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Review Article

Selective targeting of p38 MAP kinase and beyond: Triazole-based heterocycles in anticancer drug discovery

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ABSTRACT

The p38 MAP kinase signaling pathway is pivotal in modulating cellular responses to stress stimuli, inflammatory cytokines, and growth factors. The dysregulation of this system strongly contributes to cancer growth, metastasis, inflammation, and therapy resistance, rendering p38 MAP kinase a compelling molecular target for anticancer drug development. In recent years, triazole-based scaffolds, particularly 1,2,3- and 1,2,4-triazoles, have gained significant attention due to their favorable physicochemical properties, metabolic stability, and ability to interact effectively with kinase active sites. This review encapsulates current progress in triazole-based p38 MAP kinase inhibitors, emphasizes insights into SAR, and examines new perspectives for enhancing these scaffolds to generate selective and clinically efficacious anticancer drugs. SAR analysis reveals that strategic substitution, heterocyclic hybridization, and incorporation of electron-withdrawing or lipophilic groups significantly enhance biological activity. Several compounds demonstrated potent inhibitory effects in the submicromolar range, while others exhibited dual or multi-target activity against key oncogenic pathways, including EGFR, AKT, ERK, and GSK3. Notably, fused triazole hybrids and multi-target-directed ligands showed improved anticancer activity across various cancer cell lines. Despite promising *in vitro* results, challenges such as isoform selectivity, toxicity, and pharmacokinetic limitations remain to be addressed. Overall, triazole-based hybrids represent a promising class of compounds for anticancer drug development, and further structure-guided optimization and *in vivo* studies are essential to facilitate their clinical translation.

Keywords:
MAP kinase; 1,2,3-triazole; 1,2,4-triazole; Anticancer agents; Structure-activity relationship (SAR); Kinase inhibitors.

1. INTRODUCTION

The p38 MAP kinase (p38 Mitogen-Activated Protein Kinase) pathway is essential for modulating cellular responses to cytokines and stress. The overactivation of this pathway is associated with inflammatory disorders, such as rheumatoid arthritis, and cancer; thus, the development of small-molecule inhibitors is a significant focus on research[1].

The p38 MAP kinase are a family of serine/threonine protein kinases. The p38 kinase family comprises four major isoforms: p38α (MAPK14), p38β (MAPK11), p38γ (MAPK12/ERK6), and p38δ (MAPK13/SAPK4). p38α and p38β exhibit significant resemblance, with approximately 74% sequence homology, whereas p38γ and p38δ are more distantly related, with around 62% sequence identity. The genes encoding p38α and p38β are extensively expressed in multiple organs, with notable abundance in the heart and brain. Conversely, p38γ and p38δ exhibit a more selective distribution across tissues. p38γ is mostly located in skeletal muscle, while p38δ is chiefly expressed in organs including the kidneys, lungs, pancreas, testis, and small intestine [2]. The expression of p38γ can be induced during muscle differentiation and may also be modulated at various developmental stages.

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The p38 MAP kinase consists of two unique structural domains: an N-terminal domain comprising approximately 135 amino acids and a C-terminal domain consisting of around 225 amino acids. The N-terminal area is generally defined by β-sheet secondary structures, while the C-terminal section primarily comprises α-helical elements [3]. The catalytic active site is located at the junction of these two domains. The phosphorylation loop of p38 comprises 13 amino acid residues, extending from Leu-171 to Val-183, with protein activation facilitated by phosphorylation at two critical residues within this loop: threonine (Thr-180) and tyrosine (Tyr-182). Distinct p38 isoforms have changes in their three-dimensional structures, especially with the relative positioning of the N- and C-terminal domains, resulting in variants in size and shape of the ATP-binding pockets [4].

The p38 MAP kinase pathway is activated by cellular stress, inflammatory cytokines, and growth factors via a phosphorylation cascade that includes MAPKKK, MKK3/6, and p38 MAP kinase. Upon activation, p38 translocate to the nucleus, modulating transcription factors and downstream kinases, consequently impacting essential cellular processes like proliferation, apoptosis, inflammation, angiogenesis, metastasis, and drug resistance [5]. The dysregulation of this pathway greatly contributes to tumor emergence and progression (Figure 1). Among MAPKs, JNK, ERK1/2, and p38 are the most significantly implicated in cancer-associated signaling.

Beyond p38 MAP kinase, various signaling pathways are intricately linked to cancer progression, including EGFR, PI3K/AKT, RAS/RAF/MEK/ERK, VEGFR, and various kinase-mediated networks. The activation of EGFR triggers downstream signaling pathways that enhance cellular proliferation, survival, and resistance to apoptosis [6]. The PI3K/AKT pathway is crucial for controlling cell survival and metabolic adaptability, whereas ERK/ERK2 signaling controls proliferation, differentiation, and metastasis. Mutations in B-Raf result in the persistent stimulation of the MAP kinase pathway, thereby expediting tumor proliferation[7]. Furthermore, VEGFR-mediated signaling facilitates angiogenesis, hence promoting tumor vascularization and development. Enzymes like GSK3, Aurora kinase-1, ARK-1, and DNA topoisomerase-IIα play essential roles in cell cycle regulation, mitosis, and DNA replication; their dysregulation results in genomic instability and unregulated cell division [8]. These pathways collectively constitute an integrated network that facilitates tumor formation and ser ves as critical targets for anticancer therapy.

Diverse heterocyclic frameworks have been studied as p38 MAP kinase inhibitors and prospective anticancer drugs, functioning by inhibiting the p38 MAP kinase pathway and associated signalling pathways. Imidazole [9], quinazoline [10], indole [11], pyridine [12], indazole [13] and related compounds have garnered significant interest for their capacity to interact with the kinase active site and regulate enzymatic activity.

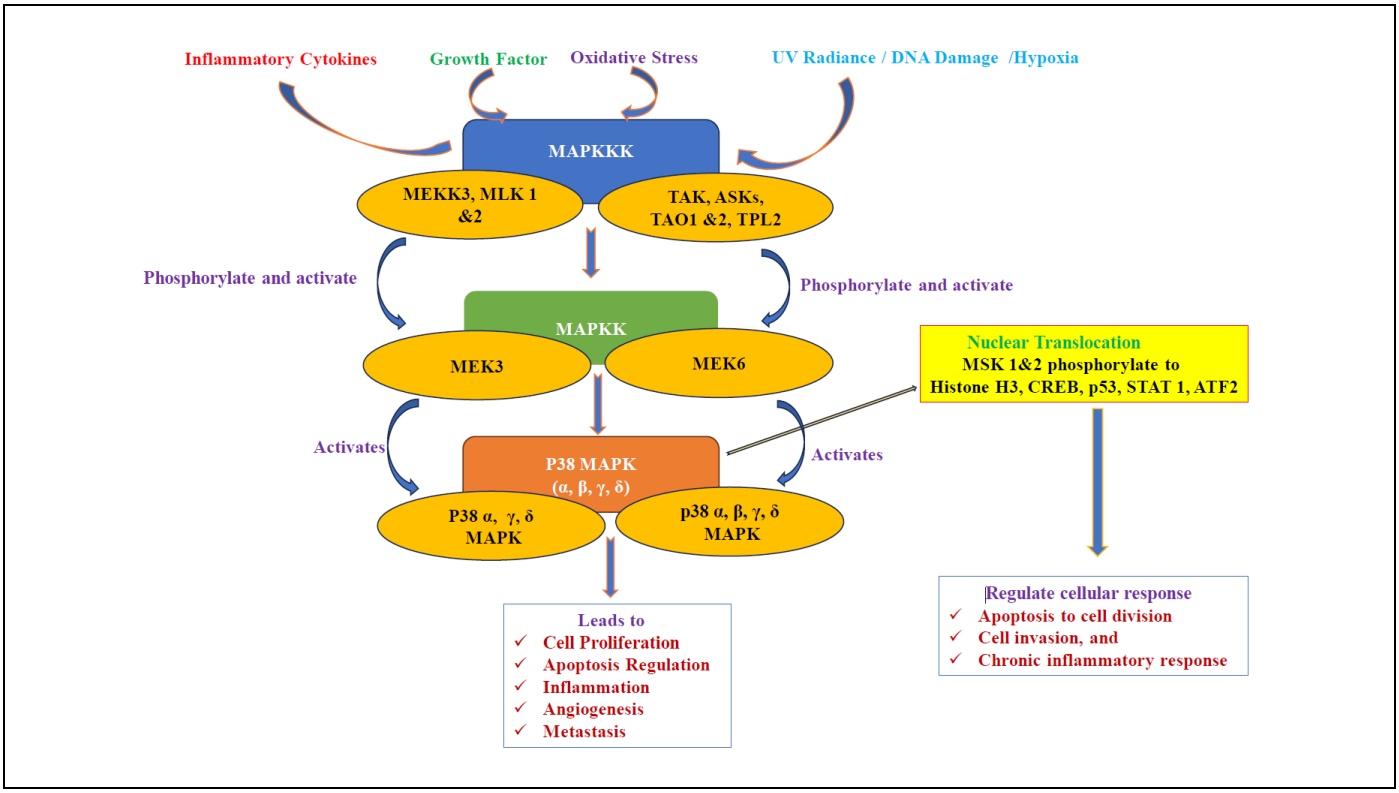


Figure 1. p38 MAP kinase signalling in cancer progression.

The triazole nucleus is a prominent and extensively researched heterocyclic compound, noted for its exceptional stability, diverse reactivity, and broad range of biological activities. Triazoles are five-membered aromatic rings composed of three nitrogen atoms, which impart distinctive physicochemical features, including robust hydrogen-bonding capacity, metabolic stability, and improved solubility. Triazole derivatives serve as crucial structural elements in various natural products and manufactured pharmaceuticals, significantly enhancing pharmacokinetic, pharmacodynamic and physicochemical characteristics. The triazole nucleus is a privileged heterocyclic scaffold widely recognized for its diverse pharmacological properties and extensive applications in medicinal chemistry. Triazole-containing compounds have been reported to exhibit a broad spectrum of biological activities [14-15], including antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, anticancer, antihypertensive, antimalarial, local anaesthetic, anxiolytic, antidepressant, antihistaminic, antioxidant, antitubercular, antiparkinsonian, and antidiabetic activities. The broad range of biological activities linked to triazole-containing compounds is mostly due to the electronic characteristics of the nitrogen atoms in the ring, which improve binding interactions with biological targets. The triazole nucleus is chemically stable, resistant to metabolic degradation, and able to generate stable complexes, rendering it very appropriates for drug creation.

Triazole rings, namely 1,2,3-triazoles and 1,2,4-triazoles, are preferred scaffolds in medicinal chemistry for the development of p38 MAP kinase inhibitors owing to their distinctive structural and electronic properties. Their significance can be elucidated through various essential characteristics. Triazoles demonstrate significant bioisosteric properties. They can proficiently replicate functional groups, such as amide bonds and other heterocyclic systems, enabling their substitution in therapeutic compounds without substantially modifying biological activity [16]. This alteration frequently promotes metabolic stability and increases binding affinity for the target enzyme. Furthermore, the presence of numerous nitrogen atoms within the triazole ring facilitates effective hydrogen bonding interactions. The nitrogen atoms serve as hydrogen bond acceptors and particularly engage with amino acid residues in the hinge region of the p38 MAP kinase enzyme, a crucial site for inhibitor binding. These interactions enhance the stability of the ligand–enzyme complex and augment selectivity. Additionally, triazoles have a notable dipole moment, facilitating appropriate molecular alignment inside the hydrophobic ATP-binding pocket of the enzyme. This polarity facilitates the molecules alignment in an advantageous conformation, enhancing non-covalent interactions such as van der Waals forces and electrostatic interactions. Collectively, these characteristics render triazole rings very appropriate pharmacophores for the development of effective and selective p38 MAP kinase inhibitors [17].

Triazole-based p38 MAP kinase inhibitors are classified as Type I or Type II inhibitors according to their binding mode and the enzyme's conformational state they affect. Type I inhibitors (ATP-competitive inhibitors) attach to the active conformation of p38 kinase and occupy the ATP-binding site [18]. In numerous molecules, the triazole ring is essential as it structurally resembles the adenine segment of ATP. This enables the molecule to form crucial hydrogen-bonding connections with residues in the enzyme's hinge region, notably with amino acids like Met109 [19]. These interactions stabilize the inhibitor within the catalytic pocket and augment binding affinity. Type II inhibitors (DFG-out inhibitors) are predominantly found among triazole compounds. These compounds interact with an inactive conformation of the kinase, wherein the Asp-Phe-Gly (DFG) motif assumes an outward orientation, thereby forming an extra hydrophobic pocket close to the ATP-binding site. In this binding strategy, the triazole moiety typically serves as a linker or a core pharmacophore that penetrates and occupies the allosteric pocket. These inhibitors typically interact with conserved residues such as Glu71 and Asp168, which are linked to the DFG motif and play a crucial role in preserving the enzyme's inactive state [20].

The novelty of the present review lies in its integrated examination of both 1,2,3- and 1,2,4-triazole-based hybrids developed as p38 MAP kinase inhibitors and related kinase-targeted anticancer agents. Particular emphasis is placed on recent advances in molecular hybridization strategies, SAR trends, kinase selectivity profiles, and multitarget mechanisms involving p38 MAP kinase and other oncogenic kinases, including EGFR, ERK, Aurora kinase A, GSK3β, and B-Raf. Furthermore, this review critically evaluates the structural determinants governing anticancer activity, identifies current limitations in the field, and highlights future directions for the rational design of more potent and selective triazole-based kinase inhibitors.

Various triazole derivatives have been reported to demonstrate considerable anticancer efficacy by targeting molecular pathways other than p38 MAP kinase.

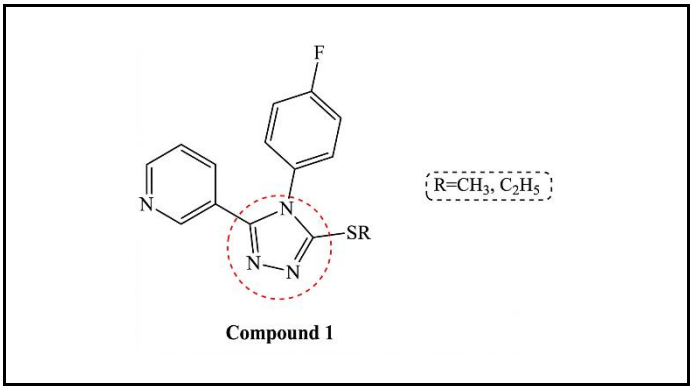
1.1. Notable triazole derivatives in research

This review provides a comprehensive overview of p38 MAP kinase inhibitors reported over the past fifteen years, highlighting their anticancer potential through modulation of p38 MAP kinase and related signaling pathways.

1.1.1. Triazole derivatives as p38 MAP kinase inhibitors as anticancer agents

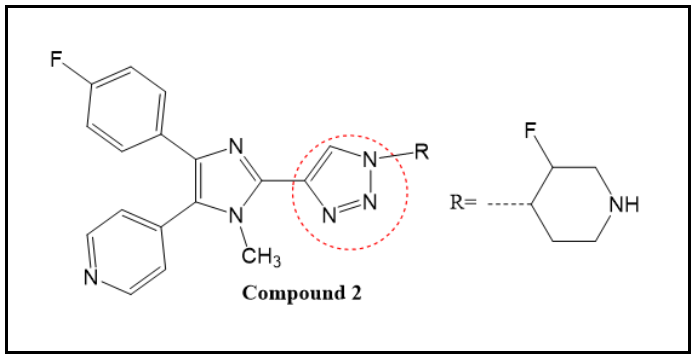
Recent years have seen substantial advancements in the development of triazole-containing drugs as effective p38 MAP kinase inhibitors. Modifications to the triazole framework have resulted in the development of several derivatives exhibiting enhanced binding affinity, selectivity, and pharmacological aspects. Both 1,2,3- and 1,2,4-triazole structures have been thoroughly investigated as fundamental pharmacophores owing to their abilities to establish strong hydrogen-bonding interactions with hinge-region residues and efficiently occupy the ATP-binding pocket. Numerous newly synthesized triazole-based compounds, such as triazole–urea, triazole–amide, and fused triazole hybrids, have exhibited significant inhibitory activity against p38 MAP kinase due to improved interactions inside the catalytic and allosteric regions. [21-22].

A series of 5-alkylthio-1-aryl-2-(4-pyridinyl) triazoles (compound 1) was synthesized as structural analogues of pyridinylimidazole-based p38 MAP kinase inhibitors, whereby the imidazole core was selectively substituted with a triazole ring. Their inhibitory efficacy against p38 MAP kinase was assessed. Among the examined drugs, fluoro-substitution appears to enhance p38 MAP kinase inhibitory activity. Increasing the alkyl chain (-R) from methyl to ethyl maintains or slightly broadens activity across concentrations, suggesting that small hydrophobic substitutions at the R position are well tolerated without loss of potency. Their activity was analogous to that of the reference inhibitor SB202190, with no statistically significant difference seen. Analysis of the SAR revealed that particular modifications on the triazole ring significantly affected binding affinity and enzyme inhibition. Pyridinyltriazole compounds are promising frameworks for optimizing p38 MAP kinase inhibitors. [23].



Compound 1.

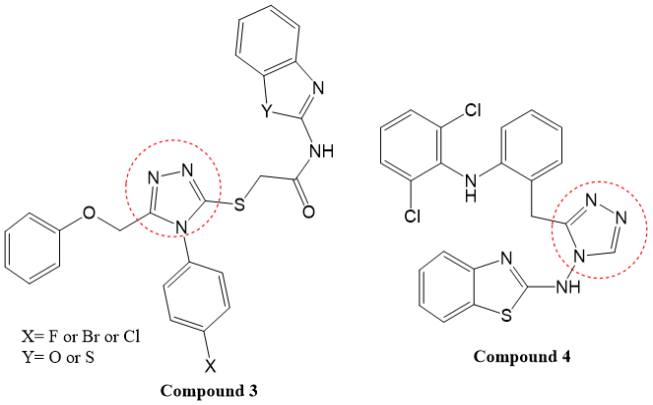
Novel triazolyl p38 MAP kinase inhibitors were designed, synthesized, and biologically evaluated via a click chemistry approach involving the reaction of functional azides with 2-alkynyl imidazoles and their isosteric oxazoles, leading to libraries of 1,4-disubstituted 1,2,3-triazole derivatives (compound 2) as potential p38 MAP kinase inhibitors. SAR analysis revealed that the R substituent (water-solubilizing group) plays a critical role in activity, with polar or basic groups enhancing aqueous solubility and cell permeability. In particular, compound 2, bearing a piperazine moiety, showed potent *in vitro* p38 MAP kinase inhibitory activity (IC_{50} = 0.096 µM), likely due to hydrogen-bonding interactions at the solvent interface, whereas bulky or nonpolar substituents resulted in reduced activity [24].



Compound 2.

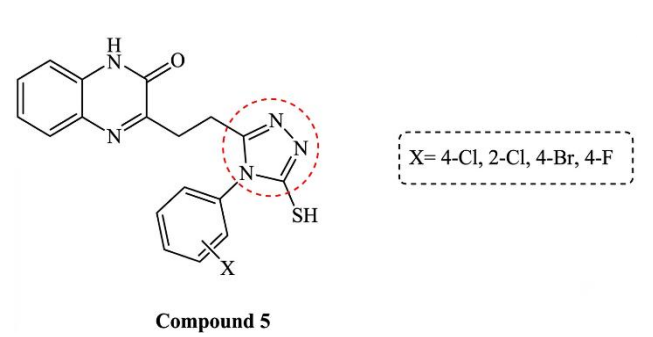
Tariq et al. synthesized novel N-(benzothiazol/ oxazol-2-yl)-2-[(5-(phenoxymethyl)-4-aryl-4H-1,2,4-triazol-3-yl)thio]acetamide derivatives (compound 3) [25] and N-[3-(substituted-4H-1,2,4-triazol-4-yl)]benzo[d]thiazol-2-amine derivatives (compound 4) [26], subsequently assessing their p38 MAP kinase inhibitory potential. SAR analyses of compound 3 demonstrated that substituting X with fluorine (F) markedly improved inhibitory action in comparison to bromine (Br) and chlorine (Cl). Electron-donating groups at the para or ortho locations of the phenyl ring diminished activity, while electron-withdrawing groups enhanced potency. Furthermore, the isosteric substitution of the sulfur atom at position Y of the benzothiazole ring with an oxygen atom resulted in diminished activity. Compound 4 exhibited the highest binding affinity for p38 MAP kinase, attributed to the 2-[(2,6-dichlorophenyl)amino]benzyl moiety and the enhanced flexibility conferred by the methylene linker (-CH_2-) between the 2,6-dichloroanilinophenyl group with the triazole ring. The replacement of this moiety with other groups, like 1-(4-isobutylphenyl) ethyl, 4-chlorophenoxymethyl, or 2,4-dichlorophenoxymethyl, led to diminished activity. Moreover, chlorine substitution at the fifth position of the benzothiazole ring resulted in a reduction in inhibitory action.

A library of 3-[2-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)ethyl]quinoxalin-2(1H)-one derivatives (compound 5) was created and evaluated for its inhibitory efficacy against p38 MAP kinase. SAR relationship indicated that a 2-fluorophenyl substituent at the 4-position



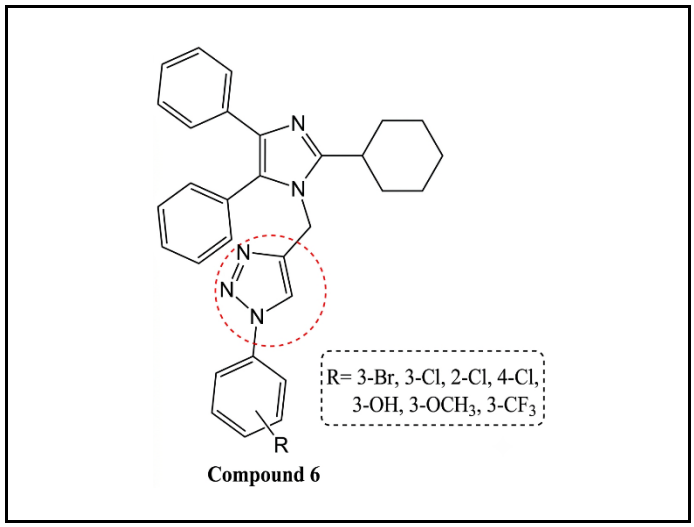
Compound 3 and 4.

of the triazole ring imparted the highest potency. Substitution with a 2-chlorophenyl group resulted in a slight reduction in activity, but relocating the halogen (-X) to the para position (4-fluoro, 4-chloro, or 4-bromo) significantly decreased inhibition. A discernible trend was noted wherein an increase in halogen size correlated with diminished activity. The inclusion of a chloro group at the 6-position of the quinoxaline ring negatively impacted potency. Derivatives with electron-withdrawing groups exhibited greater activity than those with electron-donating substituents, and ortho-substituted phenyl analogues proved more potent than their para-substituted groups [27].



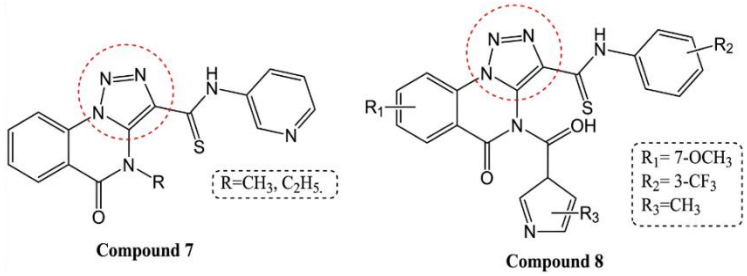
Compound 5.

A series of 1,2,3-triazole-linked hybrids (compound 6) were synthesized using a click-chemistry approach as prospective p38 MAP kinase inhibitors. Docking studies identified the compounds with para substitution with -OH, -Br and -CF_3 as the most effective binders. *In vitro* p38 MAP kinase inhibitory analysis demonstrated that these three compounds shown superior inhibitory action compared to the reference drug Adezmapimod. ADME and metabolic assessments revealed that compound with p-hydroxy substitution had excellent oral bioavailability, advantageous gastrointestinal absorption, and no CYP450 interaction, indicating a safe profile. Para-substituted derivatives bearing bulkier groups, such as -OH (IC_{50} =0.222 µM), Br (IC_{50} = 0.234 µM) and CF_3 (IC_{50}= 0.241 µM), exhibited the highest activity, surpassing the reference drug Adezmapimod (IC_{50}= 0.257 µM). Substitution with chlorine at the ortho and para positions also resulted in notable activity, with IC_{50} values of 0.364 µM and 0.318 µM, respectively. In contrast, replacing the hydroxy group with a methoxy group at either position led to a marked reduction in activity. Compound with para hydroxy substitution with IC_{50} value of 0.222 µM was identified as the most promising candidate [28].



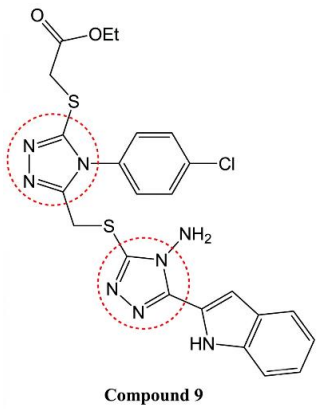
Compound 6.

Two series of triazoloquinazoline carbothioamide derivatives were developed and synthesized as prospective inhibitors of p38 MAP kinase, exhibiting significant anticancer efficacy. In the first series, substituted 4-alkyl-5-oxo-N-(pyridin-3-yl)-4,5-dihydro[1,2,3]triazolo[1,5-a] quinazoline-3-carbothioamide derivatives (compound 7) were assessed against MCF-7 breast cancer cells, with compound methyl group (-R) demonstrating the highest cytotoxic efficacy (IC_{50}=39.76 µM) and significant p38 MAP kinase inhibition (IC_{50}= 0.293µM), establishing it as the most potent compound in this series. In the second series, trisubstituted 5-oxo-4-(3H-pyrrole-3-carbonyl)-N-phenyl-4,5-dihydro[1,2,3]triazolo[1,5-a]quinazoline-3-carbothioamide derivatives (compound 8) were produced and evaluated via the MTT assay against MCF-7 cells. Compound 8 (R_1=7-OCH_3, R_2= 3-CF_3 and R_3-CH_3) exhibited the highest cytotoxic activity (IC_{50}= 29.52). Moreover, compound 8 exhibited the most potent suppression of p38 MAP kinase (IC_{50}= 0.392 µM). Compounds 7 and 8 were identified as the most promising inhibitors in their respective series, demonstrating significant anticancer potential and efficient p38 MAP kinase inhibition. [29-30].



Compound 7 and 8.

A variety of new 3-S-alkylated 4-amino-5-indolyl-triazoles were synthesized and assessed for anticancer efficacy. The compound ethyl 2-[(5-(4-amino-5-(1H-indol-2-yl)-4H-1,2,4-triazol-3-yl)thio)methyl)-4-(4-chlorophenyl)-4H-1,2,4-triazol-3-yl)thio]acetate (compound 9) exhibited notable cytotoxicity against A549 and Jurkat cell lines, with IC_{50} values of 11 µM and 8.5 µM, respectively. Incorporation of the indol-2-yl moiety significantly enhances anticancer activity, likely due to favorable π–π stacking interactions and improved cellular uptake. The 4-amino substitution on the triazole ring further contributes to activity by acting

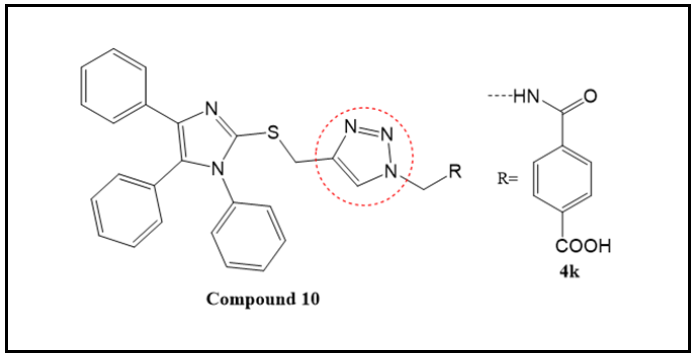


Compound 9.

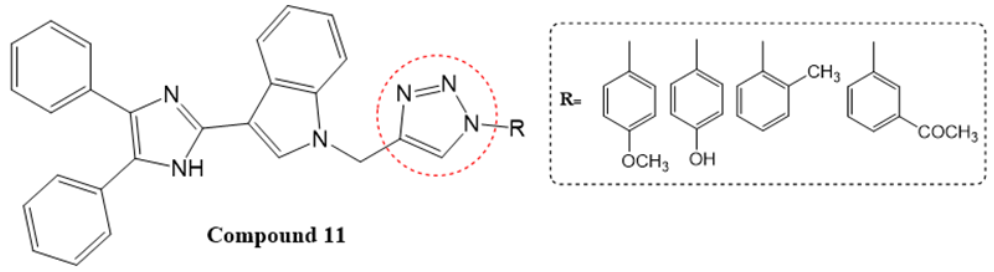
as a hydrogen bond donor, strengthening interactions within the active sites of kinases. Additionally, the S-alkyl thioether linkages impart optimal flexibility and lipophilicity, enabling proper spatial orientation of pharmacophoric groups. The presence of a para-chlorophenyl substituent enhances hydrophobic interactions and binding affinity, while the ethyl ester functionality improves membrane permeability and may contribute to favorable pharmacokinetic properties. It significantly increased apoptosis and triggered S-phase cell cycle arrest. Furthermore, the molecule exhibited significant inhibitory effects on EGFR, AKT, ERK, and p38 MAP kinase in both enzyme-based and molecular docking studies, underscoring its potential as a multi-target anticancer drug [31].

1.2. Triazole derivatives as anticancer agents other than targeting p38 MAP kinase pathway

An optimized library of imidazole-1,2,3-triazole hybrids (compound 10) with diverse alkyl or aryl side chain substitutions was generated using the effective copper(I)-catalyzed click reaction of imidazole-derived alkyne 2. The reaction was conducted in the presence of several organoazides. A compelling strategy was disclosed for the development of novel anticancer drugs aimed at the GSK3 enzyme for the treatment of breast cancer. Variation at the terminal side chain (R group) significantly influences anticancer activity, where functionalized aromatic substituents outperform simple alkyl groups, indicating the importance of π–π stacking and additional polar interactions. In particular, the incorporation of a p-carboxybenzamide moiety (-R) markedly enhances anticancer activity, likely due to improved hydrogen bonding and electrostatic interactions within the binding pocket. The presence of a thioether linkage (–S–) contributes to optimal flexibility and lipophilicity, ensuring proper orientation of the pharmacophoric units. Overall, an optimal balance between hydrophobic aromatic regions and polar functional groups is critical for activity, which exhibited potent anticancer activity, especially against the MCF-7 cell line (IC_{50} = 0.38 µM) [32].



Compound 10.

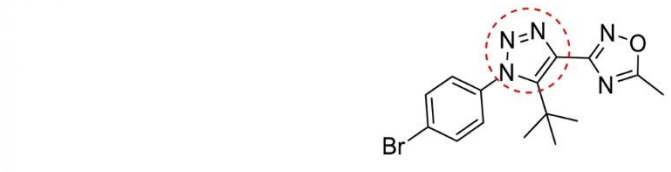


Compound 11

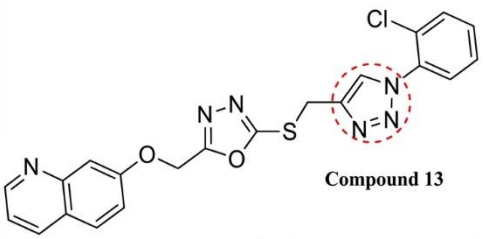
Compound 11.

A series of 1,2,3-triazole-linked imidazole and indole hybrids (compound 11) revealed that the indole scaffold is essential for anticancer activity, contributing to π–π stacking interactions and enhancing binding affinity with biological targets such as Aurora kinase-1 and DNA topoisomerase-IIα. The 1,2,3-triazole linker plays a critical role by providing structural rigidity and facilitating hydrogen-bonding interactions within the active site. Substitution on the terminal phenyl ring (R group) significantly influences activity, where electron-donating and moderately electron-withdrawing groups, such as 4-hydroxy, 4-methoxy, 2-methyl, and 3-acetyl as in compound 11, enhance cytotoxic effects against both MCF-7 and HepG-2 cell lines. These substituents likely improve binding through a combination of hydrogen bonding and hydrophobic interactions. Overall, the results emphasize that an optimal balance between the indole core, triazole linker, and suitably substituted aromatic moieties is crucial for enhanced anticancer activity [33].

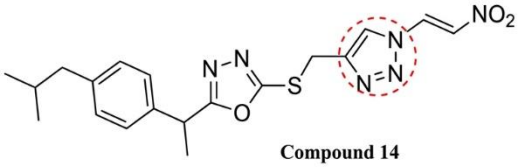
The anticancer potential of 1,2,3-triazole–oxadiazole-based hybrids has been demonstrated through several structurally diverse derivatives. A series of triazolo–oxadiazole hybrids was developed as small-molecule B-Raf inhibitors and evaluated against Skmel-23 (B-Raf wild-type) and A375 (B-Raf mutant) melanoma cell lines. Among the synthesized compounds, 3-(1-(4-bromophenyl)-5-(tert-butyl)-1H-1,2,3-triazol-4-yl)-5-methyl-1,2,4-oxadiazole (compound 12) emerged as the most potent derivative, exhibiting IC_{50} values of 26.95 µM and 16.64 µM against Skmel-23 and A375 cells, respectively. Morphological studies further confirmed its ability to inhibit cell proliferation and induce apoptosis, highlighting its potential as a lead candidate for targeting both wild-type and mutant B-Raf melanoma [34]. Similarly, a library of pyridine-linked 1,2,3-triazol-4-yl-1,3,4-oxadiazole derivatives (compound 13 and 14) was synthesized via click chemistry and evaluated against A549, HepG2, and PC-3 cancer cell lines. Several derivatives displayed notable cytotoxic activity across all tested cell lines, suggesting that incorporation of a pyridine moiety into the triazole–oxadiazole framework further enhances its anticancer potential. Collectively, these findings emphasize the triazole–oxadiazole scaffold as a versatile and promising pharmacophore for the development of novel anticancer agents [35].



Compound 12

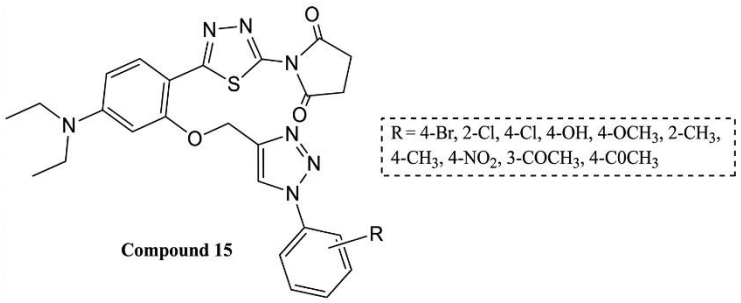


Compound 13



Compound 14

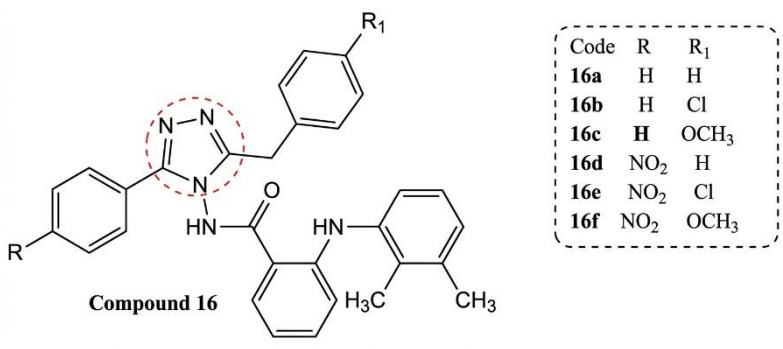
Compound 12, 13 and 14.



Compound 15.

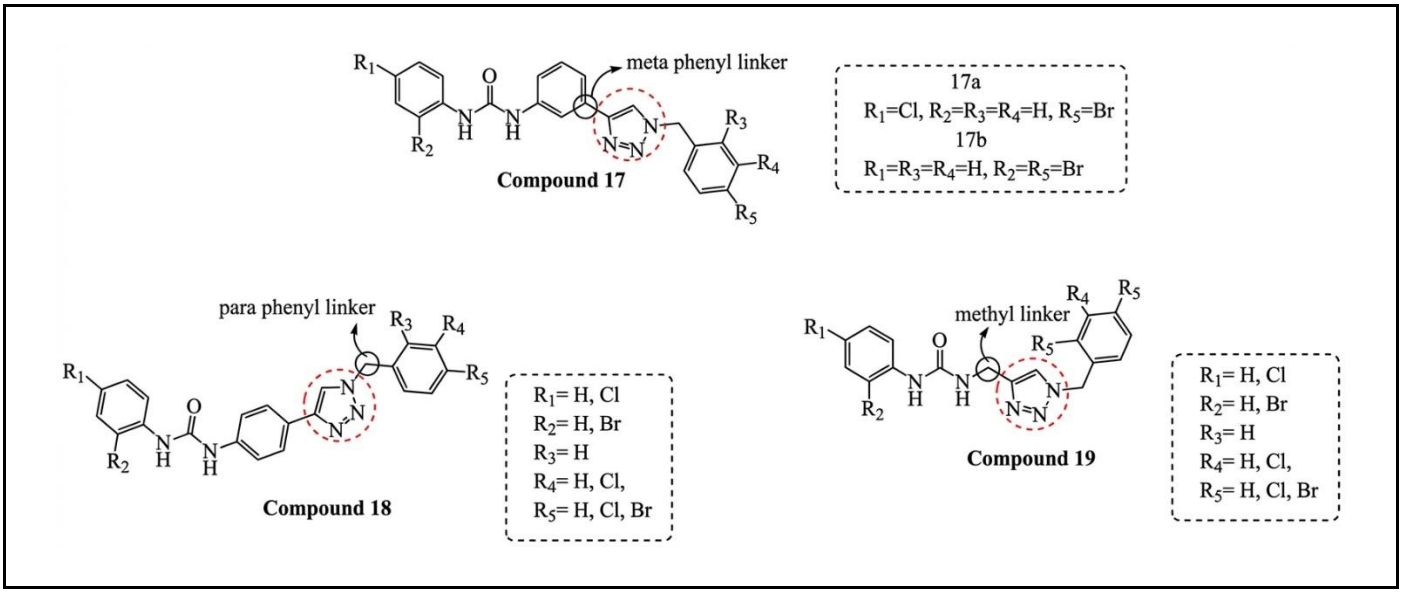
1,2,3-triazole–thiadiazole molecular hybrids, namely 5-(4-(diethylamino)-2-((1-substitutedphenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1,3,4-thiadiazol-2-yl) pyrrolidine-2,5-dione derivatives (compound 15), were produced and evaluated for their anticancer efficacy. SAR of the synthesized 1,2,3-triazole–thiadiazole hybrids revealed that the triazole–thiadiazole framework is essential for anticancer activity, likely due to its ability to facilitate key hydrogen-bonding and π–π interactions with biological targets. Substitution on the terminal phenyl ring significantly influences activity, where both electron-donating groups and weak electron-withdrawing groups enhance cytotoxic effects. Compounds bearing substituents, particularly 4-bromo, 4-methyl, 3-acetyl and 4-nitro, exhibited improved antiproliferative activity against KYSE-450 and MIA PaCa-2 cell lines. Among these, the derivative with a 3-acetyl substituent was the most potent and exhibited dual against both cell lines (KYSE-450, IC_{50} = 23.74 µM; MIA PaCa-2, IC_{50} = 20.62 µM), indicating that a balanced electronic effect at the para and meta positions is favorable for activity. Additionally, compound bearing 4-nitro substituents demonstrated strong potency against MIA PaCa-2 cells (IC_{50} = 19.17 µM). Overall, the results suggest that appropriately substituted aromatic rings with moderate electronic effects are critical for enhancing anticancer activity, potentially through dual inhibition of ARK-1 and ERK2 [36].

1,2,4-triazole-benzamide derivatives (compound 16) were produced and assessed via the MTT assay against A549 lung cancer and Hep G2 hepatocellular carcinoma cells, as well as normal WI-38 lung fibroblasts. The mechanisms of cell death and effects on the cell cycle were evaluated using flow cytometry, and the inhibition of EGFR tyrosine kinase was examined. All compounds demonstrated cytotoxic effect against cancer cell lines, with compound 16e displaying the lowest IC_{50} value of 2.87 µM against Hep G2 cells and significant cancer selectivity. Compound 16e prompted apoptosis instead of necrosis by reducing EGFR tyrosine kinase activity, thereby suppressing cell proliferation and cell cycle progression. The SAR of compounds 16a-16f indicates that an aryl group at the hydrophilic linker is essential for anticancer activity. Both 4-nitrophenyl and 4-phenyl substituents show comparable activity, while chloro substitution in the hydrophobic tail significantly enhances potency (16b and 16e). Additionally, para-nitro substitution is preferred over unsubstituted analogs. Overall, the chloro derivative (16e) exhibits superior activity compared to methoxy (16f) and phenyl (16d) analogs. [37].



Code	R	R_1
16a	H	H
16b	H	Cl
16c	**H**	OCH_3
16d	NO_2	H
16e	NO_2	Cl
16f	NO_2	OCH_3

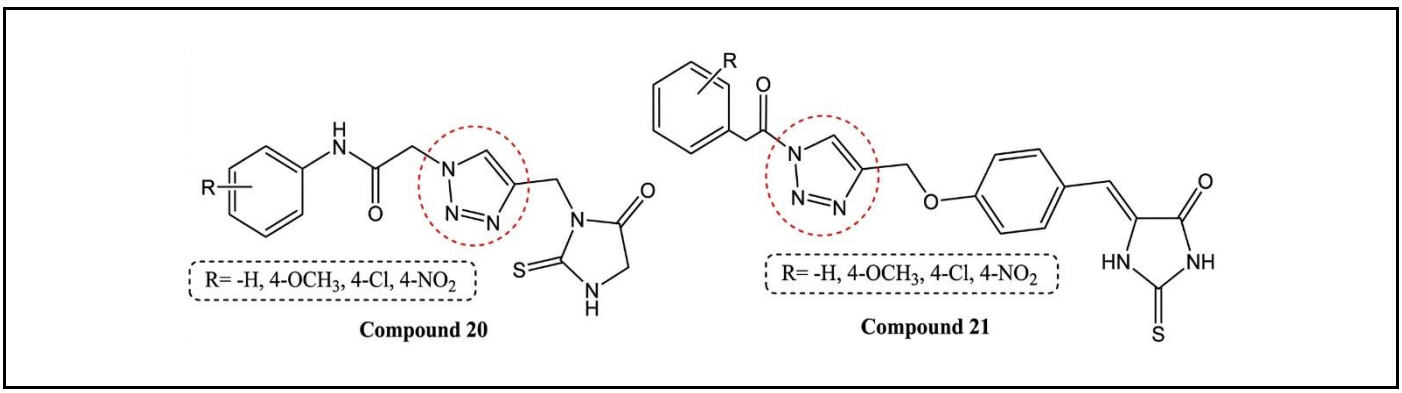
Compound 16.



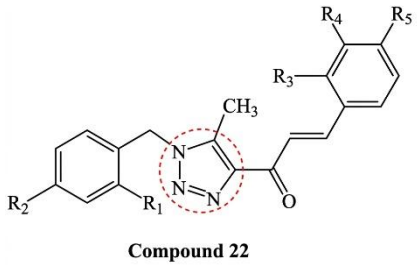
Compound 17, 18 and 19.

A series of diarylurea–1,2,3-triazole derivatives (compound 17, 18 and 19) was synthesized through nucleophilic addition followed by 1,3-dipolar cycloaddition. The incorporation of the urea moiety was based on its recognition as a privileged scaffold capable of forming strong hydrogen-bonding interactions with biological targets. Three different linkers meta-phenyl (compound 17), para-phenyl (compound 18), and methyl (compound 19) were employed to connect the urea and 1,2,3-triazole fragments. The synthesized compounds exhibited selective *in vitro* anticancer activity against various tumor cell lines, including lung cancer (H460, H1299, A549, and PC-9), hepatocellular carcinoma (Huh-7), and breast cancer (MCF-7), with pronounced potency toward Huh-7 cells. Among the series, compounds 17a (IC_{50} = 10.23 µM) and 17b (IC_{50} = 12.25 µM) demonstrated the highest antiproliferative activity against Huh-7 cells. Overall, the results indicate that the meta-phenyl linker provides superior activity compared to para-phenyl and methyl linkers [38].

Thiohydantoin-1,2,3-triazole hybrid derivatives (compound 20 and 21) revealed that substitution at the para position of the terminal phenyl ring significantly influences anticancer activity. Evaluation against HepG2, HT-29, and MCF-7 cancer cell lines demonstrated that the presence of a 4-methoxy substituent markedly enhanced cytotoxic potency. In compound 20, the 4-methoxy-substituted derivative exhibited strong antiproliferative activity, with IC_{50} values ranging from 8.06 ± 0.36 to 11.54 ± 0.01 µM, likely due to improved molecular interactions with biological targets. Notably, the corresponding 4-methoxy-substituted derivative in compound 21 showed the highest anticancer activity and the best selectivity profile among all tested compounds, displaying IC_{50} values ranging from 7.85 ± 0.05 µM to 13.73± 0.10 µM. These findings suggest that incorporation of an electron-donating methoxy group at the para position is favorable for anticancer activity and selectivity, identifying thiohydantoin–triazole compound 21 as a promising lead compound for further anticancer drug development [39].



Compound 20 and 21.



Compound 22

Code	R_1	R_2	R_3	R_4	R_5
22a	H	Cl	H	H	Br
22b	H	Cl	H	H	OCH_3
22c	H	Br	H	Br	H
22d	H	Cl	H	NO_2	H
22e	H	Br	OCH_3	H	H
22f	H	H	Cl	H	Cl
22g	Cl	Cl	H	H	Cl
22h	OCH_3	H	H	H	Br

Compound 22.

Chalcone-linked 1,2,3-triazole derivatives (compound 22) were synthesized via an ultrasound-assisted method and evaluated for cytotoxicity against G415, Gb-d1, T98G, HeLa, and U937 cell lines. The compounds exhibited significant activity against U937, T98G, and Gb-d1 cells, while activity against G-415 was minimal. SAR analysis revealed that the triazole–chalcone scaffold is crucial for anticancer activity, and substitution patterns on the aromatic rings (R_1–R_5) strongly influence potency. Electron-withdrawing groups (Cl, Br, NO_2) enhance activity by improving hydrophobic and binding interactions, whereas electron-donating groups (OCH_3) also contribute when optimally positioned. Compounds with halogen or mixed substituents (22a, 22c, 22d and 22g) showed enhanced activity, while combinations of donating and withdrawing groups (22b, 22e, 22f, 22h) supported target-specific interactions. Molecular studies indicated that 22a and 22b preferentially bind VEGFR (U937), 22g and 22h are most active against T98G, 22e and 22f interact with MEK (Gb-d1), and 22c and 22d show strong affinity toward DHFR (HeLa). Overall, a balanced electronic profile and appropriate substitution pattern promote multi-target binding and enhanced anticancer activity in both adherent and non-adherent cancer cells [40].

2. SAR OF 1,2,3 TRIAZOLE AND 1,2,4 TRIAZOLES DERIVATIVES AS ANTICANCER AGENT

Both 1,2,3-triazole and 1,2,4-triazole derivatives have been extensively investigated as potential anticancer agents owing to their ability to modulate p38 MAP kinase and other oncogenic signaling pathways. SAR studies revealed that compounds 1–9, containing either 1,2,3-triazole or 1,2,4-triazole scaffolds, were specifically designed to target the p38 MAP kinase enzyme. In contrast, the remaining compounds were developed to act on various alternative cancer-related molecular targets. Biological activities of all the compounds are shown in Table 1.

Table 1. Anticancer activity of 1,2,3 and 1,2,4 triazole derivatives.

Compound scaffolds	Target/enzyme/cell lines	Biological Activity (IC_{50}) / Significance
Pyridinyl based 1,2,4 triazole hybrids (Compound 1)	p38 MAP kinase	Highly potent
Imidazole based 1,2,3-triazoles (Compound 2)	p38 MAP kinase	0.096 µM (Highly potent)
Benzothiazole/oxazole based 1,2,4-triazole derivatives (Compound 3)	p38 MAP kinase	Moderate activity
Benzothiazole based 1,2,4–triazole amines (Compound 4)	p38 MAP kinase	Highly potent
Quinoxaline based 1,2,4 triazole hybrids (Compound 5)	p38 MAP kinase	Moderate activity
Cyclohexyl linked imidazole- based 1,2,3-triazole hybrids (Compound 6)	p38 MAP kinase	0.222–0.241 µM (Significant inhibitory activity)
Pyridine linked 1,2,3 triazoloquinazoline based hybrids (Compound 7)	p38 MAP kinase / MCF-7	0.293 µM /39.76 µM (Significant inhibitory activity)
Pyrrole linked 1,2,3 triazoloquinazoline based hybrids (Compound 8)	p38 MAP kinase / MCF-7	0.392 µM / 29.52 µM (Significant inhibitory activity)
Indole linked 1,2,4 triazole based 1,2,4 triazole hybrids (Compound 9)	EGFR, AKT, ERK, p38	8.5–11 µM (Significant inhibitory activity)
Imidazole linked 1,2,3 triazole based hybrids (Compound 10)	GSK3 / MCF-7	0.38 µM (Highly potent)

Table 1. Anticancer activity of 1,2,3 and 1,2,4 triazole derivatives (Continued).

Compound scaffolds	Target/enzyme/cell lines	Biological Activity (IC_{50}) / Significance
Imidazole linked indole based 1,2,3 triazole hybrids (Compound 11)	Aurora kinase-1, Topo IIα	Significant inhibitory activity
Oxadiazole linked 1,2,3 triazole hybrids (Compound 12)	B-Raf kinase	16–27 µM (Highly potent)
Pyridine linked oxadiazole based 1,2,3 triazole hybrids (Compound 13)	A549, HepG2, PC-3	Significant inhibitory activity
Pyridine linked oxadiazole based 1,2,3 triazole hybrids (Compound 14)	A549, HepG2, PC-3	Significant inhibitory activity
Thiadiazole linked 1,2,3 triazole hybrids (Compound 15)	ARK-1, ERK2	20–24 µM (Significant inhibitory activity)
Benzamide linked 1,2,4 triazole hybrids (Compound 16)	HepG2	2.87 µM (Significant inhibitory activity)
Diarylurea linked 1,2,3 triazole hybrids with m-phenyl linker (Compound 17)	Huh-7	10–12 µM (Highly potent)
Diarylurea linked 1,2,3 triazole hybrids with p-phenyl linker (Compound 18)	Huh-7	>50 µM (Less potent)
Diarylurea linked 1,2,3 triazole hybrids with methyl linker (Compound 19)	Huh-7	>50 µM (Less potent)
Thiohydantoin linked 1,2,3 triazole hybrids (Compound 20)	HepG2, HT-29, MCF-7	8.06 to 11.54 µM (Moderate activity)
Thiohydantoin linked 1,2,3 triazole hybrids (Compound 21)	HepG2, HT-29, MCF-7	7.85–13.73 µM (Highly potent)
Chalcone linked 1,2,3 triazole hybrids (Compound 22)	U937, T98G, Gb-d1	Significant inhibitory activity

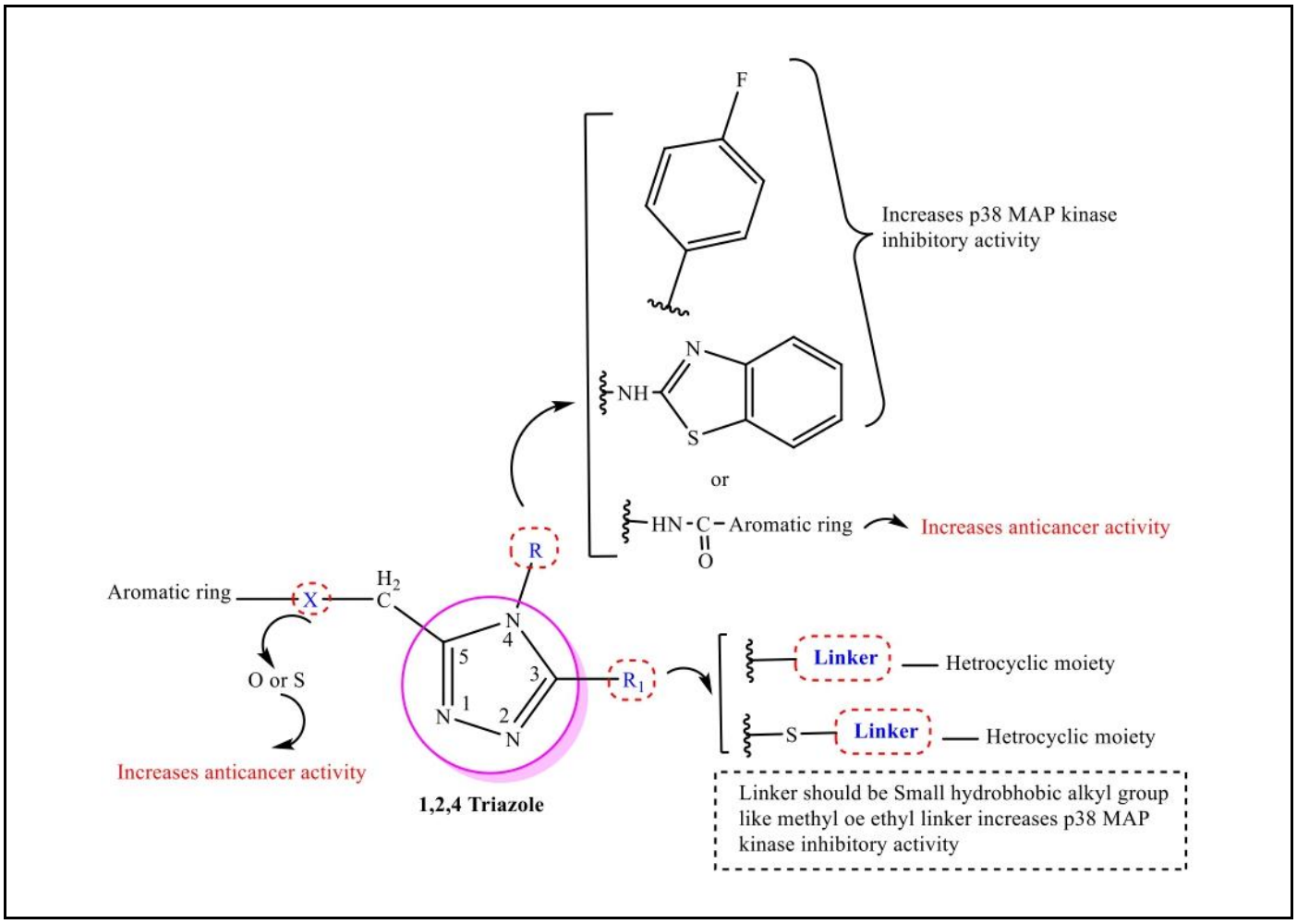


Figure 2. SAR of 1,2,4 Triazole derivatives as anticancer agents.

SAR analysis of the 1,2,4-triazole derivatives (Figure 2) indicated that the substituent at the 3rd position plays a crucial role in anticancer activity. Small hydrophobic alkyl linkers at this position, as observed in compounds 1, 4, and 6, were associated with enhanced activity. In several derivatives (compounds 3, 5, and 9), the linker was attached through a sulfur atom, further highlighting the significance of the 3rd-position linker in modulating biological activity. The substituent attached to the nitrogen atom at the 4th position (-R) consisted of various heterocyclic or substituted aromatic moieties, which contributed to improved p38 MAP kinase inhibitory activity. Additionally, the substituent at the 5th position (-X-) was either oxygen (ether) or sulfur (thioether) linked to an aromatic ring, a feature that appeared to enhance anticancer potency.

For the 1,2,3-triazole derivatives (Figure 3), the substituent attached to the nitrogen atom at the 3rd position (-R_1) generally comprised heterocyclic or substituted phenyl groups, which were favorable for anticancer activity. Incorporation of a fused ring system between the 3rd and 4th positions, as observed in triazoloquinazoline carbothioamide derivatives (compounds 7 and 8), significantly improved p38 MAP kinase inhibitory activity. Furthermore, the substituent at the 5th position (-R) could be either aliphatic or aromatic; however, derivatives containing an imidazole-linked moiety exhibited superior p38 MAP kinase inhibition and anticancer activity. Comparative analysis indicated that 1,2,3-triazole derivatives generally exhibited superior anticancer activity relative to their 1,2,4-triazole counterparts, highlighting the potential of the 1,2,3-triazole scaffold for the development of novel anticancer agents.

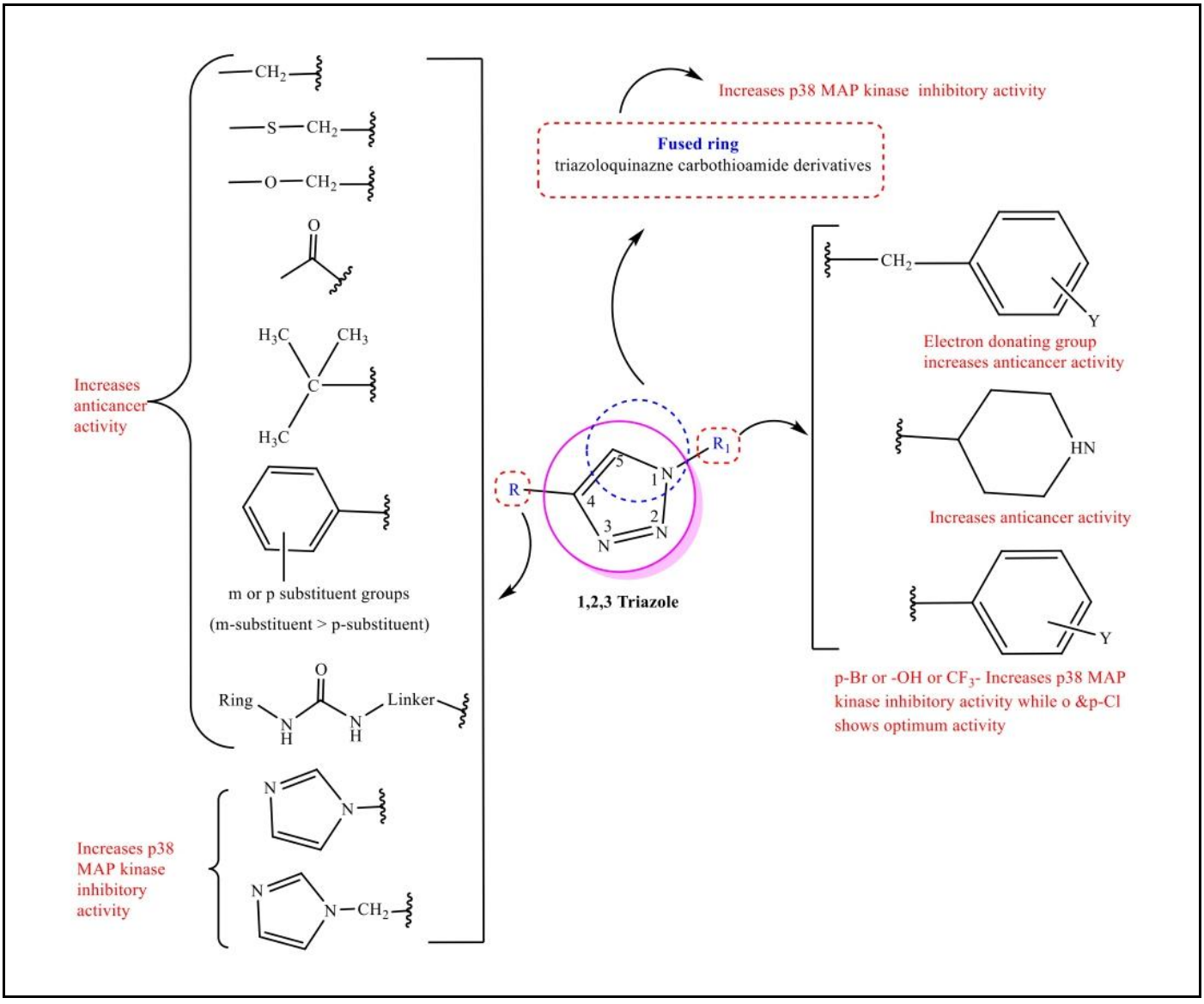


Figure 3. SAR of 1,2,3 Triazole derivatives as anticancer agents.

3. CONCLUSION

This review highlights the significant potential of 1,2,3- and 1,2,4-triazole-based hybrids as promising anticancer agents, particularly through the modulation of kinase-mediated signaling pathways such as p38 MAP kinase. Biological evaluations and SAR analyses collectively demonstrate that the triazole nucleus serves as a versatile pharmacophore capable of establishing favorable interactions with ATP-binding and allosteric sites of diverse kinases. Among the reported compounds, imidazole-based 1,2,3-triazoles exhibited the highest potency against p38 MAP kinase, achieving submicromolar inhibitory activity, while cyclohexyl-linked imidazole–triazole hybrids further emphasized the importance of hydrophobic interactions and steric complementarity for effective kinase inhibition. In addition, fused triazoloquinazoline derivatives displayed dual kinase inhibitory and antiproliferative activities, whereas pyrrole-containing analogues generally outperformed their pyridine counterparts, underscoring the critical influence of subtle structural and electronic modifications on biological activity.

The incorporation of complementary heterocyclic pharmacophores, including indole, oxadiazole, thiadiazole, and benzamide motifs, further enhanced the anticancer potential of triazole hybrids. Notably, several compounds demonstrated activity against multiple key oncogenic pathways involving EGFR, AKT, ERK, p38 MAP kinase, GSK3β, Aurora kinase A, and B-Raf, underscoring the broad therapeutic potential of triazole-based hybrids. This multi-target approach may help overcome pathway redundancy and acquired resistance, which often limit the long-term efficacy of single-target anticancer therapies. SAR findings consistently revealed that substitution patterns, linker architecture, and the physicochemical properties of attached heterocycles play decisive roles in determining potency and selectivity, with lipophilic and electron-withdrawing substituents frequently contributing to enhanced kinase inhibition.

Despite these encouraging findings, several important limitations must be acknowledged. Most reported studies remain confined to *in vitro* enzymatic and cellular assays, with limited *in vivo* validation of efficacy, safety, pharmacokinetics, and bioavailability. Furthermore, many compounds have been evaluated against a restricted panel of kinases, leaving unresolved questions regarding kinase isoform selectivity and potential off-target effects. Given the high structural homology among kinase families, achieving selective inhibition of specific kinase isoforms remains a major challenge that must be addressed to minimize toxicity and improve therapeutic outcomes. In addition, the lack of comprehensive mechanistic studies, long-term toxicity assessments, and clinically relevant animal models limits the current understanding of their translational potential. Overall, the available evidence supports the continued exploration of triazole-based hybrids as valuable scaffolds for anticancer drug discovery. Future research should prioritize isoform-selective kinase targeting, detailed mechanistic investigations, pharmacokinetic optimization, and rigorous *in vivo* studies, followed by clinical validation. The integration of rational drug design, molecular hybridization, computational modeling, and SAR-guided optimization will be essential for translating these promising compounds from experimental leads into clinically useful anticancer therapeutics.

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Author contributions

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Ethics approval

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