Chapter IV
Section-I
Synthesis of β-diketones and 2-Pyridyl chromones
Chapter IV: Synthesis of $\beta$-diketones and 2-pyridyl chromones

Synthesis of

- $1$-(2-hydroxyphenyl)-3-(pyridin-3-yl)propane-1,3-diones
- $2$-(pyridin-3-yl)-$4H$-chromen-4-ones
4.1.1. Introduction

We are witnessing today a dramatic world-wide increase of serious infections by resistant and multi-resistant microbes [1,2]. Infectious diseases are nowadays the second major cause of death worldwide and the third leading cause of death in developed countries [3]. Multiresistant strains of *Staphylococcus aureus*, such as *MRSA* (Methicillin resistant *S. aureus*) are often a source for severe and life-threatening infections in patients during their stay in hospitals or in immunosuppressed persons. Therefore, the search for new lead structures and new chemical entities (NCEs) for the development of antimicrobial agents is an increasingly important problem in medicinal chemistry. Unfortunately, pharmaceutical companies are more and more leaving this area, due to economic reasons [4]. Despite much technological advances in the field of genomics, combinatorial synthesis, and high throughput screening (HTS), chemical companies have been unable to identify new and valid antimicrobial agents by random screening of compound libraries [4]. For several decades no innovative antibiotics were launched on the market. In 2000 and 2003, one of the more recent examples of such a scaffold is the antibacterial linezolid, an optically active oxazolidinone [5] and the lipopeptide daptomycin [6] were the first new chemical entities which appeared on the market after a long period of time, respectively. Noteworthy, new and structurally unusual lead structures for the development of antibiotics are often found based on the screening of natural products and their analogues [6].

The chromones represent one of the largest groups of natural products known; several thousand derivatives have been identified [7]. The chromones are based on the flavones (2-phenyl-4*H*-chromone) and related ring systems and constitute an important class of widely distributed plant secondary metabolites. In addition to the various functions of chromones in plants, their widespread distribution in nature, their structural variability and their antioxidant activities have increased the interest in chromones as beneficial for human health [8]. Several therapeutically interesting biological activities of certain chromones have been reported including anticancer [9], anti-HIV [10], anticholesterenic, antidiabetic, antiallergic, their glycosides are cardiac stimulants, vaso contractors diuretic activity [11,12] coupled with low toxicity [13]. Chromones have been reported to exert
multiple biological effects including cytotoxicity [14], anti-inflammatory [15] as well as antitumor activities [16]. Chromones having heterocyclic substituents at 2 and 3 positions have been reported to possess antiallergic activity [17], muscular relaxation effect and antimicrobial activity [18].

There are several methods reported for the synthesis of 2-phenyl chromone such as Wann-Robinson synthesis [19], Baker-Venkata raman method [20] and oxidative cyclization of 2′-hydroxychalcones [21]. However, the cyclodehydration of flavones obtained by Baker-Venkataraman rearrangement of 2-aryloxy acetophenones remains the most practical method for their preparation [22]. The cyclodehydration of 1,3-diketones required strong drastic condition such as heating under strongly acidic condition using hydrochloric acid, [23] sulphuric acid, [24] and p-tolunesulphonic acid [25]. Recently, the cyclodehydration of these 1,3-diketones has been reported with CuCl$_2$ in ethanol [26] under microwave irradiation. However, most of these reported methods suffer from major or minor drawbacks such as harsh reaction conditions, generally reactions are carried out at elevated temperatures, Herein, we report the simple synthesis of β-diketones and 2-phenylchromone using ultrasound irradiation with comparative analysis through classical approach in almost quantitative yields.

The use of ultrasound in organic transformations is now well known to enhance reaction rates and yields/selectivity of reactions, and in several cases facilitates organic transformations at ambient conditions which otherwise require drastic conditions of temperature and pressure [27,28]. The driving energy is provided by cavitation, the formation and collapse of bubbles which liberates considerable energy in short times. From this phenomenon it is reflected that molecules that can be activated for Sonochemical transformations are those that can penetrate the atmosphere of the bubble, which in turn constitutes a limitation of the method. The use of non-volatile solvents should provide a clue to force less volatile substrates to undergo the cavitation activation. Continuing our investigations in this area, we report the ultrasound promoted synthesis of various biologically active pharmacophores like flavones, thiopyrimidines, iso-oxazoles, benzodiazepines involves the synthesis of 1,3-diketone incorporated with nicotinic acid.
4.1.2. Methods of Synthesis

Swaminathan et al. [29] reported the synthesis of 1,3-diketone by direct coupling of enolate to acid chloride in hydrocarbon solvent which disfavored the formation of charged intermediate only allowing the enolate to react with electrophilic acid chloride (Scheme 4.101).

\[
\text{OLi} + \text{Cl} = \text{O} \rightarrow \text{LiHMDS} \rightarrow \text{O}
\]

\[\text{R}_1 \text{R}_2 \quad \text{Toluene} \quad \text{R}_1 \text{R}_3 \]

Scheme 4.101

Ana et al. [30] synthesized 2-phenylchromones by cyclodehydrogenation of \(o\)-hydroxychalcones and by the Baker-Venkataraman approach, starting from \(o\)-hydroxyacetophenones and benzoic acid derivatives (Scheme 4.102).

\[
\begin{align*}
\text{HOOC} & \quad \text{POCl}_3, \text{py} \quad \text{Reflux} \\
\text{R}_4 & \quad \text{NaH/THF} \quad \text{Reflux} \\
\text{HO} & \quad \text{DMSO/I}_2 \quad \text{OR} \\
\text{OR} & \quad \text{DMSO/p-TSA} \quad \text{OR} \\
\text{OR} & \quad \text{DMSO/AcOH} \quad \text{OR}
\end{align*}
\]

Scheme 4.102
George *et al.* [31] described microwave synthesis of functionalized flavones and chromones (Scheme 4.103).

\[
\begin{align*}
\text{X} &= \text{Br, Cl, CH}_3, \text{OH} \\
\text{R} &= \text{Ar, CH}_3, \text{CF}_3; \text{R}_1 = \text{CH}_3\text{OH}; \text{R}_2 = \text{OH}
\end{align*}
\]

Scheme 4.103

Giorgos *et al.* [32] explained a simple synthesis of functionalized 2-amino-3-cyano-4-chromones by application of the *N*-hydroxybenzotriazole methodology (Scheme 4.104).

Scheme 4.104

Maria *et al.* [33] identified a new telomerase inhibitor with a catecholic flavonoid structure endowed with an interesting activity profile. (Scheme 4.105).

Scheme 4.105
Y. W. Kim [34] described the design, synthesis, and biological evaluation of a novel series of 2-(4’-methyl)thioisoflavones as the first example of synthetic isoflavone-based aromatase inhibitors. (Scheme 4.106).

J. Rocha-Pereira et al. [35] reported the 12 structure related chromone and (E)-2-styrylchromones were evaluated for their potential anti-norvirus activity (Scheme 4.107).

3-haloflavones are another important scaffold that can be used for the synthesis of various 3-substituted flavones. Chalcone when treated with the CuCl$_2$ in DMSO gives 3-chloro flavones. Hideyoshi et al. [36] reported synthesis of 3-bromo flavones from 1-(2-hydroxyphenyl)-3-arylp propane-1,3-dione using CuBr$_2$ (Scheme 4.108).
Scheme 4.108
4.1.3. Present Work

We extended our work to search biologically active heterocyclic compounds by incorporating nicotinic acid moiety in different heterocyclic compounds. The synthetic route designed for the purpose involve synthesis of 2-acetylphenyl nicotinate 23 (a-g) via esterification of o-hydroxy acetophenones 3 (a-g) and nicotinic acid (22) and transformation to 1-(2-hydroxyphenyl)-3-(pyridin-3-yl)propane-1,3-diones 24 (a-g) in presence of pyridine and KOH by Baker-Venkataraman rearrangement under ultrasonication.

![Scheme A](image)

The synthesis of various substituted 2-(pyridin-3-yl)-4\(H\)-chromen-4-ones 25 (a-g) by the cyclodehydration of 1-(2-hydroxyphenyl)-3-(pyridin-3-yl)propane-1,3-diones 24 (a-g) and acetic acid under ultrasonication.

![Scheme B](image)
4.1.4. Experimental

4.4A. Experimental procedure for the synthesis of various substituted 2-acetylphenyl nicotinate 23 (a-g)

To the mixture of 5-chloro-2-hydroxyacetophenone 3e (2.50 gm, 0.0146 mmole) and nicotinic acid 22 (2.34 gm, 0.026 mmole) in dry pyridine (20 mL) POCl₃ (4.71 gm, 0.037 mmole) was added drop wise at 0 °C. The reaction mixture was irradiated for about 3-4 hr under ultrasound. After completion of the reaction (monitored by TLC), reaction mass was poured on crushed ice and the solid obtained was dissolved in ethyl acetate (25 mL) and washed with saturated solution of NaHCO₃. The organic layer was dried over anhydrous sodium sulphate and was concentrated under reduced pressure to afford 23 (a-g). The obtained solid was used for next reaction without purification.

4.4A. Experimental procedure for the synthesis of various substituted 1-(2-hydroxyphenyl)-3-(pyridin-3-yl)propane-1,3-diones 24 (a-g)

Compound 23e (2.25 gm, 0.078 mmole) was dissolved in dry pyridine (20 mL). To this powdered KOH (0.87 gm, 0.015 mmole) was added and the reaction mixture was irradiated for 2-3 hr under ultrasound. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice cold water and acidified with Conc. HCl. The yellow solid obtained was filtered off and crystallized from ethanol. The physical data of the compounds 24 (a-g) were recorded in Table 7. Their structures have been confirmed by ¹H NMR, Mass and IR spectra.

4.4B. Experimental procedure for the synthesis of various substituted 2-(pyridin-3-yl)-4H-chromen-4-ones 25 (a-g)

Compound 24e (1.0 gm, 0.002 mmole) was dissolved in glacial acetic acid (15 mL) to this catalytic Conc. HCl (1-2 drops) was added in a round bottom flask and reaction mixture was irradiated under ultrasonication at 65 °C for about 15 min. After completion of the reaction (monitored by TLC), reaction mass was cooled to the room temperature and poured on crushed ice. The solid obtained was filtered and crystallized from ethanol. The physical data of the compounds 25 (a-g) were recorded in Table 7. Their structures have been confirmed by ¹H NMR, Mass and IR spectra.
Table 7: Physical data of the compounds 24 (a-g) and 25 (a-g)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>M. P. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>109-111</td>
<td>88</td>
</tr>
<tr>
<td>24b</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>130-132</td>
<td>81</td>
</tr>
<tr>
<td>24c</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>105-107</td>
<td>80</td>
</tr>
<tr>
<td>24d</td>
<td>H</td>
<td>CH₃</td>
<td>Cl</td>
<td>123-125</td>
<td>83</td>
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<tr>
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<td>H</td>
<td>Cl</td>
<td>131-133</td>
<td>82</td>
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<td>H</td>
<td>H</td>
<td>CH₃</td>
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<td>86</td>
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<td>H</td>
<td>H</td>
<td>F</td>
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<td>H</td>
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<td>H</td>
<td>H</td>
<td>F</td>
<td>167-169</td>
<td>90</td>
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Elemental analysis

Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer.

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<th>Entry</th>
<th>Calculated</th>
<th>Observed</th>
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<tr>
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<td>C %</td>
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</tr>
<tr>
<td>24b</td>
<td>71.36</td>
<td>5.61</td>
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<td>5.13</td>
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<td>4.67</td>
</tr>
<tr>
<td>24g</td>
<td>69.71</td>
<td>3.34</td>
</tr>
</tbody>
</table>
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4.1.5. Spectral analysis

\(^1\)H NMR spectra were recorded in CDCl\(_3\) on a Brucker instrument at 400 MHz using TMS as an internal standard.

IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

Mass spectra were recorded on a PEP-SCIUX-APIQ pulsar (electron pre ionization) mass spectrometer

\[
\text{24f}
\]

\(^1\)H NMR: (24f) (CDCl\(_3\)) δ ppm: 2.35 (s, 3H, CH\(_3\)), 2.62 (s, 3H, CH\(_3\)), 6.85 (d, 1H, Ar-H), 6.94 (dd, \(J = 8 \& 1\) Hz, 1H, Ar-H), 7.33 (d, \(J = 1.8\) Hz, 1H, Ar-H), 7.45 (s, 2H, CH\(_2\)), 7.54 (dd, 1H, Ar-H), 8.21 (dd, \(J = 3.4 \& 1.8\) Hz, 1H, Ar-H), 8.76 (d, 1H, Ar-H), 9.16 (dd, 1H, Ar-H), 11.80 (s, 1H, -OH), 15.45 (s, 1H, Enolic-OH).

IR.: (24f) (cm\(^{-1}\)): 3404 (-OH), 1594 (C=O), 1463 (C=N), 1198 (C-O).

ES-MS (m/z): 269.1 (M+) & 270.2 (M+1)

\[
\text{25f}
\]

\(^1\)H NMR: (25f) (CDCl\(_3\)) δ ppm: 2.43 (s, 3H, CH\(_3\)), 2.57 (s, 3H, CH\(_3\)), 6.83 (s, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 7.47 (d, \(J = 4.84\) Hz, 1H, Ar-H), 7.85 (dd, 1H, Ar-H), 8.19 (d, \(J = 6.5\) Hz & \(J = 1.56\) Hz, 1H, Ar-H), 8.77 (d, \(J = 4.08\) Hz, 1H, Ar-H), 9.20 (dd, 1H, Ar-H).

IR.: (25f) (cm\(^{-1}\)): 1634 (C=O), 1596 (C=N), 1261 (C-O).

ES-MS (m/z): 252.2 (M+1)

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$^1$H NMR (Comp. 24f)

Mass (Comp. 24f)
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IR (Comp. 24f)

$^1$H NMR (Comp. 25f)
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Mass (Comp. 25f)

IR (Comp. 25f)
4.1.6. References


Chapter IV: Synthesis of β-diketones and 2-pyridyl chromones


Section-II
Synthesis of Substituted Novel Isoxazoles and Thiopyrimidines
Synthesis of

- 2-(5-(pyridin-3-yl)isoxazol-3-yl)phenols
- and
- 4-(2-hydroxyphenyl)-6-(pyridin-3-yl)pyrimidine-2(1H)-thiones
Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines

4.2.1. Introduction

Three main strategies are used by medicinal chemists for the design of new biological active agents: ligand-based, fragment based, and structure-based molecular design [1–3]. The first two approaches are generally interfaced with diversity-oriented organic synthesis (DOS) protocols while the targeted-oriented organic synthesis (TOS) protocols are adopted when the three-dimensional structure of the addressed target is known [4].

Over the years isoxazoles and pyrimidines have emerged as an interesting class of five and six membered heterocycles with an astonishingly wide range of applications in pharmaceutical chemistry. The isoxazole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with vital medicinal value [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat the signs and symptoms of inflammation, particularly arthritic pain [6,7]. NSAIDs exert their anti-inflammatory effect mainly through inhibition of cyclooxygenases (COXs). There are at least two mammalian COX isoforms, COX-1 and COX-2 [8,9]. Hence, the selective inhibition of the COX-2 enzyme, sparing COX-1, emerged as a new concept in treating chronic inflammation [10,11]. Some isoxazole compounds have been identified as potent, injectable analgesics for a rapid relief from unbearable pain (selective COX-2 inhibitors) with good pharmacokinetic profiles for the patients undergoing surgery. Among these, isoxazoles bearing sulfone and carboxamide moieties demonstrated to have significant pharmacological applications. For examples, parecoxib [12] a prodrug of valdecoxib [13] is currently prescribed for the treatment of arthritis and inflammatory diseases (Fig. 1).

Oxacillin and its derivatives are useful compounds because of their narrow spectrum antibiotic properties [14] (Fig 1). Hence, there remains a demand for more efficacious and safer COX-2 inhibitors with higher patient acceptability to completely abandon the use of steroidal and narcotic drugs. Heteroaryl substituents attached to the sulphones have a great importance, in which structure-activity studies for the class of selective COX-2 inhibitors have shown that contain sulphone substituent which usually confers optimal COX-2 inhibitory potency [15]. Highly substituted isoxazoles are core components of many natural products, biologically active compounds, and functional materials [16–18]. Thus, synthesis of these molecules with high efficiency is highly desirable [19–26].
Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines

The isoxazole nucleus is well known for its medicinal importance [27] and a number of related compounds are known to exhibit antitumor [28], anti-HIV [29], and cestoidal [30] agents. Diaryl isoxazole derivatives have a wide range of biological properties and commercial application in various realms of therapy, including anti-inflammatory [31] and cytotoxic [32] agent. Isoxazole derivatives are also employed in the treatment of leprosy [33] and diabetes [34]. The marketed drugs of isoxazole, such as, acetylsulfisoxazole, Cycloserine, Drazoxol on, Sulfisoxazole and Zonisamide have a great medicinal value. These drugs show antimicrobial [35-38], tuberculostatic [39], anticonvulsant [40], neurotoxic [41], and antiepileptic [42,43] and these activities are also observed in their derivatives, led to the search for newer bioactive compounds of this class.

Heterocyclic nucleus imparts an important role in medicinal chemistry and serves as a key template for the development of various therapeutic agents. Synthetic studies of

Fig. 1. Biologically active iso-oxazole drugs
fused pyrimidines have been reported extensively because of their structural diversity and association with a wide spectrum of biological activity. Pyrimidine derivatives have been very well known in medicinal chemistry for their therapeutic applications [44]. One possible reason for their activity is presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids [45], DNA and RNA. The chemistry of the pyrimidines and its derivatives have been studied since the past century due to their diverse pharmacological properties. Pyrimidine was first isolated by Gabriel and Coloman in 1899. Though pyrimidinidine itself does not exist in the nature but substituted pirimidine moietyes are found as a part of more complex system and are widely distributed. Pyrimidines have been recognized as important heterocyclic compounds due to their diverse biological activities such as Tie-2 kinase inhibitors [46], HIV-1 inhibitor [47], antimalarial [48], secretive adenosine A1 receptor antagonist [49], antibacterial [50], anticancer [51], analgesic [52], cardiovascular [53], and antiallergic [54] activities. The thio analogues of pyrimidine bases, including 2-thiouracil, are minor components of t-RNA. Their S-, N- or S, N-disubstituted analogs have shown therapeutic properties, especially antiviral, antithyroid and antitumor activities [55-57] due to their incorporation into polynucleic acids [58] and therefore act as potential inhibitors of protein and polynucleic acid syntheses [59]. Some imidazo[1,2 a]pyrimidine compounds are reported to have significant anti-inflammatory and analgesic action in experimental animal models [60-62]. Pyrimidines represent a broad class of compounds, which have received considerable attention due to their wide range of biological activities and chemotherapeutic importance [63,64]. Several patents have been reported on the preparation of these heterocycles, derivatives of which are useful as bronchodilators, vasodilators, antiallergic, antihypertensive [65], anti-inflammatory, and anticancer agents [66]. In fact, there are many pyrimidine derivatives with pharmacological activities [67]. They also play an essential role in several biological processes, found in nucleoside antibiotics, anti-bacterials, and cardiovascular as well as considerable chemical reactions. Due to the great potential of both of the moiety, different scientists synthesized thiazolopyrimidine to evaluate their various pharmacological activities. Thiazolo[4,5-d]pyrimidine derivatives have acquired a growing importance in the field of medicinal
chemistry and considered as thia-analogues of the natural purine bases such as adenine and guanine, because of their biological potential while some thiazolo[3,2-a]pyrimidines have been demonstrated to be associated with potent immunomodulating properties [68]. Consequently, synthetic methodologies for synthesis of novel pyrimidines or pyrimidine fused compounds are of particular interests to organic and medicinal chemists. For example, synthetic methods have been reported for the efficient syntheses of benzopyrano[4,3-d]pyrimidine [69] dihydropyrido[2,3-d]pyrimidine [70] pyrimido[1,2-a]pyrimidine [71] fluorinated 2-amino-pyrimidine-N-oxide [72].
4.2.2. Methods of Synthesis of Pyrimidines and Isoxazoles

Hubert-Habert et al. have carried out reactions of guanidine, acetamide, thiourea, urea and cyanoguanidine on various chromones in presence of sodium ethoxide and obtained corresponding pyrimidine derivatives in good yields [73,74] (Scheme 4.201).

For the synthesis of the substituted pyrimidine synthesis S-alkylthioureas are frequently used instead of thiourea. The 2-alkylthio group is readily exchangeable, especially after oxidation. One typical example, thiourea with benzoyleacetonate in acidic ethanol gives 6-methyl-4-phenyl-2-(1H)pyrimidinethione [75] (Scheme 4.202).

Supaluk et al. [76] considering that some thiopyrimidines were previously reported as potential therapeutics, the present study achieved novel analogs of bioactive 2-substituted thiopyrimidines-4-(3H)-ones via base catalyzed alkylation reaction of 2-thiouracil using alkyl and aralkyl bromides (Scheme 4.203).
Mosaad *et al.* [77] described synthesis and biological evaluation of some thio containing pyrrolo [2,3-d] Pyrimidine derivatives for their anti-inflammatory and anti-microbial activities (Scheme 4.204).

![Scheme 4.204](image)

Abd *et al.* [78] explained the synthesis, and analgesic and antiparkinsonian activities of thiopyrimidine and thiazolopyrimidine derivatives from 2-chloro-6-ethoxy-4-acetylpyridine (Scheme 4.205).

![Scheme 4.205](image)

Enones derived from disaccharides melibial and gentobial reacted with hydroxyl amine to afford isoxazolines as an inseparable epimeric mixture. By treatment with *p*-toluenesulfonic acid, underwent dehydration to give isoxazole derivatives [79] (Scheme 4.206).

![Scheme 4.206](image)

Debnath *et al.* [80] have reported an efficient synthesis of isoxazoles and isoxazolines from aldoximes using Magtrieve™ (CrO₂) (Scheme 4.207).
Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines

Scheme 4.207

Issa et al. [81] reported the synthesis of isoxazoles through the reaction of activated acetylenes and alkyl 2-nitroethanoates in the presence of triphenylphosphine (Scheme 4.208).

Scheme 4.208

Atul Kumar et al. [82] designed the synthesis of 3,5-diarylisoxazole derivatives as novel class of anti-hyperglycemic and lipid lowering agents (Scheme 4.209).

Scheme 4.209

Patrizia et al. [83] reported the synthesis and antitumor activity of 2,5-bis(3'-indolyl)-furans and 3,5-bis(3'-indolyl)-isoxazoles, nortopsentin analogues (Scheme 4.210).
4.2.3. Present Work

The synthesis of various substituted 2-(5-(pyridin-3-yl)isoxazol-3-yl)phenols 26 (a-g) and 4-(2-hydroxyphenyl)-6-(pyridin-3-yl)pyrimidine-2(1H)-thiones 27 (a-g) from 2-(pyridin-3-yl)-4H-chromen-4-ones 25 (a-g) using thiourea and hydroxylamine hydrochloride in KOH and ethanol under ultrasonication has been carried out.

Scheme A

Scheme B
4.2.4. Experimental

4.2.4A. General experimental procedure for the synthesis of various substituted 2-(5-(pyridin-3-yl)isoxazol-3-yl)phenols 26 (a-g)

(0.2gm, 0.00077 mmole) of chromone 25g was dissolved in 5 mL of ethanol. To this reaction mixture, hydroxylamine hydrochloride (0.11 gm, 0.0015 mmole) and potassium hydroxide (0.05gm, 0.0007 mmole) was added. The reaction mass was irradiated under ultrasonication for 32 min at 65 °C. After completion of reaction (monitored by TLC), reaction mixture was cooled to room temperature. At the end 10 mL cold water was slowly added to the flask and neutralized with 2N HCl, the separated product was filtered and washed with cold water for several times and crystallized from ethanol to afford 26 (a-g). The physical data of the compounds 26 (a-g) were recorded in Table 8. Their structures have been confirmed by 1H NMR, Mass and IR spectra.

4.2.4B. Experimental procedure for the synthesis of various substituted 4-(2-hydroxyphenyl)-6-(pyridin-3-yl)pyrimidine-2(1H)-thiones 27 (a-g)

To a mixture of Comp. 25e (0.2 gm, 0.00078 mmole) and KOH (0.05 gm, 0.05 mmole) in ethanol (10 mL) thiourea (0.065 gm, 0.0025 mmole) was added and reaction mass was irradiated under ultrasonication for 42 min at 65 °C. After completion of the reaction (monitored by TLC), reaction mass was cooled to the room temperature and poured on crushed ice, and acidified with Conc. HCl to get yellow solid. The solid was filtered off and crystallised from ethanol. The physical data of the compounds 27 (a-g) were recorded in Table 8. Their structures have been confirmed by 1H NMR, Mass and IR spectra.
Table 8. Physical data of the compounds. 26 (a-g) and 27 (a-g)

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**Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines**

**Elemental analysis**
Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer.

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<td>60.15</td>
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4.2.5. Spectral analysis

$^1$HNMR spectra were recorded in CDCl$_3$ on a Brucker instrument at 400 MHz using TMS as an internal standard.

IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES).

![Diagram of 26f]

$^1$H NMR: (26f) (CDCl$_3$) δ ppm: 2.56 (s, 1H, CH$_3$), 6.67 (s, 1H, -CH of Isoxazole), 7.64 (d, $J = 8.9$ Hz, 1H, Ar-H), 7.78 (dd, $J = 2.4$ Hz & $J = 9.0$ Hz, 1H, Ar-H), 7.91 (d, 1H, Ar-H), 8.11 (dd, $J = 2.2$ Hz & $J = 2.2$ Hz, 1H, Ar-H), 8.72-8.83 (m, 3H, Ar-H), 12.21 (s, 1H, -OH).

IR.: (26f) (cm$^{-1}$): 2920 (OH), 1636 (C=N), 1550 (C=C).

ES-MS (m/z): 253.4 (M+1)
Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines

\[ \text{27e} \]

**\(^1\)H NMR:** (27e) (CDCl\(_3\)) \(\delta\) ppm: 7.11 (d, \(J = 4.2\) Hz, 1H, Ar-H), 7.26 (dd, 2H, Ar-H), 7.39 (dd, \(J = 1.6\) Hz \& \(J = 8.1\) Hz, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 8.45 (br s, 1H, -NH), 8.48 (dd, \(J = 1.9\) Hz \& \(J = 6.0\) Hz, 1H, Ar-H), 8.86 (dd, \(J = 1.5\) Hz \& \(J = 3.2\) Hz, 1H, Ar-H), 11.78 (s, 1H, -OH).

**IR.:** (27e) (cm\(^{-1}\)): 3065 (OH), 1587 (C=S), 1465 (C=C).

**ES-MS (m/z):** 316.6 (M+1) \& 318.6 (M+3)
Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines

$^1$H NMR (Comp. 26f)

Mass (Comp. 26f)
Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines

IR (Comp. 26f)

\[ \text{IR (Comp. 26f)} \]

\[ \text{H NMR (Comp. 27e)} \]
Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines

Mass (Comp. 27e)

IR (Comp. 27e)
4.2.6. References


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    61c, 1.

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    Appl. 45956 01 March 1987, 14.

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Chapter IV: Synthesis of substituted Novel Isoxazole and Thiopyrimidines


Section-III
Synthesis of Substituted Novel 1,5-Benzodiazepines
Chapter IV: Synthesis of substituted Novel 1,5-Benzodiazepines

Synthesis of

- 2-((1E,4E)-2-(pyridin-3-yl)-3H-benzo[b][1,4]diazepin-4-yl)phenols
4.3.1. Introduction

Benzodiazepines are important organic molecules with a wide range of array of biological activities and therapeutic functions. Particularly 1,5-benzodiazepines are useful precursor for the synthesis of some fused benzodiazepine derivatives, such as triazolo-, oxadiazolo-, oxazino- or furano-benzodiazepines [1-3]. Particularly, 1,5 benzodiazepines (1,5-BDZ) have received much attention because of their potential structural diversity as a privileged scaffold in arrays of compounds bioactive toward several major drug target families, which include cholecystokinin receptors [4-6], interleukin converting enzymes [7,8] and ion channels [9,10]. Their activity against cancer, HIV and central nervous system disorder [11] attracted strong interest. Clinical usage of 1,5-BDZ [12] in anticonvulsant, anti-inflammatory, anti-anxiety, hypnotic, and antidepressive agents are well known. The neurotransmitter dopamine plays an important role in the development of several neurological and psychiatric disorders such as schizophrenia [13,14], Huntington’s disease, and Parkinson’s disease [15]. Thus, the investigation of the dopaminergic system has become an important target in research in order to understand the etiology of these diseases and to find efficient drugs for their treatment. Making use of modern molecular biological techniques, five dopamine receptor subtypes (D1–D5) were characterized and divided into two main families, the D1-like (including the D1 and D5 subtype) and the D2-like (D2, D3, and D4) [16,17].

Clozapine which has 1,5-benzodiazepine core (Fig 1), is an important atypical neuroleptic agent, blocks preferentially the D4 receptor with significant selectivity versus the D2 subtypes. The 1,5-benzodiazepine-2-one core is also a “privileged scaffold” found in compounds active against a variety of target types (protease inhibitors, 7-TM receptors; examples are given in (Fig 1) [18-20].
Combinatory strategy is used in the design and the synthesis of 1,5-benzodiazepine libraries [21]. Due to their wide range of pharmacological activity in synthetic and industrial applications, the synthesis of these compounds have recently received a great deal of attention for the discovery of improved protocols towards milder and high yielding approaches.
4.3.2. Methods of Synthesis

Nabih et al. [22] synthesized 8,13-tetrahydro-4H-bis[1,2,4-oxadiazolo][4,5-a:50,40-d][1,5]benzodiazepines regio and distereosectively by the dipolar cycloaddition reaction of nitrile oxides to 2,4-dimethyl-3H-1,5-benzodiazepines (Scheme 4.301).

![Scheme 4.301](image)

There are several methods for the synthesis of 1,5-benzodiazepine core. direct condensation of the \( o \)-phenylenediamine and ketones catalyzed by the acid are the straightforward approaches among the devised methods (Scheme 4.302).

![Scheme 4.302](image)

Recently, a plethora of acids, such as \( \text{P}_2\text{O}_5/\text{Al}_2\text{O}_3 \) [23], \( \text{Yb(OTf)}_3 \) [24], \( \text{CeCl}_3/\text{NaI} \) supported on silica gel [25], polyacids \( \text{Ag}_3\text{PW}_{12}\text{O}_{40} \) [26], molecular iodine [27,28], \( \text{(Pro)}_2\text{Zn} \) [29], poly(4-vinylpyridine) (PVP)-supported \( \text{FeCl}_3 \) [30], zeolites [31], \( \text{HClO}_4 \) on silica gel [32], \( \text{SmI}_2 \) [33], \( \text{ZrSO}_4 \) [34], \( \text{InBr}_3 \) and \( \text{InCl}_3 \) [35], \( \text{Sc(OTf)}_3 \) [36], \( \text{Ce(NH}_4)_2\text(NO}_3)_6 \) [37], \( \text{YbCl}_3 \) [38], and \( \text{SbCl}_3/\text{Al}_2\text{O}_3 \) [39] as well as alternative methods.
Chapter IV: Synthesis of substituted Novel 1,5-Benzodiazepines

such as Amberlyst-15 in ionic liquid [40], in ionic liquid alone [41] or under microwave irradiation [42], have been employed in the direct transformations.

Y. Du and co-workers synthesized 1,5-benzodiazepines from chalcone and o-phenylenediamine in presence of acidic ionic liquid. (Scheme 4.303) [43].

\[
R_1\text{-cinnamaldehyde} + \text{o-phenylenediamine} \xrightarrow{\text{Acidic Ionic Liquids}} \text{1,5-Benzodiazepine}
\]

Scheme 4.303

Ma and Zhang [44] used low-valent titanium reagent for the synthesis of the 2,3-dihydro-1H-1,5-benzodiazepines from o-nitro aniline and chalcones (Scheme 4.304).

\[
\text{O} \quad \text{NO}_2 \quad \text{NH}_2 \quad \text{X} \quad \text{TiCl}_4/\text{Sm, THF} \quad 5 \text{ min, rt} \quad \text{R}_1\text{-cinnamaldehyde} + \text{o-nitro aniline} \xrightarrow{\text{TiCl}_4/\text{Sm, THF}} \text{1,5-Benzodiazepine}
\]

Scheme 4.304

Ching-Fa et al. [45] reported 2,4,6-Trichloro-1,3,5-triazine (TCT) catalyst for the synthesis of 1,5-benzodiazepines in good to excellent yields (Scheme 4.305).

\[
\text{O} \quad \text{NH}_2 \quad \text{NH}_2 \quad 4 \text{ mol\% TCT} \quad \text{RT} \quad \text{R}_1\text{-cinnamaldehyde} + \text{o-phenylenediamine} \xrightarrow{\text{4 mol\% TCT}} \text{1,5-Benzodiazepine}
\]

Scheme 4.305
Majid et al. [46] described synthesis of 3H-1,5-benzodiazepine derivatives catalyzed by heteropolyacids as a heterogeneous recyclable catalyst (Scheme 4.306).

Scheme 4.306

Naim et al. [47] described A facile synthesis of quinazolinol[1,4]benzodiazepine alkaloids via reductive \(N\)-heterocyclization of \(N\)-(2-nitrobenzoyl)amides: Total synthesis of asperlicin C, circumdatin H, and analogues (Scheme 4.307).

Scheme 4.307
4.3.3. Present Work

The synthesis of various substituted 2-((1\(E\),4\(E\))-2-(pyridin-3-yl)-3\(H\) benzo[b][1,4]diazepin-4-yl)phenols 29 (a-g) from 1-(2-hydroxyphenyl)-3-(pyridin-3-yl)propane-1,3-diones 24 (a-g), \(o\)-phenylenediamine (28) and ceric ammonium nitrate (CAN) under reflux condition, has been carried out.

![Scheme A](image-url)
4.3.4. Experimental

4.3.4A. Experimental procedure for the synthesis of various substituted 2-((1E,4E)-2-(pyridin-3-yl)-3H benzo[b][1,4]diazepin-4-yl)phenols 29 (a-g)

To a mixture of o-phenylenediamine (0.080 gm, 0.00074 mmole) and β-diketone (0.20 gm, 0.00074 mmole) a ceric ammonium nitrate (0.40 gm, 0.00074 mmole) was added and the mixture was refluxed in ethanol (15 mL). The reaction mass was refluxed for 2 hr. After completion of reaction (monitored by TLC), the solvent was evaporate on rotavapour and poured on crushed ice. The orange coloured solid obtained was filtered off and crystallized from ethanol. The physical data of the compounds 29 (a-g) were recorded in Table 9. Their structures have been confirmed by $^1$H NMR, Mass and IR spectra.
Chapter IV: Synthesis of substituted Novel 1,5-Benzodiazepines

Table 9. Physical data of the compounds 29 (a-g)

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Elemental analysis

Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer.

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4.3.5. Spectral analysis

$^1$H NMR spectra were recorded in CDCl$_3$ on a Brucker instrument at 400 MHz using TMS as an internal standard.

IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES).

$^1$H NMR: (29f) (CDCl$_3$) $\delta$ ppm: 2.14 (s, 3H, CH$_3$), 2.57 (s, 2H, N=C-CH$_2$), 7.28 (d, $J = 7.9$ Hz, 1H, Ar-H), 7.30 (d, 1H, Ar-H), 7.48 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.50-7.76 (m, 4H, Ar-H), 7.87 (dd, $J = 4.4$ Hz & $J = 10.6$ Hz, 1H, Ar-H), 8.18 (dd, 1H, Ar-H), 8.75 (dd, $J = 6.1$ Hz, 1H, Ar-H), 8.80 (d, 1H, Ar-H), 12.11 (s, 1H, -OH).

IR.: (29f) (cm$^{-1}$): 2926 (OH), 1644 (C=N), 1587 (C=C).

ES-MS (m/z): 328.2 (M+1)
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$^{1}$H NMR (Comp. 29f)

![H NMR spectrum](image1)

Mass (Comp. 29f)

![Mass spectrum](image2)
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IR (Comp. 29f)
4.3.6. References


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