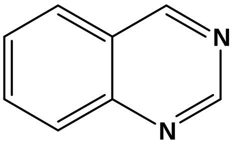
GENERAL INTRODUCTION

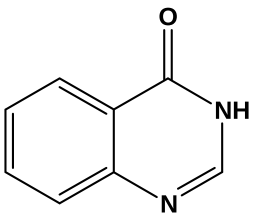
Synthesis of quinazoline derivatives

Quinazoline and its fused analogues appear in many alkaloids. Quinazoline, 1,3-diazanaphthalene (1), is also known as phenmiazine, benzyleneamidine, benzo-1,3-diazine or 5,6-benzo-pyrimidine[1], quinazolinone are important pharmacophore showing many types of pharmacological activities e.g 4(3H)-quinazolinone (2), metolazone (3), fenquizone (4), quinethazone (5) are used as diuretic drugs[2,3] and Mecloqualone (6, R = Cl) , methaqualone (6, R = Me) are used as sedative and hypnotic[4], Rutaecarpine[5](7), chrysogine[6](8) and derivatives of auranthine[7,8](9) .

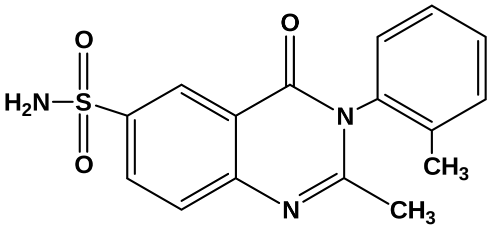
Many quinazolinone derivatives are antimetabolite, CNS depressant[9,10] antimicrobial[11-13] antibacterial[14-16] antimalarial[17-19] analgesic[20] antifungal[21-22] anti-inflammatory[23] antiulcer[24] anti-convulsant[25] antihypertensive[26], anaesthetic[27] tranquilizing and muscle relaxant’[28] antidepressant[29] antihelmentic[30] inhibition of AMDA receptor activation[31] antihistamine[32] insecticidal[33] H_2-antagonist and antisecretion activity[34], tyrosine kinase inhibiting effect and useful to inhibit turn our growth. It's also found application as heat stable epoxy resins[35], fiber reactive dyes[36] and polymers[37].



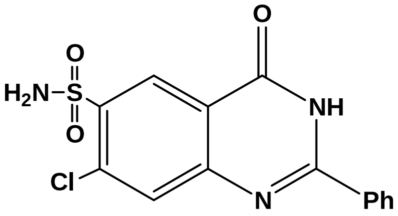
Quinazoline **(1)**



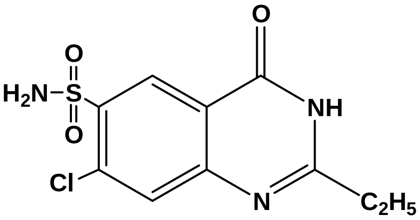
3*H*-Quinazolin-4-one(2)



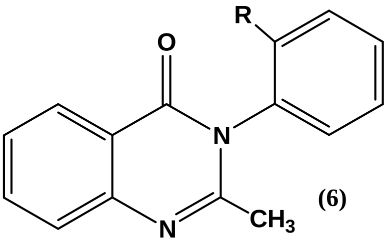
Metolazone **(3)**



Fenquizone **(4)**

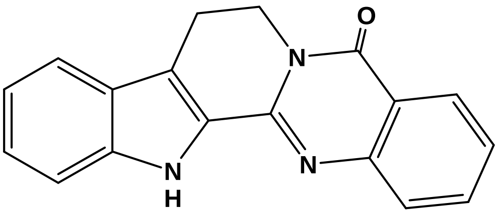


Quinethazone **(5)**

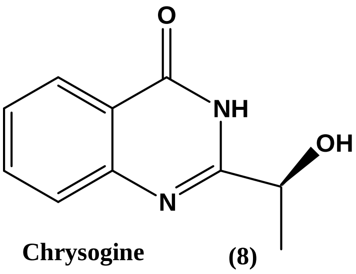


(6)

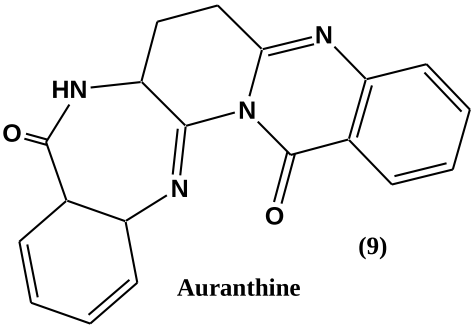
Mecloqualone (R= Cl)
and Methaqualone (R = CH3)



Rutae carpine **(7)**



Chrysogine **(8)**

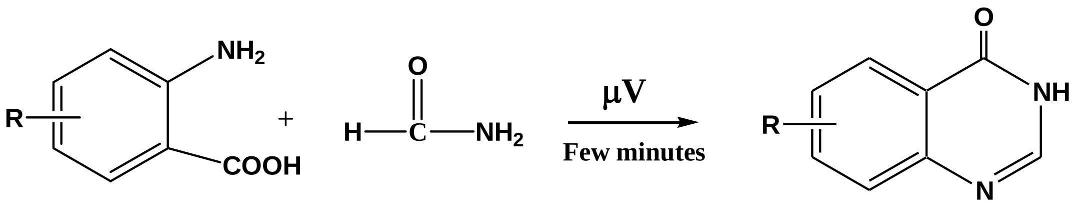


(9)

Auranthine

Synthesis of quinazolinone from anthranilic acid:

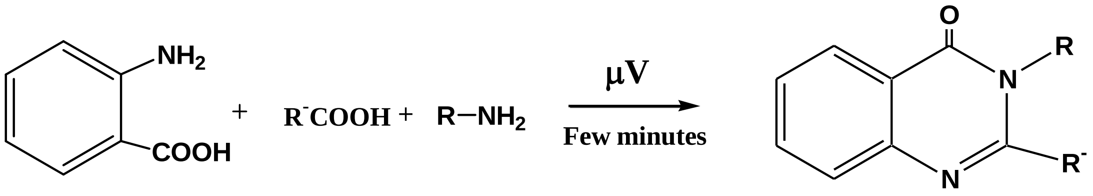
4(3H)-Quinazolinone (11) were prepared in few minutes under microwave irradiation by cyclocondensation reaction of anthranilic acid or its derivatives and formamide[38, 39].



R =6-Cl , 6-MeO , 7-Cl , 7-N0$_2$, H

(10) **(11)**

Also one-pot synthesis of quinazolin-4(3H)-one (14a-g) were carried out by microwave irradiation a mixture of anthranilic acid, carboxylic acid and amines[40].

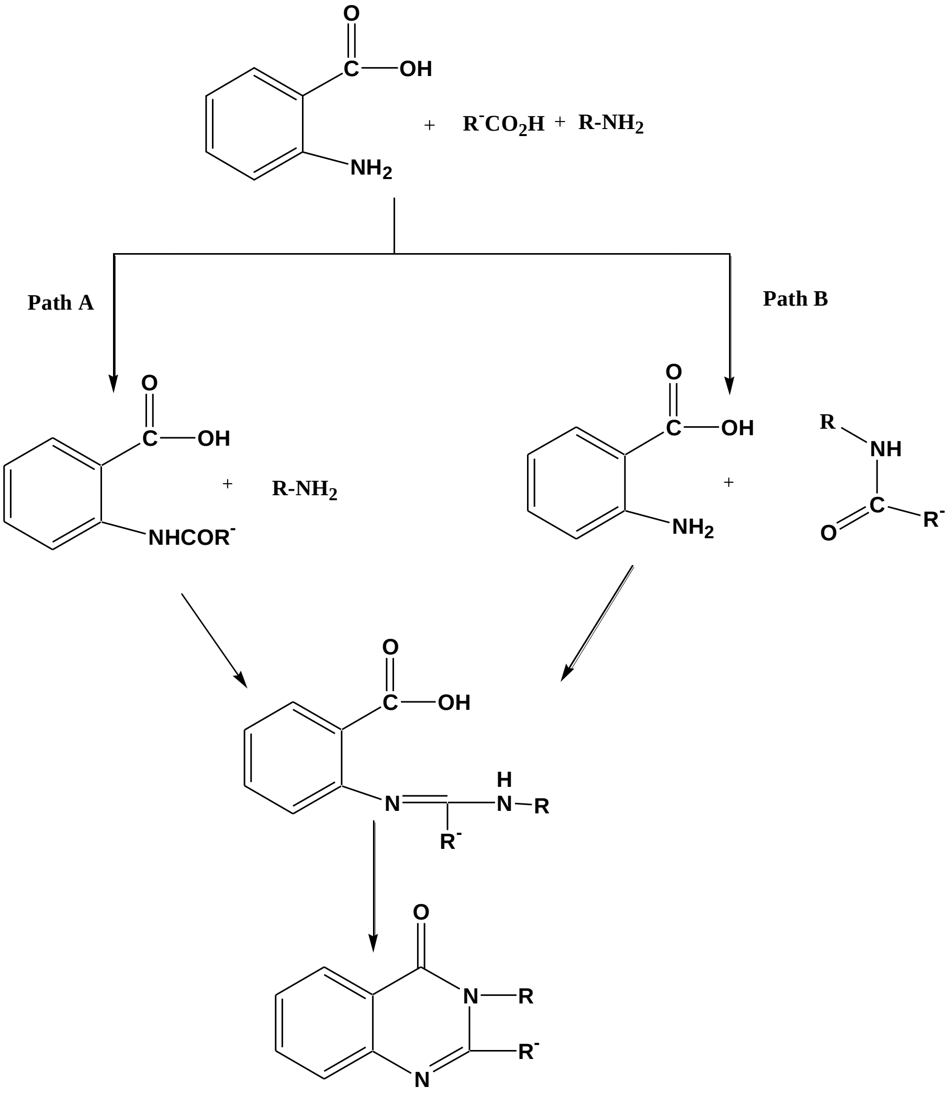


(10) **12a-e** **13a-b** **14a-g**

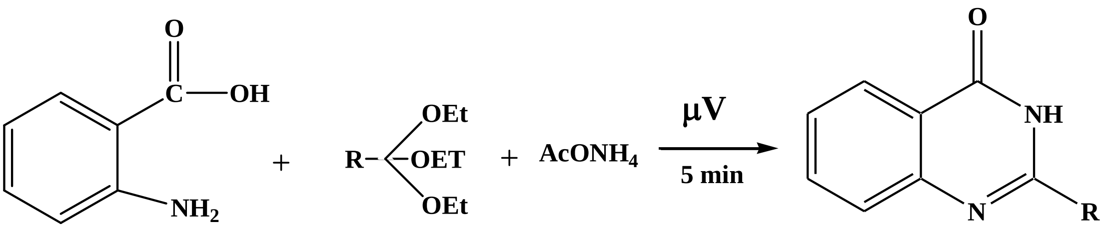
12a R$^-$ = phenyl
12b R$^-$ = 2-hydroxyphenyl
12c R$^-$ = methyl
12d R$^-$ = octanyl
12e R$^-$ = 3-nicotinyl

13a, R = Phenyl
13b, R = 2-furfuryl

14a, R= R$^-$ = phenyl
14b, R = Phenyl, R$^-$ = 2-hydroxyphenyl
14c, R = Phenyl, R$^-$ = methyl
14d, R = phenyl, R$^-$ = octanyl
14e, R = 2-furfuryl, R$^-$ = phenyl
14f, R = 2-furfuryl, R$^-$ = 2-hydroxyphenyl
14g, R = 2-furfuryl, R$^-$ = 3-nicotinyl



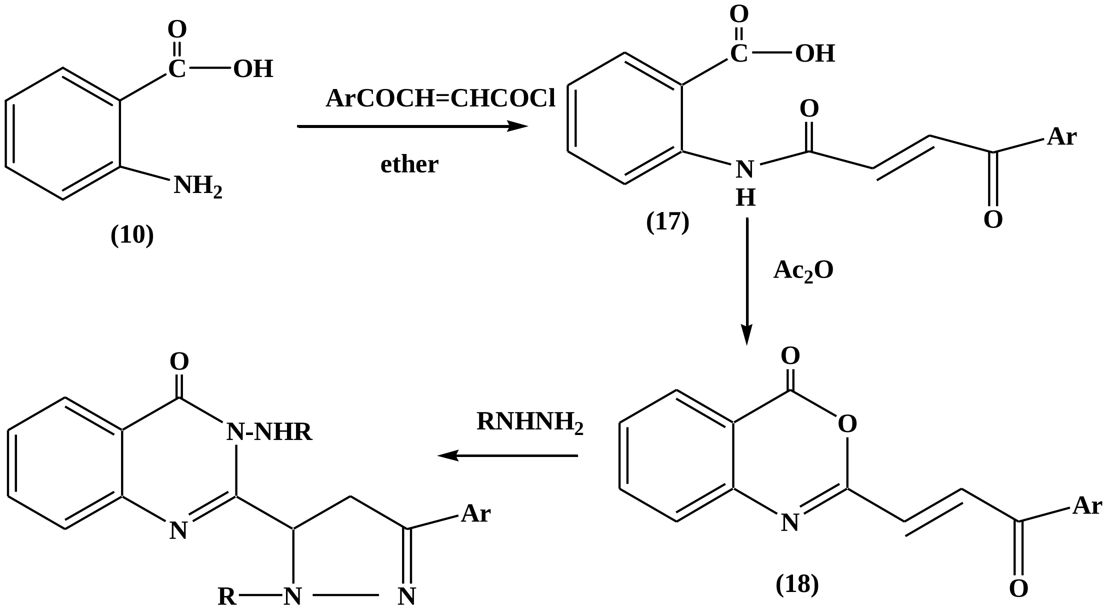
Rad-Moghadam et. al.[41] reported the synthesis of 2-Substituted quinazolin-4(3H)-one (16) under microwave conditions by condensation of anthranilic acid, orthoesters and ammonium acetate.



(10) (15) R = H, Me, Et, Pr, Bu, Ph

(16)

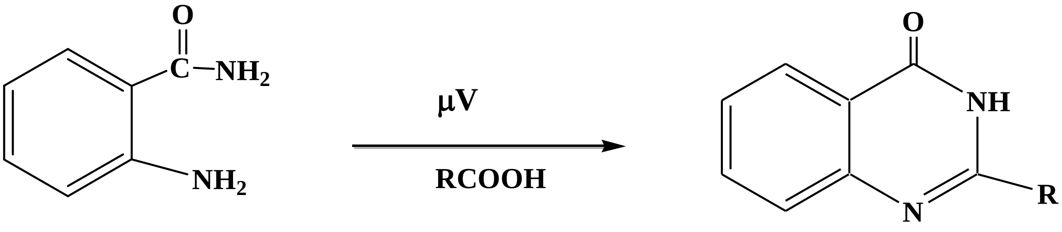
Soliman and co-workers[42] reported the synthesis of 2-pyrazoyl-4(3H)-quinazolinone derivative (19) using 3-aroylpropenoyl chloride and anthranilic acid in the presence of hydrazine hydrate derivatives as the following scheme.



(19)

Synthesis of quinazolinone from anthranilamide derivatives:

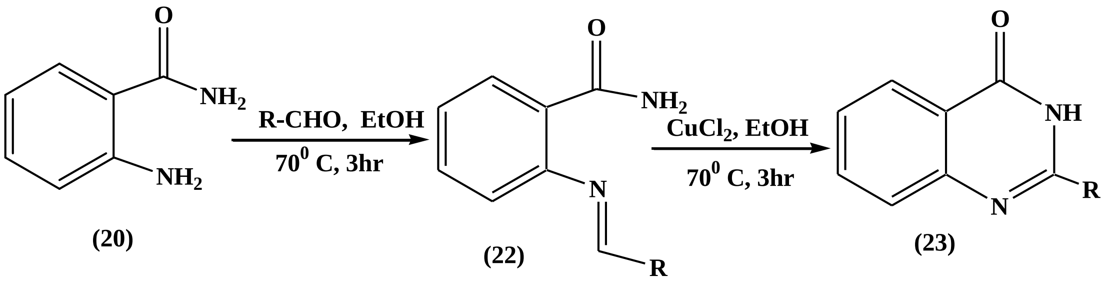
Preparation of 2-substituted-4(3H)-quinazolinone (21) in high yields was developed by microwave induced heterocyclization of 2-aminobenzamide (20) with carboxylic acids, it was found the rat of reaction is 40-60 time faster under the microwave irradiation[43].



(20) (21)

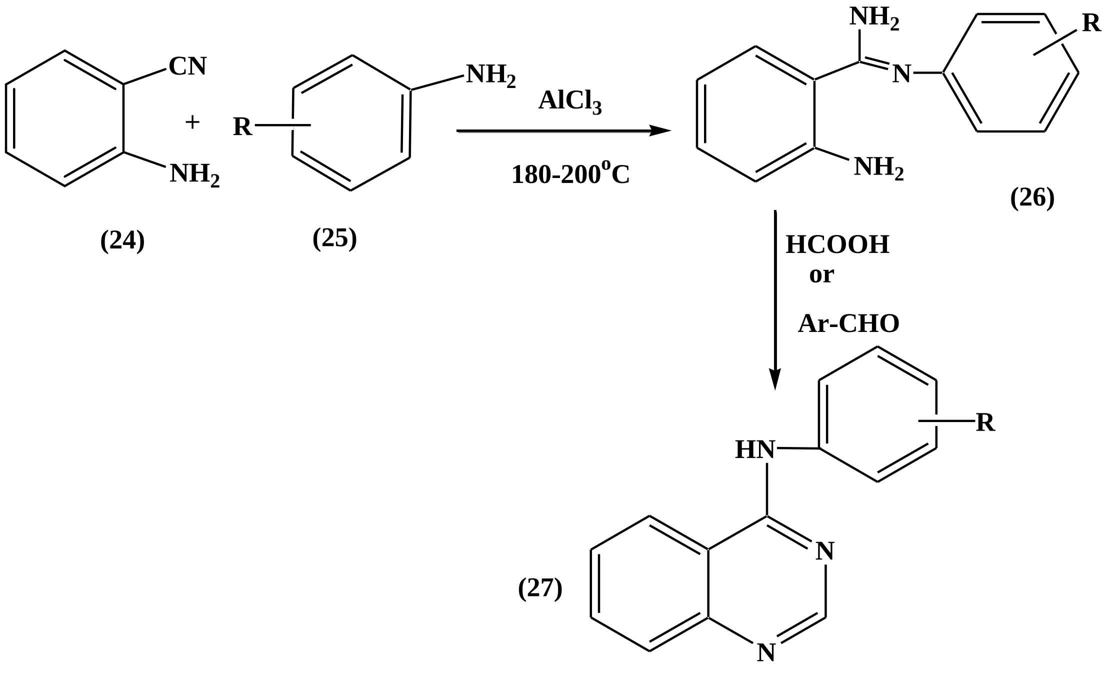
R = H, Me, Ph, 2-Cl-C_6H_4 …

Abdel-Jalil et. al.[44], reported, the reaction between aldehyde, anthranilamide and 3-equivalent of $CuCl_2$ in ethanol under refluxed for 2-3 hr afforded 2-substituted-4(3H)-quinazolinone (23).



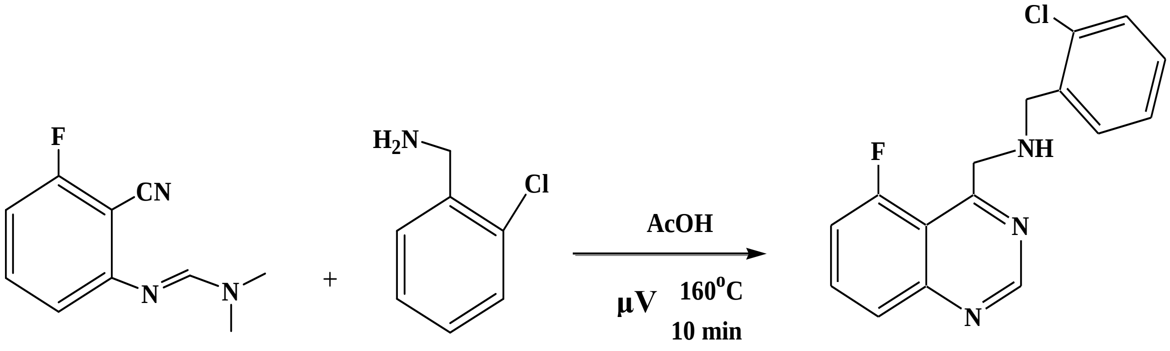
Synthesis of quinazolinone from nitrile:

The reaction of 2-aminobenzonitrile with aniline and anhydrous aluminum chloride gave (26) 2-amino-N-phenylbenzamide[45] which in turns afforded the 4-phenylamino quinazolinone (27) when heated with formic acid or benzaldehyde.



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

Yoon et al.[46] reported the reaction of N,N-dimethylamidino benzamide derivatives (28) with 2-chlorobenzyl amine (29) under microwave irradiation to afforded quinazoline derivatives (30).

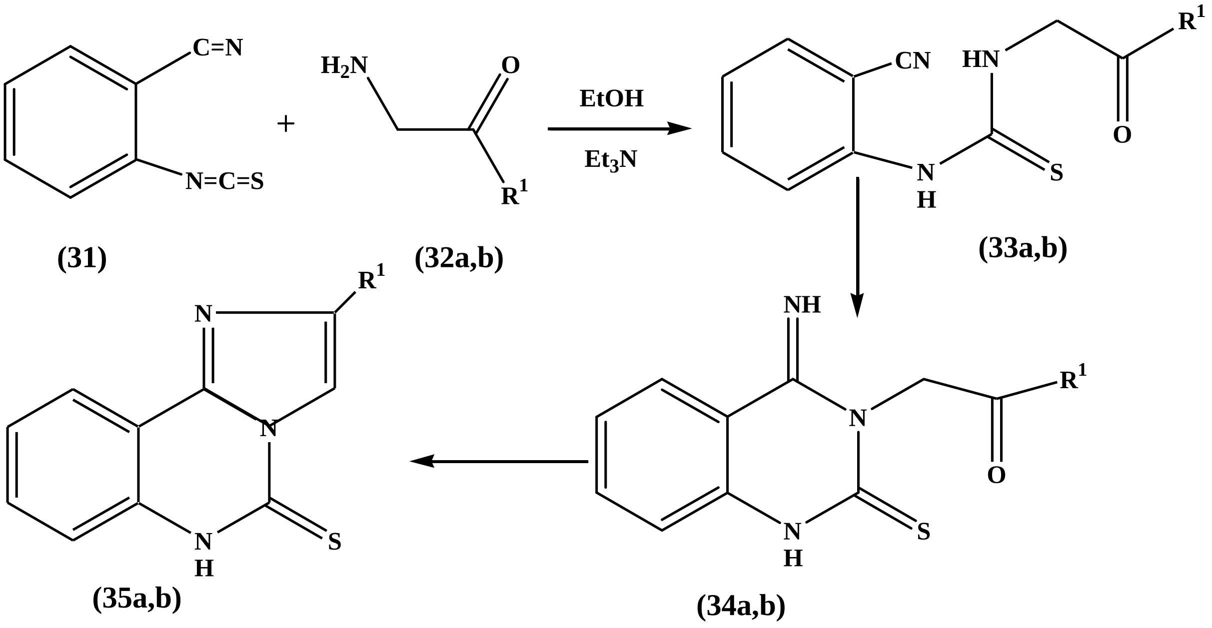


(28) (29) (30)

Synthesis of fused quinazolines

1-Imidazoloquinazoline:

Refluxing of 2-isothiocyanobenzonitrile (31) with α-amino-acetophenone derivatives (32a,b) in ethanol provided (33a,b) which cyclized to give quinazolines (34a,b). Further cyclization of (34a,b) afforded 5-thioxo-6H-imidazolo[1,2-c]quinazolines (35a,b)[47]

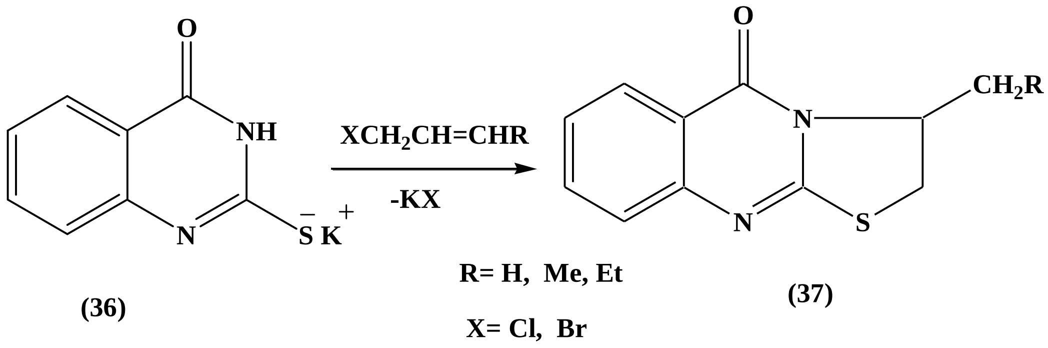


a. $R^1=C_6H_5$,

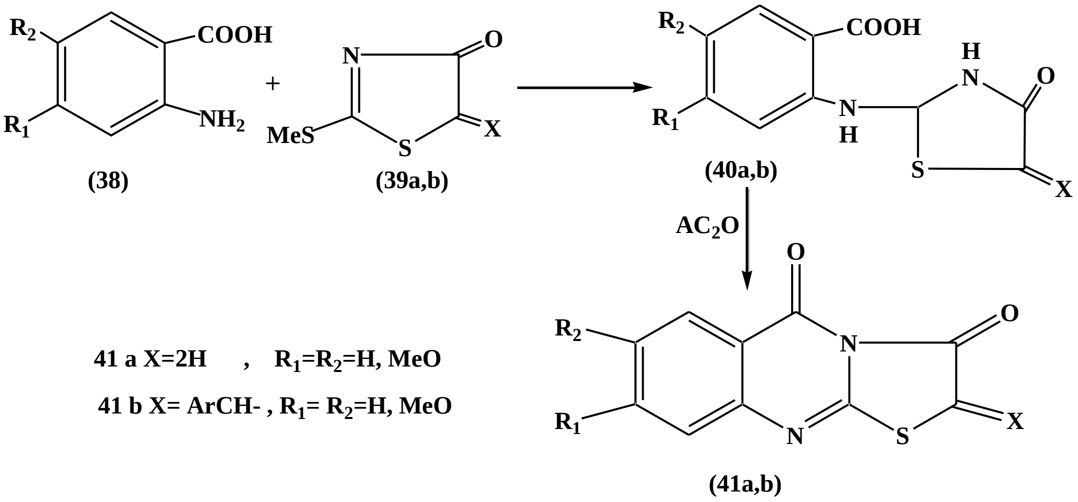
b. $R^1=Me\text{-}C_6H_5$,

2- Thiazoloquinazolinone:

Interaction of the potassium salt of quinazolin-2-thiol-4-one (36) with γ-substituted allyl halides gives thiazoloquinazolinone (37)[48].

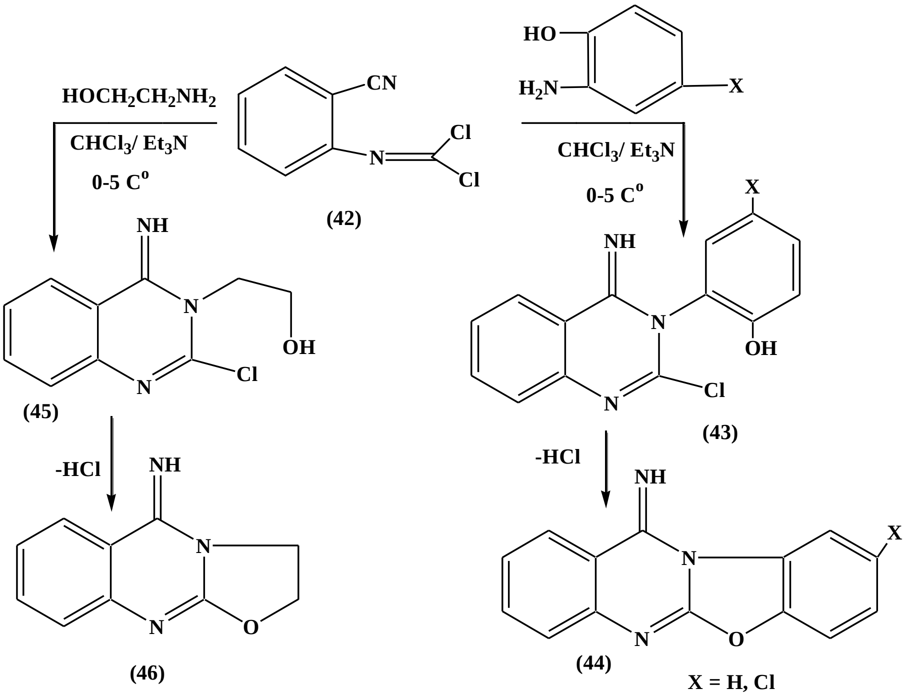


5H-thiazolo[2,3-b]quinazolin-3,5(2H)-dione (41) were prepared via the condensation of 2-methylmercapto-4-thiazolidinone (39a) and or 5-arylidene-2-methylmercapto-4-oxo-thiazolidine (39b) with anthranilic acid derivatives (39) in boiling ethanol to give thiazolo derivatives (40a,b) in acetic anhydride to afford the corresponding 5H-thiazolo[2,3-b] quinazoline 3,5-(2H)-diones (41a) or 2-arylidene-5H-thiozolo[2,3-b]-quinazoline-3,5-(2H)-diones (41b)[49].



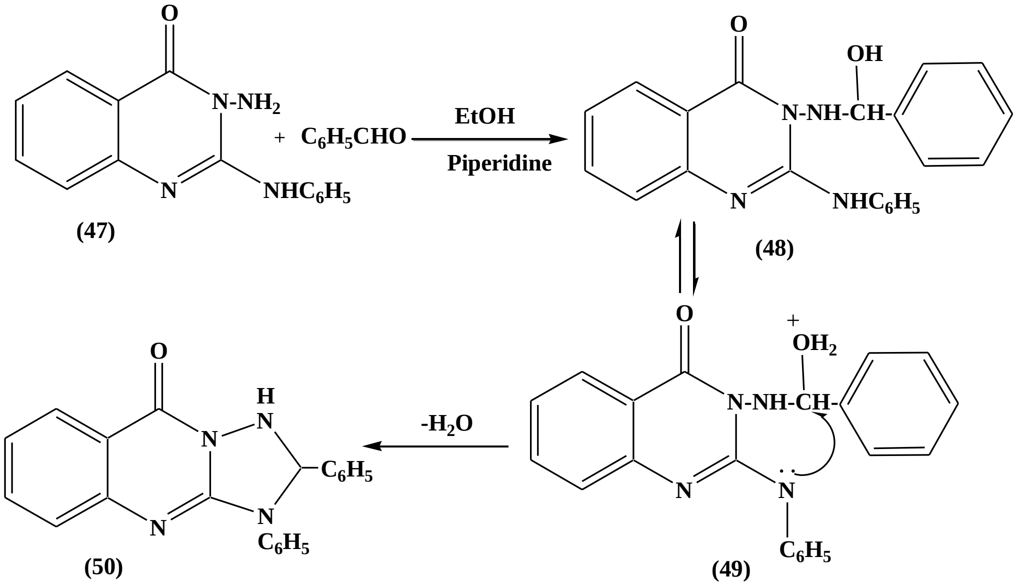
3- Oxazoloquinazolines:

1,3-Benzoxazolo[2,3-b]quinazolin-5-imine (44) and 2,3-dihydro-5H-1,3-benzoxazolo[2,3-b]quinazolin-5-imines (46) were synthesized in one-pot reaction by the Reaction of N-(2-cyanophenyl) chloromethanimidoyl chloride (42) with 2-aminophenols and/or 2-aminoethanol in the presence of base[50].

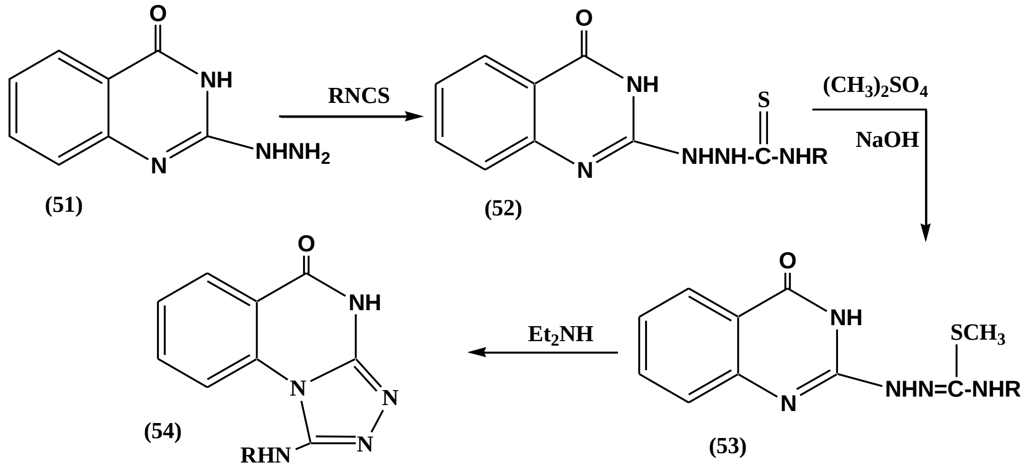


4- 1,2,4-Triazoloquinazolinones:

Refluxing of 3-amino-2-phenylamino quinazolinone (47) with benzaldehyde in ethanol and in the presence of piperidine gives (48) as intermediate. Spontaneously intramolecular cyclization occurs to produce 1,2,4-triazolo[3,2-b]quinazoline-9(1H) ones (50)[51]

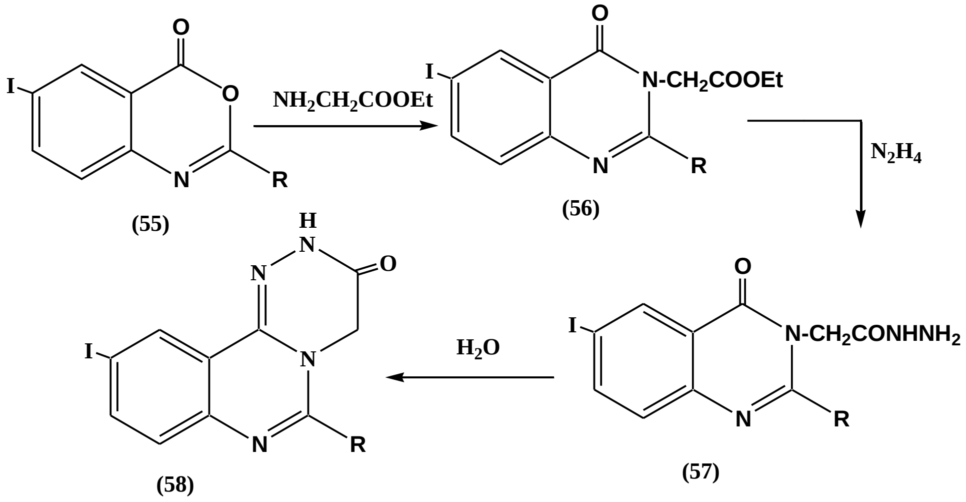


The reaction of 2-hydrazinoquinzolinone (51) with isothiocyanate gives thiourea derivatives (52) methylation of the latter compound (52) with dimethylsulphate gives (53) which on cyclodesulfurization in the presence of base produced 1,2,4-triazolo-[4,3-a] quinazolinones(54)[52]



5-Triazinoquinazolinones:

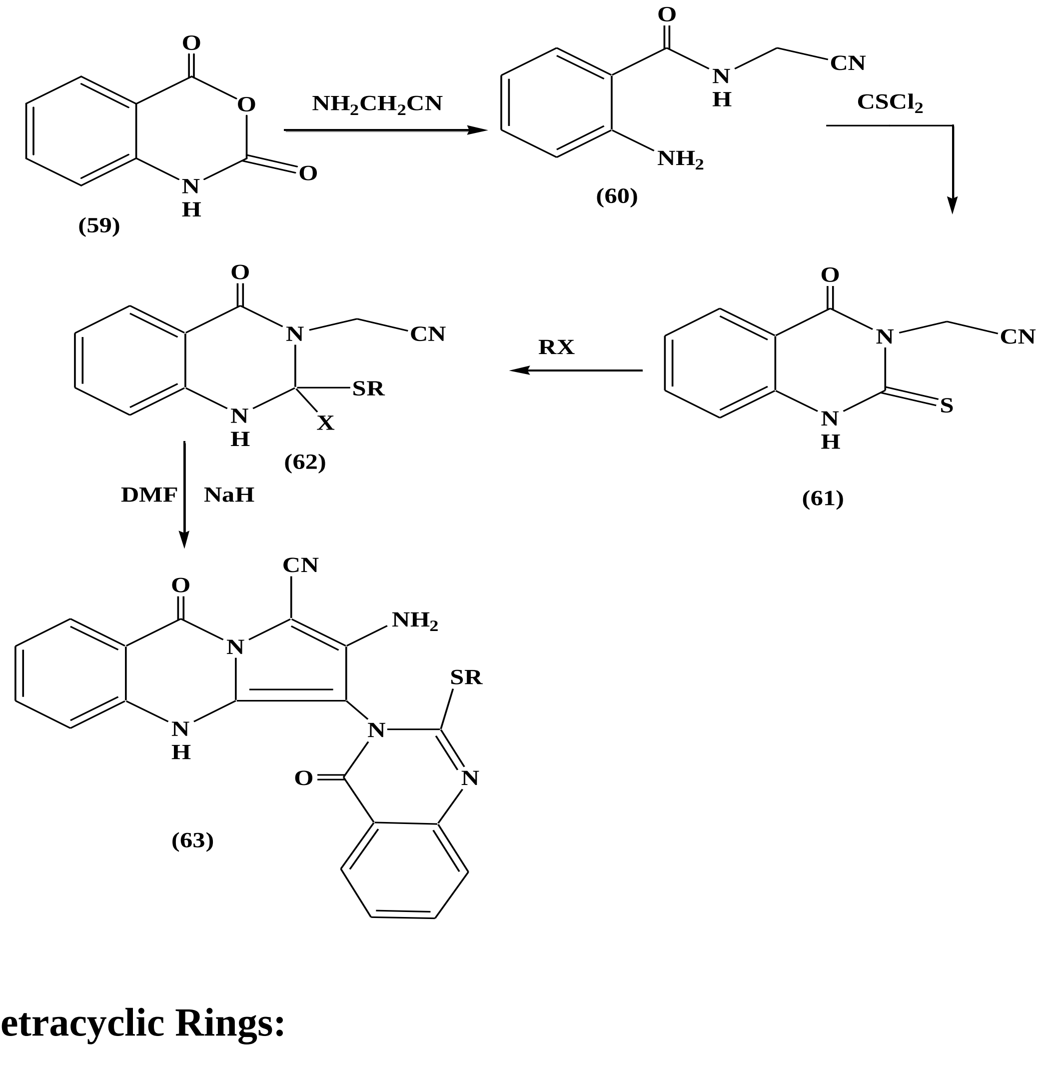
Condensation of 2-substituted-6-iodo-3,1-benzoxazin-4-one (55) with ethylglycinate hydrochloride gave the quinazoline ester derivatives (56). Reduction of ester with hydrazine hydrate furnished hydrazide derivative (57) which was used for synthesis of 1,2,4-triazino[4,3-c]- quinazoline derivatives (58) via cyclization by removal of water molecule.[53-54]



R= Et , Ph

6- Pyrroloquinazolinone:

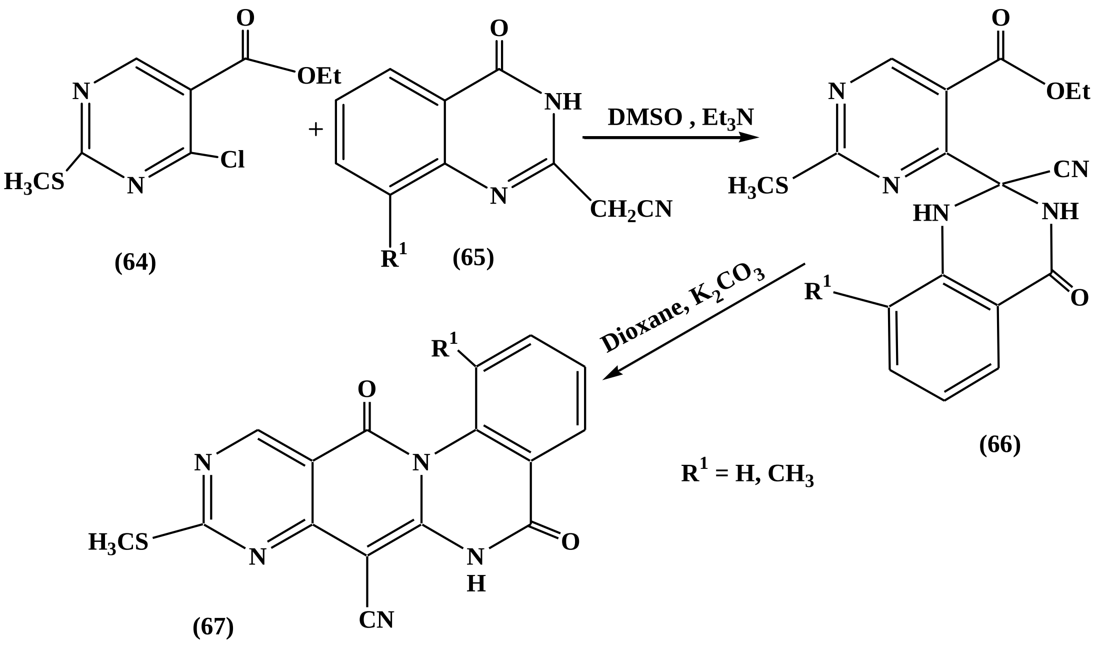
Treatment of isatoic anhydride (59) with aminoacetonitrile afforded 2-amino-N-(cyanomethyl)benzamide (60) which cyclized in the presence of thiophosgene to form thioquinazoline derivatives (61) the alkylation of (61) with appropriate alkyl halide was afforded (62), followed by further cyclization and dimerization in the presence of sodium hydride and dimethylformamide gave pyrroloquinazolinone(63).[55]



7- Tetracyclic Rings:

2-Acetonitrile quinazolinone derivative (65) reacted with 5-ethoxycarbonyl-pyrimidine derivative (64) in dimethylsulfoxide and in the presence of triethyl amine to provide the intermediate (66) which followed by cyclization in dioxane and potassium carbonate to form 3-methylsulfanyl-5-

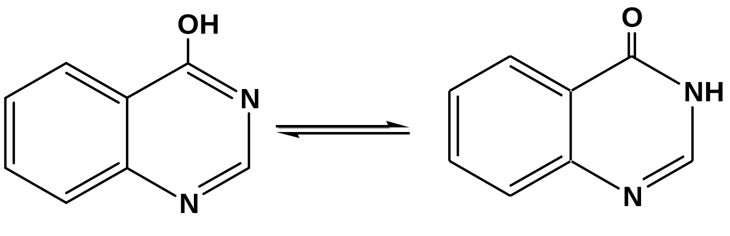
cyano-pyrimido[4`,5`,4,5]pyrido[1,2-a]-quinazoline-7,13-dione (67) in high yield.[56]



Chemical reactions of quinazoline derivatives

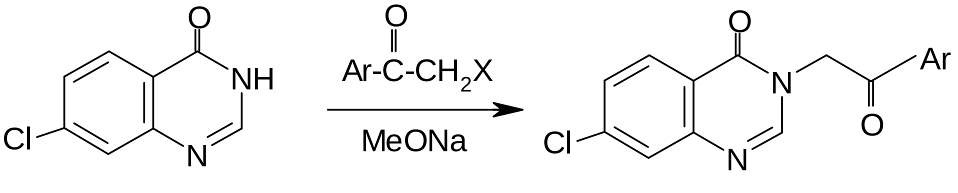
Chemical properties of 4(3H)-quinazolinones:

Knowledge of the behavior of heterocyclic systems under conditions of the principal reactions is required to perform the direct synthesis. Many studies were devoted to the use of various quinazolinone derivatives in the synthesis of linearly and angularly polyannelated, including previously unknown heterocyclic systems. Hydroxyquinazolines are a tautomeric with ketodihydro derivatives (68).



1- Alkylation reactions:

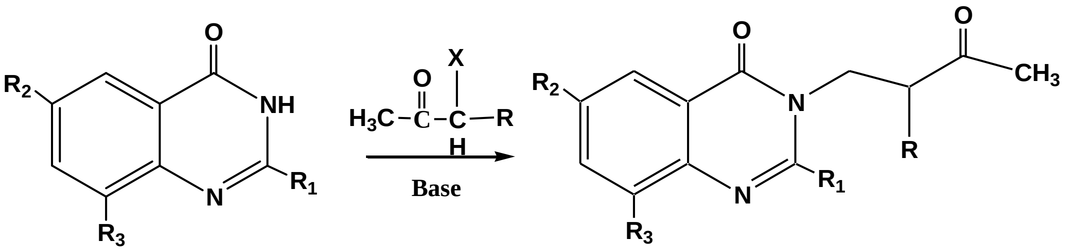
3-Substituted quinazolin-4(3H)-one derivatives (69) were obtained by alkylation of 7-chloro-4(3H)-quinazolinone (68) with α-halocarbonyl compounds in the presence of sodium methoxide[57].



(68) (69)

Ar = Ph, 4-MeOC_6H_4, 2-thiophene , X = Cl, Br, F

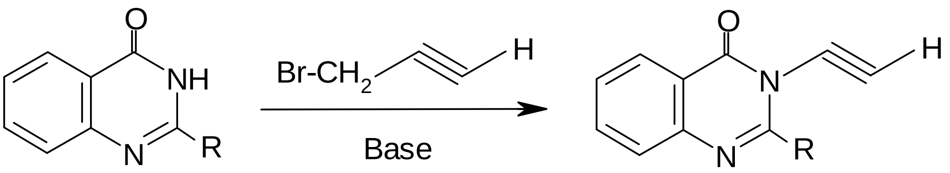
Also alkylation of 4(3H)-quinazolinone derivatives (70) by α-halo-ketone yielded the corresponding 3-(acylalkyl)-2,6,8-trisubstituted quinazolin-4(3H)-ones[58](71).



(70) **(71)**

R = (Me, C_2H_5, Ph, R_1 = H, Me, Ph, 4-ClC_6H_4, R_2, R_3=Cl$_7$Br, OMe, NO_2, Me, X = O, S)

2-Substituted-3-propargyl-4-quinazolinones (73), (R = H, Me, Ph) were prepared by the reaction of 4-quinazolones (72) with CH≡C-CH_2Br in the presence of base [59].

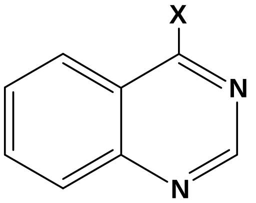


(72) (73)

R = H, Me, Ph

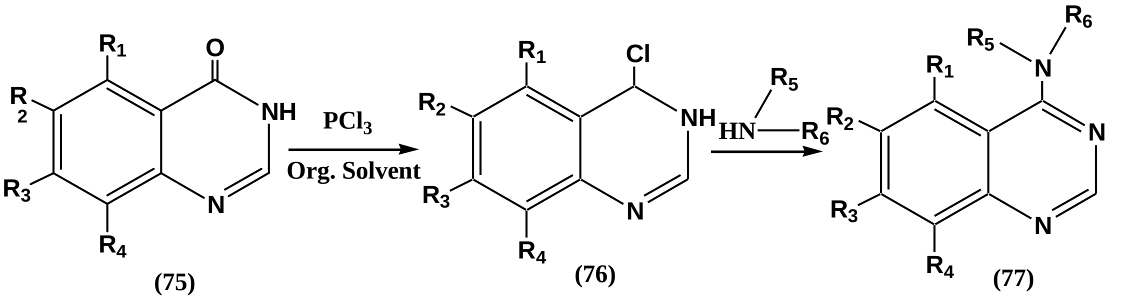
2- Halogenation reactions:

The introduction of chlorine at the 4-position in quinazolinone skeleton (74) can be achieved through the use of $POCl_3$ or thionyl chloride[60-63]. The using $POCl_3$ is reported by Sugimoto *et al.*[64] This involves chlorination with a potassium salt of N-chlorosuccinimide. Treatment of quinazoline with this salt in refluxing in dioxane for 4hr. furnished 4-chloro quinazoline.



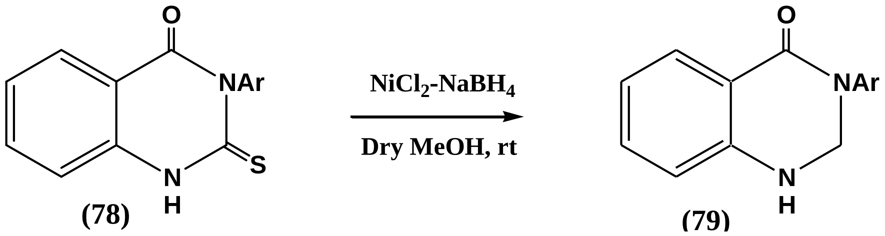
(74)

Quinazolin-4-one derivative (75) was reacted with chlorinating agent in the presence of an organic base. Subsequently, the product (76) reacted with an amine represented by formula (R^5 R^6)NH to give 4-(disubstituted) aminoquinazoline derivatives (77), which are useful intermediates for drugs and in agrochemistry.[65]



3- Desulfurization reactions:

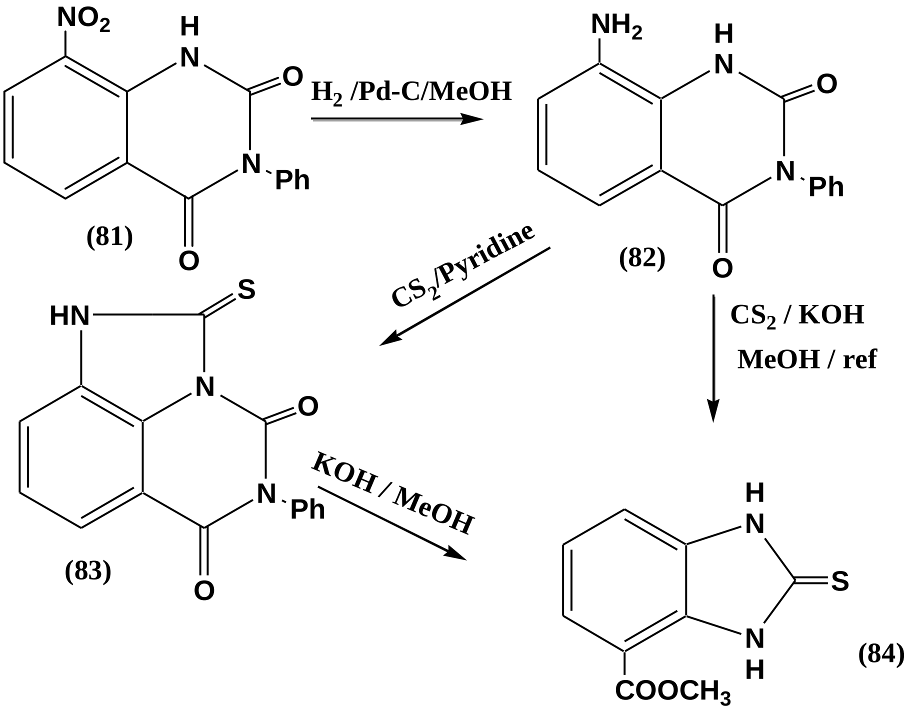
Reductive desulfarization of 2-thioxo-4(3H)-quinazolinone (78) with nickel chloride-sodium boron hydride in dry methanol at ambient temperature give a mixture from 2, 3-dihydro-4(3H)-quinazolinones (79)[66].



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

4-Ring transformation:

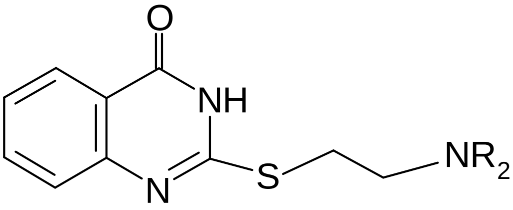
Reduction of 8-nitroquinazolines (81) in methanol and the presence of palladium over carbon gave 8-aminoquinazolines (82) which in turne refluxed with carbon disulfide and pyridine in methanol to obtain the tricyclic derivatives (83). The latter compound was treated with potassium hydroxide in methanol to afford benzimidazol-2-thione (84)[67].



Biological Activity of some Quinazolin4-ones

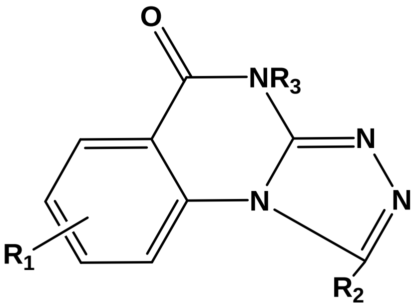
Quinazolinone derivatives are characterized by a very broad spectrum of biological activities[9-33] which includes several dozens of activates. e.g. anticonvulsant[68] hypnotic[69], tranquillizing[70], analgesic[71], anti-inflammatory[72], amoebicidal[73], antimalarial,[74] and antibacterial[75]. Also great interest was found on 4(3H) quinazolinone derivatives such as halogen substituted quinazolinone which exhibit reducing of total cholesterol, cholesterol ester levels and triacylglycerol level.[76-78]

It was that the quinazolinones (85) [NR_2 = NMe2, piperidino, 2,2,6,6-tetramethylpiperidino] exhibited remarkable inhibitory effect on PARP enzyme in vitro[79].



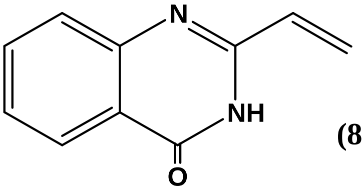
(85)

The 1-alkyl or 1-cycloalkyltriazolo[4,3-a]quinazolin-5-ones (86) are useful for the treatment of pathologies[80].



(86)

2-Vinyl-quinazolin-4(3H)-one (87) is used as starting material to synthesize a series of inhibitors of poly 2-substituted-4(3H)-quinazolinones (ADP-ribose) polymerase[81].



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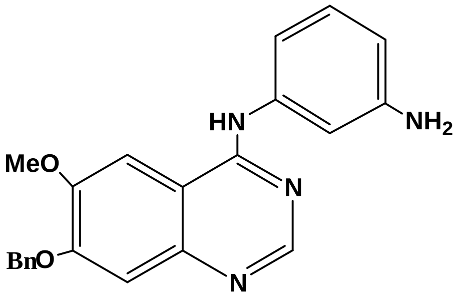
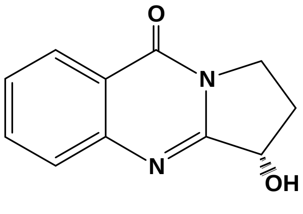
Compound (88) was used as an intermediate in the synthesis of Ax 7593, a quinazoline-derived photo affinity probe for epithelial growth factor receptor (EGFR)[82].

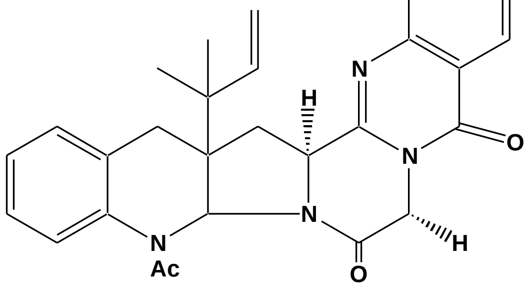


(88)

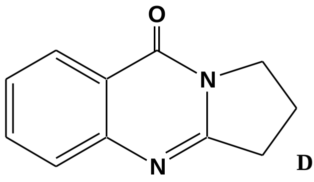
Vasicinone (89), deoxyvasicinone (90), N-acetylardeemin (91) are important pharmacologically for synthesis multi drug resistance reversal agent[83]



Vasicinone (89)



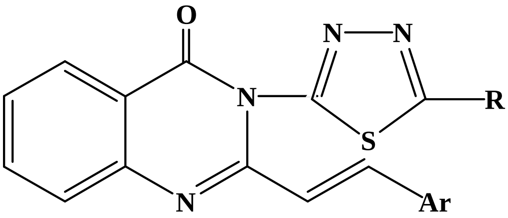
N-acetylardeemin (91)



(90)

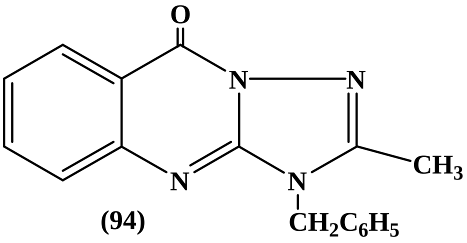
Deoxyvasicinone

3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones (92) evaluated for anticonvulsant, sedative-hypnotic and CNS depressant activities.[84]



(92)

A series of 3-benzyl-2-substituted-3H-[1,2,4]triazolo[5,1b]-quinazolin-9-ones (93) evaluated for their in vivo antihypertensive activity using spontaneously hypertensive rats (SHR). 3-benzyl-2-methyl-3H-[1,2,4]triazolo[5,1-b] quinazolin-9-one(94) exhibited antihypertensive activity more than the reference standard prazocin.[85]



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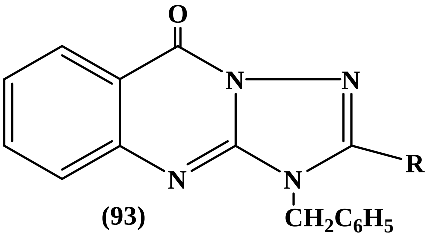
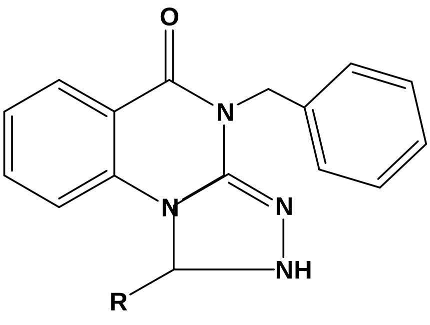


(93)

A series of novel 1-substituted-3-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-ones (95) all the test compounds protected the animals from histamine induced bronchospasm significantly. [86]

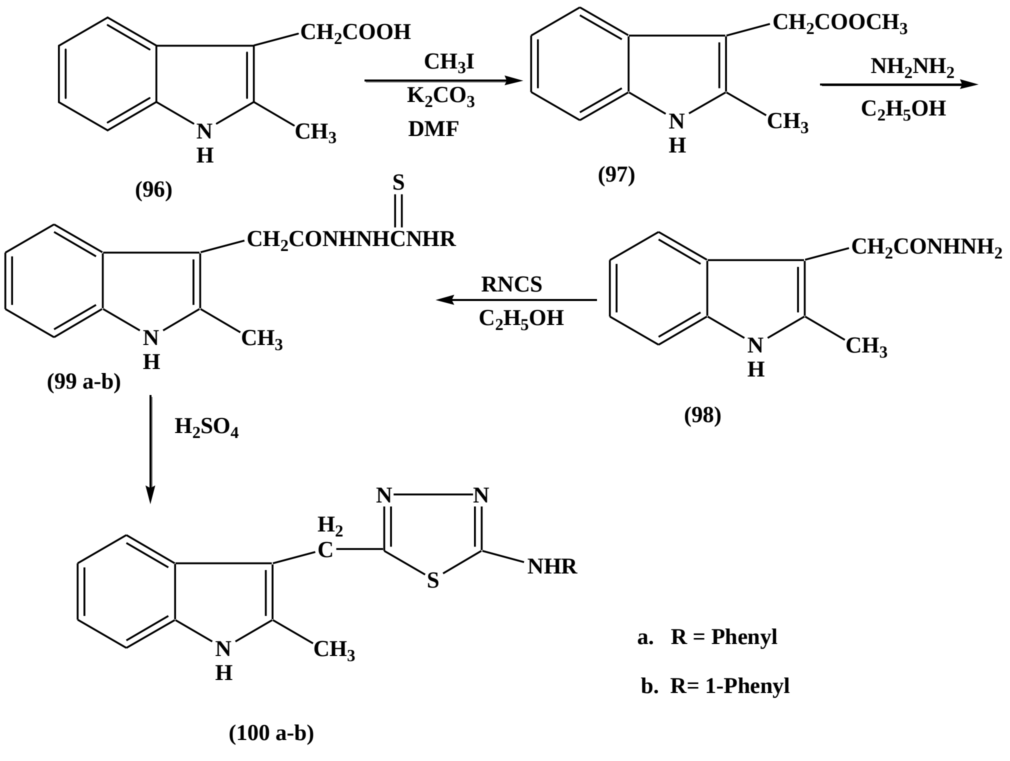


(95)

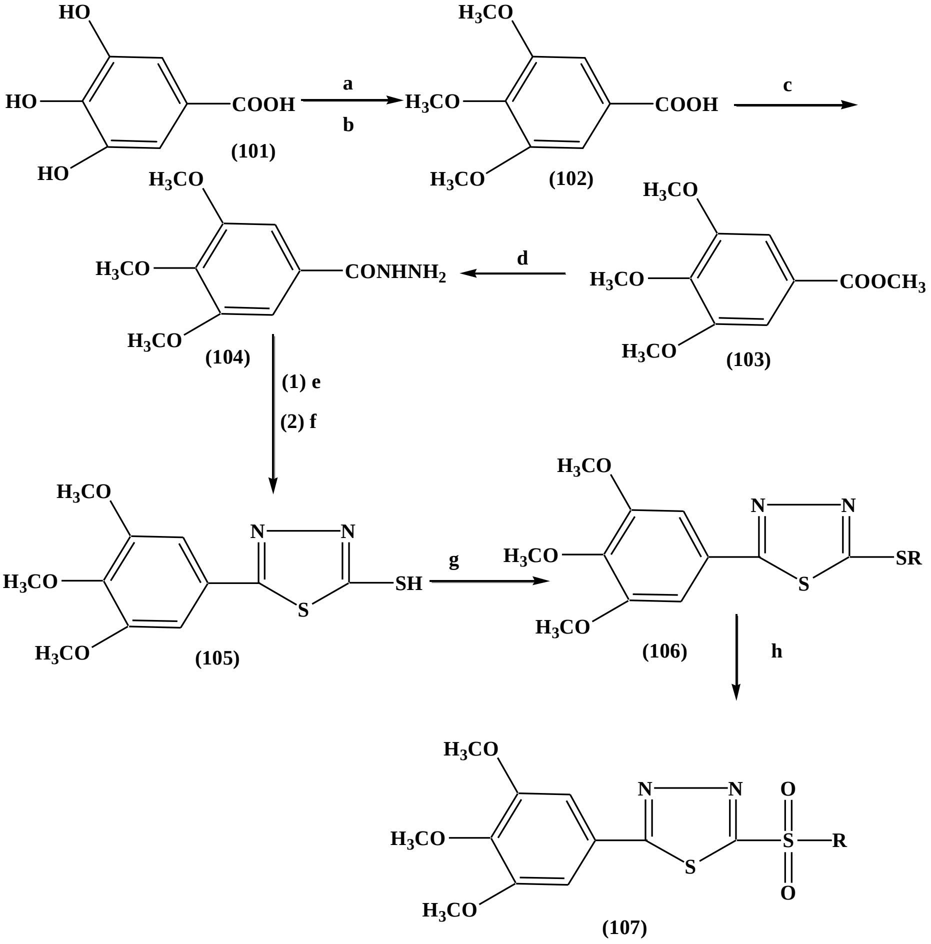
Synthesis of Thiadiazole derivatives

Thiadiazole nucleus has been employed as a basis for the synthesis of biologically active compounds. Also a large number of Thiadiazole derivatives have been reported to possess various biological properties such as analgesic[87], anti-inflammatory[88,89], antimicrobial[90], anti-proliferative[91] and antitubercular[92].

2-methyl-3-indoleacetic acid (96) was reacted with iodomethane in the presence of potassium carbonate to give ester (97). The latter was converted to the desired hydrazide (98) in 73% yield upon treatment with hydrazine hydrate in ethanol. The heteroacetyl thiosemicarbazides (99) were obtained upon the reaction of acid hydrazide (98) with aryl isothiocyanates in ethanol. Cyclization of (99a-b) with sulfuric acid resulted in the formation of N-5-[(2-methyl-1H-3-indolyl) methyl]-1,3,4-thiadiazol-2-yl)- N-aryl amines(100 a-b).[93]

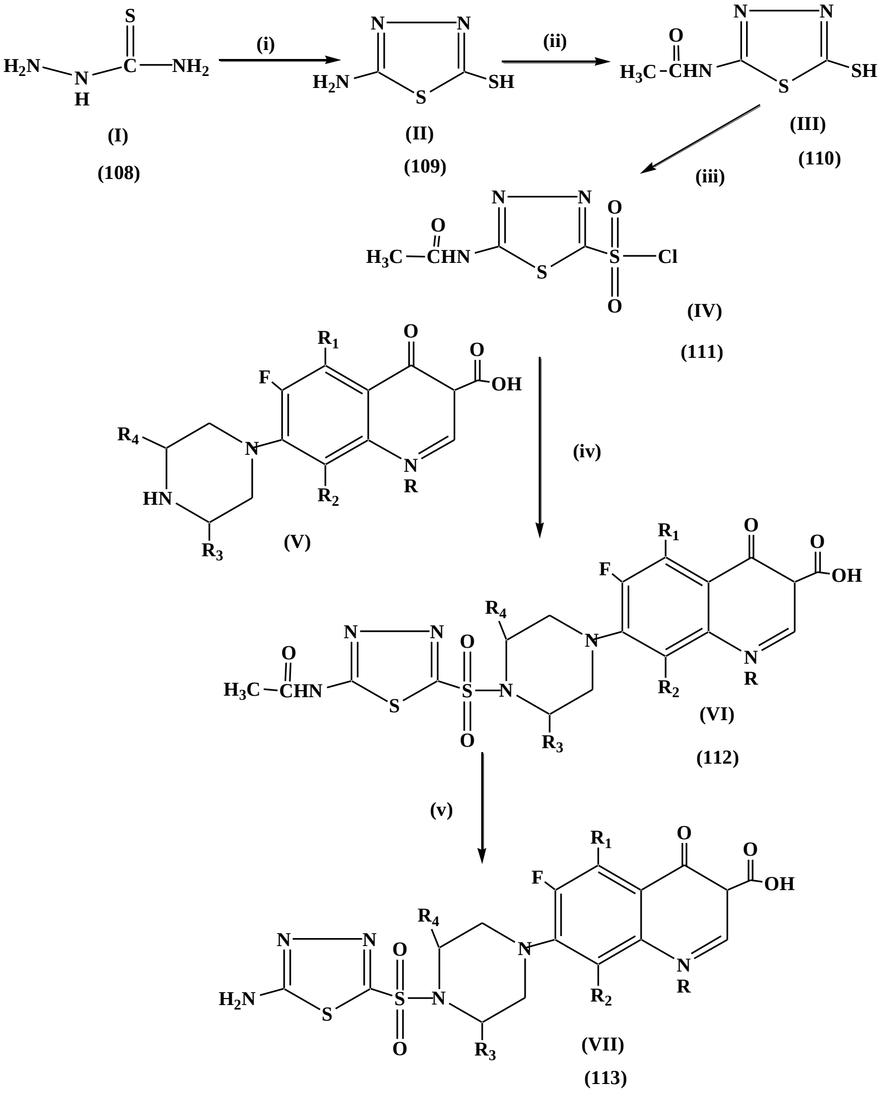


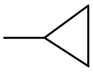
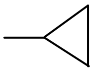
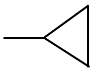
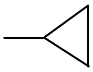
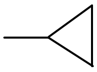
5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole-2-thiol (105) was synthesized from gallic acid in five steps: etherification, esterification, hydrazidation, salt formation, and cyclization to afford 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole-2-thiol (105) which converted to thioether derivatives containing thiadiazole (106) by a thio etherification reaction with halide (RX). Treatment of (106) by H_2O_2 catalyzed by ammonium molybdate in ionic liquid afforded the heterocyclic sulfones (107), with good yields.[94]



Reagents and conditions: (a) $(CH_3)_2SO_4$, 10% NaOH; (b) 35% HCl; (c) CH_3OH, 98% H_2SO_4,reflux; (d) $NH_2NH_2.H_2O$, CH_3OH, reflux for 5 h; (e) KOH, CS_2, C_2H_5OH , rt; (f) 98% H_2SO_4 , 0–5 C°(g) In, 3% NaOH,H_2O, RX ; (h) 30%H_2O_2, $(NH_4)_6Mo_7O_{24}$ (1 mol%), ionic liquid, 40 C°, 2 h.

A series of 7-[4-(5-amino-1,3,4-thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives VII a–d (113) were synthesized in good yields using the starting material 5-acetylamino-[1,3,4]thiadiazole-2-sulfonyl chloride IV (111) was synthesized by oxidative chlorination of 2-acylamino-5-mercapto-1,3,4-thiadiazole III (110) in an aqueous acid solution and passing in the chlorine gas. Compound IV (111) was refluxed with various 7-(1-piperazinyl)FQs Va–d producing the intermediates 7-[4-(5-acetylamino-[1,3,4]thiadiazole-2-sulfonyl)-piperazin-1-yl] FQs VIa–d (112) in good yields, which were later hydrolyzed to form 7-[4-(5-amino-1,3,4-thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives VII a-d (113).[95]

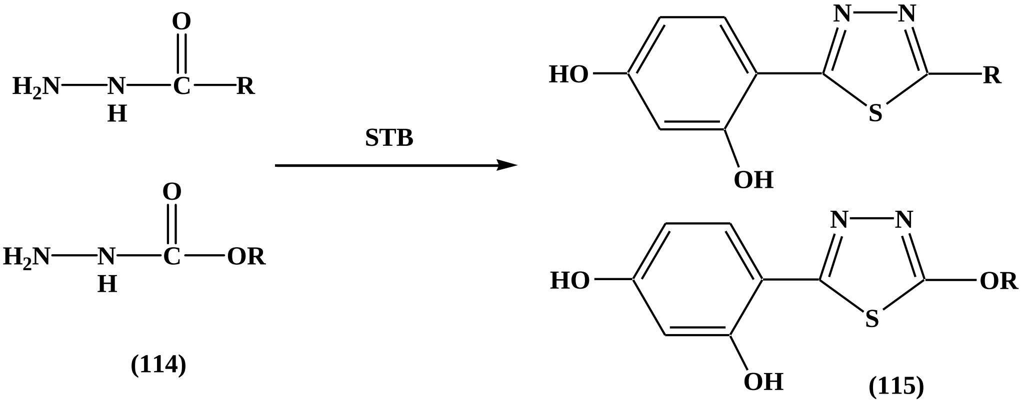


	R	R^1	R^2	R^3	R^4
V-VIIa		H	H	H	H
V-VIIb	$-CH_2CH_3$	H	H	H	H
Vc		$NHCOCH_3$	F	CH_3	CH_3
VIc		$NHCOCH_3$	F	CH_3	CH_3
VIIc		NH_2	F	CH_3	CH_3
V-VIId		H	OCH_3	H	CH_3

Reagents and conditions:

(i) EtOH, CS_2, reflux, 4 h; (ii) acetic acid anhydride, reflux, 2 h; (iii) 33% acetic acid, gaseous chlorine (iv) dried acetone, reflux, 2 h; (v) 2 N NaOH reflux, 4 h; 10% acetic acid.

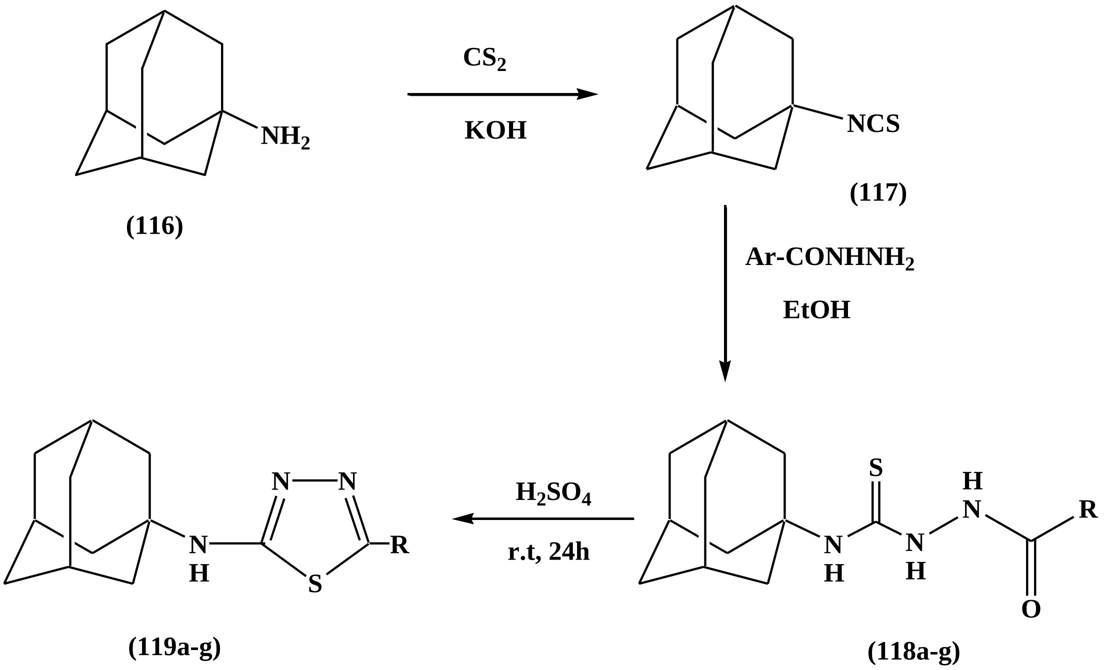
5-Substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles(115) were obtained by the reaction of the sulphinyl bis(2,4dihydroxythiobenzoyl) (STB) with the commercially available hydrazides or carbazates (114) in the endocyclising process. STB was obtained from 2,4-dihydroxybenzene carbodithioic acid and $SOCl_2$ in diethyl ether.[96]



(114)

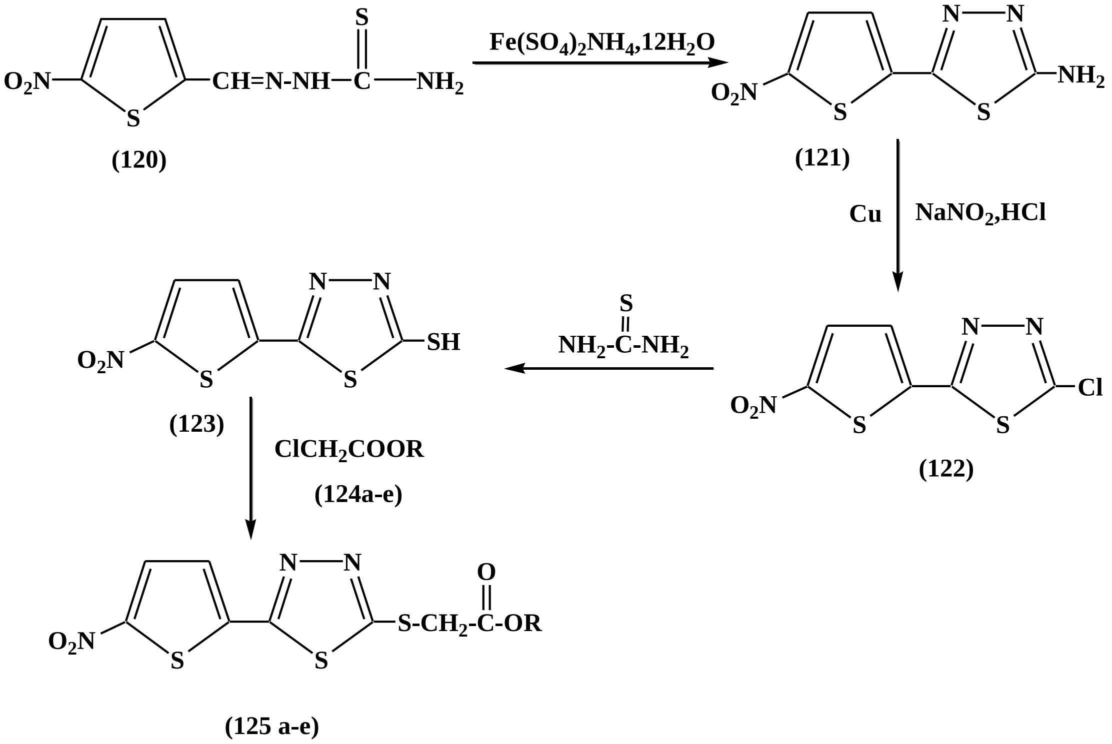
(115)

When 1-adamantyl amine (116) was allowed to react with carbon disulphide in the presence KOH to form 1-adamantylisothiocyanate (117) which reacted with some carboxylic acid hydrazides in ethanol to yield the corresponding 1-acyl-4-(1-adamantyl)-3-thiosemicarbazides (118a-g), which were cyclized to the corresponding 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazole derivatives (119a-g).[97]



119 a	**C_6H_5**	**119 e**	**4-$NO_2C_6H_4$**
119 b	**4-FC_6H_4**	**119 f**	**2-Thienyl**
119 c	**4-ClC_6H_4**	**119 g**	**1-Adamantyl**
119 d	**4-BrC_6H_4**		

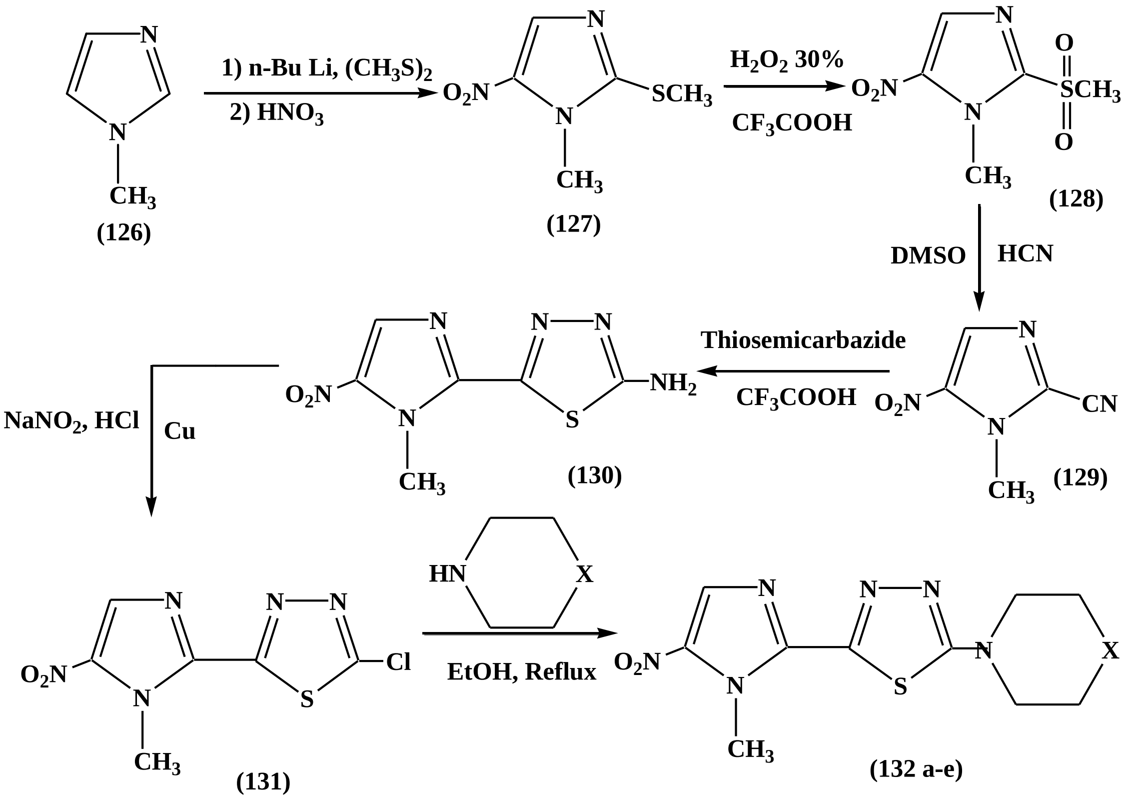
The 2-amino-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole (121) was obtained by oxidative cyclization of 5-nitro-2-thiophene carboxaldehyde thiosemicarbazone (120) in high yield. Diazotization of (121) in hydrochloric acid in the presence of copper powder gave 2-chloro-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole (122). The reaction of (122) with thiourea in refluxing ethanol afforded 2-mercapto-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole (123). Treatment of the latter with alkyl chloro acetates (124a-e) gave alkyl a-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-ylthio] acetates (125a-e).[98]



125 a	Methyl	125 d	n-butyl
125 b	Ethyl	125 e	benzyl
125 c	n-propyl		

The synthesis of 2-(1-methyl-5-nitro-1H-2-imidazolyl)-5-substituted-1,3,4-thiadiazoles (127) was prepared via the reaction of 1-methylimidazole (126) with n-butyl lithium at –30 °C and subsequent addition of dimethyl disulfide gave 1-methyl-2-(methylthio)-1H-imidazole . Nitration of the latter compound with concentrated nitric acid at 70 °C afforded the corresponding 5-nitroimidazole (127). Oxidation of (127) by hydrogen peroxide in trifluoroacetic acid leads to the sulfone (128) where a nucleophilic substitution by cyanide anion produces the corresponding carbonitrile (129) in good yield. Compound (130) was obtained by treatment of (129) with thiosemicarbazide in an acid catalyzed reaction followed by a ring closure process. Diazotization of amine (130) in hydrochloric acid in the presence of copper powder gave 2-chloro-5-(1-methyl-5-nitro-1H-2-imidazolyl)-1,3,4-

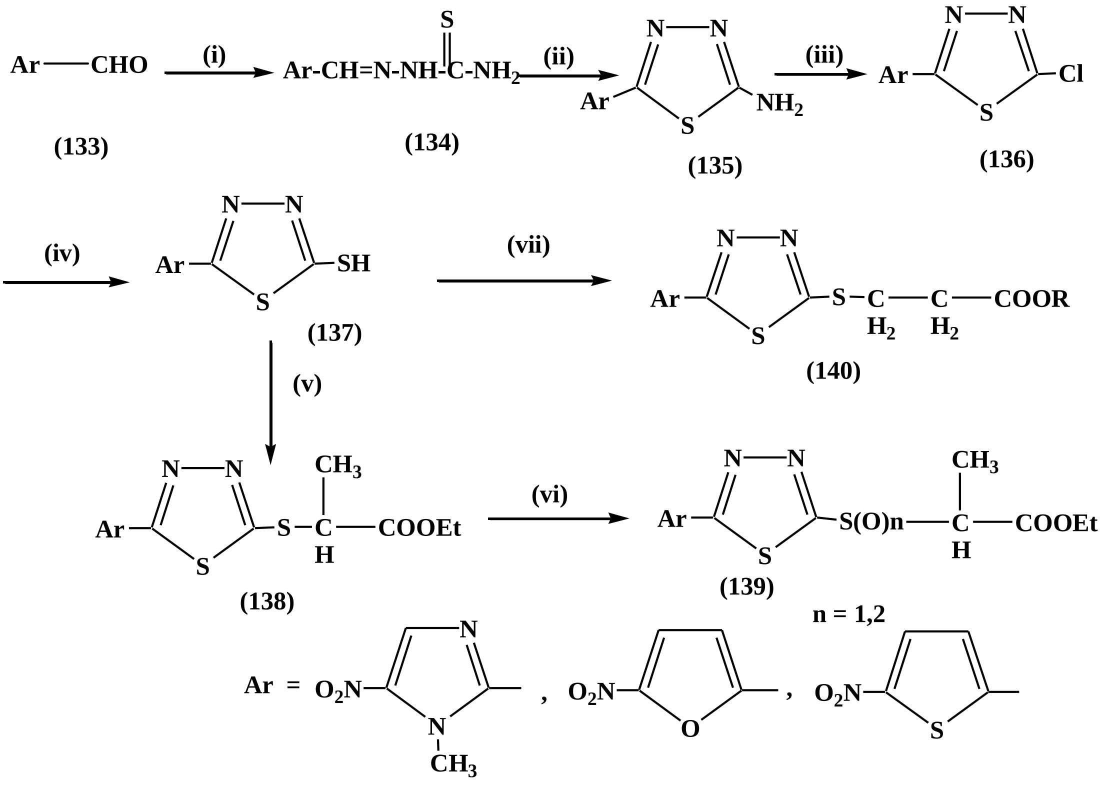
thiadiazole (131) . Reaction of compound (131) with compounds (a-e) in refluxing ethanol gave compounds (132 a-e).[99]



a: X = CH_2
b: X = O
c: X = NH
d: X= NMe
e: X = NPh

Reaction of nitro-aryl aldehyde (133) with thiosemicarbazide in refluxing ethanol afforded compound (134). The 2-amino-5-aryl-1,3,4-thiadiazole (135) was prepared by oxidative cyclization of aryl carboxaldehyde thiosemicarbazone (134). Diazotization of (135) in hydrochloric acid in the presence of copper powder gave 2-chloro-5-aryl-1,3,4-thiadiazole (136). The reaction of (136) with thiourea in refluxing ethanol afforded the 2-mercapto-5-aryl-1,3,4-thiadiazole (137). Treatment of the latter with 2-bromopropionic acid ethyl ester in the presence of basic ethanol provided 2-[5-aryl-1,3,4-thiadiazol-2-ylthio] propionic acid ethyl ester (138). The target compounds

(140) were prepared by treatment of 2-mercapto-5-aryl-1,3,4-thiadiazole (137) with alkyl 3-bromo-propionates in the presence of basic in ethanol.[100]

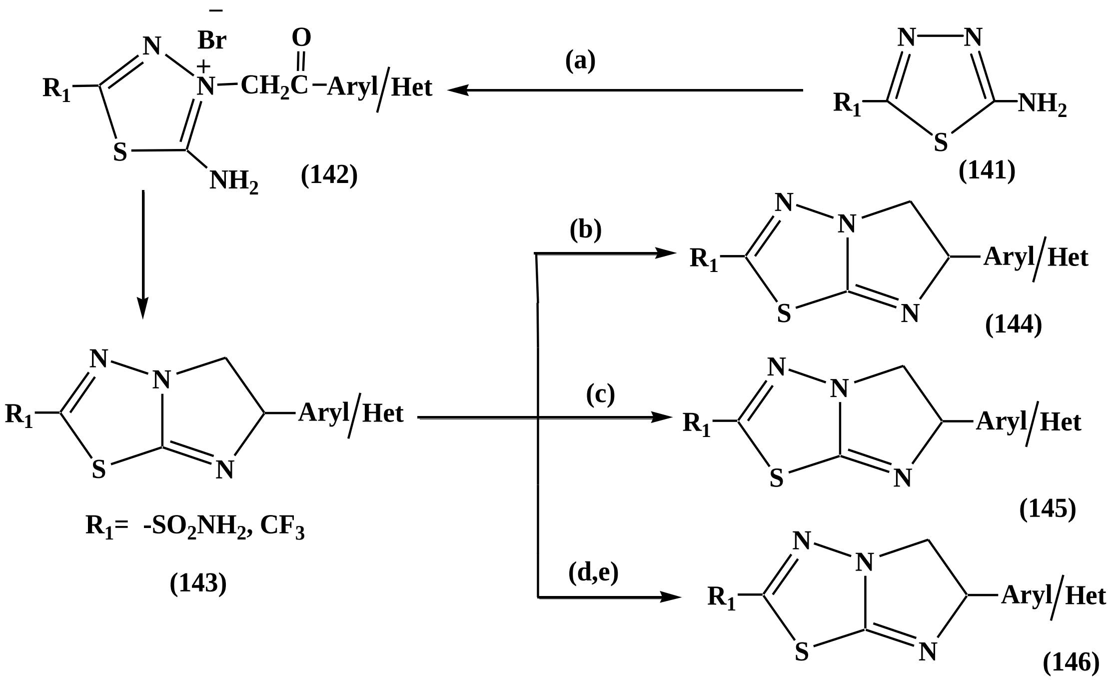


Reagents and conditions:

(i) thiosemicarbazide, EtOH, HCl, reflux; (ii) ammonium ferric sulfate, H_2O,reflux; (iii) $NaNO_2$, HCl, Cu; (iv)thiourea, EtOH, reflux; (v) ethyl 2-bromopropionate, KOH, EtOH; (vi) MCPBA, $NaHCO_3$, CH_2Cl_2, rt; (vii) alkyl-3-bromopropionate, KOH, EtOH, rt.

Reactions of thiadiazole derivatives

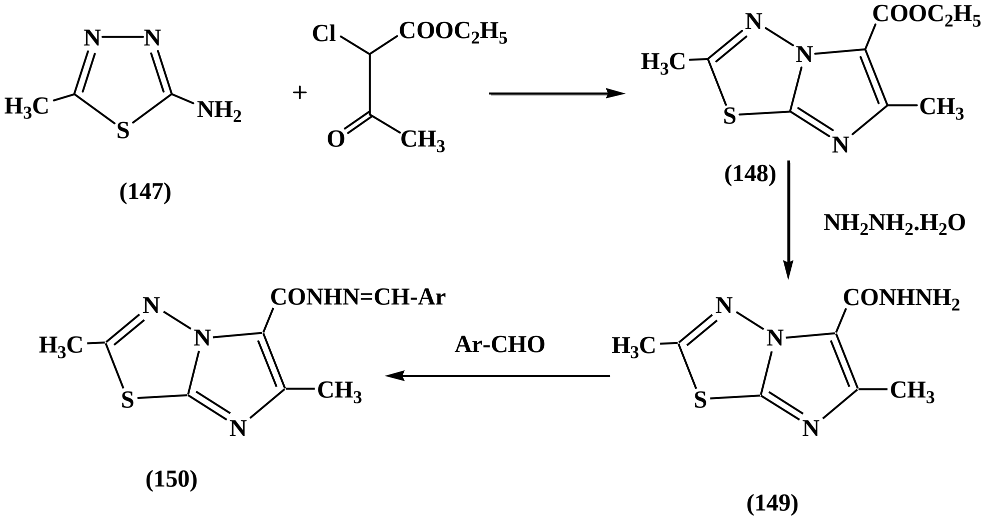
Imidazo[2,1-b]-1,3,4-thiadiazoles were prepared by the condensation of (141) with a α-haloaryl/heteroaryl ketone under reflux in ethanol to form the intermediate iminothiadiazole (142), which under reflux in ethanol to form the desired fused heterocycle (143) with good yields. The obtained 2-sulfonamido/trifluoromethyl-6-aryl/ heteroaryl-imidazo[2,1-b]-1,3,4-thiadiazole derivatives (143) were subjected to electrophilic substitution reaction with bromine in the presence of sodium acetate in acetic acid to obtain 5-bromo derivative (144). 5-Thiocyanato (145), 5-guanidyl hydrazone (146) derivatives were prepared by earlier reported methods.[101]



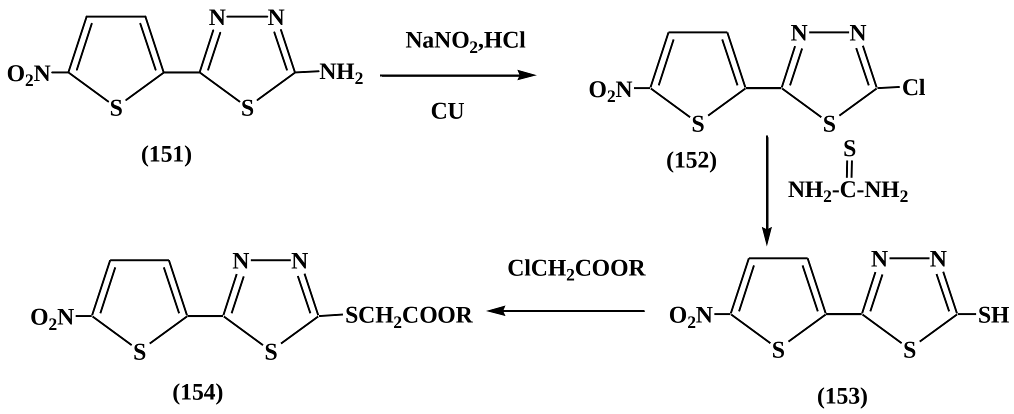
Reagents and conditions:

(a)Br-CH_2-CO-Aryl/Het , EtOH, reflux, 12h, Na_2CO_3; (b) Br_2, CH_3COONa, CH_3COOH;(c) KSCN, Br_2,CH_3COOH, 0-5 C^o; (d) Vilsmeier reagent, 80-90 C^o, 4h; (e) aminoguanidine HCl, EtOH, reflux, 0.5 h.

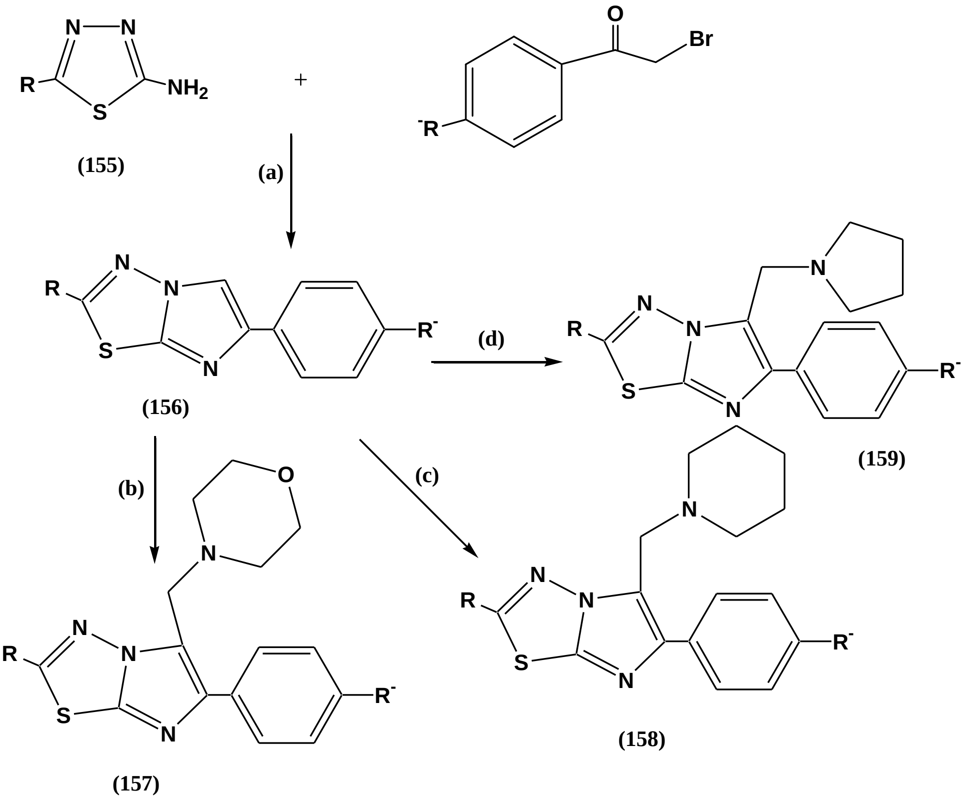
The reaction of 2-amino-5-methyl-1,3,4-thiadiazole (147) and ethyl 2-chloroacetoacetate afforded ethyl-2,6-dimethylimidazo[2,1b][1,3,4] thiadiazole-5-carboxylate(148) which in turn was refluxed with hydrazine hydrate to obtain 2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide(149). Condensation of (149) with appropriate aldehydes yielded the corresponding hydrazide hydrazones (150).[102]



Diazotization of 2-amino-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole (151) in hydrochloric acid in the presence of copper powder gave 2-chloro-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole (152). The reaction of (152) with thiourea in refluxing ethanol afforded 2-mercapto-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole (153). Treatment of the latter with alkyl chloroacetates (153) gave alkyl α-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-ylthio] acetates (154).[103]



Synthesis of the basic nucleus imidazo[2,1-b][1,3,4]thiadiazole (156) is brought about by the condensation of 2-amino-1,3,4-thiadiazole (155) with α-bromoaryl ketone under reflux in dry ethanol . Mannich reaction of imidazo[2,1-b][1,3,4]thiadiazole (156) with different cyclic secondary amines (morpholine, piperidine, and pyrrolidine) and formaldehyde in methanol with catalytic amount of acetic acid yielded corresponding derivatives (157), (158), and (159).[104]

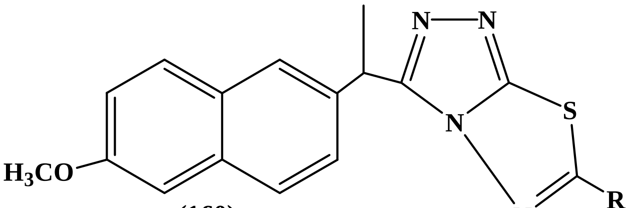


Reagents and conditions:

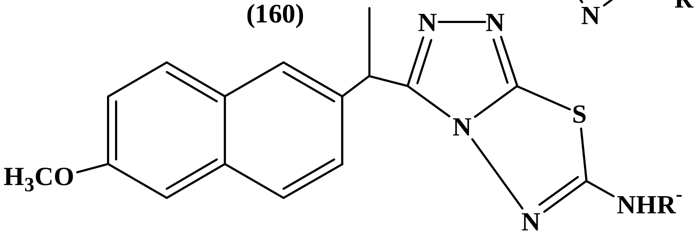
(a) dry ethanol, reflux, 12 h, Na_2CO_3; (b) morpholine, HCHO, AcOH, MeOH, reflux, 4 h; (c) piperidine, HCHO, AcOH, MeOH, reflux, 4 h; (d) pyrrolidine, HCHO, AcOH, MeOH, reflux, 4 h.

Biological activity of thiadiazole

The target compounds (160), (161) were pharmacologically evaluated for their anti-inflammatory and analgesic potentials by known experimental models.[105]

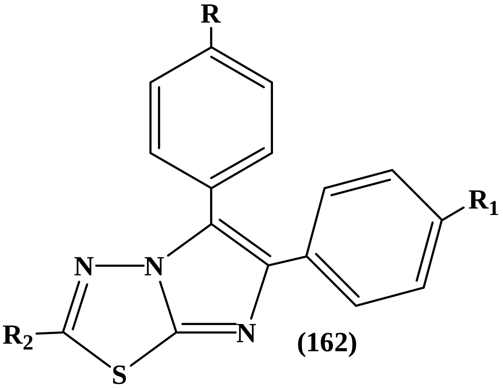


(160)



(161)

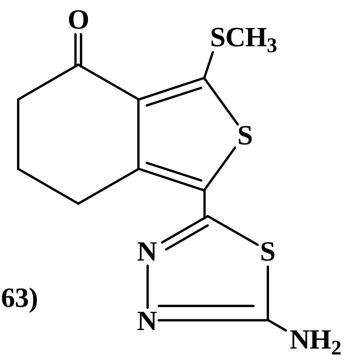
The selected compounds (162) were evaluated for their preliminary in vitro cyclooxygenase inhibitory activity against COX-2 and COX-1enzymes using colorimetric method. These compounds also exhibited significant anti-inflammatory activity (70.09–42.32%), which is comparable to that of celecoxib in the carrageenan induced rat paw edema method. [106]



(162)

1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[c]thiophen-(5H)ones (163) , (164) tested to demonstrate in vitro antimicrobial activity.

Some of these compounds exhibited a good activity against Staphylococcus, S. epidermidis and Bacillus subtilis. [107]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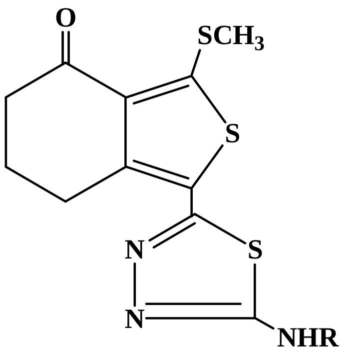
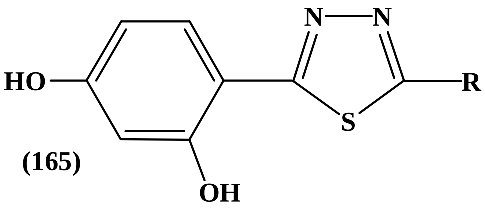

(164)

Substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles evaluated for their antiproliferative activity (165), (166).[108]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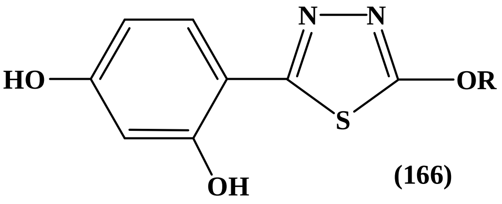

(166)

Synthesis of surface active agents containing heterocyclic moiety

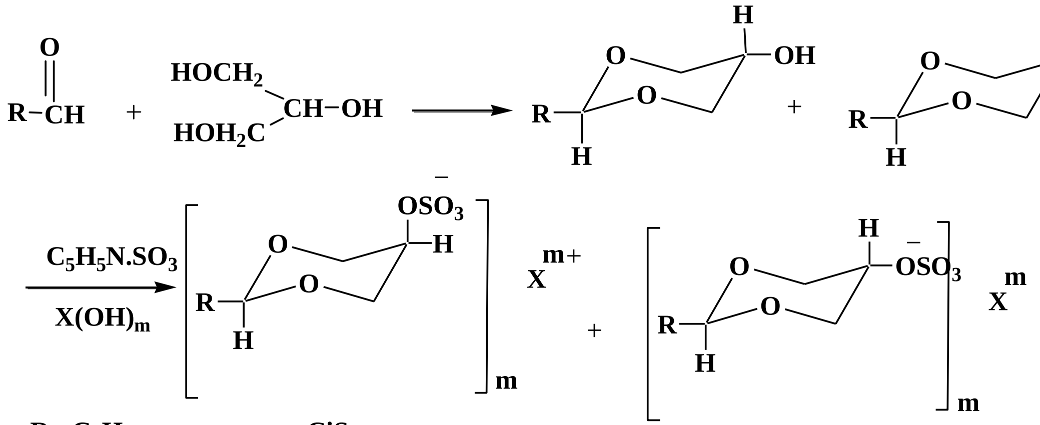
Surfactant containing heterocyclic moiety are used in a varieties of industrial applications .The classification of surfactants is made on the basis of the charge of the polar head group. It was divided into four different main types, anionic, cationic, non ionic and amphoteric surfactants. Anionic and cationic surfactants carry negative and positive charges on their head groups, respectively; the non ionic are uncharged head group, and amphoteric surfactants which may be anionic or cationic depending on the pH of the solution.

1. Anionic surfactants:

They are used in greater volume and are as excellent detergents, good foaming, dry cleaning, antistatic, lime soap dispersion agents, carpet cleaner, bar soap and agriculture formulations. The best detergency is obtained by alkyl or alkylaryl chains in the C_{12-18} rang. Carboxylate, sulfate, sulfonate and phosphate are the polar groups found in anionic surfactant.

1.1- Anionic surfactants containing dioxane ring .

Synthesis and surface properties of chemodegradable anionic surfactants (167a-b) were described. These surfactants were prepared from the reaction of aliphatic aldehydes with glycerol followed by separation in high yields of individual geometric cis and trans 2-n-alkyl-5-hydroxy-1,3-dioxanes, followed by sulfation with sulfur trioxide-pyridine complex and finally neutralization with NaOH, KOH, LiOH, $Mg(OH)_2$, $Ca(OH)_2$, $Ba(OH)_2$, and/or NH_4OH. It was shown that the surface activity of these compounds is influenced by both their geometric and mono-and divalent counter ion.[109,110]



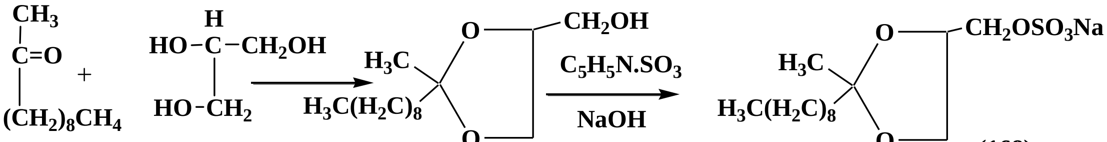
$R= C_nH_{2n+1}$ CiS (167a) Trans (167b)

n=7-13, m=1,2

X=Na, K, Li, Mg, Ca, Ba, or NH_4

1.2- Anionic surfactants containing dioxolane ring .

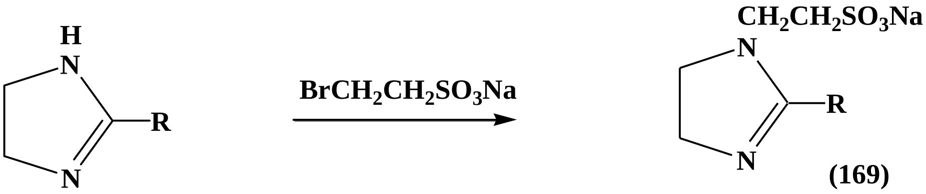
An anionic dioxolane surfactant prepared from condensation of 2-undecanone with glycerin and sulfated to give (168) with surface tension at CMC (Critical Micelle Concentration) 39.6 dyne/cm, Kraft point (1%) < 0˚, and critical micelle concentration 1.0×10^{-2} mol/L. Anionic surfactant (168) was completely decomposed by 1.0 N HCL at 25˚C for 1hr due to the presence of easily degradable dioxolane ring. [111]



(168)

1.3- Anionic surfactants containing imidazoline ring

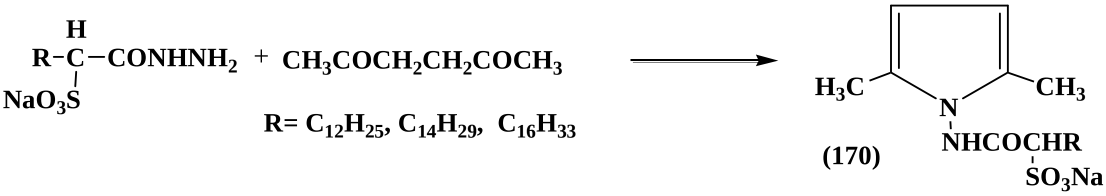
Sulfo-imidazoline betaine anionic surfactants (169) were synthesized by the reaction of hydrophilic material Na 2-bromoethyl sulfonate with alkyl imidazoline (alkyl in surfactant range). The surfactants have low surface tension, good foaming and low critical micelle concentration.[112]



(169)

1.4- Anionic surfactants containing pyrrole ring.

N-(sodium salt of α-sulphonatedamidoalkyl)-pyrrole derivatives (170) were prepared and showed an excellent emulsification power. The CMC (Critical Micelle Concentration) values of surfactants (170) show a fall with the rise in the number of methylene groups in alkyl chain, as would be expected from the increase in hydrophobicity.[113]

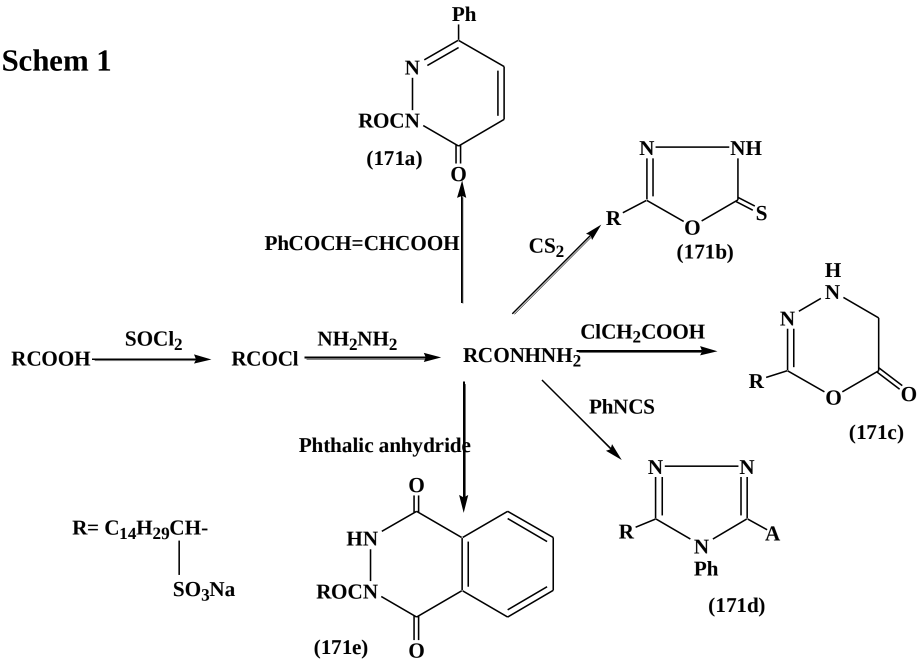


(170)

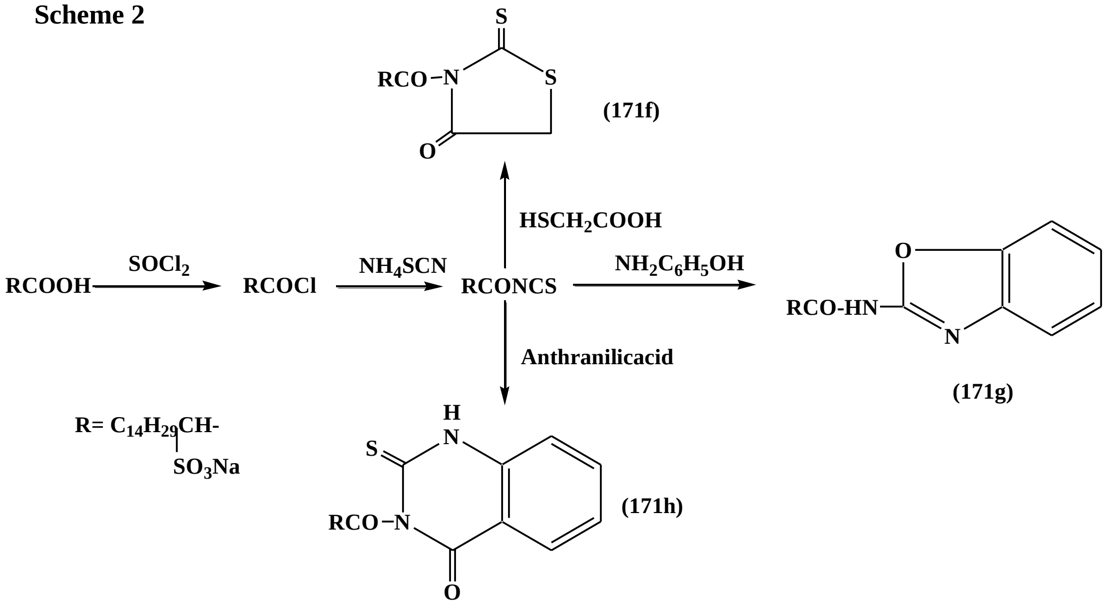
1.5- Anionic surfactants containing triazole, thiazole, oxadiazole, benzoxazole, pyridazine, oxadiazine, phthalazine and quinazoline ring.

Sodium salt of α-sulphonated fatty acid hydrazide was used as starting material to synthesize a group of anionic surfactants having different heterocycles as pyridazine (171a), oxadiazole (171b), oxadiazine (171c), triazole (171d), and phthalazine (171e) derivatives. Also, anionic surfactants containing thiazole (171f), benzoxazole (171g) and quinazoline (171h) derivatives were prepared from α-sulphonated fatty acid isocyanate. The prepared surfactants show a good emulsifying properties, high calcium stability and good wetting agents. All the prepared surfactants have antimicrobial activity, especially (171b, 171d, 171f) were relatively more active, this may be due to the heterocyclic ring contain extra sulphur atom. [113.114] Synthetic routes of the synthesized surfactants are shown in the following schemes 1 and 2.

Schem 1



Scheme 2



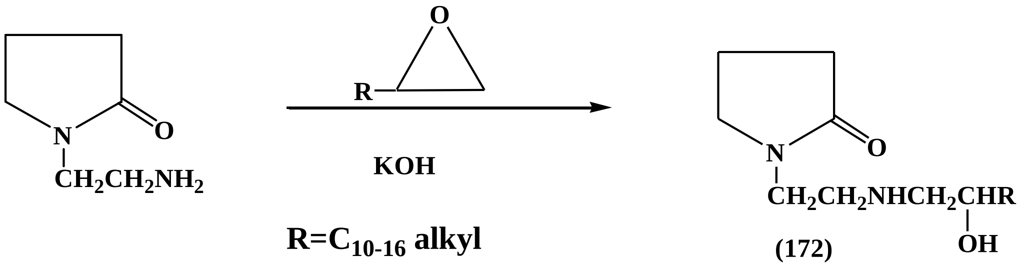
Antimicrobial and surface activities of compounds derived from 3-methyl-1,2,4-triazole-5-thione were prepared by a new method. Micellization of three anionic surfactants in formamide was followed by surface tension measurements and their critical micelle concentration values were determined. Only the surfactants containing a carboxylic acid group were effective against Staphylococcus epidermis and Staphylococcus aureus.[115]

2. Nonionic surfactants:

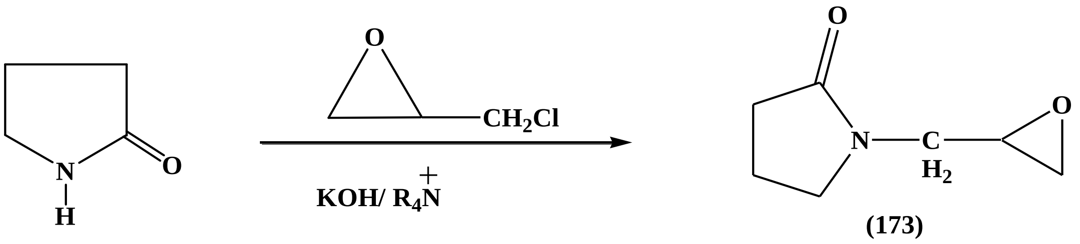
Nonionic surfactants are widely used as emulsifiers, wetting agents, lubricants, plasticizers, detergents, suspension polymerization and as anti-foaming agent.

2.1- Nonionic surfactants containing pyrrolidone ring.

N-Aminoethylpyrroidones reacts with epoxides, such as fatty alpha-olefin epoxides, to produce hydroxyl secondary amine surfactants (172). Such derivatives are thought to be useful as complexing aqueous solubilizers for medicinal and agriculture chemicals [116] .

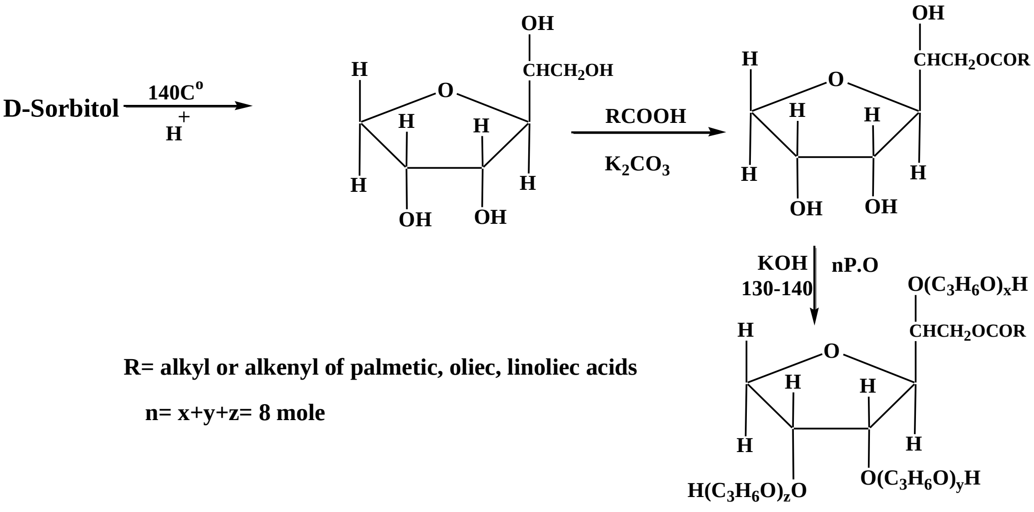


Pyrrolidone reacts under alkaline conditions with epichlorohydrine to form the N-epoxypropyl pyrrolidone (173) in model yield[116]. The use of quaternary ammonium phase-transfer catalysts has shown to improve the yield from 20-30% to about 70%.



2.2- Nonionic surfactants containing oxolidine ring.

Oxypropylated sorbitan monoester (174) was prepared by esterification of sorbitan by long chain fatty acids in DMF as solvent and K_2CO_3 as catalyst followed by Oxypropylated by average number of propylene oxide (n), in presence of KOH as catalyst, at 130-140°C. Those are generally used as emulsifier for creams[117].



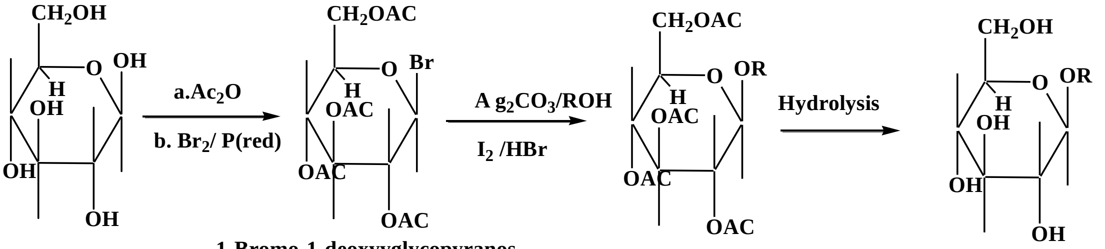
R= alkyl or alkenyl of palmetic, oliec, linoliec acids

n= x+y+z= 8 mole

(174)

Sorbitol monostearate and palmitate are particularly effective in removing silt and clay from fabric[118] and good surfactant with low surface and interfacial tension respectively.[119-121].

Alkylglucoside surfactant having a bright color, good foaming properties, low skin irritation were used as dish washing cleaners. So, n-decyl and n-dodecyl glucoside (175) were prepared as good detergents.[112,123]



1-Bromo-1-deoxyyglycopyranos e-2,3,4,6-tetra acetate

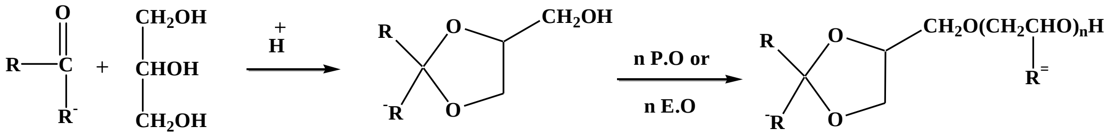
R= $C_{12}H_{25}$, $C_{10}H_{21}$

B-alkylglucopyranoside

(175)

2.3- Nonionic surfactants containing dioxolane ring.

Chemodegradable nonionic surfactants bearing 1,3-dioxolane ring (176) were prepared by the acid-catalyzed condensation of ketones and glycerol, followed by ethoxylation or propoxylation. These surfactants had good surface activity, excellent detergency and easily hydrolyses under acidic conditions.[124]



R,R$^-$= alkyl(in surfactant range) **(176)**
R$^=$= H or CH$_3$
n = 3-8

2.4- Nonionic surfactants containing triazole, thiazole, oxadiazole, benzoxazole, pyridazine, oxadiazine, phthalazine and quinazoline ring.

Fatty acid isocyanate was used as starting material to prepare some important triazole (177a), benzoxazole(177b) and quinazoline(177c) derivatives by treatment types of nucleophiles. [125]Also, Fatty acid hydrazide was utilized as a new cheap starting material in the manufacture of important biologically active heterocycles as oxadiazine (179a), phthalazine (179b) and oxadiazole(179c). All the above synthesized compounds were subjected to react with different moles (n) of propylene oxide (n=3,5 and 7) to produce a novel groups of nonionic compounds (178a-d and 180a-c) having a double function as antimicrobial and surface active agents.[126] Synthetic routes the synthesized surfactants are shown in the following schemes 3 and 4.

Scheme 3

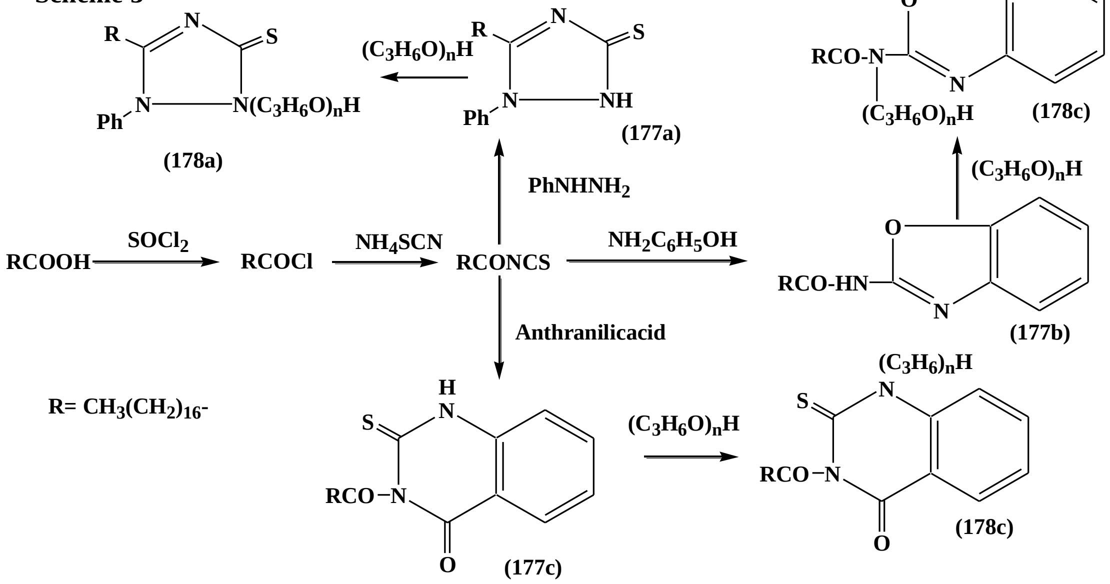
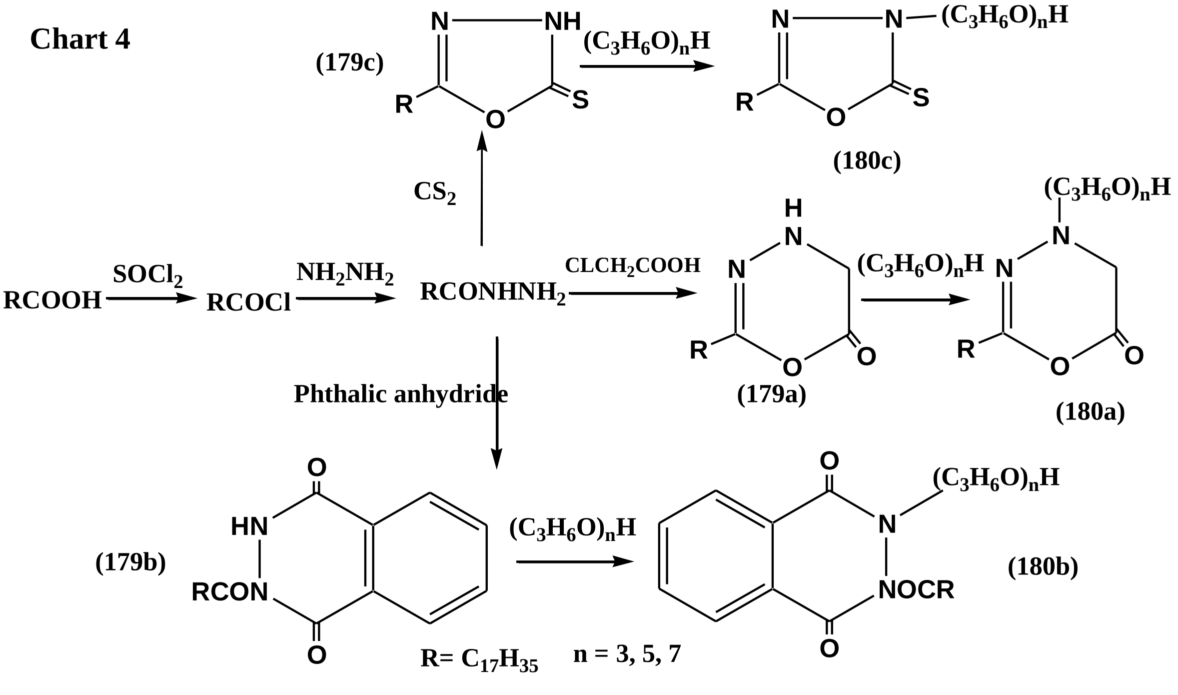
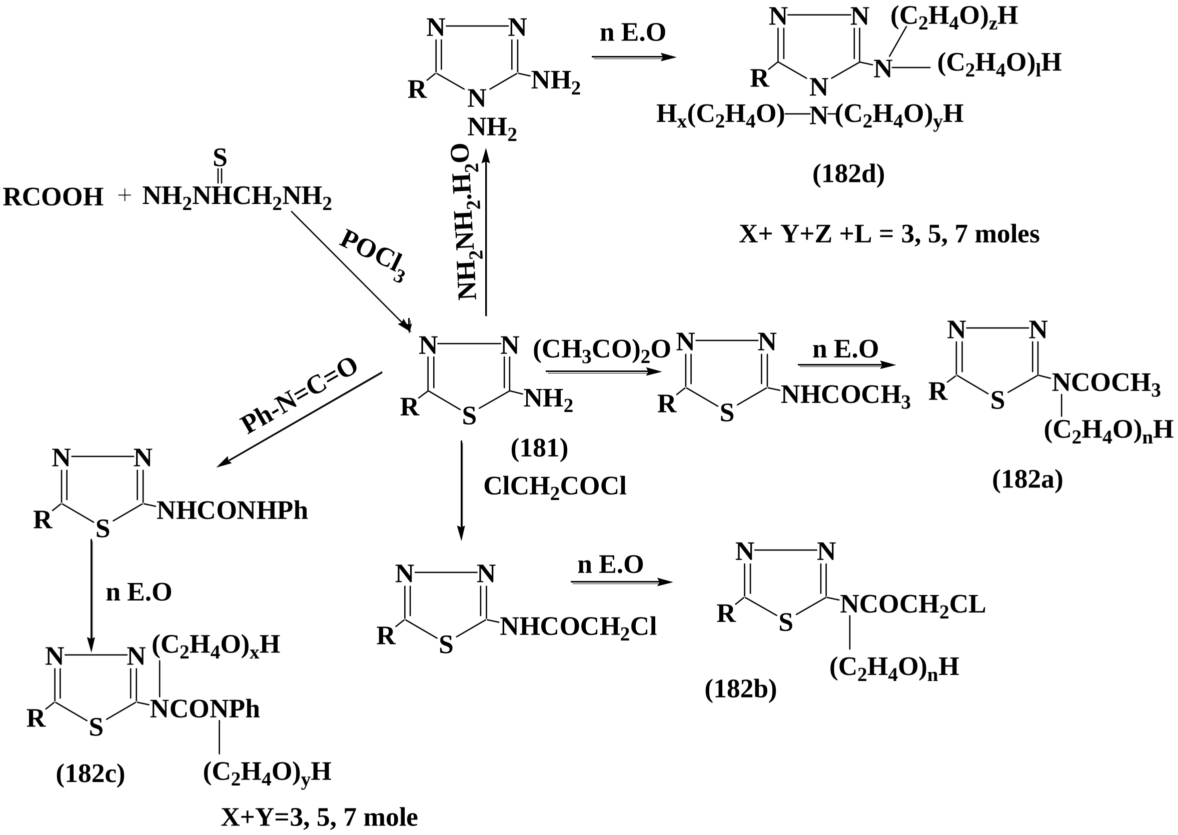


Chart 4



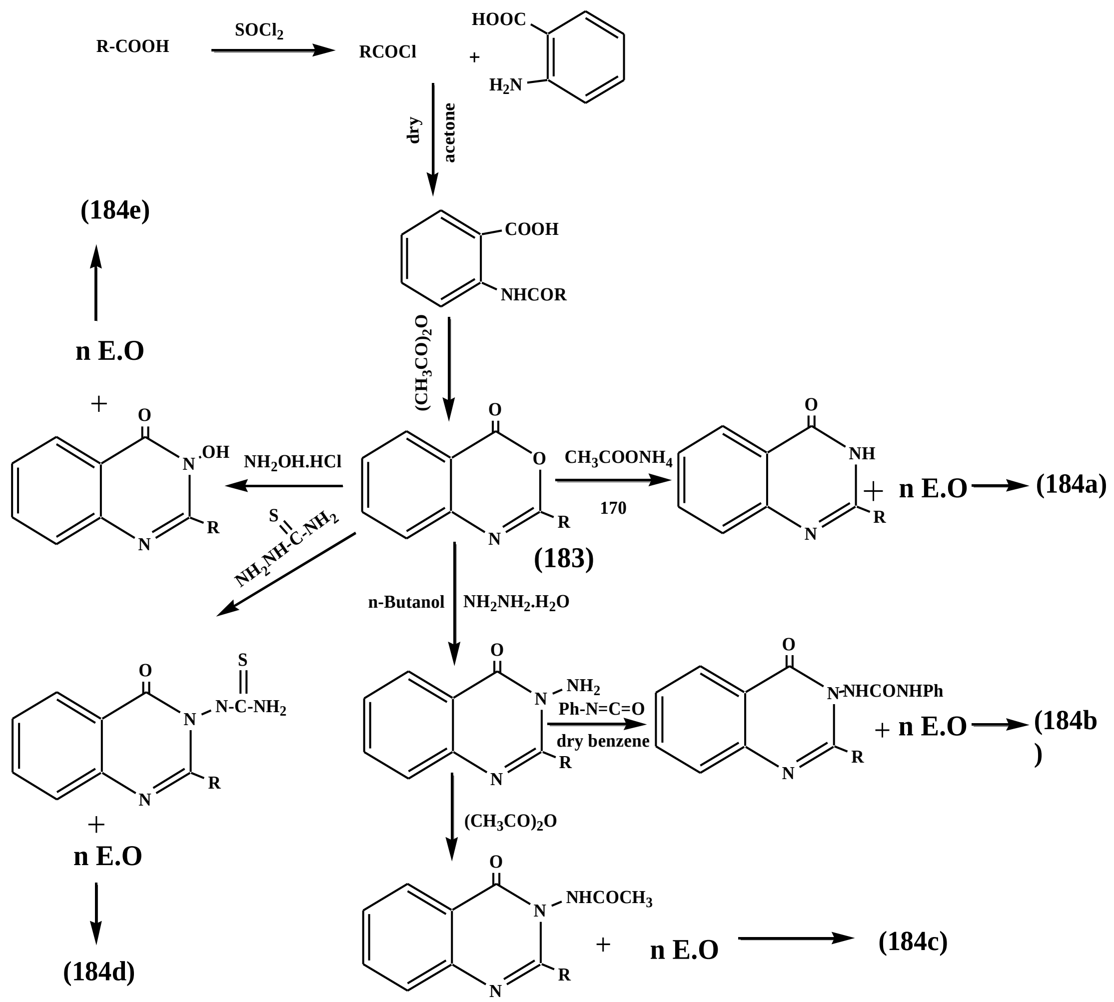
2.5- Nonionic surfactants containing thiadiazole ring.

Reaction of stearic acid with thiosemicarbazide in the presence of $POCl_3$ to produce 2-amino-5-heptadecyl-1,3,4-thiadiazole(181) which used as starting material to prepare some thiadiazole derivatives having biological activity .when thiadiazole derivatives produced allowed to react with different moles (n) of propylene oxide (n=3,5 and 7) to produce a novel groups of nonionic compounds (182a-d) having a double function as antimicrobial and surface active agents.[127]



2.6- *Nonionic surfactants containing quinazolinone ring*.

Acid chloride of stearic acid was reacted with anthranilic acid to produce 3,1-benzoxazinone (183). This benzoxazinone was utilized as starting material to synthesis quinazolinone derivatives. These quinazolinone derivatives bearing an active hydrogen atom (NH, OH or COOH) which could be propoxylated using propylene oxide with different moles, 3 ,5 and 7 moles to produce nonionic surfactants (184a-e).[128]



Biodegradable surfactants containing Heterocyclic Moiety.

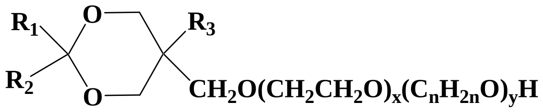
Biodegradation is a process carried out by bacteria in nature. By a series of enzymatic reactions, a surfactant molecule is ultimately converted into carbon dioxide, water and oxides of other elements. If the product does not undergo natural biodegradation then it is stable and persists in the environment. The rate of biodegradation depends on surfactant structure, water solubility, concentration, pH and temperature. In order to speed up the rate of biodegradation the bonds in surfactant structure must be weak.

Another factor to take into account in addition to presence of cleavable bonds is the degree of branching of non-polar part of the surfactant molecule. Extensive branching of the hydrocarbon tail leads to a reduced rate of biodegradation. This is probable due to the side chains causing steric hindrance in the approach of the surfactant into the active site of the enzyme.

It was noticed that the rate of biodegradation various from 1-2h for fatty acids, via 1-2 days for linear alkyl benzene sulfonates, to months for branched alkylbenzene sulfonates.[129,130]

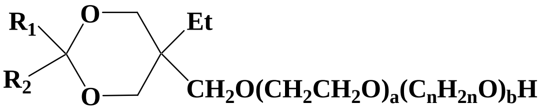
Surfactants containing 1,3-dioxane (195), (196), (197), (198) and 1,3-dioxolane ring (199), (200), (201), (202) are easily biodegradable and exhibit surface properties, and used as nontoxic surfactants, dish washing detergents and anti-foaming properties[131-137]. In compound (201) when [R_1=C_7, R_2=C_1, R_5O =CH_2CH_2O, n=8, m= 2, R_3=C_7, R_4=C_1] it exhibited surface tension 29 dyne/cm at 25C°, stable foam (height =110 mm after 3 min). and had biodegradability 93%.

R_1+ R_2+R_3 =$C_{6\text{-}20}$ hydrocarbyl
x =1-20, y=3-20, n=3-4



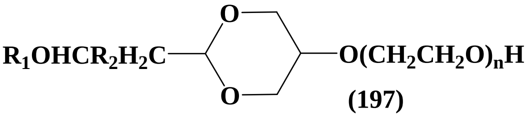
(195)

R_1+ R_2 =$C_{6\text{-}20}$ hydrocarbyl
a =1-20, =2-15, n=3-4



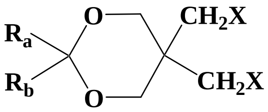
(196)

R_1 = $C_{4\text{-}18}$ alkyl, cycloalkyl
R_2+ H, $C_{1\text{-}14}$ alkyl, n= 1-20



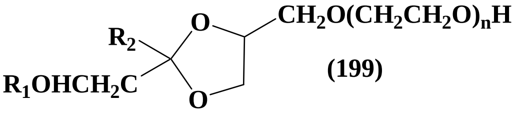
(197)

R_a, R_b =$R_1(OR_2)$
R_1 =$C_{1\text{-}22}$ alkyl or alkenyl
R_2 =$C_{2\text{-}4}$ alkenyl;
X=So_3Na or OH



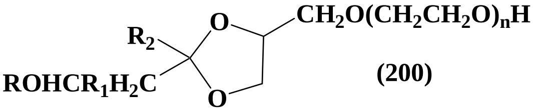
(198)

R_1 =$C_{4\text{-}18}$ alkyl or alkenyl
R_2=$C_{1\text{-}4}$ alkenyl; n= 1-20



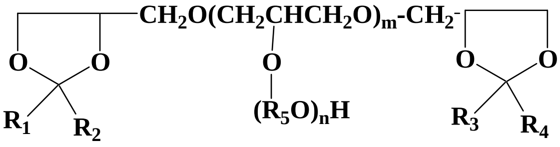
(199)

R =$C_{4\text{-}18}$ alkyl or alkenyl
R_1=$C_{1\text{-}4}$ alkenyl; n= 1-20

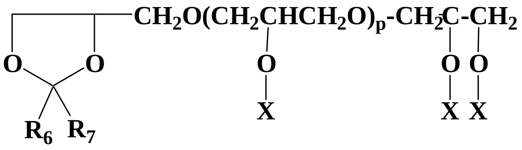


(200)

R_1, R_4, R_6, R_7 =H, hydrocarbon
R_5 = alkylene
X= H, n>0 ,m>1, p>0

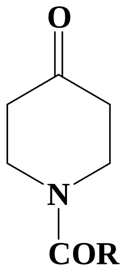


(201)

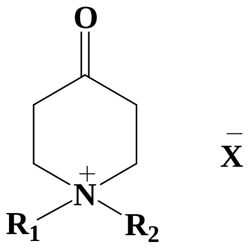


(202)

Biodegradable, environmentally safe bleach compositions effective from below room temperature to higher temperature, comprise a bleaching compound and N-acylpiperidone[138] (201) or oxopiperidinium salt (202).[139] [R=H, $C_{6\text{-}10}$aryl,$C_{7\text{-}20}$ alkaryl, R_1,R_2=$C_{1\text{-}18}$ alkyl, X=R_1SO_4, Br,CL]

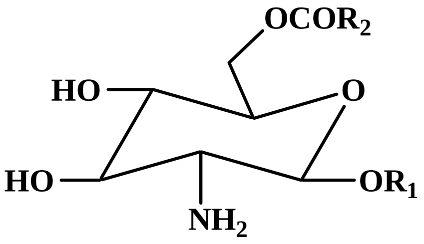


(203)



(204)

Surfactants (203) have good biodegradability were prepared[140] and when[R1=Me, R2= C11H23 n-alkyl] the compound (methyl-6-O-lauroyl-β-D-glucosam-inide is obtained with surface tension 27.5 dyne/cm
and (CMC) 0.001 mol/L.



(205)

The surfactant biodegradation is an oxidation process. There are three biochemical mechanisms [214] encountered as follows:

a) β-Oxidation:

This mechanism causes the degradation of fatty acids. The carboxyl group of the fatty acids is first esterified with coenzyme A,(complex organic mercaptant compound).Dehydrogenation gives the α,β-unsaturated fatty acid – coenzyme A ester, which is converted to the β-keto derivatives by hydration and dehydrogenation. Another coenzyme A reaction then takes place between the α- and β-carbon atoms of fatty acid. Finally, acetyl coenzyme A splits off, leaving a fatty acid- coenzyme A-ester shorter by two carbon atoms. Further fatty acid degradation then takes place in similar steps.

b) Methyl Oxidation:

This involves the oxidation of a terminal methyl group to a carboxyl group. Then, this can be followed by a β- oxidation.

c) Aromatic Oxidation:

This process breaks down the aromatic rings; benzene, phenol, salicylic acid, or other derivatives are first oxidized to catechol. The benzene ring is then splitted between the two hydroxyl groups, giving the dicarboxylic acid, and this is converted by three successive rearrangements into β-keto adipic acid. The latter can then be Biodegraded by the β- oxidation mechanisms.

Fluorescence emission Spectroscopy

Many chemical systems are photoluminescent, that is, they can be excited by electromagnetic radiation then consequently, reemit radiation . manifestations of photoluminescence are fluorescence and phosphor-rescence which are produced by different mechanisms.

Measurements of fluorescent intensity, permits the quantitative determination of many inorganic and organic species in trace amounts; many useful fluorometric methods exist, particularly for biological systems[141].

(i) Fluorescence and phosphorescence processes:

Luminescence is one of the oldest analytical techniques and its theory is well documented in the literature, photoluminescence describes the luminescence process where excitation is achieved by the interaction of the molecules with photons of electromagnetic radiation.

It involves the two major processes of fluorescence and phosphorescence which were confused until 1944 [142].

The initial step in a photoluminescence process is the absorption of a photon in a time period of about 10^{-15} seconds. Prior to the absorption of radiation, the molecule in solution is usually in its ground electronic state S_0.

When a molecule absorbs light it is said to become excited and the electrons in the molecule are promoted to higher electronic orbitals.

Electronic excitation of the molecules is accompanied with additional vibrational energy as well as electronic energy. The excess vibrational energy is rapidly lost in about 10^{-12} seconds and the molecule returns to the lowest excited metastable state S_1.

When the electrons return to vibrational levels of the ground state from the lowest vibrational level of the first excited singlet state the energy released may be dissipated in one of several ways. It may be emitted as radiation , via a process known as fluorescence or radiationless transitions. These radiationless transitions may involve conversion into rotational, vibrational or kinetic energy i.e. heat or chemical energy.

Photodecomposition may also take place before the electron reaches the lowest vibrational level of the first excited state thus the transitions from the excited to the ground state may occur by a number of routes other than fluorescence emission see Fig. (1)

Thus molecules that have chromophores and hence can absorb light, will have the potential to exhibit fluorescence, but not all absorbing compound are fluorescence due to the possibility radiationless process.[143].

A molecule in an excited state is a highly energetic species with a very short lifetime. Fluorescence usually occurs from the lowest vibrational level of the first excited state with the mean lifetime about 10^{-8} seconds.

Since some energy is lost in the short period between the excitation and the emission the observed emission spectral band is at a longer wavelength than to the observed absorption band. This differences in wavelength is called the ‘Stoke’s shift’ Fluorescence involves emission originating and terminating in states of the same multiplicity normally singlet states in which the electrons in the molecules have antiparallel spins.

Radiationless transitions between energy levels of the same multiplicity are referred to as internal conversions. Radiationless transitions occurring between energy levels of different multiplicities are referred to as intersystem crossing. At triplet state (T) the electrons occupy an orbital with a parallel spin.

The vibrational levels of the triplet state may be involved, but by radiationless vibrational relaxation and internal conversion and inter system crossing from S_1, the lowest vibrational level T_1, is quickly attained. The molecule returns directly to the ground state, S_o , by emitting radiation . This is observed as phosphorescence. See fig. (1)

Phosphorescence thus is a radiative emission originating from and terminating in different multiplicities. It has a longer lifetime, T_p, of about 10^{-4} seconds to 10 seconds.

Phosphorescence is, therefore, usually studied at 77k, in rigid glass solvent media, on thin layer plates or other rigid support [144].

(ii)- Determination of quantum yield:

The quantum yield, or quantum efficiency, for a fluorescent process is simply that ratio of the molecules that fluoresce to the total number of excited molecules.

From a consideration of figure (1), the fluorescent quantum yield φ_f for a compound must be determined by the relative rates for the processes by which the lowest excited singlet state is deactivated namely, fluorescence, intersystem crossing, external and internal conversion, predissociation, and dissociation. We may express these relationship by the equation [145].

$$\varphi_f = K_f / (K_f + K_i + K_{ec} + K_{ic} + K_{pd} + K_d) \quad \text{.........(1)}$$

where the K terms are the respective rate constant for the several processes enumerated above. The magnitude of K_f, K_{pd} and K_d are mainly dependent upon chemical structure, the remaining constants are strongly influenced by environment and a somewhat lesser by structure.

The recent method[146] for measuring quantum yields are the comparative methods which are based on fact that, if two substance 1 and 2 are studied in the same apparatus, and using the incident light intensity, the integrated areas under their corrected fluorescence spectra (S_1 and S_2) are simply related as follows:

$$S_2/S_1 = (\varphi_2 / \varphi_1) \times (A_2 / A_1) \quad \text{...........(2)}$$

where φ value are quantum yields, and A values absorbances at the respective excitation wavelength. The application of this method has been thoroughly discussed else where.[147]

As corrected spectra are becoming more readily available, this method is likely to remain the most popular approach to quantum yield determinations.

However, it requires a series of suitable standard materials of it is to be used over a range of wavelength (See Table 1)

Table (1): Fluorescence quantum yield standard in various emission ranges.

Region	**Compound**	**Solvent**	**φ**
270 – 300 nm	Benzene	Cyclohexane	0.05±0.002
300 – 380 nm	Tryptophan	H_2O (pH 7.2)	0.14 ± 0.02
300 – 400 nm	Naphthalene	Cyclohexane	0.23 ± 0.02
360 – 480 nm	Anthracene	Ethanol	0.27 ± 0.03
400 – 500 nm	9, 10-DPA	Cyclohexane	0.90 ± 0.02
400 – 600 nm	Quinin Bisulfate	1N H_2SO_4	0.546