China Petroleum Processing and Petrochemical Technology

Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378

A REVIEW ON BIOLOGICAL ACTIVITIES IMIDAZOLE CONTAINING COMPOUNDS

[1]Mohd Khursheed, [2]Preeti Yadav, [3]Dr.Rustam Ekbbal, [4]Aditya Vikram Jain and [5]Himanchal Sharma

IIMT College of Medical Sciences, IIMT University Meerut

Email Id: mdkhursheed646@gmail.com

Abstract

Imidazole is a four-membered heterocyclic moiety made up of two double bonds, three carbon atoms, two nitrogen atoms, and four hydrogen atoms. Another name for it is 1, 3-diazole. It has two nitrogen atoms, one of which bears a hydrogen atom and the other of which is referred to as pyrrole type nitrogen. In 1887, Arthur Rudolf Hantzsch (1857–1935) reported the term imidazole. Since 1, 3-diazole exhibits both acidic and basic properties, it is an amphoteric compound. It is a white or colorless solid that dissolves readily in polar solvents like water. It exhibits two equivalent tautomeric forms because one of the two nitrogen atoms has a positive charge. Because glyoxal and ammonia were used in its first synthesis, Imidazoles was initially known as glyoxalin. It serves as the fundamental building block of many natural products, including DNA-based structures, histamine, purines, and histamine. Due to its wide spectrum of chemical and biological properties, Imidazoles is one of the several heterocyclic compounds that were better known. Imidazole has grown to be a significant drug development synthon. According to reports in the literature, the 1, 3-diazole derivatives exhibit a variety of biological activities, including antibacterial, antifungal, and Anti-tubercular Activity. The pharmacological actions of a few imidazole derivatives as well as a few other types of synthetic pathways were summarized in this review.

Keywords: 1, 3-diazole, Antibacterial, Anti-tubercular and Antifungal

Introduction:

The amino acid histidine, vitamin B12, a component of DNA base structure, and purines, histamine, and biotin are among the well-known components of human creatures that have an imidazole nucleus as their primary structural component. Cimetidine, azomycin, and metronidazole are a few examples of natural or manufactured medicine compounds that contain it. Drugs containing imidazole have a wider range of applications in treating different clinical conditions [1].

Heinrich Debus created imidazole for the first time in 1858, but several imidazole derivatives had already been found by the 1840s. In his synthesis, imidazole was created by combining glyoxal and formaldehyde with ammonia [2].

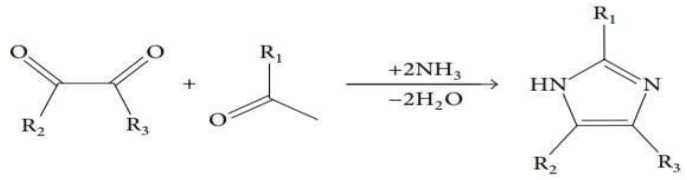
Despite having very low yields, this synthesis is nevertheless employed to make C-substituted imidazoles (see Scheme 1).

Imidazole is a five-membered planar ring that is soluble in polar solvents such as water. Because the hydrogen atom can be found on either of the two nitrogen atoms, it can exist in two identical tautomeric forms. Imidazole is completely soluble in water and is a strongly polar molecule with an estimated dipole of 3.61D. Amphoteric imidazole is what is, it can function as both an acid and

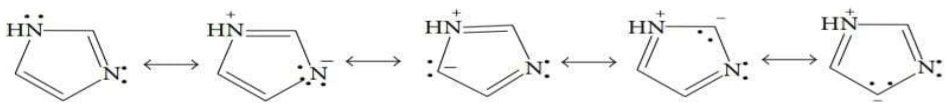
Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378

a base. The compound is classified as aromatic due to the presence of a sextet of π- electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Some resonance structures of imidazole are shown in Scheme 2. Medicinal chemistry concerns with the discovery, development, interpretation, and identification of the mechanism of action of biologically active compounds at the molecular level [3].

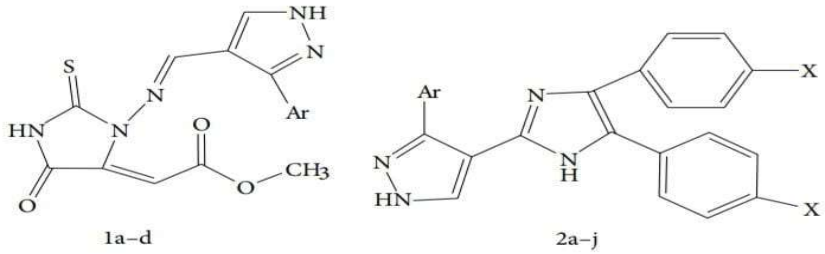
Pharmacological Activities Imidazoles are well-known heterocyclic compounds which are common and have an important feature of a variety of medicinal agents. On the basis of various literature surveys, imidazole derivatives show various pharmacological activities [4].



SCHEME 1



SCHEME 2

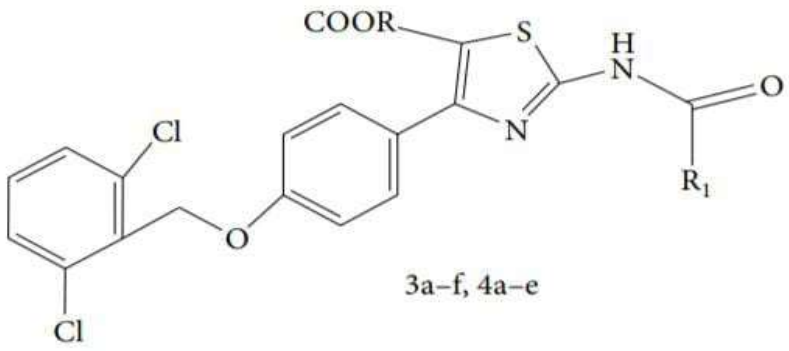


1a–d 2a–j

Antibacterial Activity:

Vijesh et al. carried out the in vitro antibacterial activityof newly synthesized compounds 1a–d and 2a–j. Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhimvrium, Clostridium perfringens, and Pseudomonas aeruginosa were used to investigate the activity. The antibacterial screening revealed that some of the tested compoundsshowed good inhibition against various tested microbialstrains. 1c showed excellent activity against P. aeruginosa and C. perfringens compared to standard drug streptomycin [5]. (see Scheme 3). A series of substituted 4-(2, 6-dichlorobenzyloxy) phenyl thiazole, oxazole, and imidazole derivatives (3a–f, 4a–e) were synthesized by Lu et al. The derivatives were screened for in vitro antibacterial activity against S. aureus, E. coli, S. pneumonia, and penicillin-resistant S. pneumonia [6-8] (see Scheme 4-6).

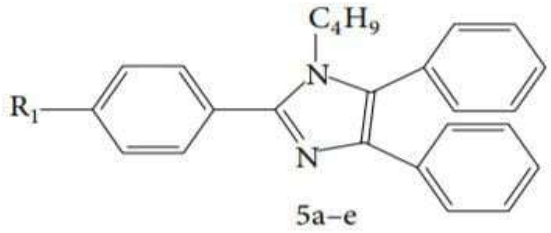
Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378



3a–f, 4a–e

	R	R_1
3a	Et	Ph
4a	H	Ph
3b	Et	4-Cl-Ph
4b	H	4-Cl-Ph
3c	Et	2,4-Cl-Ph
4c	H	2,4-Cl-Ph
3d	Et	4-CH_3O-Ph
4d	H	4-CH_3O-Ph
3e	Et	*n*-Pr
4e	H	*n*-Pr
3f	Et	Ethylene

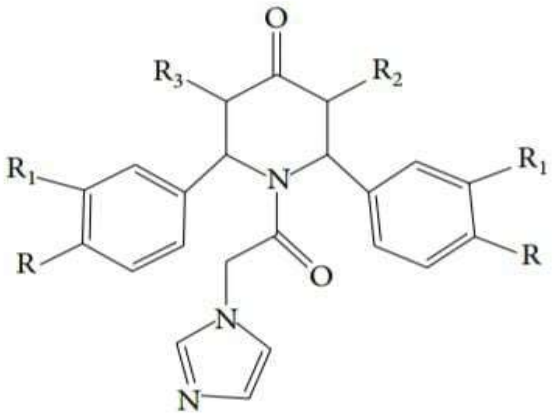
SCHEME 4



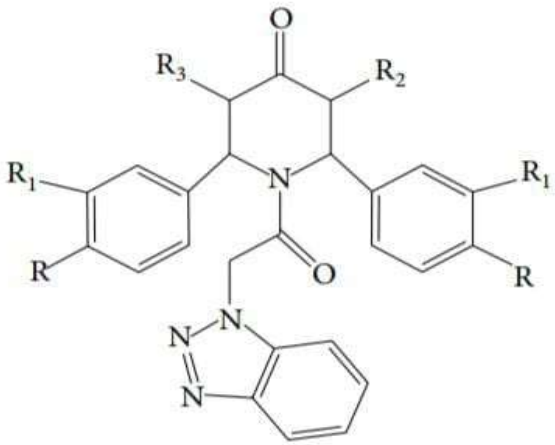
5a–e

5a-*p*-NO_2
5b-*m*-NO_2
5c-*p*-Cl
5d-*o*-Cl
5e-*m*-Br

SCHEME 5



6–11



12–15

Compounds	R	R_1	R_2	R_3
6	H	H	CH_3	H
7	H	H	CH_3	H
8	H	H	$CH(CH_3)_2$	H
9	H	H	CH_3	CH_3
10	F	H	CH_3	CH_3
11	H	OCH_3	CH_3	CH_3
12	F	H	CH_3	CH_3
13	H	F	CH_3	CH_3
14	H	OCH_3	CH_3	CH_3
15	H	F	CH_2CH_3	H

SCHEME 6

idazole derivatives. and evaluate their antibacterial activity. All the synthesized compounds were evaluated for antibacterial activity against S. aureus, B. subtilis, and E. coli. Out of 5a–e only 5a and 5b showed some short of activity but none of them had considerable activity compared with that of the standard (see Scheme 5) [9].

Ramachandran et al. synthesized imidazole/benzotriazole substituted piperidin-4-one derivatives. Compounds 6–15 were screened for their in vitro antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Salmonella typhi, Escherichia coli, and Klebsiella pneumonia. Among the compounds, 7 and 10 against B. subtilis, 9 against S. aureus, 8 and 13 against K. pneumonia, and 15 against E. coli did not show any inhibitory activity even at maximum concentration. However, piperidine ring containing compounds 8 against B. subtilis and 9 against E. coli explored good inhibitory activity. Compound 13 increased the growth inhibition activity against E. coli. And compound 15 showed superior inhibition activity against B. subtilis (see Scheme 6) [10].

5. Antitubercular Activity Lu et al. synthesised a series of substituted 4-(2, 6-dichlorobenzyloxy) phenyl thiazole, oxazole and imidazole derivatives. The derivatives were screened forin vitro Antitubercular activities against Mycobacterium tuberculosis H37Rv (see Scheme 12) [11].

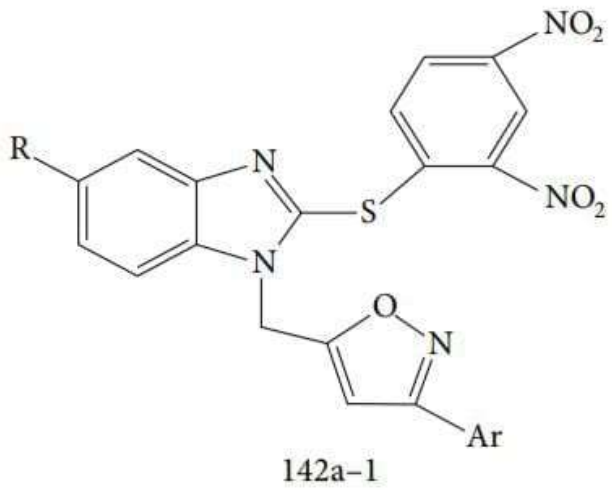
Lee et al. synthesised monocyclic nitroimidazole derivatives, and the anti-tubercular activity of the synthesized compounds against Mtb H37Rv was determined by the microdilution Alamar blue assay. Compounds 89a, 89b, and 89d were moderately active. In case of 90a, 90d, 90e, and 90g, the activity was increased 4-fold, compared with 89b, 89e, 89f, and 89g, respectively. While 90c and 90h were 8-fold more active than 89d and 89h, respectively, 90b was 16-fold more active than 90c (see Scheme 13) [12].

Alegaon et al. synthesized imidazo [2, 1-b] [1, 3, 4] thiadiazole derivatives, and the anti-tubercular activities have been assessed against M. tuberculosis H37Rv (ATCC 27294) and found that compounds (91, 92a, 92b, 92c, 92d, 93a, 93b, 93c, 93d, and 93e) are active against M. tuberculosis (see Scheme 14) [13].

According to Fassihi et al. a series of 4-substituted imidazolyl-2, 6-dimethyl-N3,N5-bisaryl-1,4-dihydropyridine-3, 5- dicarboxamides (94a–j) were prepared and tested in vitro against M. tuberculosis H37RV strain ATCC 27294 which is susceptible to rifampicin and isoniazid (see Scheme 15) [14].

According to Zampieri et al. a series of 1-(3, 5-diaryl-4, 5- dihydro-1H-pyrazol-4-yl)-1H-imidazole and 1-[(1-aralkyl) - 3, 5-diaryl-4, 5-dihydro-1H-pyrazol-4-yl]-1H-imidazole derivatives were synthesized and evaluated for anti-mycobacterial activities. Compounds 95a–t were tested against a strain of M. tuberculosis H37Rv and showed a good anti-mycobacterial activity (see Scheme 16) [15].

Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378



142a–1

Compounds	R	Ar
a	H	4-$OCH_3C_6H_4$
b	H	4-FC_6H_4
c	H	4-CNC_6H_4
d	Br	4-$OCH_3C_6H_4$
e	Br	4-FC_6H_4
f	Br	4-CNC_6H_4
g	OCH_3	4-$OCH_3C_6H_4$
h	OCH_3	4-FC_6H_4
i	OCH_3	4-CNC_6H_4
j	NO_2	4-$OCH_3C_6H_4$
k	NO_2	4-FC_6H_4
l	NO_2	4-CNC_6H_4

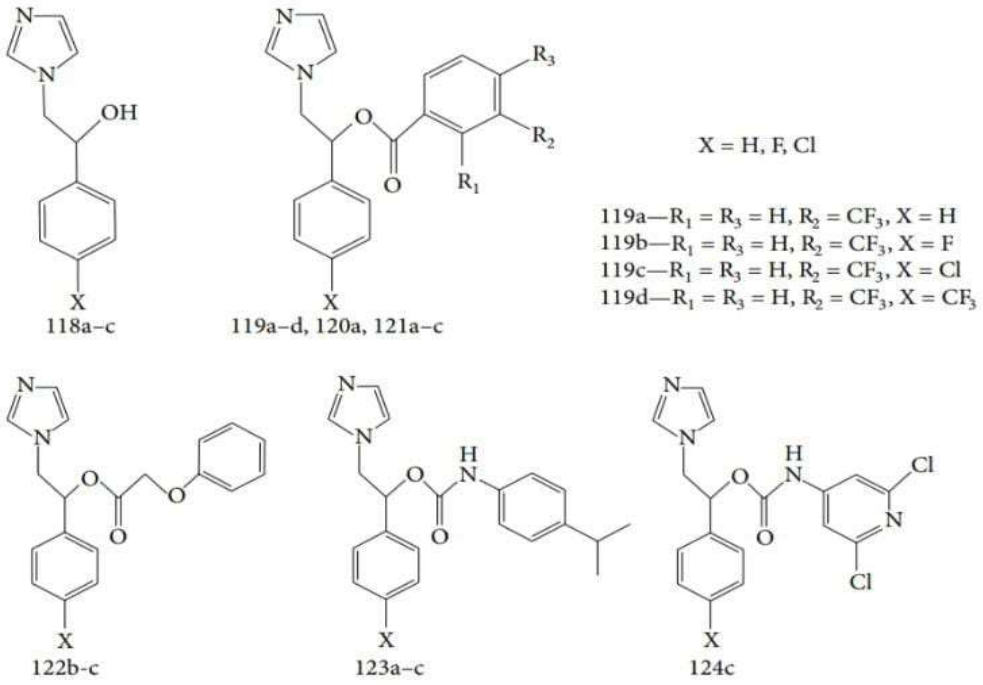
Antifungal Activities:

The fungicidal activities of several N-cyano-1H-imidazole-4-carboxamide derivatives were examined against six different fungi at a concentration of 50 lg/ml, including Fusarium oxysporum, Rhizoctonia solani, Botrytis cinerea Pers, Gibberella zeae, Dothiorella gregaria, and Colletotrichum gossypii. Among the six examined fungi, the newly synthesized compounds have good antifungal activity specifically against Rhizoctonia solani. With an EC50 of 2.63 lg/ml against R. Solani, compound 117h in particular was shown to be the most promising candidate (see Scheme 19). [16]. Vita et al. tested the in vitro antifungal activity of the imidazole derivatives 118a-c, 119a-d, 120a, 121a-c, 122b-c, 123a-c, and 124c against seven strains of Candida species and four strains of Candida albicans (see Scheme 20). A. niger, C. neoformans, Rhizopus sp., C. albicans, and A. Flavus were tested for their ability to inhibit the growth of fungi by Ramachandran et al. (see Scheme 21). N-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)(aryl)amides (135a-l) were synthesized by Desai et al. At different doses, the substances were evaluated in six sets for their ability to inhibit the growth of Candida albicans, Aspergillus niger, and Aspergillus clavatus. A substantial amount of potency against various microbial strains was demonstrated by compounds 135c, 135d, 135f, 135h, and 135j among them (see Scheme 22). For their antifungal efficacy against Aspergillus flavus, Aspergillus niger, Candida albicans, Microsporum gypseum, and Trichophyton rubrum, Vijesh et al. produced and tested compounds 136a- d and 137a-j. Comparing the investigated compounds to the industry standard, fluconazole, compound 136c has shown to be active against T. rubrum [17–18].

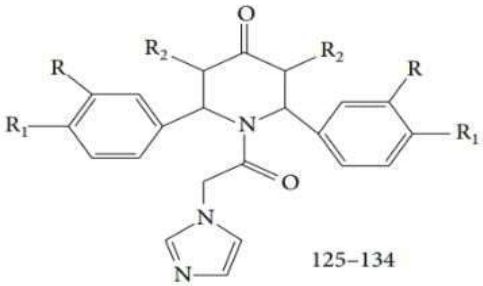
The aforementioned study on various imidazole derivatives, a significant class of heterocyclic compounds, has fascinating results for its antibacterial, anticancer, antitubercular, antifungal, analgesic, and anti-HIV activities. It also showed promising results for most pharmacological activities. Modifications to the imidazole nucleus have so far been seen to have interesting biological activity. It will be interesting to see how many additional pharmacological profiles are

Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378

added to it in the future because they are still unknown and can be used as a guide for future research to produce safer and more potent molecules.

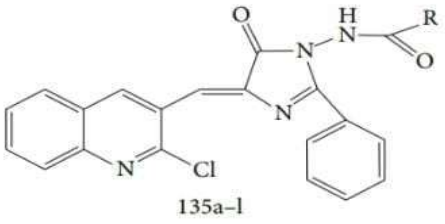


SCHEME 20



	R	R_1	R_2	R_3
125	H	H	CH_3	H
126	H	H	CH_2CH_3	H
127	H	H	$CH(CH_3)_2$	H
128	H	H	CH_3	CH_3
129	F	H	CH_3	CH_3
130	H	OCH_3	CH_3	CH_3
131	F	H	CH_3	CH_3
132	H	F	CH_3	CH_3
133	H	OCH_3	CH_3	CH_3
134	H	F	CH_2CH_3	H

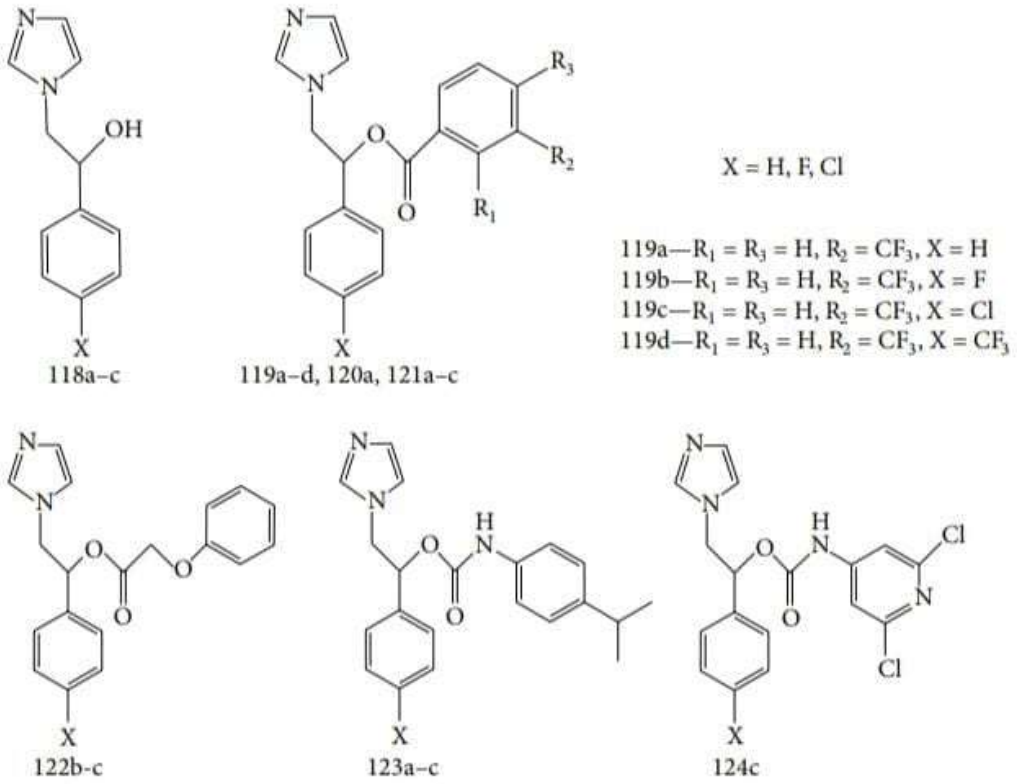
SCHEME 21



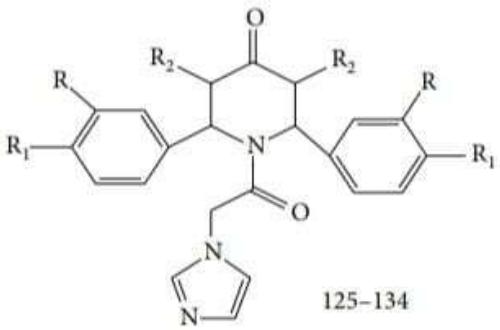
	-R		-R
135a	$-C_6H_5$	135h	$-4-NO_2-C_6H_4$
135b	$C_6H_5-CH_2$	135i	$-2-OH-C_6H_4$
135c	$-3-Cl-C_6H_4$	135j	$-3-OH-C_6H_4$
135d	$-4-Cl-C_6H_4$	135k	$-2-OH-4-Cl-C_6H_3$
135e	$-2,5-(Cl)_2-C_6H_3$	135l	$-C_5H_4N$
135f	$-4-F-C_6H_4$		
135g	$-3-NO_2-C_6H_4$		

SCHEME 22

Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378

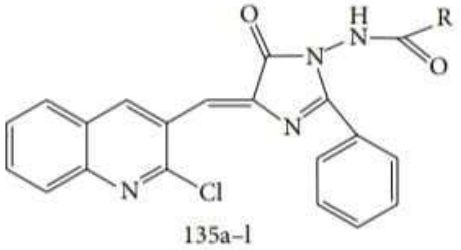


SCHEME 20



	R	R_1	R_2	R_3
125	H	H	CH_3	H
126	H	H	CH_2CH_3	H
127	H	H	$CH(CH_3)_2$	H
128	H	H	CH_3	CH_3
129	F	H	CH_3	CH_3
130	H	OCH_3	CH_3	CH_3
131	F	H	CH_3	CH_3
132	H	F	CH_3	CH_3
133	H	OCH_3	CH_3	CH_3
134	H	F	CH_2CH_3	H

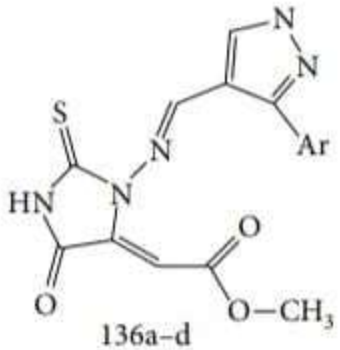
SCHEME 21



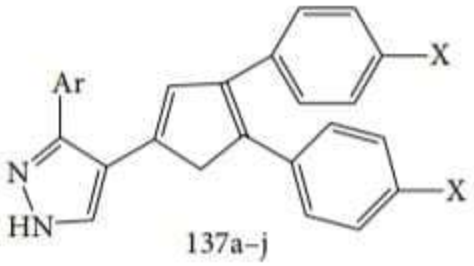
	-R
135a	$-C_6H_5$
135b	C_6H_5-CH_2
135c	-3-Cl-C_6H_4
135d	-4-Cl-C_6H_4
135e	-2,5-$(Cl)_2$-C_6H_3
135f	-4-F-C_6H_4
135g	-3-NO_2-C_6H_4
135h	-4-NO_2-C_6H_4
135i	-2-OH-C_6H_4
135j	-3-OH-C_6H_4
135k	-2-OH-4-Cl-C_6H_3
135l	$-C_5H_4N$

SCHEME 22

Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378



136a–d



137a–j

	Ar	X
136a	2,4-Dichlorophenyl	
136b	2,5-Dichlorothiophene	
136c	4-SCH_3-C_6H_4	
136d	4-CH_3-C_6H_4	
137a	4-SCH_3-C_6H_4	H
137b	2,4-Dichlorophenyl	H
137c	Biphenyl	H
137d	4-CH_3-C_6H_4	H
137e	2,5-Dichlorothiophene	H
137f	4-SCH_3-C_6H_4	Br
137g	2,4-Dichlorophenyl	Br
137h	Biphenyl	Br
137i	4-CH_3-C_6H_4	Br
137j	2,5-Dichlorothiophene	Br

SCHEME 23

Conclusion:

The aforementioned study on various imidazole derivatives, a significant class of heterocyclic compounds, has fascinating results for its antibacterial, antifungal, Antitubercular Activity. It also showed promising results in most pharmacological activities. Modifications to the imidazole nucleus have so far been seen to have interesting biological activity. It will be interesting to see how many additional pharmacological profiles are added to it in the future because they are still being discovered and can be used as a guide for future research to produce safer and more potent substances.

References:

1. Kleeman, J. Engel, B. Kutscher, and D. Reichert, Pharmaceutical Substances: Syntheses, Patents, Applications of the Most Relevant APIs, Thieme Medical, New York, NY, USA, 3rd edition, 1999.
2. H. Debus, “Ueber die Einwirkung des Ammoniaks auf Glyoxal,” Annalen der Chemie und Pharmacie, vol. 107, no. 2, pp. 199–208, 1858.
3. H. Singh and V. K. Kapoor, Medicinal and Pharmaceutical Chemistry, vol. 2, Vallabh Prakashan, Delhi, India, 2008.

4. A. M. Vijesh, A. M. Isloor, S. Telkar, S. K. Peethambar, S. Rai, and N. Isloor, "Synthesis, characterization and antimicrobial studies of some new pyrazole incorporated imidazole derivatives," European Journal of Medicinal Chemistry, vol. 46, no. 8, pp. 3531–3536, 2011.
5. Narasimhan B, Sharma D, Kumar P, Yogeeswari P, Sriram D (2011) Synthesis, antimicrobial and antimycobacterial evaluation of [2-(substituted phenyl)-imidazol-1-yl]-pyridin-3-yl-methanones. J Enzyme Inhib Med Chem 26(5):720–727.
6. Bhatt, Pankaj, Ajeet Kumar, and Rahul Shukla. "Nanorobots Recent and Future Advances in Cancer or Dentistry Therapy- A Review." American Journal of PharmTech Research, vol. 9, no. 3, 2019, pp. 321–331, doi:10.46624/ajptr.2019.v9.i3.027.
7. Reyes-Arellano A, Gómez-García O, Torres-Jaramillo J (2016) Synthesis of azolines and imidazoles and their use in drug design. Med Chem (Los Angeles) 6:561–570.
8. Verma A, Joshi S, Singh D (2013) Imidazole: having versatile biological activities. New J Chem. https://doi.org/10.1155/2013/329412.
9. A. K. Jain, V. Ravichandran, M. Sisodiya, and R. K. Agrawal, "Synthesis and antibacterial evaluation of 2-substituted-4,5- diphenyl-N-alkyl imidazole derivatives," Asian Pacific Journal of Tropical Medicine, vol. 3, no. 6, pp. 471–474, 2010.
10. Kaur, Tejinder, and Suruchi Singh. "Controlled Release of Bi-Layered Malvidin Tablets Using 3D Printing Techniques." Journal of Pharmaceutical Research International, 2021, pp. 70–78, doi:10.9734/jpri/2020/v32i4031034.
11. X. Lu, X. Liu, B. Wan et al., "Synthesis and evaluation of anti-tubercular and antibacterial activities of new 4-(2, 6- dichlorobenzyloxy) phenyl thiazole, oxazole and imidazole derivatives," European Journal of Medicinal Chemistry, vol. 49, pp. 164–171, 2012.
12. S. Lee, S. Kim, M. Yun et al., "Synthesis and antitubercular activity of monocyclic nitroimidazoles: insights from econazole, Bioorganic and Medicinal Chemistry Letters, vol. 21, no. 5, pp. 1515–1518, 2011.
13. S. G. Alegaon, K. R. Alagawadi, P. V. Sonkusare, S. M. Chaudhary, D. H. Dadwe, and A. S. Shah, "Novel imidazo[2,1- b][1,3,4]thiadiazole carrying rhodanine-3-acetic acid as potential antitubercular agents," Bioorganic and Medicinal Chemistry Letters, vol. 22, no. 5, pp. 1917–1921, 2012.
14. A. Fassihi, Z. Azadpour, N. Delbari et al., "Synthesis and antitubercular activity of novel 4-substituted imidazolyl-2,6- dimethyl-N3,N5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides," European Journal of Medicinal Chemistry, vol. 44, no. 8, pp. 3253–3258, 2009.
15. D. Zampieri, M. G. Mamolo, E. Laurini, G. Scialino, E. Banfi, and L. Vio, "Antifungal and antimycobacterial activity of 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives," Bioorganic and Medicinal Chemistry, vol. 16, no. 8, pp. 4516–4522, 2008.
16. W. C. Yang, J. Li, J. Li, Q. Chen, and G. F. Yang, "Novel synthetic methods for N-cyano-1H-imidazole-4-carboxamides and their fungicidal activity," Bioorganic and Medicinal Chemistry Letters, vol. 22, no. 3, pp. 1455–1458, 2012.

Catalyst Research Volume 23, Issue 2, August 2023 Pp. 369-378

17. D. de Vita, L. Scipione, S. Tortorella et al., “Synthesis and antifungal activity of a new series of 2-(1H-imidazol-1-yl)- 1-phenylethanol derivatives,” European Journal of Medicinal Chemistry, vol. 49, pp. 334–342, 2012.
18. N. C. Desai, A. S. Maheta, K. M. Rajpara, V. V. Joshi, H. V. Vaghani, and H. M. Satodiya, “Green synthesis of novel quinoline based imidazole derivatives and evaluation of their antimicrobial activity,” Journal of Saudi Chemical Society, 2011.