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REVIEW ARTICLE ON BENZOFURAN

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ABSTRACT

Benzofuran derivatives are an important heterocyclic compounds that are possess vital biological activities such as antidepressant, anticancer, antiviral, antifungal, antioxidant, anti-psychotic etc. Substituted benzofuran also possess other applications such as fluorescent sensor, antioxidants, oxidant, brightening agents and in other field of chemistry and agriculture. Benzofuran presents in various natural products with various physiological, pharmacological and toxic properties.

KEYWORDS: Benzofuran derivatives; Heterocyclic compounds; Biological properties; Antidepressant; Anticancer; Antiviral; Antifungal; Antioxidant activities.

INTRODUCTION

Polycyclic and or aromatic compounds containing furan ring constitute a group of compounds which are occurs widely throughout the plant kingdom.

The origin of furan chemistry has been outlined by partington. 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 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 syntheticproducts.

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.[1]

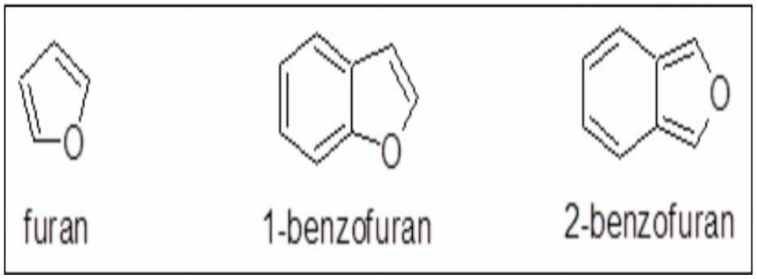


Fig no. 1: Benzofuran derivatives.

Chemistry of Benzofuran: The benzene ring is fused with five member furan ring and formed bicyclic ring benzofuran or coumarone.

Methods of Synthesis of Benzofuran Derivatives

Benzofuran was first synthesized by Perkin from coumarin as 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 to afford benzofuran in good yields.[2]

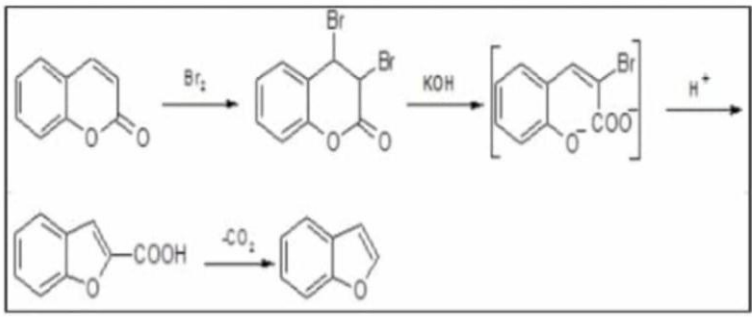


Fig no. 2: Perkin Benzofuran Synthesis.

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, generallyreferred to as “McMurry reaction”

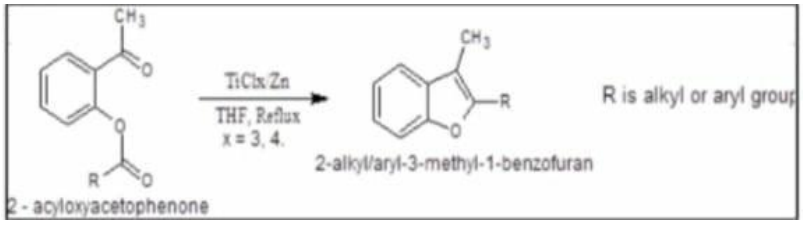


Fig no. 3: McMurry reaction approach for benzofuran synthesis.

Recently, other less popular approaches for the synthesis of 2-substituted 1-benzofurans include p-toluenesulfonic acid-mediated cyclization of o-(1-alkynyl)anisole to obtain 2-arylsubstituted benzofuran, rearrangement and cyclization reactions of 2-hydroxybenzophenones with Corey-Chaykovsky reagent, cyclization of 2-acyloxy-1-bromomethylarenes with Cr(II)Cl2/BF3-OEt2 catalyst, boron tribromide-promoted tandem deprotectioncyclization of 2-methoxyphenylacetones, (2-methoxyphenyl) methanols, and 2-hydroxy-3-arylpropenoic acids, leading respectively to 2-methyl, 2-carboxy, and 2-arylbenzofurans. However, these methods often require expensive catalysts and/or multi-step synthesis. 2-(2-Methoxyaryl)-1-arylethanone derivative when subjected to hydrogenation by passing hydrogen gas in presence of palladium based on charcoal in ethanol containing hydrochloric acid produces 2-arylbenzofuran reaction approach for benzofuran synthesis.

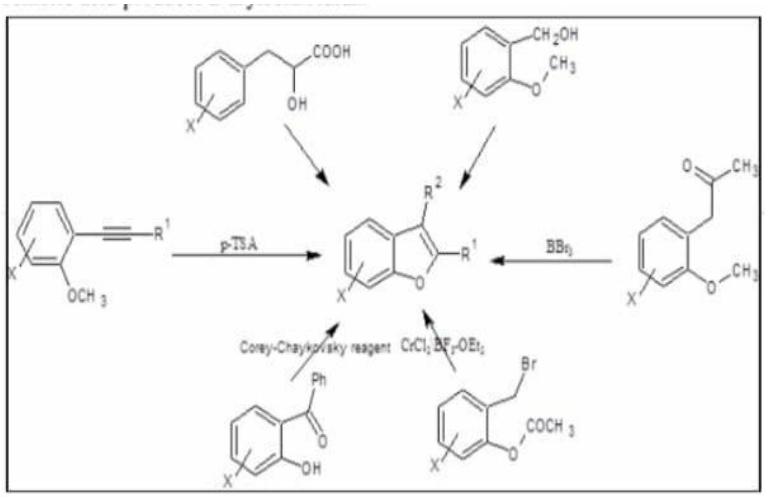


Fig no. 4: Synthesis of various substituted benzofurance derivatives.

In an alternative approach, 2-(2-Methoxyaryl)-1-arylethanone derivative are cyclised using HI in acetic acid to give 2-arylbenzofurans .Another route involves. 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 . To forming 2arylbenzofurans. The most commonly used approach. For the synthesis of 2-arylbenzofuran was the coupling of cuprous

aryl acetylenes with o-halophenols in pyridine under reflux conditions.

Aryl acetylenes the were treated with o-halophenols in presence of Cu (I) iodide and triethylamine using (PPh3)2PdCl2 as a catalyst also forming 2-arylbenzofurans. During this conversion, reaction proceeds through cuprous aryl acetylene intermediate. The benzofuran was undergoes arylation] at 2-position by using arylmercuric halide in presence of Li2PdCl4. 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 in presence of benzene to furnish 2-arylbenzofuran. Benzyloxybenzaldehydes 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 2arylbenzofuran from 2-hydroxystilbenes. One of the approach involves the reaction of 2-hydroxystilbenes with lead tetra-acetate in benzene at cold condition (temperature should be maintained at 17-18°C) forming 2arylbenzofuran. In another approach the protected 2-hydroxystilbenes were subjected to hydrogenation followed by the oxidation (aromatisation) using DDQ to 2-arylbenzofuran. In some known synthesis of 2arylbenzofuran, intramolecular condensation of Wittig reagent was employed. The o-acyloxybenzylidene phosphoranes undergoes intra-molecular condensation in presence of base in toluene under reflux conditions. Nayak and Banergi 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. The Copper-acetylide approach has been widely used for the synthesis of 2arylbenzofuran-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.[3]

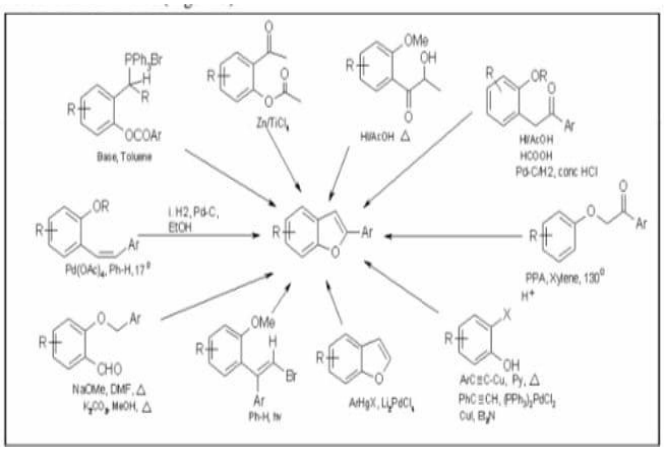


Fig no. 5: Methods of the synthesis of 2-alkyl/2-arylbenzofurans derivatives.

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 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) DNA double helix and makes transient breaks in both stands. The drug hydroxyurea destroys the free radicalrequired 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 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 5FdUMP 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. 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. 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 theskeleton 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). 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.

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 playa significant role. In particular benzofuran ring is a common moiety in many biologically active natural and therapeutic products, some of which having chiral substituents, and represent a very important heterocyclic pharmacophore.

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, along with several analogues, was found to possess desirable lipid-altering activity and is a coronary vasodilator: i.e., lowering the atherogenic VLDL + LDLcholesterol fraction and elevating the antiatherogenic (i.e., protective against atherosclerosis) HDL-cholesterol fraction, in animal models as well as in man.

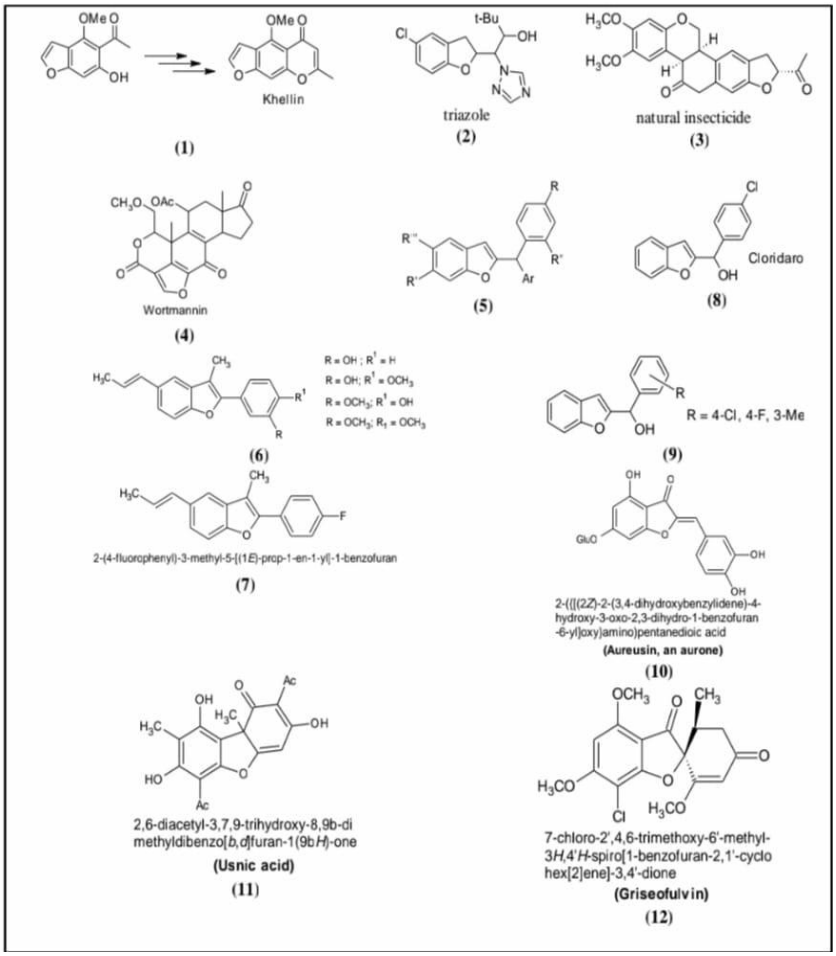


Fig no. 6: Chemical structures of biologically active benzofuran derivatives.

Are vasodilators. 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, triazo, was found to act as a plant growth regulator of summer rapes, while compound is a natural insecticide (Compound 03; Figure 18) that is found in derris root.

Kinase Inhibitors

Some benzofuran such as wortmannin is used as kinase inhibitors. It is selective PI3K inhibitor in complex with PI3K has been reported. Achintya S. has been studied the applicability of benzofuran derivatives as potential CYP19 aromatase inhibitor.

Benzofuran derivatives have emerged as a new class of potent AIs; which showed promising as chemotherapeutic agents for the treatment of estrogen dependant tumors.

Antimicrobial Agents: Benzofuran derivatives possess a wide range of biological activities.

They have been reported to possess antimicrobial, antitumor, anti-inflammatory activity etc. Benzothiazolesplay a significant role as antibacterial and antifungal activity.

Azetidinones with heterocyclic molecule has created an excellent drug for antimicrobial activity. Several benzofuran derivatives containing heterocyclic ring substituents linked to the benzofuran currens nucleus at C-2 by a two- to four-atom spacer as potential anti-HIV-1, anticancer and antimicrobial agents.

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 deand illustrated the structure of the compound. Greisiele LP et al. have evaluated the activity of compound against gram positive and gram negative bacteria.

Antifungal Agents: Cloridarol was used in for treatment of lipidemia and as an anticoagulant Racemates of 2- benzofuranyl carbinols like have been shown to display antifungal and aromatase inhibitingactivities. These carbinols were prepared in racemic form in good yields and recently synthesis of aryl 2-benzofuranyl in high enantiomeric purity was reported.

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’, a group of plant pigments isomeric with co-occurring flavones, usnic acid, a yellow pigment found in many lichens, to griseofulvin from penicillium griseofulvum, used in medicine as an antifungal agent.[4,5]

Antihypertensive Agent: Benziodarone and cloridarol are vasodilators.

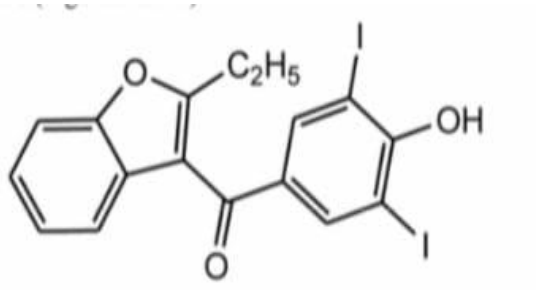


Fig no 6: Benziodarone.

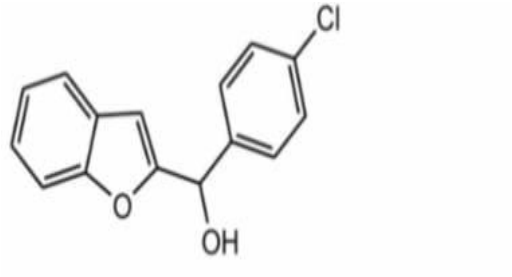


Fig no.7: cloridol.

Serotonin Receptors Agonist: Dimemebfe is an agonist of the 5-HT1A and 5-HT2 serotonin receptors.

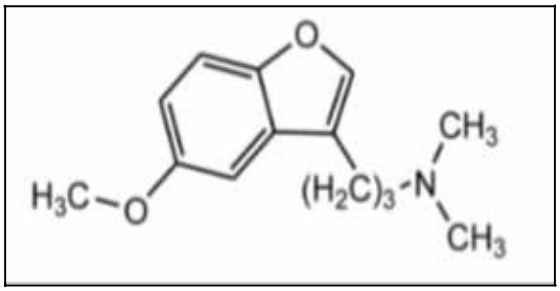


Fig no. 8: Dimemefe.

A2-Adrenergic Agonist: Efaroxan is a α2-adrenergic antagonist.

These are the class of simpathomemetic agents that selectively stimulates α2-adrenergic receptors. The α2-adrenergic receptors has two sub-classes are associated with sympatholytic properties α2-adrenergicantagonist.

Alpha adreno receptor ligands memic the action of epinephrin and nor-epinephrin. The activation of α1 stimulates the membrane bound enzyme phospo lypase enzyme.

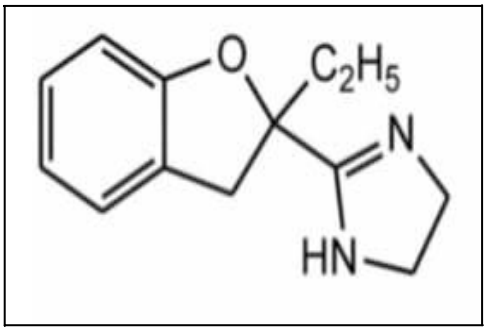


Fig no. 9: Efaroxan.

ANTIPSYCHOTIC AGENTS

Elopiprazole is a phenylpiperazine class drug and have antipsychotic activity.

ANTIGOUT AGENTS

Benzbromarone is a uricosuric agent used for the treatment of gout, mainly when first-line treatment (by useof allopurino) fails or produces intolerable adverse effects.

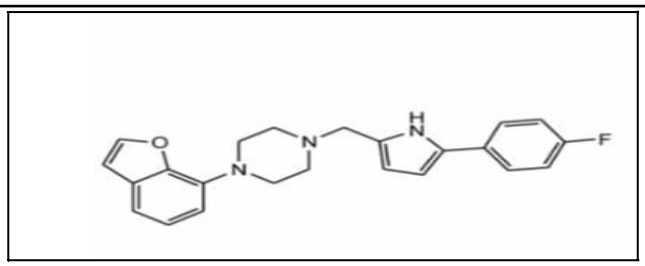


Fig no. 10: Elopirazo.

ANTIDEPPRESSANT AGENTS: Vilazodone is an antidepressant and used for the treatment of mental depressive sorders.

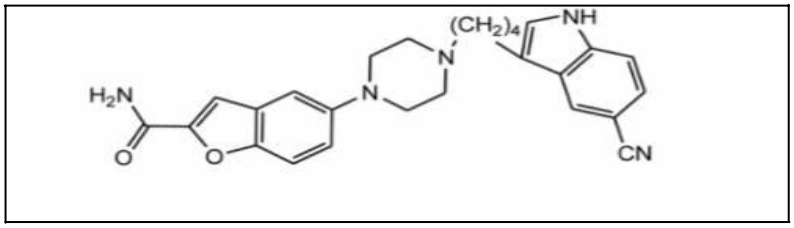


Fig no. 11: Vilazodone.

MUSCLES RELAXANTS: TC-5619 is acts as a partial agonist at the α7 subtype of the neural nicotinicacetylcholine receptors.[6]

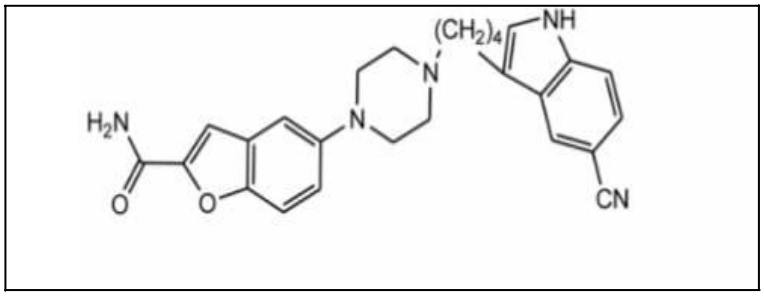


Fig no. 11: TC-5619.

REACTIVITY OF BENZOFURAN DERIVATIVE

According to the frontier orbital theory, as the frontier electron populations of the parent benzo[b]furan 1a are greater, the corresponding carbons are more reactive toward electrophiles.

CRAFTS FRIEDAL REACTION

Friedel– Crafts aroylation of benzo furan derivatives 2 with 4-methoxy benzoyl chloride in CS2 = SnC l4afforded the corresponding methanones (2 – benzy l, 7dihy drobenzo furan- 3- y l) - (4 - methoxy – pheny l) - methanone3 and (4 – methoxy - phenyl) (2-methyl - 4,7- dihydro- benzofuran-3-yl)- methanone.

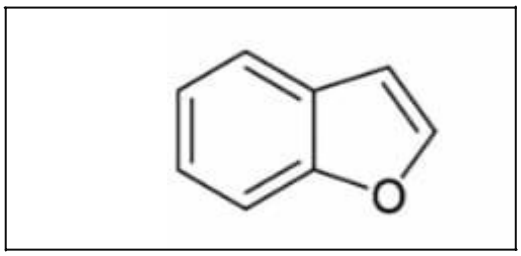


Fig no. 12: Benzofuran.

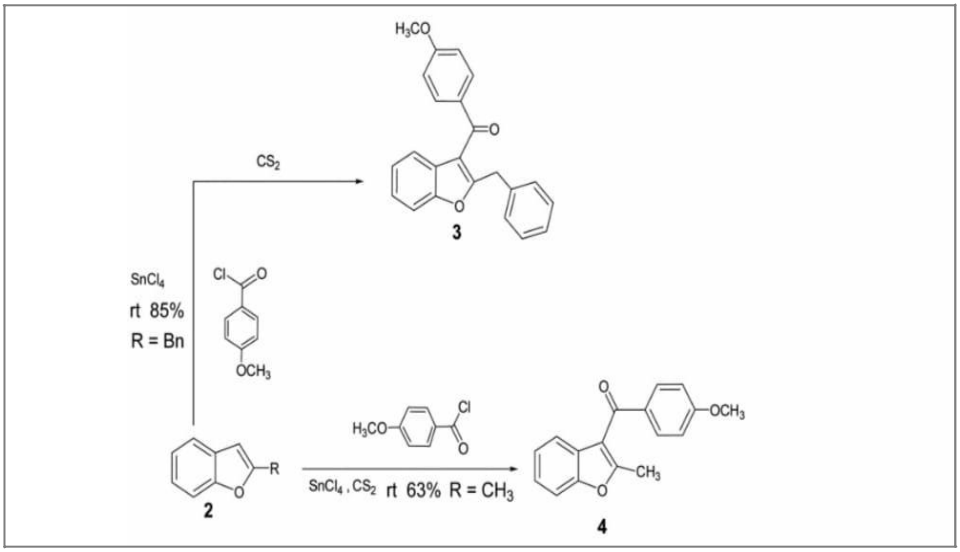


Fig no. 13: Synthesis of 3 - aroyl benzofurans derivatives.

Formylation

5 – alkyl – 7 – Formy lation of Vilsmeier formylation of 3 – phenyl - 5, 7-dimethoxybenzo [b] furan 5 with N, Ndi methylformamide and phosphrous oxychloride (Vilsmeier reagent) gave the formyl derivative 5,7-dimethoxy-3-phenyl-benzofuran-2-carbaldehyde methoxy-2-phenyl benzo [b] furans 7 with Zn CN = HCl afforded the 3-[3-formyl - 2 - (4-hydroxy-3-methoxy-phenyl)-7-methoxy-4,7-dihydrobenzofuran-5-yl]-propionic acidmethyl ester.

Halogenation

Since halogen-substituted benzo[b]furans play an important role in the transition-metal-catalyzed coupling of benzo [b] furans with other substrates, synthetic methods to

regioselectively synthesize substituted benzo [b]furan halides have become very critical routes. Several syntheses of benzo [b] furan-based aryl halides are described here. When benzo [b] furan-derived polycyclic phenol 43 was allowed to react with bromine, 2,6-dibromo-4-(6-bromo-1,4-dihydro-benzo[b]naphtha[2,3d]furan-11-yl)-phenol was formed in good yield.[18] 3-Bromo-2-methyl-benzo[b] furan could also be made by reaction of N-bromosuccinimide (NBS) with 2-methyl benzo [b] furan. Sequential treatment of the benzo[b]furans with bromine followed by reaction of the formed tribromide 7 with KOH gave the dibromo derivative, which brominated with Br2=CHCl3 to give Anodic fluorination of ethyl 3-benzo [b] furanyl acetate was applied to the synthesis of a 2,3-difluoro-2,3-dihydrobenzo [b] furan derivative1 and 2-fluoro-3hydroxyl derivative.

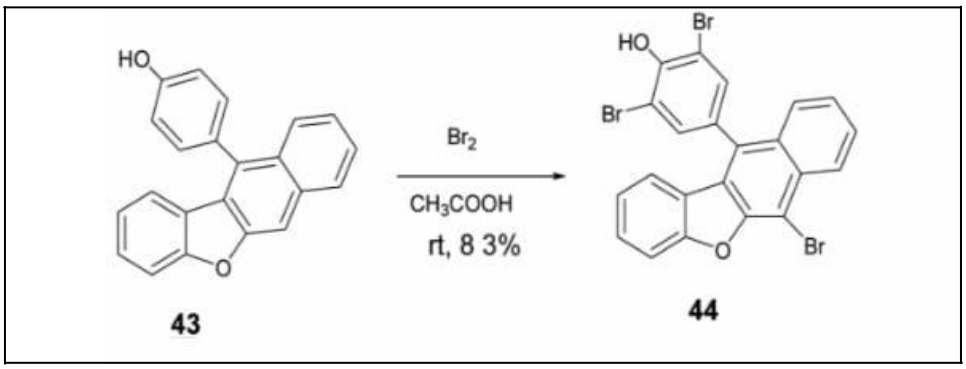


Fig no. 14: Synthesis of 2,6-dibromo-4-(6-bromo-1,4-dihydro-benzonaptha(2,3-d)furan-11-yl)- phenol.

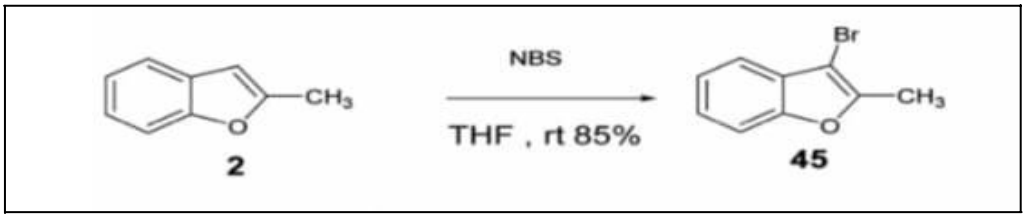


Fig no. 15: Synthesis of 3-bromo-2-methyl-benzo[b]furan.

Alkylation

Alkylation of bezofuran 1a with ethyl bromide gave 2- ethyl-benzofuran, which reacted with NBS to afford 3-bromo-2-ethyl-benzofuran Refluxing with C5F8 gave 2-ethyl-3-(3,3,4,4,5-pentafluoro-cyclopent-1-enyl) benzofuran.

Reactions with Aldehydes And Ketones

Because of the electronic richness of the C-3 of benzo [b] furan 1a, the Yb- catalyzed electrophilic substitution of benzo [b] furan with glyoxalate led to benzo [b]furan ester in a

regioselective manner.

The C-2 proton of benzo [b]furan 1a underwent regioselective metallation by treatment with n-butyllithium to form 2-lithiated benzo [b]furan, which directly reacted with electrophiles, such as 1,4-cyclohexadienoneto form 4-(benzo [b] furan-2-yl)-4-hydroxy-2,5-cyclohexadien-1-one in good yield. Benzo[b]furan derivative was realized by reaction of benzo[b]furan 1a with 4,4-dimethoxy-4Hnaphthalen-1-one 60, followed by hydrolysis.

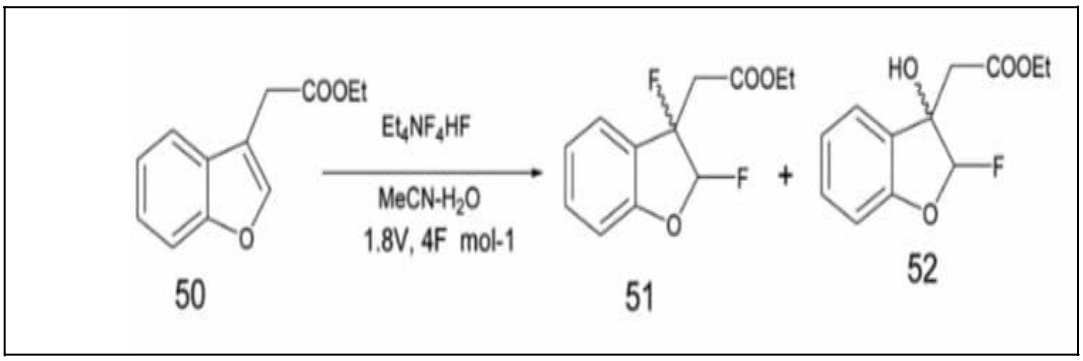


Fig no. 16: Fluorination of ethyl 3-benzofuranyle acetate.

Lithiation of 1-benzofuran-2-ylmethyl-1H-benzotriazole with n-BuLi, followed by addition of a, b-unsaturated aldehyde,] gave 4-benzo-furan-2-yl-4benzotriazol-1-yl-3-phenyl-butyraldehyde, which wasrefluxed without further purification in 1,4-dioxane in the presence of p – toluenesul fonic acid to give 3- phenyldibenzofuran.

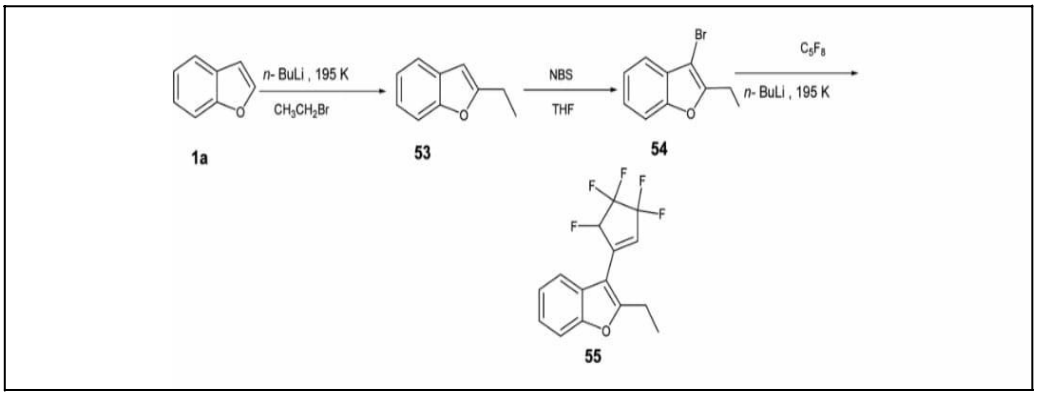


Fig no. 17: Alkylation of benzofuran 1a with ethyl bromide.

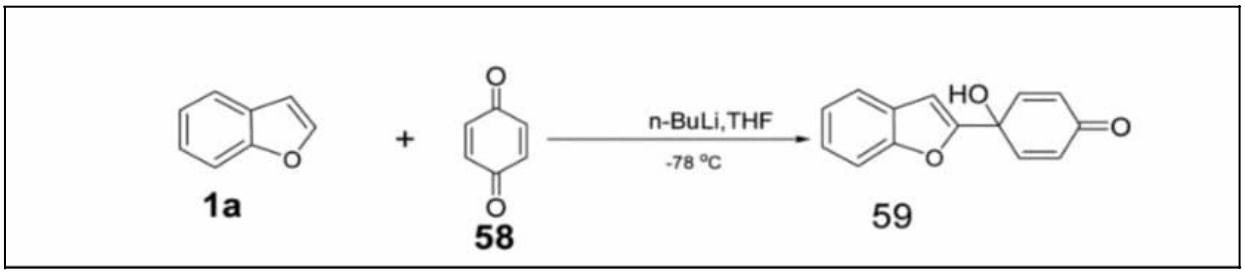


Fig no. 18: synthesis of 4-(Benzo[B]furan-2-yl)-4-hydroxy-2,5-cyclohexadien-1-one.

Aldol condensation of benzofuran with 4-hydroxy-3-methoxy-benzaldehyde the corresponding chalcones, which undergo further Claisen–Schmidt condensationwith hydrazine hydrate to give 4-(5-benzofuran-2-yl-3, 4-dihydro2H-pyrazol-3-yl)-2-methoxy-henol 68. Treatment of 68 with phosgene in the presence of triethylamine (TEA) urnished3-(benzofuran-2-yl)-5-(4-hydroxy-3methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl hloride. Finally, condensation of with substituted anilines in the presence of potassium carbonate accomplished the carboxamide products.

Nitration

Benzo[b]furan can undergo regioselective nitration to give 2-nitrobenzo[b] furan by using sodium nitrateand ammonium nitrate under ultrasonic conditions.

Oxidation

Photochemical cycloaddition of benzo [b]furan occurs readily on the C-2=C-3 double bond. For example, photooxygenation of 2, 3-dimethyl benzo-[b]furan at C produced dioxetane, which was isomerized at room temperature to give 2-acetoxy acetophenone. 3-Alkylbenzo[b] furans, were oxidized by chloroperoxidase from Caldariomyces fumago to their trans-2, 3-diols as major products and in addition to methy lacetate.

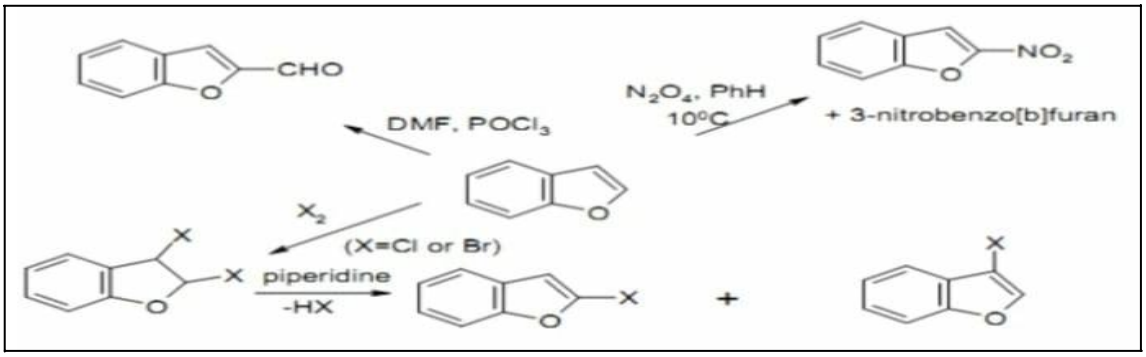
PALLADIUM COUPLING REACTIONS

The palladium-catalyzed coupling reaction of C-3 stannylated benzo-[b] furanwith vinyl triflate was employed as a key step to build up the framework of the final target. A palladium-catalyzed cyclization was applied to establish the skeleton of the benzo[b]furan tetracyclic ring in frondosin The regioselective coupling reactions of 2,3-dibromobenzo[b]furan with several terminal acetylenes were achieved using a palladium-catalyzed reaction afforded.[7,8]

General Physical and Chemical Properties of Benzofurans

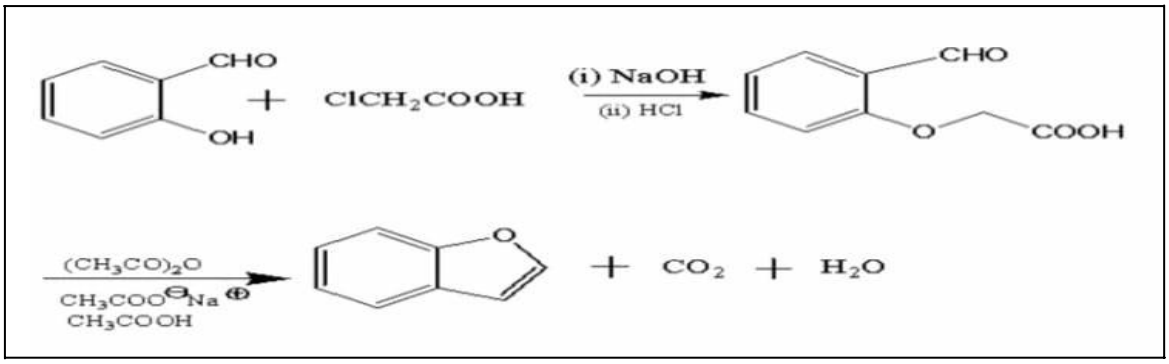
The aromaticity of benzofuran is weaker than in indole and this ring is easily cleaved by

reduction and oxidation. Electrophilic reagents tends to react with benzofuran at C-2 position in preference to C-3, reflecting the reduced ability of hetro atom to stablise the intermediate for 3-substitution. Attack in hetrocycle is often accompanied by substitution in benzoid ring. Nitration with nitric acid in acetic acid gives mainly 2-nitrobenzofuran., plus the 4-, 6-,7-isomers. When the reagent is N2O4 in benzene maintained at 10°C, both 3- and 2-nitrofurans are formed in the ratio of 4:1. Under vilsmeier reaction condition, benzofuran gives 2- formylbenzofuran in 40% yield. Chlorine or Bromine add across the C=C bond of the furan ring giving 2-,3-dihydrobenzo furans. Base promoted ehydrohalogenation of the dihalides offord mixture of the corresponding 2- and 3- halobenzofuran.



Reactions of Benzofuran[8]

The benzene ring is fused with five member heterocyclic ring i.e. furan and formed bicyclic ring benzofuran. It also called as Coumarone and obtained from salicylaldehyde by conversion into the aryloxyacetic acid by reaction with sodium chloroacetate in the presence of alkali followed by cyclisation with a mixture of acetic anhydride, acetic acid and sodium acetate. The reactions proceed by an internal Perkin's reaction followed by decarboxylative dehydration.



Some laboratory synthesis that involving benzofuran

Step1: Synthesis of o-formylphenoxyacetic acid: A solution of 80.0g of sodium hydroxide pellets in 200 ml of distilled water is added to a mixture of 106 ml(122 g) of salicylaldehyde, 94.5g of chloroacetic acid and 800 ml. of water. The mixture is stirred slowly and heated to boiling. The resulting black solution is heated under reflux for 3 hours. The solution is acidified with 190 ml. of concentrated hydrochloric acid and is steam-distilled to remove unchanged salicylaldehyde. The residual acidic mixture is cooled to 20°, and the precipitated product is collected on a Buchner funnel and rinsed with water. The light tan solid when dry weighs 99–100 g. (82–83% based anhydrous granular sodium sulfate. The ether is removed at water-bath temperature and the product is distilled, b.p. 166.5–168.0°. The water-white benzofuran weighs 37.5–40.0 g. (63.5–67.8%, 52–56% overall from salicylaldehyde) λmax 245 nmrecovered salicylaldehyde), MP- 130.5–133.0°C.

Step2: Synthesis of Benzofuran

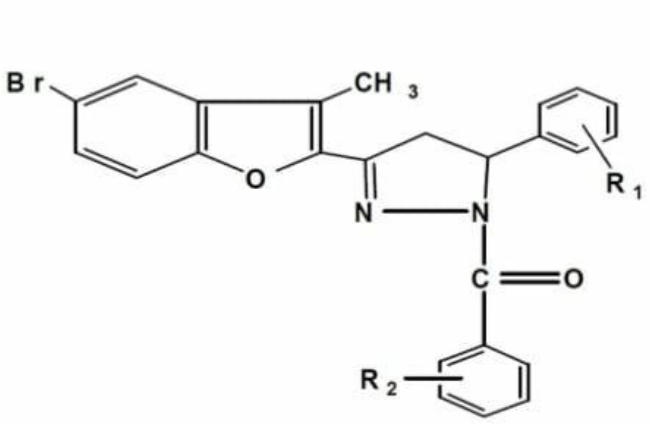
A mixture of 90.0 g. of crude, dry o-formylphenoxyacetic acid, 180 g. of anhydrous, powdered sodium acetate, 450 ml. of acetic anhydride, and 450 ml. of glacial acetic acid in a flask is heated under gentle reflux with stirring for 8 hours. Then the hot black solution is poured into ice water and extracted with one 600- ml. portion of ether. The ether layer is washed with one 600-ml. portion of water and then with several portions of cold dilute 5% sodium hydroxide solution until the aqueous layer is basic. The ether layer is washed successively with water and saturated sodium chloride solution and is partially dried ove ranhydrous granular sodium sulfate. The ether is removed at water-bath temperature and the product is distilled, b.p. 166.5–168.0°. The water-white benzofuran weighs 37.5–40.0 g. (63.5–67.8%, 52–56% overall from salicylaldehyde) λmax 245 nm.

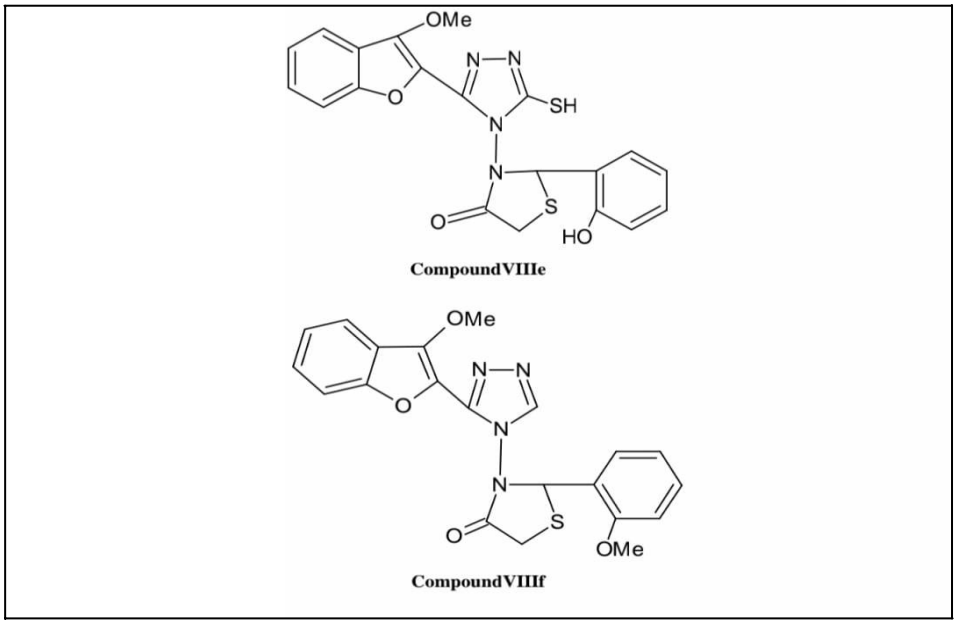
Applications of the benzofuran ring system in drug synthesis

Antimicrobial activity

Swarup jyoti Chattarjee and Co-workers: synthesized series of Thiazolidine-4-one substituted 1, 2, 4- triazole and incorporating 3-methoxy benzofuran moiety derivatives and then check the antibacterial activity against Gram positive and negative microorganism. From the derivatives the 2 have the broad- spectrum activity inhibition against all the strains tested when compared to the reference drug then other. Other derivatives show the moderate activities. Compounds VIIIe and VIIIf comp ounds showed. significant show the moderate.

Asrondkar al and co-workers: Synthesized the series of Pyrazolene-Benzofuran derivatives and Antimicrobial Activity of it. Antimicrobial activity was screening against one Gram positive and one Gram negative bacteria like, Staphylococcus aureus and Salmonella typhi using the Ampicillin reference drug drug against gram positive Staphylococcus aureus and Trimethoprim reference drug drug against gram negative Salmonella typhi. All the synthesized derivatives showed moderate activity, from which 4-Hydroxy and 2, 4-dimethoxy (Sr.No 4 & 5) against Staphylococcus aureus and 4-fluoro derivative (Sr. No 3) exhibited activity, The other remaining compounds exhibited activity against Salmonella typh.



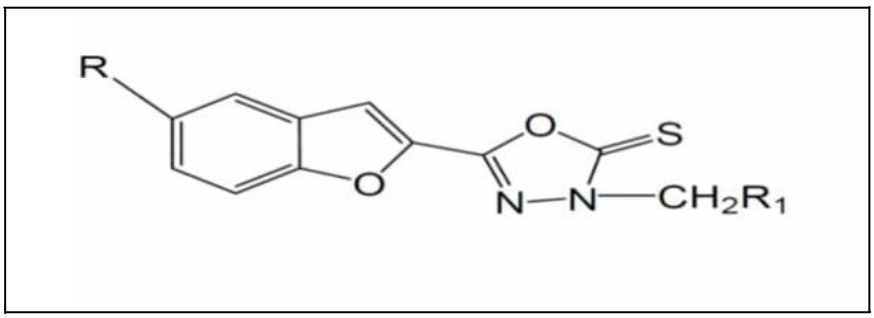


Compound VIIIe

Compound VIIIf

Riddhi Madhu and Co-Workers: Synthesized the series of 5CHLORO BENZOFURAN compound derivatives and to check the Anti-bacterial activity against using specific type of gram positive and gram negative bacteria like Escherichia coli and Staphylococcus aureus.

The screening showed that derivatives 5Chloro Benzofuran VI (a-d) had significant activity comparable to that of standard. The ciprofloxacin and ampicillin used as a reference drug.



Madappa B. HALLI and Co-workers: they synthesized the series of (E)-N_ - ((thiophen2-yl)methylene)benzofuran-2-carbohydrazide and its metal(II) complexes and check the antimicrobial activity. The synthesized and characterize Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Hg(II) metal complexes with newly synthesized Schiff base derived from benzofuran-2carbohydrazide and thiophene-2-aldehyde. The antimicrobial activity against a bacteria like, Escherichia coli, Staphylococcus aureus, and Salmonella typhi bacteria and Aspergillus niger, Aspergillus flavus, and Cladosporium spp. The metal complexes exhibited higher antimicrobial activity than the free ligand. The Fluconazole was use as reference drug.[8;9]

ANTIOXIDANT ACTIVITY

Free radicals produced by normal biochemical reactions in the body play an important role in the human body and become harmful only when they are produced in large quantities. The human body has an innate defense mechanism to resist free radicals such as superoxide dismutase, catalase and glutathione peroxidase. 90 Studies have found that benzofuran compounds have good antioxidant activity. A new line of benzofuran compounds 59 and 60 were isolated from D. latifolia. These compounds had moderate antioxidant activity and were tested by DPPH free radical scavenging test with an IC50 value of 96. 7 mm. 93.

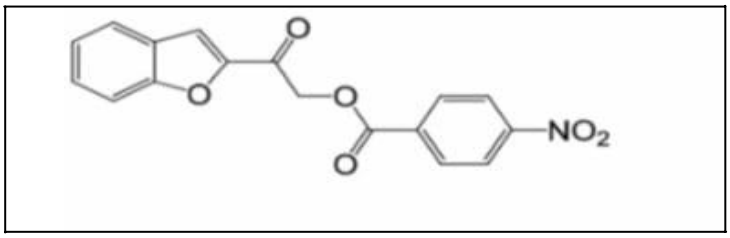
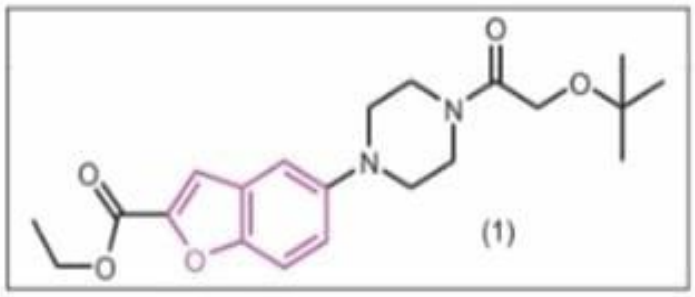


Fig no. 18: chemical structure of benzofuran ester compound having antioxidant activity.

Benzofuran as both antibacterial and anrifungal agent

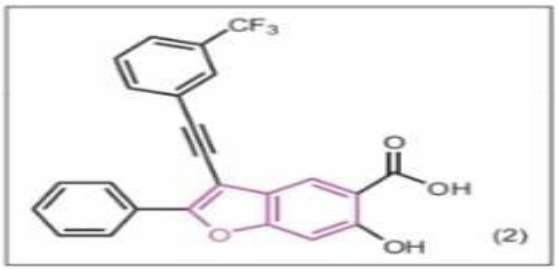
Due to the emerging and increasing bacterial resistance, development of new antibiotics is very important for public health globally. Several benzofuran derivatives have been prepared and introduced as antibacterial agents. Renuka et al. designed and synthesized a series of substituted benzofurans as DNA gyrase B inhibitors of Mycobacterium tuberculosis (MTB). DNA gyrase of MTB is a type II topoisomerase and is a well-established and validated target for the development of novel therapeutics. The compounds were tested for their biological activity; compound 1 emerged as the most active potent lead with an IC50 of 3.2 ± 0.15 μM against Mycobacterium smegmatis DNA gyraseB enzyme and 0.81 ± 0.24 μM in MTB supercoiling activity. Subsequently, the binding of compound 1 to the DNA gyraseB enzyme by the docking study indicated good interaction with the enzyme. This ligand with a glide score of −8.66 kcal/mol showed A H-bond with Arg141 and a well-fitted pose in the hydrophobic pocket within the vicinity of Ile84, Val128, Ile171, Val49, Ala53, Leu135, Val128, Val123, and Val99, and a few polar amino acid residues Glu 48, Ser126, Glu 56, Gln 102. The binding pattern within the active site pocket of the crystal ligand and reference ligand was quite similar and additionally the van der Waals and columbicforcesbetwEENThr170, Asn52, Ala53, Ile84, and Glu48 and theligand were observed.



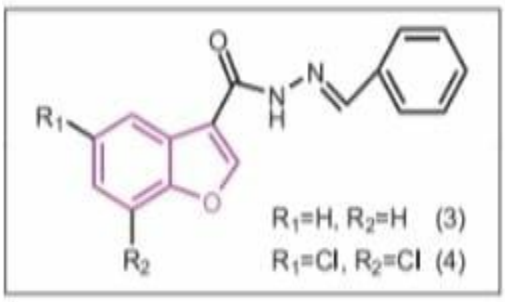
(1)

He et al. synthesized a series of inhibitors of Mycobacterium protein tyrosine phosphatase B (mPTPB) from 6-hydroxy-benzofuran-5-carboxylic acid scaffold. mPTPB is a virulence factor secreted by the pathogen and mediates mycobacterial survival in macrophages by targeting host cell immune responses. Consequently, mPTPB represents an exciting new target to combat tuberculosis (TB) infection. He et al. described a medicinal chemistry-oriented approach that transforms a benzofuran salicylic acid scaffold into a highly potent (IC50 = 38 nM) and selective mPTPB inhibitor [>50-fold against a large panel of protein tyrosine phosphatase (PTPs)]. Importantly, the inhibitor is capable of reversing the altered

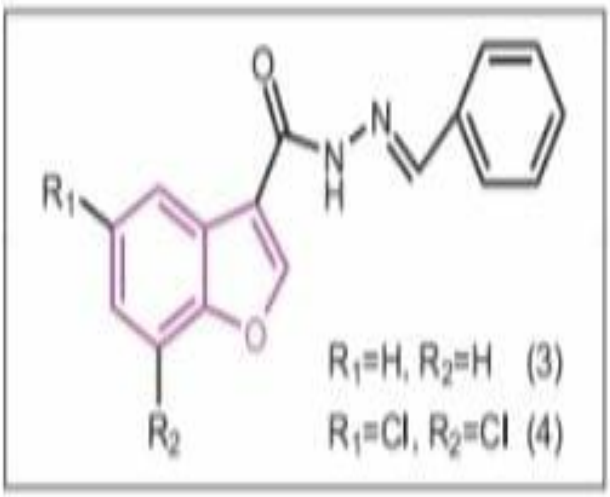
host immune responses induced by the bacterial phosphatase and restoring the macrophage's full capacity to secrete interleukin-6 and undergo apoptosis in response to interferon-γ stimulation, validating the concept that chemical inhibitionof mPTPB may be therapeutically useful for novel TB treatment.



Telveka et al. synthesized a series of benzofuran-3- carbohydrazide derivatives and evaluated them for in vitro inhibitory activity against M. tuberculosis H37Rv strains. The synthesized compounds showed promising antimycobacterial and antifungal activities. Compounds 3 and 4 were found to be the most active compounds with minimum inhibitory concentration (MIC) of 8 µg/mL and 2 µg/mL, respectively. For antitubercular activity, orthohydroxyl and protected hydroxyl groups' substitution on the benzylidene group have showed good antitubercular activity while for antifungal activity, the unsubstituted benzofuran ring and highly substituted side.



In another study, 6-benzofuryl purines were synthesized and their in vitro activities against M. tuberculosis H37Rv and mammalian cells (Vero cells) were determined. The results indicated that several compounds displayed profound antimycobacterial activity in combination with low toxicity toward mammalian cells. 6-Benzofurylpurine where the benzofuran substituent is connected directly to C-6 in the purine was found to be highly potent inhibitors of MTB (IC90 < 0.60 µM).[10,11]



The synthesis of and spectral properties of benzofuranderivative bis chalcone

METHODS AND MATERIALS

Terephthalaldehyde, Sodium hydroxide (NaOH) and the organic solvents were analytical grade and usedwithout further purification.

The plant material was harvested in September 2014 near Hatay region of Turkey and a voucher specimen have been deposited in the Herbarium of Biology Department, Mustafa Kemal University.

The melting points were determined with a Thermo Scientific 9100 melting point apparatus and are notcorrected.

Elemental analyses were performed with a LECO CHNS-932 (USA) elemental analyzer. The electronicspectra were measured on a uv via spectromter.

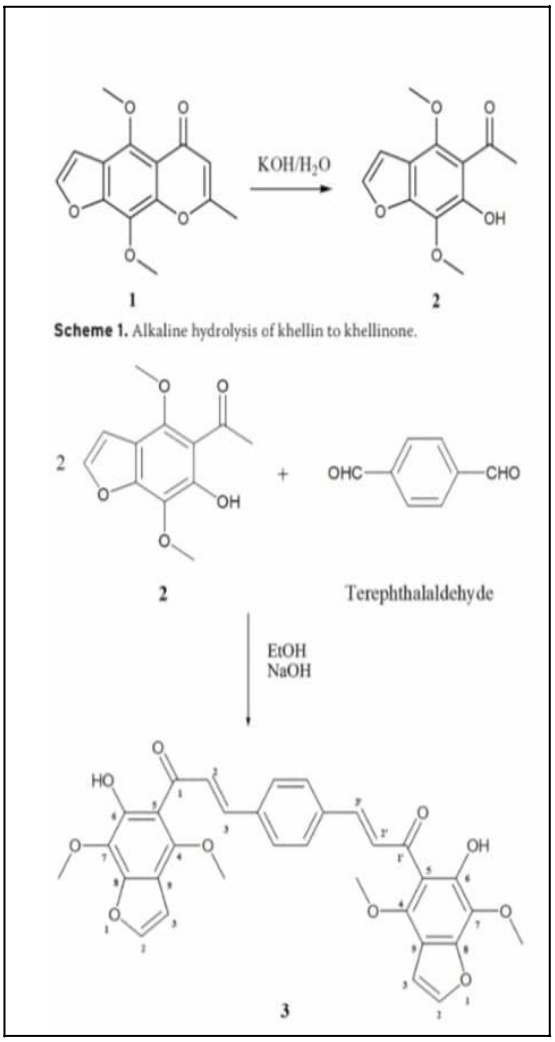


Fig no. 19: The synthetic route of bis chalcone.

The mass spectra have been obtained by Agilent (USA) LC/MSD spectrometer using the ESI technique. The FT-IR spectra (4000-400 cm-1) were recorded by Perkin Elmer (USA) Spectrum Two with U-ATR FTIR spectrometer. 1 HNMR (600 MHz) and 13C NMR (600 MHz) spectra were recorded on a Bruker Advance III HD (USA) spectrometer using CDCl3 and tetramethylsilane (TMS) was used as an internal reference. Thin-layer chromatography (TLC) was performed on Merck silicagel plates (60F254), and visualized with ultraviolet light (366 and 254nm)

Isolation of khellin, 1

The ripe fruits (500 g) of Ammi visnaga L. were dried, grounded and extracted with 1 L hot water by a Soxhlet apparatus for 30h and the extract was concentrated by rotary evaporator to its half-volume. It was then extracted with 150 mL hexane many times, dried over Na2 SO4 and concentrated to dryness under vacuum. The presence of khellin in the hexane residue was

detected by thin layer chromatography. Khellin gave yellowish brown fluorescence under 254 nm UV light with Rf value 0.56 in solvent system EtOAc:CHCl3 (60:40).[12] The hexane residue was purified by column chromatography on silica gel G 60. The fraction eluted with dichloromethane-ethyl acetate (90:10) were concentrated and recrystallized from MeOH-water to obtain 0.9 g khellin. The structure of khellin (4,9-dimethoxy-7-methylfuro[3,2-g]chromen-5- one) was confirmed by comparing its melting point with the value reported as 154-155°C.

Synthesis of khellinone, 2

Khellinone (4,7-Dimethoxy-5-acetyl-6-hydroxybenzofuran) was prepared by alkaline hydrolysis of khellin according to the literature.[2,15] 1.00 g of khellin (3.84 mmol) was dissolved in 15 mL of hot 10% KOH solution while the temperature was maintained at 70-80°C. At the end of the 2h reflux period, the reaction mixture was allowed to cool to room temperature and 3 mL of concentrated HCl was added dropwisely. The resulting precipitate was filtered off, recrystallized from hot MeOH and dried under vacuum to obtain 0.81 g(3.43 mmol) of khellinone with a yield of 89% (m.p. 99-100°C)

Synthesis of Bischalcone

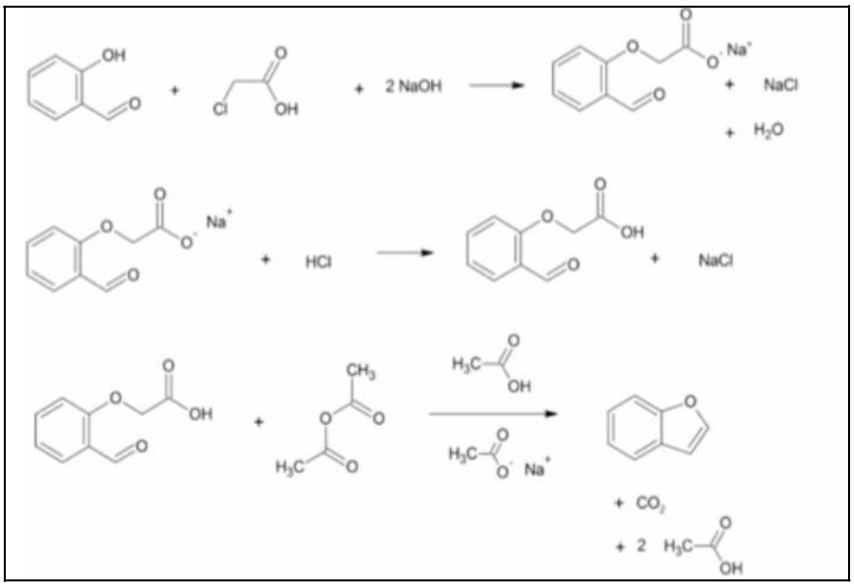
Khellinone (4.23 mmol) was dissolved with terephthalaldehyde (2.15 mmol) in 30 mL of ethanol. The solution was treated with 5 mL of 50% sodium hydroxide solution and left overnight. The reaction mixture was neutralized with dilute acetic acid (10%) and the separated product was collected, washed with water and recrystallized from hot MeOH.[12;13]

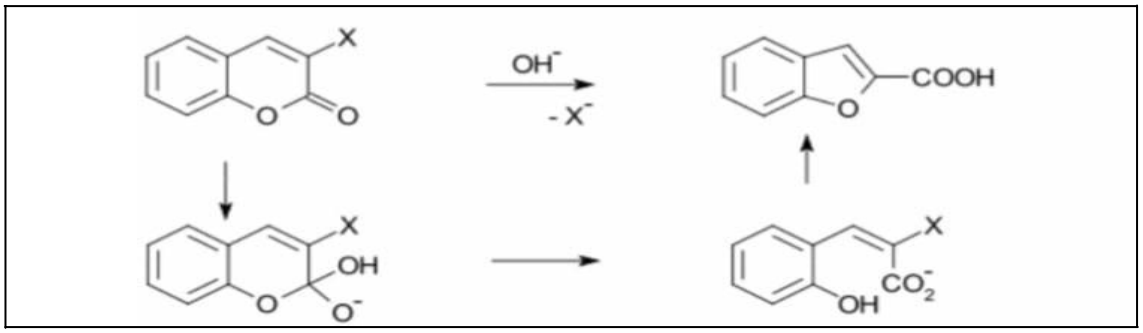
Preparation of Benzofuran

Benzofuran is extracted from coal tar. It is also obtained by dehydrogenation of 2-ethylphenolBenzofuran is extracted from coal tar. It is also obtained by dehydrogenation of 2-ethylphenol.

• O-alkylation of salicylaldehyde with chloroacetic acid followed by dehydration (cyclication) of theresulting ether and decarboxylation.

Perkin arragement, where a coumarin is reacted with a hydroxide.





CONCLUSION

Benzofurans and its derivatives have enormous potential to find importance in medicinal chemistry and display multiple biological activities. They developed as a cancer chemo-preventive agent and be useful in cancer therapy to sensitize tumor cells. Many efficient clinical drugs are developed by modifying the benzofuran derivatives. They are playing vital role in HIV treatment, and acts as anti-viral, anti-microbial, anti-fungal, anti-allergic activities. They are used as in oestrogenic, anti-platelet activities, and in modulating the regulation of anti-inflammatory activities. They also help in enzyme inhibition and acts as mosquito repellants too. In short, we can say that benzofuran derivatives show tremendous health benefits, which showed numerous scopes in medicinal, pharmaceutical industrial branches.

This review has highlighted the various aspects of benzofuran derivatives including their important natural product sources, biological activities and drug prospects, and chemical synthesis. Benzofuran compounds exhibit potent biological properties including analgesic, anti-inflammatory, antibacterial, antifungal, antitumor, antiviral, and enzyme inhibitory

activities. There are also recently active benzofuran compounds which have received increasing attention. Substitutions at the C-2, C-3 position in the benzofuran ring, as well as compounds substituted on the phenyl ring, encompass most of the benzofuran derivative ring systems. The most well-known benzofuran derivatives are amiodarone, geranium xanthine toxin, bergapten, globulin and usnic acid compounds, most of which have been used as lead compounds in drug design and new drug development. Benzofuran scaffolds have a wide range of biological activities, and the review of such compounds can further understand the application of such compounds in medicinal chemistry. This review details the various pharmacological activities of benzofuran derivatives and several compounds that have been successfully used in clinical practice. The clinical pharmacological activities of these compounds provide a new basis for the study of benzofuran analogs and novel potential scaffolds. In the synthesis of benzofuran compounds, this review summarizes the synthesis of benzofurans by classifying the activity of the compounds. These methods can be further used to synthesize benzofuran compounds with promising active structural units. In the natural source part, by summarizing the activity and structure of the natural products of benzofuran in the past ten years, important references are provided for structural modifcation of natural products in the yield of medicinal chemistry to improve biological activity. Although great progresses have been made in benzofuran skeleton activity and synthesis research the structure optimization and modi□cation of benzofuran compounds still needs more work to improve the selectivity of the compounds. It is hoped that the ideas in this review article and the cited examples will motivate and further optimize the full potential of benzofuran compounds, to improve the design selectivity, optimization and multifunctional opportunities of benzofuran compounds, and to help in the treatment of multifactorialdiseases in the future This review gives an overview of the broad spectrum of pharmacological activities displayed by Benzofuran. The pharmacological activities of Benzofuran derivatives have attracted considerable attention giving to the use full of this moiety in the field of medicinal chemistry. Further development can be carried out by making slight change leading to severe changes to yield better drug .The Benzofuran importance of moiety can be seen by carrying out further studies on its possible substitution. Thus this paper proves to be significant for further research work on the bioactive Benzofuran ring and biological profiles of these new generations of Benzofuran would represent a successful matrix for further circumstances of better medicinal agents.

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