Review On A Synthesis of Benzotriazole

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Abstract :-

Benzotriazoles are a derivative of a nitrogen-containing heterocycle with three nitrogen atoms located at the 1st, 2nd, and 3rd positions. Each nitrogen atom contains lone pairs of electrons in an unshared state, allowing the five-membered ring to exhibit tautomeric forms. This bicyclic heterocyclic system, consisting of three nitrogen atoms and a fused benzene ring, showcases a wide range of biological and pharmacological properties. The synthesis of benzotriazole involves combining benzene-1,2-diamine and carboxylic acid. Benzotriazole and its derivatives play a crucial role in medicinal chemistry, being utilized by chemists to address various therapeutic conditions. This paper discusses the application, principles, and chemistry of benzotriazoles, as well as provides an overview of the synthesized drug method.

Key words :- Benzotriazole ; heterocyclic; antimicrobial activity; synthesis ; pharmacological.

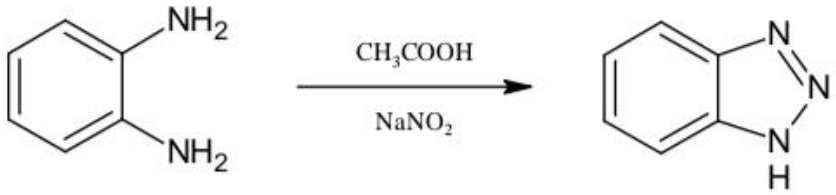
Introduction:-

The ongoing genetic changes and increasing resistance of micro-organisms against antibiotics and therapeutic agents pose a significant challenge in the fight against infectious diseases. Unfortunately, the development of new drugs has not kept pace with these changes, making it a never-ending battle. In recent decades, there has been a growing interest in the triazole class of compounds due to their extensive use in industry and agriculture. Benzotriazole and its derivatives hold great importance in the field of medicinal chemistry. Incorporating the benzotriazole nucleus is a crucial synthetic strategy in drug discovery, as it has been found to possess high therapeutic properties. This has motivated medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Organic compounds containing nitrogen and sulfur, along with their metal complexes, exhibit a wide range of biological activities such as antitumor, antibacterial, antifungal, and antiviral properties. Benzotriazoles are commonly utilized as corrosion inhibitors, radioprotectors, and photo stabilizers in the production of plastic, rubber, and chemical fiber. Additionally, benzotriazole plays a vital role as a precursor in the synthesis of peptides, acid azides, and the preparation of 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans. N-Substituted benzotriazoles exist in two isomeric forms: 1H- and 2H-substituted. It is generally observed that the 1H-substituted form dominates in solid and solution phases, while the proportion of the 2H-tautomer increases in the gas phase. However,the energy difference between the two isomers is minimal. Furthermore, benzotriazoles containing Mannich bases have recently been synthesized through amine exchange reactions using N,N-dimethylaminopropiophenone hydrochlorides and benzotriazole, respectively.

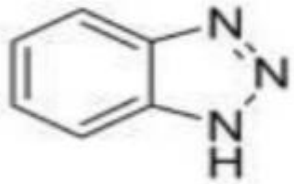
Benzotriazole, derived from benzo-fused azoles, belongs to a group of heterocyclic compounds that hold significant importance in the field of pharmaceutical and medicinal chemistry. Benzotriazole exhibits remarkable properties such as electron-donating nature, group release, and anion direction in its surroundings. It can be easily incorporated into molecules through various addition, condensation, and substitution reactions. Comprising of two fused rings, benzotriazole's five-membered rings have the ability to exhibit tautomerism (2).

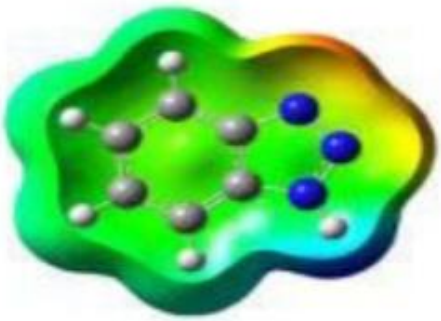
Benzotriazoles are a group of nitrogen-containing heterocyclic compounds that are essential in both synthetic organic chemistry and medicinal chemistry. These compounds are utilized in various ways in organic synthesis, serving as auxiliaries, intermediates, protecting groups, activating groups, and ligands. Moreover, benzotriazoles are employed in the production of a diverse array of functional materials, polymers, dyes, corrosion inhibitors,

pharmaceuticals, agrochemicals, and more. On the other hand, derivatives of benzotriazole have found applications as dopamine antagonists (e.g., Alizapride), sunscreen agents, antineoplastic agents (e.g., Vorozole), and in other medicinal uses. Furthermore, certain benzotriazole derivatives have demonstrated activities against cancer, malaria, bacteria, viruses, fungi, and HIV.



Physical properties :-





Name; Benzotriazole

Molecular formula; C6H5N3

Molecular weight; 119.1240

Melting point; 98.5-100°C

Nature White to brown crystalline powder

Density; 1.36 g/cm3

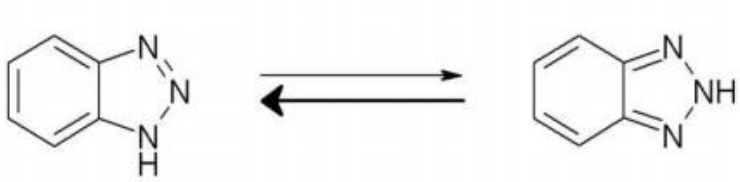
Solubility in water g/100 ml is 2 (moderate)

CAS Registry Number 95-14-7

UV absorbance 286 nm (4)

N-Substituted Benzotriazole exist in two tautomeric isomers in 1H- and 2H- forms in which the 1H- form predominates(99%) over the 2H- form at room temperature in both gas and solution (5)

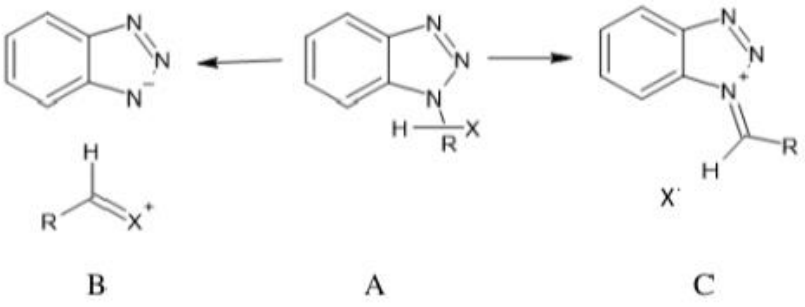
Phase**.**



1*H*-form 2*H*-Form

Benzotriazole is inexpensive, stable compound. It is soluble in ethanol, benzene, toluene, chloroform, and DMF, sparingly soluble in water but highly soluble in basic solution because it is an acidic appreciable strength with acid pKa 8.2 as well as weak base (pKa < 0) and because of this acid-base property.

Benzotriazole also acts as an electron-donor or a precursor of radicals or carbanions. This molecule also shows not only electron donating but also electron attracting ability, which leads to various synthetic applications. Because of this compounds with and R hetero atom(most commonly N,O and S) attached to a Benzotriazole nitrogen can ionize in two ways, either to form Benzotriazole anion and an immonium, oxonium, tionium cation to give B or to ionize of the hetero atom substituent to give C.



B A C

X = NR2,OR,SR. X = Halogen, OH

Benzotriazole derivatives are found active against the wide spectrum of target Species.

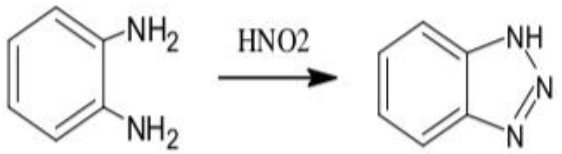
Also Benzotriazole of biological and industrial importance, to find most active sites of Pantoprazole and to investigate target Species.(5)

SYNTHETIC METHODS:-

Benzotriazole was initially documented as a synthetic auxiliary in organic chemistry in 1980. Subsequently, it has been employed in the synthesis of diverse monocyclic and bicyclic heterocyclic compounds that pose challenges when prepared using alternative approaches.

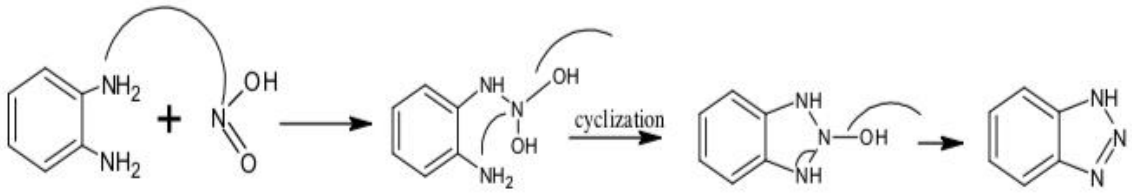
Benzotriazole possesses a wide range of appealing properties, making it an exceptionally versatile synthetic auxiliary. Numerous distinct methods exist for the preparation of Benzotriazole.

l) The synthesis of benzotriazoles involves the cyclocondensation of o-phenylenediamine with nitrite in acetic acid. This process leads to the conversion of the diamine into the monodiazonium derivative, which then undergoes spontaneous cyclization.

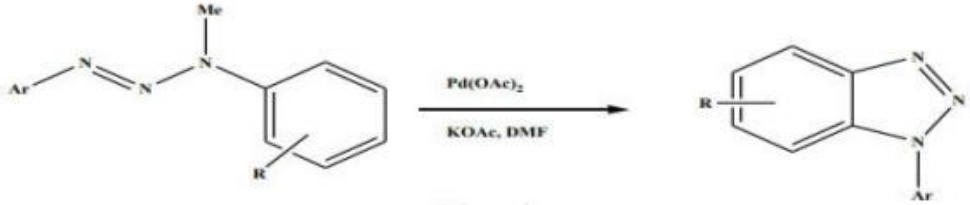


o-phenylenediamine Benzotriazole

Mechanism

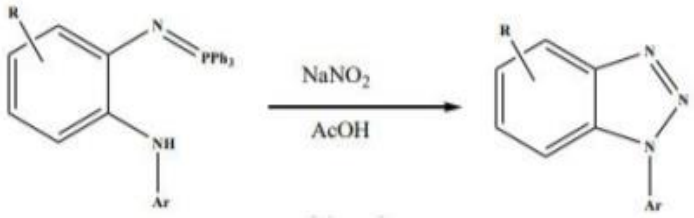


II) The regioselective synthesis of benzotriazoles using 1, 7-palladium migration cyclization dealkylation sequence. These reactions showed high regioselectivity and high yield

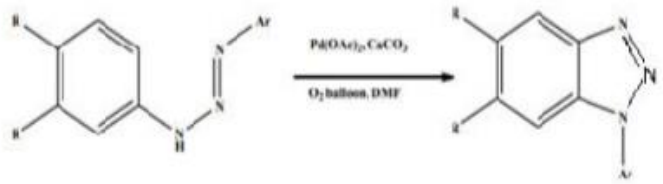


III) Synthesized 1-aryl-1,2,3-benzotriazole via cyclocondensation of 2-(arylamino)

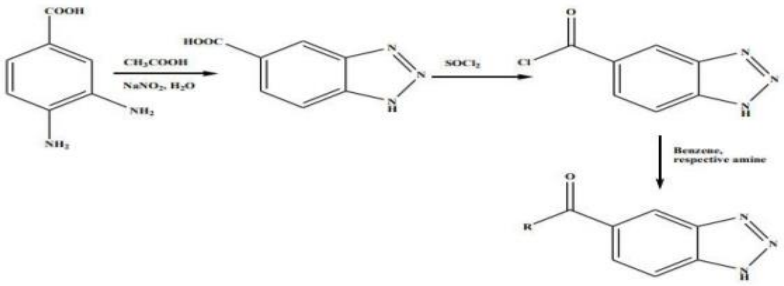
Aryliminophosphoranes in mild conditions. It involved three-step, halogen-free route of synthesis From simple nitroarenes and arylamines.



IV) Cyclization at moderate temperature was achieved by utilizing a catalytic amount of Pd (O Ac)2 to synthesize 1-aryl-1H-benzotriazoles.



V) Benzotriazole can be synthesized using both conventional and microwave methods.

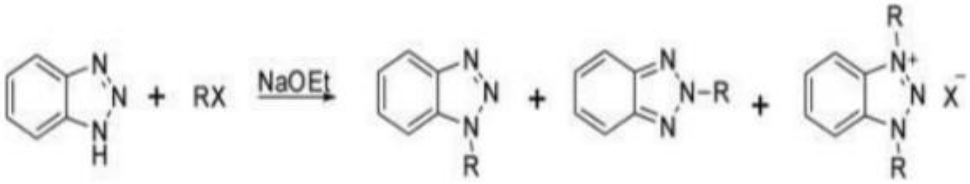


CHEMICAL REACTIONS :-(25)

I)Formation of Benzotriazole- C bond substitution:-

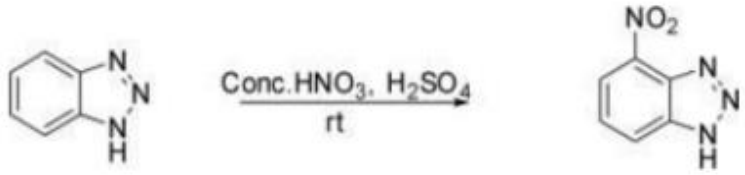
N-alkylation

The utilization of NaOH or NaOEt as a base in the alkylation process of 1H-benzotriazole with alkyl halide resulted in the formation of 1-alkylbenzotriazole as the primary product. Additionally, minor products such as 2-alkylbenzotriazole and 1,3-dialkylbenzotriazolium salt were also obtained.



Nitration

4-Nitro-1H-benzotriazole has been synthesized by nitrating 1H-Benzotriazole using a combination of concentrated nitric acid and sulfuric acid at ambient temperature, resulting in a 50% yield.

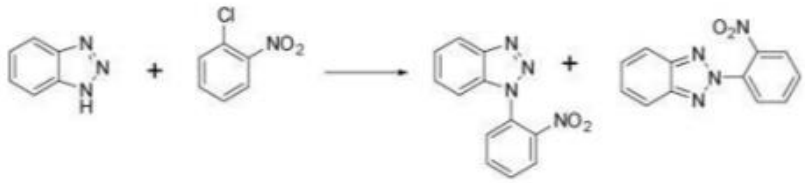


II) Formation of Benzotriazole –Ar substitution

N-arylation

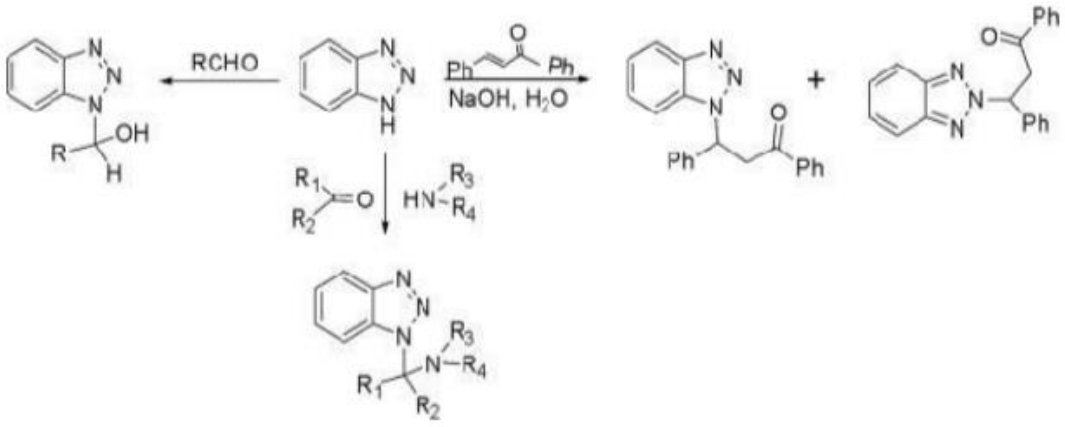
1H-Benzotriazole on reaction with activated aryl and heteroaryl halides afforded 1-Arylbenzotriazole. Here, 1-chloro-2-nitrobenzene reacting with 1H-benzotriazole gave a mixture Of 1- and 2-(2-nitrophenyl) Benzotriazole.

III) Formation of Benzotriazole-C bond by addition reaction



Reaction with carbonyl compounds

Reaction of 1H-benzotriazole with α,β-unsaturated ketones underwent 1,3-conjugated addition to give a mixture of 1-H- and 3-(2H-benzo[d][1,2,3-triazol-2-yl)-1,3-diphenylpropan-1-one,but reaction with aliphatic aldehyde afforded 1-hydroxyalkyl benzotriazole as an addition product. However reaction with ketone in the presence of dialkylamine delivered 1(dialkylaminoalkyl) Benzotriazole

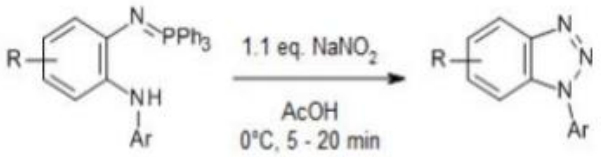


IV) Condensation reaction

Cyclocondensation of 2-(arylamino)aryl iminophosphoranes:

A cyclocondensation of 2-(arylamino)aryl iminophosphoranes enables the synthesis of 1-aryl-1,2,3-benzotriazoles under mild conditions. The reaction involves a three-step, halogen-free

route starting from simple nitroarenes and arylamines.



PHARMACOLOGICAL ACTIVITY :-

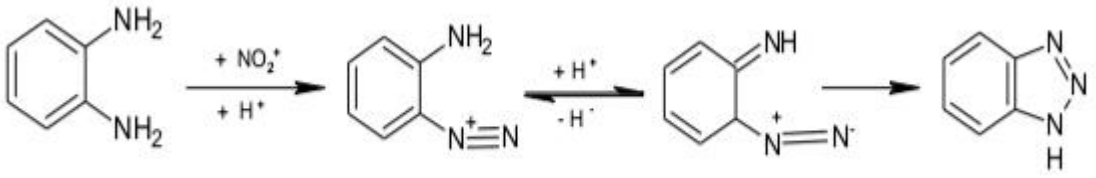
The 1H-benzo[d] [1,2,3] triazole possesses various pharmacological activities, making it a privileged structure. It serves as a valuable framework for the creation of novel pharmacologically active compounds. Benzotriazole is currently experiencing significant advancements in the synthesis of heterocycles.

A survey of literature reveals that the benzotriazole nucleus is found to have various Pharmacological activities like anti-inflammatory, antimicrobial, antifungal and anticancer Activity. It is also known from the literature that molecules containing benzotriazole nucleus Possess CNS activity and various other pharmacological activities. It has been considered as Prime importance to take up such synthesis of new compounds containing benzotriazole nucleus With a view to get more potent compounds and screen them for CNS activity.(5)

Synthesis:-

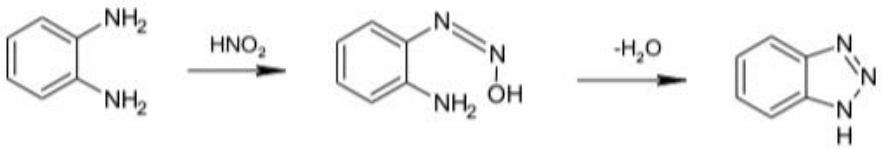
Scheme-I for synthesis of benzotriazole

Benzotriazoles are synthesized by cyclocondensation of o-phenylenediamines with sodium nitrite in acetic acid. The Reaction involved the simple heating the reagents together. Conversion of the diamine into the monodiazonium Derivative is followed by spontaneous cyclization.(8)



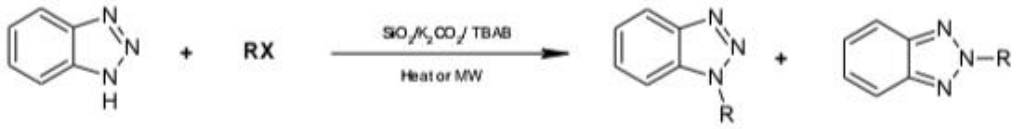
Scheme-II

1,2,3-Benzotriazole has been prepared directly by the action of nitrous acid on o-phenylenediamine and by the hydrolysis of an acylated or aroylated benzotriazole which has been previously prepared by the action of nitrous acid on the corresponding mono acylated or aroylated o-phenylenediamine. The above procedure is the direct method and gives better over-all yields than the methods involving several intermediate steps(9)



Scheme-III N-Alkylation of Benzotriazole under Solvent-Free Conditions

N-Alkylation of Benzotriazole under Solvent-Free Conditions: An efficient, simple and solvent-free method for highly regioselective N-alkylation of benzotriazole in the presence of SiO2, K2CO3 and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions has been described. In this method, 1-alkyl benzotriazoles were obtained regioselectively in moderate to high yields and short reaction times(10).



R= Alkyl, Aryl

Benzotriazoles are formed by cooling and stirring of benzene-1,2-diamine with carboxylic acid. Benzotriazole moiety possessing antifungal activity (Compound b had good activity).(11)

Pharmacological Study:-

Antimicrobial activity :-

The efficacy of various analogues of 1H-benzimidazole and 1H-benzotriazole, including their N-alkyl derivatives with chloro, bromo, and methyl substitutions, was evaluated through in vitro testing against Acanthamoeba castellanii protozoa. The results demonstrate that 5,6-dimethyl-1Hbenzotriazole and 5,6-dibromo-1H-benzotriazole outperform the antiprotozoal agent chlorohexidine.

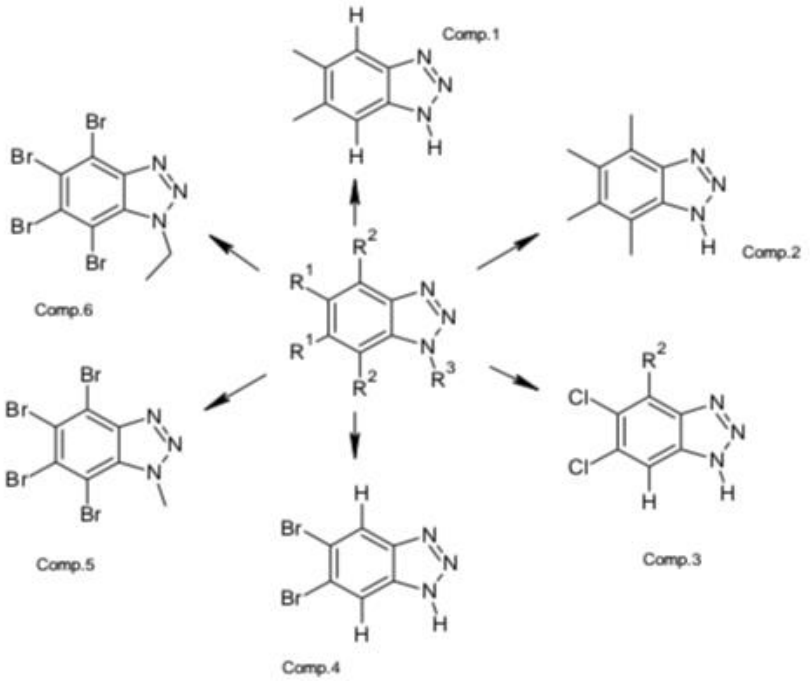


Figure 1 Derivatives of antimicrobial activity

Antiviral activity :-

The most potent compound in the series was discovered to be a novel set of dialkylamino side chain derivatives of benzotriazole, which were synthesized and reported as potential inhibitors of respiratory syncytial virus.

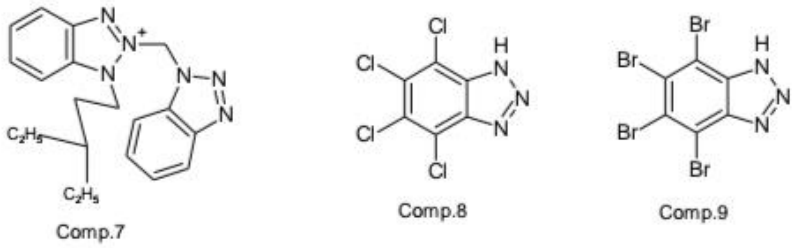


Figure 2 Derivative of antiviral activity

Halogenated benzotriazole nucleosides were synthesized and antiviral activity was tested against hepatitis C virus and other viral NTPase/helicases was found to be good inhibitor of the West Nile virus enzyme with an RNA substrate (IC50-0.3 μm) also reported selective antiviral activity.

Anticancer activity :-

4, 5, 6, 7-tetrabromobenzotriazolewas found to be most effective with high selective inhibition against proteinkinase CK2 reported excellent anticancer activity.

Antitubercular Benzotriazole :-

Tuberculosis, caused primarily by Mycobacterium tuberculosis, is a highly contagious disease. There are several drugs available in medical practice to treat tuberculosis, such as isoniazid and rifampicin. However, the effectiveness of these medications is limited due to drug-resistant strains and adverse reactions that can damage the stomach, intestines, and liver. Developing new drugs for tuberculosis treatment that are potent and do not share resistance with existing antimycobacterial agents is crucial. Recent studies have shown that nitrogen heterocyclic benzotriazole compounds have significant potential in combating tuberculosis. Adding halogen atoms to the benzene ring of benzotriazole derivatives has been found to enhance their effectiveness. Sydnones, with unique structural characteristics and biological activities, have attracted attention in both heterocyclic chemistry and medicinal chemistry. Some amide benzotriazole derivatives synthesized from the sydnone fragment have shown promising results. Amino benzotriazole has demonstrated strong antitubercular properties, outperforming standard drugs like streptomycin and pyrazinamide in inhibiting M. tuberculosis. Pyrazole Naryl derivatives have been extensively studied in the pharmaceutical industry due to their diverse range of bioactivities, including anti-hyperglycemic, analgesic, anti-inflammatory, antipyretic, and antibacterial effects. The incorporation of a pyrazole ring into molecules enhances the electron density of the system, making the chromophore more resistant to enzymatic reduction by radical species.

.**Antioxidative Benzotriazoles :-**

Free radicals, which are reactive oxygen nitrogen species resulting from human metabolism, can generate harmful substances through various metabolic pathways, leading to health issues like aging, cancer, and numerous neurodegenerative diseases. Consequently, the elimination of excess oxidized free radicals and enhancement of the body's antioxidative activities to combat age-related illnesses have become increasingly crucial. Antioxidants serve as reducing agents that help stabilize certain free radicals produced during cellular metabolism.

Benzimidazoles compounds have shown remarkable antioxidative properties and hold significant promise as novel antioxidative agents or candidates. Primaquine (PQ) derivatives are well-known and widely used antimalarial drugs. However, they also possess intriguing characteristics that position them as potential molecules for the development of antioxidative agents, primarily due to their prooxidant effects in the blood. The benzotriazole-substituted primaquine 58 demonstrated a higher interaction rate of 73.8% compared to the parent compound primaquine, which only exhibited a 31% interaction rate. Moreover, it effectively inhibited lipoxygenase (LOX) activity, further underscoring its potential as an antioxidative agent.

Cyclooxygenase(COX):

Cyclooxygenase (COX) is an enzyme (EC 1.14.99.1) responsible for the formation of essential biological mediators known as prostanoids, which include prostaglandins, prostacyclin, and thromboxane. Inhibiting COX pharmacologically can alleviate symptoms of inflammation and pain. Non-steroidal anti-inflammatory drugs like aspirin and ibuprofen work by inhibiting COX. COX-1 and COX-2 have similar molecular weights, around 70 and 72 kDa respectively, with 65% amino acid sequence homology and nearly identical catalytic sites.

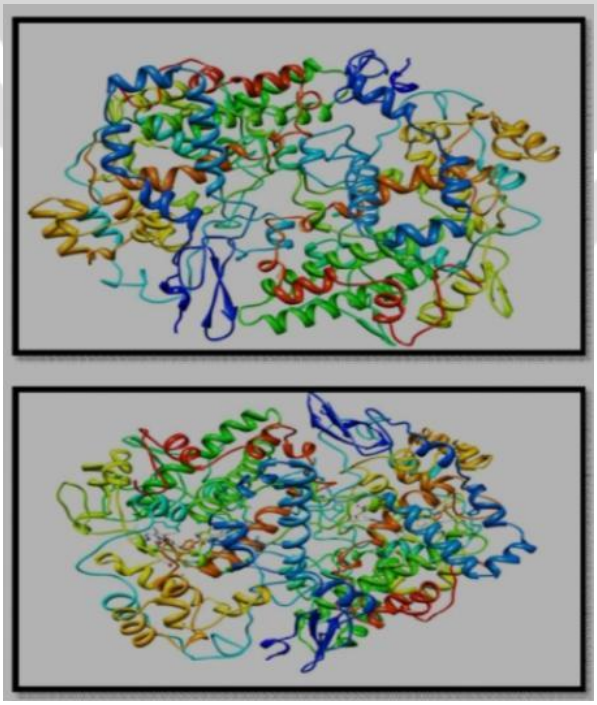


Figure.1COX 1Figure.2 COX 2

The traditional COX inhibitors are non-selective and inhibit all COX types. This inhibition of prostaglandin and thromboxane synthesis leads to reduced inflammation, as well as antipyretic, antithrombotic, and analgesic effects. The most common adverse effect of NSAIDs is irritation of the gastric mucosa since prostaglandins play a protective role in the gastrointestinal tract. Additionally, some NSAIDs are acidic, which can further damage the gastrointestinal tract.

Natural COX inhibition:-

Culinary mushrooms, like maitake, possess the ability to partially inhibit both COX-1 and COX-2 enzymes. Various flavonoids have also been discovered to have inhibitory effects on COX-2. Fish oils naturally contain a substance that hinders COX activity. Hyperforin, a compound found in certain plants, significantly inhibits COX-1 more than aspirin, with a range of 3-18 times. Additionally, calcitriol (vitamin D) has been proven to significantly suppress the expression of the COX-2 gene. It is crucial to exercise caution when combining low dose aspirin with COX-2 inhibitors, as this may potentially result in increased damage to the gastric mucosa. Moreover, it is important to note that COX-2 is upregulated when COX-1 is suppressed by aspirin, which holds significance.

Experimental Methods :-

The melting points of all substances were measured using open capillaries and remain uncorrected. The IR spectra were obtained using a Shimadzu spectrometer with KBr as the medium. The 1H-NMR and 13C-NMR analyses were conducted in DMSO-d6 using a Bruker instrument.

Thin Layer Chromatography:-

The utilization of thin layer chromatographic technique is an exceptional method to determine the purity of a compound. In order to prepare the slurry, a mixture of 50 grams of silica powder, 9 milliliters of $CHCl_3$, and 1 milliliter of methanol was combined in a beaker. This slurry was then evenly applied onto the activated TLC plate and subsequently dried, allowing the TLC plate to be utilized for the experiment. By creating a solitary spot on the TLC silica gel glass plate, we were able to verify the purity of the compound.(6)

Instrumental analysis:-

HPLC-Flu-UV detection analysis

The HPLC chromatographic separations were carried out using a system consisting of a 600E pump with a gradient controller from Waters in Milford, MA, USA, and a UV-Vis diode array and fluorescence detectors in series from HP Series 1100 – Agilent in Waldbrom, Germany. The injector, a Rheodyne Model 7725i from Cotati, CA, USA, was equipped with a 20 µL loop. The analytical column temperature was controlled using a MetaTherm 9540 oven from MetaChem in Torrance, CA, USA. The analytical column used was a 250 mm x 4.6 mm I.D. Waters C18 column with a particle size of 5 µm. To protect the analytical column, a Phenomenex C18 guard cartridge (4 mm × 3 mm) from Phenomenex in Torrance, CA, USA, was employed. Data acquisition was performed using Agilent Chemstation Software (Rev. A. 06.03 [509]). For chromatographic separations, a binary solvent system consisting of CAN and water (0.05% acetic acid) was utilized at a flow rate of 0.5 mL min^{-1}. The gradient elution program followed the following sequence: initial conditions of 17% CAN for 12 min, followed by a linear ramp to 100% CAN in 20 min, holding at 100% CAN for 6 min, and finally returning to the initial conditions in 2 min. The column temperature was maintained at 35 °C

LC-ESI-MS/MS analysis:-

To validate the developed analytical methodology and for comparison purposes, actual water samples were also analyzed using LC-ESI-MS/MS. The LC-ESI-MS/MS analysis was conducted using a Varian system from Walnut Creek, CA, USA. The LC instrument consisted of two ProStar 210 high-pressure mixing pumps from Varian, a vacuum membrane degasser from Metachem Technologies in Bath, UK, and a ProStar 410 module from Varian, which included an autosampler and a thermostated compartment for the LC column. The LC system was connected to a triple-quadrupole 1,200 L mass spectrometer equipped with an ESI source from Varian. The compounds were separated using the same column, guard cartridge, and mobile phases mentioned earlier. Benzotriazoles and benzothiazoles were determined by operating the ESI source in both negative and positive ionization modes. The gradient elution program used was as follows: initial conditions of 17% CAN for 18 minutes, followed by a linear ramp to 95% CAN in 20 minutes, and then holding at 95% CAN for 3 minutes. The mobile phase flow rate was set at 0.5 mL min−1, and the column was maintained at a temperature of 35 °C. The LC-ESI-MS/MS analysis of the 11 compounds took approximately 43 minutes. For both standards and sample extracts, an injection volume of 20 µL was used, utilizing the partial loopfill option in the autosampler. Nitrogen (99.999%) was employed as the nebulizing gas (50 psi) and drying gas (200 °C, 19 psi) in the ESI source, which was supplied by a high-purity generator from Domnick Hunter in Durham, UK. The temperature of the ESI housing was kept at 50 °C, and the voltage of the ESI needle was fixed at 5,000 V. Argon (99.999%) was used as the collision gas (2.9 × 10−5 psi) for MS/MS measurements. Instrument control and data acquisition were performed using Varian MS Workstation software.(7)

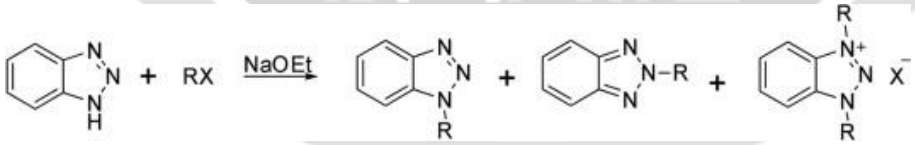
Application:-

Benzotriazole-based compounds possess diverse pharmacological properties and are utilized as corrosion inhibitors for copper and copper alloys in both atmospheric and immersed conditions. The pharmaceutical industry finds this structural motif highly valuable for the discovery of new drugs.(15)

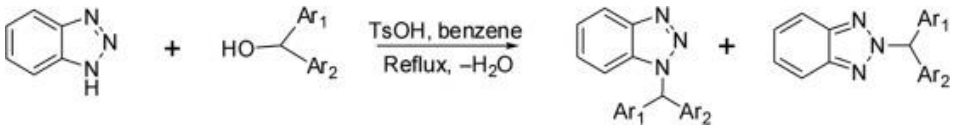
Electrophilic Substitution at the Nitrogen Atom

Alkylation

Various methylating agents, including methyl sulfate, diazomethane, and methyl halide, were reacted with 1H-benzotriazole. This reaction resulted in a mixture of 1-methyl- and 2-methylbenzotriazole, with a ratio of 5:17. On the other hand, when 1H-benzotriazole was alkylated with alkyl halide using NaOH or NaOEt as a base, the major product obtained was 1-alkylbenzotriazole. Additionally, minor products such as 2-alkylbenzotriazole and 1,3-dialkylbenzotriazolium salts were also formed.(16)

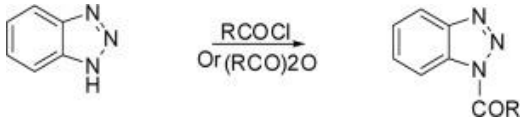


A mixture of the corresponding 1- and 2-diarylmethylbenzotriazoles was obtained when 1H-Benzotriazole reacted with diarylmethanols in the presence of 4-toluenesulfonic acid as a catalyst.



Acylation

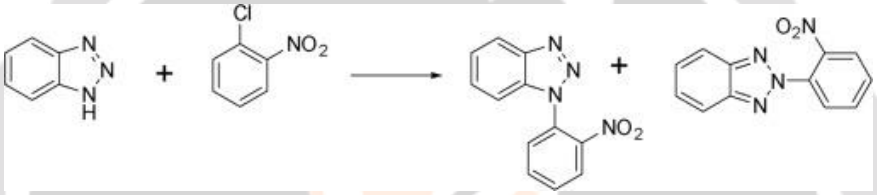
1- Acylbenzotriazoles were obtained through the reaction of 1H-Benzotriazoles with acid chloride or acid anhydride.



The synthesis of 1H-benzotriazole has been conveniently achieved by reacting it with formic acid in the presence of dicyclohexylcarbodiimide.(17)

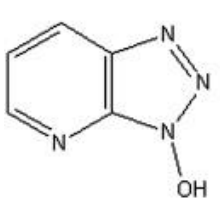
Arylation

1-arylbenzotriazole is obtained when 1H-Benzotriazole reacts with activated aryl and heteroaryl halides. Conversely, a combination of 1-chloro-2-nitrobenzene and 1H-benzotriazole results in a mixture of 1- and 2-(2-nitrophenyl)benzotriazole(18).

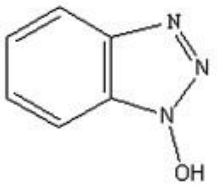


Uses

Benzotriazole-based peptide coupling reagents and additives, such as activators or additives (Figure 1), find application in peptide bond formation reactions in both solution and solid-phase synthesis. Various peptide coupling reagents exist, including carbodiimides, aminium/uranium salts, and phosphonium salts. The selection of method(s) and reagent(s) depends on several factors, such as the specific peptide sequence to be synthesized, the preferred deprotection method, the desired solvents, and the type of active intermediate required(19).



HOAt



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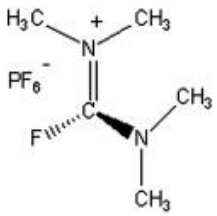
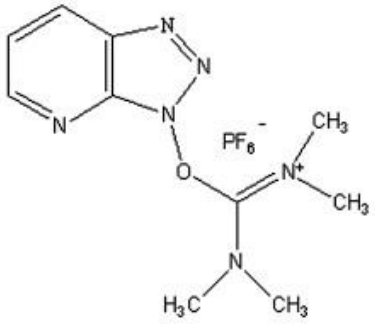


TFFH



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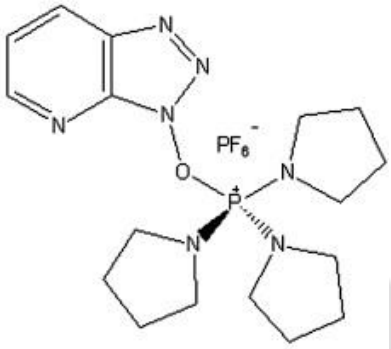
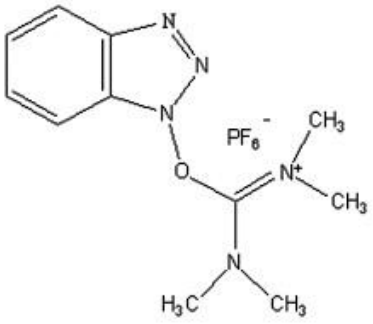


PyAOP



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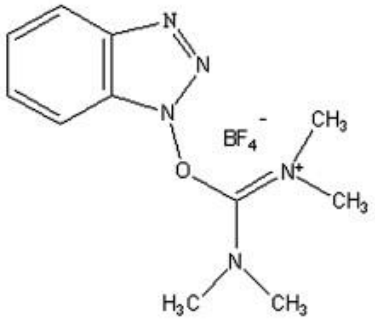

TBTU

Procedure :-

I)Dissolve 10.8 g (0.1 mol) o-phenylenediamine in a mixture of 12 g (11.5 ml, 0.2 mol) of glacial acetic acid and 30 ml of water contained in a 250 ml beaker; slight warming may be necessary.

Cool the clear solution to 15°C, stir magnetically and then add a solution of 7,5 g (0.1-1 mol) of sodium nitrite in 15 ml of water in one portion. The reaction mixture becomes warm and within 2-3 minutes reaches a temperature of about 85°C and then begins to cool while the colour changes from deep red to pale brown. • Continue stirring for 15 minutes, by which temperature will have dropped to 35-40°C and then thoroughly chill in an ice-water bath for 30 minutes. Collect by vacuum filtration and wash with three 30 ml portions of ice-cold water.

Dissolve the solid in about 130 ml of boiling water, add decolourising charcoal, filter and allow the filtrate to cool to about 50°C before adding a few crystals of the crude benztriazole which have been retained for seeding. Allow the

mixture to attain room temperature slowly (to avoid separation of the material as oil). Then thoroughly chill in ice and collect the benztriazole which separates as pale straw-coloured needles, M.P. 99-100°C.

A second crop may be obtained by concentrating the filtrate. The yield is about 8 g 67% (20).

II)Synthesis of Benzotriazole:

A mixture of 12g (11.5 ml) of glacial acetic acid and 30 ml of water is prepared. To this mixture, 10.8gm of o-phenylenediamine is added. The temperature of the mixture is cooled to 15°C and stirred. Then, a solution of 7.5g of sodium nitrite in 15 ml of water is added gradually. As a result, the temperature slowly rises to 85°C and then gradually cools down. When the temperature reaches 45°C, the mixture is chilled in an ice bath for 30 minutes. As a result of this process, a pale brown solid is formed and separated by filtration. To further purify the solid, recrystallization is carried out using benzene as the solvent(21).

Conclusion:-

The extensive body of research documented In this review highlights the diverse range of pharmacological effects demonstrated by benzotriazole derivatives. The biological characteristics of these novel benzotriazole compounds provide a solid foundation for the advancement of improved medicinal agents. This review aims to emphasize various synthetic approaches to benzotriazole, such as N-Alkylation under Solvent-Free Conditions and Copper-free 'click' methods. These methods serve as valuable tools for medicinal chemists in the development of novel compounds containing the benzotriazole moiety, which may exhibit enhanced efficacy and safety profiles.

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