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Review Article

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IMIDAZOLE-A NEW PROFILE OF VARIOUS PHARMACOLOGICAL ACTIVITIES

***Anupam, Supriya Maity, Shamim Ahmad, Sudha Singh and Gopalji Baranwal**

Department of Pharmaceutical Chemistry, Translam Institute of Pharmaceutical Education and Reasearh, Meerut, 250001, U.P. India.

***Corresponding Author: Anupam**

Department of Pharmaceutical Chemistry, Translam Institute of Pharmaceutical Education and Reasearh, Meerut, 250001, U.P. India.

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ABSTRACT.

Imidazole, a five member heterocyclic compound involved in research aimed to evaluate new products that possess interesting biological activities. These compounds reported for their antimicrobial, anti-inflammatory and antifungal activities. Successful introduction of a imidazole nucleus is a common feature in the chemical structure of several COX-2 inhibitors. These derivatives are also known to possess antitubercular, anti-inflammatory, antitumor, anti-HIV, antiparkinsonian, antidiabetic and vasopressin via antagonist activities. The present review article focuses on the pharmacological profile of Imidazole with their potential activities.

KEYWORDS: Imidazole, Five member heterocyclic ring, Pharmacological activities.

1. INTRODUCTION

Imidazole ring is bioisoster of pyrazole ring means both have five membered structure and two nitrogen and in particular some of pyrazole derivatives were in depth investigated as nonsteroidal anti inflammatory drugs (NSAIDs). Imidazole contains two nitrogen and three carbon atoms. The mechanism of action of this class of compounds is linked to the inhibition of cyclooxygenase COX-2. The presence of a pyrazole nucleus is a common feature in the chemical structure of several COX-2 inhibitors, like-celecoxib.[1] These derivatives have broad applications in various areas of medicine.The derivatives of imidazole are currently used as tools in pharmacological studies. Imidazole containing compounds shows various biological activities such as antimicrobial[2, 3, 4], antiviral[5, 6], anti-inflammatory[7, 8], anti tubercular[9, 10] and so on. Imidazole is amphoteric in nature so it shows both the acidic and the basic nature. There is a wide scope of research in this moiety which encourages the medicinal chemists to discover and synthesize new compounds.The present review article focuses on the pharmacological profile of imidazoles with their potential activity.[11]

2. Chemistry

Imidazoles have properties which are similar to both pyrrole as an acid and pyridine as a base. The electrophilic reagent would attack on the unshared electron pair on N-3 position, but not that on the 'pyrrole' nitrogen since it is the part of thearomatic sextet. While the imidazole ring is rather susceptible to electrophilic attack on an annular carbon, it is much less likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituent's elsewhere in the ring. In the absence of such activation the position most probable site to nucleophilic attack is C-2.The fused benzene ring in benzimidazole provides sufficient electron withdrawal to allow a variety of nucleophilic substitution reaction at C-2.

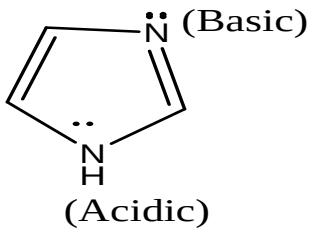


Fig. 1

The overall reactivity of imidazole is referred from sets of resonance structure in which the dipolar contributors have finite importance. These predict electrophilic attack in imidazole at N-3 or any ring carbon atom, nucleophilic attack at C-2 or C-1 and also the amphoteric nature of the molecule. In benzimidazole the nucleophilic attack is predicted at C-2. The reactivity of benzimidazole ion at the C-2 position with nucleophiles is enhanced compared with the neutral molecule.

3. Biological activities of Imidazole

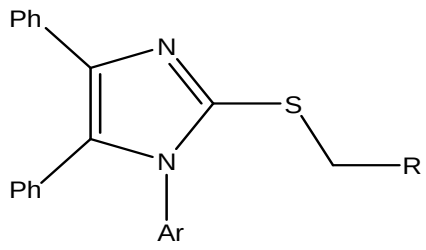
The imidazole scaffold is extremely versatile and has featured in a number of clinically used drugs. The wide range of pharmacological profile shown by imidazole can be classified into the following categories.

1. Antimicrobial Activity

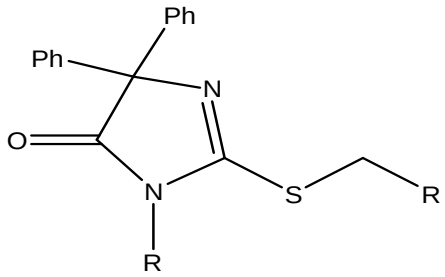
2. Anti-Viral Activity
3. Anti-Cancer Activity
4. Anti-Depressant Activity
5. Anti-Inflammatory Activity
6. Anti-Tubercular Activity
7. Anticonvulsant Activity
8. Anthelmintic Activity
9. Antilishmanial Activity

3.1 Antimicrobial Activity

A. S. Salman *et al.*, (2015)[12] have reported a two new series of S-alkyl-imidazolidin-4-one and S-alkyl-imidazole derivatives as antimicrobial and antioxidant agents. Their antioxidant potential were evaluated using DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical method *In vitro*. Their antibacterial screening against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeuroginosa* and *Escherichia coli* and antifungal activity against *Aspergillusfumigates*, *Syncephalastrumracemosum*, *Geotrichumcandidum* and *Candida albicans* were also evaluated, most of the compounds showed to potent and significant results when compared to the respective standards..

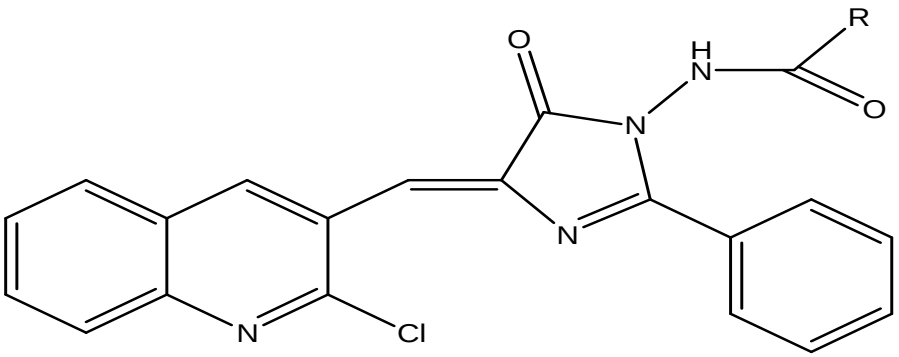


Ar = 4-ClC_6H_4, 4-$NO_2C_6H_4$ R = Ph, Ph



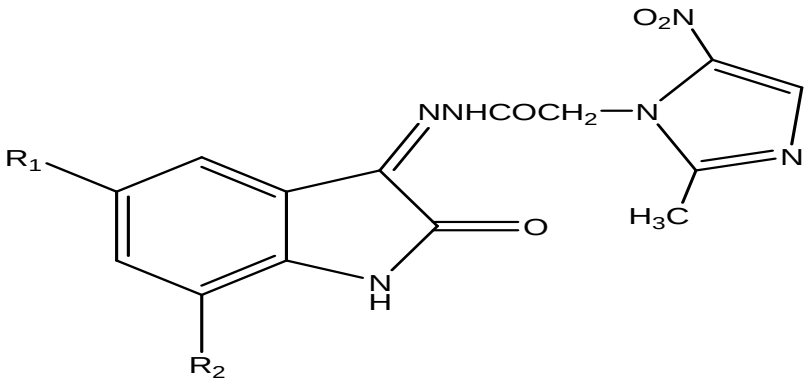
R = Ph, H

N. C. Desai *et al.*, (2014) [13] have described the conventional and microwave method for the synthesis of *N*-(4-((2-chloroquinolin-3-yl) methylene)-5-oxo-2-phenyl-4, 5-dihydro-1*H*-imidazole-1-yl) (aryl) amides. It was observed that the solvent-free microwave thermolysis is a convenient, rapid, high-yielding, and environmental friendly protocol for the synthesis of quinoline based imidazole derivatives when compared with conventional reaction in a solution phase. Antimicrobial activity of the newly synthesized compounds is screened in vitro on the various microbial species: *Escherichia coli* (MTCC 443), *Pseudomonasaeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), *Candida albicans* (MTCC 227), *Aspergillusniger* (MTCC 282), *Aspergillusclavatus* (MTCC 1323). All the synthesized bio-active molecules are tested for their in vitro antimicrobial activity by bioassay namely serial broth dilution.



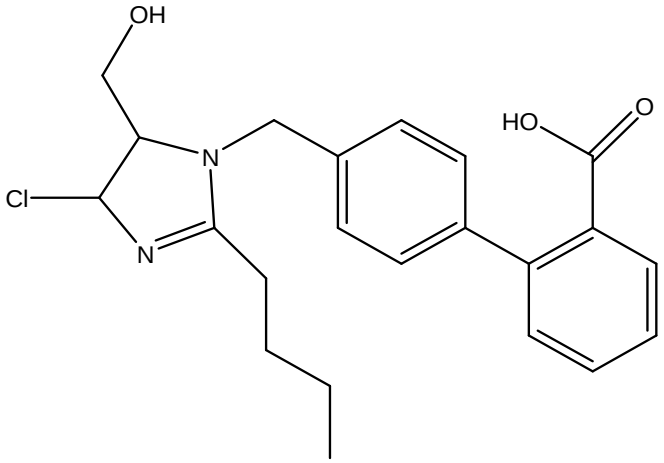
R= different aryl substituents

J. Jays *et al.*, (2011)[14] have screened antibacterial activity of newly synthesized Isatin derivatives by agar diffusion method against *Staphylococcus aureus* and *Bacillus Subtilis* (gram- positive) and *Klebsiella* and *Proteus Vulgaris* (gram-negative) using Amoxicillin and Ciprofloxacin as standard reference drugs. All compounds have shown antibacterial activity against the gram-positive and gram-negative bacteria tested. The order of the antibacterial activity for the synthesized compounds is as follows.



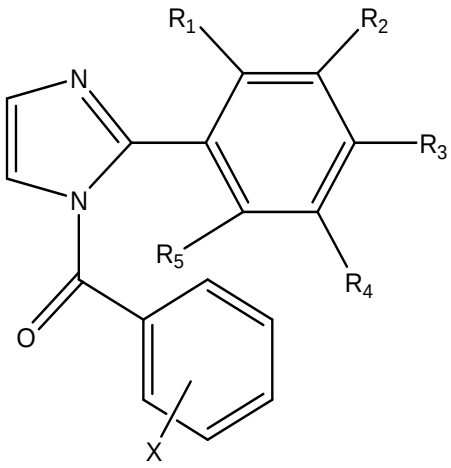
R_1= H, NO_2,Cl, I, F, Br, CH_3
R_2= H, F

M. D. Shreenivas *et al.*, (2011)[15] have synthesized newly imidazole derivatives, which were screened for their in-vitro antibacterial activity against *S. aureus* and *B. subtilis* employing cup-plate method at the concentration of 100 µg/ml in nutrient agar media and also for in-vitro antifungal activity against *C. albicans* and *A. Niger* by cup plate method at 100 µg/ml. concentration using sabouraud-dextrose agar. DMSO was used as solvent control for antimicrobial activity. Streptomycin was used as standard for antimicrobial. The area of inhibition of zone measured in cm.



R= H, o-Cl, p-F, p-Me,
-2,4$(OMe)_2$,
-2,4$(OEt)_2$

D. Sharma *et al.*, (2009)[16] have synthesized 2-(substituted phenyl)-1*H*-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-menthanone analogues and tested for antimicrobial activity against gram positive, Gram negative, and fungal species. Norfloxacin used as standard drug.



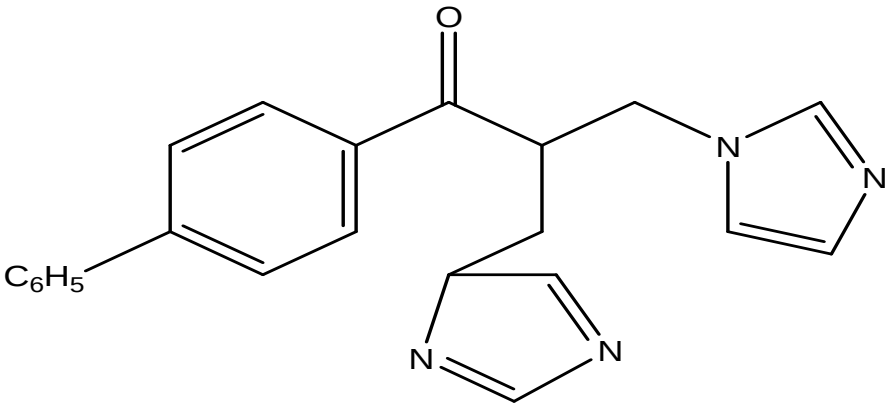
1.R_1=Cl, R_2=H, R_3=H, R_4=H, R_5=H, X=4-NO_2

2.R_1=COOH, R_2=H, R_3=H, R_4=H, R_5=H, X=4-NO_2

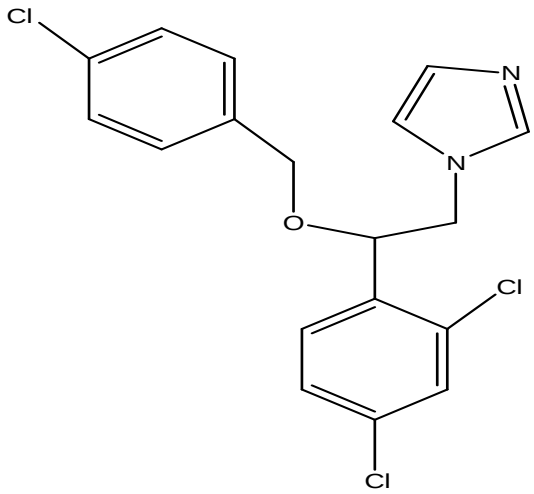
3.R_1=H, R_2=H, R_3=Cl, R_4=H, R_5=H, X=2-Br

4.R_1=H, R_2=H, R_3=NO_2, R_4=H, R_5=H, X=2-Br

D. Zampieri *et al.*, (2007)[17] have synthesized bis-imidazole derivatives and screened for antifungal and antimycobacterial activity. All compounds showed moderate to good activity against *Candida albicans* and *Candida glabrata.* Miconazole used as reference drug.



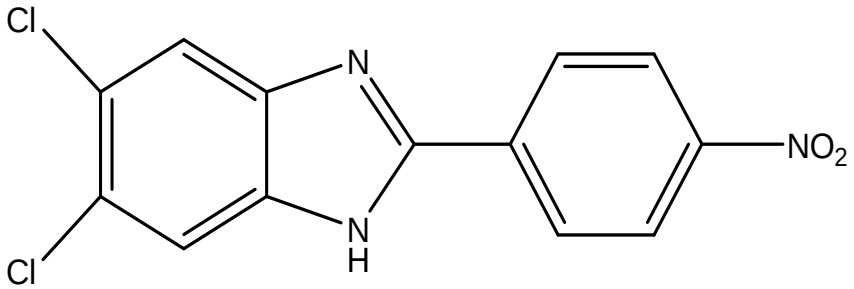
R. Wyler *et al.*, (1979)[18] have synthesize a new derivative which is found to be active against various species of fungus such as *Aspergillus Fumigatus, Candida albicans, Penicillium Sp.*Econazole, an imidazole derivative, was tested as an antifungal agent in different cell culture systems. Econazole was used for comparison which has the following properties: higher stability, higher solubility, better antifungal activity against contaminants of cell cultures.



1-(2-(4-chlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1*H*-imidazole

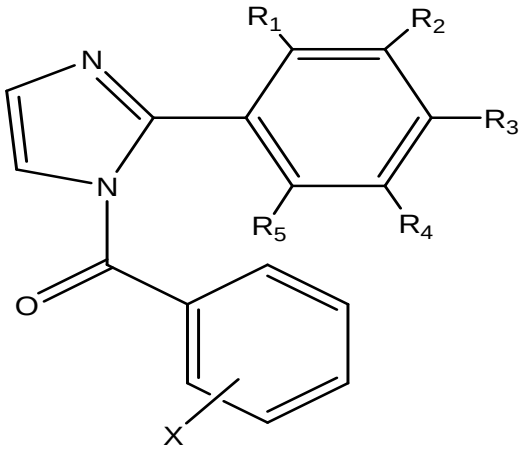
3.2 Anti-Viral Activity

M. Tonelli *et al*, (2010)[19] have synthesized seventy six 2-phenylbenzimidazole and derivatives evaluated for cytotoxicity and antiviral activity against a panel of RNA and DNA viruses. Compound ([56- dichloro-2-(4-nitrophenyl) benzimidazole]) exhibited a high activity resulting more potent than reference drugs smycophenolic acid and 6-azauridine.



5,6-dichloro-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole

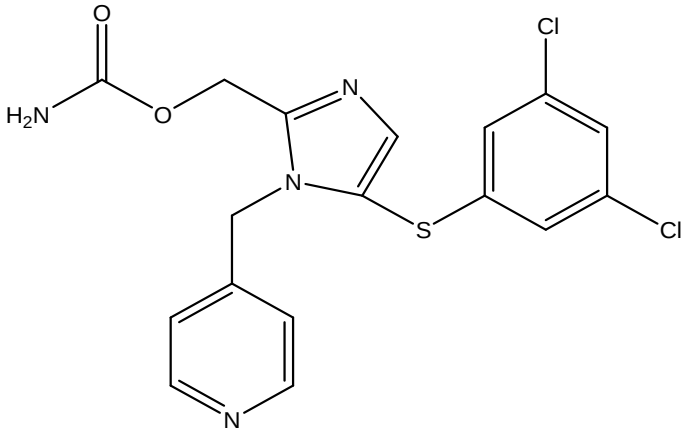
D. Sharma *et al.*, (2009)[20] have synthesized imidazole derivatives and the antiviral screening of (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones against viral strains indicated that compounds A and B selected as the most potent antiviral agents. Ribavirin was used as standard drug.



A, B

R_1= H, H
R_2= H, H
R_3= Cl, NO_2
R_4= H, H
R_5= H, H
X= $4NO_2$, $4NO_2$

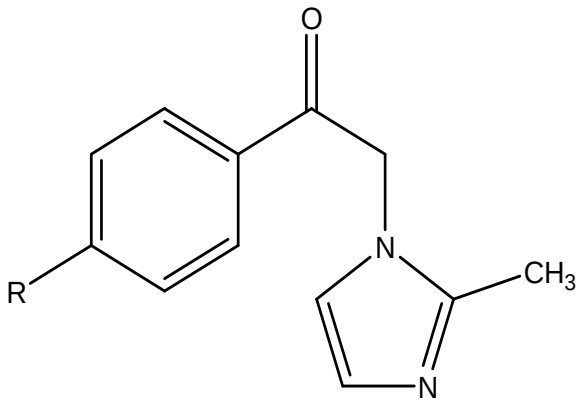
Y. Al-soud *et al.*, (2007)[21] have tested compounds for their *in vitro* anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay, in which the data for Efavirenz and capravirine were included for comparison.



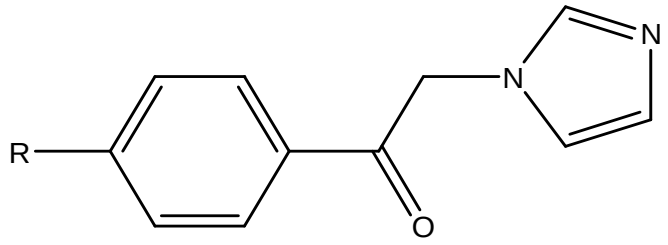
(5-(3,5-dichlorophenylthio)-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-yl)methyl carbamate

3.3 Anti-Cancer Activity

B. Lakshmanan *et al.*, (2011)[22] have reported the synthesis of 1-(4-substitutedphenyl)-2-(2-methyl-1H-imidazol-1-yl) ethanone and 1-(4-substituted phenyl)-2-(1H-imidazol-1-yl) ethanone by the reaction of para substituted phenacyl bromides with imidazoles which showed the significant antitumor activity.

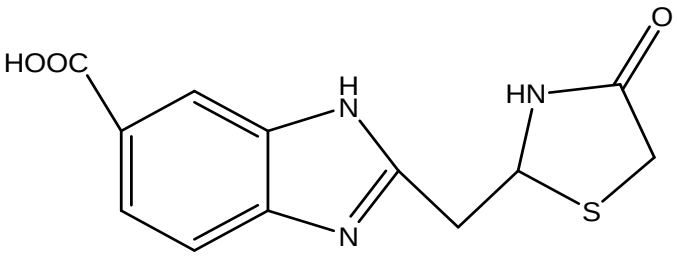


1-(4-substitutedphenyl)-2-(2-methyl-1H-imidazol-1-yl) ethanone

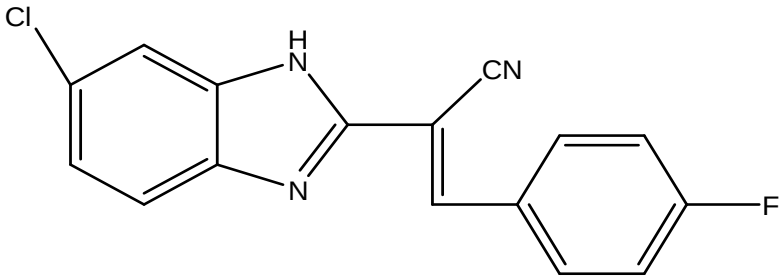


1-(4-substitutedphenyl)-2-(1H-imidazol-1-yl) ethanone

H. M. Refaat, (2010)[23] has synthesized various series of 2-substituted benzimidazole. Several of the synthesized products were subjected for anticancer screening which revealed that all the tested compounds exhibited antitumor activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon carcinoma. Given compounds showed the highest potency against human hepatocellular carcinoma.

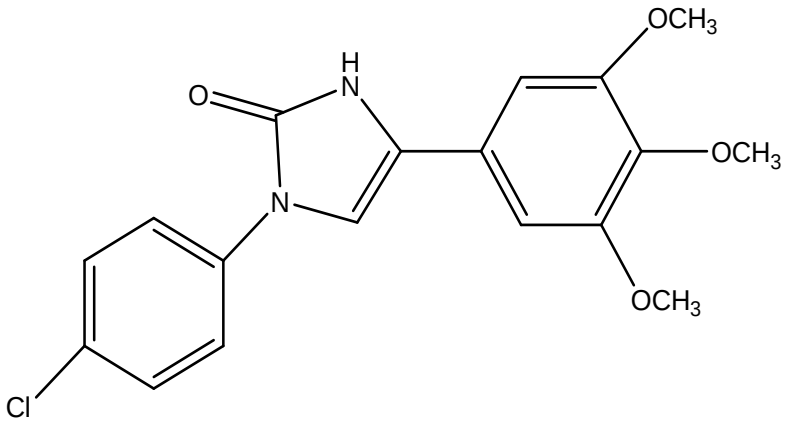


2-((4-oxothiazolidin-2-yl)methyl)-3*H*-benzo[*d*]imidazole-5-carboxylic acid



(*Z*)-2-(6-chloro-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-fluorophenyl)acrylonitrile

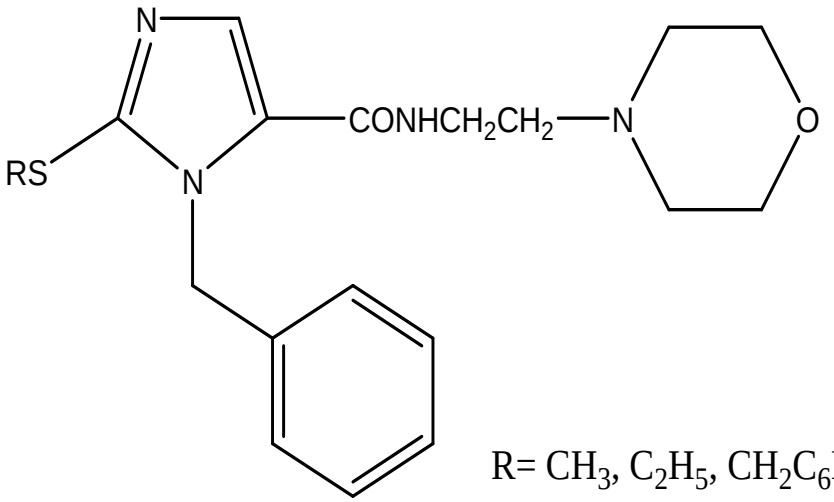
C. congiu *et al*., (2008)[24] have synthesized a series of 1, 4-diarylimidazole-2(3*H*)-one derivatives and their2-thione analogues and evaluated antitumor activity. This Compound show potent antitumor activity.



1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1*H*-imidazol-2(3*H*)-one

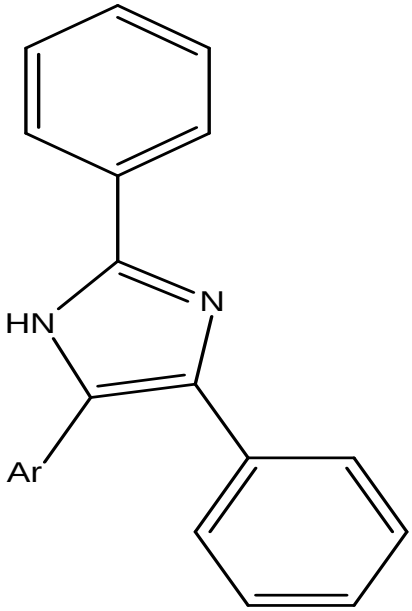
3.4 Anti-Depressant Activity

F. Hadizadeh *et al.*, (2008)[25] were described that Moclobemide is a selective and reversible monoamine oxidase-A inhibitor, which is used as an antidepressant. Three moclobemide analogues were synthesized by replacing moclobemide phenyl ring with substituted imidazoles and studied for the antidepressant activity using forced swimming test in mice. Analogues were found to be more potent than moclobemide.



R= CH_3, C_2H_5, $CH_2C_6H_5$

J. Subbarao, *et al*., (2014)[26] synthesized a new series of 2, 4, 5- trisubstituted imidazoles derivatives were synthesized taking different aldehydes as substitutions. The preliminary characterization of synthesized compounds was identified by physical constants determination and TLC. The chemical structures were confirmed by means of IR, ^{1}H-NMR and Mass spectral data. The compounds were also screened for their antidepressant activities using forced swimming test in mice in which 1, 2 and 3 are found to be most significant while compounds 4 and 5 showed moderate activity as compared to standard drug Fluoxetin. The compound 4 phenol exhibited excellent activity.



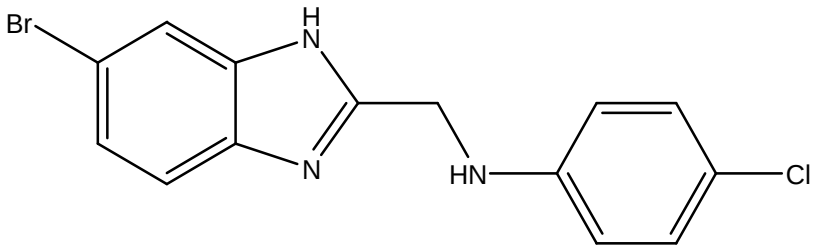
2,4,5 triphenyl imidaole

Where, Ar

1. $-C_6H_5$
2. -4-hydroxy phenyl
3. -3- hydroxy phenyl
4. -4-methoxy phenyl
5. -furan

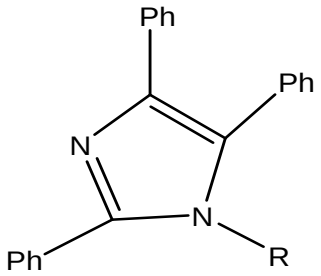
3.5 Anti-Inflammatory Activity

K. C. S. Achar *et al.,* (2010)[27] has synthesized a series of 2-methylaminibenzimidazole derivatives and newly synthesized compounds were screened for analgesic and anti-inflammatory activities. This compound shows analgesic activity and compared with standard nimesulide drug.

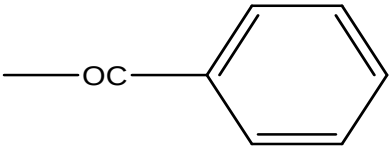


N-((6-bromo-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-chloroaniline

A. Yashoda *et al.*, (2009)[28] have synthesized a series of 1-substituted 2, 4, 5 triphenyl imidazoles by the reaction equimolar mixture of 2, 4, 5 triphenyl imidazole with chloro compound in the presence of anhydrous potassium carbonate. Anti-inflammatory activity was screened by carrageenan induced rat paw edema method. Antimicrobial activity was screened by disc-plate method. All the compounds showed mild to moderate activities.



R= 1.



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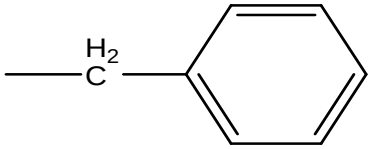

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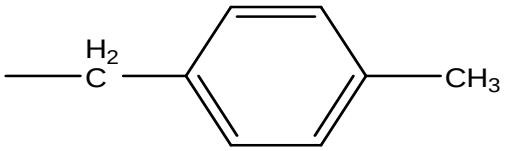
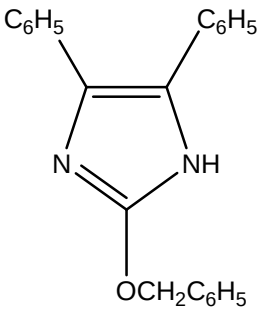


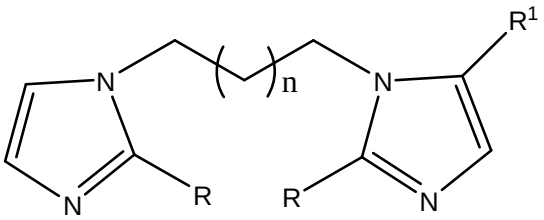
A. Puratchikody *et al.*, (2007)[29] have described on 2-substituted-4, 5-diphenyl-1H-imidazoles and checked the anti-inflammatory activity based on Carrageenan-induced paw edema method. This compound shows maximum activity and indomethacin used as reference drug.



2-(benzyloxy)-4,5-diphenyl-1*H*-imidazole

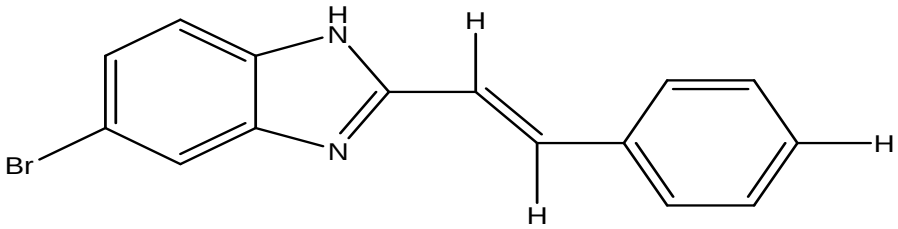
3.6 Anti-Tubercular Activity

J. Pandey *et al.*, (2009)[30] have a series of imidazole based compounds which were synthesized by reacting simple imidazoles either with alkyl halides in presence of tetrabutylammonium bromide (TBAB) or by conjugate addition of imidazoles to ethyl acrylate or glycosylolefinic ester. Synthesized compounds were screened against *M. tuberculosis* where compound exhibited good in-vitro antitubercular activity that may serve as a lead for further optimization.



n= 1
R= Propyl
R^1= H

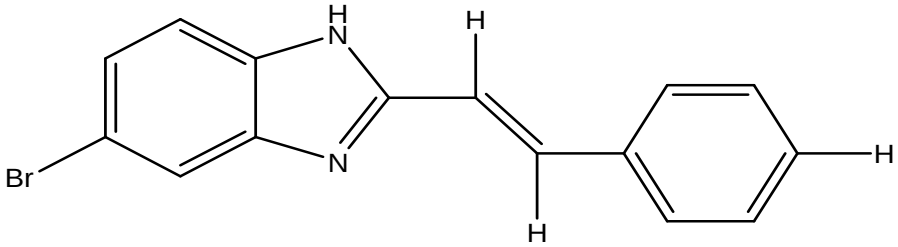
R. V. Shingalapur *et al.*, (2009)[31] have synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazoles derivatives and screened for in vitro anti-tubercular activity against *Mycobacterium tuberculosis*, and these compounds showed good antitubercular activities. Streptomycin was used as reference drug.



(*E*)-5-bromo-2-styryl-1*H*-benzo[*d*]imidazole

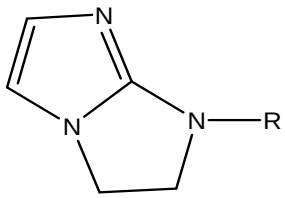
3.7 Anticonvulsant Activity

D. D. Bhragual *et al*., (2010)[32] have evaluated the anticonvulsant activity by Maximal Electroshock Method (MES). Substitution of chloro and nitro group at second position in the substituted ring showed significant anticonvulsant activity without showing neurotoxicity while hydrogen and 4-nitro substitution does not showed the anticonvulsant activity.

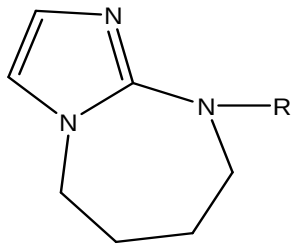


(*E*)-5-bromo-2-styryl-1*H*-benzo[*d*]imidazole

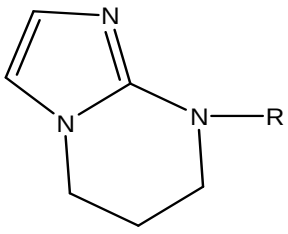
V. P. Arya *et al.*,(1997) [33] have synthesized a number of imidazole compounds such as imidazo [1,2-*a*]imidazole, imidazo[1,2-*a*] pyrimidine and imidazo [1,2-*a*]-1,3-diazepine derivatives. Imidazoimidazoles showed good anticonvulsant activity. The most active compound of this series is imidazoimidazole derivative having an ED_{50} of 24 mg/kg *p.o.* in protecting against electroshoch induced seizures one hour after oral administration.



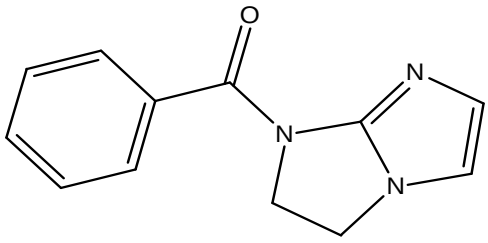
imidazo[1,2-a]imidazole



Imidazo[1,2-*a*][1,3]diazepine



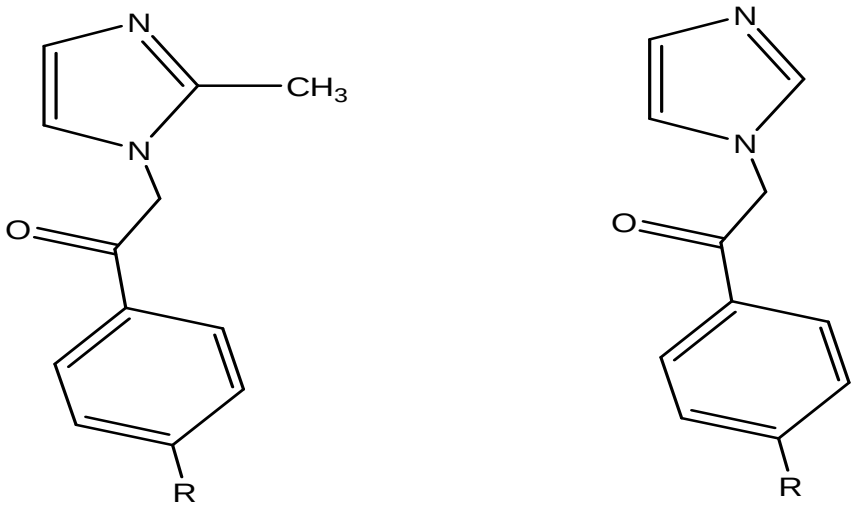
imidazo[1,2-a]pyrimidine



5,6 dihydro-7-(*o*-phenylcarbomoyl)-7*H*imidazo[1,2-a]imidazole

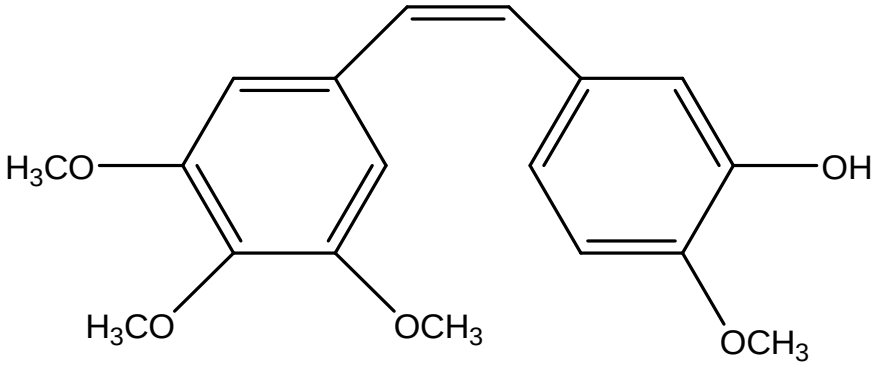
3.8 Anthelmintic Activity

B. Lakshmanan *et al.*, (2011)[34] formed all prototypes which were tested in this bioassay at various concentrations of 10, 50 and 100 µg/ml. When evaluated against Histamine all the compounds at 100µg/ml significantly ($P<0.05$) antagonized the contraction of guinea pig atria, in a competitive and concentration dependent manner.



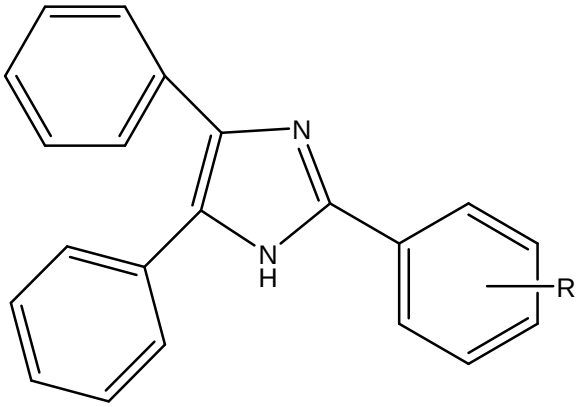
R= Cl, Br, Phenyl,NO_2

A. Batnagar *et al.*, (2011)[35] told that imidazole is an entity which is being synthesized in many of its derivative form from past few years. He review the chemistry of imidazole and its pharmacological actions as antihelmintics, anticancer, antifungal , anti-inflammatory agent by studying its various new synthesized derivatives like antimitotic activity.



(*Z*)-5-(3,4,5-trimethoxystyryl)-2-methoxyphenol

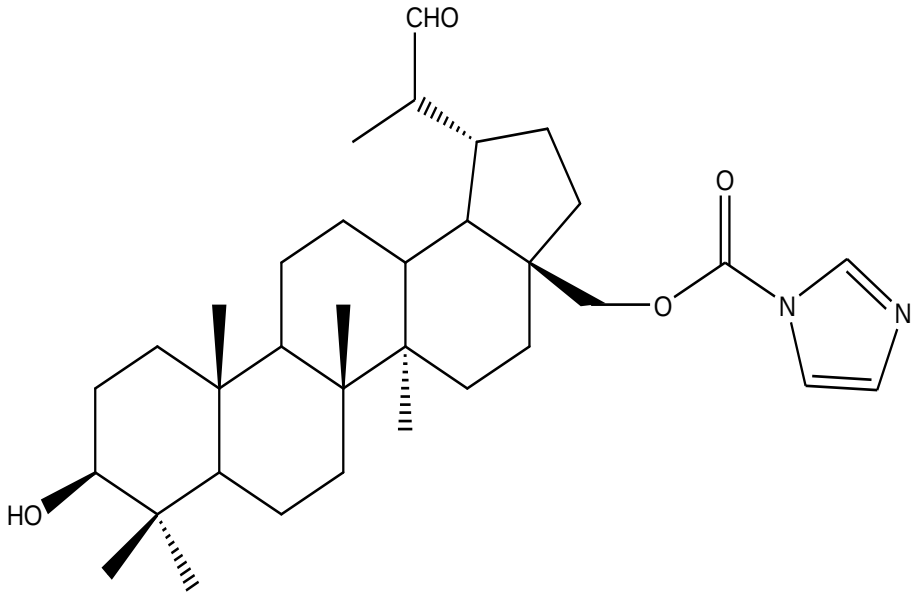
S. Datta *et al.*, (2010)[36] designed a series of 2-substituted-4, 5-diphenyl imidazoles which were synthesized by refluxing benzil with different substituted aldehydes in the presence of ammonium acetate and glacial acetic acid. Compounds were screened for anthelmintic activity. Test results revealed that compounds showed paralysis time of 0.24 to 1.54 min and death time of 0.39 to 4.40 min while the standard drugs albendazole and piperazine citrate showed paralysis time of 0.54 and 0.58 min and death time of 2.16 and 2.47 min, respectively, at the same concentration of 1%(m/v).



3.9 Antilishmanial Activity

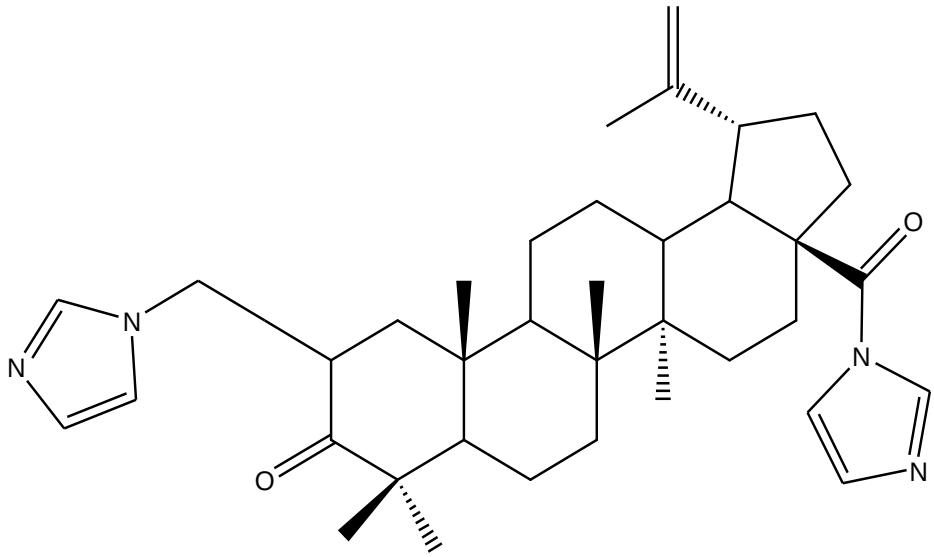
M. C. Sousa, *et al.*, (2014)[37] told that the anti-Leishmania activity of sixteen semi-synthetic lupane triterpenoids derivatives of betulin (BT01 to BT09) and betulinic acid (AB10 to AB16) were evaluated. Drug interactions between the active compounds and one

current antileishmanial drug, miltefosine, were assessed using the fixed ratio isobologram method. In addition, effects on the cell cycle, apoptosis/necrosis events, morphology and DNA integrity were studied. The derivatives BT06 (3b-Hydroxy-(20R)-lupan-29-oxo-28-yl-1H-imidazole-1-carboxylate) and AB13 (28-(1H-imidazole-1-yl)-3,28-dioxo-lup-1,20(29)-dien-2-yl-1H-imidazole-1-carboxylate) were found to be the most active, with IC50 values of 50.8 mM and 25.8 mM, respectively.



((1*R*,3a*S*,5a*R*,5b*R*,9*S*,11a*R*)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-((*R*)-1-oxopropan-2-yl)-icosahydro-1*H*-cyclopenta[*a*]chrysen-3a-yl)methyl 1*H*-imidazole-1-carboxylate

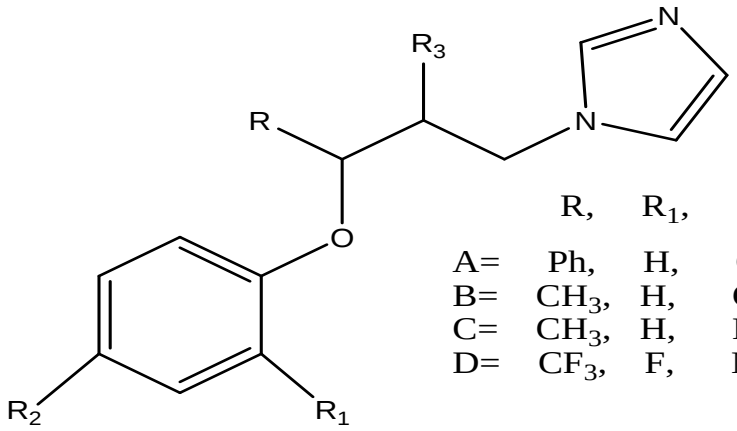
(BT06)



(1*R*,3a*S*,5a*R*,5b*R*,11a*R*)-10-(2-(1*H*-imidazol-1-yl)ethyl)-3a-(1*H*-imidazole-1-carbonyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-hexadecahydro-1*H*-cyclopenta[*a*]chrysen-9(5b*H*,10*H*,13b*H*)-one

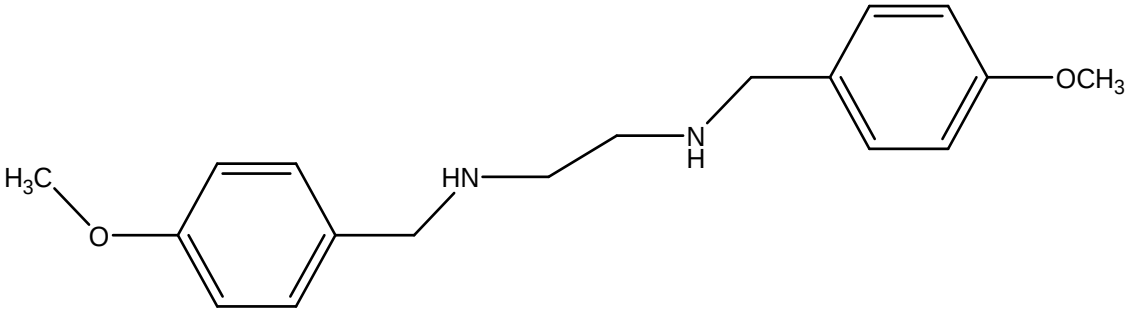
(AB13)

K. Bhandari *et al.*, (2010)[38] have synthesized a series of substituted aryloxy, alkyl and aryloxy aryl alkyl imidazole and evaluated in vitro as antileishmanial against *Leshmaniadonovani*. Among all compounds exhibited 94–100% inhibition.

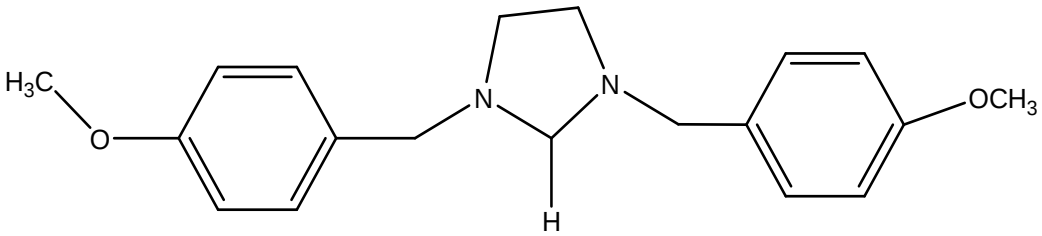


	R,	R_1,	R_2,	R_3
A=	Ph,	H,	CF_3,	H
B=	CH_3,	H,	CF_3,	H
C=	CH_3,	H,	NO_2,	H
D=	CF_3,	F,	NO_2,	H

D. Carvalho *et al.*, (2010)[39] told about a new series of N, N'-disubstitutedethylenediamine and imidazolidine derivatives which have been synthesized and their in vitro biological activities against Leishmania species have been evaluated. Of the nine synthesized compounds, five displayed a good activity in both L. amazonensis and L. major promastigotes. The compounds 1, 2-Bis (p-methoxybenzyl) ethylenediamine 20 and 1,3-Bis (p-methoxybenzyl) imidazolidines showed the best activity on intracellular amastigotes, with IC50 values of 2.0 and 9.4 μg mL-1, respectively.



N[1],*N*[2]-bis(4-methoxybenzyl)ethane-1,2-diamine



1,3-bis(4-methoxybenzyl)imidazolidine

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