Asian Journal of Pharmaceutical and Health Sciences
http://www.ajphs.com
ISSN: 2231- 2331(Print) | ISSN: 2231–234X(Online)

Review Article

Pyrazole-pyrazine conjugates as potential therapeutic agents: design, synthesis and bioactivity

Arya S Kumar* **and Seba M C**

Department of Pharmaceutical Chemistry, The Dale View College of Pharmacy and Research Center, Punalal P.O., Poovachal, Thiruvananthapuram, Kerala, India.

Article History
Received :04.06.2025
Revised :13.07.2025
Accepted :11.08.2025

DOI

10.5530/ajphs.2025.15.84

Keywords
Pyrazole
Pyrazine
Synthetic strategies
SAR
Heterocyclic compounds
Pyrazine-Pyrazole hybrids

***Corresponding Author:**
Arya S Kumar
Email: aryaskumar34@gmail.com
Phone: +919061447552

ABSTRACT

Heterocyclic compounds linked with a pharmacophore exhibit better biological activity. The pyrazole molecule linked to pyrazine-2-carbohydrazide derivatives represents a novel class of compounds with various therapeutic potential. This review mainly focused on the design and synthesis of dual heterocyclic scaffolds, including conventional and green synthetic strategies. It also includes ADMET profiling, which helps predict pharmacokinetic properties, target interactions, etc., as well as structure-activity relationships. Comprehensive biological activities, including antimicrobial, anticancer, anti-inflammatory, and anticonvulsant, of these dual heterocyclic compounds are also included. Through structure-activity relationships, the influence of different functional groups on activity can be determined. This review emphasizes the significant therapeutic promise of pyrazole-pyrazine conjugates and proposes future research pathways.

1. INTRODUCTION

Heterocyclic compounds form the backbone of many pharmaceutical agents due to their flexible chemical reactivity and extensive biological activities (Arora et al., 2012). More than 75% of FDA-approved drugs contain at least one heterocyclic ring, underscoring its significance in drug discovery and development (Vitaku et al., 2014). Pyrazole ($C_3H_3N_2H$) is a five-membered aromatic heterocyclic ring containing two nitrogen atoms in adjacent positions and belongs to the azole class (Hm et al., 2024) (Figure 1). The inclusion of the pyrazole ring in various moieties contributes a wide range of pharmacological activities, such as anti-inflammatory, antipsychotic, and antidepressant, which underscore its versatility across

different disease areas (Hm et al., 2024; Sahu et al., 2024).

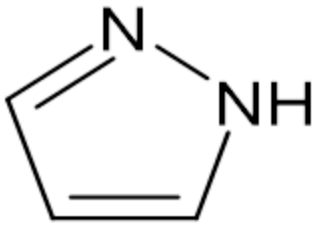

Figure 1: Structure of pyrazole

The nitrogen atom in the first position (N1) has a lone pair of electrons and participates in resonance with the aromatic system, which is described as "pyrrole-like". In contrast, the Nitrogen atom in the second position (N2) has unshared electrons that are not involved in resonance and are termed "pyridine-like" (Marek and Lycka, 2002). Due to the divergence between the two nitrogen atoms, pyrazoles show reactivity towards pyrrole and pyridine. Pyrazine is a six-membered aromatic heterocyclic compound with two nitrogen atoms in the para position (Aljamali, 2014) (Figure 2).

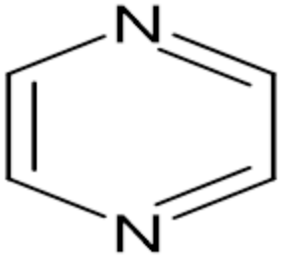

Figure 2: Structure of Pyrazine

The Nitrogen atom in pyrazine is in the para position because it has the weakest basicity among the diazines (Wren et al., 2012). The broad spectrum of pharmacological activities, such as antibacterial, antifungal, antimycobacterial (Ogryzek et al., 2016), anti-inflammatory, analgesic, and antiviral activities, exhibited by pyrazine derivatives has attracted significant attention from researchers, leading to increased investigation of this scaffold in drug development (Hou et al., 2023). Merging the pyrazole and pyrazine rings into a single molecular structure presents a novel and successful strategy for designing biologically active compounds. Due to the high electron density and strong hydrogen-bond-forming ability of the pyrazole ring, it enhances binding interactions with biological targets such as receptors and enzymes (Faisal et al., 2019). Besides, the pyrazine ring is electron-deficient, which increases metabolic solubility and stability (Juhas and Zitko, 2020). When these two heterocyclic moieties are combined into a single molecule, a synergistic effect is observed, i.e., the molecule exhibits the pharmacological properties of both heterocyclic rings. It results in enhanced bioavailability, increased target specificity, and better pharmacokinetic properties.

Structure-activity relationship plays a crucial role in determining how the different functional groups present in pyrazole and pyrazine rings alter biological activity. Modifications at the 3rd and 5th positions of the pyrazole ring, such as electron-donating groups (methyl, methoxy) and electron-withdrawing groups (halogens, nitro), produce noticeable effects on receptor binding affinity and pharmacological activity (Li et al., 2022; Singh et al., 2020a). Substitutions at the 2nd and 6th positions of the pyrazine ring enhance the membrane penetrability, stability, and solubility. The heteroatom-containing substituents, such as hydroxyl, amino, and nitro groups, may enhance hydrogen bonding interactions with biological targets, and the incorporation of aryl, alkyl, halogen, etc., groups balances lipophilicity and improves cellular uptake. The substitution of hydrophilic groups (hydroxyl and amino groups) at the 2nd and 6th positions of the pyrazine ring enhances enzyme inhibition and antimicrobial properties. Introduction of bulky aryl substituents increases π-π interactions with DNA, thereby enhancing anticancer activity (Singh et al., 2020a; Kitawat and Singh, 2014).

2. SYNTHETIC STRATEGIES

2.1 **Preparation of pyrazole** (Karrouchi et al., 2018; Tınmaz et al., 2020)

2.1.1 Cyclocondensation of hydrazine and its derivatives on 1,3-difunctional systems

The most popular technique for producing substituted pyrazoles is a cyclocondensation process involving a carbon unit such as a 1,3-dicarbonyl molecule, a 1,3-dicarbonyl derivative, or an α,β-unsaturated ketone, and a suitable hydrazine functioning as a bidentate nucleophile. The reactions are shown in Figure 3.

2.1.2 From 1,3-diketones

A quick and easy method for producing polysubstituted pyrazoles is the cyclocondensation of 1,3-dicarbonyl compounds with hydrazine derivatives. In 1833, Knorr et.al. performed the first synthesis of the substituted pyrazoles by reacting β-diketone 1 with hydrazine derivatives to produce two regioisomers, 2 and 3. The reactions are shown in Figure 4.

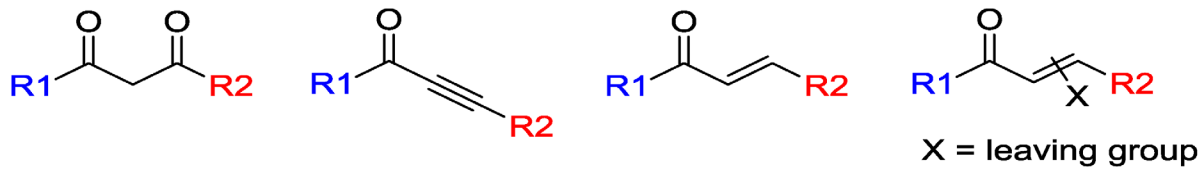

Figure 3: Cyclocondensation of hydrazine and its derivatives on 1,3-difunctional systems (Karrouchi et al., 2018, Tınmaz et al., 2020)

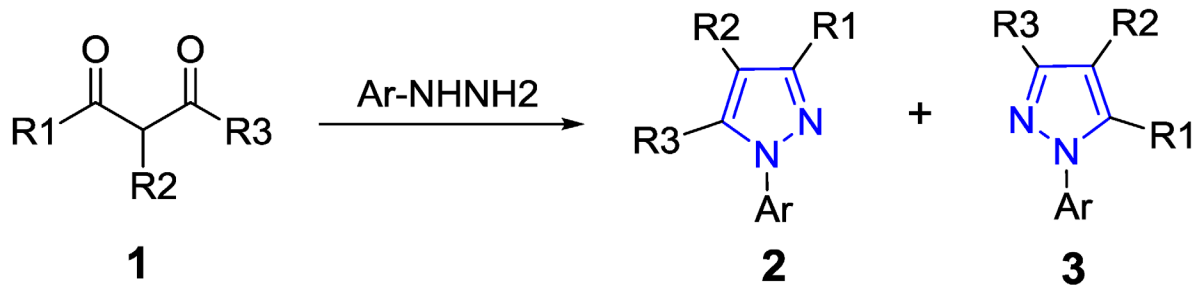

Figure 4: Synthesis from 1,3-diketones (Karrouchi et al., 2018, Tınmaz et al., 2020)

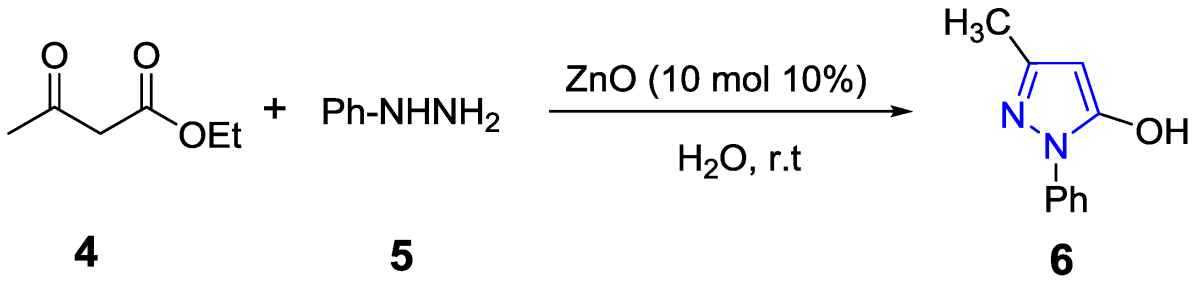

Figure 5: Synthesis of 1,3,5-substituted pyrazoles from ethyl acetoacetate (Karrouchi et al., 2018, Tınmaz et al., 2020)

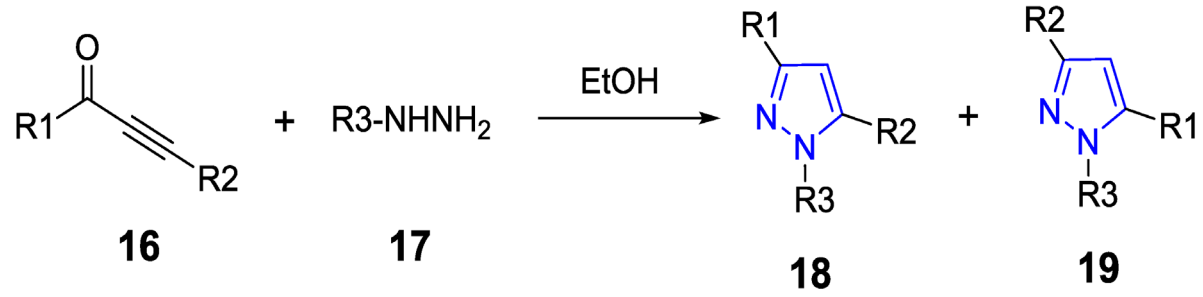

Figure 6: Synthesis from Acetylenic Ketones (Karrouchi et al., 2018, Tınmaz et al., 2020)

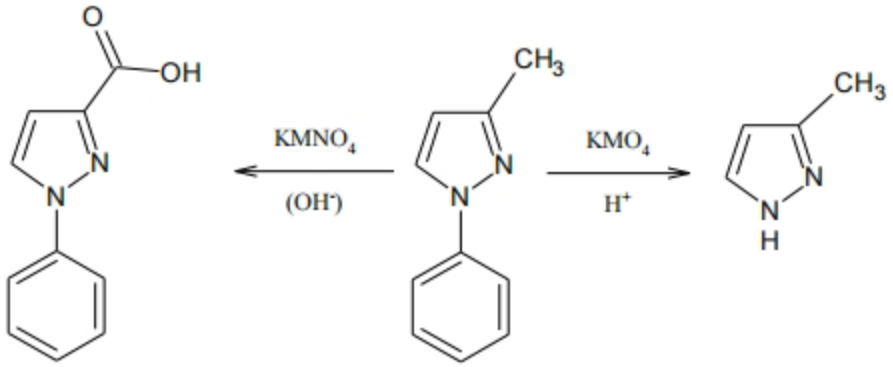

Figure 7: Oxidation reactions (Elderfield, 1950, Grimmett et al., 1979)

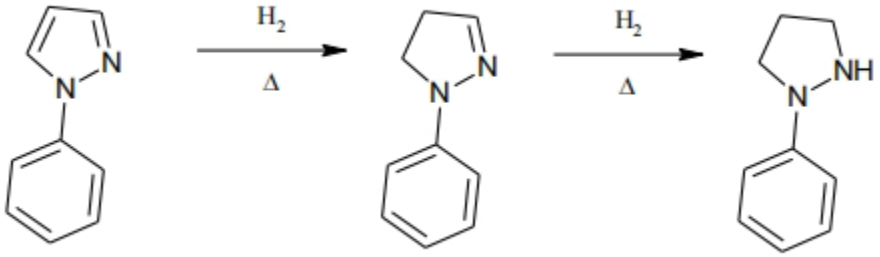

Figure 8: Reduction of the pyrazole ring (Elderfield, 1950, Grimmett et al., 1979)

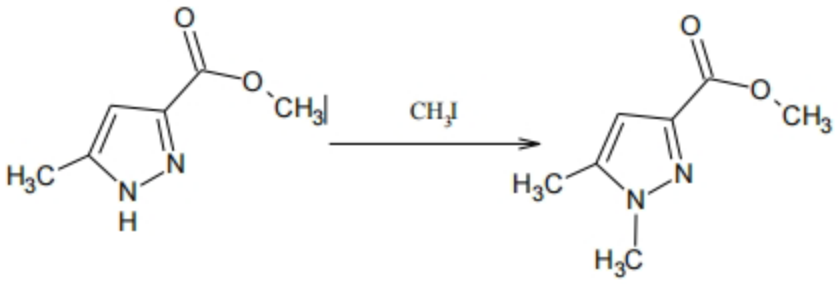

Figure 9: Alkylation reactions of the pyrazole ring (Elderfield, 1950, Grimmett et al., 1979)

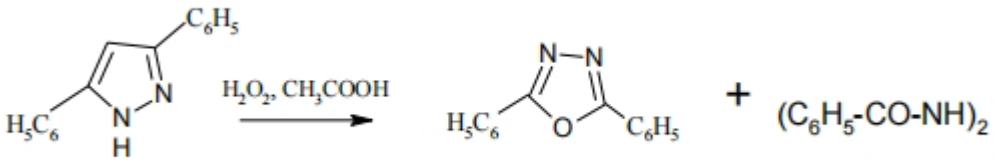

Figure 10: Oxidative cleavage of the Pyrazole (Elderfield, 1950, Grimmett et al., 1979)

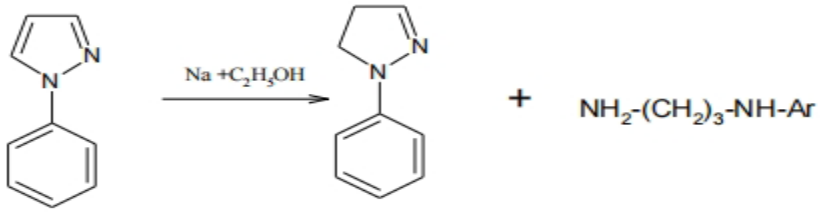

Figure 11: Reductive cleavage of the Pyrazole (Elderfield, 1950, Grimmett et al., 1979)

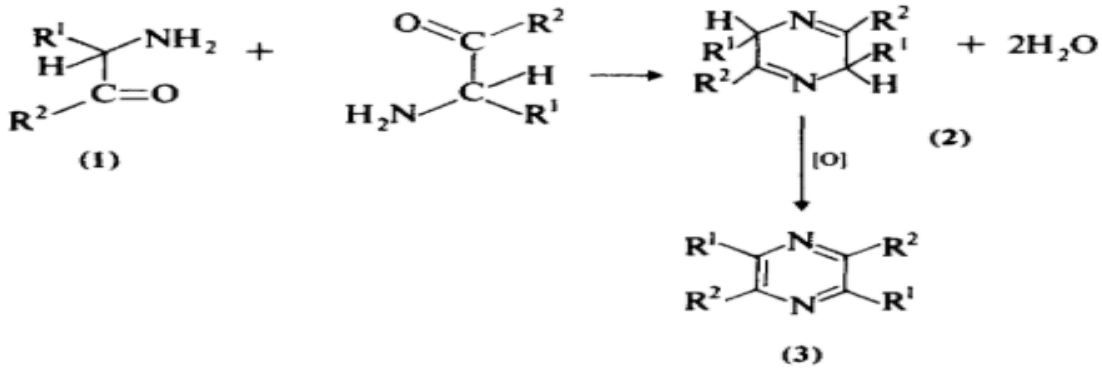

Figure 12: Self-condensation of a (primary amino) carbonyl compounds (Barlin, 2009, Akiyama et al., 1978)

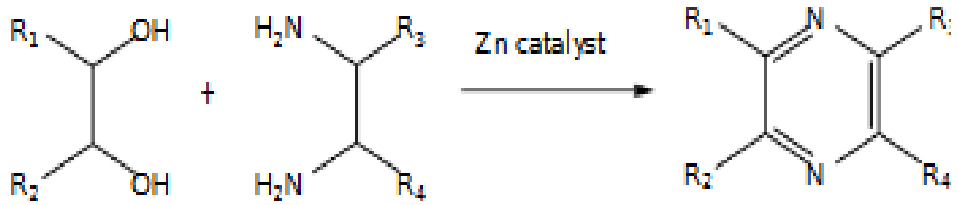

Figure 13: Formation of pyrazines in the presence of zinc (Barlin, 2009, Akiyama et al., 1978)

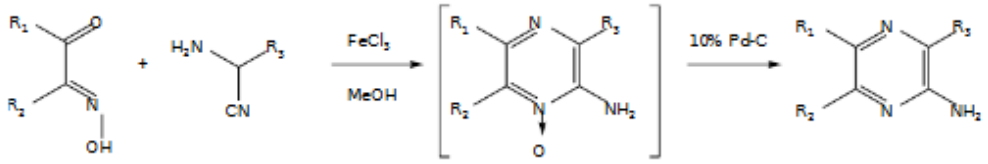

Figure 14: Catalytic formation of pyrazine using $FeCl_3$ (Barlin, 2009, Akiyama et al., 1978)

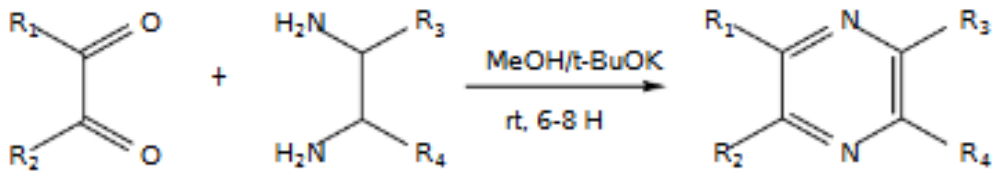

Figure 15: Green approach in producing pyrazine (Barlin, 2009, Akiyama et al., 1978)

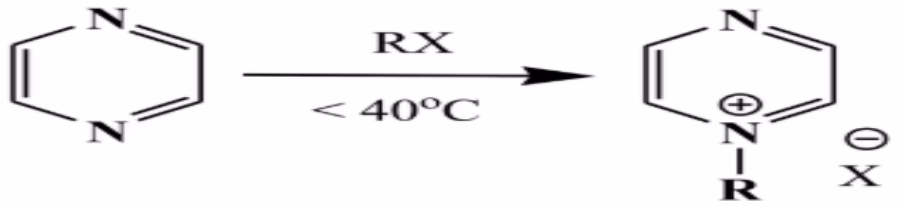

Figure 16: Alkylation at Nitrogen (Duffin, 1964, Maklad, 2012)

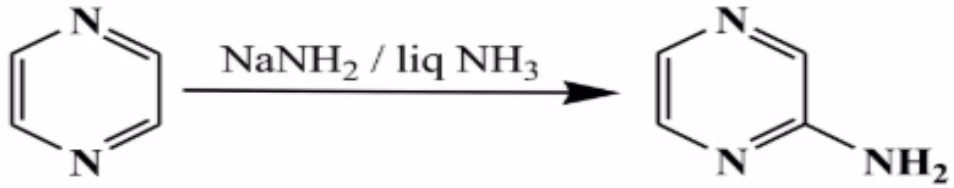

Figure 17: Chichibabin reaction (Duffin, 1964, Maklad, 2012)

2.1.3 Synthesis of 1,3,5-substituted pyrazoles from ethyl acetoacetate

An effective green method using nano-ZnO catalysis for the condensation of phenylhydrazine (5) with ethyl acetoacetate (4) to produce 1,3,5-substituted pyrazole derivatives (6). This protocol's primary benefits are its high yield (95%), quick reaction time, and simple work-up. The reactions are shown in Figure 5.

2.1.4 From Acetylenic Ketones

For over a century, it has been known that hydrazine derivatives 17 undergo a cyclocondensation reaction with acetylenic ketones 16 to produce pyrazoles. Nevertheless, the reaction yields a combination of two regioisomers, 18 and 19, once more. The reactions are shown in Figure 6.

2.2 **Reactions of pyrazole** (Elderfield, 1950; Grimmett et al., 1979)

2.2.1 Oxidation reactions

Generally, oxidizing agents only target side chains because the pyrazole ring is highly resistant to oxidation. Potassium permanganate has been the most widely used agent for side-chain oxidation; it's typically used in neutral or alkaline media, though sulfuric acid is sometimes present as well. Any side chain on the pyrazole ring can be readily changed into carboxylic acid groups by this oxidizing agent. The reactions are shown in Figure 7.

2.2.2 Reduction of the pyrazole ring

Pyrazole rings are directly involved in reduction responses, which can affect the contemporaneous reductive elimination of pyrazolines and pyrazolidines. When reducing pyrazole derivatives, the most commonly used reagents are sodium and alcohols, amalgamated sodium, hydrogen with different catalysts (substantially precautionary measures supported on barium sulfate), and rarely, zinc and acetic acid. The reactions are shown in Figure 8.

2.2.3 Alkylation reactions of the pyrazole ring

Alkyl halides (usually iodides and bromides), dialkyl sulfates, arylsulfonates, and diazomethane have been used as alkylating agents on the pyrazole ring. The reactions are shown in Figure 9.

2.2.4 Cleavage of the pyrazole ring

i.Oxidative cleavage of the pyrazole

In oxidation reactions, the pyrazole ring is tough to cleave. As a result, such reactions are rare. When 3,5-diphenyl pyrazole is oxidized with hydrogen peroxide in glacial acetic acid, 1,2-dibenzoylhydrazine and 2,5-diphenyl-1,3,4-oxadiazole are produced; the latter is most likely the result of the former product being dehydrated. The reactions are shown in Figure 10.

ii.Reductive cleavage of the pyrazole

Very little research has been conducted on the reductive cleavage of the pyrazole ring. Along with the corresponding pyrazolines, aryl tri-methylenediamines are produced when sodium and alcohol reduce 1-

Phenyl and 1-P-tolylpyrazole. The reactions are shown in Figure 11.

2.3 Preparation of pyrazine (Barlin, 2009; Akiyama et al., 1978)

2.3.1 Self-condensation of a (primary amino) carbonyl compound

The self-condensation of a (primary amino) carbonyl compound (1) to form dihydropyrazines, such as (2), which are then oxidized to the pyrazines, as demonstrated in the transformation of (1) to (3), is the most general method for the synthesis of 2,5-disubstituted and 2,3,5,6-tetrasubstituted pyrazines (3). The reactions are shown in Figure 12.

2.3.2 Formation of pyrazines in the presence of zinc

The reaction between a diamine and a diol in the presence of zinc as the catalyst, via a gas-phase contact reaction at 300-600 °C, using silica, alumina, or silica-alumina as the carrier for the catalyst, successfully afforded pyrazine at 55-78% yield. The reactions are shown in Figure 13.

2.3.3 Catalytic formation of pyrazine using $FeCl_3$

Isonitroso-acetophenone and aminoacetonitrile were reacted in the presence of one equivalent of $FeCl_3$ to produce N-oxide pyrazine, which was then hydrogenated with 10% Pd-C to produce 55-80% pyrazine. The reactions are shown in Figure 14.

2.3.4 Green approach in producing pyrazine

72-88% pyrazine was obtained by a straightforward condensation of 1,2-diamine and 1,2-dicarbonyl at room temperature with potassium tert-butoxide present. It was determined that the reaction first produced dihydropyrazine, which was then aromatized to pyrazine. The reactions are shown in Figure 15.

2.4 Reactions of pyrazine_(Duffin, 1964; Maklad, 2012)

2.4.1 Alkylation at Nitrogen

Pyrazine reacts with an alkyl halide to give a monoquaternary salt, but it is unstable and best prepared at temperatures below 400 °C. The reactions are shown in Figure 16.

2.4.2 Chichibabin reaction

Pyrazine reacts with $NaNH_2$ in liquid NH_2, similar to pyridine, to form aminopyrazine. The reactions are shown in Figure 17.

3. STRUCTURE ACTIVITY RELATIONSHIP

Structure-activity relationship plays a crucial role in determining how the different functional groups present in pyrazole and pyrazine rings alter biological activity. N-alkyl/aryl often **increases lipophilicity** and blocks H-bond donation—can improve cell permeability or alter selectivity. N-acylation / formation of ureas, carbamates: introduces **H-bond acceptors/donors** and metabolic handles. Unsubstituted N (N–H) may be required when the NH forms a key H-bond in the target binding site. The modifications made in the 3rd and 5th positions of the pyrazole ring, such as electron-donating groups (methyl group, methoxy group) and electron-withdrawing groups (halogens, nitro group), produce noticeable outcomes in receptor binding affinity and pharmacological activity. Highly influential for binding orientation. Substituents at C4 frequently point into a distinct pocket and are significant determinants of potency/selectivity. Aryl or heteroaryl at C4 is common to gain extra interactions (π–π, H-bond via substituents on the aryl). Polar substituents (sulfonyl, carbonyl, heterocycles) at C4 often improve selectivity by forming directional H-bonds (Li et al., 2022; Singh et al., 2020a).

In the Pyrazine ring, the two electron-withdrawing nitrogens decrease the electron density of the ring, making it more electrophilic. Nitrogens can act as hydrogen bond acceptors, crucial for enzyme binding and receptor interactions. Substitutions at the 2nd and 6th positions of the pyrazine ring enhance membrane permeability, stability, and solubility. The heteroatom-containing substituents, such as hydroxyl, amino, and nitro groups, may enhance hydrogen bonding interactions with biological targets, and the incorporation of aryl, alkyl, halogen, etc., groups balances lipophilicity and improves cellular uptake. The substitution of hydrophilic groups (hydroxyl group, amino group) in the 2nd and 6th position of the pyrazine ring enhances the enzyme inhibition and antimicrobial properties. Introduction of bulky aryl substituents increases the π-π interaction with DNA, thus showing better anticancer activity (Singh et al., 2020a, Kitawat and Singh, 2014).

4. ADMET AND PHARMACOKINETIC PROFILING

Pyrazine and pyrazole derivatives have diverse biological activities. So they are promising candidates in drug development. Many pyrazole derivatives exhibit good oral bioavailability due to their balanced lipophilicity, which facilitates permeation across biological membranes and absorption in the

gastrointestinal tract. Pyrazole derivatives, which show high solubility in aqueous media (Ebenezer et al., 2022). Similarly, pyrazine derivatives show both systemic and central nervous system (CNS) targeting due to their high permeability. These derivatives exhibit better blood-brain barrier (BBB) penetration, which is excellent for targeting CNS disease (Feng et al., 2024; Hou et al., 2023). Pyrazole derivatives lead to efflux limitation by interacting with P-glycoprotein. Both pyrazole and pyrazine derivatives show a promising profile with minimal cytochrome P-450 enzyme inhibition, which reduces the risk of drug-drug interactions (Correia et al., 2005). Pyrazole and pyrazine derivatives often fulfill the criteria outlined in Lipinski's rule of five, indicating their suitability as orally active drug candidates with favorable pharmacokinetic properties (Das et al., 2022).

5. PHARMACOLOGICAL ACTIVITIES OF PYRAZOLE-PYRAZINE CONJUGATES

5.1 Anticancer activity

The ongoing search for new, efficient, and selective chemotherapeutic agents is necessary because cancer is still one of the leading causes of death worldwide. Because of their extensive pharmacological characteristics, which include strong anticancer activity, heterocyclic scaffolds like pyrazole and pyrazine have garnered a lot of interest in medicinal chemistry in recent years. Although pyrazine moieties contribute to molecular planarity and electron-deficient properties that facilitate interactions with biological targets, such as DNA and enzyme sites, pyrazole derivatives are known to exhibit kinase inhibitory activity (Zhang et al., 2023).

- DNA intercalation: DNA intercalation is the disruption of transcription and replication processes caused by insertion between base pairs of DNA due to the planar nature of the pyrazine ring that causes damage to DNA and ultimately results in cell death (Singh et al., 2020b).
- Kinase inhibition: Numerous compounds based on pyrazoles are recognized to be kinase inhibitors. The conjugates in this work may inhibit serine/threonine kinases (eg, CDKs) or receptor tyrosine kinases (eg, EGFR, VEGFR), which would stop angiogenesis and cell division (Hosamani et al., 2024).
- Induction of Apoptosis: certain conjugates showed the capacity to trigger intrinsic apoptotic pathways, as evidenced by the disruption of mitochondrial membranes, activation of caspase-3/9, and upregulation of pro-apoptotic proteins.

5.2 Antimicrobial activity

Multidrug-resistant bacterial and fungal strains are rapidly emerging, endangering global public health and emphasizing the urgent need for new antimicrobial agents with unique mechanisms of action. Because they can break down microbial cell walls, inhibit important enzymes, and obstruct the synthesis of nucleic acids, heterocyclic scaffolds like pyrazoles and pyrazines are well known for their antimicrobial qualities. Pyrazole-pyrazine conjugates, which combine these two pharmacophores in a single molecular framework, may increase their bioactivity target specificity and foster synergistic interactions (Abu-Zaied et al., 2024; Kumar et al., 2017).

Pyrazole-pyrazine conjugates are thought to work against bacteria by,

- A breakdown in the integrity of the cell membrane that allows intracellular contents to seep out.
- The essential metal ions needed for the pathogen's enzymatic activity are chelated.
- Inhibiting protein synthesis by attaching to microbial subunits.

5.3 Anticonvulsant activity

The pyrazole nucleus increases GABAergic neurotransmission and decreases neuronal hyperexcitability; it has been extensively studied for its anticonvulsant properties. In models such as pentylenetetrazole (PTZ), maximal electroshock (MES), and kindling assays, structural changes, such as aryl, acyl, or heteroaryl substitution on the pyrazole ring, significantly increase its activity. Many compounds based on pyrazoles work as sodium channel blockers or positive allosteric modulators of GABA-A receptors, which stop abnormal neuronal firing and the progression of seizures.

Similar to this, the pyrazine nucleus has demonstrated significant promise in the development of anticonvulsant medications. Effective binding interactions with enzymes and neuronal receptors are made possible by its electron-deficient nature. Carbohydrazides and fused pyrazolo[3,4-b]pyrazines are derivatives that have shown broad-spectrum anticonvulsant activity, lowering tonic and clonic seizures in animal models. GABA receptor modulation and voltage-gated ion channel regulation are primarily

responsible for the mechanism, which makes pyrazine derivatives attractive options for new antiepileptic treatments (Farghaly et al., 2014; Bhandari et al., 2013).

5.4 Antiviral activity

As a core scaffold for substances that block important viral enzymes like RNA-dependent RNA polymerase, neuraminidase, and viral DNA polymerase, the pyrazine ring demonstrates strong antiviral activity by preventing viral replication and maturation. While other pyrazine-based compounds exhibit activity against HIV, HCV, influenza, and coronaviruses, derivatives such as pyrido[2,3-b]pyrazines have demonstrated strong efficacy against herpes viruses (HSV, HCMV, and EBV). The pyrazine nucleus is regarded as a flexible chemotype for creating broad-spectrum antiviral drugs because of its electron-deficient aromatic nature and capacity to establish robust binding interactions (Seliem et al., 2021; El-Sabbagh et al., 2009).

5.5 Anti-inflammatory activity

The combined pharmacological potential of both heterocyclic nuclei has drawn significant attention to pyrazole–pyrazole conjugates as promising anti-inflammatory drugs. While the pyrazole moiety improves lipophilicity, hydrogen-bonding ability, and metabolic stability, the pyrazine core helps create electron-deficient interactions that enable strong binding with inflammatory targets like cyclooxygenase (COX) enzymes. These conjugates have been shown to significantly reduce inflammation in a variety of experimental models by inhibiting COX-2 activity, lowering prostaglandin synthesis, and modulating pro-inflammatory mediators. Improved selectivity toward COX-2 over COX-1 is possible thanks to their dual framework, which also reduces the gastrointestinal side effects that are frequently linked to non-selective NSAIDs (Zang and Wang, 2023; Chen et al., 2023).

6. FUTURE PERSPECTIVES

Future investigations should focus on,

- Designing new derivatives through in silico modeling and fragment-based approaches to enhance selectivity toward specific therapeutic targets such as COX-2, kinases, and CNS receptors.
- In-vivo validation of the most promising candidates to confirm their safety, bioavailability, and efficacy profiles.
- Green synthetic methodologies utilizing recyclable catalysts and solvent-free conditions to support sustainable pharmaceutical development.
- Nanoformulation and targeted-delivery studies to improve tissue selectivity and reduce systemic toxicity.

7. CONCLUSION

Pyrazole–pyrazine conjugates represent a promising dual-heterocyclic framework that combines the pharmacological strengths of both rings into a single molecular entity. The pyrazole nucleus, with its high electron density and hydrogen-bonding ability, contributes to strong receptor binding and versatile biological activity. In contrast, the pyrazine core, being electron-deficient and metabolically stable, enhances solubility, stability, and target specificity. Their integration results in a synergistic system that exhibits improved bioavailability, pharmacokinetic properties, and receptor selectivity.

Acknowledgements

The authors would like to thank the college for its support.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

REFERENCES

Abu-Zaied, M. A., Elgemeie, G. H., & Mohamed-Ezzat, R. A. (2024). Novel Acrylamide-Pyrazole Conjugates: Design, Synthesis and Antimicrobial Evaluation. *Egyptian Journal of Chemistry*, *67*(13), 529-536. https://doi.org/10.21608/ejchem.2024.258180.9074

Akiyama, T., Enomoto, Y., & Shibamoto, T. (1978). A new method of pyrazine synthesis for flavor use. *Journal of Agricultural and Food Chemistry*, *26*(5), 1176-1179.

Aljamali, N. M. (2014). Review in cyclic compounds with heteroatom. *Asian Journal of Research in Chemistry*, *7*(11), 975-1006.

Arora, P., Arora, V., Lamba, H., & Wadhwa, D. (2012). Importance of heterocyclic chemistry: A review. *International Journal of Pharmaceutical Sciences and Research*, *3*(9), 2947.

Barlin, G. B. (2009). *The Pyrazines, Volume 41* (Vol. 41). John Wiley & Sons.

Bhandari, S., Tripathi, A. C., & Saraf, S. K. (2013). Novel 2-pyrazoline derivatives as potential anticonvulsant agents. *Medicinal Chemistry Research*, *22*(11), 5290-5296. https://doi.org/10.1007/s00044-013-0530-7

Chen, G.-Q., Guo, H.-Y., Quan, Z.-S., Shen, Q.-K., Li, X., & Luan, T. (2023). Natural products–pyrazine hybrids: a review of developments in medicinal chemistry. *Molecules*, *28*(21), 7440. https://doi.org/10.3390/molecules28217440

Correia, M. A., & Ortiz de Montellano, P. R. (2005). Inhibition of cytochrome P450 enzymes. *Cytochrome P*, *450*, 247-322. https://doi.org/10.1007/978-1-4757-2391-5_9

Das, B., Baidya, A. T., Mathew, A. T., Yadav, A. K., & Kumar, R. (2022). Structural modification aimed for improving solubility of lead compounds in early phase drug discovery. *Bioorganic & Medicinal Chemistry*, *56*, 116614. https://doi.org/10.1016/j.bmc.2022.116614

Duffin, G. (1964). The quaternization of heterocyclic compounds. In *Advances in Heterocyclic Chemistry* (Vol. 3, pp. 1-56). Elsevier. https://doi.org/10.1016/S0065-2725(08)60540-1

Ebenezer, O., Shapi, M., & Tuszynski, J. A. (2022). A review of the recent development in the synthesis and biological evaluations of pyrazole derivatives. *Biomedicines*, *10*(5), 1124. https://doi.org/10.3390/biomedicines10051124

El-Sabbagh, O. I., Baraka, M. M., Ibrahim, S. M., Pannecouque, C., Andrei, G., Snoeck, R., Balzarini, J., & Rashad, A. A. (2009). Synthesis and antiviral activity of new pyrazole and thiazole derivatives. *European Journal of Medicinal Chemistry*, *44*(9), 3746-3753. https://doi.org/10.1016/j.ejmech.2009.03.038

Elderfield, R. (1950). Heterocyclic compounds. John Wiley & Sons, Inc.

Faisal, M., Saeed, A., Hussain, S., Dar, P., & Larik, F. A. (2019). Recent developments in synthetic chemistry and biological activities of pyrazole derivatives. *Journal of Chemical Sciences*, *131*(8), 70. https://doi.org/10.1007/s12039-019-1646-1

Farghaly, A.-R., Esmail, S., Abdel-Zaher, A., Abdel-Hafez, A., & El-Kashef, H. (2014). Synthesis and anticonvulsant activity of some new pyrazolo [3, 4-b] pyrazines and related heterocycles. *Bioorganic & Medicinal Chemistry*, *22*(7), 2166-2175. https://doi.org/10.1016/j.bmc.2014.02.019

Feng, F., Xu, D.-Q., Yue, S.-J., Chen, Y.-Y., & Tang, Y.-P. (2024). Neuroprotection by tetramethylpyrazine and its synthesized analogues for central nervous system diseases: A review. *Molecular Biology Reports*, *51*(1), 159. https://doi.org/10.1007/s11033-023-09068-y

Grimmett, M., Lim, K. R., & Weavers, R. (1979). The N-Alkylation and N-arylation of unsymmetrical pyrazoles. *Australian Journal of Chemistry*, *32*(10), 2203-2213. https://doi.org/10.1071/CH9792203

Hm, A. B., & Dubey, S. (2024). Fundamental chemistry of n-heterocycles: pyrrole and pyrazole chemistry, imidazole chemistry, triazole chemistry advances in heterocyclic ring systems. *Paving the Path to Discoveries and Unlocking the Secrets of N-Heterocycles*, Cambridge Scholars Publishing. 64.

Hosamani, K. R., K, H., Pal, R., Matada, G. S. P., B, K., I, A., & Aishwarya, N. V. S. S. (2024). Pyrazole, Pyrazoline, and Fused Pyrazole Derivatives: New Horizons in EGFR-Targeted Anticancer Agents. *Chemistry & Biodiversity*, *21*(11), e202400880. https://doi.org/10.1002/cbdv.202400880

Hou, W., Dai, W., Huang, H., Liu, S.-L., Liu, J., Huang, L.-J., Huang, X.-H., Zeng, J.-L., Gan, Z.-W., & Zhang, Z.-Y. (2023). Pharmacological activity and mechanism of pyrazines. *European Journal of Medicinal Chemistry*, *258*, 115544. https://doi.org/10.1016/j.ejmech.2023.115544

Juhas, M., & Zitko, J. (2020). Molecular interactions of pyrazine-based compounds to proteins. *Journal of Medicinal Chemistry*, *63*(17), 8901-8916. https://doi.org/10.1021/acs.jmedchem.9b02021

Karrouchi, K., Radi, S., Ramli, Y., Taoufik, J., Mabkhot, Y. N., Al-Aizari, F. A., & Ansar, M. H. (2018). Synthesis and pharmacological activities of pyrazole derivatives: A review. *Molecules*, *23*(1), 134. https://doi.org/10.3390/molecules23010134

Kitawat, B. S., & Singh, M. (2014). Synthesis, characterization, antibacterial, antioxidant, DNA binding and SAR study of a novel pyrazine moiety bearing 2-pyrazoline derivatives. *New Journal of Chemistry*, *38*(9), 4290-4299. https://doi.org/10.1039/C4NJ00594E

Knorr, L. (1883). Einwirkung von acetessigester auf phenylhydrazin. Berichte der deutschen chemischen Gesellschaft, 16(2), 2597-2599. https://doi.org/10.1002/cber.188301602194

Kumar, B., Smita, K., Cumbal, L., & Debut, A. (2017). Green synthesis of silver nanoparticles using Andean blackberry fruit extract. *Saudi Journal of Biological Sciences*, *24*(1), 45-50. https://doi.org/10.1016/j.sjbs.2015.09.006

Li, G., Cheng, Y., Han, C., Song, C., Huang, N., & Du, Y. (2022). Pyrazole-containing pharmaceuticals: target, pharmacological activity, and their SAR studies. *RSC Medicinal Chemistry*, *13*(11), 1300-1321. https://doi.org/10.1039/D2MD00206J

Maklad, N. S. (2012). Chichibabin Amination Reaction. *ChemInform*, *43*(19), no-no.

Marek, R., & Lycka, A. (2002). 15N NMR spectroscopy in structural analysis. *Current Organic Chemistry*, *6*(1), 35-66. https://doi.org/10.2174/1385272023374643

Marinescu, M. (2021). Synthesis of antimicrobial benzimidazole–pyrazole compounds and their biological activities. *Antibiotics*, *10*(8), 1002. https://doi.org/10.3390/antibiotics10081002

Ogryzek, M., Chylewska, A., Królicka, A., Banasiuk, R., Turecka, K., Lesiak, D., Nidzworski, D., & Makowski, M. (2016). Coordination chemistry of pyrazine derivatives analogues of PZA: Design, synthesis, characterization and biological activity. *RSC Advances*, *6*(57), 52009-52025. https://doi.org/10.1039/C6RA03068H

Özdemir, A., Turan-Zitouni, G., Kaplancikli, Z. A., & Tunali, Y. (2009). Synthesis and biological activities of new hydrazide derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *24*(3), 825-831. https://doi.org/10.1080/14756360802399712

Pathak, S., Agrawal, N., & Gaur, S. (2024). A review on diverse biological activity of heterocyclic nucleus pyrazine and its derivatives: A key for the researchers. *Letters in Organic Chemistry*, *21*(4), 351-361. https://doi.org/10.2174/0115701786273932309270626616

Sahu, B., Sahu, R., Gidwani, B., & Mishra, A. (2024). Pyrrole: An Essential Framework in the Development of Therapeutic Agents and Insightful Analysis of Structure-Active Relationships. *ChemistrySelect*, *9*(31), e202401604. https://doi.org/10.1002/slct.202401604

Seliem, I. A., Girgis, A. S., Moatasim, Y., Kandeil, A., Mostafa, A., Ali, M. A., Bekheit, M. S., & Panda, S. S. (2021). New pyrazine conjugates: synthesis, computational studies, and antiviral properties against SARS-CoV-2. *ChemMedChem*, *16*(22), 3418-3427. https://doi.org/10.1002/cmdc.202100476

Singh, G., Chandra, P., & Sachan, N. (2020). Chemistry and pharmacological activities of pyrazole and pyrazole derivatives: a review. *International Journal of Pharmaceutical Sciences Review and Research*, *65*(1), 201-214. https://doi.org/10.47583/ijpsrr.2020.v65i01.030

Singh, I., Luxami, V., & Paul, K. (2020). Synthesis, cytotoxicity, pharmacokinetic profile, binding with DNA and BSA of new imidazo [1, 2-a] pyrazine-benzo [d] imidazol-5-yl hybrids. *Scientific Reports*, *10*(1), 6534. https://doi.org/10.1038/s41598-020-63605-4

Tınmaz, F., İlhan, İ. Ö., & Akkoç, S. (2020). Preparation and Properties of Some New Pyrazole Derivatives. *Organic Preparations and Procedures International*, *53*(1), 89-94. https://doi.org/10.1080/00304948.2020.1846449

Vitaku, E., Smith, D. T., & Njardarson, J. T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. *Journal of Medicinal Chemistry*, *57*(24), 10257-10274. https://doi.org/10.1021/jm501100b

Wren, S. W., Vogelhuber, K. M., Garver, J. M., Kato, S., Sheps, L., Bierbaum, V. M., & Lineberger, W. C. (2012). C–H bond strengths and acidities in aromatic systems: Effects of nitrogen incorporation in mono-, di-, and triazines. *Journal of the American Chemical Society*, *134*(15), 6584-6595. https://doi.org/10.1021/ja209566q

Zang, B., & Wang, L. (2023). Synthesis and protective effect of pyrazole conjugated imidazo [1, 2-a] pyrazine derivatives against acute lung injury in sepsis rats via attenuation of NF-κB, oxidative stress and apoptosis. *Acta Pharmaceutica*, *73*(3), 341-362. https://doi.org/10.2478/acph-2023-0031

Zhang, Y., Wu, C., Zhang, N., Fan, R., Ye, Y., & Xu, J. (2023). Recent advances in the development of pyrazole derivatives as anticancer agents. *International Journal of Molecular Sciences*, *24*(16), 12724. https://doi.org/10.3390/ijms241612724

Cite this article: Arya S Kumar and Seba M C. Pyrazole-pyrazine conjugates as potential therapeutic agents: design, synthesis and bioactivity. Asian J. Pharm. Health. Sci.. 2025;15(3):3122-3132. DOI:10.5530/ajphs.2025.15.84