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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.

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## 1. Introduction

Heterocyclic chemistry is currently receiving increased focus due to its classification of molecules that have been utilized in medicinal chemistry applications.<sup>1–3</sup> 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.<sup>4,5</sup> 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,<sup>6</sup> 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.<sup>7</sup> For example, Cyclotheonaeallazole A (1) and Oriamide (2) are cyclic peptides containing thiazolyl propenoic acid that have been found in the marine sponge *Theonella* sp.<sup>8,9</sup> Apratoxin A (3), which is derived from *Lyngbya majuscula*, is

a well-known marine product with anticancer properties.<sup>10,11</sup> Dendroamide A (4), obtained from the cyanobacterium *Stigonema dendroideum fremy*, is used in the treatment of tumors that develop resistance.<sup>12</sup> Argyrin A (5), a cyclic peptide from the myxobacterium *Archangium gephyra*, is known for its strong anti-tumor effects,<sup>13</sup> Fig. 1.

Furthermore, thiazole derivatives, including vitamin B1 (6), are naturally present in various foods and marine sources *e.g.* 7a–c and 8.<sup>14</sup> 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,<sup>15</sup> 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.<sup>16</sup> It functions as a significant pharmacophore core with extensive pharmaceutical applications, including carbonic anhydrase inhibitory, anti-malarial, antiparasitic, anti-SARS-CoV-2, antimicrobial, anti-inflammatory, and anticancer activities.<sup>17–24</sup> 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.<sup>25</sup> 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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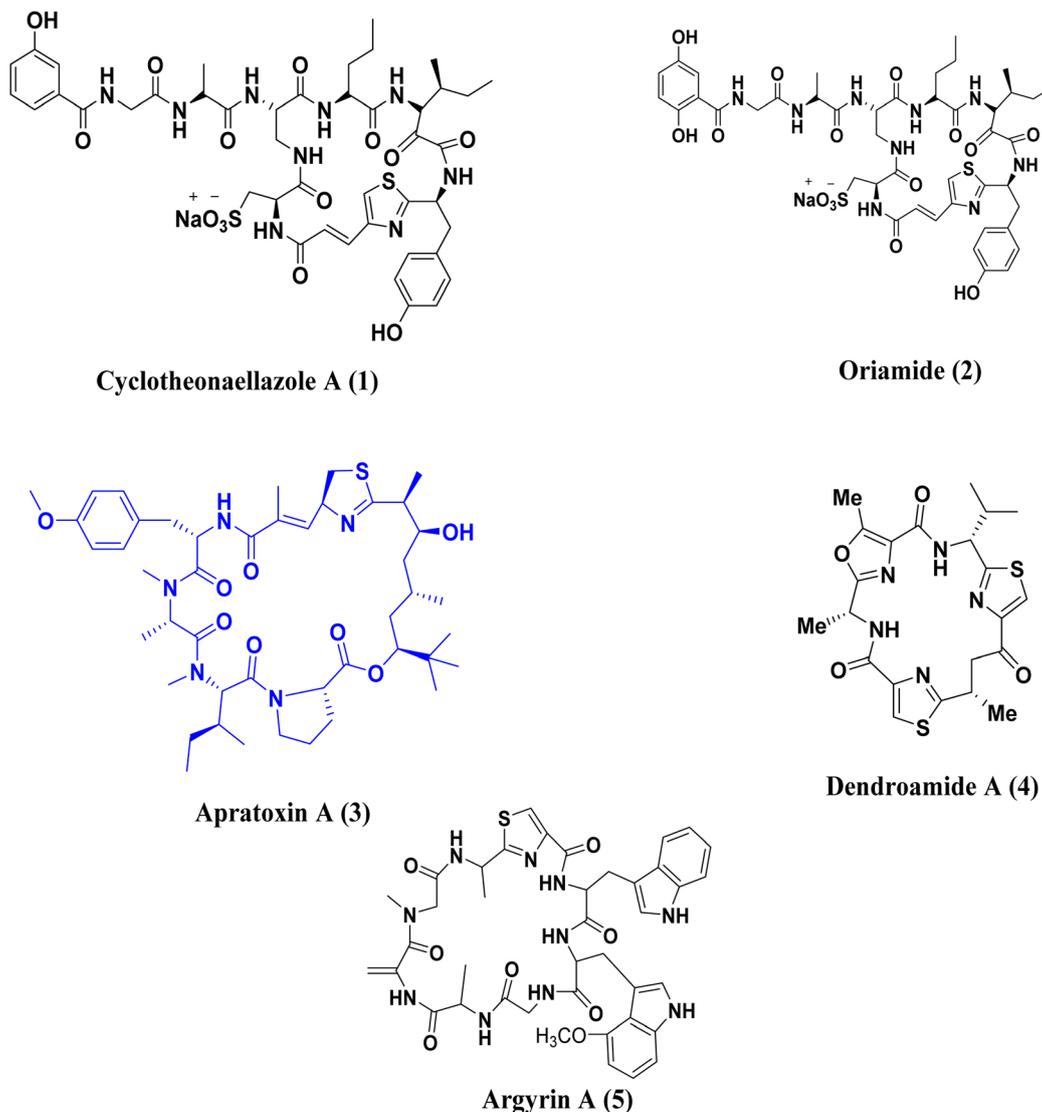



Fig. 1 Various natural compounds containing thiazole ring.

such as Vosaroxin (9),<sup>26</sup> Dabrafenib (10),<sup>27</sup> patellamide A (11),<sup>26–28</sup> dasatinib (12), epothilones (13), ixabepilone (14), tiazofurin (15), Kud 773 (16), and bleomycin (17)<sup>29</sup> 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.<sup>30</sup>

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  $6\pi$  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  $\pi$  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.<sup>31,32</sup> (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



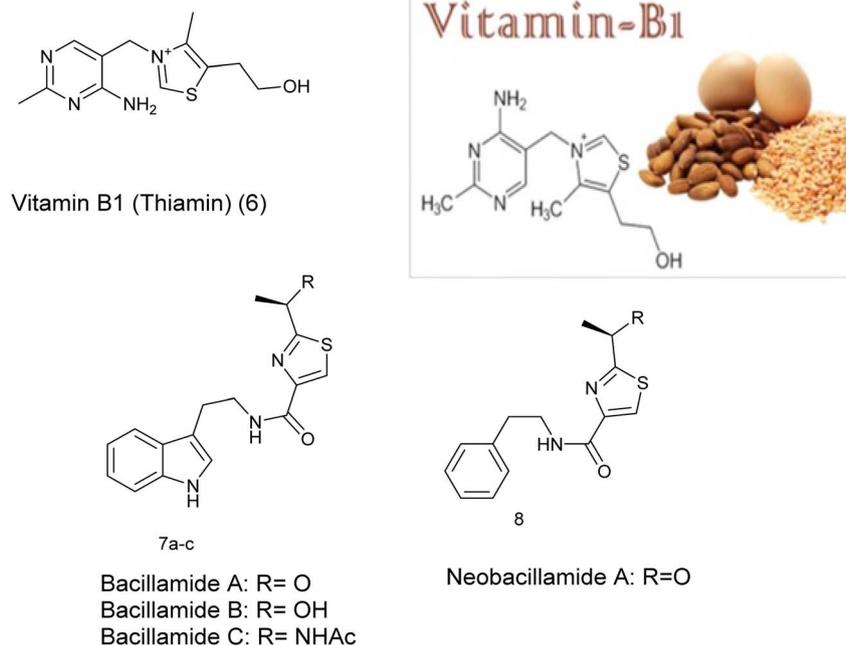


Fig. 2 Thiazole ring present in many foods and marine source.

widely used technique for the synthesis of thiazole rings. The procedure involves cyclizing  $\alpha$ -halocarbonyl compounds with thioamide or thiourea to form thiazole.<sup>33</sup> Earlier, historical syntheses of thiazole derivatives have been listed previously in many reviews<sup>15,16,34–36</sup> 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%.<sup>37</sup>

**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).<sup>38</sup>

Moreover, the application of  $\text{Fe}_3\text{O}_4$  and  $\text{SiO}_2$ -bipyridine- $\text{CuCl}_2$  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.<sup>39</sup>

**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).<sup>40</sup>

**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.<sup>41</sup>

**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  $\text{K}_2\text{CO}_3$  as a catalyst, resulting in the formation of 2-aminothiazoles within a matter of minutes and achieving excellent yields 87%.<sup>42</sup>

**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).<sup>43</sup>

## 3. Cancer disease

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



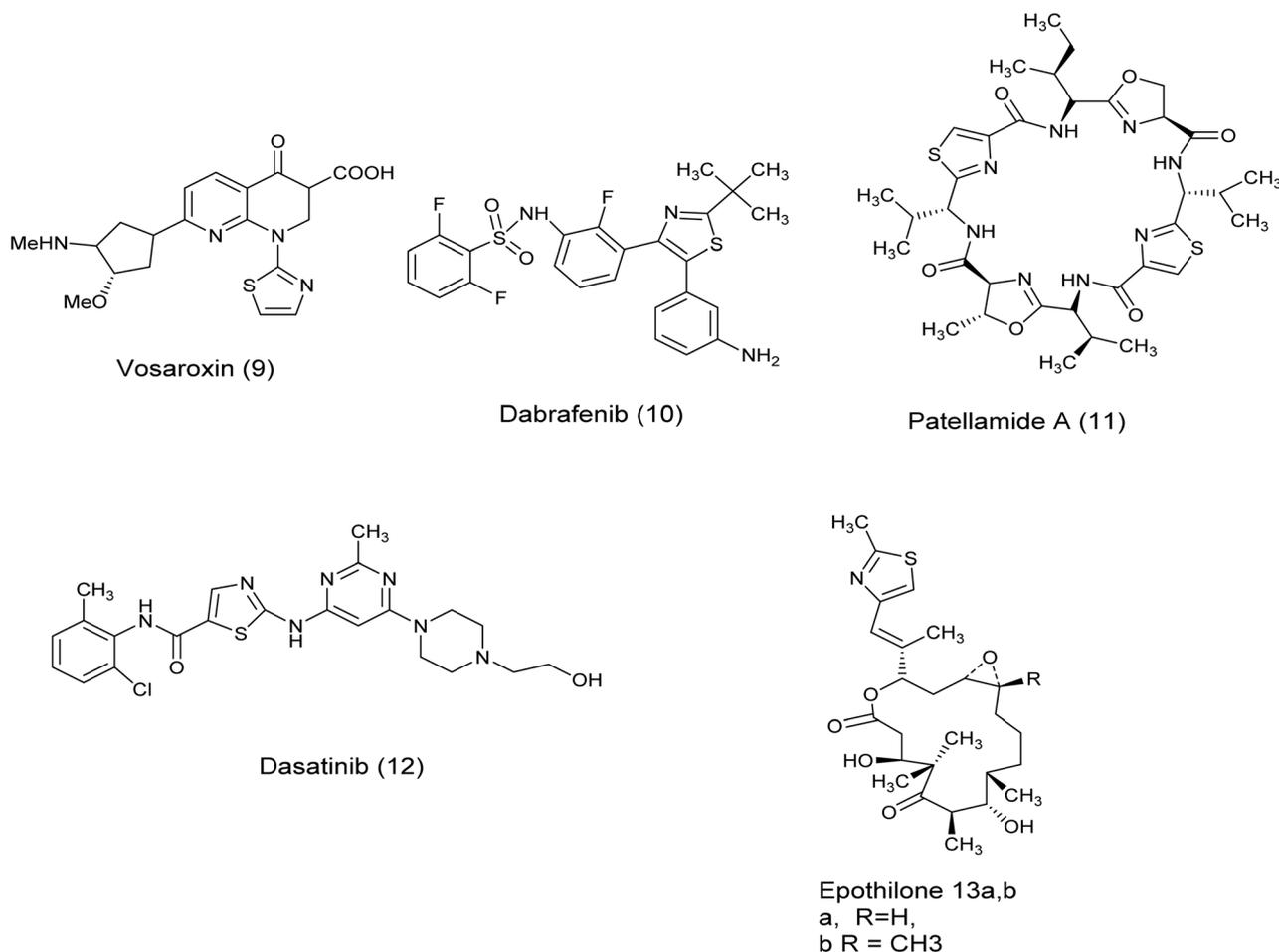


Fig. 3 Some clinically available thiazole-containing anti-cancer drugs.

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.<sup>44,45</sup> 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 anti-neoplastic 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.<sup>46</sup> In recent years, researchers have extensively investigated the role of dysregulated kinases, particularly in cancer and other human diseases.<sup>47,48</sup> 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).<sup>49</sup> 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



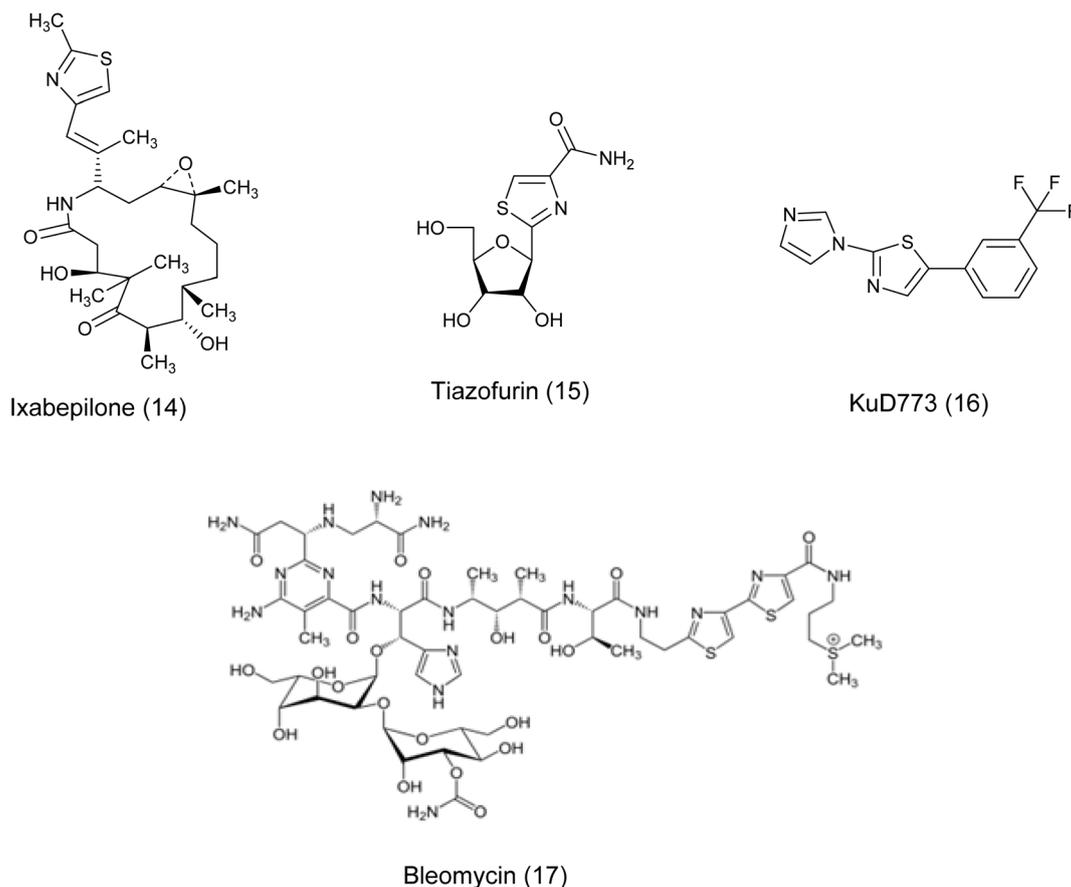


Fig. 4 Continuous: some clinically available thiazole-containing anti-cancer drugs.

Table 1 Physical properties of thiazole

Chemical formula	C <sub>3</sub> H <sub>3</sub> NS
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.<sup>50</sup>

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<sub>50</sub> 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.<sup>51</sup>



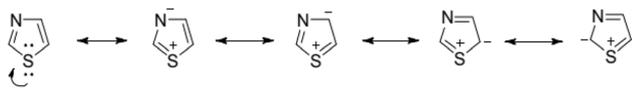


Fig. 5 The resonance structure of thiazole.

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 ( $IC_{50} = 0.30\text{--}0.45\ \mu\text{M}$ ). 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.<sup>52</sup>

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  $IC_{50}$  values varying from 9–290 nM.<sup>53</sup>

A novel set of inhibitors has been developed to target the PI3K $\beta$  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 PI3K $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , and mTOR (Mammalian target of rapamycin). Compound **22**, Fig. 9 exhibited the highest potency and selectivity against PI3Ks/mTOR, demonstrating potent activity PI3K $\beta$  with an  $IC_{50}$  value of 0.02  $\mu\text{M}$ . 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.<sup>54</sup>

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  $IC_{50}$ ;  $0.184 \pm 0.01$ ,  $0.719 \pm 0.04$ , and  $0.131 \pm 0.007$ , respectively.<sup>55</sup>

In 2024, Salem and colleagues introduced a new class of bis-thiazoles 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  $IC_{50}$  of 4.96 nM. Furthermore, the inhibitory efficacy of this compound was qualitatively assessed using western blotting,

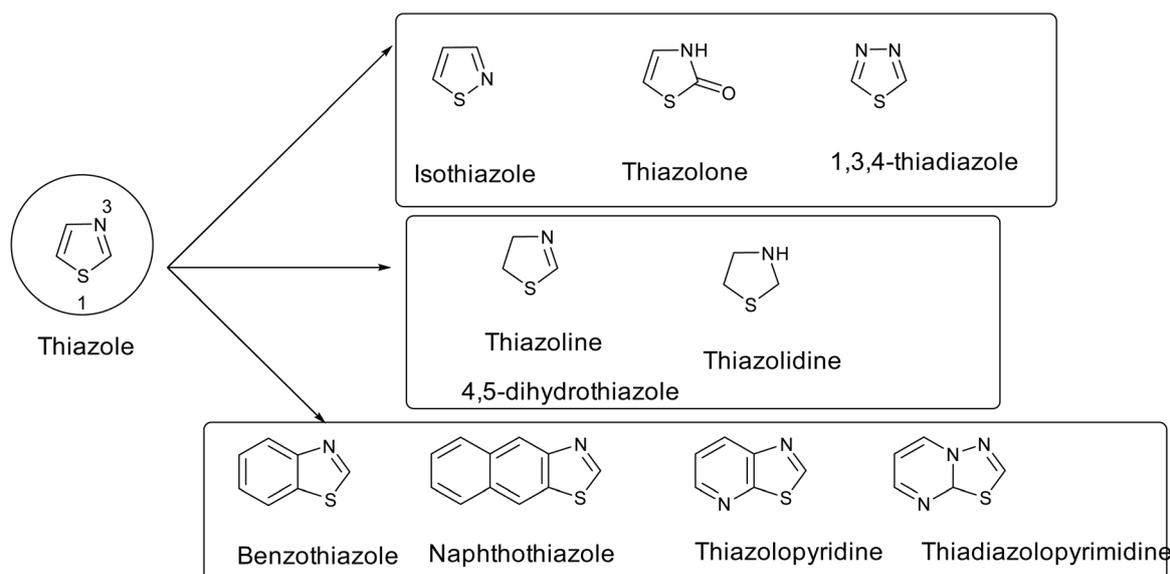
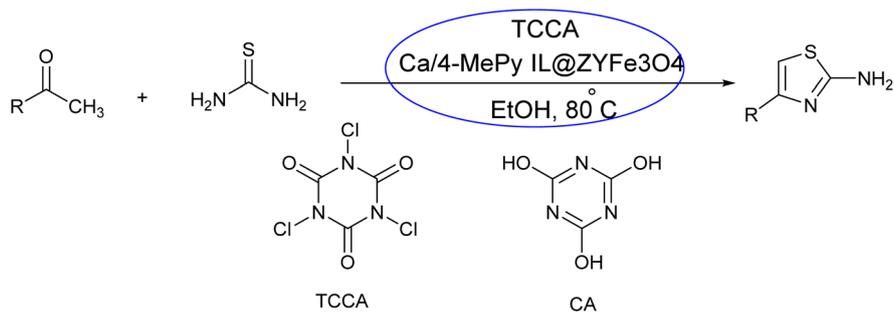


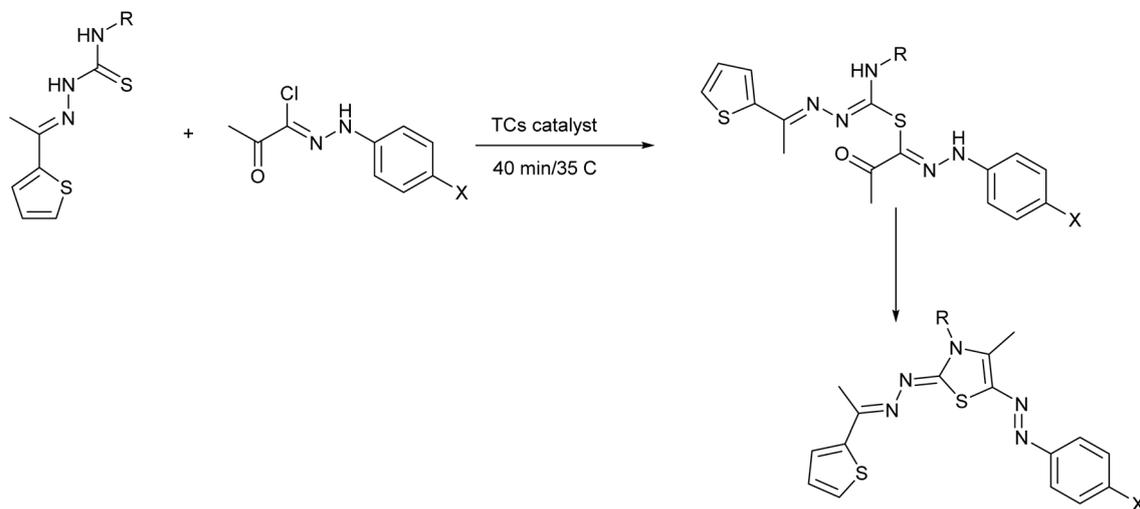
Fig. 6 Analogues of thiazole.



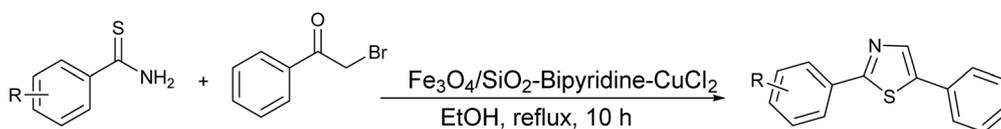




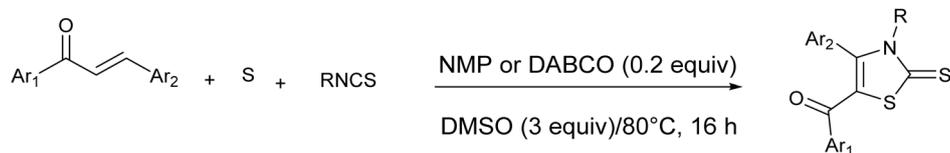
Scheme 1 Synthesis of 2-aminothiazole using catalytic nanosystem.



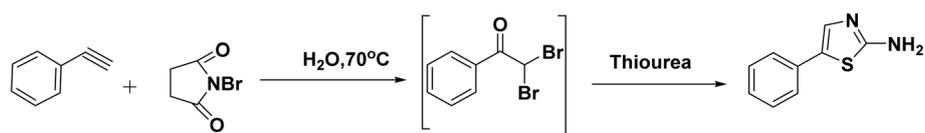
Scheme 2 Synthesis of thiazole derivatives by TCs catalyst.

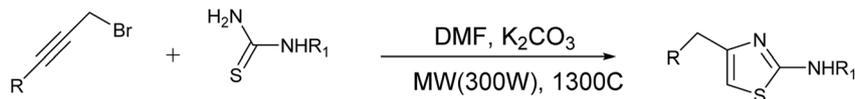


Scheme 3 Synthesis of thiazole derivatives by ecofriendly catalyst.

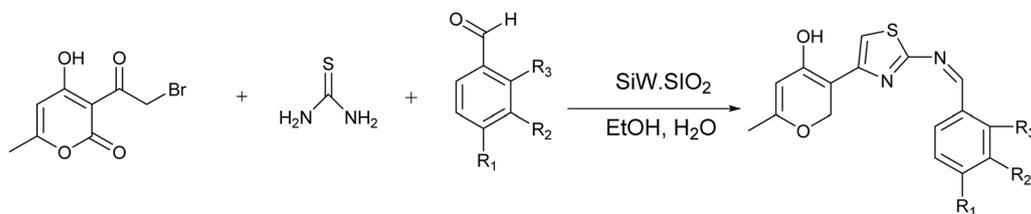


Scheme 4 Synthesis of thiazole derivative by three component reactants.

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.

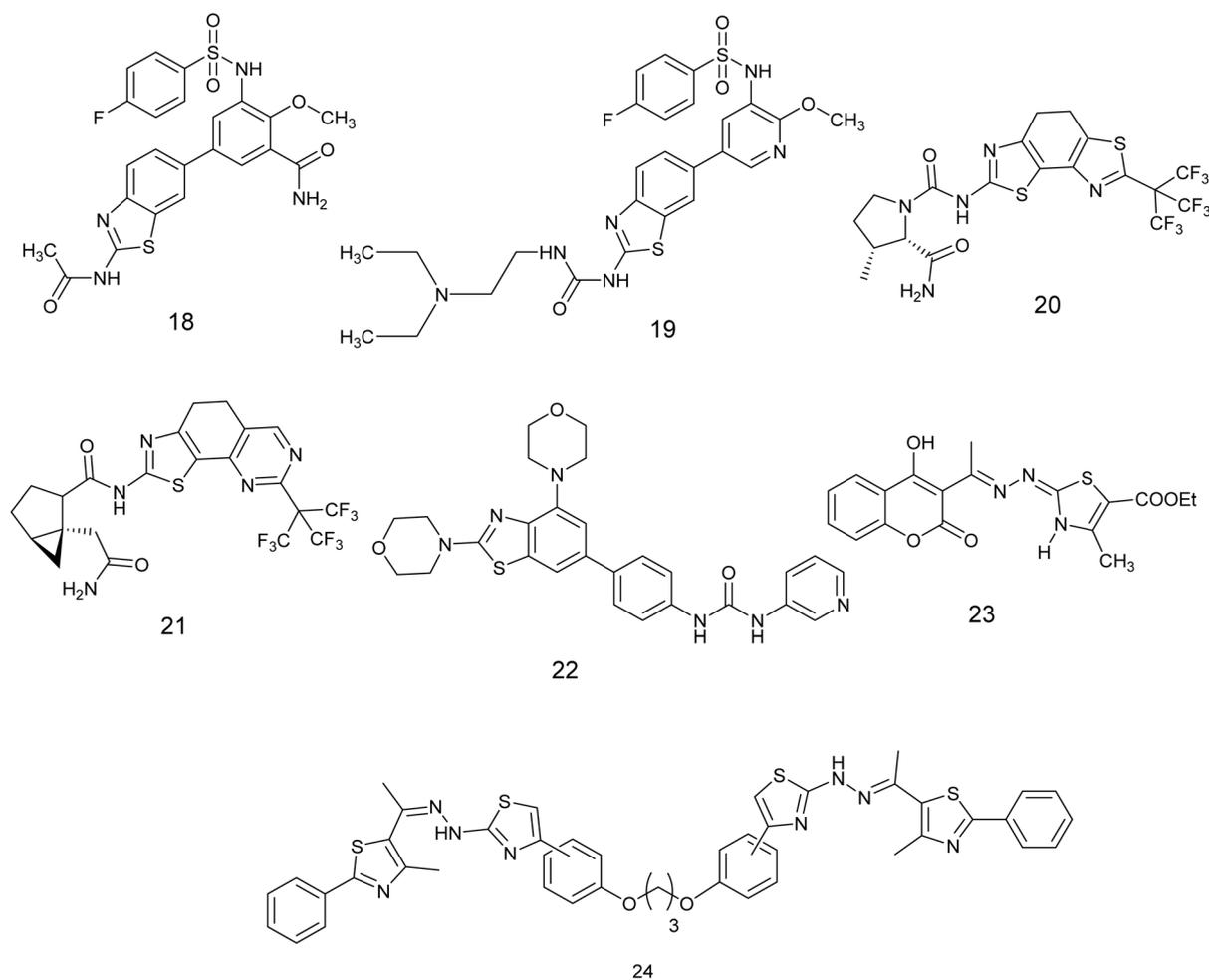


Fig. 9 Thiazole derivatives as PI3K/AKT/mTOR signaling pathway inhibitors (18–24).

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,



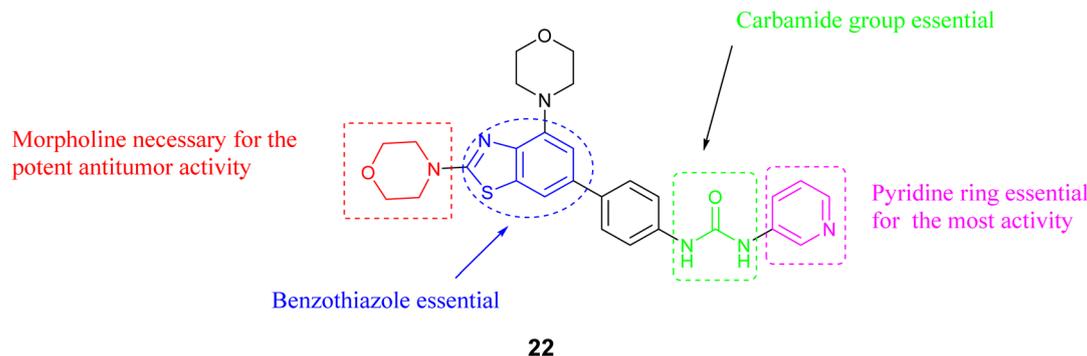


Fig. 10 SAR for compound 22.

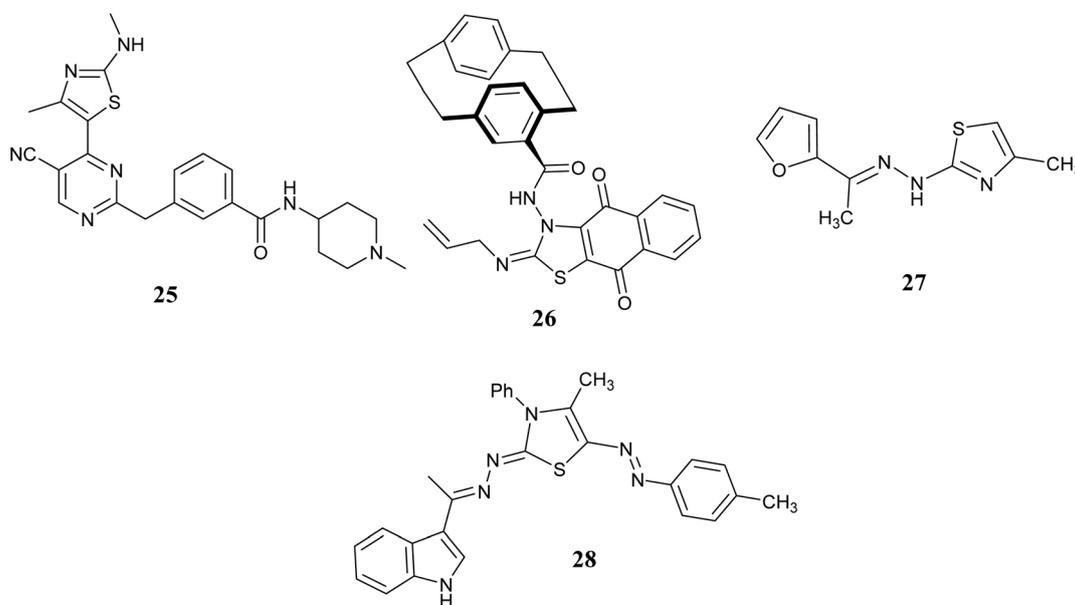


Fig. 11 Thiazole derivatives as cyclin-dependent kinases (CDKs) inhibitors (25–28).

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.<sup>61</sup>

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  $0.35 \pm 1.07 \mu\text{M}$ , in contrast to roscovitine's  $IC_{50}$  value of  $0.39 \pm 0.47 \mu\text{M}$ .<sup>62</sup>

**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.<sup>63,64</sup>

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



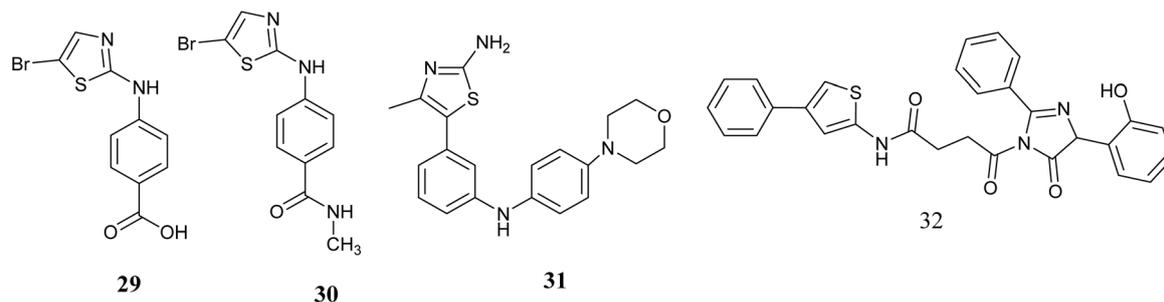


Fig. 12 Thiazole derivatives as Aurora kinase inhibitors(29–32).

experiments is hindered by limited cellular penetration, necessitating further refinement through chemical optimization.<sup>65</sup>

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.<sup>66</sup>

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.<sup>67</sup>

**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.<sup>68</sup>

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  $IC_{50} = 0.4 \mu\text{M}$ .<sup>69</sup>

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 GSK3 $\beta$ . The results revealed that compound 34, Fig. 13 demonstrated the highest efficacy in inhibiting dual kinases effects against CK2 and

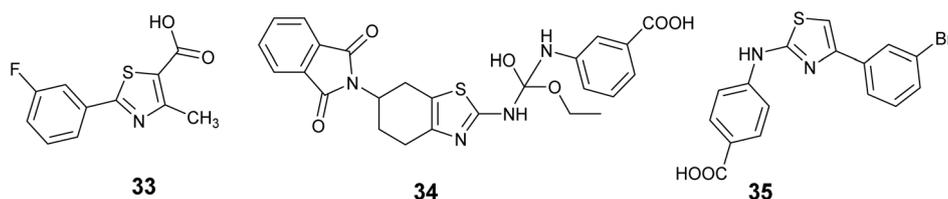


Fig. 13 Thiazole derivatives as casein kinases II (CK2) inhibitors (33–35).



GSK3 $\beta$  in the *in vitro* kinase inhibition assay, with IC<sub>50</sub> values of 1.9  $\pm$  0.05 and 0.67  $\pm$  0.27  $\mu$ M, respectively.<sup>70</sup>

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  $\alpha$ C helix and the flexible glycine-rich loop. Significantly, compound 35, Fig. 13 exhibited the most potent activity against purified CK2 $\alpha$ , as evidenced by an IC<sub>50</sub> value of 3.4  $\mu$ M, and displayed a favorable selectivity profile.<sup>71</sup>

**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.<sup>72</sup>

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<sub>50</sub> values of 0.16  $\mu$ M and 0.12  $\mu$ M, respectively, surpassing the efficacy of sorafenib. Compound 36 also exhibited strong bioactivity against V600E mutant B-RAF kinase IC<sub>50</sub> = 0.05  $\mu$ M. Furthermore, this compound triggered notable apoptosis in WM266.4 and MCF-7 cells in a manner that was dependent on the dosage administered.<sup>73</sup>

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  $\mu$ M compared to sorafenib. Compound 37, Fig. 14 demonstrated increased effectiveness against MCF-7 cells with a notably lower IC<sub>50</sub> value of 0.475  $\mu$ M compared to reference drug sorafenib with the value of IC<sub>50</sub>; 2.51  $\mu$ M. Additionally, Compound 37 exhibited similar potency to sorafenib when tested against wild-type B-RAF, CRAF (IC<sub>50</sub>; 19 nM), V600E-B-RAF (IC<sub>50</sub>; 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.<sup>74</sup>

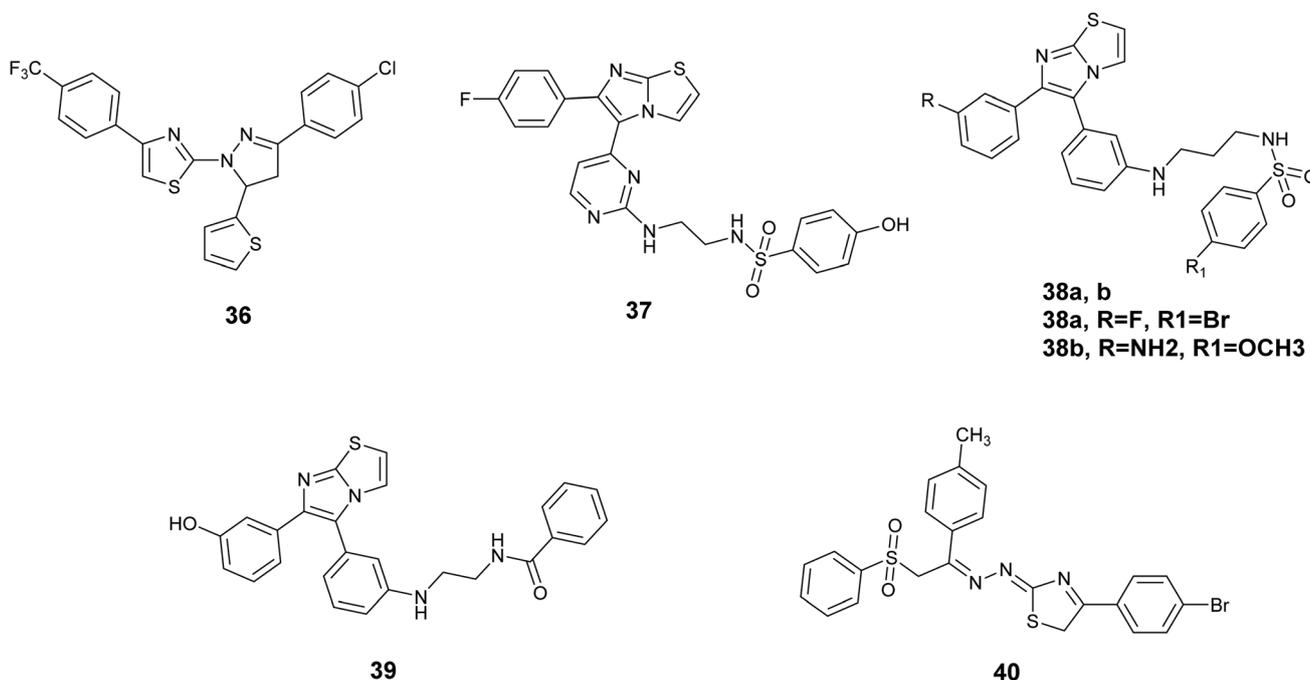


Fig. 14 Thiazole derivatives as B-RAF inhibitors (36–40).



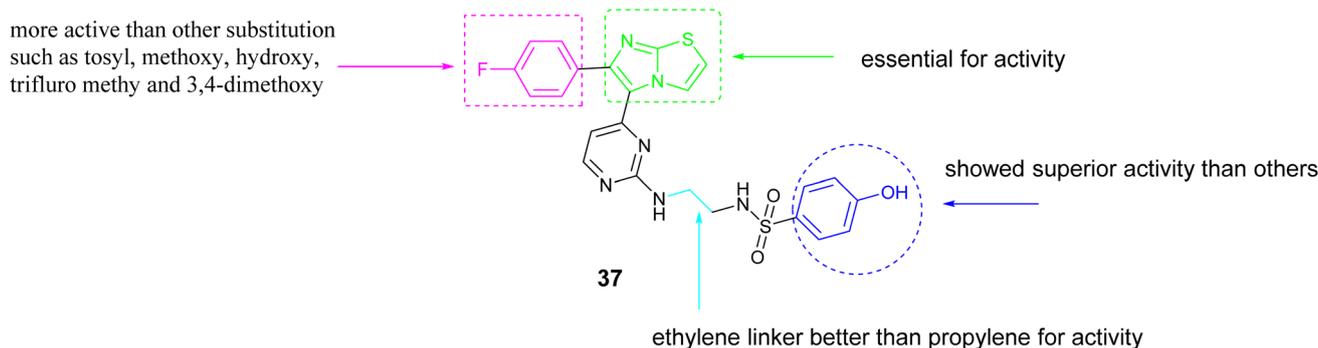


Fig. 15 SAR of compound 37.

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 WTBRFAF, V600EBRAF, and CRAF, revealing that Compound 38a, Fig. 14 exhibited the highest inhibitory effect on V600EBRAF at 9.30 nM.<sup>75</sup> 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.<sup>76</sup>

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 ( $IC_{50} = 0.18\text{--}0.59\ \mu\text{M}$ ) in comparison to the reference drug sorafenib ( $IC_{50}$  1.95–5.45  $\mu\text{M}$ ). Subsequent whole-cell kinase assays revealed that compound 39 effectively inhibited in-cell V600E-B-RAF kinase activity ( $IC_{50} = 0.19\ \mu\text{M}$ ). 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.<sup>77</sup>

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  $IC_{50}$ ;  $23.1 \pm 1.2\ \text{nM}$ , surpassing the standard drug dabrafenib which had an  $IC_{50}$  of  $47.2 \pm 2.5\ \text{nM}$ . 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  $\mu\text{M}$ , in comparison to dabrafenib ( $IC_{50} = 16.5 \pm 0.91\ \mu\text{M}$ ).<sup>78</sup>

**5.1.6. Inhibitors of glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ).** 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 GSK3 $\alpha$  and GSK3 $\beta$ . GSK-3 has been associated with a range of diseases, such as cancer, where the GSK-3 $\beta$  isoform is significantly involved in regulating activity of the nuclear factor (NF)  $\kappa\text{B}$  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.<sup>79,80</sup>

The thiazole compound AR-A014418 (41), Fig. 16 created by Astra Zeneca, functions as a selective and ATP-competitive inhibitor of GSK3 $\beta$ . 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  $\beta$ -amyloid-induced neurodegeneration.<sup>81</sup>

Shivaprakasam and colleagues (2019) conducted a study on the structural optimization of acylaminopyridines to develop highly effective and specific inhibitors of GSK-3 $\beta$ . 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-3 $\beta$ , with an  $IC_{50}$  value of  $0.29 \pm 0.01\ \text{nM}$ , 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  $1.1 \pm 0.1\ \text{nM}$ . 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  $30\ \text{mg}\ \text{kg}^{-1}$  as a nano-suspension to LaFera 3xTg-C57BL6 male mice.<sup>82</sup>

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,



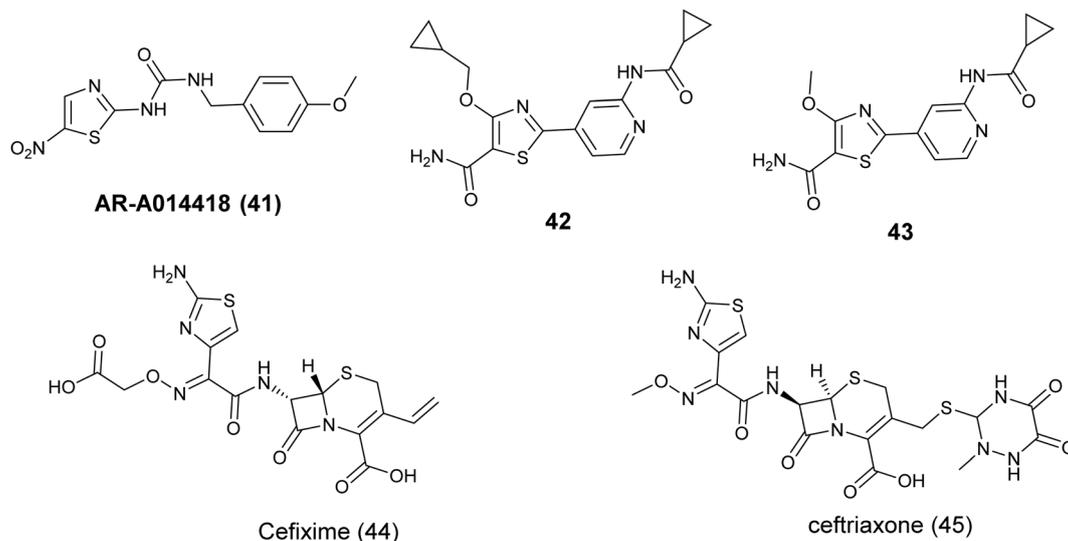


Fig. 16 Thiazole derivatives as Glycogen synthase kinase 3 (GSK-3) inhibitors (41–45).

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  $2.55 \mu\text{M}$ .<sup>83</sup>

## 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/ $\beta$ -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.<sup>84</sup>

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  $0.18 \mu\text{M}$  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 ( $IC_{50} = 17.6 \text{ nM}$ ).<sup>85</sup>

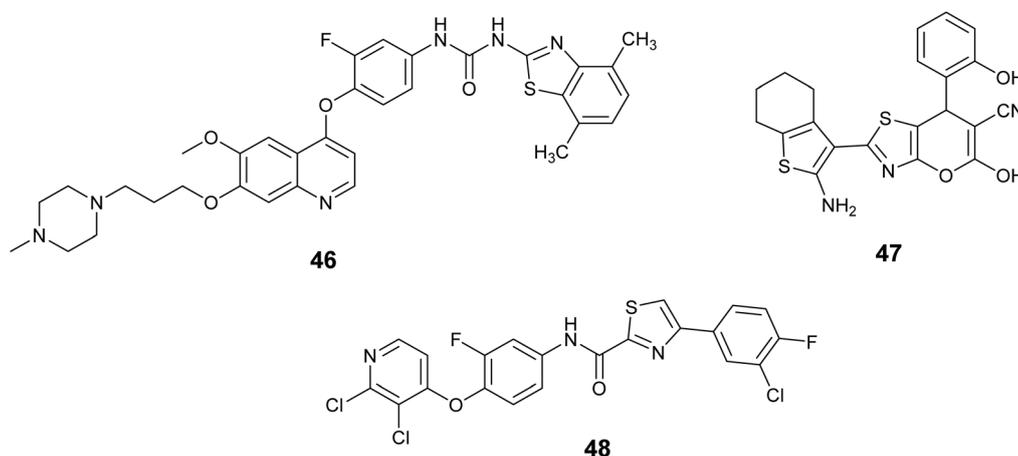


Fig. 17 Thiazole derivatives as c-MET inhibitors (46–48).



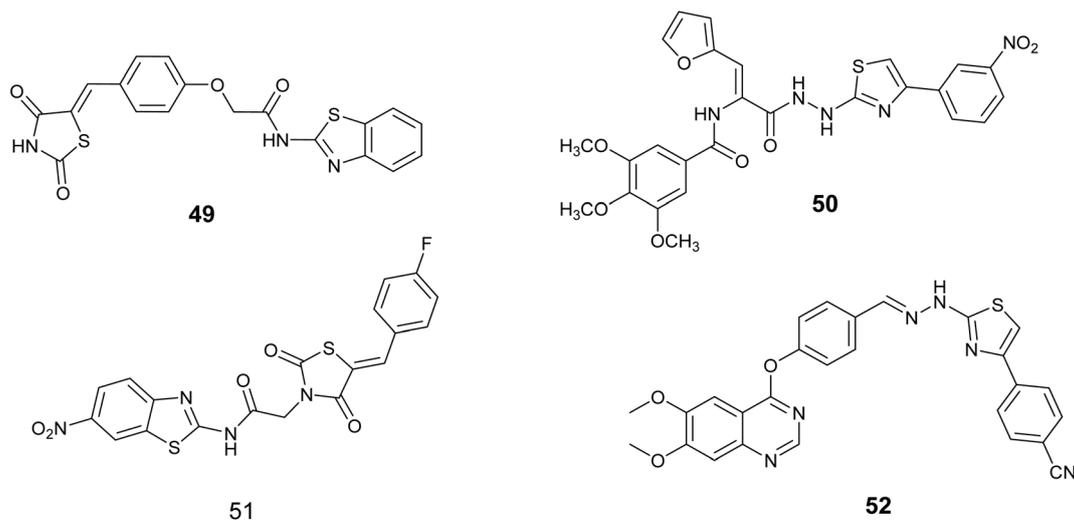


Fig. 18 Thiazole derivatives as Vascular endothelial growth factor receptor (VEGFR) inhibitors (49–52).

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).<sup>86</sup>

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.<sup>87</sup>

**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.<sup>88</sup>

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  $0.5 \mu\text{M}$ .<sup>89</sup>

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  $1.21 \pm 0.09 \mu\text{M}$ . 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 carbonyl 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.<sup>90</sup>

A novel series of compounds derived from amino-benzothiazole 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  $7.92 \mu\text{M}$  against the respective cell lines, while also displaying favorable safety characteristics against noncancer WI-38 cells. Compound 51 significantly inhibited S phase cell proliferation



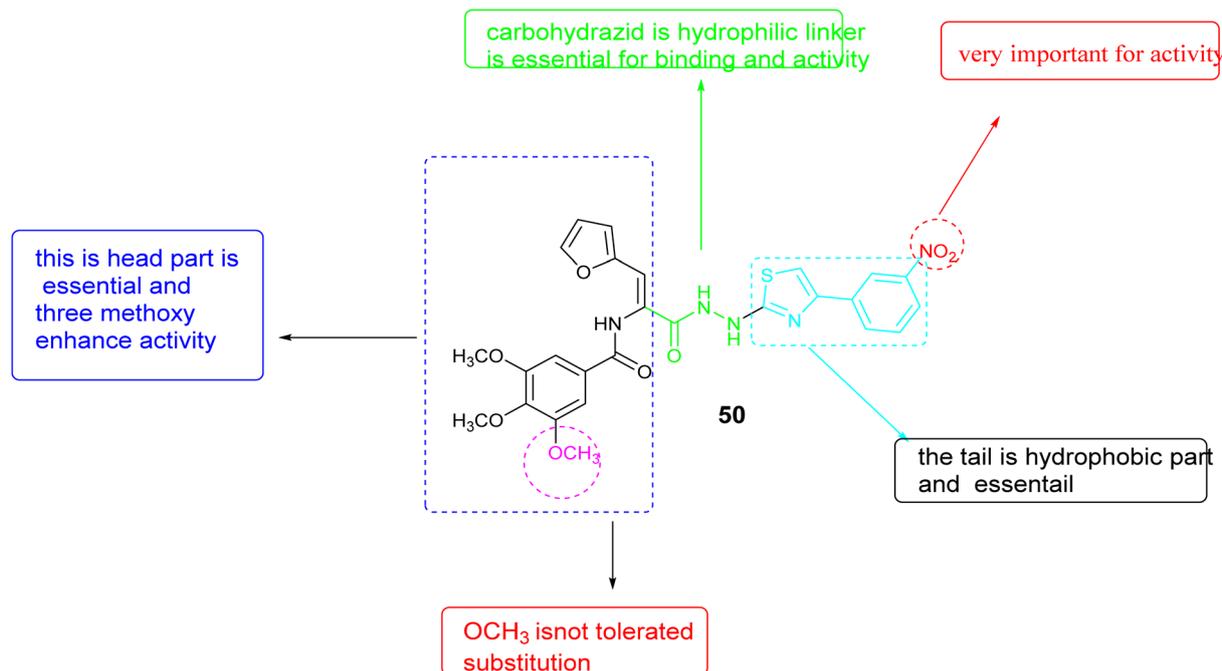


Fig. 19 SAR for compound 50.

in MCF-7 cells as determined by flow cytometry. Further analysis revealed that compound 51, with an IC<sub>50</sub> value of 91 nanometers, was the most effective inhibitor of VEGFR-2.<sup>91</sup>

In 2024, Sandor and colleagues introduced a new set of quinazoline-thiazole hybrid compounds with potential anti-proliferative and anti-angiogenic agents. The majority of these compounds exhibited enhanced antiproliferative activity (IC<sub>50</sub> = 1.83–4.24 μM) against HepG2 cells compared to sorafenib (IC<sub>50</sub> = 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<sup>−1</sup>), which closely approximated the value for sorafenib (−69.39 ± 3.63 kcal mol<sup>−1</sup>).<sup>92</sup>

**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.<sup>93</sup>

Z. Liu and colleagues introduced a novel series of 2-(thiazol-2-amino)-4-arylamino-pyrimidines 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<sub>50</sub> = 24.1 nM). Furthermore, derivative 53 dose-dependently inhibited ALK phosphorylation and its related signaling pathways.<sup>94</sup>

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<sub>50</sub> value of 0.8 nM in contrast to 80 nM for Crizotinib. Additionally, compound 55 demonstrated high potency against ROS1 with a K<sub>i</sub> 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<sub>50</sub> of 6.6 nM.<sup>95</sup>

**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



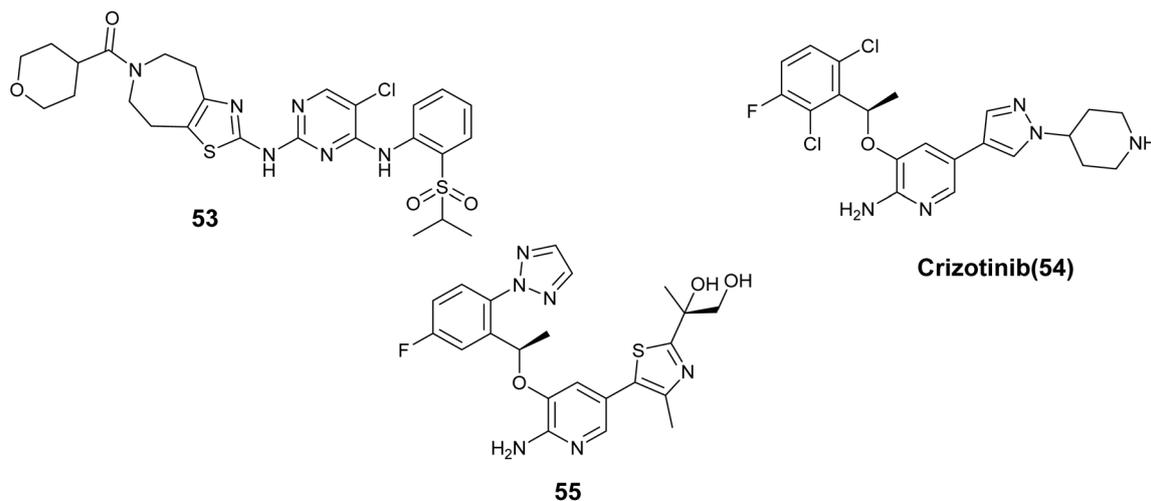


Fig. 20 Thiazole derivatives as anaplastic lymphoma kinase (ALK) inhibitors (53–55).

for treating people with AML that has mutations in FLT3, demonstrating promising clinical outcomes in this patient population.<sup>96</sup>

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.<sup>97</sup> Furthermore, a set of imidazo-thiazole 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  $\mu$ M and 0.022  $\mu$ M, respectively.<sup>98</sup>

**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.<sup>99</sup>

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. BJK-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. BJK-03-025(58) is a useful chemical tool for evaluating biological processes related to FAK.<sup>100</sup>

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  $4.83 \pm 0.28$   $\mu$ M 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

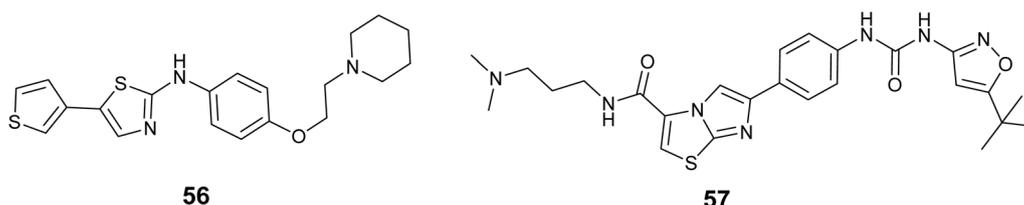


Fig. 21 Thiazole derivatives as FMS-like tyrosine kinase 3 (FLT3) inhibitors (56 and 57).

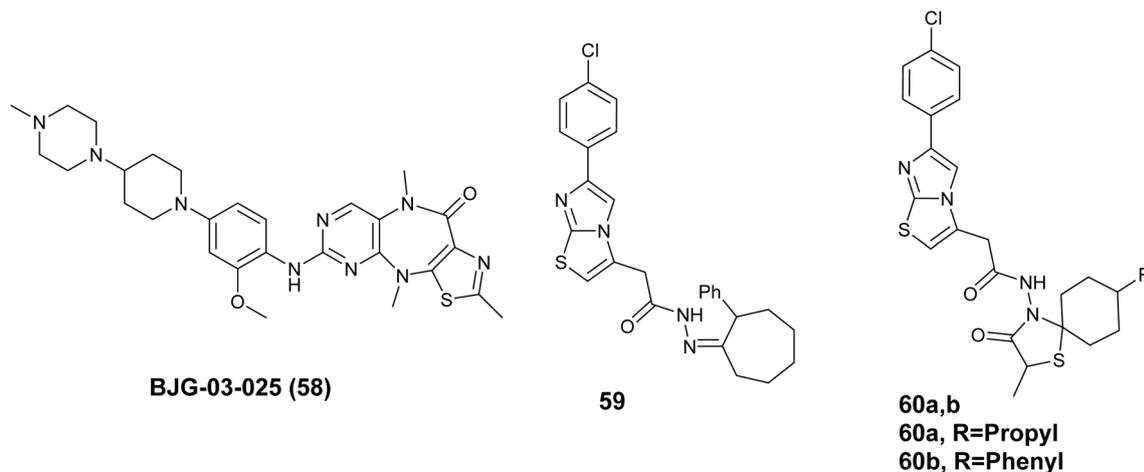


Fig. 22 Thiazole derivatives as focal adhesion kinase (FAK) inhibitors (58–60a–b).

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  $72.54 \pm 3.6\%$ .<sup>101</sup>

#### 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.<sup>102</sup>

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.<sup>103</sup>

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 ( $IC_{50} = 170, 274, \text{ and } 111 \text{ nM}$ , 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.<sup>104</sup>

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

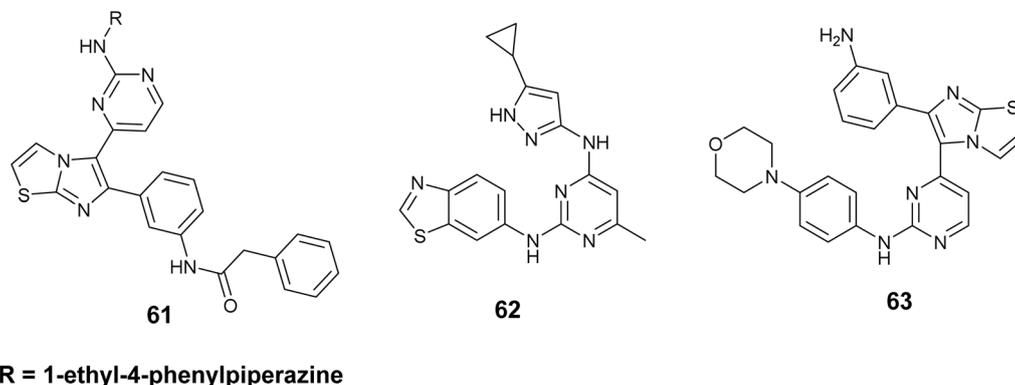


Fig. 23 Thiazole derivatives as insulin-like growth factor type 1 receptor (IGF-1R) (61–63).



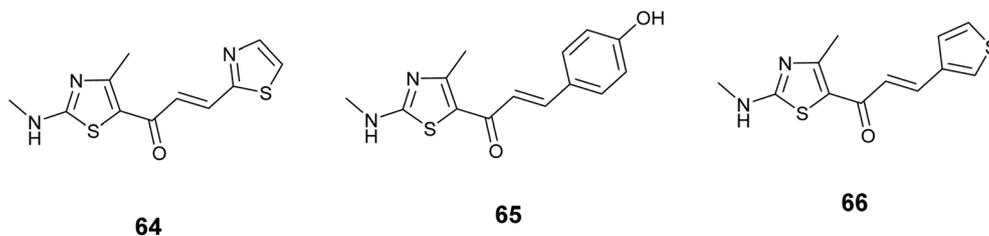


Fig. 24 Thiazole derivatives as Janus kinase (JAK) inhibitors (64–66).

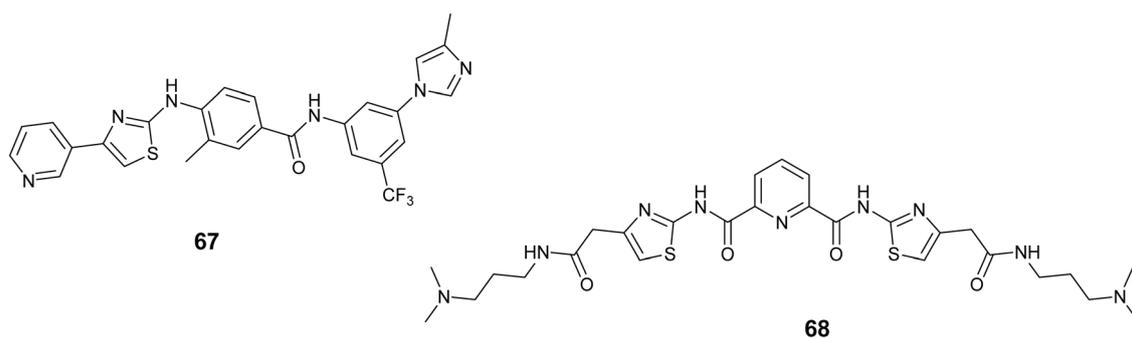


Fig. 25 Thiazole derivatives as KIT inhibitors (67 and 68).

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

**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.<sup>106</sup>

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

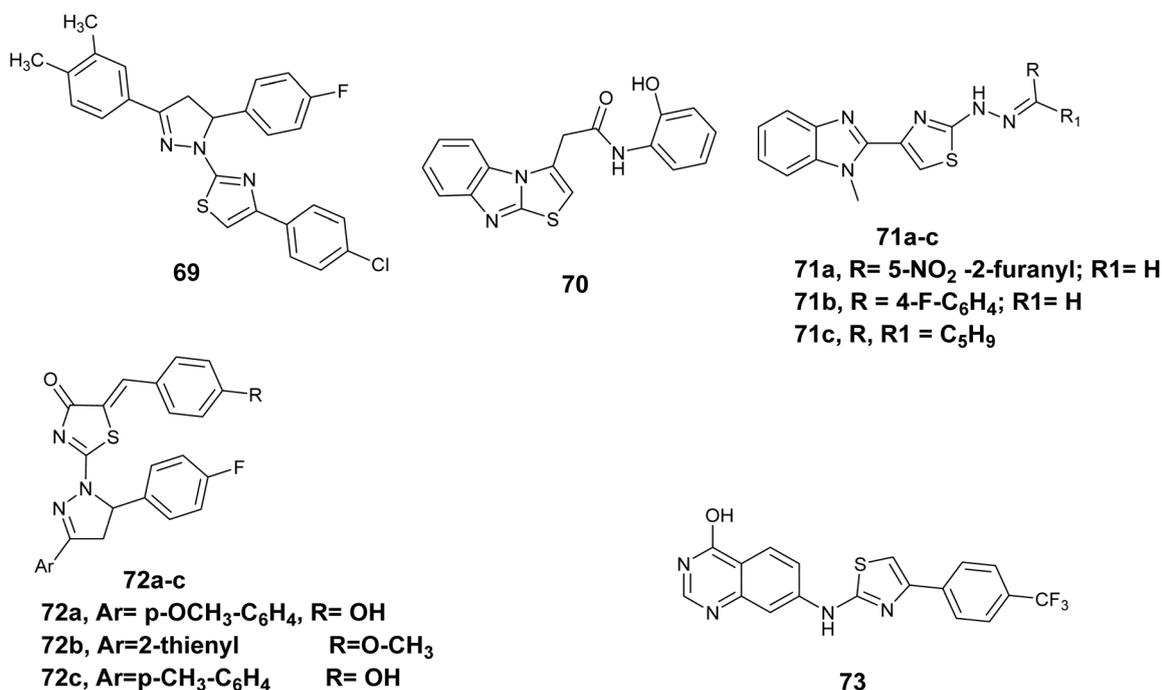


Fig. 26 Thiazole derivatives as epidermal growth factor receptor (EGFR) inhibitors (69–73).



Table 2 Activities of the target compounds

	Compounds	Activity values of IC <sub>50</sub>	
<b>Serine/threonine thiazole-based kinase inhibitors</b>			
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
Aurora kinase inhibitors	28	0.35 μM	
	29	79 nM	
Inhibitors of the enzyme casein kinases II (CK2)	30	140 nM	
	31	K <sub>i</sub> = 8.0 & 9.2 nM	
	32	ND	
	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	
Inhibitors of glycogen synthase kinase 3β	40	23.1 nM	
	41	100 nM	
	42	0.29 nM	
	43	1.1 nM	
	44	2.55 μM	
	45	7.35 μM	
<b>Inhibitors of kinases that are based on tyrosine thiazole</b>			
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%
Anaplastic lymphoma kinase (ALK) inhibitors	51	91 nM	
	52	ND	
	53	24.1 nM	
	54	11–24 nM	
	55	0.8 nM	
FMS-like tyrosine kinase 3 (FLT3) inhibitors	56	22 nM	
Inhibitors of focal adhesion kinase (FAK)	57	0.022 μM	
	58	20 nM	
	59	Inhibition% = 68.71%	
Insulin-like growth factor type 1 receptor (IGF-1R)	60a	Inhibition% = 47.78%	
	60b	Inhibition% = 72.54%	
	61	41 nM	
Janus kinase (JAK) inhibitors	62	74 nM	
	63	52 nM	
	64	6.89 μM	
	65	8.04 μM	
KIT inhibitors	66	17.64 nM	
	67	56.0 nM & 20.0 nM	
Epidermal growth factor receptor (EGFR) inhibitors	68	DC <sub>50</sub> = 0.88 μM & a K <sub>d</sub> = 0.69 μM	
	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 <sub>50</sub>
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<sub>50</sub> = 6.89 ± 0.38 μM, while derivative **65** demonstrated strong effectiveness against tested cell A431, IC<sub>50</sub> = 8.04 ± 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<sub>50</sub> = 17.64 ± 1.68 nM), and derivative **65**, Fig. 24 displayed the most significant activity targeting EGFR (IC<sub>50</sub> = 28.46 ± 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.<sup>107</sup>

**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<sup>108</sup>

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<sub>50</sub> 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.<sup>109</sup>

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<sub>50</sub> = 0.88 μM and a K<sub>d</sub> = 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.<sup>110</sup>

**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).<sup>111</sup> 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<sub>50</sub> = 0.06 μM. Furthermore, Compound **69** showed notable inhibitory effects on the growth of MCF-7 cells in laboratory tests, with an IC<sub>50</sub> value of 0.07 μM, which is similar to the standard medication erlotinib (IC<sub>50</sub>; 0.02 μM). Molecular docking analysis revealed that Compound **69** formed three hydrogen bonds when bound to the EGFR kinase.<sup>112</sup>

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<sub>50</sub> = 0.42 μM, and also displayed significant activity toward EGFR with IC<sub>50</sub> = 55 nM. Additionally, these compounds showed negligible cellular toxicity towards human normal cell lines HL7702.<sup>113</sup>

In 2020, Srour and colleagues created a new set of compounds based on a combination of benzoimidazole 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<sub>50</sub> 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<sub>50</sub> value of 5.96 μM, in comparison to the IC<sub>50</sub> 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  $109.71 \pm 3.55$  nM and  $6.30 \pm 0.37$   $\mu$ M, 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

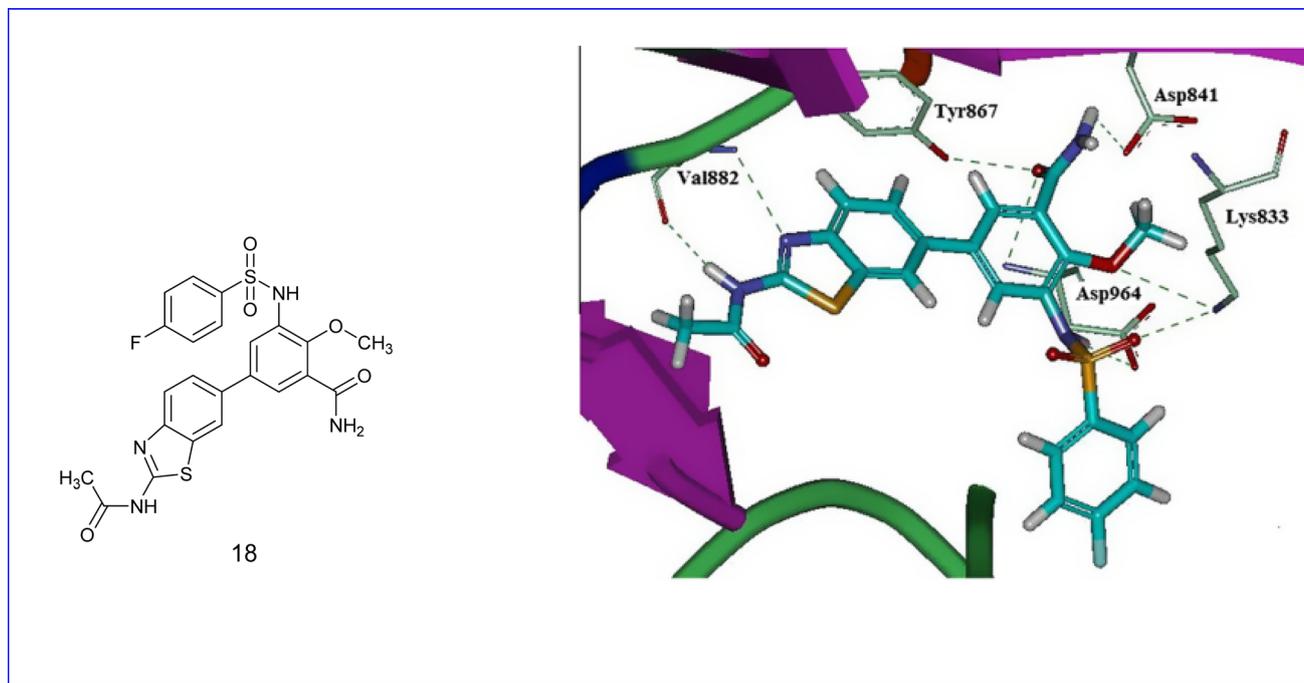


Fig. 27 Docking mode of compound **18** with PI3Kc.

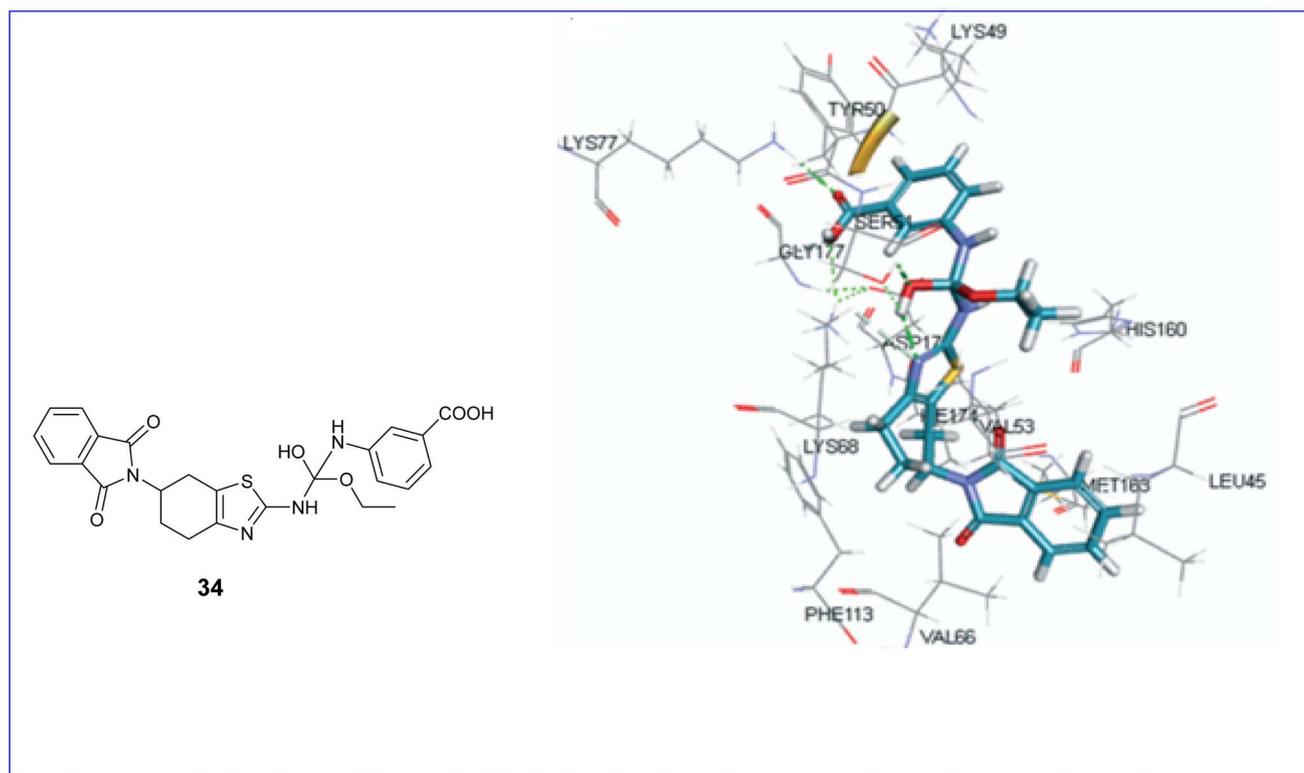


Fig. 28 Molecular docking of compound **34** with CK2 protein.



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

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  $\mu$ M, while T-47D cells the value of  $IC_{50}$ ; 0.88 and 0.75  $\mu$ M, 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.<sup>115</sup>

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  $IC_{50}$  values of  $2.86 \pm 0.31$ ,  $5.91 \pm 0.45$ , and  $14.79 \pm 1.03$   $\mu$ M, 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).<sup>116</sup>

## 6. Molecular modeling studies

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

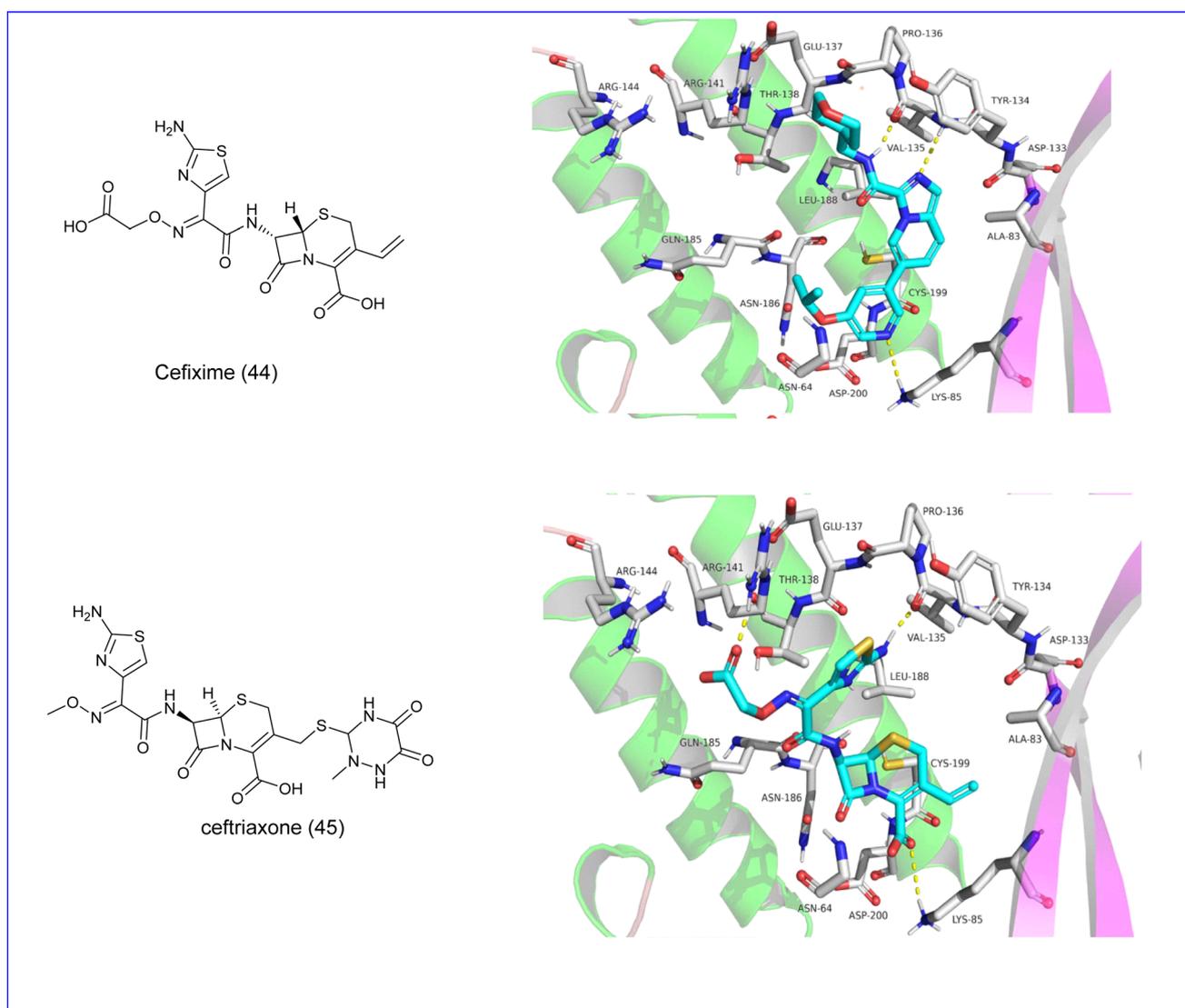


Fig. 29 (A) Molecular docking of cefixime (44) GSK3 protein. (B) Molecular docking of ceftriaxone (45) with GSKS protein.



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.<sup>51</sup>

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.<sup>70</sup>

Furthermore, the two compounds, cefixime (**44**) and ceftriaxone (**45**), underwent molecular docking analysis against GSK3 $\beta$  (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.<sup>83</sup>

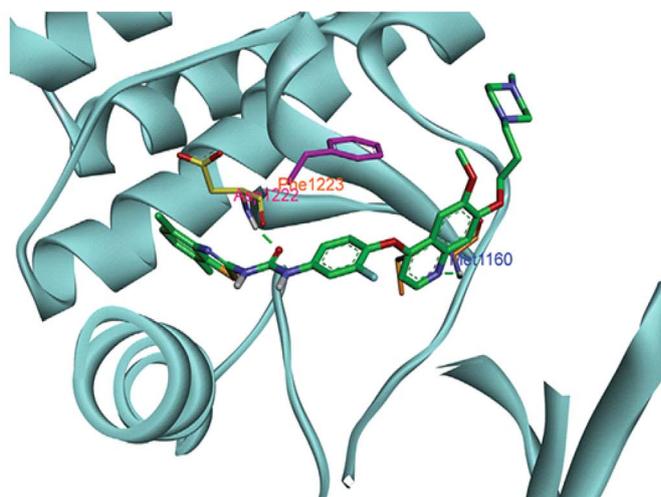
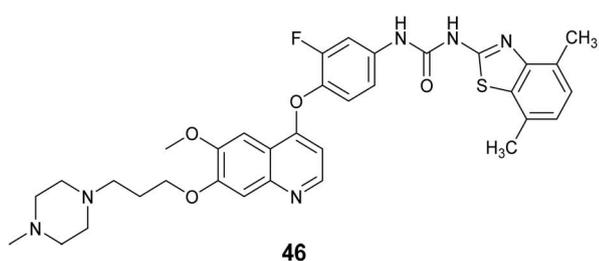


Fig. 30 The active site of c-Met interacting with compound **46**.

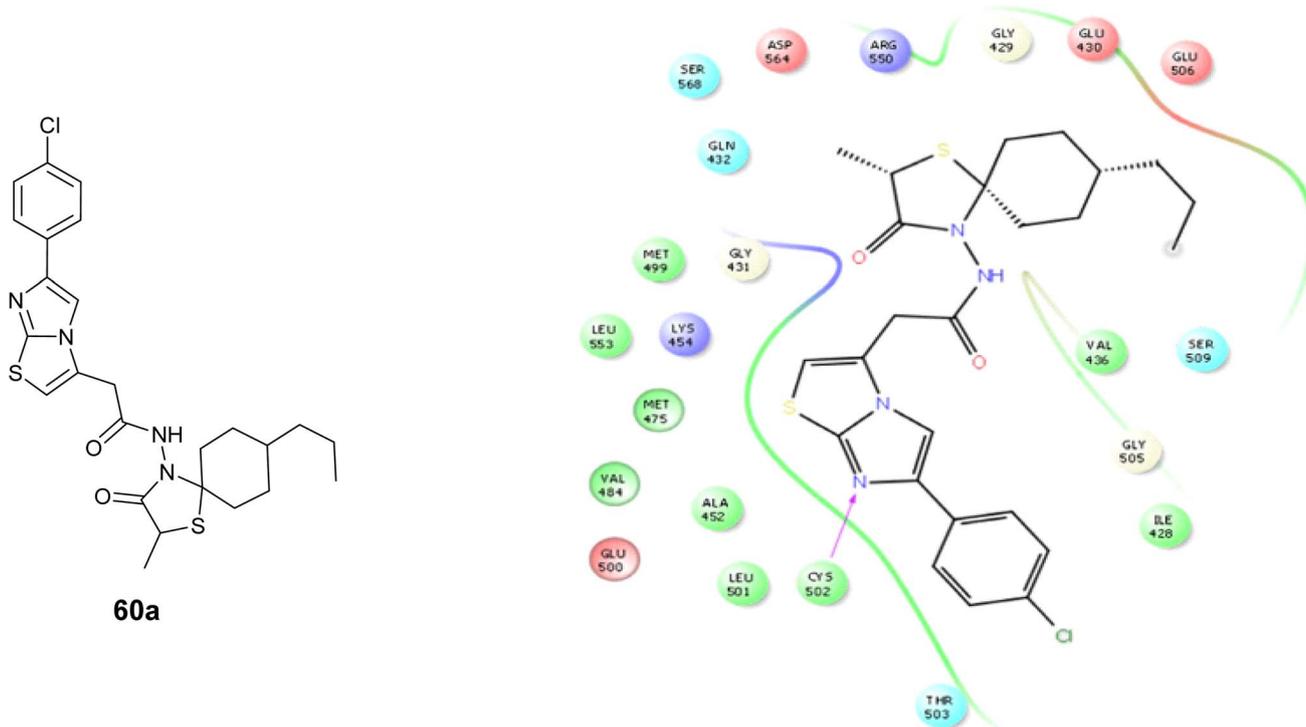


Fig. 31 Molecular modeling for compound **60a** with focal adhesion mont (FAK).





## 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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