HETEROCYCLES, Vol. 94, No. 3, 2017, pp. 389 - 440. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 2nd November, 2016, Accepted, 11th January, 2017, Published online, 21st March, 2017
DOI: 10.3987/REV-16-852

CHEMICAL REACTIONS OF FUROCHROMONES, VISNAGIN AND KHELLIN

Magdy A. Ibrahim, Al Shimaa Badran,* Nasser M. El-Gohary, and Noura A. Abdel-fatah

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, 11711, Cairo, Egypt; *E-mail: badran.shimaa@yahoo.com

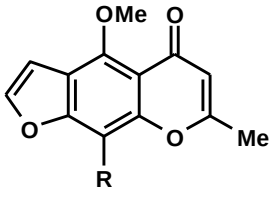
Abstract – This review represents the chemical reactivity of the natural products visnagin and khellin towards various chemical reactions, as well as summarizes the chemical behavior of some related compounds obtained from the rupture of the furan and γ-pyrone rings. In addition, the chemical reactivity of 6-formylnorvisnagin and 6-formylnorkhellin was summarized towards a variety of nucleophilic reagents.

CONTENTS

1. INTRODUCTION

Furochromone derivatives (visnagin and khellin) are important synthetic targets which showed a many of interesting biological activities. *Ammi visnaga* (Umbelliferae) is the most famous source of these derivatives. *Ammi visnaga* L., a common annual herbaceous plant which belongs to the family umbelliferea, grow freely in the waste lands of the Eastern Mediterranean and has been successfully cultivated in the colder climate of Minnesota. It is commonly known in Egypt by the name khella Baladi Chala or Khella in distinction from *Ammi majus* L., commonly known as khella shitani.[1,2]

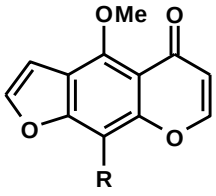
The present literature survey aimed to highlight the chemical reactivity of the natural products visnagin [4-methoxy-5-oxo-7-methylfuro[3,2-*g*][1]benzopyran] (**1a**) and khellin [4,9-dimethoxy-5-oxo-7-methyl-furo[3,2-*g*][1]benzopyran] (**1b**), in addition to their important derivative towards a variety of chemical reagents. Visnagin and khellin without methyl group at position 7 are known as norvisnagin (**2a**) and norkhellin (**2b**). Benzofurans obtained after degradation of the γ-pyrone ring are known as visnaginone (**3a**) and khellinone (**3b**).[3]



1

a; R=H (visnagin)

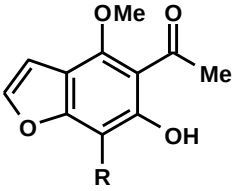
b; R=OMe (khellin)



2

a; R=H (norvisnagin)

b; R=OMe (norkhellin)



3

a; R=H (visnaginone)

b; R=OMe (khellinone)

2. REACTION OF VISNAGIN AND KHELLIN

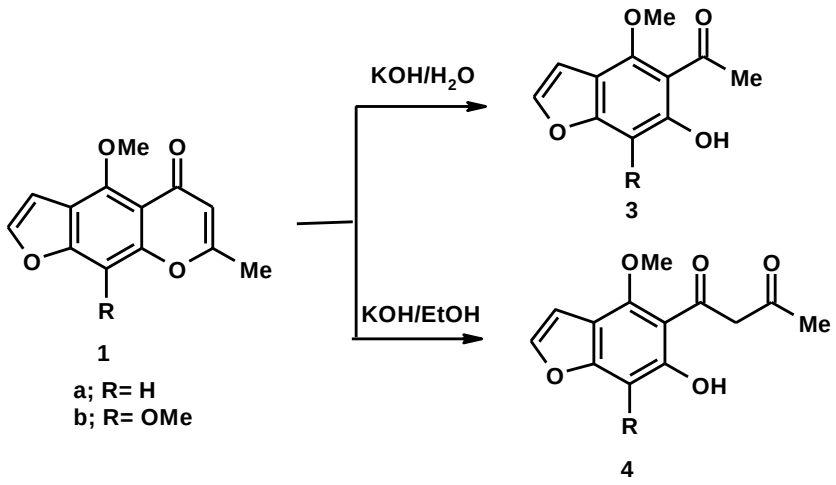
2.1. Color reactions

Visnagin (**1a**) and khellin (**1b**) give color reactions with a number of reagents. These colors are of particular interest since they can be used as a mean for differentiation and sometimes for isolation. Khellin gives intense reddish-violet color with potassium or sodium hydroxide pellets, this reaction has

been developed for colorimetric estimation.[4,5,6] However, this color reaction is not specific for khellin, since visnagin and other 2-methylchromones give the same test.[7] Also, Schönberg and Sidky[8,9] found that both visnagin and khellin give an intense reddish-violet colour with *m*-dinitrobenzene and alkali.

2.2. Action of alkali

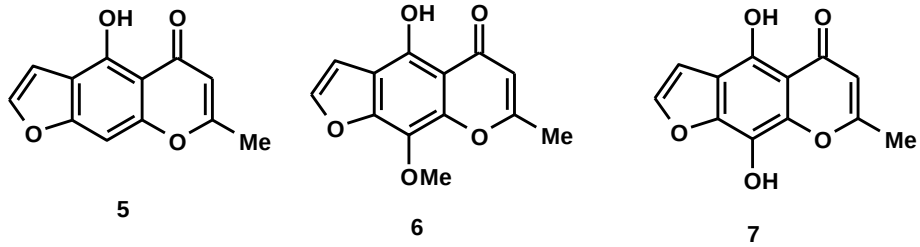
The naturally occurring furochromones, visnagin (**1a**) and khellin (**1b**), are very sensitive to alkali due to the presence of γ-pyrone ring. Aqueous alkaline hydrolysis of visnagin (**1a**) and khellin (**1b**) using potassium hydroxide (10%) afforded visnaginone (**3a**) and khellinone (**3b**), respectively. While, with alcoholic potassium hydroxide (3%) yielded different products known as ω-acetovisnaginone (**4a**) and ω-acetokhellinone (**4b**) (Scheme 1).[10,11]



Scheme 1

2.3. Demethylation

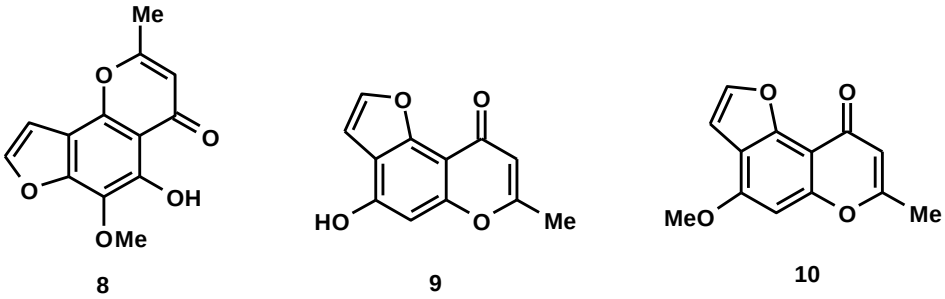
Visnagin (**1a**) and khellin (**1b**) are demethylated with several reagents producing a variety of products. Treating visnagin (**1a**) with dilute hydrochloric acid afforded the simple demethylated product **5**.[12] Khellin (**1b**) was partial demethylated using aniline hydrochloride affording 4-hydroxy-5-oxo-9-methoxy-furo[3,2-*g*][1]benzopyran (**6**).[13] Also, demethylated products **5** and **6** were obtained from demethylation



Scheme 2

of visnagin (**1a**) and khellin (**1b**) using thiophenol and/or *p*-thiocresol[14] or aluminium isopropoxide.[15] Demethylation of khellin (**1b**) using two equivalents of magnesium iodide in dry toluene followed by decomposition with dilute sulfuric acid yielded 4,9-dihydroxy-7-methylfuro[3,2-*g*][1]benzopyran (**7**) which is called khellinquinol (Scheme 2).[16]

Demethylation of khellin (**1b**) with hydrogen iodide or moderately concentrated hydrobromic acid is accompanied by the simultaneous rearrangement through opening of the γ-pyrone ring and its subsequent closure on the hydroxyl group at position-4 to give isovisnagin **8**, which upon methylation using methyl iodide afforded isokhellin (Scheme 3).[17] Clarke *et al*.[18] reported that, during the demethylation of visnagine (**1a**) with hydroiodic acid, the furan ring undergoes rearrangement to form norisovisnagin **9**. The structure of the latter compound is confirmed by synthesis of isovisnagin **10**, through methylation using methyl iodide (Scheme 3).



8 **9** **10**

Scheme 3

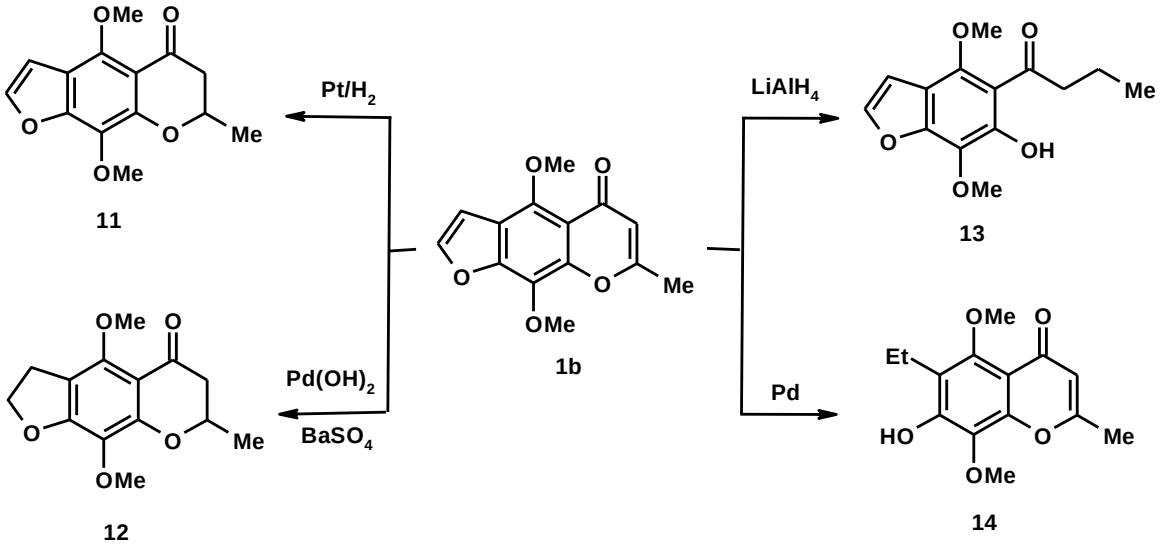
2.4. Reduction

Reduction of khellin **1b** afforded different types of products **11-14** depending on the reducing agents which are used.[19,20] Reduction using Pt/H_2 afforded furo[3`,2`:6,7]chromanone derivative **11**, while in the presence of $Pd(OH)_2/BaSO_4$ produced 4`,5`-dihydrofuro[3`,2`:6,7]chromanone **12**. On the other hand, reduction of khellin **1b** using $LiAlH_4$ resulted in reduction of γ-pyrone ring with ring opening producing compound **13**, while furan ring was reduced and opened by Pd giving 7-hydroxy-5,8-dimethoxy-2-methyl-6-ethylchromone **14** (Scheme 4).

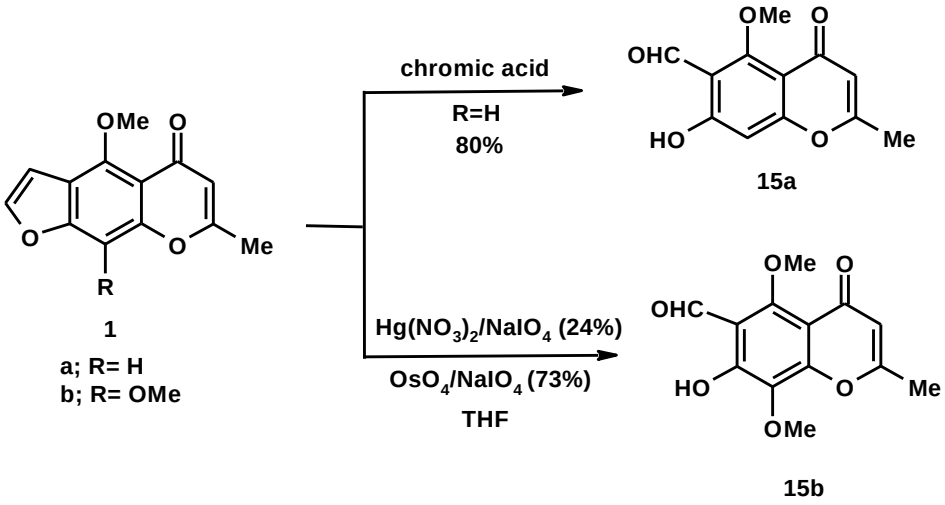
2.5. Oxidation

Oxidation of visnagin (**1a**) with chromic acid (10% potassium dichromate and 10% H_2SO_4) at 60-70 °C gives 6-formyl-7-hydroxy-5-methoxy-2-methylchromone (**15a**), in good yield.[3,21] Whereas, oxidation of khellin (**1b**) with chromic acid under the same conditions was failed to produce the corresponding hydroxy aldehyde derivative **15b**. Catalytic oxidation of khellin (**1b**) using mercuric(II) nitrate in

tetrahydrofuran (THF) followed by treatment with sodium periodate gives 6-formyl-7-hydroxy-5,8-dimethoxy-2-methylchromone (**15b**) in 24% yield. While oxidation using osmium tetroxide in the presence of sodium periodate in THF at 50 °C gave the hydroxy aldehyde **15b** in 73% yield (Scheme 5).[21,22]

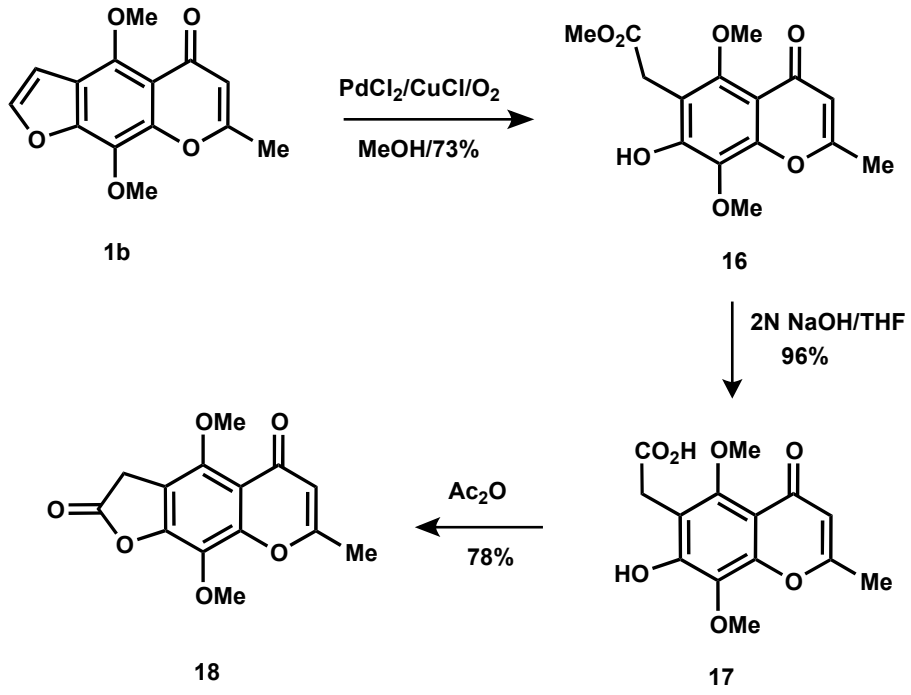


Scheme 4



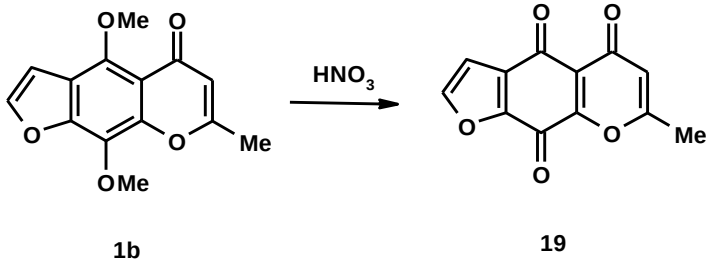
Scheme 5

The catalytic oxidation of khellin (**1b**) using palladium chloride under oxygen in the presence of CuCl in methanol afforded the hydroxy ester **16**, which upon basis hydrolysis using 2N aqueous NaOH at room temperature afforded the corresponding acetic acid derivative **17**. Cyclization of compound **17** in boiling acetic anhydride produced the lactone derivative **18** (Scheme 6).[21]



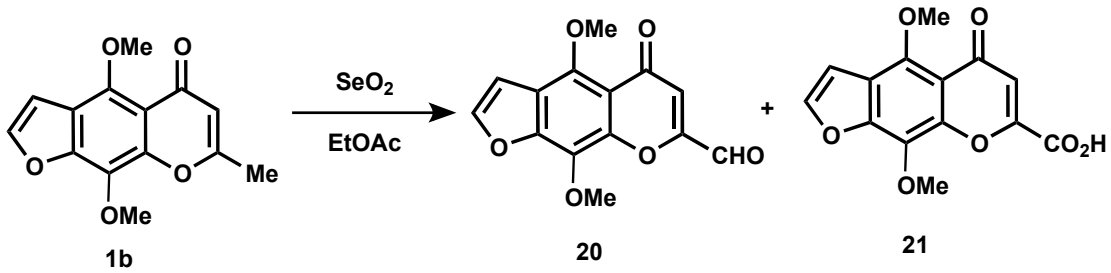
Scheme 6

Oxidative demethylation of khellin (**1b**) using concentrated nitric acid yielded the corresponding furochromone-5,8-quinone **19** (Scheme 7).[12,13,23]



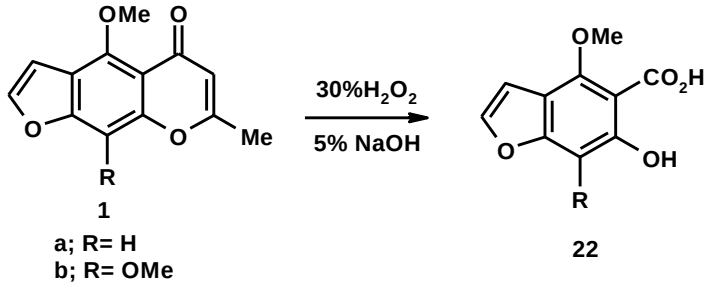
Scheme 7

Oxidation of khellin (**1b**) with selenium dioxide in ethyl acetate gave a mixture of the corresponding aldehyde **20** and carboxylic acid **21** (Scheme 8).[24]



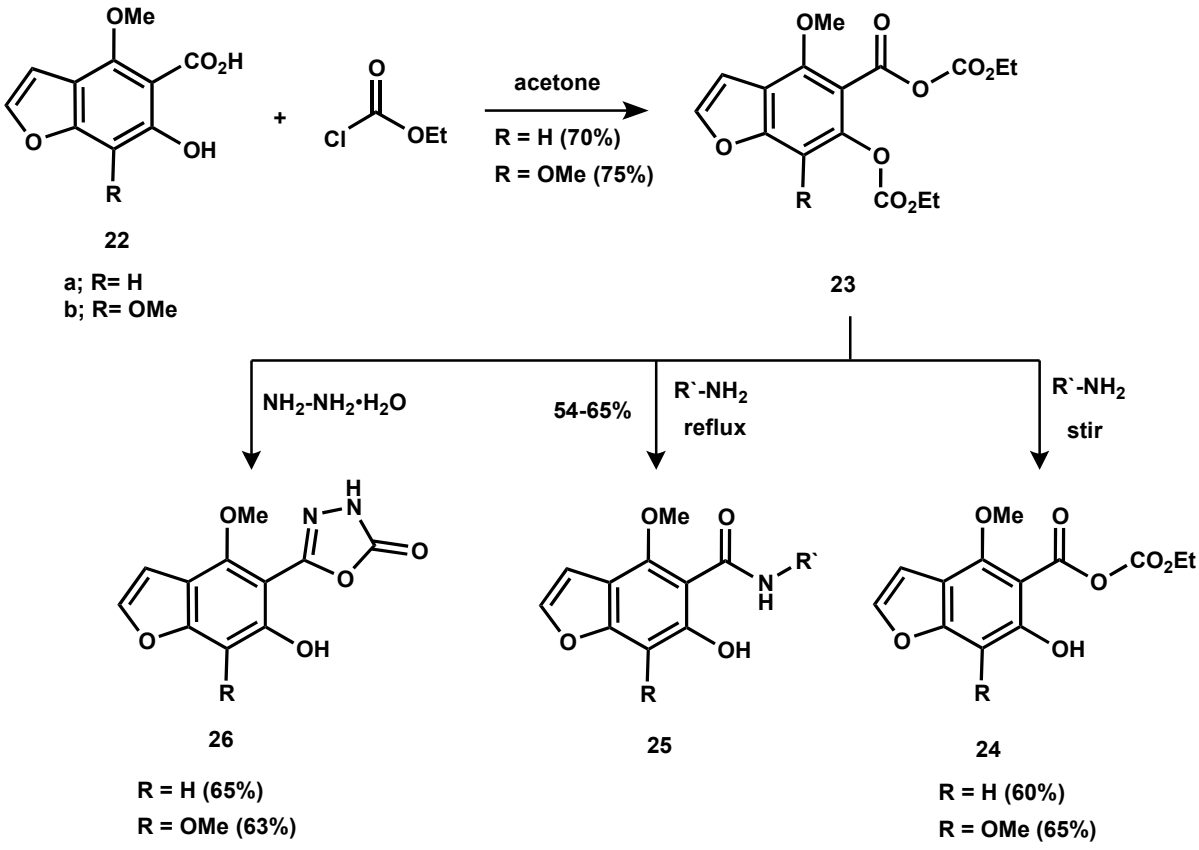
Scheme 8

Controlled oxidation of visnagin (**1a**) and khellin (**1b**) with hydrogen peroxide in presence of alkali gave the corresponding 4-methoxy/4,7-dimethoxy- 6-hydroxybenzofuran-5-carboxylic acids (**22**) (Scheme 9).[3]



Scheme 9

On treating the sodium salt of the latter compounds **22** with ethyl chloroformate in dry acetone, the corresponding dicarboxy derivatives **23** are obtained.[25] Reaction of dicarboxy derivative **23** with some amines under stirring conditions at room temperature produced the mono-carboxy derivative **24**, while repeating the reaction under reflux afforded the carboxamide derivative **25**. Treating the dicarboxy derivative **23** with hydrazine hydrate proceeds *via* the initial hydrolysis of the ester group at position 6

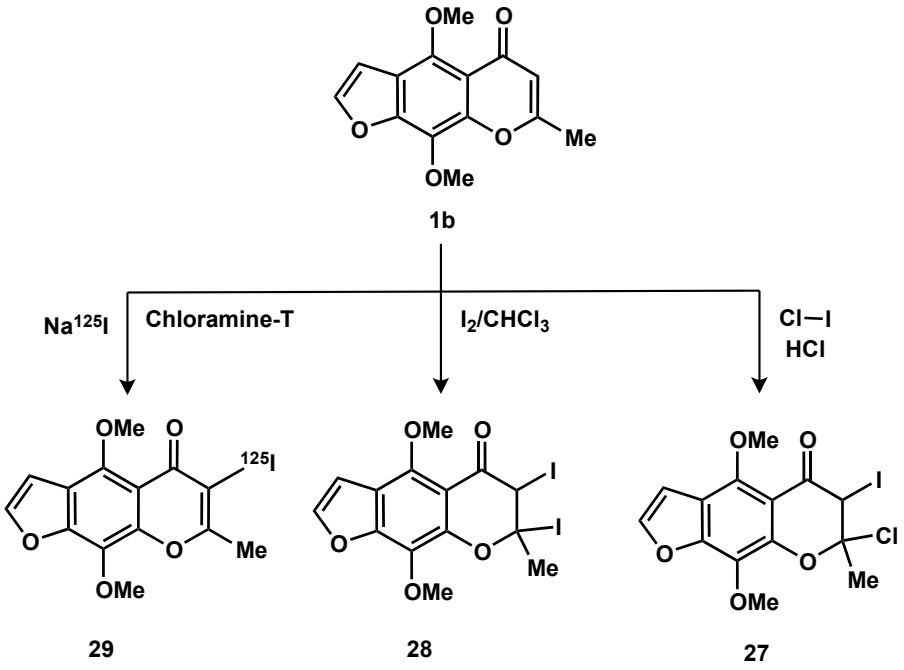


Scheme 10

followed by the formation of the corresponding hydrazides (non-isolable) which spontaneously cyclized to afford 5-substituted-2,3-dihydro-1,3,4-oxadiazol-3-one (**26**) (Scheme 10).[25]

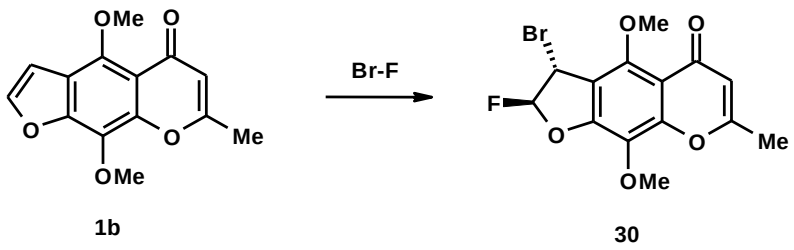
2.6. Addition reactions

The addition of iodine monochloride solution in hydrochloric acid to a cold solution of khellin (**1b**) in acetic acid afforded 7-chloro-7-methyl-6-iodo-4,9-dimethoxy-6,7-dihydro-5*H*-furo[3,2-*g*][1]benzofuran-5-one (**27**), similarly 7-methyl-6,7-diiodo-4,9-dimethoxy-6,7-dihydro-5*H*-furo[3,2-*g*][1]benzofuran-5-one (**28**) was prepared by addition of iodine to solution of khellin in chloroform.[19] Meanwhile, radio-iodination of khellin (**1b**) using ^{125}I was found to proceed through electrophilic substitution reaction yielding 6-iodonated khellin **29** which used for urinary tract imaging (Scheme 11).[26]



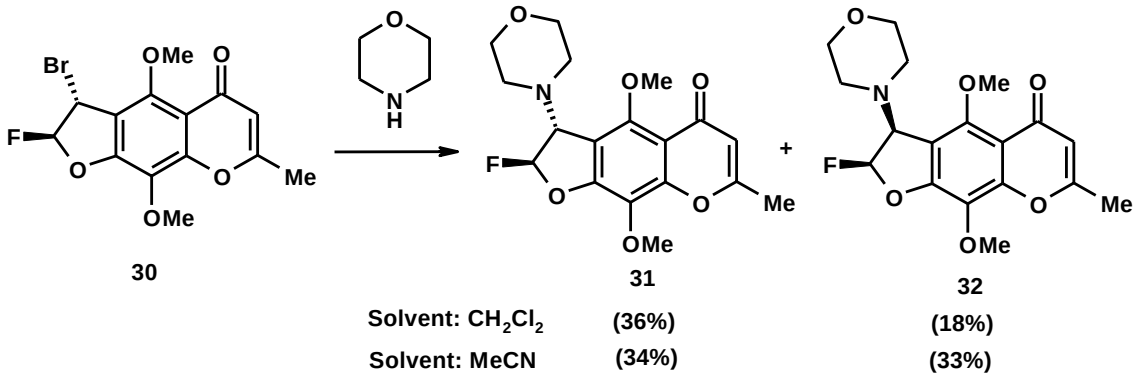
Scheme 11

On the other hand, Nash and Gammill reported that, bromofluorination of khellin (**1b**) with BrF (HF/dibromotin/THF/CH_2Cl_2) (84%) or poly HF/NBS/CH_2Cl_2 (82%) afforded *trans*-3-bromo-2-fluoro-2,3-dihydrokhellin (**30**), in excellent yield (Scheme 12).[27]



Scheme 12

Addition of morpholine to compound **30** afforded *cis*/*trans* mixture of compounds **31**,**32** and the product distribution was influenced to some extent by the solvent used (Scheme 13).[27]

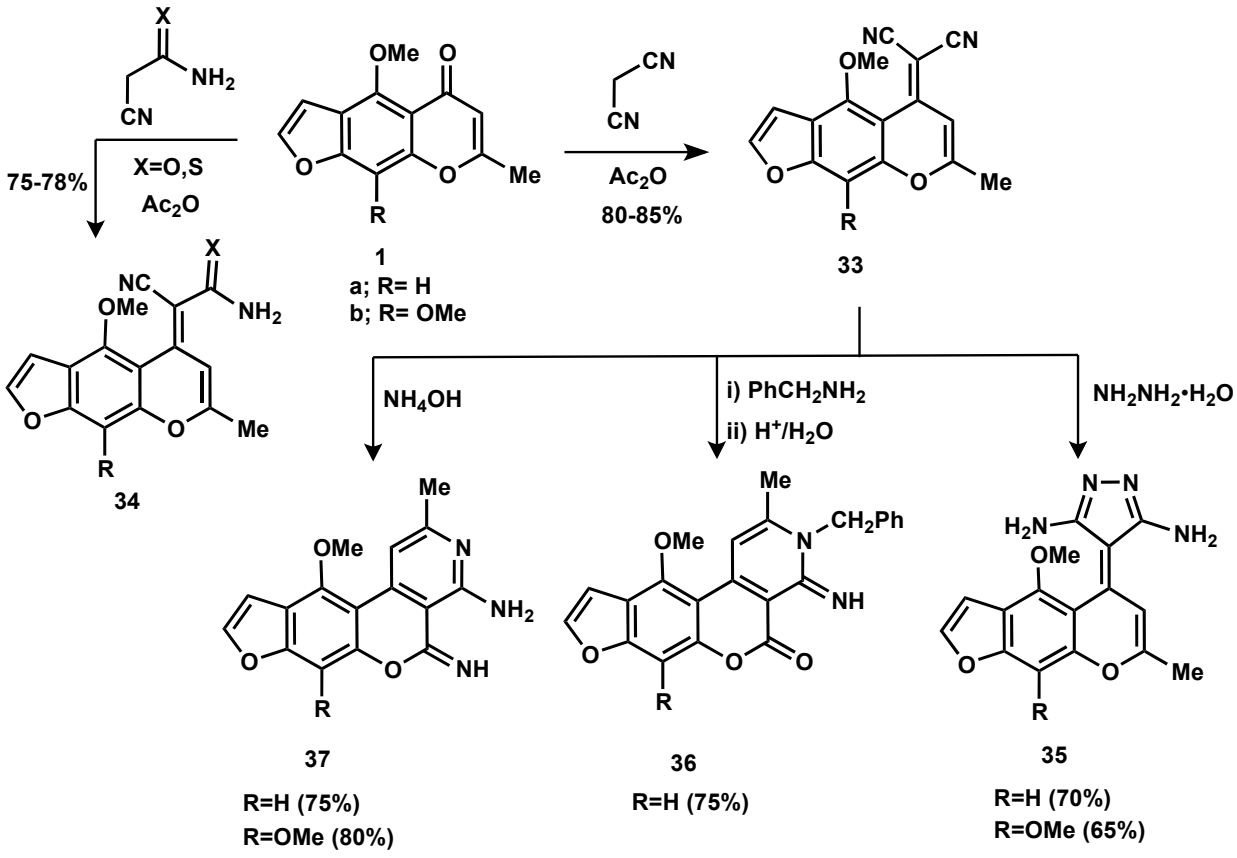


Scheme 13

2.7. Condensation reactions

2.7.1. Reactions of carbonyl group

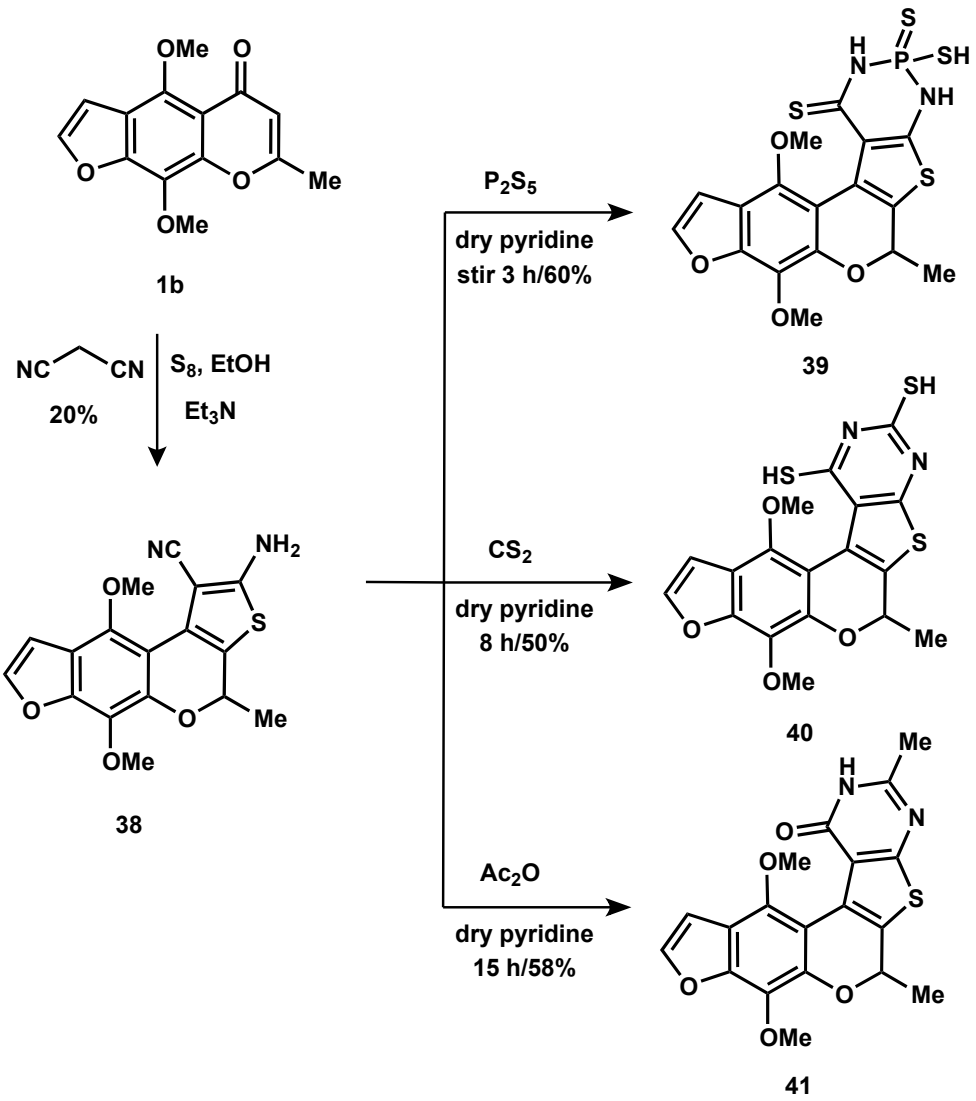
Condensation reaction of visnagin (**1a**) and khellin (**1b**) with malononitrile, cyanoacetamide and/or cyanothioacetamide[28,29] proceed *via* condensation of active methylene group with the γ-pyrone carbonyl group, affording the corresponding condensation products **33** and **34**, respectively. Treating compound **33**



Scheme 14

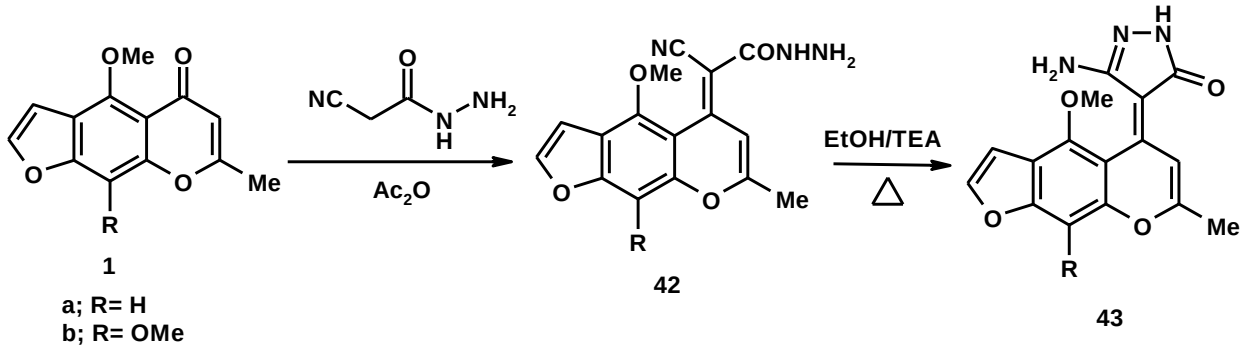
with hydrazine hydrate in boiling ethanol gave the 4-(4-methoxy/4,9-dimethoxy-7-methyl-5*H*-furo-[3,2-*g*][1]benzopyran-5-ylidene)-4*H*-pyrazole-3,5-diamine (**35**),[29] while treating compound **33** with benzylamine followed by acid hydrolysis afforded furo[3`,2`:6,7][1]benzopyrano[3,4-*c*]pyridin-5-one **36**.[29] Also, heating ylidenenitrile **33** with ammonia solution afforded furobenzopyranopyridine **37** (Scheme 14).[29]

Reaction of khellin (**1b**) with malononitrile in the presence of sulfur resulted in the formation of thienopyrane derivative **38**. Compound **38** reacted with phosphorus pentasulphide in dry pyridine forming thienophosphadiazine derivative **39**, while reaction of compound **38** with carbon disulfide and/or acetic anhydride in dry pyridine under reflux provided thienopyrimidine derivatives **40** and **41**, respectively (Scheme 15).[30]



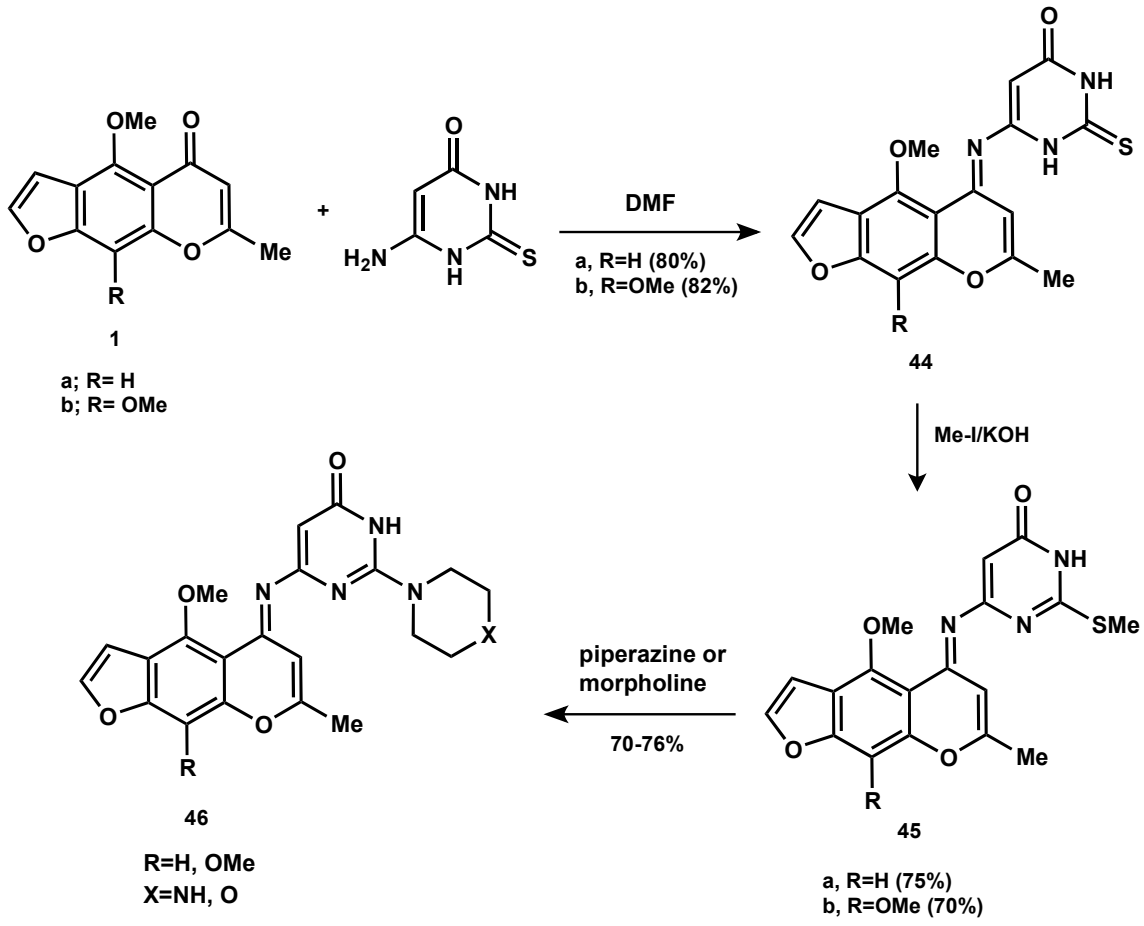
Scheme 15

Also, visnagin (**1a**) and khellin (**1b**) reacted with 2-cyanoacetohydrazide in acetic anhydride to give the condensation products **42**. Cyclization of the latter compounds upon heating in ethanol containing triethylamine gave furochromenylidenepyrazolone **43** (Scheme 16).[28]



Scheme 16

Condensation of visnagen (**1a**) and khellin (**1b**) with 6-aminothiouracil in DMF yielded 6-(((4-methoxy/4,9-dimethoxy)-7-methylfuro[3,2-*g*]chromen-5-ylidene)amino)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-ones (**44**). Compounds **44** reacted with methyl iodide in aqueous ethanolic KOH solution to

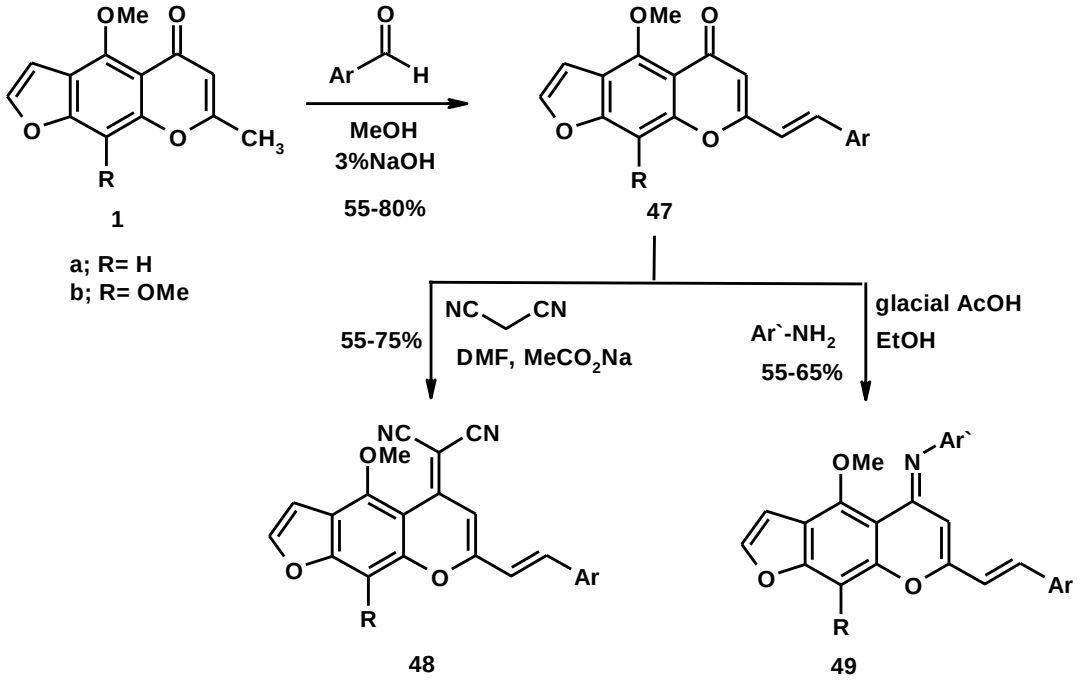


Scheme 17

afford the corresponding *S*-methylated product **45**. Reaction of the 2-methylsulfanyl derivatives **45** with secondary aliphatic amines, namely piperazine and morpholine, in methanol produced the yielded 2-((piperazin/morpholin)-1-yl)pyrimidin-4-ones **46** (Scheme 17).[31]

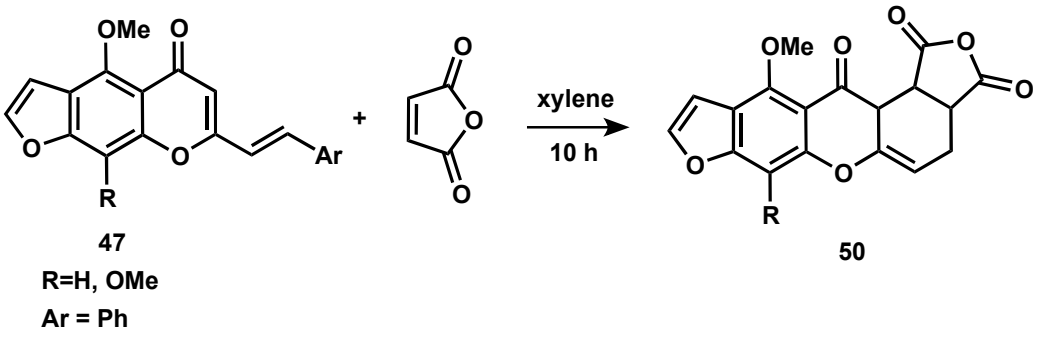
2.7.2. Reactions of methyl group

Reaction of visnagen (**1a**) and khellin (**1b**) with different aromatic aldehydes in methanol in the presence of 3% sodium hydroxide solution gave the corresponding condensation products **47**, *via* condensation of the aldehyde group with the active methyl group at the position 7 of visnagen (**1a**) and khellin (**1b**). The formation of dicyano derivatives **48** was achieved through Knoevenagel condensation of arylvinyl derivatives **47** with malononitrile, in DMF in the presence of sodium acetate. The carbonyl functional group in compounds **47** has been utilized to synthesize the corresponding imine derivatives **49** through the reaction with different primary amines in absolute ethanol in the presence of glacial acetic acid (Scheme 18).[32]



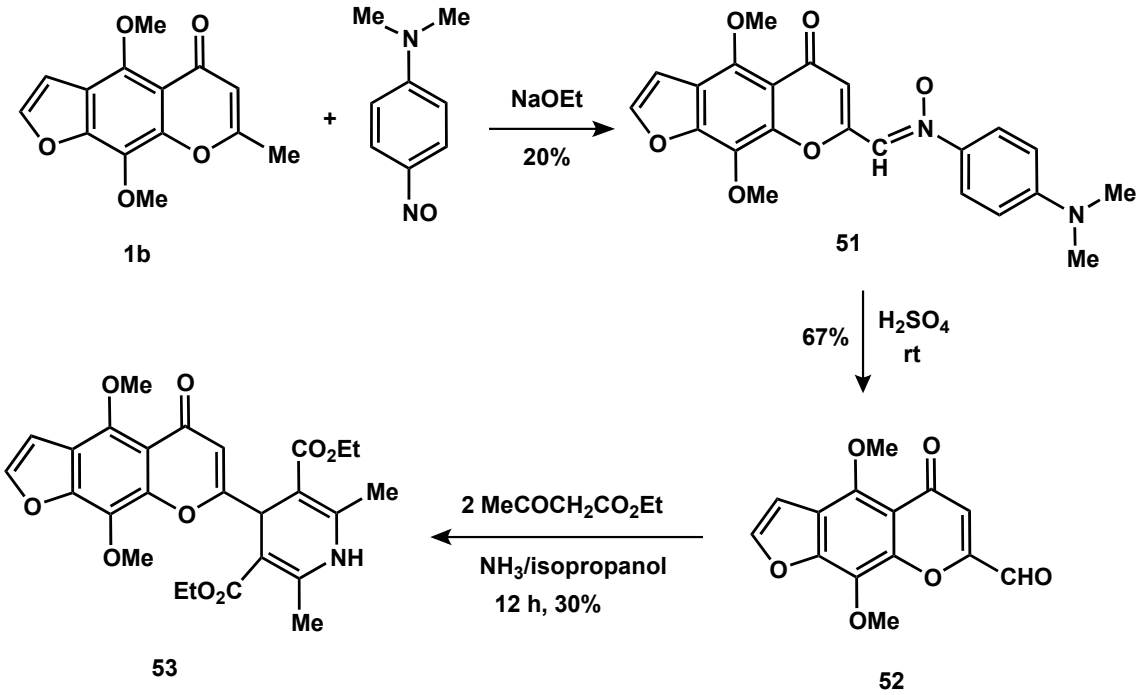
Scheme 18

Diels-Alder reaction between 7-styrylvisnagin **47a** and 7-styrylkhellin **47b** as diene with maleic anhydride as dienophile in boiling xylene led to the Diels-Alder adducts which were identified as 5a,6,7,8-tetrahydro-4-methoxy/4,11-dimethoxy-5*H*-5-oxofuro[3,2-*b*]xanthene-6,7-dicarboxylic anhydride (**50**) (Scheme 19).[33]



Scheme 19

Condensation of khellin (**1b**) with 4-nitrosodimethylaniline in the presence of sodium ethoxide afforded nitrone derivative **51**. Hydrolysis of the latter compound with 5*M* sulfuric acid at room temperature gave furochromone-2-carboxaldehyde **52**. Dihydropyridine-3,5-dicarboxylate **53** was prepared using the Hantzsch reaction, *via* the reaction of aldehyde **52** with two equivalents of ethyl acetoacetate and ammonia, in isopropanol under reflux (Scheme 20).[34]

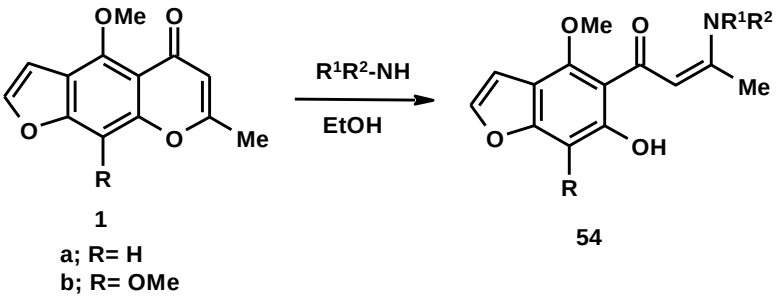


Scheme 20

2.8. Reactions with nitrogen nucleophiles

2.8.1. Ring opening reactions

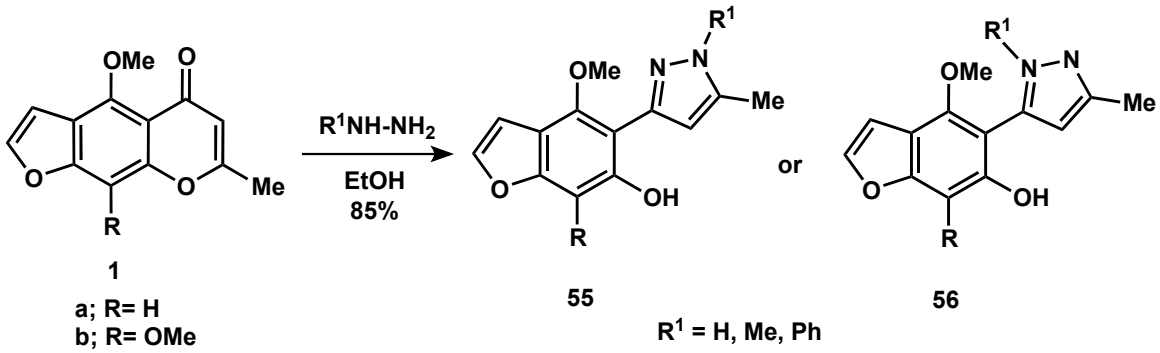
Visnagin (**1a**) and khellin (**1b**) reacted with primary and secondary aliphatic amines in refluxing ethanol gave enaminoketones **54**, through nucleophilic attack at C-7 with γ-pyrone ring fission (Scheme 21).[35,36]



Scheme 21

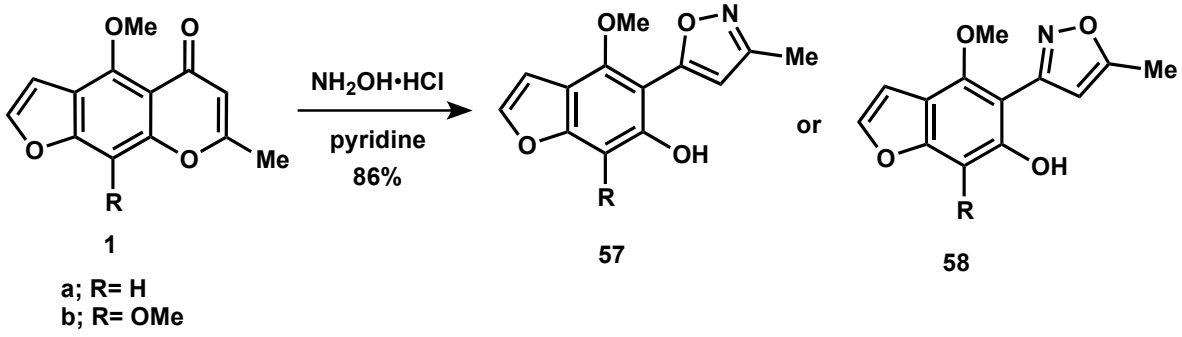
2.8.2. Ring opening and ring closure (RORC) reactions

Visnagin (**1a**) and khellin (**1b**) react with hydrazine hydrate and its derivatives and the products may be pyrazole derivatives **55** or **56**, the reaction proceeds through simultaneous opening of the γ-pyrone ring, followed by intramolecular cyclization (Scheme 22).[9]



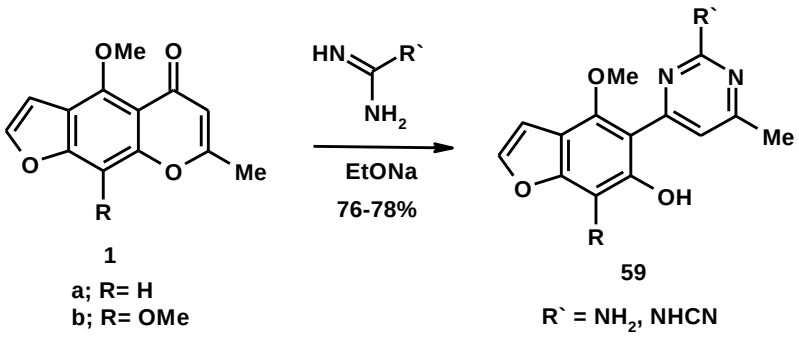
Scheme 22

Similarly, reaction of visnagin (**1a**) and khellin (**1b**) with hydroxylamine hydrochloride in boiling pyridine formed the corresponding isoxazoles **57** or **58** (Scheme 23).[9,37]



Scheme 23

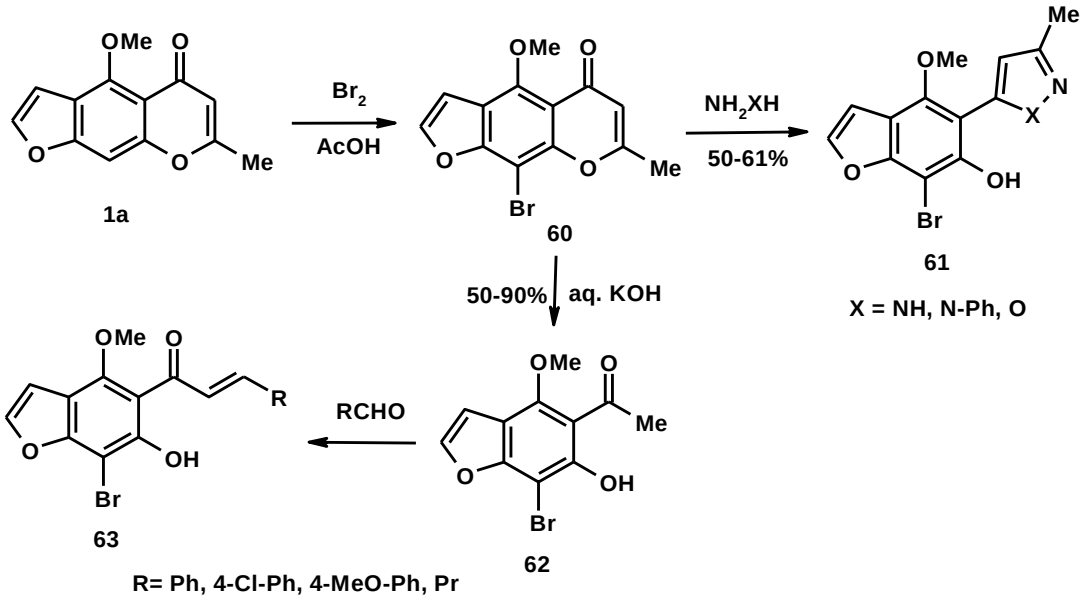
On the other hand, visnagin (**1a**) and khellin (**1b**) reacted with guanidine and/or cyanoguanidine in the presence of sodium ethoxide producing pyrimidine derivatives **59** (Scheme 24).[38]



Scheme 24

2.9. Electrophilic reactions

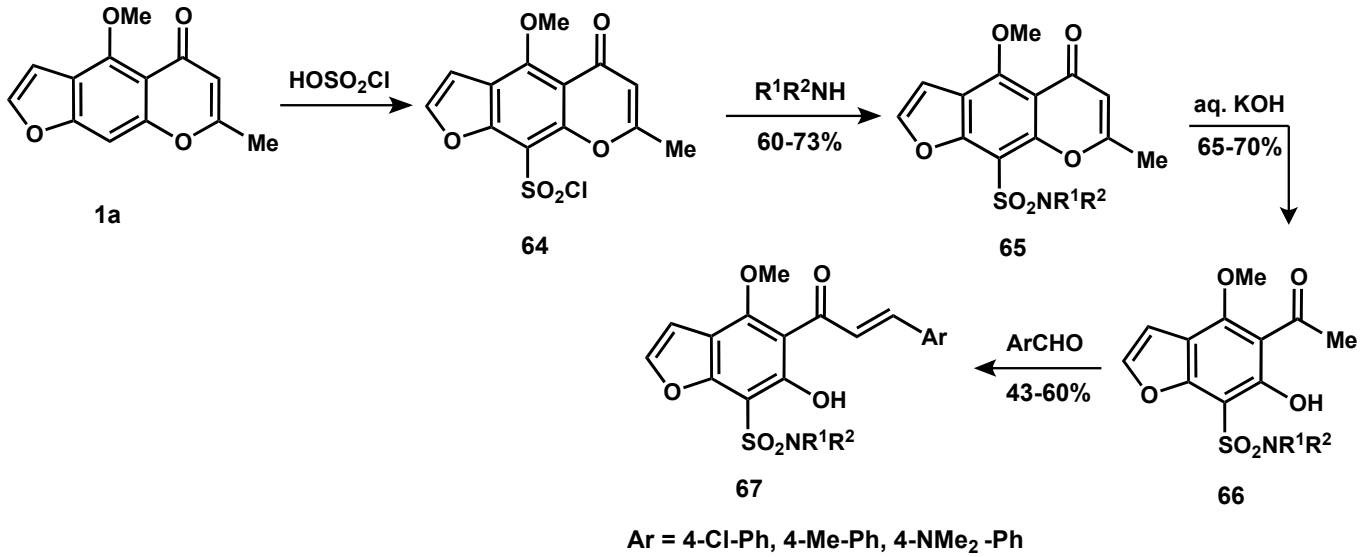
The preparation of bromovisnagine (**60**) was obtained by the bromination of visnagin (**1a**) using bromine in acetic acid. Ring opening and ring closure reaction of compound **60** with hydrazine hydrate, phenyl-hydrazine and/or hydroxylamine hydrochloride afforded the corresponding pyrazole and isoxazole derivatives **61**, respectively.[39] On the other hand, 4-methoxy-5-acetyl-6-hydroxy-7-bromobenzofuran (**62**) which was prepared by the alkaline hydrolysis of **60** followed by a retro-aldol reaction was condensed with some aromatic aldehydes namely, benzaldehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, and butyraldehyde to yield the corresponding α,β-unsaturated ketones **63** (Scheme 25).[39]



Scheme 25

Chlorosulfonation of visnagine (**1a**) using chlorosulfonic acid at room temperature without solvent yielded visnagin-9-sulfonyl chloride (**64**) which upon amidation using different primary and secondary amines in dioxane provided the new visnagin-9-sulfonamides **65**. Alkaline hydrolysis of the latter compound by 3% aqueous potassium hydroxide led to 4-methoxy-5-acetyl-6-hydroxy-

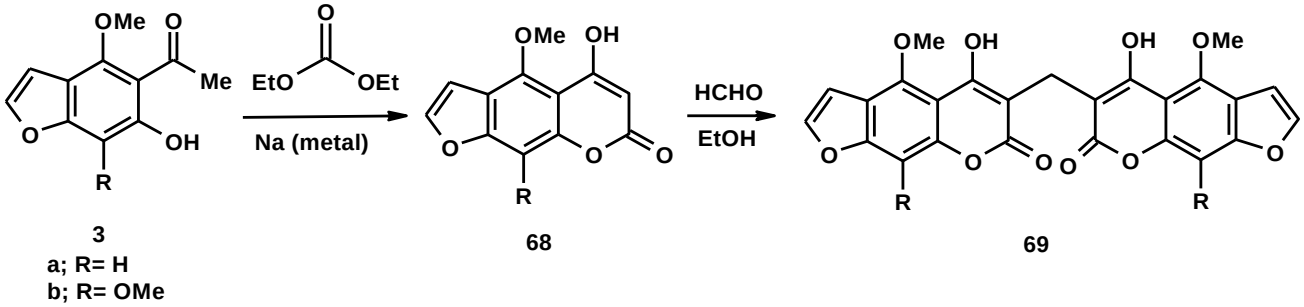
7-sulfonamidobenzofuran derivatives **66** which were condensed with some aromatic aldehydes namely, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, and dimethylaminobenzaldehyde in alkaline medium to yield the corresponding α,β-unsaturated keto derivatives **67** (Scheme 26).[39,40]



Scheme 26

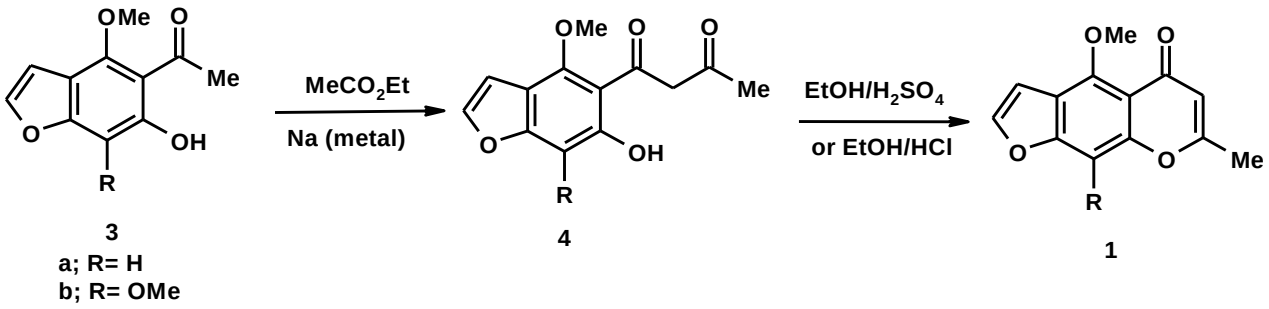
3. REACTIONS OF VISNAGINONE AND KHELLINONE

Condensation of visnaginone (**3a**) [6-hydroxy-4-methoxy-5-benzofuranyl methyl ketone] and khellinone (**3b**) [6-hydroxy-4,7-dimethoxy-5-benzofuranyl methyl ketone] with ethyl carbonate in the presence of sodium metal under reflux followed by acidification with dilute hydrochloric acid produced furocoumarine derivative **68**. Boiling 4-hydroxycoumaines **68** with 40% formaldehydes in ethanol afforded dicoumarol derivatives **69** (Scheme 27).[5]



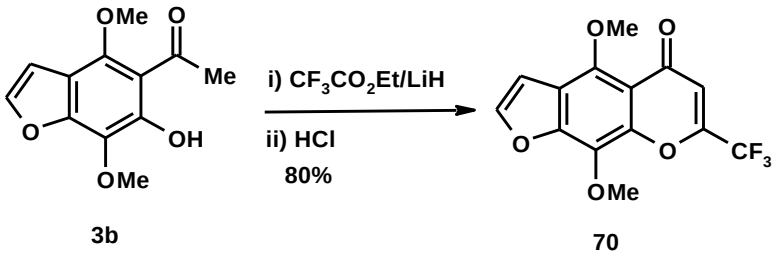
Scheme 27

Claisen condensation of visnaginone (**3a**) and khellinone (**3b**) with ethyl acetate in the presence of metallic sodium resulted in the formation of β-diketone derivatives **4** which underwent intramolecular cyclization under acidic condition producing visnagin (**1a**) and khellin (**1b**) (Scheme 28).[16,41]



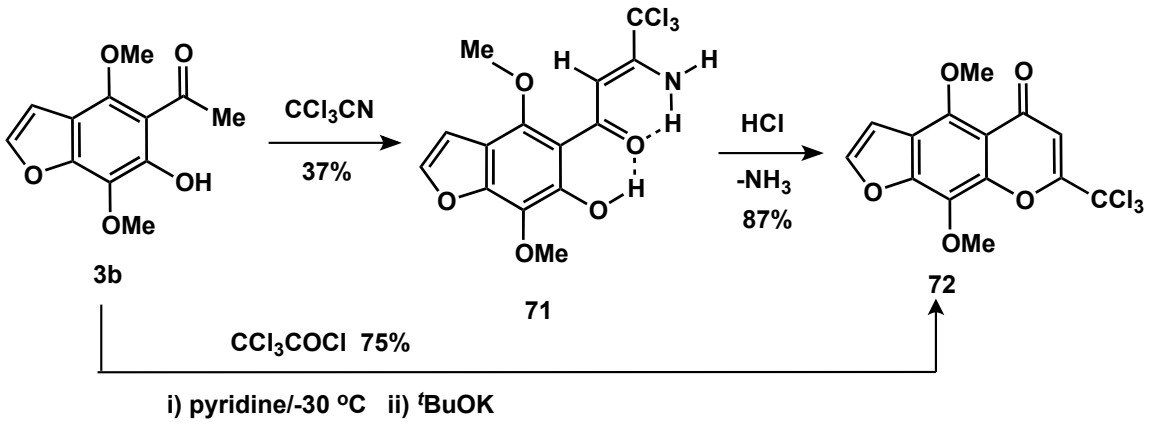
Scheme 28

Similarly, Claisen condensation of khellinone (**3b**), with ethyl trifluoroacetate in the presence of lithium hydride (LiH) in tetrahydrofuran followed by acidification with a catalytic amount of hydrochloric acid afforded 7-trifluoromethylnorkhellin (**70**) (Scheme 29).[42]



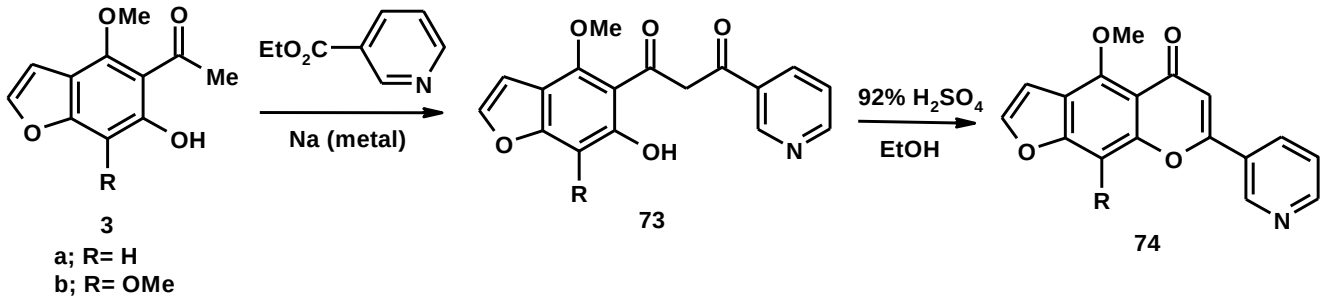
Scheme 29

In the same way, reaction of khellinone (**3b**) with trichloroacetonitrile in the presence of *N*-methylanilinomagnesium bromide afforded aminoenone derivative **71** which cyclized with concentrated HCl at room temperature to produce 7-trichloromethylnorkhellin (**72**).[42] The same product **72** was also synthesized, in 75% yield, from the reaction of khellinone (**3b**) with trichloroacetyl chloride in pyridine at -30 °C followed by treating the reaction mixture with potassium *tert*-butylate (Scheme 30).[43]



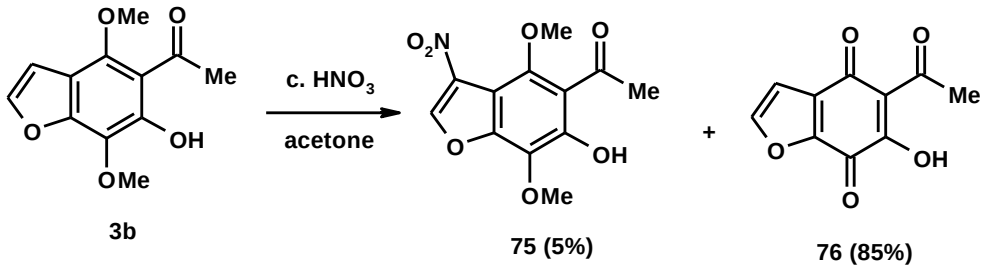
Scheme 30

Claisen condensation of visnaginone (**3a**) and khellinone (**3b**) with ethyl nicotinate produced 5-nicotinoylaceto-4-methoxy/4,7-dimethoxy-6-hydroxybenzofurans (**73**), which cyclized in ethanolic sulfuric acid to give 2-(pyrid-3-yl)furochromone derivatives **74** (Scheme 31).[6]



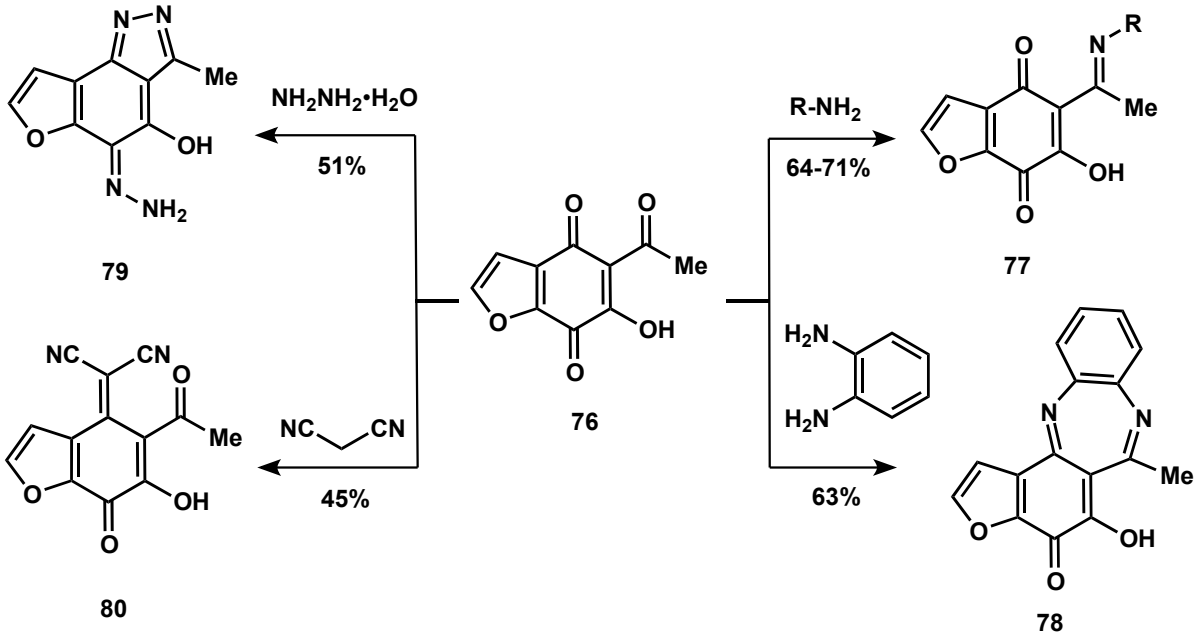
Scheme 31

Nitration of khellinone (**3b**) using concentrated nitric acid in dry acetone gave small amount of 3-nitrokhellinone (**75**) and 5-acetyl-6-hydroxybenzofuran-4,7-dione (khellinonequinone) (**76**) as a main product (Scheme 32).[44]



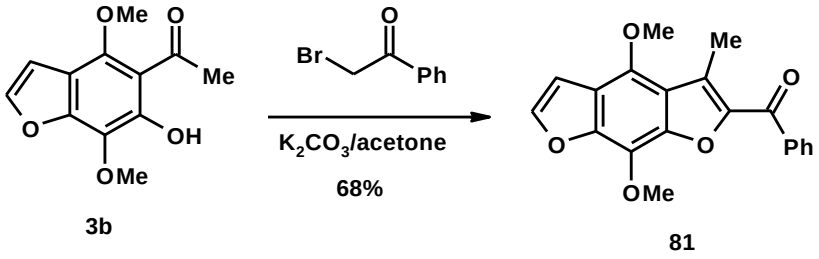
Scheme 32

Stirring khellinonequinone (**76**) with primaty amines at room temperature gave the corresponding imino compounds **77**. While, boiling khellinonequinone (**76**) with *o*-phenylenediamine in ethanol gave benzodiazepine derivative **78**, *via* condensation followed by cyclization. Pyrazolobenzofuran derivative **79** was obtained by the action of hydrazine hydrate on khellinonequinone (**76**). Stirring khellinonequinone (**76**) with malononitrile in ethanol at room temperature gave the ylidene derivative **80** (Scheme 33).[44]



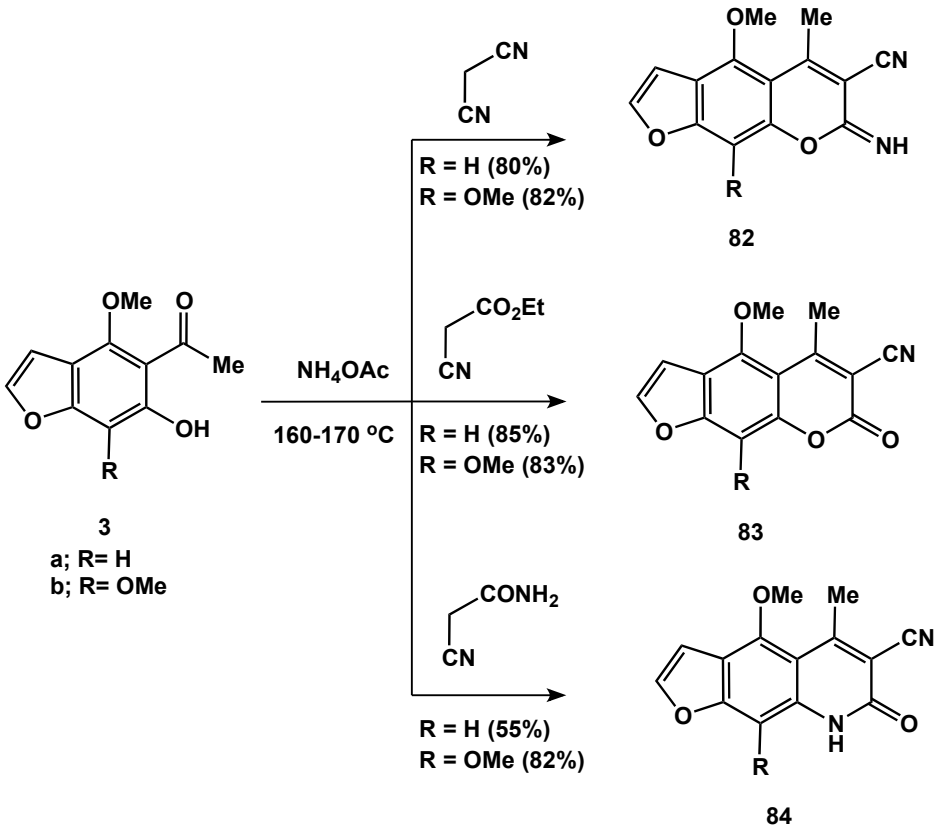
Scheme 33

Reacting khellinone (**3b**) with phenacyl bromide in boiling acetone in the presence of potassium carbonate afforded benzodifuran derivative **81** (Scheme 34).[21]



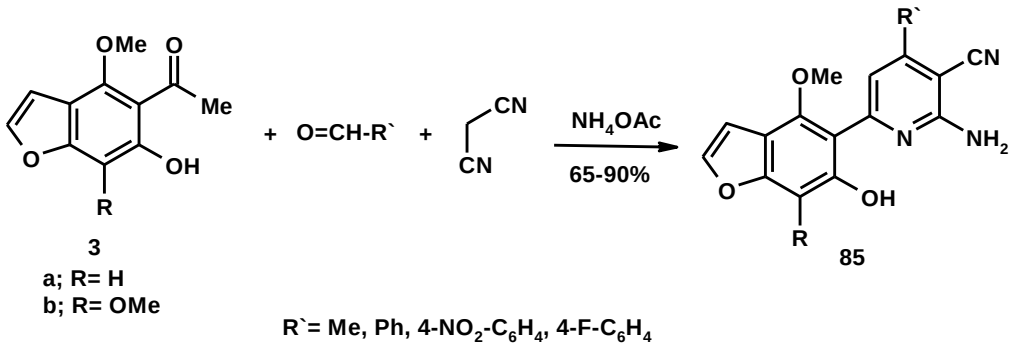
Scheme 34

Condensation of visnaginone (**3a**) and khellinone (**3b**) with malononitrile and ethyl cyanoacetate in the presence of ammonium acetate under fusion condition at 160-170 °C for 1 h afforded 6-cyano-7-imino-4-methoxy/4,9-dimethoxy-5-methyl-7*H*-furo[3,2-*g*]chromene (**82**) and 6-cyano-4-methoxy/4,9-dimethoxy-5-methyl-7*H*-furo[3,2-*g*]chromen-7-one (**83**). On the other hand, condensing visnaginone (**3a**) and khellinone (**3b**) with cyanoacetamide under the same condition gave the corresponding furo[3,2-*g*]quinolin-7-ones **84** (Scheme 35).[45]



Scheme 35

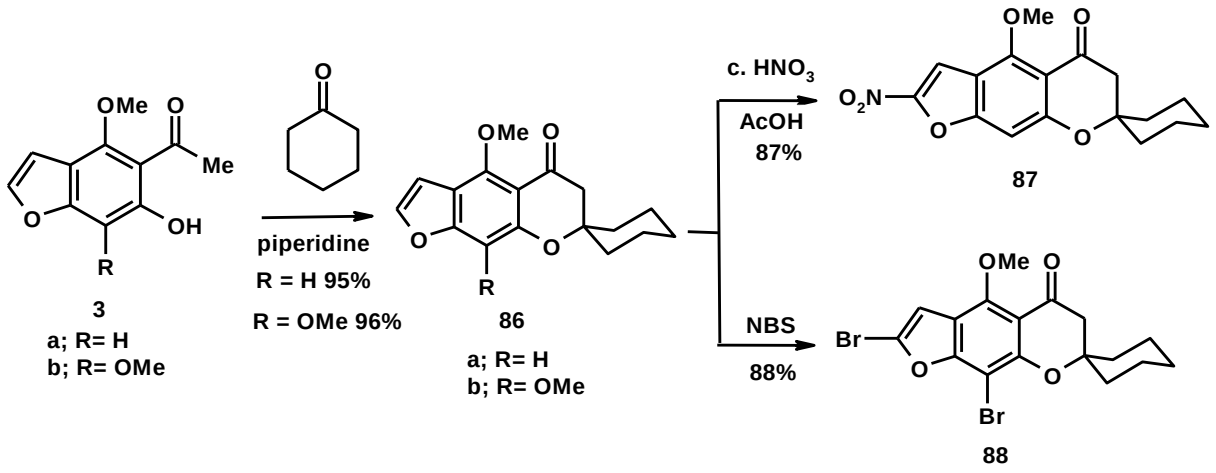
Reaction of visnaginone (**3a**) and khellinone (**3b**) with aldehydes and malononitrile in the presence of ammonium acetate at 160-170 °C for 1 h led to 2-amino-4-substituted pyridine-3-carbonitrile derivatives **85** (Scheme 36).[45]



Scheme 36

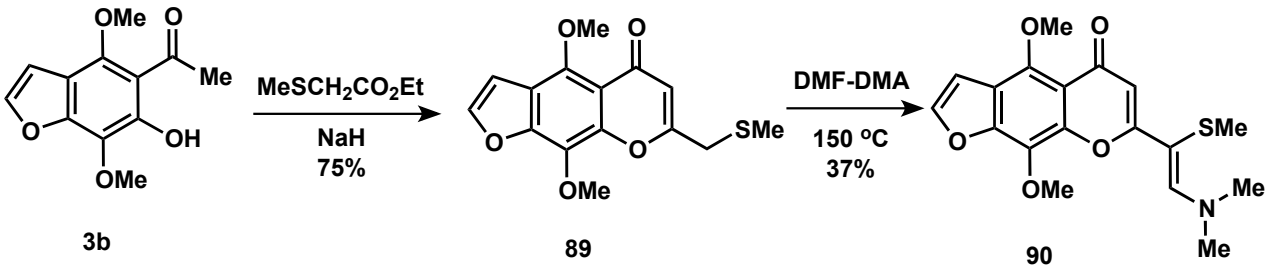
Spiro cyclization of visnaginone (**3a**) and khellinone (**3b**) with cyclohexanone in the presence of piperidine afforded the corresponding spiro furo[3,2-*g*][1]chromanone **86** in quantative yield. Nitration of compound **86a** (R=H) using nitric acid resulted in entering the nitro group at position 2 of furan ring producing 4-methoxy-2-nitro spiro furo[3,2-*g*][1]chromanone derivative **87**. Bromination of compound

86 with NBS in chloroform under reflux gave 2,9-dibromo spiro furo[3,2-*g*][1]chromanone derivative **88** (Scheme 37).[46]



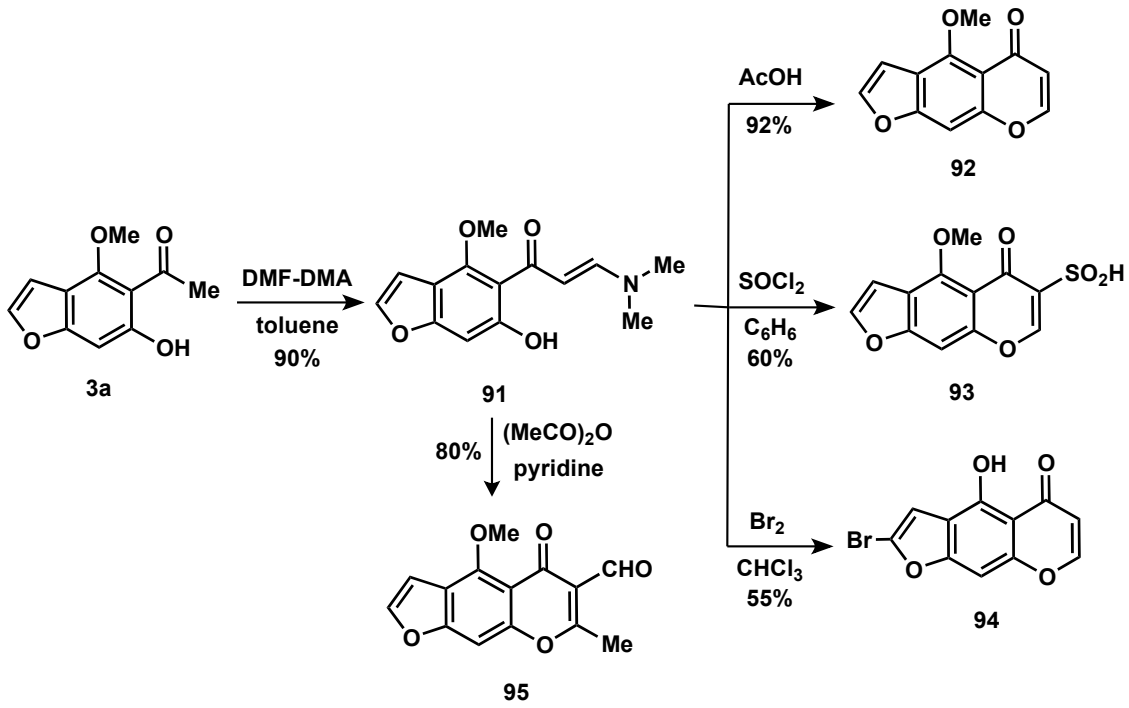
Scheme 37

Condensation of khellinone (**3b**) with ethyl 2-(methylthio)acetate in THF in the presence of sodium hydride afforded 4,9-dimethoxy-7-((methylthio)methyl)-5*H*-furo[3,2-*g*]chromen-5-one (**89**). Condensation of the latter compound **89** with dimetylformamide dimethyl acetal gave an enaminone derivative **90** (Scheme 38).[47]



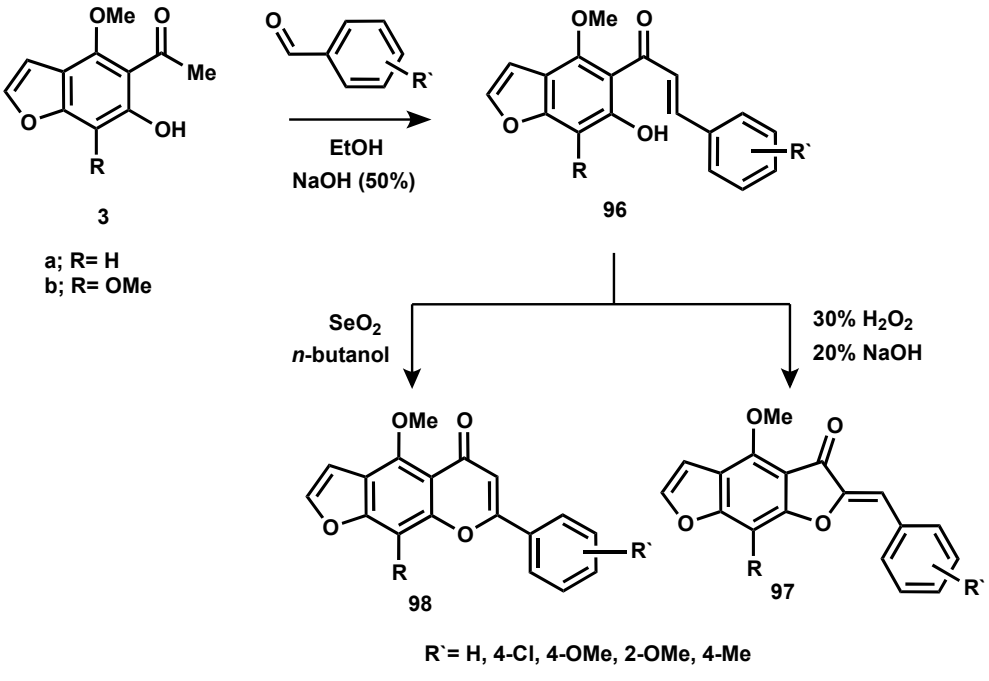
Scheme 38

Treatment of visnaginone (**3a**) with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in boiling toluene afforded the enaminone derivative **91**. Boiling the latter compound in acetic acid resulted in ring closure with elimination of dimethylamine, yielded norkhellin [4-methoxy-5*H*-furo[3,2-*g*]-[1]benzopyran-5-one] (**92**). Treatment of enaminone (**91**) with thionyl chlorid in dry benzene afforded the benzopyran-6-sulfinic acid **93**. Treatment of enaminone **91** with bromine at 40 °C afforded 2-bromo-4-hydroxy-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**94**). Acetylation of enaminone **91** with acetic anhydride afforded the carboxaldehyde **95** (Scheme 39).[48]



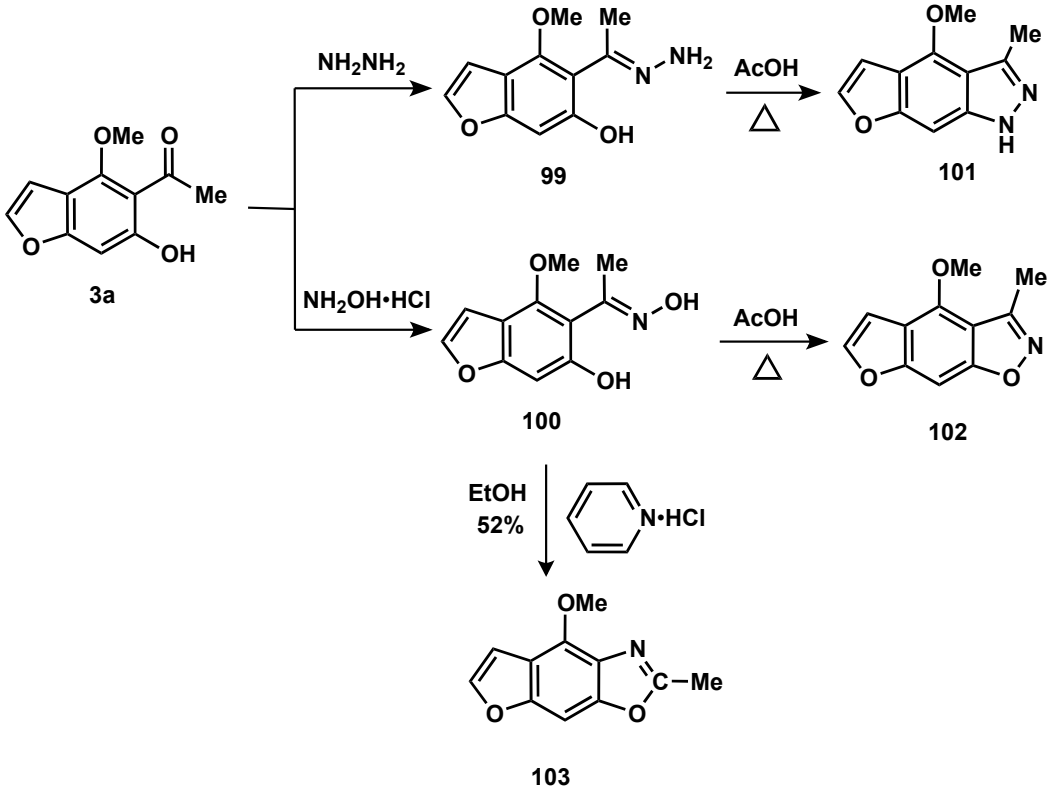
Scheme 39

Condensation of visnaginone (**3a**) and khellinone (**3b**) with some aromatic aldehydes in ethanol in the presence of aqueous sodium hydroxide (50%) led to the formation of the corresponding cinnamoyl derivatives (chalcones) **96**.[3,10,16,49,50] Oxidative cyclization of chalcones **96** using 30% H_2O_2 and 20% NaOH produced furoaurones **97**,[3,51] while oxidation using selenium dioxide in *n*-butanol under reflux gave furoflavones **98** (Scheme 40).[51]



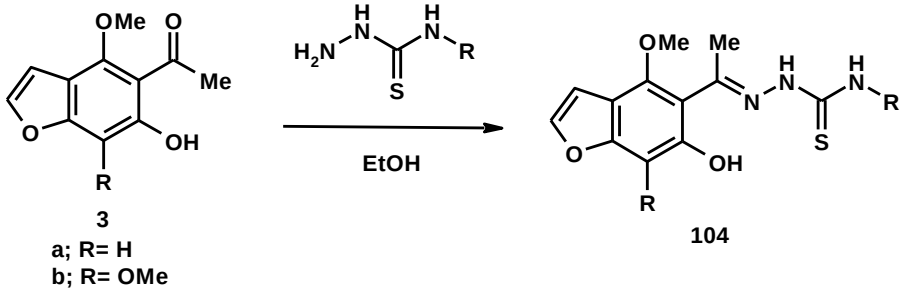
Scheme 40

Condensation of visnaginone (**3a**) with hydrazine hydrate and hydroxylamine hydrochloride led to the formation of the corresponding hydrazone **99** and oxime **100**. Cyclization of the latter compounds upon heating in acetic acid resulted in pyrazole **101** and isoxazole **102**, respectively.[52] On the other hand, refluxing visnaginone oxime **100** with excess pyridine hydrochloride for 20 min afforded 8-methoxy-2-methylfuro[3,2-*f*]benzoxazoles **103**, *via* Beckmann rearrangement (Scheme 41).[53]



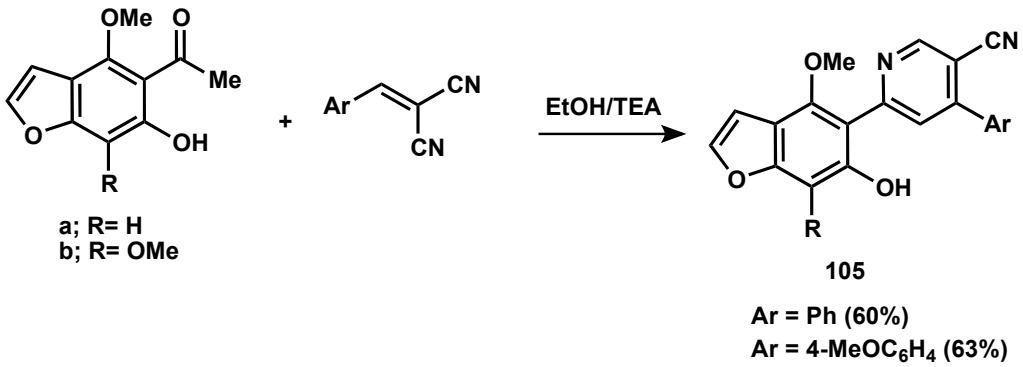
Scheme 41

Visnaginone **3a** and khellinone **3b** reacted with some selected thiosemicarbazides in ethanol containing catalytic amount of acetic acid under reflux for 72 h to form thiosemicarbazone derivative **104** (Scheme 42).[54]



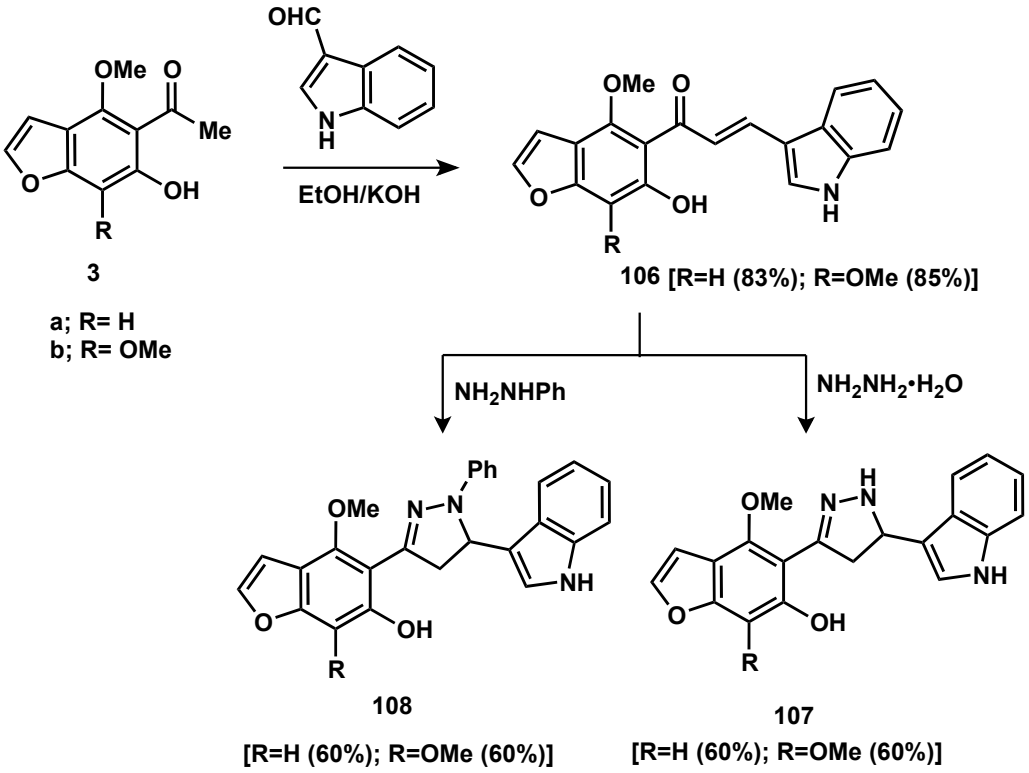
Scheme 42

Reaction of visnaginone (**3a**) and khellinone (**3b**) with cinnamonitriles in ethanol containing triethylamine (TEA), *via Michael* addition, led to the formation of 4-methoxy/4,7-dimethoxy-5-(4-aryl-5-cyano-2-pyridyl)benzofurans **105** (Scheme 43).[55]



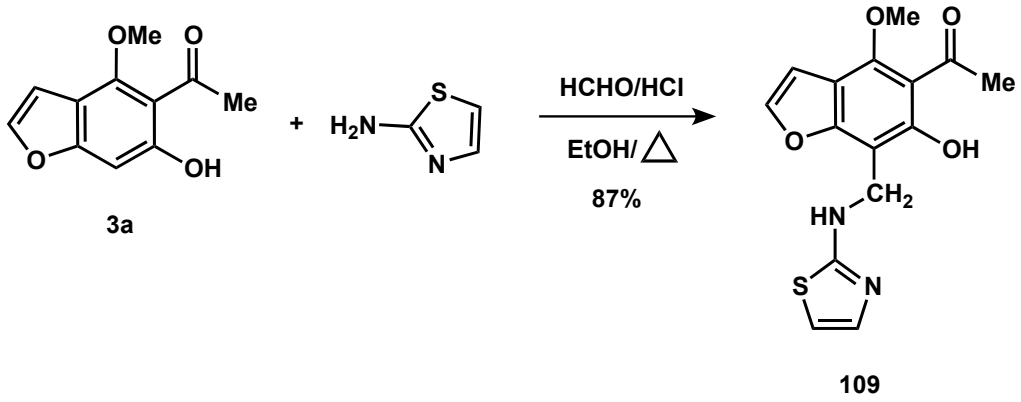
Scheme 43

Condensation of visnaginone (**3a**) and khellinone (**3b**) with indole-3-carboxaldehyde in ethanol containing aqueous potassium hydroxide solution (10%) gave 1-(4-methoxy/4,7-methoxybenzofuran-5-yl)-3-(indol-3-yl)propen-1-one (**106**). Cyclization of the latter compounds using hydrazine hydrate and phenylhydrazine afforded the corresponding pyrazoline **107** and *N*-phenylpyrazoline **108**, respectively (Scheme 44).[56]



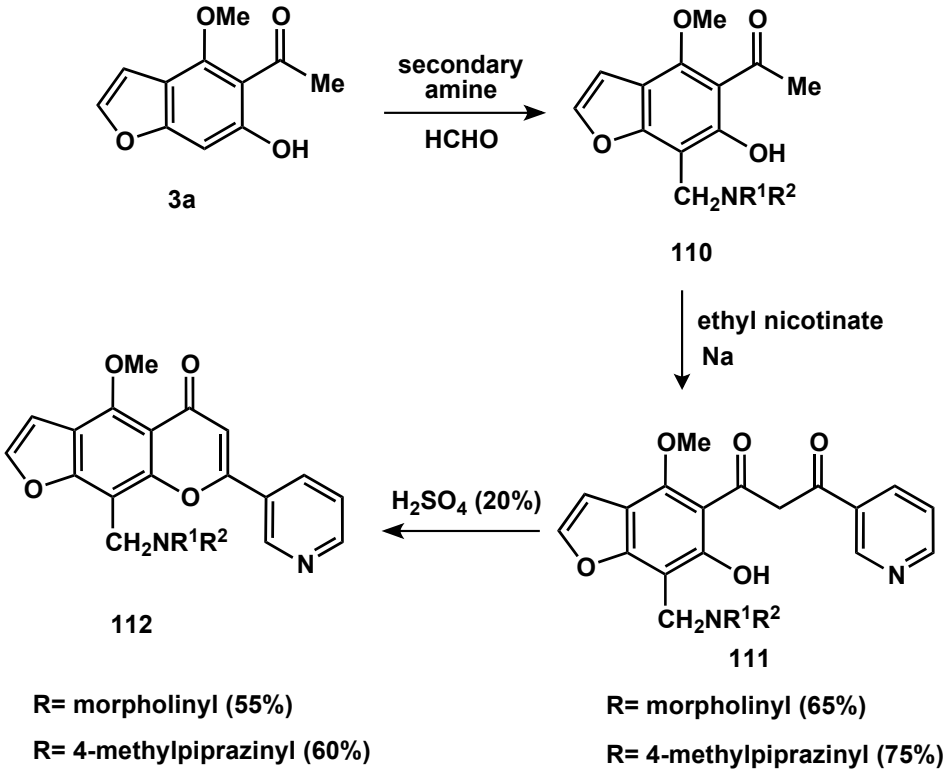
Scheme 44

Mannich reaction of visnaginone (**3a**) with 2-aminothiazole in the presence of formaldehyde gave [4-methoxy-5-acetyl-6-hydroxy-7-(thiazol-2-ylamino)methyl]]benzofuran (**109**) (Scheme 45).[57]



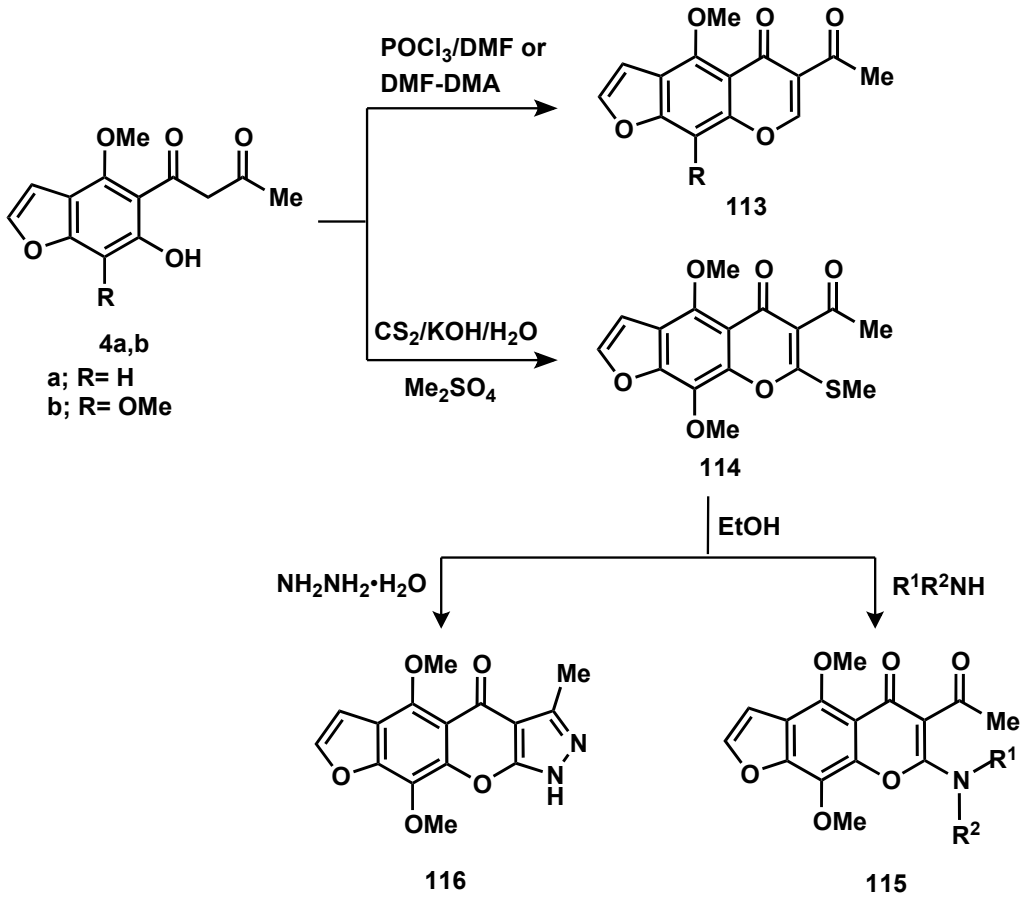
Scheme 45

Also, *Mannich* reaction of visnaginone (**3a**) various secondary amines gave 7-alkylaminomethyl-benzofuran derivatives **110** which underwent Clasien condensation with ethyl nicotinate producing β-dicarbonyl derivative **111**. The acid catalyzed cyclodehydration of compounds **111** using sulfuric acid gave the corresponding 2-pyridylfurochromones **112** (Scheme 46).[58]



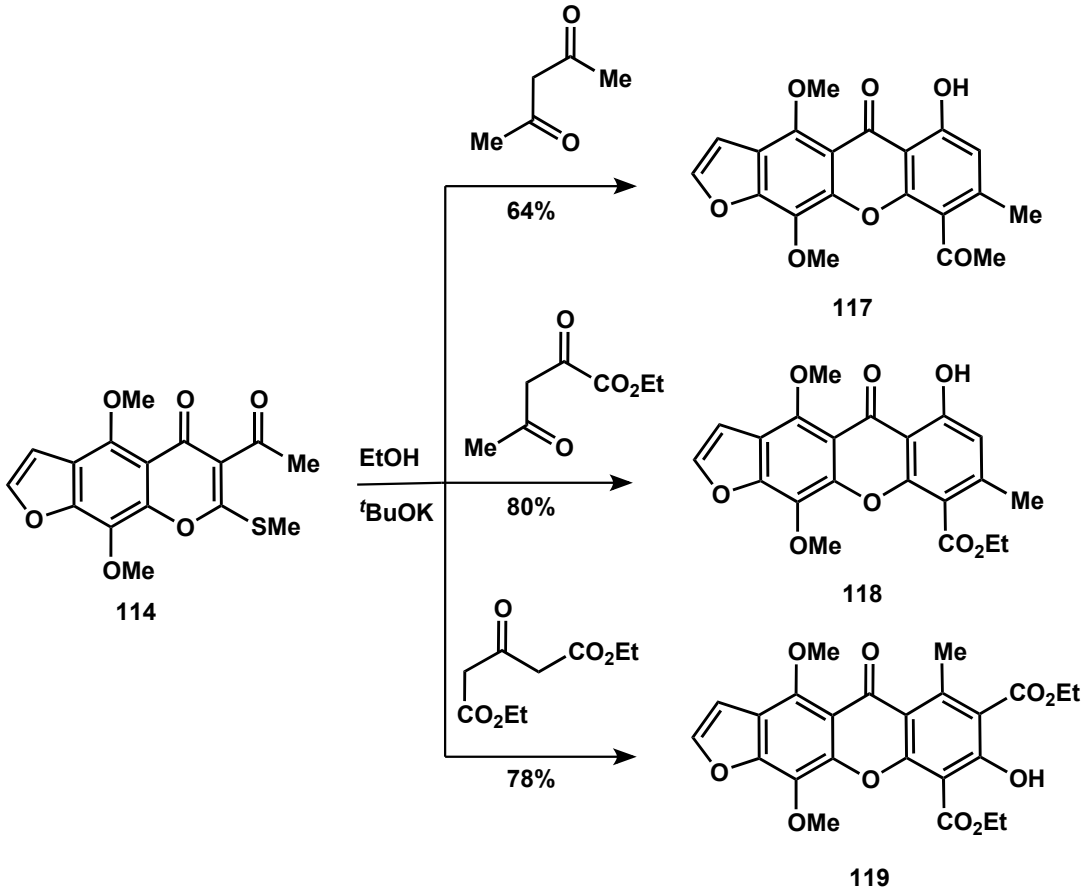
Scheme 46

6-Acetylnorvisnagin (**113a**) and 6-acetylnorkhellin (**113b**) were synthesized *via* the reaction of diketones **4a**,**b** with Vilsmeier–Haack reagent or dimethylformamide dimethyl acetal (DMF-DMA).[59] While, treating β-diketone **4b** with CS_2 in aqueous potassium hydroxide followed by addition of dimethyl sulfate produced 6-acetyl-7-methylthionorkhellin **114**.[60] Nucleophilic displacement of methylthio group was achieved by the reaction of compound **114** with a variety of primary or secondary amines producing the 7-aminonorkhellin derivatives **115**.[60] On the other hand, reaction of compound **114** with hydrazine hydrate in boiling ethanol afforded pyrazolonorkhellin derivative **116** (Scheme 47).[60]



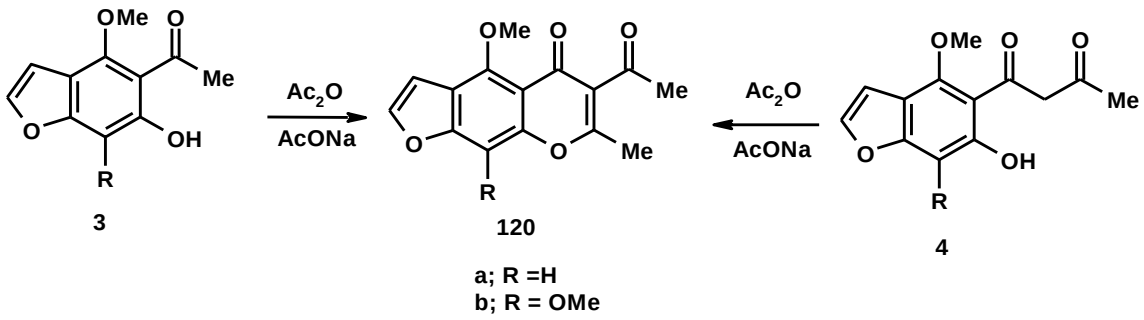
Scheme 47

Norkhellin derivative **114** was allowed to react with some active methylene compounds namely; acetylacetone, ethyl acetoacetate and acetone diethylcarboxylate in potassium *tert*-butylate to produce the functionalized furoxanthones **117**-**119**, respectively (Scheme 48).[61]



Scheme 48

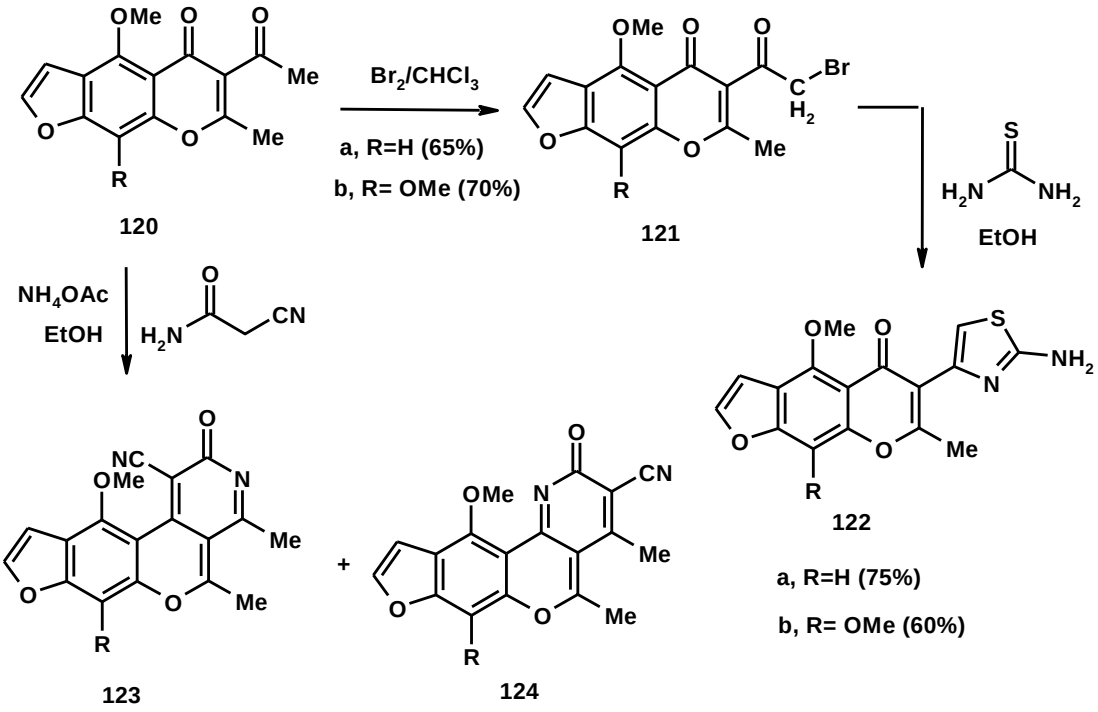
Treatment of visnaginone (**3a**) and khellinone (**3b**) with acetic anhydride in the presence of anhydrous sodium acetate afforded 6-acetyl-7-methylnorvisnagine (**120a**) [(6-acetyl-4-methoxy-7-methyl-5*H*-furo-[3,2-*g*]chromen-5-one) and 6-acetyl-7-methylnorkhellin (**120b**) [(6-acetyl-4-methoxy/4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*]chromen-5-one).[62] Compounds **120a**,**b** were also obtained from β-diketones **4** under the same reaction conditions (Scheme 49).[63]



Scheme 49

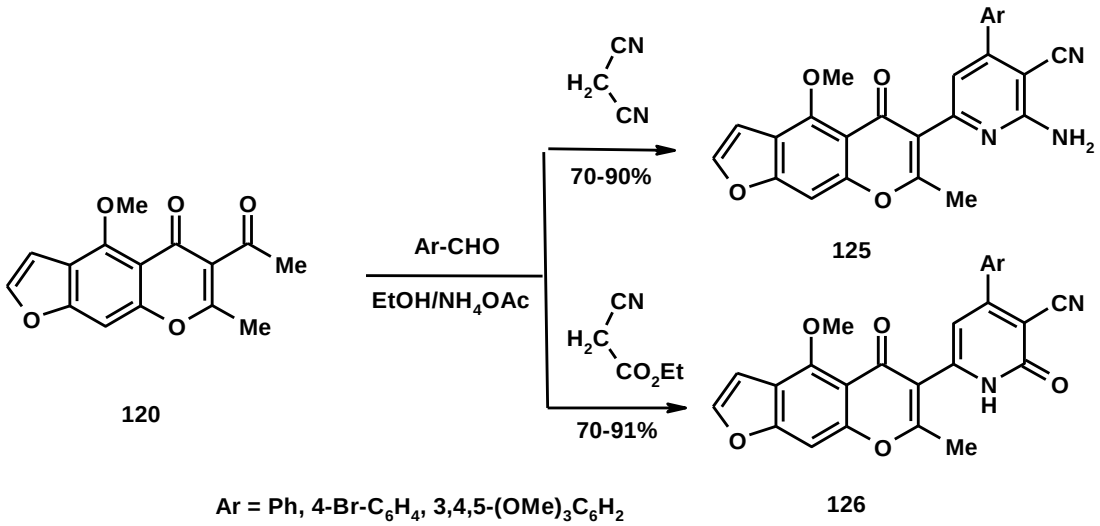
Bromination of compounds **120** with bromine in chloroform gave the corresponding bromoacetyl derivatives **121**, which underwent cyclocondensation with thiourea in boiling ethanol giving

2-aminothiazole derivatives **122**.[64] While, condensation of compound **120** with cyanoacetamide in boiling ethanol in the presence of ammonium acetate gave a mixture of isomeric products **123** and **124** (Scheme 50).[64]



Scheme 50

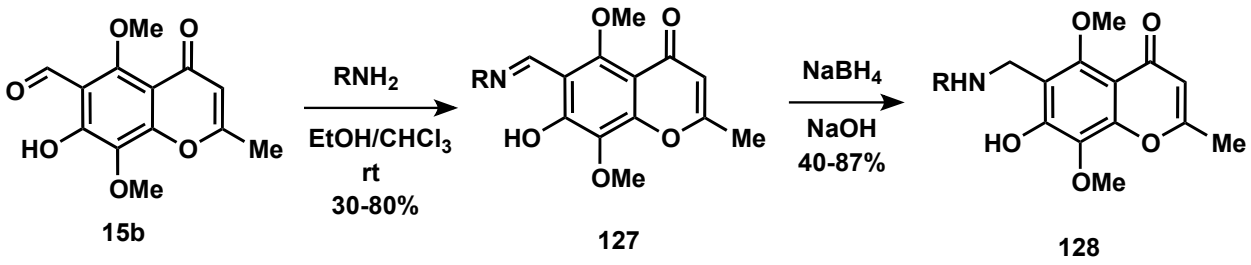
Refluxing 6-acetyl-7-methylnorvisnagin (**120a**) with aromatic aldehydes in the presence of malononitrile and/or ethyl cyanoactate and ammonium acetate gave pyridine derivatives **125** and **126**, respectively, which showed promising activity towards antiprostate cancer cell lines (Scheme 51).[65]



Scheme 51

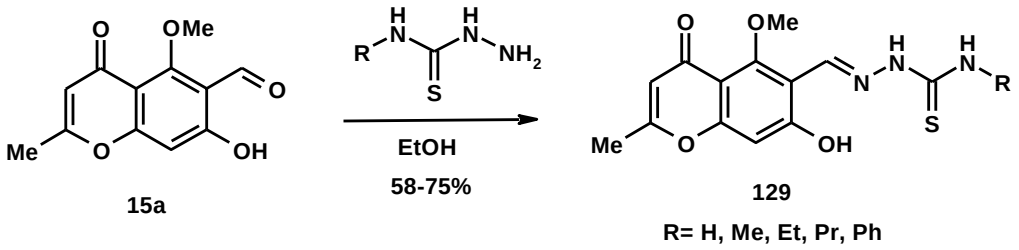
4. REACTIONS OF 6-FORMYL-7-HYDROXY-5-METHOXY-2-METHYLCHROMONES

Treatment of 6-formyl-7-hydroxy-5,8-dimethoxy-2-methylchromone (**15b**) with different primary aromatic amines, in absolute ethanol containing few drops of chloroform, yielded the corresponding 6-iminomethyl derivatives **127**. Reduction of compounds **127** with sodium borohydride in sodium hydroxide gave the corresponding 6-aminomethyl derivatives **128**. Compounds **127** and **128** showed similar analgesic effect as Novalgin (Scheme 52).[66]



Scheme 52

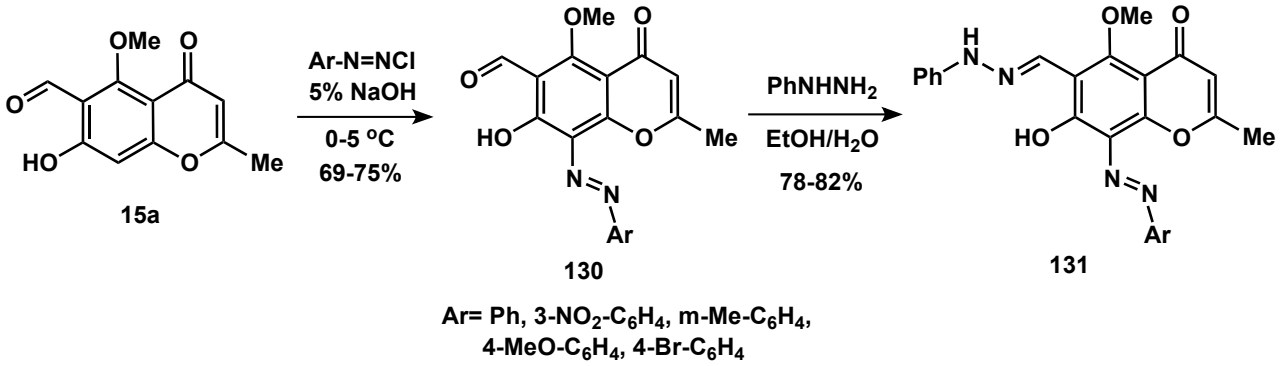
Condensation of aldehyde **15a** with *N*-substituted thiosemicarbazide gave the corresponding thiosemicarbazones **129** (Scheme 53).[57,67]



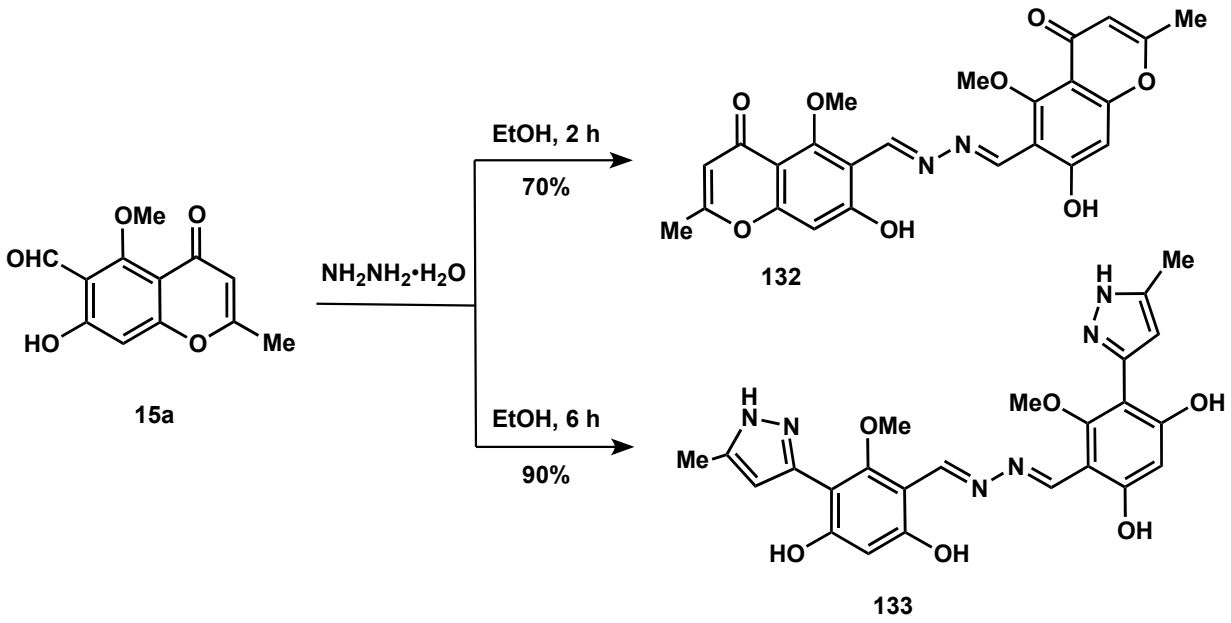
Scheme 53

Coupling of aldehyde **15a** with aryldiazonium chloride led to insertion of arylazo group into position 8 of the chromone nucles producing 8-arylazo-6-formyl-7-hydroxy-2-methylchromones **130**. Condensation of the latter compounds with phenylhydrazine in ethanol afforded the corresponding hydrazones **131** (Scheme 54).[67]

Refluxing aldehyde **15a** with hydrazine hydrate in ethanol for 2 h afforded the *bis* hydrazone derivative **132**, while repeating the reaction under the same conditions for 6 h produced the pyrazole derivative **133** (Scheme 55).[68]



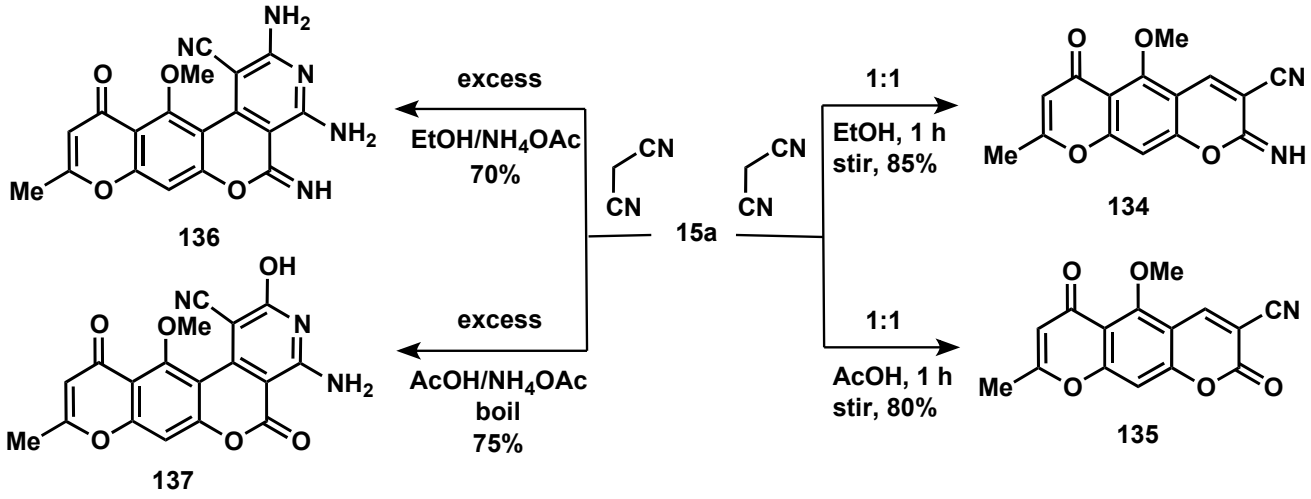
Scheme 54



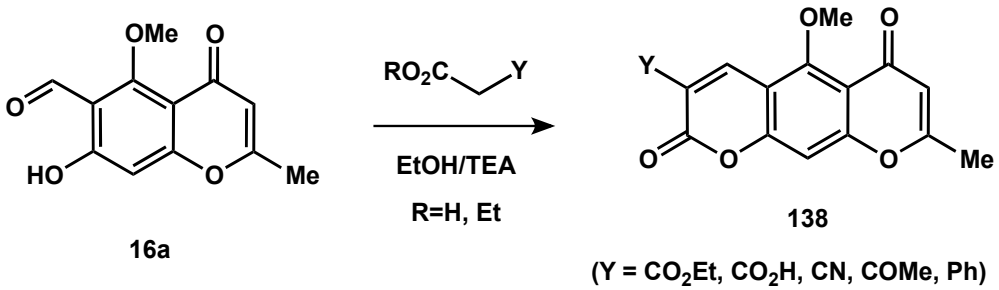
Scheme 55

Condensation reaction of aldehyde **15a** was studied toward malononitrile under different reaction conditions. Stirring aldehyde **15a** with malononitrile in 1:1 molar ratio at room temperature for 1 h gave 3-cyano-2-imino-5-methoxy-8-methyl-6-oxo-2*H*,6*H*-benzo[1,2-*b*:5,4-*b*`]dipyran (**134**). Repeating the reaction in acetic acid gave 2,6-dioxo analog **135**. Meanwhile, boiling aldehyde **15a** with excess malononitrile in ethanol containing ammonium acetate gave annulated system; 1-cyano-2,4-diamino-12-methoxy-9-methyl-11-oxo-5*H*,11*H*-pyrano[3`,2`:6,7][1]benzopyrano[3,4-*c*] pyridine (**136**). Repeating the latter reaction in acetic acid instead of ethanol gave 4-amino-1-cyano-2-hydroxy-12-methoxy-9-methyl-5,11-dioxo-5*H*,11*H*-pyrano[3`,2`:6,7][1]benzopyrano[3,4-*c*]pyridine (**137**) (Scheme 56).[69]

Also, benzodipyranones **138** were prepared from the condensation of aldehyde **15a** with diethyl malonate, malonic acid, ethyl cyanoacetate, ethyl acetoacetate, and phenylacetic acid (Scheme 57).[70,71]

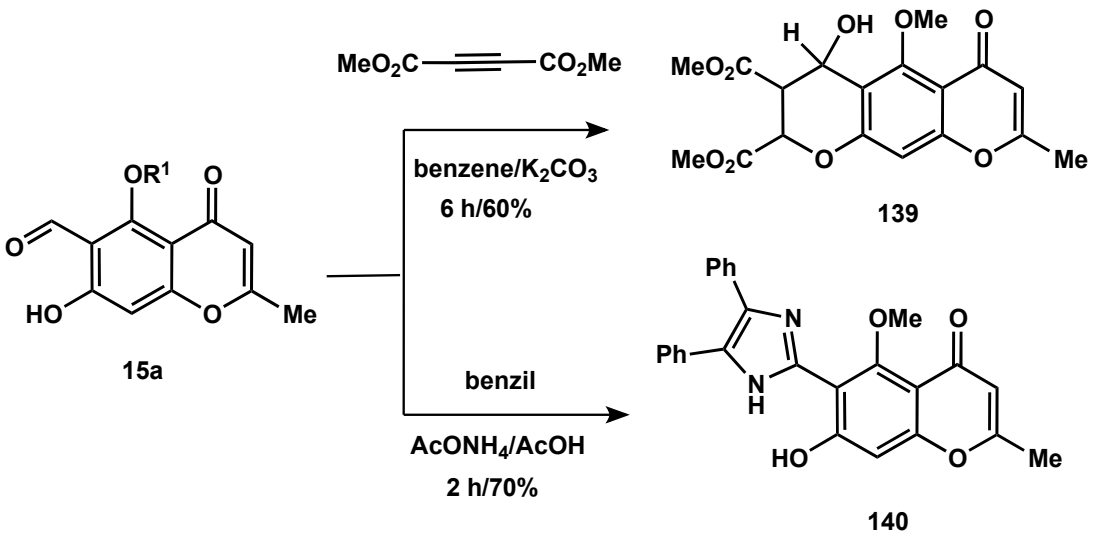


Scheme 56



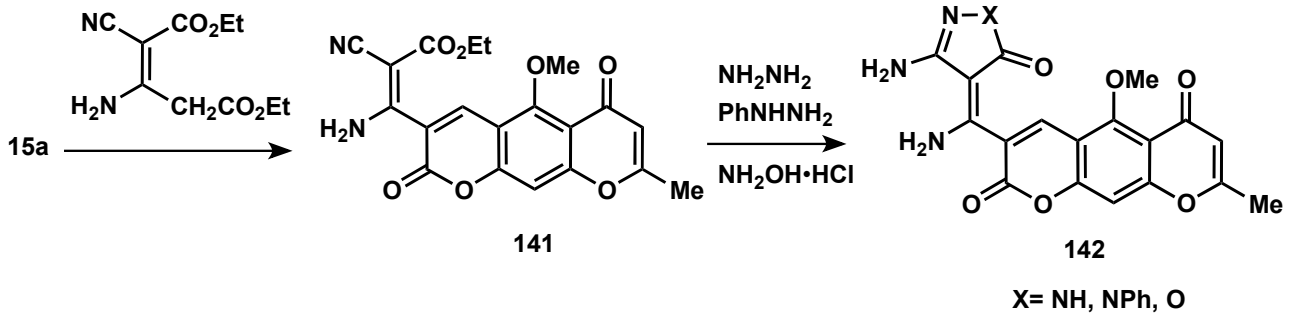
Scheme 57

When aldehyde **15a** was reacted with dimethyl acetylenedicarboxylate, it yielded the 7,8-bis(methoxy-carbonyl)pyrano[3,2-*g*]chromene derivative **139**. The condensation of the same aldehyde with benzil in acetic acid in presence of ammonium acetate, the imidazole derivative **140** was obtained (Scheme 58).[72]



Scheme 58

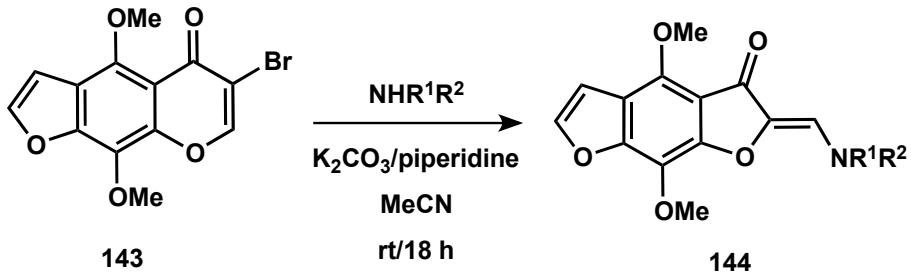
Moreover, dialkyl 2-amino-1-cyanopropene-1,3-dicarboxylate reacted with aldehyde **15a** to afford the benzodipyran derivatives **141** which reacted with hydrazine hydrate, phenylhydrazine and hydroxylamine hydrochloride to yield the corresponding pyrazole and oxazole derivatives **142** (Scheme 59).[73]



Scheme 59

5. REACTIONS OF 6-BROMONORKHELLIN

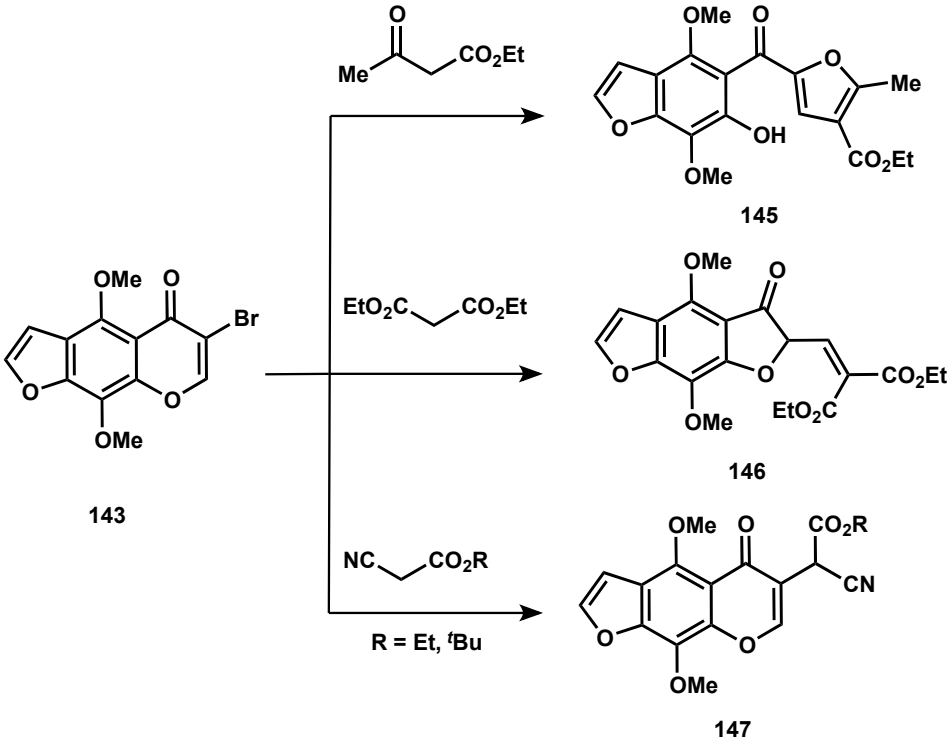
The research on the chemistry of to 6-bromonorkhellin (**143**) is too rare. Addition of primary and secondary amines to 6-bromonorkhellin (**143**) resulted in the ring contraction to the γ-pyrone ring leading to benzodifuran derivative **144** (Scheme 60).[74]



R = pyrroline, morpholine, benzylamine, cyclohexylamine

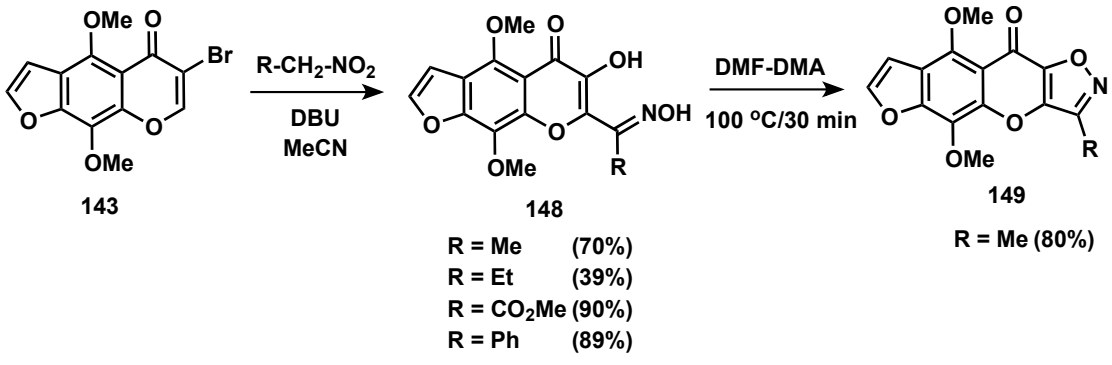
Scheme 60

Addition of ethyl acetoacetate to 6-bromonorkhellin (**143**) under basic condition afforded furan derivative **145**, *via* rupture of the γ-pyrone ring. However, addition of diethyl malonate to 6-bromonorkhellin (**143**) afforded the ring contraction product **146** and not the expected 6-substituted product. While, addition of both ethyl and *t*-butyl cyanoacetate to 6-bromonorkhellin (**143**) afforded 6-substituted products **147** (Scheme 61).[75]



Scheme 61

Drop-wise addition of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to an acetonitrile solution of 6-bromonorkhellin (**143**) and nitroethane resulted in smooth conversion to 3-hydroxy-2-[1-(hydroxyimino)methyl]furochromone (**148**). Likewise, nitropropane, α-nitroacetate and α-nitrotoluene added smoothly to 6-bromonorkhellin (**143**) affording the corresponding (hydroxyimino)methylfuro-chromones **148**.[76] Treating the latter compound **148** (R=Me) with DMF-DMA at 100 °C led to furo[3`,2`:6,7]benzopyrano[2,3-*d*]isoxazole **149**, through loss of water molecule (Scheme 62).[76]

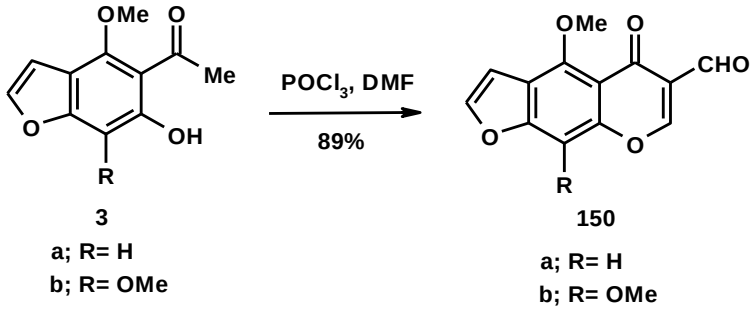


Scheme 62

6. REACTIONS OF 6-FORMYLNORVISNAGIN AND 6-FORMYLNORKHELLIN

Vielsmeier–Haack formylation of visnaginone (**3a**) and khellinone (**3b**), using phosphorous oxychloride and dimethylformamide, yielded 4-methoxy/4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-

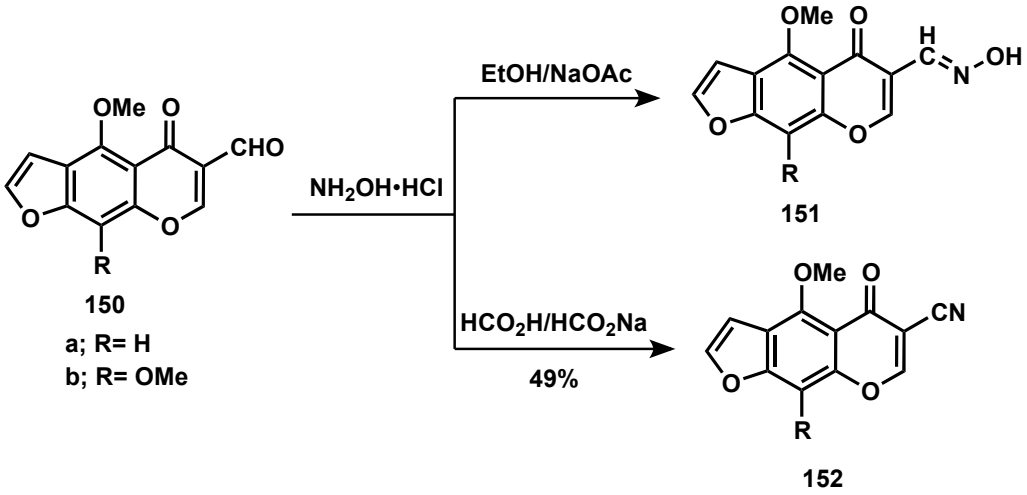
carboxaldehydes [6-formylnorvisnagin (**150a**) and 6-formylnorkhellin (**150b**)].[59,77-79] These compounds possess more than electron deficient centers and therefore very sensitive to nucleophilic reagents. Herein, we aimed to summarize the chemical reactivity of aldehydes **150a**,**b** towards different nitrogen and carbon nucleophiles (Scheme 63).



Scheme 63

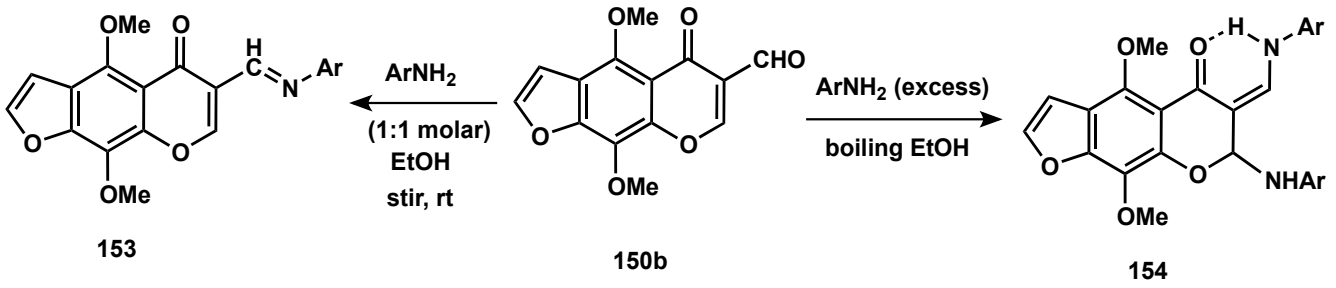
6.1. Reactions with nitrogen nucleophiles

Reaction of 6-formylvisnagin (**150a**) and 6-formylkhellin (**150b**) with hydroxylamine hydrochloride in refluxing ethanol using sodium acetate for 30 min gave the corresponding oximes **151a**,**b**.[80] While, repeating the reaction in formic acid in the presence of sodium formate afforded the corresponding 6-cyanonorvisnagin (**152a**) and 6-cyanonorkhellin (**152b**) (Scheme 64).[59]



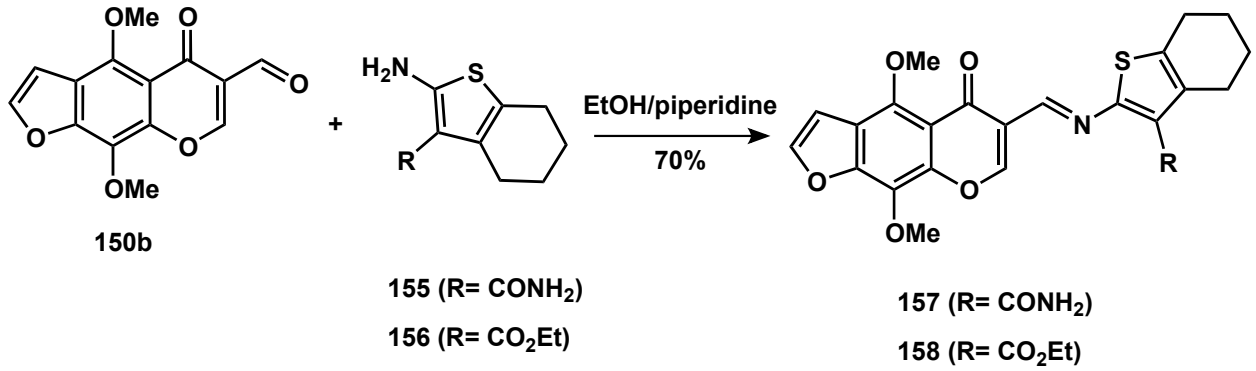
Scheme 64

Stirring 6-formylnorkhellin (**150b**) with primary aromatic amines (molar ratio 1:1), in ethanol at room temperature, produced the corresponding anils **153**. While, repeating the reaction with excess amines (1:2 molar ratio) in ethanol under reflux gave the corresponding 6-aminomethylene-7-amino derivatives **154** (Scheme 65).[81]



Scheme 65

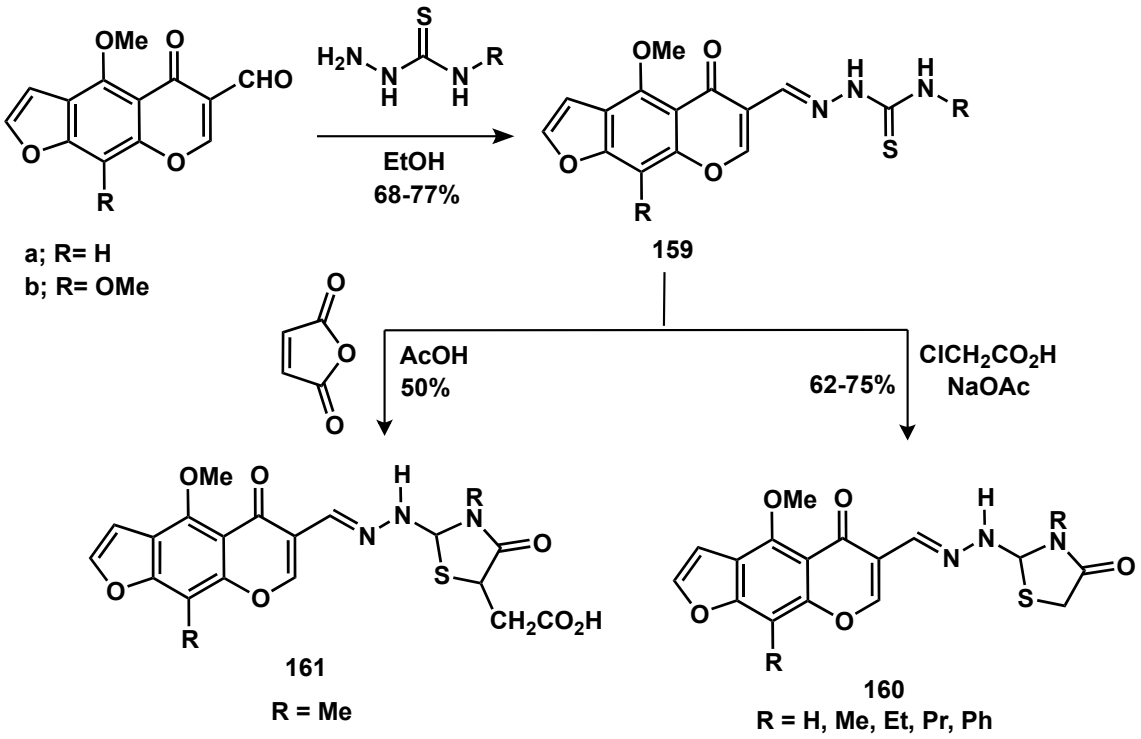
Reaction of 6-formylnorkhellin (**150b**) with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**155**) and ethyl 2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate (**156**) in boiling ethanol resulted in the formation of the corresponding Schiff bases **157** and **158**, respectively (Scheme 66).[82]



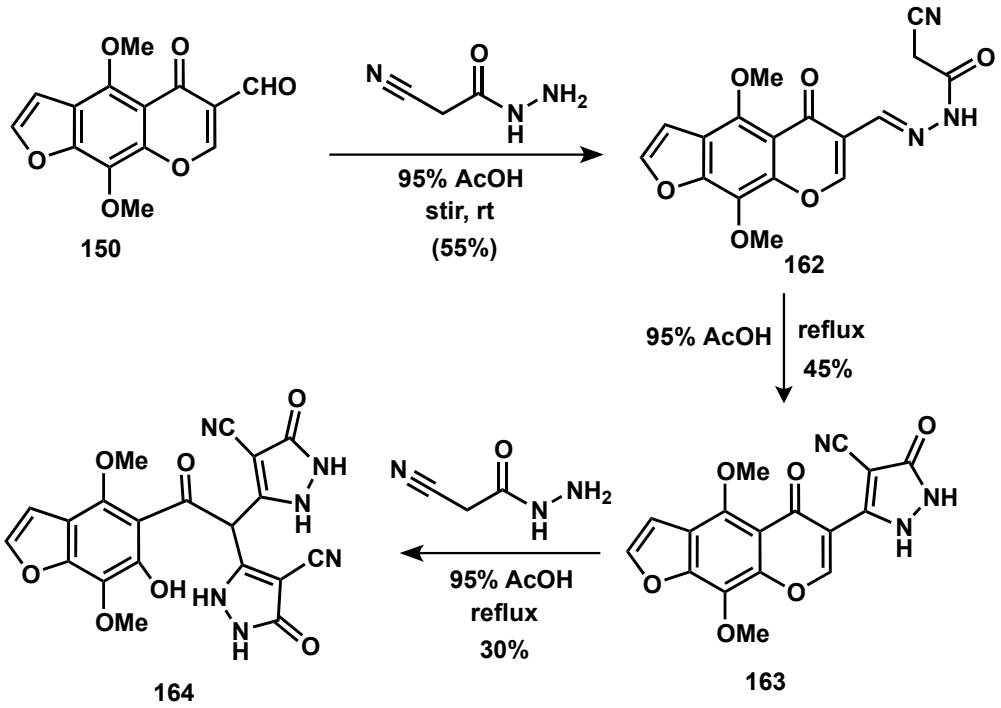
Scheme 66

Stirring 6-formylnorvisnagin (**150a**) and 6-formylnorkhellin (**150b**) with some substituted thiosemicarbazide in ethanol at room temperature provided the corresponding thiosemicarbazones **159** in good yield. Cyclization of the latter compound **159** with chloroacetic acid in the presence of sodium acetate gave the corresponding 1,3-thiazolidinone derivative **160**, while reaction of thiosemicarbazones **159** (R=Me) with maleic anhydride in glacial acetic acid under reflux gave (1,3-thiazolidin-5-yl)acetic acid derivative **161** in moderate yield (Scheme 67).[57]

Condensation of 6-formylnorkhellin (**150b**) with 2-cyanoacetohydrazide in 1:1 molar ratio under stirring at room temperature in 95% acetic acid to yield cyanoacetohydrazone **162** which cyclized in 95% acetic acid under reflux to yield pyrazolone derivative **163**. Reaction of the latter compound with 2-cyanoacetohydrazide gave benzofuran **164** in low yield (Scheme 68).[83]

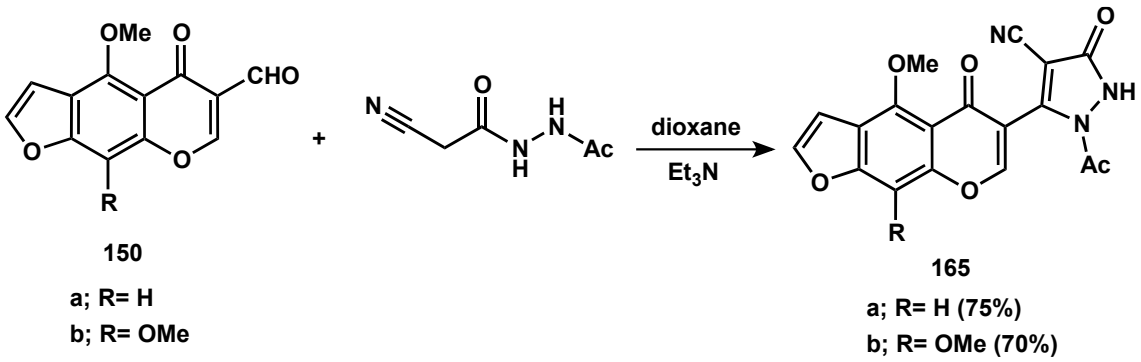


Scheme 67



Scheme 68

Moreover, reaction of 6-formylnorvisnagin (**150a**) and 6-formylnorkhellin (**150b**) with 2-acetyl-2-cyanoacetohydrazide in dioxane in the presence of triethylamine (TEA) yielded the pyrazolinone derivatives **165** (Scheme 69).[83]



150

a; R= H

b; R= OMe

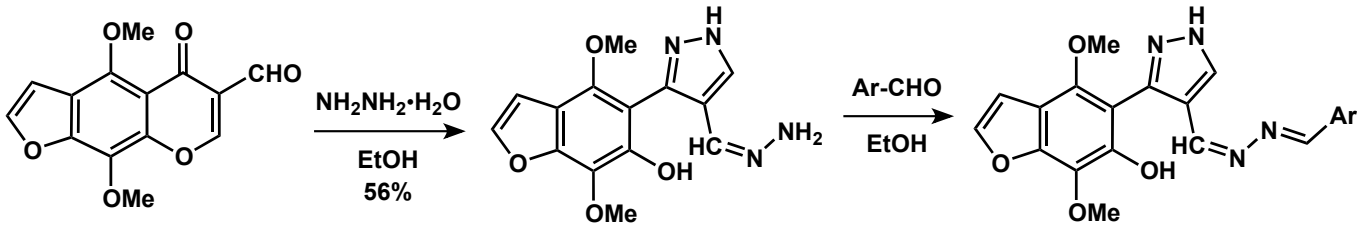
165

a; R= H (75%)

b; R= OMe (70%)

Scheme 69

Stirring 6-formylnorkhellin (**150b**) with hydrazine hydrate in ethanol resu1lted in pyrazole-4-carboxaldehyde hydrazone **166**, *via* condensation of hydrazine hydrate with the aldehyde function followed by γ-pyrone ring opening by another molecule of hydrazine hydrate with concomitant pyrazole ring closure.[84] The latter hydrazone condensed with some aromatic amines in ethanol giving unsymmetrical hydrazones **167** (Scheme 70).[84]



150b

166

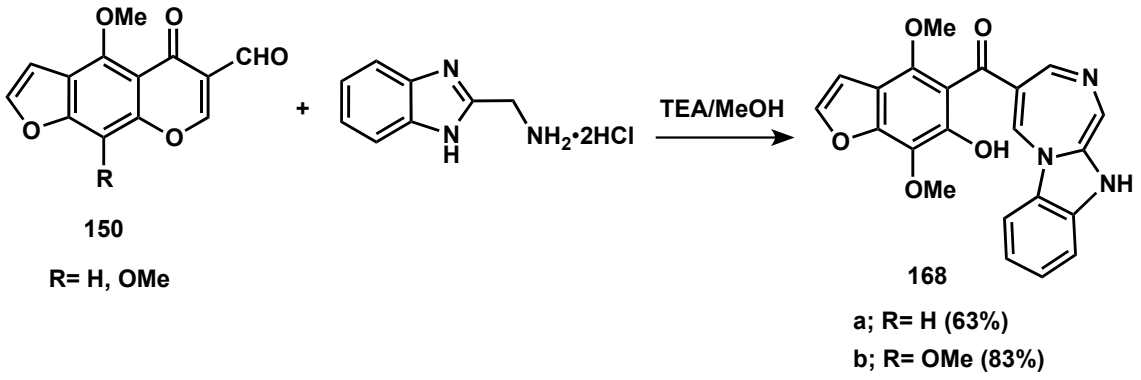
167

Ar=Ph, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-MeO-C_6H_4, 2,5-$(MeO)_2C_6H_3$

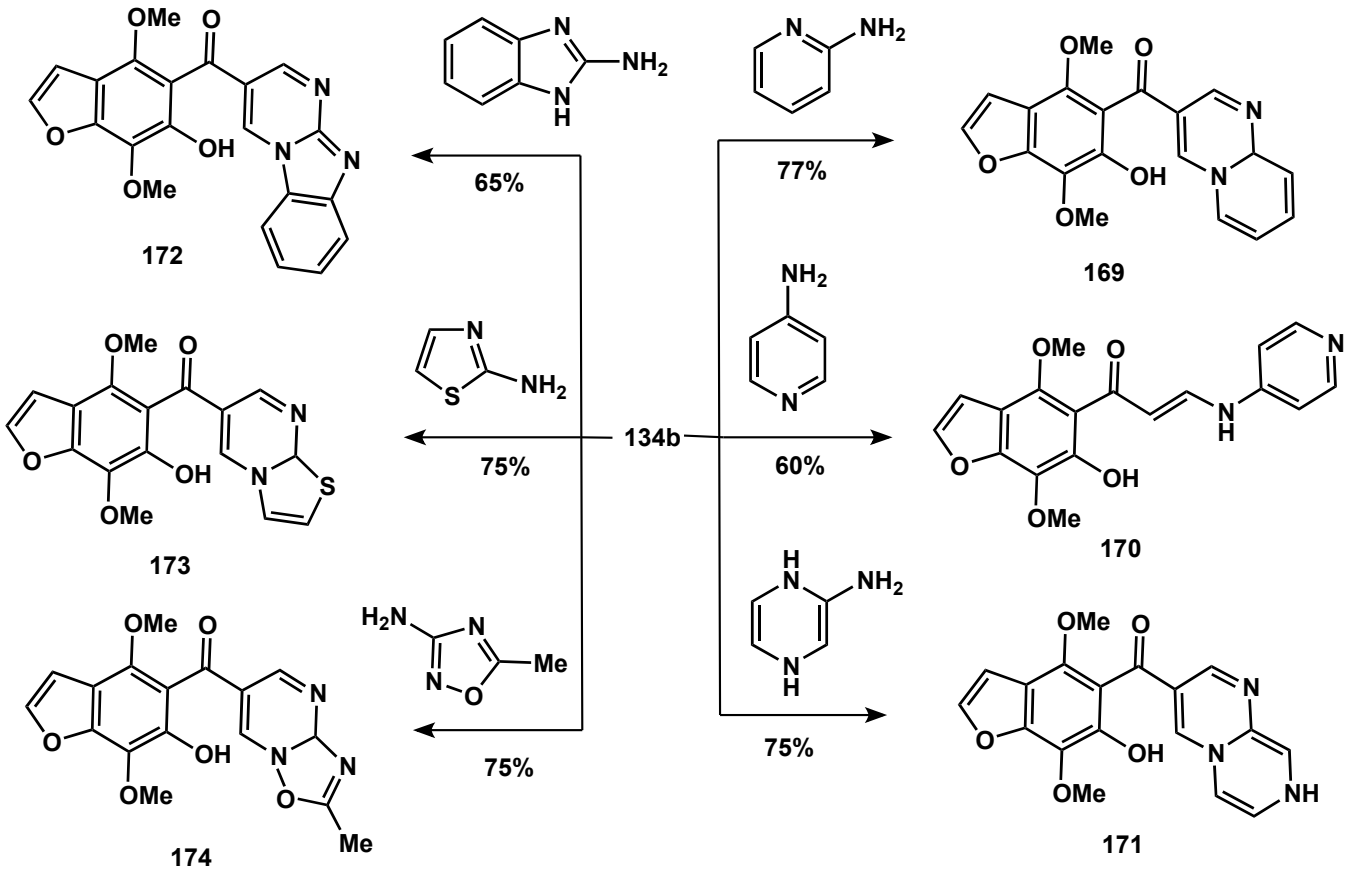
Scheme 70

Condensation of 6-formylnorvisnagin (**150a**) and 6-formylnorkhellin (**150b**) with (1*H*-benzimidazol-2-yl)methylamine dihydrochloride produced benzo[4,5]imidazo[1,2-*a*][1,4]diazepine derivative **168** *via* the formation of the Schiff base followed by a nucleophilic attack of the benzimidazole nitrogen at C-7 with concomitant γ-pyrone ring opening (Scheme 71).[85]

Benzofuran derivatives **169**-**174** were obtained from the reaction of 6-formylnorkhellin (**150b**) with each of 2-aminopyridine, 4-aminopyridine, 2-aminopyrazine, 2-aminobenzimidazole, 2-aminothiazole and 3-amino-5-methyloxazole, respectively, in the presence of alcoholic KOH (Scheme 72).[85]

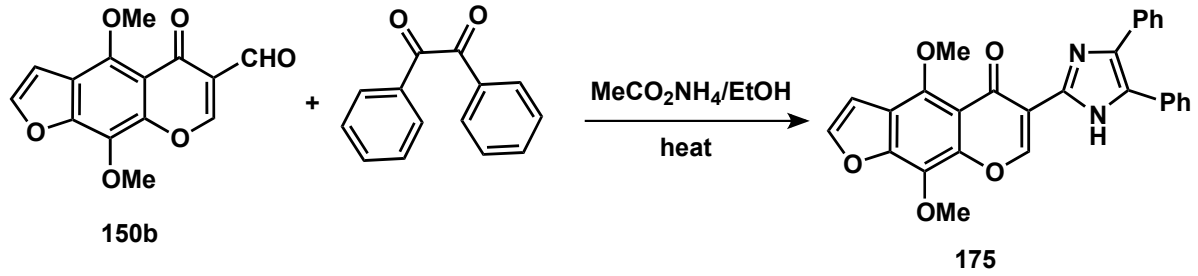


Scheme 71



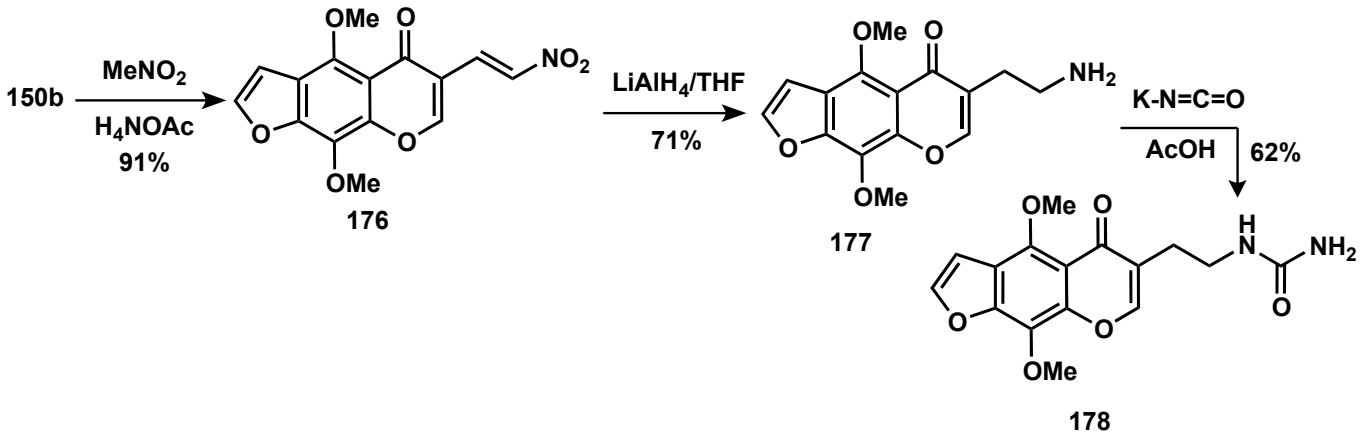
Scheme 72

6-Formylnorkhellin (**150b**) reacted with benzil under reflux in ethanol containing ammonium acetate to afford imidazole derivative **175** (Scheme 73).[86]



Scheme 73

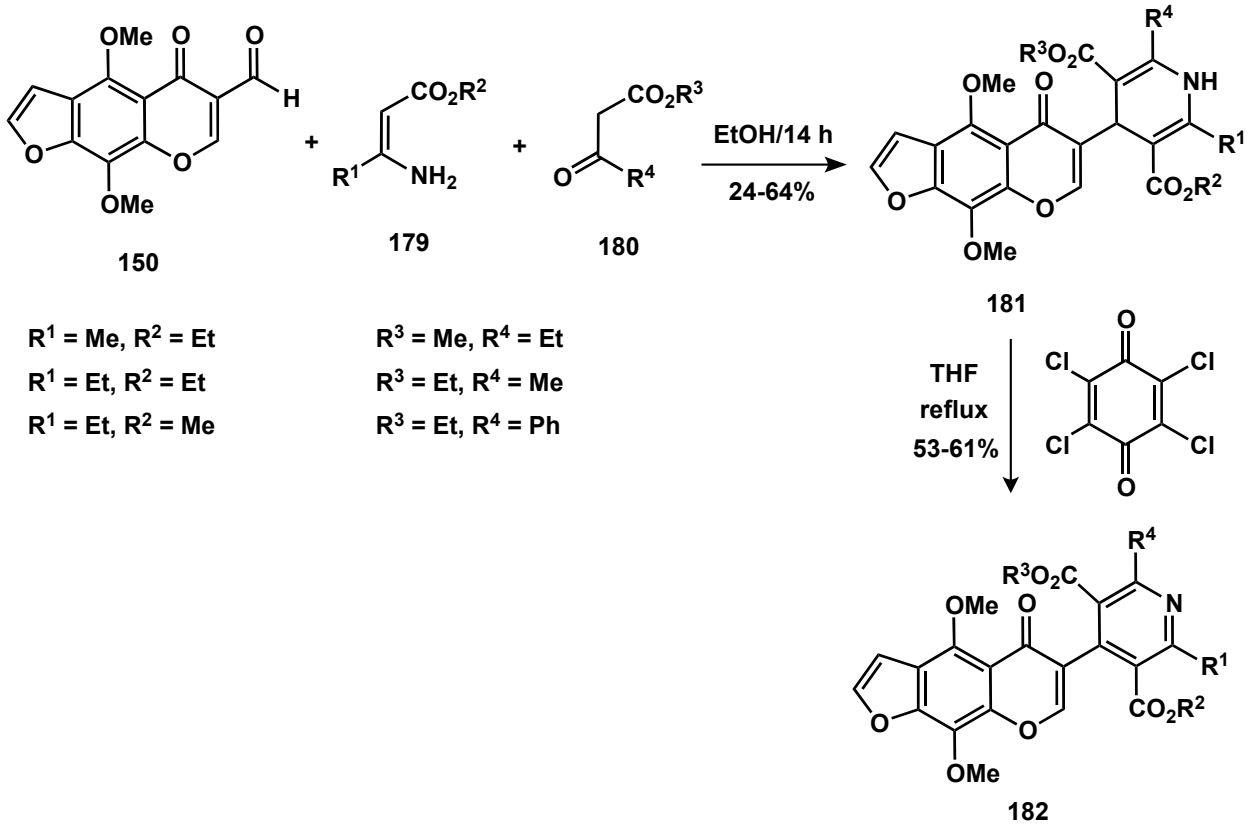
Treatment of 6-formylnorkhellin (**150b**) with nitromethane in the presence of ammonium acetate afforded 4,9-dimethyl-6-(2-nitrovinyl)-5*H*-furo[3,2-*g*]chromen-5-one (**176**) which upon reduction using lithium aluminium hydride in tetrahydrofuran (THF) afforded the corresponding 6-aminoethyl derivative **177**. Addition of potassium cyanate to compound **177** in aqueous acetic acid at room temperature led to urea derivative **178** in good yield (Scheme 74).[87]



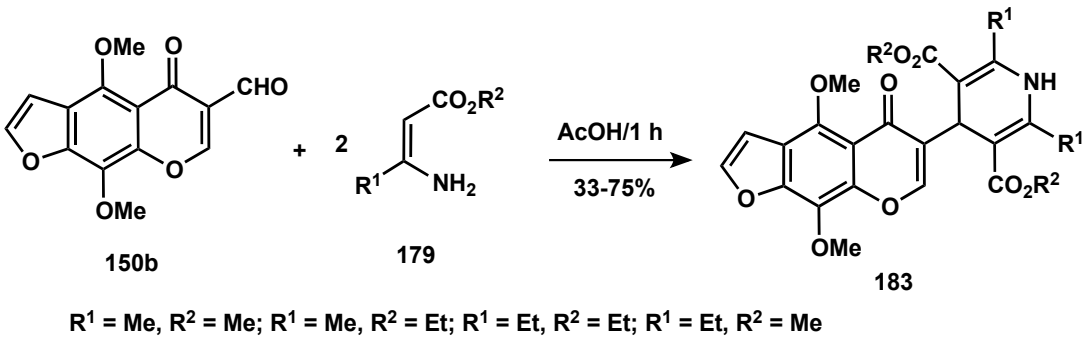
Scheme 74

Condensation of equimolar amounts of β-enaminoesters (**179**), β-ketoesters (**180**), and 6-formylnorkhellin (**150b**) yielded the corresponding 1,4-dihydropyridine derivatives; 4-(4,9-methoxy-5-oxo-5*H*-furo[3,2-*g*]-chromene-2,6-dialkyl-1,4-dihydropyridine-3,5-dicarboxylate **181**, in low to moderate yields.[88] Oxidation of 1,4-dihydropyridines **181** using tetrachloro-1,4-benzoquinone (chloranil) in THF gave the corresponding pyridine derivatives **182** (Scheme 75).[88]

Also, condensation of two equivalents of β-enaminoesters **179** with 6-formylnorkhellin (**150b**) in acidic medium produced the corresponding 1,4-dihydropyridine derivatives **183** (Scheme 76).[88]



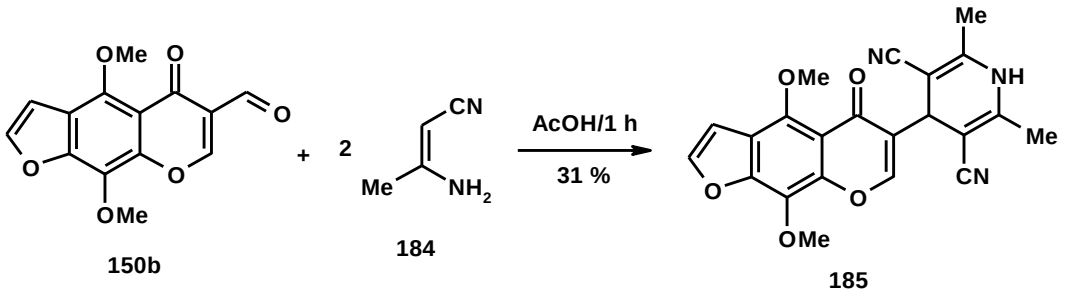
Scheme 75



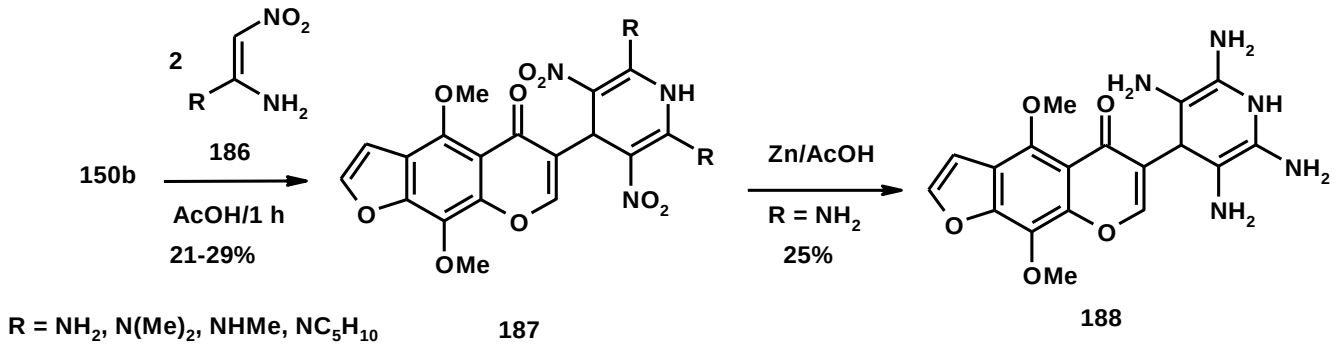
Scheme 76

In the same manner, condensing 6-formylnorkhellin (**150b**) with β-enaminonitrile (3-aminocrotononitrile) **184** in 1:2 molar ratio in acid medium gave 4-(4,9-methoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (**185**) (Scheme 77).[88]

Similarly, treating 6-formylnorkhellin (**150b**) with two equivalents of nitroketenaminals **186** in ethanol/acetic acid (3:1 volume) under reflux for 6 hours furnished 3,5-dinitro-1,4-dihydropyridines **187**. Reduction of compound **187** (R=NH_2) afforded the corresponding 2,3,5,6-tetraamino-1,4-dihydro-pyridine **188** (Scheme 78).[88]

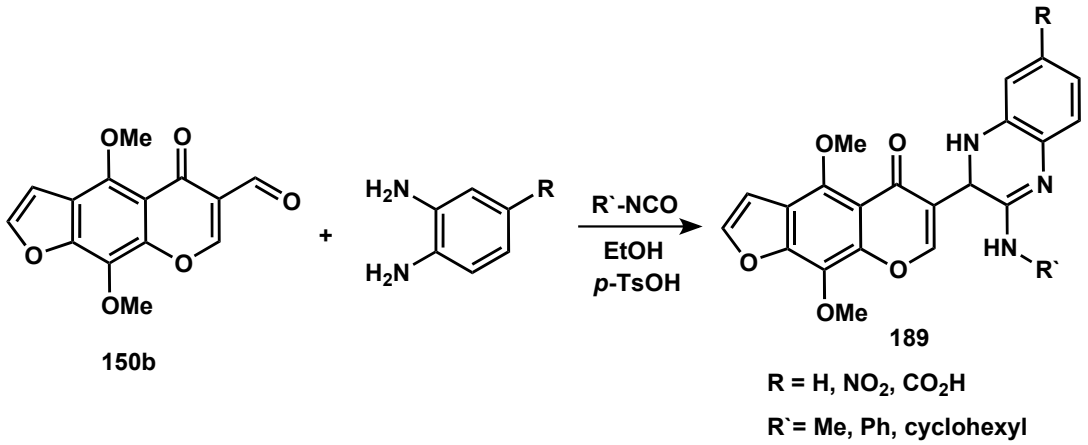


Scheme 77



Scheme 78

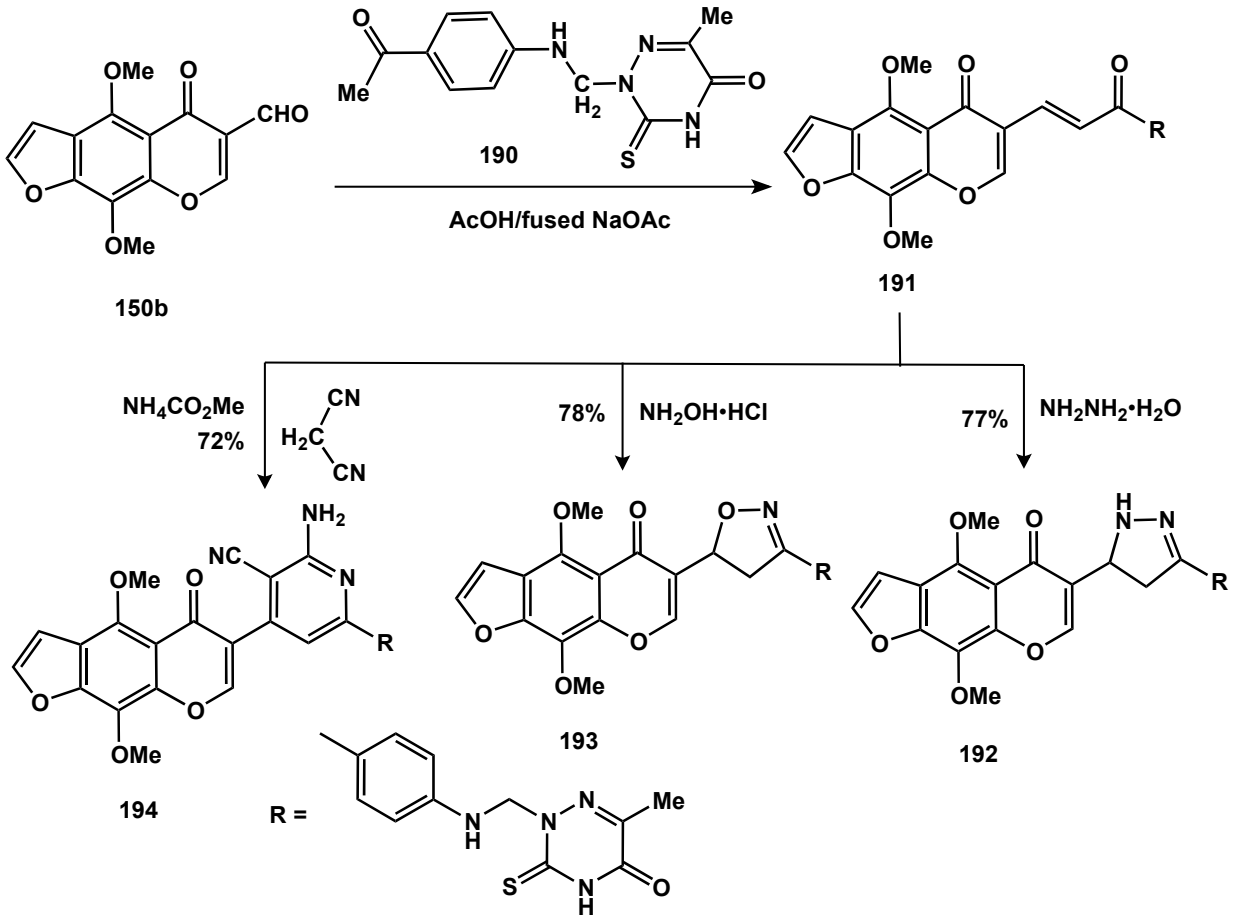
Multi-component reaction of 6-formylnorkhellin (**150b**), *o*-phenylenediamine and isothiocynate in ethanol in the presence of *p*-toluenesulfonic acid produced substituted (quinoxalin-2-yl)-4,9-dimethoxy-5*H*-furo[3,2-*g*]chromen-5-ones **189**. These compounds showed an efficient inhibition capacity in two human cancer cell lines, hepto cellular carcinoma (HEP G 2) and breast cancer (MCF-7) in comparison to the know anti-cancer drugs, 5-fluoruracil and doxorubicine (Scheme 79).[89]



Scheme 79

Knoevenagel condensation of 6-formylnorkhellin (**150b**) with *Mannich* base 2-[(4-acetylphenylamino)-methyl]-3-thioxo-1,2,4-triazin-5-(2*H*)-one (**190**) in glacial acetic acid in the presence of anhydrous

sodium acetate produced substituted chalcone **191**. Treatment of the latter compound with hydrazine hydrate, hydroxylamine·HCl, and malononitrile afforded pyrazolines **192**, oxazole **193** and pyridine **194**, respectively. These compounds showed high inhibition activity towards cancer cell lines (Scheme 80).[90]

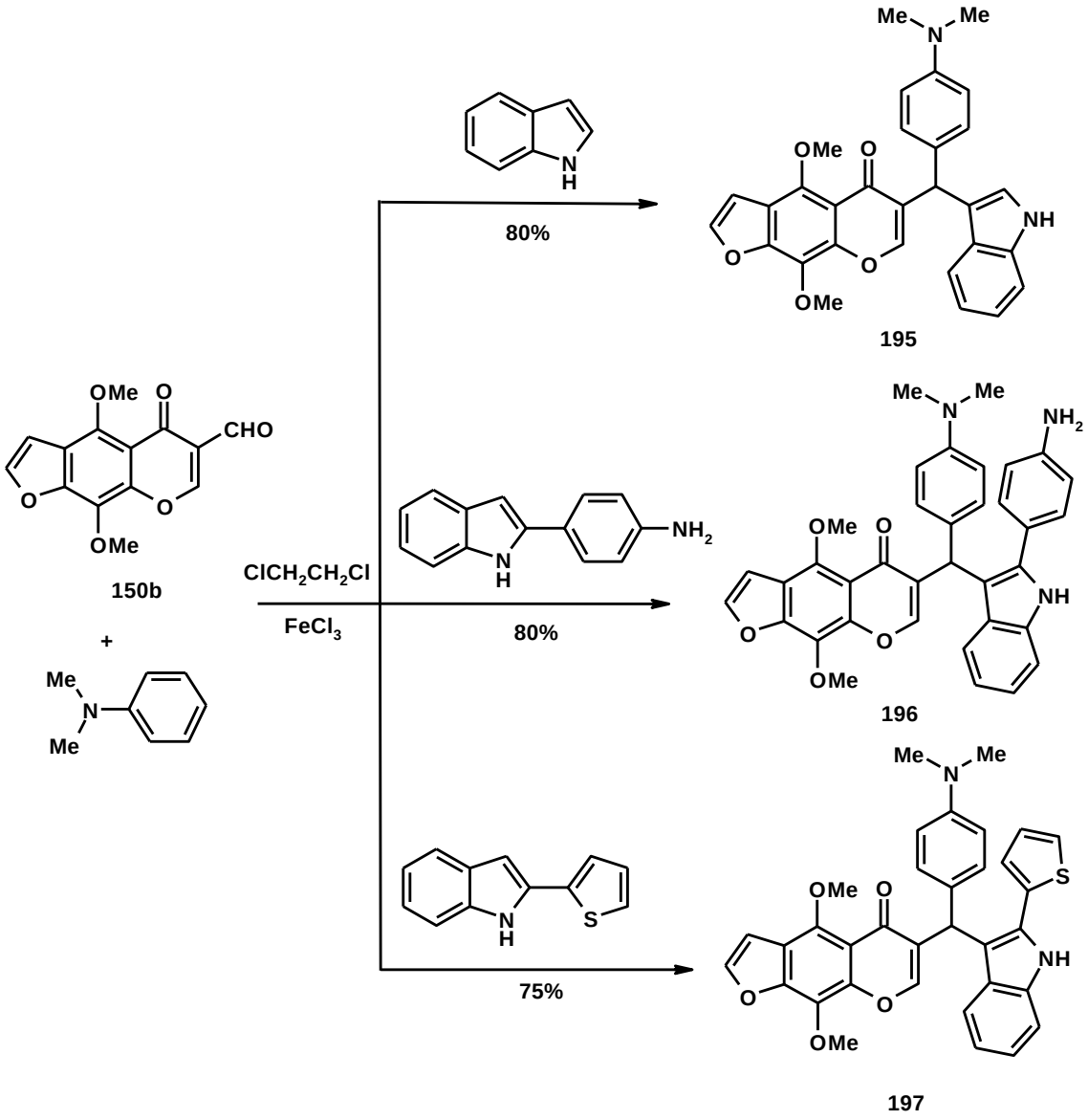


Scheme 80

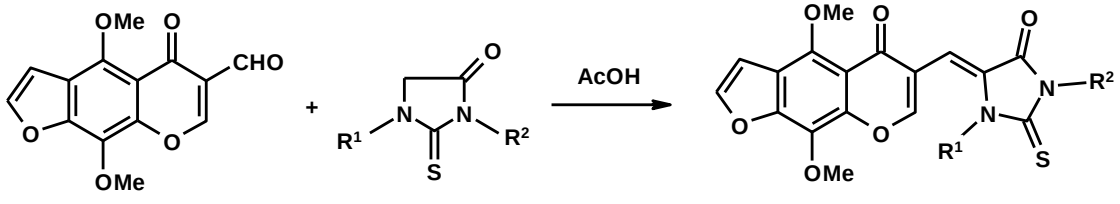
6.2. Reactions with carbon nucleophiles

Refluxing 6-formylnorkhellin (**150b**) with dimethylaniline and substituted indole afforded furochromone derivatives **195-197**, in good yields. These compounds revealed anti-tumor activity against breast (MCF 7) and liver (HEPG 12) cell livers (Scheme 81).[91]

Condensation of 6-formylnorkhellin (**150b**) with 2-thiohydantion derivatives afforded the corresponding 4-arylidene-2-thiohydantion **198** (Scheme 82).[92]



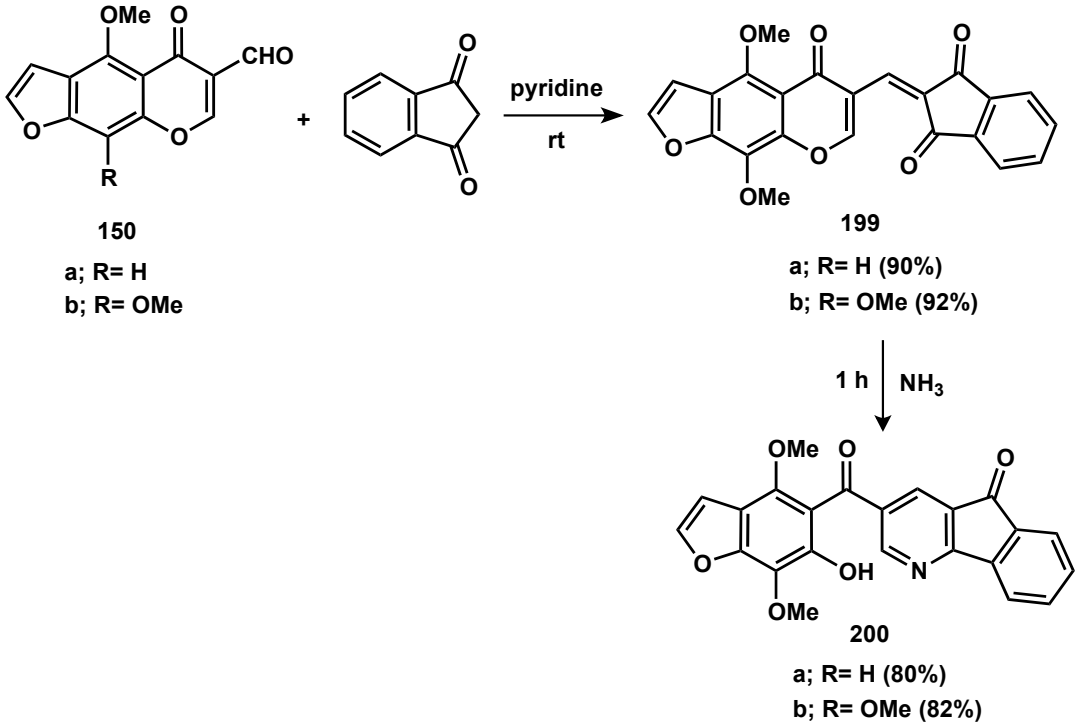
Scheme 81



Scheme 82

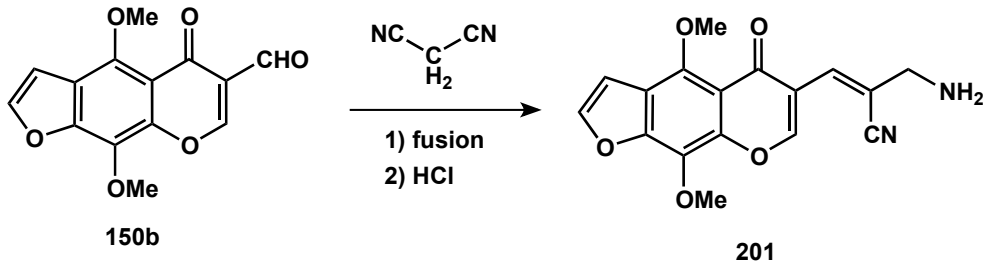
Condensation of 6-formylnorvisnagin (**150a**) and 6-formylnorkhellin (**150b**) with indan-1,3-dione in pyridine with stirring at room temperature gave furo[3,2-*g*][1]benzopyran-6-ylmethylidene-1,3-diones

199. Refluxing compound **199** with concentrated ammonium hydroxide gave oxoindeno[3,2-*b*]pyridine **200** (Scheme 83).[93]



Scheme 83

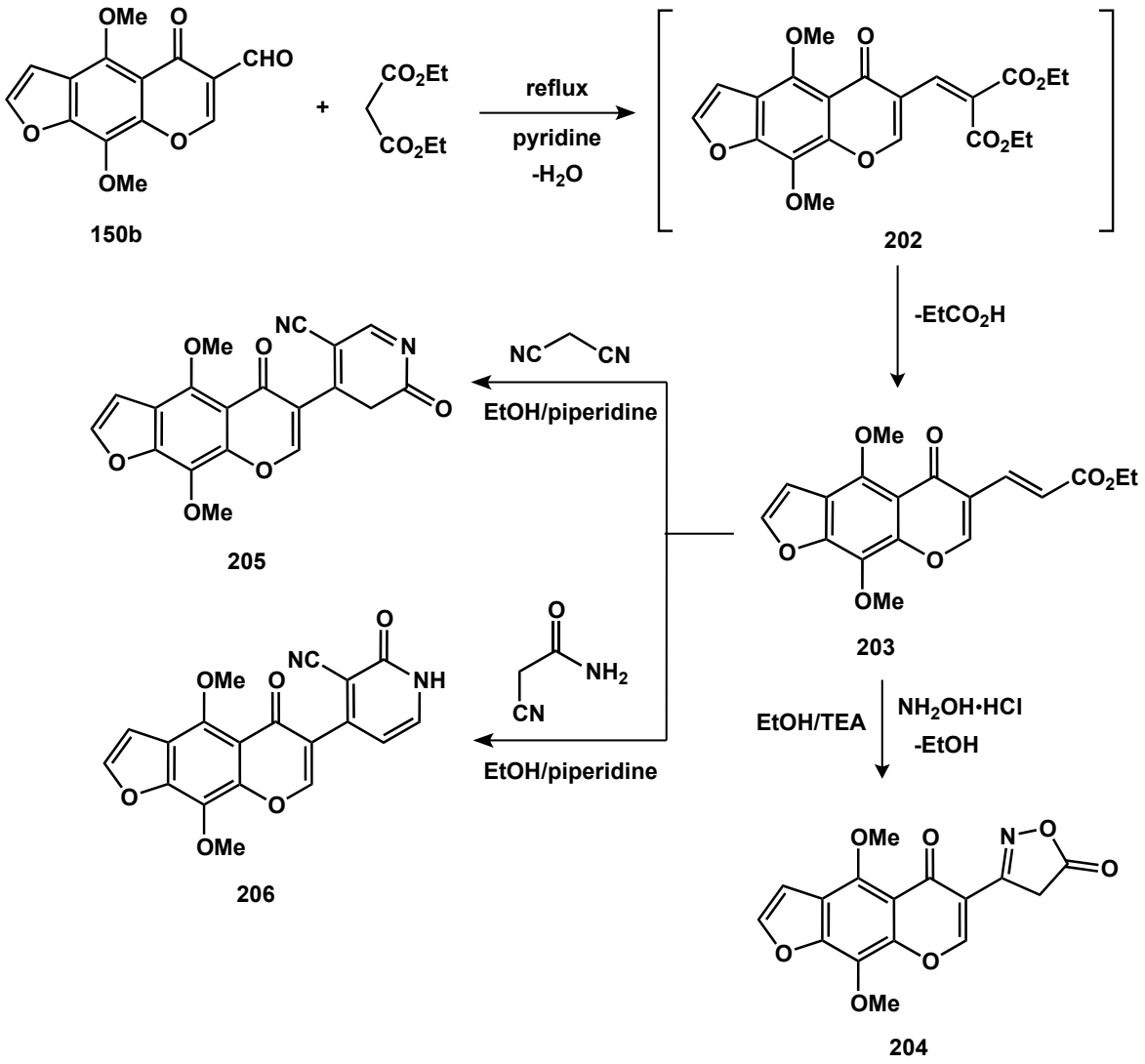
Fusion of 6-formylnorkhellin (**150b**) with malononitrile afforded after hydrolysis with hydrochloric acid, 2-cyano-3-(4,9-dimethoxy-5-oxofuro[3,2-*g*]benzopyran-6-yl)acrylamide (**201**) (Scheme 84).[94]



Scheme 84

Refluxing 6-formylnorkhellin (**150b**) with diethylmalonate in boiling pyridine yielded ethyl acrylate **203**, *via* the non-isolable intermediate **202**. Treating ethyl acrylate **203** with hydroxylamine hydrochloride afforded isoxazol-5(4*H*)-one derivative **204**. While, refluxing ethyl acrylate **203** with malononitrile and cyanoacetamide in ethanol in the presence of catalytic amount of pipredine afforded 4-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-6-oxo-5,6-dihydropyridine-3-carbonitrile (**205**) and 4-(4,9-dimethoxy-5-oxo-5-*H*-furo[3,2-*g*]chromen-6-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile

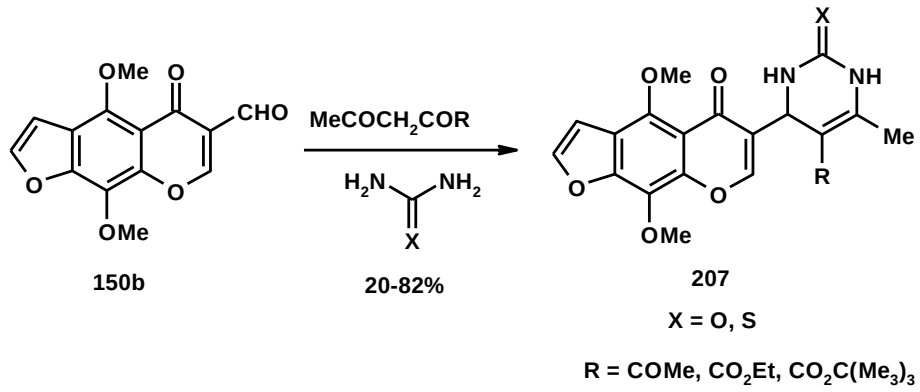
(**206**), respectively (Scheme 85).[95]



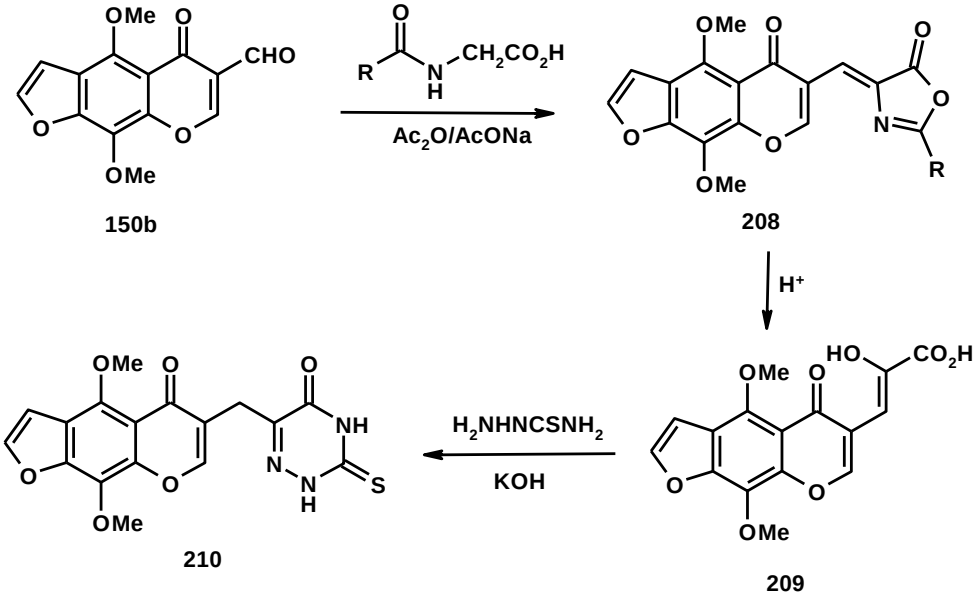
Scheme 85

Condensation of 6-formylnorkhellin (**150b**), urea or thiourea with β-diketones namely, acetylacetone, ethyl acetoacetate or *tert*-butyl acetoacetate in absolute ethanol in the presence of piperidine led to pyrimidines **207** linked norkhellin in the same molecular frame.[80] The same products **207** were also synthesized using microwave irradiation (Scheme 86).[96]

Condensation of 6-formylnorkhellin (**150b**) with *N*-acetylglycine and/or *N*-benzoylglycine in acetic anhydride in the presence of anhydrous sodium acetate gave oxazolone derivatives **208**.[97,98] Acid hydrolysis of oxazolone **208** produced hydroxyacrylate **209**. Condensation of the latter compound with thiosemicarbazide in the presence of aqueous potassium hydroxide (2%) afforded triazine derivative **210**, linked norkhellin in the same molecular frame (Scheme 87).[98]

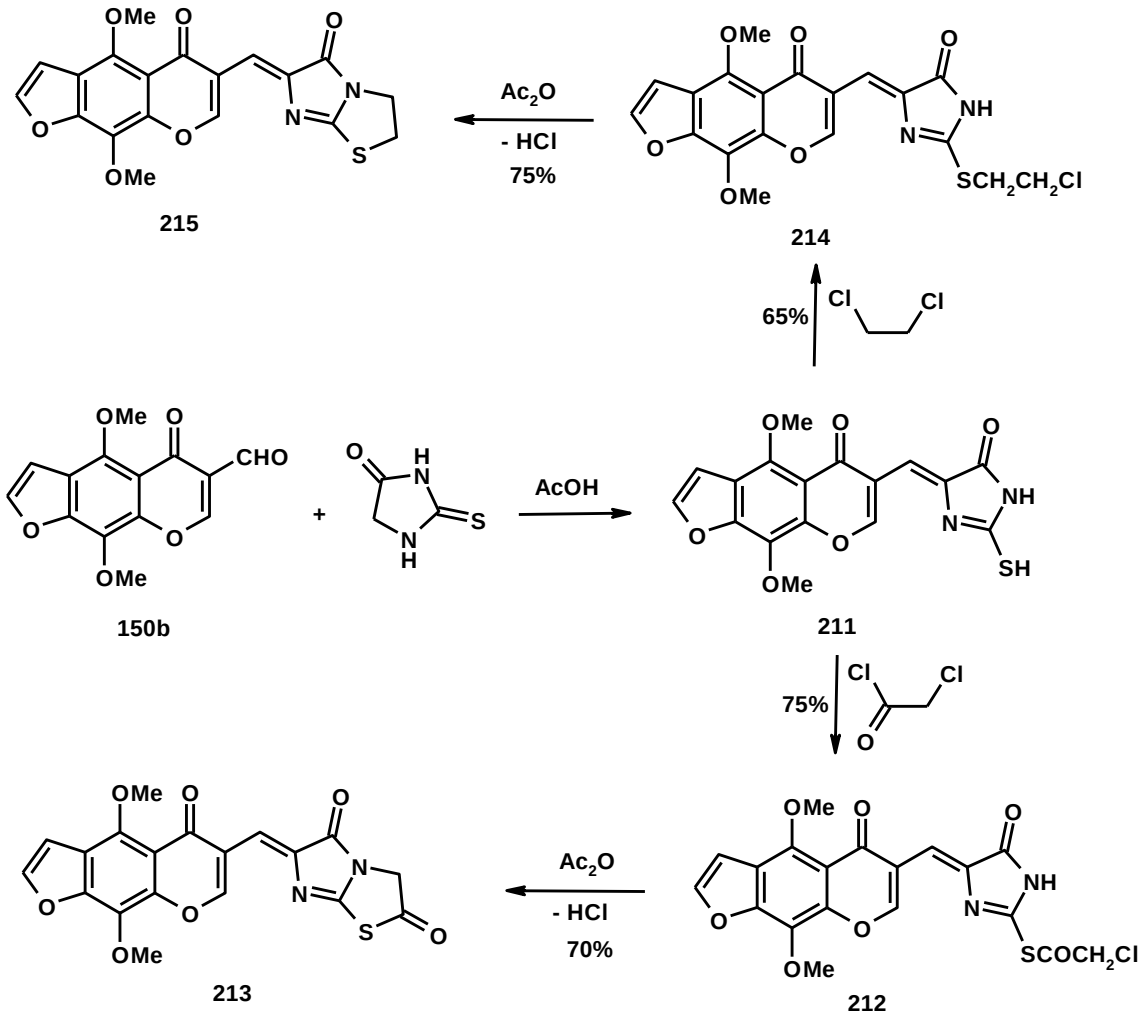


Scheme 86



Scheme 87

6-Formylnorkhellin (**150b**) condensed with 2-thioxo-4-imidazolinone to form the corresponding condensation product **211**. Treatment of compound **211** with chloroacetyl chloride provided *S*-acylated poduct **212** which cyclised with acetic anhydride leading to [(furo[3,2-*g*]chromen-6-yl)methylene]-imidazo[2,1-*b*]thiazole-2,5(3*H*,6*H*)-dione **213**. Similarly, reaction of compound **211** with 1,2-dichloro-ethane resulted in the formation of S-alkylated poduct **214** which cyclized with acetic anhydride to give [(furo[3,2-*g*]chromen-6-yl)methylene]imidazo[2,1-*b*]thiazol-5(6*H*)-one derivative **215** (Scheme 88).[99]



Scheme 88

7. CONCLUSION

In conclusion, *Ammi visnaga* (Umbelliferae) is the most famous source to obtain furochromones, which showed a numerous interesting biological properties especially in folk medicine for millennia targeting different ailments, skin disease and treatment of angina as well as in facilitating the passage of urethral stones, alleviating renal colic pain and urethral spasms. Different types of reactions carried out on naturally occurring furochromones (visnagin and khellin) are briefly summarized. Diverse synthetic methodologies were utilized to prepare a variety of heterocyclic rings using furochromone derivatives. Also, different procedures were developed for preparation of functionalized benzofurans and chromones as well as their utilization as the blocks for many biologically active compounds. Moreover, 6-formylnorvisnagin and 6-formylnorkhellin are very sensitive to nucleophiles and their chemical reactivity are summarized.

REFERENCES

1. A. A. Abu-Hashem, *Eur. J. Med. Chem.*, 2015, **90**, 633.
2. C. P. Huttrer and E. Dale, *Chem. Revs.*, 1951, **48**, 543.
3. A. Schönberg, N. Badran, and N. A. Starkowsky, *J. Am. Chem. Soc.*, 1953, **75**, 4992.
4. A. Schönberg, N. Badran, and N. A. Starkowsky, *J. Am. Chem. Soc.*, 1955, **77**, 5390.
5. A. Schönberg, N. Badran, and N. A. Starkowsky, *J. Am. Chem. Soc.*, 1955, **77**, 5438.
6. A. Schönberg, N. Badran, and N. A. Starkowsky, *J. Am. Chem. Soc.*, 1955, **77**, 5439.
7. A. Schönberg and A. Sina, *J. Chem. Soc.*, 1950, 3344.
8. A. Schönberg and M. M. Sidky, *J. Org. Chem.*, 1956, **21**, 476.
9. A. Schönberg and M. M. Sidky, *J. Am. Chem. Soc.*, 1953, **75**, 5128.
10. A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, 1950, **72**, 1611.
11. F. Ati, S. El-Aoufi, A. Chergui, H. Y. Aboul-Enein, and B. Maouche, *J. Iran. Chem. Soc.*, 2008, **5**, 506.
12. A. Schönberg and N. Badran, *J. Am. Chem. Soc.*, 1951, **73**, 2960.
13. A. Schönberg and G. Aziz, *J. Am. Chem. Soc.*, 1953, **75**, 3265.
14. W. Asker, A. F. A. Shalaby, and S. M. A. Zayed, *J. Org. Chem.*, 1958, **23**, 1781.
15. A. Mustafa, N. A. Starkowsky, and T. I. Salama, *J. Org. Chem.*, 1961, **26**, 886.
16. A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, 1950, **72**, 3396.
17. J. R. Clarke and A. Robertson, *J. Chem. Soc.*, 1949, 302.
18. J. R. Clarke, G. Glaser, and A. Robertson, *J. Chem. Soc.*, 1948, 2260.
19. L. Fabbrini, *Ann. Chim. (Rome)*, 1956, **46**, 130.
20. O. Dann and G. Volz, *Liebigs Ann. Chem.*, 1965, **685**, 167.
21. R. B. Gammil and S. A. Nash, *J. Org. Chem.*, 1986, **51**, 3116.
22. R. B. Gammil and S. A. Nash, *Tetrahedron Lett.*, 1984, **25**, 2953.
23. V. V. S. Murti and T. R. Seshardi, *Proc. Indian Acad. Sci.*, 1949, **30A**, 107.
24. G. Benzi and P. Perini, Farmaco, *Ed., Sci.*, 1969, **24**, 1073 (*Chem. Abstr.*, 1970, **72**, 78917k).
25. O. H. Hishmat, A. M. Nasef, Sh. I. A. El-Naem, and A. M. Shalaby, *Arch. Pharm. Res.*, 1989, **12**, 259.
26. S. I. Khater, S. A. Kandil, and H. Hussien, *J. Radioanal. Nucl. Chem.*, 2013, **295**, 1939.
27. S. A. Nash and R. B. Gammill, *Tetrahdron Lett.*, 1987, **28**, 4003.
28. H. A. Regaila, A. K. Goher, and G. G. Abdel-Sadek, *Egypt. J. Pharm. Sci.*, 1989, **30**, 159.
29. A.-K. M. N. Goher and G. G. Abdel-Sadek, *Arch. Pharm.*, 1987, **320**, 823.
30. A. S. H. Elgazwy, M. M. Edrees, and N. S. M. Ismail, *J. Enzyme Inhib. Med. Chem.*, 2013, **28**, 1171.
31. A. A. Abu-Hashem and M. M. Youssef, Molecules, 2011, **16**, 1956.

32. M. A. A. El-Sayed, S. R. Gedara, and N. I. Abdel-Aziz, *J. Am. Sci.*, 2012, **8**, 851.
33. A. Schönberg, A. Mustafa, and G. Aziz, *J. Am. Chem. Soc.*, 1954, **76**, 4576.
34. G. A. Kilcigil, M. Tuncbilek, and R. Ertan, Turk. *J. Chem.*, 2000, **24**, 255.
35. S. M. Sh. Atta, D. S. Farrag, A. M. K. Sweed, and A. H. Abdel-Rahman, *Eur. J. Med. Chem.*, 2010, **45**, 4920.
36. R. B. Gammill, [The Upjohn Company (Kalamazoo, MI)], USP, 4,284,569 (*Chem. Abstr.*, 1981, **95**, 203917).
37. B. Beugelmans and C. Morin, *J. Org. Chem.*, 1977, **42**, 1356.
38. K. Takagi and M. Hubert-Habart, *Eur. J. Med. Chem. Chim. Ther.*, 1974, **9**, 14.
39. O. M. Abdelhafez, N. A. Abdelatif, and F. A. Badria, *Arch. Pharm. Res.*, 2011, **34**, 1623.
40. S. A. Hessein, A. M. Sh. El-Sherief, S. Y. Abbas, H. Kh. Thabet, and Y. A. Ammar, *Croat. Chem. Acta*, 2016, **89**, 91.
41. A. Raval and N. Shah, *J. Org. Chem.*, 1958, **23**, 748.
42. V. Ya. Sosnovskikh and V. A. Kutsenko, *Mendeleev Commun.*, 2000, **10**, 238.
43. V. Ya. Sosnovskikh and B. I. Usachev, *Synthesis*, 2002, 1007.
44. O. H. Hishmat, S. S. Mabrouk, A. M. M. Nasef, and N. M. A. Shayeb, *Z. Naturforsch.*, 1988, **43b**, 343.
45. O. H. Hishmat, N. M. Y. Zohair, and J. A. A. Miky, *Z. Naturforsch.*, 1983, **38b**, 1690.
46. E. I. El-Desoky, M. A. Hammad, N. Grant, E. M. El-Telbany, and A. H. Abdel-Rahaman, *Tetrahedron*, 1997, **53**, 15799.
47. R. B. Gammill, *J. Org. Chem.*, 1984, **49**, 5035.
48. A. H. Abdel-Rhaman, E. M. Keshk, and E. M. El-Telbani, *Z. Naturforsch.*, 2002, **57b**, 557.
49. O. M. Abdel-Hafez, K. M. Ahmed, A. M. Mandour, and A. M. El-Khirsy, *Pak. J. Sci. Ind. Res.*, 1990, **33**, 197.
50. E. R. El-Sawy, M. S. Ebaid, H. M. Abo-Salem, S. El-Hallouty, E. M. Kassem, and A. H. Mandour, *J. Adv. Res.*, 2014, **5**, 337.
51. F. A. Ragab, T. A. A. Yahya, M. M. El-Naa, and R. K. Arafa, *Eur. J. Med. Chem.*, 2014, **82**, 506.
52. C. Musante, *Gazz. Chim. Ital.*, 1958, **88**, 910 (*Chem. Abstr.*, 1958, **52**, 1156b).
53. O. H. Hishmat, K. M. Khalil, N. M. A. El-Ebrashi, and M. N. M. Khodeir, *Z. Naturforsch.*, 1978, **33b**, 1491.
54. F. A. Ragab, N. A. M. EL-Sayed, A. A. M. Eissa, and A. M. El-Kerdawy, *Chem. Pharm. Bull.*, 2010, **58**, 1148.
55. M. Khodeir, F. El-Taweel, and A. El-Gamey, *Pharmazie*, 1992, **47**, 486.
56. T. H. El-Shini, N. A. Abdel-Latif, and E. R. El-Sawy, *Egypt. J. Chem.*, 2004, **34**, 365.

57. S. A. Hessein, *Int. J. Adv. Res.*, 2015, **3**, 654.
58. F. A. Ragab, G. S. Hassan, H. A. Yossef, and H. A. Hashem, *Eur. J. Med. Chem.*, 2007, **42**, 1117.
59. F. Eiden and J. Schünemzinn, *Arch. Pharm.*, 1983, **316**, 201.
60. F. Eiden and J. Schünemzinn, *Arch. Pharm.*, 1984, **317**, 203.
61. F. Eiden, G. Rademacher, and J. Schünemzinn, *Arch. Pharm.*, 1984, **317**, 539.
62. P. R. Iyer, C. S. R. Iyer, and K. J. R. Prasad, *Indian J. Chem.*, 1983, **22B**, 1055.
63. C. B. Rao, G. Subramanyam, and V. Venkateswarlu, *J. Org. Chem.*, 1959, **24**, 685.
64. J. A. A. Miky and H. H. Sharaf, *Indian J. Chem.*, 1998, **37B**, 68.
65. O. M. Abdelhafez, H. I. Ali, K. M. Amin, M. M. Abdalla, and E. Y. Ahmed, *Royal. Soc. Chem.*, 2015, **5**, 25312.
66. H. I. El-Diwani and H. El-Sahrawi, *Indian J. Chem.*, 1995, **34B**, 27.
67. H. Abu-Shady, S. T. Hassib, A. N. Mikhael, and S. El-Ansary, *Egypt. J. Pharm. Sci.*, 1988, **29**, 471.
68. O. H. Hishamt, Hh. M. A. Khalil, Sh. E. El-Naem, and A. H. Abdel-Rahman, *Egypt. J. Chem.*, 1987, **30**, 171.
69. O. H. Hishmat, N. M. A. Ebrashi, and Sh. E. El-Naem, *Synthesis*, 1982, 1075.
70. O. H. Hishmat, N. M. Fawzy, S. I. El-Naem, A. A. M. El Din, and A. S. Abd El-All, *Pol. J. Appl. Chem.*, 1998, **41**, 369.
71. O. H. Hishmat, N. M. Fawzy, D. S. Farag, A. S. Abd El-Aal, and A. H. Abdel-Rahman, *Boll. Chim. Farm.*, 1999, **8**, 239.
72. A. H. Abdel-Rahman, A. M., Khalil, S. I. El-Dosoky, and E. M. Keshk, *Chem. Pap.*, 1999, **53**, 323.
73. F. F. Abdel-latif and A. K. M. N. Gohar, *Bull. Soc. Chim. Belg.*, 1986, **95**, 211.
74. R. B. Gammill, S. A. Nash, and S. A. Mizsak, *Tetrahedron Lett.*, 1983, **24**, 3435.
75. R. B. Gammill, S. A. Nash, L. T. Bell, and W. Watt, *Tetrahedron Lett.*, 1992, **33**, 997.
76. R. B. Gammill, S. A. Nash, L. T. Bell, and W. Watt, *Tetrahedron Lett.*, 1992, **33**, 993.
77. F. Eiden, G. Rademacher, and J. Schünemann, *Arch. Pharm.*, 1984, **317**, 539.
78. F. Eiden and G. Rademacher, *Arch. Pharm.*, 1985, **318**, 926.
79. E. I. El-Desoky and S. S. Al-Shihry, *J. Heterocycl. Chem.*, 2008, **45**, 1855.
80. N. M. Fawzy, A. H. Mandour, and M. E. A. Zaki, *Egypt. J. Chem.*, 2000, **43**, 401.
81. O. H. Hishmat, H. I. El-Diwani, Sh. I. El-Naem, and N. M. Fawzy, *Pol. J. Chem.*, 1993, **67**, 1987.
82. A. A. Magd El-Din, S. M. Sh. Atta, A. S. Abd El-All, S. A. Galal, and M. M. Abdalah, *World J. Chem.*, 2009, **4**, 112.
83. E. R. El-Sawy, K. H. Shaker, A. H. Mandour, A. Shehab El-Din, and M. M. Abdula, *Indian J. Chem.*, 2008, **47B**, 1451.
84. F. A. Ragab, M. K. El-Said, and S. A. K. Kenawy, *Egypt. J. Pharm. Sci.*, 1992, **33**, 83.

85. S. A. Galal, A. S. Abd El-All, M. M. Abdallah, and H. I. Diwani, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2420.
86. N. M. Fawzy, S. A. Swelam, and S. A. Batran, *Boll. Chim. Farm.*, 2004, 143, 24 (*Chem. Abstr.*, 2005, **142**, 113936d).
87. N. M. Fawzy, *Int. J. Pharm. Res.*, 2009, **1**, 1697.
88. N. M. Fawzy, *Heterocycl. Commun.*, 2008, **14**, 169.
89. E. A. Elhefny, S. M. Abu-Bakr, N. M. Fawzy, A. M. Nasef, and M. M. Aly, *Int. J. Pharm. Sci. Rev. Res.*, 2015, **32**, 85.
90. A. S. Abd El-All, S. A. Osman, H. M. F. Roaiah, M. M. Abdalla, A. A. Abd El Aty, and W. H. Abd El-Hady, *Med. Chem. Res.*, 2015, **24**, 4093.
91. I. F. Zaeid, A. M. Nasef, N. M. Fawzy, A. M. Soliman, and M. M. S. El-Baroudy, *Int. J. Pharm. Sci. Rev. Res.*, 2015, **30**, 306.
92. M. A. Abdel-Aziz, O. H. Hishmat, Sh. I. El-Naem, and N. M. Fawzy, *Sulfur Lett.*, 1990, **10**, 255.
93. A. H. Abdel-Rahman, A. M. Khalil, and E. M. Keshk, *Chem. Pap.*, 2000, **54**, 324.
94. N. M. Fawzy, *Boll. Chim. Farm.*, 2004, 143, 70 (*Chem. Abstr.*, 2005, **142**, 197996I).
95. A. A. Magd-El-Din, A. S. Abd-El-All, A. H. Abd El-Rhaman, and M. M. S. El-Baroudy, *Nat. Sci.*, 2010, **8**, 12.
96. N. M. Abdel-Rhaman, N. M. Fawzy, and M. E. A. Zaki, *Int. J. Pharm. Res.*, 2009, **1**, 857.
97. N. M. Fawzy, *Bull. Fac. Sci. Mansura Univ.*, 1997, **24**, 101.
98. O. H. Hishmat, N. M. Fawzy, D. S. Farrag, and A. S. Abd El-All, *Rev. Roum. Chim.*, 1999, **44**, 161 (*Chem. Abstr.*, 2000, **133**, 30598h).
99. A. A. Magd-El-Din, A. S. Abd-El-All, H. M. F. Roaiah, and M. M. S. El-Baroudy, *J. Am. Sci.*, 2010, **6**, 251.

Magdy Ahmed Mohamed Ibrahim was born in Cairo, Egypt, in 1977. He received his B.Sc. degree in physics and chemistry (1999) and his M.Sc. degree in organic chemistry (2004). Also, he received his Ph.D. degree (2007) from the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. He won the award for the best research article in heterocyclic chemistry field at the Egyptian universities and research centers in 2010. In 2012 he was promoted to assistant professor in organic chemistry. His research is focused on the synthesis of new heterocyclic compounds containing chromone, khellin, pyridine, quinolin-2(1*H*)-one and 1,2,4-triazine. In addition, he has published about 55 scientific papers in international scientific journals. He is the supervisor on the M.Sc. and/or Ph.D. degrees of the present co-authors.

Al shimaa Badran Abd-el Monem was born in Cairo, Egypt, in 1987. She received his B.Sc. degree in chemistry (2008) and her M.Sc. degree in organic chemistry (2013). Also, she received her Ph.D. degree (2016) from the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. Her research is focused on the synthesis of new heterocyclic compounds containing γ-pyrone and quinolin-2(1*H*)-one moiety.

Nasser Mohamed Ahmed El-Gohary was born in Giza, Egypt, in 1980. He received his B.Sc. degree in physics and chemistry (2001) and his M.Sc. degree in organic chemistry (2009). Also, he received his Ph.D. degree (2012) from the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. His research is focused on the synthesis of new heterocyclic compounds containing chromone nuclus.

Noura Ali Abdel-fatah was born in Cairo, Egypt, in 1986. She received her B.Sc. degree in physics and chemistry (2008) from Helwan University. She registered her M.Sc. degree in organic chemistry (2016) in the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. Her research is focused on the synthesis of new heterocyclic compounds using naturally occurring khellin.