

Coumarin Derivatives And Their Chemical Synthesis

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ABSTRACT: Coumarin derivatives are all considered phenylpropanoids.^[1]

Some naturally occurring coumarin derivatives include umbelliferone (7-hydroxycoumarin), aesculetin (6,7-dihydroxycoumarin), herniarin (7-methoxycoumarin), psoralen and imperatorin.

4-Phenylcoumarin is the backbone of the neoflavones, a type of neoflavonoids.

Coumarin pyrazole hybrids have been synthesized from hydrazones, carbazones and thiocarbazones via Vilsmeier Haack formylation reaction.

Compounds derived from coumarin are also called coumarins or coumarinoids; this family includes:

- brodifacoum^{[2][3]}
- bromadiolone^[4]
- difenacoum^[5]
- auraptene
- ensaculin
- phenprocoumon (Marcoumar)
- PSB-SB-487
- PSB-SB-1202
- scopoletin can be isolated from the bark of Shorea pinanga^[6]
- warfarin (Coumadin)

Coumarin is transformed into the natural anticoagulant dicoumarol by a number of species of fungi.^[7] This occurs as the result of the production of 4-hydroxycoumarin, then further (in the presence of naturally occurring formaldehyde) into the actual anticoagulant dicoumarol, a fermentation product and mycotoxin. Dicoumarol was responsible for the bleeding disease known historically as "sweet clover disease" in cattle eating moldy sweet clover silage.^{[7][8]} In basic research, preliminary evidence exists for coumarin having various biological activities, including anti-inflammatory, anti-tumor, antibacterial, and antifungal properties, among others.^[7]

KEYWORDS: coumarin, chemical, derivatives, synthesis, family, disease, antibacterial, antifungal

I. INTRODUCTION

Brodifacoum is a derivative of the 4-hydroxy-coumarin group. Compound numbers are found next to their respective compounds in the image below. Compound 1 is the starting ester needed to synthesize brodifacoum.¹ To obtain this starting Compound 1, a simple Wittig condensation of ethyl chloroacetate with 4'-bromobiphenylcarboxaldehyde is accomplished. Compound 1 is transformed into Compound 2 by consecutive hydrolysis, halogenation to form an acid chloride, and then reacted with the required lithium anion. This is done using KOH and EtOH for hydrolysis, and then adding SOCl₂ for chlorination to form the acid chloride which reacts with the addition of lithium anion. Compound 2 is

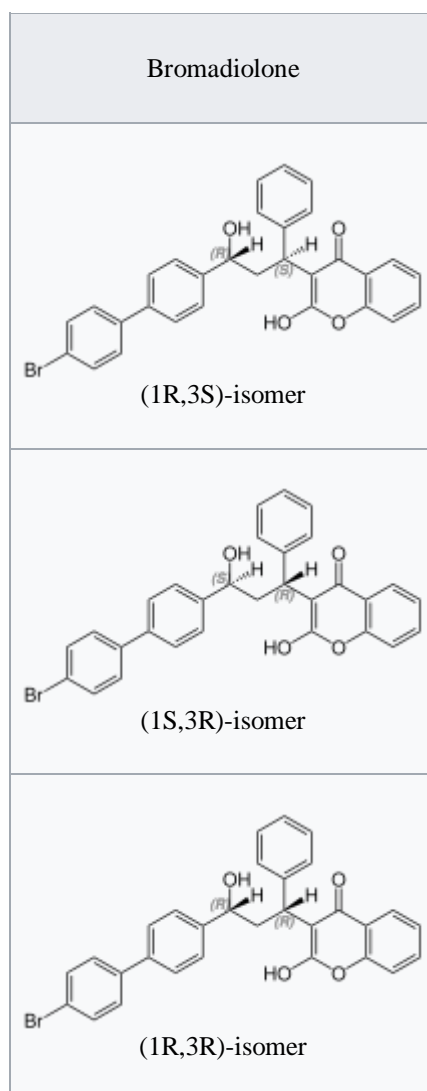
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then transformed ² using organocopper chemistry to yield Compound 3 with good stereoselectivity of about 98%. Typically, a Friedel-Crafts type cyclization would then be used to obtain the two-ring system portion of Compound 4, but this results in low yield. Instead, trifluoromethanesulfonic acid in dry benzene catalyzes the cyclization with good yield.³ The ketone is then reduced with sodium borohydride yielding a benzyl alcohol. Condensation with 4-hydroxycoumarin under HCl yields Compound 5, brodifacoum.⁴

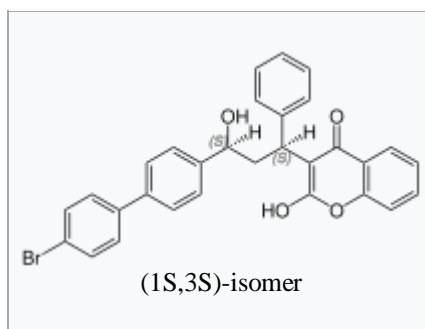


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The compound is used as a mixture of four stereoisomers. Its two stereoisomeric centers are at the phenyl- and the hydroxyl-substituted carbons in the carbon chain of the substituent at the 3 position of the coumarin.⁶

Enzaculin (KA-672) is a drug from the coumarin family, which has been researched as a potential treatment for dementia. It acts on a number of receptor systems, being both a weak NMDA antagonist and a 5HT_{1A} agonist.^{[1][2]} Animal studies have shown promising nootropic effects,^{[3][4]} although efficacy in humans has yet to be proven. It was well tolerated in human trials, with the main side effect being orthostatic hypotension (low blood pressure).^[5]

Phenprocoumon is used for the prophylaxis and treatment of thromboembolic disorders after heart bypass surgery and myocardial infarction (heart attack), long-term treatment of myocardial infarction with increased risk of thromboembolism, thrombophilia (abnormal blood clotting), antithrombin III deficiency, atrial fibrillation⁷ (a kind of abnormal heart rhythm) with artery embolisms, after venous thrombosis, pulmonary embolism and artificial heart valve surgery, as well as chronic ventricular aneurysm (bulging of the heart wall) and congestive cardiomyopathy (enlarged heart).^[1] When phenprocoumon therapy is started, the clotting tendency of the blood is measured daily by determining the prothrombin time, more specifically the international normalized ratio (INR). After the desired INR has been reached, which typically takes five to six days, intervals between measurements are increased to twice or three times a week for a week or two, then to two to four weeks if the patient is stable. INR monitoring continues throughout the therapy, often for life.^{[1][4]} This is necessary because people need different doses depending on the genetic makeup of their enzymes, activity of coagulation factors, vitamin K concentrations in the body, other drugs, and diet.^{[2][6]}

If a fast onset of action is needed, as after an acute thromboembolism, phenprocoumon therapy has to be accompanied with a subcutaneous or intravenous low-molecular-weight heparin (LMWH) for the first 36 to 72 hours.⁸ Similarly, if the blood thinning effect has to be stopped before a surgery, phenprocoumon is paused up to two weeks beforehand, and the therapy gap is "bridged" with LMWH until after the surgery. Alternatively, phenprocoumon can be antagonised with vitamin K, for example before an unplanned surgery, or when severe bleeding occurs after overdosing.^{[1][4]}

II. DISCUSSION

PSB-SB-487 is a coumarin derivative which is an antagonist at the former orphan receptor GPR55. Unlike older GPR55 antagonists such as O-1918, PSB-SB-487 has good selectivity over the related receptor GPR18, with an IC₅₀ of 113nM at GPR55 vs 12500nM at GPR18.^[1] However it has poorer selectivity over other related receptors, acting as a weak antagonist at CB₁ with a Ki of 1170nM, and a partial agonist at CB₂ with a Ki of 292nM.^[2] PSB-SB-1202 is a coumarin derivative which is an agonist at the cannabinoid receptors CB₁ and CB₂, with a CB₁ Ki of 32nM and a CB₂ Ki of 49nM.^[1] It is also a weak antagonist at the related receptor GPR55, with an IC₅₀ of 6350nM, but has no significant affinity for GPR18.^[2] Scopoletin is a coumarin found in the root of plants in the genus Scopolia such as Scopolia carniolica and Scopolia japonica, in chicory, in Artemisia scoparia, in the roots and leaves of stinging nettle (*Urtica dioica*), in the passion flower, in Brunfelsia, in Viburnum prunifolium, in Solanum nigrum,^[1] in Datura

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metel,^[2] in *Mallotus resinusus*,^[3] or and in *Kleinhovia hospita*. It can also be found in fenugreek,^[4] vinegar,^{[5][4]} some whiskies or in dandelion coffee. A similar coumarin is scoparone. Scopoletin is highly fluorescent when dissolved in DMSO or water and is regularly used as a fluorimetric assay for the detection of hydrogen peroxide in conjunction with horseradish peroxidase. When oxidized, its fluorescence is strongly suppressed. Warfarin is an anticoagulant used as a medication under several brand names including Coumadin,^[8] and as a poison for rats and other pests.^{[9][10]} While the drug is described as a "blood thinner", it does not reduce viscosity but inhibits coagulation, and is commonly used to prevent blood clots in the circulatory system such as deep vein thrombosis and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation, valvular heart disease, or artificial heart valves.^[8] Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery.^[8] It is usually taken by mouth, but may also be administered intravenously.^[8]

The common side effect, a natural consequence of reduced clotting, is bleeding.^[8] Less common side effects may include areas of tissue damage, and purple toes syndrome.^[8] Use is not recommended during pregnancy.^[8] The effects of warfarin are typically monitored by checking prothrombin time (INR) every one to four weeks.^[8] Many other medications and dietary factors can interact with warfarin, either increasing or decreasing its effectiveness.^{[8][11]} The effects of warfarin may be reversed with phytonadione (vitamin K₁), fresh frozen plasma, or prothrombin complex concentrate.^[11]

Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an enzyme that reactivates vitamin K₁.^[11] Without sufficient active vitamin K₁, clotting factors II, VII, IX, and X have decreased clotting ability.^[11] The anticoagulant protein C and protein S are also inhibited, but to a lesser degree.^[11] A few days are required for full effect to occur, and these effects can last for up to five days.^{[8][12]} Because the mechanism involves enzymes such as VKORC1, patients on warfarin with polymorphisms of the enzymes may require adjustments in therapy if the genetic variant that they have is more readily inhibited by warfarin, thus requiring lower doses.^{[13][14]}

Warfarin first came into large-scale commercial use in 1948 as a rat poison.^{[15][9]} It was formally approved as a medication to treat blood clots in humans by the U.S. Food and Drug Administration in 1954.^[8] In 1955, warfarin's reputation as a safe and acceptable treatment was bolstered when President Dwight D. Eisenhower was treated with warfarin following a massive and highly publicized heart attack.^[16] Eisenhower's treatment kickstarted a transformation in medicine whereby coronary artery disease, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. It is on the World Health Organization's List of Essential Medicines.^{[17][18]} Warfarin is available as a generic medication^[19] and under many trade names.^[11] In 2012, it was the 58th most commonly prescribed medication in the United States, with more than 11 million prescriptions.^{[20][21]} Warfarin is used to decrease the tendency for thrombosis, or as secondary prophylaxis (prevention of further episodes) in those individuals who have already formed a blood clot (thrombus). Warfarin treatment can help prevent formation of future blood clots and help reduce the risk of embolism (migration of a thrombus to a spot where it blocks blood supply to a vital organ).^[22]

Warfarin is best suited for anticoagulation (clot formation inhibition) in areas of slowly running blood (such as in veins and the pooled blood behind artificial and natural valves), and in blood pooled in dysfunctional cardiac atria. Thus, common clinical indications for warfarin use are atrial fibrillation, the presence of artificial heart valves, deep venous thrombosis, and pulmonary embolism (where the embolized clots first form in veins). Warfarin is also used in antiphospholipid syndrome. It has been used occasionally after heart attacks (myocardial infarctions), but is far less effective at preventing new thromboses in coronary arteries. Prevention of clotting in arteries is usually undertaken with antiplatelet drugs, which act by a different mechanism from warfarin (which normally has no effect on platelet function).^[23] It can be used to treat people following ischemic strokes due to atrial fibrillation, though direct oral anticoagulants (DOACs) may offer greater benefits.^[24]

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III. RESULTS

Coumarin is used in the pharmaceutical industry as a precursor reagent in the synthesis of a number of synthetic anticoagulant pharmaceuticals similar to dicoumarol.^[1] 4-hydroxycoumarins are a type of vitamin K antagonist.^[1] They block the regeneration and recycling of vitamin K.^{[1][22]} These chemicals are sometimes also incorrectly referred to as "coumadins" rather than 4-hydroxycoumarins. Some of the 4-hydroxycoumarin anticoagulant class of chemicals are designed to have high potency and long residence times in the body, and these are used specifically as rodenticides ("rat poison").^[1] Death occurs after a period of several days to two weeks, usually from internal hemorrhaging. Coumarin dyes are extensively used as gain media in blue-green tunable organic dye lasers.^{[25][26][27]} Among the various coumarin laser dyes are coumarins 480, 490, 504, 521, 504T, and 521T.^[27] Coumarin tetramethyl laser dyes offer wide tunability and high laser gain,^{[28][29]} and they are also used as active medium in coherent OLED emitters. Coumarin is often found in artificial vanilla substitutes, despite having been banned as a food additive in numerous countries since the mid-20th century. It is still used as a legal flavorant in soaps, rubber products, and the tobacco industry,^[1] particularly for sweet pipe tobacco and certain alcoholic drinks.^{30,31} Coumarin is moderately toxic to the liver and kidneys of rodents, with a median lethal dose (LD₅₀) of 293 mg/kg in the rat,^[32] a low toxicity compared to related compounds. Coumarin is hepatotoxic in rats, but less so in mice. Rodents metabolize it mostly to 3,4-coumarin epoxide, a toxic, unstable compound that on further differential metabolism may cause liver cancer in rats and lung tumors in mice.^{[33][34]} Humans metabolize it mainly to 7-hydroxycoumarin, a compound of lower toxicity, and no adverse affect has been directly measured in humans.^[35] The German Federal Institute for Risk Assessment has established a tolerable daily intake (TDI) of 0.1 mg coumarin per kg body weight, but also advises that higher intake for a short time is not dangerous.^[36] The Occupational Safety and Health Administration (OSHA) of the United States does not classify coumarin as a carcinogen for humans.^[37]

European health agencies have warned against consuming high amounts of cassia bark, one of the four main species of cinnamon, because of its coumarin content.^{[38][39]} According to the German Federal Institute for Risk Assessment (BFR), 1 kg of (cassia) cinnamon powder contains about 2.1 to 4.4 g of coumarin.^[40] Powdered cassia cinnamon weighs 0.56 g/cm³,^[41] so a kilogram of cassia cinnamon powder equals 362.29 teaspoons. One teaspoon of cassia cinnamon powder therefore contains 5.8 to 12.1 mg of coumarin, which may be above the tolerable daily intake value for smaller individuals.^[40] However, the BFR only cautions against high daily intake of foods containing coumarin. Its report^[40] specifically states that Ceylon cinnamon (*Cinnamomum verum*) contains "hardly any" coumarin.

The European Regulation (EC) No 1334/2008 describes the following maximum limits for coumarin: 50 mg/kg in traditional and/or seasonal bakery ware containing a reference to cinnamon in the labeling, 20 mg/kg in breakfast cereals including muesli, 15 mg/kg in fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labeling, and 5 mg/kg in desserts.⁴¹

An investigation from the Danish Veterinary and Food Administration in 2013 shows that bakery goods characterized as fine bakery ware exceeds the European limit (15 mg/kg) in almost 50% of the cases.^[42] The paper also mentions tea as an additional important contributor to the overall coumarin intake, especially for children with a sweet habit.⁴²

Coumarin was banned as a food additive in the United States in 1954, largely because of the hepatotoxicity results in rodents.^[43] Coumarin is currently listed by the Food and Drug Administration (FDA) of the United States among "Substances Generally Prohibited From Direct Addition or Use as Human Food," according to 21 CFR 189.130,^{[44][45]} but some natural additives containing coumarin, such as the flavorant sweet woodruff are allowed "in alcoholic beverages only" under 21 CFR 172.510.^[46] In Europe, popular examples of such beverages are Maiwein, white wine with woodruff, and Żubrówka, vodka flavoured with bison grass.⁴⁵

Coumarin is subject to restrictions on its use in perfumery,^[47] as some people may become sensitized to it, however the evidence that coumarin can cause an allergic reaction in humans is disputed.^[48]

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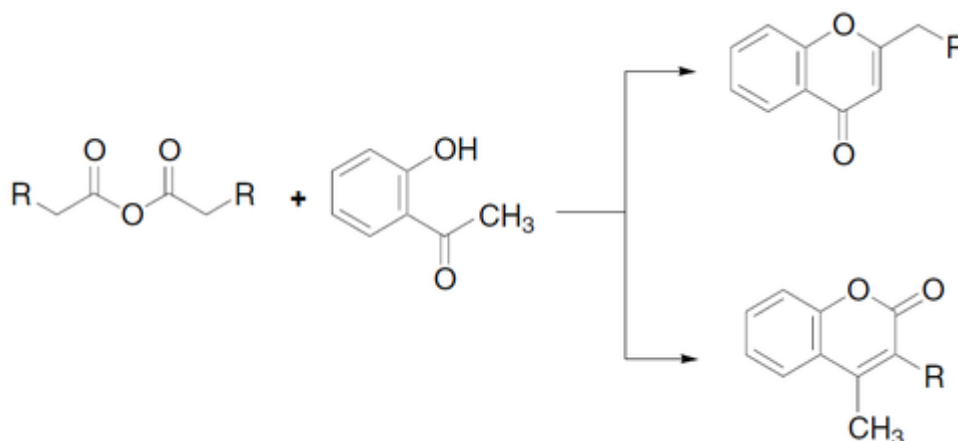
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Minor neurological dysfunction was found in children exposed to the anticoagulants acenocoumarol or phenprocoumon during pregnancy. A group of 306 children were tested at ages 7–15 years to determine subtle neurological effects from anticoagulant exposure^{46,47}. Results showed a dose–response relationship between anticoagulant exposure and minor neurological dysfunction. Overall, a 1.9 (90%) increase in minor neurological dysfunction was observed for children exposed to these anticoagulants, which are collectively referred to as "coumarins." In conclusion, researchers stated, "The results suggest that coumarins have an influence on the development of the brain which can lead to mild neurologic dysfunctions in children of school age."^{49]}

Coumarin's presence in cigarette tobacco caused Brown & Williamson executive^[50] Dr. Jeffrey Wigand to contact CBS's news show 60 Minutes in 1995, charging that a "form of rat poison" was in the tobacco. He held that from a chemist's point of view, coumarin is an "immediate precursor" to the rodenticide coumadin. Dr. Wigand later stated that coumarin itself is dangerous, pointing out that the FDA had banned its addition to human food in 1954.^[51] Under his later testimony, he would repeatedly classify coumarin as a "lung-specific carcinogen."^[52] In Germany, coumarin is banned as an additive in tobacco.⁴⁹

Alcoholic beverages sold in the European Union are limited to a maximum of 10 mg/L coumarin by law.^[53] Cinnamon flavor is generally cassia bark steam-distilled to concentrate the cinnamaldehyde, for example, to about 93%. Clear cinnamon-flavored alcoholic beverages generally test negative for coumarin, but if whole cassia bark is used to make mulled wine, then coumarin shows up at significant levels.

The Kostanecki acylation is a method used in organic synthesis to form chromones^[1] or coumarins^[2] by acylation of O-hydroxyaryl ketones with aliphatic acid anhydrides, followed by cyclization.^[3] If benzoic anhydride (or benzoyl chloride) is used, a particular type of chromone called a flavone is obtained.



IV. CONCLUSIONS

Coumarin can be prepared by a number of name reactions, with the Perkin reaction between salicylaldehyde and acetic anhydride being a popular example. The Pechmann condensation provides another route to coumarin and its derivatives, as does the Kostanecki acylation, which can also be used to produce chromones⁵³. The Pechmann condensation is a synthesis of coumarins, starting from a phenol and a carboxylic acid or ester containing a β -carbonyl group.^[1] The condensation is performed under acidic conditions. The mechanism involves an esterification/transesterification followed by attack of the activated carbonyl ortho to the oxygen to generate the new

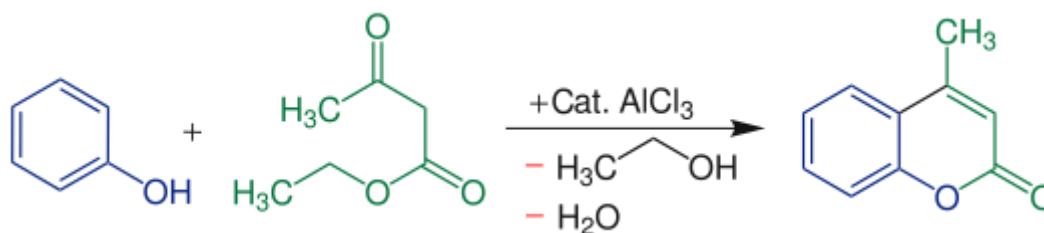
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ring. The final step is a dehydration, as seen following an aldol condensation. It was discovered by the German chemist Hans von Pechmann^[2].



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