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REVIEW ARTICLE **OPEN ACCESS**

Review on Designing and synthesis of some of new benzofuran derivatives for Immunomodulatory and antibacterial activity

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ABSTRACT

Because of their versatility as well as unique physicochemical qualities, an astonishing figure of heterocycle combinations and heterocycle components were included in many drugs and have become an important factor in therapeutic chemistry. The problem of bacterial resistance can potentially be solved by using natural and synthetic membrane active antibacterial drugs, since their nature confers a low tendency for resistance formation. We are concentrating on research on the design and synthesis of certain novel benzofuran derivatives for Immunomodulatory and antibacterial properties in this review. The benzofuran analogue oxazetidine was also discovered for being a promising flexible chemical, as well as due to its significant proliferation-resistant properties, it can be used to treat cancers. It is anticipated that benzofuran molecules would play a significant role in the treatment of multifactorial disorders.

Keywords: *Oxidative stress, Immunomodulatory, heterocyclic, benzofuran structure activity relationships.*

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INTRODUCTION

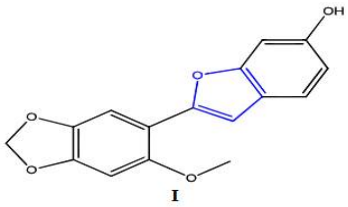
Because of their versatility as well as unique physicochemical qualities, an astonishing figure of heterocycle combinations and heterocycle components were included in many drugs and has become an important factor in therapeutic chemistry. [1] Numerous momentous normal items as well as regular drugs have these designs. Certain drugs and clinical treatment prospects are mostly derived from everyday objects that contain benzofuran rings. A crucial building block of several naturally robust ordinary instructions as well as made synthetic raw materials is a heterocyclic molecule with a benzofuran ring at its core.[2] The wide range of therapeutic uses for benzofuran subsidiaries demonstrates many mechanism of action of this series of mixes, and as a result benzofuran and its subsidiaries have attracted significant attention due to their physiological activities (Fig. 1 rate dispersion of different subject classifications) as well as possible uses as pharmaceuticals (under various subject groupings). Higher plants including Asteraceae, Rutaceae, Liliaceous, and Cyperaceae typically circulate benzofuran molecules.[3]

The majority of those blends occur in the Asteraceae family. [4] Studies have demonstrated that benzofuran and its metabolites possess different natural characteristics and may be discovered within regular and odd mixtures. The frequently utilised benzofuran compounds Krameria ramosissima, *Machilus glaucescens, Ophryosporus lorentzii, Ophryosporus charua*, and Zanthoxylum ailanthoidol are mostly isolated from the compounds. These mixtures include an extensive variety of compounds and pharmacological activities, resulting in these unique characteristics in the investigation of new drugs. [5] In addition, benzofuran subsidiaries are biodynamic specialists that could be utilised to create and nourish the formation of the future anticipated restorative specialists.

As of late, specialists have tracked down that such mixtures have different natural exercises including: against growth, antibacterial, hostile to oxidative, hostile to Promotion, hostile to parasitic, against acetylcholine, and against inflammatory exercises. [6] They may be utilised by fluorescent indicators for relief from pain and bone anabolic experts. The substances with the benzofuran ring structure ailanthoidol, amiodarone, and bufuralol are among the most well-known and acknowledged. Furthermore, several types of 2-arylbenzofurans produced from natural sources have advantageous biological characteristics, such as antibacterial, anti-inflammatory, and anti-oxidative capabilities. [7] An

oral active and blood-brain barrier permeable benzofuran analogue, which has recently been shown to have substantial anti-amyloid aggregation action, may offer an alternative therapy for Alzheimer's disease (AD).[8]Because of its strong anti-proliferative properties, oxyazolidine, a benzofuran analogue that has also been found to be a potential multifunctional drug, can be used to treat cancer. It is anticipated that benzofuran molecules would play a significant role in the treatment of multifactorial diseases.[9,10].

Several approved medicines are obtained from natural sources and demonstrate a wide spectrum of pharmacological activity [11,12]. Benzo furan, a naturally occurring heterocyclic that is often encountered, plays a significant role in both drug development and chemical biology. Cicer bijugum, a wild species of chickpea, has the first naturally occurring hydroxylated benzofuran cicerfuran(I), which has been detected in the roots and is thought to play a significant role in the plant's defence mechanism against Fusarium wilt [13].



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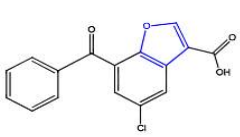

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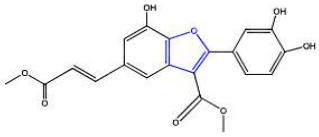

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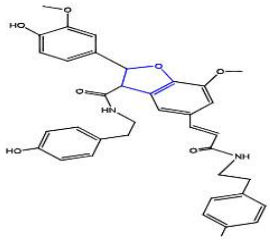


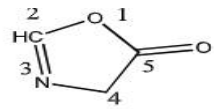
IV

As analgesics (e.g., BRL 37959, II) and prospective anti-cancer medicines, these benzofurans are broadly rooted in synthetic and physiologically intriguing molecules (III and IV) [14] In addition to being utilised in a variety of chemical and agricultural disciplines, substituted benzofuran also finds usage as as anti-oxidants, brighteners, and cures for ulcers, rheumatism, and asthma. [15]

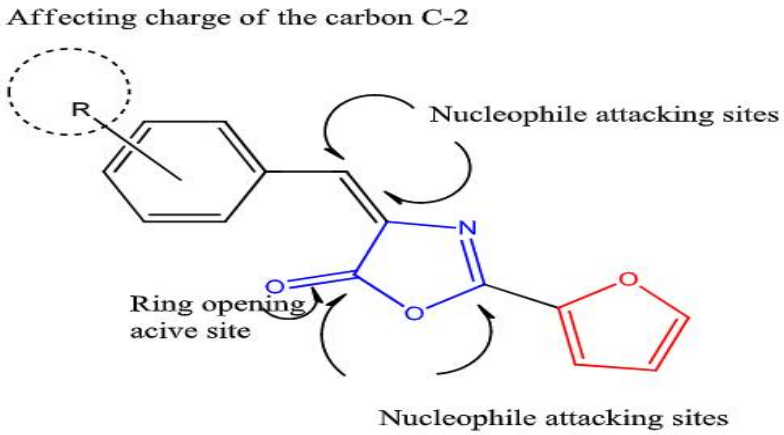
Oxazolone with a furan basis

Oxazolone is used in the production of several physiologically active medications, including those that are the following properties: analgesic, anti-inflammatory, antidepressant, cancer-preventative, anti-microbial, antidiabetic, and anti-obesity [16,17].

Pancratistatin, a phenanthre alkaloid and cancer medication is created by an intramolecular Diels-Alder process [18]. Many human and marine cancer cell lines are inhibited from proliferating by the oxyzolone ring [19].



Chemistry



The activity and immunosuppressive activity are significantly impacted by C-4 and C-2 position substitution. Tyrosine's inhibitory effect is mediated by functional groups at the C-4 and C-2 positions. Conjugation through the C-4 double bond, by the functional group, and by the C-2 location of the phenyl ring for the aforementioned structure is crucial to the activity [20]. By increasing the phenyl substituent's electron-donating groups, the ring opening is reduced [21]. Unsaturated oxazolone' carbonyl groups are activated by Lewis acids, which gives the carbonyl group an electrophilic character [22]. Nucleophiles then attack the carbonyl group, which causes a ring opening. Exocyclic double bonds have the ability to function as dienophiles and Intermolecular Diels-Alder reactions include substituted oxazolone [23]

Examples of medicines with a benzofuran moiety comprise:

Some of the most well-known benzofuran compounds with several pharmaceutical applications are amiodarone, angelicin, bergapten, nodekenetin, xanthotoxin, and usnic acid. These compounds offer great clinical application potential for benzofuran compounds as well as strongfuture drug development possibilities for these compounds. These substances have been widely used in dermatological, anticancer, and antiarrhythmic treatment.

A good illustration of a benzofuran medicine is the all-purpose antiarrhythmic medicament amiodarone. The medication slows myocardial and atrial conduction speed, inhibits rapid sodium ion induction, and diminishes sinus node autonomy. Additionally, it successfully manages premature atrial beats, premature ventricular contractions, and paroxysmal supraventricular tachycardia. Its primary uses are as an anti-arrhythmic and anti-anginal medication [24].

MATERIAL AND METHODS

In both homogeneous and heterogeneous catalytic pathways, several techniques have been conceived to produce benzofuran. But only heterogeneously catalysed reactions are discussed in this article. The Sonogashira cross-coupling reaction between o-halo phenol and terminal alkynes, followed by sequential 5- endo - dig cyclization, is one of the finest techniques to make benzofuran derivatives.

Dehydro-viniferin (1, Figure 1), a compound containing benzofuran, was shown to be efficient against Gram-positive bacteria by Mattio, L.M. et al. Gram-positive bacteria used as a model, Listeria monocytogenes Scott A, were shown to be highly sensitive to its antimicrobial activity (MIC and MBC values, respectively, of 4.42 and 35.3 M) [24]. Significant morphological alterations, membrane depolarization, and loss of membrane integrity are all brought on by the substance. and major damage to the cytoplasmic membrane.

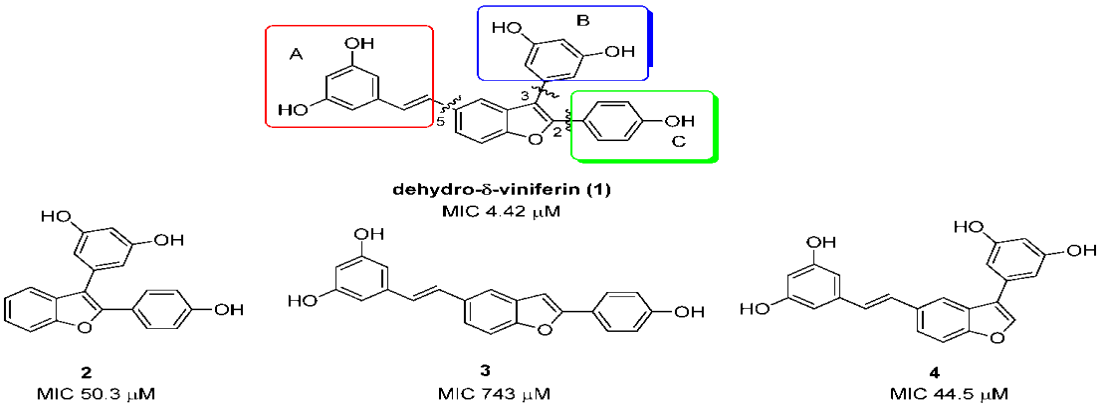


Figure 1. Structures and MIC values of model compounds 2, 3, and 4.

G. Catinella *et al*. demonstrated that an earlier SAR analysis our team carried outWhen the moieties linked at positions two, three, and five of the benzofuran core were specifically removed, more analogues of 1 (intensifies 2, 3, 4) [25] were generated, proving thatNone of the compounds that have been actually improved upon showed out to be more dynamic than the predecessor (Figure 1). Particularly, the absence of ring B caused a substantial decline in the antibacterial activity for component 3 (MIC value of 743 M vs 4.42 M of Dehydro-viniferin), indicating that the aryl ring plays a crucial function in position three of the benzofuran centre.A less evident, but still significant, decline in antibacterial activity was observed.MIC upsides of 50.3 M(2) and 44.5 M(4) as compared to 4.42 M(1) were achieved for intensities 2 and 4, which were generated by individually deleting the aryl group ring in position two and the styryl bunch at position five (Figure 1). So, we set out to create a brand-new range of Dehydro-viniferin. Analogues and isosteres can be produced by altering the styryl moiety A (Figure 1) while leaving the rings B and C alone.

By eliminating double bond or substituting it with moieties such an amidealkyne, or saturated chain, it may be possible to better understand the significance of geometric and stereo electronic effects for the

antibacterial activity. Additionally, we wanted to make Dehydro-viniferin analogues with aromatic rings different from those in resorcinol but yet maintaining the stilbene double bond[26].

To build 2,3-diaryl benzofuran ring with the suitable functional group (X) on C-5 for the insertion of the necessary fragment, we need a flexible technique (Figure 2).

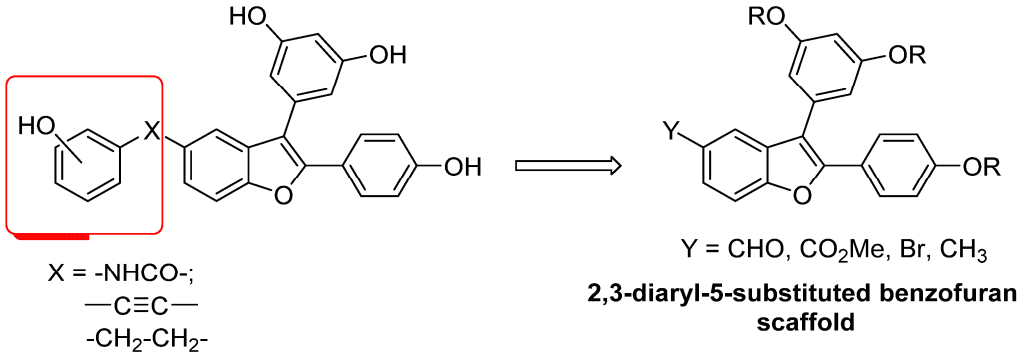


Figure 2: Analysis of retro synthesis to yield the desired molecules

Palladium catalysed processes have been shown to be one of the most efficient ways to make 2,3-diaryl-5-substituted benzofurans. At normal temperature, an orthoiodophenol and an aryl-substituted terminal alkyne undergo a Sonogashira coupling in order to make the matching internal alkyne.Cacchi and colleagues developed this strategy, which Markina and colleagues [30] thereafter used. At 100 °C and microwave irradiation, the alkynylphenol formed as an intermediate is simultaneously subjected to cyclization with the adjacent phenol group and oxidative addition with the aryl-iodide-palladium complex with CuI. These three-component one-pot procedures allowed us to synthesise C5-substituted 2, 3-diarylbenzofurans with yields ranging from 48 to 72%.

To be more specific, we reacted 4,5-Dimethoxy-1-iodobenzene and 4-ethylanisoleto make the intermediate 8 with a bromo functional (Scheme 1). Compound 9 was produced in 91% yield by subjecting compound 8 to a Suzuki-coupling procedure for 20 minutes at 120 °C [30] using (3,5-dimethoxyphenyl)boronic acid, Pd(PPh3)4, and aqueous 1 M Cs2CO3. By using BBr3,, the final demethylation of our successful chemical 1 resulted in 10, a simpler variant without the double bond in the stilbene.

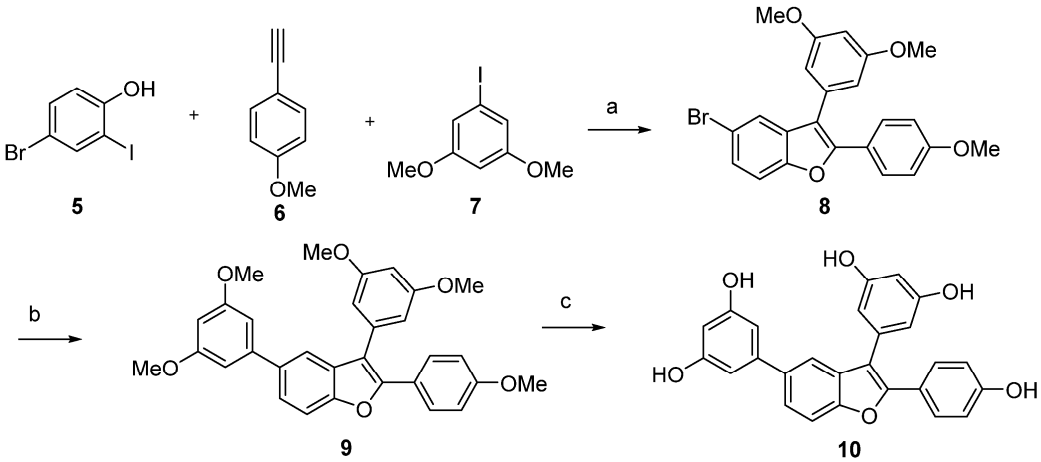


Figure-3 Scheme of benzofuran derivative

The elements and circumstances utilised in above scheme are as follows:

(1)3,5-Dimethoxyphenylboronic acid PdCl2(PPh3)2DCM, CuI, acid, Pd(PPh3)4, BBr3 1 M DCM, DCM, 78 °C to overnight, 96% Resveratrol amide, THF/TE, DMF/EtOH 1:1, aq 1 M CssCO3, 120 °C, 20 min, MW.

Resveratrol amide isosteres have shown activity on par with the original compound. The amide linkage, which also confers enhanced solubility, greater polarity, and changes in electronic perturbations,[27]should preserve the structural integrity of the trans-transoid stilbene. Thus, analogy number 15 (Scheme 2) was created. When the readily available commercial.

Following Sonogashira/Cacchi type cyclization of methyl 4-hydroxy-3-iodobenzoate 11, 4-ethynylanisole 6, and 3,5-dimethoxy-1-iodobenze 7, the required benzofuran 12 was produced in 66% of the yield. The ester 12 was hydrolyzed in a 1:1 THF/water solution for 24 hours using LiOHH2O. In the presence of EDC-HCl and HOBt, the resultant carboxylic acid 13 was reacted with 3,5-dimethoxyaniline to produce.

DISCUSSION

Along with their distinctive adaptability and amazing physicochemical qualities, the majority of heterocyclic compounds and typically standard heterocyclic components discovered in numerous currently offered medications have prepared them as clear foundations of restorative research. Due to some degree to the similarities with various regular and designed atoms with known natural movement, oxygen heterocyclic in this particular situation exhibit a variety of chemical and pharmacological activities. Because of their well-articulated natural activities and potential uses as pharmacological specialists like cell reinforcement, antitumor, ant platelet, ant malarial, calming, energizer, and anticonvulsant properties, benzofuran (engineered and naturally secluded) and its descendants have attracted the attention of therapeutic scientific experts and pharmacologists among oxygen-containing heterocyclic.

CONCLUSION

In an effort to promote future innovation, recent advancement in benzofuran derivatives as Immunomodulatory, antimicrobic, and antioxidant agents (including natural substances) are summarized. The researchers working on a substitution pattern around the nucleus with the aim of assisting medicinal chemists in developing structure activity relationships (SAR) on these derivatives as antibacterial drugs will also benefit from this study's systematic reporting of recent developments in benzofuran-based compounds as antioxidant agents. The remarkable advancements made in a very short period of time using benzofuran derivatives in a range of illnesses serve as evidence of its significance for medicinal chemistry research.

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