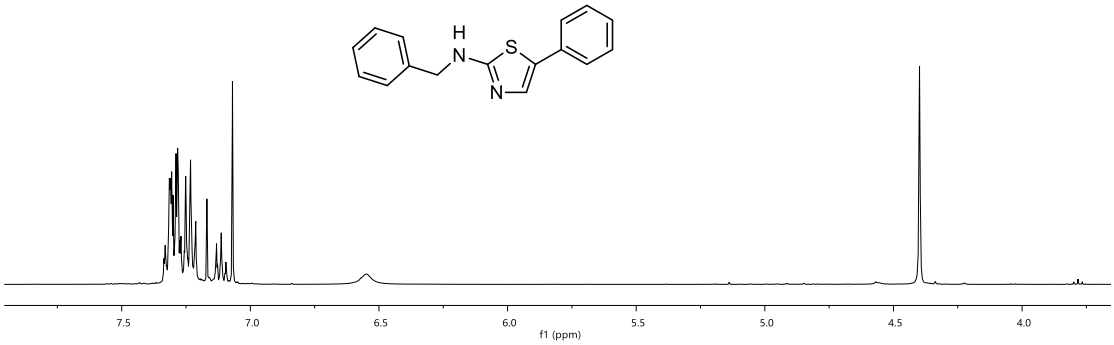


Figure 36. *^{1}H-NMR spectrum of thiazole **8**.*

Table 10. ^{1}H-NMR spectrum data *of thiazole **8**.*

Chemical Shift (ppm)	Multiplicity
7.36 - 7.19	m
7.15 - 7.08	m
7.07	s
4.40	s

The ^{1}H-NMR spectrum of the thiazole ring exhibits a fairly simple profile with two distinct regions. On one hand, the aromatic region displays two separate signal ranges, namely 7.36-7.19 and 7.15-7.08 ppm, corresponding to the benzyl and phenyl groups located on either side of the thiazole ring. Notably, the H-4 proton of the thiazole ring is observed as a singlet at 7.07 ppm. Lastly, the methylene system of the benzyl group appears as a singlet at 4.40 ppm.

An inspection of the ^{13}C-NMR spectrum of the compound reveals a prominent and unshielded signal observed at δ 169.4, assigned to C-2. Additionally, a cluster of signals in the aromatic region is observed within the range of 137.5 to 125.3 ppm, corresponding to the carbon atoms C-3 and C-4 of the thiazole ring, as well as the two phenyl groups. Lastly, the carbon atom of the benzyl methylene group resonates at 50.0 ppm.

4. CONCLUSIONS

Based on the work developed and described in the previous sections, the following conclusions can be drawn:

- The transformation of simple alcohols into thiazoles using the radical 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) as an oxidant and trichloroisocyanuric acid (TCCA) as a chlorinating agent is possible.
- The use of microwave irradiation is a suitable method for carrying out this type of transformation. The reactions occur within minutes, and the reaction mixtures are clean, facilitating purification. All of this is in line with the principles of Green Chemistry, which promote energy savings and waste minimization.
- The preparation of seven thiazoles, described here for the first time, has been achieved.

5. ABBREVIATIONS

P_2S_5 - Phosphorus pentasulfide

H_2S - Hydrogen sulfide

CS_2 - Carbon disulfide

NaH - Sodium hydride

DMF - Dimethylmethanamide

K_2CO_3 - Potassium carbonate

HBr - Hydrogen bromide

CuI - Copper(I) iodide

CuCl - Copper(I) chloride

CuBr - Copper(I) bromide

$CuBr_2$ - Copper bromide

$Cu(OAc)_2$ - Copper(II) acetate

$Cu(OTf)_2$ - Copper(II) triflate

$Fe(OAc)_2$ - Iron(II) acetate

$FeBr_2$ - Iron(II) bromide

$FeBr_3$ - Iron(III) bromide

$FeCl_3$ - Iron(III) chloride

$PdCl_2$ - Palladium(II) chloride

AgCl - Silver(I) chloride

NaSCN - Sodium thiocyanate

KSCN - Potassium thiocyanate

Na_2S - Sodium sulfide

S - Sulfur

NH_4SCN - Ammonium thiocyanate

N_2 - Nitrogen

CuI - Copper(I) iodide

DMSO - Dimethyl sulfoxide

O_2 - Dioxygen

S_8 - Octasulfur

$Pd(OAc)_2$ - Palladium(II) acetate

AcOH - Acetic acid

MW - Microwave

MAOS - Microwave-assisted organic synthesis

MCR - multi-component reaction

NMR - nuclear magnetic resonance

TLC - Thin layer chromatography

GC - Gas chromatography

HPLC - High Performance Liquid Chromatography

TCCA - Trichloroisocyanuric Acid

TEMPO - 2,2,6,6-tetramethyl-1-piperidinyloxy

DCMD - Dichloromethane

t-BuOH - *tert*-Butyl alcohol

$CDCl_3$- Deuterated chloroform

$NaHCO_3$ - Sodium bicarbonate

CH_3CN - Acetonitrile

EtOH- Ethanol

a - Broad

s - Singlet

d – Doublet

t - Triplet

q - Quartet

m - Multiplet

dd - Doublet of doublet

dt - Doublet of triplet

ddd - Doublet of doublet of doublet

ppm- Parts per million

J - Coupling constants

C_3H_7-Propyl group

Hz- Hertz

MHz- Megahertz

GHz- Gigahertz

6. BIBLIOGRAPHY

1. I. H. A. Ripain, N. Ngah, A brief review on the thiazole derivatives: Synthesis methods and biological activities, Malays. J. Anal. Sci **25** (2021) 257-267.

2. S. J. Kashyap, V. K. Garg, P. Sharma, N. Kumar, R. Dudhe, J. Gupta, Thiazoles: having diverse biological activities, Med. Chem. Res. **21** (2012) 2123-2132, doi: https://doi.org/10.1007/s00044-011-9685-2.

3. H. A. Sukinah R. S. Abdelwahed, Review of the synthesis and biological activity of thiazoles, Synth. Commun. **51** (2021) 670-700, doi: https://doi.org/10.1080/00397911.2020.1854787.

4. A.-M. Borcea, I. Ionuț, O. Crișan, O. Oniga, An overview of the synthesis and antimicrobial, antiprotozoal, and antitumor activity of thiazole and bisthiazole derivatives, Molecules **26** (2021) 624, doi: https://doi.org/10.3390/molecules26030624.

5. C. B. Mishra, S. Kumari, M. Tiwari, Thiazole: A Promising heterocycle for the development of potent CNS active agents, Eur. J. Med. Chem. **92** (2015) 1–34, doi: https://doi.org/10.1016/j.ejmech.2014.12.031.

6. G. S. Lingaraju, T. R. Swaroop, A. C. Vinayaka, K. S. S. Kumar, M. P. Sadashiva, K. S. Rangappa, An easy access to 4,5-disubstituted thiazoles via base-induced click reaction of active methylene isocyanides with methyl dithiocarboxylates, Synthesis **44** () 1373–1379, doi: https://doi.org/10.1055/s-0031-1290762.

7. D. Castagnolo, M. Pagano, M. Bernardini, M. Botta, Domino alkylation-cyclization reaction of propargyl bromides with thioureas/thiopyrimidinones: A new facile synthesis of 2-aminothiazoles and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones. Synlett. **13** (2009) 2093–2096, doi: https://doi.org/10.1055/s-0029-1217700.

8. X. Tang, J. Yang,Z. Zhu, M. Zheng, W. Wu, H. Jiang, Access to thiazole via copper-catalyzed [3+1+1]-type condensation reaction under redox-neutral conditions, J. Org. Chem. **81** (2016) 11461–11466, doi: https://doi.org/10.1021/acs.joc.6b02124.

9. X. Wang, X. Qiu, J. Wei, J. Liu, S. Song, W. Wang, N. Jiao, Cu-catalyzed aerobic oxidative sulfuration/annulation approach to thiazoles via multiple Csp3–H bond cleavage, Org. Lett. **20** (2018) 2632–2636, doi: https://doi.org/10.1021/acs.orglett.8b00840.

10. B. Chen, S. Guo, X. Guo, G. Zhang, Y. Yu, Selective access to 4-substituted 2-aminothiazoles and 4-substituted 5-thiocyano-2-aminothiazoles from vinyl azides and potassium thiocyanate switched by palladium and iron catalysts, Org. Lett. **17** (2015) 4698–4701, doi: https://doi.org/10.1021/acs.orglett.5b02152.

11. M. Asif, A. Ali, A. Zafar, M. Farhan, H. Khanam, S. M. Hadi, Microwave-assisted one pot synthesis, characterization, biological evaluation and molecular docking studies of steroidal thiazoles, J. Photochem. Photobiol. B **166** (2017) 104–115, doi: https://doi.org/10.1016/j.jphotobiol.2016.11.010.

12. S. Mamidala,S. R. Peddi,R. K. Aravilli, P. C. Jilloju, V. Manga, R. R. Vedula, Microwave irradiated one pot, three component synthesis of a new series of hybrid coumarin based thiazoles: Antibacterial evaluation and molecular docking studies, J. Mol. Struct. **1225** (2021) 129114, doi: https://doi.org/10.1016/j.molstruc.2020.129114.

13. M. V. N. de Souza, Synthesis and biological activity of natural thiazoles: An important class of heterocyclic compounds, J. Sulfur Chem. **26** (2005) 429-449, doi: https://doi.org/10.1080/17415990500322792.

14. P. M. Jadhav, S. Kantevari, A. B. Tekale, S. V. Bhosale, R. P. Pawar, S. U. Tekale, A review on biological and medicinal significance of thiazoles, Phosphorus Sulfur Silicon Relat. Elem. **196** (2021) 879-895, doi: https://doi.org/10.1080/10426507.2021.1945601

15. M. F. Arshad, A. Alam, A. A. Alshammari, M. B. Alhazza, I. M. Alzimam, M. A. Alam, G. Mustafa, M. S. Ansari, A. M. Alotaibi, A. A. Alotaibi, S. Kumar, S. M. B. Asdaq, M. Imran, P. K. Deb, K. N. Venugopala, S. Jomah, Thiazole: A versatile standalone moiety contributing to the development of various drugs and biologically active agents, Molecules **27** (2022) 3994, doi: https://doi.org/10.3390/molecules27133994.

16. S. Kumar, R. Aggarwal, Thiazole: a privileged motif in marine natural products, Mini-Rev. Org. Chem. **16** (2019) 26-34, doi: http://dx.doi.org/10.2174/1570193X15666180412152743.

17. R. Dahiya, S. Dahiya, N. K. Fuloria, S. Kumar, R. Mourya, S. V. Chennupati, S. Jankie, H. Gautam, S. Singh, S. K. Karan, S. Maharaj, S. Fuloria, J. Shrivastava, A. Agarwal, S. Singh, A. Kishor, G. Jadon, A. Sharma., Natural bioactive thiazole-based peptides from marine resources: structural and

pharmacological aspects, Mar. Drugs. **18** (2020) 329. doi: https://doi.org/10.3390/md18060329.

18. D. Sharma, V. Sharma, A. Sharma, R. Goyal, R. K. Tonk, V. K. Thakur, P. C. Sharma, , Green chemistry approaches for thiazole containing compounds as a potential scaffold for cancer therapy, Sustain. Chem. Pharm. **23** (2021) 100496, doi: https://doi.org/10.1016/j.scp.2021.100496

19. A. S Grewal, K. Kumar, S. Redhu, S. Bhardwaj, Microwave assisted synthesis: a green chemistry approach, Int. Res. J. Pharm. App. Sci. **3** (2013) 278-285.

20. R. N. Rao, S. Jena, M. Mukherjee, B. Maiti, K. Chanda, Green synthesis of biologically active heterocycles of medicinal importance: a review, Environ. Chem. Lett. **19** (2021) 3315–3358, doi: https://doi.org/10.1007/s10311-021-01232-9.

21. A. de la Hoz, A. Díaz-Ortiz, P. Prieto, Microwave-assisted green organic synthesis, in G. Stefanidis, A. Stankiewicz (Eds.), Alternative Energy Sources for Green Chemistry. Vol. 47, RSC Green Chemistry, Cambridge, UK, 2016, pp. 1-33.

22. S. Nain, R. Singh, S. Ravichandran, Importance of microwave heating in organic synthesis, Adv. J. Chem.-Sect. A, **2** (2019) 94–104, doi: https://doi.org/10.29088/SAMI/AJCA.2019.2.94104.

23. C. O. Kappe, The use of microwave irradiation in organic synthesis. From laboratory curiosity to standard practice in twenty years, Chimia, **60** (2006) 308, doi: https://doi.org/10.2533/000942906777836273.

24. F. Langa, P. de la Cruz, A. de la Hoz, A. Díaz-Ortiz, E. Díez-Barra, Microwave irradiation: More than just a method for accelerating reactions, Contemp. Org. Synth., **4** (1997) 373–386, doi: https://doi.org/10.1039/CO9970400373.

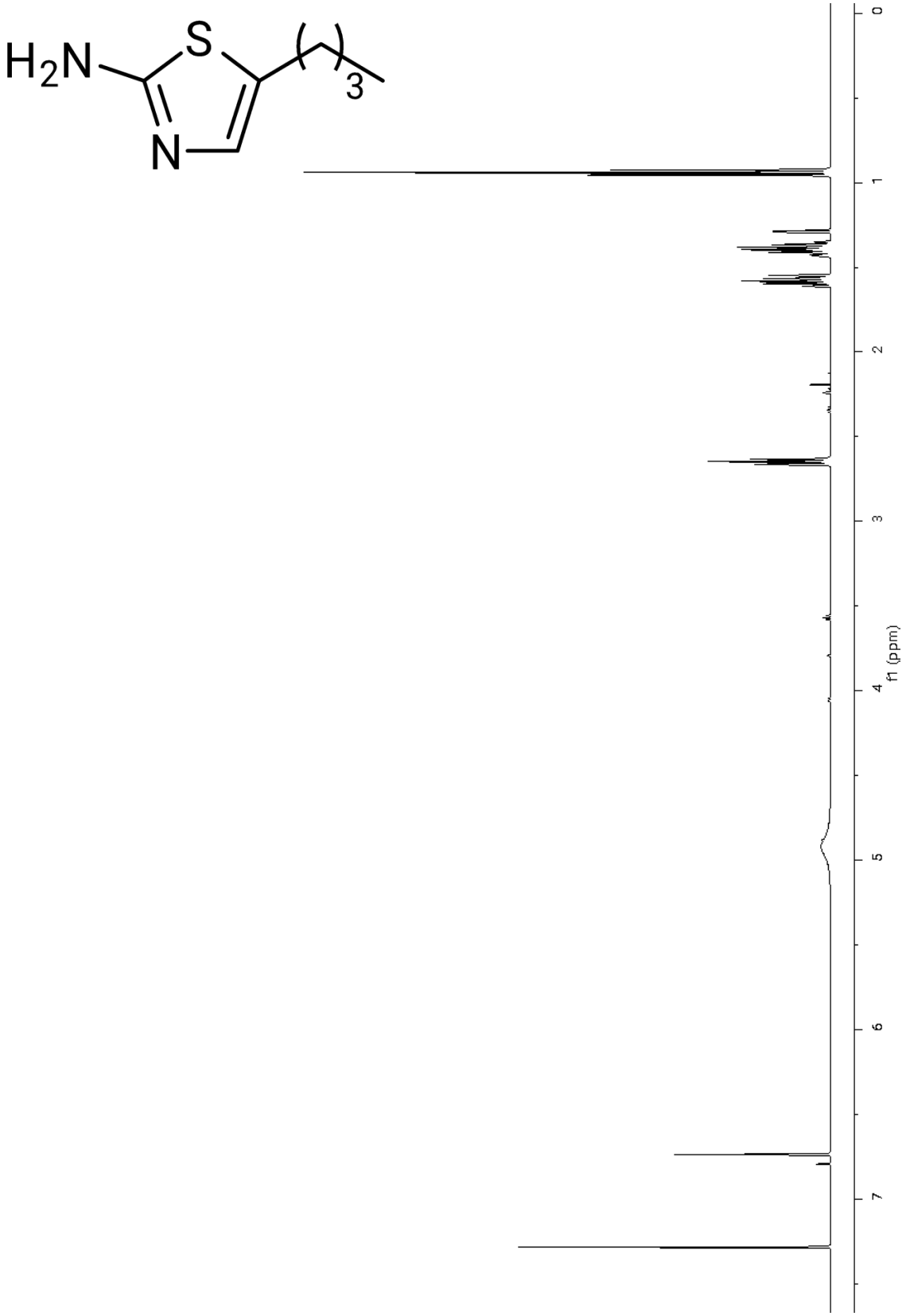
25. A. R.Yadav, K. M. Shrinivas, A brief review: Microwave chemistry and its applications, Res. J. Pharma. Dosage Forms and Tech. , **12** (2020) 191-197, doi: https://doi.org/10.5958/0975-4377.2020.00033.6.

26. Y. Jing, C. G. Daniliuc, A. Studer, Direct conversion of alcohols to α-chloro aldehydes and α-chloro ketones, Org. Lett. **16** (2014) 4932–4935, doi: https://doi.org/10.1021/ol5024568.

7. SUPPLEMENTARY

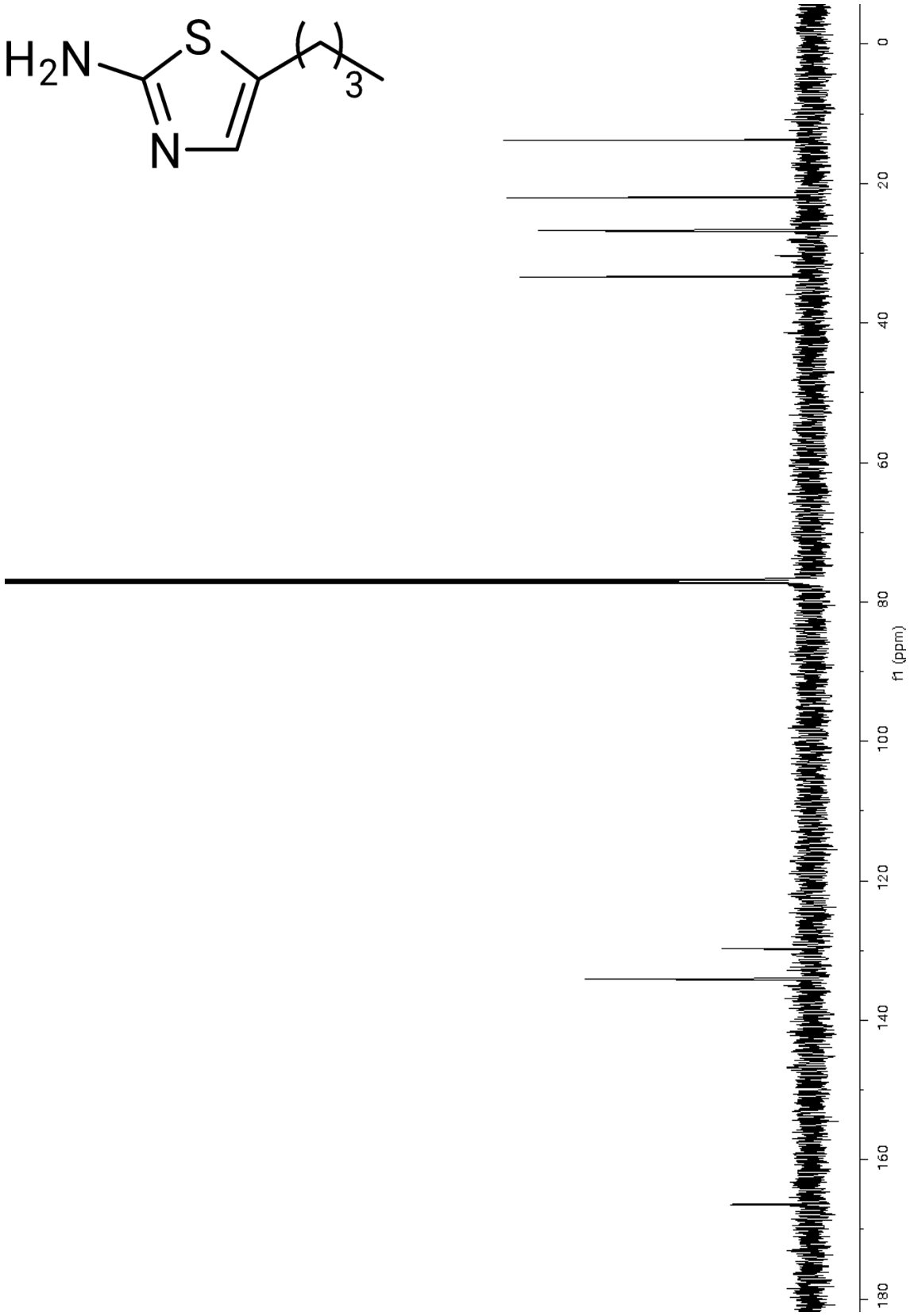
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 2.65 (t, *J* = 2,65 Hz, 2H), 1.62 – 1.53 (m, 4H), 1.39 (dq, *J* = 14.5, 7.3 Hz, 4H), 0.94 (t, *J* = 7.4 Hz, 3H).

Figure S1. *^{1}H-NMR spectrum of 5-butylthiazol-2-amine,* ***3***



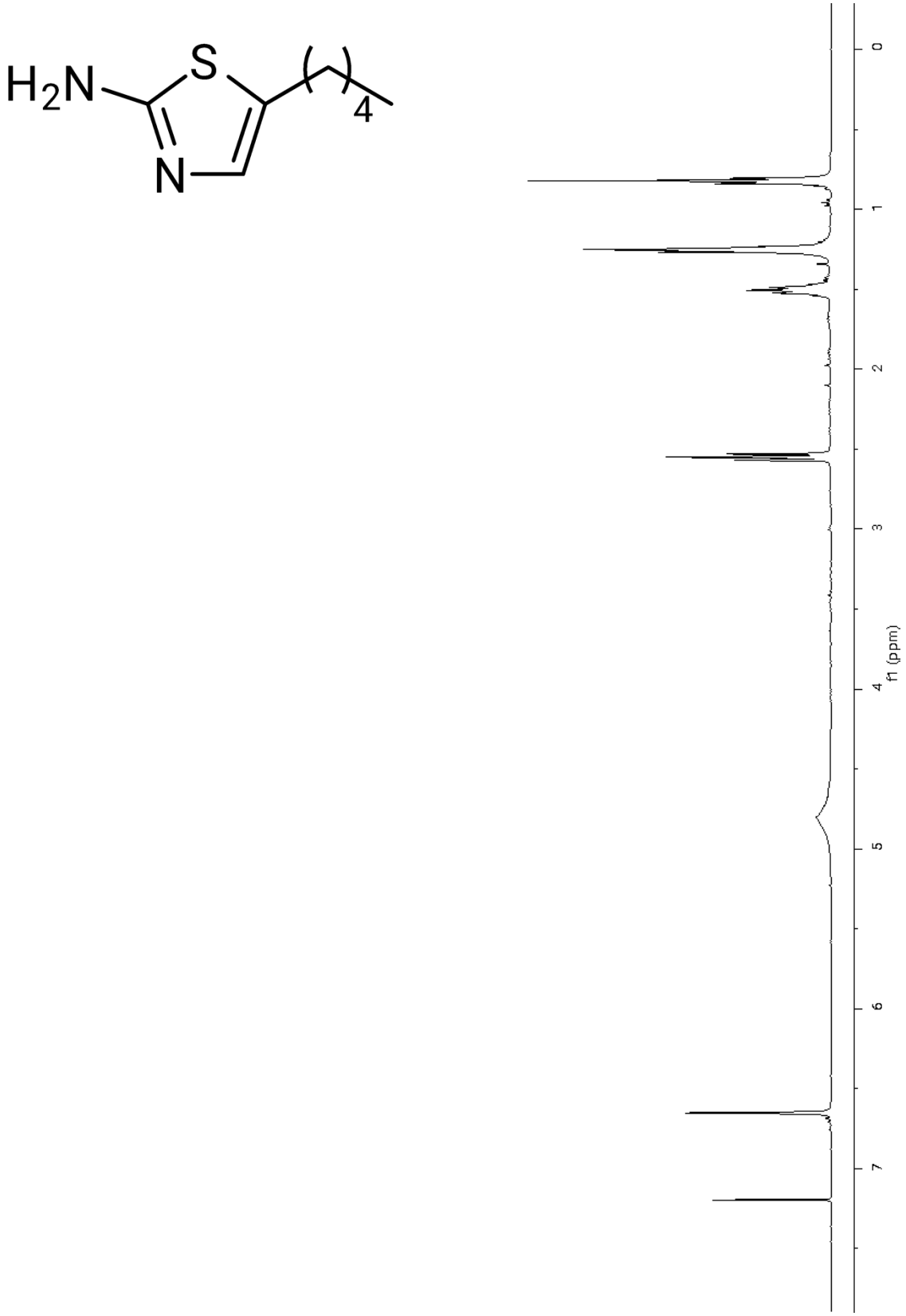
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 134.1, 129.7, 33.4, 26.8, 22.0, 13.8.

Figure S2. *^{13}C-NMR spectrum of 5-butylthiazol-2-amine,* ***3***



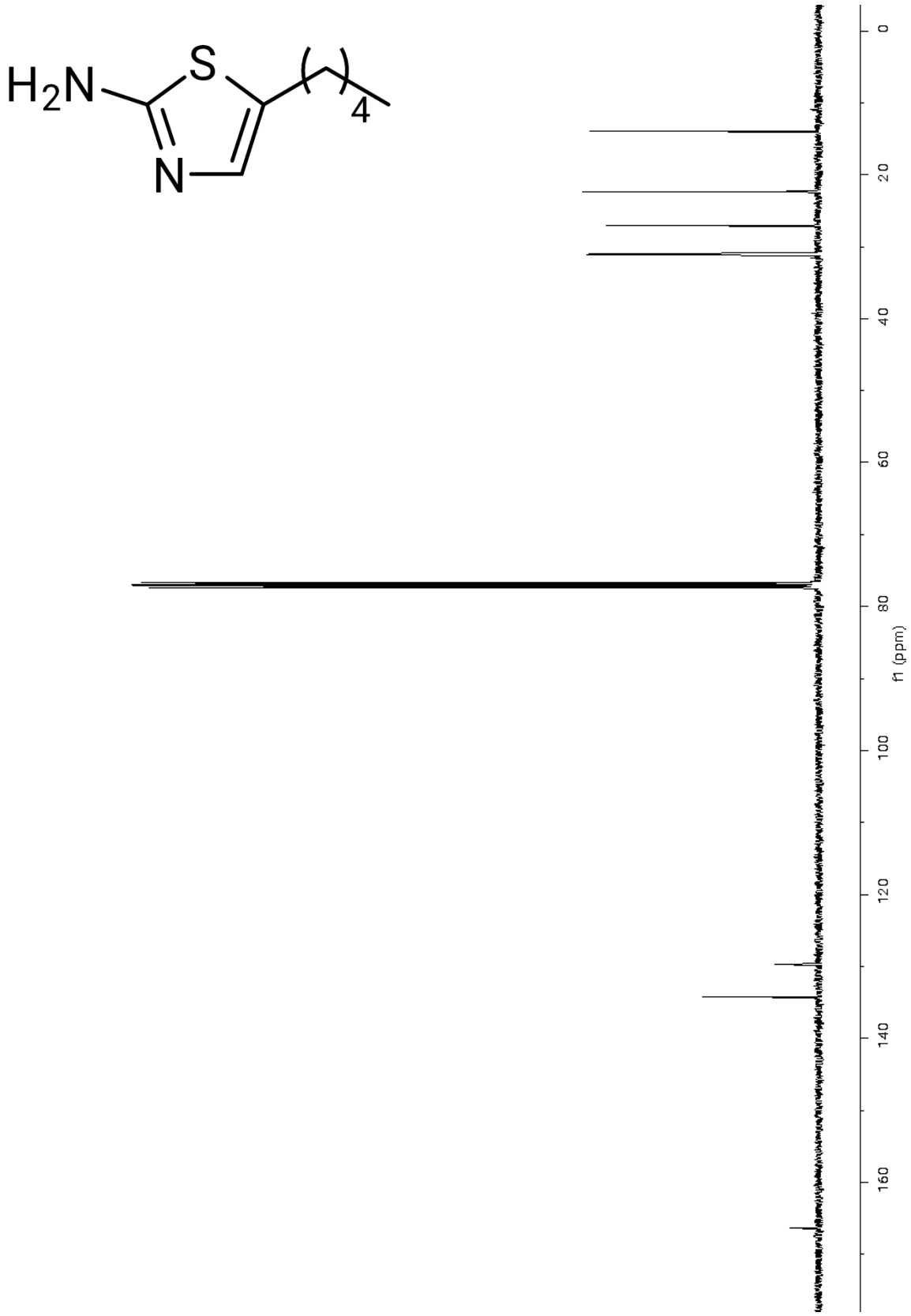
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 2.55 (t, *J* = 7.1 Hz, 2H), 1.61 – 1.39 (m, 2H), 1.33 – 1.14 (m, 4H), 0.82 (t, *J* = 6.7 Hz, 3H).

Figure S3. *^{1}H-NMR spectrum of 5-pentylthiazol-2-amine,* ***4***



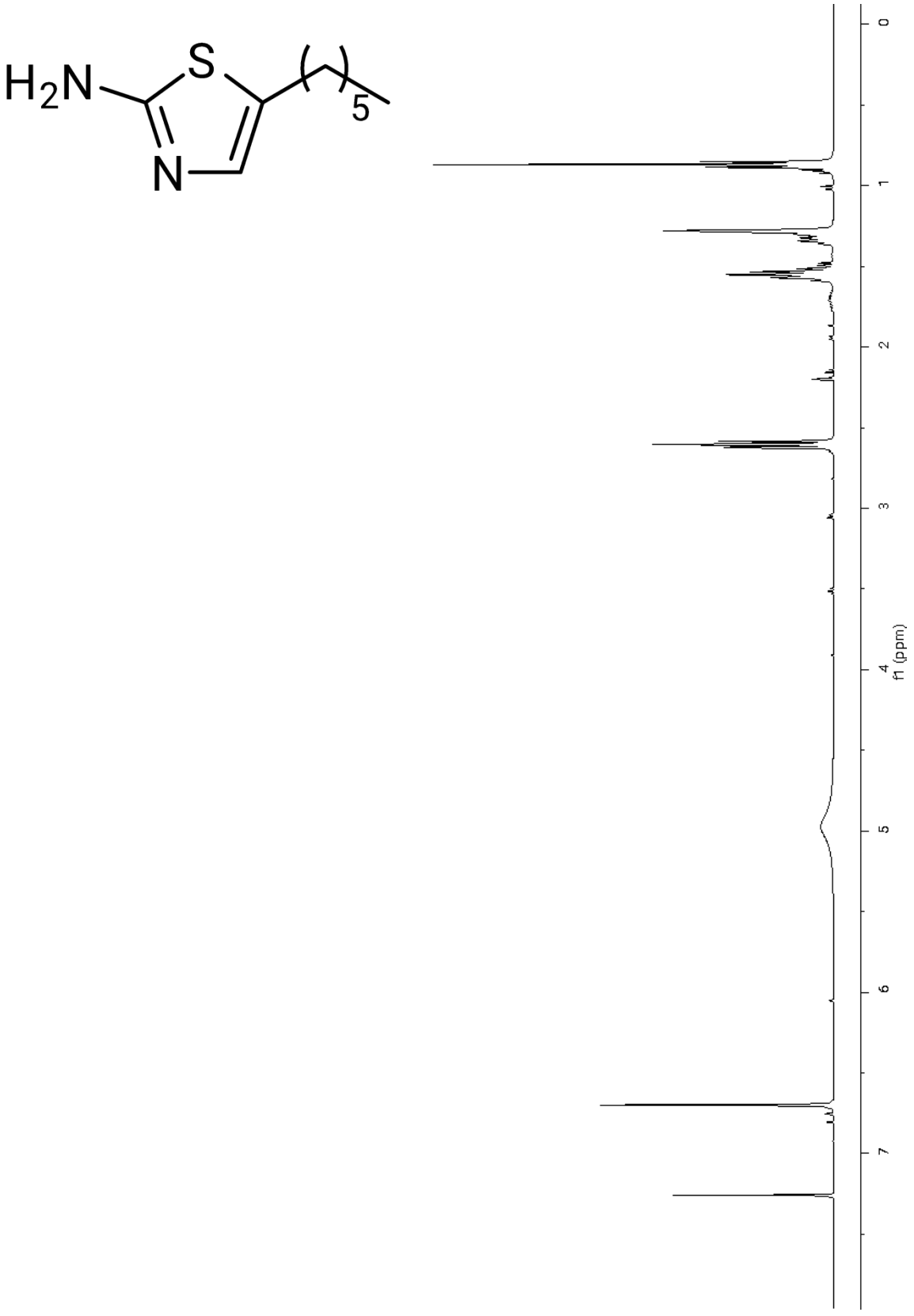
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.3, 129.8, 31.1, 31.0, 27.1, 22.4, 14.00.

Figure S4. *^{13}C-NMR spectrum of 5-pentylthiazol-2-amine,* ***4***



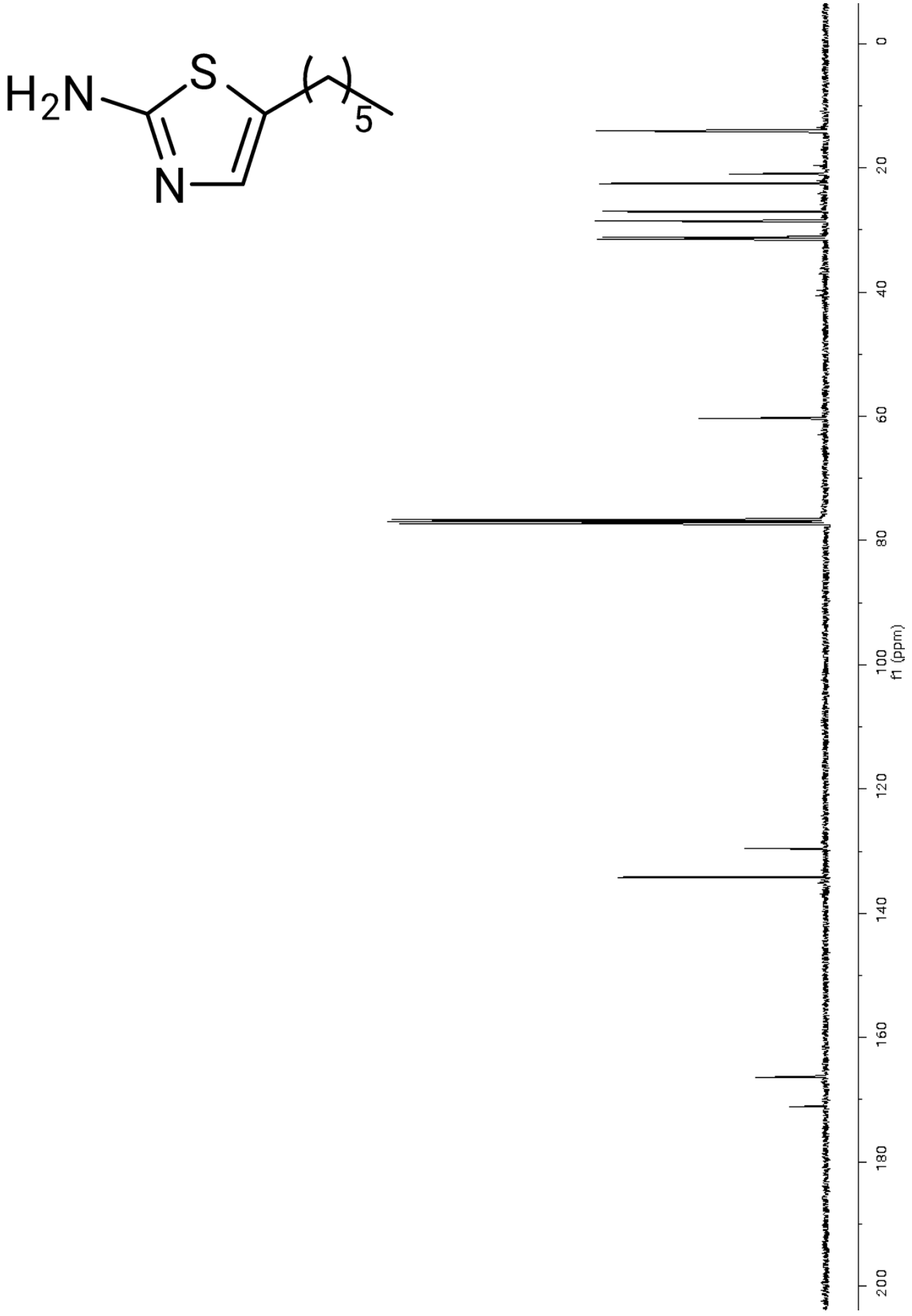
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 2.60 (td, *J* = 7.3, 1.0 Hz, 4H), 1.65 – 1.49 (m, 5H), 1.42 – 1.15 (m, 6H), 0.87 (t, *J* = 6.7 Hz, 3H).

Figure S5. *^{1}H-NMR spectrum of 5-hexylthiazol-2-amine,* ***2***



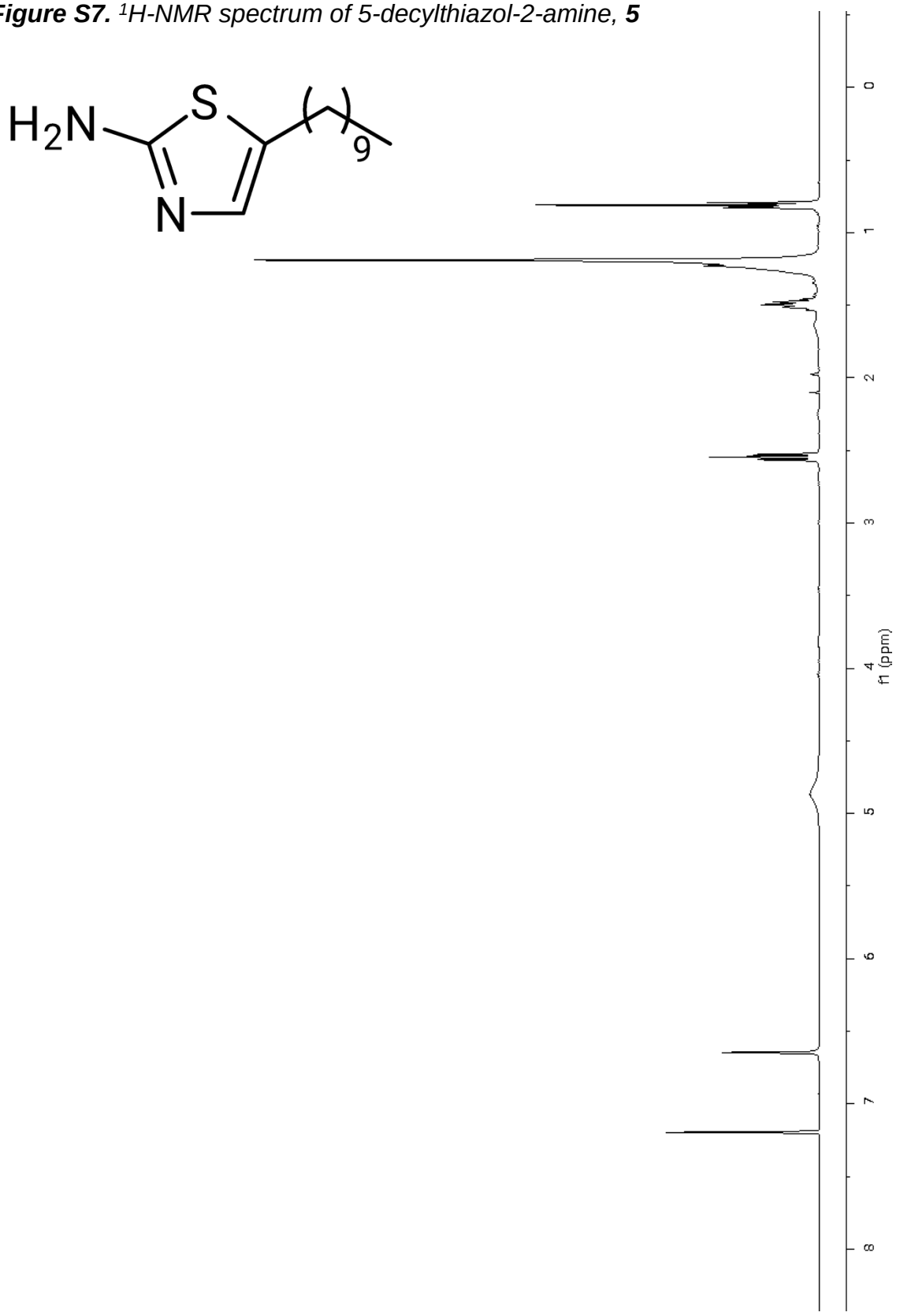
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.2, 129.6, 31.5, 31.2, 28.6, 27.0, 22.5, 14.0.

Figure S6.*^{13}C-NMR spectrum of 5-hexylthiazol-2-amine,* ***2***



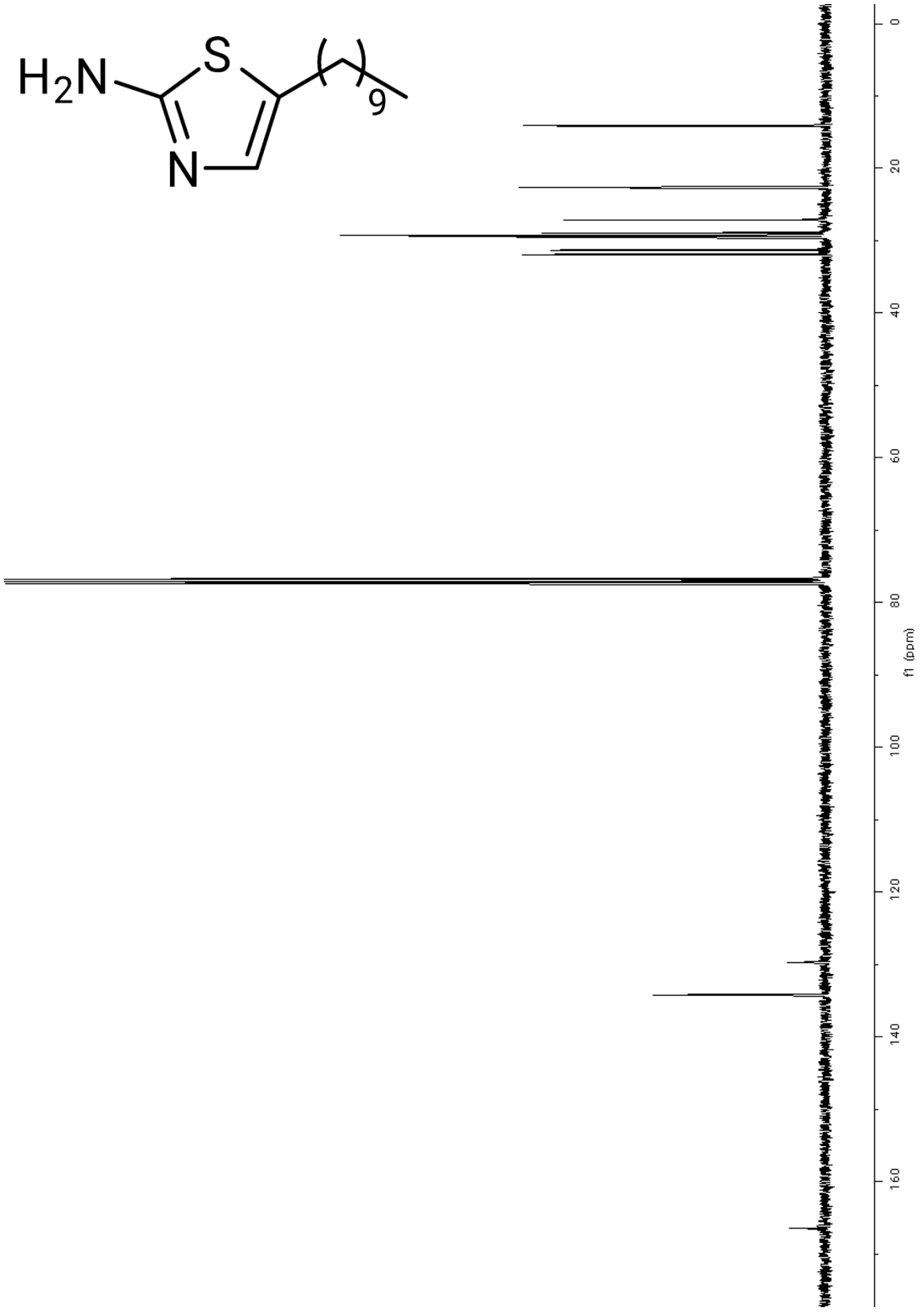
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 2.66 – 2.44 (m, 3H), 1.59 – 1.41 (m, 3H), 1.21 (d, *J* = 15.8 Hz, 20H), 0,81 (t, *J* = 6.6 Hz, 3H).

Figure S7. *^{1}H-NMR spectrum of 5-decylthiazol-2-amine,* ***5***



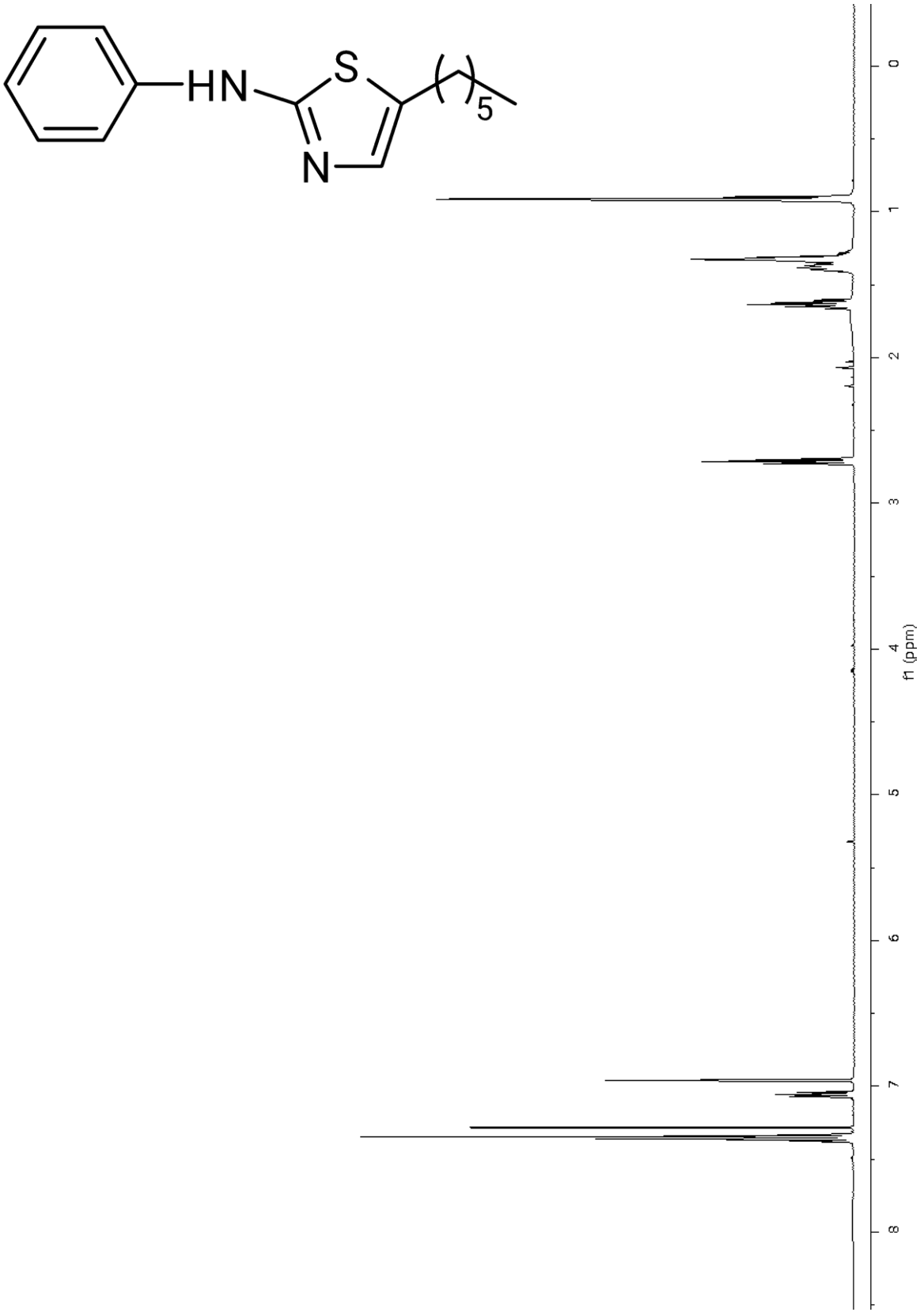
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 134.2, 129.7, 31.9, 31.3, 29.6, 29.6, 29.3, 29.0, 27.1, 22.7, 14.1.

Figure S8. *^{13}C-NMR spectrum of 5-decylthiazol-2-amine,* ***5***



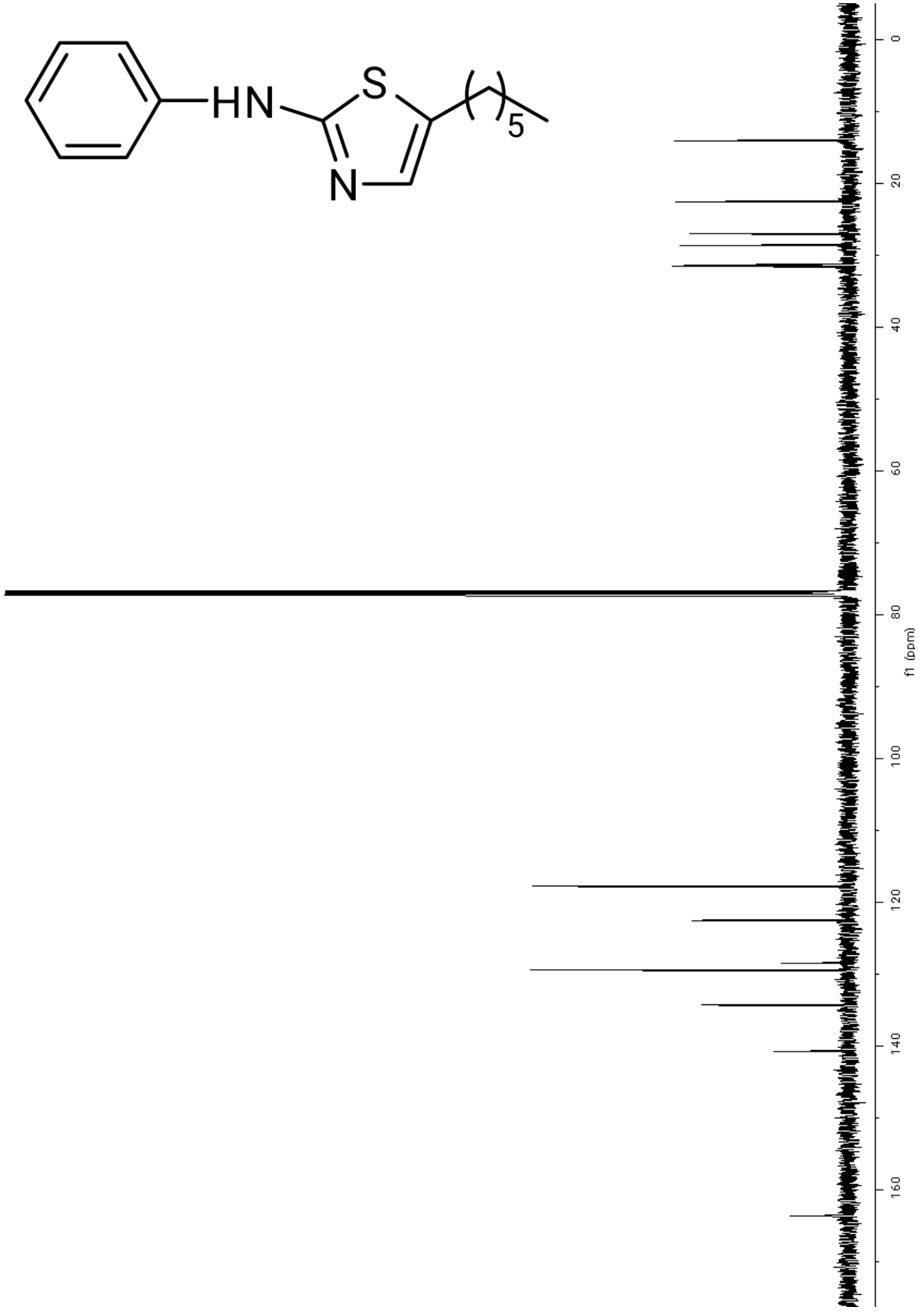
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 4H), 7.13 – 7.01 (m, 1H), 6.96 (t, *J* = 1.1 Hz, 1H), 2.71 (td, *J* = 7.5, 1.1 Hz, 2H), 1.71 – 1.50 (m, 2H), 1.44 – 1.20 (m, 6H), 0.91 (t, *J* = 6.5 Hz, 3H).

Figure S9. *^{1}H-NMR spectrum of 5-hexyl-N-phenylthiazol-2-amine,* ***6***



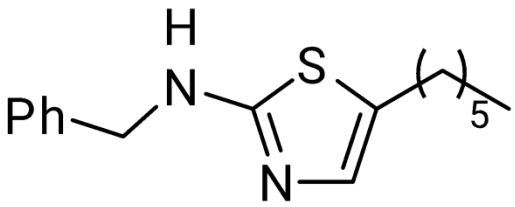
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7, 140.7, 134.3, 129.4, 128.4, 122.5, 117.8, 31.5, 31.3, 28.7, 27.0, 22.6, 14.1.

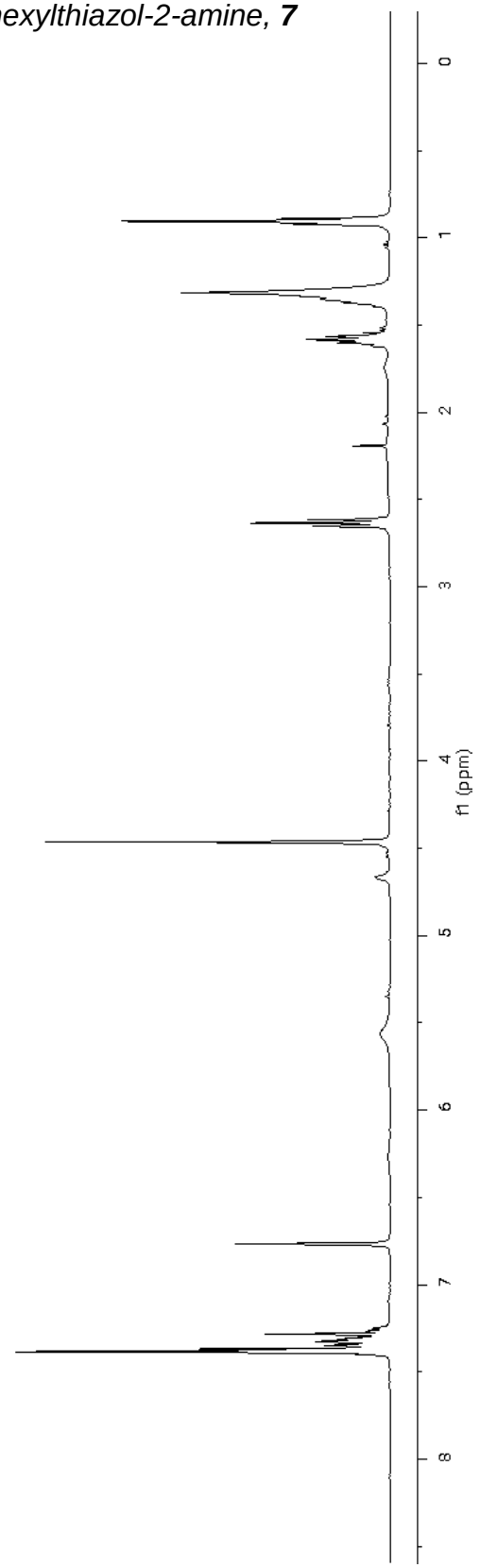
Figure S10.*^{13}C-NMR spectrum of 5-hexyl-N-phenylthiazol-2-amine,* ***6***



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.10 (m, 5H), 6.77 (s, 1H), 4.46 (s, 2H), 2,63 (t, *J* = 7.6, 2H), 1.58 (m, 2H), 1.47 – 1.18 (m, 7H), 0.91 (t, *J* = 6.6, 3H).

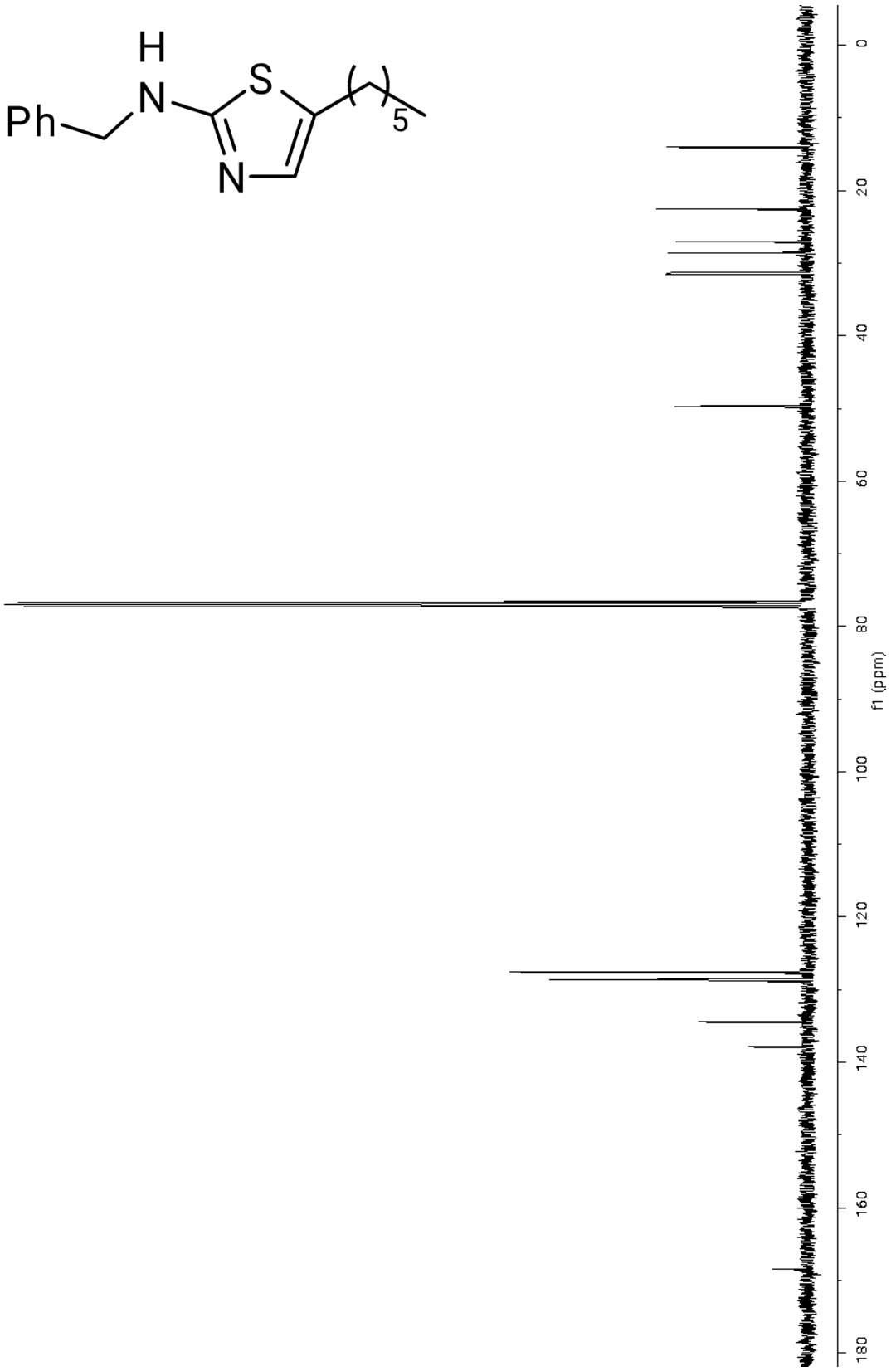
Figure S11. *^{1}H-MR spectrum of N-benzyl-5-hexylthiazol-2-amine,* ***7***





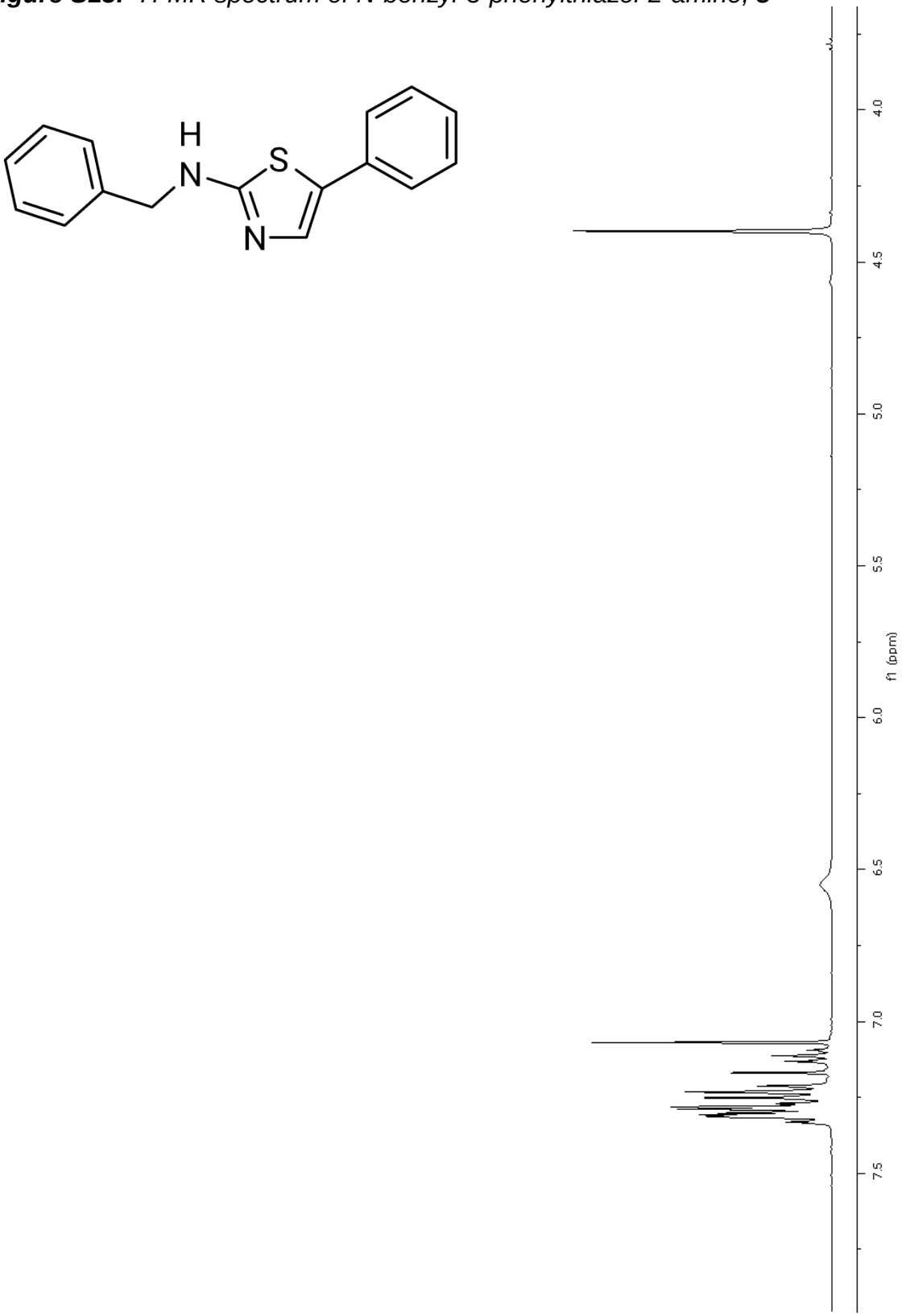
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 137.9, 134.5, 128.9, 128.7, 127.6, 127.6, 127.5, 49.7, 31.5, 31.2, 28.6, 27.1, 22.6, 14.1.

Figure S12. *^{13}C-NMR spectrum of N-benzyl-5-hexylthiazol-2-amine,* ***7***



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 9H), 7.15 – 7.08 (m, 1H), 7.07 (s, 1H), 4.40 (s, 2H).

Figure S13. *^{1}H-MR spectrum of N-benzyl-5-phenylthiazol-2-amine,* ***8***



^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 137.5, 134.5, 132. 4, 128.9, 128.8, 127.9, 127.8, 126.7, 126.6, 125.3, 50.0.

Figure S14.*^{13}C-NMR spectrum of N-benzyl-5-phenylthiazol-2-amine,* ***8***