Chapter – 1

Introduction
Introduction

From the earlier days of development of organic chemistry to present, heterocyclic compounds have held center stage in the development of molecules to enhance quality of human life. For example, more than seventy percent of drugs used today are heterocyclic compounds. They are widely distributed in nature and are key intermediates in many biological processes. Generally, heterocyclic compounds isolated from natural sources act as lead compounds for the development of new molecules of biological interest [1-3]. Today, most of the heterocyclic drugs are not extracted from natural sources but are synthesized from readily available fine chemicals. In this aspect, synthesis and characterization of new molecular entities incorporating heterocyclic structures is of high importance [4]. There are multiple benefits in exploring this type of organic chemistry. Firstly, this research helps to unravel intrinsic chemical behavior of small molecules which still remain mysterious. Secondly, this research may generate development of new methods for synthesis. Thirdly, characterization of a set of compounds by spectral means would create benchmarks for the characterization of similar molecules. Finally, biological evaluation of the prepared compounds may expose lead compounds for further structural fine tuning. Among organic compounds, the compounds incorporated with one or more hetero atoms are interesting because of the unique properties imparted by these elements [5-7]. Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds [8, 9]. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and as reactive pharmacophore has largely contributed to their unique value as traditional key elements of numerous drugs.

Importance of heterocycles to life and Industries

Observation of life in nature by primitive communities led humans to the discovery of many healing materials. Many pharmaceutical products are mimics of natural products with good biological applications which contain many heterocycles. Some heterocycles are fundamental to life, such as haem derivatives in blood and the chlorophyll essential for photosynthesis [10].
Similarly, the paired bases found in RNA and DNA are heterocycles, dyestuffs of plant origin include indigo blue, used to dye jeans. A poison of detective novel fame is strychnine which is obtained from the plant resin curare [11].

The biological properties of heterocycles in general make them one of the prime interests of pharmaceutical and biotechnology industries. A selective biologically active pyridine or piperidine derivatives includes the following three natural products: Nicotine (additive drug and an insecticide), pyridoxine (Vitamin B₆), cocaine (a local anesthetic and drug of abuse), and two synthetic compounds namely Nifedipine (Cardiovascular drug) and Paraquat (Herbicide, interfering with photosynthesis) [12, 13].
The routinely used antibiotics, like penicillin, cephalosporin, alkaloids such as vinblastine, elliptine, morphine, reserpine and cardiac glycosides such as the class of digitalis are some significant heterocyclic natural products for human and animal health. Inspired by these findings, pharmaceutical researchers have constantly designed and produced better pharmaceuticals for a better living. In the same light, pesticides, insecticides, rodenticides, and weed killers followed natural models, and a significant part of such biologically active compounds are heterocycles. Heterocycles play a vital role in the biochemical processes in living cells, nucleic acids containing pyrimidine (cytosine and uracil) and purine (adenine and guanine) bases are major constituents [14, 15].

Modern life and civilization opened the way to other important practical applications of heterocycles which includes dyestuffs, copolymers, solvent extraction, photographic sensitizers, vulcanization accelerators and antioxidants in rubber industry [16].

In recent years much attention has been focused on the synthesis of heterocycles containing oxygen atom because of their biological importance including ontological research. They are widely distributed in nature and are essential for life [17]. Chemistry of oxygen containing heterocyclic compounds is a sub-discipline within the area of heterocyclic compounds. The interest in this type of compounds stem from the fact that many sugars have biological roles in the body that is manifested as their involvement in certain biochemical processes. For example, glucose and fructose have important metabolic functions at the cellular level inside the body. Sugars can have open chain structure as well as a cyclic structure. The cyclic form is the more thermodynamically stable compound among the two possible forms.

Furan nucleus is often found fused with oxygen heterocycles rather than nitrogen heterocycles in nature. Although these 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, contain a furan nucleus condensed with nitrogen heterocycles. Furan ring has proved to be an essential part of the structure of the molecule for its medicinal properties in these drugs [18]. This encouraged us to investigate the chemistry and biological activities of benzofurans substituted at C-2 position with other heterocycles.

Coumarin derivatives are important source of heterocyclic compounds of pharmacological interest as they possess a wide spectrum of biological activity viz antibacterial, antifungal, antioxidant, anti-inflammatory, analgesic, herbicidal, and antitumor activities. Furthermore, it has been reported by different scientists that the coumarin derivatives incorporating pyrazole, pyridine, azetidine and oxazole ring were also found to possess interesting antibacterial and antifungal activities. In light of these observations, several new coumarin derivatives fused with different heterocycles have been synthesized with the hope to possess better biological agents.

In view of the significant biological properties of benzofuran and coumarins, the work compiled in this thesis mainly describes the synthesis of benzofuran and coumarin derivatives fused with several heterocycles. Most of the work is concentrated on the synthesis of benzofuran derivatives fused with pyrazole, barbiturates and thiazolo benzimidazole and coumarin derivatives with pyridine and pyrazole nucleus. The synthesized compounds were evaluated for different biological activities.

Keeping in view of the above facts, it was felt necessary to give a brief account of general properties of naturally occurring benzofuran and coumarin derivatives.

**Nomenclature and General Properties of Benzofuran**

The accepted name for ring system 1 in chemical abstracts is benzo (b) furan. In order to shorten, (b) is conveniently dropped and it is commonly known by the generic name benzofuran. The name coumarone used in the earlier literature for this nucleus is now rejected. The benzofuran ring is numbered starting from heteroatom as shown below.
Benzofuran is a hetero aromatic molecule containing 10 \( \pi \) electron systems and is called \( \pi \) excessive hetero aromatic compound. It is a resonance hybrid of structure 1 which is the major contributor. Minor contributions are made by charged structures 2 and 3.

As anticipated of \( \pi \) excessive compounds, benzofuran ring is highly reactive towards electrophilic substitution. The resonance considerations of such condensed systems indicate that electrophilic substitution should preferentially occur at the 3-position but in contrast to this prediction, benzofuran preferentially undergoes substitution almost exclusively at the 2-position. Farrar and Levine [19] have discussed this difference in orientation between benzofuran and benzothiophene and concluded that it is associated with relative electro negativities of oxygen and sulphur. As oxygen is more electronegative than sulphur, the unshared electrons around the oxygen are held more tightly than those of sulphur. Hence the distortion of electrons in benzofuran due to greater electronegativity of oxygen would lead to the greater importance of ionic structure 2 and consequently the electrophilic substitution at 2-position is favoured. This also tends to decrease the aromaticity of benzofuran and make it behave more like an olefin. In benzothiophene, the electronegativity of sulphur is secondary and the ionic structure 4 having negative charge in 3-position is of greater importance.

Thus, benzofuran is reactive and is attacked by strong acids. Probably because of these reasons, the chemistry of benzofuran is not much developed when compared to that of benzothiophene and indole.
Naturally occurring benzofuran derivatives

Benzofuran fused with oxygen heterocycles

Benzofuran compounds occur in nature in a variety of structural forms, which ranges from a simple molecule such as 5-methoxybenzofuran to a highly complicated molecule like morphine. Benzofuran compounds exist in large numbers with great structural variety in nature. Several monographs devoted to the study of such natural and synthetic benzofuran have appeared in literature from time to time. The acetyl group of benzofuran at 2-position has extensive utilities in the synthetic chemistry. They are conveniently grouped depending upon their chemical structure into following types.

Simple benzofuran

3-Methoxybenzofuran, the simplest of the naturally occurring benzofurans was discovered as a result of fungal contamination of oak beer barrel which led to the beer having a strong, persistent distasteful odour. This odour is characteristics of benzofuran. Okada discovered egonol 5 from a seed-oil of the plant 'Egonoki' commonly found in Japan. It is an effective synergist for rotenone and pyrethrum against house flies, mosquitoes, aphids and many other insects [20]. Baker’s yeast 6 has been found to contain 2-(2-hydroxy-6-methoxy-4, 5-methylenedioxyphenyl) benzofuran that acts as an antioxidant and prevents haemorrhagic liver necrosis in rats and diets which would normally induces this condition. It also prevents haemolysis of red cells in vitamin-E deficient rats.

\[ \text{\textbf{5}} \]

\[ \text{\textbf{6}} \]

Euparin 7 that was isolated from gravel root of *Eupatorium purpureum* and *E. cannabum* and pongamol 8 which was isolated from the seeds oil (karanja oil) of *Pongamia glabra* are other naturally occurring benzofurans.

\[ \text{\textbf{7}} \]

\[ \text{\textbf{8}} \]
The recently recognized simple benzofurans are amiodarone 9, ailanthoidol 10 and bufuralol 11 compounds. Ailanthoidol, a neolignan with a 2-arylbenzofuran skeleton, was isolated from the Chinese herbal medicine *Zanthoxylum ailanthoides*. It has been reported that neolignans and lignans possess a variety of biological activities such as anticancer, antiviral, immune suppressive, antioxidant, antifungal and antifeedant activities [21, 22].

Kapache and coworkers isolated five 2-aryl benzofuran derivatives namely moracin Q 12, moracin R 13 and moracin S 14, from the methanol extract of *Morus Mesozygia* plant native of Africa. These compounds were found to exhibit potent antioxidant activity [23].

Soyoung Kim *et al* isolated a novel cyclopenta[b]benzofuran derivative, silvestrol 15, from the fruits and twigs of *Aglaia foveolata* and has been found to exhibit very potent *in vitro* cytotoxic activity against several human cancer cell lines [24]. As secondary metabolite of plant *Ficus tikoua bur*, Shao-Peng Wei and coworkers isolated benzofuran glucoside 16 [25].
**Dibenzo furans**

A German scientist W. Knop isolated dibenzofuran derivatives like stripsilin 17 and porphyrilic acid 18 from lichens. Later in the year 1937, for the first time Curd and Robertson were able to achieve the total synthesis of these compounds [26, 27]. A didymic acid 19 and hydroxylated dibenzofurans, isolated from lichens have shown antibacterial activity against *Avian tuberculosis* and *Staphylococcus aureus* [28].

Usnic acid 20, a yellow pigment and constituent of lichens occurs in both the optically active and racemic forms in several plant species. The most interesting activity of this compound is its inhibiting effect [29] on *Mycobacterium tuberculosis* against which it is potent in conjunction with small quantities of streptomycin.

**β-Coumaranones**

3-Hydroxybenzofurans which exist preferentially in the ketonic form are called β-coumaranones. Brain, Curtius and Hemming found that a metabolite of the fungus *Penicillium janczewkii zal* and *P. griseofulvum D* [30, 31], contain numerous coumaranones and among them Griseofulvin 21 is an important benzofuran derivative possessing potent fungicidal activity [32, 33].
In 1943, Geissman discovered a new type of plant pigments called aurones and these aurones are characterized as glycosides of hydroxylated benzylidene coumaranones. Examples of aurones are auresin 22 and leptosin 23 [34].

Furochromones

The extracts of the plant *Ammi visnaga* L. have been used for centuries as a home remedy to relieve spasms of all kinds and also as a chemopharmacademy in the eastern regions of the Mediterranean. The active principles of this crude drug were found to contain two furochromones, khellin 24 and visnagin 25. As they induce muscular relaxation, they are used to combat bronchial asthma and similar spasms in cases that do not respond to adrenalin or aminophyllin [35]. Khellin 26 is used in the treatment of the heart diseases and whooping cough. It has selective antispasmodic effect upon the ureter, bronchial muscles, gall bladder and bile duct [36].

Furoflavones

Limaye succeeded in isolating active principle constituent Karangin 27 from the seed oil of *Pongamia glabra* which was used for the treatment of leucoderma by Ayurvedic practitioners [37].
Furoisoflavones

Furoisoflavones are naturally occurring oxygen heterocycles that possess \( \gamma \)-pyrano benzofuran ring. The two furoisoflavones namely Nepseudin 28 [38] and Neotenon 29 [39] were isolated from the root of *Neorautanenia pseudopachyrrhiza*.

\[
\begin{align*}
\text{28} & \quad \text{H}_3\text{CO} \quad \text{OCH}_3 \\
\text{29} & \quad \text{H}_3\text{CO} \quad \text{OCH}_3
\end{align*}
\]

Furoxanthones

Sterigmatocystin 30 and 6-methylsterigmatocystin are the examples of furoxanthones, which are crystalline metabolites produced from some strains of *Aspergillus varsicolor* [40, 41].

\[
\begin{align*}
\text{30}
\end{align*}
\]

Rotenoids

Rotenoids are naturally occurring heterogenous compounds, e.g., rotenone. Rotenone and related compounds have been known for a long time and they possess furan ring along with rotenone. Elliptone 31 and malaccol are isolated from *Derris elliptica* and *Derris malacensis*, respectively [42, 43]. The importance of rotenones is due to their valuable selective insecticidal action.

\[
\begin{align*}
\text{31}
\end{align*}
\]
Synthetic benzofurans fused with Nitrogen ring systems

In view of interesting biological properties of benzofuran nucleus fused with nitrogen heterocycles, these systems have received much attention of researchers in recent years. In connection with the present investigation, it is felt appropriate and necessary to give a comprehensive presentation of work in this field. The present discussion covering almost up to date literature is made as brief as possible and describes synthetic condensed benzofurans in which the benzofuran is fused with the various types of nitrogen ring systems.

1. Benzofuroazirines

Jones reported [44, 45] the formation of a derivative of benzofuroazirine, 1a, 6b dihydro-1-phthalimidobenzofuro [2, 3-b] azirine 32 as an unstable product during the addition of phthalimidonitrene to benzofuran.

![Benzofuro [2, 3-b] azirine](image1)

2. Benzofuroazetidates

Raga Basawaraj et al reported the synthesis and antitubercular activities of azetidinone and thiazolidinone derivatives from 5-chloro-3-methylbenzofuran 33(a-d). Compounds substituted with o-hydroxyl group on phenyl ring (4b) and (5b) exhibited good antitubercular activity against Mycobacterium tuberculosis H37RV [46].

Harish et al reported the synthesis of 4-(1-Benzofuran-2-yl)-1-(1, 3-benzothiazol-2-yl)-3-chloro-4-methylazetidin-2-One derivative 34(a-j) and screened their antibacterial activity [47].

![Compounds](image2)
Murat et al synthesized some (benzofuran-2-yl) (3-phenyl-3-methylcyclobutyl) ketoxime derivatives 35, 36 and 37 using salicylaldehyde and 1-phenyl-1-methyl-3-(2-chloro-1-oxoethyl) cyclobutane as starting materials and screened for their antimicrobial activity [48].

3. Benzofuropyroles

The following three isomeric benzofuro pyrroles 38, 39, and 40 are reported in the literature. Among these, benzofuro [3, 2-c] pyrrole 39 is the first known isomer of this series. The synthesis of several complex derivatives of these ring systems was reported and some of these compounds have been shown to possess muscle relaxant and tranquillizing properties [49, 50].

A partially hydrogenated derivative of benzofuro [3, 2-d] indole 41 and 42 has been isolated from degradation products of morphine alkaloids.
Recently, R. L. Hudkins and coworkers have reported the synthesis of new fused heterocycles structurally related to indole carbazoles, benzo[b]furan [2, 3-a] pyrrolo [3, 4-c] carbazoles. E.g. benzofuran [2, 3-a] pyrrolo [3, 4-c] carbazo-7-lone 43 [51].

Maria-Joao and co-workers have reported the synthesis of heteroaryls 44 and tetracyclic heteroaromatic indoles 45 fused with benzofuran and studied their antitumor, photophysical and electrochemical studies of interaction with DNA activity [52, 53].

4. Benzofuropyrazoles

Benzofuran associated with pyrazole nucleus displayed broad spectrum of biological significance. Benzofuro [3, 2-c] pyazole 46 derivatives were prepared by ring closure of phenyl hydrazones of 2-carbethoxy-3(2H)-benzofuranone in acetic acid [54].

Several derivatives of benzofuropyrazoles were synthesized conveniently by cycloaddition of hydrazone to benzofuran [55, 56] and also by the reaction of benzofuranone with hydrazines [57]. 1, 3-Disubstituted benzofuro [3, 2-c] pyrazole 47
derivative has been prepared by ring contraction process during the transformation of flavones [58].

Shehry and co-workers have reported dibenzofuran pyrazoles fused with pyrazoline 48, 6-dihydropyrimidine-2-(1H)-thione 49 and amino pyridine carbonitrile derivative 50 and six membered heterocycle, 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo[1,5-a]imidazolothiadiazines 51 fused with benzofuran and screened their molluscicidal and anti-inflammatory activities. The mortality data of compounds towards *B. alexandrina* snails showed promising result especially the compounds that possess pyrazolo and triazolo residues [59, 60].

5. Benzofuro imidazoles

Benzofuro [2, 3-d] imidazole derivatives have been synthesized by Curtius rearrangement of 3-benzamido-2-benzofuran carbonylazide in anhydrous benzene to give 1-arylidene-3-dihydro-2-oxobenzofuro [2, 3-d] imidazole 52 [61].
Xue-Quan Wang et al synthesized novel hybrid compounds of imidazole scaffold-based 2-benzylbenzofuran 53(a-d) as potent anticancer agents and exhibited cytotoxic activities selectively against breast carcinoma (MCF-7) and myeloid liver carcinoma (SMMC-7721) [62].

6. Benzofuro triazoles

Recently, Rama P. Tripathi et al synthesized 1-(2, 3-dihydrobenzofuran-2-yl)methyl [1, 2, 3]-triazoles 54(a-f) by the application of Huisgen (3+2) cycloaddition reaction and evaluated their antitubercular activity [63].

7. Benzofurobenzoxazole

Several derivatives of benzofuro [3, 2-e] benzoxazole 55 were synthesized in connection with dyes [64].
Sabiha Alper-Hayta and coworkers reported the synthesis, antimicrobial activity and pharmacophore analysis of some new 2-substitutedphenyl/benzyl)-5-[(2-benzofuryl) carboxamido] benzoxazoles 56(a-j) [65].

\[
\begin{array}{c}
\text{X-CH}_2, \quad \text{R-H, CH}_3, \text{F, Cl, Br, C}_2\text{H}_5, \text{C (CH}_3)_3, \quad \text{R}_1\text{-H, Br}
\end{array}
\]

8. Benzofuroisoxazoles

Several condensed systems such as benzofuro [2, 3-d] isoxazole and benzofuro [3, 2-d] isoxazole 57 and 58 have been reported in the literature [66].

Shehry et al have reported benzofuran isoxazoline 59 and screened their molluscicidal activity against *B. alexandrina* snails [67].

9. Benzofurothiazole

The synthesis of two isomeric benzofurothiazoles are reported, benzofuro [3, 2- d] thiazole 60 and benzofuro [2, 3-d] thiazole 61 [68].
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2-Amino benzofuro [2, 3-f] benzothiazole 62 was formed by treating 3-thioureido dibenzofuran with bromine in chloroform [69].

\[
\text{NHCSNH}_2 \quad \rightarrow \quad \text{NH}_2
\]

Hanan A. Mohamed and co-workers have reported the synthesis of fluorinated 2 (3-(benzofuran-2-yl) pyrazol-1-yl) thiazoles 63 and screened their antimicrobial activity [70].

Samia M. Rida and their co-workers synthesized some new benzofuran 2-thioxo-2, 3-dihydro-6H-thiazolo [4, 5-d] pyrimidin-7-ones 64(a-c). The synthesized compounds were evaluated for their in vitro anti-HIV, anticancer, antibacterial, and antifungal activities [71].

10. Benzofuropyridines

Benzofuropyridines are the most extensively investigated systems among the condensed benzofurans. Henecka prepared some derivatives of partially hydrogenated...
benzofuro [2, 3-c] pyridine heterocycles 65 and are found to possess high analgesic and analeptic properties [72, 73].

Number of heterocycles containing benzofuro pyridine ring system were prepared and were found to possess analgesic and spasmylytic activity [74]. Descamps and coworkers reported, the work on benzofuro [3, 2-c] pyridine 66 ring system.

The amino derivatives of 1, 2, 3, 4-tetrahydrobenzofuro [3, 2-c] pyridine have been found to be useful as central nervous system blocking agents for white mice [75].

Recently, a number of convenient methods for the synthesis of various substituted derivatives of benzofuro [3, 2-b] pyridine 67 ring system have been reported [76]. Synthetic approach involved the interaction of compounds containing active methylene groups like diethyl malonate and ethyl cyanoacetate with ethyl 3-amino-2- benzofuran carboxylate and 3-amino-2-benzofuran carbonitrile.

\[ R = \text{COOEt, CN, OH, NH}_2 \]

Mashelkar and coworkers synthesized some benzofuropyridinones by the action of dimethyl formamide in phosphorous oxychloride on 2-carboxy-6-methylbenzofuran-3-acetic acid [77]. Recently novel 18 F-labeled pyridyl benzofuran derivative 68 have been synthesized for the imaging of β-amyloid plaques in Alzheimer’s brains [78].
11. Benzofuroquinolines

Benzofuro [3, 2-g] quinoline 69 and benzofuro [2, 3-f] quinoline 70 isomers were synthesized using 3-aminodibenzofurans by Skraup synthesis [79].

Different derivatives of these two isomers were found to possess important physiological properties such as analgesic, general depressant, muscular disturbances, emesis and antipyretic. Benzofuro [2, 3-g] quinoline 71 and benzofuro [3, 2-f] quinoline 72 ring systems were synthesized by Skraup synthesis using 2-aminodibenzofuran hydrochloride.

Some of the derivatives of benzofuro [2, 3-g] quinoline 73 reported by Daniel were found to possess antimicrobial properties [80, 81]. Many benzofuro [2, 3-g] quinoline derivatives were synthesized and evaluated for biological properties [82-85].

Royer and coworkers reported the synthesis of some benzofuro [6, 5-c] acridine derivatives 74 in connection with investigation on benzofuran analogues as carcinogenic compounds [86].
12. Benzofuropyridazine

![Benzofuropyridazine Structure](image)

[1] benzofuro [2, 3-c] pyridazine

3-phenyl [1] benzofuro [2, 3-c] pyridazine 76 [87] has been synthesized in 1972 from 3-(bromomethyl)-1-benzofuran-2(3H)-one 75.

Huntress and coworkers prepared 1, 2, 3, 4-tetrahydro-1, 4-dioxobenzofuro [2, 3-d] pyridazine 77 by the condensation of 2, 3-dicarboxylic ester of benzofuran with hydrazine [88].

In 2000, J. A. Patankar and coworkers prepared 1-substituted-3-(4-methylphenyl)-3, 4-dihydro-4-oxobenzofuropyridazinones 78 in a single step from 7-methoxy-4-(4-methylphenylhydrazono)-1H-pyrano [3, 4-b] benzfuran-1, 3-dione [89].

Nu: =OH, OEt and morpholine
13. Benzofuro pyrimidines

In an attempt to synthesize diphenyl barbituric acid, Bareness and co-workers reported the formation of 1, 2, 3, 4-tetrahydro-2, 4-dioxobenzofuro [2, 3-d] pyrimidine as a byproduct [90].

The chemistry of these compounds received significance recently when Hess and Cronine [91] reported the synthesis of several derivatives of 5, 6, 7, 8-tetrahydrobenzofuro [2, 3-d] pyrimidine by condensing 2-hydroxycyclohexane with foramide. The following compound 79 was found to exhibit relaxing properties on smooth muscles with bronchial dilation and lowering of the arterial pressure by their activity on 3'-adenosine monophosphate.

Japanese workers [92] reported a useful method for the synthesis of various derivatives of the above ring system 79. Their method involves the acetylation and cyclization of 2-amino-3-benzofurancarbonitrile to produce 3-substituted -1, 2-dihydro-1-oxobenzofuro [2, 3-d] pyrimidines 80.
Malik and coworkers reported the synthesis of 2-substituted-3, 4-dihydro-4-oxobenzofuro [3, 2-d] pyrimidines 81 by the reaction of 2-carbethoxy-3(2H)-benzofuranone with amidine in alkaline media [54].

\[
\text{Amidine} \quad \text{Alkali} \quad \text{81}
\]

14. Benzofuroazepines

Some derivatives of benzofuro [2, 3-b] azepine ring system 82 were reported by Granik and coworkers [93, 94]. During their studies on photochemical isomerisation, Becker and coworkers reported the formation of the following derivative of benzofuro [3, 2- b] azepine 83 [95].

15. Benzofurodiazepines

The first member of fused diazepine series, 3,4-dihydro-1H-[1]benzofuro[2,3-e][1,4]diazepine-2,5-dione 84a, 84b was synthesized from ethyl-3-[(chloroacetyl) amino]- 1-benzofuran-2-carboxylate on heating with atropine [96].

Biheterocycles of Benzofuran

In nature, benzofuran compounds linked with heteroaryl system either directly (biheterocycles) or through a carbon or nitrogen bridge are less common. Such ring systems have received considerable interest in recent years due to their physiological properties. Since the work embodied in this thesis deals with heteroaryl substituted
benzofurans, it was felt appropriate to review such works reported so far. While investigating the reactions of naturally occurring furocoumarins and chromones with hydrazine and phenyl hydrazine, Mustafa and coworkers [97] isolated a number of pyrazolyl benzofuran derivatives 85, 86(a-c), 87 and 88.

\[
\begin{align*}
&\text{R} = \text{H, OCH}_3 \\
&\text{R}^1 = \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{CH}_3
\end{align*}
\]

Abdel-Wahab and coworkers reported the synthesis of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles and evaluated their antimicrobial activity 89 [98].

\[
\begin{align*}
\text{Ar} &= \text{Ph, 4-ClC}_6\text{H}_4 \\
\text{Ar}^1 &= \text{Ph, 4- Br-C}_6\text{H}_4
\end{align*}
\]

Manna and Agarwal [99] reported the synthesis of indophenazine 1, 3, 5-trisubstruted pyrazoline derivatives of benzofuran 90 conveniently by both conventional and microwave method and evaluated for antimicrobial activity.
Similar biheterocyclic benzofuran compounds were synthesized by the addition of nucleophilic reagents such as diazomethane, benzonitrile oxide, hydrazine hydrate, phenyl hydrazine, hydroxylamine, thiourea and semicarbazide to benzofuran chalcones. Many compounds containing benzofuran nucleus linked with pyrazolone by an amide bridge were prepared [100]. These compounds were reported as magenta colour couplers for color photography.

El-Zahari and coworkers [101] synthesized different benzofuran-2-yl pyrazolo pyrimidine derivatives 91(a-c) and were found to possess antitumor activity.

![Chemical structures](image)

Abdel-Wahab and coworkers [102] reported the synthesis of potassium hydrazine-carbodithioate by the treatment of acid hydrazides with carbon disulfide in the presence of potassium hydroxide. The reaction of potassium salt with hydrazine hydrate, phenacyl bromide or hydrazonoyl chlorides afforded 1, 3, 4-thiadiazoles 92a and 1, 2, 4-triazole 92b. Reaction of 1,2,4-triazole with phenacyl bromide or hydrazonoyl chlorides afforded the corresponding 1,2,4-triazolo[3,4-b][1,3,4]-thiadiazines 92c. All these new compounds were screened for antibacterial and antifungal activities.

![Chemical structures](image)

Yan Shi et al explained that the compound 93 shows a selective FXa inhibitor relative to trypsin-like serine proteases and is active in rats after intravenous administration by measurement of in vivo clotting time [103].
Samia et al synthesized some novel benzofuran derivatives 94 and studied their potential Anti-HIV-1, anticancer, and antimicrobial activities [104].

\[ R = \text{CH}_2, \text{C}_6\text{H}_5, \text{C}_6\text{H}_5, 4-\text{CH}_3\text{C}_6\text{H}_4 \]

Hutchinson et al synthesized 5-(3-hydroxypropyl)-7-methoxy-2-(3'-methoxy-4'-hydroxyphenyl) benzo[b]furan-3-carbaldehyde 95 and was found to be a potent A1 adenosine antagonist [105]. Luc Pieters and coworkers reported the synthesis of 4-[3-(hydroxymethyl)-5-(3-hydroxypropyl)-7-methoxy-1-benzofuran-2-yl]-2-methoxy phenol and its derivatives 96(a-d). These compounds were found to be useful as potential antitumor agents that inhibit tubulin polymerization and exhibited anti-HIV-1 activity [106].

\[ R = \text{H, OH, OCH}_3 \quad R' = \text{H, CH}_3 \]

Schoepfer and coworkers [107] designed 2-benzylidene-benzofuran-3-ones 97 and 98(a-e) as flavopyridol mimics and these compounds were found to inhibit cyclin-dependent kinases (CDKs) enzymes which play vital role in the cell division of cancer cell.
There are several reports found on 2-substituted benzofurans used as drugs such as Amiodarone 99, a clinically used drug for controlling intractable cardiac arrhythmias [108]. The others compounds 100, 101 are known as inhibitors of receptor kinases that are promising candidates for the treatment of disorders related to vasculogenesis or angiogenesis [109, 110]. 2-Substituted benzofurans can also inhibit HIV-1 reverse transcriptase [111], and act as anti-aging agents [112].
Introduction to coumarin

Distribution, structure and nomenclature of coumarins

The study of coumarin began more than 200 years ago. The name of coumarin is derived from the Caribbean word "coumarou", popular name of the tonka tree of the family *Coumarouna odorata* Aube (*Dipteryx odorata*), from which it was isolated for the first time. The parent heterocycle, coumarin (Figure 1) was first isolated in 1920 as an oxygen heterocycle by Vogel; the systematic name of this compound is 2H-1-benzopyran-2-one [113, 114].

![Figure 1. Structure and numbering of coumarin nucleus](image)

Many compounds, which contain the coumarin moiety exhibit diverse biological activities and, in recent years, there has been a growing interest in their synthesis [115]. Some of these coumarin derivatives have been found to be useful in photo chemotherapy, antitumor and anti-HIV therapy [116], as CNS-stimulants [117], antibacterial, [118] anticoagulants [119] and dyes. Coumarin is extensively occurring in secondary metabolite that occurs naturally in several plant families and essential oils, and has been used as a fragrance in food and cosmetic products.

Naturally occurring coumarin derivatives

Coumarins are widely distributed throughout the plant kingdom, with the vast majority carrying an oxygen substituent at the C-7 position and are present in notable amounts in several species, such as Umbelliferae, Rutaceae and Compositae. 7-Hydroxycoumarin (Umbelliferone) is often regarded as the parent (in a structural and biogenetic sense) of a large number of structurally more complex coumarins [113]. However, the specific roles of these compounds are not well understood and have been the topic of some debate. Numerous coumarins have been isolated since the first example was reported in 1812 [112].
Coumarins have been roughly categorised as follows:

a) Simple coumarins

These are the hydroxylated, alkoxylated and alkylated derivatives of the parent compound coumarin, along with their glycosides.

\[ \text{Novobiocin} \]

\[ \text{4-Hydroxycoumarin} \]

b) Furanocoumarins

These compounds consist of a five-membered furan ring attached to the coumarin nucleus, divided to linear and angular types with substituents at one or both of the remaining benzenoid position. The examples are Psoralene and Angelicin.

\[ \text{Psoralene} \]

\[ \text{Angelicin} \]

c) Pyranocoumarins

Members of this group are analogous to the furanocoumarins, but contain a six-membered ring. Ex: Seselin and Xanthyletin.

\[ \text{Seselin} \]

\[ \text{Xanthyletin} \]

d) Pyrone substituted coumarins

These type of compounds contain substitution on pyrone ring, often at C-3 or C-4 position. Ex: Warfarin.

\[ \text{Warfarin} \]
e) Biscoumarins

This type of coumarins, Dicoumarol was isolated from spoiled sweet clover hay and were discovered in 1941. This discovery led to the synthesis of a series of coumarin derivatives with anticoagulant properties [120].

Dicoumarol

Dimeric coumarin derivatives (phebalin, thamnosin, toddasin) were identified from Rutaceae and synthesized through expedites method [121]. The relative stereochemistries of toddalosin isolated from Toddaliaasiatica, and of edgeworoside C isolated from Edgeworthia chrysantha, were established by X-ray crystallography or from the CD spectrum of the aglycone, respectively [122].

Other interesting dimeric compounds were also isolated and synthesized, namely those described in the review of Estevez-Braun and González [123].

Edgeworoside C

f) Triscoumarins

Recently triscoumarins have been isolated from Daphne mezereum and from Daphne oleoides [122, 124]. It is important to mention that the stereochemistry of the triscoumarin edgeworoside B, isolated from Edgeworthia chrysantha was concluded to be S from the CD spectrum of the aglycone [122].

Edgeworoside B
Human exposure to coumarins from food and cosmetics

Human beings are exposed to coumarin from fragrance use in cosmetic products [125]. Such products include antiperspirant deodorants, bath products, body lotions, detergents, toothpaste, tobacco product, some alcoholic beverages, face creams, fragrance creams, hair sprays, shampoos, shower gels and toilet soaps. The exposure to coumarin from fragrance use in cosmetic products can be estimated in a number of ways. Coumarins are also used in rubber, plastic materials, paints and sprays to neutralize unpleasant odour [126].

Coumarins were banned in the USA in 1954 based on reports of hepatotoxicity in rats, prior to the existence of any carcinogenicity and mutagenicity data and was recommended for withdrawal from use in the UK in 1965 [125]. It is estimated that, the maximal human daily exposure to coumarin from food sources for a 60 kg person is 20 μg/kg/day, and from cosmetic sources 40 μg/kg/day. The total daily human exposure from dietary sources together with fragrance used in cosmetic products is 60 μg/kg/day. No adverse effects of coumarin have been reported with a dose 100 times larger than that contained in food sources [127].

Coumarin comprises a group of natural compounds found in variety of plant sources. The very long association of plant coumarins with various animal species and other organisms through evolution may account for the extraordinary range of biochemical and pharmacological activities of these chemicals in mammalian and other biological systems.

A lot of biological parameters should be evaluated to increase our understanding of mechanisms by which these coumarins act. Coumarins have important effects in plant biochemistry and physiology acting as antioxidants, enzyme inhibitors and precursors of toxic substances. In addition, these compounds are involved in the action of plant growth regulators, the control of respiration, photosynthesis as well as defense against infection. The coumarins have long been recognized to possess anti-inflammatory, antioxidant, antiallergic, anticoagulant, spasmolytic, hepatoprotective, antithrombic, anti-HIV, antiviral and anticarcinogenic activities. The hydroxycoumarins are typical phenolic compounds and therefore, act as potent metal chelators and free radical scavengers. They are powerful chain-breaking antioxidants.
Coumarin and its derivatives have attracted substantial interest in a wide range of research areas from their key role in pharmaceutical agents, such as anti-inflammatory, antioxidant [128], HIV inhibitors [129] and anticoagulants [130] to their widespread industrial use as dye lasers [131]. Coumarin is known to develop tumor, hepatotoxicity, and necrosis in rodents [127]. Various tests have shown that coumarin and its metabolites are nonmutagenic, exert antitumor activity over human tumor cell lines, and do not produce hepatotoxicity even in individuals with deficient 7-hydroxylase activity [132, 133] revealing the nontoxic effect of coumarin to humans. In recent years, there has also been a drive to synthesize coumarin-based organic dyes for use in high-efficiency dye-sensitized solar cells (DSCs) [134, 135].

**Biological importance of coumarin derivatives fused with different heterocyclic nucleus**

Coumarins bearing heterocyclic system fused at C-3 and C-4 positions have been reported. Heteroatoms such as oxygen, nitrogen, sulphur or combinations thereof have been incorporated into the heterocycle.

**Coumarin azetidine**

Mulwad *et al* have synthesized some azetidinones of 4-hydroxy coumarin 102 and screened for antibacterial activity [136].

![Coumarin azetidine](image)

Pawar *et al* synthesized various 4-hydroxy coumarin pyrazole derivatives 103 from 4-hydroxy coumarin chalcones. All the compounds were screened for their antimicrobial activity and the antimicrobial data of the compounds revealed that the compounds having methoxy group i.e. 5-(4-methoxyphenyl)-N-[(3-chloro-2-oxo-4-phenylazetidin-1-ylamino) acetyl]-3-[2H-4-hydroxy-2-oxo-benzopyran-3-yl]-4, 5-dihydropyrazole showed most significant activity [137].
Coumarin pyrazole

Xin-Hua Liu et al, reported the synthesis and molecular docking study of novel coumarin derivatives containing 4, 5-dihydropyrazole moiety 104(a-j) and the synthesized compounds were assayed for telomerase inhibition by a modified TRAP assay [138].

Naceur Hamdi et al, synthesized substituted chromeno [4, 3-c] pyrazol-4(1H)-ones 105(a-c) by the interaction of 3-formyl-4-chloro-coumarin with substituted phenyl hydrazine using triethyl amine as a base and evaluated their antibacterial and DPPH radical scavenging activities [139].

Coumarin oxadiazole

Mashooq et al, synthesized Schiff bases of coumarin-incorporated 1, 3, 4-oxadiazole derivatives 106(a-r). The compounds were screened against bacterial and fungal strains [140].
Samir et al. synthesized 1, 3, 4-oxadiazole fused with coumarin moiety 107 and studied their in-vitro anticancer effect via the standard MTT method against a panel of four human tumor cell lines namely; hepatocellular carcinoma HepG2, lung fibroblasts WI 38, kidney of a normal adult African green monkey VERO, and breast cancer MCF-7 [141].

![Chemical structure of 107]

**Coumarin pyridine**

Khadijah M. Al-Zaydi et al reported the rapid solventless synthesis of mixture of pyridine substituted coumarins 108 by the reaction of enaminones 1 with 2 under microwave irradiation [142].

![Chemical reaction of 108]

Koneni et al. synthesized some new coumarin-pyridine hybrids 109(a-c) and 110(d-m) and were evaluated in primary cultures of rat calvarial osteoblasts in vitro, some of the compounds were potent in stimulating osteoblasts differentiation and mineralization as assessed by the alkaline phosphatase production and alizarin red-S staining assay [143].

![Chemical structures of 109 and 110]

R- Propyl, sec-butyl, ter-butyl;  R'^1- ethyl, methyl;  R'^2- ethyl, methyl;  R'^3- H, methyl
Imtyaz A. Khan et al reported synthesis of an array of angularly fused polycyclic heterocycles 111(a-g) with coumarin, benzofuran and pyridine rings from 4-bromomethylcoumarins and salicylonitrile. All the final compounds were screened for anti-microbial, anti-inflammatory and analgesic activities [144].

\[ R - 7-\text{CH}_3, 7-\text{Cl}, 6-\text{CH}_3, 7-\text{OCH}_3 \]

**Coumarin thiazole**

Nadeem Siddiqui et al synthesized some new coumarin incorporated thiazolyl semicarbazones 112(a-w). The compounds were tested for anticonvulsant activity utilizing pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES) tests. Neurotoxicity of the compounds was also assessed [145].

\[ R' - \text{H, CH}_3, \text{C}_2\text{H}_5 \]

Khalilah et al synthesized thiol-disulfide linked coumarin thiazole derivatives 113 and studied their fluorescent properties [146].

Recently, the synthesis of many substituted coumarin derivatives 114(a-c) having thiazole moiety have been reported in literature which possess antimicrobial, analgesic and anti-inflammatory activities [147, 148].
Coumarin pyrrole

Lokesh Shastri et al synthesized pyrrole bis-coumarins 115 from 1, 4-dicoumarinyl-1, 4-diones by heating in the presence of a catalytic amount of acetic acid and studied their fluorescent properties [149].

The rediscovery of old reactions invented in the middle of the last century have encouraged the researchers to develop new chemistry in terms of atom economy, ecofriendly nature, yield and simplicity. The advantages of 100% atom economy and simple purification method of the resulting products have led to explorations of different catalysts and reaction conditions in accessing compound libraries. These reactions have a high status in synthetic organic chemistry as various agrochemicals, polymers, biochemicals, and functional materials [150-152] have been prepared via these reactions. Synthesis and biological evaluation of novel benzofurans and coumarin either fused or coupled with nitrogen, oxygen and sulphur containing heterocycles are still in need. Hence, an alternative approach regarding synthesis of such compounds has been initiated in our laboratory. In continuation of our earlier work, we have now undertaken a systematic investigation of synthesis and biological investigation of new series of heterocyclic compounds comprising benzofuran and different heterocycles either in fused or coupled form.

The work embodied in this thesis mainly comprises the synthesis of 2-substituted benzofuran and 3-substituted coumarin derivatives. Many different heterocycles comprising nitrogen, sulphur, and oxygen such as Mannich bases, pyridines of bis coumarin, barbiturates, Meldrum's acid, Schiff bases and pyrazoles were synthesized. In addition to this, some imidazo benzothiazole derivatives of benzofuran were also designed. The chemistry of these systems involves considerable biological interest as both benzofuran and coumarin with other heterocyclic nucleus are known to exert biological effects. The interest lies in the present investigation is based on the fact that the chemistry of benzofuran is less explored compared to that of indole and benzo thiophene. On the other hand, interest in the coumarin derivatives is due to easy accessibility with appropriate functionality for further
fusion or coupling with different heterocyclic ring systems like Mannich bases, pyridines and pyrazoles.

Logically, there appears to be at least two different synthetic strategies for the proposed benzofurans/coumarins fused with nitrogen or oxygen heterocycles or biheterocycles as its another partner.

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

b) Benzofuran or coumarin ring system may be fused or coupled on a preformed nitrogen heterocycles with suitable functionalities.

In the present investigation, the synthetic strategy involves the construction of desired nitrogen or sulphur heterocycle on to a preformed benzofuran or coumarin. This is because of easy accessibility of appropriately substituted benzofuran and coumarin derivatives through convenient synthetic methods.

The work carried out in the present investigation have been organized in the following chapters:

Chapter-1 Introduction

Chapter- 2 Synthesis of β-amino carbonyl derivatives containing coumarin and benzofuran nucleus

Chapter- 3 Synthesis of some 2, 6-bis (1-coumarin-2-yl)-4-(4-substituted phenyl) pyridine derivatives

Chapter- 4

Part A: Synthesis of benzofuran barbitone and benzofuran thiobarbitone derivatives

Part B: Synthesis of benzofuran derivatives condensed with Meldrum’s acid

Chapter- 5

Part A: Synthesis of coumarin derivatives fused with pyrazole and indenone rings

Part B: Facile synthesis of benzofuran derivatives fused with pyrazole and indenone rings

Chapter- 6 Synthesis of novel benzofuran derivatives containing thiazolo benzimidazole nucleus

Chapter-7 Evaluation of Biological and pharmacological activities
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Chapter-1

Introduction