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Synthesis and Anticancer Potentials of 1,8-Naphthyridine Analogues: A Review of Literature

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Abstract

This review focuses on the potential of 1,8-Naphthyridine derivativesinchemotherapeuticcancer treatment and highlights significant recent progress in the synthetic development of 1,8-naphthyridines as antitumor agents. The present review provides the classical (Skraup, Doebner-Von-Miller, Gould– Jacob, Meth-Cohn, Friedlander, Pfitzinger, Knorr and Conard Limpach, Combes, Niementowski and Pictet-Spengler)and green approaches (metal free ionic liquid mediated reactions, microwave irradiation reactions) for 1,8-naphthyridines synthesis. Their derivatives which exert their anticancer activity via several mechanismslike apoptosis-inducing agents, cell cycle arrest, topoisomerase I and II inhibitors, tubulin polymerization inhibitors, protein kinase inhibitors, intercalation with DNA, angiogenesis inhibitors, Ras protein inhibitors and telomerase inhibitors, are highlighted with proper synthetic methods, SAR studies and molecular docking of these derivatives.

Keywords: 1,8-Naphthyridine; Anticancer agents; Structure-activity relationship; Human cancer cell line; Molecular modelling.

1. Introduction

After cardiovascular disorders, cancer continues to be one of the world's most terrifying and potentially fatal diseases. [1].

The International Agency for Research on Cancer (IARC) published its most recent global cancer estimate on 15 December 2020, and it showed that there are currently 19.3 million new cancer cases worldwide and 10.3 million deaths. The majority of newly diagnosed cases (11.7%) were breast cancer, followed by (11.4%) lung cancer, (10%) colorectal cancer, (7.3%) prostate cancer, and (5.6%) stomach cancer. However, the majority of cancer-related deaths were due to lung cancer (18%) [2].

In the United States in 2022, there will be around 10,470 cases of cancer in children and 5,480 teenager cases, with 1050 and 550 deaths, respectively. The most prevalent childhood cancer is leukemia, whereas brain and other nervous system tumors are the most common cancer in teenagers [3].

The worldwide cancer burden is assumed to exceed 28.4 million cases in 2040, 47% higher than in 2020, with a greater increase in developing (64%) than developed (32%) countries owing to the demographic changes, this may be aggravated by increasing risks associated with global economy [2].

Cancer therapy is divided into traditional therapy such as surgery, radiation, and chemotherapy or targeted therapy that interferes with a specific molecular target which plays a crucial role in inhibiting tumor progression with minimal side effects comparable to chemotherapy [4, 5].

Naphthyridines are nitrogenous heterocyclic compounds that are formed from two fused pyridine rings [6].

Pyridopyridines, benzodiazines, and diazanaphthalenes are some of the names given to naphthyridines. Six main naphthyridine isomeric structures have been identified according to the position of nitrogen atoms in the fused ring system are listed in (Figure 1)[7].

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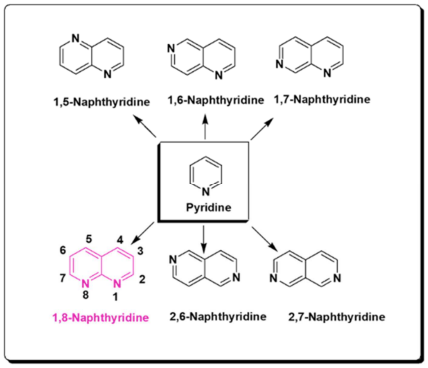


Figure 1: Isomeric structures of naphthyridine

Among all the six isomeric forms, 1,8-naphthyridine have received excessive attention because of its valuable biological activities (Figure 2), including analgesic, anti-inflammatory[8], antihypertensive[9], antibacterial[10],anti-tuberculosis[11], antiviral[12], antimalarial[13], anticancer[14], anti-allergic [15], anticonvulsant[16], antioxidant[17], gastric antisecretory[18], bronchodilator[19], antiplatelet[20], anti-osteoporotic[21],β-3 antagonist[22] and for treating neurological diseases like Alzheimer's[23], depression[24] and multiple sclerosis[25]. Nalidixic acid is the first 1,8-naphthyridine derivative discovered in 1962 which exhibited antibacterial activity. It is used for the treatment of urinary tract infections by gram-negative bacteria [26].Other clinically approved drugs containing 1,8-naphthyridine scaffold in their structures such as gemifloxacin, enoxacin, tosufloxacin, trovafloxacin mesylate, alatrofloxacin as antibiotics, and voreloxin as anticancer agent (Figure 3)[6]. In this review, we have summarized the synthetic methods of 1,8-naphthridine scaffold and explored particularly the antitumor potential of 1,8-naphthyridine derivatives on target-oriented basis, which could provide medicinal chemists for discovering more effective anticancer drugs.

2. 1,8-Naphthyridines synthesis.

Numerous synthesis methods of naphthyridine have been reported, most of which are like the quinoline synthesis through thermal cyclization of intermediate that was produced from the reaction of aminopyridine as starting material instead of aniline with carbonyl compounds. Different isomeric forms of naphthyridine can be synthesized depending on the amino group position in the pyridine ring. 1,8-napthyridine is produced from 2-aminopyridine. 1,5 and 1,7-naphthyridine are produced from 3-aminopyridine. 1,6-naphthyridine is produced from 4-aminopyridine. Methods of synthesis, namely Skraup, Doebner Von Miller, Knorr, Conard-Limpach, Combes, and Gould-Jacobs, were not productive for the synthesis of naphthyridine as quinolone synthesis. The inefficiency of these methods is due to the low electron density of the pyridine ring which is comparable to the benzene ring of aniline in the cyclization process [27,28].

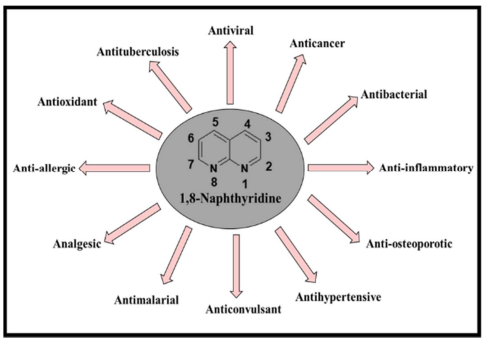


Figure 2: Pharmacological screening for 1,8-naphthyridines

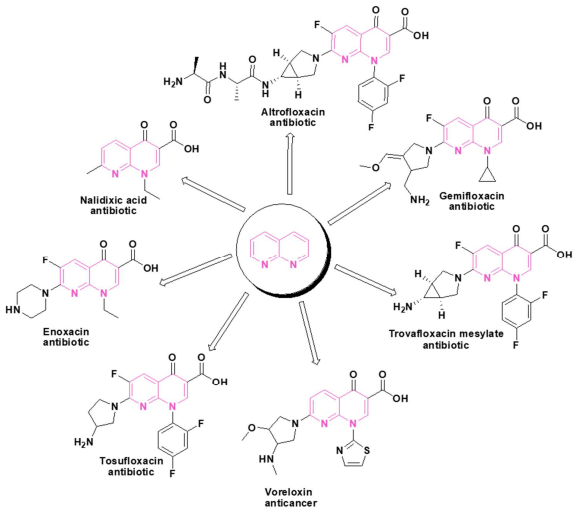


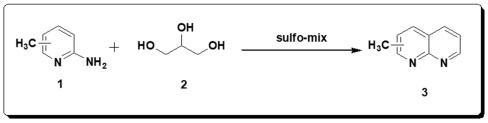
Figure 3: Examples of marketed drugs based on 1,8-naphthyridine core

2.1. Skraup and Doebner Von Miller reaction

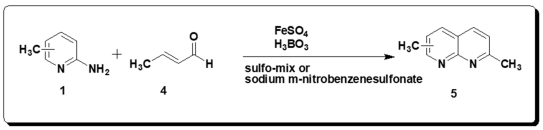
Skraup reaction is a condensation reaction of glycerol with primary aromatic amines catalyzed by H_2SO_4 to convert glycerol to acrolein and oxidizing agents such as nitrobenzene, and [29]. While the modified Skraup reaction Doebner Von Miller reaction, is the condensation of α, β unsaturated carbonyl compounds with primary aromatic amines in the presence of ZnCl2 with HCl or iodine [29,30]. Paudler and coworker[31]reported that condensation of methyl-2-aminopyridines **(1)**, with glycerol **(2)** using sulfo-mix via Skraup reaction giving methyl-1,8-naphthyridine derivatives **(3)**, but this reaction gives an unsatisfactory yield for 1,8-naphthyridine derivatives (**Scheme 1**).

Furthermore, Hamada *et al*. [32]have modified the Skraup reaction to improve the yield of methyl-substituted 1,8-naphthyridine derivatives **(5)** through the condensation of 2-aminopicolines **(1)** with glycerol or α,β unsaturated carbonyl compounds such as

crotonaldehyde **(4)**, methacrolein and methyl vinyl ketone using ferrous sulfate and boric acid in addition to sulfo-mix or sodium m-nitrobenzenesulfonate **(Scheme 2).**



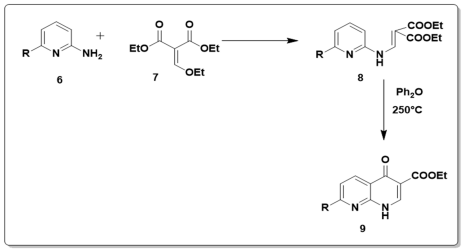
Scheme 1: formation of methyl 1,8-naphthyridines from 2-aminopicoline and glycerol



Scheme 2: Synthesis of 1,8-naphthyridine from 2-aminopicoline and crotonaldehyde

2.2.Gould-Jacobs reaction

This reaction involves the condensation of 6-substituted-2-aminopyridine **(6)** with diethyl ethoxymethylenemalonate (EMME) **(7)** to give the intermediate diethyl-N-(6-substituted-2-pyridyl) aminomethylenemalonate **(8)**, which undergoes thermal cyclization at 250°C in diphenyl ether (Ph_2O) to yield ethyl-7-substituted-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate **(9)(Scheme 3)** [33,34]. Multiple reports have been published regarding this method for 1,8-naphthyridine synthesis [35–38].

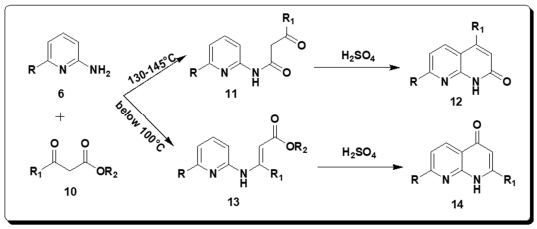


Scheme 3: Synthesis of ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate

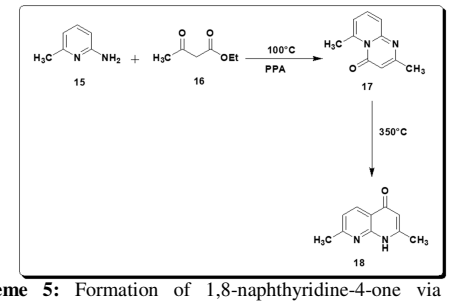
2.3. Knorr and Conard-Limpach reactions

The reaction of 6-substituted-2-aminopyridines **(6)** with β-keto esters **(10)** either on the ester group at 130-140°C to give anilide intermediates **(11)** or on the keto group at room temperature or below 100°C to produce crotonate intermediates **(13)** followed by an acid catalyzed thermal cyclization of anilides and crotonates to obtain 2-naphthyridinones **(12)** (Knorr reaction)and 4-naphthyridinones **(14)** (Conard-Limpach reaction), respectively **(Scheme 4)**[39].

Chandler *et al*.[40] and Ferrarini *et al*.[41]suggested the formation of 2,7-dimethyl-1,8-naphthyridine-4-(1H)-one **(18)** via the Conard-Limpach method through the reaction between 6-methyl-2-aminopyridine **(15)**, ethyl acetoacetate **(16)** and polyphosphoric acid (PPA) at 100°C then ring transformation of 2,6-dimethylpyrido[1,2-a]pyrimidin-4-one **(17)** in paraffin oil or diphenyl ether at 350°C **(Scheme 5)**.



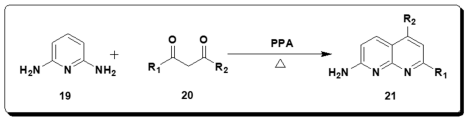
Scheme 4: Synthesis of 1,8-naphthyridinone via Knorr and Conard-Limpach reactions



Scheme 5: Formation of 1,8-naphthyridine-4-one via Conard-Limpach reaction

2.4.Combes reaction

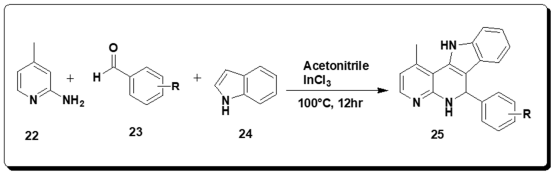
2-amino-5,7-disubstituted-1,8-naphthyridine derivatives **(21)** were synthesized via Combes reaction through the condensation of 2,6-diaminopyridine **(19)**with 1,3-diketones **(20)** in the presence of PPA **(Scheme 6)** [42,43].



Scheme 6: Formation of 1,8-naphthyridines via Combes reaction

2.5.Povarov reaction

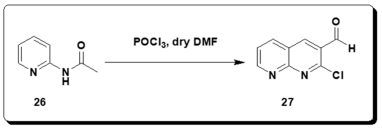
Makhanya and coworkers[44]synthesized indolo[3,2-c][1,8]naphthyridines **(25)** via intramolecular Povarov reaction through three-components condensation between 2-amino-4-methylpyridine **(22)**, aromatic aldehydes **(23)** and indole (activated olefin) **(24)(Scheme 7)**. Upon testing of different solvents (acetonitrile, ethanol, water, benzene, 1,4-dioxane and DMSO), catalysts (PTSA, $InCl_3$, $BF_3.Et_2O$ and TFA) and temperatures, the best yield was displayed in acetonitrile at 100°C and using $InCl_3$ catalyst.



Scheme 7: Povarov reaction for the formation of indolo-naphthyridines

2.6.Meth-Cohn reaction

Kumar *et al*. [45] synthesized 2-chloro-3-formyl-1,8-naphthyridine **(27)** via Meth-Cohn reaction, where N-(pyridin-2-yl)acetamide **(26)** was treated with Vilsmeier's reagent ($POCl_3$+DMF) **(Scheme 8).**



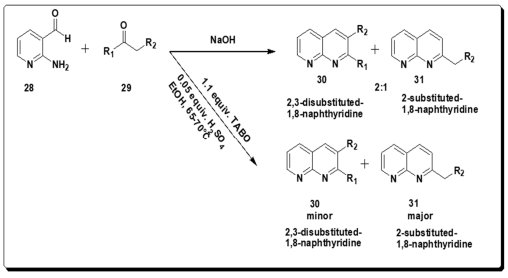
Scheme 8: Formation of 2-chloro-3-formyl-1,8-naphthyridine

2.7.Friedlander reaction

Friedlander reaction is the most effective method for 1,8-naphthyridine synthesis. Acidic or basic catalyzed reaction of 2-aminonicotinaldehyde **(28)** with α-substituted methylene carbonyl compounds **(29)**. Thisclassical Friedlander reaction requires harsh conditions and a longer reaction time [46].

Friedlander reaction has some limitations when unactivated, unsymmetrical ketones have been employed due to the lack of regioselectivity in the formation of disubstituted and monosubstituted-1,8-naphthyridines **(30)** and **(31)** with a ratio of 2:1 **(Scheme 9)**. While in the case of symmetrical ketones or ketones containing activated α-methylene group between two electron-withdrawing groups like β-keto esters and 1,3-diketones were used, the product is 2,3-disubstituted-1,8-naphthyridine [47].

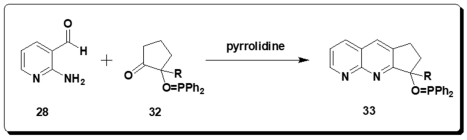
Dormer *et al*. introduced the solution for the regioselectivity problem by the slow addition of inactivated methyl alkyl ketone *(29)* to an ethanolic solution of **28** and 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO), providing the major regioisomer 2-substituted-1,8-naphthyridine **(31)(Scheme 9)**[48].



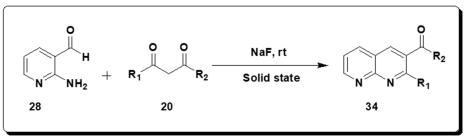
Scheme 9: Friedlander synthesis of mono and disubstituted naphthyridines

Furthermore, Lemport*et al*.[49] described another solution to give only the regioisomer 2-substituted-1,8-naphthyridine through modifying ketones by alkyl substitutions. for example, the reaction of **28** with 2-(diphenylphosphoryl)cyclo-pentanone (**32**) in the presence of a catalytic amount of pyrrolidine, yielding the desired regioisomer of 8-(diphenylphosphoryl)-7,8-dihydro-6H-cyclopenta[b][1,8]naphthyridine **(33)(Scheme 10)**.

Also, Mogilaiah*et al*. [50] improved Friedlander reaction time and yield for 1,8-naphthyridines **(34)** was carried out by the reaction of **28** with 1,3-diketones **(20)** at room temperature catalyzed by sodium fluoride **(Scheme 11)**.



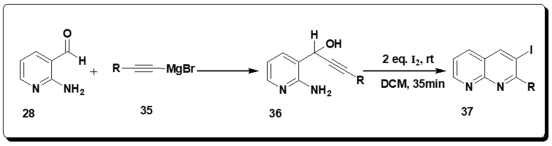
Scheme 10: Reaction of 2-aminonicotinaldehyde with 2-(diphenyl phosphoryl)cyclo-pentanone



Scheme 11: Solvent-free Friedlander synthesis of 1,8-naphthyridines

2.8.Grignard reaction

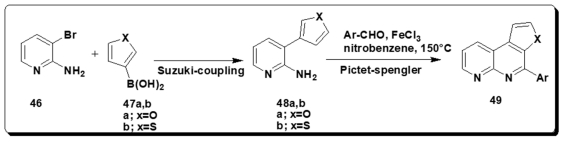
Grignard reaction is a well-known method for creating carbon-carbon bonds by the reaction of organomagnesium species with carbonyl compounds [51]. Sakraman*det al*. published a method of 3-iodo-2-substituted-1,8-naphthyridine derivatives **(37)** synthesis, where 2-aminonicotinaldehydes (28) were reacted with different alkyl and aryl magnesium bromides **(35)** followed by electrophilic cyclization of intermediate **(36)** in dichloromethane (DCM) as a solvent and iodine [52] **(Scheme 12)**.



Scheme 12: Synthesis of 1,8-naphthyridines via Grignard reaction.

2.9. Niementowski reaction

Niementowski reaction is an expansion of Friedlander synthesis which differs in the reactants [53]. Hawes and coworker described the synthesis of 7-phenyl-1,8-napthyridine-2,4-diols **(40)** from a condensation reaction between ethyl-2- amino-6-phenyl nicotinate **(38)** and simple esters **(39)** with a catalytic amount of metallic sodium **(Scheme 13)**[54].

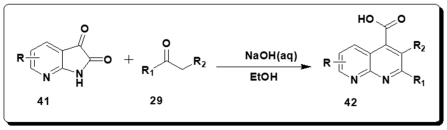


Scheme 13: Niementowski reaction for the formation of 1,8-naphthyridine-2,4-diols derivatives

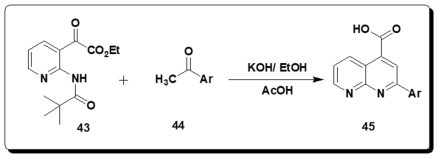
2.10. Pfitzinger-Borsche reaction

Pfitzinger-Borsche reaction for quinolone-4-carboxylic acid synthesis could be also used to produce its 1,8-naphthyridine analogues **(42)** by reacting 7-azaisatin **(41)** instead of isatin and α-methylene carbonyl compounds **(29)** under basic conditions **(Scheme 14)**[55,56].

Zong*et al*. [55] reported the formation of 2-aryl-1,8-napthyridine-4-carboxylic acid **(45)**, using another starting material that could react similarly to 7-azaisatin via the Pfitzinger reaction. This synthon namely [2-(pivaloylamino)pyrid-3-yl]oxoacetic acid ethyl ester **(43)** was condensed in ethanolic KOH solution with acetyl compounds **(44)** in ethanolic KOH followed by acidification with acetic acid **(Scheme 15)**.



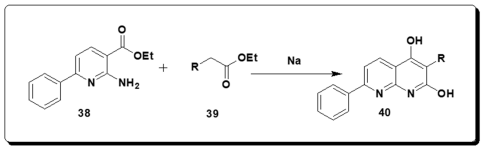
Scheme 14: Reaction of azaisatin and α-methylene carbonyl compound



Scheme 15: Pfitzinger synthesis of 2-aryl-1,8-napthyridine-4-carboxylic acid

2.11.Pictet-Spengler reaction

Akula and co-workers synthesized thieno/furo-[2,3-c][1,8]naphthyridine derivatives **(49)** through two-step reactions. The first step is a Suzuki-coupling reaction between 2-amino-3-bromopyridine **(46)** and furan-3-boronic acid or thiophene-3-boronic acid **(47a,b)** to afford 3-(furan-3-yl)pyridine-2-amine or 3-(thiophen-3-yl)pyridine-2-amine **(48a,b)**, respectively. The next step is a Pictet-Spengler reaction of **48a,b** with different substituted aldehydes to yield the desired compounds **(Scheme 16)** [57].



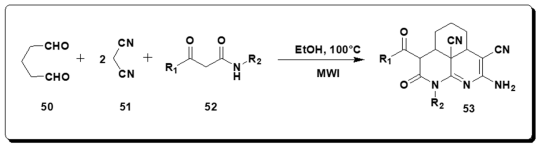
Scheme 16: Pictet-Spengler synthesis of 1,8-naphthridines

2.12. Green synthesis of 1,8-naphthyridines

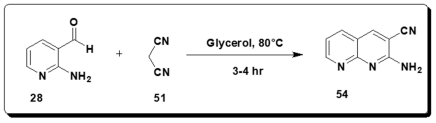
Feng *et al*.[58] reported a catalytic-free, one pot synthesis of 1,8-naphthyridine analogs **(53)** in high yields through the reaction of glutaraldehyde (50), malononitrile **(51)** and β-ketoamides **(52)** in ethanolic solution at 100°C using microwave irradiation for 20 min **(Scheme 17)**. This methodology characterized by simple handling, fast reaction, good yields, catalyst-free and mild reaction conditions.

Furthermore, Shivhare*et al*.[59] reported the synthesis of 2-amino-1,8-naphthyridine-3-carbonitrile **(54)** via knoevenagel condensation of 2-aminonicotinaldehyde **(28)** with malononitrile **(51)** under a catalyst-free condition **(Scheme 18)**. Upon testing of different solvents and temperatures, it was found that the best yield was obtained in an inexpensive and environmentally glycerol at 80°C.

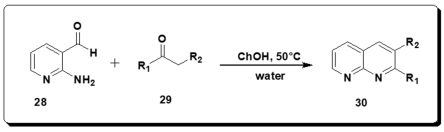
Choudhury *et al*. [60] recommended Friedlander reaction for 1,8-naphthyridines synthesis **(30)** in high yields. Aqueous solutions of 2-aminonicotinaldehydes **(28)** were condensed with α-methylene carbonyl compounds **(29)** in absence of metal, nontoxic and water-soluble choline hydroxide (ChOH) as a catalyst **(Scheme19)**.



Scheme 17: 1,8-naphthyridines formation using microwave irradiation



Scheme 18: Glycerol promoted Knoevenagel synthesis of 1,8-naphthyridine



Scheme 19: Friedlander 1,8-naphthyridines synthesis catalyzed by ionic liquid

3. 1,8-naphthyridines: anticancer agents

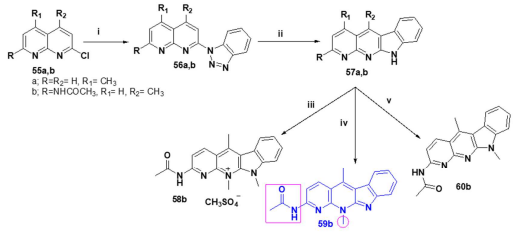
The 1,8-naphthyridine pharmacophore is essential for the creation of new, more effective anticancer medications, and its derivatives have demonstrated promising results through several modes of action, including DNA intercalating agents[61], topoisomerase I and II inhibitors [62,63], induction of apoptosis, cell cycle arrest [64], angiogenesis inhibitors [65], telomerase inhibitors [66], antimitotic agents and tubulin polymerization inhibitors [67], protein kinase inhibitors [68] and Rat sarcoma protein inhibitors (Ras)[69].

3.1. 1,8-naphthyridines as intercalating agents

In 2004,Mastalarza and colleagues published the synthetic method of 6H-Indolo[2,3-b][1,8]naphthyridineanalogs as described in **Scheme 20.**Their cytotoxic activities against a panel of cancer cells in comparison to ellipticine were tested.

The IG50, TGI, LC50 results revealed that compound**59b** was the most effective and exerts its cytotoxic effect through the formation of hydrogen bonds withDNA's guanosine base **Scheme 20** [61].

Margiotta*et al.*[70]synthesized 1,8-naphthyridine ligand complexed with platinum II **(64)**as depicted in **Scheme 21** and assessed its cytotoxic activity against various tumor cell lines, including cervical (A431), lung (A549), melanoma (A375), pancreas (BxPC3) and colon (DLD1, HCT-15, LoVo and LoVo-OXP) cell lines, taking cisplatin and oxaliplatin drugs as reference for the studyby MTT assay. In addition, measurement of cellular absorption and DNA platination levels in colon cancer cells compared with quinoplatin. Compound **64** was found to be more cytotoxic than cisplatin, but it was similar to oxaliplatin against cancerous cell lines and showed no-cross resistance against oxaliplatin-resistant colon cancer cells. Furthermore, this compound provides a pure monofunctional binding affinity to DNA by reacting with just one equivalent of 5'-GMP without removing ammonia or naphthyridine carrier ligands, but it differs in its interaction with GSH that is co-translocation with ammonia and naphthyridine ligands.



Reagents and conditions: i) benzotriazole, oil bath, 125°C; **ii)** diphenyl ether, 240°C, 4 h; **iii)** Me_2SO_4, 110°C; **iv)** MeI, K_2CO_3, DMF, 24 h; **v)** Me_2CO_3, K_2CO_3, 6 h.

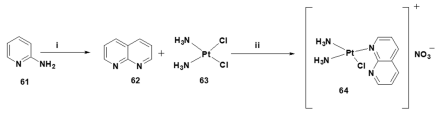
Key findings

a. Compound 59b is the most active one against tumor cell lines.

b. The presence of acetylamino group at position 3 is essential for cytotoxic activity

c. The presence of an additional methyl group at position 5 increases cytotoxic potential compared with unmethylated compound 57b.

Scheme 1:6H-Indolo[2,3-b][1,8]naphthyridinessynthesis



Reagents and conditions: i) glycerol, sodium 3-nitrobenzensulfonate, H_2SO_4, 130°C, 5 h; **ii)** AgNO3, DMF, 55°C, 16 h.

Structure features

a. The activity of compound 64 related to the presence of a hydrophobic naphthyridine moiety that increases cellular absorption and DNA-binding affinity

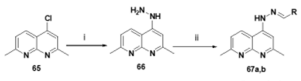
b. An extra nitrogen atom in the naphthyridine moiety can induce cytotoxic activity by better inhibition of RNA polymerase compared to quinoplatin.

Scheme 2: Synthesis of 1,8-naphthyridine ligand complexed with platinum II

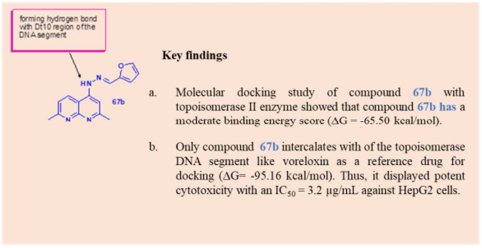
3.2.1,8-naphthyridines as topoisomerase I, II inhibitors

Topoisomerase enzymes (Topo) are responsible for conserving the integrity of genome by modification of topological DNA changes during replication and transcription processes, relaxation of positively or negatively supercoiled DNA and resolving tangles from twisted strands of DNA through the formation of reversible phosphotyrosine covalent bond between tyrosine residue in the catalytic site of topoisomerase and phosphate group in DNA (cleavable complex)[71]. The most important anticancer compound containing 1,8-naphthyridine moiety under clinical investigation for the treatment of acute myeloid leukemia is voreloxin (SNS-595) which exerts its cytotoxic effect by inhibiting topoisomerase II enzyme with intercalation of DNA [72,73].

Ewease*t al.*[63], in 2013, synthesized a novel 2,7-dimethyl-1,8-naphthyridine series incorporated into different Schiff's base derivatives and tested against liver cancer cell line (HepG2). Schiff's bases **(67a,b)** were synthesized according to (**Scheme 22**). The findings revealed that compound **67b** wasshown to be the most active candidate (IC_{50} = 3.2 µg/mL) compared to doxorubicin (IC_{50}= 3.56 µg/mL) and 5-Fluorouracil (IC_{50}= 5 µg/mL).



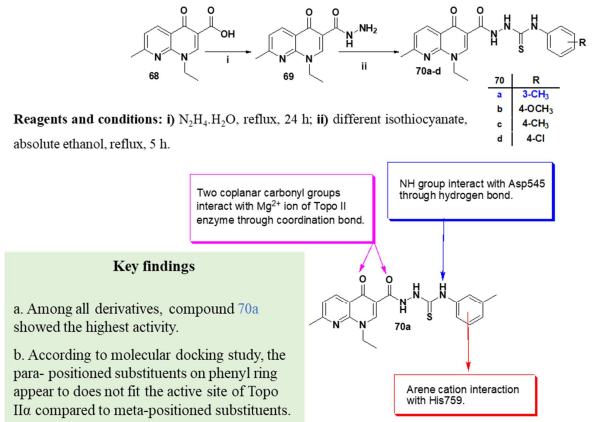
Reagents and conditions: i) $N_2H_4.H_2O$, ethanol, reflux; **ii)** aldehyde, dry ethanol, CH_3COOH, reflux.



Scheme 3: Synthesis of compounds 67a,b

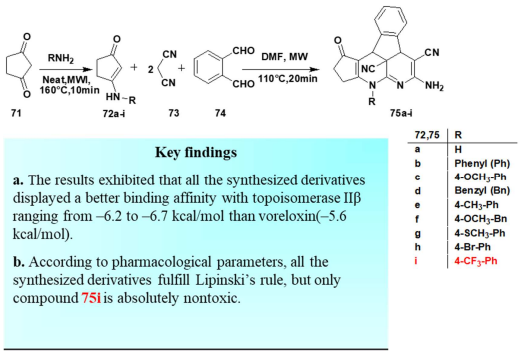
In 2019, novel 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide derivatives were prepared for testing their anticancer activity against several types of cancer cell lines [74]. Desired compounds**70a-d**were synthesized as described in **Scheme 23**. Compound **70a** was the most effective against leukemia cell lines compared to doxorubicin and staurosporine, it induced cell cycle arrest at the G2/M phase and apoptotic cell percentage increase compared to control. This compound was further evaluated for inhibition of topoisomerase IIα and IIβ. The results revealed that compound **70a** exhibited potent inhibitory activity for topoisomerase IIα compared to doxorubicin and for topoisomerase IIβ

compared with topotecan. The molecular docking study of compound 70a with Topo IIα is discussed in **Scheme 23**.



Scheme 4: Synthesis of compounds 70a-d

In 2021, Garg *et al.*[75]reported a green synthesis of cyclopenta[b]indeno[1, 2, 3-de] [1,8]naphthyridines (**75a-i**) by catalytic, solvent-free reaction of cyclopentane-1,3-dione with different amines at 160°C for 15 min to yield **72a-i** followed by one pot reaction between 72a-i, malononitrile and o-phthalaldehyde at 110°C under microwave irradiation (MW) for 20 min (**Scheme 24**). These compounds **75a-i** were predicted for in silico anticancer activity through molecular docking analysis against human topoisomerase IIβ compared with voreloxin as a standard anticancer agent, and in silico pharmacological parameters such as toxicity, ADME, and drug-likeness.



Scheme 5: Green synthesis of compounds (75a-i)

In 2021, Encinas and coworkers[62]reported methods of synthesis for novel chromeno and quinolino[4,3-b][1,8]naphthyridine derivatives (**83-88**) as shown in **Scheme 25**. The cytotoxicity of candidates was screened against human ovarian carcinoma (SKOV3), human lung adenocarcinoma (A549) and benign lung fibroblasts (MRC-5). All the synthesized compounds were nontoxic against MRC-5 contrary to camptothecin and compound **87a** was the most active one with IC_{50} 1.78 and 1.23 µM against SKOV3 and A549 cell lines, respectively compared with camptothecin (IC_{50} values of 5.5µM forSKOV3 and 1µM for A549). All compounds were further evaluated for inhibition of topoisomerase I. It was found that compounds **85a** and **88a,b** presented better inhibitory activity against topoisomerase I by acting as poisons compared with camptothecin. The molecular docking study showed better topoisomerase I binding affinity with compounds **85a** and **88a,b**.

3.3. 1,8-naphthyridines as apoptosis-inducing agents

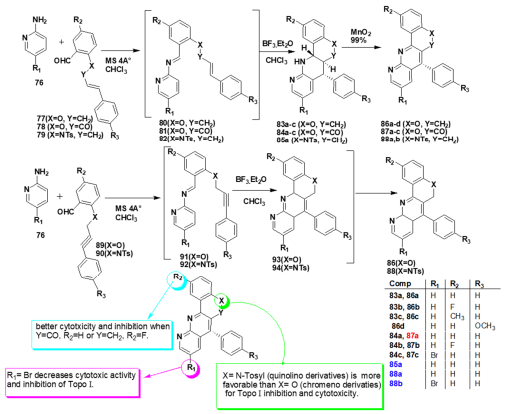
An important regulator of tissue homeostasis and the management of physiological growth is apoptosis. Extrinsic and intrinsic mechanisms both play a role in regulating the apoptotic process. The extrinsic mechanism is started by activating apoptotic receptors located on the plasma membrane of cells such as (Fas, TNF-1, and TRAIL), which is followed by the induction of initiator caspases and effector caspases. The intrinsic mitochondrial mechanism is modulated by the levels of Bcl-2 family proteins, which include anti-apoptotic proteins (Bcl-2 and Bcl-XL) and pro-apoptotic proteins [77].

In 2011, a new series of dihydrobenzofuro[4,5-b][1,8]naphthyridin-6-one derivatives (**98-106**) were obtained as mentioned in **Scheme 26** and their anticancer activity evaluated against prostate cancer cell lines (LNCaP, DU145 and PC-3) and breast cancer cell lines (MCF-7 and doxorubicin-resistant MCF-7/ADR) compared to doxorubicin. The results revealed that the diastereoisomeric compounds **105** and **106** were the most potent anticancer activity. Compound**106** has a cytotoxic activity similar to doxorubicin against all five cancerous cell lines, while compound **105** demonstrated better cytotoxicity and induced arrest of the cell cycle at the G2/M phase in the MCF-7/ADR cell line[78]. In 2012, Hwang *et al.*[64]further evaluated the efficacy of compounds **105** and **106** as cytotoxic agentsagainst human colon cancer cell line (HCT116) and elucidation the mechanisms underlying G2/M cell cycle arrest and apoptosis. Compound **105** was found to be more potent than 106 against HCT116. The cellular mechanism was mentioned in **Scheme 26**.

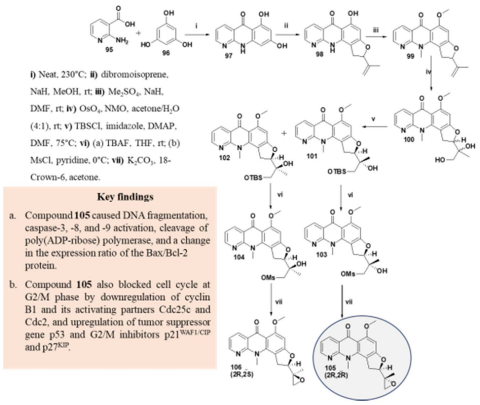
3.4. 1,8-naphthyridines as angiogenesis inhibitors

Angiogenesis is an important marker of tumorigenesis, which describes the formation of new blood vessels induced by several angiogenic factors such as transforming growth factors-alpha and beta (TGF-α and TGF-β), acidic and basic fibroblast growth factors (aFGF and bFGF), vascular endothelial growth factor (VEGF), epidermal growth factors (EGF) and tumor necrosis factor-alpha (TNF-α). These factors facilitated proliferation, migration of endothelial cells and tube formation[79].

In 2009, Banti*et al*.[65]synthesized a novel series of 2,3-dihydro-1,8-naphthyridine oxime ether derivatives (**109a-p**)through the reaction between oxime (**107)** and various amines to yield 7-N-substituted oxime (**108a-p**), followed by reaction with appropriate arylmethylhalogenide (**Scheme 27**). The cytotoxicity of compounds **109a-p** was evaluated against pancreatic cancer cells (MIAPaCa-2) according to their concentration and time of exposure for 72 h., compound **109i**was the most potent after 24 h. with IC_{50}=11 ± 0.5 µM and less toxic than 5-fluorouracil as reference. In addition, this compound exerts its cytotoxic effect by different mechanisms including the stimulation of caspase 3/7-related apoptosis and anti-angiogenic. The SAR study was illustrated in **Scheme 27**.



Scheme 6: Synthesis of chromeno and quinolino derivatives (83-88)



Scheme 7: Synthesis of derivatives (98-106)

3.5. 1,8-naphthyridines as telomerase inhibitors

Telomeres are nucleoprotein complexes that are composed of double-stranded DNA and 3′ single-stranded extends of G-rich TTAGGG sequences and shield the ends of eukaryotic chromosomes from damage[80]. Their gradual shortening throughout successive cell divisions causes senescence and cell death [81]. The length of telomeres is maintained by the telomerase enzyme. This enzyme activity is exhibited in approximately 90% of cancer cells, while it is low or absent in somatic cells so telomerase inhibition is a critical target for cancer treatment[82].

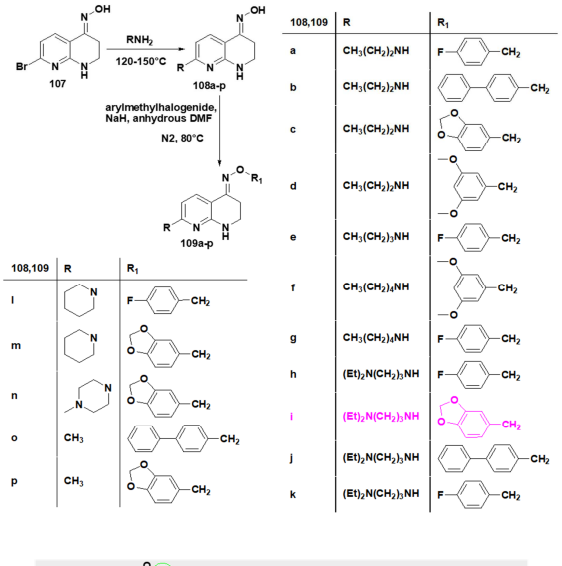
Nakatani *et al*.[66,83]reported the formation of 2-amino-7-methyl-1,8-naphthyridine in a dimeric form (**114)** as described in **Scheme 28** which acts as ananticancer agent due to its ability for binding to G-G mismatches in duplex DNA through three hydrogen bonds. According to the telomeric sequence's guanine abundance, the naphthyridine dimer could bind to the telomeric sequence and inhibits the telomerase enzyme from elongation the telomere.

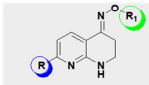
3.6. 1,8-naphthyridines as antimitotic agents

Mitosis is the fifth phase in the cell cycle process that is responsible for cell division[84]. Microtubules play an important role during the mitotic cycle through the formation of the mitotic spindle for the arrangement of replicated chromosomes along the cell equator and interceding the separation of an equal chromosome number to two daughter cells [85].

In 1997, Chen and coworkers synthesized 2′,3′,4′,5,6,7-substituted-2-phenyl-1,8-naphthyridine-4-one analogs (**122-153**) by two different methods. The first technique produces pyridopyrimidinones via condensation of 2-aminopyridines and ethyl benzoylacetates in the presence of polyphosphoric acid. The second method is a reaction of substituted 2-aminopyridines with different aldehydes to yield Schiff's bases which were cyclized with chloroacetyl chloride with trimethylamine to give pyridopyrimidinones. The formed pyridopyrimidinonesfrom two methods were converted thermally at a temperature of 350°C in paraffin oil to desirable compounds **122-153** (**Scheme 29).** Anticancer activity of compounds **122-153** against 60 human cancer cell lines and tubulin polymerization inhibitory activity were evaluated. The key findings of cytotoxic activity were described in **Scheme 29** [86].

In 2012, Capozzi*et al*.[87]assessed the anti-proliferative activity of the previously synthesized 4-phenyl-2,7-di(piperazin-1-yl)-1,8-naphthyridine (**156**) as a tuberculostatic activity through the reaction of 2,7-dichloro-4-phenyl-1,8-naphthyridine with *N*-carbethoxypiperazine in a sealed tube at 140°C, the formed product was treated with 10% aqueous sodium hydroxide (**Scheme 30**)[88]. Anticancer activity was evaluated against larynx carcinoma cells (Hep-2) compared to the reference drug paclitaxel. Effects of**156** on cell cycle, Topo II activity, apoptosis and microtubules were studied. The key findings were mentioned in **Scheme 30**.





Key findings and SAR

a. Compound 109i was found to be the most active one.

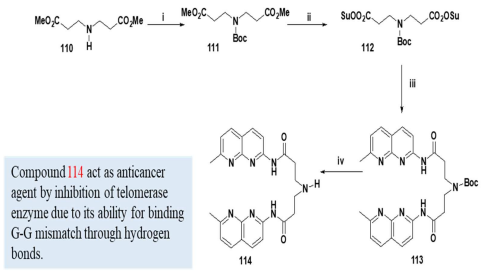
b. The cytotoxic activity is affected by substituents on phenyl ring that bound to methylenoxy-iminic linker at position 4.

c. Aminoalkyl chain at position 7 is more favored than methyl and cyclic amines.

d. Carbon atom number in the aminoalkyl group shows no significance on the biological activity.

e. diaminoalkyl chain improved anticancer activity.

Scheme 8: Synthesis of derivatives (109a-p)

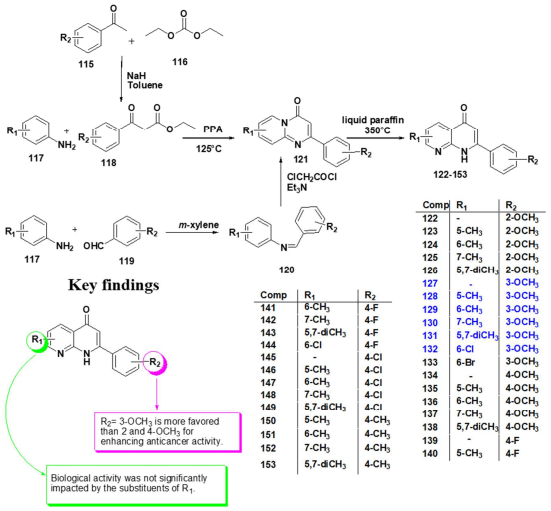


Reagents and conditions: i) Boc_2O, $CHCl_3$; **ii)** (a) aq NaOH, THF, (b) *N*-hydroxysuccinimide, EDCL, DMF; **iii)** 2-amino-7-methyl-1,8-naphthyridine, $CHCl_3$; **iv)** HCl, AcOEt, $CHCl_3$.

Scheme 28: Synthesis of dimeric form (114)

3.7. 1,8-naphthyridines as kinase inhibitors

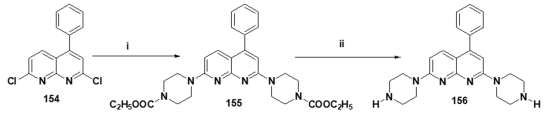
By transferring a phosphate group to the target protein, protein kinases are essential enzymes for controlling cellular processes such as metabolism, transcription, cell division, and apoptosis. Any disturbance of regulation may cause a diseased state. Overexpression of protein kinases accelerates the proliferation of cells, survivaland migration in various cancer types, so they are important targets for cancer therapy[89–91].



a. Compounds **127-132** demonstrated potent cytotoxic effects on leukemia (HL-60), non-small lung cancer cell line (NCI-H460), breast (MDA-N and MDA-MB-435), colon (HCT-116), prostate (PC-3),renal (786-0), ovarian (OVCAR-3), CNS (SF-295, U-251) and melanoma (SK-MEL-5) cell lines.

b. Compounds **127-132** showed strong tubulin polymerization inhibitory effect and less interaction at colchicine binding site of tubulin than natural antimitotic agents as podophyllotoxin and combretastatin A-4.

Scheme 29: Synthesis of compouds (122-153)



Reagents and conditions: i) N-Carbethoxypiperazine, 140°C; **ii)** 10% aqueous NaOH, ethanol.

Key findings of compound 156

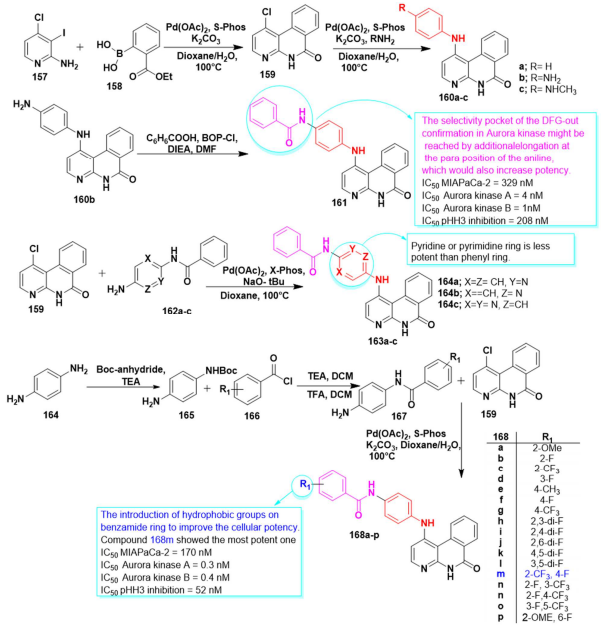
a. it showed a powerful anti-proliferative activity.
b. It induced apoptosis through mitochondrial hyperpolarization.
c. It inhibit of microtubules depolymerization.
d. It arrest the cell cycle at G2/M phase.
e. Did not affect Topo II activity.

Scheme 9: Synthesis of compound **156**

In 2013, Karra *et al.*[68]published the synthetic routes of 5*H*-benzo[c][1,8]naphthyridin-6-one derivatives (**159-161,163a-c,168a-p**) with various structural modifications at position 1 as shown in **Scheme 31**. Compounds were screened for their cytotoxicity against the MIAPaCa-2 cell line and their inhibitory activity against Aurora kinases. Compound **161** exhibited moderate anti-proliferative activity against MIAPaCa-2 (IC_{50}=329 nM) with good selectivity for Aurora kinases. Molecular docking of the compound **161** with Aurora kinase A showed interactions of carbonyl of benzamide with Lys162 and the terminal phenyl ring interacts with residues Leu208, Leu196 and Phe275 in the hydrophobic pocket that stimulates a DFG-out conformation in the kinase in addition three

hydrogen bonds between two nitrogen atoms of naphthyridine with Ala213 in the protein hinge region. The oxygen atom at position 6 with Gly216. Compound **161** was further optimized by the introduction of hydrophobic groups on the benzamide ring to improve cellular potency. Among all derivatives, compound **168m** displayed an increase in cytotoxic activity on MIAPaCa-2 with IC_{50}= 170 nM, strong inhibition of histone H3 phosphorylation, Aurora kinases A and B with IC_{50} = 52, 0.3 and 0.4nM, respectively.

In 2018, Duan *et al.*[92]formed a new series of 2-substituted-4-phenoxypyridine derivatives containing 1,8-naphthyridin-2-one fragment (**180- 206**) as shown in **Scheme 32** and tested for their cytotoxicity against: colon (HT-29), lung (A549, H460) and glioblastoma (U87MG) cell lines. Eleven compounds showed cytotoxicity higher than foretinib against one cancer cell line at least, but compound **200** was the most active candidate against all the cell lines under investigationand a good inhibitor for c-Met enzyme. This compound was further evaluated for its inhibitory activity against other eight tyrosine kinases. The results revealed that compound **200** has inhibitory effects on Flt-3 and VEGFR-3. The molecular docking of compound **200** with c-Met and Flt-3, and SAR studies are mentioned in **Scheme 32.**



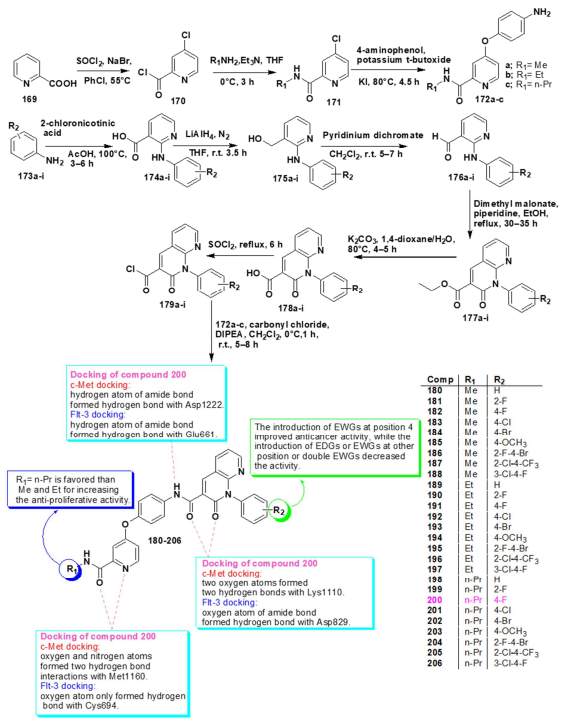
Scheme 10: Synthesis of derivatives (159-161,163a-c, 168a-p)

Tang and co-workers further synthesized a new series of 1,8-naphthyridin-2-one nucleus hybridized with 6,7-disubstituted-4-phenoxyquinoline derivatives (**216-247**) instead of 4-phenoxypyridine. The 1,8-naphthyridine-2-one scaffold was synthesized as illustrated in **Scheme 32**. While 4-phenoxyquioline was synthesized using 1-(4-hydroxy-3-methoxyphenyl)ethaone **(207)** as a starting material followed by eight successive steps as depicted in **Scheme 33**. The cytotoxicity of all synthesized compounds was evaluated against MCF-7, HepG2 and A549 cell lines and c-Met inhibitory activities. It was found that compound **225** exhibited more cytotoxic effects against three tumor cells than foretinib. This Compound **225** was further investigated for anti-proliferative activity mechanism, concentration dependence, and selectivity on c-Met against other tyrosine kinases on HepG2 cells. The key findings, SAR and molecular docking studies were described in **Scheme 33**[93].

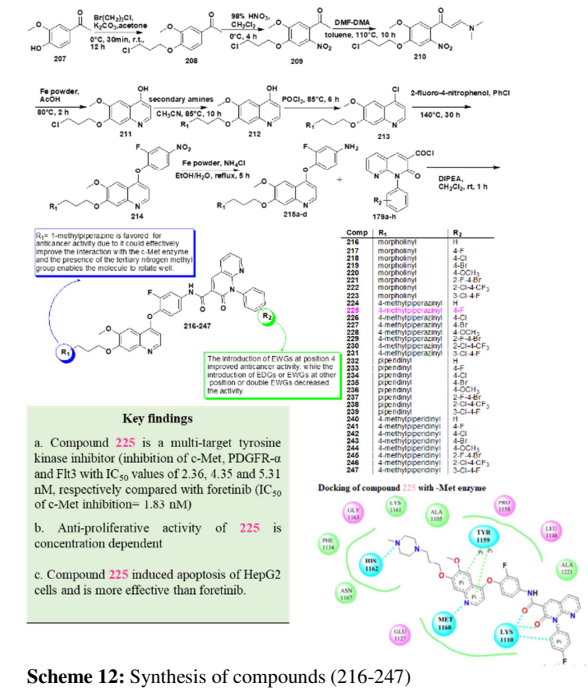
Tang and co-workers[94]demonstrated the synthesis of pyrrolo[2,3-b]pyridine analogs bearing the 1,8-naphthyridin-2-one fragment (**252-283)** (**Scheme 34**) and evaluation of *in vitro* cytotoxic activities against HT-29, A549, H460 and U87MG tumor cell lines and six tyrosine kinases inhibition activities (Flt-3, c-Kit, VEGFR-2, c-Met, EGFR and PDGFR-β). Synthesis of pyrrolo[2,3-b]pyridine fragment through a condensation reaction between 4-chloro-1*H*-pyrrolo[2,3-b]pyridine or 4-chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridine **(248a,b)** and 2-substituted-4-nitrophenol derivatives. The formed product was reduced using $FeCl_3$, hydrazine hydrate and activated carbon to yield **251a-d (Scheme 34)**. While 1,8-naphthyridinone nucleus was obtained as mentioned in previous **Scheme 32**. The results of IC_{50} values revealed that some compounds exhibited better cytotoxicity against one or more cell lines than foretinib, but only compound **261** is most potent against all four cell lines. Further evaluation for the selectivity of compound **261** on c-Met over other tyrosine kinases was tested. The key findings, SAR and molecular docking were mentioned in **Scheme 34**.

In 2021, Zhang *et al.*[95]reported the synthesis of 7*H*-pyrrolo[2,3-d]pyrimidines incorporated into 1,8-naphthyridinone moiety (**293-324**) as depicted in **Scheme 35.** The cytotoxicity for the previous compounds were tested against MCF-7, Hela and A549 cell lines compared with cabozantinib as a reference drug using MTT assay. Compared to cabozantinib, the majority of derivatives showed greater efficacy against one or more cancer cells and decreased cytotoxic action against normal human liver cells LO2. Especially, compound **299** has a great cytotoxic effect with IC_{50} values of 0.66, 0.38 and 0.44 μM comparable to cabozantinib 0.76, 0.32 and 0.45 against A549, Hela and MCF-7, respectively. Compound **299** was further screened for selective inhibition of c-Met enzyme over other tyrosine kinases (PDGFR-b, Flt-3, RON, KDR, c-Kit, ALK), and examine the morphological changes of A549 cells when treated with compound **299** using acridine orange assay and the relationship between concentration and anti-proliferative activity using MTT

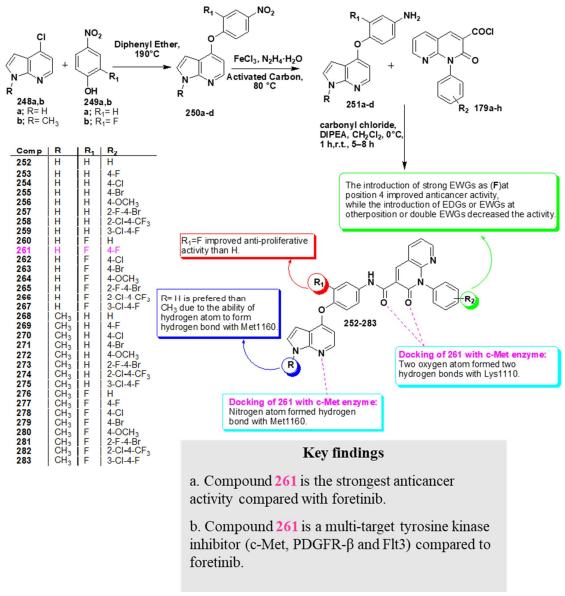
assay. The key findings and molecular docking of compound **299** were described in **Scheme 35**.



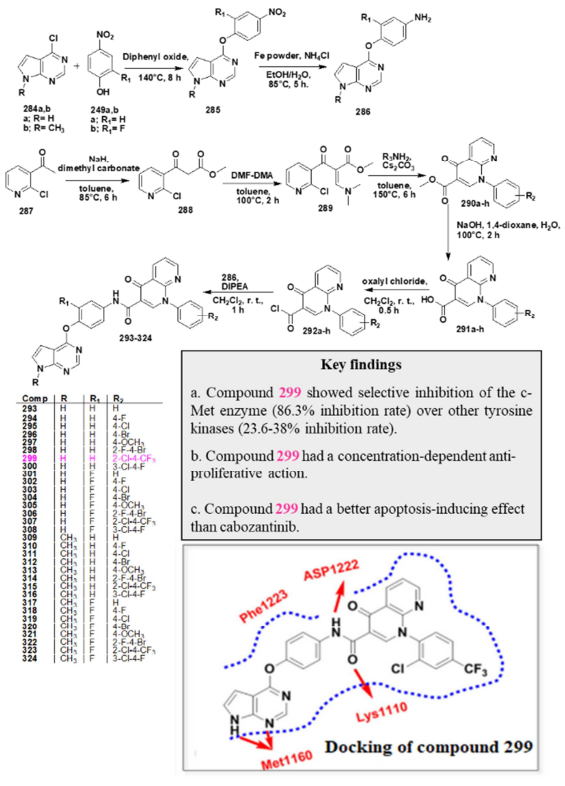
Scheme 11: Synthesis of Compounds (180- 206)



Scheme 12: Synthesis of compounds (216-247)



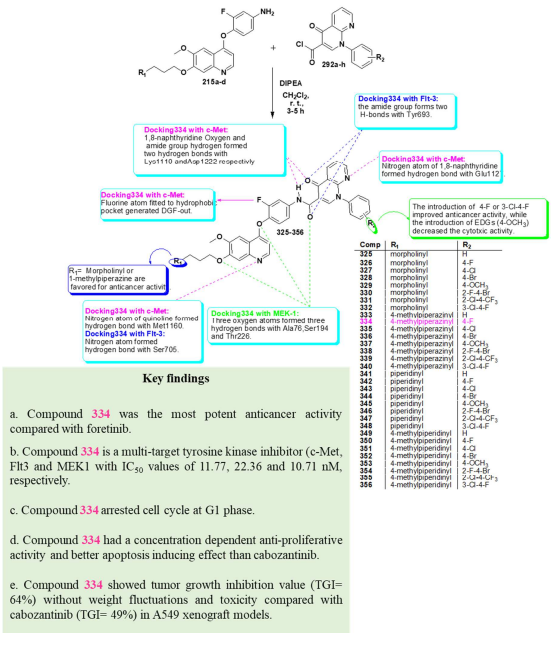
Scheme 13: Synthesis of derivatives (252-283)



Scheme 14: Synthesis of derivatives (293-324)

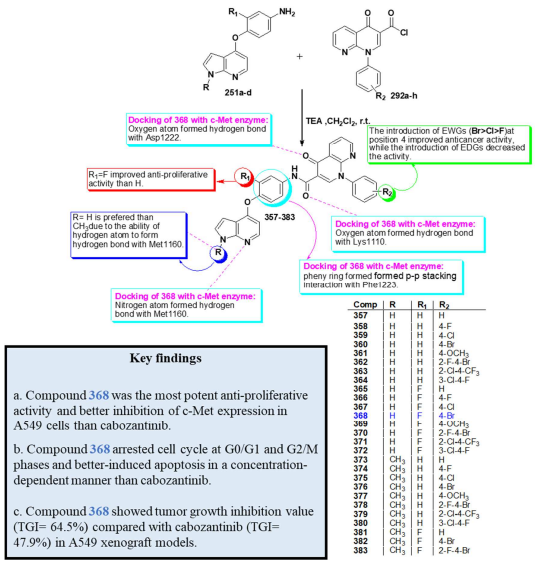
In 2022. Chen and co-workers synthesized a new series of 4-oxo-1,8-naphthyridine-3-carboxamide nucleus hybridized with 6,7-disubstituted-4-phenoxyquinoline derivatives (**325-356**) as mentioned in **Scheme 36**. The 4-oxo-1,8-naphthyridine-3-carboxamide scaffold (**292a-h**) was synthesized using 3-acetyl-2-chloropyridine (**287**) as a

starting material followed by five successive steps as illustrated in previous **Scheme 35**. Compound **287** was refluxed in tetrahydrofuran (THF) with dimethyl carbonate and in the presence of NaH for 5 h followed by the formed intermediate **288** was treated with DMF-DMA in toluene at 115°C for 3 h to give **289**. The methyl esters **(290a-h)** were produced by refluxing **289** with different anilines in toluene and N-methyl pyrrolidine (NMP) at 100°C for 2 h. Subsequently, hydrolysis of methyl esters (**290a-h)** by 10% aqueous NaOH and methanol for 4 h to generate the corresponding acids which were reacted with oxalyl chloride in THF at room temperature for 30 min yielding acyl chlorides (**292a-h**). While 4-phenoxyquioline (**215a-d**) was synthesized as depicted in previous **Scheme 33**. The cytotoxicity of all synthesized compounds was evaluated against three cancer cell lines: MCF-7, Hela and A549. It was found that ten compounds showed more cytotoxic activity than foretinib against one or more cell lines, but compound **334** exhibited a better cytotoxic effect against three tumor cells. This Compound **334** was further investigated for anti-proliferative mechanism and concentration dependence, selectivity on c-Met against other tyrosine kinases and *in vivo* antitumor activity using a xenograft mouse model on A549 cells. The key findings, SAR and molecular docking studies were described in **Scheme 36**[96].



Scheme 15: Synthesis of derivatives (325-356)

In 2022, Zhang and co-workers demonstrated the synthesis of pyrrolo[2,3-b]pyridine analogs bearing the 1,8-naphthyridin-4-one fragment **(357-383)** (**Scheme 37**) and evaluation of *in vitro* cytotoxic activities against three cell lines A549, Hela, and MCF-7. Synthesis of pyrrolo[2,3-b]pyridine fragment through a condensation reaction between 4-chloro-1*H*-pyrrolo[2,3-b]pyridine or 4-chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridine **(248a,b)** and 2-substituted-4-nitrophenol derivatives in chlorobenzene at 190°C for 30 h. The formed products **250a-d** were reduced using $FeCl_3$, hydrazine hydrate and activated carbon at 90°C for 4 h yielding **251a-d** as described in **Scheme 34**. While 1,8-naphthyridinone nucleus was synthesized by refluxing of **287** in chlorobenzene with dimethyl carbonate and a catalytic amount of NaH at 95°C, the formed intermediate **288** was treated with DMF-DMA in chlorobenzene at 115°C for 1 h to give **289**. The methyl esters **(290a-h)** were produced by refluxing **289** with different amines in NMP at 120°C for 5 h followed by cyclization using cesium carbonate and potassium carbonate in NMP at 160°C for 16 h. Subsequently, hydrolysis of **290a-h** by 10% aqueous NaOH generate the corresponding acids which were reacted with thionyl chloride at 85° for 30 min yielding **292a-h** as described in the previous **Scheme 35**. According to the results of IC_{50} values, Compound **368** is more potent than cabozantinib against MCF-7 and Hela cell lines. This Compound**368** was further evaluated for inhibition of c-Met expression using fluorescence quantitative PCR analysis, cell cycle arrest, apoptosis analysis and *in vivo* anticancer activity on A549 cells. The key findings, SAR and molecular docking were mentioned in **Scheme 37**[97].

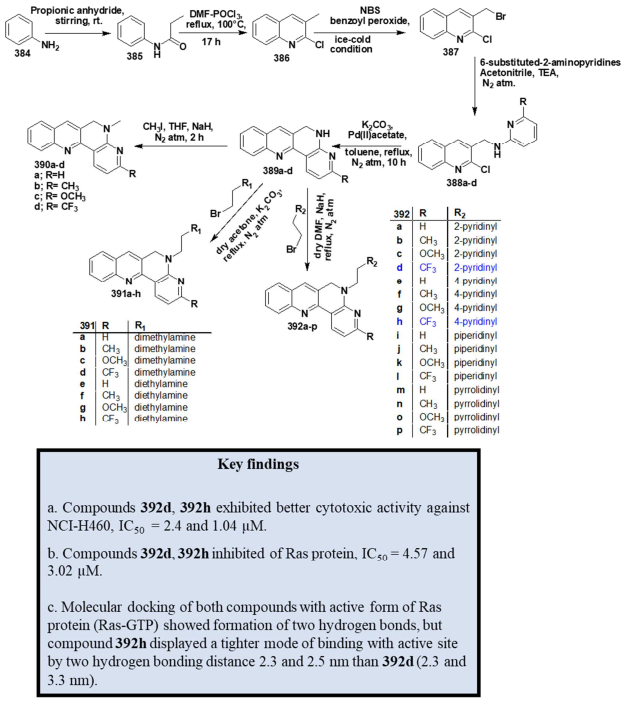


Scheme 16: Synthesis of derivatives 357-383

3.8.1,8-naphthyridines as Ras protein inhibitors

Ras protein is regarded as a key sign for cancer development since it is more abundant in 30% of cancer cells than in normal cells. Ras protein exists in the states ON and OFF. Guanosine triphosphate (GTP) binds to the active site of Ras protein and stimulates the downstream signaling cascade that causes cell proliferation in the ON state, whereas guanosine diphosphate (GDP) binds to the active site of Ras protein in the OFF state. Ras activation and its associated downstream pathways are controlled by the balance between two proteins GTPase activating protein (GAPs) which hydrolyze GTP to GDP and guanine nucleotide exchange factor (GEF) which is responsible for the conversion of GDP to GTP[98,99].

In 2021, Mahalingam *et al.*[69]synthesized quinolino-1,8-naphthyridine analogues (**389- 392)** and screened the anti-proliferative activity against three cancer cells: MCF-7, lung (NCI-H460) and CNS (SF-268) using MTT assay. The reaction of aniline with propionic anhydride at room temperature yielded an N-phenylpropionamide intermediate which was then treated with Vilsmeier Haack reagent to produce 2-chloro-3-methylquinoline **(386)**. Subsequently, compound **386** was subjected to a bromination reaction using N-bromosuccinimide (NBS) to give 3-(bromomethyl)-2-chloroquinoline **(387)**.The condensation reaction between **387** and different 6-substituted-2-aminopyridines followed by palladium-catalyzed cyclization of the formed intermediates under the basic condition to give **389a-d**. The N-substituted quinolino-1,8-naphthridine derivatives (**390-392)** were synthesized by a condensation reaction between **389a-d** and appropriate halo-alkyl amino derivatives under different conditions as described in **Scheme 38**. The results of cytotoxicity revealed that 16 compounds showed moderate to potent anticancer activity and were further evaluated for Ras-GTP inhibitory activity. The key findings were depicted in **Scheme 38**.



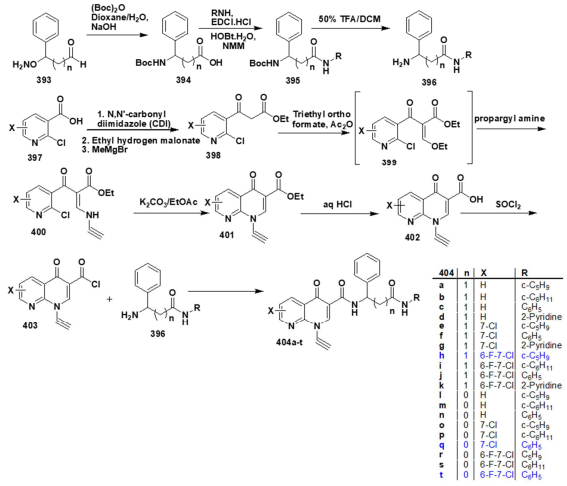
Key findings

a. Compounds **392d**, **392h** exhibited better cytotoxic activity against NCI-H460, IC_{50} = 2.4 and 1.04 µM.

b. Compounds **392d**, **392h** inhibited of Ras protein, IC_{50} = 4.57 and 3.02 µM.

c. Molecular docking of both compounds with active form of Ras protein (Ras-GTP) showed formation of two hydrogen bonds, but compound **392h** displayed a tighter mode of binding with active site by two hydrogen bonding distance 2.3 and 2.5 nm than **392d** (2.3 and 3.3 nm).

Scheme 17: Synthesis derivatives (389-392)



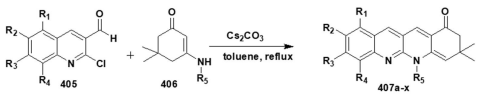
Scheme 18: Synthesis of 1,8-naphthyridine-3-carboxamide analogs (404a-t)

3.9.Miscellaneous

There are numerous documented 1,8-naphthyridine compounds with anticancer potential that are not target-based. These 1,8-naphthyridine derivatives are listed here under the miscellaneous category.

In 2009, Kumar synthesized novel 1,8-naphthyridine-3-carboxamide analogs (**404a-t**) as described in **Scheme 39** and tested against nine cancerous cell lines including colon (SW620), leukemia (K562), ovary (PA1), breast (HBL100), oral (KB), prostate (DU145), endothelial (ECV304), pancreas (MIAPaCa2) and lung (A549), and normal fibroblast cell lines (NIH3T3) for prediction of their cytotoxicity and safety index using MTT assay. Compounds **404h**, **404q** and **404t** have remarkable cytotoxic activity against more than one cell line compared with doxorubicin [100].

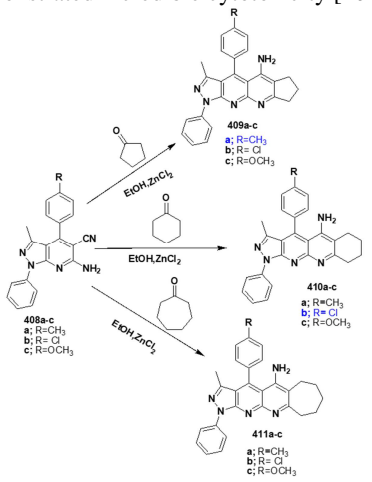
In 2015, Fu *et al.*[101]published a novel method to synthesize functionalized 1,8-naphthyridines (**407a-x**) through the reaction of different substituted 2-chloroquinoline-3-carbaldehyde **(405)** with enaminones **(406)** with a catalytic amount of Cs_2CO_3 as mentioned in (**Scheme 40**). The antiproliferative activity was assessed for all compounds against HepG2 cell lines. Some compounds that exhibited inhibitory rates exceeding 50% were further tested for determination of IC_{50} values. The results revealed that compounds (**407k-n)** were the most active among all series obtained.



407	R_1	R_2	R_3	R_4	R_5
a	H	H	H	H	phenyl (Ph)
b	H	H	H	H	4-NO_2-Ph
c	H	H	H	H	4-CH_3-Ph
d	H	H	H	H	2-Cl-Ph
e	H	H	H	H	naphthyl
f	H	tert-butyl	H	H	4-tert-butyl-Ph
g	H	tert-butyl	H	H	4-F,3-Cl-Ph
h	H	tert-butyl	H	H	4-NO_2-Ph
i	H	tert-butyl	H	H	4-Cl-Ph
j	H	tert-butyl	H	H	3,5-di-CH_3-Ph
k	H	tert-butyl	H	H	Ph
l	H	tert-butyl	H	H	4-CH_3-Ph
m	H	tert-butyl	H	H	4-OCH_3-Ph
n	H	tert-butyl	H	H	naphthyl
o	H	isopropyl	H	H	4-CH_3-Ph
p	H	isopropyl	H	H	Ph
q	H	isopropyl	H	H	4-NO_2-Ph
r	H	H	H	Ethyl	3,5-di-CH_3-Ph
s	H	CH_3	H	H	4-CH_3-Ph
t	CH_3	H	CH_3	H	4-CH_3-Ph
u	H	H	CH_3	CH_3	4-CH_3-Ph
v	H	H	CH_3	CH_3	4-Cl-Ph
w	H	OCH_3	H	H	4-CH_3-Ph
x	H	OCH_3	H	H	Ph

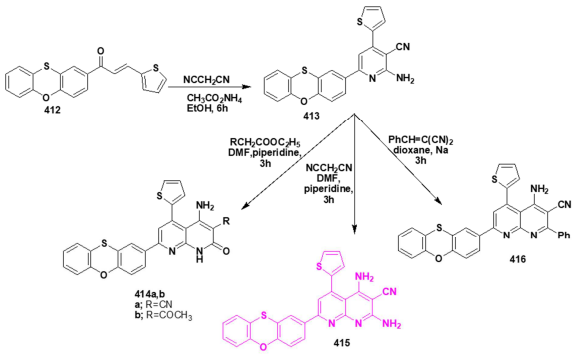
Scheme 19: Synthesis of derivatives (407a-x)

In 2015, Acosta and co-workers reported the synthesis of pyrazolo[3,4-g] [1,8]naphthyridin-5-amine analogs **(409-411a-c**) by the aid of microwave irradiation through the Friedlander reaction of o-aminonitrile **(408a-c)** with cyclic ketones in the presence of anhydrous zinc chloride as a catalyst (**Scheme 41**). This method is characterized by simple procedure and workup, high yields and fast reaction. The newly synthesized compounds **(409-411a-c**) were screened against 60 cancerous cell lines for prediction of their anticancer activity. Compounds **409a** and **410b** demonstrated incredible cytotoxicity [102].



Scheme 20: Synthesis of derivatives(409-411a-c)

In 2016, Behalo*et al*.[103]synthesized and studied the cytotoxicity of new derivatives of pyrido[2,3-d]pyrimidine and 1,8-naphthyridine using two cancerous cell lines: MCF-7 and PC-3. The 1,8-naphthyridine derivatives (**414a,b-416**) were synthesized by refluxing of 2-amino-6-(phenoxathiin-2-yl)-4-(thiophene-2-yl)nicotinonitrile**(413)** with ethyl cyanoacetate or ethyl acetoacetate in DMF and in the presence of a catalytic amount of piperidine to yield **414a,b**. Compound **413** was reacted with malononitrile in DMF and piperidine yielding compound **415** or with benzylidenemalononitrile in dioxane containing sodium metal giving compound **416**. The starting material **413** was synthesized by the reaction of *E*-1-(phenoxathiin-2-yl)-3-(thiophene-2-yl)prop-2-en-1-one **(412)** with malononitrile in the presence of ammonium acetate for 6 h (**Scheme 42**). Compound **415** was found to be the most effective one with IC_{50} values of 7.93µg/ml for MCF-7 and 8.13µg/ml for PC-3 compared with 5-fluorouracil as a reference drug with IC_{50} values of 4.73 and 4.91 µg/ml for MCF-7 and PC-3, respectively.

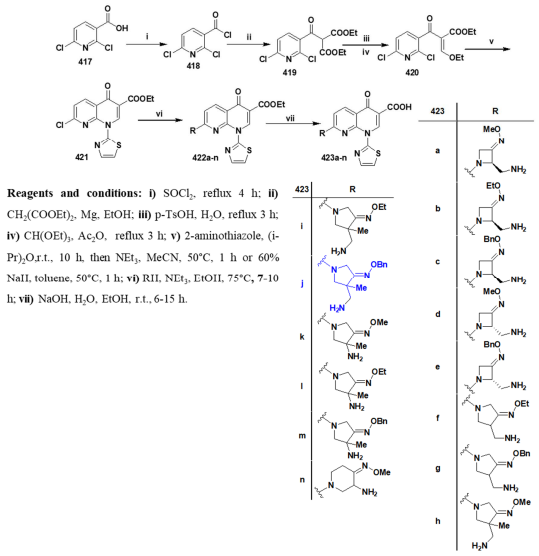


Scheme 21: Synthesis of Compounds (414a,b-416)

In 2016, A novel series of 4-oxo-1,8-naphthyridine-3-carboxylic acid bearing heterocyclic motifs at C-7 and N-1 positions were prepared and their cytotoxic activities were assessed against HL60 cell lines at concentration 30 µM using Sulforhodamine B assay. The results showed that the best heterocyclic ring substituent at the *N*-1 position of 1,8-naphthyridine is thiazol-2-yl followed by 1*H*-imidazol-2-yl and thiophen-3-yl. The synthesis of 1-(thiazol-2-yl)4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives (**423a-n**) was illustrated in **Scheme 43**. The IC_{50} values of 1-(thiazol-2-yl)naphthyridinone derivatives that had >70% inhibition were determined against various cancer cell lines namely A549, HepG2, HeLa, HCT116, HL60, MCF-7, MCF/DOX, prostatic (DU145), pancreatic (PANC-1) and SKOV-3 cell lines. Compound **423j** showed potent cytotoxicity against all tumor cell lines compared with etoposide [104].

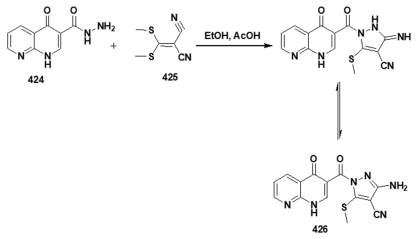
In 2017, Melha*et al*.[105]designed and synthesized a series of 3-heteroaryl carbonyl-1,8-naphthyridine analogs. These analogs were evaluated for their cytotoxic potential against Ehrlich Ascites Carcinoma cells (EAC). Compound **426** was the most active one with moderate cytotoxic activity (49% dead cells) compared with 5-fluorouracil (98%). Compound **426** was synthesized as mentioned in (**Scheme 44),** by using 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carbohydrazide as a starting material which was refluxed with dimethylthiomethylene malonate in dry

ethanol and a catalytic amount of glacial acetic acid.



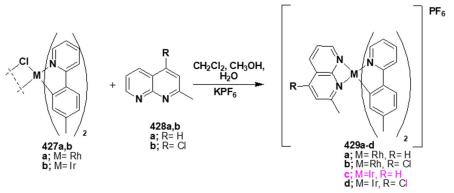
Reagents and conditions: i) $SOCl_2$, reflux 4 h; **ii)** $CH_2(COOEt)_2$, Mg, EtOH; **iii)** p-TsOH, H_2O, reflux 3 h; **iv)** $CH(OEt)_3$, Ac_2O, reflux 3 h; **v)** 2-aminothiazole, $(i\text{-}Pr)_2O$,r.t., 10 h, then NEt_3, MeCN, 50°C, 1 h or 60% NaH, toluene, 50°C, 1 h; **vi)** RH, NEt_3, EtOH, 75°C, 7-10 h; **vii)** NaOH, H_2O, EtOH, r.t., 6-15 h.

Scheme 22: Synthesis of derivatives (423a-n)



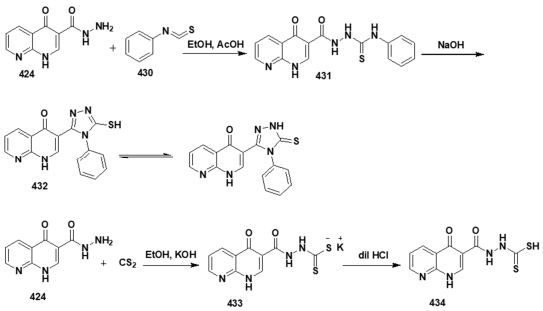
Scheme 23: Synthesis of compound426

Graf and co-workers published the synthesis of 1,8-naphthyridine derivatives complexed with iridium or rhodium metals (**429a-d**) by refluxing of cyclometalated 2-(p-tolyl)pyridinato ligands with 2-methyl-1,8-naphthyridine or 4-chloro-2-methyl-1,8-naphthridine in a mixture of DCM, methanol and water for 3 h (**Scheme 45**) and screening them against MCF-7 and colon (HT-29) cell lines for prediction of their anti-proliferative activity using the reference drug cisplatin. The results showed that compound **429c** had better cytotoxic activity than cisplatin against HT-29 and MCF-7, respectively[106].



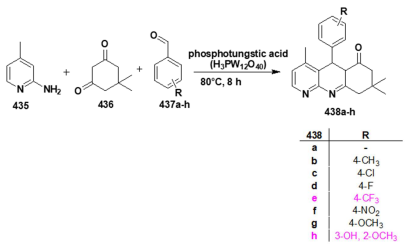
Scheme 24: Synthesis of derivatives (429a-d)

In 2018, El-Hadidy*et al.*[107]synthesized 1,8-naphthyridine carboxamide derivatives incorporated into triazole and oxadiazole scaffolds and assessed *in vitro* for their cytotoxicity against EAC cell lines. Compounds **432** (78% dead tumor cells) and **434** (79% dead tumor cells) were found to be the most potent using the effective dose at 50 µL (ED50)values compared with 5-fluorouracil (98% dead tumor cells). Both compounds were further evaluated *in vivo* for their survival time and hematological parameters against seven mice and compared with 5-fluorouracil. The results revealed that compounds **432**, **434** and 5-fluorouracil increased life span with minimal ascites and a slight increase in body weight contrary to the control group.1,8-naphthyridine-3-carbohydrazide (**424**) as a starting material was reacted with different reagents as phenyl isothiocyanate in dry ethanol containing a catalytic amount of glacial acetic acid followed by cyclization of the formed product by aqueous NaOH solution to produce compound **432** or react with carbon disulfide in ethanol and KOH followed by neutralization with dilHCl to yield compound **434** (**Scheme 46**).



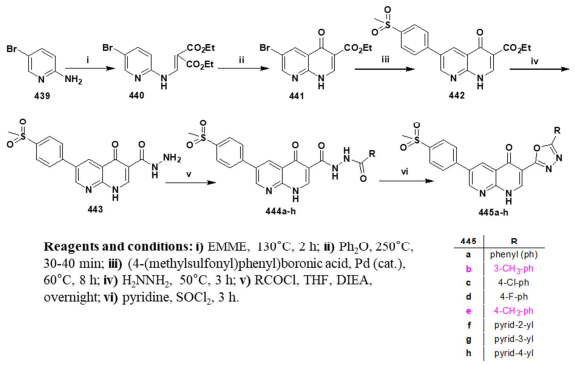
Scheme 25: Synthesis of derivatives (432, 434)

A novel series of 4,8,8-trimethyl-5-phenyl-5,5a,8,9-tetrahydrobenzo[b] [1,8]naphthyridin-6(7*H*)-one derivatives (**438a-h**) were prepared and their *in vitro* anticancer potential against A549 cell line were screened. The naphthyridine derivatives **438a-h**were synthesized through a one-pot three components reaction of 2-amino-4-picoline,hexadione and benzaldehyde derivatives (**Scheme 47**).Cytotoxicity results reported that both compounds **438e** and **438h** have better cytotoxic [108].



Scheme 26: Synthesis of compounds (438a-h)

In 2018, Derivatives of 3-(1,3,4-oxadiazol-2-yl)-1,8-naphthyridin-4(1*H*)-one were synthesized and evaluated for cisplatin sensitization and their cytotoxic activity against six cancerous cell lines including A549, MCF-7, HepG2, HCT116, Hela and oral epidermoid carcinoma (KB) cells using MTT assay. The results showed that all compounds have low cytotoxic activity, but only compounds **445b** and **445e** were good cisplatin sensitizing agents by inhibition of DDR response and decrease in CHK1 expression that induced by cisplatin treatment using Western blot analysis and also induced apoptosis of HCT116 cancerous cells in combination with cisplatin by Hoechst staining and annexin V-FITC/PI dual-labeling assay. Compounds **445b** and **445**e were synthesized through a condensation reaction between 5-bromo-2-amino-pyridine and EMME at 130°C. The formed intermediate was heated in Ph_2O at 250°C to afford 4-oxo-1,8-naphthyridine which was reacted with 4-(methylsulfonyl)phenylboronic acid and dichloro-bis(triphenylphosphine)palladium(II)via Suzuki coupling reaction to give compound **374**. Treating of compound **374** with hydrazine hydrate in methanol followed by the hydrazide product was reacted with different aroyl chloride derivatives to yield **376a-h** which were cyclized to the 1,3,4-oxadiazole ring by using pyridine and $SOCl_2$ (**Scheme 48**) [109].

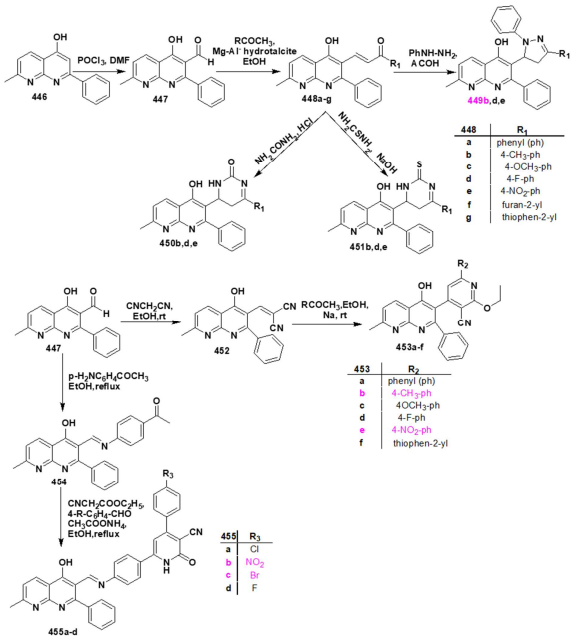


Reagents and conditions: i) EMME, 130°C, 2 h; **ii)** Ph_2O, 250°C, 30-40 min; **iii)** (4-(methylsulfonyl)phenyl)boronic acid, Pd (cat.), 60°C, 8 h; **iv)** H_2NNH_2, 50°C, 3 h; **v)** RCOCl, THF, DIEA, overnight; **vi)** pyridine, $SOCl_2$, 3 h.

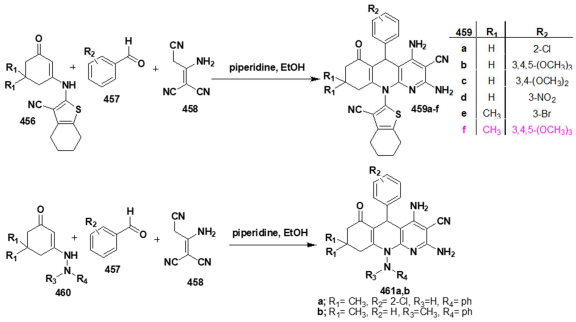
Scheme 27: Synthesis of compounds (445a-h)

In 2019, Al-Romaizan *et al.*[110] synthesized anovel series of 4-hydroxy-7-methyl-2-phenyl-1,8-naphthyridine conjugated with substituted heterocyclic scaffolds (**449-451b,d,e, 453a-f and 455a-d**) as depicted in **Scheme 49** and screenedfor their anti-proliferative activity against MCF-7 cell lines.Results revealed that derivatives**449b**, **453b**, **453e**, **455b** and **455c** were more potent cytotoxic activity with IC_{50}values of 1.68, 1.47, 2.30, 3.19, 1.62 µM, respectively against MCF-7 thanstaurosporine (IC_{50}= 4.51 µM).

In 2020, Bardasov*et al.*[111]synthesized *N*-substituted 2,4-diamino-5-aryl-5,6,7,8,9,10 hexahydrobenzo[b][1,8]napththyridine-3-carbonitriles(**459a-f and 461a,b**) through a reaction of 1-substituted amino-3-oxocyclohex-1-ene derivatives with different aldehydes and 2-aminoprop-1-ene-1,1,3-tricarbonitrile in dry ethanol containing piperidine (**Scheme 50**). The cytotoxicity was evaluated against 59 cancerous cell lines using NCI-60 one-dose screen method. It was found that compound **459f**was the most active one, particularly against leukemia cells (61% growth inhibition) compared with cisplatin, busulfan and hydroxycarbamide as reference drugs**.**



Scheme 28: Synthesis of compounds (449-451b,d,e, 453a-f and 455a-d)



Scheme 29: Synthesis of compounds (459a-f and 461a,b)

4. Conclusion

Cancer is a complicated multifactorial disease with uncontrollable treatment due to medication resistance, high toxicity, and other long-term side effects Thus, the quest for novel, potent anticancer medications is never-

ending. Numerous heterocycles have emerged playing important roles in a range of human-beneficial medicines. From a variety of heterocycles, the 1,8-naphthyridine scaffold exhibited multiple biological activities for the treatment of cancer, bacterial and viral infections, hypertension, osteoporosis, Alzheimer, multiple sclerosis, inflammation, allergy and convulsion. In this review, we have assembled the traditional and recent synthetic methods of 1,8-naphthyridine pharmacophore and focused on the brief discussion of the anticancer potential of 1,8-naphthyridine analogues on a target-oriented basis such as apoptosis-inducing agents, cell cycle arrest, topoisomerase I and II inhibitors, tubulin polymerization inhibitors, protein kinase inhibitors, intercalation with DNA, angiogenesis inhibitors, Ras protein inhibitors and telomerase inhibitors with proper synthetic methods, SAR studies and molecular docking of these analogues.

5. Conflicts of interest

The authors declare no conflict of interest.

6. References

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