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Review Article

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Review on Synthetic Routes for Synthesis of Benzofuran-Based Compounds

Kishor R More*

Ipca Laboratories Ltd, Chemical Research Division, Kandivli Industrial Estate, Kandivli (W), Mumbai, India

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ABSTRACT

Benzofuran and its derivatives are widely used for industrial purposes and also exhibit a broad range of biological activities. This review compiles examples synthetic methodologies used for the preparation of benzofurans are also described.

Keywords: Benzofuran; Synthesis; Rearrangement; Cyclization

INTRODUCTION

Polycyclic and or aromatic compounds containing furan ring [1], constitute a group of compounds which are occurs widely throughout the plant kingdom. The origin of furan chemistry has been outlined by partington [2]. When Scheele and co-worker subjected mucic acid to dry distillation, they obtained first furan derivative, pyromucic acid known as furan-2-carboxylic acid or 2-furoic acid. Furan itself was not described until Limpricht isolated [3] it from pinewood. It was also obtained by heating the barium salt of 2-furoic acid. The furan ring has received remarkable attention, since this five member heterocyclic ring encountered as a building block in a variety of natural and synthetic products. The furan derivatives include the benzofused compounds which exist in two forms 1-benzofuran and 2-benzofuran. Usually these are called as benzofuran and isobenzofuran respectively (Figure 1).

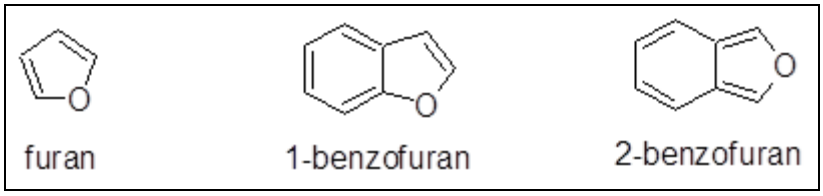

Figure 1: Furan derivatives

Methods of Synthesis of Benzofuran Derivatives

Benzofuran was first synthesized by Perkin [3] from coumarin as shown in Figure 2. Ketoesters derived from the acylation of *o*-hydroxyacetophenone with aliphatic as well as aromatic acid chlorides undergo intramolecular cyclization in the presence of low-valent titanium [4] to afford benzofurans in good yields.

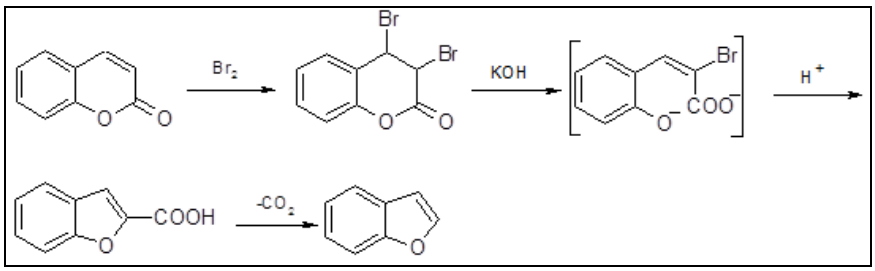

Figure 2: Perkin benzofuran synthesis

The reduction of titanium trichloride with dry zinc powder in refluxing THF takes place in the presence of the ketoester which simultaneously cyclizes as the titanium catalyst is formed, rendering the pre-reduction of titanium trichloride in a separate step. On account of oxophilicity and electron transfer capability of low valent titanium, it promotes the reductive deoxygenation of carbonyl compounds to olefins, generally referred to as "McMurry reaction" [5] (Figure 3).

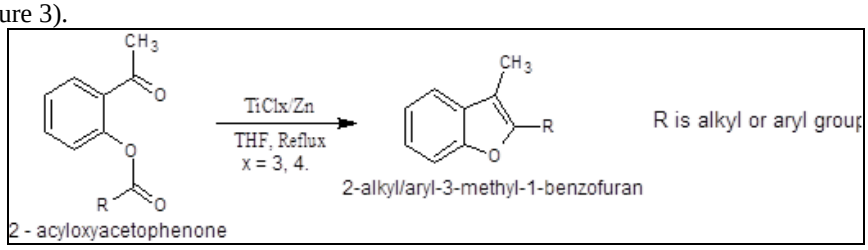

Figure 3: McMurry reaction approach for benzofuran synthesis

Recently, other less popular approaches for the synthesis of 2-substituted 1-benzofurans include *p*-toluenesulfonic acid-mediated cyclization of *o*-(1-alkynyl)anisoles to obtain 2-arylsubstituted benzofurans [6], rearrangement and cyclization reactions of 2-hydroxybenzophenones with Corey-Chaykovsky reagent [7], cyclization of 2-acyloxy-1-bromomethylarenes with $Cr(II)Cl_2/BF_3$-OEt_2 catalyst [8], boron tribromide-promoted tandem deprotection-cyclization of 2-methoxyphenylacetones [9], (2-methoxyphenyl) methanols [10], and 2-hydroxy-3-arylpropenoic acids [11] leading respectively to 2-methyl, 2-carboxy, and 2-arylbenzofurans. However, these methods often require expensive catalysts and/or multi-step synthesis. (Figure 4) 2-(2-Methoxyaryl)-1-arylethanone derivative [12] when subjected to hydrogenation by passing hydrogen gas in presence of palladium based on charcoal in ethanol containing hydrochloric acid produces 2-arylbenzofuran.

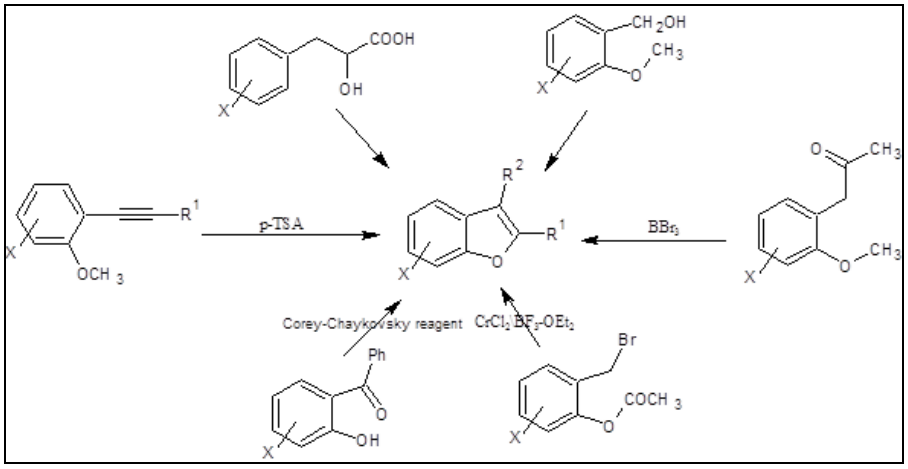

Figure 4: Synthesis of various substituted benzofuran derivatives

In an alternative approach, 2-(2-Methoxyaryl)-1-arylethanone derivative are cyclised using HI in acetic acid to give 2-arylbenzofurans [13,14]. Another route involves [15] cyclisation via condensation reaction of phenacyl phenyl ether by using PPA in xylene at 130°C or same condensation has been carried out by using acids [16] to forming 2-arylbenzofurans. The most commonly used approach [17] for the synthesis of 2-arylbenzofuran was the coupling of cuprous aryl acetylenes with o-halophenols in pyridine under reflux conditions.

The aryl acetylenes were treated with o-halophenols in presence of Cu (I) iodide and triethylamine using $(PPh_3)_2PdCl_2$ as a catalyst also forming 2-arylbenzofurans [18]. During this conversion, reaction proceeds through cuprous aryl acetylene intermediate. The benzofuran was undergoes arylation [19] at 2-position by using arylmercuric halide in presence of Li_2PdCl_4. But this approach for the synthesis of 2-arylbenzofuran was not convenient because of poisonous mercuric by-products. Another photolytic synthesis approach has also been used for the synthesis of 2-arylbenzofuran. β,β-Bis-(o-methoxyphenyl)vinylbromides undergoes photolysis [20] in presence of benzene to furnish 2-arylbenzofuran. Benzyloxybenzaldehydes [21-23] were obtained by the benzylation of substituted salicyladehydes (ortho position was not substituted) on reaction with sodium methoxide in DMF under reflux conditions yields 2-arylbenzofuran. In another approach, benzyloxybenzaldehydes are refluxed with potassium carbonate in methanol to obtain 2-arylbenzofuran. There are literature known for the synthesis of 2-arylbenzofuran from 2-hydroxystilbenes. One of the approach [24] involves the reaction of 2-hydroxystilbenes with lead tetra-acetate in benzene at cold condition (temperature should be maintained at 17-18°C) forming 2-arylbenzofuran. In another approach [25] the protected 2-hydroxystilbenes were subjected to hydrogenation followed by the oxidation (aromatisation) using DDQ to 2-arylbenzofuran. In some known synthesis of 2-arylbenzofuran, intramolecular condensation of Wittig reagent was employed. The o-acyloxybenzylidene phosphoranes undergoes intra-molecular condensation [26] in presence of base in toluene under reflux conditions (Figure 5). Nayak and Banergi [27] have been achieved the synthesis of 2-arylbenzofuran from o-aryloxy acetophenones using titanium (IV) chloride and Zinc in dioxane under reflux conditions. The o-Methoxybenzoins in presence of excess of 47% of hydroiodic acid in glycial acetic acid undergoes demethylation followed by cyclisation to 2-arylbenzofuran [28]. The Copper-acetylide approach has been widely used for the synthesis of 2-arylbenzofuran-5-carbaldehyde involving either multistep sequence of reactions with low yields. In view of the importance of 2-aryl/2-alkyl-1-benzofuran-5-carboxaldehyde, for the synthesis of naturally, synthetically and biologically important benzofuran compounds, it can be synthesised by number of ways. Some of them are described are described as follows (Figure 5).

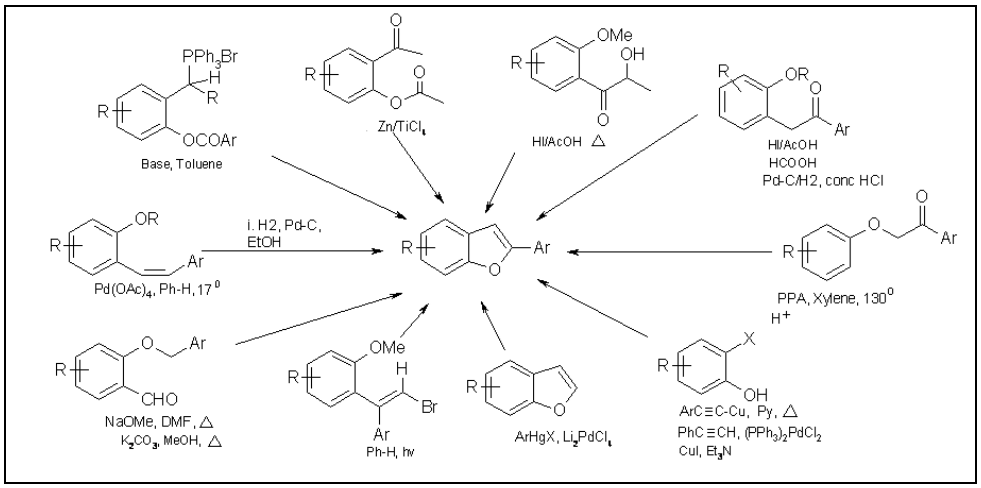

Figure 5: Methods of the synthesis of 2-alkyl/2-arylbenzofurans derivatives

Condensation of Organo Copper Acetylenes with 2-halophenols

The 2-Aryl-1-benzofuran-5-carboxaldehyde has been synthesised by using organocuprate and 2-halophenol [29]. The steps involved in this route are shown in Figure 6.

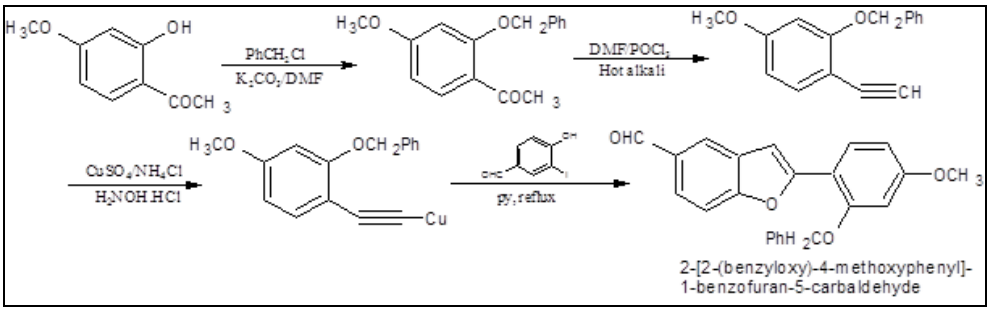

Figure 6: Synthesis of 2-Aryl-1-benzofuran-5-carboxaldehyde

The Cu(I)-2-benzyloxy-4-methoxyphenyl acetylide obtained from 2-hydroxy-4-methoxyacetophenone in three steps condensed with 3-iodo-4-hydroxybenzaldehyde in presence of pyridine to get 2-[2-(benzyloxy)-4-methoxyphenyl]-1-benzofuran-5-carbaldehyde. 2-(3-formyl-2,4,6-trimethoxyphenyl)-1-benzofuran-5-carbaldehyde [30] (Figure 7), 7-methoxy-2-(3,4-methylenedioxyphenyl)-1-benzofuran-5-carbaldehyde [31] (Figure 8), 7-iodo-2-phenyl-1-benzofuran-5-carbaldehyde [32] (Figure 9) and 2-(4-benzyloxyphenyl)-7-methoxy-1-benzofuran-5-carbaldehyde [33] (Figure 10) has been synthesised by similar approach.

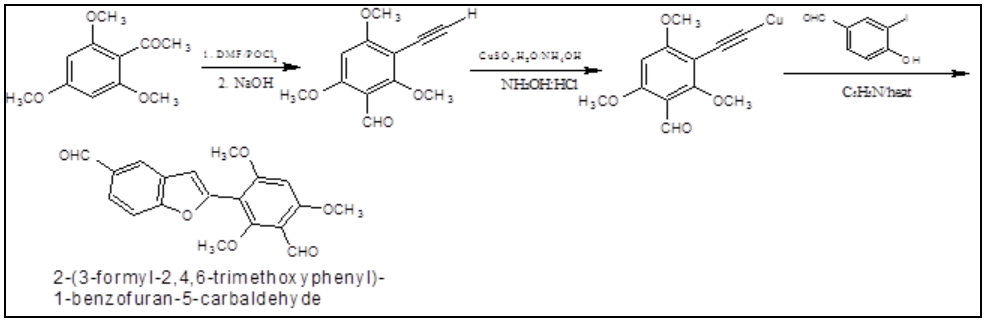

Figure 7: Synthesis of 2-(3-formyl-2,4,6-trimethoxyphenyl)-1-benzofuran-5-carbaldehyde

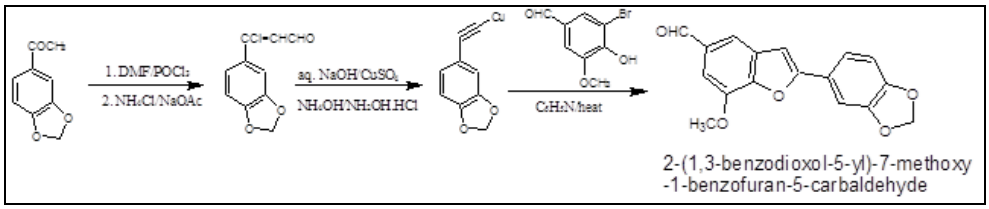

Figure 8: Synthesis of 7-methoxy-2-(3,4-methylenedioxyphenyl)-1-benzofuran-5-carbaldehyde

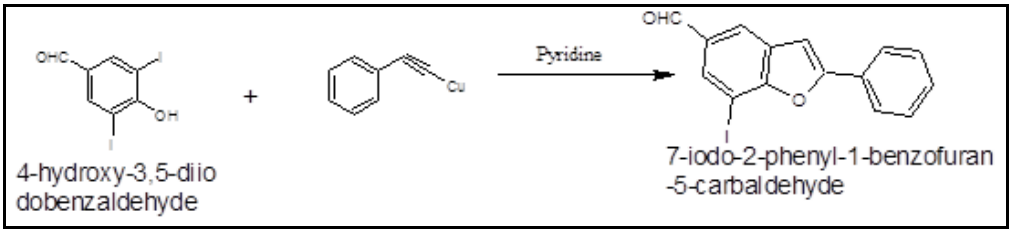

Figure 9: Synthesis of 7-iodo-2-phenyl-1-benzofuran-5-carbaldehyde

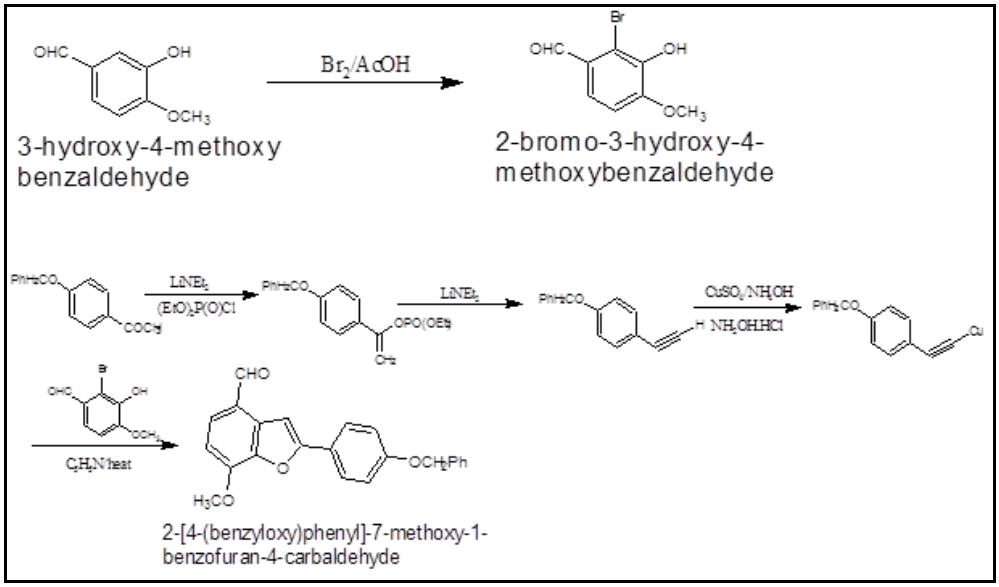

Figure 10: Synthesis of 2-(4-benzyloxyphenyl)-7-methoxy-1-benzofuran-5-carbaldehyde

Condensation of Aryl Acetylene and 2-halophenols in Presence of Organo-Pd Catalyst

The 7-Methoxy-2-phenyl-1-benzofuran-5-carbaldehyde has been synthesized by coupling of 5-iodo vanillin with phenyl acetylene in presence of Pd-catalyst and copper (I) iodide [34] as co-catalyst (Figure 11).

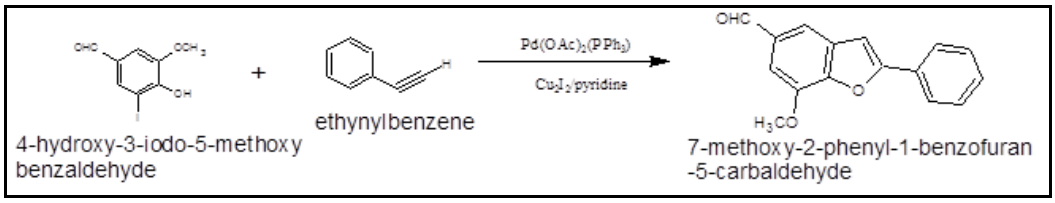

Figure 11: Synthesis of 7-methoxy-2-phenyl-1-benzofuran-5-carbaldehyde

By using 2-benzyloxyacetophenone oxime:

The 2-aryl-5-formyl-1-benzofuran synthesized from 2-hydroxyacetophenone [35] by the series reactions shown in following Figure 12. The hydroxyl group of 2-hydroxyacetophenone has been protected to benzyloxy group and then converted into oxime and then into O-aryl oxime by the treatment of NaH and aromatic haloaldehyde. The O-aryl oxime on reaction with HCl-AcOH, provided 7-hydroxy-2-(2-benzyloxyphenyl)-1-benzofuran-5-carbaldehyde.

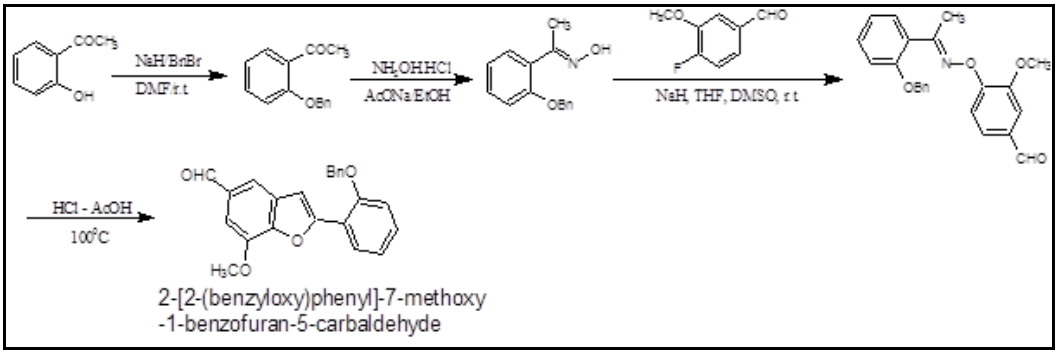

Figure 12: Synthesis of 2-aryl-5-formyl-1-benzofuran

By cyclisation:

The 2-cyclopentyl-7-methoxy-1-benzofuran-4-carbaldehyde has been synthesised from isovanillin and ethynyl alcohol [36]. The steps involve in this route are represented in Figure 13. The ethynyl cyclopentanol reacts with isovanillin to give an ether intermediate followed by cyclisation to produce the 2-cyclopentyl-7-methoxy-1-benzofuran-4-carbaldehyde.

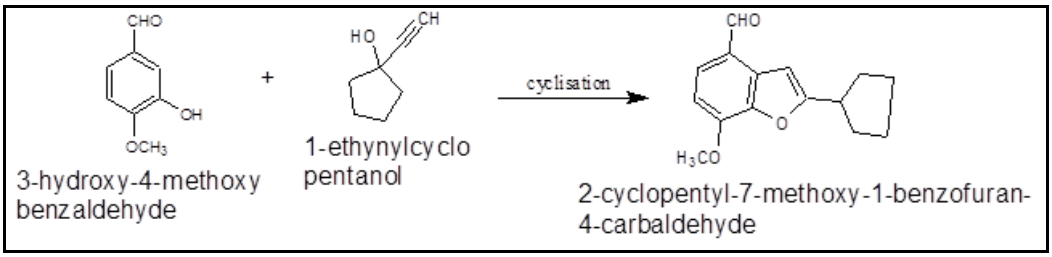

Figure 13: Synthesis of 2-cyclopentyl-7-methoxy-1-benzofuran-4-carbaldehyde

By intramolecular condensation of arylalkynyl ether:

Synthesis of the 7-methoxy-2-methyl-1-benzofuran-5-carbaldehyde (useful intermediate for the synthesis of naturally occurring coumarin derivative) has been achieved [37] from vanillin as starting material shown in Figure 14. Vanillin on reaction with propargyl bromide in DMF in presence of K_2CO_3 gives propargyl ether, which was then converted to 7-methoxy-2-methyl-1-benzofuran-5-carbaldehyde. The last step of the reaction is cesium fluoride mediated Claisen rearrangement used for the construction of 2-methylbenzofuran ring.

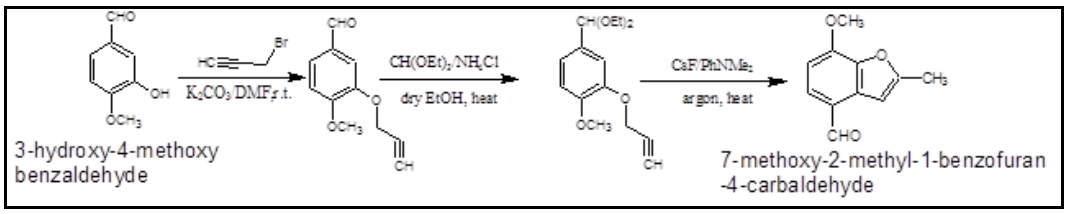

Figure 14: Synthesis 7-methoxy-2-methyl-1-benzofuran-5-carbaldehyde

The usual method for the synthesis of 2-ethylbenzofuran uses the salicylaldehyde as the starting material heating together with 1-chloroacetone under basic conditions to give 2-acetylbenzofuran followed by Woulf-Kishner reduction forming 2-ethylbenzofuran. The other methods uses benzofuran as starting material which reacts with acetic anhydride and phosphoric acid to give 2-acetylbenzofuran which is reduced further to 2-ethylbenzofuran also by Wolff-Kishner reduction. Benzofuran has been synthesised from phenol via the key intermediate 2-ethylbenzofuran which can be synthesised by intramolecular Wittig reaction. The aqueous solution of phenol and formaldehyde were refluxed with zinc nitrate hexahydrate for about 24 hours forming 2-hydroxymethylphenol which is further treated with triphenylphosphonium bromide in ethanol under reflux temperature to give the salt (2-hydroxybenzyl)triphenylphospho -nium bromide. The salt was then treated with proponic anhydride and triethyl amine in toluene under reflux conditions for about 8 hours to give 2-ethylbenzofuran which is further treated with p-ansoyl chloride followed by bromination in acetic acid gives benzobromarone [38-41] (Figure 15).

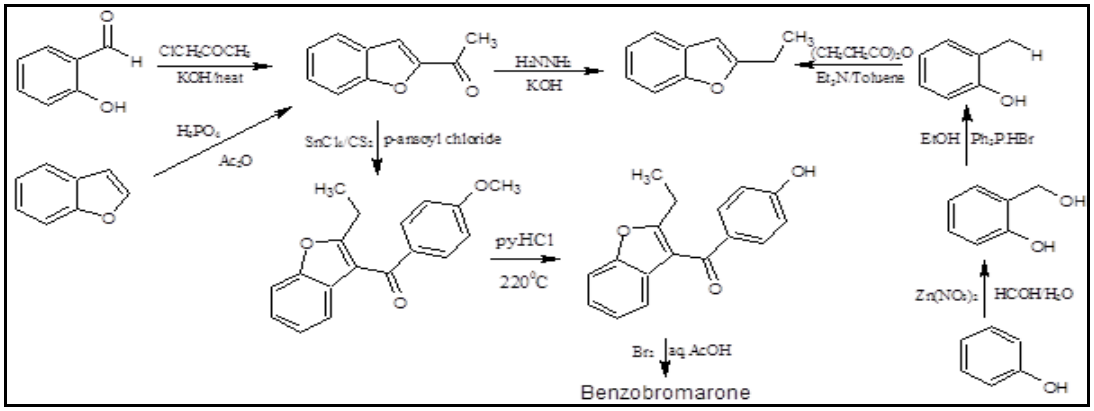

Figure 15: Synthesis of benzofuran derivatives from salicylaldehyde and benzofuran

By using Triphenylphosphene Bromohydride and o-hydroxy Aldehydes/Ketones

Guillaumel J et al. synthesized derivatives of benzofurans substituted at 2-position by a 5-nitrofuryl, 5-nitrothienyl, 5-nitro-2-furylethenyl or 5-nitro-2-thienylethenyl group by heterocyclisation of 2-acyloxybenzyl triphenylphosphonium bromide derived from 2-hydroxybenzyl triphenylphosphonium bromides [42], themselves obtained by the action of triphenylphosphine bromohydrate on ortho-hydroxylated benzyl alcohols. Along with these, 5-nitro-2-furoylbenzofuran derivatives also synthesised by the condensation of diversely substituted salicylaldehydes and 2-bromoacetyl-5-nitrofuran. These compounds show moderate parasiticidic and antibacterial properties (Figure 16).

Biological Activities of Benzofuran Derivatives

Anticancer agents:

DNA chain can be blocked by the incorporation of certain nucleosides analogs that have been modified in the sugar portion of the nucleosides [43]; e.g. Removal of hydroxyl group from the 3'-carbon of deoxyribose ring as in 2',3'-dideoxyinosine (Dedanosine or DDT) or of the conversion of deoxyribose to another sugar as in arabinose, prevent further chain elongation and hence growth of cell. The sugar moiety has been chemically modified as seen in zidovudine (AZT) (Figure 17).

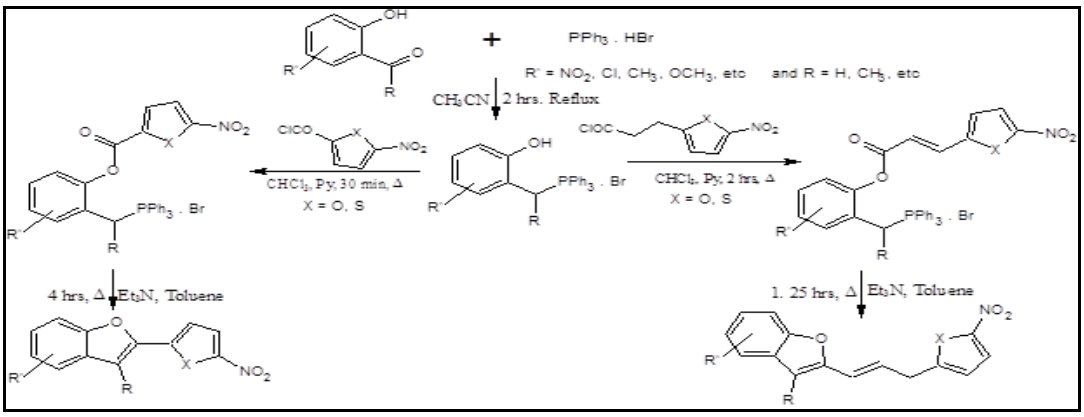

Figure 16: Synthesis of 2-substituted benzofurans

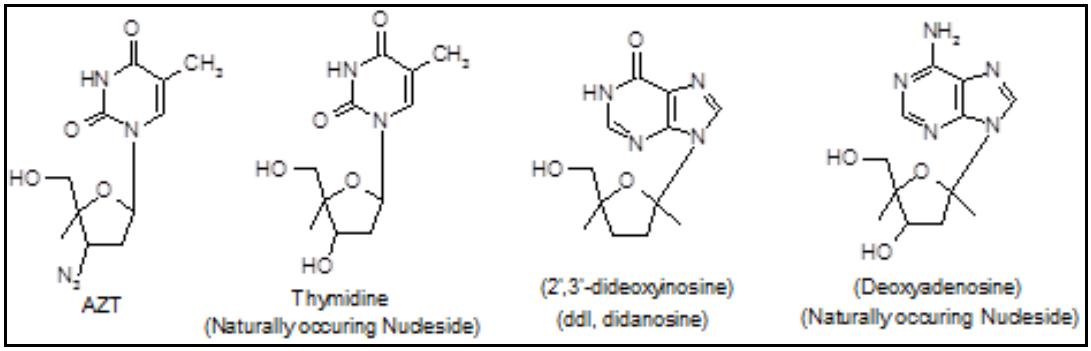

Figure 17: Biologically important furan derivatives

Anticancer agents such as etoposide [43] target human topoisomerase (II). This enzyme binds tightly to the DNA double helix and makes transient breaks in both stands. The drug hydroxyurea destroys the free radical required for the enzyme activity of ribonucleotide reductase and thus inhibits the generation of substrate for DNA synthesis. It has been used for the treatment of cancer such as chronic myelogenous leukemia. Some purine synthesis inhibitors, such as folic acid analogues (e.g. methotrexate [43]) are used pharmacologically to control the spread of cancer by interfering with the synthesis of nucleotides and therefore DNA and RNA. But these are toxic to all dividing cells specially those cells replicating rapidly including bone marrow, skin, gastrointestinal (GI) tract, immuno system, or hear follicles. As a result, individuals taking such anticancer drugs can experience adverse effect including anemia, scaly skin, GI track disturbance, imminodifficiencies, and baldness. Thymidylate synthase is used to convert dUMP to dTMP. It is not only the source of methyl group but also source of 2H atoms for oxidation. Thymidylate synthase can be inhibited by inhibitors include thymine analogous such as 5-fluorouracil which is metabolically convert to 5-FdUMP and get permanently bonded to the inactivated thymidylate synthase; this class of drugs are called as "suicide" inhibitors. The enzyme dihydrofolate reductase (used to reduce DHF to THF) is inhibited in presence of drugs such as methotrexate. Therefore purine synthesis is stopped and hence cell growth slowed. The anticancer drugs such as dactinomycin (actinomycin) excert their cytotoxic effect by interacting into the narrow groove of the DNA double helix, thus interfering with DNA and RNA synthesis [43]. These drugs are only used to decrease the growth rate of cancer. During the development of antitumor drugs, it is necessary to determine potency as well as cell type selectivity. Natural product based drug discovery continue to be active of research throughout the world [44-47]. Most of chemotherapeutic used for the treatment of tumor are plant based, that are currently used or clinical trials e.g. Vinica alkaloids, lignans, taxanes, stilbenes, flavones, cepbalotaxanes, camptothecins, and taxanes. They having wide range of organic structures, type and functions, and greater similarity between the skeleton of compound and organic materials involved for the growth of cancer. A very few of the more promising cancer chemopreventing (prevention, delay or reversal of carcinogenesis) [48] agents are brusatol, zapotin, apigenin, deguelin, brassinin, resveratrol, butyrolactone and staurosporine. Various proteins from sponges have been reported to selectively kill human tumor cells; e.g. Protein from the sponge tethya ingalli lyses ovarian cancer cells [49,50].

The development of general methods for the synthesis of chiral compounds having biological activity has long constituted a challenge for synthetic organic chemists. In this context, heteroaromatic compounds play a significant role. In particular benzofuran ring is a common moiety in many biologically active natural and therapeutic products

[51], some of which having chiral substituents, and represent a very important heterocyclic pharmacophore [52]. On the other hand, benzofuran-containing entities may constitute important target for pharmaceutical researches, including the possibility of being mentioned as drug candidates in clinical and preclinical studies. Khellin is one of several furochromones that can be isolated from *Ammi visnaga L.*, a perennial herbaceous plant that grows wild in many Eastern Mediterranean countries. Recently, khellin, (Figure 18) along with several analogues, was found to possess desirable lipid-altering activity and is a coronary vasodilator: i.e., lowering the atherogenic VLDL + LDL-cholesterol fraction and elevating the antiatherogenic (i.e., protective against atherosclerosis) HDL-cholesterol fraction, in animal models [53] as well as in man.

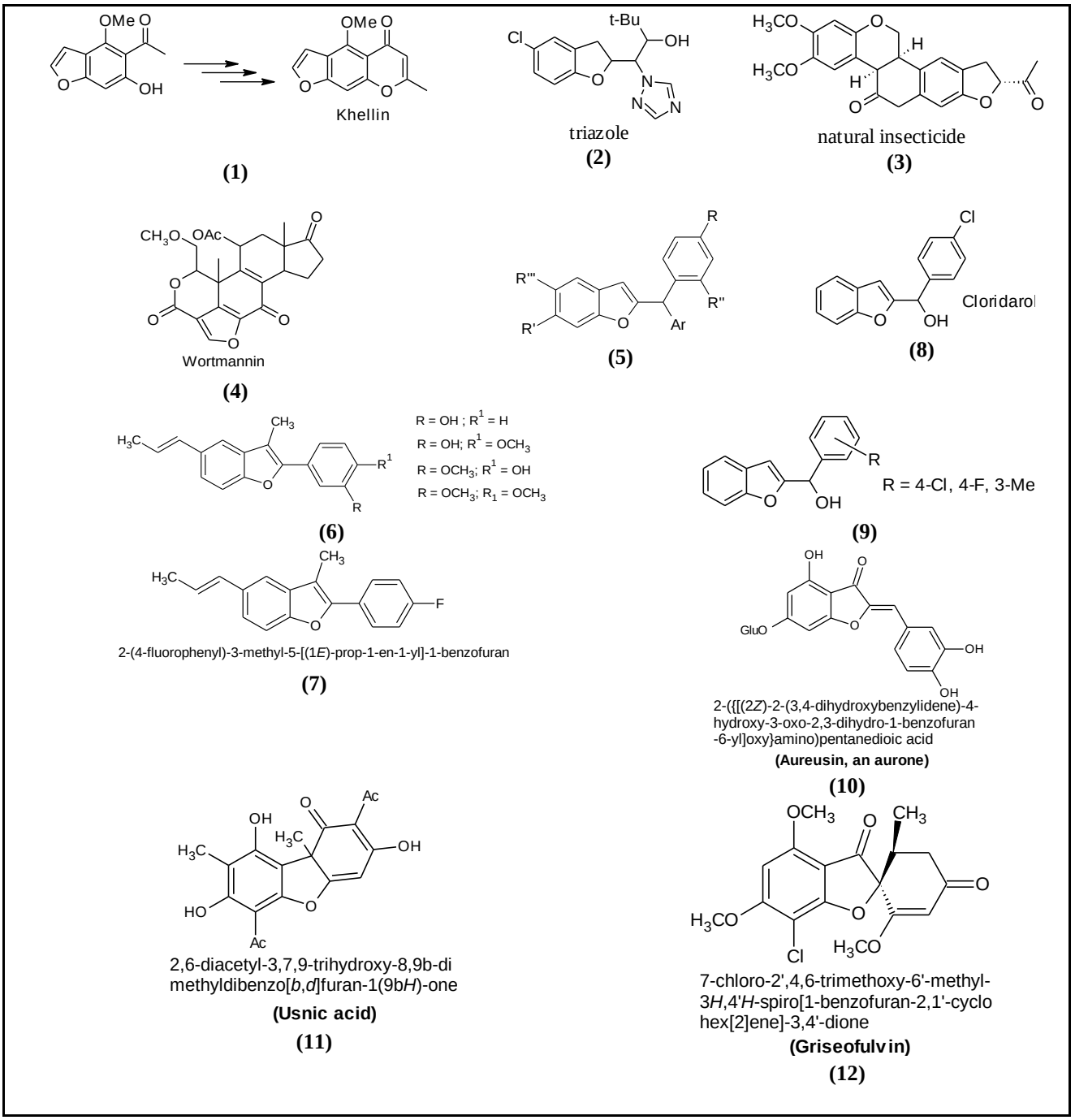

Figure 18: Chemical structures of biologically active benzofuran derivatives

Turning our attention to the importance of 2-substituted benzofurans in medicinal and/or biological utilize, there is to note that most of them have been shown to display biological properties. In particular, triazole (compound 02; Figure 18) was found to act as a plant growth regulator of summer rapes [54], while compound is a natural insecticide (Compound 03; Figure 18) that is found in derris root [55].

Kinase inhibitors:
Some benzofuran such as wortmannin (Compound 04; Figure 18) is used as kinase inhibitors. It is selective PI3K inhibitor in complex with PI3K has been reported [56]. Achintya S et al. [57] has been studied the applicability of benzofuran derivatives as potential CYP19 aromatase inhibitor. Benzofuran derivatives have emerged as a new class of potent AIs (Compound 05; Figure 18), which showed promising as chemotherapeutic agents for the treatment of estrogen dependant tumors [58].

Antimicrobial agents:
Benzofuran derivatives posses a wide range of biological activities. They have been reported to possess antimicrobial [59-62], antitumour [63,64], anti-inflammatory [65] activity etc. Benzothiazoles play a significant role as antibacterial [66-68] and antifungal activity. Azetidinones with heterocyclic molecule has created an excellent drug for antimicrobial [69-71] activity. Several benzofuran derivatives containing heterocyclic ring substituents linked to the benzofuran nucleus at C-2 by a two- to four-atom spacer as potential anti-HIV-1, anticancer and antimicrobial agents [72]. Chauert et al. have reported for the first time in a species of piperaceae; three known neolignans (conocarpan, eupomatenoid-5 and eupomatenoid-6) were isolated from Piper decurrens and illustrated the structure of the compound 06 (Figure 18). Greisiele LP et al. [73] have evaluated the activity of compound 07 (Figure 18) against gram positive and gram negative bacteria.

Antifungal agents:
Cloridarol was used in for treatment of lipidemia and as an anticoagulant [74]. Racemates of 2- benzofuranyl carbinols (compound 8,9; Figure 18) like have been shown to display antifungal and aromatase inhibiting activities. These carbinols were prepared in racemic form in good yields and recently synthesis of aryl 2-benzofuranyl in high enantiomeric purity was reported [75]. Benzo(b)furan has been occurred in a range of plant- and microbial derived natural products, ranging in complexity from 5-methoxybenzofuran, through the orange ‘aurones’, (Compound 10; Figure 18) a group of plant pigments isomeric with co-occurring flavones, usnic acid, a yellow pigment (Compound 11; Figure 18) found in many lichens, to griseofulvin (Compound 12; Figure 18) from *penicillium griseofulvum*, used in medicine as an antifungal agent [76].

CONCLUSION

Benzofuran and its derivatives have attracted much attention in medicinal chemistry for their wide range of various biological activities, including insecticidal, fungicidal, antimicrobial and antioxidant properties. Although the research on this subject is incipient, a number of reports disclosing the effects of the benzofuran compounds on the pathogens of clinical interest have recently been increasing. Benzofuran compounds have been shown to be promising leads for the design of more efficient antimicrobial agents.

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