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A REVIEW ON RECENT ADVANCES IN SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF PYRANO [2,3-C]PYRAZOLES

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ABSTRACT

Pyrano [2,3-c] pyrazoles have emerged as a privileged class of heterocyclic scaffolds in medicinal chemistry due to their structural versatility and broad spectrum of biological activities. This review critically examines recent advances in sustainable synthetic strategies for pyrano[2,3-c]pyrazole derivatives, with particular emphasis on green chemistry approaches such as aqueous reaction media, solvent-free protocols, and microwave-assisted multicomponent reactions. These methodologies, typically involving one-pot condensations of pyrazolones, aldehydes, and malononitrile, offer high atom economy, operational simplicity, and a reduced environmental footprint. In parallel, the pharmacological relevance of pyrano[2,3-c]pyrazoles is systematically discussed, highlighting their reported antimicrobial, anticancer, anti-inflammatory, analgesic, and antifungal activities. The review also addresses current challenges related to reaction scalability, mechanistic understanding, and structure–activity relationships, while outlining future perspectives for the rational design of biologically potent and environmentally benign pyranopyrazole-based therapeutics. Overall, the integration of sustainable chemistry principles with efficient synthetic technologies positions pyrano[2,3-c]pyrazoles as promising multifunctional pharmacophores for next-generation drug discovery.

Keywords: Lead Optimisation, Pyrano [2,3-c] Pyrazole Scaffolds, Microwave-Assisted Synthesis, Eco-Friendly Reaction Media, Pharmacological Profiling.

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INTRODUCTION

In the past, a lot of medications were either found by accident or by separating active ingredients from natural treatments. Finding possible lead compounds, synthesising them, describing their structure, physiologically screening them, and evaluating their therapeutic efficacy are all steps in the contemporary drug development process. A substance advances to the drug development stage in preparation for clinical trials if it demonstrates promising results during these early phases.[1] Pharmaceutical chemistry, which

encompasses three fundamental areas—the design and synthesis of novel drug molecules, their analytical evaluation, and pharmacological analysis—is the cornerstone of pharmacy education and research. Finding a potential lead molecule that can serve as a structural foundation for creating related analogues is the main goal of this field.[2] The centuries-long search for safer and more therapeutic drugs has fueled unrelenting efforts to treat a variety of illnesses. Many powerful and clinically useful medications have been found as a result of these tenacious efforts. Numerous biological activities depend on heterocyclic molecules, which are abundant in nature. These substances are important in medicinal chemistry research because of their distinct physicochemical characteristics and structural diversity.[2] The past two to three decades have seen significant progress in heterocyclic chemistry, particularly regarding the synthesis and functional applications of medium-sized heterocyclic rings.[3,4,5] The pharmacological characteristics of fused heterocyclic systems have garnered significant interest. The pyranopyrazole class, which combines a five-membered pyrazole ring with a six-membered pyran ring, serves as an example. This unique structural pattern serves as a preferred framework for creating bioactive compounds. The four isomeric forms of pyranopyrazoles are pyrano[2,3-c]pyrazole, pyrano[4,3-c]pyrazole, pyrano[3,2-c]pyrazole, and pyrano[3,4-c]pyrazole. Due to its significant pharmacological importance, the pyrano[2,3-c]pyrazole isomer (1) has received the greatest amount of research. The 1,4-Dihydropyrano-[2,3-c]pyrazol is shown in Fig.-1. The various biological effects associated with its heterocyclic core demonstrate the significance of pyrazoles in the development and production of medications.[6] Pyrano[2,3-c]pyrazole derivatives have been documented in scientific literature since the early 1800s.

It is important to note that the groundbreaking research done in 1973 by Junek *et al.*[7] and Otto *et al*.[8] marked a turning point that accelerated the development of functionalized pyrano[2,3-c]pyrazoles. Since then, these heterocyclic frameworks have garnered significant interest in medicinal chemistry because of their varied pharmacological potential. The several biological activities associated with pyrano[2,3-c]pyrazole compounds of pharmacological importance are highlighted in this review. Among the most researched heterocycles, pyrazoles are five-membered members of the azole family that are highly valued for their usage in chemical synthesis. Numerous synthetic techniques and structural analogues have been produced over the years as a result of intensive research.

Applications in a number of industries, including materials science, agrochemicals, and pharmaceuticals, have arisen by incorporating a pyrazole core into molecular structures. Pyrazole-containing compounds have been identified as potent drugs with a variety of bioactivities, including preventing protein glycation and displaying antiviral, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, and anti-tuberculosis qualities.[9] Recent years, have seen a resurgence of interest in pyrazoles' potential as biomolecular candidates due to their unique pharmacological properties. The fact that this heterocyclic theme is seen in many clinically authorised medications across various therapeutic categories emphasises its importance in contemporary medicinal chemistry.[10] Figure-1 shows the 1,4 dihydropyrano[2,3-c]pyrazole.

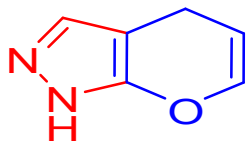


Fig.-1: 1, 4 dihydropyrano[2,3-c]pyrazole

In this review, we look at and evaluate the main synthetic approaches and the pharmacological properties of heterocyclic frameworks produced from pyrazoles. Pyranopyrazoles are an important class of heterocyclic ring systems that can be produced in a variety of ways [11] exhibit remarkable pharmacological activities [12, 13] and have been thoroughly studied in theoretical studies[14]highlighting their significance in both academic and industrial fields [15, 16]

The pyranopyrazole scaffold exists in four distinct isomeric forms: pyrano[2,3-c]pyrazole (2), pyrano[4,3-c]pyrazole (3), pyrano[3,2-c]pyrazole (4), and pyrano[3,4-c]pyrazole (5). The synthesis, biological activity, and structural derivatives of these substances are well documented, as shown in Fig.-2.[11,1 2]

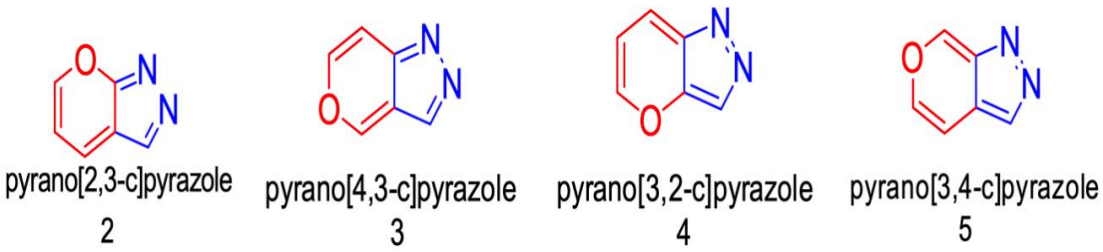


Fig.-2: Structure of Isomeric Pyranopyrazoles

Stollé created the first synthesis of pyrano[2,3-c]pyrazoles (2) by reacting hydrazine with ethyl acetoacetate.[13] Wolff's independent publication around the same time marked a significant advancement.[14] When Junek and Aigner synthesised several polynitrile derivatives in 1973, including important compounds like pyrano[2,3-c]pyrazol-6-one (6), pyrano[2,3-c]pyrazol-4-one (7), and 4H-pyrano[2,3-c]pyrazole (8), as shown in Fig.-3, a major advancement in the functionalization of pyrano[2,3-c]pyrazoles. Building on this basis, Khan and associates synthesized many derivatives of compounds 6 and 7 to further broaden the chemical space and enhance the collection of bioactive pyranopyrazole analogues.

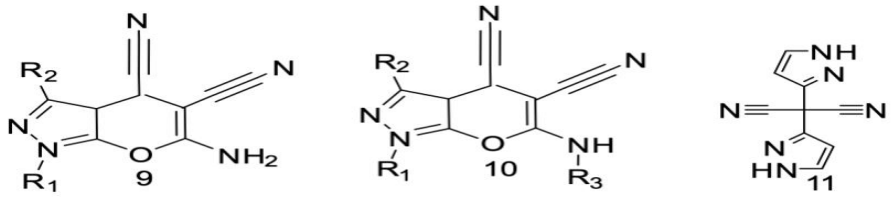


Fig.-3: Derivatives of Pyranopyrazoles

Despite the extensive exploration of pyrano [2,3-c]pyrazole derivatives in medicinal chemistry, a clear and integrated understanding of how sustainable synthetic methodologies influence their pharmacological potential remains insufficiently addressed. Most existing studies focus either on developing greener synthetic routes or on evaluating biological activities, with limited efforts to correlate eco-friendly synthesis with structure–activity relationships and therapeutic efficiency. The present review aims to bridge this gap by critically analysing recent advancements in green and sustainable strategies such as aqueous media, solvent-free conditions, and microwave-assisted multicomponent reactions, while simultaneously examining their impact on the biological performance of the resulting compounds. By consolidating these dual aspects, this work seeks to provide a comprehensive framework that not only promotes environmentally benign synthesis but also supports the rational design and optimisation of pyrano [2,3-c]pyrazole-based drug candidates, thereby enhancing their relevance in modern drug discovery.

EXPERIMENTAL

Synthesis of Pyrano[2,3-c] Pyrazoles

Two Component Synthesis of Pyrano[2,3-c]Pyrazoles

As shown in Fig.-4, Junek and Aigner demonstrated that the reaction of tetracyanoethylene with pyrazol-5-one and 5-aminopyrazole under various circumstances yields a variety of heterocyclic compounds, such as pyrano[2,3-c]pyrazoles (9), pyrazolo[3,4-b]pyridines (10), and dipyrazolylmalonodinitriles (11).[15,17] 6-amino-1,3-disubstituted-4,4,5-tricyanopyrano [2,3-c]pyrazole (9) was produced by refluxing the proper pyrazolone with tetracyanoethylene in ethanol, indicating a versatile synthetic route to this biologically relevant scaffold. Otto used sodium acetate as a catalyst in a reflux reaction of 4-benzylidene-pyrazol-5-one (12) with malononitrile (13) in methanol, producing pyrano[2,3-c]pyrazole (14)18. Figure-4 shows the structure of 1- [2,3-c]pyrazole.

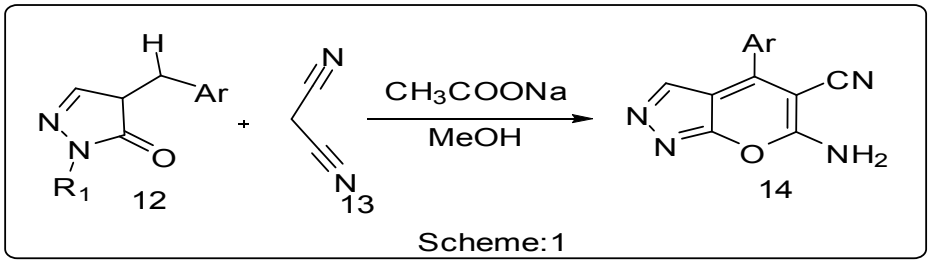


Fig.-4: 1- [2,3-*c*]pyrazole

Wang *et al.* synthesised 6-hydroxy-6-trifluoromethyl-pyrano[2,3-c]pyrazoles (17) using 10 mol% 1,4-diazobicyclo[2.2.2]octane (DABCO) as the base in DCM at room temperature. Outstanding yields (85-99%) were found in the results.[19] Additionally, triethylamine, N-N-dimethylaniline (C6H5N(CH3)2), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4, and 2-dimethylaminopyridine (DMAP) were examined in various solvents. While all bases yielded good results, DABCO was found to be an excellent catalyst for permitting diastereoselective control of the production of pyranopyrazoles (6:1-30:1) at a concentration of 20 mol%. The trans-products were mostly produced, according to the X-ray crystallographic study of the main isomer [Fig.-5: [2,3-c]pyrazole].

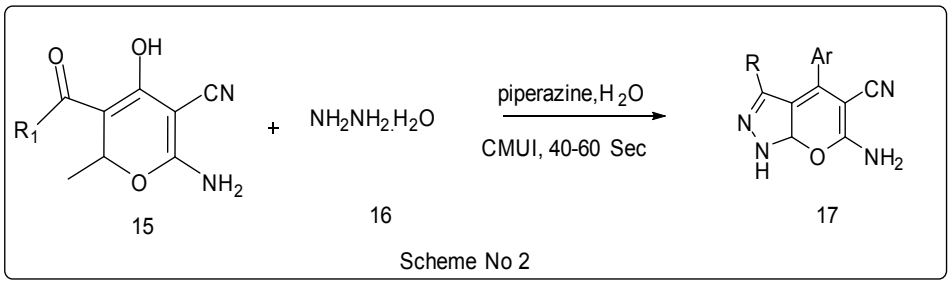


Fig.-5: [2,3-*c*]pyrazole

As a green solvent, water is the most economical, safe, and environmentally beneficial choice for lowering pollution, toxicity, and reaction costs.[20] Peng and associates used three distinct heating techniques to react 5-alkoxycarbonyl-2-amino-4-aryl-3-cyano-6-methyl-4H-pyrans (18) with hydrazine hydrate in the presence of a catalytic quantity of piperazine in pure aqueous media.

(i) being exposed to microwave radiation;

(ii) being exposed to a combination of microwave and ultrasound radiation; the latter showed exceptional yield in a short amount of time.[21] Strong ultrasound irradiation was thought to produce cavitation and fast interparticle collisions that would clean the surface, improving mass transfer between the two phases and speeding up the process without the need for an organic co-solvent Figure-6 [2,3-c] Pyrazol

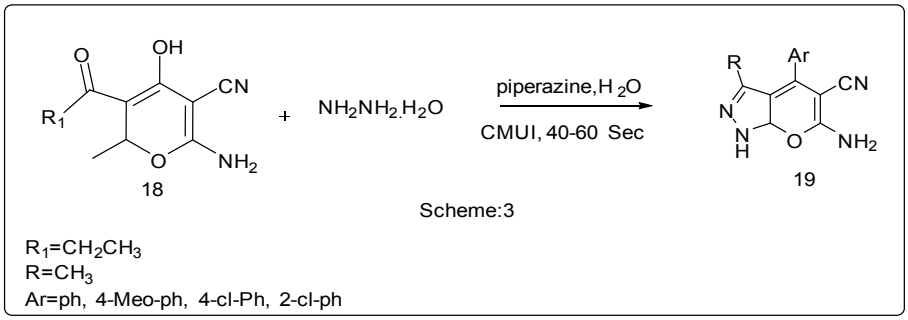


Fig.-6: [2,3-*c*] Pyrazole

Titanium dioxide was developed by Shaterian *et al.*[22] as a nanocatalyst for the one-step synthesis of dihydropyrano-[2,3-c]-pyrazoles (21). Malononitrile, hydrazine hydrate, ethyl acetoacetate, and the substituted aldehydes (20) reacted to promote condensation at room temperature without the need for solvents. Additionally, exceptional product yields ranging from 81% to 96% were shown by 0.25 mmol

of nano-titania. A Knoevenagel condensation of malononitrile and aldehyde was proposed as the chemical process, yielding 2-benzylidenemalononitrile as an intermediate. A Michael addition and subsequent intramolecular cyclisation of the pyrazolone with the intermediate produced the end product. Throughout the fifth cycle, the nanocatalyst material's activity stayed similar. Figure-7 shows the [2,3-c] pyrazole.

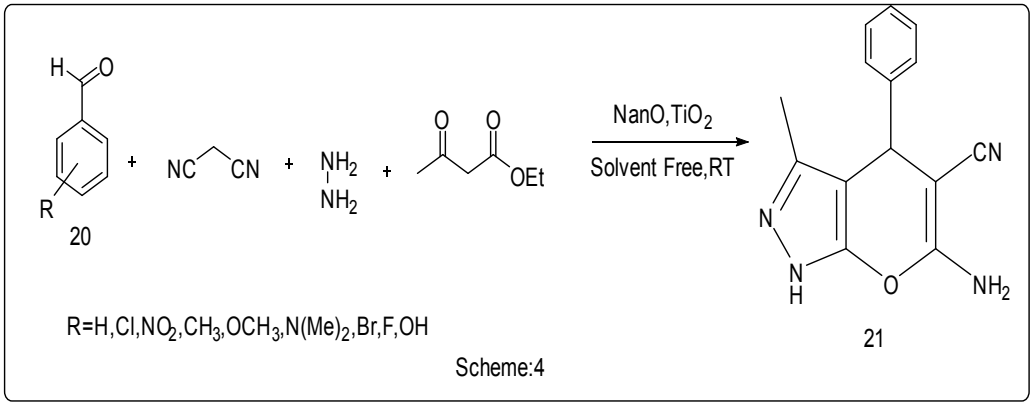


Fig.-7: [2,3-*c*] Pyrazole

Three-Component Synthesis of Pyrano[2,3-C]Pyrazoles

In most of these cases, pyrazolone, aldehydes, and malononitrile were reacted under different conditions to yield a variety of pyranopyrazoles. Jin and associates used p-dodecylbenzenesulfonic acid (DBSA) as a phase transfer catalyst to guarantee homogeneous reactant dispersion and a higher yield (84–94%).[23] When the reaction was first investigated without a catalyst, 4-dimethylaminobenzaldehyde showed either traces of product or no product at all. Reduced reactivity results from this compound's strong electron-donating dimethylamino group, which greatly contributes to the quinoid resonance shape. The synthesis of Pyranol [2, 3-c] pyrazoles without a catalyst is shown in Fig.-8.

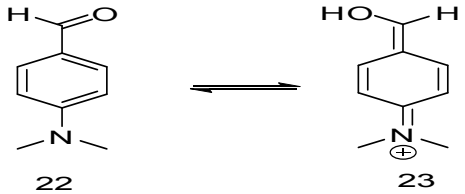


Fig.-8: Synthesis of Pyranol [2, 3-c] Pyrazoles in the Absence of Catalyst

In a second attempt, a number of PTCs were tested on similar reactants, including TBAB, DBSA, sodium dodecyl sulphate (SDS), and HTMAB; HTMAB produced the best results.[24] Because of their poor reactivity, aliphatic aldehydes did not respond well to the reaction conditions, but aromatic aldehydes with both electron-withdrawing and donating substituents did. Prajapati and associates used a piperidine catalyst to reflux substituted aldehydes, malononitrile, and 1-(2,4-dinitrophenyl)-3-methylpyrazol-5-one in ethanol. The related pyranopyrazoles from this reaction had strong antibacterial properties.[25] Figure-9 illustrates the overall synthetic pathway for the one-pot multicomponent synthesis of substituted pyrano [2,3-c]pyrazole derivatives through the reaction of pyrazolone (24), malononitrile (25), and aromatic aldehydes (26) under conditions A–C. Table-1 shows the Comparison of different synthetic schemes

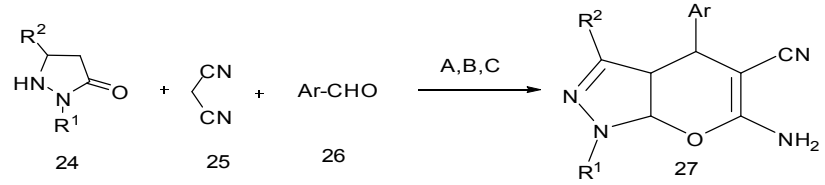


Fig.-9: General Synthetic Route for the One-Pot Multicomponent Synthesis of Substituted Pyrano [2,3-c]pyrazole Derivatives via the Reaction of Pyrazolone (24), Malononitrile (25), and Aromatic Aldehydes (26) Under Conditions A–C

Table-1: Comparison of Different Synthetic Schemes for the Preparation of Substituted pyrano[2,3-c]pyrazole Derivatives, Illustrating the Influence of R^1 and R^2 Substituents, Aryl (Ar) Groups, Reaction Conditions, and Corresponding Isolated Yields

S. No.	Scheme	R_1	R_2	Ar	Condition	Yield
1	A	Ph	CH_3	Ph,4-me-ph, 4-meoph,2-cl-ph	H_2O, DBSA,10 mol % ,60˚c , 3hours	84-94 %
2	B	Ph	CH_3	Ph, 2-cl-ph, 3-cl-ph	H_2O, 10 mol %, HTMAB, 85-90˚c	79-92 %
3	C	2-4, dinitro-ph	CH_3	Ph, 4-cl-ph, 2-cl-ph	EtOH, Piperidine, Reflux 3 hours	70-76 %

Aldehydes, malononitrile, and trifluoromethylpyrazol-5-one were reacted in water at 90°C without the use of a catalyst to create pyranopyrazoles with a trifluoromethyl group at the 3-position. Within three to five hours, the reaction produced positive results.[26] The yield of the product is unaffected by the electronic character of the aryl substituents. Bhavanarushi and associates produced fluoropyranopyrazoles by using DBU as a catalyst to grind comparable reactants in a mortar and pestle. They also clarified the molecular mechanism of DNA binding for the resultant compounds.[27] Pyranopyrazoles can be synthesized in 2–8 minutes using dry ethanol and a piperidine catalyst thanks to microwave irradiation, which also enhances the reaction rate and eliminates the requirement for heat[28]. Diaminopyrano[2,3-c]pyrazoles were prepared at room temperature in an ethanol-based solution using secondary amine/organic bases such as pyridine, piperidine, and pyrrolidine.[29] Some of the resultant compounds exhibited antifungal action in addition to being recognised as potential antibacterial agents. The generalised multicomponent reaction pathway for the synthesis of substituted pyrano [2,3-c]pyrazole derivatives (31) from pyrazolone (28), malononitrile (29), and aromatic aldehydes (30) under conditions A–D is shown in Fig.-10. Table-2 displays the substrate scope and reaction conditions for the synthesis of substituted pyrano[2,3-c]pyrazole derivatives under various catalytic/solvent systems, as well as isolated yields.

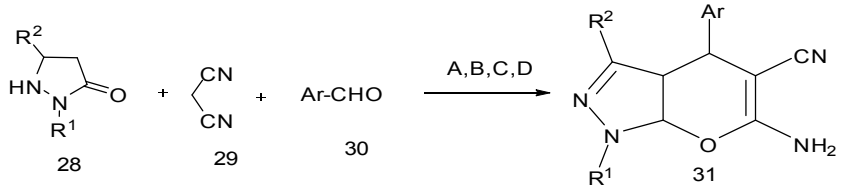


Fig.-10: Generalised Multicomponent Reaction Pathway for the Synthesis of Substituted pyrano [2,3-c]pyrazole Derivatives (31) from Pyrazolone (28), Malononitrile (29), and Aromatic Aldehydes (30) under Conditions A–D

Table-2: Substrate Scope and Reaction Conditions for the Synthesis of Substituted pyrano[2,3-c]pyrazole Derivatives under Different Catalytic/Solvent Systems, Showing Substituent Effects (R^1, R^2, Ar), Reaction Conditions, and Isolated Yields

Scheme	R_1	R_2	Ar	Condition	Yield
A	Ph	CF3	Ph, 4-cl-ph	H_2O, 90˚c, 3-5 hrs	78-90%
B	Ph, 3-cl-ph	CF3	Ph, 4-No2-ph,	DBU, grinding at RT	81-88%
C	Ph	Me	Ph, 4-cl-ph,	Piperidine/EtoH	61-91%
D	Ph	NH_2	Ph, 2-cl-ph,	EtoH, RT	64-90%

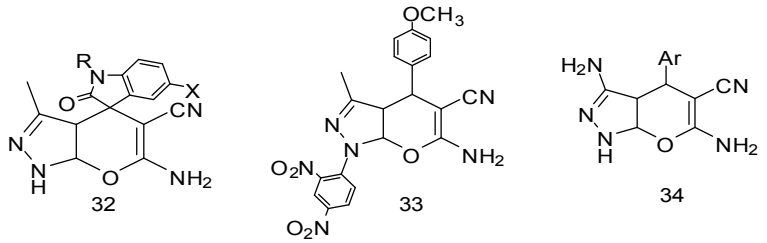
RESULTS AND DISCUSSION

Biological Activities

Antibacterial Activity

Hogale *et al.*[30] produced a series of antimicrobial pyrano[2,3-c]pyrazoles. Ahdi *et al.*[31] used piperidine as a catalyst in a one-pot, four-component synthesis of β-ketoesters, hydrazine hydrate, malononitrile, and isatines in aqueous media to create spiro-pyranopyrazoles. Through a simple work-up process, the reaction produced spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitriles 32 with high yields and purity at room temperature. These substances' antibacterial properties were also examined in vitro. One

difficult issue in the development of antibacterials is bacterial drug resistance, which arises from the extensive use and abuse of traditional antimicrobial medicines.[32] To address the issue of multi-drug resistant (MDR) bacteria and fungi, effective syntheses and research into some powerful chemicals are constantly necessary. Pyrano[2,3-c]pyrazoles have a special place in medicinal chemistry because of their potent microbial activity, according to recent studies. Under Michael reaction circumstances, Ei-Tamany *et al.*[33] produced pyrano[2,3-c]pyrazole derivatives using 4-arylidene-3-methyl-1-phenyl-2-pyrazolinones with several active methylene compounds. After testing each of the newly created chemicals against a variety of bacteria, it was discovered that some of them were physiologically active. The 2-(4-(Un)-substitutedphenylI)-1H-Indole is shown in Fig.-11.
S. Abdullah El-Assiery *et al.*[34] synthesised derivatives of pyranopyrazole, and the disk diffusion method was used to assess the compounds' antimicrobial activity. 35 Gram-positive strains of Staphylococcus aureus and Bacillus cereus, Gram-negative strains of Serratia marcescens and Proteus mirabilis, and fungi of Aspergillus fungytus were used to test the compounds. The microbiological activity of the compounds was moderate to high. Compound 33 showed modest efficacy against fungi and moderate activity against strains of Gram-negative bacteria. A number of spiro pyranofused heterocycles were created by Abdel *et al.*[36] and their antibacterial activity was evaluated.



R = H, Me, Et, X = H, Br, NO

Ar = 2-(4-(Un)-substitutedphenyl)-1H-indole

34a: H, 34b: CH3; 34c: OMe; 34d: Cl, 34e: Br, 34f: F

Fig.-11: 2-(4-(Un)-substitutedphenylI)-1H-Indole

Anticancer Activity

In a cytotoxicity bioassay using the human tumour cell line (HEPG2), Mohamed *et al.*[37] produced pyranopyrazole and pyranopyridines. Human liver cancer cells (HEPG2) were used to investigate the compounds' cytotoxicity. The results demonstrated that pyranopyrazole compounds produced the greatest results and showed moderate activity. Abidi *et al.* [38] generated a series of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-carbonitrile derivatives using a four-component coupling process that was catalysed by borax in water. Using the MTT colourimetric assay, the in vitro cytotoxic activity of the synthesised compounds against cancer cell lines (SW48, A549, KB, and HepG2) was evaluated in comparison to the well-known anticancer medication doxorubicin. 2, 4 Dimethoxy b is shown in Figure 12: R=3,4,5 Trimethoxy R=2 chloro d R=3 chlore R=4 chlore f R=nitro. When compared to doxorubicin, the synthesized compounds' cytotoxicity was good and reasonable in some of the cell lines that were investigated. Compounds 35a, 35b, and 35d in the KB cell line (IC50 values of 8±2.217 µM, 7±2.77 µM, and 7.5±1.49 µM, respectively), 35f in the A549 cell line (IC50 = 31.5±2.02 µM), 16e in the HepG2 cell line (IC50 = 22.5±3.09 µM), and 35c and 35f in the SW48 cell line (IC50 values of 23±0.772 µM, 6.3±0.65). The 2,4-Dimethoxy b is shown in Fig.-12: R=3,4,5-Trimethoxy R=2-chlor R=3-chlor R=4 chloro f R=nitro. Using the MTT method[39], Erugu *et al.*[40] created derivatives of 6-amino-5-cyno-3-trifluoromethylpyranopyrazole-4-spiro-oxindole and evaluated their in vitro cytotoxicity against U937 (human histiocytic lymphoma) and B16F10 (mouse melanocarcinoma) cell lines. Twelve different chemicals were examined. When a nitro group was present in the Spiro oxindole moiety and a chlorine atom was present in the pyrazole moiety, Compound 36 had the highest potency. When the nitro group in oxindole was removed or replaced with different halogen groups, the compounds' potency marginally decreased, but the chlorine atom remained in the pyrazole moiety.

Antiplatelet Activity

Agents that lessen platelet aggregation and stop thrombus formation are referred to as antiplatelet drugs.[41] 3-Methyl-4-phenyl-1,4-dihydropyrano [2,3-c]pyrazol-6-one, 4-(4-Methoxybenzyl)-3-methyl-1,4-dihydropyrano [2,3-c]pyrazol-6-one, and 6-Amino-4-(3,4-dihydroxyphenyl)-3-cyano-1,4-dihydropyrano [2,3-c]pyrazol]. Huang *et al.* [42] developed a series of 1- and 2-arylmethyl-3,4-dimethylpyrano[2,3-c]pyrazol-6-one derivatives and assessed their antiplatelet properties. Many of these substances showed strong inhibitory effects. The most efficient ones were 1-phenylmethyl-3,4-dimethylpyrano[2,3-c]pyrazol-6(1H)-one (38) and 2-(2'-methoxyphenyl)methyl-3,4-dimethylpyrano[2,3-c]pyrazol-6(2H)-one (39). The concentration of these inhibitors determined how they worked.

Chk1 Kinase Inhibitory Activity

A key component of the DNA damage response, a biochemical network in charge of maintaining genome integrity, is checkpoint kinase 1 (Chk1).[43] However, cancer cells abuse these circuits to evade the cytotoxicity of chemotherapy. Chk1 inhibitors have been developed as a chemopotentiating method, and many molecular processes that contribute to their synergy with chemotherapeutics have been identified. The compound 4-(6-amino-3-methyl-2,4-dihydropyrano[2,3-c]pyrazol-4-yl)benzene-1,2-diol (20) was identified by Foloppe *et al.*[45] as a potential inhibitor of human Chk1 kinase [15] due to its important role in the regulation of the G2M cell cycle.

Anti-Inflammatory Activity

The synthesis of 1,3,4,5-tetrasubstituted pyrazole derivatives and their in vitro anti-inflammatory properties were reported by Bhale *et al.*[31] (Fig.-6). Compound 40 showed exceptional inhibition (93.80%) at a concentration of 1 mM compared to the conventional diclofenac sodium (90.21%). El-Karim *et al.* [32] substances 40(a-f) (with oedema inhibition% values of 98.16%, 96.73%, 88.81%, 81.5%, 76.17%, and 76.68%) are potential prospects for generating a positive GIT safety profile and a quick and long-lasting anti-inflammatory action. Meanwhile, the analgesic evaluation revealed that, in comparison to the conventional drugs, 40b–40e produced robust and long-lasting analgesia as well as a significant decrease in the inflammatory cytokine TNF-α level. The suppression of protein denaturation in bovine albumin has an IC50 value of 34.1 μg/mL when diclofenac sodium is used as the reference drug (IC50 = 31.4 μg/mL). With IC50 values of 71.11, 81.77, 76.58, and 73.35 μg/mL, respectively, compared to the standard diclofenac, 41a–43d of the 15 new compounds synthesised by Akhtar *et al.*[33] showed considerable in vitro anti-inflammatory action. The linked benzylidene substituent has a major impact on the anti-inflammatory potency. A novel class of pyrazole compounds was created by Abdellatif *et al.*[34] The target compounds' ability to inhibit human recombinant COX-2 and ovine COX-1 was evaluated using an immunological enzyme assay (EIA) kit. With IC50 values between 0.02 and 0.04 μM, most of the investigated drugs showed significant COX-2 inhibition. Meanwhile, compounds 40a and 40b showed COX-2 selectivity indices (SIs) of 462.91 and 334.25, respectively, which were better than those of indomethacin (SI = 1.37) and celecoxib (SI = 313.12). With ED50 values of 136 and 126 μmol/kg, respectively, compounds 40a and 40b (with SO2NH2 acting as the selective COX-2 pharmacophore) showed the strongest anti-inflammatory action. Additionally, their expected safe gastrointestinal profiles are indicated by their lowest ulcerogenic liability (Ulcer Index values of 1.25 and 1.00, respectively). 41 was found by Shi and colleagues[35] to be the most effective anti-inflammatory drug (IC50 = 3.17 μM), with minimal toxicity and substantial inhibitory NO production (inhibitory rates (IR) = 90.4% at 10 μM). With an IC50 of 1.12 μM, this chemical likewise demonstrated strong suppression of iNOS.

Similar to the aspirin-treated group, compound 41 demonstrated a significant inhibitory effect on hind paw swelling and body weight loss in acute inflammatory models utilising AA rats. In the anti-inflammatory assay using the protein denaturation method, the para-nitrophenyl moiety connected to pyrazole conjugate 41 (93.53 ± 1.37%) showed the most anti-inflammatory activity among the compounds examined by Sivaram Karthikeyan *et al.*[36] This is higher than the diclofenac sodium standard value of 90.13 ± 1.45%.

Compound 42a showed exceptional sodium and celecoxib properties, with IC50 values of 55.65 and 44.81 μg/mL, respectively, according to Nayak *et al.*[37] The powerful compounds' in vitro COX-2

inhibitory effects were evaluated using an enzyme immunoassay. Compound 43d demonstrated a noteworthy capacity to preferentially target COX-2 with a selectivity index (SI) of 80.03, as opposed to the conventional celecoxib, which has a SI of 95.84. Compound 44 showed a good analgesic effect when given subcutaneously and intracerebroventricularly in vivo, according to Dimmito *et al.*[38] Furthermore, 44a showed a strong anti-inflammatory response after subcutaneous injection, indicating possible peripheral activation. Using the carrageenan rat paw oedema model, Harras *et al.*[39] synthesised many pyrazole compounds and evaluated their COX-1/COX-2 inhibition in vitro as well as their anti-inflammatory properties in vivo. Compared to COX-1, the targeted compounds were shown to exhibit a more inhibitory effect against COX-2. Meanwhile, all drugs' selectivity indices (SI) were analysed and compared to celecoxib (SI = 8.17). Compounds 45a and 45b had impressive COX-2 selectivity indices of 8.22 and 9.31, respectively. The safety of these derivatives was demonstrated by the histological analysis of the rats' kidneys, liver, and stomach, which revealed that 45a and 45b caused very minor degenerative alterations. Sivaram Karthikeyan *et al.*[40] reported that pyrazole compounds had anti-inflammatory properties. The derivative with the most anti-inflammatory profile was the one without substitution on the aryl entity 46. Abdellatif *et al.*[41-45]) synthesised a series of substituted pyrazole derivatives. The targeted compounds' capacity to inhibit COX-1/COX-2 was evaluated. Additionally, a histological analysis and the carrageenan-induced rat paw oedema model were used to evaluate their gastrointestinal safety and anti-inflammatory effectiveness. Compound 47 was determined to be the most effective anti-inflammatory agent (ED50 = 65.6 µmol/kg) when compared to the reference medication celecoxib (ED50 = 78.8 µmol/kg). Additionally, the potent compound showed very little ulcerogenic action (Ulcer Index = 7.25).

CONCLUSION

Pyrano[2,3-c]pyrazoles represent a versatile class of fused heterocycles with significant pharmacological potential and accessible synthetic routes. This review highlights recent progress in sustainable synthesis, particularly multicomponent, aqueous, solvent-free, and energy-efficient techniques, which align with green chemistry principles by enhancing atom economy and minimising environmental impact. The diverse biological activities reported further reinforce their importance as multifunctional pharmacophores in drug discovery. However, challenges such as limited mechanistic insights, incomplete structure–activity relationships, and the need for scalable and clinically validated protocols remain. Future research should focus on integrating sustainable synthetic strategies with advanced biological evaluation and translational studies. In alignment with United Nations Sustainable Development Goal SDG 12: Responsible Consumption and Production, this work recommends the development of eco-friendly, scalable methodologies that support responsible and sustainable pharmaceutical innovation.

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CONFLICT OF INTERESTS

The authors of this article attest that they are not associated with or involved in any organisation or entity that has a financial or non-financial interest in the topics or materials covered in it.

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