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Quinoline: A Versatile Heterocyclic with Multiple Pharmacological Activities

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Abstract

Quinoline is a fused heterocyclic compound containing benzene ring and pyridine ring. It is an important compound due to their versatile applications in the diverse fields including organic & medicinal chemistry. The derivatives of quinoline exhibits multiple therapeutic activities such as antimalarial, anti-inflammatory, anti-asthmatic, anti-bacterial, anti-hypertensive, anti-cancer, anti-viral and anti-amoebic. A number of drugs having quinoline nucleus are available in the market for different therapeutic applications. There are a number of well-established protocols for the synthesis of this heterocyclic ring. This paper summarizes some of the approaches of synthesis of quinoline derivatives having different pharmacological activities.

Key words: Quinoline; 1-Aza-napthalene; Benzo [*b*] pyridine; Anti-malarial

1. Introduction

Quinoline (1) or benzo[*b*]pyridine or 1-aza-napthalene or 1-benazine is a heterocyclic compound having a single nitrogen atom in the ring. The calculated molecular formula of the compound is C_9H_7N which corresponds to molecular weight of 129.16 g/mol. It is a colorless

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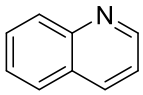
liquid, which turns yellow on standing and possess a characteristic odour of resembling that of pyridine. It has freezing point of -15.6 ℃, boiling point of 237 ℃ and density 1.097. It is hygroscopic, slightly soluble in cold water but dissolve readily in hot water and most organic solvents [1, 2]. The log P value is 2.04 and has an acidic pK_b of 4.85 and a basic pK_a of 9.5. Due to the presence of tertiary nitrogen, quinoline act as weak base and form salt with acids. The chemical properties of quinoline are those that might be anticipated from an amalgamation of those of pyridine and naphthalene. The effect of nitrogen is largely confined to its own ring, which possesses most of the chemical properties of quinoline. Quinoline mainly undergoes addition reaction, ring-opening reaction and substitution reactions (electrophilic and nucleophilic substitution) [3, 4].



(1)

Figure 1: Chemical structure of quinoline

A German chemist, Friedlieb Ferdinand Runge, first extracted the quinoline from coal tar in 1834 and it is still the principal source of quinoline [5]. Later on in 1842, French chemist Charles Gerhardt obtained quinoline by heating alkaloids quinine and cinchonine with potassium hydroxide [6, 7]. Quinoline nucleus also occurs in various natural products obtained from plants like *Cinchona officinalis*, *Camptotheca acuminate*, *Ruta graveolensl* and *Haplophyllum dubium* [8]. It was first isolated from bark of bark of the Cinchona tree by Pelletier and Caventou in 1820 and was used in treatment of malarial until 1930. A diastereomer of quinine i.e. quinidine has totally different pharmacological action and is used in treatment of arrhythmia.

Quinoline nucleus possesses a wide range of pharmacological activities such as anti-bacterial, anti-fungal, local anesthetic, anti-asthmatic, anti-cancer, anti-psychotic, anti-glaucoma and anti-malarial. Due to its versatile nature, a number of derivatives of quinoline have been synthesized and are used in clinical practice. Some of the marketed drugs having quinoline nucleus have been listed in **Table 1**.

Table 1: Marketed drugs having quinoline nucleus

Comp. No.	Drug	Chemical structure	Therapeutic class	Reference

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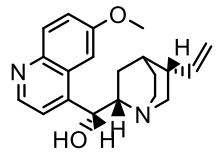
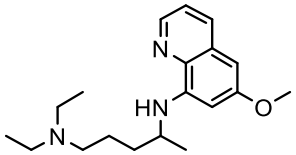
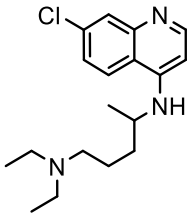
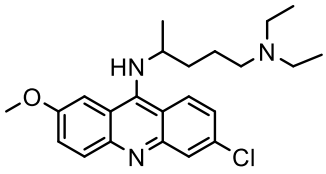
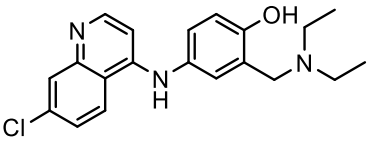
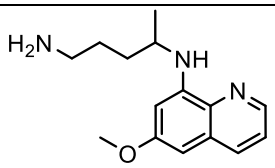
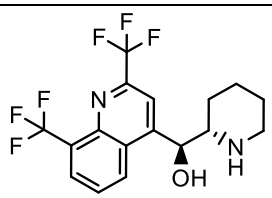
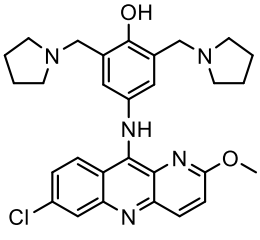
2	Quinine		Anti-malarial	[9]
3	Pamaquine		Anti-malarial	[10]
4	Chloroquine		Anti-malarial	[11]
5	Mepacrine		Anti-malarial	[9]
6	Amodiaquine		Anti-malarial	[12]
7	Primaquine		Anti-malarial	[13]
8	Mefloquine		Anti-malarial	[14]
9	Pyronaridine		Anti-malarial	[14]

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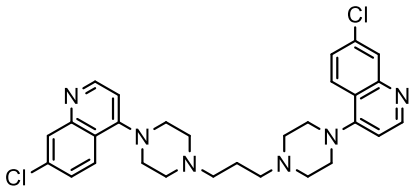
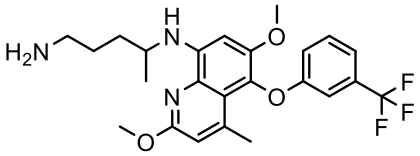
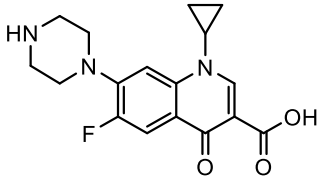
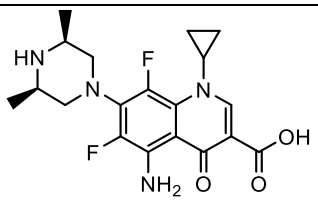
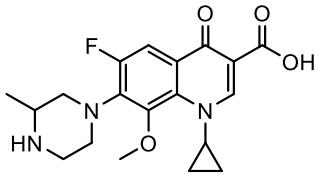
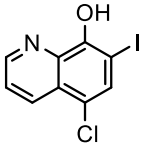
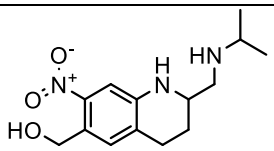
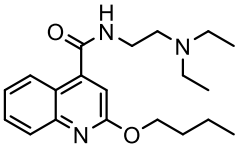
10	Piperaquine		Anti-malarial	[14]
11	Tafenoquine		Anti-malarial	[14]
12	Ciprofloxacin		Anti-bacterial	[15]
13	Sparfloxacin		Anti-bacterial	[15]
14	Gatifloxacin		Anti-bacterial	[15]
15	Cliquinol		Anti-protozoal	[16]
16	Oxamniquine		Anthelmintic	[17]
17	Dibucaine		Local anesthetic	[18]

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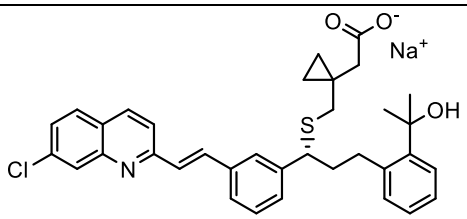
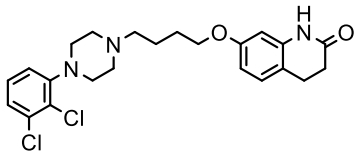
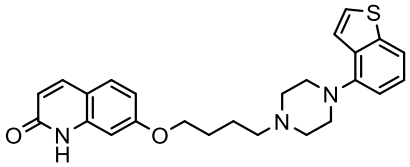
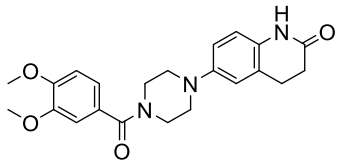
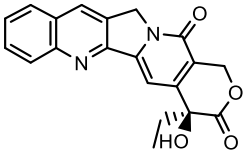
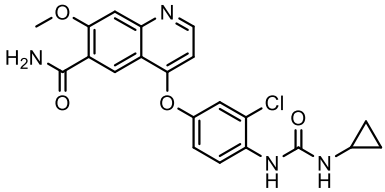
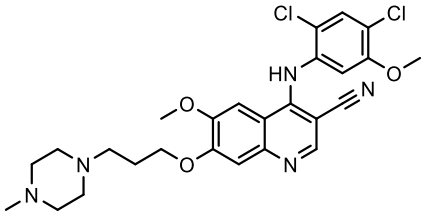
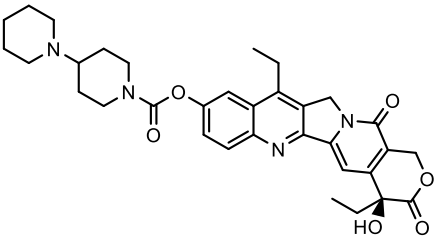
18	Montelukast		Anti-asthmatic	[19]
19	Aripiprazole		Anti-psychotic	[20]
20	Brexpiprazole		Anti-psychotic	[21]
21	Vesnarinone		Cardiotonic	[22]
22	Camptothecin		Anti-cancer	[23]
23	Lenvatinib		Anti-cancer	[23]
24	Bosutinib		Anti-cancer	[23]
25	Irinotecan		Anti-cancer	[23]

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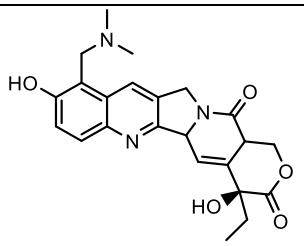
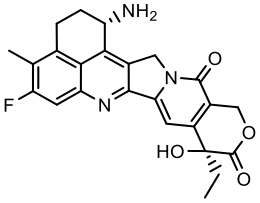
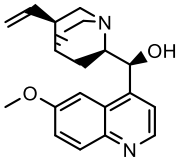
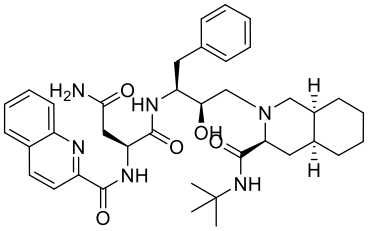
26	Topotecan		Anti-cancer	[23]
27	Exatecan		Anti-cancer	[23]
28	Quinidine		Anti-arrhythmic	[24]
29	Saquinavir		Anti-viral	[25]

2. Synthetic methods

Quinoline was first synthesized by Skraup over a century ago and thus the method is known as Skraup synthesis. The method is used for the synthesis of many quinoline derivatives, provided the substituents present are unchanged by the reaction conditions. In this method, aniline is heated with glycerol, sulphuric acid and oxidizing agent like nitrobenzene, stannic chloride, ferric salts or arsenic pentoxide [26, 27]. The other approaches for the synthesis of quinoline are Combes synthesis [28], Conrad-Limpach synthesis [29], Doebner-Miller reaction [30], Gould-Jacobs reaction [31], Camps synthesis [32], Friedländer synthesis [33], Knorr synthesis [34], Niementowski synthesis [35], Pfitzinger reaction [36] and Povarov reaction [37]. A number of derivatives of quinolines have been synthesized and some of these studies have been discussed below.

3,4-Dihydroquinolin-2-one derivatives (30), which are difficult to synthesize by intramolecular radical cyclization, had been successfully synthesized from 2-iodoanilines and ethyl acrylate

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in neutral reaction conditions by intermolecular tandem reactions involving radical and ionic processes [38].

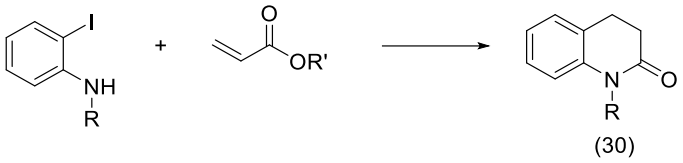

Figure 2: Intermolecular tandem reaction between 2-iodoanilines and acrylates

An efficient method for the synthesis of 4-alkoxy-2-aryl quinolines (31) had been developed which involve heating of 2-(2-trimethlysiyl) ethynyl) aniline with aromatic aldehydes in alcoholic solvents in the presence of sulphuric acid as catalyst [39].

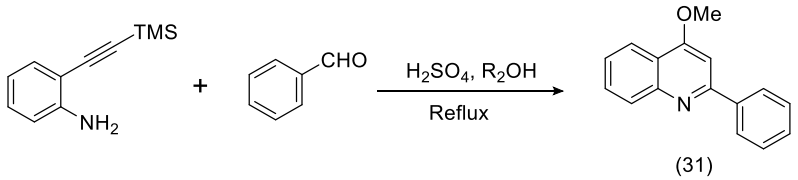

Figure 3: Sulphuric acid catalyzed cyclization of 2-(2-trimethlysiyl) ethynyl) aniline with aldehydes

Transition-metal free indirect Friedländer synthesis of poly-substituted quinolines (32) had been successfully accomplished by the reaction of 2-aminobenzylic alcohol derivatives with ketones or alcohols in the presence of base [40].

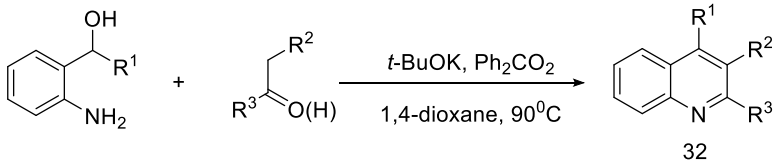

Figure 4: Transition-metal free synthesis of poly-substituted quinolines

2-Phenyl quinoline (33) was synthesized by reacting ethyl vinyl ether or ethyl vinyl sulfide and *N*-arylaldimine in the presence of boron trifluoride etherate to yield 2,4-disubstituted tetrahydroquinolines, which were then converted to 2-phenyl substituted quinolines under vacuum distillation with tosylic acid [41].

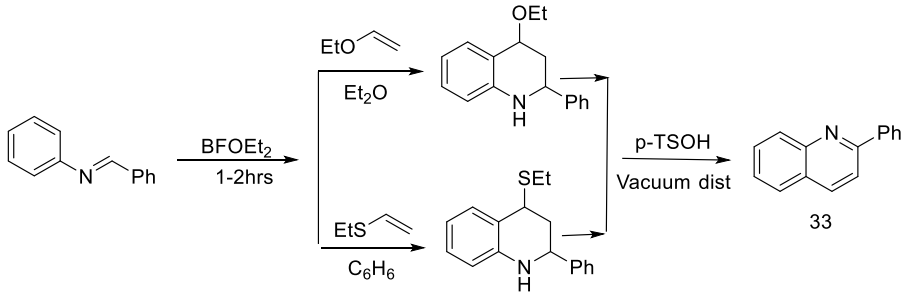

Figure 5: Synthesis of 2-Phenyl quinoline

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Synthesis of quinoline-4-carboxylic acid derivatives (34) from pyruvic acid, aldehydes and amines in the mild conditions in water had been carried out by Doebner reaction using Ytterbium perfluorooctanoate as catalyst [42].

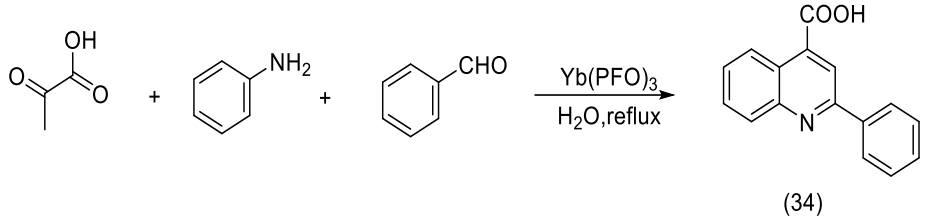

Figure 6: Synthesis of Quinoline-4-carboxylic acid

The condensation and cyclization of two molecules of *o*-halo acetophenones with urea or primary amines gave halogenated quinolines (35) in catalyst-free conditions. The reported method was the first example of catalyst-free cleavage of C(sp^2)-X bond and the formation of C-C bond [43].

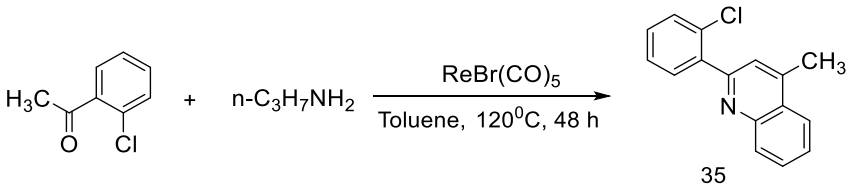

Figure 7: Reaction of *o*-chloro acetophenone with *n*-propylamine affording quinoline derivative

Ultrasound promoted synthesis of quinolines (36) using basic ionic liquids (BIL) in aqueous media has been reported. The reaction involved condensation of isatin with ketones and is considered to be superior method over conventional synthesis due to requirement of mild reaction conditions, short reaction time and results in high yield of product [44].

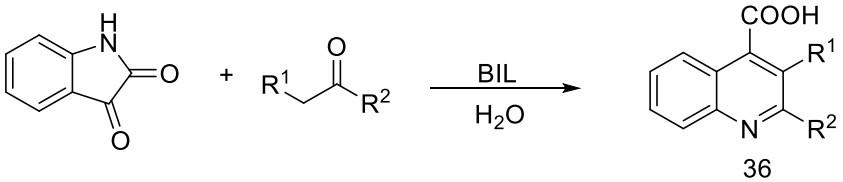

Figure 8: Ultrasound promoted synthesis of quinolines (36) using basic ionic liquids (BIL)

3. Pharmacological actions of quinolines

3.1 Anti-malarial

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Malaria is acute, often severe and protracted, disease caused by parasitic protozoa P*lasmodium falciparum, P. malariae, P. ovale* and *P. vivax* [45]. A huge number of clinically available anti-malarial drug have quinoline nucleus and still this heterocyclic ring is further explored in the search of more potent and less toxic anti-malarial drug.

Two series of novel bisquinoline compounds (37 and 38) that inhibit the growth of both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* had been developed by Raynes and his co-workers. Structure activity relationship studies revealed that the optimum chain length for the linker group is 6 carbons and linking through 8-position is better than through the 6-position. The chlorine substituent at 6-position is not required and may be replaced with amide group [46].

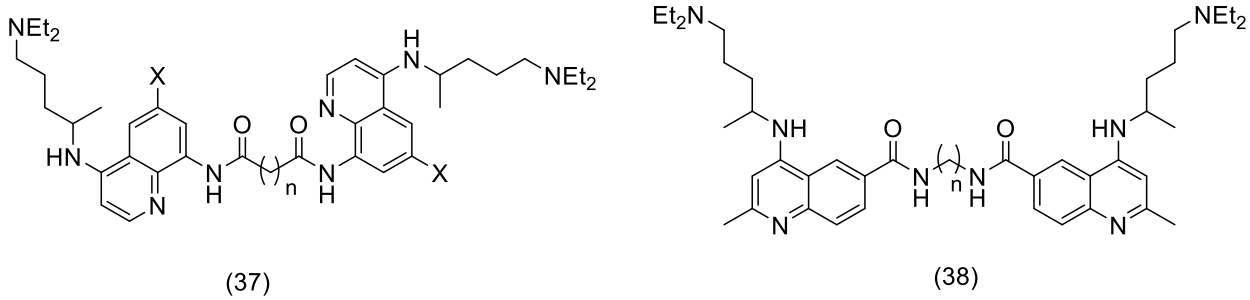

Figure 9: Series of novel bisquinoline compounds

A series of 2-Methyl-6-ureido-4-quinolinamides (39) was found to exhibit anti-malarial activity against chloroquine-sensitive *P. falciparum* strain. The derivatives having 3,4-disubstituted phenyl ring elicited better biological activity. Introduction of chloro and amide group were best suited for anti-malarial activity [47]. [44]

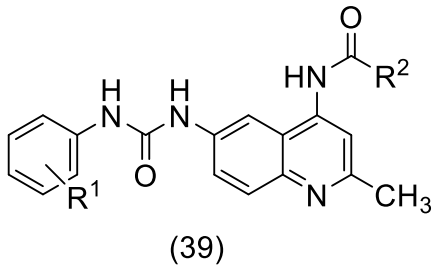

Figure 10: 2-Methyl-6-ureido-4-quinolinamides derivatives

In vitro anti-malarial activity of a new class of hybrid 4-aminoquinoline triazines (40) has been evaluated against chloroquine sensitive strain 3D7 of P. *falciparum*. Compound having piperidine and cyclohexylamine groups was found to be most potent among the different derivatives [48].

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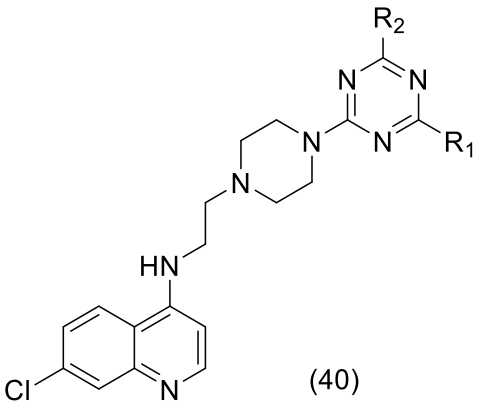
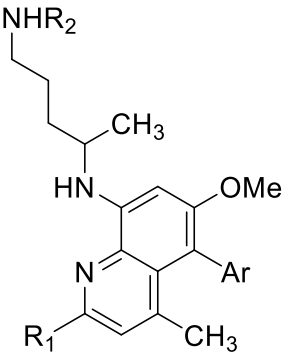


(40)

Figure 11: 4-Aminoquinoline triazine derivatives

A series of 5-aryl-8-aminoquinoline (41) derivatives were screened for anti-malarial activity in order to distinguish the anti-malarial activity of tafenoquine from its hemolytic side effects. The synthesized compounds were found to be metabolically stable in human and mouse microsomal preparations with potency equal to more than primaquine. Analogues with electron donating groups exhibited better activity that those having electron withdrawing groups [49].



(41)

Figure 12: 5-Aryl-8-aminoquinoline derivatives

Anti-malarial potential of hybrid pyridine quinoline molecules (42-44) has been explored in chloroquine sensitive strain of *P. falciparum.* The molecules were found to be very good haem polymerization inhibitors but showed poor antimalarial activity. This was attributed to their low vacuole accumulation ratio in comparison to chloroquine. These molecules can be used as templates for designing new antimalarials targeting haem detoxification pathway of malaria parasite [50].

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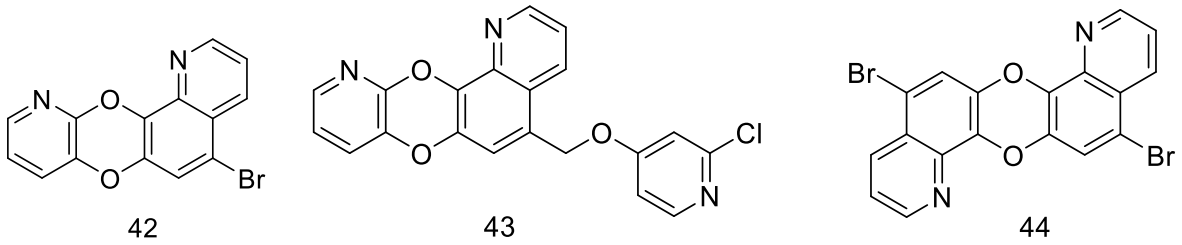
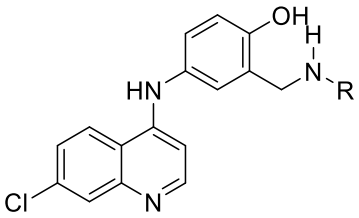


42 43 44

Figure 13: Pyridine-quinoline bis-quinoline hybrids

The anti-malarial potential of 4-anilinoquinoline ring has been explored by Singh and his co-workers in 2011. All the synthesized derivatives (45) were evaluated for anti-malarial activity by in vitro and in vivo evaluation studies against *P. falciparum* and *P. yoelii*. The compound containing morpholine ring was found to be more potent as compared to other derivatives [51].



R = H, Phenyl, Butyl, Isopropyl, n-Butyl

45

Figure 14: Derivatives of 4-anilinoquinoline ring

3.2 Anti-microbial

Microorganism's resistance to conventional antibiotics is major challenge in the treatment of infectious diseases. A few new anti-microbial agents are available in the market and many are in the clinical development stages. The anti-microbial potential of quinoline molecule has been explored in many of the studies and some of these studies have been discusses briefly here.

Anti-microbial activity of quinoline based heterocyclic compounds have been evaluated against both gram positive and gram negative bacteria as well as against fungi. All the synthesized derivatives exhibited potent antimicrobial activities [52].

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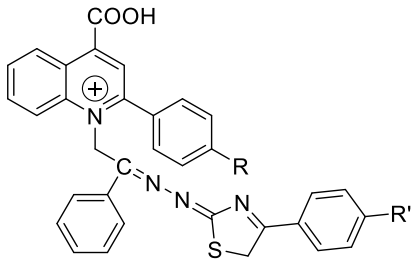

46a-f

(a) R=H; R'=NH_2; (b)R=Cl; R'=NH_2; (c) R=CH_3; R'=NH_2; (d) R=H; R'=H; (e) R=Cl; R'=H; (f) R=CH_3; R'=H

Figure 15: Anti-microbial activity of synthesized quinoline derivatives

In vitro anti-bacterial potential of novel triazolo[4,3-a]quinoline derivatives have been evaluated against both gram positive and gram negative bacteria by agar well diffusion method. The compounds having pyrazole moiety were found to be more potent against gram positive bacteria [53].

3.3 Anti-cancer

5-Oxo-2,4,5,6-tetrahydro-1H-thiopyrano[3,4-c]quinoline-9-carboxamide derivatives, a poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors, were prepared from carboxylic acid and amine and evaluated by cell based assay [54].

4. Conclusion

Quinoline is a versatile nucleus having a wide range of pharmacological activities such as anti-malarial, anti-inflammatory, anti-asthmatic, anti-bacterial, anti-tuberculosis, anti-hypertensive, anti-cancer, anti-HIV and anti-amoebic. Although most of anti-malarial compounds available in the market are based on quinoline nucleus, but this heterocyclic ring exhibits potential in other therapeutic areas also. In order to explore more applications of this nitrogen containing heterocyclic ring, a number of derivatives of quinoline have been synthesized by different group of scientists and evaluated for different pharmacological activities. In many cases, potency of the synthesized compound was found to be comparable to already marked drugs; hence further investigations are required.

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