PART -A : Synthesis

CHAPTER-1

Introduction
1.1. Introduction

Heterocyclic compounds have been an important and major class of organic compounds. Heterocycles play vital role in the human life as basic moieties in dyes, drugs, polymers, food flavours etc. Some of the heterocycles such as pyridine, pyrimidine, purine, indole etc. are known to play important role in biological process in the form of vitamins, nucleic acid, proteins, enzymes and so on. Several heterocyclic compounds are widely distributed in the nature particularly in plant kingdom. Alkaloids which have been used in the form of crude extract in earlier systems of medicine are nitrogen heterocycles. Plant preparations used since ancient times for the treatment of several diseases are known to contain oxygen heterocycles such as flavones, coumarins, chromones, benzofurans. Most of these medicinally useful heterocyclic natural products have served as lead compounds for many of the drugs currently in use. Thus the drugs may be

1) Natural products isolated from plant or animal sources.
2) Degradation products of natural products.
3) Microbiologically transformed products.
4) Biosynthetic or semisynthetic products.
5) Chemically modified natural products.
6) Synthetic compounds by random synthesis or based on drug design.

The synthetic approach based on structural analogy with the existing drugs is a most common approach for the drug discovery in most of the laboratories all over the world. The structural modifications of existing drug molecules have often yielded fruitful results. The present investigation is a similar effort.
1.2. Objectives

Among a variety of heterocycles that have been explored for developing pharmaceutically important molecules, benzofurans have played an important role in medicinal chemistry. Benzofuran derivatives have acquired a special place in the heterocyclic filed because of their broad spectrum biological activities. Most of the natural products containing benzofuran moiety are endowed with useful medicinal properties.

The natural products containing naphthofuran ring system are very rare. However a few naphthofuran compounds of natural origin have been found to possess interesting pharmacological and cytotoxic properties. This has been the main reason for the interest focused on benzofuran and naphthofuran compounds in the drug discovery.

Pyrimidine is an another important biheterocycle. This is associated with important biodynamic agents. It plays vital role in the biological process as an heterocyclic component in nucleic acids, vitamins, proteins etc. Several clinically used drugs are derived from pyrimidine.

Combination of these two heterocycles (benzofuran / naphthofuran and pyrimidine) with well established biological activities, in the form of biheterocyclic system, would be of great interest to investigate their biological and pharmacological activities.

With this aim, series of biheterocyclic benzofurans and naphtho[2,1-b]furans with 2-thio, 2-hydroxy and 2-aminopyrimidines as the other heterocyclic partner have been prepared.
For similar reasons biheterocycles in which isoxazoline and pyrazolidines possessing wide spectrum of biological activities are coupled with benzofuran.

A series of biheterocycles in which naphtho[2,1-b]furan is coupled with quinoxalines are also prepared.
1.3. Benzofuran compounds of biological interest in nature.

The interest in the chemistry of benzofurans is mainly due to the frequent occurrence of this ring system in natural products, most of which are associated with significant medicinal properties. During the last several years continuous efforts are being made to isolate, identify and assess the pharmacological behaviour of such compounds. As a result of such investigations, so far several natural products possessing benzofuran nucleus are brought to light. Such compounds which possess one or the other useful biological activity have wide range of chemical structures varying from simple monosubstituted benzofuran, such as 5-methoxybenzofuran, (1) to complex polycyclic structures as in viridine (2), morphine (3) and galanthamine (4). They have been surveyed from time to time and covered by comprehensive reviews\(^3\)\(^-\)\(^7\). Such natural products generated enormous interest in the laboratory synthesis of their analogues to improve the efficacy. This has been resulted in voluminous work.
As the present synthetic investigation is inspired by the naturally occurring benzofuran derivatives possessing useful physiological properties, it is desirable to give a brief account of natural products containing benzofuran nucleus with an emphasis on their physiological properties. The natural products containing benzofuran nucleus are conveniently classified into following types depending upon their chemical structures.

a. Simple benzofurans
b. Dibenzofurans
c. β- Coumaranones
d. α- Pyronobenzofurans (furocoumarins)
e. γ-Pyronobenzofurans
   (i) furochromones
   (ii) furoflavones
   (iii) furoisoflavones
   (iv) furoxanthones
f. Furoisoflavanoids and Rotenoids
g. Benzofurans fused with nitrogen heterocycles.

a. Simple Benzofurans:

5-Methoxybenzofuran (I), produced by the fungus, is the simplest of the naturally occurring benzofurans. Egonol, a benzofuran derivative isolated from the seed oil of the common plant "Egonoki" in Japan is shown to be effective synergist for rotenone and pyrethrum against house flies, mosquitoes, aphids and many other insects. Bakers yeast is found to contain 2-(2-hydroxy-6-methoxy-3,4-methylene-dioxyphenyl) benzofuran which acts as an antioxidant and prevents haemorrhagic liver necrosis in rats.
on diets, which would normally induce this condition. It also prevents haemolysis of red cells in “vitamin E deficient rats.” The important class of euparinoids (extracts of plants of the compositae family) contains a mixture of benzofurans and dihydrobenzofurans. Among these, tremetol and tremetone are ichthyotoxic and responsible for ailments such as “trembles” in cattle and “milk sickness” in human beings. The toxic compound responsible for these illnesses seems to be a minor component toxol. The bacteriostatic action of this compound has been investigated. Tremetone also seems to have insecticidal properties similar to that of rotenone. It has been suggested that the ‘toxophore’ in rotenoids might be the sequence =CH-CH=CH-O-. The same sequence is found in euparinoids such as euparin and forms part of structures of morphine alkaloids. It has been extensively investigated in attempts to produce synthetic analgesics and similar drugs.

b. Dibenzofurans:

Dibenzofuran derivatives such as strepsilin, porphyrilic acid and didymic acid (5), are isolated from lichens. Didymic acid and other hydroxylated dibenzofurans have some activity against Avian tubercle organisms and Staphylococcus aureus. Usnic acid (6), which occurs in optically active and recemic forms in several plant species has been found to inhibit many Gram-Positive organisms. The most interesting activity of this compound is its potent inhibition effect on Mycobacterium tuberculosis in conjunction with small quantities of streptomycin.

\[
\begin{align*}
\text{(5)} & \quad \text{MeO} \\
\text{(6)} & \quad \text{H}_3\text{C} \quad \text{H}_3\text{O} \quad \text{COOH}
\end{align*}
\]
c. β-Coumaranones:

3-Hydroxybenzofuran, which exists predominantly in ketonic form, is known as β-coumaranone. The metabolic products of fungus, *Pencillium janczewskii* Z., *Pencillium griseofulvum* D7. etc. contain numerous coumaranones among which griseofulvin, (7) is of importance as a fungicide. It is sufficiently active and harmless to the host. For these reasons griseofulvin is effective against the ring worm and other pathogenic fungi when administered orally18.

Geissman17 discovered a new type of plant pigments aurones, which are the glycosides of hydroxylated benzylidine coumaranones. Such compounds, for example, are aureusin (8), leptosin19 etc.. They impart bright yellow to orange yellow colour to flower petals and yellow green colour to chlorophyll containing tissues20.

![Chemical结构](image)

(7)  (8)

d. α-Pyronobenzofurans (Furocoumarins):

This is the largest and earliest known group. The active principles of the seeds of *Psoralae corylifolia* L., which are in use in Ayurvedic system of medicine since ancient times for the treatment of skin diseases and psoriasis are shown to be furocoumarins, psoralen (9) and angelicin21 (13). They are also used as laxatives, diuretics and anthelmintics. Among furocoumarins, psoralen has occupied a prominent position because of its high photodynamic activity.
The seeds of *Ammi majus*, a plant originally grown in Egypt and later as an ornamental plant in India, are effective in the treatment of leucoderma. Fahmy and Abu-Shady\(^2\), Schonberg and Sina\(^3\) have isolated a number of active principles which are furocoumarins, xanthotoxin \(^10\), imperatorin and bergapten \(^11\). Xanthotoxin is strongly ichthyotoxic\(^24\).

"Furocoumarins" is the only class of benzofuran derivatives which shows photosensitising properties. Musajo and Rodighiero\(^25\) have studied the photosensitising effect of psoralen and a number of related compounds and tried to establish the relationship between the structure and photodynamic property. Photodynamic activity is fundamentally linked to furocoumarinic ring system and seems to depend upon the position of furan ring. The linear furocoumarinic structure (as in psoralen) is found to be more effective than the angular one (as in angelicin). Some compounds, such as 5,9-dihydroxy psoralen\(^26\), are used as radiosensitising drugs and trioxasalene (2,5,9-trimethyl psoralen) is used as radioprotective\(^13\).

Furocoumarins such as xanthotoxin, apparently increases the sensitivity of ehrlish tumor cells for \(\gamma\)-rays\(^27\). Significant inhibition of growth of *Tubercle bacillus* was observed by Rodighiero *et al*\(^28\). Furocoumarins are used as fish poisons and some of them like bergapten, isopimpellin (12) and xanthotoxin were shown to possess molluscicidal activity\(^29\). Chakraborty and coworkers\(^30\) have studied the antifungal activity of furocoumarins and reported that psoralen and imperatorin were most effective antifungal agents. Some furocoumarins are also highly spasmolytic\(^31\).
(9) \( R = R' = H \);
(10) \( R = H \) and \( R' = \text{OCH}_3 \);
(11) \( R = \text{OCH}_3 \) and \( R' = H \);
(12) \( R = R' = \text{OCH}_3 \);

e. \textbf{\( \gamma \)-Pyronobenzofurans:}

(i) \textbf{Furochromones:}

The extracts of the plant \textit{Ammi visnaga L.} have been used for centuries in the eastern regions of the Mediterranean as a home remedy to relieve spasms of all kinds and also as a cure for leucoderma.\(^{32}\) The active principles of this crude drug were found to be the two furochromones-khellin (14) and visnagin, (15). As they induce muscular relaxation, they are used to combat bronchial asthma and similar spasms in case that do not respond to adrenalin or aminophyllin\(^{33}\). Although 2-arylbenzofurans relax histamine and acetylcholine spasms more effectively than khellin, they can not be used clinically because they are also estrogenic\(^{34}\). Khellin is also useful in the treatment of heart diseases and whooping cough. It is confirmed that khellin has a selective antispasmodic effect upon ureter, bronchial muscles, gall bladder and bile duct\(^{35}\). It is found to be a potent coronary vasodilator\(^{36}\). The inhibiting action of khellin on gastric ulcers and intestinal activity has been studied\(^{17}\).

\[(14) \ R=R'=\text{OCH}_3 \]
\[(15) \ R=\text{OCH}_3 \text{and} \ R'=H \]
Besides khellin and visnagin, *Ammi visnaga L* is shown to contain a number of other furochromones. The most important ones among these are ammiol and visammiol. A study of relation between structure and antispasmodic activity of furochromones has revealed that the loss of furan ring leads to 70-80% diminution in activity\(^3\).

(ii) **Furoflavones:**

Limaye\(^3\) has isolated first member of this group, karanjin (16), from the seed oil of *Pongamia glabra*. It is found to be active against leucoderma. The root bark of *Pongamia pinnata* contains karanjin along with three more furoflavones, pongapin, gamatin (17), and pinnatin.

![Structure of karanjin (16)](16)

![Structure of pongapin (17)](17)

(iii) **Furoisoflavones:**

The compounds of this type are nepseudin\(^4\) (18) and neotenone\(^5\) (19). These furoisoflavones are isolated from the root of *Neorautanenia pseudopachyrrhiza*.

![Structure of nepseudin (18)](18)

![Structure of neotenone (19)](19)
(iv) **Furoxanthones**:

Sterigmatocystin\(^\text{20}\) (20), a crystalline metabolite, produced by some strains of *Aspergillus versicolor* is shown to be furoxanthone. The other compound belonging to this group is 6-methylsterigmatocystin. It was isolated as a new metabolite from the mycelium of a variant strain of *Aspergillus versicolor* \(^\text{743}\).

\[
\begin{array}{c}
\text{OH} & \text{O} & \text{OMe} \\
\text{O} & \text{O} & \text{O} & \text{Me} \\
\text{O} & \text{O} & \text{O} & \text{Me}
\end{array}
\]

(20)

f. **Furoisoflavanoids and Rotenoids**:

Comparatively this is a large group and includes compounds of heterogenous structures. They have structural connections with true isoflavones and appear to have common biosynthetic origin. Therefore, they are regarded as isoflavanoids. The compounds such as coumaranochromones, coumaranocoumarins and coumaranofurocoumarins constitute this group.

The insoluble red woods which have been used as vegetable dyes from ancient times are shown to contain some colourless crystalline compounds belonging to isoflavanoid group. They have a coumaranochromonic structure. The most important of these are homopterocarpin\(^\text{44}\) (21) and pterocarpin\(^\text{45}\) (22). They are isolated from a number of species of genus pterocarpus and are known to serve as antifungal agents in plants. Recently another compound, pterocarpanphaseolidin\(^\text{46}\), is also shown to be an antifungal and lipophilic.
Coumaranocoumarins which have a benzofuran nucleus fused with coumarin are the most interesting class of isoflavanoids. Coumestrol\(^{47,48}\) (23), is one of the phytoestrogenic substances (non-steroid estrogen) that stimulates animal growth. Methylation of the hydroxyl group, considerably reduced estrogenic activity. Furan ring is also known to contribute substantially to this activity. The estrogenic activity of coumestrol is used in ways similar to those of stilbestrol\(^{49}\).

Erosnin\(^{50}\) (27), isolated from *Phachyrhitis erasus* (Yam beans), is the only coumaranofurocoumarin known so far.

![Chemical structures](image)

Rotenone and related compounds have been known for a long time. Their valuable selective insecticidal action has made them important. Many rotenoids which have a furan ring, e.g., elliptone\(^{51}\) (25), malaccol\(^{52}\) (26), are isolated from *Derris elliptica* and *Derris malacensis* respectively, along with rotenone.

![Chemical structures](image)
g. **Benzofurans fused with nitrogen heterocycles:**

Benzofuran nucleus is very rarely associated with a nitrogen heterocycle in naturally occurring compounds. The opium alkaloids which contain a dihydrobenzofuran nucleus are regarded as belonging to this group. The efficacy of opium in relieving pain is known since ancient times. The chemical substances responsible for this effect, in this drug, were shown to be morphine\(^3\) (3), and related alkaloids like codeine\(^5\) (27) and heroin\(^5\). The analgesic and euphoric properties of morphine have made it an alkaloid of great importance. Morphine sulphate\(^3,5\), diamorphine hydrochloride\(^5\) (28), codeine\(^5\), dihydrocodeine phosphate\(^5\) etc., possess potent narcotic analgesic properties and are used in clinical practice.

![Chemical Structures](image)

Small and coworkers\(^5\) have extensively investigated morphine and related alkaloids. They found some interesting correlations between the structure and physiological activity of these alkaloids. It was observed that the cleavage of ether bridge (dihydrofuran ring) diminished the activity. Hence, furan ring in morphine and its analogues is proved to be an essential part of the structure for their physiological properties.

Another interesting alkaloid galanthamine\(^5\) (4), isolated from *haemanthus* and *galanthus* has also a dihydrobenzofuran nucleus fused with a nitrogen heterocycle azepine. It has received much attention because of its wide range of physiological
properties. It is shown to have strong bactericidal properties\textsuperscript{57} and is known to inhibit cholinesterase activity in animals particularly in blood and brain\textsuperscript{58}. Due to this property, it is used in the treatment of hemiplegics and hemiparetics with cerebral haemorrhage, thrombosis or thromboembolic diseases\textsuperscript{59}. It has also got twitch potentiating and tetanus sustaining action\textsuperscript{60}. When given intravenously, galanthamine causes, in rabbits and cats, a fall in blood pressure as well as increase in tonus and peristalsis of intestine\textsuperscript{61}.

A series of alkaloids in which furan ring is fused to an acridine nucleus are isolated from various plants. They include rutacridone\textsuperscript{62} (29), gravacridondiol\textsuperscript{62} (30), atalanine\textsuperscript{63}, ataline\textsuperscript{63} etc.

\begin{center}
\includegraphics[width=\textwidth]{images/chemistry.png}
\end{center}

Lastly, furoquinoline alkaloids represent another class of naturally occurring compounds containing a furan ring. Many of these are reported to possess toxic properties. The accurate study of their pharmacology is rendered difficult due to highly insoluble nature of free bases and high acidity of the solution of their salts\textsuperscript{64}. dictamine\textsuperscript{65} (31), skimmianine\textsuperscript{66} (32) and acronycidine\textsuperscript{67} (33) are some typical examples belonging to this group.

\begin{center}
\includegraphics[width=\textwidth]{images/chemistry.png}
\end{center}

\textbf{14}
1.4. **Biologically active synthetic benzofurans fused with nitrogen heterocycles.**

It is evident from the above facts that the organic molecules possessing benzofuran nucleus are often endowed with useful pharmacological properties. It is also established in some cases like morphine, furocoumarins, furochromones and coumestrol that the furan ring is an essential part of structure for the biological activity. In view of these facts benzofurans coupled with nitrogen heterocycles have received considerable attention of research workers during the last few decades.

Benzofuran nucleus may be combined with nitrogen heterocycles in different ways. The two ring systems may be fused together as in most of the natural products or both ring systems may be linked to each other directly to produce biheterocycles or through a carbon or nitrogen bridge. Although there is considerable amount of work done on such heterocyclic systems, this is still a most fruitful field for further investigations.

There are very rare instances of benzofuran fused with three or four membered nitrogen ring systems. Benzofuro[2,3-b]azirine (34) is known only in the form of an unstable product formed by the addition of pthalimidonitrene to benzofuran and benzofuro[2,3-b]azete (35) as 2,7a-dihydrobenzofuro[2,3-b]azete formed during the photolysis of isoquinoline-N-oxide.70

![Chemical Structures](image)

The five membered pyrrole ring can be fused on furan ring of benzofuran nucleus in three different ways to produce the following three isomeric molecules-benzofuro[2,3-b]pyrrole71,72 (36), benzofuro[2,3-c]pyrrole73-75 (37) and benzofuro[3,2-b]pyrrole76 (38).
All the three systems are known in the form of their derivatives. Among these some benzofuro[2,3-c] pyrrole derivatives have been shown to possess muscle relaxant and tranquilising properties\textsuperscript{75}.

Benzofuro [3,2-b] indole and its derivatives were reported as early as 1938. They have been prepared by Fischer indole synthesis\textsuperscript{77,78} from appropriate hydrazones. Following this procedure Schroeder and coworkers\textsuperscript{79} prepared a number of benzofuro[3,2-b]indole derivatives (39) and showed them to possess antidepressant properties\textsuperscript{80}. Sonntag et al., prepared some substituted derivatives of benzofuro[3,2-c] indole (40) which were found to stimulate central nervous system in mammals\textsuperscript{81}. The other isomeric benzofuro[3,2-d]indole\textsuperscript{82,83}, benzofuro[2,3-f] indoles\textsuperscript{84}, benzofuro[3,2-f] indole\textsuperscript{85,86}, benzofuro[2,3-g]indole\textsuperscript{84}, benzofuro[3,2-g]indole\textsuperscript{84}, benzofuro[3,2-e] indole\textsuperscript{85,86} and benzofuro[2,3-e]indoles\textsuperscript{84} are also reported.

Benzofuro[3,2-c]pyrazole derivatives were first reported to be formed by ring closure of phenylhydrazones of 2-carbethoxy-3(2H)-benzofuranone in acetic acid\textsuperscript{87}. Subsequently several derivatives of this ring system were prepared by different methods\textsuperscript{88-92}. Annelation of aminopyrazole ring system on benzofuran nucleus has been
shown to result in compounds which possess analgesic and anticonvulsant activity\textsuperscript{92}. Thus 2-methyl-3-amino-6-chloro[3,2-c]pyrazole (41), is reported to have an analgesic activity with ED\textsubscript{50} of 122 mg/kg i p in mice\textsuperscript{92}.

There are a few reports about the synthesis of isomeric benzofuroindazoles\textsuperscript{93} and benzofuroimidazoles\textsuperscript{94}. However, the biological activity of these fused heterocycles are not investigated.

Kirchmayr\textsuperscript{95,96} reported the formation of a series of substituted 3-phenyl-7[2H-(1)benzofuro[2,3-d]triazol-2-yl]coumarins (42), as fluorescent whiteners for polyesters, by the reaction of monooxime of benzofuran-2,3-dione with 3-phenyl-7-hydrazinocoumarin in ethylene glycol monomethylether and 50\% acetic acid followed by the cyclisation of intermediate \(\alpha\)-oxime hydrazone by treating with potassium acetate and acetic anhydride.

\begin{equation}
\begin{array}{c}
\text{R'} \\
\text{R''} \\
\text{R'''}
\end{array}
\quad
\begin{array}{c}
\text{R'} \\
\text{R''} \\
\text{R'''}
\end{array}
\end{equation}

\text{N} \\
\text{O}

(42)

\(R = \text{H, Cl, Me, Bu}\)
\(R' = \text{H, Cl, Me}\)
\(R'' = R''' = \text{H, Me}\)

The cycloaddition reactions involving \(\text{C} = \text{C}\) bond of heteroaromatics and 1,3-dipolar reagents provided convenient route for the synthesis of several condensed systems. Thus, in such a reaction between benzofuran and benzonitrile-N-oxide, a mixture of the following benzofuro[2,3-\(d\)]isoxazole (43) and benzofuro[3,2-\(d\)]isoxazole (44) derivatives were formed\textsuperscript{89,97}.
The reaction of 2-bromo-3-(2H)benzofuranone with thioacetamide and subsequent cyclisation with concentrated sulphuric acid furnished 2-methylbenzofuro[3,2-\(d\)]thiazole\(^{45}\) (45).

The ring closure of 2-bromoacetylaminobenzofuran with phosphorous pentasulphide gave the other isomer, 2-methylbenzofuro[2,3-\(d\)]thiazole\(^{99}\).

The benzofuropyridines are the most extensively investigated systems among the condensed benzofurans. Although the synthesis, bacteriostatic and anti-inflammatory activities of 2-chloro-5,6,7,8-tetrahydrobenzofuro[2,3-\(b\)]pyridine (46), were reported in 1969\(^{100,101}\), the extensive investigation of this heterocycle commenced only when Cocker and coworkers\(^{102}\) prepared a series of 1,3-disubstituted derivatives of this heterocycle and showed them to possess antiviral activity. These compounds were prepared by the condensation of 2,6-dichloro-3-nitropyridine with substituted sodium phenoxides followed by reduction and cyclisation.
While investigating the photochemical cyclisation of 2-phenoxy polyhalopyridines, the formation of 1,2,3-trichlorobenzofuro[2,3-b]pyridine and related compounds is reported\textsuperscript{103}. Following the work of Cocker and coworkers 2-methyl and 4-methylbenzofuro[2,3-b]pyridines were synthesised\textsuperscript{104,105}. The subsequent utilisation of these compounds in the synthesis of dyes has been investigated\textsuperscript{106,107}. The reaction of 5-hydroxybenzofuran with lactam acetals also led to the formation of this system\textsuperscript{71,72}. Recently a novel rearrangement of N-aryloxypyridinium salts has been observed to produce substituted derivatives of benzofuro[2,3-b]pyridines\textsuperscript{108}.

Benzofuro[2,3-c]pyridine is the earliest known isomer among benzofuropyridines. Heneka\textsuperscript{109,110} has prepared a few derivatives of partially hydrogenated ring system (47) and found them to possess high analgesic and analeptic properties.

This method has been extended to the synthesis of numerous derivatives of this heterocycle with suitable modifications\textsuperscript{111-113}.

Oxygen analogues of harman containing furan instead of pyrrole ring are benzofuro[2,3-c]pyridines. Investigations\textsuperscript{114} of these compounds revealed that inhibition of monoamine oxidase \textit{in vivo} was much less than that of harman compounds. The subsequent work on this heterocycle has provided a number of convenient methods\textsuperscript{115-118} for its synthesis and its various derivatives, which were shown to have analgesic and spasmolytic activity\textsuperscript{116}.
Very recently the synthesis of some substituted 1,2,3,4-tetrahydrobenzofuro [2,3-c]pyridine derivatives (48), is achieved from both benzofuran-2-carboxaldehyde\textsuperscript{119} and benzofuran-3-carboxaldehyde\textsuperscript{120} and compounds so obtained exhibited antinflammatory and antidepressant activities\textsuperscript{119}.

\[
\begin{align*}
\text{R} = & H, \text{substituted aryl, substituted aralkyl} \\
(48)
\end{align*}
\]

The work on benzofuro [3,2-c]pyridine ring system was initiated by Descamps and coworkers\textsuperscript{121}. They were able to synthesise 1-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzofuro[3,2-c]pyridine (49), from benzofuran-2-carboxaldehyde through a series of reactions.

\[
\begin{align*}
(49)
\end{align*}
\]

While elucidating the structure of streptoligrin, which is an antibiotic isolated from metabolic products of \textit{Streptomyces flocculus}, the formation of a substituted derivative of this heterocycle is reported\textsuperscript{122}. A number of O-(o-nitrophenyl) oximes of 1-alkyl-4-piperidones were cyclised with ethanolic hydrogen chloride to give 4a-alkoxy-1,2,3,4-4a, 9b-hexahydrobenzofuro[3,2-c]pyridines which on heating with p-toluene sulphonic acid eliminated a molecule of alcohol producing the corresponding tetrahydrobenzofuro[3,2-c]pyridines\textsuperscript{123} (50).
This method has been widely employed by several investigators for the synthesis of various tetrahydro compounds of this heterocycle. It has been possible to transform benzofuro[3,2-c]pyrylium perchlorate to the corresponding benzofuro[3,2-c]pyridine on treatment with ammonia. Thermolysis of 3-(1-benzyl-2-pyrrolyl)acrylazide and benzofuran-2-yl azides are reported to produce ethyl benzofuro[3,2-c]pyridine-3-carboxylate along with other condensed benzofurans. The amino derivatives of 1,2,3,4-tetrahydro benzofuro[3,2-c]pyridine have been found to be useful as central nervous system blocking agents in mice. Recently stereochemical investigations and hydrogenation reactions of some derivatives of this heterocycle are made.

Benzofuro[3,2-b]pyridine has not received much attention. Abramovitch and co-workers while investigating the reaction of benzene with pyridine-N-oxides observed the formation of some 3-substituted benzofuro[3,2-b]pyridines. This has been claimed as a convenient method and suitable mechanism has been proposed for the formation of these compounds. Another report concerning this heterocycle is thermolysis of benzisoxazolo pyridinium salt in benzene which underwent intramolecular cyclisation to give 8-nitrobenzofuro[3,2-b]pyridine. Recently, the synthesis of several substituted benzofuro[3,2-b]pyridine derivatives has been reported from this laboratory.
3- Phenylbenzofuro[2,3-c]pyridazine (52), the only derivative of this ring system has been prepared from 2,3-dihydro-2-oxo-3-phenylethylidene benzofuran.

A common approach for the synthesis of benzofuro[2,3-d]pyridazine involves the condensation of 2,3-dicarbonyl compounds of benzofuran with hydrazine. Huntress et al. prepared 1,2,3,4-tetrahydro-1,4-dioxobenzofuro[2,3-d]pyridazine, (53) from benzofuran-2,3-dicarboxylic ester and hydrazine following this procedure.

The parent heterocycle itself is prepared by the reaction of benzofuran-2,3-dicarboxaldehyde with hydrazine hydrate. This ring system also has been prepared by different methods.

The formation of 1,2,3,4-tetrahydro-2,4-dioxobenzofuro [2,3-d]pyrimidine as a bye-product in an attempted synthesis of diphenylbarbituric acid was reported as early as 1937. The chemistry of these compounds received impetus only when Hess and Cornin reported the synthesis of several derivatives of 5,6,7,8-tetrahydrobenzofuro[2,3-d]pyrimidine by condensation of
α-hydroxy cyclohexanone with malononitrile and subsequent cyclisation with formamide. The compounds with the following structures (54) were shown to possess relaxing properties on smooth muscles with bronchial dilation and lowering of the arterial pressure by their activity on 3'-AMP. The details of drug preparation in the form of tablets using the 4-amino compounds or its salt is described\textsuperscript{143}.

\[ \text{R, R'} = \text{or alkyl} \]

(54)

Photocyclodehydrogenation of 5-iodo-6-phenoxy-1,3-dimethyluracil in benzene and acetonitrile is shown to produce derivatives of this heterocycle in poor yield\textsuperscript{144}. Attempts to improve the yield were successful and suitable mechanism was proposed for this transformation\textsuperscript{145}. An useful method for the synthesis of various derivatives of this ring system is due to Japanese workers\textsuperscript{146}. Their method consists of acetylation and cyclisation of 2-amino-3-benzofurancarbonitrile to produce 3-substituted-1,2-dihydro-1-oxobenzofuro[2,3-\textit{d}] pyrimidines (55).

\[ \text{R} = \text{alkyl} \]

(55)

In another report\textsuperscript{147}, the synthesis of polycyclic heterocycle enclosing this ring system is described (56). It involves the reaction of 2-methyl-1,5-isopropyl-l,4-benzoquinone with substituted acetonitrile and subsequent cyclisation of the intermediate 2-amino benzofuran compound by refluxing with acetic anhydride.
The first report on the synthesis of benzofuro [3,2-\(d\)] pyrimidine is due to Malik and coworkers\(^\text{87}\). They reported the formation of 2-substituted-3,4-dihydro-4-oxobenzofuro[3,2-\(d\)]pyrimidines by the reaction of 2-carbethoxy-3(2H)-benzofuranone with amidines in alkaline medium.

The subsequent investigations which appeared in patent literature\(^\text{148}\) described a novel method for the synthesis of numerous derivatives of this ring system. The method involved the condensation of o-chlorobenzonitrile with ethyl glycolate to form ethyl 3-amino-2-benzofuran carboxylate and further cyclisation to 3,4-dihydro-4-oxobenzofuro[3,2-\(d\)]pyrimidine by heating with formamide. The oxo compound was converted into 4-chloro derivatives and successfully employed in several nucleophilic displacement reactions leading to wide variety of benzofuro[3,2-\(d\)] pyrimidine derivatives. Many compounds thus obtained were found to be useful for inhibiting thrombus formation and they also inhibited collagen induced platelet aggregation in plasma from dogs\(^\text{149}\).

This ring system has been the subject of intensive research work in this laboratory for the last few years. The work has been published in a series of papers. Convenient methods for the synthesis of suitable intermediates like, 3-amino benzofuran-2-carboxamide, 3-aminobenzofuran-2-carbonitrile and ethyl 3-amino benzofuran-2-carboxylate have been found out\(^\text{150}\). They are successfully converted into 3,4-dihydro-4-oxo\(^\text{150}\), 2-alkyl and aryl-3,4-dihydro-4-oxo\(^\text{151}\), 3-alkyl and
aryl-3,4-dihydro-4-oxo\textsuperscript{152} (57), 2,3-disubstituted-3,4-dihydro-4-oxo\textsuperscript{153} and 4-amino-benzofuro[3,2-\textit{d}]pyrimidine\textsuperscript{150} by various routes. The nucleophilic displacement reaction of 4-chlorobenzofuro[3,2-\textit{d}]pyrimidine produced compounds such as 4-mercapto\textsuperscript{150}, alkoxy\textsuperscript{150}, aryloxy\textsuperscript{154}, alkylthio\textsuperscript{154}, arylthio\textsuperscript{154}, alkylmino\textsuperscript{154}, arylamino\textsuperscript{154}, hydrazinobenzofuro[3,2-\textit{d}]pyrimidines\textsuperscript{154} (58). The parent heterocycle\textsuperscript{155} and some tetracyclic triazolo and tetrazolobenzofuro[3,2-\textit{d}]pyrimidines also have been prepared through 4-chloro compounds\textsuperscript{156} (59,60). Some of these compounds exhibited considerable antimicrobial activity\textsuperscript{157}.

![Chemical Structures](image)

R, R' = H, alkyl or aryl; X = Cl, SH, SR, OR, NRR'

Among the various nitrogen ring systems quinoxaline is the earliest one to be built upon benzofuran moiety. The method employed, involved the condensation of o-phenylene diamine with 4-methyl-7-isopropylcoumarone-2,3-dione\textsuperscript{158}. Fries\textsuperscript{159}, in connection with the studies on dyes, prepared 6,8-dimethylbenzofuro[2,3-\textit{d}] quinoxaline by a similar method. Surprisingly this heterocycle remained uninvestigated nearly for the next three decades. After this notable gap, Mueller\textsuperscript{160} synthesised some derivatives of this ring system following the procedure of Mameli. The compounds of this ring system were found to be effective catalysts for silver dye bleach bath. The added
advantage of these compounds was that they did not stain gelatin. This important property stimulated interest in these compounds. A further account of this work was published by Mueller in 1936 under the title ‘Furoquinoxalines and thienoquinoxalines as catalyst in dye bleach agents’. On similar lines Chatterjee and Mehrotra prepared numerous derivatives of this ring system. Recently several investigators have synthesised a number of benzofuro[2,3-\textit{b}] quinoxalines (61) by developing a benzofuran nucleus on appropriately substituted quinoxaline nucleus.

![Image of compound 61]

Some partially hydrogenated N-methyl derivatives of benzofuro[2,3-\textit{b}] azepine, ring system have been prepared by Granik and coworkers either by heating caprolactum diethyl acetal with 5-hydroxybenzofuran or by the Nenitzescu reaction of caprolactum diethyl acetal with benzoquinone.

![Image of compound 62]

Becker and Gustafsson during their studies on photochemical isomerisation, observed the formation of the following benzofuro[3,2-\textit{b}]azepine (63).

![Image of compound 63]
1,2,3,4-Tetrahydro-4-oxodibenzofuran oxime on treatment with polyphosphoric acid underwent Beckman rearrangement producing lactam, which on reduction with lithium aluminum hydride gave 7,8,9,10-tetrahydro-9H-benzofuro[2,3-c]azepine\(^{169}\) (64).

Benzofuro[3,2-c] [1] benzazepine is known in the form of its dione, which is prepared from benzofuran-2,3-dione and o-nitrophenacyl bromide through a series of reaction\(^{170}\). The same investigators described the synthesis of a trimethoxy derivative of isomeric system benzofuro [2,3-c] [1] benzazepine (65), by an almost similar procedure in a later communication\(^{171}\).

The 6-carbethoxy derivative of benzofuro [2,3-d] [1] benzazepine is known to be formed by the thermolysis of benzofuran-2-yl-vinyl azide\(^{76}\).

The first member of fused diazepine series 1,3-dihydro-5-phenyl[2H] benzofuro[3,2-e]-1,4-diazepin-2-one, (66) was prepared from 3-chloroacetamido-2-benzoylbenzofuran on heating with atropine\(^{172}\).

Recently similar ring closure of 3-chloroacetamido-2-acylbenzofuran has been effected using methanolic ammonia\(^{73}\).
1.5. Biheterocyclic benzofurans of biological interest

Benzofuran nucleus can be coupled with other heterocyclic systems by a direct linkage or through carbon or nitrogen bridges. This type of mixed or biheterocycles with benzofuran as one of the component have been of much interest to explore biological activities. Several research workers have designed and synthesised such molecules in a search for potent drug molecules. Most of this work has come up during the last three decades. The work presented in this thesis is an outcome of similar efforts. In the following table investigation of this type are summarised briefly along with the structures of target molecules, reported activities and references.
<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Structure of Compound</th>
<th>Reported activities and uses</th>
<th>Reference No.</th>
</tr>
</thead>
</table>
| 1      | R = H, Cl, CH₃ or Piperidinomethyl  
R' = alkyl | Useful in the treatment of fear in emotions of psychogenic origin | 174 |
<p>| 2      | R = Cl, OMe | Possess antibacterial activity. The minimum inhibitor concentration (MIC) of all these compounds is 2.5-100 mg/ml for <em>E.coli</em>, <em>B.subtilis</em>, <em>P.aureginosa</em> and <em>S.aureus</em>. The MIC value of these compounds for <em>C.albicans</em> is 100 mg/ml. | 175 |</p>
<table>
<thead>
<tr>
<th>3</th>
<th>Possess antihypertensive activity in rats.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = Ac; X = -CH₂CH(OH)CH₂</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4</th>
<th>In the form of acid salts, they are useful in antidepressant preparations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R, R' = H, alkyl or R, R' = alkylene</td>
<td></td>
</tr>
<tr>
<td>R'' = H, alkyl, aralkyl</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5</th>
<th>5-Methoxy-2-methyl-3-(2-pyridyl) benzofuran was found to lower the serum cholesterol up to 70.5 percent at the dose of 200 mg/kg body weight in rats when orally administered. It was also found to lower the serum triglycerides up to 34.7 percent and serum β-lipoprotein up to 87 percent when orally administered at the dose of 20 mg/kg body weight.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1.png" alt="Chemical Structure 6" /></td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>6</td>
<td>R = H, CH$_2$CN</td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Chemical Structure 7" /></td>
</tr>
<tr>
<td>7</td>
<td>R = H, halogen R' = Ph, halophenyl</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>R = H, alkyl, alkoxy carbonyl, phenoxy carbonyl, CN, alkanyl, aralkanyl, hydroxy alkyl, benzoyl alkyl, C(NH₂), NOH (CH₂)x NR'''' R'''', (x = 2,3 ; R'', R''''' = H, alkyl) R' = H, alkyl; R'' = H, halo m, n = 1,2 ; m + n = 3,4</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td></td>
<td>R = Ph; p-chlorophenyl R' = NHCH₂CH₂NEt₂, NHBu</td>
</tr>
<tr>
<td>10</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>----</td>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td>R, R' = H, alkyl</td>
</tr>
<tr>
<td></td>
<td>R' = alkyl or halo</td>
</tr>
<tr>
<td>11</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td></td>
<td>R' = H, OMe, Cl, Br</td>
</tr>
<tr>
<td></td>
<td>R'' = H, Me</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
</tr>
<tr>
<td>12</td>
<td><img src="image1.png" alt="Structure 1" /></td>
</tr>
<tr>
<td>13</td>
<td><img src="image2.png" alt="Structure 2" /></td>
</tr>
<tr>
<td>14</td>
<td><img src="image3.png" alt="Structure 3" /></td>
</tr>
<tr>
<td>15</td>
<td><img src="image4.png" alt="Structure 4" /></td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>----</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>R = 4,5,6,7-OMe  R' = OMe(4), OMe(6)</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td></td>
<td>R = H, Me  R' = Ph, anisyl, dimethoxyphenyl</td>
</tr>
<tr>
<td>193</td>
<td>Reported for bactericidal and fungicidal activities.</td>
</tr>
<tr>
<td>------</td>
<td>------------------------------------------------------</td>
</tr>
</tbody>
</table>

![Chemical Structure](image)

R, R' = H, halo, alkoxy, NO₂, CN, NH₂
R'' = Ph, phenyl alkyl
R''' = H, alkyl, CN

<table>
<thead>
<tr>
<th>194, 195</th>
<th>Reported as antiarrhythmics and calcium antagonists.</th>
</tr>
</thead>
</table>

![Chemical Structure](image)

H₂C₃OOC
H₃C

CH₃

36
Benzofurans coupled with a single or more than one nitrogen heterocycles such as pyrimidine and tetrazole through a bridge are reported to be useful antihypertensive agents.

The preliminary in vitro and in vivo antineoplastic properties of this compound were described in the human epidermoid cell lung carcinoma.
<table>
<thead>
<tr>
<th>23</th>
<th>Reported for estrogenic activity.</th>
<th>198</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure]</td>
<td>![Chemical Structure]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24</th>
<th>Reported for antiinflammatory activity</th>
<th>199</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure]</td>
<td>![Chemical Structure]</td>
<td></td>
</tr>
</tbody>
</table>
Reported to possess antibacterial and antifungal activities

Screened for sedative and hypnotic properties

---

Chemical structures:

![Chemical structure 1](image1)

![Chemical structure 2](image2)
<table>
<thead>
<tr>
<th>202</th>
<th>203</th>
<th>204</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found to possess antimicrobial activity</td>
<td>Reported for antimicrobial activity</td>
<td>Screened for antimicrobial activity</td>
</tr>
</tbody>
</table>

![Chemical structures](image)

<table>
<thead>
<tr>
<th>27</th>
<th>28</th>
<th>29</th>
</tr>
</thead>
</table>

- These structures have been reported or screened for their antimicrobial activity.
| 30 | Investigated for antimicrobial activity. |
| 31 | Evaluated for antimicrobial activity |

\[ R = \text{H, Cl, CH}_3 \]
In addition to heteroaryl-substituted benzofurans, there are numerous examples of benzofuran derivatives even with some substituents either in benzene or furan ring are reported to possess interesting biological activities. Thus benzofurans containing alkylamino side chain are known for antihypertensive\textsuperscript{207,208}, dopaminergic\textsuperscript{209}, antidiabetic\textsuperscript{210}, insecticidal\textsuperscript{211}, asricidal\textsuperscript{211}, antiobesity\textsuperscript{212}, anticholinesterase\textsuperscript{213}, hypnotic and anticonvulsant\textsuperscript{214}, antimicrobial\textsuperscript{215,216}, antiviral\textsuperscript{217}, analgesic\textsuperscript{218} and antiinflammatory\textsuperscript{218} activities. Several phenyl substituted benzofuran derivatives are reported to possess antiasthmatic\textsuperscript{219}, antibacterial and spasmytic\textsuperscript{220}, diuretic\textsuperscript{221,222} hypertensive\textsuperscript{221}, antiinflammatory\textsuperscript{223-225}, anthelmintic\textsuperscript{226} and antiarrhythmic\textsuperscript{227} activities.

Recently several benzofuran derivatives with various substituents are reported to possess pesticidal, insecticidal and acaricidal activities\textsuperscript{228}, antidiabetic activity\textsuperscript{229}, analgesic activity\textsuperscript{230}, serotonergic activity\textsuperscript{231}. Many such compounds are also reported to be useful in cosmetics like sun screen formulations\textsuperscript{232,233}, inhibition of cyclooxygenase-2\textsuperscript{234} by 94% and to function as cannabinoid antagonists\textsuperscript{235}. Most of these recent findings are under patent literature.
1.6. Naphthofurans of biological importance in nature

Naphthofuran can exist in several isomeric forms. Among these, naphtho [2,1-b]furan (67), naphtho[1,2-b]furan (68), naphtho[2,3-b]furan (69) and naphtho [3,2-b]furan (70) derivatives are known to exist in nature.

Generally natural products containing naphthofuran moiety are very rare as compared to those containing benzofuran ring system. However a few compounds such as laevigatin\textsuperscript{236} (71) and (+) heritol\textsuperscript{237} (72) which are dihydro and tetrahydro naphtho[2,1-b]furan derivatives have been isolated and shown to possess interesting pharmacological and cytotoxic properties\textsuperscript{2}.
Rubicordifolin (73) isolated from Chinese medicinal plant *Rubia cordifolia* shows significant cytotoxic activity. This contains naphthofuran as one of the substituent\(^{238}\).

Some of the naphthofurans occur in nature in the form of quinones or diones. Two compounds (74 and 75) of this type isolated from *Tabebuia ochracea*\(^{239}\) exhibited inhibitory activity against *Trypanosoma cruzi* epimastigotes\(^{240}\), (Protozoa) which causes Chagas disease\(^{241}\) (American trypanosomiasis).

![Chemical structure of Rubicordifolin (73)]

Balsaminone A (76) is a polyclic compound of this type. It possess interesting pharmacological and cytotoxic properties\(^{2}\).

![Chemical structures of compounds 74 and 75, and Balsaminone A (76)]]

In addition to these, many compounds of these type are isolated from natural sources. However they are not reported to possess any appreciable pharmacological properties.
1.7. Biologically important naphthofurans fused or coupled with nitrogen heterocycles

Naphthofurans fused or coupled with nitrogen heterocyclic system do not occur in nature. Even the synthetic compounds of this type were not reported till recently. A research programme on the synthesis and pharmacological investigation of naphthofurans fused or coupled with various nitrogen heterocyclic systems, such as pyrazole, isoxazole, oxidiazole, pyridine, pyrimidine and quinoline was initiated a few years back. Many of these compounds were found to be associated with wide spectrum of biological and pharmacological activities such as antibacterial, antifungal, anthelmintic, analgesic, antiinflammatory and diuretic. The results of such investigations are published in a series of papers.\(^{242-244}\)

Structure of such compounds

\[
\text{(77)} \\
\text{(78)} \\
\text{(79)} \\
\text{(80)} \\
\text{(81)}
\]
Reference


64. A. Ogata, J. Pharm. Soc., Japan, 50, 1124 (1930).


CHAPTER-2

Synthesis of Benzofuran and Naphthofuran Analogues of Chalcones
Introduction

1,3-Diphenyl prop-1-en-3-one is called as chalcone. This is also known as (i) benzylacetophenone, (ii) benzylidine acetophenone, (iii) \( \beta \)-phenylstyrilketones.

\[
\begin{align*}
\text{C} & \quad \text{O} \\
\text{C} & \quad \text{CH} = \text{CH} - \text{CH} \\
\end{align*}
\]

Chalcones are an interesting class of compounds containing an \( \alpha,\beta \)-unsaturated ketonic group. A few chalcones are known to occur in nature, for example Butelin (2,4,3,4-tetrahydroxy chalcone) occurs in the flowers of *Butea frondesa*. Fedicin (2,5-dihydroxy-3,5,6-trimethoxy chalcones) and pedicellin (2,3,4,5,6-pentamethoxy chalcone) are the active constituents of the Himalayan drug *Didymocarpus pediellata*.

During the studies on the structure of clavacin Geiger and Conn\(^3\) found that the structural feature, \(- \text{CH}=\text{CH} - \text{CH} - \) which was common to both penicillic acid and clavacin was responsible for their antibacterial activity.

\[
\begin{align*}
\text{MeO} & \\
\text{HO} & \\
\text{H}_3\text{C} & \\
\text{C} & \\
\text{CH}_2 & \\
\end{align*}
\quad \xrightarrow{\text{Penicillic acid}}
\begin{align*}
\text{O} & \quad \text{OMe} \\
\text{OMe} & \\
\text{CH}_3 & \\
\text{C} & \\
\text{C}=\text{CH} - \text{COOH} \\
\text{CH}_2 & \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \\
\text{C} & \\
\text{O} & \\
\text{Clavacin} & \\
\text{Acrylophenone} & \\
\end{align*}
\]

Based on these findings, they further studied the bacterostatic action of various \( \alpha,\beta \)-unsaturated ketones. Acrylophenone was found to possess bacterostatic action...
against gram positive organisms as clavacin and considerably more powerful than pencillic acid. Though its activity against gram negative organism is less marked but still it is considerably greater than that of penicillic acid. It also exhibited fungistatic activity.

Inspired by these observations several researchers prepared a number of substituted chalcones to investigate their antibacterial activity. Some of the chloro substituted chalcones\textsuperscript{4-7} were shown to possess antibacterial activity equal to that of powerful antibacterial, DADS (p-p'-Diamino Diphenyl Sulfone). A few bromo-hydroxy substituted chalcones were found to be active against \textit{S. aureus} at as a low concentration as 1 in 6,40,000. It was observed that the antibacterial activity of chalcone was due to its unsaturation\textsuperscript{8}. Hydrogenation of the double bond destroyed the activity partially or completely. This established that the \(\alpha,\beta\)-unsaturated carbonyl group (\(-\text{CH} = \text{CH} -\)) is a pharmacopic group.

Hydroxy and methoxy chalcones were studied for insecticidal properties against fresh water fish. In case of hydroxy chalcones the symptoms of toxicity developed more slowly but lasted longer. The methoxy chalcones were comparatively less toxic\textsuperscript{9}. The reputed anthelmintic property of Kamala is attributed to its active constituent Rottlerin, which has the chalcone structure.

\begin{center}
\includegraphics[width=0.8\textwidth]{rotterin.png}
\end{center}

Rottlerin
The α,β-unsaturated carbonyl group -CH=CH\text{-C}- which is responsible for bacteriocidal activity of chalcones is also of great use in further chemical modifications in to various heterocyclic moieties such as pyrazole, isoxazole, thiazine, oxopyrimidine, thio pyrimidine, aminopyrimidine, benzothiazepine, flavone and flavonol etc. Therefore chalcones are considered as most potential synthons in the synthesis of various heterocyclic systems. 2-Hydroxy chalcones have been most widely investigated particularly because of their synthetic potential and biological activity. However, 2-aminochalcones have not received considerable attention. Recently Donelly and Farrell\textsuperscript{10} reported synthesis and some reactions of 2-aminochalcones. The fact that 2-aminochalcones undergo intramolecular Michael addition to give 1,2,3,4-tetrahydro-4-quinolones lead Ujjina Matada Ravi \textit{et al.}, to synthesise benzofuran analogues of 2-aminochalcones and convert them in to benzofuro-[3,2-d]pyridones\textsuperscript{11}.

The wide spectrum of activities exhibited by various substituted chalcones and their great synthetic potential has created enormous interest in the synthesis of various heterocyclic analogues of chalcones for investigation of their pharmacological properties and also for further chemical modification into biheterocyclic systems. Heterocycles used in such studies include quinoline\textsuperscript{12}, indole\textsuperscript{13}, coumarin\textsuperscript{14-16}, benzofuran\textsuperscript{11} and several other heterocycles\textsuperscript{17-26}.  

62
Present work

a) Benzofuran analogues of chalcones

The objective of the present work is to synthesise various biheterocyclic benzofurans and napthofurans. A convenient method for the synthesis of these target molecules involves the benzofuran and napthofuran analogues of chalcones as the key starting materials. Hence a series of such chalcone analogues are prepared.

2-Acetyl-3(2H) benzofuranone was identified as a suitable starting material for the synthesis of required benzofuran analogues of chalcones. This was prepared by following a single step literature procedure. This involved the condensation of bromoacetone with methyl salicylate in acetone in presence of anhydrous potassium carbonate. The required bromoacetone was prepared by bromination of acetone. The synthesis of chalcone analogues of benzofuran was carried out by the condensation of 2-acetyl-3(2H) benzofuranone with various aldehydes in an ethanolic solution in presence of aqueous sodium hydroxide (60%) at 5-10°C (Claisen-Schmidt condensation). The following aldehydes were selected for investigation of activities.

1. Benzaldehyde.
2. p-Methoxybenzaldehyde.
3. o-Hydroxybenzaldehyde
4. m-Nitrobenzaldehyde
5. p-Chlorobenzaldehyde
6. p-Tolualdehyde
7. Furfuraldehyde
As 2-acetyl-3(2H) benzofuranone is known to exist in keto, enol tautomeric forms, the reaction was not very clean. Hence 2-acetyl-3(2H) benzofuranone was converted into 2-acetyl-3-methoxybenzofuran by methylation using dimethylsulfate in presence of anhydrous potassium carbonate in acetone. 3-Methoxy-2-acetylbenzofuran when subjected to condensation with various aldehydes under the alkaline conditions mentioned above, the various 3-methoxybenzofuran analogues of chalcones, 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2a-g) were obtained in excellent yields ranging from 68-98 percent. The following scheme-1 depicts the reaction thus carried out.

All the compounds (2a-g) thus obtained were purified by crystallisation from benzene-pet. ether. The purity of the compounds were checked by TLC (chloroform-methanol, 9:1).
The IR spectra of compounds (2a-g) showed characteristic absorption bands due to C=O group in the region of 1640-1655 cm\(^{-1}\), due to C=C in the region of 1550-1577 cm\(^{-1}\) and due to C-O-C in the range of 1090-1160 cm\(^{-1}\). IR spectral data of all these compounds is summarised in Table-1.

Table-1

IR spectral data of 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2a-g)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C-O-C</td>
</tr>
<tr>
<td>2 a</td>
<td>-C(_6)H(_5)</td>
<td>1090</td>
</tr>
<tr>
<td>2 b</td>
<td>4-OCH(_3)-C(_6)H(_4)</td>
<td>1180</td>
</tr>
<tr>
<td>2 c</td>
<td>2-OH-C(_6)H(_4)</td>
<td>1175</td>
</tr>
<tr>
<td>2 d</td>
<td>3-NO(_2)-C(_6)H(_4)</td>
<td>1165</td>
</tr>
<tr>
<td>2 e</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>1165</td>
</tr>
<tr>
<td>2 f</td>
<td>4-CH(_3)-C(_6)H(_4)</td>
<td>1160</td>
</tr>
<tr>
<td>2 g</td>
<td>2-Furyl</td>
<td>1160</td>
</tr>
</tbody>
</table>

As a representative example of the series of compounds, the NMR spectrum of 2b revealed two singlets at δ 3.87d and 4.27 due to two OCH\(_3\) groups and a doublet of a doublet at δ 6.95 and 7.27 due to -CH=CH- protons and multiplet at δ 7.38- 7.9 due to aromatic protons. The IR and NMR data of all these compounds are in good agreement with the assigned structures.

Mass spectrum of compound 2b exhibited the molecular ion peak M\(^+\) at m/z 308 which is the molecular weight of this compound.
IR Spectrum

%T

OMe

C=CH-CH-OMe

2b

No. of Scans; 10

Resolution; 4 [1/cm]

Apodization; Happ-Genzel

Date/Time; 09/12/2005 18:10:51

User; PRINCIPAL

Comment;

HS-CH-6b
'H NMR Spectrum

2b

Current Data Para
NAME
EXPNO
PROCNO
F2 - Acquisition Parameters
Date:
Time:
INSTRM:
PROBD:
PULPROG:
T0:
SOLVENT:
NS:
GS:
SMH:
FDRRES:
AQ:
AG:
DM:
DE:
TE:
D1:

F2 - Processing Parameters
SI:
SF:
HDM:
SSB:
LB:
GB:
PC:

1D NMR plot parameters
CX:
CY:
F1P:
F1:
F2P:
F2:
PPMCM:
HZCM:

5995.204 Hz
0.182959 Hz
2.732901 sec
362
83400 usec
6.00 usec
300 0 K
7.00
20.00 cm
50.00 cm
8.750 ppm
28.26 ppm
-0.634 ppm
-190.38 Hz
0.48293 ppm/cm
140.82991 Hz/cm.
MANIPAL COLLEGE OF PHARMACEUTICAL SCIENCES, MANIPAL
Dept. of Pharma. Quality Assurance
GC-MS Analytical Report

Sample Information

9:43:53 AM Unknown
Analyzed by: Admin
Analyzed: 8/30/2006 12:22:33 PM
Sample Type: Unknown
Level #: 1
Sample Name: 9B
Sample ID: 9B

Chromatogram 9B C:\OCMSolution\Data\Project1\9B.QGD

Mass Spectrum

OMe

\[ \text{2b} \]
b) Naphthofuran analogues of chalcones

2-Acetyl-3-aminonaphtho[2,1-b]furan, reported from this laboratory\textsuperscript{28} was chosen as an appropriate starting compound for the synthesis of desired 3-aminonaphthofuran analogues of chalcones. This was prepared from 2-hydroxy-1-naphthonitrile by condensation with bromoacetone in anhydrous acetone in presence of potassium carbonate following the literature procedure\textsuperscript{29}. During the Claisen-Schmidt condensation of 2-acetyl-3-aminonaphtho[2,1-b]furan with various aromatic aldehydes, the protection of amino group to avoid the possible reaction of free amino group with aldehydes is shown to be not necessary. Both amino and N-acetyl amino-2-acetyl naphthofurans gave the same chalcones, under the strong alkaline conditions of reaction N-acetyl group underwent hydrolysis\textsuperscript{28}. Hence, 2-acetyl-3-aminonaphtho[2,1-b]furan was subjected to Claisen-Schmidt condensation in presence of strong aqueous sodium hydroxide (60%) in an ethanolic solution with the following aldehydes.

1. Benzaldehyde.
2. p-Methoxybenzaldehyde.
3. o-Hydroxybenzaldehyde
4. m-Nitrobenzaldehyde
5. p-Chlorobenzaldehyde
6. p-Tolualdehyde
7. p-Hydroxy-m-methoxybenzaldehyde
8. p-N,N-dimethylbenzaldehyde
9. Furfuraldehyde
The various 1-(3-amino-2-naphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3a-i) were obtained in yields ranging from 38-96 percent. All the compounds were purified by crystallisation from aqueous alcohol. The purity of the compounds was assessed by TLC (chloroform-methanol 9:1). All the reactions thus carried out are outlined under scheme-2.

**Scheme-2**

\[
\begin{align*}
\text{CN} & \quad \text{Br} \quad \text{CH}_2 \quad \text{CO} \quad \text{CH}_3 \\
\text{OH} & \quad \text{+ acetone / K}_2\text{CO}_3 \text{ (anhyd.)} \\
\text{NH}_2 & \quad \text{C} \quad \text{CH}_3 + \text{ArCHO}
\end{align*}
\]

\[
\text{NaOH/EtOH}
\]

\[
\begin{align*}
\text{Ar} & \\
a. \quad \text{-C}_6\text{H}_5 & \quad f. \quad \text{4 - CH}_3\text{-C}_6\text{H}_4 \\
b. \quad \text{4 - OCH}_3\text{-C}_6\text{H}_4 & \quad g. \quad \text{4-OH-3-OCH}_3\text{-C}_6\text{H}_3 \\
c. \quad \text{2 - OH-C}_6\text{H}_4 & \quad h. \quad \text{4-N(CH}_3)_2\text{-C}_6\text{H}_4 \\
d. \quad \text{3 - NO}_2\text{-C}_6\text{H}_4 & \quad i. \quad \text{2-Furyl} \\
e. \quad \text{4 - Cl-C}_6\text{H}_4
\end{align*}
\]

Compounds (3a-i) exhibited IR absorption bands in the region of 3310-3360 cm\(^{-1}\) due to symmetric and asymmetric stretching frequencies of NH\(_2\) group, in the region of 1632-1640 cm\(^{-1}\) due to \(\alpha,\beta\)-unsaturated carbonyl and in the region of 1575-1600 cm\(^{-1}\) due to C=C. IR spectral data of all these compounds is summarised in Table-2.
Table-2
IR spectral data of 1-(3-amino-2-naphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3a-i)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>NH₂</td>
</tr>
<tr>
<td>3a</td>
<td>C₆H₅</td>
<td>3360, 3300</td>
</tr>
<tr>
<td>3b</td>
<td>4-OCH₃-C₆H₄</td>
<td>3400</td>
</tr>
<tr>
<td>3c</td>
<td>2-OH-C₆H₄</td>
<td>3320</td>
</tr>
<tr>
<td>3d</td>
<td>3-NO₂-C₆H₄</td>
<td>3340, 3300</td>
</tr>
<tr>
<td>3e</td>
<td>4-Cl-C₆H₄</td>
<td>3340</td>
</tr>
<tr>
<td>3f</td>
<td>4-CH₃-C₆H₄</td>
<td>3310, 3300</td>
</tr>
<tr>
<td>3g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>3325</td>
</tr>
<tr>
<td>3h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>3310</td>
</tr>
<tr>
<td>3i</td>
<td>2-Furyl</td>
<td>3330, 3300</td>
</tr>
</tbody>
</table>

As a typical example of this series of compounds, ¹HNMR spectrum of 3b exhibited the following signals. A singlet at δ 3.8 was attributed to OCH₃ protons, two broad singlets at δ 5.97 and 6.20 were attributed to NH₂ protons (hydrogen bonded NH and free NH), a doublet of doublet at δ 6.96 and 7.2 was assigned to -CH=CH₂ protons, and finally a multiplet at δ 7.38-8.16 was attributed to aromatic protons. The melting points of a few chalcone analogues were found to be identical with those reported earlier from this laboratory. The structures of the compounds (3a-i) are in good agreement with IR and NMR spectral data.
SCS College Of Pharmacy, Harapanahalli

IR Spectrum

Comment: HSN-CH-3g
No. of Scans: 10
Resolution: 4 [1/cm]

Date/Time: 20/12/2005 20:28:50
User: PRINCIPAL
Experimental

Bromoacetone

To a 1 litre two necked flask equipped with a reflux condenser and a dropping funnel, water (160 ml), acetone (50 ml) and glacial acetic acid (37 ml) were added. The mixture was kept under stirring magnetically and heated on a water bath to 70-80°C so that the mixture in the flask is at 65°C. Bromine (35.4 ml, 0.73 mol) was added through the dropping funnel carefully. The entire bromine was added dropwise in about 1 hr. The reaction solution was decolourised within 20 minutes after the addition of bromine was completed. The decolourised solution was diluted with cold water (80 ml) and further cooled to 10°C. The solution was neutralised using anhydrous sodium carbonate (about 100 g). The bromoacetone which separated as an oil was extracted with ether. The ethereal solution was dried over anhydrous calcium chloride. After removal of ether the crude product was distilled under reduced pressure. The fraction boiling at 40-42°C/13 mm was collected. Yield 40 g.

2-Acetyl-3(2H) benzofuranone

A 500 ml round bottom flask equipped with a reflux condenser and a magnetic stirrer was charged with methyl salicylate (37.2 g, 31.5 ml, 0.245 mol), bromoacetone (33.2 g, 21 ml, 0.245 mol) and anhydrous acetone (200 ml). Freshly roasted anhydrous potassium carbonate (60 g) was added. The reaction mixture was heated under reflux for 12 hrs while stirring magnetically. The cooled reaction mixture was diluted with sufficient water and the aqueous solution was extracted thrice with ether. The aqueous layer when acidified with dilute hydrochloric acid, the product separated as a pale yellow solid. It was collected by filtration after washing with water and further purified by recrystallisation from petroleum ether (60-80°C). Yield 10 g, m.p. 86°C.
2-Acetyl-3-methoxybenzofuran

To a solution of 2-acetyl-3(2H) benzofuranone (8.8 g, 0.05 mol) in anhydrous acetone (150 ml), dimethyl sulphate (6.3 g, 4.84 ml, 0.05 mol) and freshly roasted anhydrous potassium carbonate (20 g) were added. The reaction mixture was heated under reflux on a water bath for 4 hrs. The reaction mixture was filtered while hot and the potassium salts were washed with acetone. The filtrate and washings were combined. The solvent and excess of dimethyl sulphate were distilled off under reduced pressure. The product which was obtained as a pink liquid when treated with water liberated a fine crystalline solid. It was collected and crystalised from petroleum ether (60-80°C). Yield 8.2 g, m.p. 98°C. It gave a negative colour test with aqueous ferric chloride.

2-Hydroxy-1-naphthonitrile

A mixture of 2-hydroxy-1-naphthaldoxime (9.35 g, 0.05 mol) and acetic anhydride (15 ml) was refluxed for 30 min. Acetic anhydride was removed by distillation under reduced pressure and dark coloured dense liquid of naphtho[1,2-d] isoxazole was treated with freshly prepared sodium ethoxide (prepared by adding freshly cut dry sodium (20 g) in to absolute ethanol (100 ml) at 0°C). The mixture was stirred for 30 min at room temperature and poured into ice water. On acidification with dilute hydrochloric acid, it gave 2-hydroxy-1-naphthonitrile as light brown solid, which was collected and recrystalised from aqueous ethanol. Yield 8 g, m.p. 72°C.

2-Acetyl-3-aminonaphtho[2,1-b]furan

To a solution of 2-hydroxy-1-naphthonitrile (8.5 g, 0.05 mol) in anhydrous acetone (75 ml), bromoacetone (6.95 g, 4.3 ml, 0.05 mol) and anhydrous potassium carbonate (10 g) were added. The reaction mixture was heated under reflux on a water
bath while stirring magnetically. The hot reaction mixture was filtered and potassium salts were washed with acetone. The removal of solvent from the combined filtrate and washings under reduced pressure gave 2-acetyl-3-aminonaphtho[2,1-b]furan as dark coloured solid (7.2 g). The potassium salts were suspended in water and neutralised with concentrated hydrochloric acid. The 2-acetyl-3-aminonaphtho[2,1-b]furan which separated as an insoluble solid was collected by filtration and dried (1.2 g), total yield 8.4 g. It was further purified by treatment with acetone and petroleum ether. The resulting pale yellow solid was further recrystallised from DMF. m.p. 140°C.

General method for preparation of 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2a-g)

A solution of 2-acetyl-3-methoxybenzofuran (0.95 g, 0.005 mol) and appropriate aromatic aldehyde (0.005 mol) in ethanol (15 ml) was cooled in ice bath to 5 to 10°C. Aqueous sodium hydroxide (60%, 2.5 ml) was added dropwise while stirring magnetically. The reaction mixture was stirred overnight at room temperature and then poured on to ice water and carefully acidified with dilute hydrochloric acid. The product which separated as a solid was collected by filtration after washing with aqueous sodium bicarbonate (10%) and then with water. The product was further purified by recrystallisation from suitable solvent.

Following this procedure compounds (2a-g) were prepared from 2-acetyl-3-methoxybenzofuran and different aromatic aldehydes.

2a 1-(3-Methoxybenzofuran-2-yl)-3-phenyl-2-propen-1-one
2b 1-(3-Methoxybenzofuran-2-yl)-3-(p-methoxy phenyl)-2-propen-1-one
2c 1-(3-Methoxybenzofuran-2-yl)-3-(o-hydroxy phenyl)-2-propen-1-one
2d 1-(3-Methoxybenzofuran-2-yl)-3-(m-nitro phenyl)-2-propen-1-one
\[ 2e \quad 1-(3\text{-Methoxybenzofuran-2-yl})-3-(p\text{-chloro phenyl})-2\text{-propen-1-one} \]
\[ 2f \quad 1-(3\text{-Methoxybenzofuran-2-yl})-3-(p\text{-toluyl})-2\text{-propen-1-one} \]
\[ 2g \quad 1-(3\text{-Methoxybenzofuran-2-yl})-3-(2\text{-furyl})-2\text{-propen-1-one} \]

The melting point, % yield and elemental analysis of all these compounds are described under Table-3.

**Table-3**

1-(3-Methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2a-g)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
<th>C</th>
<th>H</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>-C(_6)H(_5)</td>
<td>121</td>
<td>98</td>
<td>C(<em>{18})H(</em>{14})O(_3)</td>
<td>77.57 (77.68)</td>
<td>5.01</td>
<td>17.08</td>
<td></td>
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<td>(5.07)</td>
<td>(17.25)</td>
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</tr>
<tr>
<td>2b</td>
<td>4-OCH(_3)-C(_6)H(_4)</td>
<td>127</td>
<td>90.90</td>
<td>C(<em>{19})H(</em>{16})O(_4)</td>
<td>74.02 (74.01)</td>
<td>5.07</td>
<td>20.38</td>
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<td></td>
<td>(5.23)</td>
<td>(20.76)</td>
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</tr>
<tr>
<td>2c</td>
<td>2-OH-C(_6)H(_4)</td>
<td>146</td>
<td>68.02</td>
<td>C(<em>{18})H(</em>{14})O(_4)</td>
<td>73.39 (73.46)</td>
<td>4.51</td>
<td>21.67</td>
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<td></td>
<td>(4.79)</td>
<td>(21.75)</td>
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<tr>
<td>2d</td>
<td>3-NO(_2)-C(_6)H(_4)</td>
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<td>72.75</td>
<td>C(<em>{18})H(</em>{13})O(_3)N</td>
<td>66.71 (66.87)</td>
<td>4.01</td>
<td>24.37</td>
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<td>(4.05)</td>
<td>(24.74)</td>
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<tr>
<td>2e</td>
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<td>96.00</td>
<td>C(<em>{18})H(</em>{13})O(_3)Cl</td>
<td>69.10 (69.13)</td>
<td>4.07</td>
<td>15.13</td>
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<td>(4.19)</td>
<td>(15.35)</td>
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<td>2f</td>
<td>4-CH(_3)-C(_6)H(_4)</td>
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<td>85.60</td>
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<td>78.01 (78.06)</td>
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<td>16.26</td>
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<td>(16.42)</td>
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<td>2g</td>
<td>2-Furyl</td>
<td>106</td>
<td>91.04</td>
<td>C(<em>{16})H(</em>{12})O(_4)</td>
<td>71.37 (71.64)</td>
<td>4.37</td>
<td>23.76</td>
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<td>(4.51)</td>
<td>(23.86)</td>
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Solvent of crystallisation: Benzene-pet. ether
General method for preparation of 1-(3-amino-2-naphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3a-i)

A solution of 2-acetyl-3-aminonaphtho[2,1-b]furan (0.9 g, 0.004 mol) and appropriate aromatic aldehyde (0.004 mol) in ethanol (10 ml) was cooled to 5 to 10°C in an ice bath. Aqueous sodium hydroxide (3.5 ml, 60%) was added drop wise while stirring the mixture magnetically. The reaction mixture was stirred for further period of 2 hrs and left over night in refrigerator. The reaction product was poured in to ice water and carefully acidified with dilute hydrochloric acid. The product which separated as solid was collected by filtration after washing with aqueous sodium bicarbonate (10%) and then with water and further purified by recrystallisation from suitable solvent.

Compounds (3a-i) were prepared similarly by following this procedure from 2-acetyl-3-aminonaphtho[2,1-b]furan and the respective aromatic aldehydes.

3a 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-phenyl-2-propen-1-one
3b 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-methoxy phenyl)-2-propen-1-one
3c 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(o-hydroxy phenyl)-2-propen-1-one
3d 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(m-nitro phenyl)-2-propen-1-one
3e 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-chloro phenyl)-2-propen-1-one
3f 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-tolyl)-2-propen-1-one
3g 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-hydorxy-m-methoxy phenyl)-2-propen-1-one
3h 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-N,N-dimethyl phenyl)-2-propen-1-one
3i 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(2-furyl)-2-propen-1-one

The melting point, % yield and elemental analysis of all these compounds described under Table-4.
Table 4

1-(3-Amino-2-naphtho[2,1-b] furyl)-3-aryl-2-propen-1-ones (3a-i)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
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<tr>
<td>3a</td>
<td>-C₆H₅</td>
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<td>96</td>
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<td>3b</td>
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<td>76.63 (76.95)</td>
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<td>4.07 (4.25)</td>
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<tr>
<td>3d</td>
<td>3-NO₂-C₆H₄</td>
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<td>66.43</td>
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<td>70.17 (70.39)</td>
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<td>3.89 (4.06)</td>
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<td>3.91 (4.03)</td>
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<td>80.43 (80.71)</td>
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<td>4-N-(CH₃)₂-C₆H₄</td>
<td>129</td>
<td>85.29</td>
<td>C₂₃H₂₀O₂N₂</td>
<td>77.49 (77.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.34 (5.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.79 (7.86)</td>
</tr>
<tr>
<td>3i</td>
<td>2-Furyl</td>
<td>140</td>
<td>95.04</td>
<td>C₁₉H₁₃O₃N</td>
<td>75.04 (75.24)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>4.29 (4.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.39 (4.62)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Benzene pet. ether
Reference


CHAPTER-3

Synthesis of 2-(4-aryl-2-mercapto-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans and 2-(4-aryl-2-mercapto-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans.
Introduction

Pyrimidine is an important bioheterocycle. Several pyrimidine derivatives are structural components of nucleic acids, vitamins, enzymes, coenzymes etc, which play vital role in biological process. Important basic components of nucleic acids are pyrimidine derivatives – uracil, cytocine, thymine. Several natural products of plant origin containing pyrimidine nucleus as part of their structure are known to possess useful medicinal properties.

Vitamin-B1

Adenine

Guanine

Cytosine

Thymine

Uracil
Riboflavin

These facts are the source of inspiration for synthetic investigations and pharmacological evaluation of various pyrimidine derivatives. As a result of such investigations a number of pyrimidine derivatives are now in clinical use for the treatment of several health disorders.

Sulfamerizine

Sulfadimidine

Sulfadiazine

For these reasons the synthesis of compounds containing pyrimidine ring system and their biological and pharmacological evaluation has been the major target of research in several laboratories. The pyrimidine ring system may be tagged with other biologically interesting heterocyclic molecules either by fusion or by coupling directly or through carbon or nitrogen bridges. Pyrimidine condensed with various heterocycles
like furan, thiophene, pyrrole, pyrazole, thiazole, imidazole, pyridine, pyrazine, indole, etc., have been synthesised and screened for biological and pharmacological activities. The compounds formed by the fusion of pyrimidine ring with thiophene and furan nucleus are reported to possess gastric anti-secretory activity. The fusion of pyrimidine ring with triazolo derivatives produced compounds which exhibited cytotoxic activity.

In recent years there has been considerable interest in the synthesis of biheterocycles containing pyrimidine ring system as one of the heterocyclic partner. 2,4,6-Trisubstituted pyrimidine derivatives (I and II) which act as potential antimalarial agents are some compounds of this type.

Pyrimidine nucleosides and nucleotides, the components of DNA and RNA are also biheterocycles. There are a few reports in which pyrimidine ring is fused with substituted furan are shown to exhibit various biological and pharmacological activities.
In view of these facts an exhaustive research programme devoted to synthesis and biological evaluation of benzofurans fused or coupled with pyrimidine has been undertaken by Agasimundin et al. The results of such investigations are published\textsuperscript{28-36}. These facts stimulated our interest in the synthesis of naphthofurans fused with pyrimidine and biheterocyclic naphthofurans involving pyrimidine as one of the heterocycle. The results of such investigations have been published in a series of papers\textsuperscript{37-39}.

Biheterocyclic systems containing thiopyrimidine as one of the heterocycle have been synthesised and subjected to screening to various biological activities. Some such compounds have been shown to exhibit antimicrobial\textsuperscript{40,41}, antitumor\textsuperscript{42} and antifungal\textsuperscript{43,44} activities.
Present work

In view of these facts and in continuation of our work we have prepared a series of biheterocycles in which a series of 4-aryl-2-mercapto-4,5-dihydropyrimidines are coupled with 3-methoxybenzofuran and 3-aminonaphtho[2,1-b]furans.

A convenient synthetic route for coupling dihydro thiopyrimidine ring system is to modify α,β-unsaturated carbonyl group of chalcone analogues into dihydro thiopyrimidine ring system. Hence chalcones are the appropriate synthons for the target molecules. The benzofuran and naphthofuran analogues of chalcones reported in the previous chapter have been subjected to chemical modification into desired biheterocycles. All the 3-methoxybenzofuran analogues of chalcones (2a-g) were reacted with two equivalents of thiourea in an ethanolic solution in presence of ethanolic potash for 20 hrs. The target molecules 2-(4-aryl-2-mercapto-4,5-dihydropyrimidine-6-yl)-3-methoxybenzofurans (4a-g) were obtained in yields ranging from 34-95%. The synthesis of various aryl substituted thiopyrimidinyl benzofurans is outlined below schematically.
All the compounds (4a-g) thus prepared are described under Table-3 along with physical data and elemental analysis. IR spectra of the compounds (4a-g) revealed the absence of carbonyl group indicating its involvement in the reaction. The various absorption bands due to NH, C=N, C=S, C=S-NH, C-O-C functional groups were observed. The IR data of all these compounds is given under Table-1.

$^1$H NMR spectrum of compound 4b, as an example of this series revealed the following signals δ 6.6-7.6 (m, 6H, Ar H); 3.9 (s, 6H, 2 OCH$_3$); 3.78 (t, 1H, pyrimidine CH) and 2.9 (d, 2H, CH$_2$).

**Table-1**

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm$^{-1}$</th>
<th>NH</th>
<th>C=N</th>
<th>C=C</th>
<th>S=C-NH</th>
<th>C=S</th>
<th>C-O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>-C$_6$H$_5$</td>
<td>3190</td>
<td>1602</td>
<td>1530</td>
<td>1460</td>
<td>1180</td>
<td>1090</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>4-OCH$_3$-C$_6$H$_4$</td>
<td>3190</td>
<td>1603</td>
<td>1520</td>
<td>1470</td>
<td>1250</td>
<td>1180</td>
<td></td>
</tr>
<tr>
<td>4c</td>
<td>2-OH-C$_6$H$_4$</td>
<td>3160</td>
<td>1595</td>
<td>1540</td>
<td>1460</td>
<td>1240</td>
<td>1175</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>3-NO$_2$-C$_6$H$_4$</td>
<td>3320</td>
<td>1602</td>
<td>1560</td>
<td>1450</td>
<td>1300</td>
<td>1165</td>
<td></td>
</tr>
<tr>
<td>4e</td>
<td>4-Cl-C$_6$H$_4$</td>
<td>3210</td>
<td>1605</td>
<td>1540</td>
<td>1440</td>
<td>1280</td>
<td>1160</td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>4-CH$_3$-C$_6$H$_4$</td>
<td>3150</td>
<td>1595</td>
<td>1525</td>
<td>1462</td>
<td>1260</td>
<td>1165</td>
<td></td>
</tr>
<tr>
<td>4g</td>
<td>2-Furyl</td>
<td>3180</td>
<td>1580</td>
<td>1550</td>
<td>1450</td>
<td>1230</td>
<td>1160</td>
<td></td>
</tr>
</tbody>
</table>
**1H NMR Spectrum**

![NMR Spectrum Image]

**1D NMR plot parameters**
- **CX**: 20.00 cm
- **CY**: 29.00 cm
- **F1P**: 0.103 ppm
- **F1**: 2732.17 Hz
- **F2P**: -0.664 ppm
- **F2**: -199.21 Hz

**FID parameters**
- **FIDRES**: 0.182505 Hz
- **AG**: 2.7329011 sec
- **RG**: 574.7
- **DW**: 83.400 usec
- **DE**: 6.00 usec
- **TE**: 300.0 K
- **DI**: 2.0000000 sec

**Processing parameters**
- **SC**: 16384
- **SF**: 300.128989 MHz

**Parameters**
- **Current Data Parameters**
  - **NAME**: 10b
  - **EXPNO**: 1
  - **PROCNO**: 1

**Acquisition Parameters**
- **Date**: 20060724
- **Time**: 3:43
- **INSTRM**: 50000000
- **PROBHD**: 6.0 mm DUL 13C-1
- **PULPROG**: zg30
- **TD**: 32768
- **SOLVENT**: CDC13
- **NS**: 50
- **DS**: 0
- **SNR**: 5995.204 Hz
- **FIDRES**: 0.182959 Hz
- **AG**: 2.7329011 sec
- **RG**: 574.7
- **DW**: 83.400 usec
- **DE**: 6.00 usec
- **TE**: 300.0 K
- **DI**: 2.0000000 sec

**Additional Information**
- **CHANNEL**: f1
- **MUC1**: 1H
- **PI**: 8.00 usec
- **PL**: -1.00 db
- **SF01**: 300.1026912 MHz

**Chemical Structure**

![Chemical Structure Image]
Mechanism

The following two possible mechanisms are proposed for the conversion of \(-\text{C}-\text{CH} = \text{CH}-\) functionality into dihydropyrimidine ring system by the action of thiourea, urea and guanidine nitrate. One of the mechanism (a) involves the initial formation of schiff base and subsequent intramolecular Michael addition. An alternate mechanism (b) may involve the initial Michael addition followed by intramolecular nucleophillic attack at carbonyl carbon followed by loss of water molecule.

\[ \text{OMe} \quad \text{CH}=\text{CH-Ar} \quad \xrightarrow{\text{CH} = \text{CH-Ar}} \quad \text{OMe} \quad \text{CH}=\text{CH-Ar} \]

\[ \text{OMe} \quad \text{CH}=\text{CH-Ar} \quad \xrightarrow{\text{CH} = \text{CH-Ar}} \quad \text{OMe} \quad \text{CH}=\text{CH-Ar} \]

\[ X = \text{S, O, -NH} \]
2-(4-Aryl-2-mercapto-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans (5a-i)

The various 1-(3-aminonaphtho[2,1-b]furyl-3-aryl-2-propen-1-ones (3a-i), the synthesis of which are described in the previous chapter are subjected to reaction with thiourea.

Scheme-4

The reaction was carried out under similar conditions (as described above) with two equivalents of thiourea in presence of ethanolic potash in refluxing ethanol for 15 hrs. The desired 2-(4-aryl-2-mercapto-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans (5a-i) were obtained in yields ranging from 47-84%. All the compounds (5a-i), thus prepared are described under Table-4.
The IR spectra indicated the absence of carbonyl group. The various characteristic peaks supported the formation of dihydrothiopyrimidine ring system. The characteristic absorption bands are given in Table-2.

### Table-2

**IR spectral data of 2-(4-aryl-2-mercapto-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b] furans (5a-i)**

![Chemical structure of 5a-i](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NH(_2)</td>
</tr>
<tr>
<td>5 a</td>
<td>-C(_6)H(_5)</td>
<td>3280</td>
</tr>
<tr>
<td>5 b</td>
<td>4-OCH(_3)-C(_6)H(_4)</td>
<td>3310</td>
</tr>
<tr>
<td>5 c</td>
<td>2-OH-C(_6)H(_4)</td>
<td>3315</td>
</tr>
<tr>
<td>5 d</td>
<td>3-NO(_2)-C(_6)H(_4)</td>
<td>3305</td>
</tr>
<tr>
<td>5 e</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>3304</td>
</tr>
<tr>
<td>5 f</td>
<td>4-CH(_3)-C(_6)H(_4)</td>
<td>3302</td>
</tr>
<tr>
<td>5 g</td>
<td>4-OH-3-OCH(_3)-C(_6)H(_3)</td>
<td>3320</td>
</tr>
<tr>
<td>5 h</td>
<td>4-N-(CH(_3))(_2)-C(_6)H(_4)</td>
<td>3315</td>
</tr>
<tr>
<td>5 i</td>
<td>2-Furyl</td>
<td>3250</td>
</tr>
</tbody>
</table>
IR Spectrum

Comment:
HSN-TH-4d

No. of Scans: 10

Resolution: 4 [1/cm]

Apodization: Happ-Genzel

Date/Time: 20/12/2005 17:29:47
User: PRINCIPAL
Comment: HSN-TH-4g

No. of Scans; 10

Resolution; 4 [1/cm]

Apodization; Happ-Genzel

Date/Time; 20/12/2005 20:33:12
User; PRINCIPAL
Experimental

2-(2-Mercapto-4-phenyl-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofuran (4a)

To a solution of 1-(3-methoxybenzofuran-2-yl)-3-phenyl-2-propen-1-one (2a), (0.556 g, 0.002 mol) and thiourea (0.304 g, 0.004 mol) in ethanol (20 ml), a solution of potassium hydroxide (0.224 g in 6 ml of ethanol) was added. The reaction mixture was heated under reflux on a water bath for 20 hrs. The progress of the reaction was monitored by TLC (chloroform-methanol 9:1). The reaction mixture after leaving overnight was poured into crushed ice. It was carefully acidified with dilute hydrochloride acid and the product separated as an yellow solid was filtered, washed with water and dried. It was crystallised from aqueous ethanol. Yield (0.480 g, 71%), m.p. 214°C.

All other compounds (4b-g) of this series were prepared by the reaction of thiourea with 1-(3-methoxybenzofuran-2-yl)-3-ary1-2-propen-1-ones (2b-g) under similar reaction conditions.

The compounds thus prepared are

4b 2-[2-Mercapto-4-(p-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran
4c 2-[2-Mercapto-4-(o-hydroxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran
4d 2-[2-Mercapto-4-(m-nitro phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran
4e 2-[2-Mercapto-4-(p-chloro phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran
4f 2-[2-Mercapto-4-(p-toluyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran
4g 2-[2-Mercapto-4-(2-furyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran

The m.p., % yield and elemental analysis data is given under Table-3.
Table 3
2-(4-Aryl-2-mercapto-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans (4a-g)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>-C₆H₅</td>
<td>214</td>
<td>71.42</td>
<td>C₁₉H₁₆O₂N₂S</td>
<td>66.66 (67.84)</td>
<td>4.77</td>
</tr>
<tr>
<td>4b</td>
<td>4-OCH₃-C₆H₄</td>
<td>140</td>
<td>95.02</td>
<td>C₂₀H₁₈O₃N₂S</td>
<td>65.39 (65.55)</td>
<td>4.69</td>
</tr>
<tr>
<td>4c</td>
<td>2-OH-C₆H₄</td>
<td>165</td>
<td>62.50</td>
<td>C₁₉H₁₆O₃N₂S</td>
<td>64.69 (64.76)</td>
<td>4.37</td>
</tr>
<tr>
<td>4d</td>
<td>3-NO₂-C₆H₄</td>
<td>218</td>
<td>34.12</td>
<td>C₁₉H₁₅O₄N₃S</td>
<td>59.51 (59.83)</td>
<td>3.77</td>
</tr>
<tr>
<td>4e</td>
<td>4-Cl-C₆H₄</td>
<td>114</td>
<td>67.56</td>
<td>C₁₉H₁₅O₂N₂S</td>
<td>61.33 (61.53)</td>
<td>4.12</td>
</tr>
<tr>
<td>4f</td>
<td>4-CH₃-C₆H₄</td>
<td>143</td>
<td>57.14</td>
<td>C₂₀H₁₇O₂N₂S</td>
<td>68.28 (68.55)</td>
<td>5.01</td>
</tr>
<tr>
<td>4g</td>
<td>2-Furyl</td>
<td>119</td>
<td>66.66</td>
<td>C₁₇H₁₄O₃N₂S</td>
<td>62.37 (62.56)</td>
<td>4.08</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Aqueous ethanol

2-(2-Mercapto-4-phenyl-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furan (5a)

To a solution of 1-(3-aminonaphtho[2,1-b]furyl)-3-phenyl-2-propen-1-one (3a), (0.626 g, 0.002 mol) and thiourea (0.304 g, 0.004 mol) in ethanol (25 ml), an ethanolic solution of potassium hydroxide (10 ml, 2.25%) was added and the reaction mixture was heated under reflux on a water bath. The progress of the reaction was monitored by TLC (chloroform-methanol 9:1). The reaction was completed in 15 hrs. The reaction
mixture was left over night and then poured into ice water. After acidification the liberated product was collected by filtration, washed with water and dried. It was further purified by crystallisation from aqueous ethanol. Yield, (0.46 g, 62%), m.p. 195°C.

Similarly compounds (5b-i) were prepared by the condensation of the respective 1-(3-aminonaphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3b-i) with thiourea.

The compounds thus prepared are

5b 2-[2-Mercapto-4-(p-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
5c 2-[2-Mercapto-4-(o-hydroxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
5d 2-[2-Mercapto-4-(m-nitro phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
5e 2-[2-Mercapto-4-(p-chloro phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
5f 2-[2-Mercapto-4-(p-toluyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
5g 2-[2-Mercapto-4-(p-hydroxy-m-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
5h 2-[2-Mercapto-4-(p,N,N-dimethyl phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
5i 2-[2-Mercapto-4-(‘2-furyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

The physical constants, % yield and elemental analysis data is recorded in Table-4.
Table 4
2-(4-Aryl-2-mercapto-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans (5a-i)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>5a</td>
<td>-C₆H₅</td>
<td>195</td>
<td>62.42</td>
<td>C₂₂H₁₁ON₃S</td>
<td>71.04 (71.14)</td>
</tr>
<tr>
<td>5b</td>
<td>4-OCH₃-C₆H₄</td>
<td>216</td>
<td>69.42</td>
<td>C₂₃H₁₉O₂N₃S</td>
<td>68.79 (68.81)</td>
</tr>
<tr>
<td>5c</td>
<td>2-OH-C₆H₄</td>
<td>206</td>
<td>61.03</td>
<td>C₂₂H₁₇O₂N₃S</td>
<td>68.09 (68.20)</td>
</tr>
<tr>
<td>5d</td>
<td>3-NO₂-C₆H₄</td>
<td>191</td>
<td>73.9</td>
<td>C₂₃H₁₆O₃N₄S</td>
<td>63.25 (63.45)</td>
</tr>
<tr>
<td>5e</td>
<td>4-Cl-C₆H₄</td>
<td>186</td>
<td>69.97</td>
<td>C₂₂H₁₆ON₃SCl</td>
<td>65.01 (65.10)</td>
</tr>
<tr>
<td>5f</td>
<td>4-CH₃-C₆H₄</td>
<td>180</td>
<td>68.40</td>
<td>C₂₃H₁₉ON₃S</td>
<td>71.58 (71.66)</td>
</tr>
<tr>
<td>5g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>130</td>
<td>71.80</td>
<td>C₂₃H₁₉O₃N₃S</td>
<td>66.07 (66.17)</td>
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<tr>
<td>5h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>169</td>
<td>84.95</td>
<td>C₂₄H₂₂ON₄S</td>
<td>69.49 (69.54)</td>
</tr>
<tr>
<td>5i</td>
<td>2-Furyl</td>
<td>157</td>
<td>47.63</td>
<td>C₂₀H₁₅O₂N₃S</td>
<td>66.36 (66.46)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Aqueous ethanol
Reference


91


CHAPTER-4

Synthesis of 2-(4-aryl-2-hydroxy-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans and 2-(4-aryl-2-hydroxy-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans.
Introduction

In the previous chapter the synthesis of biheterocyclic benzofurans and naphthofurans coupled with thiopyrimidine ring system is described. The present chapter deals with the synthesis of biheterocycles in which hydroxypyrimidine ring system is coupled with benzofurans and naphthofurans. The importance of pyrimidine skeleton has been highlighted in the previous chapter.

In several comprehensive review articles the diverse biological activities of pyrimidine compounds have been surveyed and summarised. Pyrimidine derivatives particularly, are much investigated for anticancer and antiviral activities. Some such compounds which have received much attention are AZT, DDC and DDI.

\[
\begin{align*}
\text{N} &= \text{N}^{+} = \text{N}^{-} \\
\text{Zidovudine (AZT)} & \quad \text{Didanosine (DDC)} & \quad \text{Zalcitabine (DDI)}
\end{align*}
\]

Their activities are manifested in the dioxo (dihydroxy) pyrimidine skeleton (I). Another related pyrimidine framework which is under intensive investigation is oxo (hydroxy) pyrimidine (II).

\[
\begin{align*}
\text{(I)} & \quad \text{(II)} \\
R = R' = H, \text{ alkyl or aryl} & \quad R = \text{CH}_3, R' - \text{COCl}_3, \text{COOC}_2\text{H}_5, \text{ etc.}, \\
& \quad X = \text{alkyl or aryl}
\end{align*}
\]
This is because it has very broad pharmacological profile in the form of calcium channel blocker, antihypertensive agent and $\alpha_{1a}$ antagonist\textsuperscript{18-20}. These findings have lead several researchers to synthesise various biheterocyclic systems containing hydroxypyrimidine as one of the heterocycle\textsuperscript{21-23}. 
Present work

One of the routine and established method for the construction of hydroxy (oxo) pyrimidine ring involves the reaction of α,β-unsaturated carbonyl compounds with urea. Chalcones which contain such functional group have been the appropriate precursors for conversion into dihydrohydroxypyrimidine ring system.

1-(3-Methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2a-g) described in chapter-2 were subjected to reaction with urea in an ethanolic solution in presence of aqueous sodium hydroxide under reflux conditions. The target compounds 2-(2-hydroxy-4-phenyl-4,5-dihydropyrimidimin-6-yl)-3-methoxybenzofuran (6a-g) were obtained in yields ranging from 48-97%. The synthesis of all these compounds is outlined below schematically.

Scheme-5

\[
\begin{align*}
2a-g & \quad + \quad \text{H}_2\text{N-C} = \text{NH}_2 \\
\text{EtOH/aq NaOH (10\%)} & \quad \Delta, 20 \text{ hrs.} \\
6a-g & \quad \text{Ar}
\end{align*}
\]

Ar

a. -C\textsubscript{6}H\textsubscript{5}  

b. 4 - OCH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}  

c. 2 - OH-C\textsubscript{6}H\textsubscript{4}  

d. 3 - NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}  

e. 4 - Cl-C\textsubscript{6}H\textsubscript{4}  

f. 4 - CH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}  

g. 2-Furyl
The IR spectra of all these compounds revealed appropriate absorption bands due to OH, C=C, C=N and C-O-C functional groups. The IR data of all these compounds is summarised under Table-1.

\(^1\)H NMR spectrum of 7\(\text{e}\) exhibited signals at \(\delta\) 7.3-8.1 (m, 10H, ArH); 5.0 (br s, 3H, \(\text{NH}_2/\text{OH}\)); 3.9 (t, 1H, Pyrimidine CH) and 3.7 (d, 2H, \(\text{CH}_2\)).

**Table-1**

**IR spectral data of 2-(4-aryl-2-hydroxy-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans (6a-g)**

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm(^{-1})</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>-C(_6)H(_5)</td>
<td>3425</td>
<td>1605</td>
<td>1545</td>
<td>1165</td>
<td></td>
</tr>
<tr>
<td>6b</td>
<td>4-OCH(_3)-C(_6)H(_4)</td>
<td>3420</td>
<td>1605</td>
<td>1515</td>
<td>1180</td>
<td></td>
</tr>
<tr>
<td>6c</td>
<td>2-OH-C(_6)H(_4)</td>
<td>3400, 3100</td>
<td>1610</td>
<td>1555</td>
<td>1150</td>
<td></td>
</tr>
<tr>
<td>6d</td>
<td>3-NO(_2)-C(_6)H(_4)</td>
<td>3420, 3150</td>
<td>1612</td>
<td>1530</td>
<td>1180</td>
<td></td>
</tr>
<tr>
<td>6e</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>3400, 3150</td>
<td>1602</td>
<td>1545</td>
<td>1145</td>
<td></td>
</tr>
<tr>
<td>6f</td>
<td>4-CH(_3)-C(_6)H(_4)</td>
<td>3415, 3125</td>
<td>1602</td>
<td>1560</td>
<td>1180</td>
<td></td>
</tr>
<tr>
<td>6g</td>
<td>2-Furyl</td>
<td>3415</td>
<td>1608</td>
<td>1545</td>
<td>1180</td>
<td></td>
</tr>
</tbody>
</table>

Similarly 1-(3-aminonaphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3a-i) when reacted with urea in an alcoholic solution in presence of aqueous sodium hydroxide under reflux furnished the biheterocyclic dihydropyrimidinyl naphthofurans (7a-i). The synthesis of all these compounds is outlined in the following scheme.
Scheme-6

\[
\text{3a-i} 
\xrightarrow{\text{Ethanol/aqueous NaOH(10%) } \triangle, 10 \text{ hrs.}} 
\text{7a-i}
\]

\text{Ar}

a. \(-C_6H_5\)  

b. \(4 - \text{OCH}_3\cdot C_6H_4\)  

c. \(2 - \text{OH} \cdot C_6H_4\)  

d. \(3 - \text{NO}_2 \cdot C_6H_4\)  

e. \(4 - \text{Cl} \cdot C_6H_4\)  

f. \(4 - \text{CH}_3 \cdot C_6H_4\)  

g. \(4 - \text{OH} - 3 - \text{OCH}_3 \cdot C_6H_3\)  

h. \(4 - \text{N(CH}_3)_2 \cdot C_6H_4\)  

i. \(2 - \text{Furyl}\)
The IR data of all these compounds is in good agreement with the structures. The characteristic IR absorption bands are summarised in Table-2.

### Table-2

**IR spectral data of 2-(4-aryl-2-hydroxy-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-\textit{b}] furans (7a-i)**

![Chemical structure of 7a-i](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>NH₂</th>
<th>NH</th>
<th>C=C</th>
<th>C=O</th>
<th>C=N</th>
<th>C-O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>-C₆H₅</td>
<td>3310</td>
<td>3175</td>
<td>1620</td>
<td>1630</td>
<td>1540</td>
<td>1180</td>
</tr>
<tr>
<td>7b</td>
<td>4-OCH₃-C₆H₄</td>
<td>3320</td>
<td>3160</td>
<td>1620</td>
<td>1630</td>
<td>1540</td>
<td>1170</td>
</tr>
<tr>
<td>7c</td>
<td>2-OH-C₆H₄</td>
<td>3320</td>
<td>3140</td>
<td>1618</td>
<td>1630</td>
<td>1540</td>
<td>1170</td>
</tr>
<tr>
<td>7d</td>
<td>3-NO₂-C₆H₄</td>
<td>3315</td>
<td>3150</td>
<td>1618</td>
<td>1630</td>
<td>1540</td>
<td>1170</td>
</tr>
<tr>
<td>7e</td>
<td>4-Cl-C₆H₄</td>
<td>3320</td>
<td>3130</td>
<td>1590</td>
<td>1630</td>
<td>1540</td>
<td>1160</td>
</tr>
<tr>
<td>7f</td>
<td>4-CH₃-C₆H₄</td>
<td>3310</td>
<td>3150</td>
<td>1590</td>
<td>1630</td>
<td>1540</td>
<td>1150</td>
</tr>
<tr>
<td>7g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>3320</td>
<td>3140</td>
<td>1620</td>
<td>1630</td>
<td>1540</td>
<td>1140</td>
</tr>
<tr>
<td>7h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>3310</td>
<td>3150</td>
<td>1608</td>
<td>1635</td>
<td>1540</td>
<td>1160</td>
</tr>
<tr>
<td>7i</td>
<td>2-Furyl</td>
<td>3315</td>
<td>3160</td>
<td>1602</td>
<td>1640</td>
<td>1520</td>
<td>1150</td>
</tr>
</tbody>
</table>
IR Spectrum

Comment:
HSN-UR-6a

No. of Scans; 10
Resolution; 4 [1/cm]

Date/Time: 20/12/2005 16:23:29
User: PRINCIPAL

Annotiation: Henn-Genzel
IR Spectrum

7d

Comment; HSN-UR-61

No. of Scans; 10
Resolution; 4 [1/cm]

Apodization; Happ-Benzel

Date/Time; 20/12/2005 17:43:44
User; PRINCIPAL
Experimental

2-(2-Hydroxy-4-phenyl-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofuran (6a)

To a solution of 1-(3-methoxybenzofuran-2-yl)-3-phenyl-2-propen-1-one (2a), (0.556 g, 0.002 mol) and urea (0.120 g, 0.002 mol) in ethanol (20 ml) was added aqueous sodium hydroxide (4 ml, 10%). The reaction mixture was heated under reflux for 20 hrs. Completion of the reaction was indicated by TLC (chloroform-methanol 9:1). After cooling the reaction mixture was poured into excess of ice water. The product was carefully acidified with dilute hydrochloric acid. The product separated was collected by filtration after washing with water. Crystallisation from benzene-pet ether gave pale yellow crystalline solid. Yield (0.40 g, 62%), m.p. 170°C.

The similar reactions of 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2b-g) with urea gave the following compounds.

\[ 6b \quad 2-[2-\text{Hydroxy-4-(p-methoxy phenyl)-4,5-dihydropyrimidin-6-yl}]\-3\text{-methoxybenzofuran} \]

\[ 6c \quad 2-[2-\text{Hydroxy-4-(o-hydroxy phenyl)-4,5-dihydropyrimidin-6-yl}]\-3\text{-methoxybenzofuran} \]

\[ 6d \quad 2-[2-\text{Hydroxy-4-(m-nitro phenyl)-4,5-dihydropyrimidin-6-yl}]\-3\text{-methoxybenzofuran} \]

\[ 6e \quad 2-[2-\text{Hydroxy-4-(p-chloro phenyl)-4,5-dihydropyrimidin-6-yl}]\-3\text{-methoxybenzofuran} \]

\[ 6f \quad 2-[2-\text{Hydroxy-4-(p-toluyl)-4,5-dihydropyrimidin-6-yl}]\-3\text{-methoxybenzofuran} \]

\[ 6g \quad 2-[2-\text{Hydroxy-4-(2-furyl)-4,5-dihydropyrimidin-6-yl}]\-3\text{-methoxybenzofuran} \]

The m.p., % yield and elemental analysis data of all these compounds is given in Table-3.
Table 3

2-(4-Aryl-2-hydroxy-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans (6a-g)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>-C₆H₅</td>
<td>170</td>
<td>62.89</td>
<td>C₁₉H₁₆O₃N₂</td>
<td></td>
<td>71.04</td>
<td>5.01</td>
<td>8.59</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(71.24)</td>
<td>(5.03)</td>
<td>(8.74)</td>
</tr>
<tr>
<td>6b</td>
<td>4-OCH₃-C₆H₄</td>
<td>240</td>
<td>97.14</td>
<td>C₂₀H₁₈O₄N₂</td>
<td></td>
<td>68.39</td>
<td>5.07</td>
<td>7.82</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>(68.56)</td>
<td>(5.18)</td>
<td>(8.00)</td>
</tr>
<tr>
<td>6c</td>
<td>2-OH-C₆H₄</td>
<td>160</td>
<td>44.91</td>
<td>C₁₉H₁₆O₄N₂</td>
<td></td>
<td>67.39</td>
<td>4.62</td>
<td>8.20</td>
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<td></td>
<td></td>
<td>(67.85)</td>
<td>(4.79)</td>
<td>(8.33)</td>
</tr>
<tr>
<td>6d</td>
<td>3-NO₂-C₆H₄</td>
<td>241</td>
<td>52.19</td>
<td>C₁₉H₁₅O₅N₃</td>
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<td>62.42</td>
<td>4.10</td>
<td>11.35</td>
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<td></td>
<td>(62.46)</td>
<td>(4.14)</td>
<td>(11.50)</td>
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<tr>
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<td>4-Cl-C₆H₄</td>
<td>126</td>
<td>71.02</td>
<td>C₁₉H₁₅O₃N₂Cl</td>
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<td>64.22</td>
<td>4.16</td>
<td>7.82</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>(64.32)</td>
<td>(4.26)</td>
<td>(7.90)</td>
</tr>
<tr>
<td>6f</td>
<td>4-CH₃-C₆H₄</td>
<td>258</td>
<td>97.89</td>
<td>C₂₀H₁₈O₃N₂</td>
<td></td>
<td>71.59</td>
<td>5.32</td>
<td>8.26</td>
</tr>
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<td></td>
<td></td>
<td>(71.84)</td>
<td>(5.43)</td>
<td>(8.38)</td>
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<td>6g</td>
<td>2-Furyl</td>
<td>123</td>
<td>64.93</td>
<td>C₁₇H₁₄O₄N₂</td>
<td></td>
<td>65.72</td>
<td>4.44</td>
<td>9.01</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>(65.80)</td>
<td>(4.55)</td>
<td>(9.03)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Benzene-pet. ether

2-(2-Hydroxy-4-phenyl-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans (7a)

To a solution of 1-(3-aminonaphtho[2,1-b]furyl)-3-phenyl-2-propen-1-one (3a), (0.626 g, 0.002 mol) and urea (0.120 g, 0.002 mol) in ethanol (20 ml) was treated with aqueous sodium hydroxide (2 ml, 10%). The reaction mixture was heated under reflux while monitoring the reaction by TLC (chloroform-methanol 9:1). The reaction was
completed in 10 hrs. The reaction mixture was poured into ice water and then acidified carefully using dilute hydrochloric acid. The product which separated was filtered, washed with water and dried. Recrystallisation from benzene-pet ether gave the product as a pale yellow crystalline solid. Yield (0.6 g, 85 %), m.p. 190°C.

The other compounds of this series (7b-i) were similarly prepared by the reaction of 1-(3-aminonaphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3b-i) with urea. The m.p., % yield and elemental analytical data of all these compounds is summarised in Table-4.

7b 2-[2-Hydroxy-4-(p-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
7c 2-[2-Hydroxy-4-(o-hydroxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
7d 2-[2-Hydroxy-4-(m-nitro phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
7e 2-[2-Hydroxy-4-(p-chloro phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
7f 2-[2-Hydroxy-4-(p-tolyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
7g 2-[2-Hydroxy-4-(p-hydroxy-m-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
7h 2-[2-Hydroxy-4-(p-N,N-dimethylphenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
7i 2-[2-Hydroxy-4-(2-furyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
Table 4

2-(4-Aryl-2-hydroxy-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans (7a-i)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>7a</td>
<td>-C₆H₅</td>
<td>190</td>
<td>85.55</td>
<td>C₂₂H₁₁O₂N₃</td>
<td>74.29 (74.35)</td>
</tr>
<tr>
<td>7b</td>
<td>4-OCH₃-C₆H₄</td>
<td>224</td>
<td>86.16</td>
<td>C₂₃H₁₉O₃N₃</td>
<td>71.57 (71.67)</td>
</tr>
<tr>
<td>7c</td>
<td>2-OH-C₆H₄</td>
<td>197</td>
<td>81.30</td>
<td>C₂₂H₁₇O₃N₃</td>
<td>71.11 (71.15)</td>
</tr>
<tr>
<td>7d</td>
<td>3-NO₂-C₆H₄</td>
<td>235</td>
<td>83.16</td>
<td>C₂₂H₁₄O₄N₄</td>
<td>65.88 (66.00)</td>
</tr>
<tr>
<td>7e</td>
<td>4-Cl-C₆H₄</td>
<td>218</td>
<td>83.97</td>
<td>C₂₂H₁₆O₂N₃Cl</td>
<td>67.68 (67.78)</td>
</tr>
<tr>
<td>7f</td>
<td>4-CH₃-C₆H₄</td>
<td>240</td>
<td>83.92</td>
<td>C₂₃H₁₉O₂N₃</td>
<td>74.59 (74.78)</td>
</tr>
<tr>
<td>7g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>312</td>
<td>81.95</td>
<td>C₂₃H₁₉O₄N₃</td>
<td>68.58 (68.82)</td>
</tr>
<tr>
<td>7h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>313</td>
<td>78.48</td>
<td>C₂₄H₂₂O₂N₄</td>
<td>72.24 (72.34)</td>
</tr>
<tr>
<td>7i</td>
<td>2-Furyl</td>
<td>310</td>
<td>76.96</td>
<td>C₂₀H₁₃O₃N₃</td>
<td>69.41 (69.56)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Benzene-pet. ether

102
Reference


Synthesis of 2-(2-amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans and 2-(2-amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans.
Introduction

Aminopyrimidine skeleton is known to play specific role in biological process, through hydrogen bonding due to NH$_2$ group. For example guanine, cytosine and thymine containing aminopyrimidine moiety are responsible for hydrogen bonding in base pairs of nucleic acids. Many compounds derived from aminopyrimidines are clinically used as drugs. For these reasons aminopyrimidine ring system has received considerable attention in exploration of newer drugs. A number of biheterocycles containing aminopyrimidine as one of the heterocycle have been investigated in recent years$^{1-7}$. Some of these compounds are reported to possess antibacterial activities.
Present work

In view of these facts a series of heterocyclic systems of benzofuran and naphthofuran with dihydroaminopyrimidine as another heterocyclic component are now prepared for investigating their biological and pharmacological activities.

The synthetic method involves the chalcone analogues of 3-methoxybenzofuran and 3-aminonaphthofurans as the key starting materials. The reaction of 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2a-g) with guanidine nitrate in alkaline medium in an ethanolic solution by heating under reflux for 20 hrs. gave the respective 2-(2-amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans (8a-g) in reasonably good yields. The synthesis of all these compounds is outlined in the following scheme.

Scheme-7

\[
\begin{align*}
\text{OMe} & \\
\text{C} & \text{- CH = CH - Ar} & + \\
\text{H}_2\text{N} & \text{C} & \text{NH}_2 \cdot \text{HNO}_3 \\
\text{Ethanol/aqueous NaOH(10\%)} & \Delta, 20 \text{ hrs.} \\
\text{OMe} & \\
\text{Ar} & \\
\text{2a-g} & \\
\text{8a-g} & \\
\text{Ar} & \\
a. & -\text{C}_6\text{H}_5 & e. & 4 - \text{Cl-C}_6\text{H}_4 \\
b. & 4 - \text{OCH}_3\text{-C}_6\text{H}_4 & f. & 4 - \text{CH}_3\text{-C}_6\text{H}_4 \\
c. & 2 - \text{OH-C}_6\text{H}_4 & g. & 2\text{-Furyl} \\
d. & 3 - \text{NO}_2\text{-C}_6\text{H}_4
\end{align*}
\]
The characteristic IR absorption bands due to NH$_2$ group in the range of 3350 to 3125 cm$^{-1}$, due to C=C in the region of 1600 cm$^{-1}$, C=N in the region of 1540 cm$^{-1}$ and C-O-C in the region of 1150 cm$^{-1}$ were exhibited by all these compounds. Such characteristic IR absorption bands of all the compounds are tabulated under Table-1.
Table-1

IR spectral data of 2-(2-amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans (8a-g)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm(^{-1})</th>
<th>NH</th>
<th>C=C</th>
<th>C=N</th>
<th>C-O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>-C(_6)H(_5)</td>
<td>3350, 3175</td>
<td>1599</td>
<td>1550</td>
<td>1160</td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>4-OCH(_3)-C(_6)H(_4)</td>
<td>3325</td>
<td>1605</td>
<td>1540</td>
<td>1130</td>
<td></td>
</tr>
<tr>
<td>8c</td>
<td>2-OH-C(_6)H(_4)</td>
<td>3315, 3160</td>
<td>1565</td>
<td>1550</td>
<td>1150</td>
<td></td>
</tr>
<tr>
<td>8d</td>
<td>3-NO(_2)-C(_6)H(_4)</td>
<td>3320, 3125</td>
<td>1610</td>
<td>1530</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>8e</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>3300, 3125</td>
<td>1606</td>
<td>1550</td>
<td>1165</td>
<td></td>
</tr>
<tr>
<td>8f</td>
<td>4-CH(_3)-C(_6)H(_4)</td>
<td>3300, 3125</td>
<td>1602</td>
<td>1545</td>
<td>1150</td>
<td></td>
</tr>
<tr>
<td>8g</td>
<td>2-Furyl</td>
<td>3310, 3175</td>
<td>1600</td>
<td>1550</td>
<td>1135</td>
<td></td>
</tr>
</tbody>
</table>

Similar reaction of 1-(3-aminonaphtho[2,1-b]furyl-3-aryl-2-propen-1-ones (3a-i) with guanidine nitrate yielded the respective 2-(2-amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b] (9a-i) in yields ranging from 73-95\%. The synthesis of all these compounds is outlined in the following scheme.
The IR spectral data is in good agreement with the expected structure. The characteristic absorption bands due to NH$_2$, C-O-C, C=C and C=N of all these compounds is described under Table-2.

$^1$H NMR spectra of 9e and 9f exhibited the following signals

9e: $\delta$ 7.1 - 8.1 (m, 10H, ArH); 4.5 (t, 1H, pyrimidine CH); 4.3 (d, 2H, CH$_2$) and 1.68 (br s, 4H, 2NH$_2$).

9f: $\delta$ 7.28 - 8.04 (m, 10H, ArH); 5.9 (s, 2H, NH$_2$); 5.7 (s, 2H, NH$_2$); 3.77 (t, 1H, pyrimidine CH); 3.70 (d, 2H, CH$_2$) and 2.57 (s, 3H, CH$_3$).
Table-2

IR spectral data of 2-(2-amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans (9a-i)

\[
\text{IR (Nujol) cm}^{-1}
\]

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>NH₂</th>
<th>C=C</th>
<th>C=N</th>
<th>C-O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>-C₆H₅</td>
<td>3310</td>
<td>1610</td>
<td>1550</td>
<td>1160</td>
</tr>
<tr>
<td>9b</td>
<td>4-OCH₃-C₆H₄</td>
<td>3300</td>
<td>1620</td>
<td>1545</td>
<td>1170</td>
</tr>
<tr>
<td>9c</td>
<td>2-OH-C₆H₄</td>
<td>3310</td>
<td>1612</td>
<td>1545</td>
<td>1170</td>
</tr>
<tr>
<td>9d</td>
<td>3-NO₂-C₆H₄</td>
<td>3320</td>
<td>1611</td>
<td>1540</td>
<td>1160</td>
</tr>
<tr>
<td>9e</td>
<td>4-Cl-C₆H₄</td>
<td>3315</td>
<td>1610</td>
<td>1540</td>
<td>1160</td>
</tr>
<tr>
<td>9f</td>
<td>4-CH₃-C₆H₄</td>
<td>3310</td>
<td>1615</td>
<td>1545</td>
<td>1170</td>
</tr>
<tr>
<td>9g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>3310</td>
<td>1620</td>
<td>1540</td>
<td>1165</td>
</tr>
<tr>
<td>9h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>3320</td>
<td>1605</td>
<td>1545</td>
<td>1160</td>
</tr>
<tr>
<td>9i</td>
<td>2-Furyl</td>
<td>3310</td>
<td>1610</td>
<td>1540</td>
<td>1150</td>
</tr>
</tbody>
</table>
Comment: HSN-GN-5d

No. of Scans: 10

Resolution: 4 [1/cm]

Apodization: Hap-Genzel

Date/Time: 20/12/2005 17:39:36

User: PRINCIPAL
1H NMR Spectrum

**Chemical Structure:**

- The molecule contains aromatic rings with substituents.
- Notation: 9e

**NMR Parameters:**

- **Channel 1:**
  - **NUC:** 1H
  - **P1:** 8.00 usec
  - **PL1:** -1.00 dB
  - **SFD1:** 300.137012 MHz

- **F2:**
  - **SI:** 16384
  - **SF:** 300.129999 MHz
  - **MDM:** EM
  - **SSB:** 0
  - **LB:** 1.00 Hz
  - **GB:** 0
  - **PC:** 7.00

- **1D NMR plot parameters:**
  - **CX:** 20.00 cm
  - **CY:** 50.00 cm
  - **F1P:** 8.986 ppm
  - **F1:** 2696.85 Hz
  - **F2:** -1.005 ppm
  - **F2:** -181.55 Hz
  - **PPMCH:** 0.47953 ppm/cm
  - **H2CH:** 143.92020 Hz/cm
Experimental

2-(2-Amino-4-phenyl-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofuran (8a)

To a suspension of 1-(3-methoxybenzofuran-2-yl)-3-phenyl-2-propen-1-one (2a), (0.556 g, 0.002 mol), guanidine nitrate (0.244 g, 0.002 mol) in ethanol (20 ml), aqueous sodium hydroxide (4 ml, 10%) was added and the reaction mixture was heated under reflux for 20 hrs. The completion of the reaction was indicated by TLC (chloroform-methanol 9:1). The reaction mixture was poured into water. The product biheterocycle that separated was collected by filtration after washing with water and dried. It was obtained as yellow crystalline solid and crystalised from aqueous ethanol. Yield (0.5 g, 78 %), m.p. 252°C.

The various 4-aryl-analogues (8b-g) were similarly prepared from 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2b-g) and guanidine nitrate. The physical constants, % yield and analytical data are described under Table-3.

8b 2-[2-Amino-4-(p-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran

8c 2-[2-Amino-4-(o-hydroxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran

8d 2-[2-Amino-4-(m-nitro phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran

8e 2-[2-Amino-4-(p-chloro phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran

8f 2-[2-Amino-4-(p-tolyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran

8g 2-[2-Amino-4-(2-furyl phenyl)-4,5-dihydropyrimidin-6-yl]-3-methoxybenzofuran
Table 3
2-(2-Amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-methoxybenzofurans (8a-g)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>8 a</td>
<td>-C₆H₅</td>
<td>252</td>
<td>78.86</td>
<td>C₁₉H₁₇O₈N₃</td>
<td>71.43 (71.46)</td>
</tr>
<tr>
<td>8 b</td>
<td>4-OCH₃-C₆H₄</td>
<td>247</td>
<td>86.45</td>
<td>C₂₀H₁₉O₃N₃</td>
<td>68.37 (68.75)</td>
</tr>
<tr>
<td>8 c</td>
<td>2-OH-C₆H₄</td>
<td>176</td>
<td>93.09</td>
<td>C₁₉H₁₇O₃N₃</td>
<td>67.88 (68.05)</td>
</tr>
<tr>
<td>8 d</td>
<td>3-NO₂-C₆H₄</td>
<td>231</td>
<td>44.19</td>
<td>C₁₉H₁₆O₄N₄</td>
<td>62.43 (62.63)</td>
</tr>
<tr>
<td>8 e</td>
<td>4-Cl-C₆H₄</td>
<td>121</td>
<td>85.47</td>
<td>C₁₉H₁₆O₂N₃Cl</td>
<td>64.36 (64.50)</td>
</tr>
<tr>
<td>8 f</td>
<td>4-CH₃-C₆H₄</td>
<td>233</td>
<td>93.65</td>
<td>C₂₀H₁₉O₂N₃</td>
<td>72.01 (72.05)</td>
</tr>
<tr>
<td>8 g</td>
<td>2-Furyl</td>
<td>235</td>
<td>94.46</td>
<td>C₁₇H₁₃O₃N₃</td>
<td>65.76 (66.01)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Aqueous ethanol
2-(2-Amino-4-phenyl-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furan (9a)

A mixture of 1-(3-aminonaphtho[2,1-b]furyl)-3-phenyl-2-propen-1-one (3a), (0.626 g, 0.002 mol), guanidine nitrate (0.244 g, 0.002 mol) in ethanol (20 ml) was treated with aqueous sodium hydroxide (4 ml, 10%). The reaction mixture was heated under reflux for 10 hrs. while monitoring the progress of the reaction by TLC (chloroform-methanol 9:1). The reaction mixture was poured in to water, the product which separated as an yellow solid was collected by filtration after washing with water. Further purification of the compound was accomplished by crystallisation from aqueous ethanol. Yield (0.536 g, 76%), m.p. 240°C.

Using similar procedure the other compounds of this series (9b-i) were prepared from 1-(3-aminonaphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3b-i) and guanidine nitrate. The physical constants, % yield and analytical data are described under Table-4.

9b 2-[2-Amino-4-(p-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

9c 2-[2-Amino-4-(o-hydroxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

9d 2-[2-Amino-4-(m-nitro phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

9e 2-[2-Amino-4-(p-chloro phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

9f 2-[2-Amino-4-(p-toluyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

9g 2-[2-Amino-4-(p-hydroxy-m-methoxy phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

9h 2-[2-Amino-4-(p-N,N-dimethyl phenyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan

9i 2-[2-Amino-4-(2-furyl)-4,5-dihydropyrimidin-6-yl]-3-aminonaphtho[2,1-b]furan
Table 4

2-(2-Amino-4-aryl-4,5-dihydropyrimidin-6-yl)-3-aminonaphtho[2,1-b]furans (9a-i)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
</thead>
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<tr>
<td>9a</td>
<td>-C₆H₅</td>
<td>240</td>
<td>85.62</td>
<td>C₂₂H₁₈O₄N₄</td>
<td>74.42 (74.56)</td>
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<tr>
<td>9b</td>
<td>4-OCH₃-C₆H₄</td>
<td>249</td>
<td>94.12</td>
<td>C₂₃H₂₀O₂N₄</td>
<td>71.66 (71.86)</td>
</tr>
<tr>
<td>9c</td>
<td>2-OH-C₆H₄</td>
<td>272</td>
<td>94.22</td>
<td>C₂₂H₁₈O₂N₄</td>
<td>71.22 (71.34)</td>
</tr>
<tr>
<td>9d</td>
<td>3-NO₂-C₆H₄</td>
<td>235</td>
<td>94.33</td>
<td>C₂₂H₁₇O₃N₅</td>
<td>66.01 (66.16)</td>
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<tr>
<td>9e</td>
<td>4-Cl-C₆H₄</td>
<td>225</td>
<td>73.77</td>
<td>C₂₂H₁₇O₄Cl</td>
<td>67.79 (67.95)</td>
</tr>
<tr>
<td>9f</td>
<td>4-CH₃-C₆H₄</td>
<td>263</td>
<td>95.41</td>
<td>C₂₃H₂₀O₄N₄</td>
<td>74.72 (74.98)</td>
</tr>
<tr>
<td>9g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>193</td>
<td>90.12</td>
<td>C₂₃H₂₀O₃N₄</td>
<td>68.72 (68.99)</td>
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<tr>
<td>9h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>183</td>
<td>95.02</td>
<td>C₂₄H₂₃O₅</td>
<td>75.31 (72.52)</td>
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<tr>
<td>9i</td>
<td>2-Furyl</td>
<td>200</td>
<td>94.05</td>
<td>C₂₀H₁₆O₂N₄</td>
<td>69.51 (69.76)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Aqueous ethanol
Reference


CHAPTER-6

Synthesis of 2-(5-aryl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans,
Microwave assisted synthesis of 2-(5-aryl-1-thiocarbonyl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans
and
2-(5-aryl-4,5-dihydroisoxazol-3-yl)-3-methoxybenzofurans
Introduction

Pyrazolyl and thiocarbomyl pyrazolyl benzofurans

Pyrazolines have been reported to possess wide spectrum of biological activities such as antiinflammatory\(^1\), antioxidant\(^2\,^6\), antimicrobial\(^7\), antidepressant\(^8\), antiviral\(^9\) and anti-HIV\(^10\). A number of 1,3,5-trisubstituted pyrazolines are known to possess antiinflammatory, antiproteolytic\(^11\), antibacterial, antifungal\(^12\) and insecticidal activities\(^13\).

The first report on benzofurans coupled with pyrazole nucleus was due to Inford Ltd Brit (I)\(^14\). The compound thus reported to contain substituted pyrazoline ring coupled with benzofuran through amide bridge. They were found to be useful in colour photography, in the course of investigations of the reactions of naturally occurring furocoumarins and furochromones with various reagents. The formation of pyrazolyl benzofurans (II) in which pyrazole ring system was linked to benzene moiety of benzofuran has been reported\(^15,16\). Some of these compounds were shown to possess antibacterial activity.

\[
\begin{align*}
\text{R} & = \text{H, CH}\,^3 \\
\text{X} & = \text{H, Cl, CH}\,^3, \text{OCH}\,^3, \text{Cl}\,^2 \\
\end{align*}
\]

(I)

\[
\begin{align*}
\text{R} & = \text{H, CH}\,^3 \\
\end{align*}
\]

(II)

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Pyrazolyl benzofurans which were of only synthetic interest initially are now finding greater interest as biologically active molecules. Hishmath and coworkers\textsuperscript{17,18} prepared several substituted benzo furyl pyrazolones and found many of them possess bactericidal activity.

Recently a series of substituted 3-(1-phenyl pyrazole-4-yl)benzofuran-2-carboxylic acids (III) have been prepared and are shown to possess promising antifeedant activity against \textit{Spodopteralitures}\textsuperscript{19}.

![Chemical structure of III](image)

\[ R = H, \text{CH}_3, \text{Cl, Br} \]
\[ R' = H, \text{CH}_3 \]

(III)

Recently this has aroused considerable interest in the synthesis of biheterocyclic systems containing pyrazoline as one of the heterocycle. Many of these compounds have exhibited antitubercular\textsuperscript{20}, antiinflammatory\textsuperscript{20} and antimicrobial activities\textsuperscript{20-23}.

\textbf{Thiocarbomyl pyrazolyl benzofurans}

In the last few years microwave assisted organic reactions have gained popularity as the non-conventional technique for rapid organic synthesis\textsuperscript{24}.

A large number of papers have appeared proving the synthetic utility of this technique in organic synthesis\textsuperscript{25,26}. Such reactions are eco-friendly, economical, effective and easy to carry out.
**Isoxazolyl benzofurans**

Isoxazoles\(^{27,28}\) and isoxazolines\(^{29}\) are known to play significant role in the field of medicinal chemistry. A number of biheterocycles containing isoxazole ring system have been prepared and screened for biological and pharmacological activities. Recently a series of naphtho[2,1-b]furan isoxazolines have been prepared. Many of these compounds are shown to possess considerable analgesic, antimicrobial and anthelmintic activities\(^{30}\). These facts prompted us to synthesise a series of biheterocyclic isoxazolinylbenzofurans for investigation of their biological and pharmacological activities.
**Present work**

**Pyrazolyl benzofurans**

These facts lead us to synthesise the series of pyrazolyl benzofurans for investigating their biological and pharmacological activities. As chalcones containing $\alpha,\beta$-unsaturated carbonyl function are known to serve as suitable synthons for the synthesis of dihydropyrazole ring system, 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones. (Benzofuran analogues of chalcones, 2a-g) have been subjected to such chemical modification. The reaction of compounds (2a-g) with hydrazine hydrate in presence of freshly fused sodium acetate in ethanol at room temperature gave the target compounds, 2-(5-aryl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (10a-g) in good yields. The synthesis of these compounds is outlined below schematically.

![Scheme 9](image-url)

**Scheme-9**

- **OMe**
- **2a-g**
- **C - CH = CH - Ar + NH$_2$.NH$_2$.H$_2$O**
- **Ethanol / CH$_3$COONa**
- **$\Delta$, 4.5 hrs.**
- **OMe**
- **10a-g**

**Ar**
- a. $-C$_6$H$_5$
- b. 4 - OCH$_3$-C$_6$H$_4$
- c. 2 - OH-C$_6$H$_4$
- d. 3 - NO$_2$-C$_6$H$_4$
- e. 4 - Cl-C$_6$H$_4$
- f. 4 - CH$_3$-C$_6$H$_4$
- g. 2-Furyl

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The structures of all these biheterocycles were evident by their infrared spectral data which revealed characteristic absorption bands due to NH, C=N and aromatic C=C functions Table-1.

**Table-1**

IR spectral data of 2-(5-aryl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (10a-g).

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NH</td>
</tr>
<tr>
<td>10 a</td>
<td>-C(_6)H(_5)</td>
<td>3370</td>
</tr>
<tr>
<td>10 b</td>
<td>4-OCH(_3)-C(_6)H(_4)</td>
<td>3350</td>
</tr>
<tr>
<td>10 c</td>
<td>2-OH-C(_6)H(_4)</td>
<td>3340</td>
</tr>
<tr>
<td>10 d</td>
<td>3-NO(_2)-C(_6)H(_4)</td>
<td>3350</td>
</tr>
<tr>
<td>10 e</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>3350</td>
</tr>
<tr>
<td>10 f</td>
<td>4-CH(_3)-C(_6)H(_4)</td>
<td>3400</td>
</tr>
<tr>
<td>10 g</td>
<td>2-Furyl</td>
<td>3360</td>
</tr>
</tbody>
</table>
Mechanism

In analogy the mechanism proposed for the formation of pyrazoline ring system involving this type of cyclisation, the following mechanism is proposed.

The following mechanism is also probable. This involves 1,2-addition of hydrazine on to carbonyl group as a first step with the loss of water and nucleophilic cyclisation in succession.
Microwave assisted synthesis of thiocarbomyl pyrazolyl benzofurans

In view of these facts we attempted the synthesis of the series of 2-(5-aryl-1-thiocarbomyl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (11a-g). The synthesis of compounds (11a-g) involved the reaction of 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2a-g) with thiosemicarbazide hydrazide. An equimolar quantities of compounds 2a-g and thiosemicarbazide were adsorbed over anhydrous potassium carbonate and subjected to microwave irradiation for about 5-16 minutes at 600 watts.

The reaction was monitored by TLC and the desired biheterocycles (11a-g) were obtained in excellent yields. The synthesis of these compounds is outlined below schematically.

Scheme-10

\[
\text{2a-g} \quad \text{C-CH = CH - Ar} \quad + \quad \text{NH}_2 - \text{C - NH - NH}_2
\]

\[
\text{Acetone / K}_2\text{CO}_3 \quad \text{MWI}
\]

\[
\text{11a-g} \quad \text{S} \quad \text{H}_2\text{N - C = S}
\]

<table>
<thead>
<tr>
<th>Ar</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>-C\text{}_6\text{H}_5</td>
</tr>
<tr>
<td>b.</td>
<td>4 - OCH\text{}_3\text{-C}_6\text{H}_4</td>
</tr>
<tr>
<td>c.</td>
<td>2 - OH-C\text{}_6\text{H}_4</td>
</tr>
<tr>
<td>d.</td>
<td>3 - NO\text{}_2\text{-C}_6\text{H}_4</td>
</tr>
<tr>
<td>e.</td>
<td>4 - Cl-C\text{}_6\text{H}_4</td>
</tr>
<tr>
<td>f.</td>
<td>4 - CH\text{}_3\text{-C}_6\text{H}_4</td>
</tr>
<tr>
<td>g.</td>
<td>2-Furyl</td>
</tr>
</tbody>
</table>

All the compounds were characterised by IR spectral data Table-2.

\(^1\text{H NMR spectrum of 11e revealed the following signals}

\[\delta \text{ 6.8 - 7.85 (m, 8H, ArH); 4.3 (s, 3H OCH}_3\text{); 4.15 (t, 1H, pyrazole CH); 3.9 (d, 2H, CH}_2\text{) and 1.9 (br s, 2H, NH}_2\text{)}\]
### Table-2

IR spectral data of 2-(5-aryl-1-thiocarbomyl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (11a-g)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm⁻¹</th>
<th>NH₂</th>
<th>C=Ν</th>
<th>C=C</th>
<th>C=S</th>
<th>C-O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 a</td>
<td>-C₆H₅</td>
<td></td>
<td>3350</td>
<td>1602</td>
<td>1560</td>
<td>1280</td>
<td>1150</td>
</tr>
<tr>
<td>11 b</td>
<td>4-OCH₃-C₆H₄</td>
<td></td>
<td>3280</td>
<td>1590</td>
<td>1520</td>
<td>1300</td>
<td>1170</td>
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<tr>
<td>11 c</td>
<td>2-OH-C₆H₄</td>
<td></td>
<td>3320</td>
<td>1580</td>
<td>1540</td>
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<td>3310</td>
<td>1600</td>
<td>1530</td>
<td>1265</td>
<td>1140</td>
</tr>
<tr>
<td>11 e</td>
<td>4-Cl-C₆H₄</td>
<td></td>
<td>3330</td>
<td>1585</td>
<td>1525</td>
<td>1275</td>
<td>1165</td>
</tr>
<tr>
<td>11 f</td>
<td>4-CH₃-C₆H₄</td>
<td></td>
<td>3315</td>
<td>1610</td>
<td>1545</td>
<td>1290</td>
<td>1175</td>
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<tr>
<td>11 g</td>
<td>2-Furyl</td>
<td></td>
<td>3350</td>
<td>1595</td>
<td>1540</td>
<td>1280</td>
<td>1160</td>
</tr>
</tbody>
</table>
SCS College Of Pharmacy, Harapanahalli

IR Spectrum

HS-PZT-15c

Comment:
No. of Scans: 10
Resolution: 4 [1/cm]
Apodization: Happ-Genzel

Date/Time: 02/03/2006 16:47:33
User: PRINCIPAL
Microwave assisted synthesis of isoxazolyl benzofurans

The compounds containing α-β-unsaturated group are conveniently converted into isoxazoline ring system reacting with hydroxylamine hydrochloride. Hence compounds (2a-g) which contain such α,β-unsaturated carbonyl function are subjected to reaction with hydroxylamine hydrochloride. The reaction by traditional method was not satisfactory. Hence microwave technique was attempted. A mixture of benzofuran analogues of chalcones (2a-g) and hydroxylamine hydrochloride in 1:2 molar proportion in pyridine were irradiated at 300 watts under microwave conditions for 3-6 minutes, with short intervals of about 30 sec to avoid excessive evaporation of solvent.

The progress of reaction was monitored by TLC. The products isoxazolinyl benzofurans (12a-g) were obtained in good yields. The synthesis of all these compounds is outlined in the following scheme.

\[
\text{OMe} + \text{NH}_2\text{OH . HCl} \quad \text{2a-g} \quad \text{Pyridine MWI} \quad \text{OMe} \quad \text{12a-g}
\]

\[\text{Ar} \]
\[\begin{align*}
a. & \quad -\text{C}_6\text{H}_5 \\
b. & \quad 4 - \text{OCH}_3\text{-C}_6\text{H}_4 \\
c. & \quad 2 - \text{OH-C}_6\text{H}_4 \\
d. & \quad 3 - \text{NO}_2\text{-C}_6\text{H}_4 \\
e. & \quad 4 - \text{Cl-C}_6\text{H}_4 \\
f. & \quad 4 - \text{CH}_3\text{-C}_6\text{H}_4 \\
g. & \quad 2\text{-Furyl}
\end{align*}\]
The absence of carbonyl group is indicated in IR spectra and presence of other characteristic absorption bands due to C=N, C=C and C-O-C in IR spectra indicated the expected ring closure producing isoxazolinyl ring system Table-3.

**Table-3**

IR spectral data of 2-(5-aryl-4,5-dihydroisoxazol-3-yl)-3-methoxybenzofurans (12 a-g)

![Structure of 12a-g](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>IR (Nujol) cm⁻¹</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C=N</td>
<td>C=C</td>
<td>CH₂</td>
<td>C-O-N</td>
<td>C-O-C</td>
<td></td>
</tr>
<tr>
<td>12 a</td>
<td>-C₆H₅</td>
<td>1603</td>
<td>1555</td>
<td>1460</td>
<td>1260</td>
<td>1140</td>
</tr>
<tr>
<td>12 b</td>
<td>4-OCH₃-C₆H₄</td>
<td>1605</td>
<td>1545</td>
<td>1460</td>
<td>1250</td>
<td>1190</td>
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<tr>
<td>12 c</td>
<td>2-OH-C₆H₄</td>
<td>1610</td>
<td>1550</td>
<td>1462</td>
<td>1248</td>
<td>1180</td>
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<tr>
<td>12 d</td>
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<td>1600</td>
<td>1500</td>
<td>1465</td>
<td>1260</td>
<td>1185</td>
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<tr>
<td>12 e</td>
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<td>1145</td>
<td>1260</td>
<td>1140</td>
</tr>
<tr>
<td>12 f</td>
<td>4-CH₃-C₆H₄</td>
<td>1608</td>
<td>1520</td>
<td>1150</td>
<td>1255</td>
<td>1150</td>
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<tr>
<td>12 g</td>
<td>2-Furyl</td>
<td>1620</td>
<td>1540</td>
<td>1470</td>
<td>1255</td>
<td>1165</td>
</tr>
</tbody>
</table>
Experimental

General method for preparation of 2-(5-aryl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (10 a-g)

To a solution l-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-l-ones (2a-g), (0.0025 mol) in ethanol (7 ml), hydrazine hydrate (99%, 0.12 ml, 0.0025 mol) and freshly fused sodium acetate (0.5 g) was heated on a steam bath for 4.5 hrs. The contents of the flask were poured on to ice water. The pyrazoline which separated as solid was collected by filtration after washing with water and dried. Recrystallised from suitable solvent.

The following benzofuryl pyrazolines (10a-g) were thus prepared.

10a  2-[5-Phenyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
10b  2-[5-(p-methoxy phenyl)-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
10c  2-[5-(o-hydroxy phenyl)-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
10d  2-[5-(m-nitro phenyl)-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
10e  2-[5-(p-chloro phenyl)-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
10f  2-[5-(p-toluyl)-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
10g  2-[5-(2-furyl)-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran

The m.p., % yield and elemental analysis data are given in the Table-4.

125
Table 4
2-(5-Aryl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (10a-g)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>10 a</td>
<td>-C₆H₅</td>
<td>180</td>
<td>95.89</td>
<td>C₁₈H₁₆O₂N₂</td>
<td>73.69 (73.95)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>5.42 (5.52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.36 (9.58)</td>
</tr>
<tr>
<td>10 b</td>
<td>4-OCH₃-C₆H₄</td>
<td>140</td>
<td>63.68</td>
<td>C₁₉H₁₈O₃N₂</td>
<td>70.62 (70.79)</td>
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<tr>
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<td></td>
<td></td>
<td>5.49 (5.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.52 (8.69)</td>
</tr>
<tr>
<td>10 c</td>
<td>2-OH-C₆H₄</td>
<td>155</td>
<td>94.15</td>
<td>C₁₈H₁₆O₂N₂</td>
<td>70.02 (70.12)</td>
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<td></td>
<td></td>
<td>5.08 (5.23)</td>
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<td></td>
<td></td>
<td>9.01 (9.09)</td>
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<tr>
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<td>64.01 (64.09)</td>
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<td></td>
<td>4.27 (4.48)</td>
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<td>12.39 (12.46)</td>
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<tr>
<td>10 e</td>
<td>4-Cl-C₆H₄</td>
<td>118</td>
<td>92.87</td>
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<td>66.08 (66.16)</td>
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<td>4.57 (4.63)</td>
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<td></td>
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<td>8.25 (8.57)</td>
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<tr>
<td>10 f</td>
<td>4-CH₃-C₆H₄</td>
<td>110</td>
<td>49.01</td>
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<td>74.37 (74.49)</td>
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<td>5.78 (5.92)</td>
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<td></td>
<td></td>
<td></td>
<td>9.02 (9.14)</td>
</tr>
<tr>
<td>10 g</td>
<td>2-Furyl</td>
<td>115</td>
<td>65.84</td>
<td>C₁₆H₁₄O₃N₂</td>
<td>68.01 (68.07)</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td>4.83 (5.00)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>9.78 (9.92)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Benzene-pet. ether
General method for preparation of 2-(5-aryl-1-thiocarbomyl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (11a-g)

To a solution of 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propen-1-ones (2 a-g, 0.0025 mol) and thiosemicarbazide (0.0025 mol) in acetone (5 ml) and ethanol (5 ml), anhydrous potassium carbonate (3 g) was added. The mixture was stirred for 5 min and the solvent was removed on a water bath under reduced pressure. The resulting solid was powdered and transferred to a dry beaker. The solid reaction mixture was irradiated in a microwave oven for about 5-16 min at 600 watts. The completion of reaction was indicated by TLC (chloroform-methanol 9:1). The reaction mixture was treated with excess of water. The insoluble product was filtered, washed with water dried and crystalised from suitable solvent.

The following N-thiocarbomyl pyrazolyl benzofurans were prepared by this procedure.

11a 2-[5-Phenyl-1-thiocarbomyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
11b 2-[5-(p-methoxy phenyl)-1-thiocarbomyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
11c 2-[5-(o-hydroxy phenyl)-1-thiocarbomyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
11d 2-[5-(m-nitro phenyl)-1-thiocarbomyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
11e 2-[5-(p-chloro phenyl)-1-thiocarbomyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
11f 2-[5-(p-toluyl)-1-thiocarbomyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran
11g 2-[5-(2-furyl)-1-thiocarbomyl-4,5-dihydropyrazol-3-yl]-3-methoxybenzofuran

All the compounds thus prepared are given in the Table-5 along with the time of reaction, m.p., % yield and elemental analysis data.
Table 5

2-(5-Aryl-1-thiocarbonyl-4,5-dihydropyrazol-3-yl)-3-methoxybenzofurans (11a-g)

![Chemical structure of 11a-g](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar</th>
<th>Time min.</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>11 a</td>
<td>-C₆H₅</td>
<td>5</td>
<td>167</td>
<td>96.86</td>
<td>C₁₉H₁₇O₂N₃S</td>
<td>64.68 (64.94)</td>
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<tr>
<td>11 b</td>
<td>4-OCH₃-C₆H₄</td>
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<td>120</td>
<td>97.11</td>
<td>C₂₀H₁₉O₃N₃S</td>
<td>62.67 (62.97)</td>
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<tr>
<td>11 c</td>
<td>2-OH-C₆H₄</td>
<td>14</td>
<td>111</td>
<td>96.73</td>
<td>C₁₉H₁₇O₃N₃S</td>
<td>62.01 (62.11)</td>
</tr>
<tr>
<td>11 d</td>
<td>3-NO₂-C₆H₄</td>
<td>5</td>
<td>174</td>
<td>90.90</td>
<td>C₁₉H₁₆O₄N₄S</td>
<td>57.37 (57.57)</td>
</tr>
<tr>
<td>11 e</td>
<td>4-Cl-C₆H₄</td>
<td>5</td>
<td>181</td>
<td>94.24</td>
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<td>59.03 (59.14)</td>
</tr>
<tr>
<td>11 f</td>
<td>4-CH₃-C₆H₄</td>
<td>15</td>
<td>125</td>
<td>95.89</td>
<td>C₂₀H₁₉O₂N₃S</td>
<td>65.49 (65.73)</td>
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<tr>
<td>11 g</td>
<td>2-Furyl</td>
<td>11</td>
<td>137</td>
<td>73.52</td>
<td>C₁₇H₁₅O₃N₃S</td>
<td>59.68 (59.81)</td>
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Solvent of crystallisation: Benzene-pet. ether
General method for the preparation of 2-(5-aryl-4,5-dihydroisoxazol-3-yl)-3-methoxybenzofurans (12a-g)

A mixture of 1-(3-methoxybenzofuran-2-yl)-3-aryl-2-propene-1-ones (2a-g, 0.001 mol) and hydroxylamine hydrochloride (0.14 g, 0.002 mol) in pyridine (2 ml) was irradiated at 300 watts under microwave conditions for 3-6 min with short intervals of 30 sec - 1 min to avoid excessive evaporation of solvent. After completion of reaction as indicated by TLC (chloroform-methanol 9:1), the reaction mixture was cooled, acidified with dilute hydrochloric acid and kept in the refrigerator. The resulting product was filtered and thoroughly washed with water. Further purification was effected by recrystallised from benzene-pet. ether.

The following isoxazolinyl benzofurans were prepared by this procedure. The time of reaction, m.p., % yield and elemental analytical data are presented in the Table-6.

12a 2-(5-Phenyl-4,5-dihydroisoxazol-3-yl)-3-methoxybenzofuran
12b 2-[5-(p-methoxy phenyl)-4,5-dihydroisoxazol-3-yl]-3-methoxybenzofuran
12c 2-[5-(o-hydroxy phenyl)-4,5-dihydroisoxazol-3-yl]-3-methoxybenzofuran
12d 2-[5-(m-nitro phenyl)-4,5-dihydroisoxazol-3-yl]-3-methoxybenzofuran
12e 2-[5-(p-chloro phenyl)-4,5-dihydroisoxazol-3-yl]-3-methoxybenzofuran
12f 2-[5-(p-toluyl)-4,5-dihydroisoxazol-3-yl]-3-methoxybenzofuran
12g 2-[5-(2-furyl)-4,5-dihydroisoxazol-3-yl]-3-methoxybenzofuran

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## Table 6

2-(5-Aryl-4,5-dihydroisoxazol-3-yl)-3-methoxybenzofurans (12a-g)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar</th>
<th>Time min.</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
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<td>-C₆H₅</td>
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<td>135</td>
<td>88.73</td>
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<td>73.62 (73.71)</td>
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<td>5.03</td>
</tr>
<tr>
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<td>4-OCH₃-C₆H₄</td>
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<td>139</td>
<td>83.59</td>
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<td>70.51 (70.58)</td>
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<td>5.27</td>
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<td>69.73 (69.89)</td>
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<td>4.73</td>
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<td>12d</td>
<td>3-NO₂-C₆H₄</td>
<td>4</td>
<td>178</td>
<td>82.84</td>
<td>C₁₈H₁₄O₅N₂</td>
<td>63.83 (63.90)</td>
</tr>
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<td></td>
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<td></td>
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<td></td>
<td>4.01</td>
</tr>
<tr>
<td>12e</td>
<td>4-Cl-C₆H₄</td>
<td>5</td>
<td>137</td>
<td>74.07</td>
<td>C₁₈H₁₄O₃NCl</td>
<td>65.86 (65.96)</td>
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<td>4.23</td>
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<td>81.43</td>
<td>C₁₉H₁₇O₃N</td>
<td>74.07 (74.25)</td>
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<td>5.37</td>
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<tr>
<td>12g</td>
<td>2-Furyl</td>
<td>4</td>
<td>115</td>
<td>56.73</td>
<td>C₁₆H₁₃O₄N</td>
<td>67.73 (67.84)</td>
</tr>
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<td></td>
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<td>4.53</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Benzene-pet. ether
Reference


CHAPTER-7

Introduction

Quinoxalines are well known for their antibacterial\textsuperscript{1}, antitumour and antiviral properties\textsuperscript{2}. It has been reported that chalocone dibromides when reacted with benzene\textsubscript{1,2}-diamine (BDA) in presence of triethylamine produced various aziridinyl ketones and their cyclic anils which subsequently underwent acid catalysed isomerisation to quinoxalines\textsuperscript{3}. The formation of aziridinyl ketones and their cyclic anils as intermediates is established\textsuperscript{4}. The intermediate cyclic anils have been isolated and isomerised to quinoxalines in presence of acid catalyst. Recently several chalcone dibromides have been reacted with benzenediamine in presence of sulphuric acid in methanol to obtain various 2,3-disubstituted quinoxalines\textsuperscript{5,6}.

This aroused our interest in the synthesis of biheterocyclic substituted quinoxalinyl naphthofurans and benzofurans for investigating their biological activities. In this investigation a series of quinoxalinyl naphthofurans are prepared and their activities are investigated.
Present work

1-(3-Amino-2-naphtho[2,1-b]furyl)-3-aryl-propen-1-ones (3a-i), were subjected to bromination in glacial acetic acid by using equimolar quantity of bromine in acetic acid. The resulting 1-(3-amino-2-naphtho[2,1-b]furyl)-3-aryl-2,3-dibromopropan-1-ones (13a-i), were then condensed with benzenediamine (BDA) in methanolic solution in presence of concentrated sulphuric acid. The products 2-(3-amino-2-naphtho[2,1-b]furyl)-3-substituted benzylquinoxalines, which were obtained were further purified by crystallisation. The synthesis of these compounds is outlined below schematically.

Scheme-12

\[
\begin{align*}
&\text{NH}_2 \\
&\text{C} = \text{CH} - \text{Ar} \\
&\text{Br} (	ext{in CH}_3\text{COOH}) \\
&\text{NH}_2 \\
&\text{C} = \text{CH} - \text{Ar} \\
&\text{Br} \\
&\text{NH}_2 \\
&\text{Ar}
\end{align*}
\]

Ar

a. -C\textsubscript{6}H\textsubscript{5}

b. 4 - OCH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}

c. 2 - OH-C\textsubscript{6}H\textsubscript{4}

d. 3 - NO\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}

e. 4 - Cl-C\textsubscript{6}H\textsubscript{4}

f. 4 - CH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}

g. 4-OH-3-OCH\textsubscript{3}-C\textsubscript{6}H\textsubscript{3}

h. 4-N(CH\textsubscript{3})\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}

i. 2-Furyl
The IR spectra of compounds (14a-i) showed the absence of carbonyl group indicating its involvement in the reaction. The other characteristic IR absorption bands due to NH$_2$, C=N, C=C and C-O-C functional groups are observed. The IR spectral data of all these compounds is described under Table-1.

$^1$H NMR spectrum of dibromo compound 13b showed the following signals δ 6.9 - 8.3 (m, 12H ArH and CH-CH) and 3.9 (s, 3H, OCH$_3$). 3-Aminonaphthofuryl quinoxaline 14e displayed $^1$H NMR signals at δ 7.2 - 7.99 (m, 14H, ArH); 3.88 (s, 2H, CH$_2$) and 3.5 (br s, 2H, NH$_2$).

### Table-1

IR spectral data of 2-(3-amino-2-naptho[2,1-b]furyl)-3-substituted benzylquinoxalines (14a-i)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar.</th>
<th>NH$_2$</th>
<th>C=N</th>
<th>C=C</th>
<th>C-O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 a</td>
<td>-C$_6$H$_5$</td>
<td>3160</td>
<td>1618</td>
<td>1550</td>
<td>1170</td>
</tr>
<tr>
<td>14 b</td>
<td>4-OCH$_3$-C$_6$H$_4$</td>
<td>3150</td>
<td>1610</td>
<td>1545</td>
<td>1150</td>
</tr>
<tr>
<td>14 c</td>
<td>2-OH-C$_6$H$_4$</td>
<td>3155</td>
<td>1610</td>
<td>1565</td>
<td>1150</td>
</tr>
<tr>
<td>14 d</td>
<td>3-NO$_2$-C$_6$H$_4$</td>
<td>3178</td>
<td>1620</td>
<td>1550</td>
<td>1175</td>
</tr>
<tr>
<td>14 e</td>
<td>4-Cl-C$_6$H$_4$</td>
<td>3300</td>
<td>1625</td>
<td>1510</td>
<td>1180</td>
</tr>
<tr>
<td>14 f</td>
<td>4-CH$_3$-C$_6$H$_4$</td>
<td>3175</td>
<td>1615</td>
<td>1547</td>
<td>1175</td>
</tr>
<tr>
<td>14 g</td>
<td>4-OH-3-OCH$_3$-C$_6$H$_3$</td>
<td>3302</td>
<td>1618</td>
<td>1545</td>
<td>1170</td>
</tr>
<tr>
<td>14 h</td>
<td>4-N-(CH$_3$)$_2$-C$_6$H$_4$</td>
<td>3350</td>
<td>1620</td>
<td>1550</td>
<td>1150</td>
</tr>
<tr>
<td>14 i</td>
<td>2-Furyl</td>
<td>3155</td>
<td>1615</td>
<td>1540</td>
<td>1180</td>
</tr>
</tbody>
</table>
IR Spectrum

14e

Comment: HS-1. e

No. of Scans: 15

Resolution: 4 [1/cm]

Apo: Hagen-Benzel

Date/Time: 27/05/2006 10:32:30

User: PRINCIPA_
'H NMR Spectrum

13b

Current Data Parameters
NAME 0625-shivaku-1
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060625
Time 14.15
INSTRUM amx400
PROBHD 5 mm QNP 1H
PULPROG zg
TD 16384
SOLVENT cdc13
NS 256
DS 0
SWH 6250.000 Hz
FIDRES 0.381470 Hz
AQ 1.3107700 sec
RG 4096
DW 80.000 usec
DE 100.00 usec
TE 300.0 K
H11 1 dB
D1 1.00000000 sec
P1 11.50 usec
SFO1 400.1369639 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 32768
SF 400.1343938 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 0.30
$^{1}$H NMR Spectrum

14e
The reaction of chalcone dibromides with benzenediamine (BDA) in presence of triethylamine is known to produce substituted aziridinyl ketones and their cyclic anils as intermediates, which underwent acid catalysed isomerisation to give quinoxalines.

\[
\begin{align*}
\text{OMe} & \quad \text{OMe} \\
\text{CH - CH-Ar} & \quad + \\
\text{H}_2\text{N} & \quad \text{aziridinyl ketone} \\
\text{H}_2\text{N} & \quad \text{cyclic anil} \\
\text{OMe} & \quad \text{OMe} \\
\end{align*}
\]
Experimental

General method for the preparation 1-(3-amino-2-naphtho[2,1-b]furyl)-3-aryl-2,3-dibromopropan-1-ones (13a-i)

To a solution of 1-(3-aminonaphtho[2,1-b]furyl)-3-aryl-2-propen-1-one (3a-i, 0.001 mol) in glacial acetic acid (5 ml), a solution of bromine (0.176 g, 0.0011 mol) in acetic acid (5 ml) was added dropwise while stirring magnetically at room temperature. After 2 hrs the reaction mixture was poured into ice water. The product separated as a crystalline solid was filtered, washed with water and dried.

Following this procedure all the 1-(3-aminonaphtho[2,1-b]furyl)-3-aryl-2-propen-1-ones (3a-i) were converted into the following dibromo derivatives.

13a 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-phenyl-2,3-dibromopropan-1-one

13b 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-methoxy phenyl)-2,3-dibromopropan-1-one

13c 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(o-hydroxy phenyl)-2,3-dibromopropan-1-one

13d 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(m-nitro phenyl)-2,3-dibromopropan-1-one

13e 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-chloro phenyl)-2,3-dibromopropan-1-one

13f 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-toluyl)-2,3-dibromopropan-1-one

13g 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-hydroxy-m-methoxy phenyl)-2,3-dibromopropan-1-one

13h 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-N,N-dimethyl phenyl)-2,3-dibromopropan-1-one

13i 1-(3-Amino-2-naphtho[2,1-b]furyl)-3-(2-furyl)-2,3-dibromopropan-1-one

The m.p., % yield and elemental analysis data are given in the Table-2.
Table 2

1-(3-Amino-2-naphtho[2,1-b]furyl)-3-aryl-2,3-dibromopropan-1-ones (13a-i)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>13 a</td>
<td>-C₆H₅</td>
<td>121</td>
<td>95.84</td>
<td>C₂₁H₁₅O₂NBr₂</td>
<td>53.27</td>
</tr>
<tr>
<td>13 b</td>
<td>4-OCH₃-C₆H₄</td>
<td>108</td>
<td>97.66</td>
<td>C₂₂H₁₇O₃NBr₂</td>
<td>52.39</td>
</tr>
<tr>
<td>13 c</td>
<td>2-OH-C₆H₄</td>
<td>82</td>
<td>96.65</td>
<td>C₂₁H₁₅O₃NBr₂</td>
<td>51.42</td>
</tr>
<tr>
<td>13 d</td>
<td>3-NO₂-C₆H₄</td>
<td>104</td>
<td>96.52</td>
<td>C₂₁H₁₄O₄N₂Br₂</td>
<td>48.57</td>
</tr>
<tr>
<td>13 e</td>
<td>4-Cl-C₆H₄</td>
<td>87</td>
<td>82.42</td>
<td>C₂₁H₁₄O₂NBr₂Cl</td>
<td>49.59 (49.69)</td>
</tr>
<tr>
<td>13 f</td>
<td>4-CH₃-C₆H₄</td>
<td>100</td>
<td>81.34</td>
<td>C₂₂H₁₇O₂NBr₂</td>
<td>54.20 (54.24)</td>
</tr>
<tr>
<td>13 g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>80</td>
<td>81.89</td>
<td>C₂₂H₁₇O₄NBr₂</td>
<td>50.77 (50.89)</td>
</tr>
<tr>
<td>13 h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>106</td>
<td>62.57</td>
<td>C₂₃H₂₀O₂N₂Br₂</td>
<td>53.37 (53.51)</td>
</tr>
<tr>
<td>13 i</td>
<td>2-Furyl</td>
<td>66</td>
<td>77.88</td>
<td>C₁₉H₁₃O₃NBr₂</td>
<td>49.07 (49.28)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Benzene-pet. ether
General method for the preparation 2-(3-amino-2-naphtho[2,1-b]furyl)-3-substituted benzylquinoxalines (14a-i)

A mixture of dibromo compounds (13a-i, 0.005 mol), o-phenylene diamine (0.450 g, 0.005 mol), methanol (4 ml) in presence of catalytic amount of concentrated sulphuric acid was heated under gentle reflux at 70-75°C for 30 min. The reaction mixture was poured into ice water, neutralised with sodium bicarbonate and extracted with ether. The ethereal solution was dried over calcium chloride. Removal of solvent gave the biheterocycle as yellow solids. The product was filtered, dried and triturated with pet. ether. Further purification was effected by crystallisation from suitable solvent.

Biheterocyclic quinoxalinyl naphthofurans (14a-i) were prepared.

14a 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-phenyl benzylquinoxaline
14b 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-methoxy phenyl)benzylquinoxaline
14c 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(o-hydroxy phenyl)benzylquinoxaline
14d 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(m-nitro phenyl)benzylquinoxaline
14e 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-chloro phenyl)benzylquinoxaline
14f 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-toluyl)benzylquinoxaline
14g 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-hydroxy-m-methoxy phenyl)benzylquinoxaline
14h 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(p-N,N-dimethyl phenyl)benzylquinoxaline
14i 2-(3-Amino-2-naphtho[2,1-b]furyl)-3-(2-furyl)benzylquinoxaline

The m.p., % yield and elemental analytical data of all these compounds are given in the Table-3.
Table 3

2-(3-Amino-2-naphtho[2,1-b]furyl)-3-substituted benzylquinoxalines (14a-i)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Ar</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Found (Calc.) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a</td>
<td>-C₆H₅</td>
<td>105</td>
<td>71.42</td>
<td>C₂₇H₁₉ON₃</td>
<td>80.69 (80.78)</td>
</tr>
<tr>
<td>14b</td>
<td>4-OCH₃-C₆H₄</td>
<td>66</td>
<td>60.46</td>
<td>C₂₈H₂₁O₂N₃</td>
<td>77.78 (77.94)</td>
</tr>
<tr>
<td>14c</td>
<td>2-OH-C₆H₄</td>
<td>61</td>
<td>84.13</td>
<td>C₂₇H₁₉O₂N₃</td>
<td>77.51 (77.68)</td>
</tr>
<tr>
<td>14d</td>
<td>3-NO₂-C₆H₄</td>
<td>75</td>
<td>64.12</td>
<td>C₂₇H₁₈O₃N₄</td>
<td>73.34 (72.64)</td>
</tr>
<tr>
<td>14e</td>
<td>4-Cl-C₆H₄</td>
<td>78</td>
<td>69.12</td>
<td>C₂₇H₁₈O₃N₃Cl</td>
<td>73.27 (74.39)</td>
</tr>
<tr>
<td>14f</td>
<td>4-CH₃-C₆H₄</td>
<td>85</td>
<td>75.36</td>
<td>C₂₈H₂₁O₃N₃</td>
<td>80.79 (80.94)</td>
</tr>
<tr>
<td>14g</td>
<td>4-OH-3-OCH₃-C₆H₃</td>
<td>70</td>
<td>70.53</td>
<td>C₂₈H₂₁O₃N₃</td>
<td>75.13 (75.15)</td>
</tr>
<tr>
<td>14h</td>
<td>4-N-(CH₃)₂-C₆H₄</td>
<td>90</td>
<td>46.84</td>
<td>C₂₉H₂₄O₄N₄</td>
<td>78.24 (78.36)</td>
</tr>
<tr>
<td>14i</td>
<td>2-Furyl</td>
<td>76</td>
<td>42.52</td>
<td>C₂₅H₁₇O₂N₃</td>
<td>76.69 (76.71)</td>
</tr>
</tbody>
</table>

Solvent of crystallisation: Benzene-pet. ether
Reference


