A progress report

# Comparison of conventional and microwave-assisted synthesis of Benzotriazole derivatives and biological studies

Submitted to
Lovely Professional University, India
For the partial fulfillment of the award
Of

**Masters of Science in Chemistry (Hons.)**

By

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(Registration No. 11607332)

Under the guidance of
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Lovely Professional University

## CERTIFICATE

This is to certify that the progress report for dissertation entitled **"Comparison of conventional and microwave-assisted synthesis of Benzotriazole derivatives and biological studies",** submitted by Vanika Priya to the Lovely Professional University, Punjab, India is documentation of research work approved under my guidance and is commendable of consideration for the honour of degree of Masters of Science in Chemistry (Hons.) of the University.

_____

Supervisor

Dr. Navneet Singh

Associate Professor

## DECLARATION

I certify that

- The work enclosed on this progress report is innovative and has been carried out by me under the guidance of my supervisor, Dr. Navneet Singh.

- The present work has not been submitted earlier to any other University for any degree.
- I have been following the guiding principle provided by the university in thepreparation of the report.
- Whenever I have used resources (such as data, theoretical representations, any figure, and text) from other sources, I have given due recognition to them by citing them in the report and providing their details in the bibliography.

Date Vanika Priya

## ACKNOWLEDGEMENT

It gives me immense pleasure to show appreciation to my supervisor for their constant guidance, suggestion and encouragement to complete my literature survey to start my project. I am thankful to my parents and friends for their support. I am thankful to Dr. Ramesh to provide me opportunity to start my research project with Dr. Naveneet singh chauhan.

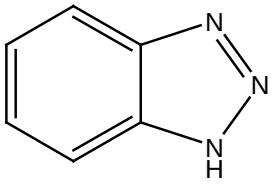
## INDEX

## 1. INTRODUCTION:

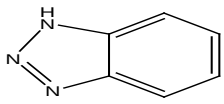
### BENZOTRIAZOLE-A molecule of Interest

Benzotriazole is widely used for industrial, domestic and pharmacuetical purposes.It is used in paints, coatings and films. In 1950s the commercial production of the Benzotriazole has introduced in US. The Initial patent of benzotriazole was on corrosion inhibitor.

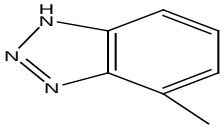
It is also used in inhibiting corrosion, UV stablizers. In 1990s Benzotriazole was declared as anticorrosion additives. The compound was widely used in cooling system and as the lubricating agents and in the protection from oxidation. The phenolic benzotriazole has been used as UV absorber in 1961.The easy synthesis of benzotriazole can be done by diazotization phenylenediamine, sodium nitrite, and acetic acid. Benzotriazole act as precursor for many drugs. As this molecule has a characteristic stability therefore it is widely used in the variety of reactions. Benzotriazole is a 3 nitrogen containing hetrocyclic compound. It has the chemical formula $C_6H_5N_3$.The structure contains two fused rings. In general primary triazole molecule contains five- membered heterocyclic compound which is having three nitrogen atoms and a vicinal pair of carbon atoms. Benzene ring and triazole forms Benzotriazole stated by **Mark G. Cantwell, et al**.



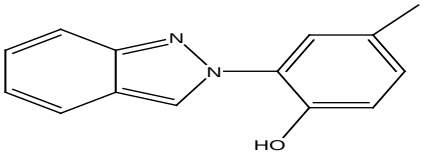

Benzotriazole is found to have wide pharmacological and industrial applicabilities. It is acting as inhibitor to several microbes, like bacteria, fungi. Benzotriazole is also effective in inhibiting the growth of helminths. These compounds can be in the form of an ester, chlorine atom, or additional functional groups (e.g., phenol and methyl) as part of the molecule.[1]



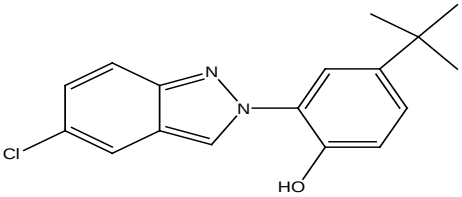

1H-Benzotriazole




1H-Benzotriazole,4Methyl 4-TT




Phenol 2-(2H-Benzotriazole-2-yl)4-Methyl



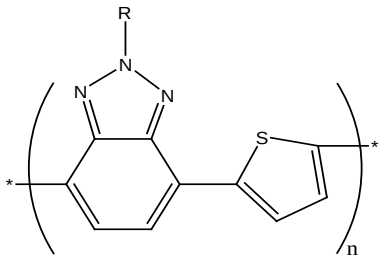

Phenol, 2-(5-chloro-2H-benzotriazol-2-yl) -6-(1,1-dimethylethyl)-4-methyl

## 2. **LITERATURE REVIEW:**

### 2.a. PHARMACOLOGICAL CHARACTERISTIC OF BENZATRIAZOLE

### PHOTOVOLTAIC PROPERTY OF BENZOTRIAZOLE

Generally photovoltaic property of a substance is an ability to convert the light in to electricity. The Organic polymeric solar cells are efficient solar energy converters as they have unique ability of processibility with the potential use among flexible devices and have low cost. This property is observed that benzotriazole as acceptor and thiophene ring as donor substituted in the series of variable alkyl chain length in bulk heteroconjunction solar cells.[2]




Chemical structures of polymers

R: $C_6H_{13}$ PTBT-DA6 ,R: $C_{10}H_{21}$ PTBT-DA10,R: $C_{12}H_{25}$ PTBT-DA1.

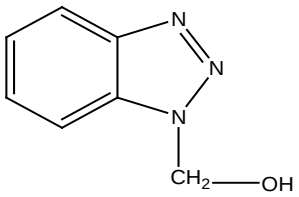
### BENZOTRIAZOLE AS CORROSION INHIBITOR

Corrosion is the destruction of the metals with chemical and electrochemical interaction of particles with the surrounding environment. Here, the metals are converted in to their more stable form of sulfides, oxides, hydroxides etc.

**Y.H.Lie**.et.al. Reported the anticorrosive effect of Benzotriazole (BTA) added in polypyrrole

immersed in oxalic acid filmmed on copper. The estimated protection of copper from corrosion was 3.5 wt.% NaCl solution. With the 400 h protection efficiency of 80% was found in copper as compared to unfilmmed copper. Therefore, The corrosion protection and adhesion were improved by adding BTA and Self-healing property of PPy was also improved due to the BTA.[3]

**Ravi chandaran et al** shows the effect of benzotriazole derivative as anticorrosive on brass.[4]




1-Hydroxymethylbenzotriazole

Corrosion inhibition of brass

## TOXICITY OF BENZOTRIAZOLE

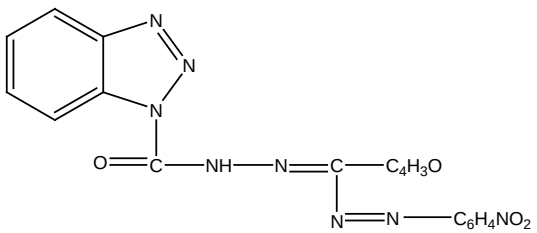
**X.WU et.al** worked on the toxicity and degrading effect of benzotriazole. The Benzotriazoles and methylbenzotriazole which are present in soil and water has been found to be the inhibitor of plant growth, and also cause death of several species.[5]

| Treatment | Length of time plants survived |
|---|---|
| Benzotriazole or Methylbenzotriazole at 0.05%(0.5mg/ml)applied to the soil | Alfa alfa :2-3 weeks<br>Popular :2-4 weeks |
| 0.05%(0.5mg/ml) Benzotriazole<br>0.005%(0.05mg/ml)In water | Pumpkin 2 days<br>Pumpkin 10 days |
| 0.02%(0.2mg/ml)Benzotriazole<br>0.01%(0.1mg/ml) in water | Cork screw willow 10 days<br>Cork screw willow 3 weeks |
| 0.02%(0.2mg/ml)in benzotriazole<br>0.01%(0.1mg/ml)in water | Horseradish 3 months<br>Horseradish >3 months |

## ANTIFUNGAL BENZOTRIAZOLE

Benzotriazoles have been found to inhibit the growth of fungus which is single cell spore

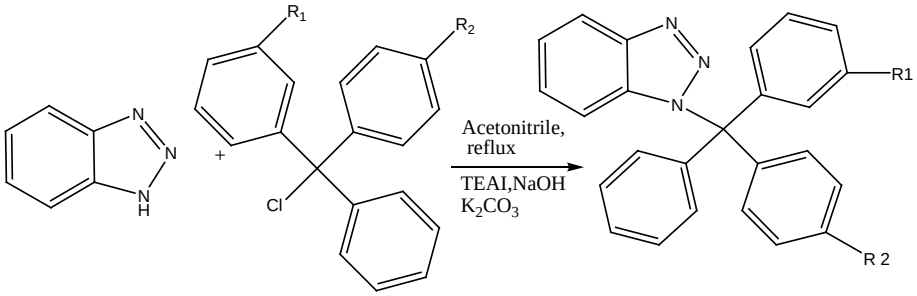
producing organism . **Muvvala S.Sudhir et.al.** synthesized derivatives of benzotriazole, these compounds are found to have in-vitro antifungal activity against *Trichophyton rubrum, Epidermophyton floccosum* .[6]




1-(1H-benzol(d)[1,2,3]triazole-1-carbonyl)derivative

**Zahra et.al.** reported that 1,2,4-triazole and benzotriazole derivatives are able to inhibit the cytochrome P450 14α-demethylase (14DM) and shows antifungal property against *Microsporum*

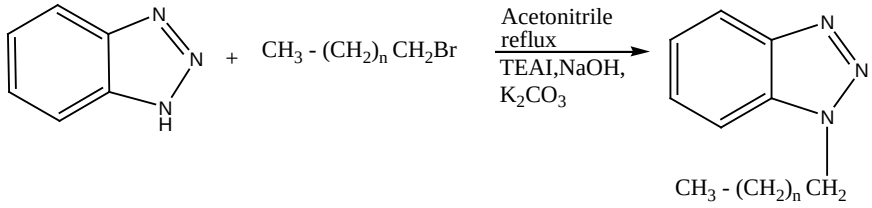
*canis*, *Trichophyton mentagrophyte*, *Trichophyton rubrum*, *Epidermophyton floccosum*, and *Candida albicans* comparable to fluconazole and clotrimazole.[7]




R1=R2=H

R1=H,R2=OCH3

R1=R2=OCH3

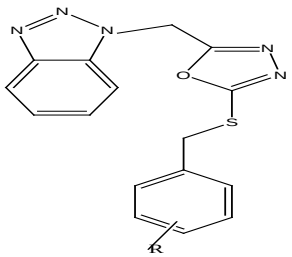



(n)=3

(n)=6

## ANTICANCER PROPERTY OF BENZOTRIAZOLE

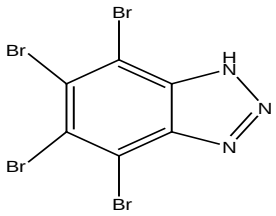
Nowadays cancer is being spreading as worldwide killer disease which is due to the uncontrolled growth of the tumor cells. The researchers are working in the discovery of drugs that can be beneficial in curing cancer. Benzotriazole derivatives have been found to posses anticancer activity. **Shuai Zhang et.al** observed 1,3,4oxadiazole derivatives possessing benzotriazole moiety as FAK (Focal adhesion kinase) inhibitors shows anticancer activity. The cytotoxic activity has been shown by these compounds against Human Leukemia jurkat T- cell line, Murine Leukemia L1210 cell Line, Estrogen resistant human breast adenocarcinoma MDA_MD231 cell line, Estrogen sensitive human adenocarcinoma MDF-7 Cell line.[8]



R=2-F,2-Cl,2-$CH_3$,2-$OCH_3$

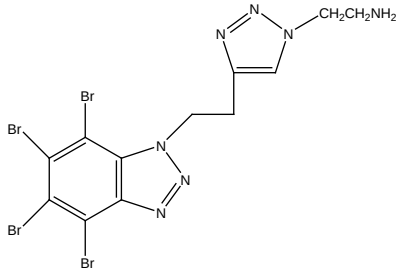
1,2,4 oxadiazole derivative.

**R.Swider et al** reported the derivatives of 4,5,6,7-tetra bromobenzotriazole(TBB) is effective in restricting the activity of CK2(Caesin Kinase).

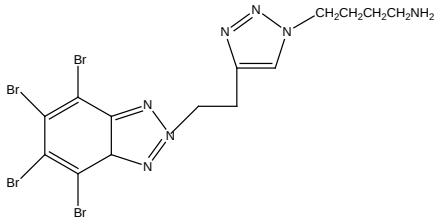


TBB

It is found that the enzyme is composed of two sub units CK2α,CK2α' and a dimer of regulatory subunit CK2β.The inhibitingt of any of these CK2 subunits can kill cells. CK2 is found in tumor cells protect them from self destruction.Thus on inhibition of CK2 activity can proved effective in treating cancer.[9]



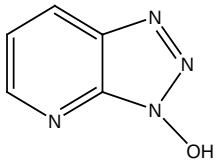
2-(4-(2- Perbromo (1-H-Benzo[d] triazole-1-yl)ethyl)-1H,1,2,3 triazole-1-yl)ethanamine



4-(4-(2- Perbromo(2-H-Benzo[d] triazole-2-yl)ethyl)-1H,1,2,3 triazole-1-yl)Butane-1-amine

## BENZOTRIAZOLE REACTIVATING OF LATENT HIV-1

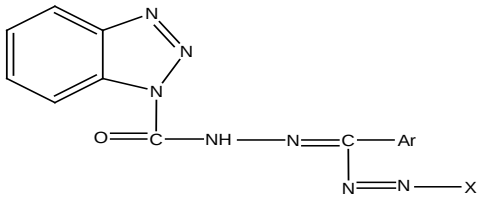
**Alberto bosque et al** shows a different strategy to cure HIV by using the activity of benzotriazole in reactivating latent HIV-1. It inactivate STAT5 SUMOylation. As the latent HIV-1 act as an obstacle in the vanishment of HIV-1. Benzotriazoles block SUMOylation of phosphorylated STAT5, increasing STAT5's activity and occupancy of the HIV-1 the latent reservoirs has been reduced in primary cells without inducing cell proliferations . Here, benzotriazoles act as latency reversing agents and STAT5 signaling and SUMOylation as targets for HIV-1 eradication strategies. Thus it has made the researchers to research regarding the eradication of HIV in a different direction in the search for "shock and kill" therapies.[10]




1-hydroxy-7-aminobenzotriazole

## ANTIHELMINTIC ACTIVITY

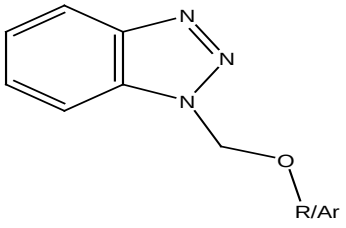
Helminths are nowadays becoming the cause of many diseases. Newer 1,2,3 benzotriazole derivatives were synthesized by **S.S Pawar et al** and tested for anthelmintic activity against adult earthworms(*P. posthuma*) due to their anatomical and physiological resemblance with the intestinal roundworm parasites of human beings.[11]

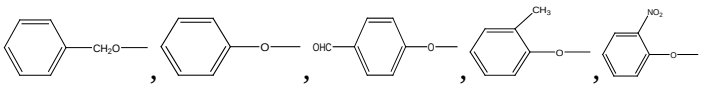


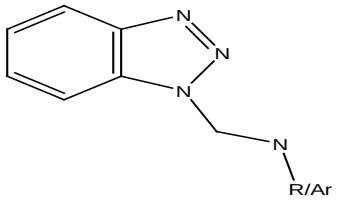

A.Ar=$C_6H_5$,X=$C_6H_4NO_2$;B. Ar=$C_4H_3O$,X=$C_6H_4NO_2$;C.$C_6H_4NO_2$,X=$C_6H_4NO_2$;D. Ar=$C_6H_4Cl$,X=$C_6H_4NO_2$

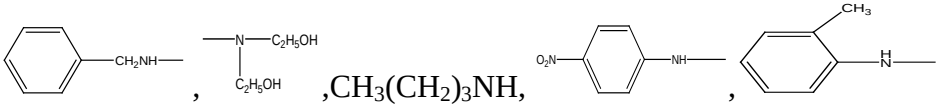
The benzotriazole derivatives having nitro substituent shows best antihelmintic property .

N-alkylated derivatives of benzotriazole also show antihelmintic activity. They have been applied to *P posthuma.*by **M.S.Sudhir et al**



Ar= 

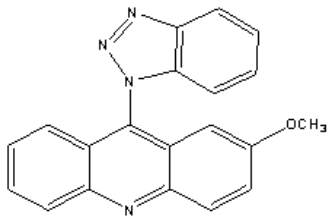



Ar= 

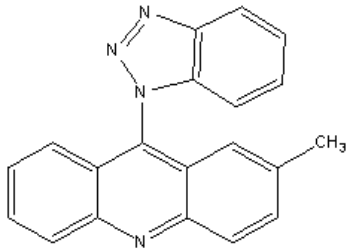

The study reveals that $N^1$-(Paranitrophenyl)-aminomethyleneBenzotriazole and $N^1$ – Benzoxymethylenebenzotriazole shows best antihelminthic activity.and benzoxymethylenebenzotriazoles are better antihelminthicthan aminomethylene Benzotriazoles.[12]

## ANTIMICROBIAL ACTIVITY

The Heterocycle compounds have been found to be very effective in the treatment of the diseases arising due to microbes. It has been found that the acridine derivatives of benzotriazoleare shows potent antibacterial activity against *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Escherichiacoli, Proteus vulgaris, Klebsilla pneumoniae, Salmonella typhi* taken as clinical specimens.[13]

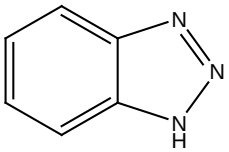



**9-(Benzotriazol-1-yl)-2-methoxy acridine**

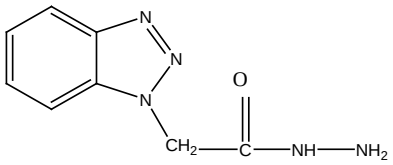



**9-(Benzotriazole-1-yl)-2-methyl acridine**

**Pramod B Kumar et. al.,** synthesized some others derivative of benzotriazole showing antibacterial activities.

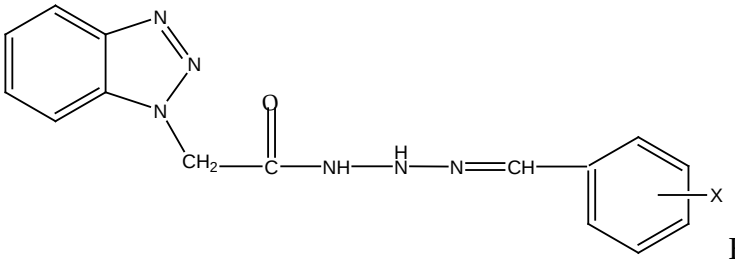


BT1

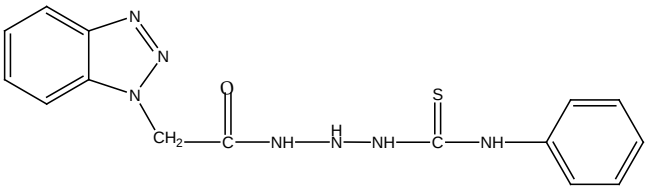


BT2

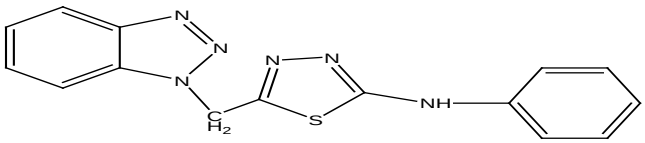
| Compounds | X |
|---|---|
| BT3 | H |
| BT4 | 2-$NO_2$ |
| BT5 | 3-$CH_3$ |
| BT7 | 2-$OCH_3$ |
| | 4-Cl |



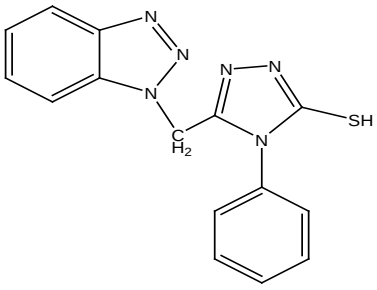
BT3-7



BT8



BT9



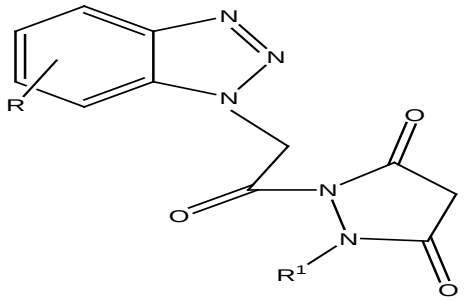
BT10

These derivatives have been tested for the antibacterial activity against *Pseudomonas aeruginosa,Staphylococcus aureus,Bacillus subtilis,Escherichia coli,Proteus vulgaris,Klebsilla pneumoniae,Salmonella typhi*.

BT1 shows high potency to kill these strains of gram positive and gram negative bacteria.

ANTIFUNGAL ACTIVITY is shown by BT1 against*Candida albicans*.[14]

**BV suma et. al.,** screened the derivatives given below to gram positive bacteria like *Staphylococcus aureus, Bacillus subtilis* and gram negative bacteria like *Escherichia coli, Proteus valgaris* and observed antibacterial property of them.[15]

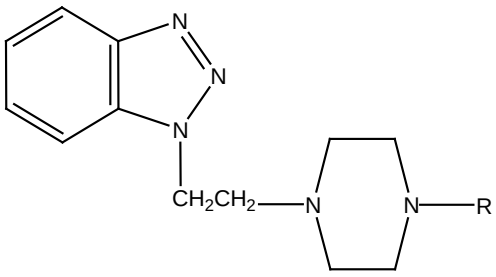


| Compound | R | $R^1$ |
|---|---|---|
| A | H | H |
| B | H | $C_6H_5$ |
| C | H | $C_6H_4N_2O_2$ |
| D | H | $C_6H_5Cl$ |
| E | Cl | H |
| F | Cl | $C_6H_5$ |
| G | Cl | $C_6H_4N_2O_2$ |
| H | Cl | $C_6H_5Cl$ |
| I | $NO_2$ | H |

Antifungal property has also been observed in all these derivatives against *Aspergillus niger and Candida albicans.*[15]

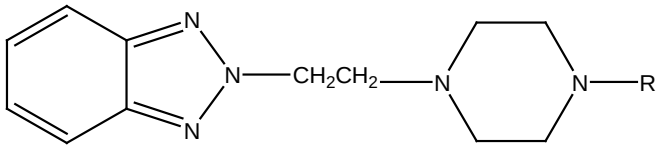
**ANTIDEPRESSANT ACTIVITY**

The pharmacological activity of benzotriazole derivatives as anti serotonergic has been found which inhibits the activity of serotonin which a neurotransmitter responsible for causing anxiety.



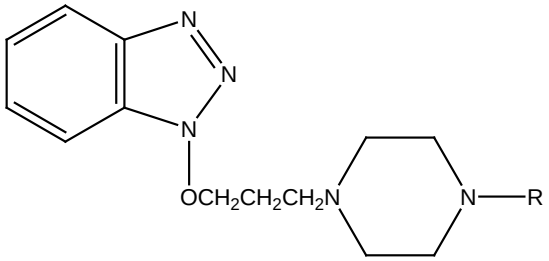
1. (a) R=$C_6H_5$;(b)R=$C_6H_4$-2-Cl;(c)R=$C_6H_4$-3-Cl;(d)R=$C_6H_4$-4-Cl;

(e)R=$CH_2C_6H_5$;(f)R=$CH_2CH_2C_6H_5$;(g)R=$CH_3$;(h)R=$CH_2CH_2OH$




2. (a) R=$C_6H_5$; (b)R=$C_6H_4$-2-Cl; (c)R=$C_6H_4$-3-Cl; (d)R=$C_6H_4$-4-Cl;

(e)R=$CH_2C_6H_5$; (f)R=$CH_2CH_2C_6H_5$;(g)R=$CH_3$; (h)R=$CH_2CH_2OH$




3.(a) R=$C_6H_5$; (b)R=$C_6H_4$-2-Cl; (c)R=$C_6H_4$-3-Cl; (d) R=$C_6H_4$-4-Cl;

(e)R=$CH_2C_6H_5$; (f)R=$CH_3$; (g)R=$CH_2CH_2OH$

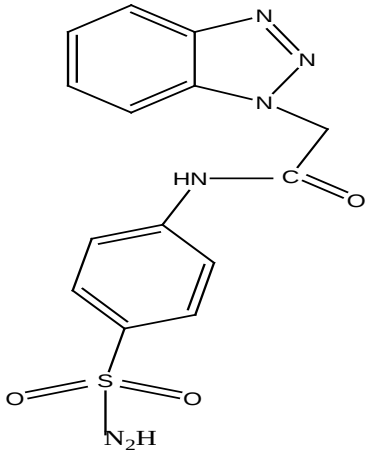
Antiserotonergic activities of 1-and2- [2-[4-(X)-1-piperazinyl]ethyl]benzotriazoles (1a-h and 2 a-h) and 1-[3-[4-(X)-1-piperazinyl]propoxy]Benzotriazoles(3a-g).**G Caliendo et al.**[16]

| Compounds | $IC_{50}$ M/L |
|---|---|
| | Anti-5-HT |
| 1.(a) | $7.0(\pm0.28)\times10^{-6}$ |
| 1.(b) | $7.4(\pm0.38)\times10^{-7}$ |
| 1.(c) | $8.8(\pm0.37)\times10^{-7}$ |
| 1.(d) | $1.2(\pm0.40)\times10^{-5}$ |
| 1.(e) | $3.5(\pm0.36)\times10^{-6}$ |
| 1.(f) | $4.2(\pm0.38)\times10^{-5}$ |
| 1.(g) | $>1.0\times10^{-4}$ |
| 1.(h) | $>1.0\times10^{-4}$ |
| 2.(a) | $8.6(\pm0.30)\times10^{-6}$ |
| 2.(b) | $6.2(\pm0.26)\times10^{-6}$ |

| | |
|---|---|
| 2.(c) | $1.3(\pm0.23)\times10^{-6}$ |
| 2.(d) | $2.4(\pm0.35)\times10^{-5}$ |
| 2.(e) | $6.4(\pm0.38)\times10^{-5}$ |
| 2.(f) | $4.6(\pm0.40)\times10^{-5}$ |
| 2.(g) | $>1.0\times10^{-4}$ |
| 2.(h) | $>1.0\times10^{-4}$ |
| 3.(a) | $1.0(\pm0.30)\times10^{-6}$ |
| 3.(b) | $1.1(\pm0.38)\times10^{-6}$ |
| 3.(c) | $7.0(\pm0.40)\times10^{-7}$ |
| 3.(d) | $4.7(\pm0.28)\times10^{-6}$ |
| 3.(e) | $6.2(\pm0.32)\times10^{-6}$ |
| 3.(f) | $3.4(\pm0.42)\times10^{-5}$ |
| 3.(g) | $7.0(\pm0.38)\times10^{-5}$ |

## ANTIOXIDANT ACTIVITY

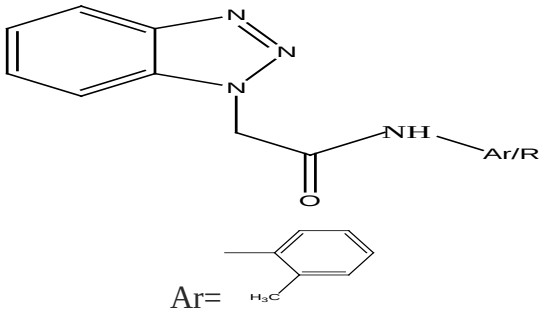
Antioxidants are the reducing agents that are stabilizing the free radicals that have been produce during cellular metabolism. The free radicals like ROS (Reactive Oxygen Species ) that has been imposing destruction to the cells so they must be neutralize the benzotriazole derivatives of N-phenyl acetamide and carbamic acid shows antioxidative activity.[17]




2-(1H-benzotriazole-1-yl)-N-(4-Sulfamolyphenyl)acetamide

## ANTIINFLAMMATORY ACTIVITY

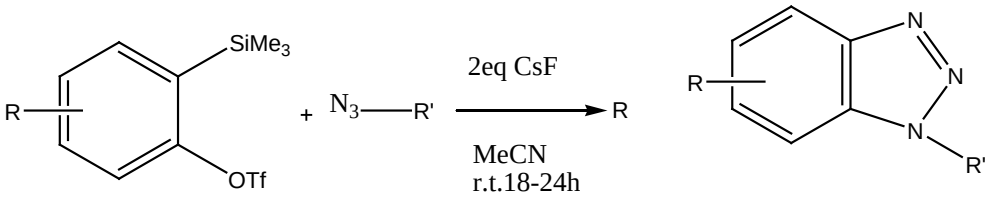
Inflamation is a condition in which symptoms of swelling and pain is observed. It is the response of our immune system to the injury or any attack of antigen. Jain N.P. et. al. has investigated the anti-inflammatory action of N-(Alkyl or Aryl)-2-(1H-benzotriazol-1-yl)acetamide derivatives of benzotriazole. [18]



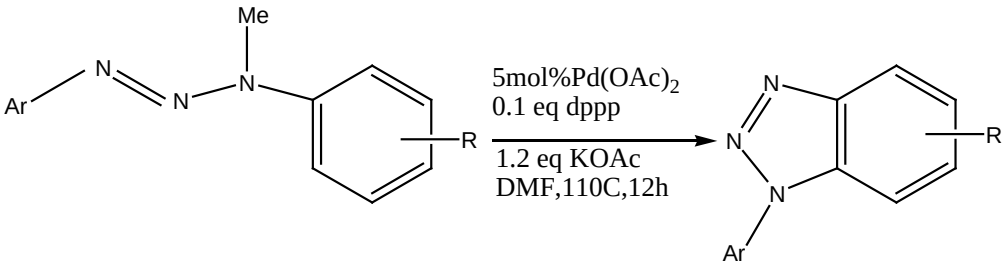

N-(2-Methylphenyl)-2-(1H-benzotriazol-1-yl)acetamide.

## 2.b. SYNTHESIS FOR BENZOTRIAZOLE THROUGH MICROWAVE ASSISTED AND CONVENTIONAL MODE

**Feng Shi et al** synthesized a large number of substituted benzotriazoles by [3 + 2] cycloaddition of azides to benzynes. The reaction method is easy so further substitution can occur under the mild conditions.[19]

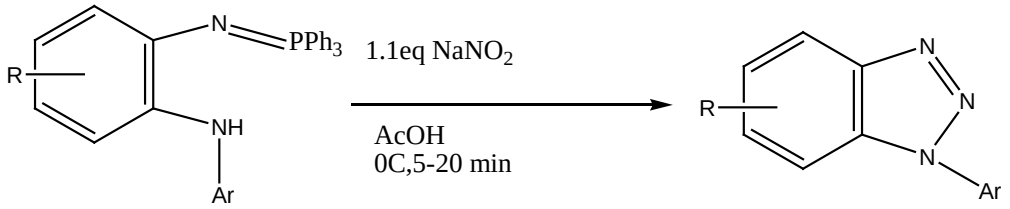



**Jun Zhou et al** gave the method for the regioselective synthesis of benzotriazoles, in which 1,7-palladium migration cyclization dealkylation sequence had been done. These reactions shows high regioselectivity and high yields.[20]



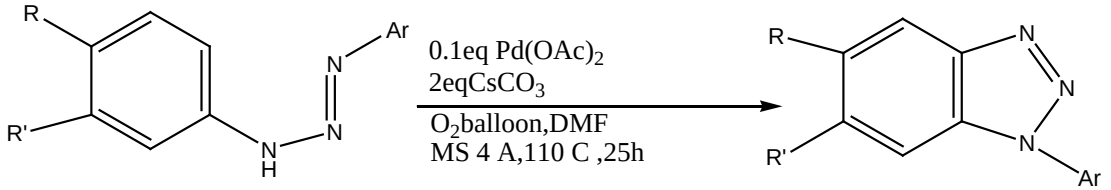

Benzotriazole

**Emilia Lukasik et. al.** synthesized 1-Aryl-1,2,3-benzotriazole via cyclocondensation of 2-(arylamino)aryliminophosphoranes in mild conditions. It involves three-step, halogen-free route of synthesis from simple nitroarenes and arylamines.[21]



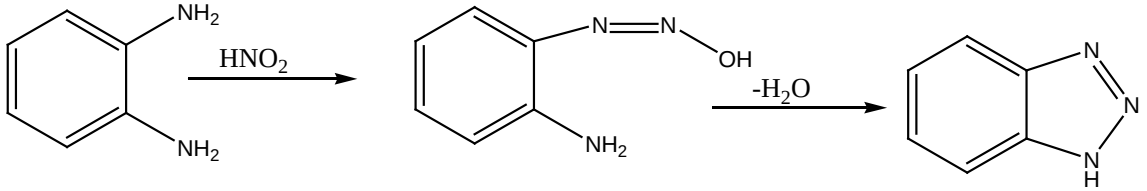

2-(arylamino)aryliminophosphoranes 1-Aryl-1,2,3-benzotriazole

**Rapolu Kiran Kumar et. al.** synthesize 1-aryl-1H-benzotriazoles by using the catalytic amount of $Pd(OAc)_2$ that effects the cyclization at the moderate temperature.[22]



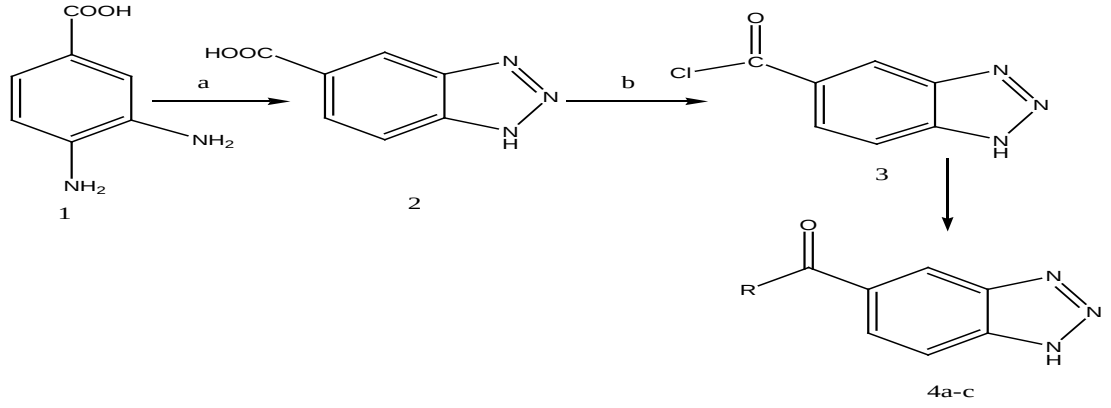

R=H,R`=H,COMe,$CO_2$Et,Cl,Br,$NO_2$ 1-aryl-1H-benzotriazoles

**R.E.Damschroder et. al.** prepared 1,2,3-Benzotriazole by reacting nitrous acid with o-phenylenediamine and then hydrolysis. This is the direct method involves many intermediate steps. [23]




o-phenyldiamine Benzotriazole

**J.J.Shah et al** did the conventional and microwave synthesis of Benzotriazole



Scheme for synthesis of 5-substituted benzotriazole amides (4a-c)

R=2-methylaniline (4a), n-butylamine (4b), benzylamine (4c).

Reaction conditions:

(a) CH3COOH, $NaNO_2$, $H_2O$, RT, stirring, 30 min, 88%;

(b) $SOCl_2$, reflux, 30 min, 83%;

(c) Benzene, respective amines, reflux or MW (180 W),

Yields: conventional/MW,

4a=72%/83%

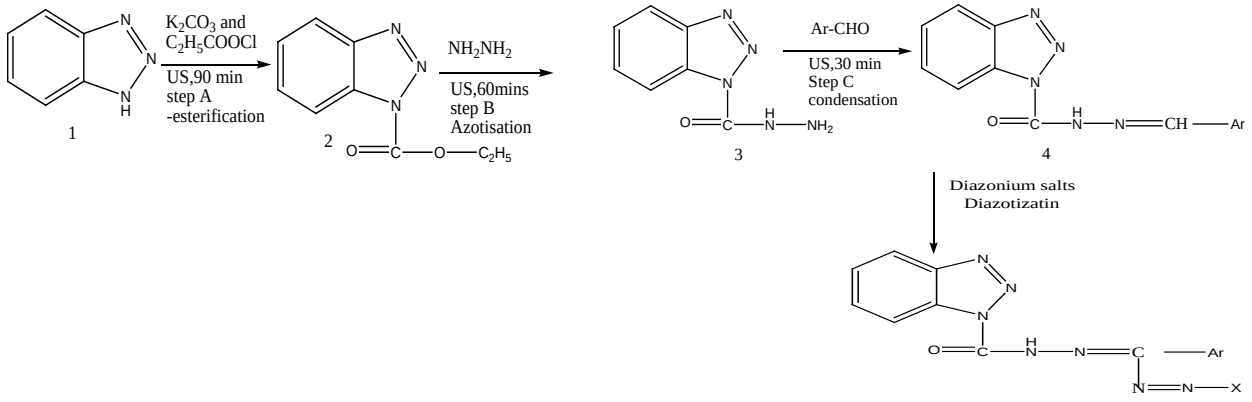
4b=65%/85%,

4c=70%/93%.[24]

And obtained the following data.

| **Compound** | **%Yield conventional** | **%Yield microwave** | **Reaction time conventional** | **Reaction time microwave** |
|---|---|---|---|---|
| 2 | 88 | - | 30 min | - |
| 3 | 83 | - | 30 min | - |
| 4a | 72 | 83 | 4 hrs | 4 mins,30 secs |
| 4b | 65 | 85 | 3hrs 30 min | 4 min 10 secs |
| 4c | 70 | 93 | 2hrs 45min- | 4 min |
| | | | | |

**Radhika Sugreevu etal** using conventionl and microwave ultrasonification has synthesized the 1,2,3 benzotriazole derivatives.[25]




5A-P

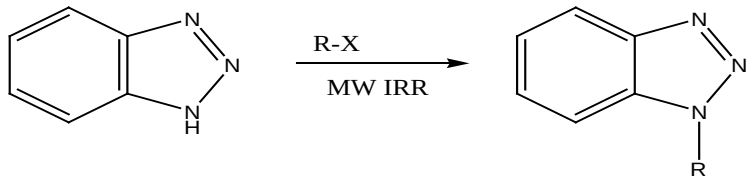
5A – D: Ar = $C_6 H_5$ ; 5E – H: Ar = $C_4 H_3 O$ ; 5 I – L: Ar = $C_6 H_4 NO_2$ and 5M – P: Ar = $C_6H_4$ Cl

5A, E, I, M: X = $C_6 H_5$ ; 5B, F, J, N: X = $C_6 H_4 NO_2$ ; 5C, G, K, O: X = $C_6 H_4$ Cl and 5D, H, L, P: X = $C_6 H_4$ Br

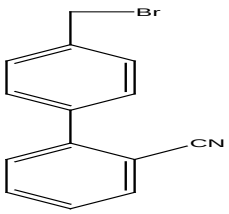
Time taken for the synthesis of 1,2,3 Benzotriazole

| **Steps** | **Conventional** | **Microwave** | **Ultrasonification** |
|---|---|---|---|
| A | 8 hrs | 15 min | 1.5 hrs |
| B | 6 hrs | 12 min | 1 hr |
| C | 3 hrs | 6 min | O.5 hr |

**S.Nanjunda swammy et.al.** Synthesized N-alkylated benzotriaziole derivatives. The *N*-alkylation of the benzotriazole is done with different bioactive alkyl halides in the presence of powdered $K_2CO_3$ in DMF solution by the microwave irradiation method.[26]

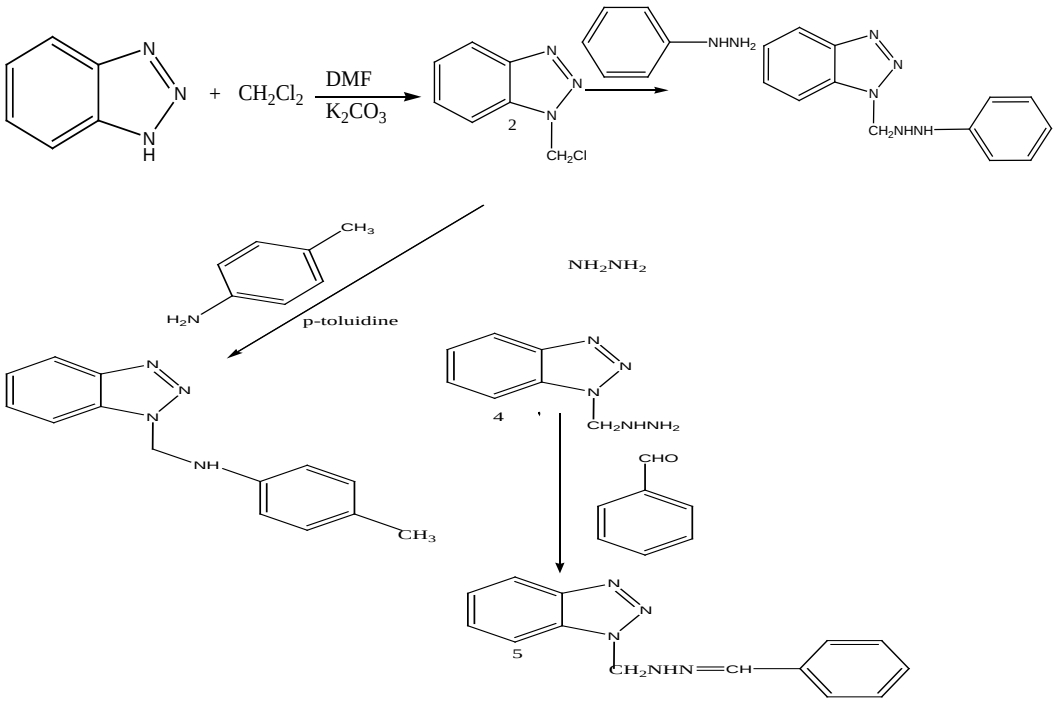



R-X =>




Yield=86% in microwave, $K_2CO_3$ /DMF=82%

## 3. PROPOSED SCHEME:




## 4. MATERIALS AND METHODS:

Melting points of the synthesized compounds will be determined by open capillary method. The purity of the compounds will be checked using TLC plates (glass) coated with silica gel. The developed chromatographic plates will be visualized under iodine chamber. IR spectra will be recorded using KBr on Shimadzu FTIR model 8400 spectrophotometer. 1H NMR spectra and mass spectra will be taken from other institutions. Biological activity will be done in Pharmacy/Biotech lab.

## 5. CONCLUSION:

From literature review, It has been observed that in the recent years the scientist has converge their interest towards the design and synthesis of benzotriazole derivatives. It has found its wide range of applications in the medicinal chemistry. 1-(1H-benzo(d)[1,2,3]triazole-1-carbonyl) derivatives are used as antifungals against *Trichophyton mentagrophyte*, *Trichophyton rubrum*, *Epidermophyton.*Benzotriazole oxazole derivatives shows the cytotoxic activities against Human Leukemia jurkat T- cell line,Murine Leukemia L1210 cell Line,Estrogen resistant human breast adenocarcinoma.TBB(tetrabromobenzotriazole) a well known anticancer drug is being used for

inhibition of CK2.Benzotriazole derivatives has been also found to reactivates latent HIV-1 that inhibits STAT5 SUMOylation. The derivatives of benzotriazole shows antihelmintic , antiserotonergic, anti-inflamatory activity. The N-phenyl acetamide derivative is found to act as antioxidant. Besides its pharmacological activities benzotriazole derivatives is also acting as anticorrosive and UV stabilizers. The researchers are due to its wide utilities, non expensive and characteristic stability are developing novel benzotriazole moieties. Benzotriazoles and their derivatives can be synthesized conventionally and by the microwave irradiation method .It is found that the time taken for the completion of the reaction is more in conventional methods as compared to the microwave irradiation method apart from environmental issues. Moreover the microwave synthesis is cost effective, time saving and a green approach towards the organic synthesis therefore it has been planned to work on the synthesis of novel benzotriazole derivatives as proposed in scheme followed by biological activity.

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