



Faculty of Sciences

Department of Chemistry and Forensic Sciences

**CHALCONES IN THE SYNTHESIS OF HETEROCYCLIC
COMPOUNDS: PYRAZOLES, FLAVANS AND PYRIMIDINES**

by

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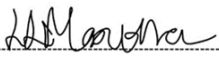
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DEDICATION

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LIST OF ABBREVIATIONS

°C: degree Celsius

FT-IR: Fourier-Transform Infrared Spectroscopy

¹H NMR: Proton Nuclear Magnetic Resonance

¹³C NMR: Carbon-13 Nuclear Magnetic Resonance

TLC: Thin Layer Chromatography

TMS: Tetramethylsilane

DMF: Dimethylformamide

EAA: Ethyl acetoacetate

EBA: Ethyl bromoacetate

DABCO: 1,4-diazabicyclo [2.2.2] octane

DES: Deep eutectic solvent

DNA: Deoxyribonucleic acid

RNA: Ribonucleic acid

r.t: Room temperature

n.r: No reaction

ABSTRACT

This study was aimed at the synthesis of a library of heterocyclic compounds. The initial reactions involved the condensation of substituted acetophenones with benzaldehyde derivatives in either ethanolic solution of sodium hydroxide or by grinding method to yield chalcones. The percentage yield of the products was substantially higher by grinding method compared to that of ethanolic NaOH conventional method. It is noteworthy that the grinding technique is an environmentally friendly method that avoids the organic solvents pollution problem in organic synthesis. Thin layer chromatography was used to follow the reactions. The structures of all compounds were characterized by spectroscopic techniques and verified by comparison of their data with literature of similar compounds. In total eight chalcones were synthesized being (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **39**, (*E*)-3-(4-fluoro-2-hydroxyphenyl)-1-phenylprop-2-en-1-one **40**, (*E*)-1-(4-aminophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one **41**, (*E*)-3-(4-fluorophenyl)-1-(4-nitrophenyl)prop-2-en-1-one **42**, (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one **43**, (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one **45**, (*E*)-1,3-bis(4-fluorophenyl)prop-2-en-1-one **46**, and (*E*)-1-(4-ethylphenyl)-3-(4-fluorophenyl)prop-2-en-1-one **47** in yields of 65-79%. Methanolic 2'-hydroxychalcones **39-41**, were reduced on subsequent addition of sodium borohydride to afford alcohols, **51-53**, which in the presence of glacial acetic acid cyclized to the corresponding flavans. Three flavans were obtained namely 2-phenylchromane **54**, 5-fluoro-2-phenylchromane **55**, and 4-(chroman-2-yl) aniline **56** in 80-82% yields. The chalcones employed to make flavans were also used in the attempted synthesis of benzo[*c*]chromen-6-one using Et₃N as the base with just a 15% conversion. Reaction of chalcones with hydrazine hydrate in the presence of acetic acid produced seven pyrazolines: 2(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)phenol **60**, 5-(4-fluorophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole **61**, 1-(5-(4-nitrophenyl)-3-phenyl-

4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **62**, 1-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **63**, 1-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **64**, 1-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **65** and 1-(3-(4-ethylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **66**, in 69-77% yields. The chalcones were further reacted with thiourea in the presence of a base in ethanol, which led to the formation of pyrimidine derivatives. The pyrimidines were described as mixture made of three compounds in 67-69% yields. The pyrimidines synthesized were 2-(2-mercapto-6-phenyl-1,2-dihydropyrimidin-4-yl) phenol **67a**, 4-(2-hydroxyphenyl)-6-phenylpyrimidine-2(1*H*)-thione **67b** and 2-(2-mercapto-6-phenylpyrimidin-4-yl) phenol **67c**, 4-(4-fluorophenyl)-6-(4-nitrophenyl)-1,2-dihydropyrimidine-2-thiol **68a**, 4-(4-fluorophenyl)-6-(4-nitrophenyl)pyrimidine-2(1*H*)-thione **68b**, 4-(4-fluorophenyl)-6-(4-nitrophenyl)pyrimidine-2-thiol **68c**, 4,6-diphenyl-1,2-dihydropyrimidine-2-thiol **69** and 6-(4-fluorophenyl)-4-phenyl-1,2-dihydropyrimidine-2-thiol **70**. The reported synthetic method for compound **58-59**, is an alternative to hazardous methods reported in literature.

CHAPTER 1

INTRODUCTION

1.1 Heterocyclic Compounds

With its origins rooted in organic synthesis and medicinal chemistry, heterocyclic compounds present themselves as a fundamental division of organic chemistry. Heterocycles form by far the most extensive and most varied family of the classical divisions of organic chemistry (Rawat et al., 2021). They are essential building blocks that are most frequently encountered in pharmaceutically relevant scaffolds and numerous drugs, many of which are being used clinically, such as vincristine, morphine, chloroquine, meperidine, sulphadiazine (Shukla et al., 2017). More than 95% of pharmaceuticals contain at least one heterocyclic fragment (Jiang et al., 2010). Heterocyclic compounds may thus be defined as compounds having a ring structure either as simple aromatic or non-aromatic moiety consisting of at least one element such as nitrogen, oxygen and sulfur in addition to carbon as part of the ring (Shaik et al., 2020) (**Figure 1**).

Heterocyclic compounds are essential to life as they play a vital function in the metabolism of all living cells. Examples include the essential amino acids such as proline, histidine and tryptophan; oxygen-carrying pigment haemoglobin and its breakdown products, haem derivatives in the blood; the chlorophylls crucial for photosynthesis; the hormones kinetin, heteroauxine, serotonin and histamine, the paired nitrogenous bases found in DNA and RNA (cytosine, guanine, thymine, adenine and uracil) and most of the sugars contain different heterocyclic nuclei. They also have application in various chemical, biomedical, and industrial significances, including vulcanization accelerators, reprography, cosmetics, plastics,

antioxidants, solvents and information storage (Majumder et al., 2013). Apart from constituting the enormous diversity of organic molecules, they have immense importance in biological and industrial applications. Heterocyclics prevalently exist in numerous natural products, such as hormones, vitamins, alkaloids, antibiotics, herbicides, and dyes.

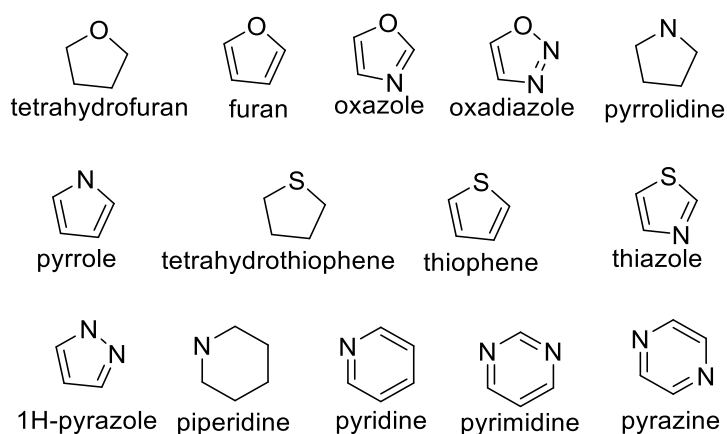


Figure 1. Examples of some heterocyclics with nitrogen, sulfur and oxygen.

1.2 Statement of the problem

Public health officials worldwide are sounding the alarm on the need for new anti-microbial and anticancer agents to counter a growing number of communicable and non-communicable diseases. Resistance to clinically used antibiotics and the ever-increasing instances of cancer-related mortality is a global health care crisis faced by the health care systems in the 21st century (Kesari et al., 2021; Rawat et al., 2021). On the other hand, there is a growing gap between the need for new active agents, discovery and development of new drugs. Heterocyclic small molecules sourced from synthetic protocols or natural products would be

solutions to the identification of potentially biologically active agents from compound libraries. The design and search for small heterocyclic molecules is on-going in the research studies the world over.

1.3 Aims of the study

The aim of the study is to synthesize chalcones which would be used as synthons for heterocyclic compounds: flavans, pyrazoles and pyrimidine. The bias would be towards compounds having fluoro- or nitro- groups.

1.4 Objectives of the study

1. To synthesize chalcones both by the conventional aldol condensation and the green aldol condensation.
2. To use chalcones as precursors in the synthesis of pyrazoles, flavans, and pyrimidines.
3. To evaluate the effects of nitro and fluoro substituents on the acetophenones and benzaldehyde derivatives on the formation of chalcones.

1.5 Significance of the Study

The diverse biological activities of small heterocyclic molecules such as antioxidant, antimicrobial, anti-tubercular, anti-inflammatory, antimalarial, cytotoxicities activities and enzyme inhibitions have sustained interest in their synthesis. Thereafter biological evaluations, following the synthesis part will be investigated. The target compounds would make-up a library of heterocyclic compounds in the form of chalcones, flavans, pyrimidines and pyrazoles for the various biological studies such as anticancer, anti-tubercular and antimicrobial to be carried out by biology graduate students.

CHAPTER 2

LITERATURE REVIEW

2.1 Pyrazoles

Pyrazoles are aromatic heterocyclic frames belonging to the azole family (Karrouchi et al., 2018). They are five-membered ring structure containing two nitrogen atoms bound to each other and three carbon atoms with double bonds at adjacent positions (Gomes et al., 2020). The nitrogen atom at position one (N1) is “pyrrole-like” because its unshared electrons are conjugated with the aromatic system, whereas nitrogen at position two (N2) is “pyridine-like” since its unshared electrons are not compromised with resonance (Kumar et al., 2019; Kumar et al., 2013; Kumari et al., 2012; Tigreros & Portilla, 2020) (**Figure 2**). Pyrazole is considered as structural isomer of imidazole, which has a π -access aromatic molecule with the nitrogen atom at positions 1- and 2- dissimilar to imidazole having nitrogen atom at positions 1 and 3. Pyrazole is thus also identified by the name “1, 2-diazole” (Alnufaie, 2020; Faria et al., 2017).

An essential structural characteristic of pyrazole is its prototropic tautomerism, generating three tautomers, with the structure of 1*H*-pyrazole being the most relevant for it preserves aromaticity. Varying the position, the number of double bonds, the degree of saturation or unsaturation, presence of hydrogen in the pyrazole nucleus, the fusion of the pyrazole moiety to the benzene ring, about nine structural isomers can be generated, which are further classified into four categories (pyrazoles, benzopyrazoles, pyrazolines and pyrazolidine) (Kumar et al., 2013).

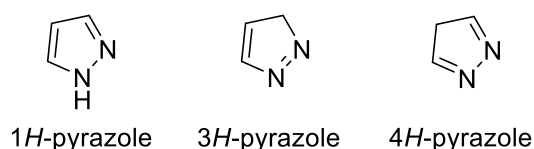


Figure 2. Structures of three types of pyrazoles.

The first pyrazole isolated from natural sources was 3-*n*-nonyl-1*H*-pyrazole **1**, which was extracted from *Houttuynia cordata*, a common plant from tropical Asia. β -(1-pyrazolyl)

alanine **2** was

isolated from watermelon

seeds (**Figure**

3).

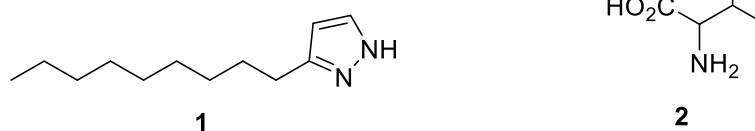


Figure 3. Pyrazoles extracted from natural products.

2.1.1 Pyrazole biological importance

Even though pyrazoles are rarely found in natural products, they have engrossed a unique position in the design and synthesis of novel biologically active agents that exerts important pharmacological activities. Pyrazole represents a critical motif that constitutes the core structure of numerous biologically active compounds and thus represents an exciting template for medicinal and combinatorial chemistry (Kumar et al., 2011). Pyrazole and its derivatives exhibit a wide range of bioactivities (Aziz et al., 2020; Lv et al., 2010), such as antimicrobial (Piste, 2014a), antiviral, antitumor, anti-inflammatory, analgesic, fungistatic, anti-hyperglycemic (Vujasinović et al., 2012), antipyretic, antipsychotic, pesticidal and insecticidal (Emtiazi et al., 2015), anticancer, sodium channel blockers, anti-tubercular, antihypertensive, anti-glaucoma, antioxidant, antidepressant, anxiolytic, neuroprotective and

antidiabetic activities (Kumar et al., 2013). Although the skeleton of pyrazole plays an important role in biological effects, the type of peripheral substituent is also crucial (Zheng et al., 2010). Literature reveals that various *N*-substituted pyrazoles have been implemented as antitumor, anti-leukemic, anti-angiogenic, anti-proliferative, proapoptotic, autophagy, DNA interacting and anti-tubulin agents (El-Karim et al., 2015). Among these, *N*-aryl pyrazoles have remarkable pharmacological activities such as tumour-necrosis inhibitor, hypoglycemic, hypolipidemic and anti-inflammatory properties (Assali et al., 2020; Inkaya et al., 2012). Some aryl pyrazoles are reported to possess nonnucleoside HIV-1 reverse transcriptase inhibitory activity (Genin et al., 2000).

In addition, some are established to be exerting anticancer effects through the inhibition of different types of enzymes, proteins and receptors that play a significant role in cell division (Kasiotis et al., 2014). Compound **3** orientated with *N*-phenylpyrazole nucleus was invented by Vertex pharmaceuticals as an inhibitor of Src and c-Jun *N*-terminal kinases (JNKs) (**Figure 4**) (Parang and Sun, 2005).

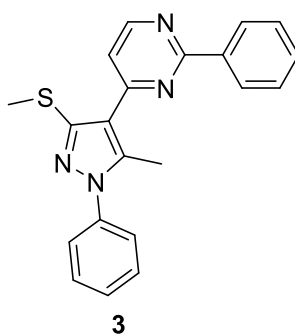
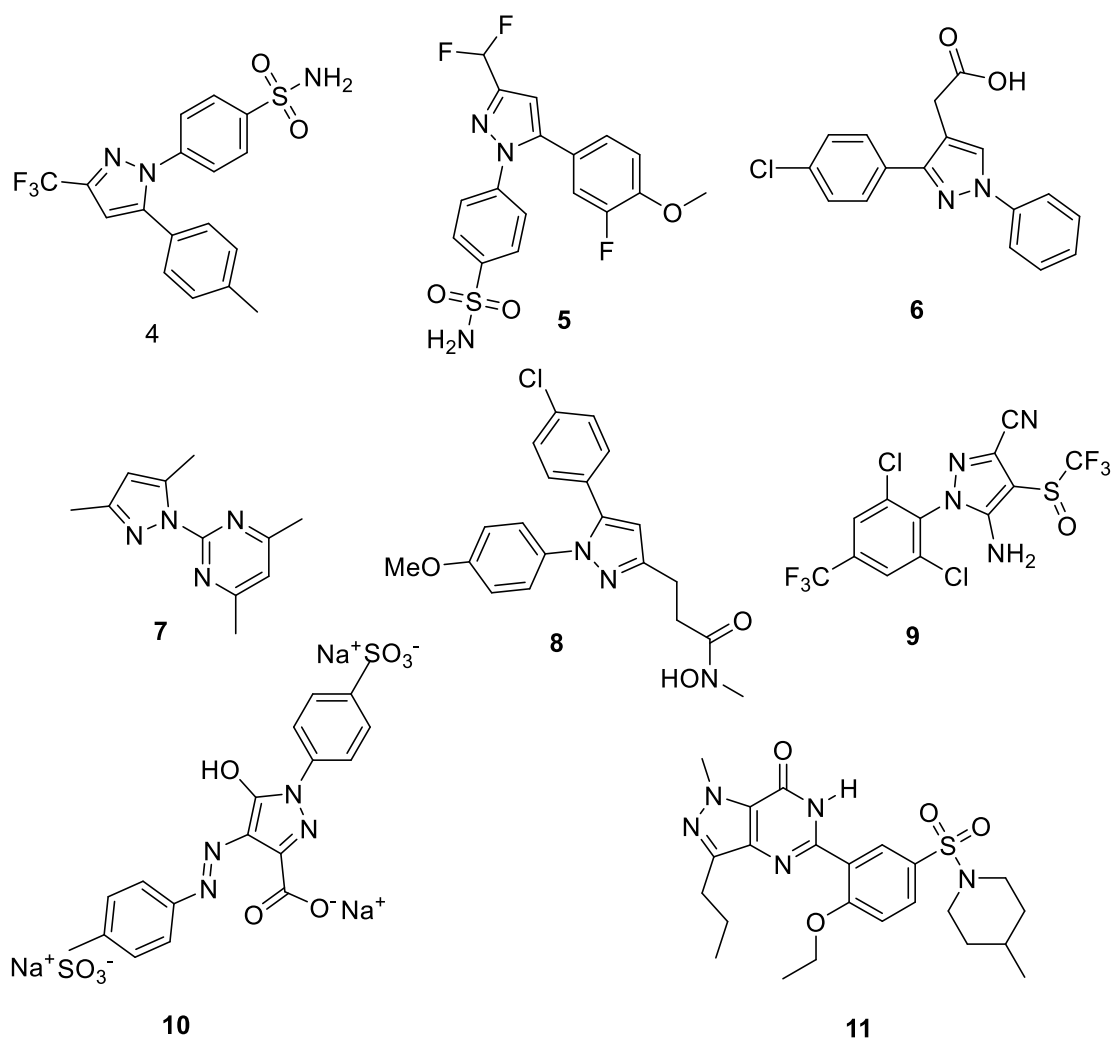


Figure 4. Example of *N*-substituted pyrazole as Src protein tyrosine kinase inhibitor

Some of the clinical drugs (**Figure 5**), consisting of pyrazole as a basic moiety and approved for use, includes celecoxib **4**, deracoxib **5**, lonazolac **6**, mepirizole **7** and tepoxalin **8** as COX-2 selective nonsteroidal anti-inflammatory drugs (NSAID's), fipronil **9**, an insecticide, tartrazine **10** an azo dye employed as a food colourant, sildenafil **11** used to treat erectile dysfunction; dipyrone **12** and difenamizole **13** potent analgesics, the antipsychotic and the

antidepressant CDPPB **14** and fezolamide **15** respectively, an H2-receptor agonist, betazole **16** and rimonabant **17** compound showing high affinity for the CB-1 cannabinoid receptor and implemented for the treatment of obesity (Abdellatif et al., 2015; Faria et al., 2017; Karrouchi et al., 2018).



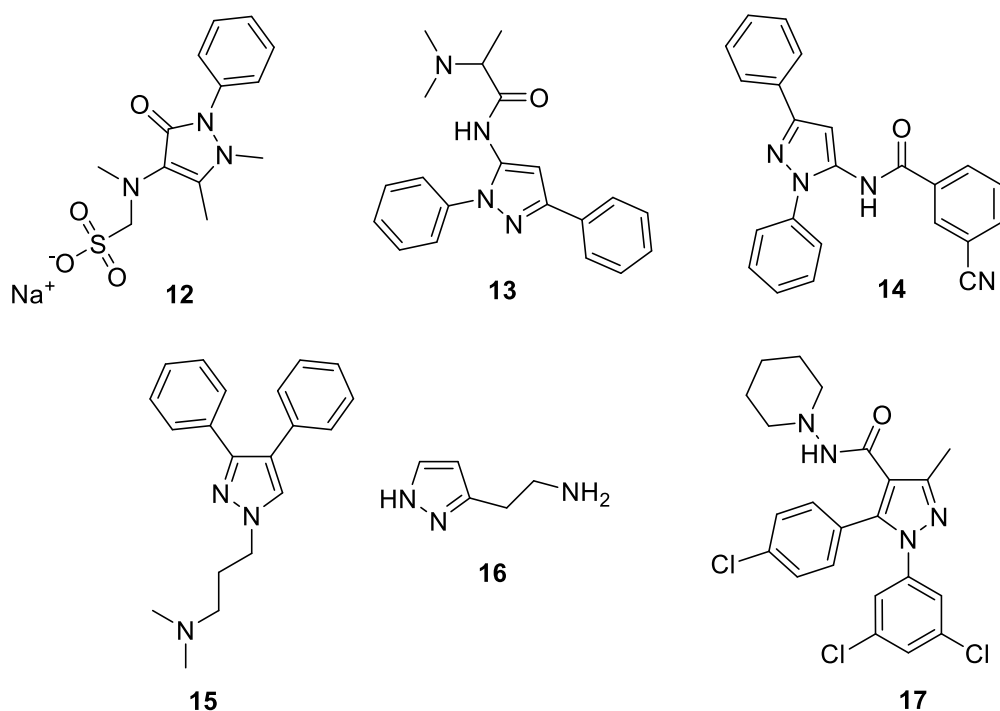


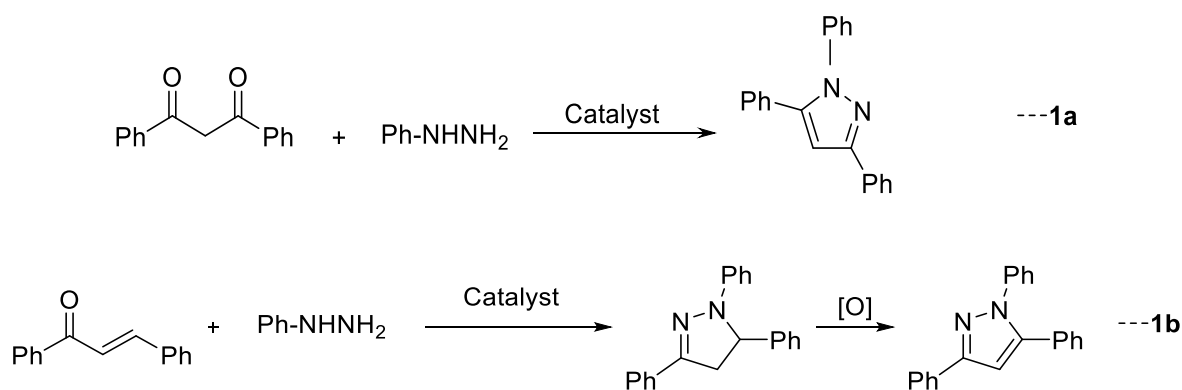
Figure 5. Examples of pharmaceutical drugs bearing a pyrazole unit.

2.1.2 Pyrazole synthetic protocols

The various access to the pyrazole nucleus can be summarized into three generally used methods.

2.1.2.1 Cyclocondensation of hydrazine with 1,3-dicarbonyl and vinyl ketones

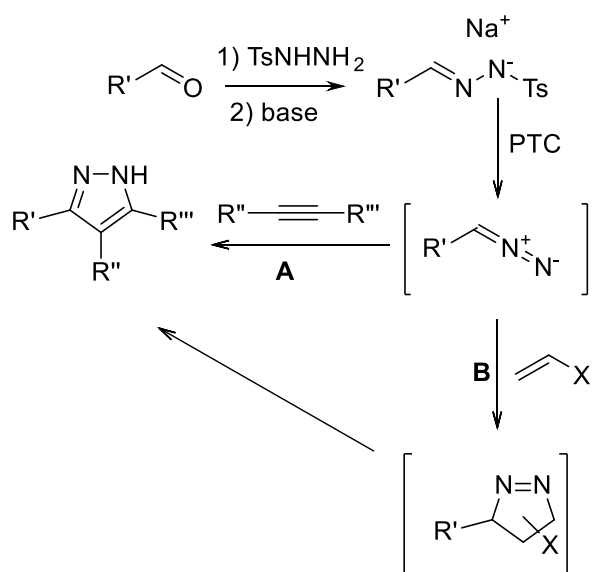
The hydrazine in the synthesis of pyrazoles acts as the bidentate nucleophile in the presence of an acidic catalyst. The condensation of 1,3-dicarbonyl systems and hydrazines is the most straightforward procedure with the versatility to be carried out in various catalysts such as H_2SO_4 , polystyrene-supported sulfuric acid, layered zirconium sulfophenyl phosphonate, Y-zeolite, $\text{Mg}(\text{ClO}_4)_2$ and silica sulfuric acid or nano silica sulfuric acid (**Scheme 1a**) (Emtiazi et al., 2015). The condensation of hydrazine hydrate with unsaturated ketones yields pyrazolines which undergoes oxidation to pyrazoles with catalyst such as copper triflate, iodine and manganese oxide (Karrouchi et al., 2018), **Scheme 1b**.



Scheme 1: The addition of hydrazine derivatives to carbonyl systems.

2.1.2.2 Dipolar cycloadditions

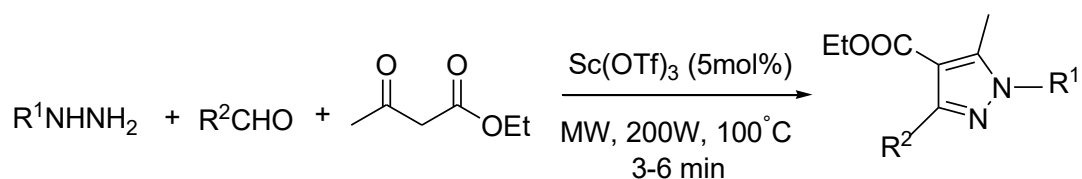
This method involves a [3+2] cycloaddition reaction between an olefin or alkyne, a 1,3-dipolar compound like diazo compounds and sydnone or nitrilimines (**Scheme 2**). The technique is quite important for preparative purposes owing to the need for the preparation and handling of diazo compounds, which are notorious of being toxic and potentially explosive (Vuluga et al., 2009). Aggarwal et al. developed a convenient one-pot, highly effective and safe method of handling aryldiazomethanes to prepare pyrazoles using 1,3-dipolar cycloaddition involving diazo compounds. Diazo compounds were reacted with alkynes to yield 3,5-disubstituted pyrazoles regioselectively. The reaction of *N*-vinylimidazole and diazo compounds gave 3-substituted pyrazoles in a one-pot strategy (Aggarwal et al., 2003).



Scheme 2: Various pathways to produce pyrazoles using diazo compounds. Path A, the 1,3-cycloaddition of diazo compounds to alkynes and Path B, employing an olefin bearing a leaving group X.

2.1.2.3 Multi-component reactions

Kumari and coworkers described an efficient and effective use of $Sc(OTf)_3$ and microwave combination for a rapid, benign and convenient synthesis of functionalized pyrazoles through the one-pot three-component coupling of phenyl hydrazine, aldehydes and ethyl acetoacetate under solvent-free conditions (**Scheme 3**) (Kumari et al., 2012).



Scheme 3: Multi-component synthesis of pyrazoles.

2.2 Flavans

Flavan (2-aryl-chroman) is a generic structural core present in various natural flavonoid products, possessing a 2-phenyl-3,4-dihydro-2*H*-chromene nucleus. The substituted chromans are a class of compounds copiously in the kingdom plantae with >17000 natural flavans isolated and exhibiting beneficial biological and pharmacological activities (Abdel-Razik et al., 2005; Bharate et al., 2012; Mazimba et al., 2011; Syam et al., 2012). The extensive variety of bioactivities exhibited by molecules containing this core element has led to their description as “privileged structures” (Horton et al., 2003). Given that the vital scaffold in these compounds remains constant, one can attribute their biological selectivity to the nature, stereochemistry and pattern of substituents that adorn the chroman core (Li et al., 2006). Examples of benzopyrans include α -tocopherol (Vitamin E), antibiotic LLD253 α , the aromatase inhibitor pinostrobin, 4'-hydroxy-7-methoxyflavan, which was identified as a chemical component of *Stypandra grandis* and later characterized as one of the *anti*-feedent compounds in *Lycoris radiata*. 7-hydroxy-3',4'-methylenedioxyflavan was isolated from the native American medicinal herb *Zephyranthes flava* and traditionally used to cure ear and chest ailments, diabetes, and viral infections. 4',6-Dichloroflavan (BW683C) hinders rhinovirus replication *in vitro*, whilst potent inhibitory activity on mushroom tyrosinase was exhibited by morusyunnansin E (Hodgetts, 2005; Li et al., 2001; Ramulu et al., 2013).

Common flavans are catechins (polyphenols) and epicatechins, **18-21** which are the major constituents in plants such as cocoa, tea and catechu, and are notably known to possess various biological properties such as anticarcinogenic (inhibit cell-growth of cancer), anti-inflammatory, hypoglycemic, antihypertensive, antioxidative and immunomodulatory properties and bone resorption inhibition. Fully substituted monomeric flavans sideroxylonal B **22** and grandinal **23** have been documented from *Eucalyptus sideroxylon* and *E. grandis*, which exhibited inhibition of aldose reductase and antibacterial activities against Gram-

positive bacteria. Benzodipyran- and benzotripyran type compounds have been delineated to portray potent angiogenic activities. Structures of flavans **18-23** are shown in **Figure 6** (Bharate et al., 2012).

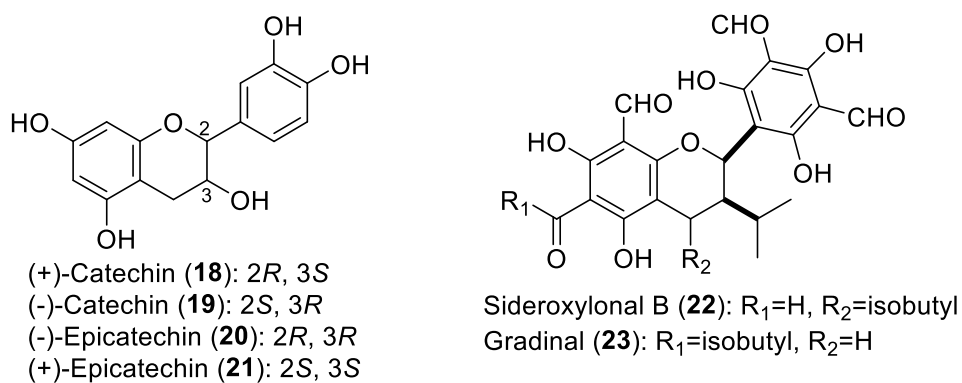
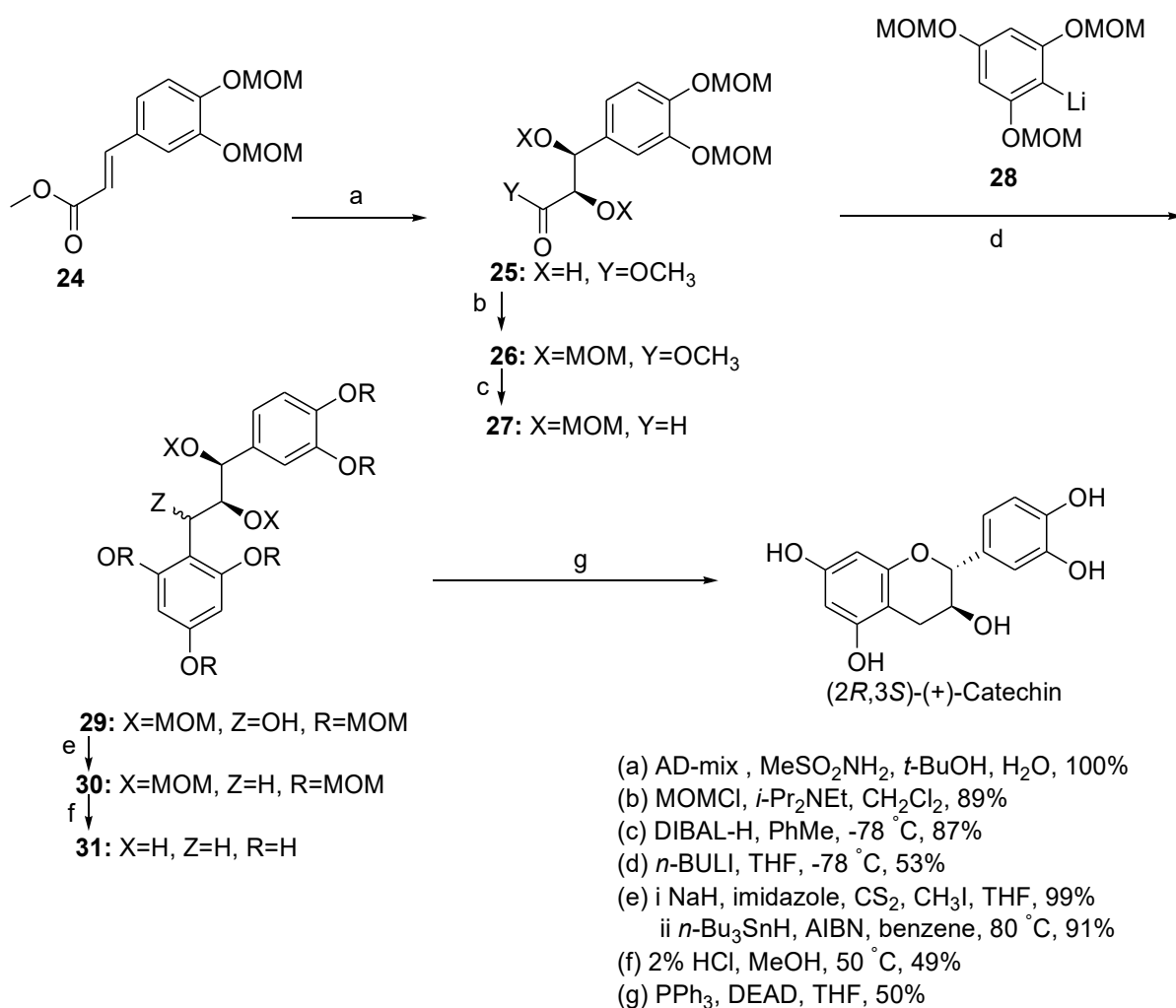


Figure 6. Examples of biological active flavans existing in nature.

2.2.1 Flavans synthesis protocols

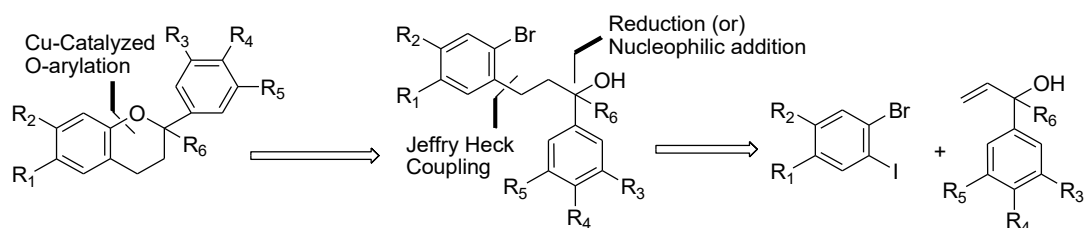
Owing to their unique structural features and their widespread occurrence and valuable properties, numerous synthetic strategies for the construction of flavans have been developed, including inter-and intramolecular Mitsunobu reaction (**Scheme 4**) (Murlykina et al., 2018; Yang et al., 2019)



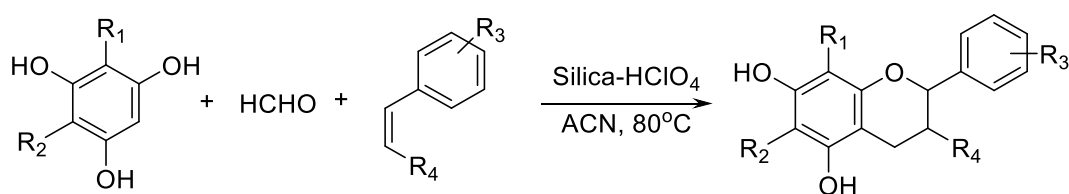
Scheme 4: Intramolecular Mitsunobu reaction pathway of flavans.

The cyclization of chalcones was reported as another pathway to obtain flavans. Chalcone in methanol was treated with NaBH₄ reducing both the double bond and the ketone to afford alcohols, which under acid assisted cyclization afforded the flavans (Masesane & Desta, 2012; Masesane & Mazimba, 2014b; Mazimba et al., 2011). The reduction of flavanones or flav-2-enes is also worth mentioning (Masesane & Mazimba, 2014b). Zhang et al. employed a straightforward synthetic procedure of flavans via the Pd-C catalyzed hydrogenation/hydrogenolysis of corresponding flavones (Zhang et al., 2007). Ramulu and co-workers (2013) developed a method based on intramolecular [Cu]-catalyzed C-O and intermolecular [Pd]-catalyzed C-C bond formations in the synthesis of flavans (**Scheme 5**).

Bharate and co-workers described an efficient direct one-step, one-pot multi-component construction of flavans by use of perchloric acid supported on silica as a recyclable heterogeneous catalyst. The straightforward one-step construction of a flavan skeleton from a phenolic precursor involves a Knoevenagel-type condensation of formaldehyde with phloroglucinol or mono- or disubstituted phloroglucinols leading to the *in-situ* formation of transient O-quinone methide, which further undergoes [4 + 2]-Diels–Alder cycloaddition with styrene to yield flavan (**Scheme 6**) (Bharate et al., 2012). Most of the reported protocols involve multiple steps to construct the flavan skeleton; they obligate expensive, anhydrous conditions and hazardous chemicals. Several protocols encompass protection/deprotection steps and use of homogeneous catalytic systems.



Scheme 5: Retrosynthetic plan for flavan synthesis from 1-bromo-2-iodobenzenes.



Scheme 6: One-pot multi-component reaction approach to flavan synthesis.

2.3 Pyrimidines

Pyrimidines are heterocyclic compounds consisting of six-membered ring structures comprising of two nitrogen atoms at positions 1 and 3 (**Figure 7**) (Farooq & Ngaini, 2020; Khalid et al., 2021). Pyrimidine is a basic nucleus found in the deoxyribonucleic (DNA) and ribonucleic acids (RNA). Three of their five building blocks, thymine is found in DNA, uracil in RNA only, while cytosine is present in both DNA and RNA, they are pyrimidine derivatives. Therefore pyrimidine plays a significant key role in cellular processes making them valuable leads for drug discovery (Ribeiro et al., 2014). A new antiviral for COVID 19, Sofosbuvir, possess the uracil moiety (Moghaddampour et al., 2021). Pyrimidine ring is also found in vitamin B, thiamine, riboflavin and folic acid (Ghali & Tomma, 2017). Pyrimidine has been discovered to be associated with diverse biological activities such as antioxidant, antidepressant, antiviral activities (Solankee et al., 2012), antitubercular (Srilaxmi et al., 2021), antibacterial, anti-tumour (Durga et al., 2017), anti-inflammatory (Kachroo et al., 2014; Rashid et al., 2021), antifungal, analgesic and calcium antagonist activities (Jagwani & Joshi, 2015). The structure of pyrimidine derivatives is shown in **Figure 8**.

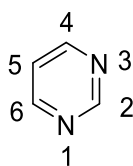


Figure 7. Pyrimidine (1,3-diazine)

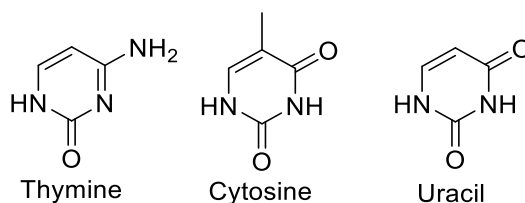


Figure 8. Pyrimidine found in DNA and RNA nucleic acid

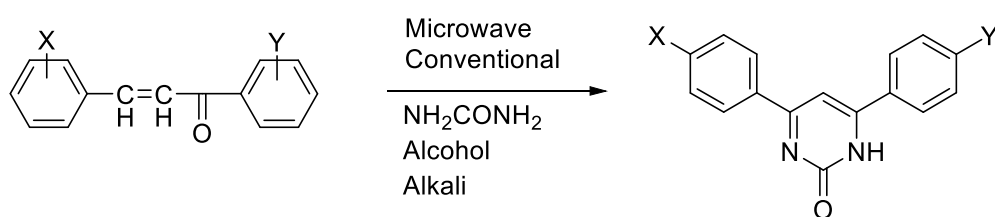
2.3.1 Pyrimidine synthesis

Pietro Biginelli was the first to synthesize dihydropyrimidines by the combination of aldehyde (benzaldehyde), β -keto ester (ethyl acetoacetate) and urea at reflux in the presence of HCl-acidified ethanol (Kappe & Stadler, 2004; Tu et al., 2004). The reaction benefits were avoiding the isolation of intermediates, protection-deprotection strategies and a time-consuming purification process. Several enhanced reaction protocols for the synthesis of Biginelli compounds have been communicated, either by modifying the classical Biginelli reaction or using environmentally benign techniques (Srivastava, 2013). One of the most functional pathways is the reaction between urea derivatives such as thiourea and guanidine with 1,3-dicarbonyl compounds in alcoholic solvent and alkali as presented in **Scheme 7** (Gürdere et al., 2017). Kachroo et al. followed the general procedure discussed above with slight variation using acetic acid instead of HCl in workup (Kachroo et al., 2014). These reported procedures suffer from impediments such as longer reaction time, complicated workup procedures, use of acids or bases, hazardous solvents and moderate yields 58-65%.

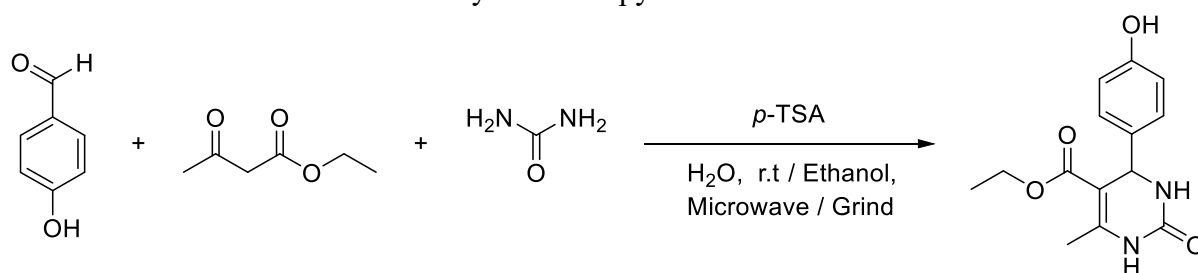
Sahoo et al. followed an environmentally benign (green chemistry) approach by using microwave-induced energy to synthesize pyrimidines, maximizing the atom economy, thus evaluating the efficiency of chemical transformation of reactant materials (Sahoo et al., 2017). Jagwani and Joshi incorporated *p*-toluenesulfonic acid as a catalyst employed in Biginelli synthesis assisted by grindstone chemistry, a green chemistry approach (**Scheme 8**) (Jagwani & Joshi, 2015). Grindstone chemistry, apart from being energy efficient, results in high reactivity and fewer waste products. The reaction is simple to handle, comparatively cheaper to operate, reduce pollution hence regarded as more economically and ecologically favourable. Toda mentioned that “Solid-state reactions occur more efficiently and selectively than does the solution reaction” (Toda, 1995). The microwave-assisted method required less

time with enhanced reaction rates and provided better yields (79-85%) with pure products.

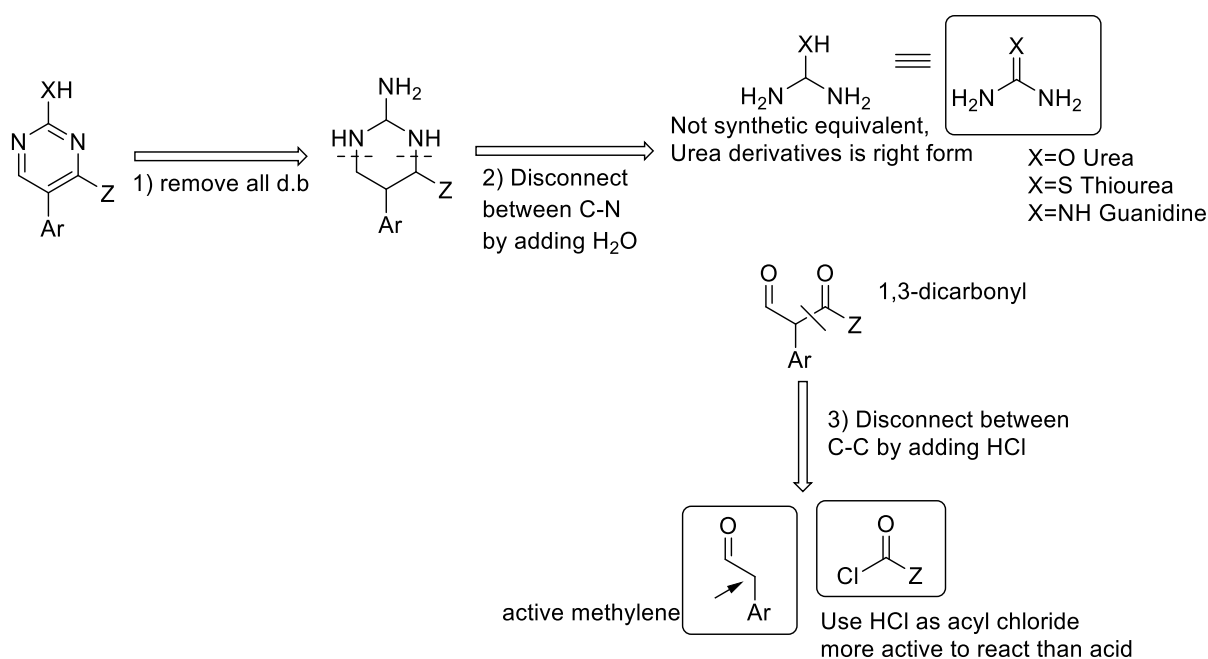
Scheme 9 reveals the retrosynthesis pathway for pyrimidine design synthesis.



Scheme 7: Synthesis of pyrimidine derivatives



Scheme 8: Modified Biginelli reaction with *p*-TSA as a catalyst



Scheme 9: Retrosynthesis analysis of pyrimidine

2.4 Chalcones synthesis and as synthons for heterocycles

Chalcones possess conjugated double bonds and a completely delocalized π -electron system on both benzene rings, **Figure 9**. They are coloured compounds due to the chromophore's presence, the reactive keto vinyl/ethylenic group ($-\text{CO}-\text{CH}=\text{CH}-$) in their structure (Custodio et al., 2020; Kamya et al., 2021; Sahoo et al., 2017; Shaik et al., 2020; Silva et al., 2021). Chalcones are widely distributed in nature. They have been identified in the fruits, vegetables, spices, tea, soy-based foodstuffs and higher plant such as licochalcone A, licochalcone D, morachalcone A and isobavachalcone isolated from *Psoralea corylifolia* (Li et al., 2019), **32** in *Macaranga denticulata*, **33** in *Uvaria siamensis* roots, **34** in *Stevia lucida*, **35** in *Pongamia pinnata* (L.) Pierre roots (Ardiansah, 2019) **Figure 10** and some new hydroxy chalcones bearing sugar functionalities (**36–38**) have been isolated and identified from the flowers of *Coreopsis lanceolata* by (Kim et al., 2019; Xu et al., 2013).

The presence of the enone functionality in chalcone moiety confers a wide range of biological activities (Piste, 2014). Numerous chalcones are found to have pharmaceutical and medicinal applications ranging from anticancer, antitumor, antispasmodic, antiulcer, anthelmintic, antibacterial, antiallergic, anti-inflammatory, antimalarial, antitubercular, antiviral, anti-HIV, antiplatelet, antihypertensive, cardiovascular, analgesic, fungicidal, germicidal, herbicidal, and insecticidal (Abdellatif et al., 2015; Saini et al., 2005; Kurt et al., 2020; Nowakowska, 2007; Qin et al., 2020; Rao et al., 2013; Silva et al., 2021; Singh & Chandra, 2021; Tanemura & Rohand, 2021; Tran et al., 2012; Tran et al., 2009; Yazdan et al., 2015).

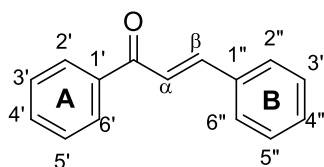


Figure 9: The general chemical structure and numbering of chalcones.

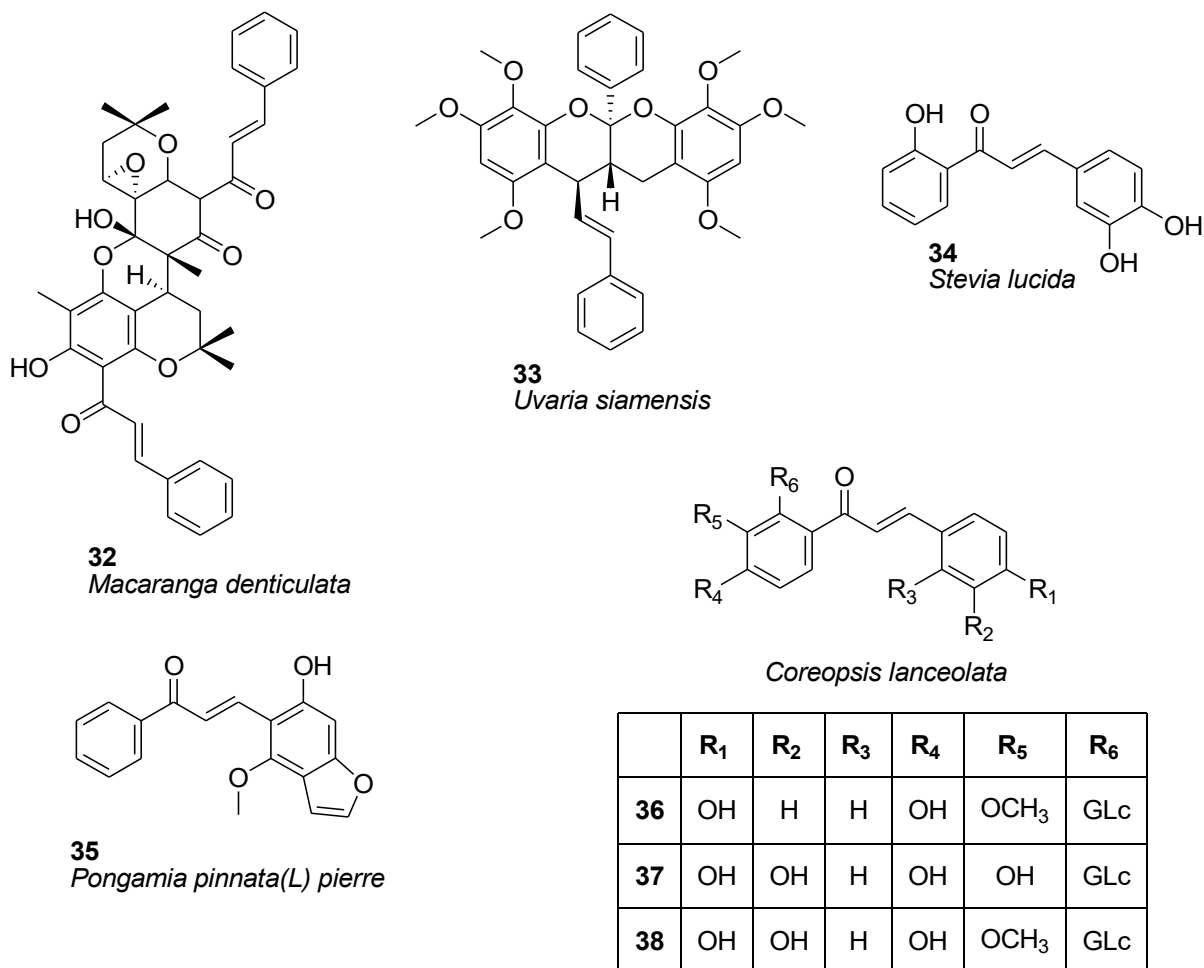
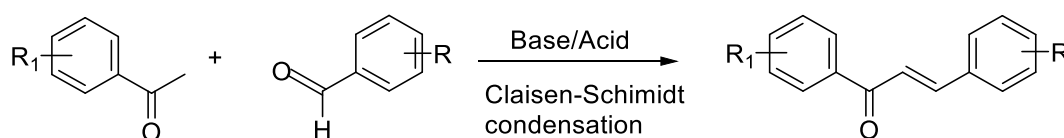


Figure 10. Examples of chalcones isolated from natural sources.

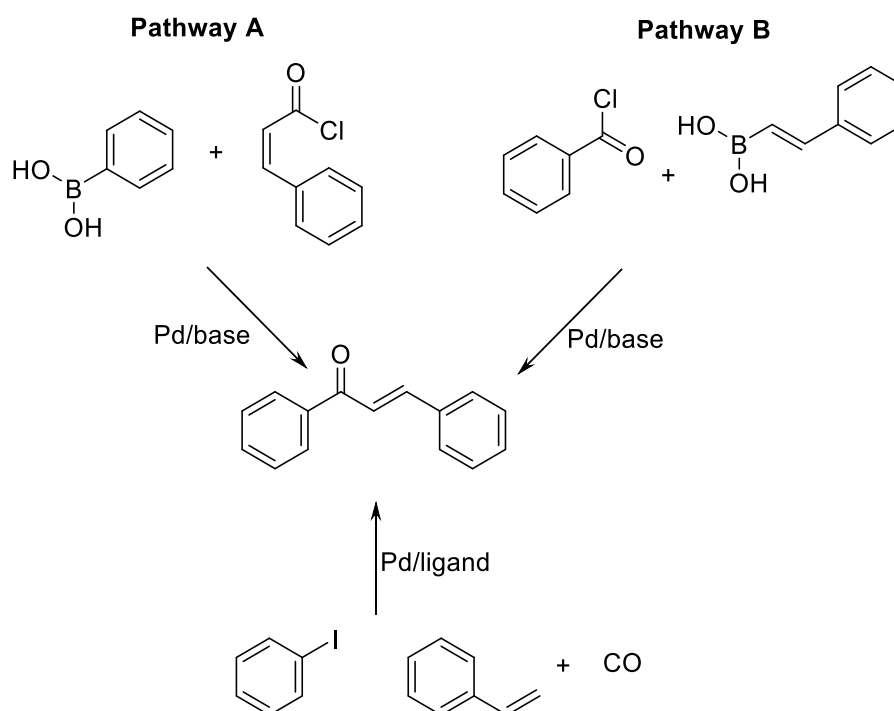
Chalcones are conventionally synthesized by Aldol condensation and Claisen Schmidt condensation reaction in which an appropriate aryl aldehyde reacts with unsubstituted or substituted acetophenone in the presence of ethanolic alkaline bases, usually aqueous KOH or NaOH or sodium ethoxide at room temperature or by refluxing method as presented in **Scheme 10** (Suwito et al., 2014; Tran et al., 2012). The Claisen-Schmidt condensation can alternatively be done in the presence of other bases (e.g., Ba(OH)₂, LiOH, anhydrous K₂CO₃)

and inclusive of acidic conditions (HCl , $\text{BF}_3 \cdot \text{OEt}_2$, B_2O_3 , *p*-toluenesulfonic acid)(Albuquerque et al., 2014). The resulting chalcones includes ring-A substituents from acetophenone and ring-B substituents from aldehyde (Albuquerque et al., 2014). Among the literature synthetic routes, the base-catalyzed Claisen-Schmidt reaction is the popular method due to the availability of the preliminary reagents such as acetophenones and benzaldehydes. Other technique utilising acidic $\text{BF}_3 \cdot \text{OEt}_2$ has relevance due to high yields, simple workup, short reaction times and elimination of side reactions.



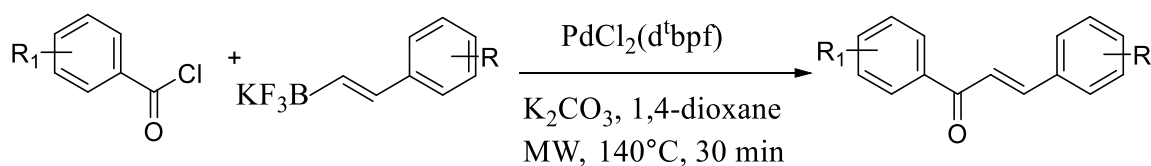
Scheme 10: Synthesis of chalcone analogues

The more exotic synthetic protocol entails palladium-mediated Suzuki coupling involving cinnamoyl chloride and aryl boronic acids **Path A** or styrylboronic acid with benzoyl chloride **Path B** or the carbonylative Heck coupling incorporating phenyl halides and styrenes in presence of carbon monoxide (**Scheme 11**) and the Heck coupling of aryl vinyl ketones with aryl iodides (Eddarir et al., 2003; Haddach & McCarthy, 1999)



Scheme 11: Pd mediated pathways to chalcones.

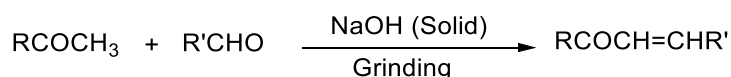
As depicted above, the Suzuki-Miyamura reaction make use of mild conditions accordant with a variety of functional groups. Improved protocols include solvent-free conditions, the grinding technique, microwave and ultrasound irradiation (Calvino et al., 2006). Al-Masum et al. applied a similar approach in employing the direct cross-coupling reaction of potassium styryl tri fluoroborates as starting material with benzoyl chlorides under microwave conditions (**Scheme 12**) (Al-Masum et al., 2011; Selepe & Van Heerden, 2013).



Scheme 12: Synthesis of chalcones utilizing cross-coupling of benzoyl chloride with potassium styryl tri fluoroborates.

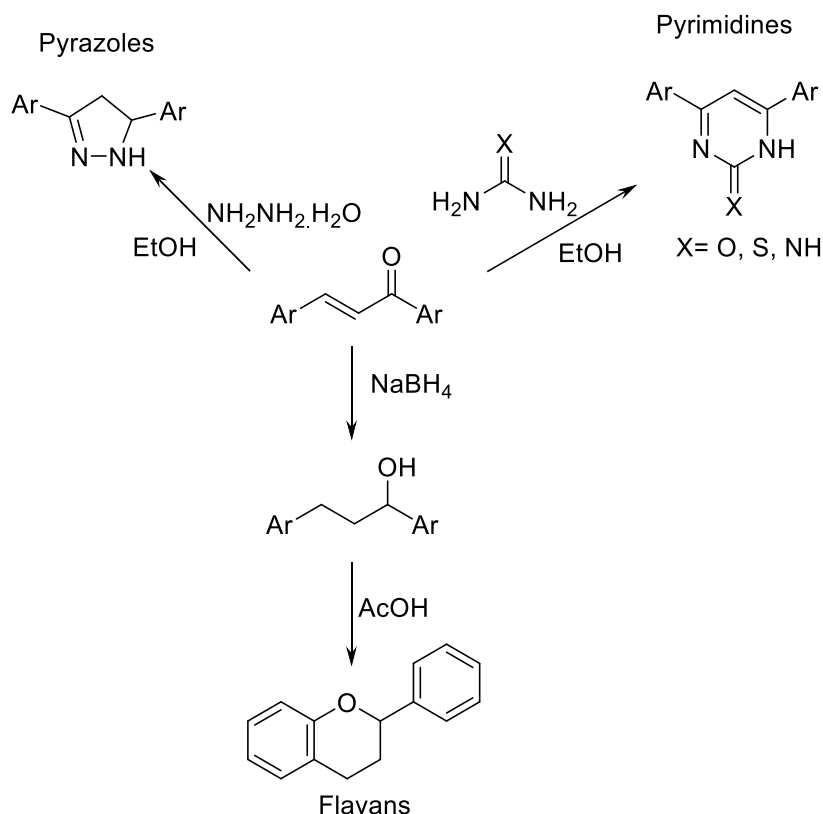
Green chemistry has attracted significant attention in recent years; hence, researchers are finding a simple, efficient and effective method in terms of reducing or eliminating adverse environmental impacts by preventing waste and generating materials with little or no toxicity

to humans and the environment thus maximizing atom economy. In this regard, Sani et al. conducted the grindstone technique of solids (or liquid and solid) in the absence of solvents performed with short reaction time and excellent yields by (Saini et al., 2005; Piste, 2014; Rateb & Zohdi, 2009) (**Scheme 13**)



Scheme 13: Grinding technique for the synthesis of chalcones.

Chalcones unsaturated system makes them attractive synthons in the preparation of heterocyclic compounds such as flavonoids, pyrazolines, pyrazoles, oxazoles, isoxazoles, cyanopyridines, thiophenes, and pyrimidines having different ring systems of physiological importance (Ghali & Tomma, 2017; Gürdere et al., 2017; Mohamed & Abuo-Rahma, 2020) (**Scheme 14**). Chalcone derivatives are fine synthons for developing novel molecular diversity in drug design and discovery projects (Ardiansah, 2019; Baluja & Hirapara, 2019). Therefore, the synthesis of these compounds is of adamant importance in both academic and industrial circles.



Scheme 14: Chalcones as synthons for target compounds.

2.5 Importance of F and NO₂ groups

Fluorine-containing compounds have been extensively researched in literature for their use as drugs or drug candidates (**Figure 11**). It is well documented that introduction of a fluorine atom or fluorine-containing group to a molecule may lead to significant influence on the biological and physical properties of compounds, including change in hydrophobic bonding, increased membrane permeability and stability against oxidation (Kuznetsova et al., 2004; Shah & Westwell, 2007). Fluorine as a substituent affects the metabolic stabilities of drugs and bonding interactions as well as impacts their selective reactivities and physical features (Hagmann, 2008). Generally, the effects of the incorporation of a fluorine atom to a molecule can be split into two categories; chemical and biological (**Table 1**) (Burmaoglu et al., 2016, 2017, 2019). Given that fluorine-containing compounds display promising pharmacological activities which originate from their uniquely high thermal stabilities and lipophilicity (

Shelke et al., 2012), the development of synthetic protocols for fluorine-containing compounds has been an essential field in organofluorine chemistry synthesis (Shelke et al., 2007).

Table 1: Properties of organofluorine compounds.

Chemical	Biological
Small size	Electronegative effect of neighbouring functionalities
Lipophilic	Strong C-F bonds resistant to metabolic processes
High electronegativity	Increases lipid solubility (bioavailability)
Low reactivity	Synthesis of isosteric analogues of drugs useful for studying biochemical processes

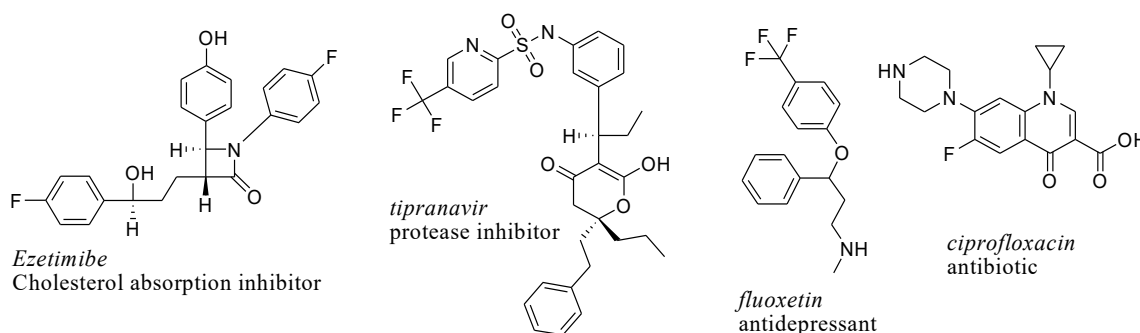


Figure 11. Some of the drugs containing fluoride groups.

The nitro compounds are versatile building blocks and a unique functional group in synthetic organic chemistry (Heaney, 2004; Manikala & Rao, 2020; Natarajan et al., 2020). This is owed to their easy transformations into other diverse functional groups leading to complex molecules containing novel groups and desired chemical features, such as conversion to an amine (*via* nitro reduction), to a carbonyl group (*via* the Nef reaction) and nitroaromatic drugs, during which various methods serve to introduce the nitro group into the aryl ring) (Hajra et al., 2020; Yan & Yang, 2013). Drugs that contain the nitro group are very active because the nitro group can potentially produce radical species such as reactive nitrogen species (RNS) and oxygen species (ROS) (Kannigadu & N'Da, 2020).

The vital role of nitro groups as valuable reagents due to their ability to be excellent activating groups that provide organic reactive intermediates and their ability to be easily

removed after serving their purpose by reductive denitration because nitro group is an excellent leaving group. The group is found in many natural products such as hormones, vitamins, alkaloids, antibiotics, pharmaceuticals, herbicides, dyes and several other compounds (Ferreira et al., 2002). The high prevalence of nitrogen-containing groups in pharmaceuticals, estimated to be more than 84% of the total makes them occupy a distinct, indispensable significance position in organic synthesis (Phillips et al., 2020; Vitaku et al., 2014).

Nitro group exhibits a strong electron attracting ability that creates localized electron deficient sites within molecules thus interacts with biological nucleophiles present in living systems, for instance amino acids, nucleic acids, proteins and enzymes. Drugs containing nitro groups (**Figure 12**) have a long history of antibiotic, antineoplastic, antiparasitic agents, tranquillizers, fungicides, insecticides, and herbicides (Karabanovich et al., 2015; Srilaxmi et al., 2021). Moreover, the nitro groups undergo reduction and serve as prodrugs due to their bioactivation by enzymatic reduction, hence generating reactive species and ultimately inducing biological effects. It is well established that some nitroaromatic or nitro heteroaromatic compounds can induce therapeutic effects via redox cycling of single-electron reduction by different flavoenzymes or from the alkylation of DNA or other cellular nucleophiles by the products of their bio-reductive activation process (Nepali et al., 2019).

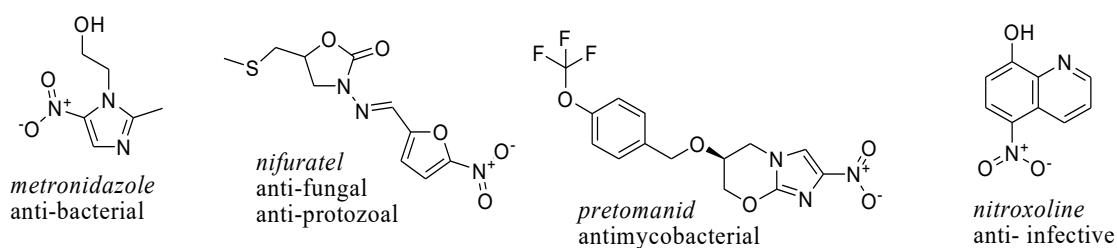


Figure 12. Some of the drugs containing nitro groups.

These aspects of the nitro group have created a renaissance in nitro chemistry research (Srilaxmi et al., 2021). Therefore, much attention has been drawn to the development of efficient and practical methods for the synthesis of aromatic nitro compounds.

CHAPTER 3

MATERIALS AND METHODS

3.1 General experimental procedures

All the chemicals and the organic solvents were purchased from Sigma-Aldrich, Alpha-Chemika or Rochelle chemicals and used as received. The reaction progress was monitored by thin-layer chromatography (TLC) on silica gel precoated aluminium foils (Sigma-Aldrich, Germany), and using hexane and ethyl acetate as solvent system and the spots were visualized in an iodine chamber or by exposure to UV lamp at λ_{254} nm. The IR spectra (ν cm⁻¹) (neat) were recorded at room temperature in the spectral regions from 400 cm⁻¹ to 4000 cm⁻¹ on Thermo scientific Smart ITR Nicolet iS10. NMR spectra were recorded at the NMR Laboratory centre at the University of Limpopo, South Africa. The ¹H NMR spectra were run on Bruker AC 400 MHz Spectrophotometer while ¹³C NMR experiments we acquired at 100 MHz. TMS was used as the internal standard. CDCl₃, acetone-d₆ or DMSO-d₆ were used as solvents, and chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS with the solvent resonance as the internal standard. Coupling constants (J) were reported in Hz and referred to apparent peak multiplications. Analytical reagents/solvents (AR) were used.

3.2 Synthetic procedures

3.2.1 Synthesis of chalcones

Method A

Equimolar quantities of various substituted acetophenones and aldehydes (0.03 mol) were taken into 15 mL ethanol in a round bottom flask. Then, sodium hydroxide (30%, 2 mL) was

introduced in a dropwise manner. The reaction mixture was magnetically stirred at 60°C for 3 hrs. The reaction medium was discharged into iced water and the pH was adjusted using 2M HCl. The yellow solid thus precipitated and was separated by filtration, washed with water, dried and recrystallized from ethanol.

Method B

Substituted acetophenones (0.03 mol), various aldehydes (0.03 mol) and solid 2.0 g NaOH were taken in a small mortar and ground thoroughly for 10 minutes at room temperature. Upon completing the grinding process, as indicated by TLC, the obtained solid mass, which was yellowish in colour, was diluted with cold water and filtered to afford a crude product. The crude product was recrystallized in ethanol, dried and weighed to give the corresponding chalcone derivatives.

3.2.2 Synthesis of flavans

Sodium borohydride powder (5 eq., 33.5 mmol) was added in small portion to a solution of the chalcone (6.7 mmol) in methanol at room temperature. The resulting mixture was stirred for 10 min, and after cooling, the reaction mixture was doused with 2 M HCl. The organic phase of the reaction mixture was extracted with EtOAc (3 × 15 ml). The combined organic phases were dried with MgSO₄ and concentrated in vacuo to obtain the alcohol. Glacial acetic acid (10 ml) was added to the alcohol (4.4 mmol). The solution was refluxed for 30 min, then cold water (15 ml) was added, and the reaction mixture was extracted with EtOAc (2 × 20 ml). The combined organic layers were dried using anhydrous MgSO₄. The solvent was then removed in vacuo, and the residue was purified using silica gel column chromatography eluted with petroleum ether-EtOAc (v/v, 4:1) solvent system to furnish the flavan.

3.2.3 Synthesis of pyrazoles

Acetic acid (1 ml) was introduced to the chalcone (0.01 mol) solution and hydrazine monohydrate (0.02 mol) in 15ml ethanol and refluxed for 4 hrs. The resulting mixture was transferred into cold water. The precipitate was filtered and purified by crystallization from ethanol to yield the desired product.

3.2.4 Synthesis of pyrimidines

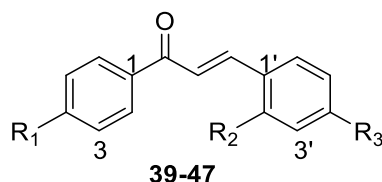
To the solution of substituted chalcone (0.01 mol) in 25 ml ethanol was introduced thiourea (0.01 mol) and potassium hydroxide (5 ml of 40%) and refluxed for 8 hrs. The reaction mixture was thereafter cooled to room temperature, poured into crushed ice and neutralized with dilute HCl. The resultant precipitate separated out was filtered, washed with water, dried and recrystallized from ethanol.

3.3 Attempted synthesis of benzo[c]chromen-6-one

Several synthetic procedures were employed in the preparation of benzo[c]chromen-6-one; initially, triethylamine was used. Triethylamine (4.8 mmol) or other bases were introduced to a solution of 2'-hydroxy chalcone (2.4 mmol) in 20 mL methanol, followed by ethyl acetoacetate (2.4 mmol). The stirring was maintained at 60 °C, while the TLC profiles monitored the reaction progress. After a series of times (1-12 hrs), the reaction mixture was acidified using hydrochloric acid (4 M), and the resulting yellowish precipitate was separated by filtration and/or recrystallized from ethanol. Deep eutectic solvents were prepared and used according to literature (Bhosle et al., 2020; Longo & Craveiro, 2018).

3.4 Physical and spectroscopic data

3.4.1 Chalcones



Compound	R ₁	R ₂	R ₃	Compound	R ₁	R ₂	R ₃
39	H	OH	H	44	H	H	H
40	H	OH	F	45	F	H	H
41	NH ₂	OH	H	46	F	H	F
42	NO ₂	H	F	47	Et	H	F
43	H	H	NO ₂				

39 was obtained as a yellow solid using Method A in 69% yield and Method B in 74%. FTIR (neat) ($\nu_{\max}$ cm⁻¹): 3280.9 (OH), 3180.2 (CH-sp²), 1638.2 (C=O), 1596.7 (C=C aromatic), 1560.3 (C=C alkenyl). ¹H NMR (400 MHz, DMSO-d₆) (δ , ppm): 6.88 (t, 1H, J = 7.4 Hz, H-4'), 6.94 (d, 1H, J = 7.9 Hz, H-3'), 7.29 (t, 1H, J = 8.4 Hz, H-5'), 7.58 (t, 2H, J = 7.7 Hz, H-3 and H-5), 7.67 (t, 1H, J = 7.4 Hz, H-6'), 7.86 (d, 1H, J = 15.8 Hz, H _{α}), 7.89 (dd, 1H, J = 7.7, 1.4 Hz, H-4), 8.06 (d, 1H, J = 15.8 Hz, H _{β}), 8.10 (d, 2H, J = 7.8 Hz, H-2 and H-6), 10.33 (s, 1H, 2'-OH). ¹³C NMR (100 MHz, DMSO-d₆) (δ , ppm): 116.7 (C-3'), 119.8 (C-5'), 121.3 (C _{α}), 121.7 (1'), 128.0 (C-2 and 6), 128.8 (C-4'), 129.3 (C-3 and 5), 132.6 (C-6'), 133.4 (C-4), 138.4 (C-1), 139.9 (C _{β}), 157.7 (C-2'), 189.9 (C=O). [M]⁺ calculated for C₁₅H₁₂O₂, m/z : 224.08.

40 was obtained using Method A and Method B as a yellow solid in 65% and 71% yield respectively. FTIR (neat) $\nu_{\max}$ cm⁻¹: 3294.1 (OH), 3082.4 (CH-sp²), 1641.6 (C=O), 1568.1 (C=C aromatic), 1514.6 (C=C alkenyl), 753.9 (C-F). ¹H NMR (400 MHz, acetone-d₆) (δ ,

ppm): 6.96 (m, 1H, H-5'), 7.03 (m, 1H, H-3'), 7.25 (t, 1H, $J = 7.3$ Hz, H-6), 7.53 (d, 1H, $J = 15.8$ Hz, H_α), 7.59-7.67 (m, 3H, H-3, 4, 5), 7.91 (m, 2H, H-2, 6), 8.43 (d, 1H, $J = 15.8$ Hz, H_β). ^{13}C NMR (100 MHz, acetone- d_6) (δ , ppm): 98.5 (C-3'), 102.2 (C-5'), 125.8 (C_α), 127.0 (C-1'), 128.4 (C-3), 128.5 (C-5), 130.3 (C-6'), 130.0 (C-2), 132.9 (C-6), 138.2 (C-1), 141.6 (C_β), 144.4 (C-4), 164.3 (C-2'), 165.5 (C-4'), 198.6 (C=O). $[\text{M}]^+$ calculated for $\text{C}_{15}\text{H}_{11}\text{FO}_2$, m/z : 242.07.

41 was obtained using Method A and B as a neutral grey solid in 66% and 73% yield respectively. FTIR (neat) (ν_{max} cm^{-1}): 3647.9 and 3622.7 (N-H), 3316.1 (OH), 3235.6 (CH-sp^2), 1,649.4 (C=O), 1584.4 (N-H), 1515.2 (C=C aromatic), 1116.4 (N-H). ^1H NMR (400 MHz, acetone- d_6) (δ , ppm): 6.49 (d, 1H, $J = 7.2$ Hz, H-3'), 6.94 (d, 1H, $J = 8.2$ Hz, H-5'), 7.07 (t, 1H, $J = 8.2$ Hz, H-4'), 7.27 (t, 2H, $J = 8.2$ Hz, H-3 and 5), 7.52 (dd, 1H, $J = 7.8, 1.7$ Hz, H-6'), 8.12 (d, 1H, $J = 15.4$ Hz, H_α), 8.19 (dd, 2H, $J = 8.9, 5.6$ Hz, H-2 and 6), 8.25 (d, 1H, $J = 15.4$ Hz, H_β). ^{13}C NMR (100 MHz, acetone- d_6) (δ , ppm): 114.2 (C-3'), 115.3 (C-3 and 5), 117.6 (C-1'), 119.6 (C-4'), 122.4 (C_α), 130.9 (C-2 and 6), 131.7 (C-6'), 136.0 (C-4'), 144.2 (C_β), 154.7 (C-4), 159.3 (C-2') 189.7 (C=O), $[\text{M}]^+$ calculated for $\text{C}_{15}\text{H}_{13}\text{NO}_2$, m/z : 239.09.

42 was obtained using Method B as a yellow solid in 76% yield. FTIR (neat) (ν_{max} cm^{-1}): 3102 and 3050 (CH-sp^2), 1664.4 (C=O), 1582.3 (C=C aromatic), 1512.1 (C=C alkenyl), 1330.9 (N=O), 852 (N-O). ^1H -NMR (400 MHz, CDCl_3) δ , ppm: 7.09 (t, 2H, $J = 8.6$ Hz, H-3' and 5'), 7.36 (dd, 2H, $J = 8.6, 2.02$ Hz, H-2' and H-6'), 7.81 (d, 2H, $J = 8.6$ Hz, H-2 and H-6), 8.26 (d, 2H, $J = 8.6$ Hz, H-3 and H-5). ^{13}C -NMR (100 MHz, CDCl_3) δ , ppm: 123.9 (C_α), 124.0 (C-3' and 5'), 126.2 (C-3 and 5), 127.9 (2' and 6'), 128.0 (C-2 and 6), 137.7 (C-1'), 138.9 (C-1), 147.3 (C_β), 161.2 (C-4), 163.6 (C-4'), 189.8 (C=O). $[\text{M}]^+$ calculated for $\text{C}_{15}\text{H}_{10}\text{FNO}_3$, m/z : 271.06.

43 was obtained using Method B as a yellowish orange solid in 73% yield. FTIR (neat) ($\nu_{\max}$ cm^{-1}): 3097.0 (CH-sp²), 1657.6 (C=O), 1591.6 (C=C aromatic), 1512.73 (C=C alkenyl), 1325.5 (N=O), 863.4 (N-O). ¹H NMR (400 MHz, DMSO-d₆) (δ , ppm): 7.58 (m, 2H, H-3 and H-5), 7.68-7.72 (m, 1H, H-4), 7.87 (d, 1H, J = 15.7 Hz, H α), 8.12 (d, 1H, J = 15.7 Hz, H β), 8.15-8.21 (m, 4H, H-2, 6, 2' and 6'), 8.31-8.34 (m, 2H, H-3', and H-5'). ¹³C NMR (100 MHz, DMSO-d₆) (δ , ppm): 123.9 (C α), 125.8 (C-3'), 125.8 (C-5'), 128.6 (C-2), 128.6 (C-6), 128.7 (C-2'), 128.7 (C-6'), 129.5 (C-3), 129.5 (C-5), 133.3 (C-4), 137.7 (C-1), 141.1 (C-1'), 141.4 (C β), 148.5 (C-4'), 188.7 (C=O). [M]⁺ calculated for C₁₅H₁₁NO₃ m/z : 253.07.

44, the *trans* chalcone was commercially sourced from Merck.

45 was obtained using Method B as a cream solid in 75% yield. FTIR (neat) ($\nu_{\max}$ cm^{-1}): 3076.2 (CH-sp²), 1675.3 (C=O), 1589.6 (C=C aromatic), 1511.6 (C=C alkenyl), 1329.4 (C-F). ¹H NMR (400 MHz, acetone-d₆) (δ , ppm): 7.34 (t, 2H, J = 8.25 Hz, H-3 and 5), 7.49 (dd, 3H, J = 7.2, 2.0 Hz, H-3', 4, and 5'), 7.82 (d, 1H, J = 15.6 Hz, H α), 7.86 (dd, 2H, J = 7.8, 2.4 Hz, H-2' and 6'), 7.92 (d, 1H, J = 15.6 Hz, H β), 8.27 (dd, 2H, J = 7.8, 2.8 Hz, H-2 and 6). ¹³C NMR (100 MHz, acetone-d₆) (δ , ppm): 115.4 (C-3), 115.5 (C-5), 121.6 (C α), 128.7 (C-2' and 6'), 128.9 (C-3' and 5'), 130.5 (C-4'), 131.3 (C-6), 131.4 (C-2), 134.7 (C-1), 135.0 (C-1'), 144.2 (C β), 166.8 (C-4), 187.5 (C=O), [M]⁺ calculated for C₁₅H₁₁FO, m/z : 226.08.

46 was obtained using Method B as an off-white solid in 74% yield. FTIR (neat) ($\nu_{\max}$ cm^{-1}): 3072.4 (CH-sp²), 1665.4 (C=O), 1594.7 (C=C aromatic), 1505.8 (C=C alkenyl), 1352.3 (C-F). ¹H NMR (400 MHz, acetone-d₆) (δ , ppm): 7.26 (t, 2H, J = 8.8 Hz, H-3', 5'), 7.34 (t, 2H, J = 8.8 Hz, H-3, 5), 7.81 (d, 1H, J = 15.6 Hz, H α), 7.90 (d, 1H, J = 15.6 Hz, H β), 7.94 (dd, 2H, J = 8.8, 3.1 Hz, H-2', 6'), 8.26 (dd, 2H, J = 8.8, 3.5 Hz, H-2 and H-6). ¹³C NMR (100 MHz, acetone-d₆) (δ , ppm): 115.4 (C-3' and 5'), 115.9 (C-3 and 5), 121.5 (C α), 130.9 (C-2'

and 6'), 131.4 (C-2 and 6), 131.5 (C-1'), 134.7 (C-1), 142.9 (C $_{\beta}$), 164.2 (C-4'), 166.8 (C-4) and 187.4 (C=O). [M]⁺ calculated for C₁₅H₁₀F₂O, *m/z*: 244.07.

47 was obtained using Method B as a cream solid in 79% yield. FTIR (neat) (ν_{max} cm⁻¹): 3072.2 (CH-sp²), 2926.6 (CH-sp³) 1653.7 (C=O), 1593.5 (C=C aromatic), 1506.6 (C=C alkenyl), 1353.5 (C-F).

¹H NMR (400 MHz, acetone-d₆) (δ , ppm): 1.26 (d, 3H, *J*=15.2, CH₃), 2.75 (q, 2H, *J* = 7.6 Hz, CH₂), 7.25 (t, 2H, *J* = 8.7 Hz, H-3' and 5'), 7.43 (d, 2H, *J* = 8.4 Hz, H-2' and 6'), 7.78 (d, 1H, *J* = 15.6 Hz, H _{α}), 7.88 (d, 1H, *J*=15.6Hz, H _{β}), 7.93 (dd, 2H, *J* = 8.7, 3.2 Hz, H-3, 5), 8.11 (d, 2H, *J* = 8.7 Hz, H-2, 6). ¹³C NMR (100 MHz, acetone-d₆) (δ , ppm): 14.8 (CH₃), 28.5 (CH₂), 115.7 (C-5'), 115.9, (C-3'), 121.9 (C _{α}), 128.2 (C-2' and 6'), 128.7 (C-3 and 5), 130.9 (C-2) 130.8 (C-6), 131.8 (C-1'), 135.9 (C-1), 142.2 (C $_{\beta}$), 149.8 (C-4), 162.6 (C-4'), 188.4 (C=O). [M]⁺ calculated for C₁₇H₁₅FO, *m/z*: 254.11.

3.4.2 Flavans



Compound	R ₁	R ₂
57	H	H
58	F	H
59	H	NH ₂

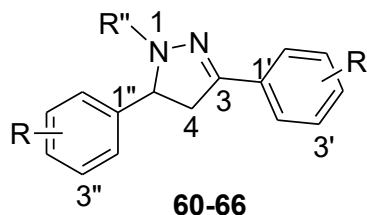
54: Orange gummy solid, 85% yield; FTIR $\nu_{\max}$ cm⁻¹: 3383.9 (OH), 2883.8 and 2791.2 (CH-sp³), 1670.1-1457.4 (C=C). ¹H-NMR (400 MHz, CDCl₃) δ , ppm: 1.96 (m, 1H, H-2a), 2.12 (m, 1H, H-2b), 2.77 (m, 1H, H-1a), 2.96 (m, 1H, H-1b), 4.63 (dd, 1H, J =10.4, 3.4 Hz, H-3), 6.88 (d, 1H, J =8.1 Hz, H-3'), 6.92 (dd, 1H, J =7.4, 0.9 Hz, H-5'), 7.14 (d, 1H, J =7.4 Hz, H-4'), 7.17 (d, 1H, J =1.7 Hz, H-6'), 7.28-7.35 (m, 5H, H-2''-6''). ¹³C-NMR (100 MHz, CDCl₃) δ , ppm: 26.0 (C-1), 39.9 (C-2), 72.9 (C-3), 116.3 (C-3'), 120.8 (C-5'), 125.8 (C-4' and 6'), 127.2 (C-1'), 127.7 (C-4''), 127.9 (C-2'' and C-6''), 128.6 (C-3'' and 5''), 130.6 (C-6'), 143.8 (C-1''), 154.5 (C-2'). [M]⁺ calculated for C₁₅H₁₆O₂, m/z : 228.12.

57: Orange gum, 82% yield, FTIR $\nu_{\max}$ cm⁻¹: 3070.9 (CH-sp²), 2904.64 (CH-sp³), 1584.7 (C=C aromatic), 1428.3 (C-C), 1236.4 (C-O), ¹H-NMR (400 MHz, CDCl₃) δ , ppm: 1.92 (m, 1H, 3a), 2.12 (m, 1H, H-3b), 2.75 (m, 1H, H-4a), 2.98 (m, 1H, H-4b), 4.63 (dd, 1H, J =10.4, 3.4Hz, H-2), 6.88 (m, 2H, H-6 and 7), 7.14 (d, 2H, H-5 and 8), 7.28-7.36 (m, 5H, H-2'-6'). ¹³C-NMR (100 MHz, CDCl₃) δ , ppm: 26.0 (C-3), 39.5 (C-4), 72.4 (C-2), 113.8, (C-8), 116.5 (C-6), 120.7 (C-7), 125.8 (C-2' and 6'), 126.2 (C-10), 127.7 (C-5), 128.5 (C-3' and 5'), 130.6 (C-4'), 143.9 (C-1'), 154.5 (C-9). [M]⁺ calculated for C₁₅H₁₄O m/z : 210.10.

58: Orange gum, 80 % yield; FTIR $\nu_{\max}$ cm^{-1} : 3190.9 (CH-sp²), 2989.1 (CH-sp³), 1598.4 (C=C aromatic), 1453.4 (C-C), 1307.9 (C-F), 1256.0 (C-O). ¹H-NMR (400 MHz, CDCl₃) δ , ppm: 2.90 (dd, 1H, J =12.4, 5.8 Hz, H-3a) 3.27 (t, 1H, J =6.3 Hz, H-3b), 3.66-3.74 (m, 1H, H-4a), 4.01 (q, 1H, J =7.15 Hz, H-4b), 4.44-4.54 (m, 1H, H-2), 6.72-6.97 (m, 5H, H-5, 6, 8, 3', 5'), 7.01-7.15 (m, 1H, H-4'), 7.78-7.97 (m, 2H, H-2', 6'). ¹³C-NMR (100 MHz, CDCl₃) δ , ppm: 26.0 (C-3), 39.5 (C-4), 72.4 (C-2), 113.8 (C-8), 116.5 (C-6), 120.7 (C-10), 127.2 (C-4'), 127.9 (C-2'), 128.4 (C-6'), 130.5 (C-3'), 131.0 (C-5'), 133.8 (C-1'), 139.3 (C-5), 154.5 (C-9), 163.3 (C-7), [M]⁺ calculated for C₁₅H₁₃FO m/z : 228.10.

59: Brown solid, yield, 81%; FTIR $\nu_{\max}$ cm^{-1} : 3385.6, 3333.5 (NH₂), 3072.0 (CH-sp²), 2928.2 (CH-sp³), 1548.2 (C=C aromatic), 1449.7 (C-C), 1239.4 (C-O), 852.6 (C-N). ¹H-NMR (400 MHz, CDCl₃) δ , ppm: 2.85 (dd, 1H, J =12.5, 6.0 Hz, H-3a), 3.15 (t, 1H, J =6.5 Hz, H-3b), 3.36-3.45 (m, 1H, H-4a), 3.56-3.65 (m, 1H, H-4b), 4.35-4.45 (m, 1H, H-2), 5.02 (s, 2H, NH₂), 6.62-6.87 (m, 5H, H-6, 7, 8, 3', 5'), 7.11-7.25 (m, 3H, H-5, 2', 6'). ¹³C-NMR (100 MHz, CDCl₃) δ , ppm: 28.1 (C-3), 31.3 (C-4), 78.2 (C-2), 110.8, (C-8), 118.4 (C-6), 118.9 (C-3' and 5'), 122.5 (C-10), 124.3 (C-7), 125.2 (C-2' and 6'), 128.4 (C-5), 129.7 (C-1'), 143.6 (C-4'), 152.4 (C-9), [M]⁺ calculated for C₁₅H₁₅NO m/z : 225.12.

3.4.3 Pyrazolines



Compound	R	R'	R''	Compound	R	R'	R''
60	OH	H	H	64	H	F	Ac
61	F	NO ₂	H	65	F	F	Ac
62	NO ₂	H	Ac	66	F	Et	Ac
63	H	H	Ac				

60: Orangish yellow solid, 72% yield. FTIR (neat) ($\nu_{\max}$ cm⁻¹): 3336.3 (O-H), 3300.1 (CH-sp²), 2980.4 (CH-sp³), 1662.2 (C=O), 1598.3 (C=N), 1516.4 (C=C), 1121.9 (C-N). ¹H-NMR (400 MHz, acetone-d₆) δ , ppm: 3.39 (dd, 1H, J = 16.2, 1.60 Hz, H-4a), 3.51 (dd, 1H, J = 16.2, 8.92 Hz, H-4b), 5.23 (d, 1H, J = 8.84 Hz, H-5), 6.65 (dd, 1H, J = 8.2, 0.96 Hz, H-3''), 6.91 (m, 1H, J = 7.78, 0.96 Hz, H-5'), 7.09 (m, 1H, J = 8.2, 1.5 Hz, H-4''), 7.19 (d, 1H, J = 7.68 Hz, H-6''), 7.31-7.38 (m, 3H, H-3', 4' and H-5'), 7.69 (dt, 2H, J = 7.88, 2.56 Hz, H-2' and 6'). ¹³C-NMR (100 MHz, acetone-d₆) δ , ppm: 40.6 (C-4), 56.9 (C-5), 116.0 (C-3''), 120.8 (C-5''), 126.3 (C-6''), 127.4 (C-4''), 128.2 (C-2'), 128.4 (C-6'), 128.6 (C-5'), 128.8 (C-3'), 133.0 (C-1'' and C-4'), 137.3 (C-1'), 151.2 (C-3), 152.8 (C-2''). [M]⁺ calculated for C₁₇H₁₆N₂O₂, m/z : 238.11.

61: Orange solid, 75% yield. FTIR (neat) $\nu_{\max}$ cm⁻¹: 3248.6 (CH-sp²), 2941.2 (CH-sp³), 1662.2 (C=O), 1589.2 (C=N), 1509.2 (N=O), 1147.7 (C-F), 814.3 (N-O). ¹H-NMR (400 MHz, CDCl₃) δ , ppm: 3.04 (dd, 1H, J = 16.4, 9.36 Hz, H-4a), 3.53 (dd, 1H, J = 16.4, 11.0 Hz, H-4b), 5.04 (dd, 1H, J = 10.9, 9.5 Hz, H-5), 6.61 (s, 1H, NH), 7.07 (t, 2H, J = 8.3 Hz, H-3'' and 5''), 7.36 (dd, 2H, J = 8.4, 2.02 Hz, H-2'' and H-6''), 7.79 (dd, 2H, J = 9.0, 2.02 Hz, H-2' and H-6'), 8.25 (dd, 2H, J = 9.0, 2.0 Hz, H-3' and H-5'). ¹³C-NMR (100 MHz, CDCl₃) δ , ppm:

40.9 (C-4), 64.3 (C-5), 115.8 (C-3''), 115.9 (C-5''), 124.0 (C-2'), 126.3 (C-6'), 135.6 (C-2''), 128.1 (C-6''), 137.6 (C-3'), 137.7 (C-5'), 138.9 (C-1''), 147.4 (C-1'), 148.3 (C-3), 161.2 (C-4'), 163.6 (C-4''). $[M]^+$ calculated for $C_{17}H_{14}FN_3O_3$, m/z : 285.09.

62: Yellow solid, 74% yield. FTIR (neat) ($\nu_{\max}$ cm^{-1}): 3103.3 (CH-sp²), 2977.9 and 2887.8 (CH-sp³), 1674.7 (C=O), 1599.3 (C=N), 1342.3 (N=O), 843.1 (N-O). ¹H-NMR (400 MHz, acetone-d₆) δ , ppm: 2.08 (s, 3H, H-2'''), 2.89 (dd, 1H, J =16.4, 11.2 Hz, H-4a), 3.63 (dd, 1H, J =16.4, 11.2 Hz, H-4a), 5.14 (q, J =11.2 Hz, 1H, H-5), 7.33-7.42 (m, 5H, H-2'-H-6'), 7.68-7.79 (m, 2H, H-2'' and 6''), 8.24-8.27 (m, 2H, H-3'' and H-5''). ¹³C-NMR (100 MHz, acetone-d₆) δ , ppm: 24.4 (C-2'''), 41.0 (C-4), 63.3 (C-5), 123.5 (C-2''), 123.6 (C-6''), 123.7 (C-5''), 123.8 (C-3''), 128.2 (C-6'), 128.3 (C-2'), 128.5 (C-5'), 128.6 (C-3'), 132.9 (C-4'), 133.3 (C-1'), 145.3 (C-4''), 147.2 (C-1''), 151.2 (C-3), 162.2 (C-1'''). $[M]^+$ calculated for $C_{17}H_{15}N_3O_3$, m/z : 309.11.

63: Brownish orange paste, 76% yield. FTIR (neat) ($\nu_{\max}$ cm^{-1}): 3040.7 (CH-sp²), 2890.4 (CH-sp³), 1678.4 (C=O), 1597.6 (C=N), 1513.1 (C=C). ¹H-NMR (400 MHz, acetone-d₆) δ , ppm: 2.08 (s, 3H, H-2'''), 2.83 (dd, 1H, J =16.9, 11.7 Hz, H-4a), 3.72 (dd, 1H, J =16.9, 11.9 Hz, H-4b), 5.18 (t, 1H, J =11.8 Hz, H-5), 7.25-7.92 (m, 7H, H-3', 5', 2'', 3'', 4'', 5'', 6''), 8.09-8.11 (m, 3H, H-2', 4' and 6'). ¹³C-NMR (100 MHz, acetone-d₆) δ , ppm: 23.4 (C-2'''), 44.7 (C-4), 64.1 (C-5), 125.6 (C-4''), 126.8 (C-2'' and C-6''), 128.1 (C-3'' and C-5''), 128.4 (C-3'), 128.4 (C-5'), 128.5 (C-2'), 128.5 (C-6'), 131.5 (C-4'), 133.4 (C-1'), 146.5 (C-1''), 146.6 (C-3), 168.2 (C-1'''). $[M]^+$ calculated for $C_{17}H_{16}N_2O$, m/z : 264.13.

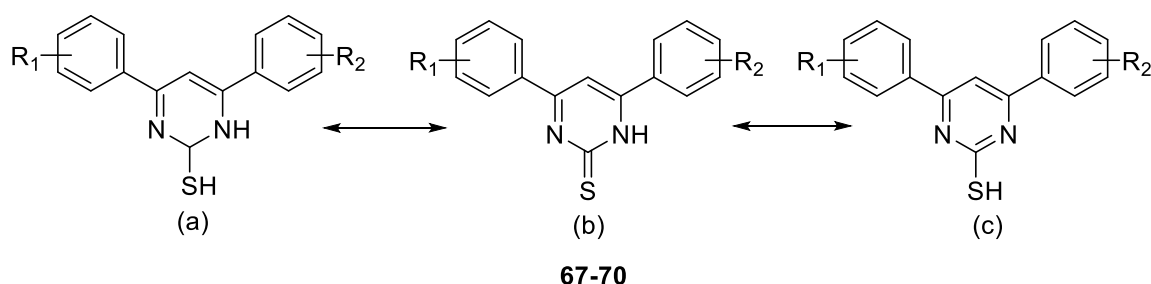
64: Orange solid, 71% yield. FTIR (neat) ($\nu_{\max}$ cm^{-1}): 3244.1 (CH-sp²), 2887.9 (CH-sp³), 1673.6 (C=O), 1597.7 (C=N), 1506.6 (C=C), 1228.1 (C-F). ¹H-NMR (400 MHz, CDCl₃) δ , ppm: 2.43 (s, 3H, H-2'''), 3.34 (dd, 1H, J =14.6, 8.6 Hz, H-4a), 3.89 (dd, 1H, J =14.4, 8.6 Hz, H-4b), 5.38 (dd, 1H, J =8.6, 3.5 Hz, H-5), 6.83 (m, 1H, H-6'), 7.14 (m, 4H, H-3', 3'', 5' and

5''), 7.45 (m, 2H, H-2' and 6'), 7.73 (m, 2H, H-2'' and H-6''). ¹³C-NMR (100 MHz, CDCl₃) δ, ppm: 26.6 (C-2'''), 43.3 (C-4), 70.0 (C-5), 115.7 (C-3'), 116.0 (C-5'), 125.6 (C-4''), 127.4 (C-2''), 127.5 (C-6''), 128.4 (C-5''), 128.8 (C-3''), 129.0 (C-6'), 130.7 (C-2'), 132.6 (C-1'), 148.5 (C-1''), 161.5 (C-3), 164.0 (C-4'), 173.4 (C-1'''). [M]⁺ calculated for C₁₇H₁₅FN₂O; *m/z*: 282.12.

65: Yellowish orange solid, 69% yield. FTIR (neat) (ν_{max} cm⁻¹): 3244.3 (CH-sp²), 2980.4 (CH-sp³), 1604.6 (C=O), 1504.1, (C=C), 1343.5(C-F), 1159.2 (C-N). ¹H-NMR (400 MHz, CDCl₃) δ, ppm: 0.89 (s, 3H, H-2'''), 2.99-3.05 (dd, 1H, *J*= 9.9, 16.6 Hz, H-4a), 3.44-3.48 (dd, 1H, *J*= 10.2, 16.6 Hz H-4b), 4.94 (t, 1H, *J*= 9.84 Hz, H-5), 7.14 (t, 4H, *J*=9.0 Hz, H-3', 3'', 5' and 5''), 7.69 (dd, 4H, *J*=3.2, 8.4, Hz, H-2', 2'', 6' and H-6''), ¹³C-NMR (100 MHz, CDCl₃) δ, ppm: 23.47 (C-2'''), 40.7 (C-4), 61.6 (C-5), 115.8 (C-3' and C-5'), 116.1 (C-3'' and C-5''), 127.3 (C-2'' and C-6''), 127.4 (C-2' and C-6'), 133.5 (C-1'), 139.1 (C-1''), 152.4 (C-3), 161.2 (C-4''), 166.3 (C-4'), 168.2 (C-1'''). [M]⁺ calculated for C₁₇H₁₄F₂N₂O, *m/z*: 300.11.

66: Pale yellow powder, 77% yield. FTIR (neat) (ν_{max} cm⁻¹): 3049.4 (CH-sp²), 2974.1 and 2889.4 (CH-sp³), 1671.5 (C=O), 1508.9 (C=C), 1347.1 (C-F), 1112.9 (C-N). ¹H-NMR (400 MHz, CDCl₃) δ, ppm: 1.12 (t, 3H, *J*=7.6 Hz, CH₃ (Et)), 1.92 (s, 3H, H-2'''), 2.57 (q, 2H, *J*= 7.8 Hz, CH₂ (Et)), 2.81 (dd, 2H, *J*=16.6, 2.12 Hz, H-4a), 3.12-3.19 (dd, 1H, *J*= 10.2, 16.6 Hz, H-4a), 4.61 (dd, 1H, *J*= 9.84 Hz, H-5), 6.89 (t, 2H, *J*=8.64 Hz, H-3'' and 5''), 7.08 (d, 2H, *J*=7.9 Hz, H-2'' and H-6''), 7.25 (d, 2H, *J*=4.0, 8.2 Hz, H-2' and H-6'), 7.52 (d, 2H, *J*= 8.2 Hz, H-3' and H-5'), ¹³C-NMR (100MHz, CDCl₃) δ, ppm: 15.2 (CH₃), 28.9 (C-2'''), 43.7 (CH₂), 46.1 (C-4), 76.7 (C-5), 115.4 (C-3''), 115.6 (C-5''), 127.9 (C-2'), 128.1 (C-6'), 129.7 (C-3'), 129.8 (C-5'), 134.5 (C-2'' and C-6''), 138.4 (C-1'), 138.5 (C-1''), 150.0 (C-4'), 160.4 (C-3), 162.8 (C-4'' and C-1'''). [M]⁺ calculated for C₁₉H₁₉FN₂O, *m/z*: 310.15.

3.4.4 Pyrimidines



Compound	R ₁	R ₂	Compound	R ₁	R ₂
67a, b, c	H	OH	69	H	H
68a, b, c	NO ₂	F	70	F	H

67: Cream solid, 68% yield. FTIR (neat) ($\nu_{\max}$ cm⁻¹): 3433.1 (NH), 3273.7 (OH), 2977.3 (CH-sp²), 1270.5 (C=N), 1181.8 (-N-C=S). ¹H-NMR (400 MHz, CDCl₃): δ , ppm: 1.48 (s, 1H), 2.47 (s, 1H), 5.44 (s, 1H), 6.02 (dd, 1H, $J=8.1, 5.2$ Hz), 6.76-6.98 (m, 1H), 7.09 (s, 1H), 7.25-8.11 (m, aromatic H's), 8.17 (s, 1H), 12.89 (s, 1H), 12.99 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ , ppm: 77.2, 108.1, 114.4, 119.2, 127.5, 127.6, 128.3, 128.7, 129.0, 129.1, 133.8, 140.3, 143.6, 148.4, 153.8, 163.2. [M]⁺ **67a**: calculated for C₁₆H₁₄N₂OS, m/z : 282.08; **67b** and **c**: calculated for C₁₆H₁₂N₂OS, m/z : 280.07.

68: Orange powder, 69% yield. FTIR (neat) ($\nu_{\max}$ cm⁻¹): 2962.7 (CH-sp²), 1593.2 and 1377.2 (N-O), 1466.2 (C-F), 1230.1 (C=N), 1098.7 (-N-C=S). ¹H-NMR (400 MHz, CDCl₃): δ , ppm: 1.12 (s, 1H), 1.19 (s, 1H), 5.87 (m, 2H), 6.71 (m, 1H) 7.11-8.18 (m, aromatic H's), 9.92 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ , ppm: 75.3, 105.3, 116.2, 117.1, 125.3, 125.4, 127.6, 127.7, 129.8, 129.9, 134.8, 141.7, 143.1, 147.4, 157.8, 165.3. [M]⁺ **68a** C₁₆H₁₂FN₃O₂S m/z : 329.06; **68b** and **68c** calculated for C₁₆H₁₀FN₃O₂S, m/z : 327.05.

69: Yellowish orange slurry, 67% yield. FTIR (neat) ($\nu_{\max}$ cm⁻¹): 2963.5 (CH-sp²), 1235.9 (C=N), 1058.3 (-N-C=S). ¹H-NMR (400 MHz, acetone-d₆): δ , ppm: 2.05-2.08 (m, 2H),

7.11(s, 1H), 7.22-7.94 (m, aromatic H). ^{13}C -NMR (100 MHz, acetone- d_6): δ , ppm: 99.4, 127.2, 127.2, 127.3, 127.3, 128.2, 128.3, 130.5, 130.5, 130.7, 130.7, 133.6, 133.6, 163.2, 163.6, 180.3 $[\text{M}]^+$ calculated for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{S}$, m/z : 266.09.

70: Yellow solid, 69% yield. FTIR (neat) (ν_{max} cm^{-1}): 3493.4 (NH), 2967.9 ($\text{Csp}^2\text{-H}$), 1359.7 (C-F), 1283.3 (C=N), 1172.4 (-N-C=S). ^1H -NMR (400 MHz, CDCl_3): δ , ppm: 1.15-1.19 (m, 2H), 6.46 (dd, 1H, $J=8.8, 6.8$ Hz), 6.62-6.87 (m, 1H), 6.93-8.03 (m, aromatic H). ^{13}C -NMR (100 MHz, CDCl_3) δ , ppm: 77.2, 108.1, 113.4, 114.2, 125.9, 126.6, 127.4, 127.9, 128.5, 128.9, 129.4, 130.4, 131.6, 140.2, 143.6, 156.3, 164.7. $[\text{M}]^+$ calculated for $\text{C}_{16}\text{H}_{13}\text{FN}_2\text{S}$, m/z : 284.08.

CHAPTER 4

RESULTS AND DISCUSSIONS

4.1 Chalcones

Several novel heterocyclic chalcone analogues were accomplished via a one-pot base-catalyzed Claisen-Schmidt condensation reactions in ethanol between appropriate benzaldehyde derivatives and substituted acetophenones (Hamada & Abdo, 2015). They were also prepared by utilizing the eco-friendly grinding technique without the use of a solvent in condensing the aryl ketones with the aromatic aldehydes.

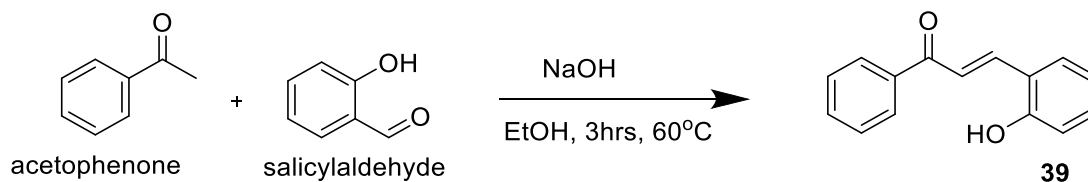
4.1.1 Compound 39

Compound **39** was obtained as a yellow solid in 69% yield after the conventional aldol condensation reaction in ethanol between salicylaldehyde (2-hydroxybenzaldehyde) and acetophenone in the presence of NaOH. Compound **39** was also synthesized by grinding the ingredients without solvent, which resulted in an improved yield of 74%. The IR spectrum displayed bands at 3180 and 1638 cm^{-1} for the hydroxy and α , β -unsaturated ketone groups. (Al-Otaibi et al., 2020; Arif et al., 2020; Elkhailifa et al., 2020). The unsubstituted chalcone (benzalacetophenone) shows a carbonyl band at 1659 cm^{-1} which was assigned to the carbonyl conjugation with two phenyl groups and an aliphatic double bond (Hergert & Kurth, 1953). The introduction of the hydroxyl group in the 6-position shifted the carbonyl frequency.

The ^1H NMR spectra of **39** showed signals for aromatic protons and the *trans* unsaturated ketone. The *trans* coupled protons ($J=15.8$ Hz) exhibited a pair of doublets at δ_{H} 7.85 (H_α) and 8.04 (H_β). ^1H NMR spectra demonstrate that the chalcone was geometrically pure with a

trans configuration. The nine aromatic protons resonated between δ_H 6.86 and 8.11. The ^{13}C NMR showed thirteen signals, inclusive of the carbonyl carbon resonating downfield at δ_C 189.9 and the C_α and C_β signals at δ_C 121.8 and 139.9, respectively. The aromatic 2'-C-OH carbon signal resonated as an oxygenated carbon signal at δ_C 157.7.

The NMR data for the chalcone revealed the characteristic vinyl ketone moiety and was comparable with the Literature data for chalcones (Borade et al., 2020; da Silva et al., 2021; Elkhailifa et al., 2020). Thus, Compound **39** structure was ascribed to be (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one, **Scheme 15** and **Figure 13** and **14**.



Scheme 15: Synthesis of (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **39**.

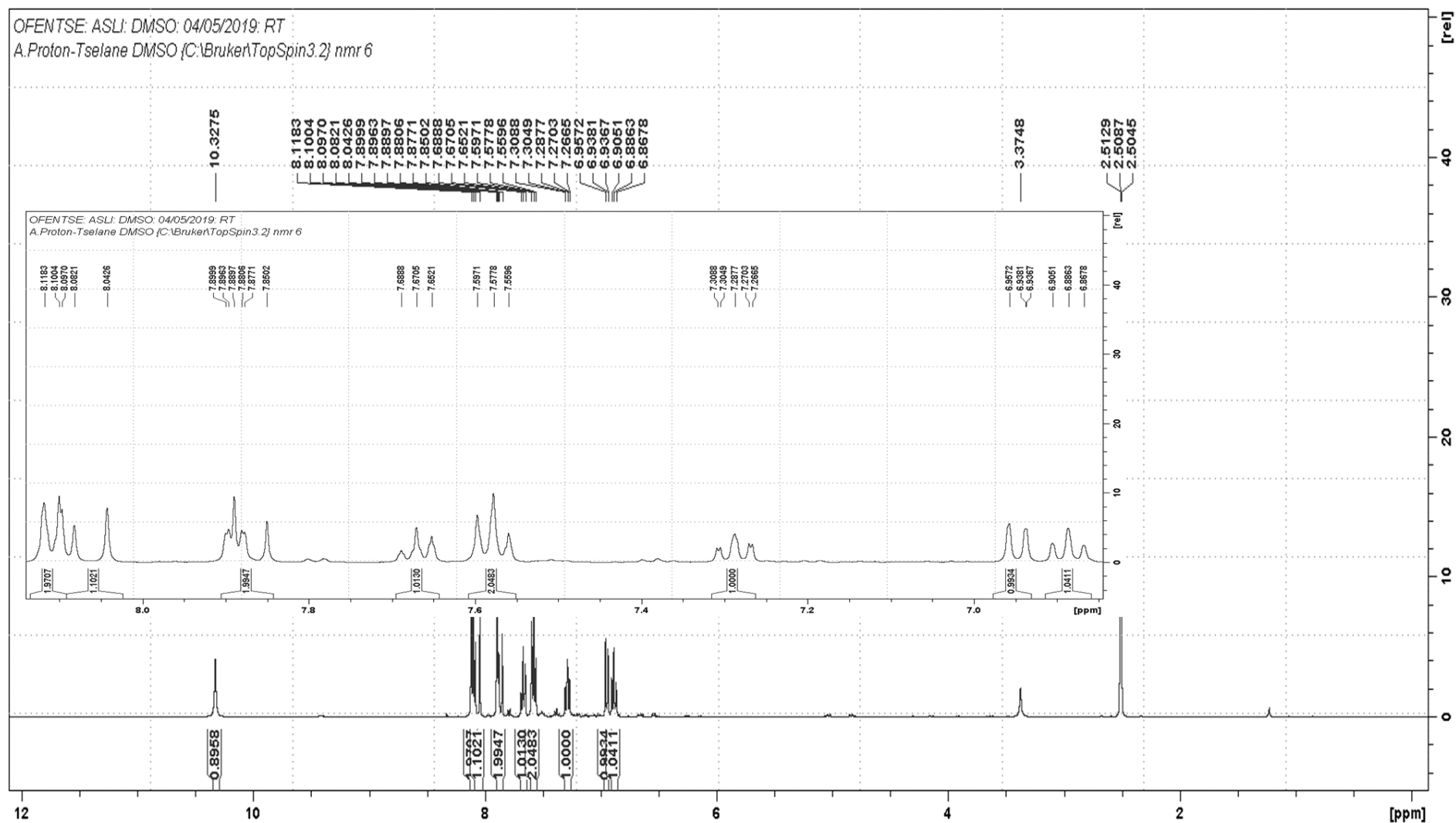


Figure 13. ^1H NMR (400 MHz, DMSO- d_6) of (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **39**

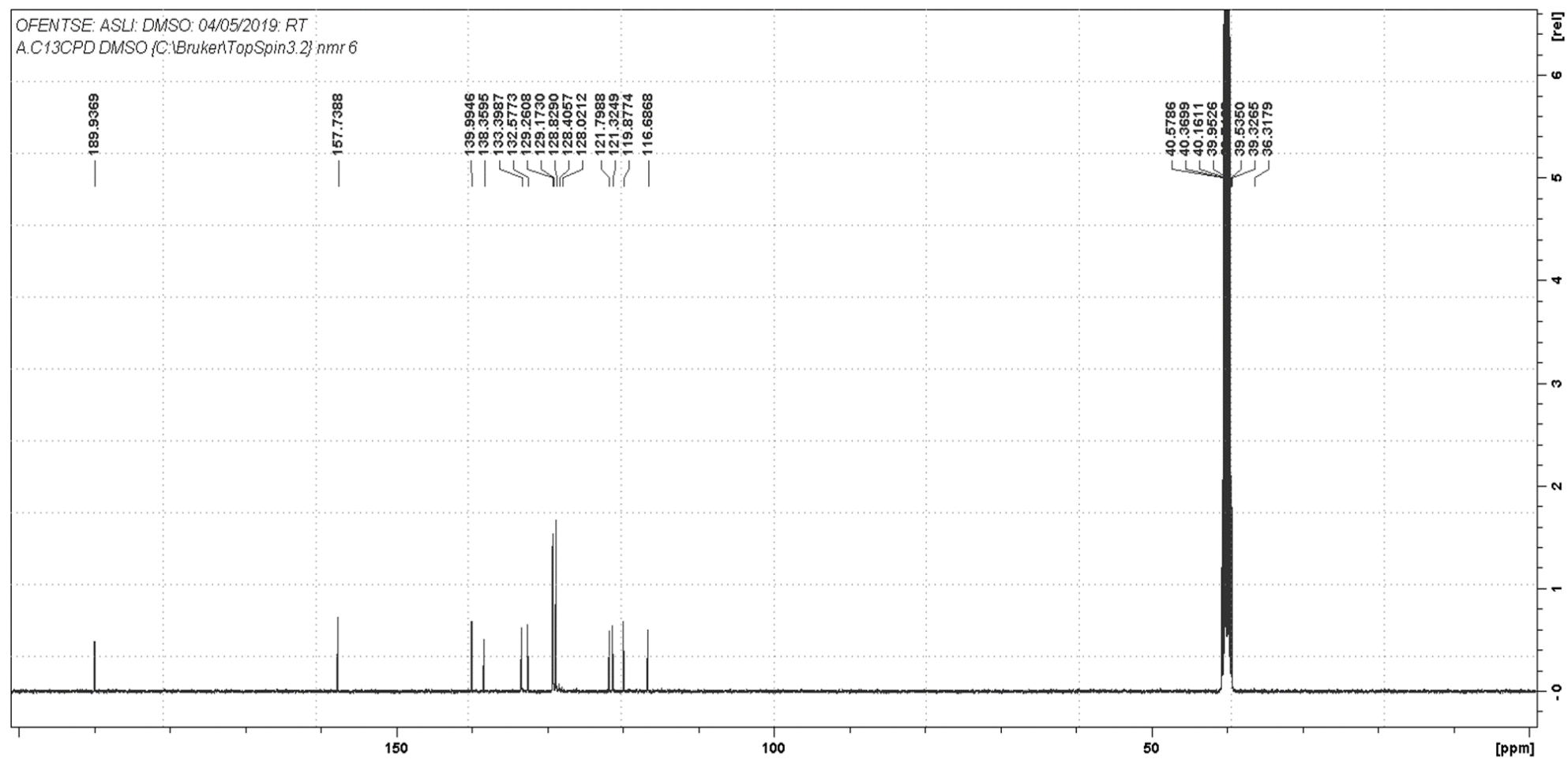
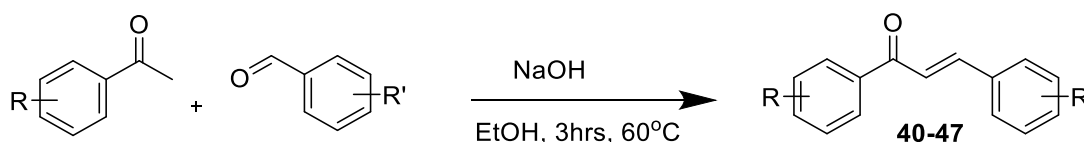


Figure 14. ^{13}C NMR (100 MHz, DMSO-d_6) of (E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **39**.

4.1.2 Compounds 40-47

Seven other chalcones (**Table 2**) were synthesized using Method A and B and were obtained in 51-67% yields. These were then characterized in a similar manner to compound **39** to note their successful preparation. The chalcones keto-ethylenic group (-CO-CH=CH-) in their structure was indicated by IR peaks near 1620-1650 cm^{-1} (El-Sayed et al., 2021; Kumar et al., 2020; Rani et al., 2019; Santiago et al., 2018). The carbonyl vibrational stretch appeared as one peak suggesting formation of one isomer rather than coexistence of both *cis* and *trans*. The bands at 1570-1610 cm^{-1} are assigned to the vibrations of the phenyl aromatic rings. The chalcones proton H_α and H_β resonated at δ_{H} 6.71-7.80 and 7.5-8.10 as *trans* doublet pairs with a characteristic coupling constant (*J*) of 15.5-16.0 Hz on the ^1H NMR spectrum, confirming the formation of chalcones possessing an α , β -unsaturated ketone. The higher coupling constant value indicates that the chalcones were geometrically *trans* (*E*) configured.



	R	R'	% Yield		R	R'	% Yield
40	H	2'-OH	71	44	H	H	-
41	4-NH ₂	2'-OH	73	45	4-F	H	75
42	4-NO ₂	2'-OH	76	46	4-F	4'-F	74
43	H	4'-NO ₂	73	47	Et	4'-F	79

Scheme 16: Claisen–Schmidt condensation of substituted benzaldehydes and acetophenones to synthesize chalcones.

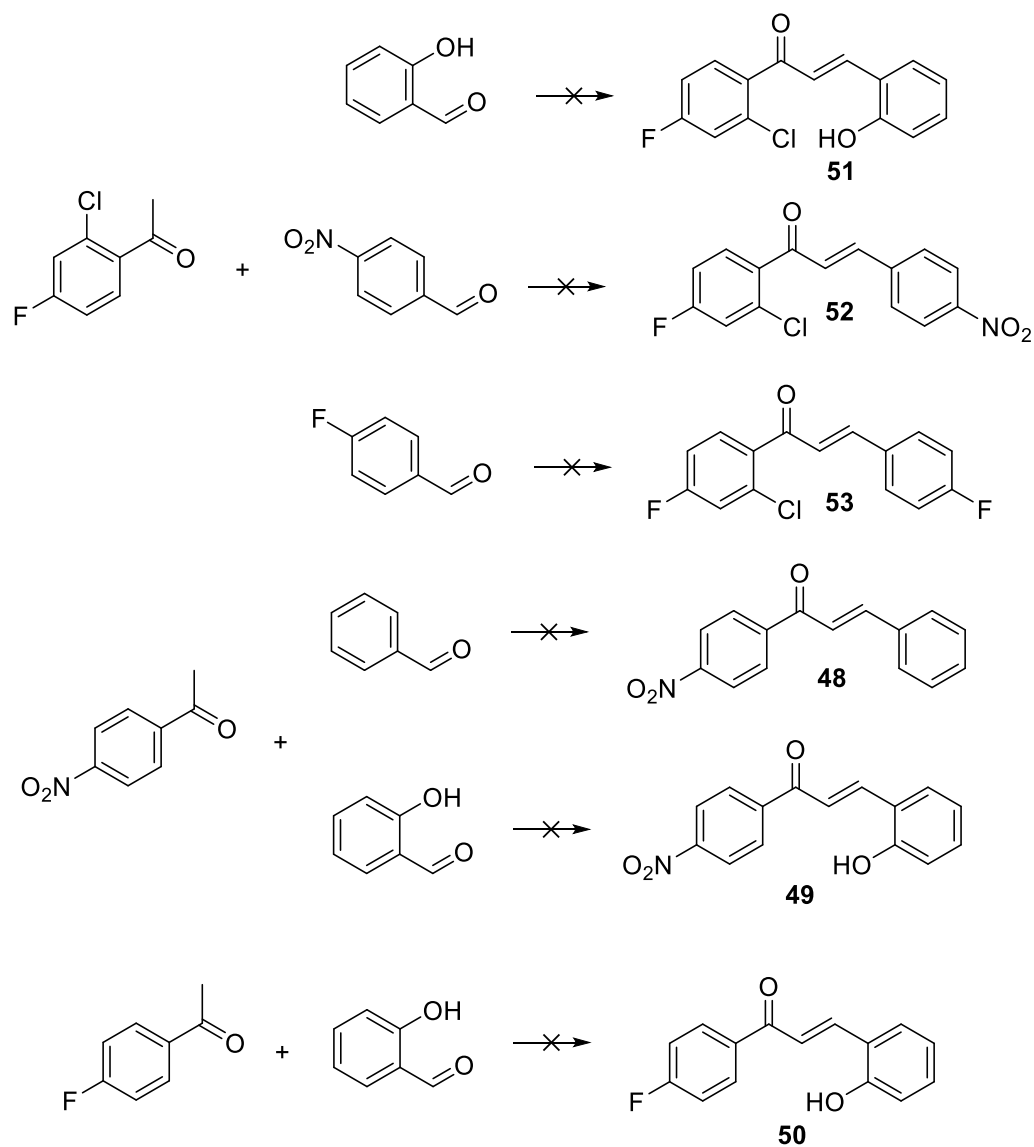
The synthesized chalcone structures (Table 2) were consistent with literature data. (Bandeira et al., 2019; Pinto et al., 2019; Salum et al., 2020; Siqueira et al., 2020). Fluorinated chalcones **45-47** were obtained in good yields. This was noteworthy because fluorination of chalcones has been shown to enhance their biological activity such as anti-inflammatory (Abdellatif et al., 2015).

4.1.3 Unsuccessful chalcone synthesis

The condensation of some acetophenones and aldehydes generated interesting results. An insoluble solid was obtained in reacting *p*-nitro/fluoro acetophenone with salicylaldehyde and *p*-nitro acetophenone with benzaldehyde. Gomez and co-workers encountered and experienced a similar situation in synthesizing the nitro chalcones and realized that the crude solid products dissolved in DMSO (Gómez-Rivera et al., 2013). Conversely, reaction with *p*-fluoro benzaldehyde with *p*-nitro acetophenone/*p*-fluoro acetophenone were successful. This observation was supported by Zhuang et al study which indicated that the aldehyde electron-withdrawing groups (EWG's) substituents favored the condensation in basic conditions, while the aldehyde electron-donating groups (EDG's) favored condensation in acidic conditions, and noted that the vinyl ketone α -carbon is not easy to dehydrate when the ketone has an electrophile like substituent (Zhuang et al., 2017). Ring B EWG's enhances the reaction rate, on the other hand EDG's decreases the reaction rate. The EDG's strengthened hydrogen bonding character and thus decreased the electrophilic character of the β -carbon (Majed et al., 2020).

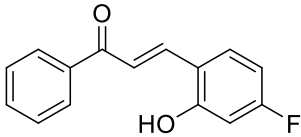
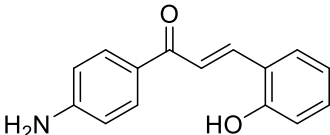
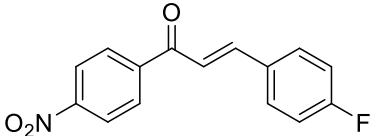
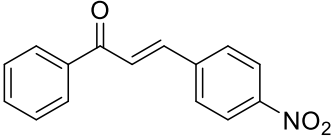
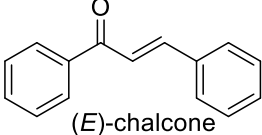
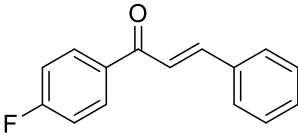
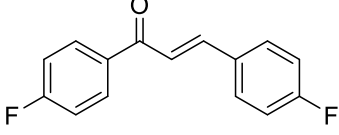
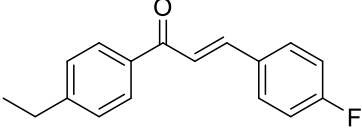
This implies that in case of the hydroxy and unsubstituted benzaldehyde an acid catalyzed protocol deemed important. Ostensibly the substituents, nature of and/or the substitution pattern on acetophenone and aldehyde dictates the outcome of the formation and isolation of the desired chalcone (Hall et al., 2020; Mustikasari & Santoso, 2020). Literature reports halogenated chalcones necessitated by use of KOH as a catalyst (Anil & Polat, 2020; Susanti & Setyowati, 2019). The incidences of failure in condensing the ketones with aldehydes calls for modified protocols; such as use of green and reusable catalysts or ionic liquids (Adnan et al., 2020; Yadav & Wagh, 2020). These may lead to successful preparation of biologically important polyfluorinated chalcones. **Scheme 17** shows the attempted synthesis of nitro and

fluoro substituted chalcones which gave no yields or inseparable and unidentifiable mixtures using both method A and B.



Scheme 17: Attempted and unsuccessful preparation of fluoro and nitro substituted chalcones in NaOH.

Table 2: Structures of the synthesized chalcone

Compound Code	Structure and Name
40	 (<i>E</i>)-3-(4-fluoro-2-hydroxyphenyl)-1-phenylprop-2-en-1-one
41	 (<i>E</i>)-1-(4-aminophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one
42	 (<i>E</i>)-3-(4-fluorophenyl)-1-(4-nitrophenyl)prop-2-en-1-one
43	 (<i>E</i>)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one
44	 (<i>E</i>)-chalcone
45	 (<i>E</i>)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one
46	 (<i>E</i>)-1,3-bis(4-fluorophenyl)prop-2-en-1-one
47	 (<i>E</i>)-1-(4-ethylphenyl)-3-(4-fluorophenyl)prop-2-en-1-one

4.2 Flavans

The treatment of a solution of the chalcone in methanol with NaBH₄ at room temperature enabled the reduction of both the carbon-carbon double bond and the keto-group of the chalcone vinyl ketone to give secondary alcohol. Dissolution of the alcohol in acetic acid followed by refluxing for 30 minutes afforded the flavans.

4.2.2 Compound 57

Sodium borohydride reduction of (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **39** afforded alcohol **54** in 83% yield, and **57** was obtained by cyclization of the alcohol **54** in acetic acid in 82% yield as an orange-brown gum.

For the structure elucidation of **54**, the IR spectrum displayed absorption bands corresponding to hydroxyl group (3383.9 cm⁻¹) and aromatic (1670.1-1455.4 cm⁻¹) groups (Moosophon et al., 2013; Soongprasit et al., 2020). The proton NMR data revealed the presence of one sp³ methine and two sp³ methylene signals at δ_H 4.64, 2.74-2.98 and 1.94-2.14 respectively. In agreement, the ¹³C NMR showed 15 carbons attributable to one CH and two CH₂ aliphatic carbons, three quaternary carbons, nine aromatic sp² CH carbons. The quaternary carbons were inclusive of the downfield oxygenated carbon signal at δ_C 154.5 (Alawaf, 2017). Compound **54** was inferred as 2-(3-hydroxy-3-phenylpropyl) phenol, **Scheme 18** and **Figure 15** and **16**.

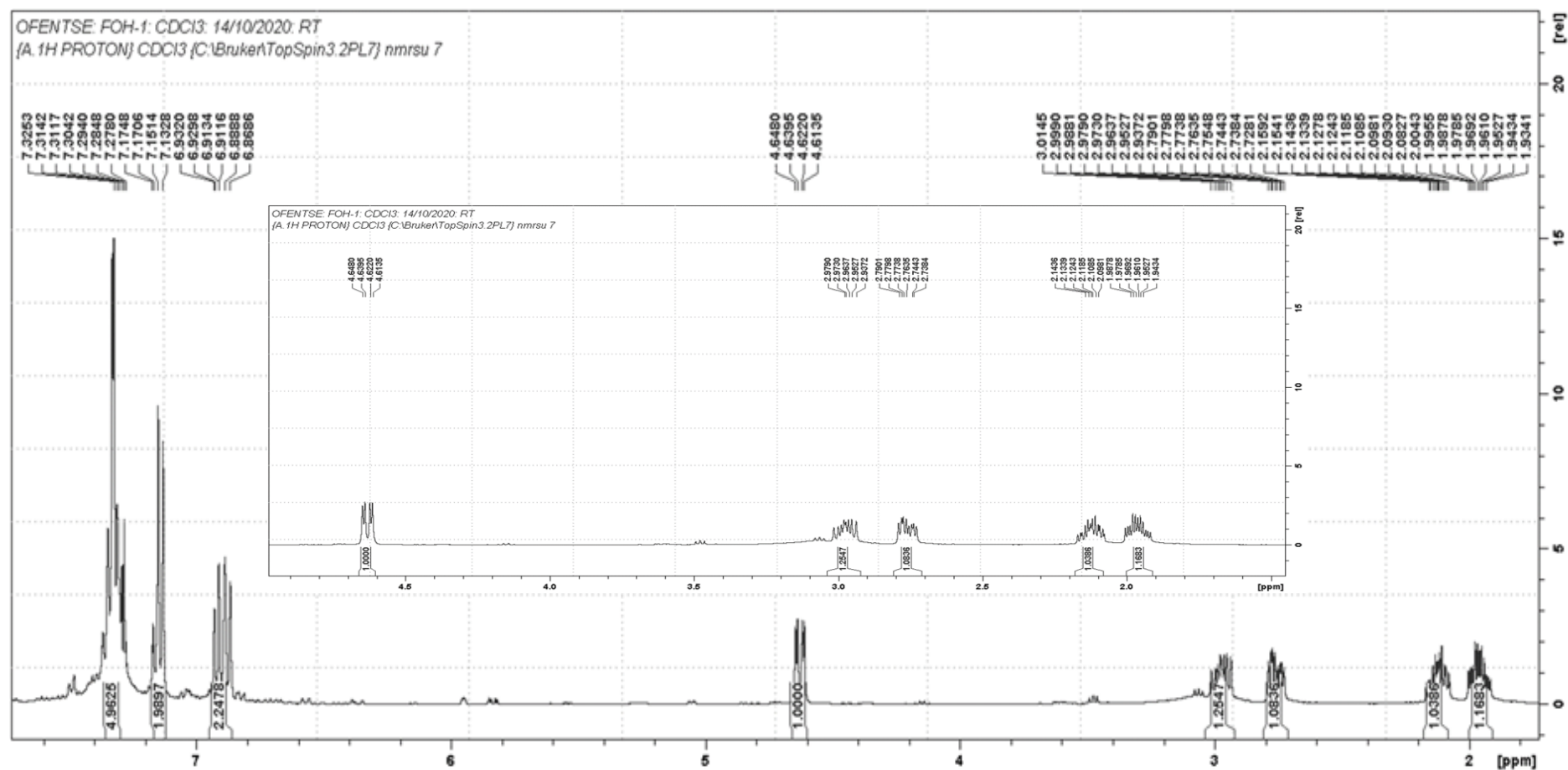


Figure 15. ¹H-NMR (400 MHz, CDCl₃) of 2-(3-hydroxy-3-phenylpropyl) phenol **54**.

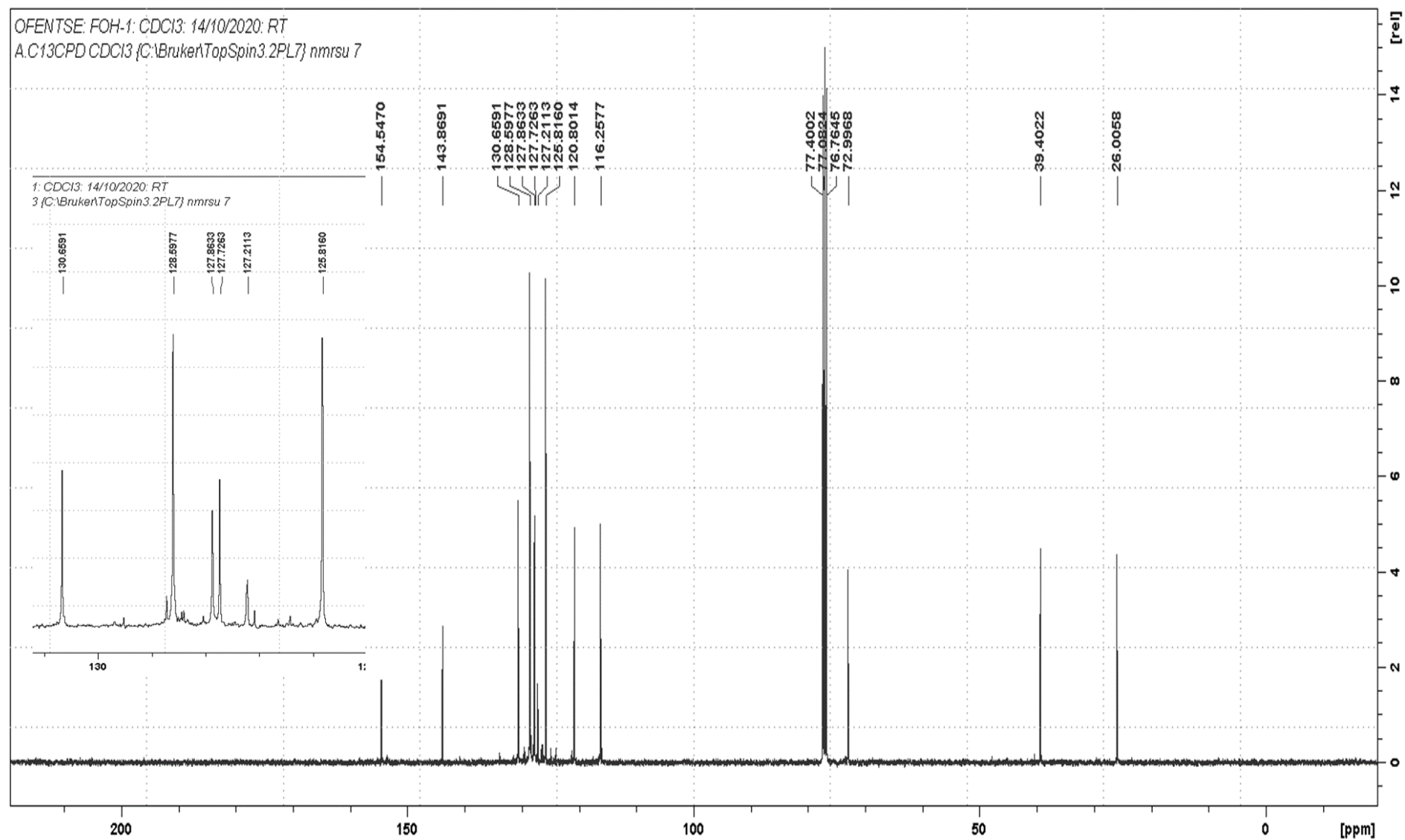
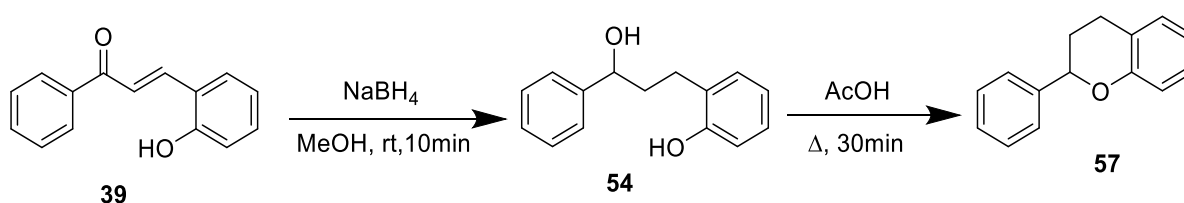


Figure 16. ¹³C-NMR (100 MHz, CDCl₃) of 2-(3-hydroxy-3-phenylpropyl) phenol **54**.

The IR spectrum of **57** showed a band at 2904 and 3270 cm^{-1} corresponding to aliphatic and aromatic C-H stretching. A band at 1619-1584 cm^{-1} observed was due to aromatic C=C stretching, and a band at 1236 cm^{-1} represented C-O stretching.

The ^1H NMR exhibited the characteristic two sets of methylene proton resonance at δ_{H} 1.92-2.12 and 2.75-2.98 for H-3 and H-4 respectively and an oxymethine proton at δ_{H} 3.53 (H-2) which frames the flavan's benzopyran ring. The ^{13}C NMR was in agreement as it detailed the three aliphatic carbons (δ_{C} 71.6, CH-2), (δ_{C} 31.5, CH_2 -4), and (δ_{C} 33.4, CH_2 -3) together with the three quaternary carbons (C1', C-9 and C-10) and nine benzene sp^2 CH showing that the cyclization of the alcohol was achieved (Banzato et al., 2020; Kuo et al., 2013). Compound **57** which was obtained in a good yield of 82% indicated to be a 2-phenylchromane, **Scheme 18** and **Figure 17** and **18**.



Scheme 18: Synthesis of 2-phenylchromane

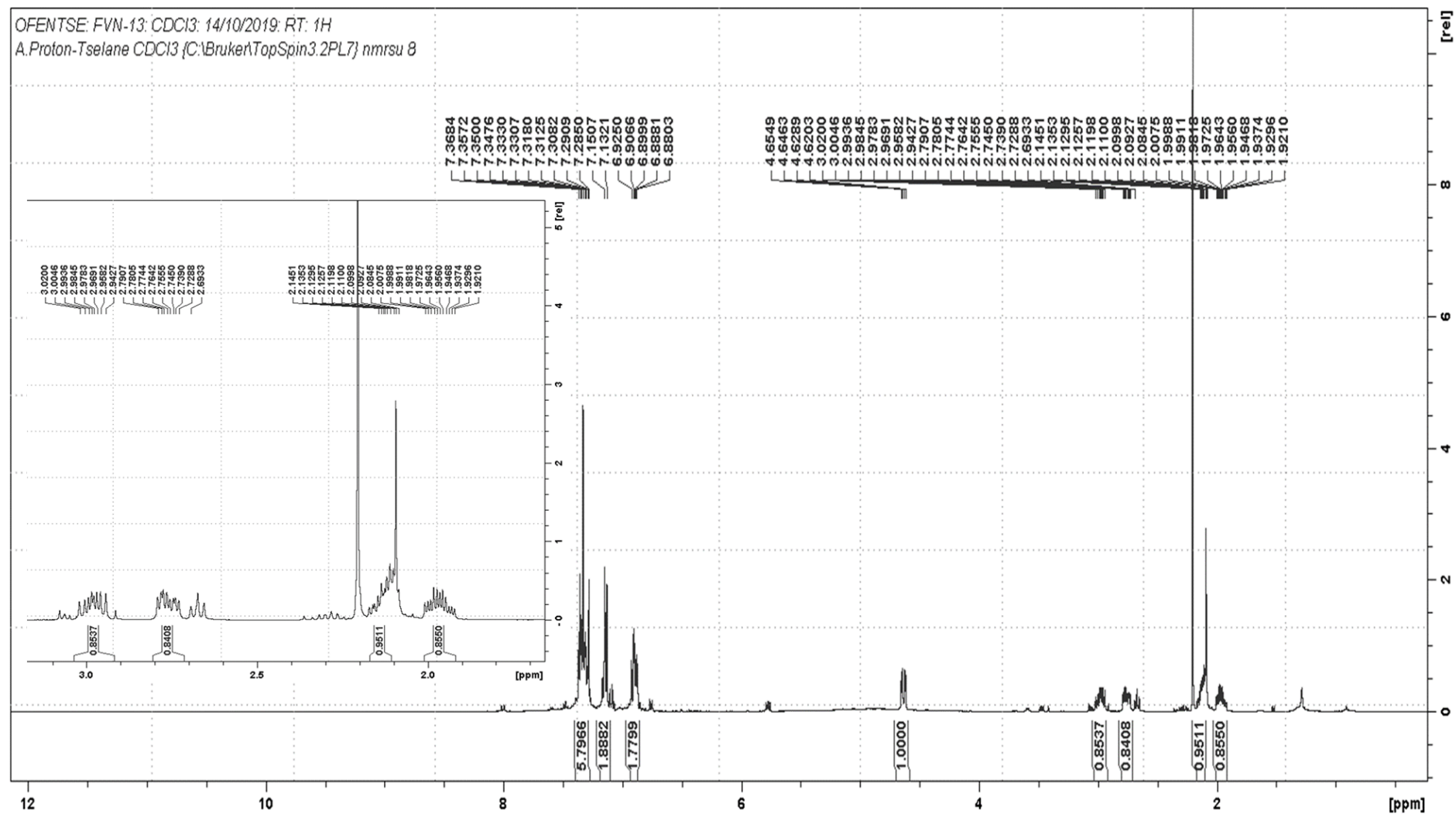


Figure 17. ^1H -NMR (400 MHz, CDCl_3) of 2-phenylchromane 57.

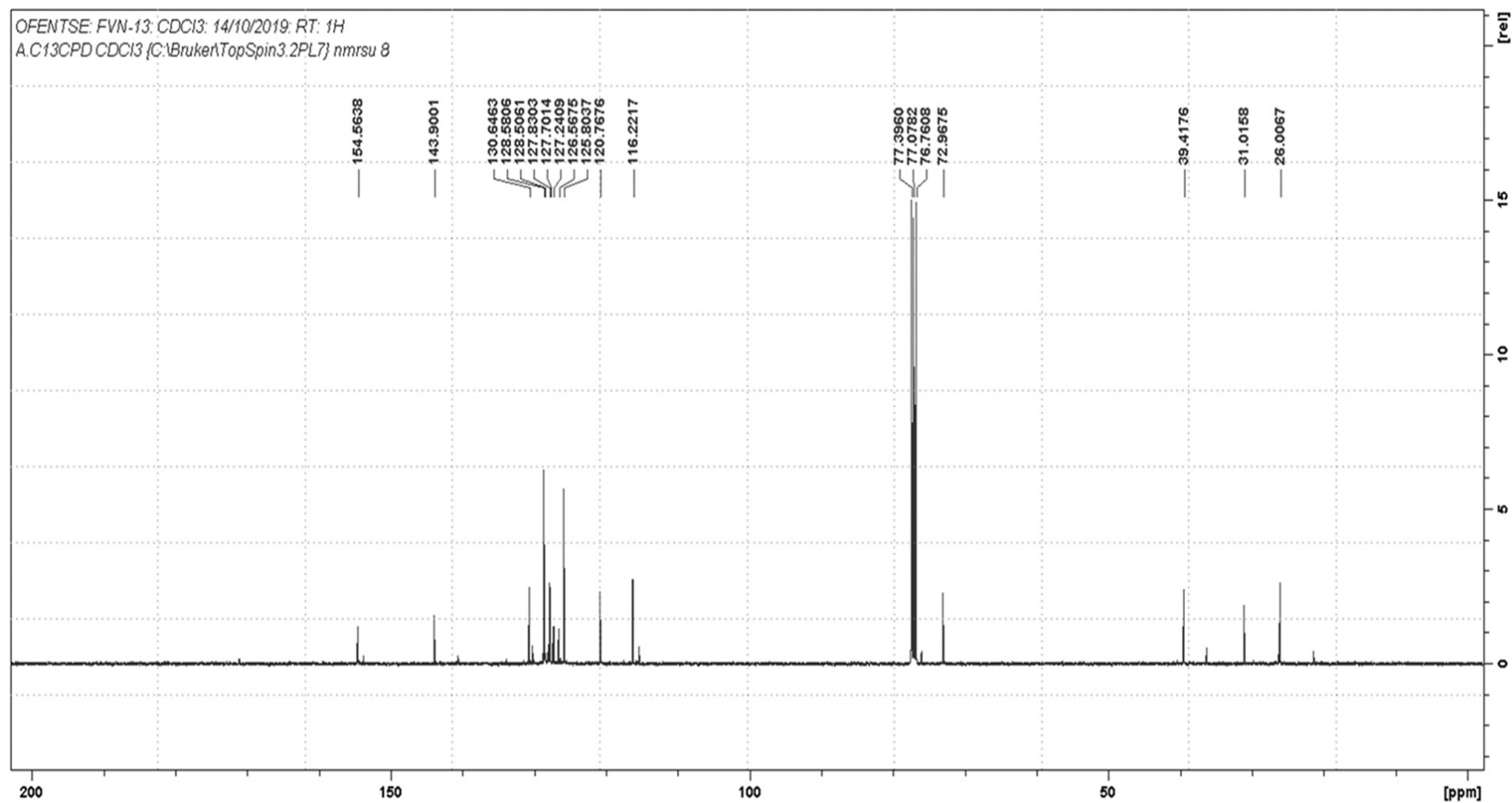
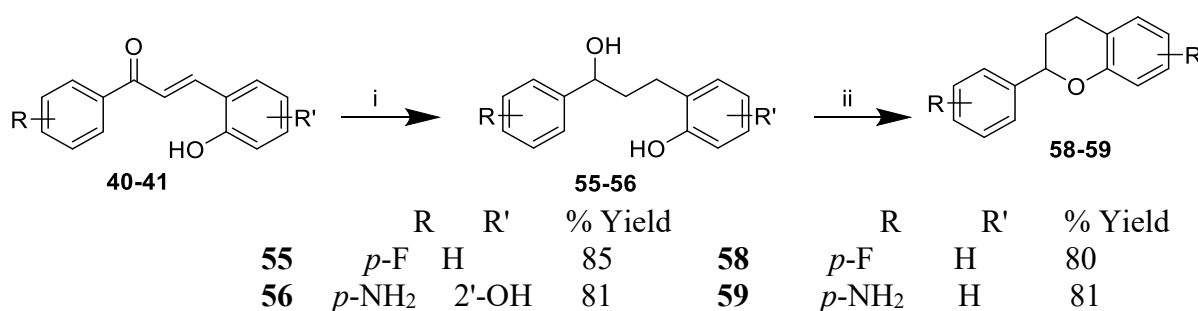


Figure 18. ¹³C-NMR (100 MHz, CDCl₃) of 2-phenylchromane **57**.

4.2.3 Compounds 58 and 59

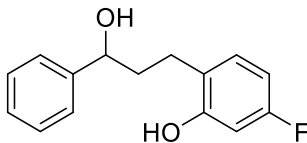
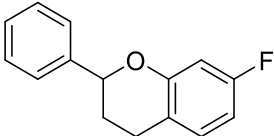
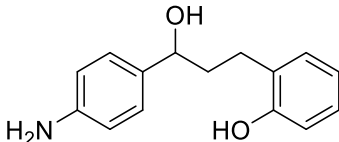
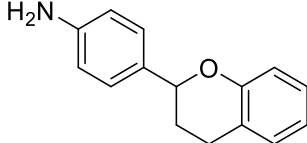
The structures of the other flavan molecules (**Table 3**) were established based on the NMR data and notable literature comparison (Kainsa & Singh, 2016; Karpakavalli et al., 2019; Nurkenov et al., 2019). The data obtained was consistent with the presence of two aromatic spin systems: the AB system, flavan A ring, and the AA'BB' system of flavan B ring. The diagnostic proton NMR peaks for the formation of the flavan ring were δ_H 1.92-2.75 (3-CH₂), 2.90-3.27 (4-CH₂), 4.44-4.63 (2-CH-OH). The different signals of the two methylene hydrogens indicated that they were magnetically non-equivalent, which may be due to the solvent effects or because of a change in the molecular conformation. The flavans were obtained in good yields of 80-81%.

Flavan **59**, is reported here using a less hazardous method, while previous method involved the preparation of flavanone using inorganic acids. The flavanones were then reduced to flavans using Clemmensen reduction (Zinc-amalgam-conc. HCl) or Zn-Hg catalyst (Bachelor, n.d. 1979, 1984). While flavan **58** was also reported from a one pot method involving use of transition metal-based catalyst (Ru-NHC complex) to cross couple primary and secondary alcohols (Shee et al., 2017) in 90% yield.



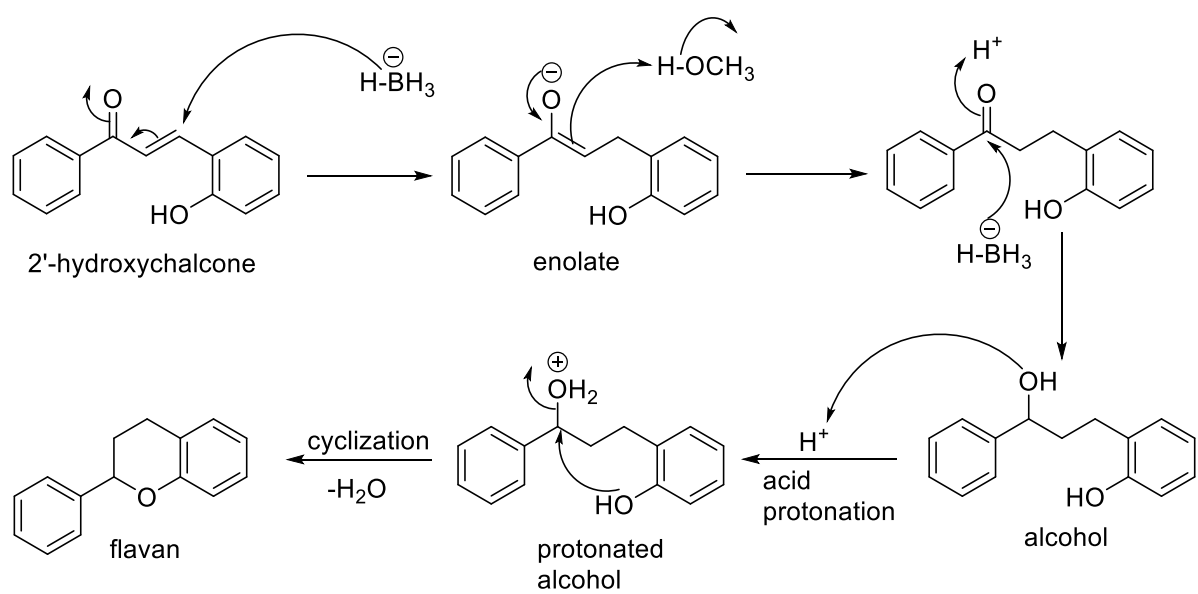
Scheme 19: General synthesis of flavans; reagents and conditions: i) NaBH₄, MeOH, rt, 10 min. ii) AcOH, reflux, 30 min.

Table 3: Structures of the synthesized saturated alcohols and flavans

Compound Code	Structure and Name
55	 5-fluoro-2-(3-hydroxy-3-phenylpropyl)phenol
58	 7-fluoro-2-phenylchromane
56	 2-(3-(4-aminophenyl)-3-hydroxypropyl)phenol
59	 4-(chroman-2-yl)aniline

4.2.4 Mechanism for the synthesis of flavans

Mechanism of the formation of flavans entails reduction of both the 2'-hydroxychalcone *trans* carbon-carbon and carbon-oxygen double bonds by NaBH₄ **Scheme 20**, yielding an alcohol for which subsequent cyclization in acid affords the flavan (Masesane & Mazimba, 2014b).



Scheme 20: Mechanism for the synthesis of flavans from chalcones.

4.3 Pyrazoline

The synthesis of pyrazoline was achieved through the cyclocondensation reaction of various chalcones with hydrazine hydrate in the presence of an organic acid. Pyrazolines are derivatives of pyrazoles, they are referred to as 4,5-dihydro-1*H*-pyrazoles (Karrouchi et al., 2018).

4.3.1 Compound 63

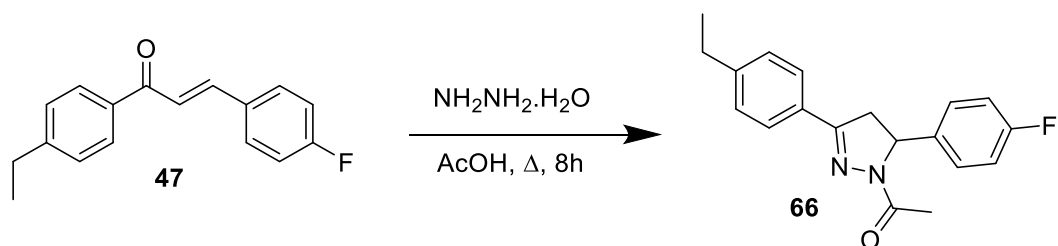
When (*E*)-1-(4-ethylphenyl)-3-(4-fluorophenyl) prop-2-en-1-one **47** was treated with hydrazine hydrate in the presence of glacial acetic acid under conventional heating, it led to the formation of **66** as a pure orange solid in 87% yield.

The IR spectrum showed the absence of *trans*- α,β -unsaturated ketone of chalcones, which suggests the formation of the expected pyrazoline ring. It illustrated the presence of several characteristic bands of stretching vibrations like aromatic CH, aliphatic (CH₃, CH₂, CH), absorption peaks for C=N (1555 cm⁻¹), C-N (1310 cm⁻¹), and N-N (1090 cm⁻¹) main functional groups. C-H stretching vibrations of the phenyl rings were assigned in the range 3120-3035 cm⁻¹, and the stretching modes of the methine, methylene and methyl groups are set at 3035-2980 cm⁻¹, which were in good agreement with the reported structurally related molecules (Naveen et al., 2021; Suma et al., 2017; Wahyuningsih et al., 2019).

The ¹H NMR spectrum revealed multiplet signals for the eight aromatic protons at region δ_H 6.87 to 7.53 ppm. The presence of the COCH₃ group was indicated by a singlet proton signal at δ_H 1.22 and the carbonyl peak at δ_c 162.8. The ethyl group was exhibited by COSY correlated proton at 1.12 (CH₃) and 2.57 (CH₂) with a coupling constant of 7.6-7.8 Hz. In addition, on the ¹H NMR spectrum there were three doublet of doublet signals at 2.81, 3.12, and 3.61 corresponding to C-4a, C-4b and C-5 of the pyrazoline ring. The high *J*= 16.6 Hz

between the protons was due to the diastereotopic germinal coupling of C-4 methylene protons, while the other J values were due to the coupling of the C-4 germinal protons with the C-5 methine proton forming the pyrazoline ring, **Figure 19** and **20**.

Moreover, the ^{13}C NMR spectrum showed the presence of aliphatic carbon signals at δ_{C} 15.2, 28.9 (CH_3), 43.7 (CH_2), 46.1 (CH_2) and 76.7 (CH), eight benzene CH carbons as well as four benzene C signals at δ_{C} 134.6, 138.4, 150.0 and 162.8. The amide and imine signals appeared at high frequencies downfield; δ_{C} 198.2 ($\text{N}-\text{C}=\text{O}$) and δ_{C} 160.4 ($\text{C}=\text{N}$) due to the carbonyl's de-shielding effect and carbon-nitrogen double bond. (Ahmed et al., 2021; Bobrova et al., 2021; Kainsa & Singh, 2016; Megally Abdo et al., 2020). Compound **66** was characterized as 1-(3-(4-ethylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethan-1-one, **Scheme 21** and **Figure 19** and **20**.



Scheme 21: Synthesis of 1-(3-(4-ethylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethan-1-one **66**.

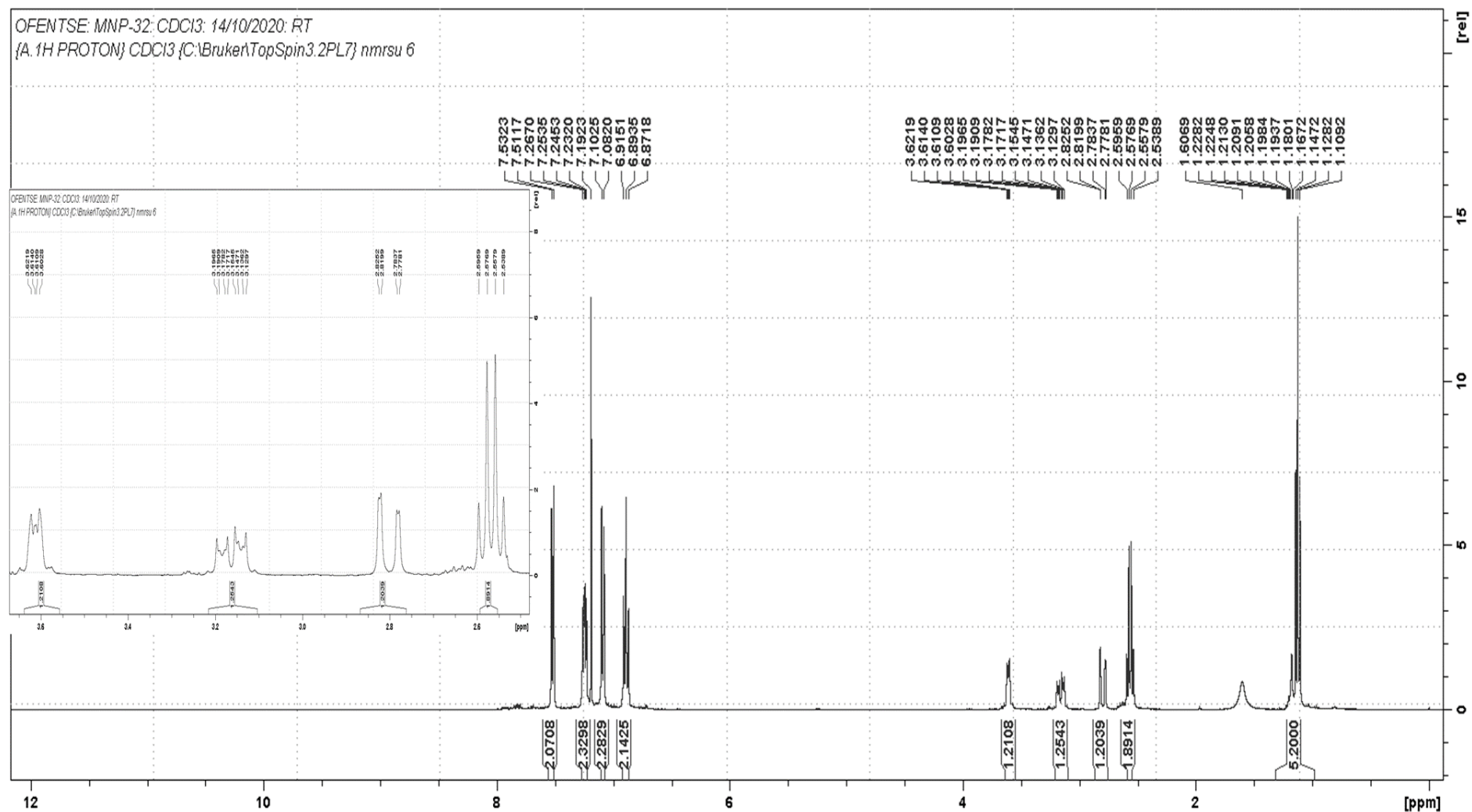


Figure 19. ¹H-NMR (400 MHz, CDCl₃) of 1-(3-(4-ethylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one **66**.

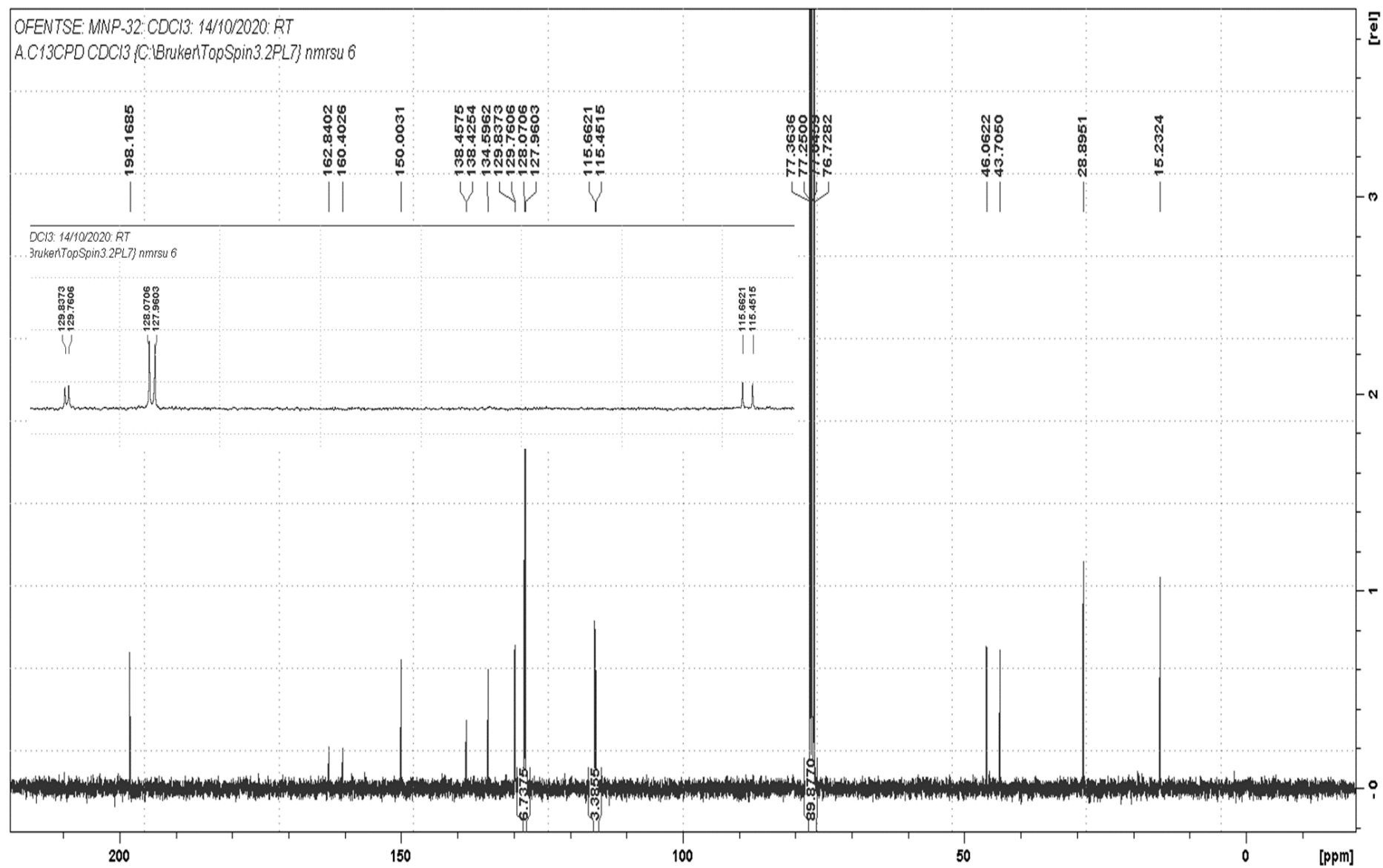
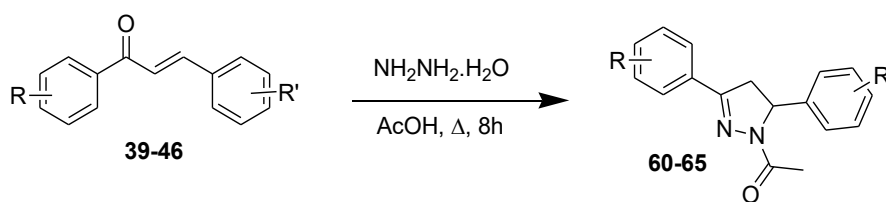


Figure 20. ¹³C-NMR (100 MHz, CDCl₃) of 1-(3-(4-ethylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethan-1-one **66**.

4.3.2 Compounds 60-65

The synthesized pyrazoline structures (**Scheme 22 and Table 4**) were consistent with the literature data. The existence of characteristic signals due to the diastereotopic methylene protons on the pyrazoline ring C-4 and C-5 methine proton signals were displayed on the ^1H NMR spectrum (Suma et al., 2017). Thus, the splitting patterns of C-4 germinal protons were exhibited as a doublet of doublets at the region of δ_{H} 3.42-3.88 ppm due to coupling with C-5 protons.

The ^{13}C -NMR spectra did not exhibit signals of chalcone *trans*-alkene carbons but showed carbon signals of the pyrazoline ring at δ_{C} 40.7-44.7, 56.9-77.2 and 146.6-160.4 corresponding to the C-4, C-5 and C-3 respectively. The ^{13}C -NMR signals literature values for pyrazoline ring C-4, C-5 and C-3 averages are δ_{C} 40.9, 60.9 and 157.7 respectively. (Bakhotmah et al., 2020; EL-Hashash & Shaban, 2019; El Shehry et al., 2019; Farooq & Ngaini, 2020; Abdellatif et al., 2015; Insuasty et al., 2013; Manju et al., 2019; Smuilovich et al., 2010). The pyrazoline were obtained in good yields (69-77%) which were comparable to yields of pyrazoline involving addition of hydrazine hydrate to chalcones (60-78%) (Abdellatif et al., 2015; Karrouchi et al., 2018). Pyrazoline **60** and **61**, NMR data indicated that they did not bear the acetyl (COCH_3) group, but rather exhibited a broad singlet at δ_{H} 6.61 for the pyrazole ring NH proton signal. The successful inclusion of both fluoro- and nitro-groups on the pyrazole substitution pattern is of importance, because **61** has exhibited moderate anti-mycobacterial activity ($\text{MIC} = 12.5 \mu\text{g/mL}$) (Gupta & Kaskhedikar, 2013) and this is one of the pathogens that the pyrazoline were prepared to be tested against for anti-tubercular activity.



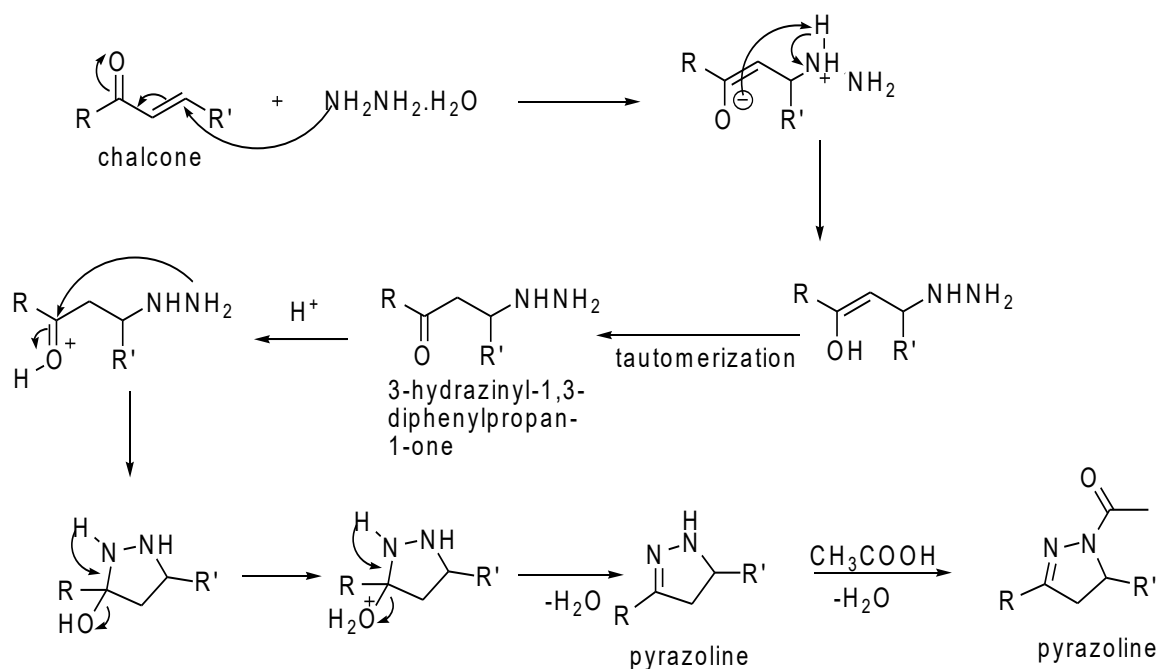
	R	R'	% Yield		R	R'	% Yield
60*	2''-OH	H	72	63	H	H	76
61*	4''-F	4'-NO ₂	75	64	H	4'-F	71
62	4''-NO ₂	2'-OH	74	65	4''-F	4'-F	69

Scheme 22: The general synthesis of pyrazolines **60-65**

*Compounds without the acetate group

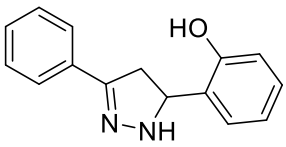
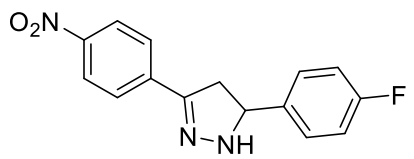
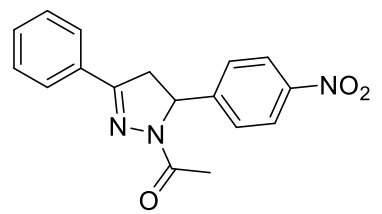
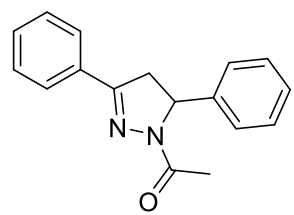
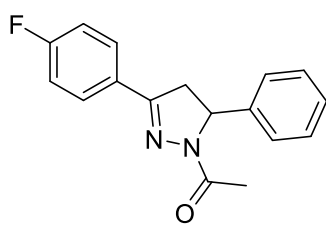
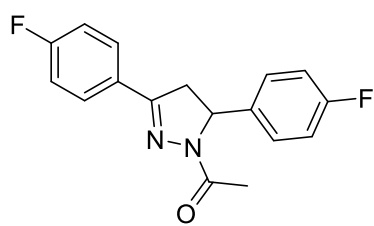
4.3.3 Pyrazole synthesis mechanism

The mechanism for the addition of hydrazine hydrate to chalcones to form pyrazolines is shown in **Scheme 23**. The initial steps involve the aza-Michael addition of the weak NH_2NH_2 nucleophile to the double bond of the α, β -unsaturated ketone (Farmer & Reusch, 2014). The final steps are the cyclization of the 3-hydrazinyl-1,3-diphenylpropan-1-one intermediate which involves the imine bond formation between the second hydrazine $-\text{NH}_2$ and the keto group to yield the pyrazoline ring (Kitawat & Singh, 2014).



Scheme 23: Mechanism for the addition of hydrazine to chalcones.

Table 4: Structures of the synthesized pyrazolines

Compound Code	Structure and Name
60	 2-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenol
61	 5-(4-fluorophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole
62	 1-(5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one
63	 1-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one
64	 1-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one
65	 1-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one

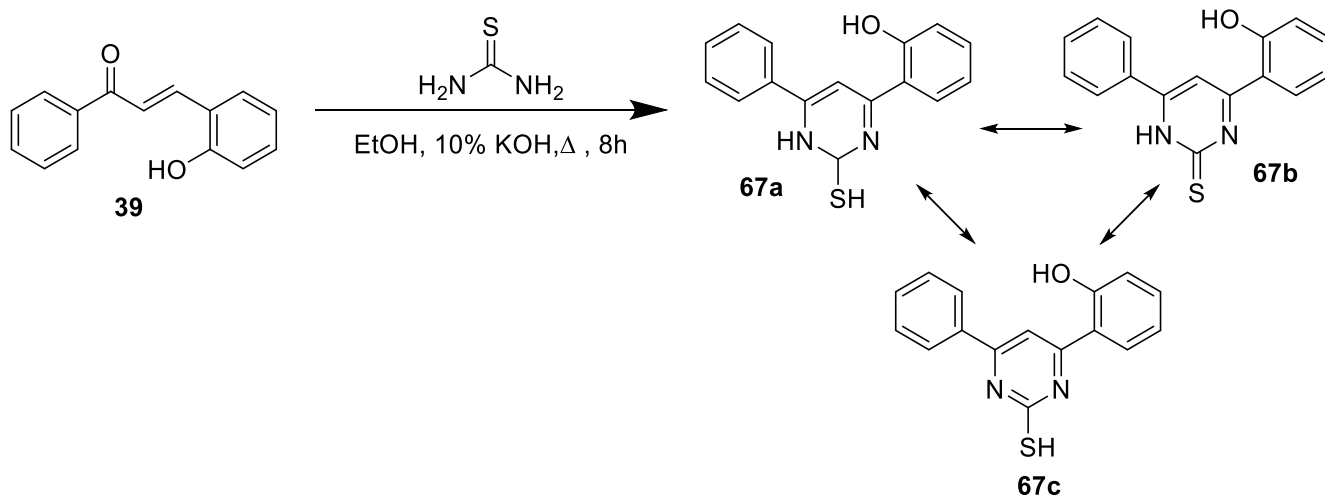
4.4 Pyrimidines

Pyrimidines were accumulated as stated in the experimental part from chalcone cyclization in ethanol in thiourea and potassium hydroxide solution.

4.4.1 Compound 67

Heating under reflux condition, (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **39** and thiourea in the presence of catalytic KOH afforded mixtures of **67a-c** as a cream solid in 72% yield.

FT-IR showed absorption band in the region 1572 cm^{-1} for C=N of thioxo pyrimidine ring, N-H at 3273 cm^{-1} and C-S band appeared at around 1181 cm^{-1} , besides, there were 2977 and 3494 cm^{-1} peaks for Ar-C-H and Ar-OH respectively (Narwal et al., 2017; Saadi & Adna, 2018). Moreover, the ^1H NMR spectrum exhibited a two singlet proton signals at δ_{H} 1.48 and 2.47 assigned to NH and SH, a singlet at δ_{H} 5.44 ppm assigned to the resonance of one proton of CH, for an un-aromatic pyrimidine. A singlet at 8.17 (CH) and 12.89 (SH) indicated the aromatic form, whereas a singlet at 12.98 could be attributed to (NH) neighbouring a C=S hence a mixture of pyrimidines was shown on the proton NMR spectrum. The existence of aromatic protons was suggested by signals at δ_{H} 6.84-8.11 ppm (Kesari et al., 2021; Kosbar et al., 2018). ^{13}C NMR signals categorized into pyrimidine carbons (C-S) at δ_{C} 77.2 (C-SH), 108.0 (C-H), 148.5 (C=C-N) and C=N resonated at δ_{C} 153.8 in addition to the benzene carbons indicative of a mixture. The mixture was identified to be consisting of 2-(2-mercapto-6-phenyl-1,2-dihydropyrimidin-4-yl) phenol **67a** as the major compound, 4-(2-hydroxyphenyl)-6-phenylpyrimidine-2(1*H*)-thione **67b** and 2-(2-mercapto-6-phenylpyrimidin-4-yl) phenol **67c**, Scheme 24 and Figure 21.

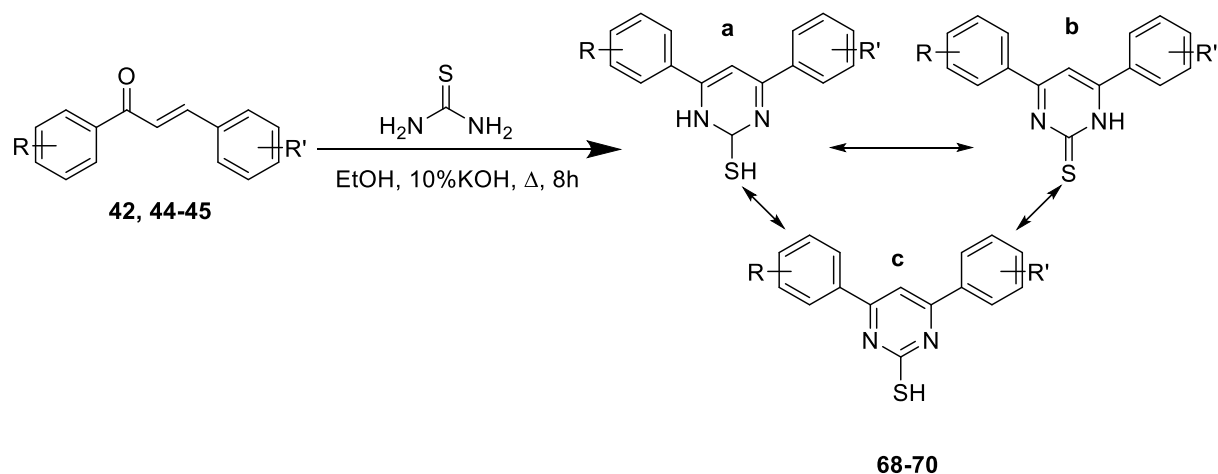


Scheme 24: Synthesis of a mixture of 2-(2-mercapto-6-phenyl-1,2-dihydropyrimidin-4-yl)phenol, 4-(2-hydroxyphenyl)-6-phenylpyrimidine-2(1*H*)-thione and 2-(2-mercapto-6-phenylpyrimidin-4-yl)phenol.

4.4.2 Compounds 68-70

To affirm the production of the pyrimidine compounds (**Table 5**), analysis by their physical and chromatographic parameters was used. Further investigation was revealed by IR and NMR spectroscopy to interpret the structures of the synthesized derivatives. Their IR spectral data showed the C=N for the pyrimidine ring absorbing in the range of 1509-1573 cm^{-1} while the multiplet signals between δ_{H} 6.33 and 8.34 ppm in ^1H NMR was indicative of aromatic protons and a key singlet signal displayed at δ_{H} 1.4-1.6 ppm attributed to (-SH and -NH neighbouring each other) protons and a singlet at δ_{H} 9.92 could be either NH or SH (Kariman et al 2020, Lamie & Philoppes, 2020). Chalcone **44** and **45** yielded compounds **69** and **70** respectively. Compounds **69** and **70** proton NMR peaks were indicative of a compound similar to the isomer **67a**, **Table 6**. There is literature precedence which shows that the addition of thiourea to chalcones is synthetically challenging as different studies have reported identification of different pyrimidine isomers at low yields of 53-60 %, due to the presence of different isomers (Kariman, 2019; Lamie & Philoppes, 2020). The 2'-

hydroxychalcones **40-41** did not yield pyrimidines. Similar to pyrazoline synthesis, the addition of hydrazine hydrate or thiourea involves aza-Michael addition to the chalcones and this is hindered by the 2'-OH group (Kachroo et al., 2014; Karrouchi et al., 2018). The methylation of 2'-OH or placement of the hydroxyl group at the chalcone C-2 resulted in pyrazoline good yields at 65 % (Abdellatif et al., 2015)



Scheme 25: General synthesis of pyrimidines **68-70**.

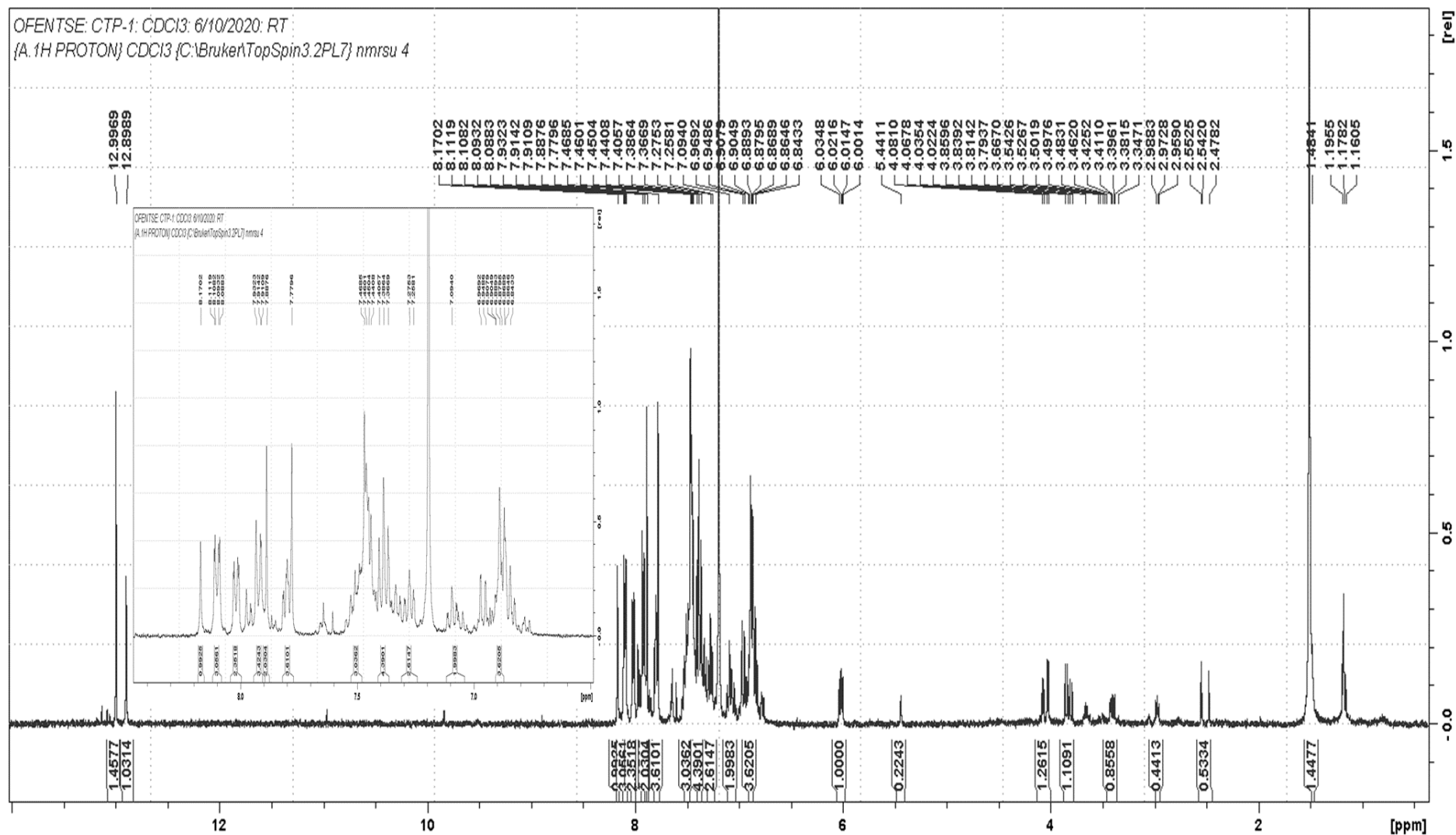
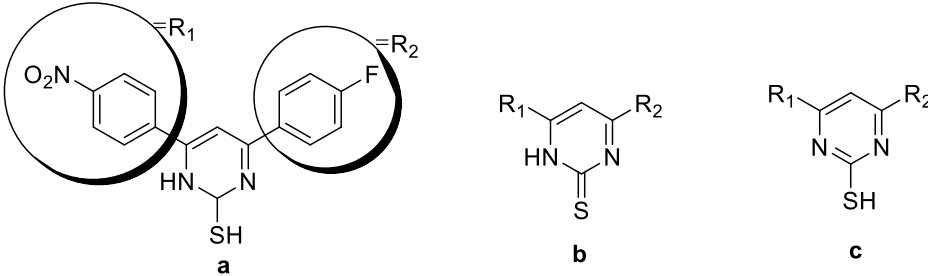
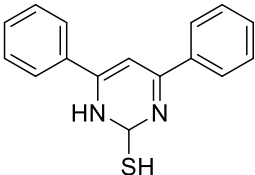
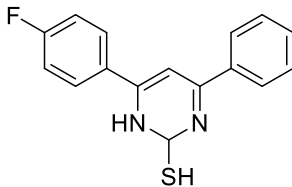


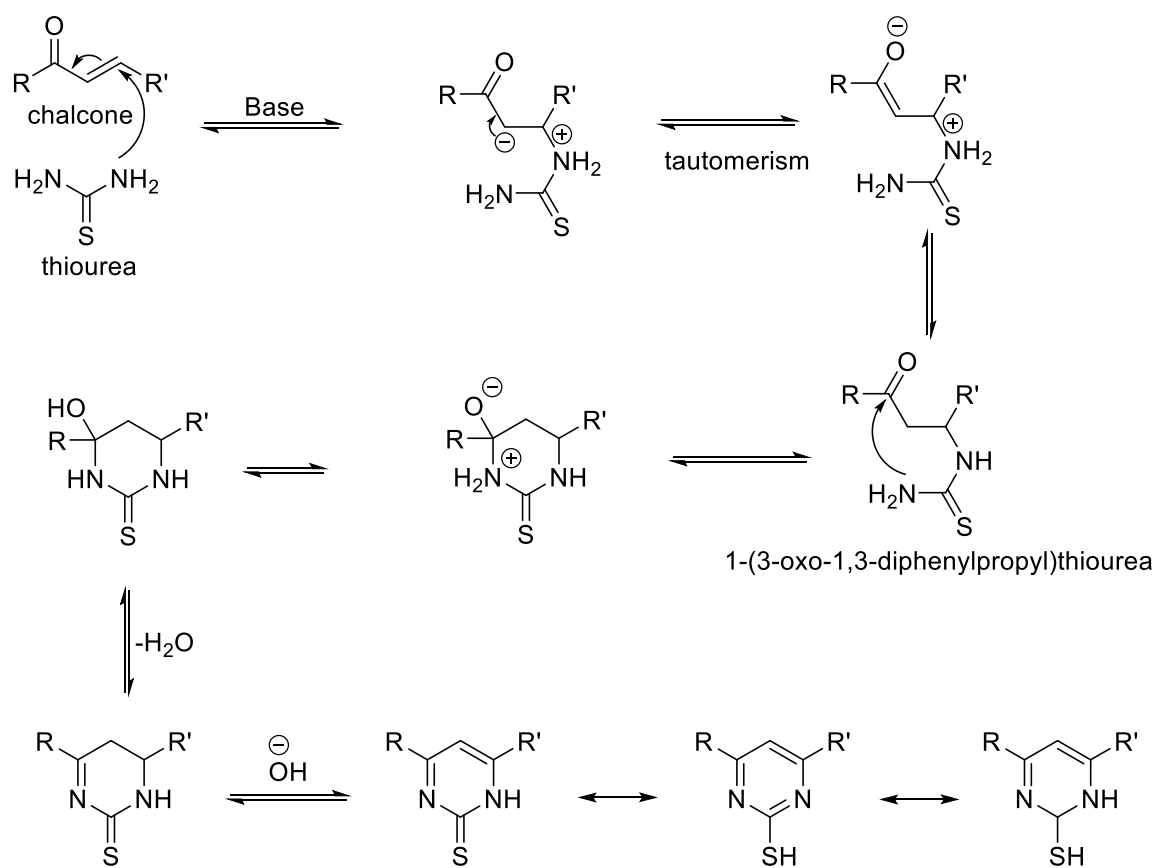
Figure 21. ¹H-NMR (400 MHz, CDCl₃) of a mixture of 2-(2-mercapto-6-phenyl-1,2-dihydropyrimidin-4-yl) phenol, 4-(2-hydroxyphenyl)-6-phenylpyrimidine-2(1*H*)-thione and 2-(2-mercapto-6-phenylpyrimidin-4-yl) phenol.

Table 5: Structures of the synthesized pyrimidines.

Compound Code	Structure and Name
68	 a) 4-(4-fluorophenyl)-6-(4-nitrophenyl)-1,2-dihydropyrimidine-2-thiol b) 4-(4-fluorophenyl)-6-(4-nitrophenyl)pyrimidine-2(1<i>H</i>)-thione c) 4-(4-fluorophenyl)-6-(4-nitrophenyl)pyrimidine-2-thiol
69	 4,6-diphenyl-1,2-dihydropyrimidine-2-thiol
70	 6-(4-fluorophenyl)-4-phenyl-1,2-dihydropyrimidine-2-thiol

4.4.3 Pyrimidine synthesis mechanism

The mechanism of thiourea addition to chalcones starts with the 1,4-aza-Michael addition of the thiourea -NH_2 to the vinyl ketone double bond. The cyclization of 1-(3-oxo-1,3-diphenylpropyl)thiourea is an imine bond formation, thereafter rearrangement and aromatization leads to formation of the different forms of pyrimidines, **Scheme 26** (Farooq & Ngaini, 2020; Sahoo et al., 2017).

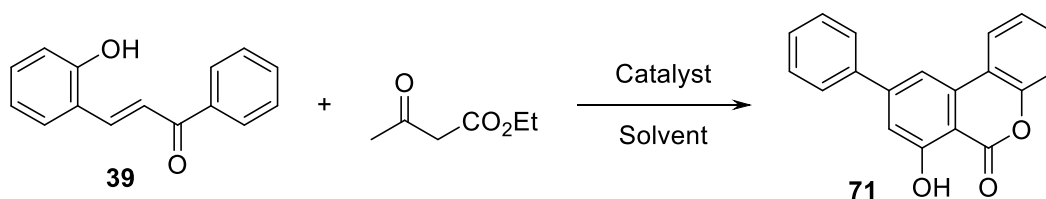


Scheme 26: Mechanism for the addition of thiourea to chalcones.

4.5 Attempted synthesis of benzo[*c*]chromen-6-one

2'-Hydroxychalcones structural features makes them suitable synthons for benzo[*c*]chromen-6-one, with the addition of ethylacetoacetate in the presence of a suitable basic catalyst. The work-up after the reaction was attempted using chalcone **39** and ethylacetoacetate yielded a yellow solid which was found to be the chalcone **39** and a 15 % conversion to benzo[*c*]chromen-6-one based on the proton NMR spectrum. The expected benzo[*c*]chromen-6-one characteristic peak was observed at 11.4 (s, 1H, 7-OH). In previous reports diethylamine was successfully used as the reaction catalyst (Masesane & Mazimba, 2014a). In this respect, it was thought that triethylamine would be more basic than diethylamine due to the three alkyl groups being electron releasing hence increasing electron density on the nitrogen atom, but this inductive effect theory was not observed (**Figure 22**). 2'-Hydroxychalcones **40** and **41** also did not yield the expected product.

Other catalysts which were investigated included, 10% NaOH and a combination of Et₃N/K₂CO₃ in methanol for 1-hr, KO^tBu in DMF for 1-3 hrs, 80% DABCO in DCM, CaO with ethyl bromoacetate in methanol and choline-urea deep eutectic solvent. Under all these conditions, these methods proved to be futile as no product was observed, **Table 6**. Deep eutectic solvents containing diethylamine may produce the expected compounds as the greener alternative to the reported methods.



Scheme 27: Attempted synthesis of benzo[*c*]chromen-6-one from 2'-hydroxychalcones.

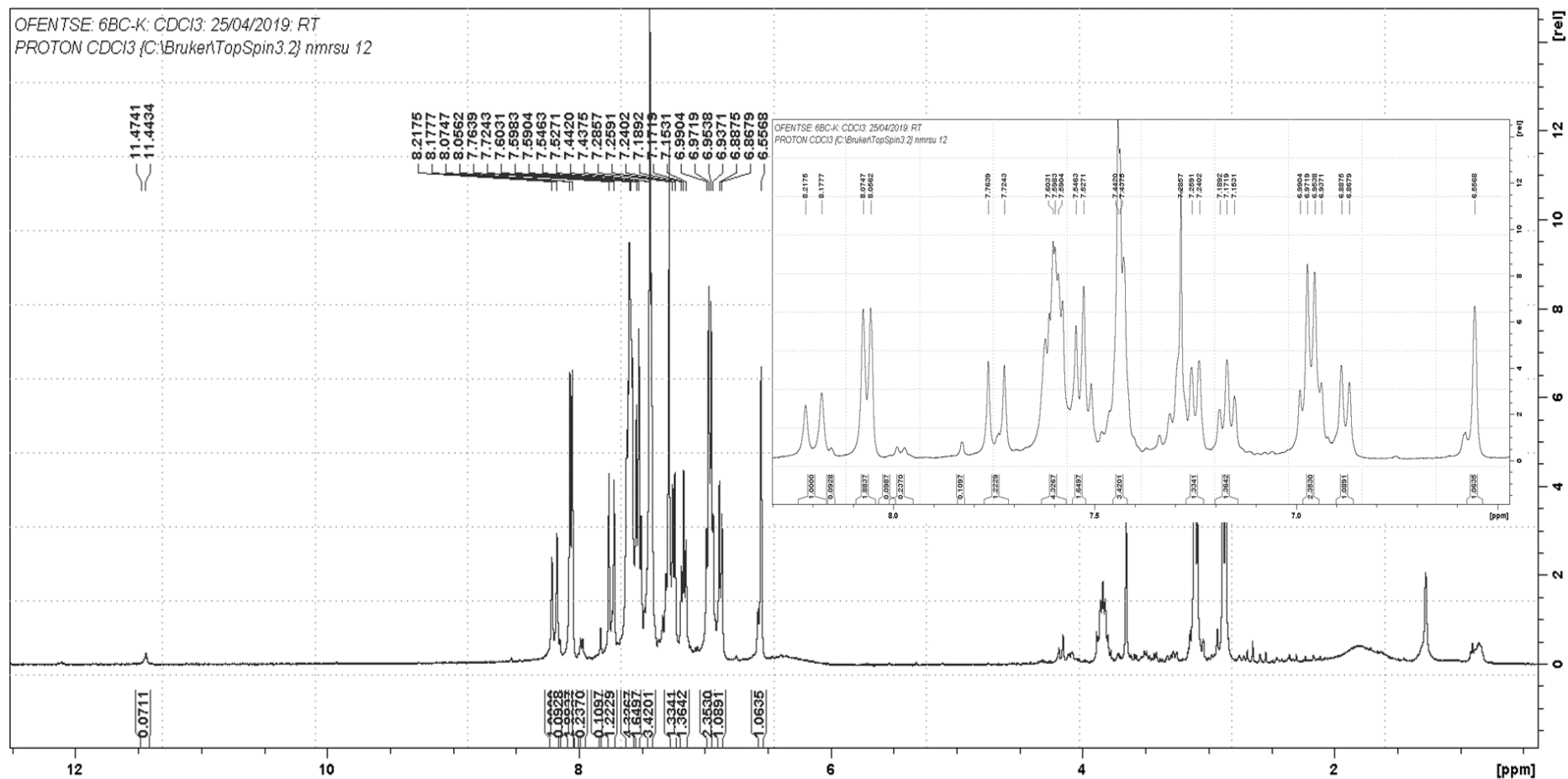


Figure 22: ¹H-NMR (400 MHz, CDCl₃) of compound **39** conversion to benzo[*c*]chromen-6-one. Showing the characteristic peak at 11.4 ppm

Table 6: Conditions and reagents of the attempted synthesis of benzo[*c*]chromen-6-one.

Chalcone	Substrate	Catalyst	Solvent	Time (h)	Temp (°C)	% Yield
40	EAA	Et ₃ H	H ₂ O	24	r.t	n.r
				48	r.t	n.r
			EtOH	24	r.t	n.r
				48	r.t	n.r
			MeOH	1	60	n.r
				3	60	n.r
				6	60	n.r
				12	60	n.r
			EtOH	3	80	n.r
				6	80	n.r
40	EBA	CaO	MeOH	1	60	n.r
				3	60	n.r
				6	60	n.r
				12	60	n.r
40	EAA	DES		0.5	r.t	n.r
				1	r.t	n.r
				1	60	n.r
				3	60	n.r
				6	60	n.r
				12	60	n.r
40	EAA	DABCO	H ₂ O	24	r.t	n.r
				48	r.t	n.r

Chalcone	Substrate	Catalyst	Solvent	Time (h)	Temp (°C)	% Yield
39	EAA	Et ₃ N	MeOH	1	60	n.r
				3	80	n.r
			EtOH	1	60	n.r
				3	60	15
39	EAA	Et ₃ N/K ₂ CO ₃	EtOH	1	80	n.r
				3	80	n.r
				6	80	n.r
				12	60	n.r
39	EAA	10% NaOH	EtOH	1	80	n.r
				3	80	n.r
				6	80	n.r
				12	60	n.r
39	EAA	KOtBu	DMF	1	80	n.r
				3	80	n.r
				6	80	n.r
				12	80	n.r
39	EAA	KOtBu/Et ₃ N	DMF	1	60	n.r
				3	60	n.r
				6	60	n.r
				12	60	n.r
39	EAA	80% DABCO	DCM	1	60	n.r
				3	60	n.r
				6	60	n.r
				12	60	n.r

DES was made of choline-urea at 80 °C.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

Heterocyclic compounds were successfully synthesized from chalcones. In summary, a series of nine chalcone derivatives were obtained by different methods; utilization of ethanol as a solvent or without use of a solvent (grinding technique). Characterization and identification of the synthesized compounds were confirmed by determination of physical properties and employing different spectroscopic techniques FT-IR, ^1H and ^{13}C -NMR spectral data. The Claisen condensation of acetophenones and aryl aldehydes generated (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **39**, (*E*)-3-(4-fluoro-2-hydroxyphenyl)-1-phenylprop-2-en-1-one **40**, (*E*)-1-(4-aminophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one **41**, (*E*)-3-(4-fluorophenyl)-1-(4-nitrophenyl)prop-2-en-1-one **42**, (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one **43**, (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one **45**, (*E*)-1,3-bis(4-fluorophenyl)prop-2-en-1-one **46**, and (*E*)-1-(4-ethylphenyl)-3-(4-fluorophenyl)prop-2-en-1-one **47** in yields of 65-79 %. (*E*)-chalcone **44** was commercially sourced. Chalcones bearing a 2'-OH group were used to construct three flavans namely; 2-phenylchromane **57**, 7-fluoro-2-phenylchromane **58** and 4-(chroman-2-yl) aniline **59** in 80-82% yields. Seven pyrazolines were attained as 2(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)phenol **60**, 5-(4-fluorophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole **61**, 1-(5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **62**, 1-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **63**, 1-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl) ethan-1-one **64**, 1-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethan-1-one **65** and 1-(3-(4-ethylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl) ethan-1-one **66** in 69-77 % yields. Pyrimidine mixtures in 67-69% yields were acquired as 2-(2-mercapto-6-phenyl-1,2-dihydropyrimidin-4-yl) phenol **67a**, 4-(2-hydroxyphenyl)-6-phenylpyrimidine-2(1*H*)-thione

67b, 2-(2-mercapto-6-phenylpyrimidin-4-yl) phenol **67c**, 4-(4-fluorophenyl)-6-(4-nitrophenyl)-1,2-dihydropyrimidine-2-thiol **68a**, 4-(4-fluorophenyl)-6-(4-nitrophenyl)pyrimidine-2(1*H*)-thione **68b**, 4-(4-fluorophenyl)-6-(4-nitrophenyl)pyrimidine-2-thiol **68c**, 4,6-diphenyl-1,2-dihydropyrimidine-2-thiol **69** and 6-(4-fluorophenyl)-4-phenyl-1,2-dihydropyrimidine-2-thiol **70**. The synthesized compounds constitute a library of synthetic organic heterocyclics suitable for the exploitation and evaluation of biological activities and further drug discoveries. Hence, this study will be a valuable and beneficial reference for organic chemistry researchers and pharmacists, which advocates candidature of heterocyclics as alternative therapeutic alternative drugs of biological significance especially anticancer, antibacterial, antifungal and anti-tuberculosis.

Green and sustainable methods or one pot multicomponent reactions for the synthesized compound should be explored for the synthesis of chalcone, pyrimidines, pyrazoles and flavans as methods such as DES could tolerate biologically relevant groups like the fluoro and nitro substituents.

CHAPTER 6

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