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Biological Significance of Pyrazole-Coupled Thiazole Derivatives: A Comprehensive Review

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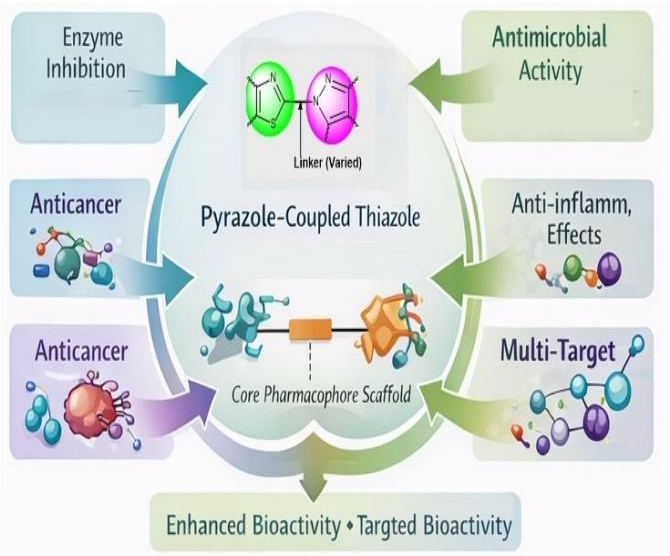
ABSTRACT

Pyrazole coupled thiazole derivatives represent an important class of heterocyclic hybrid molecules that have attracted sustained attention in medicinal chemistry over the last decade. The presence of nitrogen and sulphur containing heterocycles within a single molecular framework often leads to enhanced biological activity, improved target selectivity, and favourable pharmacokinetic properties. Pyrazole and thiazole rings are individually recognized as privileged scaffolds in drug discovery, and their hybridization has resulted in compounds with remarkable antimicrobial, anticancer, anti-inflammatory, antiviral, antitubercular, antioxidant, and enzyme inhibitory activities. This review provides a comprehensive and critical overview of research progress on pyrazole coupled thiazole derivatives. Synthetic methodologies, structure–activity relationships, molecular docking and mechanistic insights, and diverse biological applications are discussed in detail. Current challenges, limitations, and future research prospects are also highlighted to guide further development of this promising class of bioactive heterocycles.

GRAPHICAL ABSTRACT



1. Introduction

Heterocyclic compounds occupy a central position in medicinal chemistry owing to their structural diversity and wide range of pharmacological activities. Among these, pyrazole and thiazole rings are recognized as privileged scaffolds in the design of biologically active molecules.

The pyrazole nucleus is associated with anticancer, anti-inflammatory, antiviral, antimicrobial, and insecticidal properties, while the thiazole ring is frequently found in natural products and clinically relevant drugs. The molecular hybridization of these two pharmacophores into a single framework-forming pyrazole-coupled thiazole derivatives-has emerged as an effective strategy to enhance biological activity, selectivity, and target affinity. Recent investigations have demonstrated that thiazole-based heterocycles exhibit potent anticancer and antimicrobial activities [1]. Similarly, N-pyridylpyrazole-thiazole derivatives have been reported as promising insecticidal leads, highlighting the agrochemical relevance of this hybrid scaffold [2]. Pyrazolylthiazole derivatives have shown significant anti-HIV and antiproliferative activities, indicating their potential as antiviral agents [3].

Furthermore, pyrazolo-thiazole hybrids have been explored as non-nucleoside reverse transcriptase (NNRT) inhibitors against HIV-1 [4]. In the field of oncology, thiazolyl-pyrazole conjugates have attracted substantial attention due to their remarkable anticancer properties. Several studies have reported their ability to inhibit key molecular targets such as EGFR and HER2 kinases, leading to potent antiproliferative activity against various cancer cell lines [5-11]. Compounds integrating additional pharmacophores such as naphthalene, quinoline, or curcumin moieties into the pyrazole-thiazole framework have further enhanced antitumor efficacy [6, 9-14]. Structure-based drug design approaches and molecular docking studies have confirmed strong binding interactions with cancer-related targets [10, 15].

Beyond anticancer and antiviral applications, pyrazole-thiazole derivatives have demonstrated broad-spectrum antimicrobial, antifungal, antimycobacterial, and antioxidant activities [12,13,16-24]. Some derivatives have shown effectiveness against multidrug-resistant (MDR) pathogens through MurA enzyme inhibition [12], while others exhibited promising activity against breast cancer in integrated computational and preclinical evaluations [22].

The incorporation of diverse substituents and heterocyclic systems has enabled systematic structure–activity relationship (SAR) studies, leading to improved potency and pharmacokinetic properties. Advances in synthetic methodologies, including one-pot multicomponent reactions, solvent-free protocols, and green chemistry approaches, have facilitated the efficient construction of structurally diverse pyrazole-coupled thiazole derivatives [16,18,20].

Combined with in silico ADME/T profiling, molecular docking, and dynamic simulations, these strategies have accelerated the identification of promising lead molecules. In view of their synthetic versatility and broad spectrum of biological activities, pyrazole-coupled thiazole derivatives represent a highly promising class of hybrid heterocycles in modern drug discovery.

This comprehensive review aims to summarize recent developments in their synthesis, biological significance, molecular targets, and structure-activity relationships, with particular emphasis on anticancer, antimicrobial, antiviral, and enzyme inhibitory activities.

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2. Synthesis Methods

Sraa Abu-Melha et al. [1] synthesized some novel thiazole-based heterocycles (Fig. 1). Human hepatocellular carcinoma (HepG-2), colorectal carcinoma (HCT-116), and breast cancer (MCF-7) cell lines are used to test the cytotoxic activity of synthesised compounds. The results indicate that compounds **1** and **2** (Fig. 1) are the most effective [1].

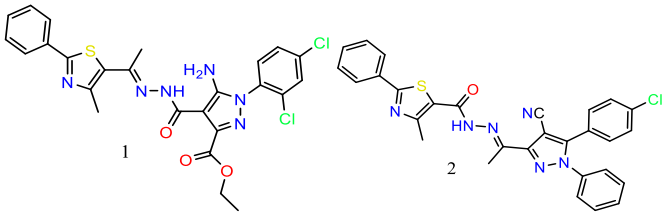

Fig. 1 Structures of novel thiazole-based heterocycles (Compounds 1 and 2).

Yang et al. [2] synthesized novel N-Pyridopyrazole thiazole derivative (Fig. 2). The insecticidal properties of these synthetic compounds were tested against *Plutela xylostella, Spodoptera exigua,* and *Spodoptera frugiperda.* The results suggest that compound **3** (Fig. 2) has good inseticidal activity [2].

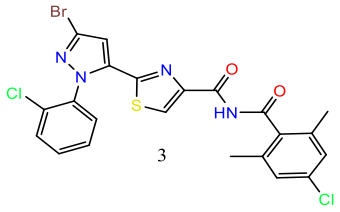

Fig. 2 Structure of novel N-pyridopyrazole thiazole derivative (Compound 3)

Madni et al. [3] synthesised a new series of N-benzylidene-2-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazole-1-yl) thiazole-4-carbohydrazide Schiff bases, including a 1,3-thiazole fused with a 2-pyrazoline moiety (Fig. 3). These synthetic compounds were tested for antiviral activity against HIV-1 and HIV-2 replication in MT4 cells using the MTT assay. The results revealed that only compounds **4** and **5** (Fig. 3) had potency against HIV-1 replication, but none of these compounds are active against HIV-2. They also tested various synthetic substances for antiproliferative properties. According to the results, compounds **4** and **5** were active solely against MCF-7 cell lines and inactive against Hep-G2, but compound **6** (Fig. 3) was active against Hep-G2 but inactive against MCF-7 [3].

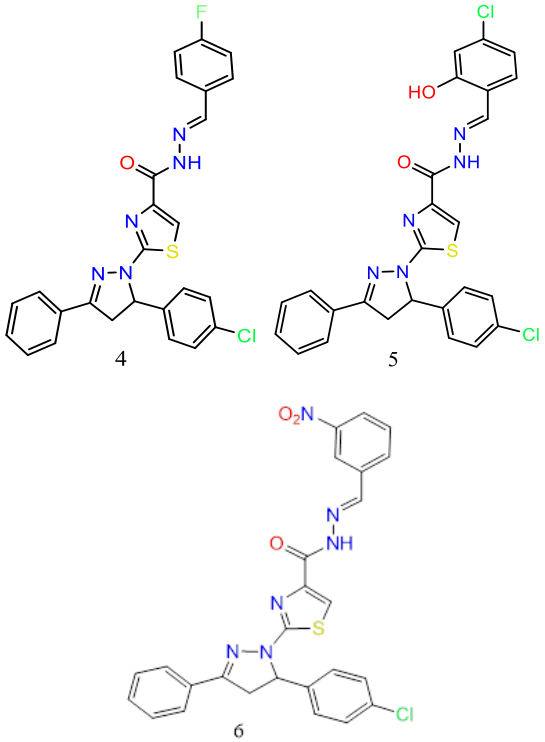

Fig. 3 Structures of N-benzylidene-2-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazole-1-yl) thiazole-4-carbohydrazide Schiff bases (Compounds 4 - 6)

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Kasralikar et al. [4] synthesised a several pyrazolo [3,4d] thiazole hybrids (Fig. 4) and tested them for anti-HIV-1 activity. Among all the synthesised pyrazolo [3,4d] thiazoles, compounds **7** and **8** (Fig. 4) were found to be strong inhibitors of the HIV-1 IIIB and HIV-1 ADA5 strains [4].

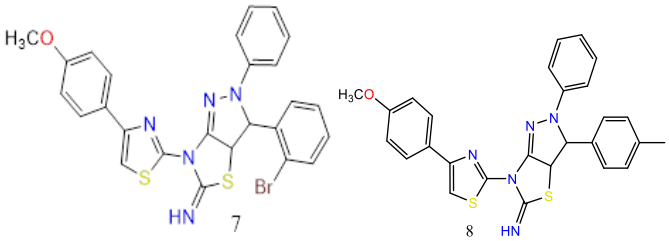

Fig. 4 Structures of pyrazolo [3,4d] thiazole hybrids (Compounds 7 and 8)

Sayed et al. [5] synthesised many thiazolyl-pyrazole derivatives (Fig. 5). Five compounds shown potential binding affinities against the active region of the epidermal growth factor receptor kinase (EGFR) (**9** - 3.4 kcal/mol, **10** - 3.0 kcal/mol, **11** - 2.2 kcal/mol, and **12** - 1.3 kcal/mol). The cytotoxicity of powerful products **9, 10, 11**, and **12** (Fig. 5) was tested against a human liver cancer cell line (HepG-2) and demonstrated activity similar to Doxorubicin, the standard medication [5].

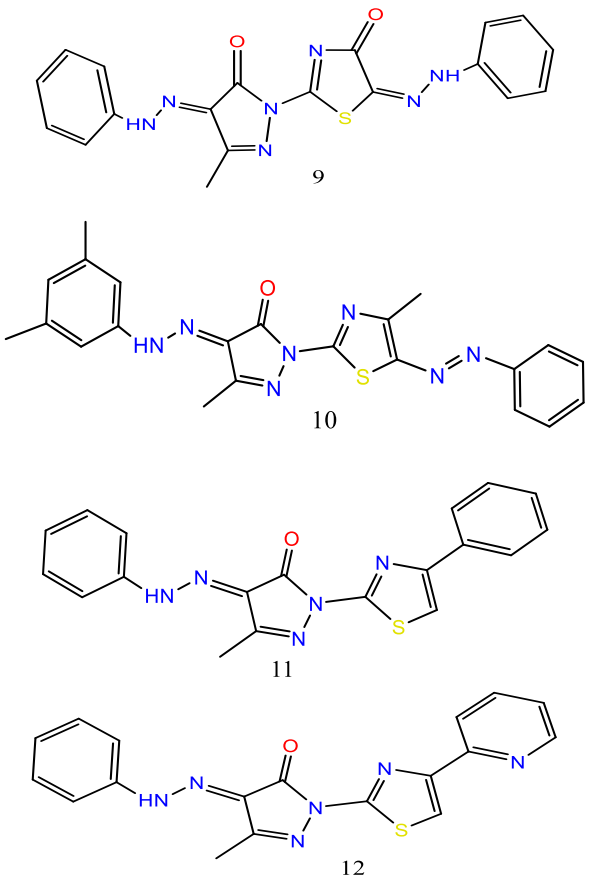

Fig. 5 Structures of thiazolyl-pyrazole derivatives (Compounds 9 - 12)

George et al. [6] synthesised various thiazole hybrids as well as unique 4,5 dihydro pyrazoles based on quinolone (Fig. 6). The most potent molecule found was **13**, (Fig. 6) a quinolinyl-pyrazolinyl 4-fluorophenylthiazole hybrid, with substantial EGFR inhibition (IC_{50} = 31.8 nM) and excellent antiproliferative activity, against the DLD1 colon cancer cell line. Compound **14** (Fig. 6) had the lowest EGFR inhibitory activity among the active drugs (IC_{50} = 405.4 nM). Structure-activity relationship (SAR) research revealed that combining quinolinyl pyrazoline and arylthiazole, particularly with tiny electron-withdrawing substituents such as fluorine, improves both anti-cancer and EGFR inhibitory efficacy. Biochemical studies, including cytotoxicity screening against MCF-7, HeLa, and DLD1 cell lines, demonstrated that compound **13** had high activity while being safe for normal WI-38 fibroblasts. Computational docking studies utilising EGFR (PDB ID: 1M17) demonstrated that compound **13** attach efficiently to the EGFR active site, creating hydrogen bonds with Met769 and cation-π interactions with Lys721, supporting its function as an EGFR inhibitor [6].

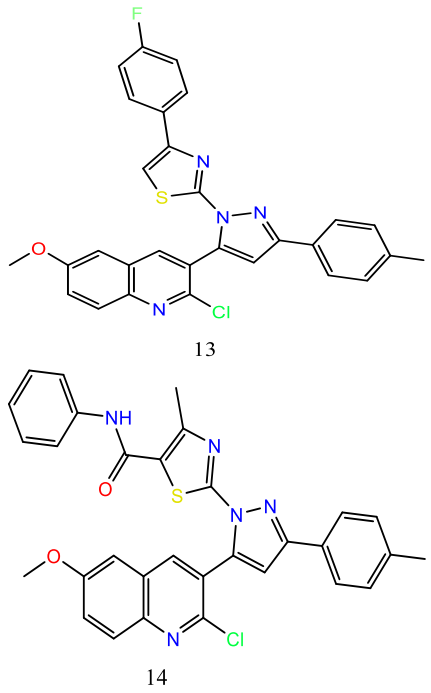

Fig. 6 Structures of 4,5 dihydro pyrazoles based quinolone thiazole hybrids (Compounds 13 and 14)

Sever et al. [7] synthesized a new class of thiazolyl-pyrazoline compounds (Fig. 7). With anticancer activity against the A549 (lung), MCF-7 (breast), and A375 (skin) cancer cell lines. Compound **15** (Fig. 7) was the most effective dual EGFR/HER2 inhibitor, with significant cytotoxicity against A549 and MCF-7 cells (IC_{50} = 10.76 ± 1.81 µM and 8.05 ± 1.47 µM, respectively) and strong EGFR (IC_{50} = 4.34 ± 0.66 µM) and HER2 (IC_{50} = 2.28 ± 0.53 µM) inhibition. Compound **16** (Fig. 7) was the least active, with IC_{50} values over 100 µM in most investigated cell lines. The presence of a 4-cyanophenyl group on the thiazole ring and a morpholine ring on the phenyl ring considerably increased antiproliferative activity and kinase inhibition, according to the structure–activity relationship (SAR), while other substituents (such as 4-nitrophenyl or 2-naphthyl) resulted in decreased activity. Biochemical tests included kinase inhibition profiling against EGFR, HER2, HER4, IGF1R, and others; apoptosis assessment with Annex in V labelling (demonstrating 68% apoptosis for **15** in A549 cells); and MTT cytotoxicity tests on A549, MCF-7, and A375 cancer cell lines. Compound **15** was found to fit well into the ATP-binding site of EGFR, forming important π–π interactions with Lys721, Val702, and Leu820. It also interacted with Asp863 in HER2, supporting its dual inhibitory mechanism and large affinity toward the receptor targets, according to computational docking studies (EGFR: PDB ID 4HJO, HER2: PDB ID 3RCD) [7].

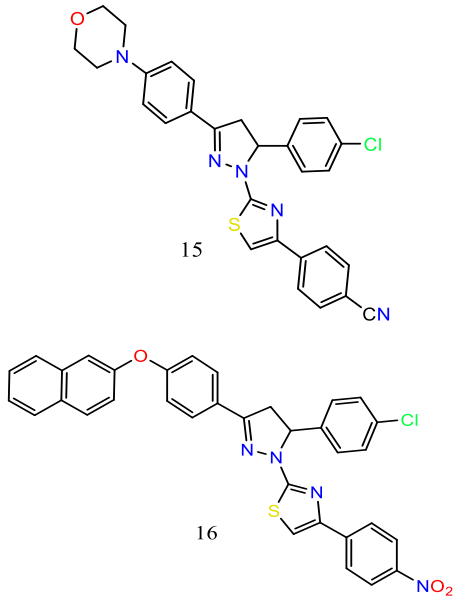

Fig. 7 Structures of thiazolyl pyrazoline derivatives (Compounds 15 and 16)

Salian et al. [8] synthesised several thiazole-linked pyrazoline scaffolds (Fig. 8) and tested their antimicrobial and antioxidant activity against *Staphylococcus aureus, Escherichia coli, Bacillus cereus, Serratia marcescens, Aspergillus niger, Candida albicans, Trichophyton mentagrophytes,* and *Candida parapsilosis.* This evaluation used both the free radical DPPH assay and the agar well diffusion method. The antimicrobial screening showed that compound **17** and **18** (Fig. 8) had substantial antioxidant activity, with IC_{50} values of 63.11 µg/mL and 67.93 µg/mL, respectively. To supplement the antimicrobial assessment, an in silico molecular docking analysis was carried out. Significantly, single crystal examinations on the synthesised compounds revealed their variable radical scavenging powers, ranging from poor to moderate, which were attributable to the destabilisation of radicals generated during oxidation [8].

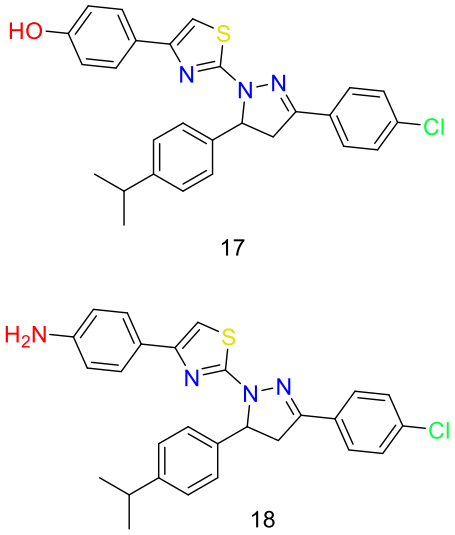

Fig. 8 Structures of thiazole-linked pyrazoline scaffolds (Compounds 17 and 18)

Yuan et al. [9] synthesized a scaffold containing pyrazole, thiazole, and naphthalene rings (Fig. 9). With the strongest anti-proliferative effect on HeLa cells (IC_{50} = 0.86 µM) and the highest EGFR inhibition (IC_{50} = 0.12 µM), compound **19** (Fig. 9) was the most potent of all the synthesized compounds. In contrast, compound **20** (Fig. 9) had the least potency (HeLa IC_{50} = 9.17 µM, EGFR IC_{50} = 6.31 µM). Structure–activity relationship (SAR) research showed that 4-thiazolinone moieties provided greater potency than 4-phenylthiazolines, and that the presence of electron-donating groups such as -OCH_3 and -CH_3 on the A-ring increased activity. Compound **19** demonstrated strong activity and low cytotoxicity in biochemical tests that included EGFR tyrosine kinase inhibition assays, CCK8-based anti-proliferative screening against HeLa, BGC823, and HepG2 cells, and cytotoxicity assessment on normal human macrophages. Computational investigations utilising molecular docking (EGFR PDB ID: 1M17) indicated that **19** developed π-π stacking interactions with LYS721 in the EGFR binding region, possibly contributing to its improved binding affinity and anti-tumour effect [9].

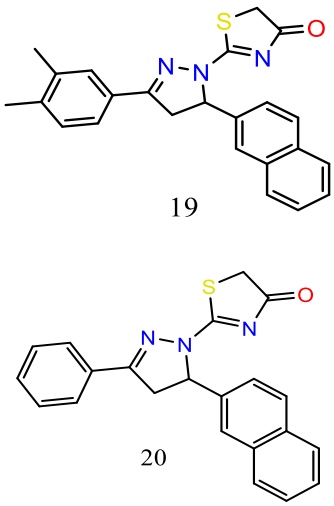

Fig. 9 Structures of compounds containing pyrazole, thiazole and naphthalene (Compounds 19 and 20)

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Wanode et.al [10] synthesized thiazole-conjugated pyrazole compounds (Fig. 10) and their anticancer potential assessed. With an IC_{50} of 126.98 µM against MCF-7 cells, compound **21** (Fig. 10) was shown to be the most effective of all the synthesised compounds, outperforming the others in terms of efficacy. On the other hand, compound **22** (Fig. 10), which had the greatest IC_{50} value and a p-nitro substitution, showed the least efficacy. SAR analysis showed that whereas bulky electron-withdrawing groups reduced efficacy, para-halogen substitutions especially bromine and fluorine increased cytotoxic activity. The anticancer efficacy of thiazole-conjugated pyrazole derivatives against MCF-7 breast cancer cells were assessed using a biochemical technique, more precisely the MTT cytotoxicity assay. By measuring mitochondrial enzyme activity, this assay offers information about the viability of cells after treatment. Molecular docking studies were performed using VEGFR-2 kinase (PDB ID: 4ASD) to investigate the derivatives' binding affinities and interaction patterns in order to supplement experimental results. According to the docking data, **21** is superior activity was attributed to the formation of hydrophobic contacts and stable hydrogen bonds with important residues, such as CYS919A, LEU840A, and PHE1047A. Furthermore, by evaluating structural stability over a 100 ns trajectory, molecular dynamics simulations verified these connections and verified **21** is potent receptor affinity. According to the findings, thiazole–pyrazole hybrids have potential for the development of anticancer drugs and should be further optimised for therapeutic uses [10].

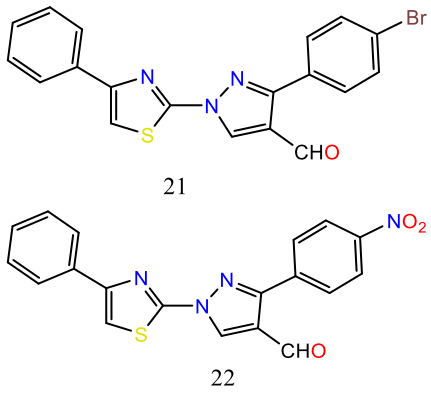

Fig. 10 Structures of thiazole conjugated pyrazole derivatives (Compounds 21 and 22)

Salem et.al [11] developed a series of mono and bis-pyrazolyl-thiazole compounds (Fig. 11) as prospective anti-liver cancer medicines that target the EGFR/HER2 pathways. Among the synthesised compounds, **23** (Fig. 11) stood out as the most potent, with an IC_{50} of 0.97 µM against HepG2 cells and significant dual inhibition of EGFR and HER2 (IC_{50} = 4.98 and 9.85 µM, respectively), exceeding the reference medication Lapatinib.

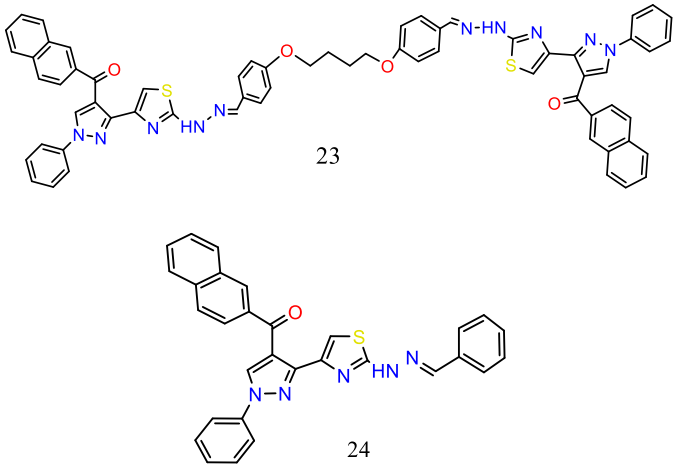

Fig. 11 Structures of mono and bis-pyrazolyl-thiazole derivatives (Compounds 23 and 24)

Compound **24** (Fig. 11), a mono-hybrid thiazole-pyrazole with a simple aryl group, has the lowest potency in the series (IC_{50}=8.64 µM). Structure-activity relationship (SAR) research found that bis-hybrids with flexible para-alkanedioxy linkers had much higher cytotoxic activity, most likely due to increased receptor binding and molecular interaction. Biochemical studies, such as MTT viability testing and kinase inhibition, revealed selective cytotoxicity against cancer cells with little effect on normal THLE2 cells. Compound **23**'s mechanism was further confirmed by computational research and apoptotic assays, which revealed S-phase arrest, caspase pathway activation, and overexpression of pro-apoptotic markers such as p53 and Bax. These results demonstrate the therapeutic potential of bis-thiazolylpyrazole hybrids, especially **23** as viable options for targeted treatment of liver cancer [11].

Ragab et al. [12] synthesised a new series of pyrazolo [4, 3-d] thiazole derivatives that contained α-aminophosphonate (Fig. 12). The in vitro antimicrobial activities of each compound were evaluated against various clinical isolates, and the results showed that two compounds **25** and **26** (Fig. 12) were the most active and show potent activity with MICs in the range of 0.06 to 0.25 $mgmL^{-1}$ when compared with standard antibiotics like fosfomycin and fluconazole. Additionally, the synthesised phosphonates showed a wide range of bactericidal and fungicidal activities based on MICs, MBCs/MFCs, and the time-kill kinetics. Additionally, active derivatives showed MurA inhibitory activity with IC_{50} values of 3.8 ± 0.39 and 4.5 ± 0.23 µM when compared with fosfomycin (IC_{50} = 12.7 ± 0.27 µM). To our wonder, treating **25** and **26** compounds to varying gamma radiation doses indicated that 7.0 kGy entirely eliminated the microbial load [12].

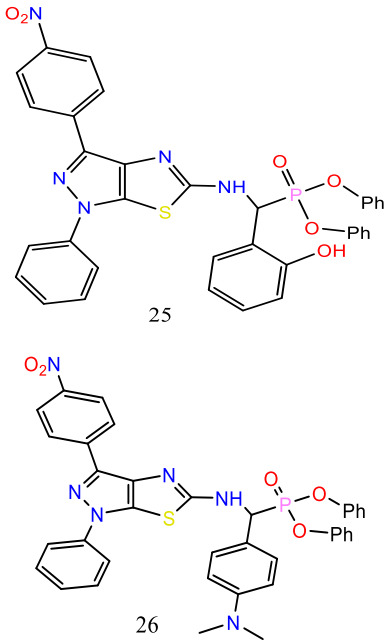

Fig. 12 Structures α-aminophosphonate containing pyrazolo [4, 3-d] thiazole derivatives (Compounds 25 and 26)

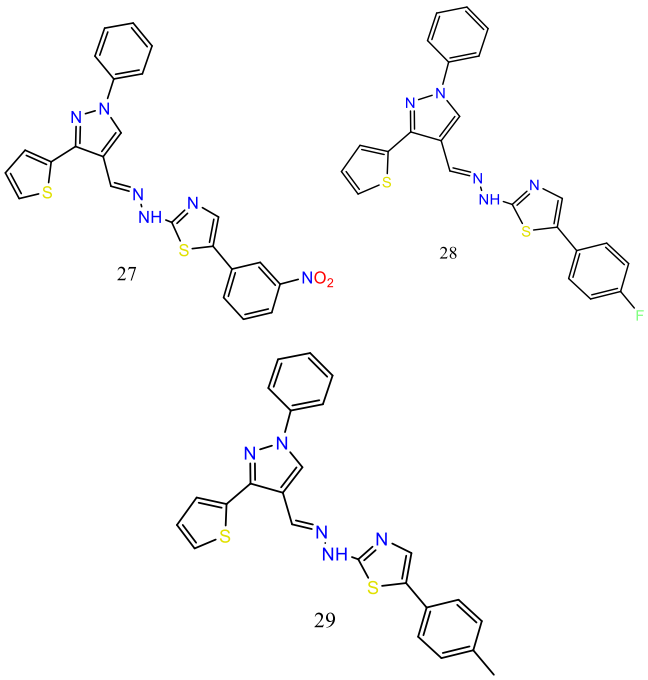

Fig. 13 Structures of thiophene containing pyrazolyl-thiazole derivatives (Compounds 27 - 29)

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Bhagwat et.al [13] synthesised a number of pyrazolyl–thiazole derivatives of thiophene (Fig. 13). The Kirby-Bauer disc diffusion method was used to evaluate each compound's antibacterial activity. With inhibition zones of 16 mm, compounds **27** and **28** (Fig. 13) had the most antibacterial activity, especially against *Bacillus subtilis* and *Bacillus megaterium*. With inhibition zones of 15–16 mm against several strains, compound **29** (Fig. 13) likewise demonstrated notable efficacy. The resazurin microtiter assay (REMA) was used in addition to the disc diffusion test to determine the minimum inhibitory concentrations (MICs) of the synthesised compounds. By determining the lowest concentration at which discernible microbial growth is reduced, this experiment yields quantitative information on the compounds' antibacterial efficacy. They carried out in-depth computer analyses to better comprehend these apparent biological activities. The compounds' HOMO–LUMO gaps varied, according to the DFT calculations; compounds **28** and **29** had lower gaps, which is a sign of greater electronic stability and reactivity. Compounds **28** and **29**, which shown the best binding affinities in docking experiments, also exhibited the strongest antibacterial properties in vitro, according to molecular docking research. These results highlight how useful computational techniques are for forecasting biological activity and directing the creation of more potent medicinal substances. According to the SAR analysis, certain substituents on the phenyl ring have a major impact on these compounds' biological activity, with electron-withdrawing groups increasing their antibacterial efficacy [13].

Palabindela et al. [14] synthesized a novel series of thiazole-pyrazole hybrid derivatives (Fig. 14) and evaluated for their anticancer potential, with a focus on inhibition of the EGFR enzyme. Among the tested compounds, derivatives **30, 31**, and **32** (Fig. 14) exhibited the most pronounced anti-proliferative activity across all screened cancer cell lines. In particular, compound **32**, bearing a 4-chlorophenyl substituent on the thiazole-pyrazole framework, demonstrated superior cytotoxic effects, with IC_{50} values of 8.57 µM (COLO-205), 9.22 µM (MCF-7), 16.75 µM (HepG-2), 8.48 µM (A549), and 7.22 µM (HeLa). The three most active derivatives (**30–32**) were further assessed for their inhibitory activity against the epidermal growth factor receptor (EGFR) tyrosine kinase.

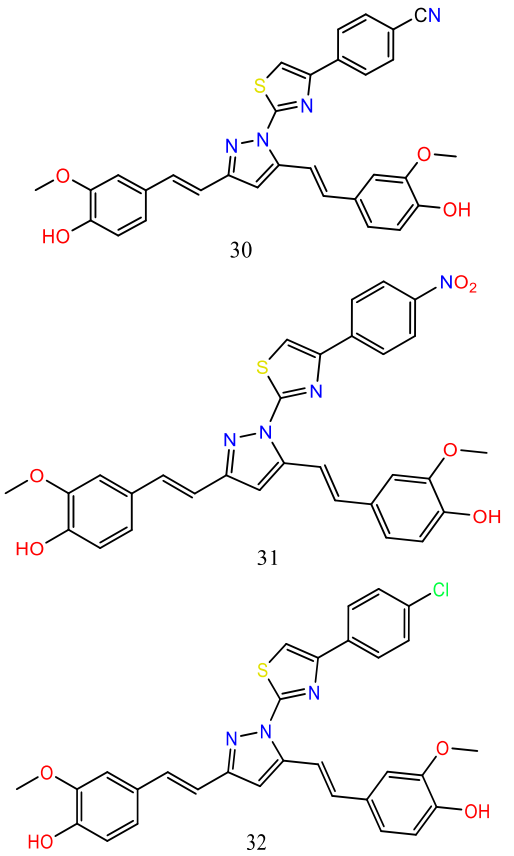

Fig. 14 Structures of novel thiazole-pyrazole hybrid derivatives (Compounds 30-32)

Compared with the reference drug Erlotinib (IC_{50} = 0.42 µM), compound **32** exhibited markedly enhanced inhibitory potency, displaying nearly two-fold stronger activity (IC_{50} = 0.18 µM). In contrast, compound **31** showed EGFR inhibition (IC_{50} = 1.84 µM) that was slightly lower than that of the reference standard. Molecular docking analysis revealed that the designed ligands exhibited strong binding affinities toward both Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). Compound **31** established three hydrogen-bond interactions within the EGFR active site one with Met769 and two with Lys721 residues. In addition, compound **30**, which showed a docking score of −10.62 kcal·mol^{-1}, interacted with Ser696 and Met769 residues of EGFR, indicating stable binding within the catalytic pocket [14].

Gabr et al. [15] designed and synthesized a novel series of acetamidobenzothiazole-pyrazole hybrids as inhibitors of the EGFR kinase (Fig. 15). Among the synthesized derivatives, compound **33** (Fig. 15) exhibited significant antiproliferative activity against breast, colon, and non-small cell lung cancer (NSCLC) cell lines, with GI_{50} values of 0.317, 0.353, and 0.0573 µM, respectively. Compound **33** was subsequently evaluated for its inhibitory activity against EGFR kinase. The assay was conducted using a 10-dose IC_{50} protocol with threefold serial dilutions starting from an initial concentration of 20 µM. Staurosporine was employed as the reference control. Compound **33** displayed an IC_{50} value of 0.239 µM, whereas staurosporine exhibited a lower IC_{50} value of 0.0533 µM, consistent with its well-known non-selective kinase inhibition profile. The notable selectivity of compound **33** toward EGFR may be attributed to differences in the geometry of the enzyme's binding pocket, which likely facilitate optimal fitting and favourable molecular interactions of the hybrid scaffold within the active site [15].

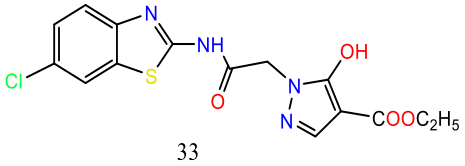

Fig. 15 Structure of novel acetamidobenzothiazole-pyrazole derivative (Compound 33)

Kaur et al. [16] synthesized a novel series of (E)-2-(3,5-dimethyl-4-(aryldiazenyl)-1H-pyrazol-1-yl)-4-arylthiazoles (Fig. 16) and systematically evaluated for their antibacterial, antioxidant, UV-induced DNA damage protection, and photocleavage properties to explore their biological potential. Biological screening revealed that the methyl-substituted derivative **34** (Fig. 16) displayed antifungal activity comparable to standard drugs. In contrast, the chloro-substituted compound **35** (Fig. 16) exhibited enhanced antifungal potency against *Candida albicans* when compared with the reference agents Ciprofloxacin and Amphotericin B. The synthesized derivatives demonstrated antibacterial activity against *Escherichia coli*; however, none showed inhibitory effects against *Staphylococcus aureus, Bacillus subtilis, Saccharomyces cerevisiae,* or *Pseudomonas aeruginosa*.

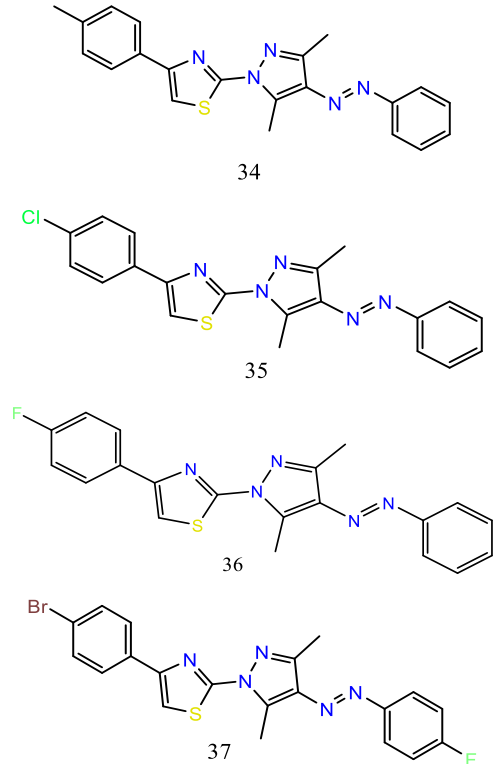

Fig. 16 Structures of (E)-2-(3,5-dimethyl-4-(aryldiazenyl)-1H-pyrazol-1-yl)-4-arylthiazoles derivatives (Compounds 34-37)

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In DNA-based studies, compounds **36** and **37** (Fig. 16) were identified as the most potent agents for UV-induced DNA damage protection and DNA photocleavage activity, respectively. Notably, none of the tested compounds exhibited significant free radical scavenging activity in the DPPH assay [16].

Mor et al. [17] synthesized a series of indenopyrazolones (Fig. 17) and evaluated for their biological activities. Their in vitro antimicrobial potential was examined against the bacterial strains *Bacillus subtilis, Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa,* as well as the fungal strains *Candida albicans* and *Aspergillus niger*, using the serial dilution method. The antioxidant activity of the synthesized derivatives was also assessed in vitro through the DPPH radical scavenging assay, with Ascorbic acid employed as the reference standard. Among the tested compounds, derivative **38** (Fig. 17) demonstrated the strongest radical scavenging activity, exhibiting an IC_{50} value of 33.14 µg/mL. Furthermore, molecular docking studies were performed to investigate the interaction of indenopyrazolones with Lanosterol 14-alpha demethylase, supporting the experimentally observed antimicrobial activity [17].

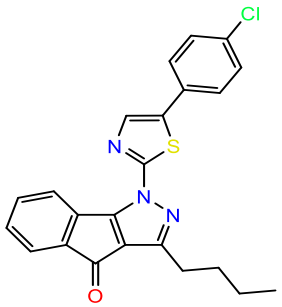

Fig. 17 Structure of indenopyrazolones thiazole derivative (Compound 38)

A series of thiazolyl-pyrazole derivatives (Fig. 18) was synthesized by Mamidala et al. [18] and screened for in vitro anticancer activity, using Nocodazole as the reference standard. Among the tested compounds, derivative **39** (Fig. 18) displayed notable cytotoxicity against MCF-7, A549, and HeLa, with IC_{50} values of 9.05, 7.12, and 6.34 µM, respectively. To identify promising lead candidates for further anticancer drug development, in silico ADME/T analyses were also conducted. Molecular docking studies further revealed that the pyrazole carbaldehyde derivatives interact with the colchicine-binding pocket of Tubulin beta chain. The docking outcomes were consistent with the observed in vitro anticancer activity, supporting their potential mechanism of action [18].

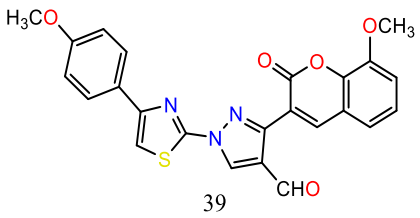

Fig. 18 Structure of thiazolyl-pyrazole derivative (Compound 39)

A series of benzimidazole derivatives incorporating pyrazolyl-thiazole frameworks was synthesized by Bakthavatchala Reddy et al. [19] (Fig. 19**)** and evaluated for antimicrobial activity using the agar well diffusion method. The compounds were tested against Staphylococcus aureus, Klebsiella pneumoniae, Bacillus subtilis, Pseudomonas aeruginosa, Aspergillus niger, and Penicillium chrysogenum.

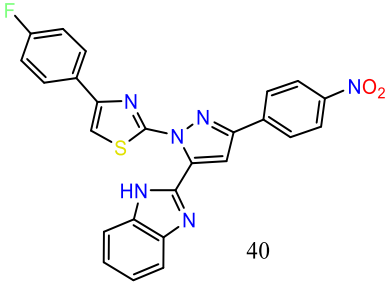

Fig. 19 Structure of benzimidazole containing pyrazolyl-thiazole derivative (Compound 40)

Among the synthesized derivatives, compound **40** (Fig. 19) bearing nitro substituents on the aromatic ring exhibited the highest antimicrobial potency. It produced significant zones of inhibition measuring 41 mm against *Penicillium chrysogenum* and 34 mm against *Pseudomonas aeruginosa*. The antimicrobial efficacy of the synthesized thiazole conjugates was compared with standard drugs, namely Chloramphenicol (antibacterial) and Ketoconazole (antifungal). Overall, the results highlight the strong antimicrobial profile of compound **40**, suggesting its potential as a promising lead for future therapeutic development [19].

A novel series of 2-(5-(3-(1,2,3-triazol-4-yl)-pyrazol-4-yl)-2-pyrazolin-1-yl)-thiazole derivatives was synthesized (Fig. 20) by Abdel-Wahab et al. [20] and evaluated for antimicrobial activity against Gram-positive and Gram-negative bacterial strains. Among the tested compounds, only derivative **41** (Fig. 20) demonstrated antifungal activity against *Candida albicans*, exhibiting a minimum inhibitory concentration (MIC) of 200 µg/mL. However, its potency was lower than that of the reference drug Clotrimazole (MIC = 25 µg/mL). Compound **41** contains an additional 1-(p-tolyl)-5-methyl-1,2,3-triazol-4-yl moiety, resulting in two triazole rings within its structure. This structural feature may enhance its similarity to Fluconazole, potentially accounting for its comparatively improved antifungal activity among the series. The authors, however, did not propose any specific molecular target for these compounds [20].

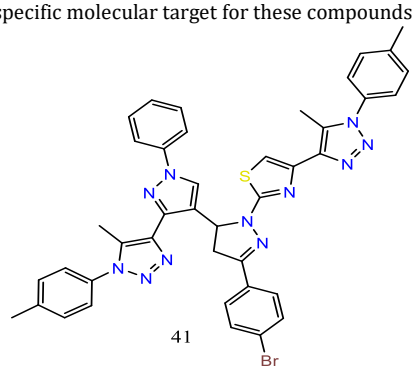

Fig. 20 Structure of 2-(5-(3-(1,2,3-triazol-4-yl)-pyrazol-4-yl)-2-pyrazolin-1-yl)-thiazole derivatives (Compound 41)

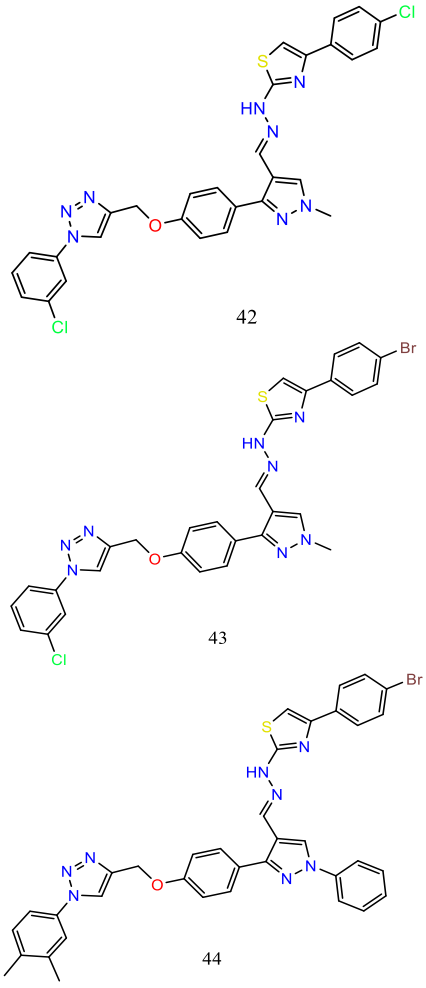

Fig. 21 Structures of 2, 4-disubstituted thiazole containing triazole-pyrazole hybrids (Compounds 42-44)

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Raghavender Matta et al. [21] had done a new series of biologically active triazole-pyrazole hybrids incorporating 2, 4-disubstituted thiazole motifs synthesis (Fig. 21) and screened for in vitro antimicrobial activity. Among the evaluated derivatives, compounds **42, 43,** and **44** (Fig. 21) exhibited the most potent growth inhibition, with MIC values of 4.8, 5.1, and 4.0 µg/mL, respectively. The antioxidant potential of these compounds was also assessed using the DPPH radical scavenging assay, where they demonstrated notable activity in comparison with a standard antioxidant. Furthermore, molecular docking studies were carried out to investigate their possible interactions with the catalytic domain of DNA topoisomerase IV from *Staphylococcus aureus.* The synthesized compounds showed binding affinities ranging from −10.0 to −11.0 kcal/mol toward topoisomerase IV. In addition, docking analysis against the SARS-CoV-2 main protease revealed binding energies between −8.2 and −9.3 kcal/mol. These findings suggest that the newly developed hybrids may serve as promising antimicrobial agents and could potentially act as inhibitors of SARS-CoV-2, highlighting their prospective value in future drug discovery efforts [21].

Rushikumar Shah et al. [22] synthesized a novel series of pyrazole-pyrazoline-thiazole derivatives (Fig. 22) and assessed for anticancer potential. Cytotoxicity was initially evaluated against the MCF-7 cell line. In a preclinical rat model, anticancer efficacy was further examined by monitoring key inflammatory and regulatory cytokines, including Transforming Growth Factor beta 1 (TGF-β), Tumour necrosis factor alpha (TNF-α), and Interleukin 6 (IL-6). Antioxidant status was determined by measuring levels of malondialdehyde (MDA). Additional parameters such as body weight, tumour volume and weight, cytokine levels, and histopathological alterations were recorded. Among the tested compounds, derivative **45** (Fig. 22) exhibited the most significant antitumor activity, as evidenced by marked reductions in TNF-α, IL-6, MDA, and TGF-β levels. These findings indicate that compound **45** possesses promising in vitro and in vivo anticancer potential [22].

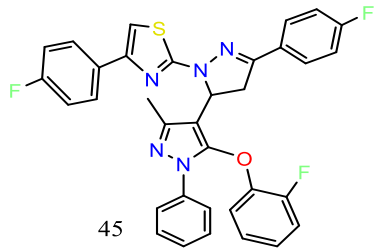


Fig. 22 Structure of pyrazole-pyrazoline-thiazole derivative (Compound 45)

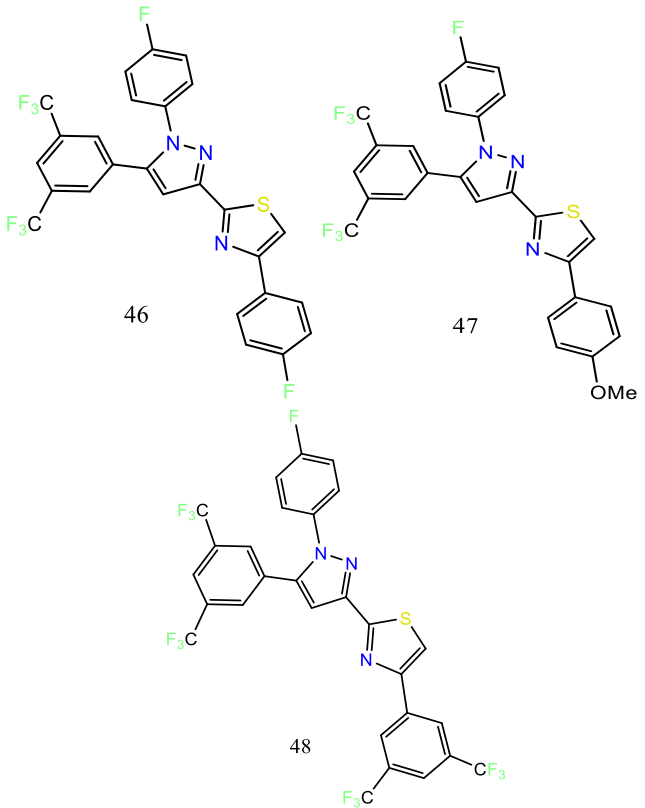
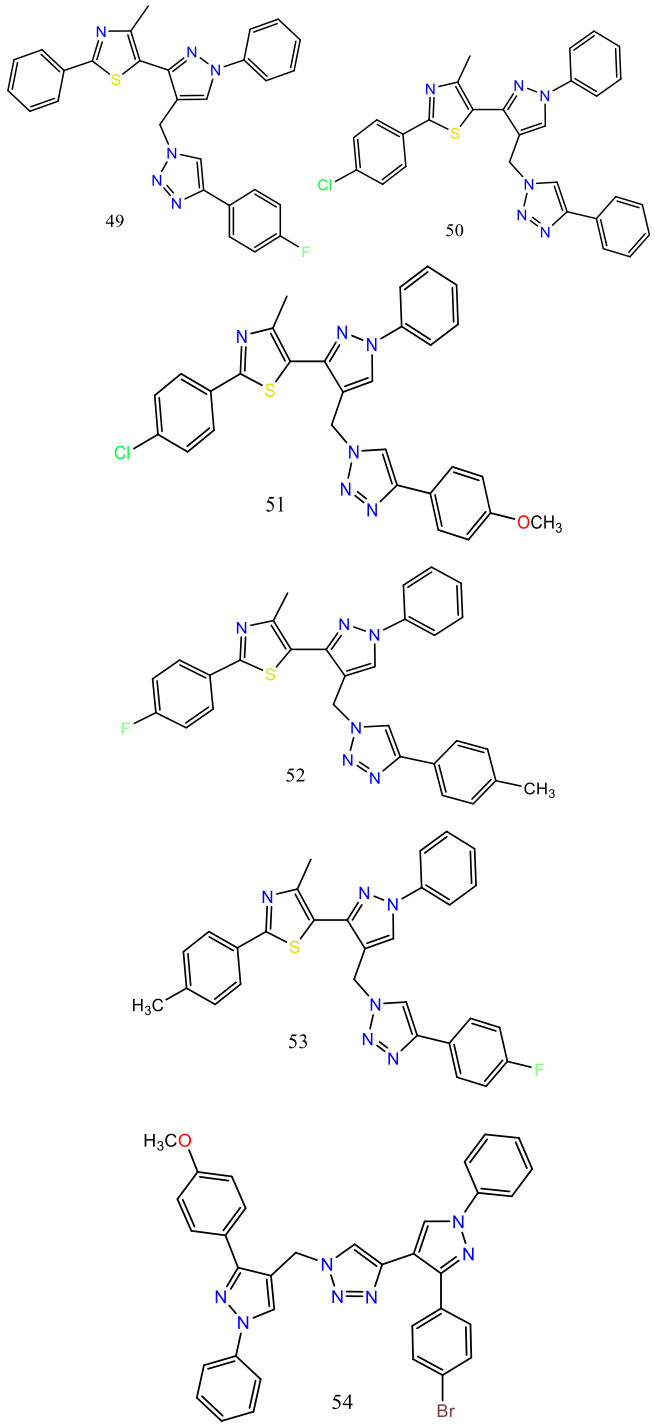


Fig. 23 Structure of 5-bis (trifluoromethyl) phenyl pyrazole-substituted thiazole derivatives (Compounds 46-48)

A series of 5-bis (trifluoromethyl) phenyl pyrazole-substituted thiazole derivatives was synthesized (Fig. 23) by Amar Patil et al. [23] and evaluated for antifungal activity using the broth micro-dilution method. The compounds were tested against four fungal pathogens: *Candida albicans, Aspergillus flavus, Aspergillus fumigatus,* and *Aspergillus niger.* The most active derivatives were further evaluated for their minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values. Notably, compounds **46, 47,** and **48** (Fig. 23) demonstrated antifungal potency comparable to the standard drug Actidione against *Candida albicans* and *Aspergillus flavus* strains [23].

Jagadale et al. [24] synthesized a series of thiazolyl–pyrazolyl–1,2,3-triazole and bis-pyrazolyl–1,2,3-triazole derivatives (Fig. 24) and evaluated for biological activity. The compounds were screened for anti-mycobacterial efficacy against Mycobacterium tuberculosis H37Ra (dormant form) and for antibacterial activity against *Escherichia coli, Pseudomonas fluorescens, Staphylococcus aureus,* and *Bacillus subtilis.* Several derivatives from both series exhibited moderate to significant antitubercular activity against the tested *M. tuberculosis* strains, along with activity against *B. subtilis*. Notably, compounds **49–56** (Fig. 24) demonstrated promising potency, with IC_{50} values ranging from 1.99 to 2.96 mg/mL [24].



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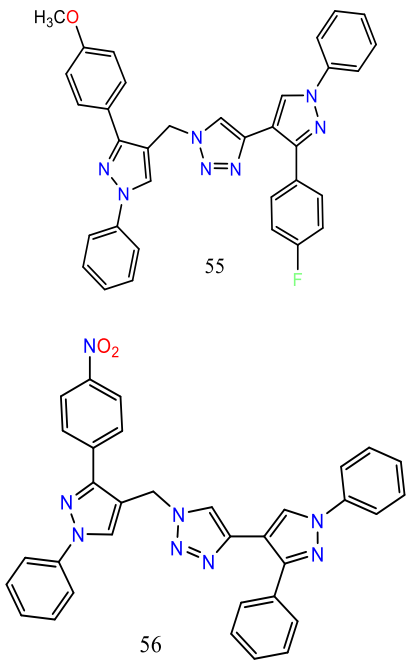

Fig. 24 Structures of thiazolyl-pyrazolyl-1,2,3-triazole and bis-pyrazolyl-1,2,3-triazole derivatives (Compounds 49-56)

3. Conclusion

Pyrazole-coupled thiazole derivatives have emerged as an important hybrid heterocyclic scaffold with broad and significant biological potential. The structural integration of pyrazole and thiazole pharmacophores results in enhanced and synergistic effects, contributing to notable anticancer, antimicrobial, anti-inflammatory, antioxidant, antitubercular, and antiviral activities. Many reported compounds exhibit promising MIC and IC_{50} values, demonstrating their effectiveness against various biological targets. Structure-activity relationship (SAR) investigations reveal that electronic factors, halogen substitution, heteroatom incorporation, and linker modifications play a crucial role in improving potency, selectivity, and target specificity. Molecular docking and mechanistic studies further support their ability to interact efficiently with enzymes, receptors, and microbial proteins, highlighting their therapeutic relevance. Despite encouraging in vitro findings, comprehensive in vivo studies, toxicity evaluation, and pharmacokinetic profiling are necessary to advance these compounds toward clinical application. Overall, pyrazole-thiazole hybrids represent a versatile and promising platform for rational drug design and future medicinal chemistry research.

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