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Review Paper

A Review on Synthesis of Quinoline Analogs as Antimalarial, Antibacterial and Anticancer agents

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Abstract

Numerous natural products possessing quinoline moiety exhibit interesting biological and pharmacological properties including antimalarial, antibacterial, antiasthmatic, antihypertensive, antiinflammatory, immunosuppressive, antileishmanial, and anticancer activities. Quinoline scaffold has been used to synthesize antimalarial drugs namely, quinine, chloroquine, amodiaquine, mefloquine, first to fourth generation antibacterial fluoroquinolones and anticancer drugs such as vosaroxin. This article provides update on the latest development in synthesis and biological evaluation of antimalarial, antibacterial and anticancer quinoline analogs. The new synthetic methodologies and the biological activities of the new quinoline analogs in the three areas were focused.

1. Introduction

Several natural products possessing quinoline moiety exhibit interesting biological and pharmacological properties, such as antimalarial, antibacterial, antiasthmatic, antihypertensive, anti-inflammatory, immunosuppressive, antileishmanial, and anticancer (Heinink 2010; Krishnakumar et al., 2012). Quinoline, quinazoline and isoquinoline are structurally simple classes of alkaloid compounds (Figure 1) (Diaz and Miranda, 2015; Shang et al., 2018). Synthetic organic chemists have developed various synthetic routes for these alkaloids and their derivatives, and their biological activities have been improved significantly (Diaz and Miranda, 2015; Shang et al., 2018). Quinine and camptothecin are two of the most famous and important quinoline alkaloids, and their discoveries opened new areas in antimalarial and anticancer drug development (Figure 1) (Shang et al., 2018).

The discovery of quinine is considered the most serendipitous medical discovery of the 17th century and malaria treatment with quinine marked the first successful use of a chemical compound to treat an infectious disease (Achan et al., 2011). Quinine which was a component of the bark of the cinchona tree, was used to treat malaria from as early as the 1600s, when it was referred to as the "Jesuits' bark," "cardinal's bark," or "sacred bark" (Achan et al., 2011). In 1820, quinine was isolated as the active ingredient and replaced the crude bark the treatment (Wiesner et al., 2003). Although quinine has relatively low efficacy and tolerability, it played a historical role in the development of quinoline alkaloids, and still plays an important role

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in the treatment of multi-resistant malaria (Wiesner et al., 2003).

Camptothecin analogs such as irinotecan and topotecan and indeno[1,2-c]isoquinolin-5,11-diones are among DNA-targeted anticancer agents contain a planar intercalating polycycle bearing one aminoalkyl side chain. Irinotecan, topotecan and antino[1,2-c]isoquinolin-5,11-diones derivatives represent a large number of antiproliferative agents exhibiting cytotoxicity through DNA intercalation, causing interference in the replication process (Ryckebusch et al., 2008). Camptothecin (a pentacyclic pyrrolo (3,4-*β*) quinoline moiety) and its derivatives (Figure 1) exert their antitumor activity by binding to topoisomerase I and have shown significant activity against a broad range of tumors including ovarian cancer, cervical cancer and human leukemia cell lines, HL60 and HL60/MX (Ulukan and Swaan, 2002).

The investigation of antibacterial activity of quinoline analogs begun in the early 1960s, from the observation of the narrow antibacterial activity of nalidixic acid, which was synthesized at the Sterling-Vinthrop Research Institute in 1958 (Figure 1) (Carroll, 1963). The quinolones are a family of 4-quinolone antibiotics containing a bicyclic quinoline core. Since their discovery in the early 1960s, they have gained increasing importance as key therapies to treat both community-acquired and severe hospital-acquired infections (Bisacchi, 2015; Blaskovich, 2019).

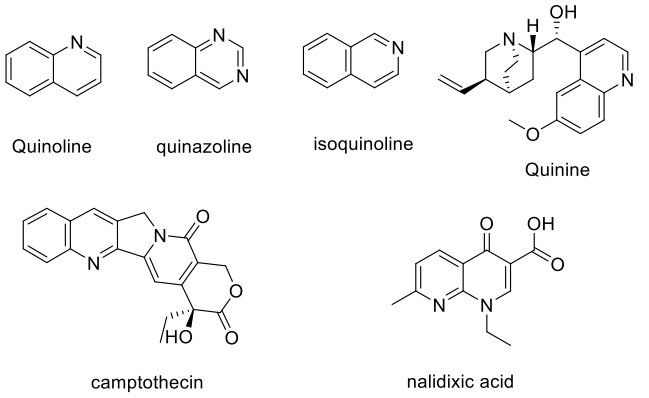


Figure 1: Quinoline Scaffolds and their nature bioactive analogs

It is our surprise to see when three various types of commercial drugs were being developed based on quinoline scaffold. To our knowledge, it is not common to come across a single scaffold which has been used to develop antimalarial, antibacterial and anticancer commercial drugs. In addition to the above three, several other biological properties of quinolones such antiasthmatic, antihypertensive, anti-inflammatory, immunosuppressive, and antileishmanial are currently being investigated. At the same time malarial species and bacterial strains have developed resistance against some of the quinoline drugs. Thus, it is important to revise all the unto date strategies on synthesis and biological evaluation of quinolones not only for understanding, and applying the existing knowledge but also to develop new synthetic strategies and evaluation techniques to develop additional effective various new quinoline drugs. Therefore, this review paper revises the latest development in antimalarial, antibacterial and anticancer synthesis and biological evaluation of quinoline analogs.

2. Antimalarial quinoline analogs

Malaria is a mosquito borne disease which is caused by five protozoa species (Snow, 2015). According to the latest estimates (Lozano et al., 2012), about half of the world's population are in danger of contracting malaria (Ding and Hall, 2013; Lozano et al., 2012). In Africa, malaria is most prevalent in the highlands of the eastern and southern parts of the continent. In the tropics, the upper limits of malaria transmission sometimes may rise to an altitude of approximately 2,500 meters with anomalous weather conditions (Kiszewski and Teklehaimanot, 2004). Globally, each year, 300–500 million people suffer from acute malaria, and 0.5–2.5 million die from the disease (Report, 2020; Wiesner et al., 2003).

The first attempts at a specific treatment of malaria date back to the early 18th century and made use of the bark of Cinchona trees (Wiesner et al. 2003). In 1891, based on the observation that methylene blue (Figure 2) was selectively taken up by the parasites in microscopic specimens, Paul Ehrlich cured two malaria patients with the dye. This was the first time that a synthetic drug was ever used in humans (Calderón et al. 2017; Wiesner et al. 2003).

Since then, quinine, chloroquine, amodiaquine, mefloquine, and artemisinin derivatives were used to treat malaria for years (Uzor 2020). Quinoline antimalarial can be classified into three categories as: 4-aminoquinolines, quinoline-methanols, and 8-aminoquinolines (Heinink 2010).

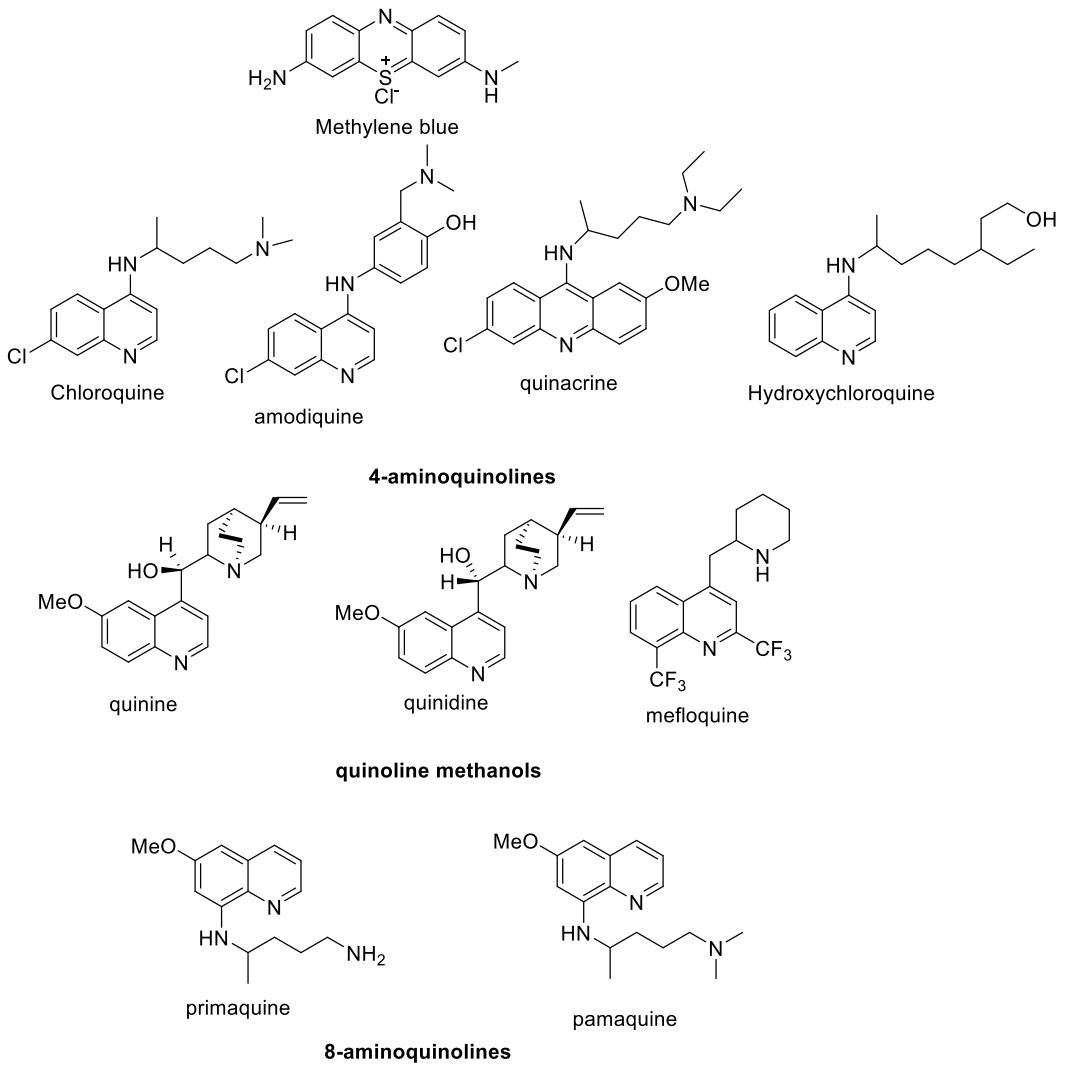


Figure 2: The structure of antimalarial quinoline analog

2.1. Quinoline-methanols Analogs

Quinine, quinidine and mefloquine are the typical examples of quinoline-methanols antimalarial drugs (Jiang et al., 2019). Even today, after 350 years, modern medicine still rely on quinine, as a life-saving medicament in severe cases of falciparum malaria (Islahudin et al., 2014). However, the future use of quinine is challenged by its poor tolerability, poor compliance with complex dosing regimens, and the availability of more efficacious anti-malarial drugs (Achan et al., 2011). On an equimolar basis, quinidine (the dextrorotatory diastereoisomer of quinine) is a more active antimalarial than quinine for *P. falciparum* (White et al., 1981). Mefloquine was developed by the United States Army in the 1970s and came into use in the mid-1980s (Lariam et al., 2007). It is a long-acting antimalarial drug known for its efficacy against chloroquine- and SP-resistant Plasmodium falciparum (Maayan et al., 2017). It is effective as prophylaxis against all five strains of malaria known to affect humans (Maayan et al., 2017; Oliveira et al., 2011).

Mode of action of 4-aminoquinoline classes of compounds is still controversial. Various theories have been proposed and reviewed. The consensus points out that CQ interacts with the parasite's ability to digest haemoglobin. During its erythrocytic stages, the parasite consumes large quantities of haemoglobin from its host cell, either for the purpose of amino acid supply, or simply to create space inside the erythrocyte(Deshpande and Kuppast, 2016). Synthesizing new safe and effective antimalarial quinoline analogs has been considered as one means to overcome the existing drawback of quinoline antimalarial drugs.

2.1.1. The structural activity relationship of antimalarial quinoline analogs

4-Aminoquinolines derivatives were the first class of compounds used for the successful treatment of malaria and drugs of choice for the present time also (Deshpande and Kuppast, 2016). Chloroquine is a 4-aminoquinoline antimalarial that contains a 7-chloroquinoline substituted ring system with a flexible pentadiamino side chain (Bray et al., 2006). The structural activity relationship study showed that 4-aminoquinoline nucleus, electron withdrawing functional groups at the 7-position of the quinoline ring, short carbon chain length (2-3 carbon atoms) or long carbon chain lengthening (10-12 carbon atoms) are the main structural features (Bray et al., 2006; Cabal et al., 2011; Deshpande and Kuppast, 2016).

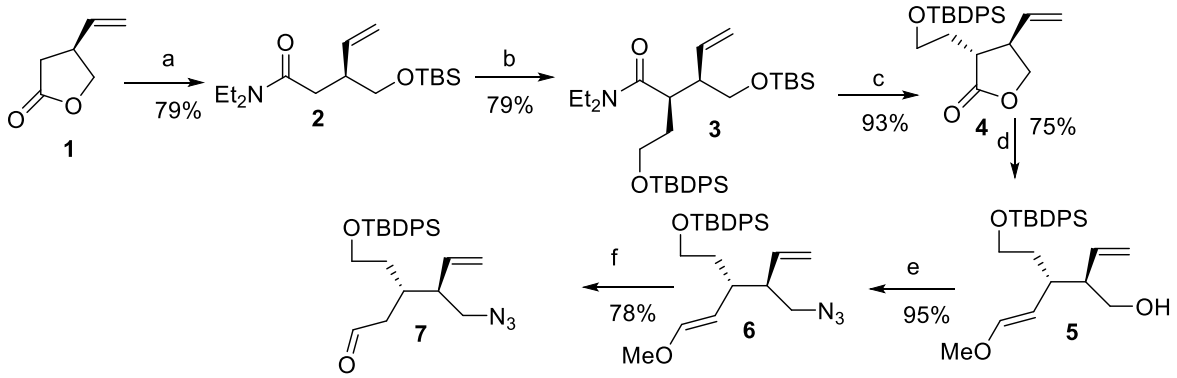
2.1.2. Synthesis of quinine

For the first time, Woodward synthesized quinine in 1944 (Woodward, 1945). The remaining steps relies on Rabe's conversion of d-quinotoxine to quinine (Biomol et al., 2012). Stork et al. (2001) accomplished the first stereoselective total synthesis of quinine (Stork et al., 2001). This synthesis was achieved using starting chiral (S)-4-vinylbutyrolactone (1) and by oxidation of deoxyquinine with oxygen in tert-butyl alcohol-DMSO, in the presence of potassium tert-butoxide, proceeded selectively, according to the Hoffmann-La Roche group hypothesis (Stork et al., 2001). In process a chiral intermediate 7 was synthesized from (S)-4-vinylbutyrolactone in seven steps (Scheme 1). Then the construction of the required piperidine was achieved with the addition of the lithium salt of 6-methoxy-4-methylquinoline (8) to the carbonyl group of 7 to produce the expected secondary alcohol 15 in ~70% yield (Scheme 2) (Stork et al., 2001).

The final conversion started with removal of the silyl protecting group with aqueous hydrogen fluoride in acetonitrile to form **13**. Then the quinuclidine ring was closed by converting the primary hydroxyl into a suitable departing group (Scheme 3). The treatment of **13** with mesyl chloride in methylene chloride, in the presence of pyridine, followed by refluxing of the crude product in acetonitrile, afforded, after liberation from the methanesulfonate salt, deoxyquinine (**15**) in ~70% yield after Flash chromatography (Stork et al., 2001).

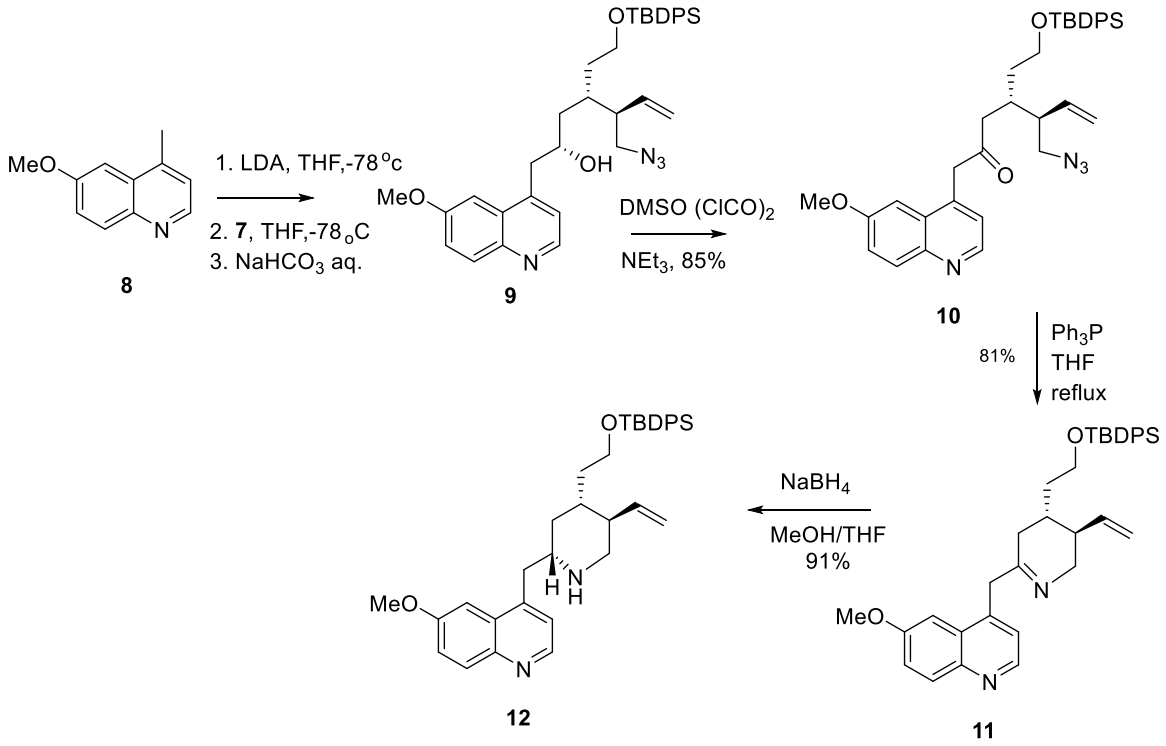
In the final step, higher stereoselectivity (quinine:epiquinine ~14:1) was obtained when the oxidation was effected in the presence of sodium hydride in anhydrous DMSO affording synthetic quinine 78% yield (Stork et al., 2001).

The latest total asymmetric synthesis of qunine and quinidine were reported by Jiang et al. (2019) via catalytic enantioselective cascade transformations (Jiang et al., 2019). Asymmetric multicomponent reactions involve the preparation of chiral compounds by the reaction of three or more reagents added simultaneously. They are powerful and economic techniques for the synthesis of chiral synthons and natural products (Jiang et al., 2019; Ramón and Yus, 2005).

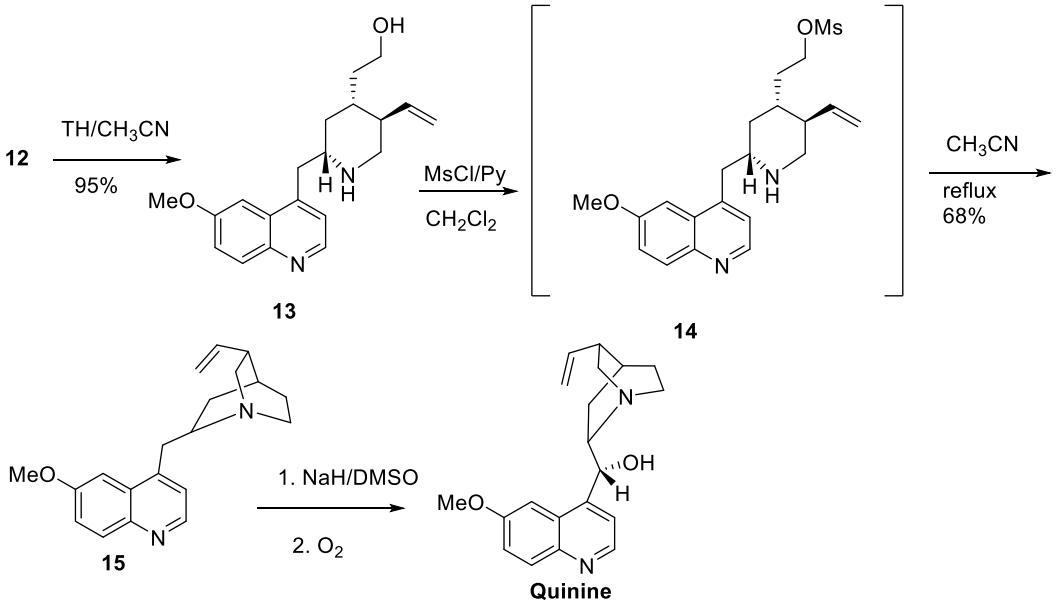


Conditions: (a) (1) $Et_2NH/AlMe_3$, (2) TBS-Cl/lmidazole/DMF. (b) LDA, -78 °C, $ICH_2CH_2OTBDPS$. (c) PPTS (0.3 equiv), EtOH, 12 h, then xylenes, reflux 8-10 h. (d) (1) DIBAL-H, -78 °C, (2) $Ph_3PdCHOMe$. (e) $PH_3P/DEAD$, $(PhO)_2P(O)N_3$. (f) 5 N HCl, THF/CH_2Cl_2.

Scheme 1. Synthesis of intermediate 7



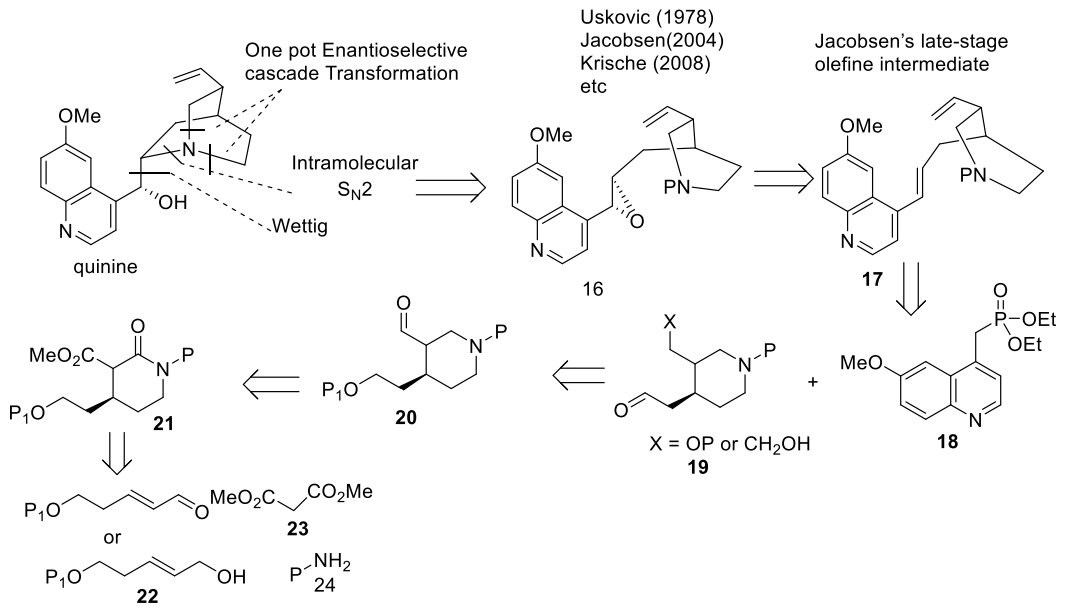
Scheme 2.Synthesis of trisubstituted piperidine



Scheme 3. Synthesis of Quinine

Jiang et al. (2019) synthesized quinine and quinidine by using the enantioselctive-Michael/iminium/reductive amination/cyclization cascade sequence with chiral amines as catalysts (**23**) (Jiang et al., 2019). First, the retrosynthetic analysis was done by considering the various synthetic methodologies such as Uskovic (Uskokovik et al., 1978), Jacobsen (Raheem et al., 2004), Krische (Webber and Krische, 2008), etc. (Scheme 4).

In order to achieve the desired configuration of lactam **21a**, the appropriate chiral amine was employed. The researcher used three different types of chiral amines (Figure 3) for catalyzing the synthesis of the desired lactams.



Scheme 4. Retrosynthetic analysis to quinine. P = protective group

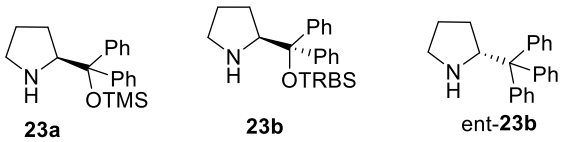
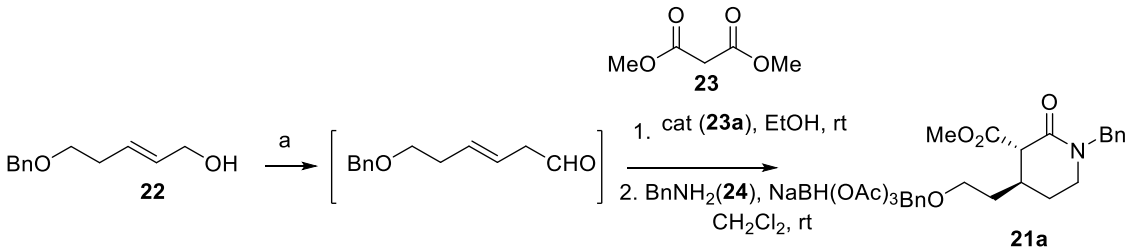


Figure 3: Chiral amine catalysts

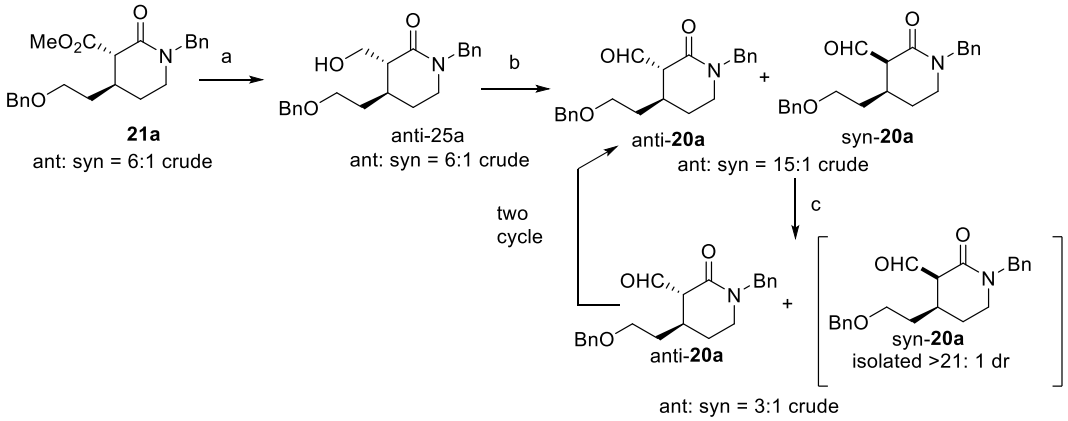


Scheme 5.One-pot catalytic enantioselective synthesis of **21**a.

(a) i. 5 mol% Pd(0)-AmP-MCF, O_2, toluene, 70°C 3.5h, ii. 3 eq, dimethyl malonate, 10 mol% 23a, EtOH, rt, 24h; iii. 3 eq. benzylamine, $MgSO_4$, 3 eq. $NaBH(OAc)_3$, CH_2Cl_2, 16h.

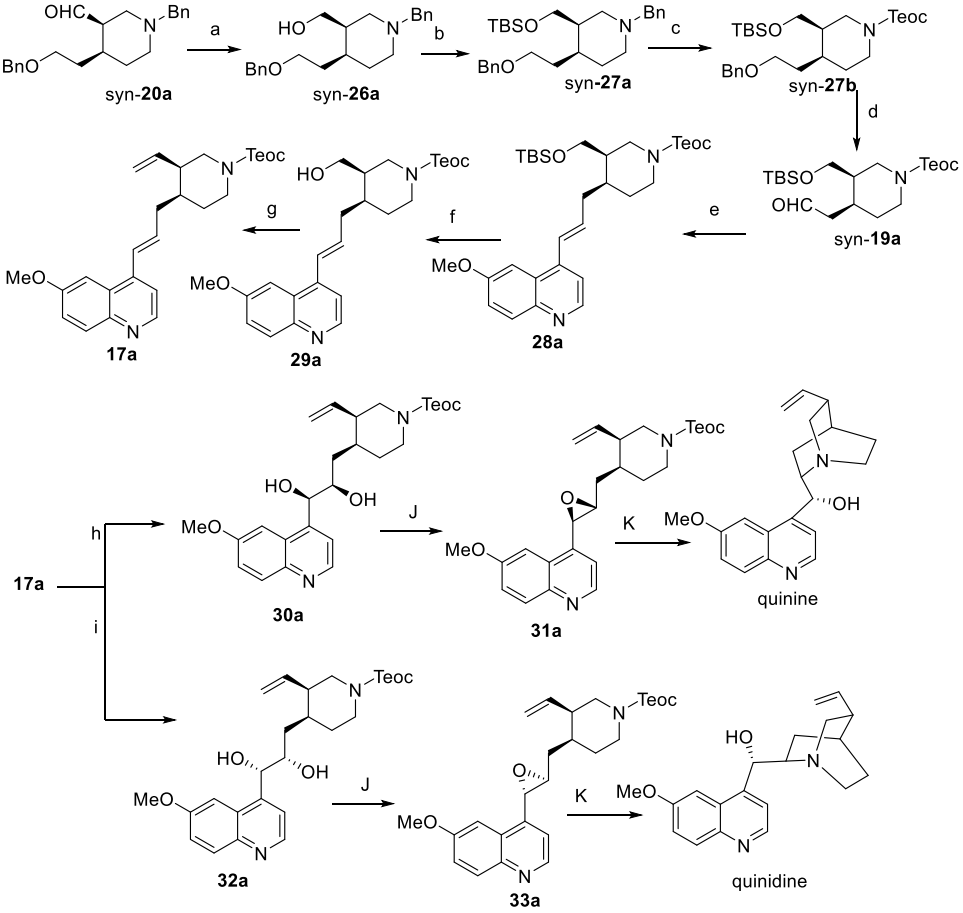
The total synthesis was sustained by reducing lactam **21a** to alcohol anti-**25a** followed by oxidation to aldehyde **20a**, which is a key early-stage intermediate (Scheme 6). Mild and catalytic epimerization of **20a** allowed for isolation of the syn-**20a** diastereoisomer (>21:1 d).

Reduction of syn-**20a** gave syn-**25a** in excellent yield. Next, O-TBS-protection of syn-**25a** and protective group exchange of intermediate **27a** gave intermediate **27b** in high yield (Scheme 7). Deprotection of **27b** by catalytic hydrogenation (Pd/C (10 mol %), H_2) was followed by oxidation to give aldehyde syn-**19a**. Subsequent reaction of this intermediate with phosphonate **18** gave olefin **28**a, which was efficiently converted to key-intermediate diolefin **17a** via **29a**. Catalytic chemo- and enantioselective dihydroxylation of **17a** using AD-mix-b gave diol **30a**, which was converted to epoxide **31a**. Final deprotection gave (-)-quinine in 20% overall yield from syn-**20a.** After this milestone, we embarked on the total synthesis of quinidine 2 (Scheme7). The same initial synthetic strategy as for quinine by construction of syn-**20a** followed by its manipulation to the diene **17a**. Next, performing the chemoselective catalytic asymmetric dihydroxylation on **17a** gave diol **32a**, which was converted to epoxide **33a** in 76% yield. Final deprotection gave (-)-quinidine in 21% overall yield from syn-**20a.**



Scheme 6. Synthesis of syn-**20a**

a) 10 eq. $LiAlH_4$, THF, 0 ºC, 30 min. then reflux 20h, >21:1 dr (isolated), 78%; b) 1.5 eq. ClCOCOCl, 3 eq. DMSO, CH_2Cl_2, N_2, -78 ºC, 1.5 h then 6 eq. TEA, 1h, 9:1 dr (isolated), 82%; c) 20 mol% pyrrolidine, 20 mol% CH_3CO_2H, CH_2Cl_2, rt, 1h, 96%.



Scheme 7. Synthesis of quinine and quinidine

a) 2 eq. $NaBH_4$, MeOH, 0ºC, 2h, 92%; b) 1.2 eq. TBSCl, 2.5 eq. imidazole, DMF (dry), rt, 24h, 85%; c) 3 eq. $TMSCH_2CH_2OH$, 1 eq. triphosgene, 10 eq. K_2CO_3, toluene, rt, 40h, 87%; d) i. 10 mol% Pd/C, H_2 (atm), MeOH, rt, 30 min, ii. 1.5 eq. ClCOCOCl, 3 eq. DMSO, CH_2Cl_2, N_2, -78ºC, 1.5 h then 6 eq. TEA, 1h, 82%; e) 1 eq. 16, 3 eq. NaH, THF, rt, 20h, 81%; f) 3 vol% HCl/MeOH, rt, 20 min, 96%; g) i. 1.5 eq. ClCOCOCl, 3 eq. DMSO, CH_2Cl_2, N_2, -78 ºC, 30 min then 6 eq. TEA, 30 min; ii. 2 eq. Ph_3P^+CH3Br-, 2 eq. KOtBu, THF, rt, 24h, 77%; h) ADmix-b, $CH_3SO_2NH_2$, tBuOH, H_2O, rt, 17h,>21:1 dr, 82%; i) ADmix-a, $CH_3SO_2NH_2$, tBuOH, H_2O, rt, 17h, >21:1 dr, 83%; j) i. trimethylorthoacetate, PPTS (cat.), CH_2Cl_2; ii. 3 eq. TMSCl, CH_2Cl_2, rt, 6h; iii. 3 eq. K_2CO_3 MeOH, 30 min, 76%; k) 5 eq. CsF, tBuOH, DMF, 110ºC, 12h, 98%.

Except countless efforts to synthesize quinine by various researcher in laboratory, up to date none of these synthesis strategies were used to synthesize quinine industrially. This latest strategy provide a nice opportunity to industrialize synthesis of quinine and its analogs. The most important achievements of this strategy were the application of various chiral catalysts. Chiral amine **23a** was utilized to establish the stereochemistry of lactam syn-**20a,** one of the crucial intermediate in the strategy besides, AD-mix-α and AD-mix-β were employed to fix the stereochemistry of the diols and the epoxide which led to the successful synthesis of quinine and quinidine.

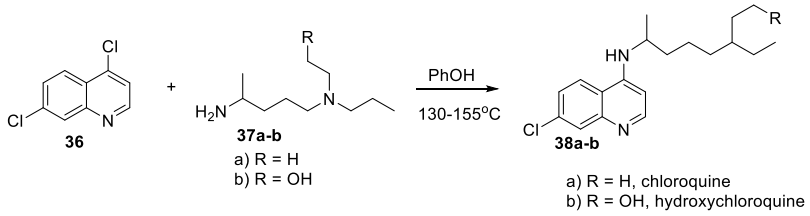
2.2. Aminoquinolines analogs

Drug candidates based on the 4-aminoquinoline scaffold continue to be considered as promising candidates for combination therapy. Chloroquine, amodiquine and quinacrine are typical example of 4-aminoquinolines (Figure 2). Among them chloroquine (CQ) has been used to treat malaria patients effectively for decades. It was first introduced in the 1940s and quickly became the drug of choice for the treatment of malaria (Burgess et al., 2010; Foley and Tilley, 1998) However, widespread resistance chloroquine has rendered it almost useless throughout the world, particularly against *P. falciparum* infections (Diseases, 2017; Singh et al., 2016).

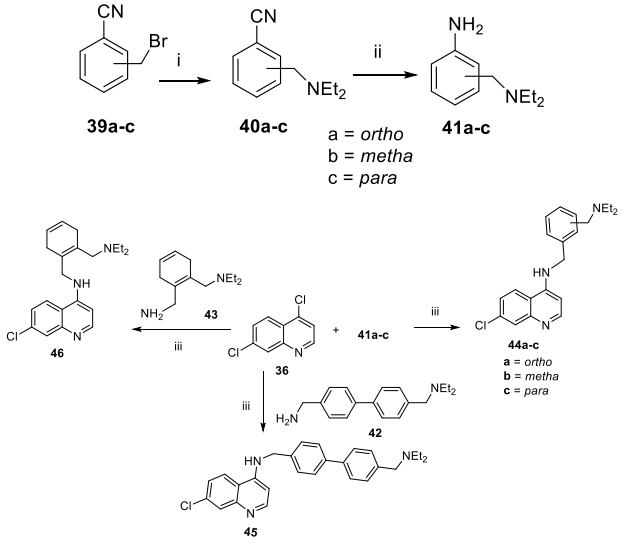
2.2.1. Synthesis of Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Among candidate drugs to treat COVID-19 are chloroquine (CQ) and hydroxychloroquine (HCQ) (Colson *et al*. 2020). In addition its uses as antimalarial agents, chloroquine and hydroxychloroquine drugs showed *in vitro* activity against SARS-CoV11 and SARS-CoV-2. Based upon *in vitro* antiviral activity data, both drugs are recommended for treating hospitalized COVID-19 patients in several countries in the near future (Bujuq and Cq, 2020).

Generally, chloroquine and hydroxychloroquin are prepared by condensing 2-amino-5-(diethylamino) pentane (37a) or N-2-hydroxyethylamino)-2-pentylamine (**37b**) with 4,7-dichloroquinoline at elevated temperature, using phenol as a solvent (Scheme 8) (Bujuq and Cq, 2020; De et al., 1998; Su et al., 2019).



Scheme 8. Synthesis route to chloroquine and hydroxychloroquine



Reagents and conditions: i) Et_2NH, MeOH, r.t, 3h; ii) $LiAlH_4$, Et_2O, r.t, 12h iii) $K2CO_3$, Et_3N, reflux 15 h

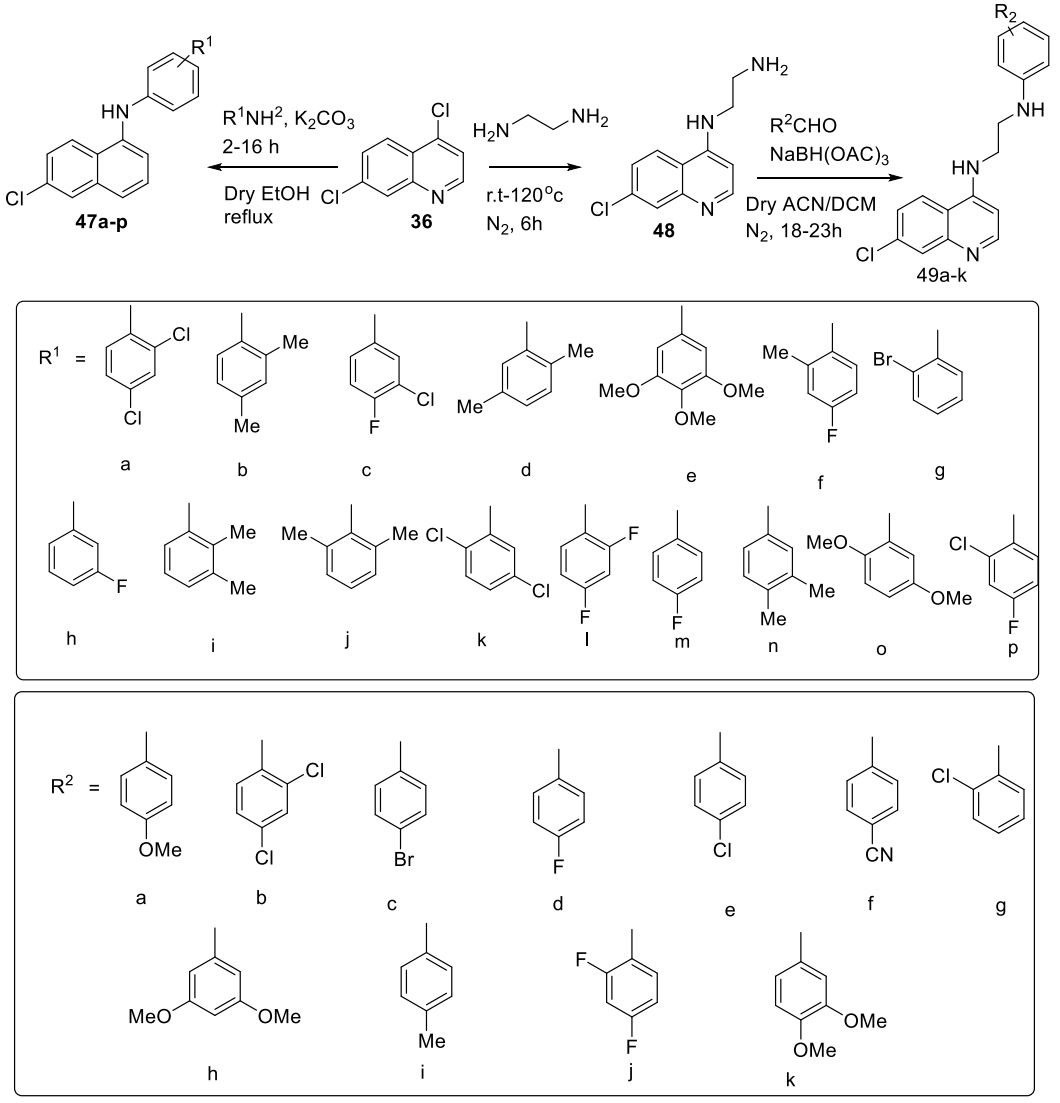
Scheme 9. Synthetic strategy of five new 4-aminoquinolines

2.2.2. Amodiaquine

In 2015, Rajapakse et al. (2015) synthesized five 4-aminoquinolines that feature rings lacking hydroxyl groups in the side chain of the molecules and are thus incapable of generating toxic quinone-imines. These compounds displayed high in vitro potency (low nanomolar IC*50*), markedly superior to chloroquine and comparable to amodiaquine, against chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum.* (Rajapakse et al., 2015)

The new 4-aminoquinolines were prepared by condensation of the appropriate amines, **41a-c**, **42**, **43** (Scheme 9) with 4,7-dichloroquinoline in N-methyl-2-pyrrolidone (NMP) in the presence of K_2CO_3 and trimethylamine (Scheme 11) (Rajapakse et al., 2015).

The effort to improve the bioactivity of 4-aminoquinolines against chloroquine resistant strains of *Plasmodium falciparum* by designing new 4-aminoquinolines remained active research area. Singh, et al. (2016) synthesized two series of new 4-aminoquinoline derivatives and evaluated their antimalarial potential activities against *Plasmodium falciparum* under *in vitro* conditions and found them to be effective (Scheme 10) (Singh et al., 2016). Amodiaquine had been applied as an alternate since it retains antimalarial activity against many CQ-resistant parasites. However, owing to its toxic quinoneimine metabolite, its use reduced since 1980s. Thus, Singh et al. (2016) antimalarial project was designed for synthesizing safe amodiaquine analogs (Singh et al., 2016).

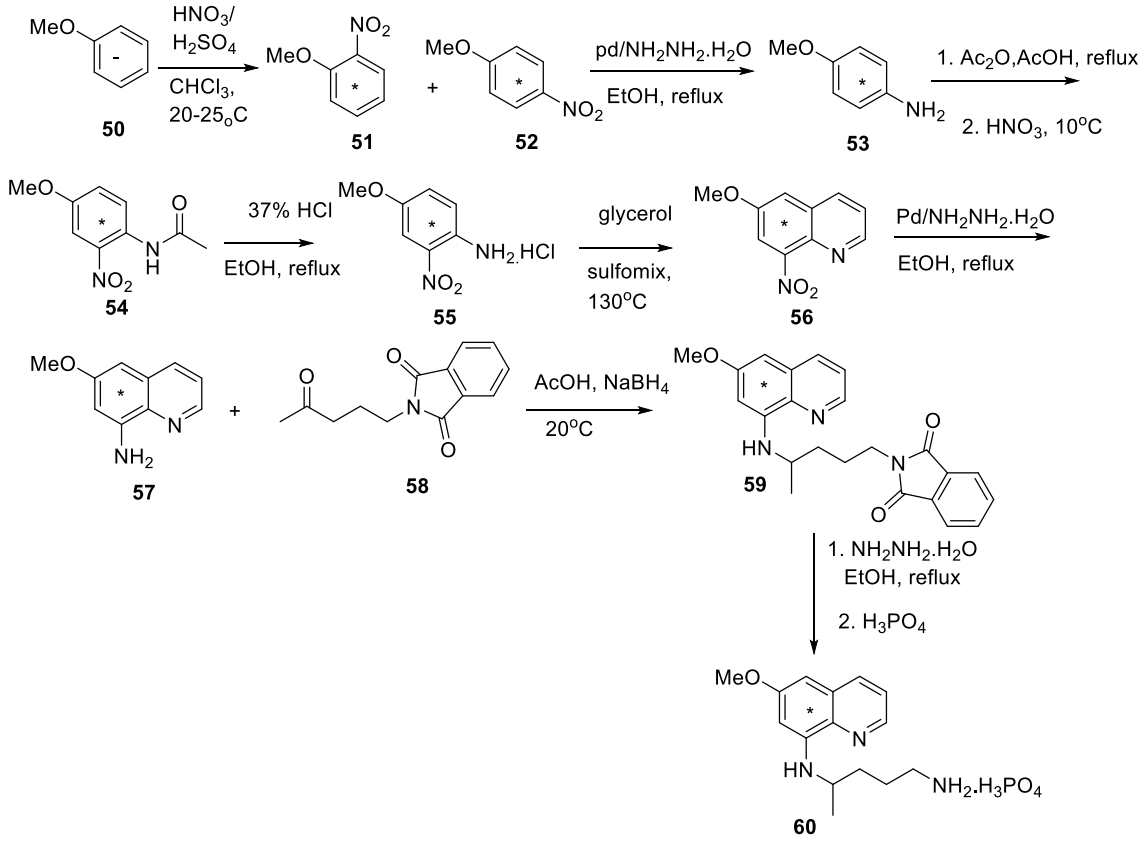


Scheme 10. Synthesis of **47a-p** and **49a-k**

2.3. The 8-aminoquinoline analogs

The 8-aminoquinolines are active against the pre–or exoerythrocytic form of malarial parasite**.** 8-Aminoquinolines have broad activity against asexual and sexual blood stages, hepatic schizonts and hypnozoites, and sporogonic stages developing in the mosquito host (Baird, 2019)**.** Pamaquine and Primaquine were typical example of 8-aminoquinolines (Baird and Hoffman, 2004). Primaquine is the only 8-aminoquinoline that has been in clinical use today (Figure 2) (Elderfield et al., 1946, 1955; Wiesner et al., 2003). Even today 70 after years, primaquine, is the only drug currently available for preventing relapsing malaria caused by *Plasmodium viva* (the dormant liver form of the parasite) (Camarda et al., 2019; Palareti et al., 2016).

Pharmaceutical and biological scientists use isotopic labelled compounds to study biosynthesis, absorption, distribution, metabolism, and excretion of those materials in animal and human studies (Herath et al., 2013). Herath et al. (2013) developed [$^{13}C_6$]-primaquine (**78**) from commercially available [$^{13}C_6$]-anisole (Scheme 11) (Herath et al., 2013). Anisole was nitrated in a biphasic system in the presence of sodium nitrite to yield a mixture of [$^{13}C_6$]-2- (**51**) and [$^{13}C_6$]-4-nitroanisole (**52**). They were separated, and [$^{13}C_6$]-4-nitroanisole was hydrogenated to yield [$^{13}C_6$]-p-anisidine (**53**), then it was acetylated and nitrated in situ to afford [$^{13}C_6$]-4-methoxy-2-nitroacetanilide (**54**). Treatment of this compound with HCl afforded [$^{13}C_6$]-4-methoxy-2-nitroaniline (**55**) which was converted to [^{13}C]-6-methoxy-8-nitroquinoline (**56**) by the Skraup reaction. This product was hydrogenated, and the resulting amine (**57**) was coupled to the side chain, 2-oxo-5-phthalimido pentane (**58**), by reductive amination to give [$^{13}C_6$]-6-methoxy-8-(1-methyl-4-phthalimidobutylamino) quinoline (**59**). Deprotection by removal of the phthalimide group yielded the free amine that was treated with H_3PO_4 and crystallized from water/methanol to yield [$^{13}C_6$]-primaquine diphosphate (60) (Scheme 14).(Herath et al., 2013).



Scheme 11. Preparation of [$^{13}C_6$]-primaquine

3. Antibacterial quinoline analogs

The study of the antibacterial activities of quinolines got significance after the discovery of nalidixic acid in 1962 and its approval for clinical use 1967 (Figure 3). It was discovered as an impurity in the chemical manufacture of the antimalarial chloroquine (Bisacchi 2015; Newman et al., 1966). In 1967, nalidixic acid was approved for clinical treatment of urinary tract infections (UTIs) caused by Gram negative bacteria even though bacteria developed resistance to it soon (Bisacchi, 2015). Then many other effective broad spectrum antibacterial quinolones (4-oxo-1,4-dihydroquinoline-3-carboxylic acid analogs) were developed (Tarushi et al., 2013). Structurally quinolones or quinolonecarboxylic acids or 4-quinolones are a group of synthetic antibacterial agents containing a 4-oxo-1,4-dihydroquinoline skeleton (Figure 3), which are commonly used in the treatment of many infection (Tarushi et al., 2013; Turel, 2002). Later 1980s the need for new treatments of diarrhea and UTIs caused by resistant *Shigella* and *Escherichia coli* led the attention of researchers to improve the activity and optimize the toxicity of the quinolones analogues and some improved analogues were made.(Blaskovich, 2019)

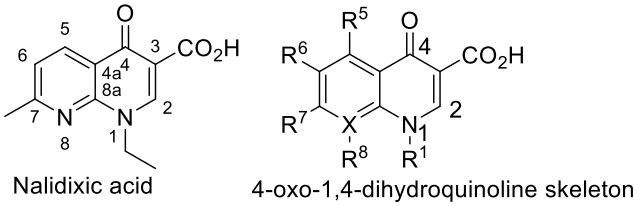


Figure 4: The structure of naldixic acid and 4-quinolone nucleus

Most bacterial species encode two distinct, but homologous, type II topoisomerases, gyrase and topoisomerase IV. These enzymes play essential roles in most nucleic acid processes, help control levels of DNA under- and over winding, and remove knots and tangles from the bacterial chromosome (Aldred et al., 2014; Martínez, 2019). Quinolone inhibit DNA synthesis by targeting two essential type II topoisomerases, DNA gyrase and topoisomerase IV (Topo IV) (Fàbrega et al., 2009). Quinolone are termed "topoisomerase poisons" because they convert gyrase and topoisomerase IV into cellular toxins (Aldred et al., 2014).

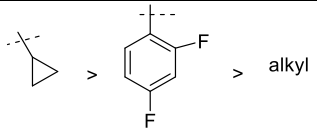
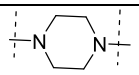
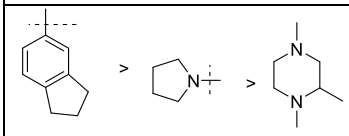
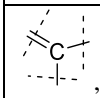
3.1. The structural activity relationship of quinolones

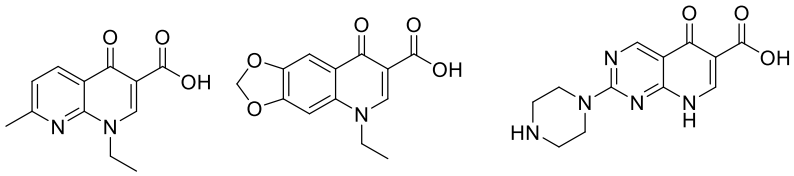
Fluoroquinolones are the most effective broad spectrum antibacterial agents. The addition of fluorine and other substituents on the basic quinolone structure afforded more bioactive fluoroquinolones. Fluorinated analogues of naldixic acid (1,8-naphthyridine) which possess a 4-quinolone nucleus (Figure 3) and 6-flourine showed significant antibacterial activity and considered clinically important compounds (Sharma et al., 2009). The structure of quinolones developed a long two aspects; the naphthyridones (with the original the naphthyridine core of naldixic acid) and fluoroquinolones where the 8th nitrogen is replace by a carbon atom and the 6th carbon bears a fluorine substituent (Ball, 2000). In general, pharmacophores required for improving antibacterial activity of the original 1,8-naphthyridine nucleus include various substituents on R^1 to R^8. The basic manipulations, including replacing hydrogen with fluorine at position 6, substituting a diamine residue at position 7 and adding new residues at position 1 of the quinolone ring, which have led to enhanced antibacterial efficacy (Table 1) (Chu et al., 2019; Turel, 2002).

Classification of Fluoroquinolones. Quinolones and fluoroquinolones are classified on the basis of their chemical structure, their spectrum of activity and their pharmacokinetic profile (Kocsis et al., 2016; Sharma et al., 2009). According to this classification, Naldixic acid, Oxolinic acid and Pipemidic acid are the first generation fluoroquinolones. They are active against some Gram negative bacteria. However they are highly protein bound drugs and have short half-life. All of them were devoid of 6-flourine atom (Figure 5) (Andersson and MacGowan, 2003; Kocsis et al., 2016; Tarushi et al., 2013).

Norfloxacin, enoxacin, ciprofloxacin, ofloxacin and lomefloxacin are second generation fluoroquinolones. They showed improved activity against gram negative bacteria and longer half-life than previous agents. Their protein binding capacity was (50%) of previous agents (Figure 6). Structurally all of the second generation fluoroquinolone contain fluorine atom at the 6 position (Andersson and MacGowan, 2003; Fluoroquinolone *et al*., 1998; Kocsis et al., 2016; Tarushi et al., 2013).

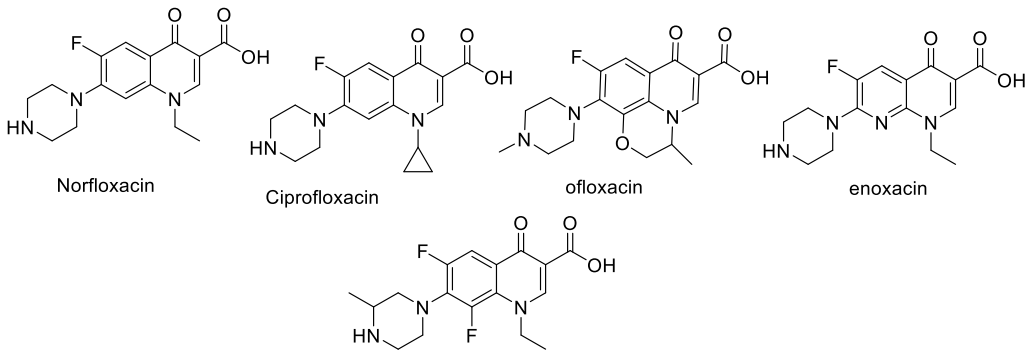
Table 1*:* The structure–activity relationships (SAR) of quinolones

positions	Types of substituents	Activity improved
R^1		Increase the overall potency
R^5	$-NH_2 > -OH > -CH_3$	Increase the gram-positive activity
R^6	F	Increase the gram-negative activity
R^7		Increase the gram-negative activity
		Increase the gram-positive activity
R^8		Increase activity of anaerobes
	 , -F, -Cl, >-OCH^3 >$OCHF_2$	Increase the gram-positive activity



Nalidixic acid Oxolinic acid Pipemidic acid

Figure 5: The Structure of the first generation fluoroquinolones



Norfloxacin Ciprofloxacin ofloxacin enoxacin Lomefloxacin

Figure 6*:* The Structure of the second generation fluoroquinolones

The third generation fluoroquinolones are active against both gram negative and gram positive bacteria. Temafloxacin, sparfloxacin, and grepafloxacin are among the third generations (Figure 7). Structurally 1-*m*-diflourophenyl, 8-flouro and 5-methyls were additional substituents than the previous generations. From structural activity relationship (SAR), the additional substituents increase the antibacterial activity of the third generation relative to the previous once. In spite of the development of numerous fluoroquinolone agents in the last decades, some of them specially the third and four generation fluoroquinolones have been interrupted or limited because of their toxicity (Kocsis et al., 2016; Zhanel et al., 1999).

Three of fourth generation fluoroquinolones contain 7-pyrrolidinyl derivatives instead of piperazine and the 8-carbon bears Chlorine or methoxy groups except trovafloxacin. Clinafloxacin, trovafloxacin, moxifloxacin, and gatifloxacin are among the fourth generation flouroquinolones (Figure 8). They showed extended activity against both strains of bacteria and against anaerobes and atypical bacteria (Zhanel et al., 1999).

However, some of the four generation fluoroquinolones showed intolerable toxicity. For instance, sparfloxacin and clinafloxacin therapy cause rashes and dysglycemia was observed after gatifloxacain and clinafloxacin therapy; hemolysis occured during temafloxacin administration, and hepatotoxicity was found in trovafloxacin treatment (Kocsis et al., 2016; Scoper, 2008; Zhanel et al., 1999).

3.2. The synthesis of 4-oxoquinolones

Two basic ways are used to synthesis quinolin-4-one-3-carboxylic acids. A modified Gould-Jacobs cyclization is one these ways. The Gould−Jacobs reaction is an important thermal cyclization method for the construction of the 4-quinolone scaffold, which is an essential heterocyclic motif in antibacterial, anticancer or antiinflammatory drugs (Wernik *et al*. 2020). The original approach involves the condensation of an aniline derivative and diethyl ethoxymethylenemalonate (Scheme 12).

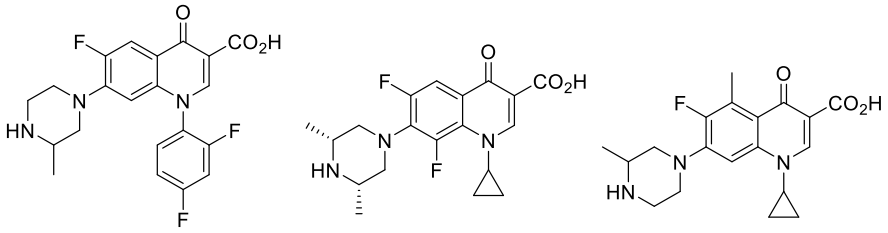


Figure 7: The Structure of the third generation fluoroquinolones

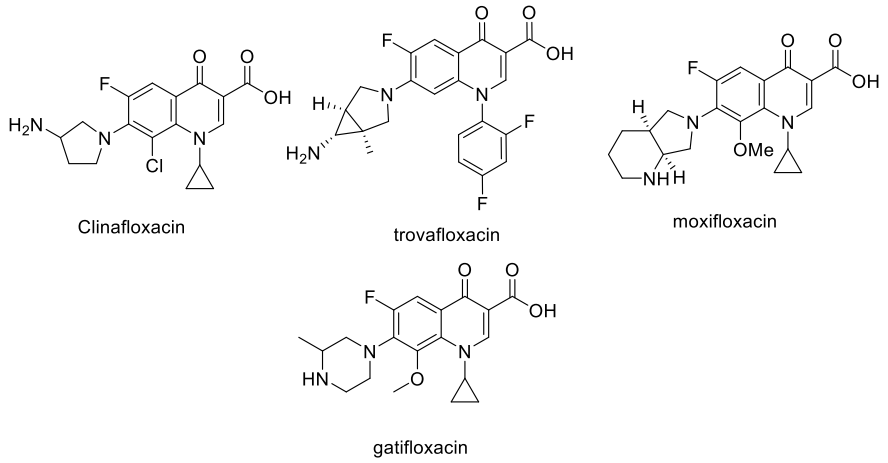
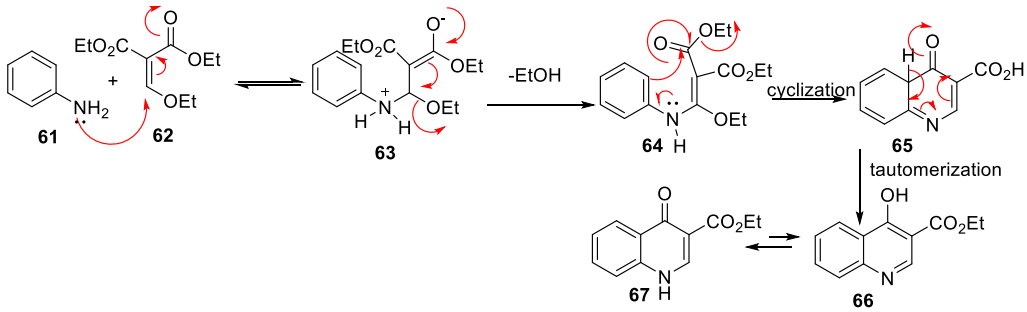


Figure 8: The Structure of the fourth generation fluoroquinolones



Scheme 12. The mechanism of the Gould−Jacobs reaction

The Gould-Jacons reactions enabled the synthesis of several substituted quinolin-4-one-3-carboxylic acids (Trah and Lamberth 2017). It involves the condensation of fluorinated anilines (**68**, A = CH, CF) or 2-aminopyridines (**68**, A = N) as starting materials with ethoxymethylene derivative of malonate, cyanoacetate or acetoacetate to form enamines. The intramolecular cyclization of compounds **69** with polyphosphoric acid (PPA) affords the corresponding fluoroquinolones (**70** , A = CH, CF) or naphthyridones (**70** , A = N) (Scheme 13) (Charushin et al., 2014; Leyva et al., 1999).

The drawback of the Gould-Jacobs reaction is the need of high-boiling solvents. Diphenyl ether which has been applied for a long time has abandoned due to environmental reasons (Urinda et al., 2009).

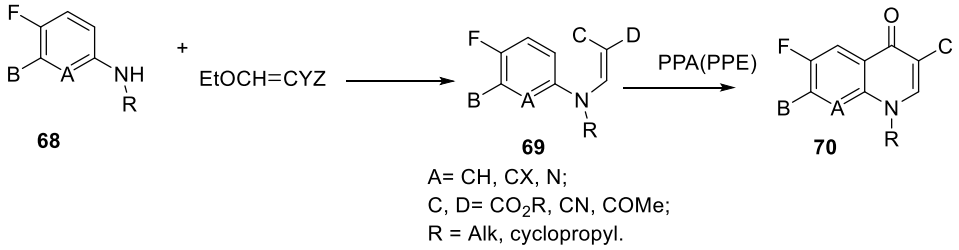
The second way, involves fluorine-containing benzoyl derivatives (**71**, A = CF, CH) or their nicotinoyl analogs (A = N) for starting (Scheme 14). The key intermediates in this case are benzoyl- or pyridinoyl acrylates **73 (**Scheme 14**)** (Aizikovich et al., 2000; Charushin et al., 2014).

74 can be cyclized by heating in DMF in the presence of bases including potassium carbonate,NaH in ethyl acetate, 1,4 diazabicyclo[2.2.2]- octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).(Charushin et al., 2014; Urinda et al., 2009)

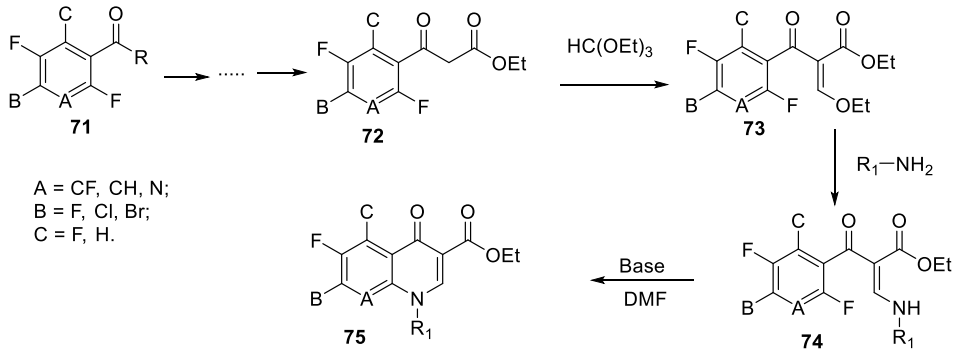
4. Anticancer quinoline Analogs

Besides antibacterial potential, some quinolones showed variable biological activities, such as anticancer (Abdel-aziz et al., 2016; Paul et al., 2007), antifungal (Musiol et al., 2006; Senerovic et al., 2020), antiviral (de la Guardia et al., 2018; Senerovic et al., 2020), and anti-inflammatory (Mukherjee and Pal, 2013; Wen et al., 2015*) a*ctivities. Some of antitumor drugs induce eukaryotic DNA topoisomerase II-mediated cleavage of DNA *in vitro*, indicating the possibility that their pharmacological target *in vivo* might be the topoisomerase (Wang, 1996). Some quinolones disturb the normal function of DNA topoisomerase enzymes (mainly type II). DNA topoisomerase are conserved enzymes and essential for all living cells including both prokaryotes and eukaryotes (Abdel-Aal et al., 2019). In eukaryotes two isoenzymes: *topoisomerase II α* and *β*, a 170 and a 180 kD proteins are essential for DNA copying and replication (Wang, 1996). These proteins share a similar catalytic cycle, the main difference resting in the fact that the active form of eukaryotic topoisomerase II (Top2) is constituted by a homodimer (Wang, 1996).

Investigation of existing quinolone drugs for their antitumor potential against different types of cancers revealed that they possess anticancer activity through inhibition of mammalian DNA topoisomerases in addition to other mechanisms (Abdel-Aal et al., 2019).



Scheme 13. Synthesis of fluoroquinolones



Scheme 14. Synthesis of fl uoroquinolones from fl uorinated benzoyl derivatives

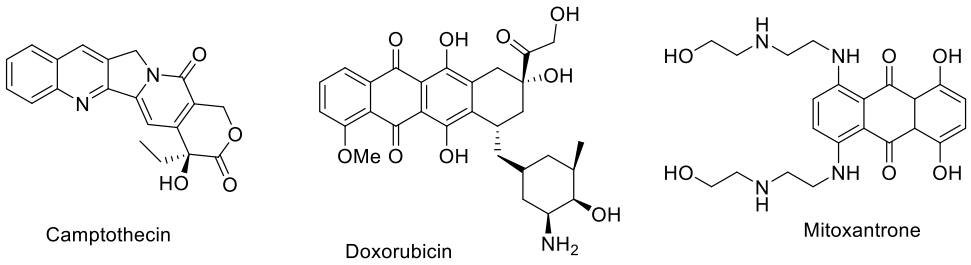


Figure 9: Topoisomerases I and II inhibitor anticancer drugs

Camptothecin is quinoline based pentacyclic molecule which is a well-known and clinically used anticancer drug that targets mammalian type I DNA topoisomerases (Figure 9). It acts via preventing religation of cleaved DNA strands and triggering apoptosis preferentially in dividing cells. On the other hand, anticancer drugs such as doxorubicin and mitoxantrone (Figure 9) target type II topoisomerases. These drugs disturb the catalytic function of type II topoisomerases either by trapping the enzyme in its complex with cleaved DNA, by preventing the process of religation, by enhancing the formation of cleavable complexes, or by intercalating DNA, preventing the enzyme from performing its catalytic function (Abdel-Aal et al., 2019; Sharma et al., 2015).

Structurally camptothecin comprised quinoline nucleus while doxorubicin and mitoxantron don't have. Camptothecin targets DNA *I topoisomerase* while doxorubicin and mitoxantrone target *DNA II topoisomerase*. Contrary to our expectation, vosaroxin (Figure 10) which is a first-in-class anticancer quinolone derivative targets *topoisomerase II* and induces site selective double-strand breaks in DNA, leading to tumor cell apoptosis (Jamieson et al., 2016). In addition to vosaroxin, some of derivatives of the existing quinolone drugs showed anticancer activity through inhibition of mammalian DNA topoisomerases in addition to other mechanisms (Chen et al., 2014; Yadav et al., 2012). Just to mention few of them, ciprofloxacin exhibited a significant activity and induced apoptosis in different cancer cell lines (S *et al*. 2011); lomefloxacin reduced the viability of the human melanoma COLO829 cells (Beberok et al., 2017); and trovafloxacin combated metastasis and spread of leukemia cells to other body tissues, and could lengthen the survival of laboratory animals (Thadepalli et al., 2005).

4.1. The anticancer Structure Activity Relationships (SAR) of quinolones

A large variety of quinolines are reported to exhibit ample anti-cancer activity through a variety of mechanisms (Jain et al., 2016); such as cell cycle arrest in the G2 phase (Kim et al., 2005); inhibition of topoisomerase (Cheng et al., 2008); inhibition of tubulin polymerization (Alqasoumi et al., 2009); and the inhibition of tyrosine kinases (Mulvihill et al., 2008; Nishii et al., 2010). Each of the variety of mechanisms affected by various structure and substituents around the quinoline scaffold. For example, a number of quinolones and related compounds were screened for eukaryotic *topoisomerase II* inhibition in order to identify chemical structure types that would interact with both the bacterial and eukaryotic enzymes (Kohlbrenner et al., 1992). The result of the study revealed that most probably a combination of the various substituents on quinolone contributes to directing the poisoning activity. Abdel-Aal et al. (2019) summarized the SAR of anticancer quinolones Figure 10 (Abdel-Aal et al., 2019).

4.1.1. Synthesis of 1,8-Naphthyridine analogs

Voreloxin is an anticancer quinolone derivative, a chemical scaffold not used previously for cancer treatment. Voreloxin is completing Phase 2 clinical trials in acute myeloid leukemia and platinum-resistant ovarian cancer (Hawtin et al., 2010). Voreloxin is a naphthyridine analog. It intercalates DNA in the presence of *topoisomerase II*, resulting in selective, replication dependent DNA damage, irreversible G2 arrest and rapid apoptosis (Al-romaizan et al., 2019).

After the anticancer activity of voreloxin was understood, synthesizing and evaluation of the cytotoxicity activity of 1,8-Naphthyridine analogs have been an active research area. Herein some of them will be discussed. Al-romaizan et al. (2019) synthesized a

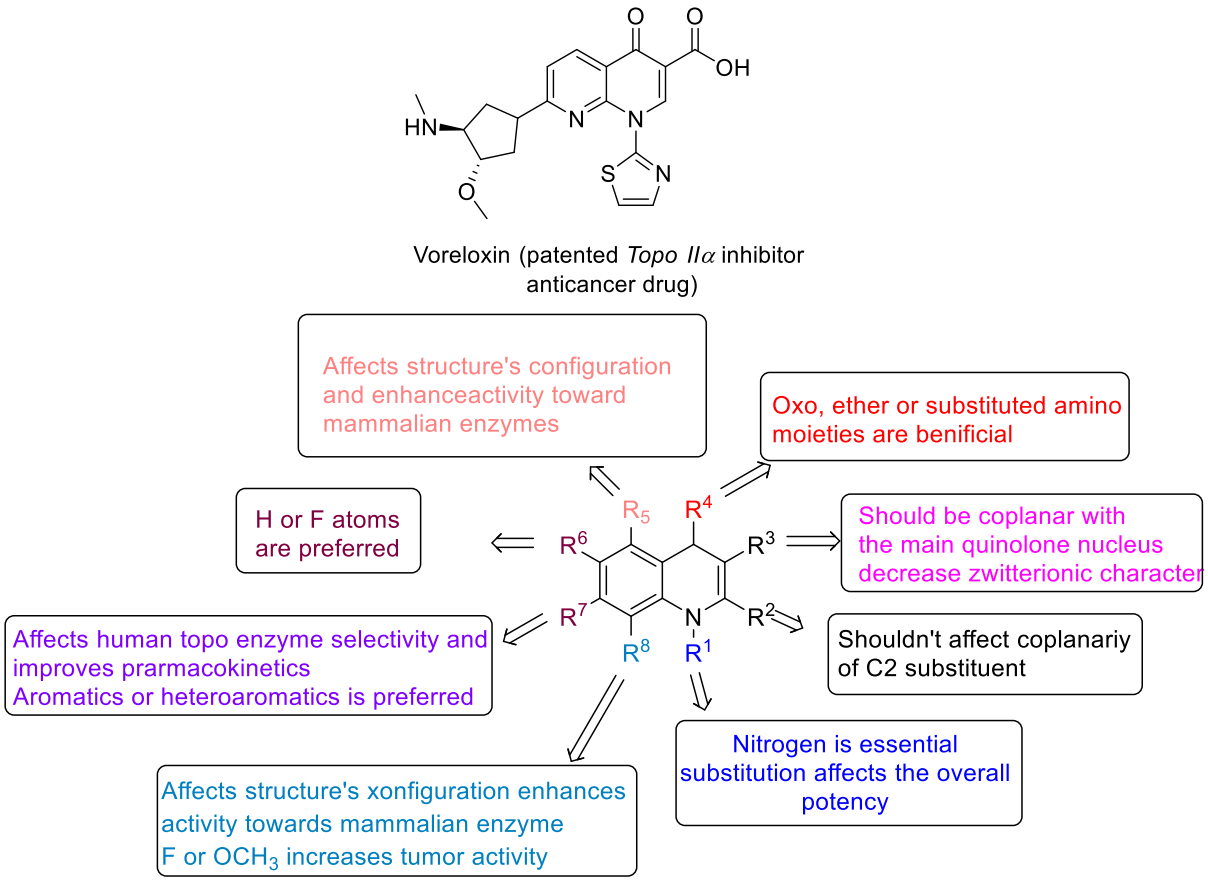


Figure 10: SAR of anticancer quinolones and typical anticancer drug structure

series of new 2-phenyl-7-methyl-1,8- naphthyridine derivatives with variable substituents at C3 and evaluated their anticancer activity *in vitro* against human breast cancer cell line (MCF7). Some of the derivatives **84c**, **82d, 79d**, **84f** and **82b** showed better activity with IC_{50} values of 1.47, 1.62, 1.68, 2.30, and 3.19 µM, respectively while IC_{50} of the standard drug (staurosporin) at the same concentration was only 4.51 µM (Al-romaizan et al., 2019). Staurosporine and etoposide were used as reference for evaluation of the anticancer properties (Figure 11). Staurosporine is the most potent and frequently used proapoptotic stimuli protein kinase inhibitor natural product (Ōmura et al., 2018) and Etoposide derives from podophyllotoxin, poisons the *Topo II* cleavage complexes (*TopoIIcc*) and inhibits the second step of the reaction (i.e. DNA religation) (Montecucco et al., 2015).

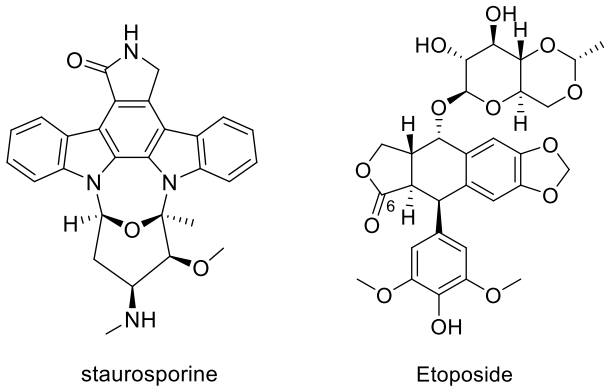
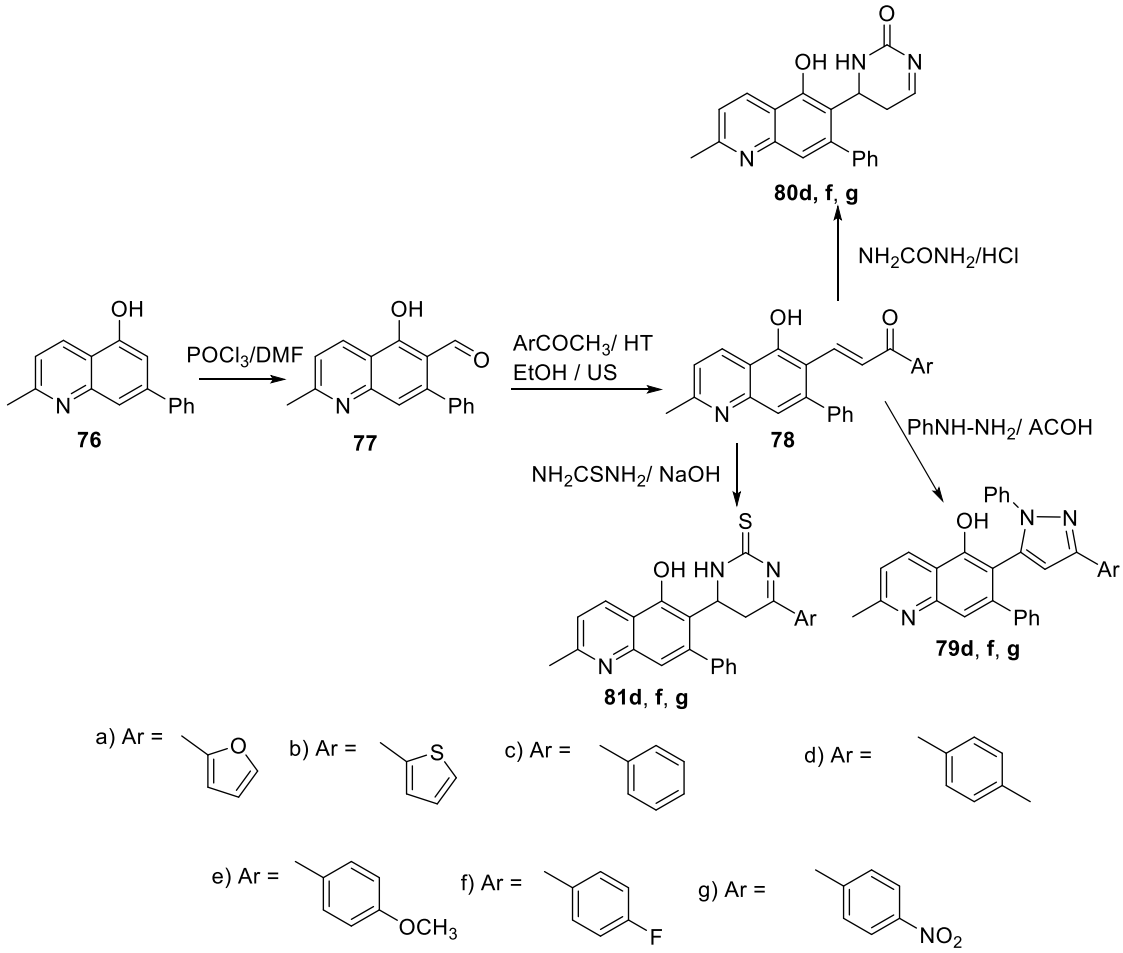


Figure 11: The structure of Staurosporine and Etoposide



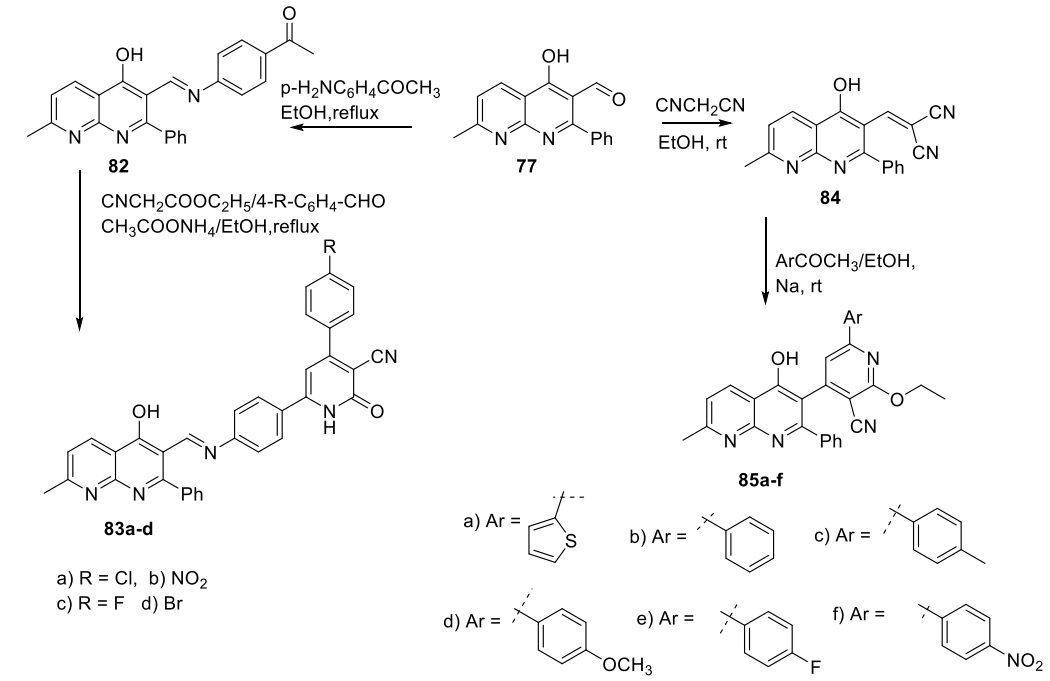
Scheme 15. Synthesis of pyrazoline dihydropyrimidinone and dihydropyrimidinethione

The synthetic methodology developed to attain target compounds is shown below (Scheme 16 and 17). In the synthesis formylation of 7-methyl- 2-phenyl-1,8-naphthyridin-4-ol 1 via Vilsmeier–Haack reaction, afforded **77**, treatment of **77** with different acetyl compounds in the presence of MgAl-hydrotalcite in refluxing ethanol provided the chalcones derivatives **78a-g** (Scheme 19) (Al-romaizan et al., 2019).

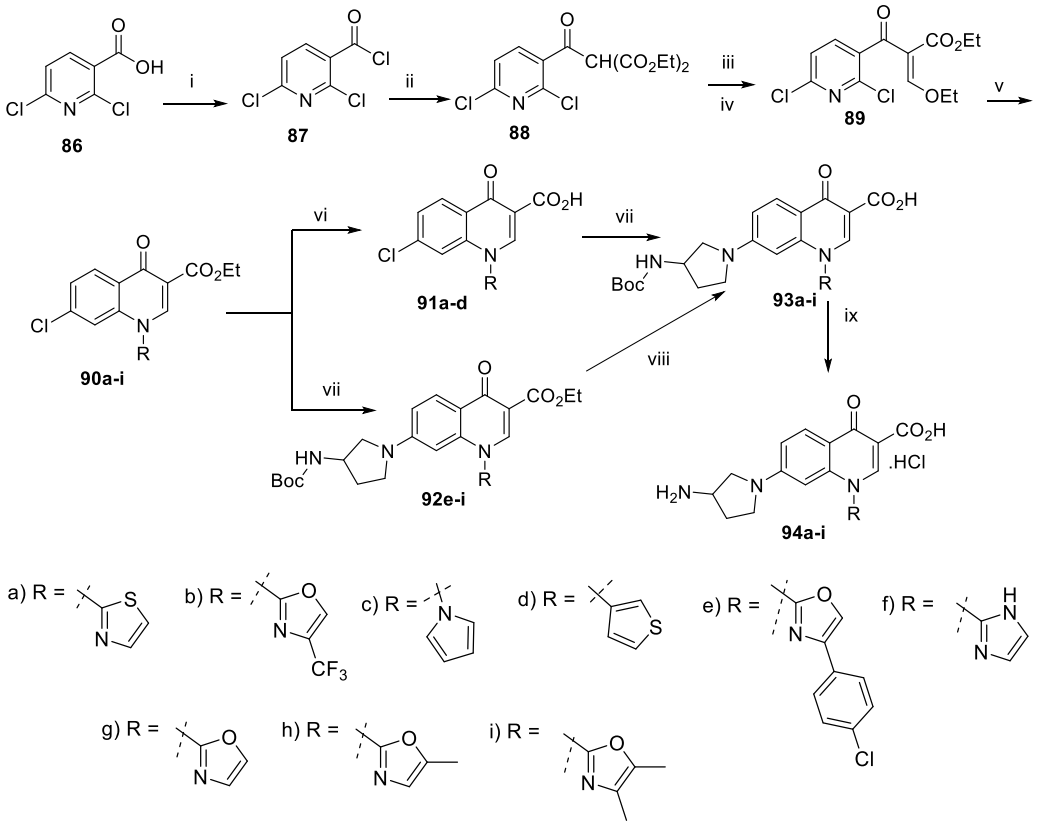
Treatment of chalcone **78a-g** with different binuclophilic agents, including phenylhydrazine, urea, and thiourea afforded the corresponding to pyrazoline **79d**, **f**, **g**, dihydropyrimidinone **80 d**, **f**, **g**, and dihydropyrimidinethione **81 d**, **f**, **g** derivatives (Scheme 16) (Al-romaizan et al., 2019).

Reaction of aldehyde **77** with p-aminoacetophenone in ethanol under reflux gave **82.** Furthermore, treatment of **82** with different aromatic aldehyde, ethylcyanoacetate, and excess ammonium acetate in EtOH under reflux afforded **83a-d** (Scheme 16). Intermediate **97** treated with malononitrile in refluxing ethanol to give **84**, which reacted with different ketones catalyzed by sodium ethoxide to afford **85a-d** (Scheme 16) (Al-romaizan et al., 2019).

Xue-Dong Jia et al. (2017) synthesized a series of naphthyridinone derivatives based on precursor of Voreloxin (Scheme 16 and 17). The synthetic compounds were evaluated for their *in vitro* antitumor activity against HL60 (leukemia) at the concentration of 30 μmol/L by SRB assay (Jia et al., 2017). And the compounds having more than 70% inhibition were subjected to IC_{50} determination against ten human cancer cell lines, including HL60, HepG2 (liver carcinoma), HCT-116 (colon cancer), A549 (lung adenocarcinoma), PANC-1 (pancreatic carcinoma), Hela (cervical cancer), DU145 (prostatic cancer), SKOV3 (ovarian carcinoma), MCF-7 (breast cancer) and MCF-7/DOX (Doxorubicin-resistant MCF-7) by SRB assay (Jia et al., 2017). This assay disclosed that thiazol-2-yl and 3- aminomethyl-4-benzyloxyimino-3-methylpyrrolidin-1-yl groups are optimal at the N-1 and



Scheme 16. Synthesis of **83a-d** and **85a-f**



Reagents and conditions: i) $SOCl_2$, reflux, 4h; ii) $CH_2(CO_2Et)_2$, $Mg_{, EtOH,}$ reflux, 1h, then -10℃, 3h; iii) p-TsOH, H_2O, reflux, 3h; iv) $CH(OEt)_3$, Ac_2O, reflux 3 h; v) RNH_2, (i-pr_2O, r.t, 10 h, then Et_3N, MeCN, 50℃, 1 h or 60% NaH, toluene, 50℃, 1 h; vi) HCl, HOAc, reflux, 3 h; vii) 3-N-Bocaminopyrrolidine, Et_3N, MeCN, reflux, 5 h v iii) NaOH, H_2O, EtOH, 50℃, 10 h; ix) CH_2Cl_2, HCl(g), r.t, 3 h.

Scheme 17. Synthesis of 7-(3-aminopyrrolidin-1-yl)naphthyridinone derivatives

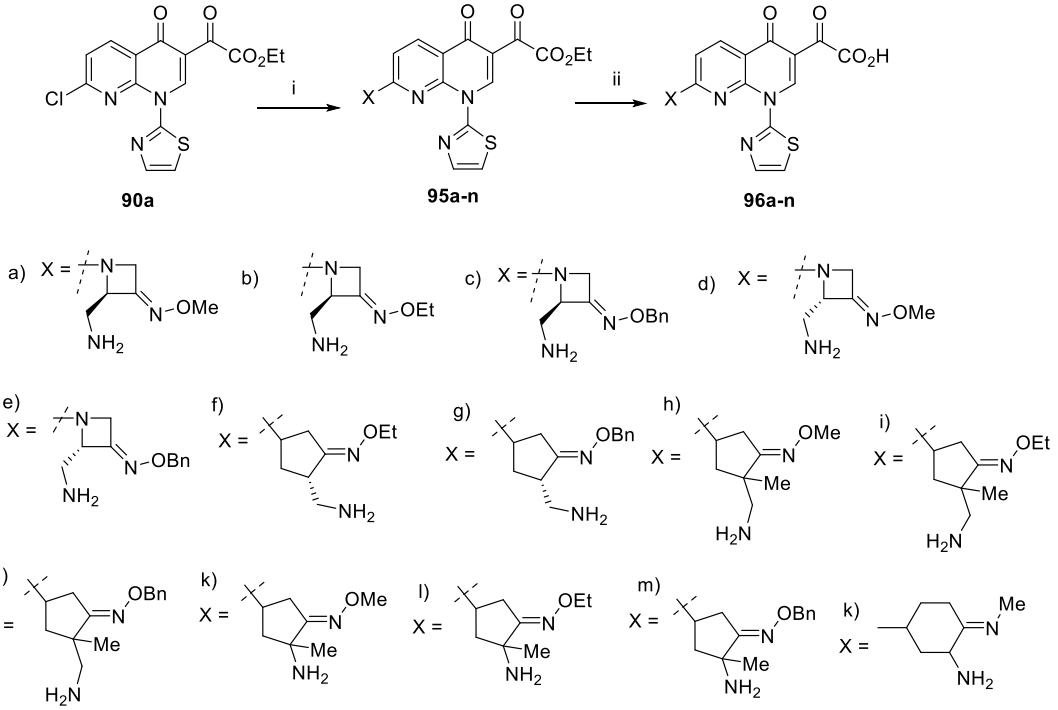
C-7 positions of naphthyridinone core, respectively. **96j** exhibited broad-spectrum activity (IC_{50}: <0.5– 6.25 μmol/L) against all of the tested cell lines and it is about 1.3 to more than 100-fold more potent than the references (Etoposide) against eight of these cell lines (Jia et al., 2017).

To study the effect of various substituents at the N-1 position of the 7-(3-aminopyrrolidin-1-yl)naphthyridinone core, eight 7-(3-aminopyrrolidin-1-yl)naphthyridinone derivatives were synthesized by route in Scheme 17 (Jia et al., 2017). The key intermediates **90a–i** were readily prepared from **86** via a five-step procedure (Liu et al., 2014; Tomita et al., 2002). Hydrolysis of the core esters **90a–d** in HCl-HOAc followed by condensation with 3-N-Boc-aminopyrrolidine in the presence of triethylamine gave **91a–d.** However, the esters **90e–i** were not converted to the corresponding acids in a similar manner as for preparation of **91a–d**. After various attempts, **92e–i** were successfully obtained from **90e–i** by condensation with the side chain compounds and then hydrolysis of the resulted esters **92e–i**. The Boc-protecting group of **93a–**i was removed by hydrogen chloride gas in dichloromethane to yield the desired naphthyridinone derivatives **94a–**i as hydrochloric acid salts (Scheme 17) (Jia et al., 2017).

The synthetic route of novel 1-(thiazol-2-yl) naphthyridinones **96a**–n containing nitrogen heterocycles with an alkoxyimino group was portrayed in Scheme 18. Condensation of **90a** with various side chain compounds and then hydrolysis of the resulted esters **95a–n** yielded **96a–n**. Since the oxime group can exist in the E or Z configuration, however, the configuration was not determine in this experiment, but the oxime geometry would be expected to have the E-configuration according to the data in published papers (Chai et al., 2010; Hong et al., 1997; Jia et al., 2017).

5. Conclusion

Numerous natural products possessing quinoline moiety exhibit interesting biological and pharmacological properties, such as antimalarial, antibacterial, antiasthmatic, antihypertensive, anti-inflammatory, immunosuppressive, antileishmanial, and anticancer activity. Synthetic organic chemists have developed various synthetic routes for various quinoline derivatives. Some natural and synthetic quinoline-derivatives showed amusing biological activities. Several antimalarial, antibacterial and anticancer quinoline drugs had been patented and commercialized for several decades. Most probable, quinoline is the only scaffold utilized to synthesize three



Reagents and conditions i) XH, Et_3N, EtOH, 75°C, 7-10 h; ii) NaOH, H_2O, EtOH, r.t, 6-15 h

Scheme 18. Synthesis of 1-(thiazol-2-yl)naphthyridinone derivatives **96a-n**

types of commercial drugs (antimalarial, antibacterial and anticancer drugs). Bacterial and cancer diseases affects anybody everywhere on the globe whereas malaria can affect half of the global community. All of the three diseases are fatal unless being treated timely and appropriately. Chewing the bark of Cinchona trees (for quinine) had been used to treat malaria since 17th century. Even today, 350 years later, modern medicine still rely on quinine as a life-saving medicament in severe cases of *falciparum* malaria. Quinine, chloroquine, amodiaquine, mefloquine, and primaquine were among common quinoline derivatives used to treat malaria for years. The study of the antibacterial activities of quinolines begun with the discovery of nalidixic acid in 1962 and its approval for clinical use 1967. Now more than 14 fluoroquinolone drugs have been patented and have been used to save millions of people from various bacterial infections. In addition to antimalarial and antibacterial quinoline drugs, some quinolone derivatives showed significant anticancer activities. vosaroxin is the first-in-class anticancer quinolone derivative that targets *topoisomerase II* . In addition to vosaroxin, some of derivatives of the existing quinolone drugs showed anticancer activity through inhibition of mammalian *DNA topoisomerases*. The research of developing new effective bioactive quinoline analogs and improving the biological activity of the existing quinolones are still active area of research. Opening up new horizons continued with development of a number of new synthetic methodologies and techniques of biological activities evaluation.

Cancer is the main cause of mortality and a serious barrier to increasing life expectancy in every country of the world. On the other hand, a large variety of quinolines are reported to exhibit substantial anti-cancer activity through a variety of mechanisms. Thus conducting extensive research on quinoline scaffold for cancer chemotherapy is both imperative and promising.

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