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Synthesis, Reactions and Biological Activities of Furochromones: A review

Ameen A. Abu-Hashem [a,b]*, Mohamed El-Shazly [c]

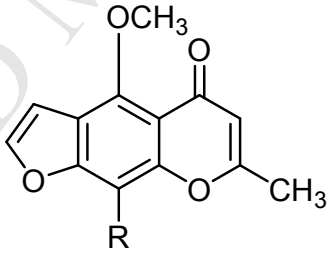
[a] *Photochemistry Department (Heterocyclic Unit), National Research Center, 12622 Dokki, Giza, Egypt*

[b] *Chemistry Departments, Faculty of Science, Jazan University, 2097 Jazan, Saudi Arabia*.

[c] *Department of Pharmacognosy and Natural Products Chemistry, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt*.

E-mail: aminaliabuhashem@yahoo.com

Graphical Abstract

Synthesis, Reactions and Biological Activities of Furochromones: A review *Ameen Ali Abu-Hashem**, Mohamed El-Shazly	 Khellin, **1a**, R = OCH_3 Visnagin, **1b**, R = H

Synthesis, Reactions and Biological Activities of Furochromones: A review

Ameen A. Abu-Hashem [a,b]*, Mohamed El-Shazly [c]

[a] *Photochemistry Department (Heterocyclic Unit), National Research Center, 12622 Dokki, Giza, Egypt*

[b] *Chemistry Departments, Faculty of Science, Jazan University, 2097 Jazan, Saudi Arabia.*

[c] *Department of Pharmacognosy and Natural Products Chemistry, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.*

Abstract

Furochromone derivatives are important synthetic targets which showed a myriad of interesting biological activities. *Ammi visnaga* (Umbelliferae) is the most famous source of these derivatives, which has been used in folk medicine for millennia targeting different ailments. Since the isolation of furochromone derivatives, different synthetic methodologies were developed for their preparation. Despite the recent interesting findings on this class of compounds, the chemical literatures lack a comprehensive summary on the synthetic methodologies and biological activities of furochromone derivatives. This review highlights recent advances in furochromones chemistry by discussing different synthetic procedures developed for the preparation of naturally occurring derivatives as well as other unique derivatives which showed promising biological activities. It also sheds light on the most common reactions of furochromone derivatives and the utilization of these derivatives as the blocks for many biologically active compounds .

Keywords: Ammi visnaga, furochromones**,** khellin, visnagin, benzofurans.

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1. Introduction:

Since the dawn of history, herbal products have played a vital role in human civilization. This role was clearly documented in ancient drawings in African caves as well as in temples of ancient Egypt, Mesopotamia, and ancient Greeks [1]. Ancient Egyptian physicians have recognized the healing properties of many Mediterranean plants including *Cassia acutifolia* (Senna), *Ammi visnaga* and *Pimpinella anisum*. These plants have contributed to the welfare and prosperity of Egyptian civilization through maintaining good health of its citizens. Among these important plants, is *Ammi visnaga* Lam. (Umbelliferae). It is a wild plant indigenous to Egypt and its dry fruits have been used for centuries in Egyptian folk medicine as a diuretic infusion and as therapy for kidney and bladder stones [2-4]. In addition to its folk use, it is currently utilized by pharmaceutical companies as a source of furochromones (khellin

and visnagin) [5]. *Ammi visnaga* seeds and fruits is a rich source of khellin, visnagin and khellol glucoside (Figure 1: Chemical structure of khellin, visnagin and Khellol glucoside).

Figure 1

A. visnaga extracts and its active components (furochromone) have been widely utilized for their therapeutic properties. The furochromone content of *A. visnaga* differs with its geographical location, and the careful selection of the correct plant part is of crucial importance for the proper medicinal use. Several techniques have been implemented for the preparation of crude furochromone fractions including fractional crystallization and preparative chromatographic procedures. *A. visnaga* and its furochromones are generally used in alleviating renal colic pain and urethral spasms as well as in facilitating the passage of urethral stones [6]. Later, it became well known that *A. visnaga* possess coronary vasodilating and spasmolytic activities [7-11]. Other biological properties of *A. visnaga* active components were also reported including antineoplastic, antianaphylactic, antiatherosclerotic, anti-inflammatory and analgesic properties [12-15].

Khellin and visnagin, 4, 9-dimethoxy- or 4-methoxy-7-methyl-furo [3,2-*g*]chromen-5-one, respectively (Figure 1) have been widely employed in several folk herbal preparations for the treatment of angina [16]. Besides their vasodilating activity on the urinary system smooth muscles, it was found that khellin and visnagin extracts significantly prolong the induction time of calcium oxalate nucleation, the main component of most kidney stones [17]. Radioiodinated khellin is used for urinary tract imaging [18]. Khellin is a potent coronary vasodilator with a pronounced antispasmodic activity and, therefore, has been used against angina pectoris and asthma [3, 19, 20].

Khellin has been used in the photo-chemotherapeutic treatment of vitiligo and psoriasis [21-23]. The photodynamic properties of khellin and visnagin and their photoreaction with DNA have been also studied [24]. Recently, khellin was shown to possess phototherapeutic properties similar to those of the psoralen, but with substantially lower phototoxic and DNA damaging effects. Its penetration into the

hair follicles is enhanced by encapsulating khellin into liposomes. Subsequent activation of khellin with UV light was found to stimulate the melanocytes in the hair follicles [25]. It also showed valuable phototoxic and genotoxic activities against various kinds of microorganisms [26, 27]. Khellin also exhibited significant Epidermal Growth Factor Receptor (EGFR) inhibitory activity [28].

2. Synthetic Methods of Furochromones:

Over the last century, many attempts have been focused on the development of efficient methodologies for the synthesis of furochromones and their derivatives [29-31]. Several commercially available starting materials have been utilized for this purpose with impressive results. Different furochromones derivatives were prepared in high yields and selectivity.

2.1. From Furan Derivatives:

A furan derivative, 3-furoic acid (**5**), has been exploited as the starting material for furochromone derivative. The addition of succinic anhydride to **5** in the presence of lithium-diisopropyl amide (LDA) followed by esterification resulted in the formation of **6** [32]. The regiospecific introduction of the dimethylamino methylene unit which is adjacent to the carbonyl group was accomplished using dimethyl formamide dimethyl acetal in the presence of *p*-toluenesulphonic acid to yield the precursor **7**. Dieckmann cyclization of **7** rendered a benzofuran derivative (**8**) which was methylated and then oxidized using *m*-chloro perbenzoic acid (*m*-CPBA) to yield **10**. Conversion of **10** to khellinone (**4a**) was achieved through the addition of methyl magnesium bromide in the presence of triethylamine dissolved in benzene. Claisen condensation of **4a** resulted in the formation of the desired product **1a** (Scheme **1**).

Scheme 1

The synthesis of different furochromone derivatives (**1a**, **b**) has been also accomplished utilizing furan methoxy (or methylthio) carbine complex (**11**) as the starting material. This subtract (**11**, X = SMe) was prepared by the reaction of 2-lithiofuran with chromium hexacarbonyl in THF at -30 $^{\circ}$C followed by the addition of

tetrabutyl ammonium bromide, to produce an isolable ammonium salt which was converted to **11** through acetylation and treatment with MeSH [33]. The cycloaddition reaction between furan methoxy (or methylthio) carbine complex (**11**) and the alkoxyalkyne derivative (**12**) furnished the benzofuran acetate derivative (**13**). The formation of this intermediate (**13**) is crucial in the synthesis of furochromones because it bears the necessary functional groups to build the γ-pyrone skeleton (**14**, **15**) which can be easily converted to the desired product (**1b**) utilizing Raney-Ni (Scheme 2) [34, 35].

Scheme 2

2.2 From Derivatives of Aryl Compounds:

The synthesis of khellinone and khellin was achieved starting from pyrogallol (Scheme 3) [36]. The esterification of benzene-1,2,3-triol (**16**) resulted in the formation of 1,3-bis-benzyloxy-2,5-dimethoxy-benzene (**17**) which was reacted under modified Gatierman conditions in the presence $ZN(CN)_2$ to yield **18**. This intermediate (**18**) was esterified with benzyl bromide providing **19**. Compound (**19**) reacted with methyl bromoacetate affording **20** which was further cyclized upon reacting with acetic anhydride to yield **21**. Compound (**21**) was converted to khellinone (**4a**) and khellin (**1a**) through a series of oxidation and reduction steps (Scheme 3).

Scheme 3

Benzene-1,3-diol (**25a-d**) derivatives were also utilized as the starting building blocks for the synthesis of furochromones. These derivatives (**25a-d**) reacted with acetic acid derivatives (**26a-b**) yielding **27a-h**, which were reacted with benzoyl chloride followed by hexamine to provide **29a-h**. The formation of furochromones (**30a-h**) was achieved through reacting **29a-h** with ethyl bromo acetate in K_2CO_3 as a phase transfer catalyst under nitrogen atmosphere (Scheme 4) [37].

Scheme 4

2.3 From Benzofuran Derivatives

Furochromones were synthesized from benzofuran derivatives through a simple straightforward cyclization reaction. The cyclization of hydroxychalcone (**31a**, **b**) was achieved through Michael addition reaction [38]. The hydroxychalcone reacted with sulfur in boiling DMF followed by oxidation to furnish 5-methoxy-2-aryl-furo [3, 2-g] benzopyran-4-one (**32a**, **b**). On the other hand, when the hydroxychalcone (**31a**) was refluxed with 20% H_2SO_4, cyclization occurred to yield 5-methoxy-2-phenyl-2,3-dihydrofuro [3,2-g] benzo-pyran-4-one (**33**) which was oxidized when boiled with sulfur in DMF to form **32a**, (Scheme 5).

Scheme 5

A number of linearly fused furochromones (**35-43**) were synthesized starting from the naturally occurring khellin and visnagin *via* enaminone formation using *N*,*N*-dimethyl formamide dimethyl acetal (**34**) followed by ring closure in an acidic medium [39]. Various reactions on the enaminone derivatives were performed and summarized in Schemes 6 and 7.

Scheme 6

Scheme 7

Condensation of khellinone **4a** with R^FCO_2Et in the presence of LiH in boiling THF proceeded at the acetyl group of **4a** and afforded benzofuran derivatives **45a–f**. This reaction was mediated through the tautomerization of the hemiketal derivative (**A**) forming the corresponding diketones (**C**) (Scheme 8) [40].

Scheme 8

3. Chemical Properties of Furochromones:

3.1. Color Reactions:

Furochromones (khellin and visnagin) give different color reactions with a number of reagents. These colors are of particular interest since they can be used as a mean for the differentiation and isolation of these compounds. It was found that khellin gives an intense red-violet color with potassium or sodium hydroxide pellets [41-45]. This reaction has been used for its colorimetric estimation [19]. However, Schönberg and Sina have shown that this color reaction is not specific for khellin, since visnagin and other 2-methylchromones give positive results in the same test [46, 47]. The nature of the violet substance obtained was proposed by Sidky and Mahran to be formed through the 1:4 addition of carbanion of one molecule to the α,β-unsaturated system of another molecule, followed by ring opening of the intermediate adduct as shown in Scheme 9 [48].

Scheme 9

3.2. Addition Reactions and Formation of Salts:

The preparation of bromovisnagin (**48**) was obtained by the bromination of visnagin (**1b**) using bromine in acetic acid. Condensation of **48** with hydrazine hydrate, phenylhydrazine and/or hydroxylamine hydrochloride afforded the corresponding pyrazole derivatives and isoxazole derivatives (**50a-c**), respectively [49]. On the other hand, 4-methoxy-5-acetyl-6-hydroxy-7-bromobenzofuran (**49**) which was prepared by the alkaline hydrolysis of **48** followed by a retro-aldol reaction was condensed with some aromatic aldehydes namely, benzaldehyde, 4-chlorobenzaldehyde, 4-methoxy-benzaldehyde, thiophene aldehyde, and butyraldehyde to yield the corresponding α,β-unsaturated keto derivatives (**51a-e**) as shown in Scheme 10.

Scheme 10

Chlorosulfonation of visnagin (**1b**) using chlorosulfonic acid at room temperature without solvent yielded visnagin-9-sulfonylchloride (**52**) which upon amidation using morpholine in dioxane provided the 9-sulfonamido derivative (**53**) Alkaline hydrolysis of the later by 3% aqueous potassium hydroxide yielded 4-methoxy-5-acetyl-6-hydroxy-7-N-morpholinosulfonamido benzofuran (**54**) which was condensed with some aromatic aldehydes namely, 4-chlorobenzaldehyde, 4-methoxy

benzaldehyde, and dimethyl aminobenzaldehyde in alkaline medium to yield the corresponding α,β-unsaturated keto derivatives (**55a-c**) as shown in Scheme 11.

Scheme 11

The addition of iodine monochloride solution in hydrochloric acid to a cold solution of khellin in acetic acid resulted in the formation of oxonium iodochlorohydrate of 7-chloro-7-methyl-6-iodo-4, 9-dimethoxy-6, 7-dihydro-5*H*-furo[3,2-g][1]benzofuran-5-one (**56**).Similarly, 7-methyl-6,7-diiodo-4,9-dimethoxy-6,7-dihydro-5*H*-furo [3,2-g] [1] benzofuran-5-one (**57**) is prepared by the addition of iodine to a solution of khellin in chloroform as shown in Scheme 12 [50].

Scheme 12

A procedure for the radioiodination of khellin (**1a**) with ^{125}I was carried out via an electrophilic substitution reaction. Different reaction parameters were studied including the amount of khellin, pH of the reaction mixture, reaction time, temperature, type of the oxidizing agents and type of the organic media aiming to optimize the conditions for khellin labeling to obtain a high radiochemical yield of ^{125}I-khellin (^{125}I-Khel) (**58**). Using 3.7 MBq of Na^{125}I, 0.96 mM of khellin as a substrate, 1 mM of chloramine-T as the oxidizing agent in ethanol at 60 °C for 10 min, a maximum radiochemical yield of ^{125}I-Khel (78%) was obtained. The specific activity of ^{125}I-Khel was 3 MBq/0.5 mM. The biological distribution in normal mice indicated that the radioiodinated khellin is a novel agent for urinary tract infection imaging as demonstrated in Scheme 13 [18].

Scheme 13

3.3. Action of Alkali and Vilsmeier-Haack Reaction:

The naturally occurring furochromones, khellin (**1a**) and visnagin (**1b**), are very sensitive to alkali and the type of alkali significantly affects the product formation [51, 52]. Aqueous alkaline hydrolysis of **1a** and **1b** using potassium hydroxide followed by a retro-aldol reaction afforded khellinone (**4a**) and visnaginone (**4b**),

respectively [53]. On the other hand, the alcoholic hydrolysis of **1a** and **1b** with potassium hydroxide followed by a retro-aldol reaction yielded different products known as x-acetokhellinone (**59a**) and x-acetovisnaginone (**59b**) [54]. The hydrolysis products are important intermediates for the synthesis of new furochromones. Compounds (**4a**) and (**4b**) were used in the synthesis of 5-oxo-5*H*-furo [3,2-g] chromene-6-carbaldehydes (**3a**) and (**3b**) directly via Vilsmeier-Haack reaction (Scheme 14) which was achieved by Eiden group as illustrated in a series of studies [55-61].

Scheme 14

The synthesis of furobenzopyran aldehyde **3** and the flavone aldehyde **60** was also accomplished from the naturally occurring furochromones khellin **1a** and visnagin **1b** [62]. Ring opening of the *γ*–pyrone ring with KOH followed by a retro-aldol reaction yielded the ketones **4a** and **4b**. The conversion of **4a** to 4,9-dimethoxy-5-oxo-5*H*furo[3,2-*γ*]chromene-6-carbaldehyde (**3**) was carried out *via* Vilsmeier–Haack reaction. Subjecting **4b** to Claisen Schmidt condensation with benzaldehyde produced 1-(6-hydroxy- 4-methoxy-1-benzofuran-5-yl)-3-phenylprop-2-en-1-one (**31**) which was converted to a furoflavone derivative (**32**) by oxidative cyclization with selenium dioxide in butanol. Cleavage of **32** furan ring by chromic acid rendered 7-hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromene-6-carbaldehyde **60** (Scheme 15).

Scheme 15

3.4. Reduction:

The reduction products of khellin differ according to the reducing agents used [50, 63]. Paleography of khellin and visnagin shows that they can be reduced at the dropping mercuric electrode (Scheme 16) [64].

Scheme 16

3.5. Oxidation:

The oxidation of furochromone is well documented in literature [65, 66]. For example, the oxidation of visnagin with chromic acid yielded the hydroxyaldehyde (**64b**). Treatment of khellin with chromic acid under the same conditions failed to yield the corresponding hydroxyaldehyde (**64a**). The oxidation of khellin with thallium III nitrate (TTN) in methanol yielded the two geometrical isomers (**65**) via the addition of two molecules of methanol across the 2,3-double bond in the furan ring. Gammill et al. reported a cleaner and higher yielding reaction by utilizing $Hg(NO_3)_2$ rather than TTN (Scheme 17) [67, 68].

Scheme 17

A salicylaldehyde derivative (**64a**) was obtained via ozonolysis or the oxidation of **1a** with mercuric (II) nitrate followed by the treatment with sodium metaperiodate ($NaIO_4$) [69]. The same aldehydes could be obtained directly from khellin in higher yields without isolation of the intermediate diols (**67**) through osmylation [70-72]. Also, the oxidation of khellin using hydrogen peroxide or vanadium pentoxide afforded benzofuran-5-carboxylic acid (**66b**) or a quinine derivative (**68**), respectively (Scheme 18) [66, 69].

Scheme 18

The oxidation of khellin with $PdCl_2$ under 30 psi of O_2 in the presence of CuCl in methanol afforded the hydroxyl ester (**71**) in 73% yield [73]. The lactone derivative (**72**) was prepared by carful hydrolysis of **71** with two equivalents of sodium hydroxide followed by refluxing in acetic anhydride as shown in Scheme 19.

Scheme 19

The oxidation of khellin with selenium dioxide in ethyl acetate resulted in the formation of a mixture of the corresponding aldehyde (**73a**) and carboxylic acid (**73b**) (Scheme 20) [30].

Scheme 20

3.6. Alkylation Reaction and Demethylation:

Demethylation of **1b** using hydrochloric acid afforded 4-demethyl-visnagin (nor visnagin) (**74**) which reacted with ethyl bromoacetate in dry acetone in the presence of anhydrous potassium carbonate to yield 4-ethoxy-5-oxo-2-methyl furo[3,2-g] benzopyran (**75**) [49]. The later compound reacted with hydrazine hydrate to furnish the corresponding 4-oxyacetohydrazide derivative (**76**). The later compound was further condensed with 3,4,5-trimethoxybenzaldehyde to yield the hydrazone derivative (**77**) which on its condensation with mercaptoacetic acid yielded thiazolidinone derivative (**78**) (Scheme 21).

Scheme 21

Chloromethylation of demethylvisnagin (**74**) afforded 9-chloromethyl norvisnagin (**79**) [49]. The tertiary amino derivatives (**80a**, **b**) were obtained either by the reaction of a primary amine such as methylamine or 2-aminopyridine with **79** or by the reaction of a primary amine in the presence of formaldehyde with norvisnagin (**74**). The Mannich bases (**81a-c**) were obtained by the treatment of **74** with a secondary amine such as diethylamine, piperidine or morpholine in the presence of formaldehyde. Benzoylation of Mannich bases (**80a**, **b**) and (**81a-c**) by benzoyl chloride in benzene afforded the corresponding the benzoyloxy derivatives (**82a-e**) (Scheme 22).

Scheme 22

Demethylation of khellin with iodide salt is accompanied by the simultaneous opening of the γ-pyrone ring and its subsequent closure on the hydroxyl group at position 4 to give **83** which on methylation yield isokhellin (**84**) [74-77]. Rearrangement can also occur upon using moderately concentrated hydrobromic acid, which can lead to demethylation resulting in the formation of norisokhellin (**83**) (Scheme 23) [78].

Scheme 23

On the other hand, during the demthylation of visnagin with hydriodic acid, the furan ring undergoes rearrangement to form norisovisnagin (**85**) [75]. The structure of the latter compound was confirmed by the synthesis of isovisnagin (**86**), (Scheme 24) [75, 79].

Scheme 24

The total demethylation of khellin has been achieved by heating with magnesium iodide in the absence of any solvent to yield 4,9-dinorkhellin (also called khellinquinol) (**87**) or by treating with pyridine hydrochloride (Scheme 25) [46, 47, 80, 81].

Scheme 25

The chromone derivatives (**90**, **94** and **97**) were synthesized using visnagin (**1b**) as the starting material [82]. For compound **90**, the chromone ring of **1b** was cleaved under basic conditions followed by a retro-aldol reaction to afford methyl ketone visnaginone (**4b**). In the following step, **4b** was subjected to aldol condensation with N,N-dimethylformamide dimethyl acetal (DMF DMA) to yield **88**. The enaminone (**88**) was refluxed with glacial acetic acid forming the chromone derivative (**89**) in an addition–elimination reaction. The chromone (**89**) was then demethylated with boron tribromide to the phenol derivative (**35b**) followed by alkylation to afford **90**. For the synthesis of compounds **94** and **97**, the furan ring of visnagin (**1b**) was oxidatively cleaved with sulfuric acid to afford (**64b**). Compound **94** was also synthesized from visnagin (**1b**) through the intermediate **64b**. This intermediate (**64b**) was reduced to (**91**) followed by alkylation with dibromomethane to yield **92** and then demethylated with boron tribromide to provide the phenolic derivative (**93**). In a final step, **93** was alkylated with 4-PBB in the presence of potassium carbonate to render **94**. For compound **97**, the same intermediate (**64b**) was subjected to a Wittig reaction followed by an intramolecular lactone ring formation. The resulting coumarin ring substituted chromone (**95**) was then demethylated using boron tribromide and afterwards followed by alkylation using potassium carbonate to yield **97** (Scheme 26).

Scheme 26

Reaction of alkyl or phenyl thiosemicarbazides with the aldehyde **3a** in ethanol at room temperature yielded thiourea derivatives (**98a-e**) [62]. The aldehyde **60b** also reacted in ethanol under reflux yielding other thiourea derivatives (**99a-e**). On the other hand, the reaction of **4a** and **4b** with some selected thiosemicarbazides was carried out in ethanol containing catalytic amount of acetic acid under reflux for 72 h providing **100a-h**. The applied drastic conditions could be attributed to the sterically hindered ketones **4a** and **4b** (Scheme 27).

Scheme 27

3.7. Condensation with Active Methylene Compounds:

Condensation of khellin and visnagin with aminothiouracil, methylation and reaction with secondary amines yielded highly functionalized derivative with potential biological activity [15]. Thus, 6-[(4-methoxy/4,9-dimethoxy)-7-methylfurochromen-5-ylideneamino]-2-thioxo-2,3-dihydropyrimidin-4-ones (**101a**, **b**) were prepared by the condensation of 6-amino-2-thiouracil with khellin or visnagin, respectively. Reaction of **101a**, **b** with methyl iodide afforded furochromen-ylidene aminomethylsulfanyl-pyrimidin-4-ones (**102a**, **b**). Compounds **102a**, **b** were reacted with secondary aliphatic amines to yield the corresponding furochromen-ylideneamino-2-substituted pyrimidin-4-ones (**103a–d**). Reaction of **103a–d** with phosphorus oxychloride yielded 6-chlorofurochromen-ylidene pyrimidinamines (**104a–d**), which were reacted with secondary amines to afford furochromen-ylidene amino-2,6-disubstituted pyrimidin-4-ones (**105a–d**). In addition, the reaction of **105a–d** with 3-chloropentane-2,4-dione furnished 3-chloro-furochromenylpyrimido pyrimidines (**106a–d**). The latter compounds were reacted with piperazine and morpholine to yield 1-(furochromenyl) pyrimidopyrimidine-3,6,8-triylpiperazines or 3,6,8-triyl morpholines (**107a–d**) (Schemes 28 and 29)

Scheme 28

Scheme 29

Refluxing of 4,9-dimethoxy-5-oxo-5*H*-furo [3,2-*γ*] benzopyran-6-carboxaldehyde (6-formylkhellin) (**3a**) with diethylmalonate in the presence of pyridine yielded ethyl (2*E*)-3-(4,9-dimethoxy-5-oxo-5*H*-furo [3,2-*γ*]chromen-6-yl) acrylate (**108**) [52]. Furochromen ethyl acrylate (**108**) was refluxed with hydrazines (as hydrazine hydrate and phenyl hydrazine) resulted in the formation of 6-(5-hydr or phenyl azino-1H-pyrazol-3-yl)-4,9-dimethoxy-5H-furo[3,2-γ]chromen-5-one (**109a**, **b**). Pyrazol-3-yl-5-hydrazino compound (**109a**) reacted with isothiocyanate namely (ethyl isothiocyanate, benzyl isothiocyanate, benzoyl isothiocyanate and phenyl isothiocyanate) yielding pyrazole thiosemicarbazide derivatives (**110a-d**). On the other hand, furochromen ethyl acrylate (**108**) stirred at room temperature with hydrazines (as hydrazine hydrate, phenyl hydrazine) in absolute ethanol yielded 6-[3-(ethylperoxy)-1-hydrazinopropyl or phenylazinopropyl] ethyl 3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-γ]chromen-6-yl)-3-hydrazinopropanoate (**111a**,**b**). These compounds (**111a**,**b**) were then refluxed in absolute ethanol to yield 5-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*γ*]chromen-6-yl)-2,4-dihydro or 2-phenylhydro-3*H*-pyrazol-3-one (**112a**,**b**). Furthermore, 1-hydrazinopropyl derivatives (**111a**,**b**) were reacted with aromatic aldehyde including benzaldehyde, anisaldehyde or *p*-bromobenzaldehyde forming arylidene derivatives (**113a-c**) (Scheme 30).

Scheme 30

4,9-Dimethoxy-5-oxo-5*H*-furo [3,2-γ] benzopyran-6-carboxaldehyde (**3a**), was condensed with 2-thiox-4-imidazolinone (**114**) to form **115** [83]. Treatment of **115** with α-chloroacetyl chloride provided **116**. Cyclization of **116** with acetic anhydride took place by heating to yield **117**. Condensation of **117** with aromatic aldehydes furnished the arylidene derivatives (**118a-c**). On the other hand, coupling of **117** with diazonium salts yielded azo derivatives (**119a-c**). The reaction was further extended to investigate the behavior of **115** with 1,2-dichloroethane which resulted in the formation of (4*Z*)-2-(2-chloroethylthio)-4-((4,9-dimethoxy-5-oxo-5*H*-furo [3,2-γ] chromen-6-yl) methylene)-1*H*-imidazol-5(4*H*)-one (**120**). This intermediate (**120**) was cyclized with acetic anhydride to give (6Z)-2, 3- dihydro-6-[(4,9-dimethoxy-5-oxo-

5*H*-furo-[3,2-γ] chromen-6-yl) methylene] imidazo [2,1-b] thiazol-5-(6H)-one (**121**) (Scheme 31).

Scheme 31

The reaction of enaminoketones (**122a, b**) with malononitrile was conducted in boiling ethanol in the presence of few drops of triethylamine (TEA) to yield the respective 7-imino-5-[2(pyrrolidin-1-yl) prop-1-enyl]furochromene-6-carbonitriles (**123a**, **b**) [30]. On the other hand, when the reaction of **122b** with malononitrile was conducted in boiling ethanol in the presence of piperidine, a mixture of 7-imino-4,9-dimethoxy-5-[(*Z*)-2-(pyrrolidin-1-yl)prop-1-enyl]-7*H*-furo[3,2-γ]chromene-6-carbonitrile (**123b**) and 7-imino-4,9- dimethoxy-5-[(*Z*)-2-(piperidin-1-yl)prop-1-enyl]-7*H*-furo[3,2-γ] chromene-6-carbonitrile (**123d**) was obtained. Similarly, the reaction of **122a** with malononitrile under the same conditions yielded a mixture of imino furochromene-6-carbonitriles (**123a** and **123c**). When enaminoketones (**122a, b**) were allowed to condense with indan-1,3-diketone (**124**) in boiling ethanol in the presence of few drops of piperidine, violet crystalline products were obtained (**125a**, **b**) (Scheme 32).

Scheme 32

3.8. Cycloaddition Reactions:

Compounds **128a**, **b** were formed probably via the formation of the Schiff's bases (**127a**, **b**) followed by a nucleophilic attack of the benzimidazole nitrogen at C-7 which opens the pyrone ring followed by intramolecular cyclization affording **128a**, **b** (Scheme 33) [51].

Scheme 33

Compounds (**129-134**) were obtained by the reaction of furochromone **3** with the following heterocyclic amines, 2-aminobenzimidazole, 2-aminopyridine, 2-aminopyrazine, 2-aminothiazole, 3-amino-5-methyloxazole, and 4-aminopyridine, respectively, in the presence of alcoholic KOH (Scheme 34) [51].

Scheme 34

Reaction of 4-amino-2,6-dihydroxypyrimidine (**135**) with **3a** led to the formation of a pyrimidopyrimidine derivative (**136**) (Scheme 35) [84].

Scheme 35

Reaction of furochromone (**1a**) with malononitrile and sulfur resulted in the formation of **137** [28]. Compound (**137**) reacted with phosphorus pentasulphide [P_2S_5] forming **138** and with carbon disulphide [CS_2] providing **139**. However, with acetic anhydride **138** yielded a thienopyrimidinone derivative (**140**) (Scheme 36).

Scheme 36

Dihydropyrimidines were synthesized utilizing microwave radiation to enforce the reaction between formylfurochromone, urea derivatives and *β*-keto esters [85]. Different reaction media have been tested to optimize the best reaction condition. Thus, the one-pot three-component condensation of 4,9-dimethoxy-5-oxo-furo-[3,2-γ] benzopyran-6-carboxyaldehyde **3a** reacted with *β*-diketones namely, acetyl acetone (**141a**), ethyl acetoacetate (**141b**) or *tert*-butyl acetoacetate (**141c**) and (thio)urea in ethanol in the presence of piperidine as a base under microwave radiation. The mechanism of this reaction was suggested via the Knoevenagel condensation of the aldehyde (**3a**) and the active methylene compound **141** to afford the benzylidene **142** as an intermediate. In the presence of piperidine, thiourea attacks the olefinic double bond, followed by the loss of water resulting in the formation of the enol form of **145** which is transformed to dihydropyrimidine derivatives **143a-f** [86-88]. The first step in this mechanism involved the acid-catalyzed formation of an N-acyliminium ion precursor of type **144** from an aldehyde and the thiourea components. The second step can be regarded as an addition reaction of π-nucleophile, i.e. the enol tautomer 1,3-dicarbonyl compounds **3a** to the electron deficient N-acyliminium species **144** yielding a dihydropyrimidine derivative (**143**) (Scheme 37) [89].

Scheme 37

4,7-Dimethoxy- (**146a**) and 4-methoxy-6-benzofuranol-5-carbohydrazide (**146b**) were condensed with dimethyl acetylenedicarboxylate and acetylenedicarboxylic acid by refluxing in absolute methanol to yield the corresponding (4,5-dihydro-1,3,4-oxadiazole-2-yl)-6-benzofuranol derivatives (**147a**–**d**) [90]. A wide variety of pharmacological properties has been shown to be associated with *N*-arylidene hydrazide derivatives. The treatment of **146b** with aromatic aldehydes, phthalic anhydride yielded the corresponding condensation products **148a-d** and **150**, respectively. The treatment of *N*-arylidene hydrazides **148a-d** with mercaptoacetic acid afforded the corresponding cyclocondensation products, 4-methoxy-5-(3-carbamide-2-substituted-thiazolidinone-4-one)-6-benzofuranols **149a-d**, (Scheme 38).

Scheme 38

Treatment of diphenylnitrilimine, prepared in situ by refluxing of *N*-phenylbenzo hydrazidoyl chloride with triethylamine (TEA) in chloroform, with 2-arylidene khellin and visnagin derivatives (**151**) for 24 h afforded a cycloadduct derivative (**152**) (Scheme 39) [91].

Scheme 39

Reaction of furochromones (**3a**, **b**) with 2-amino-4,5,6,7-tetrahydro-benzo[b] thiophene-3-carboxylic acid amide (**153**) in boiling ethanol resulted in the formation of the corresponding Schiff bases 2-[(4-methoxy-5-oxo-5*H*-furo [2,3-γ] chromen-6-yl-methylene)-amino]benzo [b]thiophene-3-carboxamide(**154a**, **b**) [92]. On the other hand, 2-amino-3-ethylcarboxylate-4,5,6,7-tetrahydrobenzothiophene (**155**) reacted with (**3a**, **b**) to provide the corresponding Schiff bases (**156a**, **b**) (Scheme 40).

Scheme 40

The reaction of 7-polyfluoro alkylnorkhellins (**157a–c**) derivatives with alkyl mercaptoacetates yielded the dihydrothienocoumarin derivatives (**158-160**) [40]. The treatment of **157a–f** with alkyl mercaptoacetates in the presence of Et_3N for two days at room temperature furnished **158a–f** (Scheme 41).

Scheme 41

Reactions of the active nitriles such as malononitrile and ethyl cyanoacetate with substituted 6-dimethylaminomethylene furocoumarins (**161a**, **b**) were described [39, 93]. Additionally, the reaction of substituted 6-dimethylaminomethylene furocoumarins with different amino acids yielded furochromen-6-ylidenemethyl amino acids (**164–166**). Compound **164** was coupled with glycine ethyl ester to form amino acetic acid ethyl ester (**167**). Heating of **43** with dimethylformamide dimethylacetyl afforded 4,9-dimethoxy-6-dimethylamino methylene-5-oxo-5*H*-furo [3,2-γ] coumarin (**161a**) and 4-methoxy (**161b**). Compounds **161a** and **161b** were used as the starting materials for the synthesis of some new furocoumarin derivatives *via* the reaction of compounds **161a** and **161b** with some active nitriles such as malononitrile and ethyl cyanoacetate. Reaction of compounds **161a** and **161b** with malononitrile yielded 6,7-dihydro-furo [3,2-γ] chromen-5-ylidene) malononitriles (**162a**, **b**). Compound **161a** was reacted with some amino acids. Substitution of the dimethylamino group with the amino acids glycine, *β*-alanine and glycine ethyl ester proceeded smoothly in glacial acetic acid at 80 °C providing [(furo[3,2-*γ*]chromen-6-ylidenemethyl)-amino]-acetic acid (**164**), 3-[(furo[3,2-*g*]chromen-6-ylidenemethyl)-amino]-propionic acid (**165**), [(furo[3,2- *g*]chromen-6-ylidenemethyl)-amino]-acetic acid ethyl ester (**166**). Coupling of compound (**164**) with glycine ethyl ester utilizing *N*,*N*-dicyclohexylcarbodiimide in dichloromethane furnished (2-[(furo[3,2-*g*]chromen-6-ylidenemethyl)-amino]-acetylamino)-acetic acid ethyl ester (**167**) in moderate yield (Scheme 42).

Scheme 42

Styryl furochromones (**151**) were prepared from the condensation of aldehydes with furochromones (**1**) in a basic medium. The products were reacted with dienophiles such as maleic anhydride and *N*-phenyl maleimide to yield the cycloadducts (**168**), (Scheme 43) [94, 95].

Scheme 43

The new heterocyclic ring system (**170**) was prepared by the regiospecific Diels-Alder reaction of *o*-quinone monoimide (**169**) with visnagin (**1b**) (Scheme 44) [96].

Scheme 44

3.9. γ-Pyrone Ring fission:

The naturally occurring furochromones (khellin and visnagin) yielded khellinone **4a** and visnaginone **4b** upon hydrolysis with aqueous potassium hydroxide followed by a retro-aldol reaction [97-99]. Khellinone **4a** and visnaginone **4b** were treated with ethyl bromoacetate in the presence of potassium carbonate to provide 4,7-dimethoxy-5-acetylbenzofuran-6-yloxy) acetic acid ethyl ester (**171a**) and (4-methoxy- (**171b**) [97]. Refluxing of **171a** or **171b** in dimethylformamide containing anhydrous potassium carbonate afforded 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b]difuran-2-carboxylic acid and 4-methoxy (**172a**, **b**). The treatment of **172a**, **b** with absolute ethanol containing 2–3 drops of concentrated H_2SO_4 yielded benzo[1,2-b:5,4-b]difuran-2-carboxylic acid ethyl esters **173a**, **b**. Refluxing **173a**, **b** with hydrazine hydrate led to the formation of 4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b]difuran-2-carbohydrazides **174a**, **b**. Compounds **174a**, **b** were reacted with isothiocyanate derivatives, namely phenyl-, benzyl-, ethyl-, and cyclohexyl isothiocyanate, to afford 1-(4-methoxy- and 4,8-dimethoxy-3-methyl benzo[1,2-b:5,4-b]difuran-2-yl-carbonyl)-4-substituted thiosemicarbazides **175a–h** (Scheme 45).

Scheme 45

Methyl 6-hydroxybenzofuran-5-carboxylic acid (**66**) derivatives reacted with hydrazines to provide the corresponding hydrazides (**146**). Benzoylation of (**146)** followed by cyclization with phosphoryl chloride afforded the oxadiazolyl benzofuran (**176**) derivatives [70, 100]. Also the hydrazides (**146**) were condensed with $R^2COCH_2COOR^3$ followed by cyclization to provide the benzofuranylpyrazolone derivative (**177**) (Scheme 46) [101, 102].

Scheme 46

Khellinone (**4a**) reacted with malononitrile in the presence of ammonium acetate to yield **178a** which was subjected to acid hydrolysis to furnish the corresponding furocoumarin (**178b**). When the above reactions was carried out in the presence of some aromatic aldehydes, 2′-pyridyl benzofuran derivative (**179**) was obtained (Scheme 47) [103].

Scheme 47

When 6-bromofurochromone (**180**) is reacted with diethyl malonate, a diacetate derivative was formed **181**, followed by the formation of a ring contracted furobenzofuranone derivative (**182**) (Scheme 48) [104].

Scheme 48

Khellin reacted with formamide, guanidine, and cyanoguanidine to provide pyrimidine derivatives (**183a-c**) (Scheme 49) [105, 106].

Scheme 49

3.10. Furan Ring Fission:

Pyranocoumarin (**95**) was obtained in a high yield by the treatment of benzopyrancarboxaldehyde (**64b**) with yilde phosphoranes $(ph)_3P^+CH\text{-}R$ (R=COOMe, COOEt) [107]. Also, benzodipyranones (**184**) were prepared from the condensation of **64b** with diethylmalonate, ethyl cyanoacetate, malonic acid, ethyl acetoacetate, phenylacetic acid, and acetyl glycine [71, 72, 108]. The treatment of **64b** with different amines yielded the corresponding Schiff base (**185**) which was tested for anticoagulant, antipyretic and analgesic activities [109]. Also, dialkyl 2-amino-1-cyanopropene-1,3-dicarboxylate reacted with chromone-6-carboxyldehyde **64b** to afford the benzodipyran derivatives **186** which was reacted with hydrazine hydrate, phenylhydrazine and hydroxylamine hydrochloride to yield **187** [49]. When the aldehyde **64b** was reacted with dimethyl acetylenedicarboxylate, it yielded the dipyran derivative (**190**). The condensation of the same aldehyde with benzil in the

presence of ammonium acetate yielded the imidazolyl chromone derivative (**188**) [110]. Also, when the benzopyronone-6-carboxyldehyde derivative (**64**) was refluxed with ethyl acetoacetate or malononitrile in the presence of ammonium acetate, the dihydropyranobenzopyranopyridine derivatives **189a** and **189b** respectively, were obtained (Scheme 50) [111].

Scheme 50

3.11. Mannich Reaction:

Khellin reacted with secondary amines and paraformaldehyde to provide the corresponding Mannich base (**191**) which was also formed when 6-hydroxy-4,7-dimethoxy-5-acetoacetyl benzofuran was subjected to the Mannich conditions [10, 78, 112-117]. When 6-dimethylaminomethyl-khellin was heated with acetic anhydride, it furnished the 6-acetoxymethyl derivative which has been transformed into 6-methylkhellin [115, 116]. Fiden and Rehse carried the aminoalkylation of khellin and visnagin in benzene and nitrobenzene and obtained the corresponding pyridinium chlorides (**192**) (Scheme 51) [55].

Scheme 51

3.12. Photochemistry:

a) Photolysis of Khellin:

Photolysis of khellin in various solvents was studied by Caffieri et al. [118]. The oxidation pathway for photolysis was carried out with a singlet oxygen species. Two different intermediates were probably formed, one being dioxentane at furan ring (**193**) and the other an endoperoxide at the benzene ring (**194**). The dioxetane intermediate was known to be unstable, it was rapidly hydrolyzed to yield the corresponding aldehyde (**64a**), or it can be easily attacked by water to provide cis- and trans-isomers of 2, 3-diol (**91**) [104, 105]. The endoperoxide intermediate was subjected to nucleophilic attack by water to yield (**87a**) and (**87b**) through losing one or both methoxy groups, respectively. The photocycloaddition of khellin and visnagin

with several olefins such as dimethyl fumarate, dimethyl maleate and thymine base has been investigated (Scheme 52) [119].

Scheme 52

b) Phototherapeutic Effect of Khellin:

Furocoumarins such as psoralen (**195**) are photoactive drugs which were extensively used in the PUVA therapy (Psoralen Plus UVA radiation) for the treatment of skin diseases e.g. psoriasis and vitiligo [120-124]. The potency and effectiveness of these photo-chemotherapeutic agents depend on their photobinding ability with deoxyribo-nucleic acid (DNA). A marked disadvantage of the usual psoralen derivatives is their propensity to from interstrand crosslink with DNA [121, 125, 126]. A consequence of their bifunctional nature (photoactive-pyrone and furan sites). Furocoumarins possess undesirable side effects such as erythema, edema, genotoxicity, risk of skin, cancer and cataract [122, 127]. For this reason, considerable efforts have been expended to develop furocoumarins which only permit monofunctional photobinding with DNA and thereby diminish the undesirable side effects. This has been accomplished in two different ways: (a) the use of angular furocoumarins such as angelicin (**196**) which cannot crosslink with DNA based on their geometry and (b) by blocking of the photoreactive pyrone double bond by the appropriate substituents such as **197**, or by the annelation of an additional aromatic ring e.g., pyridopsoralen (**198**) [128, 129]. Khellin, the most important analogue of psoralen, is one of the most promising agents against vitiligo. KUVA (khellin + UVA) therapy can restore pigmentation in the affected areas of the skin, similar to psoralen, without severe phototoxicity (Scheme 53) [21, 130].

Scheme 53

c) Photobinding with Nucleic Acid:

Furocoumarins such as psoralen and its analogues (e.g. khellin) photoreact with nucleic acids particularly DNA forming monoadducts and diadducts via nucleic acid bases, especially pyrimidine bases. Khellin forms in the dark a molecular complex

with DNA (**199**). By subsequent irradiation (UVA), khellin is photoconjugated covalently with the macromolecule. The furanyl moiety of **1a** was the main photoreactive site of **1a**-DNA (5%) [131]. Pyrone moiety of khellin did not form monoaddut (**200**) with DNA. In photoaddition with macromolecule, khellin formed interstrand cross-links (**202**) but in small amounts. The furan ring of khellin was photobound with thymine in DNA and the photoproduct was characterized by a cis-*syn* configuration (Scheme 54) [132].

Scheme 54

4. Conclusion:

Furocoumarins with its most famous members, khellin and visnagin, have shown an arsenal of interesting biological activities. These compounds were derivatized easily forming a big library of potential biologically active compounds. The symptoms of certain skin disease such vitiligo were efficiently ameliorated with certain furocoumarins. The intervening successes in targeting several ailments since the isolation of khellin and visnagin bode well for further discoveries in the future through understanding their mechanism of action and developing efficient methodologies for the synthesis of more active derivatives.

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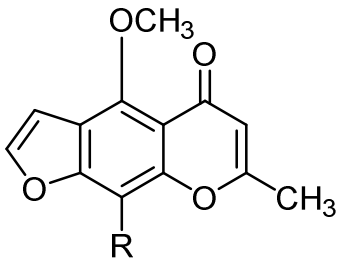
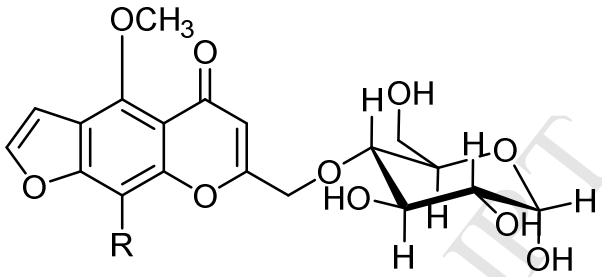
List of Figures and Schemes

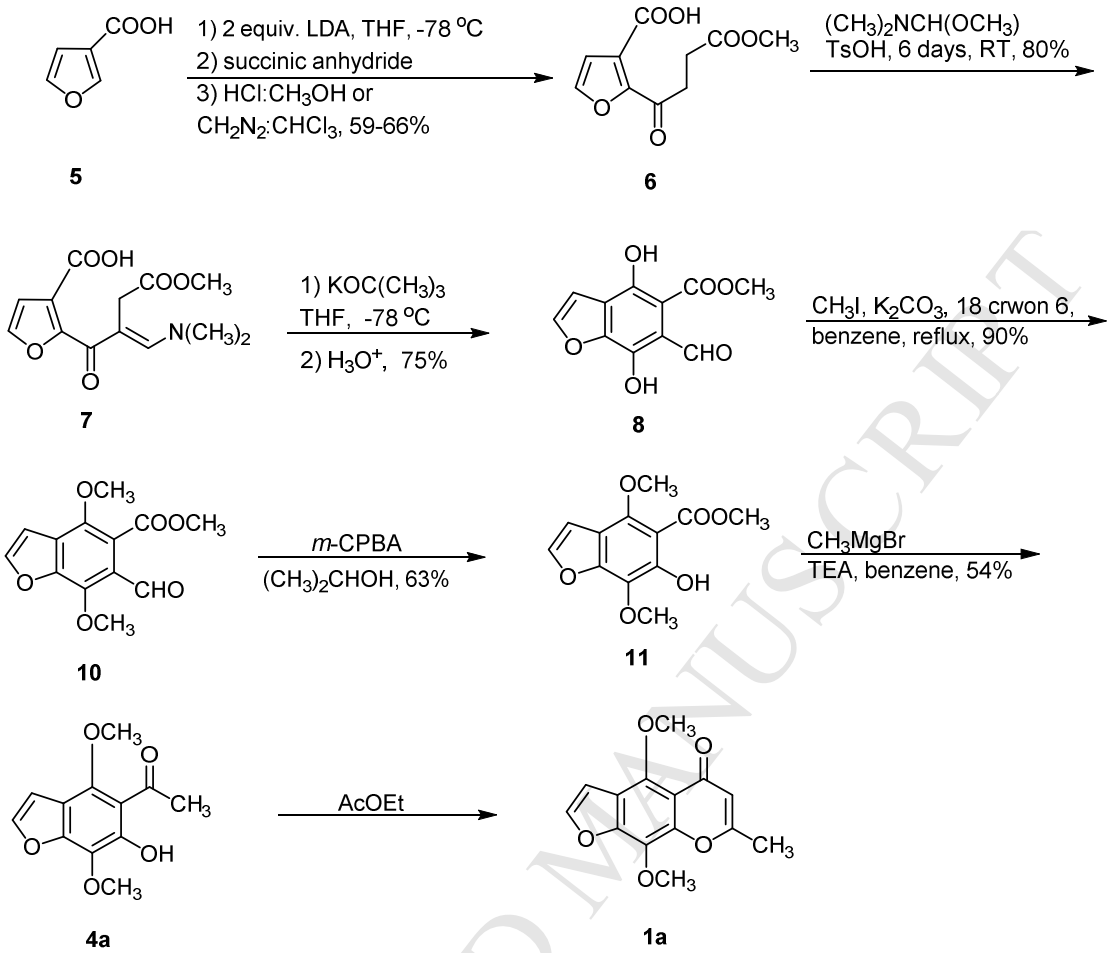


Khellin, **1a**, R = OCH_3
Visnagin, **1b**, R = H

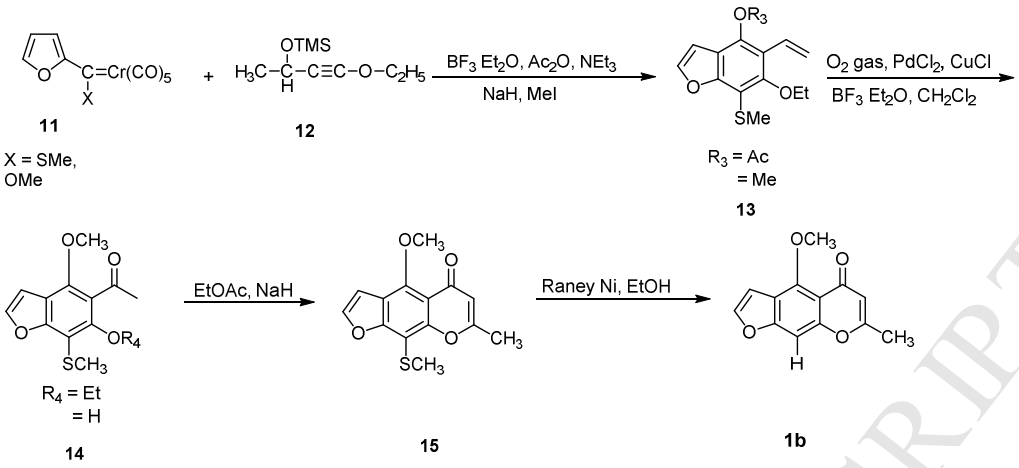


2a,**b** (Khellol glucoside)

Figure 1.



Scheme 1.



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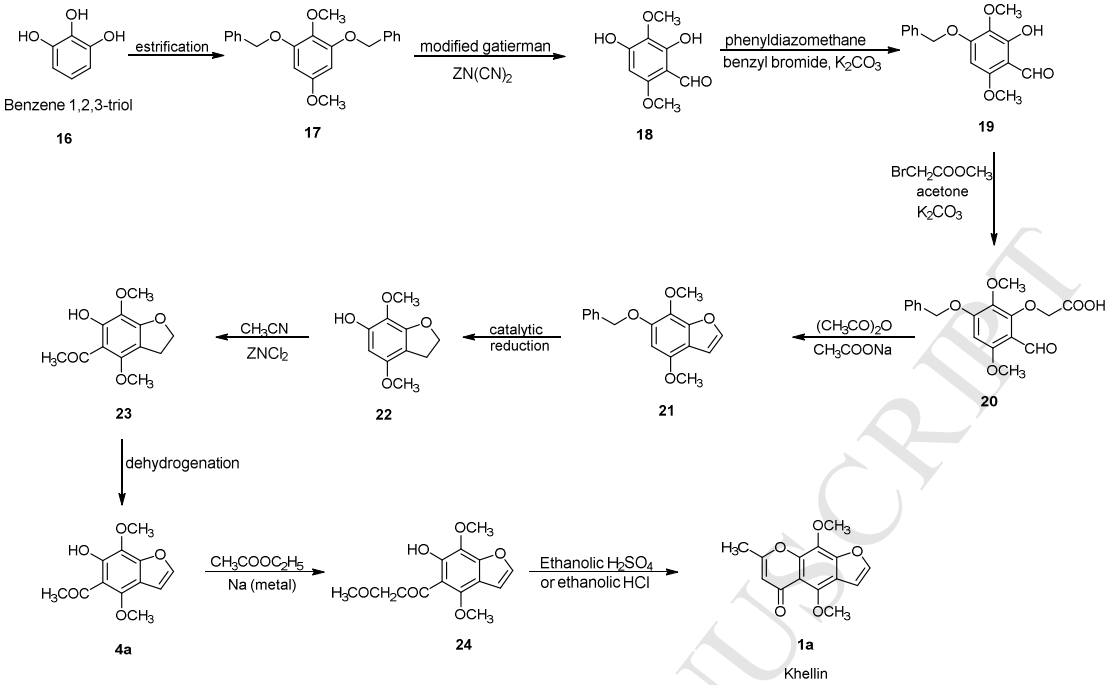

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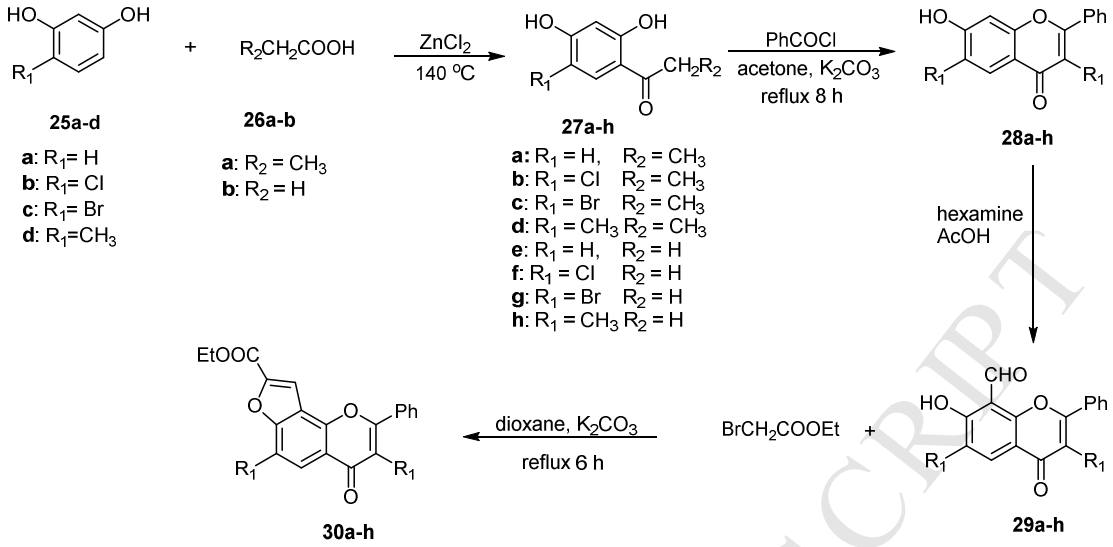

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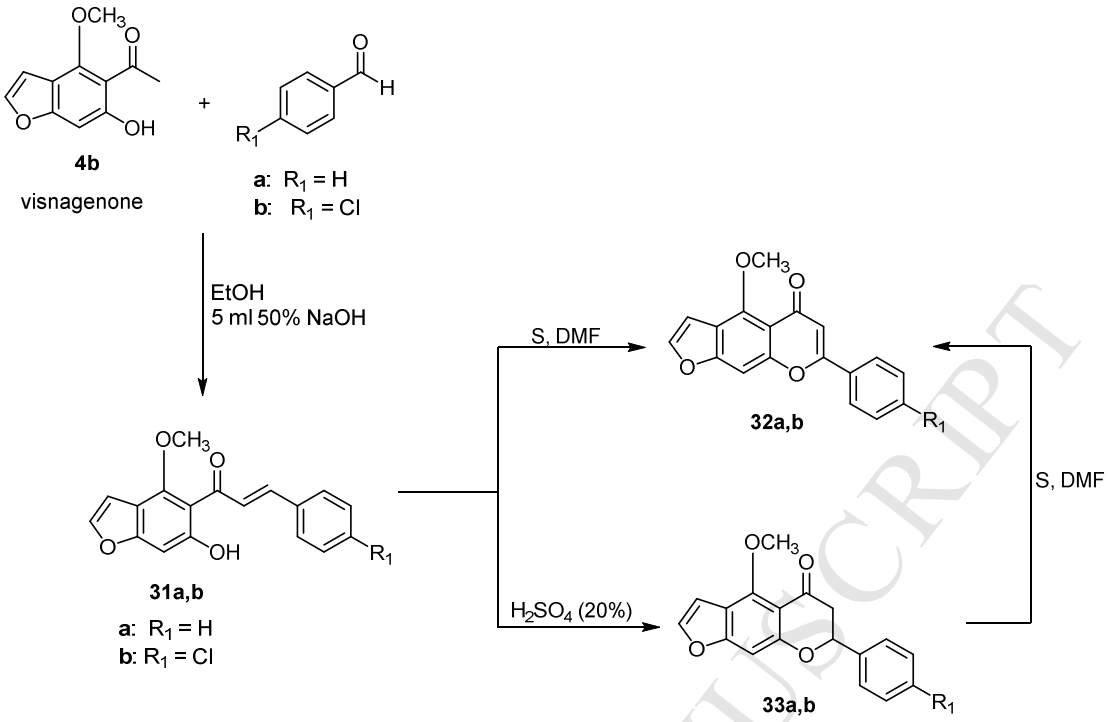

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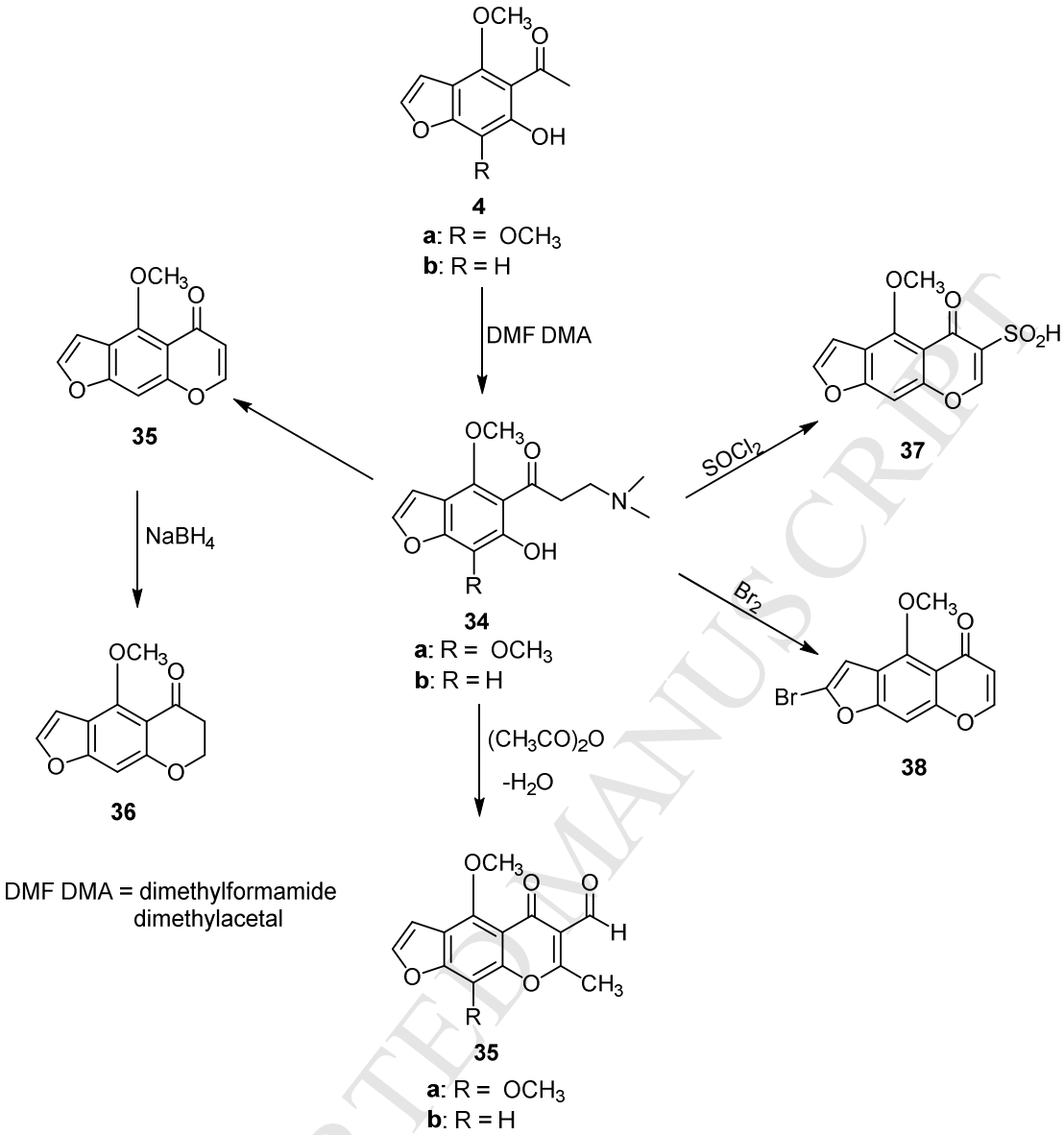

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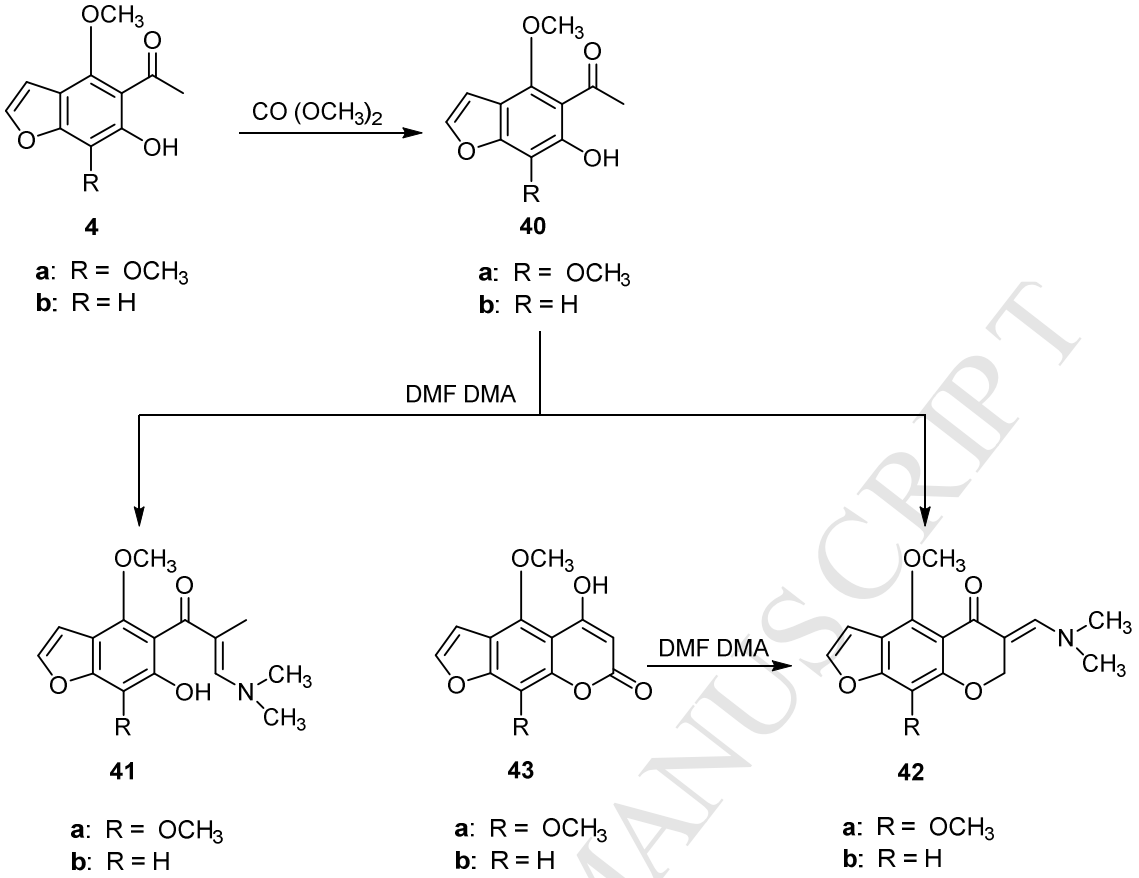

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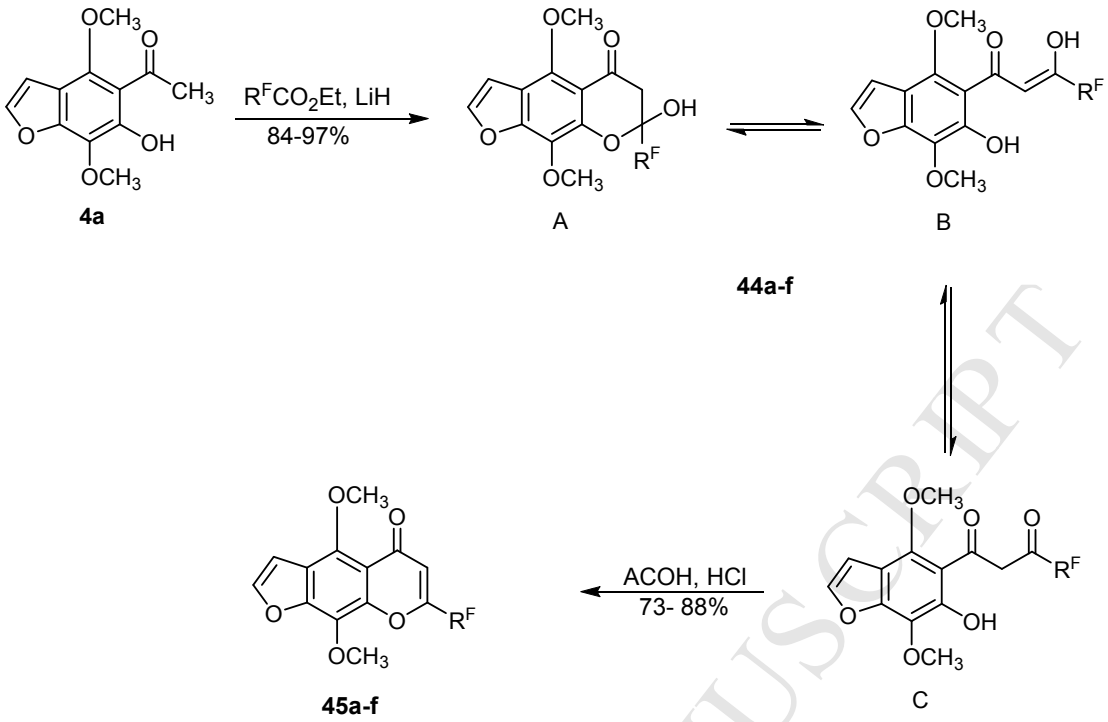
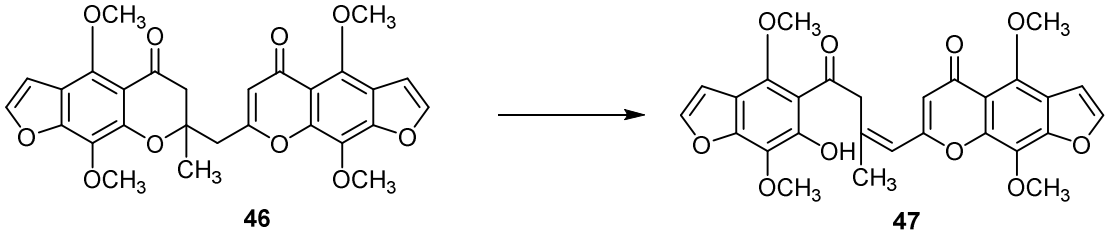


R^F = CF_3 (**a**), CF_2H (**b**), $(CF_2)_2H$ (**c**), C_2F_5 (**d**), C_3F_7 (**e**), C_4F_9 (**f**)

Scheme 8.



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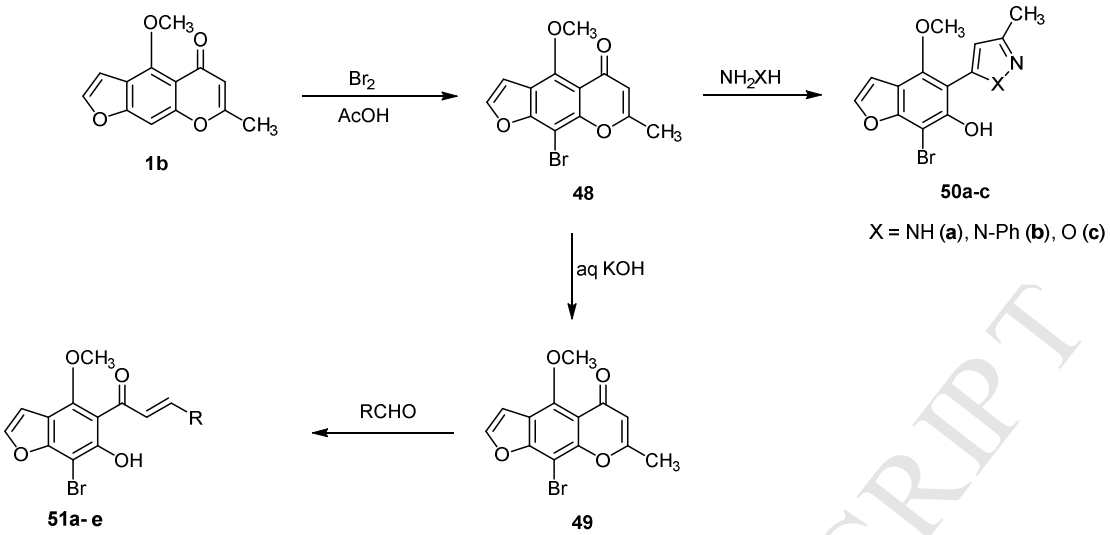
Scheme 9.



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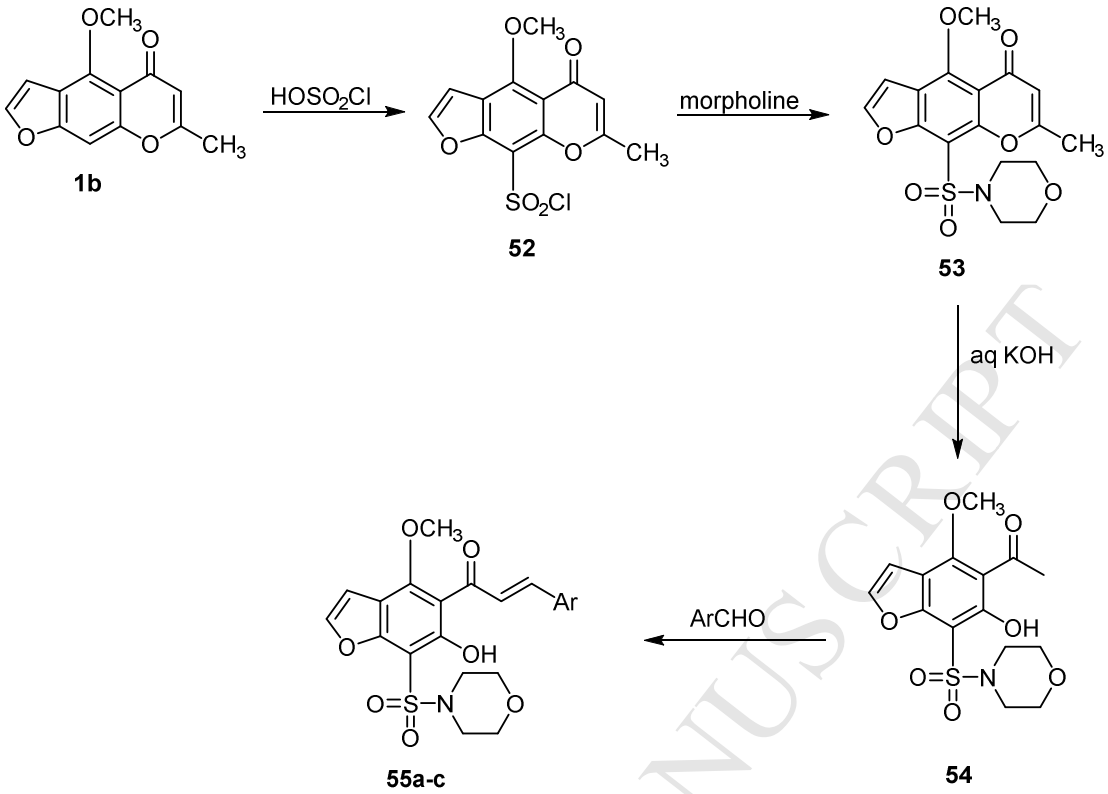
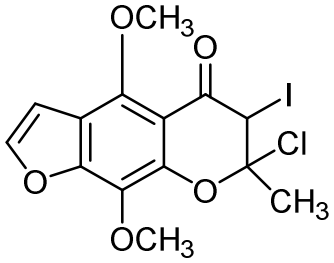


Ar = 4-Cl-Ph (**a**), 4-OCH_3-Ph (**b**), 4-$N(CH_3)_2$-Ph (**c**)

Scheme 11.



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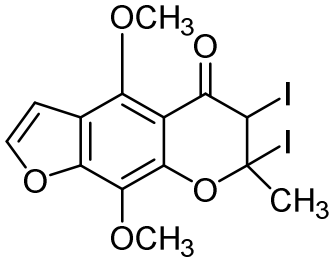

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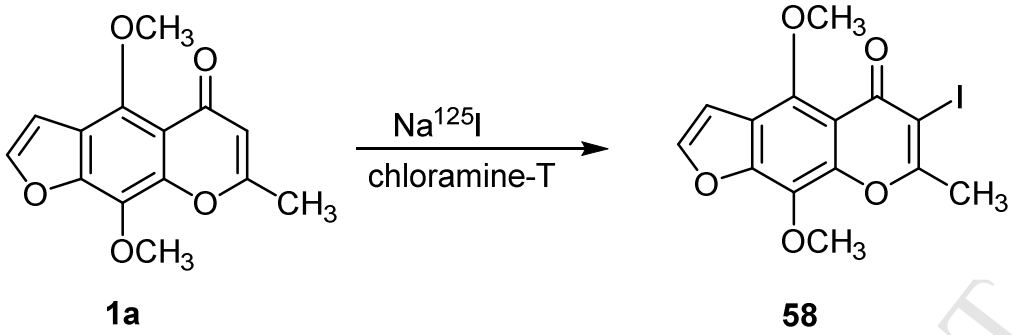
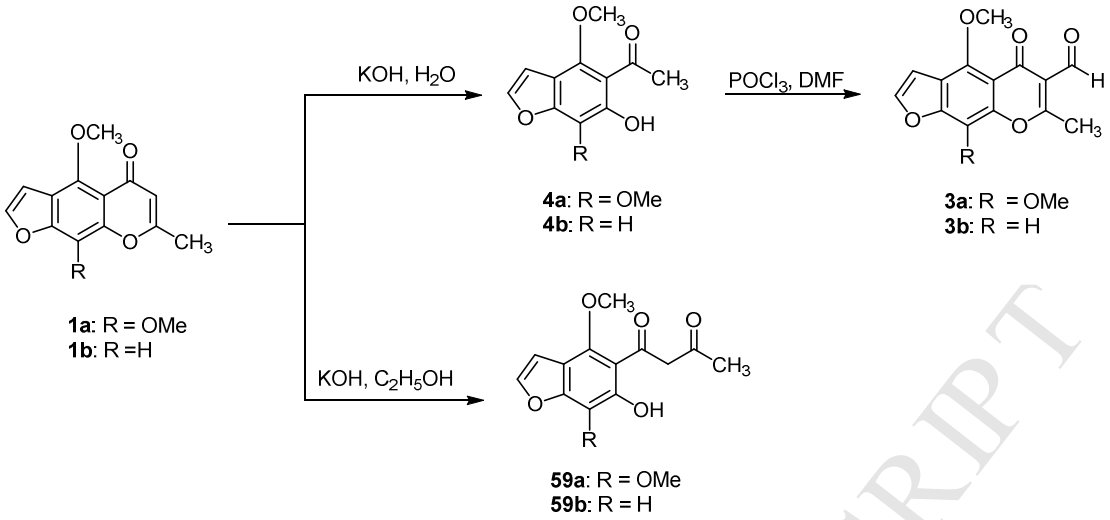
Scheme 12.



1a **58**

Scheme 13.



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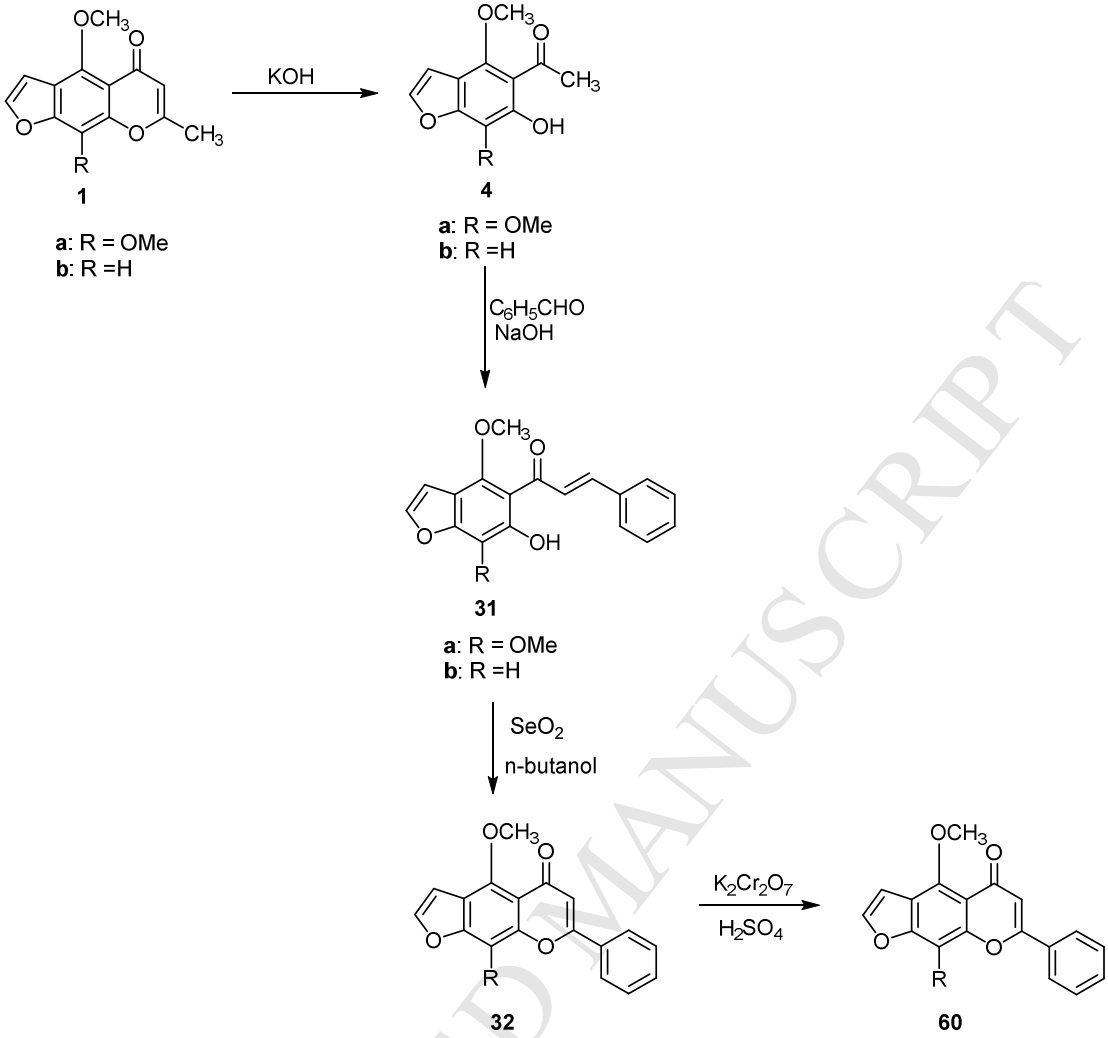

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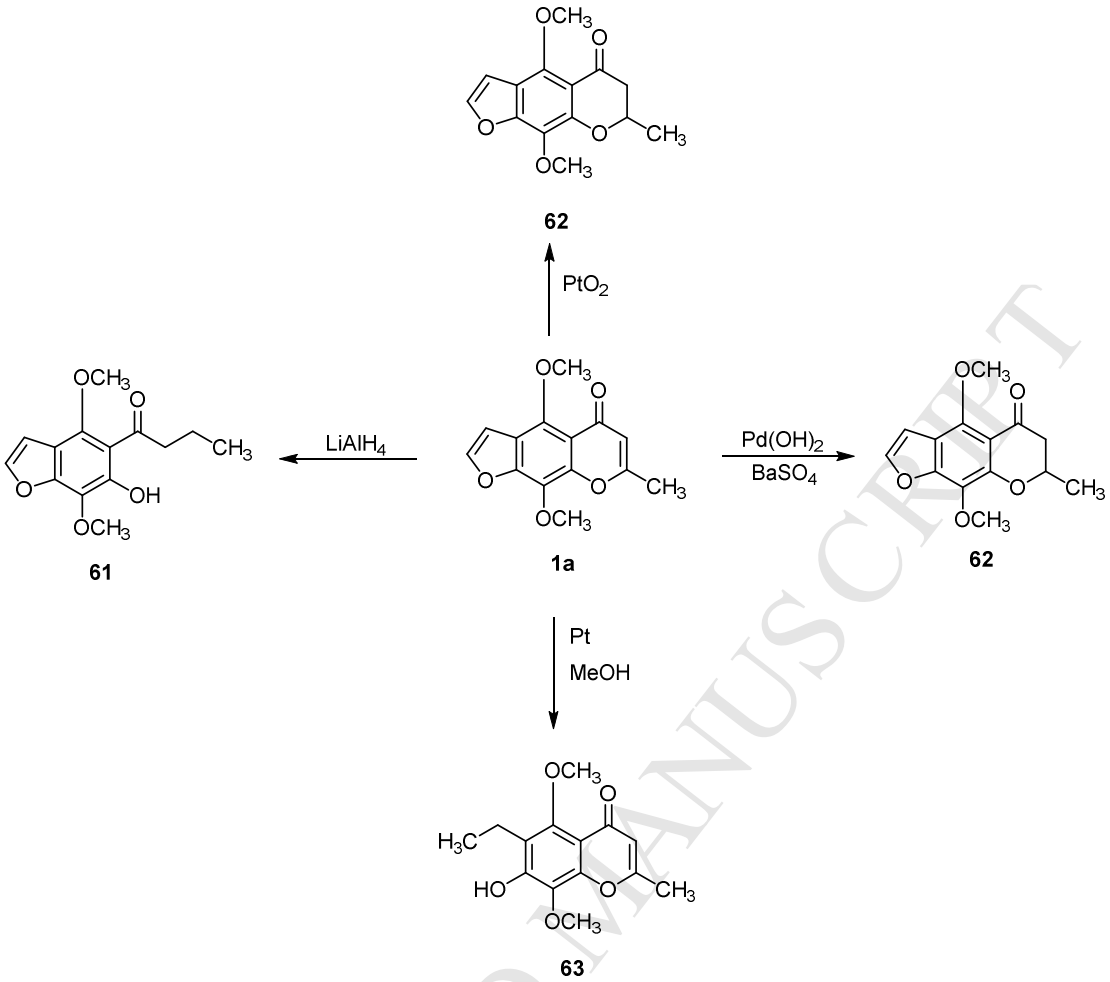

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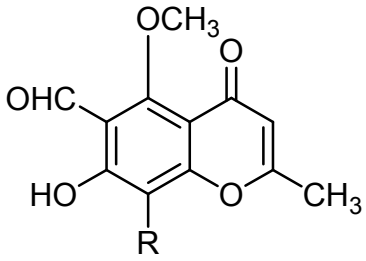

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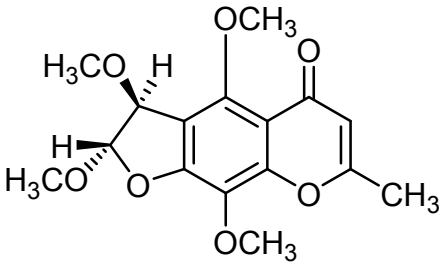
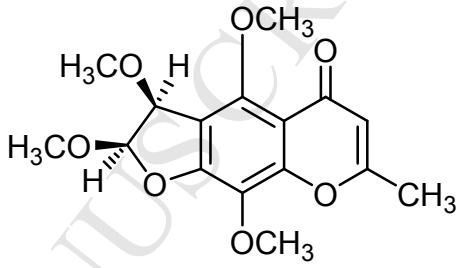
a: R = OMe
b: R = H





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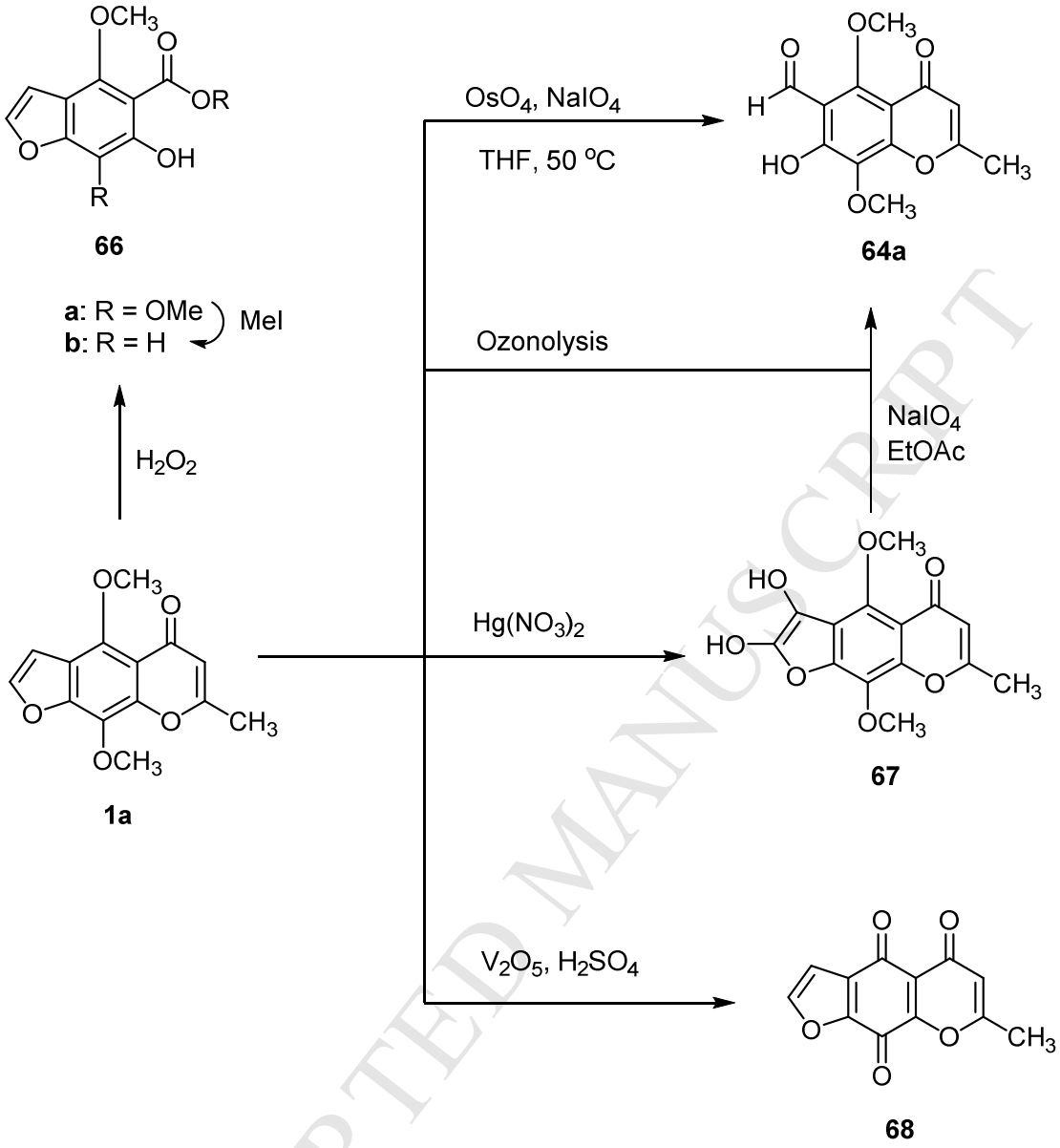
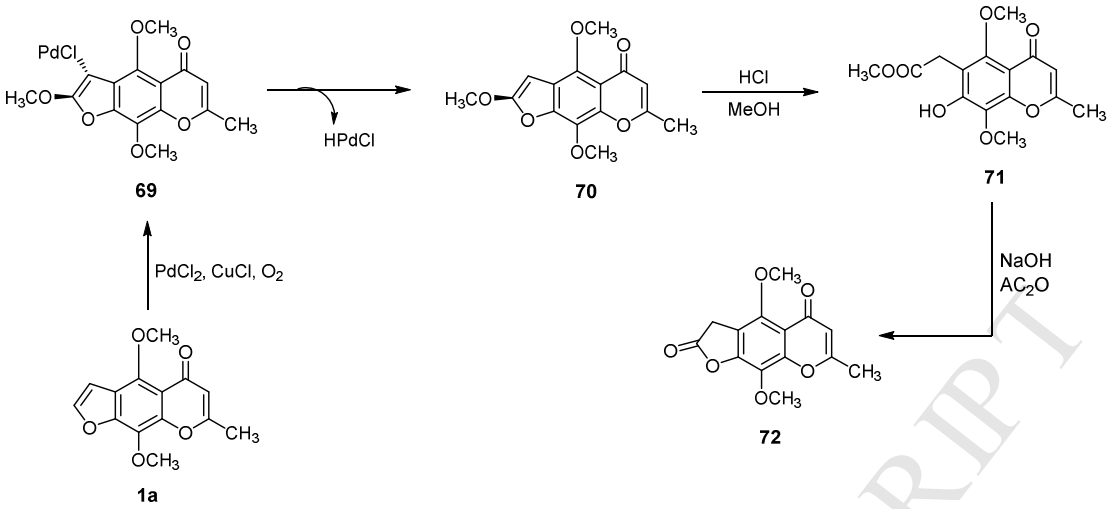
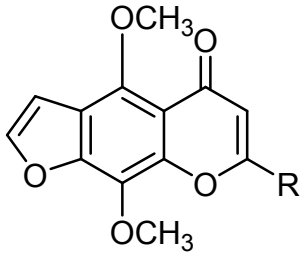
Scheme 17.



Scheme 18.



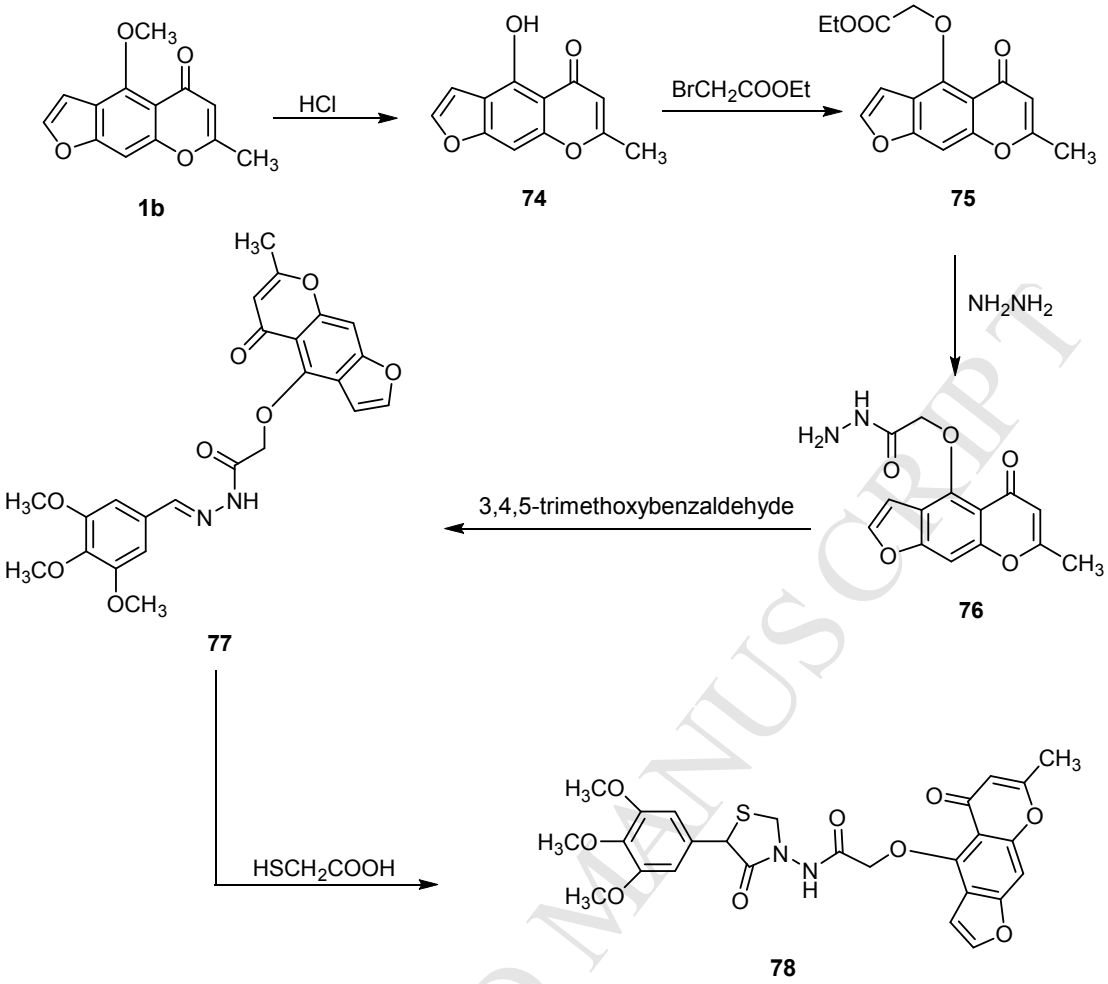
Scheme 19.



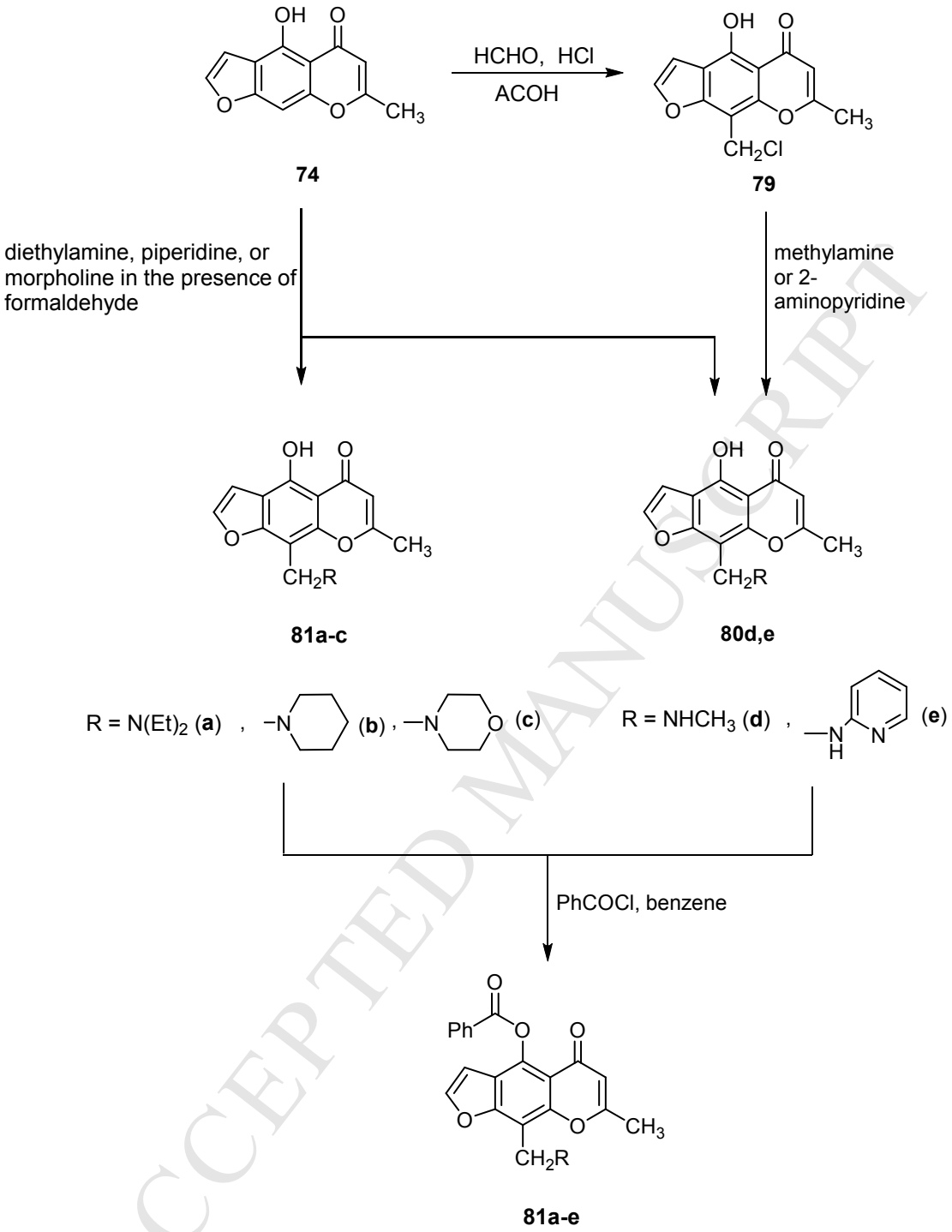
73

a: R = CHO
b: R = COOH

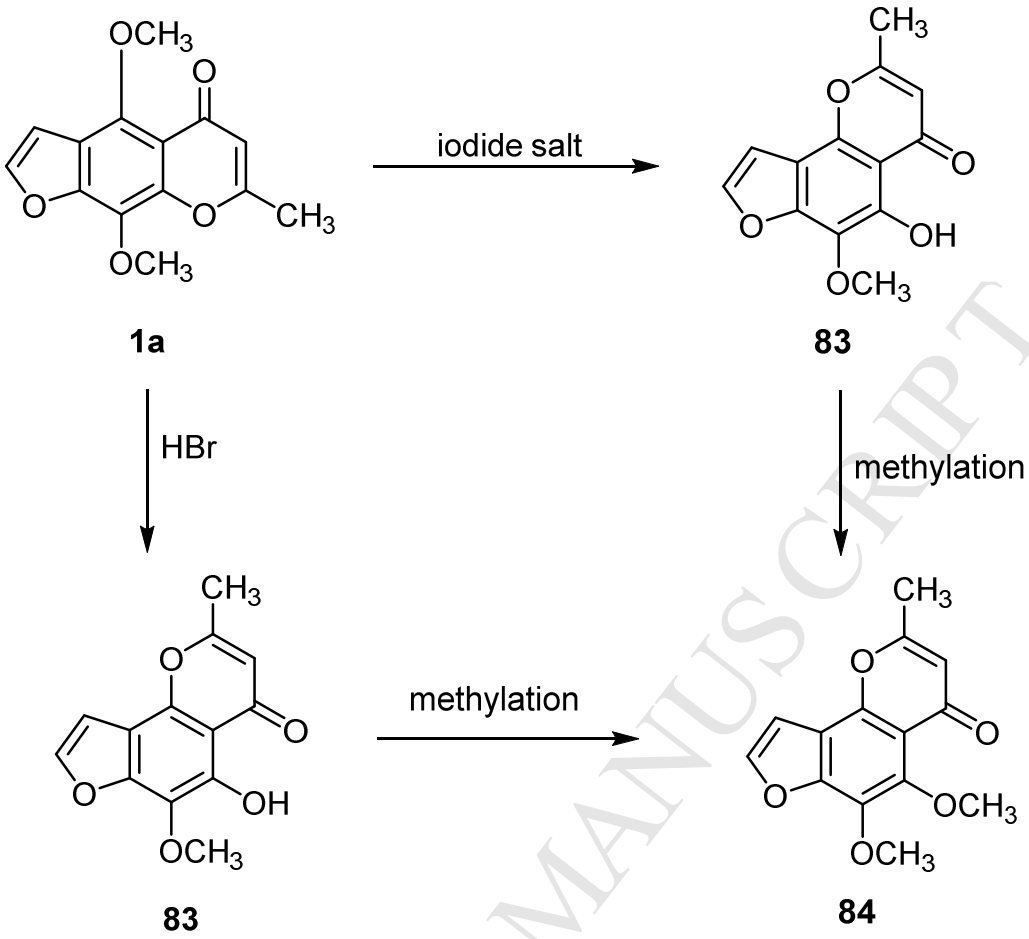
Scheme 20.



Scheme 21.

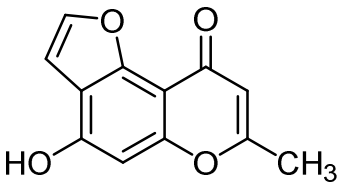


Scheme 22.

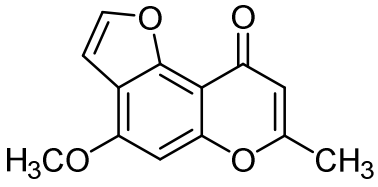


1a 83 83 84

Scheme 23.

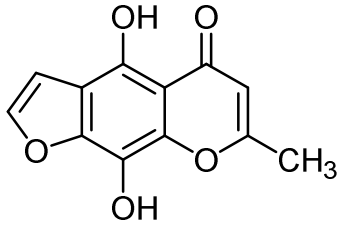


85



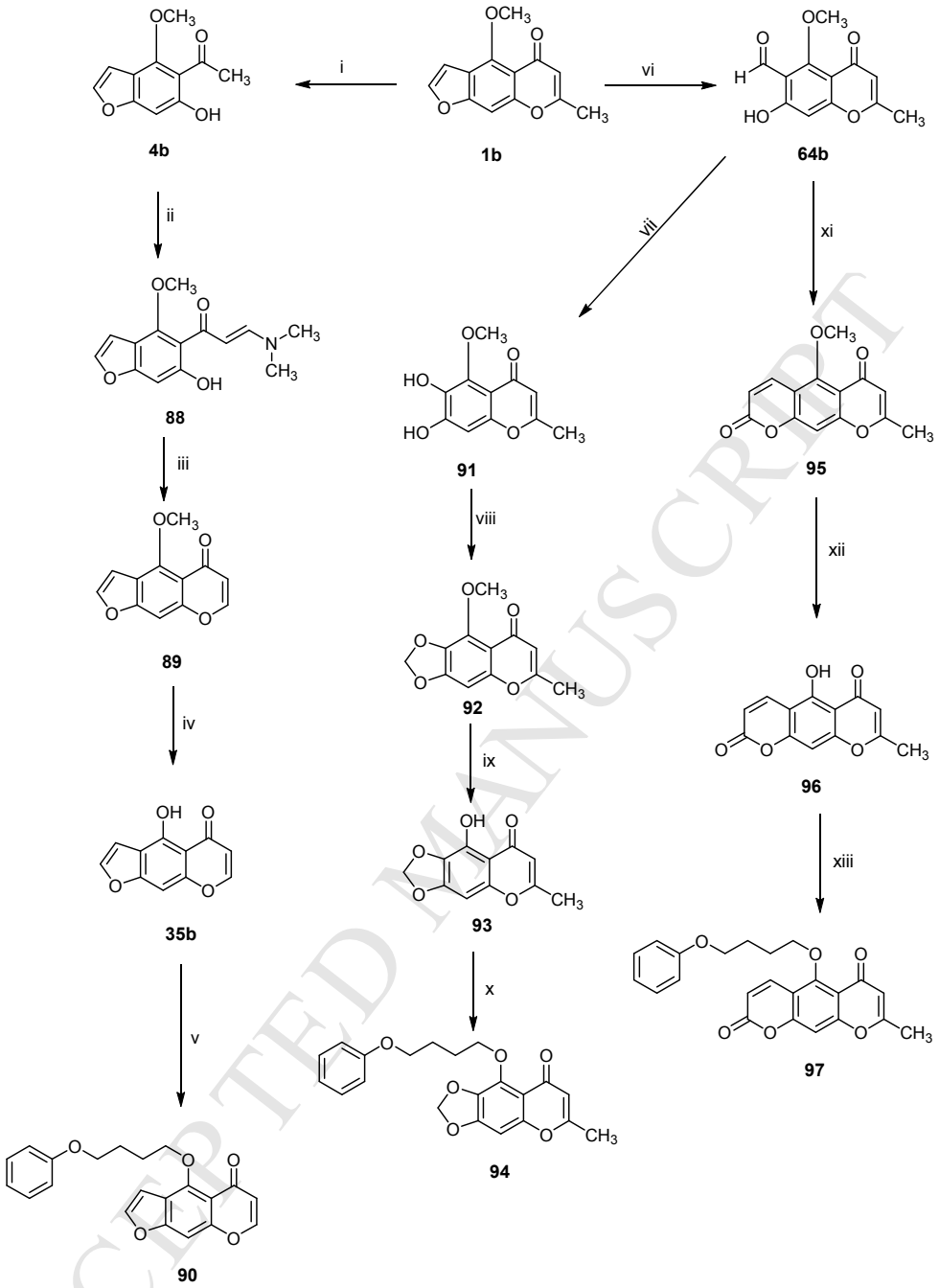
86

Scheme 24.



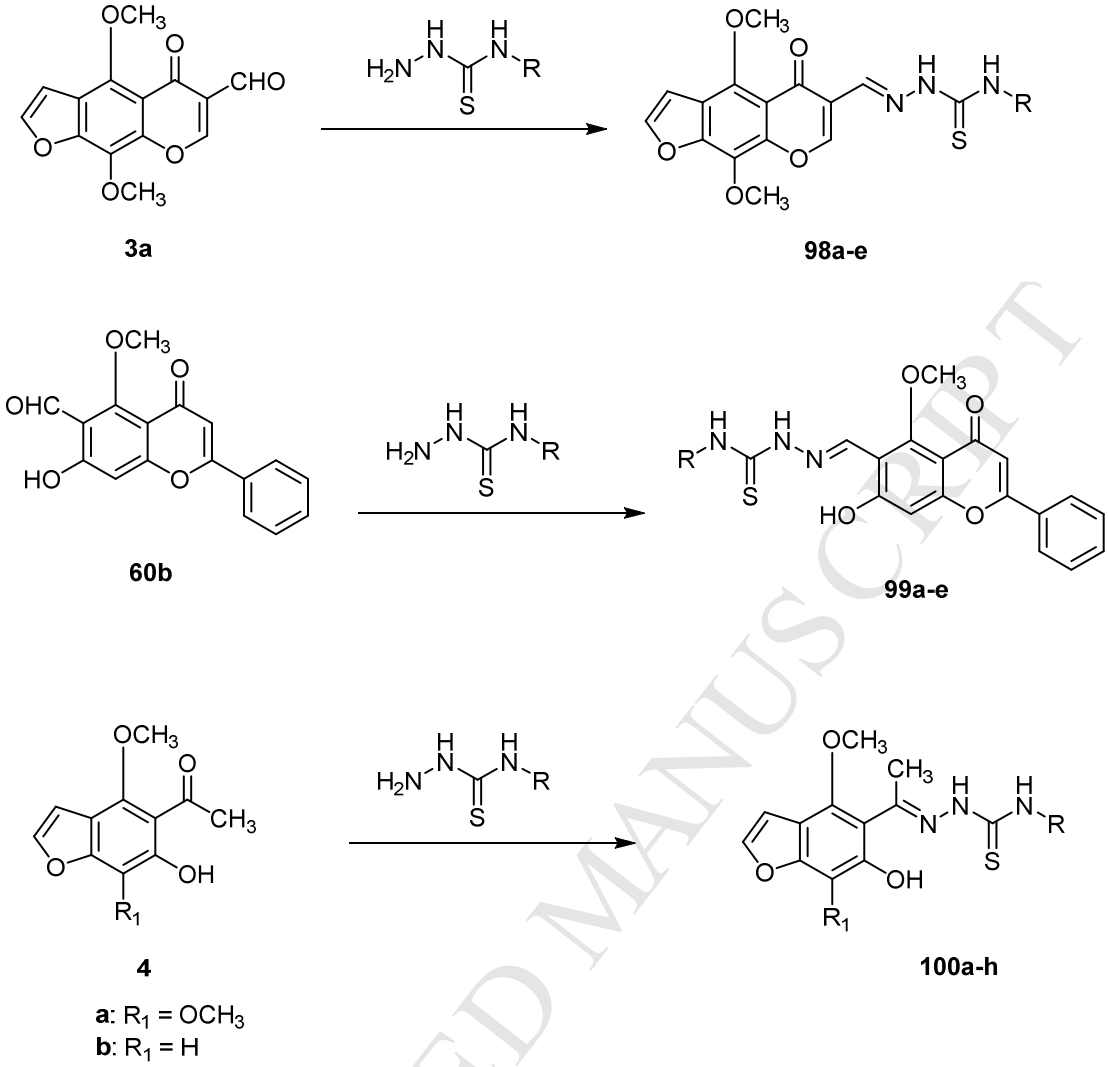
87

Scheme 25.

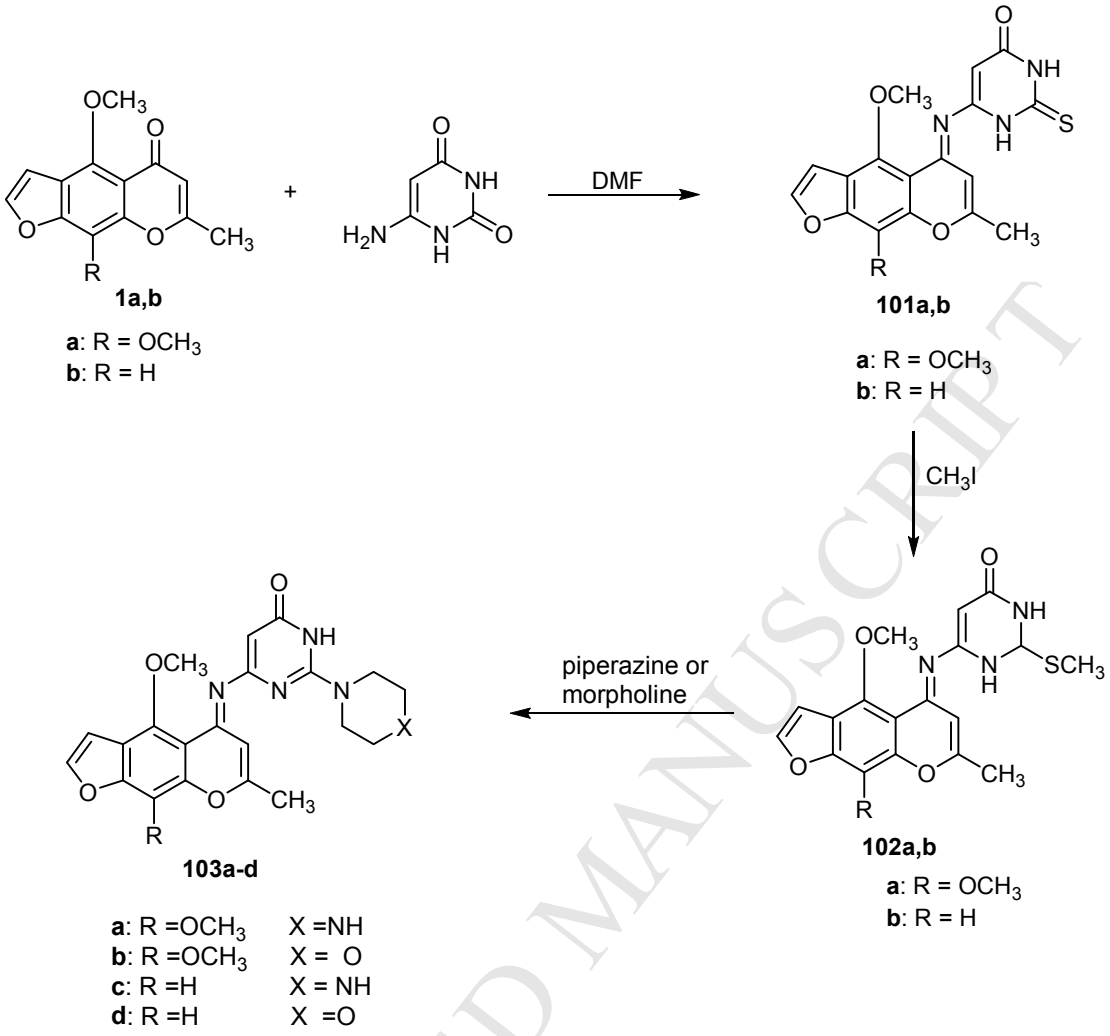


Synthesis of chromone derivatives **90**, **94** and **97**. Reagents: (i) KOH (0.2 M; reflux, 15 min); (ii) DMFDMA in toluene (reflux, 3 h); (iii) CH_3COOH (reflux, 5 h); (iv) BBr_3 (5 °C) and CH_2Cl_2 (reflux); (v) 4-PBB, CsF-Celite in CH_3CN (reflux); (vi) H_2SO_4 (1 M), $K_2Cr_2O_7$ (0.3 M, 2 h); (vii) NaOH (1 M), H_2O_2 (10 M), 25 °C (2–3 h); (viii) K_2CO_3, CH_2Br_2 in DMF (95 °C, 4 h); (ix) BBr_3 (5 °C) and CH_2Cl_2 (reflux); (x) 4-PBB, K_2CO_3/KI in DMF (reflux); (xi) $(C_6H_5)_3PCHCOOCH_3$, toluene (reflux, 6 h); (xii) BBr_3 (5 °C) and CH_2Cl_2 (reflux); (xiii) 4-PBB, K_2CO_3/KI in DMF (120 °C).

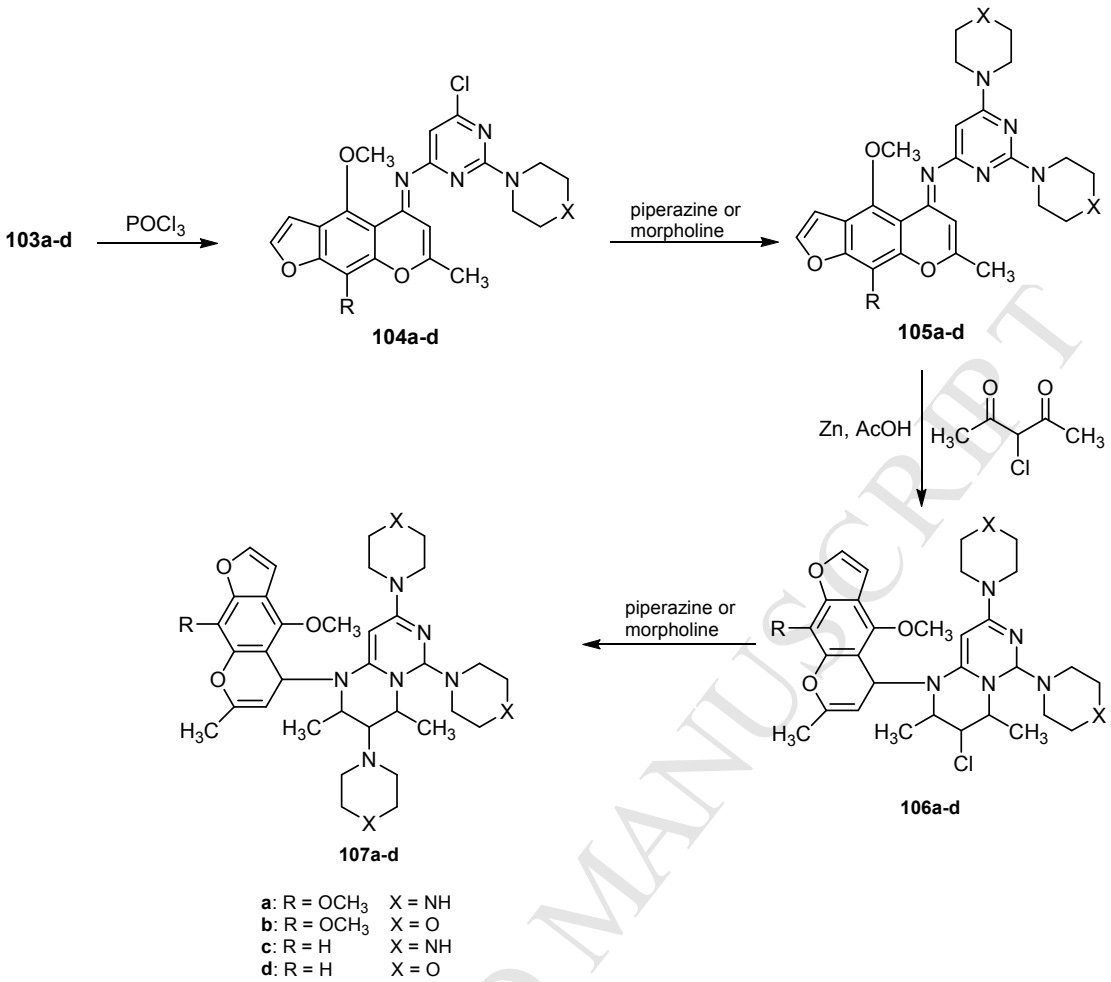
Scheme 26.



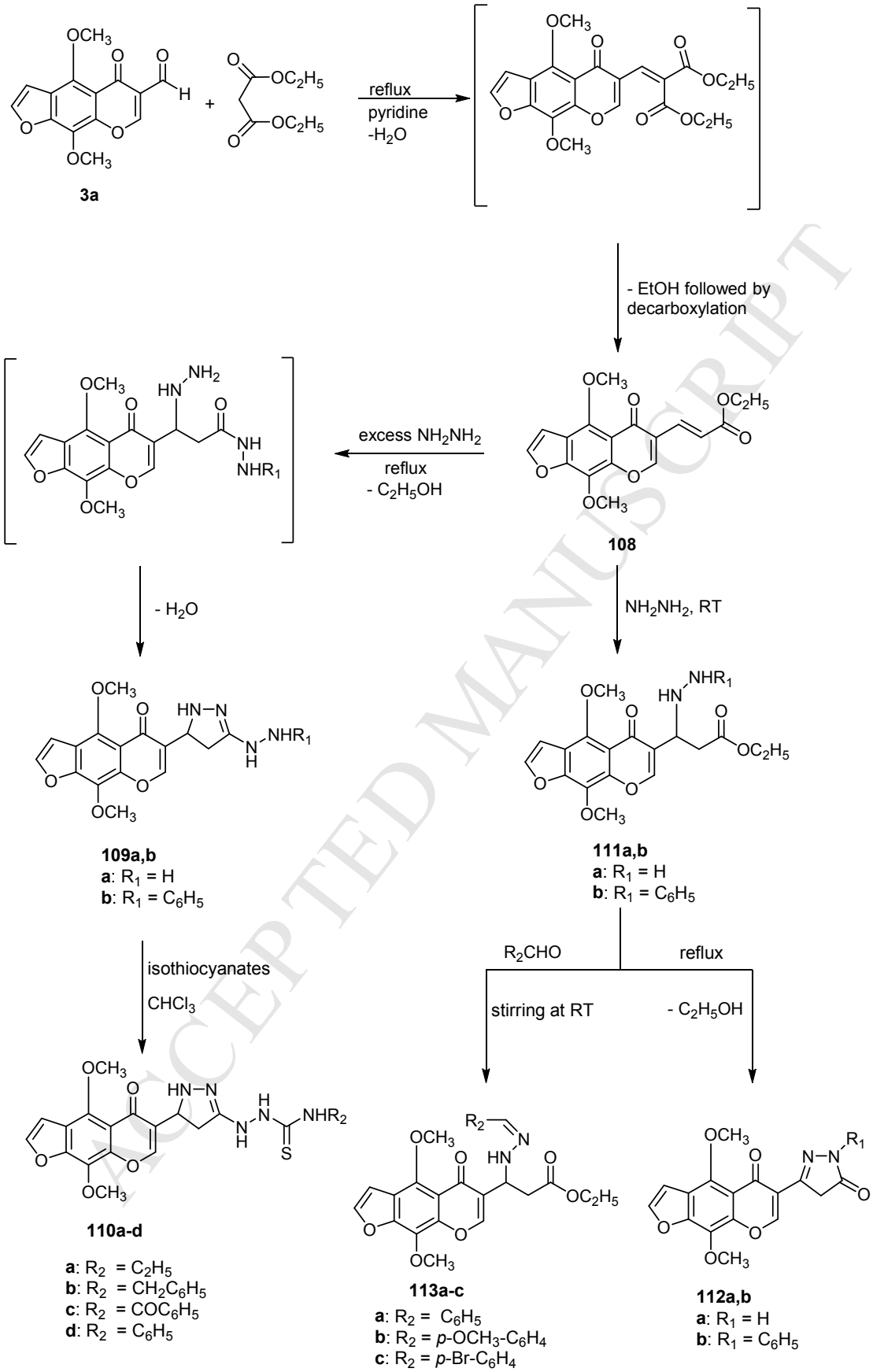
Scheme 27.



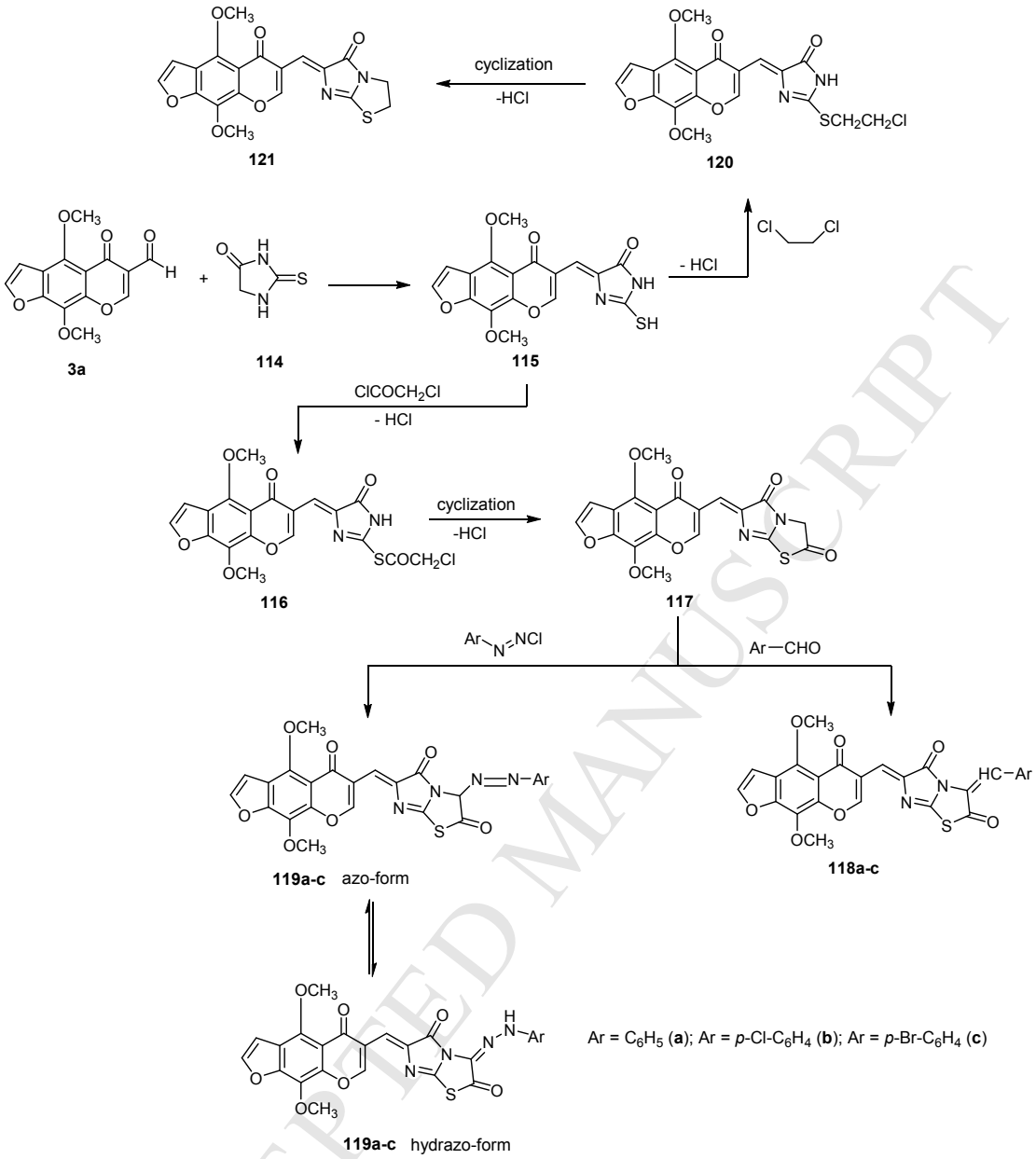
Scheme 28.



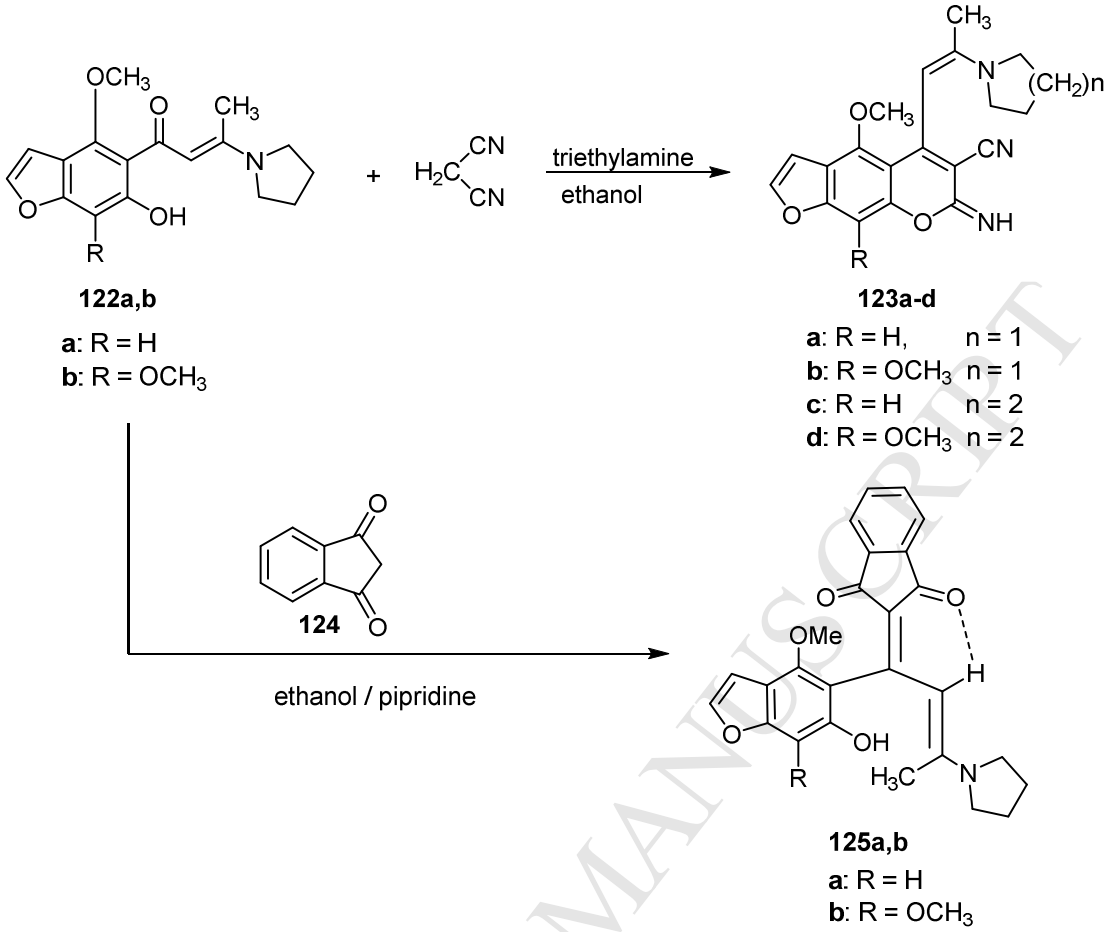
Scheme 29.


3a
reflux
pyridine
-H2O
- EtOH followed by
decarboxylation
108
excess NH2NH2
reflux
- C2H5OH
- H2O
NH2NH2, RT
109a,b
a: R1 = H
b: R1 = C6H5
111a,b
a: R1 = H
b: R1 = C6H5
isothiocyanates
CHCl3
R2CHO
reflux
stirring at RT
- C2H5OH
110a-d
a: R2 = C2H5
b: R2 = CH2C6H5
c: R2 = COC6H5
d: R2 = C6H5
113a-c
a: R2 = C6H5
b: R2 = p-OCH3-C6H4
c: R2 = p-Br-C6H4
112a,b
a: R1 = H
b: R1 = C6H5

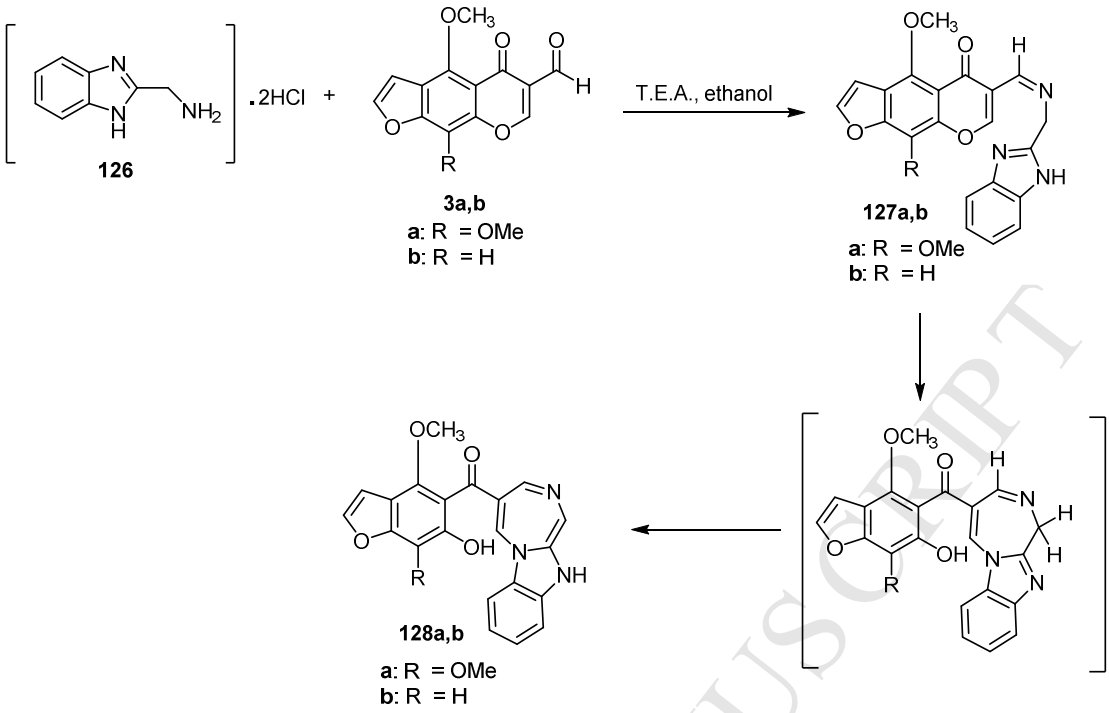
Scheme 30.



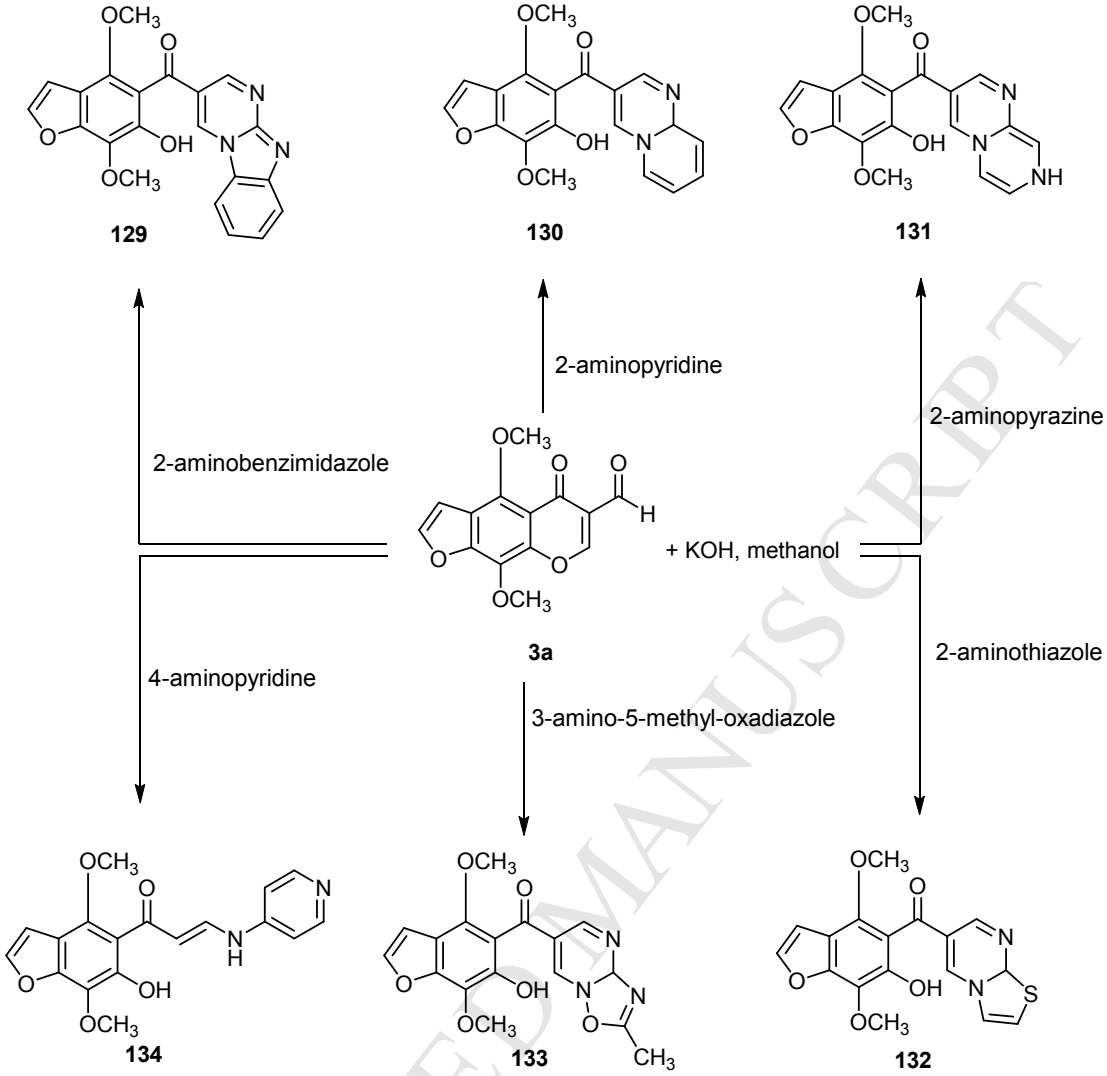
Scheme 31.



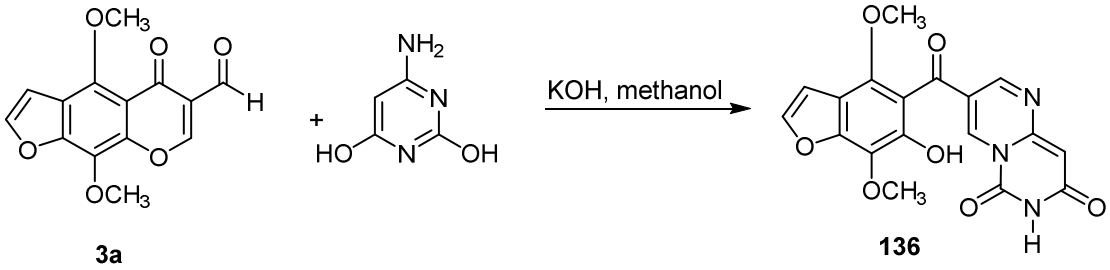
Scheme 32.



Scheme 33.

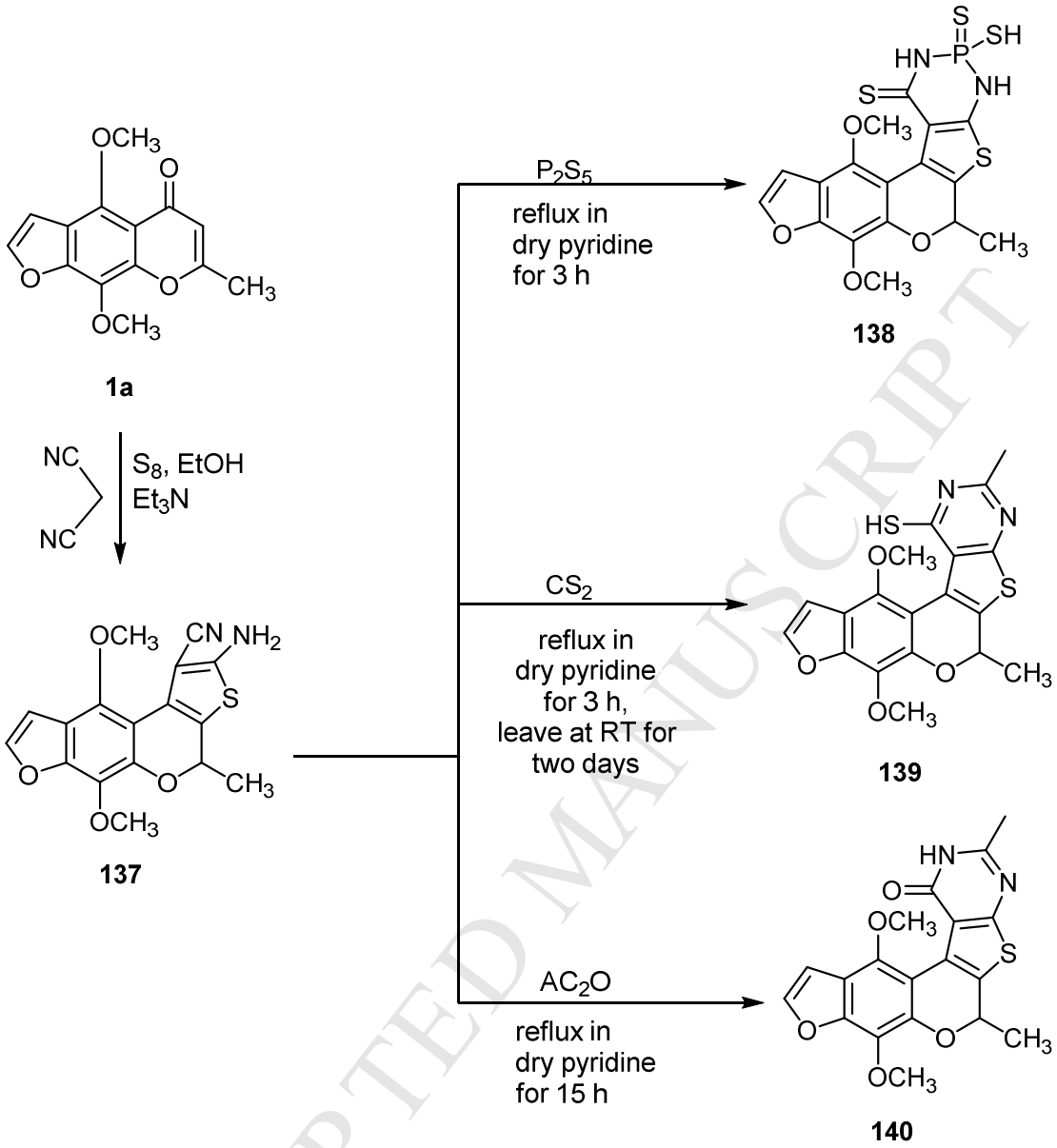


Scheme 34.

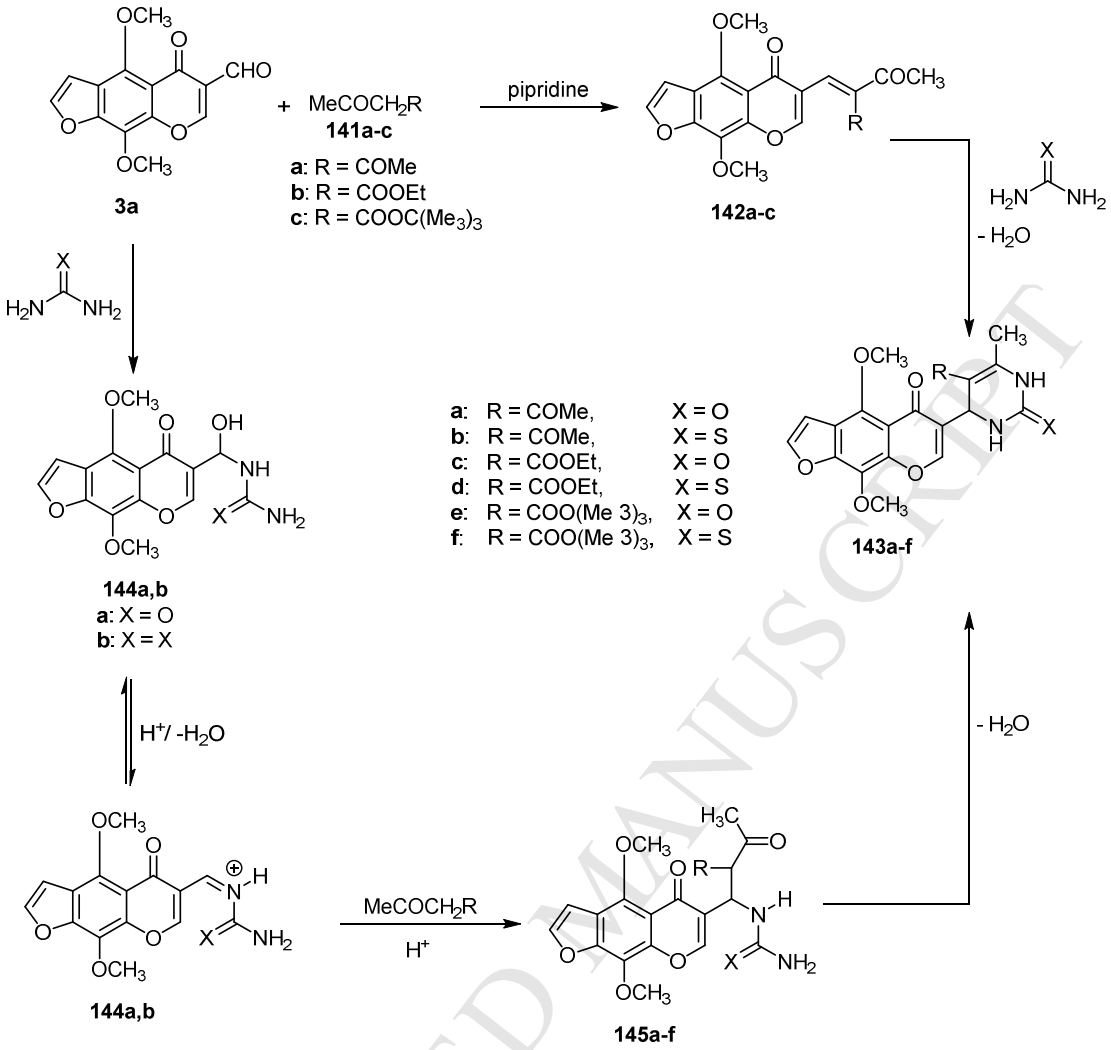


3a **136**

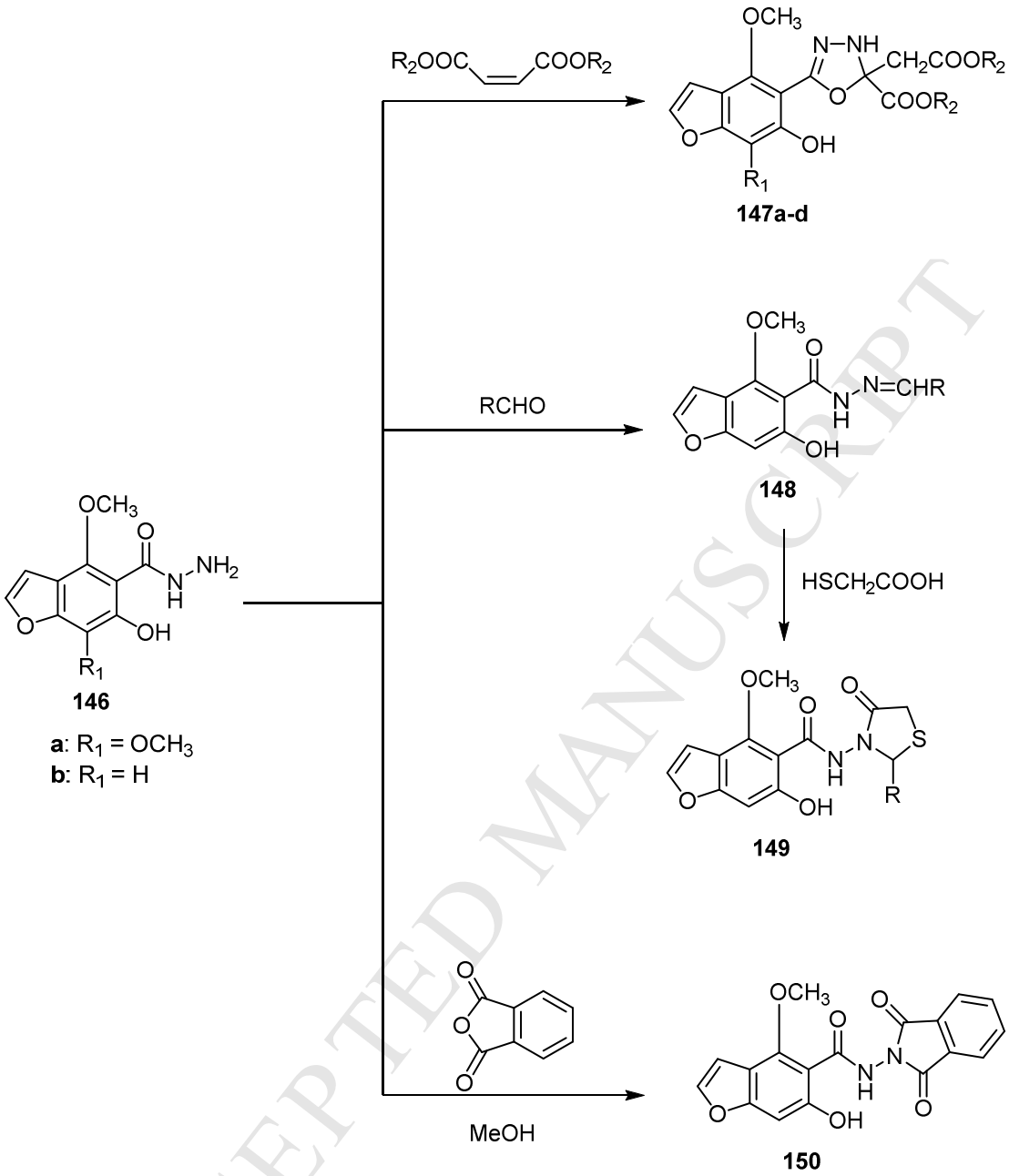
Scheme 35.



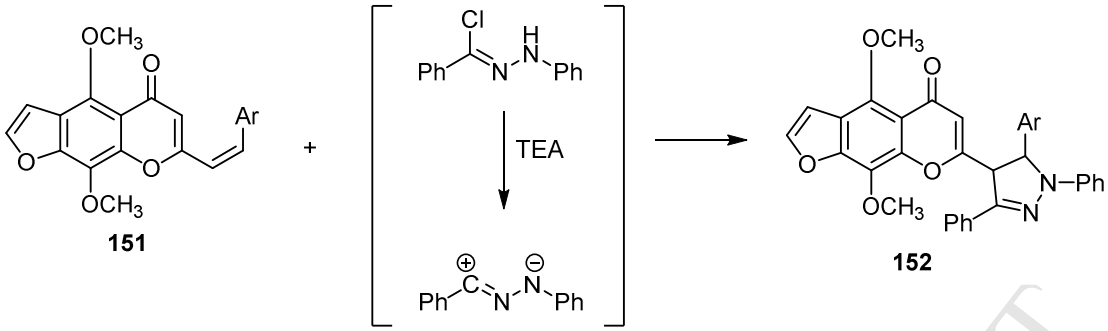
Scheme 36.



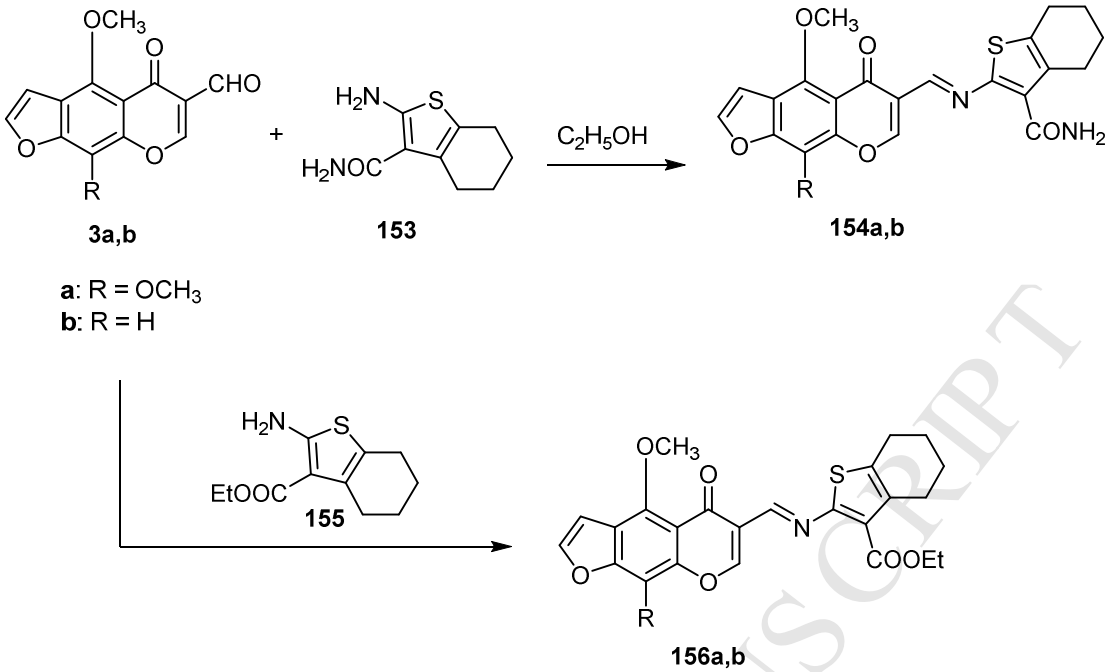
Scheme 37.



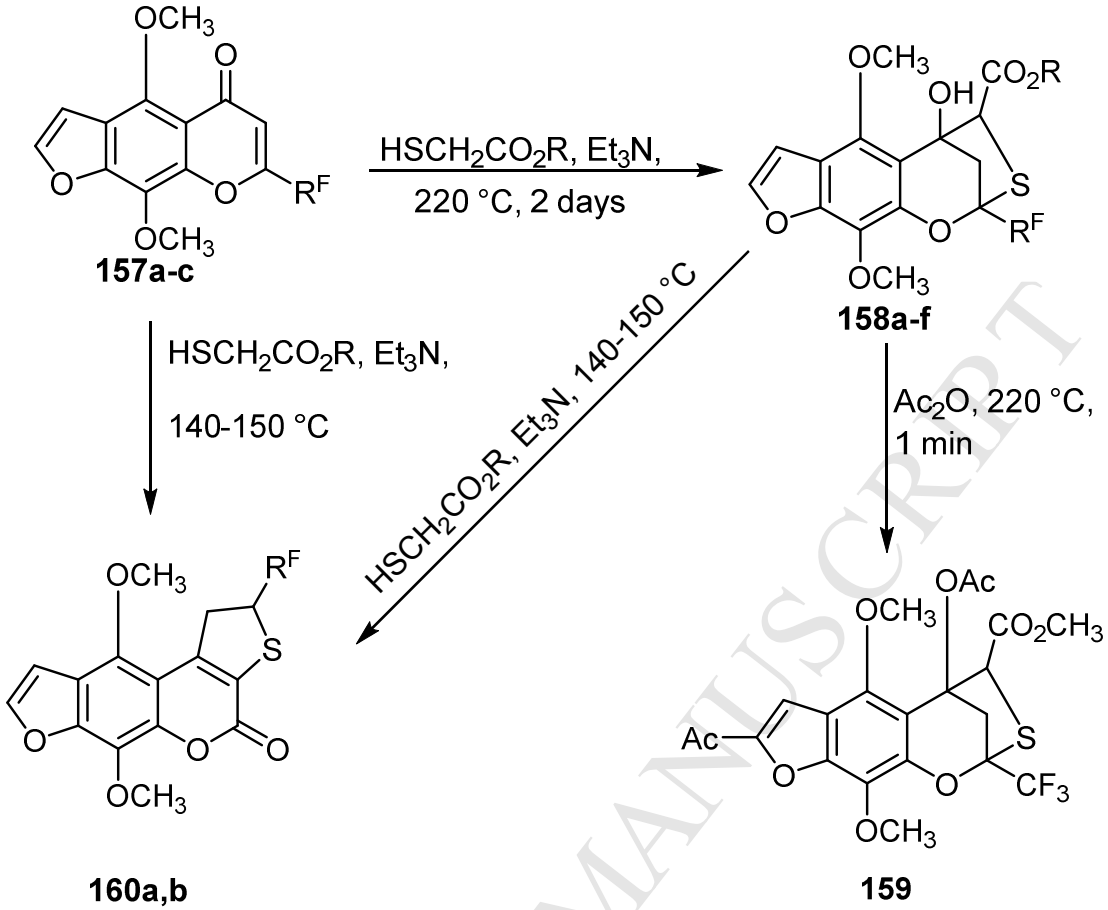
Scheme 38.



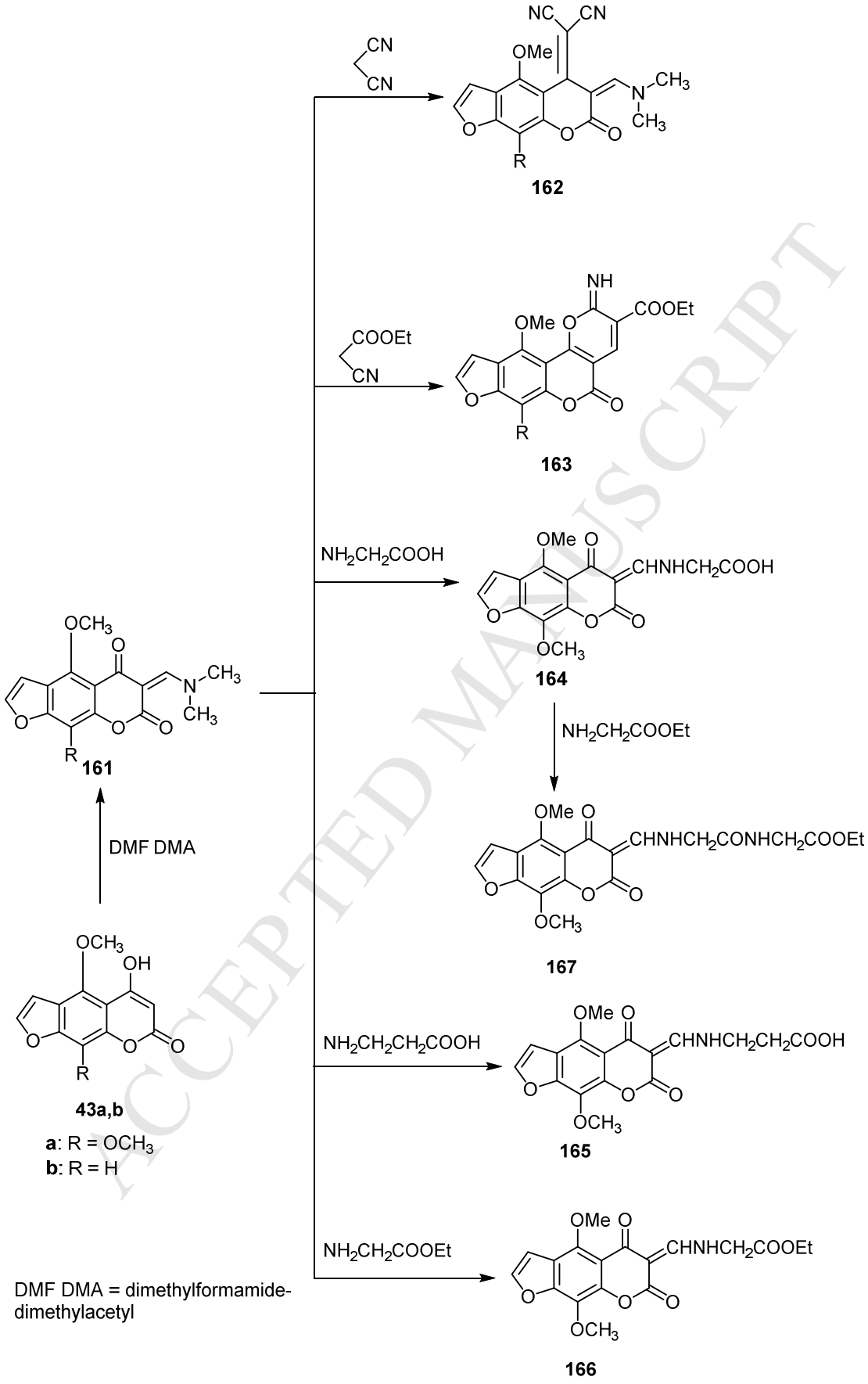
Scheme 39.



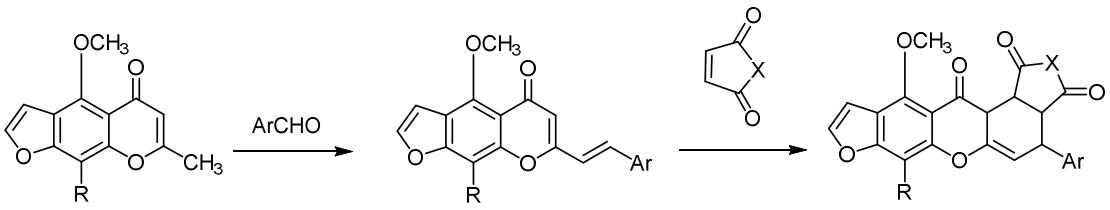
Scheme 40.



Scheme 41.



Scheme 42.



1a,b

a: R = OCH_3

b: R = H

151

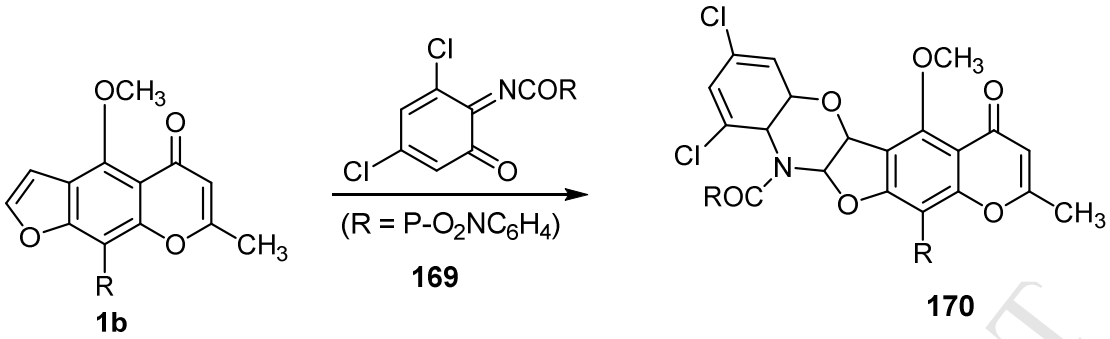
168

R = H, OMe

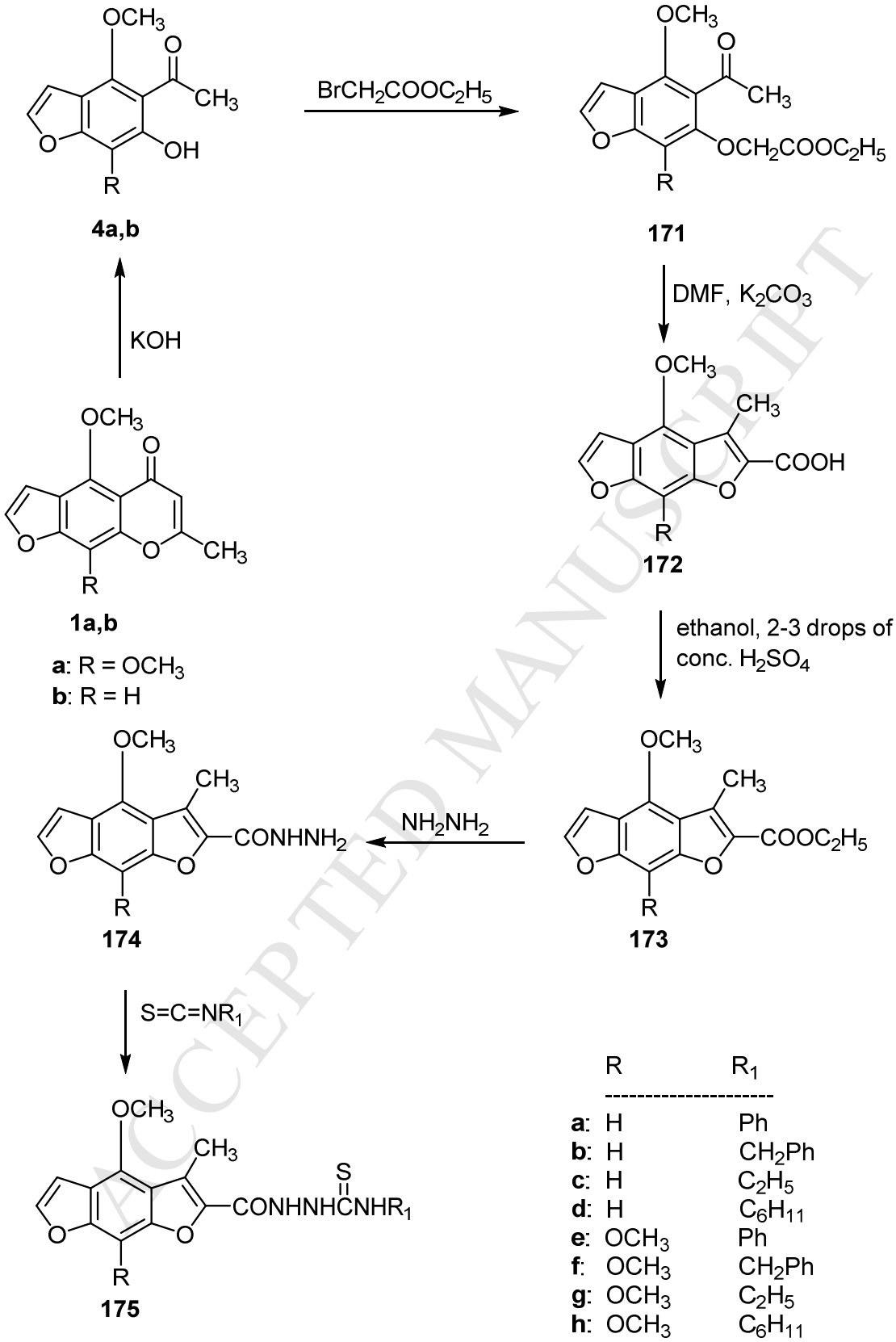
Ar = Ph, $C_6H_4CH_3$, 2- thienyl, pyridyl, furyl

X = O, NPh

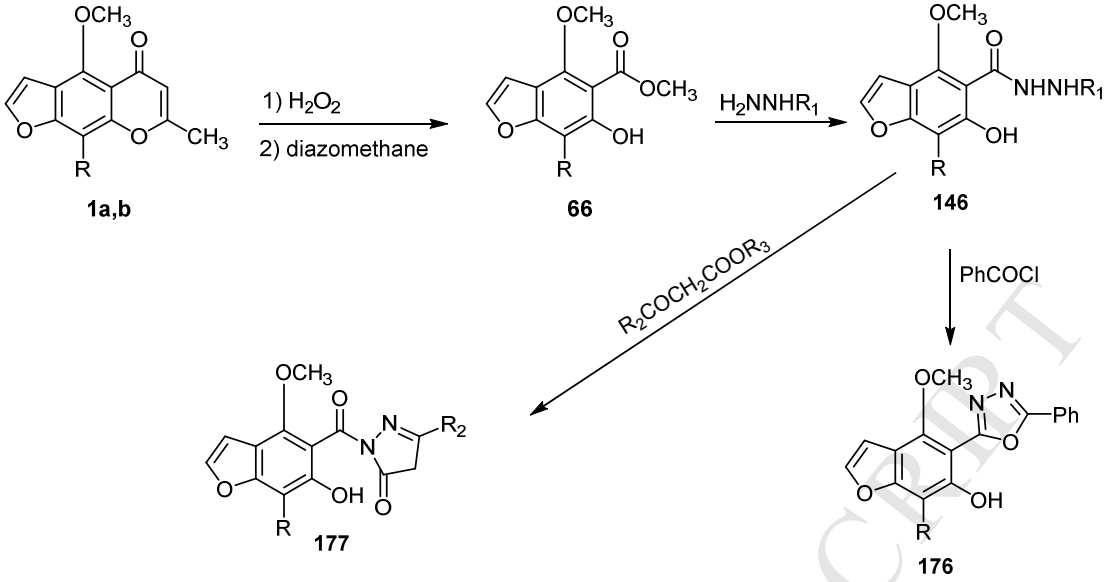
Scheme 43.



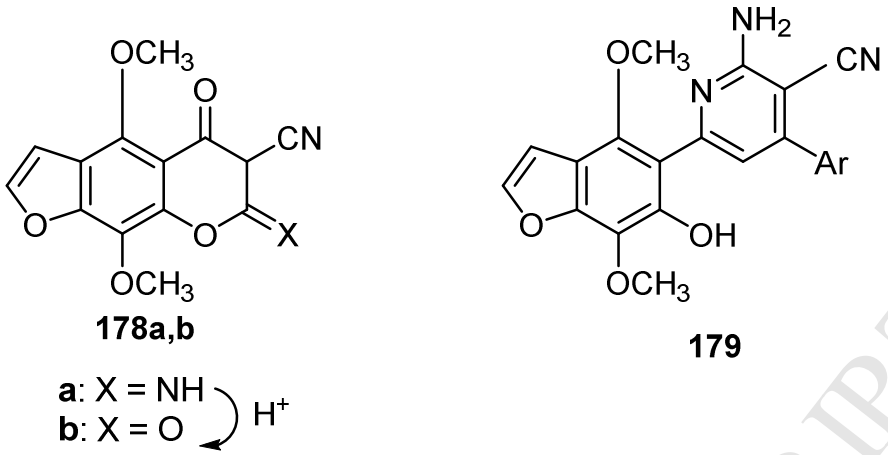
Scheme 44.



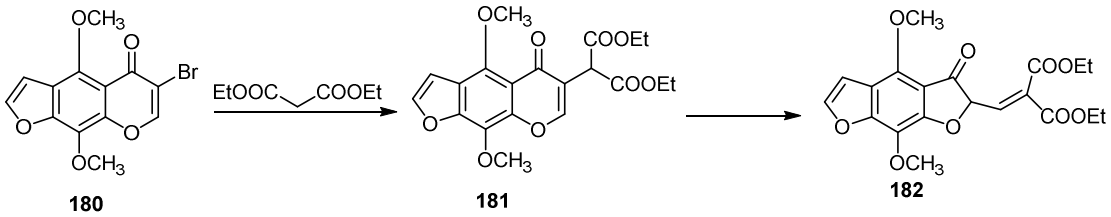
Scheme 45.



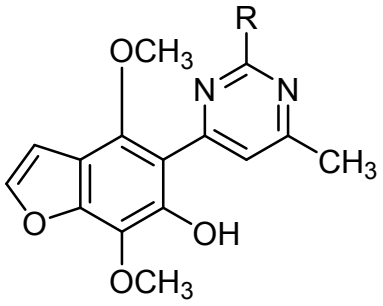
Scheme 46.



Scheme 47.



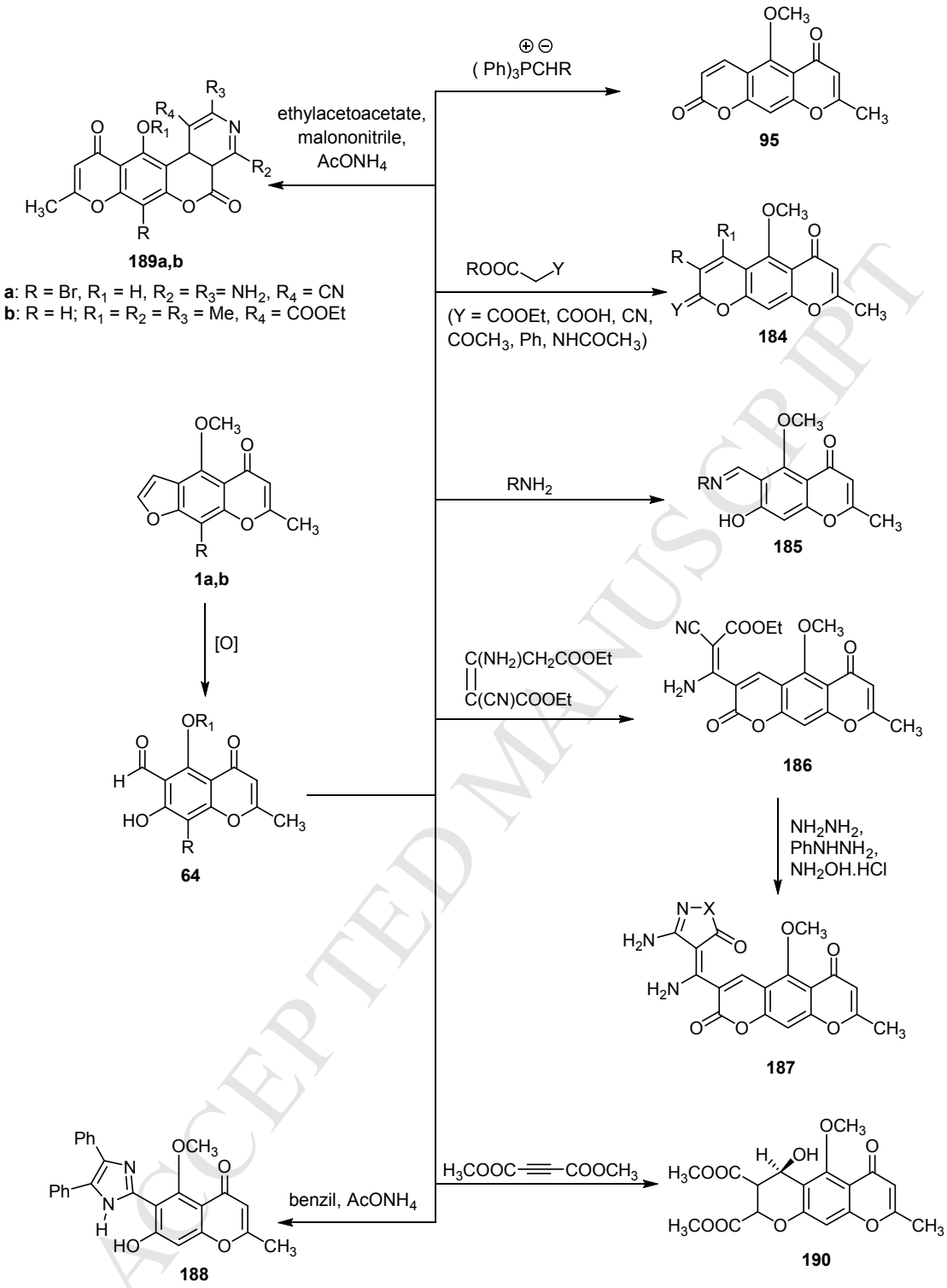
Scheme 48.



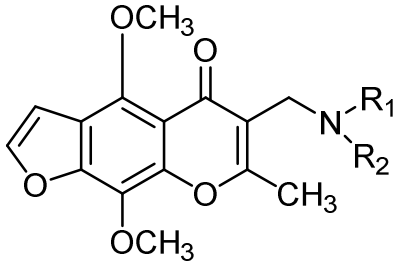
183a-c

a: R = H
b: R = NH_2
c: R = NH-CN

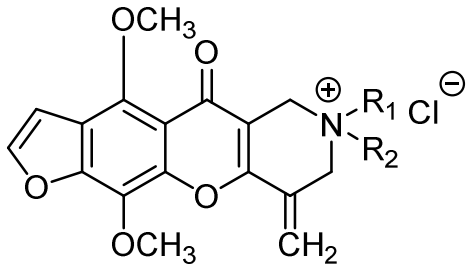
Scheme 49.



Scheme 50.



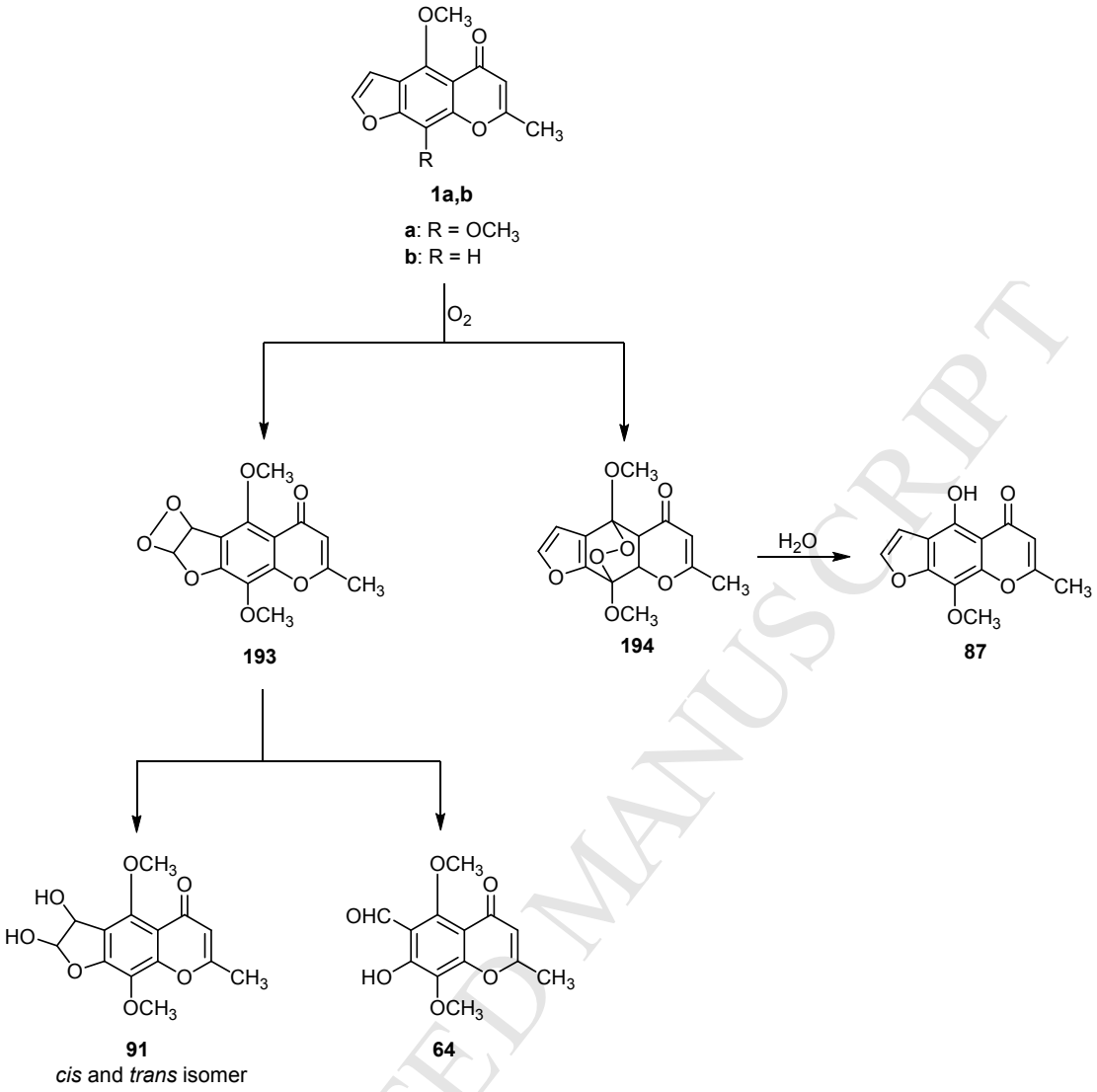
191



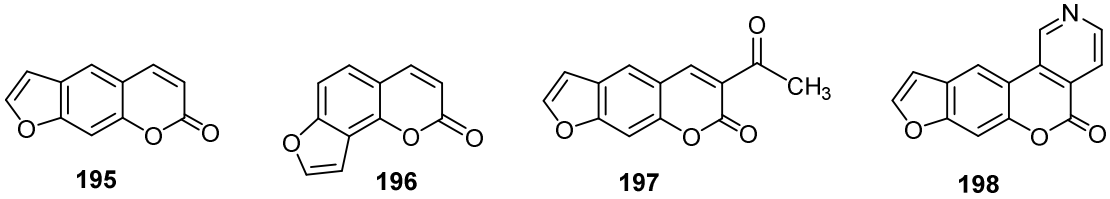
192

a: $R_1 = R_2 = CH_3$
b: NR_1R_2 = morpholino
c: NR_1R_2 = piperidino

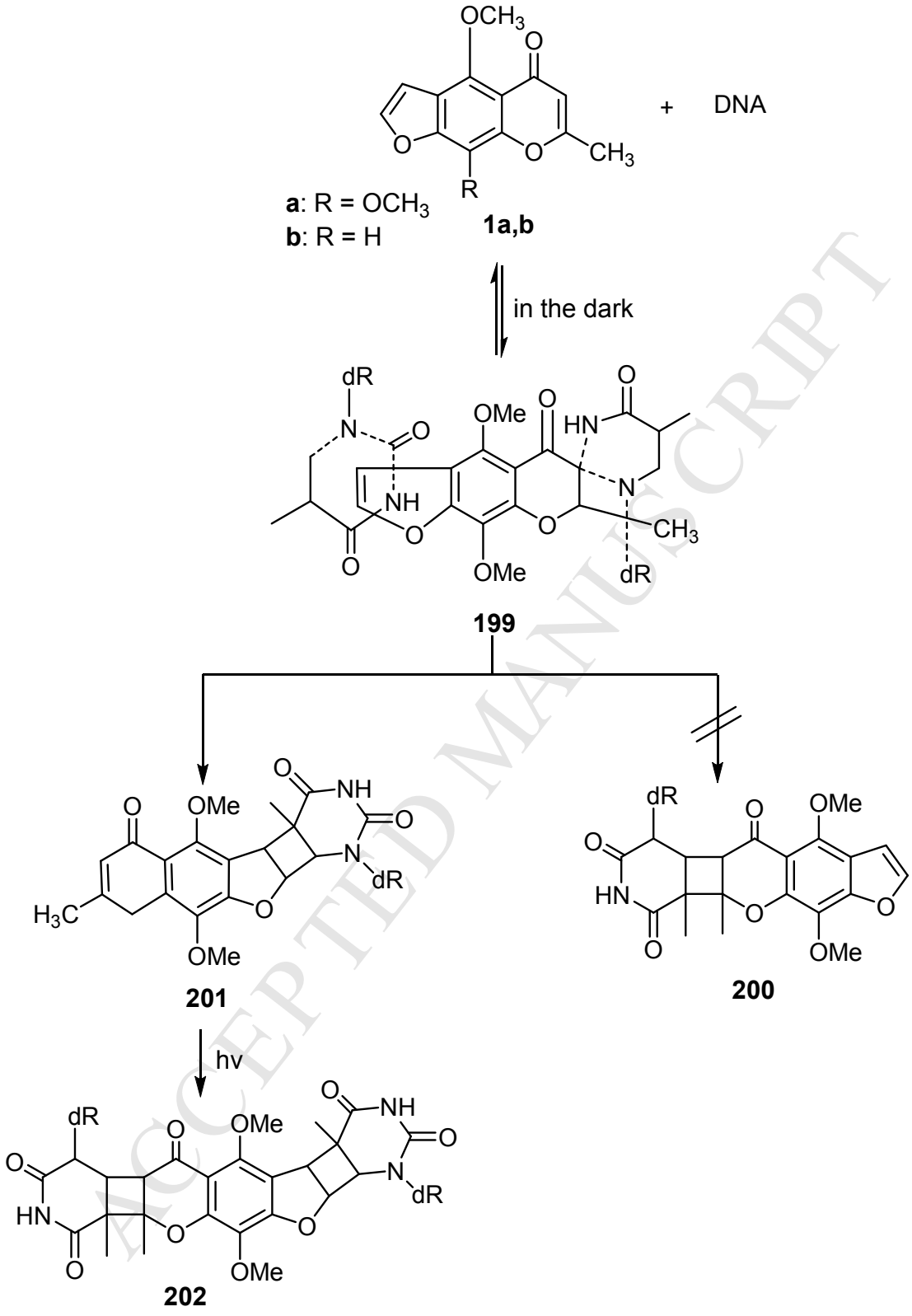
Scheme 51.



Scheme 52.



Scheme 53.



Scheme 54.

- Furochromone derivatives are important synthetic targets.
- Furochromone derivatives possess a myriad of interesting biological activities.
- *Ammi visnaga* (Umbelliferae) is the most famous source of these derivatives.
- Khellin and visnagin are the most famous derivatives isolated from *Ammi visnaga*.
- Khellin and visnagin exhibit vasodilating activity in angina and urinary colics.