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The significance of *N*-methylpicolinamides in the development of anticancer therapeutics: Synthesis and structure-activity relationship (SAR) studies

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ABSTRACT

Cancer is the second most important cause of death worldwide. There is always a demand for new anticancer drugs and continuously a wide variety of natural and synthetic compounds were developed by the researchers. Nowadays, a large number of drugs in clinical practice were found to have a high incidence of side effect and multidrug conflict. The development of novel less toxic, low cost and very energetic *N*-methylpicolinamide-bearing hybrids is a hot research topic in the community of medicinal chemistry. Herein we highlight the current advances in the synthesis of picolinamide-containing heterocyclic compounds as potent anticancer agents. In addition, briefly explore their structure-activity relationship studies for the inspiration of the innovation and development of more potent and effective drugs against various death-causing cancer diseases.

1. Introduction

Development in the area of anticancer therapeutic agents is one of the key challenges in medicinal chemistry [1]. Cancer is a fast and uncontrolled proliferation of abnormal state of cells, in medical terms as malignant neoplasm or malignant tumor. It is one of awful infections causing maximum transience rates in the world. Cancer is the second most dangerous disease next to the heart diseases causing 550,000 deaths in a year with 7.6 million cancer deaths in 2008 and an estimated 13.1 million in 2030 [2–4]. At present, a number of cutting-edge recognized researches and chemotherapies are unsuccessful due to the major limitations such as drug resistance and side effects. This continued the demand of newer and safe anticancer drugs for future cancer chemotherapy [5]. Due to the different side effects of conventional cytotoxic anticancer drugs, it is required to develop novel antitumor drugs with high efficiency and low toxicity. Recent advances and applications on multiple targeted agents may meet the expense of effective chemotherapeutics with low toxicity.

Anticancer drug innovation has been stoutly focused on the improvement of drugs to act against a definite target with high potency and selectivity. Clinical experience including the discoveries of drug resistance in cancer chemotherapy has disclosed that single targeting might not always construct the preferred biological outcome, even if the target is inactivated or reclusive [6–8]. The reason is the development of resistance either by self-modification of the target through mutation or by the approval of new pathways of a cancer cell, for the growth and reproduction. The advances of identifying and targeting a single indication on co-protein has not formed a triumphant treatment and may not be adequate to accomplish tough reduction in patients [9]. Consequently, modulation of the biological system is renowned to be precious.

Among the surfeit of compounds screened for their potential *in vitro* anti- proliferative agents, derivatives possessing the *N*-methylpicolinamide, diarylurea and/or diarylamide structural description have gained significant attention for current medicinal chemists [10–16]. Sorafenib is a diarylurea anticancer agent that was initially developed to target C-RAF (RAF1) kinase [17]. However, the structural motifs of sorafenib displayed multiple kinase inhibitory effects with potent anti-tumorigenic and antiangiogenic activities through the inhibition of a number of receptor tyrosine kinases (RTKs), like the VEGFR-2 and VEGFR-3

Abbreviations: AcOH, Acetic acid; CDI, 1-Carbonyldiimidazole; °C, Degree Celsius; DMF, Dimethylformamide; DCM, Dichloromethane; DIEPA, *N*,*N*-Diisopropylethylamine; DMSO, Dimethylsulfoxide; EWGs, Electron-withdrawing groups; EDGs, Electron-donating groups; EtOH, Ethanol; Et_3N, Triethylamine; hr, Hour; HATU, (1-Bis(dimethylamino)methylene)-1*H*-1,2,3,-triazolo[4,5–*b*]pyridinium 3-oxidhexafluorophosphate; NMP, *N*-methyl-2-pyrrolidone; PDB, Protein data bank; IC_{50}, Inhibitory concentration (inhibits 50%); GI_{50}, Percentage Growth inhibition (50% inhibition); MeOH, Methanol; µL, Microliter; µM, Micromolar; µg, Microgram; Min, Minute; µL, Milli Litre; µmol, Millimole; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MW, Microwave; RTK, receptor tyrosine kinases; Rt, room temperature; TFA, Trifluoroacetic acid; TEA, Triethylamine; THF, Tetrahydrafuran

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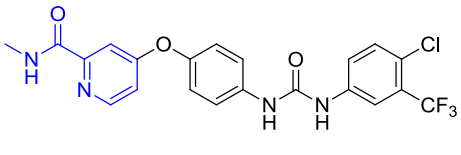
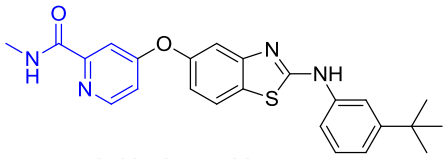


Sorafenib

Mutakinase inhibitor

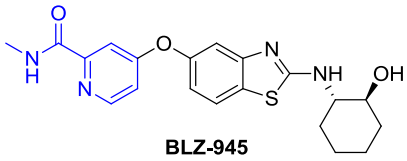
1



Anilinobenzothiazole

$BRAF_{V600}$ and c-RAF inhibitors

2

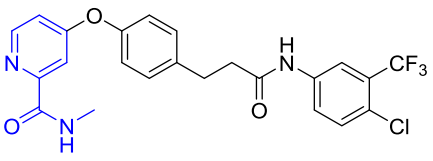


BLZ-945

FMS (CSF-1) inhibitor

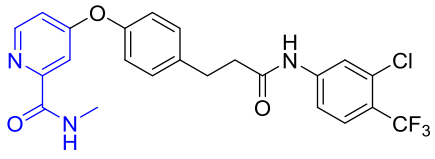
3

Fig. 1. Picolinamide based kinase inhibitors.



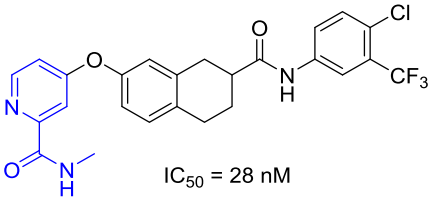
IC_{50} = 10 nM

4



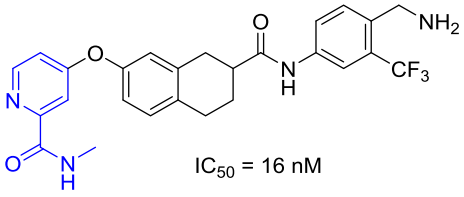
IC_{50} = 9 nM

5



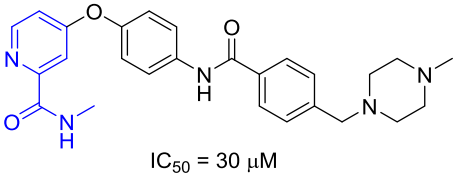
IC_{50} = 28 nM

6



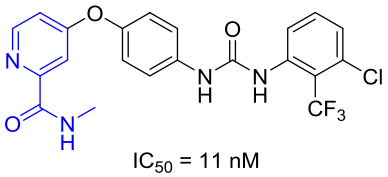
IC_{50} = 16 nM

7



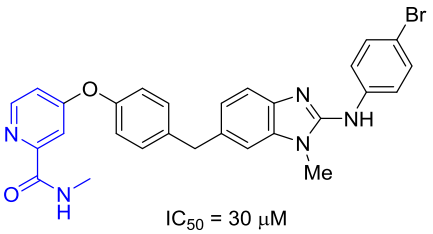
IC_{50} = 30 μM

8



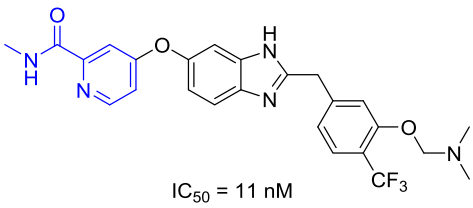
IC_{50} = 11 nM

9



IC_{50} = 30 μM

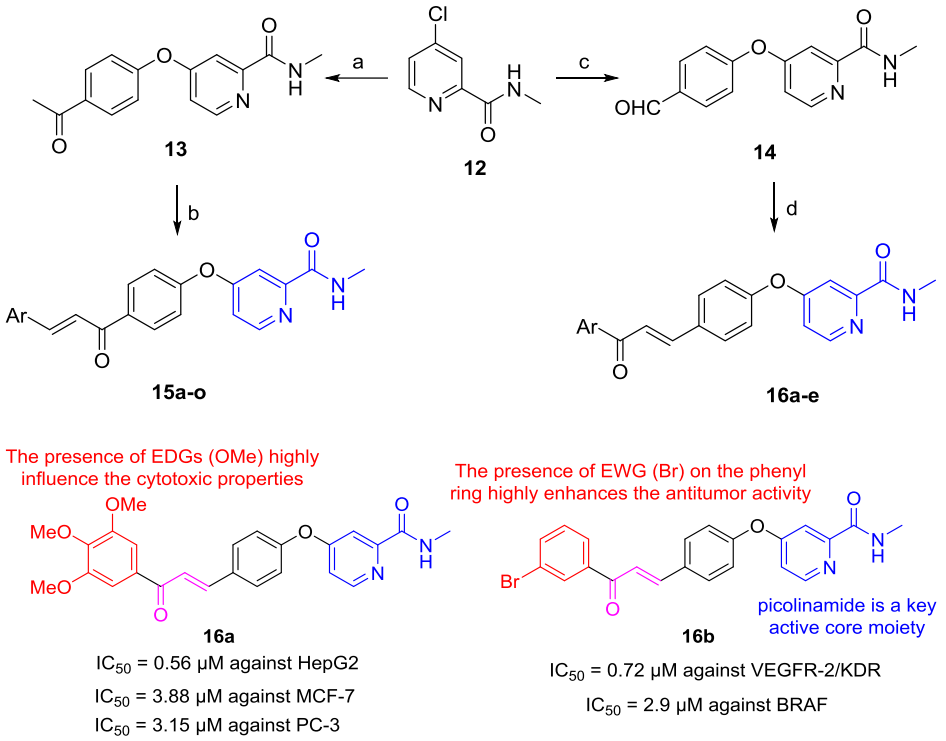
10



IC_{50} = 11 nM

11

Fig. 2. Representative *N*-methyl picolinamide derivatives.



Reagents and conditions: (a) 1-(4-hydroxyphenyl)ethanone, K_2CO_3, DMSO, reflux, 5 h; (b) aryl aldehyde, KOH, methanol, rt, 6 h; (c) 4-hydroxybenzaldehyde, *tert*-BuOK, DMF, reflux, 15 h; (d) aryl methylketones, NaH, THF, rt, 8h

Scheme 1. Synthetic approaches for picolinamide-bearing chalcone analogs as potent antitumor agents against A549, HepG2, MCF-7 and PC-3 cell lines.

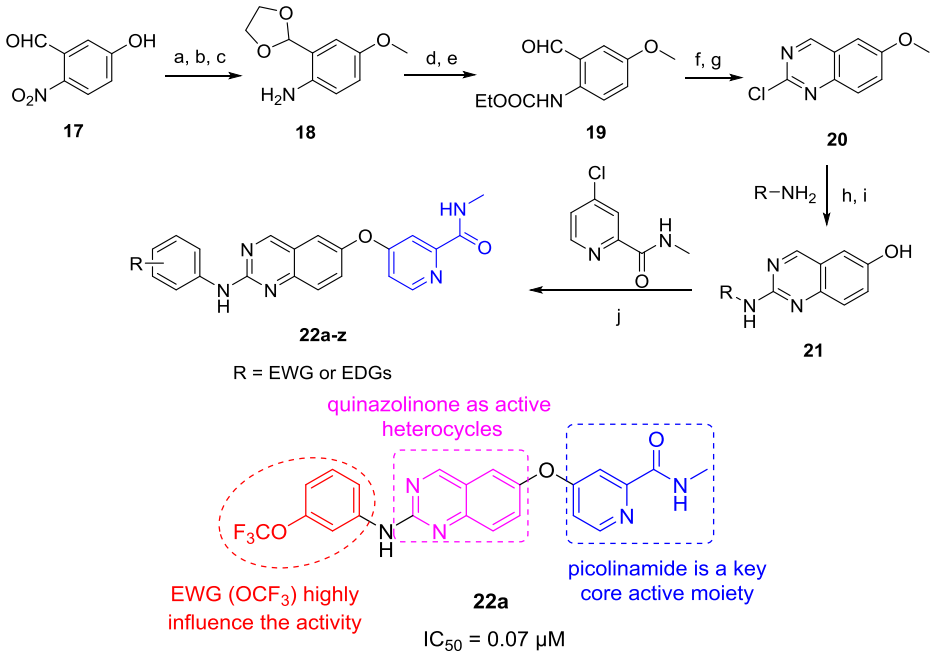
[18], FLT3 and c-KIT [19,20]. On the other hand, *N*-methylpicolinamide is an advantaged unique scaffold found in numerous potent anticancer kinase inhibitors with good physicochemical, such as sorafenib [19,21,22] and regorafenib [23–25] (multikinase inhibitors), 2-anilinobenzothiazole derivative [26] ($BRAF^{V600E}$ and C-raf inhibitor), and BLZ-945 [27–29] (FMS inhibitor) (Fig. 1). Due to the advantages of multi-mechanisms, wide-ranging anticancer potency, and well-tolerated results in combination trials, increasingly efforts have been focused on the optimization of sorafenib [30–34].

In recent period, the molecular hybrid approach has resulted in many new chemical entities with superior anticancer activity, selectivity and bridged side effects. We believe, this review article will be useful for inspiring the design, structural-activity relationship and developments of less toxic and powerful *N*-methylpicolinamide-based drugs against the various types of death-causing anticancer diseases. Some of the representative potential biologically active *N*-methylpicolinamide derivatives were illustrated in Fig. 2.

2. Synthetic routes and structure-activity relationship (SAR) of *N*-methylpicolinamide derivatives as potent anticancer agents

Zheng and co-workers [35] designed and developed a novel series of picolinamide bearing chalcone derivatives as potent antitumor activity as showed in Scheme 1. The introduction of *N*-methylpicolinamide **12**, at OH of 1-(4-hydroxyphenyl) ethanone moiety was accomplished through *O*-arylation of the 1-(4-hydroxyphenyl) ethanone with **12** using K_2CO_3 as a base in DMSO at reflux temperature for 5 h to afford **13**. The other intermediate **14** was produced from starting material **12** via *O*-arylation reaction with 4-hydroxybenzaldehyde and potassium *tert*-butoxide. The intermediate compounds **13** and **14** were reacted with substituted benzaldehydes and substituted acetophenones respectively through aldol condensation to get the target compound **15a-o** and **16a-e** respectively in good yields. Among all the synthesized derivatives, compound **16a** showed excellent cytotoxicity with IC_{50} values 9.50 μM against A549, 0.56 μM against HepG2, 3.88 μM against MCF-7 and 3.15 μM against PC-3. Compound **16b** was found to be most antitumor activity (IC_{50} = 0.72 μM against VEGFR-2/KDR and IC_{50} = 2.9 μM against BRAF) in the series. The Structure-activity relationship (SAR) raveled that, the presence of electron donating and electron withdrawing groups on the phenyl ring highly influenced the antitumor activity of **16a** and **16b**. It was showed that halogen [3-Br (**16b**)] and methoxy (substituted on C-3,4,5 position, **16a**) substitution were benefit for the increasing antitumor activity.

In 2012, Ramurthy and co-workers [36] designed and synthesized Sorafenib based quinazoline derivatives and screened for their *in vitro* raf kinase inhibitors. The synthetic route to target compounds was showed in Scheme 2. Starting from compound **17** hydroxy group was methylated followed by protection of the aldehyde with glycol in the presence of tosic acid to afford the dioxalane, which upon reduction of nitro group yielded **18** with moderate yield. Compound **18** was reacted with ethylchloroformate followed by de-protection to obtain the intermediate **19**. Subsequently, ring closure reaction was formed using ammonia under ambient reaction conditions, and then chlorination at 2-position of heterocycle ring to furnish compound **20**. Then the introduction of various substituted anilines under optimal reaction conditions followed by demethylation to get **21**, which were *O*-arylated using KHMDS and **12** in DMF as solvent to yielded compounds **22a-z** in good yields. From the set of series, compound **22a** was found to be best $Braf^{V600E}$ inhibitor with IC_{50} valve of 0.07 μM, and all potent compounds showed less toxic. The SAR indicated that, the *meta* and *par-*



Reagents and conditions: (a) K_2CO_3, MeI, DMF; (b) Glycol, tosic acid; (c) PtO_2, H_2, EtOH; (d) EtOCOCl, THF; (e) conc. HCl; (f) NH_3 at 0-130 °C; (g) $POCl_3$, 95-100 °C, 4 h; (h) EtOH, 80 °C; (i) 48% HBr, 140 °C, MW, 6 min; (j) KHMDS, K_2CO_3, DMF, MW, 170 °C, 6 min

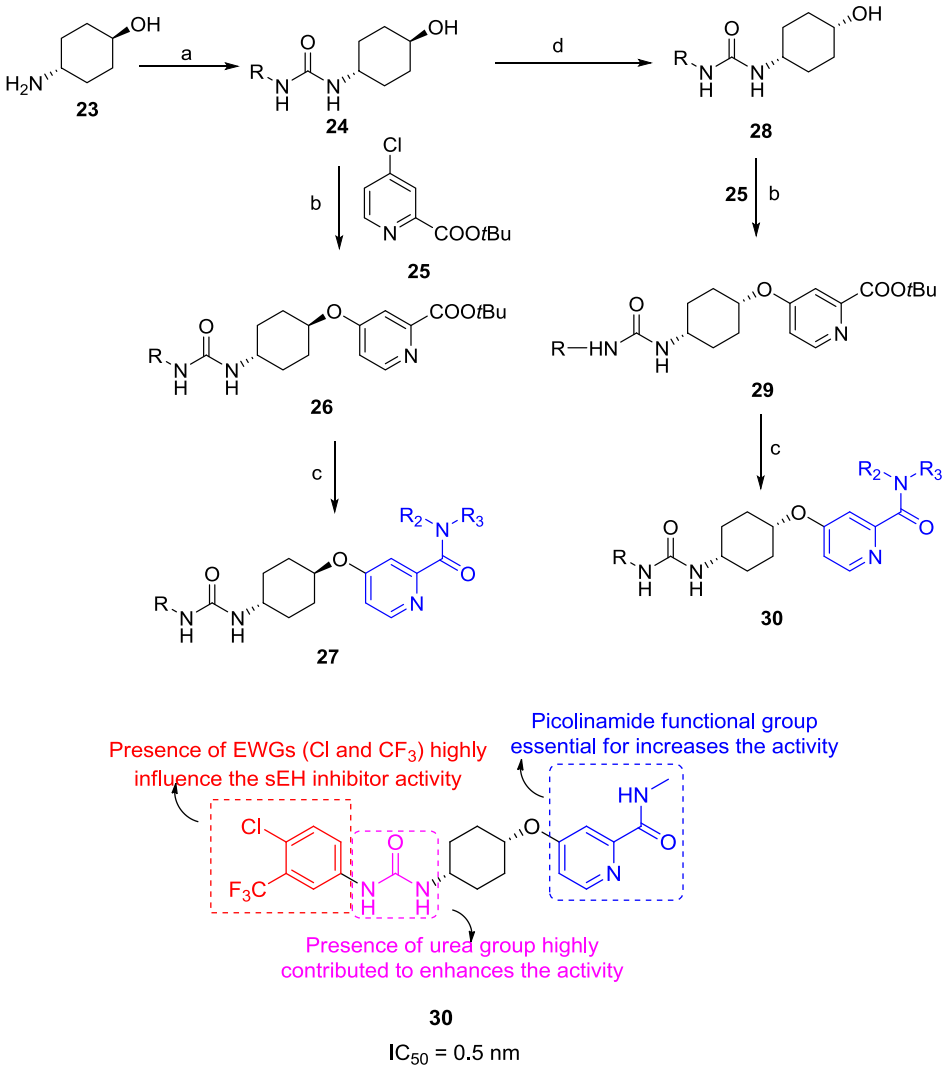
Scheme 2. Synthetic routes to picolinamide-bearing heterocyclic amides as potent raf kinase inhibitors for targeting $Braf^{V600E}$ kinase.

substitutients in the phenyl ring showed superior activity compared to *otrho*-substituents. Among them, the 3-OCF_3 substituted phenyl **22a** had the best affinity in the *meta*-substituted series. The presence of quinazoline heterocycle plays a vital role in increases the anticancer properties.

In 2013, Hammok et al. [37] reported and developed Sorafenib based cyclohexyl derivatives as potent sEH inhibitors. The synthesized route was illustrated in Scheme 3. Compound **23** was reacted with different substituted isocyanate in DMF as solvent under optimal reaction conditions to furnish *trans* urea intermediate **24**. Subsequently using Mitsunobu conditions, *trans* urea intermediate **24** was converted into *cis* urea intermediate **28.** Both of these *cis* urea **24** and *trans* urea **28** intermediates were coupled with compound **25** to yield intermediates **26** and **29** respectively. These compounds were hydrolyzed and coupled with various substituted amines to get final targeted compounds **27** and **30** respectively in good yields. Among them, compound **30** (IC_{50} = 0.5 nm) showed highest inhibition potency than Sorafenib towards sEH inhibitor, but similar against C-raf and VEGFR-2. The preliminary SAR presented that, the presence of strong electron-withdrawing groups (Cl and CF_3) on the phenyl ring highly influenced the activity. On the other hand, the presence of urea functional moiety also plays a crucial role in enhances the activity. The replacement of EWGs with EDGs on the phenyl ring showed the loss of potency.

In 2013, Ping and co-workers [38] reported the design, synthesis and SAR of Sorafenib based diarylthiosemicarbazide derivatives as potent antiproliferative agents against three cancer cell lines (human alveolar epithelial cell A549, human lung cancer cell H460 and human colorectal cancer cell HT-29). Compound **31** reacted with thiophosgen in the presence of mild base sodium bicarbonate in DCM at room temperature to obtain intermediate **32** in good yield. Subsequently, intermediate **33** was treated with hydrazine hydrate in dioxane at 0 °C to afford **33** in good yield. Finally, the various substituted aldehydes were treated with **33** under reflux conditions to get the target compounds **34a-n** in moderate to good yields (Scheme 4). Among the synthesized series, compound **34a** showed the excellent antiproliferative activity with IC_{50} values of 2.2, 1.8 and 5.2 μM against A549, H460 and HT-29 cell lines respectively, which is better than the standard drug Soraferib. The SAR study showed that the introduction of more electron-withdrawing group (Cl, F, Br and NO_2) on the phenyl ring seemed to be detrimental for the activity; the basic chlorine atoms was essential for high activity; the thiourea group was crucial for increasing antiproliferative activity. The presence of EWGs (Cl, NO_2, F and Br) on the phenyl ring highly enhanced antiproliferative activity, compared to the EDGs (OH and OMe). The presence of 2,6-dichlorophenyl substituent showed highest antiproliferative (**34a**) activity in the series. Moreover, the substitution pattern and bulk of the benzylidene group influenced the cytotoxity dramatically. Compounds with substituents at *ortho*-position on the benzylidene group were a preference for enhancing antiproliferative activity, compounds containing halogen at *ortho*-position are superior to others with the corresponding groups at *para*- or *meta*-positions.

Zhao and co-workers [39] developed a new series of Sorafenib based hydrazine and oxadiazole-containing derivatives and screened for their *in vitro* antitumor activity using MTT method. The synthetic route was outlined in Scheme 5. The starting materials **12** reacted with **35** in the presence of mild base K_2CO_3 in DMSO as a solvent under reflux conditions to obtain diaromatic ether **36**. Free carboxylic group of **36** then coupled with **37** using coupling reagent DCC in THF at room temperature to furnish the targeted hydrazine compounds **38a-d**. Then after, the targeted 1,3,4-oxadiazole compounds **39a-e** were synthesized

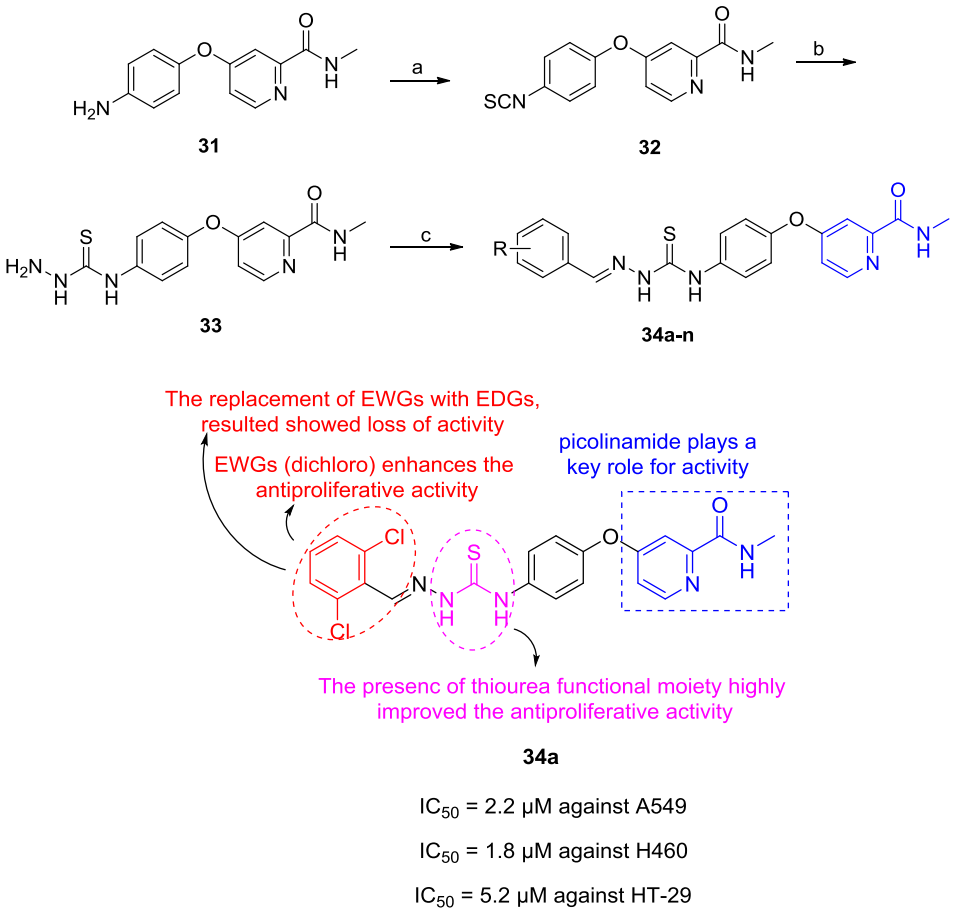


Reactions and conditions: (a) R-NCO, DMF, rt, 12 h; (b) KOt-Bu, THF, 0 °C to rt; (c) (i) 30-50% TFA in DCM, 6 h; (ii) PyBOP, R^2R^3NH, DMF, rt; (d) (i) 4-nitro benzoicacid, TPP, DIAD, THF, rt, 12; (ii) 1N NaOH, THF, rt, 12 h

Scheme 3. Synthetic approach to potent picolinamide-bearing analogs as potent sEH inhibitors against C-raf and VEGFR-2 inhibitor for targeting sEH kinase.

by the one-pot reaction between intermediates **36** and **37** in the presence of coupling reagent CDI and dehydration reagents TPP and CBr_4. The key intermediates **36** were treated with **40** in the presence of CDI to produce **41a-k** in good yields [40]. Among the synthesized analogs, compound **39a** showed excellent antitumor activity with IC_{50} value of 4.59 μM against HCT-116 cell line, which is superior to standard drug Sorafenib (IC_{50} = 6.16 μM). The preliminary SAR revealed that, the presence of oxadiazole ring significantly improved the activity along with the presence of picolinamide group. The presence of various electron-withdrawing and electron-donating groups played a crucial role in antitumor activity. The presence of electron-withdrawing (Cl, F, Br and NO_2) groups on the phenyl ring showed improved antitumor activity, while the electron-donating (OH and OMe) groups reduced the antitumor activity. Without substitution at phenyl ring of any position showed excellent antitumor activity.

Recently, El-Damasy et al. [41] developed the picolinamide containing quinoline urea and amide derivatives and evaluated for their *in vitro* antiproliferative activity against 60 cancer cell lines using MTT assay. Initially, commercially available **42** reacted with **12** in the presence of base under reflux conditions to give **43** in good yield. Free amine group of **43** then coupled with various aryl carboxylic acids using coupling reagent HATU and base DIPEA DMF at room temperature to afford the corresponding amide derivatives **44a-g**. On the other hand, the same intermediate **43** reacted with various aryl isocyanates to obtain **45a-k** in good yields under optimal reaction conditions (Scheme 6). From the two sets of compounds, compound **45a** and **45b** were showed excellent anti-proliferative activity with IC_{50} values of 0.42 μM and 1.36 μM respectively, which is superior to the standard drug Sorafinib. The SAR revealed that, the presence of electronic substituents on the phenyl groups highly influenced the anti-proliferative activity. The



Reagents and conditions: (a) Thiophosgen, $NaHCO_3$, CH_2Cl_2, rt; (b) $NH_2NH_2.H_2O$, 1,4-dioxane, O °C, 1 h; (c) aldehydes, EtOH, 60 °C, 1h

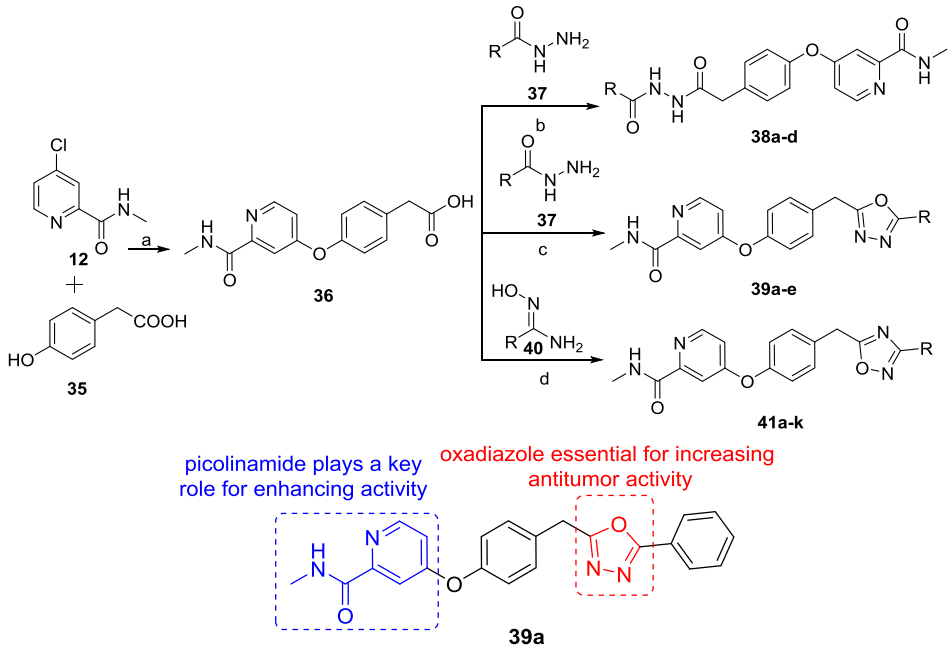
Scheme 4. Synthetic routes to potent antiproliferative agents against three cell lines: A549, H460 and HT-29.

presence of EWGs (Cl and F) increases the anti-proliferative activity of compound **45a** and **45b**. The urea and *N*-methylpicolinamide substituents also played a key role in increases the activity.

In 2014, Zhu and co-workers [42] synthesized the picolinamide containing sulfonylurea analogs and tested for their *in vitro* VEGFR2 kinase inhibitors. The synthetic route of target compounds was showed in Scheme 7. Compounds **51a-b** was synthesized from commercially available **46** *via* sulfonylation, ammonalysis and acylation reactions. Condensation of **50** and **49** in toluene furnished the target compounds **51a-b** in good yield. Compound **51a** showed good VEGFR2 kinase inhibitor with the 91% of inhibition. The SAR revealed that, the presence of chloro group on the phenyl ring and sulfonylurea functional group influenced the VEGFR2 kinase inhibitors. The presence of methyl group on the phenyl ring slightly reduced the VEGFR2 kinase inhibitors.

A new series of Sorafenib based 2-thioxothiazolidin-4-one derivatives were developed by Gong and co-workers [43] and screened for their *in vitro* antitumor activity against A549, H460 and HT29 by using MTT method. The synthetic approach was outlined in Scheme 8. Compound **50** treated with thiophosgen **51** in chloroform and mild base sodium bicarbonate to furnish intermediate **52** in good yield under optimal reaction conditions. Subsequently, the cyclization of **52** and thioglycolic in 1,4-dioxane forms an intermediate **53.** Knoevenagel condensation of **53** with different substituted aromatic aldehydes in the presence of piperidine in ethanol yields **54a-x** in good yields under reflux conditions. Among all the synthesized analogs, compound **54a** (IC_{50} values of 0.8, 1.3 and 2.8 μM against A549, H460 and HT29 cell lines, respectively) showed superior antitumor activity, which is better than the standard drug Sorafenib. The preliminary SARs exposed that substituted arylidene on the C-5″ position of the rhodanine ring is essential for the antitumor activity. The introduction of benzylidene moiety showed enhanced antitumor activity in most of the synthesized compounds. The presence of EWGs (Cl, NO_2, Br and F) on the phenyl ring exhibited promising influence on antitumor activity. Among the EWGs, fluorine is more preferable to increase the antitumor activity, while EDGs such as hydroxyl and methoxy groups reduces the antitumor activity.

Benzoxazole containing sorafenib hybrids were synthesized by Potashman and co-workers [30] and evaluated for their *in vitro* VEGFR-2 inhibitors. Compound **12** treated with **55** under ambient reaction conditions to yield intermediate **56**. Then, debenzylation of **56** was accomplished using either catalytic hydrogenation or TFA to afford **57**. Regioselective nitration of phenols **57** using nitric acid furnished compounds **58**. Reduction of the nitro groups yielding amino phenols **59** was treated with isothiocyanate **60** to get thiourea intermediates that were directly cyclized to the desired products **61a-z** using EDC with good yields (Scheme 9). Among all the synthesized compounds,



Reagents and conditions: (a) *t*-BuOK, K_2CO_3, DMSO, 90 °C, 9 h; (b) DCC, THF, rt, 5 h; (c) CDI, CBr_4, TPP, CH_2Cl_2, 0 °C, 4 h; (d) CDI, DMF, 115 °C, h

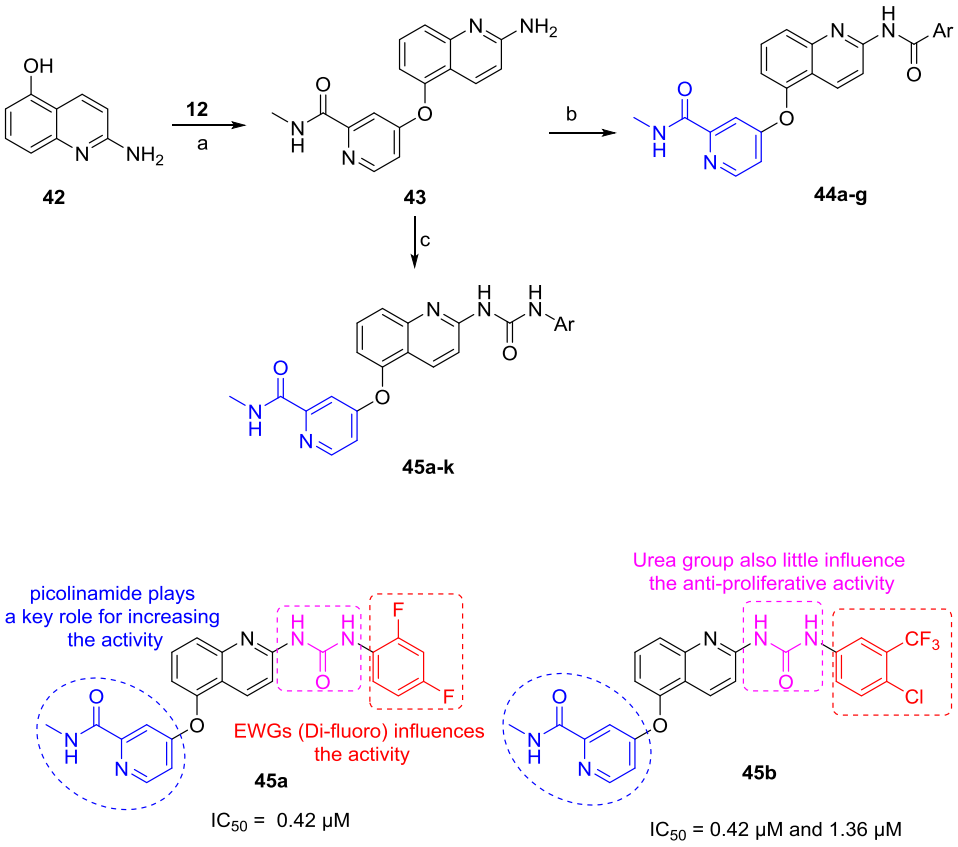
Scheme 5. Synthetic route to picolinamide analogues as potent antitumor inhibitors against HCT-116 cell lines.

compound **61a** was found to be most potent VEGFR-2 inhibitors with IC_{50} value of 15 nM against V-HUVEC. The preliminary SAR suggested that, the compounds containing an *N*-methylpyrrolidine group showed superior VEGFR-2 activity, better than the other functionalities. The replacement of *N*-methylpyrrolidine group with other phenyl ring highly decreased the activity. In addition, benzoxazole played a crucial role in increasing activity. The presence of electron-withdrawing and electron- donating groups on the phenyl ring played important role in activity. The electron-withdrawing (Cl, Br and F) groups on the phenyl ring enhanced the activity; while the electron-donating groups on the phenyl ring decreased the activity.

El-Damasy and co-workers [44] synthesized a novel series of picolinamide based benzothiazole derivatives and evaluated as potent antiproliferative active. The synthetic approach was illustrated in Scheme 10. Demethylation of the commercially available **62** [45] with 48% aqueous hydrobromic acid afforded **63**. Compound **63** reacted with **12** in the presence of the base Cs_2CO_3 in DMSO at 135 °C for 5 h to furnish **64** in good yield. Intermediate **64** then treated with various substituted amine and converted into the isocyanate intermediate using coupling reagent CDI in DMF at room temperature for 24 h to yield targeted coupling products **65a-n** in good yields. Among the synthesized analogs, compound **65a** was found to be most potent analog against both native and T315I mutant ABL with IC_{50}values of 18.2 and 39.9 nM, respectively, and showed highly selective inhibitory activity (89.8%) towards the Bcr-Abl dependent leukemia cell (K-562) at 10 μM concentration. The preliminary SAR suggest that, the propyl urea (n = 3) is usually more beneficial than the parallel ethyl or butyl urea derivatives. Moreover, *N*-methyl piperazine splinter proved to be the most active group, due to may be *N*-methyl piperazine as water solubilizing group.

A new class of potent sorafenib based analogues were developed by Yao and co-workers [46] and evaluated for their *in vitro* antitumor activity against HCT-116 and MDA-MB-231 cell lines. Compound **12** treated with various amines in presence of THF at room temperature to yield **66a-e**. Afterwards, they were treated with 4-aminophenol to produce parallel diaromatic ethers (**67a-e**). Finally, various substituted isothiocyanates (**68a-h**) were reacted with substituted diaromatic ethers (**67a-e**) in DCM to afford targeted sorafenib based thiourea derivatives (**69a-t**) in moderate yields. Compound **69a** and **69b** showed promising antiproliferative activities with IC_{50} values of 17.3 and 16.1 μM against HCT-116 cell line. The SAR indicated that the size and shape of R^1 and R^2 groups may influence the selectivity and antiproliferative activity. It was prominent that only the compounds having methyl group showed the inhibitory activity against MDA-MB-231 cell, and these compounds also have potent activities against HCT-116 cell line. The presence of thiourea functional groups played a crucial role in increasing activity. The presence of di-electron-withdrawing (Cl and F) groups containing analogues showed more active antiproliferative activity; which was better than the mono-substituted electron-withdrawing groups (see Scheme 11).

Recently, Wang and co-workers [47] developed a novel class of phenylpyrimidine-carboxamide sorafenib hybrids as potent VEGFR2/KDR kinase inhibitors. The synthetic route was illustrated in Scheme 12. Substituted carboxylic groups (**70a-h**) were converted into acid chlorides (**71a-h**) in the presence of $(COCl)_2$ in DMF and dichloromethane at room temperature. Then acid chlorides were reacted with compound **72** or **73** in the presence of DIPEA in DCM to yield final targeted derivatives **74a-h** or **75i-p** in good yields under optimal reaction conditions. From the set of series, compounds **74a** showed nearly equal activity to Sorafenib against MCF-7 cell line, with the IC_{50} values of 6.35 μM. Meanwhile, compound **74b** revealed more active than



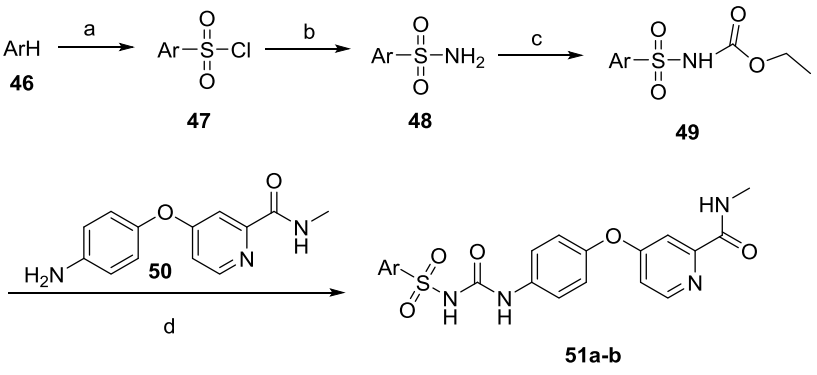
Reagents and conditions: (a) CS_2CO_3, DMSO, 135 °C, 5 h; (b) Ar-COOH, HATU, DIPEA, DMF, rt, 24 h; (c) aryl isocyanates, DCM, 0 °C to rt, 24 h

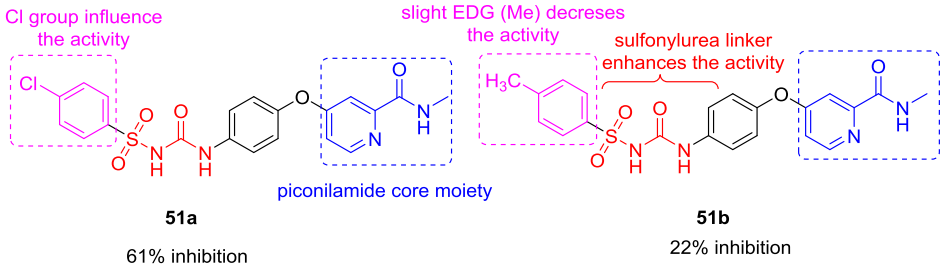
Scheme 6. Synthetic approach to picolinamide-based 2-amido and ureido quinoline derivatives as potent anti-proliferative agents against A498 RCC cell lines targeting for $BRAF^{V600E}$ and C-Raf kinase.

Sorafenib against A549 cell line, with the IC_{50}values of 3.39 μM. The SAR revealed that, the introduction of mild and strong EDGs such as CH_3, C_2H_5 and OCH_3 might be appropriate to increase the activity. On the other hand, the introduction of strong EWGs (Cl, NO_2, Br, F and CF_3) highly reduces the activity.

In 2015, El-Damacy and co-workers [41] reported the synthesis and SAR of picolinamide bearing quinolinone analogs and evaluated for their *in vitro* anti-proliferative activity against a panel of three human cancer cell lines such as MCF-7, SK-BR3 and HCT116. The chloro substituted compound **76** was reacted with excess of acetamide in the presence of K_2CO_3 at elevated temperature (200 °C) for 15 h to yield amino derivatives **77a-o** in moderate yields. Subsequently, intermediate compounds (**77a-o**) were refluxed in 48% aqueous hydrobromic acid or treated with boron tribromide (BBr_3) in DCM at 0 °C to give the demethylated derivative **78a-o** in good yields. Next, the compound **12** was reacted with intermediates **78a-o** to get the final targeted compounds **79a-o** in good yields under optimal reaction conditions. Among the synthesized series, compound **79a** showed superior potency with GI_{50} values of 0.36 μM, 0.66 μM, 0.68 μM and0.60 μM against the breast MDA-MB-468, renal A498, melanoma SK-MEL-5 and UACC-62 cell lines, respectively, which is better than the standard drug sorafenib. The preliminary SAR revealed that, the presence of EWGs (Cl and CF_3), quinoline ring and piconilamide groups are all essential for improving the anti-proliferative activity [48]. On the other hand, the presence of EDGs (OH and OMe) on the phenyl ring resulted displayed in loss of potency (see Scheme 13).

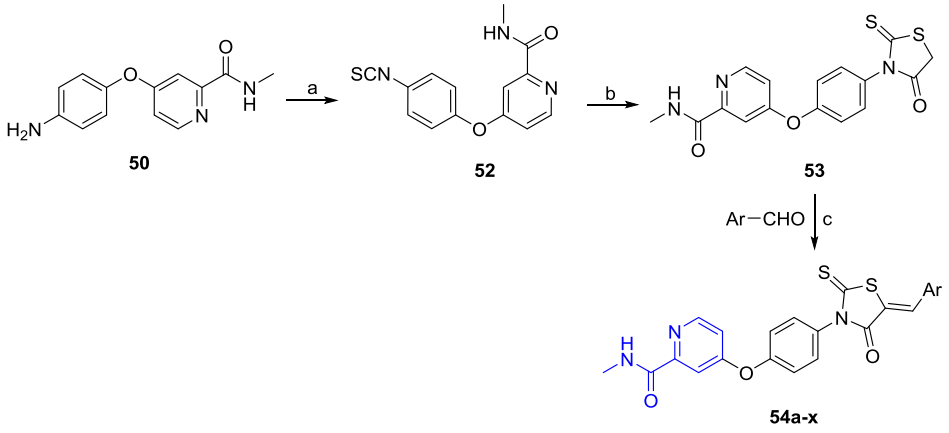
The same research group El-Damasy et al. [49] continued their interest to search new, potent and less toxic anti-proliferative drugs. A novel class of benzothiazole amides featuring pyridylamide hybrids were synthesized and tested for their *in vitro* anti-proliferative activity. Compound **12** synthesized by the reaction of methyl ester **80** with alcoholicmethyl amine at 0 °C [46]. Treatment of the commercially accessible **81** with 48% aq. hydrobromic acid furnished the demethylated phenol derivative **82** [45] in good yield. Then intermediate **12** and **82** were reacted in the presence of the base CS_2CO_3 in DMSO at 135 °C for 5 h to give **83** in excellent yield. The intermediate **83** then coupled with aryl carboxylic acids using HATU as a coupling agent and DIPEA as a base in anhydrous DMF to afford amide derivatives **84a-i** in good yields. On the other hand, compound **81** reacted with various substituted aryl isocyanates in anhydrous DMF or acetonitrile under argon atmosphere to yield ureido derivatives **85a-i** in good yields. Among all the synthesized analogs, compound **85a** was found to be most potent anti-proliferative activity with 98.4 and 96.3% inhibition against HCT-116 and SK-BR-3 cell lines at 100 μM concentration. The preliminary SAR exposed that, the presence of benzothiazole ring is essential for improving the anti-proliferative activity. In addition, the presence of strong EWGs (CF_3) on the phenyl ring highly increases the activity, whereas the presence of EDGs (OH and OCH_3) resulted in loss of

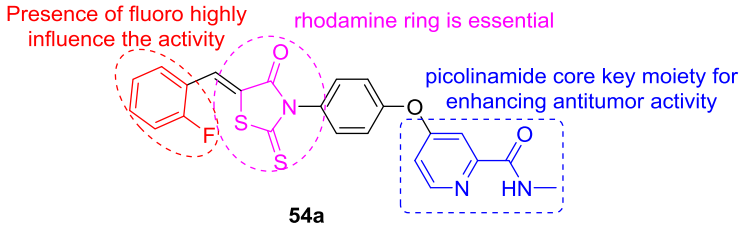




Reagents and conditions: (a) Chlorosulfonic acid, CH_2Cl_2, rt, 12 h; (b) Aq. ammonia, CH_2Cl_2, 2 h; (c) ethyl chloroformate, K_2CO_3, acetone, reflux, 15 h; (d) toluene, reflux, 6 h

Scheme 7. Synthesis of sulfonylurea analogs as VEGFR2 kinase inhibitors.





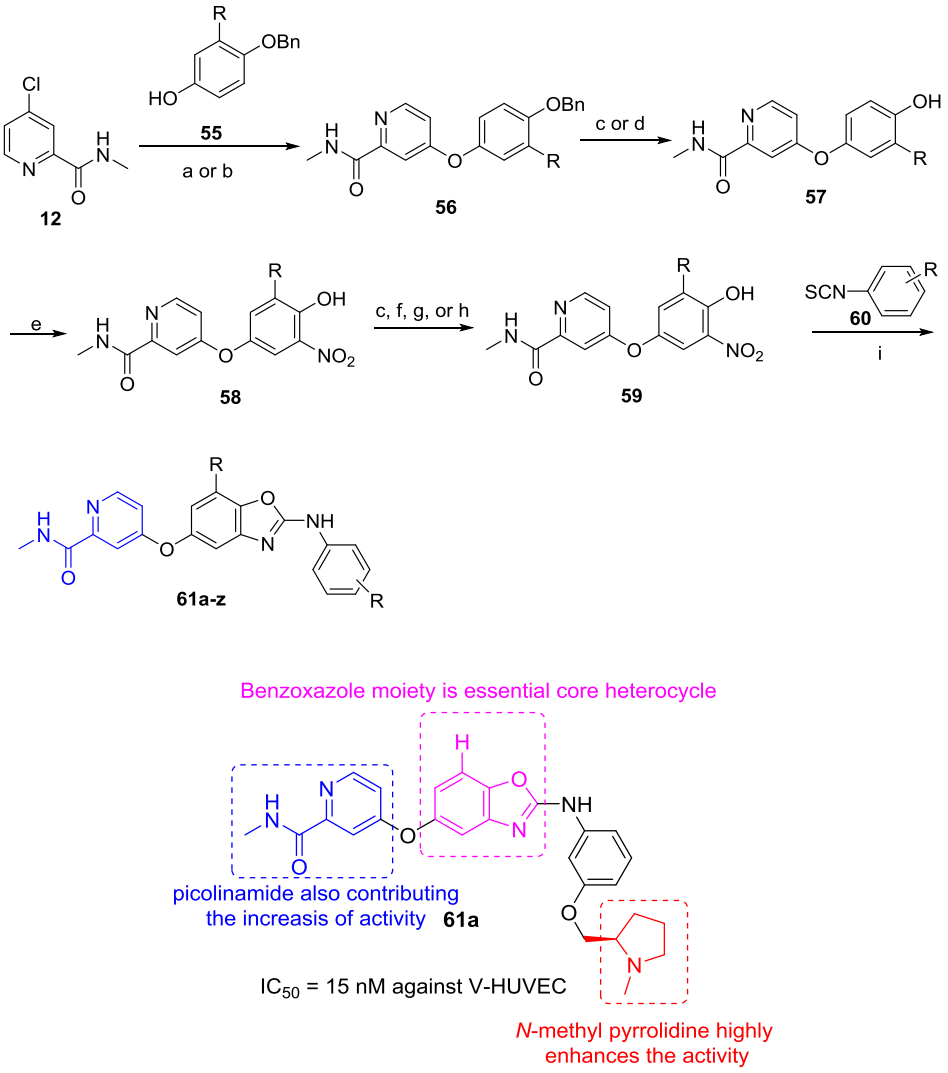
IC_{50} = 0.8 μM against A549 cell line

IC_{50} = 1.3 μM against H460 cell line

IC_{50} = 2.8 μM against HT29 cell line

Reagents and conditions: (a) 6% $NaHCO_3$, CH_2Cl_2, thiophosgene (**51**), 0 °C to rt, 5 h; (b) $HSCH_2COOH$, Et_3N, dioxane, rt, 3 h; (c) piperidine, EtOH, reflux, 2-12 h

Scheme 8. Synthetic route to sorafenib-based 2-thioxothiazolidin-4-one derivatives as potent antitumor agents against A549, H460 and HT29.



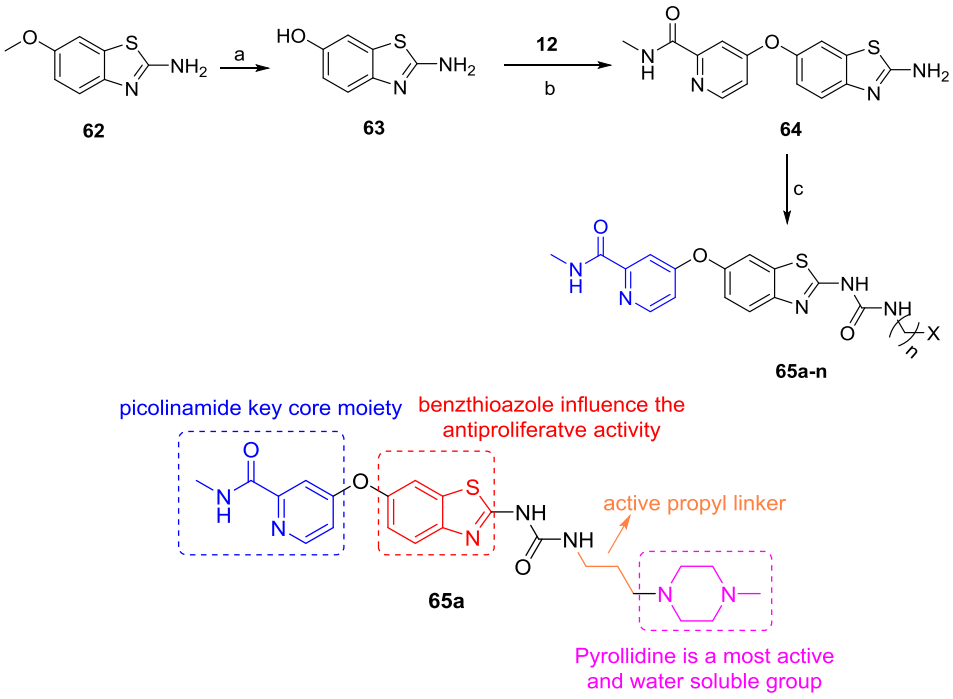
Reagents and conditions: (a) NaH, DMF, rt, 85 °C; (b) NEt_3/TFA, 150 °C; (c) Pd/C, H_2, MeOH, ethylacetate; (d) TFA, heat; (e) HNO_3, AcOH; (f) Fe, HCl, EtOH; (g) Zn, AcOH, THF; (h) $SnCl_2$, EtOH; (i) EDC, CH_3CN

Scheme 9. Synthesis of sorafenib-based benzoxazole analogues as potent VEGFR-2 inhibitors against V-HUVEC cell lines.

potency (see Scheme 14).

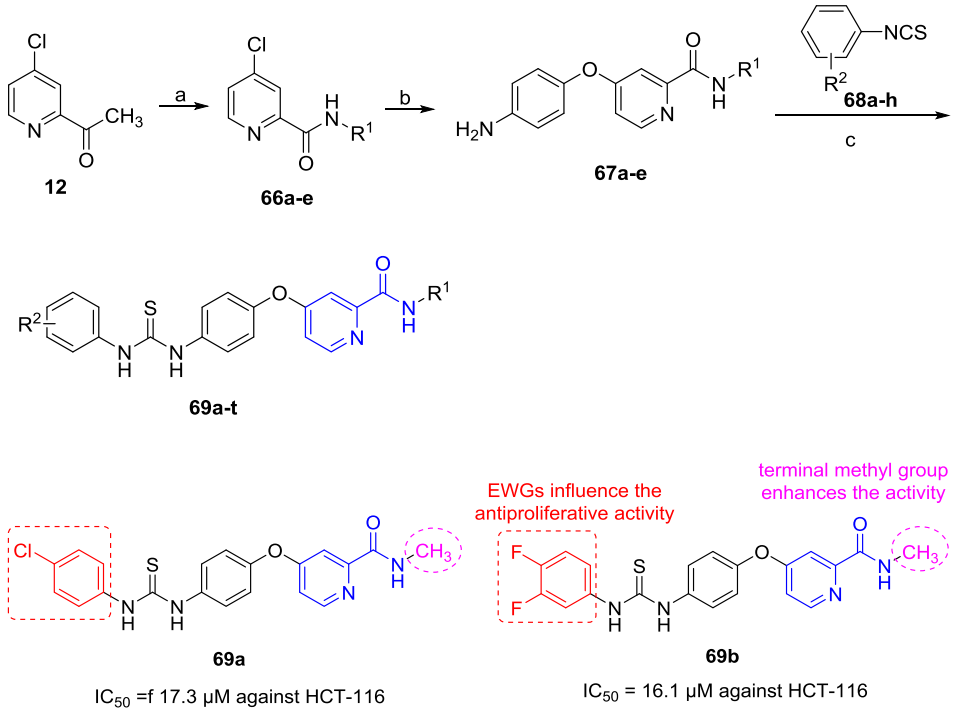
A new class of potent sorafenib based hybrids were synthesized by Babic and co-workers [50] and screened for their *in vitro* anti-proliferative activity against different cell lines such as HeLa, MCF7, HCT116 and SW620. The synthetic way has been reported in Scheme 15. Commercially existing **86** was converted into the acid chloride using thionyl chloride under ambient reaction conditions [51], then; chlorination of the pyridine ring at the *para*-position obtains intermediate **87** in good yield. Subsequent amidation of compound **87** with various amines in the presence of TEA in toluene at room temperature for 0–1 h affords amide derivative **88** in good yield. In the next step, 4-aminophenol was treated with **88** in the presence of *t*-BuOK and K_2CO_3 used as base to afford ether intermediates **89** under optimal reaction conditions. Ether derivatives **89** were reacted with isocyanate to give the final targeted hybrids **90a–e** in moderate to good yields. From the series, compound **90a** showed superior anti-proliferative activity against tested all cell lines with the IC_{50} values range between 2 and 4.3 μM. The SAR exposed that, the presence of strong EWGs (Cl and CF_3) on the phenyl ring highly enhances the anti-proliferative activity. In addition, the presence of urea functionality also plays a crucial role in increases the activity. The picolinamide group is essential core moiety for improving the activity. The replacement of EWGs (Cl and CF_3) with EDGs (OH and OMe) slightly reduced the anti-proliferative activity.

Recently, Zhang and co-workers [52] prepared a new class of potent picolinamide based urea analogs and evaluated for *in vitro* anti-proliferative activity against human cancer cell lines (ACHN, HCT116, MDA-MB-231) using MTT assay. The synthetic route was displayed in



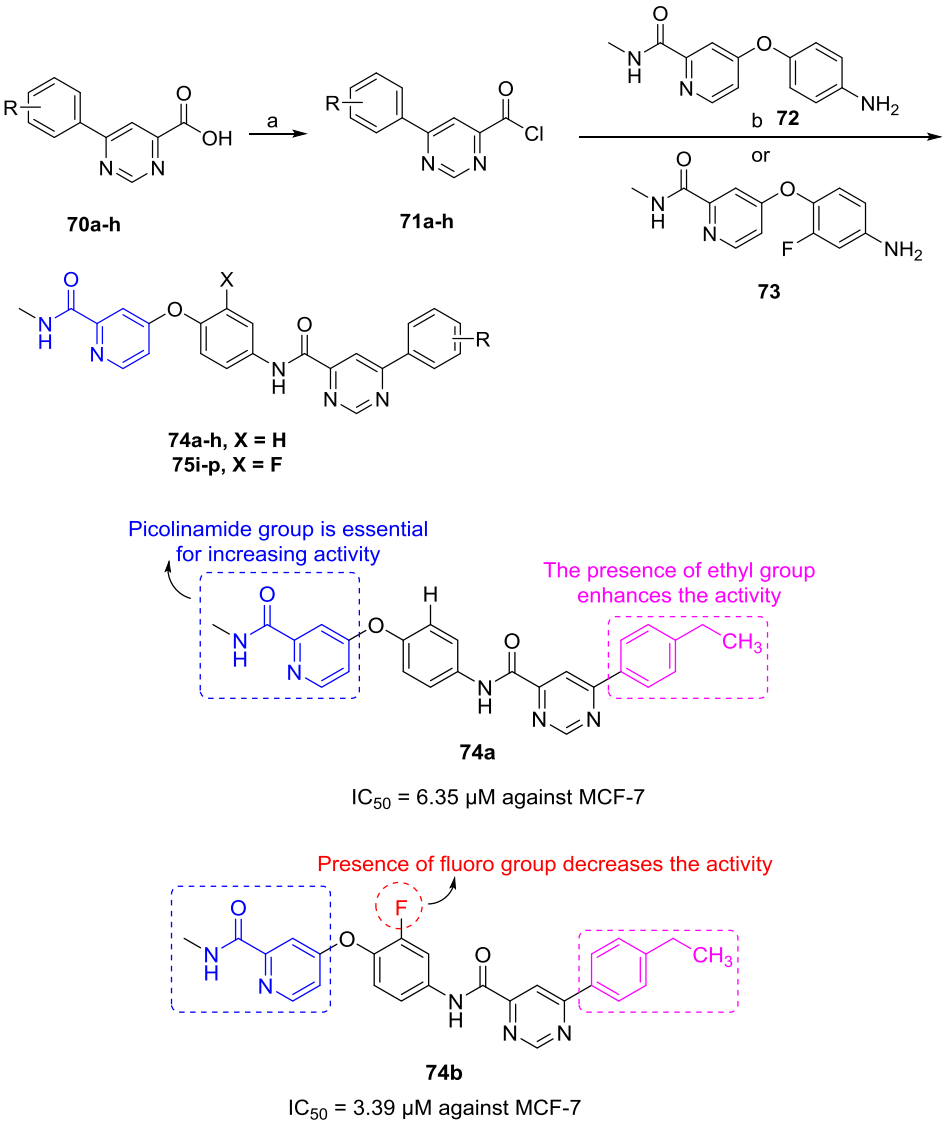
Reaction conditions and yields: (a) 48% HBr, reflux, 10 h, $NaHCO_3$, H_2O, 88%; (b) 4-chloro-*N*-methylpicolinamide, Cs_2CO_3, DMSO, rt, 15 min; 135 °C, 5 h, 22.7%; (c) 1,10-carbonyldiimidazole (CDI), DMF, rt, 24 h; then amine, rt, 24 h, 21-70%.

Scheme 10. Synthetic route to potent picolinamide-bearing analogues as targeting to both wild-type and the most resistant T3151 mutant of Bcr-Abl kinase for anti-proliferative agents.



Reagents and conditions: (a) RNH_2, THF (b) 4-aminophenol, DMF, *t*-KOBu (c) DCM

Scheme 11. Synthetic route to picolinamide-bearing thiourea analogues as potent anti-proliferative agents against HCT-116 and MDA-MB-231 cell lines.

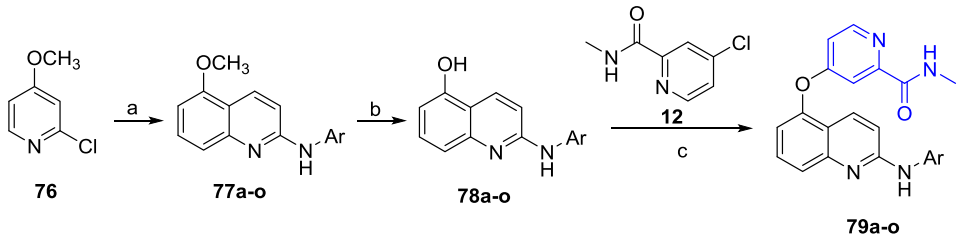


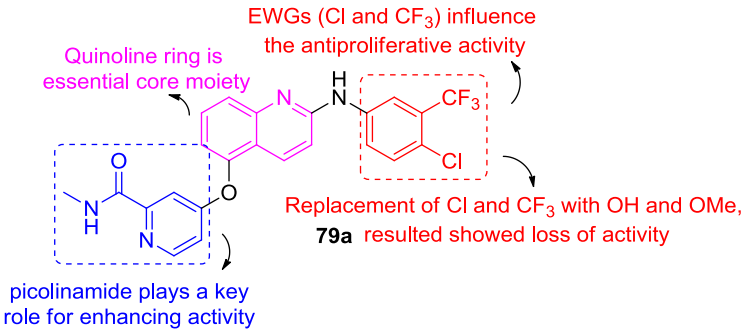
Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, rt, 0.5 h; (b) DIPEA, CH_2Cl_2, rt, 0.5 h

Scheme 12. Synthesis of phenylpyrimidine-carboxamide sorafenib derivatives as potent VEGFR2/KDR kinase inhibitors against MCF-7 and A549 cell lines.

Scheme 16. The compound **91** was esterified with $SOCl_2$ in methanol under reflux condition for 6–10 h to afford the compound **92** in good yield. Compound **93** was achieved by reaction of compound **92** with 4-chloro-3-(trifluoro-methyl)phenyl isocyanate in DCM at room temperature. Compound **94** was synthesized by hydrazinolysis of compound **93** in methanol at room temperature. Finally, compounds **95a-s** were obtained by the coupling of compound **94** with the corresponding 3-arylacrylic acids in the presence of coupling reagent HATU and using TEA as a base in DMF at room temperature. Among all the synthesized targeted analogues, compounds **95a** (IC_{50} = 1.28 μM against ACHN), **95b** (IC_{50} = 1.97 μM against ACHN) and **95c** (IC_{50} = 2.26 μM against ACHN) showed excellent anti-proliferative activity, which is better than the standard drug sorafenib (IC_{50} = 20.48 μM against ACHN). The SAR revealed that, the presence of EWGs (Cl, F and CF_3) on the phenyl ring, highly influenced the anti-proliferative activity, where as the presence of EDGs (OH and OMe) on the phenyl ring decreases the activity.

In 2012, Zhai et al. [53] reported the synthesis and SAR of picolinamide derivatives were showed potent anti-proliferative agents. The synthetic route of title compounds were illustrated in Scheme 17. The starting material **12** was synthesized from picolinic acid. Intermediate **96** was obtained by etherification of **12** with 4-aminophenol, and compound **97** was prepared by the reaction of intermediate **96** with thiophosgen in chloroform and sodium bicarbonate. Reaction of **97** with ammonium hydroxide in dioxane at 80 °C yielded the primary thiourea **98**. Then, heterocyclization of **98** with ethyl chloroacetate furnished the key intermediate **99** in the presence of sodium acetate. Knoevenagal condensation between **99** and different substituted aromatic aldehydes with sodium acetate in acetic acid under microwave





GI_{50} = 0.36 μM against the breast MDA-MB-468

GI_{50} = 0.66 μM against the renal A498

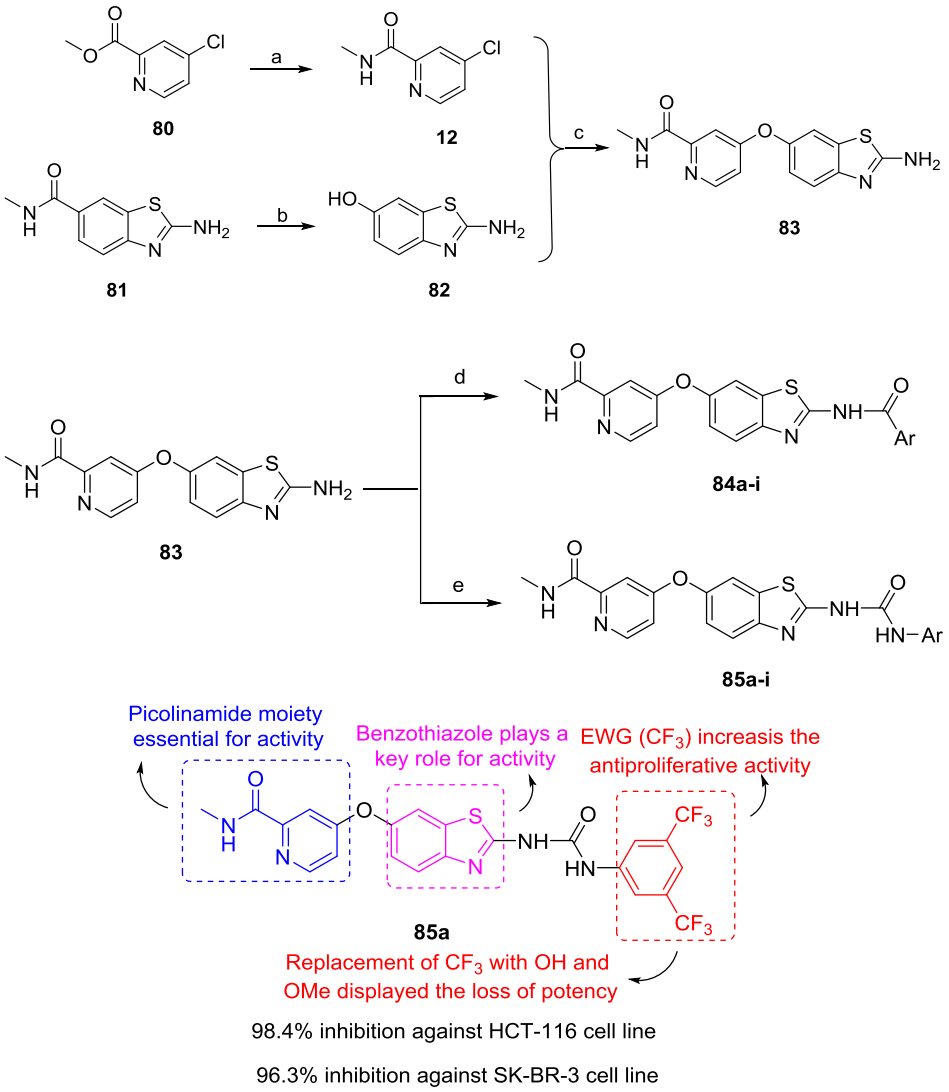
Reagents and conditions: (a) Acetamide, K_2CO_3, neat, 200 °C, 15 h, 47%; (b) (i) BBr_3, DCM, 0 °C to rt, 18 h, 51%; (ii) 48% HBr, reflux, 8 h, 88%. (c) aniline, CH_2Cl_2, 160 °C, 5-60 min,

Scheme 13. Synthetic approach to Sarafenib-based hybrids as potent anti-proliferative agents against a panel of three human cancer cell lines such as MCF-7, SK-BR3 and HCT116.

irradiation affords the target compounds **100a-y** in moderate to good yields. All the synthesized analogs were evaluated for their *in vitro* antiproliferative activity against three cancer cell lines (A549, H460 and HT29). Some of these compounds showed remarkable anti-proliferative activity against one or more cell lines in low micromolar range. The most promising compound **100a** inhibited the proliferation with IC_{50} values of 1.1, 0.01 and 1.3 μM against the A549, H460 and HT29 cell lines, respectively. The preliminary SAR suggested that substituted arylidene on C-5″ position of 2-iminothiazolidin-4-one ring is an essential for the antiproliferative activity. The introduction of benzylidene showed enhanced antitumor activity in most of the compounds. The presence of electron withdrawing fluorine atom at *para* position of benzylidine ring highly influences the antiproliferative activity, which is better than the other electron withdrawing groups (Cl, NO_2 and Br) substituents. The electron donating groups (OH and OMe) showed moderate antiproliferative activity against tested all three cancer cell lines. All the synthesized compounds showed low level of cytotoxicity against human lung carcinoma cells A549 (ATCC), human lung carcinoma cells H460 (ATCC) and human colon carcinoma cells HT29 (ATCC) by the standard MTT assay.

A new class of potent picolinamide based thiourea derivatives were showed potent anti-proliferative agents and synthesized by Yao and co-workers [54]. The synthetic route was illustrated in Scheme 18. The diaryl ether or diaryl thioether compound **105** was synthesized in a four step sequence. Commercially available **101** traded with thionyl chloride in the presence of optimal reaction conditions to give **102** in good yield, and the intermediate **102** then treated with methanol at ambient reaction conditions to produce **103**. Subsequent displacement of compound **103** with pyrrolidine provided compound **104**, which is then treated with 4-aminophenol or 4-aminobenzenethiol to afford **105** in moderate yield. The compound **105** then treated with different isothiocyanates in DCM as solvent to afford **106a-t** in moderate to good yields. Among all the synthesized compounds, compound **106a** and **106b** showed excellent antiproliferative activity with IC_{50} values of 5.2 μM and 7.2 μM against PC-3 cell line respectively, and showed less toxic against tested cell lines using MTT method. The preliminary SAR revealed that, the presence of electronic substituents on the phenyl ring plays a major role for the contributing the antiproliferative activity. The EWGs (Cl and CF_3) on the phenyl ring highly enhances the activity, which is better than the EDGs (OH and OCH_3) groups.

Yao et al. [55] designed and synthesized a new type of sorafanib derivatives by varying methyl group with different alkyl/aryl groups to improve the potency of their antiproliferative activity. The synthetic route was depicted in Scheme 18 and the synthetic procedure almost same with the above said [54]. All the prepared derivatives were demonstrated higher selectivity towards HCT-116 and PC-3 compared with MDA-MB-231. The most potent compound in this series, in which methyl group on the terminal amide was replaced with cyclo hexyl group **109a** exhibited promising antiproliferative activity with IC_{50} value 2.8 and 2.2 μM against human prostate PC-3 and human colorectal carcinoma HCT-116 cell lines, respectively. The preliminary SAR exposed that, the presence of EWGs (Cl and CF_3) on the phenyl ring to highly increase the antiproliferative activity. The presence of EDGs (OH and OMe) on the phenyl ring reduces the antiproliferative activity. The

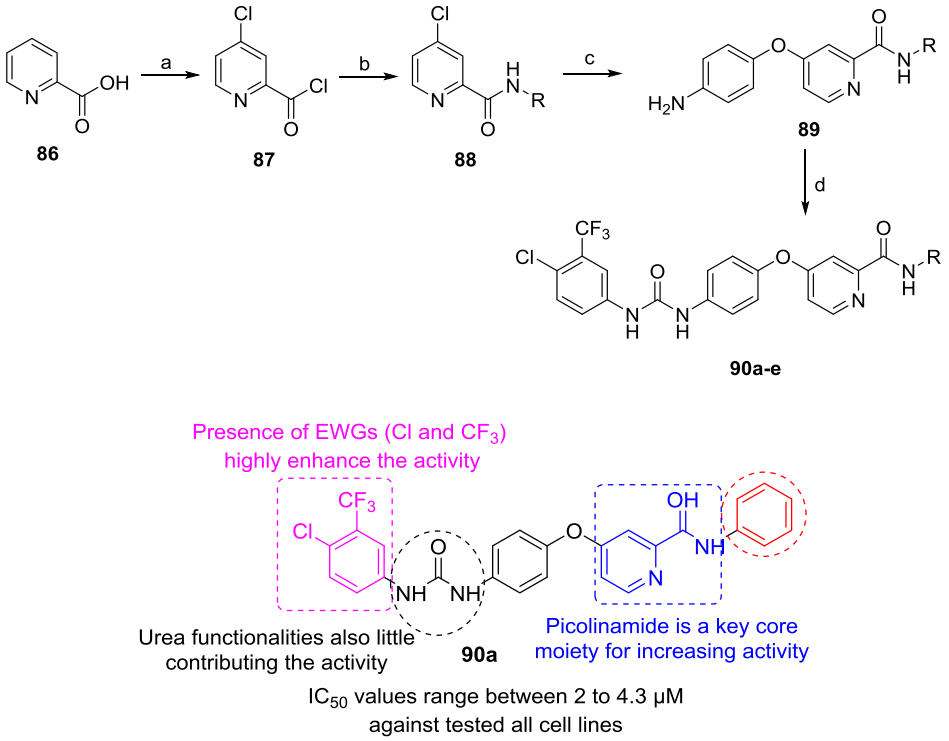


Reagents and conditions: (a) 40% CH_3NH_2, methanol 0 °C, 3 h; (b) 48% HBr, reflux, 10 h, then $NaHCO_3$; (c) Cs_2CO_3, DMSO, rt, 15 min, 135 °C, 5 h; (d) Aryl carboxylic acid, DIPEA, HATU, DMF, rt, 24 h, 53-100%; (e) aryl isocyanate, acetonitrile or DMF, rt, 24 h, CDI, DMF, rt, 24 h then arylamine, 100 °C, 3 h.

Scheme 14. Synthetic route to picolinamide-containing benzothiazole hybrids as potent anti-proliferative agents against HCT-116 and SK-BR-3 cell lines.

presence of thiourea functional group and *N*-terminal cyclohexyl groups were contributing to enhancing the activity antiproliferative activity. The replacement of terminal cyclohexyl group with phenyl group highly reduced the antiproliferative activity (see Scheme 19).

A simple two steps synthesis method was used to formulate amide group substitution **112a-x** allowing screening of the effect of electronic properties of phenyl ring substitution on cancer cell lines. In the first step, starting material **12** reacted with amino phenol **110** in the presence of base K_2CO_3 to afford intermediate **111** in good yield under optimal reaction conditions. Then in second step, intermediate **111** reacted with acylchlorides or sulfonyl chlorides in the presence of pyridine in THF solvent at room temperature to give final targeted compounds **112a-x** in good yields (Scheme 20). All the synthesized compounds were screened for their SHP-1 phosphate activity [56]. Among them, compound **112a** was found to be good SHP-1 phosphate activity with IC_{50} value of 8.4 μM against PLC-5 cell line. The preliminary SAR exposed that, SHP-1 phosphate activity depends on the presence of pyridinyl ring moiety of sorafenib, and the electronic effect of substitution on the phenyl ring of compounds. Among the four different analogs of sorafenib examined, the sulfonylamide with phenyl trifluoromethane derivative (**112a**) showed excellent SHP-1 phosphate potency, which is better than the amide, amino methylene and



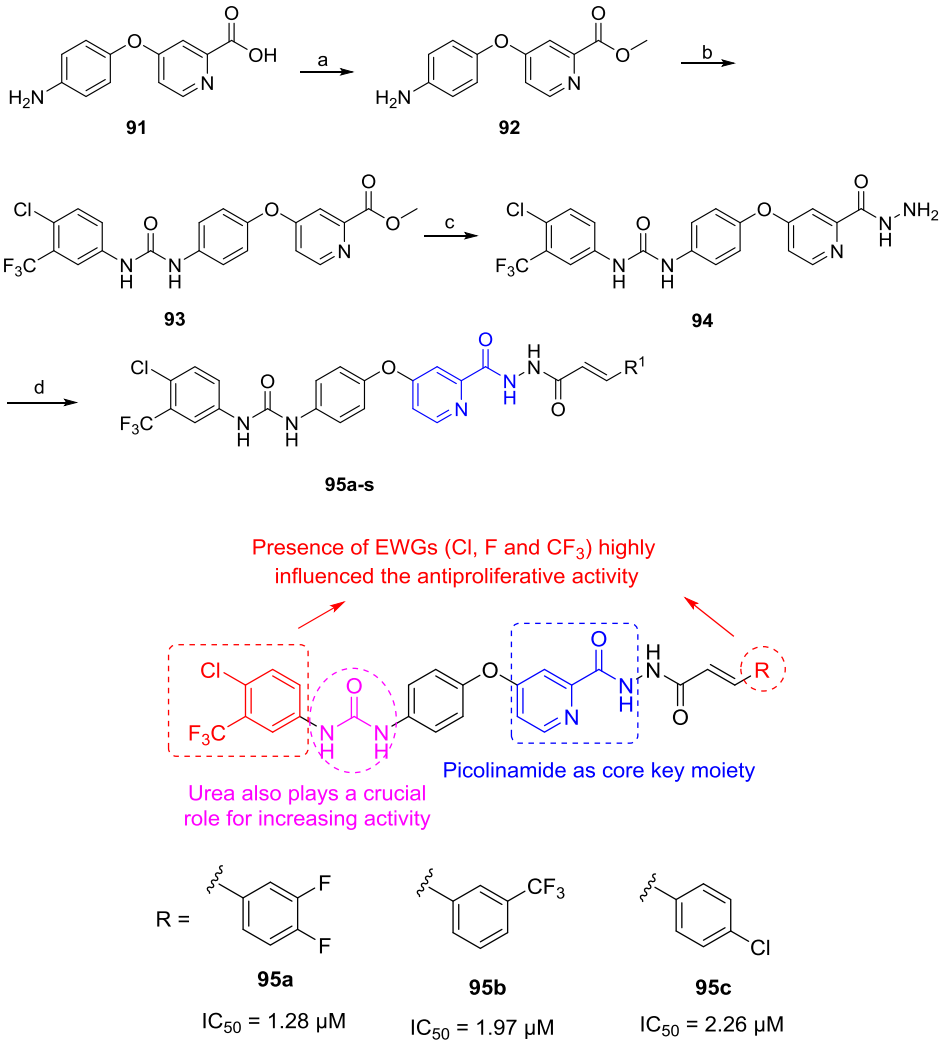
Reagents and conditions: (a) $SOCl_2$, DMF, N_2 atmosphere, 72 °C, 16 h; (b) amine, TEA, toluene, rt, 0.5 h; (c); 4-aminophenol, *t*-BuOK, DMF, K_2CO_3, DMF, 10 min, 173 °C, microwaves; (d) 4-chloro-3-(fluoromethyl)phenyl isocyanate, CH_2Cl_2, N_2 atmosphere, rt, 16 h.

Scheme 15. Synthesis of picolinamide-linked urea derivatives as potent anti-proliferative agents against different cell lines such as HeLa, MCF7, HCT116 and SW620.

phenylsulfonyl derivative counterparts respectively. The findings presented compound **112a** point to the potential use of SHP-1-activating agents in the treatment of hepatocellular carcinoma in near future.

A series of picolinamide containing 5,6 fused hetrocyclic amides were synthesized and evaluated for *in vitro* Raf kinase inhibitors by Ramurthy and co-workers [25]. The synthetic route was described in Scheme 21. The various substituted anilines were treated with the Cl and Br substituted benzisoxazole **113** in the presence of NMP at 200 °C in microwave for 7 min to afford intermediates **114a-p** in good yields [51]. Next, demethylation with 48% HBr followed by *O*-arylation using KHMDS and 4-chloro-pyridyl acetamide in DMF in microwave to furnish the desired compounds **115a-p** in good yields. Among the synthesized series, compound **115a** and **115b** showed excellent Raf activity with IC_{50} values of 0.001 and 0.001 μM respectively. As observed in the activity of benzimidazole series, the 3-*tert*-butyl group was an important for *in vitro* potency and inhibition of phosphorylation of ERK [31]. The preliminary SAR revealed that, effect of amide substituent was investigated for both benzoxazole and benzothiazole series. The primary carboxamide was found to be equipotent to the methyl amide analogs and showed a similar effect in the cellular target modulation. The presence of *tert*-butyl group at *meta*-position of the phenyl ring highly influences the Raf activity compared to the other *ortho*-substituted analogs. In addition, both benzoxazole and benzothiazolehetrocycle and picolinamide also play a major contributing the increasing Raf activity. Moreover, In order to understand the binding mode for these series, **115a** and **115b** were docked [57] in the active site of the public domain crystal structure published for (B-Raf (PDB accession code 1UWH) Fig. 3 shows the overlap of the docking models with the co-crystallized conformation of BAY43-9006. The model suggests a very similar binding mode when comparing **115a** or **115b** with BAY43-9006 [58]. Specific interactions of the benzothiazole and benzoxazole compounds in the B-Raf model) the backbone NH and C═O of Cys532 in the hinge region through the pyridyl-amidemoiety, (2) the backbone NH of Asp594 through the benzothiazoleor benzoxazole nitrogen, and (3) the side chain COO− of Glu501 through the aniline NH.

A new class of potent benzothiazole containing *N*-methylpicolinamide hybrids were synthesized by Keum and co-workers [59] and evaluated for their *in vitro* antiproliferative activity against leukemia K-562 and colon carcinoma KM12 cell lines for targeting Tie2, TrkA and ABL-1 (wild-type) kinase. The synthetic approach as outlined in Scheme 22. The starting material **116** was synthesized from literature reported method [49]. Synthesized compound **116** reacted with icocyanates in the presence of CDI and DMF to afford intermediate **117** in good yields under optimal reaction conditions. Next, compound **118** was synthesized from literature method [60] and then reacted with **117** in DMF under reflux conditions to furnish final targeted compounds **119** and **120** in good yields. Among the two final compounds **119** and **120**, compound **120** was found to be most potent antiproliferative activity

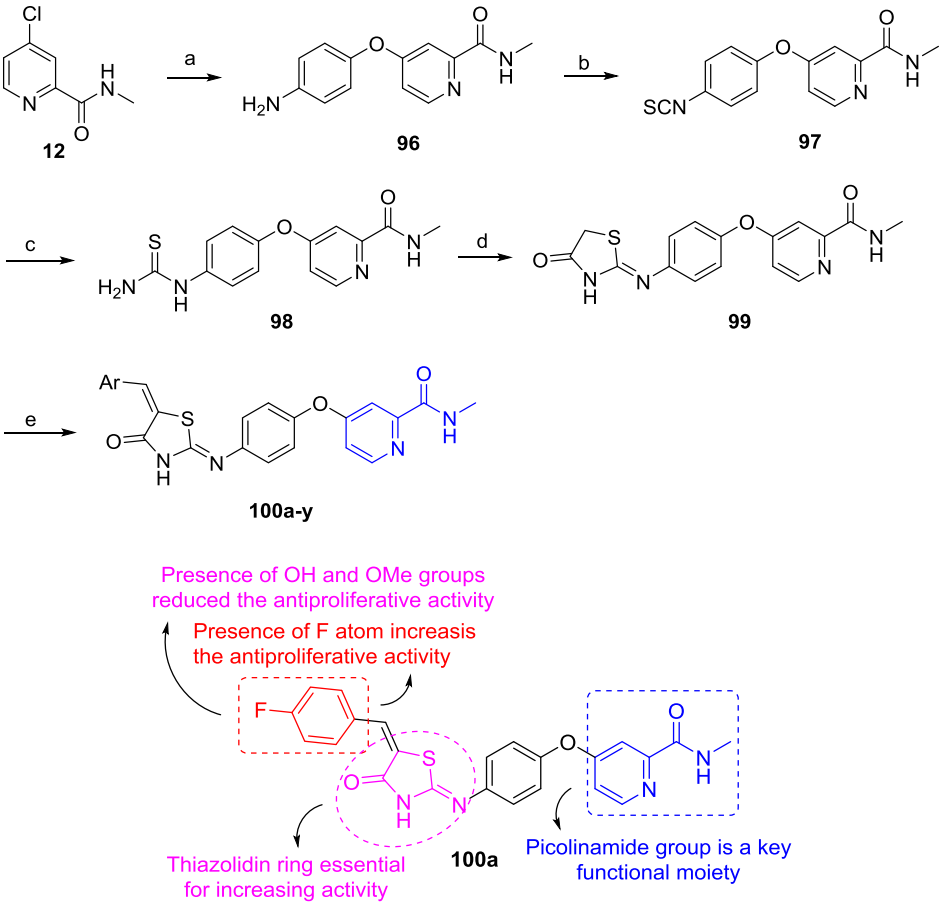


Reagents and conditions: (a) $SOCl_2$, MeOH, reflux; (b) DCM, 0 °C to rt; (c) hydrazine hydrate, MeOH, rt; (d) 3-arylacrylic acids, HATU, TEA, DMF, rt

Scheme 16. Synthetic approach to piconilamide-based urea hybrids as potent anti-proliferative agents against human cancer cell lines such as ACHN, HCT116 and MDA-MB-231.

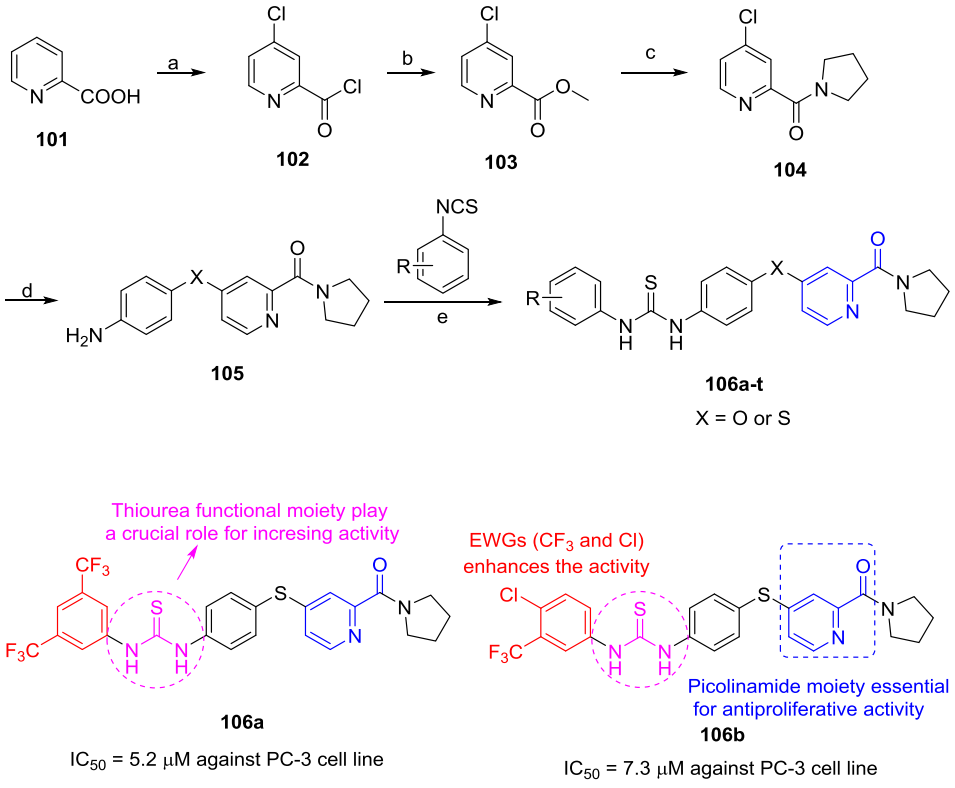
with 50% inhibition of percentage growth inhibition (GI_{50}) value of 51.4 and 19 nM against leukemia K-562 and colon carcinoma KM-12 cell lines, respectively. Furthermore, the cytotoxicity of compound 120 has been tested against the human foreskin fibroblast (HFF-1) normal cell line using MTT assay. At 1.0 mm concentration, which is close to the mean GI_{50} value over NCI-60 cancer cells, compound 120 showed low growth inhibitory activity against HFF-1 normal cell. Such finding may reveal the differential cytotoxic activity of compound 120 toward human cancer cells rather normal cell lines. The preliminary SAR exposed that, the presence of (4-ethylpiperazin-1-yl)methyl moiety (**120**) at *para*-position neighbouring to the *m*-CF_3 group led to significant enhancement in the activity. Replacement of (4-ethylpiperazin-1-yl) methyl with morpholinomethyl group led to slight reduces the antiproliferative activity. The presence of (4-ethylpiperazin-1-yl)methyl group was highly increases the lipophilicity and steric character of the potent molecule **120**.

In 2015, Zhu and co-workers [61] prepared new class of potent picolinamide containing derivatives and tested their cytotoxicity against A549, Hela, MCF-7, and PC-3 cancer cell lines. Initially, commercially available compound **12** reacted with 4-amino phenol under ambient reaction conditions to afford intermediate **121** in good yield. Then various substituted aryl sulfonyl analogs**122a-h** were treated with intermediate **121** in the presence of toluene under reflux condition for 8–10 hr to furnished final derivates **122a-f** in good yields (Scheme 23). From the set of the analogues, compound **122a** and **122b** showed excellent cytotoxicity activity with IC_{50} values of 27 μM against A549 and 16 μM against MCF-7 respectively. The SARs presented that the presence of sulfonylurea unit was essential to improve the activity. On the other hand, the presence of substitutions in the phenoxy group and EWG such as 2,4-difluoro substitution of the aryl group contributed to the activity. The results recommended that sulfonylurea sorafenib analogs are worthy of further study (see Table 1).



Reagents and conditions: a) 4-aminophenol/*t*-BuOK/DMF, 80 °C, 6 h; b) 6% $NaHCO_3$, CH_2Cl_2, thiophosgene, 0 °C, then rt. 5 h; c) NH_4OH/dioxane, 80 °C, 1 h; d) ethyl chloroacetate, AcONa, EtOH, 60 °C, 6 h; e) AcONa/AcOH, microwave, 12 min.

Scheme 17. Synthetic approach to picolinamide analogues as potent antiproliferative agents against three cancer cell lines such as A549, H460 and HT29.

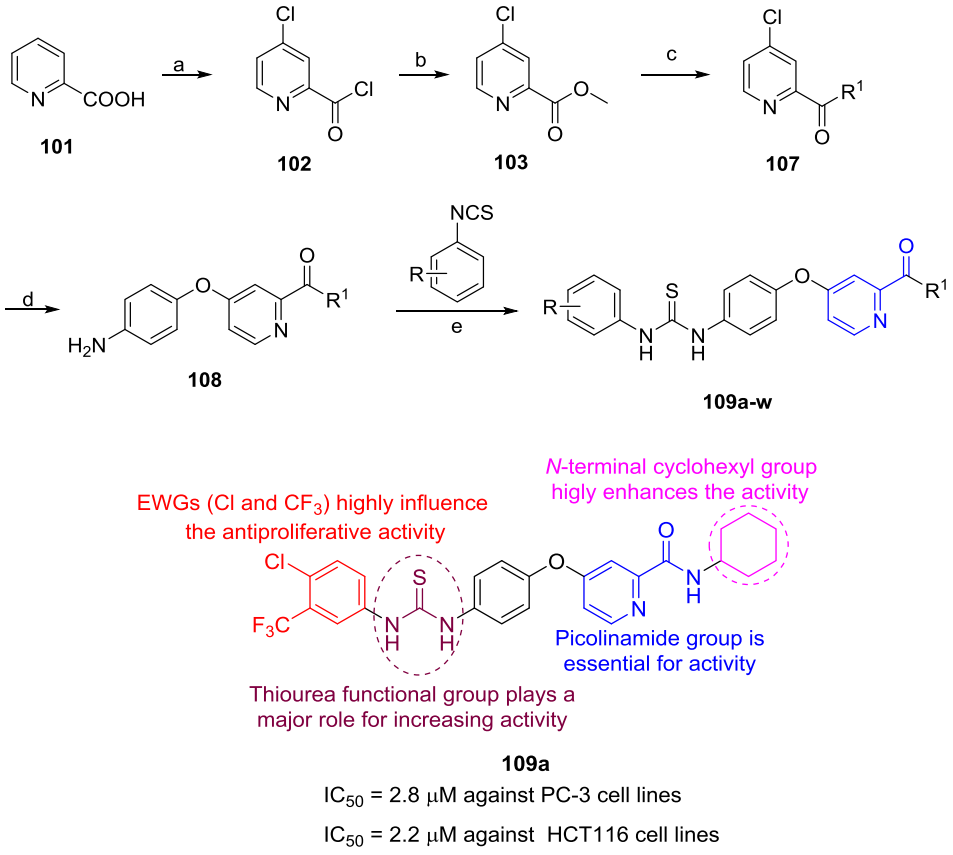


Reagents and conditions: (a) $SOCl_2$; (b) CH_3OH; (c) pyrrolidine, THF; (d) 4-aminophenol or 4-aminobenzenethiol, DMF, *t*-BuOK; (e) DCM

Scheme 18. Synthetic route to picolinamide-containing thiourea analogues as potent antiproliferative agents against PC-3 cell line.

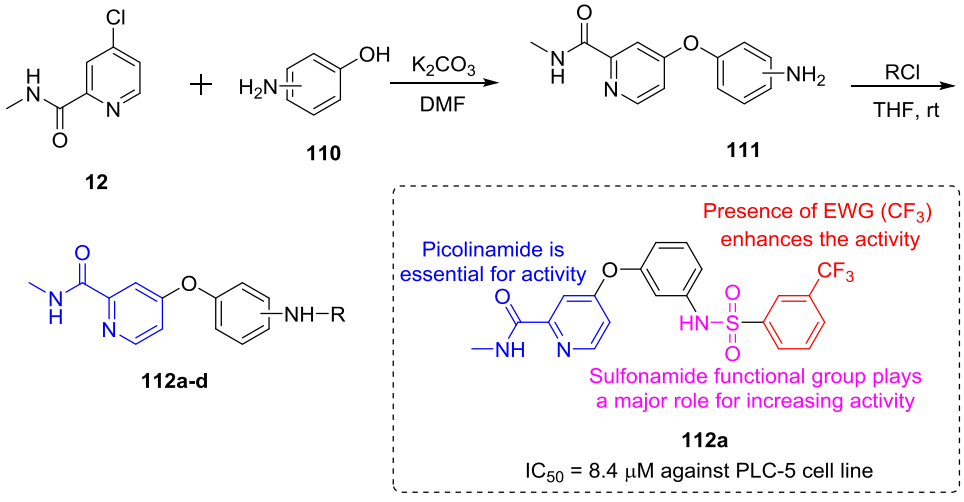
3. Conclusion

In this review article, we briefly presented various synthetic methods in drug development programs for the improvement of new-fangled various types of anti-cancer agents in the past decades. The SAR based work will possibly continue to play an imperative function in additional realizing the full prospective of *N*-methylpicolinamide based hybrids. Many of these potential drugs are not in clinical trials yet, but an accent of the need for their further derivatization/optimization shall offer an opportunity for innovation of pharmaceutically very useful therapeutics. The authors, in this work, have disclosed the roles of various picolinamide-based hybrids in the field of medicinal chemistry by discussing the insights of design, synthesis and SAR studies of these hybrids with an assortment of targets. Overall, the multidisciplinary synthetic methodologies from the usual approaches and the emerging alternatives will promote anti-cancer drug discovery and development in the future.

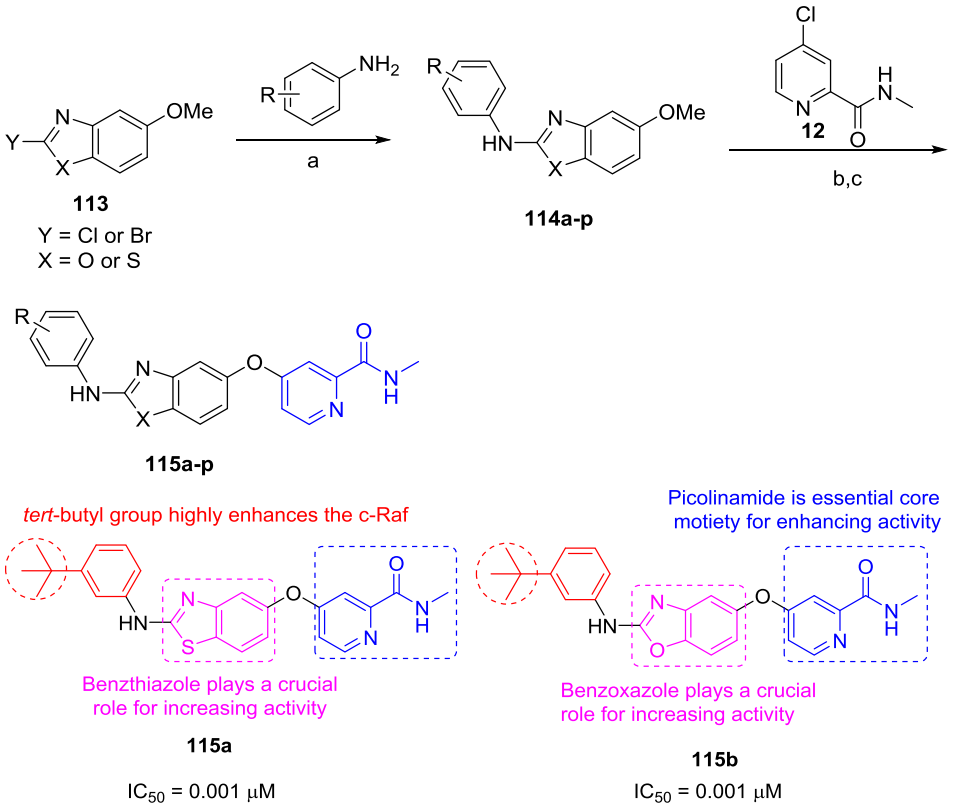


Reagents and conditions: (a) $SOCl_2$; (b) CH_3OH; (c) RNH_2/pyrrolidine, THF; (d) 3-aminophenol, DMF, *t*-BuOK; (e) DCM, rt

Scheme 19. Synthesis of thiourea-based picolinamide analogues as potent antiproliferative agents against HCT116 and PC-3 cell lines.



Scheme 20. Synthetic route to picolinamide-containing hybrids as potent anticancer agents against PLC-5 cell line.



Reagents and conditions: (a) R-NH_2, NMP, 200 °C, microwave,7 min; (b) 48% HBr, 140 °C, microwave, 6 min; (c) KHMDS, K_2CO_3, DMF, 170 °C, microwave 7 min.

Scheme 21. Synthetic route to potent picolinamide-containing hybrids as Raf kinase inhibitors.

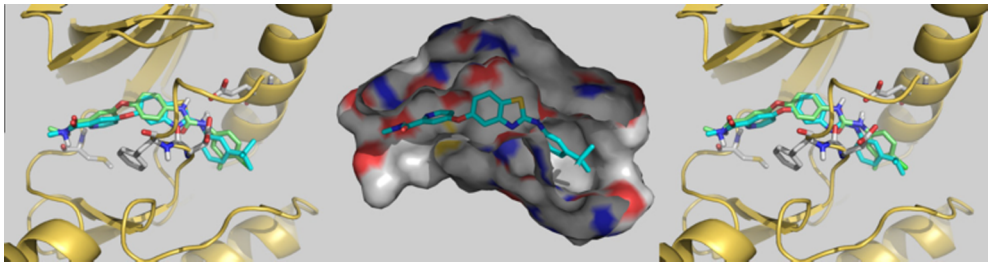
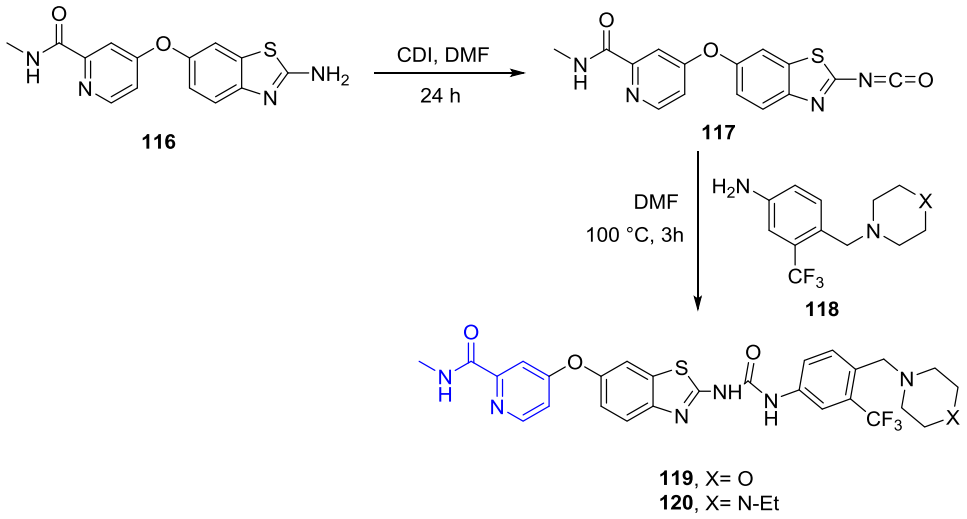
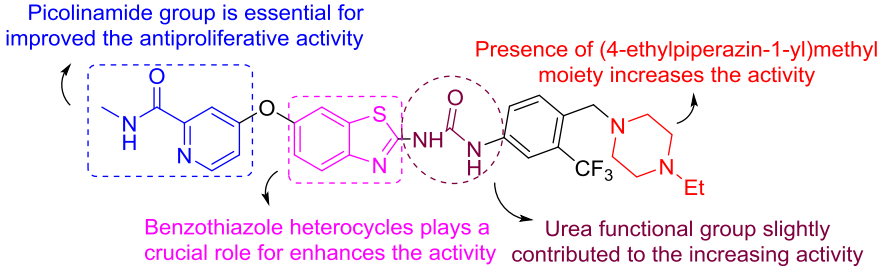


Fig.3. Binding site models for compounds **115a** (left, in cyan) and **115b** (right, in cyan) derived by docking into the crystal structure of B-Raf (PDB accession code 1UWH). The left and right pictures show cartoon representations of the kinase with selected residues in stick model (Glu501, Cys532, Phe593, Asp594) and the co-crystallized BAY43-9006 in green. The middle picture shows a surface representation, of the docking model for 3 with the surface colored by atom type (red = oxygen, blue = nitrogen, yellow = sulfur, grey = carbon/hydrogen).



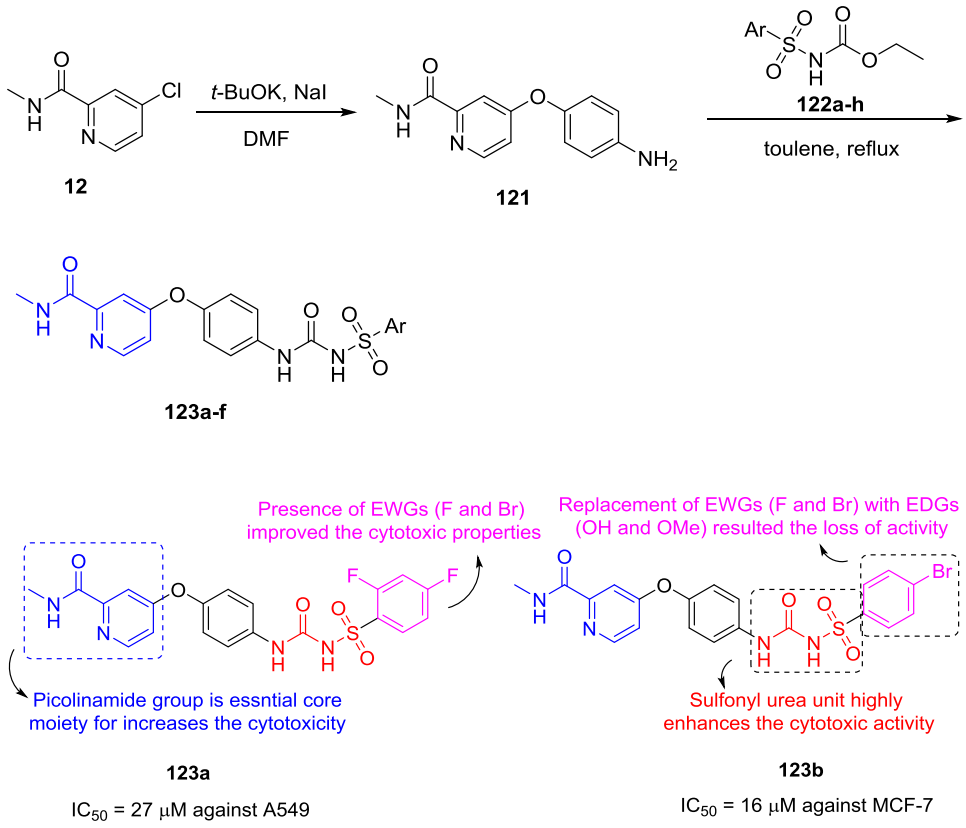


120

GI_{50} = of 51.4 nM against leukemia K-562 cell line

GI_{50} = 19 nM against colon carcinoma KM12 cell line

Scheme 22. Synthetic approach to benzothiazole-containing picolinamide hybrids as potent antiproliferative agents against leukemia K-562 and colon carcinoma KM12 cell lines for targeting Tie2, TrkA and ABL-1 (wild-type) kinase.



Scheme 23. Synthesis approach to potent picolinamide-containing sulfonyl urea derivatives with potent cytotoxicity against A549, Hela, MCF-7, and PC-3 cancer cell lines.

Table 1
Some patent works on anticancer activity of *N*-methylpicolinamide derivatives.

Sl. no	Patent no	Data	Invention disclosed	Ref.
1	US 20120225062 A1	Sep 06, 2012	Synthesis of pyridinyl picolinamides as a new class of potent kinase inhibitors for treating cancer and autoimmune diseases	[62]
2	WO 2012100135 A1	Jul 26, 2012	Development of piperazinylphenylaminopicolinamides as ALK inhibitors	[63]
3	CN 106008371 A	Oct 12, 2016	Picolinamide and their analogues treatment of cancer, tumor metastasis, viral diseases and bacterial infection diseases	[64]
4	CN 106008371 A	Nov 09, 2016	Process for synthesizing method for Regorafenib	[65]
5	CN 105949117 A	Sep 21, 2016	Synthesis and biological applications of chalcone containing sorafenib derivatives	[66]
6	CN 105801475 A	Jul 27, 2016	Method for preparation of Sorafenib to sylate	[67]
7	CN 105646340 A	Jun 08, 2016	Development of synthetic methods for sorafenib to sylate from nitrophenol	[68]
8	CN 105566215 A	May 11, 2016	Process for preparation of Regorafenib	[69]
9	CN 105503715 A	Apr 20, 2016	Synthesis of sorafenib semitoluenesulfonate hydrates as potential anticancer agent	[70]
10	WO 2016051422 A2	Apr 07, 2016	Synthesis and pharmaceutical applications of 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamides	[71]
11	CN 104788366 A	Jul 22, 2015	Synthesis of *N*-(pentafluorosulfanyl)aryl-*N′*-[[(pyridinyl)oxy]phenyl] urea analogs as potent treatment of cancer diseases	[72]
12	CN 104557689 A	Apr 29, 2015	Synthetic method and development of Regorafenib for treatment of metastatic colorectal cancer (mCRC)	[73]
13	WO 2015051149 A1	Apr 09, 2015	Sorafenib analogs as used for the treatment of cancer diseases	[74]
14	WO 2014040242 A1	Mar 20, 2014	Synthesis and potential anti-cancer agent of ureido-pyridinecarboxamides derivatives	[75]
15	WO 2013166966 A1	Nov 14, 2013	Synthesis of 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-fluorophenoxy]-*N*-(methyl-3)-2-pyridinecarboxamide analogs as potent class of anticancer agents	[76]
16	CN 103319402 A	Sep 25, 2013	Synthesis of diphenylthioureahybrids as potent anti-cancer agents	[77]
17	WO 2013097224 A1	Jul 04, 2013	Development of fused tricyclic analogs as potent raf kinase inhibitors are useful for the treatment of cancer diseases	[78]
18	CN 103087054 A	May 08, 2013	Synthesis and applications of 4-pyridiyl phenyl ethers as antitumor drugs	[79]
19	CN 102993093 A	Mar 27, 2013	Synthesis and pharmaceutical applications of *N,N′*-di-substituted diphenylthioureaanalogs for treatment of cancer diseases	[80]
20	WO 2013036232 A2	Mar 14, 2013	Development of heterocyclic urea analogues as useful for potential kinase inhibitors and the treatment of proliferative diseases	[81]
21	WO 2013022766 A1	Feb 14, 2013	Preparation and synthetic method of *ortho*-aryl 5-membered heteroaryl-carboxamide analogues as multi-targeted kinase inhibitors	[82]
22	CN 102898363 A	Jan 30, 2013	Synthesis of carbamate analogs as useful for the treatment of cancer diseases	[83]
23	CN 102731385 A	Oct 17, 2012	Synthesis of picolinamide based pyridine derivatives as antitumor agents	[84]
24	US 20120225057 A1	Sep 06, 2012	Development of heterocyclic urea derivatives as a new class of potent kinase inhibitors useful for the treatment of hyperproliferative diseases	[85]
25	WO 2012094451 A1	Jul 12, 2012	Preparation and synthetic applications of urea derivatives as protein kinase inhibitors and useful for the treatment of cancer	[86]
26	CN 102432595 A	May 02, 2012	Preparation of *N*-indole-1-carboxamide derivatives as antitumor agents	[87]
27	KR 2012038677 A	Apr 24, 2012	Preparation and application of picolinamide linked hydroxamic acid analogs as potent protein kinase inhibitor	[88]
28	CN 102336740 A	Feb 01, 2012	Synthesis of new class of benzimidazoles as potent tyrosine kinase inhibitors useful for the treatment of tumor disease	[89]
29	WO 2012012404 A1	Jan 26, 2012	Drug combinations with fluoro-substituted omega-carboxyaryl diphenyl urea for the treatment and prevention of diseases and conditions	[90]
30	WO 2012008563 A1	Jan 19, 2012	Synthesis and development of nitrogen-containing heteroaromatic analogs as potent antitumor agents	[91]
31	WO 2011130728 A1	Oct 20, 2011	Synthesis of regorafenib analog for the treatment of cancer diseases	[92]
32	WO 2011117254 A1	Sep 29, 2011	Preparation of piperidine amides as modulators of Ghrelin receptor	[93]
33	WO 2011113203 A1	Sep 22, 2011	Synthesis of picolinamide based-diphenylurea derivatives as antitumor agents	[94]
34	WO 2011113370 A1	Sep 22, 2011	Development of diphenylurea derivatives as new class of potent phosphokinase inhibitors	[95]
35	WO 2011113368 A1	Sep 22, 2011	Preparation of diphenylurea as antitumor agents and inhibitors of protein tyrosine kinase	[96]
36	WO 2011046991 A2	Apr 21, 2011	Synthesis of certain substituted ureas as modulators of kinase activity	[97]
37	JP 2011063516 A	Mar 31, 2011	Preparation of amide compounds as B-Raf kinase inhibitors	[98]
38	WO 2011034907 A2	Mar 24, 2011	Synthesis of pyridine and pyrimidine derivatives were useful for the treatment of cancer diseases	[99]
39	KR 2011006173 A	Jan 20, 2011	Synthesis of benzothiophene compounds as new class of potent tyrosine kinase inhibitors	[100]
40	WO 2010144499 A2	Dec 16, 2010	Development of picolinamide bearing urea derivatives as therapeutic kinase inhibitors	[101]
41	CN 101830847 A	Sep 15, 2010	Method for preparation of *N*-[4-chloro-3-(trifluoromethyl)phenyl]-[4-(*N*-methyl-formamide)-(4-pyridyloxy or thio)phenyl]-thiourea and application as antitumor agent	[102]
42	JP 2010138073 A	Jun 24, 2010	Synthesis of picolinic acid amide analogs as potent glucokinase agents	[103]
43	CN 101723890 A	Jun 09, 2010	Method for preparation and applications of aryl thiourea derivatives as potent antitumor agent	[104]
44	CN 101676266 A	Mar 24, 2010	Development of Sorafenib derivatives as potent tyrosine protein kinases inhibitors	[105]
45	WO 2009050228 A2	Apr 23, 2009	Synthesis of quinazolines analogs as CSF-1R inhibitors	[106]
46	WO 2009034308 A2	Mar 19, 2009	Synthesis of sorafenib analogs as potent RAF kinase inhibitor	[107]
47	CN 101362718 A	Feb 11, 2009	Synthesis of 4-phenoxy-*N*-methylpicolinamide derivatives as new class of potent antitumor agents	[108]
48	WO 2008120754 A1	Oct 09, 2008	Preparation of picolinamide compounds as potent glucokinase activating activity	[109]
49	CN 101220024 A	Jul 16, 2008	Synthesis of pyridine derivatives as potent antitumor agents	[110]
50	WO 2008079968 A1	Jul 03, 2008	Synthesis of picolinamide bearing carboxamide derivatives for useful for the treatment of cancer diseases	[111]

The inventions related to *N*-methylpicolinamide-containing derivatives, pharmaceutical compositions containing such compounds and pro-drugs are useful for treating several death causing diseases such as various types of cancer diseases, tumor and cardiovascular diseases and some other bacterial and viral diseases. These compounds are particularly precious for treating diseases attributable to kinase inhibitors, ALK inhibitors and hyperproliferative diseases. In recent years, significant work has been carried out to find multi-targeted inhibitors, in hopes of developing treatment for such disorders. The following Table showed that the invention of new types of *N*-methylpicolinamide-containing analogues as potential agents for the treatment of different types of diseases and the intermediates in the pharmaceutical industries for the preparation of potent drugs.

Acknowledgment

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.02.030.

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