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Synthesis, Characterization and Antidiabetic Evaluation of Benzimidazole Linked with Isoxazole Moiety

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ABSTRACT: A significant number of the anti-inflammatory drugs currently in use are becoming obsolete. These are exceptionally hazardous for long-term use because of their possible unfavourable impacts. Subsequently, in the ebb-and-flow decade, analysts and researchers are engaged in developing new anti-inflammatory drugs, and many such agents are in the later phases of clinical trials. Molecules with heterocyclic nuclei are similar to various natural antecedents, thus acquiring immense consideration from scientific experts and researchers. The arguably most adaptable heterocyclic cores are benzimidazoles containing nitrogen in a bicyclic scaffold. Numerous benzimidazole drugs are broadly used in the treatment of numerous diseases, showing promising therapeutic potential. Benzimidazole derivatives exert anti-inflammatory effects mainly by interacting with transient receptor potential vanilloid-1, cannabinoid receptors, bradykinin receptors, specific cytokines, 5-lipoxygenase activating protein and cyclooxygenase. Literature on structure–activity relationship (SAR) and investigations of benzimidazoles highlight that the substituent's tendency and position on the benzimidazole ring significantly contribute to the anti-inflammatory activity. Reported SAR analyses indicate that substitution at the N1, C2, C5 and C6 positions of the benzimidazole scaffold greatly influence the anti-inflammatory activity. For example, benzimidazole substituted with anacardic acid on C2 inhibits COX-2, and 5-carboxamide or sulfamoyl or sulfonyl benzimidazole antagonises the cannabinoid receptor, whereas the C2 diarylamine and C3 carboxamide substitution of the benzimidazole scaffold result in antagonism of the bradykinin receptor. In this review, we examine the insights regarding the SARs of anti-inflammatory benzimidazole compounds, which will be helpful for researchers in designing and developing potential anti-inflammatory drugs to target inflammation-promoting enzymes.

KEYWORDS: benzimidazole, cyclooxygenase, bradykinin, cannabinoid, effect of structural modification

I. INTRODUCTION

Heterocyclic compounds have a central place in medicinal chemistry, being used as therapeutic agents to treat most diseases [1,2,3]. Among these heterocycles, benzimidazole stands out, as a purine-analog pharmacophore, with a very diverse therapeutic activity. The very broad spectrum of biological activities it treats include antimicrobial [4,5,6,7,8], antiviral [9,10], antihistamine [11,12], anticonvulsant [3,13], antitumor [14,15,16], proton pump inhibitors [17], antiparasitic [16,18,19], anti-inflammatory [20,21,22], or antihypertensive [23,24] activities. Some benzimidazoles are efficient agents in Diabetes mellitus [25,26,27], while astemizole compounds possess anti-prion activity to treat Creutzfeldt-Jakob disease [5,28]. The literature also reports anti-Alzheimer [29,30], psychoactive, anxiolytic, analgesic [31,32], and anticoagulant properties [33,34] of benzimidazole derivatives.

Additionally, triazole compounds possess a diversity of biological activities as antimicrobial [35,36,37,38], antitubercular [39,40], potential inhibitors of SARS-CoV-2 [41,42,43], antiviral [43,44], anti-inflammatory [45,46],antitumor [47,48,49,50], antihypertensive [50], antioxidant [47,51,52], and antiepileptic [53,54]. Pharmacological applications of triazoles refer to their activity as α-glucosidase inhibitors [55,56], analgesics [50,57], anticonvulsants [53,58], and antimalarial agents [57,59]. Triazole derivatives are efficient in the treatment of Alzheimer's disease [60,61] and are very effective neuroprotective agents [62,63].

The successive events that occurred from the spring of 2020 until now, regarding the emergence and development of the COVID-19 pandemic, have led the scientific world to investigate more closely the possibility of treating this infectious disease with various antiviral [64,65,66], antimicrobial [67], immunomodulatory [68] or anti-

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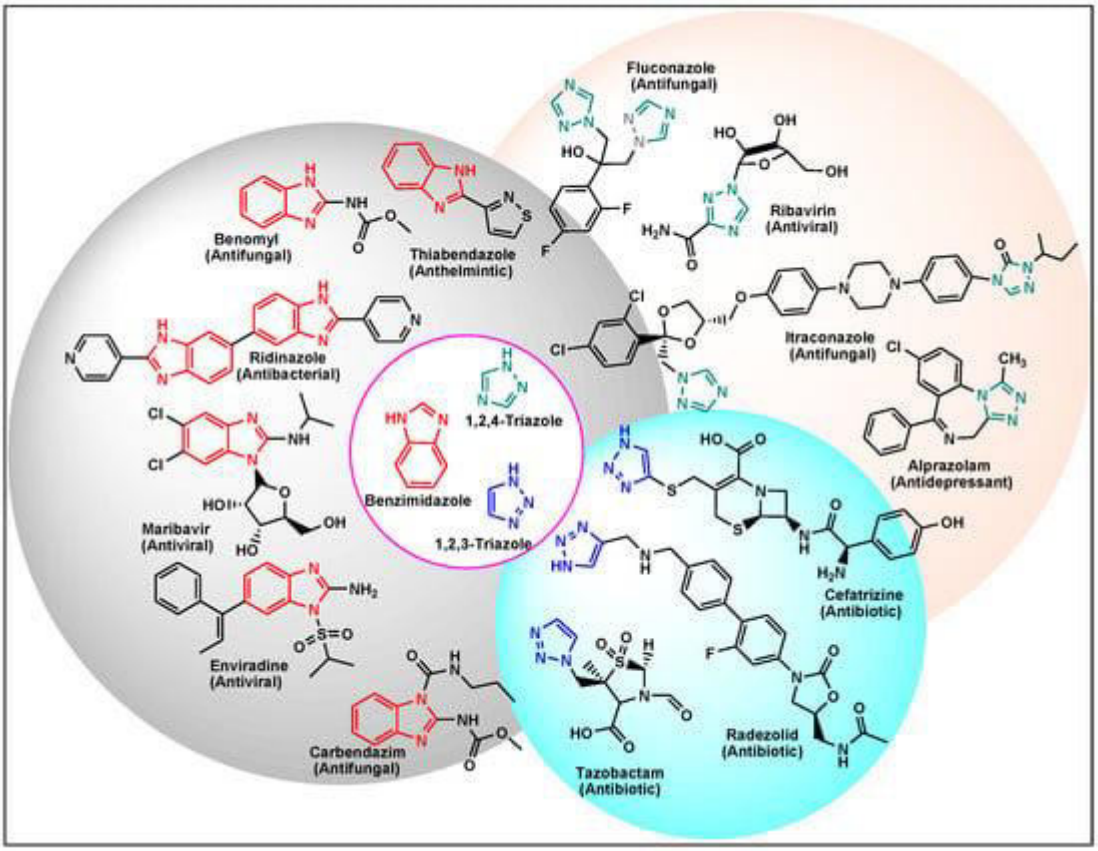
inflammatory [69] drugs, therefore, the discovery of new molecules with simple or hybrid structures, which meet the requirements of the treatment of this condition is absolutely necessary and constitutes the engine for the development of new effective therapeutic agents.

Why did I choose the study of benzimidazole-triazole compounds? Classical drugs containing benzimidazole and triazole rings recommend these heterocycles as essential in building new target compounds with antimicrobial, antiviral, antiparasitic, etc. properties (ure 1). In addition, the literature mentions a series of benzimidazole-triazole hybrids with remarkable antimicrobial properties, and antiviral activities, including new anti-SARS-CoV-2 agents [70,71,72,73,74], with particular importance in the context of the recent pandemic, which led to the study of synthesis methods, antimicrobial properties, structure–property relationships, and their biological activities.



ure :. Chemical structures of some benzimidazole, 1,2,3-triazole, and 1,2,4-triazole-based marketed drugs.

Therefore, this review aims to provide an update on the synthesis methods of the benzimidazole-triazole hybrids, along with their antimicrobial and antiviral activities, as well as the structure–activity relationship and DFT studies reported in the literature. The advantages of the study of benzimidazole-triazole hybrid compounds refer to a wider range of antimicrobial activities, compared to simple precursor heterocycles, to their better minimum inhibitory concentrations compared to simple component heterocycles, as well as to the need to hire specialized personnel to carry out this research.

The main disadvantages are material because the synthesis of some hybrid compounds requires high costs compared to simple heterocycles, as well as greater time consumption. Consequently, if the synthesized hybrids have increased biological properties compared to simple precursor heterocycles, the balance clearly tilts towards the advantage of the synthesis of hybrid compounds. However, access to hybrid compounds will not be without both sides, advantages and disadvantages, which requires careful prospecting of all the components involved in the production of hybrids.

As expected, the literature mentions benzimidazole-triazole hybrids with other biological properties than those studied in this review, such as antitumor [15,48,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92], antioxidant

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[93,94,95], anti-Alzheimer [96,97,98,99], antidiabetic [100,101,102,103,104], and anti-inflammatory [105] properties, which is additional proof of the therapeutic potential of these hybrids and the need to study these hybrids on the topic proposed in the title. As expected, the study refers to both 1,2,3-triazole-benzimidazole hybrids and 1,2,4-triazole-benzimidazole hybrids, even if it seems that the literature is richer in the second category in terms of antimicrobial activity.

The recent literature marks several strategies for the synthesis of 1,2,3-triazoles, like click reaction [106], Bouiton-Katritzky rearrangement [107], oxidative cyclization of hydrazones [108], post-cycloaddition functionalization [109], alkylation or arylation of triazoles [110]. Also, for benzimidazoles, the literature mentions several methods of synthesis, such as the reaction of o-phenylenediamine with aldehydes or ketones (Phillips-Ladenburg reaction) [3,111,112,113], with acids or their derivatives (Weidenhagen reaction) [81], or green methods of classic syntheses [111,114,115,116,117].

Why this review is necessary and what exactly it proposes I will clarify in what follows. This article summarizes for the first time in the literature: various synthesis methods of benzimidazole-1,2,3-triazole hybrids as well as benzimidazole-1,2,4-triazoles, their antimicrobial and antiviral activities, as well as SAR studies and DFT performed on the mentioned hybrids. Where necessary, for compounds with superior biological activities, several examples from the literature were given, and the various studies performed on them (in vitro, in vivo, in silico, etc.) were mentioned. All of these aim at directing the syntheses of hybrid compounds with specific structures and superior antimicrobial and antiviral properties, taking into account the mentions reported in the literature up to now.

The database search methodology used in this review was the use of keywords, which can be found in the title, such as benzimidazole, 1,2,3-triazole, click reaction, 1,2,3-triazole, benzimidazole-triazole hybrids, antimicrobial, antiviral, or therapeutic properties, in different websites, such as PubMed, MDPI, Science Direct, Springer, The Royal Society Chemistry, ACS Publications, and Taylor & Francis. The selection of scientific articles for the last ten years was made according to the novelty brought in the benzimidazole-triazole hybrids and their antimicrobial and antiviral properties, as well as the therapeutic properties of the reported compounds.

Generally, articles from the last ten years have been selected. For the hybrids found, first, the syntheses and then their biological properties were presented, with special emphasis on those with improved properties (active on a larger range of microbial strains, with better minimum inhibitory concentrations, or where SAR studies were performed, DFT, etc.). In the following, we will present syntheses of benzimidazole-triazole hybrids with antimicrobial and antiviral properties. In order to highlight the structures of the heterocycles in the discussed compounds, we colored the benzimidazole nucleus with red, 1,2,3-triazole with blue, and 1,2,4-triazole with green.

II. DISCUSSION

4H-isoxazol-5-ones were synthesized by one-pot three-component condensation of aryl aldehydes, hydroxylamine hydrochloride and ketoesters using potassium phthalimide (Kiyani and Ghorbani 2013d), sodium ascorbate (Kiyani 2013), sodium tetraborate (Kiyani and Ghorbani 2013b), sodium azide (Kiyani and Ghorbani 2013c), sodium citrate (Kiyani and Ghorbani 2013a), sodium saccharin (Kiyani and Ghorbani 2013e), N-bromosuccinimide (Kiyani et al. 2015) or boric acid (Kiyani and Ghorbani 2015) as a catalyst in aqueous medium at room temperature (Route e, . 5). Later Chavan et al. (2015) synthesized 4H-isoxazol-5-ones efficiently by one-pot uncatalyzed reaction of hydroxylamine hydrochloride, ketoesters and aromatic aldehydes substituted with electron donating group in the aqueous medium. Ji et al. (2006) synthesized 4-carbomethoxynaphtho[2,1-c]isoxazoles from methyl 3-(alkynylphenyl)-2-propenoates by the intramolecular nitrile oxide cycloaddition.

Allegretti and Ferreira (2013) reported cyclization of propargylic N-hydroxycarbamates and N-alkoxycarbonyl amino ethers, via Pt-carbene intermediate to differentially substituted regioisomeric isoxazoles. Recently, Bulanov et al. (2017) reported an efficient, catalyst-free and microwave assisted one pot method for synthesis of 5-substituted isoxazoles from α-acetylenic γ-hydroxyaldehydes and hydroxylamine. Crossley and Browne (2010) synthesized a series of iodoisoxazoles by reacting hydroximinoyl chlorides and iodinated terminal alkynes. Jeong et al. (2014) synthesized a series of fluoroisoxazoles using one-pot gold-catalyzed tandem cyclization−fluorination of (Z)-2-alkynone O-methyl oxime under mild conditions (room temperature). Further, Oakdale et al. (2014) synthesized 4-haloisoxazoles using ruthenium-catalyzed cycloaddition of nitrile oxides with electronically deficient 1-haloalkynes.

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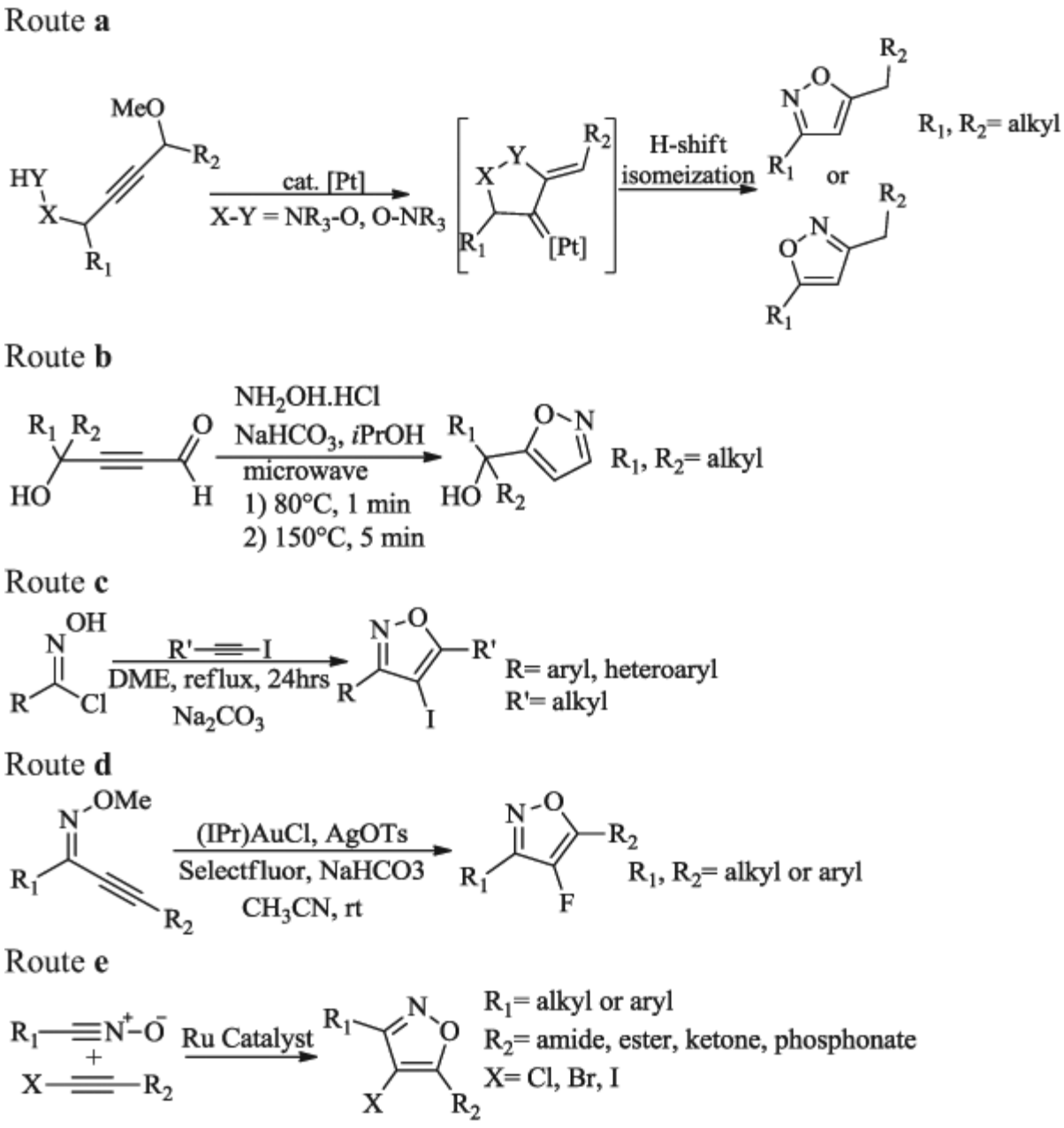

Analgesic and antiinflammatory isoxazoles

Lincy et al. [47] reported the evaluation of in vivo and in vitro antiinflammatory activity of novel isoxazole series 52 (. 7). Chalcones are prepared by the reaction of aromatic aldehydes with aromatic ketones in aqueous alcoholic alkaline medium. Then these are made to react with hydroxylamine hydrochloride in presence of sodium acetate to prepare isoxazole derivatives. The prepared isoxazole compounds were subjected to inflammatory activity by in vitro and in vivo methods. All 25 isoxazole derivatives exhibited antiinflammatory activity among tested. Out of these 25 isoxazole derivatives, 7 compounds show significant antiinflammatory activity. Pharmacological activities of some synthesized substituted pyrazole, oxazole and triazolopyrimidine derivatives 53 (. 7) were studied by Said et al. [48] A series of heterocylic compounds was synthesized from 1-(3,4-dimethoxyphenyl)-3-(4-ethoxyphenyl)prop-2-en-1-one, which was reacted with thiourea, ethyl acetoacetate, p-nitrophenylhydrazine and hydroxylamine hydrochloride afforded thioxopyrimidine, tetrahydro-terphenyl, 1,3,5-triarylpyrazole, and 3,5-diarylisoxazole derivatives, respectively. While,

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upon reaction of thioxopyrimidine with piperidine, anthranilic acid or hydrazine hydrate afforded piperidin-1-yl-1,4-dihydropyrimidine, pyrimido[2,1-b]quinazoline and 2-hydrazinyl-1,4-dihydropyrimidine derivatives, respectively. Finally, the latter compound was heterocyclized with formic acid, acetic anhydride, carbon disulfide, acetyl acetone or phthalic anhydride resulting the corresponding triazolo[4,3-a]pyrimidines, pyrazolylpyrimidine and imide derivatives, respectively. All the newly substituted pyrimidine, isoxazole, pyrazole and fused triazolopyrimidine derivatives displaying potential analgesic and anti-convulsant activities.

Panda et al. [49] reported the synthesis, antiinflammatory and antibacterial activity of novel indolylisoxazoles 54 (. 7). Initially, chalcones were synthesized by reacting indole-3-aldehyde, prepared by Vilsemeir Haack reaction with 4-substituted acetophenone in ethanolic potassium hydroxide solution. These chalcones were immediately reacted with hydroxylamine hydrochloride in presence of glacial acetic acid as reagent to obtain the corresponding isoxazole derivatives. The synthesized heterocycles were characterized on the basis of physical, chemical tests and spectroscopic data. These compounds were tested for the acute anti-inflammatory activity and antibacterial activity using carrageenan induced rat paw edema method and cup plate method, respectively. Airody et al. [50] reported the synthesis of several new pyrozolines and isoxazoles 55 (. 7) from 4-acetylthioanisole with aryl aldehydes through β-unsaturated ketones. The synthesized compounds were tested for their analgesic and antiinflammatory activity by a standard method. Bhusari et al. [51] reported the design and synthesis of some new diphenylaminoisoxazolines derivatives 56 (. 7). These compounds are auxiliary screened spectroscopically and tested for antiinflammatory activity. All the compounds showed better activity when compared with ibuprofen as standard.

Sahu et al. [52] reported the synthesis of substituted aryl-N-chalcone aminophenols by base catalysed condensation of an equimolar mixture of N-(4-hydroxyphenyl)acetamide and appropriate araldehydes. Aryl-N-chalconyl aminophenol was treated with various hydroxylamine hydrochloride results in corresponding isoxazole derivatives 57 (. 7). The synthesized compounds were investigated for their analgesic and antimicrobial activities. Two of synthesized compounds exhibited significant analgesic activity in comparison to the reference drug paracetamol. In in vitro antimicrobial screening, two compounds showed higher antibacterial and antifungal activity in comparison to the reference standard ciprofloxacin and clotrimazole, respectively. Compound bearing 4-chlorophenyl substitution at C-5 of isoxazole ring was found to be the most potent compound of the series.

Vagdevi et al. [53] synthesised a variety of novel naphtha-[2,1-b]-furopyrazolines, isoxazoles and isoxazolines 58a and 58b (. 7) and evaluated its various biological activity. The novel biheterocyclic compounds were screened for antibacterial, antifungal, anthelmintic and analgesic activities. Out of several tested derivative one compound showed promising antimicrobial activity and some of the derivatives exhibited moderate antibacterial and antifungal activity. Three compounds were found to be active as the standard drug in anthelmintic activity. One of the synthesized analogs showed maximum analgesic activity.

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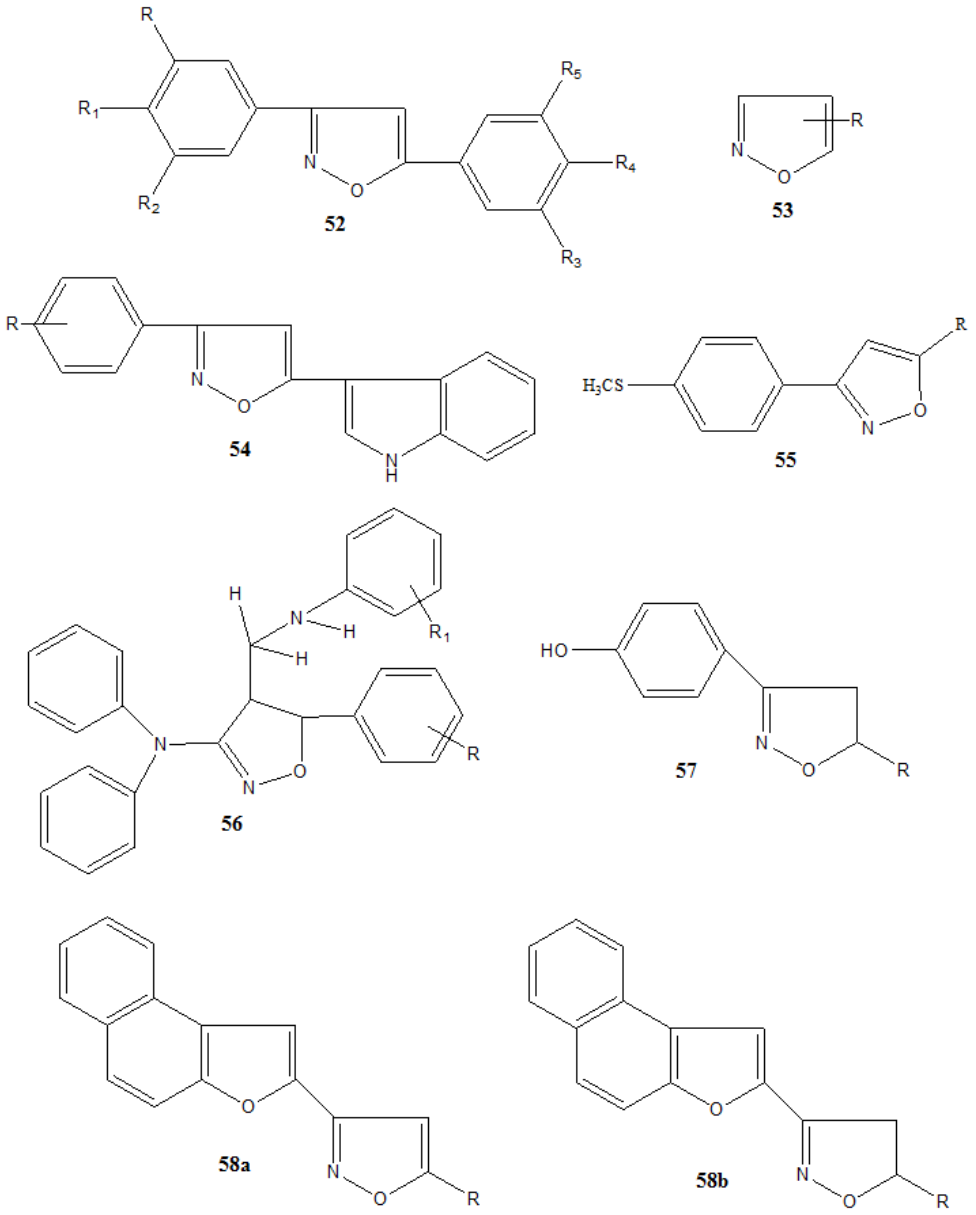

. : Structures of analgesic and anti-inflammatory isoxazoles 52-58

Antioxidant isoxazoles

Totally twenty-seven 3,5-substituted-4,5-dihydroisoxazole derivatives 59 (. 8) including 3-(2-fuorneyl)-5-(substituted phenyl)-4,5-dihydroisoxazole have been synthesized by fly-ash: H_2SO_4 catalyzed intramolecular cycloaddition of hydroxylamine hydrochloride and aryl chalcones under solvent free conditions by Ganesamoorthy et al. [54]. The yields of the isoxazoles are more than 90 %. The antimicrobial and antioxidant activities of the synthesized isoxazoles were evaluated using cup plate and DPPH radical scavenging methods, respectively.

Similarly totally thirty-one 3,5-substitutedaryl-4,5-dihydroisoxazole derivatives 60 (. 8) including 3-(2-naphthyl)-5-(substituted phenyl)-4,5-dihydroisoxazole have been synthesized by fly-ash: H_2SO_4 catalyzed cyclization of hydroxylamine hydrochloride and aryl chalcones under solvent-free conditions by Thirunarayanan et al. [55]. The yields of the isoxazoles are more than 94 %. The antimicrobial, antioxidant and insect antifeedant activities of the

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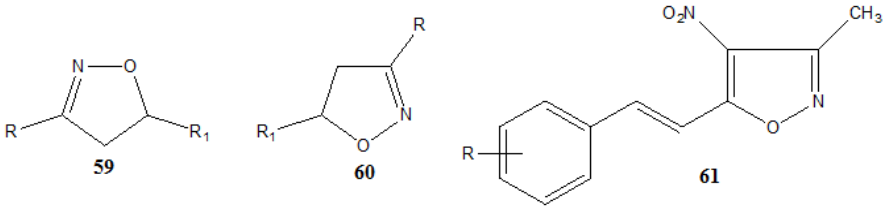
synthesized isoxazoles have been evaluated using a cup plate, DPPH radical scavenging and castor leaf disc bioassay of 4th instar larvae Achoea Janata L methods, respectively. Madhavi et al. [56] reported the synthesis and evaluation of antioxidant, anti-inflammatory and analgesic activities of a series of 3-methyl-4nitro-5-(substituted styryl) isoxazoles 61 (. 8) with a view to evaluating the effect of nitro substitution on styryl isoxazoles. Compounds with sterically hindered phenolic groups exhibited good anti-inflammatory activity with better antioxidant properties and are devoid of toxicity as well as ulcerogenic potential.



. : Structures of antioxidant isoxazoles 59-61

Anticancer isoxazoles

Hamama et al. [57] reported the synthesis and biological evaluation of some novel isoxazole derivatives 62a-62c (. 9). The reaction of 5-amino-3-methylisoxazole with formalin and secondary amines gave the corresponding Mannich bases. Alkylation of isoxazole derivative with Mannich bases hydrochloride gave unsubstitute-disoxazolo[5,4-b] pyridine derivatives at position 4. Moreover, the coupling reaction of isoxazoles with different diazonium salts gave the corresponding mono and bisazo dyes of isoxazole derivative. The newly synthesized compounds were screened for their antitumor activity compared with 5-fluorouracil as a well-known cytotoxic agent using Ehrlich ascites carcinoma cells. Interestingly, the obtained results showed clearly that six compounds exhibited high antitumor activity than 5-fluorouracil.

A novel series of thiophenes 63 (. 9) having biologically active sulfonamide, 3-methylisoxazole, 4-methoxybenzo[d]thiazole, quinoline, benzoyl phenylamino, and anthracene-9,10-dione moieties were prepared by Mostafa et al. [58]. All newly synthesised compounds were evaluated for their in vitro anticancer activity against human breast cancer cell line (MCF7). Most of the screened compounds showed cytotoxic activities compared to doxorubicin as a positive control. Four compounds (IC_{50} = 10.25, 9.70, 9.55, and 9.39 µmol/l) revealed higher cytotoxic activities than that of doxorubicin (IC_{50} = 32.00 µmol/l). Also, another three compounds were found nearly as active as doxorubicin (IC_{50} = 28.85, 23.48 and 27.51 µmol/l). A convenient synthesis of novel isoxazole-substituted 9-anilinoacridine derivatives 64 (. 9) was reported by Kalirajan et al. [59]. The compounds were screened for in vitro antioxidant activity by DPPH method, reducing power assay and total antioxidant capacity method. The cytotoxic activity of the compounds was also studied in HEp-2 cell line. The docking studies of the synthesised compounds were performed towards the key nucleoside dsDNA by using AutoDock vina 4.0 programme. All the isoxazole substituted compounds possess significant activities.

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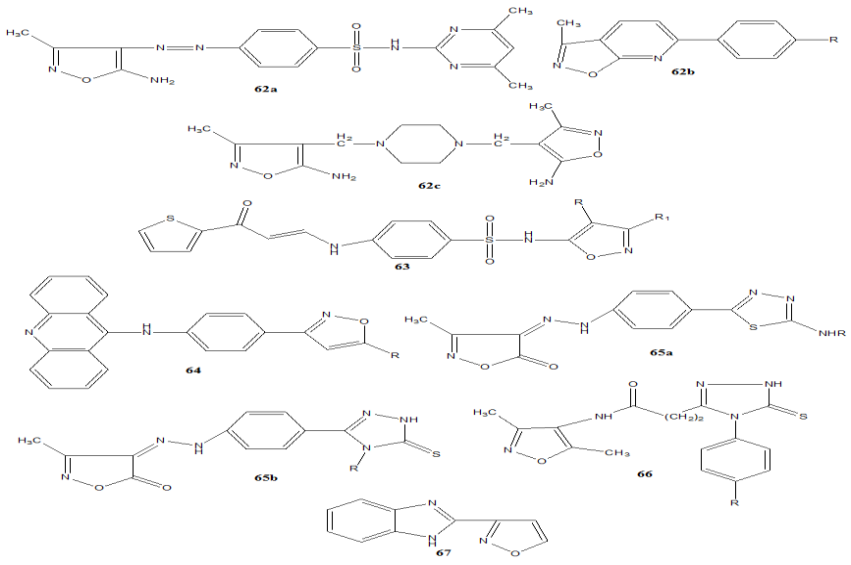

. : Structures of anticancer isoxazoles 62-67

Several isoxazoline derivatives 65a and 65b (. 9) were synthesised, from substituted 1,3,4-thiadiazoles and 1,2,4-triazole-3-thione by Sevim et al. [60]. In the first part, compounds 2-(4-aminophenyl)-5-alkyl/arylamino-1,3,4-thiadiazoles and 5-(4-aminophenyl)-4-substitude-2,4-dihydro-3H-1,2,4-triazole-3-thiones were prepared from ethyl 4-aminobenzoate. In the second part, compounds, which were prepared by coupling the diazonium salts of aromatic primary amines with ethyl acetoacetate were cyclized with hydroxylamine hydrochloride in presence of sodium acetate in ethanol yielded 3-methyl-4-[2-{4-[5 alkyl/arylamino)-1,3,4-thiadiazol-2-yl]phenyl}hydrazinylidene]isoxazol-5(4H)-one and 3-methyl-4-[2-{4-[4-(4-alkyl/aryl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]phenyl}hydrazinylidene]isoxazol-5(4 H)-one. Cytotoxicity of these compounds was evaluated by using HEK293 cell line of MTT assay. The highest inhibitions were confirmed as 45.72 % for the compound 3-methyl-4-[2-(4-{5-[(4-methoxyphenyl) amino]-1,3,4-thiadiazol-2-yl}phenyl) hydrazinylidene]isoxazol-5(4 H)-one and 33.07 % for the compound 3-methyl-4-[2-(4-{5-[(4-methylphenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl) hydrazinylidene]isoxazol-5(4H)-one.

Rajanarendar et al. [61] reported the synthesis of N-1 (3,5-dimethyl-4-isoxazoyl)-3-(4-aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-procainamide 66 (. 9) from 4-amino-3,5-dimetylisoxazole in five steps. They evaluated the antitumor activity of these compounds by a standard method. Parikh et al. [62] reported the condensation of 2-acetylbenzimidazole with various aldehydes to form 3-(benzimidazol-2'-yl)-5-arylisoxazoles 67 (. 9). The purity of compounds was identified by chromatography and screened their antimicrobial and anticancer activity. All the synthesized compounds showed in vivo growth inhibitory activity against different microbes.

III. RESULTS

Benzimidazole is a very useful heterocycle for the development of molecules of pharmaceutical and biological interest. Compounds containing benzimidazole have been widely used in drug development and researchers around the world are actively seeking new uses and applications [1]. Benzimidazole derivatives have found applications in diverse therapeutical areas including antimicrobial [2,3,4], antifungal [5,6,7,8], antiviral [9,10], antitubercular [11,12,13], antidiabetic [14,15], anti-inflammatory [16,17], antihistaminic [18], antioxidant [19,20], and anticancer activities [21,22]. Moreover, benzimidazoles are one of the early classes of anticancer agents such as bendamustine ure 1 [23]. In addition, many derivatives showed anticancer activity against human liver carcinoma (HEP-G2) cell lines [22], while others derivatives possess potent anticancer activity against other human cancer cell lines [16] such as MCF-7, THP-1, PC-3, and A-549. Thiourea and urea are classes of organic compounds which have a wide diversity and multiple applications. Their derivatives demonstrate a broad range of pharmacological activities such as antimicrobial, antidiabetic, analgesic, and anticancer activities [24,25,26]. Several anticancer agents containing urea and thiourea

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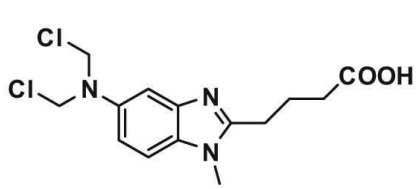
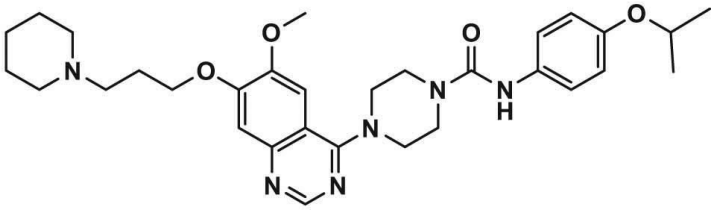
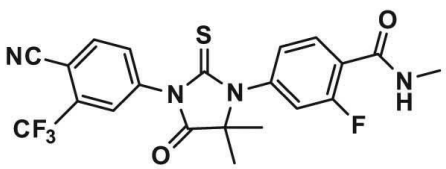
functional groups reached clinical phases [27] such as Tandutinib and Enzalutamide, respectively (ure 1). Moreover, novel series of benzimidazole-thiourea [28] and benzimidazole-urea [29] derivatives were synthesized and they exhibited potent antiproliferative activity against a group of human tumor cells compared to standard drugs. Hybrids of urea and benzimidazole showed potent anticancer activity and some derivatives are already in the drug market such as Glasdegib [30]



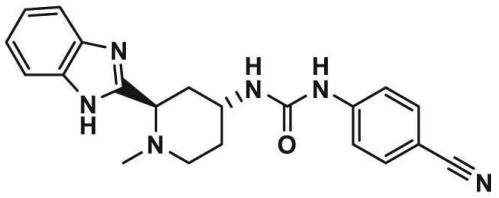
Bendamustine



Tandutinib



Enzalutamide



Glasdegib

According to the World Health Organization (WHO), the number of people diagnosed with cancer increased from 10 million in 2000 to 19.3 million in 2020. Breast cancer (BC) is the world's most diagnosed cancer as reported by International Agency for Research on Cancer (IARC) in 2020 (WHO, 2021) with metastasis and drug resistance being the main challenge for successful treatments [31]. Moreover, the drug resistance of cancer cells exerts more pressure to look for new effective chemotherapeutic agents. BC is subtyped or classified based on their genotypic differences and metastasis characteristics. The toxicity of the drug against different types of BC cells differs significantly due to variation in the metabolic outcome of their genotype [32,33].

Apoptosis is an important biological event that takes place in multicellular organisms to remove unwanted or damaged cells [34]. Apoptosis has been extensively used for therapeutic applications and biological studies and huge effort has been dedicated to the discovery of apoptosis-inducing molecules that may have antitumor potential [35].

Based on the biological activity profile of benzimidazole derivatives and thiourea and urea derivatives, the current study is aimed to synthesize novel thiourea- and urea-benzimidazole derivatives and evaluate their anticancer activity against two different cancer cell lines (MDA-MB-231$^{ER(-)/PR(-)}$ and MCF-7$^{ER(+)/PR(+)}$) with different genotypic features.

CONCLUSION

Benzimidazole is a vital scaffold in medicinal chemistry because of its diverse biological activities. Benzimidazoles act via different mechanisms in treating numerous diseases, as discussed in the Introduction of this review. Omeprazole, lansoprazole, pantoprazole, albendazole, mebendazole, thiabendazole, astemizole, enviradene, candesartan, cilexitil and telmisartan are clinically approved drugs that contain benzimidazole nuclei. Several researchers have explored the synthesis, structure–activity relationships, QSARs, molecular modelling and other physicochemical and pharmacokinetic profiles of benzimidazoles. In our view, a complete understanding of the structural, physical and chemical properties of the benzimidazoles may help researchers to better determine their potential use in treating inflammation. However, some severe side effects associated with benzimidazoles can be identified and need to be rectified. Further research in this field is need using advanced techniques, such as QSAR analysis, pharmacophore

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mapping and docking studies, and known SAR information reported in the literature will bring about novel benzimidazoles with considerable scope for use. These methods can provide a much more direct picture of the structural features contributing to the SARs of benzimidazoles

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