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Review Article

Antimicrobial Activity Of Indole, Benzimidazole And Benzotriazole And Application In Drug Discovery: Review

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ABSTRACT

Antibiotic resistance is often used to describe drug resistance, which occurs when bacteria, viruses, fungi, and parasites develop resistance to drugs intended to treat infections. Recent studies have confirmed that indole derivatives, heterocyclic benzimidazole derivatives and benzotriazole derivatives have antimicrobial activity against various microorganisms. Indole derivatives have attracted wide attention due to their diverse biological and clinical applications. Indole derivatives have antimicrobial activity against various microorganisms, including MRSA. Benzimidazole is a heterocyclic aromatic organic compound that has become an important pharmacophore and preferred structure in medicinal chemistry. Benzimidazole is a very effective compound in terms of antibacterial activity. Biochemical and pharmacological studies show that this molecule is active against several microbial species. Azoles, especially the benzotriazole ring, play an important role in heterocyclic chemistry and medicine. Benzotriazole derivatives are an important class of nitrogen-containing heterocycles believed to have a variety of pharmacological effects, including sedative, analgesic, antibacterial, and antifungal effects. In this review we discusses indoles, benzimidazoles and benzotriazoles for their antibacterial activity.

INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the major public health challenges of the 21st century, with an increasing number of infections caused by bacteria, parasites, viruses and fungi under the influence of conventional

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medicine. This threatens effective deterrence. Medicines are used to treat it. The problem of AMR is even more important when it comes to antibiotic resistance in bacteria. Over the decades, bacteria that cause a variety of common and serious infections have developed resistance to every new antibiotic on the market. Considering this fact, measures should be taken to prevent the emergence of a global health crisis [1].

The World Health Organization has long recognized the need to increase and coordinate global efforts to control AMR. In 2001, the WHO Global Strategy for Antimicrobial Resistance provided measures to slow the emergence and spread of antimicrobial resistance [2]. In 2012, the World Health Organization published The Emerging Threat of Antimicrobial Resistance - Options for Action and proposed a combination of strengthening health systems and surveillance measures. Increase the use of antibiotics in hospitals and communities. Prevention and control of infectious diseases. Encourage the development of new drugs and appropriate vaccines. and political interference [3].

A major challenge in combating AMR understands the true burden of resistance, especially in areas where surveillance and data are scarce. There is extensive literature evaluating AMR morbidity, mortality, length of hospital stay, and healthcare costs of pathogen-drug combinations in specific settings [4,5]. However, to our knowledge, there is no comprehensive estimate that covers the entire area. and many different pathogens and pathogen-drug combinations have been published to date. For example, the US Centers for Disease Control and Prevention (CDC) reported AMR infections and 18 AMR threats in the United States, and Cassini et al. published a report in 2019 using observational data. They evaluated drugs. From 2007 to 2015, the creation of the European Union and the European Economic Area. Lim et al. estimated the severity of multidrug resistance in six bacterial pathogens in Thailand in 2010 [6,7] and Temkin et al. Escherichia coli and Klebsiella suspected pneumonia. 2014 [8].

Antimicrobial resistance is often used as a definition of drug resistance, which occurs when bacteria, viruses, fungi, and parasites develop resistance to drugs intended for the treatment of infectious diseases [9,10]. Several strains of methicillin-resistant Staphylococcus aureus (MRSA) cause serious infections in intensive care units, including pneumonia, endocarditis, and skin and soft tissue infections [11,12]. Recent studies have confirmed that indole derivatives, heterocyclic benzimidazole derivatives and benzotriazole derivatives have antimicrobial activity against various microorganisms.

INDOLE DERIVATIVES:

Indole, also known as benzopyrrole, has a benzenoid nucleus, contains 10 π electrons (2 electrons from the lone pair on nitrogen and 2 electrons from the double bond forming 8 electrons), and is mostly aromatic. Like the benzene ring, indole easily undergoes electrophilic substitution due to π electron transfer [13]. Indole is an important heterocyclic ring that provides lysergic acid diethylamide (LSD), a plant-derived strychnine alkaloid. Physically, it is mostly colorless crystals with a distinct smell. By adding an indole nucleus, a biologically active pharmacophore, to the drug compound, it has become an important heterocyclic compound with various biological activities [14]. Therefore, researchers have been interested in the synthesis of different indole scaffolds to screen them for different pharmacological activities. Various natural compounds, such as tryptophan, have indole as their nucleus. Indole-3-acetic acid is a plant hormone produced by the cleavage of tryptophan in higher plants. Indole derivatives have attracted wide attention due to their diverse biological and clinical applications. Here, we have

summarized the important pharmacological activities of indole derivatives [15].

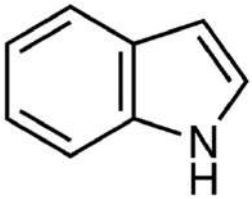

Figure 1: General chemical structure of Indole derivative.

Indole derivatives have emerged as important drugs in recent years and are known for their important biological activities, such as cytotoxic, antibacterial, anti-diabetic, and anti-inflammatory activities. Many drugs containing indole are available in the market. Some drugs containing indole are shown in Figure 2 [16].

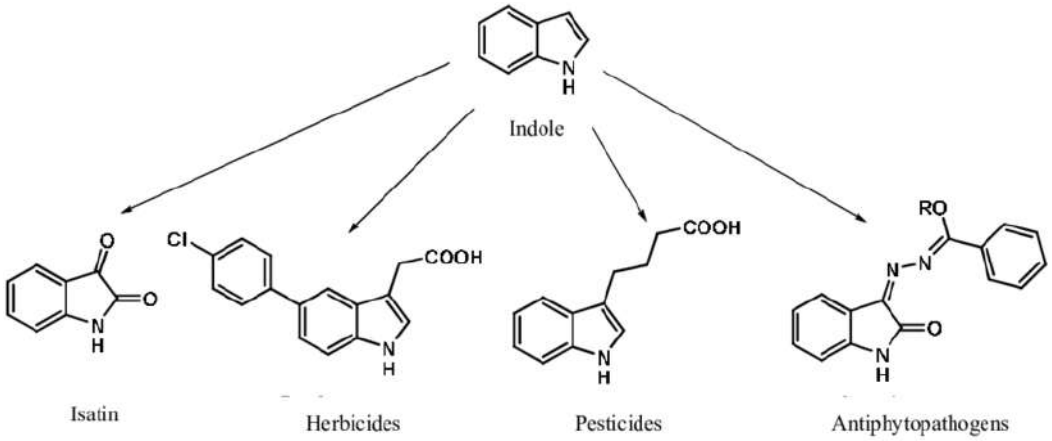

Figure 2: Antimicrobial activities of indole derivatives

Recent studies have confirmed that indole products have antibacterial activity against various microorganisms, including MRSA [17]. Studies have shown that the light efflux pump A [18,19] is one of the main causes of antibiotic resistance in Staphylococcus aureus. Nora can export a variety of non-specific drugs, including fluoroquinolones, ethidium bromide, cetamide, benzalkonium chloride, tetra-phenyl-phosphonium bromide, and acriflavine [20]. Indoles are one of the reported classes of Nor A inhibitors, such as 5-nitro-2-phenylindole, a promising lead structure that represents ciprofloxacin S. It can increase camera sensitivity by 4 times. Tert-butyl (2-(3-hydroxyurido)-2-(1H-indole-3-yl)ethyl)
carbamate, which is non-toxic to human cells, was also identified as an active endolic NORA inhibitor [21]. Azole-containing compounds such as fluconazole, ketoconazole, and itraconazole are the most commonly used antifungal drugs in the clinic [22,23]. However, some studies have shown fluconazole to be ineffective against Candida krusei, a potentially multidrug-resistant fungal pathogen [24, 25, 26]. Therefore, there is a need to develop new active compounds against fungal pathogens such as C. krusei. Multidrug-resistant infections are an emerging medical concern and attract the attention of researchers. Synthesis and antifungal activity of indole-conjugated triazole derivatives showed that almost all indole derivatives showed excellent antifungal activity against Candida albicans and Chlamydia cruzi with minimum inhibitory concentration. [27]. Antibacterial activity 1,2,4-triazole and 1,3,4-thiadiazole derivatives show antibacterial activity [29]. In addition, imidazoles and triazoles (azoles) are known to form the largest class of drugs against fungal infections. Indole derivatives are more

effective and more suitable for development in antimicrobial drug development research [30]. According to the literature, all synthesized compounds show antibacterial and antifungal effects, and the antifungal activity of these compounds gives hope for the development of new lead compounds that are more effective against C. krusei. About 17% of Candida isolates are resistant to azoles and the widespread use of fluconazole is the main reason for this resistance. C. krusei is a strain that shows resistance to fluconazole [31]. Therefore, the search for new and more effective antifungal agents against C. krusei appears to be increasing [32]. Azole compounds inhibit ergosterol synthesis by inhibiting the cytochrome P-450 enzyme lanosterol 14α-demethylase. Triazoles are widely used in the treatment of fungal infections due to their high affinity for fungal cytochrome P-450 enzymes. It is reasonable to assume that the synthesized indole-triazole derivatives have a similar mechanism of action [33]. The combination of general use of antifungal molecules and inappropriate treatment is responsible for the development of resistance of these microorganisms to the drugs used in treatment. The effects of antibacterial and antifungal activity are thought to be mediated by targeting, as the introduction of substitutions in indole leads to differences in activity [34].

BENZIMIDAZOLE DERIVATIVES:

Benzimidazoles have been reported to have antibacterial properties against bacteria or fungi [35]. Compounds with azetidinone ring show various biological activities, including antibacterial and antifungal activity. The broad therapeutic value of this nucleus led to the synthesis of benzimidazole-derived compounds and the essential oil of Citrus hystrix (Makro Lime) substituted in position 2, which have antibacterial properties. Essential oils from plants may have antibacterial properties due to their synergistic effects [36]. Essential oils usually consist of many components and their mechanism of action involves multiple targets in bacterial cells. Several essential oil compounds have been identified as antimicrobial agents, including carvacrol [2], citral, eugenol, geraniol, perylaldehyde, and thymol. In addition, essential oils have antioxidant, antiseptic, insecticidal, antifungal, antiviral, and anti-parasitic properties [37]. Lime oil has been reported to be effective against 20 serotypes of Salmonella and 5 other enteric bacteria. Essential oils and various plant extracts have long been used in medicine [36].

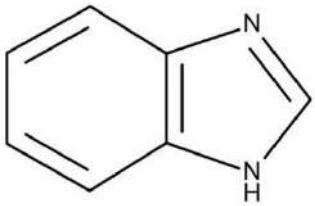

Figure 3: General chemical structure of benzimidazole derivative

This is a source of new drugs, especially against bacterial pathogens. Citrus hystrix DC, commonly known as Makrut orange, is a typical tropical plant of the Rutaceae family found in Southeast Asia [38]. Makrut is a thorny shrub with lime-scented leaves and dark green fruits that are irregularly shaped. The valuable components of lemon lime are the leaves and the skin of the fruit. Makrut lime is an important ingredient in many dishes of Thailand, Cambodia, Indonesia, Laos, Malaysia and the Philippines. Essential oils are used not only as fragrances and fragrances, but also in the preparation of perfumes and medicines. Essential oils usually consist of many components and their mechanism of action involves multiple targets in bacterial cells. Several essential oil compounds have been identified as antimicrobial agents, including carvacrol citral, eugenol, geraniol, perylaldehyde, and thymol [39-44]. Macroroot oil has been reported to be active against 20 Salmonella serotypes and 5 other enteric bacteria [45]. Citrus essential oil has significant antimicrobial activity against bacteria and fungi

[46-48]. Citrus essential oil may be a good candidate for increasing the shelf life and safety of low-processed fruit and low-fat dairy products. However, most research has focused on subtropical citrus essential oils. Essential oils from two tropical citrus cultivars, including Citrus hystrix DC and Citrus aurantifolia, have been shown to have antimicrobial activity against Bacillus spp., Staphylococcus aureus, and Salmonella typhi [49]. The structure of benzimidazoles is important in the drug discovery process. Many drugs contain a benzimidazole ring. For example: proton pump inhibitors (lansoprazole, omeprazole), antihistamines (astemizole), antihypertensives (telmisartan, candesartan), anthelmintics (albendazole, flubendazole, mebendazole) (Figure 4). Benzimidazol and others have attracted a lot of attention due to their medicinal properties. Benzimidazole analogs have several therapeutic properties including antibacterial, antioxidant, anthelmintic, antihypertensive, anti-inflammatory, antiprotozoal, anti-hepatitis B virus, anti-viral, anti-fungal, anti-inflammatory, anti-inflammatory, anti-inflammatory and anti-inflammatory swelling Cancer is beneficial in this regard [50]. Amoxicillin, norfloxacin, and ciprofloxacin are the most commonly used drugs against these bacterial infections, but are associated with serious side effects [51]. A steady increase in the number of infections caused by bacteria resistant to one or more types of antibiotics is a serious threat and can lead to treatment failure and complications. Therefore, many efforts have been made by new research groups to find new antimicrobial agents [52,53,54].

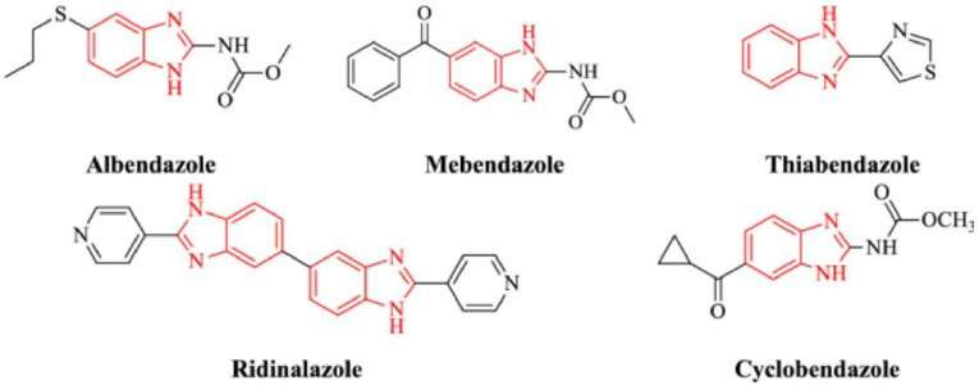

Figure 4: Benzimidazole derivatives for anti-microbial activities (anthelmintics)

Coumarin–benzimidazole hybrids as a potent antimicrobial agent:

It has been widely reported that natural compounds can play an important role as lead structures for the development of synthetic molecules. Coumarin (2H-chromene-2-one) is a natural compound with a wide range of biological activities. Coumarin-based novobiocin and chlorobiocin were identified as potent inhibitors of bacterial DNA gyrase (Figure 5) [55]. Recently, Li et al reported a coumarin-based inhibitor with strong antibacterial activity against ciprofloxacin- and methicillin-resistant Staphylococcus aureus strains. Sahoo and Padshetty reported that cobalt complexes such as 3-aryl-azo-4-hydroxycoumarin have antibacterial, wound healing and antioxidant properties [56]. Paul et al. reported the anticancer activity of a coumarin-benzimidazole hybrid [57]. Al-Majdi et al reviewed previous studies on coumarins in terms of antibacterial activity and reported that coumarin analogs showed stronger antibacterial activity than the parent molecule [58]. These and other studies led to the design and synthesis of coumarin-based hybrid analogs with antimicrobial activity. The molecular hybridization approach allows combining two or more drug units with different or similar biological activities into a molecular scaffold with new or

improved biological activity based on the respective drug unit. Hybrids are often reported to exhibit interesting multi-biological activity, high selectivity and favorable pharmacokinetics, avoiding undesirable disadvantages such as side effects and poor oral bioavailability. These advantages make hybrid molecules an attractive resource for drug discovery today. Benzimidazole is an important heterocyclic pharmacophore structure that has great application in the synthesis of drug-like molecules [62,63]. According to the literature review, many benzimidazole derivatives have been successfully developed as clinical drugs and are widely used in the treatment of various diseases. Recent studies have shown that benzimidazole can inhibit the growth of bacteria [64].

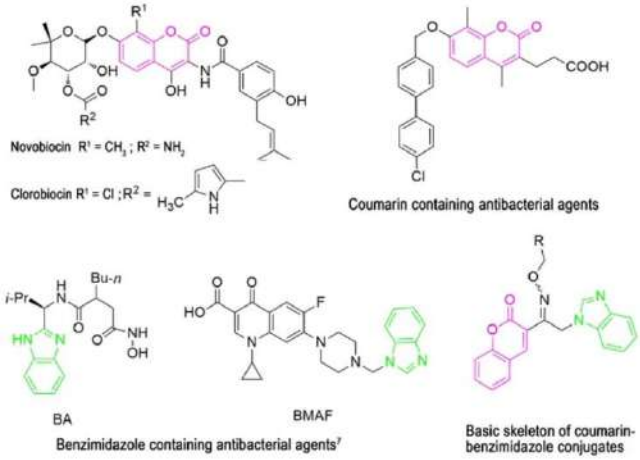

Figure 5: General structure of coumarin-benzimidazole complexes synthesized by antibacterial benzimidazole compounds.

The antibacterial potential of benzimidazole derivatives has been studied specifically since the late 1990s and early 2000s [65]. Given the extensive research on the antibacterial properties of benzimidazole derivatives since 2012, the following section summarizes their antiviral, antiulcer, antiprotozoal, and antituberculosis properties, as well as their antibacterial and antifungal activity will focus on the latest information [66].

BENZOTRIAZOLE DERIVATIVES

Azoles, especially the benzotriazole ring, play an important role in heterocyclic chemistry and medicinal chemistry [67]. For example, benzotriazole compounds are widely used in the treatment of various diseases such as anticancer, antibacterial, antifungal, antibacterial, antiprotozoal, antiviral, antifungal and antitubulin agents. [68] Benzofused azoles are a group of heterocyclic compounds that are of great interest due to their properties and applications in medicinal chemistry. Benzimidazole and its derivatives have been studied for many years [69], and drugs containing this heterocyclic reaction as the main component are widely used clinically, for example as anthelmintics in humans [70]. Benzylated azoles containing three heteroatoms, such as bisoxadiazole, benzothiazole, and benzotriazole, have been widely studied due to their various biological activities. However, some reviews have focused on it. Indeed, the purpose of this article is to provide an overview of benzotriazole-based systems and their importance in medicinal chemistry [71,72]. Benzotriazole can be considered a structure of interest for several pharmacological activities. Bt, useful for designing new pharmacologically active compounds, is developing rapidly in the synthesis of heterocycles [73].

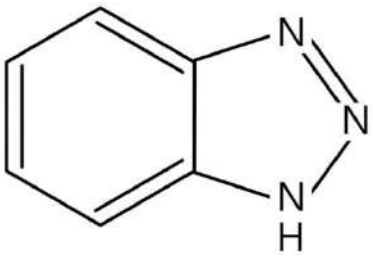

Figure 6: General chemical structure of benzotriazole derivative

Benzotriazoles also act as electron donors or radical precursors or carbanions. It can be easily converted into other chemical structures by a series of reactions such as condensation, addition reactions, and alkylation of benzotriazolyl. Several authors have reported the synthesis of stable nitrene ions using BT as a synthon. Polymer-supported benzotriazoles have also been used as catalysts for the construction of tetra-hydroquinoline libraries [73]. However, suitable substituted benzotriazole derivatives show plant growth regulatory activity, choleretic activity, antibacterial activity, antiprotozoal activity, antiviral activity, antiproliferative activity, and others. can have many different biological properties such as part [73].

Chemistry of Benzotriazole:

The benzotriazole core can have a large conjugated system that allows it to form interactions, and the three nitrogen atoms help form coordination bonds with hydrogen and other atoms. Therefore, benzotriazole derivatives have high affinity for various enzymes and receptors in biological systems, leading to various non-covalent interactions, leading to several biological activities. 1 Inorganic Benzotriazole (C6H3) is a heterocyclic nitrogen product that consists of three nitrogen atoms, each nitrogen atom has a single electron pair that can form a 5-membered ring that can exist in the corresponding tautomer [74]. It is called oxidiazole because of its five-membered ring structure with one oxygen atom and two nitrogen atoms. The arrangement of these atoms can be different, for example in Figure 7.

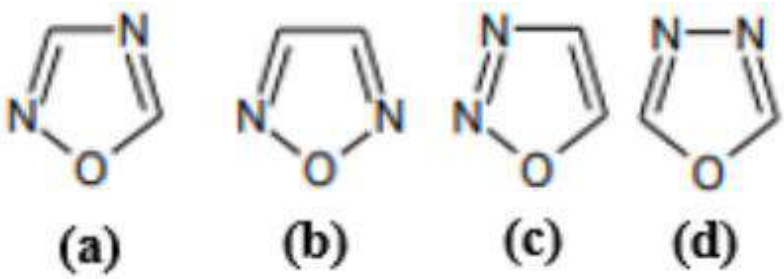

Figure 7: The compounds 1,2,4-oxadiazole (a), 1,2,5- oxadiazole (b), 1,2,3-oxadiazole (c), and 1,3,4-oxadiazole (d)

Benzotriazole as antimicrobial and antiprotozoal agent:

The antibacterial activity of benzotriazole derivatives has been widely studied since the late 1980s, and the whole azole ring has become one of the most important active ingredients in recent years [75]. The discovery and development of antibiotics in the first half of the 20th century was a major scientific breakthrough. Despite investment in the discovery of antimicrobial drugs, no new class of drugs has been discovered in the last two decades [76]. In addition, the challenge of treating infectious diseases due to increasing antibiotic resistance has highlighted the need to develop new drugs [77]. Over several decades, Speratore et al studied and characterized various

nitrogen rings and reported that BT has biological activity, especially antibacterial properties, when it is part of a larger heterocyclic ring system [78-79]. In 1989, Sanna's research group reported the relationship between the benzotriazole reaction of the closely related triazolone [4,5-f]-quinolinone carboxylic acid and oxolinic acid (1) (Figure 7). In vitro, this acid exerts antibacterial activity against E. coli with a minimum inhibitory concentration (MIC) of 12.5–25 μg/mL. They also showed that cyclization in different positions of the triazole ring, such as triazolo[4,5-h]-quinolinone carboxylic acid, leads to a partial or complete loss of antimicrobial activity [80,81].

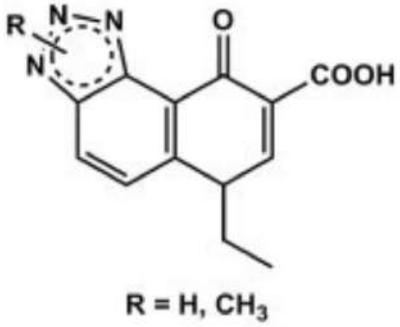

Figure 8: General formula of triazolo[4,5-f]-quinolinone carboxylic acids derivatives.

Benzotriazole as anti-bacterial:

Clinically useful 1,2,3-triazole derivatives include tazobactam, which is used in combination with beta-lactam antibiotics as antibacterial and anticonvulsant agents. Clinically important 1,2,4-triazole derivatives include rizatriptan, the antidepressant trazodone, the miotic dapiprazole (Figure 10), the antiviral drug ribavirin, the antiviral drug Irapfent, and the antidepressant drug Lotrifen (Figure 12). Lilmazafone (Figure 9) is a potent sedative and hypnotic [82,83].

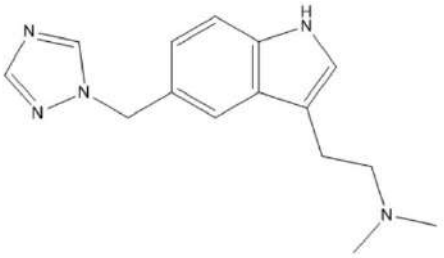

Figure 9: Rizatriptan

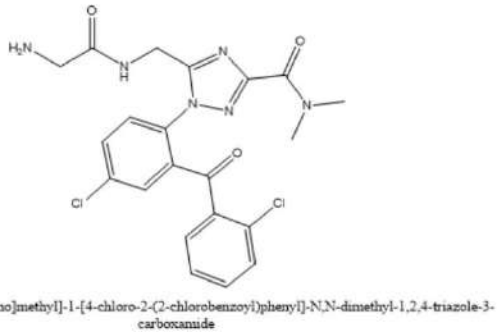

Figure 10: Rilmazafon

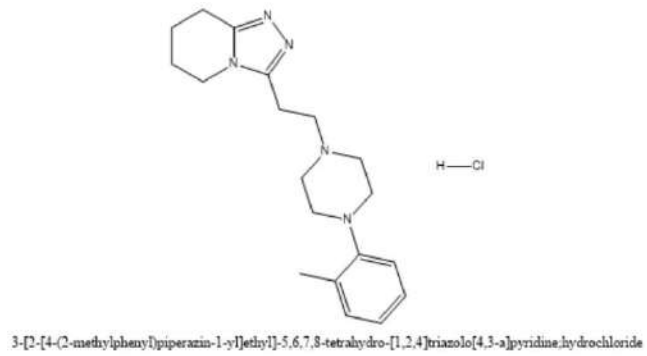

Figure 11: Dapiprazole

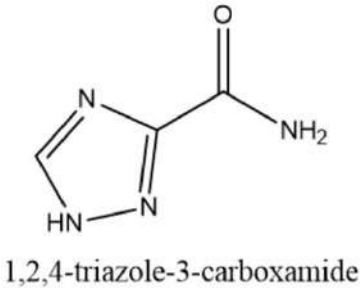

Figure 12: ibivirin

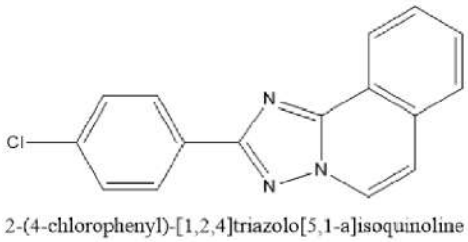

Figure 13: Lotrifen

CONCLUSION:

Indole is one of the most valuable heterocyclic compounds from a synthetic and therapeutic point of view. Indole and its derivatives have many biological properties, including anti-inflammatory, analgesic, antibacterial, anticonvulsant, anthelmintic and antiallergic effects. Considering the various biological activities exhibited by indole-containing compounds, we are investigating their antibacterial activity to save the lives of patients. Benzimidazole and pyrazole compounds have important biological properties such as antibacterial, antiviral, antipyretic, analgesic and anti-inflammatory. In addition, recent literature has suggested the synthesis of several benzimidazole-pyrazole hybrids and their antibacterial and other biological properties. Benzotriazole has anticonvulsant, anti-inflammatory and anti-cancer properties. This suggests that electron-substituted benzimidazole derivatives can be used as more effective antibiotics, antioxidants, anti-inflammatory agents, and analgesics with less gastrointestinal disturbances. It is believed that medicine can be produced. Benzotriazole derivatives are an important class of nitrogen-containing heterocycles believed to have a variety of pharmacological effects, including sedative, analgesic, antibacterial, and antifungal effects.

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