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Exploring The Therapeutic Potential Of Pyrazoles: A Comprehensive Review

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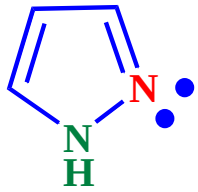
Abstract

Pyrazoles, a class of five-membered heterocyclic compounds containing two adjacent nitrogen atoms, have garnered significant attention in medicinal chemistry due to their diverse biological activities. This mini review highlights the biological importance of pyrazoles, focusing on their role as therapeutic agents, their mechanisms of action, and the structural modifications that enhance their efficacy.

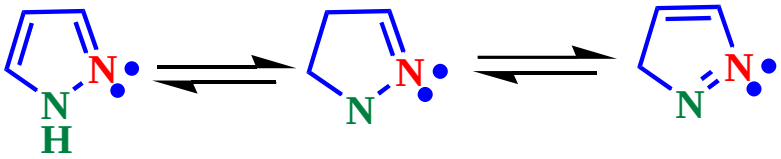
INTRODUCTION

Heterocyclic compounds are crucial in medicinal chemistry, providing a wide range of therapeutic possibilities[1]. These compounds feature ring structures composed of at least two different elements, with nitrogen, oxygen, and sulfur being the most common. Nitrogen-containing heterocyclic compounds[2] are especially important in drug development due to their structural variety and nitrogen atomscontributions to diverse biological activities. These attributes make them key components in many therapeutic agents. The inclusion of nitrogen in these ring structures often enhances their pharmacological properties, resulting in the creation of numerous essential medications for various medical conditions. Among these, pyrazoles and their derivatives are particularly significant for treating some of the most severe diseases humanity has encountered.

Pyrazoles are heterocyclic compounds with a broad spectrum of biological activities. The term "Pyrazole" was first coined by Knorr during 1883[3]. This five-member having two nitrogen atoms arranged at 1,2 position makes them unique structure allows for significant chemical versatility, making them a valuable scaffold in drug design and development[4-7]. This mini review aims to provide an overview of the key biological properties of pyrazoles and their derivatives, emphasizing recent advancements in the field.



Pyrazole



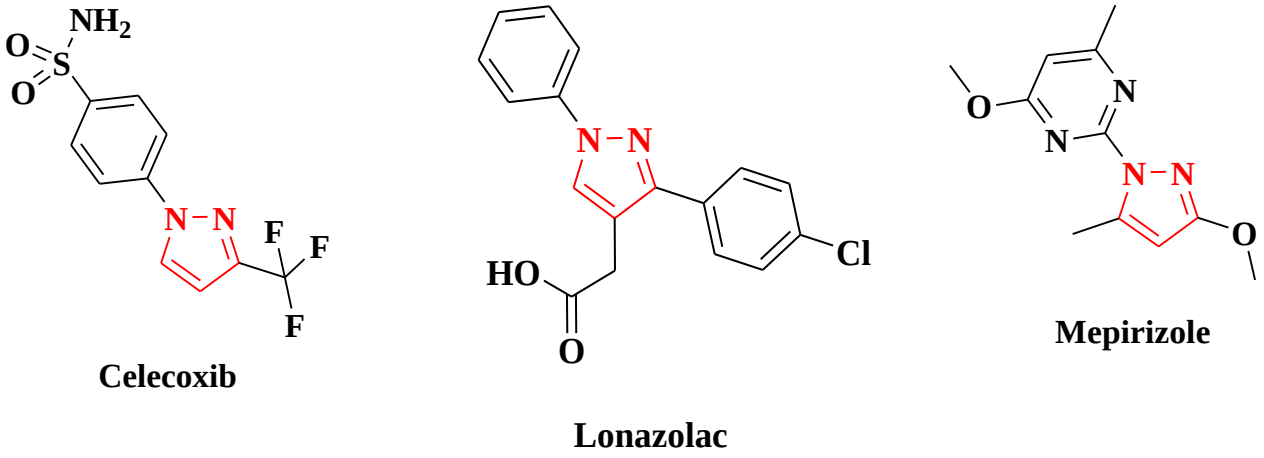
(1) **(2)** **(3)**

Tautomeric Forms of Pyrazole(Unsubstituted)

Figure 1 Biological Properties of Pyrazole and Its Derivatives

BIOLOGICAL PROPERTIES

1. **Anti-inflammatory Activity[8-10]:**Pyrazole derivatives have shown potent anti-inflammatory properties by inhibiting cyclooxygenase (COX) enzymes, particularly COX-2, which plays a crucial role in inflammation and pain.Example: **Celecoxib**, **Lonazolac** and **Mepirizole** are common anti-inflammatory drugs having pyrazole scaffolds in their structure.



Celecoxib

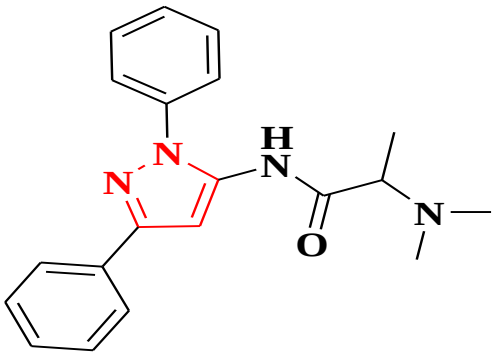
Lonazolac

Mepirizole

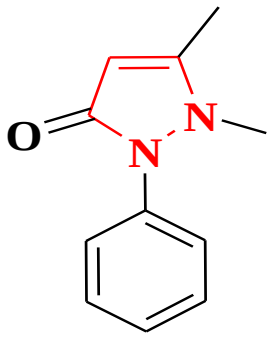
Figure 2. Anti-inflammatory Drugs having pyrazole moiety

2. **Antimicrobial Activity[11-14]:** Pyrazoles indeed have a wide range of antimicrobial activities. Introducing different substituents on the pyrazole ring, such as halogens (like fluorine, chlorine, bromine) or alkyl groups, can significantly influence their antimicrobial properties. These modifications can enhance the efficacy of pyrazoles by altering their ability to interact with microbial targets, improving their pharmacokinetic profiles, and increasing their stability and bioavailability. These modifications make pyrazoles a valuable scaffold in the development of new antimicrobial agents such as **Difenamizole** and **Phenazone.**

3.



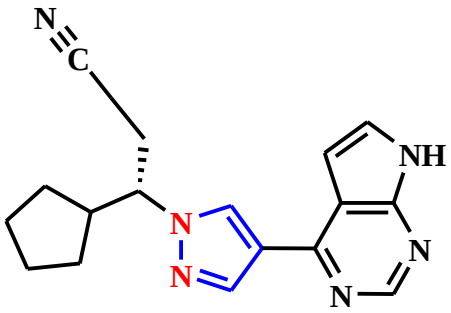
Difenamizole



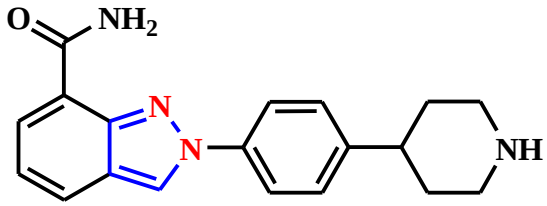
Phenazone

Figure2. Anti-microbial Drugs having pyrazole moiety

4. **A nticancer Activity[15-20]:** Pyrazole derivatives are notable for their diverse anticancer mechanisms, which include the inhibition of tubulin polymerization, leading to disrupted cell division and induced apoptosis. Compounds like **Ruxolotinib** and **Niraparib**(**Figure 3**) can also intercalate into DNA, preventing proper DNA replication and transcription, ultimately causing cell death. Additionally, pyrazole derivatives are effective kinase inhibitors, targeting enzymes crucial for signaling pathways that regulate cancer cell growth, survival, and proliferation.



Ruxolotinib



Niraparib

Figure 3. Anti-cancer Drugs having pyrazole moiety

5. **Antioxidant Activity[21-23]**: Pyrazoles have been identified as potential antioxidants, capable of scavenging free radicals and protecting against oxidative stress-related damage. Structural modifications, such as the introduction of phenolic groups, enhance their antioxidant capabilities.

6. **Antidiabetic Activity[24-26]:**Some pyrazole derivatives have shown promise in managing diabetes by modulating insulin secretion and sensitivity.Pyrazole-containing compounds

that act as dipeptidyl peptidase-4 (DPP-4) inhibitors are being explored for their potential in diabetes treatment.

7. **Neuroprotective Activity[27-30]:**Pyrazoles have demonstrated neuroprotective effects, potentially beneficial in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's.Mechanisms include inhibition of acetylcholinesterase and modulation of neurotransmitter levels.

CONCLUSION

pyrazoles represent a cornerstone in medicinal chemistry due to their structural versatility and wide-ranging biological activities. The ability to modify the pyrazole core to target specific pathways makes them invaluable in the development of novel therapeutics. With ongoing research focusing on optimizing their efficacy, safety profiles, and synthetic methodologies, pyrazole-based compounds hold significant promise for addressing diverse medical challenges. As advancements continue, particularly in green chemistry and computational design, pyrazoles are poised to remain at the forefront of drug discovery and development, offering new solutions for various diseases which are posing a high threat to human .

REFERENCES

1. Kabir E.; Uzzaman M. A review on biological and medicinal impact of heterocyclic compounds. Res. In Chem. 2022,4, 100606.
2. Joule J.A. Natural Products containing nitrogen heterocyclic. Adv Het. Chem. 2016, 119, 81-106.
3. Azzam S.H.S; Pasha A. A review on the current studies in pyrazole derivatives, their biological and pharmacological properties. EJPMR. 2020, 7. 867-887.
4. Eicher, T.; Hauptmann, S. The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications, 2nd ed; Wiley & Sons: New York, 2003. http://dx.doi.org/10.1002/352760183X.
5. Bansal, R.K. Heterocyclic Chemistry, 4th ed; New Age International Publishers: New Delhi, 2007.
6. Krygowski, T.M.; Anulewicz, R.; Cyranski, M.K.; Puchala, A.; Rasala, D. Separation of the energetic and geometric contribution to the aromaticity. Aromaticity of pyrazoles in dependence on the kind of substitution. Tetrahedron, 1998, 54, 12295-12300. http://dx.doi.org/10.1016/S0040-4020(98)00749-2.
7. Wiley, R.H.; Behr, L.C. The Chemistry of Heterocyclic Chemistry: Pyrazoles, pyrazolines, pyrazolidines, indazoles and condensed rings. London; Wiley & Sons: New York, 1967.
8. Clemett, D., and Goa, K. L. Celecoxib. Drugs. 2000. 59. 957–980.
9. M.G, P. Saunders handbook of veterinary drugs: small and large animal. Graham B, Editor., 2016, 3.

10. García-Lozano, J.; Server-Carrió, J.; Escrivà, E.; Folgado, J. V.; Molla, C.; Lezama, L. Polyhedron., 1997, 16, 939-944.
11. Saadon, K.E., Taha, N.M.H., Mahmoud, N.A. et al. Synthesis, characterization, and in vitro antibacterial activity of some new pyridinone and pyrazole derivatives with some in silico ADME and molecular modeling study. J IRAN CHEM SOC 19, 3899–3917 (2021). https://doi.org/10.1007/s13738-022-02575-y
12. H. Ali Mohamed, Y.A. Ammar, G.A.M. Elhagali, H.A. Eyada, D.S. Aboul-Magd, A. Ragab, In vitro antimicrobial evaluation, single-point resistance study, and radiosterilization of novel pyrazole incorporating thiazol-4-one/thiophene derivatives as dual DNA gyrase and DHFR inhibitors against MDR pathogens. ACS Omega (2021) https://doi.org/10.1021/acsomega.1c05801.
13. N.C. Desai, B.Y. Patel, B.P. Dave, Synthesis and antimicrobial activity of novel quinoline derivatives bearing pyrazoline and pyridine analogues. Med. Chem. Res. 26, 109–119 (2017). https://doi.org/10.1007/s00044-016-1732-6.
14. Bhat, Mashooq Ahmad, Al-Omar, Mohamed A., Naglah, Ahmed M., Khan, Abdul Arif, Enaminone-Derived Pyrazoles with Antimicrobial Activity, Journal of Chemistry, 2019, 2467970, 10 pages, 2019. https://doi.org/10.1155/2019/2467970
15. Sivaramakarthikeyan R. Shunmugan I, Lim Y.M. Vaivel S. Molecular Hybrids Integrated with Benzimidazole and Pyrazole Motifs: Desing, Synthesis,,,Biological Evaluation and Moleclar Docking Studies, ACS Omega 2020,5.10089-10098.https://dx.doi.org/10.1021/acsomega.0c00630?ref=pdf
16. Saleh N.N., El-Gazzar M.G., Aly H.M., Othman R.A. Novel Anticancer Fused Pyrazole Derivatives as EGFR and VEGFR-2 dual TK Inhibitors, Front. Chem. 7:917. https://doi.org/10.3389/fchem.2019.00917
17. Wen, S., Shao, G., Zheng, J., Zeng, H., Luo, J., and Gu, D. Apatinib regulates the cell proliferation and apoptosis of liver cancer by regulation of VEGFR2/STAT3 signaling. Pathol. Res. Pract. 2019, 215, 816–821. doi: 10.1016/j.prp.2019.01.021
18. Shafei, A., El-Bakly, W., Sobhy, A., Wagdy, O., Reda, A., Aboelenin, O., et al. . A review on the efficacy and toxicity of different doxorubicin nanoparticles for targeted therapy in metastatic breast cancer. Biomed. Pharmacother, 2017, 95, 1209–1218. doi: 10.1016/j.biopha.2017.09.059.
19. Sudhapriya, N., Perumal, P. T., Balachandran, C., Ignacimuthu, S., Sangeetha, M., and Doble, M. Synthesis of new class of spirocarbocycle derivatives by multicomponent domino reaction and their evaluation for antimicrobial, anticancer activity and molecular docking studies. Eur. J. Med. Chem. 2014, 83, 190–207. doi: 10.1016/j.ejmech.2014.05.065
20. Shukla, P., Sharma, A., Fageria, L., and Chowdhury, R. . Novel spiro/nonspiropyranopyrazoles: eco-friendly synthesis, in-vitro anticancer activity, DNA binding, and in-silico docking studies. Curr. Bioact. Compound. 2019, 15, 257–267. doi: 10.2174/1573407213666170828165512.

21. Zebbiche, Z.; ¸Sekerci, G.; Boulebd, H.; Küçükbay, F.; Tekin, S.; Tekin, Z.; Küçükbay, H.; Sandal, S.; Boumoud, B. Preparation, DFT calculations, docking studies, antioxidant, and anticancer properties of new pyrazole and pyridine derivatives. J. Biochem. Mol. Toxicol. 2022, 36, e23135. https://doi.org/10.1002/jbt.23135.
22. Shaaban, O.G.; Abd El Razik, H.A.; Shams El-Dine, S.E.A.; Ashour, F.A.; El-Tombary, A.A.; Afifi, O.S.; Abu-Serie, M.M. Purines and triazolo[4,3-e]purines containing pyrazole moiety as potential anticancer and antioxidant agents. Future Med. Chem. 2018, 10, 1449–1464.https://doi.org/10.4155/fmc-2017-0227.
23. Boateng, Samuel T., Roy,T.,Torrey,K. Basnet, D. Niedda,E. et al.Synthesis, in Silico Modelling, and in Vitro Biological Evaluation of Substituted Pyrazole Derivatives as Potential Anti-Skin Cancer, Anti-Tyrosinase, and Antioxidant Agents. J. Enzyme Inhib.Med. Chem. 2023, 38 (1). doi:10.1080/14756366.2023.2205042.
24. Naim, Mohd. Javed; Alam, Ozair; Alam, Md. Jahangir; Shaquiquzzaman, Mohammad; Alam, Md. Mumtaz; Naidu, Vegi Ganga Modi . (2018). Synthesis, docking, in vitroand in vivoantidiabetic activity of pyrazole-based 2,4-thiazolidinedione derivatives as PPAR-γ modulators. Arch Pharm Chem Life Sci. 2018;e1700223, 1-15. https://doi.org/10.1002/ardp.201700223.
25. Eduardo Hernández-Vázquez, Hugo Ocampo-Montalban, LitziaCerón-Romero, Miguel Cruz, Jaime Gómez-Zamudio, Guadalupe Hiriart-Valencia, Rafael Villalobos-Molina, Angelica Flores-Flores, Samuel Estrada-Soto. Antidiabetic, antidyslipidemic and toxicity profile of ENV-2: A potent pyrazole derivative against diabetes and related diseases,Eur.J.Pharmacol.2017, 803,159-166.https://doi.org/10.1016/j.ejphar.2017.03.036.
26. Mortada, S., Karrouchi, K., Hamza, E.H. et al. Synthesis, structural characterizations, in vitro biological evaluation and computational investigations of pyrazole derivatives as potential antidiabetic and antioxidant agents. Sci Rep 2024, 14, 1312.https://doi.org/10.1038/s41598-024-51290-6.
27. Bhat, M.A., Ahmed, A.F., Wen, ZH. et al. Synthesis, anti-inflammatory and neuroprotective activity of pyrazole and pyrazolo[3,4-d]pyridazine bearing 3,4,5-trimethoxyphenyl. Med Chem Res 2017,26, 1557–1566 . https://doi.org/10.1007/s00044-017-1870-5.
28. Özdemir, A.; Sever, B.; Altıntop, M.D.; Kaya Tilki, E.; Dikmen, M. Design, Synthesis, and Neuroprotective Effects of a Series of Pyrazolines against 6-Hydroxydopamine-Induced Oxidative Stress. Molecules 2018, 23, 2151. https://doi.org/10.3390/molecules23092151.
29. Hanaa H. Ahmed, Gamal A. Elmegeed, El-Sayed M. El-Sayed, Mervat M. Abd-Elhalim, WafaaGh. Shousha, Reham W. Shafic,Potent neuroprotective role of novel melatonin derivatives for management of central neuropathy induced by acrylamide in rats. Eur. J. Med. Chem.2010, 45(11),5452-5459. https://doi.org/10.1016/j.ejmech.2010.09.017.
30. Liping Liao, Jinguo Shi, Caibao Jiang, Liantao Zhang, Lisi Feng, Jiayong Liu, Jingxia Zhang. Activation of anti-oxidant of curcumin pyrazole derivatives through preservation of

mitochondria function and Nrf2 signaling pathway. Neurochem. Int.2019,125, 82-90. https://doi.org/10.1016/j.neuint.2019.01.026.