CHAPTER-1

INTRODUCTION
The compounds encompassing furan nucleus are widely distributed in nature, particularly amongst the plant kingdom. Many of such compounds have been reported to possess very useful pharmacological and physiological properties. This generated considerable interest in the investigation of some furan derivatives for pharmacological activities. As a result of such investigations several furan derivatives including 5-nitrofuran were brought to light and were found to exhibit wide spectrum of biological activities.

In nature, furan nucleus is frequently found associated with oxygen heterocycles such as α-pyran and γ-pyran ring systems. Many of such compounds are well known for their medicinal properties. Benzofuran formed by the condensation of furan nucleus with benzene ring are not common in nature. However, numerous synthetic benzofuran derivatives have been synthesized and found to possess wide range of biological activities such as antiviral, analeptic, antimicrobial, anti-inflammatory and analgesic.

The research work in this area was initially aimed at the isolation of biologically active products possessing furan and benzofuran ring system. The structure of such compounds range from simple 5-methoxybenzofuran 1 to highly complex molecule such as viridine 2, galanthamine 3 and morphine 4.

Thereafter, research work in this area was focused on structural modification of natural products for improving the efficacy. The development of chemistry of benzofurans is of great importance as it is analogous to indole and benzothiophene. The chemistry of benzofurans is relatively less explored when compared to those of indole and benzothiophene. Eventhen, voluminous work has been done on benzofurans and
several monographs devoted to the study of both natural and synthetic benzofurans have appeared in literature\(^1\)–\(^5\).

Furan nucleus is often found fused with oxygen heterocycles rather than nitrogen heterocycles in nature. Although the latter compounds are very less in number, they have occupied a prominent place in medicinal chemistry. Morphine and related alkaloids are the drugs, which are used as analgesic, which contain a furan nucleus condensed with nitrogen heterocycles. Furan ring has been proved to be an essential part of the structure of the molecule for its medicinal properties in these drugs\(^6\). This stimulated us to investigate the chemistry and biological activities of furans fused or coupled with other heterocycles particularly with nitrogen heterocycles. During last few years interest in this area was focussed on synthesis and evaluation of biological activities of various
benzofurans fused with nitrogen heterocycles such as thiazole, pyrazole, pyridine, pyrimidin, pyridazine, benoxazole, indole, benzothiazole, benzimidazole, quinaxaline, diazepine, triazepine, etc.7-17.

Many biheterocycles encompassing oxadiazole, thiadiazole, triazole, along with benzofuran as one of the partners have been synthesized, characterized and screened for various pharmacological and biological activities. The results of such investigation are interesting and encouraging.

However the survey of literature reveals that similar type of work has not been carried out on naphthofurans. Such type of work has been initiated in our laboratory and the compounds synthesized have been found to possess antimicrobial, analgesic, anthelmintic, anti-inflammatory and diuretic activities. Encouraged by these findings and in pursuit of exploring biologically potent synthetic leads, the present investigation of synthesis of naphthofuran fused with nitrogen heterocycles and biheterocyclic naphthofurans with nitrogen heterocycles as another heterocyclic compounds is undertaken.

The work embodied in this thesis mainly deals with synthesis of biheterocyclic naphthofurans and fused naphthofurans and evaluation of their biological and pharmacological activities.

As a background for the present investigation, a brief account of naturally occurring and synthetic benzofurans and naphthofurans was felt appropriate.
1.1 Naturally occurring benzofuran compounds

1.1.1 Benzofuran fused with oxygen heterocycles

Benzofuran compounds exist in large numbers and great structural variety in nature. They are conveniently grouped depending upon their chemical structure into following types.

a) Simple benzofurans
b) Dibenzofurans
c) β - Coumaranones
d) α - Pyranobenzofuran (Furocoumarins)
e) γ - Pyranobenzofuran
   i. Furochromones
   ii. Furoflavones
   iii. Furoisoflavones
   iv. Furoxanthones
f) Furoflavonoids and Rotenoids

The detailed discussions about these compounds is not within the limits of this thesis, hence importance of these compounds is dealt with very briefly.

a. Simple benzofurans

The simplest naturally occurring benzofuran is 5-mthoxybenzofuran which is produced by a fungus. Egonol isolated from the seed of the plant “egonoki” is shown to be an effective synergist for rotenone and pyrethrum against mosquitoes, house flies and many other insects. The mixture of benzofuran and dibenzofuran is found to be present
an important class of Euparinoids, which are obtained from the plants of compositeae family. Among these tremetol and tremetone are ichyotoxic\textsuperscript{25} and responsible for ailments such as trembles “in cattle” and “milk sickness “ in human beings. Tremetone 5 is also found to be associated with insecticidal activity. Pongamol 6 isolated from seed oil of \textit{Pongamia glabra}\textsuperscript{26}, 5-methoxy-6,7-dimethylbenzofuran found in tobacco\textsuperscript{27} and group of 2-arylbenzofurans such as eupometene\textsuperscript{28}, egono\textsuperscript{29}, pterofuran\textsuperscript{30} and many others belong to this class of natural products.

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\textbf{5} \\
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\textbf{6} \\
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\textbf{b. Dibenzofurans}

This ring system has been extensively investigated in attempts to produce synthetic analgesics and similar drugs, since this forms part structure of morphine alkaloids. Didymic acid 7 and hydroxylated dibenzofurans, isolated from lichens have some activity against \textit{Avian tubercle} and \textit{Staphylococcus aureus}\textsuperscript{31}. Usnic acid 8, which occurs in both racemic and optically active forms in several plants, has been found to be active against many gram-positive organisms\textsuperscript{32}.

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\end{tabular}
\begin{tabular}{c}
\textbf{8} \\
\end{tabular}
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c. β-Coumarinones

β-Coumarinones are the ketonic form of 3-hydroxybenzofurans. Griseofulvin 9 is of great importance as a fungicidal agent and found to be particularly effective against ringworms. Aurones which are plant pigments contain β-coumarinone ring system in their structure, were discovered by Geissman. These compounds impart bright yellow to orange colour to flower petals e.g., Aureusin 10.

\[
\begin{align*}
\text{9} & \quad \text{CH}_3\text{O} \quad \text{CH}_3\text{O} \\
& \quad \text{CH}_3\text{O} \\
& \quad \text{OH} \\
\text{10} & \quad \text{C}_6\text{H}_{11}\text{O}_3\text{O} \\
& \quad \text{CH} \\
& \quad \text{OH} \\
& \quad \text{OH}
\end{align*}
\]

d. Furocoumarins

These are found to be present in the seeds of *Psoralea corylifolia* L. These are used in ayurvedic system of medicine for the treatment of skin disease and psoriasis. These are also known to be used as anthelmintic, diuretic and luxative. Psoralen 11 and angelicin 12 have occupied a predominant position because of their high photodynamic activity. Some furocoumarins are also highly spasmolytic.

\[
\begin{align*}
\text{11} & \quad \text{CH}_3\text{O} \\
\text{12} & \quad \text{OH} \\
\end{align*}
\]
e. **γ-Pyranobenzofurans**

i. **Furochromones**

The extracts of the plant *Ammi visnaga* L., have been used for centuries in the eastern region of the Mediterranean as a home remedy to relieve spasms of all kinds and also as a cure for Leucoderma. Khellin 13 and Visnagin 14 were found to be active principles present in this crude drug. Khellin is also useful in the treatment of whooping cough and treatment of heart diseases. Beside these two components, *A. visnaga* L., is shown to contain a number of other furochromones like Visammiol. A study of relation between structure and antispasmodic activity of furochromones has revealed that the removal of furan ring from these compounds results in diminution in activity to the extent of 70-80%.

\[
\begin{align*}
13 & \quad R=R'=\text{OCH}_3 \\
14 & \quad R=\text{OCH}_3 \text{ and } R'=\text{H},
\end{align*}
\]

ii. **Furoflavones**

Limaye succeeded in isolating active principle Karangin 15 from the seed oil of *Pongamia glabra* which was used for the treatment of leucoderma by Ayurvedic practitioners.
iii. Furoisoflavones

The two furoisoflavones namely Nepseudin\textsuperscript{16} 16 and Neotenon\textsuperscript{17} 17 were isolated from the root of \textit{Neorautanenia pseudopachyrrhiza}.

iv. Furoxanthones

Sterigmatocystin 18 and 6-methylsterigmatocystin are the examples of furoxanthones, which are crystalline metabolites produced from some strains of \textit{Asperigillus varsicolor}\textsuperscript{49-50}.
f. Furoisoflavonoids and Rotenoids

Coumaranochromones, coumarinocoumarins and coumaranofurocoumarins constitute this large group of furoisoflavonoids and rotenoids. Pterocarpin\textsuperscript{51} 19 and homopterocarpin\textsuperscript{52} 20, isolated from a number of species of the genus \textit{Pterocarpus} are the two most important compounds of this class. These compounds are known to serve as antifungal agents in plants.

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\hspace{1cm}
\includegraphics[width=0.4\textwidth]{20.png}
\end{center}

Coumestrol 21 is one of the non-steroidal phytoestrogenic substance that stimulate animal growth. It is found to contain benzofuran nucleus fused with coumarin. Furan is known to contribute substantially to this activity\textsuperscript{53,54}. Rotenone and related compounds have been known for a long time especially because of their selective insecticidal properties. Furan ring is found to be present in most of the rotenoids along with rotenone. Ellipton\textsuperscript{55} 22 and Malacco\textsuperscript{56} are isolated from \textit{Derris eliptica} and \textit{Derris malacensis}.

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\includegraphics[width=0.4\textwidth]{21.png}
\hspace{1cm}
\includegraphics[width=0.4\textwidth]{22.png}
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1.1.2 Benzofurans fused with nitrogen heterocycles

Benzo[d]furan nucleus is very rarely found in combination with nitrogen heterocycles in natural products. Dihydrobenzofuran moiety is found to constitute the part structure of opium alkaloids along with other nitrogen heterocyclic systems.

The efficacy of opium alkaloids in relieving pain is known since ancient times. The active principle present in opium was shown to be morphine. Other alkaloids like heroin and codeine also contain benzo[d]uran nucleus in their structures.

\[
\text{CH}_3\text{COO} \quad \text{OCOCH}_3
\]

\[
\text{23} \hspace{1cm} \text{24}
\]

Morphine has been found to be associated with very important medicinal properties like analgesic and euphoric. Morphine sulphate, diamorphine hydrochloride, dihydrocodeine phosphate etc., possess potent narcotic, analgesic properties and are used in clinical practice.

Small and coworkers have extensively investigated morphine and related alkaloids and found some interesting correlation between physiological activity and their structure. After enormous work, in this regard, they came to conclusion that the cleavage of ether bridge (dihydrofuran ring) decreases the activity to considerable extent. Hence
furan ring in morphine and its analogues is proved to be an essential part of the structure for their analgesic activity.

Dihydrobenzofuran nucleus condensed with seven membered nitrogen heterocycles is found to be present in another interesting alkaloid, galanthamine, isolated from haemanthus and galanthus\textsuperscript{59}. Galanthamine has received much attention because of its wide range of physiological, pharmacological and biological properties. It is shown to exhibit strong bactericidal properties\textsuperscript{60} and is also known to inhibit cholinesterase activity in animals particularly in brain and blood\textsuperscript{61}. Because of these properties galanthamine is used in the treatment of thrombosis or thrombo embolic diseases, hemiplegics and hemiparetis with cerebral haemorrhage\textsuperscript{62}. It also possesses twitch potentiating and tetanus sustaining action\textsuperscript{63}. Intravenous administration of galanthamine results in fall in blood pressure with simultaneous increases in tonus and peristalsis of intestine in cats and rabbits\textsuperscript{64}.

A series of alkaloids, in which furan ring is condensed with an acridine nucleus are isolated from various plants. They include rutacridone\textsuperscript{65} 25, gravarcidondiol\textsuperscript{65} 26, ataline\textsuperscript{66} etc.
Furoquinoline alkaloids represent another class of naturally occurring compounds containing furan ring. Many of these are reported to possess toxic properties. The exact study of their pharmacological activity was difficult to carry out, due to highly insoluble nature of free bases and very high acidity of their salts in aqueous solutions. Typical examples of the compounds belonging to this group are dictamnine, skimmianine and cronycidine.

1.2 Synthetic benzofurans fused with nitrogen heterocycles

Although the examples of benzofurans fused with nitrogen heterocycles in nature are very much limited, the valuable medicinal properties associated with such fused ring systems has rendered great importance to this rare class of compounds. Further, the fact that the presence of furan ring is an essential part of the structure for medicinal properties has generated enamours interest in synthetic benzofurans.

Benzofuran moiety may be combined with nitrogen heterocycles in different ways, the two ring systems may be fused together or both ring systems may be linked to each other directly to produce biheterocycles or through a carbon or nitrogen bridge.
There are very few instances of benzofurans fused with three or four membered nitrogen ring systems. Benzofuro[2,3-b]azirine\textsuperscript{30} is known in the form of an adduct, which is unstable, formed by the addition of phthalimidonitrile to benzofurans. There is only one report available in the literature regarding the synthesis of benzofuro[2,3-b]azete \textsuperscript{31} as 2,7-dihydrobenzofuro[2,3-b]azete by the photolysis of isoquinolonoine-N-oxide.

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\begin{align*}
&\text{30} \\
&\text{31}
\end{align*}
\]

The five membered pyrrole ring can be condensed with furan moiety of benzofuran nucleus in three different ways to produce the following three isomeric molecules viz. benzofuro[2,3-b]pyrrole\textsuperscript{32}, benzofuro[2,3-c]pyrrole\textsuperscript{34-76} \textsuperscript{33} and benzofuro[3,2-b]pyrrole\textsuperscript{77} \textsuperscript{34}.

\[
\begin{align*}
&\text{32} \\
&\text{33} \\
&\text{34}
\end{align*}
\]

All these systems are known in the form of their various derivatives. Among these, derivatives of benzofuro[2,3-c]pyrrole have been reported to possess tranquilizing and muscle relaxant properties\textsuperscript{76}. 
Benzofuro[3,2-b]indole and its derivatives were reported in 1938, which have been synthesized by Fischer indole synthesis. Schroeder and coworkers prepared several benzofuro[3,2-b]indole derivatives and showed them to possess antidepressant activities. Some substituted derivatives of benzofuro[3,2-c]indole have been synthesized by Sonnatag et al., and were found to stimulate central nervous system.

There are several reports in literature in connection with fusion of benzofuran moiety with five membered rings containing two nitrogen atoms, one nitrogen and one oxygen atom, one nitrogen and one sulphur atom and three nitrogen atoms. Malik et al., synthesised benzofuro[3,2-c]pyrazole derivatives by ring closure of phenylhydrazones of 2-carbethoxy-3-[2H]benzofuranone in acetic acid. Subsequently several derivatives of this ring system were prepared by different methods.

Kirchmayr reported the synthesis of a series of substituted 3-phenyl-7-[2H-(1)-benzofuro[2,3-d]triazol-2-yl]coumarins by the reaction between monoxime of benzofuran-2,3-dione and 3-phenyl-7-hydrizinocoumarin followed by the cyclization of intermediate α-oxime hydrazone by treating with potassium acetate and acetic anhydride. These compounds found application in textile industries as fluorescent whiteners for polyester fabrics.
One of the very convenient routes for the synthesis of several condensed systems, involve cycloaddition reactions between C=C bond of heteroaromatics with 1,3-dipolar reagents. Thus, in such a reaction of benzofuran with benzonitrile-N-oxide, a mixture of benzofuro[2,3-d]isoxazole 39 and benzofuro[3,2-d]isoxazole 40 were formed.\textsuperscript{86,87}

The synthesis of 2-methylbenzofuro[3,2-d]thiazole\textsuperscript{88} 41, was accomplished by the reaction between 2-bromo-3-(2H)benzofuranone and thioacetamide followed by cyclization with concentrated sulphuric acid. Abramenko \textit{et al.}\textsuperscript{89} succeeded in synthesizing another isomer 2-methylbenzofuro[2,3-d]thiazole 42 by treating 2-bromoacetylaminobenzofuran with phosphorus pentasulphide.
Among the condensed benzofurans, the benzofuropyridines are the most extensively investigated ring system. Although the synthesis, antiinflammatory and bacteriostatic actives of 2-chloro-5,6,7,8-tetrahydrobenzofuro[2,3-b]pyridine were reported in 1969\textsuperscript{90,91}, the extensive research work of this heterocycle commenced only when Cocker and coworkers\textsuperscript{92} synthesized a series of 1,3-disubstituted derivatives of this heterocycle and showed them to possess significant antiviral activity. Following the work of Cocker and coworkers 2-methyl and 4-methylbenzofuro[2,3-b]pyridines 43 were synthesized\textsuperscript{93,94}. The subsequent utilization of these compounds in the manufacture of dyes has been investigated\textsuperscript{95,96}. Henecka prepared derivatives benzofuro[3,2-c]pyridine 44 and found them to possess analeptic and analgesic activities\textsuperscript{97}. Another isomer benzofuro[3,2-c]pyridine was synthesized by Descamps and Binon by using benzofuran-2-carboxaldehyde as starting material. A number of O-(o-nitrophenyl)oximes of 1-alkyl-4-piperidones were cyclized with ethanolic hydrogen chloride to give 4a-alkoxy-1,2,3,4,4a,9a-hexahydrobenzofuro[3,2-c]pyridine, which on heating with p-toluene sulphonic acid, eliminated a molecule of alcohol, producing the corresponding tetrahydrobenzofuro[3,2-c]pyridine\textsuperscript{98}. This method has been widely employed by several investigators for the synthesis of various terahydro compounds of this heterocyles\textsuperscript{99-102}.

Benzofuro[3,2-b]pyridine 45 has not received much attention. Abramovitch and coworkers\textsuperscript{103}, while investigating the reaction of benzyne with pyridine-3-oxides observed the formation of some 3-substituted benzofuro[3,2-b]pyridines.

\[ \text{43} \quad \text{44} \quad \text{45} \]
Amongst various isomers of condensed heterocycles, in which benzofuran is condensed with six membered ring containing two nitrogen atoms, benzofuro[3,2-d]pyrimidines have been explored to a maximum extent. Many derivatives of this isomer were found to be useful in inhibiting thrombus formation and they also inhibit collagen induced platelet aggregation in plasma from dogs. As a result of such intensive research, several papers describing synthesis, spectral studies and biological activities of this isomer have appeared in literature in the form of research papers and review article. Some partially hydrogenated N-methyl derivatives of benzofuro[2,3-b]azepine have been prepared by Granik and coworkers, either by heating caprolactum diethyl acetal with 5-hydroxybenzofurans or by Nenitzescu reaction of caprolactum diethyl acetal with benzoquinone. Becker and Gustafsson during their investigation on photochemical isomerization observed the formation of following derivative of benzofuro[3,2-b]azepine.

Owing to the importance of diazepines and triazepines as tranquilizing, sedative and CNS depressant activities, many synthetic organic chemists embarked their research
work in the synthesis of fused heterocycles encompassing these pharmacologically active heterocyclic systems.

The first member of fused diazepine series i.e., 1,3-dihydro-5-phenyl[2H]benzofuro[3,2-e]diazepine-2-one 48 was prepared from 3-chloroacetamide-2-benzoylbenzofuran on heating with atropine. Similar ring closure of 3-chloroacetamido-3-acylbenzofuran has been effected using methanolic ammonia.

![Chemical Structure](image)

Benzotriazepines are well known to possess herbicidal and pesticidal properties and are used in the manufacture of plant protecting agents. The derivatives of 1,2,5-benzotriazepines and 1,3,4-benzotriazepines are found to be associated with CNS depressant, vasodilator, hypnoanalyptic, anticonvulsant, sedative and anti-inflammatory activities. These observations encouraged several researchers to devote their work in the synthesis of compounds enclosing triazepine moiety in their structure. As a result of such investigation numerous diazepine and triazepine compounds have been patented. A few general methods of constructing these heterocycles are available in literature.
1.3 Naphthofurans

1.3.1 Naturally occurring naphthofurans

Naphthofuran and its derivatives are very rarely found in nature. However, few of them are reported to occur in some plants in the form of naphthofuroquinones.

Mansonone D was found to be present in the extract of leaves of *Mansonia alltissma* belonging to *Streculiaceae* family, by Bettolo et al\textsuperscript{125}. This compound was identified as 3,5,8-trimethyl-2,3-dihyronaphtho[2,1-b]furan-5,6-dione 49.

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\begin{align*}
\text{CH}_3 & \quad \text{O} \quad \text{O} \\
\text{O} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Dunnione 50 was first isolated from the leaves of *Streptocarpus dunnii* mast by Price and Robinson and was found to be 2,3,3-trimethylnaphtho[1,2-b]furan-4,5-dione\textsuperscript{126,127}.

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 \\
\text{O} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]
Stochigt et al.,\textsuperscript{128} carried out further research work of this plant and succeeded in isolating similar type of compounds. Recently, Inoue et al.,\textsuperscript{129} could isolate three more structurally related compounds from same natural source. Dunnione was also found to be present as a mixture of d- and l-enantiomers in the ratio of 43:57 in \textit{Calceolaria integrifolia}\textsuperscript{130}.

A mixture of cytotoxic furanonaphthoquinones have been isolated from the bark of \textit{Tabebuia impetiginosa}, the plant belonging to \textit{Bignoniaceae family}\textsuperscript{131}. On the basis of spectral studies, one of the compound isolated was identified as 5-hydroxy-2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-dione. The position of the phenolic group in this compound was established by X-ray chromatographic investigation.

Heart wood of \textit{Tabebuia pentaphylla} was found to contain many derivatives of 2-acetyl naphtho[2,3-b]furan-4,9-diones\textsuperscript{132-135} 51.

\begin{center}
\includegraphics[width=0.5\textwidth]{51.png}
\end{center}

There are few reports, available in the literature, regarding occurrence of naphtho[3,2-b]furan in various medicinal plants. Several biologically related naphthofuroquinones occur in the heartwood of tropical trees belonging to the family \textit{Bignoniaceae} particularly to the genera \textit{Kigelia} and \textit{Tabebuia}\textsuperscript{136,137}. Various derivatives
of 2-acetylnaphtho[3,2-b]furan-4,9-diones 52 were reported to be present in the trunk wood of seven different species of *Tabebuia*.

In the form of its quinone, naphtho[2,1-b]furan was found to be present, in nature, as aglycone in woody parts and roots of various plants species belonging to nineteen plant families$^{138}$.

![Chemical Structure](image.png)

1.3.2 Synthetic naphthofurans

Naphthofurans fused or coupled with nitrogen heterocycles do not occur in nature. Even the synthetic naphthofurans coupled or fused with nitrogen heterocycle are not reported so far, except some reports of such compounds from our laboratory$^{139-141}$. These synthesized compounds have been found to be associated with wide spectrum of biological and pharmacological activities such as antibacterial, antifungal, anthelmintic, analgesic, anti-inflammatory and diuretic.

These observation coupled with interesting biological activities associated with naturally occurring and synthetic benzofuran fused with nitrogen heterocycles and synthetic biheterocycles or biheteroaryl benzofurans, prompted us to under take the investigation of:
i) Naphthofuran fused with nitrogen heterocycle such as pyridine and pyrimidine

ii) Biheterocyclic naphtofurans with pyrazole, isoxazole, oxadiazole, pyridine, pyrimidine, quinoline as second heterocyclic components.

The first synthesis of naphthofuran was reported way back in the year 1897 by Stoermer. Since then the investigations on naphthofuran and its derivatives has not received much attention of organic chemists.

Amongst the several isomers of naphthofuran, only the following four isomers, naphtho[2,1-b]furan 53, naphtho[1, 2-b]furan 54, naphtho[2,3-b]furan 55 and naphtho[3,2-b]furan 56 and their derivatives are found to exists in nature and hence became subject of synthetic interest to some scientist.

Hence it is felt appropriate to give a brief introduction and literature survey about the research work carried out on these isomers of naphthofurans.
1.3.2.1 Derivatives of naphtho[2, 1-b]furan

As already mentioned, the first synthesis of naphtho[2,1-b]furan appeared in literature in 1897. Stoermer synthesized this compound from 1-naphthyloxy acetaldehyde. The same author reported the synthesis of 2-acetylnaphtho[2,1-b]furan by reacting 2-hydroxy-1-naphthaldehyde with chloroacetone in presence of dry benzene and metallic sodium\textsuperscript{143}. However the yield obtained, by this procedure was found to be unsatisfactory.

Emmott and Livingstone\textsuperscript{144}, after a gap of 54 years, have reported the synthesis of few derivatives of naphthofuran by the reaction between 2-hydroxy-1-naphthaldehyde with ethyl bromoacetate followed by hydrolysis and cyclisation in presence of acetic anhydride and sodium acetate. They could isolated naphtho[2,1-b]-2-carboxylic acid and parent heterocycle naphtho[2,1-b]furan. However, they failed to isolate the important intermediate ethyl naphtho[2,1-b]furan-2-carboxylate.

Loader and Timmons\textsuperscript{145} could obtain similar parent heterocycle \textbf{57} by photocyclodehydrogenation of 2-styrylfuran. Eventhough, they obtained this compound in pure form, the yield was exceptionally low i.e. less than 10%.

Some of the substitution reactions on naphtho[2,1-b]furan have been investigated by Chatterjea \textit{et al.},\textsuperscript{146}. They observed that formylation of 2-methylnaphtho[2,1-b]furan
produced 2-methyl-8-formyl{naphtho[2,1-b]furan 58. Interestingly the formyl group instead of entering into furan ring entered naphthalene ring.

\[ \text{Formylation} \]

Then afterwards, the research work was mainly devoted towards the synthesis of pharmacologically active naphtho[2,1-b]furan derivatives. Weillthevenet et.al.,\textsuperscript{147} and Gilotdelhalle et.al.,\textsuperscript{148} synthesized 2-nitro-7-methoxynaphtho[2,1-b]furan 59 and its methylated analogues and reported them to possess mutagenic and carcinogenic activities.

Considerable carcinogenic activity has been found to be associated with 2-nitronaphtho[2,1-b]furan and 7-methoxynaphtho[2,1-b]furan\textsuperscript{149}.

Investigation of relationship between odour and configuration of the chemical constituents present in 5b-ambrox revealed that the compound responsible for
predominant odour of 5b-ambrox is 1, 2, 3a, 4, 5ab, 6, 7, 8, 9, 9a, 9ba- dodecahydro-3ab, 6,6,9ab, tetramethylnaphtho[2,1-b]furan 60.150

Among the nitro naphthofurans, 7-methoxy-2-nitronaphtho[2,1-b]furan was proved to be a very potent mutagen that causes Sarcomas at the subcutaneous injection site and Carcinomas in the fore stomach after P. O. administration151. There are reports regarding studies in connection with the influence of methoxy and nitro groups in oxidative metabolism of naphtho[2, 1-b]furan152.

Very recently, Arrault et al.,153 have reported synthesis of ethyl-1,2-dihydronaphtho[2,1-b]furan-2-carboxylate.

1.3.2.2 Derivatives of naphtho[1,2-b]furan

Ebine154 was first to report the synthesis of naphtho[1,2-b]furan derivatives in the year 1953. However, Bernatek carried out detailed investigation of same work and synthesized various derivatives of naphtho[1,2-b]furan 61-65 by the reaction between 1,4-naphthoquinones with appropriate β-diketones in presence of methanolic zinc chloride155.
Emmott and Livingstone\textsuperscript{156} could accomplish the synthesis of 5-methoxynaphtho[1,2-b]furan \textit{66} and its 2-carboxylic acid \textit{67} by the condensation reaction of 1-hydroxy-4-methoxy-2-naphthaldehyde with ethyl bromoacetate, surprisingly similar reaction using 1-hydroxy-2-naphthaldehyde did not produce expected result.
Einhorn et al.,\textsuperscript{157} reported univocal synthesis of 2-nitro-2-methoxynaphtho[1,2-b]furan 68 following the sequence of reaction depicted in the scheme.

While investigating various terpenoids, Veluchamy and Rao\textsuperscript{158} reported the synthesis of 3,6,9-trimethoxynaphtho[2,1-b]furan 69 which is closely related to Emmotin-G.

Katritzky et al.,\textsuperscript{159} have reported one step synthesis of naphtho[1,2-b]furans by using insertion reaction, they used N-(naphthoxybenzotriazoles) as starting material for the required synthesis.
Synthesis and antimicrobial screening of amino methyl derivatives of naphtho[1,2-b]furan was carried out by Mukhanova et al. They reported that all the newly synthesized compounds showed weak to moderate antibacterial and antifungal activities. They also devised new approach for the synthesis of naphtho[1,2-b]furan derivatives. 2-Methyl-3-benzoyl-5-hydroxynaphtho[1,2-b]furan was synthesized by them by reacting enamino ketone with 4-naphthoquinones.

Toshio et al., could isolate two compounds from fermentation broth of Nocarda species TP-A0248 and purified them by the conventional column chromatographic technique. These compounds were identified as derivatives of naphtho[1,2-b]furan-4,5-diones, based on spectroscopic studies. These newly isolated compounds exhibited moderate invitro antifungal and cytotoxic activities. They also inhibited the activity of Cdc 25B, PTP 1B and FAP-1 protein tyrocin phosphates at a concentration of 10 μM.

1.3.2.3 Derivatives of naphtho[2,3-b]furans

Survey of literature revealed that the first report regarding the synthesis of naphtho[2,3-b]furan appeared in 1957. The required starting material 2-hydroxy-3-naphthaldehyde 70 was obtained by the Oppeneur oxidation of 3-hydroxymethyl-2-naphthol 71. The treatment of aldehyde 70 with ethyl bromoacetate gave the product which on reaction with acetic anhydride and sodium acetate yielded a mixture of naphtho[2,3-b]furan 72 and its 2-carboxylic acid 73.
The synthesis of methyl-3-hydroxynaphtho[2,3-b]furan-2-carboxylate 74 by the reaction between methyl-2-hydroxynaphthalene-2-carboxylate with ethyl chloroacetate has been reported in literature\textsuperscript{157}.

\[ \text{Methyl-2-hydroxynaphthalene-2-carboxylate} \overset{\text{Ethyl chloroacetate}}{\rightarrow} \text{Methyl-3-hydroxynaphtho[2,3-b]furan-2-carboxylate} \]
A number of naphtho[2,3-b]furan-4,9-diones have been isolated from plants and reported to possess wide spectrum of biological activities. These activities mainly depended on the position and the kind of substituents. Encouraged from such reports, Koyanagi et al., synthesized naphtho[2,3-b]furan-4,9-dione 75 by using a shortest route as shown in the scheme.

By using similar method, same authors reported the synthesis of various 2-substituted naphtho[2,3-b]furan-4,9-diones.

In an attempt to study structure activity relationship, Kurihara et al., synthesized a series of non-steroidal progesterol receptor compounds with structural modifications at 3,4,5,7 and 9 positions of 6-acetoxy-4a,5,6,7-tetrahydro-3,4a,5-
trimethylnaphtho[2,1-b]furan-2(4H)-one. They could also identify critical positions for high binding affinity to the progesterone receptors.

Jeffrey et al.,\textsuperscript{167} patented the preparation of naphtho[2,3-b]heteroar-4-yl derivatives for treating metabolic disorder relating to insulin resistance or hyperglycemia.

1.4 Synthetic benzofuran and naphthofuran compounds coupled with nitrogen and other heterocycles

The other way of combining various heterocycles with benzofuran and naphthofuran nucleus involve direct linkage of both the heterocyclic systems so as to produce biheterocycles or through carbon or nitrogen bridge. These types of mixed heterocycles with benzofuran as one of the component of much interest to explore biological activities. Several research workers have tried to design and synthesize such molecules in a search for potent drug. Most of such work has come up during the last two decades. However, similar type of work on naphthofuran has not been reported in literature, except some reports from our laboratory\textsuperscript{139-141}. As a result of such investigations in literature number of papers have appeared describing synthesis, characterization and biological evaluation of various biheterocycles enclosing benzofuran and five membered heterocycles such as furan, pyrrole, pyrazole, imidazole, pyrazoline,
isoxazole, isoxazoline, thiazole, oxadiazole, pyridine. However, the detailed discussion of such work is out of the scope of this thesis, hence only the important reports mentioning the structures, biological activity and appropriate references are presented briefly in Table-1.1.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Structure of compound</th>
<th>Reported activities and uses</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="#" alt="Structure 1" /></td>
<td>Possess antibacterial activity. The minimum inhibitory 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.</td>
<td>168</td>
</tr>
<tr>
<td>2</td>
<td><img src="#" alt="Structure 2" /></td>
<td>Possess antihypertensive activity in rats.</td>
<td>169</td>
</tr>
<tr>
<td>3</td>
<td><img src="#" alt="Structure 3" /></td>
<td>Useful in the treatment of fear in emotions of psychogenic origin.</td>
<td>170</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>Possess insecticidal and miticidal activity.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>In the form of acid salts, they are useful in antidepressant preparations.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>Found to be useful as fluorescent whitners for acrylic and polyester fibres.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image4" alt="Chemical Structure 4" /></td>
<td>Inhibitor properties against <em>Trycophytomentagrophytes</em> were studied and some of the compounds were found to have minimum inhibitory concentration of 3 mg/ml</td>
<td></td>
</tr>
</tbody>
</table>
R = H, Br, R' = H, OMe, Cl, Br, R'' = H, Me

Reported to exhibit good antibacterial activity.

Ar = C₆H₅, 4-Cl C₆H₄, 4-NO₂ C₆H₄, 4-OCH₃ C₆H₄, C₄H₃O,

Reported as mono amino oxidase inhibitor.

R = H, alkyl, alkoxy carbonyl, CN,
R' = H, alkyl; R'' = H, halo, m,n = 1,2; m+n = 3,4

Some of these compounds reduces the blood pressure of hypertensive rats by 50 mm Hg.

R = H, Br, R' = H, OMe, Cl, Br
R'' = H, Me.

Reported to exhibit good antibacterial activity.
Possess useful properties like vasodilation and are reported to protect against vasopressin-induced angina and antiarrhythmic. At 5mg/kg in dogs has a 136% increase in cerebral blood flow and at 15 mg/kg in rats has protection against CHCl₃ induced fibrillation.

Possess *invitro* antimicrobial activity against *S. aureus* and *E. coli* at a concentration of 100 µg.

Reported to exhibit antimicrobial activity against bacteria *S.aureus* and *K.pneumoniae* and fungi *A. niger*.

Reported to exhibit antimicrobial activity against bacteria *S.aureus* and *K.pneumoniae* and fungi *A. niger*.
In addition to heteroaryl substituted benzofurans, there are numerous examples of benzofuran derivatives even with some substituted either in benzene or furan ring are reported to possess interesting biological activities. Thus benzofurans containing alkyamino side chain are known for antihypertensive\textsuperscript{180,181}, dopaminergic\textsuperscript{182}, antidiabetic\textsuperscript{183}, insecticidal\textsuperscript{184}, antiobesity\textsuperscript{185}, anticholinesterase\textsuperscript{186}, hypnotic\textsuperscript{187}, antimicrobial\textsuperscript{188,189}, antiviral\textsuperscript{190}, analgesic\textsuperscript{191}, anti-inflammatory\textsuperscript{192} activities. Several phenyl substituted benzofuran derivatives are reported to possess antiasthamatic\textsuperscript{193}, antibacterial spasmolytic\textsuperscript{194}, diuretic, hypertensive\textsuperscript{195,196} and anthelmintic\textsuperscript{197} activities.

Recently, several benzofuran derivatives with various substituents are reported to possess pesticidal, insectidal, acaricidal\textsuperscript{198}, antidiabetic\textsuperscript{199} and analgesic activities\textsuperscript{200}. Many such compounds are also reported to be useful in cosmetics like sunscreen formulations\textsuperscript{201,202}, inhibition of cyclooxygenase-2 by 94% and to function as cannabinoid antagonists\textsuperscript{203}. Most of these recent finding are under patent literature.

There are no reports, in literature, regarding synthesis and biological evaluation of naphthofurans either fused or coupled with nitrogen heterocycle. Hence, synthesis of such compounds has been initiated in our laboratory. In continuation of earlier work, we have now undertaken a systematic investigation of synthesis and biological investigation of new series of heterocyclic compounds comprising naphthofuran and different nitrogen heterocycles either in fused or coupled form.

We have initiated particularly, investigations using naphtho[2,1-b]furan derivatives because of easy accessibility of naphtho[2,1-b]furans with appropriate functionality for further fusion or coupling different nitrogen heterocyclic systems.
Logically, there appears to be at least three different synthetic strategies for the proposed naphthofurans fused with nitrogen heterocycle or biheterocyclic naphthofurans having nitrogen heterocycle as its another partner.

a) The desired nitrogen heterocyclic ring system may be fused or coupled on a preformed naphthofuran.

b) Naphthofuran ring system may be fused or coupled on a preformed nitrogen heterocycle with suitable functionalities.

c) The two preformed naphthofuran and nitrogen heterocycles may be coupled to each other directly or fused together.

In the present investigation the synthetic strategy “a” involving the construction of desired nitrogen heterocycle onto a preformed naphthofuran is followed for the synthesis of biheterocyclic naphthofurans or condensed naphthofurans with nitrogen heterocycles, because of easy availability of appropriately substituted naphthofuran derivatives, through convenient synthetic methods.
The work carried out at present is conveniently presented as follows:

1. **Chapter-2**: Synthesis of 2-aryl-1,2,3,4-tetrahydronaphtho[2,1-b]furo[3,2-b]pyridin-4-ones.

   


6. **Chapter-7**: Biological evaluation

   - Section A - Antimicrobial activity.
   - Section B - Anti-inflammatory activity.
   - Section C - Analgesic activity.
   - Section D - Diuretic activity.
References


42. E. Spath and W. Gruber, Chem. Ber., 74, 1492 (1941).


