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Recent studies on protein kinase signaling inhibitors based on thiazoles: review to date

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Due to the important role of protein kinases in protein phosphorylation within vital cellular processes, their abnormal function, especially in cancer situations, has underscored their importance in therapy. Thiazole structures are versatile frameworks present in numerous bioactive compounds. Thiazole derivatives, as a highly favored structural motif, have garnered considerable interest from both industrial and medicinal researchers and have demonstrated notable success over past decades due to their diverse biological properties, including anticancer, antibacterial, antifungal, anti-HIV, antiulcer, and anti-inflammatory activities. Moreover, several thiazole-based drugs are widely recognized pharmaceuticals on the market. Due to their specific structural features, thiazole derivatives have a high potential for interacting with different protein kinases, leading researchers to investigate a variety of structural changes. This thorough review thoroughly examines the design and biological evaluations of small molecules utilizing thiazole as potential agents that target various kinases for anti-cancer applications. These compounds are categorized into two classes: inhibitors of serine/threonine and tyrosine kinases. The goal is to promote the development and progress of more effective, targeted compounds for cancer treatment by highlighting the potential of thiazole in inhibiting kinases.

1. Introduction

Heterocyclic chemistry is currently receiving increased focus due to its classification of molecules that have been utilized in medicinal chemistry applications.[1–3] A primary objective within the realms of organic and medicinal chemistry is the creation, synthesis, and advancement of molecules that exhibit promise for application as pharmaceutical agents.[4,5] Numerous biologically active molecules are characterized by the presence of five-membered rings containing two heteroatoms. Heterocyclic compounds containing nitrogen are particularly significant in the process of drug discovery,[6] with the thiazole ring being a notable example of such compounds.

Thiazole, while not occurring naturally, is present in various natural compounds like peptide alkaloids, metabolites, and cyclopeptides.[7] For example, Cyclotheonaellazole A (**1**) and Oriamide (**2**) are cyclic peptides containing thiazolyl propenoic acid that have been found in the marine sponge *Theonella* sp.[8,9] Apratoxin A (**3**), which is derived from *Lyngbya majuscula*, is a well-known marine product with anticancer properties.[10,11] Dendroamide A (**4**), obtained from the *cyanobacterium Stigonema dendroideum fremy*, is used in the treatment of tumors that develop resistance.[12] Argyrin A (**5**), a cyclic peptide from the *myxobacterium Archangium gephyra*, is known for its strong antitumor effects,[13] Fig. 1.

Furthermore, thiazole derivatives, including vitamin B1 (**6**), are naturally present in various foods and marine sources *e.g.* **7a–c** and **8**.[14] Vitamin B1, also known as thiamin, is an essential water-soluble vitamin crucial for mitochondrial energetics, particularly in ATP formation. Moreover, it acts as a vital coenzyme in glucose and amino acid metabolic pathways for living organisms,[15] Fig. 2.

In recent years, the thiazole ring, a heterocyclic structure composed of sulfur and nitrogen atoms, has demonstrated a wide range of biological properties.[16] It functions as a significant pharmacophore core with extensive pharmaceutical applications, including carbonic anhydrase inhibitory, antimalarial, antiparasitic, anti-SARS-CoV-2, antimicrobial, anti-inflammatory, and anticancer activities.[17–24] Moreover, the existence of thiazole rings in a variety of natural compounds, medications, and human enzymes has led to the development of numerous thiazole analogs that exhibit strong antitumor or cytotoxic properties. These analogs have been custom-made to focus on particular pathways in cancer cells.[25] It is worth mentioning that a number of existing drugs that include thiazole have been authorized for use as anti-cancer treatments

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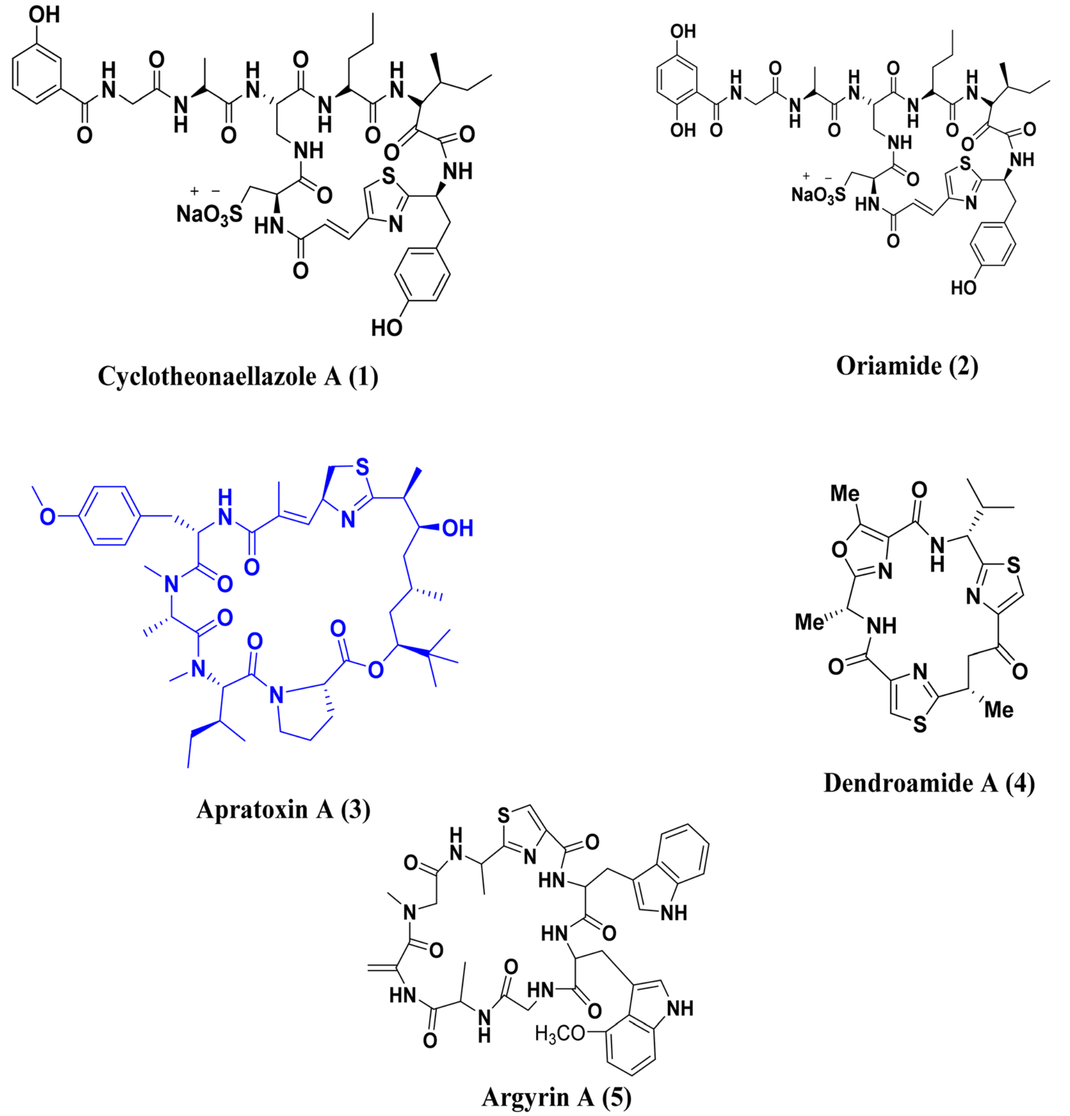


Fig. 1 Various natural compounds containing thiazole ring.

such as Vosaroxin (**9**),[26] Dabrafenib (**10**),[27] patellamide A (**11**),[26–28] dasatinib (**12**), epothilones (**13**), ixabepilone (**14**), tiazofurin (**15**), Kud 773 (**16**), and bleomycin (**17**)[29] Fig. 3 and 4.

Because of the various pharmaceutical effects linked to thiazole derivatives, they have been instrumental in the design and advancement of drugs. Research has shown that these structures have displayed significant anti-cancer properties, particularly through kinase inhibition. This review aims to summarize the studies on small molecules containing thiazole frameworks that have shown kinase inhibitory effects. The goal is to draw the interest of medicinal chemists towards identifying new leads that could potentially be developed into novel drugs in collaboration with pharmaceutical companies.

2. Chemistry of thiazole

Thiazole, also referred to as 1,3-thiazole, is a type of five-membered ring belonging to the azoles group. It contains a sulfur atom at position 1 and a nitrogen atom at position 3. The characteristics of thiazole are summarized and presented in Table 1.[30]

The resonance investigation revealed an aromatic nature attributed to the delocalization of a lone pair of electrons originating from the sulfur atom, resulting in a 6π electron system, as illustrated in Fig. 5.

Thiazole has many analogues, such as isothiazole, thiazolone, 1,3,4-thiadiazole, hydrogenated thiazole (such as thiazoline and thiazolidine), and polycyclic or fused thiazoles (benzothiazole or naphthothiazole, *etc.*), as shown in Fig. 6.

Based on the π electron density analysis, electrophilic substitution is primarily observed at the C-5 position, with the C-4 position being the next most reactive site, while nucleophilic substitution predominantly occurs at the C-2 position.[31,32] (Fig. 7).

2.1. Synthesis of thiazole derivatives

Hantzsch was the first great chemist and the pioneer of thiazole chemistry. The Hantzsch technique is the oldest and most

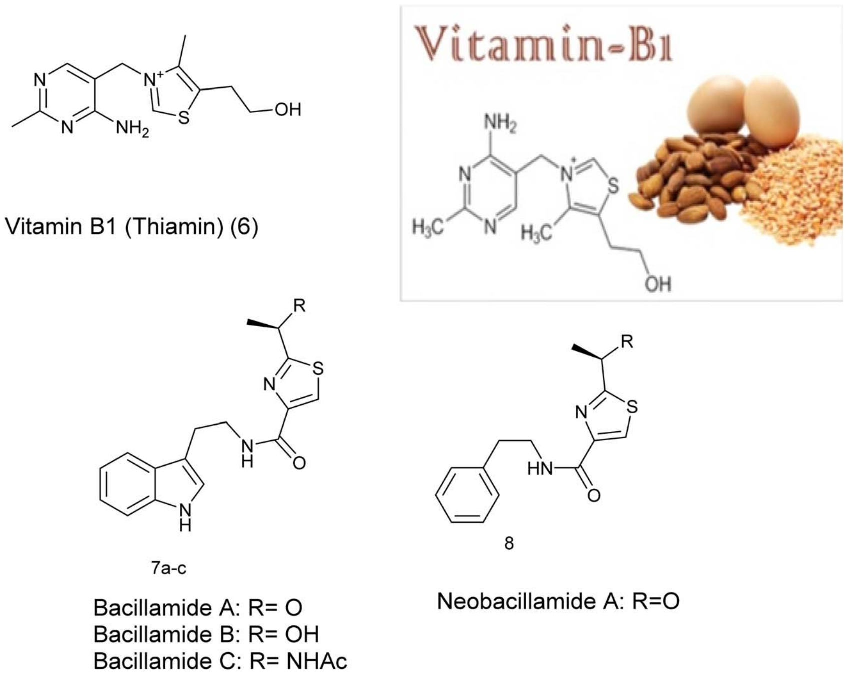


Fig. 2 Thiazole ring present in many foods and marine source.

widely used technique for the synthesis of thiazole rings. The procedure involves cyclizing α-halocarbonyl compounds with thioamide or thiourea to form thiazole.[33] Earlier, historical synthesizes of thiazole derivatives have been listed previously in many reviews[15,16,34–36] and summarized in Fig. 8.

2.2. Recent advancements in the synthesis of thiazole derivatives have been observed

2.2.1. Synthesis of 2-amino thiazole utilizing a catalytic nanosystem. The development of a distinctive multifunctional and magnetically catalytic nanosystem for the one-pot synthesis of 2-aminothiazoles employing trichloroisocyanuric acid (TCCA) is illustrated in Scheme 1, with an excellent product yield of 90%.[37]

2.2.2. Synthesis of thiazole derivatives utilizing environmentally friendly biopolymeric catalysts. Terephthalohydrazide chitosan hydrogel (TCs) was employed as an environmentally Friendly heterogeneous basic catalyst in the effective synthesis of bioactive thiazole derivatives, yielding 88% (Scheme 2).[38]

Moreover, the application of Fe_3O_4 and SiO_2-bipyridine-$CuCl_2$ in ethanol under reflux conditions for the synthesis of thioamides and phenylbromide represents a distinctive and environmentally sustainable catalytic approach to produce thiazole derivatives with an excellent yield (95%), as demonstrated in Scheme 3.[39]

2.2.3. Formation of thiazoles through a base-catalyzed reaction involving three components. The successful synthesis of thiazole derivatives (exhibiting a substantial yield of 90%) was achieved through the combination of chalcone, phenyl isothiocyanate (PhNCS), sulfur (in two equivalents), and *N*-methyl-2-pyrrolidone (NMP) as a basic sulfur activator, all conducted in dimethyl sulfoxide (DMSO) at a temperature of 80 °C. Significantly, 1,4-Diazabicyclo[2.2.2]octane (DABCO), even at a concentration of 0.2 equivalents, was determined to be the most effective base catalyst, promoting a clean reaction (Scheme 4).[40]

2.2.4. Utilization of *N*-bromosuccinimide. The interaction of the three components—phenyl acetylene, *N*-bromosuccinimide, and thiourea—in an aqueous medium led to the formation of the corresponding thiazole compounds in a good yield (73%), Scheme 5.[41]

2.2.5. Employing microwave-assisted synthesis. A domino alkylation–cyclization reaction involving propargyl bromide derivatives and thiourea has been successfully employed to produce the corresponding 2-aminothiazoles, as illustrated in Scheme 6. This process is facilitated by microwave irradiation and utilizes K_2CO_3 as a catalyst, resulting in the formation of 2-aminothiazoles within a matter of minutes and achieving excellent yields 87%.[42]

2.2.6. Utilizing catalysts, such as silica-supported tungstosilicic acid. The application of silica-supported tungstosilicic acid as a catalyst facilitates the synthesis of aminothiazole derivatives through the reaction of 3-(bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, thiourea, and a range of substituted aromatic aldehydes. This reaction can be conducted under thermal conditions or *via* ultrasonic irradiation, resulting in the production of the desired aminothiazole derivatives (resulting in a yield of 90%) (Scheme 7).[43]

3. Cancer disease

Cancer is a complex ailment resulting from a sophisticated interplay of external and internal factors. It ranks as the second

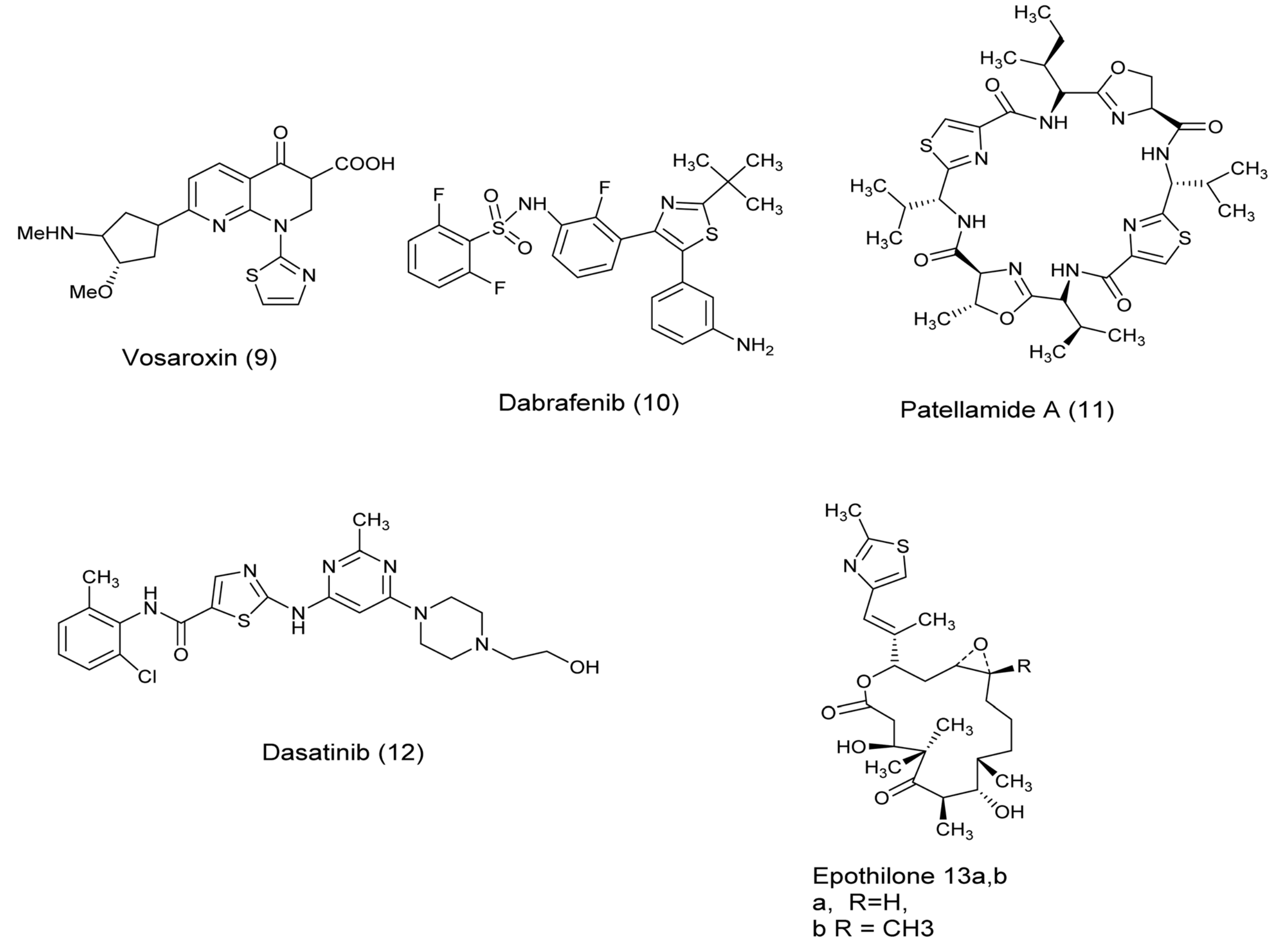


Fig. 3 Some clinically available thiazole-containing anti-cancer drugs.

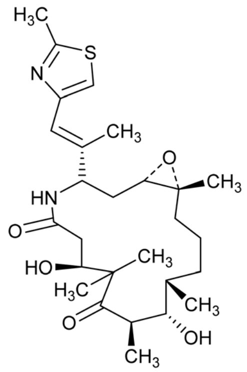
leading cause of mortality globally, following cardiovascular diseases. The World Health Organization (WHO) has reported that in 2018, there were 9.6 million deaths attributed to cancer, a figure projected to rise to 13.1 million by 2030. Over the past decade, there has been a worrisome escalation in the incidence and fatality rates of cancer. The primary clinical modalities employed in cancer treatment include chemotherapy, surgery, and radiotherapy, with chemotherapy being the most commonly utilized method. Consequently, a plethora of chemotherapeutic agents have been extensively researched and developed to combat various cancer types through diverse mechanisms.[44,45] Enzyme inhibition has emerged as a notable and viable target strategy for tumor treatment, with thiazole compounds demonstrating efficacy in inhibiting several such enzymes, particularly protein kinases.

4. Protein kinases in cancer

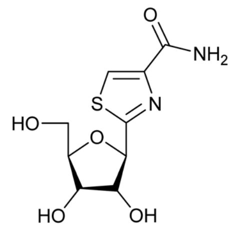
The kinase inhibitors represent a diverse class of potent antineoplastic agents that selectively target protein kinases exhibiting aberrant activity in cancer cells, contributing to their uncontrolled proliferation. Protein kinases are a large group of enzymes with over 500 members that modify other proteins by adding a phosphate group from ATP, leading to changes in their function. This phosphorylation process typically controls signaling pathways crucial for cell processes like growth, differentiation, and survival.[46] In recent years, researchers have extensively investigated the role of dysregulated kinases, particularly in cancer and other human diseases.[47,48] Eukaryotic organisms have two main types of protein kinases: serine/threonine kinases (which add phosphate to serine/threonine residues) and tyrosine kinases (which add phosphate to tyrosine residues).[49] Many protein kinases function as cell surface receptors, initiating intracellular signaling cascades upon ligand binding, often cytokines or growth factors. Inhibitors targeting these kinases are referred to as protein kinase receptor inhibitors.

5. Thiazole as kinase inhibitors

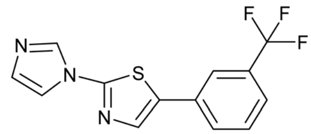
A variety of heterocyclic small molecules have been created and advanced to inhibit these kinases. Out of these fragrant heterocyclic compounds, thiazole derivatives have shown notable inhibitory properties. Therefore, this article describes the main structural features of small molecule thiazoles and how they interact within the active sites of kinases to highlight



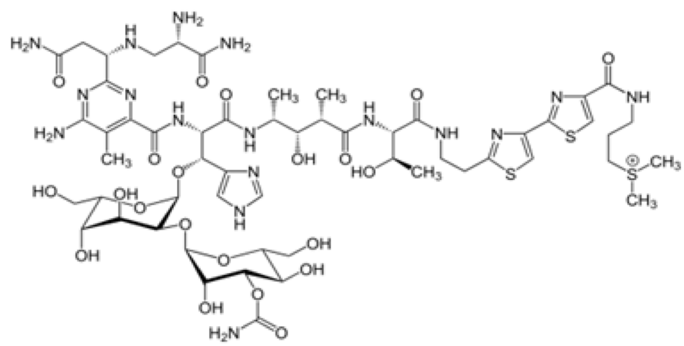
Ixabepilone (14)



Tiazofurin (15)



KuD773 (16)



Bleomycin (17)

Fig. 4 Continuous: some clinically available thiazole-containing anti-cancer drugs.

Table 1 Physical properties of thiazole

Chemical formula	C_3H_3NS
Color	Pale yellow
Odour	Like pyridine
Solubility	Soluble in alcohol, ether, acetone; slightly soluble in water and sparingly soluble on dyes and solvents of organic origin
Boiling point	116–118 °C
Relative density	1.1998
Refractive index	1.5969

the importance of this scaffold, which may be due to its unique physical and chemical properties. The review is organized based on categorizing kinases into serine/threonine and tyrosine kinases.

5.1. Serine/threonine thiazole-based kinase inhibitors

5.1.1. PI3K/AKT/mTOR signaling pathway inhibitors. The group of lipid kinases called phosphatidylinositol 3-kinase (PI3Ks) is essential for transmitting signals from a variety of growth factors and cytokines through the generation of phospholipids. This activation then leads to the activation of the serine/threonine kinase AKT, mTOR, and other pathways that carry out functions within the cell. An aberrant activation of the PI3K/AKT/mTOR pathway can disrupt cell growth and survival significantly, leading to processes such as angiogenesis and metastatic potential. As a result, focusing on the PI3K/AKT/mTOR pathway has become a hopeful approach for treatment.[50]

Li *et al.*, developed nineteen novel compounds derived from the thiazole scaffold and evaluated their efficacy in suppressing the proliferation of cancer cells in A549, MCF-7, U-87 MG, and HCT-116 cell lines. The majority of compounds exhibited favorable activity. Subsequently, these derivatives were further examined for their potential as inhibitors of the PI3K/AKT/mTOR pathway. Compound **18**, Fig. 9, showed the most potent anticancer effects among all tested cell lines, with an IC_{50} value between 0.50–4.75 μM, outperforming the reference medication (BEZ235). Additionally, western blot analysis showed that derivative 18 successfully blocked the PI3K/AKT/mTOR signaling pathway and slowed down the advancement of the tumor.[51]

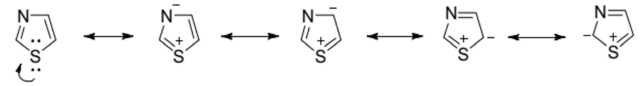


Fig. 5 The resonance structure of thiazole.

Xie *et al.* conducted an investigation on benzothiazole derivatives containing pyridine to assess their inhibitory impacts on PI3Ks and mTORC1, along with their anti-proliferative characteristics against MCF-7, U87 MG, A549, and HCT116 cell lines. The results displayed that compound **19**, Fig. 9 demonstrated the most potent antiproliferative activity across all tested cells (IC_{50} = 0.30–0.45 μM). Furthermore, findings from experiments conducted on cells showed that derivative **19** displayed notable inhibitory properties against PI3K and mTORC1. The inhibitory effects on PI3Ka, PI3Kb, and PI3Kg were discovered to be better than those of the standard medication BEZ235.[52]

Fairhurst *et al.* discovered a 4′,5-bisthiazole variant of an (*S*)-proline-amide aminothiazoleurea derivative that acts as a selective inhibitor of phosphatidylinositol-3 kinase alpha (PI3K). In their research, derivatives **20** and **21**, Fig. 9 were discovered to be highly effective in blocking signaling *via* the PI3K pathway. They were identified as the most powerful and specific inhibitors of PI3Ka, with IC50 values varying from 9–290 nM.[53]

A novel set of inhibitors has been developed to target the PI3Kβ enzyme, a component of the beta subunit of phosphatidylinositol-3-kinases, has been developed and prepared using a benzothiazole scaffold structure. The researchers evaluated the inhibitory impacts of these substances on PI3Kα, β, γ, δ, and mTOR (Mammalian target of rapamycin). Compound **22**, Fig. 9 exhibited the highest potency and selectivity against PI3Ks/mTOR, demonstrating potent activity PI3Kβ with an IC50 value of 0.02 μM. Additionally, Compound **22**, the most favorable compound exhibited significant anti-proliferative effects and selectivity among different cancer cell types, with a particular emphasis on its efficacy in prostate cancer cells. Furthermore, the structure–activity relationship (SAR) analysis of compound **22**, as illustrated in Fig. 10, indicates that the inclusion of a benzothiazole ring is critical for both the activity and selectivity of the inhibitors. Additionally, the presence of a morpholine group at the 2-position of the benzothiazole is required for significant anti-tumor efficacy. The carbamide group is also essential for activity; also the carbamide's substitutions were found to be intolerable, suggesting that the presence of a pyridine moiety is necessary for maintaining activity.[54]

A range of thiazoline and thiazolidinone-based derivatives of 4-hydroxycoumarin were synthesized through traditional methods as well as microwave-assisted techniques. These novel compounds exhibited notable efficacy and inhibition of proliferation in different cancer cell lines including HCT-116, HepG2, and MCF-7, while demonstrating no toxicity towards normal cells (BJ-1). The potential anti-proliferative agents were assessed for their capacity to hinder the activity of EGFR and PI3K/mTOR signaling pathways. Compound **23**, Fig. 9 demonstrated the most notable inhibitory effect on the signaling pathway, the value of IC_{50}; 0.184 ± 0.01, 0.719 ± 0.04, and 0.131 ± 0.007, respectively.[55]

In 2024, Salem and colleagues introduced a new class of bis-dithiazoles connected through aliphatic, aromatic, or heterocyclic frameworks and assessed their potential as anticancer agents targeting HT29 colon cancer cells. The most potent compounds were selected for further investigation as inhibitors of the PI3K enzyme. Compound **24**, Fig. 9 exhibited notable enzyme suppression with an IC_{50} value of 2.33 nm, outperforming the standard drug alpelisib which displayed an IC50 of 4.96 nM. Furthermore, the inhibitory efficacy of this compound was qualitatively assessed using western blotting,

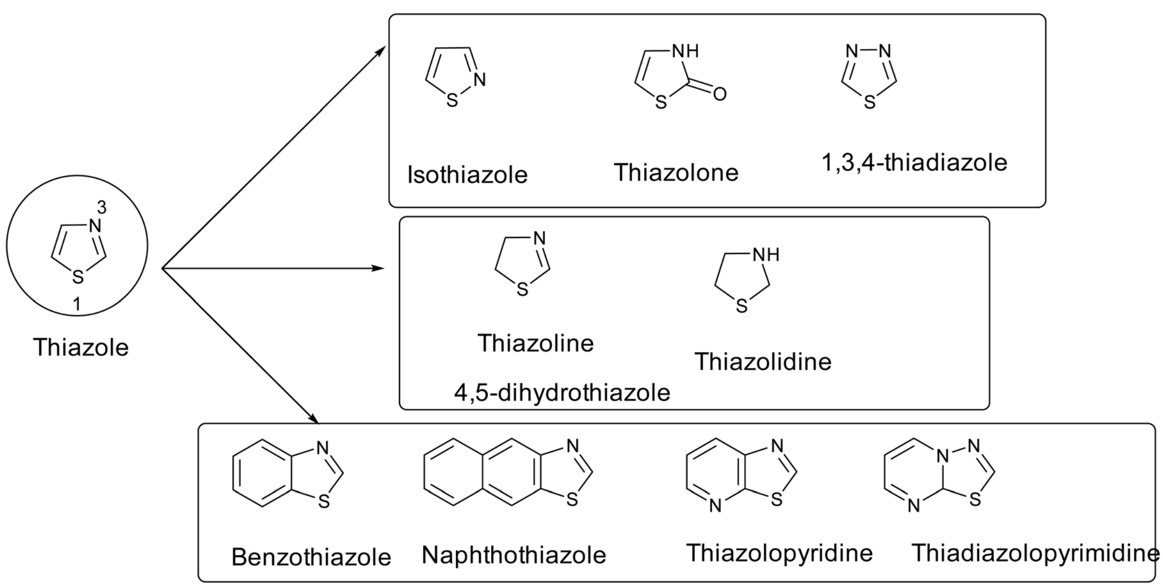


Fig. 6 Analogues of thiazole.

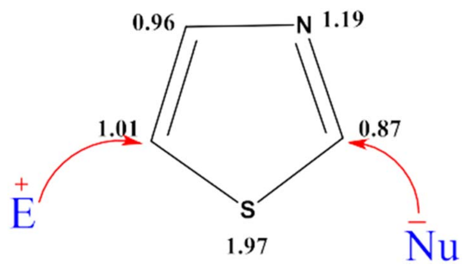


Fig. 7 Calculated π-electron density of thiazole.

revealing a significant reduction in PI3K gene expression to half of its maximum level.[56]

5.1.2. Cyclin-dependent kinases (CDKs) inhibitors. Cyclin-dependent kinases (CDKs) are a type of serine/threonine protein kinases that become active upon binding to cyclin proteins, playing a crucial role in regulating the cell cycle and influencing transcriptional activity. It is widely recognized that CDK activity escalates in conditions characterized by excessive cell proliferation, such as cancer due to the prevalent upregulation of positive regulators (cyclins) and the predominant inactivation of negative regulators of CDKs. The critical checkpoints in the G1, G2, and M phases regulate the transition between various stages of the cell cycle. As a result, CDK inhibitors can be played a critical role in cancer treatment.[57,58]

A group of researchers led by Shao H. synthesized and studied a group of pyrimidines with thiazole ring systems and tested their ability to inhibit cell proliferation and CDK activity. The researchers analyzed the relationship between the structure of the compounds and their activity, focusing on the selectivity for CDK9. Among the compounds tested, compound **25**, Fig. 11 showed the highest potency as a CDK9 inhibitor and demonstrated strong anti-proliferative effects on various cancer cell lines, with IC_{50} values ranging from 0.64 to 2.01 μM.[59]

In 2020, Abdelhafez *et al.* introduced three novel series of new compounds to evaluate their efficacy by conducting anticancer screening *in vitro* on 60 different cancer cell lines. Majority of the synthesized compounds exhibited significant activity, with particular emphasis on those containing 1,4-dihydronaphthoquinone which demonstrated the highest potency without affecting normal cells. Subsequently, the most promising compounds were assessed for their potential as cyclin-dependent kinase (CDK) inhibitors. Among these, compound **26**, Fig. 11 stood out by inhibiting eight isoforms of CDK, notably displaying the lowest IC_{50} value of 54.8 nM against CDK1 compared to the reference compound Dinaciclib. Furthermore, compound **26** predominantly induced cell cycle arrest in the pre-G1 and G2/M phases upon examination of the SK-MEL-5 cell line. Notably, the sequential caspase-3 assay for compound **26** revealed a significant upregulation level.[60]

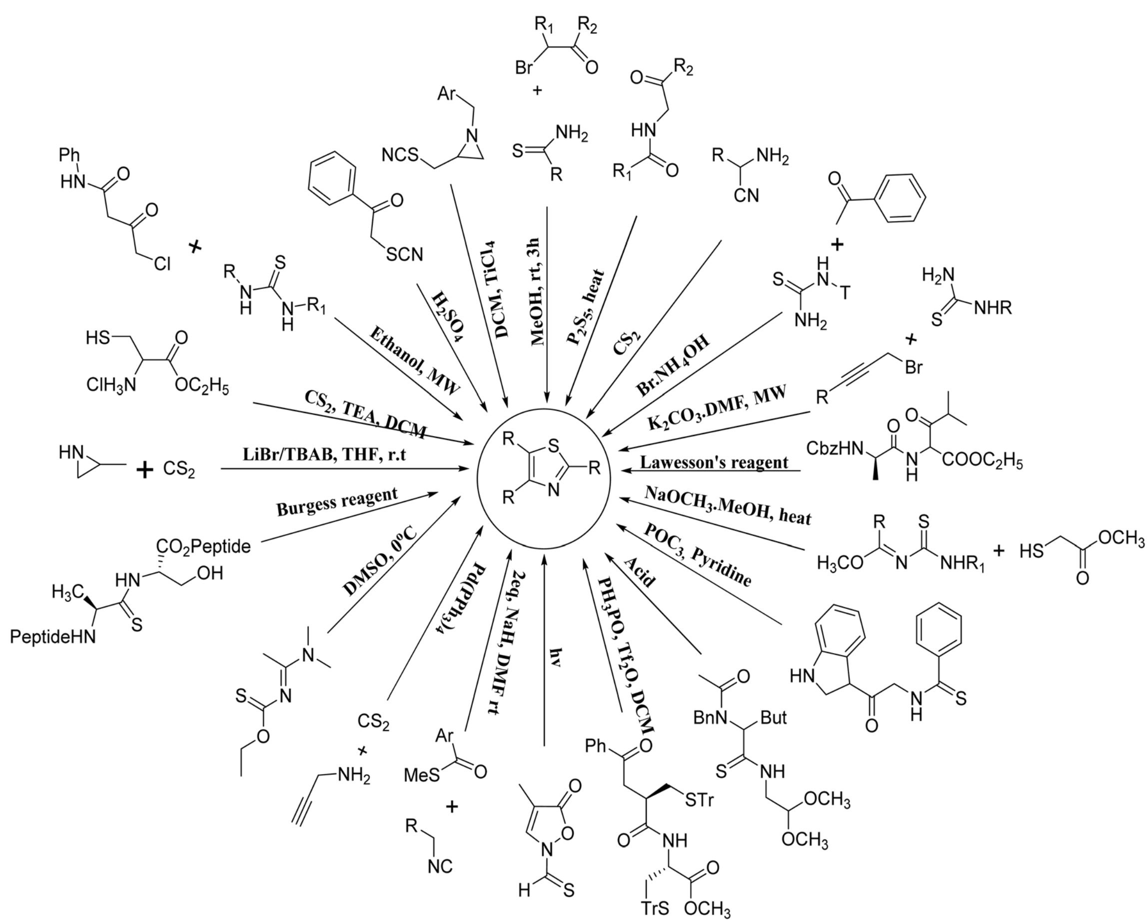
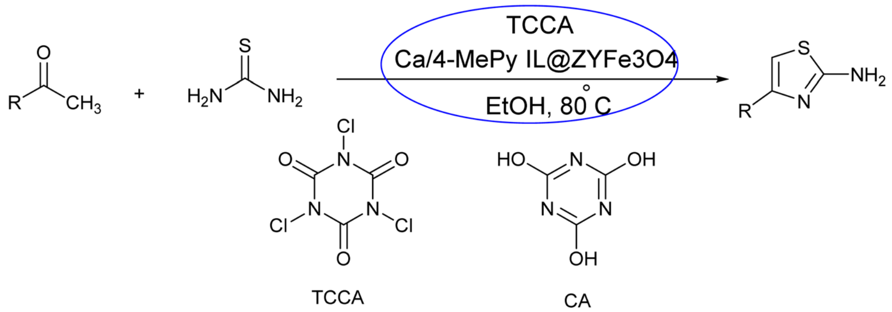
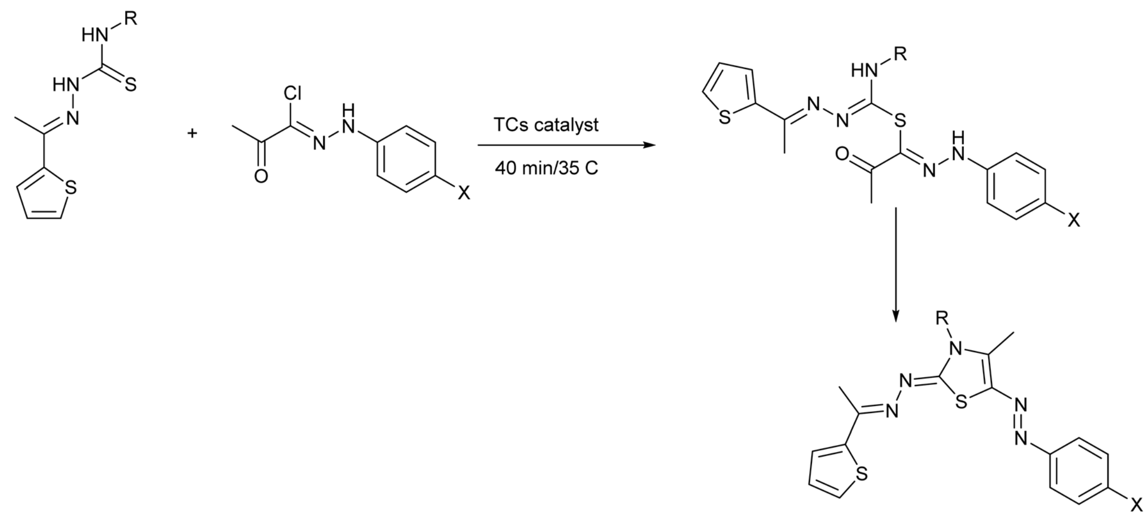


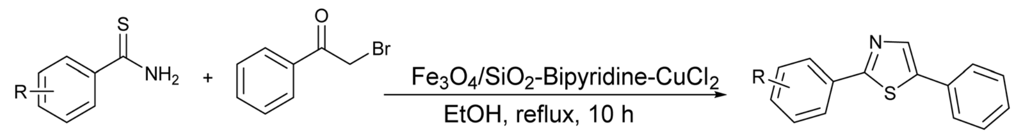
Fig. 8 A variety synthesized techniques for thiazole synthesis.



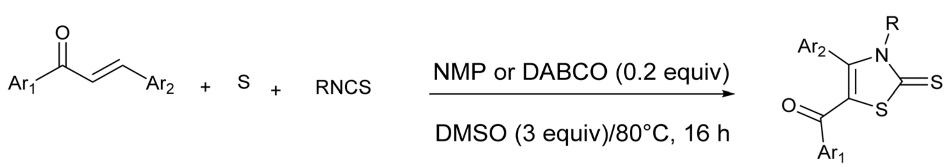
Scheme 1 Synthesis of 2-aminothiazole using catalytic nanosystem.



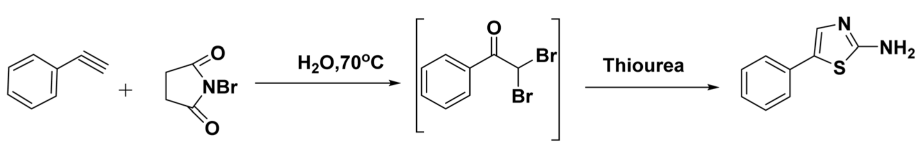
Scheme 2 Synthesis of thiazole derivatives by TCs catalyst.



Scheme 3 Synthesis of thiazole derivatives by ecofriendly catalyst.

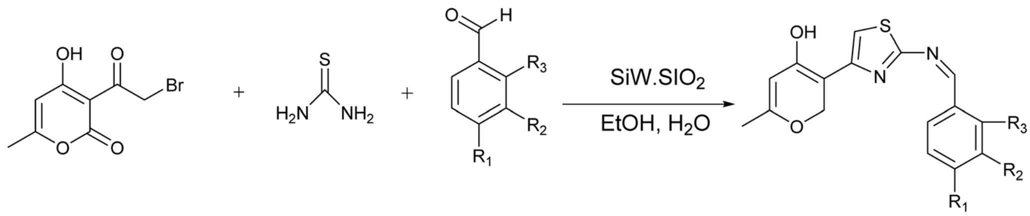


Scheme 4 Synthesis of thiazole derivative by three component reactants.



Scheme 5 Synthesis of 2-aminothiazoles *via* one-pot multicomponent reaction.

Scheme 6 Synthesis of 2-aminothiazoles *via* domino alkylation – cyclization reaction.



Scheme 7 Utilizing silica-supported tungstosilicic acid for the synthesis of 2-aminothiazoles.

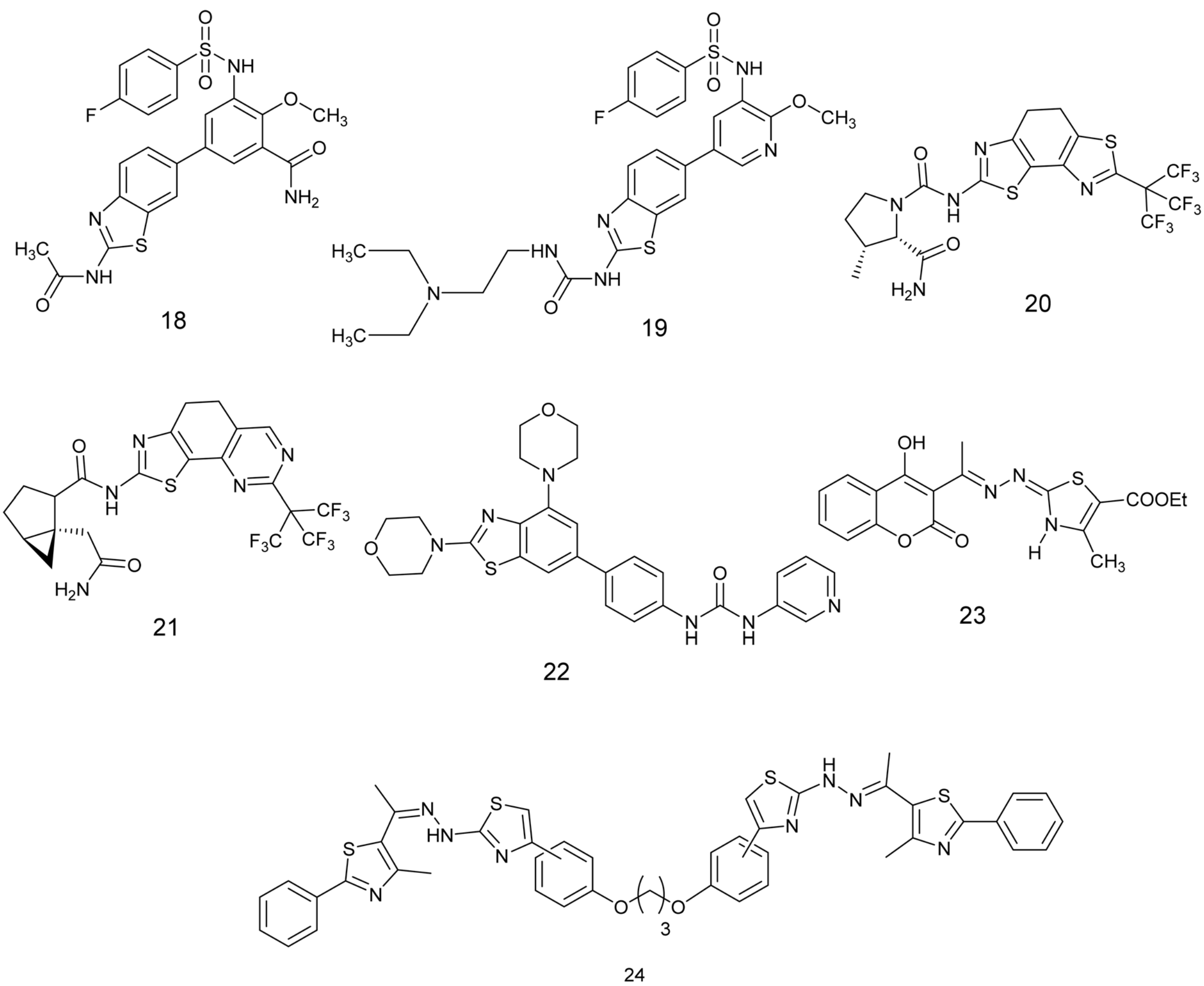


Fig. 9 Thiazole derivatives as PI3K/AKT/mTOR signaling pathway inhibitors (**18–24**).

A. M. El-Naggar and colleagues identified arylidene-hydrazinyl-thiazole as potential CDK2 inhibitors through a one-pot synthesis method conducted under conditions that are both environmentally friendly and utilize ultrasound and microwave technology. Most of the newly created compounds showed strong inhibition of growth in laboratory tests against three types of cancer cells (MCF-7, HCT-116, and HepG2). Furthermore, the compounds that exhibited the most potent anti-proliferative effects were assessed for their activity against various kinase enzymes. The efficacy of CDK2 inhibitor **27**,

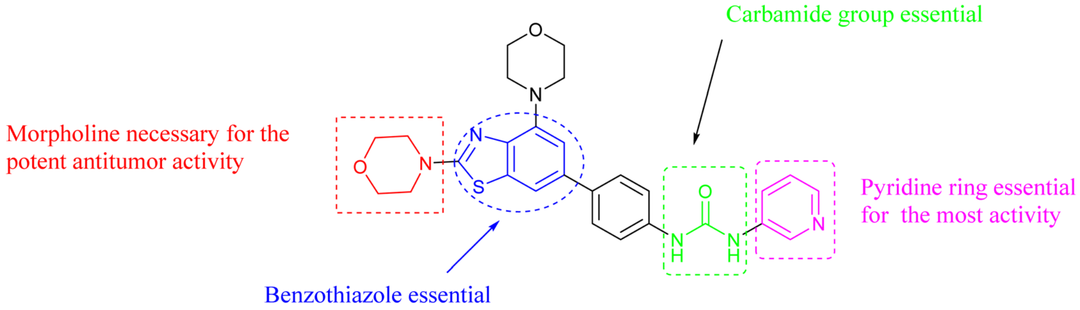


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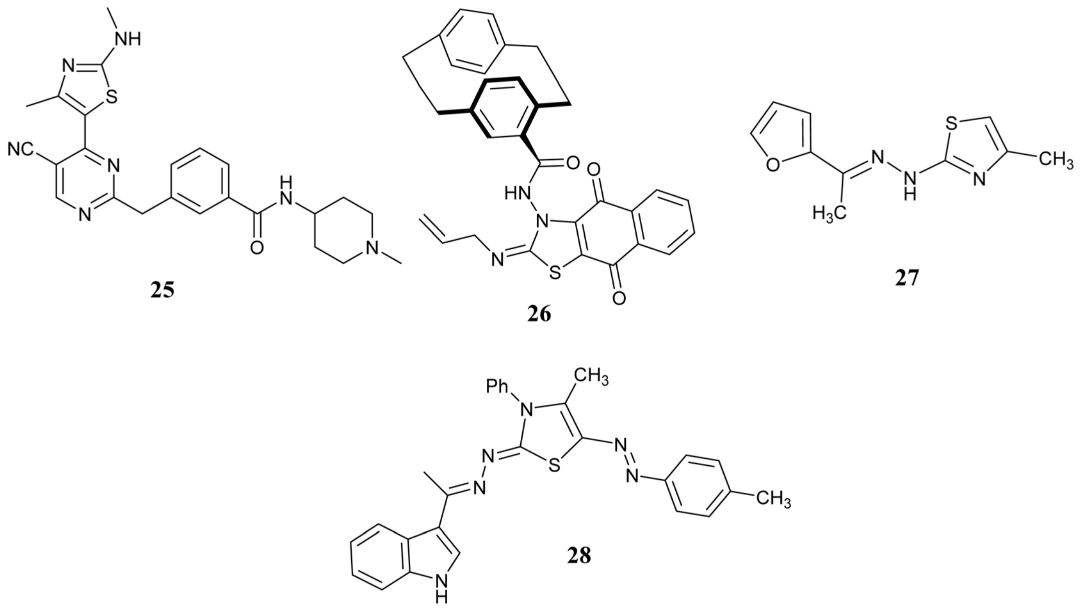
Fig. 10 SAR for compound **22**.



25 **26** **27** **28**

Fig. 11 Thiazole derivatives as cyclin-dependent kinases (CDKs) inhibitors (**25–28**).

Fig. 11 was further examined to evaluate its effects on cell cycle progression and apoptosis in the HepG2 cell line. Results indicated that this compound led to inhibition in the G2/M phase of the cell cycle and demonstrated apoptotic properties.[61]

In 2023, S. M. Gomha and colleagues synthesized a new series of 3-thiazolyl-indoles and tested their impact on the growth of three types of human cancer cells (MCF-7, HCT-116, and HepG2) in a laboratory setting. The findings indicated that a large proportion of the synthesized compounds displayed notable cytotoxic effects. Furthermore, the inhibitory capacity of the most successful compounds was assessed using a laboratory enzyme test focused on CDK2. The findings showed that compound **28**, Fig. 11 exhibited the strongest effectiveness, with an IC_{50} value of 0.35 ± 1.07 μM, in contrast to roscovitine's IC_{50} value of 0.39 ± 0.47 μM.[62]

5.1.3. Aurora kinase inhibitors. Aurora kinase, a group of serine/threonine kinases consisting of three members, is essential for multiple mitotic functions like centrosome development, chromosome separation, and cell division. The Aurora kinase family consists of three members: Aurora A, Aurora B, and Aurora C. The excessive presence of Aurora A and B has been detected in various types of cancer in humans such as colorectal, breast, seminoma, and ovarian. However, the precise function of Aurora C during mitosis is not fully understood. Inhibitors targeting these kinases have demonstrated the ability to trigger apoptosis in tumor cells, making them a promising target for cancer treatment.[63,64]

Gray and colleagues have developed novel compounds utilizing aminothiazole as specific Aurora kinase inhibitors. The findings indicate that a significant number of the synthesized compounds exhibit notable activity. Notably, compounds **29** and **30**, Fig. 12 were identified as the most potent inhibitors, demonstrating IC_{50} values of 79 and 140 nM, respectively, and displaying a high level of kinase selectivity against Aurora A. While these compounds were found to effectively inhibit histone H3 phosphorylation, impede the cell cycle, and induce siRNAs targeting Aurora A, their practical application in

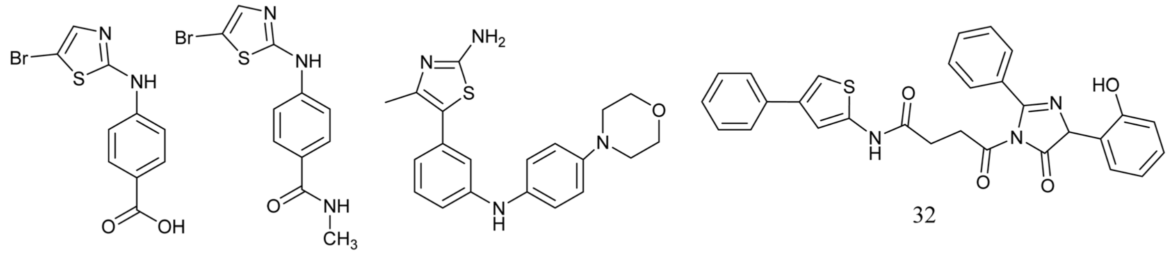


Fig. 12 Thiazole derivatives as Aurora kinase inhibitors(**29–32**).

experiments is hindered by limited cellular penetration, necessitating further refinement through chemical optimization.[65]

Wang and colleagues reported the identification of a series of modified 4-(4-methylthiazol-5-yl)-*N*-phenylpyrimidin-2-amines with potential anticancer properties targeting aurora kinase inhibitors. Compound **31**, Fig. 12 exhibited significant cytotoxic effects on cell lines derived from cancerous tissues, also the suppression of mitotic histone H3 phosphorylation was observed by this compound **31**, leading to the manifestation of atypical mitotic activities. Subsequent investigations confirmed these compounds as strong blockers of aurora A and B enzymes. Compound **31** demonstrated anticancer efficacies with K_i values of 8.0 and 9.2 nM for aurora A and B, Subsequent *in vivo* assessments demonstrated that compound 30 displayed oral bioavailability and demonstrated efficacy in combating cancer.[66]

In 2023, Shaik and colleagues utilized QSARINS software to conduct quantitative structure–activity relationship (QSAR) analysis in order to identify potential anti-breast cancer agents with aurora kinase inhibitory properties. Following this analysis, the most promising compounds were further investigated through molecular docking studies against the aurora kinase protein (1MQ4). Compound **32**, Fig. 12 emerged with the highest docking score (−9.67) and was subsequently subjected to molecular dynamic simulation for 100 nanoseconds to assess its stable binding with 1MQ4. The confirmation of compound **32**'s binding stability with 1MQ4 was validated through various analyses including RMSD, RMSF, RoG, H-bond interactions, molecular mechanics-generalized Born surface area (MM-GBSA) calculations, free binding energy assessments, and solvent-accessible surface area (SASA) evaluations. Additionally, the newly designed compound **32** demonstrated favorable ADMET properties. These results suggest that compound **32** could serve as a promising theoretical lead for future experimental investigations aimed at selectively inhibiting aurora kinase.[67]

5.1.4. Inhibitors of the enzyme casein kinases II (CK2). Casein kinase II (CK2) is a type of serine/threonine kinase that holds importance in the pathogenesis of multiple diseases, notably cancer and cardiac hypertrophy. Studies have demonstrated that CK2 plays a role in the biology and advancement of cancer cells by supporting pathways that prevent cell death, enhance cell survival, increase the activity of oncogenes, and decrease the activity of tumor suppressor genes. The upregulation of CK2 has been documented in various cancer forms, including breast, colon, and prostate cancer. Due to the significant involvement of CK2 in tumorigenesis, there is ongoing investigation into the potential of compounds that can suppress its activity as promising candidates for chemotherapy.[68]

In 2018, Yarmoluk *et al.* conducted a study aimed at discovering new CK2 inhibitors. Virtual screening experiments were carried out utilizing Autodock software to identify potential compounds. Subsequently, the top-scoring compounds were subjected to *in vitro* testing through P32 radioactive kinase assay. The findings revealed the presence of small-molecular inhibitors targeting protein kinase CK2 within the derivatives of 1,3-thiazole-5-carboxylic acid. Notably, compound **33**, Fig. 13 exhibited the highest activity, displaying potent inhibition of CK2 $IC_{50} = 0.4$ μM.[69]

Furthermore, Vasu and colleagues employed molecular docking techniques to discover and produce a new lead compound with comparable characteristics to Hit15 (ZINC20464516, a molecule sourced from the ZINC database) as dual kinase inhibitors targeting CK2 and GSK3β. The results revealed that compound **34**, Fig. 13 demonstrated the highest efficacy in inhibiting dual kinases effects against CK2 and

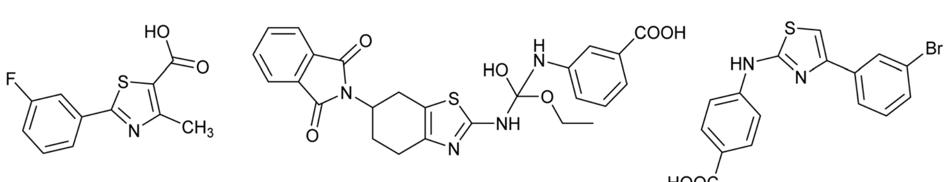


Fig. 13 Thiazole derivatives as casein kinases II (CK2) inhibitors (**33–35**).

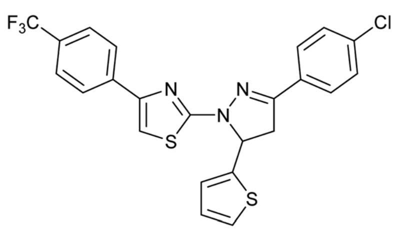
GSK3β in the *in vitro* kinase inhibition assay, with IC_{50} values of 1.9 ± 0.05 and 0.67 ± 0.27 μM, respectively.[70]

In the current investigation, a novel series of aryl 2-aminothiazoles was identified as a fresh category of CK2 inhibitors, showcasing a mode of action that is non-competitive with ATP and leading to the stabilization of an inactive conformation of CK2 in solution. Through a range of experimental methodologies including enzyme kinetics investigations, STD-NMR analysis, circular dichroism spectroscopy, and native mass spectrometry, it was demonstrated that these substances interact with an allosteric cavity located adjacent to, but distinct from, the ATP-binding region. Molecular docking studies further supported these findings, indicating that this newly identified binding site is positioned at the junction of the αC helix and the flexible glycine-rich loop. Significantly, compound **35**, Fig. 13 exhibited the most potent activity against purified CK2α, as evidenced by an IC_{50} value of 3.4 μM, and displayed a favorable selectivity profile.[71]

5.1.5. B-RAF inhibitors. Numerous studies have indicated that alterations in the B-RAF serine/threonine kinase are prevalent in various human tumors associated with cellular growth, survival, and differentiation. The B-RAF gene (V600E) mutation, characterized by the substitution of valine with glutamic acid at position 600, is particularly common in human cancers. Targeting B-RAF inhibition has become a key strategy in contemporary cancer therapeutics.[72]

In this context, Zhao *et al.* synthesized a series of 4,5-dihydropyrazole derivatives incorporating thiazole and thiophene groups, which were assessed for their potential as inhibitors of the V600E mutant B-RAF kinase enzymes implicated in tumor initiation and progression. The biological assessment indicated that most of the compounds displayed notable inhibitory effects against B- RAFV600E and showed antiproliferative properties on MCF-7 and WM266.4 cell lines. Significantly, Compound **36**, Fig. 14 exhibited the highest antiproliferative efficacy against MCF-7 and WM266.4, demonstrating IC_{50} values of 0.16 μM and 0.12 μM, respectively, surpassing the efficacy of sorafenib. Compound **36** also exhibited strong bioactivity against V600E mutant B-RAF kinase IC_{50} = 0.05 μM. Furthermore, this compound triggered notable apoptosis in WM266.4 and MCF-7 cells in a manner that was dependent on the dosage administered.[73]

Abdel-Maksoud and colleagues investigated a new group of compounds that included imidazo[2,1-*b*]thiazole for their effects on inhibiting cell growth in 57 different human cancer cell lines at the National Cancer Institute (NCI). Certain compounds demonstrated similar average inhibition percentages at a concentration of 10 μM compared to sorafenib. Compound **37**, Fig. 14 demonstrated increased effectiveness against MCF-7 cells with a notably lower IC_{50} value of 0.475 μM compared to reference drug sorafenib with the value of IC_{50}; 2.51 μM. Additionally, Compound **37** exhibited similar potency to sorafenib when tested against wild-type B-RAF, CRAF (IC_{50}; 19 nM), V600E-B-RAF (IC_{50}; 39 nM), ERK and MEK kinases. Furthermore, the structure–activity relationship (SAR) analysis for compound **37**, Fig. 15 indicated that the presence of a 4-fluoro substituent on the phenyl ring is critical for biological activity. Additionally, the incorporation of an ethylene linker generally enhances the activity of most compounds in comparison to a propylene linker. Moreover, the *para*-hydroxyphenyl terminal ring exhibited superior activity relative to analogs such as trifluoromethyl, tosyl, and fused thiazole, which are also deemed essential for activity.[74]



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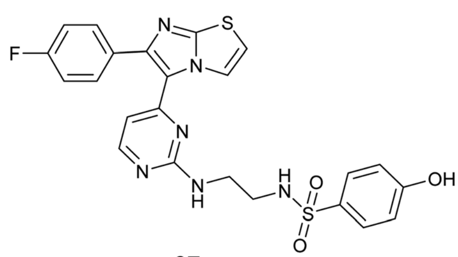

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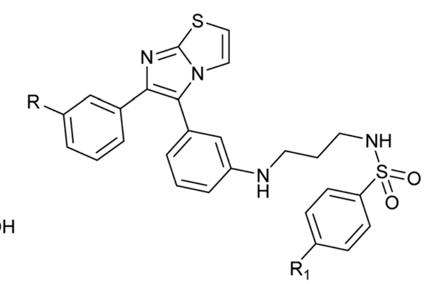
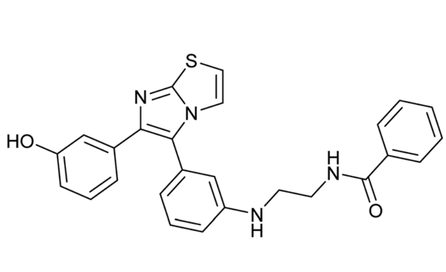


38a, b
38a, R=F, R1=Br
38b, R=NH2, R1=OCH3



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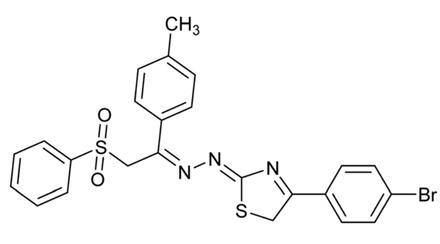

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Fig. 14 Thiazole derivatives as B-RAF inhibitors (**36–40**).

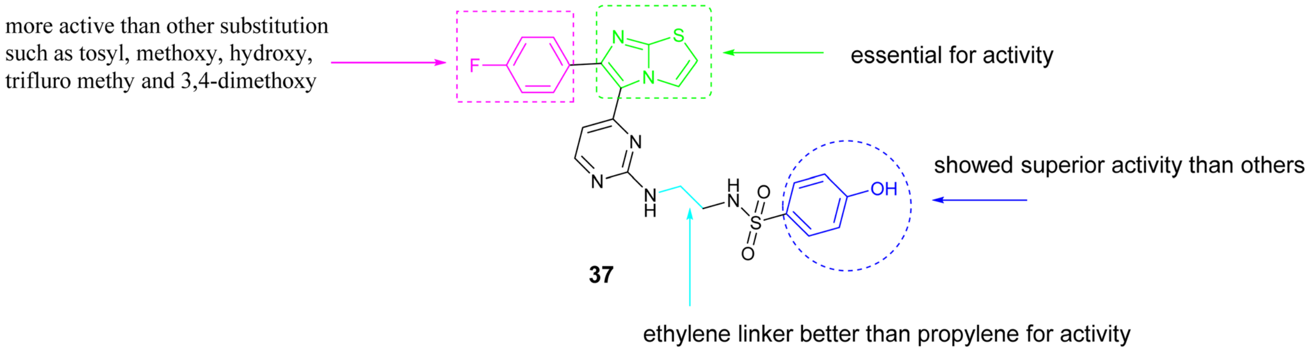

Fig. 15 SAR of compound **37**.

Additionally, a novel set of imidazothiazole compounds incorporating pyrimidine were formulated and produced in order to design potential anticancer drugs. These compounds were studied on NCI 60 cell lines, with many showing notable inhibition percentages, especially against melanoma and colon cancer cell lines. The most successful substances were then subjected to additional testing on WTBRAF, V600EBRAF, and CRAF, revealing that Compound **38a**, Fig. 14 exhibited the highest inhibitory effect on V600EBRAF at 9.30 nM.[75] The identical research team synthesized additional derivatives utilizing imidazothiazole, with compound **38b**, Fig. 14 demonstrating the highest activity against V600E B-Raf kinase, exhibiting an IC_{50} value of 1.20 nM.[76]

A study was conducted to investigate the molecular mechanism of action of a set of imidazothiazole derivatives that show promise in targeting melanoma cells. The compounds were evaluated for their effects on RAF1 and V600E-B-RAF kinases. Out of the compounds examined, **39**, Fig. 14 exhibited the most significant efficacy against both kinases, displaying IC_{50} values of 8.2 and 0.978 nM, respectively. Notably, it exhibited a certain degree of selectivity towards the V600E mutant B-RAF kinase. Furthermore, compound **39** was evaluated for its activity against four melanoma cell lines, demonstrating enhanced effectiveness (IC_{50} = 0.18–0.59 μM) in comparison to the reference drug sorafenib (IC_{50} 1.95–5.45 μM). Subsequent whole-cell kinase assays revealed that compound **39** effectively inhibited in-cell V600E-B-RAF kinase activity (IC_{50} = 0.19 μM). Moreover, it was noted that compound **39** triggered apoptosis instead of necrosis in the UACC-62 melanoma cell line, which exhibited the highest level of responsiveness.[77]

Thiazole derivatives containing a phenyl sulfonyl group were synthesized with the purpose of acting as inhibitors of the B-RAFV600E kinase. All synthesized compounds exhibited notable inhibition of the B-RAFV600E kinase enzyme at nanomolar concentrations. Particularly, Compound **40**, Fig. 14 demonstrated exceptional inhibitory effects on B-RAFV600E with the value of IC_{50}; 23.1 ± 1.2 nM, surpassing the standard drug dabrafenib which had an IC_{50} of 47.2 ± 2.5 nM. Furthermore, the most potent compounds were subjected to evaluation for their anticancer properties against both B-RAFV600E-mutated and wild-type melanoma cells. The findings indicated that the tested compounds effectively suppressed the proliferation of WM266.4 melanoma cells, with IC_{50} values ranging from 1.24 to 17.1 μM, in comparison to dabrafenib (IC_{50} = 16.5 ± 0.91 μM).[78]

5.1.6. Inhibitors of glycogen synthase kinase 3β (GSK-3β).

Glycogen synthase kinase 3 (GSK-3) is a type of serine/threonine protein kinase that is predominantly located in the cytoplasm. It exists in two isoforms, namely GSK3α and GSK3β. GSK-3 has been associated with a range of diseases, such as cancer, where the GSK-3β isoform is significantly involved in regulating activity of the nuclear factor (NF) κB within the nucleus. Thus, focusing on this isoform could be a beneficial strategy for cancer treatment, with the thiazole scaffold playing a crucial role in this therapeutic endeavor.[79,80]

The thiazole compound AR-A014418 (**41**), Fig. 16 created by Astra Zeneca, functions as a selective and ATP-competitive inhibitor of GSK3β. This compound has demonstrated notable efficacy as a selective competitor of the ATP binding site, with an IC_{50} value of 100 nM. Furthermore, it has shown inhibitory effects on tau phosphorylation, safeguarded neuronal cells against apoptotic triggers, and hindered β-amyloid-induced neurodegeneration.[81]

Shivaprakasam and colleagues (2019) conducted a study on the structural optimization of acylaminopyridines to develop highly effective and specific inhibitors of GSK-3β. Their research demonstrated that incorporating a primary carboxamide group on the thiazole ring significantly improved the potency of compounds, with nanomolar activity observed. Specifically, compound **42**, Fig. 16 exhibited the most potent inhibition of GSK-3β, with an IC_{50} value of 0.29 ± 0.01 nM, attributed to the presence of larger ether groups at the C-4 position. Furthermore, compound **43**, Fig. 16 exhibited strong efficacy against Glycogen synthase kinase-3 (GSK-3) with an IC_{50} value of 1.1 ± 0.1 nM. Moreover, in investigations into the mechanism of action of compound **43**, a notable decrease in pTau396 levels was observed when it was orally administered at a dosage of 30 mg kg^{-1} as a nano-suspension to LaFerla 3xTg-C57BL6 male mice.[82]

Recent research has highlighted the potential benefits of cephalosporin antibiotics in cancer treatment. In a study conducted in 2023 by Nassar *et al.*, these antibiotics were examined for their capacity to suppress the activity of GSK3b. The study focused on four specific cephalosporins – cefixime, ceftriaxone,

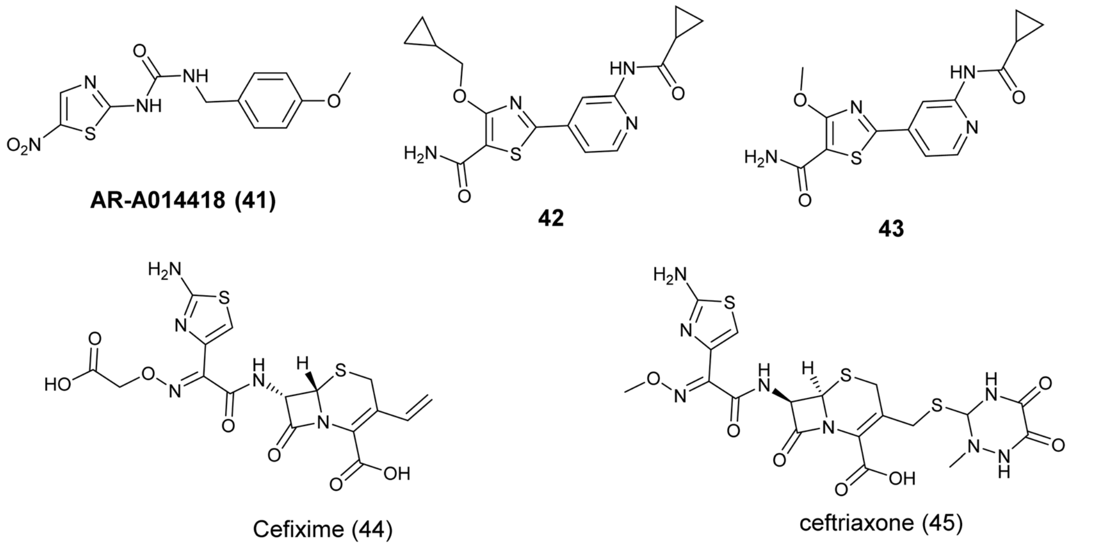
AR-A014418 (41) 42 43 Cefixime (44) ceftriaxone (45)

Fig. 16 Thiazole derivatives as Glycogen synthase kinase 3 (GSK-3) inhibitors (**41–45**).

cephalexin, and cefadroxil – and their interaction with the GSK3b binding pocket through molecular docking. The findings indicated that cefixime (**44**) and ceftriaxone (**45**) showed the most favorable docking scores (−7.36 and −7.06) attributed to hydrogen bonding between their aminothiazole group and hinge residues of GSK3b. Subsequent *in vitro* experiments were conducted to measure the inhibitory effects of these cephalosporins on GSK3b. Consistent with the docking results, Cefixime (**44**), Fig. 16 demonstrated the most potent inhibitory activity, with IC_{50} values of 2.55 μM.[83]

5.2. Inhibitors of kinases that are based on tyrosine thiazole

5.2.1. Inhibitors of the c-MET protein. The c-MET receptor, also referred to as the hepatocyte growth factor receptor (HGFR), is a specific type of tyrosine kinase receptor that belongs to the family of the MET (MNNG HOS transforming gene). Irregularities like MET gene amplification, MET gene mutations, and increased c-MET expression can cause abnormal growth, movement, and prevention of cell death in cancer cells. This is accomplished by activating multiple signaling pathways, such as Ras/MAPK, PI3K/AKT, JAK/STAT, Wnt/β-catenin, and SRC. Therefore, the targeting of c-MET has emerged as a significant area of interest in the realm of cancer pharmaceutical research and advancement.[84]

A set of novel 4-phenoxyquinoline derivatives containing the benzo[*d*]thiazole-2-yl urea moiety were synthesized and evaluated for their cytotoxic properties on the MKN-45, H460, and HT-29 cell lines. The results indicated that the majority of these compounds demonstrated varying levels of efficacy against the three cell lines under investigation. Notably, compound **46**, Fig. 17, exhibited the highest activity among the tested compounds, with IC_{50} values of 0.01, 0.06, and 0.18 μM against the H460, MKN-45, and HT-29 cell lines, respectively. Also, this compound emerged as a promising candidate against c-Met with nanomolar activity (IC_{50} = 17.6 nM).[85]

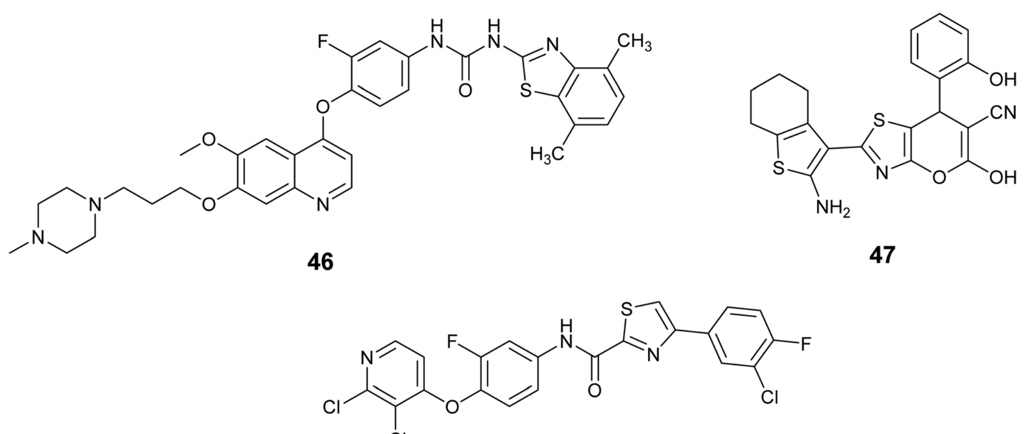
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Fig. 17 Thiazole derivatives as c-MET inhibitors (**46–48**).

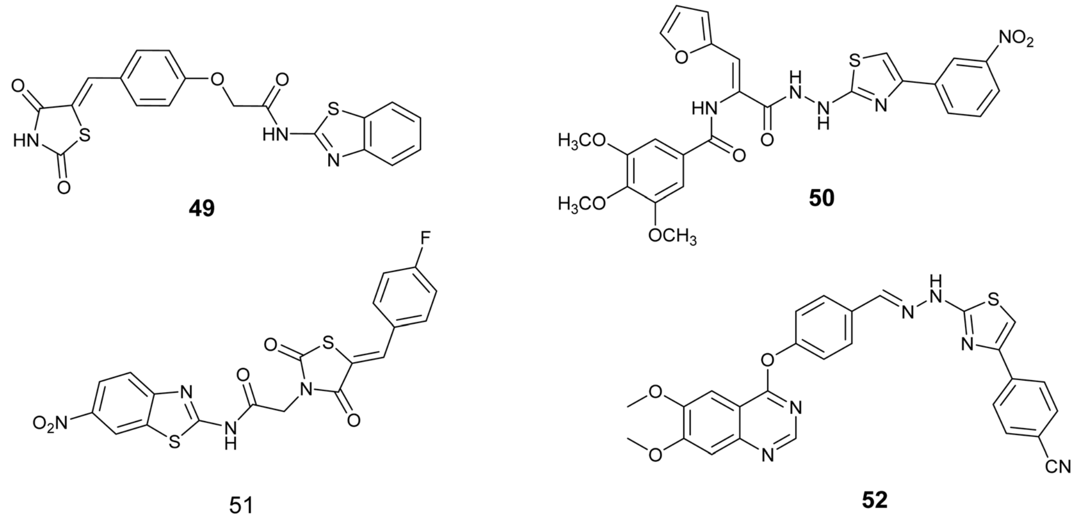


Fig. 18 Thiazole derivatives as Vascular endothelial growth factor receptor (VEGFR) inhibitors (**49–52**).

In 2018, Abdallah *et al.* employed multicomponent reactions (MCRs) for the synthesis of novel thiazole derivatives. These substances were tested in a laboratory setting to determine their effectiveness in fighting cancer, using six different types of cancer cells. The findings indicated that a significant number of compounds exhibited notable activity, leading to the selection of promising candidates for further investigation as enzymatic inhibitors of c-Met. Compound **47**, Fig. 17 demonstrated the highest potency with nanomolar activity ($IC_{50} = 0.06 \pm 0.01$ nM), surpassing the standard drug foretinib ($IC_{50} = 1.16 \pm 0.17$ nM).[86]

In 2023, Nan *et al.* aimed to identify new c-Met inhibitors with potential antitumor properties by designing, synthesizing, and testing four series of thiazole/thiadiazole carboxamide-derived analogues against c-Met and four human cancer cell lines *in vitro*. Compound **48**, Fig. 17 demonstrated significant potency toward c-Met, with the value of $IC_{50} = 2.54 \pm 0.49$ nM. Moreover, compound **48** was found to cause cell cycle arrest and apoptosis in MKN-45 cells, suppress c-Met phosphorylation in cellular and cell-free environments, and exhibit advantageous pharmacokinetic properties in BALB/c mice.[87]

5.2.2. Inhibitors of the receptor for vascular endothelial growth factor (VEGFR). The Vascular Endothelial Growth Factor Receptor (VEGFR) is a receptor with tyrosine kinase activity that consists of three main subtypes: VEGFR-1, which is essential for hematopoietic cell development; VEGFR-2, crucial for vascular endothelial cell development; and VEGFR-3, significant for lymphatic endothelial cell development. VEGFR-2 is particularly important in pathological angiogenesis, notably in cancer. Activation of VEGF receptors by VEGF leads to angiogenesis, facilitating cancer cell metastasis, migration, and survival. Elevated VEGFR-2 expression is linked to various human cancers like ovarian, thyroid, and melanoma. Consequently, there has been a growing interest in cancer therapies targeting the VEGF/VEGFR-2 pathway in recent years.[88]

Bhanushali and colleagues conducted a screening of a new group of 5-benzylidene-2,4- thiazolidinediones and assessed their potential as inhibitors of VEGFR-2 kinase *in vitro* to investigate their anti-angiogenic properties. Compound **49**, Fig. 18, exhibited significant inhibitory effects in both CAM and zebrafish assays, leading to its selection for further evaluation as a VEGFR kinase inhibitor. Subsequent findings indicated that this compound effectively inhibited the kinase with an IC_{50} value of 0.5 μM.[89]

In 2022, Zaki and colleagues synthesized novel series based on thiazole core and assessed their activity as anticancer agent toward the breast cancer (MDA-MB-231) cell line. The results showed that derivative **50**, Fig. 18, demonstrated notable effectiveness, with an IC_{50} value of 1.21 ± 0.09 μM. Furthermore, this compound demonstrated the ability to inhibit VEGFR-2, with an inhibition percentage of 85.72%. Following DNA flow cytometry analysis showed that compound **50** caused cells to stop at the G1 and G2/M stages of the cell cycle. Additionally, it triggered apoptosis, as shown by a rise in the percentage of cells in the pre-G1 phase. Furthermore, the structure–activity relationship (SAR) analysis for compound **50**, Fig. 19 indicated that the carbohydrazide linker exhibits flexibility and hydrophilicity, which are advantageous for anti-VEGFR-2 activity. The presence of a 4-nitro group on the phenyl ring is critical for the compound's efficacy, while the combination of these two components with the thiazole ring functions as a tail segment. The head portion of the compound is characterized by trimethoxy substitutions on the phenyl ring, which is vital for its biological activity, and is connected to the furan moiety through an amide linker.[90]

A novel series of compounds derived from aminobenzothiazole was created and tested for their ability to inhibit tumor growth in laboratory settings using three different types of cancer cells (MCF-7, HCT-116, and HEPG-2). Compound **51**, Fig. 18 exhibited the highest potency among the tested compounds, demonstrating IC_{50} values of 3.84, 5.61 and 7.92 μM against the respective cell lines, while also displaying favorable safety characteristics against noncancer WI-38 cells. Compound **51** significantly inhibited S phase cell proliferation

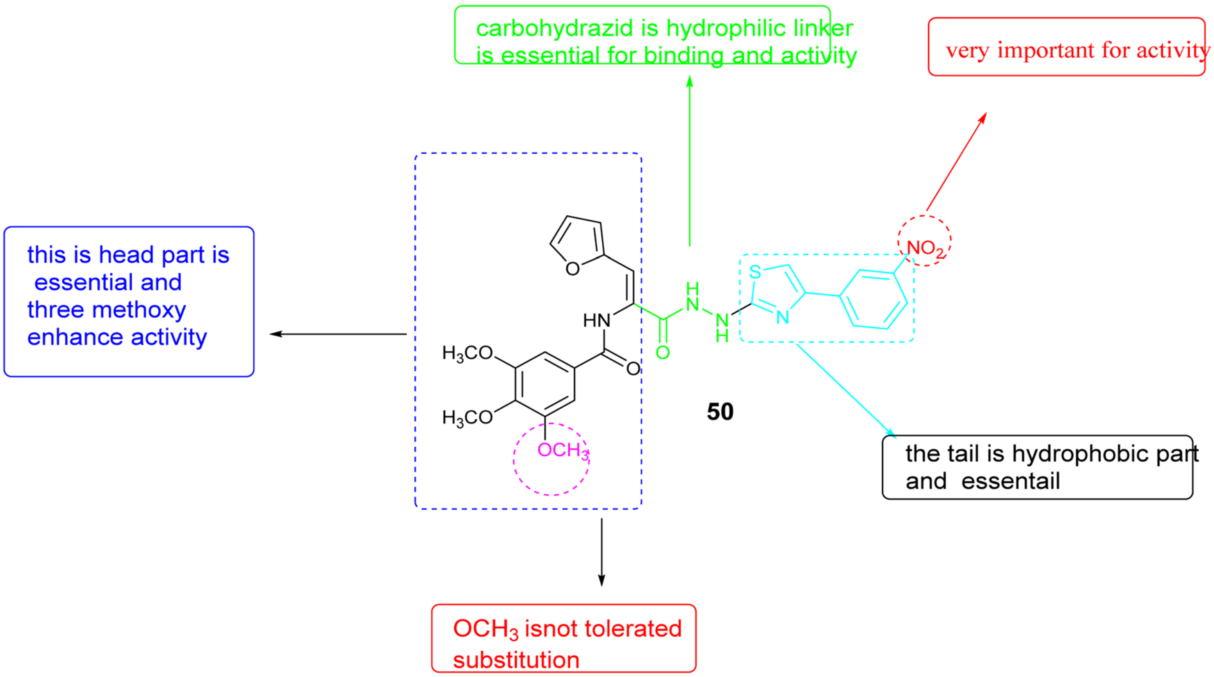


Fig. 19 SAR for compound **50**.

in MCF-7 cells as determined by flow cytometry. Further analysis revealed that compound **51**, with an IC_{50} value of 91 nanometers, was the most effective inhibitor of VEGFR-2.[91]

In 2024, Sandor and colleagues introduced a new set of quinazoline-thiazole hybrid compounds with potential antiproliferative and anti-angiogenic agents. The majority of these compounds exhibited enhanced antiproliferative activity (IC_{50} = 1.83–4.24 μM) against HepG2 cells compared to sorafenib (IC_{50} = 6.28 μM). The interaction with the VEGFR2 kinase domain was evaluated using computational methods such as molecular docking, molecular dynamics simulations, and MM-PBSA. The compound series demonstrated a notable resemblance to sorafenib in terms of binding orientation within the VEGFR2 active site, with compound **52**, Fig. 18, forming the most stable complex with VEGFR2 in comparison to sorafenib. The highest free energy was observed for **52** (−71.23 ± 5.29 kcal mol^{-1}), which closely approximated the value for sorafenib (−69.39 ± 3.63 kcal mol^{-1}).[92]

5.2.3. Anaplastic lymphoma kinase (ALK) inhibitors. Anaplastic lymphoma kinase (ALK), alternatively known as ALK tyrosine kinase receptor or CD246, is a member of the insulin receptor (IR) protein-tyrosine kinase superfamily. ALK has the ability to activate multiple signaling pathways such as JAK-STAT, MAPK-ERK, CRKL-C3G and PI3K-AKT. The development of different ALK fusion proteins is predominantly linked to chromosomal rearrangements identified in numerous human malignancies. Consequently, ALK represents a promising therapeutic target in cancer treatment, with the development of several small molecule inhibitors targeting ALK already underway.[93]

Z. Liu and colleagues introduced a novel series of 2-(thiazol-2-amino)-4-arylaminopyrimidines designed as inhibitors of Anaplastic lymphoma kinase (ALK). These compounds exhibited varying levels of effectiveness toward ALK kinase, Compound **53**, Fig. 20 showed the strongest potency at 12.4 nM, although it had only moderate effectiveness in SUP-M2 cells with NPM-ALK. However, it displayed significant selectivity for kinases and effectively inhibited the ALK gatekeeper mutation L1196M (IC_{50} = 24.1 nM). Furthermore, derivative **53** dose-dependently inhibited ALK phosphorylation and its related signaling pathways.[94]

Crizotinib (**54**), Fig. 20 is a drug that inhibits the ALK receptor tyrosine kinase and has shown effectiveness in patients who test positive for ALK and ROS. However, the development of point mutations in the kinase domain of ALK under crizotinib treatment leads to resistance and disease progression. To address this issue, Huang *et al.* conducted optimization studies to identify a novel drug candidate with enhanced lipophilic efficiency capable of overcoming resistance in cell lines. The results indicated that compound **55**, Fig. 20 demonstrated significant efficacy against various engineered ALK mutant cell lines, displaying an IC_{50} value of 0.8 nM in contrast to 80 nM for Crizotinib. Additionally, compound **55** demonstrated high potency against ROS1 with a K_i value of 0.02 nM. Furthermore, it exhibited favorable preclinical pharmacokinetic properties and substantial suppression of tumor progression observed in a resistant cell line (H3122-L1196M) with an IC_{50} of 6.6 nM.[95]

5.2.4. FMS-like tyrosine kinase 3 (FLT3) inhibitors. The FLT3 protein, which acts as a receptor tyrosine kinase, is essential for regulating the development, growth, and programmed cell death of blood cells. Mutations, overexpression, or correlation with unfavorable outcomes in certain cancers, notably acute myeloid leukemia (AML), are commonly observed in FLT3. Inhibitors that target this enzyme have been approved

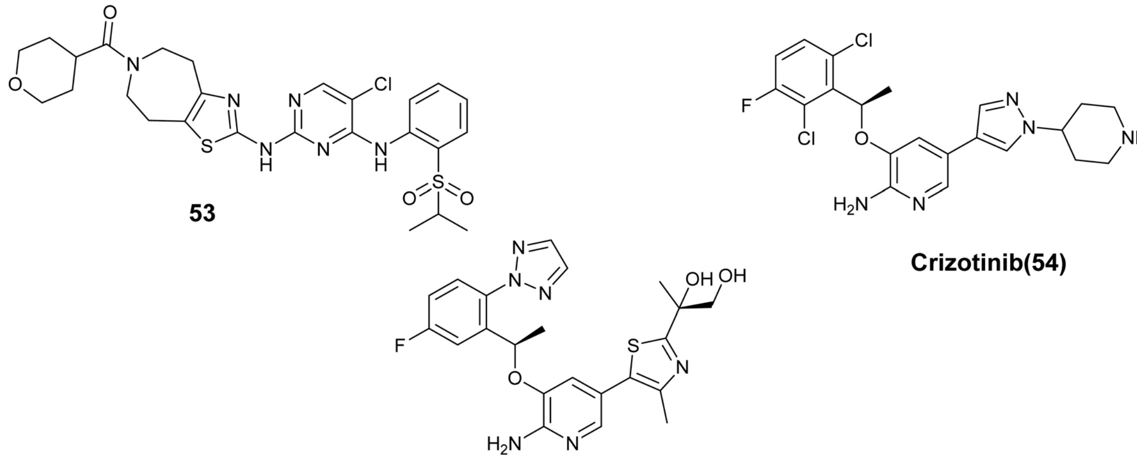


Fig. 20 Thiazole derivatives as anaplastic lymphoma kinase (ALK) inhibitors (53–55).

for treating people with AML that has mutations in FLT3, demonstrating promising clinical outcomes in this patient population.[96]

Novartis developed a group of thiazole derivatives that function as Flt3 inhibitors. Compound **56**, Fig. 21 a representative of this series, Showed notable effectiveness with an IC_{50} value of 22 nM toward Flt3.[97] Furthermore, a set of imidazothiazole derivatives was synthesized. By examining the relationship between the structure and activity of these compounds through cellular tests, Multiple compounds were found to be highly effective against FLT3-dependent human acute myeloid leukemia (AML) cell line MV4-11, but showed little to no impact on FLT3-independent human cervical cancer cell line HeLa. Following experiments were carried out on the most effective compounds to inhibit FLT3 kinase. Compound **57**, Fig. 21 emerged as the most effective, demonstrating high potency in both cellular MV4-11 and enzymatic (FLT3) assays with the value of IC_{50}; 0.002 μM and 0.022 μM, respectively.[98]

5.2.5. Inhibitors of focal adhesion kinase (FAK). Focal adhesion kinase (FAK) is a non-receptor protein tyrosine kinase that is mainly controlled by integrin signaling. It is essential for various cellular activities like movement, attachment, growth, and viability. FAK is activated in the cytoplasm in response to different external signals from cell-surface receptors such as cytokines, G protein-coupled receptors, integrins, and growth factors, leading to the initiation of diverse cellular processes. Overexpression of FAK is commonly observed in many advanced human cancers, contributing significantly to malignant characteristics in cancer progression. Inhibitors that target FAK have shown significant effectiveness in reducing tumor growth and spread.[99]

In 2020, Groendyke B. J. has launched a new collection of small molecules based on a tricyclic pyrimidothiazolodiazepinone core, which demonstrates notable effectiveness and selectivity against FAK. BJG-03-025 (**58**), Fig. 22 was developed through the use of Structure–Activity Relationship (SAR) studies and modifications. This compound shows potent biochemical suppression of FAK ($IC_{50} = 20$ nM), high selectivity within the kinome, effectiveness in breast and gastric cancer models grown in 3D settings, and positive pharmacokinetic properties in mouse models. BJG-03-025(**58**) is a useful chemical tool for evaluating biological processes related to FAK.[100]

A new group of imidazo[2,1-*b*]thiazole compounds was created and tested for their ability to cause cell death and apoptosis in glioma C6 cancer cells. The findings indicated that the investigated compounds unveiled significant activity toward the tested cells, particularly derivative **59**, Fig. 22 which demonstrated an IC_{50} value of 4.83 ± 0.28 μM with minimal toxicity towards normal NIH/3T3 cells. Additionally, compound **60a**, Fig. 22 exhibited higher apoptotic activity against the C6 cancer cell line compared to cisplatin 5.7 and 2.2%, in the order given. Furthermore, the most promising compounds were further examined as focal adhesion kinase (FAK) inhibitors. The

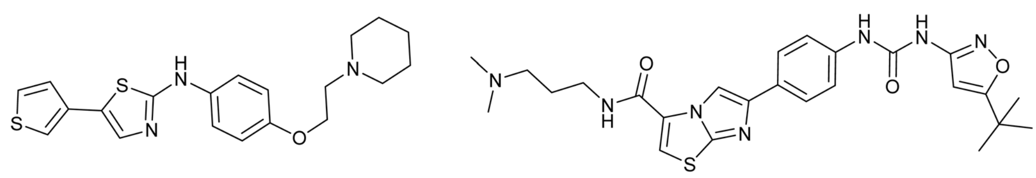
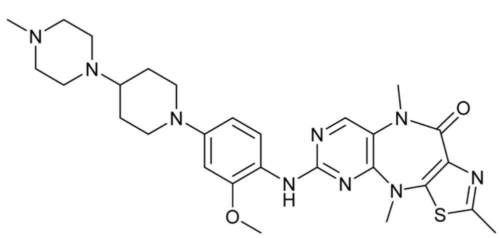
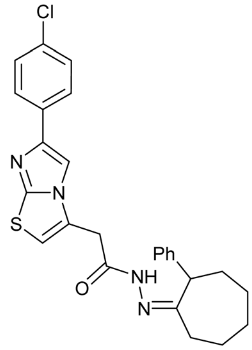


Fig. 21 Thiazole derivatives as FMS-like tyrosine kinase 3 (FLT3) inhibitors (56 and 57).



BJG-03-025 (58)



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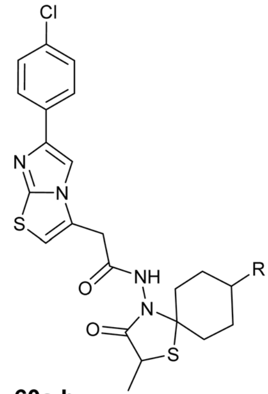


60a,b
60a, R=Propyl
60b, R=Phenyl

Fig. 22 Thiazole derivatives as focal adhesion kinase (FAK) inhibitors (**58–60a–b**).

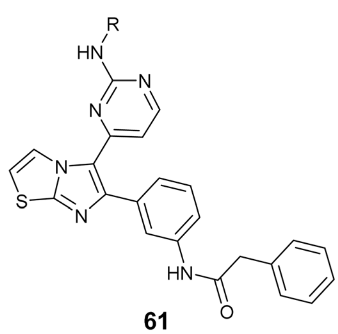
findings showed that the compounds tested had significant inhibitory effects on FAK, with compound **60b**, Fig. 22 being identified as the most potent inhibitor of FAK on the C6 cancer cell line 72.54 ± 3.6%.[101]

5.2.6. Insulin-like growth factor type 1 receptor (IGF-1R). The IGF-1R, a receptor belonging to the tyrosine kinase family, is essential for a range of normal tissue and cellular functions such as growth, cardiac and neurological system processes, and glucose regulation. Studies have indicated that the signaling of IGF-1R plays a role in the growth and advancement of cancer. The ligands of IGF-1R (IGF1 and IGF2) have been found to stimulate cell growth in multiple cancer cell lines. Additionally, IGF-1R plays a role in both the Ras-Raf-MEK and PI3K-AKT signaling pathways, potentially keeping the MAPK pathway active. Consequently, small molecule inhibitors of IGF-1R primarily induce apoptotic cell death in cancer cells.[102]

Hubbard *et al.* have documented advancements in this field through the utilization of the single-drug multi-target strategy, focusing on a group of IGF-1R inhibitors derived from imidazo [2,1-*b*] thiazole. The imidazo[2,1-*b*]thiazole compound series, exemplified by compound **61**, Fig. 23 demonstrated notable efficacy against IGF-1R in A431 cells, exhibiting an IC_{50} value of 41 nM, along with moderate potencies towards EGFR and ErbB2 at 350 and 310 nM, respectively.[103]

Additionally, Tandon and colleagues developed and synthesized compound **62**, Fig. 23 as a dual inhibitor targeting both IGF-1R and EGFR, which was derived from a bis-arylamino-pyrimidine scaffold. This compound exhibited potent activities against IGF-1R and EGFR, with the value of IC_{50}; 74 and 45 nM, respectively. Furthermore, derivative **62** demonstrated notable anti-proliferative effects across various cell lines, including A431, HT29, and A549 (IC_{50} = 170, 274, and 111 nM, respectively). Notably, derivative 62 exhibited sensitivities in inhibiting proliferation in H1975 cells, with a GI_{50} of 1.3 M. It is important to highlight that H1975 cells carry an EGFR mutation (T790M) and are known to be resistant to erlotinib, as evidenced by a GI_{50} of 47 M.[104]

Gadekar and colleagues outlined the development, creation, evaluation of a group of compounds derived from a pyrimidine-containing imidazothiazole structure as dual kinase inhibitors that target IGF1R and EGFR for potential use in cancer treatment. The findings indicated that numerous compounds exhibited significant activity at the nanomolar level. Notably, compound **63**, Fig. 23 demonstrated the most potent and



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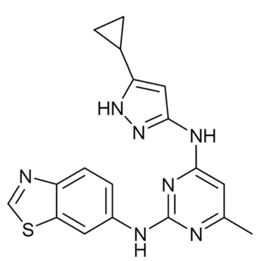

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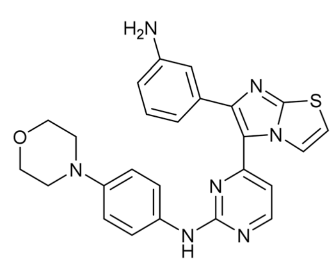

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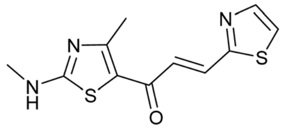
R = 1-ethyl-4-phenylpiperazine

Fig. 23 Thiazole derivatives as insulin-like growth factor type 1 receptor (IGF-1R) (**61–63**).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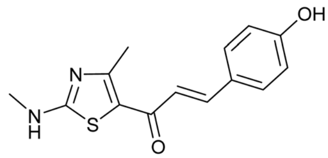
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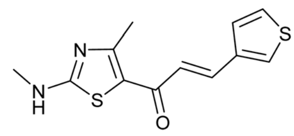
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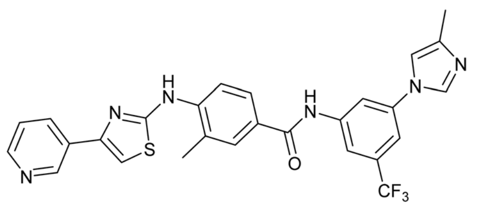
Fig. 24 Thiazole derivatives as Janus kinase (JAK) inhibitors (**64–66**).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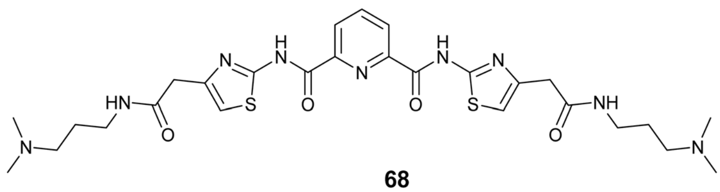
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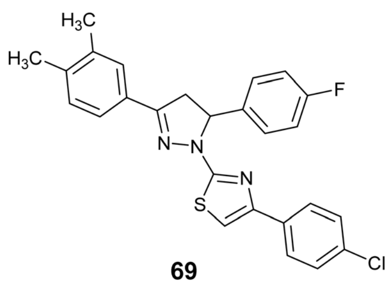
Fig. 25 Thiazole derivatives as KIT inhibitors (**67** and **68**).

encouraging effect on IGF1R, $IC_{50} = 52$ nM and EGFR $IC_{50} = 35.5$ nM, in addition to possessing a favorable pharmacokinetic profile.[105]

5.2.7. **Janus kinase (JAK) inhibitors.** Janus kinase (JAK) is a non-receptor tyrosine kinase that belongs to a family responsible for transmitting cytokine-mediated signals through the STAT3 pathway by upregulating cytokine expression. Research has shown that mutations in JAKs, particularly JAK-2, are associated with a range of cancers. Consequently, JAK inhibitors have been investigated as potential anticancer treatments for solid tumor patients.[106]

Sanachai and colleagues employed both experimental and theoretical approaches to investigate new substances that could be effective in fighting cancer targeting JAK2 and EGFR. They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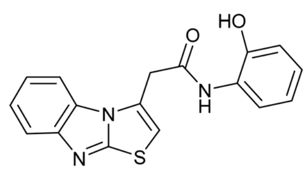
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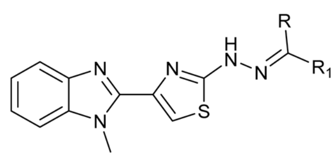
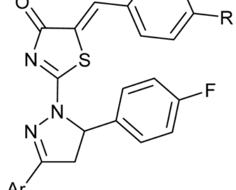

71a-c
71a, R= 5-NO$_2$ -2-furanyl; R1= H
71b, R = 4-F-C$_6$H$_4$; R1= H
71c, R, R1 = C$_5$H$_9$


72a-c
72a, Ar= p-OCH$_3$-C$_6$H$_4$, R= OH
72b, Ar=2-thienyl R=O-CH$_3$
72c, Ar=p-CH$_3$-C$_6$H$_4$ R= OH

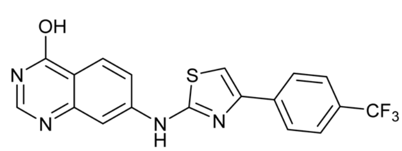

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Fig. 26 Thiazole derivatives as epidermal growth factor receptor (EGFR) inhibitors (**69–73**).

Table 2 Activities of the target compounds

	Compounds	Activity values of IC_{50}
Serine/threonine thiazole-based kinase inhibitors		
PI3K/AKT/mTOR signaling pathway inhibitors	18	0.50–4.75 μM
	19	0.30–0.45 μM
	20	9.0 nM
	21	290 nM
	22	0.02 μM
	23	0.719 & 0.131 μM
	24	2.33 nM
Cyclin-dependent kinases (CDKs) inhibitors	25	0.64 to 2.01 μM
	26	54.8 nM
	27	ND
	28	0.35 μM
Aurora kinase inhibitors	29	79 nM
	30	140 nM
	31	K_i = 8.0 & 9.2 nM
	32	ND
Inhibitors of the enzyme casein kinases II (CK2)	33	0.4 μM
	34	1.9 μM
	35	3.4 μM
B-RAF inhibitors	36	0.05 μM
	37	19 nM
	38a	9.30 nM
	38b	1.20 nM
	39	8.2 & 0.978 nM
	40	23.1 nM
Inhibitors of glycogen synthase kinase 3β	41	100 nM
	42	0.29 nM
	43	1.1 nM
	44	2.55 μM
	45	7.35 μM
Inhibitors of kinases that are based on tyrosine thiazole		
Inhibitors of the c-MET protein	46	17.6 nM
	47	0.06 nM
	48	2.54 nM
Inhibitors of the receptor for vascular endothelial growth factor (VEGFR)	49	0.5 μM
	50	% Inhibition = 85.72%
	51	91 nM
	52	ND
Anaplastic lymphoma kinase (ALK) inhibitors	53	24.1 nM
	54	11–24 nM
	55	0.8 nM
FMS-like tyrosine kinase 3 (FLT3) inhibitors	56	22 nM
	57	0.022 μM
Inhibitors of focal adhesion kinase (FAK)	58	20 nM
	59	Inhibition% = 68.71%
	60a	Inhibition% = 47.78%
	60b	Inhibition% = 72.54%
Insulin-like growth factor type 1 receptor (IGF-1R)	61	41 nM
	62	74 nM
	63	52 nM
Janus kinase (JAK) inhibitors	64	6.89 μM
	65	8.04 μM
	66	17.64 nM
KIT inhibitors	67	56.0 nM & 20.0 nM
	68	DC_{50} = 0.88 μM & a K_d = 0.69 μM
Epidermal growth factor receptor (EGFR) inhibitors	69	0.06 μM
	70	55 nM
	71a	71.67 nM
	71b	109.71 nM
	71c	6.30 μM
	72a	ND
	72b	ND

Table 2 (*Contd.*)

Compounds	Activity values of IC_{50}
72c	83 nM
73	2.17, 2.81 &3.62 nM

prepared derivatives of aromatic alkyl-amino analogs based on a thiazole scaffold and evaluated their inhibitory effects on JAK2 and EGFR proteins, Additionally, their ability to combat cancer in human cancer cell lines. *In vitro* cytotoxicity screening results indicated significant activity of the tested compounds, notably compound **64**, Fig. 24 exhibited notable efficacies against HEL cell lines $IC_{50} = 6.89 \pm 0.38$ μM, while derivative **65** demonstrated strong effectiveness against tested cell A431, $IC_{50} = 8.04 \pm 0.90$ μM. The most promising compounds were further assessed as inhibitors of JAK2 and EGFR proteins, revealing that compound **66**, Fig. 24 displayed significant activity against JAK2 ($IC_{50} = 17.64 \pm 1.68$ nM), and derivative **65**, Fig. 24 displayed the most significant activity targeting EGFR ($IC_{50} = 28.46 \pm 3.09$ nM). Based on molecular docking analysis, these three compounds suit the active site well and form hydrogen bonds to Lys857, Leu932, and Glu930 Situated in the area where the enzyme bends and JAK2's catalytic site, it hydrophobically contacts Leu983.[107]

5.2.8. KIT inhibitors. The c-kit gene is a well-known proto-oncogene responsible for encoding a receptor tyrosine kinase (RTK) that interacts with stem cell factor (SCF). The signaling pathway of c-KIT plays a crucial role in controlling cell proliferation, survival, and movement, and is involved in various physiological functions such as pigmentation, hematopoiesis, and gastrointestinal motility. Research findings indicate that aberrant c-KIT activity, resulting from either increased expression or mutations in the c-kit gene, contributes to the initiation and advancement of tumors in different types of human malignancies, with a specific emphasis on gastrointestinal stromal tumors (GIST). Therefore, the efficacy of KIT inhibitors in the treatment of GISTs has been recently demonstrated[108]

Pan and colleagues synthesized two thiazole amine-based compounds and assessed the effect of these compounds on human mast cells that mutated the KIT gene. Their findings revealed that compound **67**, Fig. 25 displayed the highest activity, effectively blocking the activation of KIT and the subsequent signaling molecules Stat3 and Stat5. Moreover, compound **67** showed notable suppression of cell survival in KBM5 cells with wild-type Bcr-Abl and BaF3 cells that have FIP1L1-PDGFRa expression, with IC_{50} values of 56.0 nM and 20.0 nM, respectively. Moreover, Compound **67** inhibited the growth of cells expressing the D816V KIT mutation, triggered cell death, and reduced the levels of Mcl-1 and survivin in cancerous cells with the mutant KIT.[109]

In 2021, Paul and colleagues introduced a novel thiazole polyamide (**68**), Fig. 25 that exhibits high affinity binding to the c-KIT1 G-quadruplex (G4) at sub-micromolar levels, leading to the suppression of c-KIT proto-oncogene expression. Compound **68** demonstrated notable efficacy against the c-KIT1 G4, as evidenced by a fluorescence increase of up to tenfold upon interaction with the c-KIT1 G4, $DC_{50} = 0.88$ μM and a $K_d = 0.69$ μM. Furthermore, derivative **68** was found to enhance the presence of G4-specific antibody (BG4) foci and identify G4 structures within cancer cells.[110]

5.2.9. Epidermal growth factor receptor (EGFR) inhibitors. The epidermal growth factor receptor (EGFR) has been recognized as a promising candidate for cancer treatment. Elevated levels of EGFR have been linked to the progression of aggressive subtypes of certain cancers, including triple-negative breast cancer (TNBC).[111] Research has explored the inhibitory effects of thiazoles in combination with heterocyclic compounds on EGFR kinase activity as a promising approach for developing antitumor agents.

Lv *et al.* conducted an investigation on thiazolyl-pyrazoline derivatives to assess their efficacy as inhibitors of EGFR kinase activity. Among the compounds studied, compound **69**, Fig. 26 showed the strongest inhibitory effect on EGFR TK, with $IC_{50} = 0.06$ μM. Furthermore, Compound **69** showed notable inhibitory effects on the growth of MCF-7 cells in laboratory tests, with an IC_{50} value of 0.07 μM, which is similar to the standard medication erlotinib (IC_{50}; 0.02 μM). Molecular docking analysis revealed that Compound **69** formed three hydrogen bonds when bound to the EGFR kinase.[112]

A new series of novels containing a thiazole core and/or fused structure was created, produced, and tested for their ability to fight cancer in human cell lines, as well as their ability to inhibit EGFR in laboratory settings. Although all the created compounds showed limited effectiveness in fighting EGFR-related tumors, compound **70**, Fig. 26 demonstrated the highest potency toward the human cell line HeLa, with $IC_{50} = 0.42$ μM, and also displayed significant activity toward EGFR with $IC_{50} = 55$ nM. Additionally, these compounds showed negligible cellular toxicity towards human normal cell lines HL7702.[113]

In 2020, Srour and colleagues created a new set of compounds based on a combination of benzoimiazole and thiazole to act as inhibitors of the epidermal growth factor receptor (EGFR). These newly synthesized derivatives were evaluated in a laboratory setting to determine their ability to inhibit the activity of EGFR tyrosine kinase. The findings indicated that Compound **71a**, Fig. 26 showed the most activity, with an IC_{50} value of 71.67 nanomolar. Additionally, the findings of the MTT assay indicated that compound **71b**, Fig. 26 exhibited notable cytotoxic effects on the MCF-7 human breast cancer cell line, with an IC_{50} value of 5.96 μM, in comparison to the IC_{50} value of the reference drug erlotinib, which was 4.15 μM. Compound **71c** also exhibited notable efficacy as an agent that inhibits EGFR tyrosine kinase and acts as an anti-breast cancer treatment, with IC_{50} values of 109.71 ± 3.55 nM and 6.30 ± 0.37 μM, respectively. Additionally, compound **71c**, Fig. 26 elicited apoptotic responses and halted the cell cycle at the G2/M checkpoint, consequently interfering with the mitotic progression in MCF-7 cells. Furthermore, compound **71c** promoted the expression of oncogenic indicators including

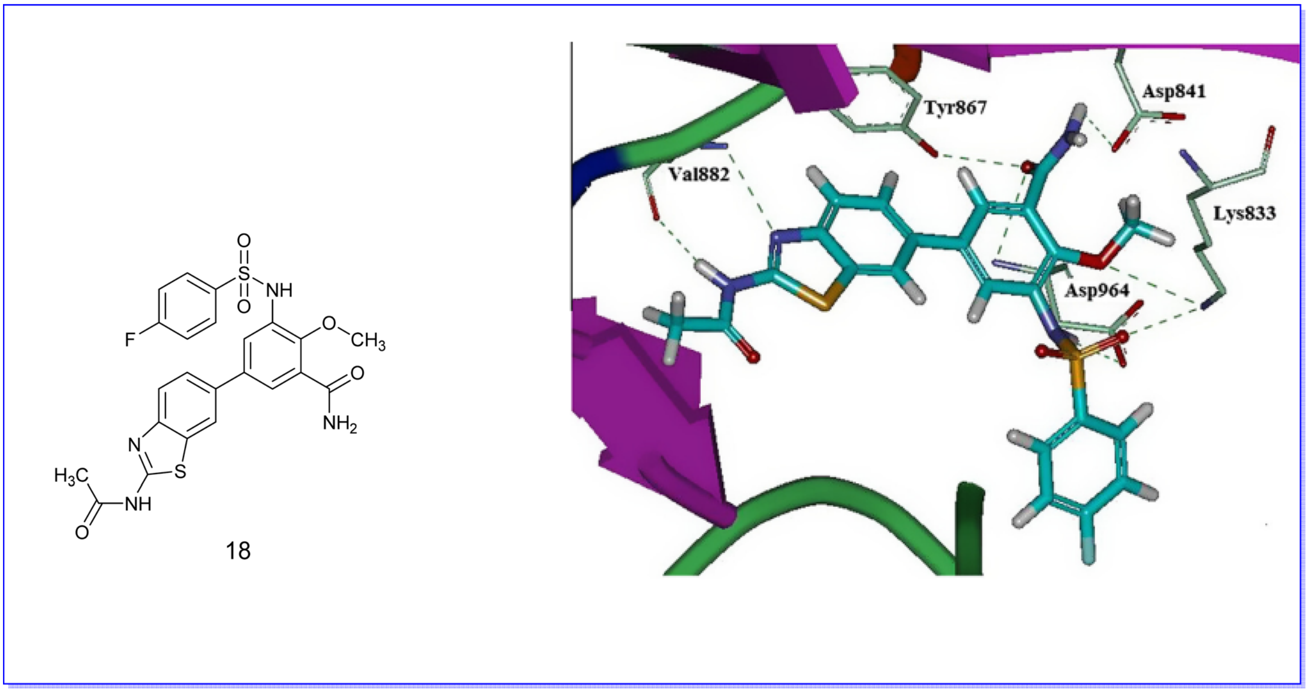

Fig. 27 Docking mode of compound **18** with PI3Kc.

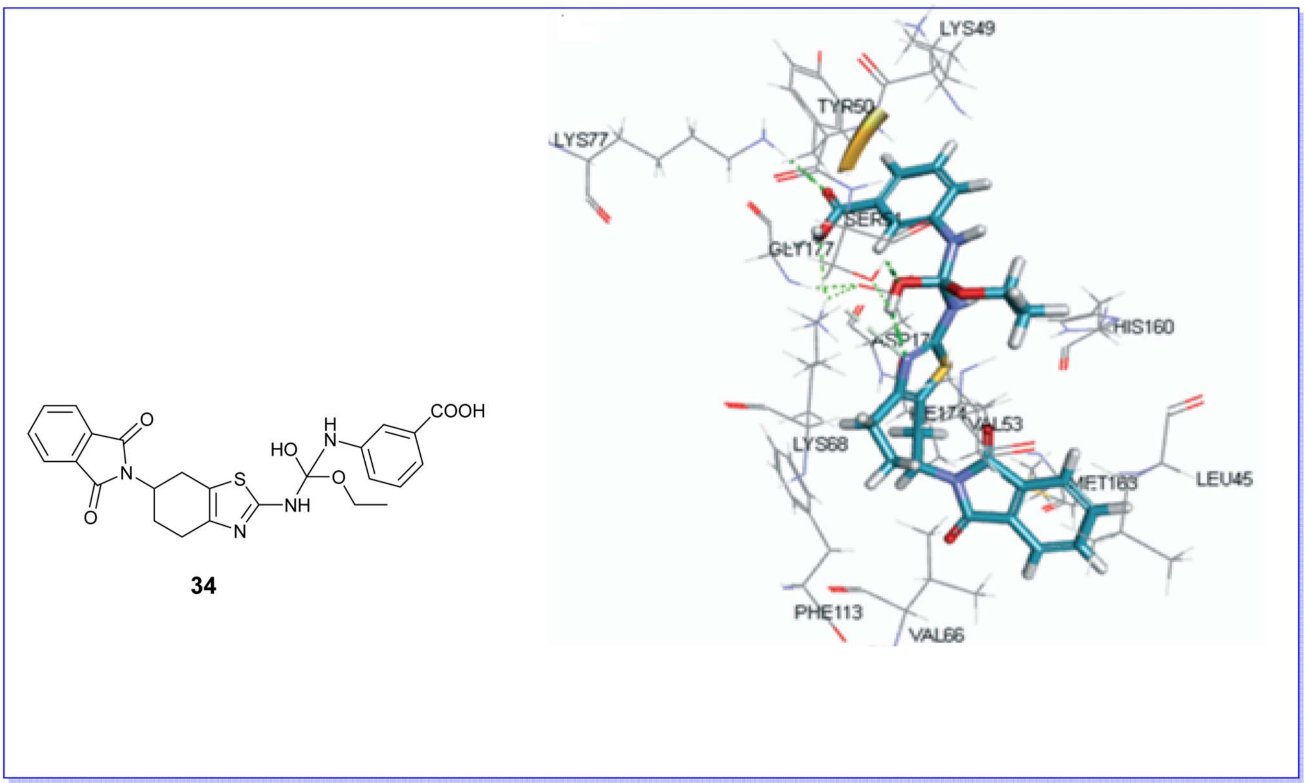

Fig. 28 Molecular docking of compound **34** with CK2 protein.

caspase-3, p53, and Bax/Bcl-2, while concurrently suppressing the functionality of the PARP-1 enzyme.[114]

Al-Warhi and colleagues conducted a study in which they synthesized various thiazolyl-pyrazoline derivatives to assess their efficacy as inhibitors of cell proliferation in the lung (A549) and breast (T-47D) cell line derived from cancer cells using the MTT assay. The findings showed that the thiazolyl-pyrazoline derivatives displayed greater anti-proliferative effects on the T-47D breast cancer cells compared to the A549 lung cancer cells. Specifically, compounds **72a** and **72b**, Fig. 26 demonstrated notable efficacy against the two tested cell lines A549 with the value of IC_{50}; 3.92 and 6.53 μM, while T-47D cells the value of IC_{50}; 0.88 and 0.75 μM, respectively. The most favorable compounds were subsequently evaluated for their ability to inhibit EGFR. with compound **72c**, Fig. 26 displays the highest activity ($IC_{50} = 83 \pm 40$ nM). Moreover, compounds **72a** and **72b** were found to cause sub-G1 phase arrest and cellular apoptosis, aligning with the expected outcomes of inhibiting EGFR.[115]

In 2023, Raghu *et al.* conducted a study where they synthesized and evaluated a novel series of quinazoline-based thiazole scaffold for their potential anti-proliferative properties toward MCF-7, HepG2, and A549 cancer cell lines *in vitro*. The results indicated that all compounds exhibited varying degrees of cytotoxicity, Compound **73** Fig. 26 exhibited the highest level of efficacy among the cell lines that have been examined (MCF-7, HepG2, and A549), displaying IC50 values of 2.86 ± 0.31, 5.91 ± 0.45, and 14.79 ± 1.03 μM, respectively. Furthermore, derivative **71**, identified as the most active compound, was also evaluated as an EGFR inhibitor. Notably, compound **73** showed strong inhibitory effects against wild-type, L858R/T790 M, and L858R/T790 M/C797S mutant EGFR kinases, with IC_{50} values of 2.17, 2.81, and 3.62 nM, respectively (Table 2).[116]

6. Molecular modeling studies

Molecular docking techniques were employed to elucidate the binding interactions between the active compounds and the

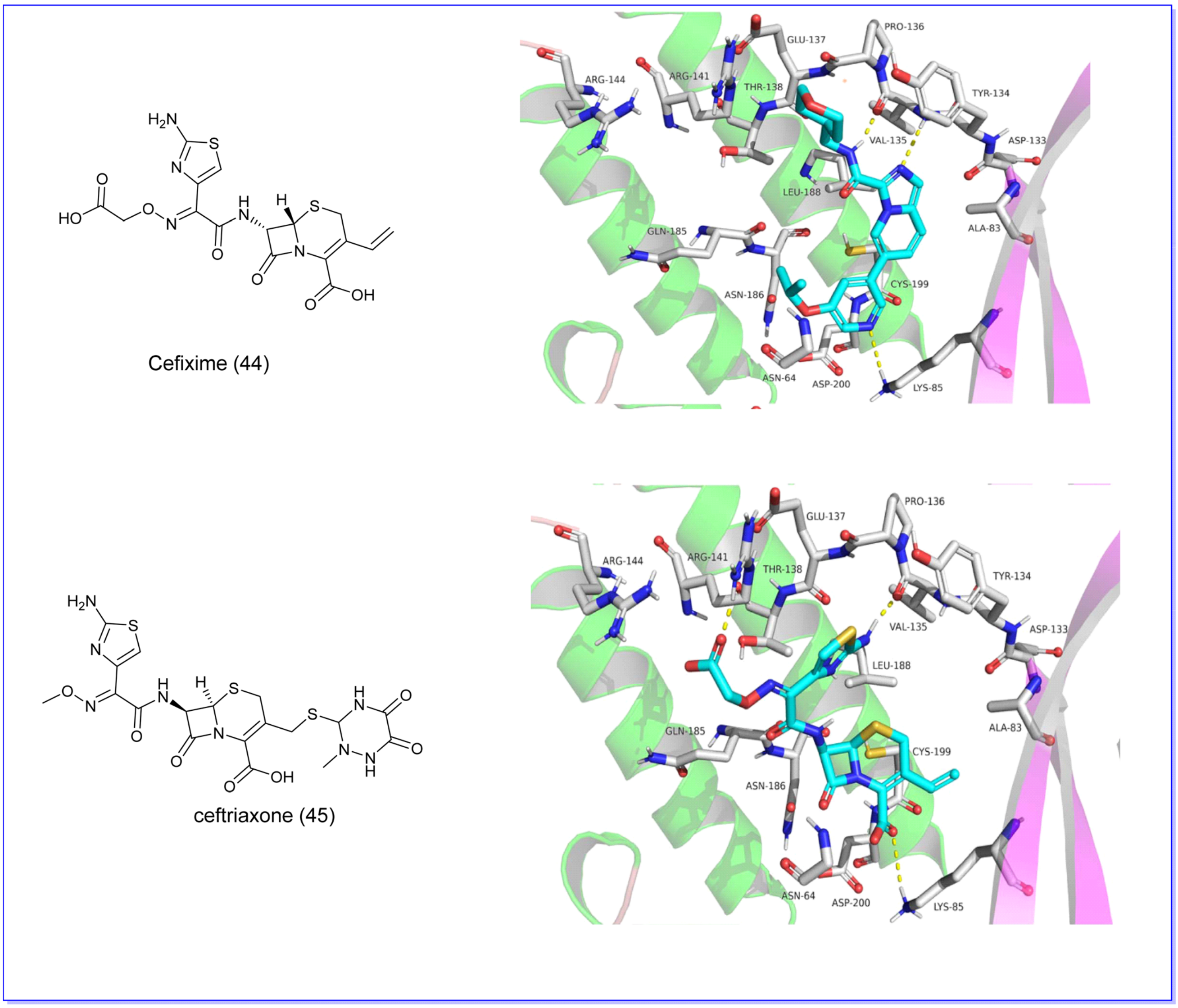

Fig. 29 (A) Molecular docking of cefixime (**44**) GSK3 protein. (B) Molecular docking of ceftriaxone (**45**) with GSKS protein.

binding pocket of the target protein. Therefore, compound **18** was selected for molecular docking studies against PI3Kc (PDB code 3QKO) due to its superior efficacy as an anticancer agent. It exhibited a notable fit by establishing five hydrogen bonds with the residues Val882, Tyr867, Lys833, Asp964, and Asp841, as illustrated in Fig. 27.[51]

Moreover, the compound **34** demonstrated favorable docking within the active site of the CK2 protein (PDB code CX-5279), as illustrated in Fig. 28. The results indicated effective binding at the active site, characterized by the formation of three hydrogen bonds involving the hydroxyl group, carboxyl group, and thiazole nitrogen with the amino acids SER51, LYS77, and LYS68. Additionally, a pi–pi interaction was observed.[70]

Furthermore, the two compounds, cefixime (**44**) and ceftriaxone (**45**), underwent molecular docking analysis against GSK3β (PDB code 6Y9S). The findings revealed that both compounds exhibited the most advantageous docking scores of −7.36 and −7.06, respectively, Fig. 29. These favorable scores are attributed to the formation of hydrogen bonds between the aminothiazole group of the compounds and the hinge residues of GSK3b.[83]

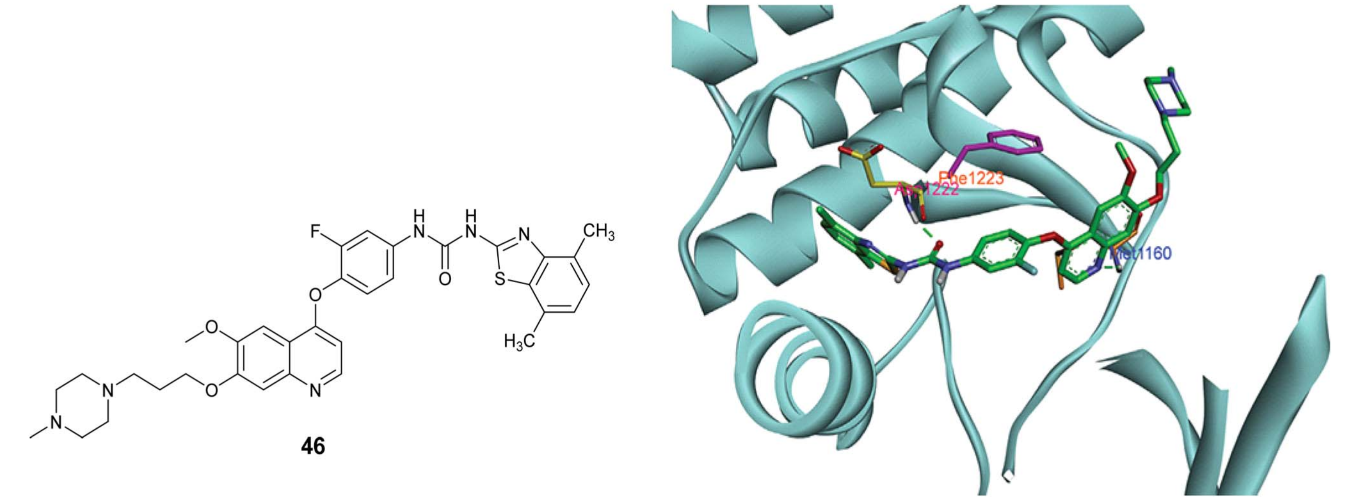

Fig. 30 The active site of c-Met interacting with compound **46**.

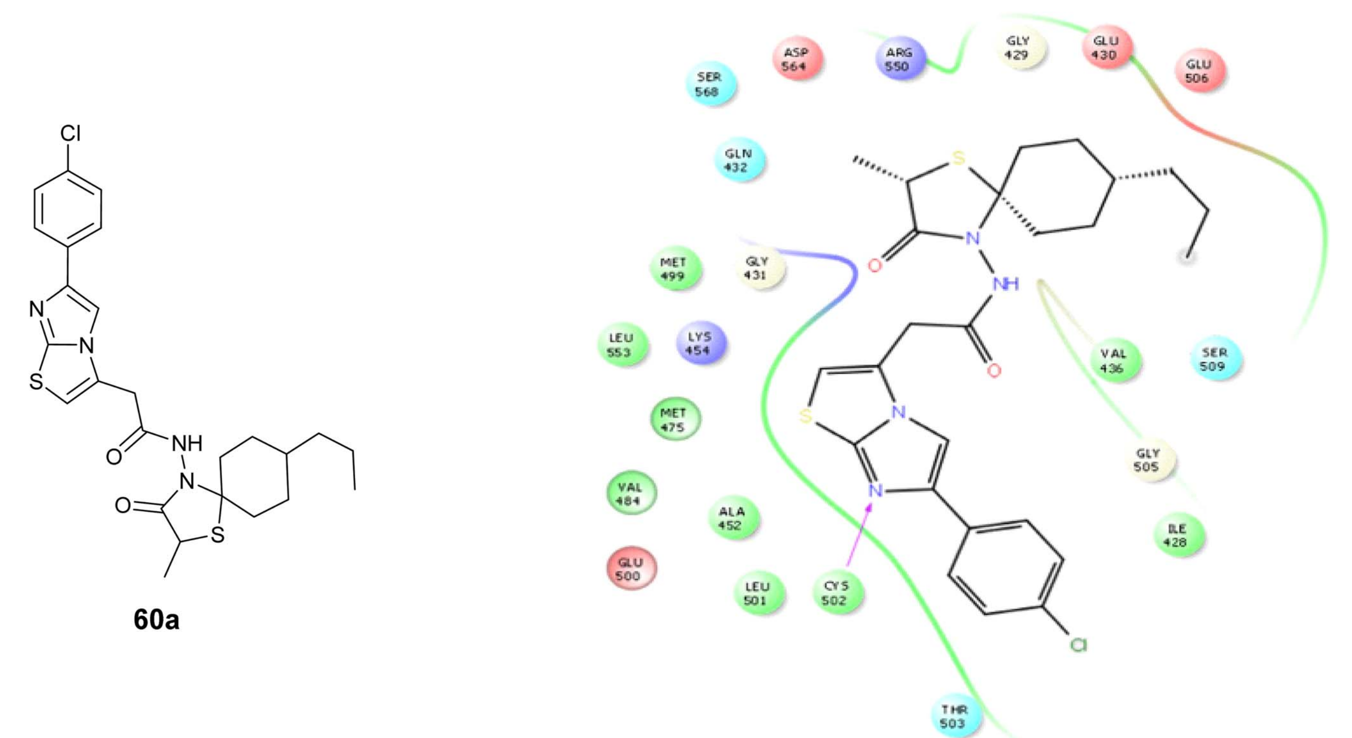

Fig. 31 Molecular modeling for compound **60a** with focal adhesion mont (FAK).

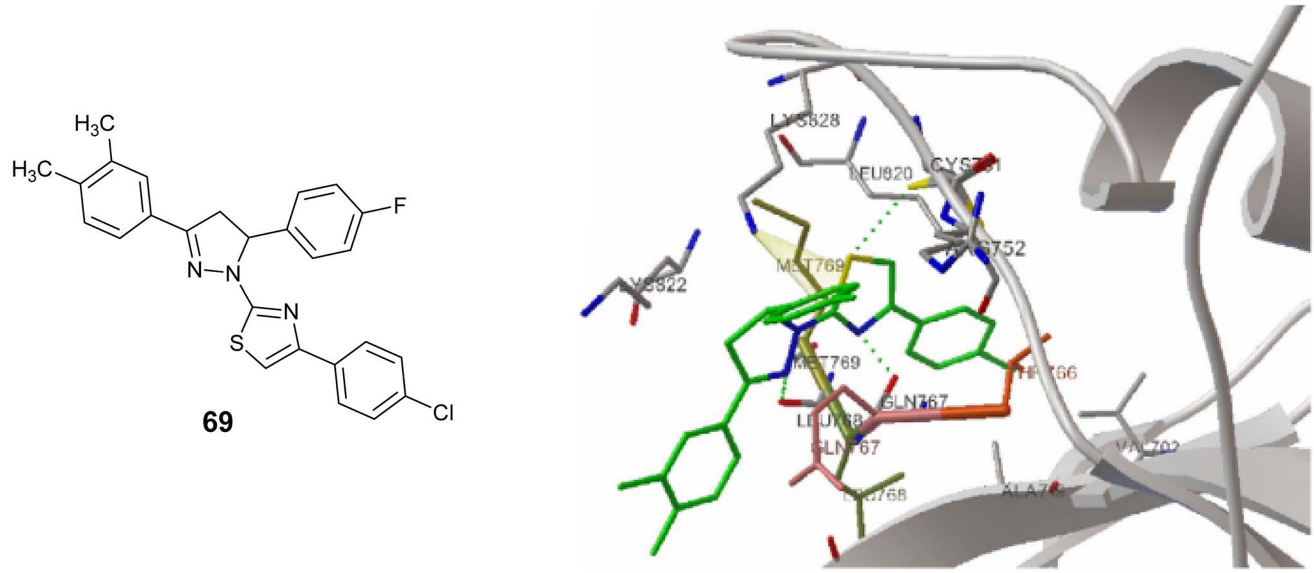

Fig. 32 Molecular docking modeling of compound **69** with EGFR Masse.

The study of the molecular docking aimed to elucidate the interaction between compound **46** and c-Met protein (PDB code 3LQ8). As illustrated in Fig. 30, the results demonstrated the establishment of two hydrogen bonds: the first bond formed between the nitrogen atom of the quinoline and the Met1160 residue, while the second bond was formed through the interaction of the carbonyl oxygen atom of the urea moiety with Asp1222. Furthermore, a π–π interaction was noted between the phenyl ring and Phe1223. Both the π–π and hydrogen bond interactions played a significant role in stabilizing the conformation of the ligand–protein complex.[85]

Moreover, compound **60a** underwent molecular docking analysis against Focal Adhesion Kinase (FAK), utilizing the PDB code 2ETM, Fig. 31. The findings revealed that Compound **60a** exhibited a more favorable docking score in comparison to the other tested compounds. Furthermore, it demonstrated effective interaction with the target by establishing hydrogen bonds with Cysteine 502 of FAK.[101]

In addition, Compound **69** was analyzed for its molecular docking properties (Fig. 32), revealing a favorable binding affinity to the EGFR kinase (PDB code 1fgk). The results indicated the formation of three hydrogen bonds with the residues Leu768, Gln767, and Cys751. Additionally, the modeling suggested the presence of a π–cation interaction between the thiazole ring of compound **69** and the residue Lys828.[112]

7. Conclusion and future aspects

This review highlights the emerging opportunities in utilizing thiazole-based heterocyclic derivatives for their potential anticancer properties. The review underscores the diverse applications of thiazole scaffold compounds in the development of drugs for combating various types of cancer. Despite the significant progress made in the field of thiazole-containing compounds, further focused research efforts are necessary. Such as, the advancement of appropriate synthesis methodologies utilizing green chemistry principles is crucial in propelling the future development of thiazole-containing compounds. Also, an in-depth investigation into the pharmacodynamic and pharmacokinetic characteristics of identified potent compounds with potential anticancer properties. Another appealing feature involves conducting research on the identification and isolation of thiazole-containing compounds that are naturally found in plants and marine organism. Finally, the findings of this analysis suggest that thiazole-derived compounds have potential as inhibitors of various enzyme targets and metabolic pathways. Further exploration into the potential adverse effects of thiazole-containing compounds represents a promising avenue for future scientific inquiry. The creation of enhanced analogues with improved efficacy, pharmacokinetics, and reduced side effects would represent a significant advancement in the field with potential benefits for human health and well-being.

Data availability

All the data supporting this review article have been included in the manuscript.

Author contributions

Conceptualization, M. S. E., A. S.; data curation, M. S. E., H. A. A. I., A. F. K.; formal analysis, A. S., H. A. A. I., A. F. K.; funding acquisition, M. S. E.; investigation, M. S. E., H. A. A. I., A. F. K.; methodology, A. S., resources, M. S. E., H. A. A. I., A. F. K., A. S.; validation, A. S.; visualization, A. S.; writing – original draft preparation, A. S.; writing – review and editing, M. S. E., H. A. A. I., A. F. K. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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