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Medicinal attributes of pyridine scaffold as anticancer targeting agents

Esraa Ali Mohamed[1], Nasser S. M. Ismail[2*], Mohamed Hagras[3] and Hanan Refaat[1]

Abstract

Background: The heterocyclic compounds particularly pyridine displayed clinical and biological implementation. Pyridine scaffolds have been detected in most relevant drug molecules that included pyridine provided a great possibility for treatment.

Main text: Pyridine-containing compounds have increasing importance for medicinal application as antiviral, anticholinesterase activities, antimalarial, antimicrobial, antidiabetic and anticancer. This has generated concern among researchers in synthesising a variety of pyridine derivatives.

Conclusion: This review focuses on different pyridine targets as anticancer and their pharmacophoric elements controlling its activity.

Keywords: Pyridines, Anticancer, Cytotoxic action, Tyrosine kinases

Background

Pyridine is a basic heterocyclic organic compound; it is a bioisostere of benzene with one carbon displaced by a nitrogen atom. Also, it exhibited cytotoxic properties against tumour cells due to ortho-position at a nitrogen atom with the impact of methyl substitution on the pyridine ring in 4 or 5 positions. In recent research, it has relied on the synthesis of new anticancer agents targeting the tubulin-microtubule with heterocyclic rings. As Nicolaou et al. manifested cytotoxic properties in some lines of human cancer cells after he had synthesised pyridine epothilones [1]. Cancer is a group of more than 100 different diseases. It can develop almost anywhere in the body. The causes of cancers are host variables such as genetics, epigenetics, microbiome, age, gender, metabolic state, inflammatory state, and immune function. Environmental factors such as food contamination, viruses, UV radiation, carcinogens from the environment and diet/lifestyle factors as nutrients, energy consumption, phytochemicals, other food ingredients, alcohol, physical activity, and smoking. There are over 200 types of cancer: carcinoma, sarcoma, melanoma, lymphoma, and leukaemia. Globally, an estimated 9.6 million deaths were associated with cancer. in 2018. About one in six deaths worldwide were due to cancer. Approximately 22% of cancer deaths is because of tobacco [2]. The processes of carcinogenesis are initiation, promotion, and progression. Initiation is the first step in cancer development. In this stage, a genetic change is caused. Promotion is associated with a raised number of many daughter cells containing the mutation created in initiation. Progression is the last phase in process of carcinogenesis. It is characterised by increasing speed of growth that leads to building up of more genetic abnormalities contributing to the development of phenotype malignant invasive (Fig. 1) [3].

Main text

Synthetic strategy

Synthetic approaches of pyridine are sufficiently well developed. It has been achieved by reaction of acetophenones and 1, 3 diamino propane which is catalysed by copper (a). This transformation providing 2-aryl pyridines [4]. Or 2-substituted pyridines were

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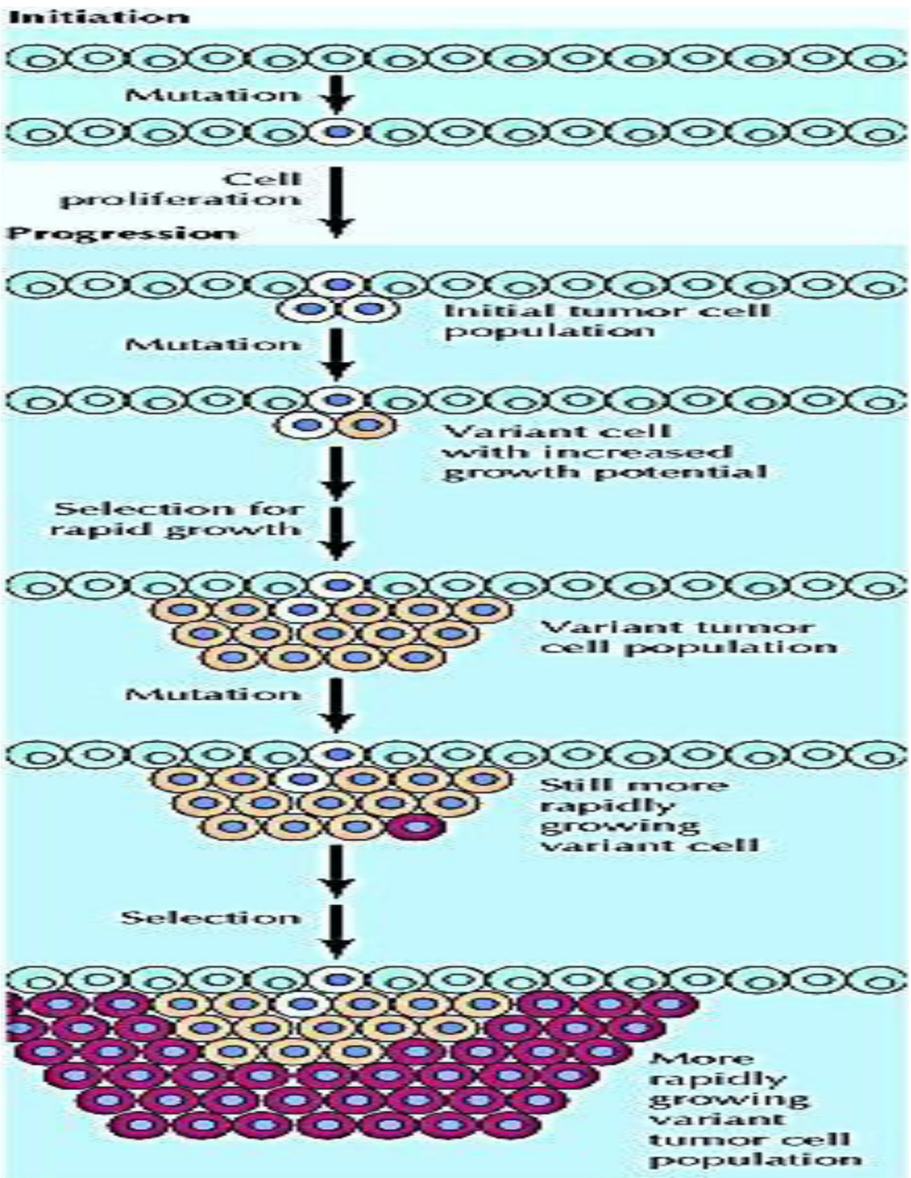


Fig. 1 Process of cancer development [3]

obtained by the addition of Grignard reagents to pyridine-N-oxides catalysed by THF at room temperature then treated by acetic anhydride at 120 °C provided 2-substituted pyridines (b) [5].

Also, pyridine can be obtained by Wittig reaction, Staudinger reaction, and Aza-Wittig reaction. As synthesis of polysubstituted pyridines from aldehydes, phousylides, and propargyl azide (c) [6] provided a wide range of polysubstituted dihydropyridine through lithiation/isomeration/intramolecular carbolithiation (d) [7]. Coupling of silyl enol ethers with α,α-difluoro-β-iodoketones using fac-Ir (ppy)3 under blue LED irradiation can be produced the substituted 3-fluoropyridines with subsequent one-pot condensation with ammonium acetate acetate (e) [8]. Synthesis of 3-hydroxyl pyridine derivatives can be achieved by olefin metathesis (RCM) (f) [9]. Another method for synthesis of pyridine is an efficient base promoted reaction of 1 aryl ethyl amines with alkyne-ones gives enaminones under metal-free conditions to substituted pyridines (g) [10]. Highly substituted pyridines can be obtained by formal dehydrated ruthenium catalysed [4 + 2] cycloaddition of enamides and alkynes (h) [11]. In the presence of $Mn(acac)_3$, reactions of vinyl azides with monocyclic cyclopropanols were produced pyridines. 2-Azabicyclo[3.3.1]non-2-en-1ol was produced from bicyclic cyclopropanols in the presence of a catalytic amount of Mn(acac)3 (i) [12]. The combination of iodine and triethylamine activates a 2-aryl-

substituted pyridine oxime-based synthesis with high chemo selectivity and strong functional group tolerance. Using this metal-free protocol, a wide variety of pyridines derivatives has been synthesised in high yields. Although this process cannot be caused by iodine or triethylamine, mechanistic experiments suggested a radical pathway (j) (Fig. 2) [12, 13].

This review focuses on the chemistry of pyridine derivatives, their potential activities as anticancer against various targets and their structure–activity relationship studies.

Anticancer activity of pyridines

Pyridines acting on carbonic anhydrase inhibitors

Carbonic anhydrase (CA) is a family of metalloenzymes that catalyses the interconversion of CO2 to $HCO3^-$ and H^+ involved in the biocatalysing mineralisation process. It is one of the important enzymes that is found in red blood cells, gastric mucosa, pancreatic cells, and even renal tubules. It maintains acid–base balance, respiration, bone resorption, ureagenesis, gluconeogenesis, electrolyte secretion, and lipogenesis. CA isoenzymes are important therapeutic targets involved in these processes with the ability to be blocked for the treatment of a variety of diseases such as cancer. There are many relationships between CA and cancer [14]. In tumour cell, the transmembrane isoenzymes are CA IX and XII which are found predominantly in normal tissue with very limited amount and in tumour cells. The role of CA IX in cancer development links to hypoxia, acidosis, and beyond (Fig. 3) [15].

Carcinoma in situ

In growing tumour, CA keeps cancer cells from intracellular acidification and hypoxia through triggering extracellular acidosis. CA intercedes cancer cells' adhesion to vessels through producing acidosis that permits for transmigration to the lumen. Also, CA IX keeps cells from anoikis and ease extravasation to the site of secondary residence. CA IX can facilitate metastatic lesion by making focal adhesion and cell spreading. In primary tumours, CA IX has a role of expansion of metastasis by protecting cells from hypoxia and acidosis [16]. The new 4-(3, 4-dichlorophenyl)piperazine moiety compounds demonstrated inhibition of broad-spectrum growth in the 25–89% range across 26 cell lines. Compound 1 displayed the most potent inhibitor with standard inhibitor KI = 10.1 nM [16]. Details of carbonic anhydrase inhibitory activity for compound 1 and normal human

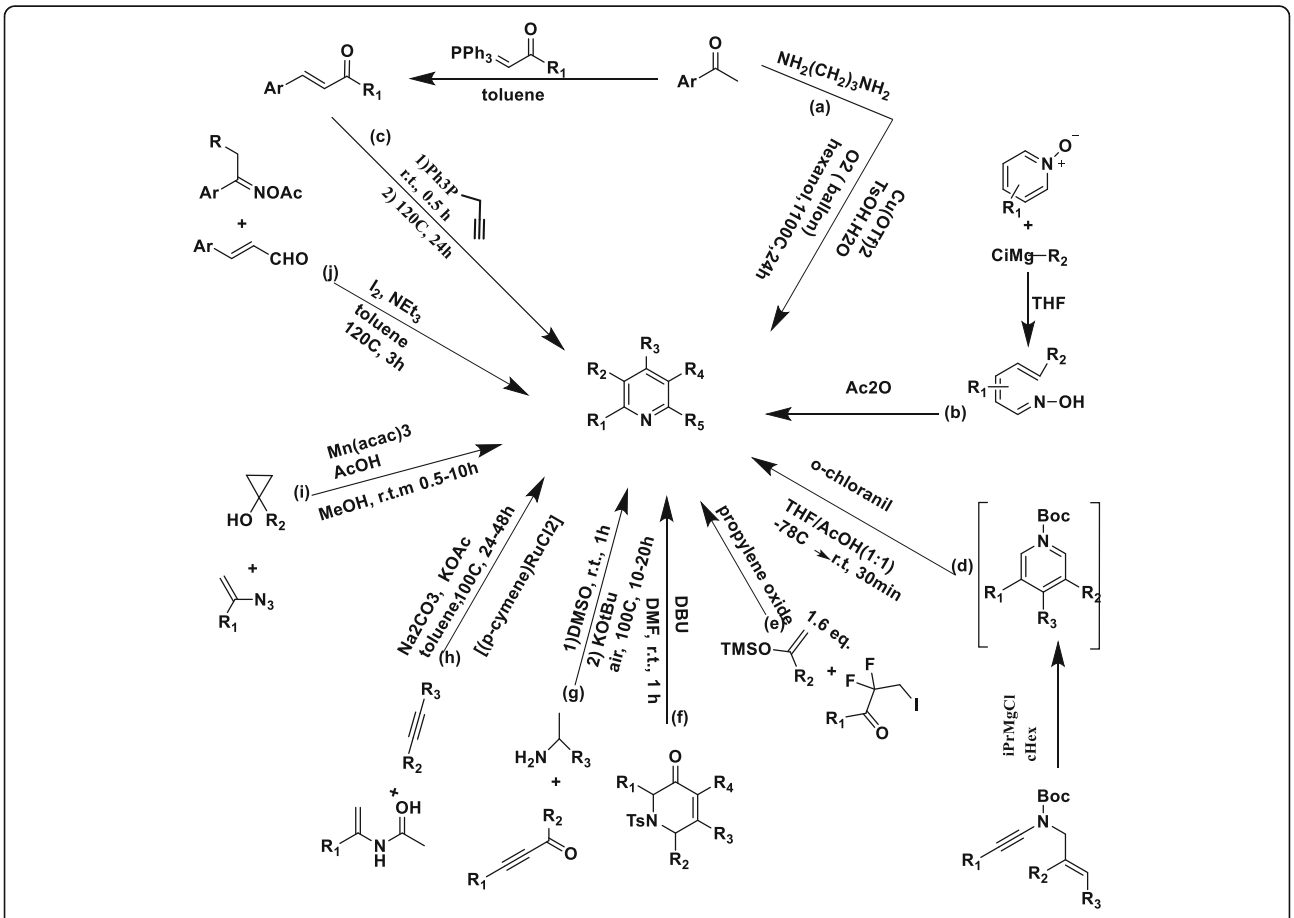


Fig. 2 Synthetic approaches for pyridines [13]

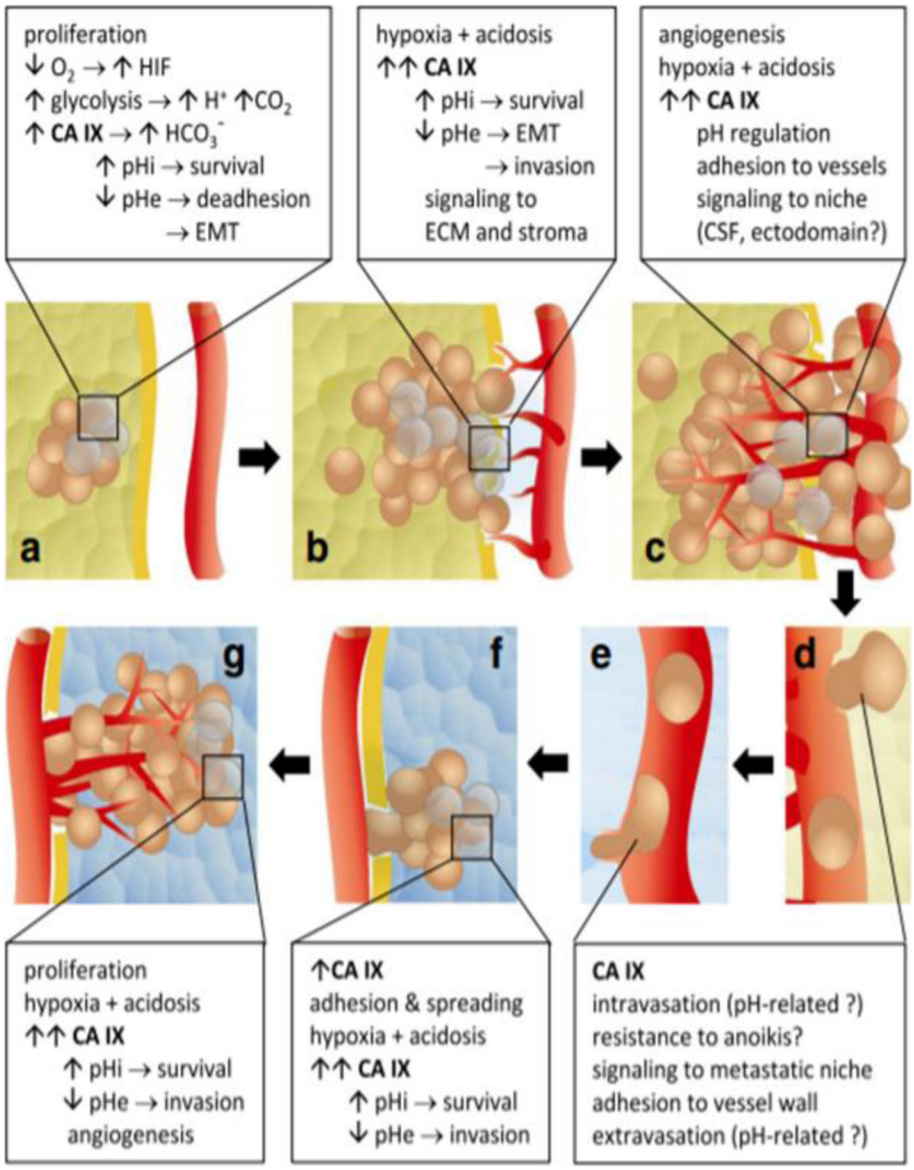
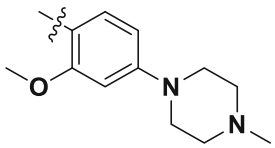


Fig. 3 CA IX involved in several steps of cancer progression [15]

isoenzyme inhibitors hCA I, II, IX, and XII showed 7910 nM, 85.5 nM, 10.1 nM, and 93.4 nM, respectively.



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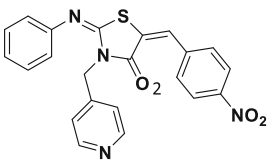
In 2017, Ansari et al. designed novel pyridine-thiazolidinone derivatives which were evaluated as targeting human carbonic anhydrase IX. Compounds 2 and 3 were the most potent CAIX inhibitor with the IC_{50} value, 1.61 μM and 1.84 μM, respectively. These have a significant binding with CAIX by H-bonds and van der Waals interactions with active side residues. Also, these compounds revealed anti-cancer activity against HepG-2 with IC_{50} value 18.9 ± 1.34 μM and 16.2 ± 1.34 μM. In addition, compounds 2 and 3 have shown selectivity for CAIX over CAII approximately 9 and 14 times, respectively [17]. Those two compounds have been tested against human CAII esterase activity with IC_{50} 14.44 and 27.18. Compounds 2 and 3 showed approximately 9 and 14 times selectivity for CAIX over CAII, respectively.



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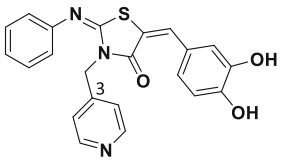

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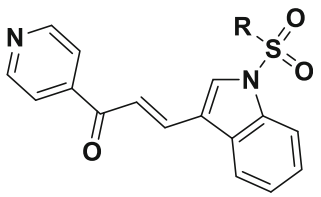
Pyridine-thiazolidinone derivatives' structure–activity relationship explained the compounds containing phenyl ring 3 without substitution and phenyl ring substitution of the alkyl group. Excellent inhibitory activity against CAIX with IC50 = 1.61 μM compound with nitro substitution on benzene ring 8. SAR showed that 7 had an excellent effect on the behaviour of CAIX inhibition in compounds with hydroxyl groups. Excellent CAIX (IC_{50} = 1.84 μM) was present in compound 2 with the di-hydroxyl group. It can be surmised on the basis of SAR studies that the compounds containing polar moieties 2 and 3 on the phenyl ring are ideal for excellent inhibitory action against CAIX. Furthermore, the inhibition of CAIX by a single compound does not depend solely on the presence of the substituents but is essential as a whole molecular skeleton for its purpose. In 2018, Peerzada et al. introduced tertiary sulfonamide derivatives of pyridyl-indole-based heteroaryl chalcone as carbonic anhydrase IX inhibitors and anticancer agents. Compounds 4a, 4b, and 4c showed inhibitory the CA IX selectively (IC_{50}: 4a = 0.15 μM, 4b = 0.13 μM, and 4c = 0.15 μM). They have a better binding affinity. Moreover, they possessed predominant antiproliferative potential and prompted apoptosis in MCF-7 cells with values in 41.75%, 89.33%, and 21.57% of cells, respectively (Table 1). Also, they have anti-tumour evaluation against HepG-2 cell lines in vitro. Thus, it can be explained that the activity of these compounds is substituent dependent [18].



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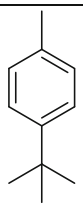
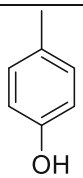
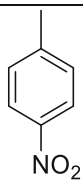
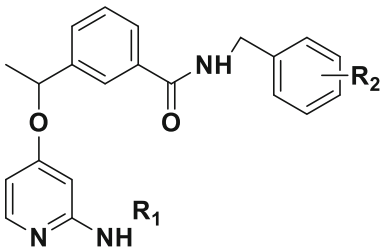
Pyridines acting on ROS1 inhibitors

Proto-oncogene tyrosine protein kinase (ROS) is an enzyme encoded in humans by the ROS 1 gene. It has an anaplastic lymphoma kinase protein (ALK) structural similarity. Like normal physiological ligands, ROS1 plays

Table 1 Biological activity of the compounds (4a–c) against various cell lines

Compound No.	R	HEK-293 IC_{50} (μM)±S.D.	MCF7 IC_{50} (μM)±S.D.	HepG-2 IC_{50} (μM)±S.D.	Esterase assay IC_{50} (μM) hCA IX
4a		150>	24.0±1.16	0.15	27±1.67
4b		150>	48.9±1.19	29.9	44.8±1.35
4c		150>	14.5±1.15	0.15	18.3±1.44

a role in normal development. In 2018, novel 2-amino-4-(1-phenylethoxy) pyridine derivatives have been synthesised by Tian et al. as possible ROS1 inhibitors with 1-phenylethoxy at positions C-3 and C-4. Anti-proliferative effects against ROS1-addicted HCC78 cell lines with IC_{50} values of 8.1 μM and 65.3 μM were demonstrated by the tested compounds, 5a and 5b. In addition, they showed the most inhibitory behaviour of ROS1, values of IC_{50} (440–370 nM). Related binding poses were shared with crizotinib, except for the selective binding site of ROS1 (Table 2) [19]. Specifically, the 1-phenylethoxy substitution of the 2-amino-pyridine ring at position C-4 showed greater activity than that at position C-3. One of the 2-NH2 hydrogen atoms, replaced by the hydrophilic group, would favour action in group R1. Of the substitution groups, the optimal group was 1-(piperidin-4-yl)-1H-pyrazol-4-yl followed by 1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl and followed by 1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl. ROS1 activities were relatively small, whereas other heterocyclics and benzenes were present in R1. For the R2 group, the methoxy groups on the benzene ring of synthesised compounds were in favour of the action. 3,4,5-Trimethoxyl was the optimal group for these groups, followed by 3,4-dimethoxyl, 3-methoxyl, 4-methyl, and 4-CN



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Pyridines acting as ALK/ROS1 dual inhibitors

In 2019, Liu et al. discovered 2-amino-4-(1-piperidine) pyridine derivatives as novel anti-crizotinib-resistant ALK/ROS1 dual inhibitors. A novel DFG-shifted conformation in the kinase domain of ALK was planned to stabilise it. Compound 6 replaced para-trifluoromethoxy at R2 with not only potent inhibitory activity approximately 6-fold over crizotinib (IC_{50}: 104.7 nM vs. 643.5 nM) in ROS1G2032R harbouring Ba/F3 cell line, but also anti-proliferative activity against ALK-addicted H3122 and ROS1-addicted HCC78 cell lines (IC_{50}: 6.27 μM and 10.71 μM, respectively). Also, interestingly, enzyme activity versus clinically crizotinib-resistant ALKL1196 M with an IC50 value of 41.3 nM was reported, which was approximately twice as potent as crizotinib. In addition, compound 8 showed an IC_{50} inhibitor of ROS1 with a value of 1.08 μM (Table 3) [19, 20]. The favoured group, oddly, was para-trifluorometoxy. By increasing the electron density, electron-donating substituents had been lightened.

Cloud on the ring of benzene strengthened the ligand-receptor interaction (Fig. 4). A 2-methoxy-4-(piperazine1-yl) substituent was adequate in the compound 6 study. SAR has shown that the electron-donating substituent is better than one at position R2.

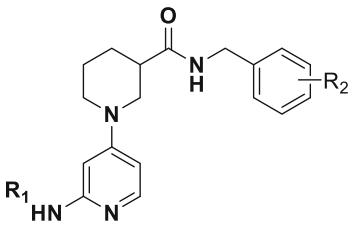

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Table 2 Inhibitory activity of the compounds 5a and 5b kinase activities and in vitro antiproliferative effects

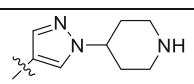
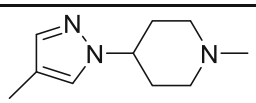
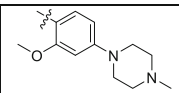
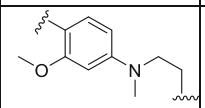
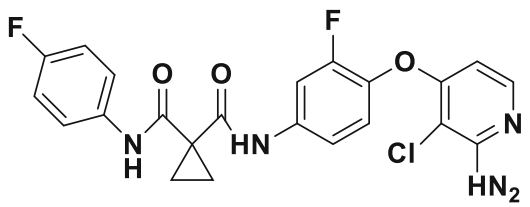
Compd.	R1	R2	Kinase activities ALK	Inhibitory IC_{50} (μM) ROS1	In vitro antiproliferative effects IC_{50} (μM) H3122	HCC78
5a		3.4-di-OMe	4.5	0.37	47.2	65.3
5b		4-Me	3.1	0.44	8.9	8.1

Table 3 The kinase inhibitory activities and in vitro anti-proliferative effects of target compounds

Compound	R1	R2	Enzyme activity				Cellular activity(μM)		
			ALK		ROS1		HCC-78	H3122	A549
			Inhibition (μM)	IC50(μM)	Inhibition (μM)	IC50(μM)			
6a		4-OCF3	90%	0.492	75%	1.08	14.94±4.71	7.53±0.72	7.79±3.63
6b		4-OCF3	95%	0.174	88%	0.530	10.71±2.30	6.45±2.90	3.64±1.27

Pyridines acting on c-Met

The receptor tyrosine kinase (RTK) c-Met is protein that termed the hepatocyte growth factor (HGF) receptor and encoded by a MET gene [22]. Zhao et al. discovered some pyridine scaffolds as type II c-Met inhibitors. C-met has pivotal cascades in formation, dissemination, and progression of many types of cancers, in addition to resistance. Stimulation of HGF is observed repeatedly in different human cancers. So, c-Met has characters that make it a remarkable target for cancer treatment. Compound 7 that holds 4-fluorophenyl substitution displayed potent c-Met inhibitory potency with IC_{50} = 12. Nitrogen-containing aromatic rings in compound 7 minimise both VEGFR inhibitory activities and side effects. Finally, this compound exhibited both an acceptable kinase selectivity profile and anti-proliferative activity (IC_{50} = 127 nM against EBC-1 cell line) [21].



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Wang et al.'s rational design in 2018 leads to the discovery of a novel and potent sequence of 1H-pyrrolo [2, 3-b] pyridine derivatives as c-Met inhibitors carrying aromatic hydrazone moiety. Many of the latest compounds tested for the IC_{50} values against cancer cell lines (A549, HepG2, MCF-7, and PC-3). Also, these compounds showed perfect cytotoxicity activity. Further, they can trigger apoptosis of A549 cells and arrest worthily the cell cycle progression in G2/M

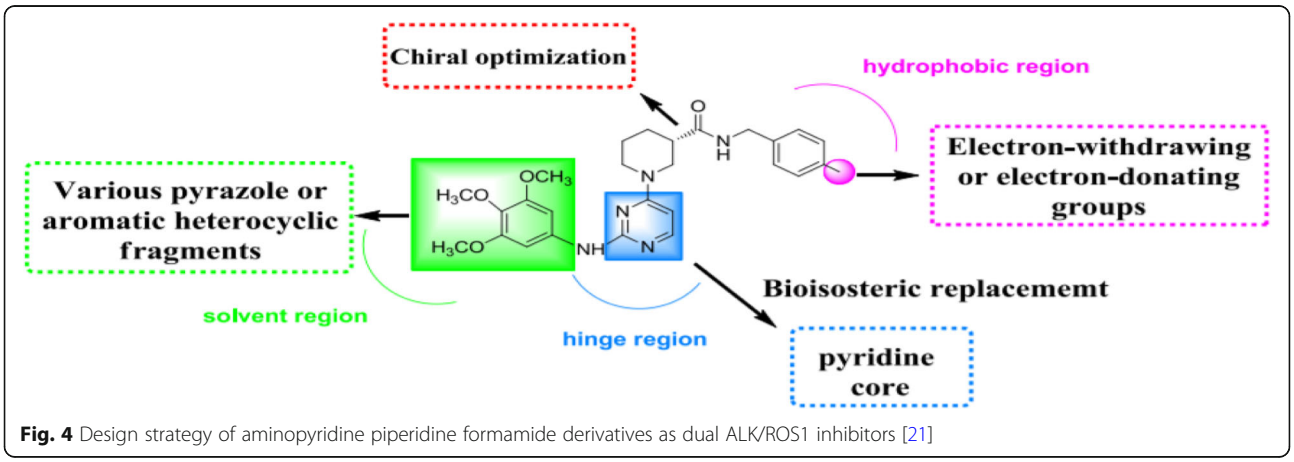
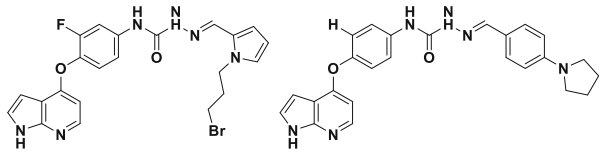


Fig. 4 Design strategy of aminopyridine piperidine formamide derivatives as dual ALK/ROS1 inhibitors [21]

phase of A549 cells. Two compounds 8 and 9 were further profiling against c-Met kinase in vitro. An ATP mobility change assay with reference compound Foretinib (Table 4) [23].



8 9

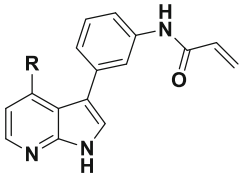
Molecular docking simulation studies were achieved for compound 8. The 3D and 2D graph were depicted, and the hydrogen was coloured with green, the pi-pi stacked bond was coloured with blue, and the halogen was coloured with pink (Fig. 5).

Pyridines acting on EGFR

Epidermal growth factor receptor is a transmembrane receptor that has a vital role in cell proliferation, survival, differentiation, and migration [25]. Also, it is carrying out both redundant and restricted functions in development. It contains an extracellular binding site for the domains of epidermal growth factors (EGF) and intracellular tyrosine kinase. Many human diseases especially cancer results from misregulation of EGFR. So, inhibiting this pathway has proven as an efficient cancer treatment (Fig. 6).

An extended conformation resulting from ligand binding induces kinase domain dimerisation and activation. ATP binding site is formed by the kinase loops of the C- and N-terminals. The X-ray structures demonstrate that the affinity of inhibitors for the binding site originates from hydrogen, bonding to the main chain between the N-1 of pyrimidine, NH from Met793. For AEE-788, an association between hydrogen bonds between N- and Thr854, bridged water was observed through water molecules [26].

Potent and novel 3,4 Diaryl 1H pyrrolo[2,3 b] pyridines scaffolds were introduced for use as irreversible inhibitors of mutant EGFR L858R/T790M through scrutinise the effect of different aromatic substituents in the 4 position that introduced by using either Suzuki or Buchwald-Hartwig cross-coupling reactions. Compound 10c exhibited the most potent in the gefitinib resistant EGFR-L858R/T790M enzyme assay and selectivity over the wild type. It was reported that compounds 10a and 10b showed the most selective compounds over 10-fold selectivity for the mutant enzyme over the wild type. It can conclude the importance of electron-rich heterocycles in the activity of compounds 10a and 10b. Moreover decoration of the 1H-pyrrolo[2,3-b]pyridine with indol-3-yl substituents in compound 10c lead to improve the activity (Table 5) [27].



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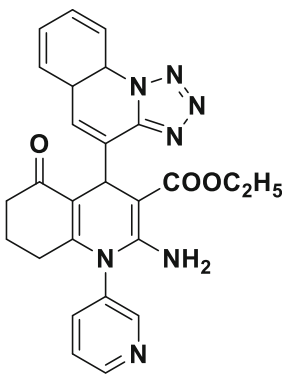
Pyridines acting as EGFR and HER-2 kinase inhibitors

EGFR family includes EGFR (HER1/ErbB-1), ErbB-2 (HER2/neu), ErbB-3 (HER3), and ErbB-4 (HER4) [27]. HER2 (human epidermal growth factor receptor 2) is a gene that has had breast cancer connection. It recently employs around 30% of breast cancer patients as an effective biomarker and therapy target. It plays a vital role in tumour development and progression. On the contrary, Sanganiet al. unmasked new class of potential EGFR and HER-2 kinase inhibitors possessing biquinoline–pyridine hybrids which intended by a base-catalysed cyclo condensation through one-pot multicomponent reaction [27]. The most outstanding activity as dual EGFR and HER-2 inhibitors was laboured by compound 11 with IC_{50} = 0.09 μM against EGFR and HER-2 kinase with IC_{50} = 0.2 μM. Molecular modelling study showed the binding mode by four hydrogen bonds and two p–cation interactions with the effective pocket of EGFR (Fig. 7). The binding energy DGb = 54.4 kcal/mol.



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Structure–activity relationship depends both the heteroaromatic bicyclic revealed that the activity in deceasing

Table 4 Action against c-Met kinase inhibitory of selected compounds 8 and 9

Compounds	IC_{50}(μM)
	C-Met
8	0.506
9	0.907
Foretinib	0.014

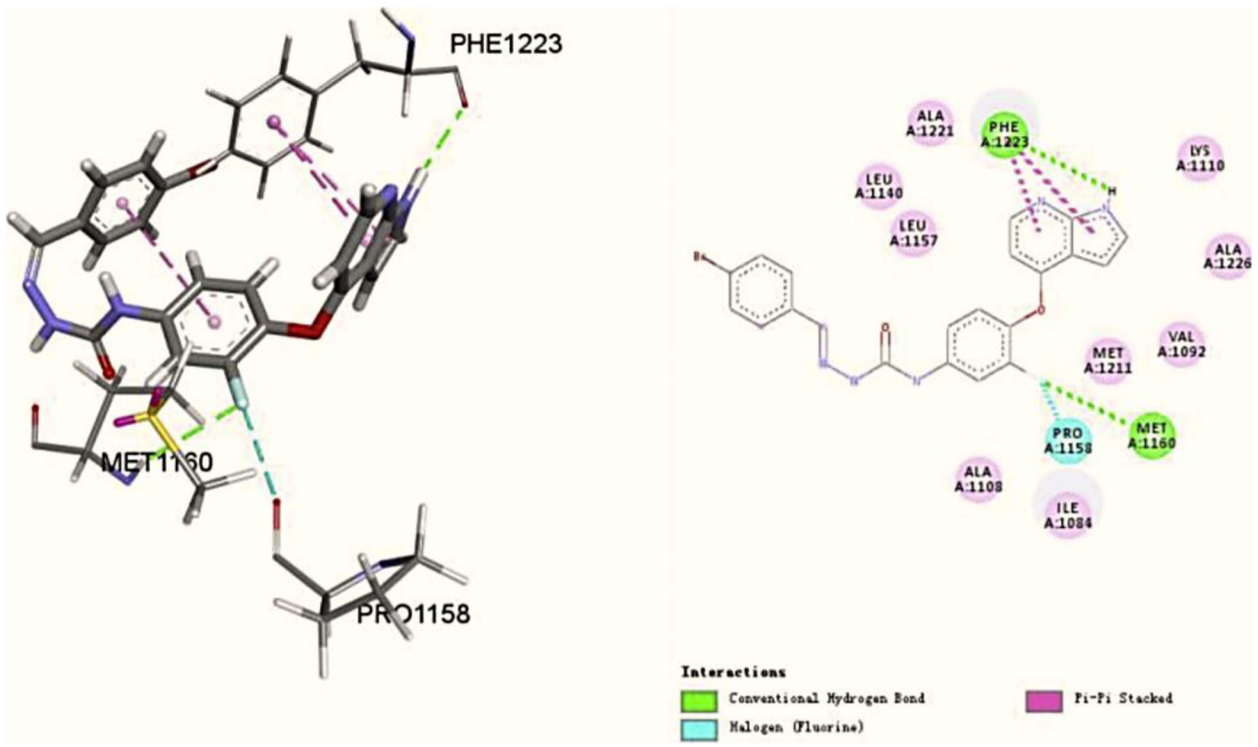


Fig. 5 The binding mode of compound 8 with c-Met [24]

order for R1 substitution is H > OCH3 > CH3 > Cl and for R2 substitution is COOEt > COOMe > CN for EGFR and HER-2 kinase inhibitors. But the activity in deceasing order for R1 substitution is Cl > H > CH3 > OCH3 and for R2 substitution is COOMe > COOEt > CN for cancer cell lines A549 and Hep G2 [27].

Pyridines as cyclin-dependent kinase (CDK) inhibitor

CDKs are a set of serine/threonine kinases. They control the eukaryotic cell cycle by their function in cell growth, development, proliferation, and death. They are answerable for the cell cycle's coincidence. CDKs, with their partner subunit cyclin, take responsibility for the

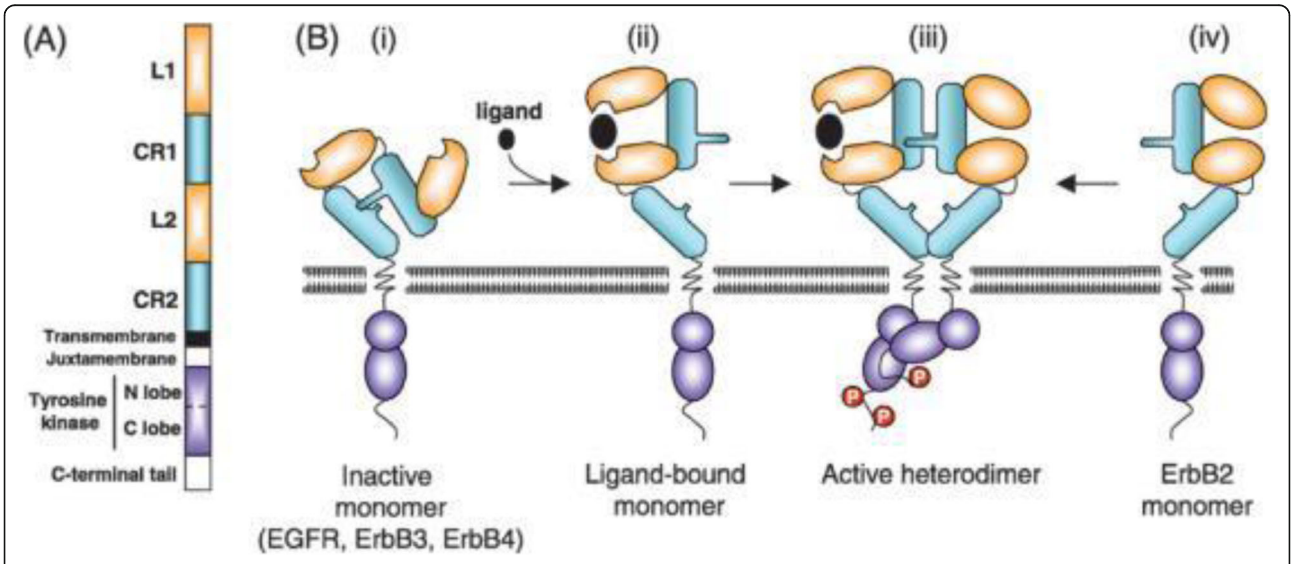
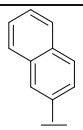
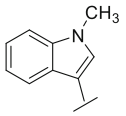


Fig. 6 Mechanism of action of receptor tyrosine kinases [25]

Table 5 IC_{50} values in an EGFR-L858R/T790M kinase assay

No.	R	IC_{50}EGFR-L858R/T790M(μM)
10a		0.198
10b		0.027
10c		0.001

harmonisation of the event series by cell progression occuring during the cell cycle. At particular levels, they become effective. They turned into active at specific phases: G1, S, G2, and M. CDK9 is a transcriptional regulator that controls the expression in cancer cells of anti-apoptotic proteins that enforce immortality. It interacts with many transcription variables (TFs) and regulates their operations. By attacking both androgen receptor activity and anti-apoptotic proteins, CDK9 inhibitors can supply a novel and greater therapeutic scope over conventional treatment choice [28, 29]. Nada et al. recently designed and synthesised of novel imidazo[4,5-b]pyridine based compounds as cyclin-dependent kinase 9. In a particular way, compounds 12 and 13 were the most active compounds CDK9 enzyme assay (IC_{50} = 0.50–1.002 μM). In addition, compound 12 found the

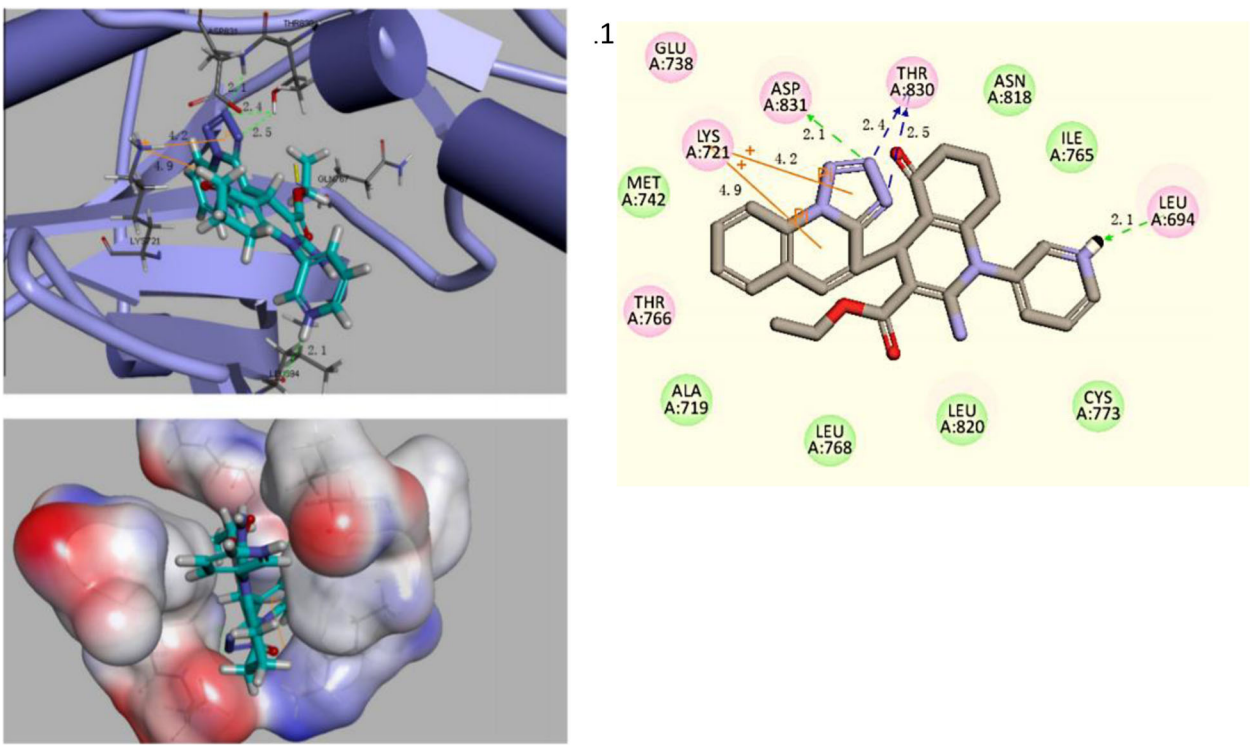
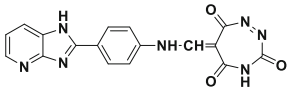


Fig. 7 a, **b** 2D and 3D binding model of compound 11 into the active pocket of EGFR [28]

most potent at a sub micromolar level against breast cancer cell line (IC_{50} = 0.63 μM), and in addition, it exhibits an optimum pharmacokinetic profile and drug-likeness. Indeed, a molecular docking study was carried out to show the most compound that has binding affinity and to test the selectivity against CDK2/4 and 6. The native ligand (T3C) and the multi-kinase inhibitor sorafenib as a reference compound used to compare them with the results of docking [30].



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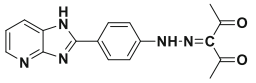
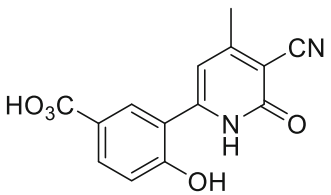


13

The tested compounds had anticancer activity and CDK9 inhibitor. Different substitutions in the Ar1 group cause the behaviour of newly synthesised compounds to change. The different modifications revealed on the SAR scheme (Fig. 8).

Pyridines as PIM-1 kinase inhibitors

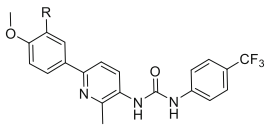
PIM kinases are serine/threonine kinases. They have three subtypes: PIM-1, PIM-2, and PIM-3. PIM-1 kinase is linked with many cellular functions like proliferation, differentiation, survival, and apoptosis. Also, it has a role on progression and initiation of some types of cancer such as lymphomas, leukaemia, and solid tumours such as prostate, pancreas, and colon [32]. So, inhibition of PIM-1 kinase is an important target for the treatment of malignancies. In 2018, Abdelaziz et al. synthesised novel pyridine and thieno[2,3-b] pyridine series with diversified inhibition activity. The results gained from IC50 values, SAR studies, and docking studies conclude that the most active compound was 14 with IC_{50} 0.019 μM which substituted with hydrophilic at 4-position and 2-hydroxy-5-methoxyphenyl at 6-position.



14

Pyridines acting on VEGFR

Inhibition of receptor tyrosine kinases leads to synergistic inhibition of solid tumours. As they existent in endothelial cells (VEGFR, PDGFR), tumour cells (FGFR, PDGFR), and pericytes/smooth muscle cells. VEGFR are vascular endothelial growth factor receptors that have three subtypes [33]. They involved in angiogenesis and vasculogenesis. They can be found on surface of some normal cells and included in cell growth. Furthermore, it may be implicated in some types of cancer cells. VEGF receptor-2 (VEGFR-2) has been specified as KDR glycoprotein. It specified for the signalling pathway which taking charge of formation of new blood vessels from tumours and prosperity through supplying with oxygen and nutrients [34, 35]. This occurs when it is activated. VEGFR-2 subjected for autophosphorylation, triggering signalling pathways leading to the proliferation of endothelial cells and then angiogenesis of tumours facilitating tumour development and metastasis. Disarray of VEGF signalling through a variety of different methods has produced in angiogenesis inhibition and tumour development. In 2018, El-Naggar et al. synthesised of target pyridine-ureas derivatives that suppress VEGF R-2 and bearing potential antitumor activity [35]. The IC_{50} values for the inhibitory activity against VEGFR-2 of compounds 15 and 16 were 5.00 ± 1.91 and 5.00 ± 1.91, respectively.



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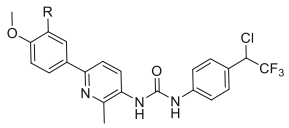


16

These compounds also were evaluated for their in vitro anticancer action according to National Cancer Institute (NCI) assay protocol with mean inhibition = 43 and 49%, respectively. Approximately 58 cancer lines are grouped into disease subpanel growth inhibition against all from nine different cancer subtypes: leukaemia, colon, melanoma, ovarian, lung, CNS, renal, breast, and prostate cancers. They demonstrated anti-proliferative activity of all checked cancer cell lines (GI for 15; 12–78%, GI for 16; 15–91%).

Pyridines acting on topoisomerases

Topoisomerases are enzymes that catalysing breaking and rejoining of phosphodiester backbone in DNA strands during the cell cycle. Currently, topoisomerase inhibitors are used in the treatment of cancer and bacterial infection. As anticancer, topoisomerase inhibitors block ligation step subsequently, leads to apoptosis and cell death as a result of producing single- and double-strand breaks which damage the whole genome. In 2019, a novel sulphur heterocyclic thiophene derivative containing 1, 2, 3-triazole and pyridine moieties namely BTPT [2-(1-benzyl-5-methyl-1H1, 2, 3-triazol-4-yl)-6-methoxy-4-(thiophen-2-yl) pyridine]. Compound 17 was designed and synthesised as a potential human topoisomerase IIα inhibiting anticancer agent [36].

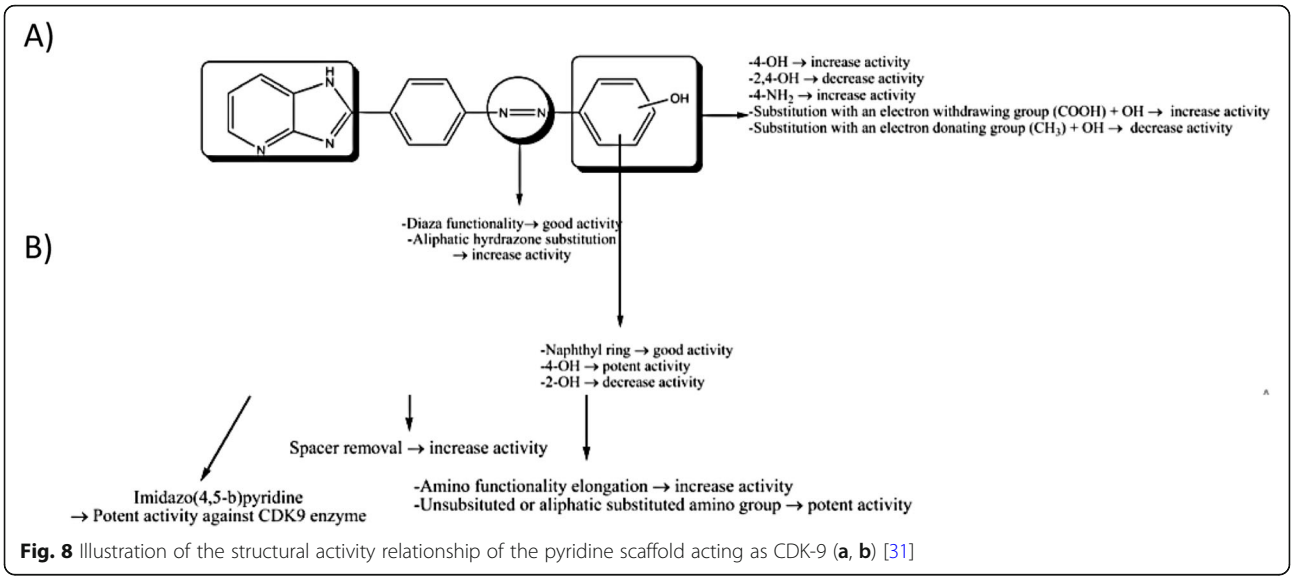
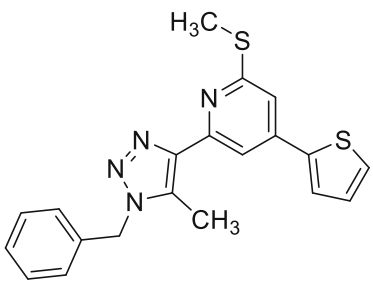


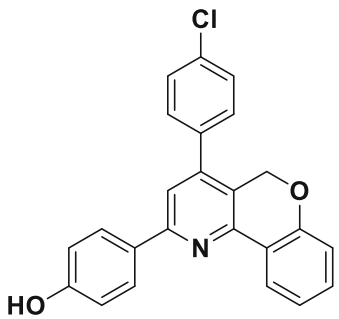
Fig. 8 Illustration of the structural activity relationship of the pyridine scaffold acting as CDK-9 (**a**, **b**) [31]



17

The design of the structure was gained by single-crystal X-ray diffraction analysis. Compound 17 elucidated cytotoxicity activity in vitro examined by MTT assay procedure against three human cancer cell lines A549, PC-3, MDAMB-231 with IC_{50} values of 0.68/0.70, 1.03/0.77, and 0.88/0.98 μM, respectively. In molecular docking study, the inhibitory behaviour of the title compound 17 targeting the human topoisomerase IIα ATP binding site (PDB ID: 1ZXM) was identified. Visual analysis of docked complexes was performed by evaluating the interactions of the hydrogen bond, linking BTPT compound 17 to target site residues active in ATP Protein 1ZXM through interactions of four hydrogen acceptors and one major interaction of the π-sulphur bonds (Fig. 9).

Bahadur et al. introduced new hydroxy and chloro-substituted 2,4-diphenyl 5H-chromeno[4,3-b]pyridines as selective topoisomerase IIa-targeting anticancer agents built on the strategy of ring expansion from constrained five-membered heterocyclic ring to more stable six-membered heterocyclic. The structure–activity relationship study for the tested compounds revealed that many compounds with 2,3,4-hydroxyphenyl group at 4-position exhibited better topo IIa inhibitory activity and the antiproliferative activity than compounds containing 2,3,4-hydroxyphenyl group at 2-position of the central pyridine ring. Such findings illustrated the significance of moiety hydroxyphenyl at 4-position and chlorophenyl moiety at 2-position for exhibiting selective topo IIa inhibitory and antiproliferative activity. Compound 18 represented % inhibition of Topo IIa = 100 μM.



18

Introduction of 3 and 4 hydroxyl group is greater than the 2-hydroxyl group at 2-phenyl ring for strongly inhibiting topo IIa activity and antiproliferation. The position of chlorine substitution on 4-phenyl ring not linked with selective topo IIa inhibitory activity and antiproliferative activity. Also, the effect of ring expansion revealed that the replacement of five-membered heterocyclic ring moiety with six-membered heterocyclic ring moiety significantly impacted the topo I and IIa

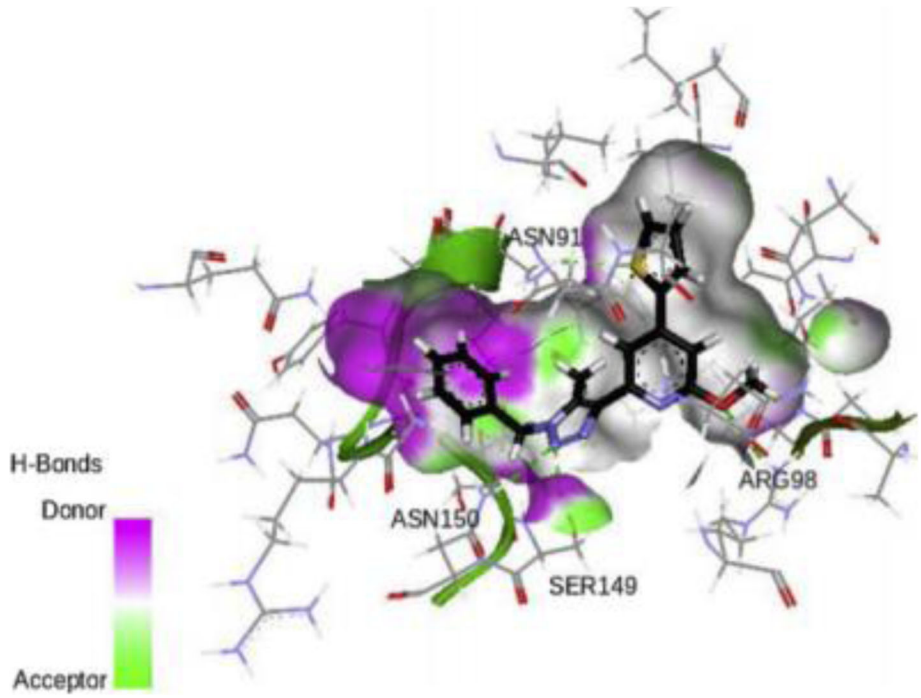


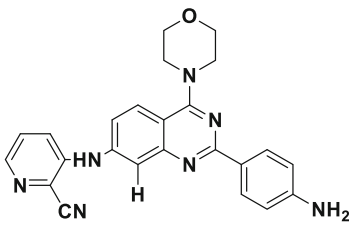
Fig. 9 3D docking pose of compound 17 with 1ZXM active site residues. Hydrogen bonds are marked with green dotted lines [37]

inhibitory properties of compounds [38]. The overall SAR study is shown in Fig. 10.

Pyridines acting on phosphoinositide 3-kinase

The mammalian target for the rapamycin signal transduction pathway (mTOR), the 3-kinase phosphoinositide, is included in numerous essential basic cellular functions such as cell formation, proliferation, differentiation, motility, intracellular transport, and reproduction. A family of lipid kinases and, on the basis of their classification, homology, and substrate preferences, are classified into three distinct groups (I, II, and III). In PI3Ks, it is possible to subdivide the most commonly known class I into class IA (PI3Ka, b, and d) isoforms and class IB (PI3Kg) isoforms. PI3 K activation occurred by receptor tyrosine kinases, GTPases of the Ras and Rho families, resulting in phosphorylation of PIP2 (phosphatidylinositol 4, 5-diphosphate) producing PIP3 (phosphatidylinositol 3, 4, 5-triphosphate) to the 3-hydroxyl position. Strong ones

Secondary messenger that causes various downstream effectors to be activated, including serine-threonine kinase, Akt (also known as protein kinase B or PKB [37]. One of the most mutated oncogenes is the isoform gene coding the PI3 K catalytic subunit P110a (PIK3CA) and has increased its mutation rates. This has been detected in cancers of the breast, colorectal, liver, and other types of cancer. It has been intensively targeted at this cancer pathway therapies. In 2016, Peng et al. synthesised the new 2-(2-aminopyrimidine-5-yl)-4-morpholino-N-(pyridine-3-yl)quinazoline-7-amine sequence of PI3K/mTOR inhibitors and anti-cancer activity against seven cancer cell lines were evaluated in vitro, namely PC-3, DU145, MCF-7, BT474, SK-BR-3, U937, and A431. The rational design in 2016 lead to the discovery of highly potent novel compounds of 2-(2-aminopyrimidin-5-yl)-4-morpholino-N-(pyridin-3-yl)quinazolin-7-amines compound 19 as PI3K inhibitors [39]. Moreover, compound 19 undergo further profiling against other kinases as PI3Kα, PI3Kβ, PI3Kγ, PI3Kδ, mTOR9 with IC_{50} 4.2, 13, 64, 50, and 78 nM, respectively. Also, it has an effect on p-Akt (S473) and cell cycle.



19

Pyridines acting on maternal embryonic leucine zipper kinase (MELK)

Maternal embryonic leucine zipper kinase (MELK) belongs to the serine-threonin family snf1/AMPK kinases involved in various cellular processes including stem cell regeneration, pre-mRNA splicing, cell proliferation,

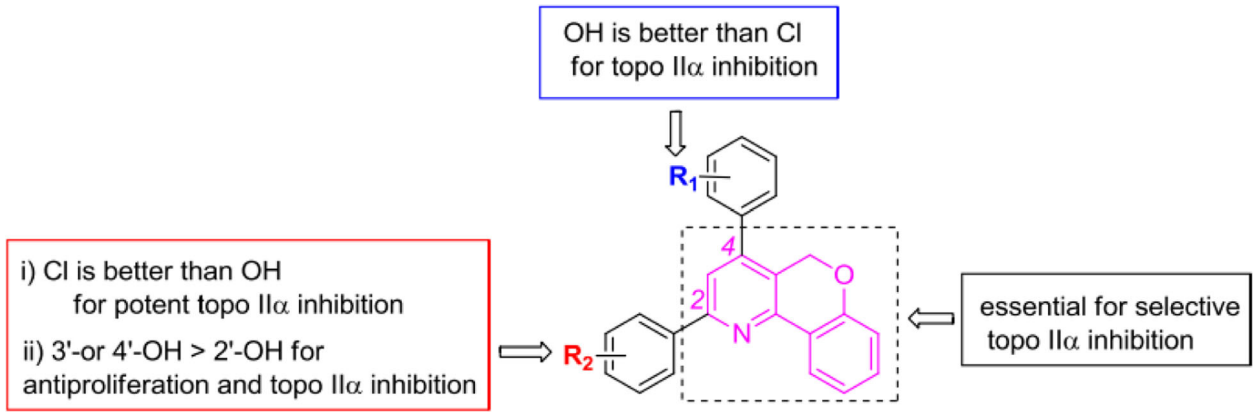
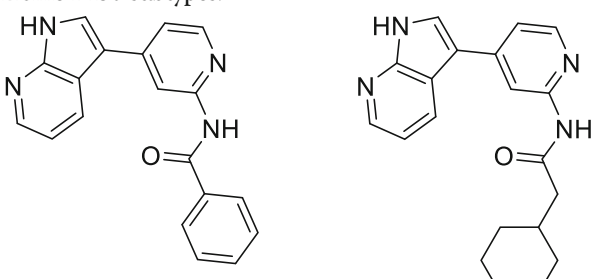


Fig. 10 Overall structure-activity relationships of hydroxy and chloro-substituted 2,4-diphenyl 5H-chromeno[4,3-b]pyridines [39]

progression of the cell cycles, and migration of cells [40, 41]. More specifically, MELK's overstatement diverse human cancers have been identified and are associated with more severe forms of astrocytoma [42], melanoma [43–45], cancer in the breast [46], and glioblastoma [47]. Increased MELK expression is also correlated to the pathological grade and expression rates of brain tumours [48] are significantly associated with poor prognosis cancer patients of prostate, breast, and glioblastoma. This has been demonstrated in several studies. Systems that have MELK-mediated/shRNA knockdown contribute to decreased viability of the liver, colon, breast, and pancreas. In 2019, Wanga et al. designed, synthesised, and evaluated for in vitro biological activities against maternal embryonic leucine zipper kinase (MELK) [47], a family of 3-substituted 1H-pyrrolo[2,3-b]pyridine derivatives. With IC50 values ranging between 122 and 558 nM, compound 20 demonstrated moderate potency against MELK. Compound 21 displayed strong enzyme inhibition (IC_{50} = 32 nM) and excellent antiproliferative effects on A549, MDA-MB-231, and MCF-7 cell lines with IC_{50} values from 0.109 to 0.245 μM. Flow cytometry tests showed that promoted apoptosis of A549 cells in a dose-dependent manner and effectively arrested A549 cells in the G0/G1 phase. Also, it potently decreases the migration of A549 cells, had fair stable liver microsomes in rats and shows moderate inhibitory activity against different cytochrome P450 subtypes.



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21

Moreover, compound 21 is a multi-target kinase inhibitor. Molecular modelling study was achieved, it was used for generation of images, and for potential binding mode data, the 1H-pyrrolo[2,3-b]pyridine scaffold establishes two hydrogen bonds with the NH of Cys89 and the backbone carbonyl oxygen of Glu87 in the hinge region. A hydrogen bond with Lys40 was formed by the pyrimidine nitrogen, hydrophobic interactions between the pyrimidine ring and Ile148, Leu86, and Leu61 hydrophobic side chains. In addition, the piperidine moiety seemed to point to the solvent area via the creation of a salt bridge with Glu93 at the edge of active pocket (Fig. 11).

Pyridines acting on potential cytotoxic agents and NF-κB inhibitors

NF-egB is a class of transcriptional eukaryotic factors that are proteins. It also occurs in the cytoplasm bound to the subunit regulator IjB in unstimulated cells. Upon activation of these cells by external rewards or cellular signalling, the active NF-egB releases its cytoplasmic complex from external stimuli or cellular signalling, translocate and binds to DNA nuclei [49, 50]. Cell signalling relevant to cell survival, cell differentiation, and cell growth is regulated by binding NF-xB to DNA. The disconnection from their regulators of NF-gunB proteins results in their composite activation. NF-κB activated is involved in various forms of carcinogenesis, for example, cancer proliferation cell, preventing apoptosis, and increasing metastatic capacity. Kamala et al. recently synthesised a new compounds of imidazo[1,2-a]pyridine linked with thiazole/thiophene motif via a keto spacer. Compound 22 had absolute NF-YB activity inhibition as determined by assay by NF-κB reporter with (IC_{50} = 6.5 ± 0.6 μM). In contrast compound 23 showed IC_{50} = 184.58 ± 1.47 μM [51].

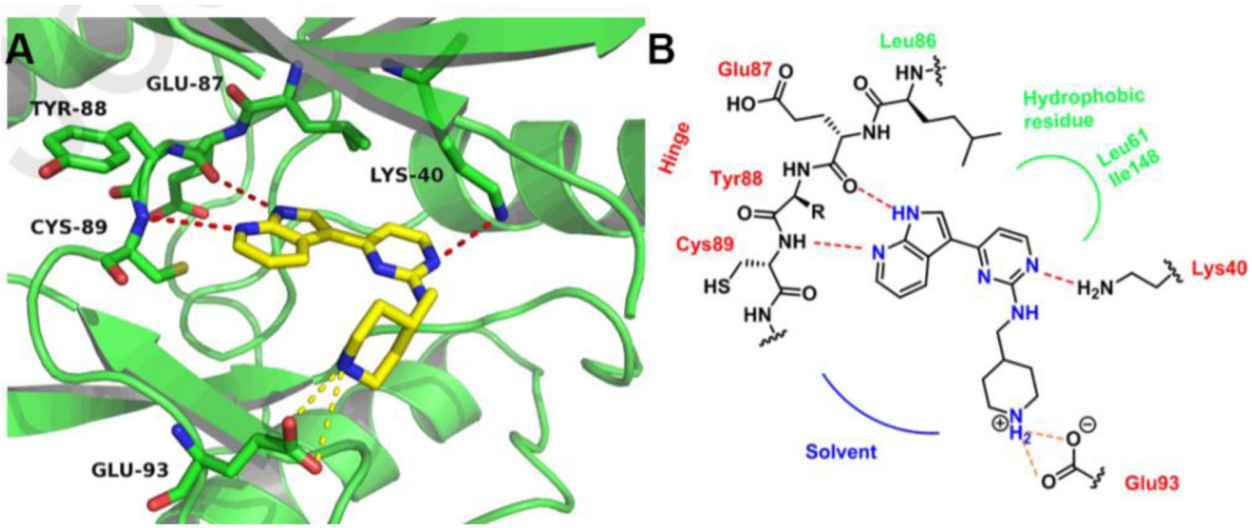
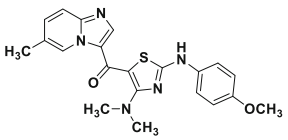


Fig. 11 Molecular docking mode of compound 21 into the MELK active site. **a** Detailed interactions with the protein residues. Each of the dashed red and yellow lines represent hydrogen bonds and salt bridges. **b** The two-dimensional interaction diagram showing the interaction of compound 21 with key amino acid residues in MELK active site [49]



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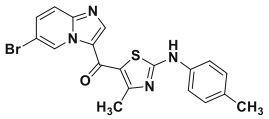

23

Conclusion

Pyridine moiety is present in several compounds representing numerous biological activities such as antiviral, antimicrobial, and anticancer. This review investigated the role pyridine scaffold as an anticancer agent that performs on carbonic anhydrase inhibitors, ROS1 inhibitors, ALK inhibitors, C-met, EGFR, HER-2 kinase, CDK, PIM-1 kinase, VEGFR, topoisomerases, phosphoinositide 3-kinase, maternal embryonic leucine zipper kinase, and potential cytotoxic agents. This review will facilitate the design and synthesis of novel prospects for drugs used as anticancer.

Abbreviations

CA: Carbonic anhydrase; RCM: Ring-closing olefin metastasis; CDK: Cyclin-dependent kinase; c-Met: c-Met proto-oncogene; HER: Human epidermal growth factor receptor; EGFR: Epidermal growth factor receptor; FGFRs: Fibroblast growth factor receptor; PDGFR: Platelet-derived growth factor receptor; PI3K: Phosphoinositide 3-kinase; SAR: Structure–activity relationship; VEGFR: Vascular endothelial growth factor receptor; ALK: Anaplastic lymphoma kinase protein; MELK: Maternal embryonic leucine zipper kinase; NCI: National Cancer Institution; PIP: Phosphatidylinositol; $Mn(acac)_3$: Manganese acetylacetonate

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Authors' contributions

All authors have read and approved the manuscript. E.A. collected all the data and wrote the review. N.S. prepared all figures and participated in writing the review. M.H. revised the methods and references section. H.R. revised the whole review and updated it.

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Consent for publication

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Competing interests

The authors declare they have no competing interest regarding this review.

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