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STUDY ON BIOLOGICAL EVALUATION OF IMIDAZOLE DERIVATIVES

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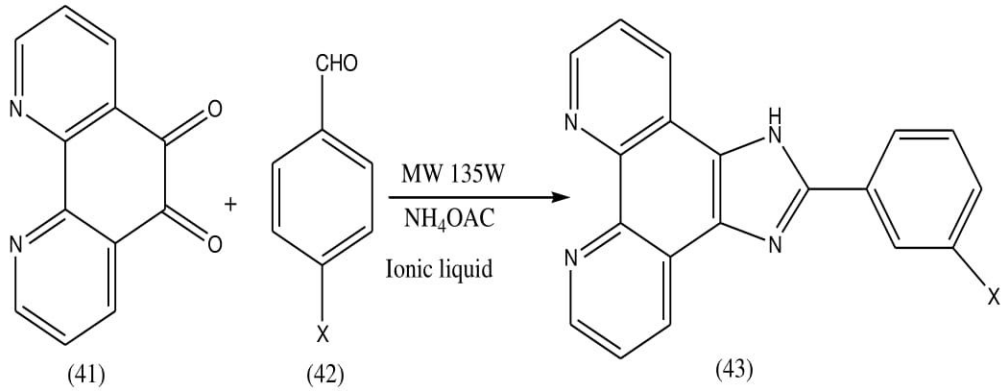
Abstract: Fungus is a parasite. The human fungi parasitic relationship results in mycotic illnesses, the majority of which involve superficial invasion of skin or the mucous membranes of body orifices. Fungi have different shapes and sizes. Some are large while others are minute parasitic and saprophytic cells. They differ from algae and protozoa.

INTRODUCTION

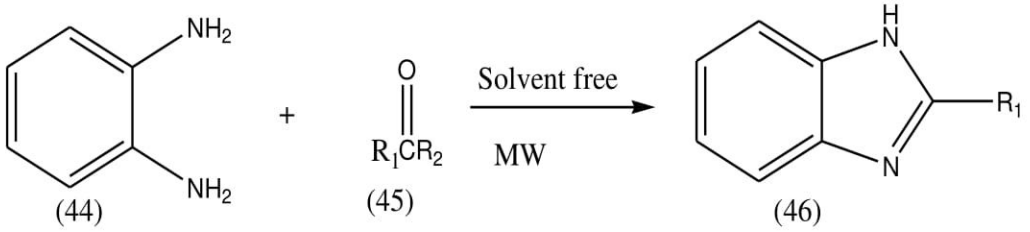
2-phenylimidazo Phenanthroline derivatives (43) were synthesized by reacting dicarbonyl compound (41) and p-substituted benzaldehyde (42), this is a type of acid catalyzed reaction with excellent yields in a neutral ionic liquid, 1-methyl-3-heptyl- imidazolium tetrafluoroborate [(HeMIM) BF4], under solvent free and microwave assisted conditions. This particular reaction accompanies all the merits of microwave reactions like easy workup, better yield, and environment friendly reaction (Qasim, et al, 2011).



(41) (42) (43)

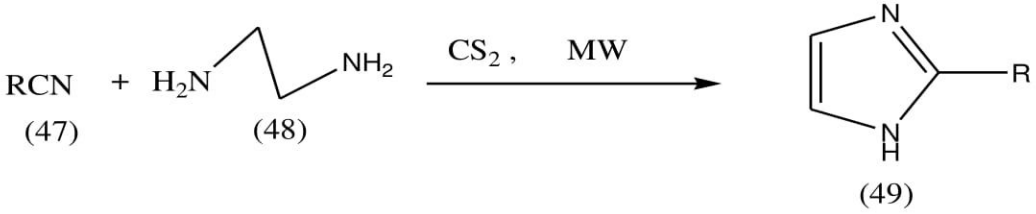
Na Zhao reported an efficient and a quick microwave-assisted synthesis of benzimidazoles and trisubstituted imidazoles (46). Three benzimidazoles

were obtained as a result of the condensation of 1, 2-phenylenediamine (44) with carboxylic acids (45) and acetoacetic ester without catalyst (Na Zhao, et al, 2005**).**

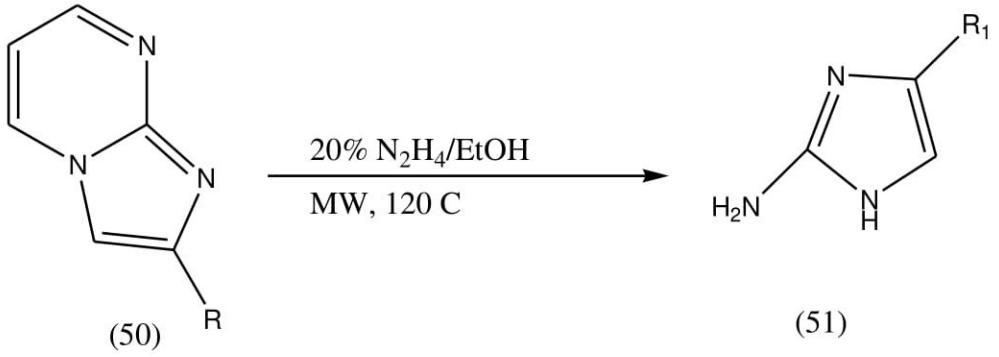


a) $R_1=C_6H_5OCH_2^-$, R_2=OH
b) R_1=2,4-$(Cl)_2$ $C_6H_3OCH_2^-$, R_2= OH
c) $R_1=CH_3$, $R_2=CH_2COOEt$
d) $R_1=C_6H_5^-$, R_2= OH
e) R_1=-CH_3, R_2= OEt

Pathan, et al reported the reaction of alkyl cyanide (47) with ethylenediamine (48) in the presence of carbon disulphide give 2-substituted 2-imidazolines (49) under microwave irradiation. The yields of product obtained using this protocol is significantly high and the reaction time is reduced (Pathan, et al, 2006).



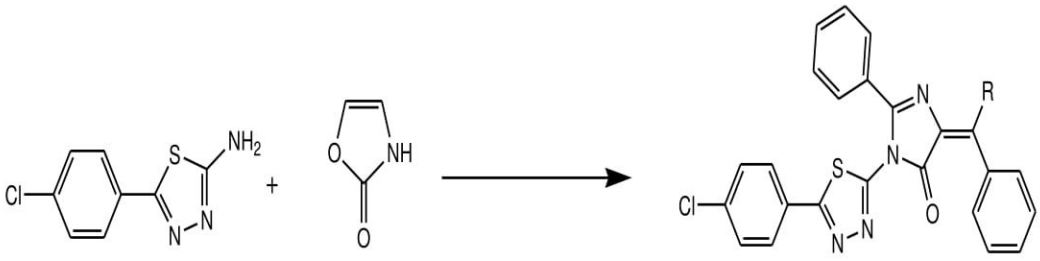
Ermolat et al synthesized mono and disubstituted-2-amino-1H imidazoles (51) via microwave assisted hydrazinolysis of substituted imidazo [1, 2 a] pyrimidines (50) is reported. This method avoids strong acidic conditions and is superior to the conventional cyclo condensation of α-halo-ketones with N-acetyl guanidine (Ermolat, et al, 2009).



(50) (51)

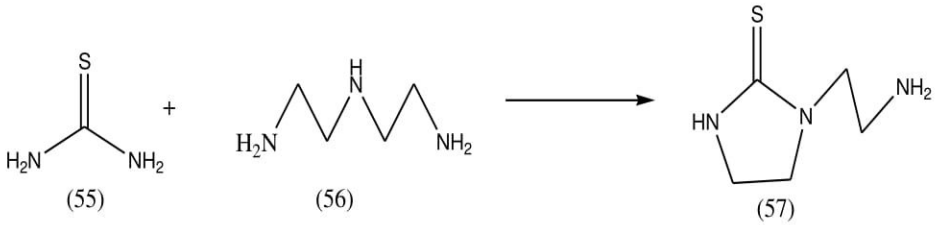
R_1= Ph
R_1= BrPh

Various 4-(Substituted benzylidene)-1-(5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-yl)-2-phenyl 1H-imidazol-5 (4H)-one (54) have been synthesized by the condensation of different oxazolones (53) (1a-f) with 5-(4-chlorophenyl)-1, 3, 4-thiadiazol- 2-amine (52) under microwave irradiation technique. The structure of the synthesized compounds 4-(Substituted benzylidene)-1-(5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-yl)-2-phenyl-1H-imidazol-5(4H)-one was confirmed on the basis of spectral and elemental analysis. The synthesized compounds were screened for in vitro antimicrobial study against E. coli, S. aureus, C. albicans and A.niger using cup plate and agar well diffusion technique (Bhanat, et al, 2011).

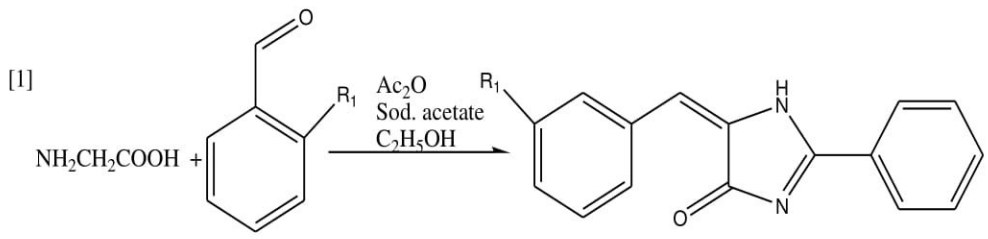


(52) different oxazolones (53) (54)

Hopfl, et al synthesize 1-(2-aminoethyl)-2-imidazolidinethione (57) by reacting thiourea (55) with N^1-(2-aminoethyl) ethane-1,2-diamine (56). The crystal and molecular structure was determined. The combination of an X-ray crystallographic study and theoretical calculations (DFT) provided insight into the understanding of the high performance of this compound as low toxicity corrosion inhibitor (Hopfl, et al, 2005).



A series of 1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5- oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl imidazole-quinolone (60) analogs were synthesized by condensation of substituted imidazole (59) and substituted quinoline (58). The title compounds were investigated for anti-inflammatory and its ulecerogenicity activities. All the lead compounds were assessed by QSAR and molecular modeling (CADD) studies to predict best physicochemical, pharmacokinetic, toxicological properties and best fit with targets like COX-1 and COX-2. The result indicated that the compounds have convincing activities against inflammation when compared with standard drug (Ibuprofen) (Raghavendra, et al, 2011).



Marek, et al synthesized via a facile 4-step reaction sequence starting from commercially available and inexpensive N-Cbz amino acids (61). The condensation of the corresponding α- bromoketones with formamidine acetate in liquid ammonia was revealed to be a useful method for the synthesis of such imidazole derivatives (62), derivatives thus prepared are structurally- related to histamine (Marek, et al, 2007).

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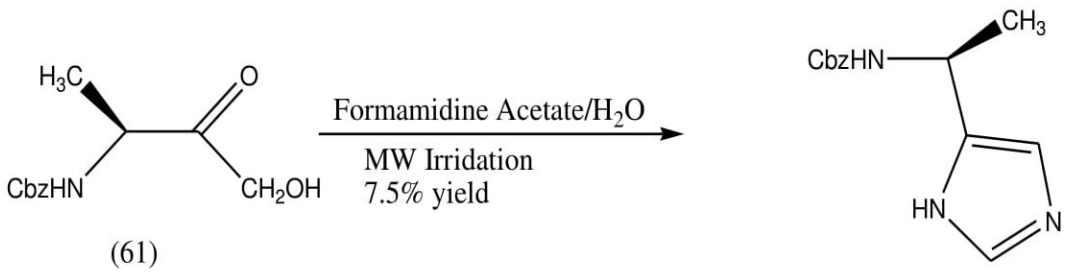

(61) (62)

ANTIFUNGAL ACTIVITY

Fungi: The fungi and yeast belong to the division of the plant kingdom known as Thallophytes, sub-division Eumycetes, and are characterised by absence of chlorophyll. It has been reported that there are approximately 80- 100 thousand species of fungi among two billion kinds of living things. The fungi are basically important in the conversion of organic materials into humus which permits the survival of higher plants and animals. The antibiotics produced by fungi and actinomycetes have been a great value of fighting diseases produced by harmful bacteria.

The fungi are pathogenic to plants, several species are pathogenic to domestic animals as well as to man. The species which are pathogenic to man belong to the class of Actinomycetes and Hypomycetes whereas the dermatophytes belong to the three genera of Microsporum, Trichophyton and Epidermophyton. The later species invade only the superficial keratinized areas of the body such as skin, hairs and nails.

Different remedies for the treatment of fungal infections have been attempted but seldom have patients recovered as a result of drug therapy. The superficial infections may not be fully eradicated due to the ineffectiveness of the locally applied drugs or due to their failure to reach the deep seated organisms and perhaps to the tendency of the patient to neglect treatment as soon as discomfort subsides. There is a need for drug of low toxicity which can be administered parenterally or orally and reach the site of these organisms in effective concentrations (Parmioo, 2006).

Fungal diseases are generally called as mycoses. Depending upon some basic differences, fungi may be classified as:

- Phycomycetes
- Ascomycetes
- Basidiomycetes
- Dueteromycetes

Mycotic infection may be categorized as:-

1. **Dermatophytoses** It is a skin infection caused by various trichophytons. It includes superficial infections of keratinized tissues like stratum corneum, hairs, nails etc.
2. **Candidiasis** affects mainly the skin and mucous membrane. It is caused by the Candida albicans. These infections mainly develop in the mouth, bowel or vagina and are called as local infections.
3. **Systemic fungal infection** is a third major category that involves fungal infections of bones, viscera, lungs and meninges (Kadam, et al, 2007).

Classification of Antifungal agent:

1. Fatty acids
2. Pyrimidine derivatives

LITERATURE REVIEW OF VARIOUS ACTIVITIES

Anti-Depressant Activity

Hadizadeh et al, 2008 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.

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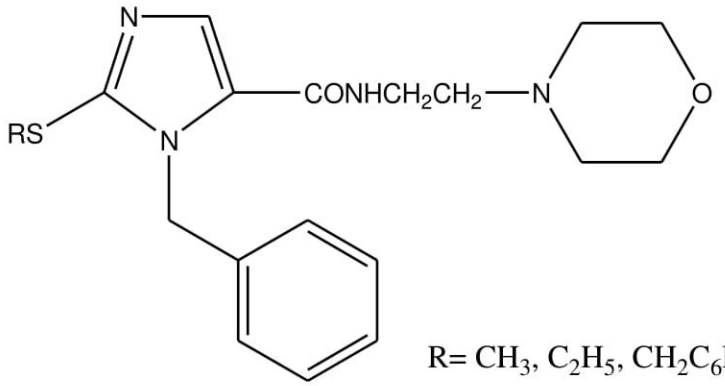
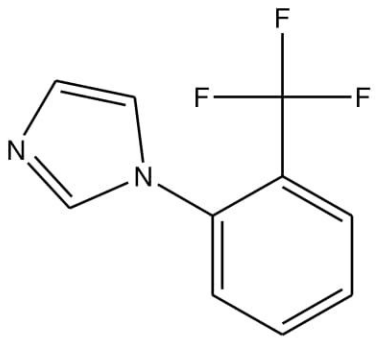


R= CH_3, C_2H_5, $CH_2C_6H_5$

Volke et al, 2003 studied and compare the behavioural effects of NOS inhibitor 7-nitroindazole with the more selective neuronal NOS inhibitor 1-(2-trifluoromethylphenyl) imidazole (TRIM) in animal models predictive of antidepressant- and anxiolytic-like activity in order to clarify the role of distinct isoforms of NOS in the regulation of depression and anxiety. The antidepressant-like effect of TRIM was counteracted by pretreatment with l-arginine (250 mg/kg). The systemic administration of TRIM (50 mg/kg), but not 7-NI (up to 50 mg/kg) increased the time spent in the light side of the apparatus in the light–dark compartment test. These motor side effects were more pronounced in the case of 7-NI and were not diminished by pretreatment with l-arginine. It was concluded that neuronal NOS seems to play the key role in the antidepressant- and anxiolytic-like effects of NOS inhibitors.

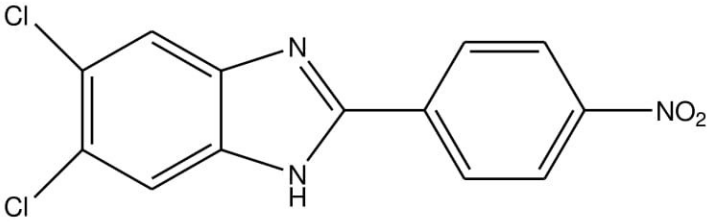


1-(2-trifluoromethylphenyl)imidazole

Anti-Viral Activity

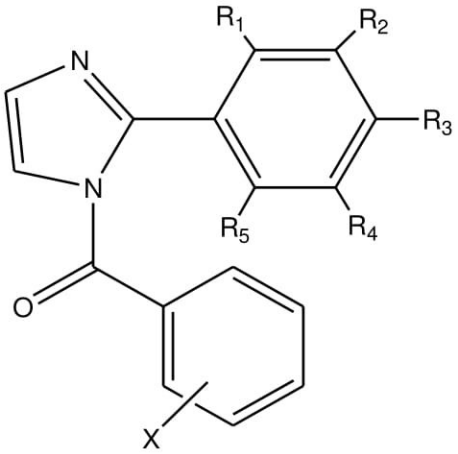
Michele Tonelli et al, 2010 synthesized seventy six 2-phenylbenzimidazole derivatives and evaluated for cytotoxicity and antiviral activity against a

panel of RNA and DNA viruses. Compound ([56- dichloro-2-(4-nitrophenyl) benzimidazole]) (85) 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

Sharma et al, 2009 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 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.

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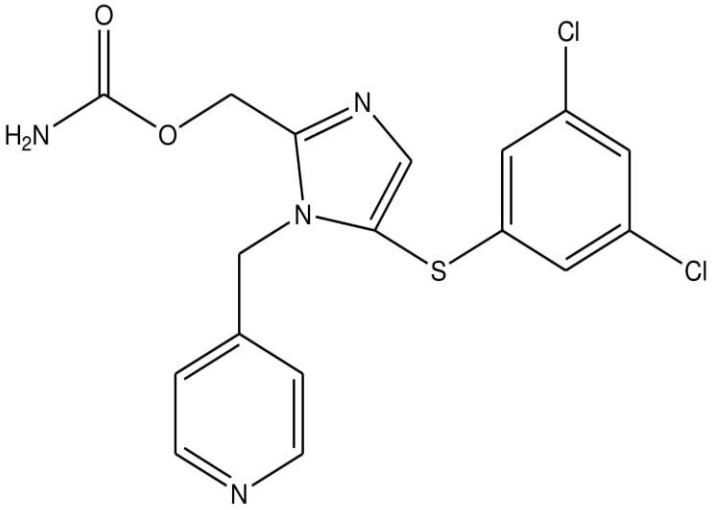
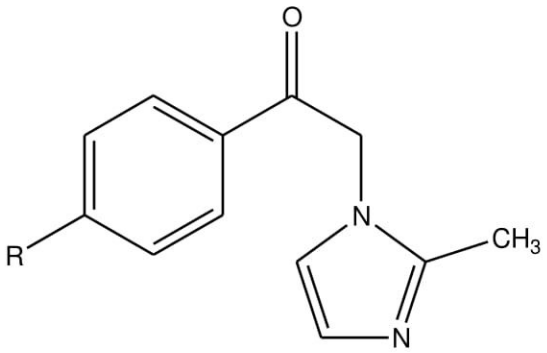


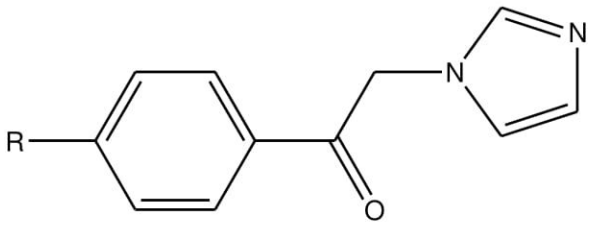
(5-(3,5-dichlorophenylthio)-1-(pyridin-4-ylmethyl)-1*H*-imidazol-2-yl)methyl carbamate

Anti-Cancer Activity

Lakshmanan et al, 2011 also 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

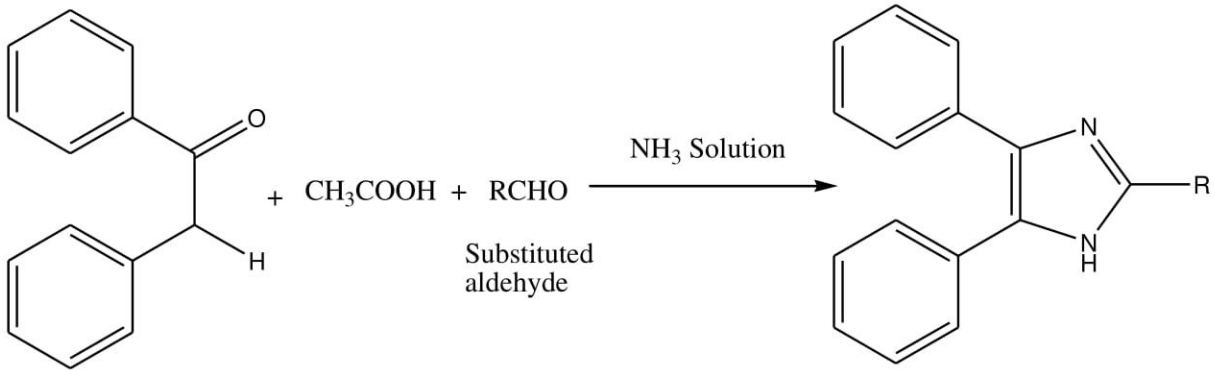
Refaat, 2010 synthesized various series of 2-substituted benzimidazole. Several of the synthesized products were subjected for anticancer screening which revealed that all the tested compounds exhibited antitumor activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon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

REACTION SCHEME 1

General Procedure For Compounds Imd8 And Imd9

Step 1

Accurately weighed quantity of benzoin (2.65 gm), ammonia solution (5 ml) and substituted aldehyde (1.5 ml) were taken and dissolved in 50 ml glacial acetic acid in a 100 ml RBF. The reaction mixture was heated to reflux for 5 hrs on heating mantle with occasionally shaking. After completion of reaction 300 ml cold water was added to reaction mixture which resulted in precipitation of product. The mixture was kept in fridge overnight. The product immediately filtered and neutralized with 5% ammonium solution. The compound was recrystallized and purified from absolute ethanol to yield colourless or pale yellow crystalline compound.



1,2-diphenylethanone

Substituted imidazole derivative

Step 2

Substituted imidazole derivatives (0.5 gm) and freshly prepared benzoyl chloride solution (2.5 ml) were taken in RBF with benzene (30 ml) as a solvent and pyridine (0.5 ml) as a catalyst for 4-5 hours. Completion of reaction was checked by the single spot on TLC. Cool the reaction mixture

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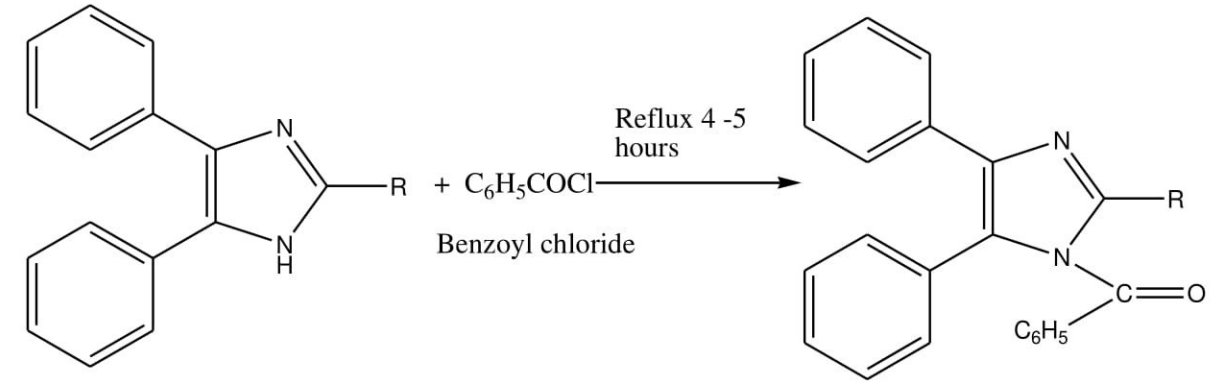
on room temperature and then pour it into the ice water. Shake the mixture well in crushed ice and kept it in cold temperature for overnight. The compounds were isolated and collected by the filtration. Product was recrystallized by ethanol. A coloureless product was obtained.



Substituted imidazole derivative

1,2,4,5-tetra substituted imidazole derivative

Table no. 1. List of various substitutes

Compounds	R
IMD 8	H
IMD 9	CH_3
IMD 10	C_2H_5

Procedure

The petridishes were thoroughly washed and sterilized in hot air oven at 160^{0}C for one hour. Inoculum was added to 30 ml of sterile nutrient agar medium and was poured into sterile petridishes for solidifying. Bores were made on the medium using sterile borer. 0.1ml of test solution was added to

the respective bores, 0.1ml of the Ampicillin at a concentration of 100 µg/ 0.1 ml was taken as standard reference. A control having only DMSO in the cup was maintained in each plate.

The petridishes were kept in the refrigerator at 4^0C for 45 minutes for diffusion to take place. After diffusion, the petridishes were incubated at 37^0C for 24 hour and zones of inhibition were observed and measured using a scale.

Antibacterial activity of all the compounds was carried out against all four microorganisms. The same media was used both for subculturing and for estimating antibacterial activity. All the reading was taken in triplicate and is reported in Standard Error Mean (± SEM).

Antifungal activity

Screening results of antifungal activity showed that synthesized compounds IMD2 possess significant activity against Candida albicans. Remaining derivatives shows moderate antifungal activity. The discussion and comparison of antifungal activity were compared with Fluconazole.

CONCLUSION

Newly synthesized imidazole (1, 3-diaza-2, 4-cyclopentadiene) derivatives were found good antifungal and antibacterial agents. Some of them are promising and need to be further investigated to get better agents. Imidazole is a better nucleus which may be used further for good and improved antimicrobial activity in future. Structures of imidazole derivatives were confirmed by IR, ^{1}H NMR and Mass spectroscopy studies. The results of antimicrobial screening showed that all compounds possess activity against all organisms used.

The compounds show good antibacterial activity against gram negative and gram positive bacteria, respectively. Nitro-imidazoles show activity against only anaerobes bacterias such as Escherichia coli and Staphhylococcus aureus. Other remaining compounds show moderate

activity with reference compound Ampicillin and Fluconazole. Compounds which have halo-substitution show good antifungal activity. As we consider all results obtained from antibacterial and antifungal tests together we can say that all imidazole derivatives tested are active against bacteria and fungi.

REFERENCES

1. Lunt, E., Newton, C.G., Smith, C., Stevens, G.P., Stevens, M.F., Straw, C.G., Walsh, R.J.,
2. Warren, P.J., Fizames, C. and Lavelle, F., 1987. J. Med. Chem., Feb, 30 (2), 357- 66.
3. Neef, G., Eder, U. and Sauer, G.J.,1981.Org. Chem, 46, 2824.
4. Puratchikodya, A. and Doble, M., 2007.Bio-organic & Medicinal Chemistry, 15, 1083–1090.
5. Purohit, M. and Shrivastava, S.K., 1991. Indian J. Pharm. Sci., 53,162.
6. Pandey K, Kali R, Bhalla T.N. and Barthwal J.P., 1987. Pharmazie, 42,269.
7. Pandeya Nath, S.N., 2004. A Text Book of medicinal chemistry, SG publisher, .1(3), 2-3.
8. Robert, C. and Elderfield., 1957, V-5, 744.
9. Ramya, V., Shingalapur, Hosamani, K. M. and Keri, R.S., 2009. European Journal of Medicinal Chemistry, 44, 4244–4248.
10. Sharma, D., Narasimhan, B., Kumar, P., Judge, V., Narang, R., Clercq, E.De. and Balzarini, J., 2009. European Journal of Medicinal Chemistry., 44, 2347–2353.
11. Shin, G.I. and Lee, J.I., 1996. J.H. Kim, Bull. Korean Chem. Soc, 17, 29.
12. Singh, H., and Kapoor, V.K., 2008. Medicinal and Pharmaceutical Chemistry, Vallabh Prakashan,2, 1 -2.
13. S. Baroniya, Z. Anwer, P. K. Sharma, R. Dudhe, N. Kumar.2010, Der Pharmacia Sinica.,1(3), 172-182.