Synthetic Methods for Novel Benzofuran Derivatives and their Biological Activities

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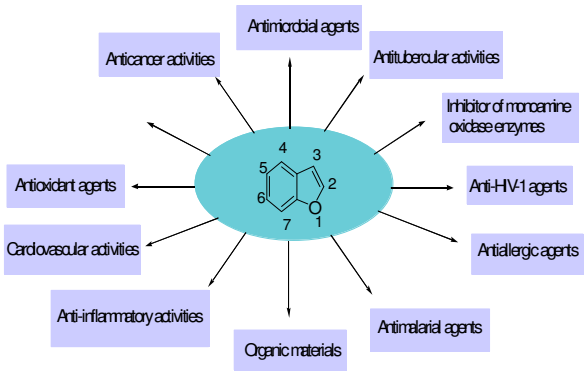
Abstract:

Benzofuran is the heterocyclic compound consisting of fused benzene and furan rings. The benzofuran moiety is widely distributed in both natural and artificial molecules. Substituted benzofurans are pharmaceutically important heterocycles that display numerous biological activities such as antimicrobial, antifungal, anti-HIV, anticancer, antimalarial, anti-inflammatory activities. Some derivatives of benzofurans are also used as organic materials due to their optical and electronic properties. Owing to their broad spectrum applications, it is of great significance to develop systematic and novel approaches to benzofurans. During the past decades, many synthetic efforts have been devoted so far to the synthesis of benzofuran derivatives. The present review highlights the recently synthesized benzofurans and their biological activities.

বেনজোফিউরান একটি হেটোরোসাইক্লিক শ্রেনীর যৌগ যাহার মধ্যে একটি বেনজিন বলয় এবং একটি ফিউরান বলয় পরস্পরের সহিত যুক্ত থাকে।এই বেনজোফিউরান নিউক্লিয়াসটি বহু প্রাকৃতিক এবং কৃত্রিমভাবে সংশ্লেষিত জৈব যৌগের মধ্যে দেখতে পাওয়া যায়।বহু গ্রুপ যুক্ত বেনজোফিউরান বিবিধ ঔষধজাত গুনাগুন দেখায়।কয়েকটি গুনাগুন হল-জীবানু বিরোধী, ছত্রাক বিরোধী, এইচ আই ভি বিরোধী, ক্যানসার বিরোধী, ম্যালেরিয়া বিরোধী ও বেদনা নাশক। কিছু বেনজোফিউরানজাত পদার্থ সরাসরি জৈব পদার্থ হিসেবে ব্যবহৃত হচ্ছে, কারন ইহারা আলোক এবং বৈদ্যুতিন ধর্ম প্রকাশ করে। বেনজোফিউরানজাত পদার্থের বহুবিধ ব্যবহারিক প্রয়োগের কারনে ইহাদের উৎকৃষ্ট এবং উপযোগী সংশ্লেষনের তাৎপর্য্য আছে।গত কয়েকদশক ধরে বিভিন্ন সংশ্লেষন পদ্ধতি আবিষ্কৃত হয়েছে।বর্তমান এই পর্যালোচনায় কিছু সাম্প্রতিক সংশ্লেষন পদ্ধতি এবং তাহাদের জৈব ক্রিয়ার ফলাফল তুলে ধরা হয়েছে।

Keywords: Benzofuran, ring-closing metathesis, Pummerer annulation, cross-coupling, anionic annulation.



1. Introduction:

Benzofuran moiety constitutes the core of several interesting pharmacologically active natural products and artificial molecules. Several derivatives of benzofuran display different biological activities which includes antimicrobial,[1a,b] antifungal,[1c] antitubercular,[1c,d] antiprotozoal,[1e] anti-HIV-1, anticancer,[1f,g] antimalarial,[1g] antiretroviral,[1h] antioxidant,[1i] cytotoxic,[1j] anticonvulsant [1k] and anti-inflammatory[1l] activities. Some derivatives of benzofurans are also used as organic materials due to their optical and electronic properties.[2] In particular, several oxygenated benzofuran derivatives are known to be biologically active compounds.[3] In addition, several benzofuran ring systems are widely distributed in nature, e.g. khellinone (**1**)[4a], khellin (**2**)[4b], visnagen (**3**)[4b], concentricolide (**4**),[4c] ailanthoidol (**5**),[1a] (–)- (+)-frondosin B (**6a**)[5] and dehydrodiconiferyl alcohol (**6b**)[6] (Figure 1).

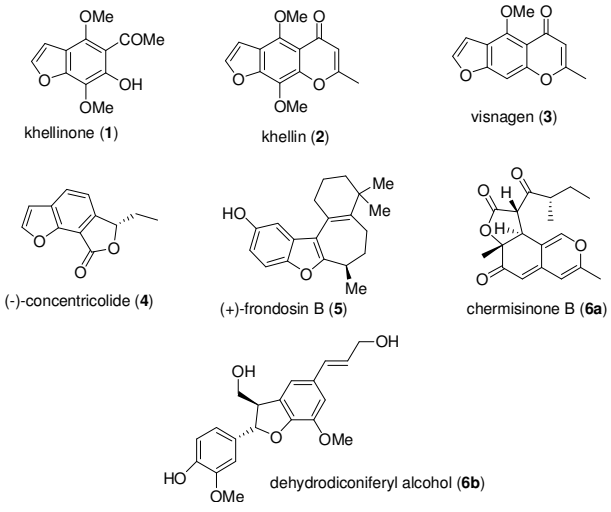


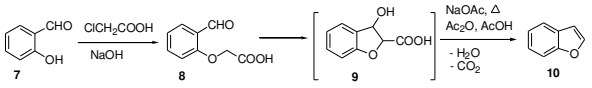
Figure 1: Selected examples of some biologically active benzofurans

2. Synthetic methods of benzofurans:

The synthetic challenges coupled with the biological activity have led to the development of many important synthetic methodologies and total syntheses in the field of benzofurans. Since the chemistry of benzofuran derivatives has been reviewed several times in the recent past, few important and selected approaches are highlighted in the following sections. The existing synthetic approaches towards the benzofuran framework can be divided into two categories based upon their starting material employed. The first group involves the formation of annellated furan ring using intramolecular cyclization of benzene derivative. On the other hand, the reverse approaches, the second group creates a benzene ring on a furan precursor.

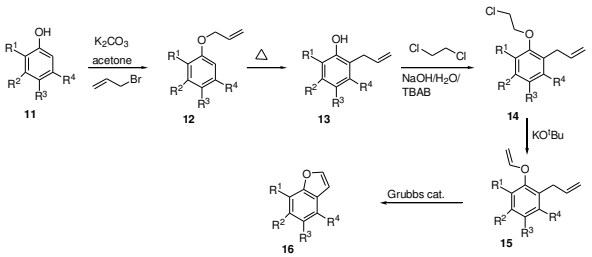
2.1 From benzene derivatives:

A. W. Burgstahler and L. R. Worden described the synthesis of benzofuran starting from salicylaldehyde.[7] Treatment of salicylaldehyde (**7**) with chloroacetic acid in presence of sodium hydroxide produced aryloxyacetic acid **8**. Cyclisation of compound **8** with a mixture of acetic anhydride, acetic acid and sodium acetate provided benzofuran **10** in 65% yield (Scheme 1). The reactions proceed by an internal Perkin's reaction followed by decarboxylative dehydration.



Scheme 1

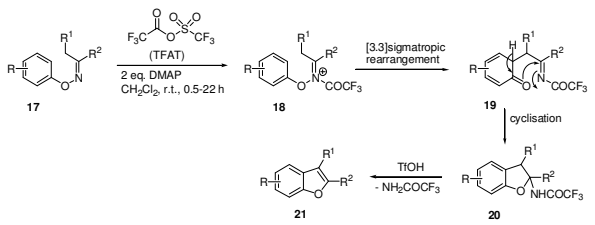
E-C Wang et al reported a new synthesis of benzofurans from phenol via Claisen rearrangement and ring-closing metathesis (RCM).[8] Various allyl phenyl ethers (**12**) were prepared from O-alkylation of various phenols (**11**) with corresponding alkyl halides. The allyl phenyl ethers underwent [3,3] sigmatropic (Claisen) rearrangement to furnish O-allylphenols (**13**), respectively which then, (**13**) underwent O-chloroethylation with an excess of 1,2-dichloroethane, sodium hydroxide in water, and terabutylammonium bromide as phase catalyst to give monoalkylated products (**14**). Treatment of compound **14** with potassium tertbutoxide in THF underwent isomerization of the allyl group together with 1,2-elimination of O-(2-chloroethyl) group to build up O-vinyl and C-propenyl function as precursor (**15**) for RCM. Finally, the cyclization of compound **15** with Grubbs' catalyst underwent RCM to give various benzofurans (**16**) in good overall yields (Scheme 2).



Scheme 2

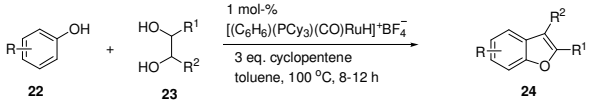
In 2007, T. Naito et al developed an efficient synthetic method for the preparation of benzofurans utilizing [3,3]-sigmatropic rearrangement triggered by *N*-trifluoroacetylation of oxime ethers.[9] Treatment of *N*-trifluoroacetyl-ene-hydroxylamine **17** with TFAT-DMAP produced compound **18** which underwent [3,3]-sigmatropic rearrangement to give compound **19**. Subsequent cyclisation of

compound **19** followed by elimination afforded desired benzofuran **21** in good yield (Scheme 3).



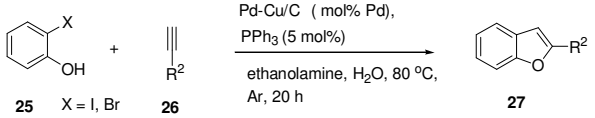
Scheme 3

Recently, C. S. Yi and co-workers reported a well-defined cationic Ru-H complex catalyzed transformation of phenols to benzofurans. The dehydrative C-H alkylation reaction of phenols (**22**) with 1,2-diols (**23**) in presence of 1 mol% of cationic Ru-H complex followed by annulation delivered benzofuran derivative (**24**) in good yields (70-94%).[10] The catalytic C–H coupling method employs cheap starting materials, exhibits a broad substrate scope, and liberates water as the only byproduct (Scheme 4).



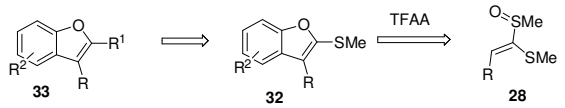
Scheme 4

F-X Felpin et al described the preparation of benzofurans in pure water by using a new heterogeneous Pd-Cu/C catalyst.[11] The Sonogashira alkynylation of 2-iodo phenol **25** with alkynes **26** followed by cyclization provided corresponding benzofurans **27** in good yields (64-98%) (Scheme 5). This procedure allows the preparation of heterocycles with good yields and is tolerant to a wide variety of functional groups.



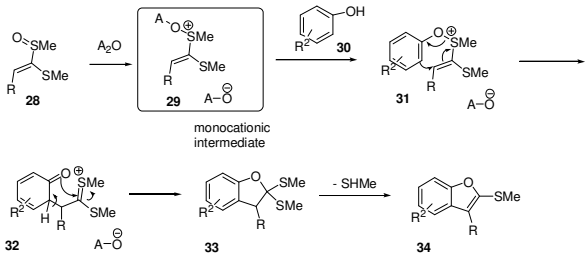
Scheme 5

H. Yorimitsu et al have synthesized various substituted benzofurans **33** through extended Pummerer annulation/cross-coupling sequence of simple phenols **30** with ketene dithioacetal monoxides **28** (KDM) in presence of trifluorocaetic anhydride (TFAA) (Scheme 6).[12]



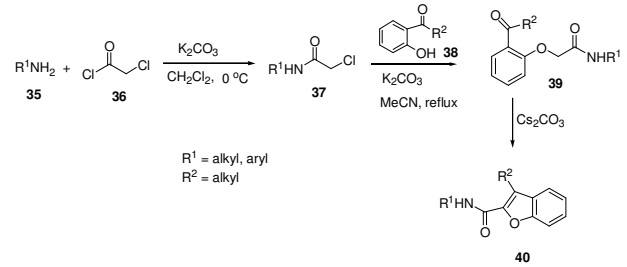
Scheme 6

A proposed mechanism of the extended Pummerer annulation with the acid anhydride A_2O is shown below. First, the KDM (**28**) is activated with A_2O to give the monocationic intermediate **29**. The intermediate **29** reacts with a phenol **30** to give **31**. Charge accelerated [3,3]-sigmatropic rearrangement of **31** provides **32** which smoothly cyclizes into **33**. Methanethiol is eliminated from **33** to afford the corresponding substituted benzofuran **34** (Scheme 7). The method is powerful enough to synthesize biologically active natural products as well as fluorescent benzofuran derivatives.



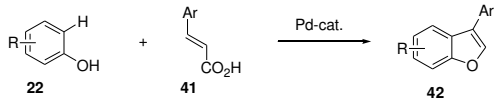
Scheme 7

Recently D-S Shin and co-workers reported an efficient protocol for the synthesis of a novel variety of benzofuran derivatives.[13] Amination of chloroacetyl chloride with primary amine **35** in presence of K_2CO_3 produced *N*-substituted-2-chloroacetamide **37**. O-alkylation of readily available *o*-hydroxy aryl ketone **38** by compound **37** in presence of K_2CO_3 gave substituted acetamide **39** in good yield. Finally, cyclisation of compound **39** in presence of cesium carbonate provided substituted benzofuran **40** in relatively short time (Scheme 8).



Scheme 8

Very recently, D. Maiti et al described an efficient synthesis of 3-substituted benzofurans (**42**) using palladium catalyzed intermolecular annulation of cinnamic acids (**41**) and phenols (**22**).[14]

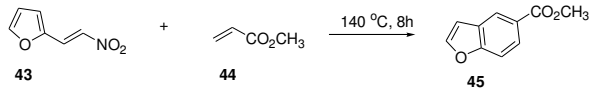


Scheme 9

2.2 From furan precursor:

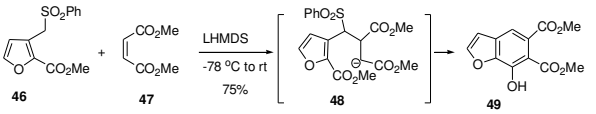
Benzofuran synthesis starting from a furan precursor has been much less explored to till date. Few literature available synthetic methods are highlighted in the following section.

R. S. Kusurkar et al reported a novel synthetic method for benzofurans using Diels-Alder reaction of nitro vinyl furan **43** with various dienophiles.[15] Diels-Alder reaction between compound **43** and methyl acrylate (**44**) produced 5-carbomethoxy benzofuran **45** in 61% yield (Scheme 10).



Scheme 10

Recently, D. Mal and co-workers reported a straightforward route to 7-hydroxy benzofuran derivatives using anionic annulation strategy.[16] When furoate **46** was submitted to annulation with dimethyl maleate (**47**) in the presence of lithium hexamethyldisilazide (LHMDS) furnished 7-hydroxybenzofuran **49** in 75% yield (Scheme 11).



Scheme 11

3. <u>Biological activity:</u>

In vitro cytotoxic and growth inhibitory activities of naturally occurring khellin (**2**) and other newly synthesized derivatives were investigated against HEPG2 cell line in comparison with the activity of the known anticancer Doxorubicin (DXR) as a reference drug.[17] The cytotoxic activities of the tested compounds were expressed as IC50 which is the concentration required for 50% inhibition of cell viability. It is evident that the tested compounds showed antitumor activities with IC50 values ranging from 2.1 to 12.2 µg/ml and reaching about one third that of DXR (IC50 = 0.6 µg/ml). In general, among the arylvinyl derivatives of khellin, compounds containing 1,5-diphenyl pyrazolyl, 4- nitrophenyl, furanyl and 1(2)-naphthalenyl moieties showed pronounced cytotoxic activities confirmed by the least IC50 values (2.1-4.3 µg/ml).

3.1 Methodology of Sulphorhodamine B (SRB) assay

This method was carried out according to the reported method (Skehan and Storeng, 1990). Cells were used when 90% confluence was reached in T25 flasks. Adherent cell lines were harvested with 0.025% trypsin. Viability was determined by trypan blue exclusion using the inverted microscope. Cells were seeded in 96-well micro titer plates at a concentration of 5x104-105 cell/well in a fresh medium and left to attach to the plates for 24 hours. After 24 hours, cells were incubated with the appropriate concentration ranges of drugs, completed to total of 200 µl volume/well using fresh medium and incubation was continued for 24, 48 and 72 hours. Control cells were treated with vehicle alone. For each drug concentration (5.0, 12.5, 25.0 and 50.0 µg/ml), 4 wells were used. Doxorubicin was used as a positive control at the same concentration range. Following 24, 48 and 72 hours treatment, the cells were fixed with 50 µl cold 50% trichloroacetic acid for 1 hour at 4 °C. Wells were washed 5 times with distilled water and stained for 30 min. at room temperature with 50 µl 0.4% SRB dissolved in 1% acetic acid. The wells were then washed 4 times with 1% acetic acid. The plates were air-dried and the dye was solubilized with 100 µl/well of 10 mM tris base (PH 10.5) for 5 min. on a shaker at 1600 rpm. The optical density (O.D.) of each well was measured

spectrophotometrically at 564 nm with an ELIZA microplate reader. The mean background absorbance was automatically subtracted and means values of each drug concentration was calculated. The experiment was repeated three times for each cell line. The percentage of cell survival was calculated as follows: Survival fraction= O.D. (treated cells) / O.D. (control cells). The relation between surviving fraction and drug concentration was plotted to get the survival curve. The concentration required for 50% inhibition of cell viability (IC50) was calculated.

4. Conclusions:

Benzofuran are the important group of heterocyclic compound, several derivatives of which have been marked as biologically and pharmacologically active product. Many synthetic methods have been reported so far to the synthesis of benzofuran derivatives. In view of continued development on synthetic strategies in this field, I have attempted to present few recent methodologies of benzofuran synthesis. Herein, I additionally overviewed the biological activities of some benzofuran natural products and their derivatives. It is hoped that this short review will generate renewed academic interest in the chemistry of benzofurans, and will enhance advancing the synthetic methods.

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Bidyut Kumar Senapati is an Assistant Professor at Prabhat Kumar College, West Bengal, India. He received his B.Sc. Hons. in Chemistry (1999, 1st class, 3rd rank) from the Midnapur College, Vidyasagar University. He scored 99.03 percentile in GATE examination (rank 19), 2001. He also awarded junior research fellowship by UGC-CSIR in 2000. After being awarded M. Sc. Degree (2001, 1st class, 2nd rank) from the Vidyasagar University, he joined the department of chemistry, Indian Institute of Technology, Kharagpur in 2001 for his doctoral research under the supervision of Prof. Dipakranjan Mal. He received his Ph. D. degree from the same institute in 2007. His areas of specialization have included the synthesis of natural products, furanosteroids, carbazole chemistry and catalytic asymmetric transformations. Prof. Senapati did postdoctoral work at the Sungkyunkwan University, Suwon, South Korea (2008-2010, under the supervision of Prof. Do Hyun Ryu). His regular teaching responsibilities include organic chemistry, advanced organic chemistry and special topics in pericyclic reactions.

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