https://doi.org/ 10.33472/AFJBS.6.10.2024.1045-1058

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

An Overview of the Phytochemistry and Pharmacological Effects of Benzofuran Derivatives

Manisha Negi[1], Mayank Yadav[1*], Ranjit Singh[1], Sanjay Singh[2]

[1]Department of Pharmaceutical Sciences, Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University, Gangoh, Saharanpur-247341, Uttar Pradesh, India

[2]Department of Pharmacy, Siddhartha Institute of Pharmacy, Sahastradhara Road, Near IT Park-248001, Dehradun Uttarakhand India

*Corresponding author E-mail: - mayankmp@gmail.com

Article History Volume 6,Issue 10, 2024

Received:28 Apr 2024

Accepted : 06 May 2024

doi: 10.33472/AFJBS.6.10.2024.1045-1058

Abstract

This overview's objective was to evaluate the efficacy of benzofuran derivatives, with a focus on phytochemistry and pharmacological applications. The drug's phytochemistry, mechanism of action, pharmacokinetics, pharmacodynamics, and clinical data has all been examined in the pertinent literature. Derivatives of benzofuran have been demonstrated to have positive effects, therefore they have been utilized in many cases in everyday patients; nevertheless, there have also been reports of serious pharmacological side effects. The relevance of the benzofuran moiety has been clarified by a number of biological studies, suggesting that it may be a useful medicinal agent. A thorough pharmacological evaluation and synthesis of benzofuran analogs are given in this review.

Keywords: Benzofuran, anticancer, antibacterial and antifungal.

1. Introduction

Nature always stands as a golden mark to exemplify the outstanding phenomena of symbiosis. Natural products from plant, animal and minerals have been the basis of the treatment of human disease. It plays an important role in the development of potent therapeutic agents [Saklani *et al.,* 2012]. Plants are crucial source of different pharmacological activities [Bisht *et al.,* 2023]. Medicinal plants represent a rich source of potent and powerful drugs. Plants are utilized for treating a variety of diseases from time im-memorial [Chandra *et al.,* 2023]. A heterocyclic compound termed benzofuran is produced when the ring structures of furan and benzene fuse together (Fig. 1). This transparent liquid is one of the components of the mixture of coal tar. Benzofuran bridges several other molecules with complex configurations as a "parent" compound. The search for innovative drugs has benefited from the large degree of variety provided by the structural diversity of these heterocyclic molecules. It has been demonstrated that such drugs have a variety of therapeutic properties [Khanam *et al.,* 2014].

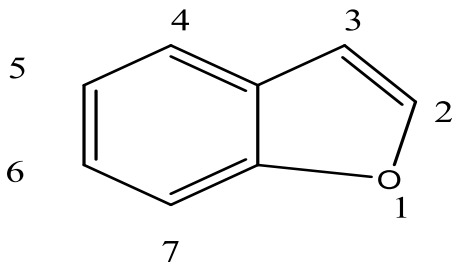


Fig.1. Chemical structure of benzofuran

Derivates of benzofuran are biodynamic compounds with several applications, it can be used to synthesize potentially beneficial pharmaceutical substances [Khatana K *et al.,* 2020]. Natural products frequently contain an extensive range of benzofurans, each with a distinct substitution molecule at the C-2 position. Zanthoxylum ailanthoidol, Ophryosporus charua, and Ophryosporus lorentzii have all been shown to have significant quantities of naturally occurring benzofuran compounds. Amiodarone and bufuralol are the most widely recognized benzofurans [Asif *et al.,* 2016].

Owing to their varied biological and pharmacological characteristics, these compounds hold great significance in the realm of innovative drug exploration [Kishore 2017: Heravi 2017]. In recent times, it has been discovered that numerous biological actions, including anti-inflammatory qualities, have been demonstrated for benzofurans and their derivatives [Xie *et al.,* 2014], anticancer agents [Xu *et al.,* 2017], antibacterial [Liang 2016: Kenchappa 2017], anti-AIDS [Hiremathad *et al.,* 2018], anti-oxidative [Aswathanaraynappa 2012: Marwa 2017], and anti-parasitic capabilities [Thevenin *et al.,* 2013]. They have dual uses: as a fluorescent analgesic sensor and as a medicine to increase bone mass [Higashi *et al.,* 2017]. Drugs containing benzofuran are anticipated to have a significant function in the treatment of complex illnesses [Miao *et al.,* 2019]. This research looks at the biological activity, synthesis, and natural sources

of numerous benzofuran compounds to illustrate to readers the extraordinary significance of benzofuran in the field of chemistry. The analysis is summarized in Fig. 2

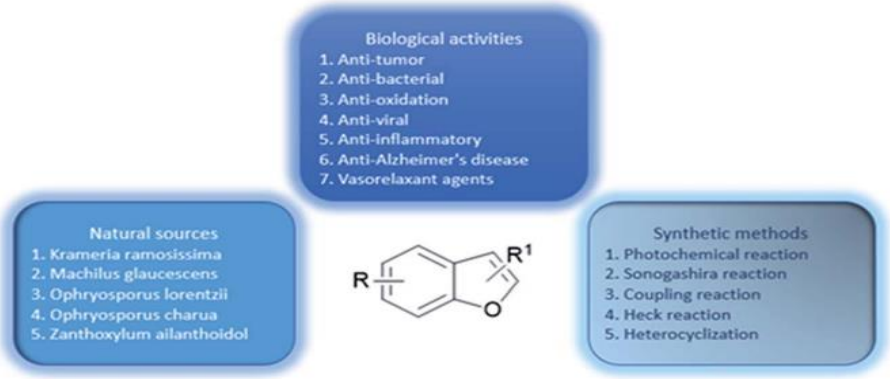


Fig. 2 Comprehensive understanding of benzofurans through biological activities, natural sources, and synthetic methods.

Benzofuran ring containing natural compounds

Fig. 3 lists a variety of bioactive molecules with a benzofuran moiety [Wang *et al.*, 2019].

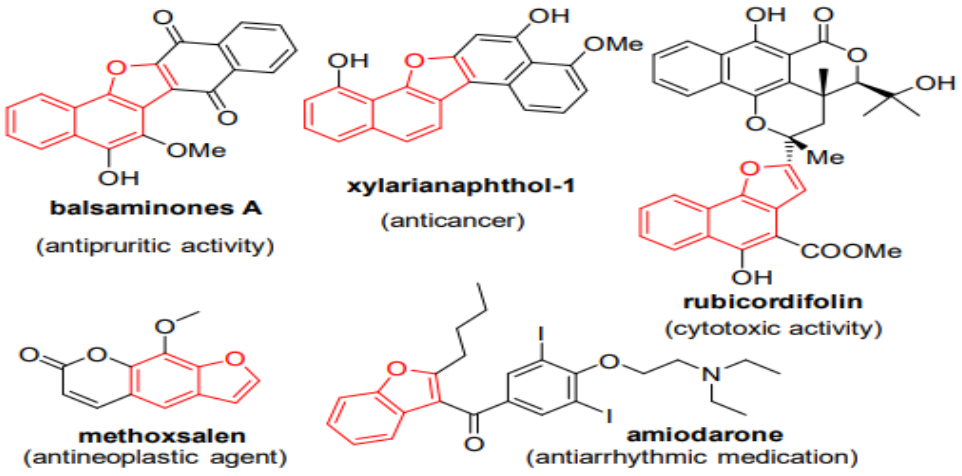
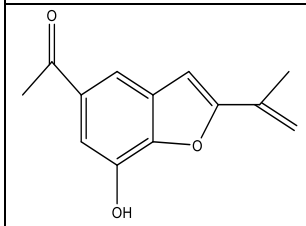
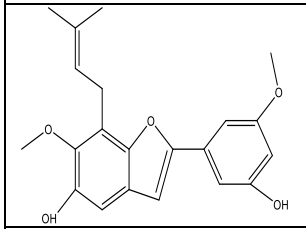
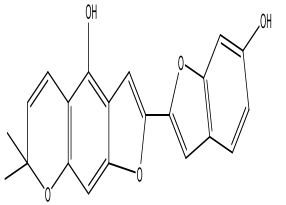
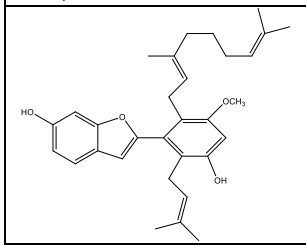
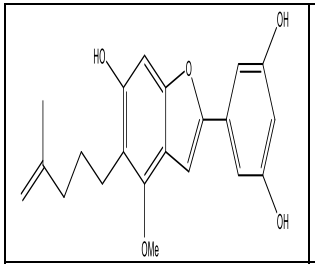
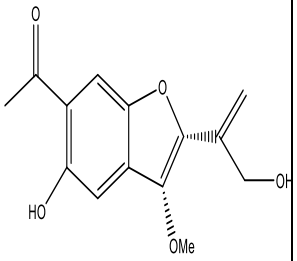
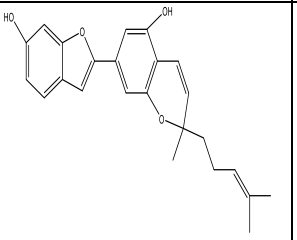
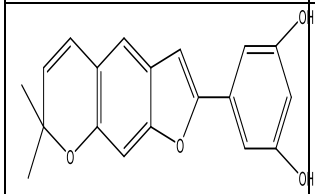


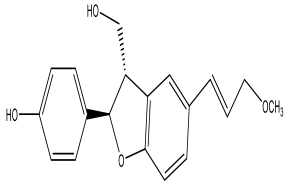
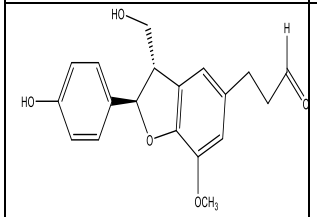
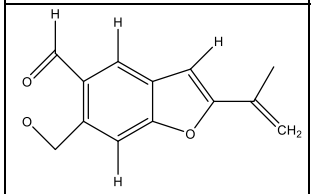
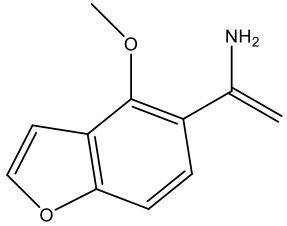
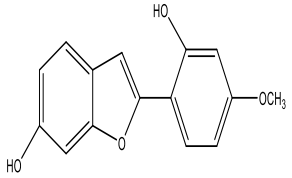
Fig: 3 Representative drug containing benzofuran core

Benzofuran-containing natural compounds

A group of chemical substances known as benzofuran compounds is frequently discovered in the environment and has long been the subject of scientific study. Several benzofuran moieties have been isolated from and exposed to plant and animal sources in the present year [Miao *et al.*, 2019]. Table 1 lists the incredible benzofuran compounds that have been found and isolated from both plants and animals.

Structure	Botanical Name	Family	Territorial	Isolation	Pharmacological activity	Methods	References
	*'Ageratina Adenophora'*	Asteraceae	Mexico.	(2018)	Anti-fungal	An environmentally friendly antifungal agent derived from dehydrotrienone benzofuran	[Zheng *et al.*, 2018]
	*'Calpocalyx dinklagei'*	Fabaceae	Central Africa's western region	(2017)	Inflammation reducing activity	Multiple target agent in inflammatory diseases	[Dwfg *et al.*, 2017]
	*'Artocarpus heterophyllus'*	Moraceae	Asian tropical areas	(2017)	Antitumor	Human cell lines for breast cancer (MCF-7), oral cancer (KB), and lung cancer (NCI-H187) were tested for cytotoxic activities.	[Boonyaketgoson *et al.*, 2017]
	*'Artocarpus lakoocha'*	Moraceae	Southeast and East Asia	(2017)	BchE and ACE nhibitory	As a possible novel anti-ChE therapeutic.	[Boonyaketgoson *et al.*, 2017]

	*'Chlorophora regia'*	Moraceae	Ghana, Senegal, Gambia, and tropical West Africa	(2016)	Inflammation reducing activity	Antioxidant	[Zelov *et al.*, 2014]
	*'Asterothamnus centrali-asiaticus'*	Asteraceae	Northeast Mongolia, Gansu, Ningxia, Qinghai, and SE Xinjiang	(2016)	Anti-oxidant	Antimicrobial and antioxidant	[Wang *et al.*, 2016]
	*'Morus alba'*	Moraceae	Asia includes China, Japan, South Korea, and Vietnam.	(2016)	Pancreatic lipase Inhibitor	One possible diet helper is to efficiently suppress pancreatic lipase.	[MT Ha *et al.*, 2016]
	*'Morus nigra'*	Moraceae	West Asia	(2018)	Cancer fighting activity	Multiple-purpose agent for preventing tumors	[Zoofishan *et al.*, 2018]

	*'Mappianthus iodoies'*	Icacinaceae	Southern china	(2017)	Cancer fighting activity	Cytotoxicity against MCF-7, A-549, HL-60, SMMC7721, and SW-480.	[Jiang *et al.*, 2017]
	*'Mappianthus iodoies'*	Icacinaceae	Southern china	(2017)	Cancer fighting activity	The cytotoxicity observed in A-549, MCF-7, HL-60, SMMC7721, and SW-480.	[Jiang *et al.*, 2017]
	*'Petasites hybridus'*	Asteraceae	North America, West Asia, and Europe	(2015)	Cancer fighting activity	Breast cancer in cytotoxic and apoptotic ways. AMC-7	[Soleimani *et al.*, 2015]
	*'Teprosia purpurea'*	Fabaceae	Central Bangladesh to Eastern India	(2015)	Anti-allergic activity	For treatment of allergy ailments such as rhinitis	[Shill *et al.*, 2015]
	*'Sophora tonkinensis'*	Leguminosae	Korea and South China.	(2014)	Anti-allergic activity	Inhibiting IL-6 synthesis in HMC-1 cells results in anti-allergic effects.	[Yoo *et al.*, 2015]

Synthesis of benzofuran

Benzofuran synthesis by Perkin rearrangement

The first coumarin preparation of benzofuran was coumarone. When low-valent titanium appears and o-hydroxy acetophenone is acylated with aliphatic and aromatic acid chlorides, intramolecularly cyclized ketoesters are formed, which leads to the production of benzofurans in good amounts [Kishore *et al.*, 2017]

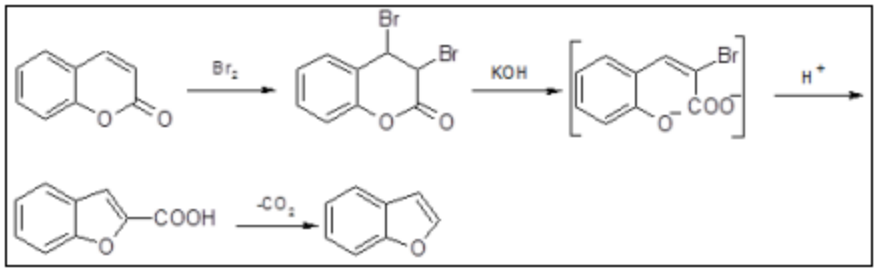


Fig: 4: Benzofuran Perkin synthesis

When titanium trichloride is reduced with powder of dry zinc in refluxing THF, a ketoester is formed. It cyclizes simultaneously with the generation of the titanium catalyst and It offers titanium trichloride pre-reduction at a different, independent stage. Low valent titanium's oxophilicity and electron transfer ability allow carbonyl compounds to undergo reductive deoxygenation to olefins, a process known as the "McMurry reaction [Gurram *et al.*, 2023].

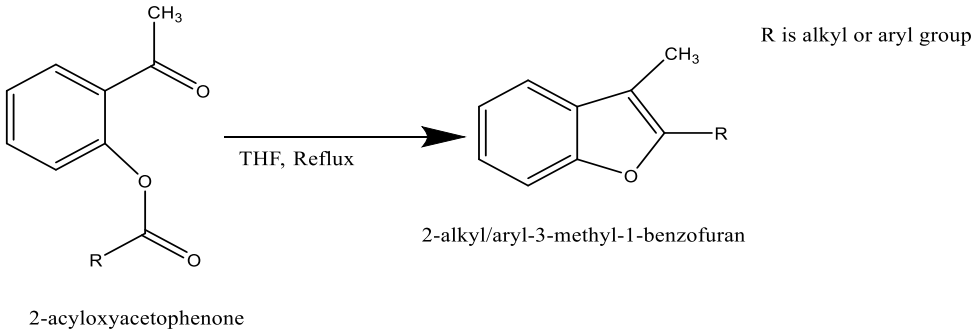
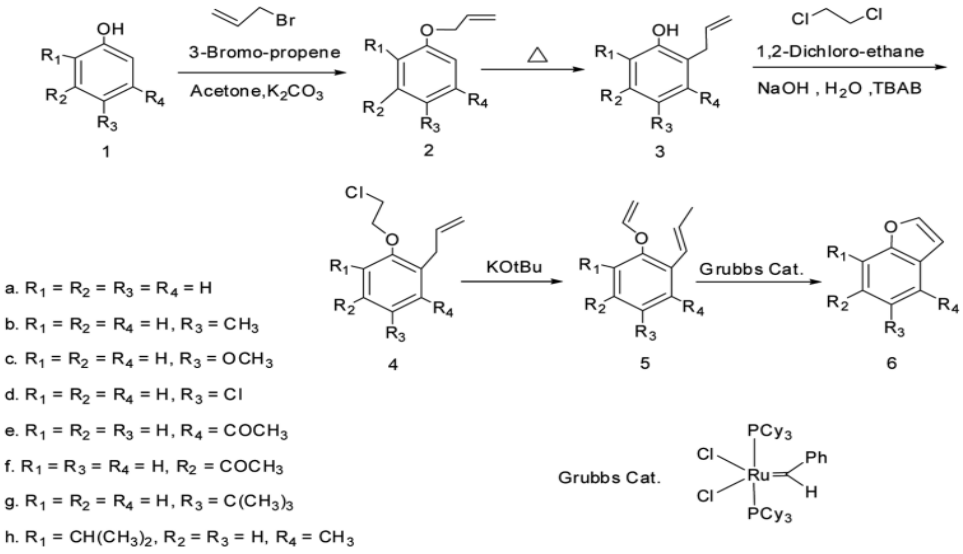


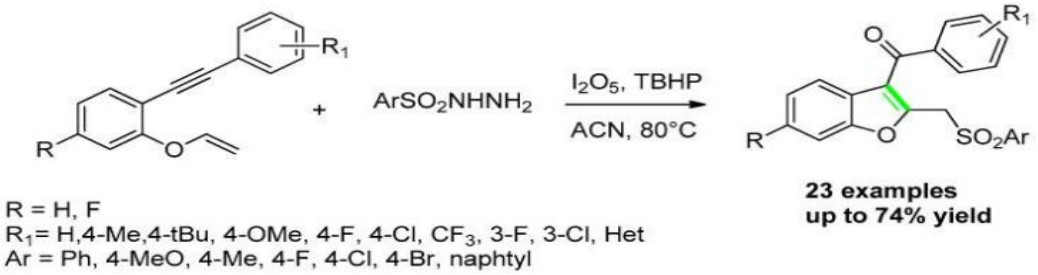
Fig: 5: Mc-Murry reaction

Preparation of benzofuran from phenol: A publication states that diverse allyl aryl ethers 2a–f can be generated through alkylating phenols 1a–f with allyl bromide in anhydrous acetone while potassium carbonate is present [Tzu 2004: Shiang 2005]. Employing a Claisen rearrangement method, after heating this allyl aryl ethers 2a–f to reflux in decalin, ortho-allyl phenols 3a–h was produced. Tetra-butyl ammonium bromide (TBAB), a phase-transfer catalyst, combined with a significant excess of dichloroethane in aqueous NaOH (20%) facilitated the easy SN2 substitution of ortho-allyl phenols 3a–h, yielding well-defined 1-allyl-2-(2-chloroethoxy)

benzenes 4a–h are monoalkylated compounds. Potassium t-butoxide was employed to treat molecules 4a through h in tetrahydrofuran (THF) at reflux. Due to this, the molecule's hydrochloric acid, or HCL, was eliminated by 1, 2-elimination, and large amounts of 5a–h were generated concurrently with double bond isomerization [Lin 2004: Huang 2001 and Wang EC 2002]. Ring-closing metathesis (RCM) was utilized to synthesize those precursors, leading to the high yield synthesis of numerous benzofurans 6a–h. Those precursors underwent ring-closing metathesis (RCM), which resulted in the high yield synthesis of several benzofurans 6a–h [Wang 2002: Chi-Lin 2011].



O-alkynylphenyl Vinylethers for Sulfonylated Benzofuran Synthesis: It has been established that the synthesis of sulfonylated benzofurans via I2O5 is an easy, metal-free approach. Oxidative cyclization of 1, 6-enynes and arylsulfonylhydrazides made it easy to carry out the current reaction and gave rise to several sulfonylated benzofurans in modest to sufficient yields [Wang *et al.*, 2019].



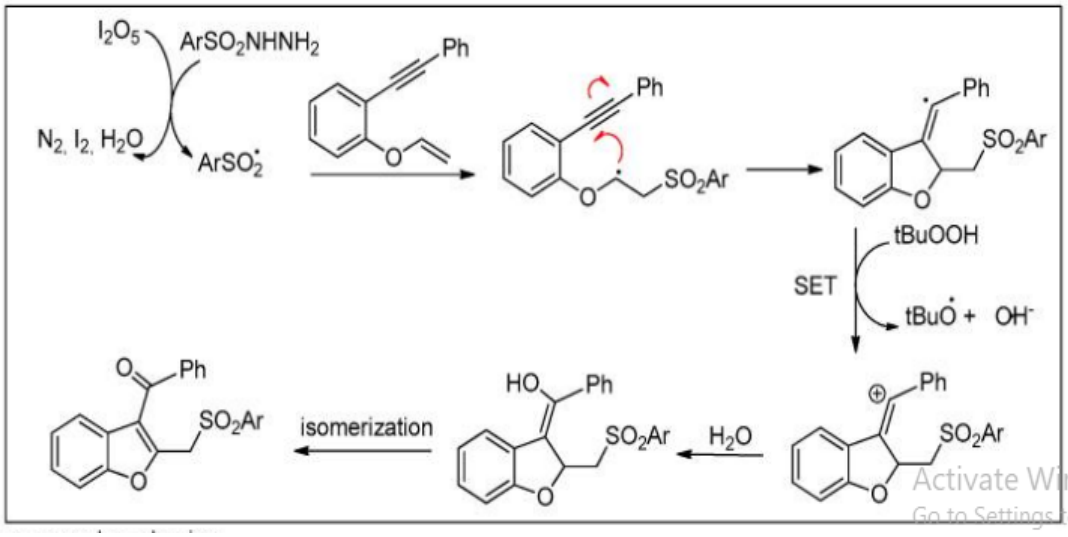


Fig: 7: Synthesis of Sulfonylated benzofurans from o-alkynylphenyl Vinylethers

Synthesis of Benzofuranoid from o-halophenol and allenes: Three components have been combined in a one-pot, copper-catalyzed reaction to produce 2-vinylbenzofurans: dichloromethane, in situ synthesised allenes, and o-iodophenols. This 2-vinylbenzofuran framework has been formed by the cascade transition of oxa-Michael addition, C-arylation, and sp3 C−H/sp3 C−Cl conversion-based vinylation [Jung *et al.*, 2016].

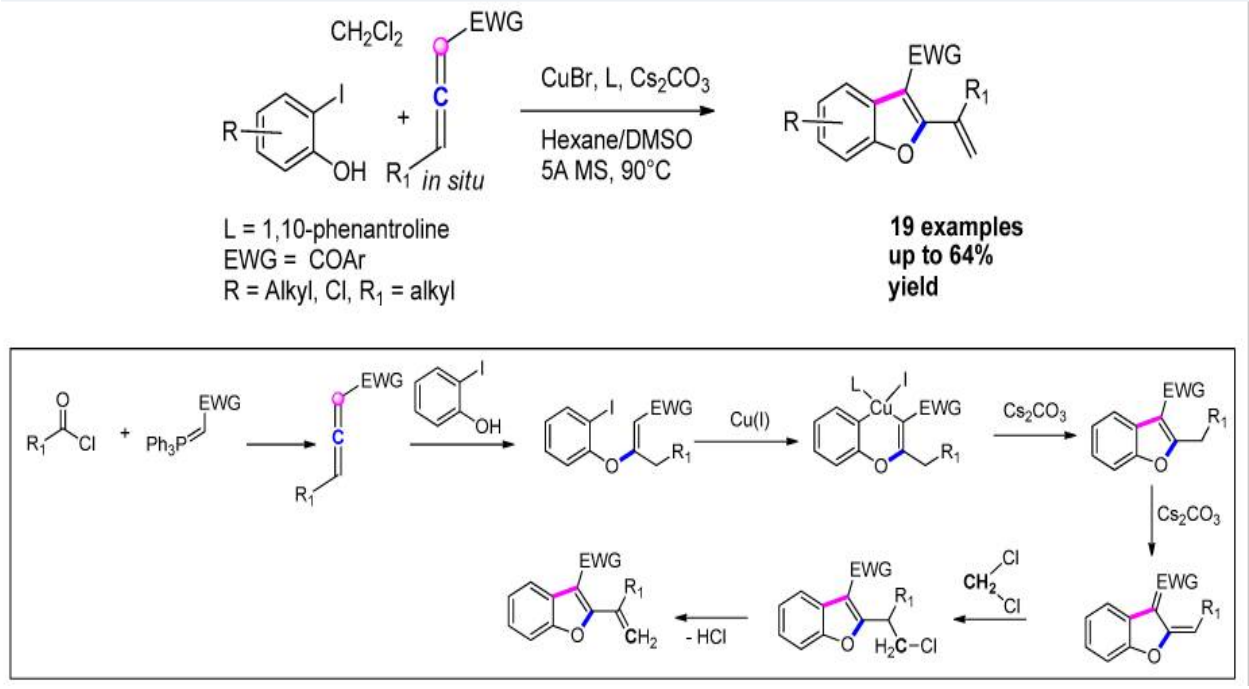
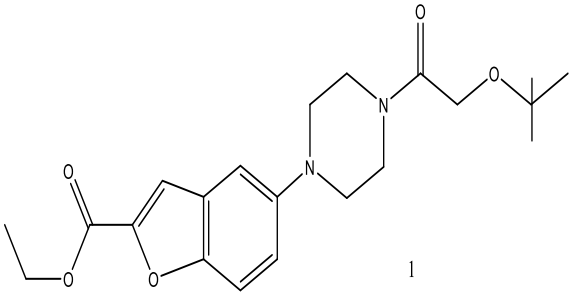


Fig: 8: Synthesis of benzofuran from o-halophenol and allenes

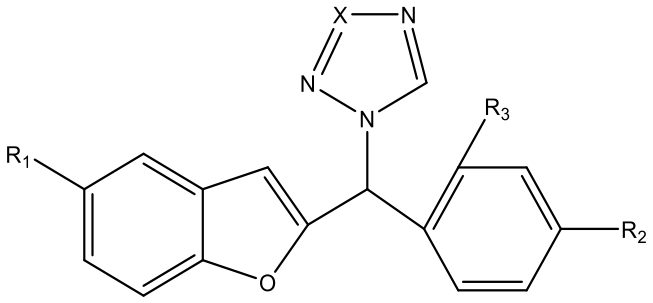
Pharmacological activities of benzofuran

Varieties of substituted benzofurans that inhibit the DNA gyrase B of Mycobacterium tuberculosis (MTB) were developed and synthesized [Renuka *et al.*, 2014]. MTB contains type 2 topoisomerase DNA gyrase, a well-known and intriguing target for developing advanced novel therapies. The most potent and effective molecule was compound 1, with an IC-50 of 3.2 ± 0.15 μM against the Mycobacterium smegmatis DNA gyrase B enzyme and 0.81 ± 0.24 μM in the MTB super coiling activity test. Chemical 1's subsequent attachment to the DNA gyraseB enzyme during the docking research demonstrated the chemical and enzyme's positive interaction. Locating it such that it forms a good fit in the hydrophobic pocket of the ligand, forming a hydrogen-bond with Arg141 and having a -8.66 kcal/mol score.



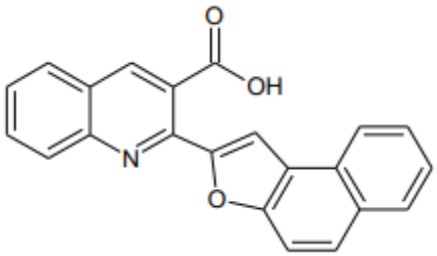
1

[1-[(benzofuran-2-yl)phenyimethyl]-triazoles and -tetrazoles were produced, and their capacity to impede human placental aromatase in vitro was examined. The aromatase enzyme's substrates were [1β-3H] -androstenedione. The triazoles' inhibitory activity was always higher than the matching tetrazoles. Replacement at the phenyl ring, specifically at R2, enhanced activity in vitro, but replacement in the benzofuran ring exerted the reverse effect. Interestingly, benzofurans substituted with imidazoles showed higher efficacy in vitro when compared to derivatives of triazole and tetrazole [Vinh *et al.*, 1999].

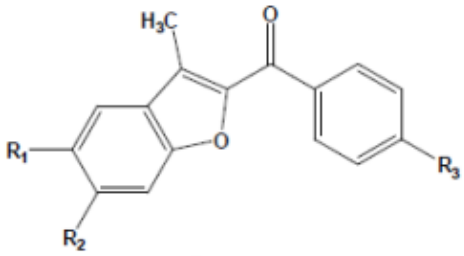


2 X=N, CH

A derivative of 2-(1-benzofuran-2-yl) quinoline-3-carboxylic acid was synthesized in a unique one-pot, three-stage process, as described [Krupa *et al.*, 2019].

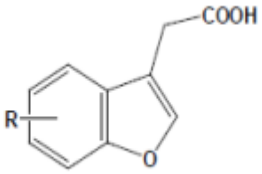


Gundogdu-Karaburuneta produced a low number of aryl [3-(imidazol-1-yl/triazol-1-ylmethyl/methyl) benzofuran-2-yl] ketoximes [Gundogdu *et al.*, 2006].
A moderate amount of activity was discovered upon examination of the compounds' antifungal characteristics.



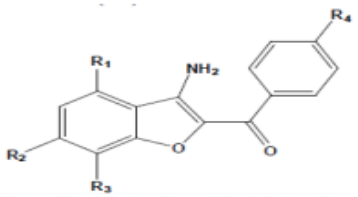
R_1=H, CH_3, Cl; R_2= H, OCH_3
R_3=H, Cl

Using a novel and easily generalized technique, 4-benzofuran-3-acetic acids were synthesized by [Santana *et al.*, 1999] in order to produce non-steroidal anti-inflammatory drugs.



R= 6-OH, 6-OH 7-CH_3, 5-CH_3, 5-OCH_3

[Radl *et al.*, 2000] infused and analyzed the analgesic properties of 3-unsubstituted 1-benzofurans and 3-amino-1-benzofurans.



R_1= H, OMe; R_2= H, OMe; R_3= H, OMe
R_4=H, Br, Ph, 2,4-diFC_6H_3

References

1. Asif M. (2016). Mini review on important biological properties of benzofuran derivatives. *Journal of analytical and pharmaceutical research*. 3(2), 12-14.

2. Aswathanarayanappa C., Bheemappa E., Bodke Y. D., Bhovi V. K. (2012). *Med. Chem. Res.*, 22, 78–87.

3. Bisht V. K., Bhandari A. K., Kandari L. S. (2023). Fatty Acids Analysis, Antioxidant, Antimicrobial and Biological Activity of Essential Oil of *Skimmia laureola* Leaves, *Vegetos*, 1-8.

4. Boonyaketgoson S., Rukachaisirikul V., Phongpaichit S. (2017). Cytotoxic arylbenzofuran and stilbene derivative from the twigs of *Artocarpus heterophyllus*. *Tetrahedron Lett*., 58, 1585–1589.

5. Chandra S., Gahlot M., Choudhary A. N. (2023). Scientific evidences of anticancer potential of medicinal plants, *Food Chemistry Advances*, 2, 100239.

6. Chi-Lin C., Chein-Hwa H., Huey-Min W., Rei-Sheu H., Ling-Ching C. (2011). Hypervalent iodine (III) reagent–mediated synthesis of 2-methyl benzofuran derivatives by Pummerertype reaction in ionic liquid, *J. Chin. Chem. Soc*., 58, 90–93.

7. Dwfg K., Lekane N. M., Kulabas S. S., Ipek H. (2017). *Phytochemistr*y, 141, 70–79.

8. Gundogdu-karaburun N., Benkli K., Tunali Y., Ucucu U. (2006). Synthesis and antifungal activities of some aryl[3-imidazol-1-yl/triazole-1-ylmethyl)benzofuran-2-yl]ketoximes. *European journal of medicinal chemistry*, 41(5), 651-656.

9. Gurram A., Chandrasekhar K., Venkata R.B. (2023). Review article on benzofuran. *World journal of pharmaceutical research*, 12 (5).

10. Heravi M.M., Zadsirjan V., Hamidi H. (2017). Total synthesis of natural products containing benzofuran rings, *RSC Adv.* 7, 24470–24521.

11. Higashi A., Kishikawa N., Ohyama K. (2017). *Tetrahedron Lett.*, 58, 2774–2778.

12. Hiremathad A., Chand K., Keri R. S. (2018). *Chem. Biol. Drug Des*., 92, 1497–1503.

13. Huang K.S., Wang E.C.A. (2001). Novel synthesis of substituted naphthalenes via Claisen rearrangement and RCM reaction, *Tetrahedron Lett.* 42, 6155–6157.

14. Jiang Z.H., Liu Y.P., Huang Z.H., Wang T.T., Feng X.Y. (2017). *Bioorg. Chem*., 75, 260–264.

15. Jung Y., Kim I. (2016). Chemoselective Reduction of Quinols as an Alternative to Sonogashira Coupling: Synthesis of Polysubstituted Benzofurans. *Org Biomol Chem,* 14(44), 10454–10472.

16. Kenchappa R., Bodke Y. D., Telkar S. (2017*). J. Chem. Bio*., 10, 1–13.

17. Khanam H, Shamsuzzaman. (2014). Bioactive benzofuran derivatives: A review. *European journal of medicinal chemistry*. 1-22.

18. Khatana K, Gupta A. (2020). An update on natural occurrence and biological activity of benzofurans. *Acta scientific medical sciences*. 4(10), 114-123.

19. Kishore R. (2017). Synthetic routes for synthesis of benzofuran-based compounds, *Journal of Chemical and Pharmaceutical Research*, 9(5), 210-220.

20. Krupa Paul M., Prashanthi Evangelin M., Phanideep V., Jaya Prakash M., Juhi Suhana S. (2019). Recent advantages in benzofuran. *Journal of pharmacognosy and Phytochemistry*, 8(4), 287-291.

21. Liang Z., Xu H., Tian Y., Guo M., Su X. (2016). Design, Synthesis and Antifungal Activity of Novel Benzofuran-Triazole Hybrids, *Molecules*, 21(6), 732.

22. Lin F., Ai-xia Y., Zhong-jian W.J. (2004). Benzofuran derivatives from *Ligularia stenocephala*, *J. Chin. Chem. Soc.*, 51, 863–868.

23. Marwa E., Abdel-motaal., Kandeel M., Abou-Elzahab M. (2017). *European Scientic Journa*l, 13, 297–313.

24. Miao Y.H., Hu Y.H., Yang J., Liu T., Wang X.J. (2019). Natural Source, bioactivity and synthesis of benzofuran derivatives. *Rsc Adv*, 9, 27510-27540.

25. MT Ha., Tran M.H., Ah K.J., Jo K.J. (2016). Potential pancreatic lipase inhibitory activity of phenolic constituents from the root barks of *Morus alba* l, *Bioorganic & Medicinal Chemistry Letter*s, 26, 2788–2794.

26. Radl S., Hezky P., Urbankova J., Vachal P. (2000). Synthesis and analgesic activity of some 1-benzofurans, 1-benzothiophenes and indoles. *Collection of Czechoslovak Chemical Communications*, 65.

27. Renuka J., Reddy KI., Srihari K., Jeankumar VU., Shravan M., Sridevi JP. (2014). Design, synthesis, biological evaluation of substituted benzofurans as DNA gyraseB inhibitors of Mycobacterium tuberculosis. *Bioorg Med Chem*, 22, 4924–34.

28. Saklani S., Chandra S., Mishra A. P., Badoni P. P. (2012). Nutritional Evaluation, Antimicrobial activity and Phytochemical Screening of Wild edible fruit of *Myrica nagi* pulp, *International Journal of Pharmacy & Pharmaceutical Sciences*, 4 (3), 407-411.

29. Santana L., Teijeira M., Uriarte E., Tearmen C., Linares B., Villar R., Laguna R. (1999). AM1theoritical study, synthesis and biological evaluation of some benzofuran analogues of anti-inflammatory arylalkanoic acids. *European journal of pharmaceutical sciences*, 7(2), 161-166.

30. Shiang K., Rong S.H., Feng L.Y., Yu-Li W., Yung-Hua L. (2005). Synthesis of certain benzo- heterocyclic compounds from 2308 A. A. ABU-HASHEM ET AL. 2-hydroxy acetophenone via cyclization and ring-closing metathesis, *J. Chin. Chem. Soc*., 52, 159–167.

31. Shill M.C., Das A.K., Itou T., Karmakar S., Mukherjee P.K. (2015). *Bioorg. Med. Chem*., 23, 6869–6874.

32. Soleimani A., Chem Comb. (2015). High Throughput Screening, 18, 505–513.

33. Thevenin M., Thoret S., Grellier P. (2013). *Bioorg. Med. Chem.*, 21, 4885–4892.

34. Tzu-Wei., Eng-Chi T., Sie-Rong W., Yu-Li L.Y.C. (2004). A new synthesis of benzofurans from phenols via Claisen rearrangement and ring-closing metathesis. *J. Chin. Chem. Soc*. 51, 1307–1318.

35. Vinh TK., Ahmadi M., Delgado PO., Perez SF., Waiters HM., Smith HJ. (1999). 1-[(Benzofuran-2-yl)phenylmethyl]-triazoles and -tetrazoles- potent competitive inhibitors of aromatase. *Bioorg Med Chem Lett*, 9, 2105–8.

36. Wang B., Zhang Q., Luo J., Gan Z., Jiang W. (2019). One-step regioselective synthesis of benzofurans from phenol and α-Haloketones. *Molecules*, 24, 2411-2187.

37. Wang E.C., Hsu M.K., Lin Y.L., Huang K.S. (2002). A new synthesis of substituted 2,5-dihydrobenzo[b]oxepines. *Heterocycles*, 57, 1997.

38. Wang E.C., Wang C.C., Hsu M.K., Huang K.S. (2002). A synthesis of substituted 3,6-dihydro-1H-benzo[c]oxocines via Claisen rearrangement and ring-closing metathesis. *Heterocycles*, 57, 2021.

39. Wang L., Zhang Y., Zhang M., Bao P., Lv X., Liu H.-G., Zhao X. (2019). Metal-free I_2O_5-mediated oxidative synthesis of sulfonylated benzofurans through cyclization reaction of 1, 6-enynes and arylsulfonylhydrazides. *Tetrahedron. Lett*., 60, 1845–1848.

40. Wang Y. M., Zhao J. Q., Zhou S. Y., Yang J. L., Yao X. J. (2016). *Tetrahedron*, 72, 4910–4917.

41. Xie Y.S., Kumar D., Bodduri V. D. V., Tarani P. S., Zhao B. X. (2014). Microwave-assisted parallel synthesis of benzofuran-2-carboxamide derivatives bearing anti-inflammatory, analgesic and antipyretic agents, *Tetrahedron Lett*., 55(17), 2796–2800.

42. Xu X. L., Yang Y. R., Mo X. F., Wei J. L., Zhang X. J. (2017). Design, synthesis, and evaluation of benzofuran derivatives as novel anti-pancreatic carcinoma agents via interfering the hypoxia environment by targeting HIF-1α pathway, *Eur. J. Med. Chem*., 137, 45–62.

43. Yoo H., Chae H. S., Kim Y. M. (2015). *Bioorg. Med. Chem. Lett*., 46, 5644–5647.

44. Zelov A. H., Hanakova Z., Cermakova Z. (2014). *J. Nat. Prod.*, 77, 1297–1303.

45. Zheng G., Luo S., Li S., Hua J., W Li. (2018). Specialized metabolites from *Ageratina adenophora* and their inhibitory activities against pathogenic fungi. *Phytochemistry*, 148, 57–62.

46. Zoofishan Z., Hohmann J., Hunyadi A. (2018). Phenolic antioxidants of *Morus nigra* roots, and antitumor potential of morusin. *Phytochem. Rev*., 13, 1–15.