

Review

A Concise Review of the Recent Structural Explorations of Chromones as MAO-B Inhibitors: Update from 2017 to 2023

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Abstract: Monoamine oxidases (MAOs) are a family of flavin adenine dinucleotide-dependent enzymes that catalyze the oxidative deamination of a wide range of endogenous and exogenous amines. Multiple neurological conditions, including Parkinson's disease (PD) and Alzheimer's disease (AD), are closely correlated with altered biogenic amine concentrations in the brain caused by MAO. Toxic byproducts of this oxidative breakdown, including hydrogen peroxide, reactive oxygen species, and ammonia, can cause oxidative damage and mitochondrial dysfunction in brain cells. Certain MAO-B blockers have been recognized as effective treatment options for managing neurological conditions, including AD and PD. There is still a pressing need to find potent therapeutic molecules to fight these disorders. However, the focus of neurodegeneration studies has recently increased, and certain compounds are now in clinical trials. Chromones are promising structures for developing therapeutic compounds, especially in neuronal degeneration. This review focuses on the MAO-B inhibitory potential of several synthesized chromones and their structural activity relationships. Concerning the discovery of a novel class of effective chromone-based selective MAO-B-inhibiting agents, this review offers readers a better understanding of the most recent additions to the literature.

Keywords: chromones; neurodegenerative disorders; monoamine oxidase-B; structure-activity relationship; Parkinson's disease; Alzheimer's disease



Citation: Ipe, R.S.; Kumar, S.; Benny, F.; Jayan, J.; Manoharan, A.; Sudevan, S.T.; George, G.; Gahtori, P.; Kim, H.; Mathew, B. A Concise Review of the Recent Structural Explorations of Chromones as MAO-B Inhibitors: Update from 2017 to 2023. *Pharmaceuticals* **2023**, *16*, 1310. <https://doi.org/10.3390/ph16091310>

Academic Editor: Nuno Manuel Xavier

Received: 22 August 2023

Revised: 11 September 2023

Accepted: 13 September 2023

Published: 15 September 2023



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1. Introduction

According to epidemiological data, Parkinson's disease (PD) and Alzheimer's disease (AD) are the most prevalent neurological illnesses. These conditions substantially negatively impact the suffering of individuals, relatives, caretakers, and the community. Unfortunately, only palliative treatments are currently available, which makes the design and creation of novel medications necessary [1–3]. AD is a neurological condition primarily affecting older people and is characterized by memory loss and dementia [4,5]. A range of illnesses, mostly related to neuronal cells in the human brain, are called neurodegenerative diseases. These disorders, often age-dependent, can be broadly characterized by the gradual degradation of the framework and functioning of the central or peripheral nervous systems [6–9]. Because neuronal cells are the basic units of the neurological system, they seldom reproduce or replenish themselves, and neuronal destruction or demise results in

an inevitable loss of memory and cognitive impairments in people; however, under rare circumstances, it could lead to impairments in movement, speech, and breathing [10].

The World Health Organization (WHO) has projected that 50 million individuals will live with dementia worldwide by 2020, with approximately 10 million new cases occurring yearly. This number is expected to increase to 152 million by 2050. According to the WHO, AD may be a factor in 60–70% of dementia cases [6,11]. Despite numerous investigations into novel treatments in various phases of clinical trials, no effective therapies cure or reduce the progression of neurodegenerative illnesses [12–14]. Existing therapies may help alleviate most associated psychological and physical symptoms [12,15].

Monoamine oxidase (MAO) is a flavin adenine dinucleotide-dependent enzyme that is mainly found on the outer surface of mitochondria and is responsible for the oxidative breakdown of monoamines, including neurotransmitters such as dopamine, norepinephrine, as well as 5-hydroxytryptamine (serotonin) [16–19]. MAO-A and MAO-B are two subtypes that differ in tissue distribution, substrate particularity, susceptibility to particular inhibiting agents, and amino acid sequence [20,21]. Specifically, MAO-A deaminates noradrenaline, whereas MAO-B preferentially deaminates phenylethylamine, serotonin (5-hydroxytryptamine), and benzylamine [22]. MAO-B is primarily present in glial cells in the brain [23], whereas MAO-A is found in noradrenergic, serotonergic, and dopaminergic nerves and extra-neuronal compartment terminals [24]. Specific MAO-B blockers have been employed with levodopa to treat PD, whereas specific MAO-A-inhibiting agents have been utilized as antidepressants and anxiolytics [25–28]. MAO catalyzes the generation of hydrogen peroxide (H_2O_2) and reactive oxygen species (ROS), which may lead to oxidative stress and cell damage, ultimately leading to the progression of neurodegenerative disorders (ND); therefore, the concurrent inhibition of MAO may provide additional advantages for the treatment of ND [29–31]. MAO inhibitors are uncommon in clinical settings because only two medications, rasagiline and selegiline, have been approved for use as MAO-B blockers [32]. Both inhibitors have irreversible effects and are used to treat PD. Another MAO-B inhibitory compound, safinamide, has been clinically tested and functions as a reversible blocker [33]. Various scientific communities have focused on searching for novel MAO-B blockers with characteristics similar to those approved because of the limited number of -B blockers accessible for clinical use [34].

This review is solely concerned with substances belonging to the chromone class with MAO-inhibitory capabilities. The well-known MAO-B blockers chalcones and coumarins share structural similarities with chromones (Figure 1).

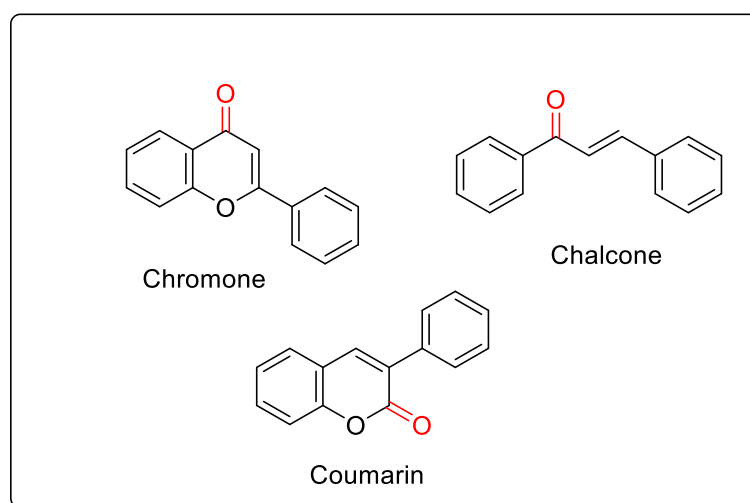


Figure 1. Structurally similar oxygen-containing MAO-B inhibitors.

As shown in Figure 1, the structures of chalcones and coumarins are closely related to those of chromones. The MAO-B inhibitory properties of coumarins and chalcones

have been reported in numerous studies [35–39]. Considering the similarities between these structures and chromones, further studies are needed to identify novel therapeutic candidates.

2. Chemistry of Chromones

Chromones (4H-chromen-4-one, 4H-1-benzopyran-4-one) are a significant class of oxygen-containing heterocyclic compounds with a benzoannulated-pyrone ring [40,41]. They belong to the flavonoid family, which includes isoflavones and flavones (Figure 2).

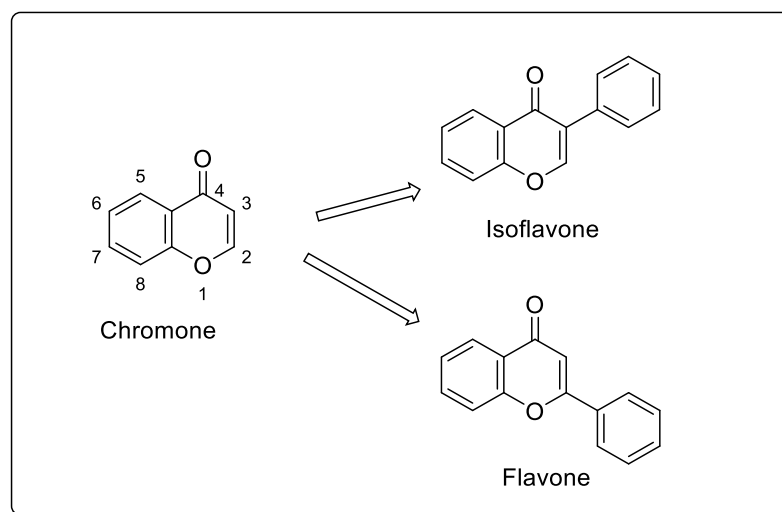
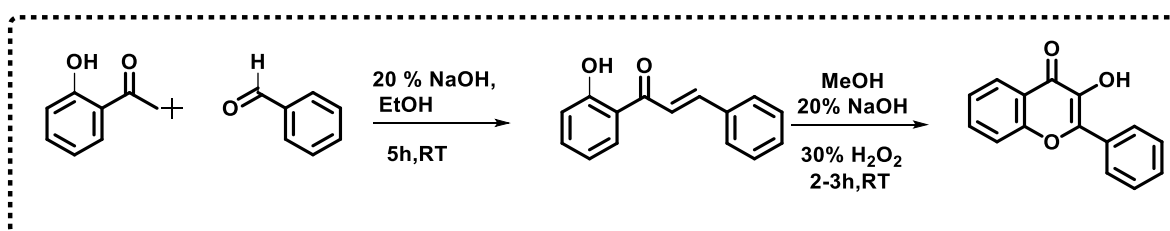


Figure 2. Structure of a chromone, isoflavone, and flavone.

The development of substituted chromone analogs has an extensive background and is of great interest [42]. One of the most frequently used methods for producing chromones is the Claisen–Schmidt condensation of an aromatic aldehyde with an *ortho*-hydroxyarylketone, followed by cyclization [43,44] (Scheme 1). The small polar surface area (PSA) of chromones promotes blood–brain barrier crossing, which is primarily responsible for chromone-derived substances’ ability to exert their effects on the CNS. Numerous heterocyclic scaffolds have been considered for developing novel MAO-B inhibitors because isoform selectivity is a major concern. Isomers of coumarin, called chromones (4H-1-benzopyran-4-one), constitute the flavone backbone. The chromone ring system is regarded as a favored scaffold owing to its range of pharmacological and biological effects and the minimal risk of toxicity associated with chromone derivatives. Compounds derived from chromone scaffolds inhibit MAO. The AChE inhibitory potential of chromones was also investigated [45,46]. As dopamine D₂ receptor agonists, chromones have been shown to mimic the actions of dopamine in the body, making them a potentially useful class of drugs for treating PD [47]. Chromones have been shown to have a significant capacity to adhere to adenosine receptors and have been studied clinically for managing PD and various CNS disorders [48–52].

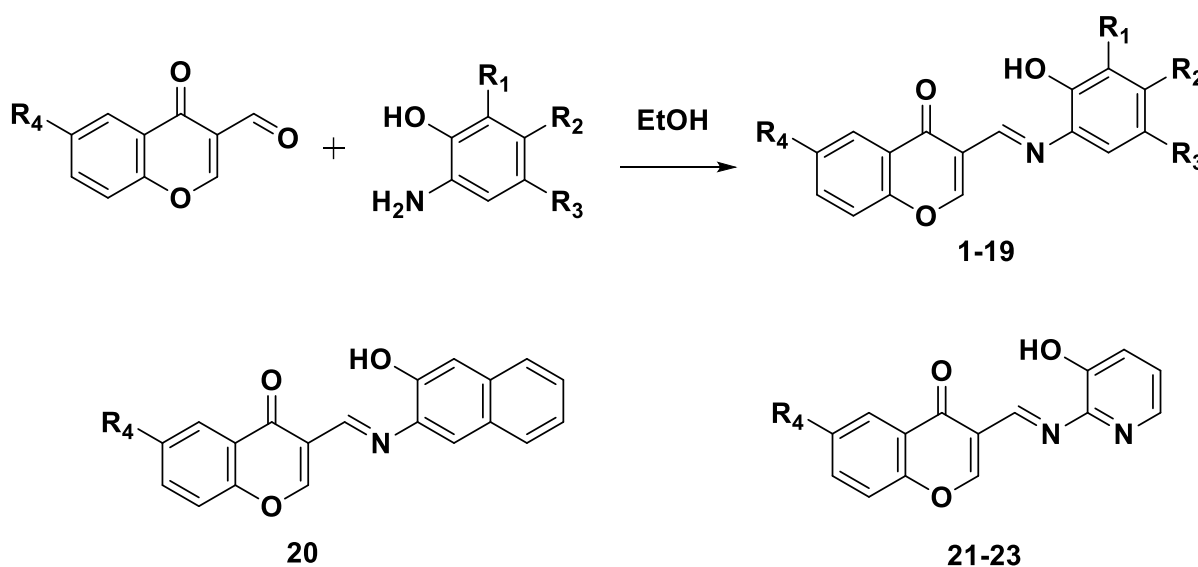


Scheme 1. The common route involved in the preparation of chromone scaffold.

Studies investigating the specificity of chromones have discovered that the methyl substitution on the chromone ring seemed more crucial for MAO-B inhibition than that of MAO-A. The current review, therefore, focuses on investigating the structure–activity relationship (SAR) and different methods of synthesis of various substituted chromones to determine how they affect MAO inhibitory activity.

3. SAR Studies of Chromone as MAO-B Inhibitors

Li et al. (2017) reported the discovery of multipurpose chromone-containing ligands with the potential for MAO inhibition, reaction with β -amyloid, chelation with metals, antioxidant activity, and regulation of reactive oxygen species [29]. They employed phenolic hydroxyl groups and Schiff bases as metal chelators. Target multifunctional ligands (MLs) were modified with phenolic substituents because they are known to have antioxidant properties. Several unique chromone derivatives were obtained and positioned at the C₃ position of the pyrone ring as a result of the functionalization of the chromone nucleus. The compounds were prepared by condensing an aldehyde with an aromatic amine in ethanol under reflux conditions, which is the traditional technique for imine synthesis shown in Scheme 2.



Scheme 2. Synthesis of chromones based on Schiff's base compounds (1–23).

Figure 3 shows that adding different substituents to the phenyl ring or chromone moiety improved hMAO-B activity compared to compound 1 with no substitution ($IC_{50} = 31.5 \mu M$). It was found to be more effective in inhibiting MAOs when the bromine substitution was at the R₄ position of the chromone, as in the cases of 8–13 and 12, with the F substitution at the R₂ position of the phenyl ring. Introducing the methyl group in the R₄ position of compounds 14–19 showed better activity than other analogs. Still, compound 18 showed the least inhibitory activity, with an IC_{50} value of $21.45 \mu M$ for hMAO-B, with the CH₃ group at the R₂ position. The highest inhibitory activity was demonstrated by compound 16, which had a methyl substitution at the R₄ position, and in the R₃ position of the phenyl ring, a chlorine group was introduced. The IC_{50} of $0.634 \mu M$ is roughly 12 times more active than the standard iproniazid ($IC_{50} = 7.98 \mu M$). A complete loss of inhibitory activity was observed when Cl group 15 was replaced with NO₂ group 14 at the R₂ position of the phenyl ring. Compounds 12, 13, 15, 16, and 19 demonstrated potent MAO inhibitory activities. The phenyl ring in the proposed compounds was changed to a different naphthalene ring 20 and pyridine rings 21–23, which were found to have less potent activity. According to this study, it can be concluded that the NO₂ and CH₃ groups at R₃ decrease MAO activity, whereas halogens such as chlorine or fluorine can cause a marked increase in activity. More potency was found with a methyl substitution at R₄.

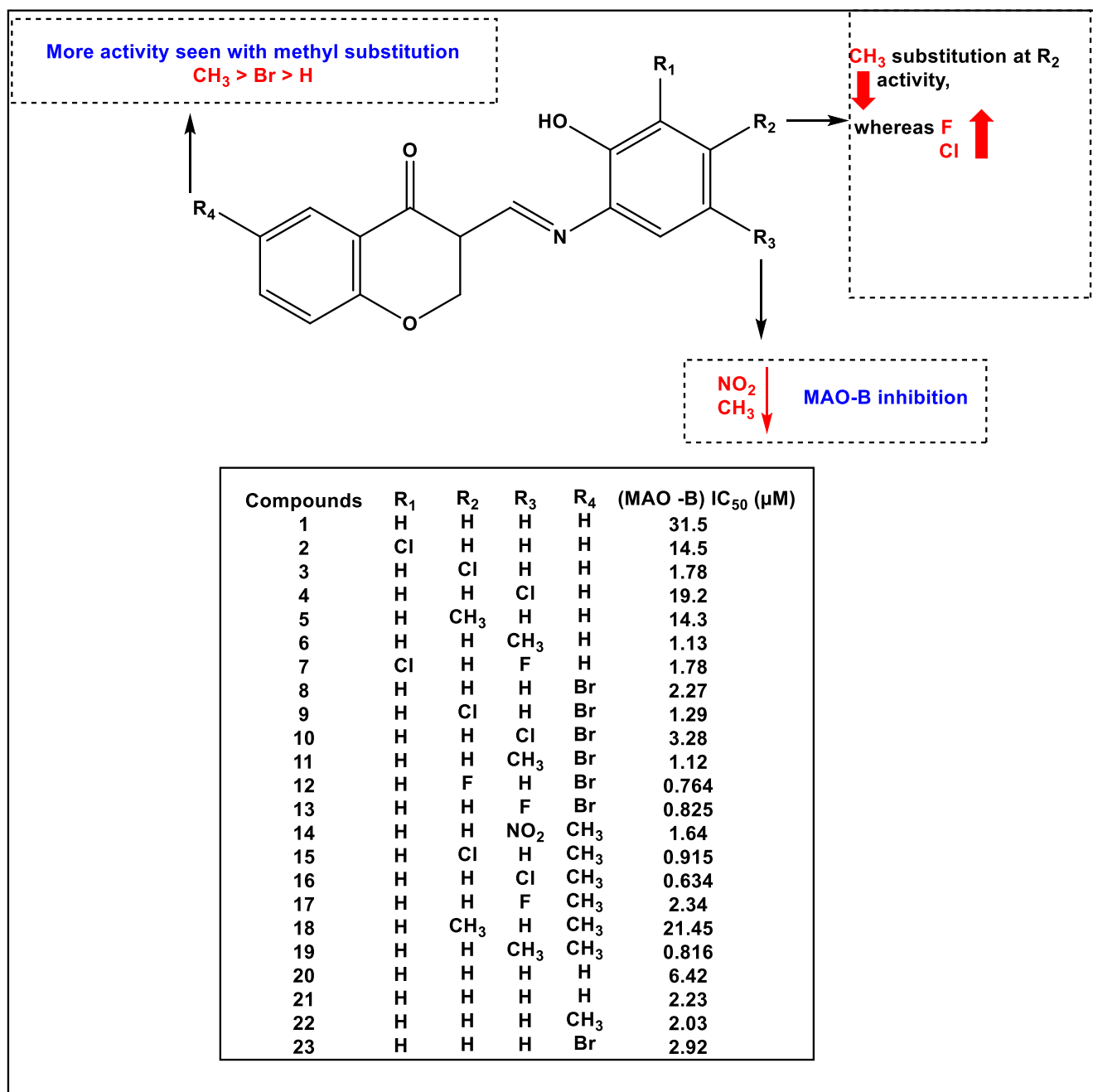


Figure 3. SAR study of chromone derivatives as MAO-B inhibitors.

A docking study was performed using this protein (PDB ID:2V61). Figure 4 explains the two-dimensional interaction, which showed that the FAD cofactor was situated near the chromone moiety of **19** and that the phenyl group of **19** had a π - π stacking interaction with Tyr435 at a distance of 3.18 Å. Tyr326 was involved in a π - π stacking contact with the amide carbonyl of **19** separated by a distance of 3.49 Å. Additionally, the hydrophobic pocket in the entrance cavity created by Leu171, Ile198, and Ile199 was occupied by the 2-amino-4-methylphenol moiety in compound **19**. These interactions may account for compound **19**'s effective inhibitory activity against MAO-B.

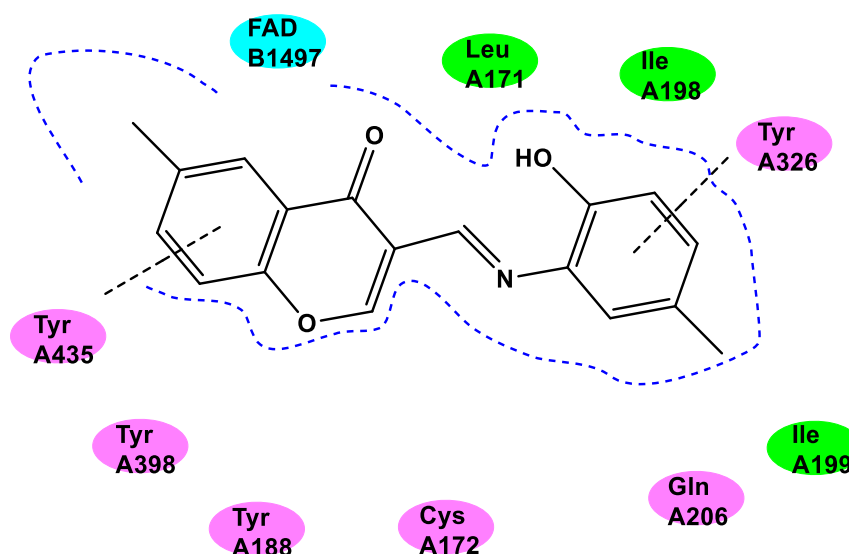


Figure 4. Docking study of compound 19. Green, hydrophobic amino acid residue; purple, hydrophilic amino acid residue; blue, FAD.

Fonseca et al. (2017) developed a set of novel coumarin and chromone derivatives and tested their biological activities against MAO-B [1]. With a focus on the lead optimization and under the guidance of the data obtained thus far, they carried out a detailed SAR examination of the two structural isomers. Compounds **34** and **54** were the most effective, selective, and reversible non-competitive MAO-B inhibitors. Searching for novel chemical compounds with pharmacological activities primarily involves using heterocyclic compounds. Benzopyrones are primarily coumarins and chromones. Chromones and coumarins are abundant and have useful therapeutic activities, such as antioxidant, anti-inflammatory, cardioprotective, and antibacterial effects. Coumarin-3-phenylcarboxamide **24** and chromone-3-phenylcarboxamide **25** (Figure 5) are desirable structures for the rational creation and identification of novel MAO-B inhibitors, according to Fonseca et al. and his research team.

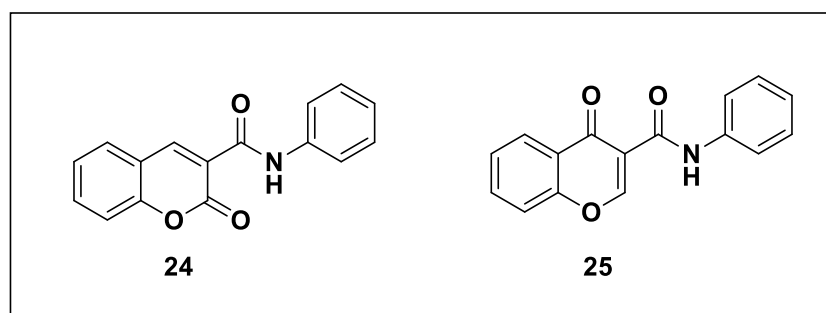
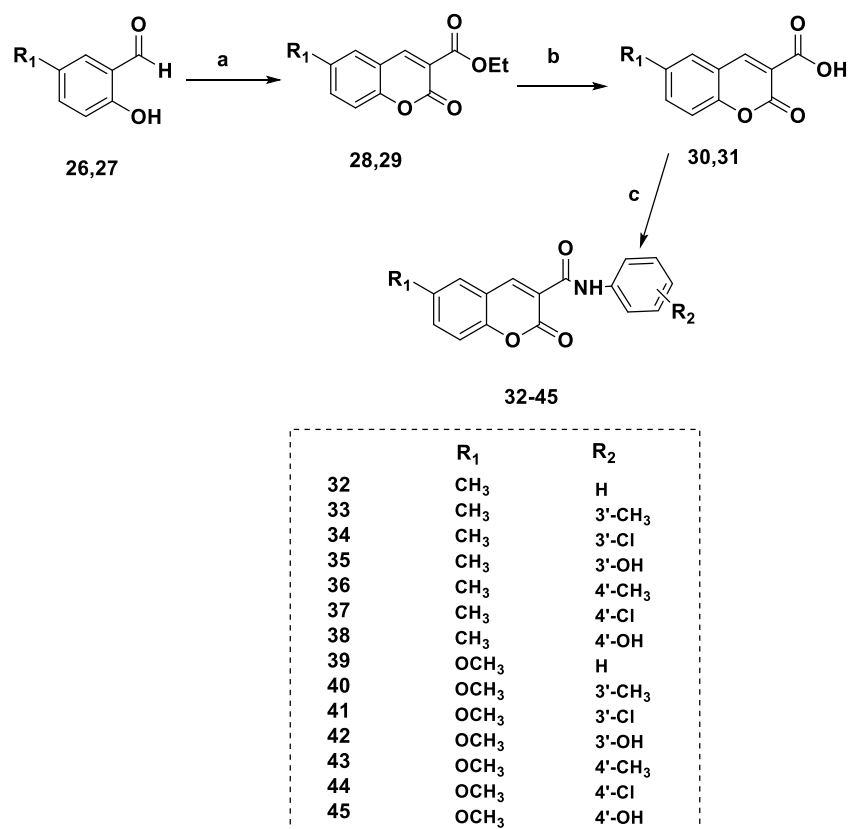
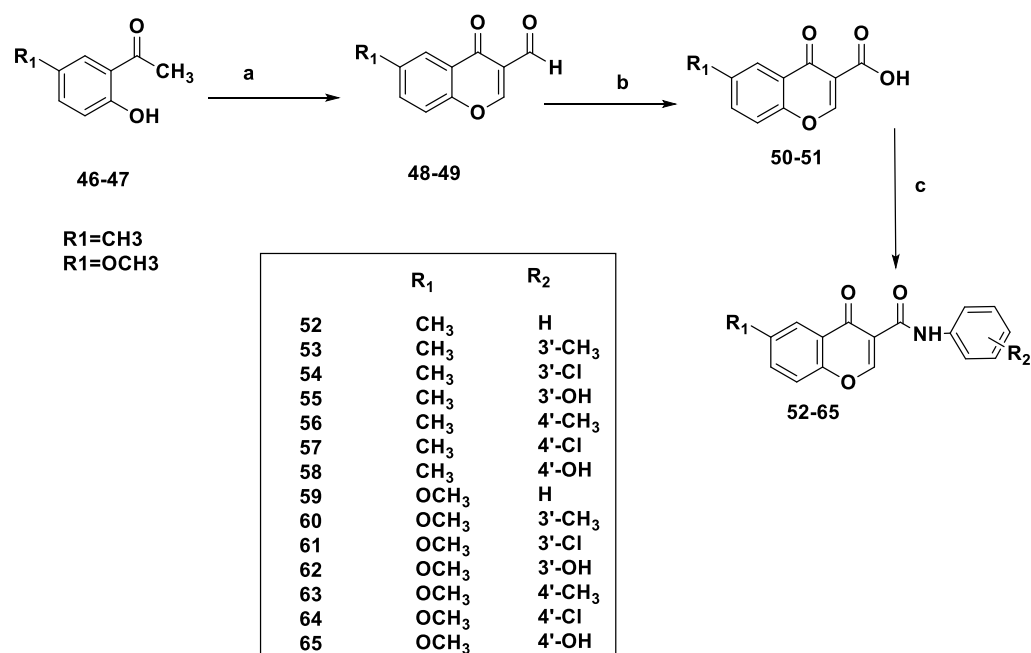


Figure 5. Coumarin-3-phenylcarboxamide (**24**) and chromone-3-phenylcarboxamide (**25**).

A library of novel coumarins **32–45** (Scheme 3) and chromones **52–65** (Scheme 4) was synthesized and evaluated for MAO-B inhibition. Scheme 3 shows the synthesis of coumarin derivatives by treating salicylaldehyde with diethylmalonate to obtain coumarin-3-carboxylates **28** and **29** and coumarin carboxylic acids **30** and **31**. The coumarin-3-carboxamide derivatives **32–45** were created via the EDC-induced coupling of compounds **30** and **31** with phenylamines.



Scheme 3. Synthesis of the coumarin derivatives 32–45. Reagents and conditions: (a) diethyl malonate, EtOH, piperidine, reflux, overnight; (b) NaOH (0.5% aq. ethanol), reflux, 4 h; (c) EDC, DMAP, DCM, substituted phenylamine, 0° to room temperature (rt), 4 h.



Scheme 4. Synthesis of chromone-3-phenylcarboxamide 52–65. Reagents and conditions: (a) POCl₃, DMF, −10 °C, 15 h; (b) H₃NSO₃, NaClO₂, 0 °C, 12 h; (c) POCl₃, DMF, phenylamine, rt, 1–5 h.

Scheme 4 explains the synthesis of chromone derivatives by treating acetophenone with phosphoryl chloride (POCl₃) and N,N-Dimethyl formamide (DMF) at −10 °C for 15 h to obtain chromone-3-carbaldehydes (48 or 49) followed by oxidation of the formyl

group with sodium chlorite to obtain chromone carboxylic acids (50–51). The synthesis of chromone-3-carboxamide derivatives (52–65) required the in situ formation of an acyl chloride intermediate, followed by the inclusion of a suitable phenylamine.

SAR analysis was conducted in response to earlier studies examining substituents' effects at comparable positions on the isomeric scaffolds of coumarin- and chromone-based compounds as MAO inhibitors. Adding 6-CH₃ or 6-OCH₃ substituents to benzopyrone-3-phenylcarboxamide scaffolds led to strong MAO-B inhibition (Table 1). However, the 6-methylcoumarin derivatives (32–38) were more potent than their 6-methoxy analogs (39–45). The addition of a 6-methyl (52–58) or 6-methoxy (39–45) group to the chromone framework had no appreciable impact on the MAO-B inhibitory activity, except for compound 52 (which lacks substituents on the exocyclic ring). Derivatives with *meta*-alternatives on the exocyclic ring were shown to have increased potency in both series. Compounds 34, 54, and 61, all of which had *m*-chlorine substituents, were the major active compounds in both sets, with IC₅₀ values of 5.07, 4.2, and 3.94 μM, respectively. The addition of substituents in the *para*-group resulted in decreased activity, except for compound 43 (IC₅₀ = 19.43 μM), which had a *p*-CH₃ group, as compared to compound 40 (IC₅₀ = 47.24 μM), which had a *m*-methyl group. The activity was reduced by the influence of an OH group at either the *meta*- or *para*-position (Figure 6). The location of the benzopyrone carbonyl group on the pyrone ring did not appear to have a significant effect, although MAO-B inhibition was a function of this group. All compounds under investigation were selective for MAO-B (Table 1).

Table 1. MAO inhibitory activities of benzopyrone derivatives 32–45 and 52–65.

Compound	IC ₅₀ (μM) hMAO-B	Compound	IC ₅₀ (μM) hMAO-B
32	15.32 ± 1.02	52	21.35 ± 1.10
33	7.52 ± 1.05	53	17.10 ± 1.17
34	5.07 ± 1.25	54	4.20 ± 1.08
35	45.40 ± 1.30	55	78.22 ± 1.30
36	13.90 ± 1.30	56	151.6 ± 5.14
37	11.08 ± 1.20	57	45.42 ± 2.32
38	621.70 ± 1.8	58	512.6 ± 2.81
39	5.95 ± 1.28	59	41.8 ± 2.2
40	47.24 ± 1.12	60	21.80 ± 1.21
41	9.03 ± 1.07	61	3.94 ± 1.08
42	228.6 ± 1.26	62	113.5 ± 1.10
43	19.43 ± 1.19	63	210.8 ± 8.1
44	18.90 ± 1.01	64	10.31 ± 1.55
45	*	65	674.2 ± 1.72
Deprenyl	16.73 ± 1.48	Safinamide	23.07 ± 2.07
Rasagiline	49.66 ± 2.26	Clorgyline	*

(*) Inactive at 100 μM.

The Reis collection of chromone was developed, synthesized, and tested for MAO and choline esterase inhibition by Reis et al. [53]. Briefly, the chromone moiety was modified by adding a phenylcarboxamide group at position C₂ or C₃ and an acrylate moiety with a tertiary amine function at position C₆. The potential byproducts of acrylate side-chain hydrolysis were also determined, and their biological activities were assessed in vitro. Additionally, testing was conducted on the most potent compounds, which were tested to determine their ability to permeate the blood–brain barrier, enzyme inhibition, kinetics and mechanisms, drug-like properties, and cytotoxicity profiles. Using models based on the crystal shapes of the targets, molecular modeling studies were performed to understand the interactions between the compounds and targets. The protein (PDB ID:2V5Z) was used as the receptor model for hMAO-B.

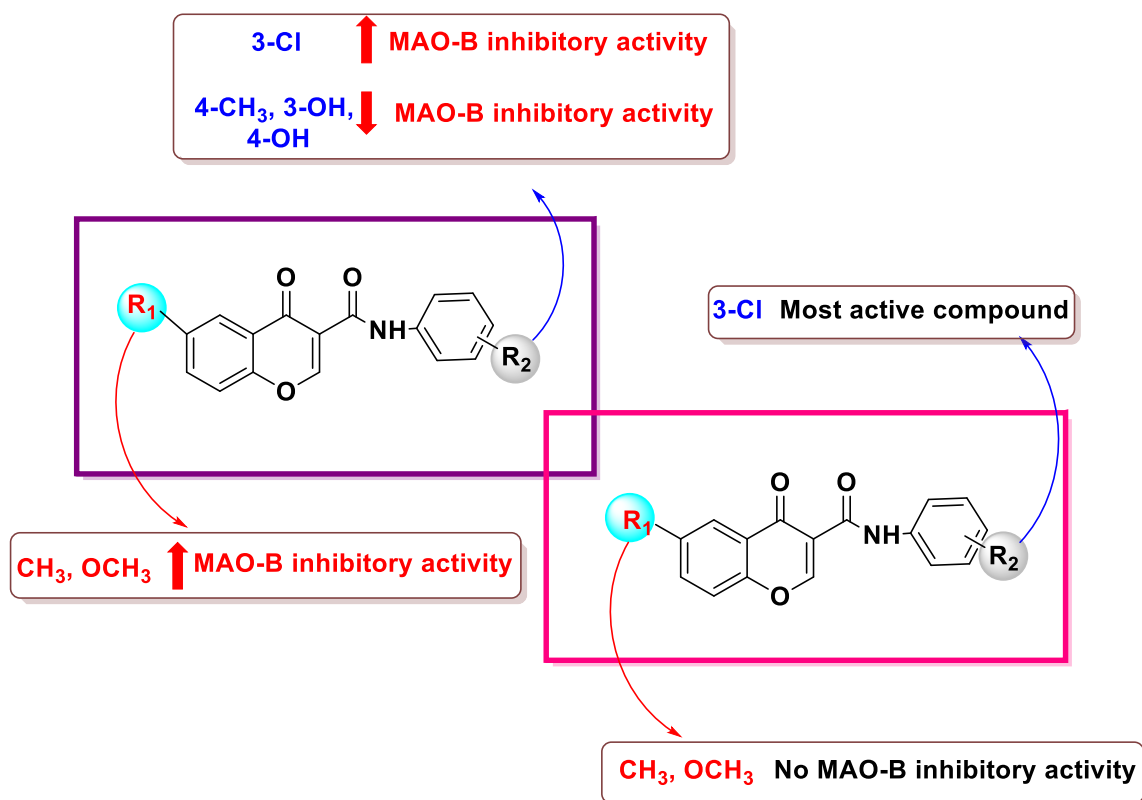
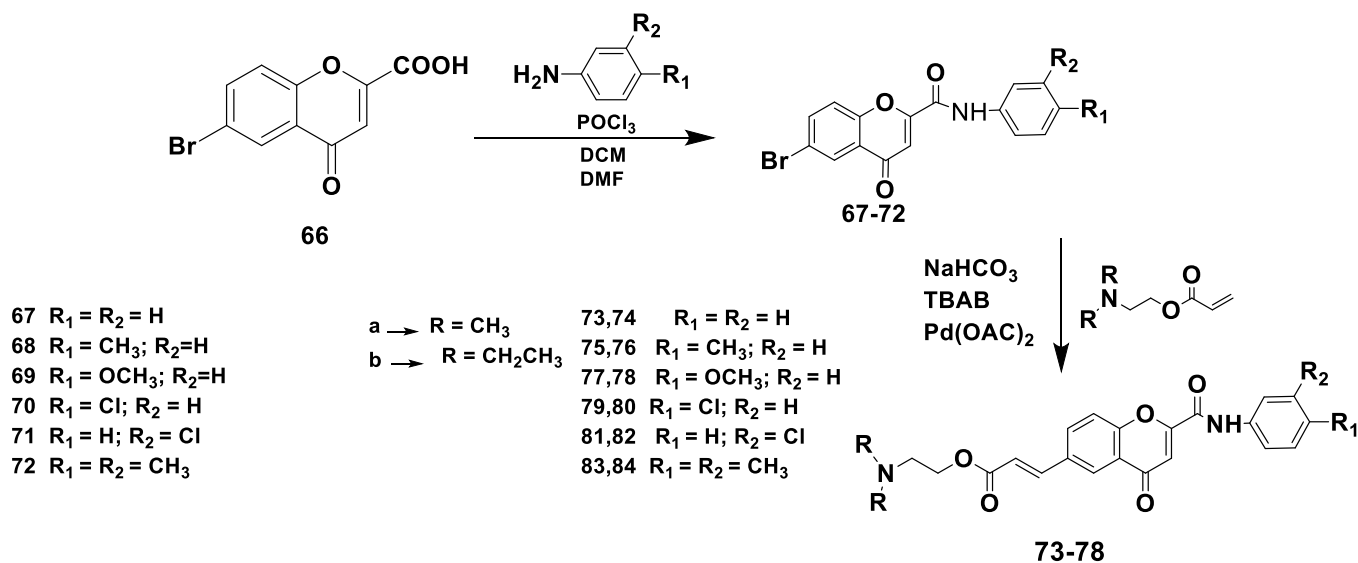


Figure 6. SAR study of chromone and coumarin derivatives as MAO-B inhibitors.

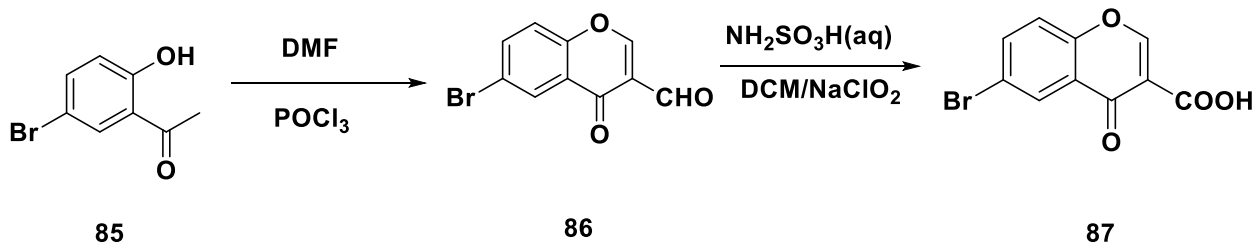
Scheme 5 shows the synthesis of chromone-2-phenylcarboxamide derivatives by treating 6-bromo-4-oxo-4H-chromene-2-carboxylic acid with phenylamine derivatives, followed by microwave-assisted Pd(II)-catalyzed Heck cross-coupling using 2-(dimethylamino)ethyl acrylates 73, 75, 77, 79, 81, and 83 or 2-(diethylamino)ethyl acrylates 74, 76, 78, 80, 82, and 84.



Scheme 5. Synthesis of three substituted amide-based chromones.

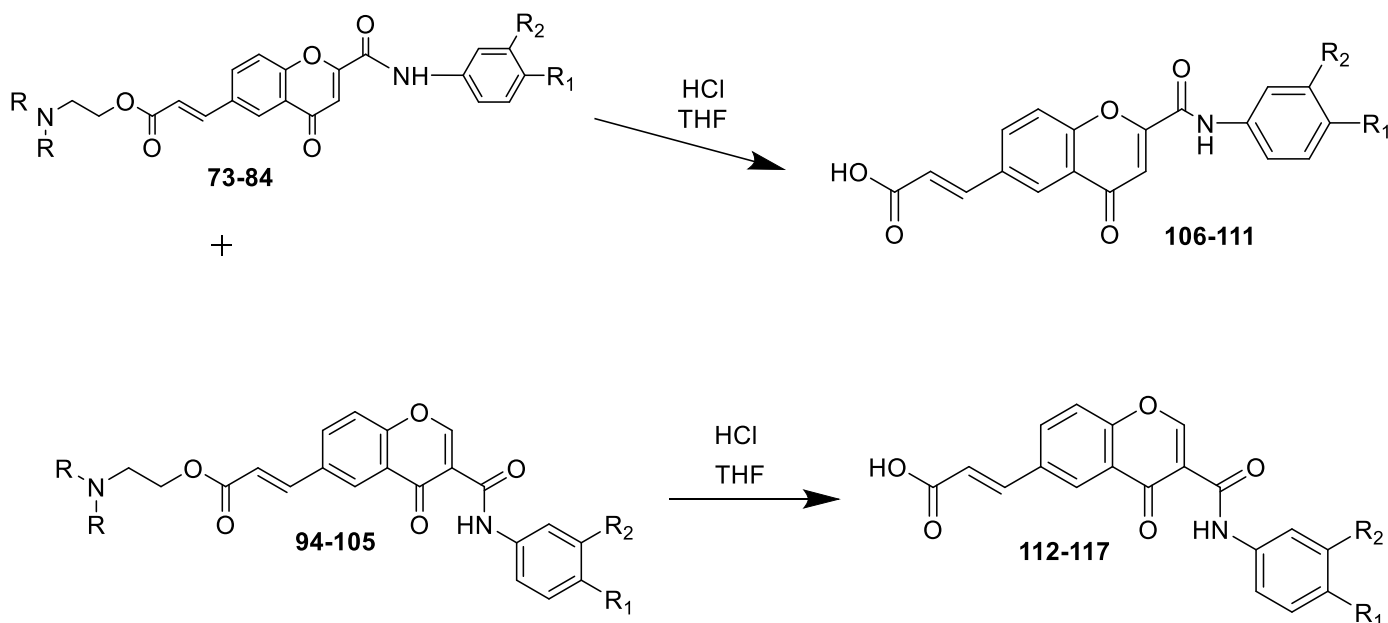
In Scheme 6, compound 86 (6-bromo-4-oxo-4H-chromene-3-carbaldehyde) was prepared from the starting material 5'-bromo-2'-hydroxyacetophenone 85 using POCl₃-induced cyclization followed by subsequent oxidation in the presence of sodium chlorite and

sulfamic acid to obtain bromo-4-oxo-4H-chromene-3-carboxylic acid (**87**). From **87**, the derivatives **88–93** were prepared by the condensation of phenylamine derivatives, followed by a microwave-assisted Pd(II)-catalyzed Heck cross-coupling reaction, as described in Scheme 5, to obtain chromone 3-phenylcarboxamides **94–105**.



Scheme 6. Synthesis of 6-bromo-chromone-3-carboxylic acid.

Scheme 7 shows the synthesis of chromones **106–111** and **112–117** prepared by the acid hydrolysis of chromone 2-phenylcarboxamides **73–84** and chromone 3-phenylcarboxamides **94–105**.



Scheme 7. Synthesis of chromone 3-phenylcarboxamides derivatives.

Compound **73**, with two methyl (CH_3) groups in the tertiary amine nucleus and no substituents on the exocyclic phenyl ring, specifically inhibited MAO-B with an IC_{50} value of $2.28 \mu\text{M}$. Derivative **74** inhibited MAO-B, which has two $-\text{CH}_3$ groups bound to the tertiary amine and a methyl group at the para position of the chromone exocyclic phenyl ring (Figure 7).

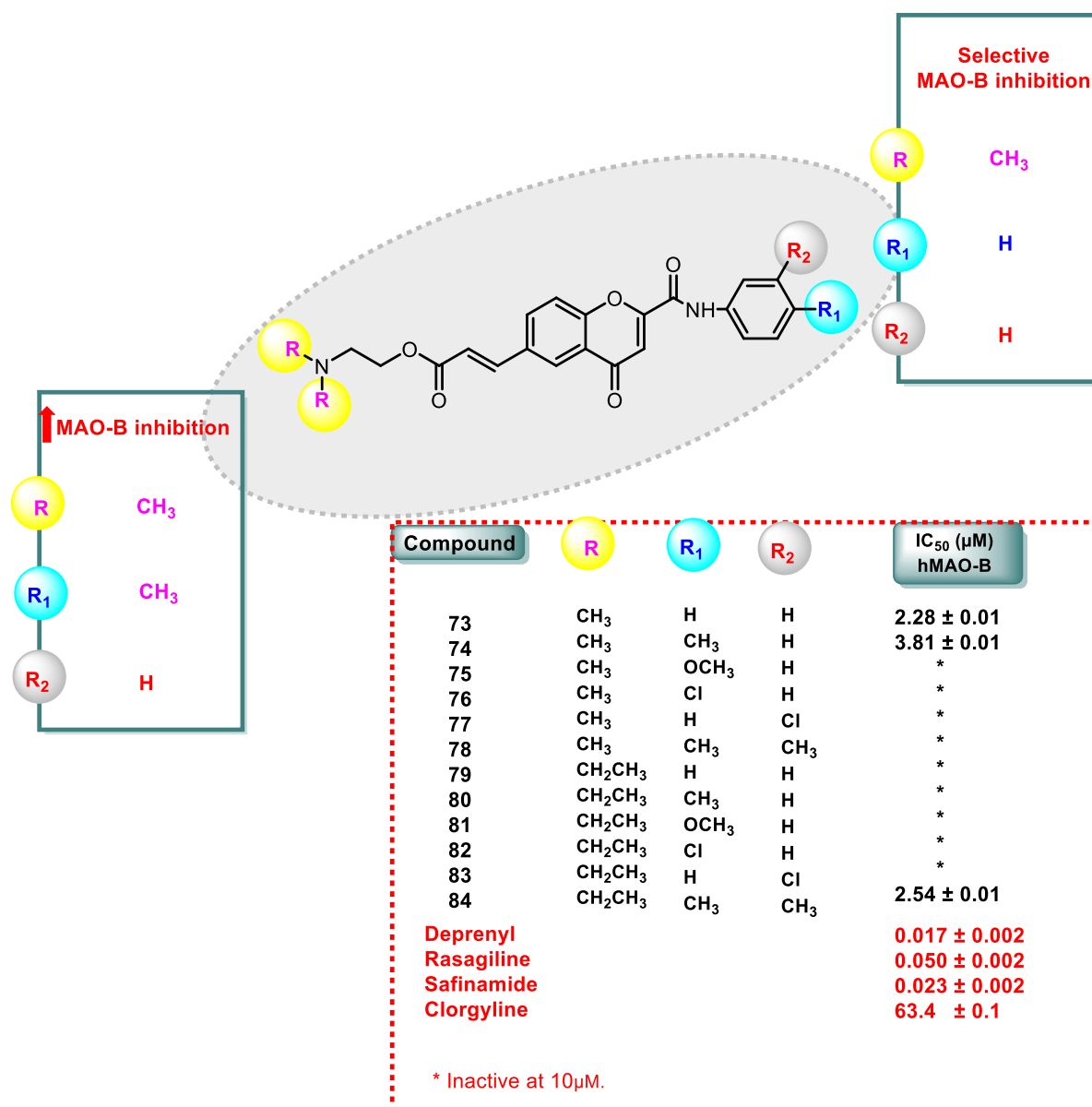


Figure 7. SAR study of chromone 2-phenylcarboxamide derivatives (73–84) and its MAO-B inhibitory activity.

Except for compounds **96**, **100–103**, and **105**, most of the chromone 3-carboxamide derivatives exhibited micromolar and sub-micromolar MAO-B-specific inhibition. In this sequence, the spatial volume of the substituent on the tertiary amine and/or in the exocyclic aromatic ring significantly influenced MAO-B inhibitory activity. Dimethyl-N-substituted compounds **100–105** were inert towards MAOs, except for compound **104**. Notable MAO-B inhibitory activity was observed for compound **94**, which had no derivatives on the exocyclic ring. The *p*-CH₃ group on compound **95** allowed it to selectively inhibit MAO-B compared to MAO-A, with an SI value > 4.2 (Figure 8).

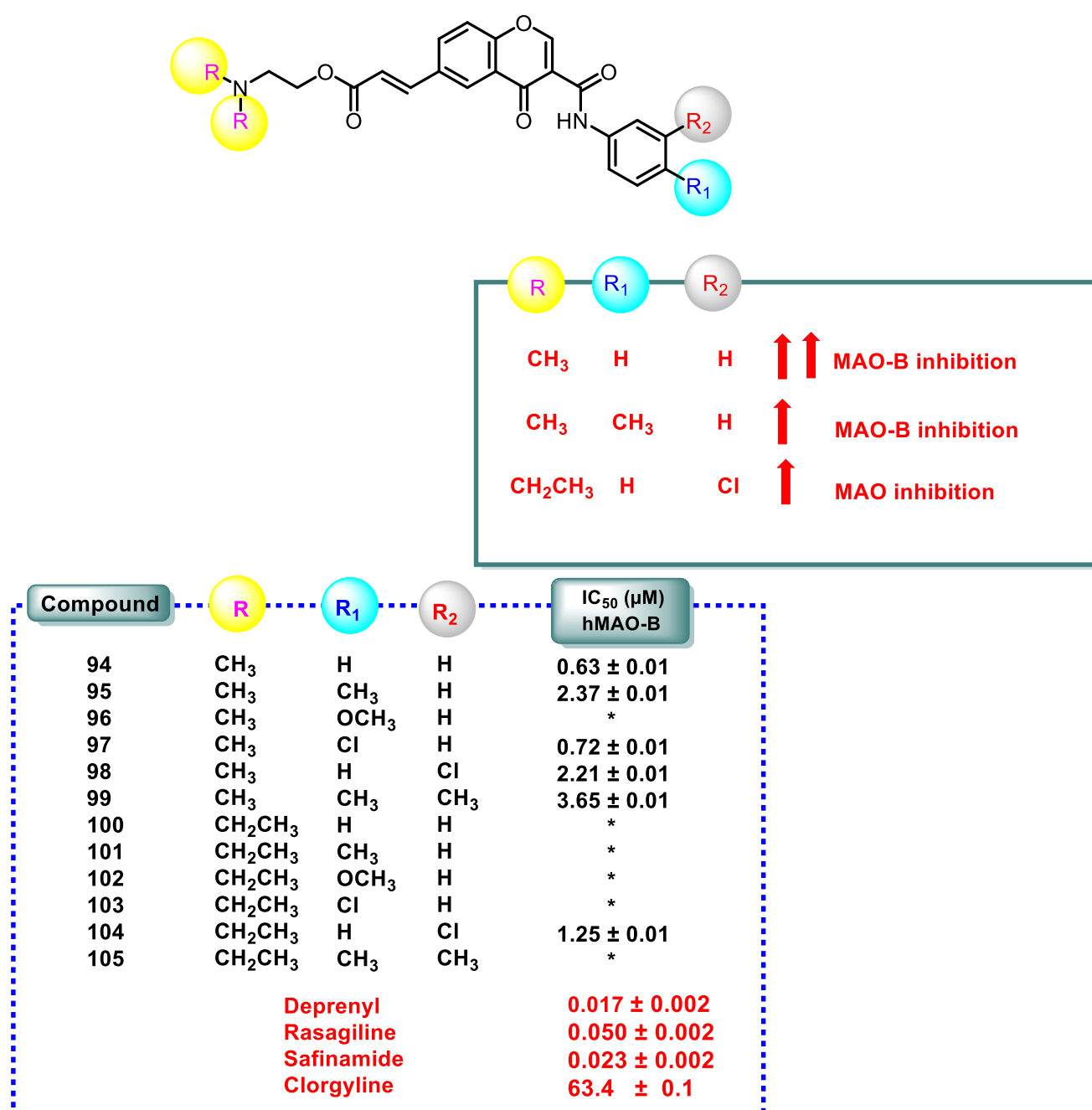


Figure 8. SAR study of chromone-3-phenylcarboxamide derivatives (94–105) and its MAO-B inhibitory activity. *, not determined.

The potential compounds 106–117, synthesized by the hydrolysis of acrylate-substituted chromones, were examined for their MAO inhibitory potential (Figure 9). The results revealed that the presence of the C6-carboxylic acid group significantly reduced the inhibitory activity of MAO. In particular, the hydrolyzed compounds of chromone 2-phenylcarboxamide 106–111 showed no effect on either of the MAO isoforms. Compared to the related precursors, compounds 94 and 99, chromone 3-phenylcarboxamide 112 and 117 exhibited micromolar MAO-B inhibitory activity.

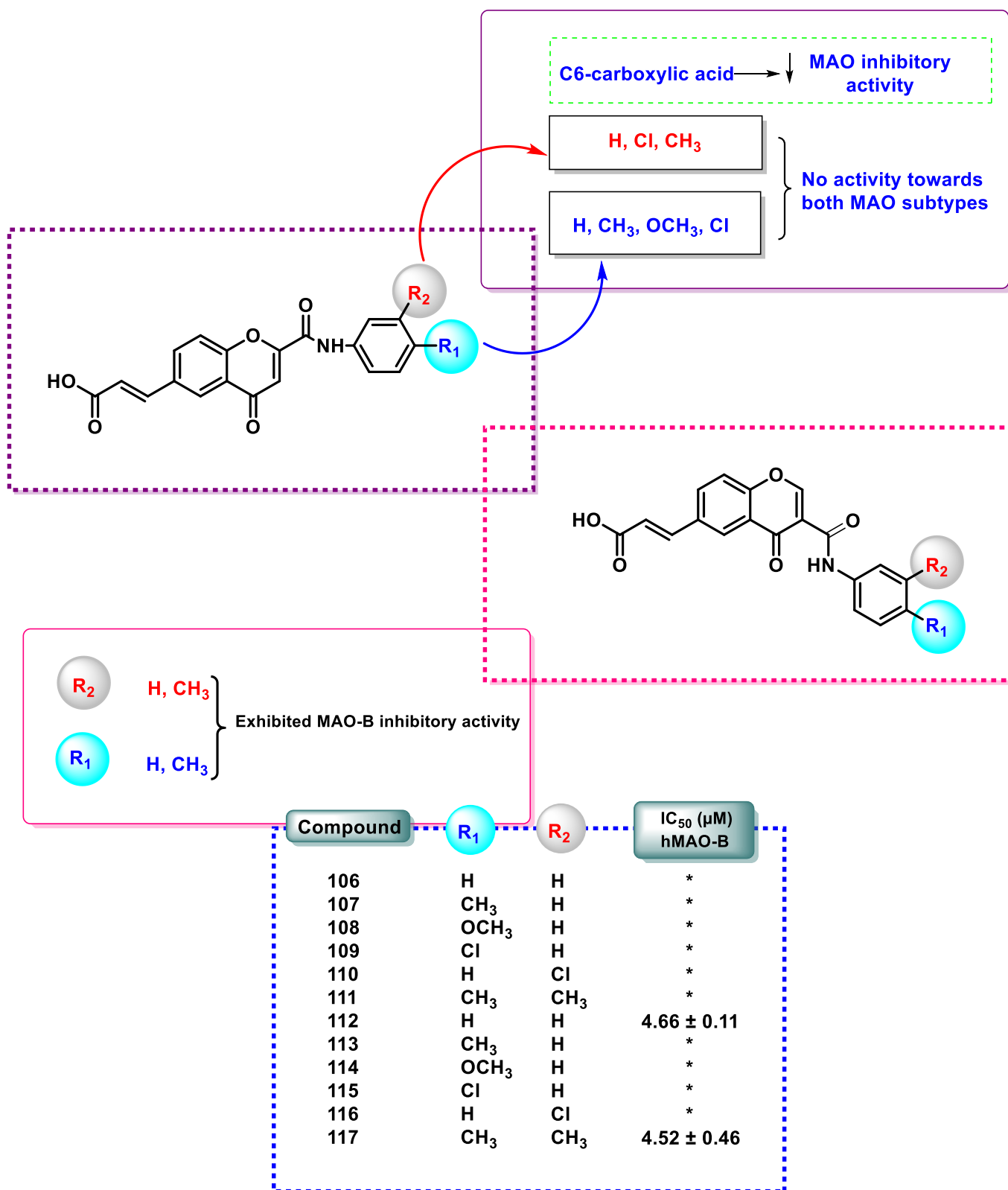
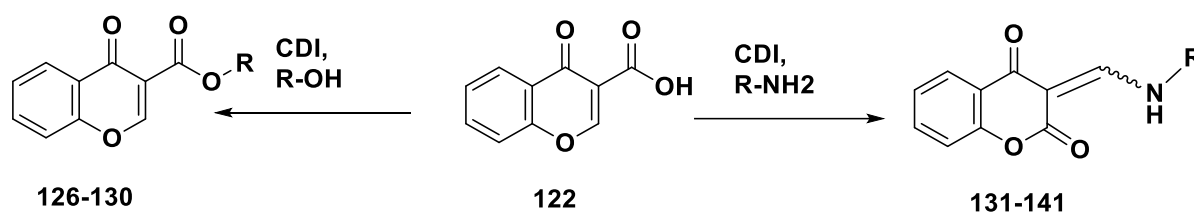


Figure 9. SAR study of chromone-2-phenyl and 3-phenyl carboxamide carboxylic acid derivatives 106–117 as MAO-B inhibitors. *, not determined.

Mpitimpiti et al. developed a novel series of 15 chromone derivatives and tested their MAO inhibitory activity in light of earlier investigations on the possible inhibition of MAO

by chromone compounds [54]. This study strongly emphasized the third position vs. the potential of MAO inhibition concerning the effect of flexible side chain replacement.

Scheme 8 illustrates the preparation of ester **126–130** and amino **131–141** derivatives of chromone by treating the chromone 3-carboxylic acid **122** with aromatic/aliphatic amines and alcohols in the presence of carbonyldiimidazole (CDI). Although the target esters were successfully synthesized, it is not surprising that the reaction of **122** with the amine compounds produced chromane-2,4-diones (**131–141**). The results of the MAO inhibition studies revealed that the ester derivatives were ineffective MAO inhibitors; however, several chromane-2,4-diones showed promising MAO-B inhibition potencies. The most effective MAO-B inhibitor was compound **133**, with an IC_{50} value of $0.638 \mu\text{M}$. Compound **131** is a reversible MAO-B inhibitor. However, compound **131** was a less potent MAO inhibitor than lazabemide, a reversible MAO-B-specific inhibitor ($IC_{50} = 0.091 \mu\text{M}$), assessed under comparable laboratory conditions. Similar to previously reported C6- and C7-substituted chromones, **135** had a much lower MAO-B-inhibiting potential. Chromones **118–120**, at least one order of magnitude more effective MAO-B inhibitors than **131**, serve as indicators.



Scheme 8. Synthesis of ester- and amino-based chromones.

For example, a group of chromone compounds with C6 and C7 substitutions were shown to be efficient reversible MAO-B inhibitors. These studies have led to the development of effective MAO-B inhibitors, including compounds **118–121**. Although some of these chromones also displayed IC_{50} values for MAO-A inhibition in the nanomolar range, these derivatives were specific inhibitors of the MAO-B isoform.

Intriguingly, chromone substitution at position C5 resulted in modest MAO-B inhibition, in contrast to the C6- and C7-substituted derivatives [55]. Chromone 3-carboxylic acid **122** is an effective and selective MAO-B inhibitor ($IC_{50} = 0.048 \mu\text{M}$), despite that the COOH group being present in location 2 of the 4-pyrone nucleus resulted in a decrease in activity compound **125** [56–58]. Similarly, a phenylcarboxamide substitution at position 3 of the 4-pyrone nucleus resulted in significant MAO-B inhibition, with derivatives **123** and **124** exhibiting IC_{50} values of 0.40 and $0.063 \mu\text{M}$ (Figure 10) [57–59].

Figure 11 illustrates the results of the MAO inhibition experiments. Ester derivatives often exhibit IC_{50} values between 18.6 and $66.7 \mu\text{M}$ and 9.74 and $27.3 \mu\text{M}$, which shows that the ester analogs are poor MAO-A and -B inhibitors, as shown in Figure 11. The benzyl derivative was more effective than the phenyl analog when comparing the potencies of compound **127** (benzyl-substituted) and compound **126** (phenyl-substituted). The MAO inhibitory efficacy increased as the chain lengthened from phenyl to benzyl. A similar phenomenon was observed when the activity of derivative **128** was compared with that of compound **126**. The MAO inhibitory action was enhanced when comparing the 4-chlorophenyl substitution **128** to the phenyl side chain without substitution **126**. A comparison of compound **130** with compound **127** revealed a similar pattern. Compound **130** was a derivative of the 4-chlorobenzyl replacement. The introduction of chlorine had little to no impact on the MAO inhibitory action, as shown by comparing 4-chlorophenyl and 3-chlorophenyl substitutions **128** and **129**. Therefore, it can be deduced that extending the side chain from phenyl to benzyl and adding a Cl atom to position 3 or 4 of the side chain improved the MAO inhibitory activity of the ester analogs.

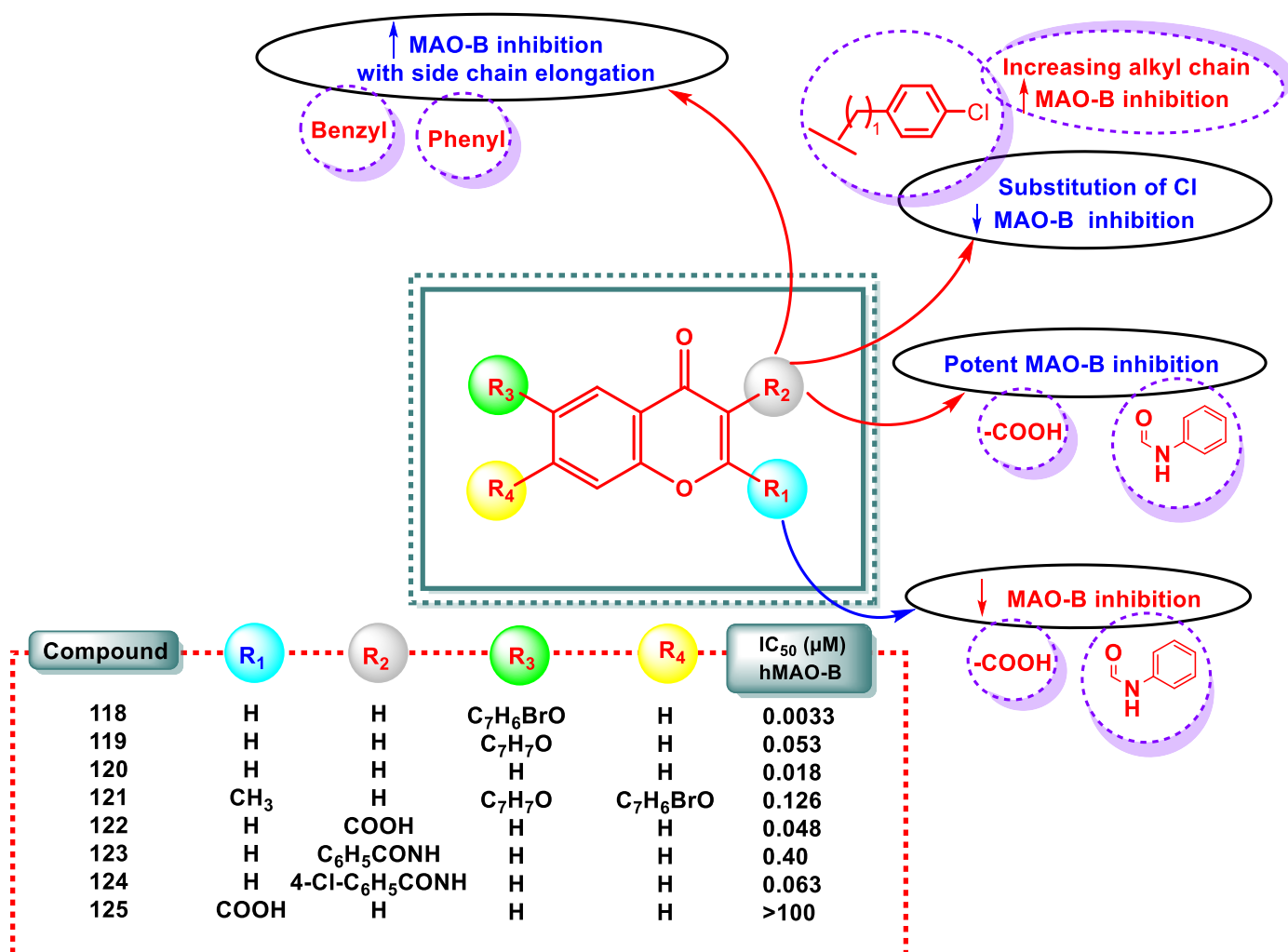


Figure 10. SAR study of chromone derivatives and the inhibition of MAO-B by chromone derivatives 118–125.

Table 2 illustrates that chromane-2,4-diones are specific MAO-B inhibitors, with IC₅₀ values of 0.638–16.66 μM. Compared to ester derivatives, chromane-2,4-diones often have higher MAO-B inhibitory effects. Compound 133, with an IC₅₀ value of 0.638 μM, is the most potent MAO-B inhibitor. Side chain elongation increased with MAO-B inhibition from compounds 132 to 133 (phenyl to benzyl); however, from compounds 134 to 135, as chain elongation increased, MAO-B inhibitory activity decreased. Compounds 136, 137, and 138 did not affect MAO-A or MAO-B, which could be attributed to adding a sterically large chlorine atom. When the MAO inhibitory activities of compounds 132–133 were compared with those of compounds 136–138, it was concluded that Cl substitution decreased the MAO-B inhibitory activity. When comparing the compounds with benzyl/phenyl substitutions to those with pyridyl substitutions, the former showed superior inhibition (Figure 12). Chain elongation from pyridyl 140 to ethyl pyridyl 141 led to a two-fold increase in MAO inhibition compared to compounds with pyridine-containing side chains. The results also demonstrate that chromane-2,4-diones are more effective MAO-B inhibitors than ester chromone analogs, with an IC₅₀ value of 0.638 μM for 133 compared to 14.7 μM for 127. For instance, phenyl-substituted molecule 132 was approximately 28 times more potent than 126. Similarly, the MAO-B inhibitory potencies of chromane-2,4-diones 133 and 137 were much greater than those of their corresponding ester derivatives 127 and 128. The 3-aminomethylidene-2,4-chromandiones are inseparable mixtures of *E*- and *Z*-isomers, and the MAO inhibitory potencies indicated are those of the mixtures, which should be

emphasized. According to a study by Cagide et al., the MAO inhibitory characteristics of four 3-(phenylamino)methylidene chromane-2,4-dione derivatives and chromane-2,4-diones are weak MAO-A inhibitors [59]. These compounds failed to suppress human MAO-A at the highest tested concentration of 10 μM . However, as reported by Cagide et al., the IC_{50} values for **132** (0.268 μM) and **137** (0.065 μM) to inhibit human MAO-B are considerably different from those found in the current study. Although the exact cause of this mismatch is unknown, it could be related to the different experimental methods employed to determine the MAO activity.

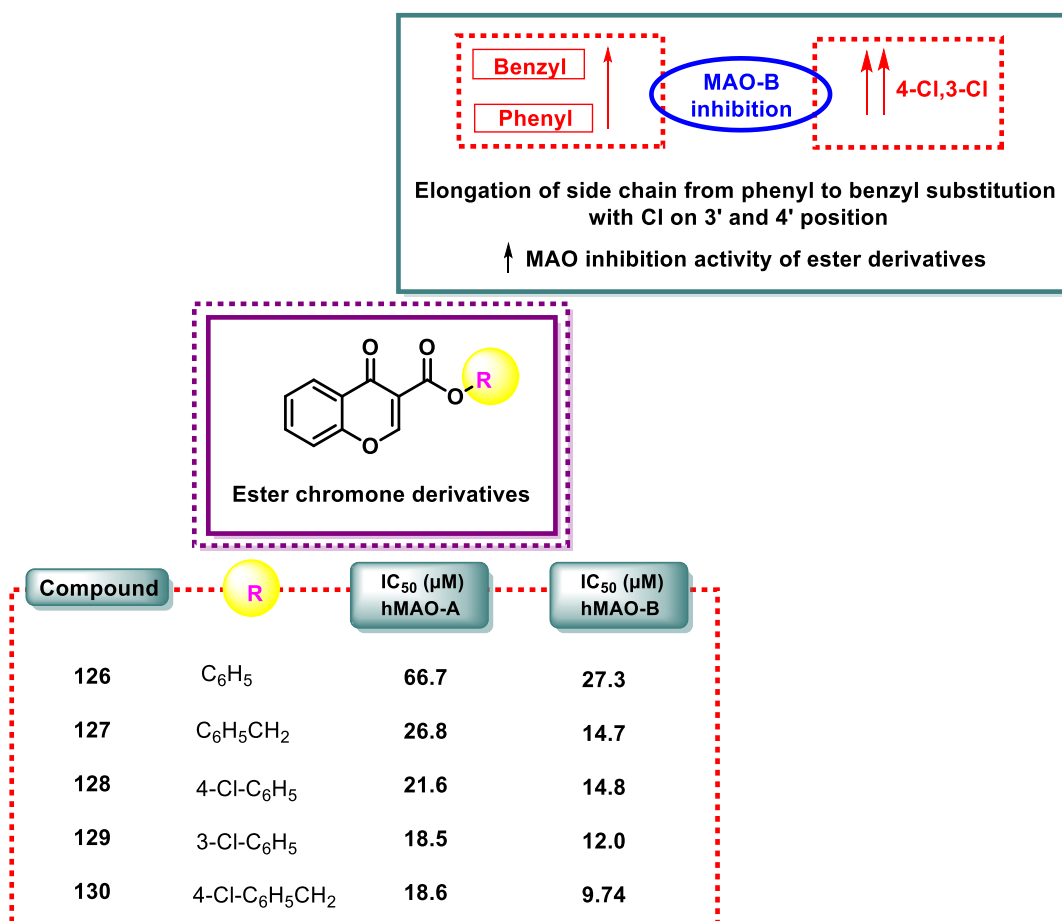


Figure 11. SAR study of ester chromone derivatives **126** and the inhibition of MAO-A and MAO-B.

Table 2. Inhibition of MAO by 3-aminomethylidene-2,4-chromandione derivatives.

Code	R	IC_{50} (μM)	
		MAO-A	MAO-B
132	C_6H_5	79.6	0.947
133	$\text{C}_6\text{H}_5\text{CH}_2$	77.9	0.638
134	$\text{C}_6\text{H}_5(\text{CH}_2)_2$	101	0.897
135	$\text{C}_6\text{H}_5(\text{CH}_2)_3$	312	1.43
136	$\text{C}_6\text{H}_5(\text{CH}_2)_4$	155	142
137	4-Cl- C_6H_5	72.1	3.08
138	4-Cl- $\text{C}_6\text{H}_5\text{cH}_2$	288	NI
139	3-Cl- $\text{C}_6\text{H}_5(\text{CH}_2)_2$	NI	NI
140	$\text{C}_5\text{H}_4\text{N}$	73.1	38.7
141	$\text{C}_5\text{H}_4\text{N}(\text{CH}_2)_2$	41.6	16.66

NI, no inhibition at a maximum tested concentration of 100 μM .

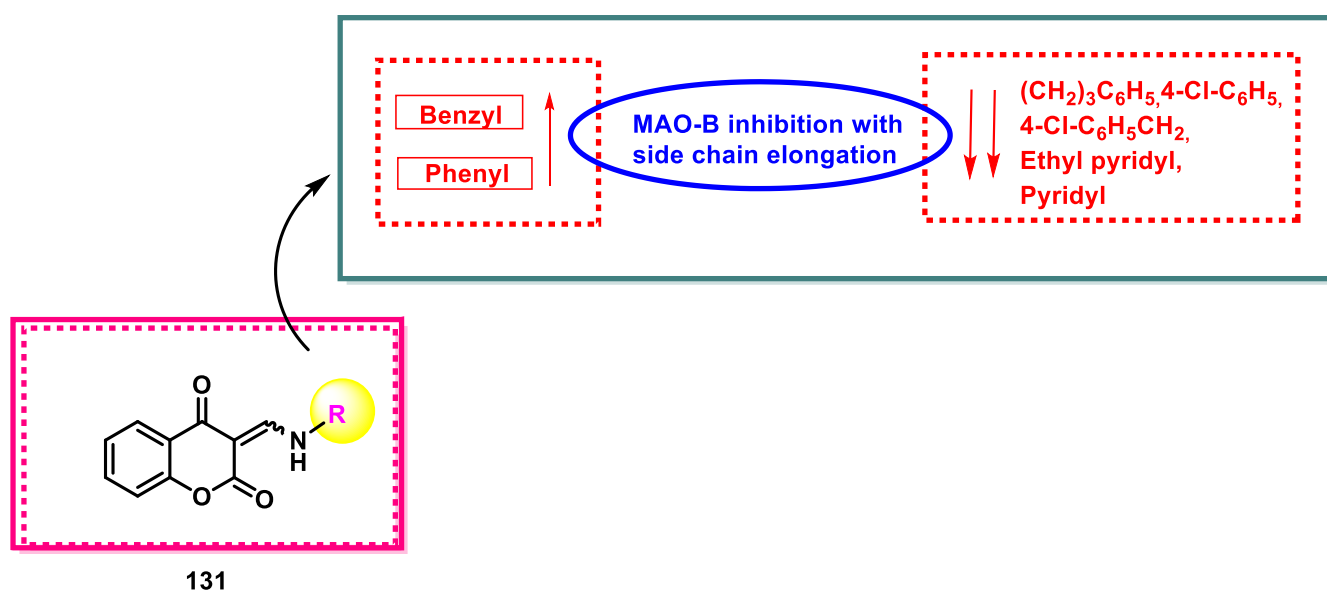


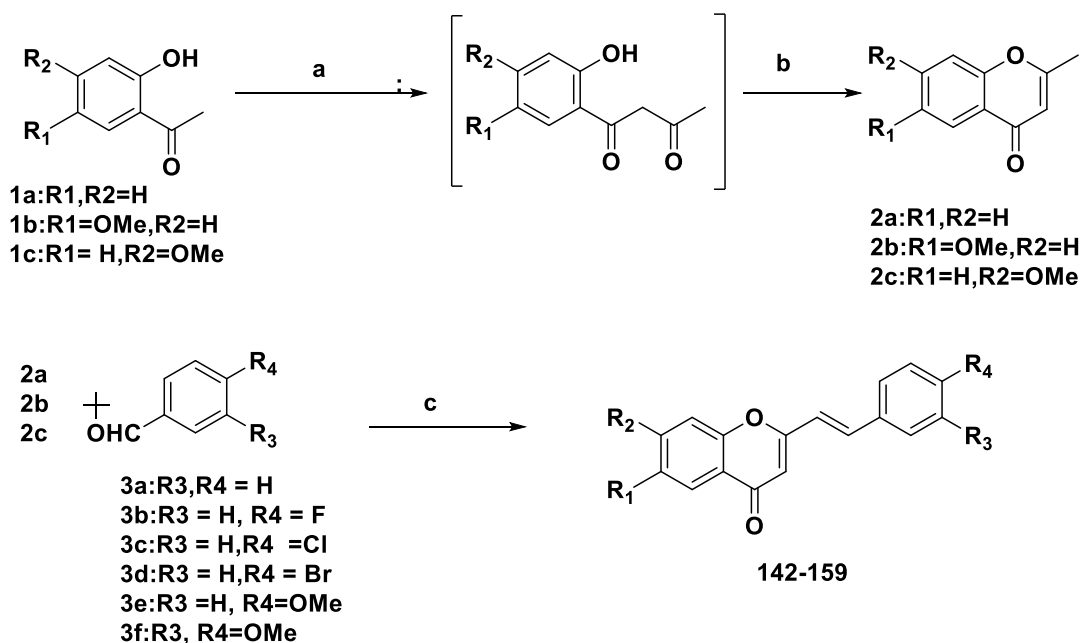
Figure 12. SAR study of 3-aminomethylidene-2,4-chromandiones.

Over the past few decades, in both academic and professional contexts, molecular docking has been frequently used as a quick and affordable approach. There is still no easy and accurate way to quickly identify real ligands among a group of molecules or to precisely pinpoint the right ligand conformation inside the binding pocket of MAO, despite the fact that this discipline has had enough time to consolidate in many ways [60]. Based on the crystal structures of MAO-B in combination with reversible inhibitors, it is possible to predict that chromane-2,4-diones will bind to the active site of their moiety close to FAD, the most polar area. The chromane-2,4-dione moiety forms hydrogen bonds with the water molecules and amino acid residues. The 3-aminomethylidene side chain is intended to fill the entrance cavity, lined mostly with nonpolar residues. Interestingly, the binding positions of the trans- and cis-isomers are comparable. A π - π stacking interaction with Tyr-398 and a π -sulfur interaction with Cys-172 are both seen, despite normal hydrogen bonding (cis isomer). The side chain phenyl ring is stabilized by π -alkyl interactions with Ile-199 and Ile-316, while π alkyl interactions between the chromane-2,4-dione and Leu-171 and Ile198 and Cys-172 (trans-isomer) create the π alkyl interactions. By forming a carbon-hydrogen bond with the benzylic H of the side chain and the C₂ carbonyl oxygen of chromane-2,4-dione, Ile-199 becomes even more significant. The phenolic oxygen of Tyr-326 additionally forms a carbon-hydrogen bond with benzylic H. Both isomers of **132** can bind to and interact with MAO-B; according to this analysis, the binding mechanisms and interactions are relatively comparable. Thus, both isomers are involved in MAO-B inhibition.

Takao et al. synthesized and assessed the MAO-A and MAO-B inhibitory properties of 18 2-styrylchromone derivatives [61]. In the prepared series, compound **150** had the greatest MAO-B inhibitory capacity and specificity with an $-\text{OCH}_3$ substitution at R1 and a Cl substitution at R4. Compound **150** inhibited MAO-B competitively and reversibly. They used the pIC_{50} values of 2-styrylchromone derivatives to perform quantitative structure-activity relationship (QSAR) studies using the molecular operating environment (MOE) and dragon, which revealed significant relationships ($p < 0.05$). Through 3D-QSAR investigations using AutoGPA, based on a molecular field analysis method using MOE, 2-styrylchromone structures were investigated as valuable scaffolds. Based on these findings, the 2-styrylchromone moiety may be a good building block for novel MAO-B antagonists.

Scheme 9 explains the synthesis of the 2-styrylchromone derivatives involved in the reaction of acetophenone derivatives with ethyl acetate, followed by intramolecular

cyclization. The generated Iia–Iic then interacted with benzaldehyde derivatives IIIa–f in the presence of a base.



Reagents and conditions: (a) Na, AcOEt, rt; (b) conc. HCl, MeOH, rt; (c) NaOMe, MeOH, reflux.

Scheme 9. Synthesis of 2-styrylchromone derivatives.

The inhibitory effects of 2-styrylchromone compounds 142–159 (Table 3) on MAO (A and B) were assessed. Modifications to R₃ and R₄ phenyl rings and R₁ and R₂ chromone rings showed several intriguing structure–activity relationships, as shown in Figure 13. We discovered that these compounds had inhibitory effects on MAO-A.

Table 3. Inhibition of MAO by 2-styryl chromone derivatives.

Compound	R ¹	R ²	R ³	R ⁴	TC ₅₀ (μM) MAO-A	IC ₅₀ (μM) MAO-B
142	H	H	H	H	0.95	0.24
143	H	H	H	F	0.59	0.17
144	H	H	H	Cl	0.29	0.079
145	H	H	H	Br	0.33	0.069
146	H	H	H	OMe	2.3	0.049
147	H	H	OMe	OMe	25	2.8
148	OMe	H	H	H	0.20	0.18
149	OMe	H	H	F	0.12	0.064
150	OMe	H	H	Cl	26	0.017
151	OMe	H	H	Br	0.53	0.024
152	OMe	H	H	OMe	0.21	0.19
153	OMe	H	OMe	OMe	21	0.68
154	H	OMe	H	H	26	0.22
155	H	OMe	H	F	35	0.12
156	H	OMe	H	Cl	>100	0.27
157	H	OMe	H	Br	>100	0.45
158	H	OMe	H	OMe	72	1.4
159	H	OMe	OMe	OMe	>100	10

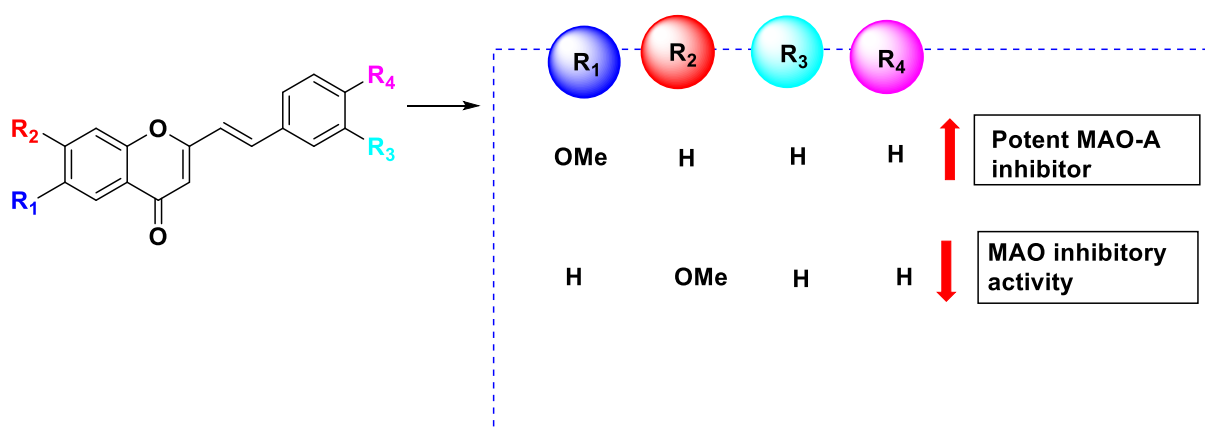


Figure 13. SAR study of 2-styrylchromone derivatives.

Compounds **142–146** and **148–151** displayed inhibitory activity, with compound **151** showing the most effective inhibition of MAO-A. Except for compound **144** vs. **150**, adding a methoxy substituent at R₁ appeared to increase the MAO-A-inhibiting properties of compounds **142** vs. **147**, **143** vs. **149**, **145** vs. **151**, and **146** vs. **152**. All MAO-A inhibitory activities, including those of compounds **142** vs. **154**, **143** vs. **155**, **144** vs. **153**, **145** vs. **157**, **146** vs. **158**, and **147** vs. **159**, were reduced when the –OCH₃ group was at position R₂. The ability of the derivatives to inhibit MAO-B was assessed, and it was found that all derivatives inhibited MAO-B more potently than MAO-A. The most effective inhibitor was compound **150**, which showed inhibitory activity nearly 13 times greater than that of pargyline, used as a positive control. Compared to pargyline, compounds **144–146**, **149**, and **151** exhibited more potent inhibition, while compounds **142**, **143**, **148**, and **152–157** displayed comparable inhibition. Additionally, **146** vs. **152**, **143** vs. **149**, **144** vs. **150**, **145** vs. **151**, and **147** vs. **153** appeared to have stronger MAO-B inhibitory effects when the methoxy group at position R₁ was substituted. Furthermore, compounds **156**, **157**, **158**, and **159** exhibited reduced MAO-B inhibitory effects when the methoxy group at position R₂ was replaced.

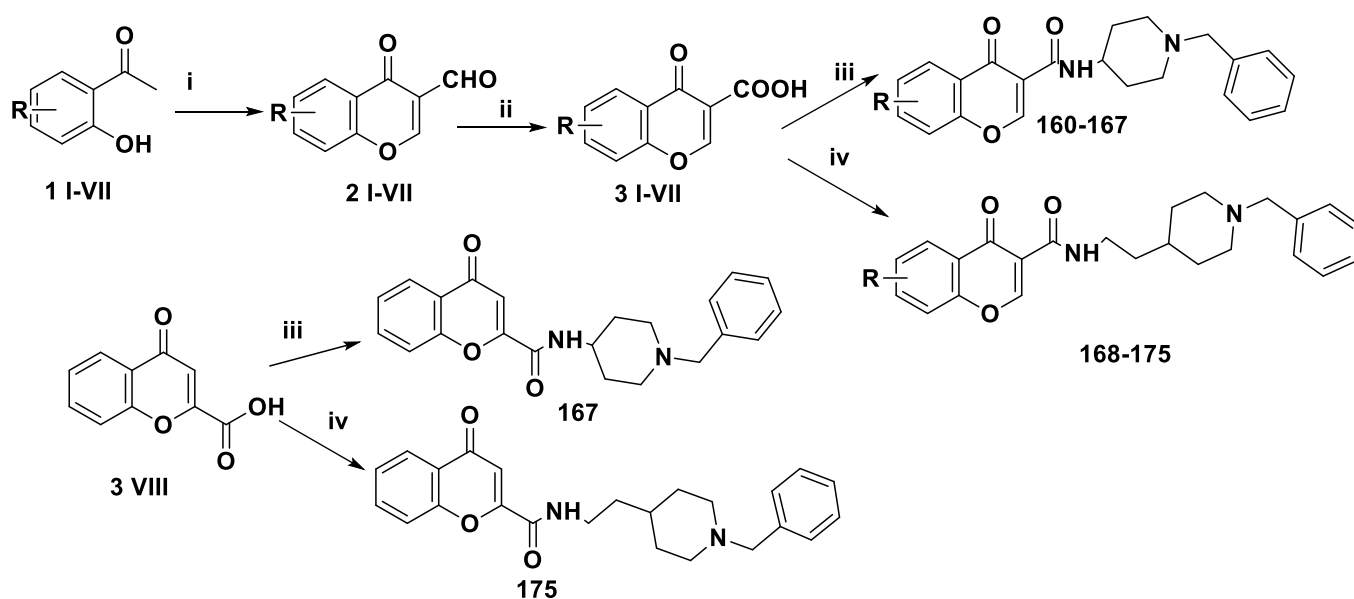
Derivatives of 2-styrylchromone demonstrated strong and selective MAO-B blocking effects. The computational analysis of the statistical significance ($p < 0.05$) of each substituted group revealed that the methoxy substitution at position R₂ substantially influenced both the selectivity and MAO-B blocking activity.

Wang et al. developed several donepezil-chromone hybrids **160–167** and **168–175** (Table 4) and tested their biological activity, including MAO inhibition and central nervous system penetration in vitro [62]. Molecular modeling studies were also conducted to evaluate the novel hybrid compounds' interaction mechanism, structure–activity connections, and binding strategy.

Scheme 10 shows the formation of donepezil-chromone hybrids **160–167** and **168–175**; they were prepared by treating 2-hydroxyacetophenone with phosphorus oxychloride (DMF) by a modified Harnisch procedure that resulted in the formation of 3-formylchromones, followed by oxidation with sulfamic acid and sodium chlorite to obtain the appropriate 4-oxo-4H-chromene-3-carboxylic acids, which were then treated with acetyl chloride and a catalytic amount of DMF in CH₂Cl₂ to produce acyl chloride and react with 1-benzylpiperidin-4-amine or 2-(1-benzylpiperidin-4-yl)ethanamine in CH₂Cl₂, resulting in the target compounds.

Table 4. Inhibitory activity of donepezil-chromone hybrids.

Compound	R	hMAO-A	hMAO-B
		IC ₅₀ (μM)	IC ₅₀ (μM)
160	H	63.8	17.68
161	6-OCH ₃	7.5	46.27
162	6-OBn	11.6	0.035
163	6-CH ₃	48.1	19.46
164	6-Br	35.5	22.82
165	7-OCH ₃	37.4	28.64
166	7-Br	31.6	19.73
167	H	29.7	33.29
168	H	68.6	35.29
169	6-OCH ₃	72.4	11.23
170	6-OBn	67.2	0.272
171	6-CH ₃	30.6	52.45
172	6-Br	48.2	26.13
173	7-OCH ₃	32.4	30.93
174	7-Br	30.3	29.46
175	H	29.5	20.03



Scheme 10. Synthesis of donepezil-chromone hybrids **160–167** and **168–175**. Reagent and condition, (i) POCl₃, DMF, 0 °C, 2 h; (ii) NaClO₂, NH₂HSO₃, CH₂Cl₂, 0 °C, 3 h; (iii) thionyl chloride, reflux; 1-benzylpiperidin-4-amine, K₂CO₃, CH₂Cl₂, rt, 8 h; (iv) thionyl chloride, reflux; 2-(1-benzylpiperidin-4-yl)ethanamine, K₂CO₃, CH₂Cl₂, rt, 8 h.

According to the SAR (Figure 14), hybrids containing a benzyloxy substitution at the sixth position of the chromone were more prone to have an inhibitory effect on hMAO-B. In particular, compound **162**, which had a benzyloxy substitution at C6 of the chromone, demonstrated the greatest inhibition with an IC₅₀ value of 0.035 μM, demonstrating an activity that was nearly three and 200 times more than that of the standards pargyline and iproniazid, respectively. All other analogs produced less activity when other groups were added instead of the benzyloxy substitution. Compound **171**, which contained a methyl substitution at the same position, exhibited the weakest performance. Additionally, there was a strong correlation between the alkylene chain length and MAO-B inhibitory efficacy. Compound **170**, an excellent MAO-B inhibitor, had an N-ethylcarboxamide connection between the chromone and benzylpiperidine. This compound had an IC₅₀ value of 0.272 μM and was 7.8 times less effective than its counterpart, compound **162**, with a car-

boxamide linker. These findings suggest that steric parameters affect the inhibitory effects of hMAO-B. Compound **170**, which showed the most balanced ability to selectively block MAO-B based on the findings of MAO inhibitory activity, is thought to be an appealing multi-purpose blocker for future research.

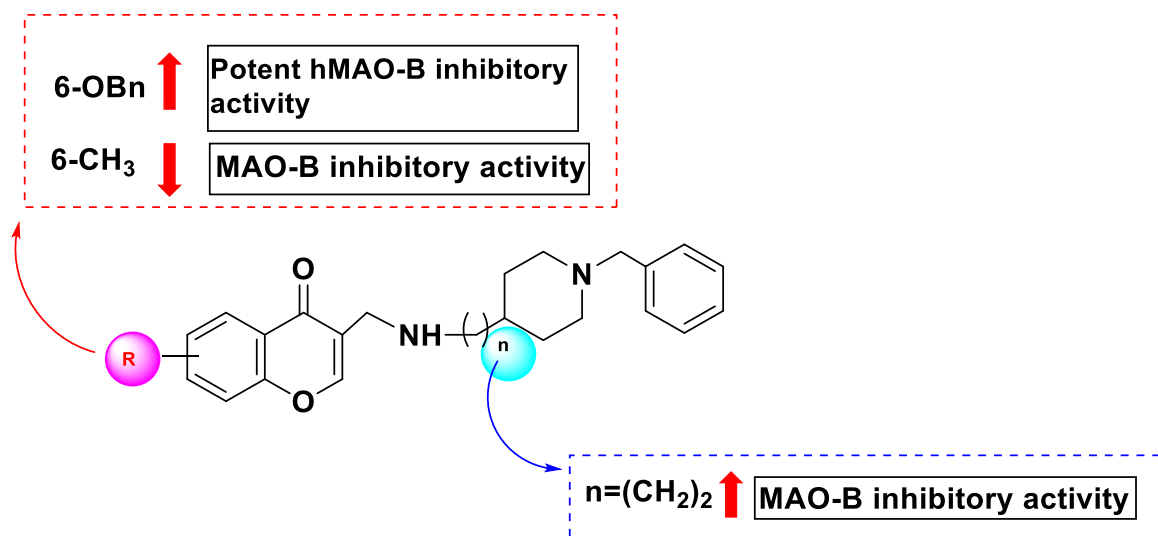


Figure 14. SAR of donepezil and chromone hybrids.

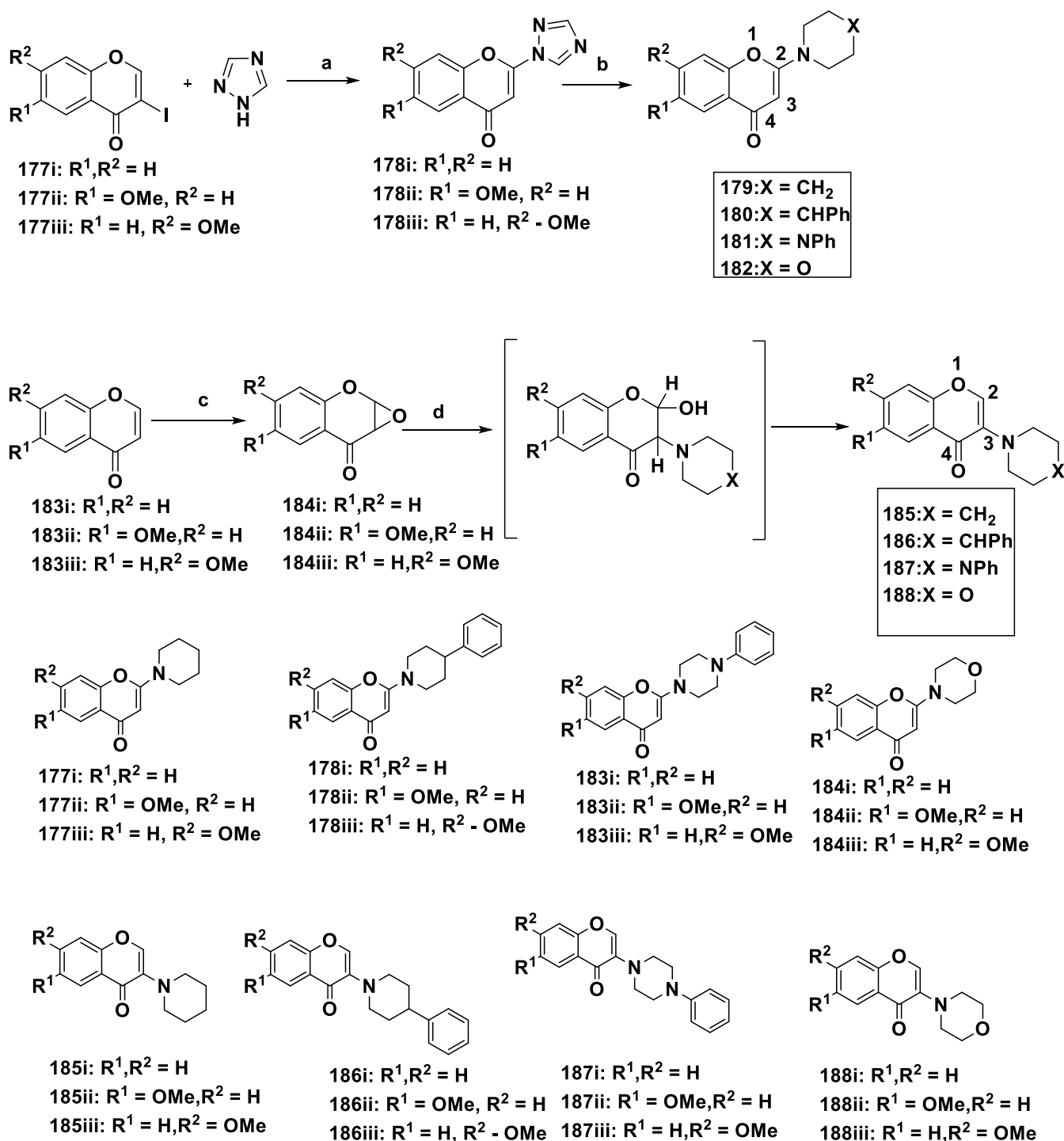
They assessed the ability of these hybrids to penetrate the BBB because brain crossing is a requirement for efficient anti-AD drugs. Di et al. developed an artificial membrane permeability test for the BBB (PAMPA-BBB) to achieve this. The three most efficient compounds (**162**, **169**, and **170**) were chosen as candidates to investigate the possible toxicological effects on rat pheochromocytoma (PC12) cells and the potential for therapy with these derivatives. Compound **170**, which had high MAO-B selectivity, was the most intriguing variant of the generated compounds. Compound **170** crossed the BBB and demonstrated minimal cell toxicity when tested in vitro on rat pheochromocytoma (PC12) cells. Overall, the multifunctional ligand **170**, which possesses balanced MAO-B inhibitory activities, may be considered a potential anti-AD target for future studies.

In the substrate cavity of the enzyme, the chromone moiety of compound **170** is located adjacent to the FAD cofactor. Its benzyloxy substitution interacts with Tyr435 and Tyr398 via π - π stacking interactions. Tyr326 interacted with the amide carbonyl of compound **172** via a hydrogen bond. In contrast, the benzylpiperidine moiety of compound **172** resides in the hydrophobic pocket formed by Pro102, Leu88, Ser200, Gly101, Glu84, Thr201, Ile199, and Ile316 in the entrance cavity. Additionally, Glu84 and the quaternary nitrogen present in piperidine form hydrogen bonds.

Takao et al. (2020) synthesized a collection of 2- and 3-(N-cyclicamino) chromone compounds and investigated their inhibitory activities against MAO [63]. Among the derivatives tested, including safinamide, which was employed as the control substance, compound **187iii**, 7-methoxy-3-(4-phenyl-1-piperazinyl)-4H-1-benzopyran-4-one, demonstrated a major antagonistic action, demonstrated the largest specificity towards MAO-B, and functioned reversibly and competitively. These findings implied that the lead substances for MAO-B inhibitory studies could be 3-(N-cyclicamino) chromone derivatives.

The formation of 2- and 3-(N-cyclic amino) chromone analogs is shown in Scheme 11. When 3-iodochromone derivatives **177i–iii** were treated along with 1,2,4-triazole in the presence of K_2CO_3 , DMF at 80 °C, it resulted in the generation of 2-(1,2,4-triazolyl)-chromone variants **178i–iii**, which then underwent a substitution reaction by interacting with the corresponding cyclic amine (DMF at 80 °C), forming the compounds of interest. Next, 3-(N-cyclicamino) chromone variants **185–188** were generated by the epoxidation of chromone derivatives **183i–iii** using an aqueous H_2O_2 solution under basic conditions to obtain 2,3-

epoxychromone derivatives **184i–iii**, which reacted with the corresponding cyclic amine to form the target compounds (Table 5).



Scheme 11. Synthesis of 2- or 3-(N-cyclic amino) chromone derivatives: (a) K_2CO_3 , DMF, and at $80\text{ }^\circ\text{C}$; (b) cyclic amine, DMF, and at $80\text{ }^\circ\text{C}$; (c) H_2O_2 , $PhCH_2N^+(CH_3)_3OH^-$, Et_2O , and at $0\text{ }^\circ\text{C}$; and (d) cyclic amine, CH_3CN , rt.

Table 5. Inhibition of MAO by 2- or 3-(N-cyclic amino)chromone derivatives.

Compound	R ₁	R ₂	IC ₅₀ (μM)	
			MAO-A	MAO-B
2-(N-Cyclic amino)chromone				
177i	H	H	38	59
177ii	OMe	H	16	27
177iii	H	OMe	57	36
178i	H	H	31	22
178ii	OMe	H	4.1	5.6
178iii	H	OMe	8.8	7.4
183i	H	H	38	22
183ii	OMe	H	2.6	2.8
183iii	H	OMe	59	12
184i	H	H	66	58
184ii	OMe	H	36	40
184iii	H	OMe	34	31
3-(N-Cyclic amino)chromone				
185i	H	H	23	2.0
185ii	OMe	H	23	0.99
185iii	H	OMe	18	14
186i	H	H	>100	1.5
186ii	OMe	H	>100	>100
186iii	H	OMe	>100	0.25
187i	H	H	>100	0.72
187ii	OMe	H	>100	>100
187iii	H	OMe	>100	0.015
188i	H	H	57	23
188ii	OMe	H	34	8.0
188iii	H	OMe	25	7.3

Compounds **178ii**, **179iii**, and **183ii** displayed equivalent IC₅₀ concentrations for MAO-B and mildly inhibited MAO-A and MAO-B. Due to the smaller site action of MAO-A compared to MAO-B, compounds **186** and **187** did not show any inhibiting effects against MAO-A at a concentration of 100 μM. The derivatives **186i**, **186iii**, **187i**, and **187iii** effectively and selectively inhibited MAO-B. Compounds **185i**, **188ii**, and **188iii** moderately inhibited MAO-B. The most effective inhibition and MAO-B specificity were observed for compound **187iii**. Safinamide used as a positive control, and it was nearly three times more effective than compound **188iii** when its efficacy and selectivity were examined. Except for compounds **186ii** and **187ii**, the 3-(N-cyclic amino) chromone derivatives specifically inhibited MAO-B, whereas the 2-(N-cyclic amino) chromone derivatives did not. The current findings clearly distinguish the two sets of compounds, which is in line with earlier studies on chromone carboxylic acids and related amides, as well as the latest studies on the MAO-inhibitory activities of flavones (chrysin) and isoflavones (genistein). These results revealed that substitutions on the chromone ring at position 3 enhance the MAO-B inhibitory activity. According to the findings for compounds **186** and **187**, a significant SAR (Figure 15), the methoxy group present at position 6 (R¹) or 7 (R²) of the chromone ring was the difference between compounds **186ii** or **187ii** and **186iii** or **187iii**, respectively, in the selective blocking of MAO-B. This indicates that incorporating a methoxy group at position 6, as in compounds **186ii** or **187ii**, caused MAO-B to be removed from the active site.

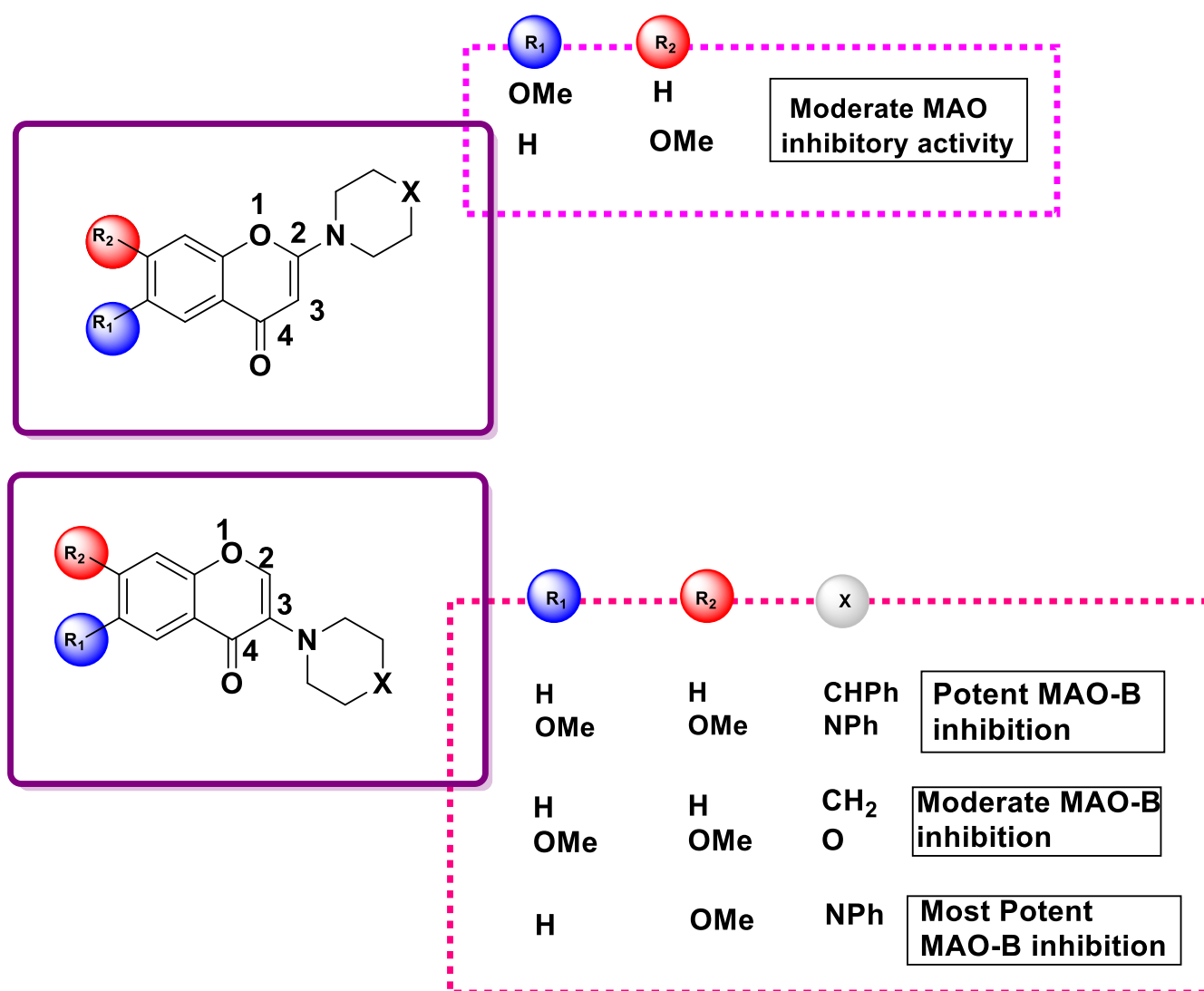


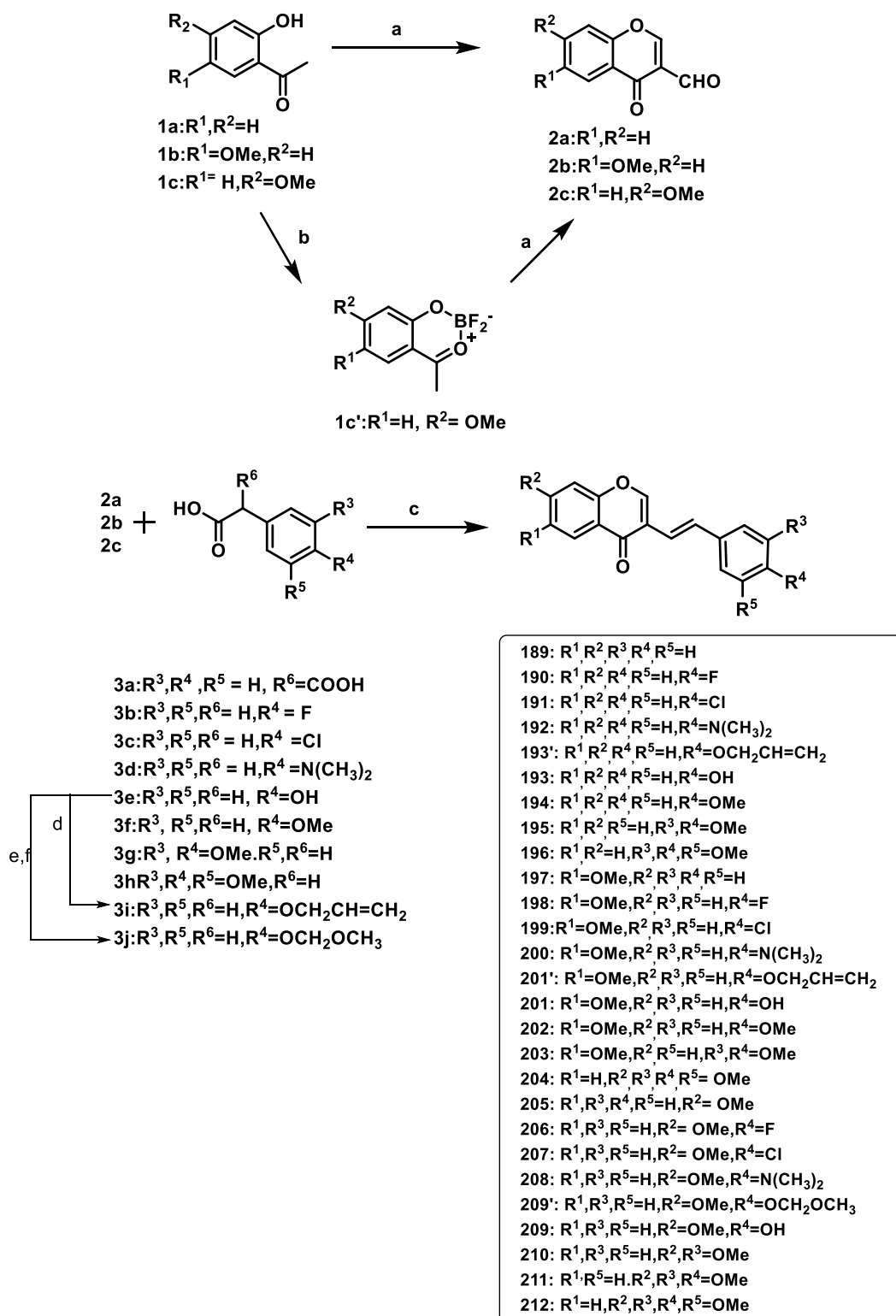
Figure 15. SAR of 2- and 3-(N-cyclic amino chromone derivatives).

In contrast, a methoxy substitution at C₇, as in compounds **186iii** or **187iii**, led to close binding at the active site. Therefore, compounds **185i** and **186i**, which lack a methoxy group, were expected to exhibit moderate MAO-B inhibition. These results are consistent with their previous analysis of the impact of -OCH₃ replacement on the chromone ring, which showed that diagonal substitutions on the chromone ring increased the MAO-B inhibitory action.

Takao et al. (2021) examined MAO-A and MAO-B inhibitory activities of several 3-styrylchromone derivatives [64]. Most derivatives inhibited MAO-B, except for compound **209**, which had an OH group at position 4 and a methoxy substitution at position 2 in its chemical structure. The chlorine atoms were located at positions 4 and 2 on the phenyl and chromone rings **207**. It efficiently inhibited MAO-B, with an IC₅₀ level of 2.2 μM. Derivative **189** showed the highest MAO-B selectivity, with a selectivity index > 3700. Compounds **189** and **207** were found to be mixed-type, reversible MAO-B blockers, suggesting that tight-binding blocking of MAO-B may be part of their mechanism of action.

As shown in Scheme 12, to create 3-styrylchromone derivatives **190–213**, various phenylacetic acid/phenylmalonic acid variants were combined with 3-formylchromone derivatives **IIa–c**. The condensation of 3-formylchromone compounds and protected 4-hydroxyphenylacetic acids **IIIi** and **IIIj**, followed by the removal of the protective group,

produced 3-styrylchromones with hydroxy groups 193, 201, and 209. Acceptable yields were obtained in all cases. The Vilsmeier–Hack reagent converted 2-hydroxyacetophenone derivatives 1a–c to 3-formylchromone derivatives 2a–c.



Scheme 12. Synthesis of 3-styrylchromone derivatives. Reagents and conditions: (a) DMF/POCl₃; (b) (CH₃CO)₂O/BF₃·O(C₂H₅)₂; (c) tert-BuOK, dry pyridine, reflux; (d) allylbromide, K₂CO₃, EtOH, and then KOH; (e) conc. H₂SO₄, MeOH, reflux; (f) chloromethyl methyl ether, K₂CO₃, acetone, reflux, and then KOH, MeOH–H₂O.

Chromone (4H-1-benzopyran-4-one) derivatives, which are extensively present in natural substances, including 2-styrylchromones, isoflavones, and flavones, are an important category of oxygenated heterocyclic compounds employed in the discovery of drugs. Researchers have developed several novel chromone compounds, such as 2-azoylchromone, 2-styrylchromone, and 3-styrylchromene, and tested their ability to inhibit MAO based on the observations of MAO inhibition by synthetic chromone derivatives. They also provided data on the production and MAO-blocking properties of 2- and 3-cyclicaminochromone analogs. Compared to 2-cyclicaminochromone derivatives, 3-cyclicaminochromone derivatives inhibited MAO-B more effectively. These outcomes led them to explore 3-styrylchromone derivatives comprising recently produced compounds for their MAO-B antagonistic action. This paper describes the synthesis of many 3-styrylchromone variants (Scheme 12) and their inhibitory actions on human MAO-A and MAO-B.

The inhibitory actions of MAO-A and MAO-B were tested on all the synthetic 3-styrylchromone derivatives **189–212**, as shown in Figure 16. Structure–activity connections were discovered by studying the impact of the substituent on the phenyl ring at positions R_3 , R_4 , and R_5 , the effects on the chromone ring at positions R_1 and R_2 , and their effects on MAO inhibitory activity.

The 3-styrylchromone derivatives **190**, **191**, **198**, **205**, and **208** had IC_{50} values for MAO-A below 1 μ M. In contrast, compounds **206**, **207**, **209**, and **210** had IC_{50} values below 0.1 μ M, showing that adding a substituent at position R_2 as well as position R_4 was successful in MAO-A inhibition. Derivatives **207** and **209** strongly inhibited MAO-A, with IC_{50} values of **25** and **22**, respectively, compared to the positive control clorgyline, which had an IC_{50} value of 4.9 μ M. Except for compound **209**, all tested 3-styrylchromone derivatives had much lower IC_{50} values for MAO-B than for MAO-A. Compounds **206** and **207** showed significantly low IC_{50} values for MAO-B, with 3.1 and 2.2 μ M, respectively, when contrasted with safinamide, which was a positive reference. This demonstrates the potential benefit of inhibiting MAO by substituting positions R_2 and R_4 .

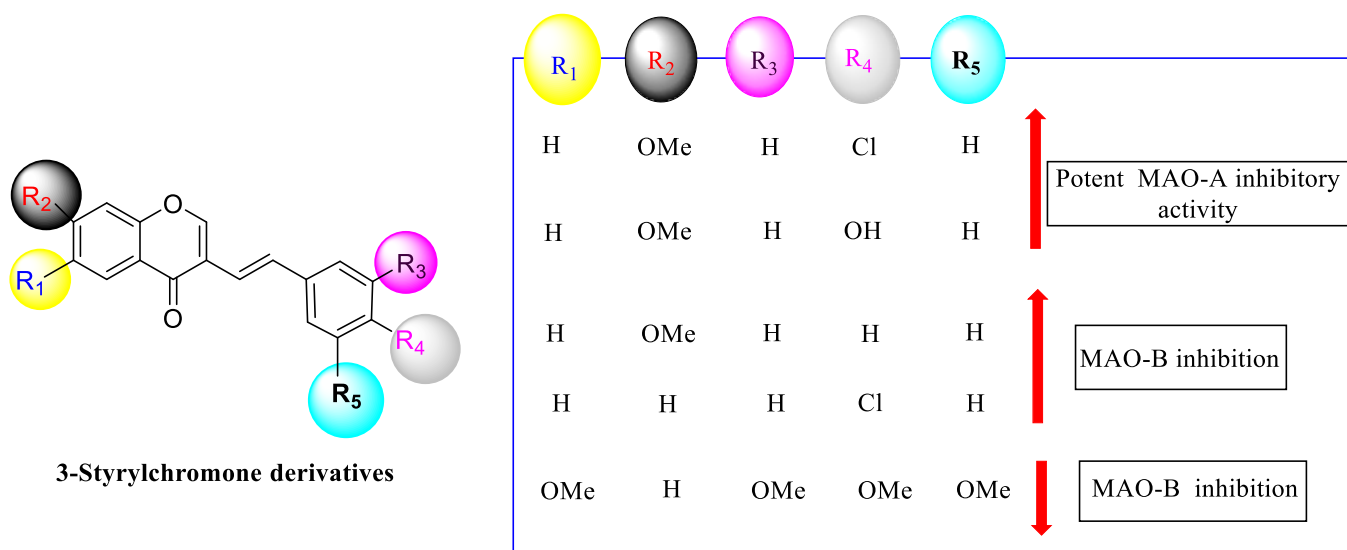


Figure 16. Cont.

Compound	R ₁	R ₂	R ₃	R ₄	R ₅	MAO-A IC ₅₀ (μM)	MAO-B IC ₅₀ (μM)
189	H	H	H	H	H	>100	0.027
190	H	H	H	F	H	0.62	0.0086
191	H	H	H	Cl	H	0.39	0.0059
192	H	H	H	N(CH ₃) ₂	H	42	0.048
193	H	H	H	OH	H	2.6	0.037
194	H	H	H	OMe	H	>100	0.029
195	H	H	OMe	OMe	H	33	0.16
196	H	H	OMe	OMe	OMe	67	0.23
197	OMe	H	H	H	H	2.5	0.075
198	OMe	H	H	F	H	0.38	0.034
199	OMe	H	H	Cl	H	4.1	0.028
200	OMe	H	H	N(CH ₃) ₂	H	59	0.23
201	OMe	H	H	OH	H	8.7	0.33
202	OMe	H	H	OMe	H	35	0.15
203	OMe	H	OMe	OMe	H	61	0.80
204	OMe	H	OMe	OMe	OMe	>100	2.5
205	H	OMe	H	H	H	0.12	0.016
206	H	OMe	H	F	H	0.041	0.0031
207	H	OMe	H	Cl	H	0.025	0.0022
208	H	OMe	H	N(CH ₃) ₂	H	0.49	0.0061
209	H	OMe	H	OH	H	0.022	0.047
210	H	OMe	H	OMe	H	0.069	0.0068
211	H	OMe	OMe	OMe	H	19	0.033
212	H	OMe	OMe	OMe	OMe	7.3	0.021

Figure 16. IC₅₀ values of 3-styryl chromone derivatives for the inhibition of MAO-A and MAO-B.

4. The Role of 3-Styryl Chromones' Substituents in Inhibiting MAO-B

MAO-B was significantly inhibited by methoxy substitutions at positions R₁, R₂, or R₃. A comparison was made between the pIC₅₀ values of compounds with hydrogen and those of analogs with methoxy substitutions at positions R₁, R₂, or R₃. The results showed that the OCH₃ groups at positions R₁ and R₃ reduced MAO-B inhibition, whereas the methoxy groups at position R₂ boosted it. The substituent at position R₄ tends to increase the MAO-B inhibitory activity, which is also true for position R₄ chloride. Compounds 196, 204, and 212 with substituents at position R₅ appeared to reduce inhibitory activity. According to Takao et al., the phenyl rings of 2-styrylchromone and 3-styrylchromone were strengthened by adding chlorine, which improved their capacity to inhibit MAO-B.

Zhang et al. developed, synthesized, and assessed several chromone-hydroxypyridinone hybrids (Table 6) as potential multimodal anti-AD ligands [65]. Compound 216 exhibited selective hMAO-B inhibitory activity, with an IC₅₀ value of 67.02 nM. Derivative 216 considerably improved scopolamine-induced cognitive impairment in AD mice by crossing the BBB.

Table 6. Inhibitory activity of chromone derivatives against MAO-B.

Compound	R	IC ₅₀ (μM) hMAO-B
213	H	0.0672
214	7-methyl	0.0827
215	6-methyl	0.0863
216	7-methoxy	0.0670
217	6-methoxy	0.0886
Pargyline		0.1113

The most promising chromone derivatives, with IC_{50} concentrations ranging from 0.067 to 0.088 μM , were modified by alkyl groups at C-6 or C-7 of the chromone nucleus (Figure 17). Compared to the reference medication (pargyline), compound 216 showed the strongest inhibitory action.

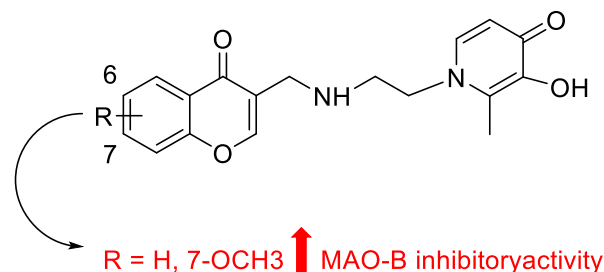


Figure 17. SAR study of chromone derivatives.

5. Conclusions

PD therapy was the indication for when MAO-B inhibitors were first made available, and they are still a frequently prescribed cornerstone of therapy. Although not conclusive, the pre- and post-clinical evidence in support of a neuroprotective and disease-modifying effect for MAO-B inhibitors is unmatched by any other class of antiparkinsonian drugs to date. An additional reason to begin using MAO-B inhibitors early in the course of the disease and to keep using them over the long term is the potential that they may reduce the progression of PD. New medicines having MAO-B inhibitory as well as non-dopaminergic activity are still being developed and tested due to the potential of neuroprotection. Considering the limited number of MAO-B blockers currently approved for clinical application, many research projects have focused on developing new MAO-B blockers with greater efficacy. This review focused on the effects of various chromone ring substituents on MAO-B inhibition. The inhibitory effect of MAO-B on chromones has been explored in a small number of studies. Chromone is a MAO-B antagonist. The following is a summary of the SARs for the inhibition of MAO-B by chromone classes:

- The methyl group at the R_4 position of chromone was shown to be a beneficial substitution.
- The R_4 position of the chromone with a bromine group demonstrated a large increase in MAO inhibition and fluorine substitution at R_2 of the phenyl ring.
- NO_2 and CH_3 groups in R_3 decreased MAO activity, whereas the electronegative halogens chlorine and fluorine caused a marked increase in activity.
- Electronegative groups, such as Cl and F substitutions at the para position of styryl chromones, demonstrated higher MAO-B inhibition, as seen in the cases of compounds 207 and 206.
- The amino chromone derivatives exhibited more powerful MAO-B inhibition than the ester derivatives 126 and 131. As demonstrated for compounds 131 and 132, phenyl-to-benzyl chain elongation increased MAO-B inhibition, but further chain elongation diminished activity, as seen for compound 135. The inhibition of MAO-B was reduced by compounds containing pyridyl side chains.
- Derivatives with meta substituents on the exocyclic ring showed increased potency.
- In the future perspective of view, researchers could modify and extend the alkyl chains at the R_1 and R_5 positions of the chromone ring to develop potent MAO-B inhibitors. The introduction of heterocyclic-based amide on the C-3 position of chromone was not explored so far for the development of MAO-B inhibition. This information will be beneficial for discovering and creating a novel category of powerful and specific MAO-B blockers based on chromones.

Author Contributions: Conceptualization, B.M. and H.K.; writing—original draft preparation, R.S.I., F.B., J.J., A.M., S.K. and S.T.S.; review and editing, G.G. and P.G.; supervision, H.K. and B.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used, analyzed, and reviewed were collected from the corresponding authors and online research databases.

Conflicts of Interest: The authors declare no conflict of interest.

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