e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:12/December-2023 Impact Factor- 7.868 www.irjmets.com

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF IMIDAZOLE DERIVATIVES

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DOI : https://www.doi.org/10.56726/IRJMETS47512

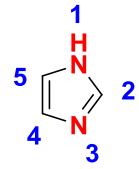
ABSTRACT

Imidazoles play an important role in medicinal chemistry, because many of its derivatives have demonstrated significant biological activity. various imidazole-containing compounds have been tested for their medical usefulness in clinical trials for several disease conditions. The rapid expansion of imidazole-based medicinal chemistry suggests the promising and potential therapeutic values of imidazole-derived compounds for treating incurable diseases. Imidazole core scaffold contains three carbon atoms, and two nitrogen with electronic-rich characteristics that are responsible for readily binding with a variety of enzymes, proteins, and receptors compared to the other heterocyclic rings.

I. INTRODUCTION

IMIDAZOLE -

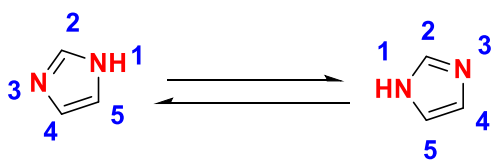
Three carbon, two nitrogen, four hydrogen atoms, and two double bonds make up the five-membered heterocyclic molecule known as imidazole. The name 1, 3-diazole is another one for it. Two nitrogen atoms are present in it; one of them is of the pyrrole type, whereas the other carries a hydrogen atom. Arthur Rudolf Hantzsch (1857–1935) first mentioned imidazole in 1887.



1*H*-imidazole

The chemical compound imidazole has the formula C3H4N2.This aromatic heterocyclic is categorised as an alkaloid and is a "1, 3-diazole." When it was first synthesised using glyoxal and ammonia, it was known as gluoxaline. The 1, 3-diazole demonstrates both basic and acidic characteristics, making it amphoteric in nature. It is a solid that is colorless or white and very soluble in polar solvents like water. Two equivalent tautomeric forms are displayed as a result of a positive charge on one of the nitrogen atoms. Additionally, there are two kinds of lone pairs in the imidazole ring: delocalized and non-delocalized (non-Huckle). This means that the dissociation constants of the two nitrogens in the 1,3-diazole differ. Delocalized lone pairs have a dissociation constant (pKa) of 7 while non-delocalized lone pairs have a pKa of 14.9. The 1,3-diazole ring's amphoteric phenomena renders it susceptible to both electrophilic and nucleophilic assaults.

The initial nitrogen atom of the imidazole ring has an acidic proton on it. The 1,3-diazole ring exhibits two identical tautomeric forms. probably the outcome of a positive charge on either of the two nitrogen atoms. It is an aromatic compound since the ring possesses a sextet of π-electrons. Since the second nitrogen atom is a member of the aromatic sextet, it has unshared pairs of electrons, making the nitrogen atom on the third position in the imidazole ring more reactive to the electrophilic molecule. Imidazole 1 has a 5-membered planar ring that makes it soluble in polar solvents like water. Since the hydrogen atom can be found on either of the two nitrogen atoms, two equivalent tautomeric forms are observed.



Tautomeric forms of imidazole

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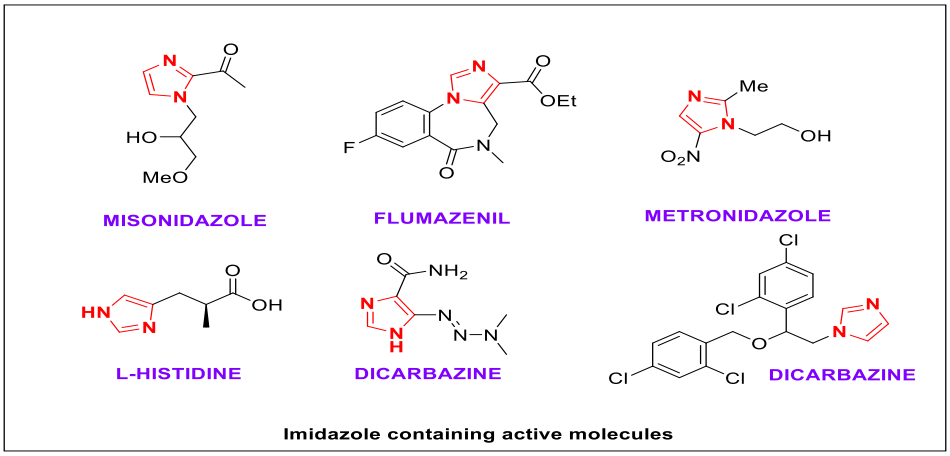
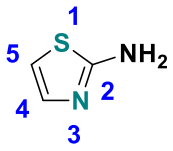
In several modern medications, imidazole has grown in importance. A lot of fungicides, antifungal, antiprotozoal, and antihypertensive medicines contain synthetic imidazoles. Tea leaves and coffee beans include theophylline, a chemical that activates the central nervous system and includes imidazole.



Imidazole containing active molecules

2-AMINO THIAZOLE-



Thiazol-2-amine

2-Aminothiazole (2-AT)is a heterocyclic amine featuring a thiazole core .the amino thaizole molecular formula $C_3H_4N_2S$.It is an important and versatile scaffold which is applied extensively in different branches of chemistry. It can also be considered a cyclic iso thiourea. It possesses an odor similar to pyridine and is soluble in water, alcohols and diethyl ether.2-aminothiazole appears as light brown crystals or brown granular solid. 2-Aminothiazole itself is mainly of academic interest, with few exceptions. Thiazoles are known with wide range of pharmacological activities. 2-ATs are used as bioactive core unit by medicinal chemists in modern drug discovery research. Several drugs containing 2-AT core, have been launched in the market. 2-Aminothiazoles (2-ATs) are known with antimicrobial, antibacterial and antifungal activity. Many researchers have recently explored the potential of the 2-AT core in different therapeutic areas.

ISO CYANIDES

Isocyanide is the most strange, fascinating, and unique functional group in organic chemistry. Its chameleonic nature allows its carbon atom to be the subject of almost all reactivities in organic chemistry. Indeed, it can act as a nucleophile attacking activated electrophiles, as an electrophile being intercepted by different nucleophiles, as a carbine involved in formal [4 + 1] cycloaddition, and as a radical acceptor to form imidoyl radical reaction intermediates.6,7 Finally, the presence of a lone pair on the terminal carbon atom accounts for its strong metal coordinative properties, which allow for the formation of an infinite number of coordination complexes. An isocyanide is an organic molecule containing a carbon-nitrogen triple bond and an alkyl or aryl group attached to the nitrogen. They have two resonance structures: one with a triple bond between carbon and nitrogen and one with a double bond between carbon and nitrogen. Although tests demonstrate that the structure with the carbon-nitrogen double bond contributes more to the resonance, the second structure is also required due to the linearity of the carbon-nitrogen bond angle (which is close to 180 degrees).

ANTI FUNGAL

Fungal infections pose a continuous and serious threat to human health and life. These fungal infections in humans can be classified into (a) allergic reactions to fungal proteins, (b) toxic reactions to toxins present in certain fungi and (c) infections (mycoses). Healthy individuals are susceptible to a host of superficial,

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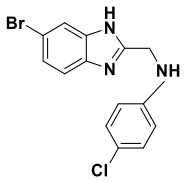
cutaneous, subcutaneous and in certain instances, systemic infections that cause a variety of conditions ranging from Athletes foot and nail infections to severe life-threatening disseminated disease (e.g., histoplasmosis). Many fungal infections are caused by opportunistic pathogens that may be endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections). the other type of fungal infection, that is, invasive fungal infections and dermatomycoses produced by fungal organisms in the individuals with increased vulnerability such as neonates, cancer patients receiving chemotherapy, organ transplant patients, and burns patients, apart from those with acquired immunodeficiency syndrome (AIDS). Other risk factors include corticosteroid and antibiotic treatments, diabetes, lesions of epidermis and dermis, malnutrition, neutropenia and surgery.

Currently, four antifungal drug classes are used by clinicians and veterinarians for systemic treatment. These classes target different parts of the fungal cell. First, the polyene class includes the heptaene amphotericin B (AMB), which interacts with ergosterol, the major part of the fungal cell membrane. AMB is highly fungicidal against Candida genera and Aspergillus fumigatus and A. flavus . Second, first- and second-generation of triazoles disrupt the ergosterol biosynthesis in the lanosterol demethylation step. Generally, triazoles exhibit the fungistatic effect against yeasts but are fungicidal for Aspergillus spp. Echinocandins block the synthesis of β-D-glucans located in the fungal cell wall. Echinocandins are fungicidal and fungistatic against Candida and Aspergillus spp., respectively . Finally, the pyrimidine analogue flucytosine (5-FC) interacts at the nucleus level of the fungus, affecting protein and deoxyribonucleic acid (DNA) biosynthesis.

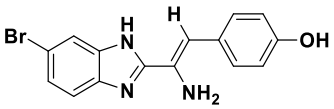
II. LITERATURE REVIEW

1. Kavitha c.s, determined that a number of 2-methylaminibenzimidazole derivatives and recently developed medications were examined for their anti-inflammatory and anti-analgesic properties. These compounds' analgesic efficacy in comparison to the typical nimesulide medication.



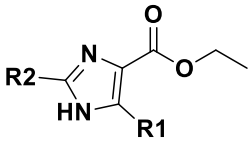
N-((6-bromo-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-chloroaniline

2. Ramya v.,unveiled a novel series of 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and conducted tests on their ability to inhibit the growth of Aspergillus fumigates and Candida albicans as well as the bacteria Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia, and Enterococcus faecalis. Using ciprofloxacin as the standard medication, this was compared.



(*Z*)-4-(2-amino-2-(6-bromo-1*H*-benzo[*d*]imidazol-2-yl)vinyl)phenol

3. Preeti Gupt highlight the ability of 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives and substituted ring -1H-imidazole-4-carboxylic acid derivatives to inhibit the growth of M. tuberculosis strains that are durg-resistent and durg-senseful. The most effective compounds as drugs were discovered to be 2f and 2h.



$R_1=R_2=C_5H_9$
$R_1=R_2=C_6H_{11}$

4. Moura and Xiaoyun Lu., When the 4-(2,6-dichlorobenzyloxy) phenylimidazoles and their derivatives were tested for anti-tuberculosis activities against the Mycobacterium tuberculosis H37Rv using the microplate

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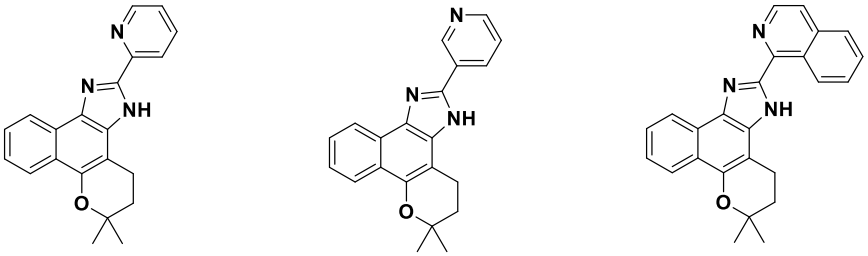
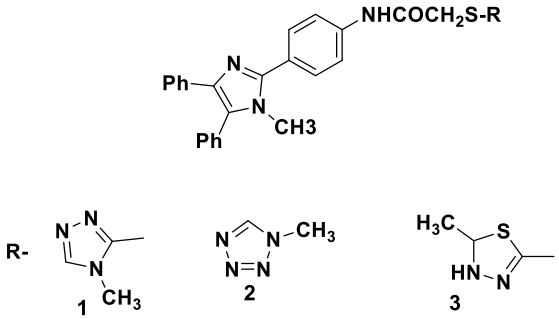
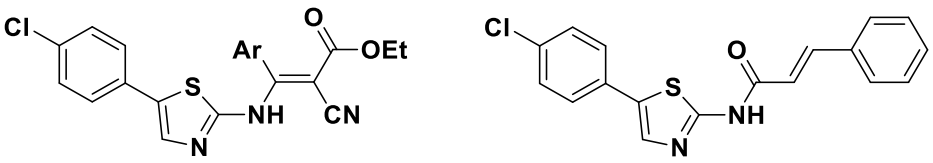
alamar blue assay (MABA), it was discovered that the compounds had good activities. Beginning with the beta-lapachone, Moura et al. (2012) synthesised the naphthoimidazoles (18–21). The M. tuberculosis H37Rv (pansusceptible), rifampicin-resistant (RIFr, ATCC 35338), and isoniazid-resistant (INHr, ATCC 35822) bacterial strains were tested for TB analysis using these compounds. Among them, the compounds with imidazole units demonstrated good to moderate activity against these strains.



5. Altindag, Firuze Diyar.**,**To counter the rising prevalence of drug-resistant fungal infections, Altindag, Firuze Diyar et al. (Anadolu University, Turkey) developed and synthesised a series of 2-(substituted dithiocarbamoyl)-N-[4-((1H-imidazol-1-yl)methyl)phenyl] acetamide derivatives in 2019. The activity of the cytochrome-dependent enzyme P450, lanosterol-14a-demethylase, was investigated using the molecular docking method. Additionally, ADME studies were conducted, and a link between the compounds' physicochemical characteristics and activity was established. The majority of the compounds had significant activity against Candida albicans and Candida krusei, according to the findings of in vitro anti-candida activity studies, docking studies, and ADME predictions.

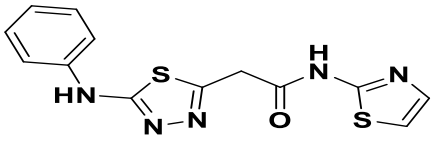


6. Bakare et al., 2019, synthesized a series of 2-(substituted) amino-1,3-thiazole derivatives and evaluated for anticancer activity. Among them, two were proved to be most potent derivatives.



a: Ar = 4-OH-Ph
b: Ar = 4-OCH_3-Ph

7. Abdel-Wahab et al., 2008, synthesized and evaluated thiazolylmalonamide, tetrachloroisoindolylimide, and triazole derivatives, for antihypertensive activity. Among the synthesized compounds many compounds showed good activity compared to the standard drug Minoxidil. These compounds were also investigated for acute toxicity study. Within these series, compound **22** showed good activity with low toxicity.



22

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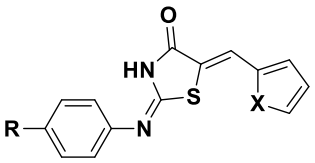
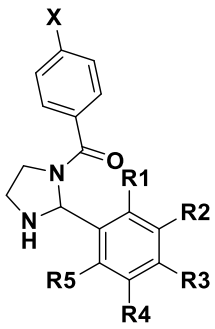
8. Patel et al.,2020, synthesized series of thiazolidin-4-one derivatives and evaluated for PTP1B inhibitory activity. Among all the compounds, 6 compounds have shown potent inhibitory activity.



a: X = S; R = CH_3
b: X = S; R = NO2
c: X = S; R = Cl
d: X = O; R = CH_3
e: X = S; R = NO_2
f: X = NH; R = NO_2

9. . Deepika Sharma., investigated the antimicrobial activity of 2-(substituted phenyl)-1H-imidazole and 2-(substituted phenyl)-imidazol-1-yl]-menthanone against gramme positive, gramme negative, and fungal species. Norfloxacin was the reference medication.



1.) R_1-Cl , R_2-H, R_3-H, R_4-H, R_5-H, X-4-NO2
2.) R_2-COOH, R_2-H, R_3-H, R_4-H, R_5H, X-NO2
3.) R_1-H, R_2-H, R_3-Cl, R_4-H, R_5-H, X-Br

10..Koushik Mukherjee.,The University of Kalyani in India's Koushik Mukherjee et al. investigated the anti-tuberculosis drug-producing properties of some imidazole and piperidine derivatives against Mycobacterium smegmatis in 2020. The compounds that inhibited M. smegmatis the best among those studied were benzyl 1H-imidazole-1-carbodithioate and allyl piperidine-1-carbodithioate. With minimal cytotoxicity, they improved the combined effects of isoniazid and rifampicin. Research examined the efficaciousness of these two compounds in combating dormant mycobacteria.

PLAN OF WORK

1. i) Synthesis of 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile
   ii) Synthesis of Thiazole amine coupled Imidazole
2. Synthesis of Benzyl bromide coupled 4-chloro-5-(p-tolyl)-1H- imidazole
3. Subsequent synthesis of Urea coupled Imidazole Derivatives

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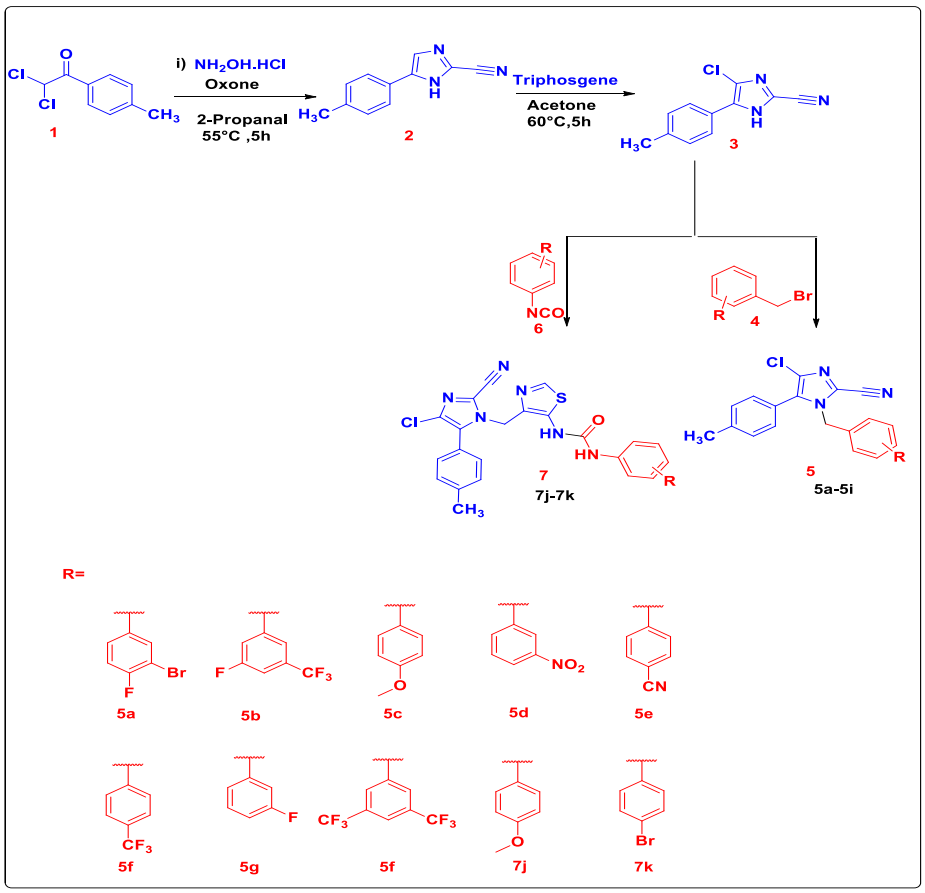
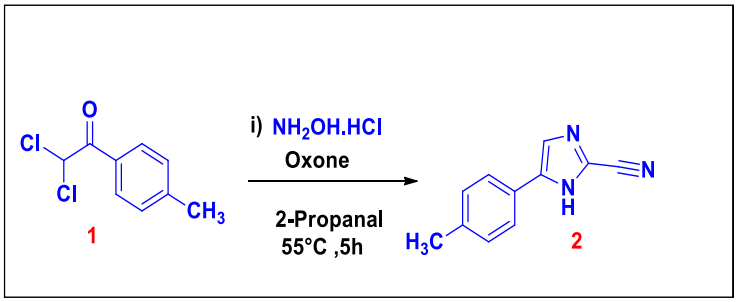


i) Synthesis of 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile

a) Synthesis of 5-(p-tolyl)-1H-imidazole-2-carbonitrile:

A mixture of 2,2-dichloro-1-(p-tolyl)ethanone (1.0 equiv), Hydroxylamine hydro chloride(**2)** (1.2equiv), Oxone and Isopropanol was stirred at 55^{0}C under an inert atmosphere, after 5min a clear solution was observed. Then after 30min the solution turned solid and it was further stirred 5 hours. The reaction was monitored through TLC. After completion, the reaction mixture was cooled to -5^{0}C and the product was isolated by Filtration, washed with cold Acetone(10ml) and dried under vacuum to afford the titled compound 5-(p-tolyl)-1H-imidazole-2-carbonitrile (**3**) as a White Solid.



b) Synthesis of 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile:

A mixture of 5-(p-tolyl)-1H-imidazole-2-carbonitrile (1.0 equiv), Triphosgene(**2)** (1.2equiv), and Acetone was stirred at 60^{0}C under an inert atmosphere, after 5min a clear solution was observed. Then after 30min the solution turned solid and it was further stirred 5 hours. The reaction was monitored through TLC. After completion, the reaction mixture was cooled to -5^{0}C and the product was isolated by Filtration, washed with cold Acetone(10ml) and dried under vacuum to afford the titled compound 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile (**3**) as a White Solid.

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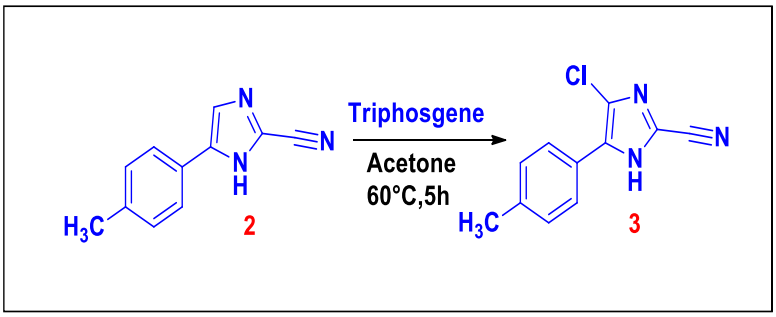
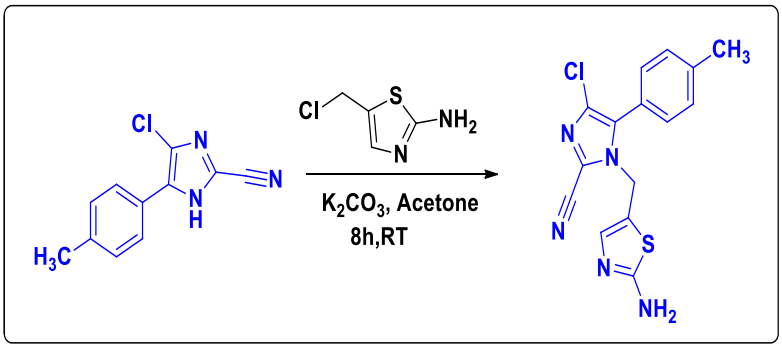


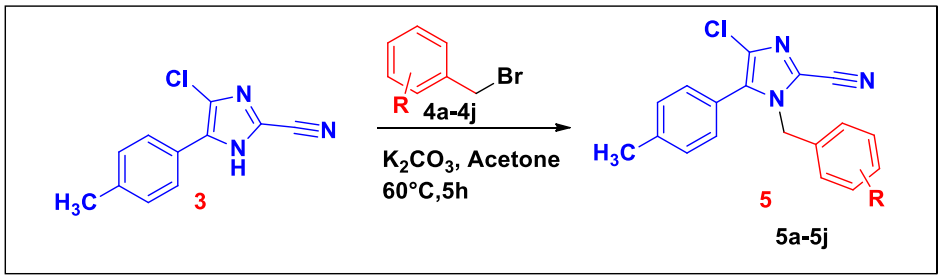
ii) Synthesis of Thiazole amine coupled Imidazole:

To the solution of N- demethylated Imidazole (7gm, 17.54mmol) in acetone (80ml), was added potassium carbonate (7.1 gm, 52.5mmol), and 4-(chloromethyl)thiazol-2-amine (3.8gm, 26.14mmol) and stirred at room temperature (RT) for 4hrs. Crude reaction mixture was then filtered, the filtrate was evaporated under vacuum, extracted with DCM, dried over anhydrous Na_2SO_4 and again evaporated under reduced pressure. The residue thus obtained was chromatographed over triethyl amine treated silica gel column eluting with Hexane: Ethyl acetate (30:70) gave **3,** as apale-yellowsolid with a yield of60%.



2. Synthesis of Benzyl bromide coupled 4-chloro-5-(p-tolyl)-1H imidazole:

To a solution of **4 (a-j)**(81.1 mmol)in Acetone (80ml),K_2CO_3(101.3 mmol) was added and stirred for 5mins and to which 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile **3** (10g, 67.6 mmol) and refluxed for 5h.Progress of the reaction was monitored through TLC. After completion, the reaction mixture was cooled to room temperature and filtered with celite pad. The filtrate was evaporated under vacuum. Water (25 mL) was added and extracted with ethyl acetate(2 × 45 mL). The combined organic layer were dried with anhydrous Na_2SO_4 and then concentrated. And the crude residue thus obtained was purified over silica gel column chromatography, eluted with Hexane: Ethyl Acetate (7:3) to give **5(a-j)**, yield (74-84%).



3. Subsequent synthesis of Urea coupled Imidazole Derivatives:

On an ice-bath having 0°C, placed a mixture of Imidazole coupledthiazole amine (0.39mmol) and isocyanate (j-k), to this DCM (5ml) was added and stirred. After 30mins, the ice-bath was removed and the reaction was continued at RT under N_2 atmosphere for 12hrs. After completion, the workup was performed with DCM and H_2O, dried with anhydrous Na_2SO_4 and was concentrated under vacuum. The crude residue was purified by column chromatography using Hexane:Ethyl acetate as elutants to give (7j-k), the titled urea derivatives of imidazole.

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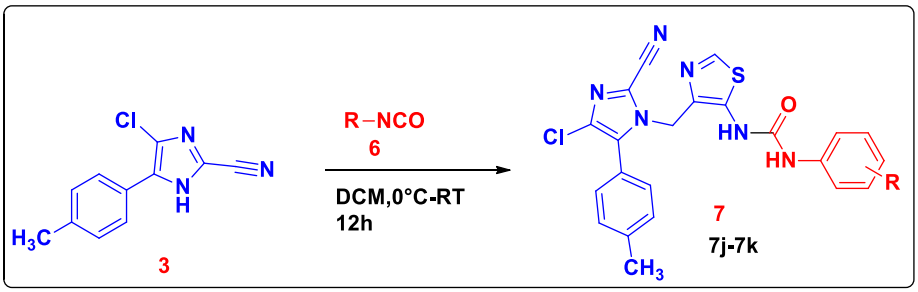
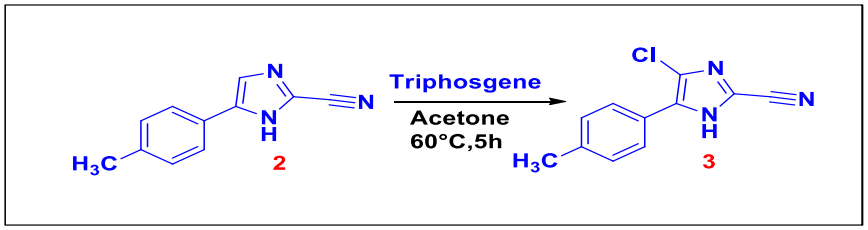


III. EXPERIMENTAL PROCEDURE

Preparation of 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile(3):

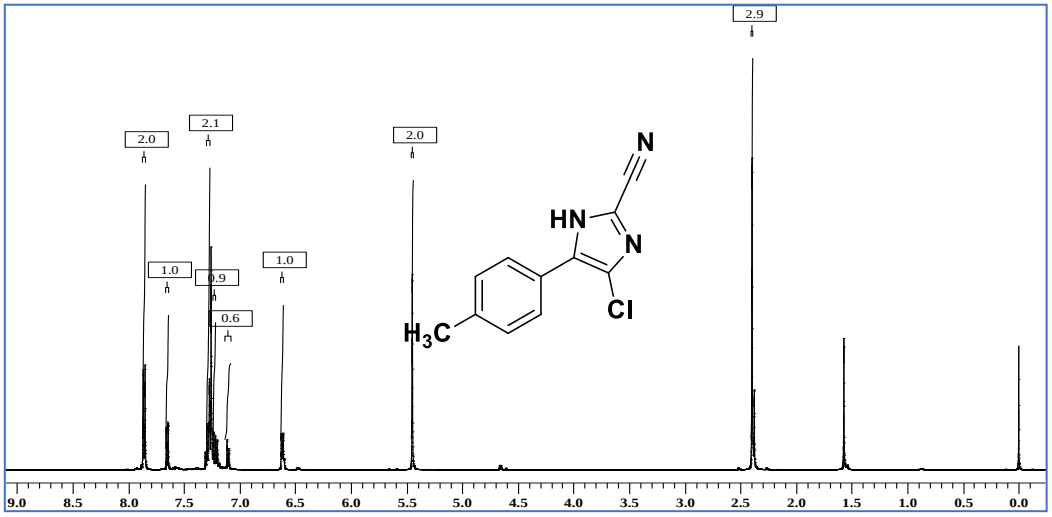


A mixture of 5-(p-tolyl)-1H-imidazole-2-carbonitrile (1.0 equiv), Triphosgene(**2**) (1.2equiv), and Acetone was stirred at 60^{0}C under an inert atmosphere, after 5min a clear solution was observed. Then after 30min the solution turned solid and it was further stirred 5 hours. The reaction was monitored through TLC. After completion, the reaction mixture was cooled to -5^{0}C and the product was isolated by Filtration, washed with cold Acetone(10ml) and dried under vacuum to afford the titled compound 4-chloro-5-(p-tolyl)-1H-imidazole-2-carbonitrile(**3**) as a White Solid (87% yield).

Molecular Formula	:	C11H8ClN3
Molecular Weight	:	217
Yield	:	87%
Melting point	:	141-143^{o}C
H NMR (500 MHz, $CDCl_3$)	:	δ 11.32 (s, 1H), 7.58 (d, J= 8.2 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H)
^{13}C NMR (500 MHz, $CDCl_3$)	:	δ 170.61, 135.97, 108.42, 37.63.
ESI-MS (m/z)	:	218

IV. RESULT AND DICUSSION

SPECTRAL DATA



H^1 Nmr Of 4-Chloro-5-(P-Tolyl)-1h-Imidazole-2-Carbonitrile

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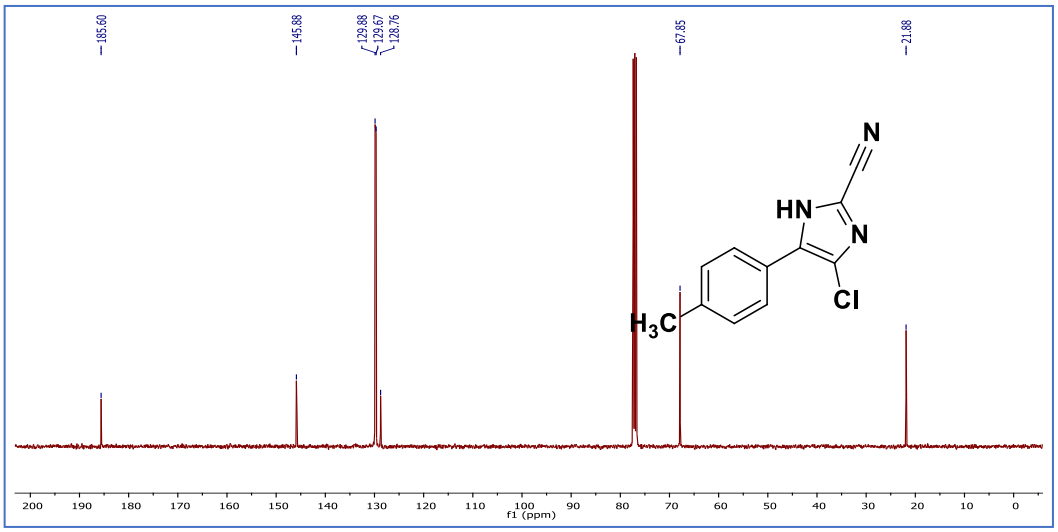
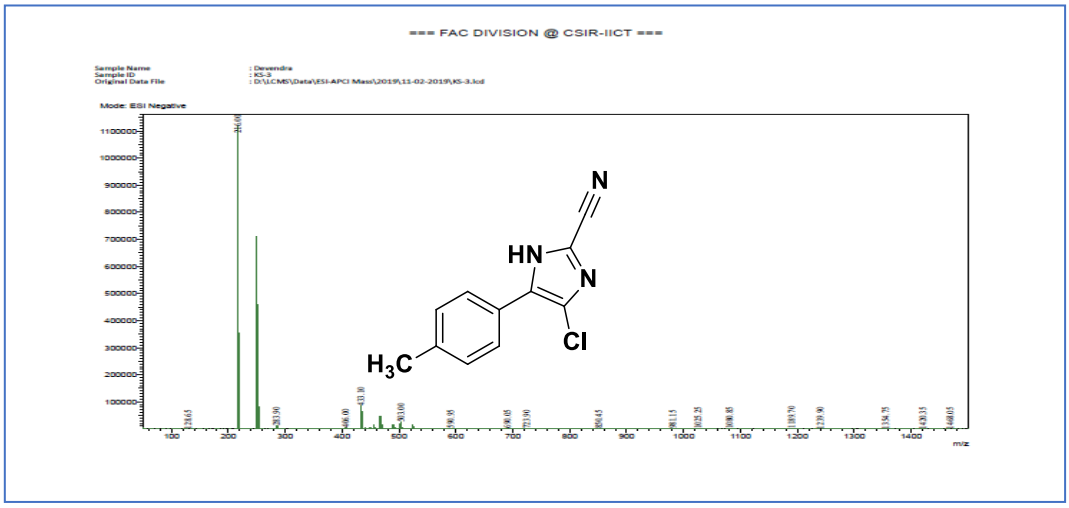
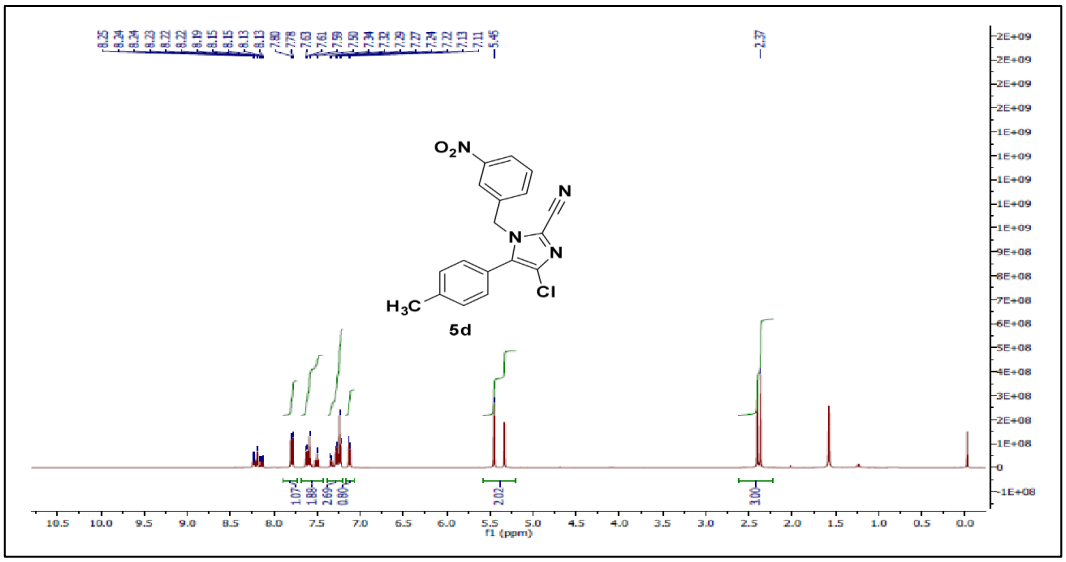


C^{13} Of 4-Chloro-5-(P-Tolyl)-1h-Imidazole-2-Carbonitrile



Lc-Ms Of 4-Chloro-5-(P-Tolyl)-1h-Imidazole-2-Carbonitrile



H1 NMR spectra of 5d compound

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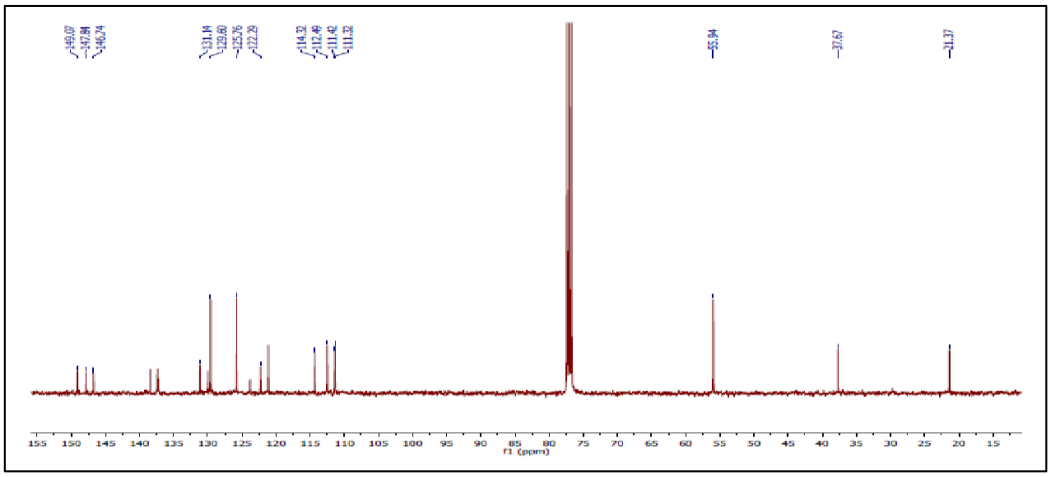
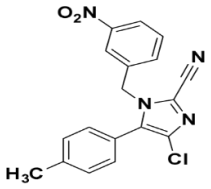
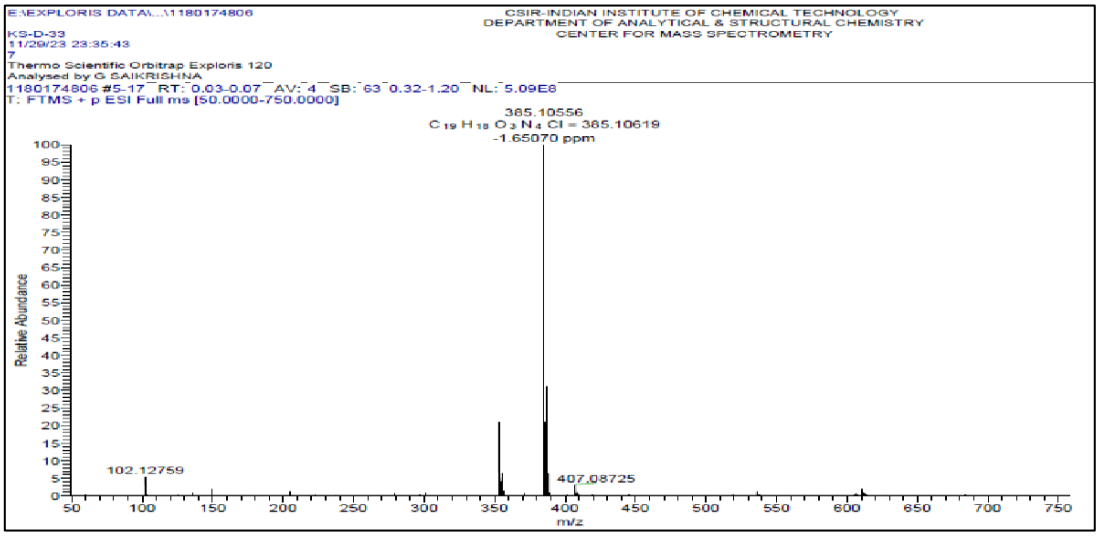
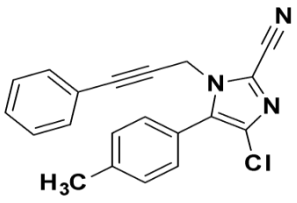


C13 NMR spectra of 5d compound



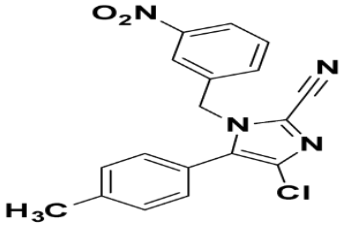
5d





5i

HRMS of 5d compound



5d

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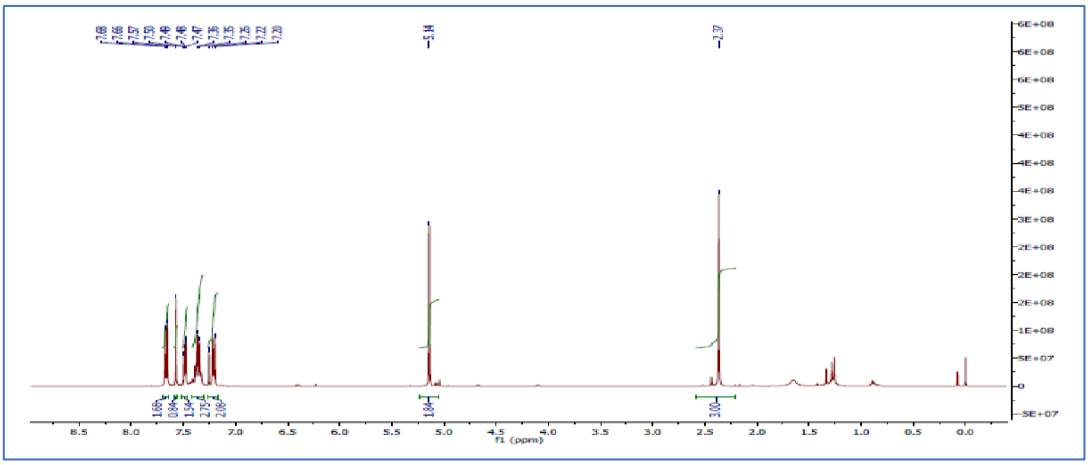
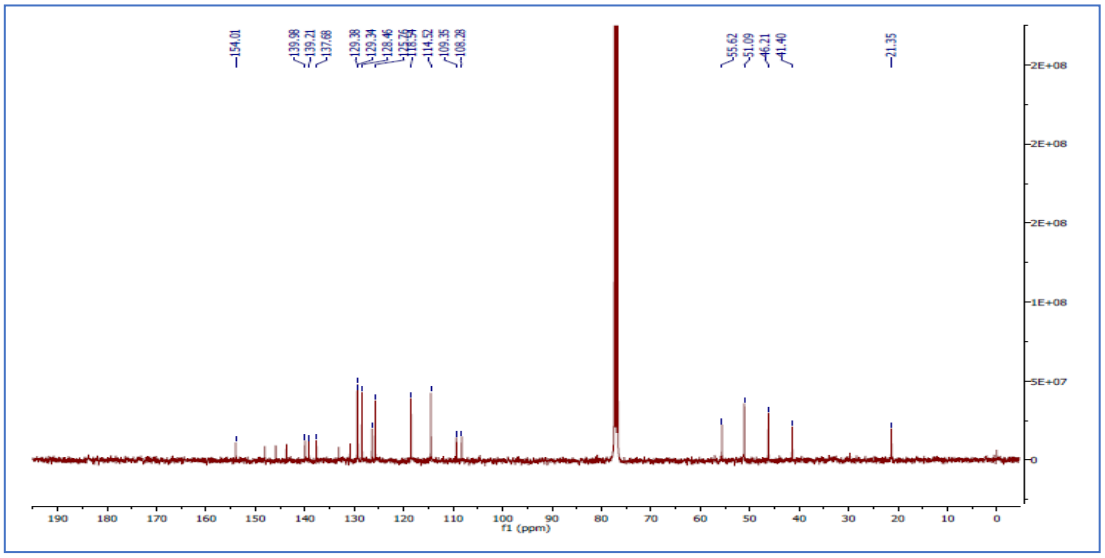
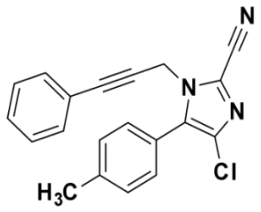


H1 NMR of 5i compound

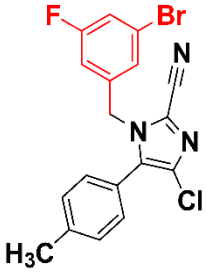




5i

C13 NMR spectra of 5i compound

Physical data of synthesised compounds

S NO	Compound	Molecular Formula	Molecular Weight	M.P (°C)	Yield%
1		$C_{13}H_{22}N_4O_2S$	402	141-143	78

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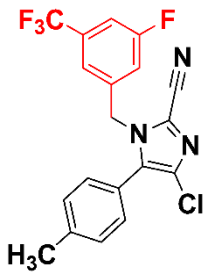
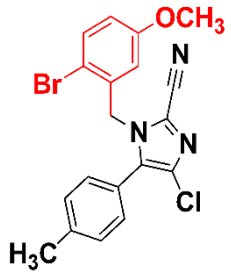
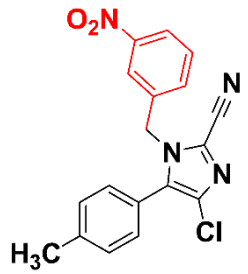
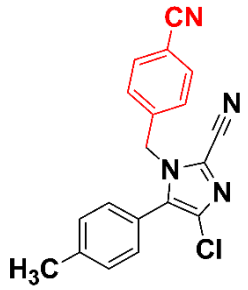
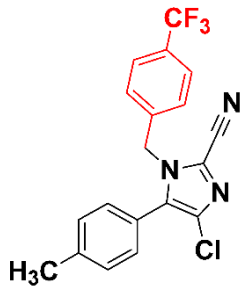
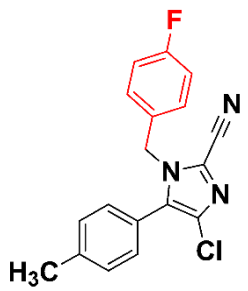
2		C14H17FN4S	393	175-177	81
3		C19H15BrClN3O	415	120-122	76
4		C18H13ClN4O2	352	108-110	85
5		C19H13ClN4	332	162-164	79
6		C19H13ClF3N3	375	207-209	82
7		C18H13ClFN3	325	110-112	85

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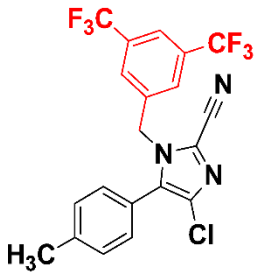
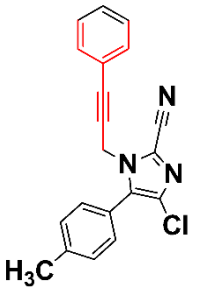
8		C20H12ClF6N3	443	203-205	79
9		C20H14ClN3	331	203-205	80

BIOLOGICAL DATA

The synthesised compounds where given for their anti-fungal activity and anti-microbial activity The well diffusion method was used to test the antifungal activity of synthesised derivatives against Candida albicans, Candida glabrata The compounds were dissolved in DMSO at the 200 mg/ml concentration, The results showed that, among synthesised derivatives two compounds that is **5d** and **5i** showed very low to high broad-spectrum antifungal activity. These compound demonstrating potent antifungal activity among tested strains which is almost equal to clotrimazole.

Anti-fungal activity of synthesised derivatives-

S.no	Sample code	Zone of inhibition in (mm) at 1mg /ml		
		Candida albicus	Candida gloabrata	Aspergillus niger
1	5a	7	8	7
2	5b	11	12	11
3	5c	10	10	10
4	5d	7	7	7
5	5e	8	11	10
6	5f	7	11	7
7	5g	11	13	11
8	5h	19	19	19
9	5i	NA	NA	NA
Standard	**Clotrimazole**	**20**	**19**	**20**

V. CONCLUSION

The increasing impact of fungal infections on society is mainly due to the increasing population of patients at risk, as well as the rather limited armory of antifungal agents and resistance development. Therefore, there is a critical need for the identification and development of new antifungal agents, or antifungal combination therapies, particularly those that are also active against fungal biofilms and do not suffer from resistance development. To accomplish this, a set of standardized, simple guidelines describing the appropriate methods to assess the performance of novel antifungal and/or antibiofilm agents is warranted. Consistent with the

recent emphasis on preventing infections, many efforts are focused on developing antibiofilm coatings for medical devices such as catheters and implants. Thus, standardized testing of such materials is of considerable importance. In this the study emphasis that the imidazole containing derivatives are having most anti fungal activity. At the end I want to emphasize that When testing the antifungal activity of a novel antifungal agent, relative to standard clotrimazoles, we defined the synthesied derivative 5i and 5d are having good anti fungal activity.

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