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A review on 2-heteryl and heteroalkylquinazolin-4(3*H*)-ones: Part-II

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ABSTRACT

The recent progress in the synthetic methods of 2-heteryl and hereteroalkyl quinazolin-4(3H)-ones and their pharmacological activity are presented and discussed.

Keywords: *Quinazolin-4(3H)-ones, 2-heteryl, 2-heteroalkyl, synthesis, pharmacological activity.*

Table of Contents

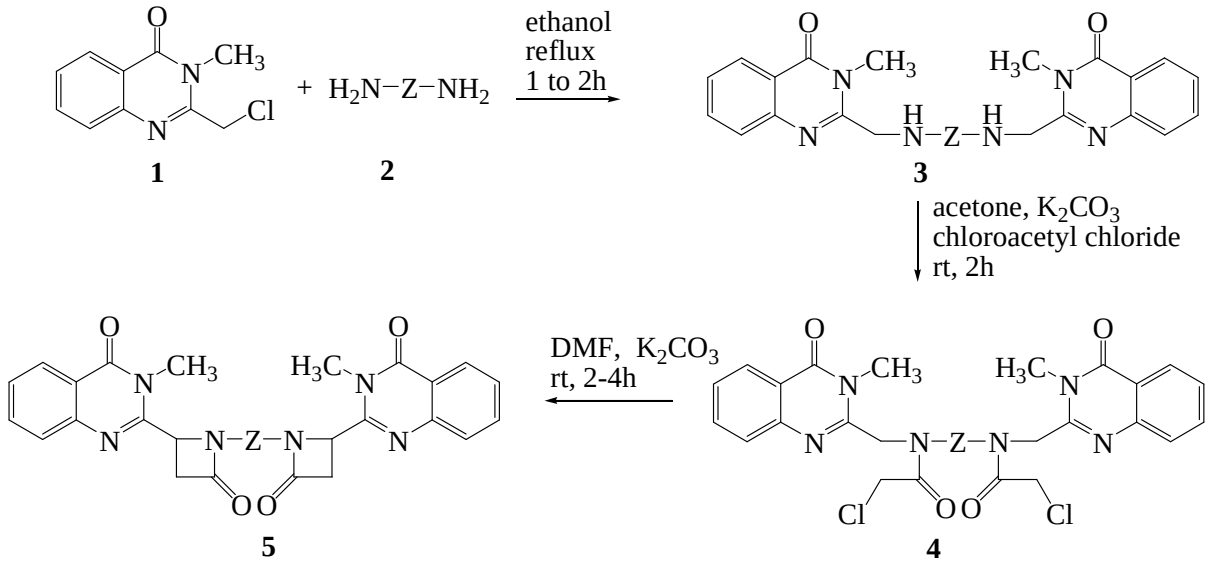
INTRODUCTION

2-Heteryl and heteroalkyl quinazolin-4(3*H*)-ones exhibited a wide range of pharmacological properties such as CNS depressant, antimicrobial, antibacterial, analgesic, antifungal, antiinflammatory, antiulcer, anticonvulsant, antihypertensive, sedative, anaesthetic, tranquilising and muscle relaxant, body temperature lowering, spore germination inhibition in Drechslera rostrata and Fussarium oxysporum, CNS active, hypnotic, antidepressant, antihelmentic, inhibition of AMPA receptor activation, antihistamine, virucidal, hypoglycemic, MAO inhibition, insecticidal, radioprotective, spasmolytic, contraceptive, antitubercular, antimonomine oxidase, H_2-antagonist and antisecretion activity[1]. They are also useful as antifeedant[2], cytotoxic[3], inhibitors of NF-kB and AP-1 mediated transcriptional activation[4-6], cycloxygenase [7], NR2B selective NMDA receptor antagonists [8], PDE5 inhibitors [9], CXCR3 receptor antagonists [10], antitubercular [11], antipsychotic [12], dihydrofolate reductase (DHFR)

inhibition [13]. They also find application as heat stable epoxy resins, fiber reactive dyes, and polymers [1]. In this context, the reported syntheses and importance of 2-heteryl, heteroaryl and heteroalkylquinazolin-4(3*H*)-ones are reviewed here as a prelude to our efforts to develop a 'drug candidate' from these heterocycles. For convenience, the review is organized according to the size of the heterocycle linked either directly or through an alkyl, alkenyl, aminoalkyl, alkylamino, thio, alkylthio, thioalkyl group to C-2 of quinazolin-4(3*H*)-one

2.1 Bisquinazolinonyl β-Lactams

Reddy and co-workers reported the synthesis of [bis-(4-(3-methylquinazolin-4(3*H*)-one-2-yl)azetidin-2-one-yl)]phenyl/biphenyl/diphenylmethane (**5**) [14]. 2-Chloromethylquinazolin- 4(3*H*)-one (**1**) was reacted with arylamine **2** to yield [*N*,*N*'-bis((3-methylquinazolin-4(3*H*)- one-2-yl)methyl)aryldiamine **3**. Conversion of compound **3** to *N*,*N*'-dichloroacetyl- [*N*,*N*'-bis((3-methylquinazolin-4(3*H*)-one-2-yl)-methyl)]aryldiamine **4** with chloroacetyl chloride followed by base catalyzed dehydrochlorinative cyclization with K_2CO_3 in DMF to isolate compound **5**. 3,3'-Dimethyl-4,4'-[*N*,*N*'-dichloroacetyl- *N*,*N*'-bis((3-methylquinazolin- 4(3*H*)-one-2-yl) methyl)]diaminobiphenyl (**5c**) is the most promising with 66.26% antifeedant activity even at 6.25µg/cm^2 concentration (Scheme 1) [2].

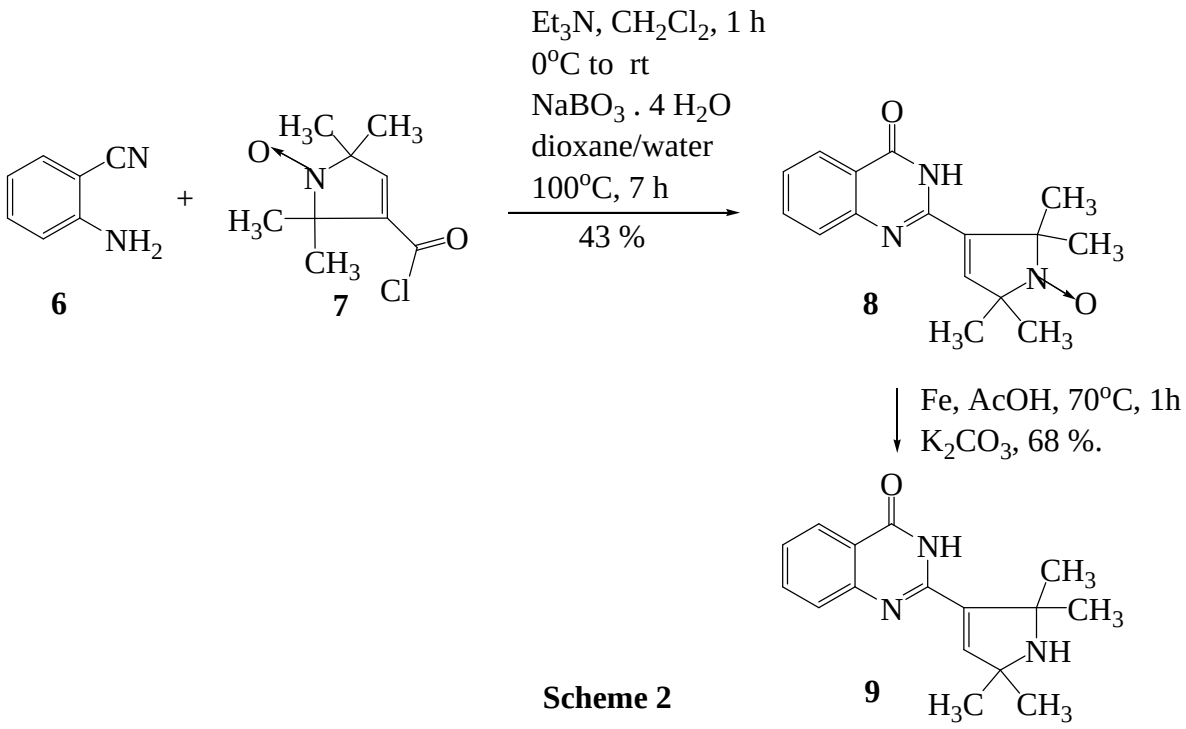


5	**a**	**b**	**c**	**d**	**e**
Z	1,4-C_6H_4-	4,4'-C_6H_4-C_6H_4-	4,4'-C_7H_6-C_7H_6-	4,4'-C_6H_4-CH_2- C_6H_4	4,4'-C_7H_6O-CH_2-C_7H_6O
Yield	80	70	85	83	72

Scheme 1

2.2 Dihydropyrrolylquinazolin-4(3*H*)-one

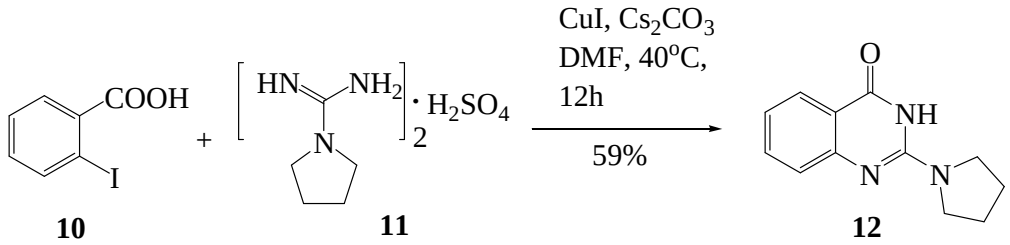
Reaction of 2-aminobenzonitrile (**6**) with 1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*- pyrrole-3-carbonyl chloride (**7**) in CH_2Cl_2 containing Et_3N followed by treatment with $NaBO_3.4H_2O$ yielded the 2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)- quinazolin-4(3*H*)-one radical (**8**). The resultant nitroxide compound was reduced with Fe powder in acetic acid to isolate 2-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-quinazolin-4(3*H*)-one (**9**, Scheme 2) [15].



Scheme 2

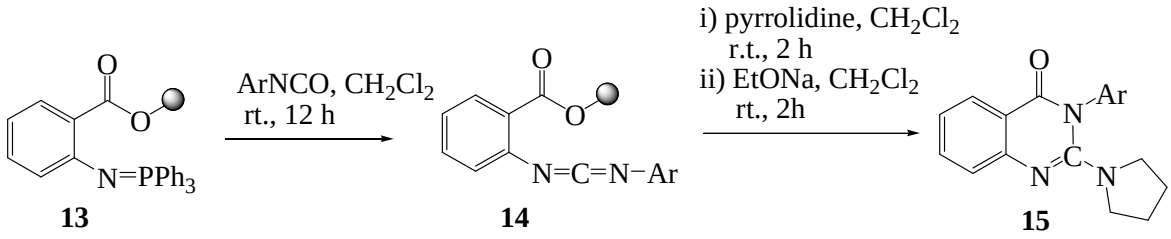
2.3 Pyrrolidinylquinazolin-4(3*H*)-ones

2-Iodobenzoic acid (**10**) was reacted with pyrrolidine-1-carboxamidine salt **11** in *N*,*N*-dimethylformamide in presence of CuI and Cs_2CO_3 under nitrogen atmosphere to isolate 2-(pyrrolidin-1-yl)-quinazolin-4(3*H*)-one (**12**). The yield of the reaction increased to 72% yield at reaction temperature of 80°C (Scheme 3) [16].



Scheme 3

Xie and co-workers prepared 2-(pyrrolidin-1-yl)-3-arylquinazolin-4(3*H*)-one (**15**) from poly(ethylene glycol) (PEG) supported aza-Wittig reaction. Quinazolinones **15** were synthesized efficiently by reaction of secondary amine with PEG-supported carbodiimides **14**, which were obtained from aza-Wittig reaction of PEG-supported iminophosphoranes **13** with isocyanates (Scheme 4) [17].

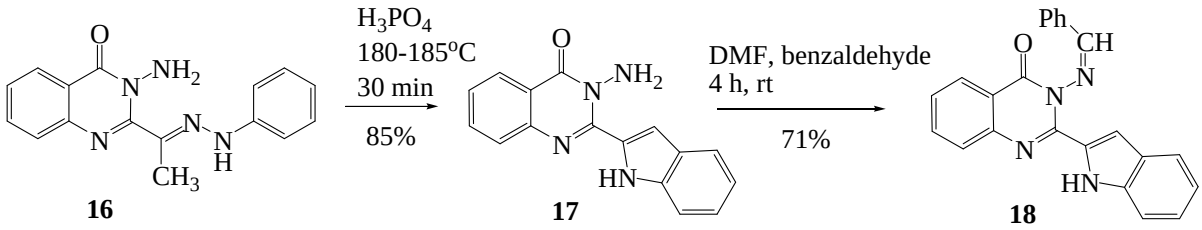


Ar	Ph	4-ClC_6H_4	4-FC_6H_4
Yield(%)	81	75	88

Scheme 4

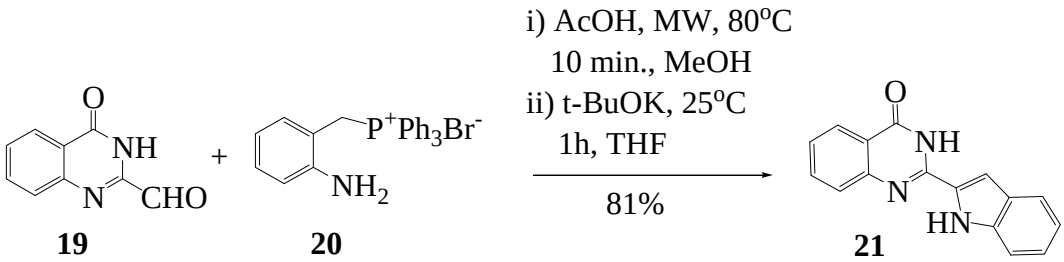
2.4 Indolylquinazolin-4(3*H*)-ones

Fischer indolization of 3-amino-2-(1-phenylhydrazonoethyl)-quinazolin-4(3*H*)-one (**16**) in presence of 85% phosphoric acid yielded 2-(2-indolyl)-3-amino-quinazolin-4(3*H*)-one (**17**) and was condensation with benzaldehyde to afford corresponding 2-(2-indol-2-yl)-3- benzylideneaminoquinazolin-4(3*H*)-one (**18**, Scheme 5) [18].



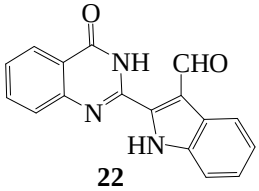
Scheme 5

Alternatively, Lee and co-workers have reported a synthesis of compound 2-(2-indolyl)- quinazolin-4(3*H*)-one (**21**) by the cyclization of (2-aminobenzyl)triphenylphosphonium bromides (**20**) with aromatic aldehydes **19** in methanol containing acetic acid under micro wave irradiation followed by treatment with potassium *t*-butoxide (Scheme 6) [19,20].



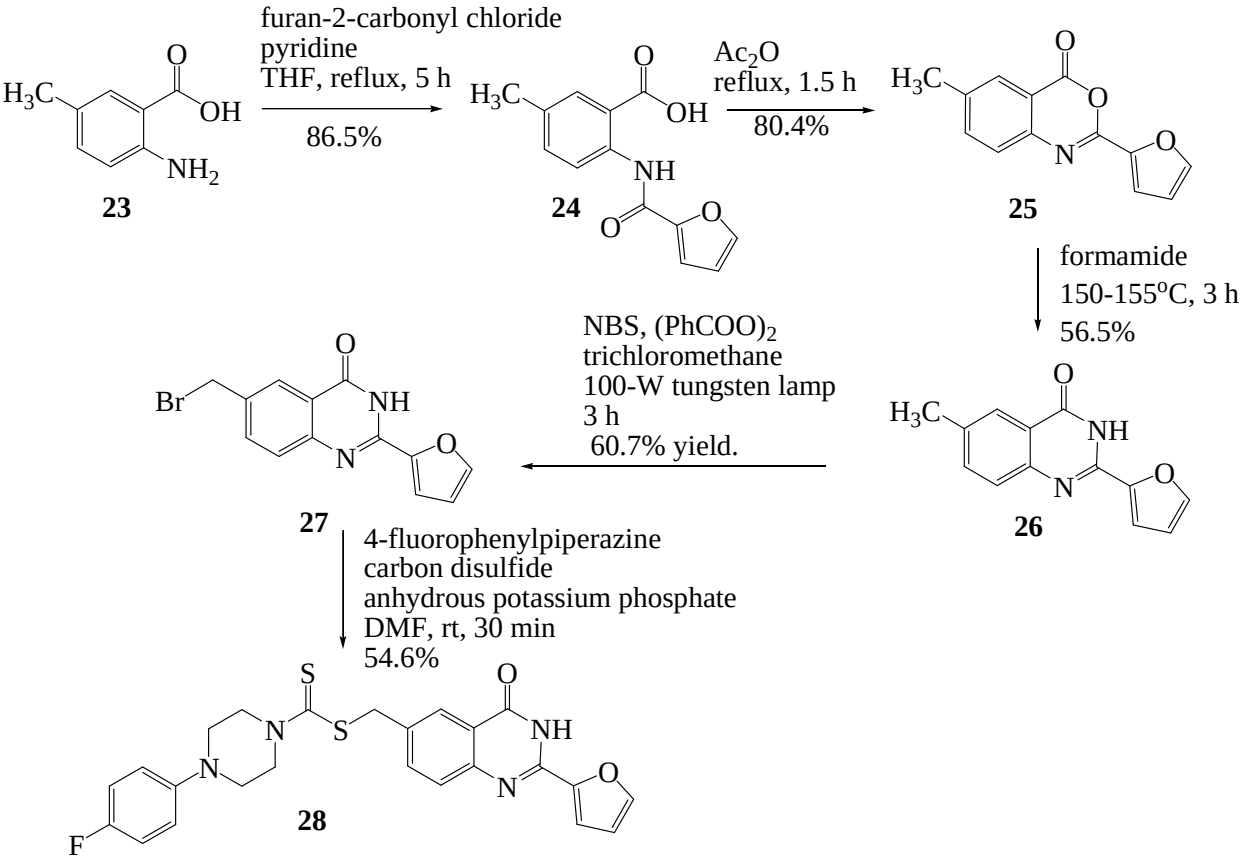
Scheme 6

Wattanapiromsakula and co-workers have been isolated Bouchardatine (**22**) as yellow amorphous powder from the aerial parts of Bouchardatia neurococca [21].



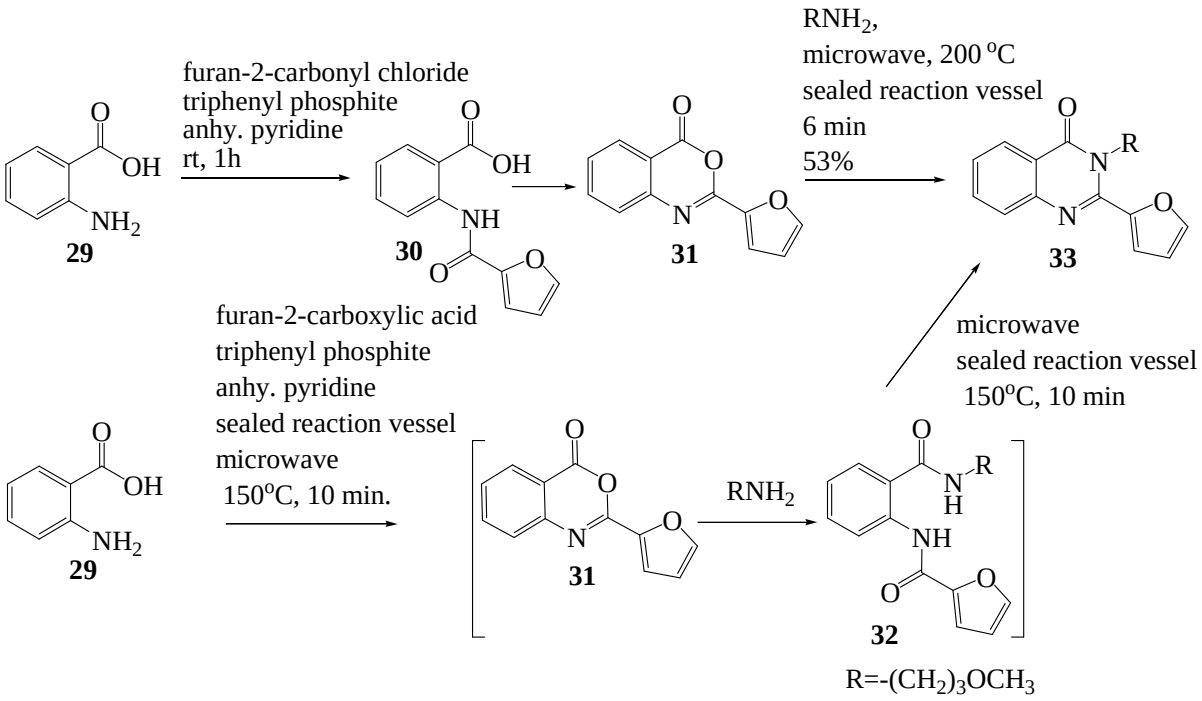
2.5 Furanylquinazolin-4(3*H*)-ones

(2-(Furan-2-yl)-quinazolin-4(3*H*)-one-6-yl)methyl-4-(4-fluorophenyl)piperazine-1-carbodithioate (**28**) was prepared starting from 2-amino-5-methylbenzoic acid (**23**). Reaction of compound **23** with acyl chloride yielded 2-(furan-2-carboxamido)-5-methylbenzoic acid (**24**). Conversion of **24** to 2-(furan-2-yl)-6-methyl-4*H*-benzo [*d*][1,3]oxazin-4-one (**25**) with acetic anhydride, reaction with formamide to 2-(furan-2-yl)-6-methylquinazolin-4(3*H*)-one (**26**), α-halogenation with NBS to compound **27**, and coupling with 4-fluorophenylpiperazine and carbon disulfide in *N*,*N*-dimethylformamide in presence of anhydrous potassium phosphate are the key steps in the synthesis of compound **28**. The prepared compound has been screened for its in-vitro cytotoxicity against A-549 (human cell lung cancer), HCT-8 (human colon cancer), $HepG_2$ (human liver cancer), and K562 (human myelogenous leukaemia) cell lines and results revealed that the replacement of methyl at the C_2 position of quinazolin-4(3*H*)-one with other heteroaryl group led to a decrease in cytotoxic activity (Scheme 7) [3].



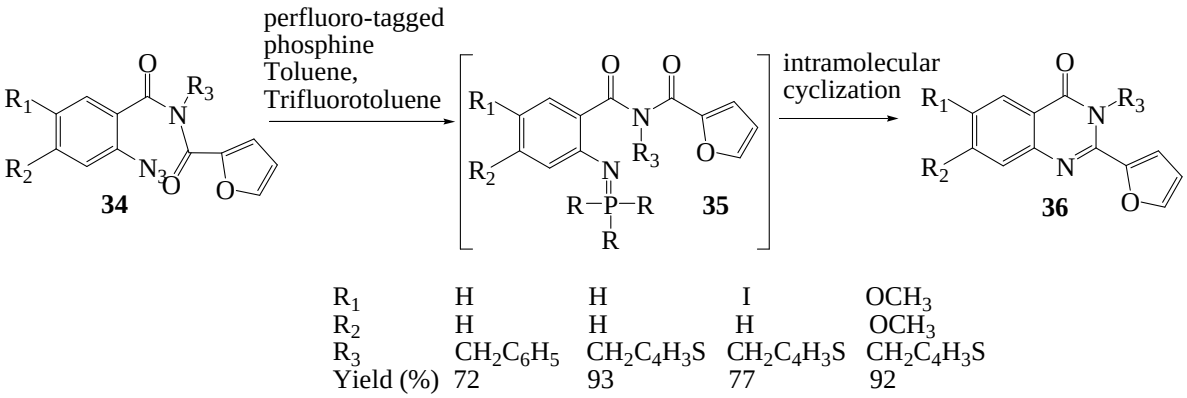
Scheme 7

Ji-Feng and co-workers have developed an efficient microwave promoted, one-pot, two-step synthesis of 2-(furan-2-yl)-quinazolin-4(3*H*)-one **33** from anthranilic acid, carboxylic acid or acyl chloride, and amine (Scheme 8) [22].



Scheme 8

In a Staudinger reaction, the 2-azidobenzamide derivative **34** reacted quantitatively with the perfluoro-tagged phosphine leading to the iminophosphoranes **35** followed by cyclisation by an intramolecular Aza-Wittig reaction to the desired quinazoline derivatives **36**. Though solid-phase bound phosphine derivative used instead of perfluoro-tagged phosphine, the yields in this reaction are not improved much (56-94%, Scheme 9) [23].

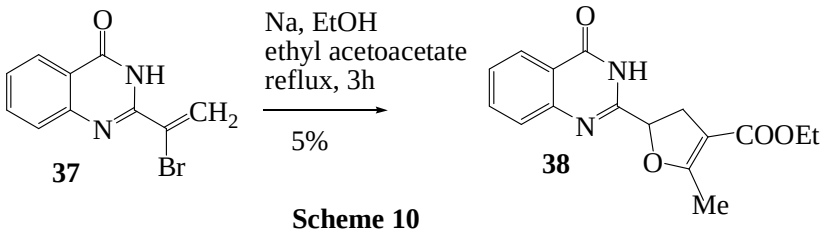


R_1	H	H	I	OCH_3
R_2	H	H	H	OCH_3
R_3	$CH_2C_6H_5$	$CH_2C_4H_3S$	$CH_2C_4H_3S$	$CH_2C_4H_3S$
Yield (%)	72	93	77	92

Scheme 9

2.6 Dihydrofuranylquinazolin-4(3*H*)-one

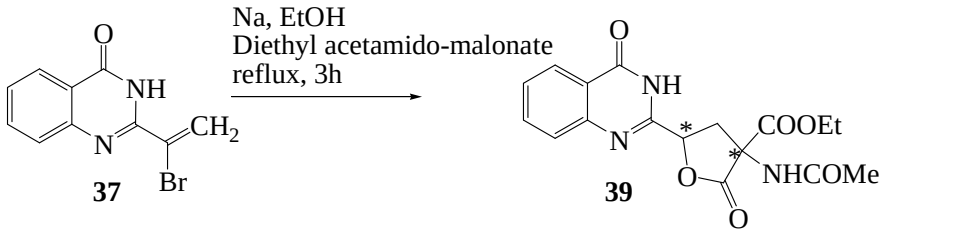
Methyl-5-(quinazolin-4(3*H*)-one-2-yl)-4,5-dihydro-furan-3-carboxylic acid ethyl ester (**38**) was prepared by the reaction of vinylquinazolinone **37** with ethyl acetoacetate in ethanol containing sodium metal (Scheme 10) [24].



Scheme 10

2.7 Tetrahydrofuranylquinazolin-4(3*H*)-ones

Two diastereomers, 3-acetylamino-2-oxo-5-(quinazolin-4(3*H*)-one-2-yl)-tetrahydrofuran-3- carboxylic acid ethyl ester (**39**, first diastereoismer (rf.0.46) in 39% yield and second diastereoisomer (rf.0.31) in 14% yield) were isolated by column chromatography from the residue, which was obtained by the reaction of vinylquinazolinone **37** with diethyl acetamidomalonate in ethanol containing sodium metal (Scheme 11) [24].

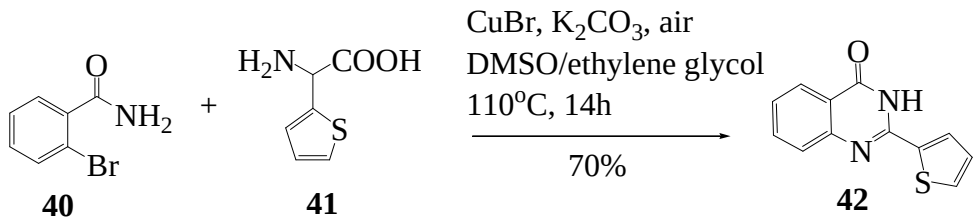


first diastereoismer (rf.0.46) - 39%
second diastereoisomer (rf.0.31) - 14%

Scheme 11

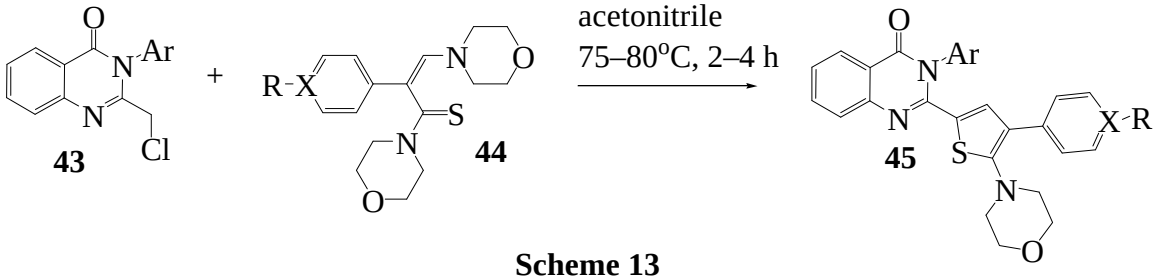
2.8 Thiophenylquinazolin-4(3*H*)-ones

Xu and Fu prepared 2-(2-thiophenyl)-quinazolinone-4(3*H*)-one (**42**) by copper-catalyzed domino method on reaction of 2-bromobenzamide (**40**) with *R*-2-amino-2-(thiophen-2-yl)acetic acid (**41**). The domino process underwent Ullmann-type *N*-arylation, decarboxylation, aerobic oxidation, and intramolecular addition for the construction of heterocycle **42** (Scheme 12) [25].



Scheme 12

Potential anti-inflammatory, anti-cancer and inhibitors of NF-kB and AP-1 mediated transcriptional activation quinazolinone derivatives, 2-(5-morpholin-4-yl-4-(aryl/pyridinyl)- thiophene-2-yl)-3-aryl-quinazolin-4(3*H*)-one **45** were prepared by the reaction of 2-chloromethyl-3-aryl-quinazolin-4(3*H*)-one (**43**) with 1,3-dimorpholin-4-yl-2-substituted- propenethione **44** (Scheme 13, Table 1) [4].



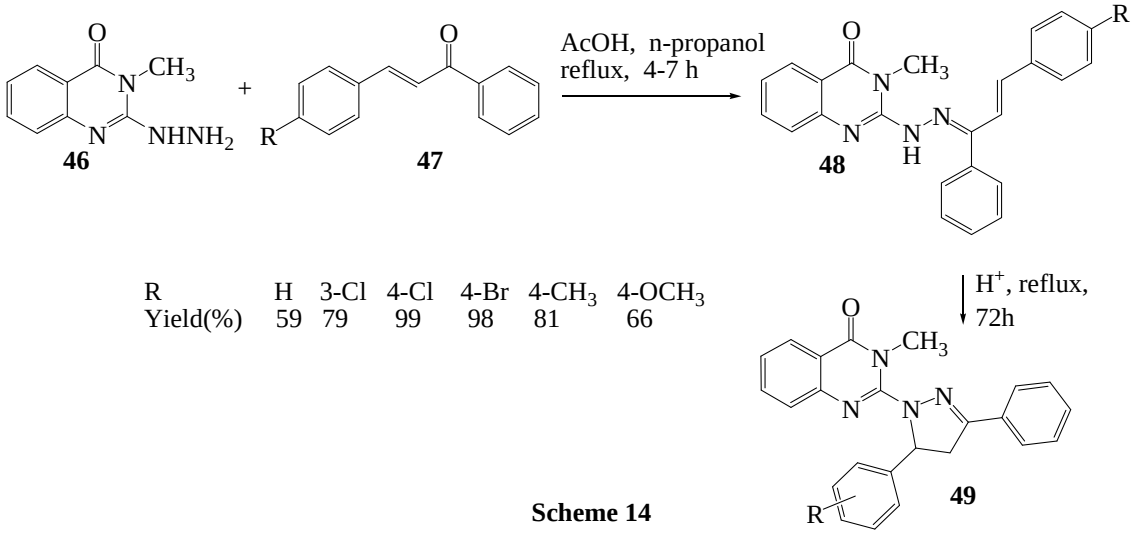
Scheme 13

Table 1. Thiophenylquinazolin-4(3*H*)-ones (45) and their yields

Ar	X	R	Yield (%)	Ar	X	R	Yield (%)
C_6H_5	C	H	58	4-$CH_3C_6H_4$	C	SO_2CH_3	57
C_6H_5	C	Cl	51	4-$CH_3C_6H_4$	C	SCH_3	42
C_6H_5	C	$NHCOCH_3$	57	4-$CH_3C_6H_4$	N	-	39
C_6H_5	C	SO_2CH_3	58.4	2-$CH_3OC_6H_4$	C	H	43
C_6H_5	C	SCH_3	46	2-$CH_3OC_6H_4$	C	SO_2CH_3	55
C_6H_5	N	-	38	2-$CH_3OC_6H_4$	N	-	41
2-$CH_3C_6H_4$	C	H	54	3-$CH_3OC_6H_4$	C	SO_2CH_3	57
2-$CH_3C_6H_4$	C	Cl	53	4-$CH_3OC_6H_4$	C	SO_2CH_3	56
2-$CH_3C_6H_4$	C	SO_2CH_3	56	2-ClC_6H_4	N	-	39
2-$CH_3C_6H_4$	C	SCH_3	56	4-ClC_6H_4	C	H	54
2-$CH_3C_6H_4$	N	-	39	4-ClC_6H_4	C	Cl	55
3-$CH_3C_6H_4$	C	Cl	56	4-ClC_6H_4	C	$NHCOCH_3$	54
3-$CH_3C_6H_4$	C	$NHCOCH_3$	52	4-ClC_6H_4	C	SO_2CH_3	57
3-$CH_3C_6H_4$	C	SO_2CH_3	54.5	4-ClC_6H_4	N	-	39
3-$CH_3C_6H_4$	C	SCH_3	43	4-$CH_3COC_6H_4$	C	H	52
3-$CH_3C_6H_4$	N	-	36	4-$CH_3COC_6H_4$	C	Cl	50
4-$CH_3C_6H_4$	C	H	54	4-$CH_3COC_6H_4$	C	SO_2CH_3	54
4-$CH_3C_6H_4$	C	Cl	51	4-$CH_3COC_6H_4$	N	-	42
4-$CH_3C_6H_4$	C	$NHCOCH_3$	40				

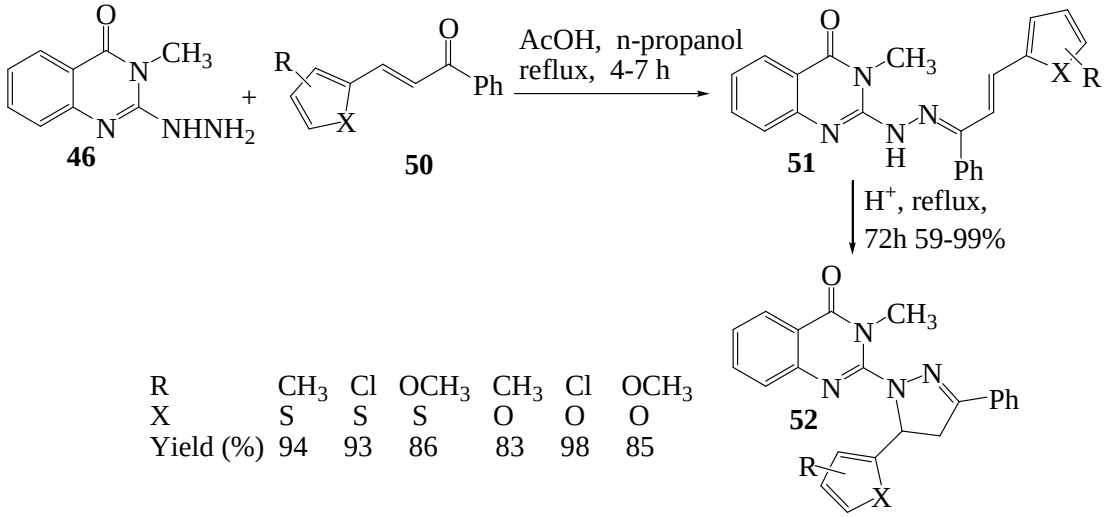
2.9 Dihydropyrazolylquinazolin-4(3*H*)-ones

Acid catalyzed condensation of 2-hydrazino-3-methylquinazolin-4(3*H*)-one (**46**) and α,β-unsaturated ketones **47** yielded 2-(1-phenyl-3-aryl-2-propenylidene)hydrazino-3- methylquinazolin-4(3*H*)-ones **48**. Subsequent cyclisation of compound **48** in glacial acetic acid afforded 2-(5-aryl-3-phenyl-2-pyrazolin-1-yl)-3-methylquinazolin-4(3*H*)-one derivatives **49** and have showed anti-inflammatory and analgesic activity (Scheme 14) [26].



Scheme 14

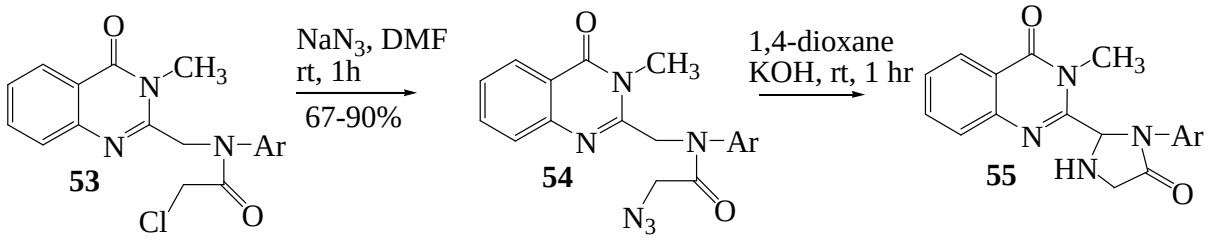
A mixture of 2-hydrazino-3-methylquinazolin-4(3*H*)-one (**46**) and chalcones **50** was refluxed under acidic conditions for the formation of hydrazones **51** and subsequent addition of N–H on the olefinic bond of the propenone moiety that form the ring-closed final products- 2-(3-substituted phenyl-5-heteroaryl-2-pyrazoline-1-yl)-3-methylquinazolin-4(3*H*)-one derivatives **52**. Most of the synthesized compounds showed high activity against both the MAO-A and the MAO-B isoforms. However, only 2-[10-(4-chlorophenyl)-3-thienyl-2- propenylidene]hydrazine-3-methyl)-quinazolin-4(3*H*)-one have showed antidepressant activity (Scheme 15) [27].



Scheme 15

2.10 Imidazolidinonylquinazolin-4(3*H*)-ones

The 2-*N*-azidoacetylarylaminomethyl-3-methylquinazolin-4(3*H*)-one **54**, which was prepared by stirring a mixture of 2-*N*-chloroacetyl-(4-aryl)aminomethyl-3-methylquinazolin- 4(3*H*)-one **53** and sodium azide in DMF, was easily underwent cyclisation in basic medium to afford 2-imidazolidinonylquinazolin-4(3*H*)-one **55** (Scheme 16) [28].

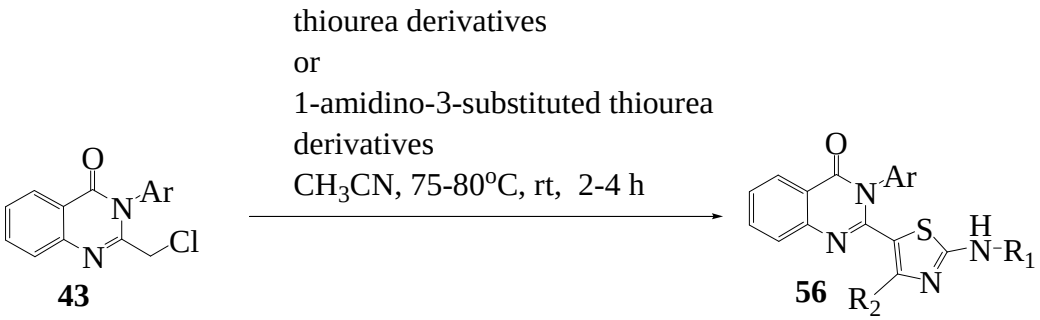


Ar	C_6H_5	4-$CH_3C_6H_4$	4-$C_2H_5C_6H_4$	4-ClC_6H_4
Yield(%)	92	94	72	97

Scheme 16

2.11Thiazolylquinazolin-4(3*H*)-ones

Rajan and co-workers synthesized 2-(2-alkylamino/arylamino-4-alkyl/phenyl/amino-thiazole-5-yl)-3-aryl-quinazolin-4(3*H*)-one derivatives **56** by condensing 2-chloromethyl-3- aryl-quinazolin-4(3*H*)-one **43** with thiourea derivatives or 1-amidino-3-substituted thiourea derivatives in acetonitrile. The quinazolinone derivatives **56** are identified as inhibitors of NF-kB and AP-1 mediated transcription activation and as potential anti-inflammatory agents (Scheme 17, Table 2) [5,6].



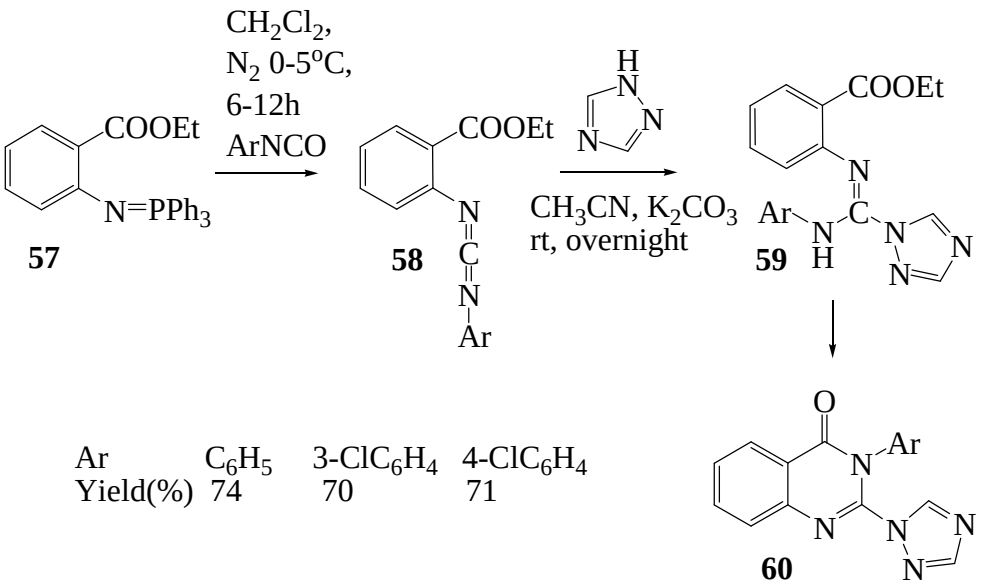
Scheme 17

Table 2, Thiazolylquinazolin-4(3*H*)-ones (56) and their yields

Ar	R_1	R_2	Yield (%)
C_6H_5	C_6H_5	CH_3	72.36
C_6H_5	4-ClC_6H_4	CH_3	39
2-$CH_3C_6H_4$	CH_3	CH_3	30
2-$CH_3C_6H_4$	C_6H_5	CH_3	49
2-$CH_3C_6H_4$	4-ClC_6H_4	CH_3	54
3-$CH_3C_6H_4$	CH_3	CH_3	30
3-$CH_3C_6H_4$	4-ClC_6H_4	CH_3	51
4-$CH_3C_6H_4$	4-ClC_6H_4	CH_3	55
2-$CH_3OC_6H_4$	4-ClC_6H_4	CH_3	41
4-$CH_3OC_6H_4$	4-ClC_6H_4	CH_3	38
2-ClC_6H_4	C_6H_5	CH_3	44
2-ClC_6H_4	4-ClC_6H_4	CH_3	41
2-ClC_6H_4	CH_3	CH_3	41
4-ClC_6H_4	C_6H_5	CH_3	51
4-ClC_6H_4	4-ClC_6H_4	CH_3	35
4-$CH_3COC_6H_4$	CH_3	CH_3	30
4-$CH_3COC_6H_4$	C_6H_5	CH_3	48
4-$CH_3COC_6H_4$	4-ClC_6H_4	CH_3	43
4-ClC_6H_4	4-ClC_6H_4	NH_2	34
4-$CH_3COC_6H_4$	4-ClC_6H_4	NH_2	32
C_6H_5	4-ClC_6H_4	C_6H_5	71
2-$CH_3C_6H_4$	4-ClC_6H_4	C_6H_5	57
2-ClC_6H_4	4-ClC_6H_4	C_6H_5	51
4-ClC_6H_4	4-$CH_3C_6H_4$	C_6H_5	27
4-$CH_3COC_6H_4$	CH_3	C_6H_5	44
4-$CH_3COC_6H_4$	4-ClC_6H_4	C_6H_5	44
C_6H_5	$COOC_2H_5$	C_6H_5	79
C_6H_5	CH_3	C_6H_5	48
C_6H_5	C_6H_5	C_6H_5	78
C_6H_5	CO C_6H_5	C_6H_5	75
C_6H_5	4-ClC_6H_4	C_6H_5	71
4-$CH_3OC_6H_4$	$COOC_2H_5$	C_6H_5	46
4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	49
4-$CH_3OC_6H_4$	CO C_6H_5	C_6H_5	57
4-$CH_3OC_6H_4$	4-Cl C_6H_4	C_6H_5	52
4-ClC_6H4	$COOC_2H5$	CH_3	46
4-ClC_6H_4	CH_3	CH_3	41
4-ClC_6H4	C_6H_5	CH_3	51
4-ClC_6H_4	4-ClC_6H_4	CH_3	-
4-ClC_6H_4	$COOC_2H_5$	C_6H_5	50
4-ClC_6H_4	CH_3	C_6H_5	45
4-ClC_6H_4	C_6H_5	C_6H_5	53
4-ClC_6H_4	COC_6H_5	C_6H_5	53
4-ClC_6H_4	4-ClC_6H_4	C_6H_5	39

2.12Triazolylquinazolin-4(3*H*)-ones

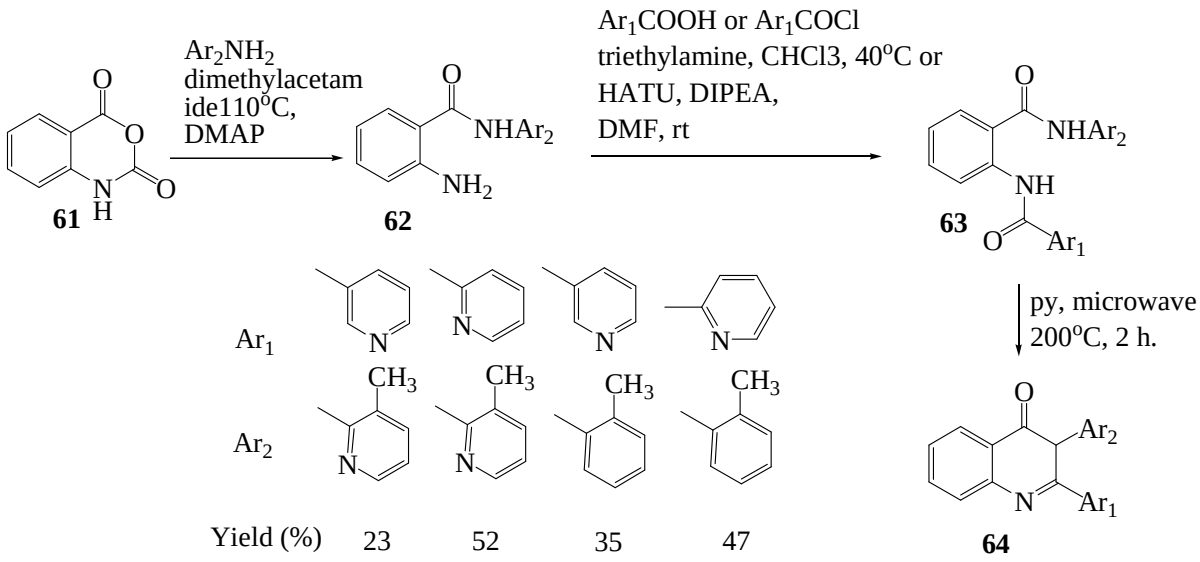
Iminophosphorane **57** was reacted with aromatic isocyanate to give functionalized carbodiimide **58**. The reaction of 1,2,4-triazole with carbodiimide **58** under solid K_2CO_3 provide a convenient and regiospecific route to 3-aryl-2-(triazol-1-yl)-quinazolin-4(3*H*)-one **60** (Scheme 18) [29].



Scheme 18

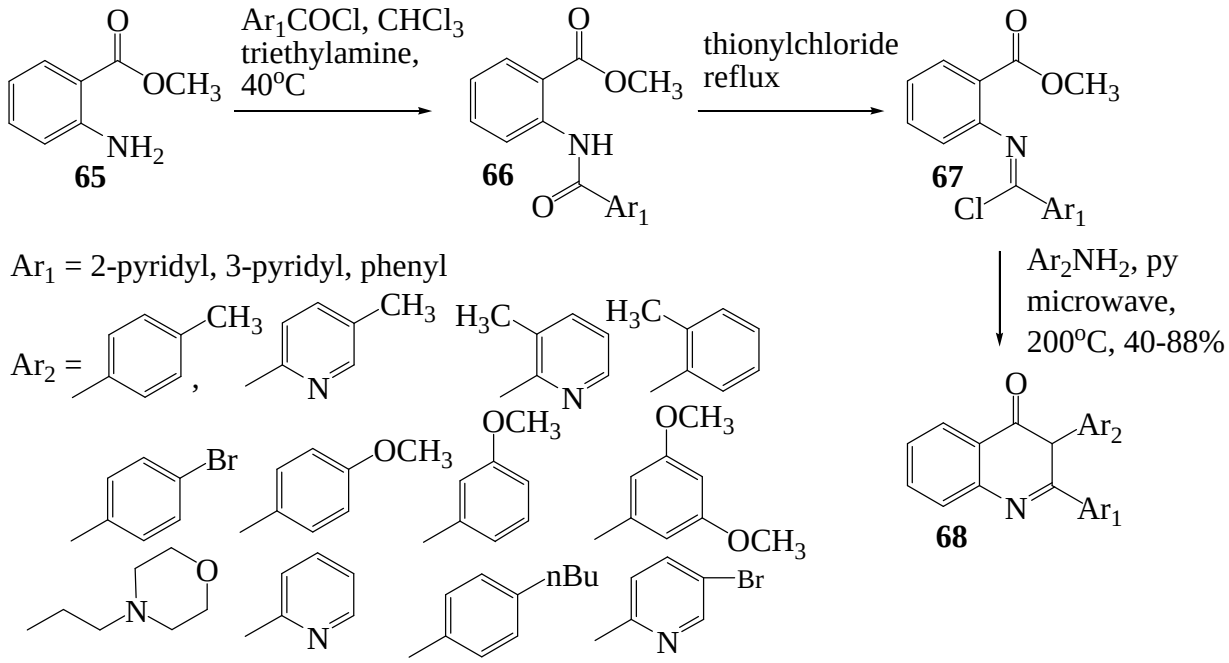
2.13Pyridylquinazolin-4(3*H*)-ones

A series of diamides **63** was prepared by condensation of the appropriate amine with isatoic anhydride (**61**) followed by coupling of the resulting amine **62** with an acyl chloride or carboxylic acid. The diamides **63** were converted to the corresponding 2,3-diarylquinazolin-4(3*H*)-ones **64** by microwave heating in pyridine at 200°C. The yields were low to moderate (Scheme 19) [30].



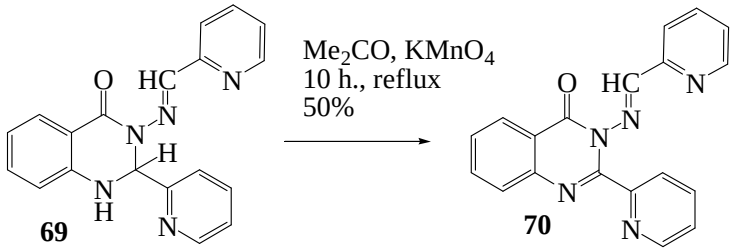
Scheme 19

However, a practical and efficient three step synthetic route has been developed by microwave-assisted condensation of an imidoyl chloride **67** with an aryl amine to isolate 2,3-diarylquinazolin-4(3*H*)-ones **68** in quantitative yield. The imidoyl chloride **67** was synthesised by acylation of methyl anthranilate **65** with acyl chloride and subsequently treated the amide derivative **66** with thionyl chloride to afford imidoyl chloride **67** (Scheme 20) [30].



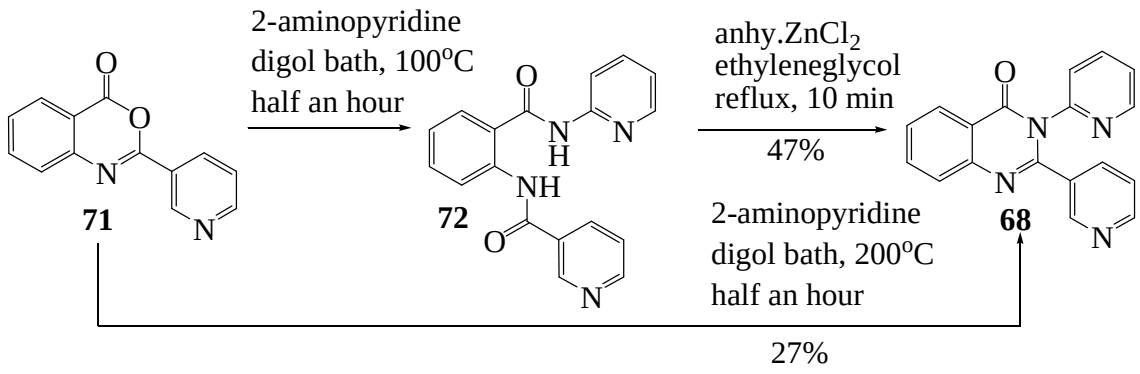
Scheme 20

Kalagouda and co-workers have oxidized 2-pyridin-2-yl-3-(pyridine-2-carboxylideneamino)-1,2-dihydroquinazolin-4(3*H*)-one **69** with $KMnO_4$ in hot acetone to isolate 2-pyridine-2-yl-3-(pyridine-2-carboxylideneamino)-quinazolin-4(3*H*)-one (**70**, Scheme 21) [31].



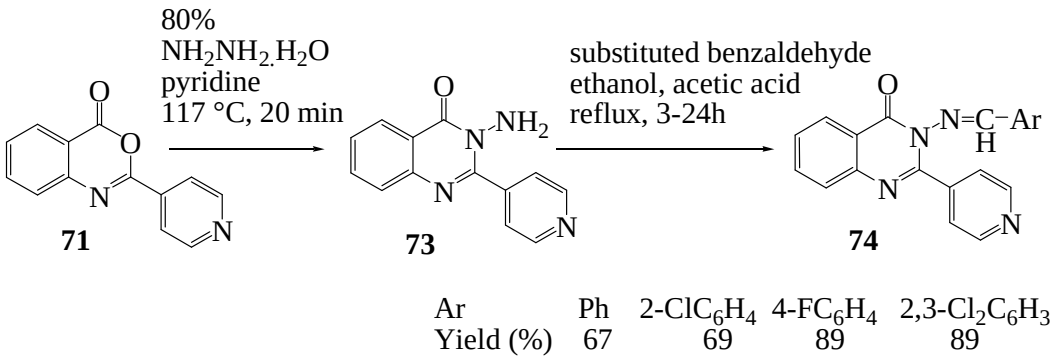
Scheme 21

Heating the mixture of 2-(pyridin-3-yl)-3,1-benzoxazin-4(3*H*)-one (**71**) and 2-aminopyridine yielded diamide **72** under milder conditions, while at higher temperatures the cyclized product quinazolin-4(3*H*)-one **68** was isolated. However, diamide **72** converted into the final quinazolinones **68** by using a catalytic amount of anhydrous zinc chloride (Scheme 22) [32].



Scheme 22

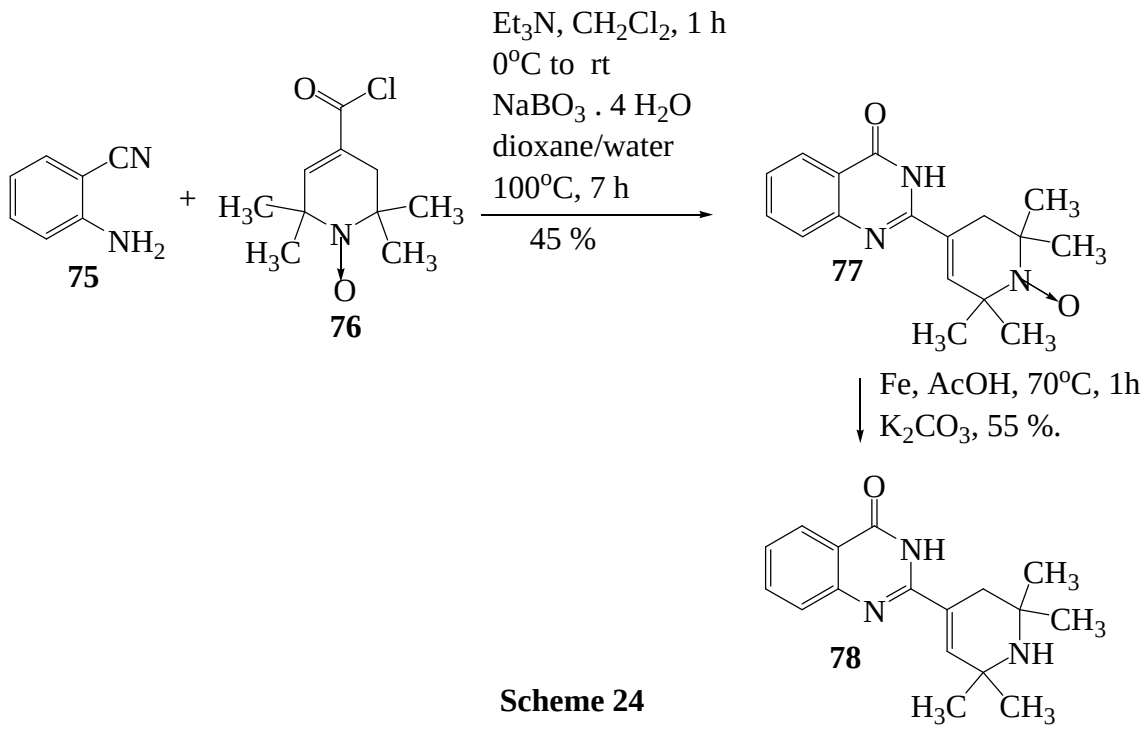
Xingwen and co-workers was reacted 2-(4-pyridinyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (**71**) with 80% $NH_2NH_2.H_2O$ and the resultant 3-amino-2-arylquinazolin-4(3*H*)-one (**73**) was condensed with appropriate substituted benzaldehyde in ethanol to isolate 2-(4-pyridinyl)- 3-(arylamino)-quinazolin-4(3*H*)-one (**74**). These compounds exhibited weak antifungal and antiviral activities (Scheme 23) [33].



Scheme 23

2.14Tetrahydropyridinylquinazolin-4(3*H*)-one

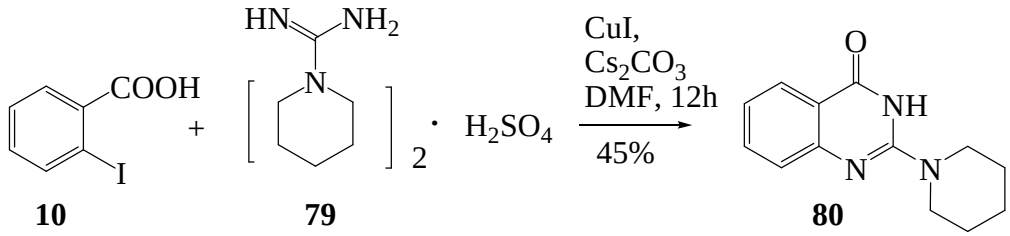
Reaction of 2-amino-benzonitrile (**75**) with 1-oxyl-1,2,3,6-tetrahydro-2,2,6,6-tetramethyl pyridine-4-carbonyl chloride (**76)** followed by treatment with $NaBO_3$. $4H_2O$ yielded the 2-(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine-4-yl)-quinazolin-4(3*H*)-one radical (**77**). The resultant nitroxide **77** was reduced with Fe powder in acetic acid to isolate 2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine-4-yl)-quinazolin-4(3*H*)-one (**78**, Scheme 24) [15].



Scheme 24

2.15Piperidinylquinazolin-4(3*H*)-ones

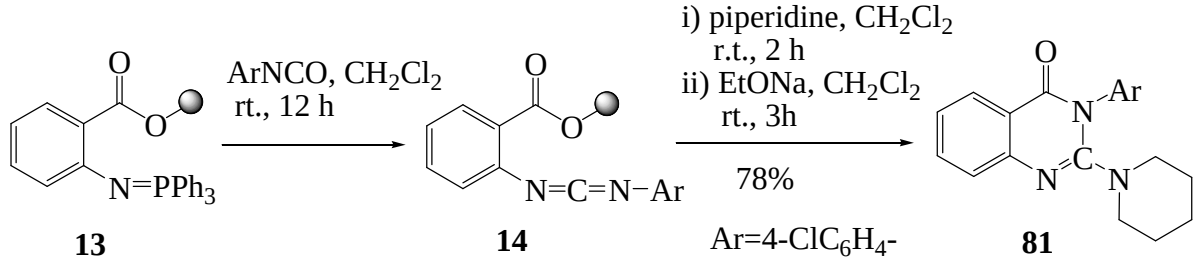
2-Iodobenzoic acid (**10**) was reacted with piperidine-1-carboxamidine salt (**79**) in *N*,*N*-dimethylformamide in presence of CuI and Cs_2CO_3 to isolate 2-(piperidin-1-yl)-quinazolin-4(3*H*)-one (**80**). The yield of the reaction increased to 70% at reaction temperature of 80°C (Scheme 25) [16].



10 **79** **80**

Scheme 25

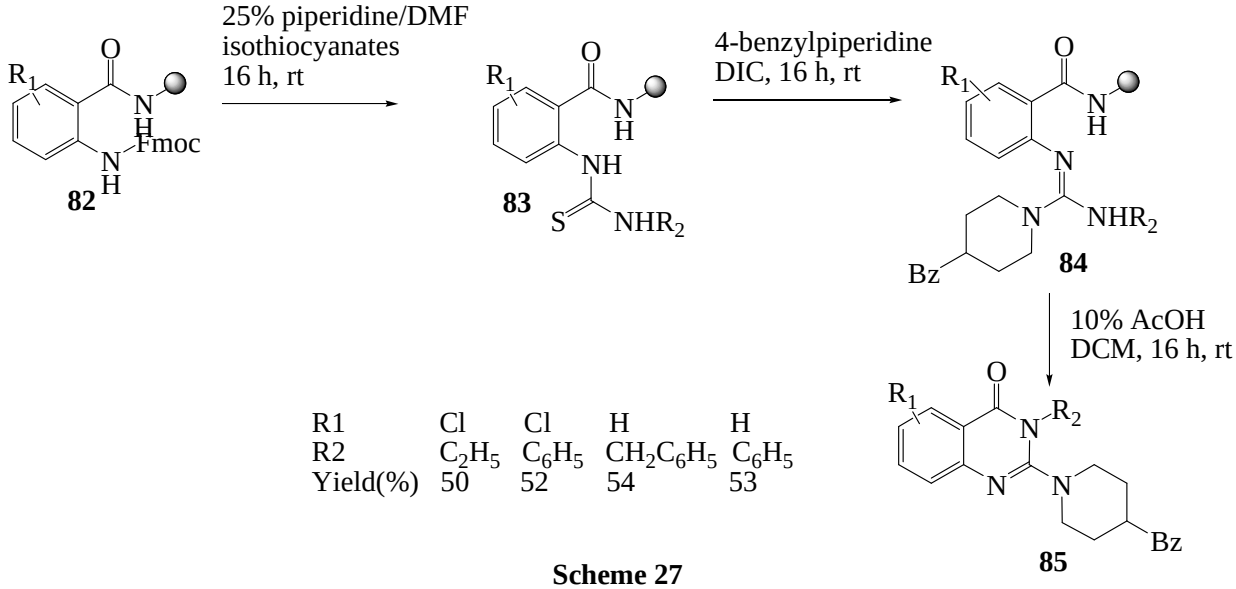
Xie and co-workers prepared 2-(piperidin-1-yl)-3-aryl-quinazolin-4(3*H*)-one (**81**) from poly(ethyleneglycol) (PEG) supported aza-Wittig reaction. Quinazolinones **81** were synthesized efficiently by reaction of secondary amine with PEG-supported carbodiimides **14**, which were obtained from aza-Wittig reaction of PEG-supported iminophosphoranes **13** with isocyanates (Scheme 26) [17].



13 **14** **81**

Scheme 26

A versatile method for the solid-phase synthesis of differentially substituted quinazolin-4(3*H*)-ones **85** has been developed using immobilized arylguanidines. The latter were obtained by treating the amino group of polymer-linked anthranilamide **82** with isothiocyanates followed by coupling the resultant amide **83** with secondary amines in the presence of DIC to generate compound **84**. Finally a cyclative cleavage strategy was applied to give the desired compounds **85** in high yields and purities (Scheme 27) [34].



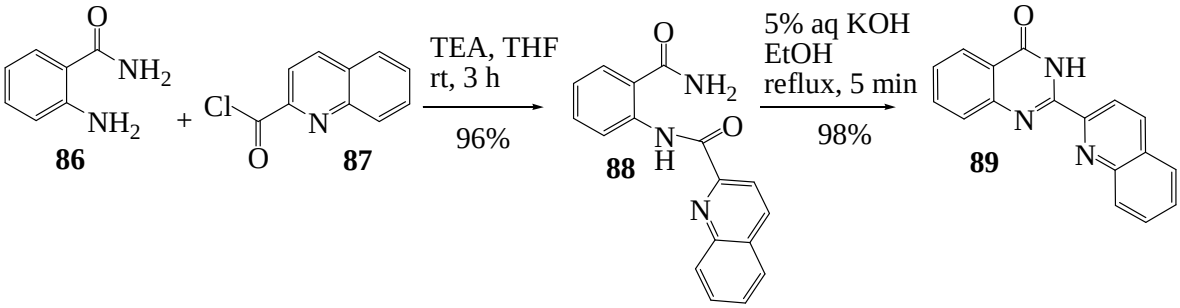
R1	Cl	Cl	H	H
R2	C_2H_5	C_6H_5	$CH_2C_6H_5$	C_6H_5
Yield(%)	50	52	54	53

82 **83** **84** **85**

Scheme 27

2.16Quinolinylquinazolin-4(3*H*)-one

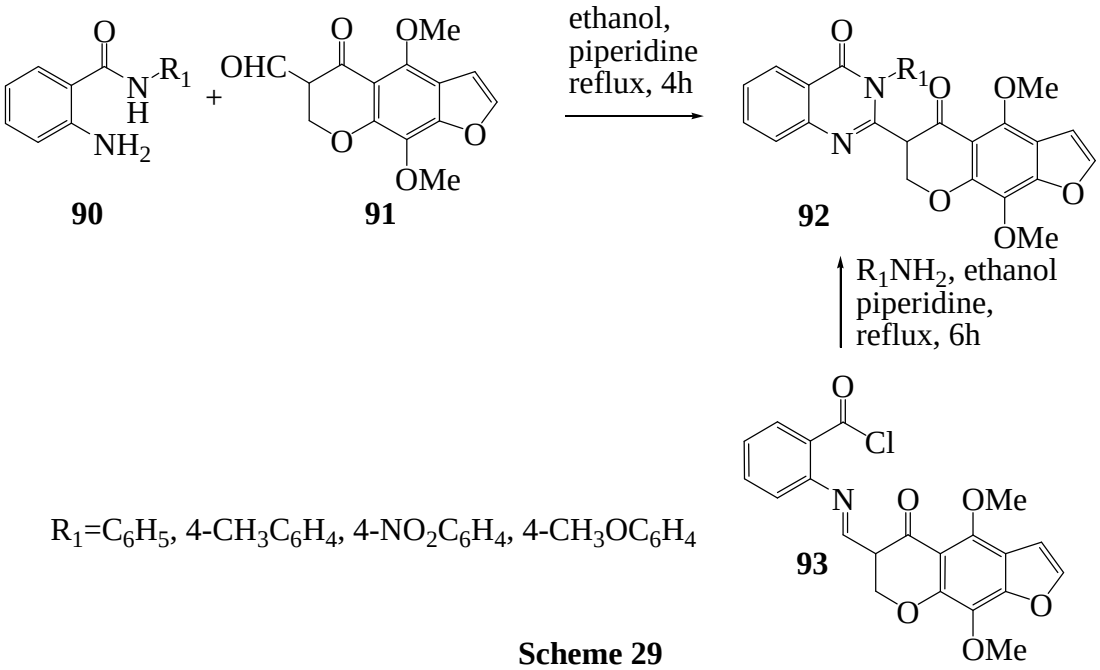
Anthranilamide (**86**) and 2-quinolinecarbonyl chloride (**87**) were reacted in presence of triethylamine to obtain 2-(2-aminocarbonylquinolinyl)benzamide (**88**) followed by cyclisation under basic conditions yielded 2-(2-quinolinyl)-quinazolin-4(3*H*)-one (**89**, Scheme 28) [35].



Scheme 28

2.17Furo[3,2-*g*]Chrominylquinazolin-4(3*H*)-ones

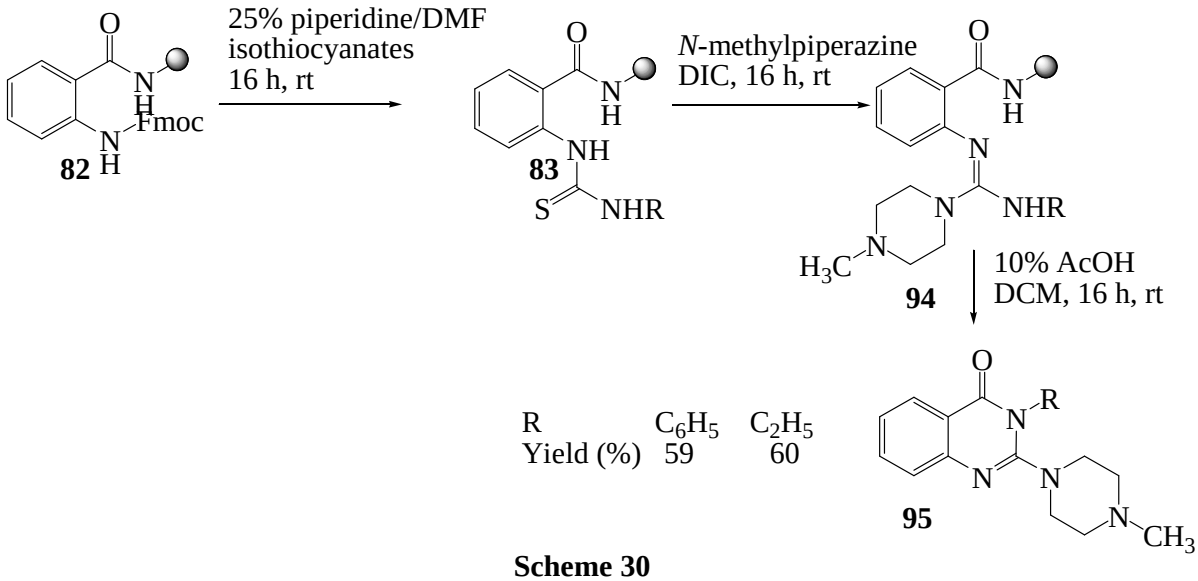
A mixture of equimolar amounts of 2-amino-*N*-substitutedbenzamide **90** and 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-4-aldehyde (**91**) in ethanol were refluxed in the presence piperidine as catalytic amount to isolate 2-(6,7-dihydro-4,9-dimethoxy-5-oxo- 5*H*-furo[3,2-*g*]chromen-6-yl)-quinazolin-4(3*H*)-one (**92**). Alternatively, a mixture of acid chloride derivative **93** and appropriate primary amine in ethanol was refluxed in the presence of piperidine as catalytic amount. These compounds have showed high activity against Gram positive, Gram negative and fungi as well (Scheme 29) [36].



Scheme 29

2.18Piperazinylquinazolin-4(3*H*)-ones

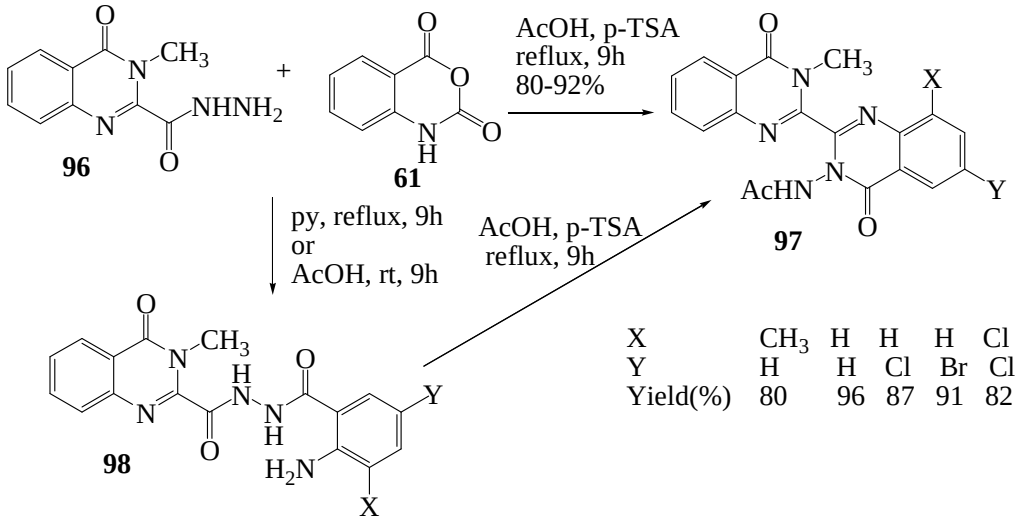
A versatile method for the solid-phase synthesis of differentially substituted quinazolin-4(3*H*)-ones **95** has been developed using immobilized arylguanidines. The latter were obtained by treating the amino group of polymer-linked anthranilamide **82** with isothiocyanates followed by coupling the resultant amide **83** with secondary amines in the presence of DIC to generate compound **94**. Finally a cyclative cleavage strategy was applied to give the desired 2-(4-methylpiperazin-1-yl)-quinazolin-4(3*H*)-ones **95** in high yields and purities (Scheme 30) [34].



Scheme 30

2.192,2'-Bisquinazolin-4(3*H*)-ones

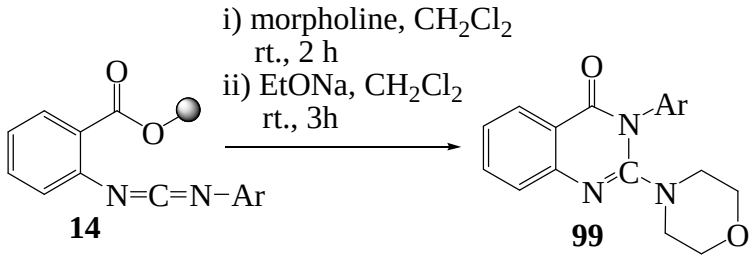
Refluxing a mixture of 2-hydrazinocarbonyl-3-methylquinazolin-4(3*H*)-one (**96**) and isatoic anhydride (**61**) in acetic acid yielded 3'-acetamido-3-methyl-2,2'-bisquinazolin-4(3*H*)-one derivative **97**. The same compound obtained by reacting same compounds in pyridine or acetic acid at room temperature followed by cyclising the resulting 2-[(2-aminobenzoyl)hydrazinocarbonyl]-3-methylquinazolin-4(3*H*)-one **98** in acetic acid at reflux [37]. 3'-Acetamido-6'-bromo-3-methyl-2,2'-bisquinazolin-4(3*H*)-one has exhibited 70.25% antifungal activity against Macrophomina sorgina at 25µg/disc (Scheme 31) [2].



Scheme 31

2.20Morpholinylquinazolin-4(3*H*)-ones

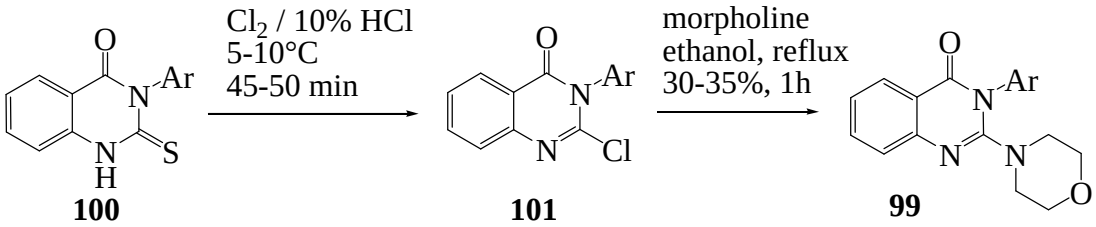
Xie and co-workers prepared 3-aryl-2-(*N*-morpholinyl)-quinazolin-4(3*H*)-one (**99**) from poly(ethylene glycol) (PEG) supported aza-Wittig reaction. Quinazolinone **99** were synthesized efficiently by reaction of morpholine with PEG-supported carbodiimides **14** (Scheme 32) [17].



Ar	4-ClC_6H_4	4-FC_6H_4
Yield(%)	83	72

Scheme 32

Gaseous chlorine was reacted with 3-aryl-2-thioxoquinazolin-4-ones **100** in 10% HCl and the resultant chloro compound **101** was treated with morpholine in ethanol at reflux to afford quinazolin-4(3*H*)-one **99** (Scheme 33) [38].

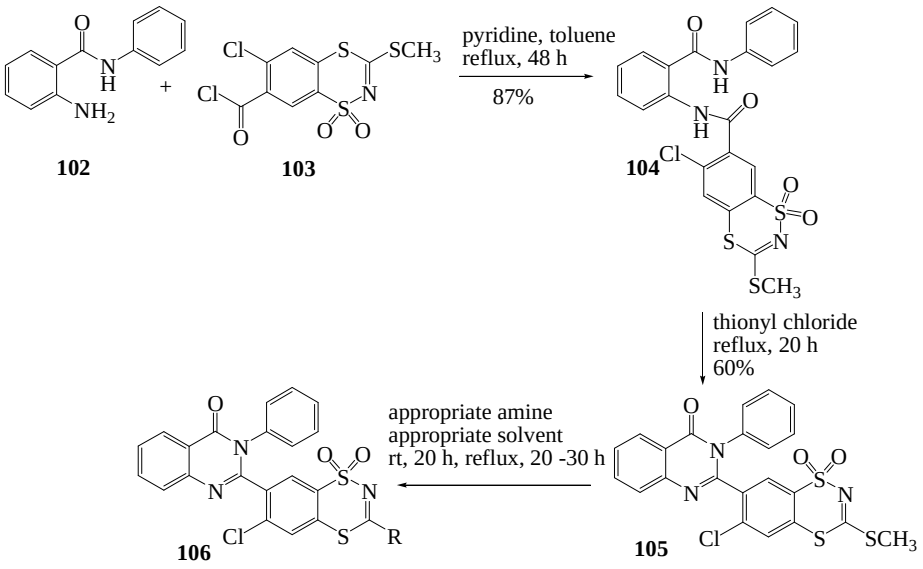


Ar	4-MeC_6H_4	4-ClC_6H_4
Yield (%)	30	35

Scheme 33

2.21Benzodithiazinylquinazolin-4(3*H*)-ones

Pomarnacka and co-workers prepared potent antiproliferative and anti-cancer agents-2-[6-chloro-3-(substitutedamino)-1,1-dioxo-1,4,2-benzodithiazin-7-yl]-3-phenylquinazolin- 4(3*H*)-ones **106**. 2-Aminobenzanilide (**102**) and 6-chloro-3-methylthio-1,1-dioxo-1,4,2- benzodithiazin-7-carbonyl chloride (**103**) were refluxed in anhy. toluene containing pyridine to isolate *N*-[2-(phenylcarbamoyl)-phenyl]-6-chloro-1,1-dioxo-3-methylthio-1,4,2-benzo- dithiazin-7-carboxamide (**104**) and then treated with thionyl chloride to isolate 2-(6-chloro-1,1-dioxo-3-methylthio-1,4,2-benzodithiazin-7-yl)-3-phenylquinazolin-4(3*H*)-one (**105**). The resultant compound **105** was treated with the appropriate amine in the appropriate solvent to isolate compound **106**. The bioassay indicated that the few derivatives possess cancer-cell growth-inhibitory properties (Scheme 34) [39].



102 **103** **104** **105** **106**

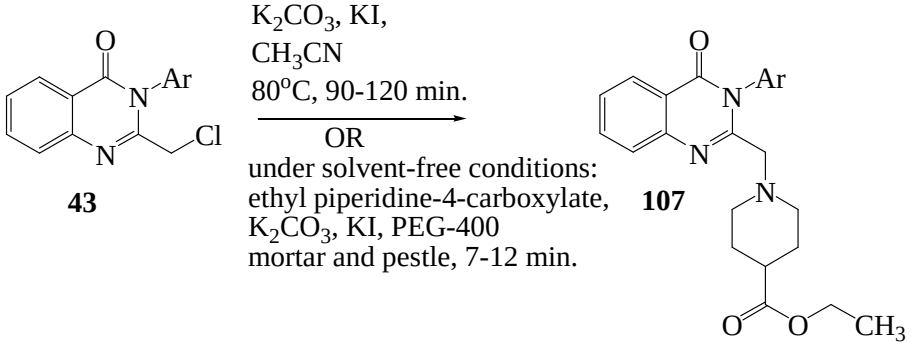
Scheme 34

Table 3. Benzodithiazinylquinazolin-4(3*H*)-ones (106) and their yields

Appropriate amine (RH)	Appropriate solvent	Yield (%)	Appropriate amine (RH)	Appropriate solvent	Yield (%)
piperidine	benzene	58	propargylamine	benzene	63
morpholine	benzene	55	benzylamine	methanol	67
pyrrolidine	benzene	48	phenethylamine	methanol	63
1-phenyl piperazine	benzene	40	tolylamine	benzene	27
2-aminopropane	methanol	59	3-(aminomethyl) pyridine	methanol	37
3-amino-1-propanol	methanol	57	2-(2-aminoethyl) pyridine	methanol	52
allylamine	benzene	68			

2.22 Piperidinylmethylquinazolin-4(3*H*)-ones

A mixture of 2-(chloromethyl)-3-arylquinazolin-4(3*H*)-one **43** and ethyl piperidine- 4-carboxylate were heated to isolate 1-[3-aryl-quinazolin-4(3*H*)-one-2-yl-methyl] piperidine-4-carboxylic acid ethyl ester (**107**). The yield of the reaction have been increased by carried out under solvent-free conditions in the presence of PEG-400 by simple physical grinding in a mortar and pestle (Scheme 35) [40].



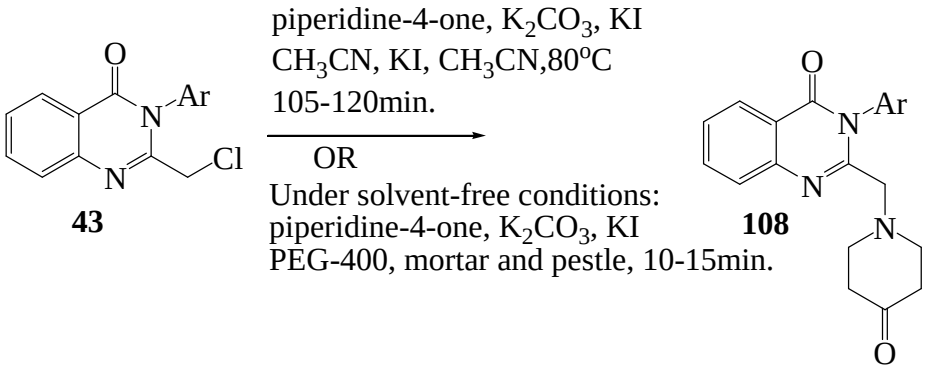
43 **107**

Ar		3-$CH_3OC_6H_4$	C_6H_5	2-$CH_3C_6H_4$	2-$CF_3C_6H_4$
Yield (%)	Solution phase	80	78	84	78
	Solvent-free	90	92	91	89

Scheme 35

A mixture of 2-(chloromethyl)-3-arylquinazolin-4(3*H*)-one **43** and piperidine-4-one were heated to isolate 3-aryl-2-(4-oxo-piperidin-1-ylmethyl)-quinazolin-4(3*H*)-one **108**. The yield of the reaction have been increased by

carried out under solvent-free conditions in the presence of PEG-400 by simple physical grinding in a mortar and pestle (Scheme 36) [40].

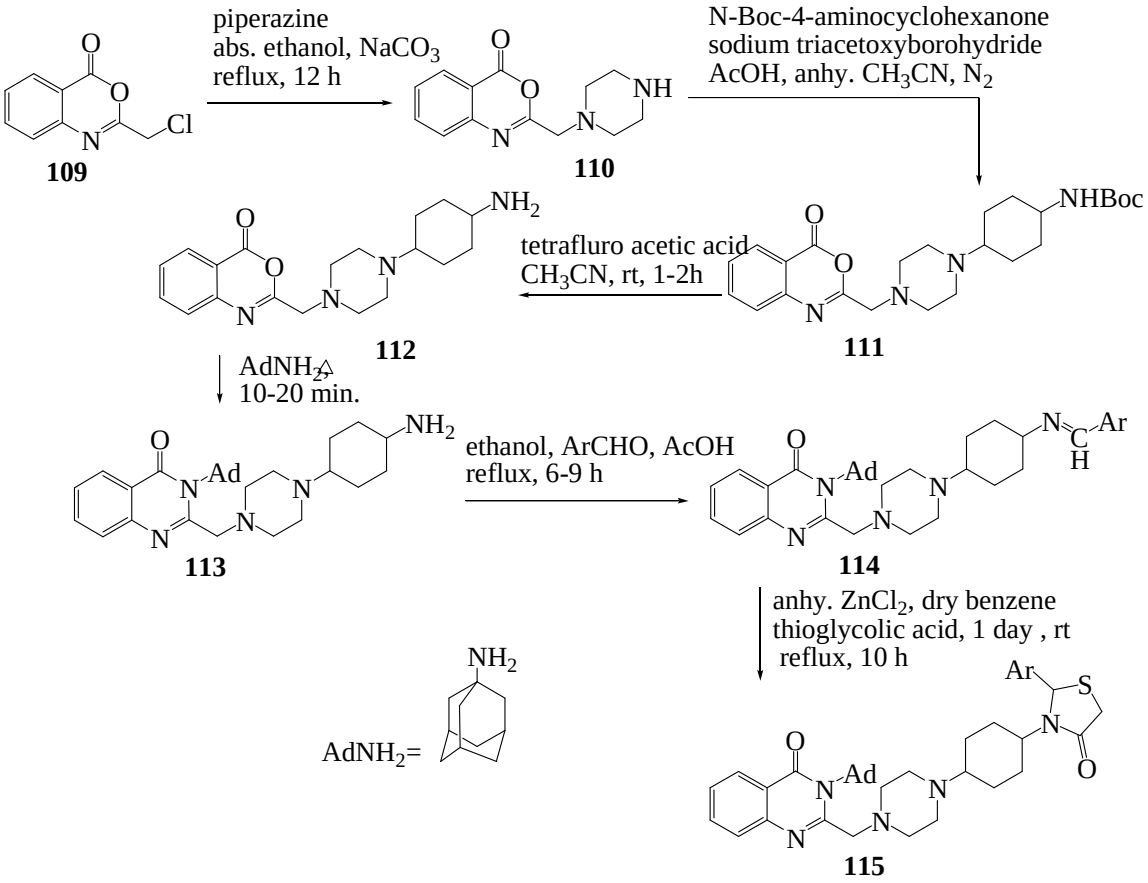


Ar		3-$CH_3OC_6H_4$	C_6H_5	2-$CH_3C_6H_4$	2-$CF_3C_6H_4$
Yield (%)	Solution phase	84	80	80	75
	Solvent-free	92	94	90	88

Scheme 36

2.23Piperazinylmethylquinazolin-4(3*H*)-ones

2-Chloromethylbenzo[*d*][1,3]oxazin-4-one (**109**) was condensed with piperazine to isolate 2-(piperazinyl)methylbenzo[*d*][1,3]oxazin-4-one (**110**) . Then compound **110** treated with *N*-Boc-4-aminocyclohexanone to give 2-[4-{(tert-butylcarbamte)cyclohexyl}piperazinyl] methylbenzo-[*d*][1,3]oxazin-4-one (**111**), deprotection of amine function to isolate 2-[4-(cyclohexylamine)piperazinyl] methylbenzo[*d*][1,3]oxazin-4-one (**112**), condensation with amantadine to 3-(admantan-1-yl)-2-[{4-(4-aminocyclohexyl)piperazin-1-yl}methyl]- quinazolin-4(3*H*)-one (**113**), reaction with substituted benzaldehydes in the presence of few drops of glacial acid to isolate 3-[(admantan-1-yl)-2-{4-(4-arylidenamino)cyclohexyl)- piperazin-1-yl}methyl]-quinazolin-4(3*H*)-one **114** and finally cyclisation with thioglycolic acid to afford 3-[(admantan-1-yl)-2-[4-{4-(2-phenyl-4-oxo-1,3-thiazolidinyl)cyclohexyl} piperazin-1-yl]methyl]-quinazolin-4(3*H*)-one **115**. These compounds exhibited moderate to good COX-1 and COX-2 inhibitory activity, antibacterial, antifungal, anti-inflammatory, analgesic and ulcerogenic activities (Scheme 37) [41].

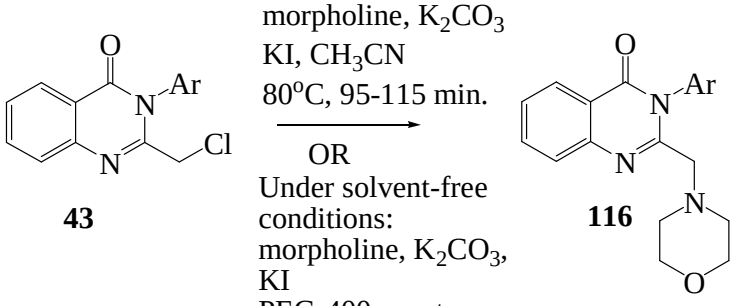


Ar	C_6H_5	2-ClC_6H_4	3-ClC_6H_4	4-ClC_6H_4	2-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	2-HOC_6H_4
Yield (%)	56	43	40	44	50	48	55	45

Scheme 37

2.24Morpholinomethylquinazolin-4(3*H*)-ones

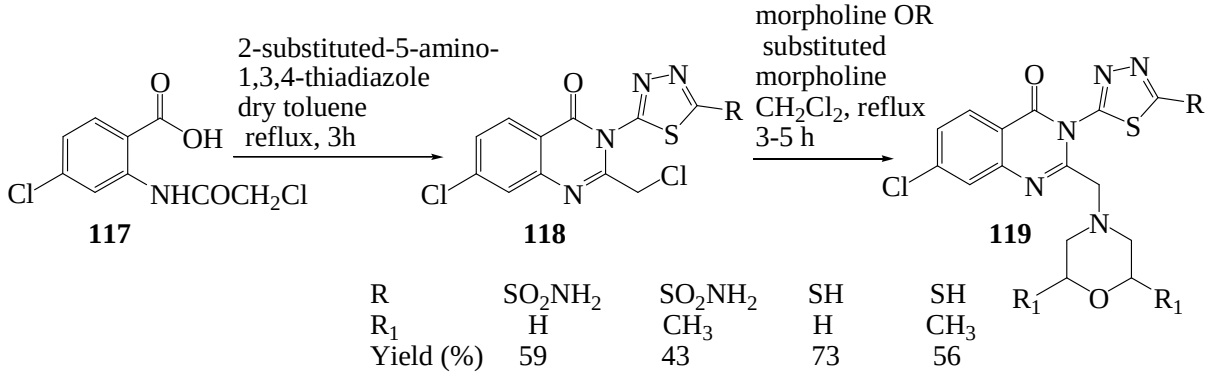
The compound **43** was reacted with morpholine in basic medium to isolate 3-aryl-2-morpholin-4-yl-methylquinazolin-4(3*H*)-one (**116**). The same reaction has been carried out under solvent-free conditions in the presence of PEG-400 by simple physical grinding in a mortar and pestle with improved yield (Scheme 38) [40].



Ar		3-$CH_3OC_6H_4$	C_6H_5	2-$CH_3C_6H_4$	2-$CF_3C_6H_4$
Yield (%)	Solution phase	86	80	82	76
	Solvent-free	95	94	92	90

Scheme 38

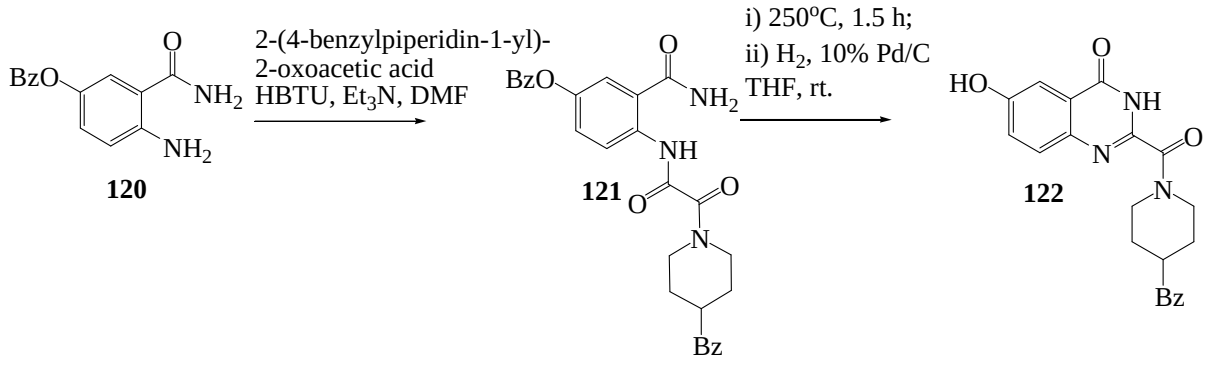
4-Chloro-2-chloroacetylaminobenzoic acid (**117**) and 2-substituted-5-amino-1,3,4- thiadiazole were reacted in dry toluene in presence of phosphorous trichloride and the resultant 7-chloro-2-chloromethyl-3-(2-substituted-1,3,4-thiadiazol-5-yl)-quinazolin-4(3*H*)- ones **118** and morpholine or substituted morpholine was refluxed to afford 7-chloro-2-(morpholinomethyl or 2,6-dimethylmorpholinomethyl)-3-(2-substituted- 1,3,4-thiadiazol-5-yl)-quinazolin-4(3*H*)-ones (**119**, Scheme 39) [42].



Scheme 39

2.25Piperidinyloxomethylquinazolin-4(3*H*)-one

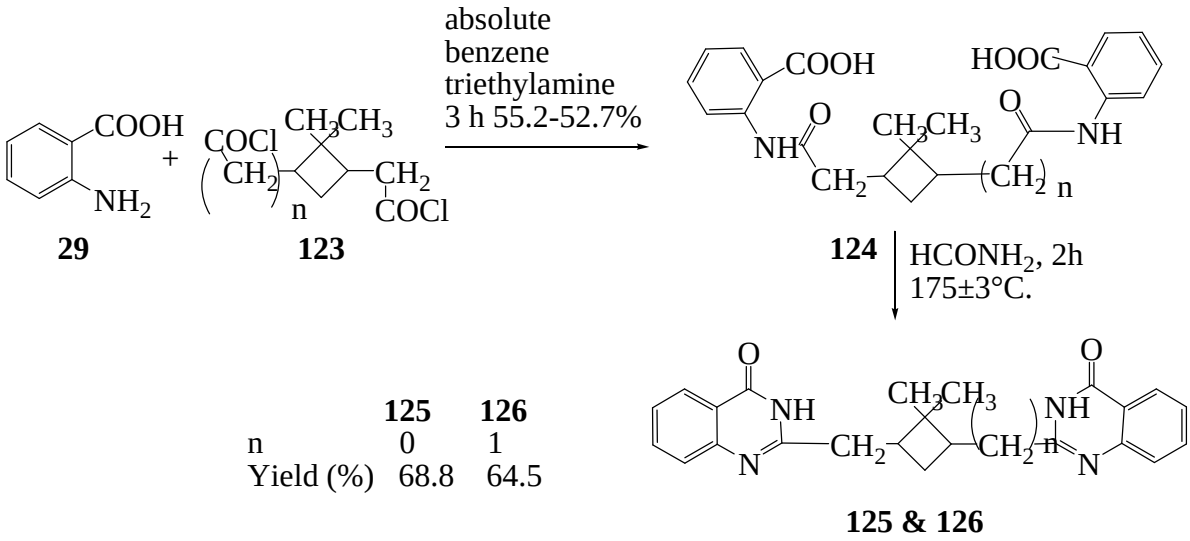
Novel NR2B selective NMDA receptor antagonists were prepared by the condensation of anthranilamide derivative **120** with 2-(4-benzylpiperidin-1-yl)-2-oxoacetic acid in presence of HBTU, Et_3N in DMF medium followed by thermal condensation of the obtained oxalic acid diamide **121** and catalytic hydrogenolysis of *O*-benzyl protecting group to afforded 2-(4-benzylpiperidin-1-yl)-oxomethylquinazolin-4(3*H*)-one (**122**, Scheme 40) [8].



Scheme 40

2.26Bisquinazolinonylcyclobutanes

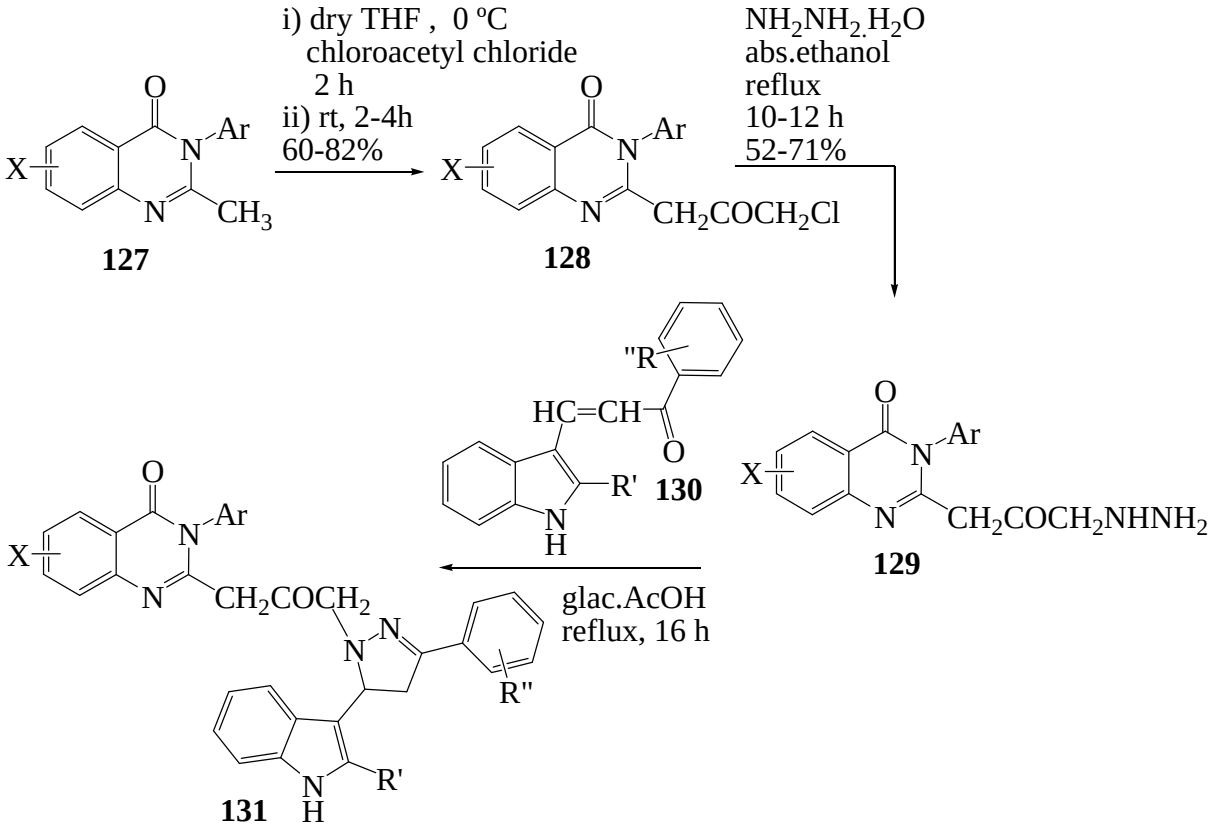
2,2-Dimethyl-1-[quinazolin-4(3*H*)-one-2-yl]methyl-3-[quinazolin-4(3*H*)-one-2-yl] cyclobutane (**125**, n=0) or 2,2-dimethyl-1,3-di[quinazolin-4(3*H*)-one-2-ylmethyl]cyclobutane (**126**, n=1) was prepared by reacting anthranilic acid (**29**) with diacid chloride **123** to compound **124** and subsequent treatment with formamide to isolate compounds **125** and **126** respectively (Scheme 41) [43].



Scheme 41

2.27Pyrazolinylacetylmethylquinazolin-4(3*H*)-ones

2-Methyl-3-aryl-substituted quinazolin-4(3*H*)-ones **127** were reacted with chloroacetyl chloride to 2-chloroacetylmethylene-3-aryl-substituted quinazolin-4(3*H*)-one **128**, conversion into 2-hydrazinoacetylmethyl-3-aryl-substituted quinazolin-4(3*H*)-one **129** with hydrazine hydrate (99 %) followed by reaction with 2-substituted indol-3-yl-substituted chalcones **130** in glacial acetic acid at reflux to afford 3-aryl-2-((3-aryl-5-(2-substituted indol-3-yl)- 2-pyrazolinyl)acetylmethylene)-substituted quinazolin-4(3*H*)-one **131**. These compounds exhibited potent antiinflammatory, analgesic, ulcerogenic, cycloxygenase and toxicity activities (Scheme 42) [7,44].



X	H	H	6-Br	6,8-di Br
Ar	3-ClC_6H_4	2,4-$Cl_2C_6H_3$	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$
R'	CH_3	CH_3	CH_3	CH_3
R"	2-OCH_3	2-OCH_3	H	H
Yield (%)	52	48	51	60

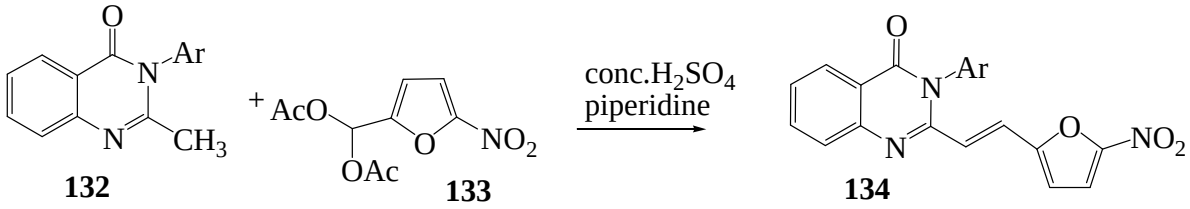
X	H	6-Br	6,8-di Br	H
Ar	2,4-$Cl_2C_6H_3$	3-$CH_3OC_6H_4$	3-$CHH_3OC_6H_4$	3-ClC_6H_4
R'	C_6H_5	C_6H_5	C_6H_5	H
R"	2-OCH_3	H	H	2-OCH_3
Yield (%)	50	42	44	47

X	H	6-Br	6,8-di Br	H
Ar	2,4-$Cl_2C_6H_3$	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	3-ClC_6H_4
R'	H	H	H	C_6H_5
R"	2-OCH_3	H	H	2-OCH_3
Yield (%)	51	42	60	39

Scheme 42

2.28Furanylvinylquinazolin-4(3*H*)-ones

2-Methyl-3-arylquinazolin-4(3*H*)-one **132** was condensed with nitrofurfural diacetate (**133**) in the presence of piperidine and drops of concentrated sulphuric acid to afford 2-(2-(furan-2-yl)vinyl)-quinazolin-4(3*H*)-one **134** and have shown potent antifungal activity (Scheme 43) [45].



132 **133** **134**

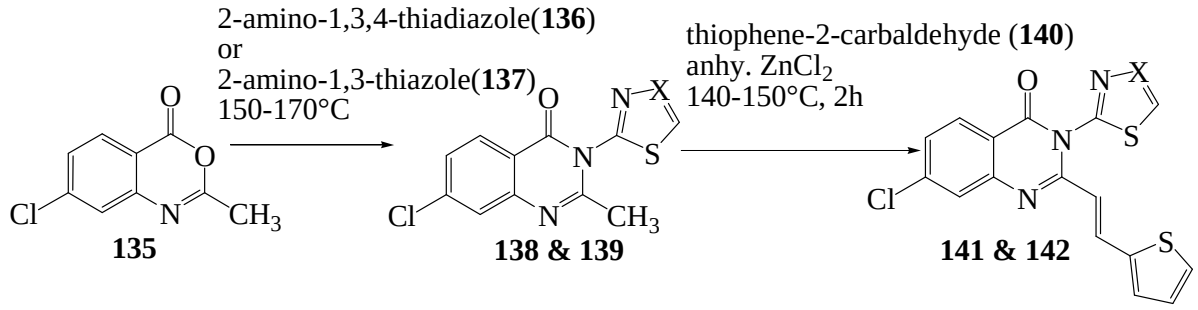
Ar	Ph	4-BrC_6H_4	4-MeC_6H_4	3-ClC_6H_4	3-Cl-4-FC_6H_3
Yield(%)	80	81	78	57	81

Ar	2-$MeOC_6H_4$	3-MeC_6H_4	4-$NO_2C_6H_4$	2,5-$Cl_2C_6H_3$
Yield(%)	51	68	50	53

Scheme 43

2.29Thienylvinylquinazolin-4(3*H*)-ones

An intimate mixture of the 7-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (**135**) and 2-amino-1,3,4- thiadiazole (**136**) or 2-amino-1,3-thiazole (**137**) was heated at 150-170°C followed by condensation of the resultant 7-chloro-2-methyl-3-(1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones (**138** & **139**) with thiophene-2-carbaldehyde (**140**) in presence of anhyd. zinc chloride to afford 2-(2-thienylvinyl)-7-chloro-3-(1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones (**141** & **142**, Scheme 44) [42].



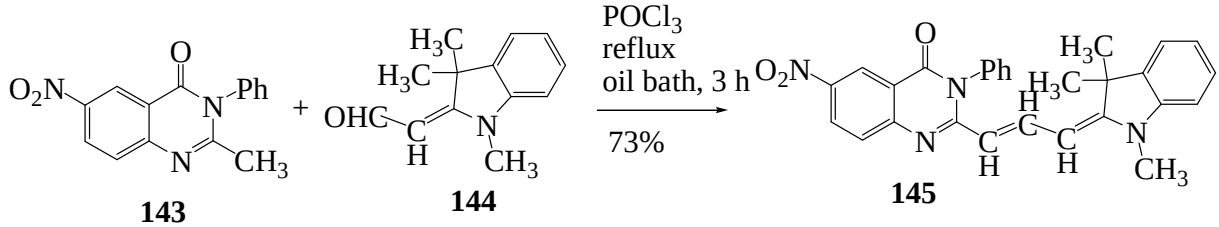
135 **138 & 139** **141 & 142**

	138/ 141	**139/ 142**
X	N	CH
Yield (%)	65	63

Scheme 44

2.30Indolinylidenepropenylquinazolin-4(3*H*)-one

Bhatti and Seshadri were prepared styryl dye, 2-(3-(indolin-2-ylidene)prop-1-enyl)- quinazolin-4(3*H*)-one (**145**) by reacting 2-methyl-6-nitro-3-phenylquinazolin-4(3*H*)-one (**143**) and 2-(1,3,3-trimethylindolin-2-ylidene) acetaldehyde (**144**) in presence of phosphorus oxychloride (Scheme 45) [46].

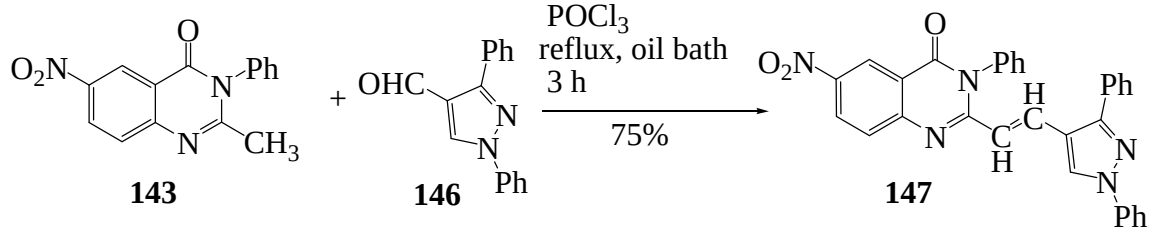


143 **144** **145**

Scheme 45

2.31Pyrazolylvinylquinazolin-4(3*H*)-one

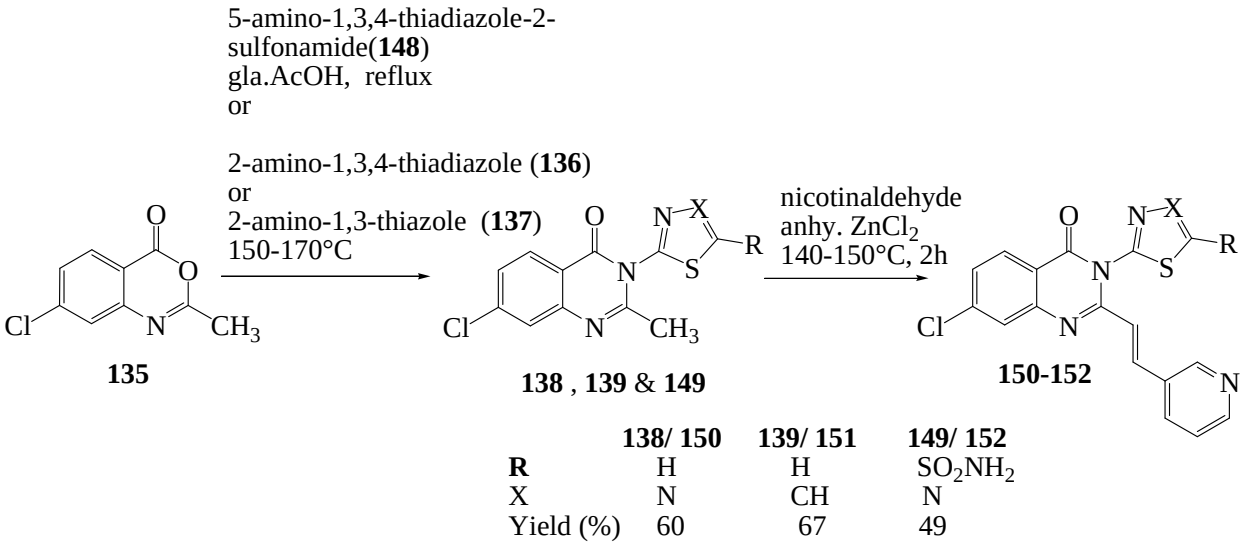
Bhatti and Seshadri were prepared styryl dye, 6-nitro-3-phenyl-2-((*E*)-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)vinyl)-quinazolin-4(3*H*)-one (**147**), by reacting 2-methyl-6-nitro-3- phenylquinazolin-4(3*H*)-one (**143**) and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**146**) in presence of phosphorus oxychloride (Scheme 46) [46].



Scheme 46

2.32Pyridinylvinylquinazolin-4(3*H*)-ones

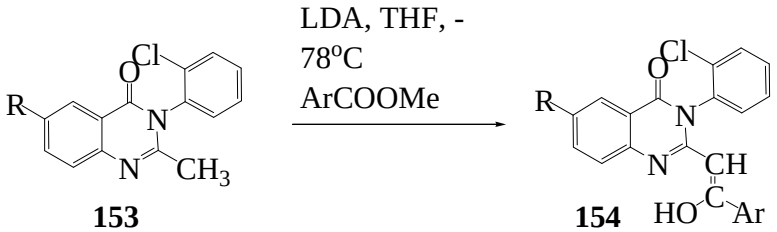
A mixture of 7-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (**135**) and 5-amino-1,3,4- thiadiazole-2-sulfonamide (**148**) or 2-amino-1,3,4-thiadiazole (**136**) or 2-amino-1,3-thiazole (**137**) was heated at 150-170°C followed by condensation of the resultant 7-chloro-2-methyl-3-(2-sulfamoyl-1,3,4-thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones (**138**, **139** & **149**) with nicotinaldehyde in presence of anhyd. zinc chloride to afford 2-(2-(pyridine-3-yl)vinyl)-7-chloro-3-(2-sulfamoyl-1,3,4- thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones (**150-152**, Scheme 47) [42].



	138/ 150	139/ 151	149/ 152
R	H	H	SO_2NH_2
X	N	CH	N
Yield (%)	60	67	49

Scheme 47

Chenard and co-workers were used LDA or NaH for the deprotonation of 2-methylquinazolin-4(3*H*)-one **153** and the obtained carbanion was quenched with various aromatic esters to produce quinazolin-4(3*H*)-one derivative **154** and are potent noncompetitive AMPA receptor antagonists (Scheme 48) [47].

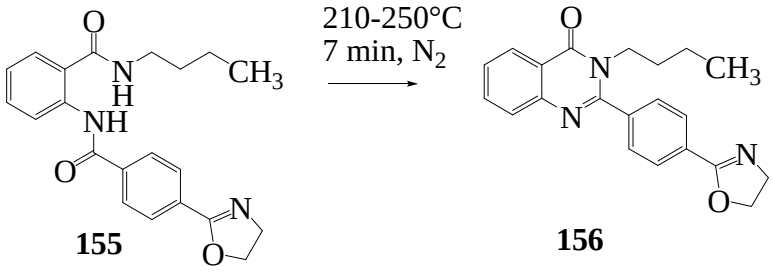


R	H	F	F	F	F
Ar	pyrid-2-yl	pyrid-2-yl	3-cyanopyrid-2-yl	6-methylpyrid-2-yl	3-cyano-6-methylpyrid-2-yl

Scheme 48

2.33Dihydrooxazolylphenylquinazolin-4(3*H*)-one

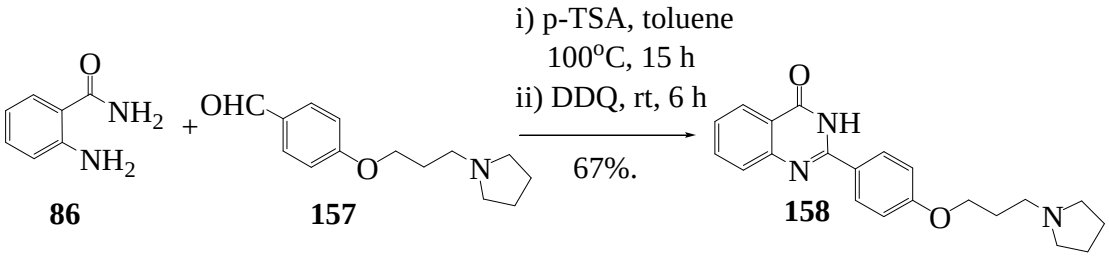
Jakisch and co-workers heated the 2-(4-(4,5-dihydrooxazol-2-yl)benzoylamino- *N*-butylbenzamide (**155**) for 7 min under nitrogen in a small glass tube at 210°C (below 250°C) to yield 3-butyl-2-(4-(4,5-dihydrooxazol-2-yl)phenyl)-quinazolin-4(3*H*)-one (**156**). The reaction at 250°C yielded a mixture of **155** and **156** (Scheme 49) [48].



Scheme 49

2.34Pyrrolidinylpropyloxyphenylquinazolin-4(3*H*)-one

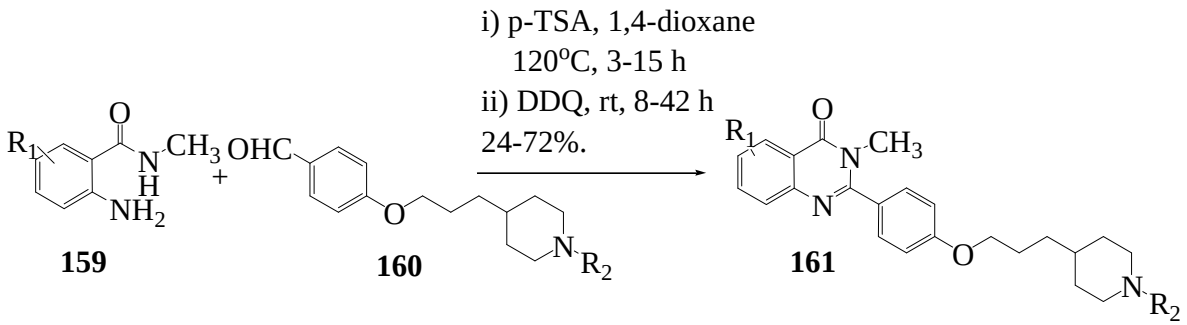
The anthranilamide (**86**) was thermally condensed with 4-[3-(pyrrolidin-1-yl)propoxy] benzaldehyde (**157**) in presence of a catalytic amount of p-toluenesulfonic acid, followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone to furnish the 2-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-quinazolin-4(3*H*)-one (**158**). This is identified as a potent and selective radioligand for histamine H_3 receptors (Scheme 50) [49].



Scheme 50

2.35Piperidinylpropoxyphenylquinazolin-4(3*H*)-ones

The amide **159** was thermally condensed with 4-aminoalkoxy benzaldehyde **160** in presence of a catalytic amount of p-toluenesulfonic acid followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone to furnish the 2-[4-(aminoalkoxy)phenyl]- quinazolin-4(3*H*)-one derivatives **161**. These derivatives were identified as potent human H_3 receptor inverse agonists (Scheme 51) [50].

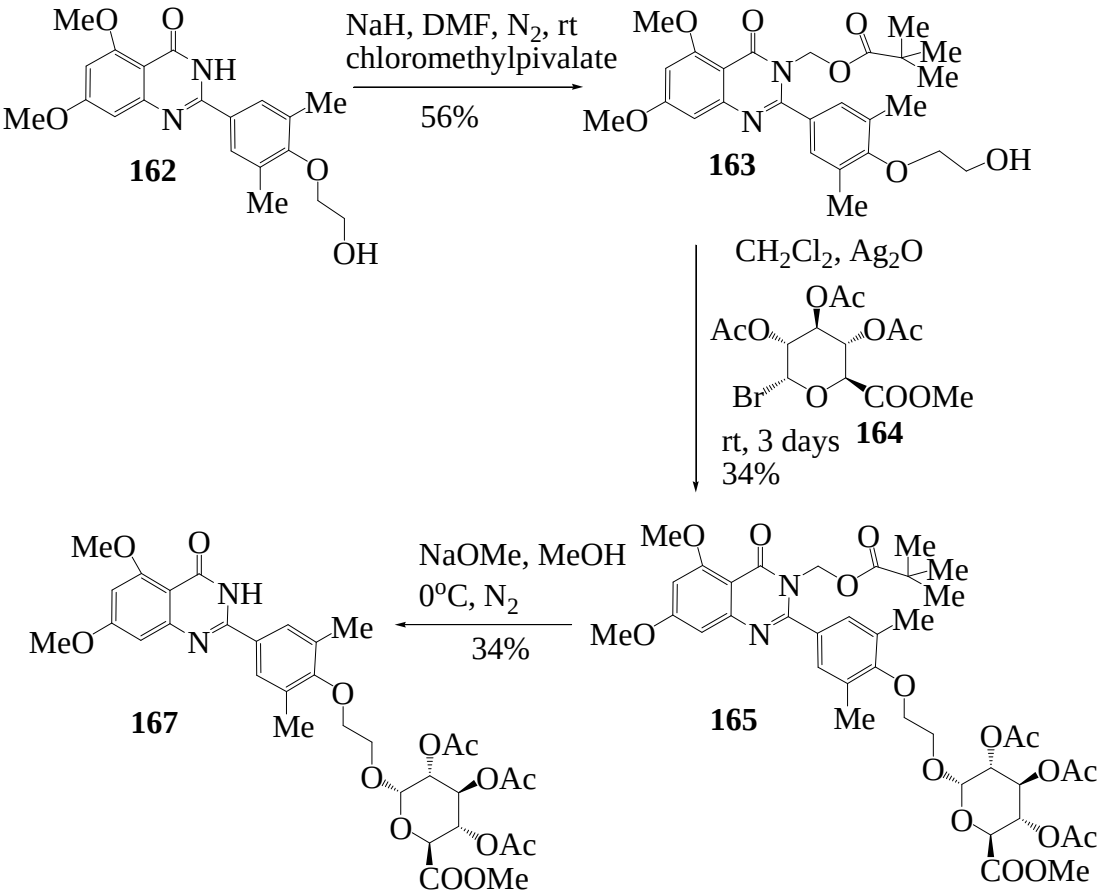


R_1 = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, $CH_2C_6H_5$, C_6H_5
R2 = cyclobutyl, cyclopentyl

Scheme 51

2.36Tetrahydropyranyloxyethoxyphenylquinazolin-4(3*H*)-one

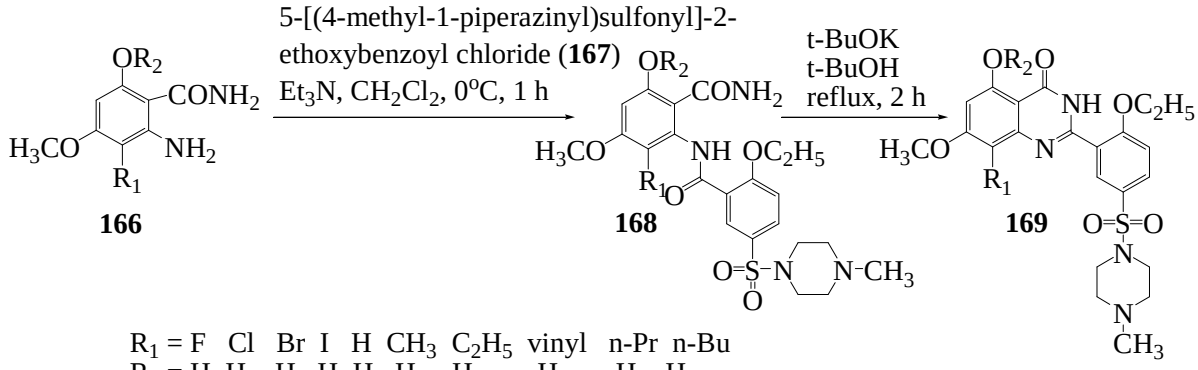
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (**162**) was reacted with chloromethylpivalate to isolate 2,2-dimethylpropionic acid 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one-3-ylmethyl ester (**163**). The compound **163** was then treated with (2*S*,3*S*,4*S*,5*R*,6*R*)-3,4,5- triacetoxy-6-bromotetrahydropyran-2-carboxylic acid methyl ester (**164**) in presence of silver (I) oxide to give 3,4,5-triacetoxy-6-(2-(4-(3-(2,2-dimethylpropionyloxymethyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one-2-yl)-2,6-dimethylphenoxy)ethoxy)tetrahydropyran-2-carboxylic acid methyl ester (**165**) and the N_3-group of **165** is deprotected with sodium methoxide to give 6-(2-(4-(5,7-dimethoxy-quinazolin-4(3*H*)-one-2-yl)-2,6-dimethylphenoxy)ethoxy)-3,4,5-trihydroxytetrahydropyran-2-carboxylic acid (**167**). This compound is predominant metabolites of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin- 4(3*H*)-one (RVX-208, Scheme 52) [51].



Scheme 52

2.37Piperazinylsulfonylphenylquinazolin-4(3*H*)-ones

A class of potent PDE5 inhibitors with high selectivity versus PDE6, 2-phenylquinazolin-4(3*H*)-one derivatives **169**, have been prepared by coupling 2-aminobenzamide derivatives **166** with 5-[(4-methyl-1-piperazinyl)sulfonyl]-2-ethoxybenzoyl chloride **167** followed by dehydrative cyclization of resulting **168** by using t-BuOK as base, in refluxing t-BuOH (Scheme 53) [9].



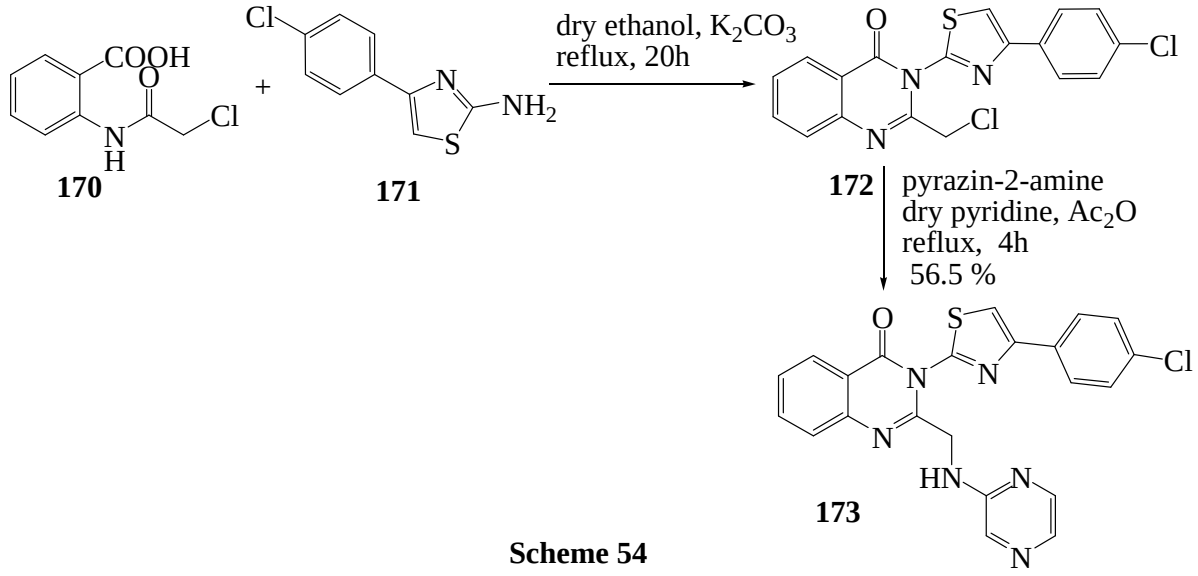
R_1 = F Cl Br I H CH_3 C_2H_5 vinyl n-Pr n-Bu
R_2 = H H H H H H H H H H

R_1 = F Cl Br I H CH_3 C_2H_5 vinyl n-Pr n-Bu
R_2 = CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3

Scheme 53

2.38Pyrazinylaminomethylquinazolin-4(3*H*)-one

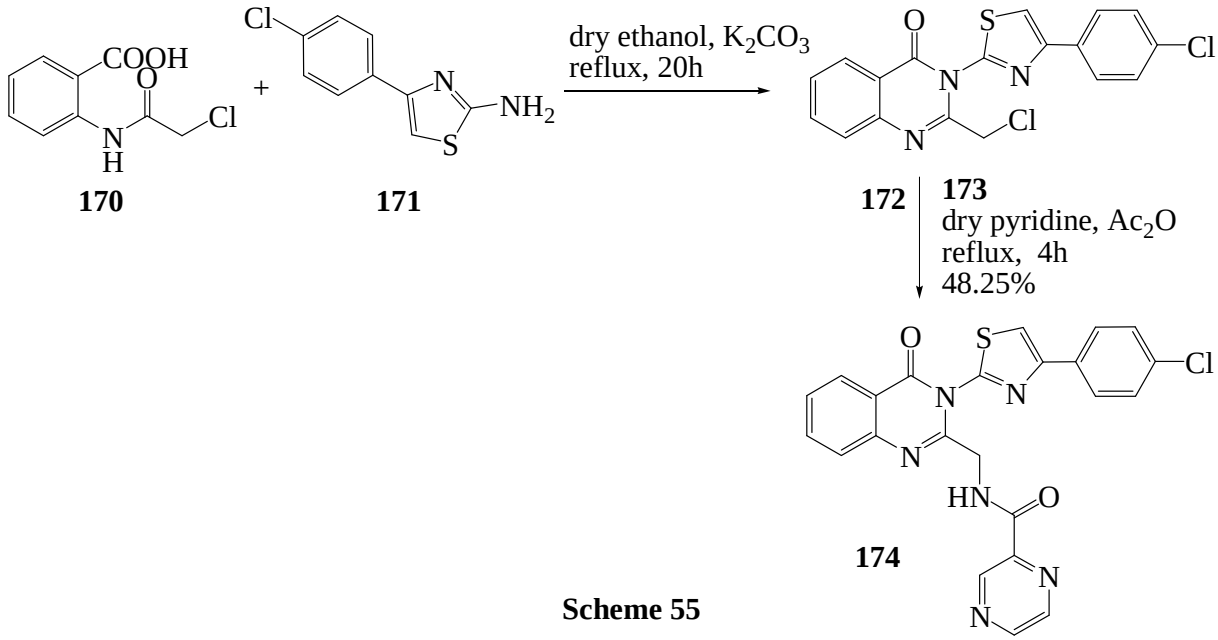
Potent Antitubercular agents, *N*-3-(4-(4-chlorophenyl)thiazol-2-yl)-2-((pyrazin-2-yl) aminomethyl)-quinazolin-4(3*H*)-one derivatives **173**, were prepared by reacting *N*-chloroacetylanthranilic acid (**170**) with 4-chlorophenyl thiazole (**171**) to 2-chloromethyl-3-[4-(4-chlorophenyl)thiazol-2-yl]-quinazolin-4(3*H*)-one (**172**) followed by condensation with pyrazin-2-amine (Scheme 54) [11].



Scheme 54

2.39Pyrazinyloxomethylaminomethylquinazolin-4(3*H*)-one

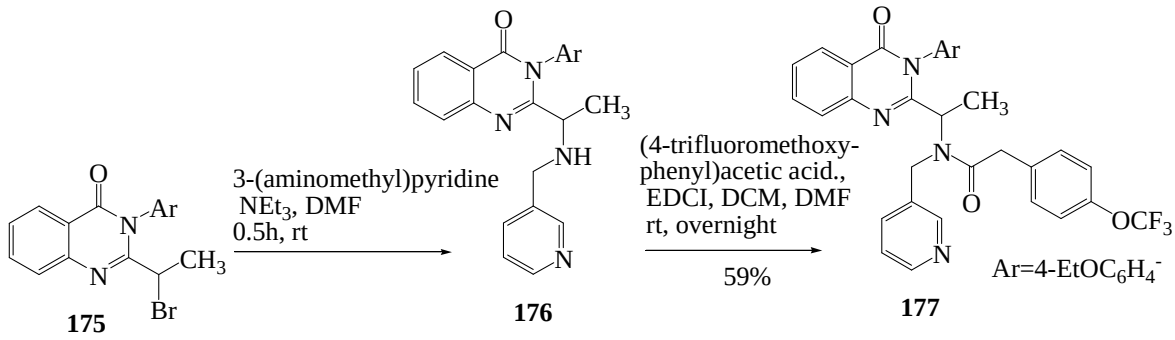
Potent Antitubercular agent, *N*-3-(4-(4-chlorophenyl)thiazol-2-yl)-(2-(amino)methyl)- quinazolin-4(3*H*)-one (**174**), was prepared by reacting *N*-chloroacetylanthranilic acid (**170**) with 4-chlorophenyl thiazole (**171**) to 2-chloromethyl-3-[4-(4-chlorophenyl)thiazol-2-yl]- quinazolin-4(3*H*)-one (**172**) followed by condensation with. pyrazine-2-carboxamide (**173**) (Scheme 55) [11].



Scheme 55

2.40 Pyridinylmethylaminoethylquinazolin-4(3*H*)-one

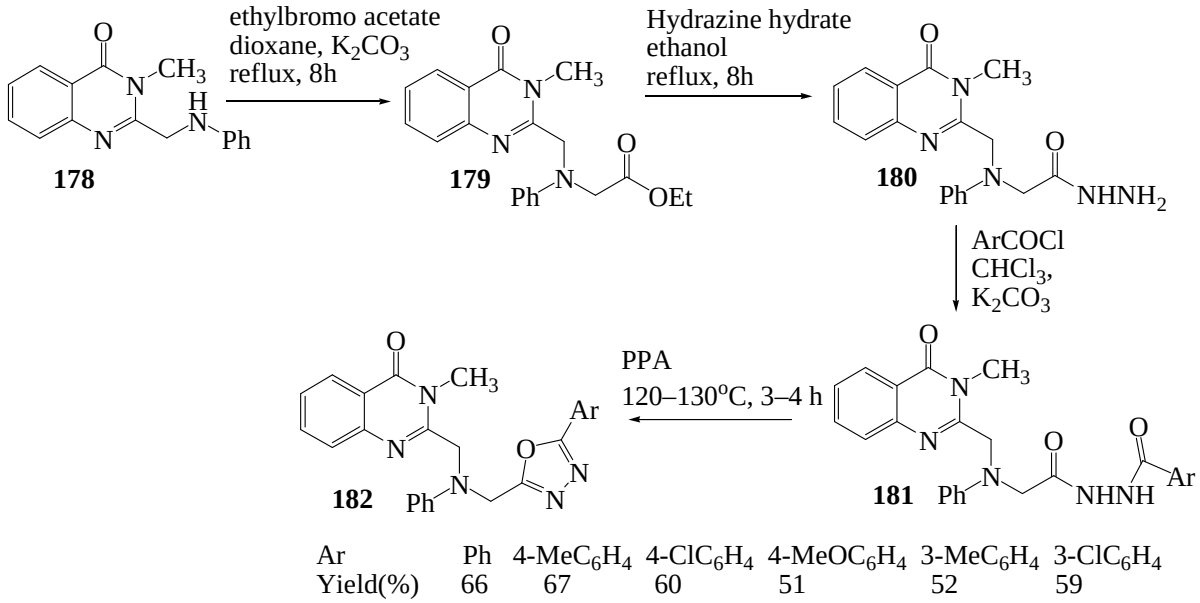
Stefania and co-workers prepared CXCR3 receptor antagonists, *N*-{1-[3-(4-ethoxy-phenyl)-quinazolin-4(3*H*)-one-2-yl]-ethyl}-*N*-pyridin-3-ylmethyl-2-(4-trifluoromethoxyphenyl)- acetamide **177** on reaction of 2-(1-bromoethyl)-3-aryl-quinazolin-4(3*H*)-one (**175**) with 3-(aminomethyl)pyridine and condensation of resultant 3-(aryl)-2-{1-[(pyridin-3-ylmethyl)- amino]-ethyl}-quinazolin-4(3*H*)-one **176** with (4-trifluoromethoxy-phenyl)-acetic acid (Scheme 56) [10].



Scheme 56

2.41 Oxadiazolylmethylanilinemethylquinazolin-4(3*H*)-ones

Alkylation of 2-phenylaminomethyl-3-oxadiazolylquinazolin-4(3*H*)-one (**178**) with ethylbromo acetate (EBA) to ethyl 2-(*N*-((3-methylquinazolin-4(3*H*)-one-2-yl)methyl)-*N*- phenylamino)acetate **179** followed by hydrazinolysis with hydrazine hydrate furnished 2-{[(3-methylquinazolin-4(3*H*)-one-2-yl)methyl]-aniline}ethanohydrazide (**180**). Aroylation of compound **180** to compound **181** and ring formation of resulting **181** on reaction with polyphosphoric acid (PPA) at 120-130^{o}C to isolate 3-methyl-2-({[5-aryl-1,3,4-oxadiazol-2-yl) methyl]aniline}methyl)-quinazolin-4(3*H*)-ones **182** (Scheme 57) [52].

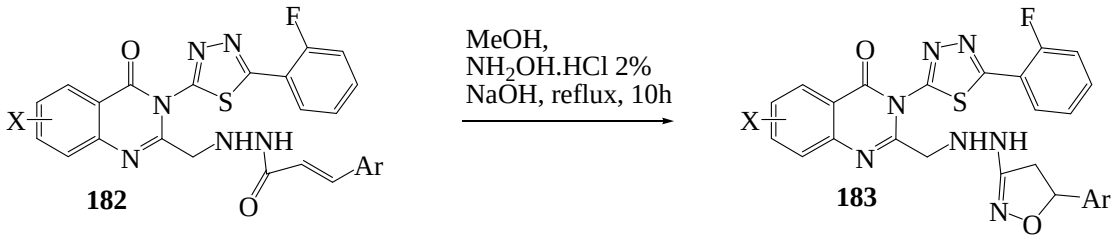


Ar	Ph	4-MeC_6H_4	4-ClC_6H_4	4-$MeOC_6H_4$	3-MeC_6H_4	3-ClC_6H_4
Yield(%)	66	67	60	51	52	59

Scheme 57

2.42Dihydroisoxazolylhydrazinylmethylquinazolin-4(3*H*)-ones

Hemlata and co-workers reacted 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5- (un/substituted hetetocyclic/arylchalconyl)-hydrazinyl)methyl)-substituted quinazolin- 4(3*H*)-one **182** with hydroxyl amine hydrochloride at reflux in methanol in presence of 2% NaOH solution to isolate potent antipsychotic and anticonvulsant agents, 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(unsubstituted heterocyclic/aryl)-4,5-dihydroisoxazol-2-yl)hydrazinyl)methyl)substituted quinazolin-4(3*H*)-one (**183**, Scheme 58) [12].



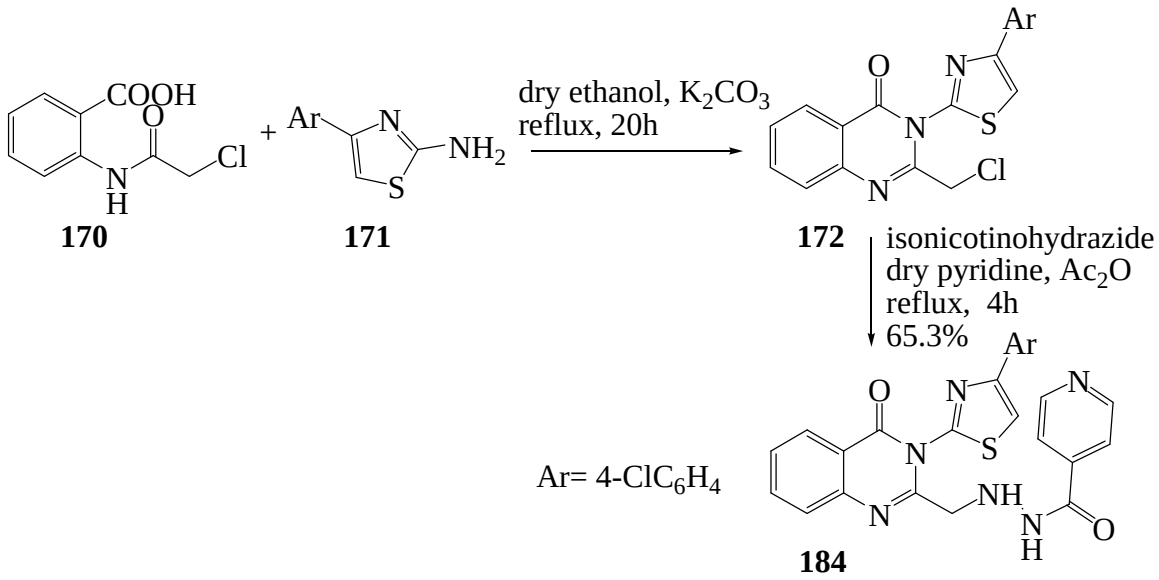
X	H	6-Br	6,8-di Br	H	6-Br
Ar	2-pyridyl	2-pyridyl	2-pyridyl	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$
Yield (%)	74	78	77	69	71

X	6,8-di Br	H	6,8-di Br
Ar	4-$CH_3OC_6H_4$	4-CH_3Oindol-3-yl	4-CH_3Oindol-3-yl
Yield (%)	79	77	75

Scheme 58

2.43Isonicotinoylhydrazinylquinazolin-4(3*H*)-one

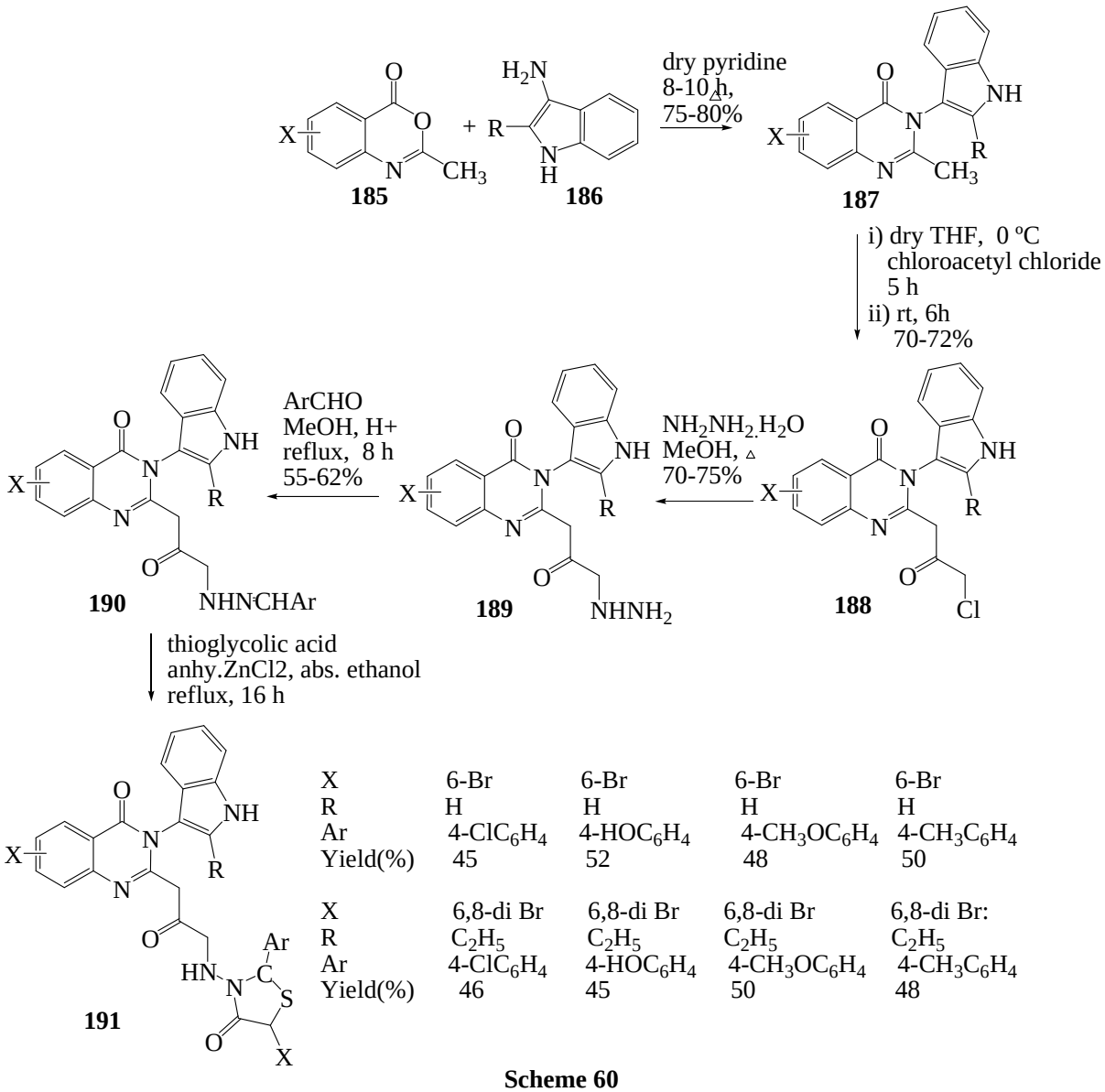
Potent antitubercular agent, *N*'-((3-(4-(4-chlorophenyl)thiazol-2-yl)-quinazolin-4(3*H*)-one-2-yl)-methyl)isonicotinohydrazide **184** was prepared by reacting *N*-chloroacetyl anthranilic acid (**170**) with 4-chlorophenyl thiazole (**171**) in presence of potassium carbonate to isolate 2-chloromethyl-3-[4-(4-chlorophenyl)-thiazol-2-yl]-quinazolin-4(3*H*)-one (**172**) followed by refluxing the resultant compound **172** with isonicotinohydrazide in dry pyridine and acetic anhydride (Scheme 59) [11].



Scheme 59

2.44Thiazolidinylaminoacetylmethylenylquinazolin-4(3*H*)-ones

Potent anti-inflammatory, analgesic and COX-II Inhibitors derivatives, 2-(*N*-(5-substituted 2-aryl-4-oxo-3-thiazolidinyl)aminoacetylmethyl)-3-(2-substitutedindol-3-yl)-substituted quinazolin-4(3*H*)-ones **191** were prepared from 2-methylsubstitutedbenzoxazines **185**. Reaction of **185** with 2-substituted-3-aminoindoles **186**, treatment with chloroacetyl chloride to compound **188**, reaction with hydrazinehydrate to 2-hydrazinoacetylmethylene-3- (2'-substitutedindol-3'-yl)-substituted quinazolin-4(3*H*)-ones **189**, condensation with substituted benzaldehyde to 2-(substituted phenylmethyleneimino)aminoacetylmethylene- 3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones **190** and finally reacted with thioglycolic acid in the presence of anhydrous $ZnCl_2$ to yield compound **191** (Scheme 60) [53,54].

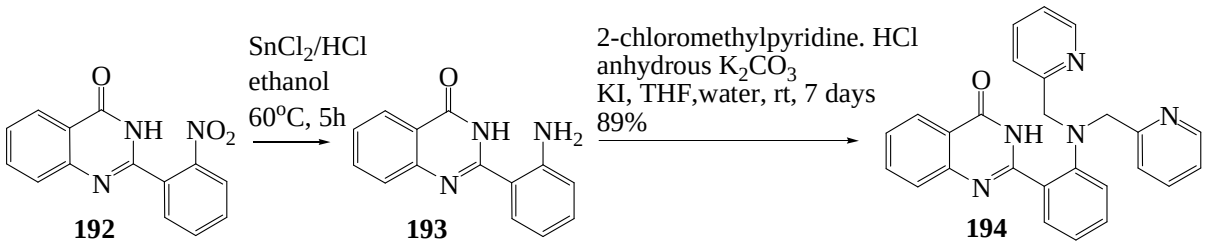


X	6-Br	6-Br	6-Br	6-Br
R	H	H	H	H
Ar	4-ClC_6H_4	4-HOC_6H_4	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$
Yield(%)	45	52	48	50
X	6,8-di Br	6,8-di Br	6,8-di Br	6,8-di Br:
R	C_2H_5	C_2H_5	C_2H_5	C_2H_5
Ar	4-ClC_6H_4	4-HOC_6H_4	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$
Yield(%)	46	45	50	48

Scheme 60

2.45 Bispyridinylmethylaminophenylquinazolin-4(3*H*)-one

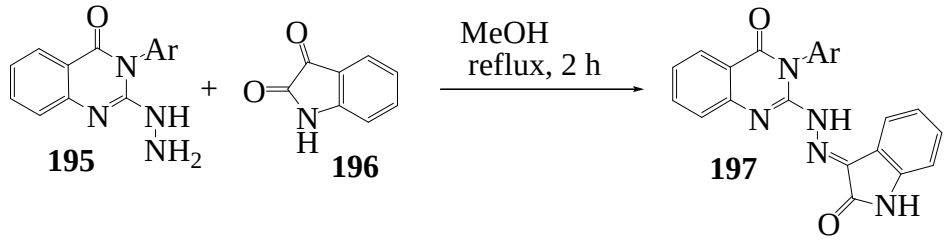
2-(2-Nitrophenyl)-quinazolin-4(3*H*)-one (**192**) was reduced with tin dichloride and the resultant 2-(2-aminophenyl)-quinazolin-4(3*H*)-one (**193**) was treated with 2-chloromethyl- pyridine hydrochloride to afford 2-(2-(bispyridin-2-ylmethyl)aminophenyl)-quinazolin- 4(3*H*)-one (**194**, Scheme 61) [55].



Scheme 61

2.46 Isatinhydrazonylquinazolin-4(3*H*)-ones

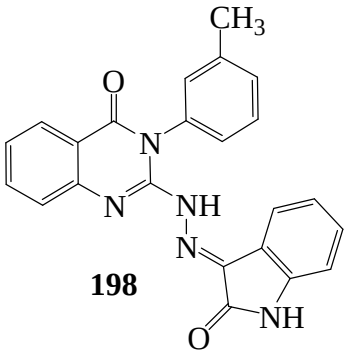
A mixture of 3-aryl-2-hydrazino-quinazolin-4(3*H*)-one **195** and isatin (**196**) in methanol was refluxed to isolate 3-aryl-2-(isatinhydrazone-3-yl)-quinazolin-4(3*H*)-ones **197** (Scheme 62) [56].



Ar	Ph	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	4-ClC_6H_4
Yield (%)	69	71	69	69

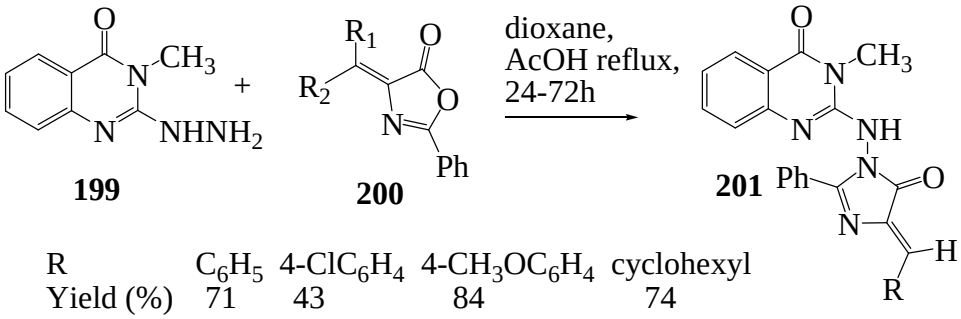
Scheme 62

The desirability-based MOOP method indicated the presence of bulky alkyl substituents at the C-2 position of the quinazoline **198** displayed a positive role on the ulcerogenic ability [57].



2.47Dihydroimidazolylaminoquinazolin-4(3*H*)-ones

Hamidian and co-workers reacted 2-hydrazino-3-methyl-quinazolin-4(3*H*)-one (**199**) with 5(4*H*)-oxazolone (**200**) in acetic acid at reflux to afford 3-methyl-2-({5-oxo-2-phenyl-4-[1-arylmethylidene]-4,5-dihydro-1*H*-imidazol-1-yl}amino)-quinazolin-4(3*H*)-one (**201,** Scheme 63) [58].

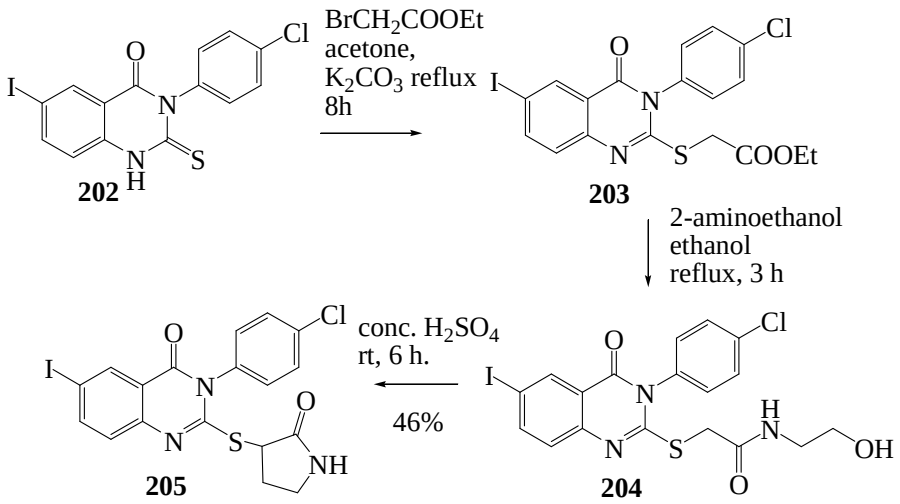


R	C_6H_5	4-ClC_6H_4	4-$CH_3OC_6H_4$	cyclohexyl
Yield (%)	71	43	84	74

Scheme 63

2.48Pyrrolidinylthioquinazolin-4(3*H*)-one

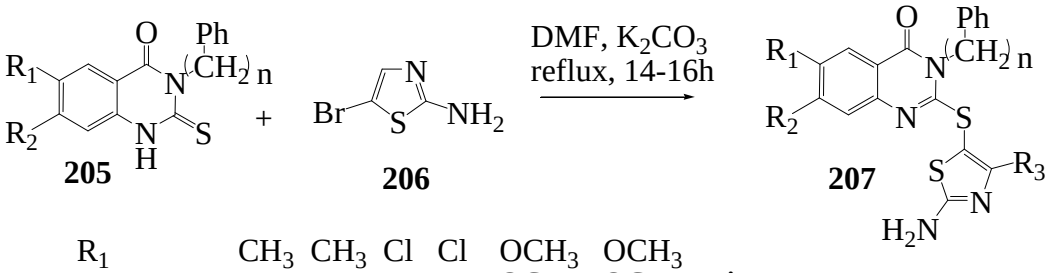
A mixture of 2-mercapto-3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one (**202**), ethyl bromoacetate and anhydrous potassium carbonate in dry acetone was heated under reflux to isolate 2-(ethoxycarbonylmethyl)thio-3-(4-chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one (**203**). The **203** was reacted with 2-aminoethanol and the resultant *N*-(2-hydroxyethyl)-2-[(3-(4-chloro)phenyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetamide (**204**) was cyclised with conc. H_2SO_4 to yield 2-[(2-oxopyrrolidin-3-yl)thio]-3-(4-chlorophenyl)-6-iodo- quinazolin-4(3*H*)-one (**205**). This compound showed a remarkably broad spectrum of antimicrobial activity (Scheme 64) [59].



Scheme 64

2.49 Thiazolylthioquinazolin-4(3*H*)-ones

Al-Omary and co-workers condensed 2-thioxo-quinazoline analogs **205** with 2-amino-5-bromothiazole (**206**) in basic medium to afford ethyl 2-amino-5-(3-phenyl/benzyl)- substituted quinazolin-4(3*H*)-one-2-ylthio)thiazole **207**. These compounds showed active dihydrofolate reductase (DHFR) inhibition, antimicrobial, and antitumor activities (Scheme 65) [13].



R_1	CH_3	CH_3	Cl	Cl	OCH_3	OCH_3
R_2	H	H	H	H	OCH_3	OCH_3
R_3	H	H	H	H	H	H
n	0	1	0	1	0	1
Yield(%)	42	25	56	48	55	30

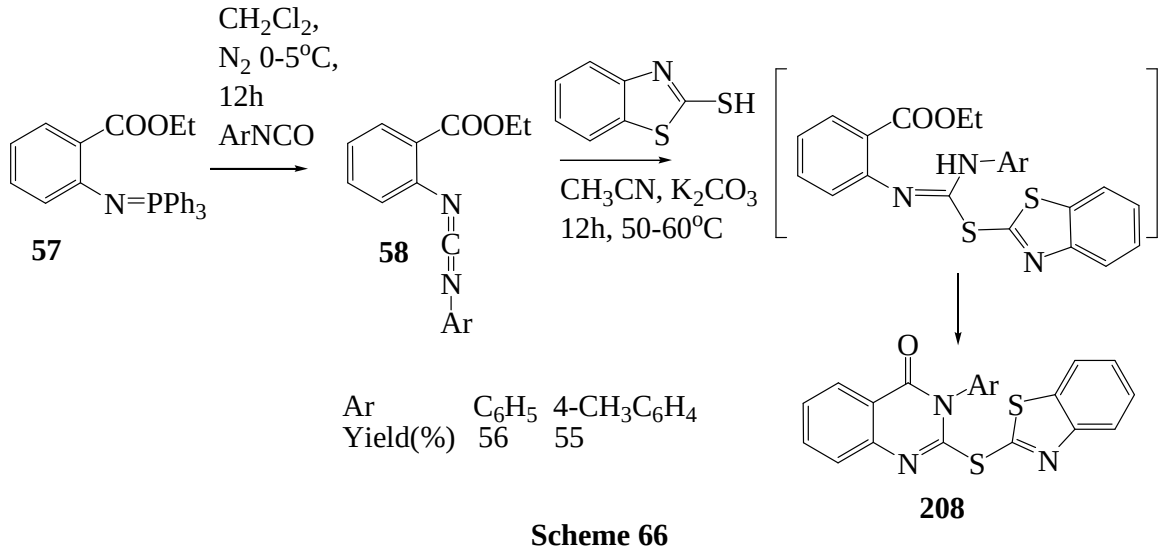
,

R_1	CH_3	CH_3	Cl	Cl	OCH_3	OCH_3
R_2	H	H	H	H	OCH_3	OCH_3
R_3	COOEt	COOEt	COOEt	COOEt	COOEt	COOEt
n	0	1	0	1	0	1
Yield(%)	44	63	31	37	63	49

Scheme 65

2.50 Benzothiazolylthioquinazolin-4(3*H*)-ones

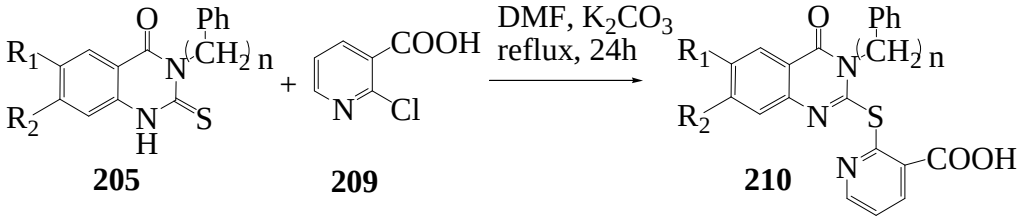
2-(2-Benzothiazolylthio)-quinazolin-4(3*H*)-ones **208** were synthesized by base catalytic reactions of 2-mercaptobenzothiazole with carbodiimides **58**, which were obtained via aza-Wittig reaction of iminophosphorane **57** with aromatic isocyanates. The compound **208** exhibited fungicidal activity (Scheme 66) [60].



Scheme 66

2.51Nicotininylthioquinazolin-4(3*H*)-ones

A mixture of 2-thioxo-quinazoline **205**, 2-chloronicotinic acid (**209**) and anhydrous potassium carbonate was heated under reflux to isolate 2-(3-phenyl/benzyl-substituted quinazolin-4(3*H*)-one-2-ylthio)nicotinic acid **210**. These compounds showed active dihydrofolate reductase (DHFR) inhibition, antimicrobial, and antitumor activities (Scheme 67) [13].

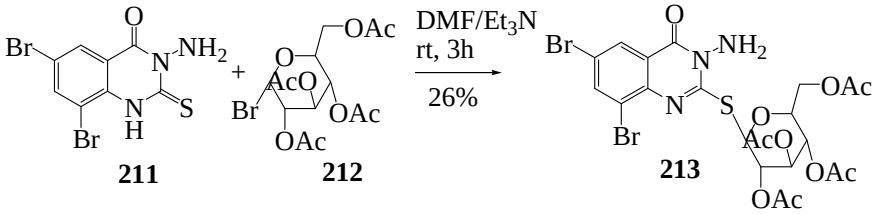


R_1	CH_3	CH_3	Cl	Cl	OCH_3	OCH_3
R_2	H	H	H	H	OCH_3	OCH_3
n	0	1	0	1	0	1
Yield(%)	49	47	61	23	46	52

Scheme 67

2.52Glucopyranosylthioquinazolin-4(3*H*)-one

The coupling of 3-amino-6,8-dibromo-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**211**) with (2,3,4,6-tetra-O-acetyl-α-D-gluopyranosyl)bromide (**212**) in DMF gave 3-amino-6,8-dibromo-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thioquinazolin-4(3*H*)-one (**213**, Scheme 68) [61].

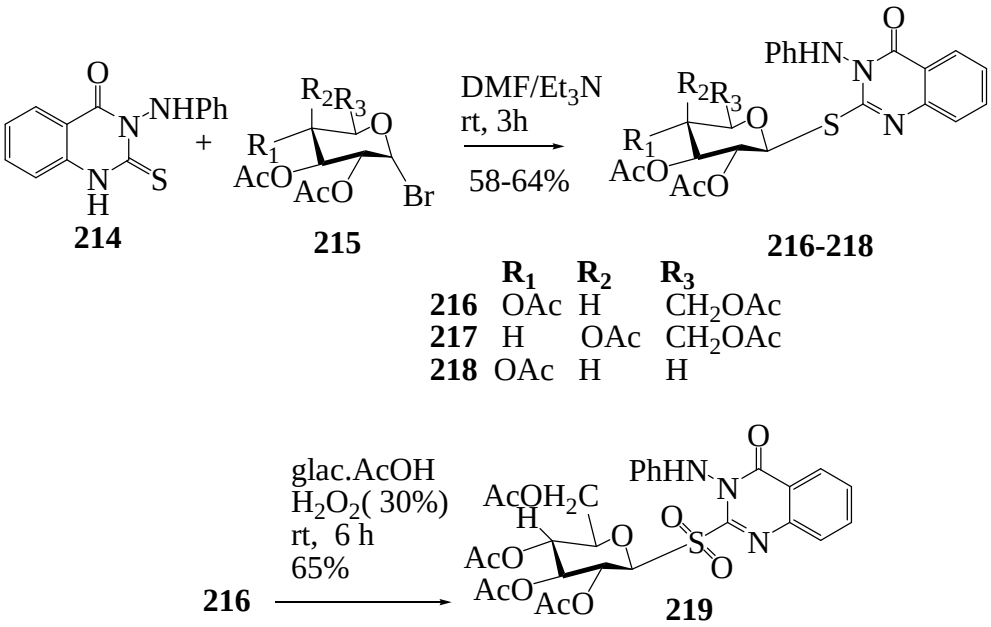


Scheme 68

2.53Glucopyranosylsulphonylquinazolin-4(3*H*)-one

Saleh and co-workers prepared most pronounced inhibitory effect when tested against S. aureus. 3-Phenylamino-2-thioxo-3*H*-quinazolin-4-one (**214**) was reacted with substituted pyranosyl bromide (**215**) to yield *S*-glycoside derivatives **216-218**, respectively. Oxidation of *S*-glucoside **216** with H_2O_2 afforded the corresponding

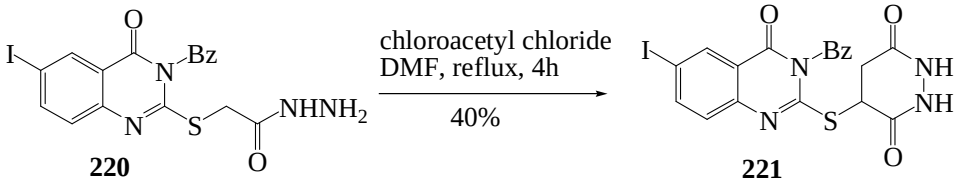
sulphone; 2-(2,3,4,6,tetra-*O*-acetyl-β-D-glucopyranosylsulphonyl)-3-phenylaminoquinazolin-4(3*H*)-one (**219**, Scheme 69) [62].



Scheme 69

2.54Pyridazinylthioquinazolin-4(3*H*)-one

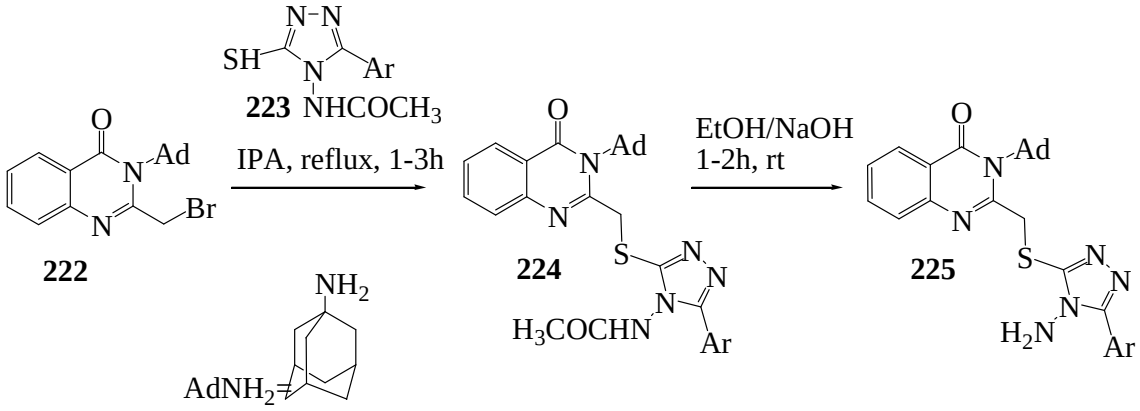
N-[2-(3-Benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thioacetyl]hydrazine (**220**) was reacted with chloroacetyl chloride in dimethylformamide under reflux to isolate 2-[(3,6-dioxopyridazin-4-yl)thio]-3-benzyl-6-iodo-quinazolin-4(3*H*)-one (**221**). This compound could be considered as useful templates for future development to obtain more potent antitumor agent (Scheme 70) [63].



Scheme 70

2.55Triazolylthiomethylquinazolin-4(3*H*)-ones

Potent antimicrobial, anti-inflammatory and analgesic activities derivatives 3-amantadinyl-2-[(4-amino-3-aryl-5-ylthio)-1,2,4-triazolo]methyl)-quinazolin-4(3*H*)-one **225** were prepared by reacting 3-amantadinyl-2-bromomethylquinazolin-4(3*H*)-ones (**222**) with 3-aryl-4-acetamido-5-mercaptotriazoles **223** to afford 3-amantadinyl-2-[(4-acetamido- 3-aryl-5-ylthio)-1,2,4-triazolo]methyl)-quinazolin-4(3*H*)-one **224** followed by deprotection in ethanolic–sodium hydroxide (Scheme 71) [64].



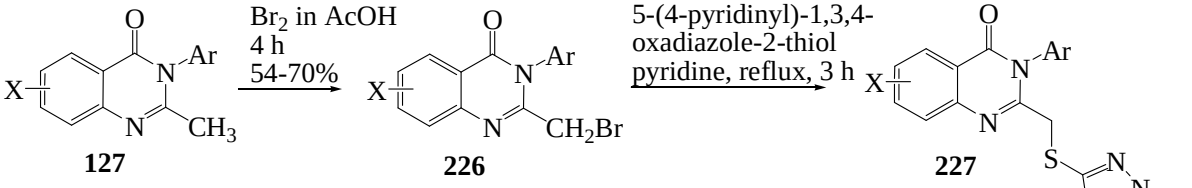
Ar	C_6H_5	2-HOC_6H_4	3-HOC_6H_4	4-HOC_6H_4	4-$C_2H_5OC_6H_4$
Yield (%)	60	60	58	62	63

Ar	4-$HOCH_2C_6H_4$	4-$C_2H_5OCH_2C_6H_4$l	2-ClC_6H_4	4-ClC_6H_4
Yield (%)	57	60	57	53

Scheme 71

2.56Pyridinyloxadiazolylthiomethylquinazolin-4(3*H*)-ones

Antiinflammatory, 2-[5'-(4-pyridinyl)-1',3',4'-oxadiazol-2'-ylthiomethyl]-3-substituted aryl-6- substituted quinazolin-4(3*H*)-ones **227** were prepared by reacting 2-methyl-3-aryl-6-substituted quinazolin-4(3*H*)-ones **127** with bromine in acetic acid to isolate 2-bromomethyl-3-substituted aryl-6-substituted quinazolin-4(3*H*)-ones **226** followed by reaction with 5-(4-pyridinyl)- 1,3,4-oxadiazole-2-thiol in pyridine at reflux (Scheme 72) [65].



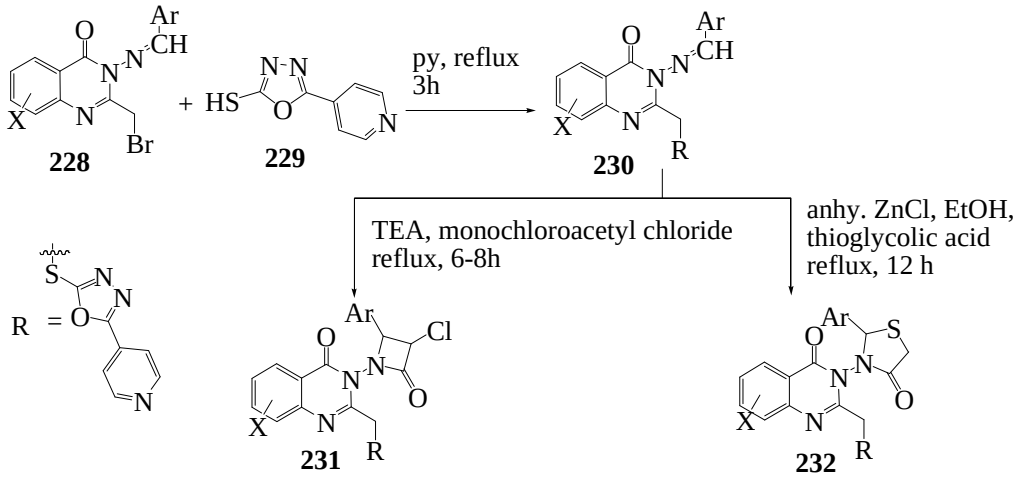
X	H	H	H	H	H	6-I	6-I
Ar	C_6H_5	2-ClC_6H_4	4-ClC_6H_4	2-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	2-ClC_6H_4
Yield (%)	59	45	40	38	55	56	44

X	6-I	6-I	6-I	6-Br	6-Br	6-Br
Ar	4-ClC_6H_4	2-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	2-ClC_6H_4	4-ClC_6H_4
Yield (%)	51	52	57	58	49	52

X	6-Br	6-Br
Ar	2-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$
Yield (%)	46	50

Scheme 72

2-Bromomethyl-3-(arylideneamino)-substituted-3*H*-quinazolin-4(3*H*)-ones **228** and 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol (**229**) were refluxed in pyridine to isolate 2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(arylideneamino)-substituted quinazolin-4(3*H*)-one **230**. The resultant **230** was reacted with i) monochloroacetyl chloride in presence of triethylamine ii) thioglycolic acid containing $ZnCl_2$ to afford 3-(3-chloro-2-oxo-4-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-quinazolin-4(3*H*)-ones **231** and 3-(4-oxo-2-aryl-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4(3*H*)-ones **232** respectively. All the compounds exhibited anti-inflammatory activity at the dose 50 mg/kg p.o. varying degree from 16.3 to 36.3% inhibition of oedema (Scheme 73) [66].



X	H	H	H	H
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$	4-OHC_6H_4
Yield(%)	50	55	40	45

X	6-Br	6-Br	6-Br
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$
Yield(%)	52	55	40

X	6-Br
Ar	4-OHC_6H_4
Yield(%)	55

X	H	H	H	H
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$	4-OHC_6H_4
Yield(%)	55	50	40	48

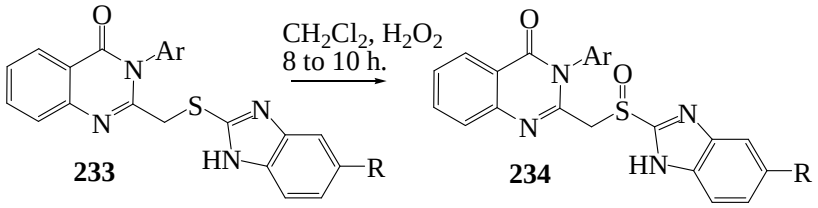
X	6-Br	6-Br	6-Br
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$
Yield(%)	52	56	40

X	6-Br
Ar	4-OHC_6H_4
Yield(%)	55

Scheme 73

2.57Benzoimidazolylsulfinylmethylquinazolin-4(3*H*)-ones

Patil and co-workers prepared 2-[{1*H*-benzo(*d*)imidazol-2-ylsulfinyl]methyl}-3-aryl quinazolin-4(3*H*)-one **234** by oxidizing 2-[{1*H*-benzo(*d*)imidazol-2-ylthio}methyl]-3- arylquinazolin-4(3*H*)-one **233** with hydrogen peroxide. These compounds have shown antiulcer activity (Scheme 74) [67].



R	H	H	H	H	H	H	H
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3COC_6H_4$	4-$CH_3OC_6H_4$	4-$C_2H_5OC_6H_4$	4-BrC_6H_4	4-ClC_6H_4
Yield (%)	45	40	48	35	46	41	42

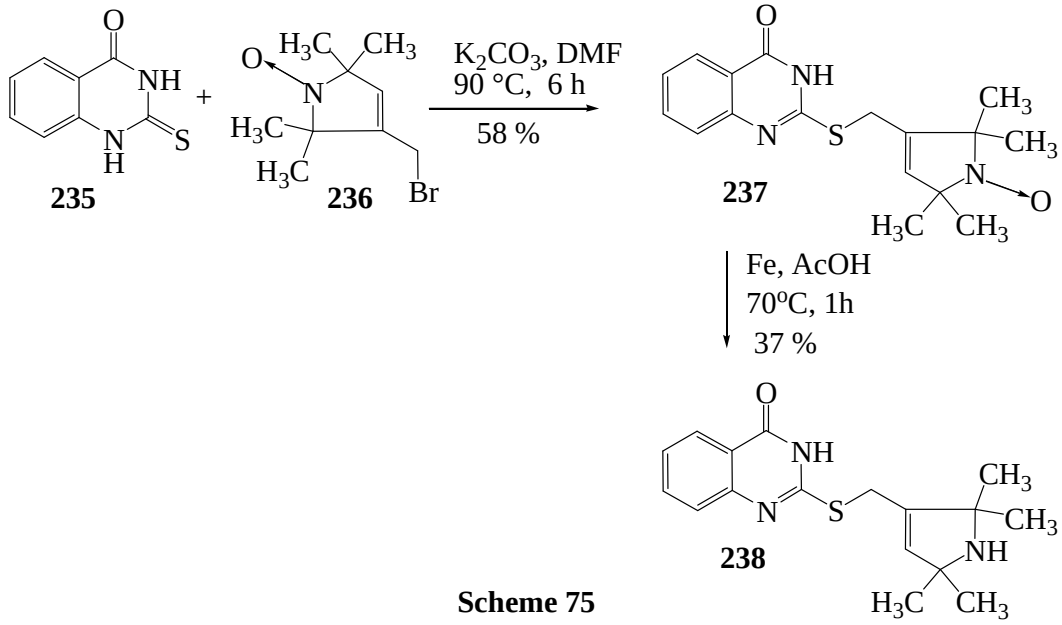
R	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3COC_6H_4$	4-$CH_3OC_6H_4$	4-$C_2H_5OC_6H_4$	4-BrC_6H_4	4-ClC_6H_4
Yield (%)	35	45	40	38	42	42	46

R	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3COC_6H_4$	4-$CH_3OC_6H_4$	4-$C_2H_5OC_6H_4$	4-BrC_6H_4	4-ClC_6H_4
Yield (%)	42	40	48	38	38	42	43

Scheme 74

2.58Dihydropyrrolylmethylthioquinazolin-4(3*H*)-one

2-Mercaptoquinazolin-4(3*H*)-one (**235**) was condensed with 1-oxyl-3-(bromomethyl)-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrole (**236**) to yield 2-{[(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl]thio}-quinazolin-4(3*H*)-one radical (**237**). The resultant nitroxide **237** was reduced with Fe powder in acetic acid to isolate 2-{[(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl]thio}-quinazolin-4(3*H*)-one (**238**, Scheme 75) [15].

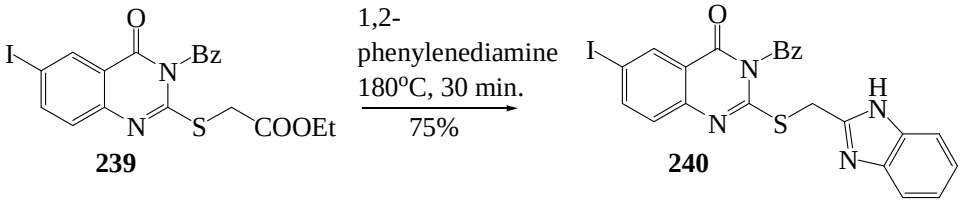


235 236 237 238

Scheme 75

2.59Benzimidazolemethylthioquinazolin-4(3*H*)-one

Equimolar amounts of 2-(ethoxycarbonylmethyl)thio-3-benzyl-6-iodo-quinazolin-4(3*H*)-one (**239**) and 1,2-phenylenediamine were fused at 180°C to generate 2-[(2-benzimidazole) methylthio]-3-benzyl-6-iodo-quinazolin-4(3*H*)-one (**240**, Scheme 76) [63].

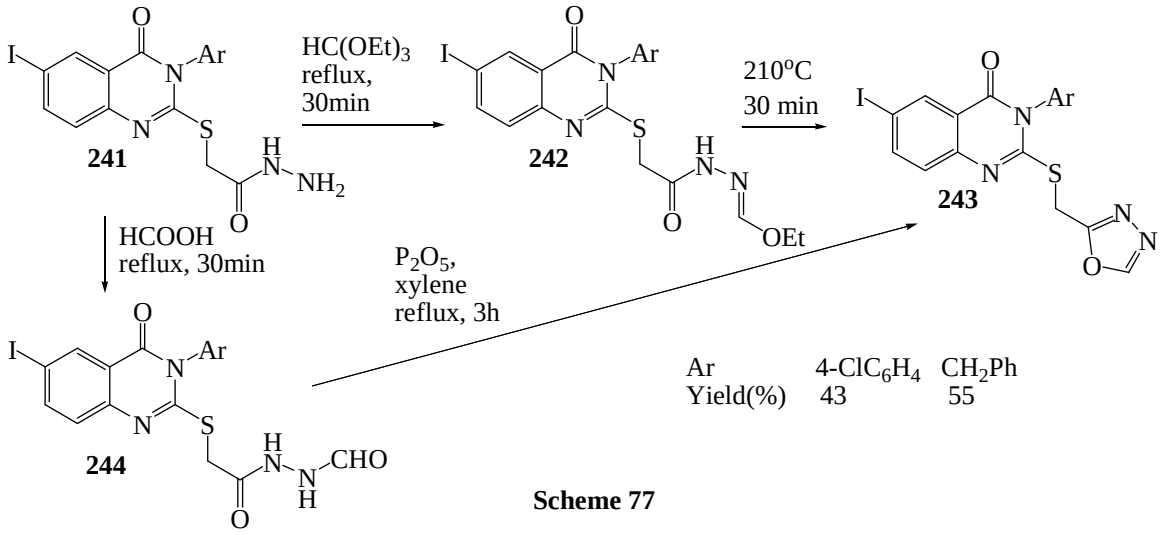


239 240

Scheme 76

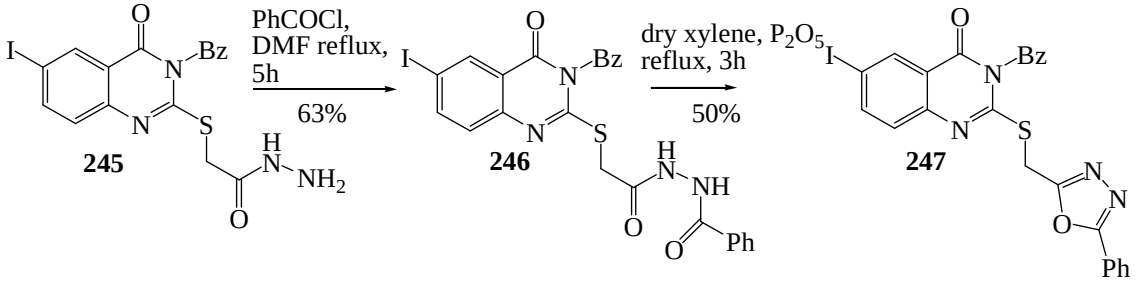
2.60Oxadiazolylmethylthioquinazolin-4(3*H*)-ones

2-[(3-(4-Chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetylhydrazine **241** and triethylorthoformate were refluxed to isolate *N*-ethoxymethine-*N*'-[2(3-(4-chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine **242** followed by thermal cyclisation yielded 2-((1,3,4-oxadiazol-2-yl)methylthio)-3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one **243**. Alternatively, **241** in formic acid was heated under reflux and the resultant N-formyl-*N*-(2-(3-(4-chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thioacetyl]-hydrazine **244** cyclised with phosphorus pentaoxide to afford compound **243**. Compounds **243** showed a remarkably broad spectrum of antimicrobial activity (Scheme 77) [59, 63].



Scheme 77

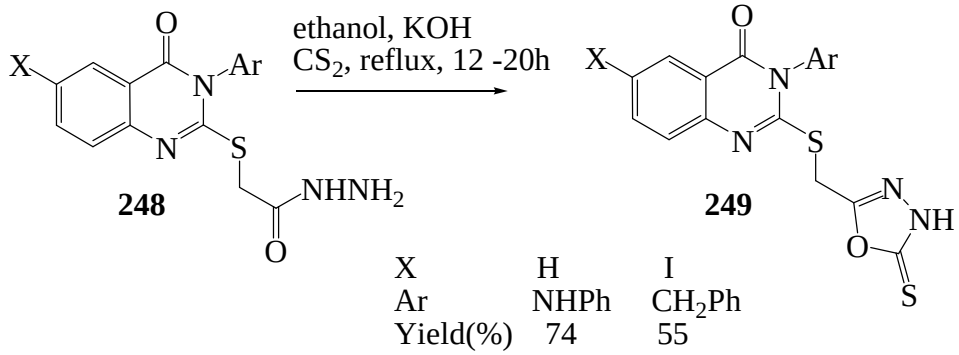
Khalil and co-workers developed an alternative method for the preparation of compounds **247** by benzoylating the compound **245** to compound **246** followed by cyclisation with phosphorus pentaoxide (Scheme 78) [63].



Scheme 78

2.61Dihydrooxadiazolylmethylsulfanylquinazolin-4(3*H*)-ones

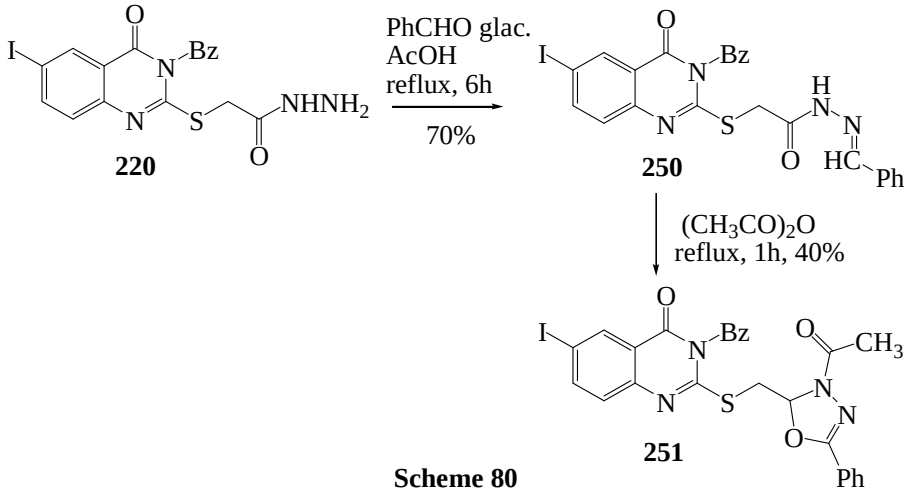
Treatment of (3-substituted quinazolin-4(3*H*)-one-2-ylthio)acetic acid hydrazide **248** with methanolic KOH and carbon disulphide afforded 3-substituted-2-(((4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)-methyl)sulfanyl)-quinazolin-4(3*H*)-one **249** (Scheme 79) [62,63].



Scheme 79

2.62Oxadiazolinylmethylthioquinazolin-4(3*H*)-one

A mixture of 2-[(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thio]acetylhydrazine (**220**) and benzaldehyde in glacial AcOH was heated under reflux to isolate *N*-benzylidine-*N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine (**250**) followed by cyclization in acetic anhydride at reflux to isolate 2-[(3-acetyl-5-phenyl-1,3,4-oxadiazolin-2-yl)methylthio]-3-benzyl-6-iodo-quinazolin-4(3*H*)-one (**251**, Scheme 80) [63].

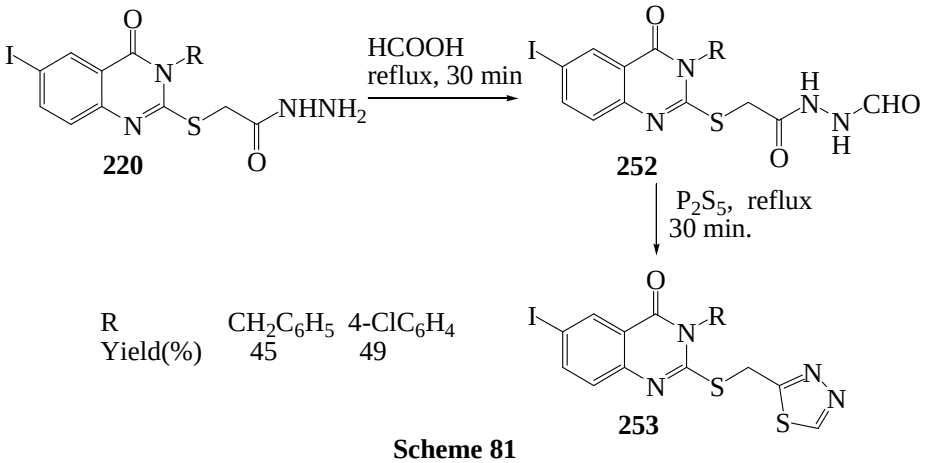


220 **250** **251**

Scheme 80

2.63Thiadiazolylmethylthioquinazolin-4(3*H*)-one

Khalil and co-workers were reacted 2-[(3-substituted-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thio] acetylhydrazine **220** with formic acid under reflux to isolate *N*-formyl-*N*-[2-(3-substituted-6-iodoquinazolin-4(3*H*)-one-2-yl)-thioacetyl]hydrazine **252** followed by treatment with phosphorus pentasulfide in xylene to isolate 2-[(1,3,4,-thiadiazol-2-yl)methylthio]-3- substituted-6-iodo-quinazolin-4(3*H*)-one **253**. These compounds identified as antitumor agents (Scheme 81) [59,63].



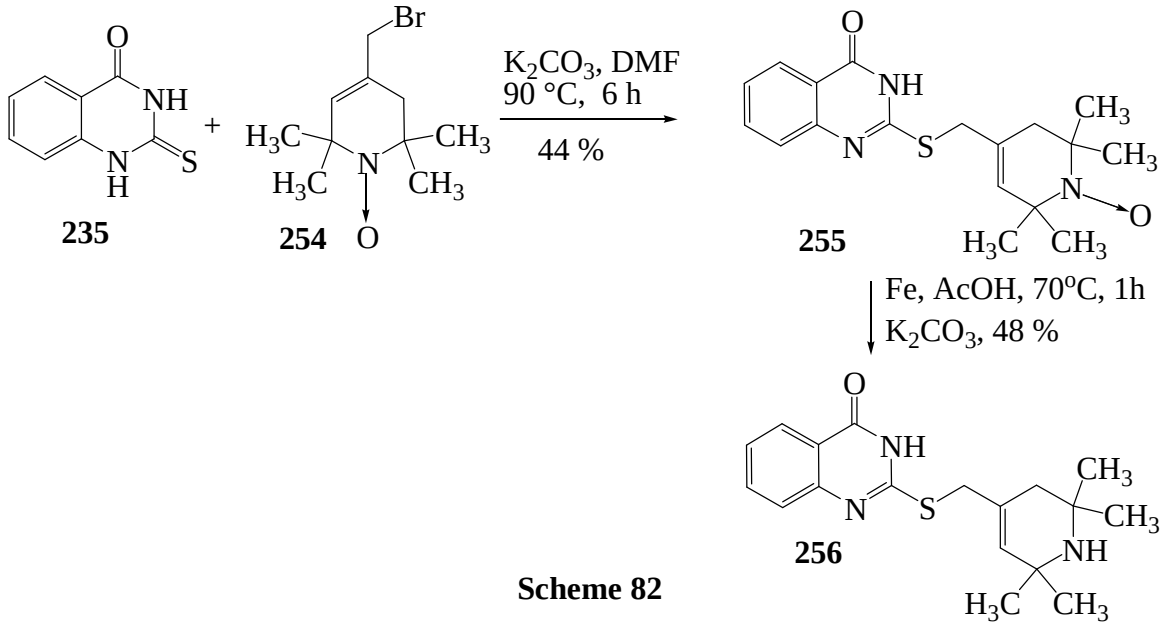
220 **252** **253**

R	$CH_2C_6H_5$	4-ClC_6H_4
Yield(%)	45	49

Scheme 81

2.64Tetrahydropyridinylmethylthioquinazolin-4(3*H*)-one

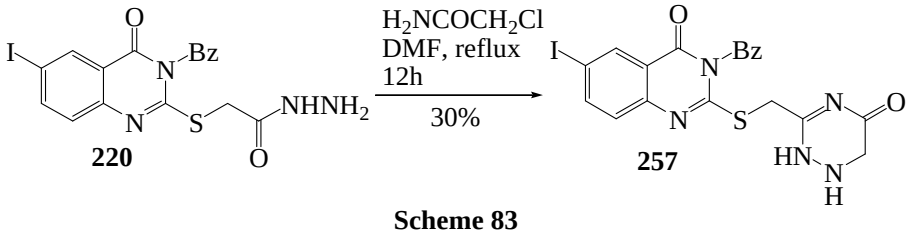
2-Mercaptoquinazolin-4(3*H*)-one (**235**) was condensed with 1-oxyl-4-(bromomethyl)-1,2,3,6-tetrahydro-2,2,6,6-tetramethylpyridine (**254**) to yield 2-{[(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl) methyl]thio}-quinazolin-4(3*H*)-one radical (**255**). The resultant nitroxide **255** was reduced with Fe powder in acetic acid to isolate 2-{[(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl]thio}-quinazolin-4(3*H*)-one (**256**, Scheme 82) [15].



Scheme 82

2.65Dihydrotriazinylmethylthioquinazolin-4(3*H*)-one.

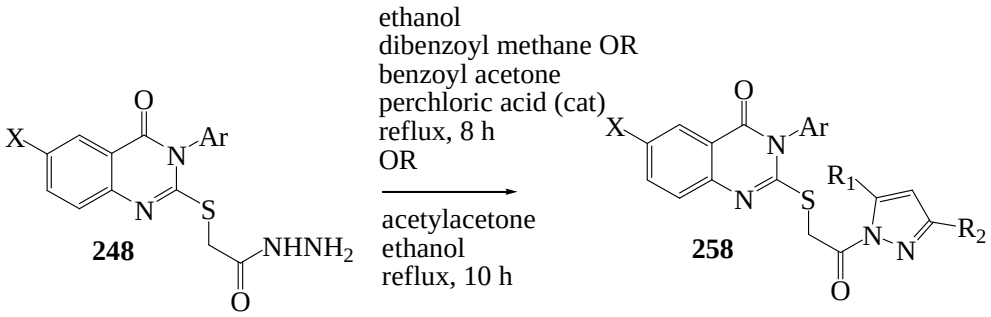
An equimolar mixture of *N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thioacetyl] hydrazine (**220**) and chloroacetamide in dimethylformamide was heated under reflux to isolate [(5-oxo-1,6-dihydro-6*H*-1,2,4-triazin-2-yl)methylthio]-3-benzyl-6-iodoquinazolin-4(3*H*)-one (**257**). These compounds identified as antitumor agents (Scheme 83) [63].



Scheme 83

2.66Pyrazoloxoethylthioquinazolin-4(3*H*)-ones

The (3-arylquinazolin-4(3*H*)-one-2-ylthio)acetic acid hydrazide **248** on reaction with benzoyl acetone or dibenzoyl methane furnished the corresponding 2-[2-(pyrazol-1-yl)-2-oxo- ethylthio]-3-arylquinazolin-4(3*H*)-ones **258**. Compound **258** (X=I, R_1=R_2=CH_3, Ar=4-Cl-C_6H_4) showed a remarkably broad spectrum of antimicrobial activity (Scheme 84) [59,62].

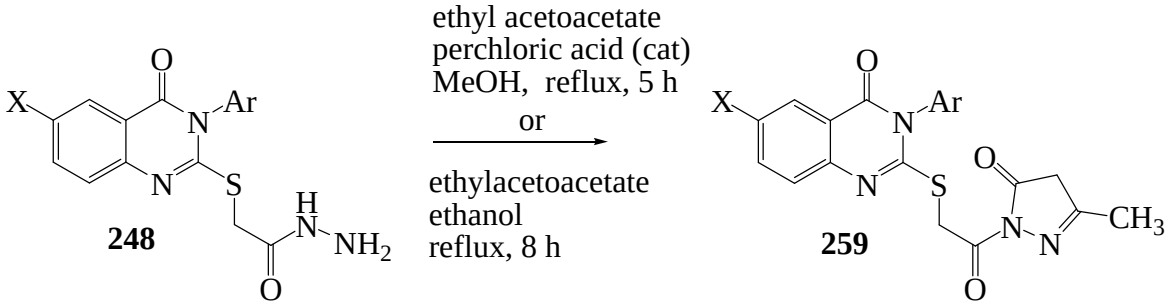


X	H	H	I	I
R1	Ph	CH_3	CH_3	CH_3
R2	Ph	Ph	CH_3	CH_3
Ar	NHPh	NHPh	4-ClC_6H_4	CH_2Ph
Yield(%)	80	72	62	55

Scheme 84

2.67Dihydropyrazolyloxoethylthioquinazolin-4(3*H*)-ones

The (3-arylquinazolin-4(3*H*)-one-2-ylthio)acetic acid hydrazide **248** on reaction with ethyl acetoacetate yielded 2-[2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-2-oxoethylthio]-3-aryl quinazolin-4(3*H*)-ones (**259**, Scheme 85) [59,62,63].

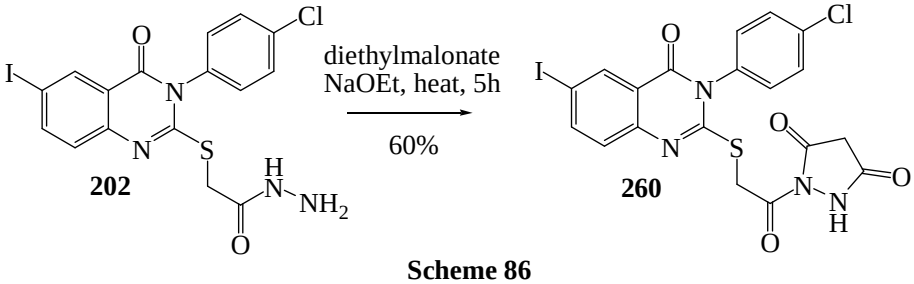


X	H	I	I
Ar	NHPh	4-ClC_6H_4	CH_2Ph
Yield(%)	65	65	50

Scheme 85

2.68Dioxopyrazolidinylcarbonylmethylthioquinazolin-4(3*H*)-one

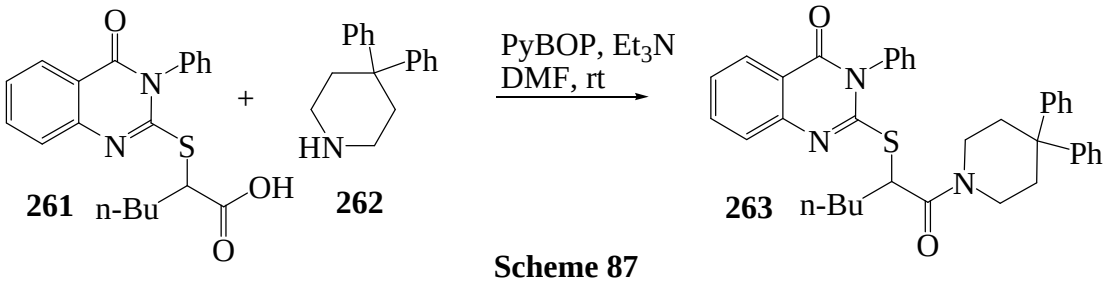
2-[(3-(4-Chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetylhydrazine (**202**) was reacted with diethylmalonate in presence of sodium ethoxide to yield 2-[3,5-dioxo-pyrazolidin-1-yl)carbonylmethylthio]-3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one (**260**, Scheme 86) [59].



Scheme 86

2.69Piperidinyloxoethylthioquinazolin-4(3*H*)-one

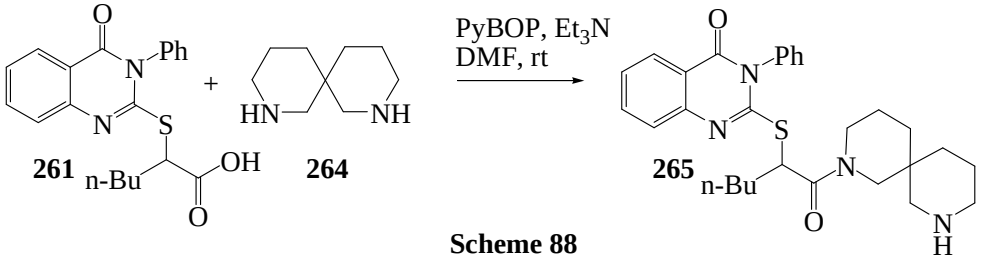
2-(3-Phenylquinazolin-4(3*H*)-one-2-ylthio)hexanoic acid (**261**) and 4,4-diphenylpiperidine (**262**) were condensed in basic medium to produce 2-(1-oxo-1-(4,4-diphenyl piperidin-1-yl)-hexan-2-ylthio)-3-phenylquinazolin-4(3*H*)-one (**263**). This compound has showed moderate antiallosteric Chk1 kinase activity (Scheme 87) [68].



Scheme 87

2.70Diazaspiro[5.5]undecanyloxoethylthioquinazolin-4(3*H*)-one

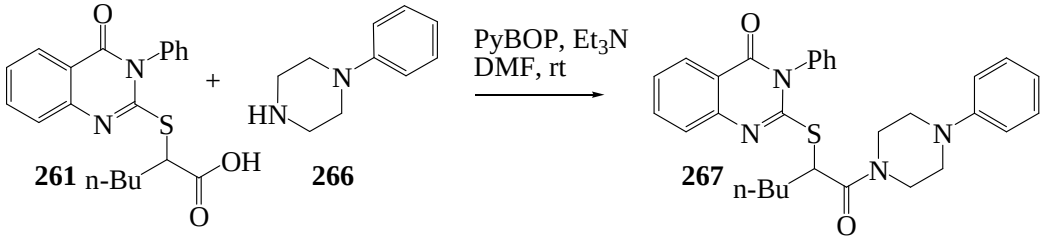
Greatest potential allosteric Chk1 kinase inhibitors have been prepared by condensing 2-(3-phenylquinazolin-4(3*H*)-2-ylthio)hexanoic acid (**261**) with 2,8-diazaspiro[5.5]undecane (**264**) in basic medium to produce 2-(1-oxo-1-(2,8-diazaspiro[5.5]undecane-2-yl)hexan -2-ylthio)-3-phenyl quinazolin-4(3*H*)-one (**265**, Scheme 88) [68].



Scheme 88

2.71Piperazinylhexanylthioquinazolin-4(3*H*)-one

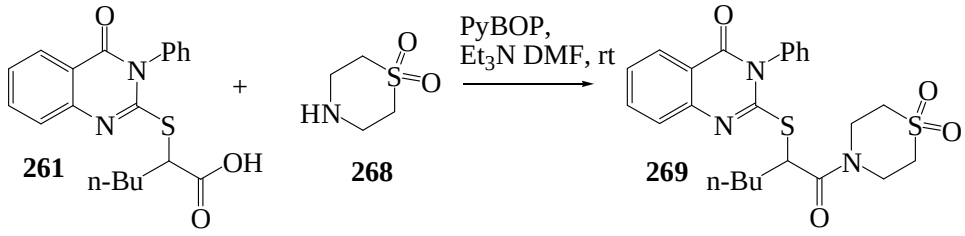
Reaction of 2-(3-phenylquinazolin-4(3*H*)-one-2-ylthio)hexanoic acid (**261**) with phenylpiperazine (**266**) yielded 2-(1-oxo-1-(4-phenylpiperazin-1-yl)hexan-2-ylthio)-3-phenyl quinazolin-4(3*H*)-one (**267**) which is a potential allosteric Chk1 kinase inhibitor (Scheme 89) [68].



Scheme 89

2.72Thiomorpholinylhexanylthioquinazolin-4(3*H*)-one

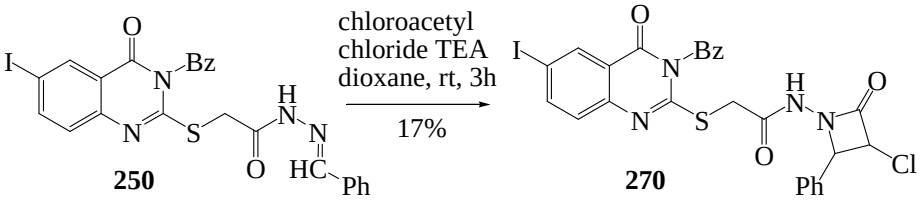
2-(3-Phenylquinazolin-4(3*H*)-one-2-ylthio)hexanoic acid (**261**) was reacted with thiomorpholine-1,1-dioxide (**268**) to isolate 2-(1-oxo-1-(thiomorpholine-1,1-dioxide-4-yl) hexan-2-ylthio)-3-phenyl quinazolin-4(3*H*)-one (**269**, Scheme 90) [68].



Scheme 90

2.73Oxoazetidinylaminooxoethylthioquinazolin-4(3*H*)-one

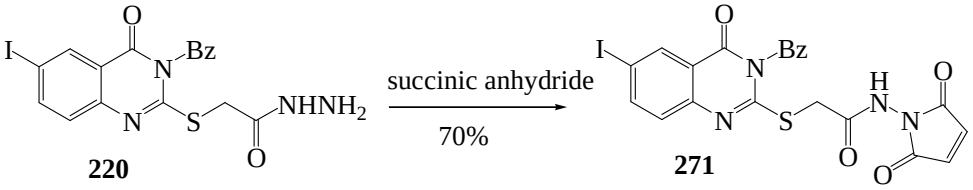
N-Benzylidine-*N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine (**250**) was reacted with chloroacetyl chloride in triethylamine to isolate *N*-(2-oxo-3-chloro-4-phenylazetidin-1-yl)-2-[(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetamide (**270**, Scheme 91) [63].



Scheme 91

2.74Dihydropyrrolylaminooxoethylthioquinazolin-4(3*H*)-one

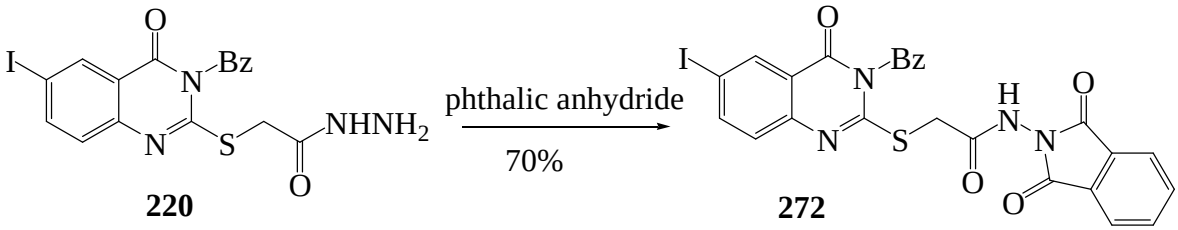
The 2-(3-benzyl-6-iodoquinazolin-4(3*H*)-one-2-ylthio)acetohydrazide (**220**) was reacted with succinic anhydride to give 2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-ylthio)-*N*-(2,5-dioxo- 2*H*-pyrrol-1(5*H*)-yl)-acetamide (**271**, Scheme 92) [63].



Scheme 92

2.75Dioxoisoindolinylaminooxoethylthioquinazolin-4(3*H*)-one

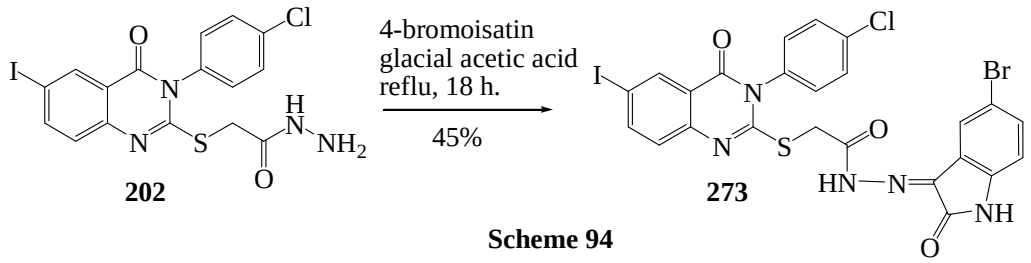
The 2-(3-benzyl-6-iodoquinazolin-4(3*H*)-one-2-ylthio)acetohydrazide (**220**) was reacted with phthalic anhydride to give 2-(3-benzyl-6-iodoquinazolin-4(3*H*)-one-2-ylthio)-*N*-(1,3-dioxo- isoindolin-2-yl)-acetamide (**272**, Scheme 93) [63].



Scheme 93

2.76Indolinylidenehydrazinooxoethylthioquinazolin-4(3*H*)-one

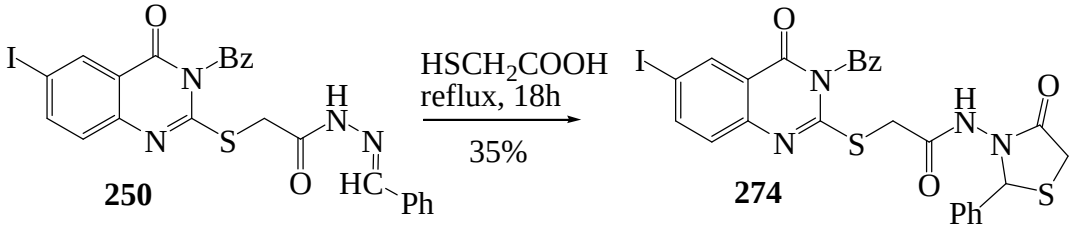
2-[(3-(4-Chlorophenyl)-6-iodoquinazolin-4(3*H*)-one-2-yl)thio]acetylhydrazine (**202**) and 4-bromoisatin were refluxed in acidic medium to afford (*E*)-*N*-(5-bromo-2-oxoindolin-3-ylidene)-2-[3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one-2-ylthio]acetohydrazide (**273**, Scheme 94) [59].



Scheme 94

2.77Thiazolidinylaminooxoethylthioquinazolin-4(3*H*)-one

N-Benzylidine-*N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine (**250**) and thioglycolic acid in dioxane was heated under reflux to isolate *N*-(2-phenyl-4-oxo-1,3-thiazolidin-3-yl)-2-[(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetamide (**274**, Scheme 95) [63].



Scheme 95

CONCLUSION

From the results presented in this review, it is evident that many of 2-heteryl and heteroalkyl quinazolin-4(3*H*)-ones are possessing a wide range of pharmacological properties and a 'drug candidate' from these heterocycles can be developed.

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