SYNTHETIC APPROACHES FOR HETEROANNULATED CHROMONES FUSED VARIOUS HETEROCYCLIC SYSTEMS

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Abstract – The main focus of this review summarized the different methods utilized for the synthesis of chromone annulated with different heterocyclic rings such as pyrroles, furans, pyrazole, imidazole, benzene, naphthalene, quinolone……and others.

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1. INTRODUCTION
Chromones (4H-chromen-4-one, 4H-1-benzopyran-4-ones) serve as the basic structural motif of a highly important oxygen-containing heterocyclic systems, which are commonly found in various flavonoids that occur as natural products in the plant world.1,2 Many chromone derivatives exhibit strong biological activity3,4 such as antioxidants,5-7 antimicrobial,7 anti-HIV,8 anti-inflammatory,9,10 antitumor,11 anticancer,12 antiviral,13 antiparkinson14 and have found applications as privileged structural motifs during the construction of various pharmaceutical molecules.15,16 Electronic absorption spectra, quantum chemical studies, DFT calculations, and optical properties were investigated for chromone derivatives.17,18 Heterocyclic ring fused on substituted chromones have become attractive targets in
organic synthesis due to their significance in biological systems and wide occurrence in natural products.\textsuperscript{19,20}

2. SYNTHESIS OF HETEROANNULATED CHROMONES

2.1. Chromones-fused five membered rings

2.1.1. Chromones annulated with cyclopentadienes

Cascade reaction between 4-hydroxycoumarine (1) with disubstituted acetylene, in dimethylacetamide (DMA) in the presence of CuBr\textsubscript{2} as an oxidant and Cs\textsubscript{2}CO\textsubscript{3} as base, afforded polysubstituted cyclopta[b]chromen-9(3H)-one derivative 2 (Scheme 1).\textsuperscript{21}

\begin{equation}
\text{Scheme 1}
\end{equation}

Treatment of 3-formylchromones 3 with dialkyl acetylenedicarboxylate in the presence of butyl isocyanide, in benzene, led to the formation of the fused cyclopentachromenedicarboxylates 4. On the other hand, reaction of 3-formylchromone 3 with isocyanides and dimethyl acetylenedicarboxylate (DMAD), in benzene gave cycloheptachromenetetracarboxylate 5 (Scheme 2).\textsuperscript{22}

\begin{equation}
\text{Scheme 2}
\end{equation}
Substituted cyclopenta[b]chromen-9(3H)-ones 7 were produced in moderate to high yields by chemoselective cyclization of 2-substitued 3-alkynylchromones 6 with 4-diethylaminophenylacetonitrile in DMF containing potassium t-butoxide and tetrabutylammonium chloride as a catalyst. The phenylacetonitrile serves as an anion transfer reagent (Scheme 3).

![Scheme 3](image_url)

2.1.2. Chromones annulated with pyrroles
Alberola et al. reported that condensation of 2-chloro-6-methylchromone 8 with α-amino ketones, in ethanol and trimethylamine, afforded 2-alkylaminochromones 9. Boiling the latter compound with acetic acid and pyrrolidine led to chromeno[2,3-b]pyrrol-4(1H)-ones 10 (Scheme 4).

![Scheme 4](image_url)

Refluxing 2-(N-methylanilino)-3-formylchromone (11) with methyl glycinate-hydrochloride, in aqueous acetonitrile in the presence of triethylamine, led to 2-methoxycarbonylmethylamino-3-formylchromone (12), in excellent yield (Scheme 5). Boiling compound 12 in aqueous acetonitrile in the presence of
potassium carbonate, gave 2-methoxycarbonylchremeno[2,3-b]pyrrol-4(1H)-one 13. The latter compound 13 was obtained directly from the reaction of chromone derivative 11 with methyl glycinate-hydrochloride, in boiling acetonitrile containing potassium carbonate instead of trimethylamine (Scheme 5).25

Cyclocondensation reaction between 2-amino-3-formylchromone (14) with chloroacetamide 15, in boiling DMF containing piperidine, gave chromeno[2,3-b]pyrrole-2-carboxamide derivative 16 (Scheme 6).26

2.1.3. Chromones annulated with indolizine

Heating 3-[hydroxy(pyrid-2-yl)methyl]chromones 17, in acetic anhydride, provided 12H-chromeno[3,2-b]indolizin-12-ones 18, in good yields (Scheme 7).27
2.1.4. Chromones annulated with benzopyrroles/benzofurans

Cyclization reactions of 2-(2-substituted-phenyl)chromones 19 in boiling in toluene/dimethyl sulfoxide (PhMe/DMSO) using Zn(OTf)$_2$ combined with copper acetate, afforded chromones fused with benzofurans and/or benzopyrroles 20 (Scheme 8).$^{28}$

2.1.5. Chromones annulated with furans

Cyclization of 5-(2-carboxysubstituted-phenoxy)furan-2-carboxylic acids 21 with polyphosphoric acid ethyl ester (PPE), under reflux, produced substituted ethyl furo[2,3-b]chromone-2-carboxylates 22, in low yield (Scheme 9).$^{29}$

Stirring an equimolar amount of 3-formylchromones 3, ninhydrin 23 and cyclohexyl isocyanide, in mixture of dichloromethane/methanol (CH$_2$Cl$_2$-MeOH) (7:1) at room temperature, produced furo[3,4-b]chromen-9-ones 24 (Scheme 10).$^{30}$
Benchmark reaction between 3-formylchromones 3, isocyanides and N-alkyl/benzisatin 25, in anhydrous dichloromethane (CH₂Cl₂), performed furo[3,4-b]chromen-1-ylindol-2-ones 26, in 55-78% yields within 6 days at room temperature (Scheme 11).³¹

Reaction of 3-formylchromones 3 with isocyanides in molar ratio 2:1, under different reaction conditions, furnished 1-[(chromon-3-yl)methylene]furo[3,4-b]chromen-9-ones 27 (Scheme 12).³⁰
2.1.6. Chromones annulated with pyrazoles

Condensation of 2-bromobenzaldehyde (28) with 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (29) in DMSO using CuI as a catalyst, and K₂CO₃ as a base afforded 3-methyl-1-phenylchromeno[2,3-c]pyrazol-4(1H)-one (30) (Scheme 13).³²

```
28  +  29
    | DMSO/ CuI
    | K₂CO₃/ 120 °C/ 74%
       30
```

Scheme 13

Condensing 2-amino-3-formylchromone (14) with some hydrazine derivatives, in boiling ethanol containing catalytic amount of acetic acid, performed the corresponding hydrazones 31. Boiling the latter compounds, in DMF, gave chromeno[2,3-c]pyrazol-4(1H)-one (33) (Scheme 14). Compound 32 can also be formed from refluxing aldehyde 14 with hydrazine hydrate in boiling DMF (Scheme 14).³³

```
14  +  NH₂NH₂
    | EtOH/AcOH reflux/ 25 min 60-84%
    | DMF/ reflux/ 2 h
       31

R= R₁= R₂= R₃= H
```

Scheme 14

On the other hand, reaction of 2-[(N-methylanilino)-3-formylchromones 11 (R= H) with phenylhydrazine, in refluxing dry acetonitrile, produced isomeric chromanopyrazoles 33 and 34. Refluxing 2-[(N-methylanilino)-3-formylchromone 11 (R= Cl) with hydrazine hydrate, in acetonitrile, afforded chromenopyrazole 33 (Scheme 15).²⁵,³⁴
2.1.7. Chromones annulated with imidazo-fused pyridine

One-pot synthesis of 12\(H\)-chromeno[2′,3′:4,5]imidazo[1,2-\(a\)]pyridin-12-ones 36 were achieved, in moderate yield, from intramolecular cyclization of 1-(2-imino-2\(H\)-chromen-3-yl)pyridinium chlorides 35, in boiling ethanol containing few drops of DABCO (1,4-diazabicyclo[2.2.2]octane) (Scheme 16).\(^{35}\)

\[
\begin{align*}
\text{Scheme 15} \\
\text{2.1.8. Chromone annulated with thiazolo-fused benzimidazole}
\end{align*}
\]

Oxidation of benzimidazo[2,1-\(b\)]thiazole derivative 37 using iodine, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), smoothly promoted the cyclized product; 5\(H\)-benzimidazo[2′,1′:2,3]thiazolo[4,5-\(b\)]chromone (38), in excellent yield (Scheme 17).\(^{36}\)
2.2. Chromones-fused six membered rings

2.2.1. Chromone annulated with benzene

Also, oxidation of tricyclic chromones 39 with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), at 220 °C for 10 min under microwave conditions, provided 1,4-dihydroxanthones 40 in excellent yields (Scheme 18).37

![Scheme 18]

Condensation of methyl 2-chlorobenzoates 41 with substituted phenols 42, in mixture of dimethylacetamide (DMAc) and dimethylformamide (DMF) in the presence of cuprous oxide (Cu₂O) and potassium carbonate (K₂CO₃) yielded ether derivatives 43, which were saponified and then cyclized by polyphosphoric acid to give xanthone-2-carboxylic acids 44 (Scheme 19).38

![Scheme 19]

4-Methyl-1-nitro-9H-xanthen-9-one (47) was synthesized from the reaction of 2-methyl-5-nitrophenol (45) with o-chlorobenzoic acid (46), in nitrobenzene and polyphosphoric acid (Scheme 20).39
Treating 3-alkenylchromone derivatives 48 with tetramethoxyethene (TME), in dichloromethane, followed by treatment with Et₂O·BF₃ (4.0 equiv.) gave 3,4-dimethoxyxanthones 49 (Scheme 21).  

Reaction of chromones 48 with freshly generated 1-(2,2-dimethoxyvinyl)pyrrolidine (50) (from dimethoxyacetaldehyde and pyrrolidine), in boiling benzene, resulted in xanthones 51 in moderate to excellent yields (Scheme 22).  

Enamine derivatives 52 reacted smoothly with chromone-3-carboxylic acid (53), in boiling DMF, to give 2-salicyloylxanthone 55 via non-isolable cycloadduct 54 which underwent decarboxylative pyran ring opening and dedimethylamination (Scheme 23).
Dimerization reaction of 3-alkynyl-2-methylchromones 56, in DMSO containing DBU in microwave irradiation at 120 °C for 10 min, led to xanthones-linked chromones 57 (Scheme 24).42

2.2.2. Chromones annulated with indenes

Reaction of 6-(chromon-3-yl)hex-5-ynenitriles 58 with 2-(4-(diethylamino)phenyl)acetonitrile, in the presence of t-BuOK and n-Bu4NCl in DMF at 110 °C for 20 min under microwave irradiation, generated 4-amino-2,3-dihydrocyclopenta[a]xanthen-11(1H)-ones 59 (Scheme 25).23

Also, dehydroiodination of annulated chromane 60, in chloroform containing DBU, gave xanthone derivative 61 (Scheme 26).43
2.2.3. Chromones annulated with indole

Refluxing enamines 52 with N-phenylmaleimide 62, in DMF under reflux, produced xanthone 64 through initially formed cycloadduct 63 which readily eliminated dimethylamine and dehydrogenated under the reaction conditions (Scheme 27).41

2.2.4. Chromones annulated with isochromene

Tetracyclic pyranoxanthene derivatives 66 were prepared from oxidation of chromone derivatives 65 by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under microwave heating conditions at 220 °C for 10 min in 1,2-dichlorobenzene (Scheme 28).37
2.2.5. Chromones annulated with naphthalenes

3-[(2-Hydroxyphenyl)carbonyl]-5-phenyl-12H-benzo[α]xanthen-12-one (69) was obtained from cascade reaction between 2-methylchromone-3-carboxaldehyde (67) and 3-(3-oxo-3-phenylprop-1-enyl)chromone (68), in tetrahydrofuran (THF) containing DBU through microwave irradiation, in quantitative yield (Scheme 29).44

![Scheme 29](image)

Reaction of 2-methyl-3-(1-alkynyl)chromones 57 with electron-deficient chromone-fused dienes 48, in DMSO using DBU as the base under microwave irradiation conditions, yielded benzo[α]xanthones 70 (Scheme 30).45

![Scheme 30](image)

Diels-Alder reaction of unsubstituted chromones 71 with o-benzoquinodimethane 72, in 1,2,4-trichlorobenzene and anhydrous AlCl₃ as a Lewis acid, led to benzo[b]xanthones 73. While, oxidation of cycloadducts benzo[b]-1,6,6a,12a-tetrahydroxanthones 74 and 75 by using iodine in DMSO gave compounds 73, in excellent yields (Scheme 31).46
Diels-Alder reactions of 3-formylchromones 3 with o-benzoquinodimethanes 76 gave rise a mixture of diastereomers 77 and 78 in excellent yields (88–93%). Oxidation of adducts 77 and 78, with iodine in DMSO, gave benzo[b]xanthones 79 in good yields (89–94%) (Scheme 32).47

Condensation reaction of chromone 71 with 4,5,7-trimethoxy-3-(phenylsulfonyl)isobenzofuran-1-(3H)-one (80), in THF in the presence of lithium tert-butoxide (LiO-t-Bu), furnished polysubstituted benzo[b]xanthone derivative 81, in 27% yield (Scheme 33).48
Reaction of 3-iodochromones 82 with \( p \)-iodotoluene (83) in aqueous norbornadiene, promoted by Pd(OAc)\(_2\), aqueous DMF, and cesium pivalate (Me\(_3\)CCO\(_2\)Cs), as the base, generated the desired benzoxanthones 84 (Scheme 34).\(^{49}\)

One-pot synthesis of benzo[c]xanthones 86 were achieved from benzylidene-1-tetralones 85 under the ultraviolet radiation (Scheme 35).\(^{50}\)

2.2.6. Chromones annulated with pyridines

Reaction of 3-formylchromones 87 with \( N \)-methylhydroxylamine, in dichloromethane at an ice-cold
temperature, led to chromonopiperidine-fused isoxazolidines 88, in excellent yields, in addition to the corresponding amides 89, in low yields (Scheme 36).51

![Scheme 36](image)

Dialkyl chromeno[2,3-b]pyridine-2,3-dicarboxylates 91 were obtained from treatment of 2-(alkylamino)chromone-3-carboxaldehydes 90 with acetylenic esters and triphenylphosphine (Ph₃P) (Scheme 37).52

![Scheme 37](image)

3-(2-Hydroxybenzoyl)-2H-chromeno[2,3-b]pyridine-2,5(1H)-dione (93) was obtained from self-condensation of chromone-3-carboxamide (92), in sodium methoxide solution (Scheme 38).53

![Scheme 38](image)

2-(Alkyl/arylamino)chromone-3-carboxaldehyde 90 reacted with hippuric acid, Meldrum’s acid and/or 4-hydroxycoumarine under different conditions produced chromeno[2,3-b]pyridine-2,5-diones 94 (Scheme 39).54
Refluxing chromone-3-carbonitrile (95) with hippuric acid, in acetic anhydride, yielded \(N\)-acetylchromenopyridine derivative 96 (\(R^2 = \text{H}\)), in 59% yield (Scheme 41).\(^{37}\) While, chromeno[2,3-\(b\)]pyridin-2-yl acetate 97 (\(R^2 = \text{Me}\)) was prepared from the reaction of 6-methylchromone-3-carbonitrile (95) with hippuric acid in boiling acetic anhydride (Scheme 40).\(^{55}\)

Condensing 2-amino-3-formylchromones 14 with malononitrile and/or ethyl cyanoacetate, in boiling ethanol containing piperidine, furnished 2-amino-3-substituted chromeno[2,3-\(b\)]pyridines 98 (Scheme 41).\(^{56}\)
Scheme 41

Condensation reaction of 2-amino-3-formylchromone (14) (R² = Et) with cyanoacetyl chloride, in dichloromethane, gave cyanoacetamide derivative 99, which by heating in pyridine converted to 7-ethyl-2-hydroxy-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile (100) (Scheme 42).\(^5^7\)

Scheme 42

Condensation of 2-amino-3-formylchromone 14 (R² = i-Pr) with malonaldehyde bis(dimethylacetal), in the presence of formic acid in boron trifluoride etherate, gave 7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carboxaldehyde 101 (Scheme 43).\(^5^7\)
Stirring chromone-3-carbonitriles 95 with chloroacetone, in dichloromethane in the presence of Brockman neutral alumina, led to chromeno[2,3-\textit{b}]pyridines 102, in very low yields (12 -14\%) (Scheme 44).58

Heteroannulated chromeno[2,3-\textit{b}]pyridines 103 were synthesized by condensation of chromone-3-carbonitriles 95 with a variety of active methylene compounds, in the presence of ethanol containing DBU as a catalyst. Also, compounds 103 were synthesized from Friedländer reaction of 2-amino-3-formylchromone derivatives 14 with active methylene compounds under the same reaction conditions (Scheme 45).55,59-62
Reaction of chromone-3-carbonitriles 95 with 1,3-\textit{bis}(trimethylsilyloxy)-1,3-butadienes, in trimethylsilyl trifluoromethanesulfonate as Lewis acid, produced chromane derivatives 104, which upon treatment with triethylamine resulted in 1-azaxanthones (5-oxo-5\textit{H}-chromeno[2,3-\textit{b}]pyridines) 105 (Scheme 46).

![Scheme 46](image)

Benzochromeno[2,3-\textit{b}]pyridines 106 were obtained, in good yield, from treatment of chromone-3-carbonitriles 95 with ethyl 3-aminocrotonate. Compounds 106 were also be prepared from Friedländer reaction of 2-amino-3-formylchromones 14 and ethyl acetoacetate (Scheme 47).

![Scheme 47](image)
Condensation reaction of chromone-3-carbonitriles 95 with acetylacetone and/or 4-amino-3-penten-2-one, under different reaction conditions, produced 2-methyl-3-acetyl-5-oxo-5H-chromeno[2,3-b]pyridines 107. The latter compounds 107 were also be prepared from reaction of 2-amino-3-formylchromones 14 with acetylacetone, in boiling ethanol in the presence of piperidine (Scheme 48).56,65,66

Reaction of 2-amino-3-formylchromones 14 with ethyl propiolate, in DMF containing triethylamine (TEA), gave aminoacrylate 108 which was converted, by further heating, to ethyl 5-oxo-5H-chromeno[2,3-b]pyridine-3-carboxylates 109. On the other hand, compounds 109 were obtained directly from the reaction of compounds 14 with methyl malonyl chloride, in boiling DMF (Scheme 49).66
Treating 2-amino-3-formylchromone 14 \((R^2=\text{-Pr})\) with cyanoacetylene, gave 5-oxo-5\(H\)-chromeno[2,3-\(b\)]pyridine-3-carbonitrile 110. Also, compound 14 \((R^2=\text{Et})\) reacted with \(\alpha\)-chloroacrylonitrile, in the presence of triethylamine, produced compound 110. Treating aldehyde 14 \((R=\text{H})\) with cyanoacetyl chloride, in DMF, afforded the same product 110 (Scheme 50).57

Siddiqui et al.,68 observed that 3-acetoacetyl-5-oxo-5\(H\)-chromeno[2,3-\(a\)]pyridine 112 was formed from the reaction of 2-amino-3-formylchromone (14) and triacetic acid lactone (111), in boiling pyridine containing piperidine. This reaction occurred through condensation followed by intramolecular translactonizations (Scheme 51).

Treatment of chromone-3-carbonitriles 95 with 4,6-diacetylresorcinol in 1:1 and 2:1 molar ratio, in absolute ethanol containing a few drops of DBU, gave 2-(5-acetyl-2,4-dihydroxyphenyl)-5-oxo-5\(H\)-chromeno[2,3-\(b\)]pyridine (113) and 4,6-bis(5-oxo-5\(H\)-chromeno[2,3-\(b\)]pyridin-2-yl)resorcinol (114), respectively (Scheme 52).59,69
Condensation reaction of chromone-3-carbonitrile (95) with some acetyl heterocycles namely 2-acetylthiophene, 3-acetylpyridine, 5-acetyl-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione, 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one, 4-chloroacetophenone, in absolute ethanol containing DBU as a basic catalyst, afforded 2-heteroaryl-5-oxo-5H-chromeno[2,3-b]pyridines 115. The transformation of carbonitrile 95 into chromeno[2,3-b]pyridines 115 can be regarded as a domino "Michael/retro-Michael/nitrile-addition/cyclocondensation reaction". Compounds 115 were obtained by the classical Friedländer condensation of 2-amino-3-formylchromone (14) (R = allyl) with the same acetyl derivatives under the same reaction conditions (Scheme 53).59,69

Treatment of chromone-3-carbonitrile (95) with (1H-benzimidazol-2-yl)acetonitrile (116) produced 2-amino-3-(1H-benzimidazol-2-yl)-7-methyl-5H-chromeno[2,3-b]pyridin-5-one (117). The latter
compound 117 can also be obtained from of 2-aminochromone-3-carboxaldehydes 14 with 1H-benzimidazol-2-ylacetonitrile (96) under the same conditions (Scheme 54).\textsuperscript{70}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_54}
\end{center}

Scheme 54

Refluxing 3-acetylchromones 118, in the presence of ammonium acetate as source of NH\textsubscript{3} in acetic acid, produced chromeno[3,2-c]pyridin-10-ones 119 (Scheme 55).\textsuperscript{71}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_55}
\end{center}

Scheme 55

Also, treatment of 3-acylchromones 118 with hydroxylamine and/or acetylhydrazine, in refluxing acetic acid containing fused sodium acetate, gave chromeno[3,2-c]pyridinium salts 120 (Scheme 56).\textsuperscript{71}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_56}
\end{center}

Scheme 56
Chromeno[3,2-c]pyridines 121 were synthesized from reaction of 3-(1-alkynyl)chromones 56 and aromatic aldehydes (1.5 equiv.), in the presence of AcONH₄ in DMF (Scheme 57).⁷²

\[
\begin{align*}
\text{Scheme 57}
\end{align*}
\]

2.2.7. Chromone annulated with pyrido-fused cyclopentene

Cyclopenta[b]chromeno[3,2-e]pyridin-10-one (122) was obtained from condensation reaction of chromone-3-carbonitrile (95) with cyclopentanone, in boiling ethanol containing DBU (Scheme 58).⁵⁹

\[
\begin{align*}
\text{Scheme 58}
\end{align*}
\]

2.2.8. Chromones annulated with pyrido-fused indene

Friedländer condensation of 2-amino-3-formylchromones 14 and indanedione 123 in the presence of Zn(L-proline)$_2$ as an efficient, stable and inexpensive Lewis acid catalyst in water, produced 11,13-dioxochromeno[2,3-b]indeno[2,3-e]pyridines (124) (Scheme 59).⁷³
2.2.9. Chromones annulated with pyrido-fused pyrazole

Chromone-3-carbonitriles 95 reacted with pyrazoline-3,5-dione, in boiling ethanol containing DBU, yielded chromeno[2,3-b]pyrazolo[4,3-e]pyridin-5(1H)-ones 125, in good yields. The latter compound 125 (R= allyl) was synthesized from condensation of 2-amino-3-formylchromone 14 with pyrazoline-3,5-dione under the same reaction conditions (Scheme 60).55,59,69

Scheme 60

3,8-Dimethylchromeno[2,3-b]pyrazolo[4,3-e]pyridin-5(1H)-one (127) was obtained by reacting 2-amino-3-formylchromone 14 with 5-amino-3-methyl-1H-pyrazole (126) in refluxing DMF/DBU (Scheme 61).74

Scheme 61
2.2.10. **Chromone annulated with pyrido-fused benzimidazole**

Reaction of chromone-3-carbonitrile (95) with (1H-benimidazol-2-yl)acetonitrile (116), in boiling ethanol containing triethylamine (TEA), gave angular heteroannulated chromone; identified as chromeno[2',3':6,5]pyrido[1,2-a]benzimidazole-6-carbonitrile (128) (Scheme 62).

```
R\_2 O\_2 CN + N\_2 N\_N\_H\_CN  \xrightarrow{EtOH/ TEA \text{ reflux/ 30 min}}  55\%
95 116 128
R= R' = R" = H
```

Scheme 62

2.2.11. **Chromone annulated with pyrido-fused oxazole**

Chromenopyridoxazolones 129 were synthesized from reacting 2-amino-3-formylchromone 14 and N-acetylglycine, in boiling acetic anhydride containing fused sodium acetate. Compounds 129 were prepared from condensation of chromone-3-carbonitriles 95 with hippuric acid or aceturic acid under the same reaction conditions (Scheme 63).

```
R\_2 O\_2 CHO + N\_2 N\_Me\_O\_H  \xrightarrow{Ac\_2O/ AcONa \text{ reflux/ 3 h/ 70%}}  70\%
14 129
R, R' = H, benzo R" = Me, Ph
R\_2, R"' = H, OH, Cl, Br, OAc, benzo
```

Scheme 63

2.2.12. **Chromones annulated with pyrido-fused thiazole**

Treating chromone-3-carbonitrile (95) with 2-phenyliminothiazolidin-4-one, in ethanol containing DBU, led to 2-anilinochromeno[2,3-b][1,3]thiazolo[5,4-e]pyridin-10-one 130. Friedländer condensation of 2-amino-3-formylchromones 14 (R = allyl) with 2-phenyliminothiazolidin-4-one afforded the same compound 130 (Scheme 64).

```
R\_2 O\_2 CN + N\_2 N\_O\_H  \xrightarrow{Ac\_2O/ AcONa \text{ reflux/ 2-3 h/ 47-80%}}  47-80%
95 130
```

Scheme 64
2.2.13. Chromones annulated with quinolines

Ghosh et al.\textsuperscript{76} demonstrated that an efficient synthesis of 6-aryl-8,8-dimethyl-8,9-dihydro-5\textit{a}H-chromeno[2,3-\textit{b}]quinoline-10,12(7\textit{H},10\textit{H})diones \textbf{131} was achieved from a three-component reaction involving 3-formylchromones \textbf{3}, an aromatic amine, and dimedone in aqueous tetrabutylammonium bromide (TBAB) solution (Scheme 65).

Sequential reaction of chromone-3-carbonitrile (\textbf{95}) with 1,3-\textit{bis}-silyl enol ethers \textbf{132}, afforded ethyl 8,9,10,12-tetrahydro-12-oxo-7\textit{H}-chromeno[2,3-\textit{b}]quinoline-7-carboxylate (\textbf{133}) (Scheme 66).\textsuperscript{63}
Reaction of chromone-3-carbonitriles 95 with 5,5-dimethyl-1,3-cyclohexanedione (dimedone), in boiling ethanol containing fused ammonium acetate, led to chromeno[2,3-b]quinolinediones 134, in 41-63% yields. Compounds 134 were also prepared from reaction of 2-amino-3-formylchromone 14 with dimedone, in ethanol containing piperidine (Scheme 67).56,66,69

\[ R, R_1 = \text{benzo}, \ H \]
\[ R_2, R_3 = \text{benzo}, \ H, \ Cl \]
\[ R = \text{H}, \ \text{allyl} \]

Scheme 67

Chromeno[2,3-b]quinolinedione derivative 135 was prepared from condensing carbonitrile 95 with 1,3-cyclohexanedione, in absolute ethanol containing DBU, by using molar ratio 1:1 (Scheme 68). While, reaction of carbonitrile 95 with 1,3-cyclohexanedione using molar ratio 2:1 resulted in the formation of the angular heptafused system 136 in which two chromeno[2,3-b]pyridine moieties exist in the same molecule (Scheme 68).77 On the other hand, repeating the previous reaction in 1:2 molar ratio resulted in produced the novel angular heterocyclic system 137 (Scheme 68).78
Base-catalyzed reaction of carbonitrile 35 with 1,2-cyclohexanediione resulted in the formation of the angular heptacyclic system, 7,8-dihydro-5H,10H-bis[1]chromeno[2,3-b:3′,2′-j][1,10]phenanthroline-5,10-dione (138) (Scheme 69). While, the isomeric product, 7,8-dihydro-15H,18H-bis[1]-chromeno[3,2-b:2′,3′-j][4,7]phenanthroline-15,18-dione (139) was obtained from condensation reaction of carbonitrile 95 with 1,4-cyclohexanediione resulted in the formation of the angular heptacyclic system, (Scheme 69). 77,78
Condensation of 3-formylchromones 3 with nitroarene/nitroalkane under stirring or reflux conditions gave C-(chromon-3-yl)-N-substituted nitrones 140 which cyclized in ethanol containing few drops of piperidine to give chromonoquinoline 141 (Scheme 70).79-84
Refluxing equimolar amounts of 2-(N-methylanilino)-3-formylchromones 11 with m-phenylenediamine, in aqueous acetonitrile solution led to 8-aminochromonoquinolines 142, in good yields (Scheme 71).85

Scheme 71

Reactions of 3-formylchromone (3) with aniline derivatives, in DMF and trimethylsilyl chloride (TMSCl), led to 7H-chromeno[3,2-c]quinolin-7-ones 143 in 39-63% yields (Scheme 72).86

Scheme 72

2.2.14. Chromones annulated with naphthyridines
2,4-Diamino-8-methyl-6-oxo-6H-chromeno[2,3-b][1,8]naphthyridine-3-carbonitrile (144) was synthesized via reaction of 2-amino-3-aminochromones (14) with malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile), in boiling ethanol containing few drops of DBU (Scheme 73).61 On the other hand, reaction of aldehyde 3 with malononitrile dimer, in boiling ethanol containing few drops of piperidine, afforded buta-1,3-diene derivative 145 (Scheme 73).78
Benzo[\(h\)]chromeno[2,3-\(b\)][1,6]naphthyridines 147 were also synthesized from reaction of chromone-3-carbonitriles 95 with 1-ethyl-4-hydroxy-3-nitroacetylquinolin-2(1\(H\))-one (146). Compounds 147 were also obtained from condensation of 2-aminochromone-3-carboxaldehydes 14 with 4-hydroxyquinolines and/or 4-hydroxy-3-substituted-acetylquinolin-2(1\(H\))-ones 146 (Scheme 74).55,74,87

\[
\text{Scheme 73}
\]

2.2.15. Chromones annulated with pyrido-fused coumarin

Friedländer condensation reaction of 2-amino-3-formylchromones 14 with 4-hydroxycoumarin (1), in boiling DMF containing few drops of DBU, afforded dichromeno[2,3-\(b\):3'-\(a\)',4'-\(e\)]pyridine-6,8-diones 148 (Scheme 75).74,88
2.2.16. Chromones annulated with pyrido-fused pyranoquinoline

Chromeno[3’’,2’’:5’,6’’]pyrido[3’,2’’:5,6]pyrano[3,2-c]quinoline-6(5H),7,9-triones 150 were synthesized from DBU catalyzed condensation reaction of 2-aminochromone-3-carboxaldehydes 14 with 4-hydroxy-2H-pyrano[3,2-c]quinoline-2,5(6H)-dione (149) (Scheme 76).74,89

![Scheme 76](image_url)

2.2.17. Chromone annulated with pyrido-fused pyrimidine

Chromeno[2’’,3’’:2,3]pyrido[6,5-d]pyrimidines 151 were obtained from condensation of chromone-3-carbonitriles 95 with 6-aminouracil, barbituric and/or thiobarbaturic under different reaction conditions. Compounds 151 were prepared authentically from reaction of aldehyde 14 with 6-aminouracil and thiobarbaturic acid, in DMF, in good yields (Scheme 77).56,59,69,74
Reaction of 2-amino-3-formylchromone 14 with 2-hydroxy-4H-pyrido[1,2-α]pyrimidin-4-one (152) in refluxing DMF/DBU yielded polyfused 13H,15H-chromeno[3″,2″:5″,6″]-dipyrido[1,2-α:2′,3′-d]pyrimidine-13,15-dione (153) (Scheme 78).74

Scheme 78

2.2.18. Chromone annulated with pyridoxazine

Fused oxazine 154 was obtained, from reaction of carbonitrile 95 with dimethyl β-keto-α-oximinoglutarate, in boiling ethanol containing triethylamine (Scheme 79).90

Scheme 79
2.2.19. Chromones annulated with pyrido-fused dioxine

Cyclocondensation of 2-amino-3-formylchromones 14 with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum’s acid) (155) afforded 2,2-dimethyl-4H,6H-[1,3]dioxino[4,5-b]chromeno[3,2-e]pyridine-4,6-dione (156) (Scheme 80).73

![Scheme 80](image)

2.2.20. Chromones annulated with pyran

Refluxing an equimolar amount of chromone-3-carboxylic acids 53 with diethyl malonate, in absolute ethanol containing a few drops of triethylamine, produced 2-(2-hydroxyphenyl)-4H,5H-pyrano-[2,3-b]chromen-5-ones 157 (Scheme 81).91 Pyrano[2,3-b]chromene derivatives 157 were also prepared from boiling ω-formyl-2-hydroxyacetophenones 158, in ethanol containing drops of Et3N (Scheme 81).92

![Scheme 81](image)

3-(Chromon-3-yl)-1-(N-cyclohexylimino)pyrano[4,3-b]chromones 159 were obtained, in moderate yields, by heating 3-formylchromones 3 with cyclohexyl isocyanide, (Mr 2:1), in acetonitrile (Scheme 82).93
2.2.21. Chromones annulated with isochromenes

Photoirradiation of 2-aryl-3-[[thiophen-2-yl]methoxy]chromones 160, in methanol with pyrex filtered UV light from a 125 W Hg vapor lamp under the nitrogen atmosphere, produced annulated pyranochromones 161 and 162 (Scheme 83).  

2.2.22. Chromones annulated with pyrano-fused pyrroloindole

2.2.23. Chromones annulated with pyrano-fused pyrazolothiopyran

Thiopyrano[4',3':4,5]pyrano[2,3-b]chromenes 167 and thiopyrano[4',3':4,5]pyrano[3,2-c]coumarins 168 were prepared via domino Knoevenagel hetero Diels–Alder reactions between 4-hydroxycoumarins 1 and 3-methyl/phenyl-5-(3-methylbut-2-enylsulfanyl)-1-phenyl-1H-pyrazole-4-carboxaldehydes 166, in ethanol under reflux (Scheme 85).96

2.2.24. Chromones annulated with pyrimidines

Chromono[2,3-d]pyrimidines 170 were synthesized from reaction of 2-aminochromone-3-carbonitriles 169 and urea, thiourea, and/or guanidine, in an ethanolic solution and sodium ethoxide (Scheme 86).97
Condensation reaction of 2-amino-3-formylchromone (14) with \( o \)-aminophenol in boiling ethanol produced the corresponding Schiff base 171. Refluxing Schiff base 171 in boiling acetic acid furnished chromeno[2,3-\( d \)]pyrimidin-5-one 172 in 67% yield (Scheme 87).  

\[
\begin{align*}
\text{R} &= \text{R}' = \text{R}'' = \text{H}
\end{align*}
\]

Scheme 87

When chromone-3-carbonitriles 95 were refluxed with a potential ammonia source such as ammonium acetate in acetic acid, produced 2-(chromon-3-yl)-5\( H \)-chromeno[2,3-\( d \)]pyrimidin-5-ones 173 (Scheme 88).  

\[
\begin{align*}
\text{R} &= \text{R}' = \text{H}, \text{OH}, \text{Cl}, \text{Br} \\
\text{Ar} &= 3\text{-MeOPh}, 2\text{-MeOPh}, 4\text{-MeOPh}, 3\text{-ClPh}, 2\text{-ClPh}, 4\text{-ClPh}, 3\text{-CF}_3\text{Ph}, 2\text{-CF}_3\text{Ph}, 4\text{-CF}_3\text{Ph}, 3\text{-MeO}\text{Ph}, 2\text{-MeO}\text{Ph}, 4\text{-MeO}\text{Ph}, 3\text{-CF}_3\text{Ph}, 2\text{-CF}_3\text{Ph}, 4\text{-CF}_3\text{Ph}
\end{align*}
\]

Scheme 88

Chromone-3-carbonitriles 95 reacted with aromatic aldehydes, in the presence of ammonium acetate and CuCl\(_2\) to form chromeno[2,3-\( d \)]pyrimidines 174 (Scheme 89).  

\[
\begin{align*}
\text{Ar} &= 3\text{-MeOPh}, 2\text{-MeOPh}, 4\text{-MeOPh}, 3\text{-ClPh}, 2\text{-ClPh}, 4\text{-ClPh}, 3\text{-CF}_3\text{Ph}, 2\text{-CF}_3\text{Ph}, 4\text{-CF}_3\text{Ph}, 3\text{-MeO}\text{Ph}, 2\text{-MeO}\text{Ph}, 4\text{-MeO}\text{Ph}, 3\text{-CF}_3\text{Ph}, 2\text{-CF}_3\text{Ph}, 4\text{-CF}_3\text{Ph}
\end{align*}
\]

Scheme 89
Schurreit\textsuperscript{79} has reported the formation of chromeno[2,3-\(d\)]pyrimidine linked to chromeno[2,3-\(b\)]pyridines 175 by refluxing three molecules of chromone-3-carbonitrile 95 and 4-hydroxycoumarin (1), in refluxing ethanol containing piperididine (Scheme 90).\textsuperscript{100}

![Scheme 90](image)

**2.3. Chromone-fused seven membered ring**

**2.3.1. Chromone annulated with diazepine**

9-Chloro-2,3,4,5-tetrahydro-7-isopropyl-10-methylchromeno[2,3-\(b\)][1,4]diazepin-11(1\(H\))-one (177) was synthesized from reaction of 2-(dimethylamino)chromone 176 with 1,3-diaminopropane, in boiling toluene (Scheme 91).\textsuperscript{101}

![Scheme 91](image)

**2.3.2. Chromone annulated with benzodiazepine**

There is contradictory information in literature regarding the structure of the product obtained from the reaction between carbonitrile 95 and \(o\)-phenylenediamine. Hence, Ghosh and Tewari,\textsuperscript{102} postulate the formation of chromeno[2,3-\(b\)][1,5]benzodiazepines 178. While, Risitano and his coworkers,\textsuperscript{103} repeated the reaction and postulate the formation of benzodiazepines 179. Next, the reaction was reinvestigated and the product was expected to be 3-(benzimidazol-2-yl)chromones 180 (Scheme 92).\textsuperscript{104}
On the other hand, heating 3-formylchromone 3 with \( o \)-phenylenediamine, in 95% ethanol for 1 min, produced the addition product, 3-\{[(2-aminophenyl)amino](hydroxy)methyl\}-2-hydroxy-6,8-dimethyl-2,3-dihydro-4\( H \)-chromen-4-one (181), as an orange crystals in high yield (Scheme 93). Repeating the previous reaction under reflux for 2 h. Furnished the annulated benzochromenodiazepine derivative 182 via the formation of compound 181 followed by elimination of two molecules of water with subsequent dehydrogenation (Scheme 93).}\(^{105}\)
Also, reaction of 3-formylchromones 3 with ortho-substituted anilines such as o-phenylenediamine, o-aminophenol and o-aminothiophenol, in boiling ethanol, afforded benzoazepine derivatives 183 (Scheme 94).106

Moreover, reaction of 2-(N-methylanilino)-3-formylchromones 11 with ortho-substituted anilines such as o-phenylenediamine, o-aminophenol, and o-aminothiophenol, furnished chromono-heterocyclic systems (chromono[2,3-b][1,5]benzdiazepine, chromono[2,3-b][1,5]benzoxazepine, and chromono-[2,3-b][1,5]benzothiazepine 184, respectively), in high yields (Scheme 95).107,108

2.4. Chromone-fused eight membered rings
2.4.1. Chromones annulated with diazocine

Reaction of chromone-3-carbonitrile (95) with ethylenediamine in boiling ethanol was firstly studied by Ghosh and Tewari,102 and isolated 1-(2-hydroxyphenyl)-2-imidazol-2-ylidene)ethanone (185) (15%) together with 2-aminochromone-3-carboxaldehyde 14 (45%). When the reaction was performed in boiling ethanol for 3 h in 1:1 molar ratio (Scheme 96). While, Ghosh et al.109 postulated the formation of bis-chromeno[2,3-b:2′,3′-f][1,5]diazocine (186) when the reaction was carried in boiling ethanol for 10 min in 2:1 molar ratio. Hydrolysis of compound 186 under acidic conditions afforded compound 14 (Scheme 96), in this reaction ethylenediamine, as aliphatic amine, induced self-condensation of carbonitrile 95.
The previous reaction was next studied by Sosnovskikh et al., and isolated \( N',N' \)-ethylene-bis(2-amino-3-iminomethylchromones) 187, when the reaction was performed in boiling ethanol for 10 min in 1:1 molar ratio. Depending on the time of refluxing in acetic acid, the later compound gave either 2-amino-3-formylchromones 14 or dimerization products, 2-(chromen-3-yl)-5H-chromeno[2,3-d]pyrimidin-5-ones 188 (Scheme 97).

Double condensation of 2-amino-3-formylchromone (14) with \( o \)-aminoaldehyde namely, 6-amino-1,3-dimethyluracil-5-carboxaldehyde (189), in boiling ethanol containing catalytic amount of concentrated sulfuric acid, yielded the diazocine derivative 190 (Scheme 98).
3. CONCLUSION

Chromones are a group of compounds widely distributed in nature with a wide range of biological activities including antitumor, antimicrobial, antiviral, anti-inflammatory, antioxidant, and so on. Diverse synthetic methods were utilized to prepare a variety of heterocyclic rings using substituted chromones. The annulation of chromone moiety with different heterocycle scaffolds gives rise a new class of hybrid heterocycles with improved biological activity. In the future work, we hope to investigate the reactivity of chromone bearing electron withdrawing functional groups with a diversity of nucleophilic reagents aiming to synthesis a novel derivatives of annulated chromones, in addition to examine the biological properties of the new synthesized compounds.

4. REFERENCES


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