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Review Article

A Review on Pyranopyrazole as an Antibacterial Agent

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ABSTRACT

Aim: In our review of various literary works, we have discovered numerous therapeutic properties associated with pyranopyrazole. Additionally, we have postulated that pyranopyrazole may exhibit antibacterial effects. Pyranopyrazole derivatives are known to have biological significance, such as exhibiting anticancer, analgesic, and anti-inflammatory activities. They are also widely used in biodegradable agrochemicals and pharmaceutical constituents. Due to their applicability, the synthesis of pyranopyrazoles is currently receiving much attention. **Data Source:** For this purpose we have reviewed various types of research, review articles and some case reports on online platforms like Google scholar, PubMed, Wikipedia etc. **Study Selection:** So, as we hypothesized that the Pyranopyrazole drug also exhibits antibacterial activities, we focused on researching articles related to this. **Result and Conclusion:** This review provides recent developments in the synthesis methods of pyranopyrazoles, including reaction conditions such as the presence of catalysts, varying substrates, and reaction temperatures. And also it covers all the therapeutic effects identified by the various researchers.

INTRODUCTION

Pyranopyrazoles play a crucial role in medicinal chemistry and drug discovery due to their strong biological activity. The use of multicomponent reactions (MCRs) has been extensively studied for the synthesis and design of pyranopyrazoles, resulting in the formation of new C–C, C–N, and C–O bonds. This review aims to emphasize the biological importance of pyranopyrazoles and to present various synthetic methods for their production, including the use of catalytic systems such as acid-catalyzed, base-catalyzed, ionic liquids, green media-catalyzed, nano-particle-catalyzed, metal oxide-supported catalysts, and silica-supported catalysts. It summarizes the advancements in pyranopyrazole synthesis from the last two decades to mid-2023, along with research papers highlighting the significance of these compounds. [1]

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Table no.1: Drug profile of Pyranopyrazole

Molecular Formula	$C_{18}H_{20}N_4O_2$ [2]
IUPAC Name	6-amino-4-(2-ethoxyphenyl)-3-propyl-2,4-dihydropyrano(2,3-c) pyrazole-5-carbonitrile [2]
Molecular Weight	324.4 g/mol [2]
Therapeutic Use	Antibacterial Agent [2]

Literature Survey:

1. The synthesis of pyranopyrazole derivatives has been challenging due to issues such as difficult workup, long reaction times, expensive catalysts, and the use of organic solvents. This article introduces a new method for synthesizing pyranopyrazole derivatives using a low melting mixture as a catalyst and solvent. The physical properties of the new Lactic Acid: Urea: NH4Cl low melting mixture, including density, viscosity, acidity, refractive index, and surface tension, are also studied. Furthermore, IR spectra, 1H NMR spectra, emission spectra, polarity, and cytotoxicity are investigated. This new method offers a simple procedure, easy workup process, and does not require organic solvents. The components used in the mixture are readily available, and the reaction can be completed in less time at a temperature of 28°C.. [3]
2. The utilization of an eco-friendly synthetic route to produce therapeutic heterocycles with thiadiazolyl-pyranopyrazole fragments represents an innovative approach. The attainment of compounds in quantitative yields is noteworthy. The assessment of antimicrobial effectiveness against diverse microbes and beneficial fungi, accompanied by the determination of minimum inhibitory concentrations (MIC and MBC/MFC) and the examination of structure-activity relationships (SARs), yields valuable insights. The identification of potential activity enhancement through the incorporation of a nitro substituent within the composite is a compelling discovery. In summary, the validation of the suitability of these biologically active motifs for further preclinical studies marks a significant advancement in the pursuit of novel drug development. [4]
3. The catalyst CuSnO3:SiO2 was created using a hydrothermal method. The solid products were analyzed using various physical techniques such as XRD, SEM, TEM, and BET surface area. This study focuses on a simple method for producing pyranopyrazoles by mixing aldehydes, malononitrile, hydrazine hydrate, and ethyl acetoacetate with a small amount of Silica-grafted CuSnO3 in ethanol at 70°C. This method yields pyranopyrazoles quickly, and the catalyst is readily available while the product is easy to purify. [5]
4. The current study focuses on the synthesis of a compound called 6-amino-4-(4-hydroxyl-3-methoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2). This compound is created by combining 2-(4-hydroxyl-3-methoxybenzylidine) malononitrile (1) with 3-methyl-1-phenyl-2-pyrazolin-5-one. The resulting compound 2 is then used to produce a range of Schiff base derivatives (3a-h) by reacting it with various aldehydes. Two of these Schiff base derivatives (3a and 3b) are further reacted with mercaptoacetic acid to yield thiazolidinone derivatives (4a and 4b). The structures of the prepared compounds are confirmed using FT-IR, 1H NMR, and 13C NMR spectroscopies. These compounds are

then evaluated for their effectiveness as copper corrosion inhibitors, anti-rust agents, and antioxidants. The evaluation is carried out by mixing the compounds with a base medium lubricating oil (type 60 stock) provided by the Iraqi Midland Refineries Company/Al-Daura, according to the American Society of Testing and Materials ASTM-D130, ASTM-D665, and Institute of Petroleum's testing method, oxidation stability test (IP-280). [6]

5. The hospital environment promotes the spread of drug-resistant bacteria. In response to this public health issue, a researcher aimed to find a better tool for managing patient care. The study focused on assessing the effectiveness of synthetic molecules against multidrug-resistant bacterial isolates from patients with suspected hospital-acquired infections. After synthesizing and characterizing five specific compounds (5a-e), a sensitivity test was conducted to evaluate their antibacterial activity using microbiological methods such as diffusion and microdilution. The results showed that compound 5c exhibited the highest potential against all the bacterial strains tested, with a minimum inhibitory concentration (MIC) ranging from 6.25 - 50 mg/mL. The lowest MIC values were observed with Klebsiella pneumonia, while the highest value was found with Listeria monocytogenes. Additionally, in silico pharmacological studies including ADME and docking data were carried out for the selected compounds (5a-e) to understand their potential mode of interaction with the target. The docking results indicated that compounds 5c and 5b showed significant binding energy towards the active sites of Escherichia coli MurB and Staphylococcus aureus DNA gyrase B. Both in vitro and in silico data confirmed the antimicrobial potential of the five synthetic compounds, contributing to the literature on the bioactivity of pyrano[2,3-c] pyrazole. [7]
6. The compound 2,5-diphenyl-2,4-dihydro-pyrazol-3-one (1) was treated with 2-chloro-benzaldehyde (2) in an ethanol/sodium hydroxide solution, resulting in the formation of the chalcone derivative (3). This derivative was then reacted with malononitrile to produce 6-amino-4-(2-chloro-phenyl)-1,3-diphenyl-1,4-dihydro-pyrano[2,3-c] pyrazole-5-carbonitrile (4). Compound 4 was further reacted with formic acid, acetic anhydride, formamide, thiourea, urea, concentrated cold sulfuric acid, D-glucose, p-methoxy benzaldehyde, 4-dimethyl aminobenzaldehyde, benzoyl chloride, and triethyl orthoformate to yield a series of pyranopyrazole derivatives (5-15). The formimidic acid ethyl ester 15 was reacted with hydrazine hydrate to produce 4-(2-chlorophenyl)-5-imino-1,3-diphenyl-1,4-dihydropyrazolo [4',3':5,6] pyrano[2,3d] pyrimidin-6(5H)-amine (16). Compound 16 was then reacted with D-xylose to yield the sugar derivative 17. Additionally, compound 16 was reacted with CS2 to produce 18 in a good yield. The newly synthesized compounds were evaluated for their antimicrobial, antioxidant, and anticancer activities through a docking study. [8]
7. They have discovered a new method for producing pyrano[2,3-c]pyrazoles and how they bind to p38 MAP kinase. Pyrano[2,3-c]pyrazole derivatives were created through a four-component reaction involving benzyl alcohols, ethyl acetoacetate, phenylhydrazine, and malononitrile in the presence of sulfonated amorphous carbon and eosin Y as catalysts. All products were identified using melting point, 1H and 13C NMR, and HRMS (ESI). The products were then virtually tested for their binding activities to both the ATP-

binding pocket and the lipid-binding pocket of p38 MAP kinase, using a structure-based flexible docking provided by the ADFR engine. The results showed that eight synthesized compounds had a higher affinity to the lipid pocket than to the ATP-binding pocket, suggesting potential applications as allosteric inhibitors. Finally, the most biologically active compound, 5, exhibited a binding affinity similar to other known lipid pocket inhibitors, with an affinity to the target pocket reaching −10.9932 kcal/mol, and also had the best binding affinity to the ATP-binding pockets among all the products. Therefore, their research presents a new method for synthesizing pyrano[2,3-c]pyrazoles and provides evidence of their biological capability to block p38 MAP kinase pockets, which could be valuable for developing cancer or immune drugs. [9]

8. Pyranopyrazoles are important in medicinal chemistry due to their pharmacological and biological activities. These include antibacterial properties comparable to cefazolin and ciprofloxacin, as well as antimicrobial, antifungal, antitumor, anticancer, analgesic, anti-inflammatory, anti-Alzheimer's disease, and antioxidant properties. They also have the potential to inhibit human Chk1 kinase. Dehbalaei et al. synthesized 6-amino-4-aryl-2,4-dihydro-3-phenyl pyrano[2,3-c]pyrazole-5-carbonitriles using a one-pot, four-component reaction of aryl aldehydes, hydrazine hydrate, ethyl benzoylacetate, and malononitrile under ultrasonic irradiation conditions. The reaction conditions were optimized using various catalysts such as alumina, DABCO, l-proline, benzyl triphenyl phosphonium chloride (BTPPC), and choline chloride:thiourea and choline chloride:urea (DES). [10]
9. A new method using taurine as a catalyst has been developed to create a range of therapeutic core dihydropyrano[2,3-c]pyrazoles efficiently and in an environmentally friendly way. The method has been used to produce a series of new 1,4-dihydropyrano[2,3-c]pyrazoles with isonicotinamide, spirooxindole, and indole components. These compounds have shown potential in binding to both wild-type and antibiotic-resistant forms of dihydrofolate reductase, an important enzyme targeted by drugs to combat antibiotic-resistant strains of Staphylococcus aureus. This research suggests that the dihydropyrano[2,3-c]pyrazole derivatives could be developed into effective treatments for staphylococcal infections in the future. [11]
10. Shaabani et al. have described the method of synthesis by using Catalyst free condition and by using acid as a catalyst.

Method 1: Using catalyst-free conditions

Shaabani et al. described a three-component reaction for the synthesis of pyranopyrazoles using acetylenedicarboxylate, isocyanides, and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (Scheme 1). The reaction afforded the corresponding pyrano[2,3-*c*] pyrazole derivatives in good yields without using any catalyst. A catalyst-free synthesis of a series of pyranopyrazoles at the short reaction times (3–11 min) via a four-component reaction between an aromatic aldehyde, hydrazine hydrate, ethyl acetoacetate and malononitrile at room temperature under neat conditions was reported.

Method 2: Using Acid as a catalyst:

In 2011, a series of pyrano[2,3-*c*] pyrazoles, was efficiently synthesized via one-pot, four component reaction of ethyl acetoacetate, hydrazine hydrate, aldehydes and malononitrile in the presence of a catalytic amount of environmentally friendly silicotungstic acid

($H_4[SiW_{12}O_{40}]$) at 60 °C under solvent-free condition.[12]

CONCLUSION AND FUTURE SCOPE:

Pyranopyrazole derivatives can be synthesized through two-, three-, four- or five-component reactions. One-pot four-component syntheses are the most common method for constructing fused pyran and pyrazole rings. Various types of materials catalyze these reactions to afford the corresponding pyranopyrazole derivatives. In the future, exploring new synthetic methods for pyranopyrazoles would be an interesting research area due to their potential as biologically active compounds.

REFERENCE

1. Ashok R. Yadav, et, al. Review on advancements of pyranopyrazole: synthetic routes and their medicinal applications, Molecular Diversity, 18Jan2024
2. https://pubchem.ncbi.nlm.nih.gov/compound/644905
3. Letcy V. Theresa, et. Al., Sustainable multicomponent one pot synthesis of pyranopyrazole derivatives in the presence of Lactic acid: Urea: NH4C, Current Research in Green and Sustainable Chemistry 4 (2021) 100194.
4. G. M. Reddy, et. Al., PYRANOPYRAZOLES AS EFFICIENT ANTIMICROBIAL AGENTS: GREEN, ONE POT AND MULTICOMPONENT APPROACH, Yekaterinburg, Russia, November 15–17
5. S. L. Sangle*, et. Al., EFFICIENT SYNTHESIS OF PYRANOPYRAZOLE DERIVATIVES USING SILICA GRAFTED COPPER STANNATECATALYST, Journal of Advanced Scientific Research, 2022; 13 (2): 38-43
6. Ahmad R. Salih, et. Al., Synthesis, Characterization and Evaluation of Some Pyranopyrazole Derivatives as Multifunction Additives for Medium Lubricating Oils, Iraqi Journal of Science, 2022, Vol. 63, No. 7, pp: 2827-2838
7. Boutaina Addoum, Al., Synthesis, in vitro Antimicrobial Activity, and Docking Studies of some Pyrano[2,3-c] Pyrazole Derivatives, Biointerface Research in Applied Chemistry, Volume 12, Issue 4, 2022, 4705 – 4730
8. Ibrahim F. Nassar et. Al., Design, Synthesis and Biological Evaluation of Novel Pyrano[2,3- c]pyrazoles And Their Sugar Derivatives as Antimicrobial, Antioxidant and Anticancer Agents, Egyptian Journal of Chemistry, 2022.143253.6253
9. Hai Truong Nguyen, et. Al., A New Pathway for the Preparation of Pyrano[2,3-c]pyrazoles and molecular Docking as Inhibitors of p38 MAP Kinase, ACS Omega 2022, 7, 17432−17443
10. Sarita Khandelwal, et. Al., Use of sustainable organic transformations in the construction of heterocyclic scaffolds in Green Approaches in Medicinal Chemistry for Sustainable Drug Design, 2020 Pages 245-352.
11. Ghanshyam Mali, et. Al., Design, Synthesis, and Biological Evaluation of Densely Substituted Dihydropyrano[2,3-*c*] pyrazoles *via* a Taurine-Catalyzed Green Multicomponent Approach ACS Omega. 2021 Nov 16; 6(45): 30734–30742.
12. Manouchehr Mamaghani, et. Al., A Review on the Recent Multicomponent Synthesis of Pyranopyrazoles, Polycyclic Aromatic Compounds Volume 41, 2021-Issue 2

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