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Review Article

A REVIEW ON "IMIDAZOLES": CHEMISTRY AND PHARMACOLOGICAL ACTIVITY

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Imidazole is nitrogen-containing heterocyclic ring which has biological and pharmaceutical importance. Imidazoles have involved an extraordinary situation in heterocyclic chemistry, and its derivatives have pulled in extensive interests as of late for their flexible properties in chemistry and pharmacology. In this way, imidazole compounds have been a fascinating hotspot for specialists for over a century. The imidazole ring is a constituent of a few significant normal items, including purine, histamine, histidine, and nucleic acids. Being a polar and ionisable aromatic compound, it improves pharmacokinetic qualities of lead molecules and accordingly is utilized as a solution for advance solvency and bioavailability boundaries of proposed ineffectively solvent lead molecules. The imidazole derivatives have broad spectrum of biological activity, like anticancer , antitubercular, antifungals, anti-inflammatory, antiviral, antibacterial, antidepressant, anticonvulsant, antitumor, antileishmanial, analgesic, and against HIV actives. This paper intends to audit the natural exercises of imidazole during the previous years.

Key Words: Imidazole, Properties, Pharmacological activity.

INTRODUCTION

Imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar five-member ring framework with 3Carbon and 2Nitrogen atom in 1 and 3 positions the least difficult individual from the imidazole family is imidazole itself, a compound with atomic recipe $C_3H_4N_2$. The foundational name for the compound is 1, 3 diazoles, one of the annular Nitrogen bear a Hydrogenatom and can be viewed as a pyrrole type N. It is dissolvable in water and other polar solvents. It exists in two identical tautomeric structures on the grounds that the hydrogen atom can be situated on both of the two nitrogen particles. Imidazole is a profoundly polar compound, as confirmed by a determined dipole of 3.61D, and is totally dissolvable in water. The compound is delegated fragrant because of the presence of a sextet of π-electrons, comprising of a couple of electrons from the protonated nitrogen atom and one from every one of the leftover four atoms of the ring. Imidazole is amphoteric, for example it can work as both a corrosive and as a base. As a corrosive, the pKa of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, yet somewhat more acidic than alcohols.

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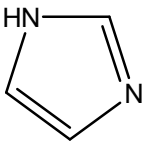
The acidic proton is situated on N-1. As a base, the pKa of the form corrosive (referred to above as pKBH + to evade disarray between the two) is roughly 7, making imidazole around multiple times more fundamental than pyridine. The basic site is Nitrogen-3. [13]

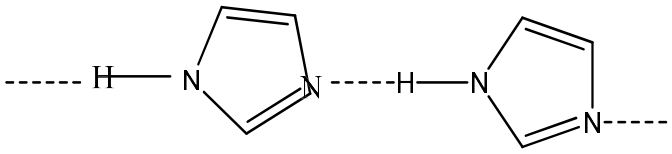


Imidazole

Imidazole is fused into numerous important biological molecules. The most inescapable is the amino acid "histidine", which has an imidazole side chain. Histidine is available in numerous proteins and enzyme and has an indispensable influence in the design and restricting elements of hemoglobin.One of the utilizations of imidazole is in the purging of His labeled proteins in immobilized metal fondness chromatography (IMAC). Imidazole has become a significant piece of numerous drugs. Engineered imidazoles are available in numerous fungicides and antiprotozoal, antifungal and antihypertensive prescriptions. The thermostable polybenzimidazole (PBI) contains imidazole fused to a benzene ring and connected to benzene, and goes about as a fire retardant. Imidazole can likewise be found in different compounds which are utilized for photography and electronics. This survey basically enlights the drug significance of the imidazole moeity.

Physical Properties-

It is colourless liquid having a high B.P. of 256 ^{o}C than any remaining 5-membered heterocyclic compounds because of the intermolecular H-holding, where there is linear association of molecule



Imidazoles shows an enormous estimation of dipole snapshot of 4.8 D in dioxane. Imidazole shows amphoteric properties and has pKa of 7.2 more than pyrazole and pyridine. Imidazoles are an aromatic compound having a reverberation estimation of 14.2 K cal/mol, which is practically a large portion of the incentive for pyrazole.

Chemical Properties-

Imidazole can be considered as having properties like both pyrrole and pyridine. The electrophilic reagent would assault the unshared electron pair on Nitrogen-3, yet not excessively on the 'pyrrole' nitrogen since it is the part of the aromatic sextet. While the imidazole ring is somewhat vulnerable to electrophilic assault on an annular carbon, it is significantly less prone to get engaged with nucleophilic reaction response except if there is an unequivocally electron pulling out substituents somewhere else in the ring. In the absence of such activation the position most prone to nucleophilic

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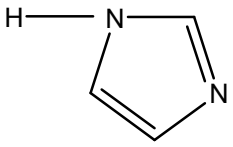
attack is Carbon-2. The fused benzene ring in benzimidazoles provides sufficient electron withdrawal to allow a variety of nucleophilic substitution reaction at Carbon-2.



Imidazole (Acidic Hydrogen)

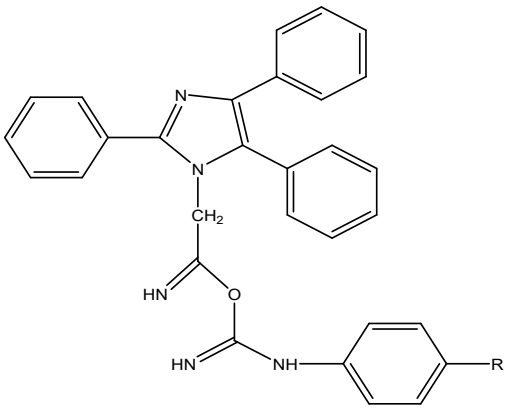
The general reactivity of imidazole and benzimidazole is alluded from sets of resonance structure in which the dipolar benefactors have limited significance.

1. Pharmacological activities

Imidazoles are notable heterocyclic compounds which are common and have a significant feature of a variety of medicinal agents. based on writing overviews Imidazole derivatives shows different pharmacological activities, [14]

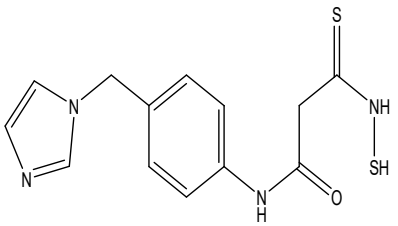
1.1. Antifungal and antimicrobial activity:

Iftikhar Ahsan et al. (2015),A progression of Oxadiazole derivatives(4a-d) (1- {[2-(4-substituted phenyl amino)- (1, 3, 4-oxadiazol-5-yl)] methyl}-2, 4, 5-triphenyl imidazole) have been synthesized from (2, 4, 5-triphenyl-imidazole-1-yl)- acetic acid hydrazide (4a) under different reaction conditions. The anti-fungal activity of the recently synthesized compounds was contrasted and the standard drug Voriconazole. The oxadiazole derivatives demonstrated moderate to great anti-fungal activity. The compounds having 4-methoxy group demonstrated great action (81%). The Oxadiazole derivatives having 4-flourophenyl group indicated highest activity (82.14%). The results of anti-microbial and antifungal activity….by using ……method plainly demonstrated that oxadiazole ring bearing 2, 4, 5-triphneylimidazole have moderate activities.[15]



4a) R= OCH_3 4c) R=F
4b) R=CH_3 4d) R=Cl

Firuze Diyar Altındağet al. (2019), A progression of 2-(substituteddithiocarbamoyl)- N-[4-((1H-imidazol-1-yl) methyl) phenyl] acetamide derivatives was designed and synthesized to battle the expanding occurrence of medication safe parasitic contaminations. A large portion of the final compounds show important activity



2-(dithiocarbamoyl)- N-[4-((1H-imidazol-1-yl) methyl) phenyl] acetamide

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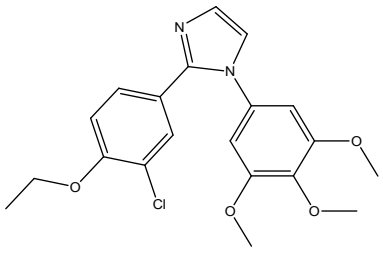
against Candida albicans and Candida krusei with MIC50 esteem 12.5 lg/mL.[16]

1.2. Anticancer activity:

Romeo Romagnoli et al.(2016) was synthesized a series of tubulin polymerization inhibitors, in view of the 1-(3',4',5'-trimethoxyphenyl)- 2-aryl-1H-imidazole scaffold and designed as cis-restricted combretastatin A-4 analogs, with the objective of assessing the impacts of different examples of substitution on the phenyl at the 2-position of the imidazole ring on biological activity. A chloro and ethoxy group at the meta- and para-positions, respectively, produced the most dynamic compound in the series (4o), with IC50 estimations of 0.4-3.8 nM against a board of seven malignancy cell lines. Besides in HL-60 cells, 4o had more noteworthy antiproliferative than CA-4, demonstrating that the 3'-chloro-4'-ethoxyphenyl moiety was a decent substitute for the CA-4 B-ring. Experiments completed in a mouse syngenic model showed high antitumor action of 4o, which fundamentally diminished the tumor mass at the dose thirty times lower than that needed for CA-4P, which was utilized as a reference compound. [17]

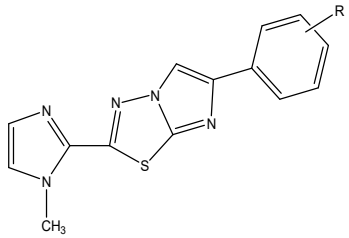


2-(3'-Chloro-4'-ethoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)-1H-imidazole

4o

1.3. Anti-tubercular activity:

Harun M. Patel et al.(2017), In the current examination, a series of imidazo[2,1-b] [1,3,4] thiadiazole derivatives 5(a–j) were evaluated for their in vitro antitubercular activity against Mycobacterium tuberculosis H37Rv strain by utilizing Alamar Blue vulnerability test as a feature of the TAACF TB screening program under bearing of the US National Institutes of Health, the NIAID division. Among the tested compounds, 2-(1-methyl-1H-imidazol-2-yl)- 6-(4-nitrophenyl) imidazo[2,1-b] [1,3,4] thiadiazole (5f) has indicated the most noteworthy (98%) inhibitory activity with MIC of 3.14 lg/ml when contrasted with other tested compounds. Further, some potent compounds were likewise evaluated for their cytotoxic action against a mammalian Vero cell line utilizing MTT test.[18]



Imidazo[2,1-b][1,3,4]thiadiazole derivatives 5(a–j)

R= a) 3-Nitro, b)4-Bromo, c)4-chloro, d)4-fluro, e)2-hydroxy, f)4-nitro, g)4-methyl, h)3-hydroxy, i) 2,4-Dichloro, j)2,4Dihydroxy

Snehlata Yadav et al.(2018), The examination depicts the antitubercular activity, evaluation of a series of 2-(1-benzoyl-1H-benzo[d]imidazol-2-ylthio)- N-substituted acetamide derivatives (18) were surveyed for in vitro antitubercular activity against Mycobacterium tuberculosis H37Rv in mice models and for their inhibitory activity on vital mycobacterial enzyme viz, isocitrate lyase,

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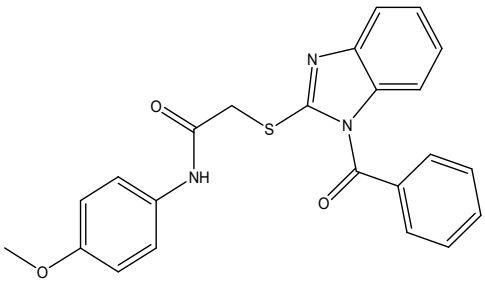
pantothenate synthetase and chorismate mutase.[19]



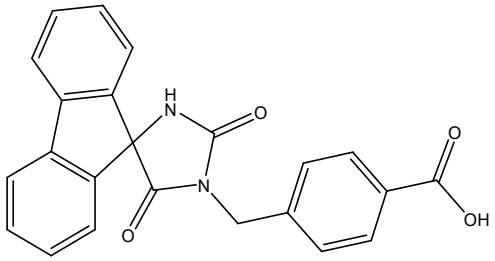
2-(1-Benzoyl-1H-benzo[d] imidazol-2-ylthio)-N-(4-methoxyphenyl)acetamide

(18)

1.4. Anticonvulsant activity:

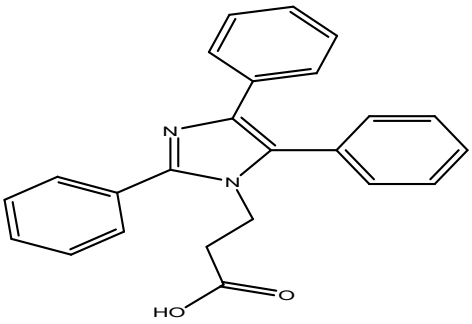
Adel A. Marzouk et al. (12 June 2020) Newimidazolidindiones and tetra-substituted imidazole derivatives were designed, synthesized, and assessed for the anticonvulsant activity through pentylenetetrazole (PTZ)- incited seizures and maximal electroshock (MES) tests utilizing valproate sodium and phenytoin sodium as reference drugs, separately. Most of the targated compounds demonstrated incredible activity against pentylenetetrazole (PTZ)-initiated seizures with reasonable for no-activity against MES. Compounds 3d, 4e, 11b, and 11e demonstrated higher activityt (120 %) than that of valproate sodium in PTZ model. Practically all compounds demonstrated no neurotoxicity, as shown by the rotarod test. Assessment of physicochemical properties and pharmacokinetic profiles of the targated compounds were contemplated.[20]

Hafiz Mawasiet al.(2016) Regardless of the



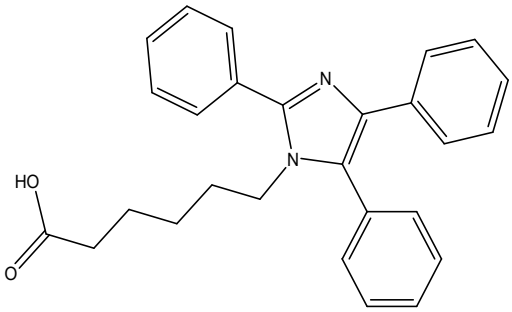
4-((2',5'-Dioxospiro[fluorene-9,4'-imidazolidine]-1'-yl)methyl) benzoic acid

(4e)



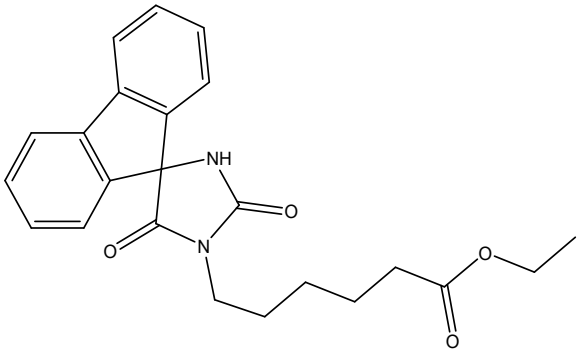
3-(2,4,5-Triphenyl-1H-imidazol-1-yl)propanoic acid

(11b)



6-(2,4,5-Triphenyl-1H-imidazol-1-yl)hexanoic acid

(11e)



Ethyl 6-(2',5'-dioxospiro[fluorene-9,4'-imidazolidine]-1'-yl)hexanoate

(3d)

close structural features of the carbamoyl imidazole derivatives just compounds **7, 8, 13** and **16** were active at the MES test with **ED50** values ranging from **12 to 20 mg/kg** combined

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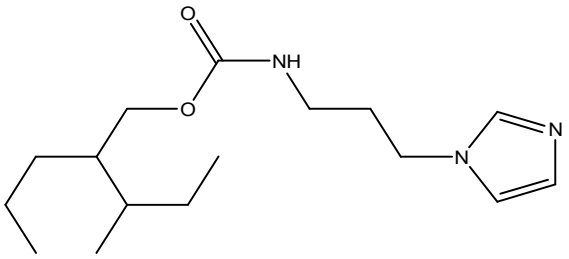
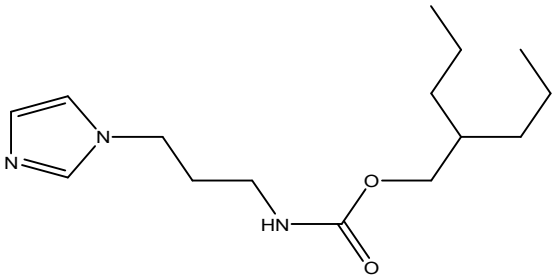
with high defensive index (**PI = TD50/ED50**) estimations of **4.1–7.3** after ip administration to rats. A comparative phenomenon was seen in mice where compounds **7, 8, 9, 12** had MES-ED50 estimations of 14–26 mg/kg. compounds **7** and **13** likewise showed anticonvulsant action



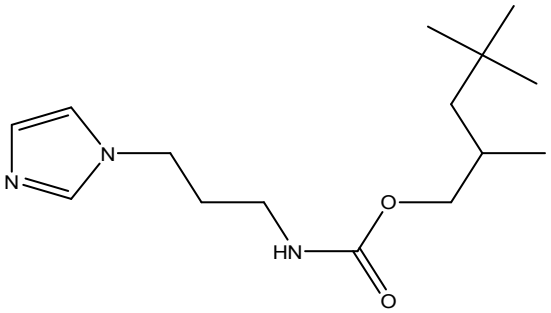
3-Methyl-2-propylpentyl (3-(1H-imidazol-1-yl) propyl)carbamate

(8)



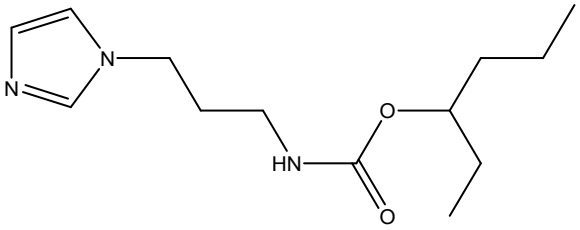
2-Propylpentyl (3-(1H-imidazol-1-yl)propyl)carbamate

(7)



2,4,4-Trimethylpentyl (3-(1H-imidazol-1-yl) propyl)carbamate

(13)



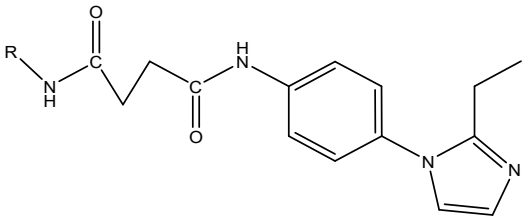
Hexan-3-yl (3-(1H-imidazol-1-yl)propyl)carbamate

(16)

in the **6 Hz** model with ED50 estimations of 32 and 44 mg/kg, separately. As the most active substances, compounds 7, 8 followed by 13 and 16, along these lines offer an ideal viability security profile and thusly, may be promising contender for advancement as new antiepileptics.[21]

1.5. Antitumar Activity:

Zhen-Wang Li et al. (2020) Novel imidazole compounds were designed, prepare, and evaluated in vitro for antitumor activity. Most of the tested compounds showed improved antiproliferative activity compared with the positive control drugs 5-FU and MTX. Among them, compound 4f displayed extraordinary antiproliferative activity against three malignant growth cell lines and was significantly more intense than both 5-FU and MTX. Specifically, the selectivity file demonstrated that the tolerance of normal L-02 cells to 4f was 23–46-overlay higher than that of tumor cells**.** This selectivity was fundamentally higher than that displayed by the positive control drugs.



4f- (p-Br)C_6H_4

Moreover, compound 4f incited cell apoptosis by expanding the protein articulation levels of Bax

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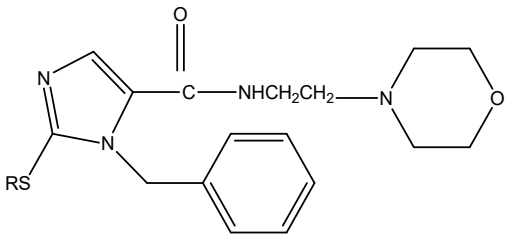
and diminishing those of Bcl-2 of a time-dependant way. In this manner, 4f could be a possible contender for the advancement of a novel antitumor specialist.[22]

1.6. Antidepressant Activity:

Farzin Hadizadeh et al. (2008) Moclobemide is a particular and reversible monoamine oxidase-An inhibitor, which is used as an antidepressant. Three moclobemide analogs were synthesized by replacing moclobemmide phenyl ring with substituted imidazoles. Accordingly, N-[(4-morpholinyl) ethyl)]-1-benzyl-2-(alkkylthio)- 1H-imidazole-5-carboxamides (7a-c) were synthesized and read for antidepressant activity using obliged swimming test in mice. Analogs 7a-c were found to be more serious than moclobemide. Least powerful measurements for moclobemide and analogs 7a-c were found to be 20, 2.5, 1.25 and 2.5 mg/kg i.p. separately.[23]

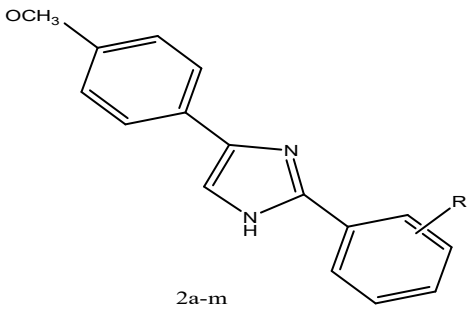


N-[(4-morpholinyl) ethyl)]-1-benzyl-2-(alk kylthio)-1H-imidazole-5-carboxamides (7a-c)

a)R=CH,b)R=C_2H_5 ,c)$CH_2C_6H_5$

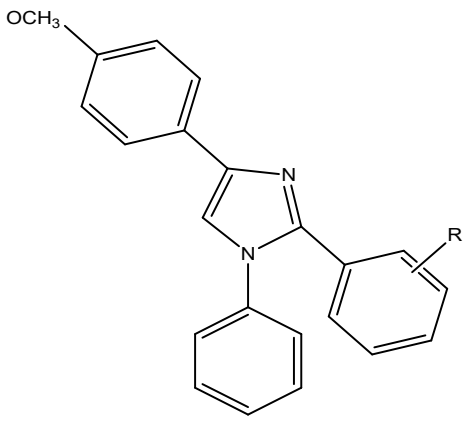
1.7. Anti-inflammatory activity and analgesic activity:

Asif Husain et al. (2013) The potential pharmacophoric nature of imidazole nucleus, two series of imidazole derivatives, 2,4 disubstituted 1 H imidazoles(2a m) and 1,2,4 trisubstituted 1 H imidazoles(3a m), were synthesized with a point of acquiring double acting compounds i.e., Anti-inflammatory.The compounds were synthesized from 4 methoxyphenyl glyoxal following multistep synthesis, and their structures were set up based on modern analytical techniques (IR, NMR and MS). The combined imidazoles were tested for their in vivo Anti-inflammatory activity. Moreover, a few compounds were estimated assessed for theiranalgesic and ulcerogenic effect.[24]



2a-m

2,4 disubstituted 1 H imidazoles



3 a-m

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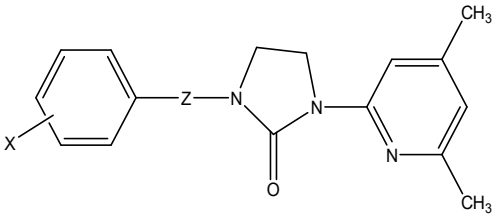
diphenyl-1H-imidazol-2-yl)- phenol, 3d was the only compound which showed activity against Klebsiella pneumoniae while rest of the compounds didn't show huge action against the micro-organism action. compounds 3a–d and 3f satisfies Lipinski's rule of Five and could be projected as potent new antibacterial drugs.[26]

1.8. Antileishmanial Activity:

Jean-Michel H. Robert et al. (2003) Nitrogen3 - acyl, arylsulfonyl and benzyl derivatives of Nitrogen1 - (4,6-dimethylpyridin-2-yl), (5-methylthiazol-2-yl) or (3-methylisoxazol-5-yl) imidazolidin-2-ones were synthesized and assessed as potential antileishmanial agents. Determination of their cytotoxic effect was completed utilizing MRC5 cells. Two compounds, 1-(4,6-dimethylpyridin-2-yl)- 3-(napht-2-ylsulfonyl) imidazolidin-2-one, 18, and 1-(3-methylisoxazol-5-yl)- 3-(4-bromobenzyl) imidazo-lidin-2-one, 25, applied critical antileishmanial activity in promastigotes of Leishmania (L) mexicana and Leishmania infantum, with IC50 in the scope of 8/16 mmol L1. Antiparasitical activity of the less toxic compound, 25, was affirmed against intracellular amastigote of L. Mexicana, the clinically significant stage; its low IC50 esteem (2.4 mmol L1) and its favourable toxicity/activity record (11) comprise empowering results for continuous pharmacomodulation in the comparing subseries.[25]

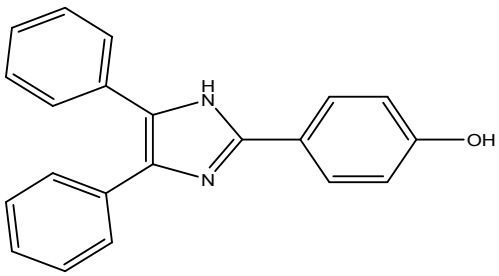


Z =CH_2, CO, SO_2
X=CH_3, Cl, di-Cl,F,di-F,Br

Imidazolidin-2-one derivatives of 2-amino-4,6-dimethylpyridine

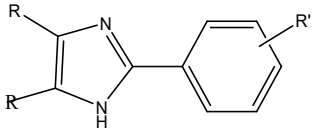
1.9. Anti-bacterial Activity:

Mohd Sajid Khan et al. (2008) Some novel chemically synthesized 2,4,5-trisubstituted imidazoles from aryl aldehydes and 1,2-diketones or a-hydroxyketone were screened against eight different human pathogenic microscopic bacteria and fungi. Seven compounds were discovered to be against various microscopic bacteria. These compounds

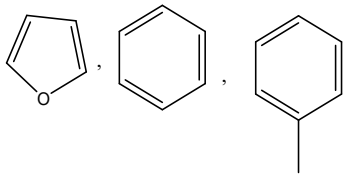


4-(4,5-Diphenyl-1H-imidazol-2-yl)-phenol

(3d)



3a-g

R= 

R'= p-OCH_3, m-OCH_3, p-OH,o-OH, p-NO_2

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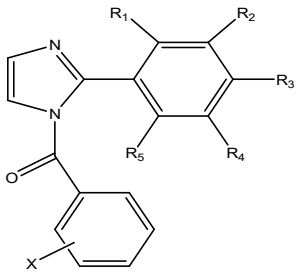
showed variety in activity and were discovered to be active against Gram-positive as well as Gram-negative bacteria. Compound 4-(4,5-diphenyl-1H-imidazol-2-yl)- phenol, 3d was the only compound which showed activity against Klebsiella pneumoniae while rest of the compounds didn't show huge action against the micro-organism action. compounds 3a–d and 3f satisfies Lipinski's rule of Five and could be projected as potent new antibacterial drugs.[26]

1.10. Anti-viral Activity:

Deepika Sharma et al. (2008) have synthesized (substituted phenyl)- [2-(substituted phenyl)-imidazol-1-yl]-methanone (13–26) analogues. The antiviral screening of (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-



(Substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]methanones 13-23

compound	R_1	R_2	R_3	R_4	R_5	X
13	H	NO_2	H	H	H	4-NO_2
23	Cl	H	H	H	H	4-NO_2

methanones (13–26) against a panel of viral strains indicated that compounds 16 and 19 can be selected as lead compounds for the development of novel antiviral agents.[27]

CONCLUSION

According to various studies in the literature, imidazole derivatives show a variety of antimicrobial, anti-inflammatory, analgesic, antituberculosis, anticancer and other activities. By slightly modifying the substituents on the basic imidazole nucleus, its activity can be further improved. Compared to some other heterocyclic moieties, the structural similarity to the imidazole histidine compounds can be more easily combined with protein molecules. Therefore, imidazole provides better pharmacodynamic properties. Also, some imidazole drugs can directly inhibit the membrane at high concentrations without interfering with sterols and sterol esters. Recently, several new drug developments in imidazole derivatives have shown better effects and lower toxicity.

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