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.](image-url)

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 antimicrobial2) 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, Turner and Aldridge, Napolitano, Bin, and Saeed 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. The IUPAC names of isocoumarins and their 3,4-dihydroanalogues 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. Names such as alternariol (Alternaria sp.), peniolactol (Peniophora sanguinea), cladosporin (Cladosporium sp.), and homalicine (Homalium zeylanicum) 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, alternensol, oospolactone, agrimonolide, ustic acid, β-callaletic 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. 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. Baciphelacins 8 have good potential for the treatment of bacterial and viral infections. Among dihydroisocoumarins, PM-94128 9 and Y-05460M-A 10 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. Amicoumacin Sg17-1-4 11 isolated from a marine fungus, Alternaria tenuis Sg17-1, shows cytotoxic activity against HeLa cell lines (Figure 2).

![Figure 2. 3,4-Dihydroisocoumarins with antibacterial and antitumor activities.](image-url)
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). 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. These compounds possess a broad range of pharmacological properties including antibacterial, antiinflammatory, antiulcer, gastroprotective, and anti-Helicobacter pylori activities. However, they are famous for their remarkable gastroprotective activity. The family members of the A1-77s include compounds AI-77-A, -B, -C, -D, -F, and -G, which vary in their acyl hydroxy amino acid chains (Figure 3).

AI-77-B is the most abundant compound of the amicoumacin family. It is also known as amicoumacin B, which is a major product of the fermentation process and has been found to exhibit potent gastroprotective β-amino acid. Amicoumacin B shows antiinflammatory (rats), antiulcer (human stomachs), and herbicidal (Lemna) activities and is also used as an acaricide. 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.

Bergenin isolated from Flueggea microcarpa and Flueggea virosa, and an isocoumarin coriandrin isolated from Coriandrum sativum, have been found to show anti-HIV activity (Figure 4). In addition to anti-HIV, bergenin also possesses antiulcer and antihepatotoxic activity. It was observed that extracted from the aboveground parts of Flueggea virosa, was proved to have good potential to treat cardiac arrhythmias. The one isolated from Flueggea microcarpa showed antifungal activity against several plant-pathogenic fungi.
The 9,10-dihydroxy-5,7-dimethoxy-1H-naphtho-(2,3c)pyran-1-one (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).\(^{40}\)

![Diagram of structures](image)

**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-hydroxyisocoumarins \(^{28}\), 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).\(^{45}\)
Figure 6. Structures of antiallergic and inhibitor isocoumarins 25a–25c and 26–27.

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

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). Some isocoumarin derivatives, 8-hydroxy-6-methoxy-3-pentyl-1H-isochromen-1-one 38a–38b and halorosellins 39, isolated from the bark and stem of *Tessmannia densiflora* and *Halorosellinia oceanica*, respectively, also showed antimalarial activity (Figure 9).

![Figure 9. Structures of antimalarial molecules.](image)

*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).

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).

![Figure 10. Structures of isocoumarins 40 and dihydrocoumarins 41.](image)

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*, and isocoumarins 43a–43b have been found to exhibit mutagenic effects (Figure 11).

![Glucose derivatives of isocoumarins.](image)

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). Monocerin 45 and its different analogues have been isolated from numerous fungal sources, such as *Drechslera monoceras* (Figure 12). They possess excellent antifungal properties.

![Structure of antifungal isocoumarines 44–45 and erythocentaurin 46.](image)

Erythocentaurin 46 is isolated from *Enicostema hyssopifolium*, which is widely distributed in southern Pakistan. This plant is considered medicinally important and is 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.

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

The isocoumarins and 3,4-dihydropisocoumarins are naturally occurring lactones that display a wide range of biological and pharmacological activities and serve as key intermediates in the synthesis of biologically active molecules. These are identified as highly attractive molecules in organic chemistry. A wide spectrum of synthetic methods have been used for the synthesis of isocoumarins and 3,4-dihydropisocoumarins. A number of new methods are being developed and reported each year. Some of these methods provide the isocoumarins directly, whereas others lead to the 3,4-dihydropisocoumarins. 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. 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).

\[
\begin{align*}
51 & \xrightarrow{\text{a}} 52 \\
R^1 = R^2 = H, Me, Et, Ph
\end{align*}
\]

\[
\begin{align*}
52 & \xrightarrow{\text{b, c}} 53 \\
R^1 & \quad R^2
\end{align*}
\]

\[
\begin{align*}
53 & \xrightarrow{\text{d}} 54 \\
R^1 & \quad R^2
\end{align*}
\]

\textbf{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^+.

\textbf{Scheme 1.} Synthetic scheme of isocoumarin 54.

3.2. Synthesis of isocoumarins via electrophilic cyclization

Yao and Larock 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$_2$Cl$_2$, 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$_3$COOH.

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).$^{86}$
Reagent and conditions: a) TfOH, THF, reflux, 7 h.


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$_2$CO$_3$ under microwave atmosphere yielded isocoumarin 69 as a major product (Scheme 6).

Reagent and conditions: a) CuCCPh, C$_5$H$_5$N, reflux; b) HCCPh, Cu(I)-IPPh$_3$, K$_2$CO$_3$, microwave irradiation.

Scheme 6. Microwave-assisted synthesis of isocoumarin 69.

The oxazoline 70, upon deprotonation with $^t$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).
**Reagent and conditions:** a) Et₂O, −78 °C, 'BuLi, (S)-2-(1-pyrrolidinylmethyl)pyrrolidine Li; b) PhCHO; c) MeOTf, Et₂O, 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) SOCl₂; 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(PPh₃)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 H₂O. Under these conditions, several lactone rings 85a–85d are formed in 60%–83% yield (Scheme 12).

Reagent and conditions: a) AuCl (10 mol%), 2 eq. H₂O, MeCN, 50 °C, 24–48 h.

Scheme 12. Synthesis of isocoumarins 85 by the cycloisomerization of o-alkynylbenzoic methyl esters.
Miura and coworkers described the Rh-catalyzed direct oxidative coupling of benzoic acids with internal alkynes that leads to the formation of 6-membered lactones as the major products and naphthalene derivatives as by-products. The reaction of with dialkylacetylenes proceeded efficiently to produce 3,4-dialkylisocoumarins in good yields. Using unsymmetrical alkylphenylacetylenes, 4-alkyl-3-phenylisocoumarins were predominantly formed in 84%–89% yields along with minor amounts of their regioisomers (Scheme 13).

\[ \text{Reagent and conditions: a) } [\text{Cp}^*\text{RhCl}_2]^2 \text{ and Cu(OAc)}_2\cdot\text{H}_2\text{O}. \]

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

The total synthesis of naturally occurring dihydroisocoumarins such as hydrangenol, phyllodulcin, macrophyllol, and thumbergincol G has been accomplished using titanocene(III) chloride \((\text{Cp}_2\text{TiCl})\) as a radical initiator. The \(\text{Cp}_2\text{TiCl}\) was prepared in situ from commercially available \(\text{Cp}_2\text{TiCl}_2\) and Zn-dust. For example, ester was brominated with NBS in the presence of the radical initiator AIBN yielding in 92% yield. The bromo ester afforded lactone in 53% yield as a crystalline solid upon treatment with \(\text{Cp}_2\text{TiCl}\) in the presence of 4-methoxybenzaldehyde (Scheme 14).

\[ \text{Reagent and conditions: a) NBS/AIBN, CCl}_4; \text{ b) } \text{Cp}_2\text{TiCl}_2/\text{THF, 4-OMePhCHO}. \]


Ogawa et al. reported a convenient method for the synthesis of isocoumarin derivatives via Ag-mediated intramolecular cyclization of 2-(1-alkynyl)benzoic acids. The reaction first involves the formation of nonaflates 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 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).
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 HgSO₄ in H₂SO₄. The alkyne 99 was heated with HgSO₄ and dilute H₂SO₄ 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) PdCl₂(PPh₃)₃; b) HgSO₄, H₂SO₄.


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


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

Iwao and coworkers¹⁰² devised a direct method for the synthesis of dihydroisocoumarin 105—106 by the reaction of oxazoline 103 and silica gel in CH₂Cl₂ 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<sub>2</sub>/NaHSO<sub>3</sub> and 30% H<sub>2</sub>O<sub>2</sub> under carefully controlled conditions to afford lactone 108. The dihydroisocoumarin 108 was then transformed to AI-77-B 109 (Scheme 19).<sup>112</sup>

Reagent and conditions: a & b) silica gel, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 h.


Reagent and conditions: a) i) BnBr, K<sub>2</sub>CO<sub>3</sub>; ii) HClO<sub>4</sub>(cat.), CH<sub>3</sub>CN; iii) NaClO<sub>2</sub>, NaHSO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, KHPO<sub>4</sub>, aq. MeCN.


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.<sup>113</sup> Good yields have occasionally been reported in a few cases such as in the syntheses of the antiallergic agent 113 isolated from <i>Ginkgo biloba</i> (Scheme 20)<sup>114</sup> and in the synthesis of a variety of mellein derivatives.<sup>115</sup>

Reagent and conditions: a) (R)-1,2-epoxytetradecane; b) OH, neutralization CuCN(LiCl<sub>2</sub>); c) BBr<sub>3</sub>.

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<sub>2</sub>O followed by reaction with aldehydes in the presence of tetramethylethylenediamine (TMEDA) produced the major (S,S)-products 115 with high
stereoselectivity (84% de). The adduct was then lactonized to the corresponding (3S)-3,4-dihydroisocoumarins under acidic conditions in good optical purity (97% ee) (Scheme 21).

\[
\begin{array}{c}
\text{Li} \quad 114 \quad \text{a} \quad \text{b} \quad \text{R}\quad \text{O}
\end{array}
\]

**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[3,4-c] 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).

\[
\begin{array}{c}
\text{Y} \quad \text{X} \quad \text{O} \quad \text{O} \quad \text{X} \quad \text{Y} \quad \text{O} \\
\text{117} \quad \text{118} \quad \text{119} \quad \text{120} \quad \text{121} \quad \text{122} \quad \text{123} \quad \text{124} \quad \text{125} \\
\text{R} = \text{Me, iPr, iBu, Bn} \\
\text{Y} = \text{NPhth, Cl, NBn_2} \\
\text{X} = \text{Me, iPr, iBu, Bn} \\
\end{array}
\]

**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 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$_3$CO)$_2$Ag (Scheme 23).

\[
\text{Reagent and conditions: } a) \text{Pd(OAc)$_2$ (5 mol%), PPh$_3$ (10 mol%), } ^{^6}\text{Bu}_4\text{NBr (1 eq), DMF, 80 °C.}
\]

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. 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$_4$NBr (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).

\[
\text{Reagent and conditions: } a) \text{Pd(OAc)$_2$ (5 mol%), PPh$_3$ (10 mol%), } ^{^6}\text{Bu}_4\text{NBr (1 eq), DMF, 80 °C.}
\]

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

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). 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. 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-dibenzylxyloxy-6-[1-ethoxycarbonyl-4-(4'-methoxyphenyl)buten-1-yl]benzoic acid 135 (R = COOEt). The hydrolysis and decarboxylation yielded
2,4-dibenzylxoy-6-[4-(4'-methoxyphenyl)buten-1-yl]benzoic acid \( \text{136} \) \((\text{R} = \text{H})\), which upon cyclization with \( \text{Br}_2 \) afforded 4-bromo-3,4-dihydroisocoumarin \( \text{137} \) (Scheme 26).

![Chemical Diagram]

Reagent and conditions: a) i) \( \text{TiCl}_4 \), \( \text{CH}_2\text{Cl}_2 \), -78 °C, ii) \( \text{NaHCO}_3 \), \( \text{H}_2\text{O} \); b) \( \text{SiO}_2 \) (wet), \( \text{THF} \), 14 h.

Scheme 25. A synthetic diagram for the lactone \( \text{133} \).

![Chemical Diagram]

Reagent and conditions: a) 3- (4'-Methoxyphenyl)propanal; b) \( \text{NaOH} \); c) \( \text{Br}_2 \), \( \text{CHCl}_3 \)

Scheme 26. Synthesis of 4-bromo-3,4-dihydroisocoumarin \( \text{137} \) via Stobbe’s condensation.

Bogdanov et al. carried out dimethylaminopyridine (DMAP)-assisted Stobbe’s condensation of homophthalic anhydride \( \text{138} \) and thiophene-2-carbaldehyde \( \text{139} \) to afford 3-substituted trans-3,4-dihydroisocoumarin-4-carboxylic acids \( \text{140} \) (Scheme 27).\(^{128}\)

![Chemical Diagram]

Reagent and conditions: a) DMAP, \( \text{CHCl}_3 \), rt.

Scheme 27. Stobbe’s condensation reaction of homophthalic anhydride \( \text{138} \) and thiophene-2-carbaldehyde \( \text{139} \).

3.9.2. Claisen condensation of homophthalates with formates

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

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.\(^\text{130}\)

**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\(_2\)O, 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.\(^\text{131}\) 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).

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).\(^\text{131}\)

The 3-(4'-methoxyphenyl)isocoumarin 152 was prepared by condensation of homophthalic acid 151 with anisole (Scheme 31).\(^\text{132}\)
**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 (3S)-6,8-dimethoxy-3-phenyl-3,4-dihydroisocoumarin 157. The demethylation of 157 afforded (3S)-6,8-dihydroxy-3-phenyl-3,4-dihydroisocoumarin 158 (Scheme 32).

**Reagent and conditions:** a) PhCOCl, 200 °C, 4 h; b) 5% KOH, EtOH, 4 h, reflux; c) CH3I, K2CO3, dry acetone, 5 h; d) Baker’s yeast; e) BBr3, CH2Cl2, −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).\(^\text{134}\)

\[
\begin{align*}
\text{I} & \quad \text{C}_5\text{H}_11 \\
\text{COOMe} & \quad \text{97} & \quad \text{98} & \quad \text{a} & \quad \text{99} & \quad \text{b, c} & \quad \text{96}
\end{align*}
\]

\textbf{Reagent and conditions:} a) L\(_2\)PdCl\(_2\).Cu\(_2\)I\(_2\), Et\(_3\)N; b) KOH; c) H\(_2\)SO\(_4\).

\textbf{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).\(^\text{135}\)

\[
\begin{align*}
\text{COOEt} & \quad \text{a} & \quad \text{160} & \quad \text{161} & \quad \text{b} & \quad \text{161} & \quad \text{COOEt} \\
\text{COOEt} & \quad \text{159} & \quad \text{R} & = \text{Ph or 4-Me-Ph} & \quad \text{161} & \quad \text{R} & \quad \text{Ph or 4-Me-Ph}
\end{align*}
\]

\textbf{Reagent and conditions:} a) HX, [ X=BF\(_4\) or TfO], CH\(_2\)Cl\(_2\); b) hydrolysis.

\textbf{Scheme 34.} Synthesis of isocoumarin 161, 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).\(^\text{136}\)

\[
\begin{align*}
\text{COOEt} & \quad \text{a} & \quad \text{160} & \quad \text{161} & \quad \text{b} & \quad \text{172} \\
\text{COOEt} & \quad \text{159} & \quad \text{R} & = \text{Ph or 4-Me-Ph} & \quad \text{161} & \quad \text{R} & \quad \text{Ph or 4-Me-Ph} & \quad \text{172}
\end{align*}
\]

\textbf{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).\(^\text{137}\)
Reagent and conditions: a) CH$_2$(COOH)$_2$; b) Na/Hg; c) PPA; d) (CO$_2$Et)$_2$, NaOMe; e) H$_2$O$_2$, KOH; f) 3,4-dimethoxybenzoyl chloride, 200 °C, 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$_2$H$_6$/DMS, THF, rt, 1 h; c) H$_2$/Pd (C), THF, rt, 1 h; d) BBr$_3$, CH$_2$Cl$_2$, −78 °C, 2 h, CH$_3$OH.

Scheme 36. Synthesis of pharmacologically active isocoumarin 173.

4. Conclusion
The isocoumarin and 3,4-dihydropisocoumarins 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.

References