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Isocoumarins and 3,4-dihydroisocoumarins, amazing natural products: a review

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Abstract: The isocoumarins are naturally occurring lactones that constitute an important class of natural products exhibiting an array of biological activities. A wide variety of these lactones have been isolated from natural sources and, due to their remarkable bioactivities and structural diversity, great attention has been focused on their synthesis. This review article focuses on their structural diversity, biological applications, and commonly used synthetic modes.

Key words: Isocoumarin, synthesis, natural product, biological importance

1. Introduction

The coumarins **1** are naturally occurring compounds having a fused phenolactone skeleton. Coumarin **1** was first extracted from *Coumarouna odorata* (tonka tree).[1] The isocoumarins **2** and 3,4-dihydroisocoumarins **3** are the isomers of coumarin **1**. A number of substituted isocoumarins have been found to occur in nature; however, the unsubstituted isocoumarins have not been observed to occur naturally. Furthermore, sulfur, selenium, and tellurium analogues **4a**–**4c** have also been known since early times (Figure 1).

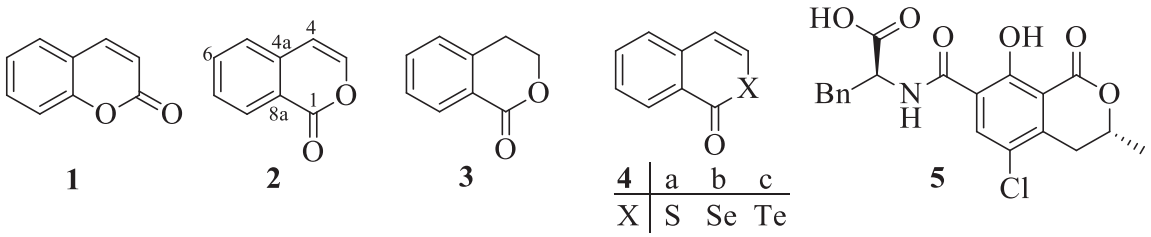

Figure 1. Some naturally occurring isocoumarins.

The isocoumarins and their analogues occur in nature as secondary metabolites (i.e. produced by living beings in response to external stimuli) of plants and lower microorganisms. A few isocoumarins are also extracted from insect pheromones and venom. These lactones are structural subunits of several natural products and serve as useful intermediates in the synthesis of different heterocyclic molecules. The isocoumarins have been found to exhibit beneficial (e.g., antitumor, antileukemic, antiviral, and antimicrobial[2]) as well as toxic biological activities; for example, ochratoxin A **5** is a potent mycotoxin produced by *Aspergillus* and *Penicillium* species, which is hepatotoxic, nephrotoxic, teratogenic, and carcinogenic in animals.[3]

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Due to the pharmacological and biochemical properties and the therapeutic applications of isocoumarins and 3,4-dihydroisocoumarins, research concerning the isolation and syntheses of isocoumarins has caught the attention of many organic chemists, which is reflected by the large number of review articles that have been published on isocoumarins. For example, Barry,[4] Turner and Aldridge,[5] Napolitano,[6] Bin,[7] and Saeed[8] published reviews about isocoumarins and 3,4-dihydroisocoumarins.

1.1. Nomenclature

The name "isocoumarin" is derived from the fact that these compounds are isomers of coumarins **3**. The IUPAC names of isocoumarins **1** and their 3,4-dihydroanalogues **2** are 1H-2-benzoxin-1-ones and 3,4-dihydro-1H-2-benzoxin-1-ones, respectively. In the literature no proper nomenclature exists for isocoumarins and 3,4-dihydroisocoumarins. Generally, the trivial names derived from specific or generic names of fungal or plant sources are used for naturally occurring isocoumarins and their 3,4-dihydroanalogues.[8] Names such as alternariol (*Alternaria* sp.), peniolactol (*Peniophora sanguinea*), cladosporin (*Cladosporium* sp.), and homalicine (*Homalium zeylancum*) are common examples of the names derived from genera and mellein (*Aspergillus melleus*), ustic acid (*A. ustus*), and duclauxin (*P. duclauxi*) are examples of names derived from specific names.

Most of the trivial names of isocoumarins end in suffixes such as -in, -ol, -one, -ide, -oic acid, or anhydride depending on the nature of the functional group present. Some examples are artemidin, altenuisol, oospolactone, agrimonolide, ustic acid, β-callatolic acid, lamellicolic anhydride, and naphthalic anhydride.

2. Pharmacological importance

The isocoumarins and 3,4-dihydroisocoumarins are an important class of naturally occurring lactones isolated from different bacterial strains, molds, lichens, and plants. They show a wide range of biological activities, ranging from antibacterial to antitumour.[9–11] Significant work has been published about their biology and chemistry. Some of the selected biological activities are discussed here.

Amicoumacin A **6** and C **7** have been found to show antiulcer, antibacterial, and antiinflammatory activities.[12] Baciphelacins **8** have good potential for the treatment of bacterial and viral infections.[13,14] Among dihydroisocoumarins, PM-94128 **9**[15] and Y-05460M-A **10**[16] have been found to exhibit antiulcer activity in addition to antibacterial and antitumor activities (Figure 2).

The activity of PM-94128 **9** was examined against four different tumor cell lines including P-388 (lymphoid leukemia), A-549 (human lung carcinoma), HT-29 (human colon carcinoma), and MEL-28 (human melanoma) in the 50 nM activity range.[17] Amicoumacin Sg17-1-4 **11** isolated from a marine fungus, *Alternaria tenuis* Sg17-1, shows cytotoxic activity against HeLa cell lines (Figure 2).[18]

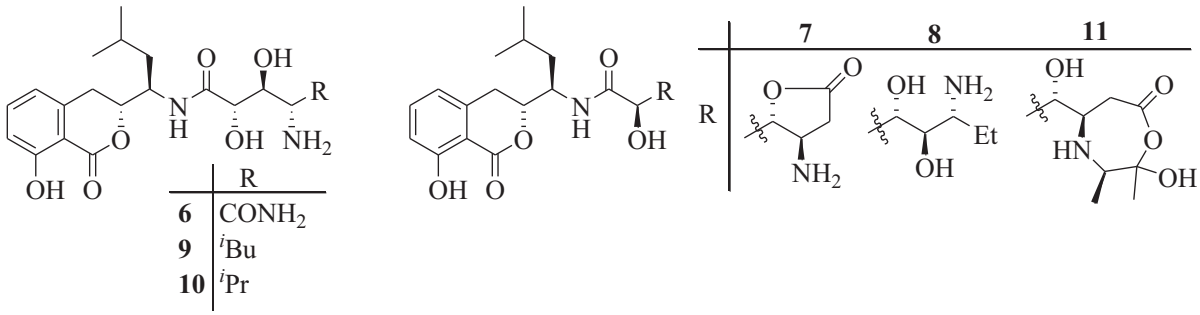


Figure 2. 3,4-Dihydroisocoumarins with antibacterial and antitumor activities.

A series of structurally related isocoumarins known as A1-77s are a small family of antibiotics isolated from a culture broth of *Bacillus pumilus* A1-77 (found in the gut of *Coenagrion* dragonfly larvae and also produced by *Nocardia jinanesis*) (Figure 3).[19] The structural feature of A1-77s comprises a dihydroisocoumarin moiety connected to different acyl hydroxy amino acid chains. It is the variation in the amino acid chain that results in various members of the family.[20,21] These compounds possess a broad range of pharmacological properties including antibacterial, antiinflammatory, antiulcer, gastroprotective, and anti-*Helicobacter pylori* activities.[12,22–24] However, they are famous for their remarkable gastroprotective activity.[19] The family members of the A1-77s include compounds AI-77-A **12**, -B **13**, -C **14**, -D **15**, -F **16**, and -G **17**, which vary in their acyl hydroxy amino acid chains (Figure 3).[12]

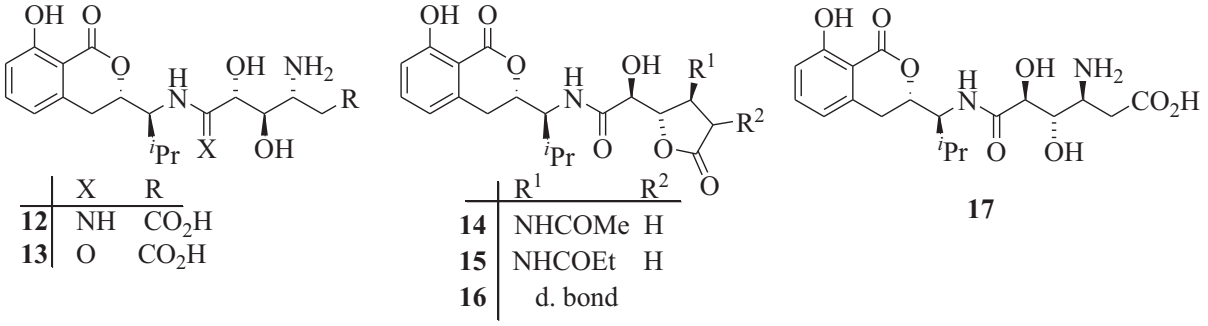


Figure 3. A series of structurally related A1-77 isocoumarins.

AI-77-B is the most abundant compound of the amicoumacin family. It is also known as amicoumacin B **13**, which is a major product of the fermentation process and has been found to exhibit potent gastroprotective β-amino acid **18**.[25] Amicoumacin B **13** shows antiinflammatory (rats), antiulcer (human stomachs), and herbicidal (*Lemna*) activities and is also used as an acaricide.[26] Besides its unique structure and its characteristic biological activity, its therapeutic potential is limited because of poor oral absorption properties. As a result, structural modifications and synthetic studies of AI-77-B have attracted a great deal of attention from synthetic chemists.[27–30]

Bergenin **19**,[31] isolated from *Flueggea microcarpa* and *Flueggea virosa*, and an isocoumarin coriandrin **20**,[32] isolated from *Coriandrum sativum*, have been found to show anti-HIV activity (Figure 4). In addition to anti-HIV, bergenin **19** also possesses antiulcer[33] and antihepatotoxic activity.[34] It was observed that **19**, extracted from the aboveground parts of *Flueggea virosa*, was proved to have good potential to treat cardiac arrhythmias.[35] The one isolated from *Flueggea microcarpa* showed antifungal activity against several plant-pathogenic fungi.[36]

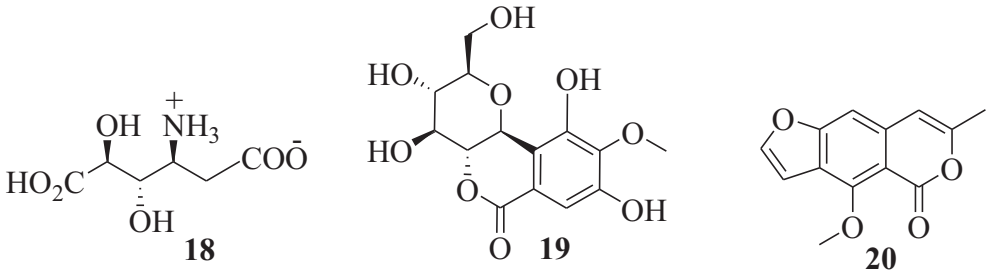


Figure 4. Structures of β-amino acid **18**, bergenin **19**, and coriandrin **20**.

The 9,10-dihydroxy-5,7-dimethoxy-1H-naphtho-(2,3c)pyran-1-one **21** (common name: paepalantine) is extracted from *P. bromelioides* and shows intense cytotoxic activity in the McCoy cell line (Figure 5). The paepalantine molecule is more lipophilic than other isocoumarins because hydroxyls at positions C^9 and C^{10} form an intramolecular bridge of a hydrogen bond. It has been found that the rate of cytotoxicity depends on the presence and position of hydroxyl group in the isocoumarin framework.[37] Thunberginol B **22a**–**22b**, naturally occurring isocoumarins, also show anticancer effect (Figure 5). In addition, thunberginol B has been found to have antiallergic, antimicrobial, antioxidant, and choragic activities.[38]

Isocoumarin derivatives 6,8-dihydroxy-4-acetyl-isocoumarin **23** and 6,8-dihydroxy-4-(1-hydroxyethyl)-isocoumarin **24** are effective angiogenesis inhibitors (Figure 5).[39] A group of 3-carboxyisocoumarins **25a**–**25c** showed antiallergic effects (Figure 6).[40]

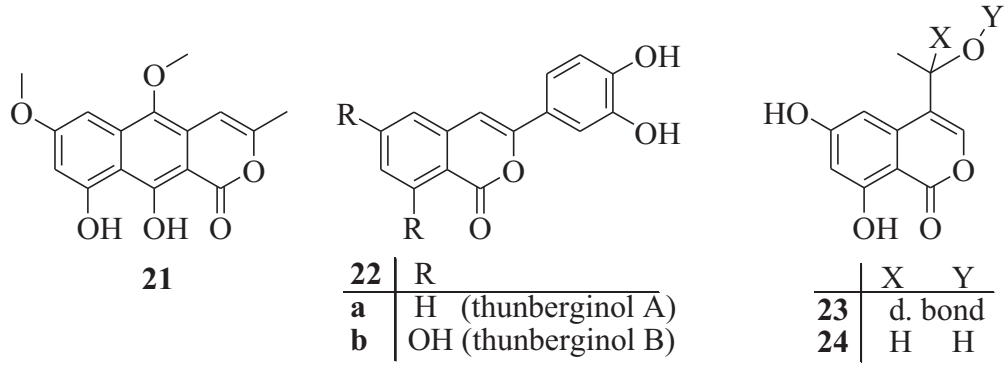


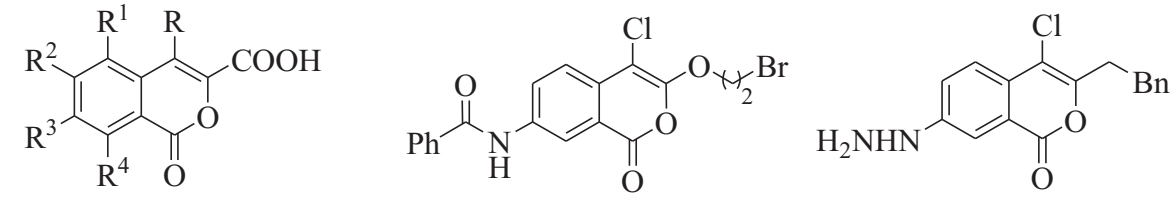
Figure 5. Structures of paepalantine **21**, thunberginol B **22**, and 6,8-substituted 3,4-dihydroisocoumarin **23**–**24**.

Inhibitors are the chemical substance that reduces the activity of enzymes by blocking the active sites of enzymes. Serine proteases are essential inhibitors that play significant roles in various physiological processes such as blood coagulation, digestion, viral infection, fibrinolysis, and fertilization. They can also be lethal if they are uncontrolled. They can cause various diseases such as tumors, cerebral infection, emphysema, vascular clotting, arthritis, and bronchial inflammation. It is thus necessary to introduce a variety of selective inhibitors for the treatment of diseases related to serine proteases.[41]

The chloro- and amino-substituted isocoumarins, e.g., 3-bromoalkoxy-4-chloro-7-benzamidoisocoumarins **26**, are well-known compounds for the development of uncharged inhibitors of urokinase-type plasminogen activator (uPA) (Figure 6). They have important contributions to the extracellular proteolytic events associated with tumor cell growth, migration, and angiogenesis.[42] The aminoalkoxy- and guanidino-substituted isocoumarins **27** have also been found as powerful inhibitors of blood coagulation serine proteases (Figure 6).[43]

Various derivatives of isocoumarins and 3,4-dihydroisocoumarins were screened for their antibiotic activity. Among the substituted isocoumarins, the 8-hydroxylisocoumarins **28**, 6,8-dihydroxy-3-(4-hydroxyphenyl)-isocoumarins **29**, and 8-dihydroxy-3-(3,4-dihydroxyphenyl)-isocoumarins **30** possess strong antibiotic effects (Figure 7). The isocoumarins **31**–**33** have also been found effective against various strains of gram-positive and gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella boydii*, *Salmonella* serovar Typhi, and *Bacillus cereus* (Figure 7).[44]

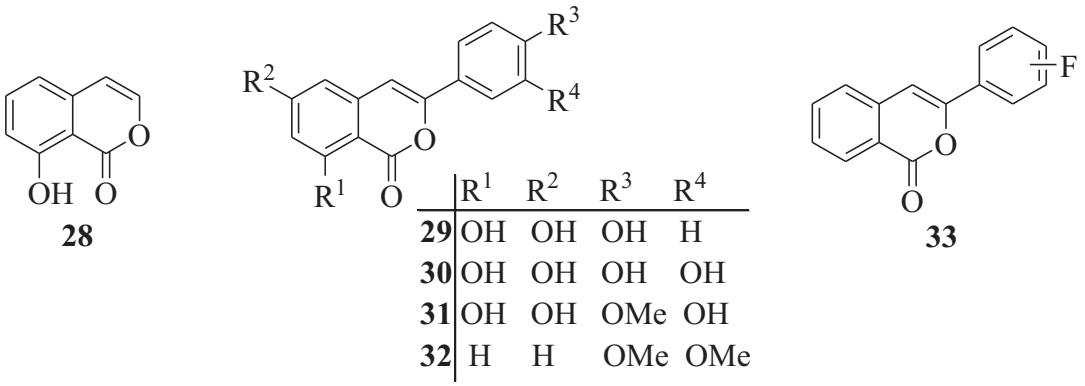
The 3,4-dihydroisocoumarins **34**–**35** were examined for antibacterial effects against different gram-positive and gram-negative bacterial strains (Figure 8).[45]



25	R	R^1	R^2	R^3	R^4
a	Me	H	H	H	H
b	H	H	OMe	OMe	H
c	H	H	H	OMe	OMe

26 **27**

Figure 6. Structures of antiallergic and inhibitor isocoumarins **25a**–**25c** and **26**–**27**.



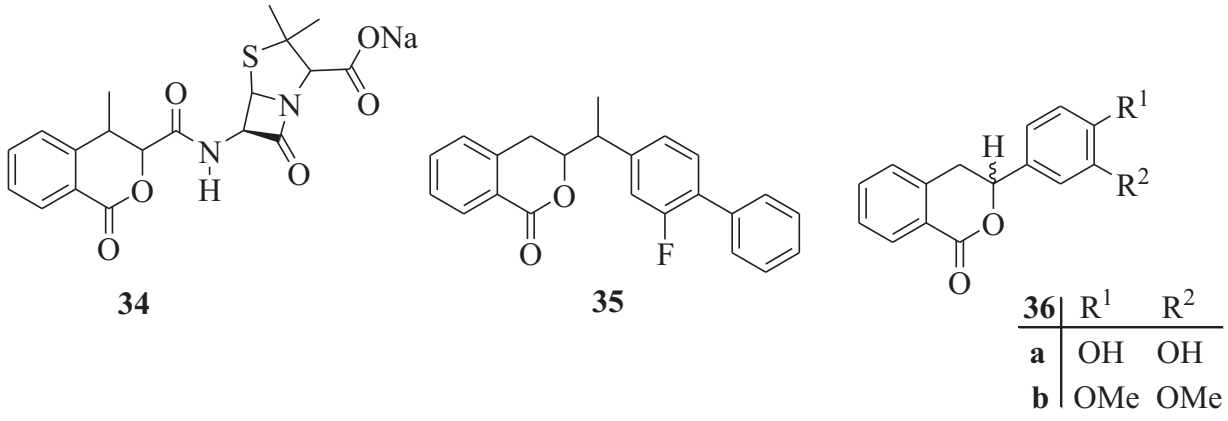
28

	R^1	R^2	R^3	R^4
29	OH	OH	OH	H
30	OH	OH	OH	OH
31	OH	OH	OMe	OH
32	H	H	OMe	OMe

33

Figure 7. Hydroxy isocoumarins possessing strong antibiotic effects.

Some other derivatives of 3,4-dihydroisocoumarins, such as 3-(3',4'-dimethoxyphenyl)-3,4-dihydroisocoumarin and 3-(3',4'-dihydroxyphenyl)-3,4-dihydroisocoumarin **36a**–**36b**, showed moderate effects when tested in vitro for antibacterial activity (Figure 8).[46]



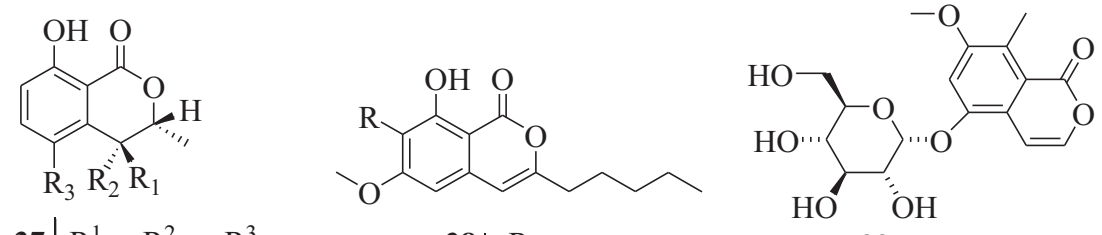
34 **35**

36	R^1	R^2
a	OH	OH
b	OMe	OMe

Figure 8. Antibacterial 3,4-dihydroisocoumarins.

Malaria is a potentially fatal blood disease of tropical climate areas. It is caused by eukaryotic protists of the genus *Plasmodium*. *Plasmodium* is present in the body of humans and an animal host, the *Anopheles*

mosquito, and is transferred to human blood by the bite of infected *Anopheles* mosquitoes. The most common drug prescribed for malaria patients is chloroquine, but some derivatives of 3,4-dihydroisocoumarin, mullein **37a**–**37d**, produced by *Botryosphaeria rhodina*, an endophytic fungus, show effective antimalarial activity (Figure 9).[47] Some isocoumarin derivatives, 8-hydroxy-6-methoxy-3-pentyl-1H-isochromen-1-one **38a**–**38b**[48,49] and halorosellins **39**,[50] isolated from the bark and stem of *Tessmannia densiflora* and *Halorosellinia oceanica*, respectively, also showed antimalarial activity (Figure 9).



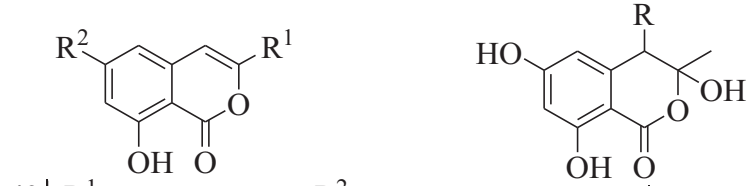
37	R^1	R^2	R^3
a	H	H	H
b	H	OH	H
c	OH	H	H
d	H	H	OH

38	R
a	H
b	Cl

Figure 9. Structures of antimalarial molecules.

Ceratocystis fimbriata, a fungus, is a source of isocoumarins **40a**–**40d** that are known for their phytotoxic activity on leaves of coffee trees, and also they are responsible for fruit withering with trunk canker in adult coffee trees (Figure 10).[51]

Other derivatives of 3,4-dihydroisocoumarin **41a**–**41b** extracted from the fungus *Ceratocystis ulmi* inhibit the growth of rice seedlings and lesions on the leaves of pear trees (Figure 10).[52]



40	R^1	R^2
a	CH_3	OMe
b	CH_2OH	OH
c	CH_2OH	OMe
d	$CH_2CH(OH)CH_3$	OH

41	R
a	H
b	OH

Figure 10. Structures of isocoumarins **40** and dihydrocoumarins **41**.

Mutation is a variation in the fundamental coding series of the hereditary material, which in most plants and animals is DNA, but in a few viruses is RNA. It occurs by new genetic recombinations of nitrogenous bases present in the hereditary material of organisms. Mutations have proved to be fatal and were found to cause various hereditary diseases. There are some other processes that create change in the genotype of an organism

but are not referred to as mutations, and these include combinations of chromosomes in the offspring, artificially induced recombinations, or the introduction of new genetic material into an organism.

Paepalantine-9-α-D-glactopyranoside **42**, a glucose derivative extracted from *Paepalanthus bromelioides*,[53] and isocoumarins **43a**–**43b** have been found to exhibit mutagenic effects (Figure 11).[53,54]

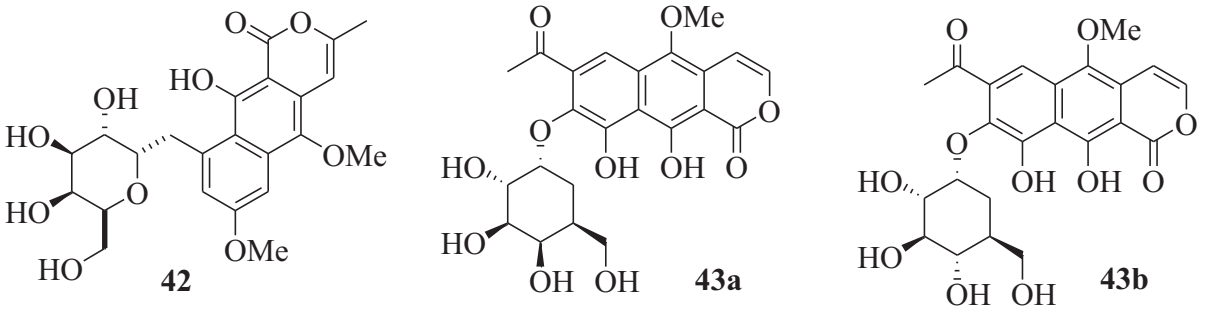
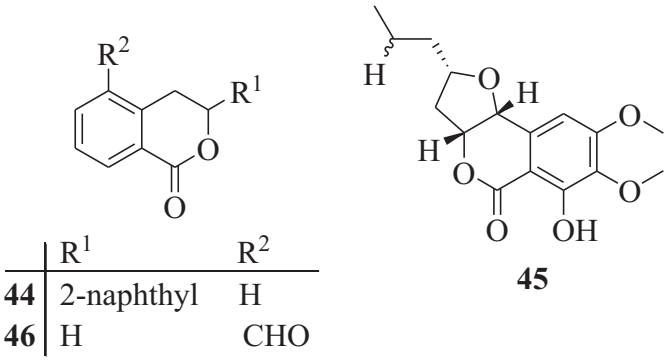


Figure 11. Glucose derivatives of isocoumarins.

The 3-(2-naphthyl)3,4-dihydroisocoumarin **44** was tested in vitro against fungal strains *C. albicans*, *F. solani*, *T. schoenleinii*, *A. niger*, *M. phaseolina*, and *P. boydii* and it was found active against all the fungal strains except *C. albicans* (Figure 12).[55] Monocerin **45** and its different analogues have been isolated from numerous fungal sources, such as *Drechslera monoceras* (Figure 12). They possess excellent antifungal properties.[56]



	R^1	R^2
44	2-naphthyl	H
46	H	CHO

Figure 12. Structure of antifungal isocoumarines **44**–**45** and erythocentaurin **46**.

Erythocentaurin **46** is isolated from *Enicostema hyssopifolium*, which is widely distributed in southern Pakistan. This plant is considered medicinally important is and used locally by the indigenous people as a remedy for malaria. In different regions of Pakistan, other species from the same family are used as digestive aids, as stomachic tonics, and for depurative, sedative, and antipyretic effects. Erythocentaurin **46** has also been found to be an active agent against serine proteases such as chymotrypsin and trypsin; these proteases are involved in the destruction of certain fibrous proteins.[57]

The derivative of 3,4-dihydroisocoumarin **47** has antileukemic activity (Figure 13).[58] Isocoumarins **48a**–**48b** have been found useful for the cure of diseases associated with an abnormality in immunological regularity function or vascularization (Figure 13).[59] 3,4-Dihydroisocoumarin **49** has been found as trail pheromone in the hindgut of ants of various species of the genera *Formica* and *Lasius*.[60] A number of derivatives of isocoumarins are used as sweetners,[61] e.g., **50** (Figure 13).

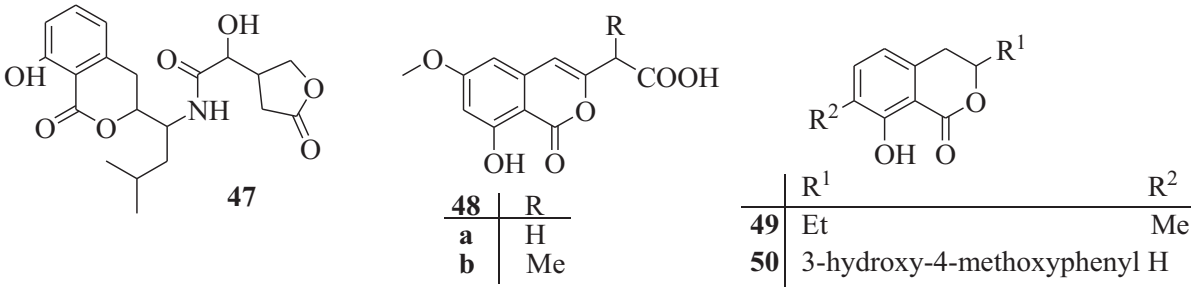


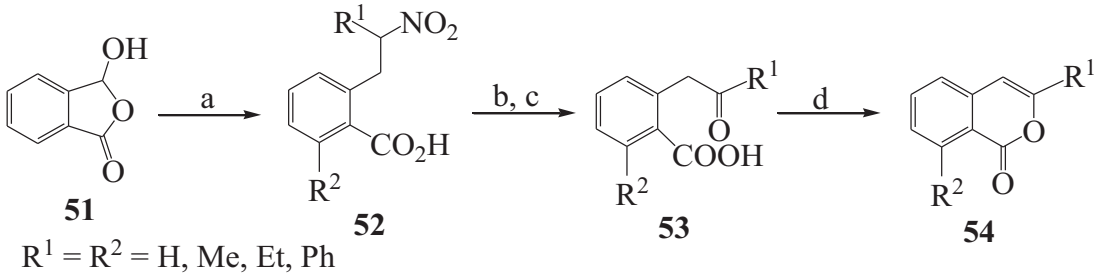
Figure 13. Structures of hydroxy coumarins **47**–**50**.

The isocoumarins and 3,4-dihydroisocoumarins are naturally occurring lactones that display a wide range of biological and pharmacological activities[62–67] and serve as key intermediates in the synthesis of biologically active molecules. These are identified as highly attractive molecules in organic chemistry.[64–67] A wide spectrum of synthetic methods have been used for the synthesis of isocoumarins and 3,4-dihydroisocoumarins.[68] A number of new methods[69–79] are being developed and reported each year. Some of these methods provide the isocoumarins directly, whereas others lead to the 3,4-dihydroisocoumarins. Some of the most important high-yielding methods applicable to the synthesis of a large number of these compounds are reported below.

3. Synthetic approaches

3.1. Regiospecific synthesis of isocoumarins

Hauser et al.[80] reported the synthesis of isocoumarin **54** from phthalaldehydic acid **51** and nitroalkanes. The condensation of **51** afforded (nitroalkyl)benzoic acids **52** in good yield (70%–95%). The Nef reaction of **52** yielded ketoacid **53**, which upon intramolecular cyclization followed by dehydration yielded isocoumarin **54** (Scheme 1).

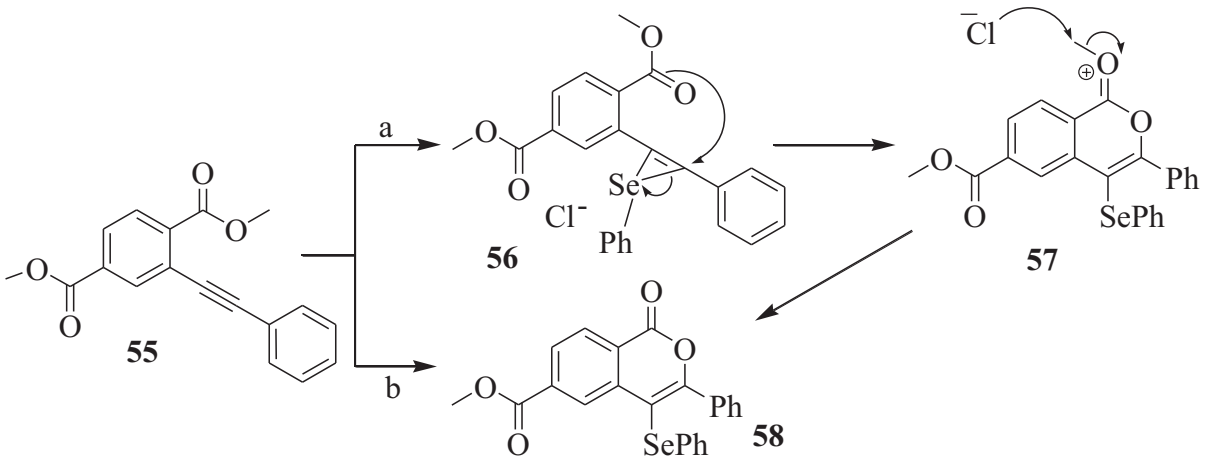


Reagent and conditions: **a**) RCH_2NO_2, Et_3N, DMSO; **b**) $NaBH_4$, DMSO; **c**) i. NaOH, ii. H_2SO_4, MeOH; **d**) Ac_2O, EtOAc, H^+.

Scheme 1. Synthetic scheme of isocoumarin **54**.

3.2. Synthesis of isocoumarins via electrophilic cyclization

Yao and Larock[76] reported the synthesis of isocoumarins via electrophilic cyclization of o-(1-alkynyl)benzoates **55**. A series of substituted isocoumarins **58** were synthesized in good yields under mild reaction conditions by the reaction of various o-(1-alkynyl)benzoates **55** with electrophiles such as ICl, I_2, PhSeCl, and HI. The reaction proceeded through intermediates **56**–**57** (Scheme 2).

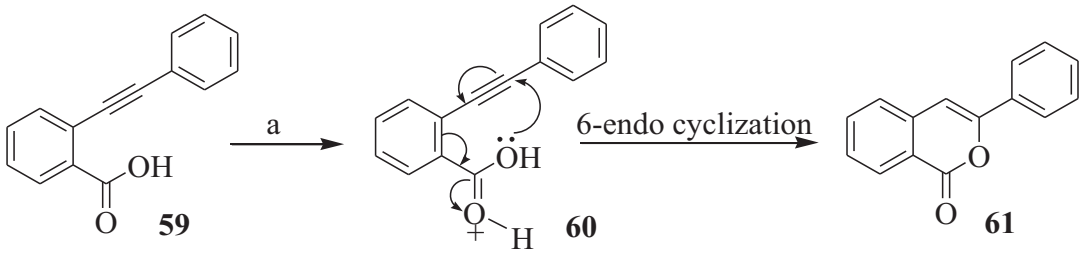


Reagent and conditions: **a**) PhSeCl; **b**) PhSeCl (1.2 eq), CH_2Cl_2, rt.

Scheme 2. A representative of electrophilic cyclization for the synthesis of various isocoumarins.

3.3. Acid-catalyzed cyclizations of 2-(phenylethynyl)benzoic acid

Uchiyama et al. carried out the acid-catalyzed selective cyclization of enynecarboxylic acid **59** to isocoumarin **61** via intermediate **60** (Scheme 3).[81]



Reagent and conditions: **a**) TfOH or CF_3COOH.

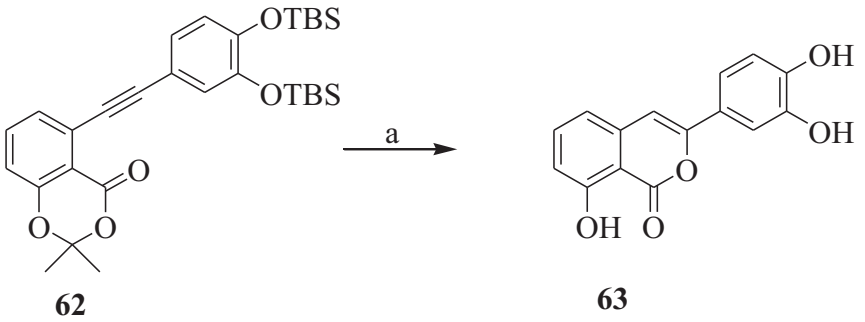
Scheme 3. Acid-catalyzed selective cyclization of an enynecarboxylic acid **59** to isocoumarin **61** via intermediate **60**.

This strategy was applied for the synthesis of thunberginol A **63** from **62**, known for having miscellaneous biological applications, such as antimicrobial and antiallergic activities (Scheme 4).[81–85]

3.4. Synthesis involving metals/metal ions/transition metal complexes

The literature shows that isocoumarins and 3,4-dihydroisocoumarins have been widely prepared in ways involving metalation at certain positions. Such strategies include lithiation and silylation.

Menashe et al. reported that diphenylacetylene **64** reacts with AcOH **65** in the presence of Ru-catalyst under reflux conditions to afford isocoumarin **66**. The mechanism of this transformation is still ambiguous; however, it was observed that the Ru-catalyst plays an important role in this reaction as the reaction does not proceed in the absence of this catalyst (Scheme 5).[86]



62 **63**

Reagent and conditions: **a**) TfOH, THF, reflux, 7 h.

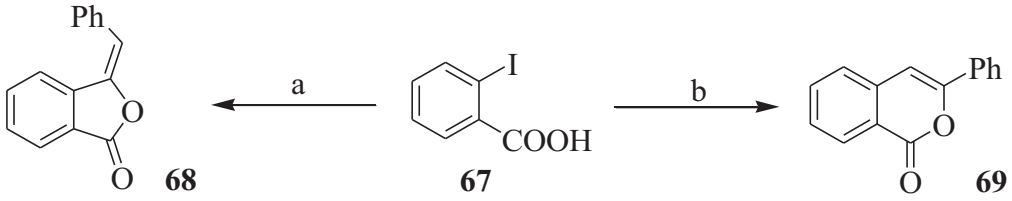
Scheme 4. Synthesis of thunberginol A **63** from **62**.

64 **65** **66**

Reagent and conditions: **a**) $Ru_3(CO)_{12}$

Scheme 5. Ru-catalyzed synthesis of isocoumarin **66** from diphenylacetylene **64**.

While o-iodobenzoic acid **67** was reacted with Cu-acetylides to yield 3-benzylidinephthalide **68** instead of the formation of isocoumarin, the same acid upon reaction with phenyl acetylene in the presence of a catalytic amount of Cu(I)-PPh_3 and K_2CO_3 under microwave atmosphere yielded isocoumarin **69** as a major product (Scheme 6).[87]

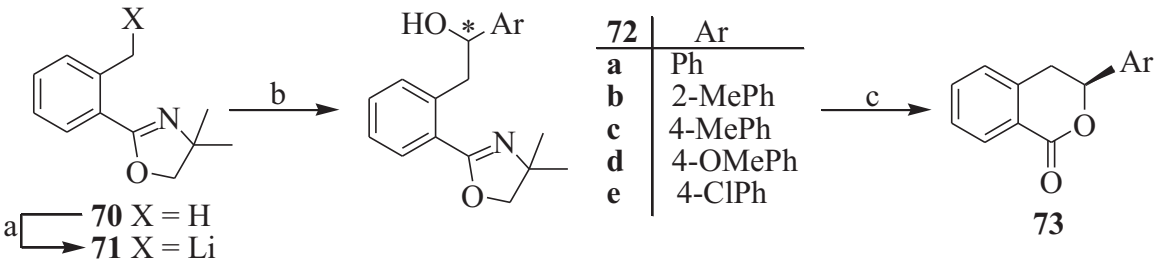


68 **67** **69**

Reagent and conditions: **a**) CuCCPh, C_5H_5N, reflux; **b**) HCCPh, Cu(I)-$IPPh_3$, K_2CO_3, microwave irradiation.

Scheme 6. Microwave-assisted synthesis of isocoumarin **69**.

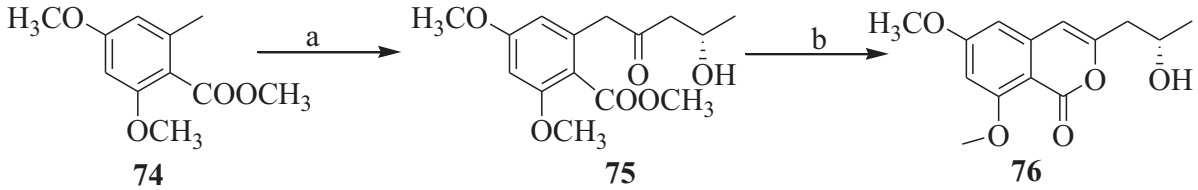
The oxazoline **70**, upon deprotonation with ^{s}BuLi followed by the addition of external chiral ligand (S)-2-(1-pyrrolidinylmethyl)pyrrolidine, yielded the lithiated species **71**. It was then treated with PhCHO to afford alcohol **72**, which upon further hydrolysis under mild conditions yielded isocoumarin **73** (Scheme 7).[88]



Reagent and conditions: **a**) Et_2O, −78 °C, ^{s}BuLi, (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine Li; **b**) PhCHO; **c**) MeOTf, Et_2O, EtOH, reflux.

Scheme 7. Scheme for the synthesis of isocoumarin **73**.

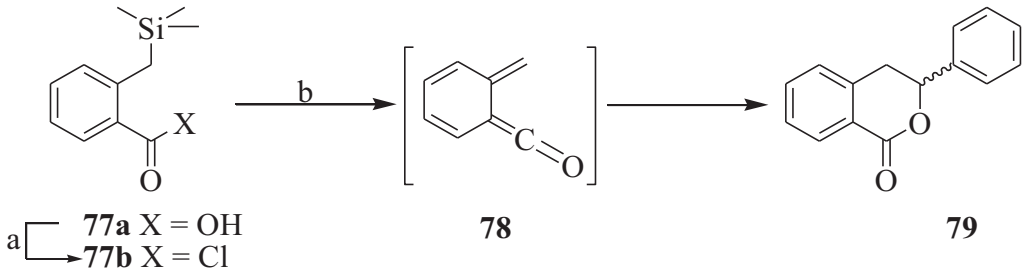
The methyl 2,4-dimethoxy-6-methylbenzoate **74** was lithiated with lithium diisopropylamide (LDA) and reacted with ethyl (*S*)-3-hydroxybutyrate to produce (*S*)-methyl-2-(4-hydroxy-2-oxopentyl)-4,6-dimethoxy benzoate **75**. The condensation of **75** with TsOH afforded 3,4-dihydroisocoumarin **76** (Scheme 8).[89]



Reagent and conditions: **a**) LDA, ethyl (*S*)-3-hydroxybutyrate, HCl; **b**) TsOH, PhH, reflux.

Scheme 8. Synthetic strategy for 3,4-dihydroisocoumarin **76**.

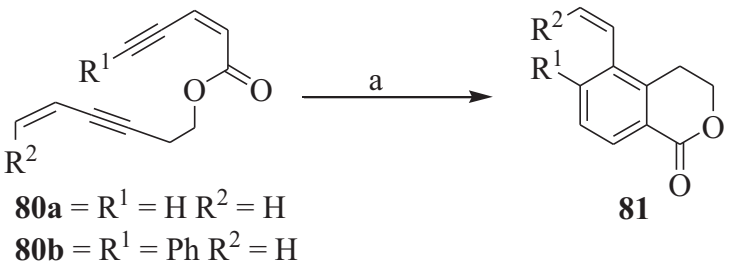
The 2-(trimethylsilylmethyl)benzoyl chloride **77b** upon desilylation followed by the reaction of ketene **78** with benzaldehyde yielded dihydroisocoumarins **79** (Scheme 9).[90]



Reagent and conditions: **a**) $SOCl_2$; **b**) CsF. ArCHO.

Scheme 9. A synthetic method for 3,4-dihydroisocoumarin **79**.

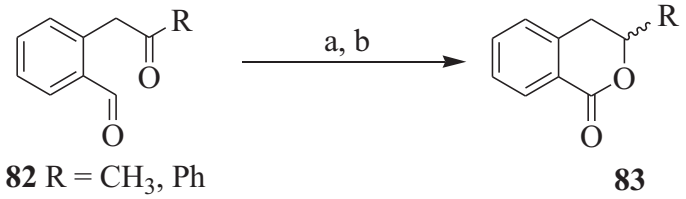
The single-step synthesis of 5,6-substituted 3,4-dihydroisocoumarins **81** was carried out by Kawasaki and coworkers via Pd-catalyzed intramolecular benzannulation reaction of bis-enynes **80** (Scheme 10).[91]



Reagent and conditions: **a**) $Pd(PPh_3)_4$, DPPF, Ph-Me, 80 °C

Scheme 10. The single-step synthesis of 5,6-substituted 3,4-dihydroisocoumarins **81** developed by Kawasaki and coworkers.[91]

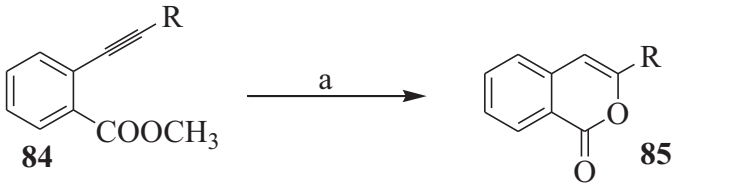
Suzuki et al. reported the oxidative lactonization of δ-ketoaldehydes **82** by exploiting an Ir-ligand bifunctional catalyst to afford coumarin derivatives. The intramolecular Tishchenko reaction of δ-ketoaldehydes afforded 3,4-dihydroisocoumarin **83** in good yields (Scheme 11).[92]



Reagent and conditions: **a**) Ir-catalyst, rt; **b**) Tishchenko reaction.

Scheme 11. Intramolecular Tishchenko reaction of δ-ketoaldehydes for the synthesis of 3,4-dihydroisocoumarin **83**.

Marchal et al.[93] carried out Au(I)-catalyzed intramolecular cyclization of esters **84a**–**84d** to various alkylidene lactones **85**. The electronic effects of the R group and bulky substituents on the alkyne strongly modify the reactivity. The formation of isocoumarins from the cycloisomerization of o-alkynylbenzoic methyl esters is catalyzed by 10 mol% AuCl in the presence of 2 equivalents of H_2O. Under these conditions, several lactone rings **85a**–**85d** are formed in 60%–83% yield (Scheme 12).

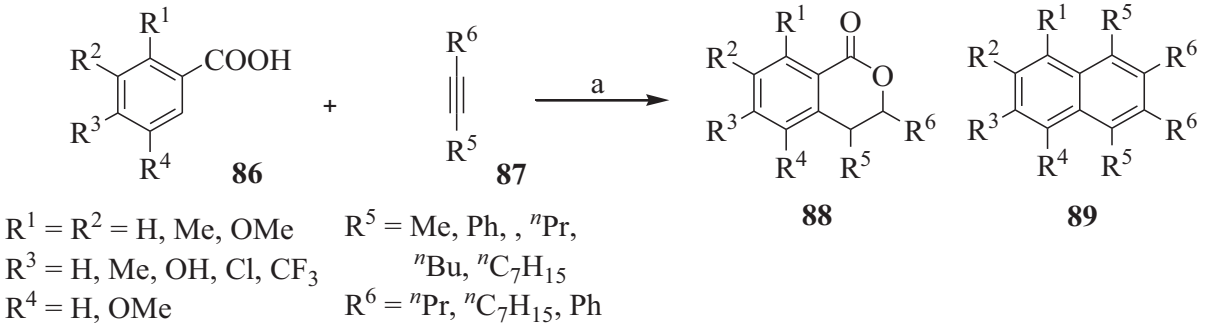


84, 85	**a**	**b**	**c**	**d**
R	Ph, p-$CH_3OC_6H_4$, m-FC_6H_4, Propyl			

Reagent and conditions: **a**) AuCl (10 mol%), 2 eq. H_2O, MeCN, 50 °C, 24–48 h.

Scheme 12. Synthesis of isocoumarins **85** by the cycloisomerization of o-alkynylbenzoic methyl esters.

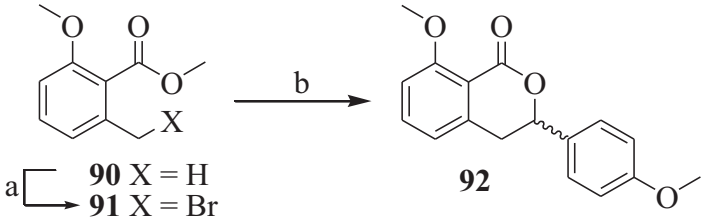
Miura and coworkers[94] described the Rh-catalyzed direct oxidative coupling of benzoic acids **86** with internal alkynes **87** that leads to the formation of 6-membered lactones **88** as the major products and naphthalene derivatives **89** as by-products. The reaction of **86** with dialkylacetylenes proceeded efficiently to produce 3,4-dialkylisocoumarins in good yields. Using unsymmetrical alkylphenylacetylenes, 4-alkyl-3-phenylisocoumarins **88** were predominantly formed in 84%–89% yields along with minor amounts of their regioisomers (Scheme 13).



Reagent and conditions: **a**) $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2.H_2O$.

Scheme 13. The synthetic diagram of 3,4-dihydroisocoumarin **88**.

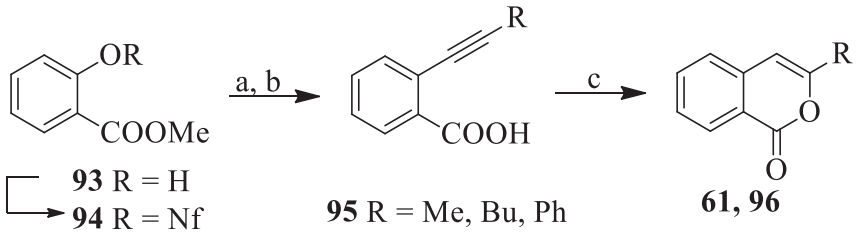
The total synthesis of naturally occurring dihydroisocoumarins such as hydrangenol, phyllodulcin, macrophyllol, and thunberginol G has been accomplished using titanocene(III) chloride (Cp_2TiCl) as a radical initiator.[95,96] The Cp_2TiCl was prepared in situ from commercially available Cp_2TiCl_2 and Zn-dust. For example, ester **90** was brominated with NBS in the presence of the radical initiator AIBN yielding **91** in 92% yield. The bromo ester **91** afforded lactone **92** in 53% yield as a crystalline solid upon treatment with Cp_2TiCl in the presence of 4-methoxybenzaldehyde (Scheme 14).



Reagent and conditions: **a**) NBS/AIBN, CCl_4; **b**) Cp_2TiCl_2/THF, 4-OMePhCHO.

Scheme 14. Synthesis of lactone **92**.

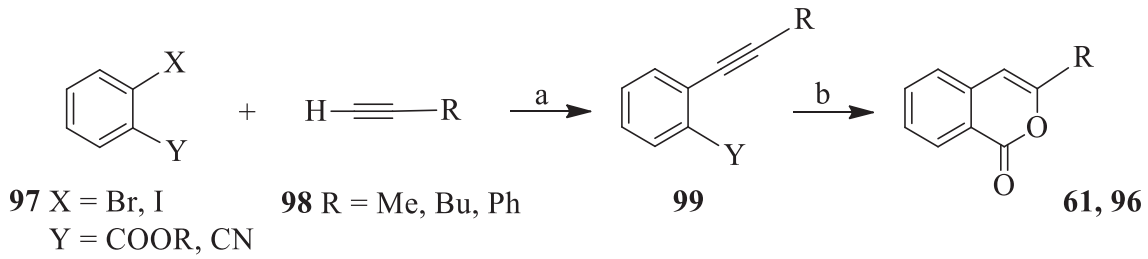
Ogawa et al. reported a convenient method for the synthesis of isocoumarin derivatives via Ag-mediated intramolecular cyclization of 2-(1-alkynyl)benzoic acids **95**. The reaction first involves the formation of nonaflates **94** from **93**, followed by their Pd-catalyzed alkynylation, conversion of esters into the corresponding acid **95**, and Ag-salt-catalyzed 6-endo-dig cyclization of these acids that afforded isocoumarin **96**. The formation of side-product **68** is quite possible in this case due to 5-exo-dig ring closure. Some of the naturally occurring isocoumarin derivatives such as 3-propynylisocoumarin and attemidin were prepared using this strategy (Scheme 15).[97–99]



Reagent and conditions: **a**) terminal alkynes; **b**) NaOH; **c)** AgI or Ag, DMF.

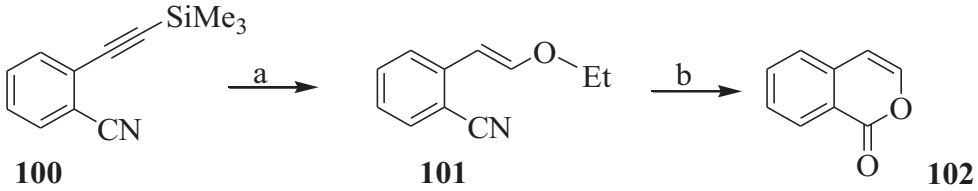
Scheme 15. Formation of isocoumarin **96** via Ag-mediated intramolecular cyclization.

The 3-substituted isocoumarin derivatives **96** were prepared by coupling reaction of **97** and **98**, followed by the hydration of **99** in the presence of $HgSO_4$ in H_2SO_4. The alkyne **99** was heated with $HgSO_4$ and dilute H_2SO_4 to afford isocoumarin derivative **96** with variable yields (Scheme 16). It was observed that alkynes from o-halobenzonitrile derivatives provide isocoumarin in poor yields; however, alkynes **100** are preferably used for the synthesis of unsubstituted isocoumarins **102** via alkene **101** (Scheme 17).[100,101]



Reagent and conditions: **a**) $PdCl_2(PPh_3)_3$; **b**) $HgSO_4$, H_2SO_4.

Scheme 16. A preparation method for 3-substituted isocoumarin derivatives **96**.



Reagent and conditions: **a**) NaOEt; **b**) HBr.

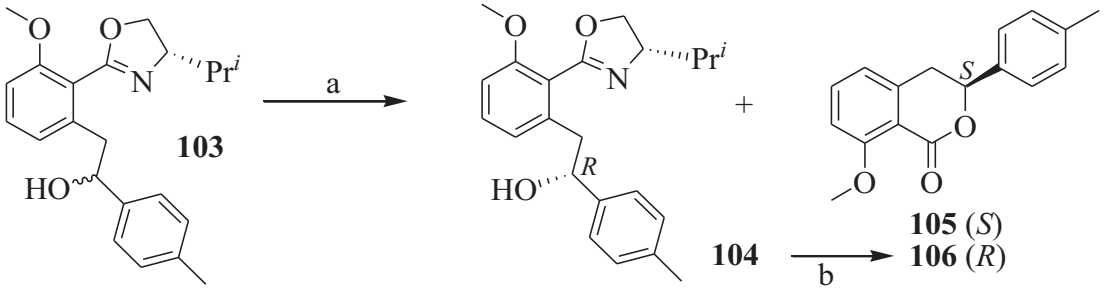
Scheme 17. Synthesis of unsubstituted isocoumarins **102** via alkene **101**.

3.5. Asymmetric synthesis of isocoumarins and 3,4-dihydroisocoumarins

Iwao and coworkers[102] devised a direct method for the synthesis of dihydroisocoumarin **105**–**106** by the reaction of oxazoline **103** and silica gel in CH_2Cl_2 at 0 °C via intermediate **104** (Scheme 18).

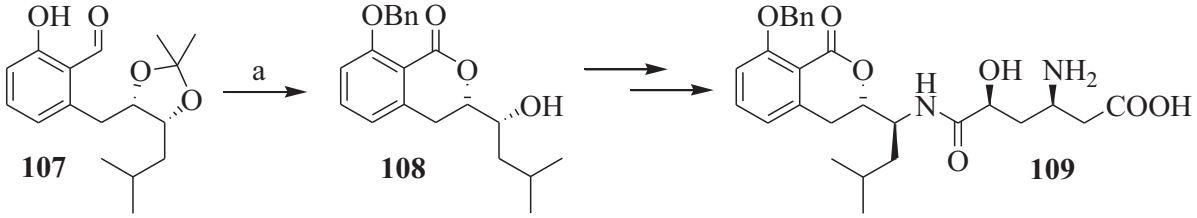
The AI-77s such as **109** are a group of 3,4-dihydroisocoumarin antibiotics that have been isolated from a culture broth of *Bacillus pumilus* AI-77.[103–109] The AI-77-B **109** has been found to exhibit potent gastroprotective activity without anticholinergic, antihistaminergic, or central suppressive effects.[110,111] The protection of **107** as its benzyl ether followed by deprotection of acetonide functionality yielded a diol, which

was further oxidized by $NaClO_2/NaHSO_3$ and 30% H_2O_2 under carefully controlled conditions to afford lactone **108**. The dihydroisocoumarin **108** was then transformed to AI-77-B **109** (Scheme 19).[112]



Reagent and conditions: **a** & **b**) silica gel, CH_2Cl_2, 0 °C, 30 h.

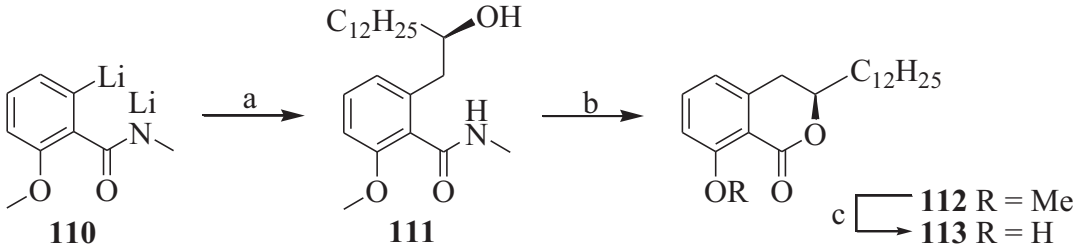
Scheme 18. A direct method for the synthesis of dihydroisocoumarins **105**–**106** from oxazoline **103.**



Reagent and conditions: **a**) i) BnBr, K_2CO_3; ii) $HClO_4$(cat.), CH_3CN; iii) $NaClO_2$, $NaHSO_3$, H_2O_2, $KHPO_4$, *aq*. MeCN.

Scheme 19. A synthetic strategy for AI-77-B **109**.

The enantiomerically pure 3,4-dihydroisocoumarins **112**–**113** have been obtained from lithiated secondary benzamides **110** and homochiral epoxides. The reaction proceeds through uncyclized intermediate **111**. However, unfortunately, the yields are generally modest and N-alkylation can complicate the reaction.[113] Good yields have occasionally been reported in a few cases such as in the syntheses of the antiallergic agent **113** isolated from *Gingko biloba* (Scheme 20)[114] and in the synthesis of a variety of mellein derivatives.[115]

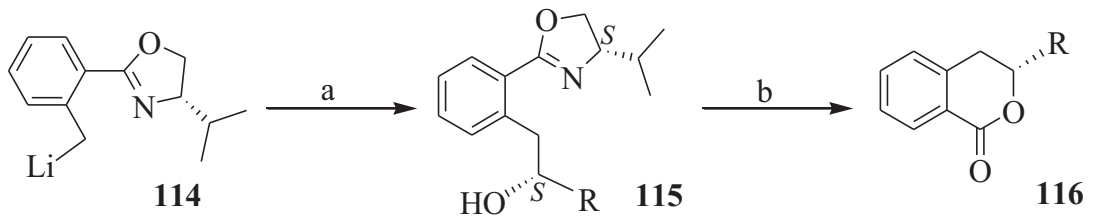


Reagent and conditions: **a**) (*R*)-1,2-epoxytetradecane; **b**) ^-OH, neutralization $CuCN(LiCl_2)$; **c**) BBr_3.

Scheme 20. A scheme for the synthesis of enantiomerically pure 3,4-dihydroisocoumarins **112**–**113.**

Lateral lithiation of (S)-4-isopropyl-2-(o-tolyl)oxazoline **114** in Et_2O followed by reaction with aldehydes in the presence of tetramethylethylenediamine (TMEDA) produced the major (S,S)-products **115** with high

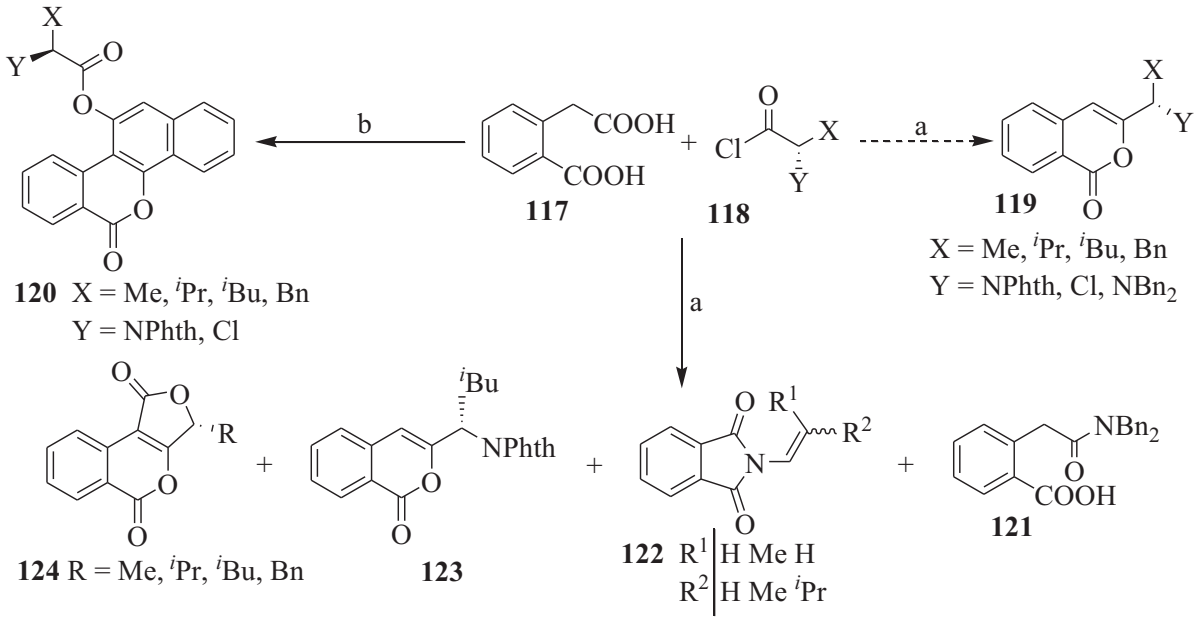
stereoselectivity (84% de).[116] The adduct was then lactonized to the corresponding (3S)-3,4-dihydroisocoumarins **116** under acidic conditions in good optical purity (97% ee) (Scheme 21).



Reagent and conditions: **a**) RCHO; **b**) H_3O^+

Scheme 21. Synthesis of dihydroisocoumarins **116** having chiral centers.

Saddiqa et al. reported the asymmetric synthesis of isocoumarins by the condensation of homophthalic acid **117** with different chiral carboxylic acids chlorides **118** at high (200 °C) and low (–5 °C) temperatures. The coupling at high temperature does not furnish **119**; instead, 3H-furo[3,4c] isochromene-1,11-diones **124** along with other side-products (**121**, **122**) are produced. Only the coupling reaction of phthaloyl *N*-protected leucine with homophthalic acid afforded **123** with poor yield (30%). The coupling at low temperature, in basic conditions, afforded chrysene-based (S)-isocoumarins **120** as a single product in high yields (Scheme 22).[117,118]



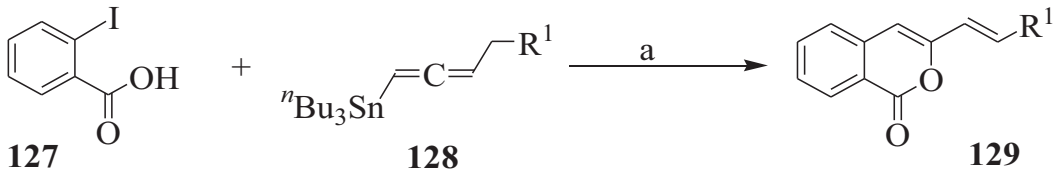
Reagent and conditions: **a**) 200 °C, neat **b**) i. $SOCl_2$, ii. Et_3N, -5 °C.

Scheme 22. The asymmetric synthesis of isocoumarins by the condensation of homophthalic acid **117** with different (S)-carboxylic acids chlorides **118**.

3.6. Lewis acids-mediated cyclization

Bihel and coworkers[119] synthesized 5-aza-3,4-dihydroisocoumarin **126** in excellent yields (up to 98%) via regiocontrolled 6-endo-dig cyclization of 2-(2-arylethynyl)heteroaryl ester **125**. The reaction was carried out

under microwave environment at 100 °C by employing a Bronsted acid in the presence of a catalytic amount of Lewis acids such as $Cu(OTf)_2$, $AuCl_3$, or $(CF_3CO_2)Ag$ (Scheme 23).

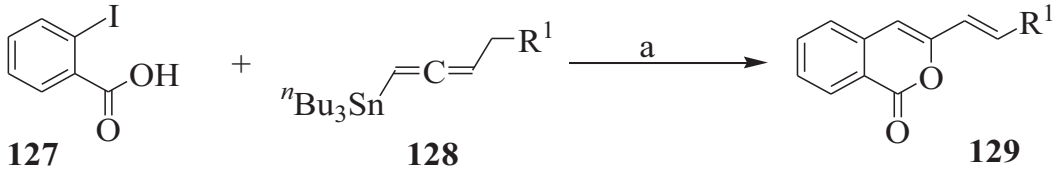


Reagent and conditions: **a**) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), ^{n}Bu$_4$NBr (1 eq), DMF, 80 °C.

Scheme 23. Microwave-assisted synthesis of 5-aza-3,4-dihydroisocoumarin **126**.

3.7. Synthesis of isocoumarins via tandem Stille coupling

A general route to 3-substituted isocoumarins **129** from 2-iodobenzoic acids **127** was described by Cherry et al.[120] The treatment of 2-iodobenzoic acids **127** with various allenyl-tri-n-butyltin reagents **128** in the presence of $Pd(OAc)_2$ [source of Pd(II)], PPh_3 (ligand), and Bu_4NBr (phase transfer reagent) in DMF provided good yields of the corresponding 3-substituted isocoumarins **129** via a tandem Stille reaction and 6-endo-dig oxacyclization (Scheme 24).



Reagent and conditions: **a**) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), ^{n}Bu$_4$NBr (1 eq), DMF, 80 °C.

Scheme 24. A general route to 3-substituted isocoumarins **129** from 2-iodobenzoic acids **127** described by Cherry et al.[120]

3.8. Regioselective cyclization of 1,3-bis(silyloxy)-1,3-butadienes

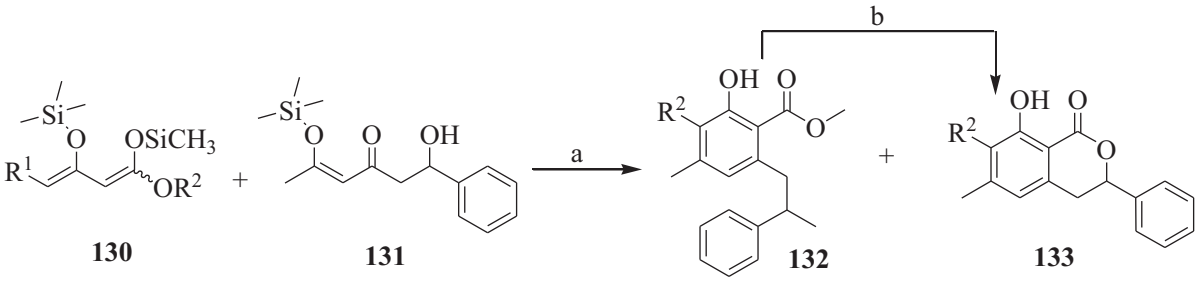
The [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes **130** with 1-hydroxy-5-silyloxy-hex-4-en-3-ones **131** resulted in the one-pot formation of 3-aryl-3,4-dihydroisocoumarins **133** (Scheme 25).[121] The reactions proceeded by regioselective cyclization to give 6-(2-aryl-2-chloroethyl)salicylates **132**, which underwent a silica gel-mediated lactonization to afford lactones **133**.

3.9. Aldol condensation

3.9.1. Stobbe's condensation

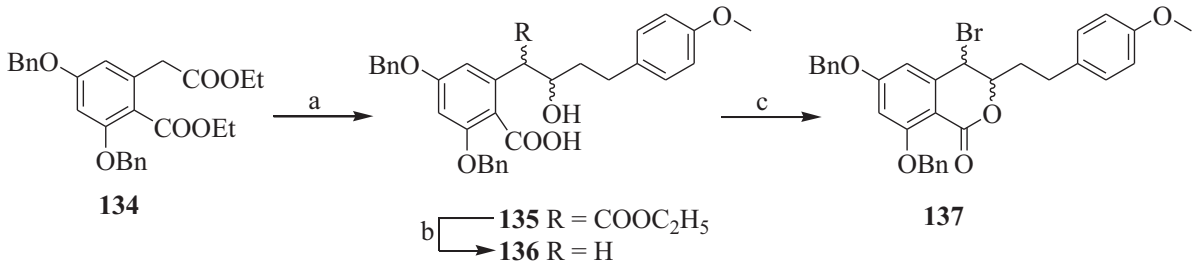
This type of condensation is mostly used in the synthesis of isocoumarins and 3,4-dihydroisocoumarins. Stobbe's condensation is used for the synthesis of a number of 3,4-dihydroisocoumarins.[122–126] Synthesis of (dl)-agrimonolide[127] provides a good example of application of Stobbe's condensation. Thus, homophthalate **134** upon condensation with 4-OMePhCHO in the presence of NaH afforded 2,4-dibenzyloxy-6-[1-ethoxycarbonyl-4-(4'-methoxyphenyl)buten-1-yl]benzoic acid **135** (R = COOEt). The hydrolysis and decarboxylation yielded

2,4-dibenzyloxy-6-[4-(4'-methoxyphenyl)buten-1-yl]benzoic acid **136** (R = H), which upon cyclization with Br_2 afforded 4-bromo-3,4-dihydroisocoumarin **137** (Scheme 26).



Reagent and conditions: **a)** i) $TiCl_4$, CH_2Cl_2 −78 °C, ii) $NaHCO_3$, H_2O; **b)** SiO_2 (wet), THF, 14 h.

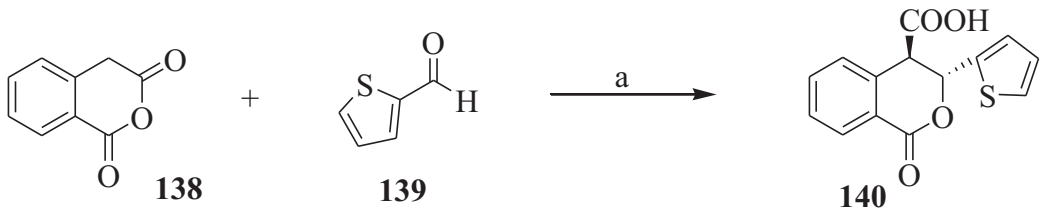
Scheme 25. A synthetic diagram for the lactone **133**.



Reagent and conditions: **a**) 3-(4′-Methoxyphenyl)propanal; **b**) NaOH; **c**) Br_2, $CHCl_3$

Scheme 26. Synthesis of 4-bromo-3,4-dihydroisocoumarin **137** via Stobbe's condensation.

Bogdanov et al. carried out dimethylaminopyridine (DMAP)-assisted Stobbe's condensation of homophthalic anhydride **138** and thiophene-2-carbaldehyde **139** to afford 3-substituted trans-3,4-dihydroisocoumarin-4-carboxylic acids **140** (Scheme 27).[128]

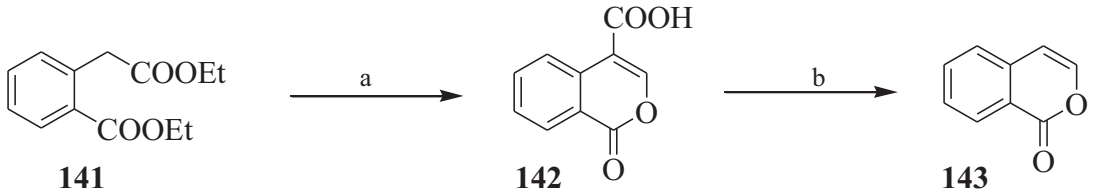


Reagent and conditions: **a**) DMAP, $CHCl_3$, rt.

Scheme 27. Stobbe's condensation reaction of homophthalic anhydride **138** and thiophene-2-carbaldehyde **139**.

3.9.2. Claisen condensation of homophthalates with formates

The condensation of diethyl homophthalate **141** with methyl formate in the presence of NaOEt affords isocoumarin-4-carboxylic acid **142** at up to 66% yield. The decarboxylation of **142** with phosphoric acid furnishes isocoumarin **143** (Scheme 28).[129]



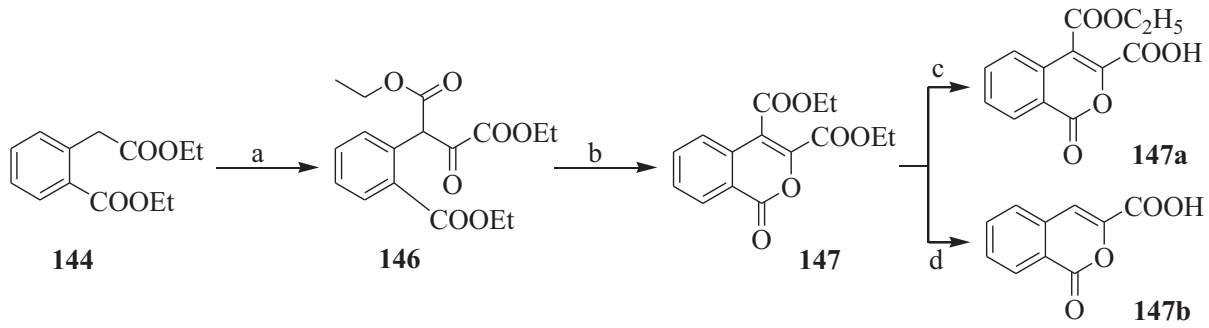
Reagent and coditions: **a**) $HCOOCH_3$, C_2H_5ONa; **b**) H_3PO_4, $-CO_2$

Scheme 28. A simple preparation method for the synthesis of isocoumarin **143**.

The 6,7-dimethoxyisocoumarin and 5,7-dimethoxyisocoumarin were also prepared by the above procedure. The ethyl 5,6,7-trimethoxyisocoumarin-4-carboxylate was prepared from the corresponding homophthalate and ethyl formate in the presence of KOEt in good yield.[130]

3.9.3. Claisen condensations of homophthalates with oxalates

The condensation between diethyl homophthalate **144** and diethyl oxalate **145** in the presence of Na in Et_2O, or better without a solvent, affords triester **146** in good yield (67%). This triester was heated, which yielded diethyl isocoumarin-3,4-dicarboxylate **147**. Under different hydrolysis conditions, different products are formed. For example, heating **147** at 68–72 °C for 3 h furnishes ethyl isocoumarin-3-(carboxylic acid)-4-carboxylate **147a**, and prolonged heating yields isocoumarin-3-carboxylic acid **147b**. Boiling HCl or heating in a sealed tube at 180–190 °C converts **147** to isocoumarin-3-carboxylic acid in 84% yield.[131] These results indicate that the ester at C^3 in **147** is hydrolyzed first but the acid at position 4 is more easily decarboxylated (Scheme 29).



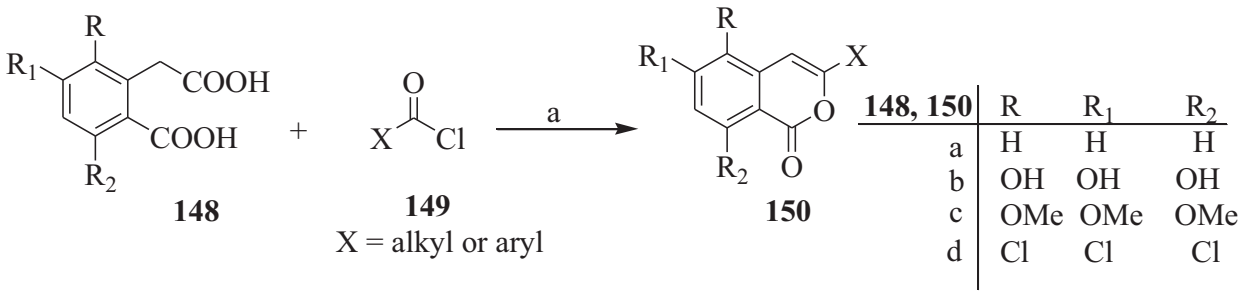
Reagent and conditions: **a**) diethyl oxalate **145**, Na; **b**) Δ; **c**) 68−72 °C; **d**) prolong heating.

Scheme 29. Synthesis of isocoumarins by Claisen condensations of homophthalates and oxalates.

3.9.4. Condensation of acid chlorides with homophthalic acids and anhydrides

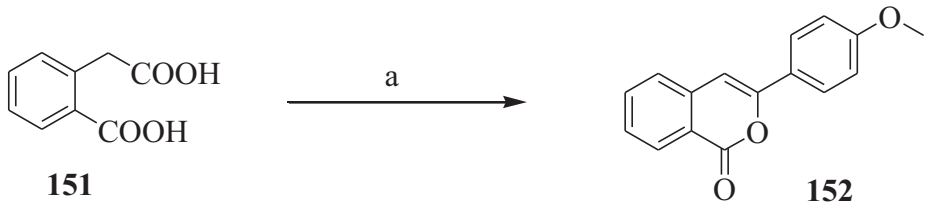
Nakajima et. al. synthesized various 3-arylisocoumarins **150** and later on 3-alkyl isocoumarins in high yields (80%) by directly heating the homophthalic acids **148** with aryl or acyl chlorides **149**. These isocoumarins were converted into corresponding 3,4-dihydroisocoumarins by reduction with $NaBH_4$ (Scheme 30).[131]

The 3-(4'-methoxyphenyl)isocoumarin **152** was prepared by condensation of homophthalic acid **151** with anisole (Scheme 31).[132]



Reagent and conditions: **a)** 200 °C, 6 h.

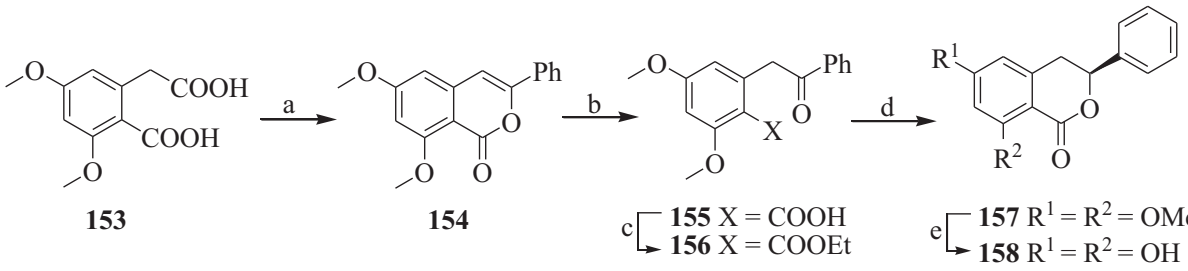
Scheme 30. Condensation of acid chlorides **149** with homophthalic acids.



Reagent and conditions: **a**) anisole, PPA (polyphthalamide), rt.

Scheme 31. The synthetic route for 3-(4'-methoxyphenyl)isocoumarin **152**.

The 6,8-dimethoxy-3-phenylisocoumarin **154** was prepared by condensation of 3,5-dimethoxyhomophthalic acid **153** with benzoyl chloride at 200 °C. The isocoumarin was hydrolyzed to **155** and esterified to furnish ketoester **156** that was further enantioselectively reduced to afford (3*S*)-6,8-dimethoxy-3-phenyl-3,4-dihydroisocoumarin **157**. The demethylation of **157** afforded (3*S*)-6,8-dihydroxy-3-phenyl-3,4-dihydroisocoumarin **158** (Scheme 32).[133]



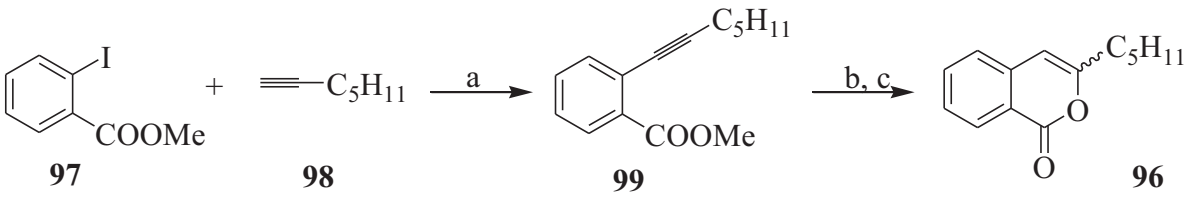
Reagent and conditions: **a)** PhCOCl, 200 °C, 4 h; **b)** 5% KOH, EtOH, 4 h, reflux; **c)** CH_3I, K_2CO_3, dry acetone, 5 h; **d)** Baker's yeast; **e)** BBr_3, CH_2Cl_2, −78 °C, overnight.

Scheme 32. Preparation of 3-phenyl-3,4-dihydroisocoumarins **157** and **158**.

3.10. Cyclization of methyl 2-heptynylbenzoate

Villemin et al. reported the synthesis of isocoumarin **96** by the coupling of o-iodobenzoic ester **97** and a terminal alkyne **98**, catalyzed by Pd salt and Cu-catalyst. The reaction proceeds under Sonogashira conditions

and yields 2-alkynyl benzoic ester **99**, which upon successive saponification and acidification gave isocoumarin **96** as a major product (Scheme 33).[134]

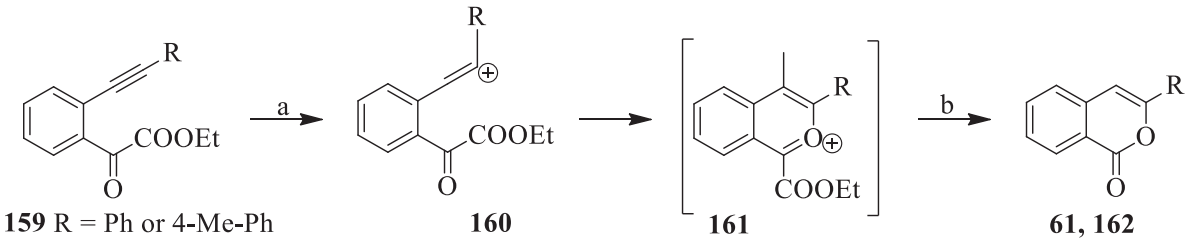


Reagent and conditions: **a**) $L_2PdCl_2.Cu_2I_2$, Et_3N; **b**) KOH; **c**) H_2SO_4.

Scheme 33. Cyclization reaction of **99** and a terminal alkyne **98**.

3.11. Synthesis via isobenzopyrylium salts

Pyrylium salts play very important roles in organic synthesis as they are useful intermediates for the synthesis of many heterocyclic nuclei and have also been used for the synthesis of different derivatives of isocoumarins. The alkyne **159** was prepared by modified Sonogashira procedure from o-iodobenzoic ester. These esters undergo quantitative cyclization in the presence of strong acids such as HBF_4 and TfOH to give salt **161** via **160**, which are unstable. The slow hydrolysis of the tetrafluoroborate salts **161** at room temperature yielded the isocoumarin **162** (Scheme 34).[135]



Reagent and conditions: **a**) HX, [X=BF_4 or TfO], CH_2Cl_2; **b**) hydrolysis.

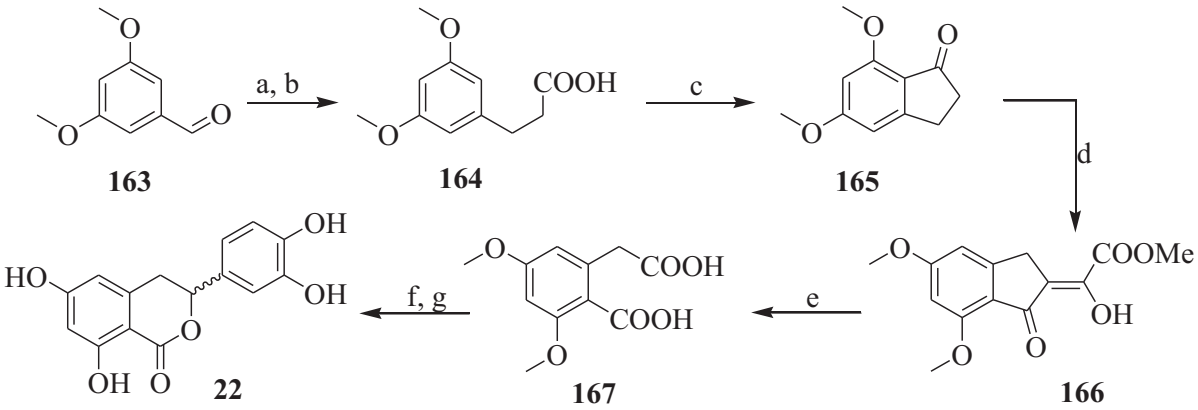
Scheme 34. Synthesis of isocoumarin **61**, **162** via isobenzopyrylium salt **161**.

3.12. Synthesis of naturally occurring isocoumarin derivatives

The synthesis of a number of naturally occurring isocoumarins is available in literature; for example, Qadeer et al. reported the synthesis of thunberginol B **22** by the coupling of 3,5-dimethoxy homophthalic acid **167** with 3,4-dimethoxybenzoic acid followed by the demethylation of the intermediate. The 3,5-dimethoxyhomophthalic acid **167** was synthesized in five steps, starting from 3,5-dimethoxybenzaldehyde **163**, and the reaction proceeded through **164**–**166** (Scheme 35).[136]

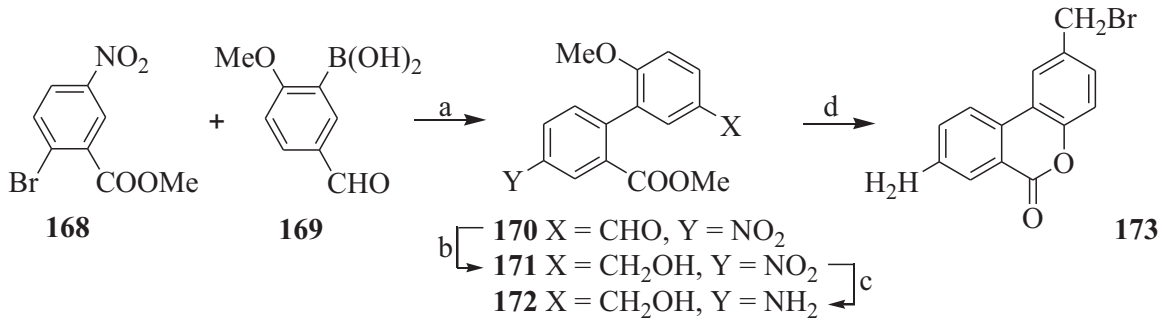
3.13. Synthesis of pharmacologically active isocoumarin derivatives

A number of compounds having an isocoumarin nucleus are found as inhibitors of various enzymes such as serine proteases, HIV aspartyl protease, and a panel of protein kinases, e.g., 2,8-disubstituted-benzo[c]chromen-6-ones. The Suzuki coupling of bromoarene **168** with boronic acid derivative **169** afforded the biaryl compound **170**, which upon successive reduction of the CHO and NO_2 group yielded the ester **172** via **171**. The cyclization of **172** provided the required isocoumarin **173** (Scheme 36).[137]



Reagent and conditions: **a**) $CH_2(COOH)_2$; **b**) Na/Hg; **c**) PPA; **d**) $(CO_2Et)_2$, NaOMe; **e**) H_2O_2, KOH; **f**) 3,4-dimethoxybenzoyl chloride, 200 ºC, reflux; **g**) HBr.

Scheme 35. Total synthesis of thunberginol B **22**.



Reagent and conditions: **a**) i. $PdCl_2$ dppf; ii. dppf, KOAc, dioxane, reflux; **b**) B_2H_6/DMS, THF, rt, 1 h; **c**) H_2 /Pd (C), THF, rt, 1 h; **d**) BBr_3, CH_2Cl_2, −78 °C, 2 h , CH_3OH.

Scheme 36. Synthesis of pharmacologically active isocoumarin **173**.

4. Conclusion

The isocoumarin and 3,4-dihydroisocoumarins ring system is found in nature with a wide spectrum of biological activities, ranging from antibacterial to anticancer. Based on this review, it can be concluded that due to distinctive pharmacological significance of these motifs, much research has been done and still going on towards the development and synthesis of their derivatives.

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