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Review Article

Mitogen-Activating Protein Kinases (MAPK) Inhibitors for Cancer Treatment

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ABSTRACT

Cancer is the leading cause of mortality globally. Millions of causalities reported globally due to cancer. Globally researchers focus for the treatment of cancer. Numbers of nuclear targets have been reported till date for the treatment of cancer. Out of these targets, kinases become fascinating targets for anticancer agents. Mitogen-activating protein kinases (MAPK) is among one of these nuclear targets getting attractions globally from the researchers. Numbers of MAPK inhibitors have been reported till date for the treatment of cancer. In the present writeup we have reported numerous pyrimidine derivatives, pyrazole derivatives, imidazole derivatives, indazole derivatives, aminopyrazine derivatives, 4-anilinoquinazolines, imidazopyridazine derivatives, 1,5-diarylpyrazoles derivatives, n-cyclopropylbenzamide benzophenone hybrids and pentacyclic ring system.

INTRODUCTION

Cancer and other human disorders can result from mutations in kinases that induce either loss or gain of function. The RAF/RAS/ERK/MEK pathway, also identified as the mitogen-activating protein kinases (MAPK) pathway, is a critical conduit between intracellular and extracellular signals reactions. MAPK transmits mitogenic signals to the nucleus from the outside of the cell via multistage phosphorylation (Figure 1). This MAPK pathway required for several physiological functions, including apoptosis, differentiation, survival, and cell proliferation [1]. A breakdown in the MAPK pathway has been reported in at least 30% of all cancers [2,3]. Researchers have focuses on this MAPK pathway as a possible treatment because they realized how important it is in cancer.

The first MAPK inhibitor, which targets the allosteric location of MEK 1/2 proteins, was introduced in 1995. Subsequent research revealed a number of additional MAPK-inhibitors (Figure 1) that target the majority of MAPK proteins, including ERK, BRAF, MEK, and KRAS [4,5]. Numerous MAPK inhibitors have got FDA-approval. Their synthetic processes, the reasons behind their discovery, and the ways in which they connect to their receptors are then thoroughly reviewed. MEK-inhibitors continue to be the most widely used type of MAPK inhibitor. Adaptive resistance to MAPK-inhibitors is caused by the activation of various compensatory feedback processes in the malignant microenvironment by the majority of these inhibitors. The majority of traditional mitogen-activated protein kinases (MAPKs) share some traits, including a three-tiered pathway design, dual phosphorylation sites for activation, and comparable substrate recognition sites. Older varieties, on the other hand, lack the characteristics that other MAPKs need in order to connect with substrates; instead, they only create two-tiered pathways and lack such dual phosphorylation sites. The term "atypical" MAPKs is typically used to describe these kinds [6].

p38 mitogen-activated protein kinases (p38s), c-Jun N-terminal kinases (JNKs) and Extracellular signal-regulated kinases (ERKs), are the three subfamilies of the mammalian MAPK family of kinase. ERKs, (or MAP kinases), are intracellular signaling molecules, play an important role in the control of meiosis, mitosis, and postmitotic processes in differentiated cells. Cytokines, growth factors, transforming agents, viral infections, carcinogens, and ligands for heterotrimeric G protein-coupled receptors are just a few of the numerous stimuli that can activate the ERK pathway. Although "extracellular signal-regulated kinases" is occasionally used interchangeably with "MAPK," it has lately been used to refer to a particular subclass of the mammalian MAPK family. Ras activates c-Raf in the MAPK/ERK pathway, which is trailed by MAPK1/2. Growth hormones normally activate Ras via GRB2/SOS and receptor tyrosine kinases, however Ras can also get additional signals. Numerous transcription factors, including ELK1 and certain downstream protein kinases, are known to be activated by ERKs. Cancers frequently disrupt the ERK pathway, particularly c-Raf, Ras, and certain receptors including HER2 [7]. JNKs, binds and phosphorylate c-Jun on both Ser-63 and Ser-73 moieties. These kinases quickly respond to stress stimuli, including cytokines, ultraviolet irradiation, heat shock, and osmotic shock. JNKs also participates in the differentiation of T cells and the cellular apoptosis pathway. Phosphorylation of tyrosine (Tyr) and threonine (Thr) residues within a Tyr-Pro-Thr motif in kinase subdomain VIII leads to activates JNKs. Activation is processed by MKK4 and MKK7 (i.e. MAP kinases), however, Tyr and Ser/Thr protein phosphatases can inactivate JNKs. This leads to inflammatory responses in mammals. p38 or Cytokinin Specific Binding Protein (CSBP) is another class of MAPKs, responsive to some stress stimuli. Phosphorylation at Thr-180 and Tyr-182 of MKK3 and SEK leads to activate p38 MAP kinase and then activate MAPKAP kinase 2 and at phosphorylate the transcription factors Mac, ATF2, MEF2, and p53.

Targeting to MAPK signaling pathway becomes an interesting approach for treating diseases. Numerous literatures have been reported till date, describing novel molecules having ability for targeting MAPK signaling pathway. These targeting abilities of molecules have utilized for cancer treatment. Many molecules have been reported till date for anticancer potential through MAPK signaling pathway.

PYRIMIDINE DERIVATIVES

Pyrimidine derivatives having p38 α MAPK inhibitory activity share distinct pharmacophores constitutes interesting core via linked to different heterocyclic rings. Lin et al. utilized designed and reported 2-aminothiazol-5-yl-pyrimidines using nitrogen–sulfur nonbonding interaction as p38 MAP kinase inhibitors. Compound 5-(6-(2-Chlorophenyl)pyrimidin-4-yl)-N-isopropyl-1,3-thiazol-2-amine (**1**) showed highest p38α inhibitory activity, utilizes nitrogen–sulfur intramolecular nonbonding interaction to stabilize the conformation required for the attachment at the active site of p38α (Figure 2) [8].

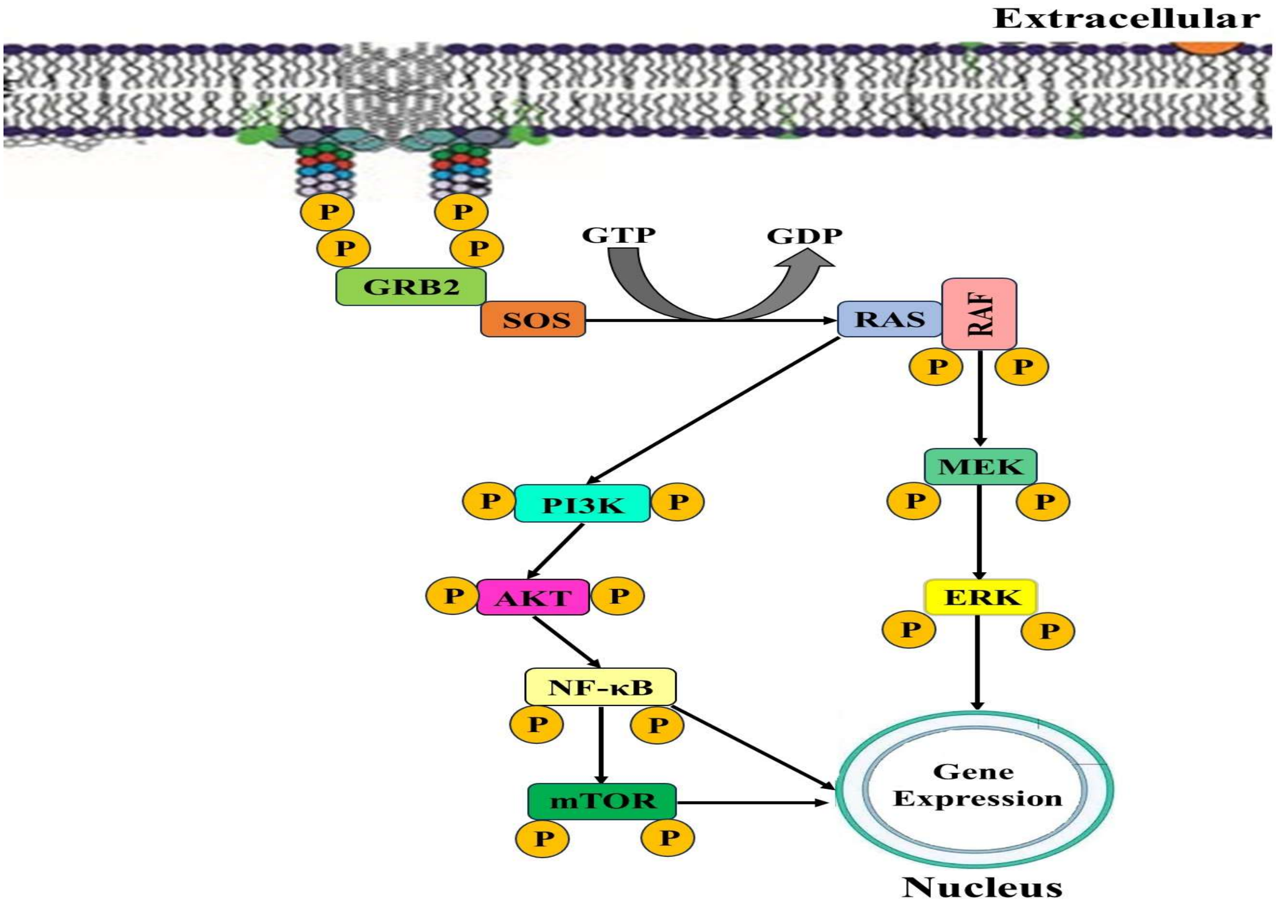
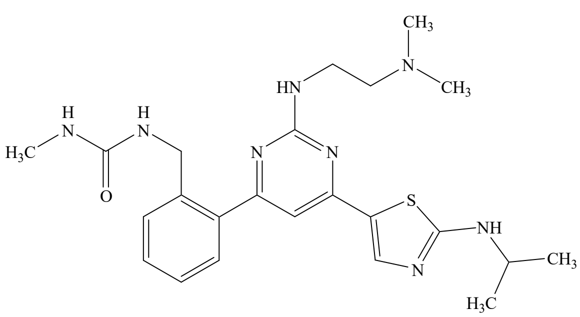


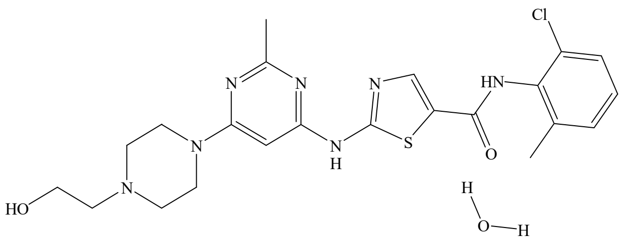
Fig. 1. MAPK signaling pathway involved in gene expression. AKT: protein kinase B; ERK: extracellular signal-regulated kinase; GDP: guanosine diphosphate; GTP: guanosine triphosphate; GRB growth factor receptor bound protein; MEK mitogen-activated protein kinase kinase; mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol 3-kinase; RAS (rat sarcoma viral oncogene) RAF (v-raf murine sarcoma viral oncogene); RTK: receptor tyrosine kinase; SOS: Son of Sevenless homolog; NF-κB: nuclear factor-kB.



(**1**)

Fig. 2. Structure of compound (**1**) showed highest p38a inhibitory activity.

Dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole carboxamide monohydrate (**2**), a pyrimidine analogue that inhibit ATP-competitive tyrosine kinase that furthermore inhibits all Src family kinases (SFKs) at with IC50 < 1.0 nM. Recently, dasatinib is approved for imatinib resistant/intolerant BCR-ABL+ leukemias (Figure 3). Furthermore, dasatinib also inhibits other tyrosine kinases including p38, Akt and FAK. Dasatinib is well reported for its antiproliferative effects on prostate and lung cell lines, while its effects on breast cancer cells are under investigation [9].

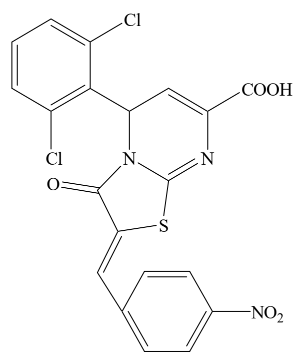


Dasatinib; (**2**)

Fig. 3. Structure of dasatinib (**2**).

Furthermore, Devadas et al. reported N-aryl-6-pyrimidinone scaffolds as selective p38 MAP kinase inhibitors [10].

El-Walki et al. produced a novel series of 5-(2,6-dichlorophenyl)-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidine-7-carboxylic acids derivatives as potential p38 α MAPK inhibitors [11]. Total seventeen compounds were synthesized and confirm their synthesis through spectroscopic techniques. Numerous compounds showed strong inhibitory activity against p38 α MAPK, out of which compounds (Z)-5-(2,6-Dichlorophenyl)-2-(4-hydroxy-3-methox ybenzylidene)-3-oxo-2,3-dihydro-5H-thiazolo[3,2-α]pyrimidine-7-carboxylic acid (**3**) and (Z)-5-(2,6-Dichlorophenyl)-2-(3,4-dimethoxybenzylidene)-3-oxo- 2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-7-carboxylic acid (**4**) demonstrated highest inhibitory activity among the synthesized compounds, with IC50 values around 8.5 high for compound (**4**) as compared to (7) (Figure 4). Both compounds showed strong cytotoxicity breast, lung, liver and colon cancer cell lines as compared to reference 5-FU. The proposed antitumor activity was due to augmented DNA binding mechanism over their kinase inhibition. Compounds (**3** and **4**) showed strong ctDNA damaging effects. Furthermore, compounds (**3**) and (**4**) arrested cell cycle at S phase in MCF-7 cells, while at G0-G1 and G2/M phases in HCT-116 treated cells. Authors also confirms apoptotic induction effects by both compounds in both HCT-116 and MCF-7 cell lines as compared to reference to 5-FU. Finally, in silico studies revealed the drug-like properties of compounds (**3**) and (**4**) with tolerable ADMET parameters without losing Lipinski's rule of five.



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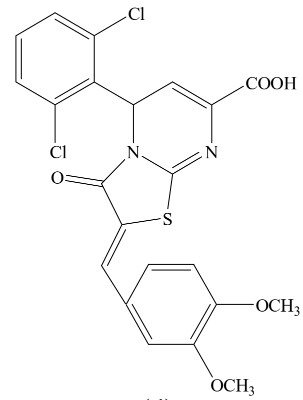
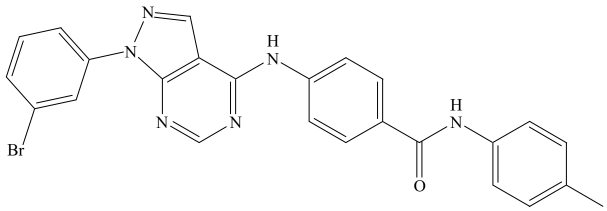


(4)

Fig. 4. Structure of compounds (**3**) and (**4**).

Very recently Ewieda and coworkers (2025) reported a series of pyrazolopyrimidine-4-amine core derivatives as potential cytotoxic agents against UO-31 carcinoma cells [12]. Compounds N-4-Tolyl-4-(1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4- ylamino) benzamide (**5**) and N-(4-Chlorophenyl)-2-[4-(1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino) benzoyl] hydrazinecarbothioamides (**6**) were found to be most cytotoxic agents against UO-31 cancer cells as compared to reference sorafenib (SOR). Both compounds showed inhibitory activity against p38 α MAPK which are about 2.53- and 2.27- times potent than SOR respectively (Figure 5). Furthermore, these compounds showed pro-apoptotic activity by 1.42- and 1.20- folds higher than SOR respectively. Compounds showed cell cycle arresting at G2/M phase. These compounds were found to reported the increase the expression of tumor suppressor gene p53, Bax/BCL-2 ratio and caspase 3/7.

The SAR of synthesized compounds demonstrated that the halide group present on the phenyl group at N-1 position of the core ring influences cytotoxicity across the series. The N-1-fluorophenyl pyrazolopyrimidine and pyrazolopyrimidin-4-amine derivatives showed improved cytotoxicity than the N-1-bromophenyl pyrazolopyrimidine derivatives. 3- or 4-methylphenyl group on anilino moieties, exhibited the augmented activity among other substituents. Presence of carboxylic acids, esters, and hydrazides decreased potency compared with methyl group. Presence of ether linkage to lead compound add cytotoxicity. Furthermore, carboxamide linkage had improved cytotoxicity compared to ether linkage.



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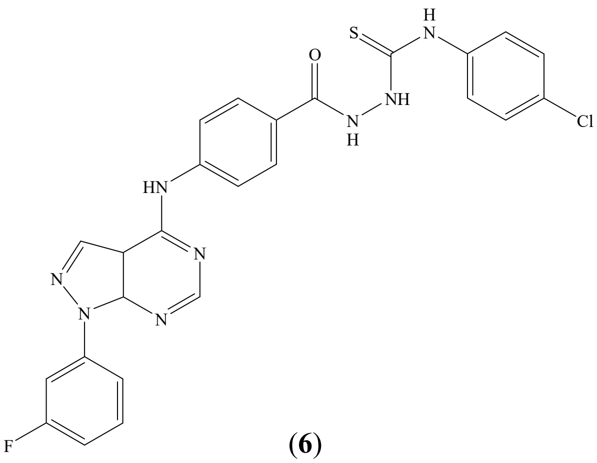


(6)

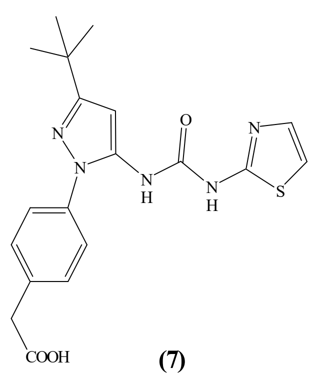
Fig. 5. Structure of compounds (5) and (6) showed most cytotoxicity against UO-31 cancer cells.

PYRAZOLE DERIVATIVES

Pyrazole derivatives are extensively used drugs in cancer treatment. Numerous anticancer agents having pyrazole scaffold possesses anticancer activity against a variety of cancer cells.

Getlik et al. reported a series of N-pyrazole and N'-thiazole-ureas as potently inhibits p38α MAPK in HeLa cells [13]. Compounds were synthesized using a convergent synthesis route based on the N'-thiazole-urea scaffold and confirm their synthesis using spectroscopic analysis. Compound 4-(3-tert-Butyl-5-{[(1,3-thiazol 2-ylamino)carbonyl]amino}-1H-pyrazol-1-yl)-phenyl]acetic acid (**7**) showed highest p38α inhibitory activity with an IC50 value of 135± 21 nM. Furthermore, compound ethyl [4-(3-tert-butyl-5-{[(1,3-thiazol-2-ylamino)carbonyl]amino}-1H-pyrazol-1-yl)phenyl]acetate (**8**) showed p38α mediated phosphorylation of the MAPK activated protein kinase 2 (MK2) in HeLa cells (Figure 6).

Rabh et al. designed, synthesised, and evaluated for anticancer activities of a novel series of pyrazole derivatives [14]. Total 21 compounds were synthesized by placing ethylene and propylene spacers between the urea and pyridine moiety; subsequently rigidification of the spacer. Four compounds showed highest antiproliferative activities against tested cell lines. Compound 1-(4-Fluorophenyl)-3-(3-((4-(3-(3-hydroxyphenyl)-1-phenyl-1H- pyrazol-4-yl)pyridin-2-yl)amino)propyl)urea (**9**) showed utmost activity against all screened cancer cell lines as compared to sorafenib and SP600125. Compounds (**9**) and 1-(3-((4-(3-(3-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)pyridin- 2-yl)amino)propyl)-3-(3-(trifluoromethyl)phenyl)urea (**10**) induced apoptosis in RPMI-8226 leukemia cells (Figure 7). Compound (**9**) was screened against 50-kinase panel. JNK3 and Flt4 (94% and 84%, respectively) are the most sensitive kinases for compound (**9**), with 8.2-fold more selective against JNK3 as compared to Flt4. For JNK3, compound (**9**) showed comparable inhibitory action as reference SP600125. JNK3 was highest sensitive for (**9**) as compared to other JNK isoforms, JNK1α1 and JNK2α2 in the whole-cell NanoBRET assay. Furthermore, the docking studies of compound (**9**) was done using Autodock vina program. The docking results showed water-bridge of urea oxygen with Glu-147 and Met-149 amino acids. The nitrogen of pyridine engaged with Ile-70 and Asn-152 and the Gln-155 of the glycine-rich loop. The aminopyridine nitrogen formed two hydrogen bonds with Met-149 (backbone, 24%) and Asn-152 residue (side chain, 19%). The pyrazole phenolic hydroxyl group established a hydrogen bod with the Pro-69. Furthermore, multiple hydrophobic interactions were reported with Ala-80, Ile-124, Met-146, Val-196 and Leu-206 residues.



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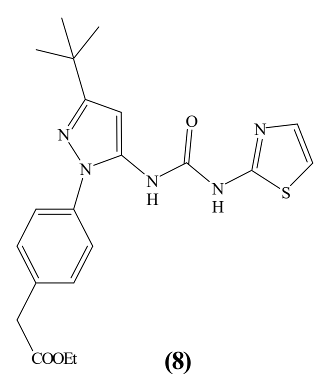

(8)

Fig. 6. Structure of compounds (**7**) and (**8**).

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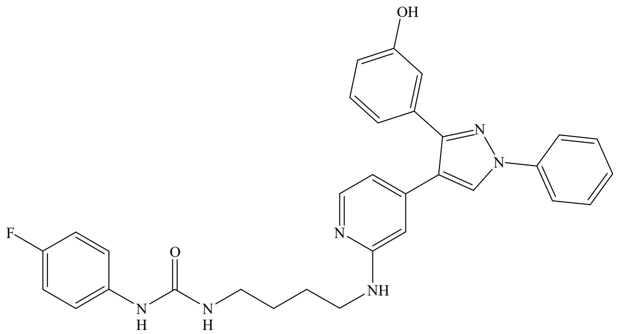
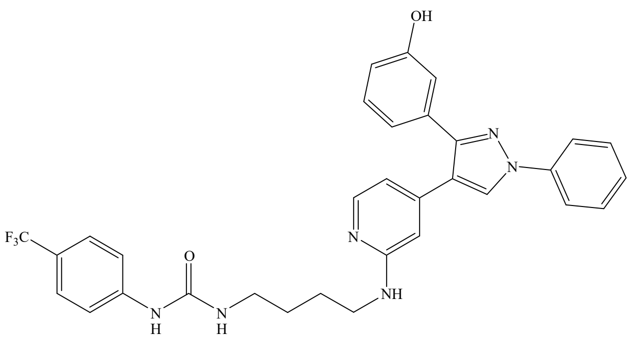


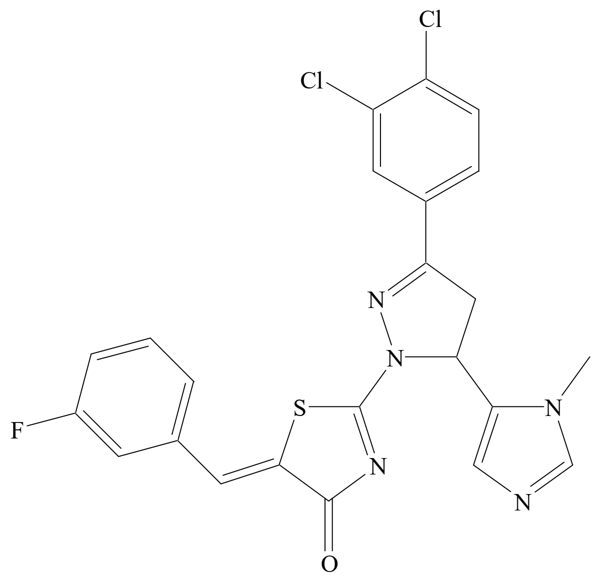
(**9**)



(**10**)

Fig. 7. Structure of pyrazole derivatives (**9**) and (**10**).

Very recently Boshta and colleagues (2024) utilized ligand-based strategy for design and synthesis of novel 1,3,5-trisubstituted-1H-pyrazole derivatives, as potential RIPK3 and ERK kinases inhibitors [15]. Total 14 compounds were synthesized via base-catalyzed Claisen-Schmidt condensation of 3′,4′-dichloro-acetophenone 2 and 1-methyl-1H-imidazole-5-carbaldehyde 1 and subsequent reaction with condensation of the chalcone in acetic acid with hydrazine hydrate. Nuclear magnetic resonance techniques were utilized for confirmation of structures of synthesized compounds. Five compounds showed significant cytotoxicity with IC50 values from 21.9-28.6 µM and 3.90–35.5 µM against prostate (PC-3) and breast (MCF-7) cancer cell lines respectively as compared to Doxorubicin as reference drug. Compound (Z)-2-(3-(3,4-Dichlorophenyl)-5-(1-methyl-1H-imidazol-5-yl)- 4,5-dihydro-1H-pyrazol-1-yl)-5-(3-fluorobenzylidene)thiazol-4 (5H)-one (**11**) showed DNA inhibition mediated cell cycle arrest in S phase of replication in PC-3 cells (Figure 8). The docking results of three compounds were also performed by Biovia Discovery Studio, utilizing binding pocket of ERK2 kinase and RIPK3 kinase (PDB code: 4QP9; PDB: 7MX3 respectively). The docking revealed interactions of synthesized compounds with vital amino acids within the active pockets of ERK and RIPK3 kinases. On the basis of these findings, authors suggested the development of new promising pyrazole derivatives for their ERK and RIPK3 kinases, mediated cancer treatments.



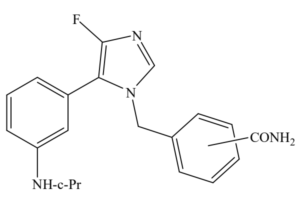
(11)

Fig. 8. Structure of compound (**11**) showed cell cycle arrest in S phase due to inhibition of DNA replication in PC-3 cells.

IMIDAZOLE DERIVATIVES

The kinase domain of transforming growth factor-b type1 receptor kinase (ALK5) is known to be the most similar to that of p38α MAP kinase29. Authors hypothesized that adding a 4-fluoro phenyl group and a pyrimidine ring moiety of SB-242235 to imidazole ALK5 scaffold might produce extremely strong and specific p38α MAP kinase inhibitors. The p38α MAP kinase inhibitory activity of a number of trisubstituted imidazole derivatives with a 4-fluorophenyl group, a pyrimidine ring, and a CN or CONH2-substituted benzyl moiety has been assessed. The series of compounds' structure–

activity connections have been determined and examined. Among the compounds in the series, compounds (**12-14**) exhibited the strongest p38α MAP kinase inhibitory activity with IC50 values of 27.6, 28, and 31 nM, respectively. The results demonstrates that methoxypyrimidine or aminopyrimidine moiety are crucial for the development of p38α MAP kinase inhibitors in order to achieve selectivity over ALK5 (Figure 9). Furthermore, it has been discovered that the approach we employed to effectively produce ALK5 inhibitors can also be applied to the design of p38α MAP kinase inhibitors. In p38a MAP kinase inhibitors, the addition of a cyano- or carboxamide-substituted phenyl substitution on a core five-membered heterocyclic ring has resulted in a notable increase in inhibitory activity [16].



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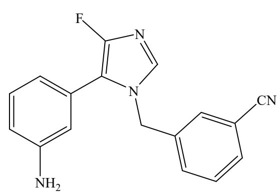

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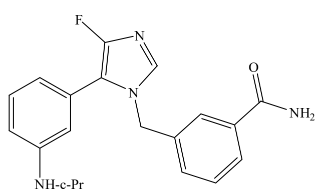
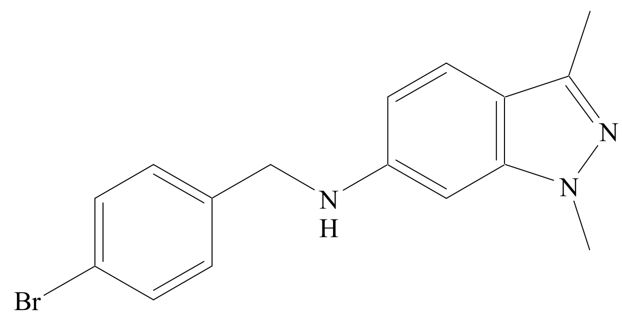


(14)

Fig. 9. Structure of compounds (**12-14**) exhibited the strongest p38α MAP kinase inhibitory activity.

INDAZOLE DERIVATIVES

Indoleamine 2,3-dioxygenase (IDO1) is accountable for the metabolism of tryptophan to kynurenine and extensively developed for the re-activation of the anticancer immune response as the IDO1 is overexpressed in cancer cells. Till date numerous anticancer compounds have been developed and reported to possessed IDO1 inhibition. Hoang et al. designed, and reported novel 1,3-dimethyl-6-amino indazoles as IDO1 inhibitors [17]. Compound N-(4-bromo benzyl)-1,3-dimethyl-1H-indazol-6-amine (**15**) was found to be highest active among the synthesized compounds with suppressed IDO1 expression in a concentration-dependent manner. Furthermore, compound (**15**) showed highest anticancer activity (Figure 10). Compound (**15**) showed selectively activated extracellular signal-regulated kinases (ERK) in MAPK pathways on hypopharyngeal carcinoma (FaDu) cells. Ultimately, compound (**15**) suppressed cell mobility with the reduced expression of matrix metalloproteinase MMP9.



(15)

Fig. 10. Structure of compound (**15**) showed highest anticancer activity.

AMINOPYRAZINE DERIVATIVES

A number of new 1-(2-aminopyrazin-3-yl) methyl-2-thioureas were identified by researchers as strong MK-2 inhibitors. These compounds showed high potency, which depends on the thiourea functionality as well as the aminopyrazine moiety. Lin and his team members (2015) looking for non-thiourea-based MK-2 inhibitors because of the possible toxicity and carcinogenicity of the thiourea function group, despite the fact that thioureas have been found to be potentially helpful as anti-HIV, anticancer, and antibacterial medicines [18]. For this, authors reported series of novel 1-(2-aminopyrazin-3-yl)methyl-2-thioureas derivatives based on the MK-2 inhibitors. All the compounds were evaluated for *in vitro* inhibitory activity against MK-2 enzyme. All the synthesized compounds showed sub-micromolar IC50 values, and suppress the lipopolysaccharide (LPS)-stimulated TNFα production in

THP-1 cells with minimum shift compared to their enzyme activity.

4-ANILINOQUINAZOLINES

4-Anilinoquinazoline is a unique structure that can be used to inhibit both EGFR and VEGFR. 4-Anilinoquinazolines can be either VEGFR selective or EGFR selective by adding different substituents to the anilino group. Kinase inhibitory 4-anilinoquinazolines are represented by the EGFR inhibitors gefitinib and lapatinib and the VEGFR inhibitor vandetanib. Furthermore, a number of modified quinazolines exhibit inhibitory effects on Aurora kinase, VEGFR, and EGFR. The Ras/Raf/MEK/ERK signal transduction pathway is largely dependent on Raf (rapid accelerated fibrosarcoma), which is made up of A-Raf, B-Raf, and C-Raf. Cell proliferation, differentiation, and survival are the results of growth signals sent to the nucleus by cell surface receptors (such as EGFR and VEGFR). B-Raf is the Raf isoform that is more commonly mutated in malignancies. Most B-Raf mutations (~90%) are constitutively active B-Raf, which is also present in melanoma (66%), thyroid cancer (38–69%), colorectal cancer (20%), hairy cell leukemia (100%), and other malignancies. Vemurafenib and dabrafenib are approved selective B-Raf V600E inhibitors for the treatment of metastatic melanoma [19-21].

Authors reported 3-(4-{4-[(5-hydroxyphenyl)amino] quinazolin -6- yl}-1H-1,2,3-triazol-1-yl) (**16**) compound side chains at the triazolyl group and fluoro substituents at the anilino group. The most effective of them was 3-(4-{4-[(2,4-Difluoro-5-hydroxyphenyl)amino]quinazolin-6- yl}-1H-1,2,3-triazol-1-yl) propanamide (**17**), which selectively inhibited B-Raf (IC50: 57 nM) and B-RafV600E (IC50: 51 nM) over C-Raf (IC50: 1.0 μM) and had a 2-carbamoylethyl side chain and C-4′/C-6′ difluoro substituents (Figure 11). EGFR (IC50: 73 nM) and VEGFR2 (IC50: 7.0 nM) were likewise actively suppressed by compound (**17**), but not for PDGFR-β or EGFRT790M (IC50: >10 μM). In the enzymatic tests, (**17**) shown good effectiveness against B-Raf and B-RafV600E; however, it was less effective in inhibiting the proliferation of melanoma A375 cells, which are caused by constitutively activated B-Raf600E. The lower activity of (**17**) for A375 was comparable to that of sorafenib, indicating that (**17**) may attach to B-Raf and B-RafV600E's dormant conformations. The binding positions of (**17**) in B-Raf, B-RafV600E, and VEGFR2 kinases could therefore be discovered via docking simulations. Docking simulations were reported to showed the binding poses of compound (**17**) in B-Raf, B-RafV600E, and VEGFR2 [22].

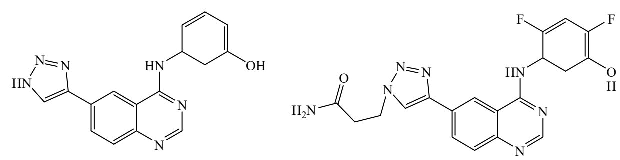
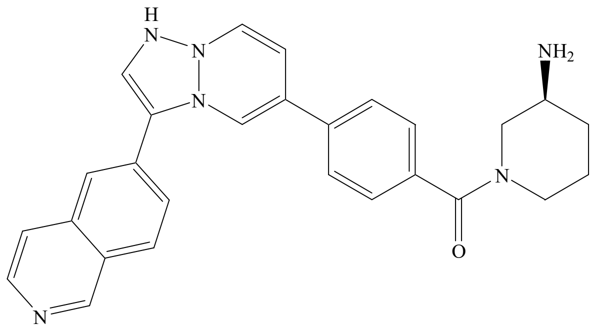


Fig. 11. Structure of compounds (**16**) and (**17**).

IMIDAZOPYRIDAZINE DERIVATIVES

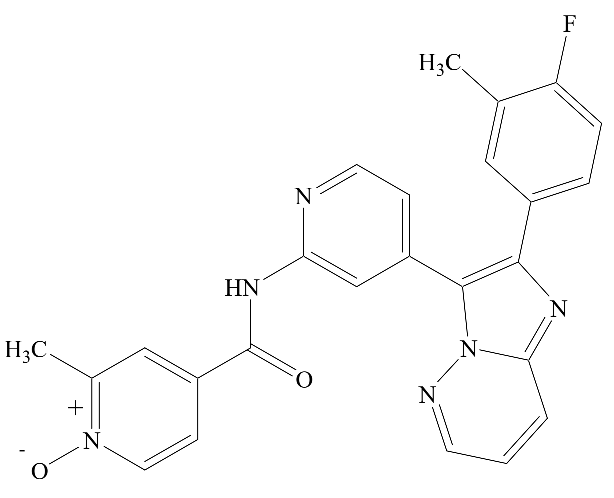
MAPK-interacting kinases (MNKs) are serine/threonine kinases, encoded by MKNK1 and MKNK2 genes, located at the downstream intersection-point of ERK and p38 MAPK signaling pathways. MNKs phosphorylate eukaryotic translation initiation factor 4E (eIF4E) and lead to translate mRNA involved in tumor-associated signaling pathways. However, selective MNK1/2 inhibition, reduces the level of phosphorylated eIF4E and leads to produce anticancer effects [23,24]. Bu et al. reported imidazopyridazine coupled isoquinoline derivatives for selective inhibition for MNK1/2 [25]. Compounds were synthesized from the starting materials 5-bromopyridin-2-amine and 2-bromo-1,1-diethoxyethane followed with Suzuki coupling reactions. Total 37 compounds were synthesized having isoquinoline substitution. The synthesis of compounds were confirmed by spectroscopic techniques using 1H NMR and Mass (MS). Compounds showed potential inhibitory activity against MNK1/2 and few of them possessed anti-proliferative activity against diffuse large B-cell lymphoma (DLBCL) cell lines. Compound (S)-(3-aminopiperidin-1-yl)(4-(3-(isoquinolin-6-yl) imidazo[1,2-a]pyridazin-6-yl)phenyl)methanone (**18**) showed utmost antiproliferative activity against B-cell lymphoma i.e. TMD-8 and DOHH-2 cell lines with IC50 value of 0.3896 μM and 0.4092 μM respectively (Figure 12). Although authors suggested further MNK1/2investigation for compound (**18**).



(**18**)

Fig. 12. Structure of compound (**18**) showed utmost antiproliferative activity against B-cell lymphoma.

Furthermore, Kaieda and colleagues focused and reported imidazo[1,2-b]pyridazine derivatives as p38 MAP kinase inhibitors with pyridine N-oxide group [26]. Authors utilized structure-based design for the synthesis of imidazo[1,2-b]pyridazine derivatives and also reported the SAR, and biological assessment of the synthesized compounds. Among the synthesized compounds, compound N-{4-[2-(4-Fluoro-3-methylphenyl)imidazo[1,2-b]pyridazin-3-yl] pyridin-2-yl}-2-methylpyridin-4-carboxamide 1-oxide sulfate (**19**) exhibited potent inhibition of p38 MAP kinase and LPS-induced TNF-α production in human monocytic THP-1 cells (Figure 13).



(**19**)

Fig. 13. Structure of compound (**19**) exhibited potent inhibition of p38 MAP kinase.

1,5-DIARYLPYRAZOLES DERIVATIVES

Pyrazole is a straightforward heteroatomic ring structure with a hydrogen bond acceptor that is utilized to create several kinase inhibitors that target the ATP adenine binding site. The tiny heterocycle pyrazole is known to have a variety of biological functions, including PK-inhibition. Diarylpyrazoles have been thoroughly investigated as inhibitors of JNK and EGFR mediated anticancer activity. A good anticancer drug that demonstrates EGFR is a dipyrazole derivative, which is the minimum concentration needed to impede cellular growth. Furthermore, high inhibitory activity against several kinases was demonstrated by a triarylpyrazole derivative having a terminal sulfonamide (SO_2NH_2) moiety [27-29]. New compounds having 1,5-diarylpyrazole as pharmacophore were synthesized using fragment-based lead generation approach. This was done because of the importance of the pyrazole ring in multi-kinase design investigations and the beneficial effects of EGFR and JNK-2 inhibitors in anticancer therapy. Vanillin or sulfanilamide-containing 1,5-diarylpyrazole derivatives are being investigated as prospective dual inhibitors of EGFR/JNK-2 for potential anticancer action. With lowest concentrations needed to block IC50 values ranging from 2.7 to 63 μM, these compounds reduced the growth of cancer cell lines. With IC50 values of 2.0 and 0.9 μM, respectively, the tests verified that compounds (**20**) and (**21**) were strong inhibitors of JNK-2, while (**22**) specifically inhibited EGFR protein kinase (EGFR-PK) (IC50 = 1.7 μM). With IC50 values of 2.7 and 3.0 μM against EGFR-PK and JNK-2, respectively, (**23**) notably inhibited both kinases, providing a guide for creating mutual inhibitors of EGFR/JNK-2 (Figure 14). The experimental inhibitory results were supported by the docking investigations, which demonstrated the pyrazole ring's capacity to attach to the hinge area of the ATP binding site. Additionally, during various cell phases, the produced chemicals may cause cell cycle arrest and apoptosis [30].

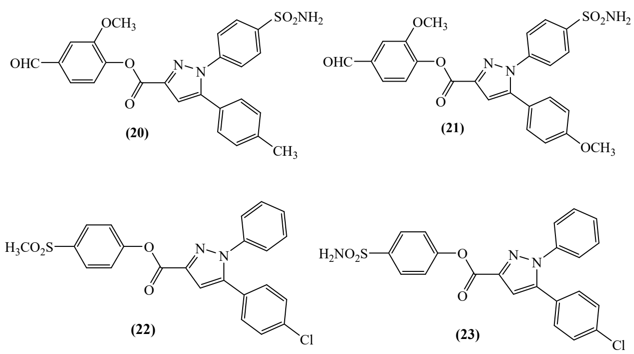


Fig. 14. Structure of 1,5-diarylpyrazoles derivatives (**20-23**).

N-CYCLOPROPYLBENZAMIDE BENZOPHENONE HYBRIDS

A series of 4-aminobenzophenone derivatives were reported as potent p38α MAPK inhibitors. Furthermore 4-aminobenzophenones were investigated within binding mode of p38α MAPK active site disclosed that oxygen of carbonyl moiety makes strong double hydrogen bondings with the NH-group of Met109 and another NH-group of Gly110 instead of amide oxygen via glycine flip (PDB ID: 3QUD) [31]. This interaction provides that the benzophenone scaffold can be a suitable backbone for tight and selective binding to p38α MAPK. Heo and co-workers reported a series of N-cyclopropylbenzamide benzophenone hybrids as novel and selective p38 MAPK inhibitors [32]. Authors synthesized N-cyclopropyl benzamides benzophenone derivatives using a concise synthetic strategy utilizing 4-alkoxy-4'-bromobenzophenones which were prepared from the 4-bromobenzoylchloride. Almost compounds showed potent p38 MAPK inhibitory activities. Compound (**24**), was the first reported compound of the series with an IC50 value of 0.109 μM. The Structure activity Relationship (SAR) of synthesized compounds revealed the presence of lipophilic moiety is conducible for the biological activity. Furthermore, presence of electron-withdrawing groups at the para position of the benzophenone reduces biological activity, whereas methoxy group at same site increase biological activity. The meta-methoxy group also displayed good activity. Compound (**25**) showed highest p38a MAPK inhibitory activity with IC50 = 0.027 μM. In particular, the analog 10g showed potent and selective p38a MAPK inhibition activity (IC50 = 0.027 μM) as well as significant anti-inflammatory properties in monocyte cells (Figure 15). The molecular modelling studies, postulated that cyclopropylbenzamide-benzophenone hybrids are advantageous for being potent and selective p38 MAPK inhibitors. Further studies were proposed by the researchers.

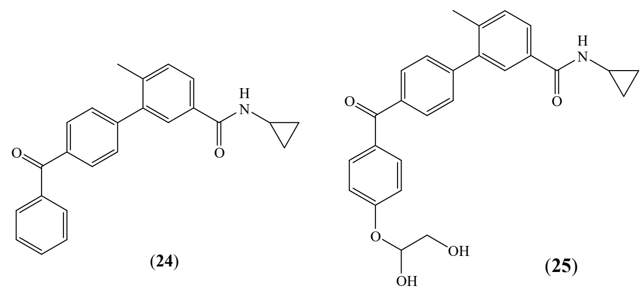
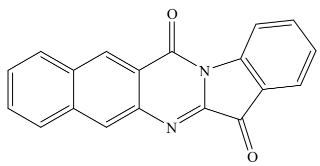


Fig. 15. Structure of compounds (**24**) and (**25**).

PENTACYCLIC RING

Recently, discovery of pseudo-natural products (PNPs) has gained attention in the discovery of novel anticancer agents. Poly heterocyclic systems, including indole and quinazolinone, have demonstrated a variety of biological activities, including anti-inflammatory, anti-hyper tensive properties, and anti-tumor. To build novel scaffolds, researchers utilizes the amalgamation of important pharmacophores including quinolines, quinazolinones, and indoles. Both synthetic and biological chemists have continuously been enthralled by the biological significance of these pharmacophores, which has prompted extensive research into creating new scaffolds and creating new derivatives. Novel pentacyclic molecules, having quinolone, quinazolinone, and indole moieties, were synthesized as an alteration of Niementowski reaction, utilizing the condensation process of several isatin derivatives with 2-aminoquinoline-3- carboxylate. This scaffold's design was informed by the structural properties of four natural products: camptothecin, rutaecarpine, luotonin A, and tryptanthrin. The successful synthesis of the indole-pyrimidine- quinoline (IPQ) scaffold involves a number of sequential processes. With their indole, quinazolinone, pyrimidone, and quinoline units, the pentacycle's constituent parts are biologically relevant. Among the chemicals studied, compound (**26**) showed notable anti-tumor activity efficacy against A549 cell lines (IC 50 values of 0.34 μM) (Figure 16). It was shown that compound (**26**) caused apoptosis in A549 cells and cell cycle arrest in both the G2/M and S phases. Its capacity to regulate the activation of MAPK signaling pathways associated with the mitochondria was credited with these effects [33].



(**26**)

Fig. 16. Structure of compound (**26**) showed notable anti-tumor activity efficacy against A549 cell lines.

CONCLUSION

MAPK becomes a primary target for numbers of anticancer agents. In the present scenario researchers primary focuses to synthesise MAPK inhibitors for cancer therapy. Numbers of MAPK inhibitors have been reported till date. In the present write up we have summarized these inhibitors which were reported in the last decade. Furthermore, we have also summarized their mechanism of action, SAR and synthesis. The present article will help the researchers to design and synthesis further MAPK inhibitors for cancer treatment.

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None.

CONFLICT OF INTEREST

None.

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