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Pyrazole Derivatives; Synthesis, Reactivity and Emerging Application in Modern Chemistry

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Abstract
Pyrazole derivatives, which are a large class of five-membered nitrogen containing heterocyclic derivatives, are known to be highly reactive and have several biological, pharmaceutical and industrially important applications, which has made them very attractive to modern chemists. Pyrazoles are unique compounds due to their electronic and structural features, which give them the capacity to be involved in several synthetic reactions, including cyclocondensation reactions, multicomponent reactions, microwave-assisted reactions, green chemistry reactions, and metal-catalyzed reactions, to obtain functionalised derivatives. The study of new synthetic methods to prepare various types of pyrazole-containing compounds in pharmaceutical and material chemistry has expanded, due to the reaction efficiency, selectivity, and environmental friendliness. Pyrazole derivatives exhibits a variety of therapeutic benefits as to its antioxidant, antiviral, anticancer, anti-inflammatory, antitubercular, antibacterial, and analgesic activities making this very interesting scaffolds for the development of new drugs. These compounds are also starting to be used in other fields such as agrochemicals, dyes, corrosion inhibition, coordination chemistry and new functional materials. All the up-to-date news on the synthesis, chemical reactivities, structural transformations and future directions of research on pyrazole derivatives is detailed. In particular, creative synthetic methods, structure-activity relationships and future perspectives for the synthesis of new molecules based on pyrazole and their potential applications in biology and commercial use are emphasized.
Keywords; *Heterocyclic Chemistry, Pyrazole derivatives, Synthesis, Structure–Activity Relationship (SAR)*

I. Introduction

The significance of heterocyclic molecules in biology and industry has grown them to be a large subject of modern chemistry. Pyrazole derivatives are quite structurally diverse, chemically stable and have a wide spectrum of pharmacological effects, which distinguishes them from other nitrogen containing heterocycles. The unique properties of the pyrazole's electrical properties and diverse reactivity patterns are contributed to by the presence of the five-membered aromatic heterocyclic ring, which contains two neighbouring N (nitrogen) atoms. Because of their potential uses in medicinal chemistry, pharmaceutical sciences, agrochemical research, and materials science, pyrazole-based compounds have garnered a lot of attention from researchers in these areas in recent decades (Elguero et al., 2002).

Most of the biological activities demonstrated by pyrazole derivatives (e.g. antibacterial, anti-inflammatory, analgesic, anticancer, antitubercular, antiviral, antioxidant, anticonvulsant and antidiabetic activities) are the major reasons of their increasing interest. Several pharmaceuticals contain the pyrazole ring which have been widely used in the clinic. Pyrazoles represent scaffolds that are beneficial for the treatment of inflammation and discomfort and may be selected ones are cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Finar, 2008). Moreover, pyrazole derivatives are very important in present investigations for modern drug developments, as they participate in enzyme modulations, receptor targeting agents and as kinase inhibitors (Kumar et al., 2013).

Recent progress in the synthesis of organic compounds has greatly enhanced the availability and diversity of pyrazole derivatives. There are several synthetic methods which have been put into practice for successful synthesis of pyrazoles such as; solvent-free synthesis, microwave-assisted Green Chemistry methods, ultrasound-assisted methods, cyclocondensation reactions and one-pot, multicomponent methods. These cutting edge methods not only minimize environmental risk but also produce higher yields and selectivity in reactions according to Katrizky et al (2010). Moreover, some techniques such as nanocatalysts and reactions catalysed by transition metal have significantly extended the application of synthesis of pyrazoles in modern research.

As well as for pharmaceutical applications, pyrazole derivatives have considerable importance in industrial and technological applications. They are often used in agrochemicals such as herbicides, fungicides and insecticides, due to their excellent biological efficiency and resistance. The optical, fluorescence, electrical, and coordination characteristics of compounds containing pyrazoles have been studied in the field of materials science. They also have excellent metal-binding capabilities, and are also utilized as corrosion inhibitors, dyes, pigments and ligands in coordination chemistry (Joule & Mills, 2010).

Due to the significant demand for synthesis of new medicinal drugs and eco-friendly synthetic methods, synthesis, reactivity and applications of pyrazole derivatives have been studied. Selectivity, toxicity and biological activity have been improved by varying the structure of the pyrazole nucleus to generate molecules that are more selective. From this point on, pyrazole chemistry is an expanding discipline that is important in organic synthesis, medicinal chemistry and in the field of industry, it is also an indispensable field in multidisciplinary studies.

The aim of this survey is to provide a comprehensive review about the synthesis, chemical reactivity and also new possible applications of pyrazole derivatives in the modern chemistry. The new compounds which are based on pyrazole are explained with their significance in the field of pharmacology, structure activity relationship, special synthesis approaches and future developments of the compounds.

Structure of Pyrazole Derivatives

Pyrazole is an aromatic molecule with 3 carbon atoms and 2 neighbouring N atoms, and is planar in its structure. Pyrazole has a chemical formula of CሐH_4N_2. Aromaticity increases when the six π-electrons in the ring system are delocalised, which aids the stability of this compound.

The molecular formula of pyrazole simplified is:

$C_3H_4N_2$

There is tautomerism, due to the movement of the H atom between the two N atoms in the pyramole ring. This is of fundamental importance to the polarity, biological activity, reactivity, as well as the tautomeric behaviour of pyrazole derivatives.

Pyrazole is aromatic (Hückel's rule):

$4n+2$ π-electrons, $n=1$

Unique pharmacological and physicochemical properties arise on derivatives in which groups have been substituted at different positions of the pyrazole ring. Molecules with substituents on the ring attached to groups with various complex properties including electron withdrawing and electron donating groups have a large degree of influence on the electrical distribution and also on the biological behaviour of the molecules. Due to above properties, medicinal chemists are actively investigating pyrazole derivatives to explore their application to develop anti-oxidant, anti-inflammatory, anti-bacterial, anti-cancer, and anti-viral medications.

Synthesis of Pyrazole Derivatives

Even the molecules with pyrazole moiety have numerous biological and commercial applications and their study on the issues of synthesis of pyrazole derivatives has enhanced in research areas of Organic and Medicinal Chemistry. The production of pyrazoles (fused pyrazole) is a mixture of traditional and modern synthetic methods, whereas pyrazole is an aromatic heterocyclic compound containing five C-atoms and two N atoms being bonded together. The key elements in determining the pathway which is to be followed are the necessary substituents, reaction conditions, yield, regioselectivity and the environmental factors.

1. Classical Cyclocondensation Method

The classic and common approach to synthesis of pyrazole derivatives is the cyclocondensation reaction of hydrazines with 1,3-dicarbonyl compounds such as beta-diketoesters, beta-di-aldehydes or beta-diketones. This reaction consists of nucleophilic addition, intramolecular cyclisation and dehydration.

This is what is shown, representing the whole response:

1,3-Dicarbonyl Compound+Hydrazine→Pyrazole Derivative+H_2O

2. Synthesis from Chalcones

Chalcones are α,β-unsaturated ketones that are intermediates in the synthesis of pyrazoles. Pyrazoline derivatives, formed from chalcone (CAL) reaction with hydrazine hydrate, can be further oxidized to form pyrazoles.

The reaction pathway is:

Chalcone+NH_2NH_2→Pyrazoline Oxidation Pyrazole

Advantages

- Easy availability of chalcones
- Mild reaction conditions
- High regioselectivity
- Formation of structurally diverse derivatives

Biologically active pyrazole molecules are synthesised using this approach, which is widely utilised in medicinal chemistry.

3. Multicomponent Reactions (MCRs)

The modern synthetic method that is efficient for the synthesis of pyrazole derivatives is also the so-called multicomponent reaction in which three or more reactants are reacted in a single reaction vessel. The reactions also shorten the time, the solvent and the purification process.

A typical multicomponent synthesis may involve:

- Aldehyde
- Active methylene compound
- Hydrazine derivative

General representation:

Aldehyde+Active Methylene Compound+Hydrazine→Substituted Pyrazole

Importance of MCRs

- One-pot synthesis
- Environmentally friendly
- High atom economy
- Suitable for combinatorial chemistry

These are very useful in the pharmaceutical industry for the rapid generation of chemical libraries.

4. Microwave-Assisted Synthesis

The microwave irradiation method is a new technology used to produce pyrazoles, as it increases the chemical processes so greatly. Techniques that make use of microwaves offer:

- Reduced reaction time
- Higher yield
- Better selectivity
- Lower energy consumption

Microwave synthesis is facilitated in the case of hydrozine and carbonyl compounds where fast cyclisation and pyrazole formation takes place during heating under microwave radiation.

Benefits

- Eco-friendly process
- Minimal solvent requirement
- Enhanced reaction efficiency
- Suitable for green chemistry applications

Most labs nowadays that work with heterocylic chemistry employ microwave-assisted synthesis.

5. Green Synthesis of Pyrazoles

In the synthesis of new compounds, "green chemistry" techniques try to reduce the use of potentially dangerous chemicals and the harmful pollutants they create. To synthesise pyrazoles, a number of environmentally safe catalysts and solvents are used, such as:

- Water as solvent
- Ionic liquids
- Biocatalysts
- Nanocatalysts
- Solvent-free conditions

Green synthesis of the reaction preserves superior reaction yields, while also improving sustainability.

An example of green synthesis is:

β-Diketone+Hydrazine→ H_2O Green Catalyst Pyrazole

6. Metal-Catalyzed Synthesis

Many regioselective pyrazole preparations use catalysts of a metallic element, typically palladium, copper, zinc and/or iron. These compounds enhance:

- Reaction efficiency

- Product selectivity
- Functional group tolerance

Metal-catalyzed reactions are particularly important for synthesizing highly substituted pyrazole derivatives used in advanced medicinal chemistry research.

7. Nanocatalyst-Assisted Synthesis

With the introduction of nanotechnology, nanocatalysts were developed and smoothed the way for the synthesis of pyrazoles considerably. The advantages nanoparticles offer are:

- Large surface area
- High catalytic activity
- Reusability
- Faster reaction rates

Common nanocatalysts include:

- ZnO nanoparticles
- Fe_3O_4 nanoparticles
- TiO_2 nanoparticles

These catalysts enhance green and sustainable synthesis protocols.

Reactivity of Pyrazole Derivatives

Pyrazole derivative is a very reactive heterocyclic molecule because two neighbouring nitrogen atoms in a five-membered aromatic ring. They show high chemical reactivity towards changes in their electrical configuration as well as their aromatic stability, tautomerisation and pattern of substitution. The characteristics of pyrazole derivatives render them convenient synthetic precursors both for organic and medicinal chemistry, as well as convenient reactants for many kinds of the organic transformations.

Following Hückel's rule, the pyrazole nucleus is considered to be aromatic due to the delocalisation of six π-electrons.

4n+2 π-electrons, n=14n+2\;\pi\text{-electrons},\; n=14n+2π-electrons,n=1

The pyrazole is an aromatic ring and the nucleophilic electrophilic substitutions occur at various positions giving rise to its aromatic character.

1H-Pyrazole ⇌ 2H-Pyrazole

Importance of Tautomerism

- Influences biological activity
- Affects polarity and solubility
- Alters reaction mechanisms
- Controls regioselectivity during substitution reactions

Tautomerism is also important in two other fields, hydrogen bonding and coordination chemistry.

2. Electrophilic Substitution Reactions

Pyrazole derivatives are good electrophilic-substitution reagents due to the presence of a favourable electron density distribution at C-4 site of pyrazole.

Common electrophilic reactions include:

- Halogenation
- Nitration
- Sulfonation
- Formylation

Example:

Pyrazole+Br_2→4-Bromopyrazole

1. Tautomerism in Pyrazole

Tautomerism is a very important aspect of pyrazole activity. Pyrazoles exist in several tautomeric forms because of the rapid change of the position of hydrogen atoms between the nitrogen atoms.

One alternative way to show the tautomeric equilibrium is:

1H-pyrazole⇌2H-pyrazole

Two interconvertible tautomeric structures are formed when the hydrogen atom moves from one nitrogen atom to the other in this equilibrium. Conversion to pyrazole derivatives is a very rapid process for all three forms that changes their chemical properties, stability and reactivity.

Electrophilic substitution is expedient for the synthesis of functionalised pyrazole derivatives bearing the desired pharmacological and commercial properties.

3. Nucleophilic Reactions

Pyrazole derivatives which are electron poor can undergo nucleophilic substitution processes. Especially prevalent among halogen-substituted pyrazoles are these reactions.

General representation:

Halopyrazole+Nu−→Substituted Pyrazole

The transformations occur very important in Medicinal Chemistry for the amino, alkoxy, or thiol group are added to the pyrazole ring.

5. Coordination Behavior

The complexes formed by pyrazole derivatives are excellent examples of ligands in coordination chemistry owing to the presence of nitrogen atoms Ligands which coordinate to the transition metals can also form stable metal complexes.

General complexation:

Metal Ion+Pyrazole Ligand→Metal-Pyrazole Complex

Applications of Metal Complexes

- Catalysis
- Magnetic materials
- Sensors
- Antimicrobial agents
- Fluorescent compounds

Extensive studies have been conducted on pyrazole-based liquids in the area of inorganic and supramolecular chemistry.

Emerging Applications of Pyrazole Derivatives

Pyrazole derivatives have been used for diverse applications, most notably in the area of industrial chemistry, agriculture, medicine and materials.

Applications of Pyrazole Derivatives in Modern Chemistry

The diversity of applications of pyrazole derivatives, found in both biological and pharmacological fields and also in the industry and for technological applications, has helped them to become at the forefront of nitrogen-containing heterocyclic chemical classes in modern chemistry. Pyrazole compounds are characterized by two nitrogen atoms in the aromatic five-membered ring that provides a unique electronic, structural, physiochemical properties of pyrazole and its derivatives are applied in various areas of research. Due to its versatile industrial uses and outstanding medicinal actions, pyrazole derivatives have been the subject of intense investigation in recent years. They have many applications such as nanotechnology, corrosion protection, material science, agrochemical and medicinal chemistry. Very important is the structural versatility of the pyrazole scaffold, which allows very easily the modification of its structural components in order to obtain molecules with the same functions but with better physicochemical properties and increased biological activity (Elguero et al., 2002).

Pyrazole derivative has one of the most important applications in medicinal chemistry. Pyrazole containing molecules are interesting scaffolds for modern drug development systems, which are endowed with wide-ranging pharmacological activities. The two categories of pyrazole compounds that exhibited promising effects were in the areas of: Inflammation, infections, cancer, antioxidants, pain, tuberculosis, seizures and diabetes. Pyrazole compounds exhibit hydrogen bonding and electrical interactions with enzymes, receptors and other biological macromolecules as one of their important biological activities. The pyrazole nucleus can also undergo structural modification to give specific therapeutic compound which is more effective with least harm. Celecoxib is one of the most effective pyrazole-based drugs and is effective in the treatment of inflammation, arthritis and pain. A medical use of pyrazole derivatives is the drug celecoxib that is used for arthritis and has fewer gastrointestinal unrelated effects as compared to conventional NSAIDs (Kumar et al., 2013). Also, other compounds are being investigated for use as kinase inhibitors and compounds that kill cells in the battle against cancer. An example of such a drug is the pyrazole derivative that has been seen to have promising properties against various cell lines of cancer.

The pyrazole derivative chemicals are also significant for agrochemical companies besides pharmaceutical industry. To extend crop-life and boost production, modern technological agriculture depends on effective and environment-friendly pesticides. Compounds with pyrazole groups are chemically stable and biologically very active. They are well suited to be used as insecticides, fungicides, herbicides, and plant-growth regulators. Pyrazole moiety is a component part of many commercial agrochemicals due to its wide spectrum activity against pests and plant diseases. The substances can fend off pests and diseases by blocking necessary metabolic pathways in the pests' life. In insects, pyrazole-based products are found in insecticides used with relatively low levels of control whereas in fungicides, a relatively high amount of antifungal activity has been demonstrated with a number of plant infections. The extended shelf life and adaptability to various climatic conditions are other benefits of pyrazole derivatives, which are known for their great chemical and thermal stability (Joule & Mills, 2010). The search of environmentally friendly pyrazole based agrochemicals having high selectivity and low environmental toxicity is more gaining momentum due to increasing worldwide demand for sustainable agriculture.

The field of material science and electronic materials is another promising area for pyrazole derivatives' potential applications. The aromatic and conjugated nature of the pyrazole compounds render impressive optical, electrical and photophysical properties. Hence, the pyrazole derivatives are widely researched in designing organic semiconductors, liquid crystals, fluorescent materials, and optoelectronics. Six pyrazole-containing compounds exhibit intense and unusual fluorescence properties and excellent charge-transfer behaviors that could prove useful in organic light-emitting diodes (OLEDs), molecular sensors, and photovoltaic devices. By tuning their tunable conductivity, luminescence and thermal stability, researchers can create materials with the properties they desire. Compounds based on pyrazole are also used for production of photoactive materials and smart polymers, which have state-of-the-art technological applications. Researchers have been interested in the application of pyrazole-functionalized nanomaterials for bioimaging, sensing and photodynamic treatment (PDT) due to their enhanced optical characteristics and biocompatibility (Katritzky et al., 2010).

Pyrazole derivatives are also very important in coordination chemistry and catalysis. The nitrogen atoms of a pyrazole ring may form stable complexes with transition metal ions that have unusually catalytic and magnetic properties. Pyrazole is frequently used by inorganic chemist to prepare organometallic complexes and coordination compounds. These metal complexes have been used to catalyse several organic transformations such as polymerisation reactions, hydrogenation and coupling reactions, and oxidation reactions. The transition metal complexes and pyrazole ligands form suitable catalysts due to their high selectivity, stability and efficiency even under moderate reaction conditions. Pyrazole-metal complexes (Finar, 2008) are suited for some applications of supramolecular chemistry, molecular recognition and magnetic materials. The reactivity and versatility of the Pyrazole ligands make it an interesting and important compound in modern chemistry research, as a variety of mono-, bi-, or polynuclear complexes with diverse geometries and properties have been synthesis.

Corrosion inhibiting properties of pyrazole derivatives are one of the important applications in industry. Corrosion is a major problem in industry, and leads to damage of metals and significant financial losses. Due to the presence of the N atoms in the ring structure which can bind more strongly to the metal surface, pyrazole compounds are very suitable as corrosion inhibitor of metal steel, copper, aluminium, and iron. A barrier is formed by this adsorption, which inhibits processes related to oxidation and corrosion. Pyrazole derivatives come in from time to time handy in the acidic environments where corrosion is a big issue. Commercial applications are found in water treatment systems, chemical industries and oil refineries where they are found to have high inhibitory effectiveness, thermal stability and ease of synthesis. Numerous studies show that substituted pyrazoles form a closer contact with metals, have a higher electron density, and are therefore very effective anticorrosives (Joule & Mills, 2010).

The use of pyrazole derivatives has been greatly enhanced in contemporary research due to recent developments in nanotechnology. Biomedicine, catalysis and environmental protection are currently in the scope of the potential applications of nanoparticles and nanocomposites functionalised with pyrazole. The introduction of pyrazole-loaded nanocarrier system is a significant advancement in pharmaceutical delivery systems, promoting targeted and controlled delivery of therapeutic agents, consequently resulting in better therapeutic efficiency and reduced potential side effects. Pyrazole derivatives are used for molecular and biosensors which detect metal ions, biomolecules and environmental contaminants. They improve the sensitivity and selectivity of sensing by their outstanding electrical and fluorescent characteristics. Pyrazoles have also been used to make nanomaterials that have potential applications in bioimaging, photodynamic treatment and antimicrobial coatings. The combination of nanotechnology and pyrazole chemistry has created new possibilities for development biocompatible materials with multifunctionality, as presented in the work made by Kumar et al. (2013).

Pyrazole derivatives are a very useful and versatile class of heterocyclic compounds with numerous applications in various fields of science and industry. They are extremely advantageous in medicinal chemistry as they possess remarkable pharmacological properties, and also have played a significant contribution in agrochemical development due to their stability and biological activities. Their optical, electrical and coordinating properties have proven valuable in Materials science, catalysis, nanotechnology and corrosion inhibition to name but a few applications. In the future, the use of pyrazole derivatives is likely to continue to grow as synthetic techniques, green chemistry, and computational drug designadvances, providing an opportunity to create new applications across a wide range of fields. The advancing field of pyrazole chemistry is the topic of growing multidisciplinary work and offers access to innovative drugs, sustainable materials of industrial use and complex functional technology.

Future Perspectives

At present, efforts are focused on:

- Green synthesis approaches
- Target-specific drug design
- Nanomedicine applications
- Sustainable agrochemicals
- Artificial intelligence-assisted molecular design

By fusing pyrazole chemistry with nanotechnology, biotechnology, and computational chemistry, it is hoped that next generation industrial and medicinal materials will be developed.

II. Conclusion

The pyrazole derivatives have several applications for today's chemistry as a result of their versatility and reactivity. Their coordination properties, tautomeric forms and special aromatic structure make them extremely useful in many areas of Medicine and synthetic Organic Chemistry. Advances in structural modification and synthetic methods have extended their parent applications in agrochemicals and medicines to a new range of applications in material science and nanotechnology. New technologies and innovative finds in green chemistry, state-of-the-art medicine and top-of-the-line manufacturing continue to abound.

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