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CHEMICAL TRANSFORMATION OF CHROMONES INTO COUMARINS

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Abstract – The essential focus of the present review is to collect the chemical reactions of chromone derivatives involving their transformation into coumarin derivatives. A diversity of coumarins was efficiently synthesized from the reactions of chromones with some nucleophilic reagents. This review includes the reactions of chromone derivatives with nitrogen and carbon nucleophiles, (acyclic and cyclic) leading to coumarins.

CONTENTS

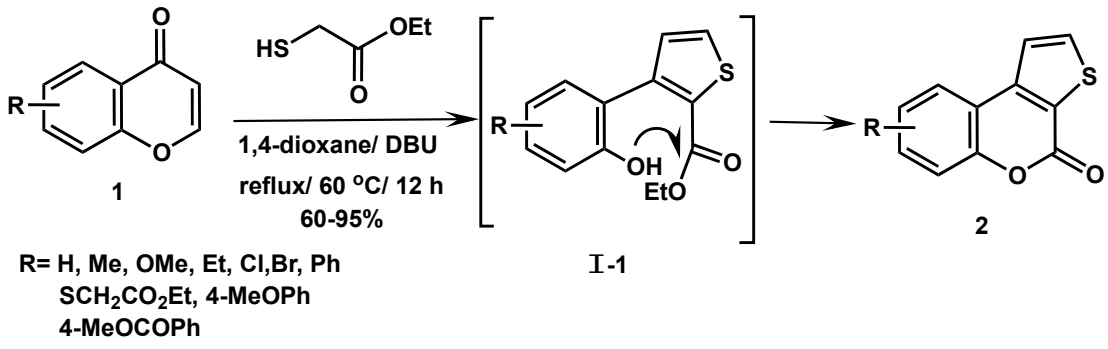
1. INTRODUCTION

The benzopyran chemical class, formed by fusion of a benzene ring and a pyran ring with various levels of saturation and oxidation, appears in many natural products. Benzopyran skeletons including coumarins and chromones are important scaffolds in many drugs and bioactive natural products.[1-3] Chromones (4*H*-chromen-4-one derivatives) belong to one of the most common natural heterocyclic systems.[4] They exhibit various types of biological activities such as antitumor,[5-7] neuroprotective,[8] HIV-inhibitory,[9] antioxidant,[10] anti-inflammatory,[11,12] antispasmolytic,[13] estrogenic[14] and antibacterial activities.[15] Also, coumarins (2*H*-chromen-2-one derivatives) possess many biological activities including anticoagulant,[16] anticancer,[17] vasorelaxant,[18] antimicrobial,[19] antioxidant,[20] anti-inflammatory,[21] and anti-HIV activities.[22] In addition to the biological activity, coumarins have used in food additives,[23] cosmetics,[24] fluorescent and laser dyes.[25] The current review article summarizes the synthetic transformations used for construction of substituted coumarins from substituted chromones.

2. SYNTHETIC METHODS FOR COUMARIN DERIVATIVES FROM CHROMONE DERIVATIVES

2.1. From chromones

Cascade reactions of chromone derivatives **1** with ethyl mercaptoacetate, in dioxane containing DBU under nitrogen atmosphere produced thieno[2,3-*c*]coumarins **2** in good-to-excellent yields, *through* intermediate **I-1**. This cascade reaction involved a *Michael* addition–Knoevenagel condensation–intramolecular cyclization (Scheme 1).[26]

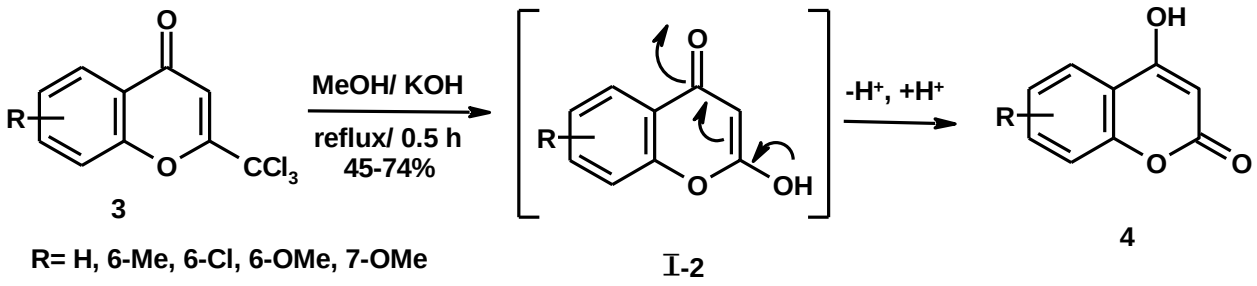


Scheme 1

2.2. From 2-substituted chromones

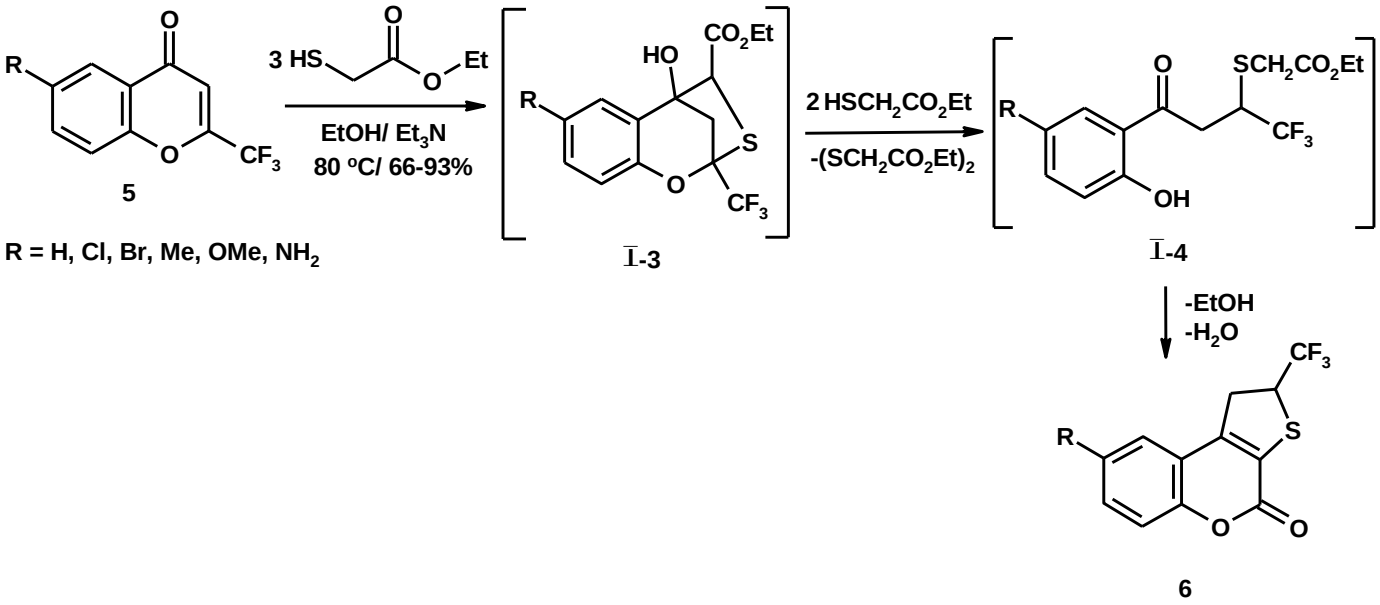
2.2.1. From 2-trihalomethylchromones

Chemical transformations of 2-trichloromethylchromones **3** with a methanolic KOH solution, upon reflux for 0.5 h, produced 4-hydroxycoumarins **4**, in 45-74% yields, *via* 2-hydroxychromones **I-2** as non-isolable intermediates (Scheme 2).[27]



Scheme 2

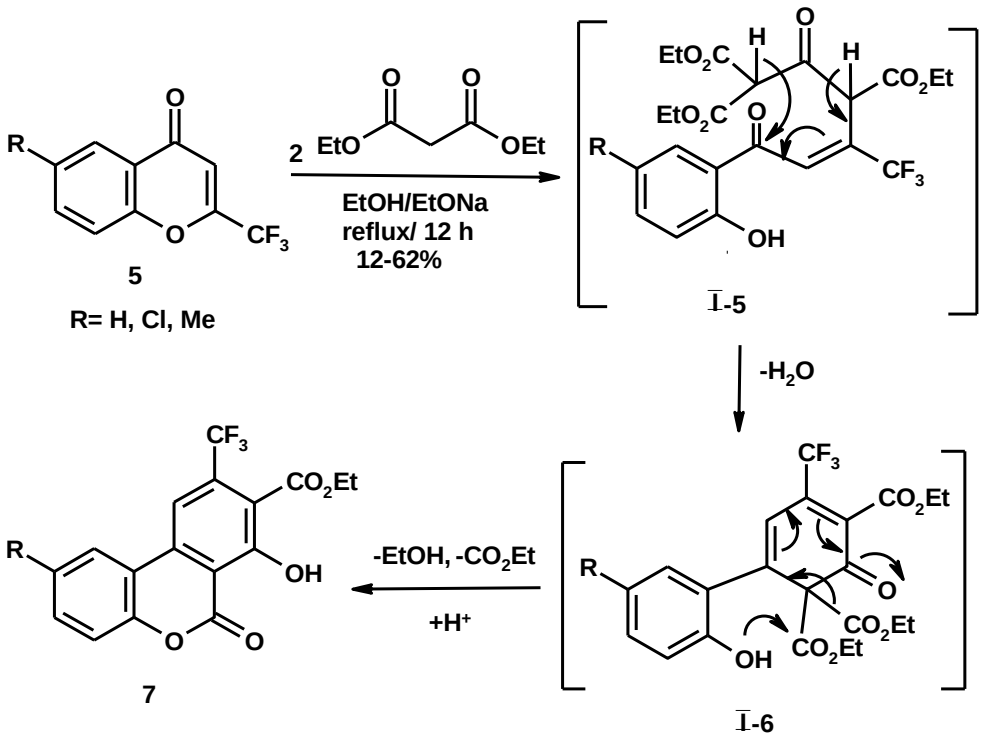
Reactions of 2-(trifluoromethyl)chromones **5** with three equivalents of ethyl mercaptoacetate at 80 °C in the presence of Et_3N as a catalyst, afforded dihydrothienocoumarins **6**, through intermediates **I-3** and **I-4** (Scheme 3).[28]



Scheme 3

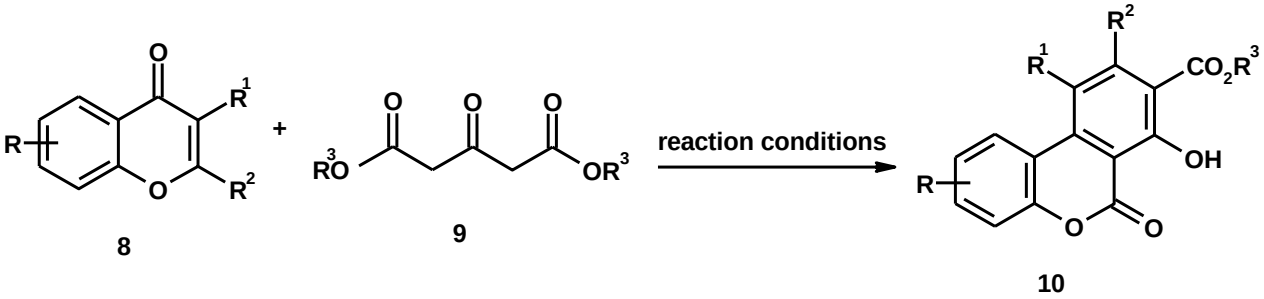
Reactions of 2-(trifluoromethyl)chromones **5** with diethyl malonate, by using molar ratio 1:2, gave ethyl coumarine-3-carboxylates **7** (Scheme 4). This reaction proceeds through a domino reaction including

nucleophilic attack at position 2 giving intermediate **I-5** followed by cyclocondensation producing intermediate **I-6** which loses ethanol and ethoxycarbonyl group giving the final product **7**.[28-31]



Scheme 4

Alkyl 7-hydroxy-6-oxo-6*H*-benzo[*c*]chromene-8-carboxylates **10** were isolated, in 27-84% yields, from reaction of chromones **8** with dialkyl 1,3-acetonedicarboxylates **9**, under various reaction conditions (Scheme 5).[30,32-35]



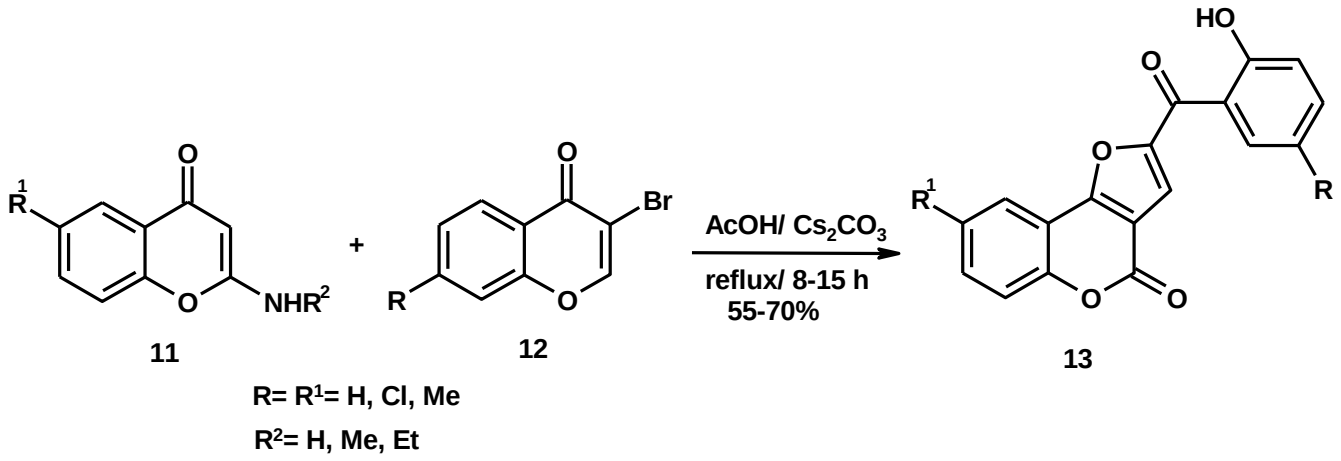
R	R^1	R^2	R^3	Reaction conditions	Yield	Ref.
H	H	CF_3	Et	EtOH/ EtONa/ reflux/ 12 h	57%	30
H	H	H	Et	EtOH/ EtONa/ reflux/ 12 h	39%	30
H	H	H	Me	THF/ DBU/ stir/ rt/ 2-3 h	56%	32
H	NO_2	H	Et	Py/ reflux/ stir/ rt/ 2 h	40%	34, 35

H	NO_2	H	Et	EtOH/ Py/ reflux/ stir/ rt/ 2 h	40%	32, 33
H	2-NO_2PhCO	H	Me	dioxane/ DBU/ stir/ rt/ 10-12 h	72%	32
6-Me	2-NO_2PhCO	H	Me	dioxane/ DBU/ stir/ rt/ 10-12 h	84%	32
7-OMe	2-NO_2PhCO	H	Me	dioxane/ DBU/ stir/ rt/ 10-12 h	73%	32
H	PhCO	H	Me	dioxane/ DBU/ stir/ rt/ 10-12 h	27%	32
H	2-F-PhCO	H	Me	dioxane/ DBU/ stir/ rt/ 10-12 h	46%	32

Scheme 5

2.2.2. From 2-aminochromones

2-Aminochromones **11** reacted with 3-bromochromones **12**, in refluxing acetic acid in the presence of Cs_2CO_3 as inorganic catalyst, producing furo[3,2-*c*]chromen-4-ones **13**, in moderate yields (Scheme 6).[33]

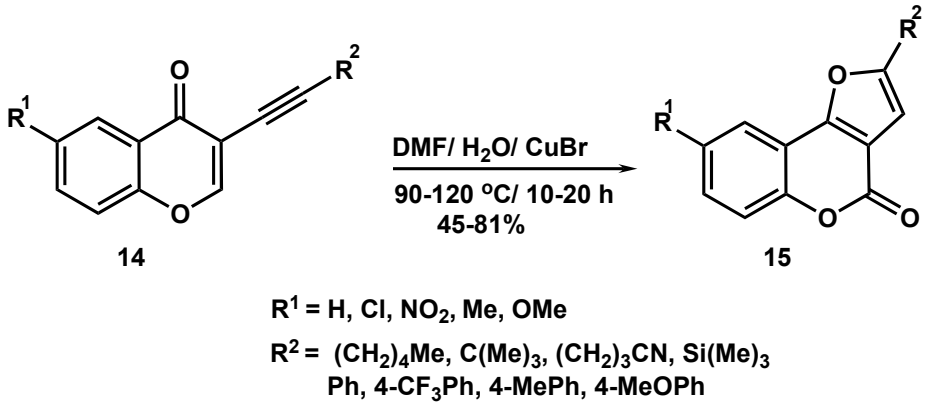


Scheme 6

2.3. From 3-substituted chromones

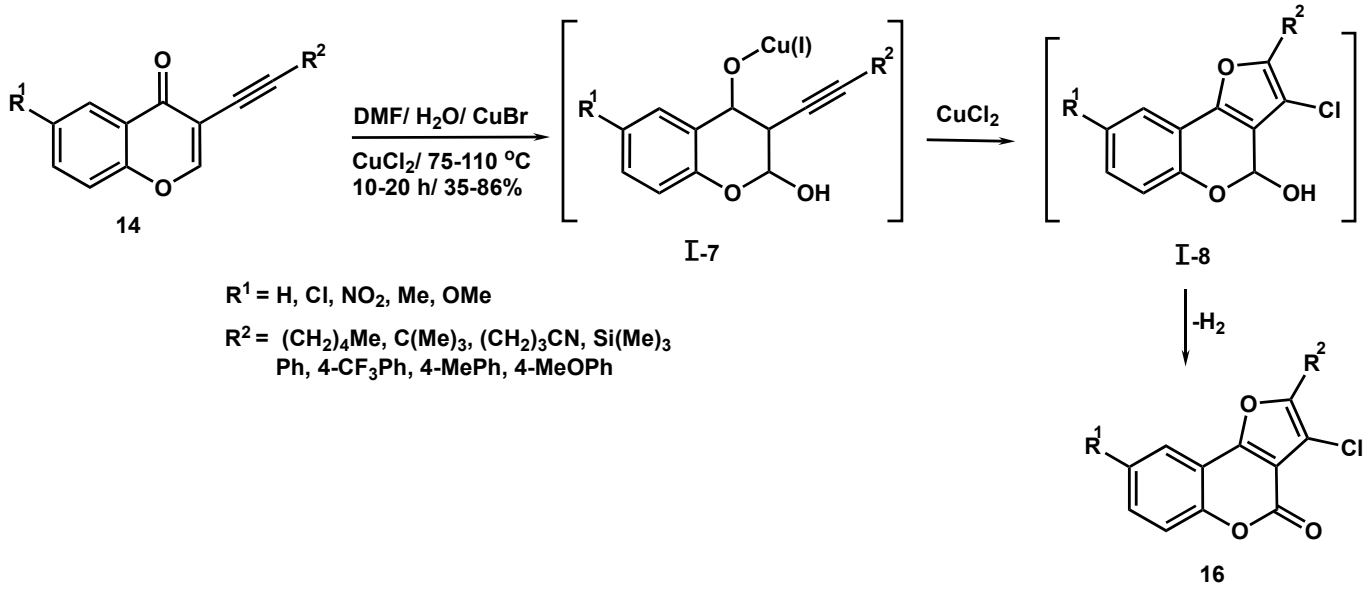
2.3.1. From 3-alkynylchromone

3-Alkynylchromones **14** underwent transformations with H_2O in the presence of 20% CuCl as Lewis acid under an air atmosphere to yield 2-substituted-4*H*-furo[3,2-*c*]chromen-4-ones **15** (Scheme 7).[36,37] The reaction proceeds through a cascade reaction involving addition, cyclization and oxidation.



Scheme 7

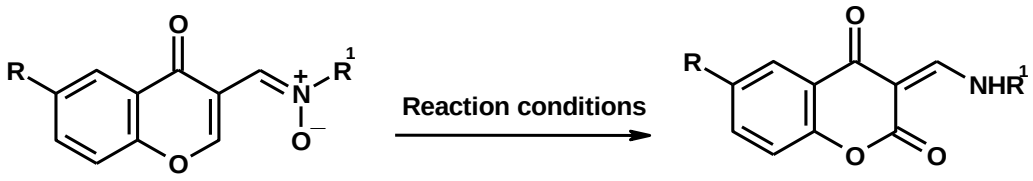
Meanwhile, the previous reaction in the presence of 10% CuBr and excess $CuCl_2$ as an oxidant afforded 3-chloro-4*H*-furo[3,2-*c*]chromen-4-ones **16**, through *Micheal* addition (intermediate **I-7**) followed by cyclization with concomitant chlorination producing intermediate **I-8** which oxidized to the final product (Scheme 8).[36,37]



Scheme 8

2.3.2. From C-(chromen-3-yl)-N-phenylnitrones

Hamdi and his coworkers, postulated the formation of 3-(arylaminomethylene)chromane-2,4-dione **18** from boiling nitrones **17** in non-polar solvents (toluene or xylene) for varying times (Scheme 9).[38]

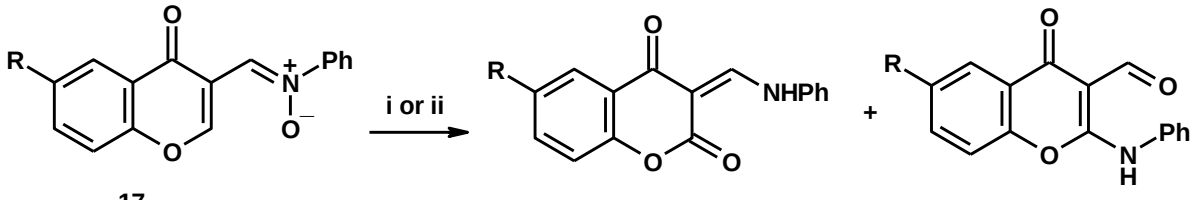


17 18

R	R^1	Reaction Conditions	Yield	Ref.
Me	Et	toluene/ reflux/ 14 h	60%	38
H	4-MePh	toluene/ reflux/ 6 h	70%	38
Me	4-MePh	toluene/ reflux/ 7 h	70%	38
Me	Et	xylene/ reflux/ 2 h	70%	38
H	Me	xylene/ reflux/ 2 h	70%	38
H	Me	xylene/ reflux/ 2 h	65%	38
Me	Me	xylene/ reflux/ 2 h	72%	38
Me	4-MePh	xylene/ reflux/ 2 h	85%	38

Scheme 9

In the previous reaction, using benzene or chloroform as a solvent, *C*-(chromen-3-yl)-*N*-phenylnitrones **17** rearranged yielding a mixture of 3-(phenyliminomethylene)chromane-2,4-diones **19** (25%) and 2-(*N*-phenylamino)chromone-3-carboxaldehydes **20** (70%) (Scheme 10).[39,40]

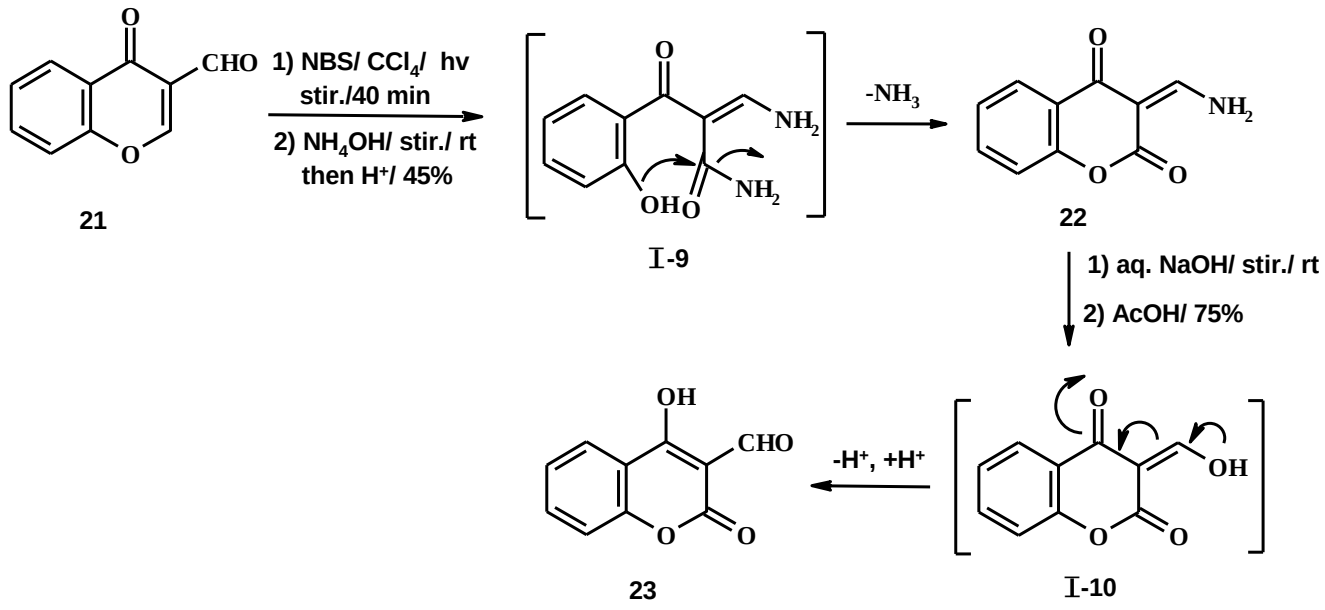


17
R= H, Cl, Me
i) dry benzene/ reflux/ 8 h
ii) $CHCl_3$/ rt/ 20 days
19
25%
20
70%

Scheme 10

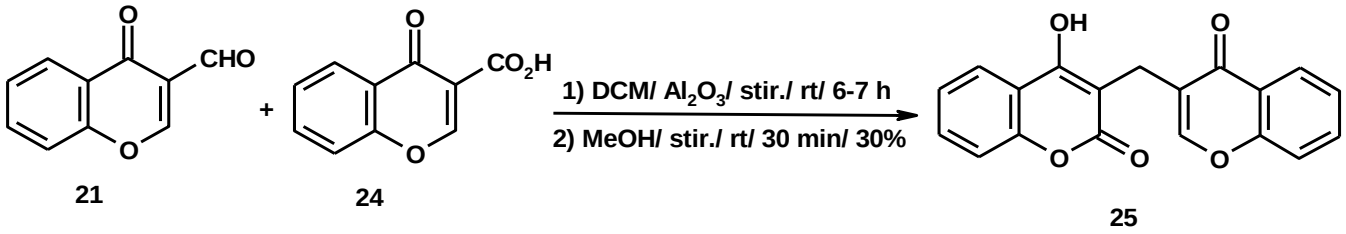
2.3.3. From chromone-3-carboxaldehydes

The conversions of some 3-substituted chromones into substituted coumarins were studied. Treating a suspension of 3-formylchromone (**21**) in CCl_4 with *N*-bromosuccinimide (NBS) under UV-irradiation afforded, after quenching with ammonia at 40 °C, chromane-2,4-dione (**22**), *via* intermediate **I-9**. Stirring compound **22** with aqueous NaOH solution followed by acidification produced 3-formyl-4-hydroxycoumarin (**23**), through intermediate **I-10** (Scheme 11).[41,42]



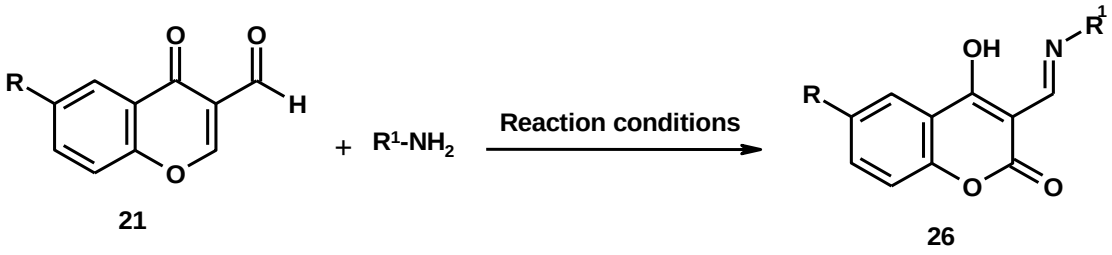
Scheme 11

Stirring chromone-3-carboxaldehyde (**21**) with chromone-3-carboxylic acid (**24**), in dichloromethane containing alumina at room temperature, gave 4-hydroxy-3-(chromon-3-yl)methylcoumarin **25**, in 30% yields (Scheme 12).[43]



Scheme 12

Condensation of chromone-3-carboxaldehyde (**21**) with some primary amines, under different reaction conditions, afforded the Schiff bases of 4-hydroxycoumarin-3-carboxaldehyde **26** (Scheme 13).[44,45]

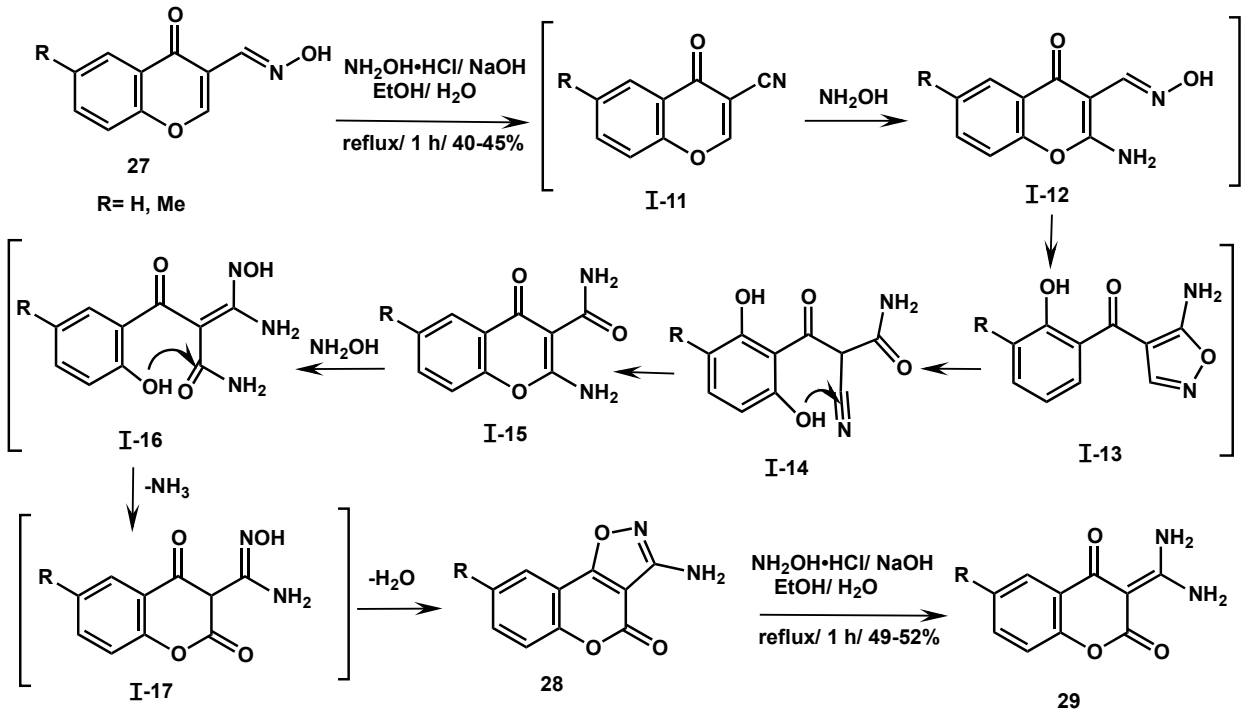


R	R^1	Reaction Conditions	Yield	Ref.
H	Ph	dry benzene/ K-10 montrillonite/ reflux/ 2 h	45%	45
H	4-MePh	dry benzene/ K-10 montrillonite/ reflux/ 2 h	40%	45
H	4-MeOPh	dry benzene/ K-10 montrillonite/ reflux/ 2 h	46%	45
Me	Ph	dry benzene/ K-10 montrillonite/ reflux/ 2 h	42%	45
Me	4-MePh	dry benzene/ K-10 montrillonite/ reflux/ 2 h	35%	45
Me	8-quinolinyl	MeOH/ stir/ 60 °C/ 3 h	76%	44

Scheme 13

2.3.4. From chromone-3-carboxaldehyde oximes

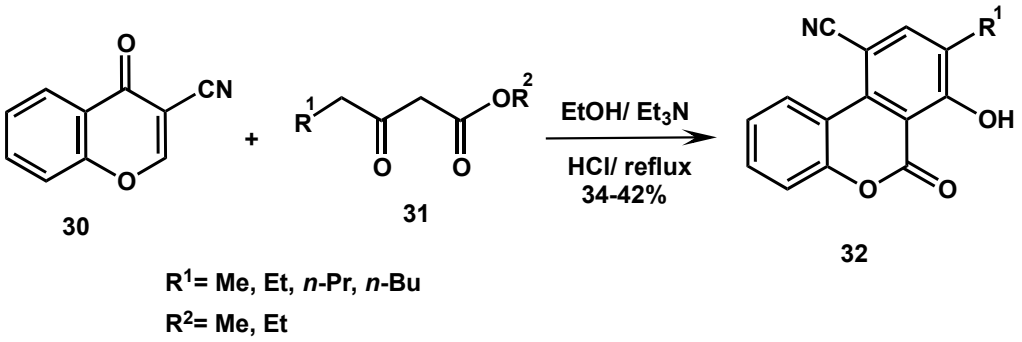
Rearrangement of chromone-3-carboxaldehyde oximes **27** with alkaline hydroxylamine gave 3-aminoisoxazolocoumarins **28**, *via* the non-isolable intermediates **I-11**− **I-17** as illustrated in Scheme 14. Further reaction of compound **28** with alkaline hydroxylamine afforded chromane-2,4-diones **29** (Scheme 14).[41,46-48]



Scheme 14

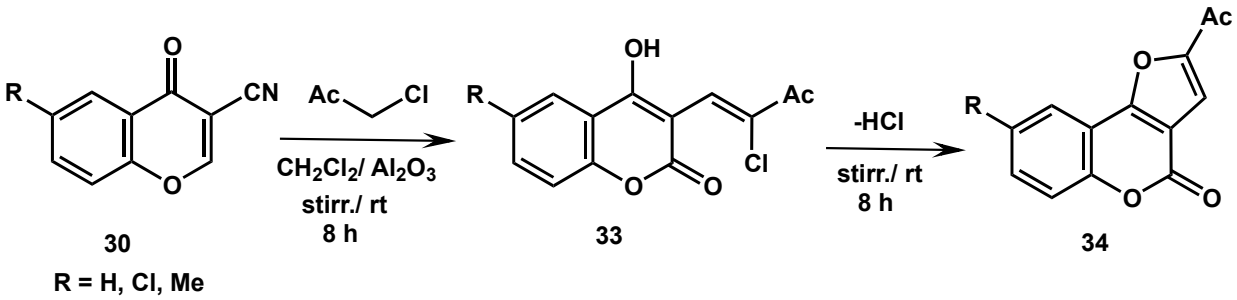
2.3.5. From chromone-3-carbonitriles

Treatment of chromone-3-carbonitrile (**30**) active methylene compounds **31** in ethanol containing triethylamine afforded dibenzo[*b*,*d*]pyran-6-ones **32** (Scheme 15).[49]



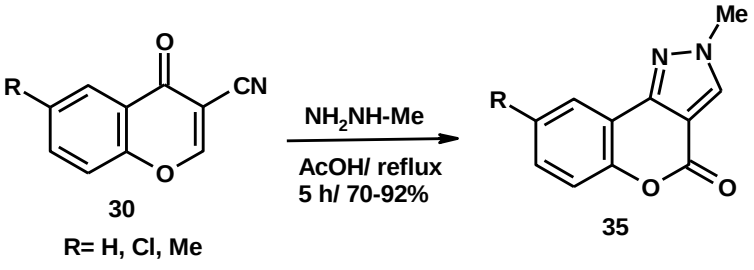
Scheme 15

Reaction of chromone-3-carbonitriles **30** with chloroacetone, in methylene chloride and aluminum oxide, afforded 4-hydroxycoumarin **33** which upon cyclocondensation afforded 2-acetylfurocoumarins **34** (Scheme 16).[50]



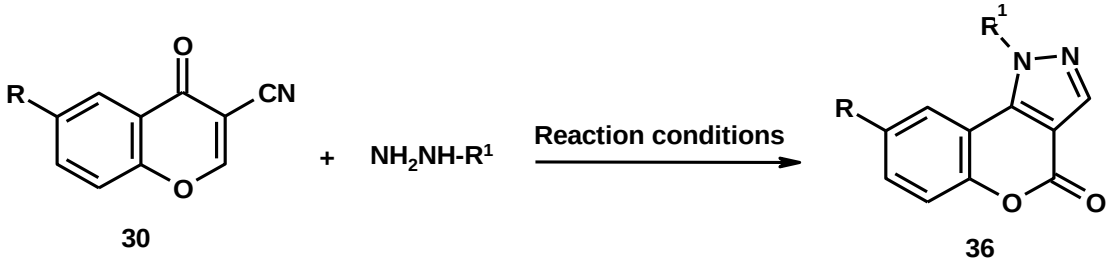
Scheme 16

On the other hand, ring opening/ring closure reactions of chromone-3-carbonitriles **30** with methylhydrazine, in acetic acid under reflux, afforded chromeno[4,3-*c*]pyrazol-4(2*H*)-ones **35**, in 70-92% yields (Scheme 17).[51,52]



Scheme 17

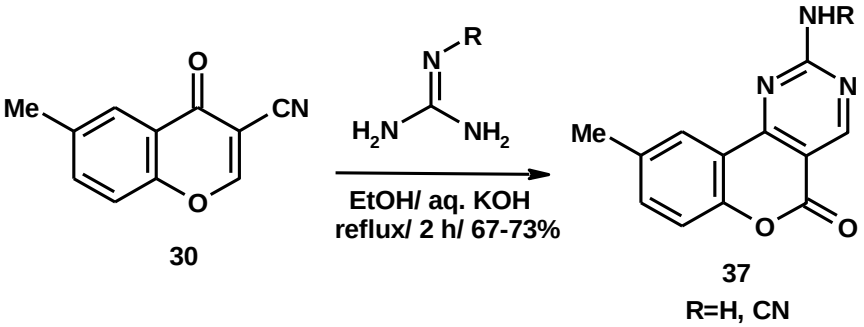
Treating chromone-3-carbonitriles **30** with some hydrazine hydrate, phenylhydrazine, S-benzyl dithiocarbazate and nicotinic acid hydrazide, under various reaction conditions, led to chromeno[4,3-*c*]pyrazol-4(1*H*)-ones **36** (Scheme 18).[51-54]



R	R^1	Reaction Conditions	Yield	Ref.
H	Ph	AcOH/ reflux/ 4 h	55%	51, 52, 53
Me	H	AcOH/ reflux/ 2 h	57%	51, 54
Me	4-COPy	AcOH/ reflux/ 4 h	45%	54
Me	$SCSCH_2Ph$	AcOH/ reflux/ 4 h	48%	54

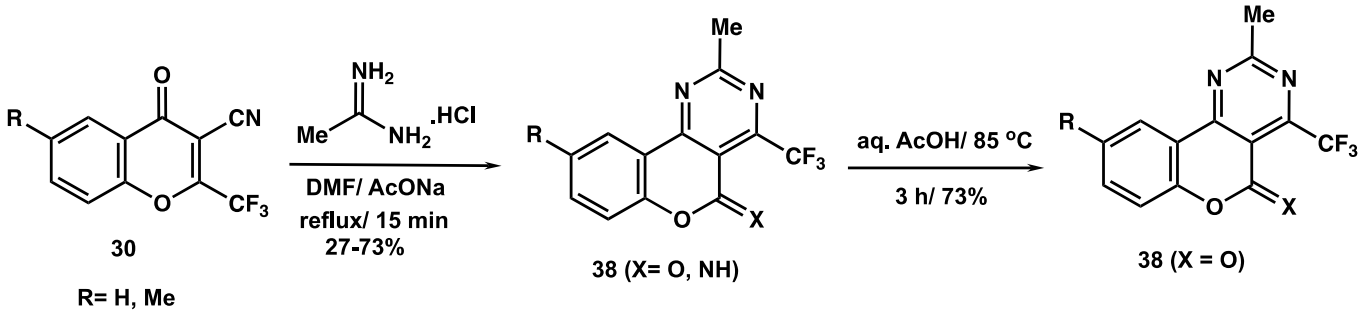
Scheme 18

The conversion of 6-methylchromone-3-carbonitrile (**30**) into 9-methyl-5*H*-chromeno[4,3-*d*]-pyrimidin-5-ones **37** was achieved from its reactions with guanidine hydrochloride and cyanoguanidine, in absolute ethanol and aqueous potassium hydroxide solution (Scheme 19).[53]



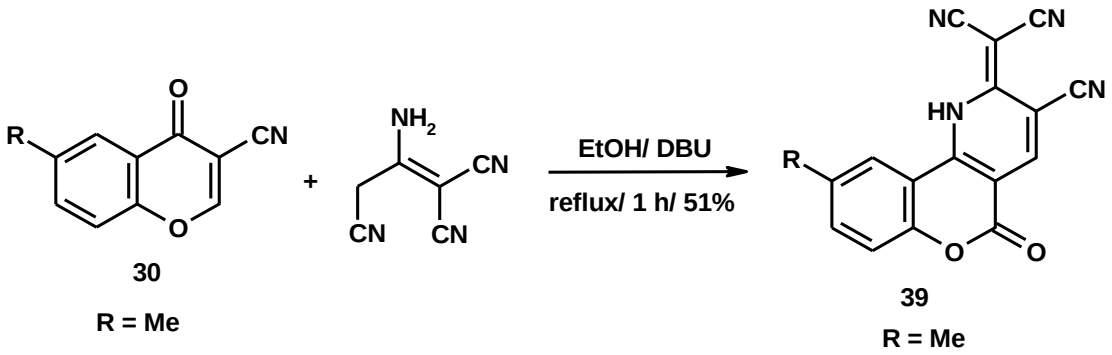
Scheme 19

Chemical transformations of chromone-3-carbonitriles **30** with acetamidine hydrochloride under weakly acidic conditions (AcONa), in refluxing DMF for 15 min, afforded a mixture of 2,9-dimethyl-4-(trifluoromethyl)-5*H*-chromeno[4,3-*d*]pyrimidine derivatives **38** (X = O, NH). When this mixture was treated with aqueous acetic acid, coumarins **38** (X = O) were obtained in good yields (Scheme 20).[55]



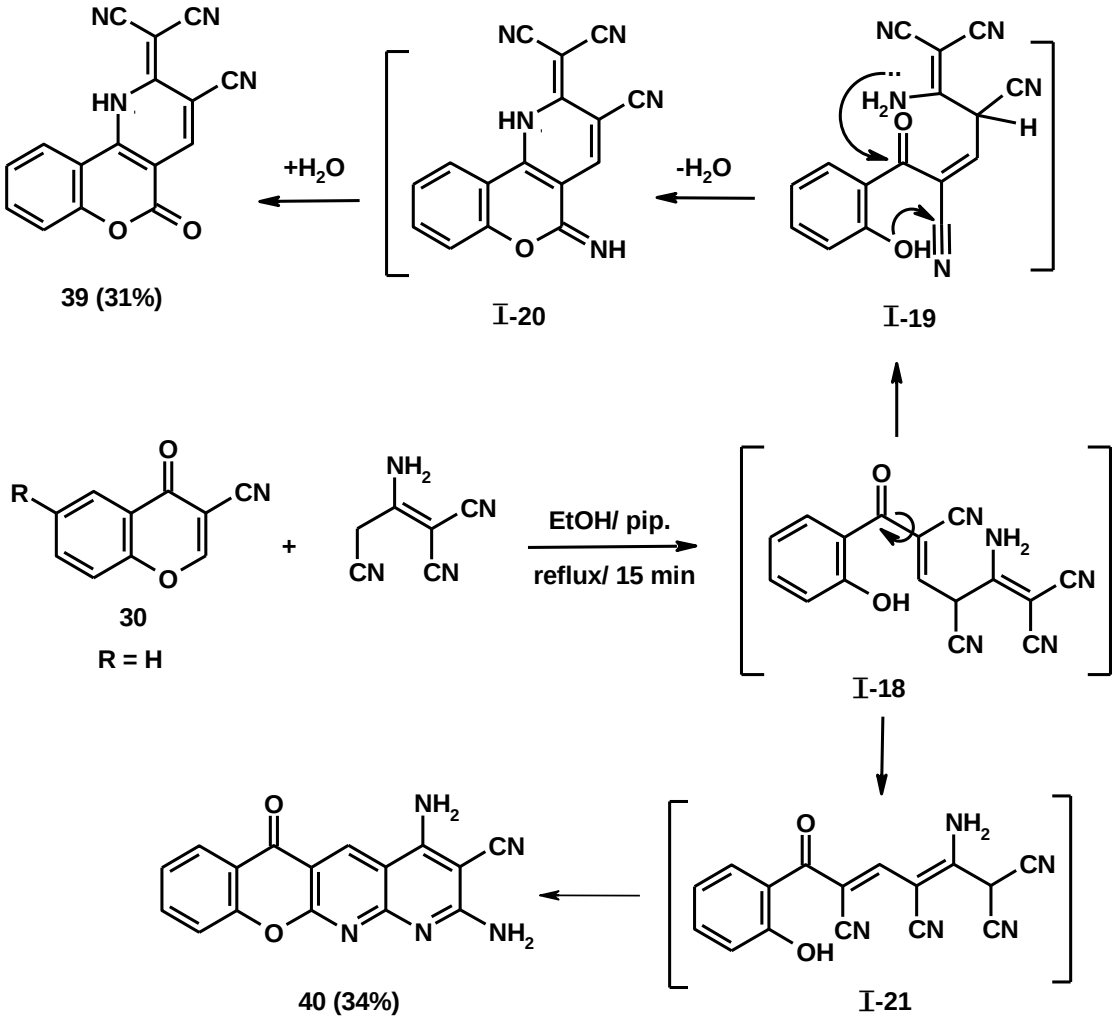
Scheme 20

The chemical transformations of chromone-3-carbonitriles **30** were investigated towards malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile) by Ibrahim and his coworkers.[55-58] Ring conversion of 6-methylchromone-3-carbonitrile (**30**) with malononitrile dimer, in absolute ethanol containing DBU as a catalyst, led to (3-cyano-5-oxo-1,5-dihydro-2*H*-chromeno[4,3-*b*]pyridin-2-ylidene)propanedinitriles **39** (Scheme 21).[54,56]



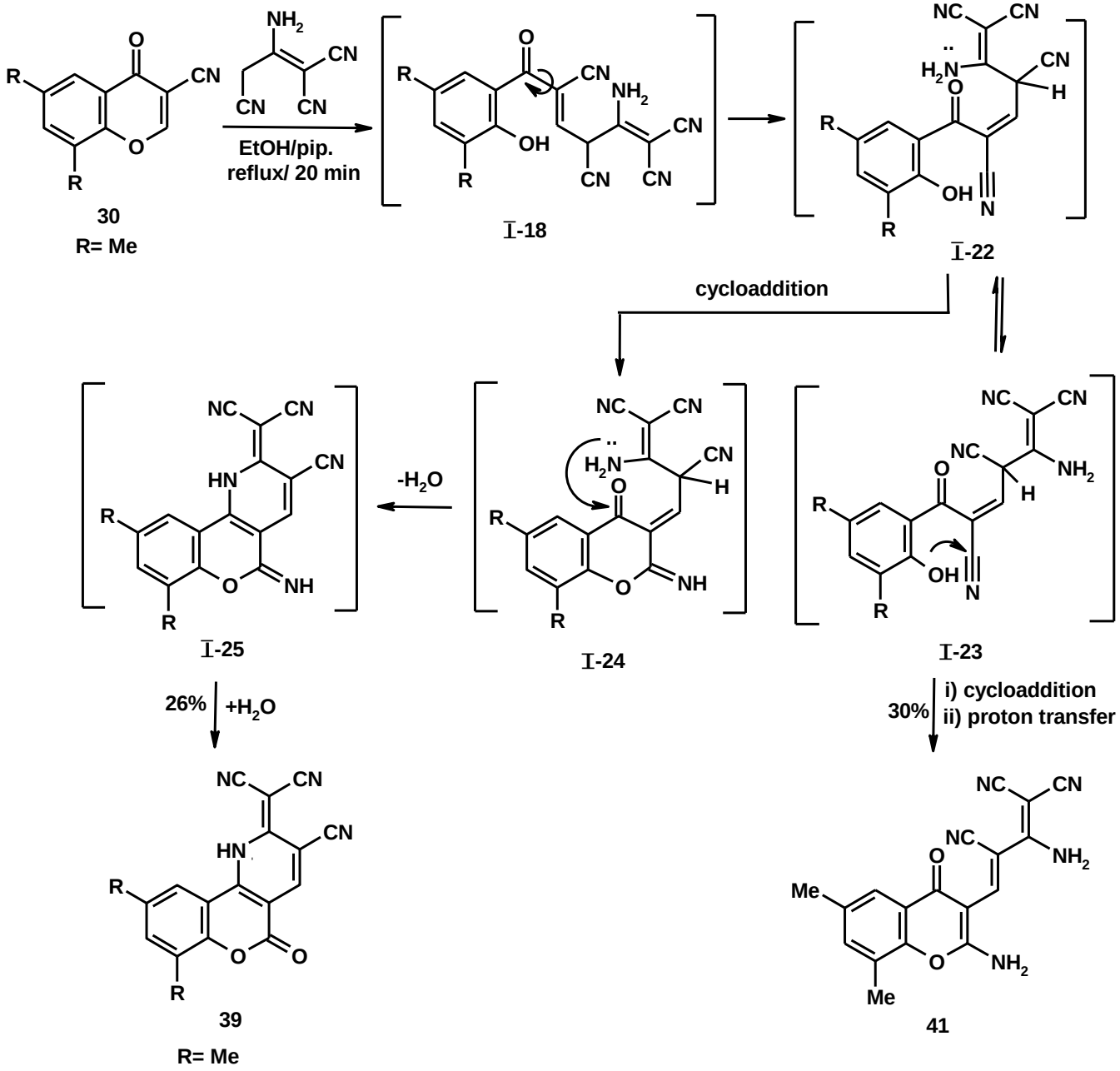
Scheme 21

While, reaction of carbonitrile **30** with malononitrile dimer, in boiling ethanol containing piperidine, produced a mixture of products identified as (3-cyano-5-oxo-1,5-dihydro-2*H*-chromeno[4,3-*b*]-pyridin-2-ylidene)propanedinitrile (**39**) and 2,4-diamino-6-oxo-6*H*-chromeno[2,3-*b*]naphthyridine-3-carbonitrile (**40**) as depicted in Scheme 22.[57] Compounds **39** and **40** formed through intermediate **I-18** which formed from nucleophilic attack at position 2. Rotation of intermediate **I-18** into intermediate **I-19** followed by dehydration and cycloaddition gave intermediate **I-20** which hydrolyzed to product **39**. While, rotation of intermediate **I-18** into intermediate **I-21** followed by consecutive cycloaddition afforded product **40** as shown in Scheme 22.



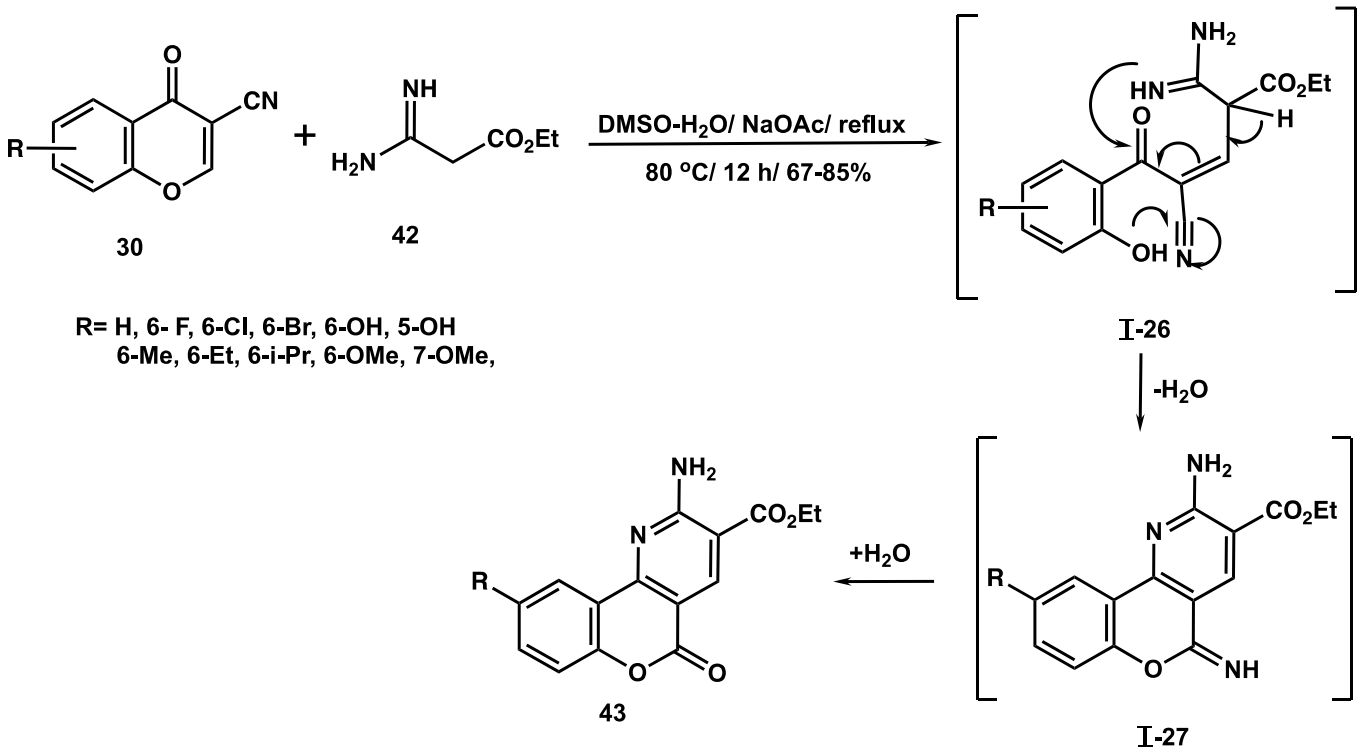
Scheme 22

Further, the previous reaction in case of 6,8-dimethylchromone-3-carbonitrile (**21**) produced a mixture of products identified as, (3-cyano-7,9-dimethyl-5-oxo-1,5-dihydro-2*H*-chromeno[4,3-*b*]pyridin-2-ylidene)propanedinitrile (**39**) and (3*Z*)-2-amino-4-(2-amino-6,8-dimethylchromon-3-yl)buta-1,3-diene-1,1,3-tricarbonitrile (**41**) as depicted in Scheme 23.[58]



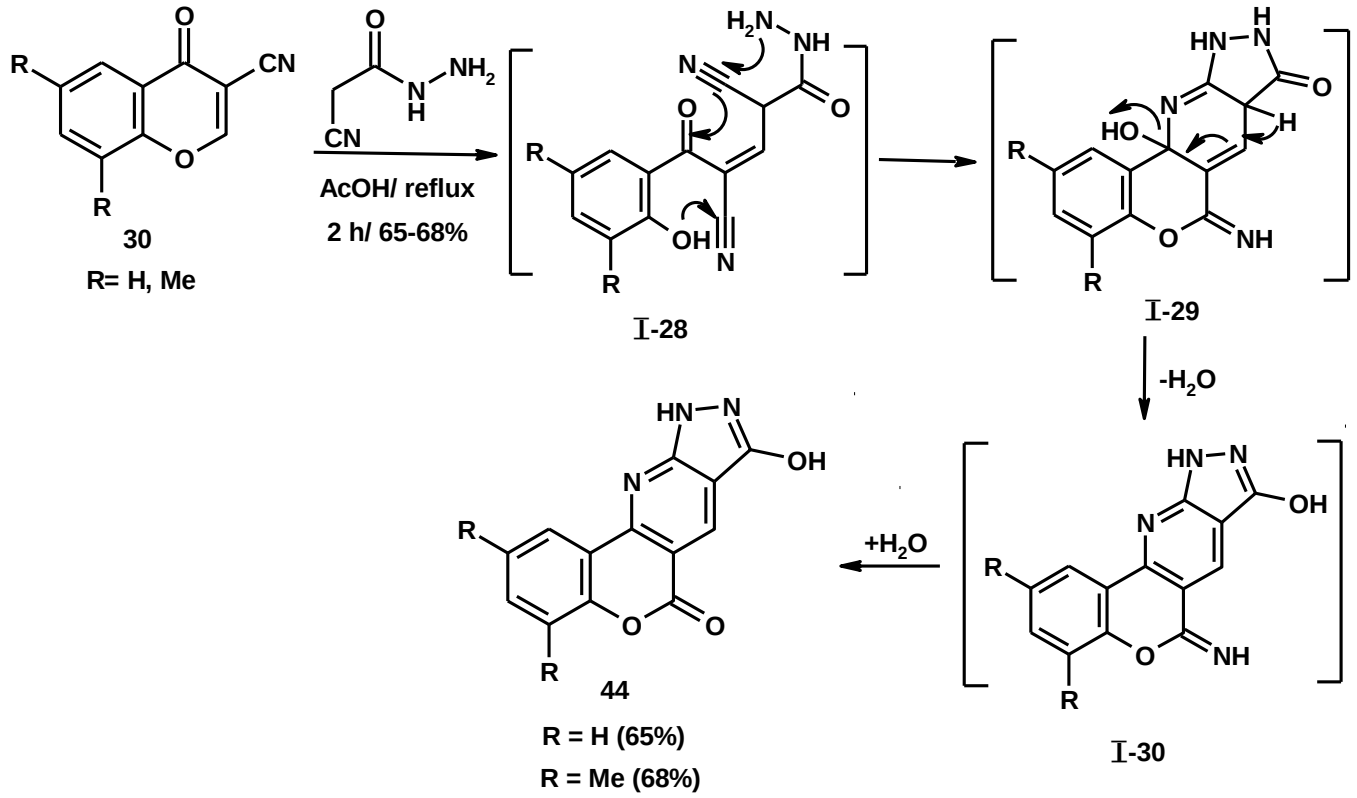
Scheme 23

Further, 2-aminochromeno[4,3-*b*]pyridine-3-carboxylates **43** were synthesized *via* a cascade reactions of chromone-3-carbonitriles **30** with carbamimidoyl-acetic acid ethyl ester in aqueous medium. This cascade reaction involves a chemoselective nucleophilic attack at C-2 position with ring opening followed by free rotation around the single bonds giving intermediate **I-26**, which underwent cycloaddition and cyclocondensation producing intermediate **I-27** that hydrolyzed to the final product **43** (Scheme 24).[59]



Scheme 24

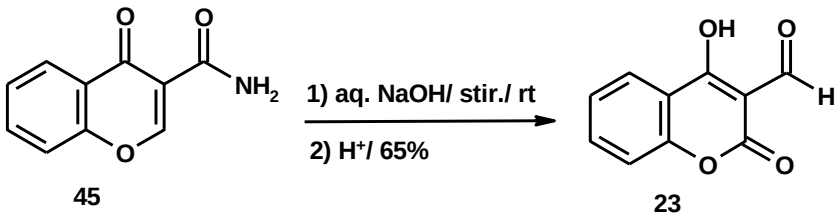
Ibrahim *et al.*,[53,57,58] prepared 3-hydroxychromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-ones **44** from chemical transformations of chromone-3-carbonitriles **30** with cyanoacetohydrazide, in boiling acetic acid (Scheme 25). These domino reactions occurred through γ-pyrone ring opening (intermediate **I-28**) with two consecutive cycloadditions (intermediate **I-29**) followed by dehydration giving intermediate **I-30** which hydrolyzed to the final product **44** as depicted in Scheme 25.



Scheme 25

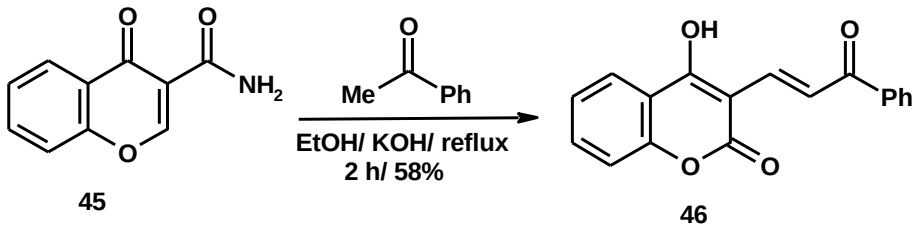
2.3.6. From chromone-3-carboxamides

Chromone-3-carboxamide (**45**) represents an excellent source for building coumarin derivatives. Stirring chromone-3-carboxamide (**45**) with NaOH solution at room temperature followed by acidification produced 3-formyl-4-hydroxycoumarin-3-carboxaldehyde (**23**) (Scheme 26).[41,42]



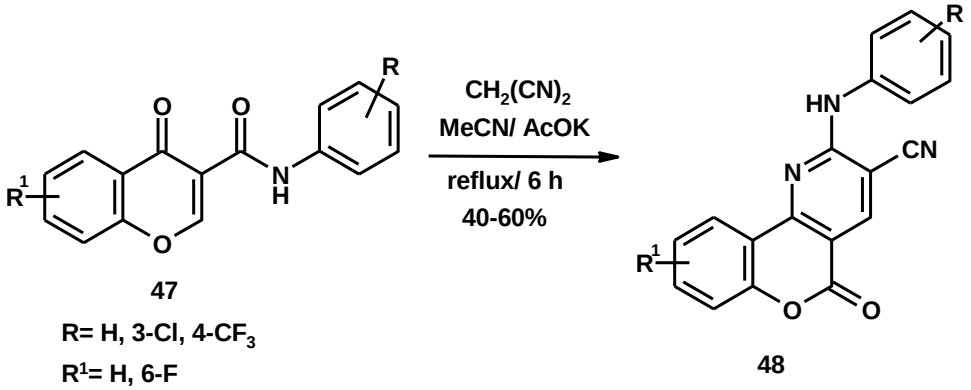
Scheme 26

Reaction of chromone-3-carboxamide (**45**) with acetophenone, in ethanolic potassium hydroxide solution, afforded 4-hydroxycoumarin derivative **46** (Scheme 27).[60]



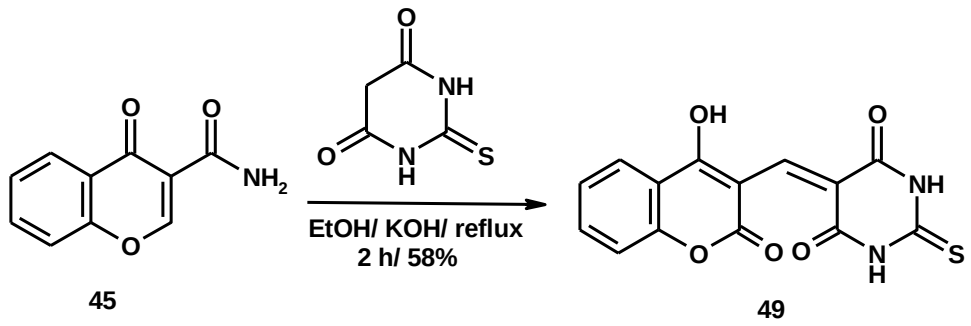
Scheme 27

Substituted chromone-3-carboxamides **47** reacted with malononitrile, in the presence of potassium acetate in acetonitrile, through *Michael* reaction followed by retro-*Michael* and heterocyclization, giving chromeno[4,3-*b*]pyridine-3-carbonitriles **48** (Scheme 28).[61]



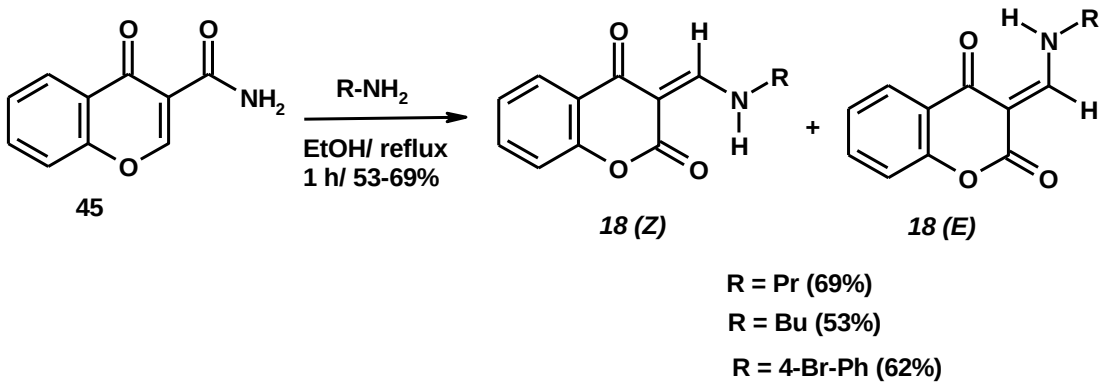
Scheme 28

Condensation of chromone-3-carboxamide (**45**) with thiobarbituric acid, in ethanolic sodium hydroxide, afforded 5-[(4-hydroxycoumarin-3-yl)methylidene]-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**49**) (Scheme 29).[60]



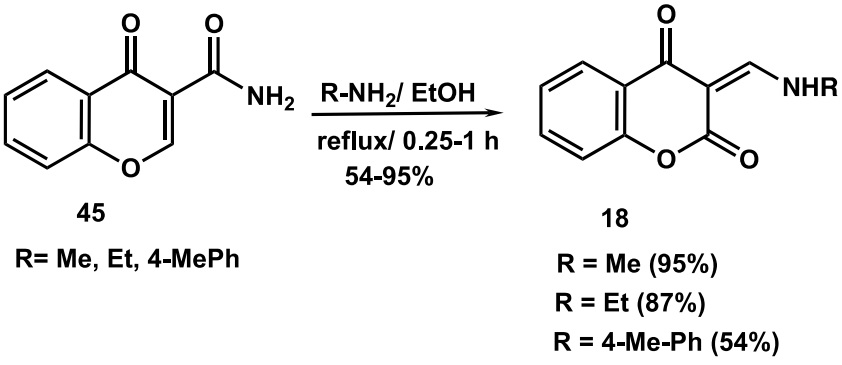
Scheme 29

Treating chromone-3-carboxamide (**45**) with some primary aliphatic and aromatic amines namely, *n*-propylamine, benzylamine and *p*-bromoaniline, under various reaction conditions, afforded chromane-2,4-diones **18** which were isolated as stereoisomeric mixtures of *Z* and *E* isomers (Scheme 30).[60]



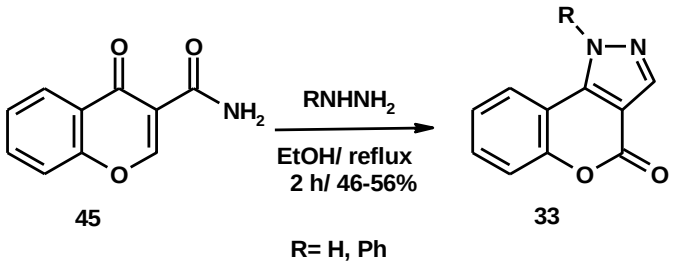
Scheme 30

Also, (3*Z*)-3-(methyl-/ethylaminomethylene)chromane-2,4-diones **18** were prepared by refluxing an ethanolic solution of carboxamide **45** with methyl or ethylamine for 15 min (Scheme 31).[42,51,54,60]



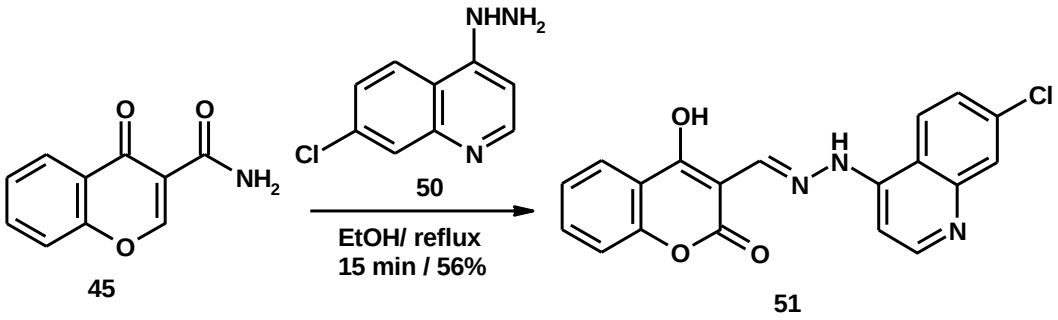
Scheme 31

Ring transformations of carboxamide **45** with hydrazine hydrate and phenylhydrazine, in refluxing ethanol for 2 h, achieved chromeno[4,3-*c*]pyrazol-4(1*H*)-ones **33** (Scheme 32).[60]



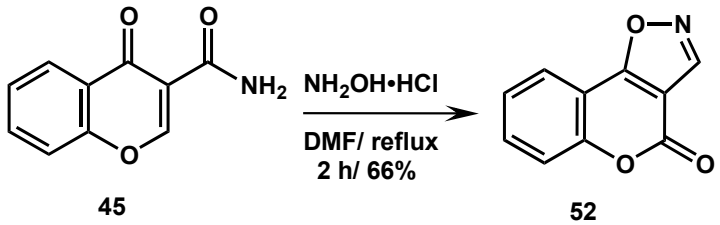
Scheme 32

Reacting chromone-3-carboxamide (**45**) with 7-chloro-4-hydrazinoquinoline (**50**), in refluxing ethanol for 15 min, afforded the rearranged product, 3-{[2-(7-chloroquinolin-4-yl)hydrazinylidene]methyl}-4-hydroxycoumarin **51** (Scheme 33).[60]



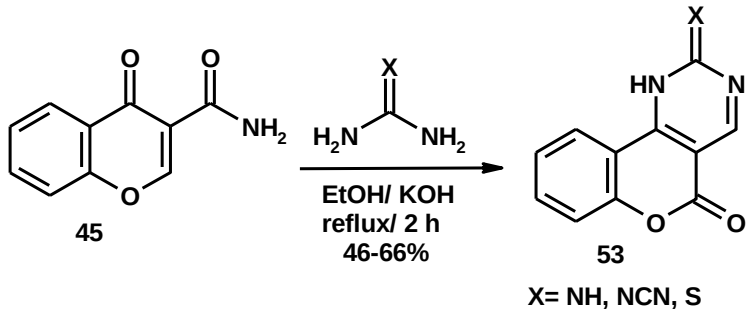
Scheme 33

Also, rearrangement of chromone-3-carboxamide (**45**) with hydroxylamine hydrochloride, in refluxing dimethylformamide (DMF) for 2 h, produced chromeno[3,4-*d*]isoxazol-4(4*H*)-one (**52**) (Scheme 34).[60]



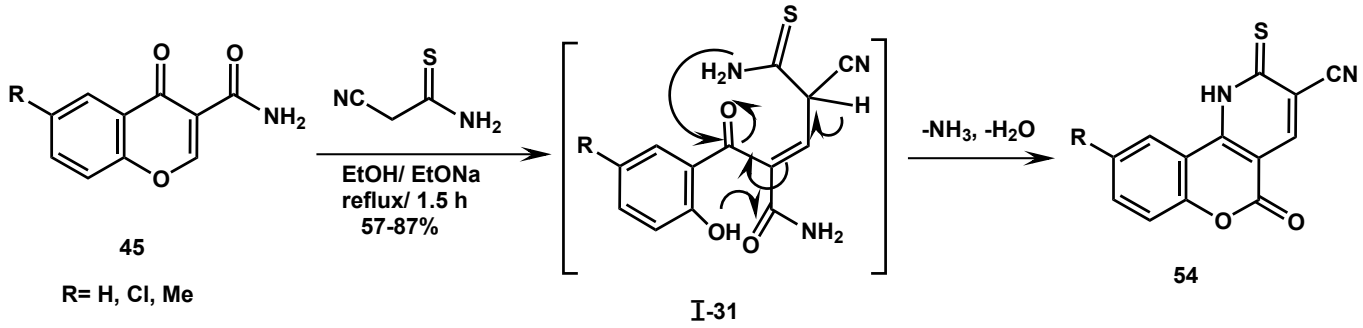
Scheme 34

Chromone-3-carboxamide (**45**) reacted with some 1,3-binucleophiles such as guanidine hydrochloride, cyanoguanidine and thiourea, in ethanolic potassium hydroxide solution, produced chromeno[4,3-*d*]pyrimidines **53** (Scheme 35).[53]



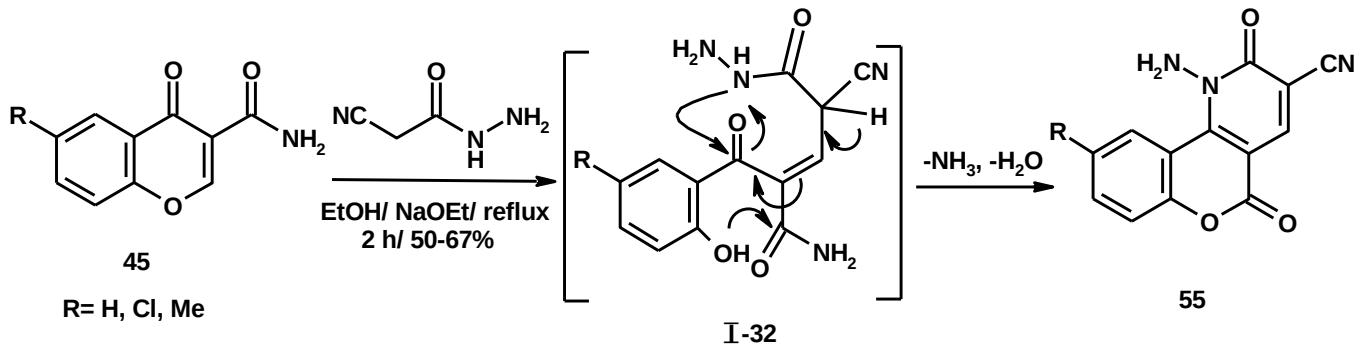
Scheme 35

Condensation of chromone-3-carboxamides **45** with cyanothioacetamide in ethanolic sodium ethoxide solution afforded chromeno[4,3-*b*]pyridine-3-carbonitriles **54**, *via* intermediate **I-31** followed by cyclization (Scheme 36).[62]



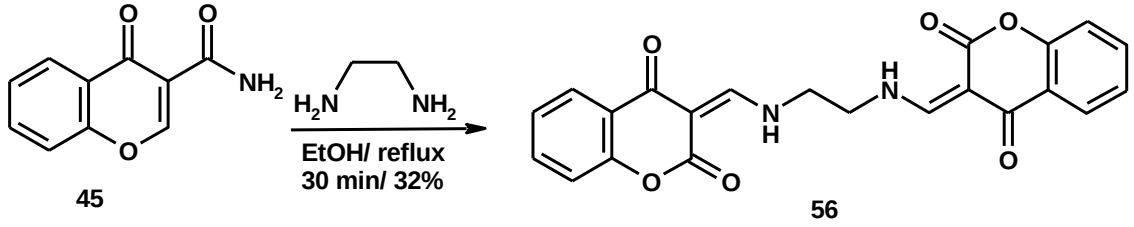
Scheme 36

Chromone-3-carboxamides **45** rearranged with cyanoacetohydrazide, in ethanolic sodium ethoxide solution, giving chromeno[4,3-*b*]pyridine-3-carbonitriles **55**, *via* intermediate **I-32** followed by cyclization with loss of water and ammonia molecules (Scheme 37).[63]



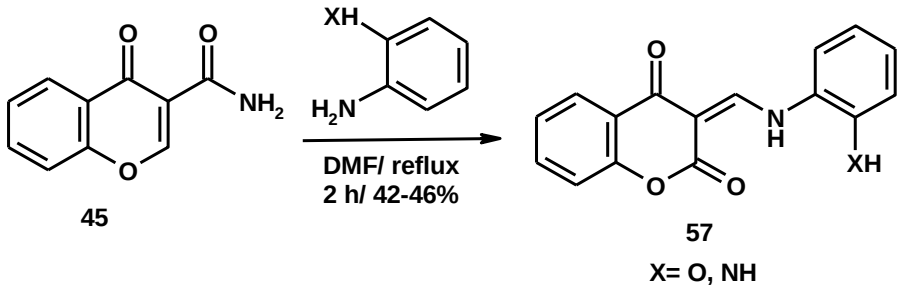
Scheme 37

Bis-chromane-2,4(3*H*)-dione **56** was synthesized by reaction of chromone-3-carboxamide (**45**) with ethylenediamine, in boiling ethanol for 30 min (Scheme 38).[60]



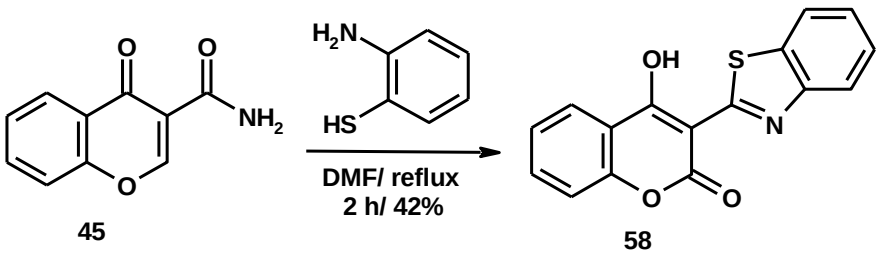
Scheme 38

Rearrangement of chromone-3-carboxamide (**45**) with some 1,4-dinucleophiles namely *o*-phenylenedimine and *o*-aminophenol in refluxing DMF afforded (3*Z*)-3-{[(2-amino/2-hydroxyphenyl)amino]methylidene}chromane-2,4(3*H*)-dione (**57**) (Scheme 39).[60]



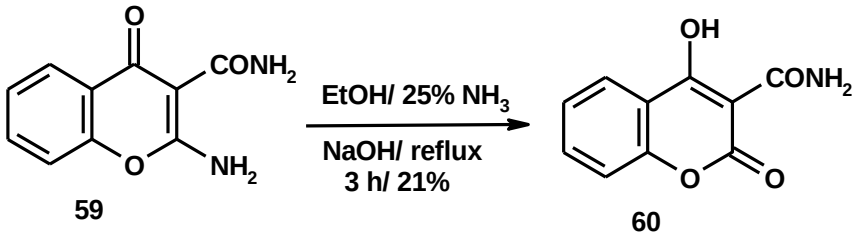
Scheme 39

Different to the previous behavior, ring transformation of chromone-3-carboxamide (**45**) with *o*-aminothiophenol, in refluxing DMF, furnished 3-benzothiazolyl-4-hydroxycoumarin **58** (Scheme 40).[60]



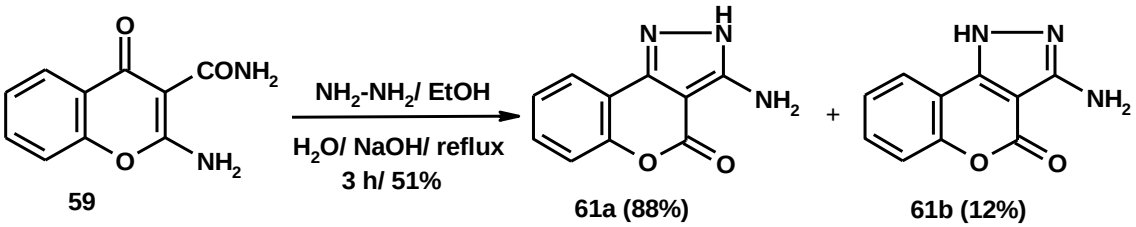
Scheme 40

On the other hand, 2-aminochromone-3-carboxamide (**59**) was also utilized for construction of coumarin derivatives. 4-Hydroxycoumarin-3-carboxamide (**60**) was efficiently synthesized from hydrolysis of 2-aminochromone-3-carboxamide (**59**) using ammonia and NaOH, in boiling ethanol for 3 h (Scheme 41).[47]



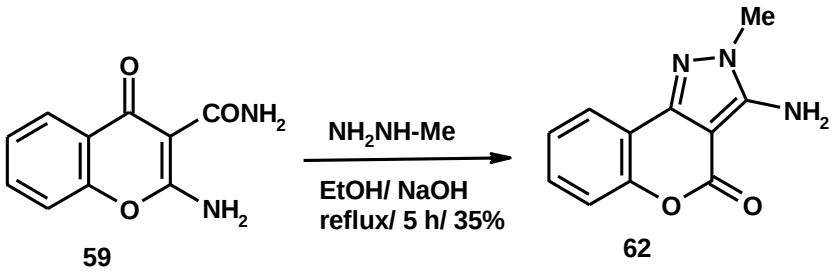
Scheme 41

Reaction of 2-aminochromone-3-carboxamide (**59**) with hydrazine hydrate, in boiling ethanol in the presence of NaOH for 3 h, produced 3-aminochromeno[4,3-*c*]pyrazolones **61a,b** (Scheme 42). The product formed as a mixture of two tautomers in the ratio 88:12, according to the ^{1}H NMR spectroscopic data.[48,49]



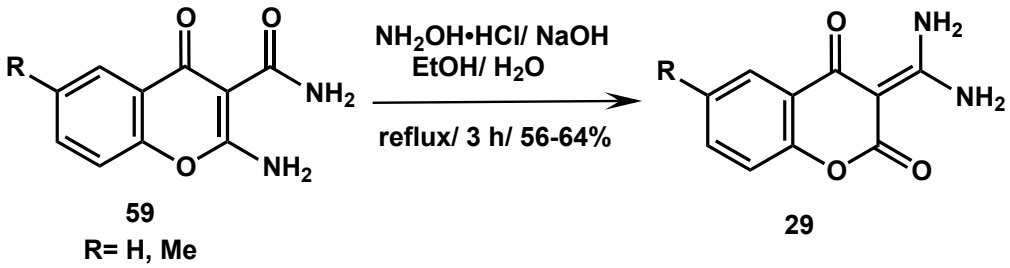
Scheme 42

On the other hand, reaction of 2-aminochromone-3-carboxamide (**59**) with methylhydrazine, in ethanolic sodium hydroxide solution, afforded 2-methylchromeno[4,3-*c*]pyrazol-4(2*H*)-one **62**, in 35% yield (Scheme 43).[47]



Scheme 43

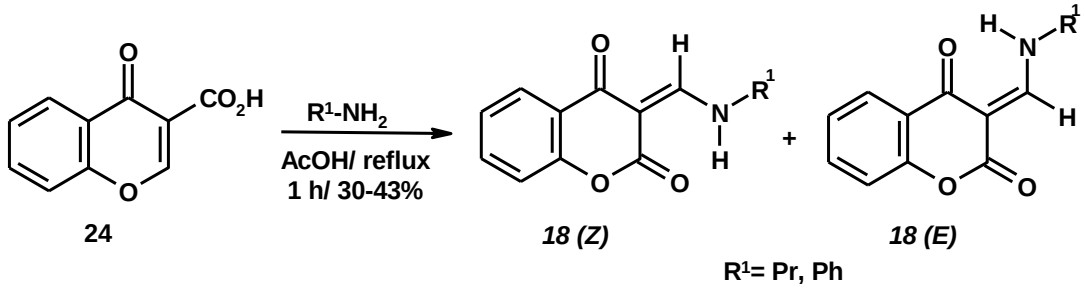
Carboxamides **59** were transformed with alkaline hydroxylamine to afford chromanediones **29** (Scheme 44).[41,46-48]



Scheme 44

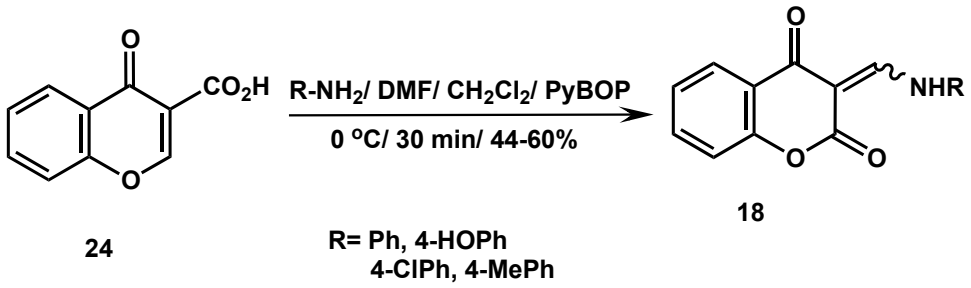
2.3.7. From chromone-3-carboxalic acids

Treating chromone-3-carboxylic acid (**24**) with some primary aliphatic and aromatic amines namely, *n*-propylamine and phenylamine, under various reaction conditions, afforded chromane-2,4-diones **18** which were isolated as stereoisomeric mixtures of *Z* and *E* isomers (Scheme 45).[64]



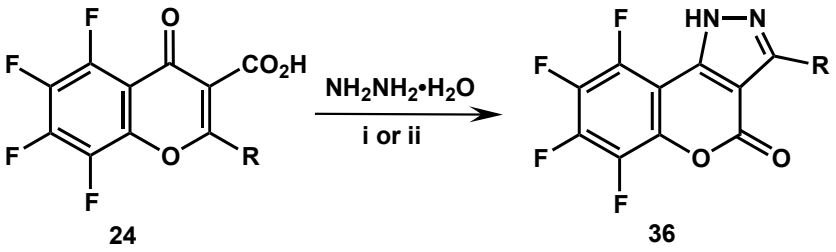
Scheme 45

Interaction of chromone-3-carboxylic acid (**x**) with aromatic amines, in mixture of DMF and dichloromethane in the presence of such activating reagent as phosphonium salt (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) gave chromanediones **18** (Scheme 46).[65]



Scheme 46

Reaction of fluorinated chromone-3-carboxylic acids **24** with hydrazine hydrate, under different reaction conditions, led to fluorinated coumarinopyrazole derivatives **36** (Scheme 47).[66,67]



24 36

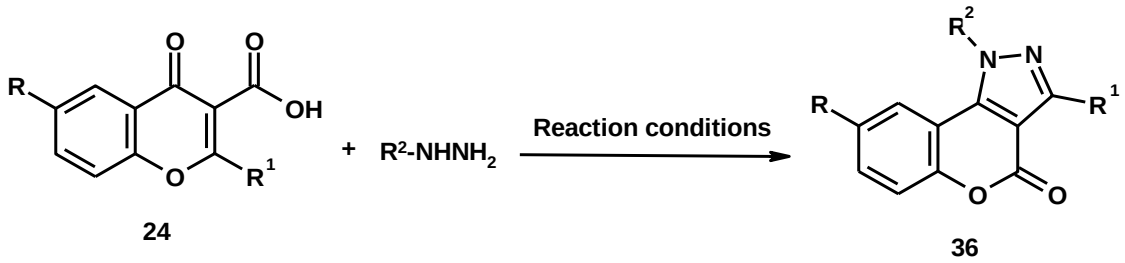
R= Me, H

i) 1- H_2O/ stir./ 24 h
2- toluene/ DMF/ SO_2Cl_2/ reflux/ 20 min/ 47-86%

ii) 1- MeOH/ TEA/ reflux/ 2 h
2- H_2SO_4/ H_2O/ reflux/ 1.5 h/ 47-82%

Scheme 47

Condensation of chromone-3-carboxylic acids **24** with some hydrazines such as hydrazine hydrate, cyanoacetohydrazide, phenylhydrazine, 7-chloro-4-hydrazinoquinoline, under various reaction conditions, provided chromeno[4,3-*c*]pyrazoles **36** (Scheme 48).[55,64,68,69]

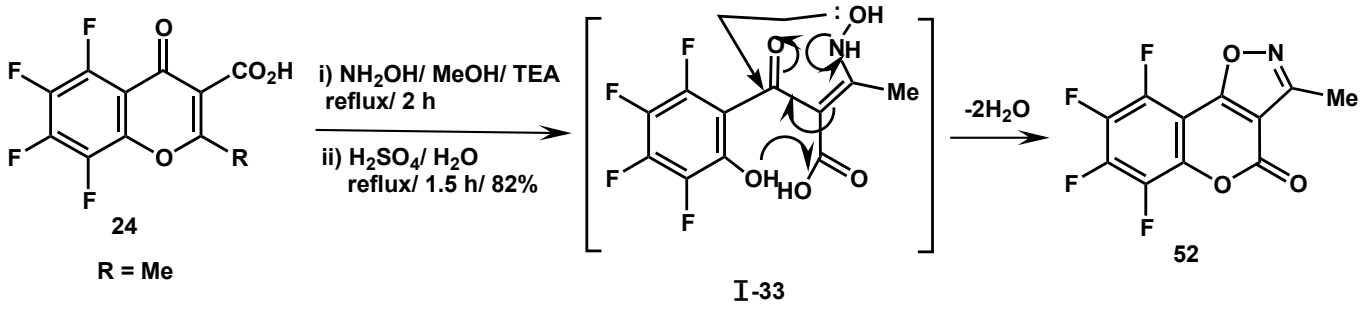


24 36

R	R^1	R^2	Reaction Conditions	Yield	Ref.
H	H	H	AcOH/ reflux/ 2 h	46%	64
H	H	-$COCH_2CN$	AcOH/ reflux/ 2 h	48%	64
H	H	7-chloroquinolinyl	AcOH/ reflux/ 1 h	32%	64
H	H	Ph	AcOH/ reflux/ 4 h	80%	68
H	Me	Ph	AcOH/ reflux/ 4 h	60%	68
H	H	7-chloroquinolinyl	EtOH/ reflux/ 1 h	44%	64
Cl	H	H	AcOH/ reflux/ 2 h	46%	69
H	H	Ph	EtOH/ reflux/ 3 h	82%	69
Me	H	Ph	AcOH/ reflux/ 2 h	80%	54
Br	H	Ph	AcOH/ reflux/ 2 h	83%	54
Cl	H	Ph	AcOH/ reflux/ 2 h	85%	54

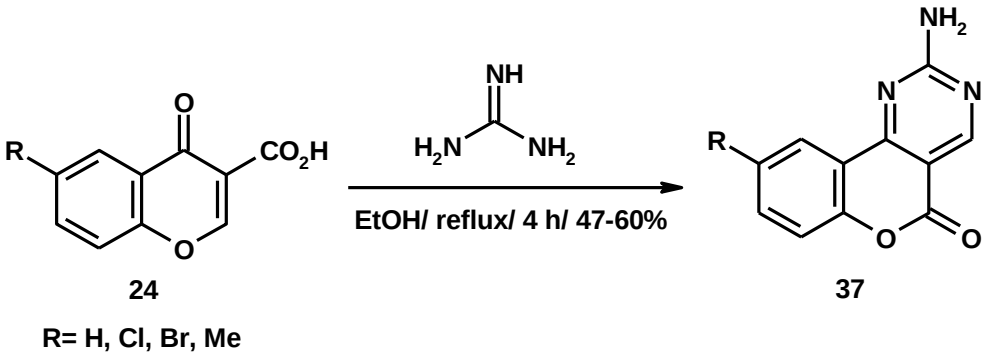
Scheme 48

Reaction of fluorinated chromone-3-carboxylic acid **24** with hydroxylamine, under different reaction conditions, afforded chromeno[3,4-*d*]isoxazole **52**, through γ-pyrone ring opening (intermediate **I-33**) followed by cyclodehydration (Scheme 49).[66]



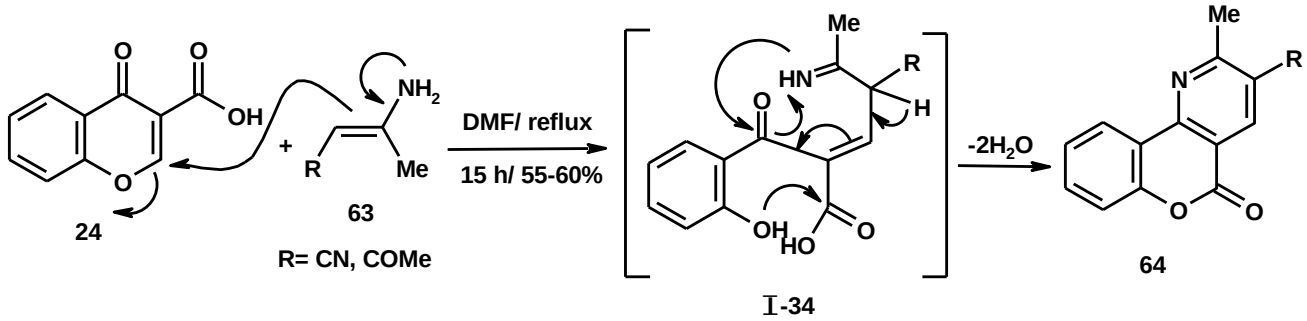
Scheme 49

Interaction of chromone-3-carboxylic acids **24** with guanidine carbonate, in boiling ethanol, led to chromeno[4,3-*d*]pyrimidine **37**, in moderate yields (Scheme 50).[69]



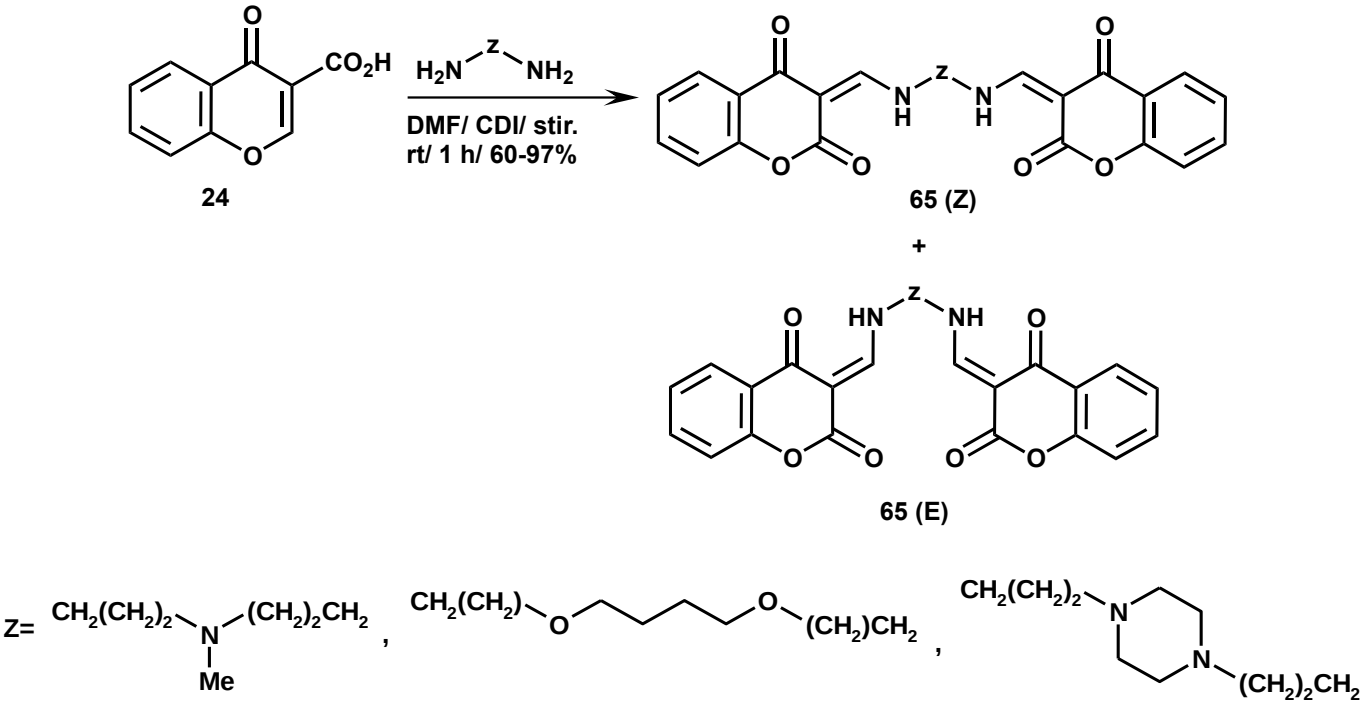
Scheme 50

Interaction of chromone-3-carboxylic acid (**24**) with push-pull enamines **63**, in boiling DMF, produced pyrido[3,2-*c*]coumarins **64**, through intermediate **I-34** (Scheme 51).[69]



Scheme 51

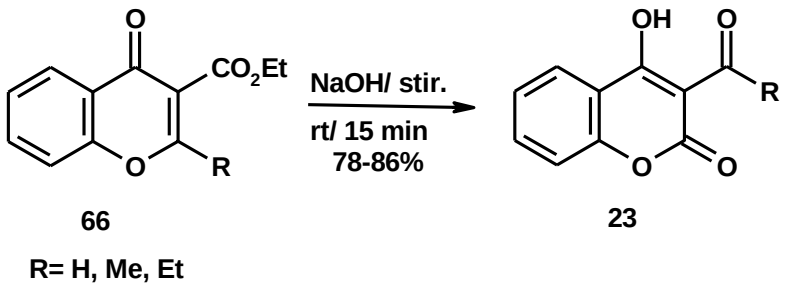
Bis-chromane-2,4(3*H*)-diones **65** were synthesized, as a stereoisomeric mixture of (*E*)- and (*Z*)-isomers from reaction of chromone-3-carboxylic acid (**24**) with aliphatic diamines, in DMF by using carbonyldiimidazole (CDI) as the activating agent (Scheme 52).[70]



Scheme 52

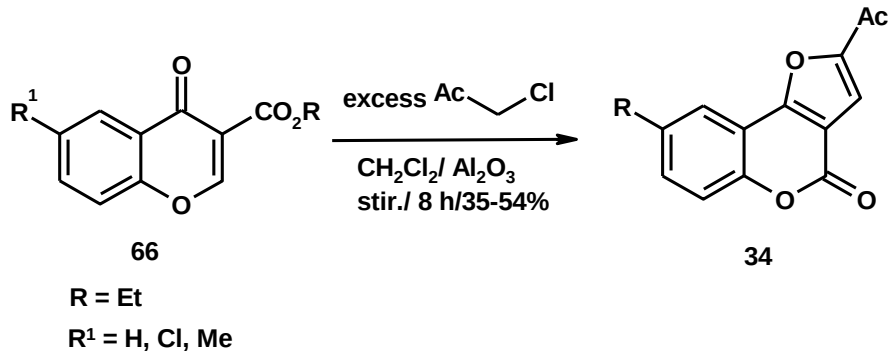
2.3.8. From alkyl chromone-3-carboxylates

Basic rearrangement of ethyl chromone-3-carboxylates **66**, in aqueous sodium hydroxide solution at room temperature, produced 3-substituted-4-hydroxycoumarins **23**, in good yields (78-86%) (Scheme 53).[55]



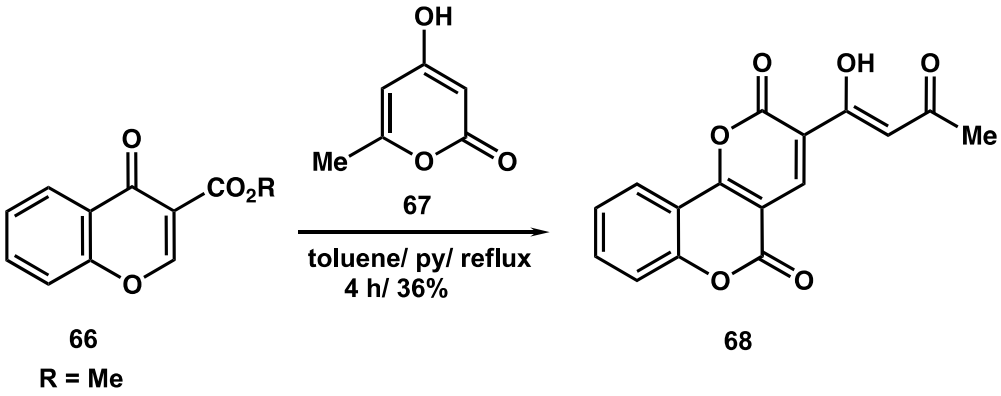
Scheme 53

Treatment of ethyl chromone-3-carboxylate **66** with excess chloroacetone, in dichloromethane in the presence of Brockman neutral alumina, afforded 2-acetylfurocoumarin **34** (Scheme 54).[50]



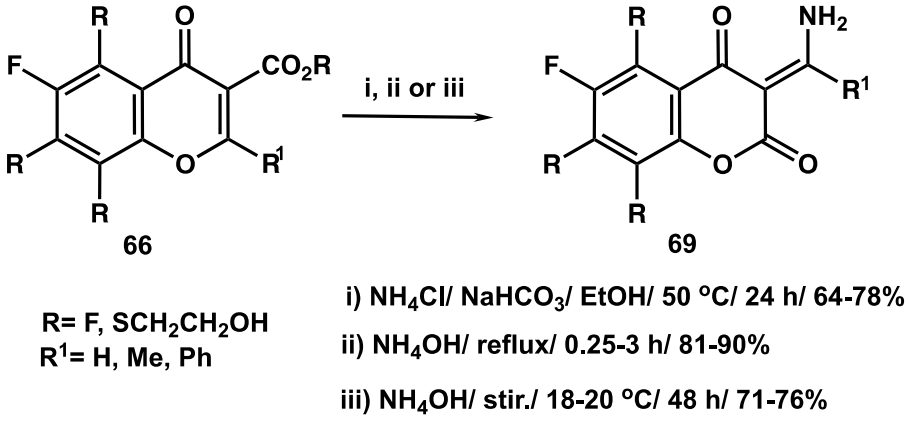
Scheme 54

Reaction of methyl chromone-3-carboxylate (**66**) with triacetic acid lactone **67**, in boiling toluene in the presence of pyridine for 4 h, afforded pyrano[4,3-*b*]coumarin **68** in 36% yield (Scheme 55).[71]



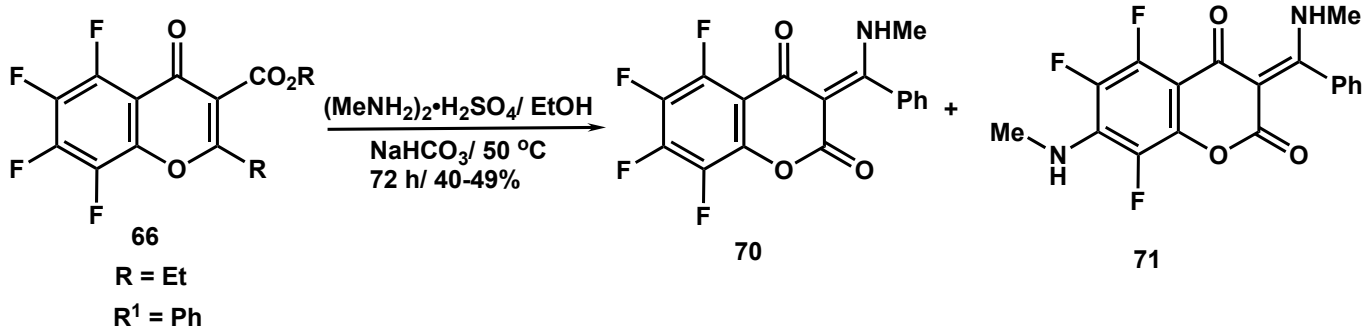
Scheme 55

While, conversions of ethyl chromone-3-carboxylates **66** into chromane-2,4(3*H*)-diones **69**, were achieved by heating with ammonium chloride or ammonium hydroxide under different reaction conditions (Scheme 56).[28,55,67,72,73]



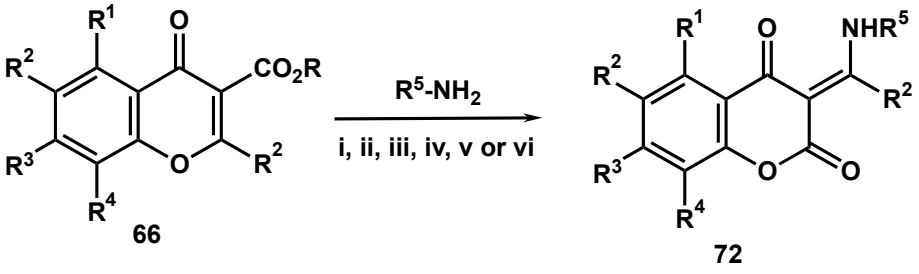
Scheme 56

Rearrangement of chromone-3-carboxylate derivative **66** with equimolar amount of methylamine sulfate, by heating in ethanol for 72 h, led to chromane-2,4-diones **70** and **71** (Scheme 57). Repeating the previous reaction using excess of methylamine salt under the same reaction conditions produced a single product **71**, in 94% yield.[66,74]



Scheme 57

Polyfluorochromone-3-carboxylates **66** reacted with a variety of primary amines, under different reaction conditions, producing chromane-2,4(3*H*)-diones **72** (Scheme 58).[66-68,72,74,75]

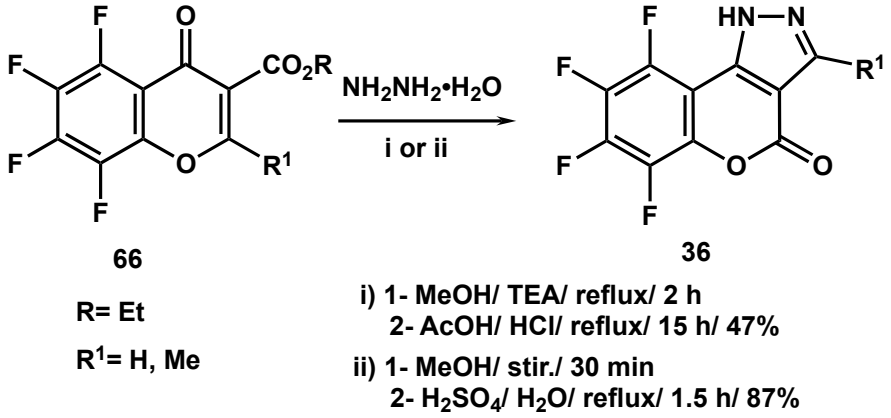


R= Me, Et
R^2= Me, Et, Ph, Bn
R^1= R^2= R^3= R^4= F, H
R^5= H, Me, hex., *c*-hex., Bn

i) NH_4Cl/ $NaHCO_3$/ EtOH/ 50 °C/ 24 h/ 64-78%
ii) EtOH/ 20-50 °C/ 24 h/ 51-78%
iii) MeOH/ stir. / 25 °C/ 5-30 min/ 69-93%
iv) NH_4OH/ EtOH/ 25 °C/ 24 h/ 58-95%
v) DMSO/ 20 °C/ 56-95%
vi) MeCN/ 20 °C/ 75%

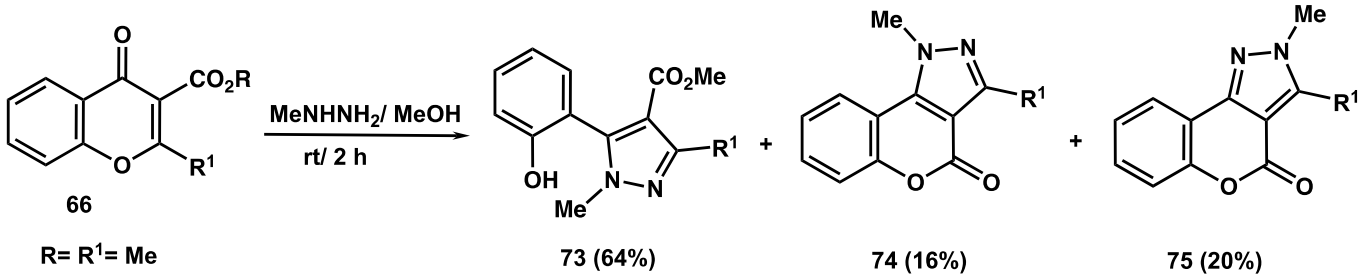
Scheme 58

Reaction of ethyl chromone-3-carboxylate **66** with hydrazine hydrate, under different reaction conditions, afforded pyrazoles **36** (Scheme 59).[28,66,67]



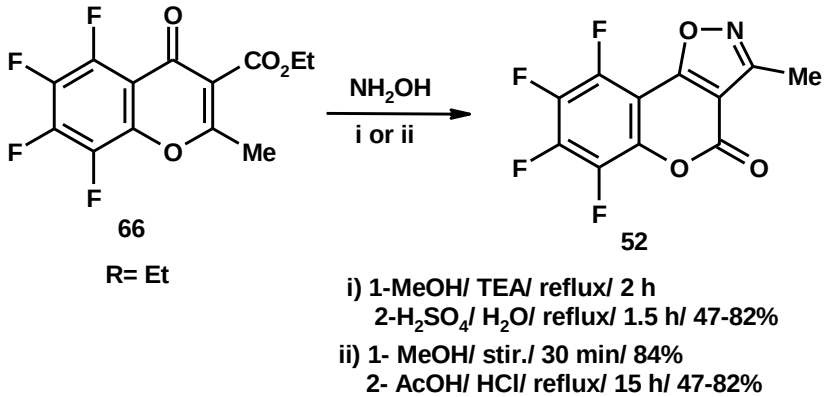
Scheme 59

Reaction of methyl 2-methylchromone-3-carboxylate (**66**) with one equivalent of *N*-methylhydrazine, in methanol for 2 h, gave a mixture of products **73** (64%), **74** (16%) and **75** (20%) (Scheme 60).[68,76]



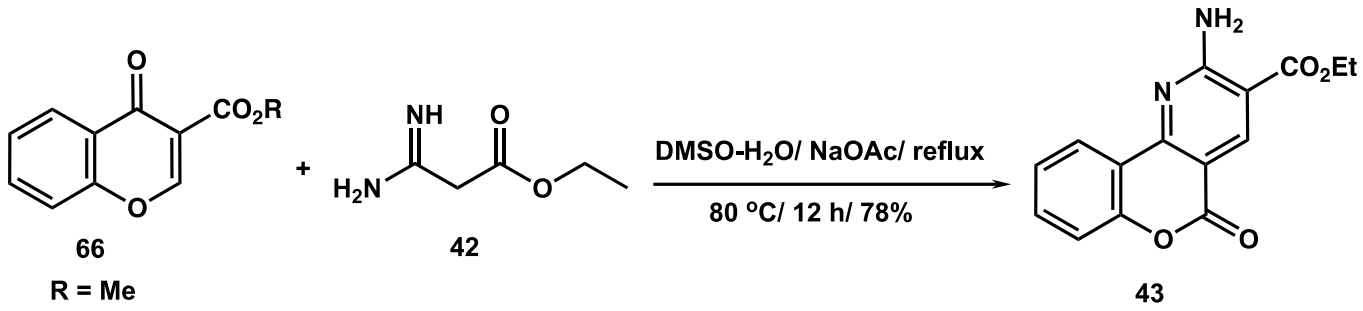
Scheme 60

Reaction of fluorinated ethyl chromone-3-carboxylate **66** with hydroxylamine, under various reaction conditions, afforded chromenoisoxazole **52** (Scheme 61).[66,67]



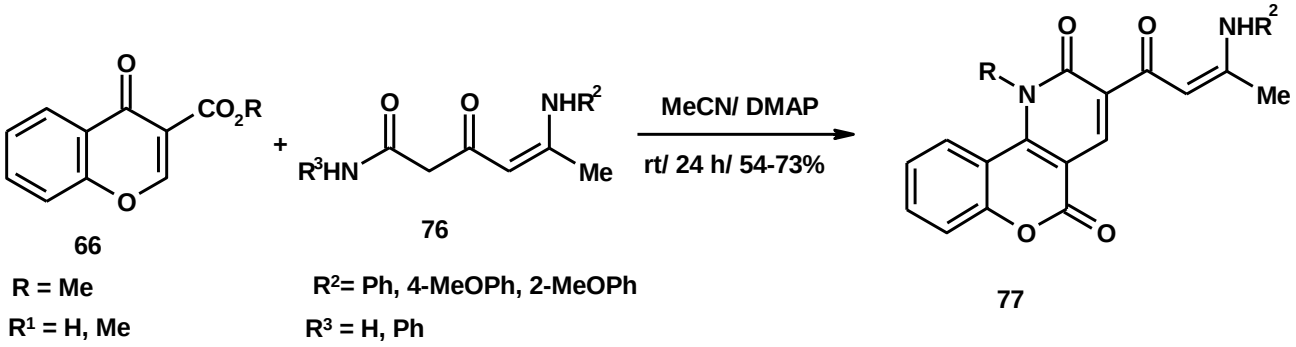
Scheme 61

2-Aminochromeno[4,3-*b*]pyridine-3-carboxylate **43** was synthesized *via* an intramolecular cyclization of methyl chromone-3-carboxaylate **66** with carbamimidoyl-acetic acid ethyl ester (**42**) in aqueous medium (Scheme 62).[59]



Scheme 62

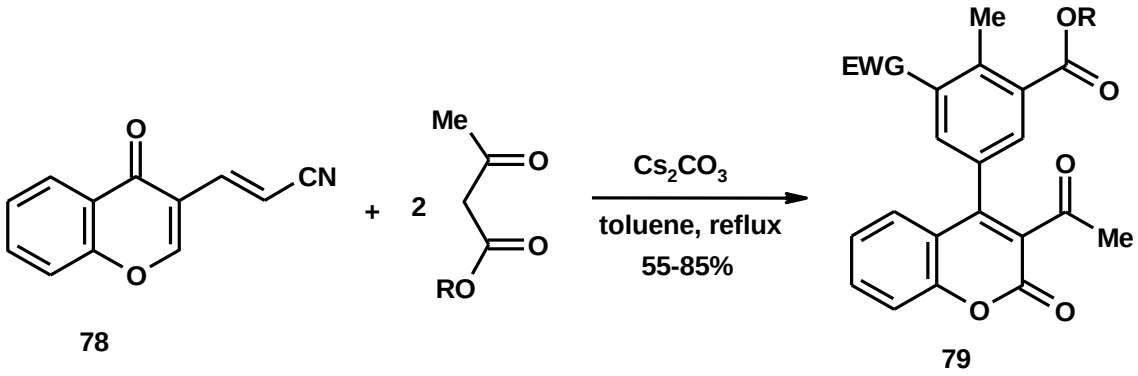
Methyl chromone-3-carboxaylate **66** reacted with some active methylene amides **76**, in the presence of 4-dimethylaminopyridine (DMAP) and MeCN, giving chromeno[4,3-*b*]pyridine-2,5-diones **77** bearing the enaminone moiety (Scheme 63).[77]



Scheme 63

2.3.9. From chromonylacrylonitrile

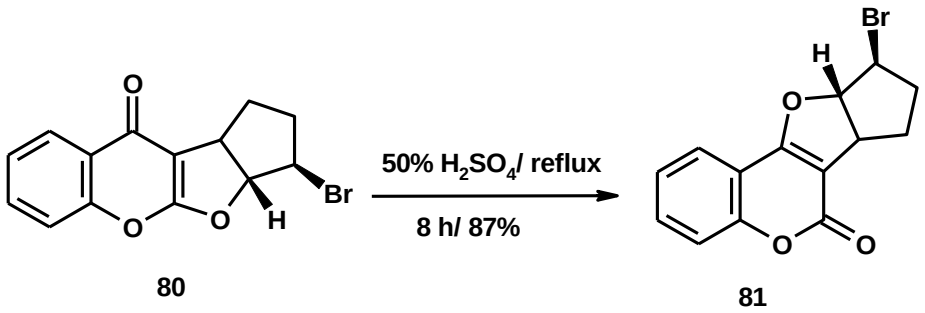
Recently, Cai *et al.*[78] reported an efficient, convenient, and safe route to functionalized 3-acyl-4-arylcoumarins **79** using a mild base-promoted (Cs_2CO_3) reaction between electron deficient chromones **78** and *β*-keto esters *via* benzannulation and transesterification. The reaction mechanism involves Michael addition, 1,5-shift and transesterification (Scheme 64).



Scheme 64

2.4. From annulated chromones

Boiling annulated furocchromone **80** in 50% sulphuric acid for 8 h, furnished the annulated furocoumarin **81**, in 87% yield (Scheme 65).[79]



Scheme 65

3. CONCLUSION

In conclusion, variable synthetic methods were utilized to synthesize a variety of coumarins and annulated coumarins from chromone derivatives. Reactions of substituted chromones especially bearing electron withdrawing group at position 3 are valuable synthon for substituted coumarins. Chemical transformations of chromone derivatives with some mono- and bi-functional nucleophiles afforded a diversity of coumarins and fused coumarins.

REFERENCES

1. J. Grover and S. M. Jachak, *RSC Adv.*, 2015, **5**, 38892.
2. J. Reis, A. Gaspar, N. Milhazes, and F. Borges, *J. Med. Chem.*, 2017, **60**, 7941.
3. F. Annunziata, C. Pinna, S. Dallavalle, L. Tamborini, and A. Pinto, *Int. J. Mol. Sci.*, 2020, **21**, 4618.
4. R. S. Keri, S. Budagumpi, R. K. Pai, and R. G. Balakrishna, *Eur. J. Med. Chem.*, 2014, **78**, 340.

5. R. Jiao, F. Xu, X. Huang, H. Li, W. Liu, H. Cao, L. Zang, Z. Li, H. Hua, and D. Li, *J. Enzyme Inhib. Med. Chem.*, 2020, **35**, 759.
6. S. M. Abu-Bakr, M. D. Khidre, M. A. Omar, S. A. Swelam, and H. M. Awad, *J. Heterocycl. Chem.*, 2020, **57**, 731.
7. N. F. L. Machado and M. P. M. Marques, *Curr. Bioact. Compd.*, 2010, **6**, 76.
8. S. Kittisrisopit, N. Bunbamrung, C. Thawai, S. Tadtong, N. Niemhom, S. Komwijit, P. Rachtawee, and P. Pittayakhajonwut, *Nat. Prod. Res.*, 2021, **35**, 2881.
9. P. Lerdsirisuk, C. Maicheen, and J. Ungwitayatorn, *Bioorg. Chem.*, 2014, **57**, 142.
10. C. Demetgül and N. Beyazit, *Carbohydr. Polym.*, 2018, **181**, 812.
11. L. C. França Opretzka, R. F. Espírito-Santo, O. A. Nascimento, L. S. Abreu, I. M. Alves, E. Döring, M. B. P. Soares, E. da S. Velozo, S. A. Laufer, and C. Villarreal, *Int. Immunopharmacol.*, 2019, **72**, 31.
12. C. F. M. Silva, D. C. G. A. Pinto, and A. M. S. Silva, *ChemMedChem*, 2016, **11**, 2252.
13. R. B. Semwal, D. K. Semwal, S. Combrinck, and A. Viljoen, *Phytochem. Rev.*, 2020, **19**, 761.
14. S. Kaushik, R. Sanawar, A. Lekshmi, L. Chandrasekhar, M. Nair, S. Bhatnagar, and T. R. Santhoshkumar, *Chem. Biol. Drug Des.*, 2019, **94**, 1352.
15. N. Aggarwal, V. Sharma, H. Kaur, and M. P. S. Ishar, *Int. J. Med. Chem.*, **2013**, 1.
16. M. Greaves, *PLoS Med.*, 2005, **2**, e342.
17. X. Song, J. Fan, L. Liu, X. Liu, and F. Gao, *Arch. Pharm.*, 2020, **353**, e2000025.
18. K. M. Amin, F. M. Awadalla, A. A. M. Eissa, S. M. Abou-Seri, and G. S. Hassan, *Bioorg. Med. Chem.*, 2011, **19**, 6087.
19. Y. K. Al-Majedy, A. A. H. Kadhum, A. A. Al-Amiery, and A. B. Mohamad, *Sys. Rev. Pharm.*, 2017, **8**, 62.
20. A. A. H. Kadhum, A. A. Al-Amiery, A. Y. Musa, and A. B. Mohamad, *Int. J. Mol. Sci.*, 2011, **12**, 5747.
21. D. J. Hadjipavlou-Litina, K. E. Litinas, and C. Kontogiorgis, *Antiinflamm. Anti-Allergy Agents Med. Chem.*, 2007, **6**, 293.
22. S. Mishra, A. Pandey, and S. Manvati, *Heliyon*, 2020, **6**, e03217.
23. F. Aguilar, H. N. Autrup, S. Barlow, L. Castle, R. Crebelli, W. Dekant, K. H. Engel, N. Gontard, D. M. Gott, S. Grilli, R. Gürtler, J. C. Larsen, C. Leclercq, J. C. Leblanc, F. X. Malcata, W. Mennes, M. R. Milana, I. Pratt, I. M. C. M. Rietjens, P. P. Tobback, and F. Toldrá, *EFSA J.*, 2008, **93**, 1.
24. C. Stiefel, T. Schubert, and G. E. Morlock, *ACS Omega*, 2017, **2**, 5242.
25. V. R. Mishra and N. Sekar, *J. Fluoresc.*, 2017, **27**, 1101.
26. Y. Yang, X. Qi, R. Liu, Q. He, and C. Yang, *RSC Adv.*, 2016, **6**, 103895.

27. Y. Sosnovskikh, V. A. Kutsenko, and I. S. Ovsyannikov, *Russ. Chem. Bull.*, 2000, **49**, 478.
28. V. Y. Sosnovskikh, 'Fluorine Heterocycl. Chem.; Fluorinated Pyrones, Chromones and Coumarins', Vol. 2, ed. by V. Y. Sosnovskikh, Springer International Publishing Switzerland, 2014, pp. 211-290.
29. V. Y. Sosnovskikh, A. V. Safrygin, V. A. Anufriev, O. S. Eltsov, and V. O. Iaroshenko, *Tetrahedron Lett.*, 2011, **52**, 6271.
30. V. Y. Sosnovskikh, A. V. Safrygin, and V. A. Anufriev, *Russ. Chem. Bull., Int. Ed.*, 2013, **62**, 2209.
31. V. Y. Sosnovskikh, A. V. Safrygin, V. A. Anufriev, O. S. Eltsov, and V. O. Iaroshenko, *Tetrahedron Lett.*, 2011, **52**, 6271.
32. V. O. Iaroshenko, I. Savych, A. Villinger, V. Y. Sosnovskikh, and P. Langera, *Org. Biomol. Chem.*, 2012, **10**, 9344.
33. V. Y. Sosnovskikh, *Chem. Heterocycl. Compd.*, 2020, **56**, 243.
34. M. A. Terzidis, C. A. Tsoleridis, J. Stephanidou-Stephanatou, A. Terzis, C. P. Raptopoulou, and V. Psycharis, *Tetrahedron*, 2008, **64**, 11611.
35. G. Haas, J. L. Stanton, and T. Winkler, *J. Heterocycl. Chem.*, 1981, **18**, 619.
36. F. G. Medina, J. G. Marrero, M. Macías-Alonso, M. C. González, I. Córdova-Guerrero, A. G. T. Garcia, and S. Osegueda-Robles, *Nat. Prod. Rep.*, 2015, **32**, 1472.
37. G. Cheng and Y. Hu, *J. Org. Chem.*, 2008, **73**, 4732.
38. N. Hamdi, M. Saoud, and A. Romerosa, *Top. Heterocycl. Chem.*, 2007, **11**, 283.
39. M. P. S. lshar, K. Kumar, and R. Singh, *Tetrahedron Lett.*, 1998, **39**, 6547.
40. G. Singh, G. Singh, and M. P. S. Ishar, *Helv. Chim. Acta*, 2003, **86**, 169.
41. C. K. Ghosh and A. Chakraborty, *ARKIVOC*, 2015, **vi**, 288.
42. M. A. Ibrahim, *Tetrahedron*, 2009, **65**, 7687.
43. C. K. Ghosh and S. Bhattacharyya, *Indian J. Chem.*, 1999, **38B**, 166.
44. M. Usman, M. Zaki, R. A. Khan, A. Alsalme, M. Ahmad, and S. Tabassum, *RSC Adv.*, 2017, **7**, 36056.
45. C. Bandyopadhyay, K. R. Sur, R. Patra, and A. Sen, *Tetrahedron*, 2000, **56**, 3583.
46. V. Y. Sosnovskikh, V. S. Moshkin, and M. I. Kodess, *Mendeleev Commun.*, 2010, **20**, 209.
47. V. Y. Sosnovskikh, M. I. Kodess, and V. S. Moshkin, *Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 1253.
48. V. Y. Sosnovskikh, V. S. Moshkin, and M. I. A. Kodess, *Tetrahedron Lett.*, 2008, **49**, 6856.
49. M. A. Rashid, N. Rasool, B. Appel, M. Adeel, V. Karapetyan, S. Mkrtchyan, H. Reinke, C. Fischer, and P. Langer, *Tetrahedron*, 2008, **64**, 5416.
50. C. K. Ghosh, S. Bhattacharyya, N. Ghoshal, and B. Achari, *J. Chem. Res. (S)*, 1998, 178.
51. C. K. Ghosh and A. Chakraborty, *ARKIVOC*, 2015, **vi**, 417.
52. V. Y. Sosnovskikh, V. S. Moshkin, and M. I. Kodess, *J. Heterocycl. Chem.*, 2010, **47**, 629.

53. N. M. El-Gohary, M. A. Ibrahim, and S. Said, *Heterocycles*, 2018, **96**, 690.
54. M. A. Ibrahim, N. M. El-Gohary, and S. Said, *Heterocycles*, 2015, **91**, 1863.
55. V. Y. Sosnovskikh, V. S. Moshkin, and M. I. Kodess, *Tetrahedron*, 2008, **64**, 7877.
56. M. A. Ibrahim and N. M. El-Gohary, *J. Heterocycl. Chem.*, 2016, **53**, 859.
57. M. A. Ibrahim and A. M. El-Kazak, *J. Heterocycl. Chem.*, 2019, **56**, 1075.
58. M. A. Ibrahim, A-S. Badran, and S. H. Hashiem, *J. Heterocycl. Chem.*, 2018, **55**, 2844.
59. H. Xiang, J. Chen, Z. Miao, and C. Yang, *RSC Adv.*, 2014, **4**, 16132.
60. M. A. Ibrahim, *J. Braz. Chem. Soc.*, 2013, **24**, 1754.
61. D. Y. Demin, K. A. Myannik, K. A. Lyssenko, M. M. Krayushkin, and V. N. Yarovenko, *ChemistrySelect*, 2019, **4**, 6090.
62. M. Y. Kornev, D. S. Tishin, and V. Y. Sosnovskikh, *Mendeleev Commun.*, 2019, **29**, 67.
63. M. Y. Kornev, V. S. Moshkin, O. S. Eltsov, and V. Y. Sosnovskikh, *Mendeleev Commun.*, 2016, **26**, 72.
64. M. A. Ibrahim, *ARKIVOC*, 2008, **xvii**, 192.
65. F. Cagide, T. Silva, J. Reis, A. Gaspar, F. Borges, L. R. Gomes, and J. N. Low, *Chem. Commun.*, 2015, **51**, 2832.
66. K. V. Shcherbakov, Y. V. Burgart, V. I. Saloutin, and O. N. Chupakhin, *Russ. Chem. Bull., Int. Ed.*, 2016, **65**, 2151.
67. V. I. Saloutin, Z. E. Skryabina, I. T. Bazyl', and S. P. Kisil', *J. Fluorine Chem.*, 1999, **94**, 83.
68. C. K. Ghosh and A. A. Chakraborty, *ARKIVOC*, 2016, **i**, 111.
69. M. Y. Kornev and V. Y. Sosnovskikh, *Chem. Heterocycl. Compd.*, 2016, **52**, 71.
70. A. Szulawska-Mroczek, M. Szumilak, M. Szczesio, A. Olczak, R. B. Nazarski, W. Lewgowd, M. Czyz, and A. Stanczak, *Arch. Pharm. Chem. Life Sci.*, 2013, **346**, 34.
71. M. Y. Kornev, D. S. Tishin, D. L. Obydennov, and V. Y. Sosnovskikh, *Mendeleev Commun.*, 2020, **30**, 233.
72. S. P. Kisil, Y. V. Burgart, and V. I. Saloutin, *Russ. J. Org. Chem.*, 2001, **37**, 1455.
73. I. T. Bazyl', S. P. Kisil', S. N. Frolov, Y. V. Burgart, and V. I. Saloutin, *Russ. Chem. Bull., Int. Ed.*, 1999, **48**, 1537.
74. K. V. Shcherbakov, Y. V. Burgart, and V. I. Saloutin, *Russ. J. Org. Chem.*, 2013, **49**, 719.
75. K. V. Shcherbakov, Y. V. Burgart, and V. I. Saloutin, *Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 2157.
76. E. Budzisz, M. Malecka, and B. Nawrot, *Tetrahedron*, 2004, **60**, 1749.
77. D. L. Obydennov, A. I. El-Tantawy, M. Y. Kornev, and V. Y. Sosnovskikh, *Mendeleev Commun.*, 2019, **29**, 234.
78. H. Cai, H. D. Khanal, and Y. R. Lee, *Asian J. Org. Chem.*, 2021, **10**, 827.

79. K. C. Majumdar, P. K. Choudhury, and M. Nethaji, *Tetrahedron Lett.*, 1994, **35**, 5927.

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