1.1. INTRODUCTION

A benzofuran is a bicyclic aromatic heterocyclic compound contains benzene ring fused with a furan ring. It can be differentiated into two kinds depending on the position of the oxygen atom with respect to the bond shared by the benzene and furan rings as benzo\[b\]furans and benzo\[c\]furans. The term benzofuran usually refers to the benzo\[b\]furan (also 1-benzofuran or coumarone) whilst the benzo\[c\]furan is denoted by its trivial name isobenzofuran (also 2-benzofuran) as shown below.

![benzo[b]furan](attachment:benzo_b_furan.png) ![benzo[c]furan](attachment:benzo_c_furan.png)

The relative stability of position isomers assessed by the role of aromaticity in which benzo\[b\]furan is 14.4 kcal/mol more stable than benzo\[c\]furan. The difference was attributed to a large decrease of aromaticity of the benzene ring in benzo\[c\]furan. Indeed, benzo\[c\]furan itself is not stable and rapidly polymerizes, although it has been identified, prepared and trapped at low temperature. This thesis is mainly focused on benzo\[b\]furans.

1.2. IMPORTANCE OF BENZO\[b\]FURAN

Benzofuran formed by the condensation of furan nucleus with benzene ring are not common in the nature. However numerous synthetic benzofuran derivatives found to possess wide range of biological activities. The research work on benzofuran was initially aimed at the isolation of biologically active products possessing furan and benzofuran ring system. The structures of such compounds range from simple 5-methoxybenzofuran to highly complex molecules. A great variety of both synthetic and naturally occurring molecules that include benzo\[b\]furan motif in their structure have been reported to show diverse biological
activities and other special features, which provide them with potential applications in the fields of biomedicine and material sciences. These derivatives exhibit significant activity including antifungal\textsuperscript{7}, antiprotozoal\textsuperscript{8}, antitubercular\textsuperscript{9}, antiinflammatory\textsuperscript{10}, anticonvulsant\textsuperscript{11}, anticancer\textsuperscript{12}, antiHIV\textsuperscript{13}, analgesic\textsuperscript{14}, antiparasitic\textsuperscript{15}, antihyperlipidemic\textsuperscript{16}, antioxidant\textsuperscript{17}, antidiabetic\textsuperscript{18}, antihypertensive\textsuperscript{19}, antiplasmodial\textsuperscript{20}, Alzheimer’s\textsuperscript{21}, vasodilating and hypotensive\textsuperscript{22}, arrhythmic\textsuperscript{23}, pharmaceutical\textsuperscript{24}, anti-histaminic\textsuperscript{25}, antidepressant\textsuperscript{26}, antitumor activities\textsuperscript{27,28}. Some of the derivatives are used in cosmetic formulations\textsuperscript{29}, as synthetic precursors for optical brighteners\textsuperscript{30} and other bioorganic properties\textsuperscript{31}. Moreover, some of the benzofuran derivatives have been demonstrated to be potent topoisomerase I inhibitors\textsuperscript{32}, sigma receptors\textsuperscript{33}, Pim-1 inhibitors\textsuperscript{34}, farnesyl transferase inhibitors\textsuperscript{35}, Histamine H\textsubscript{3} Receptor\textsuperscript{36} and carbonic anhydrase inhibitors\textsuperscript{37}.

On the other hand, this heterocyclic compound used in various branches of chemical research namely in polymers\textsuperscript{38,39}, dye industries\textsuperscript{40,41} and in silver photography\textsuperscript{42,43}. From these vast range of biological effects associated with the benzofuran ring system, this scaffold has been considered as a privileged structure in benzofuran-based medicinal agents. Pharmaceutical chemists still have a challenge to develop more effective and less toxic agents to treat infectious diseases.

In the past decades, a large amount of effort has been invested to develop benzofuran-based compounds as microbial agents that are active on different clinically approved therapeutic targets showing excellent therapeutic potency.

The following section highlights the significance of both synthetic and natural benzofuran derivatives in the field of biological and pharmaceutical.
1.2.1. Benzofuran as antimicrobial agents

V.N. Telveka et al. synthesized a new series of benzofuran-3-carbohydrazide and its analogs in search of new antifungal agents. The newly synthesized compounds [1-3] showed good antifungal activity against Candida albicans.

J. Liu and coworkers synthesized aryl substituted benzofuran derivatives at the C-3 position through a methanone linker and assessed for their in-vitro antibacterial activities against gram-negative and gram-positive bacteria. The compounds [4-6] displayed excellent antibacterial activities with MIC$_{80} = 0.78$-$12.5$ μg/mL.

Whereas compounds [7] and [8], displayed the strain-specific antibacterial activity towards S. aureus with MIC$_{80} = 3.12$-$12.5$ μg/mL.
H.A. Abdel-Aziz et al. performed synthesis of benzofuran-based (1E)-1-(piperidin-1-yl)-N-2-arylamidrazones [9] in search of better antimicrobial agents. The synthesized compounds were screened for their antifungal and antibacterial activities against two filamentous fungi, two yeast, two gram-positive and two gram-negative bacteria.

B.F. Abdel-Wahab et al. synthesized new benzofuran derivatives and evaluated for their antimicrobial activity against gram-positive, gram-negative bacteria and fungi. Compounds [10] and [11] were found to be more active (against C. albicans) compared to the reference drug fluconazole.
A series of new benzofuran derivatives substituted at C-3 position by aryl moiety through methanone linker were synthesized by X. Jiang et al. Newly prepared compounds were screened for their antibacterial and antifungal activities against four bacterial and a fungus strain. Compound [12], displayed the excellent antibacterial activity against S. aureus and MRSA (methicillin resistant staphylococcus aureus) with MIC$_{80}$ values of 0.39 and 0.78 mg/mL respectively.

![Chemical Structure of Compound 12](image)

Compounds [13] and [14] with additional substituents exhibited medium antimicrobial activities against E. coli and B. subtilis with MIC$_{80}$ values from 0.78 to 3.12 mg/mL.

![Chemical Structures of Compound 13 and 14](image)

To elucidate the contribution of benzofuran derivatives as antifungal agents, C.K. Ryu et al. synthesized benzofuran-5-ol derivatives and screened the compounds for their antifungal activity against Candida, Aspergillus species and Cryptococcus neoformans. Most of the compounds showed potent antifungal activity against all tested organisms. The antifungal
activity of compounds [15] and [16] were superior or comparable to standard drug 5-fluorocytosine\textsuperscript{49}.

![Structures of compounds 15 and 16](image)

### 1.2.2. Benzofuran as enzyme inhibitors

L. Pisani and coworkers synthesized 6-substituted-(E)-2-(benzofuran-3(2H)-ylidene)-N-alkylacetamide skeleton to develop selective monoamine oxidase (MAO) inhibitors. The results revealed that the 6-sulfonyloxy derivatives showed prominent affinity and selectivity to MAO-A more than standard drug (Moclobemide), while 6-benzyloxy derivatives showed potent MAO-B inhibitory activity and selectivity. The compounds [17] and [18] showed outstanding MAO-A inhibitory potency (IC\textsubscript{50} for 17 = 9.1 nM and 18 = 11 nM). Compound [19] was emerged as a new class of MAO-B inhibitor (IC\textsubscript{50} = 36 nM)\textsuperscript{50}.

![Structures of compounds 17, 18, and 19](image)

Benzofuran isoxazoline derivatives were synthesized by G. Ahmad \textit{et al.} and screened for their protein tyrosine phosphatases-1B (PTP-1B) inhibitory activity. The compounds [20] and [21] showed good activity (IC\textsubscript{50} for 20 = 76 μM and 21 = 81 μM) compared to standard sodium vanadate\textsuperscript{51}.
In search of potent PTP-1B inhibitors bearing benzofuran, Dixit et al. synthesized various nature-mimicking hydroxybenzofuran methyl ketones and their dimers. The results of protein tyrosine phosphatase-1B inhibitory activity revealed that they display good inhibitory activity, especially dimers [22] and [23] emerged as potent with good inhibitory activity (IC$_{50}$ = 58.8 and 56.3 mM respectively) than their monomers$^{52}$.

In search of new tyrosinase enzyme inhibitors, aurone derivatives have been synthesized and result of the inhibitory activity showed that the compound [24] (75% inhibition at 0.1mM) emerged as most active compared to standard kojic acid$^{53}$ (20% inhibition at 7mM).
1.2.3. Benzofuran as enzyme activators

Phytochemical investigation of *Erythrina abyssinica* by P.H. Nguyen *et al.* gave eight benzofuran derivatives and screened them for adenosine monophosphate-activated protein kinase (AMPK) activation\(^4\). The compounds [25] and [26] showed potent activation of AMPK enzyme at 10 μM.

![Chemical Structures](25.png)

In search of new glucokinase activators, substituted 2-methylbenzofurans were synthesized by J.A. Pfefferkorn *et al.* and subjected them for their glucokinase activation. The result revealed that the compound [27] with \(EC_{50} = 188 \ \mu M\) emerged as a suitable clinical candidate with optimal combinations of potency, activation profile, metabolic stability and solubility\(^5\).

![Chemical Structures](27.png)
1.2.4. Benzofuran as receptor agonist and antagonist

Benzofuran carboxylic acid derivatives emerged as Endothelin (ET) receptor antagonists\textsuperscript{56}. The compound [28] showed a dual ETA/ETB antagonism activity in nanomolar concentration of 23 and 930 nM respectively.

P.G. Wyatt et al. synthesized benzofuran derivatives in search of oxytocin antagonist. The compound [29] was used as a lead to identify potent and selective \textit{in-vitro} oxytocin antagonists\textsuperscript{57}.

Literature survey revealed that piperazine containing 5-benzofuranyl-2-carboxamide with substitution of cyano group at 5\textsuperscript{th} position on the indole ring is most active analogue [30] possessing dual activity as a selective serotonin reuptake and a partial agonist of the serotonin 5-HT\textsubscript{1A} (serotonin 1A) receptor\textsuperscript{58}. The result showed that compound is highly selective for 5-HT\textsubscript{1A} receptor agonist activity in nanomolar concentration and 5-HT\textsubscript{1A}
affinity in subnanomolar with $IC_{50} = 0.2$ nM. 5-HT reuptake inhibition in subnanomolar [RUI = 0.5 nM] and excellent selectivity to dopamine receptor with $IC_{50} = 666$ nM.

![Chemical Structure](image)

**1.2.5. Benzofuran as anti-inflammatory, analgesic and antipyretic agents**

New anti-inflammatory compounds were synthesized by P. Yadav and coworkers containing benzofuran carboxylic acid ester moiety and screened for their anti-inflammatory activity by using rat carrageenan induced foot paw edema model. The results revealed that the compounds [31] and [32] emerged as more active anti-inflammatory agents than standard drug and also emerged as potent cyclooxygenase-2 (COX-2) enzyme inhibitory activity.

![Chemical Structures](image)

2,2-bisaminomethylated aurone analogues were screened against the proinflammatory cytokines [Tumour necrosis factor-α (TNF-α); Interleukin-6(IL-6)]. The compounds [33] and [34] showed the high percentage of inhibition (76-100%) against both the cytokines at 10μM concentration.
In search of new anti-inflammatory agents containing benzo-furan were synthesized and evaluated for their anti-inflammatory activity. Compounds [35] (25% after 4 hr) and [36] (53.54% after 2 hr) were emerged as most active compound compared to standard drug \( \text{Ibuprofen, 67\%} \).

Y.S. Xie \textit{et al.} prepared the library of benzo-furan-2-carboxamide derivatives and discussed their \textit{in-vivo} anti-inflammatory activity along with their analgesic and antipyretic activities\(^6\). Most of the synthesized compounds showed significant analgesic activity. While, the antipyretic activity results showed that the compounds [37-39] exhibited potent antipyretic activity with reduction of rectal temperature more than 58\%.
1.2.6. Benzofuran as anticancer agents

In search of new cytotoxic agents W.C. Wan et al. synthesized a series of novel benzofuran derivatives and screened for in-vitro studies against a panel of human tumor cell lines. The result reveals that the essential requirement for modulating cytotoxicity is the presence of 2-methylimidazole ring and substitution of naphthylacyl or methoxyphenacyl group at 3rd position of the imidazole.

A series of hetero-aromatic benzofuran-2-carboxamide derivatives were prepared by M. Hranjec et al. and evaluated for their in-vitro antiproliferative potency on human tumor cell lines and normal (diploid) human fibroblasts. The compounds shown exerted different antiproliferative mechanisms and also showed detrimental for the antitumor activity when the benzo[b]thiophene replaced by benzo[b]furan.
K. Asoh et al. designed and synthesized a series of farnesyltransferase inhibitors bearing benzofuran nucleus \([45-47]\) using the X-ray structure of human FTase\(^6\). The synthesized derivatives were screened for their enzyme inhibitory activity (FTase/K-ras) and antiproliferative activity against human non-small cell lung carcinoma (QG56).

\[ \text{[45]} \]

\[ \text{[46]} \]

\[ \text{[47]} \]

Y. Chen et al. synthesized a series of benzofuran derivatives and evaluated them against four cancer cells such as HUVEC (Human umbilical vein endothelial cell), Bel-7402, A549 and MCF-7 proliferation. The compound \([48]\) showed remarkable inhibitory activity against HUVEC proliferation and no inhibitory activity against other cancer cells\(^6\).

\[ \text{[48]} \]

Y. Xiang et al. identified benzofuran-2-carboxylic acid \([49]\) through fragment based screening and X-ray structure guided medicinal chemistry optimization as a potent Pim-1 (serine/threonine protein kinase) inhibitors\(^6\).
X.Y. Li et al. reported the synthesis of novel 3-acyl-5-hydroxybenzofurans derivatives by using microwave-assisted method and application of this scaffold as potential drugs for breast cancer. The compound [50] emerged as best against MCF-7 cells with IC$_{50}$ = 43.08 mM.

R. Romagnoli et al. synthesized a new class of 2-(3',4',5'-trimethoxybenzoyl)benzofuran [51] as inhibitors of tubulin polymerization and evaluated for antiproliferative activity, inhibition of tubulin polymerization and cell cycle effects.

I.N. Gaisina et al. reported that the benzofuran-3-yl-(indol-3-yl) maleimides [52] and [53] emerged as potent glycogen synthase kinase-3β inhibitors.
S. Parekh *et al.* synthesized a new series of compounds bearing benzofuran and reported the *in-vitro* effect of synthesized compounds against human cancer cell lines and reversal of multidrug resistance on human MDR1-gene transfected mouse lymphoma cells. The result revealed that the compounds [54] and [55] showed good antiproliferative activity with lowest IC$_{50}$ = 4.569 mg/mL for [55]. The flow cytometric experiment results showed that the compound [55] with FAR value of 29.9 and compound [56] with FAR value of 26.77 emerged as most active MDR reversal agents.
C. Antczak *et al.* identified benzofuran-4,5-diones [57] as the selective Human peptide deformylase (HsPDF) inhibitors and described their selectivity profile in a panel of metalloproteases.

![Chemical structure of benzofuran-4,5-diones](image)

1.2.7. Benzofuran as antiviral agents

A series of benzofuran derivatives were designed by using induced-fit docking program (GENIUS) for hepatitis-C-virus (HCV), NS3-4A serine protease and evaluated for their enzyme inhibitory activity. Compounds [58] and [59] were found to be more active (IC$_{50}$; 58 = 8.07 μM, 59 = 8.59 μM).

![Chemical structures of benzofuran derivatives](image)

A.P. Valiraki and coworkers reported benzofuran derivatives like 1-(7-(dodecyloxy) benzofuran-2-yl) ethanone [60] and 1-(7-(tridecyloxy) benzofuran-2-yl) ethanone [61] exhibited a specific activity against respiratory syncytial virus in Hela.
S.A. Galal *et al.* designed and synthesized new transition metal complexes of benzofuran derivatives [62-64] and screened for their HIV inhibitory activity. The results showed that all of tested compounds were more potent than atevirdine.

### 1.2.8. Benzofuran as antitubercular agent

A new benzofuro[3,2-f]benzopyrans derivatives were synthesized and initial screening of compounds [65] and [66] against two *Mycobacterium* species (*Mycobacterium smegmatis*...
mc2155 and Mycobacterium tuberculosis H37Rv) results showed comparable activity with standard drug (Isoniazide). Both the compounds were then screened against 7 different species of mycobacteria (H37Rv, Beijing, H37Ra, INH resistant, RIF resistant, Mycobacterium bovis BCG, Mycobacterium microti) and showed activity in the 1-10μM range.

A series of novel natural product like 2-substituted-3H-benzofurobenzofurans were designed and synthesized by T. Yempala et al. through molecular hybridization and screened for in-vitro antimycobacterial activity against M. tuberculosis H37Rv. The result revealed that the compound [67] was found to be the most active (MIC = 3.12 mg/mL) and exhibited lower cytotoxicity with good therapeutic index.

J. Renuka and coworkers synthesized ethyl 5-(piperazin-1-yl) benzofuran-2-carboxylate derivatives and evaluated for their anti-tubercular activity. The compound [68] was found to be most active with MIC of 9.18 μM against logphase culture of MTB when compared to novobiocin and ethambutol standards.
Although pharmaceuticals can seem the most prolific field of application of benzo[b]furans, their biological activities have also been applied to the development of agrochemical bioregulators as trypanocidal (antiprotozoal). Insecticidal activities were also identified in some benzo[b]furans. Triazine [69] reported to be herbicide useful in protecting rice paddies\textsuperscript{80}. Benzo[b]furan-2-carboxylic acid derivative [70] was reported as a compound with insecticidal activity against adult sweet potato weevils (\textit{Cylas formicarius elegantulus})\textsuperscript{81}, substituted benzo[b]furan [71] a potential herbicide showing a very strong effect against weeds\textsuperscript{82} and benzofuran carbohydrazide derivative [72] exhibited an excellent larvicidal (insecticidal) activity against beet armyworm (\textit{Spodoptera exigua})\textsuperscript{83}.
In the field of material sciences, it is worth mentioning that several benzo[\textit{b}]furan derivatives have found utility as dyes and photographic materials or as subunits in the preparation of polymers. On the one hand, compounds combining one heterocyclic unit with two benzo[\textit{b}]furanyl substituents like [73] and [74] proved to be adequate fluorescent indicators (dyes) sensitive\textsuperscript{84} to cytosolic concentrations of free Na\textsuperscript{+} and K\textsuperscript{+}. Bis(sulfobenzofuranyl) biphenyls such as [75] have been used as fluorescent brighteners in stable bleach solutions\textsuperscript{85}. On the other hand, the combination of benzofuranamine [76] with some bis anhydrides resulted in polyimides with good glass transition temperatures and solvent resistance\textsuperscript{86}. Poly(4,7-benzofuran vinylene) [77] was prepared in the search for conducting polyphenylenes\textsuperscript{87}.
Benzo[b]furan unit is also present in metal-free organic dyes [78] developed for efficient dye-sensitized solar cells (DSSCs)\(^8\).

\[
\text{NaO}_3\text{S} \quad \text{H}_2\text{N} \quad \text{O} \quad \text{SO}_3\text{Na} \quad \text{NH}_2
\]

It is noteworthy to mention some important examples of clinically approved benzofuran containing drugs were given below.

**Antifungal agents:** Griseofulvin [79] is an antifungal drug.

\[
\text{O} \quad \text{Cl} \quad \text{O}
\]

**CNS stimulant agents:** 5-(2’-aminopropyl)-2,3-dihydrobenzofuran (5-APDB) [80], 6-(2’-aminopropyl)-2,3-dihydrobenzofuran (6-APDB) [81] and 1-(benzofuran-6-yl)-N-methylpropan-2-amine (6-MAPB) [82] are reputed entactogen drug of the phenethylamine and amphetamine classes.
Anti-arrhythmic agents: Amiodarone [83] is used for both ventricular and supraventricular arrhythmias. Dronedarone [84] is mainly used for the indication of cardiac arrhythmias.

Antihypertensive agents: Benziodarone [85] and Cloridarol [86] are used as vasodilators.

Serotonin receptors agonist: Dimemebfe [87] is an agonist of the 5-HT\textsubscript{1A} and 5-HT\textsubscript{2} serotonin receptors.
α-2-adrenergic antagonist: Efaroxan [88] is a α-2-adrenergic antagonist.

Antipsychotic agents: Elopiprazole [89] is a phenylpiperazine class drug and have antipsychotic activity.

Anti-gout agent: Benzbromarone [90] is a uricosuric agent used for the treatment of gout, mainly when first-line treatment fails or produces intolerable adverse effects.
Antidepressant agent: Vilazodone [91] is an antidepressant and used for the treatment of mental depressive disorders.

![Vilazodone](image)

Muscles relaxant agent: Bradanicline (TC-5619) [92] acts as a partial agonist at the α-7 subtype of the neural nicotinic acetylcholine receptors.

![Bradanicline](image)

1.3. PREPARATION OF BENZO[b]FURAN

There are two categories of synthetic approaches towards (multiple) substituted heterocycles. The first category aims at the construction of the heterocyclic core after the addition of substituents and the second category is based on the attachment of substituents to the preformed heterocyclic scaffold. The latest includes traditional aromatic substitution chemistry, direct metalation methods, halogen-metal exchange reactions, cross-coupling reactions, as well as protecting group’s removal\textsuperscript{89}. Many methods are known for the synthesis of benzofuran a selection of some of the reported synthetic approaches for the construction of the benzo[b]furan core are shown in the following section.
1.4. CONSTRUCTION OF THE BENZO[b]FURAN CORE

The retro synthetic approaches discussed below are based on the methods used for the preparation of the benzo[b]furan core as reported in the literature. Most of the methods are based on the construction of the furan ring that is incorporated into a benzene moiety (Scheme-1 A-D), which included an open-chain precursor (usually a substituted phenol derivative) cyclized into the bicyclic aromatic compound. There are fewer methods based on the construction of the benzene ring using starting material comprising furan moiety have also been reported (Scheme-1 E). Alternative approach is based on the transformation of bicyclic oxygen-containing condensed ring systems (Scheme-1 F).

Scheme-1(A-F): Retrosynthetic approaches for preparation of benzo[b]furan ring

1.4.1. Methods based on the O–C2 bond formation (A)

The retro synthetic approaches having a benzenoid scaffold as starting material based on the O–C2 bond discussed below are presented in scheme 1.1.
**Scheme-1.1**: Retrosynthetic approach based on the construction of the O-C2 bond

The most widely used approach in considering the routes based on the O–C2 bond formation, involves the intramolecular addition of the phenolic moiety to a triple C–C bond in a 2-alkynylphenol. The most employed method to carry out this heterocyclization turn to transition metal catalysis using palladium\textsuperscript{90}, copper\textsuperscript{91} or combinations of both\textsuperscript{92} are the most popular ones. In the absence of a transition metal catalyst some of the reagents like sodium, potassium and cesium salts (eg. cesium hydroxide, sodium hydroxide, potassium tert-butoxide and potassium carbonate\textsuperscript{93} and p-toluenesulfonic acid\textsuperscript{94} reported to promote the heterocyclization (Scheme 1.2).

**Scheme-1.2**: Some examples of Pd-Cu catalyzed and transition metal free benzo[b]furan preparation based on the O-C2 bond formation
1.4.2. Methods based on the C2–C3 bond formation (B)

The starting material for the reactions based on this disconnection is mainly ortho-substituted phenyl methyl ether derivatives as shown in scheme 1.3.

Scheme-1.3: Retrosynthetic approach based on the construction of the C2-C3 bond

The ortho functionalities include: aldehydes (formyl) and ketones derivatives. The transformations based on this disconnection are mainly base mediated intramolecular cyclizations. The choice of the one or another of these precursors is made according to the substituents sought in position 2 and 3 of the benzob[b]furan to be formed. Most of these reactions are found as the key benzo[b]furan ring formation step in synthetic routes towards more complex compounds.

In the case of 2-(2-oxoalkoxy)aryl aldehydes or ketones as starting materials, examples of their transformation into benzofuran-2-yl ketones via acid mediated intramolecular cyclizations were described in literature (Scheme 1.4).

Scheme-1.4: Example for acid-catalyzed benzo[b]furan preparation based on the C2–C3 bond formation
Alkyl 2-formylaryloxy or 2-(1-oxoalkylaryloxy) acetates were reported to undergo base-mediated intramolecular cyclization to afford the corresponding 3-unsubstituted (in the case of aldehydes) or 3-substituted (in the case of ketones) benzo[b]furans with an ester group in position 2. The classic base employed to perform these cyclization was sodium (or potassium) ethoxide as shown in the scheme 1.5 (or even methoxide and tert-butoxide)\textsuperscript{96}.

Scheme-1.5: Example for base-catalyzed benzo[b]furan preparation based on the C2–C3 bond formation

1.4.3. Methods based on the C3–C4 bond formation (C)

On looking at the starting material for the reactions based on this disconnection, two groups can be differentiated: the α-aryloxy carbonyl compounds i.e. aldehydes as well as their corresponding diacetals (Scheme 1.6).

Scheme-1.6: Retrosynthetic approach based on the construction of the C3-C4 bond

Different acid-catalyzed cyclizations methods from α-aryloxy aldehydes and their corresponding diacetals leading to benzo[b]furans were reported. These acidic conditions
included the employment of polyphosphoric acid\textsuperscript{97} or Amberlyst-15 (a strongly acidic cation exchanging resin)\textsuperscript{98} (Scheme 1.7).

\begin{equation}
\begin{array}{c}
\text{Scheme 1.7: Example for acid-catalyzed benzo[b]furan preparation based on the C3–C4 bond formation}
\end{array}
\end{equation}

1.4.4. Methods based on the O–C5 bond formation (D)

The starting material for the reaction based on this disconnection is typically a substituted alkyl or aryl benzyl ketone which undergoes an intramolecular \textit{O}-arylation (ring closure reaction) as shown in scheme 1.8.

\begin{equation}
\begin{array}{c}
\text{Scheme 1.8: Retrosynthetic approach based on the construction of the O-C5 bond}
\end{array}
\end{equation}

Starting with the \textit{o}-halobenzyl substituted ketones corresponding benzo[b]furans were prepared via transition metal-catalyzed ring closure reactions using typical transition metals such as copper\textsuperscript{99}, palladium\textsuperscript{100} and to a lesser extent iron\textsuperscript{101} (Scheme 1.9) to perform these transformations. The key cyclization reaction involved the coupling of the enolate oxygen to the transition metal-activated aryl halide.
“Design, Synthesis, Characterization and Biological Evaluation of Pharmacologically important Furan and its Derivatives”

Scheme 1.9: Some examples of Cu, Pd and Fe-catalyzed benzo[b]furan preparation based on the O–C5 bond formation

1.4.5. Methods based on the construction of the benzene ring (E)

As mentioned at the beginning of this section, though scarce in comparison there also exist synthetic strategies for the benzo[b]furan preparation not based on the furan ring construction. They are available from suitably substituted furans by cyclization and generation of the benzene ring. The retrosynthetic approaches having a furanoid scaffold as starting material discussed below are presented in scheme 1.10.

Scheme 1.10: Retrosynthetic approaches having a furanoid scaffold as starting material
Different Diels-Alder reactions were exploited using conveniently substituted furans as starting materials which can act both as dienes and dienophiles. 2-Nitrobenzofuran for example, proved to be efficiently react as dienophile in Diels-Alder reactions with several dienes such as the so-called Rawal’s diene (1-diethylamino-3-tert-butyldimethyl-siloxy-1,3-butadiene). The reaction selectively yields the benzo[b]furan product\textsuperscript{102} (Scheme 1.11).

\[
\begin{align*}
\text{O}_2\text{N-} & \quad \text{NEt}_2 \\
\text{O} & \quad \text{Toluene, reflux, 72h} \\
\text{O} & \quad \text{OTBS} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{OTBS}
\end{align*}
\]

**Scheme-1.11:** Example of benzo[b]furan preparation based on the benzene ring formation via Diels-Alder reaction.

### 1.4.6. Methods based on the transformation of bicyclic oxygen-containing ring systems (F)

The retrosynthetic approaches available for this category presented in scheme 1.12 are quite restricted and only a couple of representative examples will be discussed below.

\[
\begin{align*}
\text{R} & \quad \text{X} \\
\text{X} & \quad \text{Cl or Br} \\
3\text{-halocoumarins} & \\
\text{R} & \quad \text{CO}_2\text{H}
\end{align*}
\]

**Scheme-1.12:** Retrosynthetic approach based on the transformation of bicyclic oxygen-containing ring systems

The most representative transformation of ring contraction reactions is the Perkin rearrangement (coumarin benzofuran ring contraction). This transformation is the conversion of 3-halocoumarins into benzofuran-2-carboxylic acids in the presence of a base
(typically potassium or sodium hydroxide) under heating (traditionally conventional heating\textsuperscript{103}, but more recently also under microwave irradiation\textsuperscript{104}). The proposed mechanism entailed an initial base-catalyzed ring fission followed by a cyclization process leading to the benzo[b]furan moiety, as a result of the attack of the resulting anion over the vinyl halide\textsuperscript{105} (Scheme 1.13).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{X = Br or Cl}};
\node at (2,-0.5) {1) KOH, H\textsubscript{2}O, reflux, 1h};
\node at (2,-1) {2) HCl};
\end{tikzpicture}
\end{center}

\textbf{Scheme-1.13:} Example of benzo[b]furan preparation based on the coumarin-benzofuran ring contraction

\textbf{1.5. OBJECTIVES OF THE PRESENT STUDY}

Researches have so far demonstrated that the antimicrobial activities of benzofuran families are a combination of substitutions at C-2 and C-3 positions of the benzofuran ring. Keeping in view of synthetic strategies, biological importance of benzofuran derivatives and inspired by the scope of research in this field, we have carried out the research work on the synthesis of benzofuran and its derivatives resulting in C-2 and C-3 substitutions, individually and collectively. We have initiated a study focusing on substitutions at the C-2 as well as C-3 position of the benzofuran ring. Hence, the present research work is aimed at the synthesis of new benzofuran derivatives using different conditions and evaluation of biological activities of the synthesized compounds.

The results of present scientific work carried out in this regard have been presented in four chapters for the convenience of reading.
Chapter-2: Synthesis and characterization of Bis-tert-butyl-2-(di-6-hydroxybenzofuran-3-yl) ethylcarbamate [5a], 2-(6-hydroxy-1-benzofuran-3-yl) acetate [6a-c] and 2-(6-hydroxy-1-benzofuran-3-yl) acetamide [7a-d] derivatives

Chapter-3: Synthesis and characterization of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] and 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-phenylpropenone [5a-f] derivatives

Chapter-4: Synthesis and characterization of symmetric (1, 1-dibenzofuran-2-yl) ethyl terephthalamide [4a-e] derivatives

Chapter-5: In-vitro antimicrobial activity, in-silico ADMET and molecular docking studies of newly synthesized benzofuran derivatives.
1.6. REFERENCES


“Design, Synthesis, Characterization and Biological Evaluation of Pharmacologically important Furan and its Derivatives”


