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Review Article

Therapeutic Potential and Medicinal Chemistry of Benzofuran Scaffolds: A Comprehensive Review

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ABSTRACT

Benzofuran, also known as benzo[b]furan, is a 10π-electron heteroaromatic system that is considered a "privileged structure" in medicinal chemistry because of its substantial chemotherapeutic potential and adaptable core. This scaffold functions as an adaptable building block for the synthesis of novel medicinal compounds with a variety of biological profiles, such as antibacterial, anticancer, antitubercular, antioxidant, and anti-inflammatory properties. This review illustrates the creation of new benzofuran analogues as effective therapeutic agents based on thorough literature reviews. By inhibiting anti-apoptotic Bcl2 proteins and targeting vital enzymes like PI3K and VEGFR-2, benzofuran hybrids—such as those conjugated with isatin or pyrazole—exhibit strong antiproliferative effect. In tuberculosis research, the benzofuran ring is essential for attaching to Mycobacterium tuberculosis's InhA pocket and blocking the Pks13 enzyme, which is necessary for the synthesis of mycolic acid. The structure-activity relationship discussed herein provides a robust framework for the future development of next-generation multifunctional drugs designed to treat complex, multifactorial illnesses.

INTRODUCTION

Heterocyclic compounds have become the backbone of modern drug discover, with benzofuran serving as a key example. Chemists and medical researchers have shown a great deal of interest in benzofuran scaffolds because of their dynamic nature, strong chemotherapeutic potential, and adaptable physiological characteristics. These scaffolds serve as flexible building blocks for the synthesis of novel therapeutic compounds with a variety of biological activities, including as antibacterial, anti-inflammatory, analgesic, anti-hyperglycemic, anti-parasitic, and anticancer qualities [1]. Furthermore, these scaffolds enable significant

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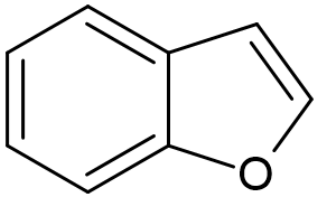
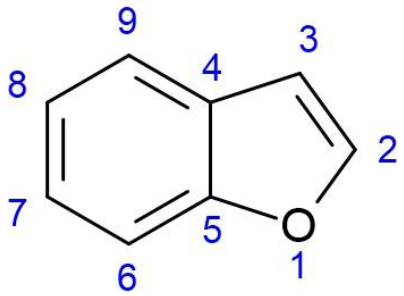
structural alterations in which the location of substituents can be tuned to improve molecular interactions and binding affinity within target proteins' catalytic pockets. These compounds are used in agricultural and other chemical industries as oxidants, brightening agents, antioxidants, and fluorescent sensors in addition to their medical uses [2].



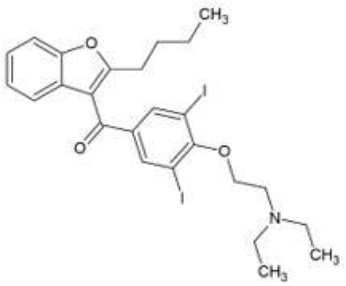
CHEMISTRY

Benzofuran, also known as benzo[b]furan, is a 10π-electron, π-excessive heteroaromatic system that is more stable than furan, mainly because of annelation of its benzene ring [3]. Its chemical reactivity is dominated by electrophilic substitution, which happens almost exclusively at the C-2 position; this particular orientation is driven by the high electronegativity of oxygen, which favors an ionic intermediate with a localized negative charge at the 2-position. Benzofuran, which is categorized as a "privileged structure" in medicinal chemistry, functions as a flexible core for a variety of biological activities, such as neuroprotection, anti-inflammatory, and antioxidant properties. By causing apoptosis, benzofuran hybrids (conjugated with moieties like isatin or pyrazole) exhibit strong antiproliferative action against liver, cervix, and colon cancer cell lines in oncology research[4].

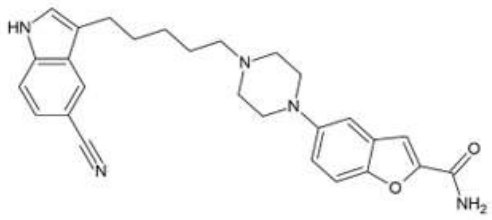


Mechanistically, it has been demonstrated that these conjugates dramatically reduce the expression of the anti-apoptotic Bcl2 protein while raising the amounts of cleaved PARP, which results in programmed cell death[5]. Its biological potency is frequently increased by the deliberate insertion of halogens, nitro, or hydroxyl groups at the 4, 5, and 6 positions of the ring system, and its antimicrobial profile is equally strong [6].

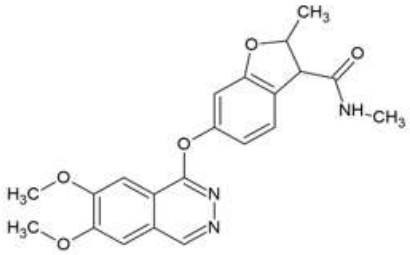
STRUCTURE OF APPROVED DRUGS CONTAINING BENZOFURAN RING



Amiodarone

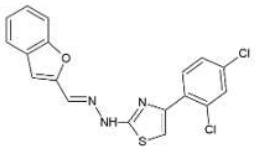


vilazodone

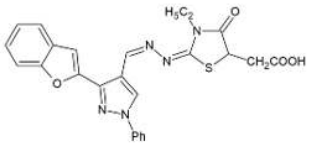


Fruquintinib

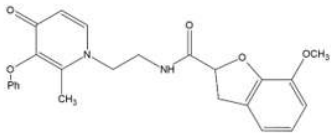
SEVERAL SUBSTITUTED BENZOFURAN HYBRIDS



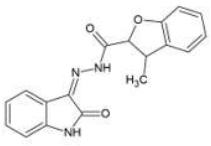
Benzofuran-Thiazolylhydrazone hybrid



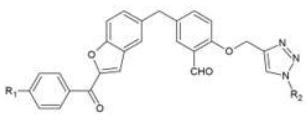
Benzofuranoyl-pyrazole hybrid



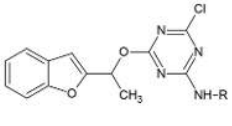
Benzofuran-hydroxypyridinone hybrid



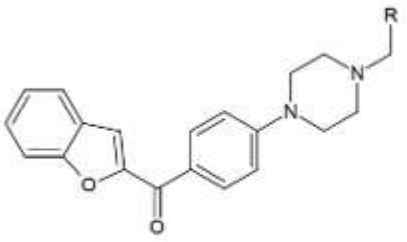
Benzofuran-isatin hybrid



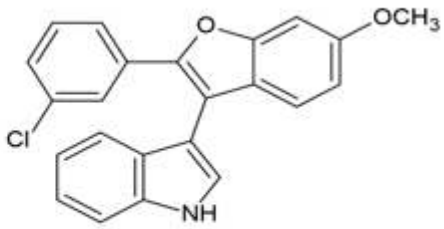
Benzofuran-1,2,3 triazole hybrid



Benzofuran-triazine hybrid



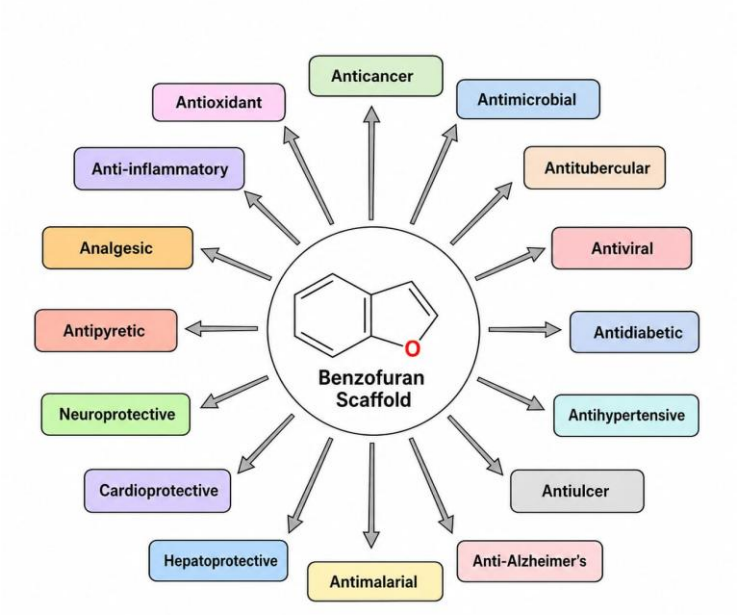
Benzofuran-*N* aryl piperazine hybrid



Benzofuran-indole hybrid

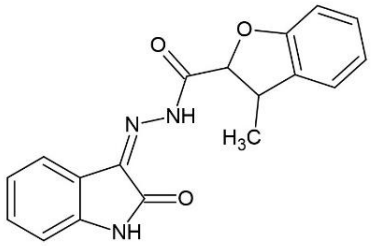
VARIOUS BIOLOGICAL ACTIVITIES OF BENZOFURAN SCAFFOLD

In nature, benzofuran compounds are a common class of chemicals. The majority of benzofuran compounds have substantial biological activity, including anti-tumor, antibacterial, antioxidative, and antiviral properties, according to numerous studies.

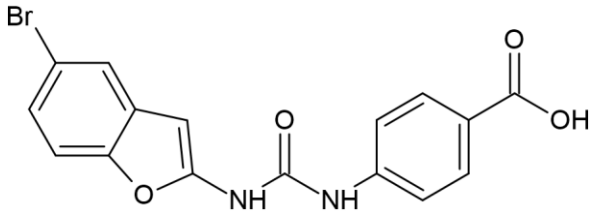


ANTICANCER

According to recent studies, the benzofuran scaffold is a flexible "privileged" core in medicinal chemistry that can be used to create powerful anticancer drugs that target a variety of cancers. In colon cancer (cell lines SW-620 and HT-29), novel benzofuran-isatin conjugates have shown strong antiproliferative action. Lead compounds 5a and 5d cause apoptosis by blocking the anti-apoptotic Bcl2 protein and raising cleaved PARP levels[5].



Benzofuran-based carboxylic acids, particularly compound 9e, selectively block the hypoxia-induced carbonic anhydrase IX and XII isoforms in the therapy of breast cancer, resulting in cell cycle arrest at the G2/M phase[7].

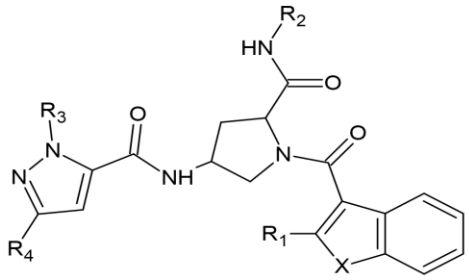


Another study describes the development of benzofuran hybrids intended for dual-target inhibition, such as derivatives of piperazine and thiosemicarbazone. In the study, Compound 8, a benzofuranyl thiosemicarbazone, was shown to be the most effective contender, exhibiting high activity against cervical (Hela) and hepatocellular (HePG2) cancer cell lines. Anticancer Mechanism included PI3K and VEGFR-2, two enzymes essential for tumor cell survival and angiogenesis (the creation of new blood vessels), are both inhibited by this chemical. It causes late apoptosis and successfully stops the cell cycle at the G1/S phase[8].

The activity of new benzofuran compounds substituted at the third and fifth positions against liver, lung, and breast cancer is reviewed. Compound BZ-16 had the strongest activity, especially against HepG2 liver cancer. The study proposes a complex mode of action that includes interference with the VEGFR-2 pathway, suppression of DNA topoisomerase, and production of ROS (reactive oxygen species). The results highlight how adding electron-withdrawing groups (such as fluorine or chlorine) and nitrogen-containing heterocycles (such as pyrrole or piperazine) at key locations on the benzofuran ring greatly increases anticancer activity[9].

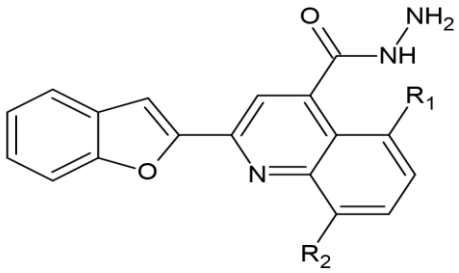
ANTITUBERCULAR ACTIVITY

Research demonstrates that the benzofuran ring is a special and adaptable heterocyclic pharmacophore with substantial therapeutic potential against *Mycobacterium tuberculosis* (Mtb). In order to combat medication resistance, it investigates several benzofuran-based compounds intended to target crucial mycobacterial enzymes as InhA and Pks13[10]. The benzofuran core is essential for binding within the InhA pocket, according to structural analyses of benzofuran pyrrolidine pyrazole derivatives. Usually, it is wedged between residues like Leu207 and Met103 and buried in hydrophobic side chains like Ile215 and Ala157. The benzofuran core is nevertheless essential for preserving strong inhibitory potency (IC50) against the enzyme, even while substituents at other locations affect cellular activity (MIC90) [11].



Chemical structure of benzofuran pyrrolidin pyrazole derivatives

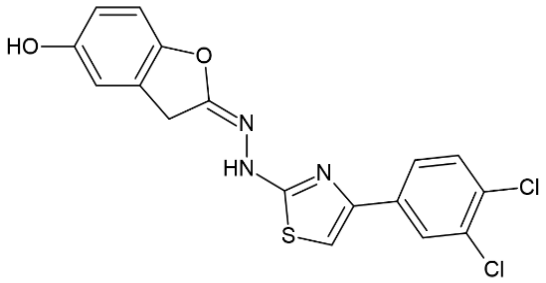
Benzofuran-1,3,4-oxadiazole hybrids that target the Pks13 enzyme—which is essential for the production of mycolic acid—have been the subject of recent in silico research. Lead compounds exhibit binding affinities (−14.82 kcal/mol) greater than those of typical inhibitors like TAM-16. These scaffolds retain a high degree of stability within the active site of the enzyme, according to molecular dynamics simulations[10]. Benzofuran must be coupled with other nitrogen heterocycles in order to inhibit the H37Rv strain, as demonstrated by the synthesis of benzofuran-quinoline-isatin hybrids. With minimum inhibitory concentrations (MIC) as low as 12.5 µg/ml, these compounds show strong antitubercular efficacy while preserving acceptable pharmacokinetic and safety profiles. When taken as a whole, these articles demonstrate that the benzofuran ring is an essential component of new, direct-acting antitubercular drugs[11].



Benzofuran-carbohydrazide derivative

ANTIOXIDANT ACTIVITY

Because of its electron-rich aromatic structure, which uses resonance to stabilize free radicals, the benzofuran ring has strong antioxidant action. In drug design, substituted derivatives—particularly those with hydroxyl or methoxy groups improve their capacity to scavenge radicals. Recent studies revealed that benzo[b]furan derivatives connected to thiazole (compound 10), thiophene (compound 11), or triazole (compound 9) rings have strong activity; in ABTS tests, some of them achieve 87.8% inhibition. Resonance effects across the fused heterocyclic system stabilize the hydrogen donation from amino groups, which is the main cause of its effectiveness[12]. In another study new thiazole hybrids based on benzofuran were done and discovered a meta, para-dichloro derivative (compound 2g) as a potent antioxidant with an IC 50 of 30.14µM in DPPH experiments, almost matching the reference standard, gallic acid[6].



Compound 2g

Studies investigated benzofuran and found a direct correlation between the quantity and location of hydroxyl groups on the arylidene moiety and the capacity to scavenge radicals. In DPPH and FRAP tests, their research revealed that 2,3,4-trihydroxybenzylidene derivatives (compound 7) and 2,5-dihydroxybenzylidene derivatives (compound 6) had a strong antioxidant activity[14]. Additionally, researchers synthesized propanehydrazide derivatives with furan and naphthalene moieties and found that certain structures (compounds 36 and 39) could outperform ascorbic acid's antioxidant power by about 1.4 times. All of these sources suggest that although the benzofuran core is a strong scaffold, its antioxidant performance is maximized through polyhydroxylation or the integration of heterocycles rich in nitrogen and sulfur[13].

STRUCTURE ACTIVITY RELATIONSHIP

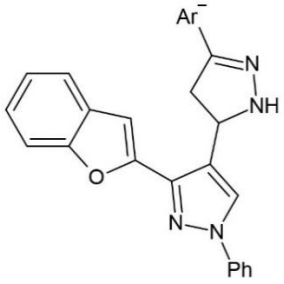
Substitutions at the C-2 position, such as esters or heterocyclic rings, are crucial for cytotoxic activity because they affect selectivity toward cancer cells over normal ones. The structure-activity relationship (SAR) of benzofuran derivatives shows that their anticancer potency and selectivity are highly dependent on the type and position of substituents appended to the core. A common structural prerequisite that provides a framework for further functionalization is the presence of a 3-methyl group [15].

The main factors influencing activity are electronic effects. Halogenation (Cl, Br, F) greatly increases binding affinity by creating halogen bonds, especially at the 3-methyl position or the para position of connected N-phenyl rings. Success in targeting the HIF-1 pathway required substituting nitrogen-containing alkyl chains for esters and adding a chlorine atom at the para position. On the other hand, neighboring ortho and para substitutions on specific phenyl rings might occasionally be harmful to activity [16]. Linkers play a critical role as well; carbohydrazide, hydrazine, or hydrazide linkers help benzofuran hybridize with other pharmacophores such as isatin. Incorporating an arylsulfone moiety for carbonic anhydrase inhibition increases selectivity for tumor-associated isoforms by promoting binding to the hydrophilic area of the active site. Additionally, the compound's drug-like profile and cytotoxic effect are frequently optimized by the addition of bulky, hydrophobic groups or hydrophilic heteroatoms like piperidine [17].

REVIEW OF LITERATURE

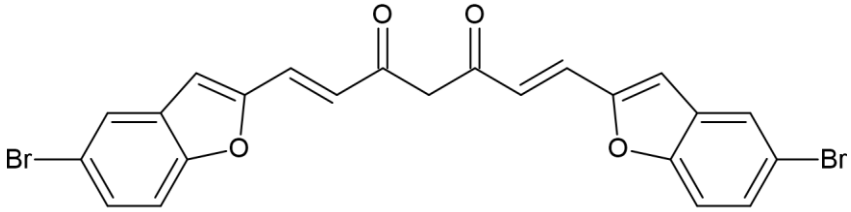
1. *Abd El-Karim et al.* synthesized a new series of benzofuran–pyrazole-based analogues as potential antiproliferative agents targeting

various protein kinases. The 1H-benzo[d]imidazole derivative 3d demonstrated the highest inhibition against sixty human cancer cell lines and showed multi-targeting PK-suppression activity against B-Raf, c-Met, Pim-1, EGFR, and VEGFR-2[18].

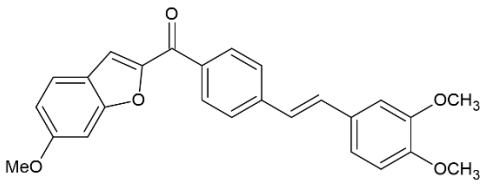


Ar = 1H-benzo[d]imidazol-2-yl

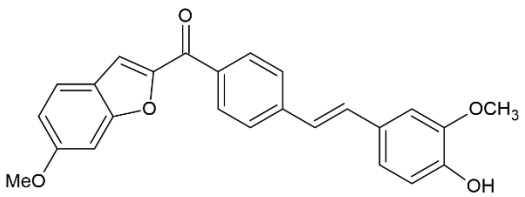
2. *Younus et al.* performed the synthesis of three novel curcumin-like compounds derived from a benzofuran nucleus and characterized them using spectroscopic techniques. Biological evaluations were done and these synthesized analogues exhibited significantly higher antimicrobial and antifungal activity compared to standard curcumin. Specifically, the 5-bromo-substituted derivative outperformed known heterocyclic analogues by exhibiting exceptional inhibition zones against pathogens like *Staphylococcus aureus* and *Candida albicans[19].*



3. *Herrera-Ramírez et al.* synthesized a novel series of benzofuran-pterostilbene hybrids using the Mizoroki-Heck cross-coupling reaction as a key synthetic step. Among the library, hybrids 6d and 6e exhibited the greatest biological activity against SW480 colorectal adenocarcinoma cells by triggering programmed cell death and chromatin condensation [20].



Compound 6d

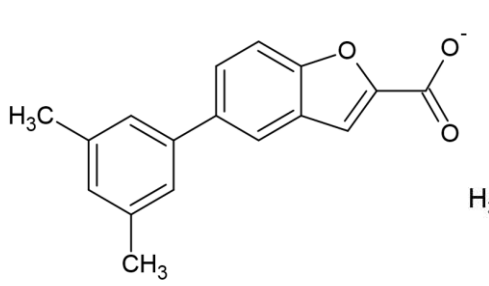


Compound 6e

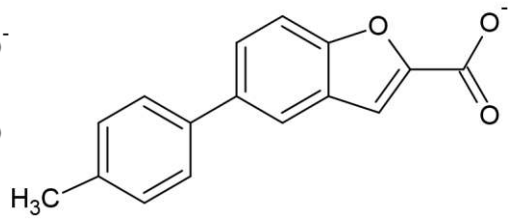
4. *Gritti et al.* explained a sustainable, microwave-enhanced process for producing 2-substituted benzofurans from substituted o-alkynylanisoles . The method makes use of an acidic deep eutectic solvent that, in mild circumstances, functions as both the catalyst and the reaction medium. The eutectic mixture was successfully recyclable for up to six cycles thanks to this environmentally friendly synthesis approach, which produced seventeen

distinct benzofuran derivatives with great efficiency [21].

5. *Khan et al.* created a number of functionalized phenylbenzofuran-2-carboxylate compounds via Suzuki-Miyaura cross-coupling processes. Compounds 4d and 4a have excellent anti-urease and α-glucosidase inhibitory actions that are equivalent to established reference medicines, according to pharmacological screening. Furthermore, the results of the hemolytic assay verified that the produced molecules are not harmful to red blood cells, suggesting their safety and potential as novel therapeutic candidates [22].



4a



4d

CONCLUSION

Benzofuran is a versatile and privileged nucleus in medicinal chemistry, according to the collective evidence presented in this review. These compounds have a wide range of pharmacological effects, most notably as strong anticancer drugs that target certain biomarkers like PI3K, VEGFR-2, and CDK2. Their strong inhibitory efficacy against enzymes implicated in neurological and metabolic disorders, such as AChE, BChE, BACE-1, MAO, urease, and alpha-amylase, further illustrates their function as multi-target ligands. it can be synthesized using various methods . SAR studies show that by incorporating halogens (Cl, F, Br) and nitro groups anticancer and antimicrobial activities can be increased by increasing lipophilicity. Drug resistance can be successfully overcome, target selectivity can be improved, and systemic toxicity can be decreased by combining active pharmacophores into single molecules, as demonstrated by the success of molecular hybridization—coupling the benzofuran ring with isatin, thiazole, or pyrazole. In the end, benzofuran offer a strong and promising foundation for the development of next-generation multifunctional medications that can treat complicated, multifactorial illnesses.

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