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Chapter

4(3*H*)-Quinazolinone Derivatives: Syntheses, Physical Properties, Chemical Reaction, and Biological Properties

Samir Y. Abbas

Abstract

4(3*H*)-Quinazolinone derivatives have considerable great interesting due to the diverse range of their biological properties. This review summarized the methods of preparation of 2-substituted-4(3*H*)-quinazolinone, 3-substituted-4(3*H*)-quinazolinone and 2,3-disubstituted-4(3*H*)-quinazolinone derivatives. Chemical reaction of 4(3*H*)-quinazolinone derivatives and the reactivity of the 2-methyl group, reactivity of the 3-amino group, electrophilic substitution, oxidation, reduction, reaction of 4(3*H*)-quinazolinones with metal ions, Mannich reaction, cycloaddition reaction as well as other reagents were discussed. Also, biological properties of 4(3*H*)-quinazolinone derivatives were given herein.

Keywords: 4(3*H*)-quinazolinones, quinazolines, syntheses, reaction, biological activity

1. Introduction

Quinazolinones are very significant heterocyclic compounds because of their potential pharmaceutical and biological activities. Quinazolinone derivatives reveal various medicinal properties such as analgesic, anti-inflammatory and anticancer activities, as well as antimicrobial activity. These heterocycles are valuable intermediates in organic synthesis. Therefore, various procedures have been developed for preparing these important compounds [1–5].

2. Syntheses of 4(3*H*)-quinazolinones

The syntheses of quinazolinones will be classified into the following three categories based on the substitution patterns of the ring system:

- 2-Substituted-4(3*H*)-quinazolinones
- 3-Substituted-4(3*H*)-quinazolinones
- 2,3-Disubstituted-4(3*H*)-quinazolinones

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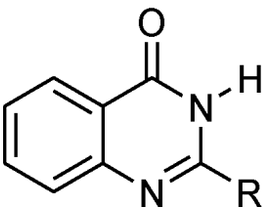
2.1 2-Substituted-4(3*H*)-quinazolinones



2.1.1 Amidation and cyclization of 2-aminobenzoic acid derivatives (anthranilic acid derivatives)

The most common approach involves amidation of 2-aminobenzoic acid derivatives (**Figure 1**). As an example, anthranilic acid derivatives **1** were coupled with the appropriate acid chloride to generate the corresponding substituted anthranilates **2** which underwent cyclization by treatment with acetic anhydride under reflux afforded the benzoxazin-4-ones **3**. Treatment of the benzoxazinones **3** with ammonia solution afforded the quinazolinone derivatives **4** [6]. Benzoxazinone derivatives can be obtained by treatment of anthranilic acid derivatives with acetic anhydride [7]. Also, the condensation of anthranilic acid derivatives with the *ortho* esters and ammonium acetate afforded the 2-substituted-4(3*H*)-quinazolinone derivatives [8, 9]. 2-Carboethoxy-quinazoline-4(3*H*)-one has been synthesized from the reaction of anthranilamide and diethyl oxalate [10].

2.1.2 Condensation of imidates with 2-aminobenzoic acid

Reaction between imidates and anthranilic acid **1** was reported for preparation of a series of quinazoline antifolate thymidylate synthase inhibitors [11]. The condensation of **1** and imidates **5** in methanol at 80°C afforded the desired quinazolinones **6** in good yield (**Figure 2**). The condensation reaction afforded the quinazolinones **6** in satisfactory to good yields. Connolly and Guiry extended this methodology to synthesize a series of 2-aryl- and 2-alkylquinazolinones [12].

2.1.3 Synthesis of quinazolinones from resin-bound isothioureas

A concise and efficient solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones **9** has been reported by involving the reaction of polymer-bound isothioureas **8** with isatoic anhydride derivative **7** with good yield and purity (**Figure 3**) [13].

2.1.4 Hetero-Diels: alder synthesis of 2-substituted quinazolinones

Synthesis of 2-substituted-quinazolinones **12** was reported by the cyclisation of 1-aryl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadienes **10** and phenyl

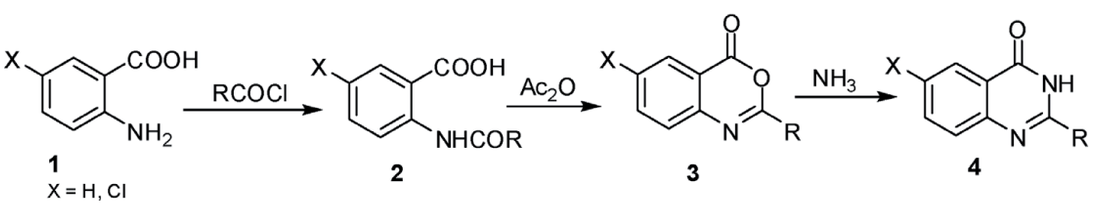


Figure 1.
*Synthesis of 2-substituted-4(3*H*)-quinazolinones **4**.*

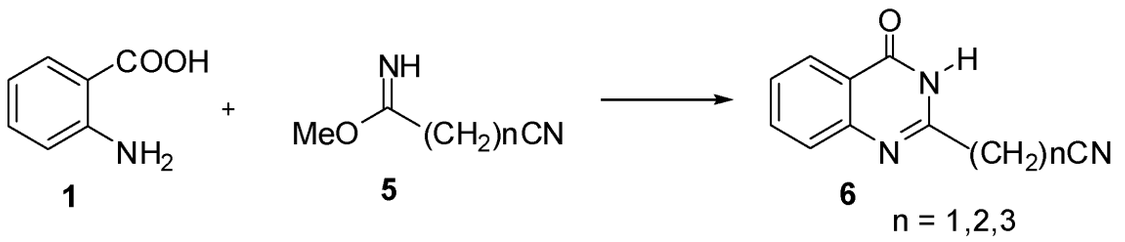


Figure 2.
Synthesis of 2-substituted-4(3H)-quinazolinones ***6****.*

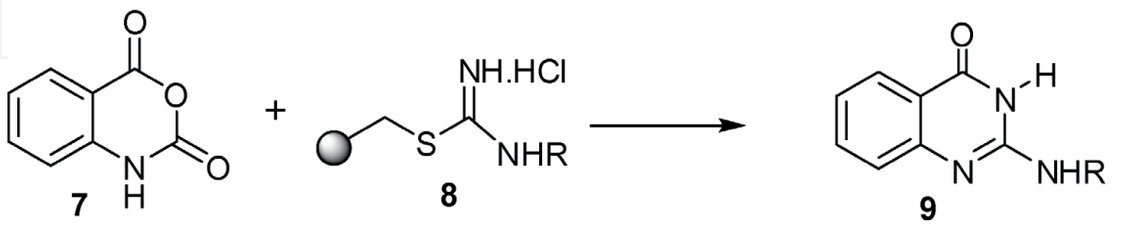


Figure 3.
Synthesis of 2-amino-4(3H)-quinazolinones ***9****.*

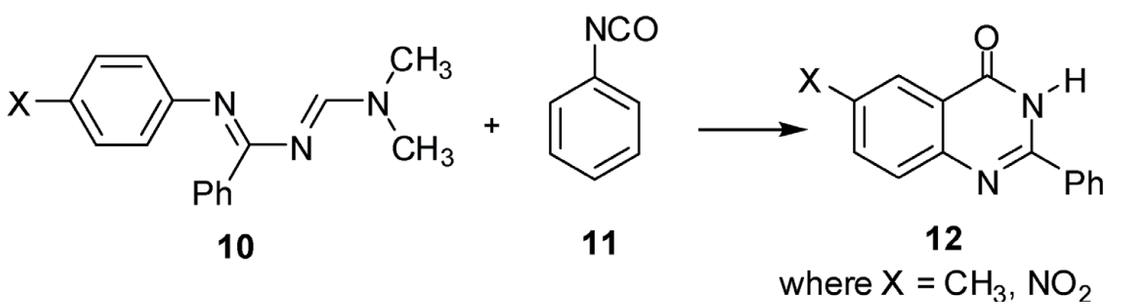


Figure 4.
Synthesis of 2-substituted-4(3H)-quinazolinones ***12****.*

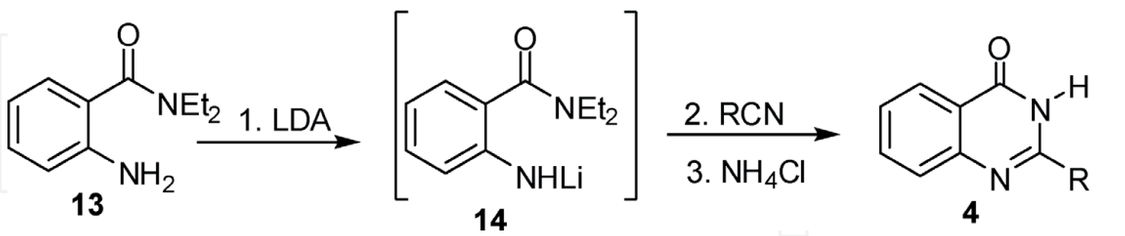


Figure 5.
Synthesis of 2-substituted-4(3H)-quinazolinones ***4****.*

isocyanate **11** [14]. The reaction was carried out under an atmosphere of nitrogen in toluene at reflux temperature, to furnish the desired products **12** in good yield (**Figure 4**).

2.1.5 Reaction of nitriles with lithiated 2-aminobenz- amides

A developed procedure for the synthesis of 2-aryl- and 2-alkyl-4(3*H*)-quinazolinones **4** by reaction of lithium 2-(diethyl aminocarbonyl) anilide **14** with the appropriate aryl or aliphatic nitrile has been reported [15]. This route is highly efficient when aryl and hetero-aryl nitriles were used. The intermediate **14** was prepared in situ by treating **13** with LDA in THF at −30°C (**Figure 5**).

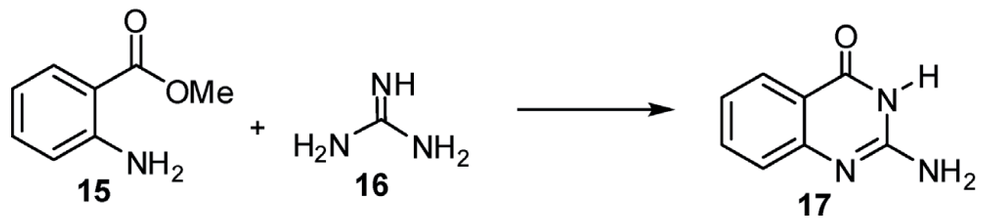


Figure 6.
*Synthesis of 2-amino-4(3*H*)-quinazolinone **17**.*

2.1.6 Condensation of anthranilate esters with guanidine

The 2-amino-4(3*H*)-quinazolinone **17** has been prepared from the reaction of methyl anthranilate **15** with excess guanidine **16** in the presence of sodium ethoxide in ethanol (**Figure 6**) [16].

2.1.7 Direct condensation of aldehydes and anthranilamide and its derivatives

Condensation of anthranilamide with aryl, alkyl and hetero-aryl aldehydes in refluxing ethanol in the presence of $CuCl_2$ generated the Schiff base intermediate **18**, which, in turn, was converted into the 2-substituted quinazolinones **4** in excellent yield (**Figure 7**). In a one-pot procedure, the aldehyde, anthranilamide and 3 equiv. of $CuCl_2$ were heated under reflux in ethanol for 2–3 h. After purification by chromatography, the 2-substituted quinazolinones **4** were isolated in 71–88% yield [17].

2.2 3-Substituted-4(3*H*)-quinazolines

2.2.1 Vilsmeier reagent in quinazolinone synthesis

3-Substituted-4(3*H*)-quinazolinone derivatives **22** have been prepared by treating 5-substituted-2-aminobenzoic acid derivatives **1** with the Vilsmeier

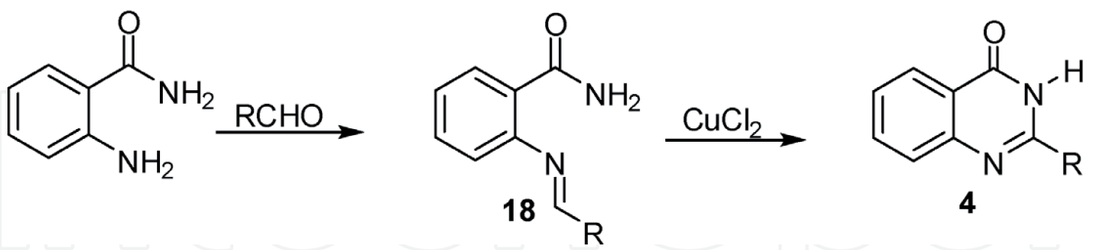


Figure 7.
*Synthesis of 2-substituted-4(3*H*)-quinazolinones **4**.*

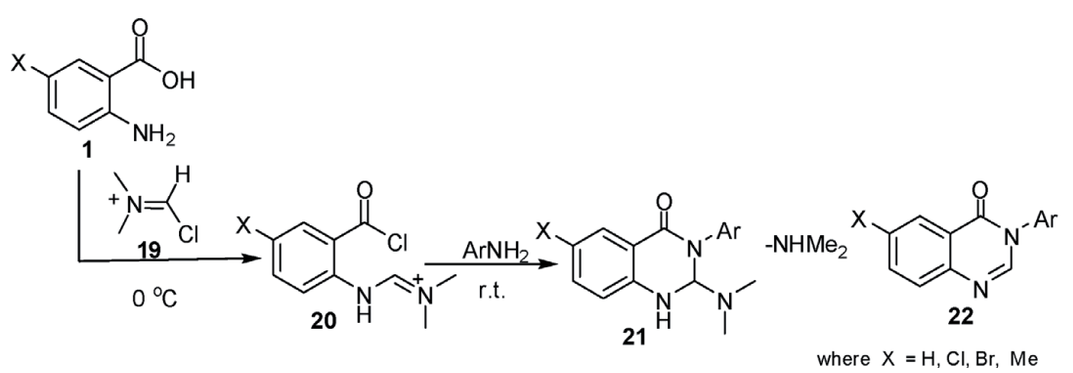


Figure 8.
*Synthesis of 3-substituted-4(3*H*)-quinazolinones **22**.*

reagent **19** [18] to give the corresponding acid chlorides **20**. When the external amine was added to the reaction mixture at low temperature, the added amine reacted with the acid chloride **20** with subsequent loss of HCl followed by cyclisation to afford the intermediate **21**, which then expels a dimethyl amino group to afford the appropriately substituted quinazolinone **22** (**Figure 8**).

2.2.2 Via benzoxazinones

The (4*H*)-3,1-benzoxazin-4-one **23** was reacted with amines under reflux to afford the quinazolinones **24** good yields (**Figure 9**) [19].

2.2.3 Via metal salts as catalyst

4(3*H*)-Quinazolinones **22** have been synthesized in high to excellent yields through the one-pot condensation of anthranilic acid **1**, trimethyl orthoformate and primary amines in the presence of 5 mol % of bismuth (III) trifluoroacetate ($Bi(TFA)_3$) immobilized on *n*-butylpyridinium tetrachloroferrate ([nbp] $FeCl_4$) as ionic liquid (**Figure 10**) [20]. Also, the one-pot reaction was carried out in the presence of lanthanum (III) nitrate hexahydrate or *p*-toluenesulfonic acid [21].

2.3 2,3-Disubstituted-4(3*H*)-quinazolines

2.3.1 Formation of 2,3-disubstituted quinazolinones via benzoxazinone

Benzoxazinones are well-known as common intermediates in the synthesis of 2,3-disubstituted quinazolinones **24**. The most common approaches to synthesize

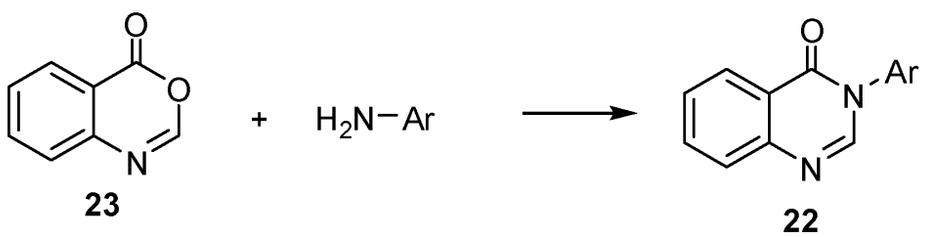


Figure 9.
Synthesis of 3-substituted-4(3H)-quinazolinones **22**.

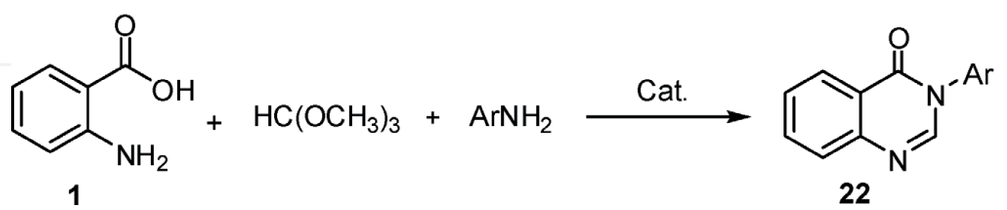


Figure 10.
Synthesis of 3-substituted-4(3H)-quinazolinones **22**.

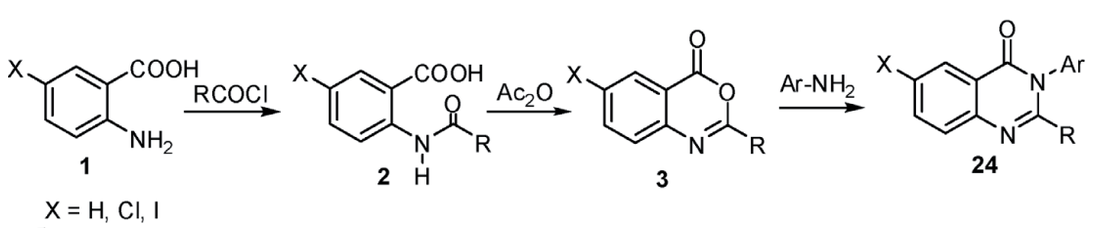


Figure 11.
Synthesis of 2,3-disubstituted quinazolinones **24**.

3,2-disubstituted-4(3*H*)-quinazolinone derivatives involve amidation of anthralinic acid derivatives **1** and then treatment of the amidated anthranilic acid derivatives **2** with acetic anhydride to afford 3,1-benzoxazin-4-ones **3** in good yield, followed by condensation with nitrogen nucleophiles such as aromatic amines [22–24] or heterocyclic amines [25] (**Figure 11**).

Condensation of benzoxazinone **3** with hydrazine hydrate in *n*-butanol afforded 3-amino-quinazolinones **25** in good yield (**Figure 12**) [26, 27]. Also, bis-quinazolinones **26** were prepared by condensation of two moles of benzoxazinones **3** with one mole of a diamine under reflux [28].

2.3.2 Formation of 2,3-disubstituted quinazolinones via amide derivatives

Xue et al. reported the optimisation of Grimmel's conditions for generating 2,3-disubstituted-4(3*H*)-quinazolinones [29]. Thus, when amide derivatives **2** were heated with anilines in toluene or xylene in the presence of dehydrating agents such as phosphorous trichloride, phosphorous oxychloride or thionyl chloride, quinazolinone derivatives **24** were afforded. Benzenesulfonyl chloride was employed as coupling agent [30]. Treatment of amide derivatives **2** with hydrazine hydrate afforded 3-aminoquinazolinone derivatives **25** (**Figure 13**).

2.3.3 Combinatorial approach to quinazolinones

Traceless and chemoselective approach for the solid-phase synthesis of 2-arylamino-substituted quinazolinones with the possibility of manipulation at three positions has been developed by Yu et al. [31]. The nitro group at compounds **27** was subjected to reduction using tin(II) to afford the *ortho*-amino derivatives **28** and subsequently reacted with some aryl isothiocyanates to give thiourea derivatives **29**. The thiourea derivatives **29** were subjected to react at first with 2-chloro-1-methyl pyridinium iodide (Mukaiyama's reagent) and then reacted with the primary amines to afforded the guanidine derivatives **30**. When the guanidine derivatives **30** were subjected to intramolecular cyclisation using hydrofluoric acid, the desired 2-amino-substituted quinazolines **31** were obtained in good yields (**Figure 14**).

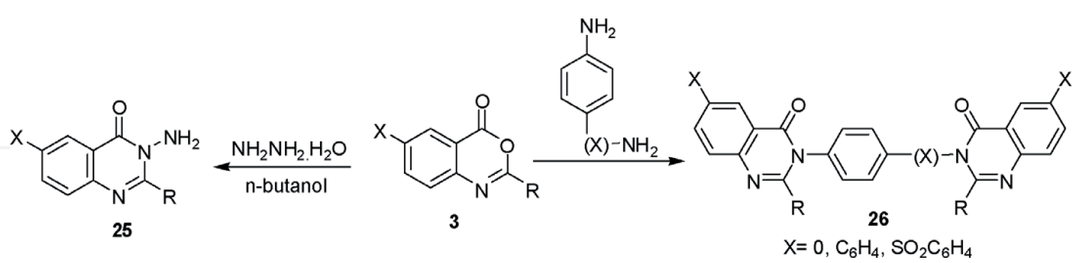


Figure 12.
Synthesis of 3-amino-quinazolinones 25 and bis- quinazolinones **26.**

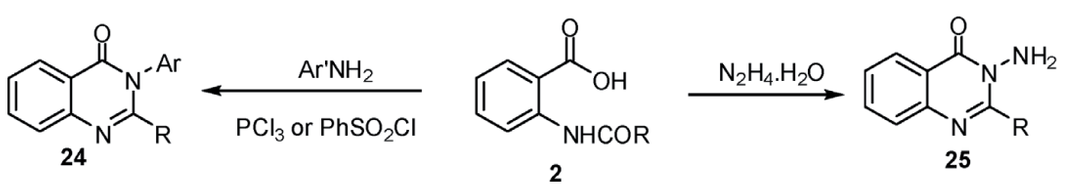


Figure 13.
Synthesis of 3-aminoquinazolinone derivatives **25.**

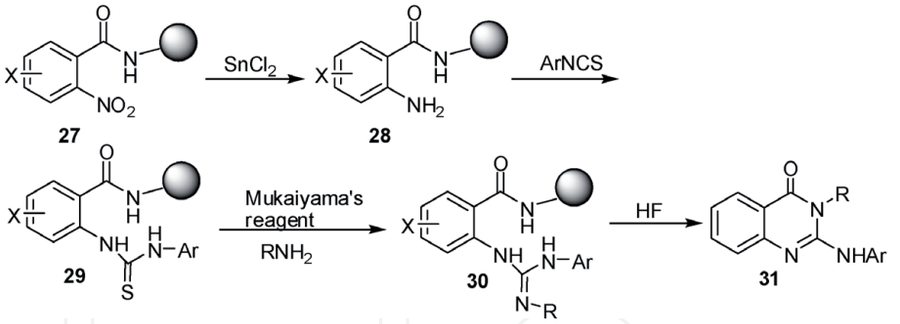


Figure 14.
Synthesis of 2-amino-substituted quinazolines ***31****.*

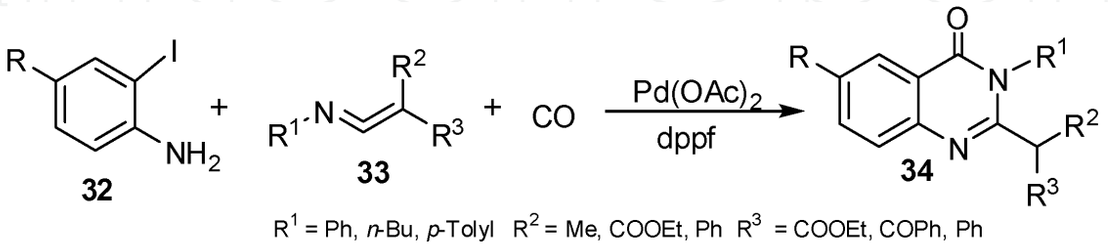


Figure 15.
*Synthesis of 2-alkyl-4(3*H*)-quinazolinones* ***34****.*

2.3.4 Quinazolinone derivatives via palladium-catalyzed cyclocarbonylation

Cyclocarbonylation of *o*-iodoanilines **32** with ketenimine **33** using a palladium acetate/diphenylphosphinoferrocene catalyst was employed under a carbon monoxide pressure to afford the 2-alkyl-4(3*H*)-quinazolinones **34** in good to excellent yields (**Figure 15**) [32].

2.3.5 Chemoselective lithiation of quinazolinone derivatives

By direct lithiation of the 2-unsubstituted quinazolinone **22,** it was possible to carry out a range of electrophilic substitutions [19]. Also, chemoselective lithiation of 3-(acylamino)-quinazolines **35** was obtained by using of LDA where the reaction was regioselective at position 2. The similar phenomenon was observed with the corresponding 2-methyl quinazolines [33]. Reactions of the dilithio reagents with a range of electrophiles resulted in the production of the corresponding 2-substituted-4(3*H*)-quinazolinone derivatives **37** (**Figure 16**).

2.3.6 Formation of 2,3-disubstituted quinazolinones via isatoic anhydride

A more attractive and atom-efficient strategy for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones **38** was reported, which involved a one-pot three-component

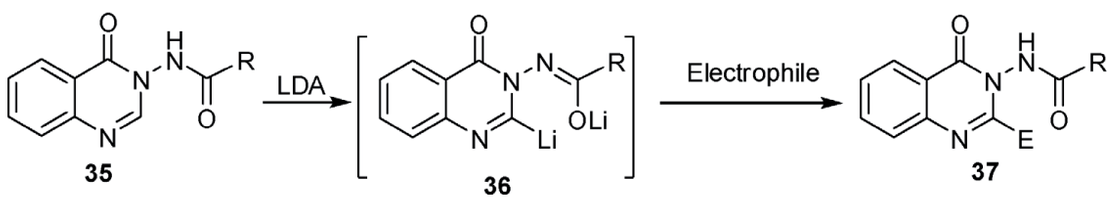


Figure 16.
*Synthesis of 2-substituted-4(3*H*)-quinazolinone derivatives* ***37****.*

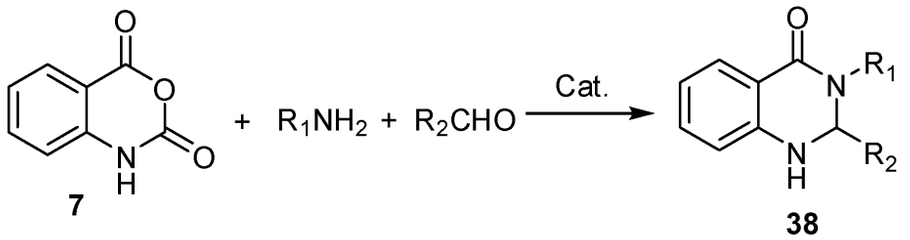


Figure 17.
*Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **38**.*

reaction of isatoic anhydride **7**, aldehydes and amines (**Figure 17**) [1, 34]. Multicomponent reactions or one-pot syntheses are attractive synthetic strategies, where the diversity may be achieved and the products are formed in a single step. A new method for the synthesis of 2-substituted-3-(phenylamino)-dihydroquinazolin-4(1*H*)-ones was developed; isatoic anhydride, phenylhydrazine and aldehyde using bentonite as catalyst in aqueous media under ultrasonic irradiation. This procedure showed good functional group tolerance [35].

3. Physical properties of 4(3H)-quinazolinones

3.1 Stability and tautomeric phase

4(3*H*)-Quinazolinones are stable to mild acid and alkaline treatment. They can be sublimated, and their parent substances can be redistillated. Weddige [36] recognized the tautomeric properties of 4(3*H*)-quinazolinones which could exit in three tautomeric forms **39a**, **39b** and **39c** (**Figure 18**). The presence of 4-hydroxy form **39b** was shown by its stability in aqueous alkali at pH 12 to give the anion. 4-Quinazolinones **39a** and **39c** are insoluble in alkali when a substitute is present on N^1 or N^3.

3.2 IR spectra

The IR spectra of 4(3*H*)-quinazolinone is characterized by a strong carbonyl band **39a** and **39c** at 1681 cm^{-1} and the N–H stretching band at 3402 cm^{-1} (inflection). Methyl groups in positions 2 and 3 have nearly the same effect in causing the carbonyl frequency to be lowered by 20–30 cm^{-1}. While methyl group at positions 1 and 2 lowered the frequency by 67 cm^{-1}, this large change was attributed to the presence of the β-double bond which is conjugated with the carbonyl group [37].

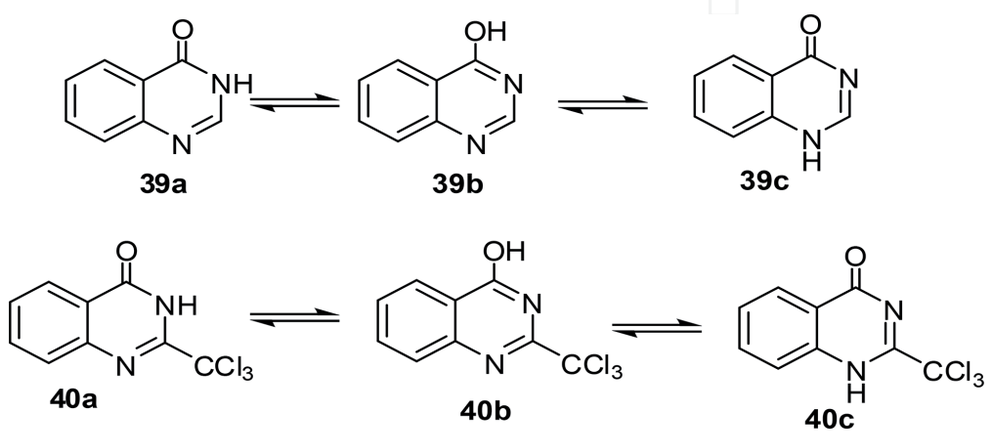
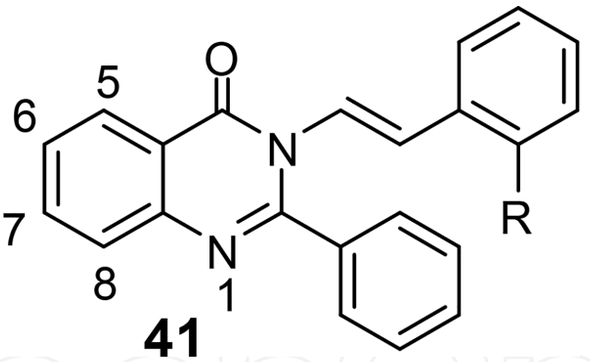


Figure 18.
*Tautomaric properties of 4(3*H*)-quinazolinones **39** and **40**.*



41

Figure 19.
*Numbering of 4(3H)-quinazolinone **41**.*

3.3 UV spectra

The apparent dissociation constants of 4(3H)-quinazolinone **39** and 2-substituted-4(3H)-quinazolinones **40** were determined (**Figure 18**). Also, Ab initio quantum chemical calculations were performed for all possible tautomeric and protonation. The observed UV spectra revealed the number of dissociation constants. They concluded that the curves of 4(3H)-quinazolinones could be accounted for a mixture of tautomers due to the mobil hydrogen atom on N-3. The results showed a good correlation between experimentally determined pK_a values and theoretically calculated energies [38].

3.4 NMR spectroscopic studies of 4(3H)-quinazolinones

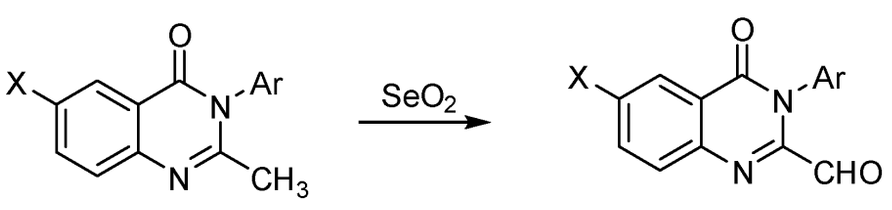
The NMR assignments of compound **41** (**Figure 19**) was based on simple ^{1}H and ^{13}C measurements and corroborated by ^{1}H-^{1}H COSY, gradient-enhanced ^{13}C-^{1}H HSQC and ^{13}C-^{1}H HMBC experiments. The ^{1}H NMR spectrum showed the aromatic protons in the range 7.27-8.56 ppm. From the 2D spectra, the signal assignments were thus at δ values: 8.56 (H5), 7.61 (H6), 7.65 (H7) and 7.27 ppm (H8) [39].

4. Chemical reaction of 4(3*H*)-quinazolinones

4.1 Reactivity of the 2-methyl group

4.1.1 Oxidation

The methyl group in the structure of 2-methyl-4(3*H*)-quinazolinones **24** has possibility for oxidation to generate further useful fictionalization at this position [22–24]. So, by using SeO_2 as oxidant agent, the methyl group in **24** was converted to



24 **42**

Figure 20.
*Synthesis of 4(3H)-quinazolinone-2-carboxaldehydes **42**.*

formyl group, and the novel 4(3*H*)-quinazolinone-2-carboxaldehydes **42** were furnished and subjected to further reaction to give new quinazoline derivatives having a azomethine, oxazolone, imidazolidine, pyrazolidine, pyridine, pyrimidine and variously substituted C-2. Also, series of 3-aryl-4(3*H*)-quinazolinone-2-carboxaldehyde thiosemicarbazones were synthesized via condensation of the 4(3*H*)-quinazolinone-2-carboxaldehydes **42** with the desired thiosemicarbazide derivatives (**Figure 20**).

4.1.2 Reaction with aldehydes

The 2-methyl group in substituted 4(3*H*)-quinazolinone is reactive as shown by the ease of its condensation with aldehydes to give the corresponding 2-styryl derivatives. 6-Chloro-2-methyl-quinazolin-4(3*H*)-one was refluxed for 12 h in glacial acetic acid with pyridine-2-carbaldehyde to give 6-chloro-2-(2-pyridin-2-yl-vinyl)-4(3*H*)-quinazolinone [7]. Also, a series of 3-[5-substituted phenyl-1, 3, 4-thiadiazole-2-yl]-2-styryl-4(3*H*)-quinazolinones **43** were synthesized by refluxing equimolar amount of 3-(1′3′4′-thiadiazolyl)-2-methyl quinazoline and aromatic aldehyde in glacial acetic acid [40] (**Figure 21**).

4.1.3 Bromination

The methyl group in 2-methyl-3-aryl-quinazoline has been found to undergo bromination by bromine to give bromomethyl compound **44** (**Figure 22**). Many compounds were synthesized via treatment compound **44** with potassium salts of organic compounds [40]. Other compounds were synthesized via treatment compound **47** with amine [41].

4.1.4 Lithiation

2-Methyl-4(3*H*)-quinazolinone **45** underwent fold metalation with alkyl lithium to form lithio salt **46** which react with electrophilies (methyl iodide, ethyl iodide, allyl bromide, benzyl chloride, etc.) exclusively at the exocyclic carbanion site to produce quinazolinone derivatives **47** (**Figure 23**) [42–44].

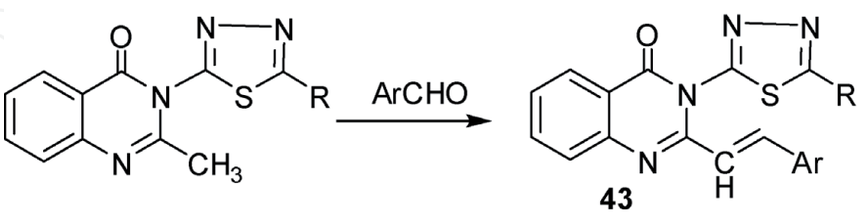


Figure 21.
*Synthesis of 2-styryl-4(3*H*)-quinazolinones **43**.*

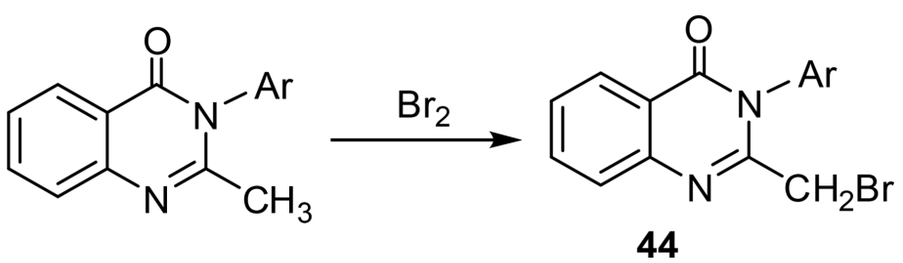


Figure 22.
*Synthesis 2-bromomethyl-3-aryl-quinazolines **44**.*

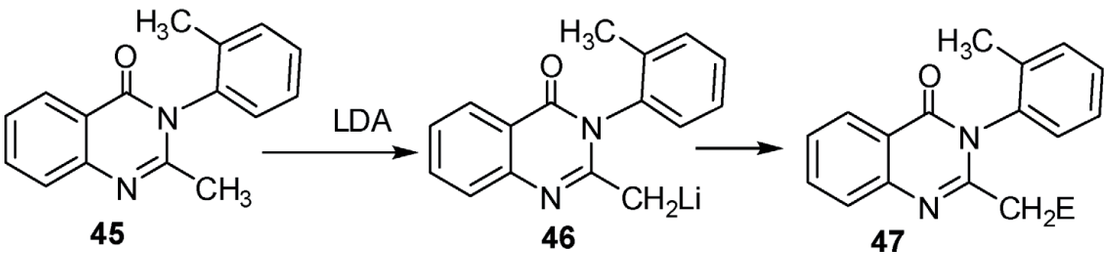


Figure 23.
Synthesis 2-substitutedmethyl-3-aryl-quinazolines ***47****.*

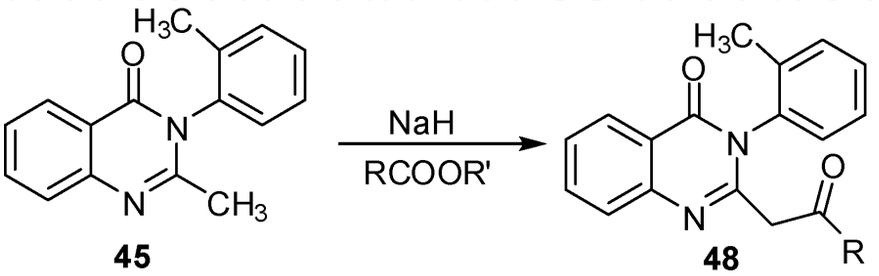


Figure 24.
Synthesis 2-substitutedmethyl-3-aryl-quinazolines ***48****.*

4.1.5 Acylation

A series of 4(3*H*)-quinazolinones **48** [45] structurally related to methaqualone (2-methyl-3-o-tolyl-4(3*H*)-quinazolinone) were synthesized and evaluated for anticonvulsant activity. They prepared by treating 2-methyl-3-aryl-4(3*H*))-quinazolinone **45** with sodium hydride followed by the appropriate methyl or ethyl ester (**Figure 24**).

4.2 Reactivity of the 3-amino group

4.2.1 Synthesis of cyanoacetamide derivative synthons

The thermal fusion of 3-amino-4(3*H*)-quinazolinone **49** with ethyl cyanoacetate afforded cyanoacetamide derivatives **50** (**Figure 25**). Cyanoacetamide derivatives **50** are highly reactive, polyfunctional compounds that possess both electrophilic and nucleophilic centres. Cyanoacetamide derivative **50** was widely used as an active synthon for the syntheses of many open-chain systems and poly-substituted heterocyclic compounds. The chemical properties of cyanoacetamide derivative **50** have been used to design various heterocyclic moieties with different ring sizes [26].

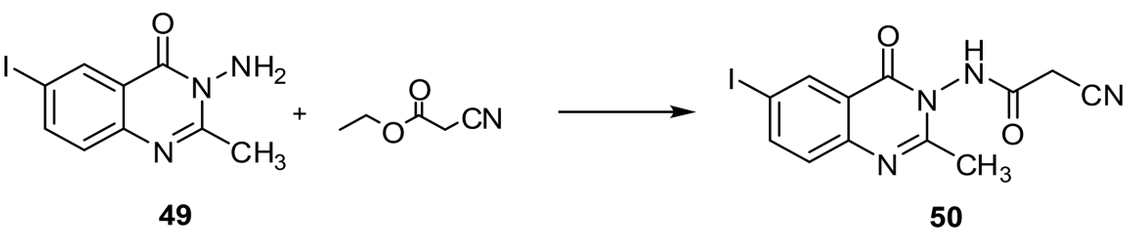


Figure 25.
Synthesis of cyanoacetamide derivatives ***50****.*

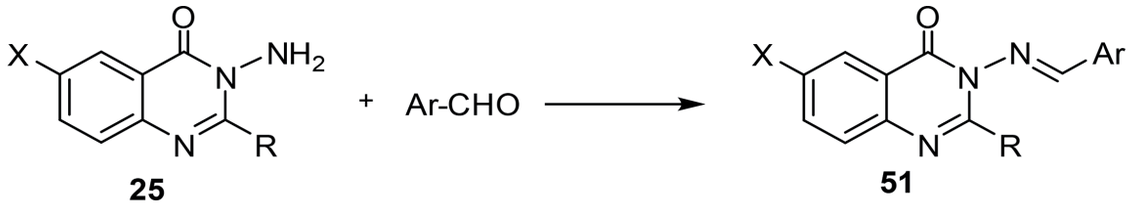


Figure 26.
Synthesis of Schiff's bases ***51****.*

4.2.2 Condensation with aldehydes

A series of Schiff's bases **51** were prepared essentially by the usual condensation reaction between the 3-amino-quinazolinone derivative **25** and the aldehydes (**Figure 26**). On the other hand, when two moles of compound **25** were treated with one mole of terephthaldehyde in ethanol under reflux, the polycyclic compound was obtained as bis-quinazolinones. Another bis-quinazolinone was obtained when two moles of compound **25** was treated with one mole of ethyl *tere*-phthalate in dimethylformamide under reflux conditions [27, 46].

4.2.3 Acylation and/or alkylation

Acylation and/or alkylation of 3-amino-4(3*H*)-quinazolinones **25** using ethyl chloroformate, ethyl chloroacetate, chloro acetylchloride and ethyl acetoacetate in proper solvent afforded 3-(*N*-acyl/aroylamino)-2-methyl-4(3*H*)-quinazolinone derivatives **52** [47] (**Figure 27**).

4.2.4 Reaction with isocyanate and isothiocyanates

Some new urea and thiourea derivatives **53** were synthesized by treatment of 3-amino-4(3*H*)-quinazolinones **25** with isocyanates and isothiocyanates [28] (**Figure 28**).

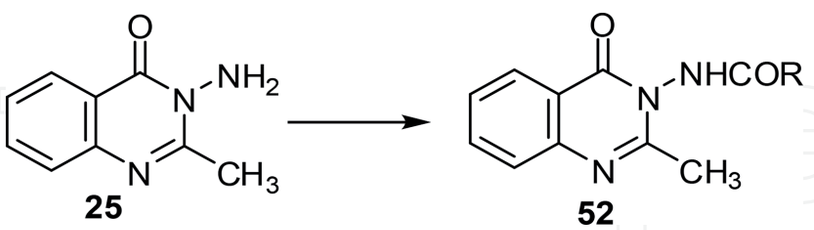


Figure 27.
*Acylation or alkylation of 3-amino-4(3*H*)-quinazolinones* ***25****.*

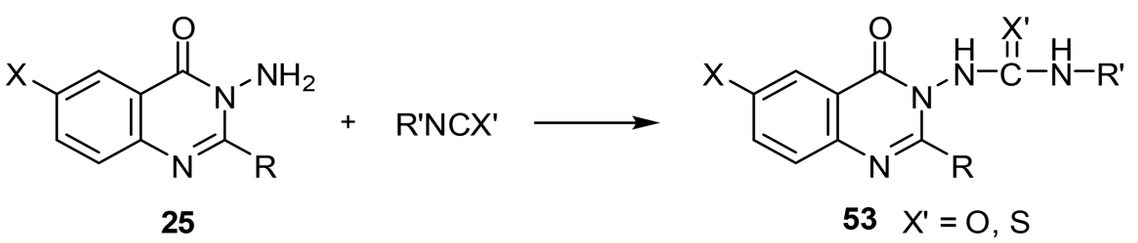


Figure 28.
Synthesis of urea and thiourea derivatives ***53****.*

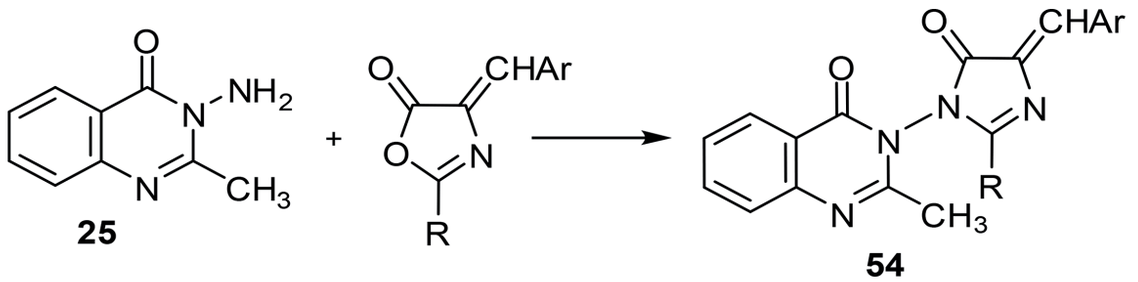


Figure 29.
Synthesis of imidazole derivatives ***54****.*

4.2.5 Reaction with oxazole

Condensation of 3-aminoquinazoline **25** with oxazole derivatives afforded imidazole derivatives **54** [47] (**Figure 29**).

4.3 Electrophilic substitution

4.3.1 Nitration

Nitration of 4(3*H*)-quinazolinone **39** with fuming nitric acid and sulphuric acid afforded 6-nitro-4(3*H*)-quinazolinone derivative **55** [48] (**Figure 30**).

4.3.2 Chlorination

Heating of 4(3H)-quinazolinones **56** with chlorination agent afforded 4-chloroquinazolines **57** [49]. Chlorination agent was phosphoryl chloride alone or a mixture of phosphorus pentachloride and phosphoryl chloride, other chlorinating agents such as thionyl chloride or phosgene was used for chlorination of quinazolinones (**Figure 31**).

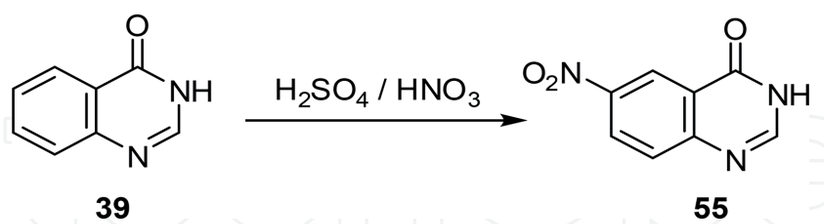


Figure 30.
*Nitration of 4(3*H*)-quinazolinone* ***39****.*

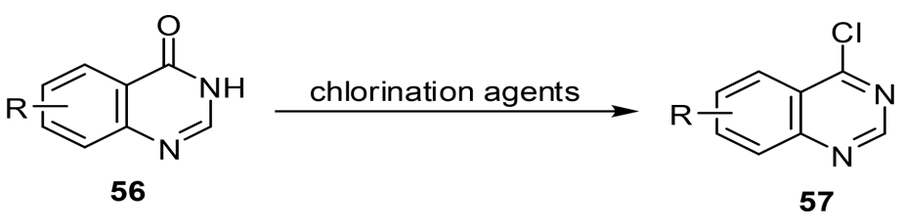


Figure 31.
*Chlorination of 4(3*H*)-quinazolinone derivatives* ***56****.*

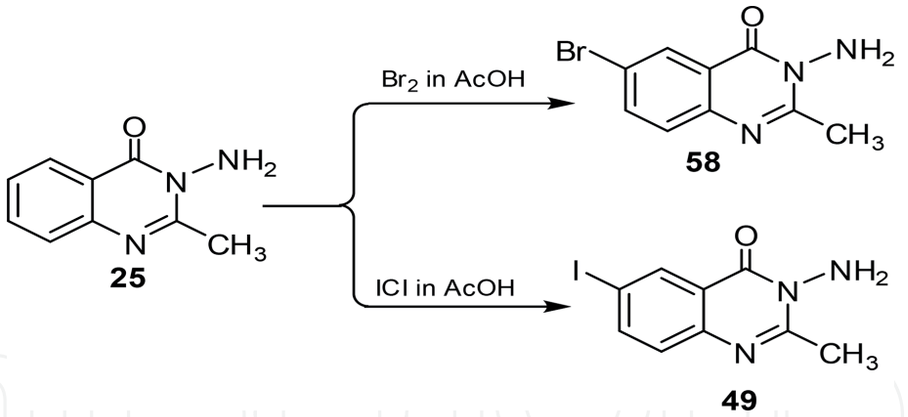


Figure 32.
*Synthesis of 6-bromoquinazolinone **58** and 6-iodoquinazolinone **49**.*

4.3.3 Bromination

The use of bromine in acetic acid for direct bromination of 3-amino-2-methylquinazolin-4(3*H*)-one **25** has been reported for the formation of 6-bromo-3-amino-2-methylquinazolin-4(3*H*)-ones **58** (**Figure 32**) [50].

4.3.4 Iodination

Treatment of 3-amino-2-methylquinazolin-4(3*H*)-one **25** with iodine monochloride in acetic acid afforded the corresponding 6-iodo-3-amino-2-methylquinazolin- 4(3*H*)-one **49** in high yields [50] (**Figure 32**).

4.4 Reaction of 4(3*H*)-quinazolinones with metal ions

3-Amino-4(3*H*)-quinazolinones **25** possess coordinating sites and they were applied to form complexes **59** and bis-complexes **60** with different metal ions (**Figure 33**) [51–53]. Also, considerable attention has been directed to the chemistry of their Schiff's bases **51** and **61** [27], where the Schiff's base complexes of 4(3*H*)-quinazolinones **62**-**65** were prepared and characterized. The complexes of metal ions with 2-substituted-3-anilino-4(3*H*) quinazolinone were prepared [54]. Moreover, the complexes of Cu (II), Co (II), Zn (II) and Cd (II) with 2-methyl-3-hydroxy-4(3*H*)-quinazolinone and 2-methyl-3-pyridinyl-4(3*H*)-quinazolinone have been prepared [55]. The analytical and spectral data indicate these ligands act as bidentate and the metal complexes are octahedral, tetragonal, square planer and tetrahedral [56].

Thiosemicarbazones can be reacting with metallic cations to give metal complexes. Thiosemicarbazones **66** as the ligands act as chelating agents which were bonding through the sulfur and azomethene nitrogen atoms (**Figure 34**). So, when metal salts such as $CuCl_2$ or $ZnCl_2$ were treated with the thiosemicarbazone derivatives **66** (0.01 mole) in dioxane the corresponding complexes **67** were obtained in good yield. On the other hand, the corresponding biscomplexes **68** were afforded when a solution of $CuCl_2$ or $ZnCl_2$ (0.01 mole) was added to a stirred solution of thiosemicarbazone derivatives (0.02 mole) in dioxane at reflux temperature [22].

4.5 Cycloaddition reaction

Reaction of quinazolinone derivatives **69** with malononitrile gave pyrrolo-quinazolinones **70** [57] (**Figure 35**). Several new pyrrolo-quinazolinone derivatives

were synthesized via a novel rote involving the action of dipolarophiles on the diionic species generated in situ from the reaction of N-chlorosuccinimide with 2-methylquinazolin-4-one and subsequent treatment with triethyl amine [58].

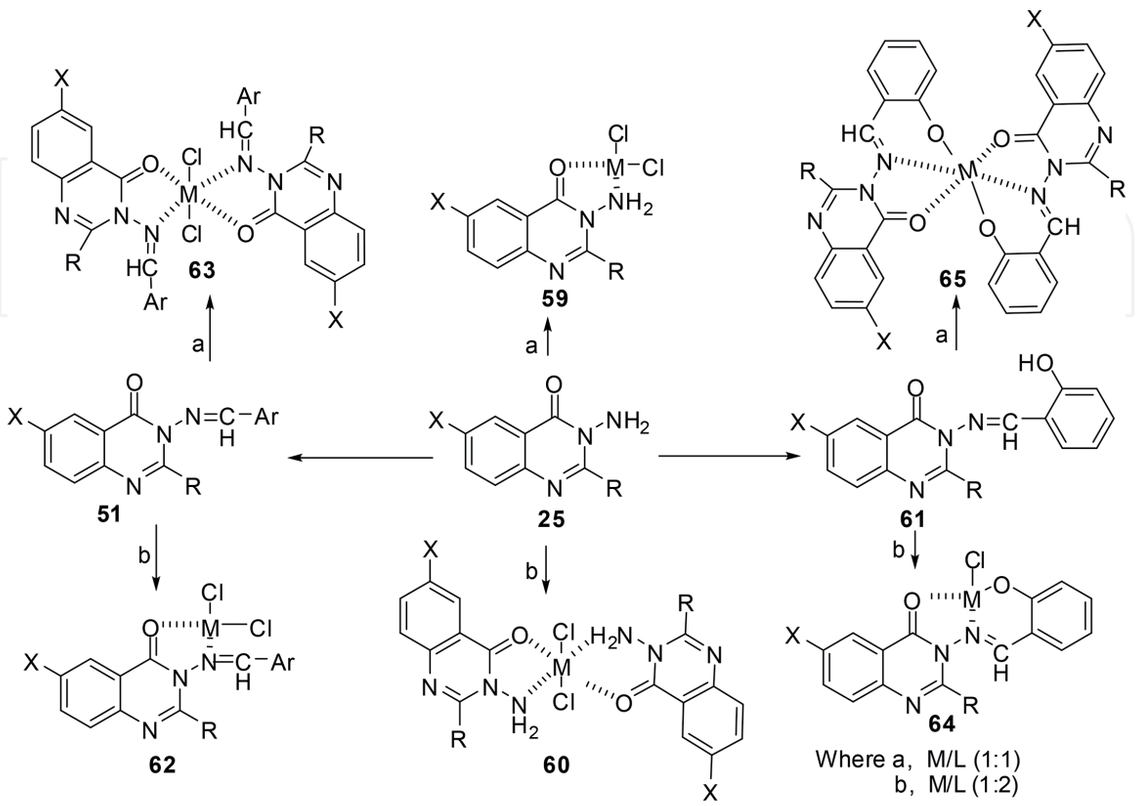


Figure 33.
*Reaction of 4(3H)-quinazolinones **25, 51** and **61** with metal ions.*

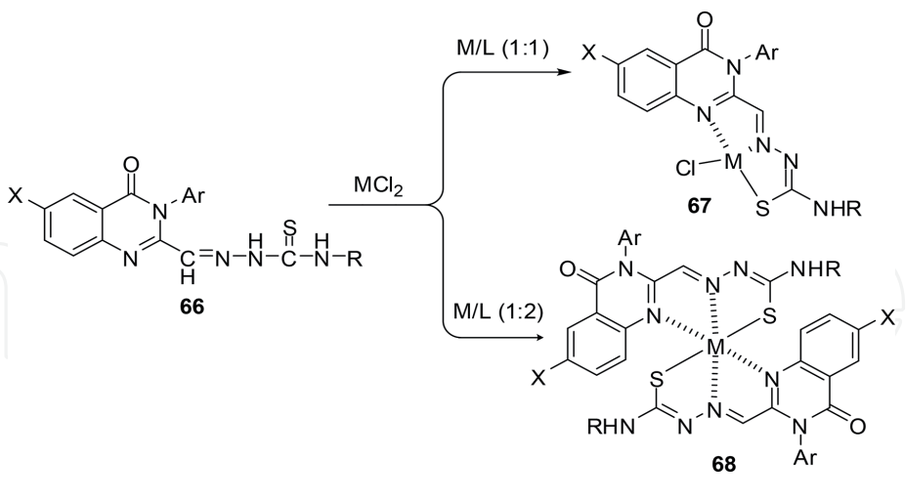


Figure 34.
*Preparation of thiosemecarbazone complexes **67** and **68**.*

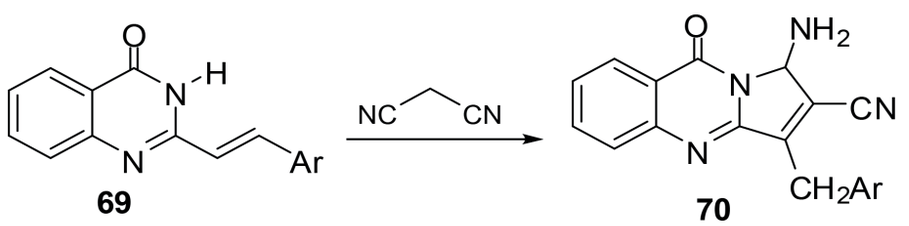


Figure 35.
*Synthesis of pyrrolo-quinazolinones **70**.*

4.6 Action of phosphorous sulphide

Treating of 4(3*H*)-quinazolinone derivatives **24** with P_2S_5 or phosphorus decasulfide in pyridine afforded the corresponding 2-methyl-3-aryl-quinazoline-4(3*H*)-thiones **71** [59] (**Figure 36**).

5. Biological properties

Quinazoline is the building stone for many naturally occurring alkaloids [60]. Many 4(3*H*)-quinazolinone derivatives represent an important category among heterocyclic compounds of medicinal interest. Other derivatives of 4(3*H*)-quinazolinones possess a wide range of biological activities especially on the central nervous system. Moreover, other quinazoline derivatives have been reported for their broad-spectrum biological activities as herein illustrated.

5.1 4(3*H*)-Quinazolinone derivatives as antitumour

Structure modification of folic acid led to the discovery of a number of antifolates as efficient anticancer agents. For example, Raltitrexed has been registered for the treatment of cancer [61]. Many quinazolinone derivatives with side chains have been reported to exhibit significant inhibitory activity against tumor cells [62]. The 2-substituted mercapto-4(3*H*)-quinazolinone bearing 6-iodo and 2-heteroarylthio is identified as active anticancer agent [63].

5.2 4(3*H*)-Quinazolinone derivatives as sedative hypnotic agents

The designation of the sedative hypnotic activity of 4(3*H*)-quinazolinones led to the discovery of methaqualone as nonbarbiturate hypnotic agent. In 1965, methaqualone was introduced as sleeping pills (nonaddictive, nonbarbiturate) under the trade name Quaalude. Due to the abuse of methaqualone, it is banned in most countries [64].

5.3 4(3*H*)-Quinazolinone derivatives as anticonvulsant agents

The search for new antiepileptic drugs with reduced toxicity and lower side-effects is continuous. 4(3*H*)-Quinazolinone represents a very good nucleus for preparation of some new sedative/hypnotic and anticonvulsant agents, since such a heterocyclic system possesses the pharmacophoric moiety. From the literature survey, it was found that the 3*H*-quinazolin-4-one has been reported to possess different pharmacological effects, namely, sedative-hypnotic and anticonvulsant ones [65].

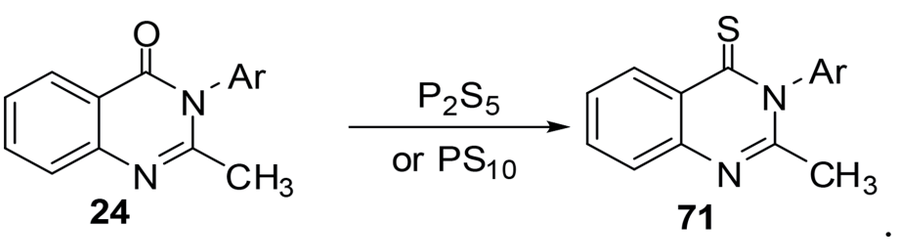


Figure 36.
*Synthesis of 2-methyl-3-aryl-quinazoline-4(3*H*)-thiones **71**.*

5.4 4(3*H*)-Quinazolinone derivatives as antimicrobial agents

A large number of quinazolinone derivatives have been synthesized and screened for their antimicrobial activities, and some of them showed their efficacy [66]. Also, quinazolinones metal complexes were synthesized, and their antimicrobial activities were screened. It is observed that the ligands exhibited less fungicidal activities than their complexes. Also the antibacterial activities were increased when quinazolines were complexed with metals.

5.5 4(3H)-Quinazolinone derivatives as anti-inflammatory agents

Thiadiazolyl-3-amino-4(3*H*)-quinazolinone derivatives was prepared in quantities yields. The products were evaluated for anti-inflammatory properties by std. in vivo and in vitro models, and they exhibited significant protection against carrageenan-induced rat paw oedema [67].

5.6 4(3H)-Quinazolinone derivatives as diuretic agents

Some 4(3*H*)-quinazolinone derivatives bearing thiazole or 1,3,4-thiadiazole moieties were prepared due to their expected diuretic activity. Some of them showed significant diuretic activity [68].

6. Conclusion

A large number of compounds which contain quinazoline moiety are known in medicinal chemistry as important compounds for their therapeutic value. Recently, there has been an increased interest in the chemistry of 4(3H)-quinazolinone system. Many derivatives of this system showed analgesic, anti-inflammatory, antiulcer, anticonvulsant, antibacterial, antifungal, anticancer and antiproliferative activities. The most common approaches to synthesize 3,2-disubstituted-4(3H)-quinazolinone derivatives involve the following steps: the amidation of 2-aminobenzoic acid derivatives and treatment of amidated anthranilic acid derivatives with acetic anhydride (or acid chloride) to afford the benzoxazinone, followed by their condensation with nitrogen nucleophiles.

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