Study of Benzofuran Derivatives and their Biological Significance
Study of comprehensive properties of benzofuran and its derivatives

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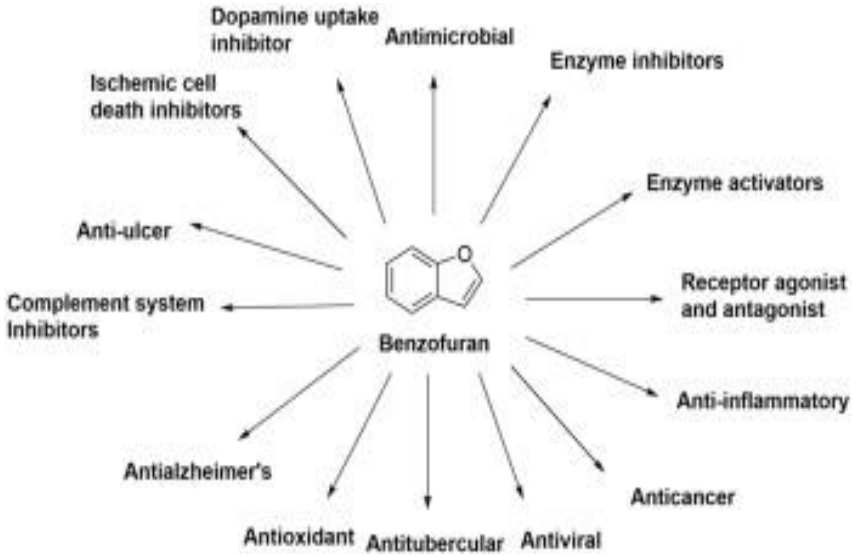
***Abstract*- Benzofuran as an important heterocyclic compound is extensively found in natural products as well as synthetic materials. Benzofuran derivatives display a diverse array of pharmacological activities. [2]**
Interest in developing new biologically active agents from benzofuran is still under consideration. In character's group of biologically alive heterocycles, benzofuran derivatives form an important group. The general of pharmacological project in individual benzofuran displays that this series of compounds is of an undisputed interest. Benzofuran and allure descendants have interested curative chemists and pharmacologists due to their evident organic exercises and their potential requests as pharmacological powers. Due to the wide range of organic ventures of benzofuran, their makeup endeavour connections have generated interest with curative chemists, and this has climaxed in the finding of various lead molecules in many ailment environments. The superior incident of benzofuran derivatives in different afflictions in very short span momentary convinces allure magnitude for curative allure research. This work endeavour to climax the progress in the miscellaneous pharmacological exercises of benzofuran derivatives [1]. Along with these this article includes structure activity relationship of benzofuran and its derivatives. The broad and potential activity of benzofuran and its derivatives has established it as one of the biological important scaffold scaffolds [57].

Keywords: **Benzofuran, heterocyclic, derivative, structure activity relationship, anticancer agent.**

INTRODUCTION:

A great number of heterocyclic compounds and heterocyclic fragments are present in many drugs due to their versatility and unique physicochemical properties and have become an important basis for medicinal chemistry. Benzofuran descendants include various biological properties in the way that anti-angering, antimicrobial, antifungal antihyperglycemic, analgesic, antiparasite, anti-tumour activities.



Such a off-course range of organic properties immensed in benzofuran encourage the thorough interest in utilizing benzofuran as construction blocks of pharmacological agents. Most of the clinically certified drugs are artificial or normally happening substituted benzofuran derivatives, few of that are melded accompanying other heterocyclic moieties. [3]

Benzofuran compounds are widely distributed in higher plants such as Asteraceae, Rutaceae , Liliaceae, and Cyperaceae . The number of such compounds discovered from Asteraceae is the highest. Studies have found that benzofuran and its derivatives are diverse in nature and exist widely in natural and non-natural compounds. The natural products containing benzofuran compounds are mainly isolated from Krameria ramosissima, Machilus glaucescens, Ophryosporus lorentzii, Ophryosporus charua and Zanthoxylum ailanthoidol. These compounds have a wide range of biological and pharmacological activities and are therefore of great value in the field of drug discovery. Moreover, benzofuran derivatives are also biodynamic agents that can be used in the design and development of new potential therapeutic agents.

The best known and recognized natural products containing the benzofuran ring structure are the allantoidol, amiodarone, and bufuralol compounds. In addition, some 2-arylbenzofurans derived from natural products also possess excellent bioactivities such as anticancer, anti-inflammatory, antioxidant and antibacterial properties. Recently, an orally active, blood-brain barrier permeable benzofuran analogue was found to exhibit potent anti-amyloid aggregation activity and may offer an alternative treatment for Alzheimer's disease (AD).

In addition, the benzofuran analogue oxazolidine has been found to be a potential multifunctional molecule and may play an important role in the treatment of tumours due to its ant proliferative activity. Benzofuran compounds are expected to be important compounds for the treatment of multifactorial diseases. The purpose of this review is to summarize the recently reported natural sources of benzofuran derivatives, advances in the study of their biological activity, and the synthesis of some common benzofuran compounds, to help the reader understand the role of benzofuran in medicinal chemistry. To help them better understand their important role.

HISTORY:

Benzofuran derivatives are present in huge number of chemical entities including compound showing interesting biological activities, among them some compounds are of natural origin. In the present letter we report on the discovery of novel synthesis towards benzofuran 2-yl-methanamines and indole -2-yl methanamines respectively. These compounds were coincidentally obtained in recent medicinal chemistry project towards the preparation of (1H)-pyrazin-2-one[58].

Although 2,3-benzofuran is not used for commercial purposes, some of the coal oil containing 2,3-benzofuran is processed into a plastic called coumarone-indene resin. This resin is resistant to corrosion and is used in the production of paints and varnishes. The resin is also water resistant and is used for coating paper products and fabrics.

It is used as an adhesive for food containers and some asphalt floor tiles. This resin is approved for use as a food packaging and citrus coating. We do not know how often resins are used or if 2,3-benzofuran is introduced into food in coatings or packaging. Liquid. (NTP, 1992). Benzofuran is a member of the amphetamine and phenyl ethylamine classes. 6-APB and 5-APB were recently identified as single-furan ring benzofuran compounds used as recreational drugs to produce sympathetic stimulation and euphoria.

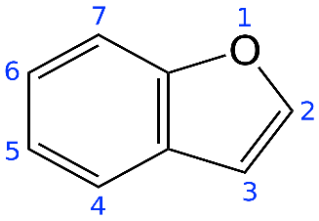
Little information is available on their toxicity. They have been hypothesized to exert their effects by stimulating catecholamine receptors and as 5-HT receptor agonists. Benzodifurans, including Bromo-DragonFLY and 2-CB-FLY, are ring-substituted phenylethylamines with potent 5HT2A agonist effects and predominantly hallucinogenic clinical effects.

Bromo-dragonFLY toxicity causes excessive sympathomimetic activity and severe vasoconstriction, possibly leading to limb amputation. Deaths from 2-CB-FLY (including Bromo-dragonFLY) misidentified as Bromo-dragonFLY have occurred in Europe and the United States. A recent survey of drug users shows that 6-APB is the most commonly used recreational benzofuran in the UK. Compared to established classical recreational drugs and other novel psychoactive substances, 6-APB and other drugs in this class are rarely used.

STRUCTURE:

Benzofuran is **a** heterocyclic compound in which **a** benzene ring and **a** furan ring are condensed. This colourless liquid is part of coal tar. Benzofuran is the **'parent'** of many related compounds with more complex structures. For example, psoralen is a benzofuran derivative found in some plants. This furan is a heterocyclic organic compound consisting of a five-membered aromatic ring with four carbon atoms and one oxygen atom. Compounds containing such rings are also called furans. Benzene also has alternating carbon-carbon single and double bonds. All CC bonds vary in length and strength.

Benzofuran



Source:

1] The broad-spectrum antiarrhythmic drug amiodarone is a representative benzofuran drug that can inhibit rapid sodium ion influx into atrial and myocardial conduction.
2] Psoralens are found in many natural plants, including limes, lemons, and parsnips. Due to its ant proliferative effect, it is used to treat various skin diseases such as psoriasis and vitiligo.
3]Angelicin gives potential effect in treatment of human neuroblastoma cancer. Use as anticancer drug
4]Bergapten is a conventional photo chemotherapy drug use in course of cancer treatment.
5] Nodekenetin and xanthotoxin are effective against skin diseases including cutaneous T-cell lymphoma, vitiligoatopic dermatitis, and psoriasis.

Description of physiochemical properties of Benzofuran molecule:

Chemical formula	C8H6O
Molecular weight	118.135 g·mol−1
Boiling point	173 °C (343 °F; 446k)
Solubility	Insoluble in water and aq alkaline solution; miscible with benzene, petroleum ether, absolute alcohol, ether.
Density	1.078 at 59 °F
Polymerization	Slowly polymerizes on standing.
Physical appearance	Volatile with steam.
Properties	2,3-Benzofuran is a colourless, sweet-smelling, oily liquid made by processing coal into coal oil. It IS not used for any commercial purposes, but the part of the coal oil that contains 2,3-benzofuran is made into a plastic called coumarone-indene resin. This resin resists corrosion.
IUPAC name	1-Benzofuran[1]
Other names	Benzofuran[1] Coumarone Benzo[b]furan

Synthesis of benzofuran:
The benzene ring is fused with five member furan ring and formed bicyclic ring benzofuran or coumarone. Benzofuran was first prepared from coumarin with name coumarone. The intermediate 3,4-dibromo-3,4-dihydrocoumarin with KOH leading to benzofuran by PERKIN rearrangement

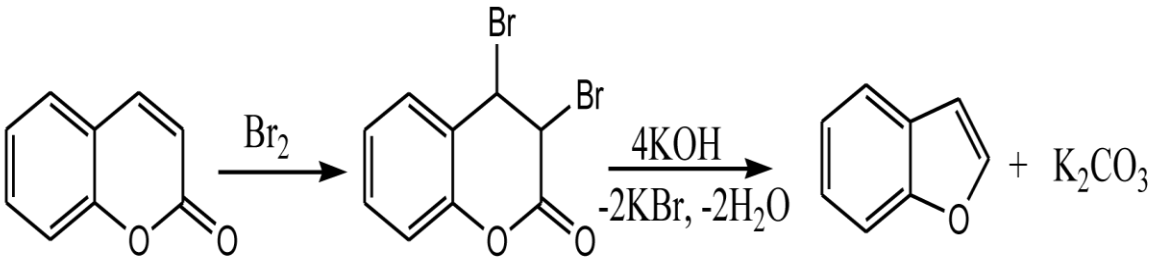


Figure 1 :The thermal cyclodehydration of 2-alkylphenols leads to 2-alkylbenzofurans.

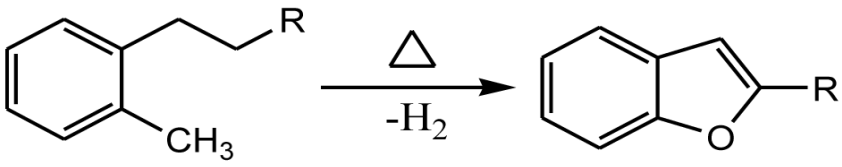
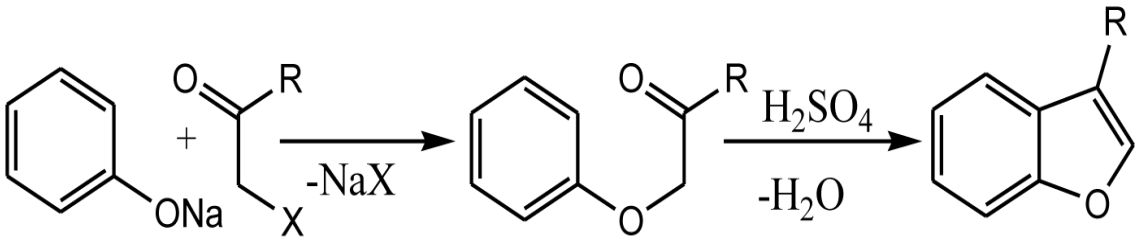


Figure 2: Benzofuran are available by reaction of phenolates with halo ketones pursued by cyclodehydration with H2SO4, polyphosphoric acid or zeolites.

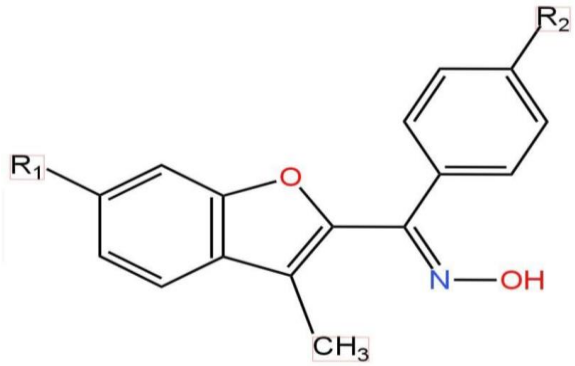


Structure relationship activity of benzofuran derivatives :

1) The thiadiazole derivative of benzofuran will the most potent anti-inflammatory compound after 2 h and it showed also reasonable anticonvulsant activity in ScMet without neurotoxicity. The pyrazole ring system is more active than the 1, 3, 4-thiadiazole one.
2) The aryl benzofuryl ketoxime moiety with azole residue—both with proven antimycotic activity and gave satisfactory increases in activity introduced alone—in a single molecule did not give the desired successful activity values
3) The pyrazole derivative of benzofuran showed a higher antinociceptive effect than all other heterocycles.

R'=H, Cl and R"=H, Cl

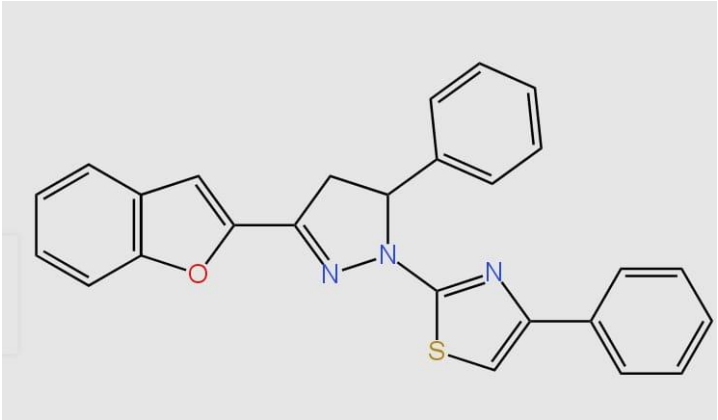
4) The N-alkyl-N-hydroxyureas are also capable of inhibiting the synthesis of leukotrienes. The Benzofuran derivatives



containing hydroxyurea fra ingments at position 3 of the benzofuran ring will show anti-inflammatory activity.

R=CH3 or CH2Ph

5) The 1-(thiazol-2-yl) pyrazoline derivatives of benzouran showed excellent activity against Gram-negative bacteria

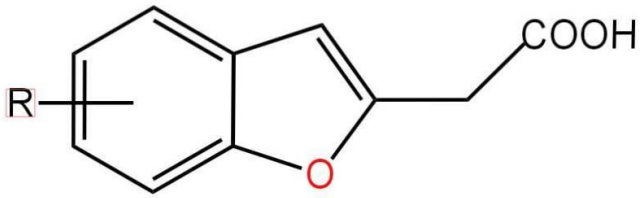


(inhibitory zone 25 mm), good activity against Gram-positive bacteria (inhibitory zone 20 mm).

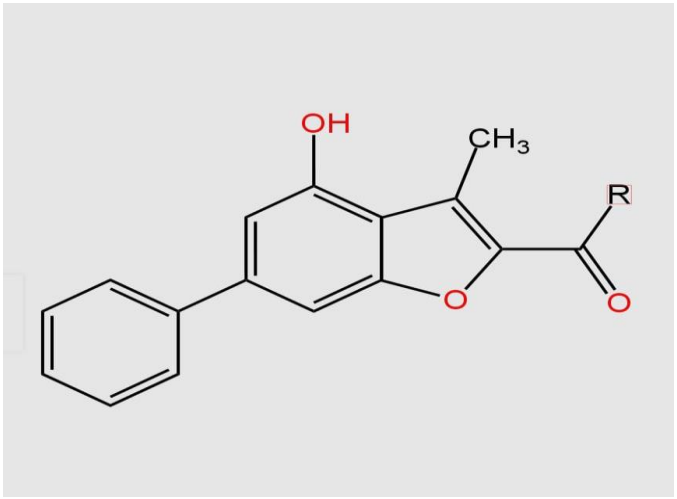
6) All following compounds showed inhibition zones and therefore antifungal activities against C. Albicans more than the reference sample Flucanazole, while compound showed similar antifungal activity against C. AAlbicans

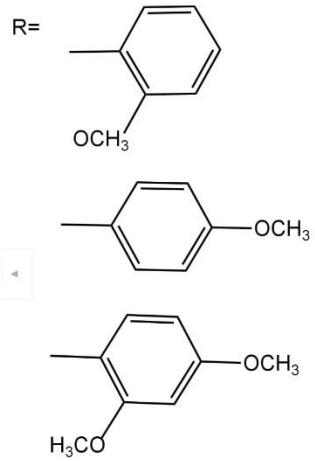
7) It can be concluded that benzofuran, pyrazoline and thiazole moieties are essential for the antimicrobial activity.

8) The anti-inflammatory activity of arylalkanoic acids derivatives of benzofuran is due primarily to their ability to inhibit cyclooxygenase and thus to disrupt prostaglandin biosynthesis.



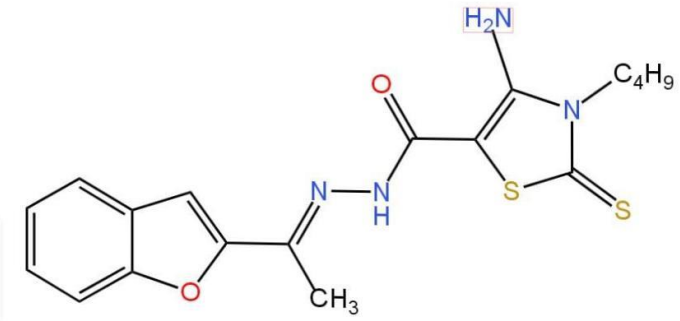
9) The phenyl ketone without a substituent on the benzene ring showed relatively weak cytotoxicity, its derivatives, which has a methoxy group at the ortho position were moderately active as an anti-tumor agent.





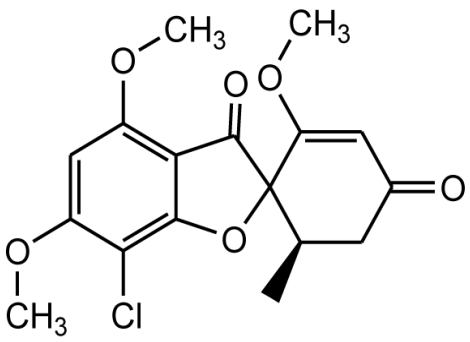
10) The methoxy group at the para position also improved the biological activity to some extent. The two methoxy groups at the ortho and para positions was the most potential anti- tumour benzofuran derivative.

11) The 4-amino-3-butyl-2-thioxo-2,3-dihydro-thiazole-5-carboxylic acid-(1-benzofuran 2-yl-ethylidene)- hydrazide will to have moderate in vitro anti-HIV-1 activity.
The 2-[(1- benzofuran-2-yl-ethylidene) hydrazono]-3-phenyl-thiazolidin- 4-one has a larger antiviral cytopathic effect.
The substituted thiazolidinon-2-ones increased the anti-HIV potency. The above compound (R = phenyl) had the highest activity, which was decreased when R = n-butyl groups was separated by one carbon atom spacers.



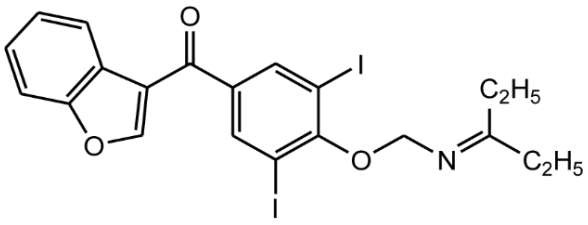
12) The p-tolyl substituted thiazole derivatives of benzofuran decreased the growth breast and lung cancer to some extent compared with compound (R = benzyl), which was completely inactive.
13) The Amiodarone, an iodinated lipophilic benzofuran derivative is widely used in the treatment of ventricular tachyarrhythmia and atrial fibrillation.[57]

Important examples of drugs which contain benzofuran moiety :-
It has been reported that Benzofuran derivatives possess a variety of biological activities such as anticancer, antiviral, immunosuppressive, antioxidant, anti-fungal and other useful activities
1] Antifungal agents:
Griseofulvin is an antifungal medicine that is used to treat infections such as ringworm, athlete's foot, jock itch, and fungal infections of the scalp, fingernails, or toenails.

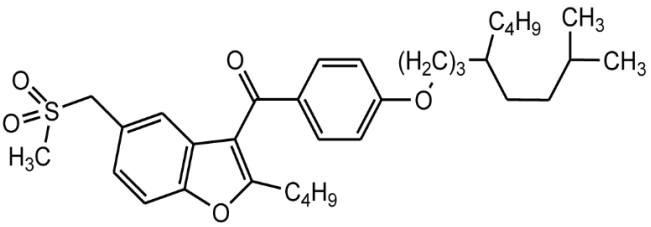


Griseofulvin

2] Anti-arrhythmic agents:
Amiodarone is an anti-arrhythmic agent used for both ventricular and supraventricular arrhythmias. Dronedarone is mainly used for the indication of cardiac arrhythmias



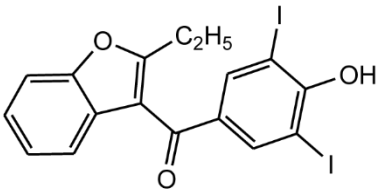
Amiodarone



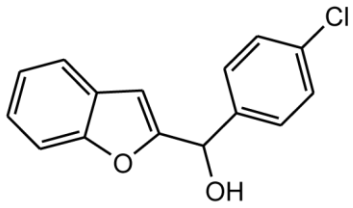
Dendideron

- Amiodarone is the most effective antiarrhythmic drug for maintaining sinus rhythm for patients with atrial fibrillation.

3] Antihypertensive agents:
Benziodarone and Cloridarol are vasodilators



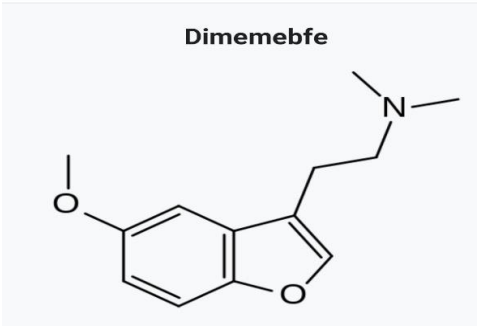
Benziodrone



Cloridoral

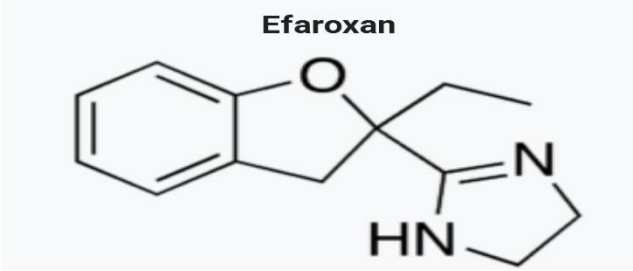
4] Serotonin Receptors agonist:

Dimemebfe is an agonist of the 5-HT1A and 5-HT2 serotonin receptors



5] A2-adrenergic antagonist:

Efaroxan is a α2-adrenergic antagonist

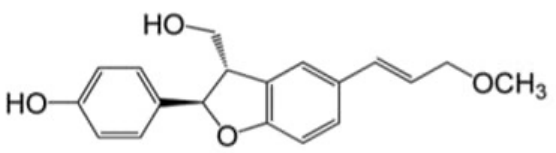


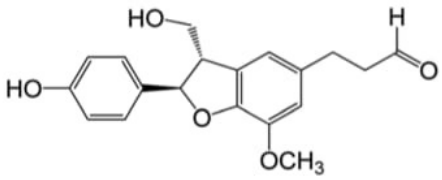
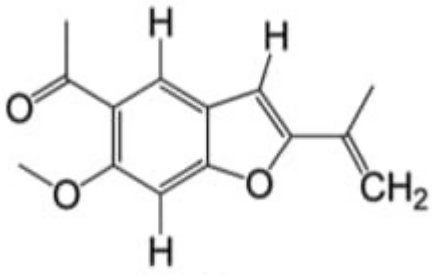
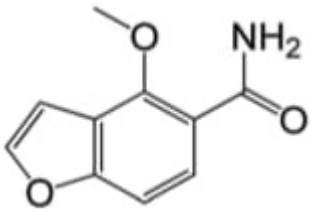
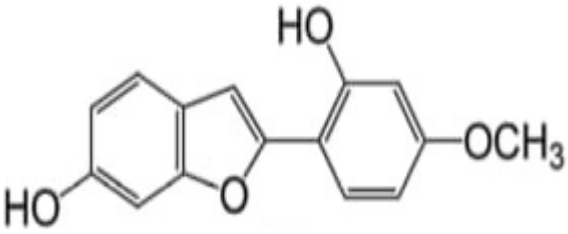
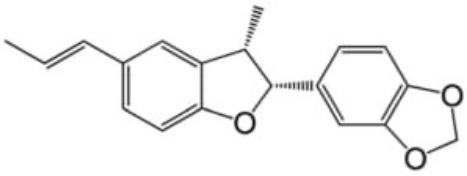
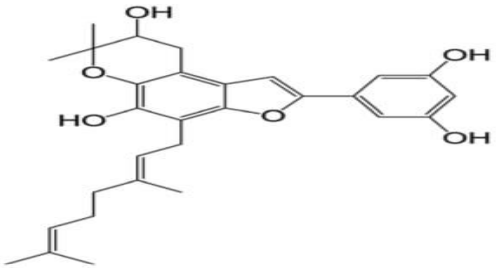
6] Antipsychotic agents:

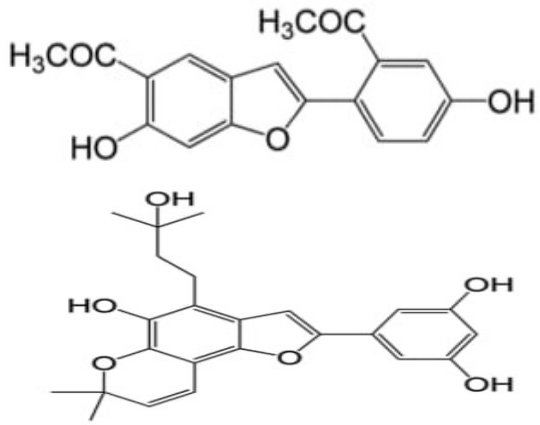
Elopiprazole is a phenylpiperazine class drug and have antipsychotic activity.

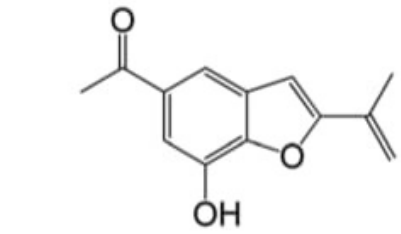
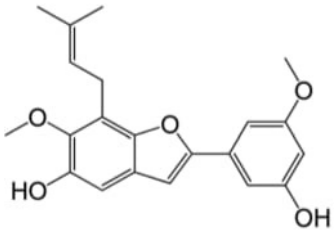
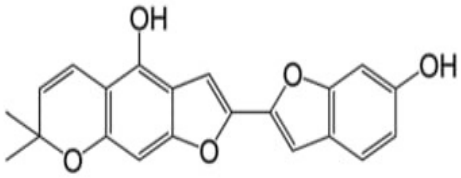
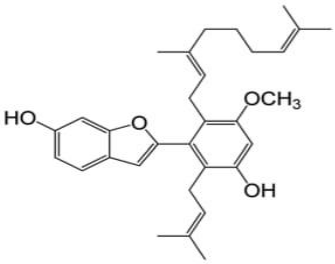
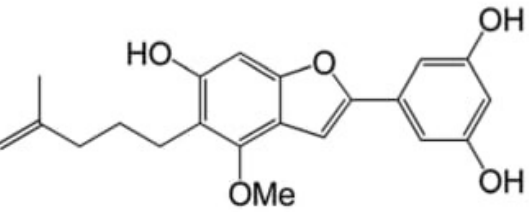
Activity of benzofuran derivatives-

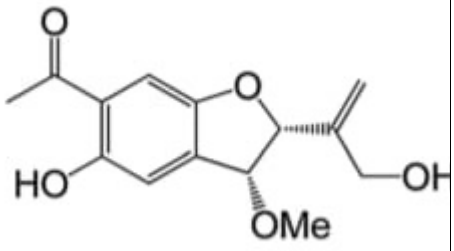
Natural products have been obtained in recent years from biologically active compounds and benzofuran compounds :-

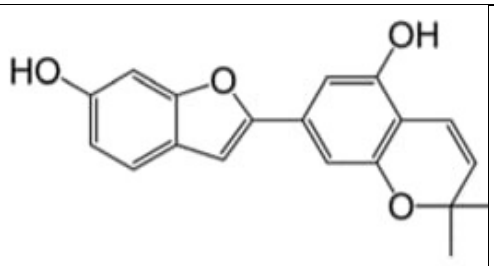
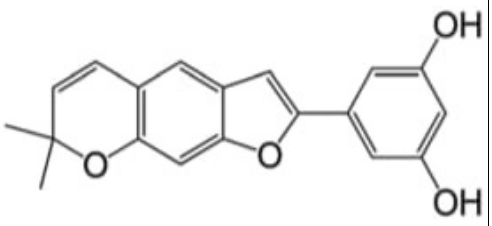
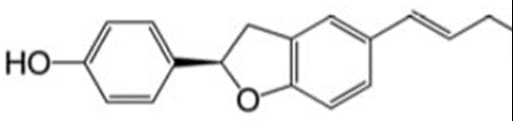
Structure	Genus and species name	Territorial	Extraction isolation	Biological activity
	(butterbure) Mappianthus iodides	Southern China	2017	Anti-cancer activity Cytotoxicity against HL-60, SMMC7721, A-549, MCF-7 and SW-480

				
	(Butterbure) Petasites hybridus	Europe, West Asia, North America	2015	Anti-cancer activity It has cytotoxic and apoptotic effects on human breast cancer MCF-7 cells
	(Fabaceae) Tephrosia purpurea	Eastern India to Central Bangladesh	2015	Anti-allergic activity For the treatment of allergic diseases, including rhinitis
	(Leguminosae) Sophora tonkinensis	South China, Korea	2014	Anti-allergic activity Inhibition of IL-6 production in HMC-1 cells produces anti-allergic effect
	philippinensis (Aristolochiaceae) Aristolochia fordiana	Southwestern China	2013	Anti-oxidation activity Inhibition of NO release in cells
	(Morus) Morus wittiorum	Tropical and Subtropical regions of Asia, Africa, South America	2014	Anti-oxidant activity Potentially effective antioxidants

	(Leguminosae) Mucuna birdwoodiana	Southern China	2009	Anti-oxidation Potentially effective antioxidants

	(Asteraceae) Ageratina adenophora	Mexico	2018	Anti-fungal activity Dehydrotrienone benzofuran derivative, eco-friendly antifungal agent
	(Fabaceae) Calpocalyx Dinklage	Western Central Africa	2017	Anti- inflammatory Inflammatory disease multi-target agent
	(Artocarpus) Artocarpus heterophyllus	Tropical regions of Asia	2017	Anti-cancer Activity Cytotoxic activity against human oral cancer (KB), human breast cancer (MCF-7) and lung cancer (NCI-H187) cell lines
	(Moraceae) Artocarpus lakoocha	Asia and Southeast Asia	2017	AChE and BChE Inhibitory As a potential new anti-ChE agent
	(Moraceae) Chlorophora regia	Tropical West Africa, Senegal, Gambia and Ghana	2016	Anti-inflammatory As an antioxidant inhibitor

	(Asterothamnu) Asterothamnus centrali-asiaticus	Gansu, Nei Mongol, Ningxia, Qinghai, SE Xinjiang (S Mongolia	2016	Anti-oxidant As a potential antioxidant

	(Moraceae) Morus alba	Asia (Vietnam, China, Japan, and South Korea)	2016	Inhibition of pancreatic lipase Effectively inhibit pancreatic lipase as a potential diet pills
 	(Moraceae) Morus nigra	West Asia	2014	Anti-tumor Multifunctional anti-tumor agent

Benzofuran derivatives as anticancer agent

1)Halogen Derivatives of Benzofuran:-

The addition of some Halogens such as bromine, chlorine, or fluorine into the benzofuran ring are resulted in a significant increase in anticancer activities. This is due to halogens have ability to form a "halogen bond"; an attractive interaction between the electrophilic halogen and a molecules nucleophilic sites, which improves the binding affinity. For example, a set of seven derivatives (1, 1'-(5,6- dimethoxy-3-methyl-1-benzofuran-2,7-diyl) dimethanone) were synthesized via standard bromination reaction and condensation with aryl/ hetroarylpiperazine. Therefore those halogens derivatives undergoes 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2h-tetrazolium bromide (MTT) assays against three cancer cell lines (human chronic (K562),and acute (HL60) leukemia cells, human cervical cancer cells (HeLa), and one normal endothelial cancer cell (HUVEC). In most cases, the halogen atoms is attached to alkyl or acetyl chains rather than the benzofuran ring .This does not deter the compounds cytotoxic activity as evidenced by electron- rich bromomethyl benzofuran , which produced pronounced cytotoxic activity in both normal and cancer cells.

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Fig.1

Fig.2

2. Hybrid Benzofuran as Anticancer Agent

Chalcone, trizole, piperazine and imidazole substituted benzofuran are the novel classes of hybrid benzofurans derivatives which come up as potent cytotoxic agents. The synergetic cytotoxic effect of heteroatom-substituted benzofuran presents good approach for the development of potent anticancer drugs with activities against malignant tumors.

3. Piperazine- Based Benzofuran derivatives

Piperazine is a six-membered ring containing two nitrogen atoms at opposite positions, which shows activities against a variety of cancers cell lines. Derivatives bearing keto- substituent on the piperazine ring (compounds **11a-d**) exhibited the most cytotoxic activity against cancer cells. (See fig 3.)

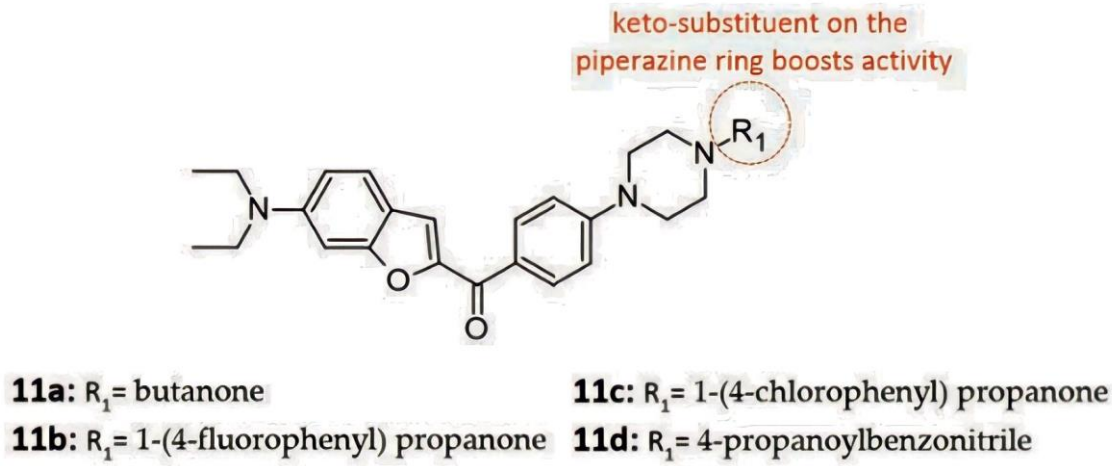

Fig.3

A hybrid of 2-benzoyl benzofuran with N-aryl piperazine linker is considered to be more biologically active than unsubstituted benzofuran. Benzofuran piperazine hybrids were designed, synthesized, and tested via MTT assays against lung cancer (A549), human cervical carcinoma (Hela), and colonic cancer (SGC7901) cell lines. The addition of halide such as fluoro-, chloro-, and cyano- at the para position of benzene in compounds **11b, 11c,** and **11d (see fig)** was beneficial for anticancer activity.

4. Pyrazole-Based Benzofuran Derivatives

Pyrazole is a five membered aromatic heterocyclic ring containing two neighboring nitrogen atoms. Pyrazole derivatives have previously shows antitumor activity against several types of cancer.

In an effort to discover novel potent c-Src(non –receptor tyrosine kinase) inhibitors as anticancer agents, a set of benzofuran-pyrazoles hybrids containing chalcones, pyrazoline, isoxazole, and thiopyrimidine substituents were in vitro-synthesized and tested for their anticancer activity.

5. Chalcone- Based Benzofuran Derivatives

Chalcone is a naturally occurring compound derived from plants, which is recognized as a valuable scaffold with potent anticancer activity. Thus the synergistic cytotoxic effect of chalcones and benzofuran, yields the compounds that are used to treat malignant tumors.

Encouraged by the anticancer potential of chalcones, a set of 1-(7-ethoxy-1-benzofuran2-yl) substituted chalcone derivatives via the base-catalyzed Claisen-Schmidt reaction was synthesized. All derivatives were then tested by sulforhodamine B (SRB) and adenosine 50-triphosphate (ATP) cell viability assays, against breast (MCF-7), non-small cell lung (A549), and prostate (PC-3) cancer cell lines.

6.Benzene- Sulfonamide- Based Benzofuran Derivatives

Benzene-sulfonamide and its derivatives are used as anticancer and antitumor. Benzene-sulfonamide-based benzofuran derivative (5-[benzyl-(4-chlorophenyl) sulfonylamino]-n-[2-(dimethylamino) ethyl]-3methyl-1-benzofuran-2-carboxamide) represented in fig 4.was designed and synthesized to inhibit the hypoxia-inducible factor (HIF-1) pathway [51], which is involved in the carcinogenesis of tumor protein(p53)-independent malignant cancers.[56]

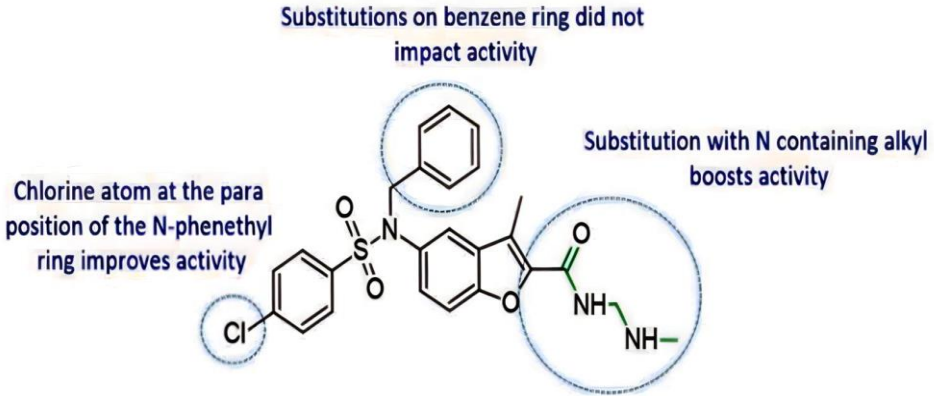

Fig.4

Conclusion: The above review of benzofuran concludes that benzofuran have broad applications in biomedical fields such as antibacterial, anti-inflammatory, anticancer, antiviral, ant tuberculous, and antioxidant activity. This review article highlights different aspects of benzofuran derivatives, including their important natural product sources, their biological activity and pharmaceutical prospects, their synthesis and structure activity relationship. The best-known benzofuran derivatives are amiodarone, angelicin, bergapten, nodeketenetin, and xantoxin compounds, most of which are used as lead compounds in drug design and drug development. The natural sources section summarizes the activity and structure of benzofuran natural substances over the last decade, providing important information on the structural modification of natural substances in the field of medicinal chemistry to improve their biological activity. Also this article studied the anticancer activity of benzofuran derivatives such as halogen derivatives, hybrid benzofurans, pyrazole based derivatives etc.

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REFERENCES:

1. K. Chand, Rajeshwari, A. Hiremathad, M. Singh,M. A. Santos and R. S. Keri, Pharmacol. Rep., 2017, 69,281–295.
2. A. Radadiya and A. Shah, Eur. J. Med. Chem., 2015, 46, 356–376.
3. J. W. Jung, J. H. Park, K. H. Seo, E. J. Oh, D. Y. Lee andD. W. Lim, J. Korean Soc. Appl. Biol. Chem., 2015, 58, 541–543
4. H. Khanam and Shamsuzzaman, Eur. J. Med. Chem., 2015,97, 483–504.
5. P. Proksch and E. Rodriguez, Phytochemistry, 1983, 22,2335–2348.
6. M. Asif, J. Anal. Pharm. Res., 2016, 3(2), 00048–00050.
7. M. M. Heravi, V. Zadsirjan, H. Hamidi and P. H. T. Amiri,RSC Adv., 2017, 7, 24470–24521.
8. M. Kamal, A. Shakya and T. Jawaid, International Journal of Medicine and Pharmaceutical Sciences, 2011, 1, 1–15.
9. X. L. Xu, Y. R. Yang, X. F. Mo, J. L. Wei, X. J. Zhang andQ. D. You, Eur. J. Med. Chem., 2017, 137, 45–62.
10. Z. Liang, H. Xu, Y. Tian, M. Guo, X. Su and C. Guo,Molecules, 2016, 21, 732.
11. R. Kenchappa, Y. D. Bodke, S. Telkar and M. A. Sindhe, J.Chem. Bio., 2017, 10, 1–13.
12. C. Aswathanarayanappa, E. Bheemappa, Y. D. Bodke,V. K. Bhovi, R. Ningegowda and M. C. Shivakumar, Med.Chem. Res., 2012, 22, 78–87.
13. E. Marwa Abdel-motaal, M. Kandeel, M. Abou-Elzahab andF. Elghareeb, European Scientific Journal, 2017, 13, 297–313.
14. A. Hiremathad, K. Chand and R. S. Keri, Chem. Biol. Drug Des., 2018, 92, 1497–1503.
15. M. Th´evenin, S. Thoret, P. Grellier and J. Dubois, Bioorg.Med. Chem., 2013, 21, 4885–4892.
16. H. M. Ragab, H. M. A. Ashour, A. Galal, et al., J. Med. Chem., 2008, 51, 2883–2886.
17. Y. S. Xie, D. Kumar, V. D. V. Bodduri, P. S. Tarani, B. X. Zhao and J. Y. Miao, Tetrahedron Lett., 2014, 55(17), 2796–2800.
18. A. Higashi, N. Kishikawa, K. Ohyama and N. Kuroda,Tetrahedron Lett., 2017, 58, 2774–2778.
19. S. Gupta, S. Adhikary, R. K. Modukuri, D. Choudhary,R. Trivedi and K. V. Sashidhara, Bioorg. Med. Chem. Lett.,2018, 28, 1719–1724.
20. C. L. Ka and J. W. Chern, Tetrahedron Lett., 2001, 42, 1111–1113.
21. V. Ugale, H. Patel, B. Patel and S. Bari, Arabian J. Chem.,2017, 10, S389–S396.
22. U. Sharma, T. Naveen, A. Maji, S. Manna and D. Maiti,Angew. Chem., 2013, 52, 12669–12673.
23. T. Promchai, P. Janhom, W. Maneerat, R. Rattanajak,S. Kamchonwongpaisan, S. G. Pyne and T. Limtharakul, Nat. Prod. Res., 2018, 1–5.
24. H. Chen, X. Zeng, C. Gao, P. Ming, J. Zhang and C. Guo, Sci.Rep., 2015, 5, 10893.
25. H. Zelov´a, Z. Han´akov´a and Z. Cerm ˇ ´akov´a, J. Nat. Prod.,2014, 77, 1297–1303.
26. J. O. Kyekyeku, S. Kusari and R. K. Adosraku, Fitoterapia,2016, 108, 41–47.
27. Y. X. Tan, H. Q. Wang and R. Y. Chen, Fitoterapia, 2012, 83,750–753.
28. H. J. Ha, D. W. Kang and H. M. Kim, J. Med. Chem., 2018, 61,396–402.
29. A. Baldisserotto, M. Demurtas, I. Lampronti, D. Moi,G. Balboni and S. Vertuani, Eur. J. Med. Chem., 2018, 156,118–125.
30. A. John and M. D. Oates, N. Engl. J. Med., 1987, 316, 455–466.
31. S. D. Leo and L. E. Braverman, The Thyroid and Its Diseases,2019, pp. 417–433.
32. P. E. Mouli, S. Parthiban, R. Priya, T. Selvakumar,M. Deivanayagi and S. Kumar, Int. J. Nutr., Pharmacol.,Neurol. Dis., 2013, 3, 229.
33. D. Z. Wei, X. Y. Guo and L. N. Lin, In□ammation, 2016, 39,1876–1882.
34. I. Lampronti, N. Bianchi and M. Borgatti, Eur. J. Haematol.,2003, 71, 189–195.
35. M. A. Rahman, N. H. Kim and H. Yang, Mol. Cell. Biochem.,2012, 369, 95–104.
36. A. Tanew, B. Ortel and K. Rappersberger, J. Am. Acad.Dermatol., 1988, 18, 333–338.
37. M. Santoro, C. Guido and F. De Amicis, Oncol. Rep., 2016,35, 568–576.
38. S. K. Bose, S. Dewanjee and R. Sahu, Nat. Prod. Res., 2011,25, 1444–1449.
39. C. S. Vijayakumar, S. Viswanathan, M. Kannappa Reddy,S. Parvathavarthini, A. B. Kundu and E. Sukumar,Fitoterapia, 2000, 71, 564–566.
40. M. Takai and Y. Uehara, J. Med. Chem., 1979, 22, 1380–1384.
41. M. Cardarelli, G. Serino and L. Campanella, Cell. Mol. LifeSci., 1997, 53, 667–672.

42. F. Odabasoglu, A. Cakir and H. Suleyman, J.Ethnopharmacol., 2006, 103, 59–65.
43. G. Zheng, S. Luo, S. Li, J. Hua, W. Li and S. Li,Phytochemistry, 2018, 148, 57–62.
44. K. Dwfg, N. M. Lekane, S. S. Kulabas, H. Ipek, T. T. Tok andB. T. Ngadjui, Phytochemistry, 2017, 141, 70–79.
45. S. Boonyaketgoson, V. Rukachaisirikul, S. Phongpaichitand K. Trisuwan, Tetrahedron Lett., 2017, 58, 1585–1589.
46. S. Boonyaketgoson, V. Rukachaisirikul, S. Phongpaichitand K. Trisuwan, Tetrahedron Lett., 2017, 58, 1585–1589.
47. Y. M. Wang, J. Q. Zhao, S. Y. Zhou, J. L. Yang, X. J. Yao andY. D. Tao, Tetrahedron, 2016, 72, 4910–4917.
48. M. T. Ha, M. H. Tran, K. J. Ah, K. J. Jo, J. Kim and W. D. Kim,Bioorg. Med. Chem. Lett., 2016, 26, 2788–2794.
49. Z. Zoo□shan, J. Hohmann and A. Hunyadi, Phytochem. Rev.,2018, 13, 1–15.
50. Z. H. Jiang, Y. P. Liu, Z. H. Huang, T. T. Wang, X. Y. Feng,H. Yue, W. Guo and Y. H. Fu, Bioorg. Chem., 2017, 75,260–264.
51. A. Soleimani, Comb. Chem. High Throughput Screening, 2015,18, 505–513.
52. M. C. Shill, A. K. Das, T. Itou, S. Karmakar, P. K. Mukherjeeand H. Mizuguchi, Bioorg. Med. Chem., 2015, 23, 6869–6874.
53. H. Yoo, H. S. Chae and Y. M. Kim, Bioorg. Med. Chem. Lett.,2015, 46, 5644–5647.
54. Z. B. Zhou, J. G. Luo and K. Pan, Planta Med., 2013, 79,1730–1735.
55 H. Li, F. Zhai, M. Yang, X. Li, P. Wang and X. Ma, Molecules,2012, 17, 7637.
56. Benzofuran Derivative ; Joviana Farhat , Lara Alzyound 2,3 , Mohammad Alwahsh 4,5,6 and Basem At Omari 1,7.
57. Ali.K.Akhtar , Waquar A . Khan , Lubna azmi Faculty of pharmacy , Integral University Lucknow .
58. J.Schlosser, E. Johannes, M. Zindler, J. L3mmerhirt, B. Sommer, M. Schitt, C. Peifer.