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Original Research Article

Pharmacological activities and activation as well as comparison of benzotriazole with other groups

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ABSTRACT

Benzotriazole has varied action in various medical fields, including medicine, pharmacology, clinical trials, and industrial applications, among others. This work, is based on a thorough review of the literature, provided the first comprehensive review of the most recent and remarkable developments in benzotriazole derivatives, which include activities such as antibiotic, antifungal, antibacterial, anticancer, anti-helmintic, antidepressant, antioxidant, antitubercular, antiviral, anticorrosive, plant growth inhibitor, and anti-inflammatory properties. Despite the fact that the overwhelming majority of pharmaceuticals are accessible to address a wide variety of ailments, they are not without their own set of problems, including resistance, toxicity, and other side effects. As a means of dealing with these issues, it is necessary to find and synthesise newer chemical entities that are more effective and have innovative mechanisms of action. Benzotriazoles are also used as restrainer(anti-fogging) in photographic emulsions, and it is also used as a reagent in determination of silver.
Benzotriazoles are also used as antifreezes, heating and cooling systems, hydraulic fluids and water phase inhibitors as well.

1. Introduction

In the case of benzotriazoles, a 5 ring is formed by three nitrogen atoms that are directly attached to each other as substituents on a central benzene ring. The benzene ring of the compounds known as methyl (or tolyl) derivatives has a methyl substituent attached to it. There are several additional derivatives that are feasible, and a number of them have been employed in a variety of applications. The principal use of benzotriazoles are as corrosion inhibitors, ultraviolet light stabilisers for polymers, and anti-foggants in photography, among other things. The fact that benzotriazoles are utilised in such huge amounts as a corrosion inhibitor is the primary way in which they end up as an environmental pollutant, according to the Environmental Protection Agency. Their usage in antifreeze at concentrations ranging from 0.01-2.0 percent as a corrosion inhibitor and fire retardant, as well as aviation de-icing/anti-icing fluids at unknown amounts ranging from 0.0 to 10 percent, is widespread.[1] Antifreeze that has been used may leak or be thrown down drains, allowing it to infiltrate the environment. A recent research also found that an estimated 80 percent of aircraft deicing/anti-icing fluids end up on the ground as a result of spray drift, jet blast, and wind shear while driving the car and departure, resulting in an increase in ice on the ground.[2] The Environmental Protection Agency (EPA) determined in 1977 that benzotriazole is

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extremely low in toxicity and poses little health risk to people. Several benzotriazole compounds were shown to be mutagenic in bacterial systems, according to the same Environmental Protection Agency assessment. The National Institutes of Health produced a study a year later stating that there was no persuasive evidence that the chemical was carcinogenic. The existence of 1-amino benzotriazole, which has an amino group attached to one of the ring nitrogens, has only recently been demonstrated to be an effective mechanism-based inhibitor of cytochrome P-450s via a benzyne intermediate,[3] indicating that benzotriazoles as a class may interact with the P-450s. When it comes to detoxifying xenobiotics, the P450 enzymes are critical since they are also responsible for the activation of many chemicals that are carcinogenic in mammalian systems.

It is well known that benzotriazole and its derivatives are extremely useful in biomedical research. Chemical activities of this scaffold are many; it can be utilised as an intermediate,[4,5] a leaving group,[6] or a structural element in other chemical structures. Since the late 1980s, researchers have been studying the antimicrobial activity of benzotriazole derivatives in depth, and several authors have published the results of their studies on the biological evaluation of imidazole derivatives and benzotriazole analogues as antibacterial, antimycotic, antitubercular, and antiviral agents.[1,7] The number of viruses, as well as the number of viral illnesses, is always expanding. In addition to poverty and fast urbanisation, developing human migratory patterns as well as re-emerging viruses, all of these factors contribute to the growing effect of viral infections. Environmental variations and derangements produced by climate change and ecological changes created by man have raised the likelihood of new interactions between the many elements involved, hence creating the circumstances for the formation of novel infectious diseases. In the recent past, viral epidemics caused by the West Nile virus (WNV), severe acute respiratory syndrome (SARS) virus, Enterovirus A71 and D68, influenza virus, measles virus (MV),[8] and coronavirus (SARS-CoV-2)[9] have been seen to spread. While vaccination efforts have been successful in preventing and eliminating some viral illnesses, there are currently no vaccines, effective medications for prophylaxis, or therapeutic therapies available for a large number of viruses. In order to defend the public health against a wide range of important viral diseases, further efforts in the development of antiviral medicines are required. Recent advances have been made in the development of azole derivatives as antibacterial, antifungal, antitubercular, and antiviral agents, including mono-nitrogen azoles (oxazoles, thiazoles, and carbazoles), bis-nitrogen azoles (imidazoles, pyrazoles, and benzimidazoles), and tri-nitrogen azoles (triazoles and benzotriazoles).[10–12] Oxazoles are mono-nitro compounds.

Following these considerations and as part of a multi-annual antiviral research programme, we have described the chemical characterization and antiviral activity of several series of azole derivatives, including benzimidazole and benzotriazoles,[13,14] and a large series of both benzimidazole and benzotriazole derivatives condensed with a pyridine ring.[15] in the last few years. Particularly interesting among these azoles are benzotriazoles derivatives containing one or two chlorine atoms on the benzene moiety of benzotriazole, in positions 5 and 6, respectively. BVDV and human rhinovirus (hRSV) were shown to be active against these derivates after a thorough screening against both RNA and DNA viruses. The deletion of a chlorine atom from the same scaffold created a shortage of activity against all viral strains tested.[16]

Benzotriazole is also hazardous to aquatic life and has a negative impact on the ecosystem.[17] It takes 48 hours to reach the tolerance limit for bluegills and minnows, and 96 hours to reach the tolerance limit for minnows and bluegills (0.2 mm). For trout, the tolerance level is 15 parts per million (ppm) after 48 hours and 12 parts per million (ppm) after 96 hours. According to the death rate, after 96 hours the mortality rate is greater than after 48 hours, indicating that there is a persistent harmful impact on fishes. There have been no reports on the impact of the chemicals on aquatic flora. On the destiny of benzotriazoles that have been discharged into the environment, there is only a limited amount of knowledge. Benzotriazoles have the potential to survive in the environment for an extremely long period of time because of their resistance to oxidation under environmental circumstances and their uv stability (under ultraviolet light). Rollinson and Callely conducted a research in 1986 and were unable to identify any microorganisms that were capable of degrading benzotriazole as a carbon or nitrogen source. The conclusion was reached that benzotriazole was not biodegradable. They also said that there had been no publications demonstrating indications of benzotriazole biodegradation in the literature.

2. Antiepileptic Activities of Various Heterocyclic Compounds

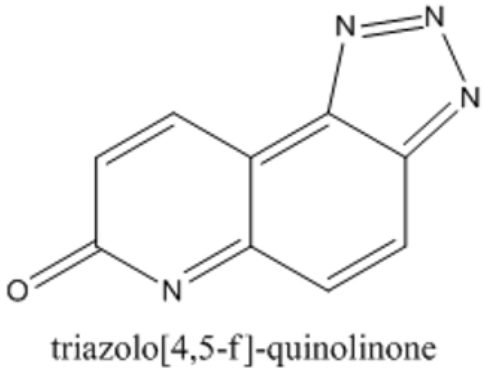
In looking for better anticonvulsant drug and the significance of semicarbazones and 2, 5-disubstituted 1,3,4- oxadiazoles, for example, 2-amino-5-{2-[(2,6-dichlorophenyl) amino] benzyl}-1,3,4-oxadiazole (1), 1- (5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl)- urea (2) and N-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}- 1,3,4-oxadiazol-2-yl) - hydrazine carboxamide (3) and N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl} -1,3,4-oxadiazol-2-yl)-N4- (4-subbed benzaldehyde)- semicarbazone (4a-f), N1-(5- {2-[(2,6-dichloro phenyl)amino]benzyl}- 1,3,4-oxadiazol-2-yl)- N4-(benzaldehyde) - semicarbazone

(4a), N1-(5-{2-[(2,6-dichloro phenyl) amino] benzyl} -1,3,4-oxadiazol-2-yl)- N4- (4-nitro-benzaldehyde)-semicarbazone (4b), N1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl} -1,3,4-oxadiazol-2-yl)- N4- (4-hydroxy benzaldehyde)- semicarbazone (4c), N1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl} -1,3,4-oxadiazol-2-yl)-N4- (4-methyl-benzaldehyde)- semicarbazone (4d), N1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl} -1,3,4-oxadiazol-2-yl) - N4-(4-methoxybenzaldehyde)-semi-carbazone (4e), and N1-(5-{2- [(2,6-dichloro-phenyl)amino]benzyl }-1,3,4-oxadiazol-2-yl)- N4-(4-chlorobenzaldehyde) - semicarbazone (4f) and N1-(5-{2-[(2,6-dichloro phenyl)amino] benzyl} -1,3,4-oxadiazol-2-yl)- N4-[1-(4-subbed phenyl) ethanone]-semicarbazone (5a-d) to be specific N1-(5-{2-[(2,6-dichloro phenyl)amino]benzyl} -1,3,4-oxadiazol-2-yl)-N4-[1-(4-hydroxy phenyl)- ethanone]-semicarbazone (5a), N1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl)- N4-[1-(4-methoxy phenyl)- ethanone]-semicarbazone (5b), N1- (5- {2-[(2,6-dichlorophenyl) amino]benzyl} -1,3,4-oxadiazol-2-yl)- N4- [1-(4-nitrophenyl)- ethanone]-semicarbazone (3c) and N1-(5-{2- [(2,6-dichlorophenyl) amino]benzyl} -1,3,4- oxadiazol-2-yl)- N4-[1- (4-chlorophenyl)- ethanone]-semicarbazone (5d) and N1- (5- {2-[(2,6-dichlorophenyl) amino]benzyl} -1,3,4-oxadiazol-2-yl)- N4-[1-(4-subbed phenyl) (phenyl) methanone]-semicarbazone (6a-d) in particular N1- (5-{2-[(2,6- dichlorophenyl) amino] benzyl} -1,3,4-oxadiazol-2-yl)- N4-[1- (diphenyl) methanone]- semicarbazone (6a), N1-(5-{2-[(2,6-dichloro-phenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl)- N4- [1-(4-hydroxyphenyl) (phenyl) methanone]- semicarbazone (6b), N1-(5-{2-[(2,6-dichloro phenyl) amino]benzyl}-1,3,4-oxadiazol - 2-yl)- N4-[1-(4-nitrophenyl) (phenyl) methanone]-semicarbazone (6c) and N1-(5-{2-[(2,6 - dichloro-phenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl)- N4-[1- (4-methoxyphenyl) (phenyl) methanone]-semicarbazone (6d) were assessed for their anticonvulsant action. Among every one of the mixtures, N1- (5-{2-[(2,6-dichlorophenyl) amino]benzyl} -1,3,4-oxadiazol-2-yl) - N4-[1-(4-hydroxyl-phenyl) (phenyl) methanone]-semicarbazone 6b arose out as the most strong compound, showing extensive action in maximal electroshock seizure (at 100 mg/kg after 0.5 h and at 300 mg/kg after 4.0 h) and subcutaneous pentylenetrazole model (at 300 mg/kg after 4.0 h) with next to no neurotoxicity (up to 300 mg/kg after 4.0 h). The after effects of the current review validated that the pharmacophore model with four restricting destinations is fundamental for anticonvulsant movement

3. Pharmacological Activities of Benzotriazole

3.1. Anti-microbial activity

Sparatore and his colleagues investigated numerous nitrogen rings as well as discovered that benzotriazole is a component of heterocyclic systems, which they named. Biochemical properties, particularly antibacterial activity, are possessed by it.[18,19] A study conducted by Sanna and colleagues in 1989 revealed that the benzotriazole moiety in triazolo[4,5-f]-quinolinone carboxylic acids (Fig 1), that are linked to oxolinic acid, was important. A Minimum Inhibitory Concentration (MIC) value was determined for these substances when they were tested in vitro against Escherichia coli in the laboratory.[20]



triazolo[4,5-f]-quinolinone

Fig. 1: General formula of triazolo[4,5-f]-quinolinone carboxylic acids derivatives.

3.2. Antioxidants

Antioxidants are reducing agents that help to stabilise the free radicals created by cellular metabolism, as well as chemicals that help to prevent oxidation from occurring. The anti-oxidative association of benzotriazole-substituted primaquine compound 21 was found to be greater (73.8 percent) than that of the parent compound primaquine (31 percent), which also shown strong Lipoxygenase Inhibitory (LOX) action (Fig 2).[21]

3.3. Analgesic activity

A number of chlorosubstituted phenoxyacetyl and propionylbenzotriazoles were synthesised and tested for their analgesic efficacy in a laboratory setting. The analgesic efficacy of the 2,5-dichlorophenoxy acetyl benzotriazole (13) (Fig. 3) was somewhat superior to that of the other compounds in the series.[22]

We generated 5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolidin-4-one derivatives out of the aldehyde and tested them for analgesic efficacy using the Eddy and Leimbach technique. In this study,

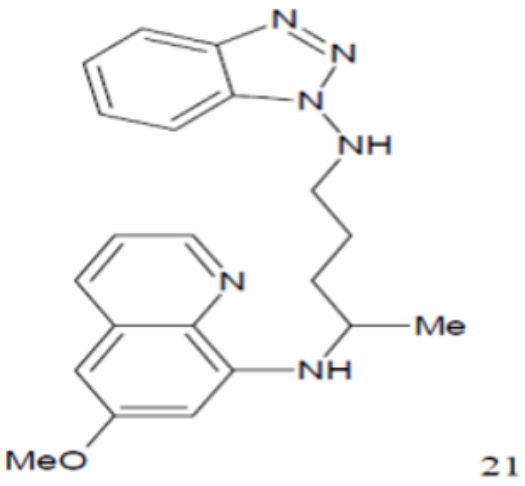


Fig. 2: Benzotriazole derivatized drugs as antioxidants

the analgesic efficacy of compounds 14h, 14i, and 14j was determined, and acetylsalicylic acid was used as a calibration curve medication (Fig.4).[23]

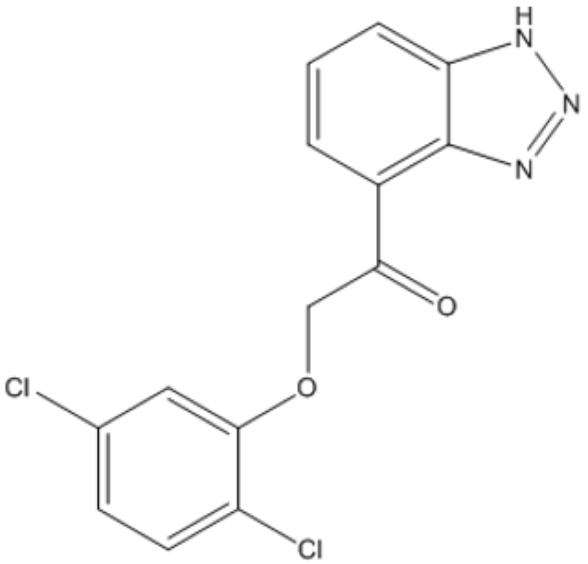


Fig. 3: 2,5 dichlorophenoxy acetyl benzotriazole

3.4. Anti-inflammatory activity

its anti-inflammatory activity. CPLA2 inhibition and significant anti-inflammatory action were shown in the compound benzotriazole-6- carboxylicacid (30). The substitution of a carboxyl indole or a carboxyl benzimidazole moiety for the carboxyl benzotriazole scaffold resulted in a reduction in the antiinflammatory effect.[24] As when contrasted to the common medicine

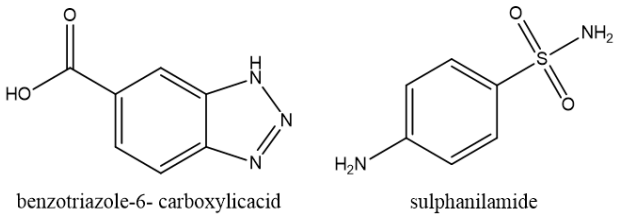


Fig. 4: Benzotriazole-based anti-inflammatory agents

paracetamol, the tetrazole-linked sulfanilamide benzotriazole derivative (31) shown much higher anti-inflammatory action. When the substituted sulfonyl moiety and benzotriazole are introduced, the anti-inflammatory action of the molecule is increased.[25]

3.5. Anti-tumor activity

The therapeutic method for cancer disorders varies depending on the kind of cancer and might involve surgical treatment, radiation therapy, immunotherapy, or chemotherapy. Currently, a wide range of anticancer medications are being used, including alkylating agents, platinum complexes, porphyrin pharmaceuticals, and azole agents, among other things. Vorozole(24), 4,5,6,7-tetrabromobenzotriazole (TBB) (25) and 4,5,6,7-tetrabromobenzotriazole (TBB) (25) are strong anticancer agents because they are selective inhibitors of the protein kinase CK2 and operate as a potent anti-cancer treatment.

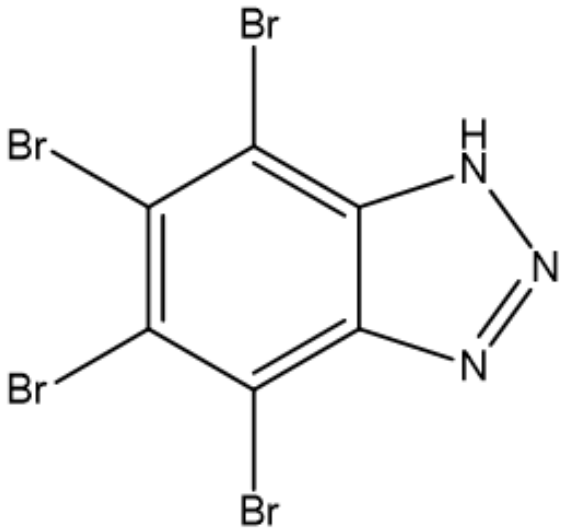


Fig. 5: Benzotriazole-based cancer drugs

4. Biological Profile of Benzimidazole

Benzimidazole is a versatile heterocyclic scaffold that may be used in the preparation of pharmaceuticals and has a wide range of pharmacological properties. Aside from that, benzimidazoles are physical isosters of nucleotides that exist naturally in the environment, which enables them to easily collaborate with the enzymes of the biological system due to their diverse biological activities. Benzimidazole-containing compounds have been shown to have biological activities as anti-allergic agents,[26] antimicrobial agents, antioxidant agents,[27] PARP inhibitors- as anticancer agents,[28] cytomegalovirus (HCMV) inhibitors,[29] antiulcer.[30] Due to their numerous applications, medicinal chemists classify them as "privileged substructures" for the purpose of developing novel drugs.[31,32] It is estimated that almost all benzimidazole derivatives, which differ in their functional substituents, result in a required adjustment of the physicochemical and pharmacokinetic characteristics of the medications under consideration. Because of their high chemotherapeutic efficacy, benzimidazole-derived compounds have received a great deal of research during the last few decades. Research has demonstrated that 2-substituted benzimidazole hybrids are physiologically more efficient than their unsubstituted counterparts, and as a result, 2-substituted benzimidazoles serve as prospective drug development and research candidates.[33–35] Benzimidazole derivatives are widely available on the market, including thiabendazole, flubendazole (anthelmintic), Enviradine (antiviral), omeprazole, rabeprazole, lansoprazole (antiulcer), telmisartan, candesartan cilexitil (antihypertensives), astimizole (antihistaminic), and several derivatives in a number of.[36]

5. Importance of Benzimidazole Derivatives

1. (a) *Antiulcer agents:* When it comes to the aetiology of gastric and duodenal ulcers, reflux esophagitis, and non-steroidal anti-inflammatory drug-induced lesions, the existence of acid is a critical element.[37] The disparity among culture of violence (such as acid, pepsin, and H. pylori infection) and local mucosa defence (such as the secretion of bicarbonates, mucus, and prostaglandin) in the human body results in acidpeptic and duodenal ulcers, gastroesophageal reflux disease, Zolinger-ellision syndrome, but instead gastritis, among other conditions. In the contemporary context of globalisation, this sickness appears to account for a significant proportion of all health-related disorders.

   (b) *Antipsychotic agents:* Benzimidazoles with a piperdinyl moiety[38] are effective antipsychotics as well as analgesics, and they are also used in dentistry.

   (c) *Antihelmintic drugs:* Benzimidazoles are now the most promising antihelmintic medicines currently available. Thiabendazole and mebendazole are extremely effective antihelmintic drugs with a broad spectrum of activity. Their applications include the treatment of nematode infestations as well as the treatment of proto myxozoa infestations. Albendazole is an anti-worm medication that is efficient towards roundworms, tapeworms, and flukes in both domestic living creatures.

   (d) *Antimicrobial and fungicidal drugs:* During the past few decades, infectious illnesses have posed a severe and rising threat to human health, particularly among the elderly. Several research organisations are focusing their efforts in this way, with the goal of developing or making a new class of medications that will be resistant to bacterium resistance strains. Because of its pharmacokinetic features, fluconazole is the first line of triazole-based antifungal drugs developed by the World Health Organization. The antibacterial activity of trihalogen benzimidazoles was found to be most strong, having a MIC of 3.12 g/ml against S.aureus.[39] A variety of benzimidazole derivatives are commercially available for the treatment of fungal infections.

   (e) *Anti-hypertensive drugs:* Anti-hypertensive medicines such as benzimidazoles are thought to be very effective.[40] Adimol is an anti-hypertensive medication that operates as a non-selective adrenergic receptor antagonist at the adrenergic receptors 1 and 2. Azilsartan medoxomil and Candesartan are angiotension-I receptor antagonists that have a benzimidazole nucleus. Azilsartan medoxomil & Candesartan are benzimidazole nucleus comprising drugs.

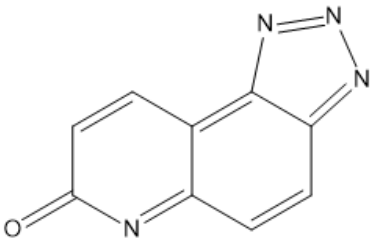
   (f) *Antiviral drugs:* Maribavir is an orally anti-viral medication that is a benzimidazole derivative. It is created to stop and cure human cytomeglo virus (HCMV) illness in patients undergoing hematopoietic stem cell/bone marrow transplantation. The method by which HCMV replication is inhibited is by suppression of an HCMV encoded protein kinase enzyme known as UL97 or pUL97, which seems found in the HCMV genome.[41]

6. VI. Benzotriazoles and Indazoles Are Scaffolds

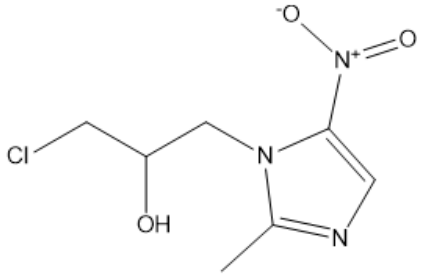
Infections of the gastrointestinal tract caused by parasitic and bacterial agents are a substantial cause of injury and death across the world, and they continue to pose

a considerable danger to public health. Amebiosis is a parasitic infection caused by the protozoan parasite Entamoeba histolytica that affects teenagers as well as the middle-aged populace. It is quite frequent in this age group. Amebiosis can manifest itself as intestinal or extra-intestinal infection.[42] Approximately 500 million individuals are believed to be contaminated with E. histolytica, according to the World Health Organization (WHO), yet 90 percent of those infected remain asymptomatic after having carried the illness for several years. Worldwide, amebiasis is accounting for roughly 70 000 deaths, the majority of which occur in developing nations. In endemic areas of wealthy nations such as the United States, the incidence ranges from 1 percent to 40 percent of the population in Central and South America, Africa, and Asia, and from 0.2 percent to 10.8 percent in endemic areas of developing countries such as the United Kingdom. 2,3 Nitroheterocycles are now being utilised in the treatment of parasitic illnesses, according to the FDA. N-nitroheterocyclic compounds were originally found as antiprotozoal agents in the 1960s; azomycin was the first active nitroimidazole to be discovered. Metronidazole (MTZ), a 5-nitroimidazole derivative, was unintentionally discovered to have antibacterial action after treating a patient who had been afflicted with Trichomonas vaginalis and bacterial gingivitis successfully.[43] Tinidazole and ornidazole are two more antiparasitic 5-nitroimidazole medications. MTZ is the most extensively used medicine in the therapy of amebiasis and other parasitic illnesses at the present time. Despite the fact that there is no proof that MTZ is carcinogenic or mutagenic in humans, the former has been recorded in rats and the latter has been found in bacteria. Methylthiouracil (4,5 MTZ) is associated with major side effects such as appetite loss, constipation and diarrhoea; severe or persistent dizziness or headache; metallic taste; nausea; genital itching; urinary tract infection; stomach distress and vomiting; and other symptoms. MTZ resistance in protozoa parasites has also been found[44,45] As a result, the discovery of novel medicinal drugs is of critical relevance.

When tested against E. histolytica, compounds based on a benzimidazole scaffold shown potential antiparasitic efficacy. The in vitro activity of several simple 1H-benzimidazole derivatives has been found to be in the low micromolar range, with an IC50 ranging from 3.8 to 0.005 M for some of the compounds.[46–48] Recently, a 3D quantitative structure–activity relationship (SAR) research of benzimidazole analogues with antiamoebic activity was carried out, and a comparative molecular field analysis (CoMFA) model was presented in order to choose the most likely bioactive tautomeric forms of these compounds.[49] This paper reports the anti-protozoan activity of 12 compounds against E. histolytica in vitro, which was carried out as part of our efforts to examine the antiprotozoan activity of new compounds. The compounds investigated against this parasite include not only benzimidazole derivatives, but also benzotriazole and indazole derivatives, which are structurally related to the benzimidazole ring but have not previously been tried against it.



triazolo[4,5-f]-quinolinone



1-chloro-3-(2-methyl-5-nitroimidazol-1-yl)propan-2-ol

Fig. 6: Representative antiparasitic compounds approved for human use. Active 5-nitroimidazole derivatives against anaerobic protozoa parasites.

7. Activation and Comparison of Benzotriazole with Other Groups

As illustrated in Scheme 1, benzotriazole, a very valuable synthetic auxiliary, may activate a wide range of groups to which it is linked, providing a variety of fascinating forms of activation. Because it is an excellent leaving group, benzotriazole forms a cation that may react with a number of nucleophiles in a variety of ways. Additionally, benzotriazole has been shown to behave as a proton activator, which can both activation and abstraction the connected a-proton by stabilising the resulting anion, allowing it to react with a wide range of electrophiles in the process. If both the benzotriazole and the leaving group are linked to the same carbon, the benzotriazole may contribute electrons to stabilise the cation generated by the loss of any other leaving group. It is also recognised as a radical precursor when used in conjunction with the single electron transfer (SET) process, such as when SmI2 is present. The connection between benzotriazole and carbon atoms can also be broken by the transfer of two electrons from a metal (for example, Li) to form a carbanion, which is then cleaved.

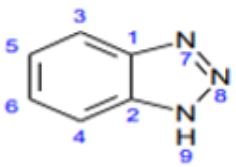
In the case of benzotriazole-based dianions, the lithiation of substituted benzotriazole (e.g., 1-vinylbenzotriazole) is well known, and the nitrogen of the triazole ring participates in cyclization in this case as well as in others. Despite the higher stability of benzotriazole, a number of reactions involving the breakdown of the benzotriazole ring have been observed. In comparison to many other substituents, such as halogens, cyano, phenylthio, phenylsulfonyl, phenyl, vinyl, and so on, benzotriazole is well known for its comparable leaving group ability as well as its superior proton activation efficiency, which makes it more preferable than any other groups in the synthesis of organic compounds. Because they are attached to a carbon atom that is a component of amino or ether functionality, benzotriazoles (X, NR2, OR) are stable and non-volatile and are simple to produce, whereas their halogen analogues are biologically risky and frequently too resistant to be used as analytical reagents in a practical manner.[50,51] In light of the durability of benzotriazole synthons, their utilisation is more economical than some other techniques due to their higher efficiency.[52]

8. Benzotriazole-Mediated Cyclization For Constructing Larger Heterocyclic Rings

The benzotriazole approach has been used to successfully synthesise a variety of pharmacologically intriguing big heterocyclic systems, including benzazepines, tetrazolotriazepines, diazapines, 1,4-benzothiazepines, 1,4-benzooxazepines, and other heterocyclic systems.[53] According to Khalaj et al., a quick and efficient benzotriazole approach for the construction of benzodiazepine carboxamide analogues was developed. N-(2,3-Dihydro-2-oxo-5-phenyl1H-1,4-benzodiazepin-3-yl)[54,55] The preparation of 2-carboxamides 156 in high yields was achieved by coupling 2-aminobenzophenones with (benzotriazol-1-yl)-N-acylglycines 154, followed by displacement of the benzotriazole with ammonia and finally cyclization of the resulting monoacyl aminals using ammonium acetate in glacial AcOH. 5Amino-4(benzotriazolylmethyl)-3-t-butyl-1-phenylpyrazole was employed in a beautiful way to synthesise the intriguing heterocyclic skeleton 157, which was discovered by accident. After being treated with methylidenetriphenylphosphorane and deprotonated with n-BuLi, 1-(triphenylphosphoranylideneaminomethyl) benzotriazole was formed, which was then treated with phthalic dicarboxaldehyde to yield 3H-2-benzazepine (158). 4- (Benzotriazol-1-yl)-6H-benzo[1,5-e][1,2,5] triazepine (159) was synthesised by reacting 1,2-dichloro-1,2-di(benzotriazol1-yl)ethane with NaN3 and resulting in the extension of the triazole ring of benzotriazole by two atoms. 1-[2-Arylthio(oxy)ethyl] -5-benzotriazolyl-2-pyrrolidinones 160 and 161, as well as 3-benzotriazolyl-2-[2-arylthio(oxy)- ethyl]benzotriazolyl-2-[2-arylthio(oxy)- ethyl]benzotriazolyl-2-[2-arylthio(oxy)-ethyl]benzotriazolyl-2-[2-arylthio(oxy The -1-isoindolinones 162 and 163 were synthesised by reacting benzotriazole with 2-(arylsulfanyl)ethylamines or 2-phenoxyethylamine with 2,5-dimethoxy-2,5-dihydrofuran or 2-formylbenzoic acid, and then purifying the resulting compound. Adding Lewis acid to the mixture produced the 1,4-benzoxazepines 164 and 165, as well as the 1,4-benzothiazepines 166 and 167, which were all obtained in moderate to good.[56]

9. Chemistry of Benzotriazole

The benzotriazole nucleus may hold a larger conjugated system, allowing for the formation of - stacking interactions, and the three nitrogen atoms keep it easy to build hydrogen bonds and coordination bonds with other molecules. Therefore, benzotriazole derivatives have a high affinity for a wide range of enzymes and receptors in biological systems, resulting in a diversified range of non-covalent interactions that result in a wide range of biological activities. 1 Inorganic benzotriazole (C6H3) is a nitrogen heterocycle derivative comprising three nitrogen atoms, each of which has an unshared lone pair of electrons, which combine to create a 5 ring that can reside in the corresponding tautomeric form.[57]



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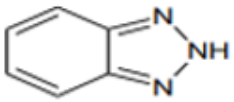
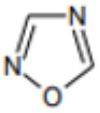
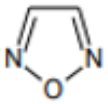


II

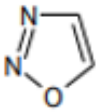
It is known as an oxidediazole because it is made up of one oxygen and two nitrogen atoms in a five membered ring structure. It is possible that the arrangement of these atoms will change. The compounds 1,2,4-oxadiazole(a), 1,2,5-oxadiazole(b), 1,2,3-oxadiazole(c), and 1,3,4-oxadiazole are examples of this (d).



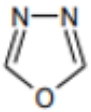
(a)



(b)



(c)



(d)

When the nucleus was already correctly replaced at the second and fifth positions, this molecule displays the least amount of drug resistance.[58]

10. Some Other Activities of Benzotriazoles

10.1. Anticancer Benzotriazoles

A wide range of anticancer medications, including alkylating compounds, platinum complexes, porphyrin pharmaceuticals, and azole agents, have been successfully created but is now being employed in clinical trials to treat a variety of tumours.[59] However, the majority of contemporary anticancer medications are toxic to normal tissues, resulting in a slew of side effects that, in turn, reduce the efficacy of the treatment in patients with cancer. Aside from medication resistance, long-term efficacy is further hampered by dose-related cumulative cardiotoxicity.[60,61] As a result, a rising number of studies are being conducted with the goal of designing and developing novel therapeutic agents for the treatment of cancer. The anticancer activity of several benzotriazole derivatives has been demonstrated, including the antineoplastic agent vorozole, which is currently in clinical trials, and 4,5,6,7-tetrabromobenztriazole (TBB)(compound 1a), which is a commercially available anticancer drug with high selectivity against the protein kinase CK2.[62] The effective discovery of TBB encourages the continuation of efforts toward the creation of new benzotriazole-based anticancer medicines that target a variety of kinases and receptors, including those involved in cancer. Furthermore, a growing number of novel structural benzotriazole derivatives, as well as benzotriazole-containing metal complexes, have shown significant promise in terms of their ability to overcome the numerous shortcomings of currently existing therapeutic medications.[63] Because of the critical functions that kinases play in cell proliferation, the inhibition of kinases is one of the most important therapeutic approaches for cancer, and it is also one of the most effective. Benzotriazole derivatives have a unique structure that allows them to easily bind with different kinases through a variety of non-covalent forces such as hydrogen bonds, coordination, ion-dipole, cation-, -stacking, hydrophobic effect, and van der Waals force, successfully hindering the ability of different kinases such as protein kinases CK2 and CHK1, histone deacetylases, and focal adhesion kinase and so on.

10.2. Benzotriazoles as anti mychotic agent

As previously reported, several authors disclosed the biological evaluation of imidazole derivatives and benzotriazole analogues as antibacterial and antimycotic agents. Unfortunately, in most cases a selectivity of action was not demonstrated.[64,65] However, the structural model of the best-known antifungal drug fluconazole offers an interesting starting point for drug design studies. Indeed, the triazolic system can be replaced by a benzotriazole ring, in order to evaluate the effects of the bioisosteric replacement on the biological behavior. Concerning the mechanism of action, it is known that antimycotic drugs, such as fluconazole, itraconazole, voriconazole, and ravuconazole[66] exert their pharmacological action by inhibiting the fungal 14 α-demethylase cytochrome P450. Known as CYP51, this is an essential enzyme in the biosynthesis of sterols. In particular CYP51 removes the 14 α-methyl group of lanosterol using oxygen and NADPH by oxidation, transforming it into ergosterol, an essential component of the fungal cell membranes . These drugs act by displacing lanosterol from CYP51 binding site, causing a block in the biosynthesis of ergosterol and an accumulation of 14 α-methylsterols.

For fluconazole and analogues, crucial interactions at the enzymatic active site are favored by these components: 1) the basic nitrogen atom in position 3 in the triazole moiety, which forms a bond with the acid iron of the CYP51 heme prosthetic group, in a position normally occupied by the oxygen, 2) the presence of aromatic rings and 3) the molecular behavior almost non-polar as described in Figure 7.

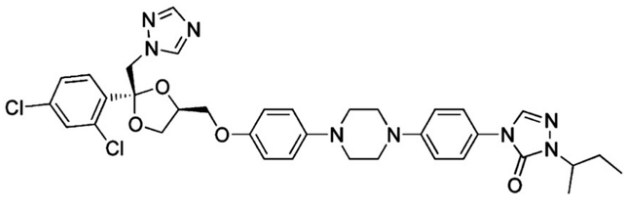


Fig. 7: Intraconazole

10.3. Benzotriazole as anti-viral agent

Some 7-(arylamidoalkyl)-3,4-diphenyl-isoquinolinyl-[1,5-c]-benzimidazoles have been synthesized and were evaluated for their in vivo against influenza virus (IV) by inoculating it in 10 day old embryonated hen's egg at the concentration of 0.5 mg per embryo in allantoic cavity. After 48 h it was found that the isoquinonyl benzimidazole derivative with nicotinamido group showed the maximum activity.[67]

Various benzimidazol-2-ylalkyl N-aryldithiocarbamates , 2-arlimino-4-methyl/H-2H, 4H[1,3,4]dithiazino[4,5-a]benzimidazole , 1-aryl-4-methyl/H-1, 2-dihydro-4H-[1,3,4]thiadiazino[4,5-a]benzimidazole-2-thiones 1-aryl-4-methyl/H-1, 2-dihydro-4H-[1,3,4]thiadiazino[4,5-a]benzimidazole-2-ones were synthesized and tested for their antiviral activity.

A set of 2-substituted-5-amidino-benzimidazole derivatives bearing amidino substistuent at C-5 of benzimidazole ring were synthesized by introducing various heterocyclic nuclei at C-2 and were evaluated for their antiviral activity towards *coxsackie viruses and echo viruses.* The most selective activity towards coxsackie viruses and echo viruses was observed with the compound having pyridine ring at C-2 Some new 10-(α-p-benzimidazolyl-1 aminobenzyl) phenothiazines have been synthesized and their antiviral activity was performed against JEV and HSV-1.

10.4. Benzotriazoles as anti-inflammatory and Analgesic agent-

Some 2-substituted benzimidazoles have been synthesized by the condensation of o-phenylenediamine with 2-coumaranonyl acetic acid derivatives and indole 3-acid and evaluated their anti-inflammatory and analgesic activities anti-inflammatory and analgesic activities. The compounds were found to have significant anti inflammatory activity at 50 mg/kg dose.[68]

A new synthesis and their anti-inflammatory activity of a group of 1H-benzimidazole were reported. The compounds were assessed on rat adjuvant arthritis screen and indomethacin as standard compound. The result gave 30% or greater reduction in non injected paw volume compared to control together with the result for indomethacin.

Some imino sugars of methylbenzimidazole have been prepared and anti-inflammatory activity of the compounds was studied by employing the cotton pellet granuloma bioassay in rats using indomethacin as reference standard. The granuloma% inhibition values were determined for each compound.[69]

1-[2,3-(2-Phenylbenzimidazole)]2-methyl/phenyl-4-(3,4-disubstituted benzylidine)-5-oxoimidazoles have been synthesized by condensing 2-(2/3 aminophenyl)benzimidazoles with appropriate 2-methyl/phenyl-4-(3,4-disubstituted) oxazoline-5-ones in dry pyridine and screened anti-inflammatory activity against carrageenan induced oedema).

A series of novel 5-substituted-1-(phenylsulphonyl)-2-methylbenzimidazole derivatives have been synthesized. Compounds were evaluated for their anti-inflammatory and analgesic pyridineactivities as well as gastric ulcerogenic effects by carrageenan-induced rat paw edema and acetic acid-induced writhing in mice using indomethacin as standard).

10.5. Benzotriazole as Herbicide

Amitrole[70] (Fig: 8) (3-amino-1H-1,2,4-triazole) is used as a herbicide and also to defoliate cotton plants before mechanical harvesting.

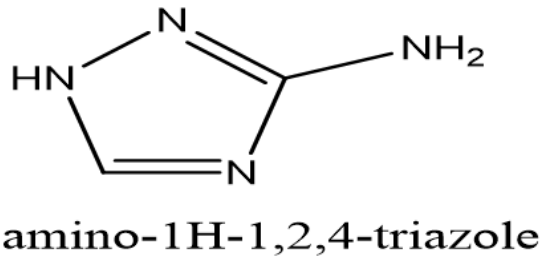


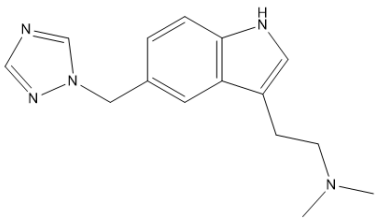
Fig. 8: 3-amino-1H-1,2,4-triazole

10.6. Benzotriazole as anti- bacterial

The clinically useful derivatives of 1,2,3-triazole includes Tazobactam which is used in combination with β-lactam antibiotics as antibacterial and (Fig:16)used as an anticonvulsant.

The derivatives of 1,2,4- triazole of therapeutic importance includes Rizatriptan,Trazodone(Fig:9) an antidepressant, Dapiprazole (Fig:10) a miotic agent, Ribavirin (Fig:11)an antiviral agent, Israpafant is an anti- asthmatic, Lotrifen(Fig:12) anabortifacient and

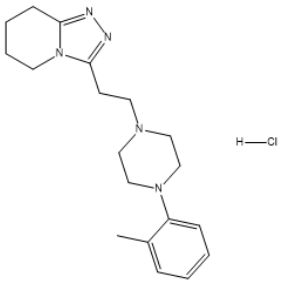
RIZATRIPTAN



2-(5-((1H-1,2,4-Triazol-1-yl)methyl)-1H-indol-3-yl)-N,N-dimethylethanamine

Fig. 9: Rizatriptan

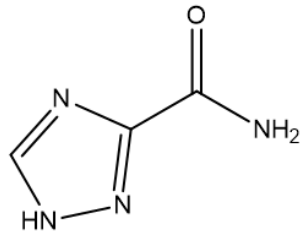
DAPIPRAZOLE



3-[2-[4-(2-methylphenyl)piperazin-1-yl]ethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine;hydrochloride

Fig. 10: Dapiprazole

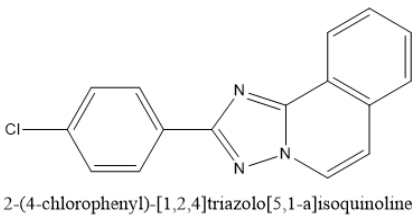
RIBAVIRIN



1,2,4-triazole-3-carboxamide

Fig. 11: ibivirin

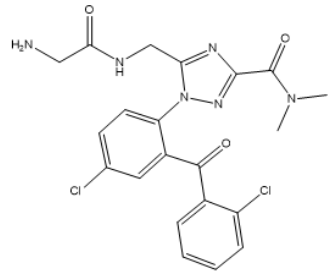
LOTRIFEN



2-(4-chlorophenyl)-[1,2,4]triazolo[5,1-a]isoquinoline

Fig. 12: Lotrifen

RILMAZAFON



5-[[(2-aminoacetyl)amino]methyl]-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-N,N-dimethyl-1,2,4-triazole-3-carboxamide

Fig. 13: Rilmazafon

Rilmazafone (Fig:13)a potent sedative and hypnotic agent.[71]

10.7. Benzotriazole as anti-Tubercular drug

Patel et al.[72] Synthesized 3-(3-pyridyl)-5-(4-methylphenyl)-4-(Nsubstituted-1,3- benzothiazol-2-amino)-4H-1,2,4-triazole analogs and evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain using Lowenstein-Jensen medium and antimicrobial activity against various bacteria and fungi using broth microdilution method. Some compounds emerged as promising antimicrobials. It was also observed that the promising antimicrobials have proved to be better antituberculars. One compound showed better antitubercular activity with MIC value of 25 μg/mL.

11. Conclusion

The analgesic, antibacterial, and antifungal activities of Benzotriazole derivatives, as well as the antimicrobial properties of Benzotriazole derivatives, were evaluated. Benzotriazole has also been shown to have anticonvulsant, anti-inflammatory, and anticancer properties. This leads us to believe that benzimidazole derivatives with electron withdrawing substituents might be exploited to develop more effective antibacterial, antioxidant, anti-inflammatory and analgesic medicines with less gastrointestinal lesions than previously reported. Further research into these derivatives is strongly recommended in order to determine the security of new substances. Other pharmacological actions of these compounds may be investigated in the future. Benzotriazole derivatives are a significant class of nitrogen containing heterocyclic and were accounted for to have a wide range of pharmacological exercises calming, pain relieving antibacterial and antifungal exercises.

12. Source of Funding

None.

13. Conflict of Interest

None.

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