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Synthesis of Quinazoline and Quinazolinone Derivatives

Heba E. Hashem

Abstract

Active heterocyclic compounds are one of the main topics of interest for the medicinal chemists as they display a number of pharmacological activities. Nitrogen, sulfur, and oxygen containing five- and six-membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry. The most important six-membered heterocyclic compounds are quinazoline and quinazolinone derivatives for their biological activities. The current chapter outlined the different methods for synthesis of quinazoline and quinazolinone derivatives that possess broad spectrum of biological activities.

Keywords: quinazoline, quinazolinone synthesis, six-membered heterocycles, biological activity

1. Introduction

Quinazoline (1,3-diazanaphthalene or 5,6-benzopyrimidine) and 4(3H)-quinazolinone derivatives have a great interest in organic synthesis and medicinal chemistry fields as they possess a broad range of pharmacological activities. They exhibit antimicrobial [1], antimalarial [2], antioxidant [3], anti-inflammatory [4], anticonvulsant [5], antihypertensive [6], antidiabetic [7], and antitumor activities [8–10].

Many quinazolinone derivatives occurred naturally in various classes of the plant kingdom, microorganisms, and different animals (**Figure 1**). The first discovery of quinazolinone alkaloid is *febrifugine* which possesses antimalarial potential, extracted from the Chinese plant *aseru* (*Dichroa febrifuga* Lour) [11].

Quinazoline is a heterocyclic compound of two fused six-membered simple aromatic rings—benzene and pyrimidine ring. It is a yellow-colored compound, found usually in crystalline form. Its oxo-derivative (quinazolinone) is classified into three types according to the position and number of carbonyl group: 2(1H)quinazolinones, 4(3H)quinazolinones, and 2,4(1H,3H)quinazolinedione (**Figure 2**).

2. Chemistry of quinazoline

Quinazoline is a compound made up of two fused six-membered simple aromatic rings—benzene and pyrimidine ring. The properties of the pyrimidine ring were affected by the presence of fused benzene ring. The two nitrogen atoms are not equivalent, and the marked polarization of the 3,4-double bond is reflected

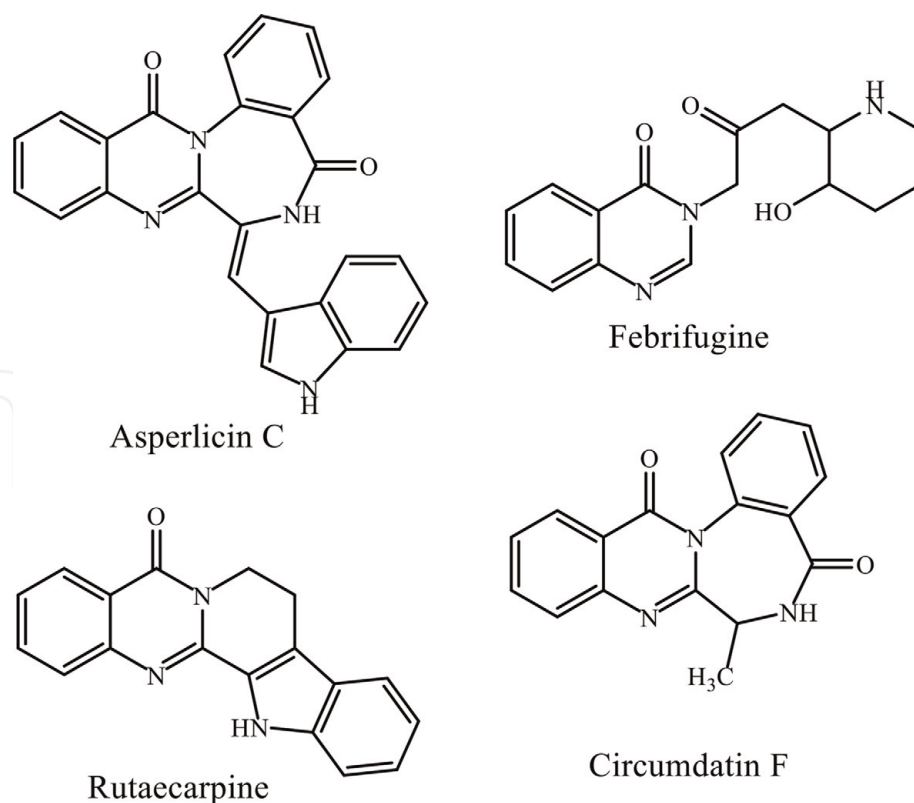


Figure 1.
Structure of different quinazolinone alkaloids.

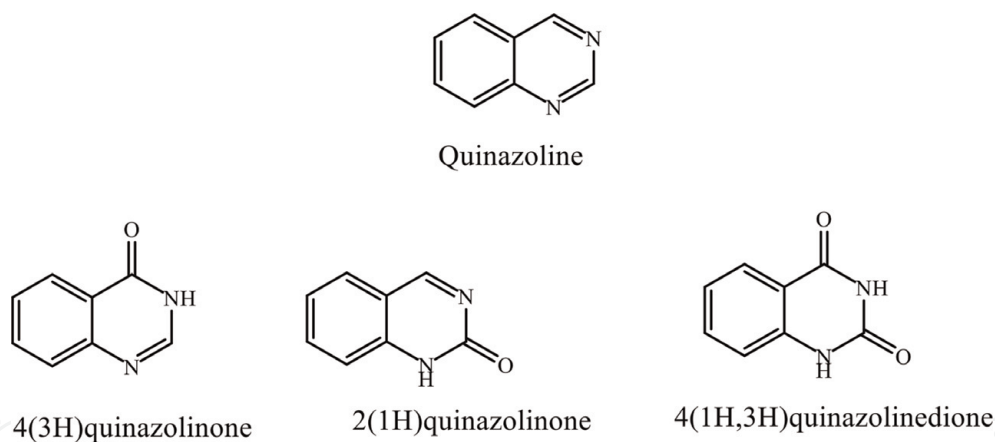


Figure 2.
Structure of quinazoline and different quinazolinone compounds.

in the reactions of quinazoline. The properties of quinazoline derivatives depend on the following three factors:

- The nature of the substituents
- The presence of substituent whether they are in the pyrimidine ring or in the benzene ring
- The presence of conjugation in the pyrimidine ring

The first synthesized quinazoline in laboratory was achieved by Gabriel in 1903 [12]. Most of quinazoline derivatives are stable in cold acidic or basic medium but can be destroyed at high temperature and undergo ring opening reaction, affording

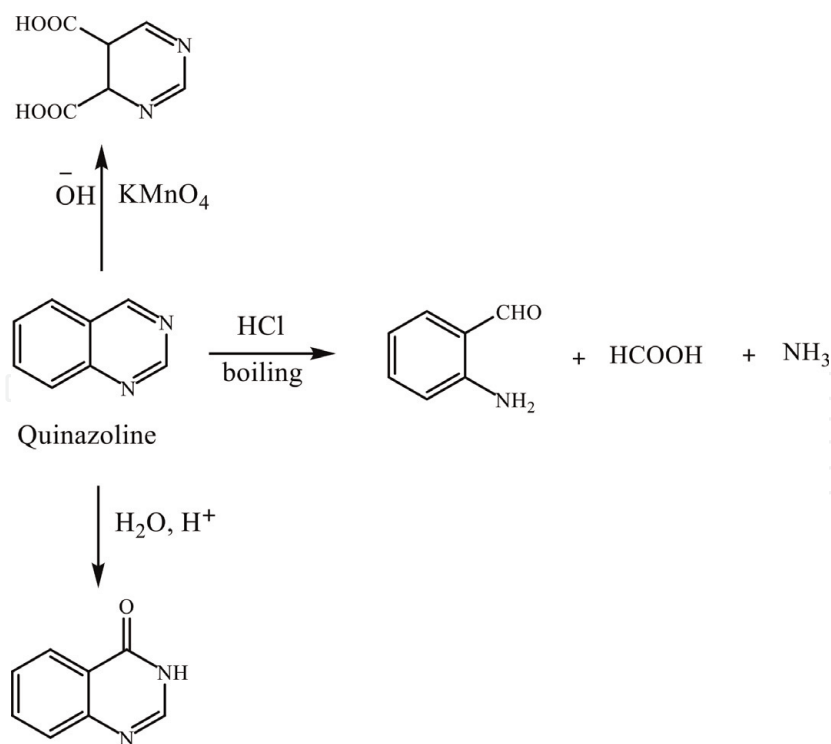


Figure 3.
 Oxidation reaction of quinazoline at different medium.

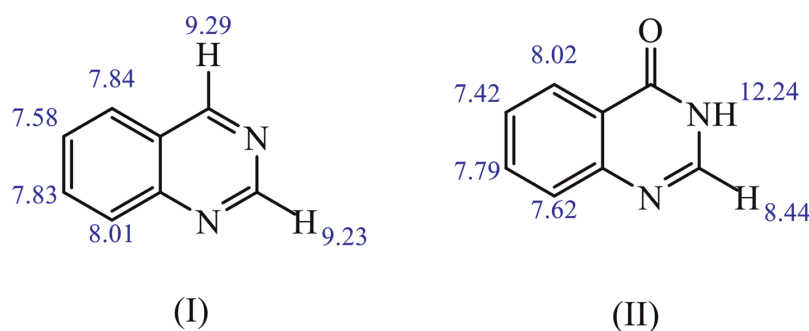
O-aminobenzaldehyde, ammonia, and formic acid. Quinazoline derivative can be easily oxidized in acidic medium at room temperature to give 3,4-dihydro-4-oxoquinazoline, while in alkaline medium using potassium permanganate will afford 3,4-dihydro-6,7-dicarboxyquinazoline (cf. **Figure 3**).

3. Spectral characterization of quinazoline and quinazolinone derivatives

The spectroscopic analysis of some synthesized quinazoline and quinazolinone derivatives was studied to investigate their structures including infrared, mass spectroscopy, ^1H NMR, and elemental analysis. The resulted data could be taken as standard for the new synthesized quinazoline analogue [13].

3.1 Infrared spectra

Quinazoline derivatives found to give mainly three absorption bands in IR spectra: $1478\text{--}1517$, $1566\text{--}1581$, and $1612\text{--}1628\text{ cm}^{-1}$; these represented bands are correlated to C--N , C=C , and C=N groups, while quinazolinone compounds showed $1680\text{--}1700$ and $1640\text{--}1660\text{ cm}^{-1}$ corresponding to C=O and C=N groups [13, 14].



The ^1H NMR spectra of quinazoline and quinazolinone derivatives are different from each other according to the presence of acidic proton and its position in the presented compound. In general the ^1H NMR spectrum of the main quinazoline (I) represents multiple signals in the aromatic region δ 7–8 and two singlet signals for the two $\text{CH}=\text{N}$ protons at δ 9–9.5 ppm, while quinazolinone (II) will show also signals of aromatic protons in the same region as well as one singlet signal for $\text{CH}=\text{N}$ proton and one broad singlet signal at the down-field region for the NH proton at δ 12–13 ppm [13, 14].

On the other hand, the ^{13}C NMR spectrum for quinazoline and quinazolinone derivatives is nearly the same, as it shows signals at δ 100–160 ppm region.

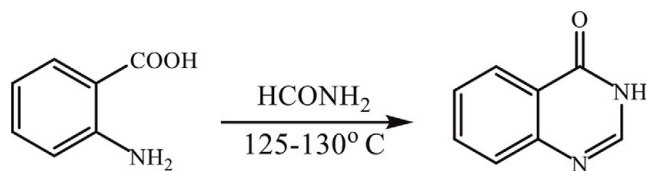
4. Synthesis of quinazoline and quinazolinone derivatives

The synthesis of various quinazoline compounds is largely based on the substitution patterns of the 1,3-diazine moiety of the system. The first quinazoline derivative (2-cyano-3,4-dihydro-4-oxoquinazoline) was synthesized in 1869 by the reaction of cyanogens with anthranilic acid [15]. Many years later quinazoline was obtained by decarboxylation of the 2-carboxy derivative (quinazolinone) which can be synthesized more easily by a different method.

4.1 Synthesis of quinazolinone

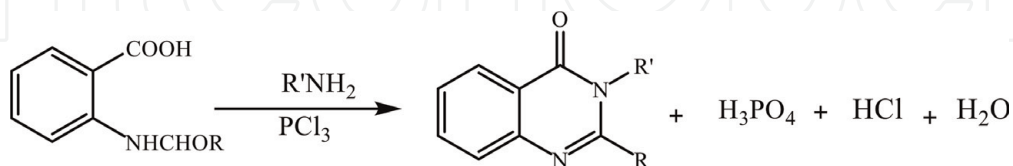
4.1.1 Niementowski's synthesis

From anthranilic acid and formamide.



4.1.2 Grimmel, Guinther, and Morgan's synthesis

From the reaction of o-amino benzoic acid with amine in the presence of phosphorus trichloride in toluene.

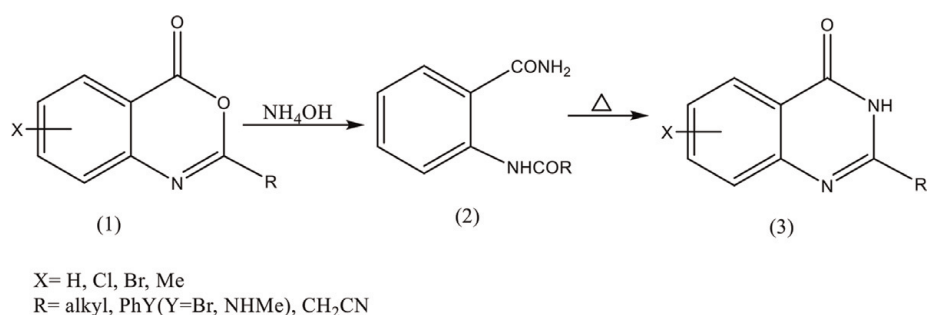


4.1.3 From 3,1,4-benzoxazones (acylanthranils) and amines

Various quinazoline and quinazolinone derivatives can be synthesized from the reaction of benzoxazinone and different amine compounds in different media.

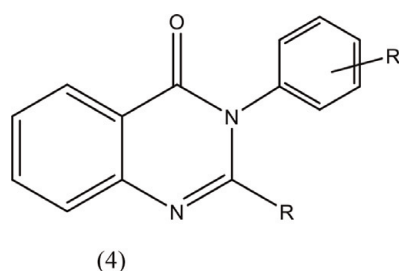
4.1.3.1 Reaction with ammonium hydroxide

When ammonium hydroxide reacted with benzoxazinone (1) over 1–3 h, it produced anthranilamides (2) which cyclizes to 4-quinazolones (3) under thermal conditions (240–280°C) or on heating with acetic anhydride [16, 17].

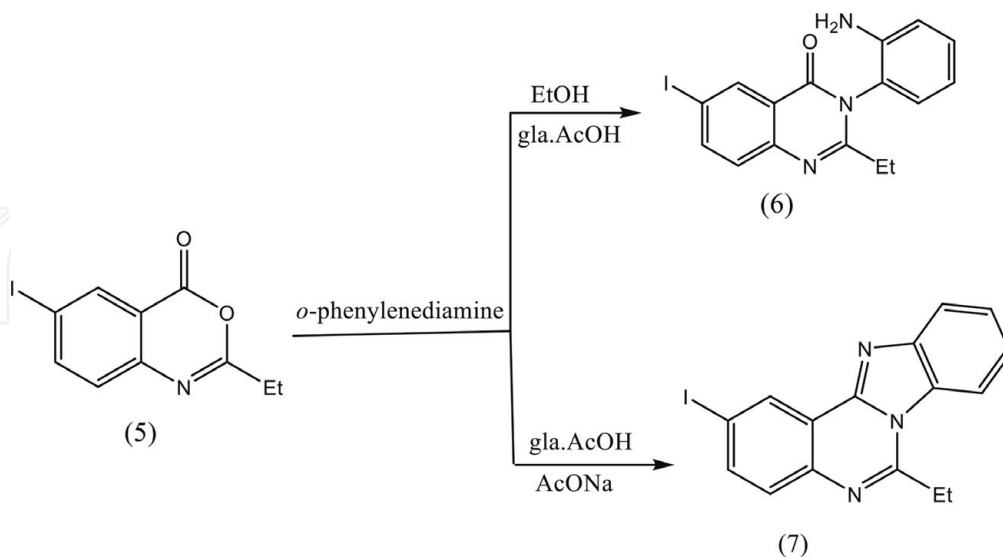


4.1.3.2 Reaction with different aromatic amines

It was stated by several authors that 2-substituted benzoxazinone reacted easily with primary aromatic amines, giving the corresponding quinazolones (4) [18].

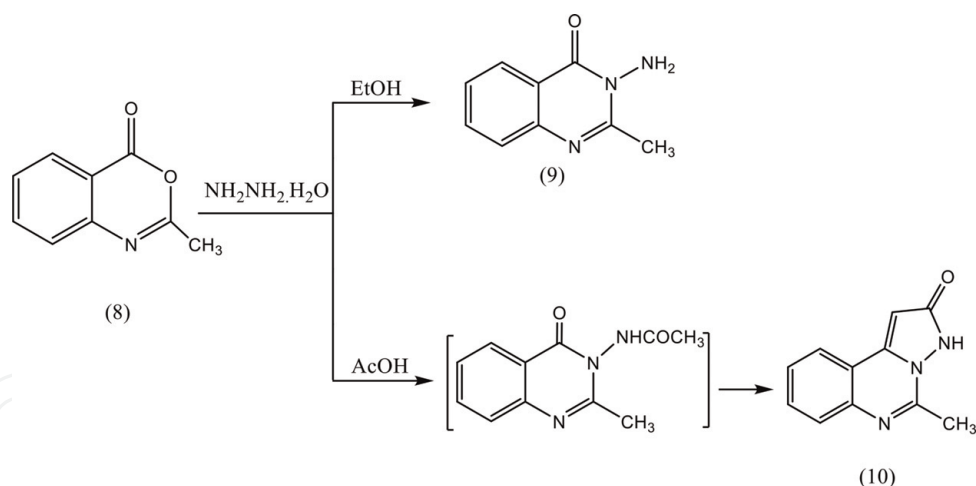


On the other hand, reaction of benzoxazinone (5) with *o*-phenylenediamine gave quinazolinone derivative (6) or the fused quinazoline derivative (7) according to the reaction medium [19].



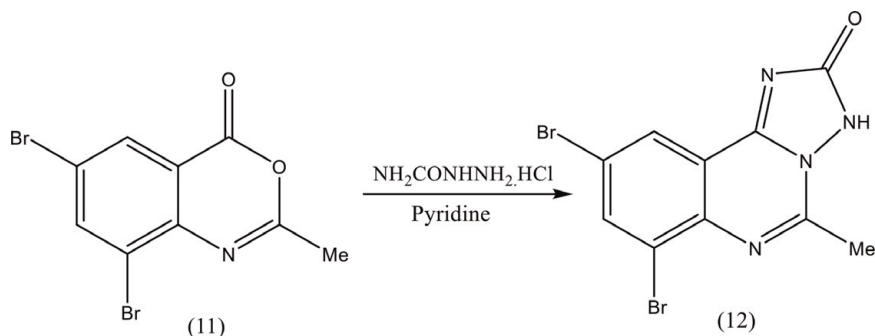
4.1.3.3 Reaction with hydrazine hydrate

It was reported that benzoxazinone (8) reacted with hydrazine hydrate in ethanol and has the corresponding quinazolinone (9), while carrying out the same reaction in boiling acetic acid glacial afforded the fused quinazoline (10) [13].

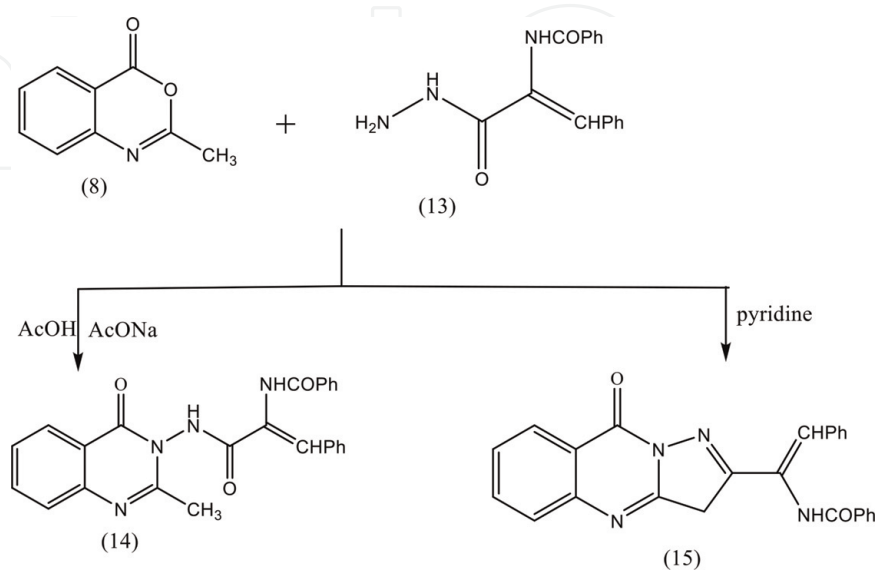


4.1.3.4 Reaction with different carbohydrazide

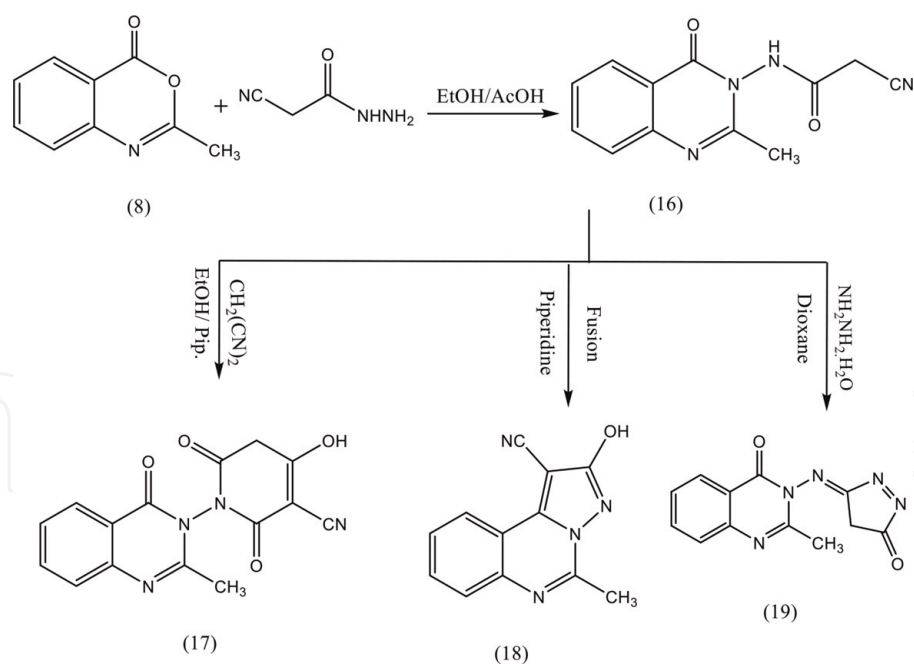
Treatment of 2-substituted-3,1-benzoxazin-4-ones (11) with semicarbazide hydrochloride in dry pyridine is a good way to construct a third heterocyclic ring condensed with quinazoline (12) [18].



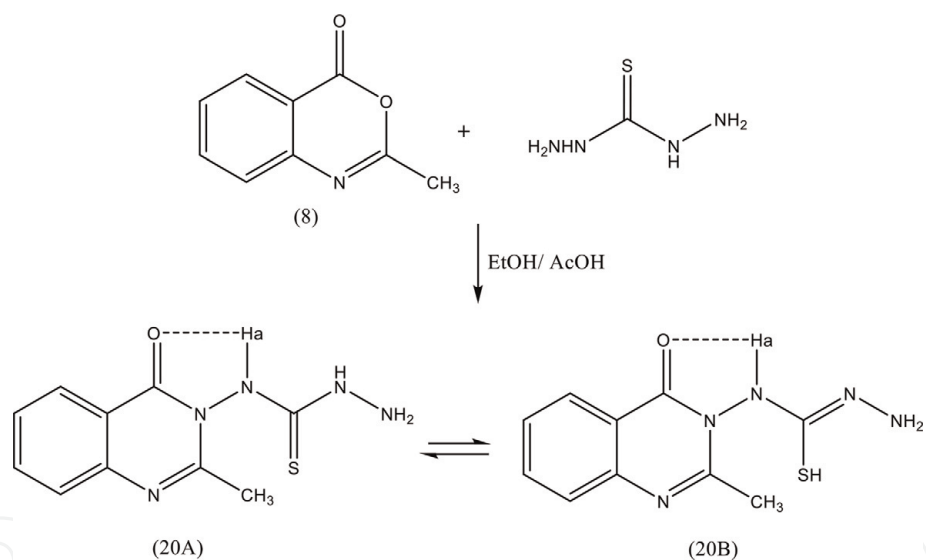
The reaction of benzoxazinone (8) with 2-benzamido-3-phenylacryloylhydrazide (13) in glacial acetic acid in the presence of fused sodium acetate gave quinazoline derivative (14). In contrast, their reaction in pyridine afforded pyrazoloquinazoline derivative (15) [13].



Reaction of benzoxazinone (8) with cyanoacetohydrazide gave the corresponding cyano quinazolinone (16) which was reacted with different nucleophiles to give fused quinazoline and annulated quinazolinone derivatives (17–19) [13].

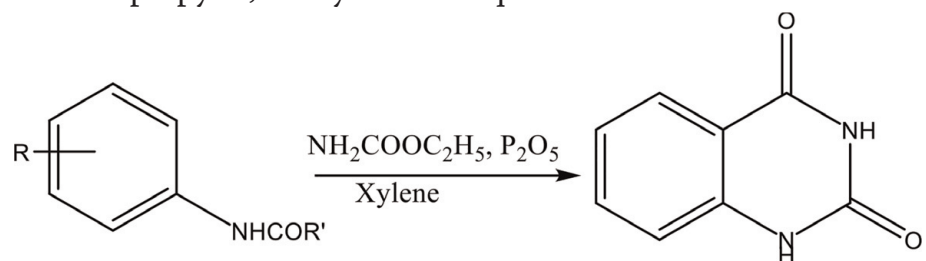


It was also reported that refluxing an equimolar amount of the benzoxazinone (8) with thiocarbonohydrazide in ethanol and in the presence of few drops of glacial acetic acid furnished quinazolinone (20) in the two isomers of thione and thiol form [13].



4.1.4 Sen and Ray's synthesis

Isobutyrylanilides with urethane and phosphorus pentoxide in xylene gave 2-propyl- and 2-isopropyl-3,4-dihydro-4-oxoquinazolines.

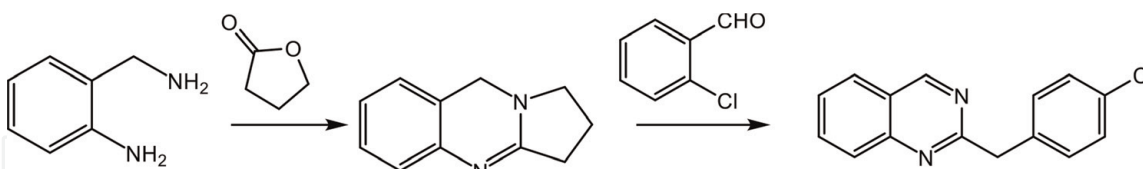


$\text{R} = \text{OMe, OEt, Me}$

$\text{R}' = \text{Me, Et, Iso-Pro, Ph}$

4.1.5 From 2-aminobenzylamine

Reaction of 2-aminobenzylamine with butyrolactone further condensed with benzaldehyde afforded 3-(2-chlorobenzylidene)-1,2,3,9-tetrahydropyrrolo-2-quinazoline.



5. Biological importance of quinazoline derivatives

As we mentioned above, the important biological activity of quinazoline and quinazolinone skeletons in various fields depends mainly on the substituents of quinazoline compounds. Different substituted quinazoline compounds are found to be active as antihypertensive, antineoplastic, antidepressant, and antipsychotic, and others are effective against analgesic, antipsychotic, antiarrhythmic, cancer, and other activities [20–22].

5.1 Anticancer

It was reported that 3-substituted quinazolin-4(3H)-ones and 3,4-dihydroquinazolin-2-(1H)-one derivatives possess broad spectrum antitumor activities toward different cell (**Figure 4**) [23].

Also, different quinazoline derivatives containing thiosemicarbazide moiety possess antitumor activity (**Figure 5**) [24].

5.2 Antibacterial activity

It was reported that some novel substituted iodoquinazoline derivatives possess remarkable activity toward Gram-negative bacteria *E. coli* (**Figure 6**) [25].

5.3 Antiviral agents

A series of Schiff bases of some 2-phenyl quinazoline-4(3H)-one derivatives have shown great activity as antiviral agents (**Figure 7**) [26].

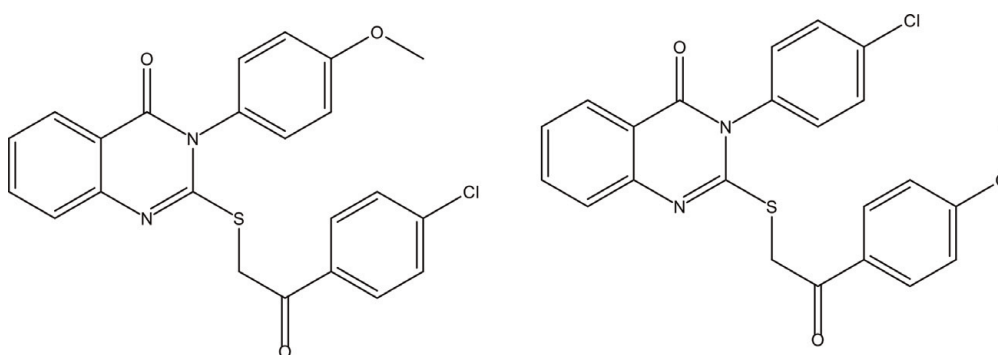


Figure 4.
Anti-tumor quinazolinone derivatives.

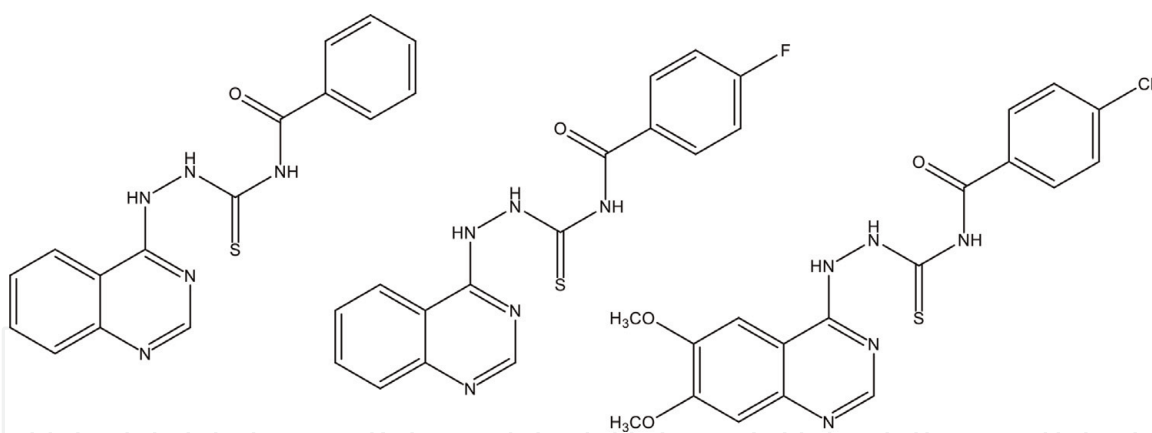


Figure 5.
Quinazoline derivatives bearing thiosemicarbazide possess anti-tumor activity.

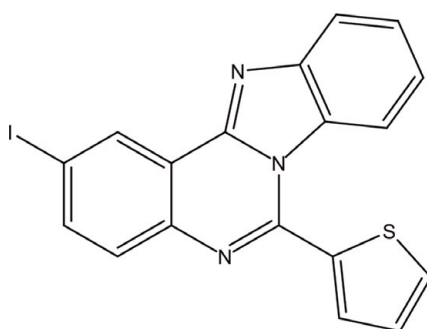
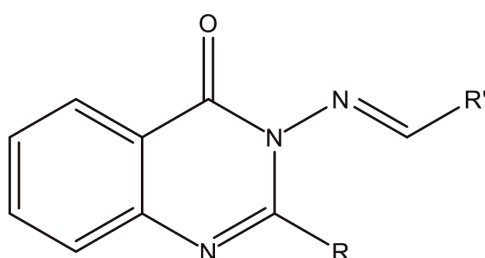


Figure 6.
Quinazoline derivatives with antibacterial activity.



R = C₆H₅

R' =

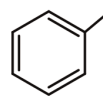
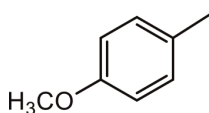
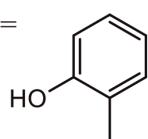


Figure 7.
Different schiff base of quinazolinone with antiviral activity.

5.4 Antimutagenic activity

The (S)-4-aminoquinazoline alcohols performed great antimutagenic activity when tested by using *Salmonella typhimurium* and *E. coli* WP2uvrA tester strains at 0.01, 0.1, and 1 lg/plate concentrations (**Figure 8**) [27].

5.5 Antioxidant activity

Some novel thiazoloquinazoline derivatives are investigated for antioxidant activity by DPPH radical assay, nitric oxide scavenging activity, and hydrogen

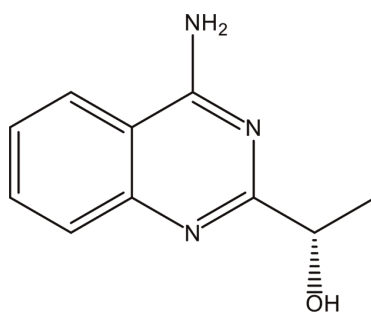


Figure 8.
Antimutagenic activity of amino quinazoline derivative.

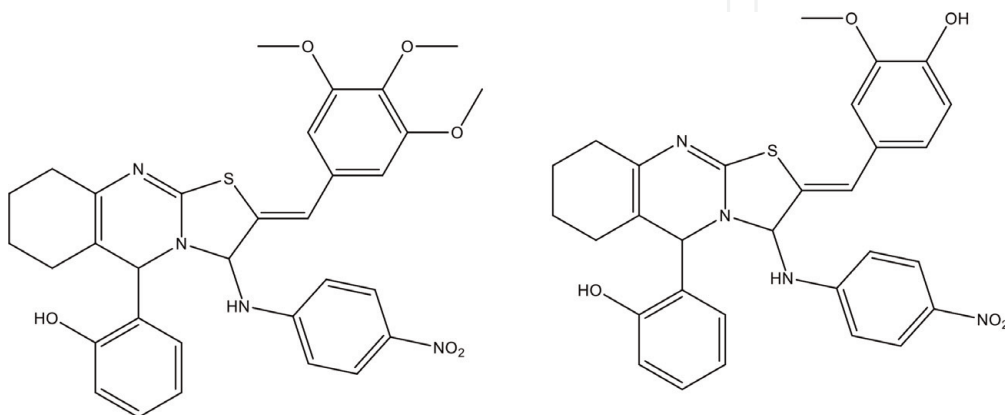


Figure 9.
Antioxidant activity of different quinazoline.

peroxide scavenging activity and possess high potent antioxidant activity (Figure 9) [28].

6. Conclusion

Quinazoline and quinazolinone compounds which have a lot of considerable pharmacological interests can be synthesized by different methods, and the most attractive method was carried out starting from benzoxazinone derivatives.

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