Journal of Advances and Scholarly Researches in Allied Education
Vol. 17, Issue No. 2, October-2020, ISSN 2230-7540

A Study of Biological Importance of Pyrazoles, Chalcones and their Derivatives

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Abstract - Pyrazoles and chalcones are important classes of organic compounds that have drawn considerable attention due to their diverse biological activities. In this study, we explored the biological importance of pyrazoles, chalcones, and their derivatives through an extensive literature review and experimental investigations. The synthesis and characterization of various derivatives were carried out, and their potential biological activities were assessed through in vitro and in vivo experiments.

Keyword - pyrazoles, chalcones

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INTRODUCTION

The study of heterocyclic compounds is an important part of modern chemistry. Heterocycles are the basis of a significant portion of present-day scientific inquiry. To create powerful and selective pharmaceuticals, several pharmacophores are assembled on heterocyclic scaffolds. As a result, heterocycles are useful building blocks for creating novel bioactive chemicals. It is constantly desirable to improve the synthetic procedure for these scaffolds.

The infectious illness tuberculosis (TB) is discussed. It has caused major health problems on a global scale. It is one of the leading infectious disease killers today. Mycobacterium TB affects around 33% of the world's population annually, and is responsible for over 2 million deaths, according to the World Health Organisation. The World Health Organisation has designated tuberculosis as a "global emergency." The rise of MDR- and XDR-TB presents a new challenge for the pharmaceutical industry.

Multidrug-resistant pathogenic bacteria have contributed significantly to the rise of microbial and fungal illnesses and disorders. After heart attacks, the main cause of mortality is microbial infections. Drug-resistant malarial parasites have caused havoc owing to the ineffectiveness of current anti-malarial medications and resistance to insecticides. New, cost-effective antimalarial medicines are the focus of pharmaceutical R&D at present.[1]

The architectures of quinoline derivatives are fundamental to several naturally occurring bioactive molecules and pharmaceutically active drugs. Heterocycles containing 1,3,4-oxadiazole ring annihilation sites are highly bioactive. Antibacterial, antitubercular, anticancer, antifungal, antiinflammatory, and antimalarial properties are just a few of their many uses that have garnered a lot of interest.

PYRAZOLES

Pyrazole is a heterocyclic molecule having two neighbouring nitrogen atoms in its five-membered structure. Heterocyclic compounds linked to pyrazole showed a wide range of chemotherapeutic activity. Anti-inflammatory, antibacterial, antimalarial, antihypertensive, antitubercular, antiviral, neuroprotective, antidepressant, anticancer, and many more biological actions were all represented. Several pyrazole derivatives found utility in clinical settings, and some of them have been shown to be a valuable entity in the creation of very effective chemotherapeutic drugs. Celecoxib, Apixaban, Fipronil, Betazole, Tepoxalin, Fezolamine, Pyrazomycin, Fomepizole, Mepirizole, Difenamizole, Lonazolac, Tolpiprazole, Deracoxib, Crizotinib, Ruxolitinib, and many more are all key pyrazole-based medications on the market. Figure 1 shows a few examples of medications that are pyrazole-based. Natural pyrazole tethered analogue pyrazofurin showed potent antiviral properties. The vast majority of pyrazole derivatives also have important uses in the fields of agriculture, horticulture, the food industry, and supramolecular and polymer chemistry. Different pyrazoles serve different purposes, such as liquid crystals, pigments, or UV stabilisers.[2]

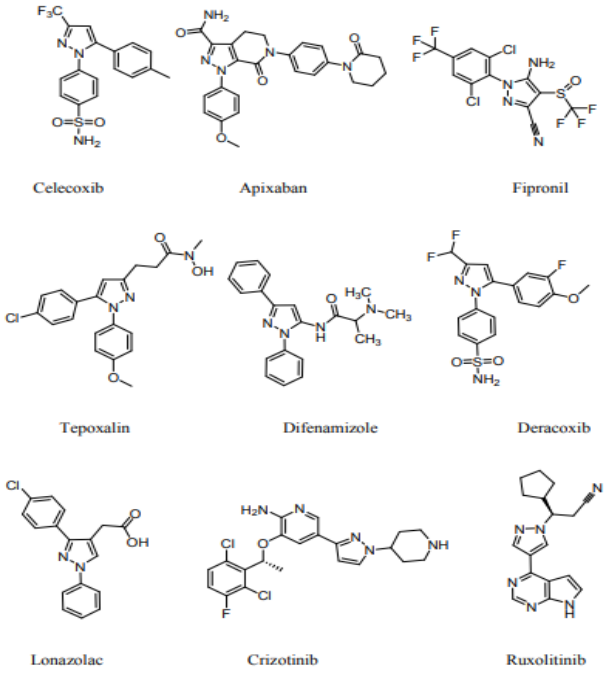


Figure 1: Pyrazole based drugs

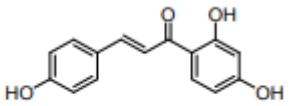
CHALCONES

Chalcones are α,β- class of,-unsaturated ketones found in a broad variety of plant species. They are just the building blocks from which flavonoids and isoflavonoids are formed. In recent decades, scientists have developed a wide variety of new chalcone derivatives. Natural and manufactured chalcones have both been explored for their potential as chemotherapeutic agents. The wide range of pharmacological actions included those against inflammation, mitosis, leishmaniasis, invasion, malaria, bacteria, fungi, protozoa, viruses, trypanosomes, and cancer. They are used to treat heart disease, pain, viruses, gastritis, parasite infections, and stomach cancer, among other conditions; certain chalcones are used in cosmetics, while others are used as food colouring or additives.[3]

Anticancer Activity of Chalcones

Numerous chalcone compounds, particularly those that suppress VEGF, have shown anticancer efficacy, thioredoxin reductase, tubulin , topoisomerase-I/II, mTOR, 5α-reductase, JAK/STAT signaling pathways , Sirtuin-1 , MMP-2 , Wnt , BRAF , cathepsin-K , NF-κB , BCRP , P-gp .[4]

The VEGF/VEGFR-2 signaling pathway was studied by Wang et al. to see whether or not isoliquiritigenin 13 inhibited breast cancer neoangiogenesis.



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PYRAZOLE (1, 2-DIAZOLE)

Pyrazole is an azole class of heterocycles having five member ring structure. Two nitrogen atoms are located at adjacent positions with the alternate double bond. During synthesis of antipyretic drug, its structure was invented by Knorr.

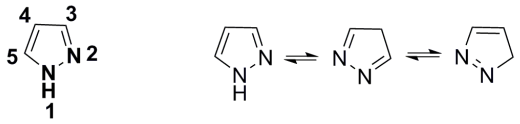


Figure 2: Structure of 1*H*-Pyrazole and its tautomeric structure

1. Natural occurrence of Pyrazole

Withaniasomnifera was the source of the pyrazole-containing alkaloids known as withasomnine, which were identified by Akira and Morimoto et al. Many of the natural medicines have many pharmacological effects, including those that are anti-inflammatory, analgesic, anti-leishmanial, anti-microbial, anti-tumor, and anti-viral. The pyrazole cores of many significant natural compounds are shown in Figure below.[5--6]

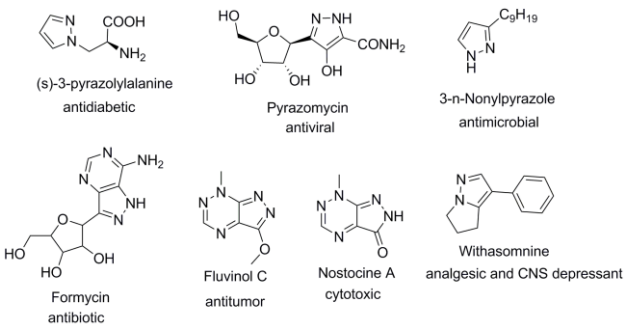
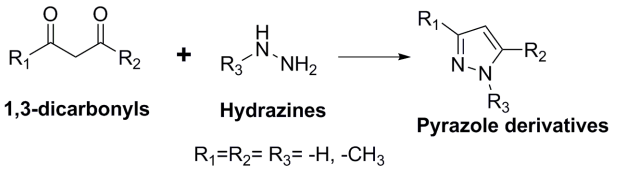


Figure 3: Pyrazole skeletal in naturally occuring drugs

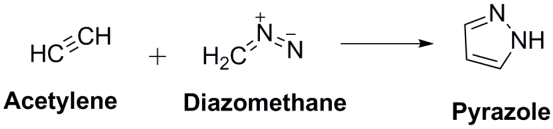
Pyrazole History and Synthetic Methods

Condensation of 1,3-dicarbonyl compounds with hydrazines led to the synthesis of the pyrazole chemical by Knorr in 1833. This conventional approach provides a shorter and simpler route to pyrazole. The manufacture of antipyretic medicines benefits greatly from the use of pyrazole and pyrazole-based derivatives.[7]



Scheme 1: Synthethesis of Pyrazole (Give by Knorr)

Another synthetic method leading to pyrazole consists of reaction between diazomethane and acetylenes which was developed in 1898 by Pechmann.



Scheme 2: Synthesis of Pyrazole (Given by Pechmann)

Phenyl-3-methyl-5-pyrazolone was created by L. Knorr by the heating of phenyl hydrazine and ethylacetoacetate. Pyrazolone is the pyrazole nucleus with a carbonyl group attached to it. Many studies have focused on pyrazole and pyrazole substituted heterocycles because of their diverse biological effects.

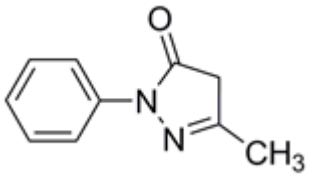


Figure 4: 1- phenyl-3-methyl-5-pyrazolone

Pyrazole as Pharmacological Agents

The pyrazole moiety is present in many pesticides and drugs molecules. Some examples are put on view in Figure:

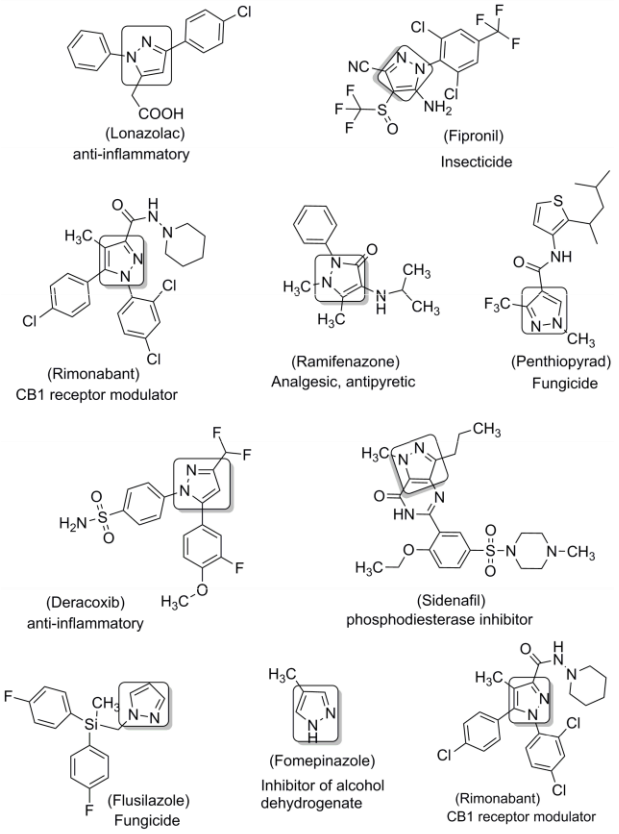


Figure 5: Drugs and perticides having pyrazole nucleus

1*H*-Pyrazole-4-Carbaldehyde

One of the most useful classes of pyrazoles as a pharmacological intermediate is 1H-pyrazole-4-carbaldehyde and its derivatives. This thesis presents a synthetic route to several pyrazole derivatives beginning with

1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde.

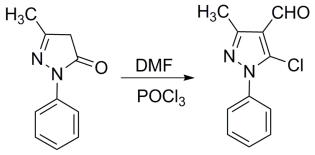
. Below, we discuss the biological and synthetic properties of 1H-pyrazole-4-carbaldehydes.

Synthesis of Pyrazole-4-Carbaldehyde derivatives

Synthesis of

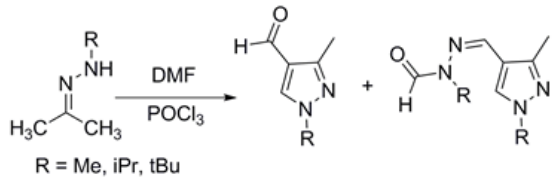
1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde

via Vilsmeier-Haack synthesis of 3-methyl-1-phenyl-pyrazol-5(4*H*)-one (Scheme 3) was reported in 1966.



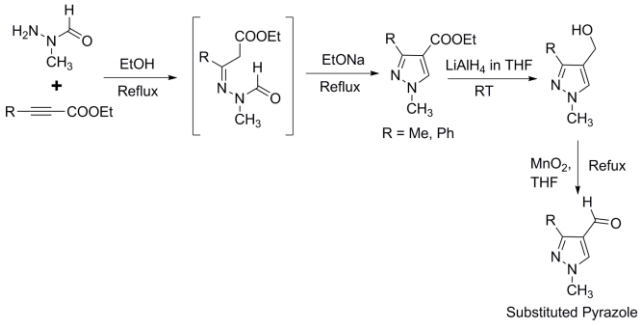
Scheme 3: Vilsmeier-Haack reaction of 3-methyl-1-phenyl-pyrazol-5(4H)-one

E.B. Rusanov and his coworkers reported non-symmetric 1,3,4- trisubstituted pyrazoles via Vilsmeier–Haack reaction of schiff base prepared from the corresponding ketone and substituted hydrazines.



Scheme 4: Reaction of acetone N-alkkylhydrazones with Vilsmeire-Haack reagent

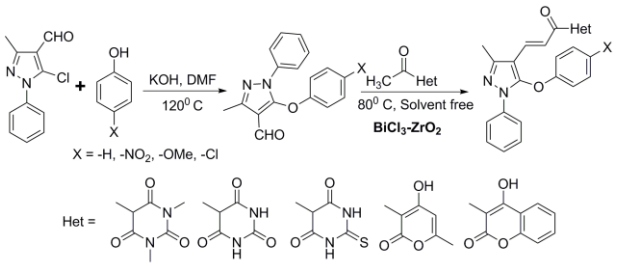
Andrew and team reported one-pot regioselective synthesis of trisubstituted-1*H*-pyrazoles. It involves three-step tandem type reactions, which have been significantly utilised in synthesis of varieties of different pharmacologically active pyrazoles based drugs.[8-9]



Scheme 5: Regioselective one-post synthesis of 1,3,4-triisubstituted-1H-pyrazoles

Reactions of Pyrazole-4-Carbaldehyde derivatives

Siddiqui and his team mates developed zirconia based heterogeneous catalyst to check its catalytic efficiency for substituted pyrazolic chalcones. The catalyst activity was reported to be prominent and gave good yield at normal reaction parameters (Scheme.6).

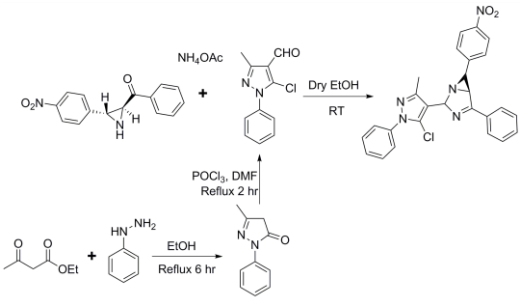


Scheme 6: Heterogeneous catalyst based synthesis of novel pyrazolic chalcones

H. Kiyani synthesized pyrazolyl-1,3-diazabicyclo[3.1.0]hex-3-ene via one- pot multicomponent synthesis of ((2S,3R)-3-(4-nitrophenyl)aziridin-2- yl)(phenyl)methanone,

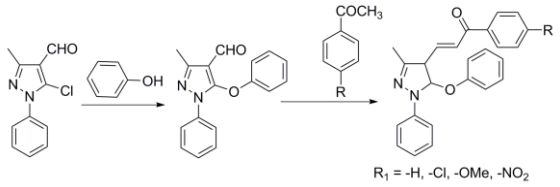
5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde

and ammonium acetate. The synthesized pyrazole based compounds showed photochromic properties (Scheme.7).



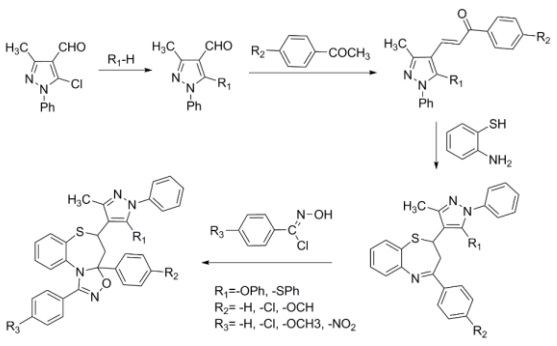
Scheme 7: Synthesis of photochromially active pyrazole compunds

Zhou Y. L. *et al*. synthesized of (*E*)-3-(3-methyl-5-phenoxy-1-phenyl-4,5- dihydro-1*H*-pyrazol-4-yl)-1-(p-substituted)prop-2-en-1-one and characterized the chalcone structure by crystallography and spectroscopic techniques (Scheme.8).



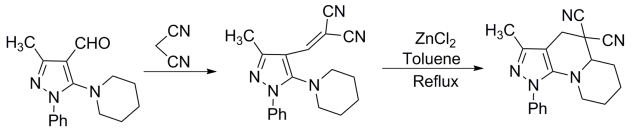
Scheme 8: Synthesis of 1,3-disubstituted-2-propyleno-1-one containg pyrazole compounds

F. M. Liu and his teammates synthesized novel pyrazole substituted- [1,2,4]-oxadiazolo-[5,4-*d*]-[1,5]-benzothiazepine derivatives *via* cycloaddition of substituted-benzohydroximinoyl chlorides and substituted-pyrazolo[1,5]benzothiazepines using triethylamine (Et_3N). The synthesized benzothiazepines were characterized via crystallographic and spectroscopic methods.



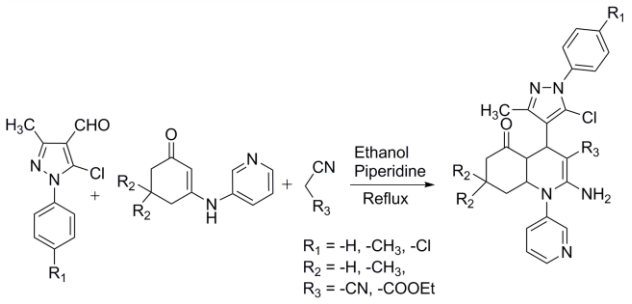
Scheme 9: Synthesis of pyrazole substituted-[1,2,4]-oxadiazolo-[5,4-d]-[1,5]-benzothiapine derivatives

By combining anhydrous zinc chloride and toluene, Prajapati et al. [made substituted fused pyrazole derivatives by cyclization of Knoevenagel product. Pyrazole carbaldehyde and malononitrile (active methylene) combined to generate the final product. Spectroscopic methods (Scheme 10) were used to examine the product.



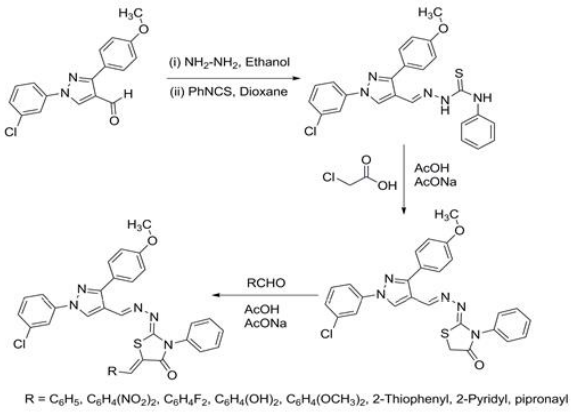
Scheme 10: Synthesis of substituted fused derivatives

C. Sangani *et al*. designed novel library of pyrazole-quinoline-pyridine hybrids. The target was achieved through multicomponent cyclocondensation approach starting from pyrazole carbaldehyde. Spectroscopy was used to determine the chemical composition of the substances. The antibacterial and anticancer efficacy of all substances was tested (Scheme 11).[10]



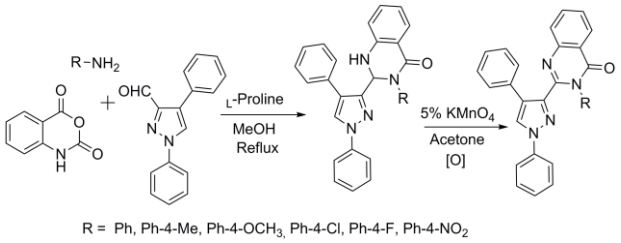
Scheme 11: Synthesis of biological active pyrazole-quinoline-pyridine hybrids

N. Khalifa and his teammates synthesized novel biologically active substituted pyrazolyl thiazolidinone derivatives using three step reaction. Synthesised compounds with promising antibacterial activity were characterised using spectroscopic methods (Scheme.12).



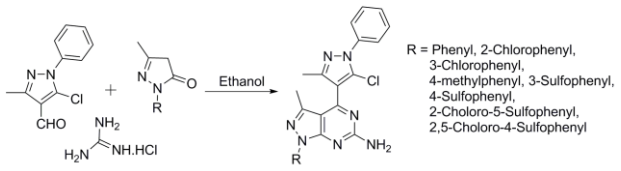
Scheme 12: systhesis of pyrazolylthiazolidinone derivatives

R. Dixit and her team reported L-Proline promoted preparation of pyrazole quinazolines analogues *via* one-pot multicomponent reaction using isatioc anhydride, various amino derivatives and substituted diphenyl pyrazole- carbaldehyde. The compounds were screened for their antitubercular and antibacterial potency (Scheme.13).



Scheme 13: Biologically active pyrazole-quinazoline derivatives

S. Jarsania and his team mates reported the facile route to novel pyrazolo[3,4-*d*]pyrimidines and characterized the products spectroscopically. The compounds were examined for their ability to inhibit the growth of tuberculosis and bacteria (Scheme.14).



Scheme 14: Antiacterial active pyrazolo[3,4-d]pyrimidinies derivatives

P. Kalaria *et al.* synthesized novel library of bipyrazolyl thiazolones using molecular hybridization method. All the synthesized derivatives were characterized by different spectroscopic techniques and elemental analysis. They were evaluated for their *in vitro* antibacterial activity against two Gram-Ve and two Gram+Ve bacteria as well as *E. coli* FabH using Penicillin G

and Kanamycin B as the standards. Molecular docking study was also performed for the synthesized derivatives (Figure 6).

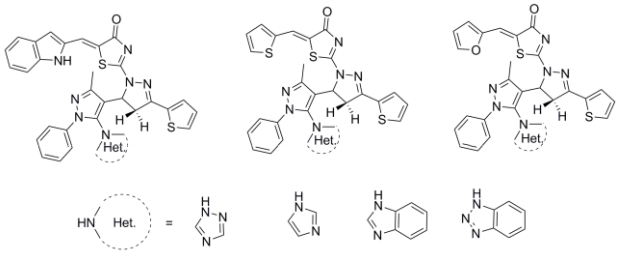
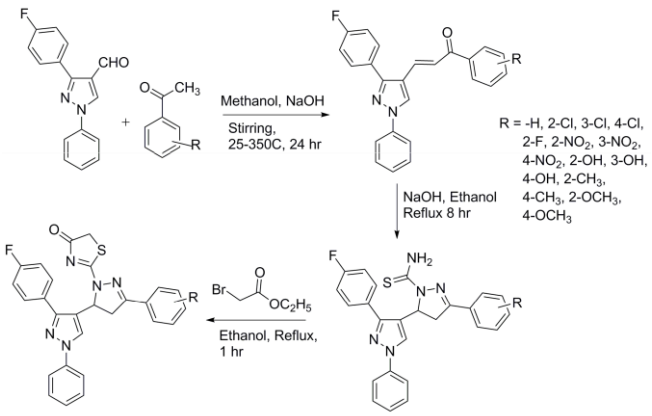


Figure 6: Synthesis and molecular docking study of novel bipyrazolyl thiazolone scaffoid

V. M. Shah and his teammates reported differently substituted 5- imidazolinones **a**, azomethines **b,** sulfonamides **c** and formazans **d** derivatives of pyrazole-4-carbaldehyde *via* multicomponent reaction and evaluated for their antimicrobial potency

N. Desai and his teammates reported facile route to fluoro substituted pyrazole based thiazolidinone derivatives and characterized spectroscopically. The compounds were screened for their *in vitro* antimicrobial activity (Scheme 15).



Scheme 15: Biologically active pyrazole based thiazolidionone

CONCLUSION

Our findings indicate that pyrazoles and chalcones exhibit a wide range of pharmacological properties, including antimicrobial, antioxidant, anti-inflammatory, anticancer, and antiviral activities. These compounds have shown promising results in inhibiting the growth of pathogenic microorganisms and suppressing the development of certain diseases. Additionally, their antioxidant properties have significant implications in scavenging free radicals and protecting cells from oxidative damage. Moreover, some derivatives have demonstrated potential in modulating inflammatory responses, offering potential therapeutic options for inflammatory disorders. In conclusion, pyrazoles, chalcones, and their derivatives hold immense biological importance and offer a rich reservoir for drug development. The diversity of their pharmacological activities makes them promising candidates for further investigation and potential therapeutic agents in various disease treatments.

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