IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

TO DESIGN AND *IN-SILICO* STUDY OF NOVEL IMIDAZOLE DERIVATIVE AS ANTIMICROBIAL AGENT

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ABSTRACT: The study of synthetic heterocyclic compounds that exhibit a variety of pharmacological actions, such as antiviral, antibacterial, anti-inflammatory, antifungal, and anti-tumor properties, is the focus of the intricate and important topic of heterocyclic chemistry in medicinal chemistry. This paper emphasizes the value of heterocyclic chemistry in industry and medicine, highlighting its use in medication development across a range of domains. The Designing of new imidazole derivatives is described in detail, and their biological significance, binding affinity to target proteins, and toxicity profiles are assessed using in silico approaches. According to the results, these compounds have favorable pharmacological traits and promising antibacterial qualities. The results highlight imidazole derivatives' potential for additional study and development, highlighting their use as antibacterial agents and their function in medicinal chemistry.

Keywords:

Imidazole derivatives, DNA Topoisomerase1, heterocyclic chemistry, binding affinity, toxicology

INTRODUCTION:

Heterocyclic compounds hold a central place in medicinal chemistry due to their complexity and diverse applications. Heterocyclic chemistry, known for its complexity, plays a vital role in both industrial and pharmaceutical fields, driven by its wide range of synthetic techniques and foundational theoretical principles. These compounds are essential across numerous fields such as polymer science, agriculture, and medicine, showcasing their versatile nature. Synthetic heterocyclic molecules are widely employed as pharmaceuticals, functioning as anticonvulsants, sedatives, anticancer agents, antiseptics, antihistamines, antivirals, and more. Each year, numerous heterocyclic drugs are incorporated into pharmacopeias, with their biological properties heavily influenced by the size and type of the heterocyclic rings and the substituent groups attached to the parent scaffold. Heterocyclic compounds have demonstrated significant roles in antiviral, antibacterial, anti-inflammatory, antifungal, and antitumor therapies. The vast scope of their applications remains a subject of ongoing exploration. Among naturally occurring heterocyclic compounds, alkaloids are particularly noteworthy for their diverse biological activities, often containing basic nitrogen atoms. This discussion emphasizes the imidazole heterocycle due to its prominent role in medicinal chemistry. Recent advancements in synthetic

methods for heterocyclic compounds focus on enhancing reaction efficiency, yield, and purity while incorporating environmentally sustainable practices.[1-10]

General features of Heterocyclic Compounds: Common heterocyclic compounds typically consist of five- or six-membered rings that include heteroatoms like nitrogen (N), oxygen (O), or sulfur (S). Examples of well-studied simple heterocycles include pyridine, pyrrole, furan, and thiophene. Pyridine comprises a six-membered ring with one nitrogen atom, while pyrrole, furan, and thiophene feature five-membered rings with four carbon atoms and one heteroatom (nitrogen, oxygen, or sulfur, respectively)[11]. Nitrogen-based heterocycles like pyridine and pyrrole are significant due to their prevalence in biological molecules. Historically, these compounds were identified in the mid-19th century during high-temperature treatment of organic materials, such as bones, which produced small quantities of pyridine and pyrrole. Today, these compounds are synthesized using well-established chemical methods.[11]

Historical Milestones in Heterocyclic Chemistry: The development of heterocyclic chemistry dates back to the early 19th century, paralleling the rise of organic chemistry. Key milestones include: 1818: Brugnatelli isolates alloxan from uric acid. 1906: Friedlander discovers the synthetic process for indigo dye, revolutionizing industrial chemistry and reducing reliance on agriculture-based dyes. 1951: Chargaff's rules highlight the significance of heterocyclic compounds (purines and pyrimidines) in genetic material.

Imidazole:

Heinrich Debus pioneered the synthesis of imidazole in 1858, a crucial breakthrough in organic chemistry. However, research into compounds with similar structures had begun as early as the 1840s, leading to the discovery of various imidazole derivatives and contributing to the growing understanding of their properties and applications. Imidazole 1, originally known as glyoxaline (Figure 1), was the end product of its production, which began with the use of glyoxal 2 and formaldehyde 3 in ammonia [12,13]. C-substituted imidazoles are still made via this process, even if the yields are somewhat poor.

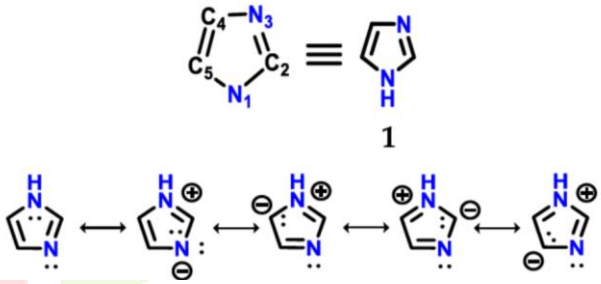


Figure 1. Structure of imidazole **1** with its respective numbering and resonance hybrids

Imidazole is a flat, five-membered ring structure containing three carbon atoms and two nitrogen atoms at positions 1 and 3. With the formula C3H4N2, it is the most basic of the imidazole derivatives.The compound's systemic name is 1, 3 diazole; one of the annular N atoms has a H atom, making it a pyrole type N. [14]

Imidazole dissolves in water and other polar solvents. The compound is considered aromatic as it contains a sextet of π-electrons, with two electrons from the protonated nitrogen atom and one from each of the other four atoms in the ring. Imidazole's amphoteric nature enables it to act as both an acid and a base. Its pKa value of 14.5 indicates that it is more acidic than alcohols but less acidic than compounds like carboxylic acids, phenols, and imides.N-1 is where the acidic proton is found. N-3 is the fundamental location.

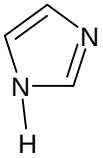


Figure.2. Structure of Imidazole

Physical Properties of Imidazole:

Because of intermolecular H-bonding, which occurs when molecules associate linearly, it is a colorless liquid with a higher B.P. of 256 ºC than any other 5-membered heterocyclic compound.

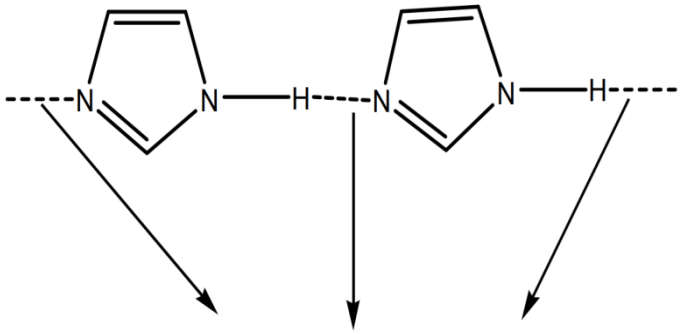


Figure .3.Intermolecular H-bonding

Imidazoles have pKa of 7.2, imidazole is a stronger base than pyrazole and pyridine, and it displays amphoteric characteristics. The resonance value of imidazoles, an aromatic molecule, is 14.2 K cal/mol, nearly half that of pyrazoles. Imidazole commonly undergoes electrophillic substitution, while nucleophillic substitution takes place when the nucleus contains an electron-withdrawing group. Imidazoles melt at 90°C and function as weak bases. They are tautomeric due to the equivalence of positions 4 and 5 in the ring structure.

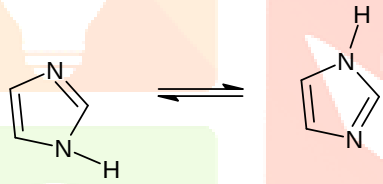


Figure .4.Tautomerism of Imidazole

structure at 4 and 5 position

Pharmacological Activities Of Imidazoles :

Imidazoles As Anthelmintics

Imidazole demonstrates lower efficacy against extraintestinal parasites, especially those that inhabit intravascular regions or the intestines, compared to its activity against intestinal parasites. In similar settings, the activity against developing phases is better than that against arrested or adult stages. At levels that are less effective against adults in vivo, hatching and larval development are impeded. Compared to cestode and trematode control, less are needed to attain effectiveness against nematodes. More medication or several treatments are required to control cestodes or trematodes.[15]

Imidazoles As Anti-Inflammatory Agents :

Finding a new and improved medication for anti-inflammatory treatment is an ongoing task. Since ancient times, people have looked for anti-inflammatory drugs to reduce the fever, pain, redness, and swelling that come with rheumatism. Work on several heterocyclic systems, either alone or in combination with other systems, is included in the synthetic studies. Given that amino acids have been shown to have anti-inflammatory properties [16,17], Kumar et al. [18] created a number of heterocyclic derivatives with both carboxylic and amino groups. Studies of the structure-activity relationship showed that the carboxylic group's transformation into a heterocyclic ring typically increased the inhibition of edema.

Imidazoles As Anti-Fungal Agents [19]

In recent years, research on imidazole and triazole compounds has been at the forefront of developing new antifungal therapies. The azole class of drugs, which includes various 1-substituted imidazole and triazole derivatives, is now widely used for treating fungal infections both topically and systemically. Imidazole is known for its strong antifungal properties, both pharmacologically and biochemically. Lipophilic imidazoles, including clotrimazole (I), econazole (II), and miconazole (III), show limited systemic absorption when administered orally, mainly because of poor absorption and significant first-pass metabolism. As a result, their use has been predominantly confined to the topical treatment of superficial fungal infections.

Imidazoles As Anti-Cancer Agents

In recent years, the imidazole moiety has been the sole focus of research as a crucial structural for antineoplastic or anticancer agents. The varied substitutions at various locations within the moiety are primarily given priority. Two classes of serine–threonine protein kinases known as the cyclin-dependent kinase (CDK) families play a part in transcriptional control and the eukaryotic cell cycle synchronization. The development of small molecule CDK cell cycle inhibitors as possible therapeutic treatments has received a lot of attention due to their crucial function in cell cycle regulation and the expression/activity pattern seen in the majority of human malignancies. [20]

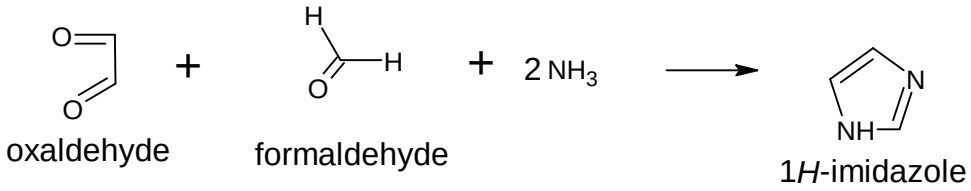
MATERIALS AND METHODS:

Software's-

- ChemSketch
- SwissADME
- Protox 3.0
- Biovia Studio
- M-cule Docking
- Openbabel
- Molinspiration

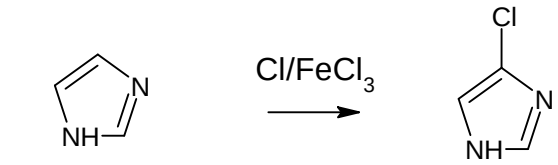
Synthesis Reactions of Novel Imidazole Darivative:

- **Step:1**



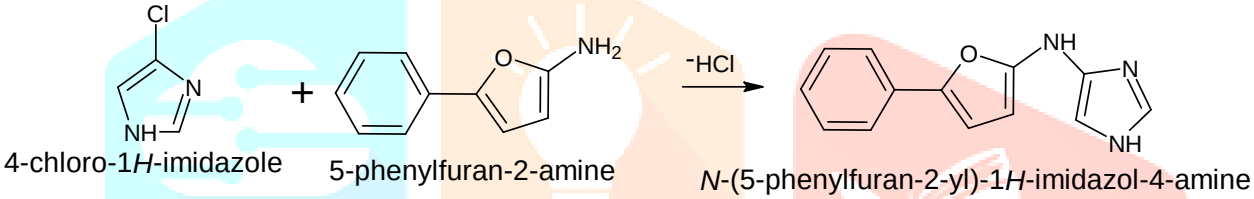
oxaldehyde formaldehyde 1*H*-imidazole

- **Step :2**



1*H*-imidazole 4-chloro-1*H*-imidazole

- **Step :3**



4-chloro-1*H*-imidazole 5-phenylfuran-2-amine *N*-(5-phenylfuran-2-yl)-1*H*-imidazol-4-amine

***In Silico* STUDY-**

Ligand preparation: Using the ChemSketch application By adding different electron-donating and electron-withdrawing groups (-CI, CH, -NH_2, Br. -CH_3) to the obtained basic moiety, ten compounds were created. Imidazole derivatives were then transformed into SDF format.

Protein preparation: Brovia Discovery Studio Visualizer36 V16.10.15350 was used to open the 3D crystal structure of the DNA Topoisomerase 1 (1cy6) protein, which was downloaded in PDB format from the RCSB Protein Data Bank. Hydroatoms, water molecules, extra chains, and the protein's pre-existing ligand were eliminated throughout the protein preparation procedure, and the file was saved as an MDL MOL/SD file.

ADMET and drug-likeness prediction: Drug-likeness prediction with ADMET CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor, intestinal absorption, blood brain barrier penetration, P-gp subs, and other pharmacokinetic characteristics of imidazole derivatives were screened using the SwissADME program. Predicted bioavailability was displayed in tabular form.

Prediction of Toxicity: The toxicity assessment of the designed imidazole derivatives was conducted using the Protox 3.0 tool. This evaluation focused on predicting various organ-specific toxicities, including liver toxicity, potential to cause cancer, genetic mutations, cell damage, and immune responses. Utilizing this computational method offers crucial insights into the compounds' safety and potential adverse effects.

Molecular Properties and Bioactivity Scores of the ligands: Molecular properties such as MlogP (partition coefficient between n-octanol and water), TPSA, the number of donors and acceptors of hydrogen bonds, molecular weight, the number of rotatable bonds, and molecular volume were predicted using the SwissADME and presented in tabular form. The ligands that modulate GPCR, ion channels, and nuclear receptors were predicted using another piece of software called Molinspiration. The ligands were also predicted to be enzyme, protease, and kinase inhibitors.

Molecular Docking Studies: The One Click Docking tool was used to conduct docking studies. After downloading the targeted protein DNA Topoisomerase 1 (1cy6) from the Protein Data Bank, a protein was prepared by eliminating the hetro atom, water molecules, extra chain, and any pre-existing ligand. In order to dock with novel derivatives, all produced proteins are now uploaded to M-cule Docking. Using Discovery Studio Visualizer36 V16.1.0.15350, the binding affinity and types of interactions between the ligand and target were investigated.

RESULTS AND DISCUSSION:

1. **Screening of designed derivatives through ADMET analysis-** Based on Lipinski's rule of five, also referred to as Pfizer's rule of five or the rule of five (RO5), which states that an oral active drug must adhere to the following guidelines: less than five hydrogen-bond donors, fewer than ten hydrogen-bond acceptors, a molecular mass less than 500, and log P less than five, Table No. 1 evaluates the synthesized SBs derivative. Measurements were also made of other significant characteristics, including molar refractivity, the quantity of rotatable bonds, and total polar surface area (TPSA). A compound should have fewer than 10 rotatable bonds and a TPSA of less than 140 Å2.

Table 1. Calculation of Lipinski rule of five for the designed derivative:

Ligand	Molecular weight	TPSA	Molar refractivity	MlogP	Rotable bonds	H-bond donors	H-bond acceptors
R-OSO_3H	323.32	121.54	86.90	0.22	5	3	6

Table 2. The Pharmacokinetic properties of the designed derivative:

Codes	GI abs.	BBB perm.	CYP 1A2	CYP2 C19	CYP2 C9	CYP2 D6	CYP3 A4	Log Kp(cm/s)	Bioavailability
R-OSO_3H	High	No	Yes	No	No	No	No	-6.90	0.56

Molecular docking- After passing all the filters and demonstrating the most drug-like characteristics, they were first screened using the Lipinski rule, ADME calculations, and bioactivity score. More powerful contacts and binding affinities with the target were demonstrated by the imidazole derivative chosen for docking against the DNA Topoisomerase 1 (1cy6) enzyme in table no. 3. The bound molecules' 2D and 3D docking postures are displayed, along with an analysis of their binding affinitics and types of interactions. The greater the negative docking score, the greater the ligand's affinity for the target.

Table 3.The Binding interaction of designed derivative with DNA Topoisomerase 1 enzyme:

Comp. Code	Binding Affinity (Kcal/mol)	Type of interaction
R-OSO_3H	-8.0	van der Waals,Conventional Hydrogen Bond,Carbon Hydrogen Bond,Pi-Cation, Pi-Anion,Amide-Pi Stacked, Pi-Alkyl

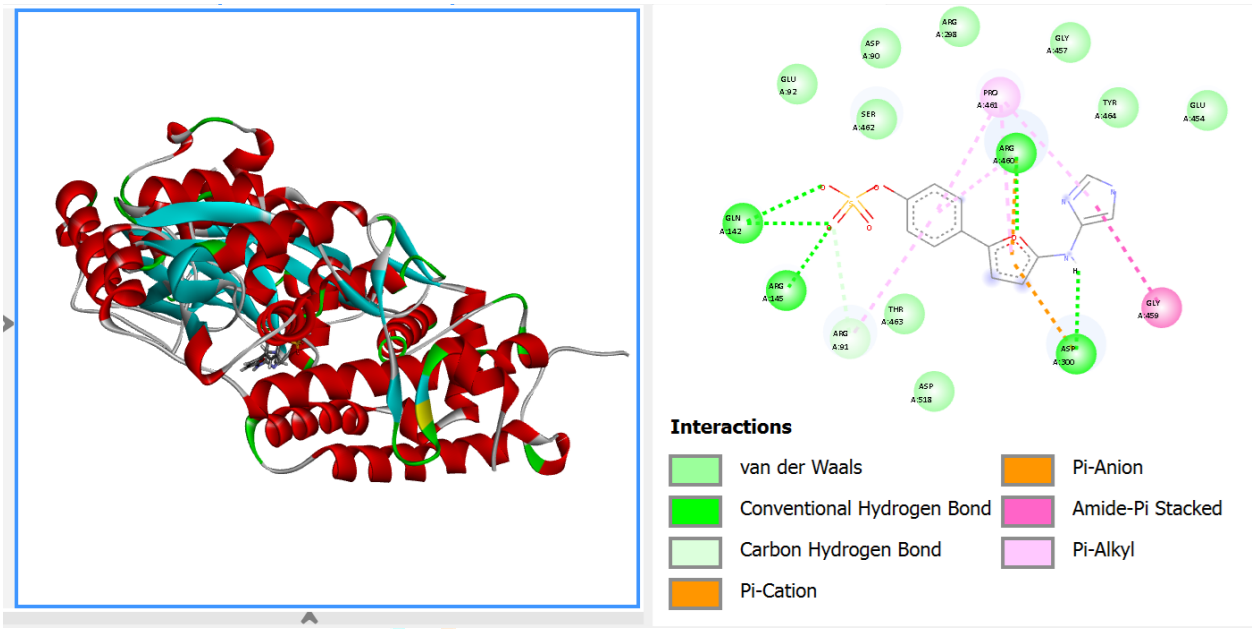


Figure.5. 3D and 2D docking poses of ligand imidazole derivative with DNA Topoisomerase 1 (1cy6).

Prediction of Toxicity: Several toxicological endpoints, including neurotoxicity, carcinogenicity, mutagenicity, cytotoxicity, and immunogenicity, were used in this work to evaluate the toxicity of imidazole derivatives. The toxicity prediction results were measured as either active or inactive.

Table 4.The toxicity profile of the designed derivative:

Ligand	Neurotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
R-OSO_3H	Inactive	Inactive	Inactive	Inactive	Inactive

Discussion:
Strong binding affinity to the target protein and advantageous ADME features were demonstrated in the in-silico investigations, which suggested promising biological significance.

Conclusion: Significant medicinal uses for heterocyclic chemistry include antiviral, antibacterial, anti-inflammatory, antifungal, and anti-tumor medications. With significant advancements in the synthesis and discovery of numerous heterocyclic molecules, the history of heterocyclic chemistry begins in the 1800s. Imidazole's promise as a vital structural element for therapeutic applications has been enhanced by the discovery of significant, pharmacological activity, and synthetic processes. There is promise for more research and development of novel imidazole derivatives since in-silico studies and molecular docking have shown promising biological significance, strong binding affinity to target proteins, and beneficial ADMET characteristics.

ACKNOWLEDGEMENT:
The corresponding authors would like to express sincere gratitude to Dr. Megha T. Salve for their aspiring guidance, valuable contributions and support throughout the preparation of this review article. Her dynamic vision, genuine sincerity, and unwavering motivation have been a profound source of inspiration for me. It was a tremendous privilege and a source of great honor to have the opportunity to learn and collaborate under their exceptional guidance.

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