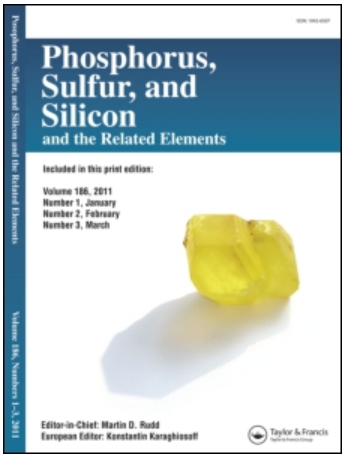

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Synthesis of Biologically Active 4-Oxo-4*H*-Chromene Derivatives Containing Sulfur-Nitrogen Heterocycles

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Synthesis of Biologically Active 4-Oxo-4*H*-Chromene Derivatives Containing Sulfur-Nitrogen Heterocycles

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The synthesis of 4-oxo-4H-chromenes containing sulfur-nitrogen heterocyclic rings as well as their biological activities are reviewed.

Keywords Biological activities; chromones; sulfur-nitrogen heterocycles; synthesis

INTRODUCTION

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.[1] A large number of articles concerning 4-oxo-4*H*-chromenes have included cyctoxic anticancer,[2–5] neuroprotective,[6] HIV-inhibitory,[7] antimicrobial,[8,9] antifungal,[10] and antioxidant activity.[11] Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the human diet.[12]

Sulfur-nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of the historical development of organic synthesis. The reason for this interest is their biological activities and unique structures, which have led to several applications in different areas of pharmaceutical and agrochemical research or, more recently, in material sciences.[13,14]

This review describes all strategies that have been developed for the synthesis of 4-oxo-4*H*-chromene derivatives containing isolated and condensed sulfur-nitrogen heterocyclic rings; e.g., 1,3-thiazole, 1,3,4-thiadiazole, 1,3-thiazine, 1,4-thiazine, 1,3,4-thiadiazine, 1,4-thiazepine

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1,5-thiazepine, and 1,2,5-oxathiazepine, as well as their biological activities.

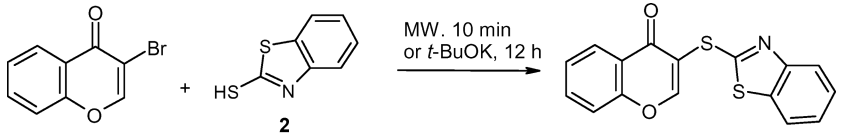
SYNTHETIC APPROACH

There are three different routes for the synthesis of 4-oxo-4*H*-chromene derivatives containing sulfur-nitrogen heterocyclic rings.

Direct Condensation of 4-Oxo-4*H*-Chromene Derivatives with Sulfur-Nitrogen Heterocycles Containing Sulfur, Nitrogen, and/or Carbon Nucleophiles

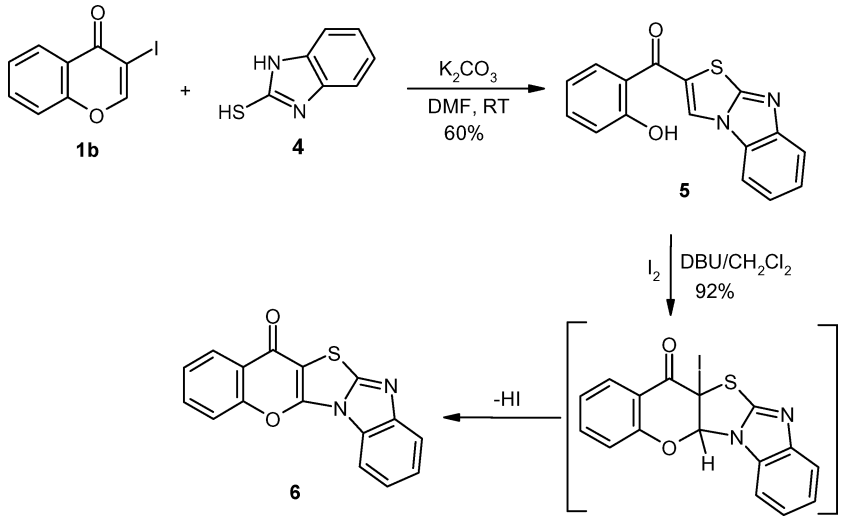
Sulfur Nucleophiles

Chromone derivative **1a** reacted with 2-mercaptobenzothiazole (**2**) in the presence of potassium *t*-butoxide at 90°C to afford 3-(1,3-benzothiazol-2-ylthio)-4*H*-chromen-4-one (**3**) in moderate yield. Compared to the reaction time of 12 h under conventional heating, it only took 10 min to finish the reaction under microwave irradiation (Scheme 1).[15] Treatment of chromone derivative **1b** with 2-mercaptobenzimidazole (**4**) in DMF containing potassium carbonate at room temperature, interestingly, gave the benzimidazo[2,1-*b*]thiazole derivative **5** in 60% yield. Reaction of **5** with iodine in the presence of DBU smoothly promoted the cyclization, and the corresponding benzimidazothiazolobenzopyran derivative **6** was obtained in excellent yield (Scheme 2).[16]



SCHEME 1

3-[(5-Amino/methyl-1,3,4-thiadiazol-2-ylthio]-4*H*-chromen-4-one (**8**) was obtained *via* reaction of chromone **1a** with the 2-mercapto-1,3,4-thiadiazole derivative **7** in the presence of potassium *t*-butoxide at 90°C for 24 h under classical heating or 20 min to finish the reaction under microwave irradiation in good yield (Scheme 3).[15]

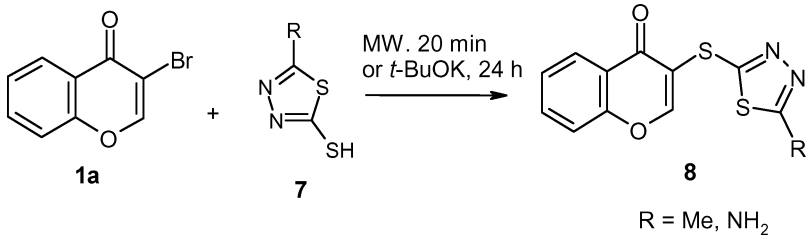


SCHEME 2

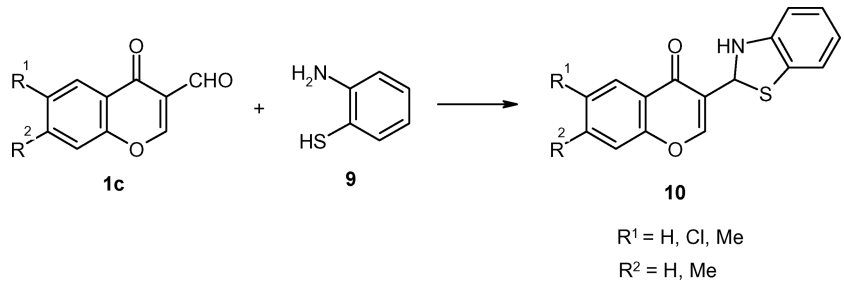
Sulfur-Nitrogen Nucleophiles

Some 3-(2,3-dihydro-1,3-benzothiazol-2-yl)chromones (**10**) were synthesized by condensing chromones **1c** ($R^3 = H$) with 2-aminothiophenol (**9**) (Scheme 4).[17]

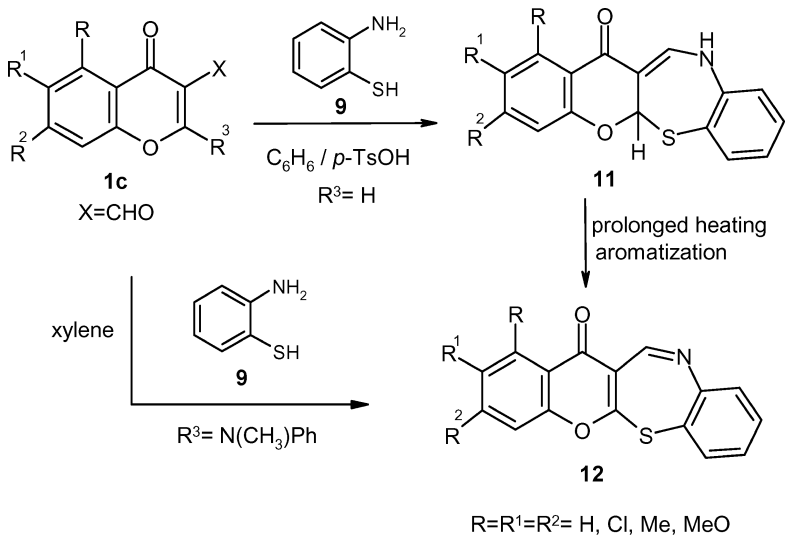
Cyclocondensation of chromones **1c** with 2-aminothiophenol (**9**) by refluxing in dry benzene containing *p*-toluenesulfonic acid gave dihydrobenzothiazepine derivatives **11**, which was aromatized upon prolonged heating to give chromono[2,3-b][1,5] benzothiazepines (**12**).[18,19] Also, compound **12** was obtained directly in high yield from the reaction of **1c** ($R^3 = N(CH_3)Ph$) with **9** by refluxing in xylene (Scheme 5).[20]



SCHEME 3



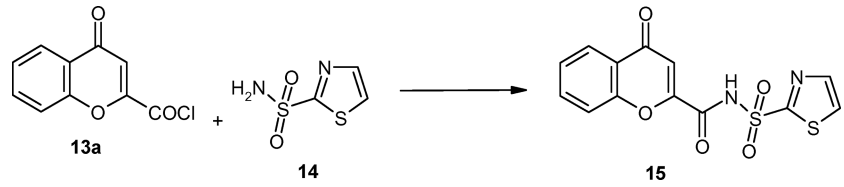
SCHEME 4



SCHEME 5

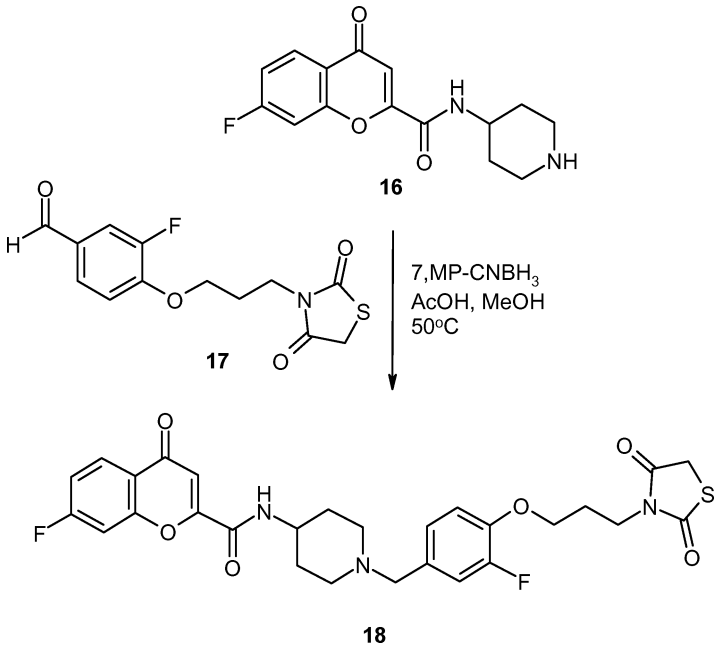
Nitrogen Nucleophiles

Reaction of chromone **13a** with thiazole-2-sulfonamide (**14**) yielded *N*-(2-sulfamoylthiazol-2-yl)chromone-2-carboxamide (**15**) (Scheme 6).[21]



SCHEME 6

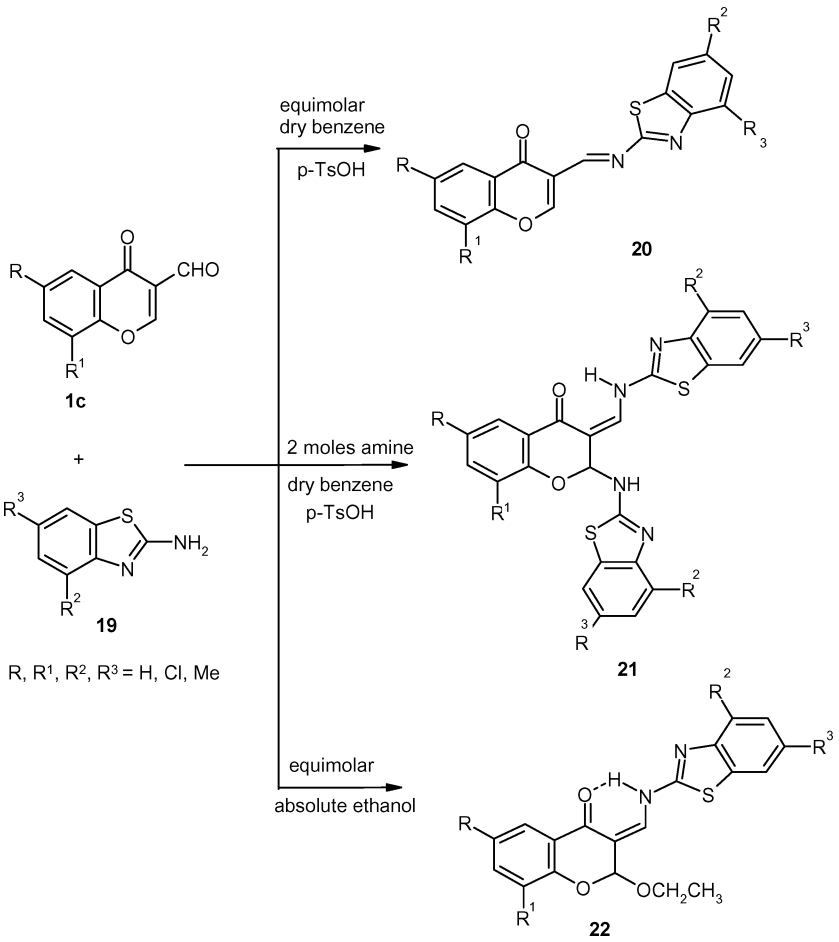
The thiazolidinedione derivative **18** was prepared from 7-fluoro-4-oxo-*N*-piperidin-4-yl-4*H*-chromene-2-carboxamide (**16**) and 4-[3-(2,4-dioxo-1,3-thiazolidin-3-yl)propoxy]-3-fluorobenzaldehyde (**17**) under reductive conditions (Scheme 7).[22]



SCHEME 7

The reaction between equimolar quantities of chromones **1c** with 2-aminobenzothiazole (**19**) or 6-aminobenzothiazole derivative **23** in dry benzene or toluene in the presence of *p*-toluenesulfonic acid as catalyst gave 3-(2-/6-benzothiazolyliminomethyl) chromones **20** and **24**, respectively. Excess of the amines **19** and/or **23** (2:1 molar ratio) produced only the 1,4-adducts **21** and **25**, respectively. The reaction between **1c** and the same amines (1:1 molar ratio) in absolute ethanol gave the 1,4-adducts **22** and **26**, respectively. The reason for the rather unusual ring-addition of ethanol was the formation of the stable hydrogen-bonded ketoenamine system (Schemes 8 and 9).[23]

The condensation reaction of chromones **1c** with 2-hydrazinobenzothiazoles (**27**) gave the corresponding hydrazones **28** in good yield without opening of the pyrone ring (Scheme 10).[23]

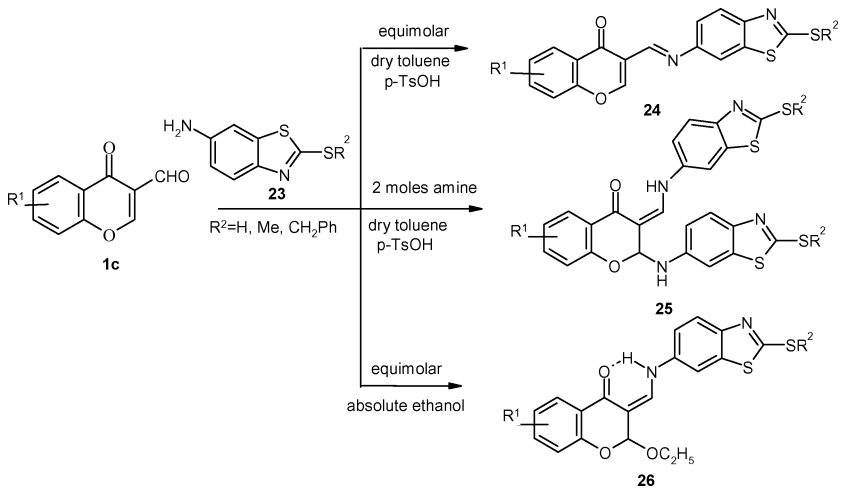


SCHEME 8

The penicillin derivative **30** was prepared by reaction of compound **29** with the chromone derivative **1d** in trifluoroacetic acid and *N*, *O*-bis(trimethylsilyl)acetamide (Scheme 11).[24]

Treatment of chromone derivative **13a** with 2-amino-5-methyl/phenyl-1,3,4-thiadiazole (**31**)[25] and/or 5-methyl-1,3,4-thiadiazole-2-sulfonamide (**33**)[21] yielded the corresponding carboxamide derivatives **32** and **34**, respectively (Scheme 12).

Chromone **1c** reacted with 2-amino-5-thioxo-1,3,4-thiadiazole (**35**) in dry benzene to give the corresponding Schiff base **36** (Scheme 13).[26]



SCHEME 9

Oxidation of chromones **1c** using *N*-bromosuccinimide, followed by quenching with 2-amino-5-methyl/phenyl-1,3,4-thiadiazoles (**31**), gave the carboxamides **37** (Scheme 14).[27]

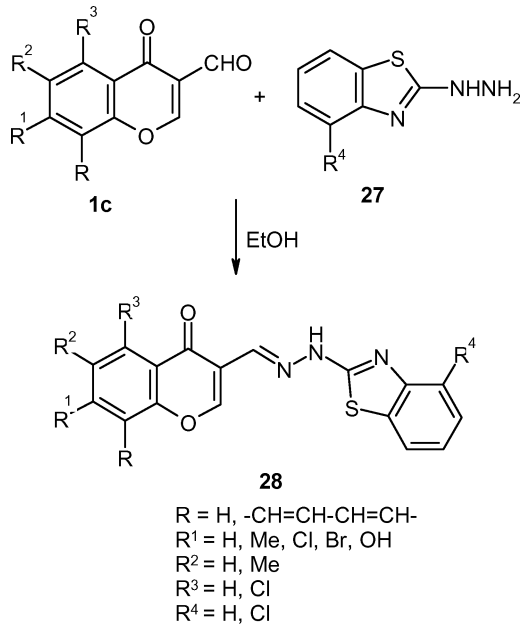
Treatment of 10-methyl-3-aminophenothiazine (**38**) with chromone derivative **13a** in CH_2Cl_2 gave 10-methyl-3-phenothiazinylamide of chromone-2-carboxylic acid (**39**) (Scheme 15).[28]

The cephalosporin derivative **41** was prepared by reaction of **40** with 6,7-dihydroxy-chromone derivative **1d** in trifluoroacetic acid and *N*, *O*-bis(trimethylsilyl)acetamide (Scheme 16).[24]

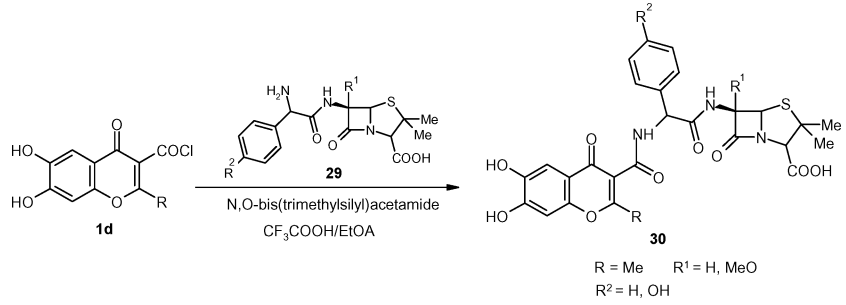
A mixture of chromones **1d** and diphenylmethyl (6*R*,7*R*,2*Z*)-3-(carbamoyl-oxymethyl)-7-[2-(2-triphenylmethylamino-4-thiazolyl)-2-(carbazoyl-alkoxy-methylimino)acetamido]ceph-3-em-4-carboxylate hydrochloride (**42**) in the presence of *O*, *N*-(bistrimethylsilyl)acetamide in dichloromethane was stirred for 1.5 h to give diphenylmethyl (6*R*,7*R*,2*Z*)-3-(carbamoyloxymethyl)-7-2-[N^2-(6,7-dihydroxy-4-oxo-4*H*-chromene-3-ylcarbonyl) carbazoyl-alkoxy-methylimino]-2-(2-triphenylmethylamino-4-thiazol-yl)acetamidoceph-3-em-4-carboxylate (**43**) (Scheme 17).[29]

Carbon Nucleophiles

2-(4-Oxo-4*H*-chromen-3-yl)vinylthiazoline (**45**) was synthesized by condensation of chromone **1c** with 2-methylthiazoline (**44**) (Scheme 18).[30]



SCHEME 10

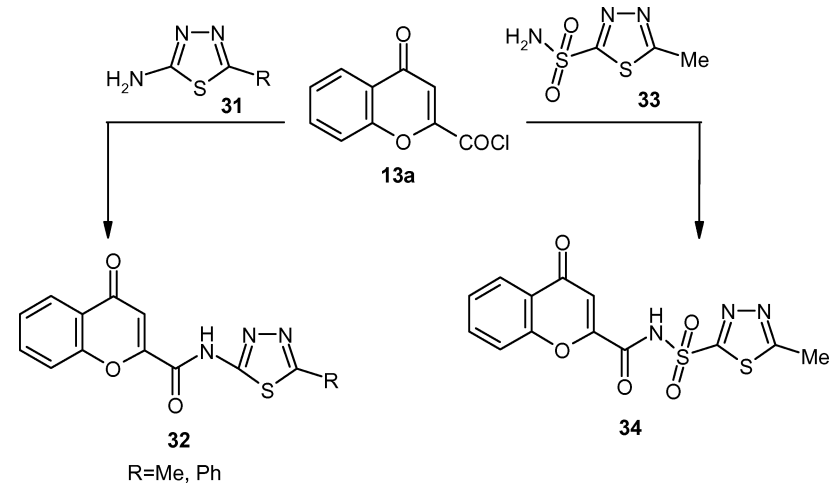


SCHEME 11

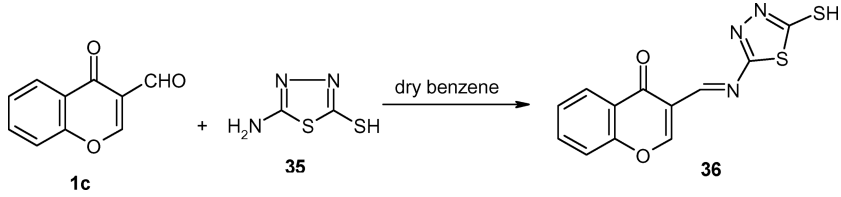
Condensation of chromones **1c** with 2-thioxothiazolidin-4-one derivatives **46** in acetic anhydride and sodium acetate medium gave products **47** under both irradiation and classical conditions (Scheme 19).[19,31–35]

The reaction of chromone **1c** with ethyl 2-cyano-2-(3-phenyl-5-oxo-1,3-thiazolan-2-ylidene)acetate (**48**) gave the corresponding arylidene compound **49** (Scheme 20).[19]

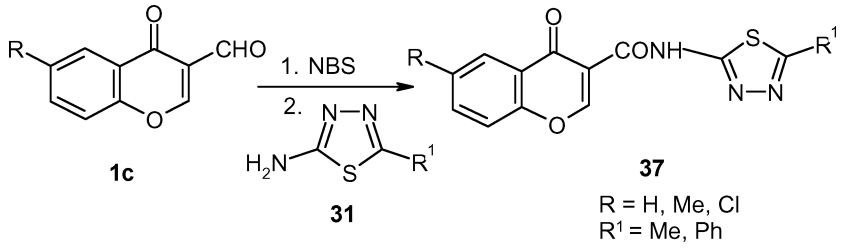
Compound **1c** reacted with 3-(4-chlorobenzyl)-1,3-thiadiazolidine-2,4-dione (**50**) to give 3-(4-chlorobenzyl)-5-(4-oxo-4*H*-chromen-3-



SCHEME 12



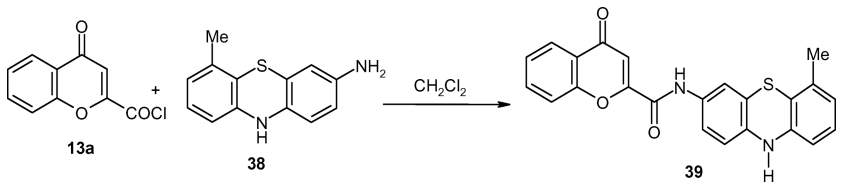
SCHEME 13



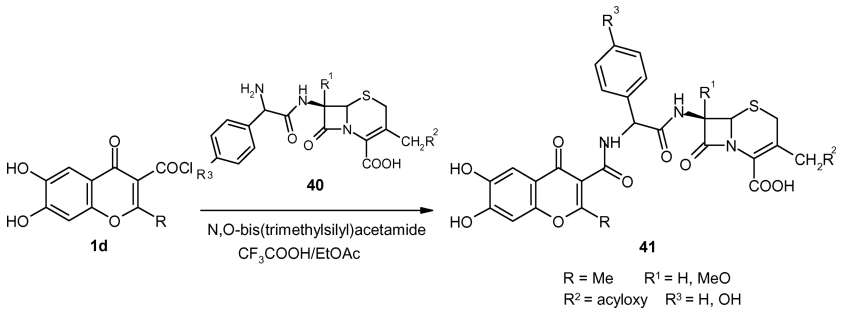
SCHEME 14

ylmethylene)-1,3-thiadiazolidine-2,4-dione (**51**). The crystal structure of **51** showed that the benzopyran ring system and the thiazolidine ring are planar (Scheme 21).[34,36]

Phenacyl-5-[(2-phenyl-4-oxo-4*H*-chromene-6-yl)methylidene]-1,3-thiazolidine-2,4-diones (**54**) were synthesized by Knoevenagel reaction of flavone-6-carbaldehyde (**52**) with 3-phenacylthiazolidine-2,4-diones (**53**) in acetic anhydride and sodium acetate (Scheme 22).[35]



SCHEME 15



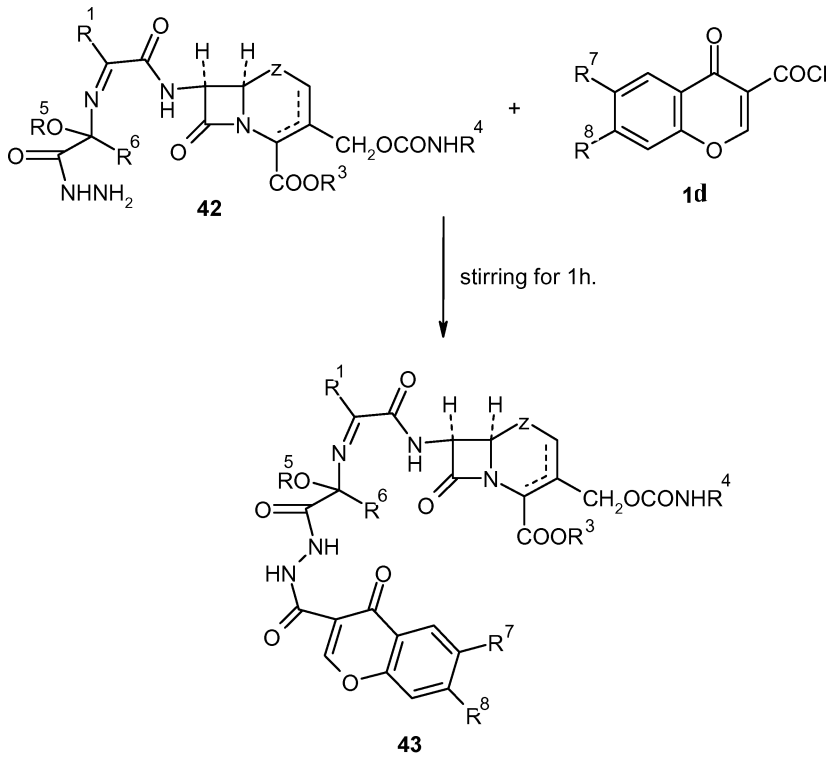
SCHEME 16

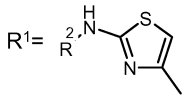
3-Benzyl/phenacyl-5-[3′-(-4-oxo-4*H*-chromene-2-yl)benzylidene]-2,4-thiazolidinediones (**56**) were synthesized by Knoevenagel reaction from 3′-flavonecarbaldehyde (**55**) with 3-substituted-2,4-thiazolidinediones **50** or **53** (Scheme 23).[37,38]

Condensation of **1c** with 2-methylbenzothiazole (**57**) was carried out in dimethyl sulfoxide and boric acid medium at 60°C to give compound **58** in 81–85% yields. An increase of the reaction temperature to 120°C led to products **59**, which reacted with methyl iodide, yielding the salt **60**. Compound **60** was prepared in another way with 29–85% yield by reacting of compound **1c** and the 2-methylbenzothiazolium salt **61** in acetonitrile after 3–35 min of microwave irradiation or 0.5–8 h of heating. Addition of a good nucleophile such as ethanol or dimethylamine to compounds **60** gave the addition products **62** (Scheme 24).[32,39]

Chromone **13b** was heated for 0.5 h with 3-methylbenzothiazole-2-sulfobataine (**63**) to give 8% yellow 2-[(3-methylbenzothiazolin-2-ylidene)methyl]chromone (**64**). Heating **64** with $POCl_3$ followed by treatment with Et_2O gave 89% orange 3-methyl-2-[(4-oxo-4*H*-chromene-2-ylidene)methyl]benzothiazolium chloride (**65**) (Scheme 25).[40]

Chromone carboxaldehyde **66** condensed with 1,3-benzothiazol-2-ylacetonitrile (**67**) followed by cyclization and oxidation to give the benzothiazole derivative **69** (Scheme 26).[41]



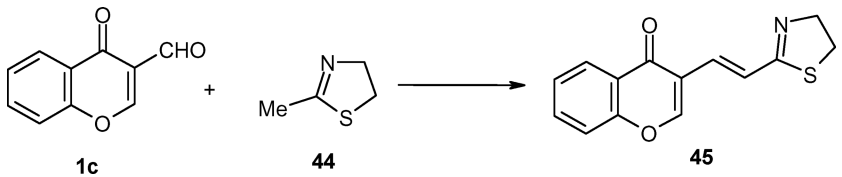


R^2 = H, amino protecting group
R^3 = H, carboxyl blocking group
R^4 = H, (substituted) $C_{1\text{-}4}$ alkyl group
R^5, R^6 = H, Cl-4 alkyl group or CR^5R^6 = $C_{3\text{-}7}$ cyclo alkyl group.
R^7, R^8 = (substituted) OH, or R^7, R^8 = cyclic protected diol group
Z = S, SO; dotted lines indicates that the compound is a 2- or 3-cephem compound

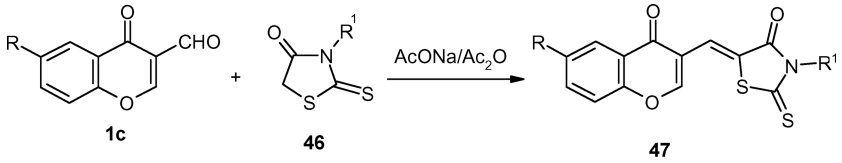
SCHEME 17

Condensation of chromones **1c** with 1,3-thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (**70**) under microwave irradiation for 18–30 min as well as by the classical heating at 130°C for 1.5–3 h in pyridine or acetic anhydride and sodium acetate led to high yields 60–97% of products **71** (Scheme 27).[42,43]

Similarly, chromones **1c** readily reacted with 2-methyl-1,3-thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one (**72**) in acetic anhydride and



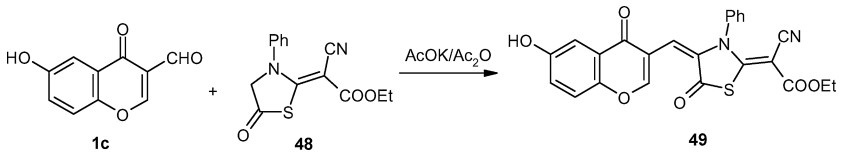
SCHEME 18



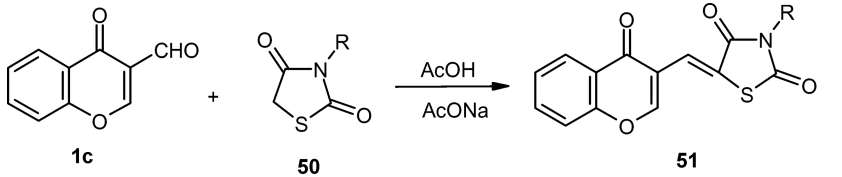
R = H, Cl, Me, OH

R^1 = H, Et, NHCOMe, Ph

SCHEME 19



SCHEME 20

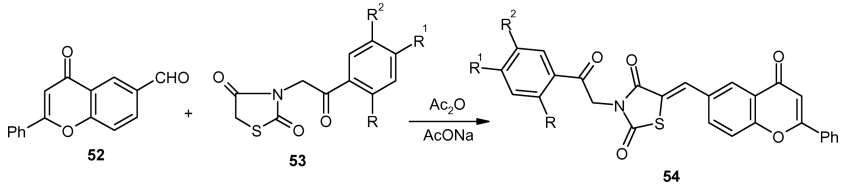


R = H, $CH_2C_6H_4Cl$-*p*, CH_2COOH

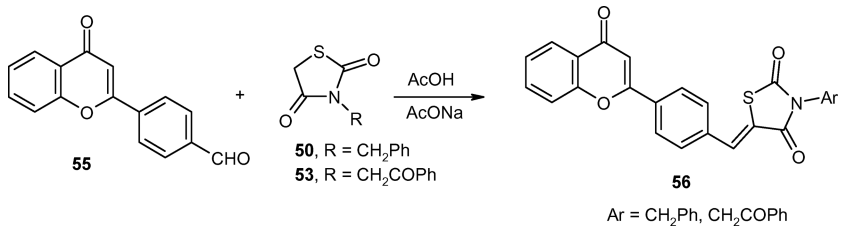
SCHEME 21

sodium acetate medium. After 8 h of refluxing, **73** was produced in 68–91% yields (Scheme 28).[44]

The Knoevenagel products **76** and **77** were obtained in low yields (15–43%) by heating **1c** with 2*H*-1,4-benzothiazin-3(4*H*)-one (**74**) and/or benzothiazin-2-one (**75**), respectively, in acetic anhydride and potassium acetate medium for 6–10 h. Using microwave irradiation, reaction times were shortened to 7–20 min with an increase of the yields to 33–62% (Scheme 29).[42,43]



SCHEME 22



SCHEME 23

Heterocyclization of *O*-Hydroxyacetophenone Derivatives Containing Sulfur Nitrogen Moieties with Electrophilic Reagents

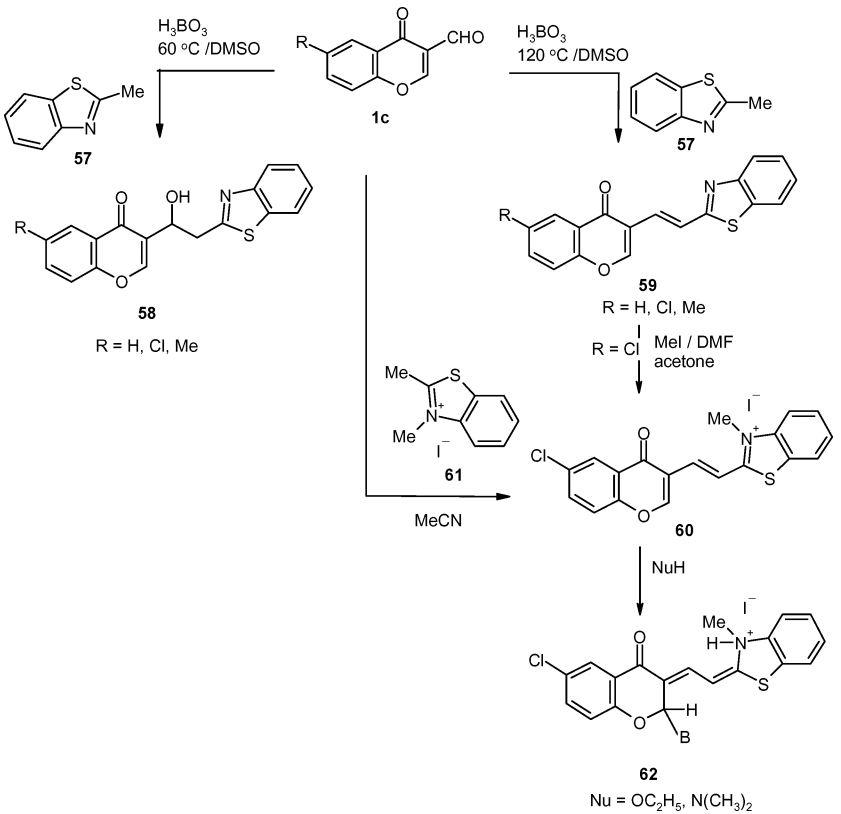
1-(2,4-Dihydroxyphenyl)-2-(1,3-thiazol-2-yl)ethanone (**78**) condensed with triethyl orthoformate in pyridine/piperidine to give the corresponding chromone derivative **79** (Scheme 30).[45]

Heterocyclization of 2-hydroxyacetophenone derivatives **78** by using a mixture of acetic anhydride and formic acid catalyzed by sodium formate is an effective method for the preparation of the 3-heteroarylchromones **80** (Scheme 31).[46]

3-[7-Hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-ethyl-4-oxo-4*H*-chromen-2-yl]propanoic acid (**82**) was synthesized by reaction of 1-(2,4-dihydroxy-5-ethylphenyl)-2-(4-methyl-1,3-thiazol-2-yl)ethanone (**78**) with succinic anhydride (**81**) in dry pyridine under stirring for 72 h at 40°C (Scheme 32).[47]

1-(2,4-Dihydroxy-5-ethylphenyl)-2-(1,3-benzothiazol-2-yl)ethanone (**78**) condensed with triethyl orthoformate and/or acid anhydride in pyridine/piperidine to give the corresponding chromone derivative **83** (Scheme 33).[45,48]

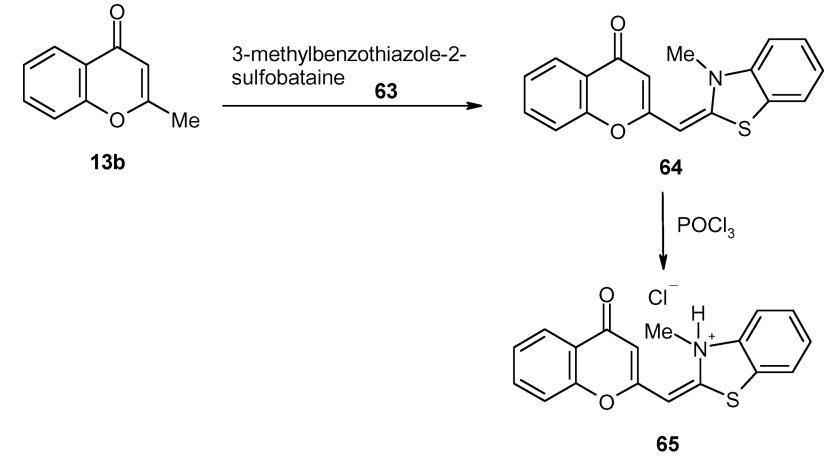
Heterocyclization of 1-(2,4-dihydroxyphenyl)-2-(2-phenyl-2,5-dihydro-1,2,3-thiadiazol-5-yl)ethanone derivative **78** by using a mixture of



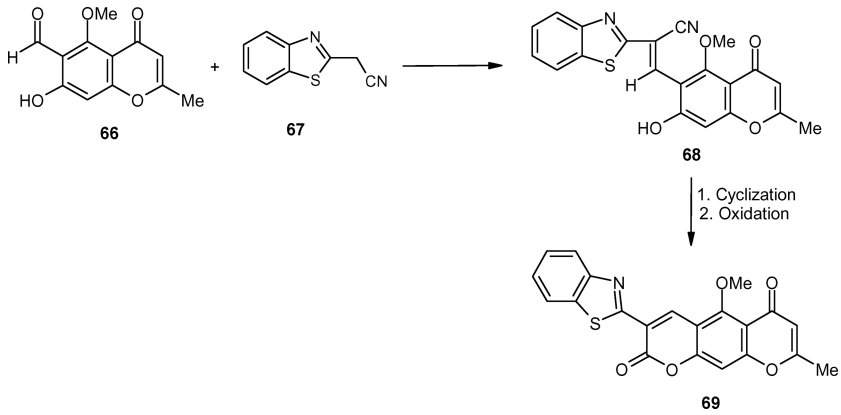
SCHEME 24

acetic anhydride and formic acid yielded 3-(2-phenyl-2,5-dihydro-1,2,3-thiadiazol-5-yl)chromone **84** (Scheme 34).[46]

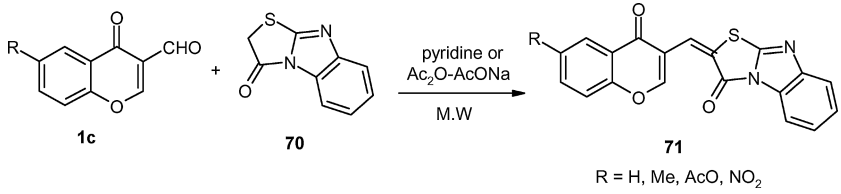
Reaction of α-(5-phenyl-1,3,4-thiadiazolyl-2)-6-ethyl-2,4-dihydroxyacetophenone (**78**) with an excess of trifluoroacetic anhydride or ethyl oxalyl chloride in pyridine did not stop at the stage of the diacyl derivative but was accompanied by cyclodehydration to give 2-trifluoromethyl/2-ethoxycarbonyl-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones (**85**). Cyclization of compound **78** with carboxylic acid anhydrides and/or halides and subsequent hydrolysis gave 2-*R*-6-ethyl-7-acetoxy-3-(5-phenyl-1,3,4-thiadiazoyl)chromones (**86**). Compound **85** is easily acylated with acetic anhydride in pyridine in the cold to give the 7-acetoxy derivatives **86** in high yield (Scheme 35).[49]



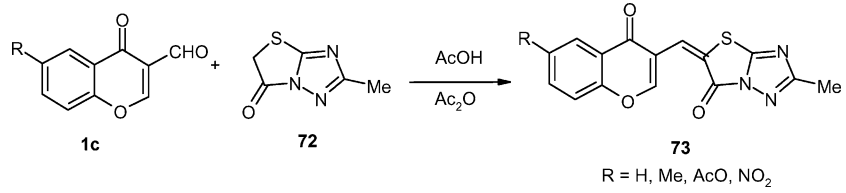
SCHEME 25



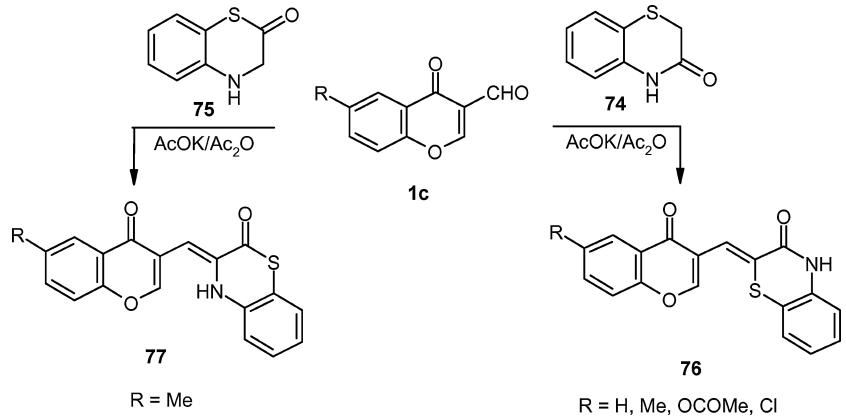
SCHEME 26



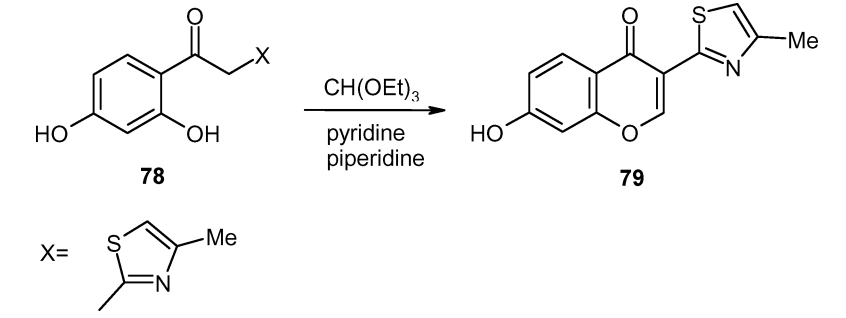
SCHEME 27



SCHEME 28



SCHEME 29

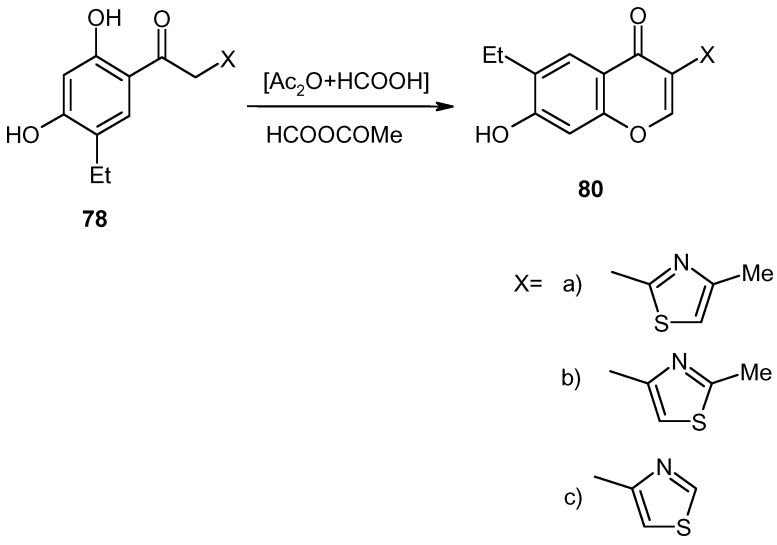


SCHEME 30

Heterocyclization of Functional Side Groups at 4-Oxo-4*H*-Chromene Moieties with Electrophilic and Nucleophilic Reagents

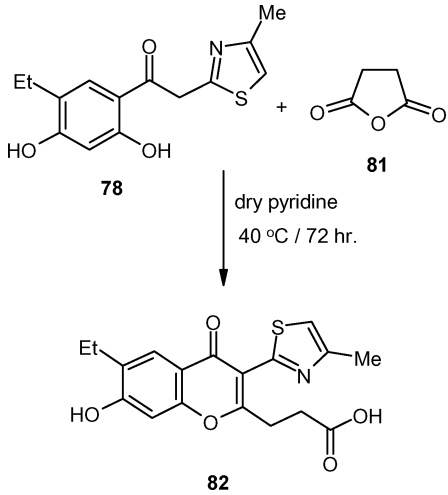
With Electrophilic Reagents

Reaction of compound **1c** with thiosemicarbazide in ethanol gave the expected hydrazones **87**. Compound **87** on treatment with



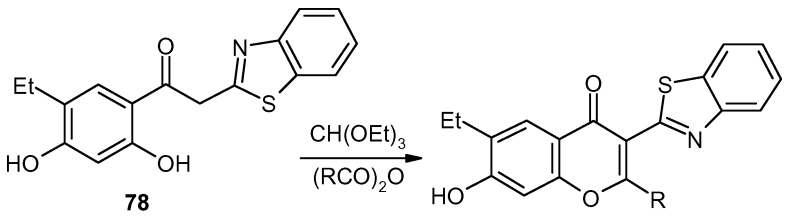
SCHEME 31

α-bromoketones in DMSO/pyridine yielded the thiazole derivative **88** (Scheme 36).[50]

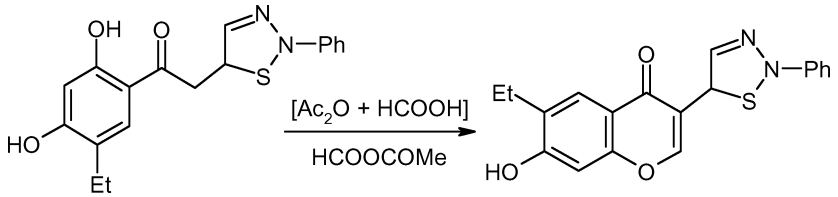


SCHEME 32

Some nucleophilic ring closure reactions of thiosemicarbazone **87** with chloroacetyl chloride in the presence of acetic acid and fused sodium acetate afforded thiazolidin-4-one derivative **89**, whereas its



SCHEME 33



SCHEME 34

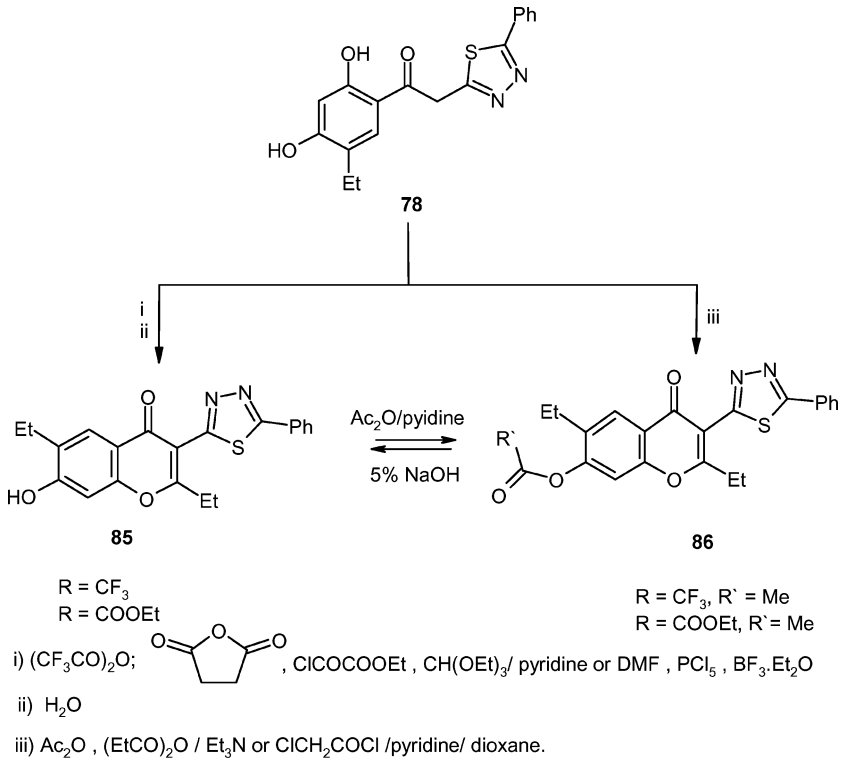
alkylation using chloroacetic acid under the same conditions furnished the isomeric thiazolidin-5-one derivative **90** (Scheme 37).[51]

Potassium *N*-[4-(6-chloro-4-oxo-4*H*-chromen-3-yl)methyleneamino] phenyldithiocarbamate (**91**) reacted with chloroacetyl chloride or phenacyl bromide in boiling dimethylformamide and led to the formation of 2-thioxo-1,3-thiazolidine-5-one **92** and 2-thioxo-1,3-thiazole **93** derivatives, respectively (Scheme 38).[52]

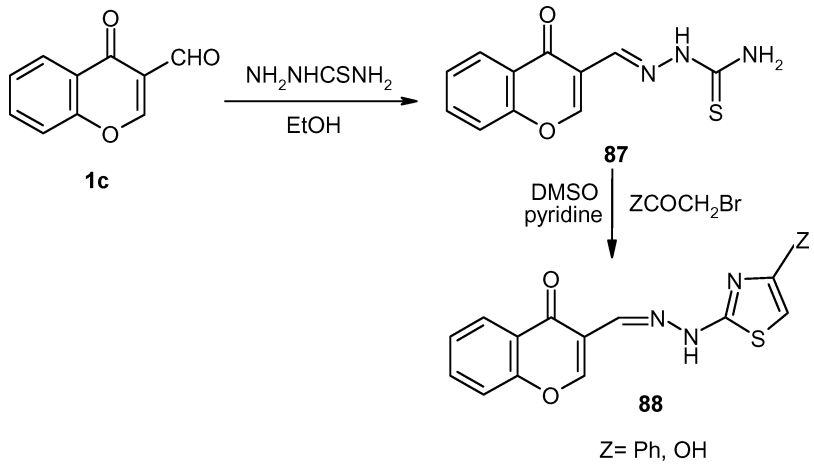
6-Aminoflavone (**94**) was treated with aroyl isothiocyanates **95** in acetone at reflux temperature to yield *N*-aroyl-*N*′-(2-phenyl-4-oxo-4*H*-chromen-6-yl)thioureas **96**, which were cyclized with PCl_5 in $POCl_3$ medium to *N*-(9-oxo-7-phenyl-9*H*-pyrano[2,3-g]benzothiazol-2-yl)benzamides (**97**) (Scheme 39).[53]

Reaction of 6-substituted 5-chromonylidine-2-thiohydantoin **98** with chloroacetic acid in ethanol in the presence of aqueous potassium hydroxide gave 2-carboxymethylthio-5-[(4-oxo-4*H*-chromen-3-yl)methylidene]imidazolidin-4-one (**99**). Cyclization of **99** in acetic anhydride yielded 5-[(4-oxo-4*H*-chromen-3-yl)methylidene]imidazo [2,1-*b*]thiazole-3,6-diones (**100**) (Scheme 40).[54]

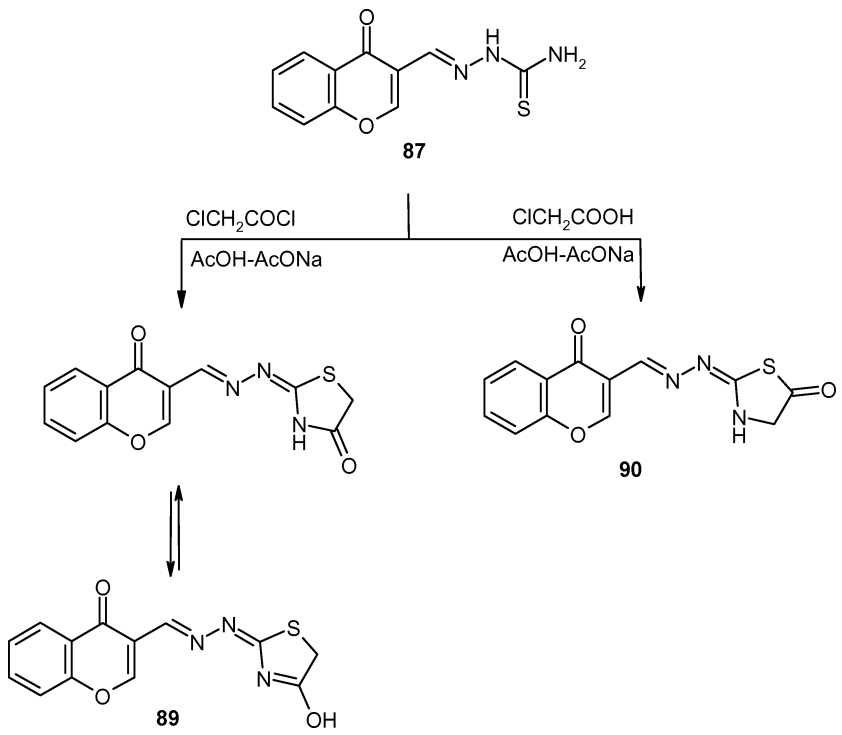
Condensation of **13c** with thiosemicarbazide led to the formation of thiosemicarbazones **101**, which on its oxidation with aqueous ferric



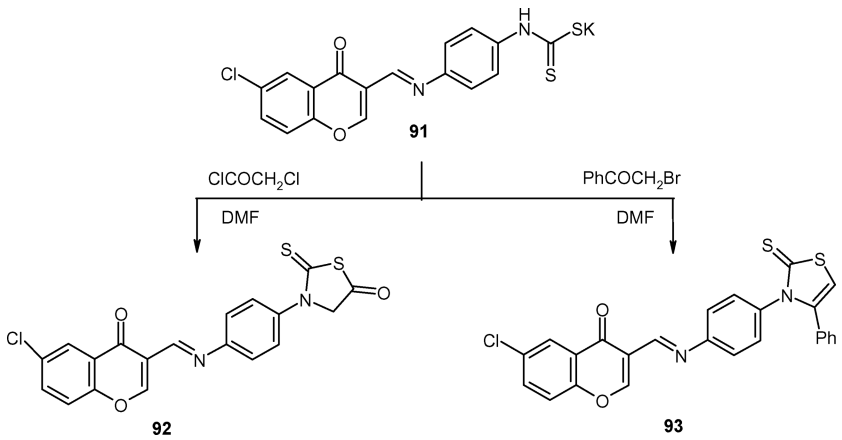
SCHEME 35



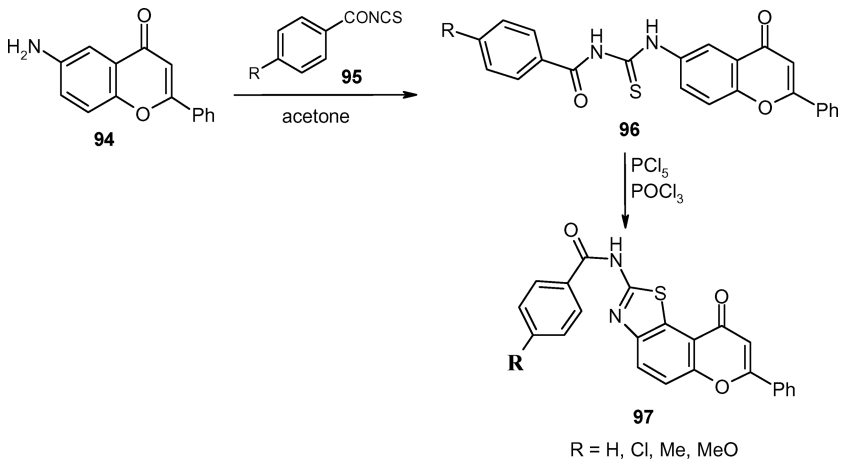
SCHEME 36



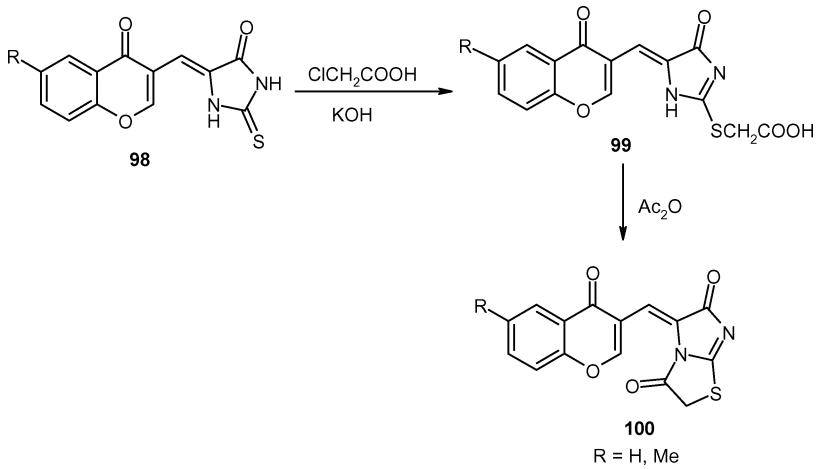
SCHEME 37



SCHEME 38



SCHEME 39

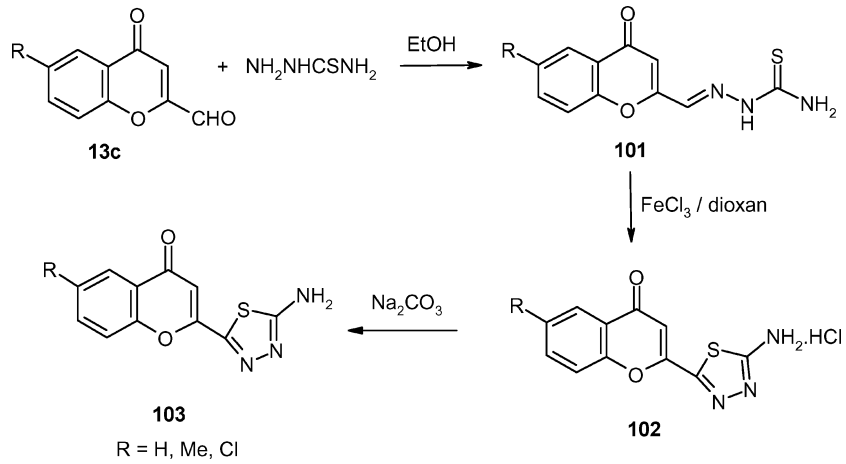


SCHEME 40

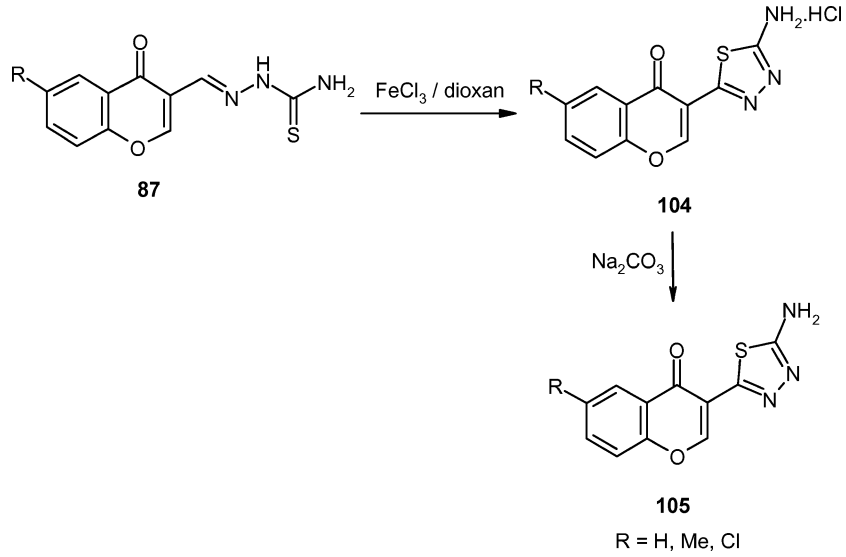
chloride in dioxane gave the corresponding free 2-aminothiadiazoles **103** (Scheme 41).[25]

Similarly, oxidation of thiosemicarbazones **87** with aqueous ferric chloride in dioxane gave, after neutralization with sodium carbonate, the corresponding free 2-aminothiadiazoles **105** (Scheme 42).[25]

Refluxing of thiocarbohydrazone **106** with excess formic acid at 95°C yielded 6-methyl-3-(1,3,4-thiadiazol-2-yl-hydrazonomethyl)-4*H*-chromen-4-one (**107**). Also, its refluxing with acetic anhy-



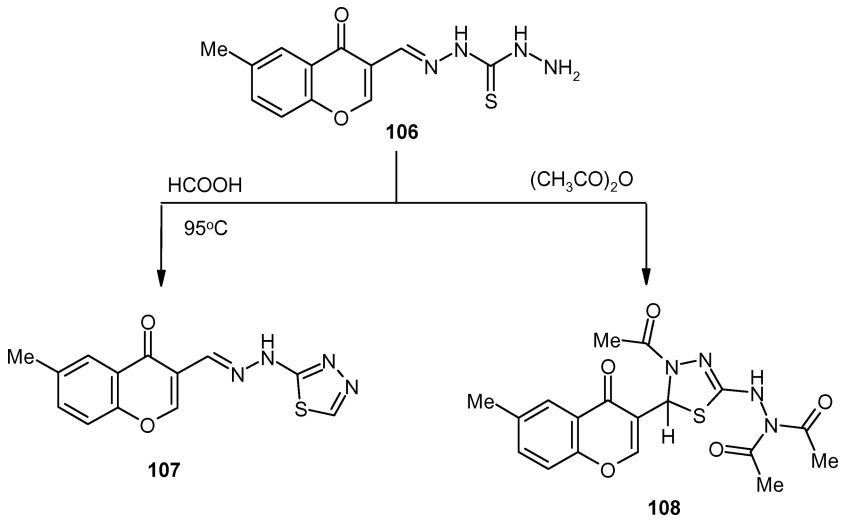
SCHEME 41



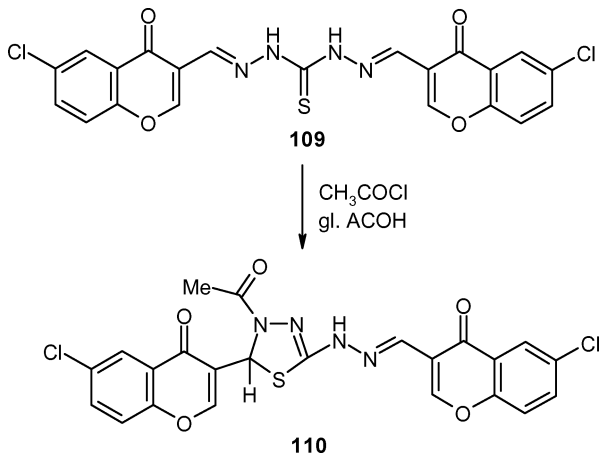
SCHEME 42

dride gave *N*-acetyl-*N*′-[4-acetyl-5-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]acetohydrazide (**108**) (Scheme 43).[55]

Cycloaddition of bisthiocarbohydrazone **109** with acetyl chloride in glacial acetic acid gave 6-chloro-4-oxo-4*H*-chromene-3-carbaldehyde[4-acetyl-5-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]hydrazone (**110**) (Scheme 44).[55]



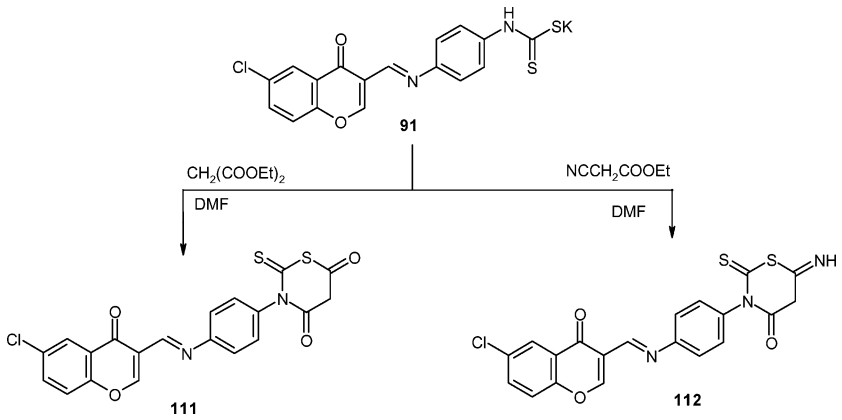
SCHEME 43



SCHEME 44

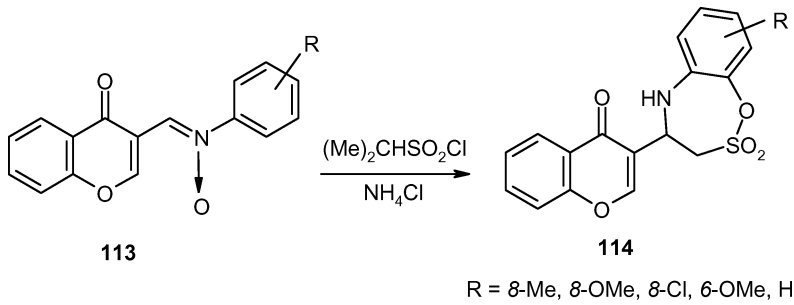
2-Thioxo-1,3-thiazine-4,6-dione derivative **111** and 6-imino-2-thioxo-1,3-thiazin-4-one derivative **112** were obtained *via* cyclization of **91** with diethyl malonate or ethyl cyanoacetate, respectively, in boiling dimethylformamide containing a catalytic amount of piperidine (Scheme 45).[52]

Chlorosulfonylmethylene(dimethyl)ammonium chloride is a highly reactive dehydrating agent that provides an efficient entry



SCHEME 45

to 4,5-dihydro-4-(4-oxo-4*H*-chromen-3-yl)-3*H*-1,2,5-benzoxathiazepine *S*, *S*-dioxides (**114**) *via* cycloaddition reactions of nitrones **113** with dimethylsulfine, generated *in situ* from propane-2-sulfonyl chloride (Scheme 46).[56]

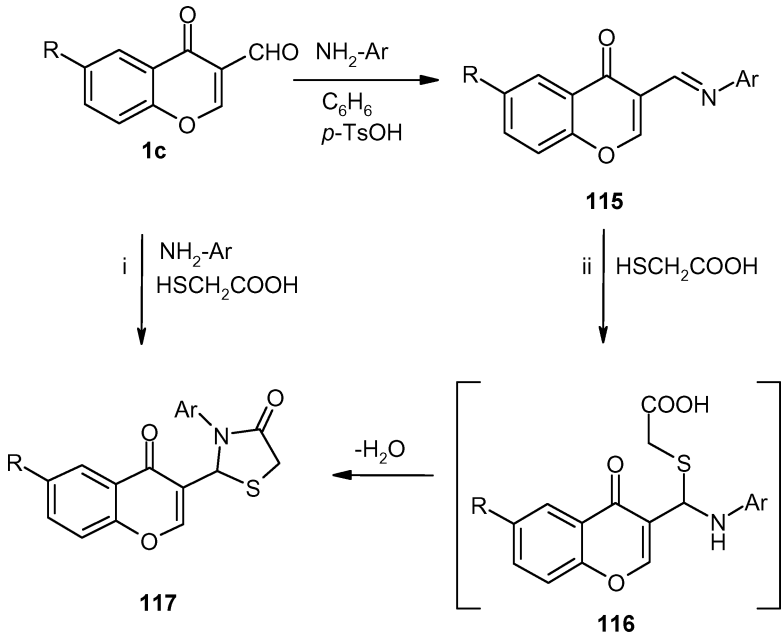


SCHEME 46

With Nucleophilic Reagents

3-(Aryliminomethyl)chromones **115** underwent 1,2-addition with thioglycollic acid in dry benzene leading to 1,2-adducts **116**, which were cyclized to 4-oxo-thiazolidines **117** (Scheme 47).[26,57–61] Also, the reaction of **1c** with amines and five equivalents of thioglycollic acid in dry benzene and a catalytic amount of *p*-toluenesulfonic acid under microwave irradiation was applied to improve the yields and shorten the reaction time.[60]

2,1,3-Benzothiadiazole-4,5-diamine (**118**) was condensed with **1c** and thioglycollic acid in benzene at reflux for 36–48 h to give the



R = H, Me, Cl, Br, NO_2

i. Microwave irradiation, 12-20 min. Na_2SO_4, *p*-TsOH, C_6H_6
ii. Classical heating, Toulene, *p*-TsOH, 9 h

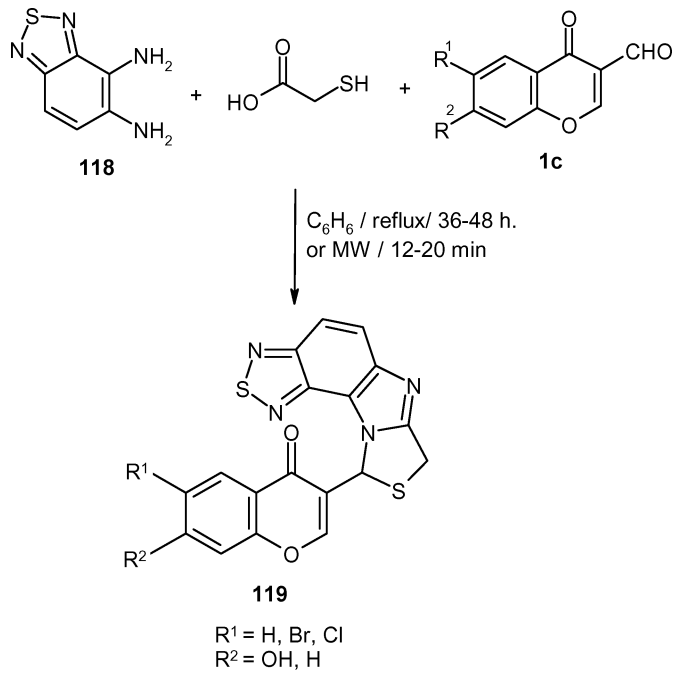
SCHEME 47

corresponding chromonylbenzothiadiazoles **119**. These compounds alternatively also were prepared by microwave irradiation at 300 W power level in an open vessel for 12–20 min in good yields (Scheme 48).[62]

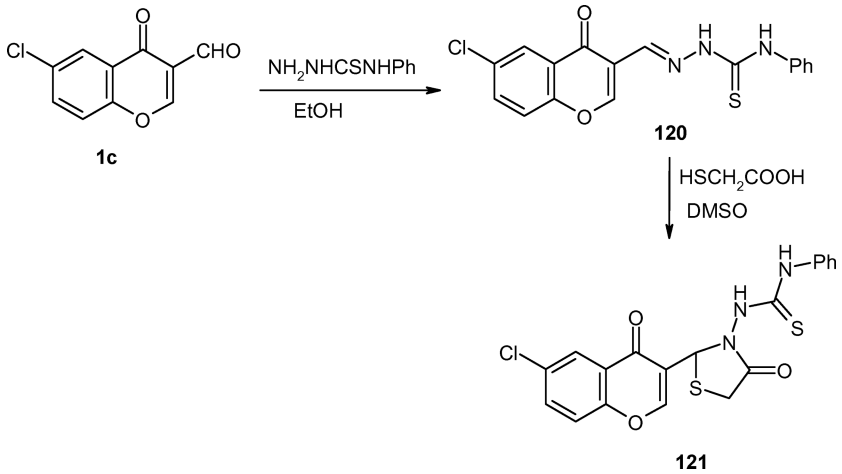
The addition condensation reaction of thioglycollic acid to thiosemicarbazone **120** in boiling DMSO furnished 1-[2-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenylthiourea (**121**) (Scheme 49).[56]

Bromination of compound **1e** under appropriate conditions[42,63] afforded the corresponding bromoethylketones **122**, which condensed with R^2–CS–NH_2 in boiling ethanol resulting in the corresponding thiazole **123**. Also, compound **123** was obtained directly from **1e** with thioamides in ethanol containing iodine (Scheme 50).[63–66]

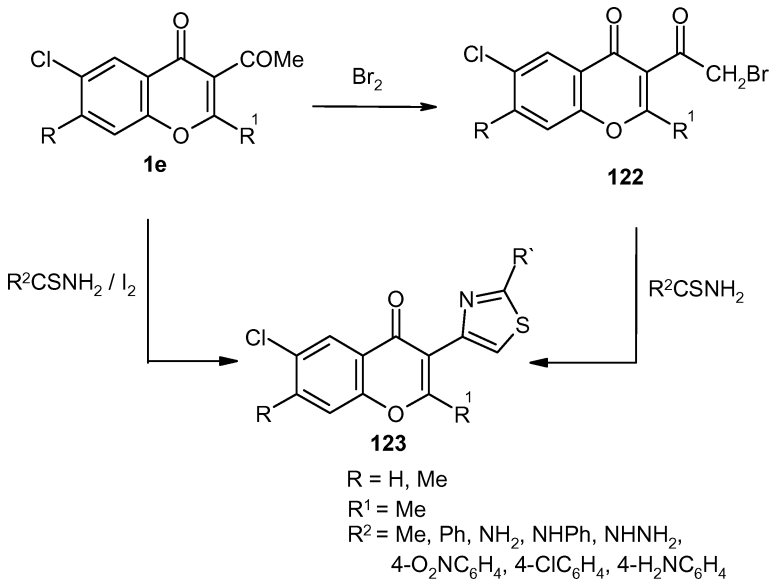
Similarly, some 6-(2-aminothiazol-4-yl)chromone derivatives **125** were synthesized by reaction of **124** with thiourea in acetone and potassium carbonate (Scheme 51).[67]



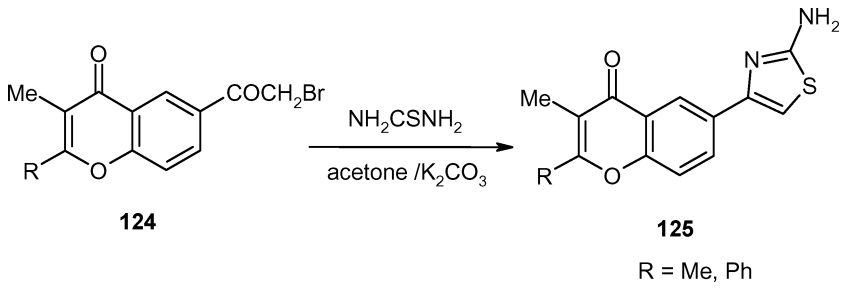
SCHEME 48



SCHEME 49



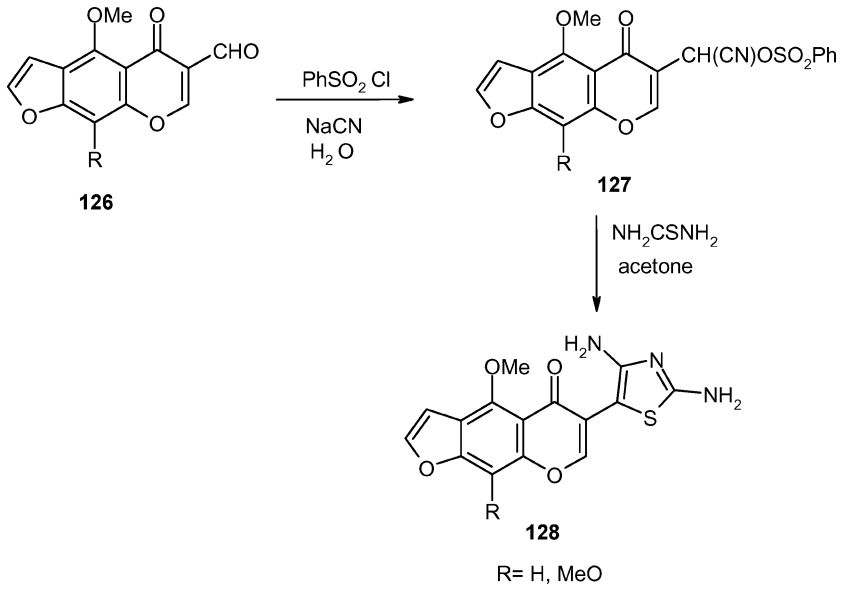
SCHEME 50



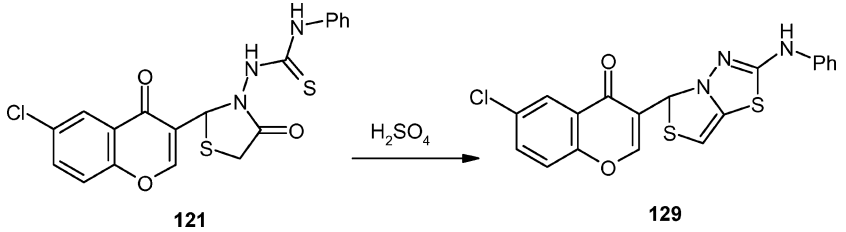
SCHEME 51

The reaction of the formyl derivatives **126** with sodium cyanide and benzenesulfonyl chloride in water gave the cyanobenzenesulfonate derivatives **127**. The acetone solution of the latter compounds **127** reacted with thiourea at room temperature to give the thiazole derivatives **128** (Scheme 52).[68]

Cyclization of 1-[2-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenylthiourea (**121**) with concentrated sulfuric acid afforded 3-(2-anilino-1,3-thiazolo[4,3-*b*][1,3,4]thiazadiazol-5-yl)-6-chloro-4*H*-chromen-4-one (**129**) (Scheme 53). The reaction pathway is assumed to proceed *via* intramolecular nucleophilic attack by the thiocarbonyl



SCHEME 52



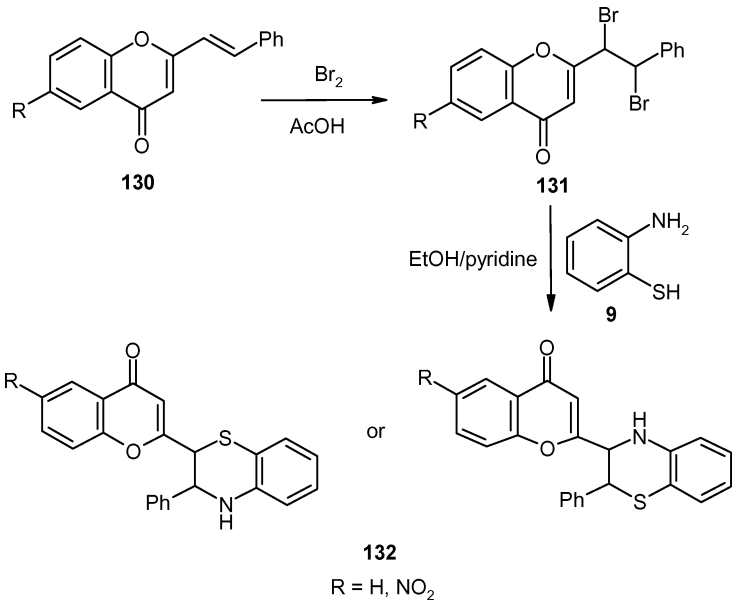
SCHEME 53

sulfur of the thiourea moiety to the electrophilic carbonyl carbon of thiazolidinone moiety followed by elimination of water molecule.[54]

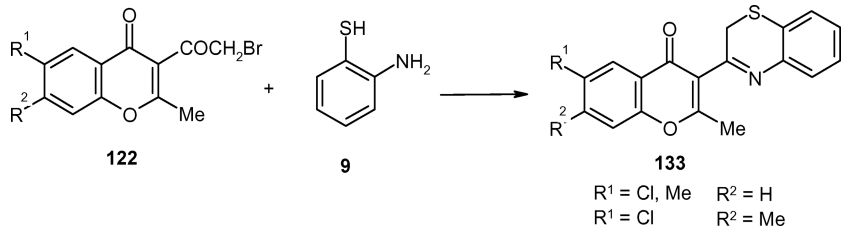
Bromination of styryl chromone **130** with bromine led to the formation of 1,2-dibromo-phenylethane derivatives **131**, which on treatment with 2-aminothiophenol (**9**) led to interesting systems that were characterized as benzothiazine derivatives **132** (Scheme 54).[69]

3-(2*H*-1,4-benzothiazin-3-yl)-2-methylchromones (**133**) were synthesized in 60–70% yields by condensation of bromoacetyl substituted chromones **122** with 2-aminothiophenol (**9**) (Scheme 55).[70]

Refluxing of the chloroacetamide derivative **134** with hydrazinecarbodithioic acid in DMF gave the 1,3,4-thiadiazine derivative **135** (Scheme 56).[71]



SCHEME 54



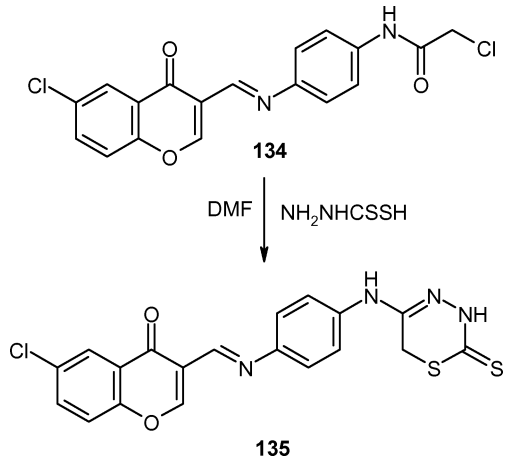
SCHEME 55

The chalcone **136** derived from chromone **1c** and aryl methyl ketones condensed with 2-aminothiophenol (**9**) to give the corresponding 2,3-dihydro-1,5-benzothiazepine **137** (Scheme 57).[72–74]

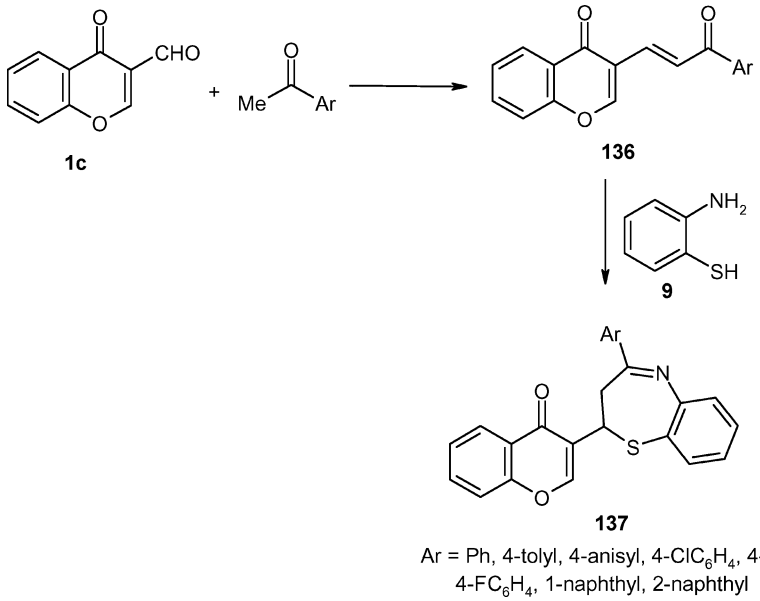
3-(Aryliminomethyl)chromones **115** underwent 1,4-addition with thioglycollic acid in dry benzene leading to 1,4-adducts **138**, which were cyclized to 3-oxo-thiazepines **139** (Scheme 58).[56–58,60,75]

BIOLOGICAL ACTIVITIES

4-Oxo-4*H*-chromene-containing sulfur-nitrogen heterocycles have been studied comprehensively with respect to their interesting biological and pharmacological activities.

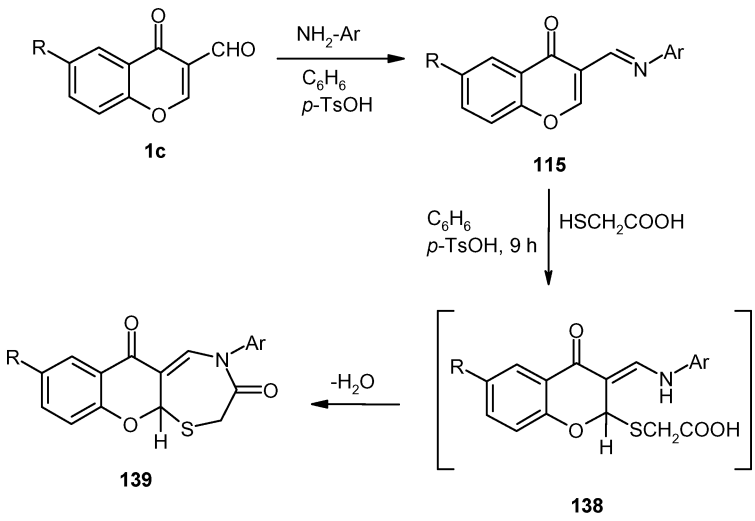


SCHEME 56



SCHEME 57

The *in vitro* antitumor activities of compounds **3** and **8** (R = Me, NH_2) showed moderate activity against Hep-2(laryngocarcinoma cell).[15] Compounds **15** and **34** have little antiepileptic and sedative properties.[21]



R = H, Me, Cl
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, *n*-C_4H_9, 4-FC_6H_4,2-$C_4H_3OCH_2$, 5-methyl[1,3,4]thiadiazol-2-yl, 2-mercapto-1,3,4-thiadiazol-2-yl

SCHEME 58

Compounds **20**, **21**, and **26** showed moderate antimycobacterial activity against *M. tuberc*, *M. kansasii*, *M. avium*, and *M. fortuitum*.[23] On the other hand, compound **26** showed antimicrobial activity against gram-positive bacteria such as *Staphylococcus aureus 29/58* and *Bacillus subtilis* 18/66 and gram-negative bacteria such as *Escherichia coli* 3247 and *Pseudomonas aeruginosa*, as well as yeasts (*Candida albicans*, *Saccharomyces*) and molds (*Microsporum gypseum*, *Aspergillus niger*, *Scopulariopsis brevicaulis*). Also, compound **26** exhibits an effect on the growth and on the plastid system of the autotrophic form of the unicellular flagellate *Euglena gracills*.[23]

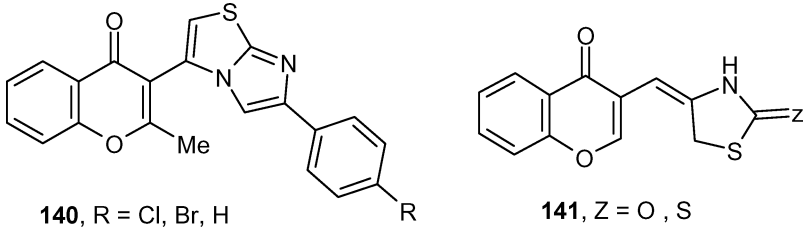
The minimum inhibition concentration of compound **41** against some common bacteria has been determined,[24] and compound **45** exhibits an interesting antiparasitic activity against *Molinema dessetae* and antifungal activity against yeasts.[30]

Compound **51** (R=H, CH_2COOH) showed ability to inhibit rat kidney aldose reductase.[36] Also, compound **54** showed moderate antibacterial and antifungal activity.[35]

In vitro insulin tropic activity[36] was observed for compound **56** annd benzothiazolium salts **60** showed antialgal activity toward *Chlorella vulgaris*.[32,38]

Compound **88** (Z = Ph, OH) has antimicrobial activity[49] against *Staphylococcus aureus FDA209P* and *Staphylococcus aureus R*. Also, compounds **93** and **112** showed high antifungal activities toward *Alternaria alternate*, *Aspergillus niger*, and *Aspergillus flavus*, and compounds **92**, **107**, and **111** showed moderate activities against these organisms.[51,54]

Compound **119** has antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and antifungal activity against *Aspergillus niger* and *C. albicans*.[62] Some substituted compounds **128** showed high activity toward yeast and fungi, moderate activity toward gram-positive bacteria, and low activity toward gram-negative bacteria.[68]



140, R = Cl, Br, H **141**, Z = O , S

SCHEME 59

Compound **140** showed diuretic activity effect on blood pressure as well as central nervous system activity in gross equal to chlorothiazide standard.[76] Also, 2,4-thiazolidene-diones **141** are used as antispasmodic agents in the treatment of angina pectoris and represent antidiabetic agents that improve the peripheral insulin resistance in type-II diabetic patients (Scheme 59).[77,78]

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