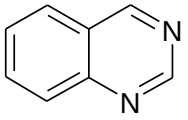
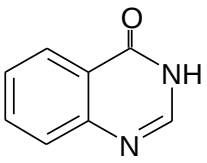
INTRODUCTION

The quinazoline and their fused analoques appears in many alkaloids. Quinazoline is 1,3-diazanaphthalene (1) is also known as phenmiazine, benzyleneamidine, benzo-1,3-diazine or 5,6-benzo-pyrimidine[1], its 4-oxoderivatives called 4(3H)-quinazolinone (2) and it is an important pharmacophore. For example, metolazone (3), fenquizone (4) and quinethazone (5) are sold as diuretic drugs [2,3]. Mecloqualone (6, R = Cl) and methaqualone (6, R = Me) are used as sedative and hypnotic [4]. Rutaecarpine[5](7) is one of several quinazolinocarboline alkaloids isolated from various plants of the Rutaced family (e.g.citrusbelongs), chrysogine[6](8) (isolated from molds) and derivatives of auranthine[7,8](9) (abenzodiazepine alkaloid, vide infra). Quinazolinone are important pharmacophore showing many types of pharmacological activities and are considered to be "Privileged structure"[9]. Many quinazolinone derivatives are antimetabolite, CNS depressant[10] antimicrobial[11-13] antibacterial[14-16] antimalarial[17-19] analgesic[20] antifugal[21-22] anti-inflammatory[23] antiuleer[24] anti-convulsant[25] antihypyertensive[26], sedative[27], anaesthetic[27] tranquilising and muscle relaxant[28] antidepressant[29] antihelmentic[30] inhibition of AMDA receptor activation[31] antihistamine[32] insecticidal[33] H_2-antagonist and antisecretion activity[34], tyrosine kinase inhibiting effect and useful to inhibit turnour growth. It's also found application as heat stable epoxy resins[35] fiber reactive dyes[36] polymers[37].



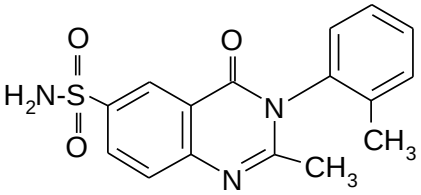
1,3-Diazanaphthalene

1



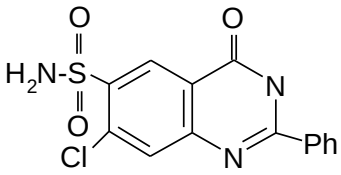
4-(3*H*)-quinazolinone

2



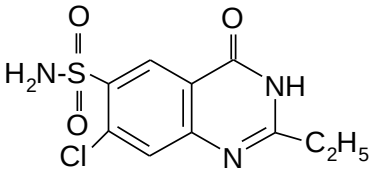
Metolazone

3



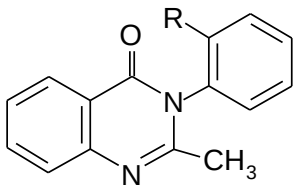
Fenquizone

4



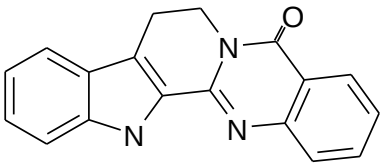
Quinethazone

5



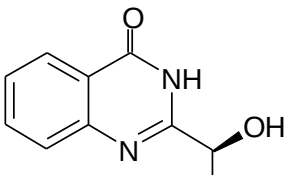
Mecloqualone (R = Cl)
and methaqualone (R = Me)

6



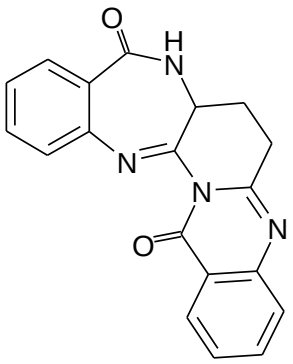
Rutaecarpine

7



Chrysogine

8



Auranthine

9

Synthesis of 4-(3H)-quinazolinones from anthranilic acid or its derivatives

Synthesis of quinazoline from ring closure of anthranilic acid or its derivatives:

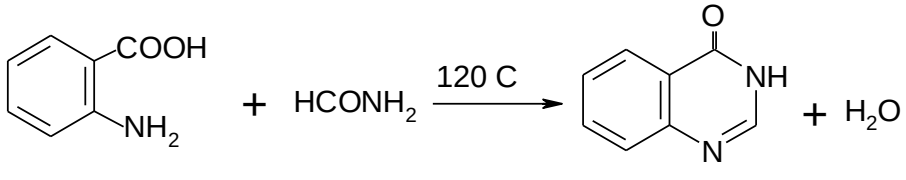
It can be carried out via one of the following types:

Direct cyclization of anthranilic acid derivatives with formic acid or its derivatives such as ester amide and urea under different reaction conditions to give 4(3H)-quinazolines. Anthranilic acid derivatives were converted to anthranilamides by acid chlorides, followed by ring closure with formamide yielded the corresponding 4(3H)-quinazolinones, and also cyclization of anthranilamides with AC_2O to give 3,1-benzoxazinones and subsequent treatment with $RCOONH_4$, RNH_2 and/or $RNHNH_2$ afforded the corresponding 4(3H)-quinazolinones. Anthranilic acid derivatives were transformed into urea or thioureds with arylisocyanate and arylisothiocyanates. Cyclization of urea or thioured derivatives by using base and amine or hydrazine to give 4(3H)-quinazolinones.

Niementowski Preparation:

The most common synthesis of 4-(3H)-quinazolinone is the reaction which was first described by Vi Niementowski in 1895[(38)] and until today bear his name.

When anthranilic acid is heated with excess formamide at 120 °C water was eliminated and nearly aquantitative conversion to 4-(3H)-quinazolinone was achieved.

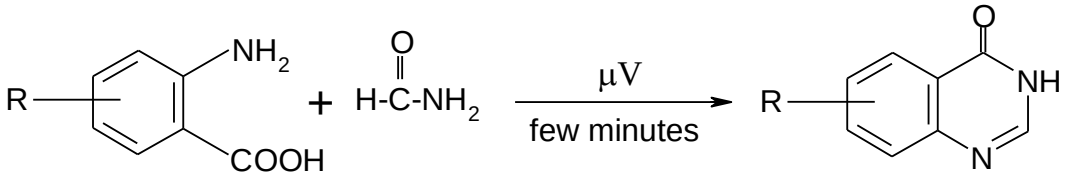


10

Microwave irrigation for synthesis quinazolinone

Modifiation of Niementowski reaction were carried out by microwave assisted synthesis,[39] an equimolar amount of the reactants were mixed and irradiated under microwaves[40] to provide the yield.

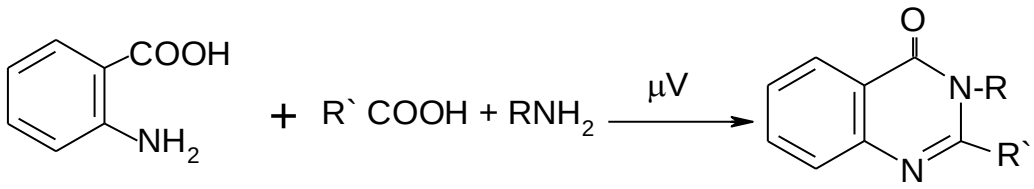
4(3H)-quinazolinone were prepared by cyclocondensation reaction under microwave irradiation for mixture of anthranilic acid or its derivatives and formamide in few minutes[41, 42].



11

R=6-Cl, 6-MeO, 7-Cl, 7-NO_2,H

Also one-pot synthesis of quinazolin-4(3H)-one from a mixture of anthranilic acid, formic acid and amines by microwave irradiation were carried.



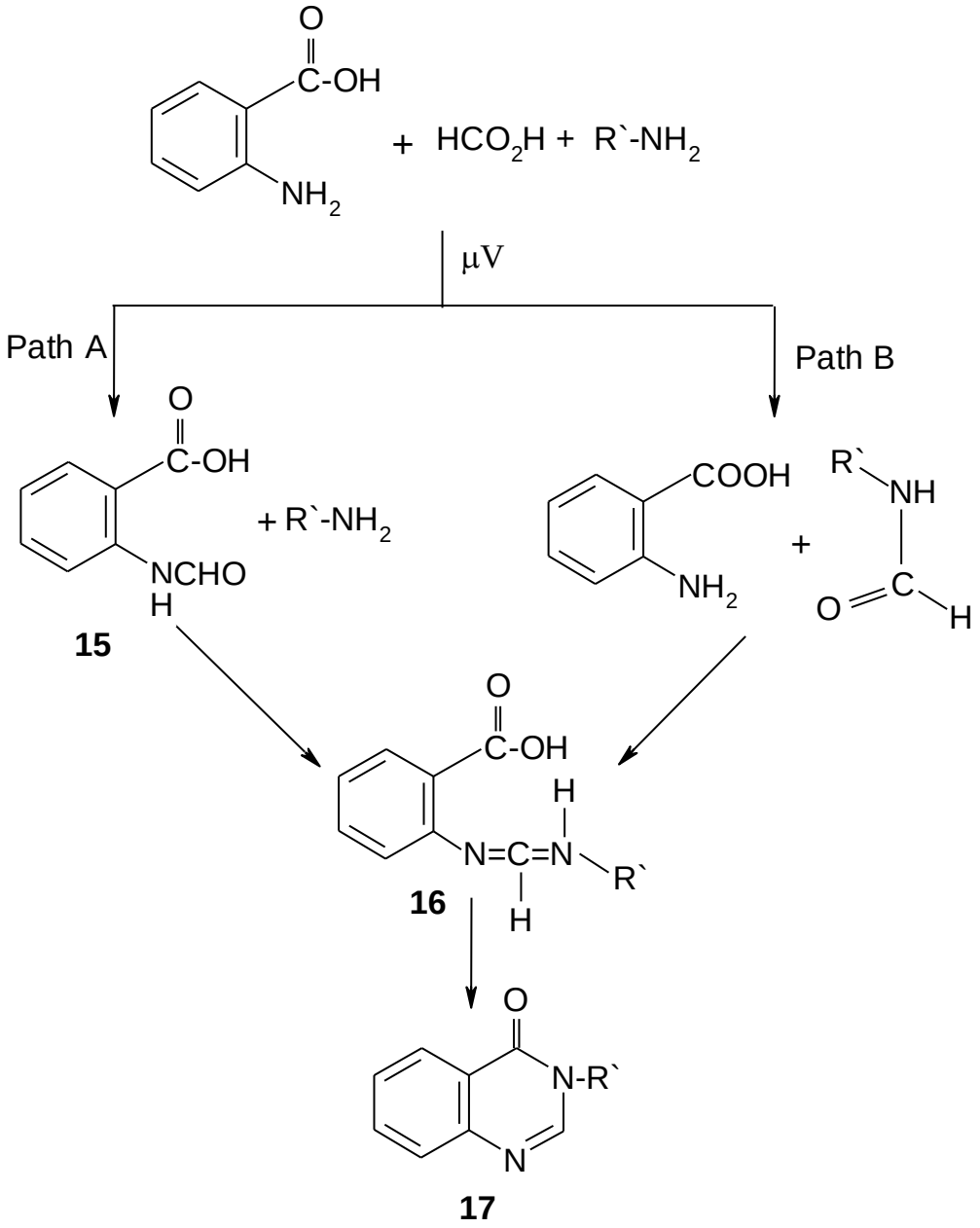
12 a-e **13 a-b** **14 a-g**

11a R^1 = phenyl
11b R` = 2-hydroxyphenyl
11c R` = methyl
11d R` = octanyl
11e R` = 3-nicotinyl

12a, R = Phenyl
12b, R = 2-Furfuryl

13a, R= R` = phenyl
13b, R = Phenyl, R` = hydroxyphenyl
13c, R = Phenyl, R` = methyl
13d, R = phenyl, R` = octanyl
13e, R = 2-furfuryl, R`=phenyl
13f, R = 2-furfuryl, R` = 2-hydroxyphenyl
13g, R = 2-furfuryl, R` = 3-nicotinyl

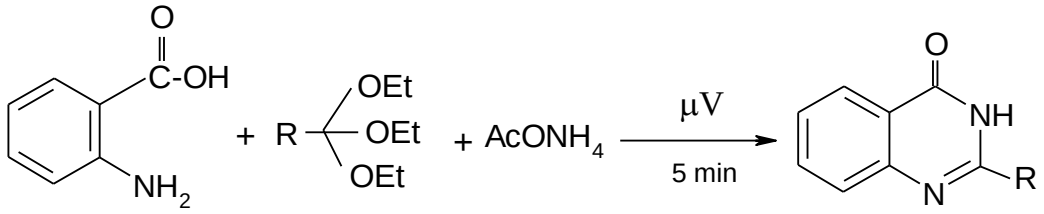
The reaction can proceed via two path ways A and B. Path A involves N-formylatioin of anthranilic acid and gave (15), treated (15) with amine form (16), followed by intermolecular cyclization to produce (17), in path (B) the amine was condensated to form (16) which was cyclized to afford (17)[43].



17 a R= Ph
17 b R = 4-Cl-C_6H_4
17 c R' = CH_2Ph

Rad-Moghadam and Mohseni*[(44)] *preparation:

2-Substituted quinazolin-4(3H)-one (18) could be synthesize under microwave conditions, this involves the condensation of anthranilic acid, ammonium acetate and orthoesters.

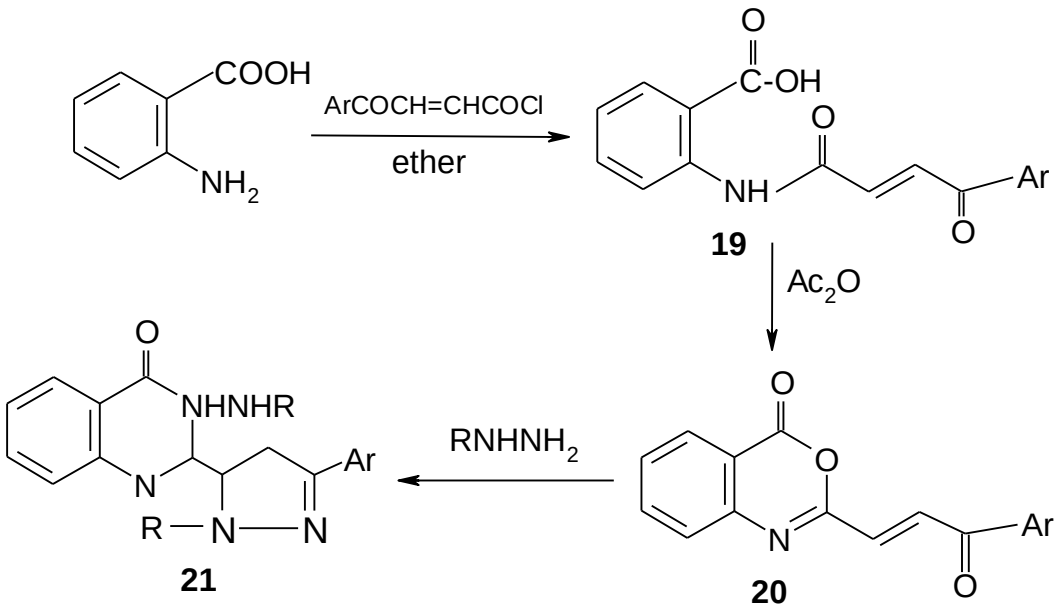


R = H, Me, Et, Pr, Bu, Ph

18

Synthesis from anthranilic acid and propenoyl chloride:

Soliman and co-workers[45] reported the synthesis of 2-pyrazoyl-4(3H)-quinazolinone starting from 3-aroylpropenoyl chloride and anthranilic acid as the following scheme.

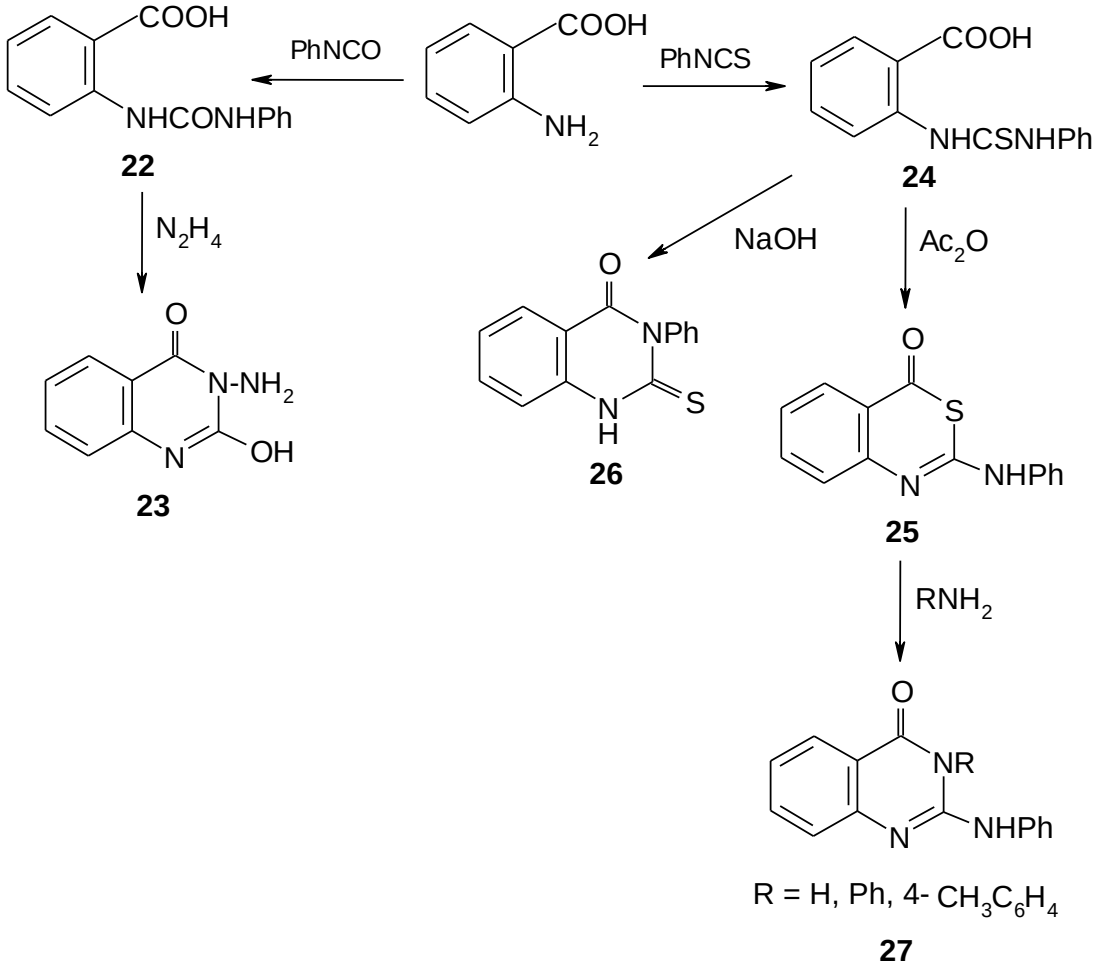


R = H, Ph, Ar = 4- $CH_2C_6H_4$, 2,4- $(CH_3)_2C_6H_3$, 2,4,6- $(CH_3)_3C_6H_2$

Synthesis from anthranilic acid and aryl isocyanate or aryl isothiocyanate[46-48]:

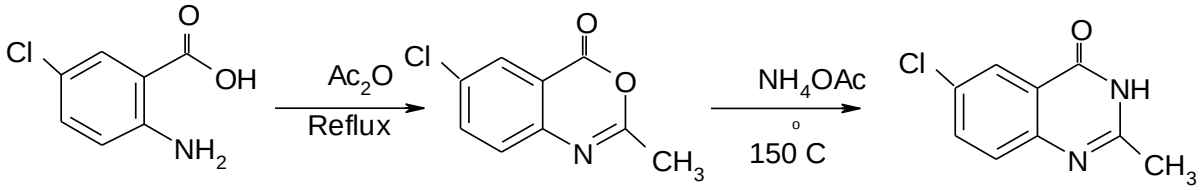
The starting substituted urea and substituted thiourea were synthesized according to the reaction of anthranilic acid with arylisocyanate and/or arylisothiocyanate. Hydrazonlysis of 2-(3-phenyl thioureado)benzoic acid (22) with hydrazine hydrate yielded the

corresponding 3-amino-2- hydroxyl-4(3H)-quinazolinone (23). Cyclization of 2-(3-phenyl-thioureado)-benzoic acid (24) with acetic anhydride or sodium hydroxide afforded the corresponding 2-N-phenylamino-4H-3,1-benzothiazin-4-one (25) and 3-N-phenyl-4(3H)-quinazolin-2-thione (26) respectively. Reaction of (25) with different amines yielded the corresponding-3-substituted-2-N-phenylamino-4(3H)quinazolinone (27).



From anthranilic acid and acetic anhydride followed by ammonium acetate[49-51]**.**

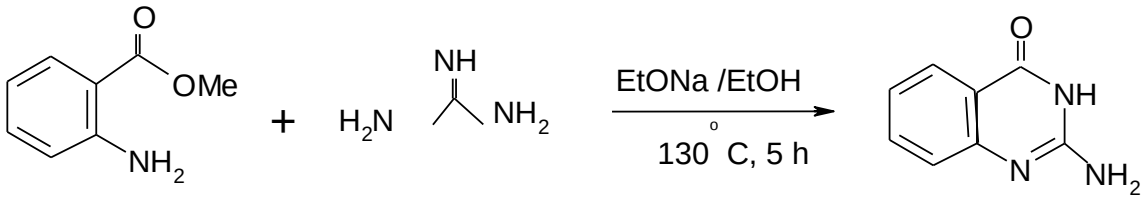
Treatment of 5-choloranthranilic acid with Ac_2O afford benzo-oxazinone (28), which on treating with ammonium acetate at an elevated temperature. It afforded 6-chloro-2-methyl quinazolin-4(3H)-one (29).



28 **29**

From anthrinalate ester and guanidine:

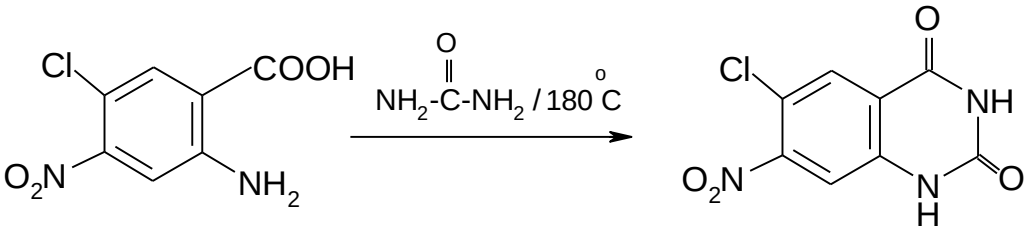
Condensation of anthrinalate esters (30) with guanidine (31), Hess et al.[52], prepared amino-quinazoline-4-3(H)-one (32). From corresponding methyl anthrinalate with access guanidine in presents of sodium ethoxide.



30 **31** **32**

From anthranili acid and urea

Cyclization of 2-amino-5-chloro-4-nitrobenzoic acid with urea at 180 °C gave the corresponding 2,4-dioxo-6-chloro-7-nitro-1,2,3,4-tetrahydro-quinazoline (33) [53].



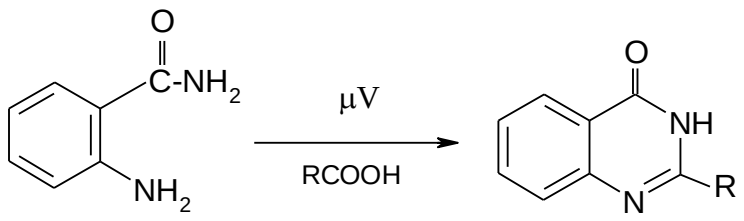
33

From Anthranilamide derivatives:

1- Reaction of anthranilamide and carboxylic acid:

Preparation of 2-substituted-4(3H)-quinazolinones in high yields was developed by microwave induced heterocyclization of 2-

aminobenzamide (34) with carboxylic acids in solvent, the reaction is 40-80 time faster under the microwave irradiation[(54)].

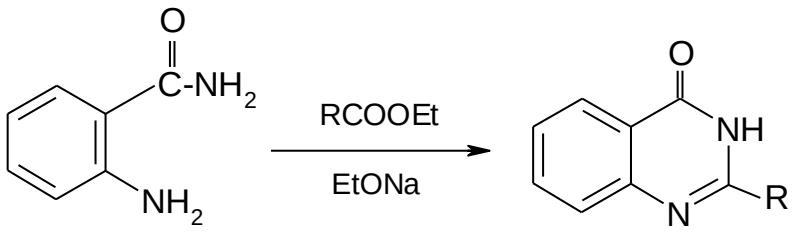


34 **35**

R = H, Me, Ph, 2-Cl-C_6H_4, ……

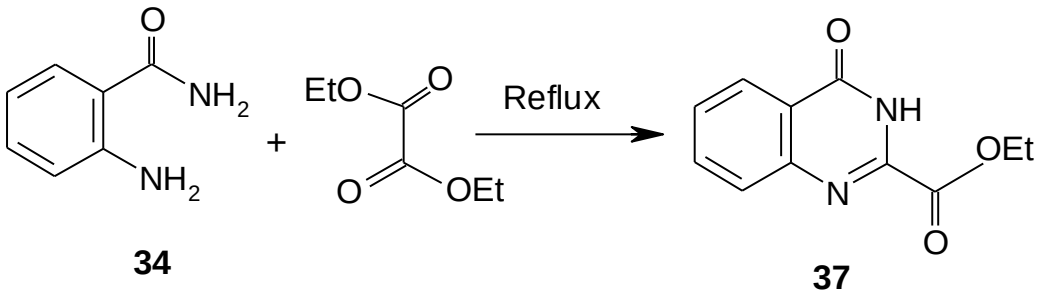
2- Reaction of anthranilamide and ester:

In the presence of sodium ethoxide, treatment of 2-amino-benzamide with ester such as ethyl formate and ethyl acetate led to the corresponding 4(3H)-quinazolinones.[(55).]



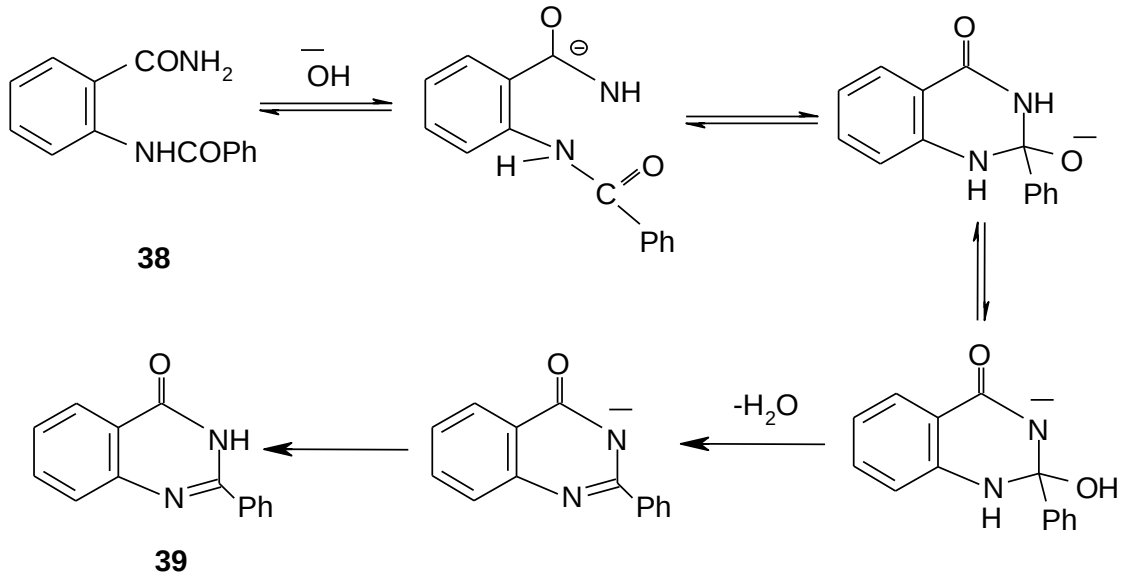
34 R = H, Me **36**

The synthesis of 2-carboethoxy-quinazolinone-4(3H)-one has been reported by Baker and Almaula in 1962[(56)] from anthranilamide and diethyl oxalate.



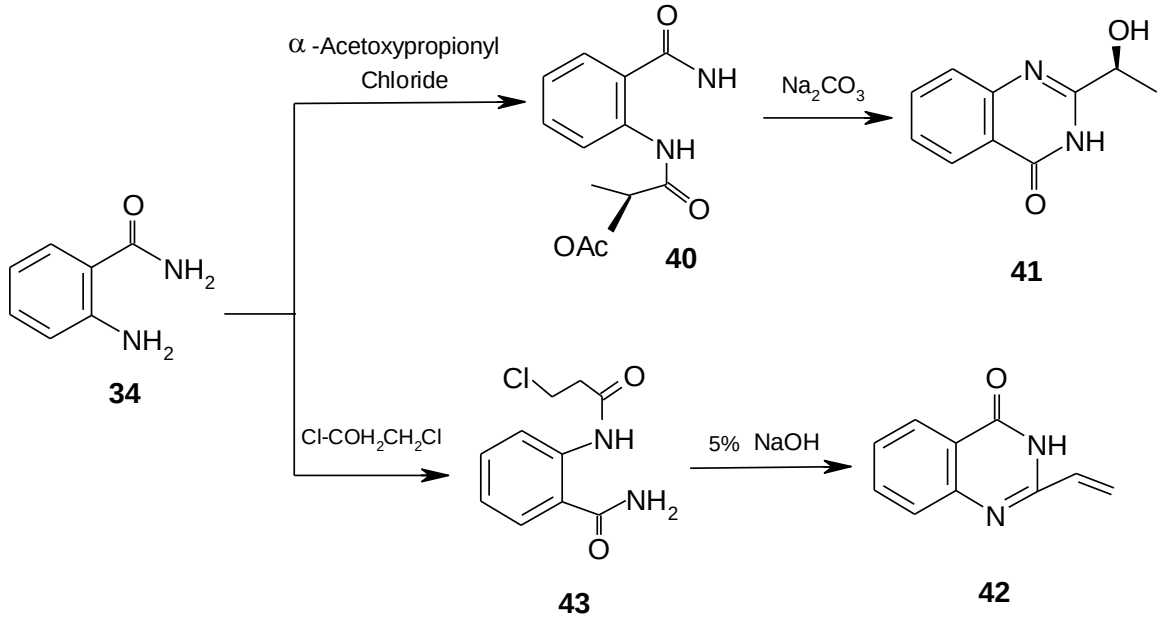
34 **37**

2-Benzamidobenzamide (28) under went intramolecular cyclization in the presence of alkali to form 2-phenyl-4(3H)quinazolinone [(57)].



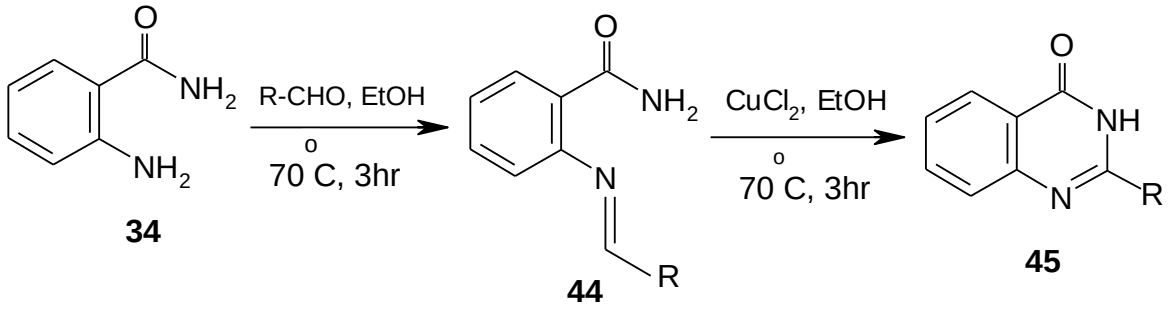
3- From anthranilamide and acid chloride:

Korner (1887)[58] reported the treatment of N-benzoyl-orthoanilamide (40) with aqueous potassium hydroxide yielded 2-phenyl quinazolin-4(3H).one. Also, when anthranilamides was allowed to reacts with acetoxypropnyl chloride or chloro proponyl chloride it produce quinazolines (41) and (43). This method used in synthesis of Chrysogine (41)[59,60].



Condensation of aldehyde and anthranilamides or its derivatives:

Abdel-Glil et al[61], reported in one pot procedure, the reaction between aldehyde, anthranilamide and 3-equivalent of $CuCl_2$ in refluxed ethanol for 2-3 hr.

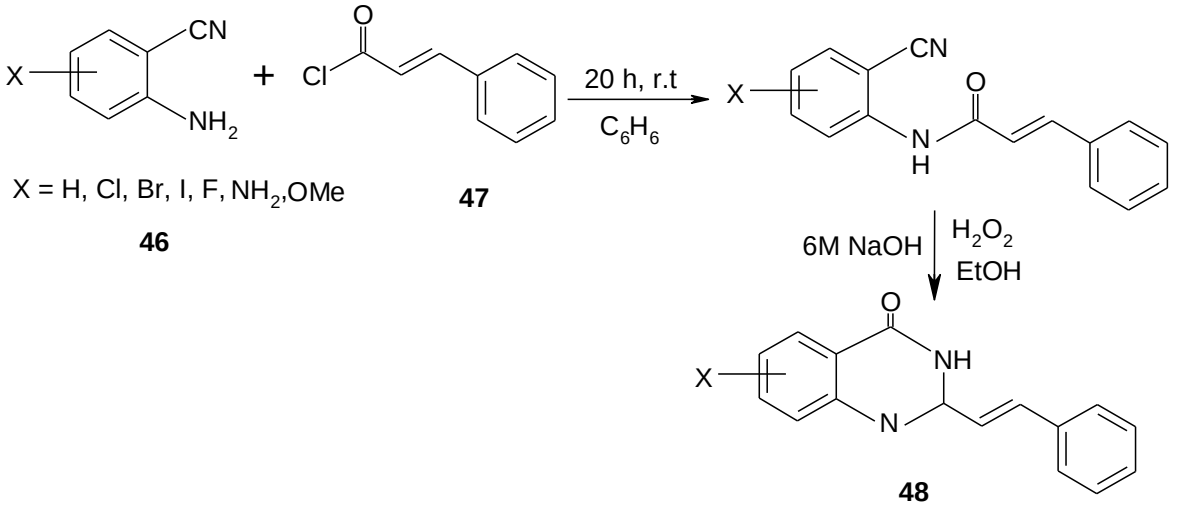


34 **44** **45**

R = Me, Bu, Ph, p-MeO C_6H_4, p-ClC_6H_4, 2-furyl, 2-thiophenyl

From nitrile:

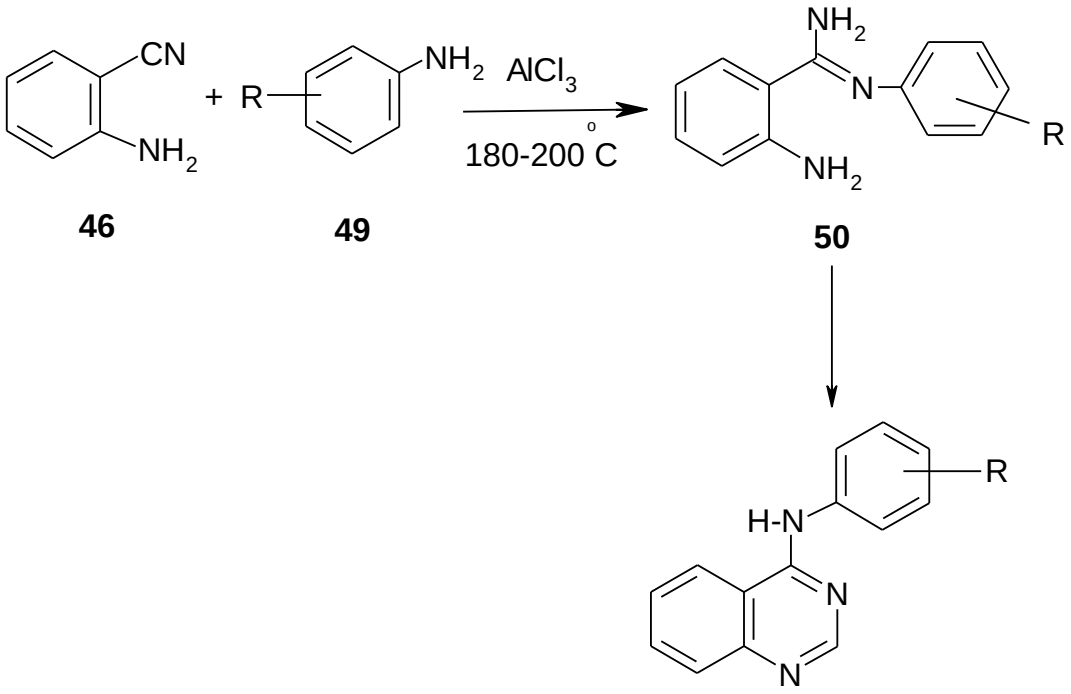
Bogert and Co-workers (1903)[62,63] reported the reaction of 2-aminobenzonitrile (X = H) with 3-phenyl-acryloyl chloride followed by oxidative ring closure under basic conditions and produced 2-styryl-4(3H)-quinazolinone (48).



X = H, Cl, Br, I, F, NH_2,OMe

46 **47** **48**

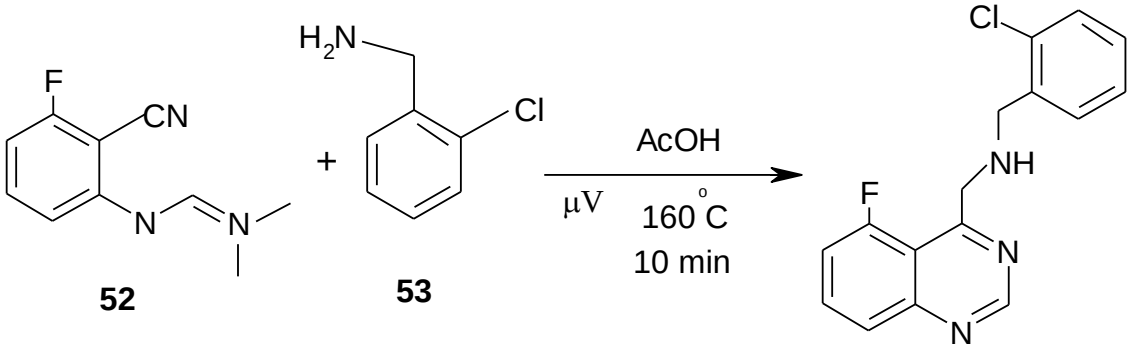
The reaction of 2-aminobenzonitrile with aniline and anhydrous aluminum chloride[64]. Gives (50) 2-amino-N-phenylbenzamide which afforded the 4-phenylamino quinazolinone (51) when heated with formic acid or benzaldehyde.



46 **49** **50**

R = H, 2-Me, 2-Br, 3-Me, 3-Cl, 3-Br, 3-I, 4-Me, 4-Cl, 4-Br **51**

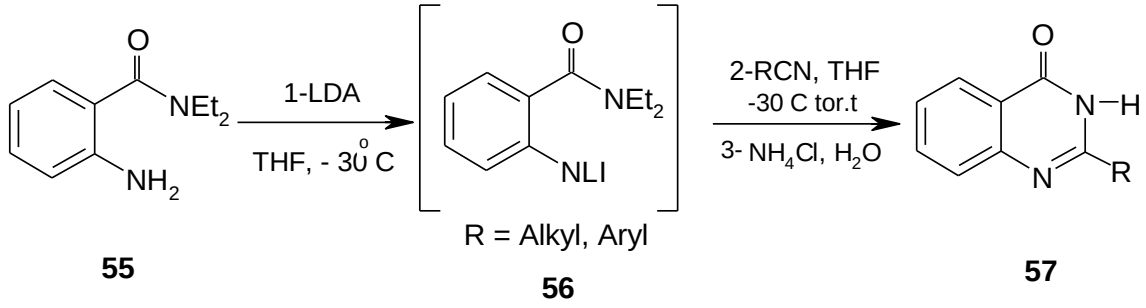
Yoon et al.[65] reported the reaction of N,N-dimethylamidino benzamide (52) with benzylamine (53) to give 4-aminoquinazoline (54) under the condition of microwave (μV) irradiation.



52 **53** **54**

From lithium compounds:

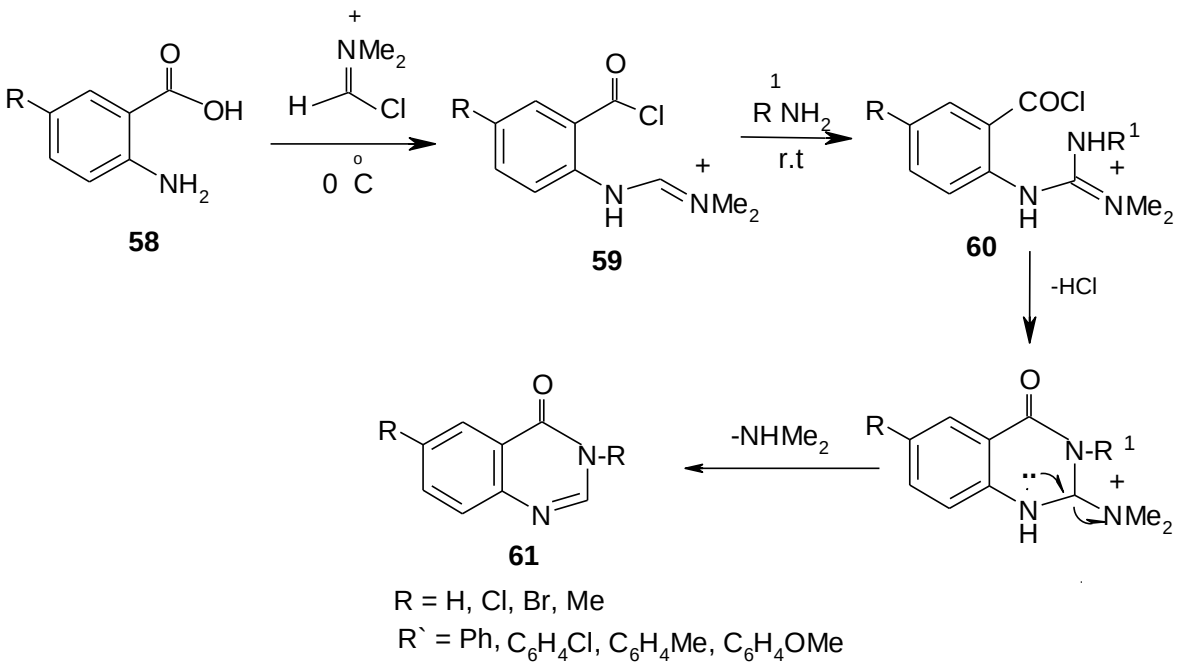
Couture and Co-workers[66] have develop the synthesis of 2-aryl- and 2-alkylquinazolin-4(3H)-ones (57) by reaction of lithium 2-(diethylamino-carbonyl)anilide (LDA) (56) with the appropriate aryl or aliphatic nitrile.



55 **56** **57**

Vilsmeier reagent for quinazolinone synthesis:

Perumal et. al [67] treated 5-substituted-2-aminobenzoic acid derivatives (58) with vilsmeier reagent (a combination of DMF and $POCl_3$).



58 **59** **60** **61**

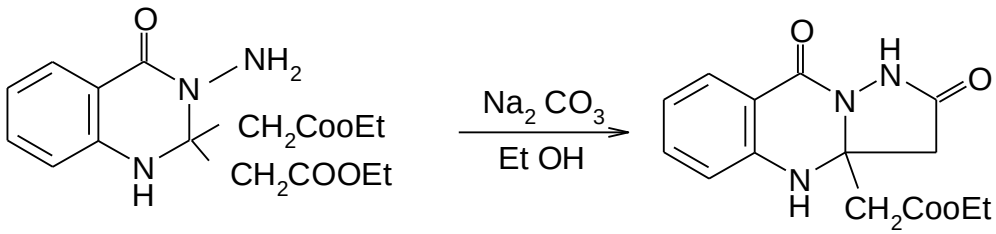
R = H, Cl, Br, Me

R` = Ph, C_6H_4Cl, C_6H_4Me, C_6H_4OMe

SYNTHESIS OF FUSED QUINAZOLINONES

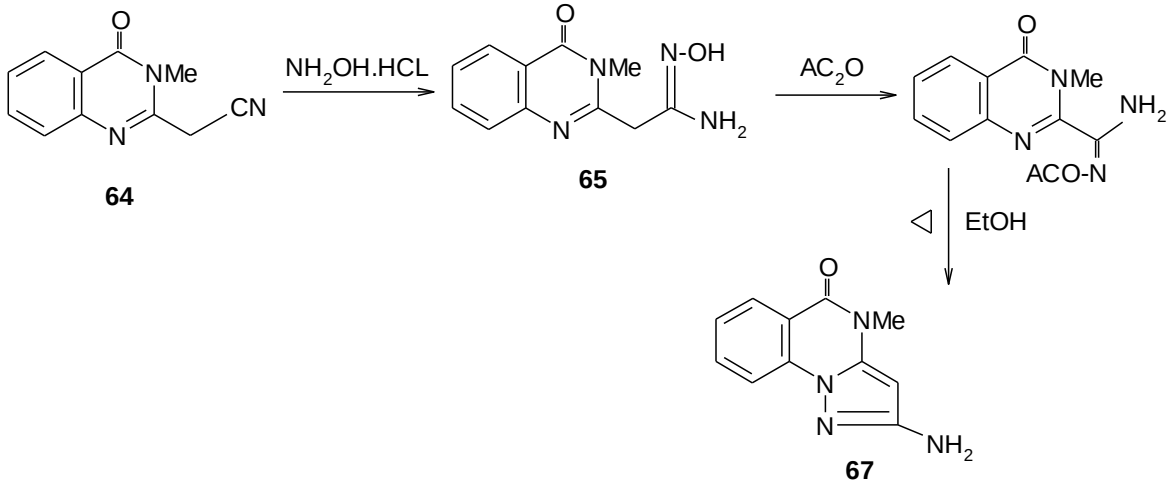
1- Pyrazoloquinazolinone

Cyclization of 3-amino-1,2,3,4-tetrahydro-4(3H)-quinazolone-diacetate (62) with sodium carbonate in ethanol gave the corresponding ethyl2,3,4,9-tetrahydro-2,9-dioxo-pyrazolo[5,1-b]-quinazolin-3(1H)-acetate (63)[68].



62 63

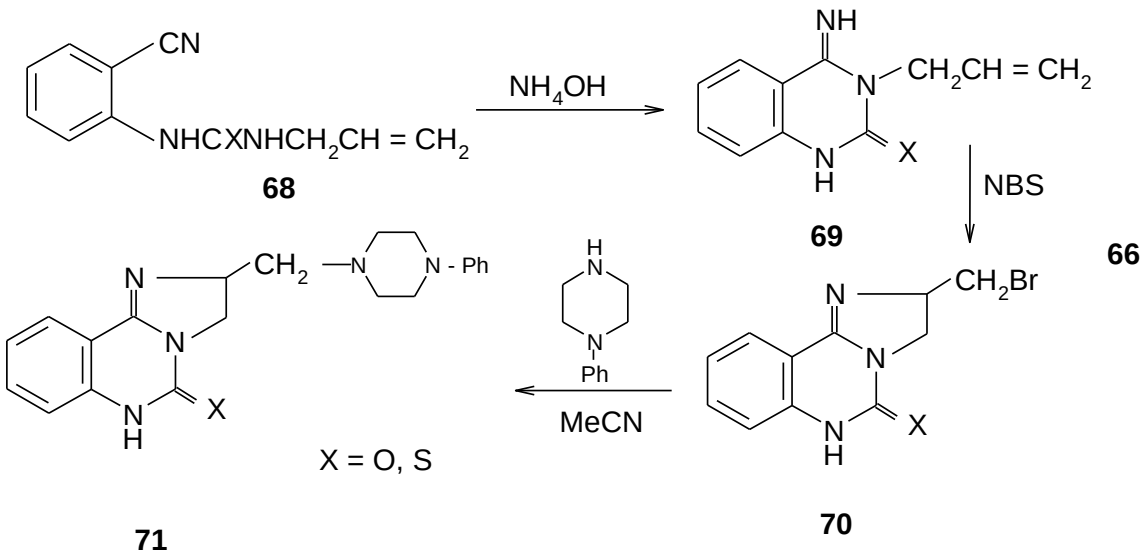
Also, pyrazoloquinazolin (67) was prepared by the reaction of the cyano group of quinazolinone (64) with hydroxylamine hydrochloride in ethanol to give amidoxime (65), which treated with acetic anhydride, o-acetyl derivative was obtained (66) and when heated in ethanol it afforded 2-amino-4-methylpyrazolo[1,5-a]-quinazolin-5(4H)-one (67) [69].



64 65 67

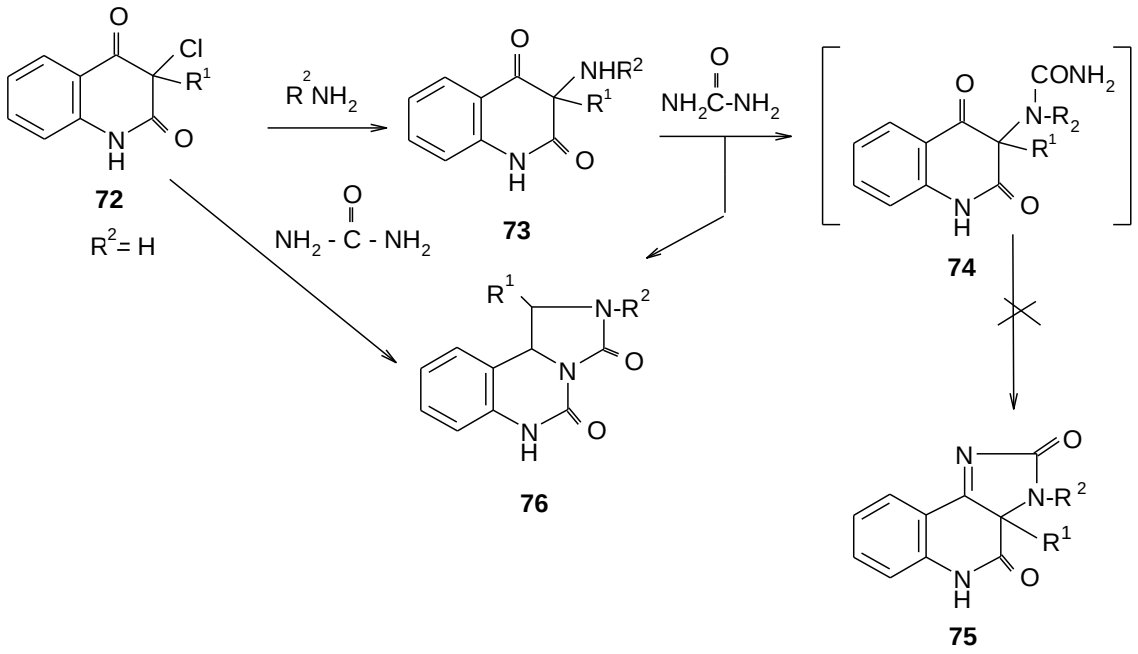
2-Imidazoloquinazolinone:

The 2-methyl-2,3-dihydroimidazolo[1,2-c]quinazolin-5-one/or thione derivatives, (useful as antihypertensive agents for treating dysuria) are prepared by cyclization of ureido or thioureido benzonitrilederivate (68) with ammonium hydroxide to give quinazolinone derivatives (69), which was treated with N-bromo-succinimide(NBS)in THF at room temperature to give bromoimidazoloquinazolines (70). Refluxing this compound with N-phenylpiperazine in acetonitrile MeCN gave 2,3-dihydroimida-zolo[1,2-c]-quinazolin-5-one or thione derivatives (71)[70].



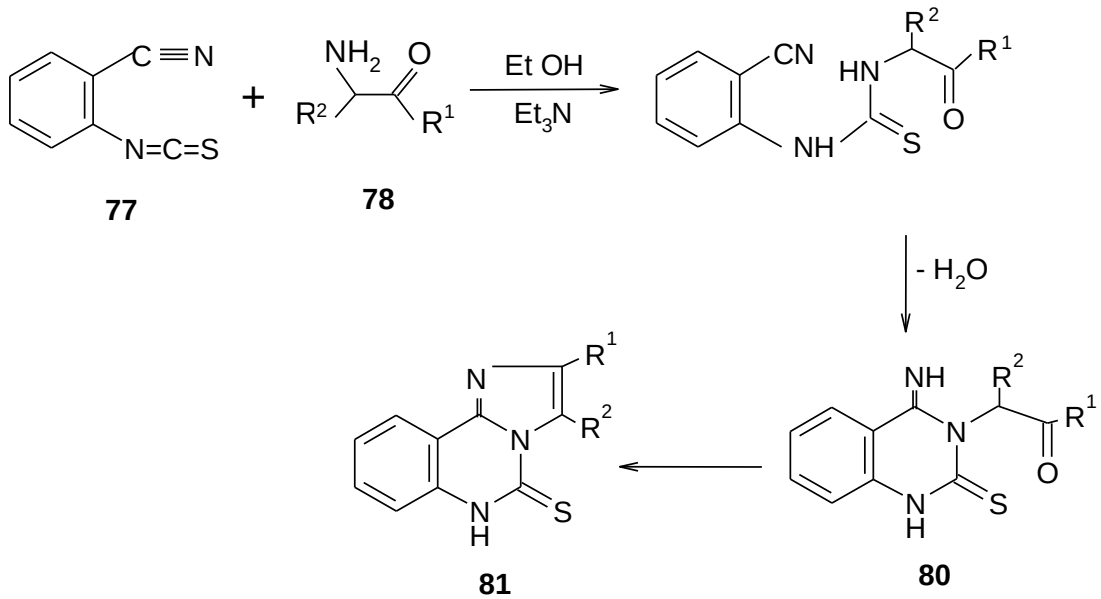
68 **69** **70** **71** **66**

Refluxing of chloroquinolines (72) with benzylamine or ammonia solution produced (73). Which by boiling with urea in a solution of acetic acid provided unexpected product of 2,6-dihydroimidazo-[1,5-c]quinazolines (76) [71]



	R^1	R^2
a	C_6H_5	H
b	CH_2Ph	CH_2Ph

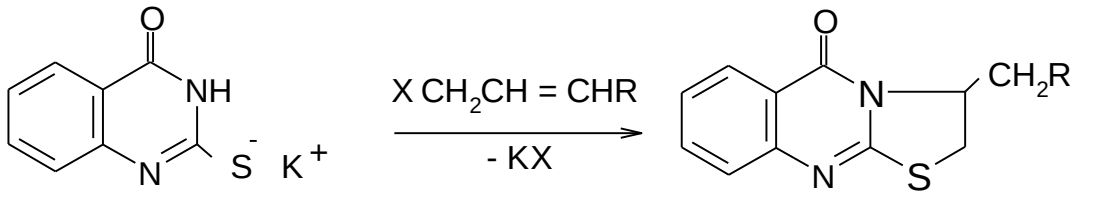
Refluxing of 2-isothiocyanobenzonitrile (77) with α-amino-acetophenone (78) in ethanol provided (79) which cyclized to give quinazolines (80). Further cyclization of (80) afforded 5-thioxo-6H-imidazolo[1,2-c]quinazolines (81) [72]



	R^1	R^2
a	C_6H_5	H
b	4-MeC_6H_4	H

3- Thiazoloquinazolinone

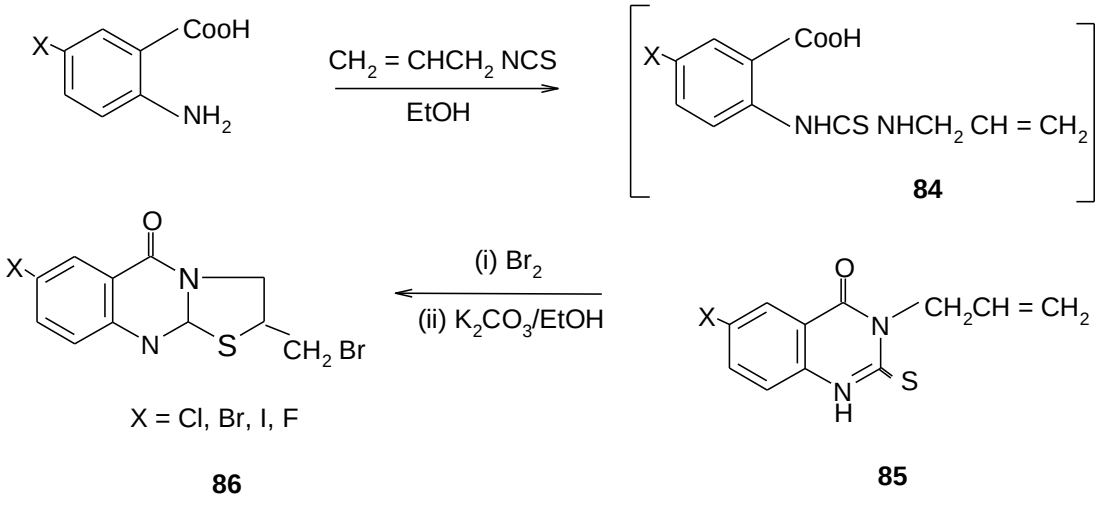
Interaction of the potassium salt of quinazolin-2-thiol-4-one (82) with γ-substituted allyl halides gave thiazoloquinazolinone (83) with linear or angular structure depending on the structure of the radical [77].



R = H, Me, Et, X = Cl, Br

82 **83**

Substituted anthranilic acid was condensed with allyl isothiocynate to yield 3-allyl-2-thioxo-6-haloquinozolin-4-ones (84) which on bromination, followed by subsequent cyclization with potassium carbonate anhydrous give the corresponding 7-halo-2-(bromo-methyl)thiazolo [2,3-b] quinozolin-5-ones (86).[74]

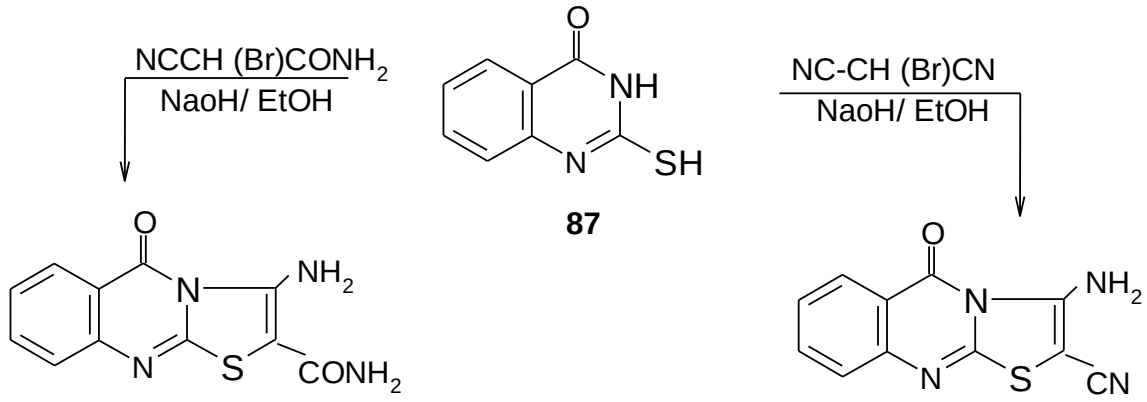


X = Cl, Br, I, F

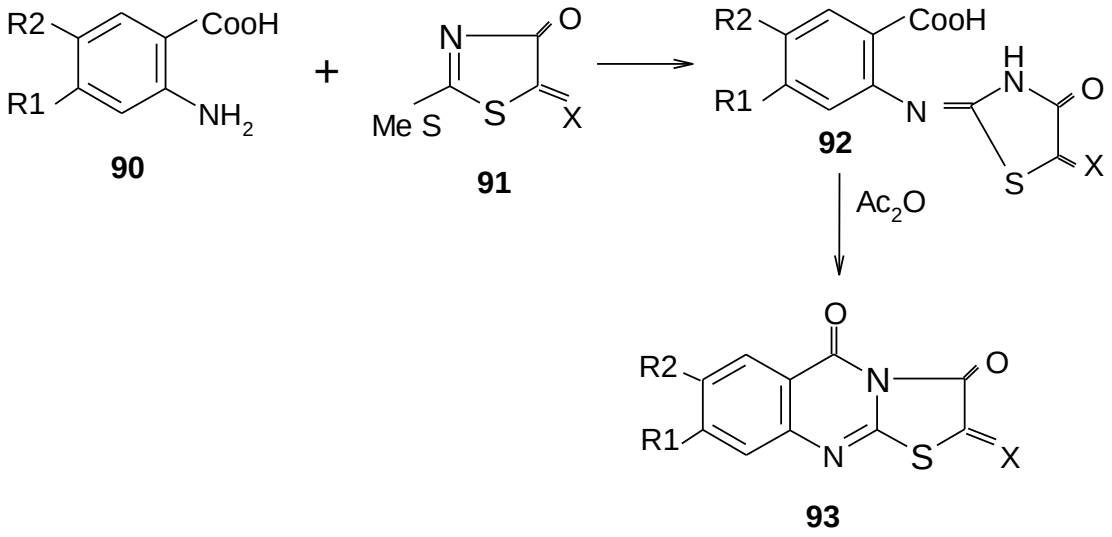
86 **84** **85**

The 3-amino-5-oxo-thiazolo[2,3-b]quinaezoline derivatives (88, 89) were prepared from 2-mercapto-4(3H)-quinazolone (87) and

bromomalonitrile or bromocyanoacetamide in ethanolic sodium hydroxide solution. [75]



5H-thiazolo[2,3-b]quinazolin-3,5(2H)-dione (93) were prepared via the condensation of 2-methylmercapto-4-thiazolidinone (91) and 5-arylidene-2-methylmercopto-4-oxo-thiazolidinone (92) with anthranilic acid derivatives (90) in refluxing ethanol the product were cyclized by refluxing acetic anhydride to afford the corresponding 5H-thiazolo[2,3-b] quinazoline 3,5-(2H)-diones (93a) and 2-arylidene-5H-thiozolo[2,3-b]quinazoline-3,5-(2H)-diones (93b)[76]

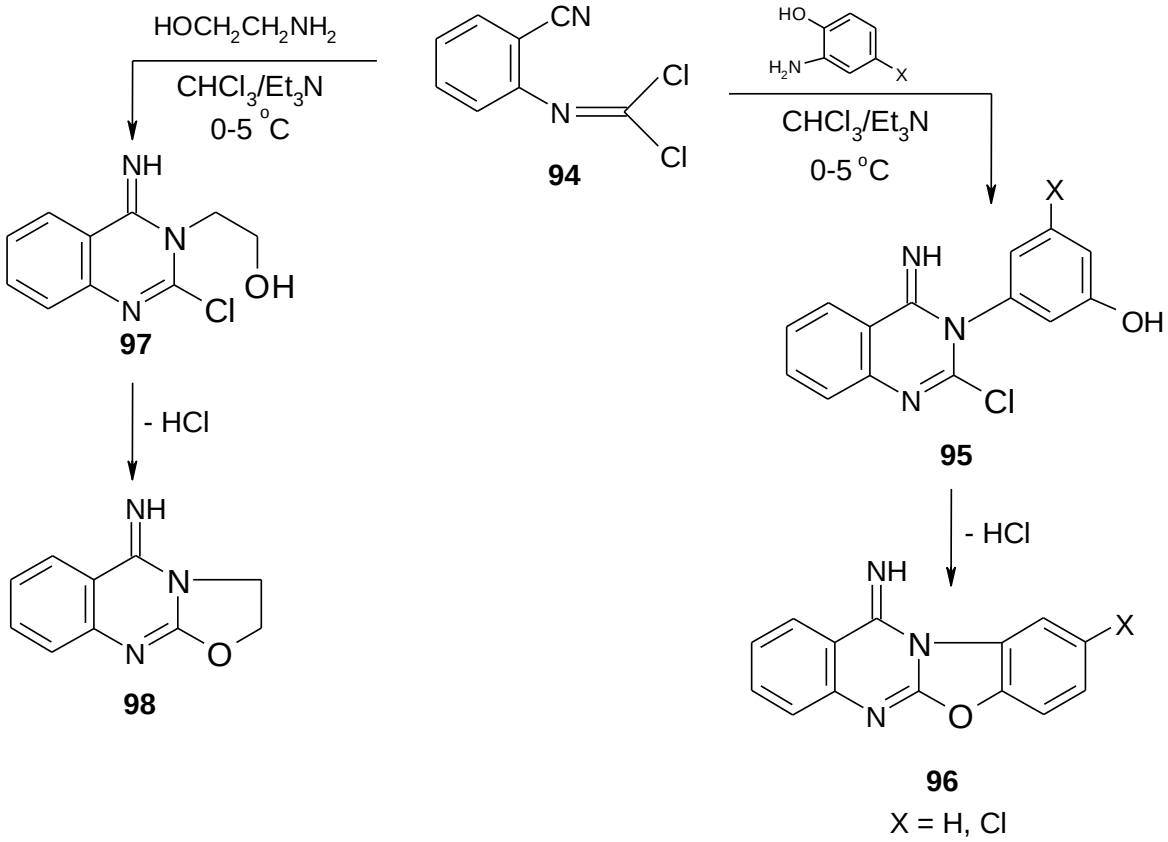


93a X = 2 H, $R_1 = R_2$ = H, MeO

93b X = ArCH - , $R_1 = R_2$ = H, MeO

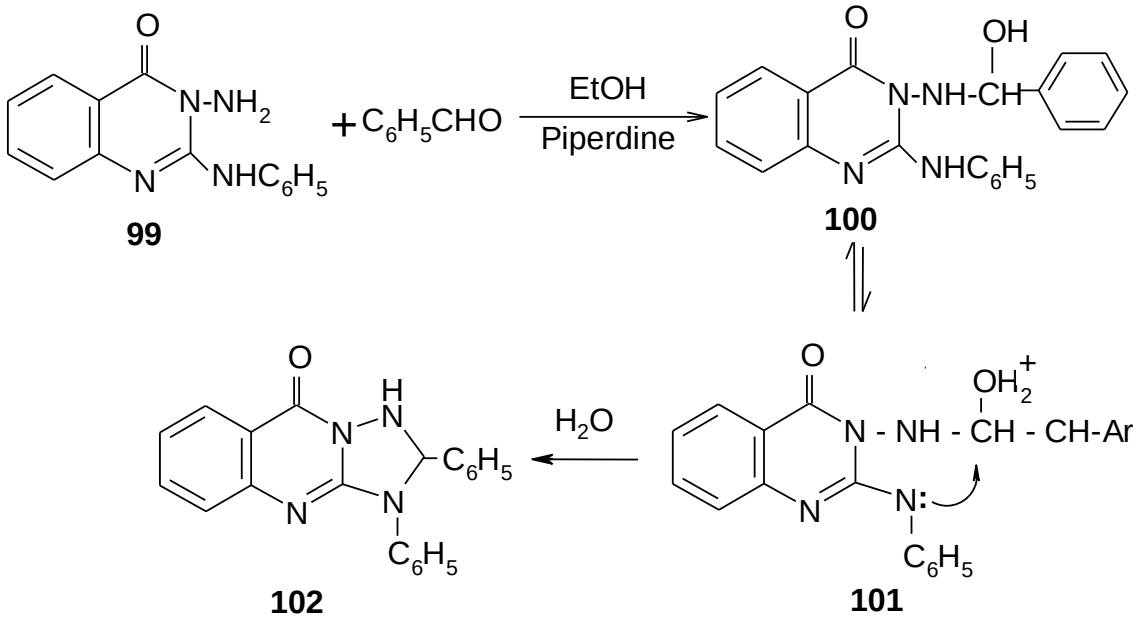
4- Oxazoloquinazolines

1,3-Benozolo[2,3-b]quinazolin-5-imine (96) and 2,3-dihydro-5H-1,3-benzooxazolo[2,3-b]quinazolin-5-imines (98) were synthesized in one-pot reaction. Reaction of N-(2-cyanophenyl) chloro-methanimidoyl chloride (94) with 2-aminophenols and/or 2-aminoethanol in the presence of abase[77].

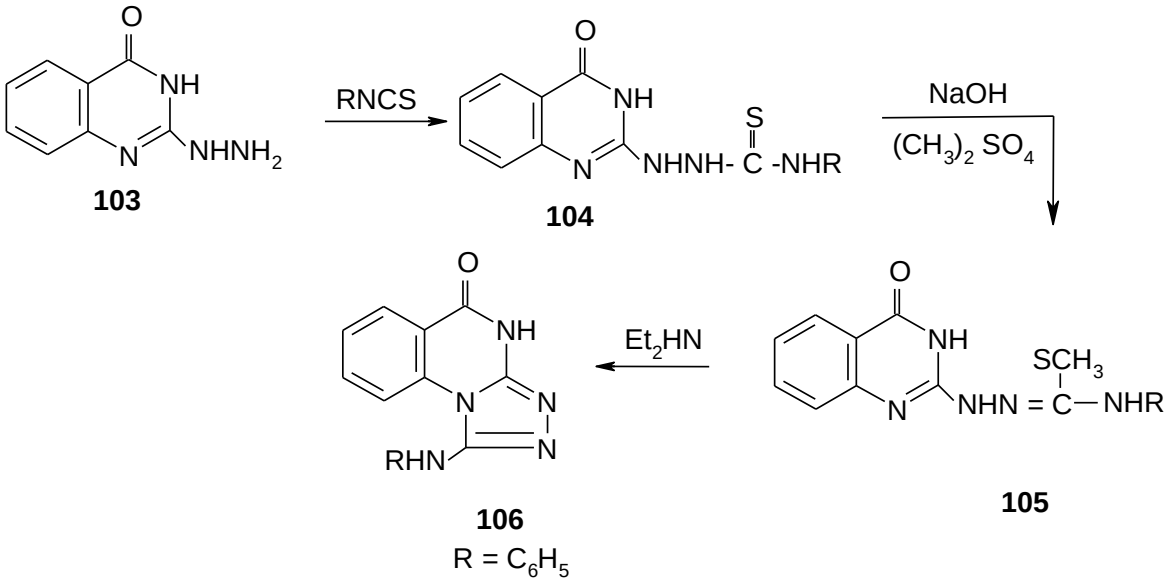


5- 1,2,4-Triazoloquinazolinones

Refluxing of 3-amino-2-phenyl amino quinazolinone (99) with benzaldehyde in ethanol and in the presence of piperidine gave (100) as intermediate. Spontaneously intramolecular cyclization occurred to produce 1,2,4-triazolo-[3,2-b]quinazoline-9(1H) ones (102).[78]

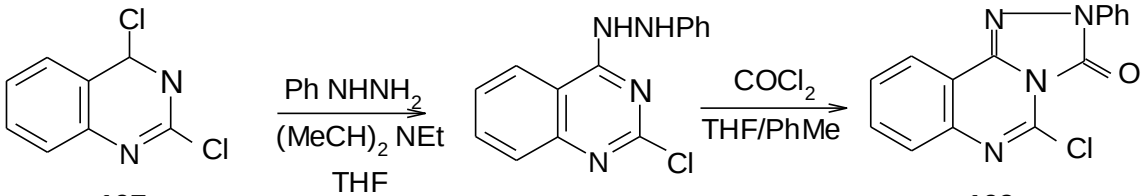


The reaction of 2-hydrazinoquinzoline (103) with isothiocyanate gave thiourea derivatives (104) methylation of the latter compound (104) with dimethylsulphate gave (105) which on cyclodesulfurization in the presence of base produced 1,2,4-triazolo-[4,3-a] quinazolinones(106).[(79)]



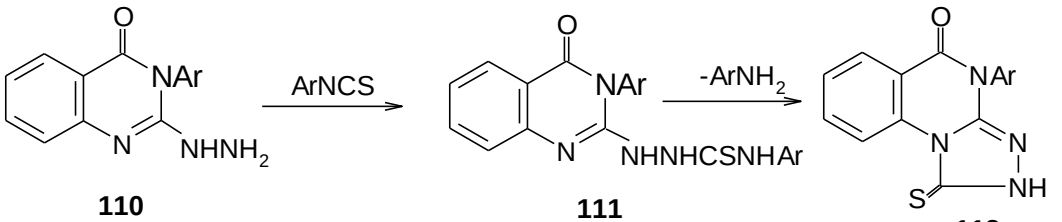
The1,2,4-triazolo[4,3-c]quinazolin-3-one (109) (highly selective agonists for GABA a brain receptors or prodrugs) and useful in the

diagnosis and treatment of anxiety, sleep, and seizure disorders, overdose with benzodiazepine drugs and enhanced the memory. Was prepared when 2,4-dichloroquinazoline (107) was stirred with phenylhydrazine and N,N-diisopropylethylamine in THF to give 2-chloro-4-phenylhydrazinoquinazoline (108) which converted by cyclization with $COCl_2$ in THF/PhMe to give 5-chloro-4-phenyl-1, 2, 4-trizolo[4,3-c]-quinazolin-3-one (109) [80- 81].



107 **108** **109**

Also, the 2-hydrazino-3-arylquinazolin-4(3H)-ones (110) have been converted into 1-(3-aryl-4-oxoquinazolin-2-yl)-4-aryl-3-thiosemicarbazides (111) by condensation with arylisothiocyanate. Cyclization of (111) gave 1-thioxo-4-aryl-1,2,4-trazolo[4,3,a] quinazolin-5-ones (112). [82]

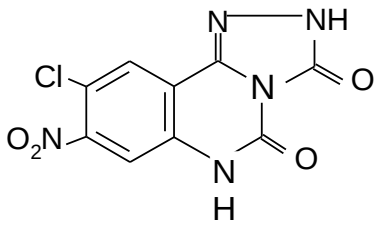


110 **111** **112**

Ar = ph, 4-MeC_6H_4, 4-Cl C_6H_4

Triazoloquinazolinedione (113) can be used as neuroprotective, especially for treatment or prevention of ischemia, hypoglycemia, hypoxia, cerebal vascular spasms, plasticity, trauma,

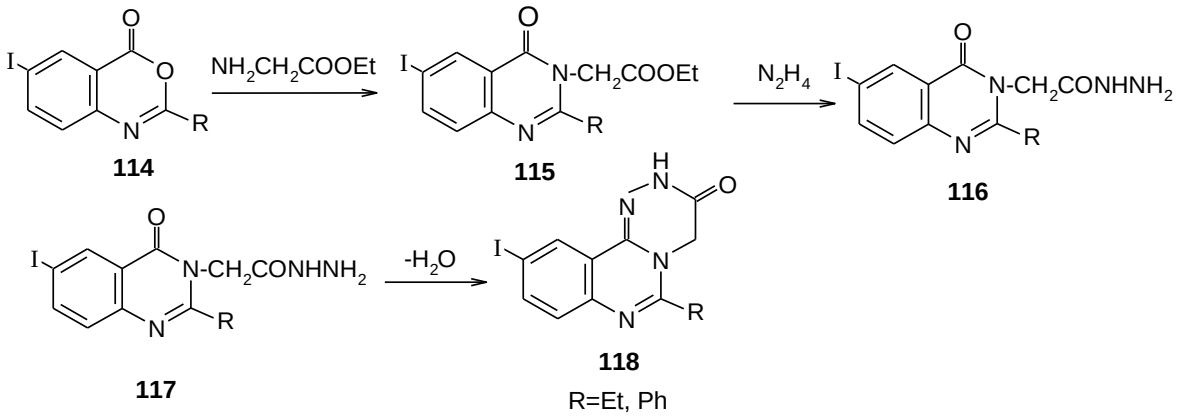
hemorr, taiga, infection, epileptic seizures, autommune diseases, with drawal symptoms, Alzaheimer's disease for instance.



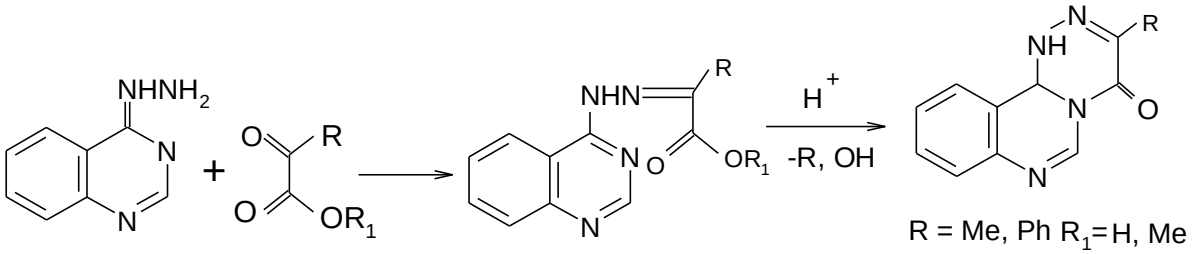
113

6-Triazinoquinazolinones

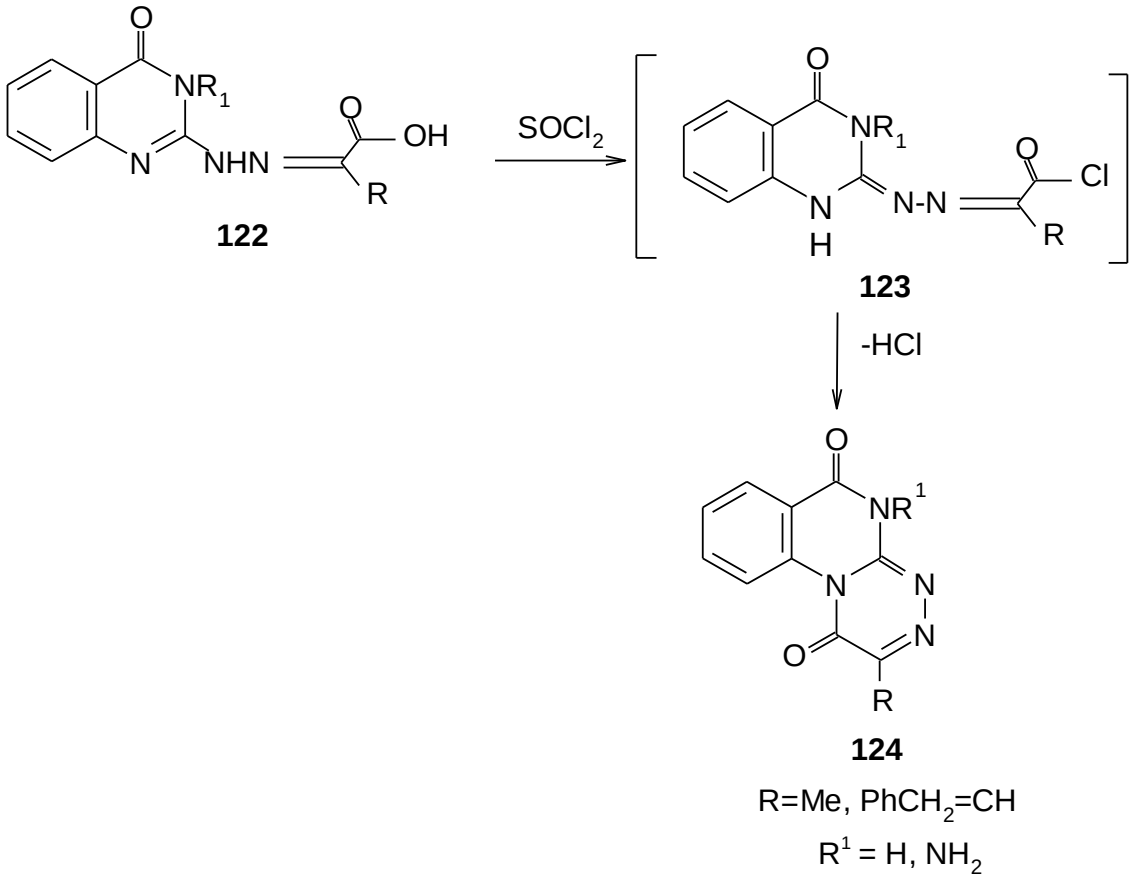
Condensation of 2-substituted-6-iodo-3,1-benzoxazin-4-one (114) with ethylglycinate hydrochloride gave the quinazoline ester derivatives (115). Reduction of ester with hydrazine hydrate furnished hydrazide derivative (116). which was used for synthesis of 1,2,4-triazino[4,3-c]- quinazolinone (118) via cyclization by removal of water molecule.[83-84]



Condensation of 4-hydrazinoquinazoline (119) with pyruvic acid, ethyl pyruvate and methylphenylgloxylate gave the corresponding hydrazone derivatives (120) which underwent acid-catalyzed hetero-cyclization to give oxotriazino[4,3-c]quindzolines (121). [85-86]



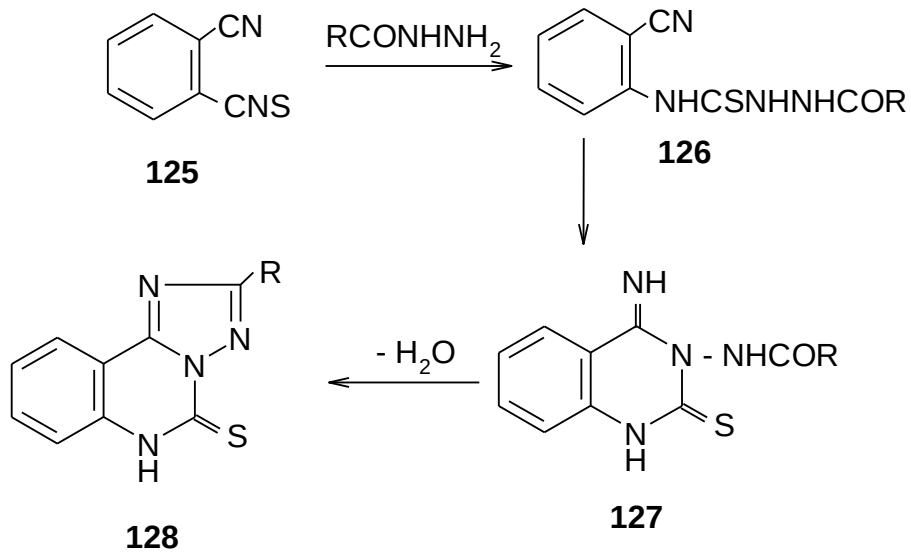
3-Substitute-2-(α-ketoacidhydrazono)quinazolin-4(3H)-ones (122) reacts with thionylchloride and undergo cyclization to give 5-substituted-5,6-dihydro-1,6-dioxo-1H-[1,2,4]triazino[4,3a]quinozolines(124).[(87)]



7- Triazoloquinazolinthiones

One-pot reaction between carboxylic acid hydrazides and 2-isothiocyanatobenzonitrile (125) via cyclization to afford

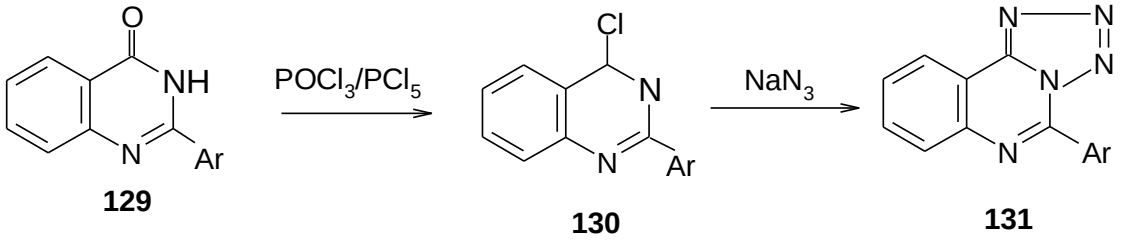
pharmacoligcal relevant 1,2,4-triazolo-[1,5-c] quinazolin-5(6H)-thiones (128)[88,89].



R = Me, Et, Ph, 4- ClC_6H_4

8- Tetrazoloquinazolines:

4-Chloro-2-(-phenyl or chlorophenyl)quinazoline (131) have been prepared by treating the 4(3H)-quinazolinone derivative (129). with $POCl_3/PCl_5$. The product (130) were allowed to react with sodium azide to give tetrazolo[4,3-c]-quinazoline derivatives (131).[90,91]

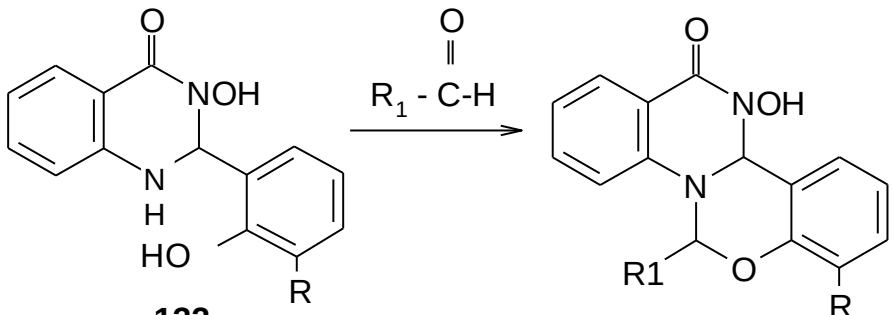


Ar = Ph, 4 -ClC_6H_4

9- Oxazinoquinazolinones

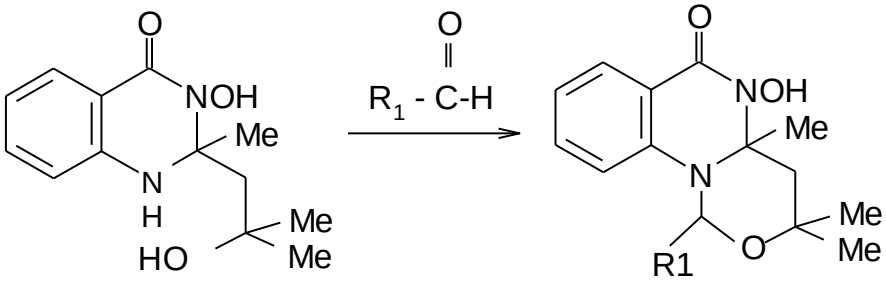
The reaction of 3-hydroxy-2-substituted-1,2-dihydro-quinazoline-4(3H)-ones (132) and (134) with formaldehyde and

acetaldehyde gave the corresponding oxozinoquinazolinone derivative (133) and (135).[92]



132 **133**

R= H, allyl group; R_1=H, Me

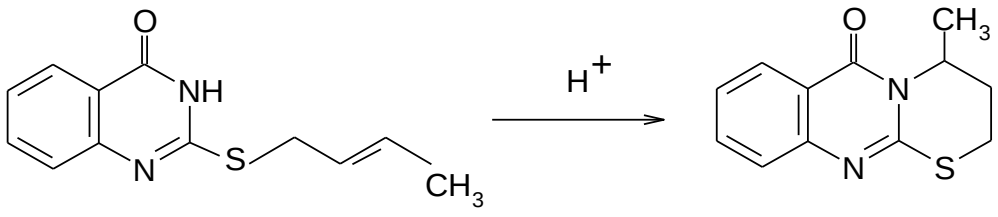


134 **135**

R_1 = H, Me

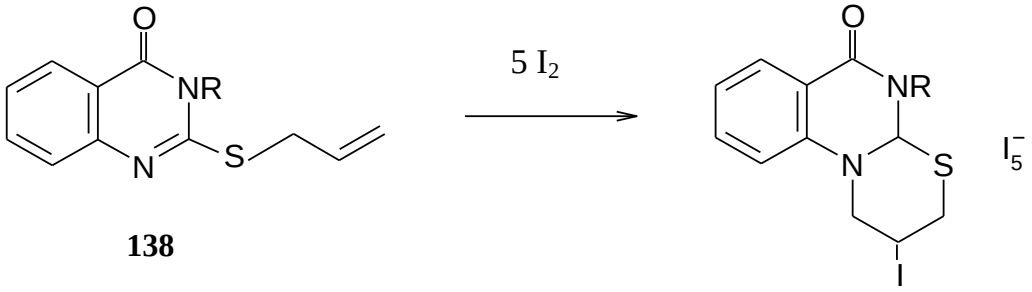
10- Thiazinoquinazolinones

Acid-catalyzed reaction of condensed Crotylthioquinazolin-4-one (136) leds to regioselectively to fused 3,4-dihydro-4-methyl-2H,6H-1,3-thiazino[2,3-b]quinazolin-6-one (137) [93]



136 **137**

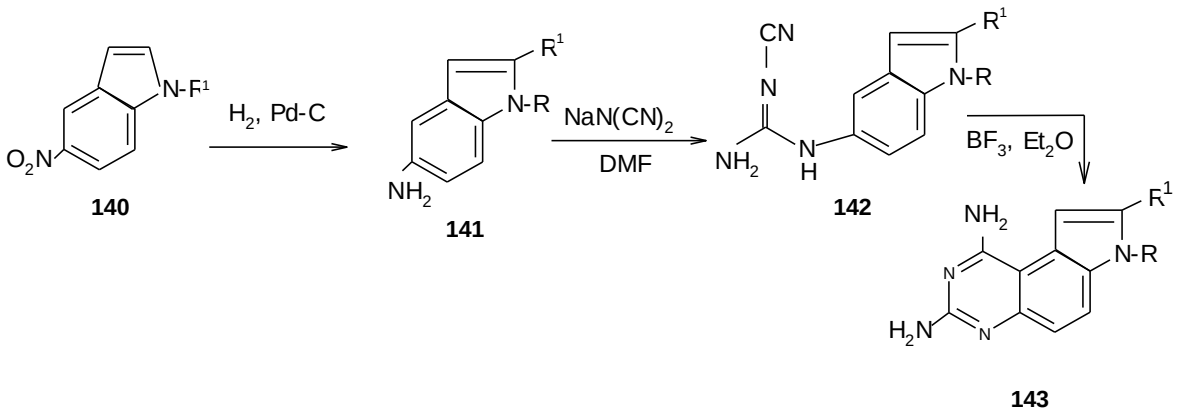
Halocyclization of 2-(2-propenylthio)- and 2-(2-propynythio)-3-substituted-4(3H)-quinazolinone (138) by iodine gave rise to-iminium salts of angular thiazinoquinazolinones (139)[94,95].



138 **139**

11- Pyrroloquinazolinone:

The reduction of nitroindoles (140) by palladium carbon afforded aminoindoles (141) which condensed with dicyanamide to provide the cyanoguanidine derivatives (142). Ring closure of this compound (142) was carried out thermally or with boron trifluoride etherate to produce 7,8-dialkyl-1,3-diaminopyrrolo-[3,2-f] quinazolines(143)[(96)]

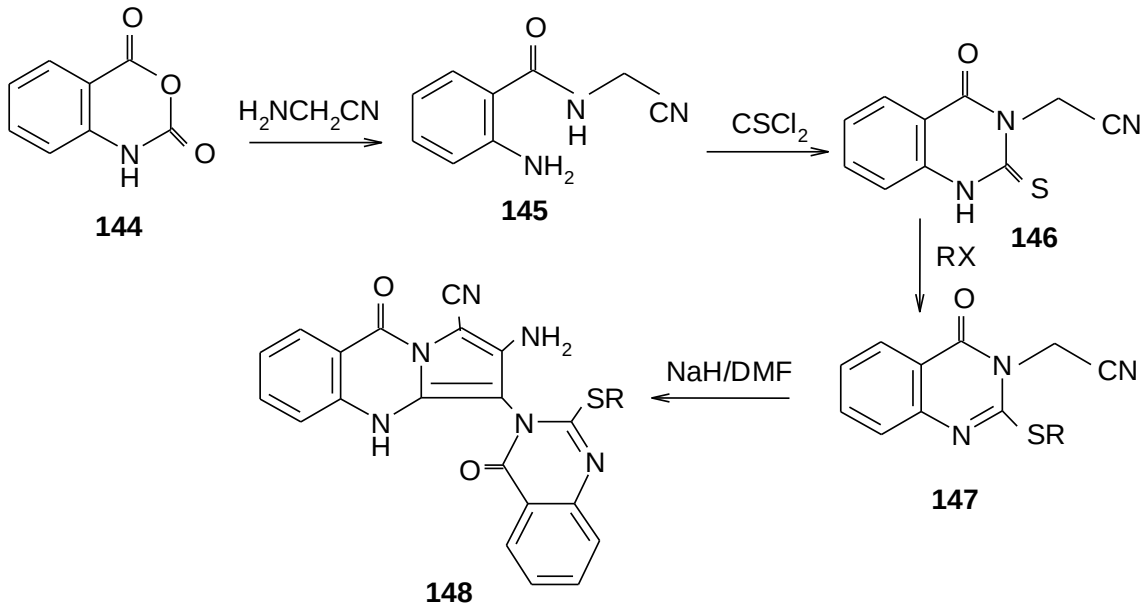


140 **141** **142** **143**

	R	R^1
a	H	H
b	Me	H

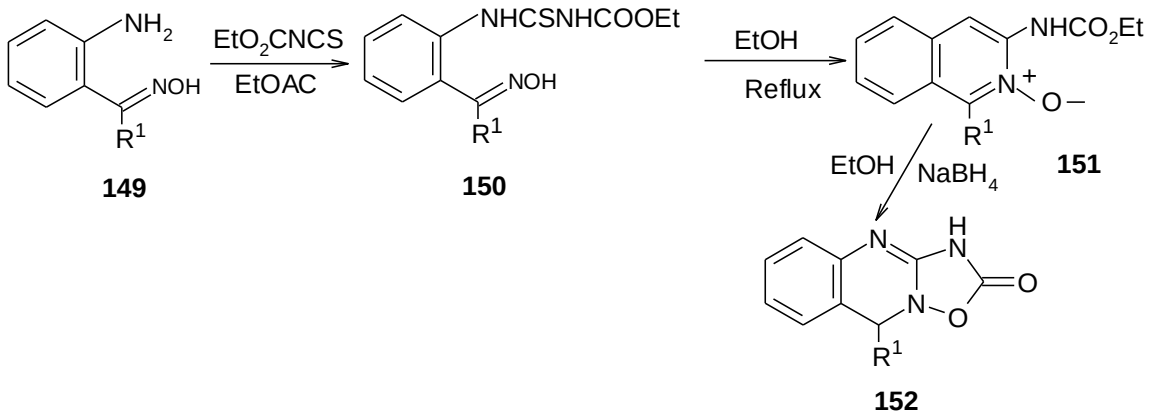
Treatment of isatoic anhydride (144) with aminoacetonitrile afforded 2-amino-N-(cyanomethyl)benzamide (145) which cyclized in presence of thiophosgene to form thioquinazoline derivatives (146) the alkylation of (146) with appropriate alkyl halide afforded

(147), followed by further cyclization and dimerization in the presence of sodium hydride and dimethylformamide gave pyrroloquinazoline(148).[97]



12- Oxadiazoloquinazolines:

The reaction of ethoxycarbonylisothiocyanate (149) with aminoxime (149) in ethylacetate gave the intermediate thiourea (150), which spontaneously cyclized in ethanol to furnish quinazolines (151). Further cyclization in ethanol and sodium borohydride afforded. 3,9-dihydro-2H-[1,2,4]oxadiazolo-[3,2-b]-quinazolin-2-one (152).[98]

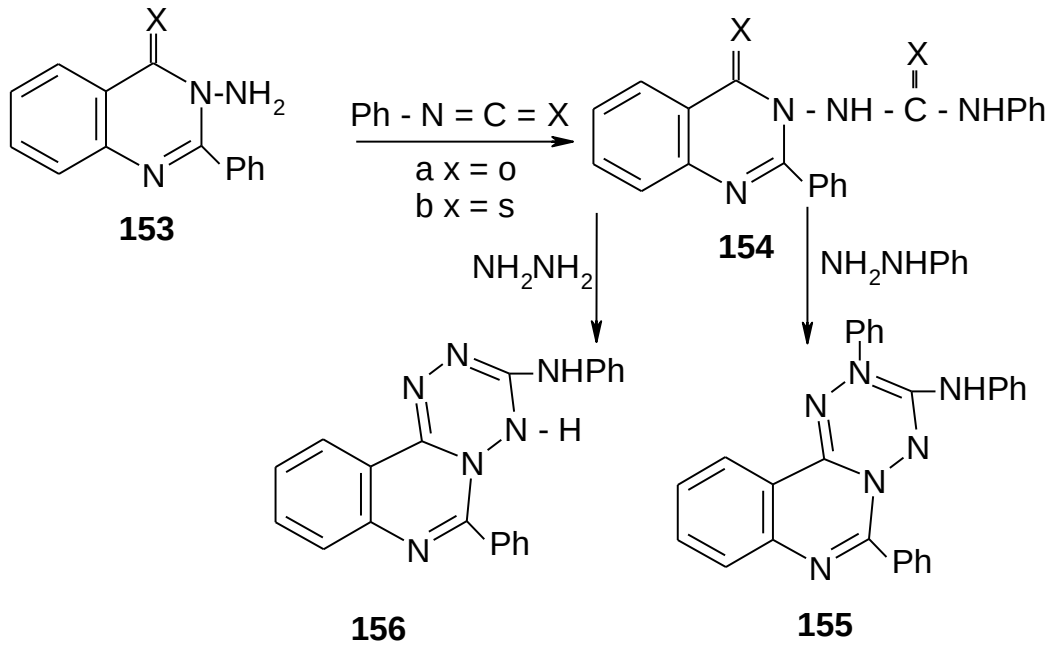


149 150 151 152

	R^1
a	Me
b	H

13- Tetrazinoquinazolines

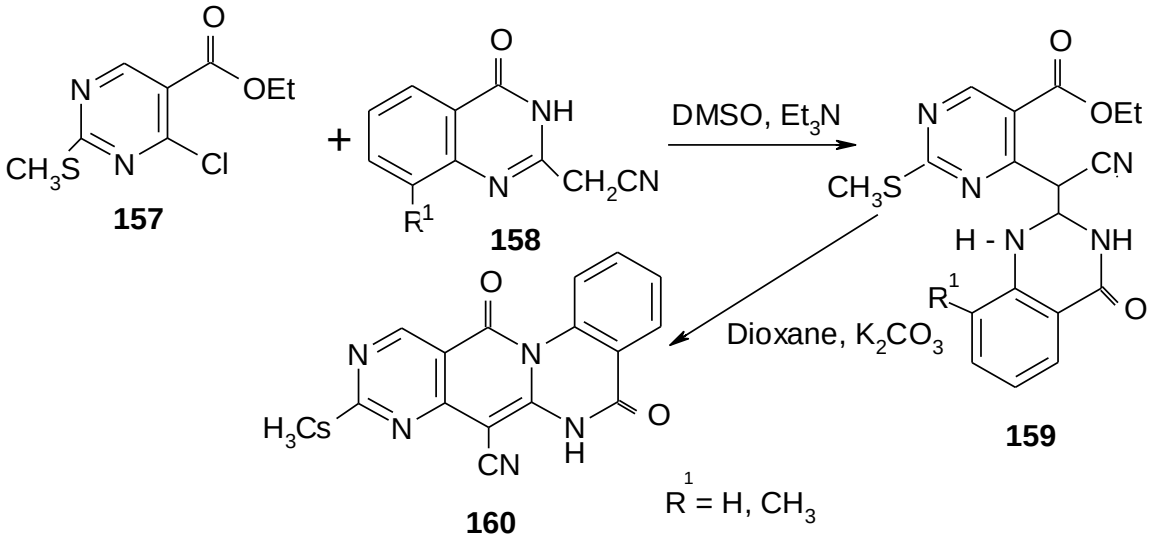
3-Aminoquinazolines (153) were reacted with phenylisocyanate or phenylisothiocyanate to give urea or thiourea derivatives (154). Treatment of (154) with hydrazine hydrate or phenyl hydrazine afforded 6H-[1,2,4,5]-tetrazino[3,2-c]quinazoline (155) and (156) respectively. (99, 100)



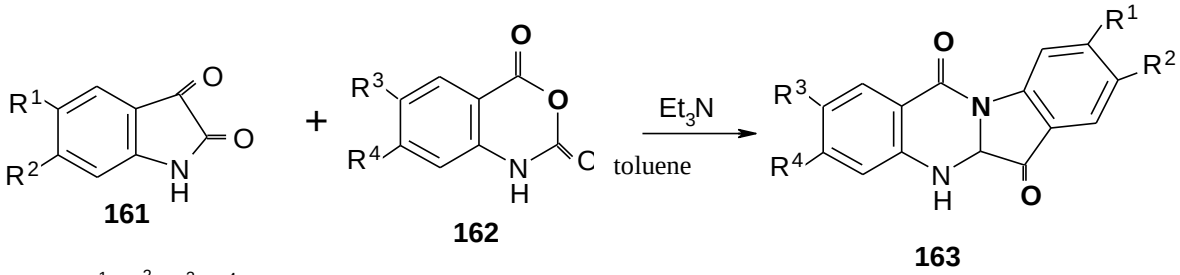
153 154 156 155

14- Tetracyclic Rings:

2-Hetarylacetonitrile (158) reacted with 5-ethoxycarbonyl-pyrimidine derivative (157) in dimethylsulfoxide and in the presence of triethyl amine to provide the intermediate (159) this compound followed by cyclization in dioxane and potassium carbonate and formed 3-methylsulfanyl-5-cyano-pyrimido[4`,5`,4,5]pyrido[1,2-a]-quinazoline-7,13-dione (160) in high yield.[101]



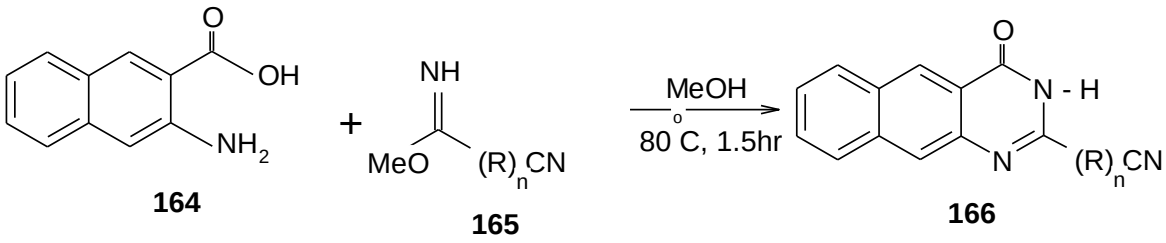
The reaction of isatoic anhydride (162) with indole (161) derivative in toluene in the presence of triethylamine furnished 6,12-dihydro-5,12-dioxoindolo[2,1-b]quinazolines (163). [102, 103]



a R^1, R^2, R^3, R^4 = H

b R^3, = Br R^1, R^2, R^4= H

The reaction of imidates (165) with 3-amino-naphalene-2-carboxylic acid (164) to produce the corresponding benzo-fused quinazolinones (166) [(104)].



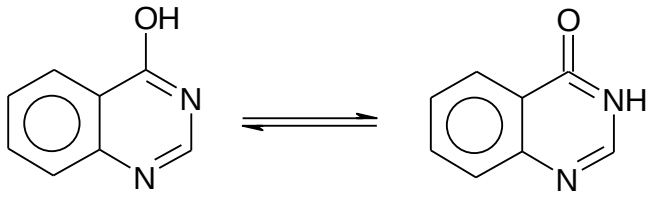
164 **165** **166**

R = (CH_2)nCN, Ph, Me, Furyl

n = 1, 2, 3

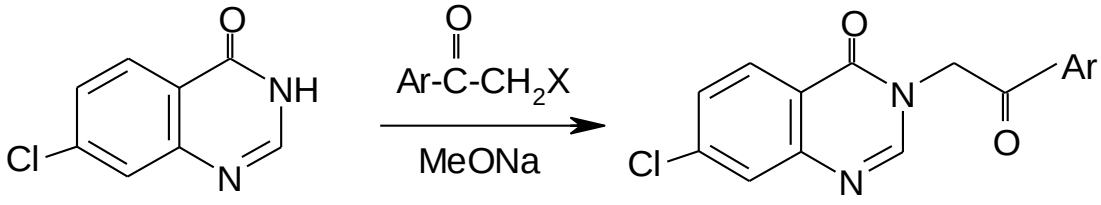
CHEMICAL REACTIONS

Chemical properties of 4(3H)-quinazolinones knowledge of the behavior of heterocyclic systems under conditions of the principal reactions is required to perform the direct synthesis of practically important many studies were devoted to the use of various quinazolinone derivatives in the synthesis of linearly and anglularly polyannelated, including previously unknown heterocyclic systems. Hydroxyquinazolines are a tautomeric with ketodihydro derivatives.



1- Alkylation reactions:

3-Substituted quinazolin-4(3H)-one derivatives (168) were obtained by alkylation of 7-chloro-4(3H)-quinazolinone (167) with α-halocarbonyl compounds in the presence of sodium methoxide[105].

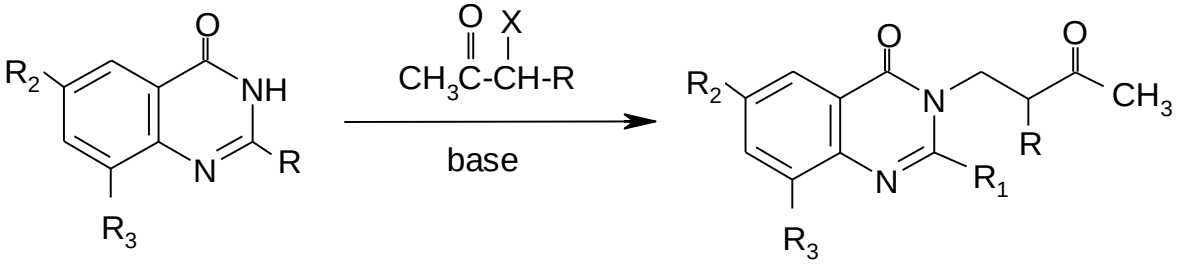


167 168

Ar = Ph, 4-$MeOC_6H_4$, 2-thiophene.

X = Cl, Br, F

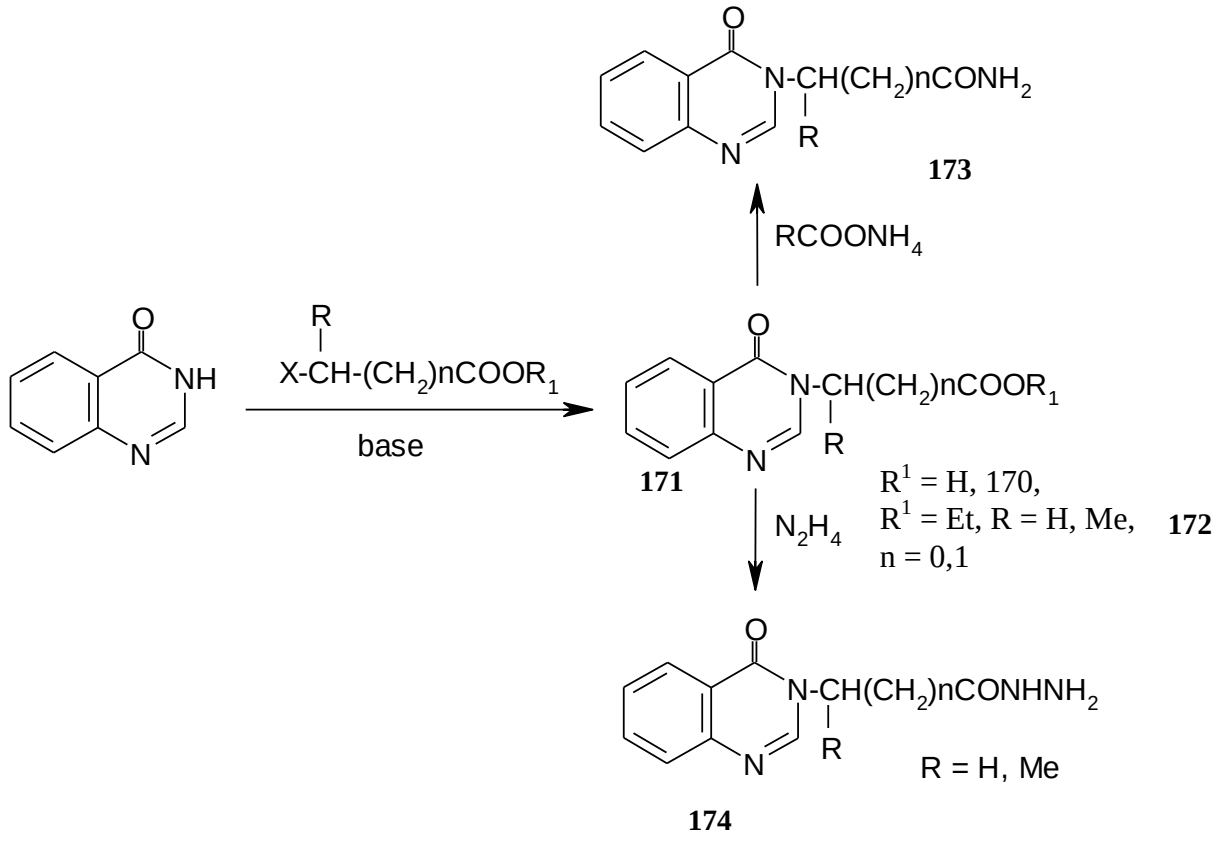
Also alkylation of 4(3H)-quinazolinones derivatives 169 by α-halo-ketone yielded the corresponding 3-(acylalkyl)-2,6,8-trisubstituted quinazolin-4(3H)-ones(170) [(106)].



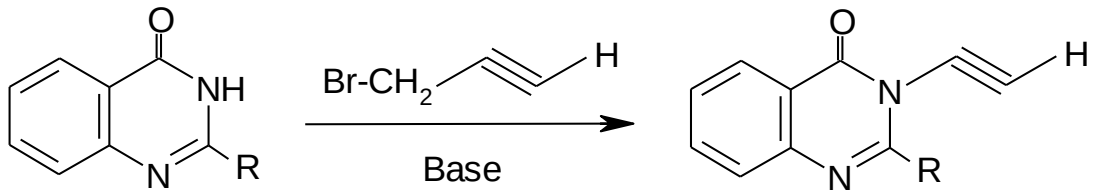
169 170

R = Me, C_2H_5, Ph, R_1 = H, Me, Ph, 4-ClC_6H_4, R_2, R_3=Cl_7Br, OMe, NO_2, Me, X = O, S

In the same way the reaction of 4(3H)-quinazolinone with halocarboxylic acids and their esters gave 4(3H)-quinazoline alkanoic acids (171) (R^1=H), and esters (172) (R^1=Et, R = H, Me), (n = 0, 1). The ester (172) converted to amides (173) and hydrazides (174) [(107)].



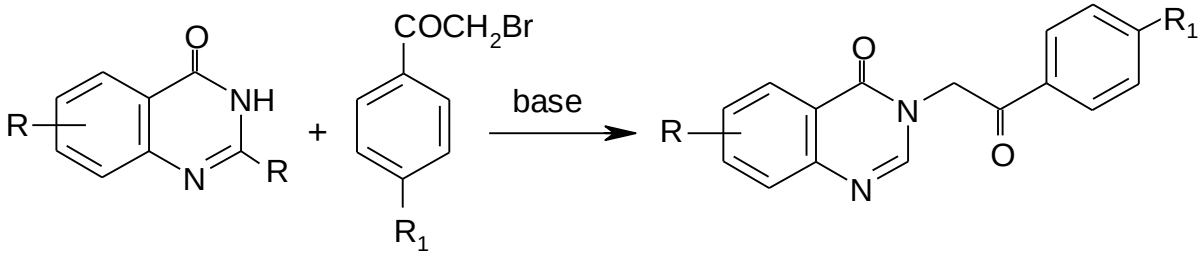
2-Substituted-3-propargyl-4-quinazolinones (176), (R = H, Me, Ph) were prepared by the reaction of 4-quinazolones (175) with CH≡C-CH_2Br in the presence of base[108].



175 176

R = H, Me, Ph

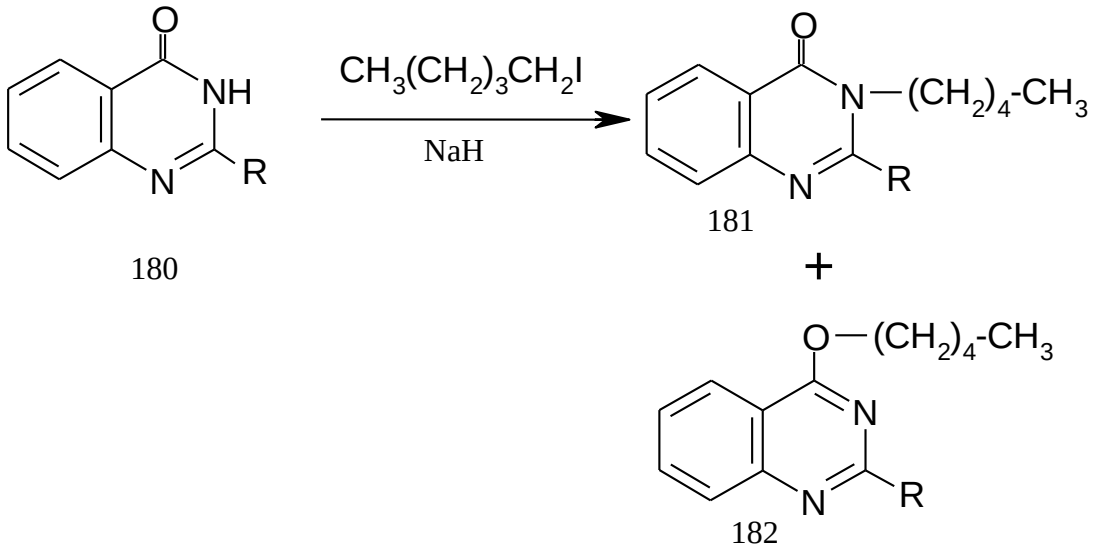
3-Phenacyl-4(3H)-quinazolinone (179), (R = H, 6-Cl) were prepared only by the reaction of R-substituted 4-(3H)-quinazolinones (177) with 4-subtituted phenacyl bromide (178) [109].



177 178 179

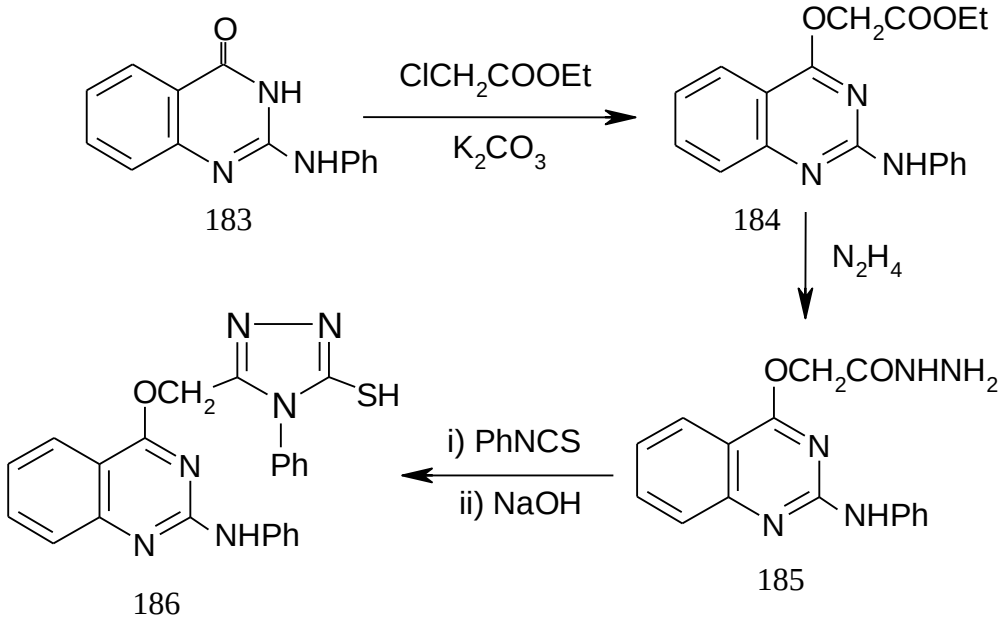
R = H, 6-Cl and 7-NO_2; R^1 = Cl, Br, I and NO_2

Alkylation of 4(3H)-quinazolinones (180, R = H, $CH(Me)_2$, $C(Me)_3$, CF_3, 4-methylpiperozino methyl), (Me) with 1-iodopentane in the presence of sodium hydride gave a mixture of 3-pentyl-2-subtituted-4(3H)-quinazolinone (181) and 2-subtituted-4-pentyloxyquin (182) [110].



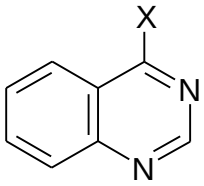
(R=H, $CH(Me)_2$ $C(Me)_3$, CF_3, (4 = methylpiperazino) methyl, $N(Me)_2$, N(Me)Ph, O-$(CH_2)_4$ Me).

5-(2-Phenylamino)quinazolin-4-yloxymethyl)-3-mercapto-4-phenyl-1,2,4-triazole (186) has been prepared *via* alkylation of 2-(phenylamino)-4(3H)-quinazolone (183) with ethyl chloracetate, followed by condensation of ester (184) with hydrazine hydrate, and subsequent cyclization of hydrazide (185) with phenyl isothiocyanate in the presence of sodium hydroxide[(111)].

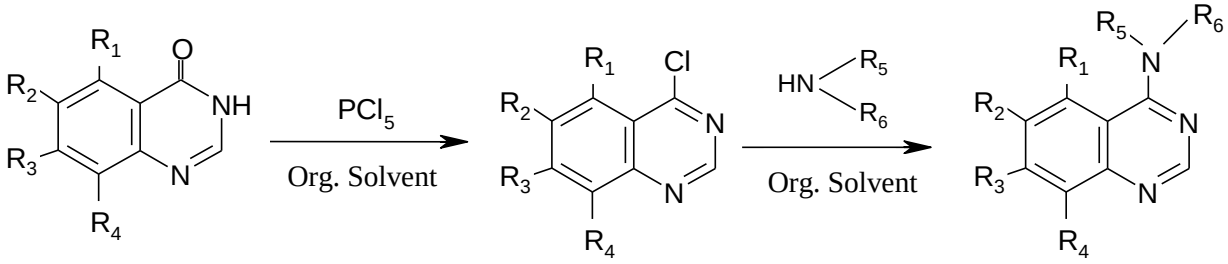


2- Halogenation reactions :

The introduction of chlorine at the 4-position in quinazolinone skelton can be achieved through the use of $POCl_3$[112] or thionyl-chloride[113-115]. The using $POCl_3$ is reported by Sugimoto et al.[116] This involves chlorinatin with a potassium salt of N-chlorosuccinimide. Treatment of quinazoline with this salt in refluxing in dioxane for 4hr. furnished 4-chloro quinazoline.



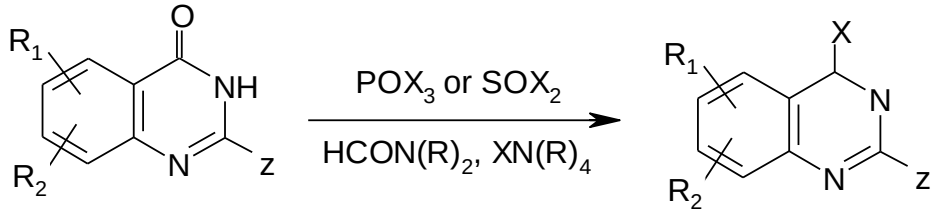
Quinazolin-4-one derivative (187) (where R^1, R^2, R^3 and R^4 are groups which do not participate in the reaction or they are linked to each to form a ring) was reacted with chlorinating agent in the presence of an organic base. Subsequently, the product (188) was reacted with an amine compound represented by formula (R^5 R^6)NH R^5 and R^6 each represented hydrogen or substituted hydrocarbon group. To give a 4-(disubstituted) aminoquinazoline derivatives (189), which are useful as an intermediate for drugs and agrochems[117].



(187) (188) (189)

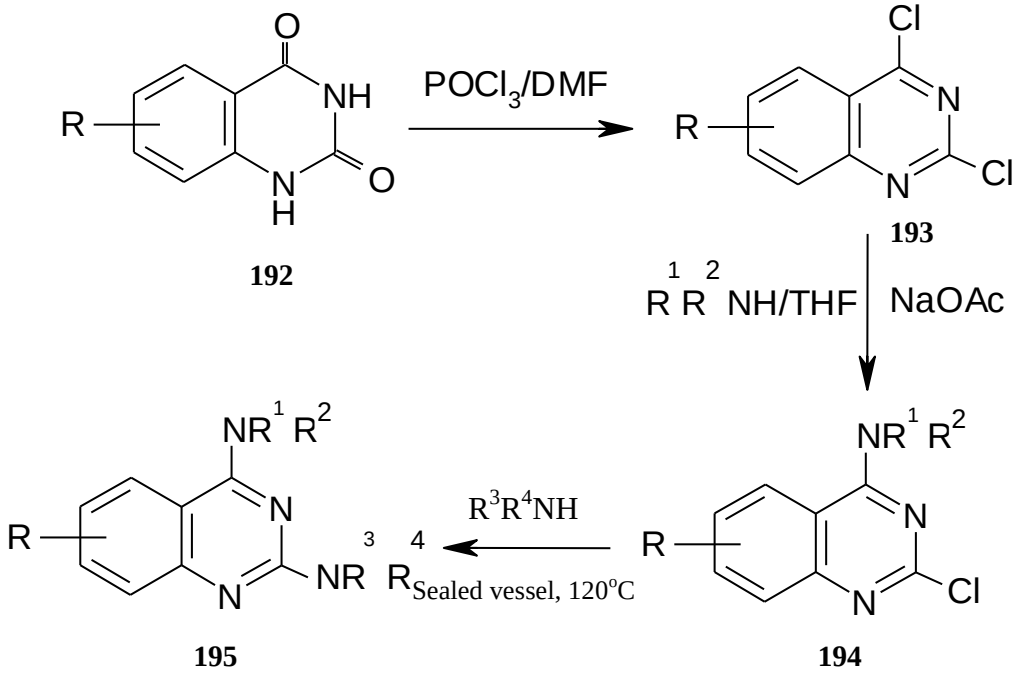
4- Haloquinazoline derivatives (191) (R^1, R^2 = H, F, Cl, Br, R, OR, SR, NO_2, R = (un) substituted Cl-4-alkyl; X = Cl, Br, Z = H, Cl, Me,

MeO)[118] are readily prepared by the reaction of 4(3H)-quinazolinone derivatives (190). With thinoylchloride or phosphoryl halide in the presence of a catalytic amount of a N, N-dialkyl formamide and a solution halide salt (tetraalkyl ammonium chloride).



190 191

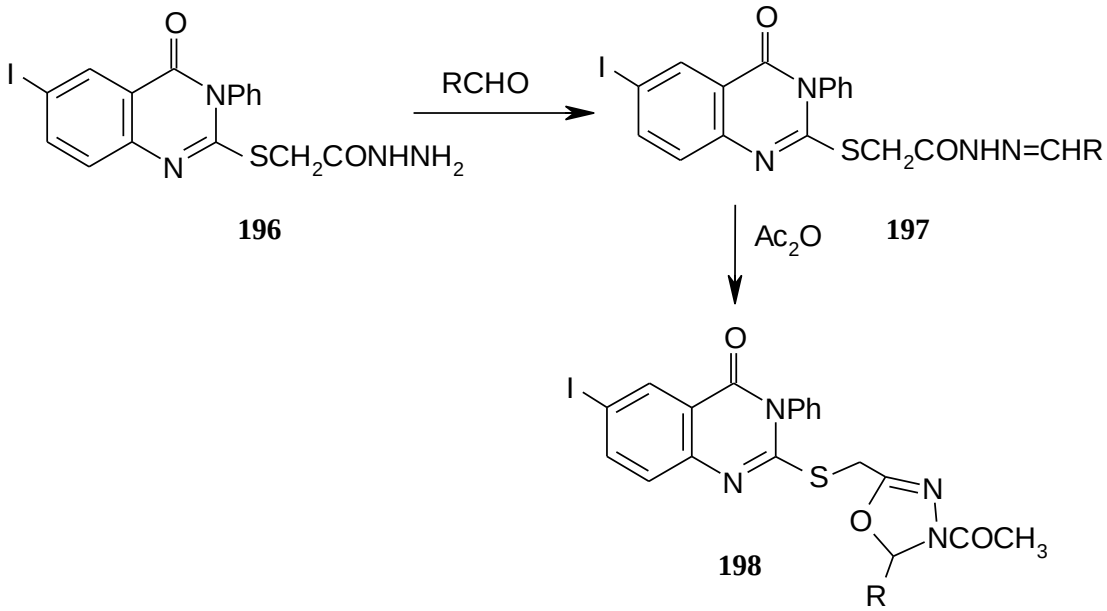
Treatment of quinazolinedione (192) with phosphoryl chloride gave 2,4-dichloroquinazoline (193) which reacts with aniline derivatives in THF and in the presence of sodium acetate at elevated temperature in sealed tube to produce 2, 4-diaminoquinazoline derivatives (195)[119].



R	R^1	R^2	R^3	R^4
H	Ph	H	Ph	H

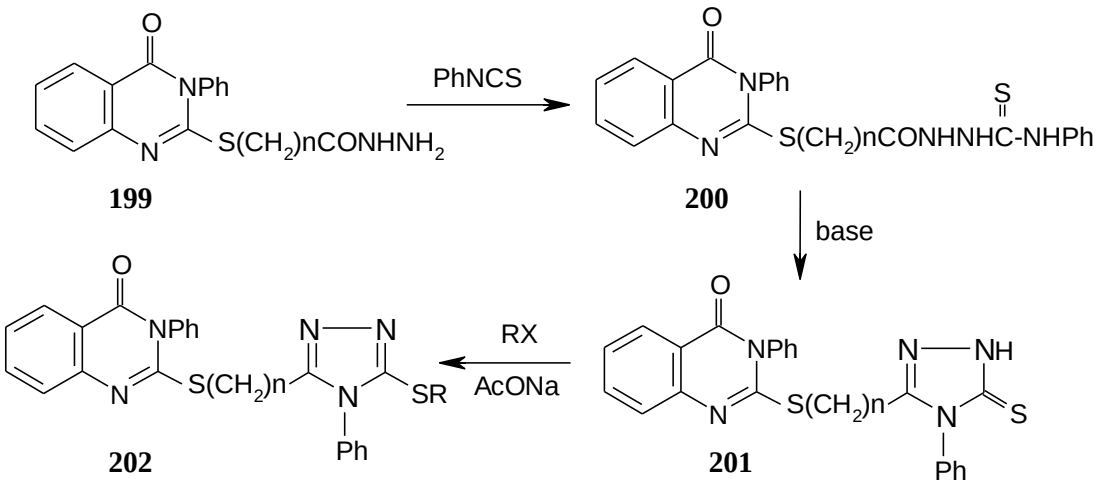
3-Condensations Reactions:

Condensation of 2-hydrazinocarbonylmethylthio-3-phenyl-6-iodo-4(3H)-quinazolinone (196) with aldehydes afforded hydrazone (197). In the presence of acetic anhydride, hydrazone(197) cyclized to2-[(3-(5-substituted-4-acetyl-1,3,4-oxadizole)methyl-thio)-3-phenyl-6-iodo-4-(3H)-quinazolinone(198)[120].

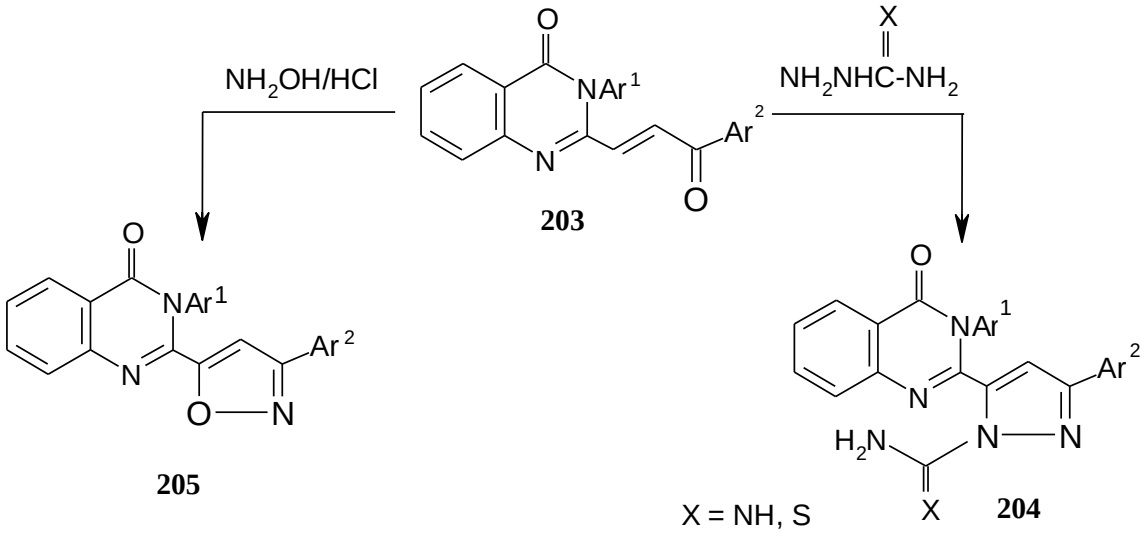


R = C_6H_5, 4-$MeOC_6H_4$, 4-ClC_6H_4.

Also,2-[(5-Thione-4-phenyl-1,2,4-triazole-3-yl)methylthio-3-phenyl 4(3H)quinazolinone (202) are useful as antibacterial agents. They were prepared by starting from (3-phenyl-4(3H)-quinazolinon-2-yl)-thioacetyl hydrazine (199). Reaction of hydrazide (199) with phenylisothiocyanate gave the corresponding 4-[3-phenyl-4(3H)-quinazolinone-2-yl]thioacetyl]-1-phenyl thiosemicarbazide (200) and the side chain in presence of base make ring closure in presence of base to give 2-[(5-alkyl thio-4-phenyl-1,2,4-triazol-3-yl)methyl-thio]-3-phenyl-4(3H)-quinazolinone (202)[121].



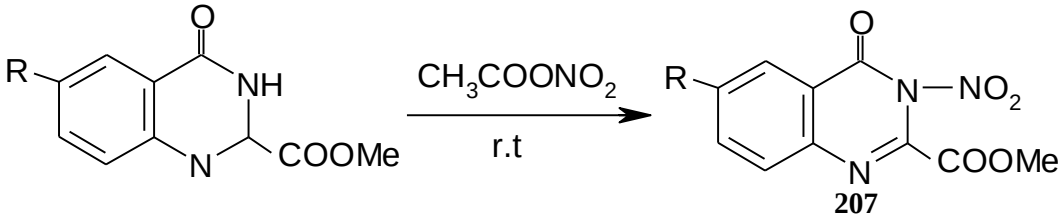
Pyrazolo and oxazole quinazolinones (204) and (205) were prepared from intermediate 3-aryl-2-(3-oxo-propenyl)-4(3H)-quinazolinone (203) by reaction with amino-guanidine, thiosemicarbazied and hydroxylamine hydrochloride to give 3-aryl-2-(3-aryl-1-imino (or thio) carbamoyl-1H-pyrazole-5-yl)-4(3H)-quinazolinones (204) and 3-aryl-2-(3-aryl-4,5-dihydro-1,2-oxazol-5-yl)-4(3H)-quinazolinone (205) [(122)].



$Ar^1 = Ar^2 = Ph , 4 – MeOC_6H_4, 4 – ClC_6H_4$

4-Nitration reactions

The novel 3-nitro-4(3H)-quinazolinone derivatives (207) was prepared from the reaction between 6-substituted-2-methoxy-carbonyl-4(3H)-quinazolinone (206) and acetyl nitrate at room temperature[(123)].

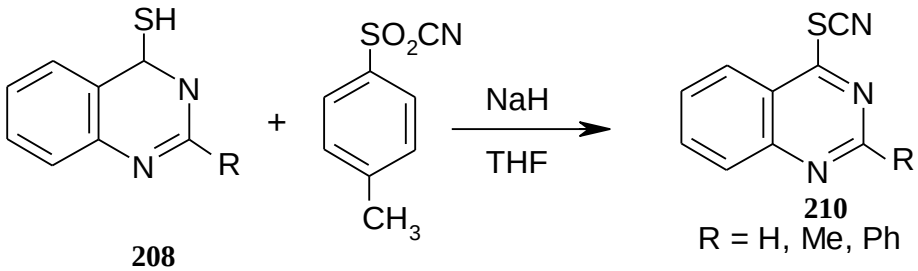


206 **207**

R = H, Me, OMe

5-Cyanation reactions

Quinazoline-4-thiol (208) under-went electrophilic cyanation with p-toluenesulfonyl cyanid (209) in THF in the presence of NaH to give the corresponding thiocyanaquinazoline (210) in good yield[(124)].

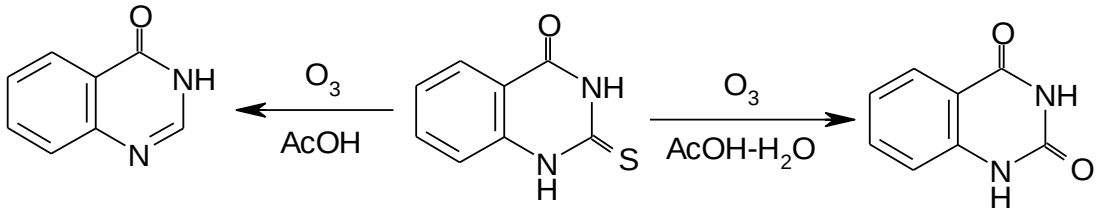


208 **209** **210**

R = H, Me, Ph

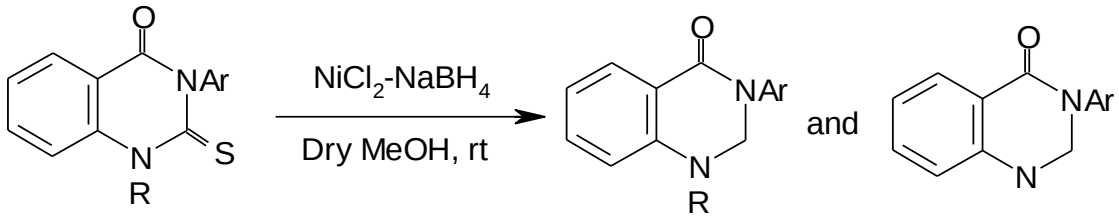
6-Desulfurization reactions

2-Thioureacil (211) underwent ozonation in acetic acid-water to give quinazolinedione(212). The thiouracile (211) underwent ozonation in acetic acid alone to give quinazolinone [(125)].



211 **212**

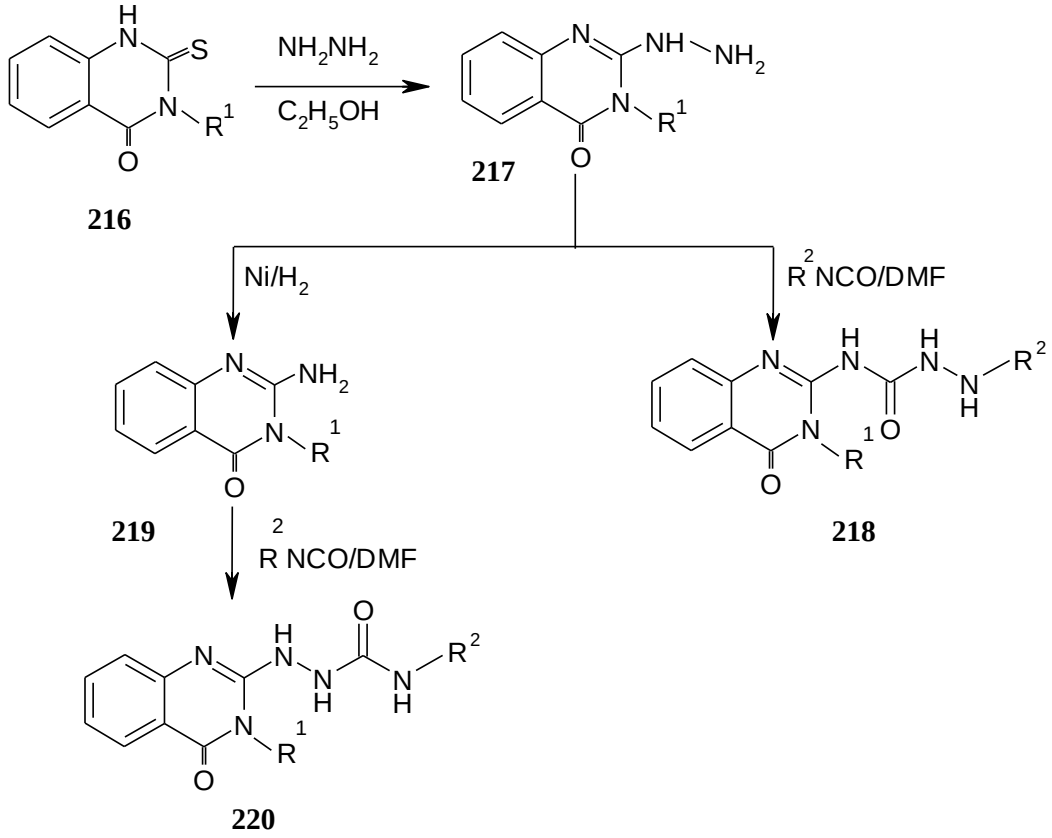
Reductive desulfarization of 2-thioxo-4(3H)-quinazolinone (213) with nickel chloride boride in dry methanol at ambient temperature give 2, 3-dihydro-4(3H)-quinazolinones (214) and quinazolin-4(3H)ones (215) [(126)].



213 **214** **215**

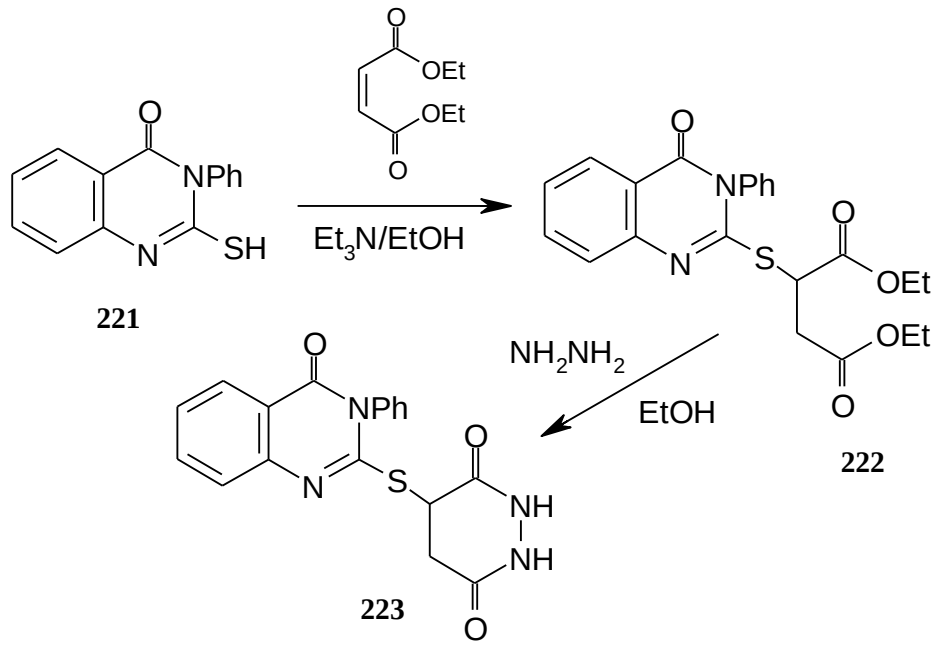
a: R = H, Ar = Ph, b: R = H, Ar = 4-$MeOC_6H_4$
c: R = H, Ar = 4-MeC_6H_4.

Refluxing of quinazoline-2-thione (216) with hydrazine hydrate in ethanol afforded 2-hydrazinoquinazoline (217), which converted to 2-aminoquinazoline by the reaction with hydrogen over nickel[(127)]. Treatment of and (218) with isocyanate in DMF in presence of sodium hydride provided urea derivative (219) and (220).



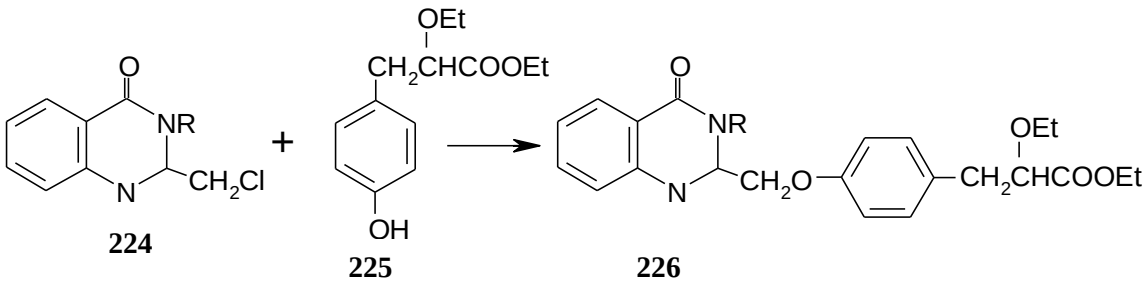
7-Reaction at Sulpher atom:

Treatment of 2-mercapto-4(3H)-quinazolinone (221) with diethyl-maleate in the presence of Et_3N leads to formation of thioderivatives (222). Reaction of (222) with hydrazine hydrate in ethanol, provides 2-(hexahydropyridazine-3,6-dione-4-yl)thio-3-phenyl-4(3H)-quinazolinone (223)[(128)].



8-Reaction with phenol:

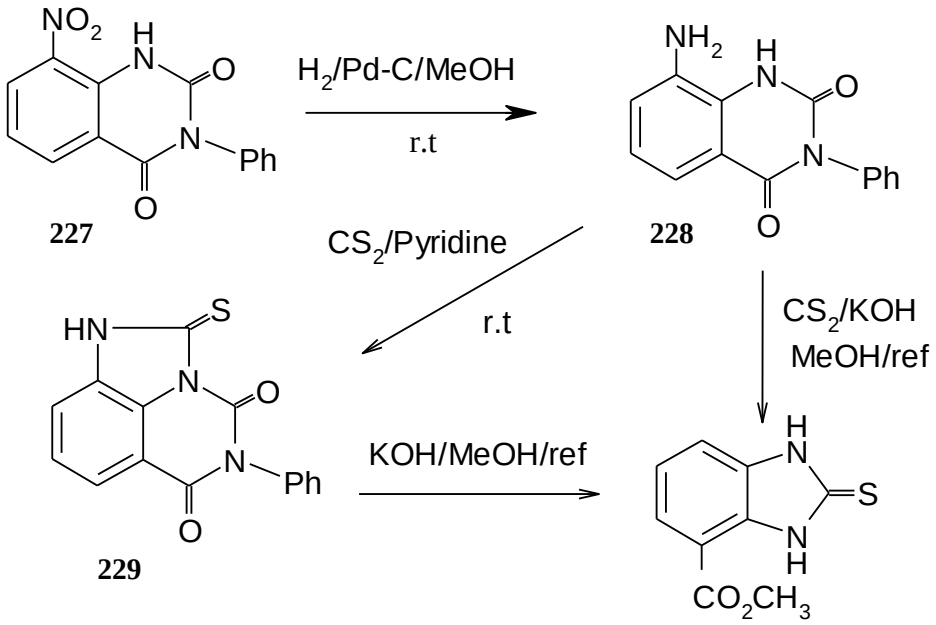
Preparation of ω-[Oxoquinazolinylalkoxy]-phenyl]alkonate) (226) and analogs as PPARα and PPARγ receptor agonists. Thus 2-chloromethyl-3-substituted-4(3H)-quinazolinone (224) was reacted with ethyl β-(4-hydroxyphenyl)-α-(ethoxy)-propionate (25) to give ω-[(oxoquinazolinyl-alkoxy)-phenyl]alkonates (226)[(129)].



9-Ring transformation:

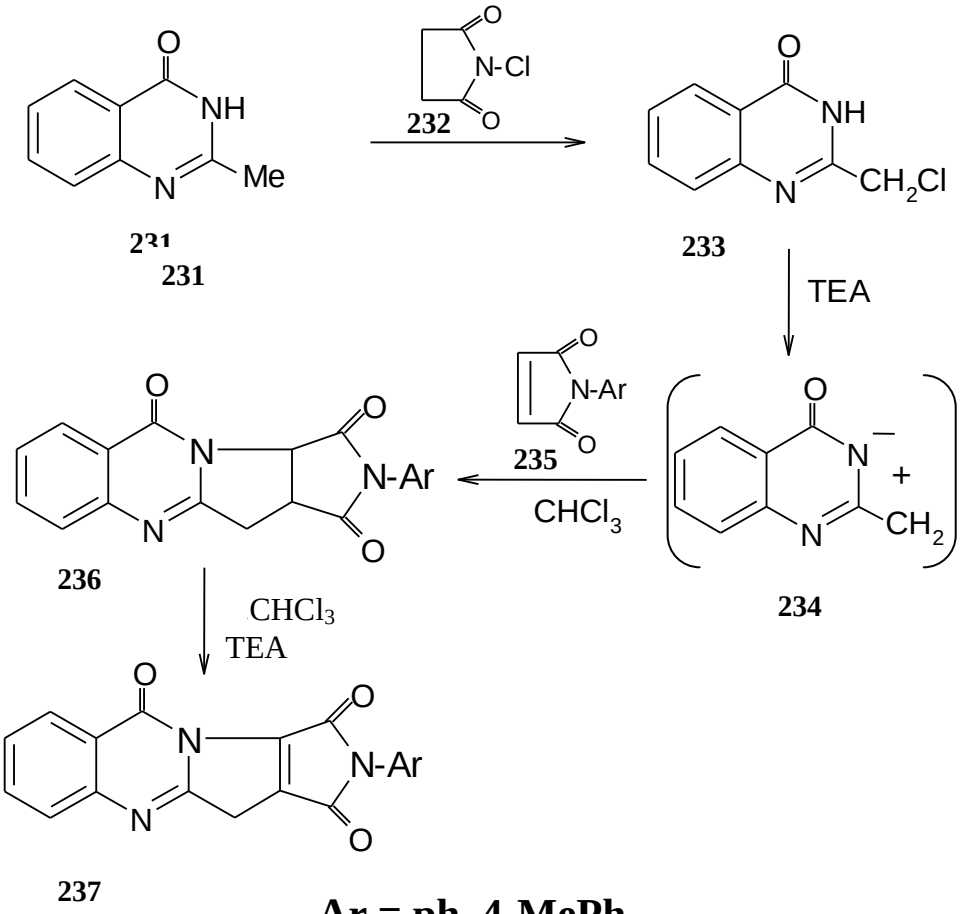
Reduction of 8-nitroquinazolines (227) in methanol and the presence of palladium over carbon gave 8-Aminoquanazolines (228)

which reacted with carbon disulfide and pyridine refluxing in methanol to obtain the tricyclic derivatives (229) which treated with potassium hydroxide to afford benzimidazol-2-thione (230)[130].



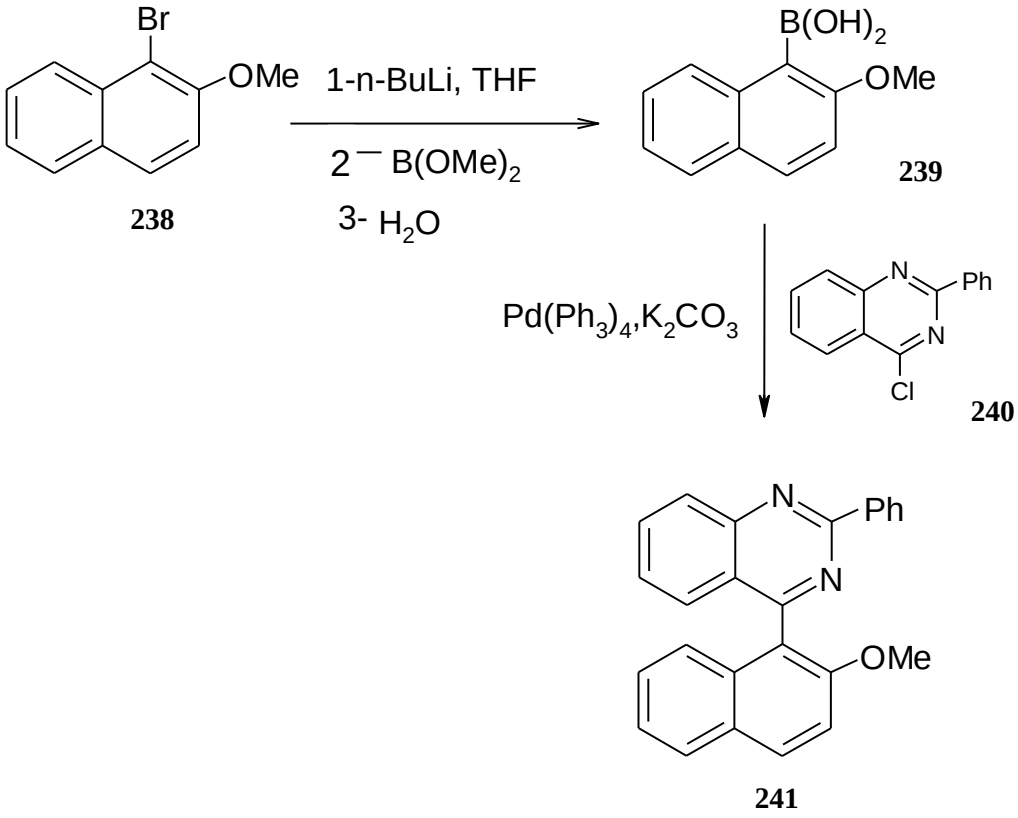
10-Formation of polycyclic rings:

2-Methylquinazolines (231) were reacted with N-chloro-succinimide (232) to yield 2-chloromethyl quinazoline (233) which treated with triethylamine (TEA) to afforded Zwitterionic compound, dipolar cycloaddition of zwiterionic with N-arylmalimides in dry chloroform in the presence of triethyl amine gave the tetracyclic compound (237) [131].



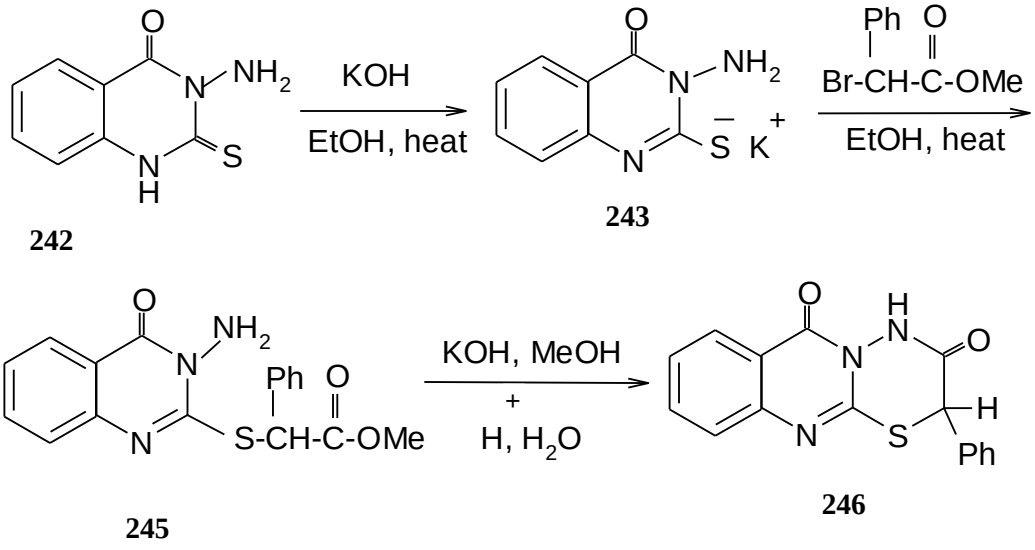
Ar = ph, 4-MePh

2-Methoxy-1-naphthylboronic acid (239) was prepared from 1-bromo-2-methoxynaphthalene (238) via lithiated derivatives. The cross coupling reaction between (239) and 4-chloroquinazoline (240) was achieved in potassium carbonate solution in the presence of palladium triphosphine to form (241)[(132)].



238 **239** **240** **241**

Refluxing of 3-amino-2-thioxoquinazoline (242) in ethanol in the presence of potassium hydroxide afforded potassium salt (243). Which reacted with α-bromophenyl acetate to give (245) which cyclized in ethanol and in the presence of potassium hydroxide to form tricyclic compound (246)[(132)].

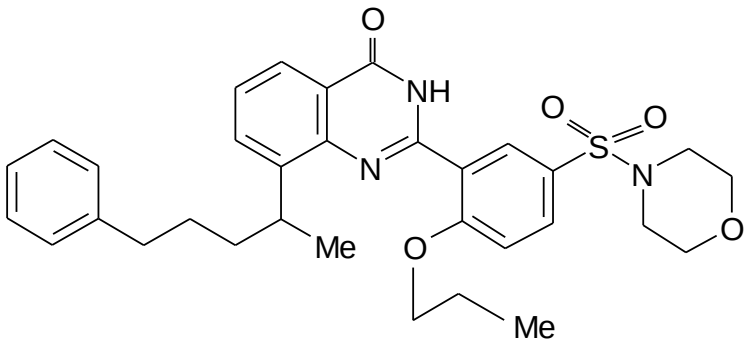


242 **243** **245** **246**

Biological Activity of some Quinazolin4-ones

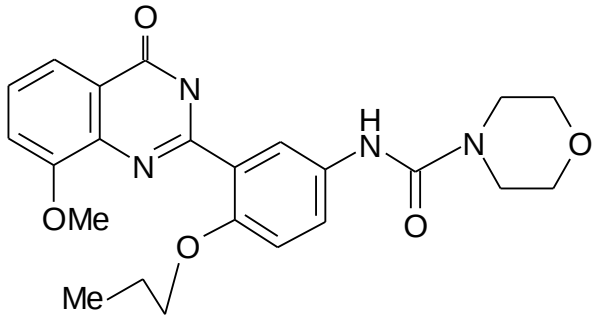
Quinazolinone derivatives are characterized by a very broad spectrum of biological activities[9-33] which includes several dozens of activates. e.g anticonvulsant[133] Hypnotic[134], tranquillizing[135], analgesic[136], anti-inflammatory[137], amoebicidal[138], antimalarial[139] and antibacterial[140]. Also great interest was found on 4(3H) quinazolinone derivatives since they exhibits reducing total cholesterol, cholesterol ester levels and triacylglycerol level were reduced by treatment with halogen substituted quinazolinone[141-143]

8-(1-Methyl-4-phenylbutyl)-2-[5-morpholinylsulfonyl)-2-propoxyphenyl]-4-(3H)-quinazolinone (247) is used for the treatment of cardiovascular and thromboemboic disorders that exhibits potent in vitro inhibition of phosphodiesterase type II and V (PDE II and PDEV) activity[144].



247

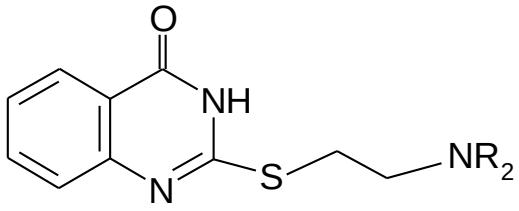
N-[3-(8-Methoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-4-propoxyphenyl]morpholin-4-carbamide (248) is a drug for the treatment of heart failure and other cardiovascular and respiratory tract/allergic disorders, with potent GMP phosphodiesterase (PDEV) inhibitory activity [145].



248

4-Oxo-quinazoline agonist ligands for liver x nuclear receptor and their use in treatment of disorders of lipid metabolism[146].

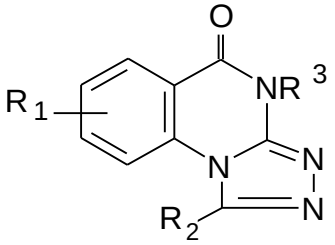
The quinazolinones NR_2 = NMe2, piperidino,2,2,6,6-tetramethylpiperidino](294) exhibited remarkable inhibitory effect on PARP enzyme in vitro [147].



249

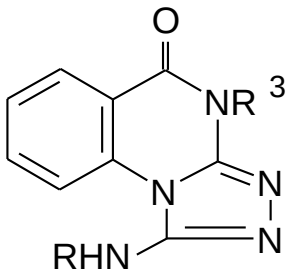
There are also presented qinazolin-4-ones belonging to new classes of pharmacologically active compounds-angiotensin II receptors antagonists, and cholecystokinin receptors antagonists[148].

The 1-alkyl or 1-cycloalkyltriazolo[4,3-a]quinazolin-5-ones (250) are useful for the treatment of pathologies in which therapy by a PDE_4 inhibitor is relevant [149].



250

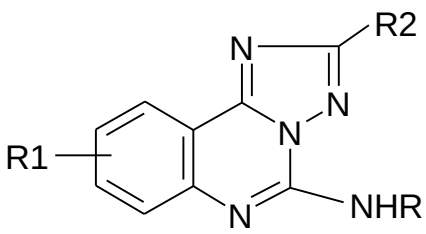
1, 2, 4-Triazolo[4,3-a]quinazoline (251) showed antitoxoplasmosis effect.



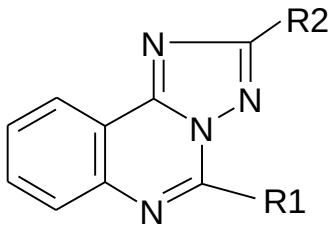
251

$R = C_6H_5$

Triazoloquinazoline derivatives (252), (253) show a selective affinity for adenosine A_3 receptor and an effect on lowering ocular tension, which makes them useful in preventing or treating glaucoma[(150)], hypertension, inflammation, allergic reaction. Mast cell degranulation. Furthermore, compounds of the invention can be used in a diagnostic application to determine the presence of tumor cells which possess a high concentration of adensoine A_3 receptors[(151)].

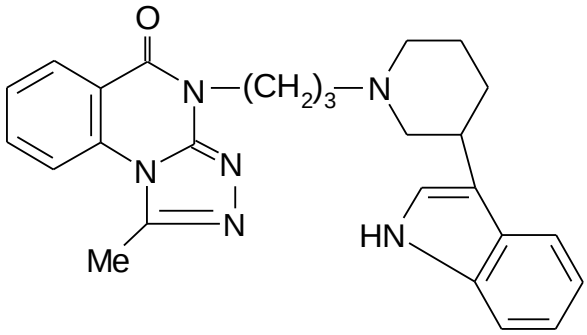


253



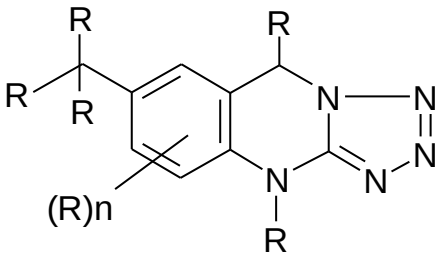
252

Triazoloquinazoline (254) is useful as a remedy for allergic diseases including bronchial asthma and a topic dermatitis, inflammatory diseases including bronchial asthma and a topic dermatitis, inflammatory diseases including rheumatoid arthritis, and autoimmune diseases including nephritis and ulcerative colitis, or anti AIDS drugs[(152)].



(254)

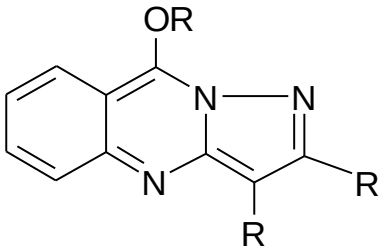
Tetrazoloquinazoline derivatives (255) were prepared for use as famesyl transferase inhibitors in the treatment of proliferative diseases[153].



255

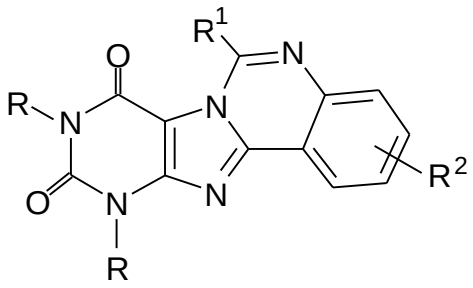
Fused tricyclic quinazoline (255) analogues as ATP site inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor[154, 155].

Pyrazolo [1,5-b]quinazoline derivatives (256) have an analgetic action and are useful in relieving symptoms with pain such as postoperative pain and migraine[156].



256

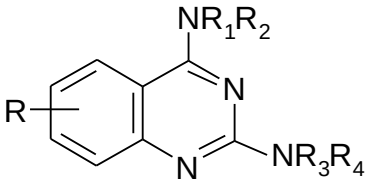
Purino [7,8-c]quinazoline derivatives (257) were reported to be active as A_1-adenosine receptors antagonists with binding values in the micromolar range[(157)].



257

R = Me, Pr
R^1 = H, C_1-C_3. alkyl
R^2 = H, 2-Cl, 3-Cl, 4-MeO

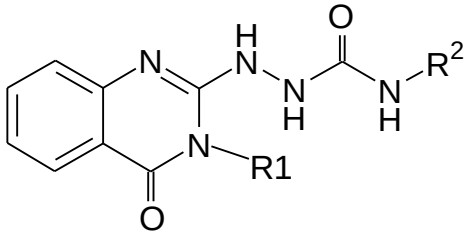
2,4-Diaminoquinazolines (258) showed as reversible inhibitors of the Gastric (H^+/K^+) – ATPase [(119)].



258

R	R^1	R^2	R^3	R^4
H	Ph	H	Ph	H

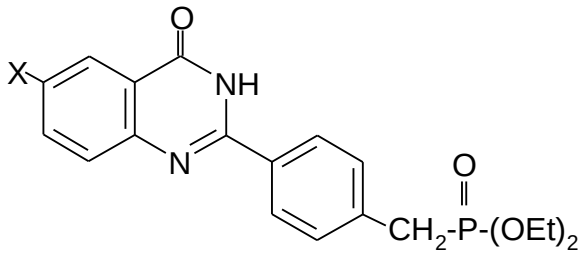
Quinazoline derivatives (259) showed potent, selective and orally active noneptide CCK-B receptors antagonists[(130)].



259

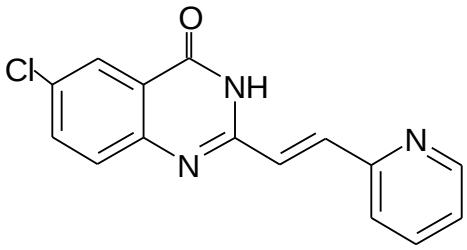
R^1	R^2
Ph	Ph
Ph	4-BrPh

Quinazolinone bearing a 4-[(diethoxyphosphoryl)]methyl phenyl group at the position 2-were found to lower triglyceride and total chlolestrol levels.[141-143]



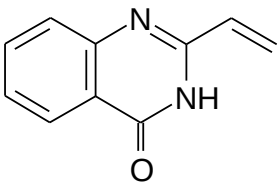
260

6-Chloro-2-(2-pyridine-2yl-vinyl)-quinazoline-4(3H)-one (261). have growth inhibitory activity against leukaemia cells. Lee et al.[158] used 2-arylquinazolinone that were active against panel of tumour cell lines.



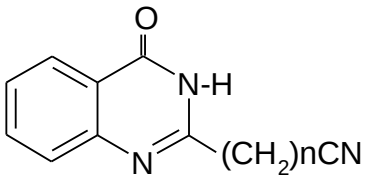
261

2-Vinyl-quinazolin-4(3H)-one used by chemists at Fujisawa Pharmaceutical Company to synthesis of a series of inhibitors of poly 2-substituted-4(3H)-quinazolinones (ADP-ribose) polymeras [159].



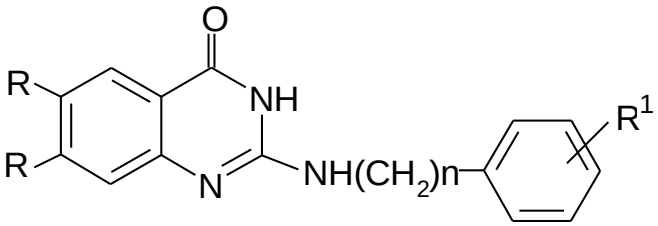
262

Derivatives of this compound have been used in the study of potential anthelmintics[160], antiallergic agents[161] and antitubercular agents[162].



263

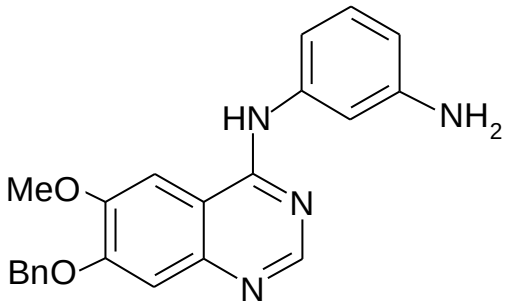
Mellen et al.[163] used compound (264) as a key pharmacophores of aldose reducates.



264

n = 0, 1; R = H, OMe; R^1 = H, 4`-OH, 4`-CO_2H, 4`-SO_3Na

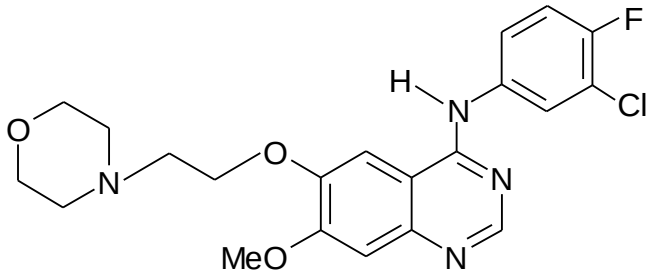
Compound (265) was used as an intermediate in the synthesis of Ax 7593, aquinazoline-derived photoaffinity probe for epithelial growth factor receptor (EGFR)[164].



265

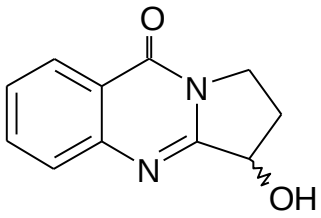
In may 2003, the food and drug administration (FDA) approved, the first epidermal growth factor receptor inhibition. Iressa, for the

treatment of lung cancer, further highlighting the importance of the 4-anilino-quinazolines in medicine[(165)].



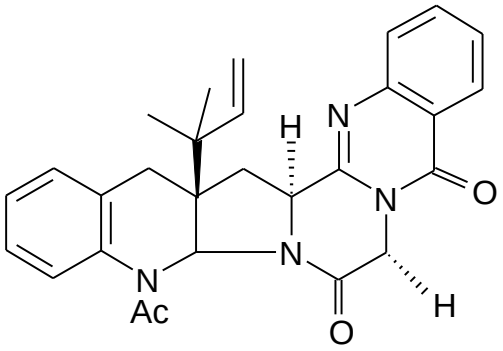
266

Vasicinone (268), deoxyvasicinone (267), N-acetylardeemin (269) are important pharmacologically for synthesis multi drug resistance reversal agent [(166)]



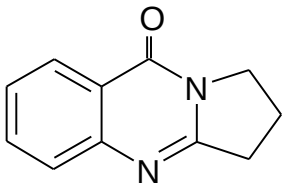
Vasicinone

268



N-acetylardeemin

269



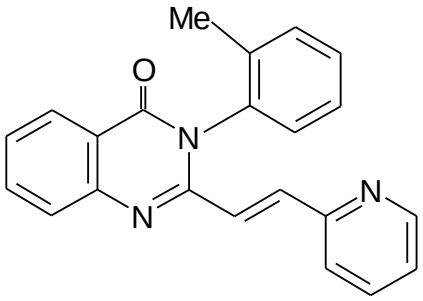
Deoxyvasicinone

267

4-Quinazoline was modified with 2,2,5,5-tetramethyl-2,5-dihdro-1H-pyrrole or 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine rings and their N-oxyl derivatives were synthesized and some of them evaluated for

protecting activity agonist H_2O_2 induced cell deathon WRL- 68 humanliver cell line[167-169].

2-(2-[(2-pyridyl)vinyl]-3-0-tolyl-)-4(3H)-quinazolinone (270) showed anticonvulsant, hypnotic and muscle relaxant activity, and was sold as drug under the trade name piriqualone[170].



270

Quinazolinones used as heat stable epoxy resins[35], fiber reactive dyes[36] and in polymers[37].