

# Docking Studies of Recently Synthesized MAO-B Inhibitors

Subjects: **Pharmacology & Pharmacy**

Contributor: Emilio Mateev , Maya Georgieva , Alexandrina Mateeva , Alexander Zlatkov , Shaban Ahmad , Khalid Raza , Vasco Azevedo , Debmalya Barh

With the significant growth of patients suffering from neurodegenerative diseases (NDs), novel classes of compounds targeting monoamine oxidase type B (MAO-B) are promptly emerging as distinguished structures for the treatment of the latter. As a promising function of computer-aided drug design (CADD), structure-based virtual screening (SBVS) is being heavily applied in processes of drug discovery and development. The utilization of molecular docking, as a helping tool for SBVS, is providing essential data about the poses and the occurring interactions between ligands and target molecules.

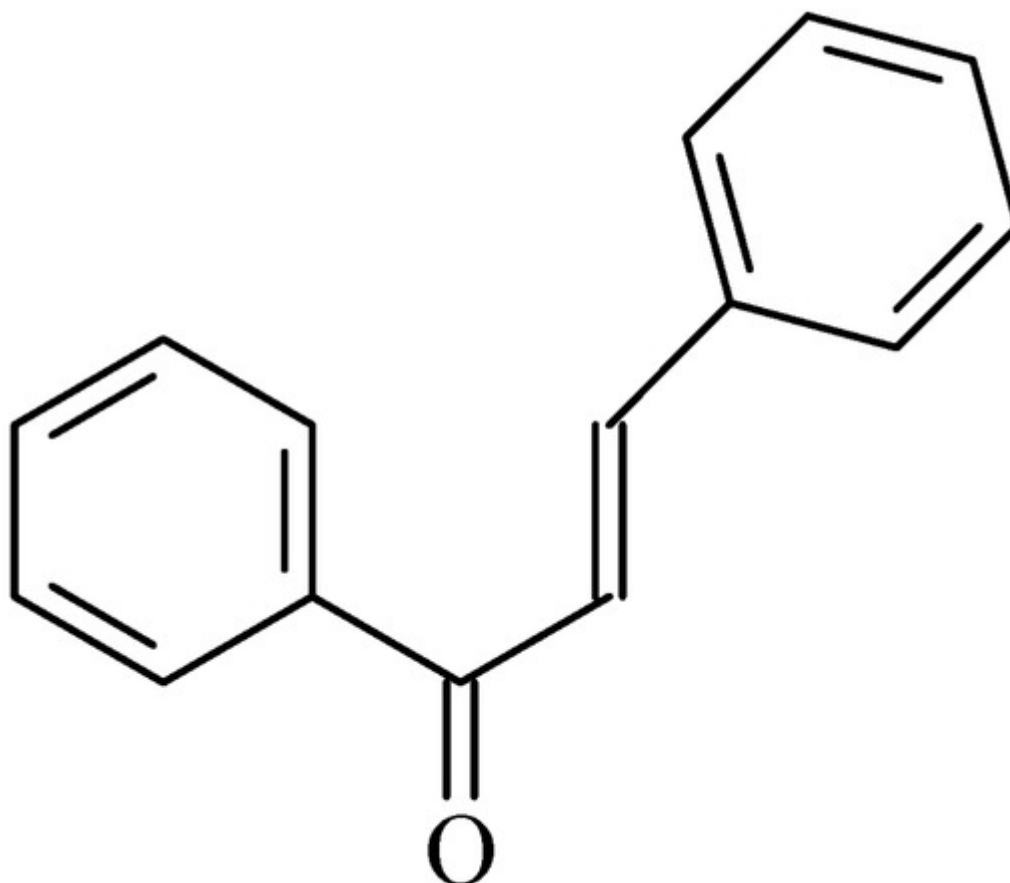
molecular docking

structure-based drug design

MAO-B inhibitors

## 1. Chalcones

Chalcone-based compounds (**Figure 1**) have various therapeutic applications considering the diverse pharmacological targets they could affect <sup>[1]</sup>. Recently, the design and synthesis of MAO-B inhibitors containing a chalcone scaffold have rapidly been growing <sup>[2]</sup>. A major scientific effort in that area has been achieved by Bijo Mathew, confirmed by his involvement in numerous published papers concerning the MAO-B activity of chalcone derivatives. Various PDB structures have been applied in the reported docking protocols. Mathew et al. discussed the synthesis and molecular docking of eleven chlorinated thienyl chalcones (**Table 1**, item 1) containing MAO-B and MAO-A inhibitory effects <sup>[3]</sup>.

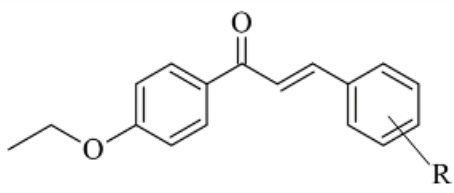
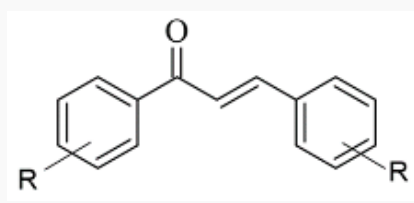
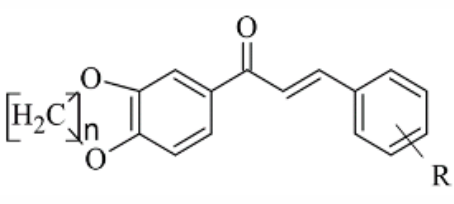


**Figure 1.** Chemical structure of chalcone.

**Table 1.** Structures of the reported chalcones evaluated as MAO-B inhibitors utilizing various docking software and PDB codes.

S. No.	Structure	MAO-B Inhibitor Activity	Docking Program	PDB Code	Ref.
1.	 <chem>Clc1cc(C(=O)/C=C/c2ccc(R)cc2)sc1</chem>	$K_i$ 5.52—0.49 ( $\mu\text{M}$ )	AutoDock 4.2	2BYB	[3]
2.	 <chem>Brc1cc(C(=O)/C=C/c2ccc(R)cc2)sc1</chem>	$K_i$ 0.11—9.30 ( $\mu\text{M}$ )	AutoDock 4.2	2BYB	[4]

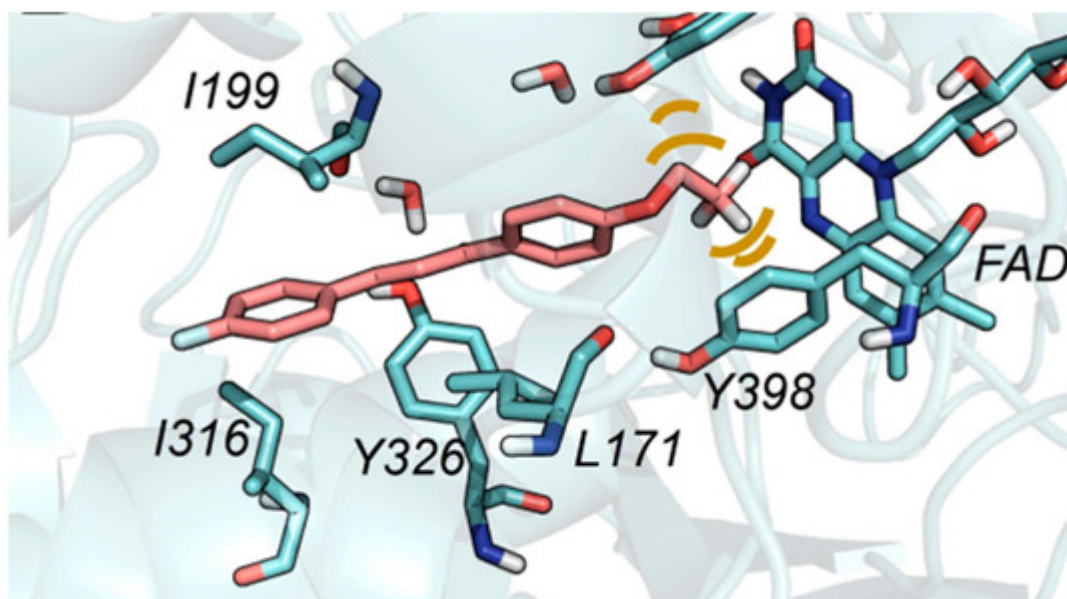
... complex with deprenyl (PDB: **2BYB**) obtained from the Protein Data Bank. Water molecules were deleted and the covalent bond between the co-crystallized ligand and N5-atom of FAD in the structure of **2BYB** was corrected. The center of

S. No.	Structure	MAO-B Inhibitor Activity	Docking Program	PDB Code	Ref.	aromatic
3.		IC <sub>50</sub> 0.68—28.50 (μM)	Glide	2V5Z	[5]	
4		IC <sub>50</sub> 0.0029—13.2 (μM)	AutoDock Vina	4A79	[6]	
5.		IC <sub>50</sub> 0.00021—0.068 (μM)	Glide	2V5Z	[7]	

LEU167

**Figure 2.** Interaction of chlorinated thienyl chalcone ligand with the active site of *h*MAO-B (PDB: **2BYB**). The yellow mesh indicates  $\pi$ - $\pi$  stacking interaction [3].

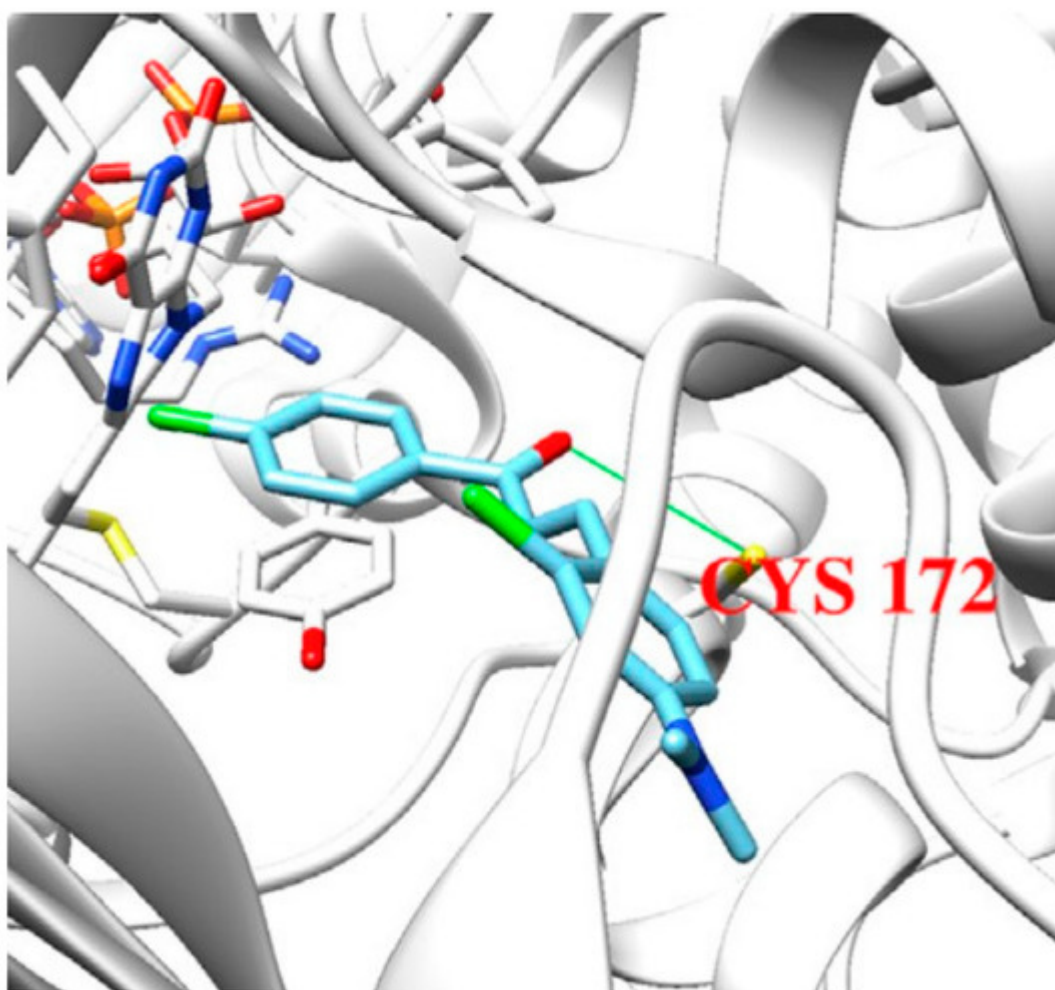
Further stabilization via  $\pi$ - $\pi$  interactions between the ligands and the aromatic cage was noted. It was concluded that the ethyl substitution in the phenyl ring led to higher MAO-B affinity. The same group published a paper of the synthesis and computational studies of brominated thienyl chalcones (**Table 1**, item 2) [4]. The utilized docking protocol of this study corresponds to the one described in the previous case. Among ethyl, methyl, methoxy, and dimethylamine groups placed at the para-position of the brominated thienyl chalcones, the dimethylamino moiety showed the best potency and selectivity. Furthermore, the docking software predicted that the indicated groups were projected into the entrance cavity. Further examination showed the dimethylamino moiety, as the bulkiest group, spanned both the entrance and the substrate pockets.  $\pi$ - $\pi$  interactions between the aromatic ring of the chalcone and the “aromatic cage” were also considered. Glide docking, for the evaluation of the MAO inhibitory activity of eleven ethoxy substituted chalcones (**Table 1**, item 3), was applied by Lakshminarayanan et al. [5]. The ligands were first synthesized, and the virtual screening was carried out on an X-ray MAO-B structure (PDB: **2V5Z**). Hydrophobic interactions between the ligands and the amino acids Ile199, Ile316, and leu171 were examined (**Figure 3**).



**Figure 3.** The active amino residues of MAO-B are presented as an cyan blue, and the ethoxylated chalcone is depicted in red [5].

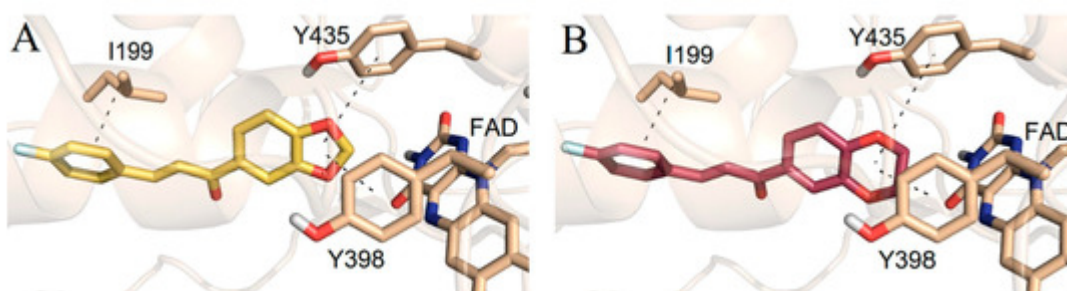
Compound 1-(4-ethoxyphenyl)-3-(4-fluorophenyl)prop-2-en-1-one displayed the best MAO-B inhibitory potential. The acquired docking poses show that the methyl group of the p-ethoxy moiety was placed in the aromatic cage of the MAO-B structure. When subjected to virtual screening in the active site of MAO-A, the interaction with FAD was absent due to a steric hindrance.

John Oh et al. [6] studied the MAO-B inhibition effect of various natural and synthetic chalcones (**Table 1**, item 4). The molecular docking simulation was carried out by AutoDock Vina using the 3D structure of MAO-B with co-crystallized pioglitazone (PDB: **4A79**). Further docking studies towards MAO-A and AChE receptors were performed, and it was discussed that the analyzed chalcones have higher selectivity towards MAO-B. The dimethoxy chalcone oxime with fluoro substitution in the acetophenone moiety showed the most prominent selectivity and blocking activity towards MAO-B. It was observed that the high MAO-B activity was due to the hydrophobic  $\pi$ - $\pi$  interactions between Tyr326 and the ligand. Furthermore, the formation of a hydrogen bond between the carbonyl oxygen of chalcones and Cys172 of MAO-B increased the binding affinity of the ligand (**Figure 4**).



**Figure 4.** Docking simulations of 2,4'-dichloro-4-dimethylaminochalcone in MAO-B [6].

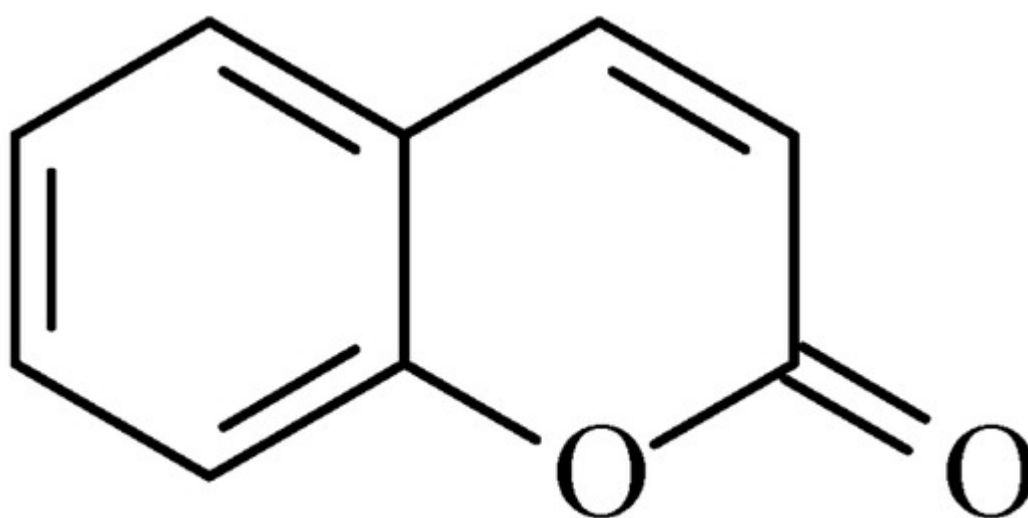
The design, synthesis, and biological evaluation of oxygenated chalcones (**Table 1**, item 5) were reported by Parambi et al. [7]. The crystal structure of MAO-B was downloaded from PDB: **2V5Z**. The Schrödinger suite was used for protein preparation, and eight molecules of water were preserved in the active site of MAO-B. The QM polarized ligand docking from Schrödinger Suite was applied as docking software. The docking study of the most active and selective oxygenated chalcone demonstrated that the benzoxazole group was close to the FAD and moderate–strong  $\pi$ - $\pi$  stacking interactions with Ile199, Tyr398, and Tyr435 formed (**Figure 5**). An additional hydrogen bond was established between Tyr326 and the hydrogen bond acceptor of the ligand, which further confirms the important role of Tyr326 for the MAO selectivity.



**Figure 5.** Docking poses of the top-ranked oxygenated chalcones in MAO-B. The ligands and the active amino residues are given as sticks [7]. Panel (A,B) represent the active conformations of 1,3-dioxolane and 1,4-dioxane chalcone-based molecules, respectively.

## 2. Coumarins

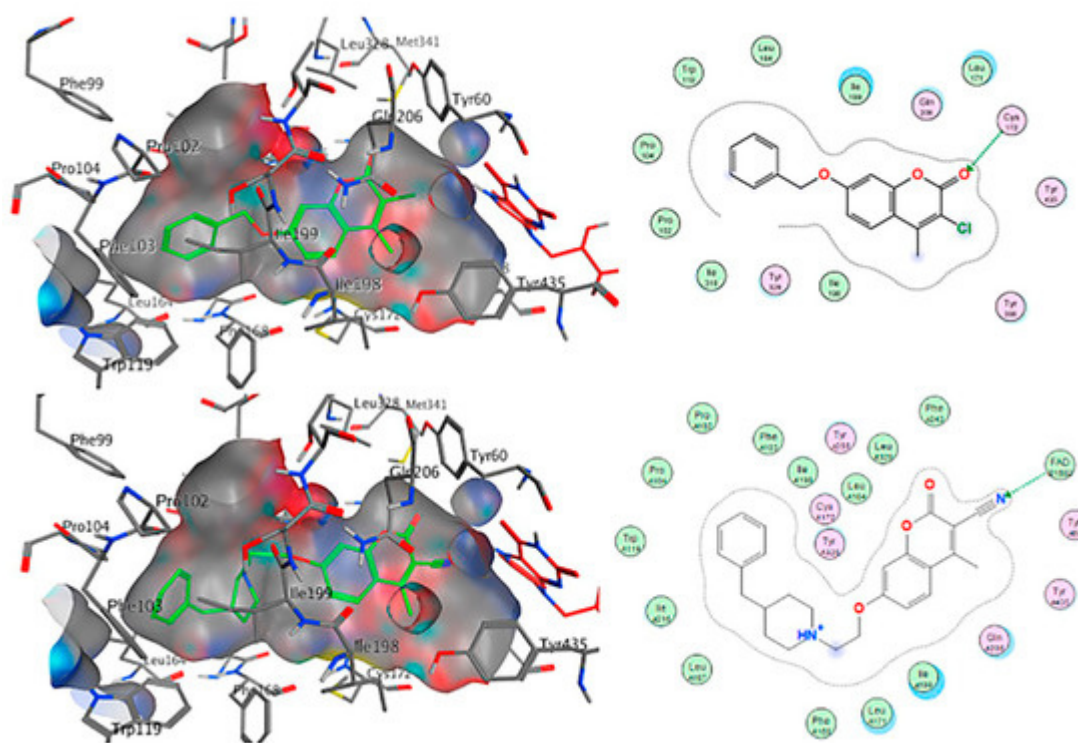
Coumarins are structural isomers of chromones and were investigated for MAO, cholinesterase, and aromatase antagonizing activities (Figure 6). The latter multitarget properties were utilized for the treatment of neurodegenerative disorders [8]. Recent papers have demonstrated the selectivity and potency of coumarins as MAO-B inhibitors [9].



**Figure 6.** Chemical structure of coumarin.

Joubert et al. reported the synthesis and virtual screening results of 7-substituted coumarin derivatives (Table 2, item 1) [10]. Molecular operating environment (MOE) software was applied for the docking study, and *h*MAO-B crystal structure with co-crystallized 7-(3-chlorobenzyloxy)-4-(methylanino)methylcoumarin (PDB: 2V61) was used. The obtained data show that the top solutions situated their coumarin moiety in the polar region of the substrate cavity (Figure 7).





**Figure 7.** The active conformations of coumarin derivatives in the active site of MAO-B. FAD is depicted in red and the compounds are shown in green [10].

Moreover, a hydrogen bond between the carbonyl group of most compounds and Cys172 was observed. Van der Waals interactions between benzyl and the N-benzylpiperidine side chain of the molecules and the hydrophobic entrance cavity further stabilized the complex.

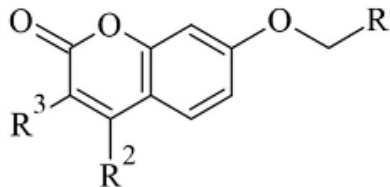
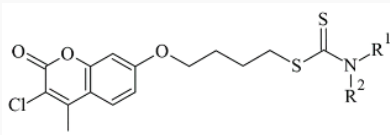
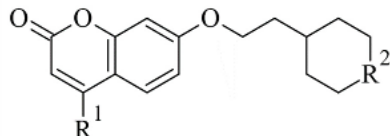
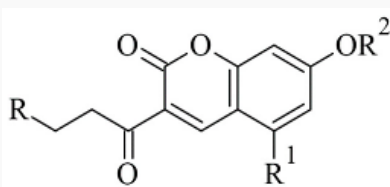
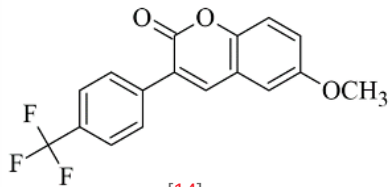
Another study reported the synthesis and determination of the MAO-B inhibitory activity of coumarin–dithiocarbamate hybrid compounds [11]. The research group applied Molecular Operating Environment (MOE, version 2008.10) software for the molecular modeling. The study concluded that the coumarin moiety (**Table 2**, item 2) was in the substrate cavity and further stabilized by binding to Tyr60, Phe343, Tyr398, and Tyr435. The dithiocarbamate part of the molecule was situated in the entrance cavity. The most active compound of the coumarin–dithiocarbamate explored class was with an  $IC_{50}$  value of 0.101  $\mu$ M. Eight compounds isolated from *glycyrrhiza uralens*, also known as Chinese licorice, were subjected to a molecular study and examined for their monoamine oxidase and cholinesterase inhibitory activities [12]. It was found that liquiritigenin has a moderate MAO-B inhibitory constant ( $IC_{50} = 0.098 \mu$ M). The virtual screening was carried out with AutoDock Vina, and MAO-B with co-crystallized pioglitazone (PDB: **4A79**) was downloaded from PDB. The active site grid was set as defined by the binding site of co-crystallized pioglitazone. The work demonstrated that in the MAO-B active site, no hydrogen bonds were formed. However, a promising correlation between in vitro and in-silico data was obtained.

Repsold et al. analyzed the MAO-B and AChE inhibitory properties of new lead compounds with coumarin moiety (**Table 2**, item 3) [13]. Piperidine, morpholine, thiophene, and erucic acid were used for the conjugation with coumarin. The software utilized in that research was Accelrys® Discovery Studio® V3.1.1, and an X-ray of MAO-B

with the co-crystallized selective inhibitor (7-(3-chlorobenzoyloxy)-4-(methylamino) methyl coumarin) was taken from PDB. The virtual screening indicated a reasonable MAO-B blocking activity of the coumarin–morpholine ether. It demonstrated a crucial p-interaction with Tyr398 and hydrogen bond with Cys172.

Discovery Studio 2016 was utilized in the molecular docking of novel Mannich bases of 3-acetyl-7-hydroxyl coumarins (**Table 2**, item 4) by Tao et al. [14]. After the initial in vitro determination of MAO-B activity, two compounds showed promising antagonism towards the enzyme and were further evaluated. The coumarin moiety was orientated in the substrate cavity between Tyr398 and Tyr435. Moreover, the complex was further supported by a hydrogen bond between Cys172 and the oxygen atom of the lactone ring (**Figure 8**).

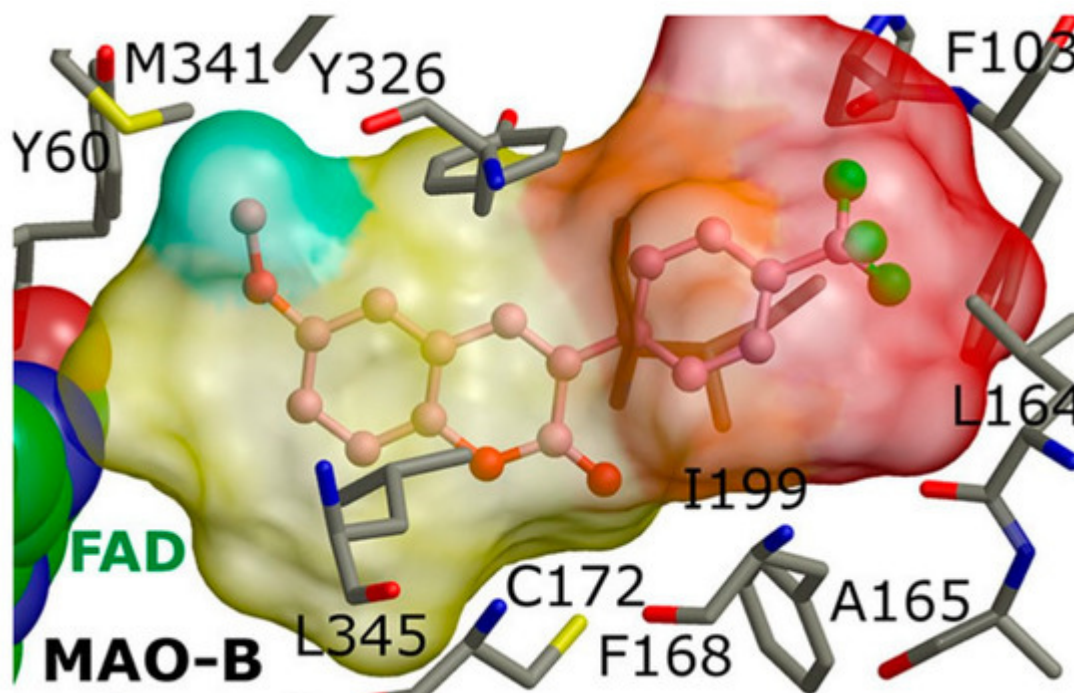
**Table 2.** Structures of the reported coumarins evaluated as MAO-B inhibitors utilizing various docking software and PDB codes.

S. No.	Structure	MAO-B Inhibitor Activity	Docking Program	PDB Code	Ref.
1.		IC <sub>50</sub> 0.0005—28.5 (μM)	Molecular Operating Environment (MOE)	2V61	[10]
2.		IC <sub>50</sub> 0.101—47.16 (μM)	Molecular Operating Environment (MOE)	2V61	[11]
3.		IC <sub>50</sub> 0.372—94.32 (μM)	Discovery Studio (DC)	2V61	[13]
4.		IC <sub>50</sub> 4.62—>200 (μM)	Discovery Studio (DC)	4A79	[14]
5.	 [14]	IC <sub>50</sub> 56—8476 (nM)	Glide	2V60	[15] hydrogen actions as

Rauhamaki et al. designed a virtual library of 3-phenylcoumarin derivatives (**Table 2**, item 5) and subjected them to a virtual screening using Glide [15]. The most promising compounds were synthesized and assessed in vivo for MAO-B activity. From the computational study, the importance of the 3-phenyl moiety of the coumarins for the



MAO-B inhibitory activity was analyzed. The hydrophobic interaction of the coumarin and 3-phenyl ring with the substrate pocket was established as an essential part of the MAO-B inhibitory activity (**Figure 9**).

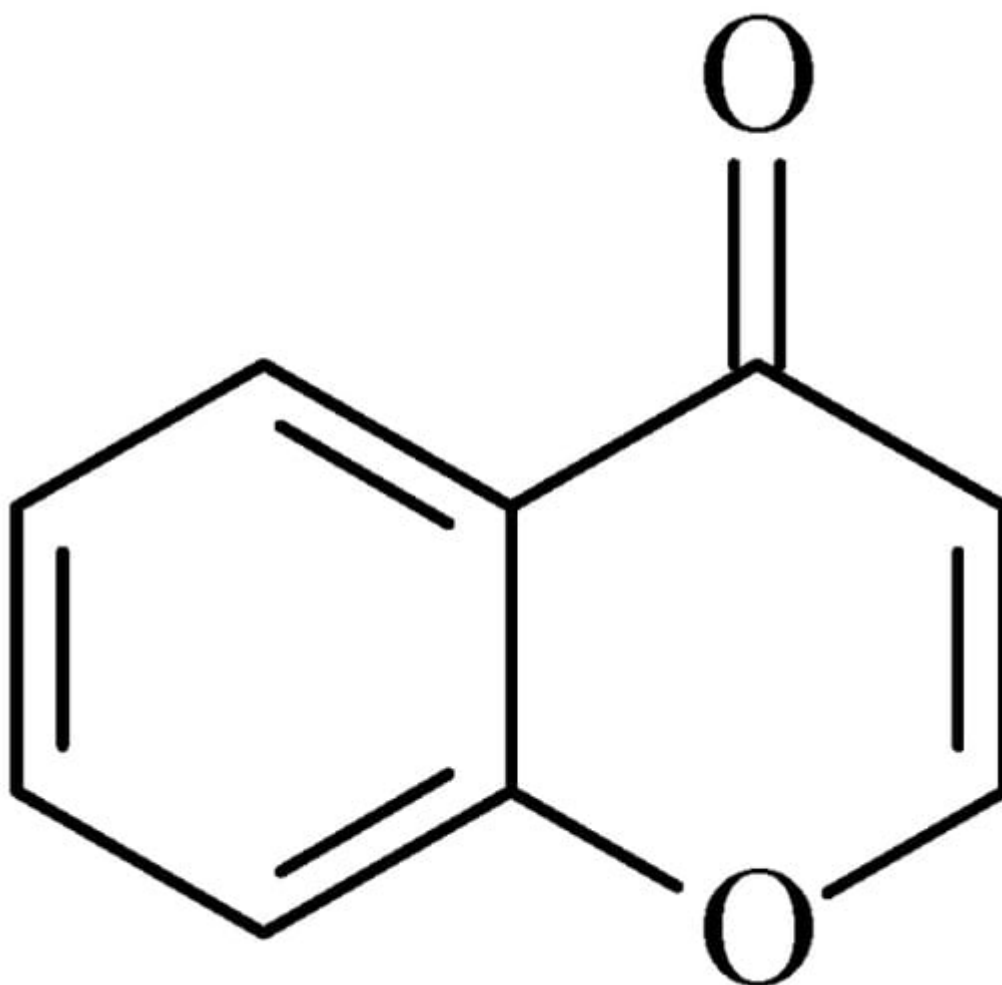


**Figure 9.** The active site of MAO-B with the docked 3-phenylcoumarin derivative [\[15\]](#).

Interestingly, the 3-phenylcoumarins were reversed in the active site compared to the validated co-crystallized ligands. Moreover, the authors discussed an atypical hydrogen bond of the 2C-carbonyl group with the thiol moiety of Cys172; however, the latter interaction did not inflict any alterations.

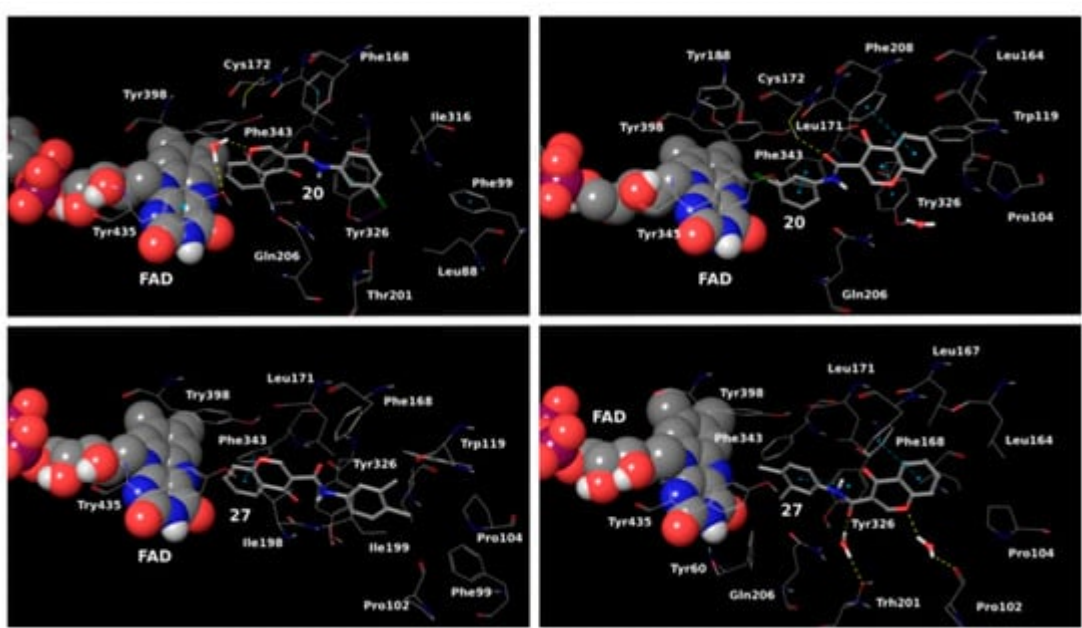
### **3. Chromones**

Recently published works have demonstrated the prominent chromone scaffold (**Figure 10**) for the design of novel MAO-B inhibitors [\[16\]](#). The majority of the chromone derivatives demonstrated high selectivity towards MAO-B, which has been explained with the smaller active gauge in MAO-A [\[17\]](#). An emphasis was placed on the chromone-3-phenylcarboxamide moiety [\[18\]](#).



**Figure 10.** Chemical structure of chromone.

Reis et al. reported the synthesis and the molecular docking of a small library of chromone-3-phenylcarboxamides (**Table 3**, item 1) with MAO-B blocking activity [19]. Glide was utilized as docking software for the virtual screening of the potent chalcones. Interactions of the chalcone derivatives with Phe102 and Tyr435 have been noted (**Figure 11**).



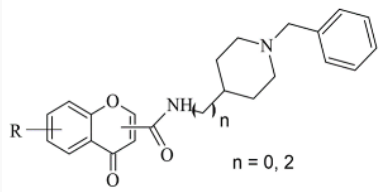
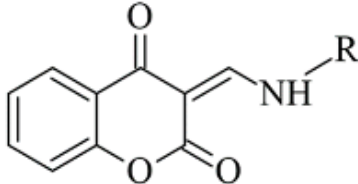
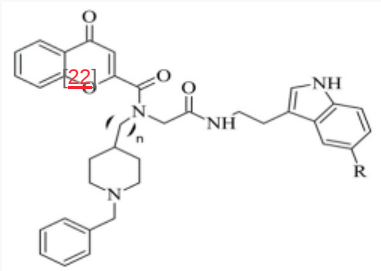
**Figure 11.** MD trajectory frames of active chromone-3-phenylcarboxamide inhibitor in the active site of *h*MAO-B [19]. Ligands are given in polytube while the FAD cofactor is depicted in the spacefill.

**Table 3.** Structures of the reported chromone derivatives evaluated as MAO-B inhibitors utilizing various docking software and PDB codes.

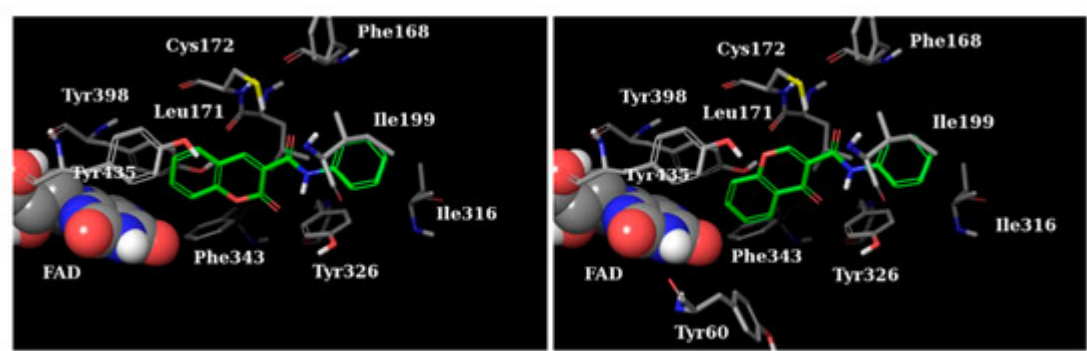
S. No.	Structure	MAO-B Inhibitor Activity	Docking Program	PDB Code	Ref.
1.		IC <sub>50</sub> 1.03—7396 (nM)	Glide	2V5Z	[19]
2.		IC <sub>50</sub> 0.63—3.81 (μM)	Glide	2V5Z	[20]
3.		IC <sub>50</sub> 0.078—2.22 (μM)	GOLD	1GOS	[21]

mined the ed strong ffect after bserved.

Another paper published by Reis et al. discussed the synthesis and the screening of selective MAO-B chromone derivatives (Table 3, item 2) [20]. The most promising compounds were virtually evaluated using the Glide module in Schrödinger Suite 2016-3. The grid was centered at N5 of FAD. As presumed, the phenylcarboxamide moiety

S. No.	Structure	MAO-B Inhibitor Activity	Docking Program	PDB Code	Ref.	ed ligand formation
4.		IC <sub>50</sub> 0.035—52.45 (μM)	Molecular Operating Environment (MOE)	2V60	[22]	zyloxy-8-
5.		IC <sub>50</sub> 5.07—621 (nM)	Discovery Studio (DS)	2Z5X	[23]	ors noted s and the nds were types of site, for a
6.		IC <sub>50</sub> 15.17—80.59 (μM)	AutoDock Vina	2V5Z	[24]	ed out by e binding atic cage carbonyl of gen bond

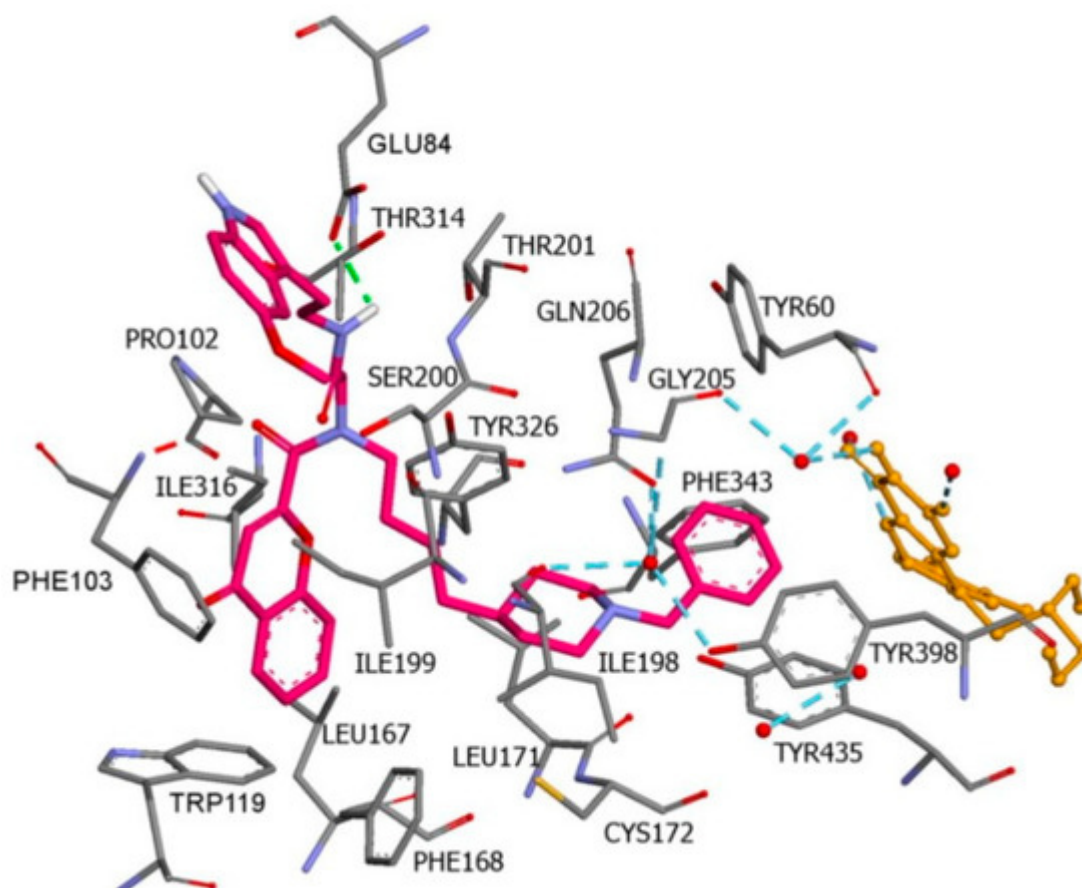
A docking study of chromone derivatives (Table 3, item 5) was carried out using Discovery Studio 3.1 [23]. X-ray structure of MAO-B was downloaded from a protein data bank (PDB: 2Z5X). It is noted that the most prominent molecules were 3-aminomethylidene-2,4-chromandiones. Two isomers of the most potent chromone with MAO-B blocking activity have been analyzed. As expected, π-π interaction of the chromone with Tyr398 and Tyr435 was observed (Figure 12).



**Figure 12.** Active conformations of 3-aminomethylidene-2,4-chromandiones into the active site of *h*MAO-B [23].

Furthermore, a notable hydrogen bond between the carbonyl group located at C2 of the chromone ring and Ile199 was examined. The molecular docking concluded that both cis and trans isomers display MAO-B inhibitory activity. Donepezil + chromone + melatonin hybrids (Table 3, item 6) were synthesized and virtually evaluated for their implementation in Alzheimer’s disease [24]. X-ray MAO-B with co-crystallized safinamide was used as a model

target (PDB: **2V5Z**). AutoDockVina was applied as docking software.  $\pi$ - $\pi$  interactions were observed between the phenyl ring of the hybrid derivatives and Tyr60, Gly205, Phe343, and Tyr398 (**Figure 13**).



**Figure 13.** A Donepezil + chromone + melatonin hybrid derivative in the active site of MAO-B. The active amino acids are color coded [24].

A hydrogen bond formed between the amide group and Glu84. The indole ring was situated at the beginning of the hydrophobic entrance pocket. The chromone moiety was positioned in the entrance cavity as well.

## References

1. Kar Mahapatra, D.; Asati, V.; Bharti, S.K. An updated patent review of therapeutic applications of chalcone derivatives (2014-present). *Expert Opin. Ther. Pat.* 2019, 29, 385–406.
2. Guglielmi, P.; Mathew, B.; Secci, D.; Carradori, S. Chalcones: Unearthing their therapeutic possibility as monoamine oxidase B inhibitors. *Eur. J. Med. Chem.* 2020, 205, 112650.
3. Mathew, B.; Haridas, A.; Uçar, G.; Baysal, I.; Adeniyi, A.A.; Soliman, M.E.S.; Joy, M.; Mathew, G.E.; Lakshmanan, B.; Jayaprakash, V. Exploration of chlorinated thienyl chalcones: A new class of monoamine oxidase-B inhibitors. *Int. J. Biol. Macromol.* 2016, 91, 680–695.

4. Mathew, B.; Haridas, A.; Uçar, G.; Baysal, I.; Joy, M.; Mathew, G.E.; Lakshmanan, B.; Jayaprakash, V. Synthesis, Biochemistry, and Computational Studies of Brominated Thienyl Chalcones: A New Class of Reversible MAO-B Inhibitors. *ChemMedChem* 2016, 11, 1161–1171.
5. Lakshminarayanan, B.; Baek, S.C.; Lee, J.P.; Kannappan, N.; Mangiatordi, G.F.; Nicolotti, O.; Subburaju, T.; Kim, H.; Mathew, B. Ethoxylated Head of Chalcones as a New Class of Multi-Targeted MAO Inhibitors. *ChemistrySelect* 2019, 4, 6614–6619.
6. Oh, J.M.; Kang, M.-G.; Hong, A.; Park, J.-E.; Kim, S.H.; Lee, J.P.; Baek, S.C.; Park, D.; Nam, S.-J.; Cho, M.-L.; et al. Potent and selective inhibition of human monoamine oxidase-B by 4-dimethylaminochalcone and selected chalcone derivatives. *Int. J. Biol. Macromol.* 2019, 137, 426–432.
7. Parambi, D.G.T.; Oh, J.M.; Baek, S.C.; Lee, J.P.; Tondo, A.R.; Nicolotti, O.; Kim, H.; Mathew, B. Design, synthesis and biological evaluation of oxygenated chalcones as potent and selective MAO-B inhibitors. *Bioorganic Chem.* 2019, 93, 103335.
8. Stefanachi, A.; Leonetti, F.; Pisani, L.; Catto, M.; Carotti, A. Coumarin: A Natural, Privileged and Versatile Scaffold for Bioactive Compounds. *Molecules* 2018, 23, 250.
9. Pisani, L.; Muncipinto, G.; Miscioscia, T.F.; Nicolotti, O.; Leonetti, F.; Catto, M.; Caccia, C.; Salvati, P.; Soto-Otero, R.; Mendez-Alvarez, E.; et al. Discovery of a Novel Class of Potent Coumarin Monoamine Oxidase B Inhibitors: Development and Biopharmacological Profiling of 7--4--2H-chromen-2-one Methanesulfonate (NW-1772) as a Highly Potent, Selective, Reversible, and Orally Active Monoamine Oxidase B Inhibitor. *J. Med. Chem.* 2009, 52, 6685–6706.
10. Joubert, J.; Foka, G.B.; Repsold, B.P.; Oliver, D.W.; Kapp, E.; Malan, S.F. Synthesis and evaluation of 7-substituted coumarin derivatives as multimodal monoamine oxidase-B and cholinesterase inhibitors for the treatment of Alzheimer's disease. *Eur. J. Med. Chem.* 2017, 125, 853–864.
11. He, Q.; Liu, J.; Lan, J.-S.; Ding, J.; Sun, Y.; Fang, Y.; Jiang, N.; Yang, Z.; Sun, L.; Jin, Y.; et al. Coumarin-dithiocarbamate hybrids as novel multitarget AChE and MAO-B inhibitors against Alzheimer's disease: Design, synthesis and biological evaluation. *Bioorganic Chem.* 2018, 81, 512–528.
12. Jeong, G.S.; Kang, M.-G.; Lee, J.Y.; Lee, S.R.; Park, D.; Cho, M.; Kim, H. Inhibition of Butyrylcholinesterase and Human Monoamine Oxidase-B by the Coumarin Glycyrol and Liquiritigenin Isolated from *Glycyrrhiza uralensis*. *Molecules* 2020, 25, 3896.
13. Repsold, B.P.; Malan, S.F.; Joubert, J.; Oliver, D.W. Multi-targeted directed ligands for Alzheimer's disease: Design of novel lead coumarin conjugates. *SAR QSAR Environ. Res.* 2018, 29, 231–255.



14. Tao, D.; Wang, Y.; Bao, X.-Q.; Yang, B.-B.; Gao, F.; Wang, L.; Zhang, D.; Li, L. Discovery of coumarin Mannich base derivatives as multifunctional agents against monoamine oxidase B and neuroinflammation for the treatment of Parkinson's disease. *Eur. J. Med. Chem.* 2019, 173, 203–212.
15. Rauhamäki, S.; Postila, P.A.; Niinivehmas, S.; Kortet, S.; Schildt, E.; Pasanen, M.; Manivannan, E.; Ahinko, M.; Koskimies, P.; Nyberg, N.; et al. Structure-Activity Relationship Analysis of 3-Phenylcoumarin-Based Monoamine Oxidase B Inhibitors. *Front. Chem.* 2018, 6, 41.
16. Gaspar, A.; Milhazes, N.; Santana, L.; Uriarte, E.; Borges, F.; Matos, M. Oxidative Stress and Neurodegenerative Diseases: Looking for a Therapeutic Solution Inspired on Benzopyran Chemistry. *Curr. Top. Med. Chem.* 2015, 15, 432–445.
17. Mathew, B.; Mathew, G.E.; Petzer, J.P.; Petzer, A. Structural Exploration of Synthetic Chromones as Selective MAO-B Inhibitors: A Mini Review. *Comb. Chem. High Throughput Screen.* 2017, 20, 522–532.
18. Gaspar, A.; Reis, J.; Fonseca, A.; Milhazes, N.; Viña, D.; Uriarte, E.; Borges, F. Chromone 3-phenylcarboxamides as potent and selective MAO-B inhibitors. *Bioorganic Med. Chem. Lett.* 2011, 21, 707–709.
19. Reis, J.; Cagide, F.; Chavarria, D.; Silva, T.; Fernandes, C.; Gaspar, A.; Uriarte, E.; Remião, F.; Alcaro, S.; Ortuso, F.; et al. Discovery of New Chemical Entities for Old Targets: Insights on the Lead Optimization of Chromone-Based Monoamine Oxidase B (MAO-B) Inhibitors. *J. Med. Chem.* 2016, 59, 5879–5893.
20. Reis, J.; Cagide, F.; Valencia, M.E.; Teixeira, J.; Bagetta, D.; Pérez, C.; Uriarte, E.; Oliveira, P.J.; Ortuso, F.; Alcaro, S.; et al. Multi-target-directed ligands for Alzheimer's disease: Discovery of chromone-based monoamine oxidase/cholinesterase inhibitors. *Eur. J. Med. Chem.* 2018, 158, 781–800.
21. Rao, Y.J.; Abhijit, K.; Mallikarjun, G.; Hemasri, Y. Design and synthesis of novel benzyloxy-tethered-chromone-carboxamide derivatives as potent and selective human monoamine oxidase-b inhibitors. *Chem. Pap.* 2020, 75, 703–716.
22. Wang, X.-B.; Yin, F.-C.; Huang, M.; Jiang, N.; Lan, J.-S.; Kong, L.-Y. Chromone and donepezil hybrids as new multipotent cholinesterase and monoamine oxidase inhibitors for the potential treatment of Alzheimer's disease. *RSC Med. Chem.* 2020, 11, 225–233.
23. Fonseca, A.; Reis, J.; Silva, T.; Matos, M.; Bagetta, D.; Ortuso, F.; Alcaro, S.; Borges, F. Coumarin versus Chromone Monoamine Oxidase B Inhibitors: Quo Vadis? *J. Med. Chem.* 2017, 60, 7206–7212.
24. Pachón-Angona, I.; Refouvelet, B.; Andrés, R.; Martín, H.; Luzet, V.; Iriepa, I.; Moraleda, I.; Díez-Iriepa, D.; Oset-Gasque, M.-J.; Marco-Contelles, J.; et al. Donepezil + chromone + melatonin

hybrids as promising agents for Alzheimer's disease therapy. *J. Enzym. Inhib. Med. Chem.* 2019, 34, 479–489.

---

Retrieved from <https://encyclopedia.pub/entry/history/show/105673>