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ANTIMICROBIAL AGENTS CONTAINING PYRAZOLE NUCLEUS AND THEIR BIOLOGICAL ACTIVITY

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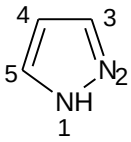
Abstract
Pyrazole and its derivatives is a pharmacologically significant active scaffold with a wide range of pharmacological properties. Pyrazole's aromatic nature and two nitrogen atoms create a five-membered ring structure with diversified activity and stereochemical complexity. Designing novel pyrazole derivatives has become a fascinating research topic due to its biological significance.

This document summarises several biologically active pyrazoles produced by a variety of researchers throughout the world. Pyrazole derivatives have attracted a lot of attention as strong bioactive chemicals having hypoglycemic, analgesic, anti-inflammatory, antibacterial, anticonvulsant, antidepressant, antimycocelecoxib, bacterial, antioxidant, antiviral, insecticidal, and anticancer properties. They have a wide range of bioactivities, including antibacterial efficacy against a wide range of bacteria strains. , we present antibacterial candidates with pyrazole nuclei that have been integrated with a variety of functions. Pyrazole is a multifunctional lead compound that was produced via chemical architecture for physiologically active compounds. The creation of pyrazole-containing reactions is given several synthetic pathways to yield a novel molecule, which is a huge opportunity in the field of medicinal chemistry.

Key words: Pyrazole, biological activity, Antimicrobial, Bioactive compound.

Introduction

Pyrazoles are five-membered heterocycles that constitute a class of compounds particularly useful in organic synthesis. They are one of the most studied groups of compounds among the azole family [1] General methods of synthesis Ludwig knorr in 1883 studied Pyrazole moieties and substituted pyrazole[34,35,72] figure - pyrazole



Because their structural subunits are found in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as medicines, agrochemicals, dyes, and many other substances, heterocycles play an important role in metabolism. [2]

Heterocycles are a very important class of chemicals, accounting for more than half of all organic molecules known.. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents. [3]

Dyestuff, fluorescent sensors, brightening agents, information storage, polymers, and analytical reagents are only a few of the heterocycles' applications in materials science. They also have uses in supramolecular and polymer chemistry, particularly in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells, organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches, and liquid crystalline compounds. [3]

Heterocycles are abundant in nature, and their structural subunits can be found in a wide range of natural products, including vitamins, hormones, antibiotics, and alkaloids, as well as medicines, herbicides, dyes, and a variety of other substances. Green chemistry is increasingly widely used to address the fundamental scientific concerns of preserving human health and the environment while also ensuring commercial viability.. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes.[4] N-containing heterocycles are molecules which have unique structural motif and found extensively in natural products such as hormones, alkaloids, and vitamins . Pyrazole represents one of the most prominent classes of heterocycles exhibiting large spectrum of biological performances such as anticancer, antitumor , anti-AID, antimicrobial, antimalarial and antitubercular. It attracted a lot of attention because the favoured structure is frequently used as an active ingredient in commercial drugs.. [5]Pyrazoles consist of a doubly unsaturated 5-membered ring containing two nitrogen atoms (1 and 2 positions of the ring) . Knorr synthesized firstly a pyrazole derived compound which led to discovery of antipyrine and its derivatives.

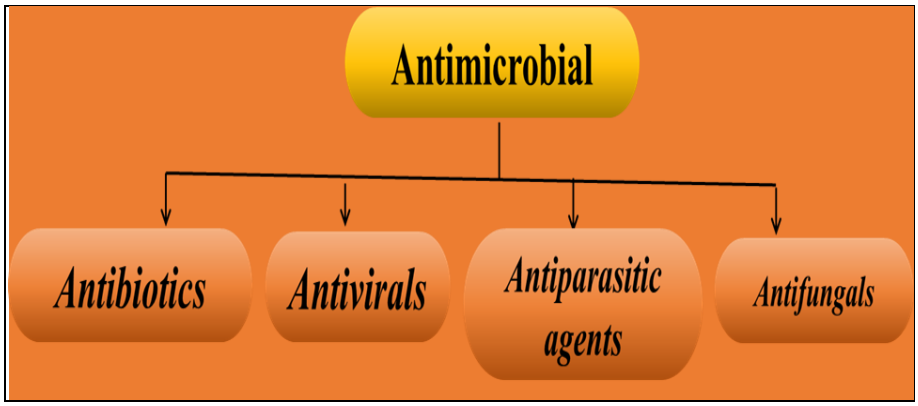
Since the introduction of antipyrine; the first pyrazolone derivative was used in the treatment of pain,inflammation and fever in 1884. Great attention has been focused on pyrazole derivatives as potent anti-inflammatory, analgesic and antipyretic agents .[6] As a result, a vast number of pyrazoles have been discovered, with some of them finding clinical use.. These compounds has diverse biological activities antimicrobial, anticancer, cytotoxic, analgesic, anti-inflammatory, antihypertensive, CNS activity like antiepileptic, antidepressant, etc. Several pyrazole derivatives possess important pharmacological activities and they have been proven as useful materials in drug research. Pyrazole derivatives play an important role among antitumor agents because of their good inhibitory activities against BRAFV600E, EGFR, telomerase, ROS Receptor Tyrosine Kinase and Aurora-A kinase. [6]

biologically active compounds, including antitumor, antibiotic,anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic,herbicidal, fungicidal, and insecticidal agents [3]. This condition is deteriorated by the emergence of multidrugs resistance (MDR) phenomena. Old antibiotics such as tetracyclines, methicillin, aminoglycosides, macrolides, and penicillin have become less and less effective day by day. For example, drug-resistant Mycobacterium tuberculosis and Staphylococcus aureus are found [7]biological activity such as anti-cancer, anti-inflammatory, anti-fungal, antibacterial, antiinsecticidal, analgesic, antiviral, anticonvulsant, anti-diabetic, antipyretic, antiarrhythmic, anti-depressant, anti-hyperglycemic, anti-oxidant, herbicidal etc. [8] pyrazoles were shown to inhibit the action of horse liver alcohol dehydrogenase (LADH) and their derivatives are good ADH inhibitors , 4-ethylpyrazole, a less toxic derivative of pyrazole, is even a stronger inhibitor of LADH. Since the discovery that 3-methylpyrazole and4-ethylpyrazole have potential medicinal value, there has been a rapid growth in synthesizing new derivatives of pyrazole as anticancer.[9] These molecules have potential applications such as antibacterial, antifungal, antibiotics, insecticide, pesticide, biosensors.[10] Many biologically active chemicals, including blockbuster medications like Celebrex2 and Viagra, have the pyrazole motif as their basic structure.

Antimicrobial activity

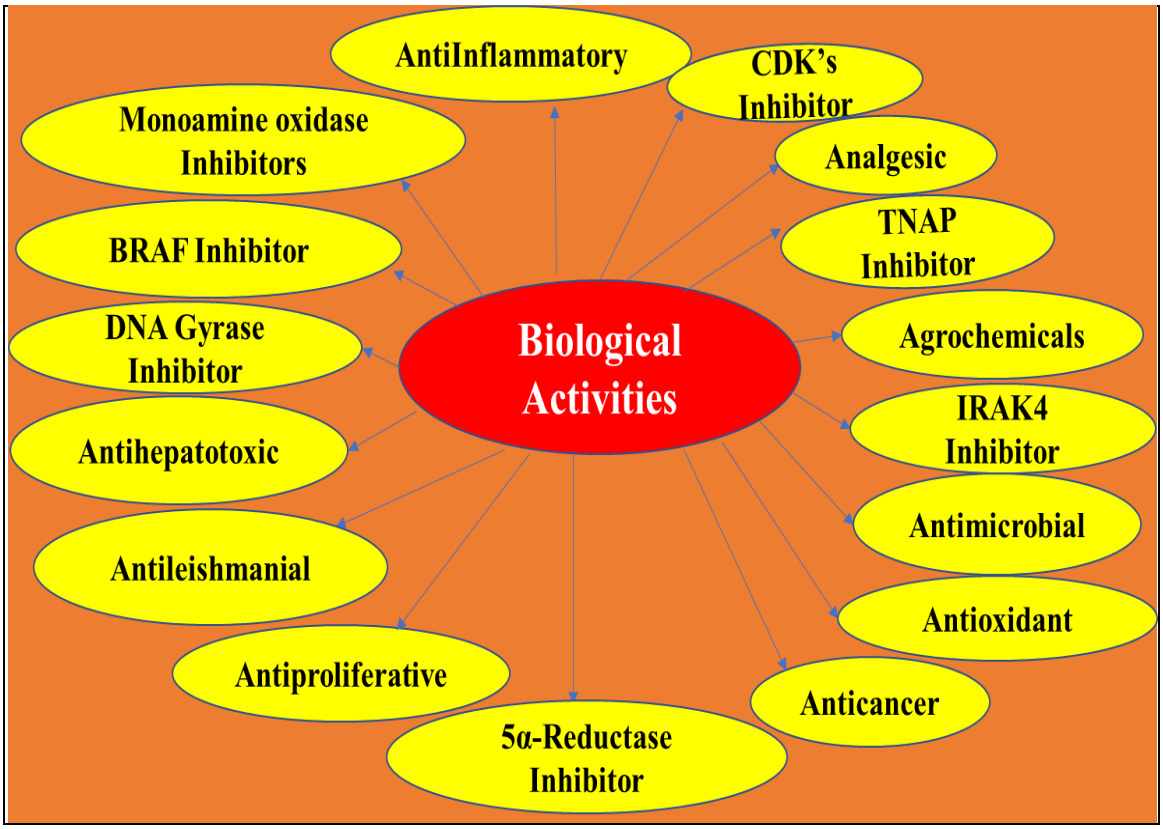
Medicinal chemists have developed a variety of anti-microbial agents but the graph of resistance against many anti-microbial drugs is increasing day-by-day in many pathogens especially in different strains of bacteria [42]. Novel anti-biotics with new modes of action, high selectivity and efficacy, and shorter treatment times are urgently needed. [43Pyrazole nucleus is a chemical entity that can be found in a variety of pharmacologically effective medications. One of the best strategies for synthesizing pyrazole rings are annulations commenced by the condensation of a monosubstituted hydrazine with a carbonyl for example, cyclocondensation of α,β-unsaturated carbonyl or 1, 3- dicarbonyl compounds with hydrazines. Following that, a group of scientists developed pharmacologically active pyrazole compounds using both traditional and unconventional methods..The intermediate thus obtained was reacted with hydrazines to give excellent yields of pyrazoles [45].The bacteriostatic activity of the synthesized heterocycles was evaluated using the two fold serial dilution technique [47]. Two fold serial dilutions of the tested compounds were prepared using the proper nutrient

broth. In particular, they are described as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, antiinflammatory, anti-tuberculosis, antioxidant as well as antiviral agents [48,49]Nowadays, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties. Celecoxib [40,]Lonazolac [41], Mepirizole [50], Rimonabant [51], acomplia [52] Cimetidine [53], Fipronil [54], Dexacoxib [55] all chemical drugs give the pharmacological activity.



Biological activities

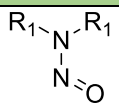
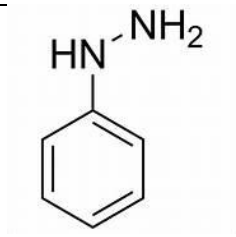
Infections and diseases may be caused by different types of organisms like bacteria, fungi, and viruses, etc., in humans and animals.



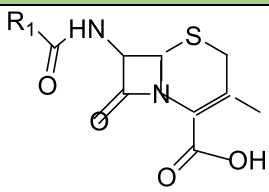
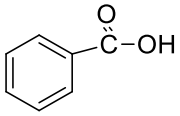
Antibacterial activity

Among the most common infectious diseases are bacterial infections. As a result, almost 50 years of intensive research has been conducted in order to develop novel antibacterial drugs derived from various sources. Despite advances in antibacterial agent development, the rise of multidrug-resistant bacteria has necessitated the creation of new antibacterial agents.[11] Natural antibiotic compounds used in the treatment and prevention of bacterial infection have become indispensable in today's health-care system, helping and supplementing the body's natural immune system in the fight against microbial infections. However, because antibiotics are frequently misused or overused to treat microbial illnesses, certain germs have acquired resistance to them. [2Plant infections have long been recognised as a global danger to crop productivity, and the use of fungicides has been, is, and will continue to be crucial for controlling most plant diseases in agriculture. e [17].These drugs contain sulfonamide group as the main moiety have shown antibacterial [28], anti-hyperglycemic [29,30]and anti-inflammatory [31] properties. Celecoxib, rofecoxib, and valdecoxib are sulfonamide derivatives which act as anti-inflammatory agents.Antimicrobial agents are considered one of the most significant milestones in modern medicines. Antibiotic-resistant bacterium infections are becoming more common, and some diseases have developed resistance to numerous types or classes of antibiotics. However, due to an increase in immune-compromised hosts, the incidence of systemic microbial infections has steadily grown..[14].

Natural drug table(antibacterial)

Serial number	Name	Stucture	Mechanism of action
1	nitrosamines		Nitrosamines exert their toxic and mutagenic effect by alkylating N-7 of guanine,leading to destabilization and increasd breakage of DNA
2	Hydrazine		Hydrazine is an drug that conducts the blood pressure lowering effect byvasoconstrictive repression.

Synthetic drug table(antibacterial)

Serial number	name	structure	Mechanism of action
1	cefoselis		It exhibit a wider antibatirrial spectrum activity than thr third generation drug.
2	,carboxylic acid		Carboxylation is a chemical reaction in which a carboxylic acid is produced by treating a substrate with carban dioxide. The opposite reaction is decarboxylation.

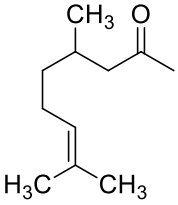
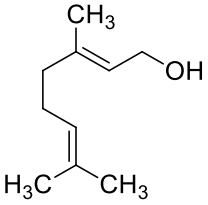
Antifungal activity

Heterocyclic structures, with their great efficiency, low toxicity, and variety of potential substituents, are undeniably essential features in natural goods, synthetic medications, and insecticides. [18-21]. Pyrazole derivatives, as an important kind of heterocyclic nitrogen compounds, have exhibited a wide range of biological activities whether in the field of pesticides or medicine, such as anticancer [22], anti-inflammatory [23], antifungal [24], insecticidal [25] et al. Structurally, it is not difficult to find that the structure of pyrazole ring is the key part of antifungal activity: bixafen, penflufen, sedaxane, fluxapyroxad, penthiopyrad, benzovindiflupyr, for example. Owing to the importance of the pyrazole-4-carboxamide derivatives in the aspect of antifungal activity and the application of bioisosterism in the design of pyrazolecarboxamide fungicides (Figure 1), we tentatively designed a series of pyrazole-5-carboxamide derivatives, looking forward to obtaining some compounds with excellent fungicidal activities. Figure 1 revealed that bioisosterism can be completely used in the design of pyrazole amide fungicides, which laid a theoretical foundation for our design. Furthermore, considering the application of thiazole and oxazole in commercial pesticides, such as thifluzamide, ethaboxam, thiabendazole, fluesulfone, oxathiapiprolin, pyrisoxazole, isoxaflutole, etoxazole , metamifop et al., we introduced the thiazole ring structure or oxazole ring structures which are taken as an active fragment being widely used in the field of pesticide and medicine as well [27]. Expecting to get high antifungal activity compounds, we obtained bioisosteres by transforming benzothiazole and benzoxazole into phenyl thiazole and phenyl oxazole, then we prepared a series of the target compounds by using the bioisosteres to replace the tert-butylbenzene structure of tebufenpyrad. A series of pyrazole-3-carboxylic acid and pyrazole-3,4-dicarboxylic acid derivatives were synthesized and evaluated for their antibacterial and antifungal activities against five bacterial and five fungal Candida parapsilosis, Candida tropicalis, and Candida glabrata strains [16].

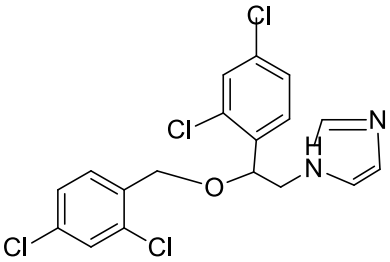
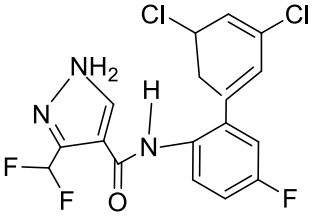
new, more effective, cheaper and safe antimicrobial agents.we continued our previous study and designed new 2H-pyrazoles bearing oxygen-bearing heterocycles targeting telomerase.[38] r, we described the synthesis and the structure–activity relationships of series of aryl-2H-pyrazole derivatives bearing 1,5-benzdioxepine or 1,4-benzodioxan or 1,3-benzodioxole moiety as potential antitumor agents, [38] much attention has been focused towards pyrazoles as antimicrobial,2,3 antiviral4,5 and anticancer6,7 agents after the discovery of the natural pyrazole C-glycoside, pyrazofurin; 4-hydroxy-3-b-dribofuranosyl-1H-pyrazole-5-carboxamide. This antibiotic was reported to possess a broad spectrum of antimicrobial

We do not discuss these here, but instead refer the interested reader to the literature cited. Typically, formation of pyrazoles has involved a suitable cyclocondensation of alkyl- or aryl-substituted carbonyl compounds with hydrazines. [15]

Natural antifungul drug

Serial name	name	structure	Mechenism of action
1	citronella		The hydrogenation reaction of citronellal generally obtain its derivative compounds i.e.menthol.
2	Geraniol`		Geraniol is known to be derived from gerenyldiphosphate by related synthesis based on a common ionization dependent reaction mechanism.

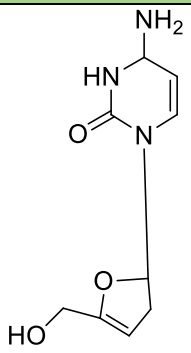
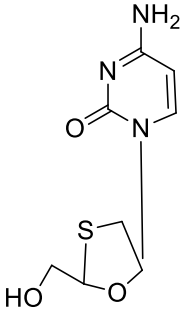
Synthetic antifungal drug

Serial number	**name**	**Structure**	Mechenism of action
1	**Miconazoles**		It interacts with yeast demethylase,which is cytochrome P-450 enzyme that converts lanosterol to ergosterol.
2	**Bixafen**		**Bixafen,like all the latest generation SDHIs,acts in a similar way to carboxin, through inhibition of mitrochondrial respiration chain complex 2.**

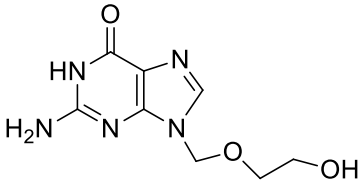
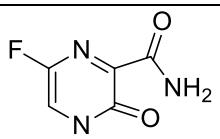
Antiviral activity:-

Antimicrobial agents are compounds used to kill microorganism or to inhibit their growth and can be grouped according to the microorganisms they act primarily against. Many diseases are indeed caused by the members of these microorganisms and these microbial infection poses a tremendous threat to the human race. Pyrazole and its derivatives have been found to possess various antibacterial, antifungal and antiviral properties.Dihydropyrano[2,3-c]pyrazole derivatives exhibited antimicrobial activity against Staphylococcus albus, Streptococcus pyogenes, Klebsiella pneumonia, Pseudomonas aeruginosa and Candida albicans and N-thiocabamoylpyrazole derivatives were cyclized to afford the novel pyrazolothiazol-4(5H)-ones (118e-118h) and pyrazolothiazoles (118i-118p). The reported compounds exhibited antiviral activities against several viruses like herpes simplex virus type 1 (KOS) [HSV-1 KOS], herpes simplex virus type 2 (G) [HSV-2G], vaccinia virus [VV], vesicular stomatitis virus [VSV], Coxsackie virus B4 [CV-B4] respiratory syncytial virus [RSV] and parainfluenza-3 virus [PI-3V]. (1) Viral long terminal repeat (LTR) has a critical role in transcription of type 1 human immunodeficiency virus (HIV1) provirus[11]. Inhibition of LTR activity can be a possible pathway for antiviral drug candidates in order to block HIV1 replication [32,33]

Natural antiviral drugs

Serial number	Name	Struture	Mechanism of action
1	Stavudine		Satavudine, a nucleoside analogue of thymidine ,inhibits the replication of HIVin human cells in vitro.
2	Lamivudine		Lamivudine must be converted intracellular to its triphosphate form ,which then competes with cytosine triphosphate for in coporation into the developing viral DNA stand.

Synthetics antiviral drugs

Serial number	name	stucture	Mechanism of action
1	Acyclovir		Acyclovir is converted ti its triphosphate form,acyclovir triphosphate which competitively inhibiteviralDNA polymerase, incorporated into and terminates the growing viral DNA chain, and inactivated the viral DNA poly merase.
2	Favipiravir		The main mode of action ofaction of favipiravir is exterted ether by(1) induction of lethal mutagenesis (2) RNA chain termination and incorporation of viral RNA stand.

Conclusion

Pyrazoles represent a major pharmacophore with various biological properties, and some pyrazole-containing derivatives have already been used for therapeutic purposes. Pyrazole derivatives were successfully synthesized using Vilsmeier–Haack reaction. The main goal of this review is focused on pyrazole heterocyclic ring decorated with various functional groups. These compounds displayed a large spectrum of biological performance, especially as antimicrobial agent. The aim of the present investigation is to synthesize different series of quinoline derivatives which bearing a pyrazole moiety at position 2- to achieve the antimicrobial effect. This current review provides important information for the upcoming design of new antimicrobial agents based pyrazole skeleton.

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