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A REVIEW ON 2-HETERYL AND HETEROALKYL-4(3*H*)-QUINAZOLINONES

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Abstract – Recent progress in the synthesis and pharmacological activity of 2-heteryl / heteroalkyl-4(3*H*)-quinazolinones is reviewed.

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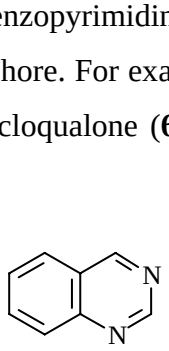
1 INTRODUCTION

Quinazoline is 1,3-diazanaphthalene (**1**). It was also known as phenmiazine, benzyleneamidine, benzo-1,3-diazine or 5,6-benzopyrimidine.[1] Its 4-oxo derivative is called 4(3*H*)-quinazolinone (**2**), and is an important pharmacophore. For example, metolazone (**3**), fenquizone (**4**), and quinethazone (**5**) are sold as diuretic drugs.[2-4] Mecloqualone (**6**, R = Cl) and methaqualone (**6**, R = CH_3) are used as sedatives and hypnotics.[5]



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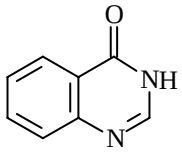

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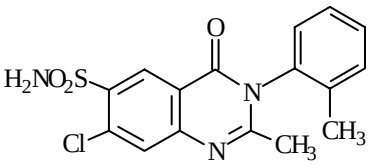

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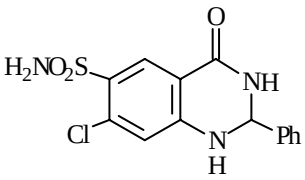

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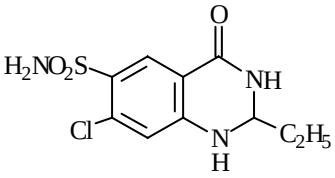

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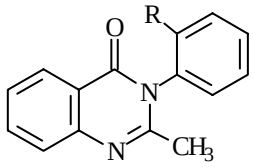


6

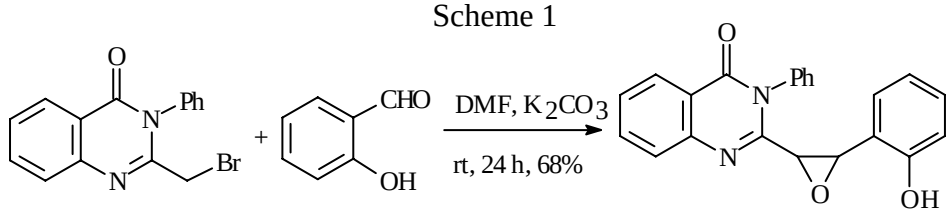
Likewise, 2-heteryl, heteroaryl and heteroalkyl-4(3*H*)-quinazolinones exhibited a wide range of pharmacological properties such as CNS depressant,[6] antimicrobial,[7-10] antibacterial,[11-15] analgesic,[16-18] antifungal,[11,19-21] antiinflammatory,[16,21-27] antiulcer,[28] anticonvulsant,[21,29-32] antihypertensive,[25,33,34] sedative,[23] anaesthetic,[23] tranquilising and muscle relaxant,[29,30] body temperature lowering,[16] spore germination inhibition in *Drechslera rostrata* and *Fussarium oxysporum*,[35] CNS active,[26,32] hypnotic,[29,30,36-38] antidepressant,[39] antihelmentic,[40] inhibition of AMPA receptor activation,[41] antihistamine,[42] virucidal,[12] hypoglycemic,[43] MAO inhibition,[44] insecticidal,[45] radioprotective,[46] spasmolytic,[47] contraceptive,[48] antitubercular,[49] antimonomine oxidase,[50] H_2-antagonist and antisecretion activity.[51] They are also useful in the treatment of gastrointestinal and appetite disorders[52] as cholecystokinin β-receptor,[53] and cholecystokinin gastric receptors.[54] They also find application as heat stable epoxy resins,[55] fiber reactive dyes,[56] and polymers.[57] In this context, the reported syntheses and importance of 2-heteryl, heteroaryl and heteroalkyl-4(3*H*)-quinazolinones 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 4(3*H*)-quinazolinone.

2.1 Oxiranyl-4(3*H*)-quinazolinone (9)

Ismail and Sayed reported the formation of 2-[3-phenyl-4(3*H*)-quinazolinone-2-yl]-3-(2-hydroxyphenyl)oxirane (**9**) in the reaction of 2-bromomethyl-3-phenyl-4(3*H*)-quinazolinone (**7**) and 2-

hydroxybenzaldehyde (**8**), conducted at room temperature in DMF containing anhydrous potassium carbonate. The reaction mechanism is analogous to Darzens condensation (Scheme 1).[58]

Scheme 1

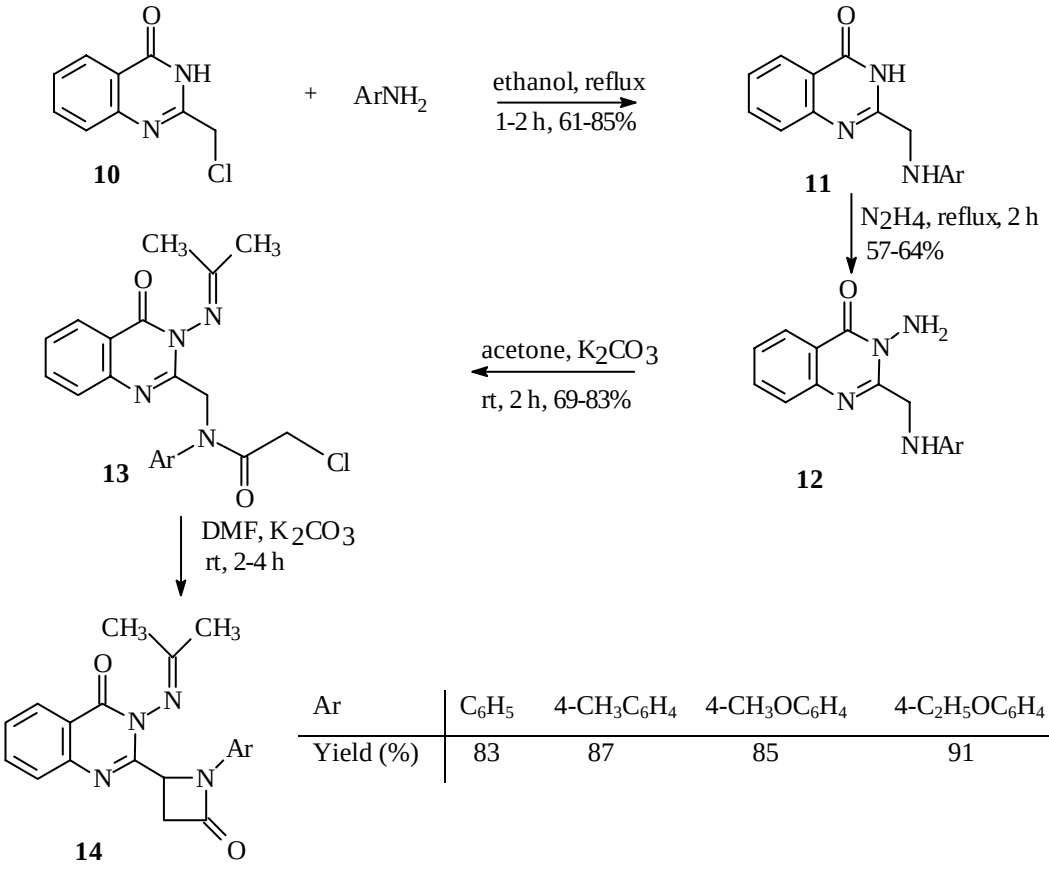


7 **8** **9**

2.2 Azetidinyl-4(3*H*)-quinazolinones (14)

This heterylquinazolinone was prepared starting from 2-chloromethyl-4(3*H*)-quinazolinone (**10**). Reaction of **10** with arylamine yielded 2-arylaminomethyl-4(3*H*)-quinazolinone (**11**). Conversion of **11** to 3-amino-2-arylaminomethyl-4(3*H*)-quinazolinone (**12**), and its chloroacetyl derivative - 2-*N*-chloroacetylarylaminomethyl-3-isopropylidineamino-4(3*H*)-quinazolinone (**13**), are the key steps in the synthesis of 2-(azetidin-2-one-4-yl)-4(3*H*)-quinazolinone (**14**). Base catalyzed dehydrochlorinative cyclization of **13** to **14** was achieved by stirring it in DMF containing K_2CO_3 at room temperature (Scheme 2).[59]

Scheme 2



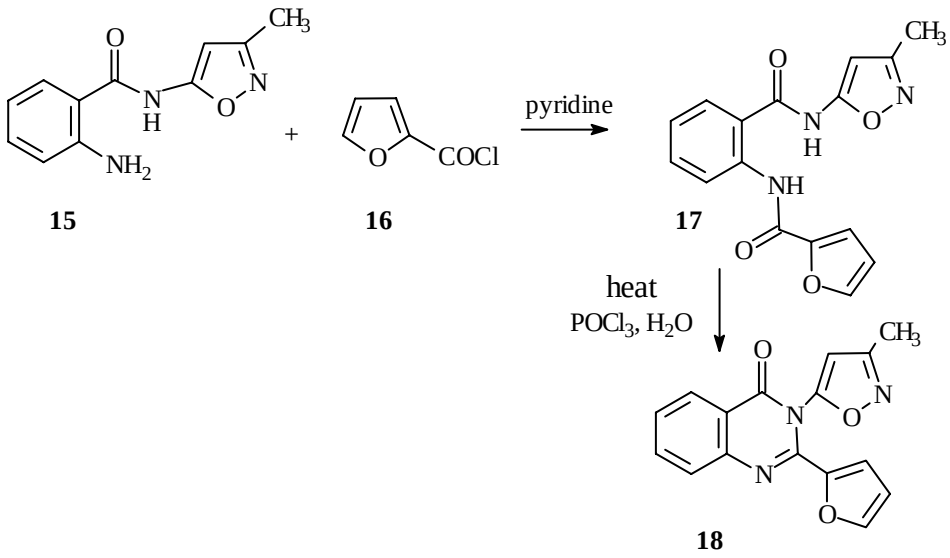
10 **11** **12** **13** **14**

Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	4-$C_2H_5OC_6H_4$	4-ClC_6H_4
Yield (%)	83	87	85	91	88

2.3 Furyl-4(3*H*)-quinazolinones (18, 20, 22)

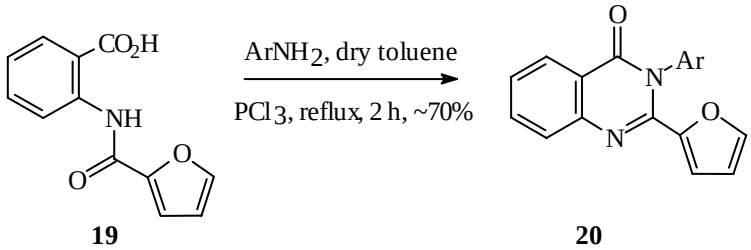
3-(3-Methyl-5-isoxazolyl)-2-(2-furyl)-4(3*H*)-quinazolinone (**18**) is an useful analgesic, antiinflammatory and body temperature lowering agent.[16] 5-[(2-Aminobenzoyl)amino]-3-methylisoxazole (**15**) was reacted with furfuroyl chloride (**16**) in pyridine to obtain 5-[2-(2-furoylamino)benzoylamino]-3-methylisoxazole (**17**). Dehydrative cyclization of **17** to yield **18** was achieved by heating in $POCl_3$ (Scheme 3).

Scheme 3



Subba Rao prepared 2-(2-furyl)-3-aryl-4(3*H*)-quinazolinone derivatives (**20)** by condensing *N*-(2-furoyl)anthranilic acid (**19)** with primary amines. The quinazolinones (**20)** showed antibacterial, antifungal, and piscicidal activity (Scheme 4).[11]

Scheme 4

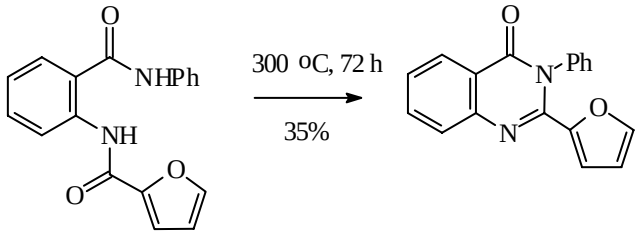


Ar = C_6H_5, 2–$CH_3C_6H_4$, 3–$CH_3C_6H_4$, 4–$CH_3C_6H_4$, 2–$CH_3OC_6H_4$, 4–$CH_3OC_6H_4$, 2–ClC_6H_4, 4–ClC_6H_4, 2,4–$Cl_2C_6H_3$, 3,4–$Cl_2C_6H_3$, 2,5–$Cl_2C_6H_3$, 2,4,6–$Br_3C_6H_2$, 2–$NO_2C_6H_4$, 3–$NO_2C_6H_4$, 4–$NO_2C_6H_4$

Ramana and Yuvaraj reported *ortho* interaction of the anilide function and *N*-acyl group in 2-(2-furoylamino)benzanilide (**21**), under electron impact, that led to dehydrative cyclization of the molecular ion.[60] The mechanism and the ion structures proposed in the mass spectral study are supported by high resolution data and Collision Activated Decomposition (CAD)-B/E linked scan spectra. This observation

was successfully translated into a laboratory synthesis by the thermolysis of **21**, and isolating 2-(2-furyl)-4(3*H*)-quinazolinone (**22**) from the pyrolysate in 35% yield (Scheme 5).

Scheme 5

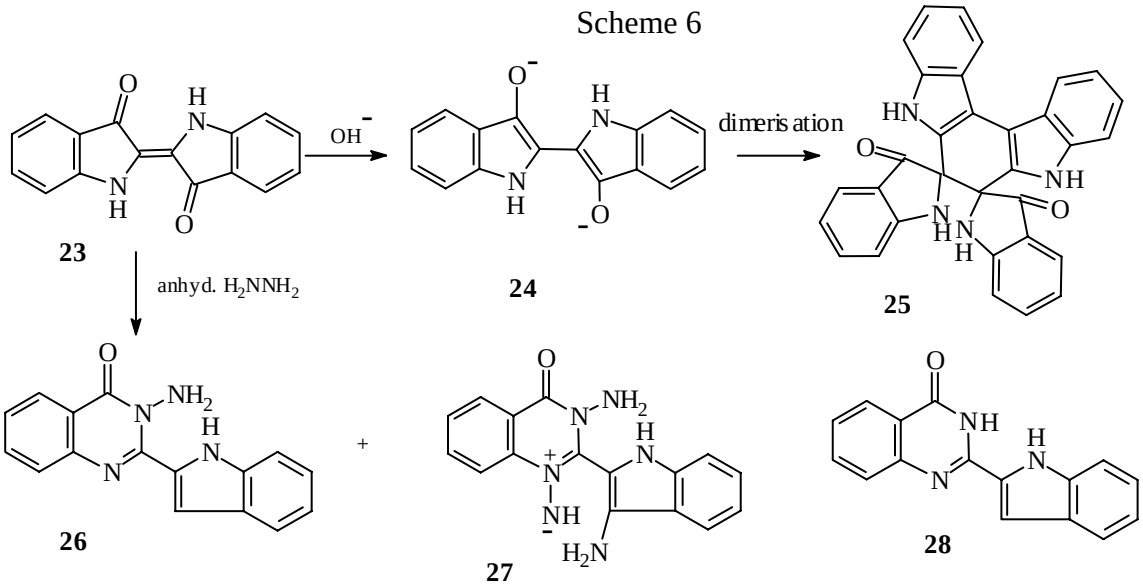


21 **22**

2.4 Indolyl–4(3*H*)-quinazolinones (27,28)

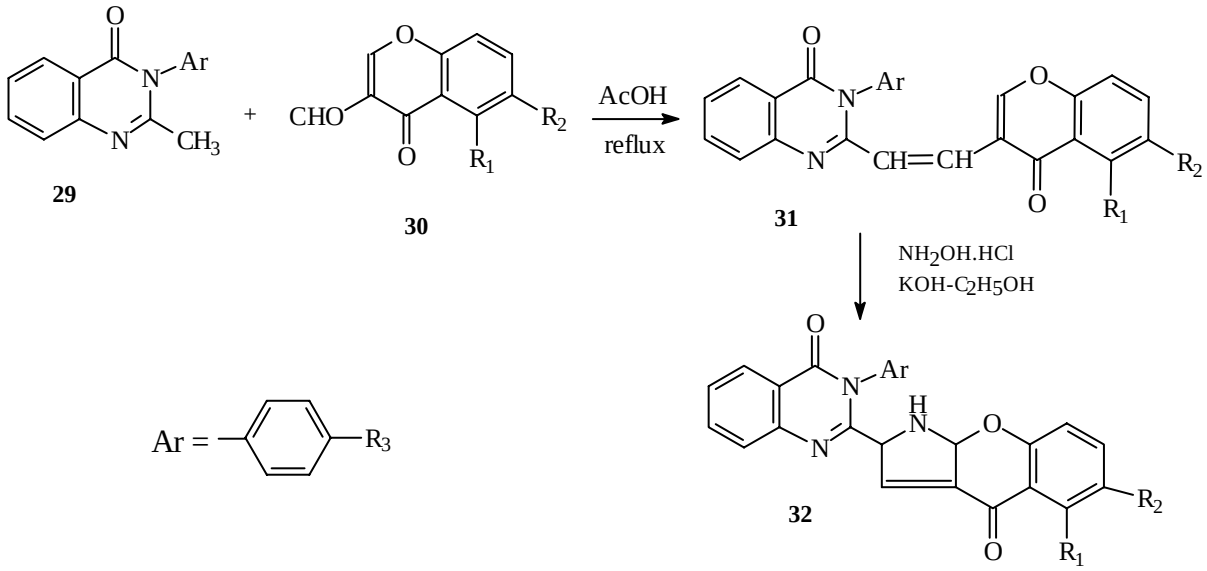
Bergman and co-workers studied the reaction of indigo (**23**) and hydrazine under basic conditions. In the presence of a strong base, the anion (**24)** was formed and rapidly underwent oxidative dimerisation to **25**.[61,62] However, anhydrous hydrazine converts indigo to 3-amino-2-(2'-indolyl)-4(3*H*)-quinazolinones (**26)** and (**27)**, depending on the temperature at which the reaction was conducted. Reduction of **26** and **27** with Raney nickel gave 2-(2'-indolyl)-4(3*H*)-quinazolinones (**28**, Scheme 6).

Scheme 6



Acid catalysed condensation of 3-formylchromones (**29**) with 3-aryl-2-methyl-4(3*H*)-quinazolinones (**30**) yielded the styryl derivatives (**31**), which reacted with hydroxylamine hydrochloride in alcoholic potassium hydroxide to yield the corresponding 3-aryl-4(3*H*)-quinazolinon-2-yl)-pyrrolino[5,4-*b*]-2,3-dihydro-4*H*-[1]-benzopyran-4-ones (**32**). These compounds showed significant antimicrobial activity (Scheme 7).[7]

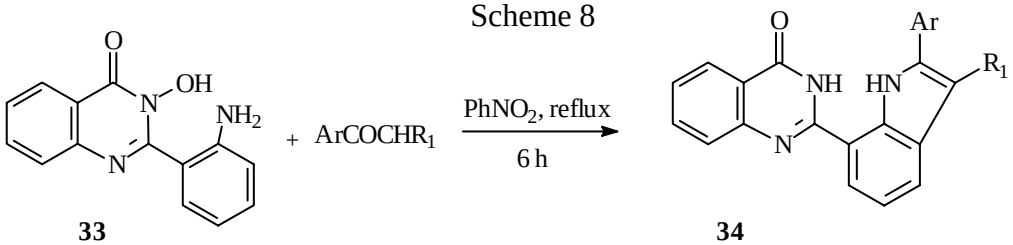
Scheme 7



R_1	H	H	H	CH_3	H	H	H	CH_3	H	H	H	CH_3
R_2	H	Cl	CH_3	Cl	H	Cl	CH_3	Cl	H	Cl	CH_3	Cl
R_3	H	H	H	H	CH_3	CH_3	CH_3	CH_3	CH_3	Br	Br	Br
Yield (%)	56	60	58	62	64	55	62	55	55	62	65	64

A novel bisazaheterocycle, indolyl-4(3*H*)-quinazolinones (**34**) was recently synthesized in our laboratory. When a mixture of 2-(2-aminophenyl)-3-hydroxy-4(3*H*)-quinazolinone (**33**) and an aryl ketone was refluxed in nitrobenzene, 2-(2-aryl-1*H*-7-indolyl)-3,4-dihydro-4-quinazolinone (**34**) was obtained in one-step (Scheme 8).[63]

Scheme 8

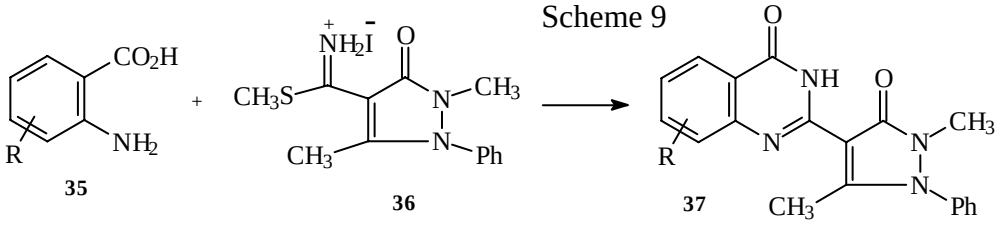


R	H	H	H	H	H	CH_3	C_6H_5
Ar	C_6H_5	4-$CH_3C_6H_4$	4-ClC_6H_4	4–$NO_2C_6H_4$	2–HOC_6H_4	H	$CH_2C_6H_5$
Yield (%)	68	81	78	74	71	69	79

2.5 Pyrazolyl-4(3*H*)-quinazolinones (37, 41, 44, 47, 49, 50, 53)

Reaction of an anthranilic acid (**35)** with 4-thioimidemethiodidoantipyrine (**36**) was found to be the most feasible route for preparing 2-(4-antipyrinyl)-4(3*H*)-quinazolinones (**37**, Scheme 9).[64]

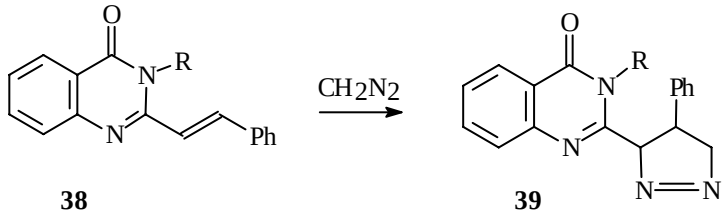
Scheme 9



R = H, 6–Cl, 7–Cl, 6–Br, 6–CH_3

In an alternative synthesis, 1,3-dipolar addition of diazomethane to C=C bond in 3-alkyl-2-styryl-4(3*H*)-quinazolinone (**38**) yielded 3-aryl-2-(4-phenylpyrazolin-3-yl)-4(3*H*)-quinazolinones (**39**) in good yields (Scheme 10).[65] No further details are reported about this reaction.

Scheme 10

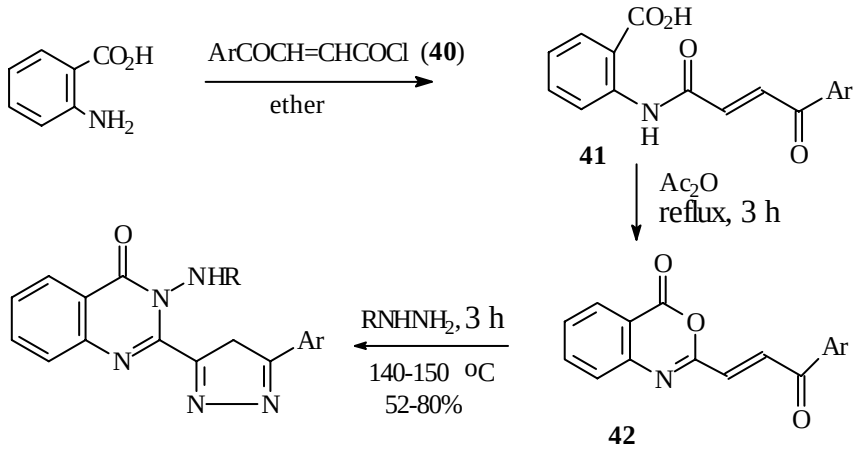


38 **39**

R = C_4H_9, C_6H_5, 4–$CH_3C_6H_4$, 2–$CH_3C_6H_4$, 4–$CH_3OC_6H_4$, 2–ClC_6H_4, 3-$NO_2C_6H_4$

Soliman and co-workers reported the synthesis of 2-pyrazolyl-4(3*H*)-quinazolinones (**43**) and (**44)** starting from 3-aroylpropenoyl chloride (**40**). [66-68] Anthranilic acid (**35**) reacts with **40** in ether to afford the benzoic acid (**41)**, which was cyclized to the benzoxazinone (**42)** by refluxing in acetic anhydride for 3 h. The benzoxazinone (**42)** reacted with hydrazine hydrate and with phenylhydrazine to yield 2-[5'-(3'-aryl-4',5'-dihydropyrazolyl)]-3-amino-4(3*H*)-quinazolinones (**43**) and 2-(1'-phenyl-3'-aryl-4',5'-dihydropyrazolyl)-3-phenylamino-4(3*H*)-quinazolinones (**44**), respectively (Scheme 11).

Scheme 11

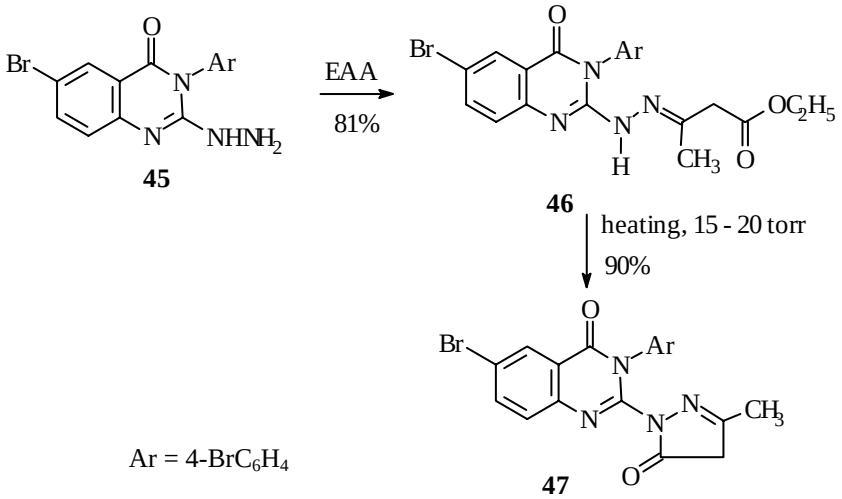


43 NHR = 4-ClC_6H_4CH=N, 4-$CH_3OC_6H_4CH$=N, $(CH_3)_2C$=N, $C_6H_{11}NHCONH$, $C_6H_5CONHCONH$, NH_2; phthalimido, Ar = 2, 4, 6-$(CH_3)_3C_6H_2$

44 R = H, Ph; Ar = 4–$CH_3C_6H_4$, 2, 4–$(CH_3)_2C_6H_3$

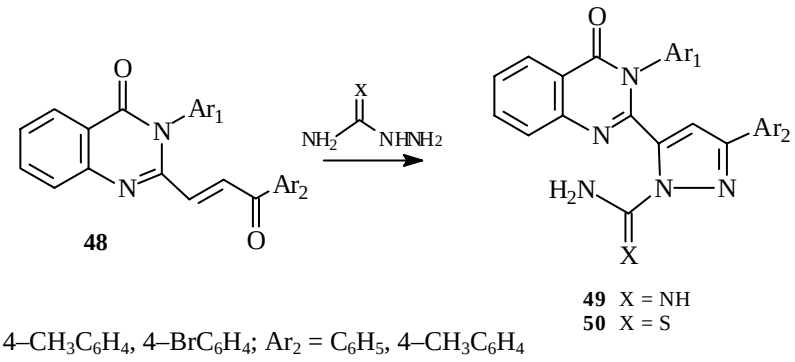
2-(1-(3-Methylpyrazolyl))-4(3*H*)-quinazolinone (**47**) was prepared in two-steps from 6-bromo-3-(4-bromophenyl)-2-hydrazino-4(3*H*)-quinazolinone (**45**). First, **45** was condensed with ethyl acetoacetate (EAA) and the hydrazone (**46)** was isolated in 81% yield. On heating in vacuum (15-20 torr) at its melting point, **46** yielded **47** (Scheme 12).[69]

Scheme 12



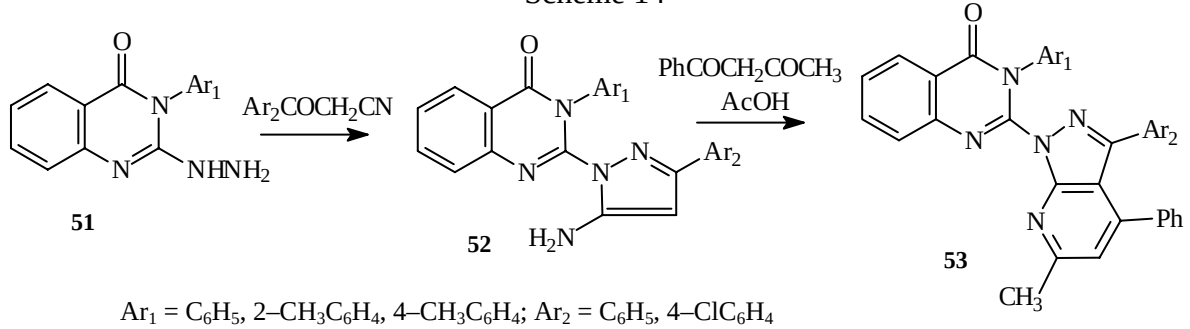
Khilil and co-workers prepared two novel quinazolinones (**49**) and (**50**) from the key intermediate, 3-aryl-2-(3-oxopropenyl)-4(3*H*)-quinazolinones (**48**).[70] For example, **48** reacted with aminoguanidine to give 3-aryl-2-(3-aryl-1-iminocarbamoyl-1*H*-pyrazol-5-yl)-4(3*H*)-quinazolinones (**49**). With thiosemicarbazide, **48** yielded 3-aryl-2-(3-aryl-thiocarbamoyl-1*H*-pyrazol)-4(3*H*)-quinazolinones (**50**, Scheme 13).

Scheme 13



El-Feky synthesized 2-pyrazolo[3,4-*b*]pyridylquinazolinone (**53)** starting from 2-hydrazino-3-aryl-4(3*H*)-quinazolinone (**51**).[71] The hydrazine (**51)** condensed with cyanoacetophenones to give 2-(3-aryl-5-aminopyrazolyl)-3-aryl-4(3*H*)-quinazolinones (**52**). Subsequent reaction of **52** with benzoylacetone in glacial acetic acid afforded **53 (**Scheme 14).

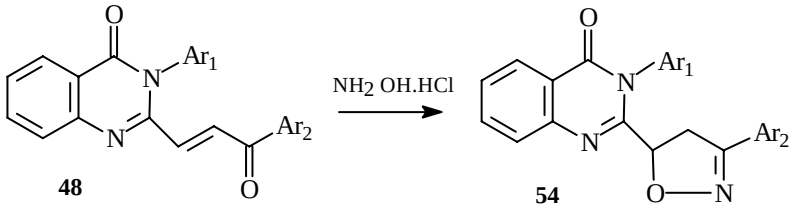
Scheme 14



2.6 Oxazolyl-4(3*H*)-quinazolinones (54)

3-Aryl-2-(3-oxopropenyl)-4(3*H*)-quinazolinones (**48**) reacted with hydroxylamine hydrochloride to yield 3-aryl-2-(3-aryl-4,5-dihydro-1,2-oxozol-5-yl)-4(3*H*)-quinazolinones (**54**, Scheme 15).[70]

Scheme 15

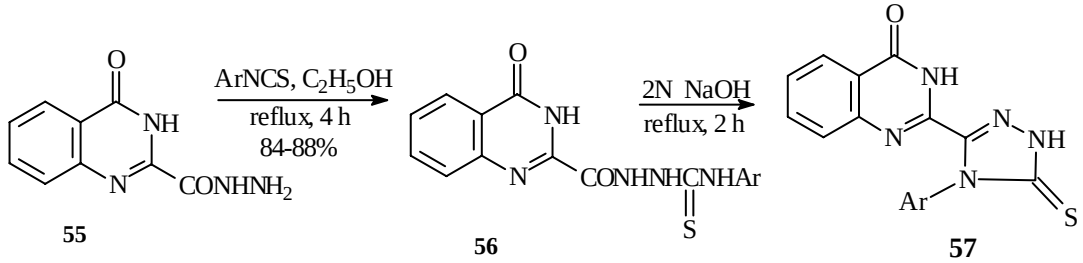


Ar_1 = C_6H_5, 4–$CH_3C_6H_4$, 4–BrC_6H_4; Ar_2 = C_6H_5, 4–$CH_3C_6H_4$

2.7 Triazolyl-4(3*H*)-quinazolinones (57)

The single report concerning the preparation of 2-(arylthiotriazolyl)-3-aryl-4(3*H*)-quinazolinones (**57**), involves the condensation of 2-hydrazinocarbonyl-4(3*H*)-quinazolinones (**55**) with arylisothiocyanates in refluxing ethanol. The resulting 4-aryl-1-[4(3*H*)-quinazolinone-2-yl]-2-carbonylthiosemicarbazides (**56**) were cyclized to **57** by refluxing in 2N sodium hydroxide solution (Scheme 16).[72]

Scheme 16

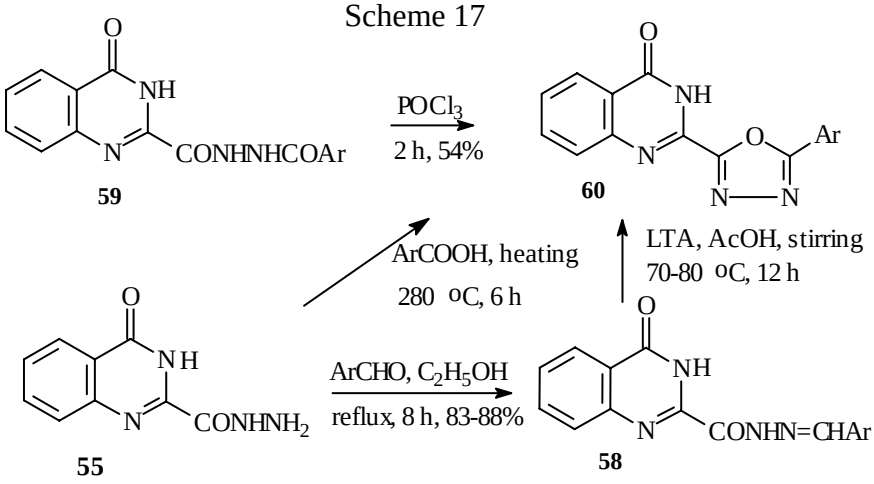


Ar	C_6H_5	4–$CH_3OC_6H_4$	4–ClC_6H_4	4–BrC_6H_4
Yield (%)	84	85	80	82

2.8 Oxadiazolyl-4(3*H*)-quinazolinones (60)

Synthesis of 2-[2-(5-aryl-1,3,4-oxadiazolyl)-4(3*H*)-quinazolinones (**60**) was first reported by George and co-workers by reacting aroylhydrazinocarbonyl-4(3*H*)-quinazolinones (**59)** with $POCl_3$.[73] As an alternative synthesis, Reddy and Reddy prepared **60** by lead tetraacetate (LTA) oxidation of 2-arylidenehydrazinocarbonyl-4(3*H*)-quinazolinones (**58**).[74] The required hydrazone (**58)** was obtained by reacting **55** with aromatic aldehydes in ethanol medium. They also synthesized 2-oxadiazolyl-4(3*H*)-quinazolinones (**60)** in one-step by dry heating a solid mixture of **55** and aromatic acid at 280 ^{0}C for 6 h. The yields, however, were 42 – 48% in this thermal reaction (Scheme 17).[74]

Scheme 17



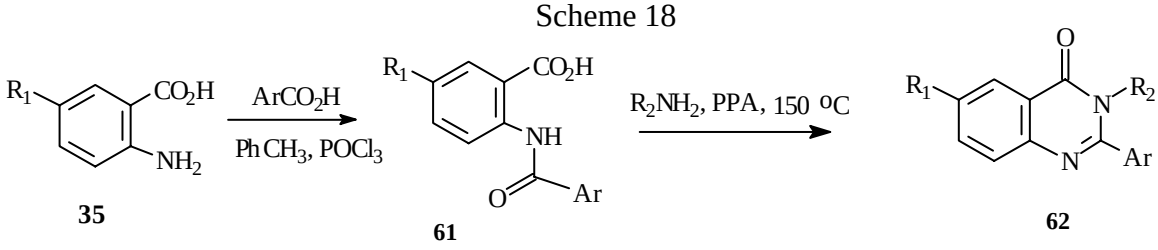
Ar =

R	H	4–CH_3	4–OCH_3	3–NO_2	4–NO_2	3–Cl	4–Cl
Yield (%) pyrolysis	45	46	48	42	44	40	45
Yield (%) LTA	66	68	70	60	66	62	65

2.9 Pyridyl-4(3*H*)-quinazolinones (62, 65, 67)

The three isomers - 2-(2/3/4-pyridyl)-3-alkyl-4(3*H*)-quinazolinones (**62**) have exhibited hypnotic, analgesic, anti-inflammatory, anticonvulsant, sedative, anaesthetic and muscle relaxant properties. Hisano and co-workers reported the preparation of 2-(2-pyridyl)-3-aryl-4(3*H*)-quinazolinones (**62**) from 2-nicotinaminobenzoic acids (**61**) and arylamines. The required amides were obtained by reacting the anthranilic acid (**35)** with picolinic acids in toluene containing phosphorous oxychloride. Use of 3-picolinic acid in the reaction yielded the isomer, (Scheme 18).[75]

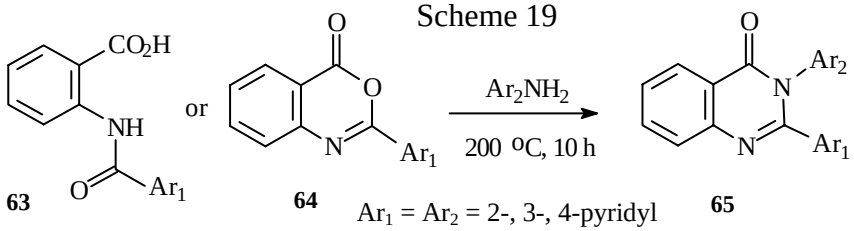
Scheme 18



R_1 = H, NO_2; R_2 = 4-ClC_6H_4, 4–$NO_2C_6H_4$, 4–$CH_3C_6H_4$; Ar = 2-, 3-, 4-pyridyl

Noda and co-workers prepared 2,3-bis(pyridyl)quinazolinones (**65**) by heating *N*-pyridylcarboxyl-anthranilic acids (**63**) or 2-pyridylbenzoxazinones (**64**) with pyridylamines at 200 ^{0}C for 10 h (Scheme 19).[23]

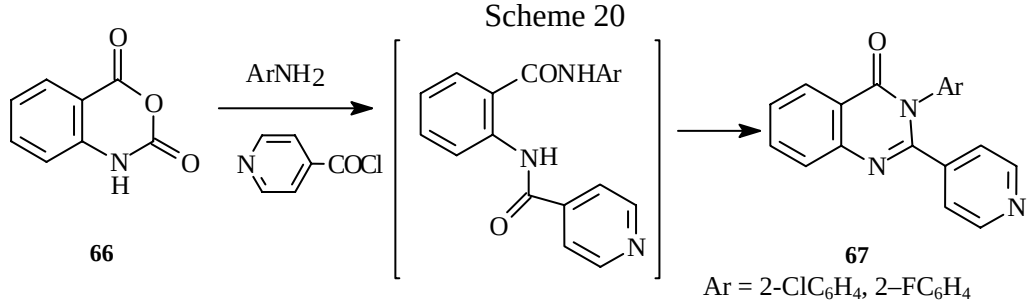
Scheme 19



Ar_1 = Ar_2 = 2-, 3-, 4-pyridyl

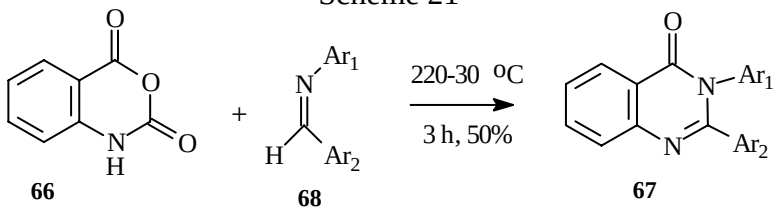
Hisano and co-workers have also reported a one-pot synthesis of 2-(4-pyridyl)-3-aryl-4(3*H*)-quinazolinone (**67**), an isomer of **62,** by reacting isatoic anhydride (**66**) with isonicotinoyl chloride and aromatic amines. Compounds (**67**) showed promising hypnotic effect in intraperitonial doses above 100 mg/kg (Scheme 20).[36]

Scheme 20



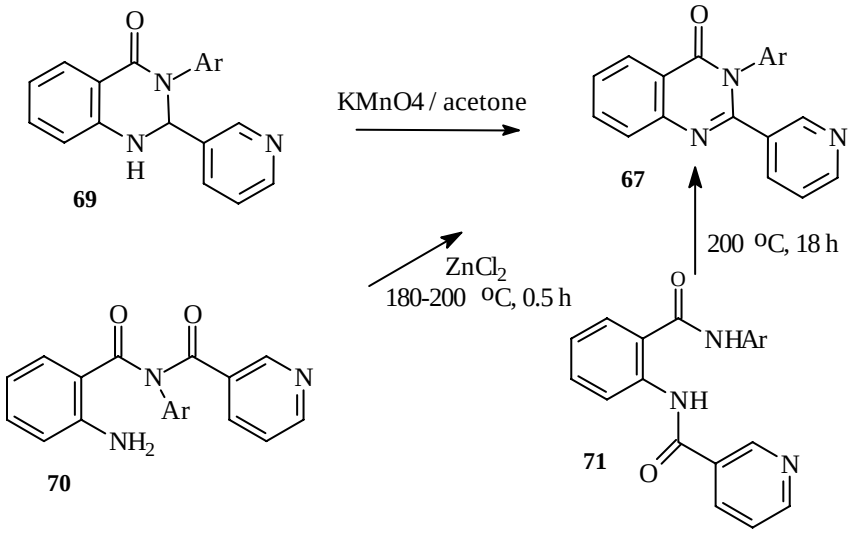
3-Aryl-2-pyridyl-4(3*H*)-quinazolinones (**67**) were also prepared by heating isatoic anhydride (**66**) with arylideneanilines (**68**) (Scheme 21).[76]

Scheme 21



Alternatively, 2-(3-pyridyl)-3-(2-tolyl)-4(3*H*)-quinazolinones (**67**) were synthesised by permanganate oxidation of 2-(3-pyridyl)-3-(2-tolyl)-1,2-dihydro-4(3*H*)-quinazolinones (**69**) in acetone. The compounds (**67**) also prepared by cyclising 2-amino-*N*-acylbenzanilides (**70**) or 2-nicotinamidobenzanilide (**71**) medium (Scheme 22).[77, 78]

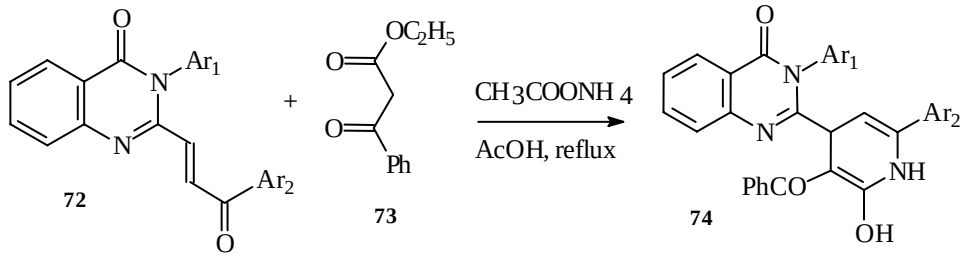
Scheme 22



2.10 Piperidinonyl-4(3*H*)-quinazolinones (69)

Salem and co-workers reported the synthesis of several 2-heterylquinazolinone derivatives by Michael addition of active methylene nucleophiles to 2-[(3-chloro-4-methylbenzoyl)vinyl-3-(4-methylphenyl)-4(3*H*)-quinazolinones (**72**).[79] Thus, 2-piperidinonyl-3-(4-methylphenyl)-4(3*H*)-quinazolinones (**74**) were the products when the quinazolinone derivative (**72**) was refluxed with ethyl benzoylacetate (**73**) in acetic acid containing ammonium acetate (Scheme 23).

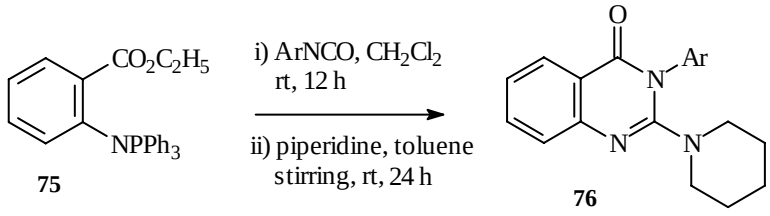
Scheme 23



Ar_1 = 4–$CH_3C_6H_4$; Ar_2 = 3-Cl-4-$CH_3C_6H_3$

2-Piperidino-3-aryl-4(3*H*)-quinazolinones (**76**) were prepared by an aza-Wittig reaction of ethyl anthranilate ylide (**75**) with aryl isocyanates and piperidine under mild conditions (Scheme 24).[80]

Scheme 24

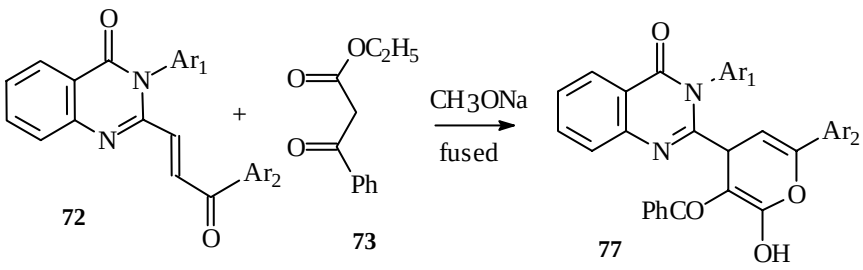


Ar	C_6H_5	4–ClC_6H_4
Yield (%)	86	72

2.11 Pyranyl-4(3*H*)-quinazolinones (77)

Salem and co-workers reported the synthesis of 3-(4-methylphenyl)-2-[4-(3-benzoyl-6-(3-chloro-4-tolyl)-5-ene-3,4-dihydro-2-oxo-2*H*-pyran-4-yl)]-4(3*H*)-quinazolinones (**77)** by the reaction of 2-[(3-chloro-4-methylbenzoyl)vinyl-3-(4-methylphenyl)-4(3*H*)-quinazolinones (**72**) with ethyl benzoylacetate (**68**) in the presence of sodium methoxide (Scheme 25).[79]

Scheme 25

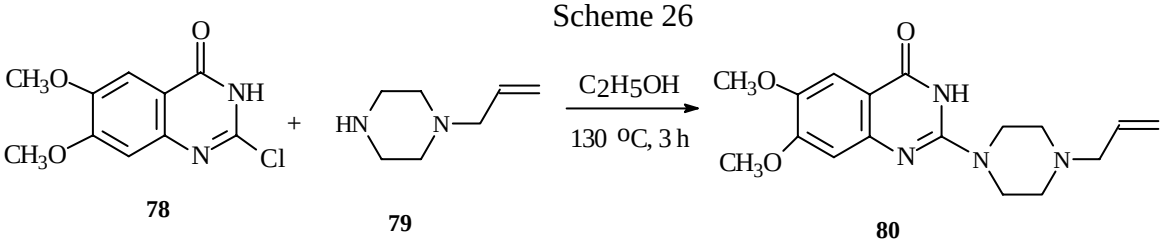


Ar_1 = 4–$CH_3C_6H_4$; Ar_2 = 3-Cl-4-$CH_3C_6H_3$

2.12 Diazino-4(3*H*)-quinazolinones (80, 82, 83)

2-(4-Allyl-1-piperazinyl)-4(3*H*)-quinazolinone (**80**) showed promising antihypertensive activity. It was prepared by heating 2-chloro-6,7-dimethoxy-4(3*H*)-quinazolinone (**78**) with *N*-allyl piperazine (**79**) in ethanol in a pressure bottle at 130 ^{0}C for 3 h (Scheme 26).[33]

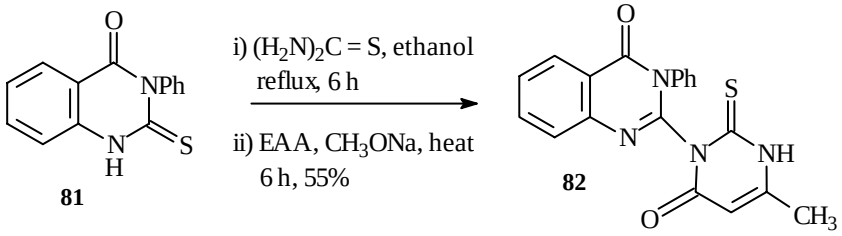
Scheme 26



78 **79** **80**

El-Desuky and co-workers reported a one pot synthesis of 3-phenyl-2(4-methyl-6-oxo-2-thioxo-1-pyrimidinyl-4(3*H*)-quinazolinone (**82**) by reacting 3-phenyl-2-thioxo-4-oxo-1,2,3,4-tetrahydroquinazoline (**81**) with thiourea and ethyl acetoacetate (EAA).[81] The mechanism involves the initial formation of a pyrimidine which then substitutes the thiol group at C-2 of the quinazolinone moiety.

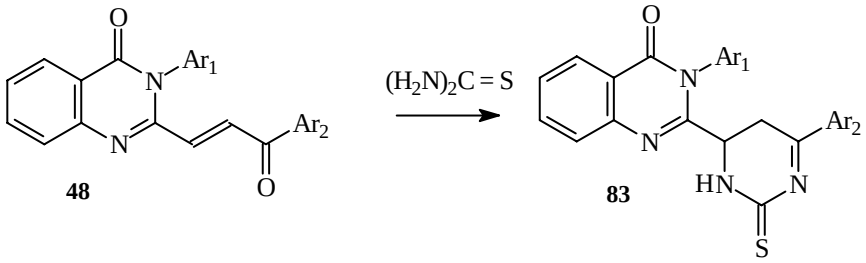
Scheme 27



81 **82**

Khilil and co-workers prepared 3-aryl-2-(4-aryl-2-thio-1,2,5,6-tetrahydro-1,3-pyrimidin-6-yl)-4(3*H*)-quinazolinones (**83**) by reacting the key intermediate, 3-aryl-2-(3-oxopropenyl)-4(3*H*)-quinazolinones (**48**) and thiourea (Scheme 28).[70]

Scheme 28



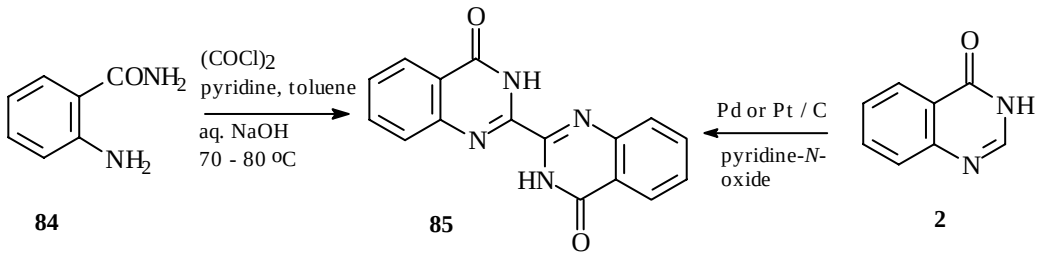
48 **83**

Ar_1 = C_6H_5, 4–$CH_3C_6H_4$, 4-BrC_6H_4, Ar_2 = C_6H_5, 4–$CH_3C_6H_4$

2.13 2,2'-Bis-4(3*H*)-quinazolinones (85, 86)

Symmetrical 2,2'-bis-4(3*H*)-quinazolinone (**85**) is useful as a heat resistant whitening agent. It was prepared by a base catalysed reaction of 2-aminobenzamide (**84**, 2 moles) with oxalyl chloride (1 mole). An alternative method involves dimerisation of 4(3*H*)-quinazolinone (**2**) in the presence of pyridine-1-oxide and Pd or Pt/C (Scheme 29).[82,83]

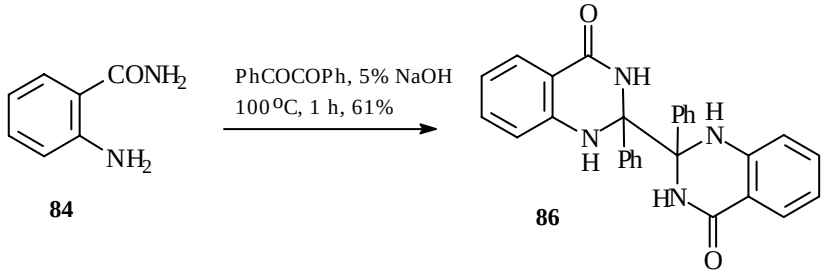
Scheme 29



84 **85** **2**

Anthranilamide (**84**) also reacts with benzil to give 2,2'-diphenyltetrahydro-2,2'-bisquinazoline-4,4'-dione (**86**) in 61% yield (Scheme 30).[84]

Scheme 30

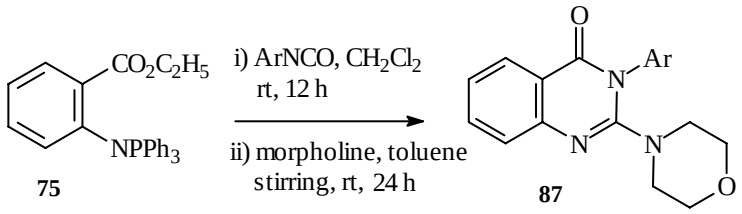


84 **86**

2.14 Morpholinyl-4(3*H*)-quinazolinones (87)

Ming-Wu Ding and co-workers prepared 2-morpholinyl-3-aryl-4(3*H*)-quinazolinones (**87**) by aza-Wittig reaction of ethyl anthranilate ylide (**75**) with a mixture of aromatic isocyanates and morpholine under mild conditions (Scheme 31).[80]

Scheme 31



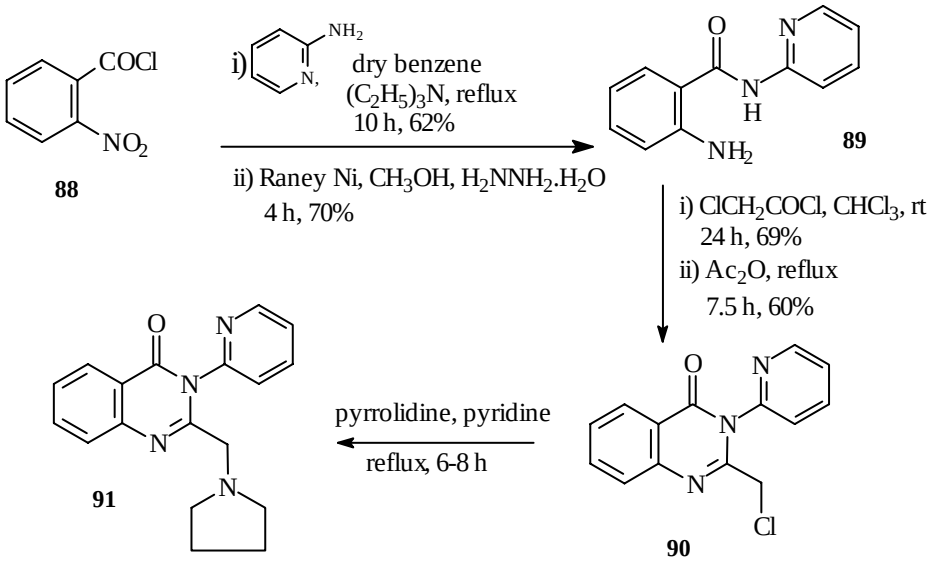
75 **87**

Ar	C_6H_5	4–ClC_6H_4	3–ClC_6H_4
Yield (%)	85	76	78

2.15 Pyrrolidinylmethyl-4(3*H*)-quinazolinones (91)

3-(2-Pyridyl)-4(3*H*)-quinazolinones linked to pyrrole, piperidine, 4-methylpiperidine, and morpholine at C_2 *via* a methylene group showed significant contraceptive activity. These heterocycles were prepared starting from 2-nitrobenzoyl chloride (**88**). For example, reaction of **88** with 2-aminopyridine followed by reduction of the nitro group gave 2-amino-*N*-(2-pyridyl)benzamide (**89**). Chloroacetylation of the amine followed by cyclization afforded 2-chloromethyl-3-(2-pyridyl)-4(3*H*)-quinazolinones (**90**) which reacts with a NH bearing heterocycle to yield 2 - heteralkyl quinazolinone. For example, reaction of **90** with pyrrolidine yielded pyrrolidinylmethyl-3-(2-pyridyl)-4(3*H*)-quinazolinones (**91**, Scheme 32).[48]

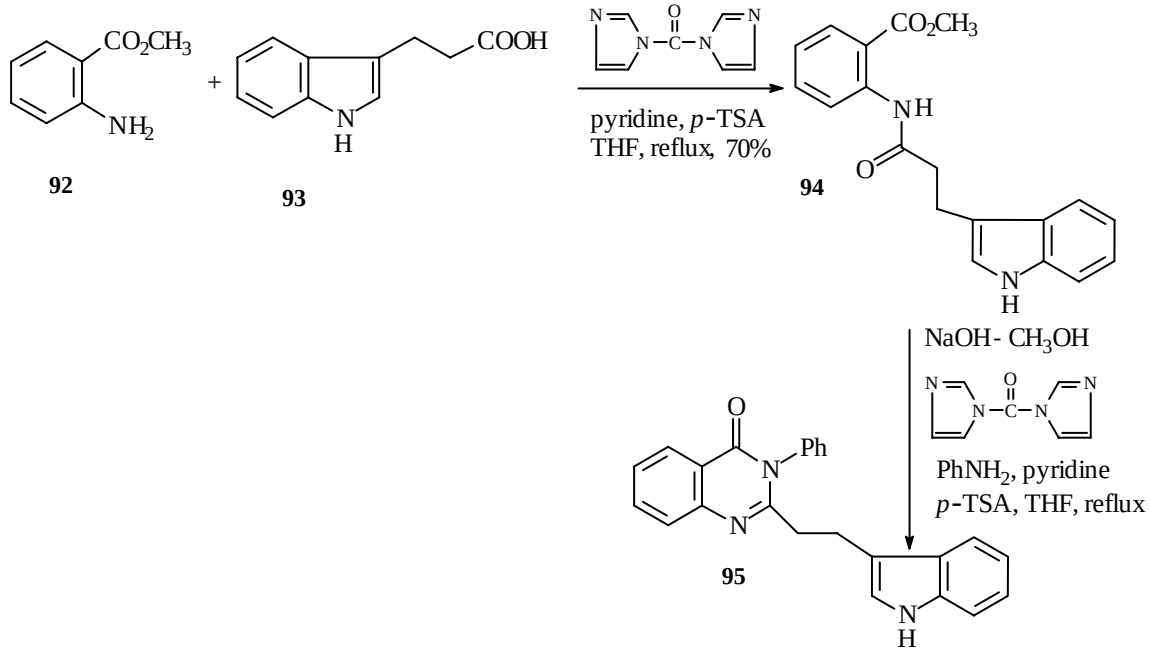
Scheme 32



2.16 Indolylethyl-4(3*H*)-quinazolinones (95, 98)

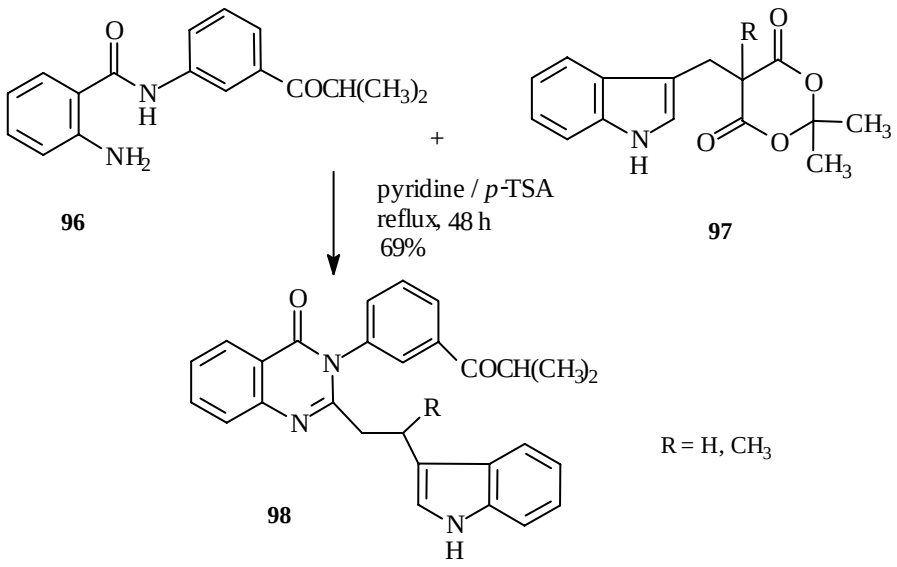
Melvin and co-workers reported the synthesis of 2-[2-(3-indolyl)ethyl]-3-phenyl-4(3*H*)-quinazolinones (**95**) that are useful in the treatment of gastrointestinal and appetite disorders, as CCK antagonists and decreases the number of spontaneously active dopamine neurons.[52,85] Reaction of methyl anthranilate (**92**) with 3-(3-indolyl)propionic acid (**93**) in the presence of 1,1'-carbonyldiimidazole and pyridinium *p*-toluenesulfonate in boiling THF yielded 3-(3-indolyl)-*N*-(2-carbomethoxyphenyl)propionamide (**94**). The compound (**94**) was treated with methanol containing sodium hydroxide, aniline, 1,1'-carbonyldiimidazole and pyridinium *p*-toluenesulfonate in refluxing in THF to give **95** (Scheme 33).

Scheme 33



Melvin extended the above synthesis to prepare quinazolinone based cholecystokinin/gastro receptor ligands. Reaction of 2-amino-*N*-(3-carboisobutanonylphenyl)benzamide (**96**) with 5-(3-indolylmethyl)-1,3-dioxane-4,6-dione (**97**) in pyridine containing pyridinium tosylate unde reflux in nitrogen atmosphere for 48 h gave 2-(3-butanoylphenyl)-4(3*H*)-quinazolinone (**98,** R=H). The X-Ray crystallographic analysis of **98** (R = H, IC_{50} = 0.026 μM) showed an extended structure with two heterocyclic rings adopting an antiperiplanar arrangement around the σ bond of the ethane link, whereas the solid-state conformation for the less active analog (**98**, R=CH_3, IC_{50}=9.1 μM) is folded with two heteroaromatic systems adopting a synclinal orientation. However, MMZ force field calculations (Macro Model V.30) suggest that the energy difference between such unfavourable steric interactions may account for the difference in receptor affinity (Scheme 34).[54]

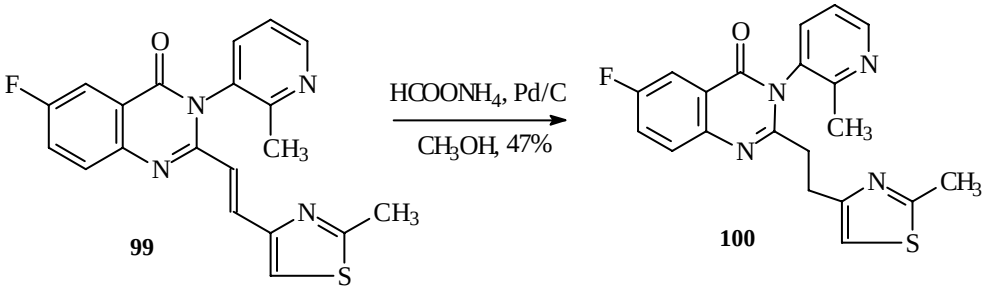
Scheme 34



2.17 Thiazolylethyl-4(3*H*)-quinazolinone (100)

Chenard and co-workers prepared the atropisomer, (*S*)-3-(2-methylpyridine)-6-fluoro-2-[2-(2-methylthiazol-4-yl)ethyl]-4(3*H*)-quinazolinone mesylate (**100**) in 47% yield by refluxing (*S*)-3-(2-methylpyridine)-6-fluoro-2-[2-(2-methylthiazol-4-yl)vinyl]-4(3*H*)-quinazolinones (**99**) with ammonium formate and Pd/C in CH_3OH and, followed by saltification with CH_3SO_3H (Scheme 35).[86]

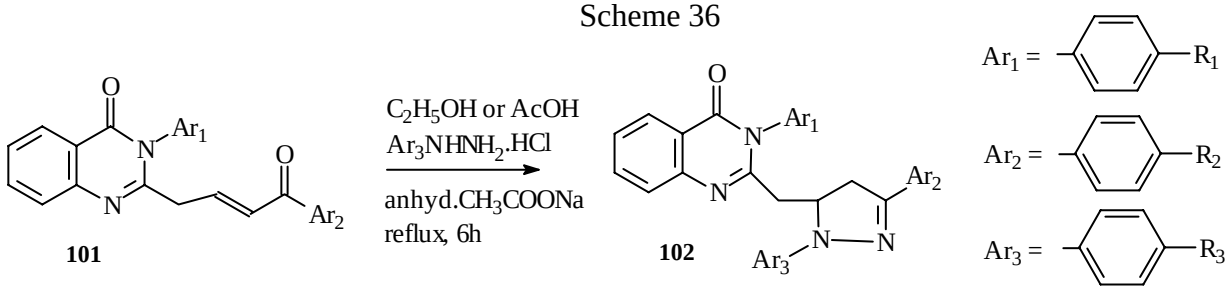
Scheme 35



2.18 Pyrazolylmethyl-4(3*H*)-quinazolinones (102)

2-(3-Pyrazolyl)methyl-3-aryl-4(3*H*)-quinazolinones (**102**) are useful as non-steroidal antiinflammatory agents. They were prepared by the condensation of 2-[3-(1-arylacryloyl)]methyl-3-aryl-4(3*H*)-quinazolinones (**101**) with hydrazine hydrate (Scheme 36).[24]

Scheme 36



101 **102**

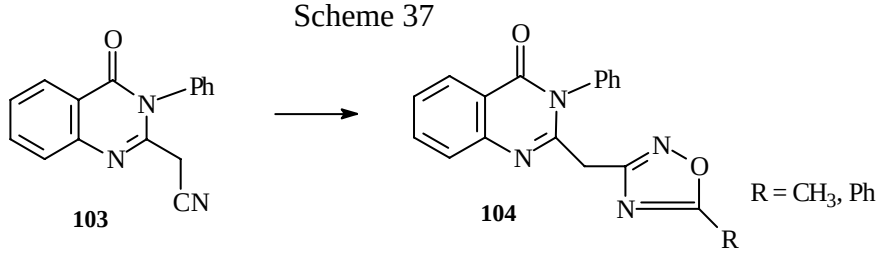
R_1	H	CH_3	Cl	Br	H	CH_3	Cl	Br	H	CH_3	Cl	Br
R_2	H	H	H	H	CH_3	CH_3	CH_3	CH_3	H	H	H	H
R_3	H	H	H	H	H	H	H	H	CH_3	CH_3	CH_3	CH_3
Yield (%)	80	69	78	72	79	68	82	76	72	81	77	67

R_1	H	CH_3	Cl	Br	H	CH_3	Cl	Br	H	CH_3	Cl	Br
R_2	CH_3	CH_3	CH_3	CH_3	H	H	H	H	CH_3	CH_3	CH_3	CH_3
R_3	CH_3	CH_3	CH_3	CH_3	Br	Br	Br	Br	Br	Br	Br	Br
Yield (%)	79	75	68	82	80	72	76	68	69	76	72	78

2.19 Oxadiazolylmethyl-4(3*H*)-quinazolinones (104)

El-Feky prepared 2-[(5-methyl / phenyl-1,2,4-oxadiazol-3-yl)methyl]-3-phenyl-4(3*H*)-quinazolinones **(104)** from 2-cyanomethyl-3-phenyl-4(3*H*)-quinazolinones (**103**) and aldehydes *via* the amide oxime derivatives (Scheme 37).[87]

Scheme 37

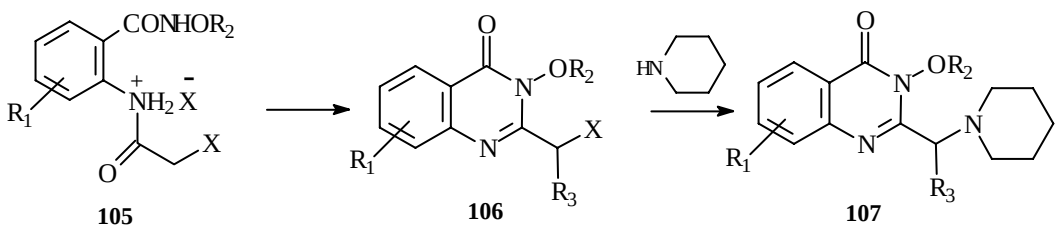


103 **104**

2.20 Piperidinemethyl-4(3*H*)-quinazolinones (107, 109)

The salts of 2-(*N*-acylamino)benzoylhydroxamates (**105**) were cyclized to 3-alkoxyquinazolinones (**106**). Nucleophilic substitution of the halogen in **106** by piperidine afforded 2-(1-piperidinemethyl)-3-alkoxy-4(3*H*)-quinazolinones (**107**, Scheme 38).[88]

Scheme 38

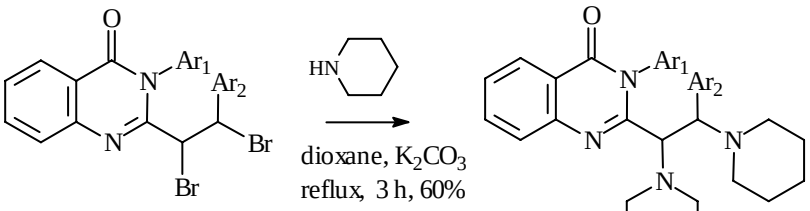


105 **106** **107**

R_1 = H, 6–NO_2, 2–Br, 7–Cl; R_2 = CH_3, $CH_2C_6H_5$, C_3H_7; R_3 = CH_3, C_6H_5; X = Cl, Br

2-α,β-Di-(1-piperidine)-β-arylethyl–3-aryl-4(3*H*)-quinazolinones (**109**) exhibited significant antiinflammatory activity, and were prepared by refluxing α,β-dibromoarylethyl-4(3*H*)-quinazolinones (**108**) with piperidine in dioxane containing K_2CO_3 for 3 h (Scheme 39).[25]

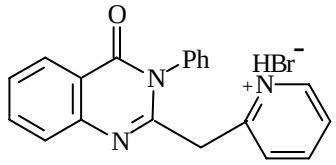
Scheme 39



108 **109**

Ar_1	2-ClC_6H_4	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$
Ar_2	2-$CH_3OC_6H_4$	2-HOC_6H_4	3-ClC_6H_4

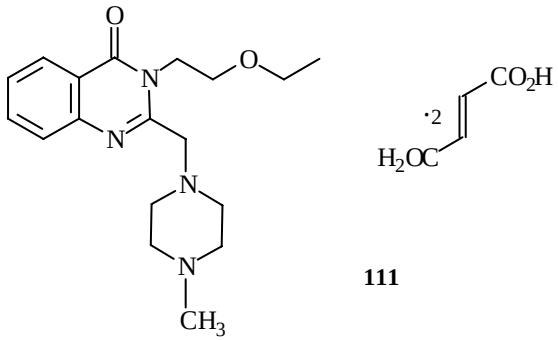
Barakat synthesized 3-phenyl-2-pyridiniummethyl-4(3*H*)-quinazolinone bromides (**110**).[89]



110

2.21 Piperazinomethyl-4(3*H*)-quinazolinones (111, 113)

3-(2-Ethoxyethyl)-2-(4-methylpiperazine-1-ylmethyl)-4(3*H*)-quinazolinone difumarate (**111**), isolated from guinea Pig ileum, was active *in vitro* against histamine induced contractions.[90]

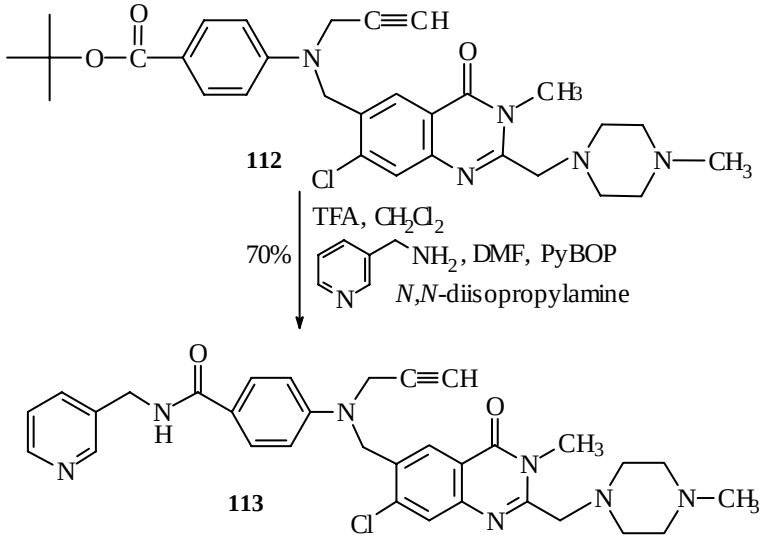


111

3-Methyl-2-(4-methylpiperazin-1-ylmethyl)-6-[*N*-(4-(3-pyridylmethylaminocarbonylphenyl)-*N*-(propyn-2-yl)amino)methyl]-7-chloro-4(3*H*)-quinazolinone (**113**) was prepared by hydrolysis of *tert*-butyl-4-[(*N*-(3-methyl-2-(4-methylpiperazine-1-ylmethyl)-7-chloro-4(3*H*)-quinazolinon-6-ylmethyl))-*N*-(propyn-2-yl)amino]benzoate (**112**) with TFA in $CHCl_3$ followed by amidation with 3-(aminomethyl)pyridine in DMF using PyBOP in the presence of *N*,*N*-diisopropylamine. Quinazolinone derivative (**113**) inhibits thymidylate synthase (TS) albeit poorly when compared to the known anticancer agents CB3717 (IC_{50} **113** / IC_{50} CB3717 > 2500). It is however active against the W_1L_2 and $W_{1/2}$:C_1 cell lines, including W_1L_2

cells incubated in the presence of folate metabolites with IC_{50} values of 0.49 nm, 0.28 nm, and 0.32 nm, respectively (Scheme 40).[91]

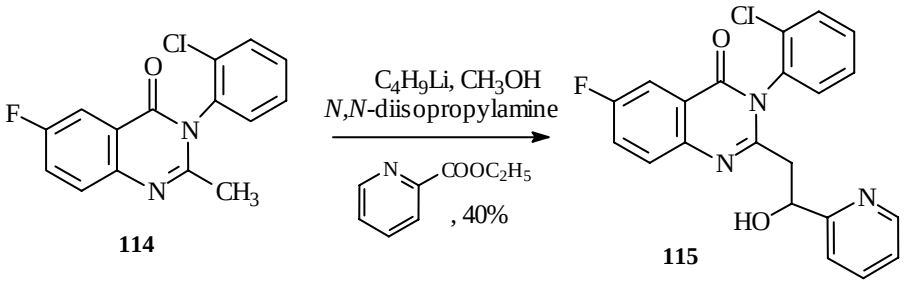
Scheme 40



2.22 Pyridinylethyl-4(3*H*)-quinazolinone (115)

Chenard and Welch have reported the preparation of the quinazolinone derivative **115**. 3-(2-Chloro-phenyl)-6-fluoro-2-methyl-4(3*H*)-quinazolinone (**114**) was reacted with BuLi, diisopropylamine in methanol, and ethyl picolinate to get 3-(2-chlorophenyl)-6-fluoro-2-[2-hydroxy-2-(2-pyridinyl)ethyl]-4(3*H*)-quinazolinone (**115,** Scheme 41).[92]

Scheme 41

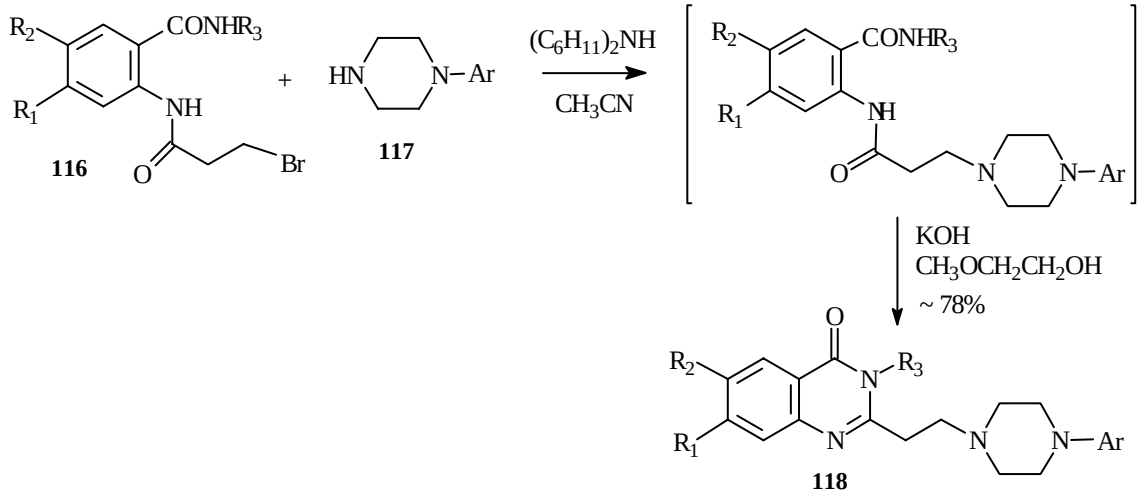


2.23 Piperazinoethyl-4(3*H*)-quinazolinones (118)

Amschler and co-workers prepared 2-[1-(4-aryl)piperazino]ethyl-4(3*H*)-quinazolinone derivatives (**118**) by treating a suitably substituted 2-carbamoylanilide (**116**) with 1-arylpiperazine (**117**) in acetonitrile

containing dicyclohexylamine, followed by dehydrative cyclization.[42] Compounds (**118**) showed hypotensive, antihistamine and analgesic properties with slight sedative effect (Scheme 42).

Scheme 42

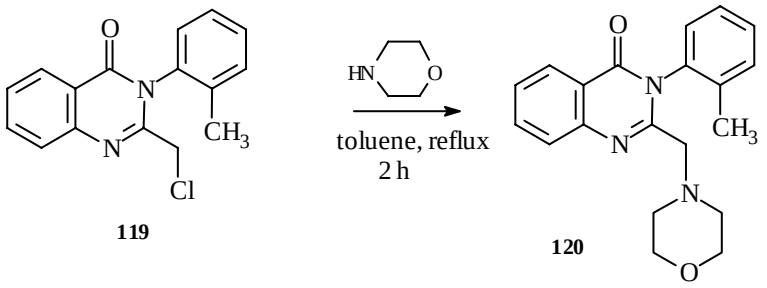


$R_1 = R_2 = H, CH_3, OCH_3$; $R_3 = CH_3, C_6H_5CH_2CH_2, (CH_3)_2CHCH_2CH_2$
Ar = C_6H_5, 2–$CH_3C_6H_4$, 3–$CH_3C_6H_4$, 4–$CH_3C_6H_4$, 4–$CH_3OC_6H_4$, 4–ClC_6H_4, 4–FC_6H_4
3–$CF_3C_6H_4$, 2–$C_2H_5OC_6H_4$

2.24 Morpholinomethyl-4(3*H*)-quinazolinones (120)

2-Morpholinomethyl-3-(2-tolyl)-4(3*H*)-quinazolinones (**120**) exhibited hypnotic and anticonvulsant activity. They were prepared by reacting 2-chloromethyl-3-(2-tolyl)-4(3*H*)-quinazolinone (**119**) with morpholine in boiling toluene (Scheme 43).[38]

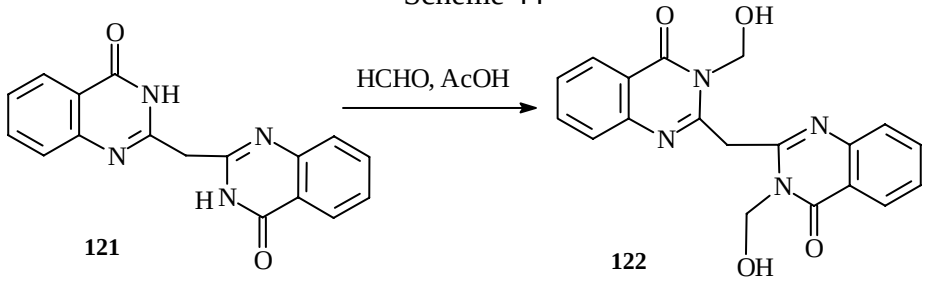
Scheme 43



2.25 2,2'-Methylenebis-4(3*H*)-quinazolinones (122)

Reaction of 2,2'-methylenebis-4(3*H*)-quinazolinone (**121**) with formaldehyde in acetic acid gave 2,2'-methylenebis[3-methylol-4(3*H*)-quinazolinone] derivative (**122**). Copolymerisation of **122** with adiponitrile in H_2SO_4 medium gave a good heat resistant polyamide (Scheme 44).[55]

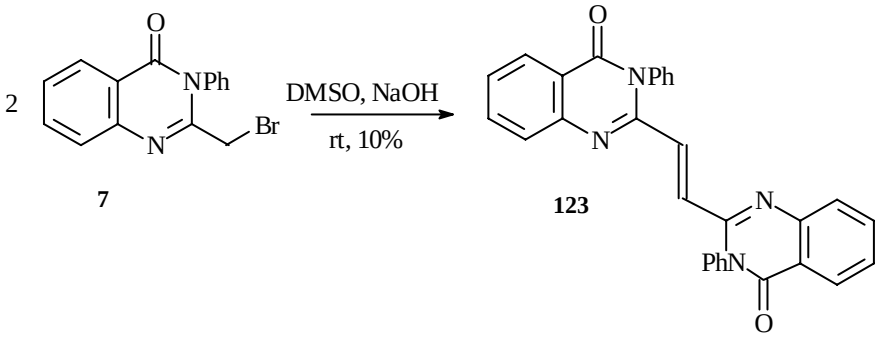
Scheme 44



2.26 1,2-Bis(3-phenyl-4(3*H*)-quinazolinone-2-yl)ethylene (123, 124)

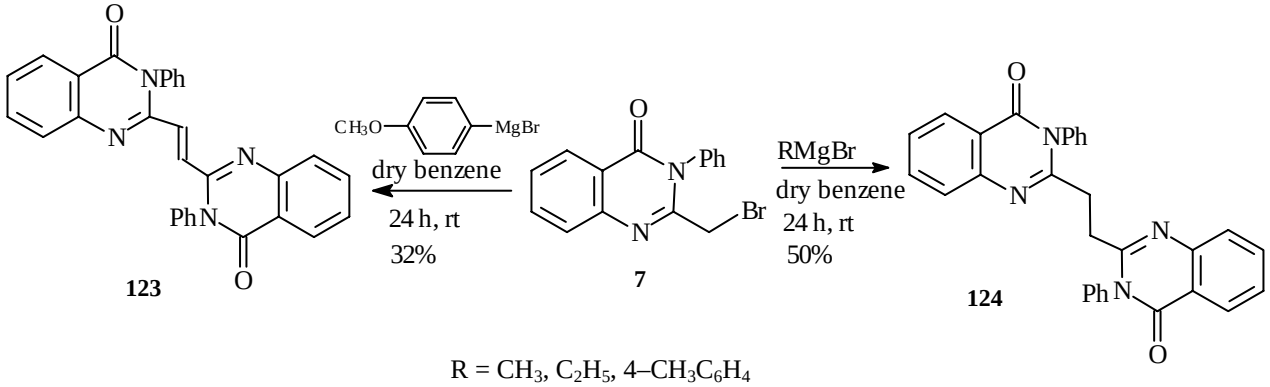
1,2-Bis[3-phenyl-4(3*H*)-quinazolinone-2-yl]ethylene (**123**) has interesting structural features with two quinazolinone moieties attached at either end of an ethylene group. It was prepared at room temperature by the self-condensation of 2-bromomethyl-3-phenyl-4(3*H*)-quinazolinone (**7**) in DMSO containing NaOH. The reaction pathway possibly involves the generation of a carbanion, followed by coupling and dehydrobromination (Scheme 45).[93]

Scheme 45



The dihydro derivative of **123**, 1,2-bis[3-phenyl-4(3*H*)-quinazolinone-2-yl]ethane (**124**) was prepared by Ismail and co-workers by treating **7** with RMgBr (R = CH_3, C_2H_5 and 4-$CH_3C_6H_4$). When 4-methoxyphenylmagnesium bromide was used to generate carbanion, the reaction yielded **123** (Scheme 46).[58]

Scheme 46

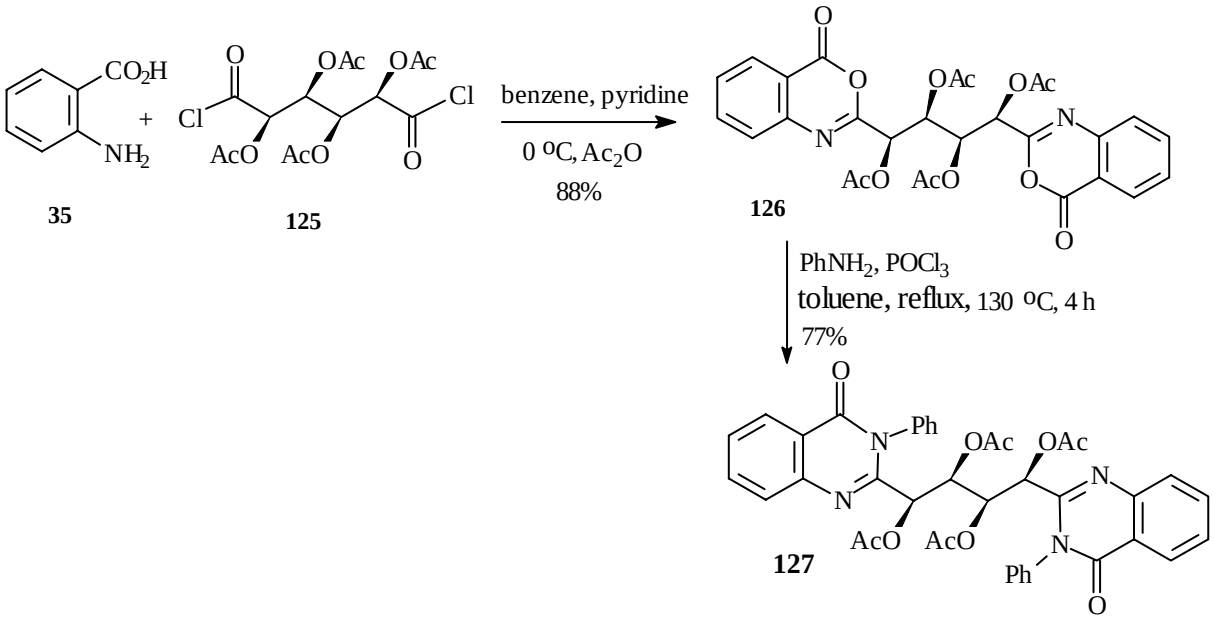


R = CH_3, C_2H_5, 4–$CH_3C_6H_4$

2.27 1,4-Bis-4(3*H*)-quinazolino-1,2,3,4-tetra-*O*-acetylgalactotetritol (127)

A novel approach to the synthesis of *C*-nucleoside analogs involves building of benzoxazine rings at the terminus of a carbohydrate moiety. 2,3,4,5-Tetra-*O*-acetylgalactoryl chloride (**125**) was condensed with anthranilic acid (**35**) in benzene containing pyridine at 0 ^{0}C and the condensed product underwent dehydrative cyclization in acetic anhydride to form 1,2,3,4-tetra-*O*-acetyl-1,4-bis(benzoxazin-4-on-2-yl)galactotetritol (**126**). The bisbenzoxazine (**126**) on reacting with aniline in the presence of $POCl_3$ in toluene afforded 1,4-bis-(3-phenyl-4(3*H*)-quinazolinone-2-yl)-1,2,3,4-tetra-*O*-acetylgalactotetritol (**127**, Scheme 47).[94]

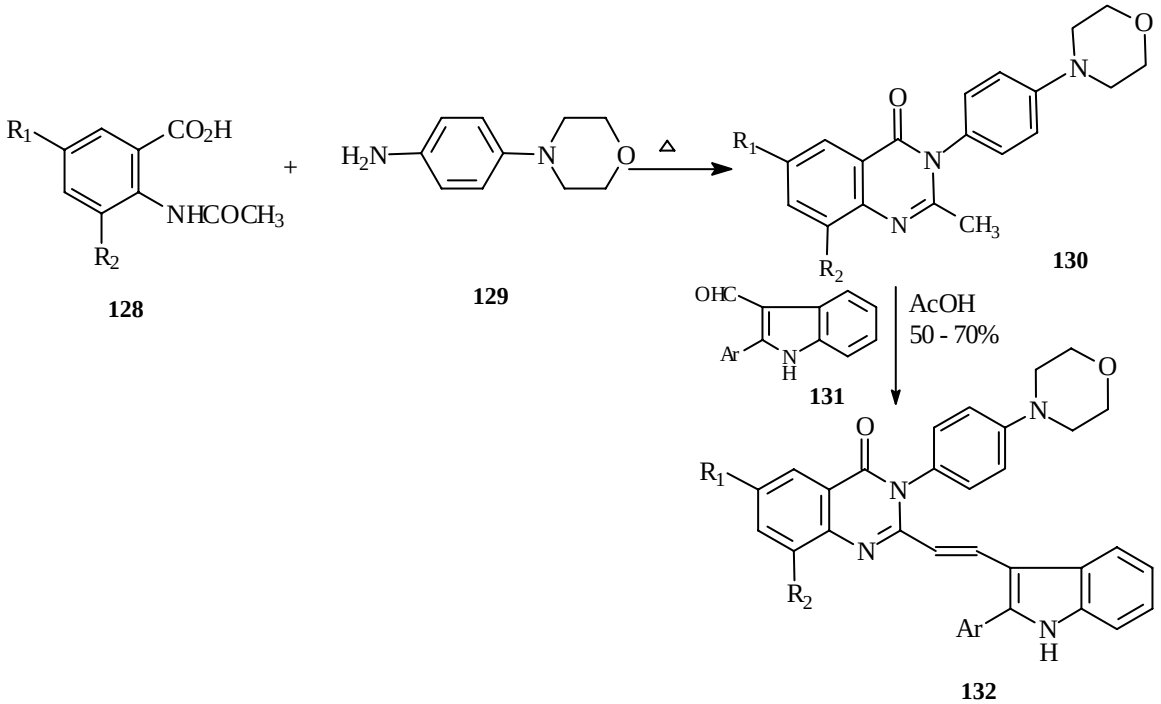
Scheme 47



2.28 Indolylethylenyl-4(3*H*)-quinazolinones (131)

2-[2-(2-Arylindole-3-yl)ethylene]-3-[4-(4-morpholino)phenyl]-6,8-disubstituted-4(3*H*)-quinazolinones (**132**) are useful as CNS active, psychotropic and antiinflammatory agents. These heteroalkenyl-quinazolinones were synthesized by Knoevenagel condensation of 2-methyl-3-(4-morpholinophenyl)-4(3*H*)-quinazolinones (**130**) and 2-arylindol-3-carboxaldehyde (**131**) in the presence of acetic acid. The required 4(3*H*)-quinazolinone derivatives (**130**) were prepared by fusion of *N*-acetylanthranilic acid (**128**) with 4-morpholinoaniline (**129**, Scheme 48).[26]

Scheme 48

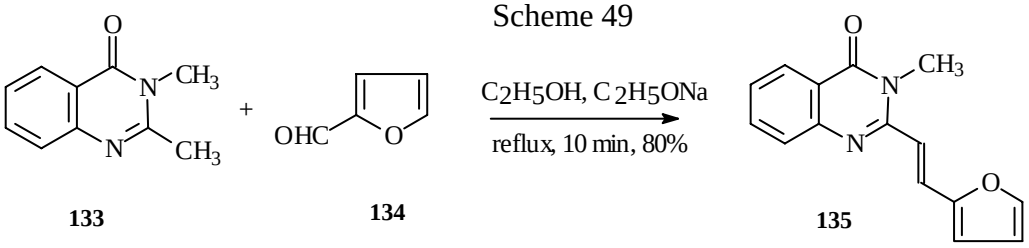


R_1 = H, Br, I; R_2 = H, Br; Ar = C_6H_5, 4–$CH_3C_6H_4$, 4–$CH_3OC_6H_4$, 4–ClC_6H_4

2.29 Furylvinyl-4(3*H*)-quinazolinones (135)

2-(2-Furylvinyl)-3-alkyl-4(3*H*)-quinazolinones (**135**) were obtained in 80-90% yields by Knoevenagel condensation of 2-methyl-3-alkyl-4(3*H*)-quinazolinones (**133**) with furfural (**134**) in absolute ethanol containing sodium ethoxide (Scheme 49).[95,96]

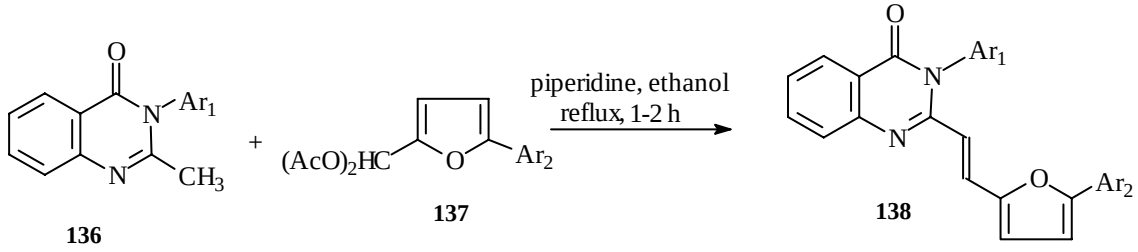
Scheme 49



133 **134** **135**

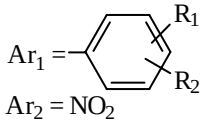
Holla and co-workers reported the synthesis and antibacterial activity of 3-aryl-2-{2-[2-(5-nitrofuryl)]vinyl}-4(3*H*)-quinazolinones (**138**). Condensation of 3-aryl-2-methyl-4(3*H*)-quinazolinones (**136**) with 5-substituted furaldehyde diacetate (**137,** Ar=NO_2) in absolute ethanol followed by refluxing with piperidine for 1-2 h provided 2-heteryl-4(3*H*)-quinazolinones (**138**). They also reported the preparation of 3-aryl-2-{2-[2-(5-arylfuryl)]vinyl}-4(3*H*)-quinazolinones (**139)** following the same procedure (Scheme 50).[97,98]

Scheme 50



136 **137** **138**

138 Ar_1 = 2–ClC_6H_4, 2–$CH_3C_6H_4$, , 4–$NO_2C_6H_4$, 4–ClC_6H_4; Ar_2 =4–ClC_6H_4, 4–BrC_6H_4, 4–$NO_2C_6H_4$

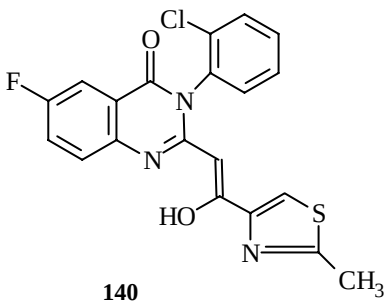


139

R_1	H	4-Br	4–CH_3	3–Cl	3–Cl	2–OCH_3	3-CH_3	4–NO_2	2-Cl
R_2	H	H	H	H	4–F	H	H	H	5-Cl
Yield (%)	80	81	78	57	81	51	68	50	53

2.30 Thiazolylvinyl-4(3*H*)-quinazolinones (140)

3-(2-Chlorophenyl)-6-fluoro-2-(2-hydroxy-2-(2-methylthiazol-4-yl)vinyl)-4(3*H*)-quinazolinones **(140)** is a neuroprotective agent and a potent AMPA receptor antagonist. The details of its synthesis are patented, and are not available.[99]

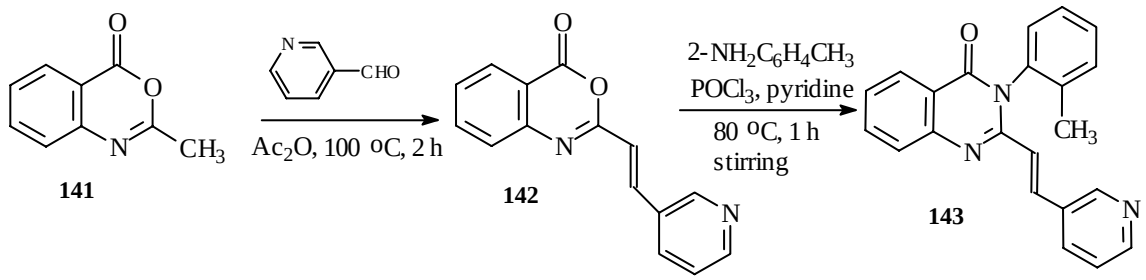


140

2.31 Pyridylvinyl-4(3*H*)-quinazolinones (143)

2-[2-(3-Pyridylvinyl)-3-(2-tolyl)]-4(3*H*)-quinazolinones (**143**) showed plasmotic, anticonvulsant, hypnotic, tranquilising and muscle relaxant activity. They were prepared in two-steps (i) condensation of 2-methyl-3,1-benzoxazin-4-one (**141**) with 3-pyridinecarboxaldehyde, to isolate 2-[2-(3-pyridylvinyl)]-3,1-benzoxazin-4-one (**142**), and (ii) reaction of **142** with *o*-toluidine (Scheme 51).[100]

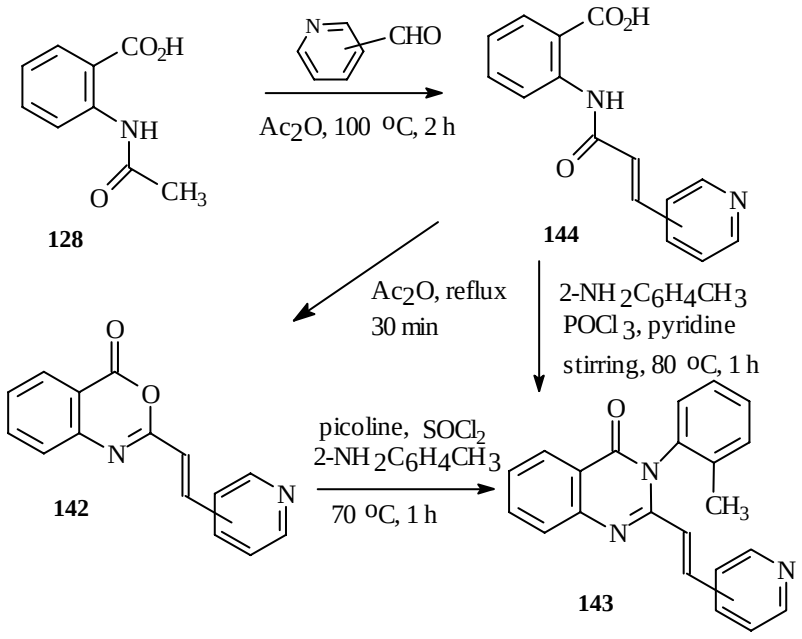
Scheme 51



141 **142** **143**

2-Pyridyl and 4-pyridyl analogs of **143**, useful as anticonvulsants, hypnotics, tranquilisers and muscle relaxants, were prepared by reaction of the corresponding *N*-(*o*-carboxyphenyl)-β-(3-pyridyl)acrylamide (**144**) or 2-[2-(3-pyridyl)vinyl]-3,1-benzoxazine-4-ones (**142**), with *o*-toluidine. Thus, heating *N*-acetylanthranilic acid (**128**) with 2-, 3- or 4-pyridinecarboxaldehyde in acetic anhydride at 100 ^{o}C for 3 h gave **144**. Dropwise addition of $POCl_3$ to a cooled suspension of **144** and *o*-toluidine in pyridine followed by stirring at 80 ^{o}C for 1 h gave **143**. Refluxing **144** in acetic anhydride for 30 minutes gave **142**. Addition of $SOCl_2$ to a cooled suspension of **144** and **142** in picoline followed by *o*-toluidine with stirring at 70 ^{o}C for 1 h also gave **143** (Scheme 52).[30]

Scheme 52

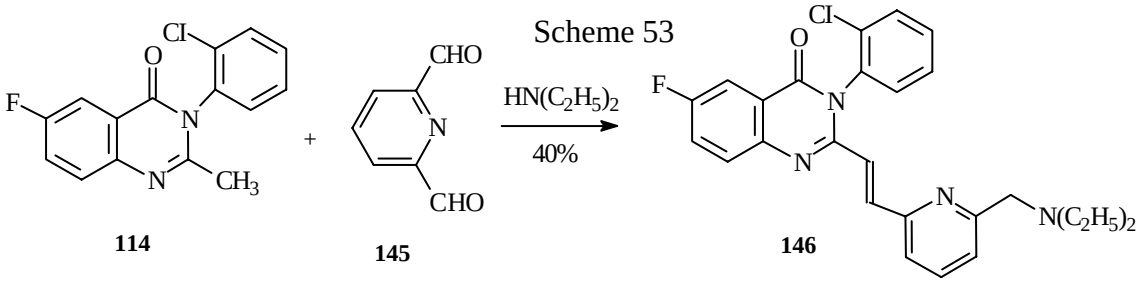


128 **144** **142** **143**

Welch and Devries have prepared the atropisomers, 2-(2-heteroarylvinyl)-3-aryl-6-fluoro-4(3*H*)-quinazolinones (**146**) which are useful as AMPA antogonists, particularly in the treatment of

neurodegenerative and CNS-trauma related conditions.[101] The (*S*)-isomer of 3-(2-chlorophenyl)-6-fluoro-2-[2-(6-diethylaminomethylpyridyl)vinyl]-4(3*H*)-quinazolinones (**146**)[101] was prepared by reacting 3-(2-chlorophenyl)-6-fluoro-2-methyl-4(3*H*)-quinazolinones (**114**), and 2,6-pyridinedicarboxaldehyde (**145**) in diethylamine (Scheme 53).[86,92,101,102]

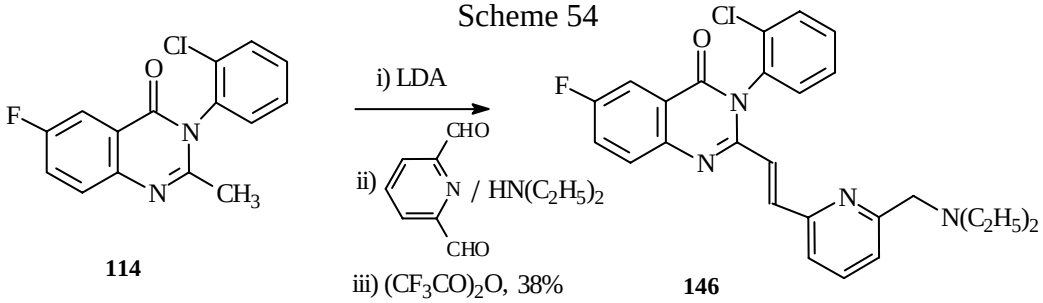
Scheme 53



114 **145** **146**

Chenard and co-workers prepared **146** by reacting the **114** with **145** in the presence of LDA/ diethylamine followed by $(CF_3CO)_2O$ mediated dehydration **(**Scheme 54).[103]

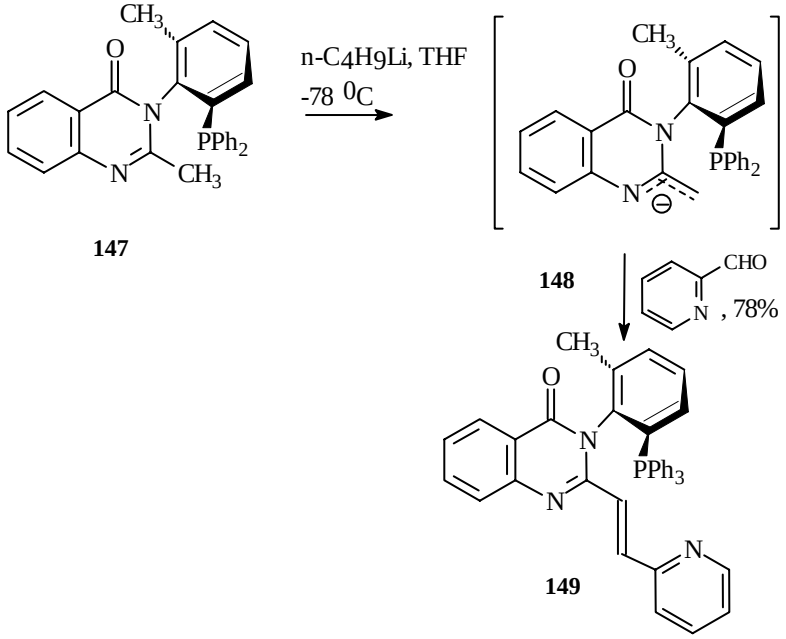
Scheme 54



114 **146**

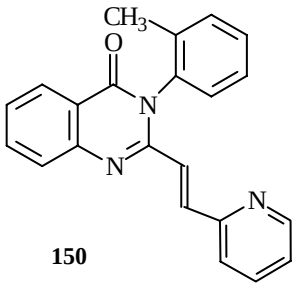
Dai and Virgil have synthesized a quinazolinone phosphine bidentate ligand (**149**) starting from monodentate ligand (**147**)**.** The quinazolinone derivative (**147**) was reacted with 1.2 equivalents of n-BuLi in THF at –78 ^oC to generate the anion (**148**), which was submitted to Claisen-Schmidt reaction with 2-pyridyl aldehyde to yield the bidentate ligand (**149**) in 78% yield. (Scheme 55).[104]

Scheme 55



147 **148** **149**

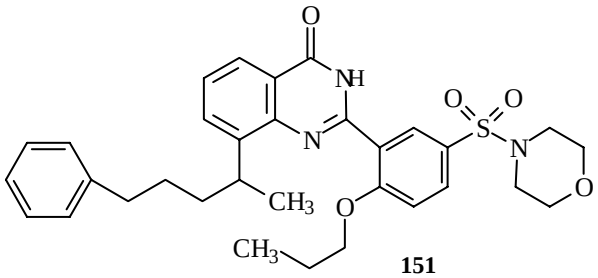
2-{2-[(2-Pyridyl)vinyl]-3-*o*-tolyl}-4(3*H*)-quinazolinone (**150**) showed anticonvulsant, hypnotic and muscle relaxant activity, and was sold as a drug under the trade name *piriqualone.*[105]



150

2.32 Morpholinylsulfonylaryl-4(3*H*)-quinazolinone (151)

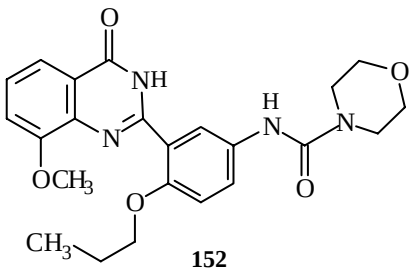
8-(1-Methyl-4-phenylbutyl)-2-[5-(morpholinylsulfonyl)-2–propoxyphenyl]-4(3*H*)-quinazolinone (**151**) is used for the treatment of cardiovascular and thromboembolic disorders that exhibits potent *in vitro* inhibition of phosphodiesterase type II to V (PDE II and PDE V) activity.[106]



151

2.33 Morpholinylcarbaminoaryl-4(3*H*)-quinazolinones (152)

N-[3-(8-Methoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-4-propoxyphenyl]morpholine-4-carbamide (**152**) is a lead drug for the treatment of heart failure and other cardiovascular and respiratory tract / allergic disorders, with potent cGMP phosphodiesterase (PDE V) inhibitory activity.[107]

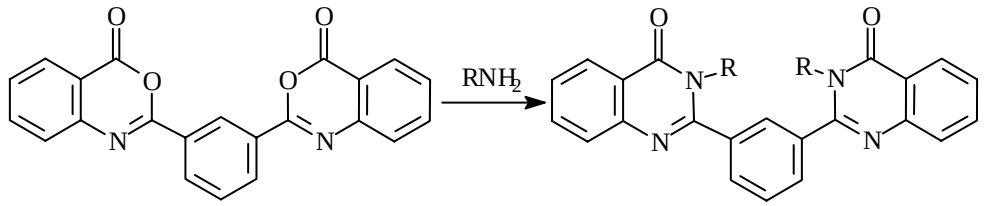


152

2.34 {2,2”-Bis[4(*3H*)-quinazolinone]}benzenes (154)

1’,3’-{2,2”-Bis[4(*3H*)-quinazolinone]}benzene (**154**) and its *N*-substituted derivatives showed broad spectrum of antibacterial activity and were synthesized by amine insertion reaction with 1’,3’-[2,2”-bis(3,1-benzoxazin-4-one)]benzene (**153**, Scheme 56).[9]

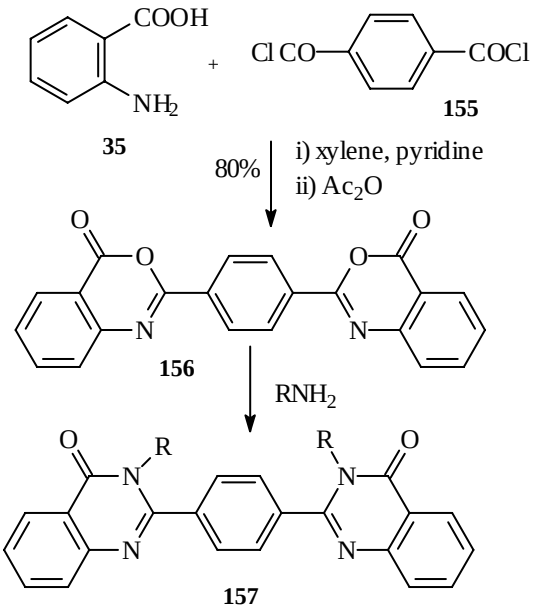
Scheme 56



153 **154**

In a similar way, 1',4'-{2,2"-bis[4(*3H*)-quinazolinone]}benzenes (**157**) were prepared by the insertion of aniline with 1',4'-[2,2"-bis(3,1-benzoxazin-4-one)]benzene (**156**). Use of hydroxylamine in the reaction yields the 3-hydroxy derivative. The **156** was prepared in 80% yield from the reaction **35** and terephthaloyl chloride (**155**) in xylene containing pyridine and subsequent treatment with Ac_2O (Scheme 57).[108]

Scheme 57



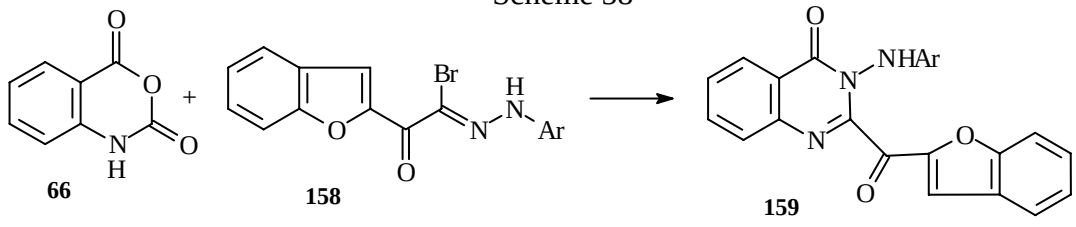
35 **155** **156** **157**

R = Ph, OH

2.35 Carbobenzofuryl-4(3*H*)-quinazolinones (159)

Abdel Hamid and co-workers reported a facile one-step synthesis of 2-(2-carbobenzofuryl)-3-(4-arylamino)-4(3*H*)-quinazolinones (**159**) by condensing 2-bromobezofurylglyoxal-2-arylhydrazones (**158**) with isatoic anhydride (**66**, Scheme 58).[109]

Scheme 58



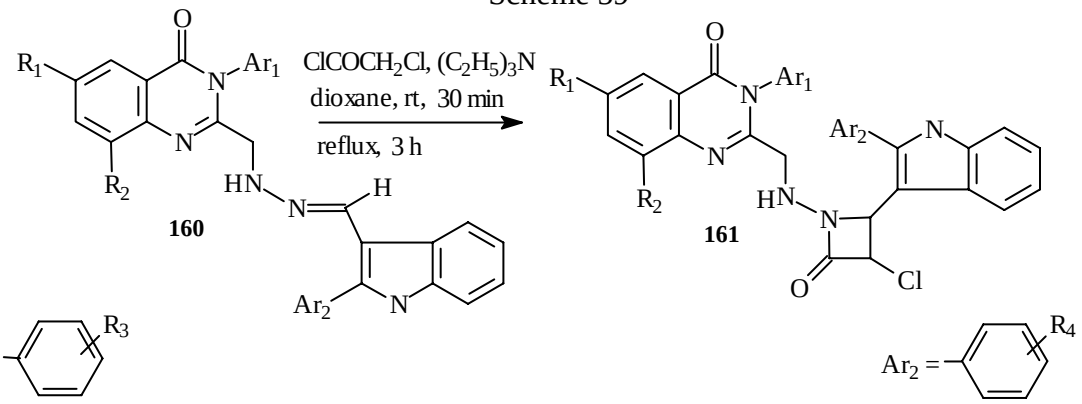
66 **158** **159**

Ar = C_6H_5, 4–$CH_3C_6H_4$, 4–ClC_6H_4

2.36 Indolylazetidinylaminomethyl-4(3*H*)-quinazolinones (161)

6,8-Disubstituted 3-aryl-2-{3'-[3"-(2"-arylindolylmethylene)]hydrazinomethyl}-4(3*H*)-quinazolinones (**160**) served as an ideal starting material for synthesizing these class of compounds. For example, chloroacetylation of **160** in triethylamine medium afforded 6-bromo-2-1'-(3'-chloro–4'-(3"-(2"-arylindolyl))azetidin-2'-one)aminomethyl)-3-aryl-4(3*H*)-quinazolinones (**161**, Scheme 59).[110]

Scheme 59

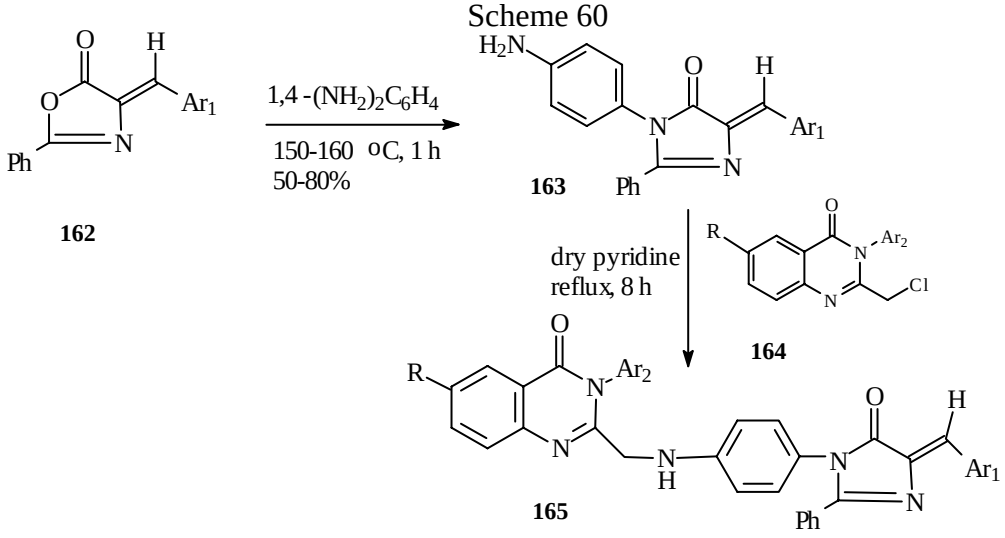


R_1	I	I	Br	Br	Br	Br	I	I	Br	Br	H
R_2	H	H	H	H	Br	Br	H	H	H	H	H
R_3	2–CH_3	2–CH_3	2–CH_3	2–CH_3	2–CH_3	2–CH_3	4–Cl	4–Cl	3–Cl	3–Cl	NH_2
R_4	H	4–CH_3	H	4–CH_3	H	4–CH_3	H	4–CH_3	H	4–CH_3	H

2.37 Imidazolylphenylaminomethyl-4(3*H*)-quinazolinones (165)

A number of 2-{1'-{4'-[4"-(arylmethylene)-4",5"-dihydro-2"-phenylimidazol-5"-one]phenyl}amino-methyl}-3-aryl-4(3*H*)-quinazolinones (**165**) showed significant antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*. The title compounds (**165**) were synthesised by first condensing 1,4-phenylenediamine with the lactone phenyl(benzylidene)oxazolinones (**162**) to isolate 1-(4-aminophenyl)-2-phenyl-(4-arylmethylene)imidazol-5-ones (**163**) and its subsequent reaction with 3-aryl-2-chloro-methyl-4(3*H*)-quinazolinones (**164**, Scheme 60).[12]

Scheme 60

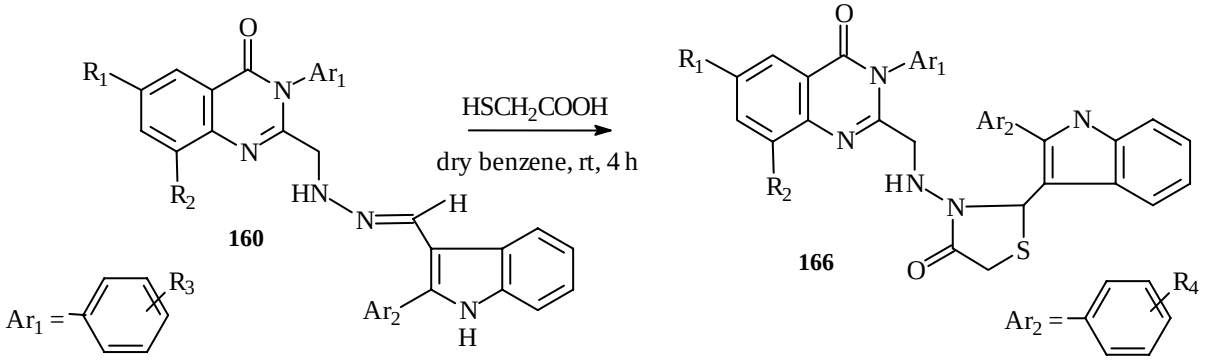


R = H, I; Ar_1 = C_6H_5, 4–ClC_6H_4, 4–$CH_3OC_6H_4$, 4–$NO_2C_6H_4$; Ar_2 = C_6H_5, 4–ClC_6H_4, 3–$NO_2C_6H_4$, 4–$CH_3OC_6H_4$, 4–HOC_6H_4, 2–HOC_6H_4

2.38 Indolylthiazolylaminomethyl-4(3*H*)-quinazolinones (166)

Reaction of **160** with thioacetic acid in dry benzene yielded 6,8-disubstituted 3-aryl-2-{[2'-(2"-arylindol-3"-yl)-4'-oxothiazolidin-1'-yl]aminomethyl}-4(3*H*)-quinazolinones (**166**, Scheme 61).[110]

Scheme 61

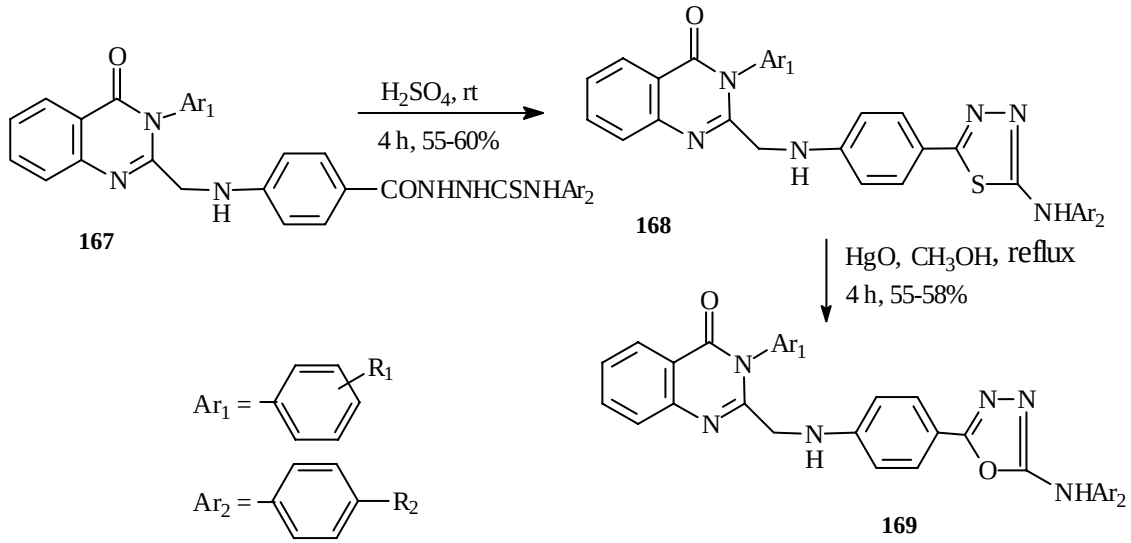


R_1	I	I	Br	Br	Br	Br	I	I	Br	Br	H
R_2	H	H	H	H	Br	Br	H	H	H	H	H
R_3	2–CH_3	2–CH_3	2–CH_3	2–CH_3	2–CH_3	2–CH_3	4–Cl	4–Cl	3–Cl	3–Cl	NH_2
R_4	H	4–CH_3	H	4–CH_3	H	4–CH_3	H	4–CH_3	H	4–CH_3	H

2.39 Oxadiazolylphenylaminomethyl-4(3*H*)-quinazolinones (169)

Hussain and Jamali prepared the hypoglycemic agents 2-{4'-[5"-(2"-arylamino-1",3",4"-thiadiazolyl)]-phenyl}aminomethyl-3-aryl-4(3*H*)-quinazolinones (**168**) by cyclizing the thiosemicarbazides (**167)** in concentrated sulfuric acid at room temperature.[43] Compounds (**168**) were converted to the corresponding oxadiazole derivatives, 2-{4'-[5"-(2"-arylamino-1",3",4"-oxadiazole)]phenyl)}aminomethyl-3-aryl-4(3*H*)-quinazolinones (**169**) by refluxing in methanol containing mercuric oxide (Scheme 62).

Scheme 62

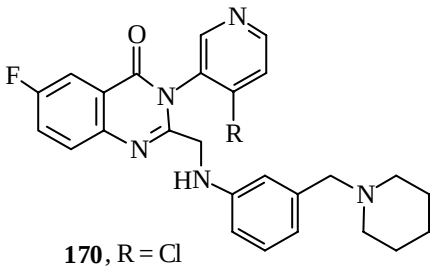


R_1	2-CH_3	4-OCH_3	4-NO_2	2-CH_3	4-OCH_3	4-NO_2	2-CH_3	4-OCH_3
R_2	H	H	H	CH_3	CH_3	CH_3	OCH_3	OCH_3

R_1	4-NO_2	2-CH_3	4-OCH_3	4-NO_2	2-CH_3	4-OCH_3
R_2	OCH_3	Cl	Cl	Cl	Br	Br

2.40 Pyrrolidinomethylphenylaminomethyl-4(3*H*)-quinazolinones (170, 171)

3-(2-Chlorophenyl)-6-fluoro-2-[3-(1-pyrrolidinomethyl)phenylaminomethyl]-4(3*H*)-quinazolinone (**170**) and 3-(2-methylpyridyl)-6-fluoro-2-(3-(1-pyrrolidinomethyl)phenylaminomethyl-4(3*H*)-quinazolinone (**171**) are neuroprotective agents, a potent AMPA receptor antagonist with an IC_{50} value < 5 μ M against AMPA receptor activation induced $^{45}Ca^{+2}$ uptake in rat cerebella granule cell cultures.[111]

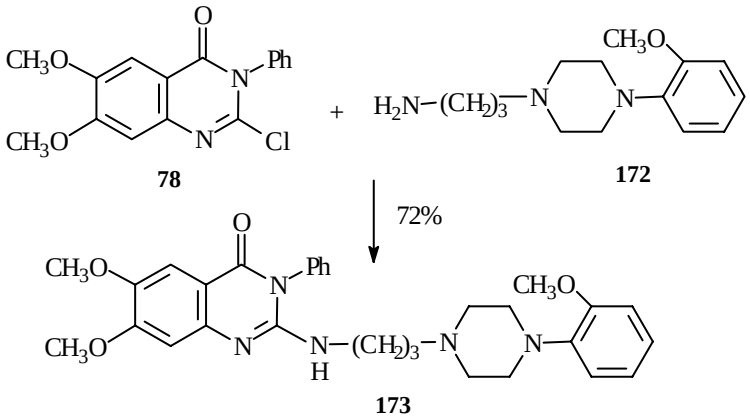


170, R = Cl
171, R = CH_3

2.41 Pyrazinylpropylamino-4(3*H*)-quinazolinones (173)

Antihypertensive pyrimidinone (**173**) was obtained in 72% yield by reacting 2-chloro-3-phenyl-6,7-dimethoxy-4(3*H*)-quinazolinone (**78**) with 1-(3-aminopropyl)-4-(2-methoxyphenyl)piperazine (**172**, Scheme 63).[34]

Scheme 63



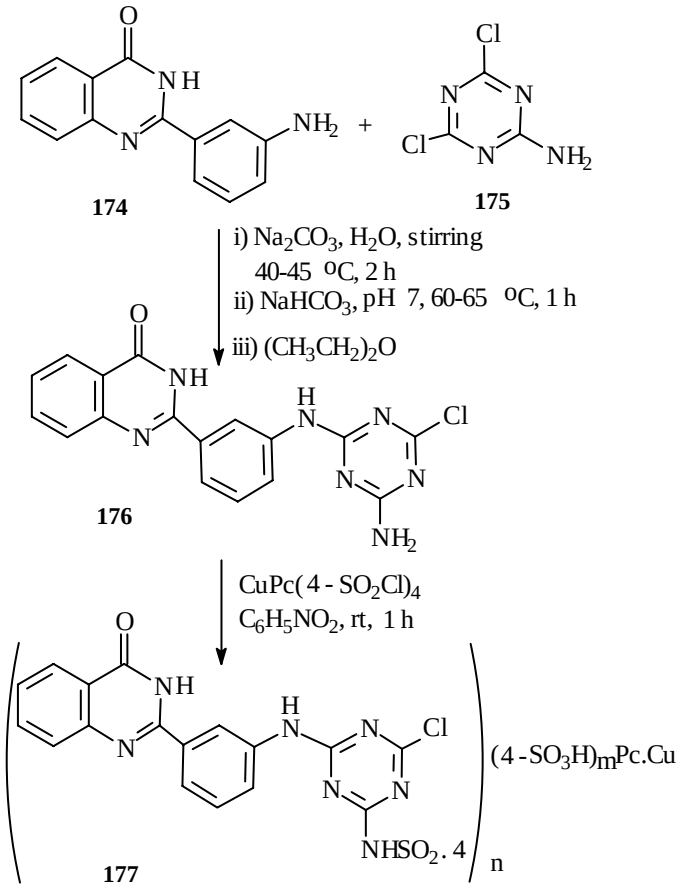
78 **172** **173**

2.42 Triazolylaminophenyl-4(3*H*)-quinazolinones (177)

2-Amino-4,6-dichloro-*S*-triazine (**175**) was reacted with 2-(3-aminophenyl)-4(3*H*)-quinazolinones (**174**) in aqueous sodium carbonate solution at room temperature to give 2-{3'-[4"-(2"-amino-6"-chloro-*S*-

triazine)]aminophenyl}-4(3*H*)-quinazolinones (**176**). Compounds (**176**) were derivatized with copper phthalocyanine and the resulting products (**177**) are useful as fiber reactive dyes (Scheme 64).[56]

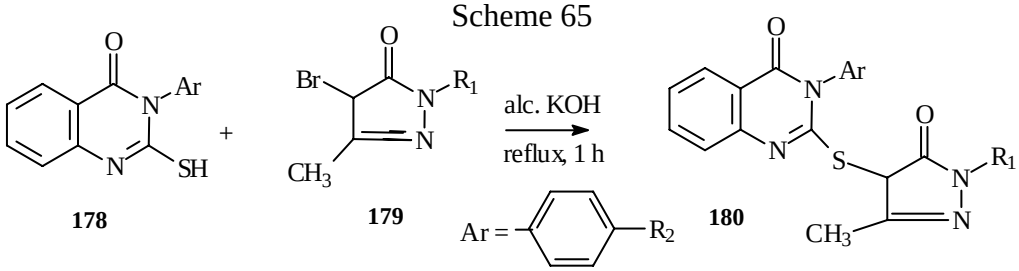
Scheme 64



2.43 Pyrazolylthio-4(3*H*)-quinazolinones (180)

Potential fungicidal quinazolinone derivatives, 2-[(1'-alkyl-3'methyl-5'-oxopyrazolin-4'-yl)thio]-3-aryl-4(3*H*)-quinazolinones (**180**) were prepared by the reaction of 4-bromo-2-pyrazolin-5-one (**179**) with 2-mercapto-3-aryl-4(3*H*)-quinazolinones (**178**) in alcoholic alkali. They are fungitoxic against the rice blast pathogen *Pyricularia oryzal* and brown leaf spot pathogen *Helmenthosporium oryzal* (Scheme 65).[112]

Scheme 65

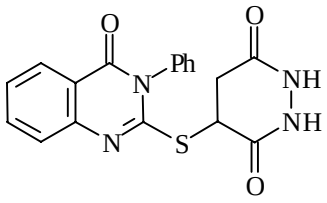


R_1	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	H	H	H
R_2	H	4-Cl	3-Cl	2-Cl	4–NO_2	4–OCH_3	2-OCH_3	4–CH_3	H	4-Cl	3-Cl
Yield (%)	80	70	50	65	55	50	45	50	75	65	60

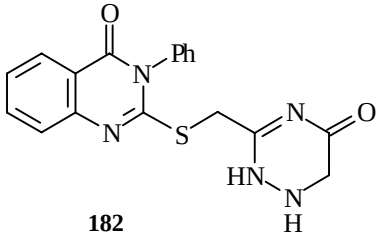
R_1	H	H	H	H	H	Ph	Ph	Ph
R_2	2-Cl	4–NO_2	4–CH_3	4-OCH_3	2–OCH_3	2-COOH	4–COOH	4–OC_2H_5
Yield (%)	55	60	65	60	40	40	50	30

R_1	H	H	Ph	Ph	H	H
Ar	2–$COOHC_6H_4$	4–$COOHC_6H_4$	1-naphthyl	2-naphthyl	1-naphthyl	2-naphthyl
Yield (%)	50	55	45	40	45	40

Quinazolinones linked at C-2 to heteryl moieties such as 1,3,4-oxadiazine, 1,2,4-triazine, pyrazolidine-3,5-dione, 1,2,4,5-tetrazin-3-one, pyridazine-3,6-dione (**181**), pyrazole, 1,2,4-triazin-5-one (1**83**) and triazole were synthesized as antitumor agents. They were tested the *in vitro* against *Ehrlich Ascites Carcinoma* cells and were found to be bacteriostatic, the most active being **181** and **182**.[113]



181

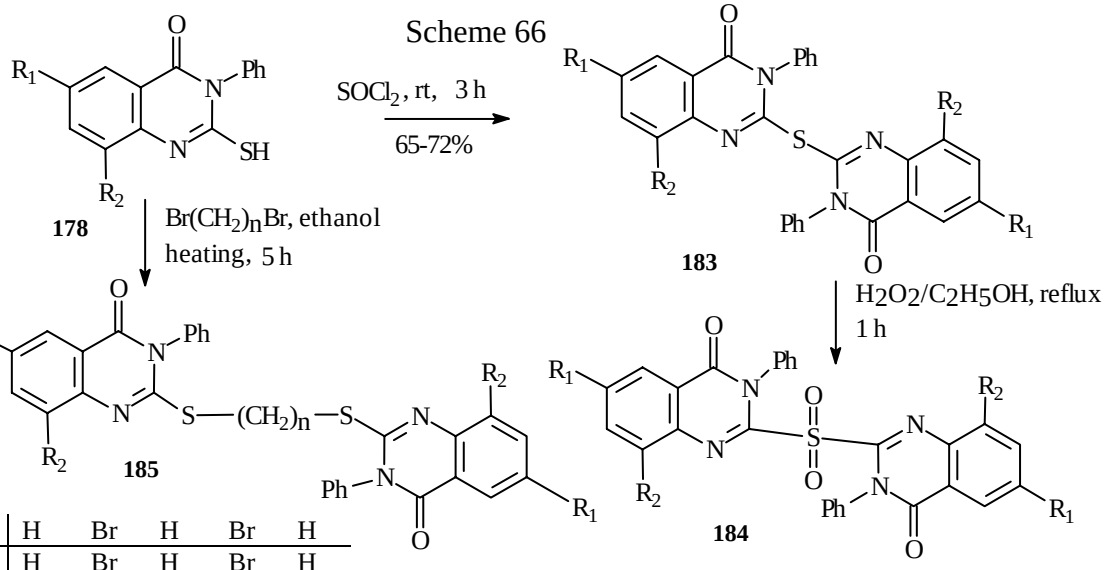


182

2.44 2,2'-Bis-[4(3*H*)-quinazolinones] (184)

2,2'-Bis[6,8-disubstituted 3-phenyl-4(3*H*)-quinazolinonyl]sulfones (**184**) showed promising CNS depressant activity. Dimerisation of 6,8-disubstituted 2-mercaptoquinazolin-4(3*H*)-ones (**178**) followed by oxidation of the sulfide derivative (**183**) afforded the bisquinazolinone derivatives (**184**). A similar bisquinazolinone derivative (**185**) was obtained from the reaction of **178** and α,ω-dibromoalkane in ethanol medium (Scheme 66).[114]

Scheme 66



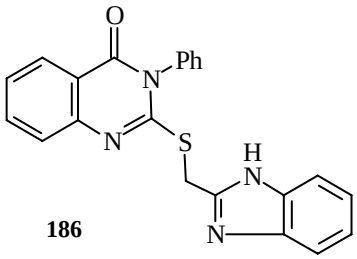
178 **183** **185** **184**

R_1	H	Br	H	Br	H
R_2	H	Br	H	Br	H
n	1	1	2	2	3
Yield (%)	68	75	80	78	70

R_1	H	Br	I	Br
R_2	H	Br	H	H
Yield (%)	72	70	70	65

2.45 Imidazolylmethylthio-4(3*H*)-quinazolinones (186)

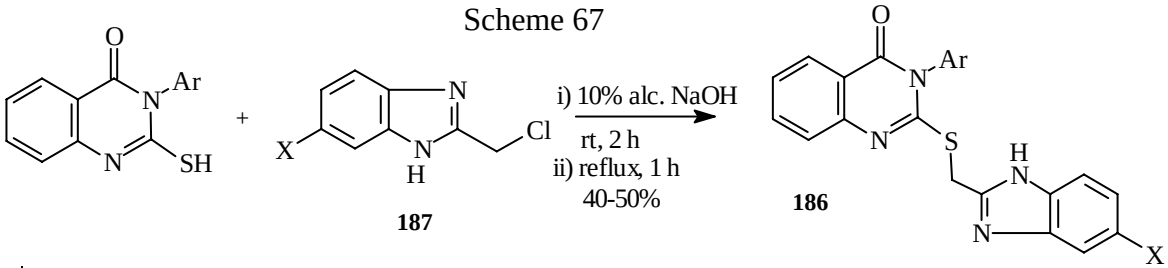
3-Phenyl-2-(2-benzimidazolyl)methylthio-4(3*H*)-quinazolinone (**186**) is a potent antiulcer agent which suppresses domathacine induced ulcers by 90% in mice at 100 mg/Kg. The suppressive effect of *cimitidine* at the same dose is 40%.[115]



186

A mixture of 3-aryl-2-mercapto-4(3*H*)-quinazolinones (**178**) and 2-chloromethylbenzimidazole (**187**) was stirred for 2 h in 10% alcoholic NaOH, kept over-night and then was refluxed for 1 h to give 3-aryl-2-(2-benzimidazolyl)methylthio-4(3*H*)-quinazolinone (**186**). The compounds (**186**) are potential antihelmentic agents (Scheme 67).[40]

Scheme 67



187 **186**

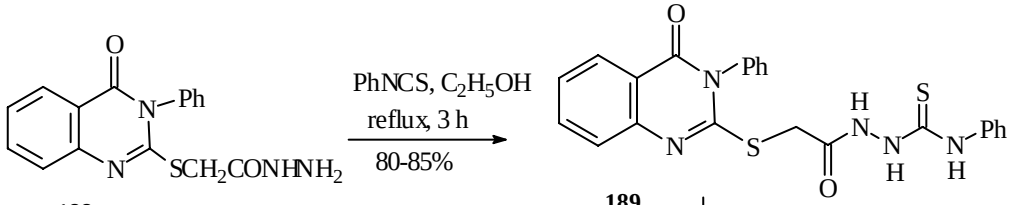
Ar	C_6H_5	4-ClC_6H_4	4-BrC_6H_4	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3-$CH_3OC_6H_4$	α-naphthyl
X	H	H	H	H	H	H	H

Ar	cyclohexyl	C_6H_5	4-ClC_6H_4	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3-$CH_3OC_6H_4$
X	H	Cl	Cl	Cl	Cl	Cl

2.46 Triazolylmethylthio-4(3*H*)-quinazolinones (190, 191, 193)

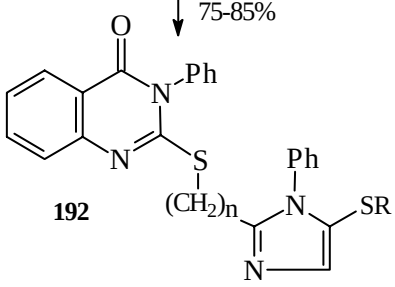
2-[(5-Thione-4-aryl-1,2,4-triazol-3-yl)methylthio]-3-aryl-4(3*H*)-quinazolinones (**190**) are useful as antibacterial agents. They were prepared in two steps starting from [3-aryl-4(3*H*)-quinazolinone-2-yl]thioacetylhydrazine (**188**). Reaction of the quinazolinone (**188**) with phenyl isothiocyanate gave 4-[(6-substituted 3-aryl-4(3*H*)-quinazolinon-2-yl)thioacetyl]-1-arylthiosemicarbazide (**189**), and the side chain at second position was subsequently subjected to ring closure in the presence of 10% Na_2CO_3 (Scheme 68).[21,116]

Scheme 68



188 **189**

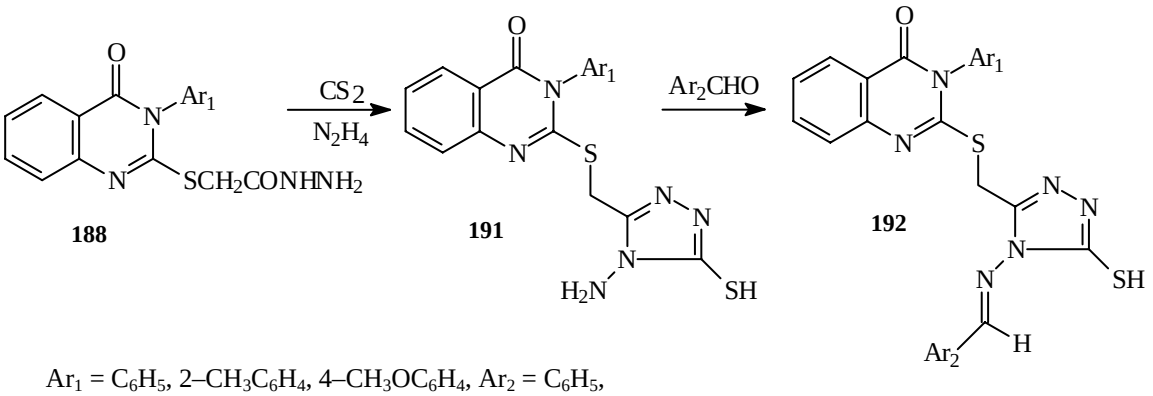
n	R
1	$CONHNHCSNHC_6H_5$
3	$CONHNHCSNHC_6H_5$
1	H
3	H
1	C_2H_5
1	$CH_2C_6H_5$
1	$CH_2(CH_2)_2CH_3$



192

El-Feky and co-workers used similar compounds i.e., [3-aryl-4(3*H*)-quinazolinon-2-yl]thioacetylhydrazine (**188**) for the preparation of 2-triazolylmethylthio-4(3*H*)-quinazolinones (**191**).[31] In this method, the hydrazide was reacted with hydrazine and carbon disulphide to obtain 2-[(4-amino-5-thiol-4*H*-1,2,4-triazol-3-yl)methylthio]-3-aryl-4(3*H*)-quinazolinones (**191**), which were converted to the corresponding Schiff's bases (**192**, Scheme 69).

Scheme 69

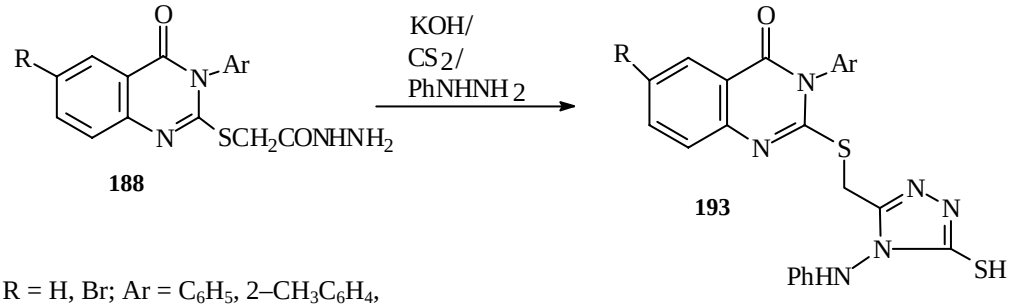


188 **191** **192**

Ar_1 = C_6H_5, 2–$CH_3C_6H_4$, 4–$CH_3OC_6H_4$, Ar_2 = C_6H_5, 4–$CH_3OC_6H_4$, 3–$NO_2C_6H_4$, 4–ClC_6H_4, 4–HOC_6H_4, 2–HOC_6H_4

The antibacterial agents triazolylquinazolinones (**193**) were also prepared from the key intermediate, (3-aryl-4(3*H*)-quinazolinon-2-yl)thioacetylhydrazine (**188**). Reaction with phenylhydrazine and carbon disulfide in alkaline medium yielded 2-((4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio)-3-aryl-4(3*H*)-quinazolinones (**193**) in one-step (Scheme 70).[13]

Scheme 70



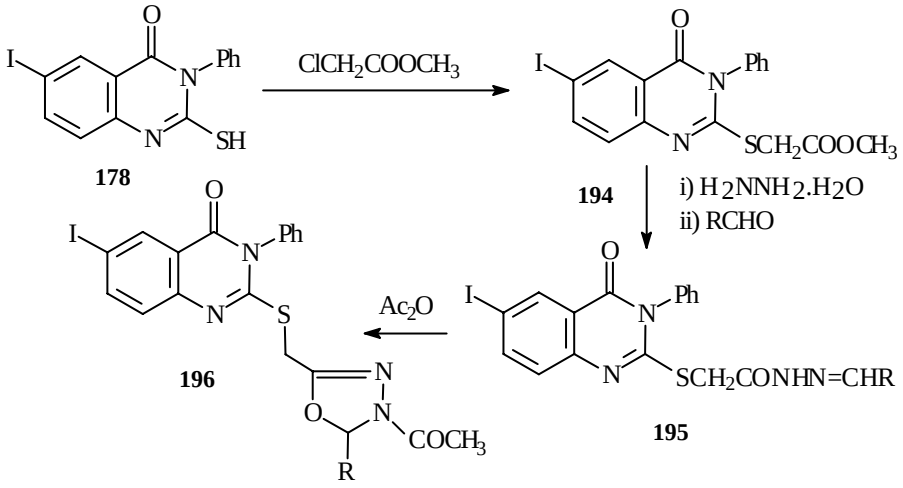
188 **193**

R = H, Br; Ar = C_6H_5, 2–$CH_3C_6H_4$,

2.47 Oxadiazolylmethylthio-4(3*H*)-quinazolinones (196)

Abdel-Hamide and co-workers reported a multi-step synthesis of 2-[(3-(5-substituted 4-acetyl-1,3,4-oxadiazole))methylthio]-3-phenyl-6-iodo-4(3*H*)-quinazolinones (**196**).[32] Reaction of 2-mercapto-3-phenyl-6-iodo-4(3*H*)-quinazolinone (**178**) with methyl chloroacetate gave 2-methoxycarbonylmethylthio-3-phenyl-6-iodo-4(3*H*)-quinazolinones (**194**) which on treatment with hydrazine hydrate followed by condensation with aldehydes afforded the hydrazone (**195)**. In the presence of acetic anhydride, **195** cyclized to **196** (Scheme 71).

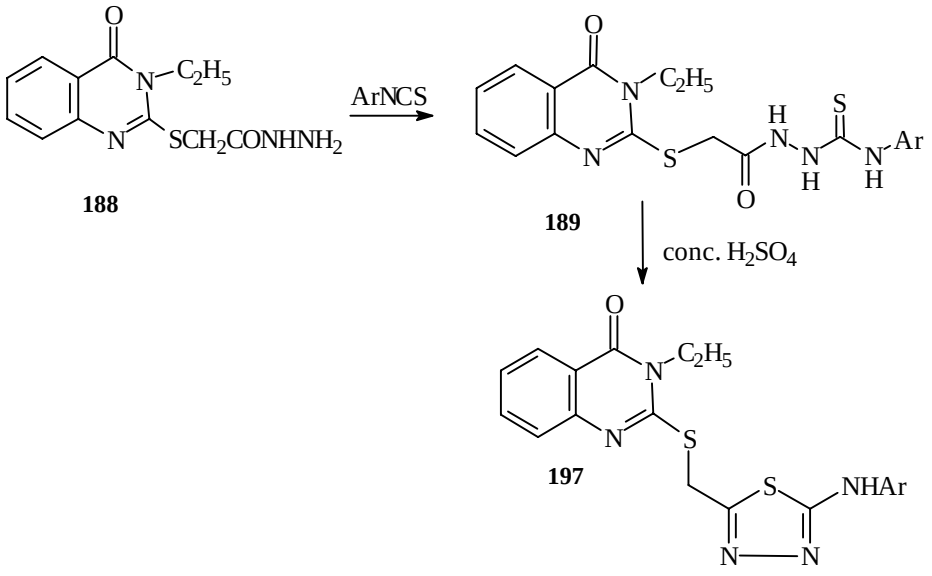
Scheme 71



2.48 Thiadiazolylmethylthio-4(3*H*)-quinazolinones (197)

2-[(5-Arylamino-1,3,4-thiadiazole-2-yl)methylthio]-3-ethyl-4(3*H*)-quinazolinones (**197**) are useful as antifungal agents. They were prepared by cyclizing 4-(3-ethyl-4(3*H*)-quinazolinone-2-yl)thioacetyl)-1-arylthiosemicarbazide (**189**) in conc.H_2SO_4 (Scheme 72).[116]

Scheme 72

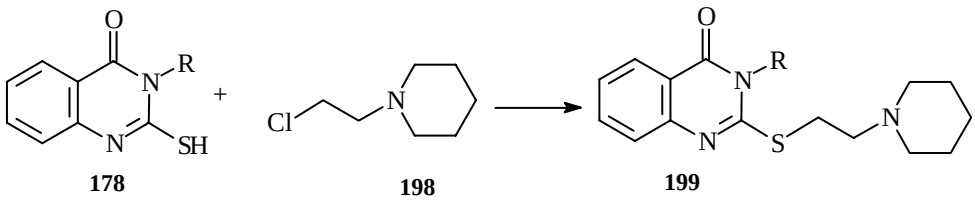


Ar = 4–$CH_3C_6H_4$, 4–$NO_2C_6H_4$, 4–ClC_6H_4, 4–BrC_6H_4, 4–FC_6H_4

2.49 Piperidinethylthio-4(3*H*)-quinazolinones (199, 202)

Bhargava and Singh prepared 2-(1-piperidinethylthio)-3-aryl/alkyl-4(3*H*)-quinazolinones (**199**) from the reaction of 3-aryl-2-mercapto-4(3*H*)-quinazolinones (**178**) with piperidinethyl chloride (**198**). These quinazolinone derivatives (**199**) inhibited *Mycobacterium tuberculosis* (Scheme 73).[49]

Scheme 73

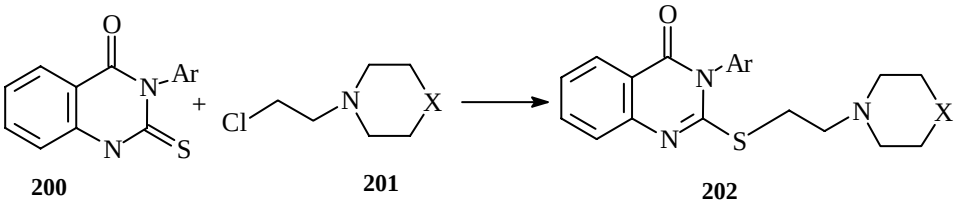


178 **198** **199**

R = C_6H_5, 2–$CH_3C_6H_4$, 3–$CH_3C_6H_4$, 4–$CH_3C_6H_4$, CH_3, C_2H_5, C_4H_9

In a similar reaction, 2-thioquinazolindiones (**200**) were reacted with piperidinyl or morpholinylethyl chloride (**201**) as a method for preparing 2-(β-piperidinyl / morpholinyl)ethyl)thio-3-aryl-4(3*H*)-quinazolinones (**202**). The hydrochloride salt of these compounds (**202**) possesses radioactive protective properties (Scheme 74).[46]

Scheme 74



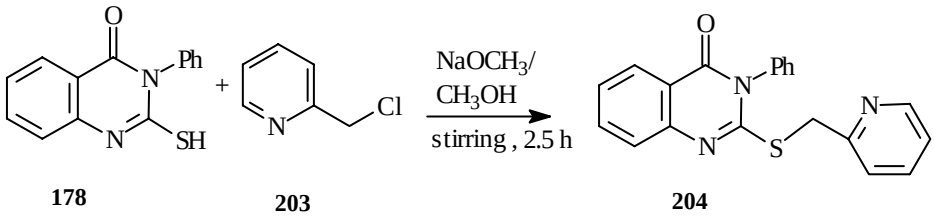
200 **201** **202**

X = O, CH_2; Ar = C_6H_5, 4–$CH_3C_6H_4$, 4–$CH_3OC_6H_4$, 4–ClC_6H_4

2.50 Pyridylmethylthio-4(3*H*)-quinazolinones (204, 205)

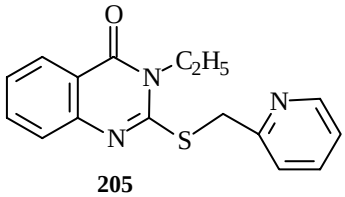
3-Phenyl-2-(2-pyridylmethylthio)-4(3*H*)-quinazolinone (**204**) was found to possess antiulcer properties. It was obtained from the reaction of 2-mercapto-3-phenyl-4(3*H*)-quinazolinones (**178**) with 2-chloromethyl pyridine hydrochloride (**203**) in the presence of sodium methoxide in methanolic solution (Scheme 75).[117]

Scheme 75



178 **203** **204**

3-Ethyl-2-(2-pyridylmethylthio)-4(3*H*)-quinazolinone (**205**) is a potent antiulcer agent which suppresses in domathacine induced ulcers by 90% in mice at 100 mg/Kg.[115]

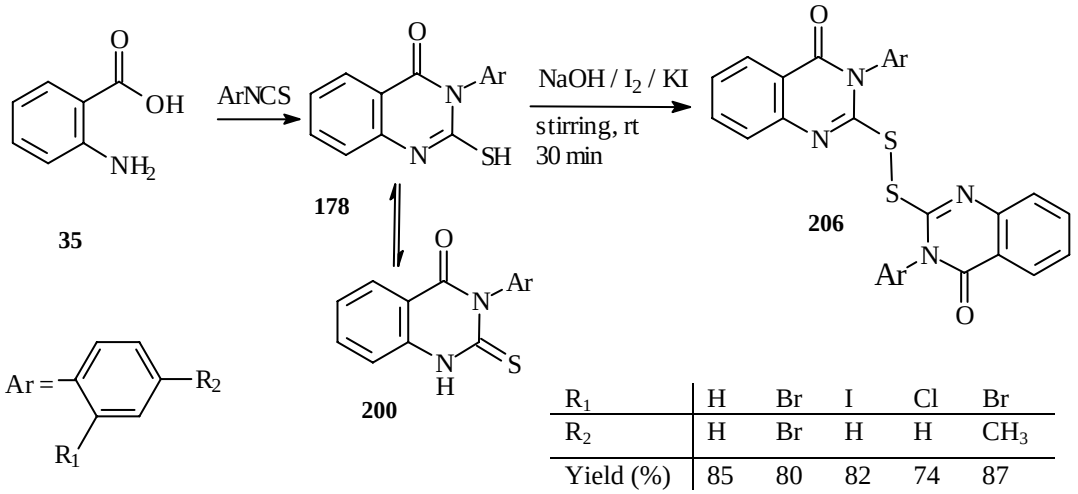


205

2.51 2,2-Dithiobis[3-aryl-4(3*H*)-quinazolinones] (206)

2.2'-Dithiobis[3-aryl-4(3*H*)-quinazolinones] (**206**) were prepared from 2-mercapto-3-arylquinazolinon-4-one (**178**), which in-turn were easily obtained by addition of arylisothiocyanate to anthranilic acid (**35**). Oxidation of **178** using I_2/KI, afforded **206** (Scheme 76).[114,118]

Scheme 76



R_1	H	Br	I	Cl	Br
R_2	H	Br	H	H	CH_3
Yield (%)	85	80	82	74	87

3 CONCLUSION

2-Heteryl / heteroalkyl 4(3*H*)-quinazolinones are synthesized mainly by condensation, dehydrohalogenation, cycloaddition and insertion reactions. Several of these derivatives exhibit wide ranging pharmacological activity such as antihistamine, anticonvulsant, hypnotic and muscle relaxant activity. For instance, 2-[2-(2-pyridyl)vinyl]-3-*o*-tolyl)-4(3*H*)-quinazolinone (**150**) is a drug with trade name *piriqualone.* 2-[2-(3-Indolyl)ethyl]-3-phenyl-4(3*H*)-quinazolinones (**95**) is useful in the treatment of gastrointestinal and appetite disorders, as CCK antagonists and decreases the number of spontaneously active dopamine neurons. 3-(2-Chlorophenyl)-6-fluoro-2-[2-hydroxy-2-(2-methylthiazol-4-yl)vinyl]-4(3*H*)-quinazolinones **(135)** is a neuroprotective agent and a potent AMPA receptor antagonist. 8-(1-Methyl-4-phenylbutyl)-2-[5-morpholinylsulfonyl-2–propoxyphenyl]-4(3*H*)-quinazolinone (**151**) is used for the treatment of cardiovascular and thromboembolic disorders. 3-Phenyl-2-(2-benzimidazolyl)methylthio-4(3*H*)-quinazolinone (**187**) and 3-ethyl-2-(2-pyridylmethylthio)-4(3*H*)-quinazolinone (**205**) are potent antiulcer agents which are 2.5 times potent than *cimitidine* at the same dose.

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