Review Article

Chemistry and Pharmacological Activity of Pyrazole and Thiazole Analogues: A Review

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ABSTRACT

Thiazoles and pyrazolines represent a class of heterocyclic compounds provides a considerable interest in medicinal chemistry due to their diverse pharmacological activities. Hybridizing thiazole and pyrazoline moieties has emerged as an innovative approach to drug discovery, enabling the synthesis of novel compounds with enhanced therapeutic potential. The hybridization of thiazole and pyrazoline derivatives allows for incorporating different functional groups and substitution patterns, which can influence the compound's bioactivity, selectivity, and pharmacokinetic profile. The hybridization of these heterocyclic moieties has resulted in compounds with diverse pharmacological properties, such as antimicrobial, antitumor, anti-inflammatory, antitubercular and antioxidant. Furthermore, thiazolyl-pyrazolines' ability to interact with specific molecular targets, such as enzymes, receptors, or signalling pathways, makes them attractive candidates for drug development. This abstract provides an overview of the thiazoles, pyrazoles derivatives as well as pyrazol-thiazole derivatives chemical properties and their pharmacological activities.

Keywords: Thiazole, pyrazole, Thiazolyl-pyrazole scaffold, anti-inflammatory, antitubercular.

INTRODUCTION

Heterocyclic compound plays an essential role in biological activity. Researchers in this discipline have always been attracted to heterocycles that include sulfur or nitrogen due to their diverse biological activities. Pharmacophoric hybridization is a modern but successful method for creating therapeutic anti-cancer, anti-microbial, anti-inflammatory, and anti-diabetic drugs.[1,2] Combines many bioactive groups into a single molecule to obtain more efficacy than single scaffolds. Interestingly, in medicinal chemistry, heterocyclic compounds with oxygen, nitrogen, and sulphur atoms, such as thiazoles and pyrazolines, are viewed as the foundation for creating newer entities.[3,4] The thiazolyl-pyrazoline scaffold offers diverse chemical functionalities, making it an attractive target for medicinal chemistry research. Thiazolyl-pyrazoline hybrids' antitubercular, anti-inflammatory, anti-microbial, anti-mycobacterial, and FabH inhibitor properties have been demonstrated.[5] Furthermore, it has been discovered that thiazolyl-pyrazole scaffolds have promise as medicines for combating cancer and as inhibitors of multi-targeting kinases.[6]

THIAZOLES

Many organic compounds with biological activity contain thiazole fragments as a part of their structure. Thiazoles are found in numerous natural products such as the secondary metabolites in marine organisms. The biological activities of these NPs have been evaluated and studied as leading structures to manufacture new drugs. For example, Latrunculin A derivatives are biologically measured as inhibitors for a prostate tumor and HIF-1 activators for a breast tumor.Thiazoles are of great importance in pharmacology for their presence in most therapeutic agents. The biological activity of compounds containing thiazole is almost infinite, they are antineoplastic, antibiotic, anti-inflammatory agents, antiulcer anti-HIV, antimicrobial, antifungal drugs. Most biologically active thiazole-containing compounds have substitutions at positions 2 and 4 or one of them. It was found that these substitutes give the compounds different biological properties depending on the difference of the substitutes themselves. Thiazole, or 1,3- thiazole, fits to the class of azoles and contains one sulfur atom and one nitrogen atom at positions 1 and 3. The thiazole nucleus is a very imperative heterocycle in many biologically active compounds that makes it one of the broadly studied heterocycles1-3. Thiazole plays vital roles in many drug structures. Tiazofurin and dasatinib (antineoplastic agents), ritonavir (anti-HIV drug), ravuconazole (antifungal agent) nitazoxanide (antiparasitic agent), fanetizole, meloxicam and fentiazac (antiinflammatory agents), nizatidine (antiulcer agent), and thiamethoxam (insecticide) are some examples for thiazole bearing products. The current reports have been stated the applications of thiazole core structure in drug design and development of novel therapeutic agents. Thiazole ring as part of five membered heterocycles has been used various roles in the lead identification and optimization, including as pharmacophoric and bio isosteric elements, and as a spacer. Also, the presence of thiazole ring as a part of drug structure can be determinant for its physicochemical and pharmacokinetic properties.

Thiazole, or 1,3-thiazole is a clear to pale yellow flammable liquid with a pyridine-like odour and the molecular formula C3H3NS. It is a 5-membered ring, in which two of the vertices of the ring are nitrogen and sulfur, and other three are carbons. The numbering system is shown below for naming derivatives of thiazole

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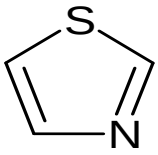
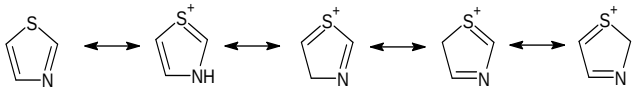


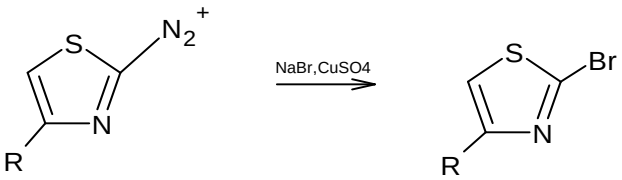
Thiazoles are a class of organic compounds related to azoles with a common thiazole moiety is a crucial part of vitamin B1 and epothilone. It is an aromatic compound, satisfies Huckel's rule. Delocalization of a lone pair of electrons from the sulfur atom complete the 6 π electrons. The resonance forms are.[7]



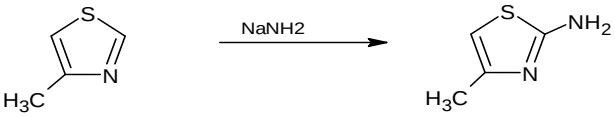
CHEMICAL PROPERTIES

➢ Nucleophilic Substitution Reaction

As evident from the electron density map, C2, the electronically poor carbon center, is the preferred site for nucleophilic substitution. Diazonium salt derived from 2-aminothiazole undergoes nucleophilic substitution with sodium bromide in the presence of copper sulfate to give 2-bromothiazole.[8]

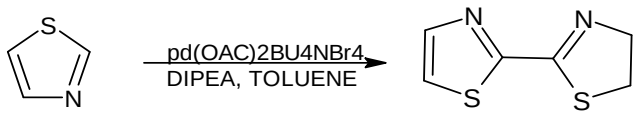


Reagents with high nucleophilicity such as sodamide on reaction with 3-methylthiazole afforded 2-amino-3-methylthiazole



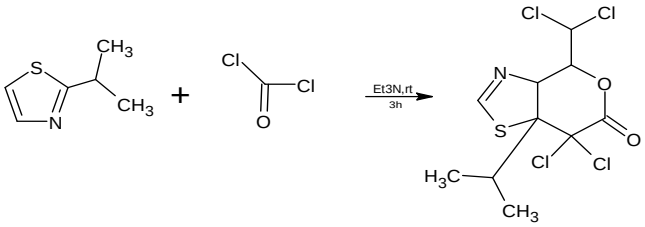
➢ Dimerization Reactions

Palladium acetate-catalyzed dimerization of 2-bromothiazole in the presence of a phase transfer catalyst (Bu4NBr) and diisopropylethylamine (DIPEA) in toluene at 105°C for 23 h gave 2,2'-bisthiazole in 86% yields.[8]



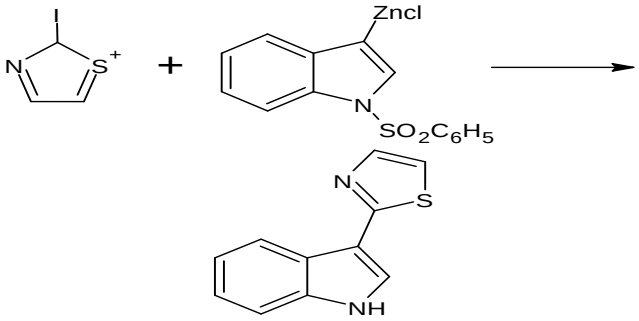
➢ Cycloaddition Reactions

2-Isopropylthiazole on reaction with dichloroketene underwent [2 + 2 + 2] cycloaddition to give a bicyclic product.[8]



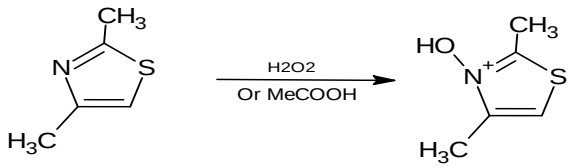
➢ Metal-Mediated Coupling Reactions

Coupling of 2-iodothiazole with 1-((phenylsulfonyl)-1 Hindol 3yl)zinc iodide afforded 2-(1- (phenylsulfonyl)- 1H-lindol-3-yl)thiazole.[8]



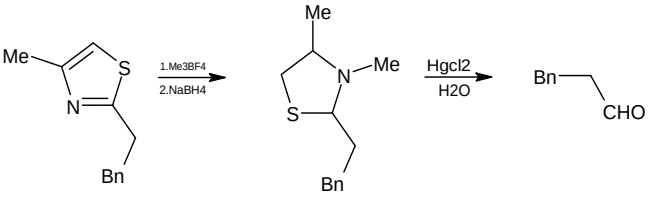
➢ Oxidation

Thiadiazoles are resistant to oxidizing agents but they do oxidize with hydrogen peroxide or peracids such as perbenzoic or peracetic acid to thiazole-N-oxide



➢ Reduction

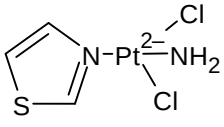
Reduction of thiazoles is a very useful method for the preparation of aldehydes in three steps. The first step is the preparation of N-methyl thiazolium salt and the second step is the reduction of thiazolium cation with NaBH4. Finally, HgCl2-promoted hydrolysis of reduced



PHARMACOLOGICAL ACTIVITIES

Antitumor activity

Marini et al. studied the effect of thiazoles implication on inactive compounds such as transplatin.



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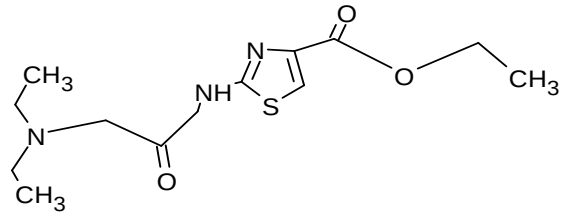
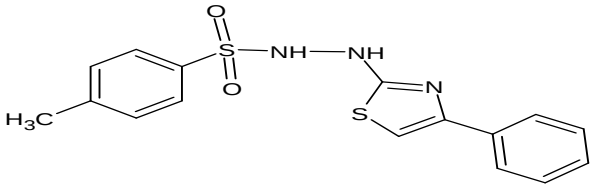
Ethyl 2-[3-(diethylamino)-propanamido]-thiazole-4-carboxylate was tested against RPMI-8226 leukemia cell line and showed a noticeable activity in this filed.



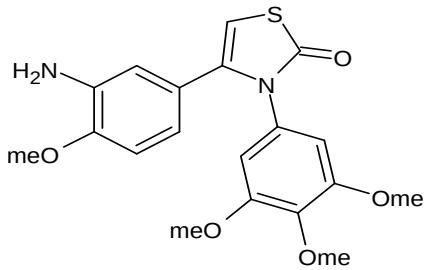
Compounds are synthesized and evaluated biologically against cancerous tumors and found to be a good inhibitor for human cancer cell lines. These compounds are derivatives of 2-amino-4-ferrocenyl-5 (1H-1,2,4-triazole-1-yl)−1.3-thiazole.

Zaharia et al. synthesized several bis-thiazoles derivatives and studied their biological activity against the most common types of cancers, prostate and liver cancer (hepatocellular carcinoma). It was found that compounds exhibited remarkable activity against previously mentioned types of cancers.



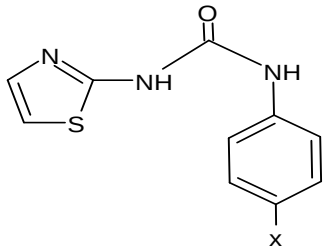
Turan-Zitouni et al. compared the biological activity of compound and its analogue to measure the effect of the presence of thiazole ring in the anticancer agents. It was found that the insertion of thiazole fragment into a bis-thiourea derivatives made it more active against A549 (human lung adenocarcinoma) and C6 (rat glioma) cell lines.[9]

Havrylyuk et al. prepared several compounds from thiazolidinones and benzothiazoles. Their biological activities were evaluated on nine types of cancers; ovarian, lung, leukemia, melanoma, colon, renal, CNS, prostate and breast cancers. Compounds are very active against the CNS cancer SF-295 cell line.



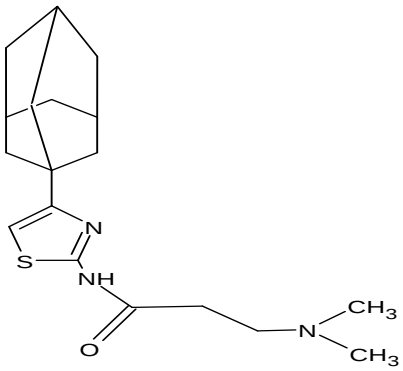
Liu et al. studied anticancer activity of thiazole compounds. It was found that compounds had a high activity against the non-solid human CEM cell line and a moderate with the solid human cancer cell lines. The researchers reviewed several factors influencing the effectiveness of the compounds and found that the presence of the 3,4,5-trimethoxy phenyl on the nitrogen atom, near the carbonyl group, enhance the efficiency. Moreover, the existence of an electron-donating group (3-amino) on the other ring also had a positive effect on the activity.

Compound (1-(4- substituted phenyl)-3-(thiazol-2-yl)urea) was found to have an average inhibitory activity for leukemia P388 tumor in mice, while the compound (1-(thiazol-2-yl)-3-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)urea) exhibited excellent activity against prostate cancer (PC-3).[10]



Anti-inflammatory activity

Kouatly et al. prepared compounds featuring thiazole within its structure to measure its anti-inflammatory properties.



Mohareb et al. prepared a group of compounds containing thiazole ring and measured its activity against inflammation.

Antifungal and Antibacterial Activity

The resistance of fungi and bacteria towards the antimicrobial drugs is increasing rapidly due to the nonselective antimicrobial activities and a limited number of drugs. To overcome this situation, many thiazole containing molecules are synthesized to cure bacterial and fungal infections. Bera et al. synthesized pyridinyl thiazole ligand having hydrazone moiety by condensing 2-bromo-4-methoxy acetophenone with 2-acetylpyridine thiosemicarbazone. They also prepared cobalt complex by treating this ligand with cobalt precursor. Both the ligand and its complex were tested for anti-bacterial properties towards gram positive bacteria including Bacillus subtilis, Streptococcus fecalis, Staphylococcus aureus and gram-negative bacteria including Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, Klebsiella pneumonia and Proteus vulgaris.

Eg:-Pyridinyl thiazole ligand with antimicrobial activity.

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Antiviral Activity

Curreli et al. studied the synthesis of thiazole derivatives carrying oxalamides unit (Fig. 18) and these molecules screened against HIV virus. According to the results both the molecules showed better activity against HIV-1. The molecules target the HIV virus and disrupt the CD-4 binding site. Thus, the molecules avoid the entry of the virus into the host cell.

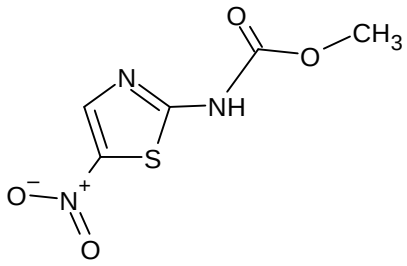
Eg:- Thiazole carrying oxalamides moiety.

Antiprotozoal Activity

Protozoan infections are very common in some regions throughout the world, being endemic in less developed countries. The development of novel molecules with antiprotozoal activity is necessary, given the small number of antiprotozoal drugs currently on the market, their relatively low efficacy and high toxicity, as well as the spread of resistance.

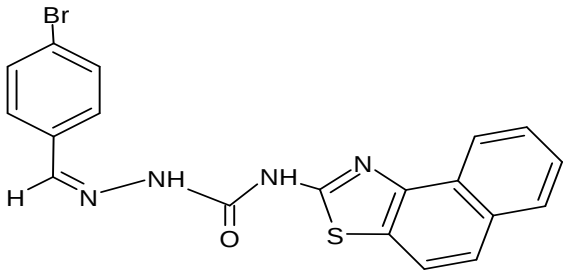
de Oliveira Filho et al. synthesized 22 novel thiazole derivatives and investigated their anti-T. cruzi activity.

A novel series of 2-acylamino-5-nitro-1,3-thiazoles was synthesized by Nava-Zuazo et al. [62] and evaluated against the following protozoa: Giardia intestinalis, Trichomonas vaginalis, Leishmania amazonensis, and Trypanosoma cruzi.



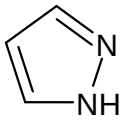
Anticonvulsant activity

The compounds exhibited high anticonvulsant activity when the activity was measured in mice using the maximal electroshock (MES) and pentylenetetrazole (PTZ) models. The compound was synthesized by Azam et al. screened for anticonvulsant activity. It exhibited high efficiency.

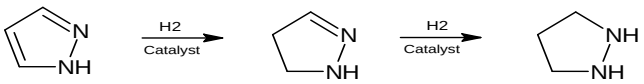


Pyrazole

Pyrazoles constitute an essential class of natural and synthetic products, many of which exhibit flexible biological activity. Antitumor, herbicides, antibacterial, antifungal, hypoglycemic, antidepressant, analgesic, anti-inflammatory, anti-cancer, enzyme inhibitor activity are shown among the pyrazoles.[14–16] As represented by the molecular formula, Pyrazole is a fivemembered ring structure consisting of three carbon atoms and two nitrogen atoms in adjacent positions. The word pyrazole was first coined by Ludwig Knorr in 1883. They are known as alkaloids because of their structures and unique pharmacological effects on human beings. 1-pyrazolylalanine was the first natural pyrazole isolated from watermelon seeds in the year 1959.[17,18]



One that possesses a cyclic structure with at least one heteroatom in the ring is a heterocyclic compound. The most popular heteroatoms are Nitrogen Oxygen and sulphur. In nature, heterocyclic compounds are very widely distributed and important to life in different ways. As is evident from a large number of publications covering their preparation and use, pyrazole constitutes a class of compounds synonymous with widespread use in the field of medicine and agrochemistry.[19] With a melting point of 70°C, Pyrazole is a colourless solid. This high value is due to intermolecular hydrogen bonding that results in a dimmer (compared with 1-alkyl or arylsubstituted pyrazoles). Pyrazole is a tautomeric substance: in pyrazole itself, the presence of tautomerism cannot be shown but can be inferred by considering pyrazole derivatives. Pyrazole exhibits aromatic properties, e.g., it is readily halogenated, nitrated and sulphonated; the group enters at position 4. The following resonating structures are possible for pyrazole.



Pyrazole has a weak base and forms salts with inorganic acids; it is possible to substitute imino hydrogen with an acyl group. Pyrazole is highly resistant to oxidizing and reducing agents, but can be catalytically hydrogenated, first with pyrazoline and then with pyrazolidine. But stronger bases than pyrazole are among these compounds.

CHEMICAL PROPERTIES

Pyrazole has a five-membered aromatic ring structure consisting of two atoms of vicinal nitrogen, acidic pyrrolelike nitrogen with a single pair of aromatic electrons, simple sp2 -hybridized nitrogen-like pyridine and three atoms of carbon,[20] and these combined features must be carefully taken into account in the context of reactivity. In the first instance, N-unsubstituted pyrazoles possess amphoteric properties, acting as both acids and bases, considering the presence of nitrogen.[21`] While the proton is easily donated by the acidic pyrrole-like NH group, the simple pyridine-like nitrogen can accept protons even more readily, and thus the basic character is typically prevalent. Nevertheless, substitutions on the ring can modulate these properties, as, for instance, electrondonating groups were shown to increase the acidity of the pyrrole-like -NH group.[22–23]

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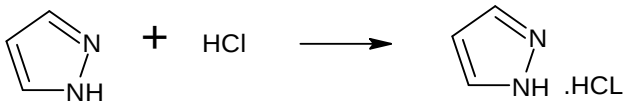
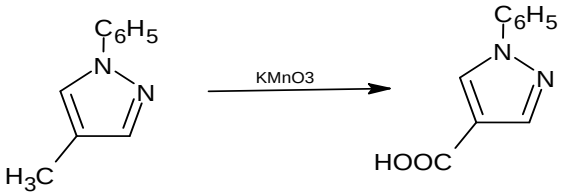
➢ **Acylation**

The introduction of the acyl or phenyl sulfonyl group into pyrazole nitrogen is usually achieved in the presence of a weak base such as pyridine. Thus, in acylation iminohydrogen atom of the pyrazole nucleus is replaced by an acyl group, to give N-acetyl pyrazole.[24]



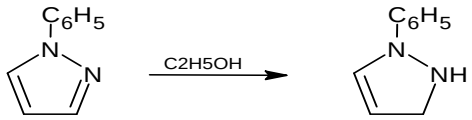
➢ **Oxidation**

Pyrazoles are mostly stable to oxidation and only C–alkylated side chains are attacked by oxidizing agents alkaline KMnO4 to yield the corresponding carboxylic acid pyrazole.[25]



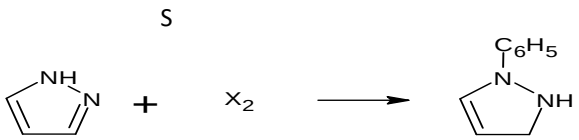
➢ **Reduction**

Although pyrazole itself is resistant to reduction by sodium-ethanol, its N-phenyl derivative may be reduced by sodium-ethanol to yield the corresponding pyrazoline.[26]



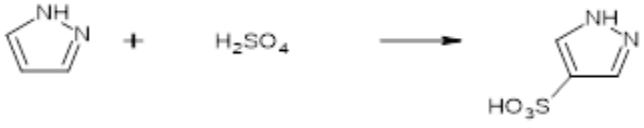
➢ **Halogenation**

Halogenation of pyrazole gives 4-mono halo pyrazoles e.g. 4-chloro, 4-iodo or 4-bromo pyrazole under controlled conditions but poor yields are obtained on the reaction of isothiazole and isoxazole. Bromine will attack at C–4, but with activating groups, present halogenation proceeds better. 3,4,5-tribromo pyrazole is formed efficiently in an alkaline solution; presumably, the pyrazole anion is the reacting species.[27]



➢ **Nitration**

Pyrazole undergo straight nitration at C-4, it gives 1-nitropyrazole but this can be rearranged to 4-nitropyrazole in acid at low temperature.[28] Sulphonation Pyrazole reacts with fuming sulphuric acid to yield pyrazole 4–sulphonic acid.[29]



PHARMACOLOGICAL ACTIONS

Anti-inflammatory Activity

Inflammation is a multi-stage process that in the critical step is supposed to be powered by acutely released arachidonic acid and its prostaglandin-like metabolites. Two cyclooxygenase (COX) isozymes are known to catalyze the rate-limiting stage of prostaglandin synthesis, COX-I and COX-11.[33] aNonsteroidal anti-inflammatory drugs Alleviate pain by conteracting by counteracting the cyclooxygenase (COX) enzyme. Some common example of NSAIDs is aspirin, ibuprofen, and naproxen.

Freddy et al (2001) have synthesized the series of 1-(3bromo-4-methoxybenzyl)-4-formyl-3-(substituted phenyl) pyrazole and their anti-inflammatory activity.[38] Bhaskar et al (2007) have reported the synthesis of 4,5-disubstituted3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c] pyrazole and their anti-inflammatory activity. Nargund et al (1992) evaluated the fluorinated phenyl styryl ketone Sayed et al (2012) reported a series of new pyrazole derivatives characterized as N-((5-(4-yl chlorophenyl)-1phenyl-3(trifluoromethyl)- 1 Hpyrazol-4-yl)methylene) 5 bis (trifluoromethyl) aniline which exhibited optimal anti-inflammatory activity as compared with reference drugs diclofenac sodium and celecoxib.[41] Bandgar et al (2009) evaluated the series of novel 1-(2,4dimethoxyphenyl)3-(1,3-diphenyl-1 pyrazol 4 propenone by the Claisen Schmidt condensation of 1(2,4dimethoxyphenyl)-ethanone and substituted 1,3 diphenyl1Hpyrazole-4-carbaldehyde. All the synthesized compounds were evaluated for anti-inflammatory activity.

Bekhit et al. synthesized a series of novel pyrazolyl benzene sulfonamide derivatives bearing thiazolyl ring and evaluated for anti-inflammatory activity. Among the synthesized compounds, compound 296 exhibited higher anti-inflammatory activity than the reference compound (indomethacin). 3,5-Diaryl pyrazole derivatives were ring and evaluated for anti-inflammatory activity.

Anti-cancer Activity

Different derivatives of pyrazole are generated by linking pyrimidine, carboxyhydrazide, as well as ferrocenyl molecule with pyrazole cap and all that are particularly effective against carcinoma of lung cells.

Ohki et al (2002) synthesized the pyrimidinyl pyrazole derivatives 1-(3,5difluorophenyl)-N-(E)-3-(1-pyrimidin-2-yl)-1H-pyrazol-4yl)piperidin-4-amine as a new scaffold of an anti-tumor agent, which also showed antiproliferative activity against human lung cancer cell lines and inhibited tubulin polymerization.

Balbi et al (2011) prepared a novel pyrazole derivatives 5methoxy-2-(1-(pyridine-2-yl)-1H-pyrazol-5-yl)phenol and reported their antiproliferative activity in human ovarian adenocarcinoma A2780 cells, human lung carcinoma A549 cells, and murine P388 leukemia cells.[47] Lv et al (2010) reported and synthesized two series of pyrazole derivatives4,5-dihydro-5-(4-methoxyphenyl)-3-(3,4

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dimethyl phenyl)pyrazole-1-caboxamide which are designing for potential EGFR kinase inhibitors, as well as antiproliferative activity against MCF-7 with potent inhibitory activity in tumor growth inhibition would bear potential anticancer activity.

Bernardino et al (2006) were synthesized and reported the in vitro leishmanicidal activities of 1H-pyrazole-4carbohydrazides. Among all the 1H-pyrazole-4carbohydrazides derivatives examined the compound (Z)N-(4-nitrobenzylidene)-1-(4-bromophenyl)-1-pyrazole-4carbohydrazide found the most active against L. amazonensis, L. chagasi and L. braziliensis species.[64] Dardari et al (2006) were reported the synthesis of new pyrazole derivatives, compound N-ethyl-2-methyl-1-(2-(1phenyl-3-p-tolyl-1H-pyrazol-4-yl)phenyl)propan-1-amine. This compound inhibited the in vitro multiplication of Leishmania tropica, Leishmania major and Leishmania infantum with IC_{50} value of 0.50 µg/mL, 0.65 µg/mL and 0.42 µg/mL, respectively.

Bandgar et al (2010) developed new series of 3,5 diarylpyrazole derivative 1-(3,5-dichlorophenyl)-4-(4,5-dihydro -1H-imidazol-2-yl) 1H-pyrazol-5-amine and evaluated for their anticancer activity.

Wei et al (2006) reported a series of novel small molecules of compound ethyl 1-[20-hydroxy30-aroxypropyl]-3-aryl-1H-pyrazole-5-carboxylate derivatives which have its potency to suppress lungs cancer cell growth.

4 Xia et al (2007) prepared a series of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohyrazide derivatives which had inhibitory effects on the growth of A549 cells and induced the cell apoptosis.45 Fan et al (2008) reported a series of novel 1-(3-(4chlorophenoxy)phenyl)3-(4-chlorophenyl)-1H-pyrazole-5-carbohydrazide which is inhibiting the growth of A549 cells.

Li et al (2012) developed a series of 1H-pyrazole-4carboxamide derivatives and reported their potential antiproliferation activity and Aurora-A kinase inhibitory activity. Among the compounds, N-(4-ethoxyphenyl)-1,3diphenyl-1H-pyrazole-4-carboxamide possessed the most potent biological activity against HCT116 and MCF-7 cell lines with IC50 value of 0.39 and 0.46 µM, respectively

Anti-tubercular Activity

Manetti et al (2006) developed new inhibitors of Mycobacterium tuberculosis. The compound (1-(chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4yl) (phenyl) methanone was found to be the most active agent with a MIC value of 25 µM/ mL.[50] As a continuation of our previous work that turned toward the identification of antimycobacterial compounds with innovative structure, the compound (1-(4-bromophenyl)-5-hydroxy3-methyl-1H-pyrazol-4-yl)(4-chlorophenyl)methanone of pyrazole derivatives were synthesized by Castagnolo et al (2008) and assayed as inhibitors of M. tuberculosis H37Rv. The pyrazole derivatives with the p-bromophenyl group at the N1 position was showed to be very active.

A new series of fluorinated pyrazoles were reported and screened by Shelki et al (2012) for their in vitro anti-tubercular activities against Mycobacterium tuberculosis H37Rv. Results the compound 4-(5-(4-chlorophenyl)-4,5-dihydro1H-pyrazol-3-yl)-3-(4-fluorophenyl)-1-phenyl-1H-pyrazole showed that pyrazoline displayed significant antitubercular activities against the M. tuberculosis H37Rv strain (MIC=6.25 µg/mL).

Fullam et al (2013) developed the inhibitory potencies of a novel series of 3,5-diaryl-1H-pyrazoles as specific inhibitors of prokaryotic arylamine N-acetyltransferase enzyme. The compound 4-methoxy-2-(5-(4-methoxyphenyl)-1Hpyrazol-3-yl)phenol was found to have good antimycobactrium activity and inhibited the growth of both M. tuberculosis with an MIC<10µg/mL. Maurya et al (2013) evaluate and reported the various substituted pyrazoles derivatives for their in vitro anti-tubercular activity against M. tuberculosis H37Rv strain.

Anti-diabetic Activity

Cottineau et al (2002) were reported and developed a new series of substituted pyrazole-4-carboxylic acids for their antidiabetic activity. The results indicated that the prepared compound 3-methoxy-1H-pyrazole-4-carboxylic acid emerges as the best hypoglycemic agent in the series.

Sharon et al (2005) were prepared a new series of 5-[(5-arly-1H-pyrazol-3-yl) methyl]-1H-tetrazoles.

Fullam et al (2013) developed the inhibitory potencies of a novel series of 3,5-diaryl-1H-pyrazoles as specific inhibitors of prokaryotic arylamine N-acetyltransferase enzyme. The compound 4-methoxy-2-(5-(4-methoxyphenyl)-1Hpyrazol-3-yl)phenol was found to have good antimycobactrium activity and inhibited the growth of both M. tuberculosis with an MIC<10µg/mL. Maurya et al (2013) evaluate and reported the various substituted pyrazoles derivatives for their in vitro anti-tubercular activity against M. tuberculosis H37Rv strain. The compound (5-(4and isolated them for their in vivo anti-hyperglycemic activity. Out of screen compound demonstrated 24.6% of blood glucose-lowering activity at 100 mg/kg.57 Humphries et al (2009) were synthesized the series of novel 4-pyrazolyl-2aminopyrimidines as inhibitors of c-Jun-N-terminal kinases. This study led to the identification of compound 1s,4s)-4-(4-(3-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-4yl) pyrimidin-2ylamino)cyclohexanol which showed good selectivity across a panel of diverse protein and lipid.

Brigance et al were reported several pyrazolopyrimidines and evaluated as inhibitors of dipeptidyl peptidase4(DPP4). Among the reported compound (7-(2,4dichlorophenyl)-2-(2-chlorophenyl)-3,3a-dihydro-5methylpyrazolo[1,5-a] pyrimidin-6-yl)methanamine displayed the greatest potency (Ki= 20 Nm) and demonstrated excellent selectivity over the other dipeptidyl peptidase.

Analgesic Activity

Rajasekaran et al (2012) novel [1-(3-(5-chloro-2-hydroxy phenyl)-5-aryl-4,5-dihydro ethanone derivatives has been

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synthesized and were screened for Results showed that all the synthesized compounds shown significant activity when compared with that of standard drug.

Antimicrobial Activity

Bondock et al (2008) reported the synthesis and antimicrobial activity of some new heterocycles incorporating antipyrine moiety. 2-cyano-N-(1,5-dimethyl3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) acetamide was utilized as a key intermediate for the synthesis of some new coumarin, pyridine, pyrrole, thiazole, pyrido, pyrazolo triazine and amino pyrazole. [55]

Thiazole and pyrazole compounds

The thiazolyl-pyrazoline scaffold offers diverse chemical functionalities, making it an attractive target for medicinal chemistry research. Thiazolyl-pyrazoline hybrids' antitubercular, anti-inflammatory, anti-microbial, anti-mycobacterial, and FabH inhibitor properties have been demonstrated.[30]. Furthermore, it has been discovered that thiazolyl-pyrazole scaffolds have promise as medicines for combating cancer and as inhibitors of multi-targeting kinases.[31]

In medicinal chemistry, nitrogen- and/or sulfur-based heterocycles, including thiazoles and pyrazoles, are regarded as a fundamental platform for constructing newer entities.[32]. Thiazole is a 5-membered ring having nitrogen and sulfur atoms,[33] while pyrazole is a 5-membered ring having two nitrogen atoms.[34,35]. A heterocyclic ring, which serves as the central component of pharmacological compounds, is a widespread occurrence in both natural and synthesized medications. One of the effective strategies utilized in the process of discovering novel drugs is the hybrid architecture of bioactive pharmacophore compounds.[36] Thiazoles clubbed with other azoles have recently been favored as scaffolding for the creation of new promising bioactive compounds.[37]

THIAZOLYL-PYRAZOLINE SCAFFOLD

From the aforementioned data about thiazole and pyrazoline as abroad spectrum scaffolds and their multifarious pharmacological activities that inspire us to review the biological activity of the hybridization of these promising scaffolds. In the last decades, many researchers have focused on synthesising different series of thiazolyl-pyrazoline, and their biological activity has been evaluated. Thiazolyl-pyrazoline hybrids have displayed antitubercular, anti-inflammatory, antimicrobial, antimycobacterial activities, FabH inhibitors, and others .[38–40]

PHARMACOLOGICAL ACTIVITY

ANTICANCER ACTIVITY

- Serine/threonine kinase inhibitors

One of the largest and most functionally varied gene families, protein kinases perform crucial regulatory roles in almost every area of cellular function. Protein kinases control the biological activity of proteins by phosphorylating particular amino acids using ATP as the source of phosphate and changing the protein's shape from an inactive to an active state. Their classification is determined based on the side chain of the amino acid that they phosphorylate. In the last decades, many researchers have designed and synthesized different series of thiazolylpyrazoline, which were biologically evaluated as kinase inhibitors.

- RAF Inhibitor

The RAF family is serine/threonine protein kinase, which phosphorylates and activates downstream MEK1/2, including A-RAF, B-RAF, and C-RAF. Meng-Yue Zhao et. Al, developed new pyrazole-based compounds as potential BRAF-targeting anticancer agents.[40] Compound 2h displayed potent activity (IC50 = 0.05 µM) against BRAFV600E kinases. Furthermore, this compound also displayed significant in vitro antiproliferative activity against MCF-7 with IC50 of 0.16 µM, comparable to the standard drug Sorafenib (IC50;0.19 µM) .[40]

- mTOR Inhibitor

Cell proliferation, autophagy, and cytoskeletal architecture are regulated by the serine/threonine kinase known as the Mammalian Target of Rapamycin (mTOR). Multiple human diseases, including malignancies like breast and lung cancer, were linked to the dysregulated activity of mTOR. The mTOR pathway has several potential uses in treating different solid tumours and haematological malignancies because of the crucial role that proliferation plays in various malignant cell types .[41] Zhao Min Lin et al. developed a series of fluorescent thiazolepyrazoline derivatives. They biologically assessed them against non-small cell lung cancer (NSCLC) A549 cells in a dose- and time-dependent manner in vitro. Compound 3 of this series displayed inhibition of mTOR via FKBP12, an mTOR activator and autophagy inhibitor. Additionally, it inhibited growth and promoted autophagy of A549 cells. Furthermore, compound 3 showed selectivity without affecting the development of chorioallantoic membrane (CAM) capillaries or normal vascular endothelial cell proliferation in chick embryos .[42]

- Tyrosine Kinase Inhibitors

Tyrosine kinase (TK) is a class of proteins that controls several physiological and biochemical processes, including cell development, differentiation, and death. The aberrant expression of TK could cause tumorigenesis, metastasis, tumor angiogenesis, and tumor chemotherapy resistance. Therefore, they have become a popular target for anti-tumor drug research. Protein-tyrosine kinases (90 members), and tyrosine kinase-like proteins (44 members). 90 protein-tyrosine kinases are present, 58 of which are receptor tyrosine kinases (RTKs), and 32 of which are non-tyrosine kinases (nRTKs) (37), the former includes the insulin receptor and the receptors for many growth factor families such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth

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factor (PDGF), and fibroblast growth factor (FGF). Tyrosine kinase inhibitors (TKI) can be classified into many types based on the mode of binding and conformation of kinase in the ATP pocket .[43–45]

ANTI-INFLAMMATORY ACTIVITY

Inflammation is a complex biological response triggered by various stimuli, such as infection, tissue injury, or immune system dysregulation. While acute inflammation is a normal protective response, chronic inflammation can lead to tissue damage and the development of various diseases, including cardiovascular diseases, neurodegenerative disorders, and certain cancers. Inflammation involves the release of pro-inflammatory mediators, such as cytokines, chemokines, and prostaglandins, which promote immune cell activation and tissue inflammation .[46,47]

For the anti-inflammatory screening of the final compounds, 19 b (91.74%) exhibited excellent anti-inflammatory activity compared to Diclofenac sodium (90.21%) as standard.

Antimicrobial Activity

Ozdemir et. al, in 2006 developed 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2- pyrazoline series. All of the compounds of this series showed effective antibacterial and antifungal activity when compared with reference drugs. Compounds 20 and 21 especially showed very high activity against S. faecalis, while compounds 22 showed strong activity. This series also showed significant activity against A. hydrophila, as compounds 20 and 22 showed very high activity..[48]

Mansour et. al, in 2019, developed a series of thiazolyl pyrazoline derivatives linked to benzo[1,3]dioxole moiety and investigated for biological properties as antimicrobial agents. Between this set, compound 23 showed interesting antimicrobial activity in addition to significant antifungal activity with inhibition zone 2.5 mm against A. funigatus. While compound 24 had a promising activity with MIC value of 0.115 mg/mL against S. aureus.[49]

Nofal et al., in 2021 developed a new set of pyrazole fragments coupled with (Nsubstituted) benzimidazole or phenyl moieties in a pyrazol-thiazole-p-substituted phenyl scaffold. This series was designed based on the biological importance of thiazole as anti-microbial, pyrazole derivatives heavily researched heterocycles in anti-microbial treatment as Lonazolac, Fipronil, and Tolpiprazole drugs bearing pyrazole nucleus, and using benzimidazole as significant core in many anti-microbial commercial drugs.[50–53] The resulting compounds were tested for their antibacterial abilities against Gram-positive bacteria (Staphylococcus aureus ATCC29213) and Gram-negative bacterium Escherichia coli .[54]. Optimization and structural improvement are required for more effective antimicrobial analogues.

CONCLUSION

In conclusion, the hybridization of thiazole and pyrazoline heterocycles has emerged as a promising strategy in medicinal chemistry, leading to the development of novel hybrid scaffolds with diverse biological activities. The combination of these two heterocyclic frameworks has proven to be highly successful in creating compounds with enhanced potency, selectivity, and therapeutic potential. The synthesis of thiazole-pyrazoline hybrids has been achieved through various synthetic methodologies, including conventional approaches and modern techniques, allowing researchers to efficiently generate a wide range of hybrid molecules, enabling researchers to explore their biological properties. One of the key advantages of thiazole-pyrazoline hybrids is their ability to exhibit multitargeted activities. These compounds have demonstrated promising results in various biological assays, including anti-proliferative, antioxidant, antimicrobial, antiviral and anti-inflammatory activities.

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