A review on coumarin backbone: An attractive scaffold for promising bioactive compounds

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ABSTRACT

Background: Coumarin moiety is found in many naturally occurring products that have been used for many decades in traditional medicine around the world. Coumarin has distinctive physicochemical properties and can be easily transformed into a wide range of functionalized coumarins. As a result, a large number of coumarin derivatives have been designed, synthesized, and evaluated to attack a variety of pharmacological targets selectively. These targets may include various selective enzyme inhibitors and the targets, tagged as multitarget-directed ligands, found in diseases like Parkinson's and Alzheimer's, which are considered as multifactorial diseases.

Objectives: The most widely used synthetic methods leading to coumarins, besides the major biological routes for their metabolic transformations and biosynthesis, are highlighted and reviewed. Also, the focus was concentrated on some pharmacological activities of coumarin derivatives involving those related to the selective inhibition of cholinesterase and monoamine oxidase enzymes and targeting specific ligands of neurodegenerative diseases.

Conclusion: The impacts of substituents pattern/type on the selectivity and potency of the studied coumarins were explained to determine the main structural and molecular factors that may affect the activity and performance of the directed targets.

Keywords: Coumarin, Multitarget-directed ligands, Monoamine oxidase inhibitors, Cholinesterase inhibitors.

المعلومات الاساسية: يوجد جزء الكومارين في العديد من المواد التي تنتج بشكل طبيعي والتي تم استخدامها لعقود عديدة في الطب التقليدي في جميع أنحاء العالم. يتمتع الكومارين بخصائص فيزيائية وكيميائية مميزة ويمكن تحويله بسهولة إلى مجموعة واسعة من الكومارين الفعالة وظيفياً. نتيجة لذلك ، تم تصميم عدد كبير من مشتقات الكومارين وتصنيعها وتقييمها لمهاجمة مجموعة متنوعة من الأهداف الدوائية بشكل انتقائي. قد تشمل هذه الأهداف العديد من مثبطات الإنزيمات الانتقائية والأهداف ، التي تم تصنيفها على أنها روابط موجهة متعددة الاهداف، موجودة في أمراض مثل باركنسون والزهايمر ، والتي تعتبر من الأمراض متعددة العوامل.

الغاية من الدراسة: يتم تسليط الضوء على الطرق الاصطناعية الأكثر استخدامًا المنتجة للكومارين ، إلى جانب الطرق البيولوجية الرئيسية لتحولاتها الأيضية وتخليقها الحيوي. تم التركيز على بعض الأنشطة الدوائية لمشتقات الكومارين التي تتضمن تلك المتعلقة بالتثبيط الانتقائي لأنزيمات الكولين إستريز وإنزيمات أوكسيديز أحادي الأمين ، واستهداف روابط محددة للأمراض التنكسية العصبية.

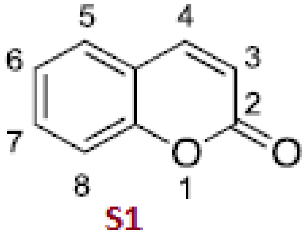
الاستنتاج: تم شرح تأثيرات نمط / نوع البدائل على انتقائية وفعالية الكومارين المدروسة لتحديد العوامل الهيكلية والجزيئية الرئيسية التي تؤثر على النشاط والأداء في الأهداف الموجهة.

الكلمات المفتاحية: الكومارين، الاهداف المتعددة الاتجاه، مثبطات انزيم تفكك الكولين، مثبطات انزيم أكسدة أحادي الأمين.

INTRODUCTION

Vogel was discovered coumarin **S1** from the seeds of the Dipteryx odorata tree, which has called tonka beans, in 1820, for the first time. It is also known as Coumarou, a French term [1]. Since then, many coumarins derived from plants, bacteria, fungi have been isolated, structurally characterized, synthetically modified, and evaluated for their various biological activities [2, 3].

S1, whose structure is shown in Figure 1, is an oxa-heterocycle with a 2*H*-chromen-2-one (2*H*-1-benzopyran-2-one or 1,2-benzopyrone) that has been extensively investigated due to the presence of its skeleton in many physiologically active products and compounds [4].



S1

Figure 1: Chemical backbone of coumarin.

Coumarin and some of its derivatives have been developed into medications, as displayed in Figure 2, including the anticoagulants acenocoumarin **S2**, phenprocoumon **S3**, and warfarin **S4,** which all act as vitamin K antagonists. Also, the antibiotic novobiocin **S5** that is a potent bacterial DNA gyrase inhibitor, and the choleretics hymecromone (4-methyl umbelliferone) **S6**, and armillarisin A **S7** [5].

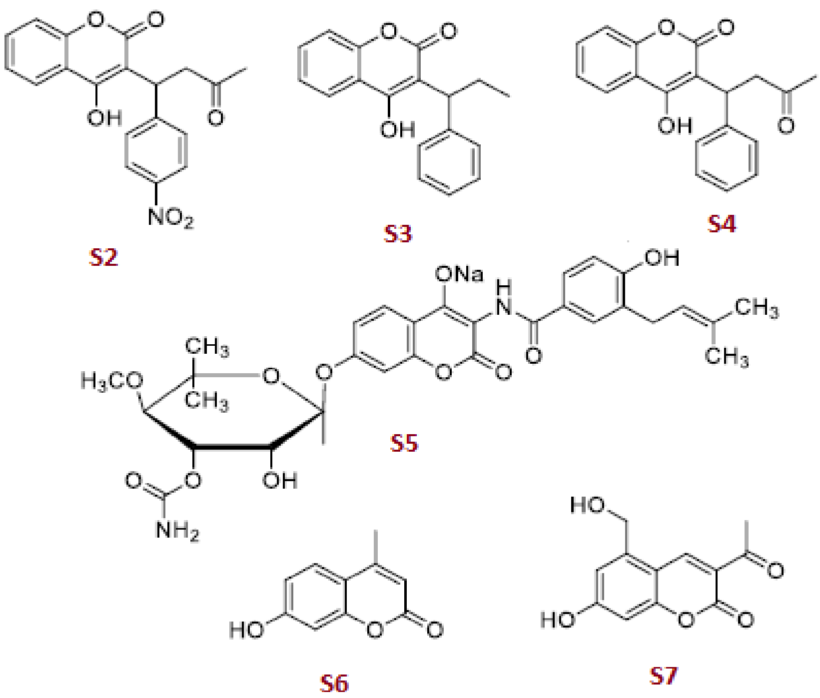
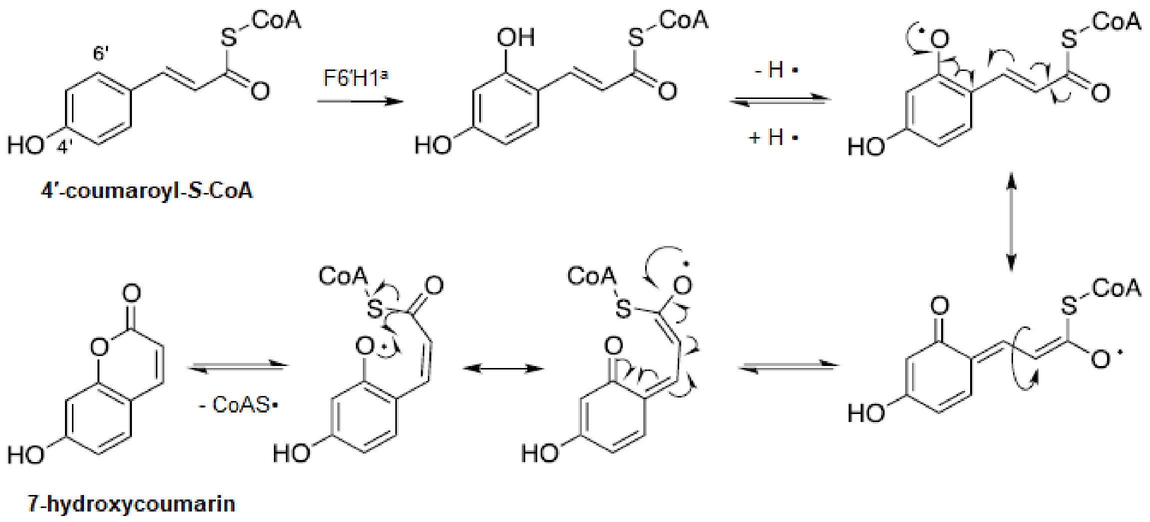


Figure 2: The chemical structures of some coumarin-based medications.

Biosynthesis of Coumarins

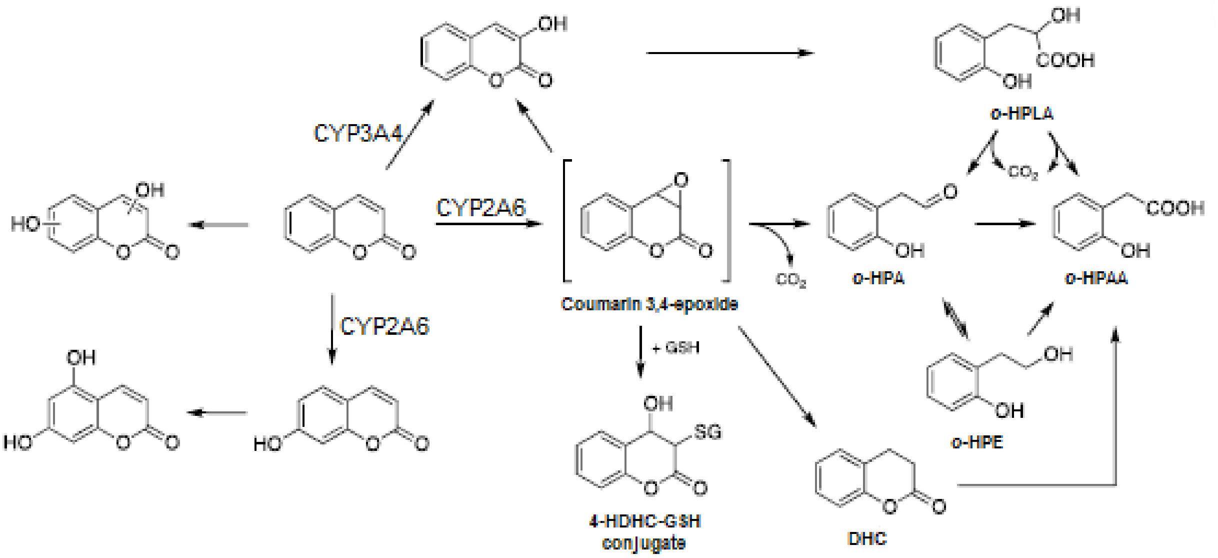
Coumarins are generated naturally via the main biosynthetic route, which leads to phenylpropanoids. The enzyme phenylalanine ammonia-lyase (PAL) converts phenylalanine (from the shikimate pathway) into *trans*-cinnamic acid, which is then converted into the core metabolite 4′-coumaroyl-*S*-CoA. The latter is then subsequently converted into a variety of phenylpropanoids [6]. Coumarin is biosynthesized from the core metabolite via *ortho*-hydroxylation, followed by *trans-cis* isomerization of the side chain, and finally cyclization process. The *ortho*-hydroxylation, mediated via the enzyme Feruloyl-CoA 6'-hydroxylase 1 (F6′H1), is the first and most important step in this natural synthesis. Kai *et al.* (2008) suggested the radical mechanism for the biosynthesis of coumarins [7], which is displayed in Scheme 1**.**



Scheme 1: Biosynthesis of 7-hydroxycoumarin from the core metabolite 4′-coumaroyl-*S*-CoA as recorded by Kai *et al*.

Metabolism of Coumarins

There are two principal routes for metabolizing coumarin-based compounds, as displayed in Scheme 2, including 7-hydroxylation and lactone ring-opening with oxidative decarboxylation. The latter occurs on the intermediate produced in the metabolic pathway's first step, which is coumarin 3,4-epoxide. Other probable coumarin metabolites, which are formed to a considerably lesser degree than at position 7, include hydroxylation of coumarins at positions 8, 6, 5, and 4, and 3,4-dihydrocoumarin (DHC) [8].



Scheme 2: Summarization of the principal coumarin metabolic pathways.

Some cytochrome P-450 isozymes (CYPs) can play a critical role in the metabolic transformation of coumarin-based compounds. The primary families of cytochrome P-450 that are important for most medication's oxidative biotransformation are CYP1, CYP2, and CYP3 [9]. In human liver microsomes, the main enzyme responsible for the metabolism of coumarin-based compounds to their corresponding 7-hydroxycoumarin metabolites is CYP2A6 [10]. Reduced CYP2A6 activity, which may be due to the CYP2A6's polymorphism and/or high gene multiplicity, may favor alternate coumarin metabolic routes, like the route that leads to 3-hydroxycoumarin via CYP3A4 catalysis. It was proposed that a higher amount of 3-hydroxycoumarin may stimulate the production of 2-hydroxyphenyl acetaldehyde (2-HPA), which is a cytotoxic product that might be involved in the coumarin-related toxicity [10].

Even though coumarin itself can be represented as an effective pharmacological therapy for lymphedema, several medical protocols have prohibited the utilization of this inexpensive and effective medication. The probable hepatotoxic consequences, as previously stated, that demonstrated in mice, rats, and even less frequently in humans may result in this precaution [11]. However, considering the prior results, patients with lymphedema who have a lower activity of CYP2A6 isozyme can be recognized and avoided coumarin treatment. The reason for that is the high possibility for metabolizing coumarin via the cytotoxic route, resulting in *o*-HPA [11]. The early phenotyping of these individuals can promote a safer application of this effective and inexpensive compound, coumarin, to all other lymphedema-suffering patients with normal CYP2A6 enzyme function [11].

Toxicity of Coumarins

The exposure of humans to various natural coumarin-based products is high since they are abundant in fruits, vegetables, nuts, seeds, tea, and coffee [12]. Metabolism-, carcinogenicity-, toxicity-, and safety-related studies concerning the coumarin itself found in foods and perfumes for cosmetic application have been reviewed. The authors of this review found that coumarin exposure from foods and cosmetics items has no risk on human health [13]. On the other hand, other publications showed that coumarin and certain coumarin derivatives are significantly hazardous. Indeed, in the hepatocytes from various species, which include humans, hepatotoxic effects have been observed [14–16]. Another important article stated that coumarin's cytotoxic effects depend on species and metabolism, so rat models can't be utilized to estimate coumarin toxicity in humans [17]. Recent human investigations have found that 0.1 mg/kg body weight is the tolerated dosage intake for coumarin. So, to avoid hazardous consequences, this dose should not be exceeded [18].

Strategies for Coumarin Synthesis

The coumarin skeleton is future in a wide range of physiologically active natural entities, medications, agrochemicals, optoelectronic, and polymeric materials [19, 20]. As a result, enormous and ongoing efforts were made to develop novel synthetic routes and protocols, which make the crucial cyclization process to the heterocyclic ring and subsequent regioselective derivatization easier to perform. To create properly designed coumarin derivatives, a lot of effort has gone into developing more efficient and environmentally friendly synthetic methods [21]. In recent years, the increased usage of enabling and new technologies, like novel catalysts, ultrasounds, microwaves, greener solvents, and solvent-free reactions, has made access to coumarin derivatives considerably easier [21, 22]. The most common and classical methods for obtaining coumarin derivatives:

the Pechmann [23] and Knoevenagel [24] reactions, which are the subjects of several coumarin-synthetic studies, concentrated primarily to improve yields, develop simple work-up procedures, and use green/recyclable catalysts and solvents. Only selected synthetic techniques that were released recently are being discussed briefly here.

Pechmann Reaction for the synthesis of coumarins

One of the most investigated synthetic methods for the synthesis of coumarin and its derived compounds is the Pechmann condensation reaction. The classical version of this coupling reaction was promoted by strong inorganic acids like HCl and H_2SO_4. The recent advances concerning this reaction type investigated various catalysts to facilitate and initiate this condensation [23]. The incoming are some examples:

A- $FeCl_3$ catalyzed the synthesis of coumarins

The condensing of various invigorated phenols and β-ketoesters was proceeded, utilizing 10% mol $FeCl_3.6H_2O$ as an initiator, produced moderate-to-good yields [25].

B- Tin tetrachloride-grafted on silica gel catalyzed the synthesis of coumarins

Under a solvent-free environment heated to 120°C, the titled heterogeneous catalyst ($SnCl_4$-grafted on silica gel) can stimulate the synthesis of substituted coumarins in good yields [26].

C- γ-Fe_2O_3@HAp-Ag nanoparticles catalyzed the synthesis of coumarins

The Pechmann reaction was effectively catalyzed by an easily produced promoter, which was silver functionalized on hydroxyapatite-core–shell magnetic gamma-Fe_2O_3 nanoparticles. The reusable magnetic promoter forms the required coumarin derivatives, under environmentally friendly experimental settings, in high yields, and with a simple work-up procedure [27].

D- Sulfonated carbon@titania composite loaded with Lewis acid catalyzed the synthesis of coumarins

At 60°C, carbon@titania composite loaded with Lewis acid was used as an efficient initiator in the Pechmann reaction. It gives coumarin derivatives in high yields under a solvent-free environment [28].

E- Molybdate sulfuric acid (MSA) catalyzed the synthesis of coumarins

At 80°C, the Pechmann reaction proceeded in the water–dioxane blend employing molybdate sulfuric acid as a novel and effective promoter, producing the required coumarins in good yields [29].

F- Ionic-liquid catalyzed the synthesis of coumarins

At 70°C and in a solvent-free environment, 1,3-disulfonic acid imidazolium-hydrogen sulfate (DSIMHS) was found to be an efficient and recyclable ionic-liquid promoter. High yields were obtained in a short period (less than 30 min) [30].

G- Sawdust–sulfonic acid catalyzed the synthesis of coumarins

The Pechmann reaction proceeded at 110°C and was initiated by a reusable solid catalyst named sawdust-sulfonic acid can form coumarins in high yields. This effort offered several benefits, including a simple work-up procedure, without solvent, and a shorter interaction period (less than 60 min) [31].

Knoevenagel Reaction for the synthesis of coumarins

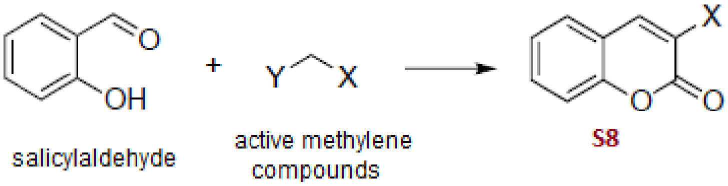
The Knoevenagel reaction is among the most frequently examined synthetic techniques for coumarin and its derivatives. An organic base like tertiary amine aided the conventional version of this coupling process that involves the interaction between benzaldehyde functionalized at position-2 with hydroxyl moiety and invigorated methylene. Recent research into this reaction type has looked at a variety of catalysts to promote and trigger this condensation phenotype. Here are a few samples from the newcomers [32]:

A- $MgFe_2O_4$ nanopromoter catalyzed the synthesis of 3-functionalized coumarins

Under ultrasound irradiation and in a solvent-free environment, $MgFe_2O_4$ is an effective nanopromoter that can initiate the condensation reaction between numerous 1,3-dicarbonyl and salicylaldehydes compounds utilizing Knoevenagel reaction. This strategy has brief reaction times, a simple work-up procedure, and high yields [33].

B- Potassium phthalimide catalyzed the synthesis of 3-functionalized coumarins

An efficient, fast, and environmentally friendly procedure for high-yielding, potassium phthalimide can promote the synthesis of 3-carboxy- and 3-cyano-coumarin phenotypes **S8**, as displayed in Scheme 3. Salicylaldehyde-based derivatives were reacted with invigorated methylene compounds in an aqueous media and at room temperature for several hours using the aforementioned catalyst and under mild reaction settings [34].



Scheme 3: Synthesis of 3-functionalized coumarins using potassium phthalimide as a catalyst.

Pharmacological Activities of Coumarins

Coumarins have impressive pharmacological effects depending on their basic backbone (for example, simple coumarin, bis-coumarin, fused polycyclic coumarin) and substitution pattern [35]. The pharmacological actions that have received the most attention including antiviral [36], antifungal [37], antibacterial [38], anti-inflammatory [39], anticoagulant [40], antithrombotic [41], anticancer [42], antimutagenic [43], antioxidant [44], cytotoxic [45], CNS stimulant [46], cholinesterase (ChE) [47], monoamine-oxidase (MAO) [46], lipoxygenase [48], and cyclooxygenase [49] activities. The coumarin ring has structural and physicochemical characteristics that making it easy for binding to many target sites.

Because the coumarin ring is aromatic, lipophilic, and planar, it can combine with physiological counterparts, primarily the lipophilic binding sites in proteins, by forming π-π stacking (non-covalent formed-forces generated among aromatic rings) and hydrophobic interactions with aromatic amino acids such as phenylalanine, tryptophan, and tyrosine. Also, coumarins may attach to positively-charged amino acids via strong ion-dipole interaction [50].

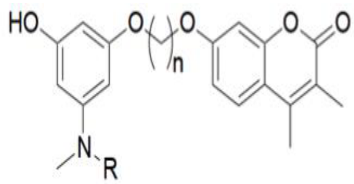
Besides, the coumarin's lactone group can offer the capacity to form strong-polar connections, such as dipole-dipole interactions and hydrogen bonds.

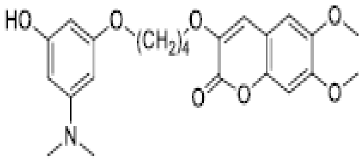
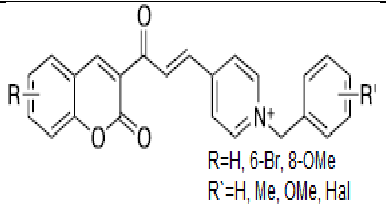
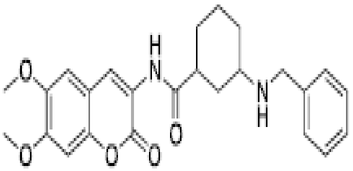
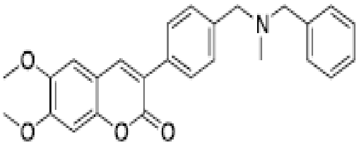
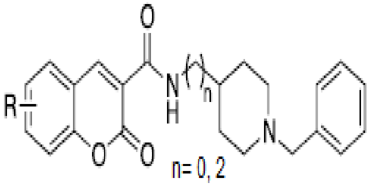
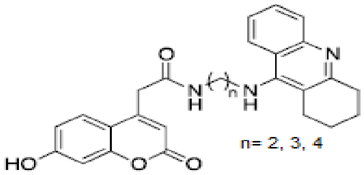
In some cases, coumarins can acylate the protein targets, as suggested for a particular enzyme's covalent inhibition mechanism. The lactone ring can also be opened by esterase-enzyme phenotypes, and biological activity may be caused by molecules that arise from that hydrolysis. In this situation, coumarins are bio-activated to release the actual active metabolites, acting as pro-drugs [50]. Several natural coumarins have been reported to have this mode of action for inhibiting carbonic anhydrase, which possesses the catalytic activity of esterase [51]. Pharmacological activities of coumarins on selected targets are discussed below.

Coumarins as ChE Inhibitors

Acetyl- and butyryl-cholinesterase (ACh-E and BCh-E), mainly ACh-E, catalyze the breakdown of acetylcholine (ACh) neurotransmitters at the synaptic gap of cholinergic neurons. Their inhibition can restore ACh levels in the nervous system, so ACh-E inhibitors were used in the treatment of Alzheimer's disease (AD), which led to rising interest in the development of new ACh-E/BCh-E inhibitors [52]. Coumarin derivatives, both synthetic and natural, are a well-studied group of compounds that function as ACh-E/BCh-E inhibitors, with several reviews published on the subject recently [47]. To achieve the maximum inhibition of these enzyme phenotypes, a highly trendy step in the designing of ChE inhibitors was used, which led to conjugated compounds having the moiety of coumarin coupled to a well-known ChEs inhibitor, usually tacrine or donepezil. Although there is no complex for co-crystallization of human ChEs (hChEs) with these kinds of coumarin hybrids yet, inhibition kinetics and docking studies propose that such coumarin-based molecules having a binding posture, typically extending from the peripheral (PAS) to the catalytic active site (CAS) of the enzyme, the term "dual binding site (DBS) inhibitor" was coined to describe these compounds [53]. Also, the crystal structure of the combination of Torpedo californica A-ChE with aflatoxin confirmed that the coumarin ring preferentially binds to a peripheral active site (PAS) of the tested enzyme [54]. As shown in Table 1, many coumarin-based compounds were investigated and identified as ChE inhibitors.

Table 1: Coumarin derivatives act as ChE inhibitors

Symbol	Compound	Activity	Characteristics	Structure
S9	3,4-Dimethyl-7-hydroxycoumarin attached to an edrophonium-like moiety (coumarin–edrophonium heterodimers) [55, 56].	DBS bovine (bAChE) inhibitors	Ammonium salts with low nM IC_{50} values. Dipole-dipole and ion–dipole interactions have been proposed for coumarin–edrophonium heterodimers, high bAChE over esBChE selectivity.	

S10	6,7-Dimethoxy-3-substituted coumarin derivative linked to 3-hydroxy-N, N-dimethylanilino via a suitable linker [57].	bAChE-selective inhibitors	The IC_{50} was 0.236 nM, and the selectivity of AChE/BChE was high (SI > 300,000).	
S11-15	Coumarin–pyridinium derivatives [58].	electric eel-(eeAChE) inhibitors	Quaternary benzylammonium salt, IC_{50}s in nM-pM range, introducing substituent in position 3 for effective binding with the peripheral active site.	
S16	Donepezil-like coumarin, 6,7-dimethoxycoumarin derivatives containing a protonatable benzylamino group, linked to position 3 via various linkers [59].	bAChE-selective inhibitor	IC_{50}= 7.6 nM, a mixed-type inhibitory activity was found, proving the binding with both the PAS and CAS of bAChE.	
S17	AP2238, class of 3-benzylaminocoumarins, bearing the 6,7-dimethoxy group [60].	hAChE-selective inhibitor	One of the donepezil-like compounds, which was early released and advanced to pharmacological and biochemical testing.	
S18 and S19	3-Carbox amidocoumarins with small substituents in coumarin ring at positions 8, 7, or 6 [61].	eeAChE-selective inhibitors	Donepezil–coumarin hybrids, high selectivity of AChE/BChE, with nM binding affinity on eeAChE, also showing promise neuroprotection effect.	
S20-22	Tacrine–coumarin hybrids [62].	hChEs-inhibitors	Potent ChE inhibitors designed by using a recurrent approachs.	

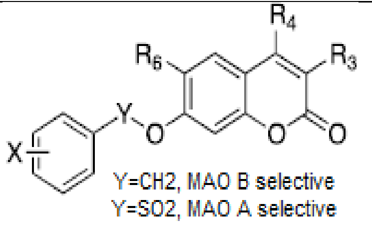
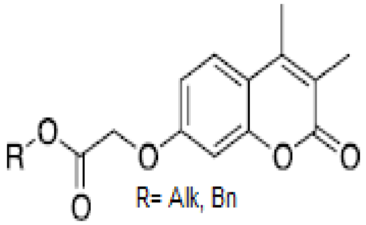
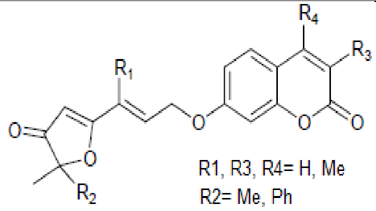
Coumarins as MAO Inhibitors

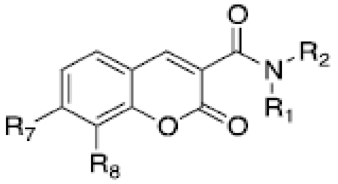
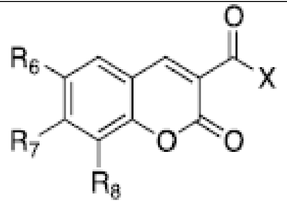
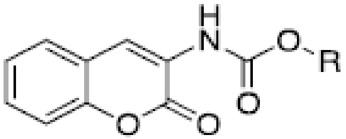
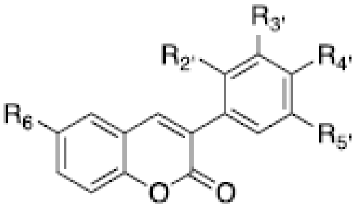
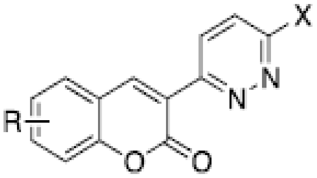
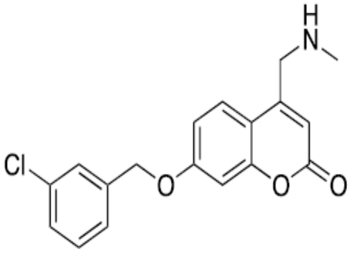
Endogenous and exogenous amines, including neurotransmitters, are oxidatively deaminated by monoamine oxidase enzymes (MAOs). In humans, there are two types of MAO enzymes: MAO-A and MAO-B, which differ in substrate selectivity and inhibitory sensitivity [63]. Selective MAO-B inhibitors are used nowadays in conjunction with levodopa to treat Parkinson's disease, whereas MAO-A inhibitors are used to treat depression [64]. Knoll AG and BASF published a joint paper in 1994 that reported for, the first time, the inhibiting action of a previous series patented, including 7-aryl sulfonyloxycoumarins and 7-aryl alkoxycoumarins as MAOs inhibitors with high selectivity [65]. Such exceptional selectivity and activity were examined further by many researchers, as shown in Table 2.

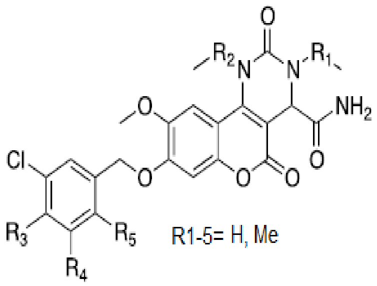
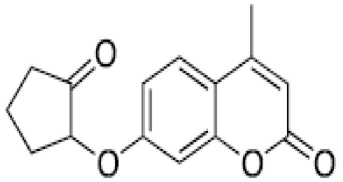
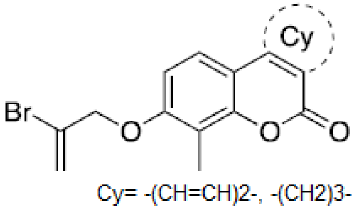
The easily functionalize coumarin backbone synthetically enables the investigation of various substitution patterns. The resolution of co-crystallized complexes of human MAOs with many reversible/irreversible inhibitors by X-ray crystallography led to an advance in the design of MAOs inhibitors [66, 67]. By using the structural information obtained from the studies of X-yay as a guide, a target-dependent design of expanded sequences of selective inhibitors of MAO-B was created, by retaining the substituent 7-*m*-chlorobenzyloxy, to ensure selectively and desirable binding to MAO-B and trying to introduce charged or polar substituent at position 4. B/A selectivity and MAO-B affinity were preserved in nearly all of the proposed compounds, which also demonstrated high solubility in water and low lipophilicity, all of which are essential requirements for progressing to pre-clinical and clinical investigations [67].

Also, to discover and justify the most significant molecular factors for high selectivity of MAO A/B and MAO affinity, as well as to give drug-like characteristics to recently developed inhibitors, different computational studies were carried out (computer-promoted molecular design) [68]. Lately, molecular dynamics (MD) simulations used to check the interaction of hMAO-B and -A with selective coumarin-based inhibitors at the molecular level. A significant finding has been the discovery of water-mediated H-bond between Flavin adenine dinucleotide (FAD) cofactor and the selective MAO-B 7-benzyl oxycoumarin, an interaction that was not anticipated by docking-studies of similar analogs [69].

Table 2: Coumarin derivatives act as MAO inhibitors

Symbol	Compound	Activity	Characteristics	Structure
S23 and S24	7-Benzyloxy and 7-arylsulfonyl oxycoumarins [70].	MAO-inhibitors	IC_{50}s in the nM range, selective and potent .	
S25 and S26	Ester derivatives of 7-hydroxy-3,4-dimethylcoumarin [71].	rMAO-inhibitors	The *ex vivo* studies on this group of coumarins were carried out on the rat's brain and liver for the first time. The half-life of esters hydrolysis in a buffer correlated with the R group's steric hindrance.	
S27-34	Series of natural and newly synthesized geiparvarins, which are 7-substituted coumarins [72].	rMAO-inhibitors	Strong selectivity of MAO B/A and high rat MAO-B inhibitory action in low- to the sub-µM range.	

S35 and S36	3-Carbox amidocoumarins [73].	hMAO-inhibitors	Different selectivity of MAO B/A, high inhibitory potency of human MAO, with IC_{50}s ranging from µM to sub- µM. A decrease in MAO-B affinity occurred due to the addition of the benzyloxy group in position 7.	 R1, R8= H, Me R7=H, BnO R2= (cyclo)alkyl, (hetero)aryl
S37-46	3-Acylcoumarin derivatives [74].	hMAO-inhibitors	Inhibitors with low potencies, except 3-carboxy hydrazidocoumarin and 7-benzyloxy-3-ethylester derivatives, having good hydrolytic stability and strong inhibition of human MAO-B (IC_{50} equal to 3.2 nM).	 R6, R8= H, Me, MeO,OH, Hal R7= H, OH, (cyclo)alkoxy, BnO, NEt2 X= Me, Ph, OH, OEt, NHNH2, NHNHAr
S47-54	3-Carbamylcoumarins [75].	MAO-inhibitors	Higher selectivity of MAO B/A and lower inhibitory potencies in comparison with 7-benzyl oxycoumarins analogs.	 R= (halo)Alk, Ph, Bn
S55-64	3-Phenyl-6-substituted coumarins [76].	hMAO-inhibitors	Potent and selective human MAO-B inhibitors and IC_{50}s in the sub-µM to the sub-nM range. The addition of substituents in position 6 of coumarins seemed tolerable, except for the insertion of a bulky group.	 R_x = H, Me, OH, MeO, Br
S65 and S66	3-Pyridazinyl coumarins [77].	hMAO-inhibitors	High selectivity of MAO B/A, an affinity for human MAO-B in the µM range, and good predicted pharmacokinetic properties (ADMET).	 R= Me, MeO, (6, 7, or 8) X= Br, Cl, MeO
S67	7-[(3-Chlorobenzyl) oxy]-4-[(methylamino) methyl]-2*H*-chromen-2-one (NW-1772 compound) [78, 79].	rMAO-inhibitor	High B/A selectivity and rat MAO-B inhibitory potency. Good pharmacokinetic properties, low cytotoxicity, and high blood-brain barrier (BBB) permeation. IC50 of MAO-A= 5.94µM and MAO-B= 13nM.	

S68-70	New 7-benzyloxycoumarin derivatives (computer-aided design)[80].	Potent hMAO-B-inhibitors	Excellent selectivity of MAO B/A and the activity on human MAO-B in the nM to the sub-nM range. These compounds developed through target- and ligand-depended screening of well-known selective inhibitors of MAO.	
S71	Coumarin derivatives designed by using Computer-aided technologies [68, 81].	Highly selective hMAO-A-inhibitors	Derived by using a combined QSAR-CN (complex networks) model approach and MARCH-INSIDE approach (computational method).	
S72 and S73	Coumarin derivatives designed by using Computer-aided technologies [68, 81].	Highly selective hMAO-B-inhibitors	Derived by using a combined QSAR-CN (complex networks) model approach and MARCH-INSIDE approach (computational method).	

Coumarins as Multitarget-Directed Ligands

The use of a multi-target drug therapy to treat neurodegenerative and other complicated illnesses has become a "revolution" in drug development. Because of their multiple etiology, multifactorial diseases are usually treated with a medication cocktail, which has a higher risk of drug-drug interactions and toxicity. The multi-target strategy is based on the idea of one drug, several targets, which intends to provide a single-drug therapy with multiple pharmacological actions that may be used to treat the same illness [82].

The benefits of this monotherapy include primarily the absence of drug-drug interactions, increased compliance of patients who are taking only one therapy for their condition, and the simplicity of ADMET screening and therapeutic and pharmacological characterization. However, such a multi-target profile necessitates a correct balance of potencies to achieve the required pharmacological activity for every target addressed. The simplest method of preparing multi-target ligands is to attach two pharmacophoric moieties, each of which is responsible for different bio-pharmacological actions, via a linker that can be cleaved metabolically (conjugation-type) or through a covalent bond that is formed directly (fusion-type). A higher advanced multi-target ligand design involves merging (hybridizing-type) two or more functional groups into a novel molecular unit, capable of displaying the original actions of both moieties [83, 84], as shown in Figure 3.

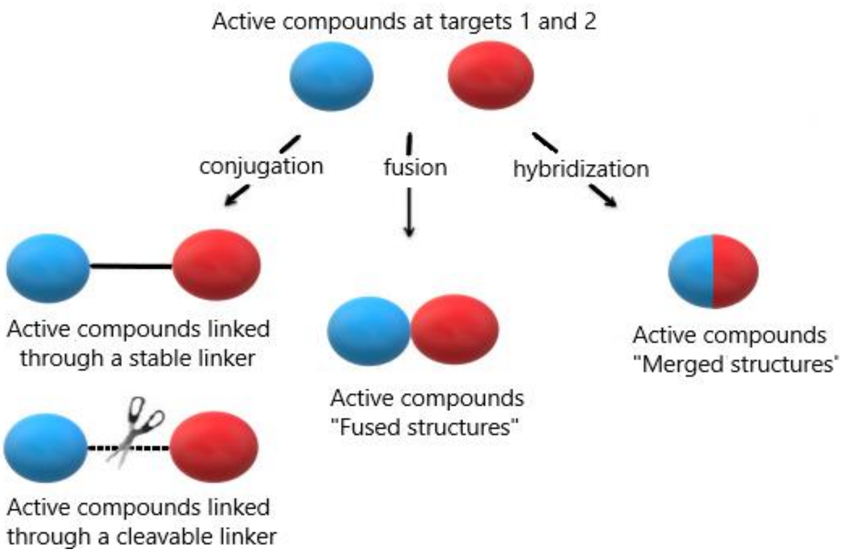
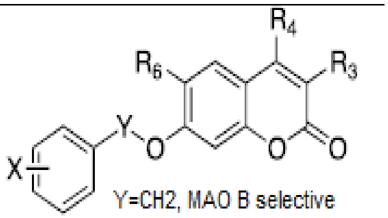
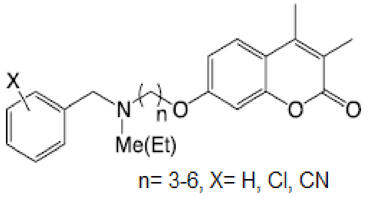


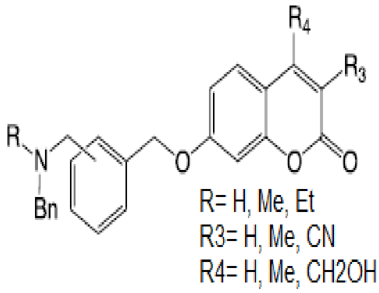
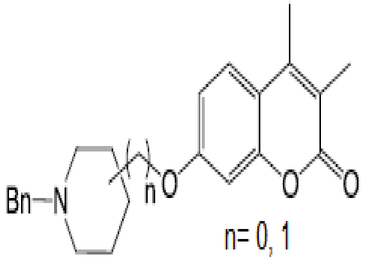
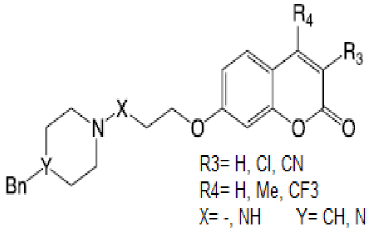
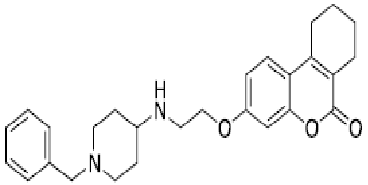
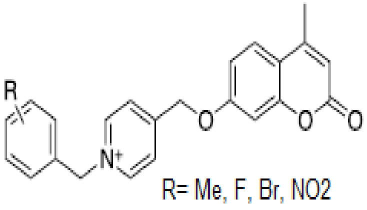
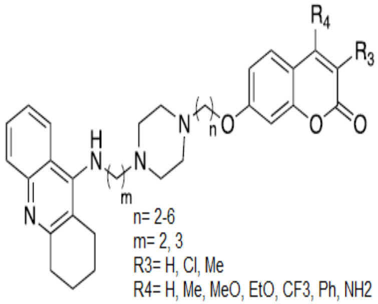
Figure 3: Different strategies of multi-target drug design.

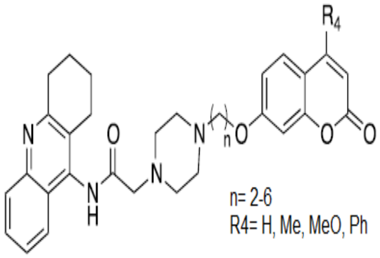
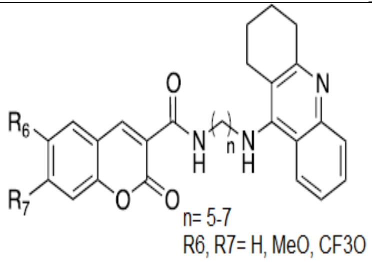
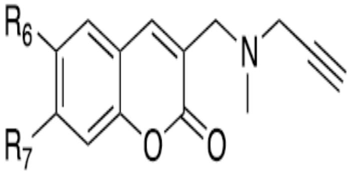
The disadvantage of creating conjugated or fused molecules is that it frequently leads to big molecules with low water solubility, high lipophilicity, high molecular weight, and a large number of rotatable bonds. As a result, these compounds are likely to have poor pharmacokinetic characteristics, including limited bioavailability and higher susceptibility to being substrates for detoxification systems. On the other hand, hybrid molecules may maintain more drug-like properties and may be easier to create as hit drugs for pharmacological investigations [85, 86].

The significant interactions of the coumarin core inside the binding sites of ChEs and MAOs enzymes lead to molecular conjugates having this skeleton, which is also known as dual ChE–MAO inhibitors [87]. Some coumarin derivatives that can act as multitarget-directed ligands are reported in Table 3.

Table 3: Coumarin derivatives act as multitarget-directed ligands

Symbol	Compound	Activity	Characteristics	Structure
S74	7-Benzyloxycoumarins [88].	Dual eeAChE-rMAO-B inhibition	Act as mixed/noncompetitive electric eel AChE inhibitors in the 3–100 µM range and rat MAO-B selective.	 Y=CH2, MAO B selective
S75-85	Protonatable 7-substituted coumarins, a flexible alkoxy chain was used to connect the basic N-benzyl group to position 7 [89].	Dual ChE–MAO-B inhibition	Good inhibitory activities at MAO-B, AChE, and BChE, but low selectivity.	 n= 3-6, X= H, Cl, CN

S86-90	Protonatable 7-substituted coumarins, A more rigid 7-benzyloxy moiety was used to connect the basic N-benzyl group to position 7 [89].	Dual ChE–MAO-B inhibition	The presence of CH_2OH group in position 4 of the coumarin led to higher selectivity of MAO B/A, better balance of MAO-B and AChE activities, and good ADMET properties. This group of congeners has the potential to be developed into hit structures in the future. Potency in the nM range for hMAO-B and sub µM for hAChE.	
S91 and S92	Protonatable 7-substituted coumarins, using N-benzyl piperidine substituent (Donepezil's pharmacophoric moiety) [90].	Dual ChE–MAO-B inhibition	High selectivity and potency, good ADMET properties, especially high water solubility and BBB permeability, high cytoprotective effect against oxidative stress, and low cytotoxicity.	
S93 and S94	Protonatable 7-substituted coumarins. Highly close congeners of **S91** and **S92** compounds [91].	Dual ChE–MAO inhibition	Excellent activity profile as **S91** and **S92** compounds.	
S95	7-Substituted coumarins using a linker with second basic nitrogen [92].	Dual ChE/MAO inhibitors	The multi-target action was retained, but the potency was reduced.	
S96-99	7-Substituted coumarins using a charged N-benzyl pyridinium group [93].	Dual ChE/MAO inhibitors	The multi-target action was retained, but the potency was reduced. The addition of charged residues, in particular, had a negative effect on hMAO-B affinity.	
S100-109	Coumarin–tacrine conjugates [94].	Multitarget-directed ligands	Good activity profiles, although protonatable piperazine is present in a spacer, the length of the linker allows for a more marked increase in the affinity of hMAO-B and hBChE.	

S110-129	Coumarin–tacrine conjugates (7-hydroxy coumarin–tacrine conjugates) [94].	Multitarget-directed ligands	The piperazine ring in a spacer connected to tacrine by an amide-bond. Efficient inhibitors of eeAChE/esBChE, with metal-chelating, and anti-amyloid properties.	 n= 2-6 R4= H, Me, MeO, Ph
S130-133	Coumarin–tacrine conjugates (3-carboxy coumarin–tacrine conjugates) [95].	Multitarget-directed ligands	Non-selective and potent inhibitors of hAChE/BChE, with extra inhibitory action of amyloid-β aggregation and β-secretase (BACE1).	 n= 5-7 R6, R7= H, MeO, CF3O
S134-137	3-Propargylamine derivatives of coumarin (the basic group was shifted topologically to the coumarin ring position 3) [96].	Dual ChE–MAO inhibitors	Act by inhibiting MAO-B through another mechanism while retaining good dual AChE-MAO-B inhibitory action, with cytoprotective effects and high BBB permeability.	 R6, R7= H, MeO

CONCLUSION

The main structural and molecular factors that affect the activity and performance in the directed targets. Such knowledge can help in designing new coumarins with more selectivity and better pharmacological action. NMR spectrophotometer and X-ray crystallography are used to determine their three-dimensional structures. The safety of coumarins is another factor to consider. The danger may occur just at extremely high coumarin doses, which is difficult to achieve in typical diets. Despite recent significant discoveries, the development of selective and potent coumarins remains a significant promising goal for pharmaceutical chemists.

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