Chapter 7

Importance of quinazoline and quinazolinone derivatives in medicinal chemistry

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Chapter outline

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Introduction

Medicinal chemistry is concerned with the discovery, development, and synthesis of the target compounds in the laboratory and identification of the physical and chemical properties, which are followed by the evolution of the drug characteristics. Quinazoline is one of such moiety in medicinal chemistry with plenty of opportunity to screening over various diseases. Quinazolinone (Fig. 7.1) [(Quinazoline-4(3H)-1] is one of the fused heterocyclic compounds, and quinazoline with the keto group is found in more than 200 natural products. Quinazolinone has the molecular formula $C_8H_5N_2O$; it is a bicyclic compound with two six-membered rings, and the benzene ring is fused with the pyrimidine ring consisting of two nitrogen's as the heteroatoms. This fused bicyclic compound is known as benazo1,3,diazine [1].

In 1887, Weddige proposed the name for the above structure as quinazoline because, on observing the quinazoline structure, it seems to be like the isomeric of the compound cinnoline and quinoxaline [2]. The history of quinazoline was established in 1869 when the Greek people synthesized the quinazoline derivatives like 2-cyano-3,4-dihydro-4-oxoquinazoline. In 1903 quinazoline was synthesized by the oxidation of 3,4–dihydroquinazoline by alkaline potassium ferricyanide in good yield [3]; from a half century of this onwards, medicinal scientists have taken more interest in the synthesizing and bioactivity of quinazoline. From the traditional Chinese herb *Dichroa febrifuga*, a quinazolinone alkaloid derivative called 3-[β-keto-g-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone was isolated, which is found to be an excellent antimalarial compound [4].The representation of the quinazoline and different structures of quinazolinone are shown in Fig. 7.2.

Based on the positions of the keto or oxo group, the compounds are classified into two types: (1) 2-(1H) quinazolinones and (2) 4-(3H)quinazolinones [5]. 4-hydroxy quinazoline tautomeric with 4-keto-3, 4-dihydroquinazoline [4(3H)-quinazolinone] is popularly known as 4-quinazolinone, this tautomerism mechanism is shown in Fig. 7.3. Thus, the oxidation of quinazoline can be converted into quinazolinone.

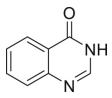


FIGURE 7.1 Structure of quinazoline-4(3H)-one.

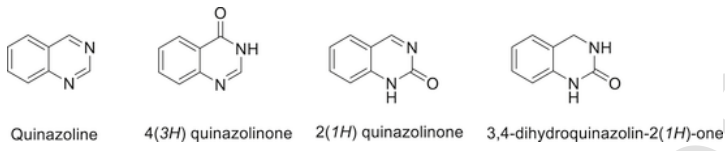


FIGURE 7.2 Core structures of quinazoline and the quinazolinones.

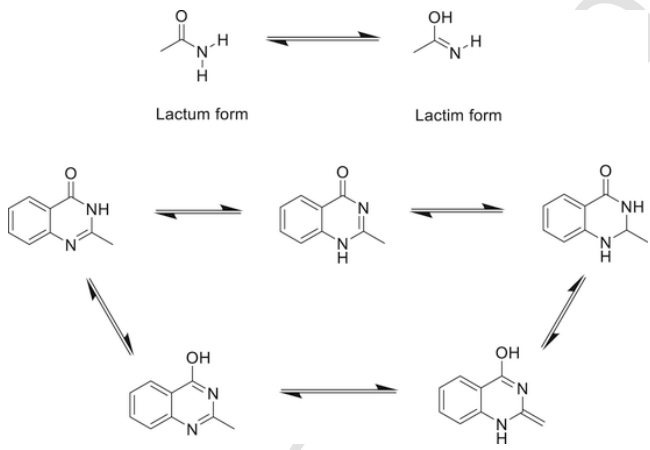


FIGURE 7.3 Representation of the different tautomeric forms of 2-methyl-4(3H)-quinazolinone.

This quinazolinone exhibits a variety of biological activity, such as antitumor [6], antifungal [7], anticancer [8], antihuman immunodeficiency virus (anti-HIV) [9], antibacterial [10], antiinflammatory [11], and quinazolinone derivatives substituted with two- and three-positions exhibited the excellent antihypertensive activity [12]. Some of the marketed drugs in the field of pharmaceuticals are shown in Fig. 7.4. Besides marketed drugs, a wide variety of quinazoline drug molecules are synthesized, reported, and mapped for various biological activities. Because of this wide variety of biological applications, quinazolinone becomes the researcher's interest. The various new drug development programs resulted in quinazolinone derivatives that are less toxic to normal cells [13,14]. Moreover, many of the synthetic methods reported in the literature were ecofriendly, using green methods, and with less toxicity to the environment [15]. The basic moiety quinazoline is not considered a hazardous substance per the Occupational Safety and Health Administration (OSHA) Hazardous Communication Standards. The present review aims to discuss various reported methods for the synthesis of quinazolinone derivatives, highlighting their evolution toward different bioactive compounds and to

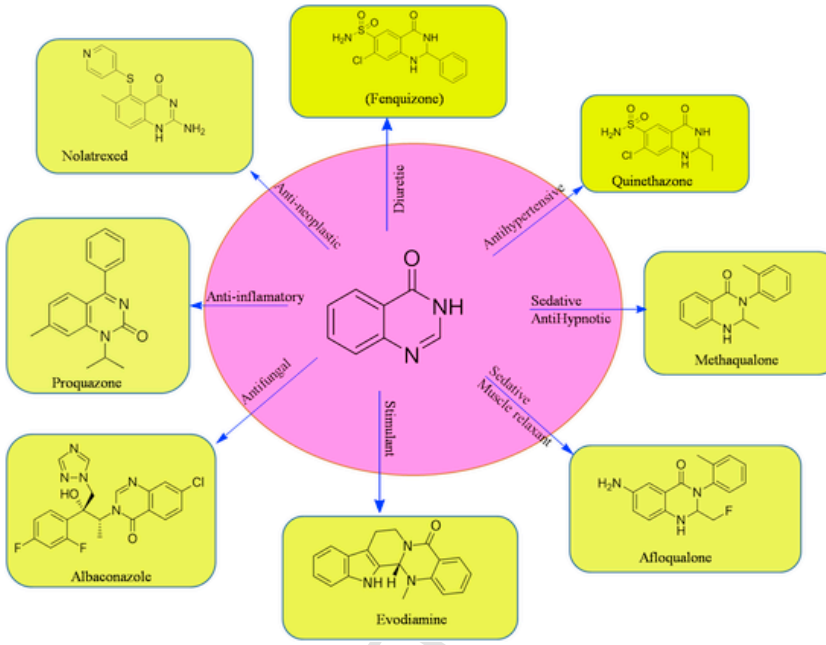
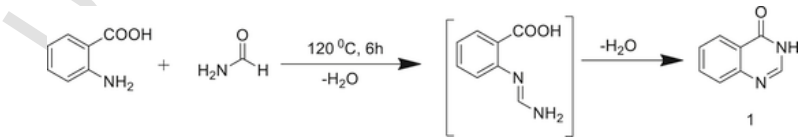


FIGURE 7.4 Privileged scaffold quinazolinone in marketed drugs.

summarize the scaffold of quinazoline in organic chemistry and their structure-activity relationship.

Methods of synthesis of 4(3H)-quinazolinone

In 1869, the first ever effort took place for the synthesis of 2-ethoxy-4(3H)-quinazolinone from the anthranilic acid and the cyanide in ethanol [16]. When anthranilic acid is heated in an open container with an excess of formamide at 130°C, which forms the 4(3H)-quinazolinone. This reaction involves the elimination of water molecules and proceeds via an *o*-amidobenzamide intermediate as shown in Scheme 7.1 [17]. The resultant method of synthesis of quinazolinone is called Niementowski synthesis. Later, this method was modi-



SCHEME 7.1 The Niementowski reaction.

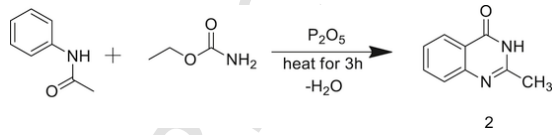
fied by Bessen et al. with the application of the microwave technique to get a better yield in an ecofriendly manner.

Another effective method for the synthesis of quinazolinone is from the condensation of a urethane derivative with aniline. The reaction between the urethanes and acetanilide on refluxing 3 h in the presence of phosphorous pentaoxidein toluene gives the 2-methyl-4(3H)-quinazolinone as shown in Scheme 7.2.

4(3H)-quinazolinone can also be synthesized by the corresponding *N*-acyl anthranilic acid on heating with ammonia or substituted primary amines. For example, 2-methyl-3-alkyl-6-nitro-4-(3H) quinazolinones can be prepared from the *N*-acyl-5-nitroanthranilic acid and various primary amines on heating above 100°C [18]. The overall reaction in this method is condensation of anthranilic acid with the formic acid or acylation and followed by reaction with the variety of primary amines. The schematic representations are shown in Scheme 7.3.

The above condensation reaction can also be synthesized by the application of PCl_3. This reaction o-amino benzoic acids heated with an amine in the presence of phosphorous trichloride in toluene for 2 h gave 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines as shown in Scheme 7.4.

Bartel et al. (2009), synthesized the quinazolinone derivatives by the one-pot method from the reaction between 2-amino-5-chlorobenzophenone and



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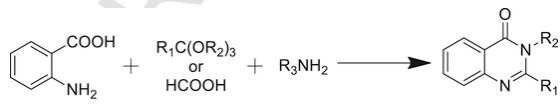
SCHEME 7.2 Synthesis of 2-methyl-4-(3H)quinazolinone.



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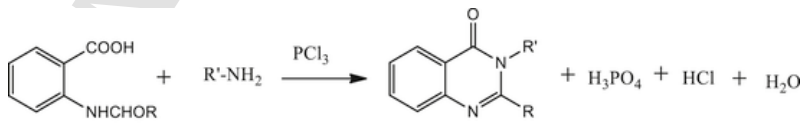
SCHEME 7.3 Condensation of anthranilic acids with primary amines.



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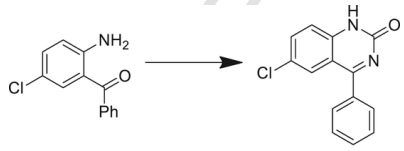
SCHEME 7.4 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines derivatives.

chlorodulfonyl isocyanate in the presence of dichloromethane as a solvent in good yield[18] [19]. This is the simple one-pot method for the preparation of 4-(3H)-quinazolinone (Scheme 7.5).

The synthesis of quinazolinone derivatives also achieved by the cyclo-condensation of anthranilamide and an aldehyde is performed in acid catalysis, for example, HCl in EtOH [20], or in association with concentrated HNO_3 [21] was used as a catalyst under reflux conditions; the same reaction can also carried out the presence of a catalytic amount of H_2SO_4 or *p*-TSA [22] (Scheme 7.6).

The quinazolinone compounds are also prepared by anthranilamide and 1-naphthaldehyde in the basic conditions (NaOH or NaOEt), by refluxing with absolute ethanol. But the drawback of the reaction is of low yield (65%–80%) [23,24]. Wang et al. synthesized the quinazolinone derivatives from the reaction of 2-aminobenzamides and triethyl orthoformate or triphosgene in the ionic liquid of $[BMIm]BF_4$ at 80°C; the reaction is catalyzed by iodine in good yields (Scheme 7.7) [25].



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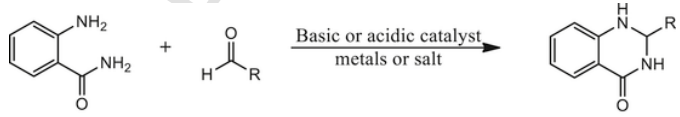
SCHEME 7.5 Synthesis of quinazolinone from 2-amino-5-chlorobenzophenone.



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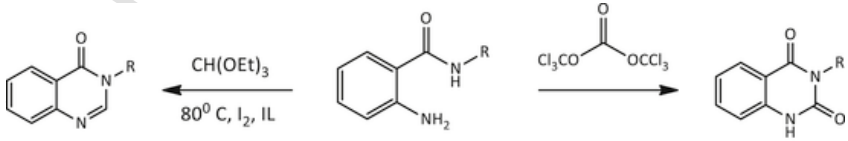
SCHEME 7.6 Cyclo-condensation of anthranilamide and aldehyde under conventional conditions.



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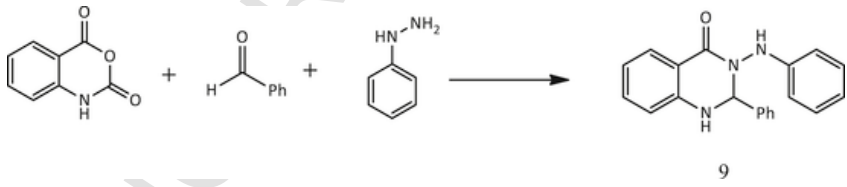
SCHEME 7.7 Synthesis from 2-aminobenzamides

Khandebharad et al. has developed a methodology for the synthesis of quinazolinone derivatives from benzaldehyde, isatoic anhydride, and phenyl hydrazine catalyzed by triethanolamine (TEOA) in the presence of NaCl as aqueous media under reflux condition via a one-pot multicomponent reaction (Scheme 7.8). Here the addition of the NaCl controls the formation of micelles and increases the hydrophobic nature [26].

Another strategy for the synthesis of quinazoline is the application of a metal catalyst for the cyclization; here, 2-amino benzoic acid and amines undergo condensation in the presence of $SiCl_4$ leads to the formation of corresponding anthranilamides. The intermediate anthranilamide undergo a reduction in the presence of sodium metal (bis(2-methoxyethoxy)-aluminum hydride) gives the o-amino benzylamines. In the final step it undergoes cyclization in presence of ethylchloroformate/pyridine [27] *p*-toluenesulfonic acid [28], copper-catalyzed cyclo-condensation [29] leads the formation of quinazolinone. Quinazolinone can also be prepared by reduction from 4(3H)-quinazolinones by $NaBH_4$ [30], $NaBH_4CN$ [31]. Transitional metal salts are also efficiently used for the cyclo-condensation of anthranilamide and aldehyde, among them Scandium [32], ytterbium [33,34] and yttrium [35]. Quinazolinone can also synthesize from the cyclization of dicyanoepoxide with anthranilamide in the presence of acetonitrile as a solvent [36] (Scheme 7.9).

Furthermore, alum [$KAl(SO_4)_2 \cdot 12H_2O$] [37], citric acid [38], and thiamine hydrochloride (VB1) [39] were used for the catalysis of one-pot three-component reaction in aqueous media, even though the protocols were longer (up to 7 h) but reported to be environmentally safe.

The one-pot three-component reaction of the synthesis of quinazoline was also efficiently performed under solvent-free conditions. By conventional heating method or microwave irradiation without using the catalyst leads to



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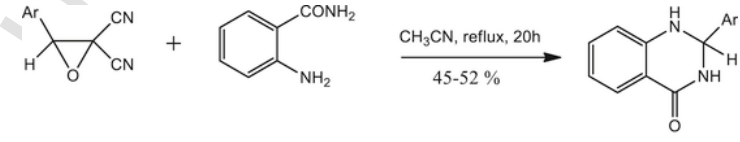
SCHEME 7.8 Synthesis of 2,3-dihydroquinazolin-4(1H)-ones from aldehyde.



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SCHEME 7.9 Synthesis of Quinazolinone from dicyanoepoxide.

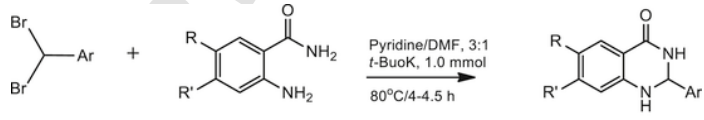
the 74%–97% yield but it takes a longer reaction time, which is a drawback of the reaction (1–6 h) [40–42].

Another method for the synthesis of benzoquinone is from 2-aminobenzonitrile and aldehydes, where formation of Schiff base takes place in the first step, subsequent cyclo-condensation in the presence of various catalysts. The yield of the reaction is over 18%–98%, and the time taken for the reaction is 0.5–8 h [43,44].

Recently one-pot tandem approach reported for the synthesis of 2,3-dihydroquinazolin-4-(1H)-ones from gem-dibromo methylarenes, in substituted anthranilamide and potassium tertiary butoxide as a base in DMF and pyridine (1:3 ratio) at reflux conditions in a good yield, but the drawback of this experiment is regarding the solvent (Scheme 7.10) as pyridine is not an ecofriendly solvent for synthesis [45].

Quinazoline also can be synthesized by the imino Diels–Alder reaction by the coupling reaction between imine and electron-rich alkenes [46,47]. In the Povarov imino Diels–Alder reaction, aniline is chosen for the reactant and ethyl glyoxylate as a substrate. In this reaction, two molecules of α-iminoesters, formed by the condensation reaction, further undergo cyclization to form the product. Chen et al. were extended from the Povarov imino Diels–Alder reaction by application of the various kinds of Lewis acid as catalysts, then followed by the refluxing with toluene for 24 h [48]. By screening the various catalysts and different conditions, it is optimized that $CuBr_2$ is an efficient catalyst for the synthesis of quinazoline derivatives (Scheme 7.11).

Aza-Wittig reaction is widely used for the synthesis of *N*-heterocycles, which is generally carried under mild reaction conditions [49]. He et al. reported the synthesis of indolo[1,2-c]quinazolines recently by Staudinger–Aza-



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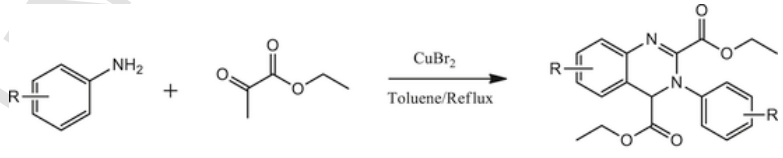
SCHEME 7.10 Synthesis of 2,3-dihydroquinazolin-4(1H)-ones.



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SCHEME 7.11 Synthesis of 2,3-dihydroquinazolin-4(1H)-one by Povarov imino Diels–Alder reaction.

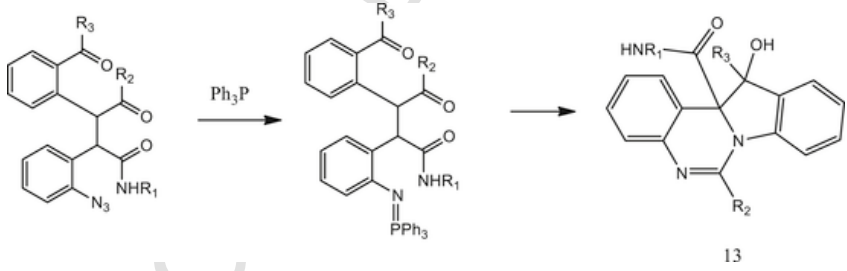
Wittig–Nucleophilic addition reaction; in this reaction the main synthetic procedure is the reaction between azides and triphenyl phosphine in toluene, stirred for 2h at RT and followed by refluxing for 6–24 h [50]. Here nitrogen is evolved through the Staudinger reaction halted during the initial 2 h and after refluxing gives the final product indolo[1,2-c]quinazolines (Scheme 7.12).

Ding et al. reported the method for the synthesis of 2-alkoxy 3H-quinazolin-4-ones, in this reaction novel quinazoline alkoxy derivatives were synthesized from carbodiimide, which is synthesized from carbodiimide imino-phosphorane and aromatic isocyanate [51] (Scheme 7.13).

Microwave-assisted synthesis

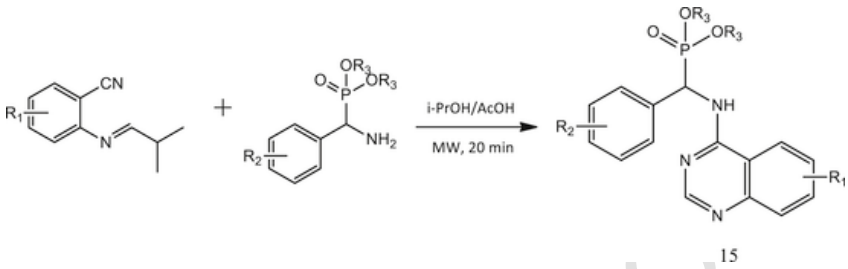
Compared to the traditional synthesis, microwave-assisted reaction can shorten the reaction time and give the product high purity. Microwave-assisted reactions are ecofriendly and are called green synthetic methods. Many quinazoline derivatives are also synthesized from the application of microwaves. Luo et al. reported the first microwave-assisted quinazoline derivatives containing α-amino phosphonate synthesis [52]. Here *N*′-(substituted-2-cyanophenyl)-*N,N*-dimethyl-formamidine derivatives react with dialkylamino (phenyl) compounds undergo cyclization on irradiation of microwave at 100°C (100 psi pressure) for 20 min in the presence of the solvent isopropanol and acetic acid (1:4) (Scheme 7.14).

Kidwai et al. synthesized quinazoline derivatives by heating an equimolar amount of aldehyde, urea/thiourea and 5,5-dimethyl-1,3-cyclohexanedione



SCHEME 7.12 Synthesis of indolo[1,2-c]quinazolines from azides.

SCHEME 7.13 Synthesis of 2-alkoxy quinazolines.



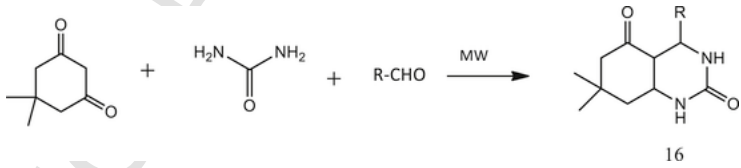
SCHEME 7.14 Microwave-assisted synthesis of quinazolines.

(dimedone) under microwave irradiation in the absence of solvent and catalyst [53] (Scheme 7.15).

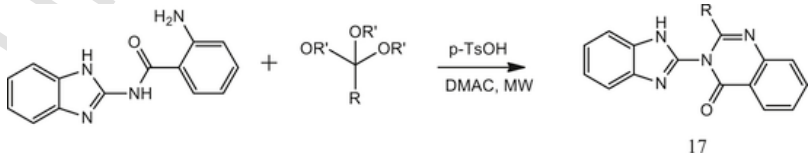
Hazarkhani et al.synthesized the fused quinazoline derivative from the isatoic anhydride and 2-aminobenzimidazole with DMAC as a solvent; they got 2-amino-*N*-(1-H - benzimidazol-2-yl) benzamide as an intermediate under microwave irradiation [54]. The intermediate formed in the first step has a nucleophilic center, so it undergoes an electrophilic substitution reaction, followed by cyclization, to form the product as 3-benzimidazolyl-4(3H)-quinazolinone in 95% yield (Scheme 7.16).

Intramolecular cyclization of Schiff's bases

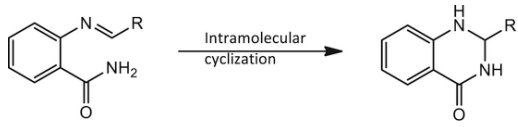
Quinazoline derivatives can be synthesized from the intramolecular cyclization of the Schiff's bases in different conditions and yields are varied from 42% to 99% in 1–16 h. The time required for the reactions is more in the presence of a strong base and time can be reduced by adding molecular nitrogen and metal oxide nanoparticles [55] (Scheme 7.17).Various reaction condi-



SCHEME 7.15 Microwave-assisted synthesis of quinazolines.



SCHEME 7.16 Microwave-assisted synthesis of 3-benzimidazolyl-4(3H)-quinazolinone.



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SCHEME 7.17 Synthesis of quinazoline by intramolecular cyclization.

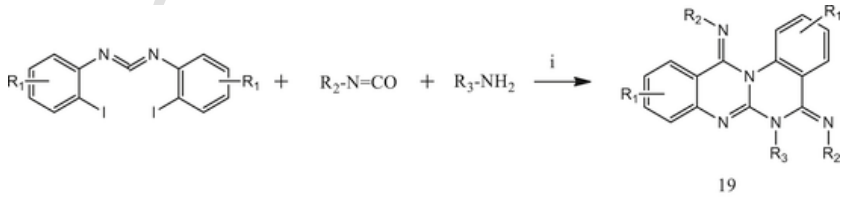
tions and time taken for completion of these intramolecular cyclization are shown in Table 7.1..

Metal-mediated reactions

Palladium-mediated metal-catalyzed coupling reaction plays an important role in synthetic organic chemistry as an efficient method for forming a C–C bond. In the synthesis of quinazoline derivatives, we can also apply the palladium-catalyzed coupling reaction. Qiu et al. synthesized quinazolino[3,2-a]quinazoline derivative via palladium-catalyzed three-component synthesis (Scheme 7.18). In this reaction amine (3.0 equivalent), isocyanide (3.0 equivalent), carbodiimide (0.2 mmol), $Pd(OAc)_2$(5 mol%), and Cs_2CO_3 (3.0 equivalent) in 3.0 mL toluene undergo one-pot reaction, and observed yields were satisfactory [60].

TABLE 7.1 Different conditions for intramolecular cyclization.

Substrate	Conditions	Time	% Yield	Refs.
Schiff base	NaH, THF, 0°C to RT	16 h	42–91	[55]
	N_2, EtOH, reflux	6h	83	[56]
	Fe_2O_3 NPs, EtOH, reflux	1–3.5 h	94–98	[57]
	AcOH, reflux	1.5h	80–92	[58,59]



19

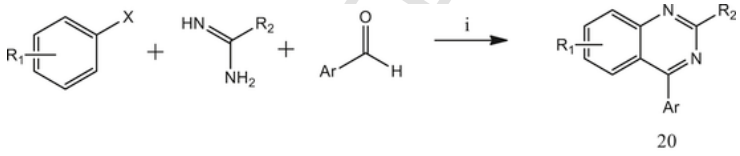
Where i) $Pd(OAc)_2Cs_2CO_3$and toluene

SCHEME 7.18 Synthesis of quinazolino[3,2-a]quinazoline derivative via palladium-catalysis. Where (i) $Pd(OAc)_2Cs_2CO_3$ and toluene.

McGowan et al. reported the synthesis of quinazoline derivatives by a palladium-catalyzed one-pot synthesis [61]. In this reaction, *N*-arylation of both aryl and alkyl amidines with a wide range of aryl bromides, chlorides, and triflates were described, reported yields of this reaction varies over a range of 32%–54% (Scheme 7.19).

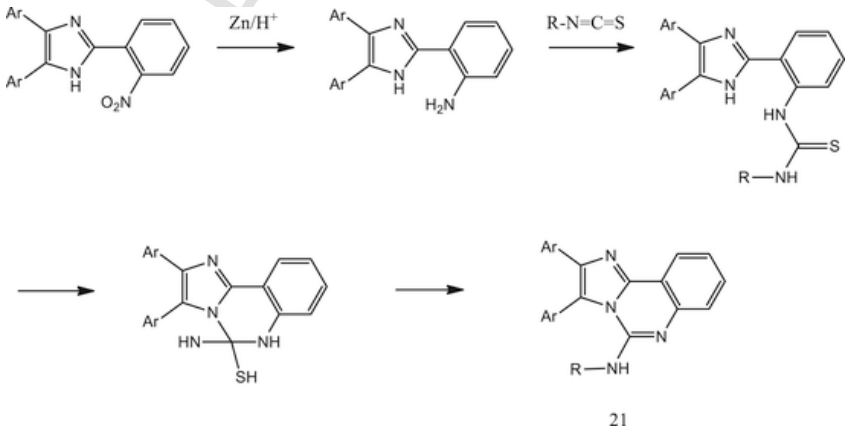
Zinc-reduced catalyst

Zinc is the most efficient metal found to participate in the water-phase Barbier reaction. It could catalyze the allylation of carbonyl and carbonyl compounds as well as participate in the benzylation of carbonyl and some special alkylation. Also, zinc participates in carbon-oxygen and carbon-nitrogen double bond barrier reaction. Shi et al. reported the synthesis of imidazo[1,2-c]quinazoline derivatives by 2-(2-nitrophenyl)-1H-imidazoles was reduced by Zn/H^+ to 2-(2-amino phenyl)-1H-imidazoles, which then reacted with isothiocyanates to get intermediate [62]. Further cyclization of an intermediate compound by a nucleophilic attack to the nitrogen atoms on C=S group, in the final step intermediate, loses H_2S to get desired products as shown in Scheme 7.20.



Where i) $Pd(OAc)_2$and Cs_2CO_3 , toluene

SCHEME 7.19 Synthesis of quinazoline derivative from metal catalyst. Where (i) $Pd(OAc)_2$ and Cs_2CO_3, toluene.



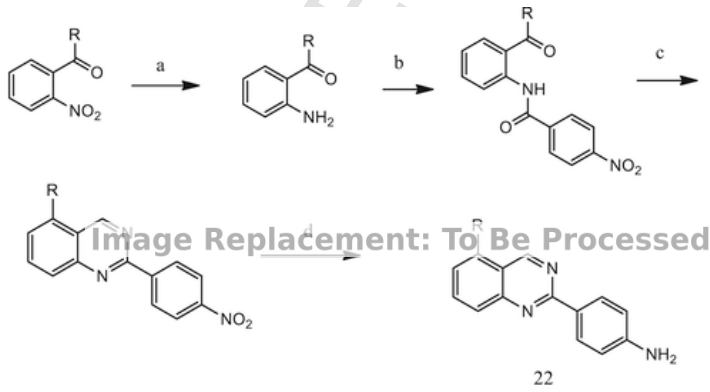
SCHEME 7.20 Synthesis of imidazo[1,2-c]quinazoline derivatives.

Ultrasound assisted synthesis

Bischler cyclization and other traditional reaction methods have also application to the synthesis of quinazoline derivatives, but the drawback of these methods is the requirement of critical reaction conditions such as high temperature (120°C), high pressure, long reaction times, and so forth [63]; this is the major drawback of the reactions. Such a reaction can be easily carried out by the application of ultrasound assistance. Various syntheses of quinazoline are involved by applying ultrasound; in this method, the passing of ammonia through a mixed melt of the amino compound and sodium acetate at a temperature higher than 160°C, Zhang et al. reported a synthesis of quinazoline derivative with ultrasound assistance, and in this reaction ultrasound is used for the cyclization of the amide compound [64] (Scheme 7.21).

Phase transfer catalyst

Phase transfer catalyst (PTC) is one of the promising and special methods for the synthesis of organic compounds, it facilitates the migration of the reactant from one phase to another phase, it is a special application in heterogeneous catalysis. PTC is widely used in organic preparation, heterocyclic compound synthesis, polymer chemistry, agrochemical, organometallic chemistry, and so forth. Khalil synthesized the quinazoline derivatives by the application of dioxane/anhydrous potassium carbonate acting as liquid/solid phases, and Tetrabutylammonium bromide (TBAB) act as the catalyst [65]. In this reaction



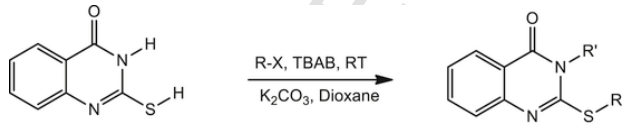
SCHEME 7.21 Synthesis of quinazoline derivatives by the use of ultrasound. Where (a) Iron powder, concentrated HCl, ethanol/water (5:1), 50°C; (b) 4-nitrobenzoic acid chloride, TEA, DCM, 0°C; (c) 25% ammonia water, ultrasound 250 W, 80°C, 3 h; (d) iron powder, concentrated HCl, ethanol/water, 50°C.

2-mercapto quinazolin-4(3H)-one was stirred with halo organic reagents under optimal conditions at 25°C for 2–4 h. Then they reacted with ethyl bromide, allyl bromide, bromoactylacetone, and diethyl malonate bromide by the molar ratio of 1:3, and afforded a series of quinazoline derivatives via S-monoalkylation. While here, synthesis of the target compound was achieved by the simultaneous *S*- and *N*-dialkylation (Scheme 7.22).

From Isatins

α-Isatin oxime rearranges to 1,2,3,4- tetrahydro-2,4-dioxoquinazoline on heating with dilute sodium hydroxide, in this reaction β-imino derivatives of isatin, was formed oxidation with hydrogen peroxide in alkaline solution to form the dioxoquinazoline (Scheme 7.23).

The Niementowski reaction has application in the synthesis of dioxoquinazoline, here the title compound can be synthesized from the reaction between anthranilic acid and urea. The fusion of anthranilic acid with urea gave 1,2,3,4-tetrahydro-2,4-dioxoquinazoline (Scheme 7.24).



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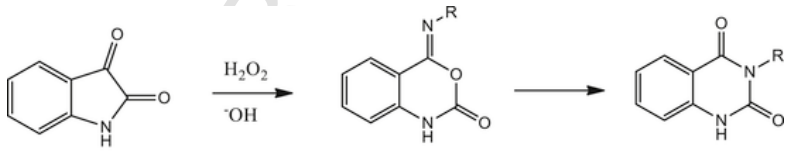
SCHEME 7.22 Synthesis of quinazoline derivatives by using PTC.



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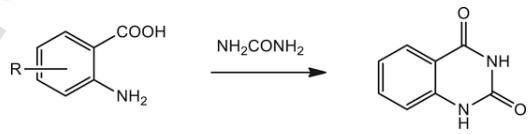
SCHEME 7.23 Synthesis of dioxoquinazoline from isatin.



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SCHEME 7.24 Synthesis of dioxoquinazoline from anthranilic acid.

Sen and Ray's synthesis

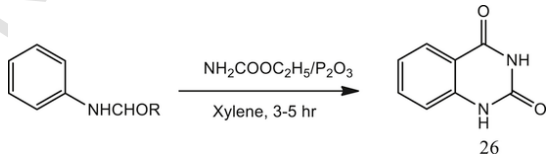
In this reaction synthesis of oxoquinazoline carried out by butyrylanilides and urethane, here boiling a solution of normal or isobutyrylanilides with urethane and phosphorous pentoxide in xylene solution gives 2-propyl and 2-isopropyl-3,4-dihydro-4-oxoquinazolines [66] (Scheme 7.25).

Biological importance of 4(3H)-quinazolinone

In the olden days, natural substances were used for their nutritional value and also for the treatment of diseases. But the drawback of natural substances is that of toxic or lethal effects. From the 19th century, new methods were brought by the treatment of diseases with synthetic drugs, even though the modification of natural products through the synthetic process gives useful semisynthetic drugs. The improvement of the lifestyle has been greatly influenced by the advancement in the field of medicinal chemistry, which makes it a much-advanced invention in synthetic chemistry because the tautomerism and stability of the molecule influenced the further reaction to the quinazolinone and inspired the synthesis of many types of conjugated derivatives.

Antimicrobial activity

Certain species of microorganisms capable of causing several diseases and infections to animals like amebiasis, typhoid, malaria, common cold, cough, tuberculosis, influenza, syphilis, acquired immune deficiency syndrome (AIDS), and so forth, which threaten mankind, is a matter of scientific concern. In the history of medicinal chemistry, many attempts have been made to develop new structural models for the invention of more effective antimicrobials, but still, quinazoline derivatives remain one of the important compounds against microbes; some of them are discussed here and structures are shown in Fig. 7.5. Albaconazole (27) is the triazole conjugated 7-chloro quinazolinone derivative, which is the marketed drug that acts as the antifungal agent. The same compound also acts as inhibitors of CYP450 hepatic enzymes [67]. Dahiya et al. synthesized the dipeptide and tripeptide derivatives of Iodo-quinazolinones (28) and screened for the antimicrobial activity and anthelmintic activity. In the synthesized compound tyrosine conjugated quinazolinone derivative ex-



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SCHEME 7.25 Synthesis of dioxoquinazoline from Sen and Ray method.

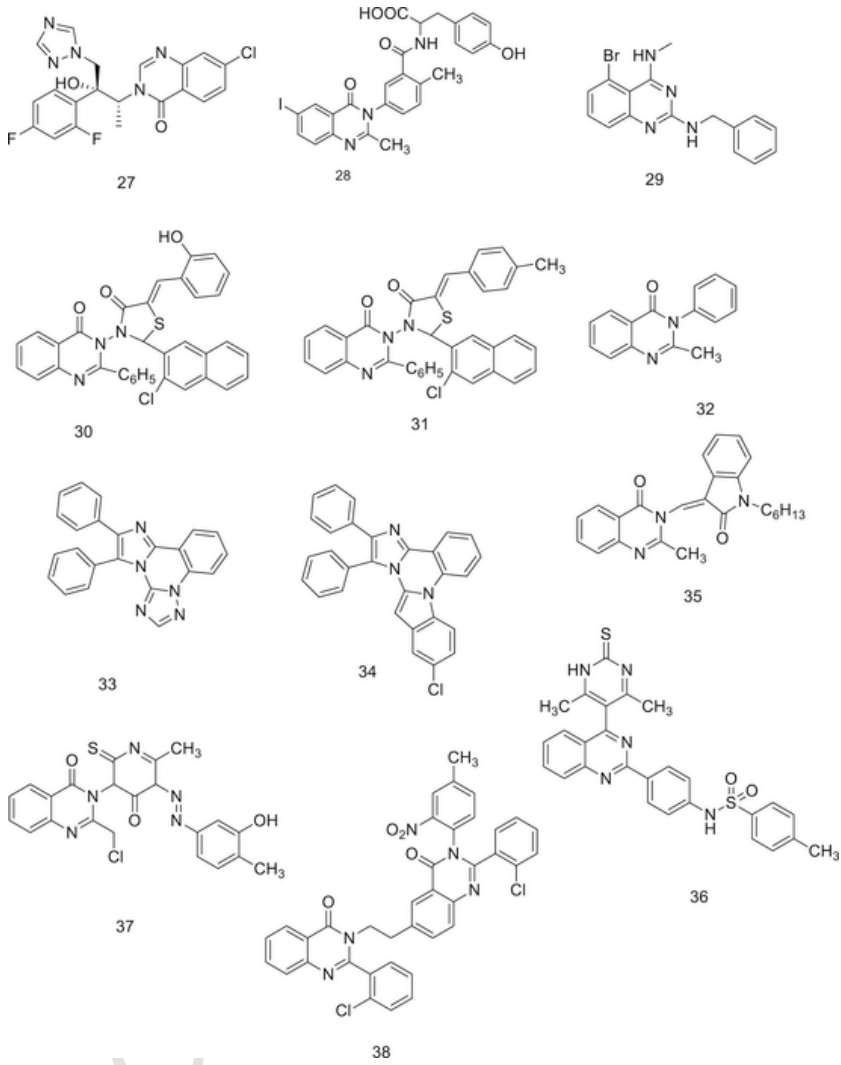

FIGURE 7.5 Antimicrobial activity of the compounds.

hibited excellent antimicrobial activity against *P. aeruginosa, K. pneumonia, C. albicans*, and comparable anthelmintic activity [68].

Fleeman et al. synthesized the N^2,N^4-disubstituted quinazoline-2,4-diamines (29) as dihydrofolate reductase inhibitors with potent *in-vitro* and *in-vivo* antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strain. In the series of the synthesized compounds, a bromo-substi-

tuted derivative was marked for the superior activity, with MIC as low as 0.5 μM concentration [69].

Desai et al. synthesized a series of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-ones have been synthesized. In the synthesized compound hydroxyl (30) and 4-methyl (31) substituted compounds exhibited superior activity and MIC value 50 μg/mL for *E.coli,* showed remarkable activity for *P. aeruginosa, S. aureus,* and *C. albicans* [70].

Nagar et al. synthesized 2,3-di-substituted quinazolin-4-(3H)-ones and its derivatives have been synthesized as a one-pot procedure from the reaction of Anthranilic acid, acid chlorides and different primary amines with the intermediate 4-(3H)-benzoxazinone to give the disubstituted quinazoline derivatives, in which methyl and phenyl substituted compound (32) exhibited the superior activity in the series [71]. Nadwana et al. synthesized a new class of fused quinazolines derivatives via copper-catalyzed Ullmann type C–N coupling followed by intramolecular cross-dehydrogenative coupling reaction. The synthesized compounds were tested for *in-vitro* antibacterial activity against three Gram-negative (*Escherichia coli, Pseudomonas putida, and Salmonella typhi*) and two Gram-positive (*Bacillus subtilis, and Staphylococcus aureus*) bacteria. Here some of the compounds exhibited superior activity (4–8 μg/mL). The bactericidal assay by propidium iodide and live-dead bacterial cell screening using a mixture of acridine orange/ethidium bromide (AO/Et·Br) showed considerable changes in the bacterial cell membrane, which might be the cause or consequence of cell death. Here triazole (33) and indole (34) substituted quinazoline derivatives showed good activity. Activity increases with halogen substitution in indole moiety [72].

Aza-isatins derivatives containing 4(3H) quinazolinones have been designed and synthesized by Devi et al. compounds showed antibacterial activity against Gram-positive bacteria *Bacillus subtilis, Staphylococcus aureus, Streptococcus pneumonia*, and Gram-negative bacteria *Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and four fungi *Aspergillus niger, Aspergillus flavus, Candida albicans*, and *Fusarium oxysporium* at 10 μg/mL [73]. Compounds with hexane (35) substitution showed superior activity and activity decreases with a decrease in the length of the carbon chain. Annelated quinazoline derivatives viz 1,2,4-triazino[4,3-c]quinazoline, thiazolidinylquinazoline, quinazolino[4,3-b]quinazolin-8-one, imidazoquinazolines were synthesized from 4-methyl-*N*-[4-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl]benzene-sulfonamide by Aly, who reported the antimicrobial activity [74]. In this series compound with a p-toluene sulfonamide (36) exhibited superior activity.

A series of 2-(chloromethyl)-3-(4-methyl-6-oxo-5-[(E)-phenyldiazenyl]-2-thioxo-5,6-dihydropyrimidine-1(2H)-yl)quinazoline-4(3H)-ones were synthesized by Kumar et al. from reaction of 2-(chloroacetyl)amino benzoic acid with 3-amino-6-methyl-5-[(E)-phenyldiazenyl]-2-thioxo-2,5-dihydropyrimi-

dine-4(3H)-one and was screened for *in-vitro* antibacterial activities, in the synthesized series methoxy and methyl (37) substituted showed superior activity compare to the standard drug, in the series activity increases with the increasing the capacity of electron donating group [75]. 3-(Aryl)-2-(2-chlorophenyl)-6-{2-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3yl)]ethyl}-3-hydroquinazolin-4-ones synthesized by the Desai et al. and assessed for the antimicrobial activity. They found that all the compounds in a series exhibit moderate activity and electron donating group example methyl (38) showed enhanced activity in the series [76]. The outcome of the above discussed SAR is that halogen substitution on quinazoline moiety can increase antimicrobial activity.

Anticancer activity

One of the major goals of medicinal chemistry is to treat life-threatening cancer disease. Cancer is most dangerous to human health. It is the second-largest cause of death after cardiovascular disease. In 2007, 13% of the deaths occurred by cancer worldwide. Cancer has threatened developing countries because of changes in lifestyle. There are about 200 types of cancers that affect the human population. Excessive revascularization leads to the uncontrolled growth of the cells, which is the major reason for cancer and depends upon angiogenesis. Some of the quinazoline derivatives exhibit remarkable activity and are discussed in the following section, and the structures are shown in Fig. 7.6.

Balaglitazone (DRF-2593) (39) is a heterocyclic conjugated quinazolinone derivative; it is a novel partial agonist of a second-generation peroxisome proliferator-activated receptor (PPAR)-gamma (γ), and this compound was developed by Dr. Reddy's laboratories India. The company had announced the results of phase III clinical trial in January-2010 [77]. This is one of the success stories of Indian medicinal chemistry and also from the quinazolinone group.

Cediranib (40) is another quinazolinone derivative developed by Astra Zeneca; it is a possible anticancer chemotherapeutic agent for oral demonstration. The trade name of the Cediranib is Recentin (AZD-2171), which shows the most potential ($IC_{50} < 1$ nmol/L) inhibitor of vascular endothelial growth factor (VEGF) all three VEGF receptors (VEGFR-1, 2, and 3) of receptor tyrosine kinesis. A combination of cediranib maleate and olaparib (Lynparza) is useful for the treatment of recurrent platinum-sensitive ovarian cancer patients [78]. Refaie et al. (2005) studied the effect of quinazolinone and halogenated quinazolinone on hypercholesterolemic and diabetic-hypercholesterolemic rats, The 4 (3H) quinazolinone, 6, 8-dibromo-2-methyl-4(3H) quinazolinone (41) and 6-iodo-2-methyl-4(3H) quinazolinone (42) found to be a highly significant effect on n serum total cholesterol and cholesterol ester levels and they appear nontoxic to normal cell lines. These results were found to be the antihyperlipidemic activity of compound 42 [79]. Nolatrexed (43) is a quinazoloni-

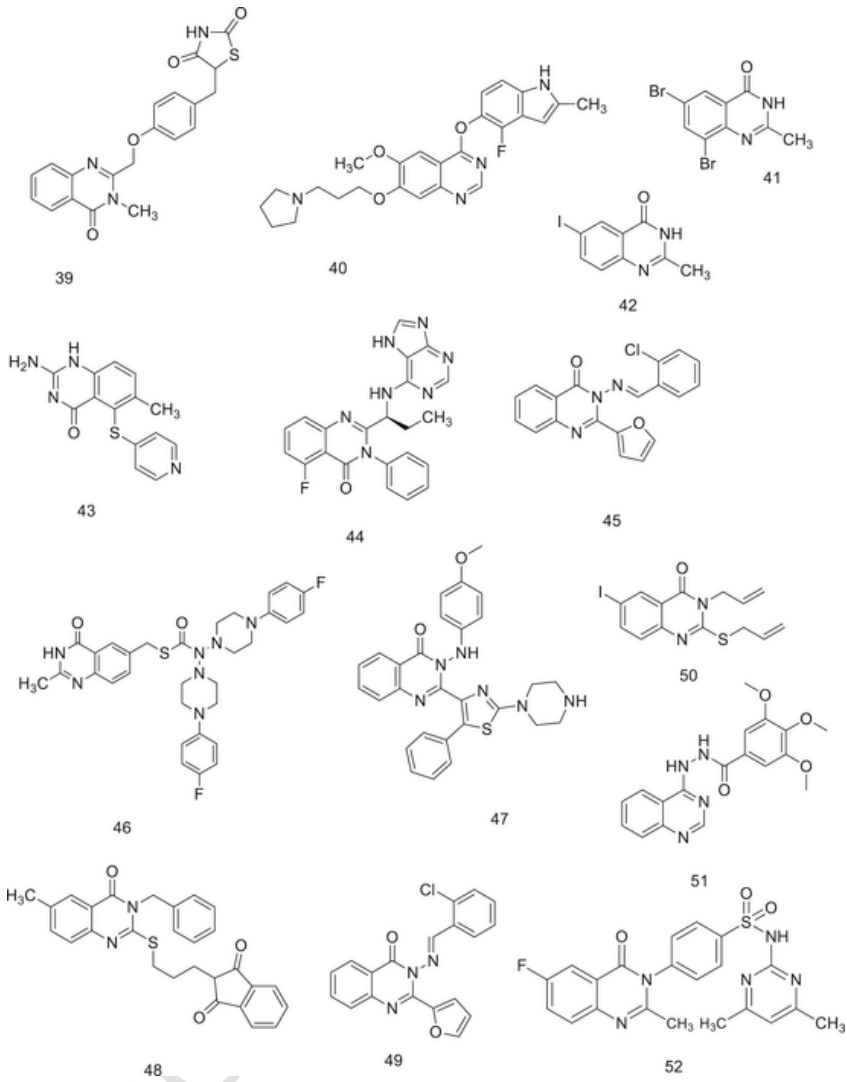

FIGURE 7.6 Anticancer active quinazoline derivatives.

none derivate. Its dihydrochloride salt can be comparable with doxorubicin in treating patients with recurrent or unrespectable liver cancer [80]. Idelalisib (44) (code named GS-1101) is a quinazolinone drug that was developed by Gilead Sciences and used for the treatment of certain hematological malignancies. Idelalisib acts as a phosphoinositide 3-kinase inhibitor, which means it blocks P110δ, the delta isoform of the enzyme phosphoinositide 3-kinase [81].

Malleshappa et al. (2011) synthesized the series of 2-furano-4(3H)-quinazolinones, diamides (open ring quinazolines), quinoxalines, and screened for antitumor activity. In the synthesized series of compound, 3-(2-chlorobenzylideneamine)-2-(furan-2-yl) quinazoline-4(3h)-one (45) is the most active compound and shows the excellent activity against ovarian OVCAR-4 and NCI–H522 with GI_{50} 1.82 and 2.14 mM respectively [82]. Shang et al. (2005) synthesized a series of 4(3H)-quinazolinone dithiocarbamate derivatives (46) and tested for *in-vitro* antitumor activity against human myelogenous leukemia K562 cells. The series of the synthesized compound piperazine-1-carbodithioate quinazolinone derivatives show remarkable activity against K562 cell lines with IC_{50} value 0.5 μM [83].

Sharma et al. (2013) synthesized the quinazolinone derivatives from the reaction between *N*-benzoyl substituted piperazine-1-carbothioamide with 2-chloromethyl quinazolinone derivatives and subjected for in vitro cytotoxic activity by MTT assay for determination of anticancer activity for MCF 7 (Breast cancer cell), NCI (human lung cancer cell), and HEK 293 (normal epidermal kidney cell). Compounds with methoxy substitution on phenylamine (47) ring shows the superior activity compare to the standard. The structure-activity relationship of the synthesized compound reveals that the presence of NH linker with aryl moiety at the third position of quinazolinone ring was important for exhibiting the superior anticancer activity [84].

Abuelizz et al. synthesized quinazoline derivatives, in this reaction of 2-amino-5-methylbenzoic acid with butyl isothiocyanate resulted in the formation of 2-thioxoquinazolin-4-one, further Alkylation and hydrazinolysis of the inherent-thioxo group afforded the corresponding thio-ethers and hydrazine derivatives, then it was further transformed into tricyclic derivative via cyclo-condensation reaction [81]. In this quinazoline derivatives were found to exhibit anticancer activity against the HeLa and MDA-MB231 cancer cell lines, with IC_{50}values ranging from 1.85 to 2.81 μM in comparison to standard gefitinib (IC_{50} = 4.3 and 28.3 μM against HeLa and MDA-MB231 cells, respectively). In the synthesized compound, phthalimido propyl (48) substituted compounds showed better activity with IC_{50} value 1.85 and 2.33 μM against HeLa and MDA-MB231 cells, respectively.

Noolvi et al. synthesized a new series of 2,3-disubstituted quinazolinones and quinoxaline derivatives that are structurally correlated to erlotinib and lapatinib and evaluated them for in vitro anticancer activities [85]. In the series the most active compound was 3-(2-chloro benzylideneamine)-2- (furan-2-yl) quinazoline-4(3H)-one (49). From SAR, it was observed that the presence of quinazoline ring as a backbone, 2-chloro benzylideneamine group at position 3 of quinazoline, and chalcone on the benzamide amide, sulfonamide, at position 3 of the quinoxaline improves the potency of the parent compound.

Alafeefy et al. synthesized a series of 2,3-disubstituted-6-iodo-3H quinazolin-4-1 derivatives and screened them for antitumor activities against different cancer cell lines [86]. When alkyl/aralkyl substituents (such as allyl, ben-

zyl, or phenacyl) are attached to an electron-rich atom it is anticipated to be a reasonably stable leaving group. Therefore, the series was designed with benzyl, allyl and phenacyl group substitution at sulfur atom on position 2, phenyl and/or benzyl groups substitution at position 3, and an iodine atom at position 6. The most active compound has allyl and/or benzyl groups at positions 2 and/or 3 of the quinazoline nucleus. Compound 50 was the most potent compound of the series and showed in vitro antitumor activity in the micromolar range against the tested cell lines. The structure-activity relationship reveals that an electron-withdrawing group at position 4 of the phenacyl group linked to 2-mercapto-3H quinazolin-4-one is most favorable for antitumor activity. Kovalenko et al. synthesized hydrazo amide substituted on the fourth position of the quinazoline, compounds were screened for antitumor activity against leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancer cell lines. In this series, 3,4,5-trimethoxy-*N*'-(quinazoline-4(3H)-ylidene)benzohydrazide (51) was found to be the most active compound, which exhibited GI_{50} in the micromolar range [87]. The fluorine atom has to enhance the significance of the lipophilicity, absorption, and bioavailability of several anticancer drugs in addition to the importance of sulfonamides as anticancer agents, Zayed et al. synthesized a small series of fluorinated quinazolinone sulfonamide conjugated pyrimidine hybrids and evaluated the in vitro cytotoxic activities [88]. The majority of the compounds showed substantial anticancer activity in the micromolar range. The most active compound of the series was found to be 4-(6-Floro-2-methyl-4-oxoquinazolin-3(4H)-yl)-*N*-(4,6- dimethlpyrimidin-2 yl)benzensulphonamide (52) (Fig. 7.6) containing sulphamethazine and displaying an IC_{50} value in the micromolar range in the NCI, MCF-7, and HEK-293 cell lines.

From the aforementioned discussion regarding structure and its anticancer activity, we can conclude that the halogens, especially fluorine, enhance the activity by increasing the lipophilicity and also observe that sulfonamide and mercapto substitution also increases the activity.

Antiinflammatory activity

Nonsteroidal antiinflammatory drugs (NSAIDs) were available to small animal practitioners for many years, but the proper application of them remained unknown. Antiinflammatory drugs are mainly involved in the reduction of inflammation. Endogenous chemical factors derived from plasma or cells and triggered by the inflammatory stimulus mediate the vascular and cellular responses for both acute and chronic inflammations. NSAIDs, were used to provide antianalgesic, antiinflammatory, and antihyretic capabilities, but the action of the mechanism was yet to be known clearly and is under investigation. The main working principles of the antiinflammatory drugs are to inhibit the effect of enzymes called cyclooxygenase (COX) enzyme and lisyl oxidase (LOX), which help to produce other chemicals called prostaglandins. Because

of these prostaglandins, pain and inflammation occur, so reducing production of prostaglandins results in lowering pain and inflammation. A wide variety of heterocyclic moieties has been explored to reduce the antiinflammatory process at any of the stages. In literature, many quinazoline derivatives are reported for antiinflammatory activity. Some of the important findings of quinazoline derivatives, which show antiinflammatory activities, are discussed here, and structures are shown in Fig. 7.7.

Kumar et al. synthesized the series of quinazolin-4-one of heterocyclic conjugated derivatives (53) and screened for antiinflammatory activity, in which 2-oxadiazole-3-thiazolyl conjugated compound exhibit a similar activity

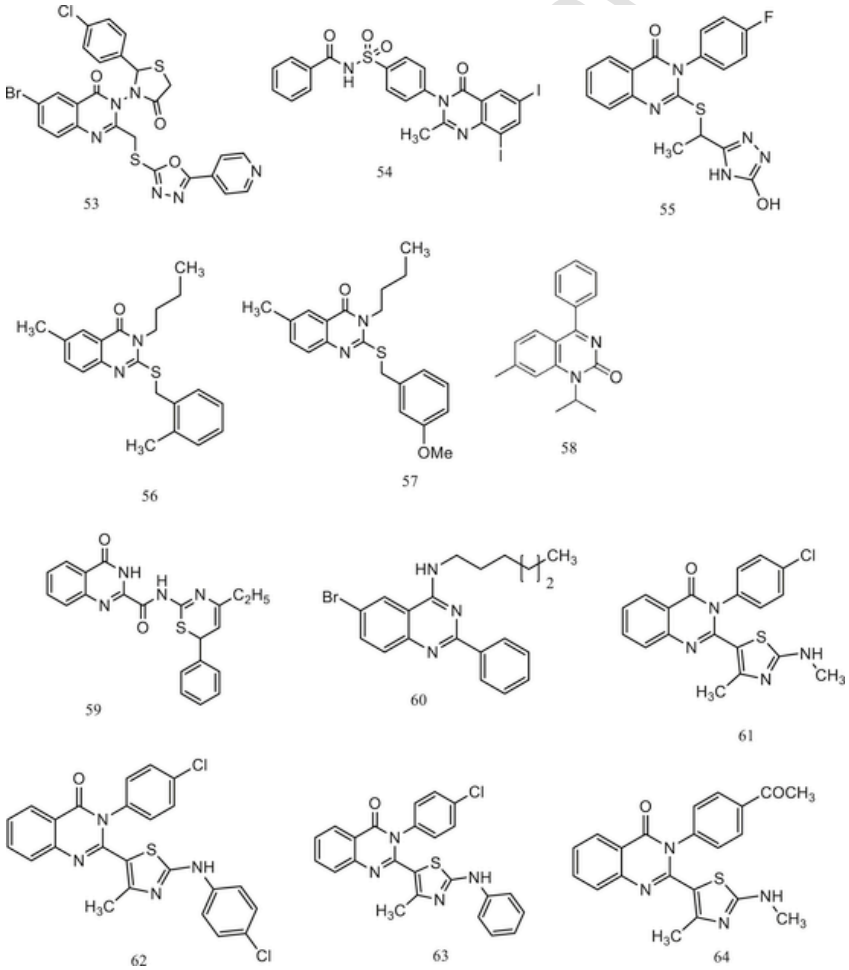

FIGURE 7.7 Antiinflammatory activity of quinazoline derivatives.

(25.2%) compare to the standard reference compound (25.4%) at 25 mg/kg dosage and they appear nontoxic to other normal cell lines. The structure-activity relationship tells about the substitution at position 6 with the electronegative atom increases the activity [89]. 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-1 bearing sulfonamide derivatives were synthesized by the Zayed et al. and evaluated for their possible antibacterial, antiinflammatory activities, and acute toxicity. Antiinflammatory activity was evaluated by the carrageenan-induced hind paw edema test and showed remarkable activity and appeared nontoxic to the normal cell line [90]. In the series of the synthesized compound, benzamide from sulfabenzamide (54) is the most potent compound; the presence of the sulfonamide is responsible for the observed activity.

El-Feky et al. synthesized several fluorinated quinazolinone derivatives and evaluated for *in-vitro* antiinflammatory activity and compounds showed strong interactions at the COX-2 binding sites [91]. In the series of the synthesized compounds, triazole-substituted derivatives (55) exhibited superior activity. Thioxoquinazolines derivatives were synthesized by Abuelizz et al. and evaluated in vivo for antiinflammatory activity using carrageenan-induced paw edema assay [92]. Compounds 56 and 57 displayed the highest antiinflammatory activity (≥80%) and further tested against complete Freund's adjuvant-induced arthritic rats. Significant reduction in the serum level of IL-1β, COX-2 and prostaglandin E2 in the complete Freund's adjuvant rats is demonstrated by these compounds. Proquazone (58) and fluoroquazone are taken as representative examples and used as antiinflammatory drugs for gout and rheumatoid [93].

Vadlakonda et al. synthesized quinazoline-linked thiazine derivatives and screened for *in-vivo* antiinflammatory activity by carrageenan-induced acute rat paw edema model [94]. In the series of the synthesized compound, ethyl substituted (59) compounds exhibit superior activity, in addition to this, the compound showed significant docking interaction with the COX-2 active site.

Jain et al. synthesized the 2, 4, 6-trisubstituted quinazoline derivatives and screened for antiinflammatory, analgesic and antibacterial agents [95]. The antiinflammatory activity was evaluated by the carrageenan-induced paw edema techniques in which a bromo (60) substitution on position 6 of the quinazoline exhibited superior activity with 59% protection compared to the standard Indomethacin, which shows 57% protection over inflammation. The presence of the bromine and sufficient alkyl chain length causes an increase in the activity. A series of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives were synthesized by Giri et al. evaluated for their inhibitory activity toward transcription factors NF-kB and AP-1 mediated transcriptional activation in a cell line based on in vitro assay and also showed similar results of antiinflammatory activity in *in-vivo* model of acute inflammation [96]. In the series, two of the compounds 61 and 62 turned out to be the most promising dual

inhibitors of NF-kB and AP-1 mediated transcriptional activation with an IC_{50} of 3.3 μM for both. Compound 63 (IC_{50} = 5.5 μM) and 64 (IC_{50} = 5.5 μM) emerged as selective inhibitors of NF-kB mediated transcriptional activation. Alagarsamy et al. reported several 2,3-disubstituted quinazoline analogs with potent analgesic and antiinflammatory activity, such as 2-phenyl-3-substituted quinazolines [97]. Aryl/heteroaryl substitution at the second position of the quinazoline moiety through the amide or sulfonamide linkage enhances the activity.

Anti-TB activity

Mycobacterium tuberculosis microorganism causes, tuberculosis and is spread through the air. It mainly affects the lungs and causes respiratory-related problems. It is a deadly disease that threatens developing countries. Statistical data of the World Health Organization (WHO) on tuberculosis is surprising to know that, nearly one-third of the world population is infected by tuberculosis and about 2 million deaths occur every year. Tuberculosis is often common for people who are suffering from HIV/AIDS. The lack of efficient anti-*Mycobacterium* agents against *Mycobacterium tuberculosis* is made to develop new multiresistant drug molecules. Some important findings of quinazoline derivatives as an anti-TB activity are discussed here, and structures are shown in Fig. 7.8.

Kunes et al. prepared 4-quinazolinol derivates (126) from anthranilic acid and formamide, and followed step hydroxyl group converted into thiol functional group then alkylated the thiol group. The synthesized compound exhibited superior anti-TB activity. In the reported series of the compounds benzyl substituted (65) derivatives show superior activity for all the tested mycobacterium species (32–125 mmol/L) concentration [98]. A series of ethyl 5-(4-substituted phenyl)-3-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazo-

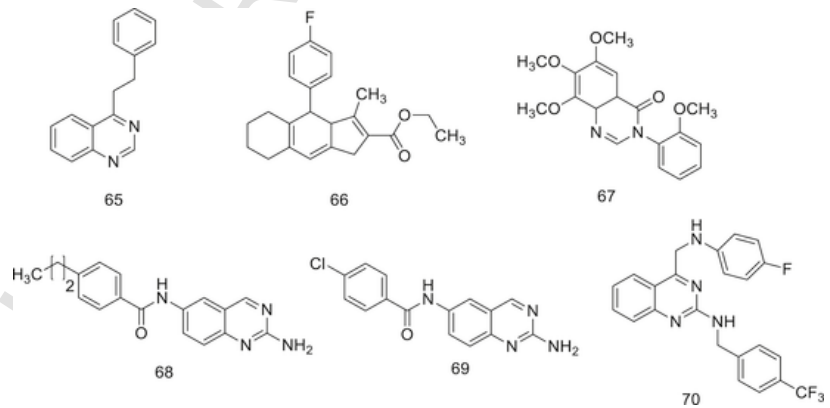

FIGURE 7.8 Anti-TB activity of quinazoline derivatives.

line-2-carboxylate were synthesized by Theivendren et al. and screened for their *in-vitro* antibacterial and *Mycobacterium tuberculosis* (MTB) activities. They observed that introduced groups which enhance the lipophilicity as well as ester substituted aromatic ring at thiazole quinazoline nucleus showed increasing anti-TB activity. Also, an electron-withdrawing group at para position (66) on the benzene ring suggests that these compounds could serve as prominent molecules for the development of novel synthetic compounds [99]. A series of quinazolinone derivatives prepared with the help of 2-amino-3,4,5-trimethoxy benzoic acid and Vilsmeier reagent by Krishnarth and screened for their antitubercular activity against bacteria mycobacterium H37Rv strain [100]. In the series of the synthesized compound methoxy substitution (67) at the ortho position of *N*-phenyl group show the enhanced activity with MIC 1.6 μg/mL.

Cox and Melander explored the antibiofilm capabilities of a library of compounds based on a 2-aminoquinazoline (2-AQ) scaffold against *Mycobacterium smegmatis*. This study resulted in the identification of 2-AQ derivatives with biofilm inhibition activity against *M. smegmatis* [101]. Compounds 68 and 69 resulted as a lead compound for biofilm inhibition with IC_{50} value 16 and 15 μM respectively, in a nontoxic manner and possessed a relatively low hemolytic index.

N-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine were synthesized by Odingo et al. and examined systematically to explore structure–activity relationships for exhibiting the antimycobacterium activity [102]. SAR results indicate that benzylic amine at position 4, piperidine at position 2, and N-1 (but not N-3) are key activity determinants and also indicates that 3-deaza analog retained similar activity to the parent molecule. They isolated and sequenced *M. Tuberculosis* mutants resistant to this compound and observed mutations in Rv3161c, a gene predicted to encode a dioxygenase. In the series of the synthesized compound, 70 showed an IC_{50} value at 6.6 μM. The majority of the study indicates that the observed activity is due to the mechanism of inhibitions of dihydrofolate reductase [103].

Antileishmanicidal activity

Many quinazoline derivatives were reported for the antileishmanicidal activity, some important findings of quinazoline derivatives as antileishmanicidal activity are discussed here and structures are shown in Fig. 7.9.

Sharma et al. (2013) synthesized the four novel series of quinazolinone hybrids derivatives as bioactive scaffolds (pyrimidine, triazine, tetrazole, and peptide-conjugated derivatives). All the synthesized hybrid derivatives exhibited potent leishmanicidal activity against intracellular amastigotes [104]. The SAR study reveals that in the synthesized quinazolinone derivatives, the compound with peptide functionality displayed the most potent antileishmanial activity. Tesfahunegn et al. synthesized hybrid scaffolds of 2,3-disubstituted-

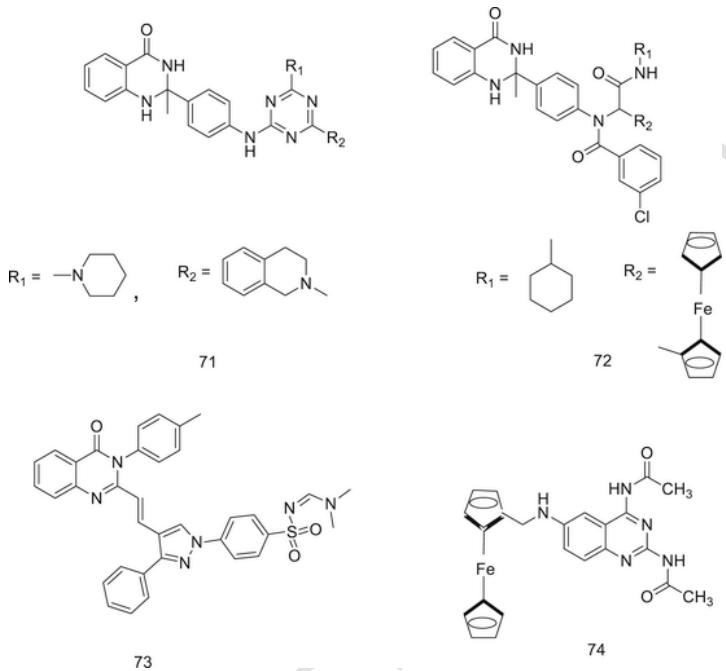

FIGURE 7.9 Antileishmanicidal activity of quinazoline derivatives.

quinazoline-4(3H)-one pharmacophore bearing biologically active quinoline and pyrazole (71) moieties and evaluate their enhanced antileishmanial activity [105]. In vitro antileishmanial activities of the synthesized compounds were evaluated using *L. donovani* strain. All the compounds show superior antileishmanial activity (IC_{50} = 0.0265–1.9146 μg/mL) compared to the standard drug miltefosine (IC_{50} = 3.1911 μg/mL). In particular, compound 73 is a potential lead compound (IC_{50} = 0.0265 μg/mL) exhibited strongest antileishmanial activity.

A series of quinazoline-2,4,6-triamine were synthesized by Mendoza-Martínez and evaluated *in-vitro* against Leishmania Mexicana. Among them, N(6)-(ferrocenmethyl)quinazolin-2,4,6-triamine (72 and 74) showed activity on promastigotes and intracellular amastigotes, as well as low cytotoxicity in mammalian cells [106].

Anti-HIV activity of quinazoline derivatives

HIV is one of the most fatal disorders and not able to be completely cured. According to the WHO survey (2015), 36.7 million people are living with HIV infections, and the disease is growing exponentially. In the modern world, advanced research has taken place, and chemotherapy and other medical aids

have not been well developed. The current treatment involves the inhibition of the human immunodeficiency virus type 1 (HIV-1), which is the source of AIDS. Herein we discuss some important literature of quinazoline derivatives, which exhibit the anti-HIV activity and structures are shown in Fig. 7.10. Kumar et al. synthesized the Quinazoline-4(3H)-1 derivatives and screened for the anti-HIV study. In the synthesized compound 4-(1-(2-(2-Methyl-4-oxoquinazolin-3(4H)-yl) Phenyl)-1H-tetrazol-5-yl) benzonitrile showed superior activity with IC_{50} value > 0.456 μg/mL for HIV III_B strain [107]. Several [2-phenyl-4(3H)-oxo-3-quinazolinylamino]-N-substituted- arylacetamides synthesized by Desai et al. have been synthesized and tested at the National Cancer Institute, Bethesda, Maryland, United States, for their anti-HIV activity against susceptible human host cells (CEM cell line) over a wide range of concentrations (6.35×10^{-8} to 2.00×10^{-4} M). In the present study, the highest protection observed is 45.67% [108].

A series of 4,6-disubstituted quinazoline derivatives have been synthesized by Chandrika et al. and screened for anticancer activity against U937 leukemia cell lines [109]. In a series of synthesized quinoline derivatives compounds 75 showed superior activity with IC_{50} = 16.11 μg/mL, which is a similar activity as that of the standard.

Quinazoline–triazine derivatives were designed and synthesized from cyanuric chloride and anthranilic acid through sequential reactions by Modh et al. and compounds were evaluated for in vitro anti-HIV activity against HIV-1 (IIIB) and HIV-2 (ROD) viral strains [110]. Here observed that compound 76 marked for superior activity with IC_{50} value > 2.22 μg/mL and CC_{50} = 2.22 μg/mL, the presence of halogens and sufficient heteroatoms in the ring compound makes more effective. A series of dihydrobenzo[H]quinazoline derivatives were synthesized by Mohamed et al. and compounds were screened for their anti-HIV activity [111]. Almost all the compounds exhibited excellent activity, and compound 77 was superior in the series and has $EC_{50} = 6.24 \times 10^{-5}$mM and IC_{50} = 2.33 μM.

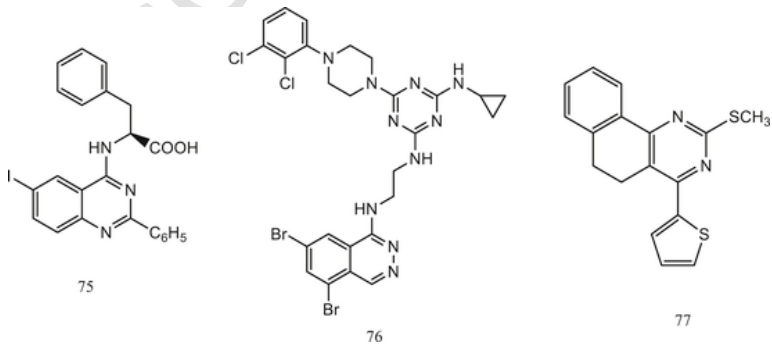

FIGURE 7.10 Anti-HIV activity of quinazoline derivatives.

Antimalarial activity of quinazoline derivatives

Malaria is one of the foremost serious diseases, mainly affecting tropical and subtropical countries and has become a serious public health concern issue in developing countries. According to the statistical data of the WHO, in 2015, there were 214 million cases of malaria. At least 300 million people are affected all over the world. Malaria is one of the most dangerous to humans and developing new drug molecules becomes a major issue globally. Among the plasmodium species, *Plasmodium falciparum* is the most dangerous and deadliest. In this section, we have discussed the antimalarial activity of the quinazoline derivatives and structures are shown in Fig. 7.11.

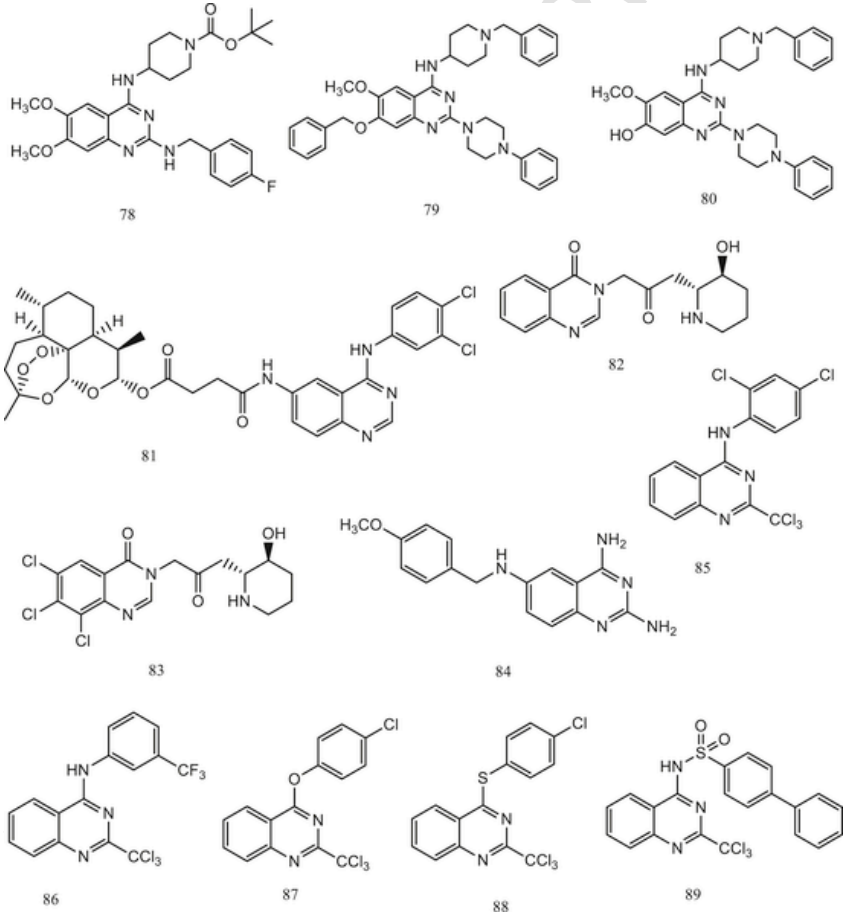

FIGURE 7.11 Antimalarial activity of quinazoline derivatives.

A series of compounds designed by Bouchut et al. to target different epigenetic enzymes were screened for activity against *Plasmodium falciparum* parasites. Based on in vitro activity against drug susceptible and drug-resistant *P. falciparum* lines, selectivity index criterion, and favorable pharmacokinetic properties, one compound showed HDAC inhibitor and three exhibited DNMT inhibitors [112]. *In-vivo* data showed that three compounds(78, 79, and 80) exhibited oral efficacy in the mouse model of *Plasmodium berghei* infection.

Frohlich et al. synthesized five novel quinazoline−artemisinin hybrids that were synthesized and evaluated for their in vitro biological activity against malarial parasites (*Plasmodium falciparum* 3D7), leukemia cells, and human cytomegalovirus [113]. Compound 81 with EC_{50} = 1.4 nM was the most active antimalarial compound of this study and was more potent than artesunic acid (EC_{50} = 9.7 nM). Febrifugine (82) is the active principle isolated 50 years ago from the Chinese herb chang shan (*Dichroa febrifuga* Lour), which has been used as an antimalarial in Chinese traditional medicine for more than 2000 years. Jiang et al. synthesized the febrifugine analogs and screened for the antimalarial activity [114]. In the synthesized 10 analogs that inhibited parasite growth in vitro, with 50% inhibitory concentrations ranging from 0.141 to 290 ng/mL. In that, trichloro substituted (83) derivative marked for the superior activity with IC_{50} value 0.98 μg/mL for *P. falciparum*.

Rojas-Aguirre et al. synthesized N^6-(4-methoxybenzyl)quinazoline-2,4,6-triamine (84) and evaluated the effects of the antiplasmodial and its inclusion complex (M4/HPβCD) with 2-hydroxypropyl-β-cyclodextrin (HPβCD) on human erythrocytes and on cell membrane molecular models were reported [115]. X-ray diffraction studies showed that 200 μM induced a complete structural perturbation of dimyristoyl phosphatidylcholine (DMPC).

Desroches et al. carried out the identification and SAR study for the antimalarial drug [116]. From four antiplasmodial hit-molecules identified (85–88) in 2-trichloromethylquinazoline series, quinoxaline series not only provided a new antiplasmodial reference hit-molecule (IC_{50} = 0.4 μM, selectivity index = 100), but also highlighted with high activity in lower concentration (IC_{50} = 0.4 μM) and quite selective (SI = 265) synthesis intermediate. Identified compounds were tested on the K1 multiresistant *P. falciparum* strain, along with a cytotoxicity evaluation on the human HepG2 cell line to define selectivity indices. Primas et al. synthesized the 2-trichloromethylquinazolines sulfonamide derivatives and screened for the antimalarial activity [117]. In the synthesized sulfonamide derivatives biphenyl substitution (89) exhibits the superior activity in the series with CC_{50} value 38.2 μM. SAR study shows that with an increase in the aromatic group on sulfonamide experience enhanced activity. From the above study, we can conclude that in the presence of methoxy and hydroxy groups increased, hydrophobicity also increases the halogen substitution, which increases the lipophilicity and helps to increase the antimalarial activity.

Quinazoline derivatives in clinical studies

More than 25 quinazoline derivatives are clinically approved for usage. Linagliptin is chemically known as 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione. It is a DPP-4 inhibitor, and a phase III clinical study showed the drug can effectively reduce blood sugar [118]. Afatinib is used to treat metastatic nonsmall cell lung cancer, which is recently approved by the FDA [119]. Substituted quinazoline sulfonamide, SRI-37330, which is orally bioavailable, has a favorable safety profile and inhibits TXNIP expression and signaling in mouse and human islets, and inhibits glucagon secretion and function. It also exhibits strong antidiabetic activity against type 1 and type 2 diabetes in mouse models [120]. GS 1101 is a chemical, 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]-4(3H)-quinazolinone. Gilead Sciences is developing this drug, which acts as an inhibitor of the delta isoform of PI3-kinase for the treatment of hematological cancer [121].

Conclusion

The chapter extensively discussed the synthesis and bioactivity of quinazoline derivatives, which gives the importance of the quinazoline moiety in the field of chemistry and in medical applications. 4-quinazolinone exhibit the tautomerism, and this tautomeric effect makes the molecule more reactive and facilitates the hydrogen bond forming between the ligand and receptors, which gives molecules a wide spectrum of activity. The notable feature of the quinazolinone ring is that it is stable for the oxidation, reduction, and hydrolysis reaction. No reaction made the ring degradation unstable, and this also adds up to the biological invention. Quinazolinone and its derivatives are one of the emerging privileged structures of pharmacare positions such as 2, 6, and 8, which are important to study for the structure-activity relationship. Substitutions of mercapto and sulfonamide derivatives to the parent moiety enhance the anticancer and antimicrobial activity. This has drawn scientist's interest in the area of drug design and medicinal application. The review is carried out to enhance the visibility and enlightened the importance of this scaffold quinazoline derivative, which may help to discover the more effective drug molecule.

Design and synthesis of the hybrid moiety are one of the major aims of the present research, which enhances the activity. Substitutions of the suitable halogen group at positions 6 and 8 are helpful for increasing the lipophobicity of the synthesized compound. Inserting the guanidine functionality can also enhance the activity of the parent moiety and guanidine functionality interacting with the functional groups of enzymes or receptors from the electrostatic interactions by hydrogen bonding. In the future, enhancement of the bioactivity of quinazoline moiety can also be achieved by the splicing method of installing various active groups to the existing moiety of quinazolines to recon-

struct the quinazoline derivatives. Substitutions other than 2, 6, and 8 positions of the quinazoline, such as the construction of the *N*-substitution by heterocyclic moieties and the introduction of the bioactive moiety at position 3 of the quinazoline core are future perspectives in this particular area.

Ethics Approval and Consent to Participate

Not applicable.

Human and Animal Rights

No Animals/Humans were used for studies that are the basis of this research.

Consent for Publication

Not applicable.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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