Bioorg. Med. Chem. Lett. 113 (2024) 129984

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design, synthesis and biological evaluation of novel benzocoumarin derivatives as potent inhibitors of MAO-B activity

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ARTICLE INFO

Keywords:
Benzo[*g*]coumarin
Benzo[*h*]coumarin
Monoamine oxidase
Parkinson's Disease
Molecular docking

ABSTRACT

The continued research of novel reversible inhibitors targeting monoamine oxidase (MAO) B remains crucial for effectively symptomatic treatment of Parkinson's disease. In this study we synthesized and evaluated a new series of 3-aryl benzo[*g*] and benzo[*h*] coumarin derivatives as MAO-B inhibitors. Compound **A6** has been found to display the most potent inhibitory activity and selectivity against the MAO-B isoform (IC_{50} = 13 nM and SI = >7693.31 respectively). Inhibition mode of **A6** on MAO-B was predicted as mixed reversible inhibition with a *Ki* value of 3.274 nM. Furthermore, in order to elaborate structure–activity relationships, the binding mode of **A6** was investigated by molecular docking simulations.

Neurodegeneration refers to a large class of disorders that are characterized by progressive degeneration of the nervous system resulting from neuronal dysfunction, which poses a wide chronic threat to human health.[1] Different neurodegenerative diseases (ND) occur as a result of brain disorders and abnormalities that affect mental and physical skills due to selective and gradual loss of neurons.[2] The etiology of ND is not comprehensively known, but various risk factors have been identified, such as genetics, environmental elements, and age.[3] ND occurs as a result of conditions such as oxidative stress, a decrease in neurotransmitter levels, neuro-inflammation, mitochondrial disorder, proteolytic stress, misfolded proteins, and neuron death.[4] The most common neurodegenerative diseases worldwide are Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease.[5] PD is characterized by decreased dopamine (DA) levels in neuronal synapses. The resulting dopamine depletion is responsible for characteristic PD symptoms such as akinesia (absence of normal unconscious movements), bradykinesia (slowness of movement), hypokinesia (decreased mobility), depression, and anxiety.[6,7] In the treatment of PD symptoms, dopaminergic agonists, or selective monoamine oxidase B (MAO-B) inhibitors are generally employed.[8,9] The structure and biological activities of some inhibitors of MAO isozymes are given in Fig. 1. (rasagiline (Azilect®), IC_{50} = 0.069 μM, SI (selectivity index) = 238,[3] selegiline (Emsam®), IC_{50} = 0.017 μM, SI = 4043,[2] and iproniazid (Rivivol®) IC_{50} = 7.690 μM, SI = 0.8.[9]

Monoamine oxidase (MAO, EC 1.4.3.4, amine-oxygen oxidoreductase) is a flavoenzyme located at the outer mitochondrial membrane in neurons, glial, and other mammalian cells.[10–12] MAO catalyze the oxidative deamination of xenobiotic amines, hormones, and monoamine neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine in the brain and other tissues.[13,14] There are two isoforms of MAO, named MAO-A and MAO-B, which differ in their amino acid sequences, three-dimensional structures, tissue distributions, inhibitor selectivity, and substrate preferences. Because of their important role in key physiological mechanisms, the development of MAO inhibitors is crucial in the treatment of various neuropsychiatric and neurological diseases.[15] In particular, MAO-A inhibitors are used for depression and anxiety, and MAO-B inhibitors are used in PD and AD.[16–18] It is known that MAO-B levels increase with aging starting from the age 50–60.[19] Furthermore, due to hydrogen peroxide is produced as a result of the deamination reaction catalyzed by MAO-B, overexpression of this isozyme promotes oxidative stress in the neurosystem.[20] MAO inhibitors without isoform selectivity have severe side effects and therefore the development of selective and effective MAO inhibitors is essential for the treatment of PD and other neurodegenerative diseases.[21–23].

Coumarins are a large family of compounds of both natural and

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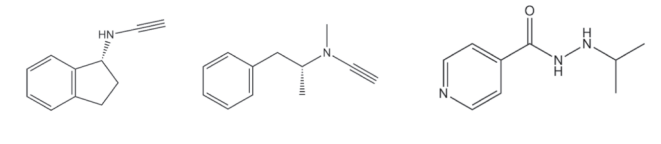
https://doi.org/10.1016/j.bmcl.2024.129984
Received 25 February 2024; Received in revised form 17 September 2024; Accepted 6 October 2024
Available online 9 October 2024



Rasagiline
Irreversible MAO-B
Case: PD
IC_{50} = 0.069 µM, SI = 238

Selegiline
Irreversible MAO-B
Case: PD
IC_{50} = 0.017 µM, SI = 4043

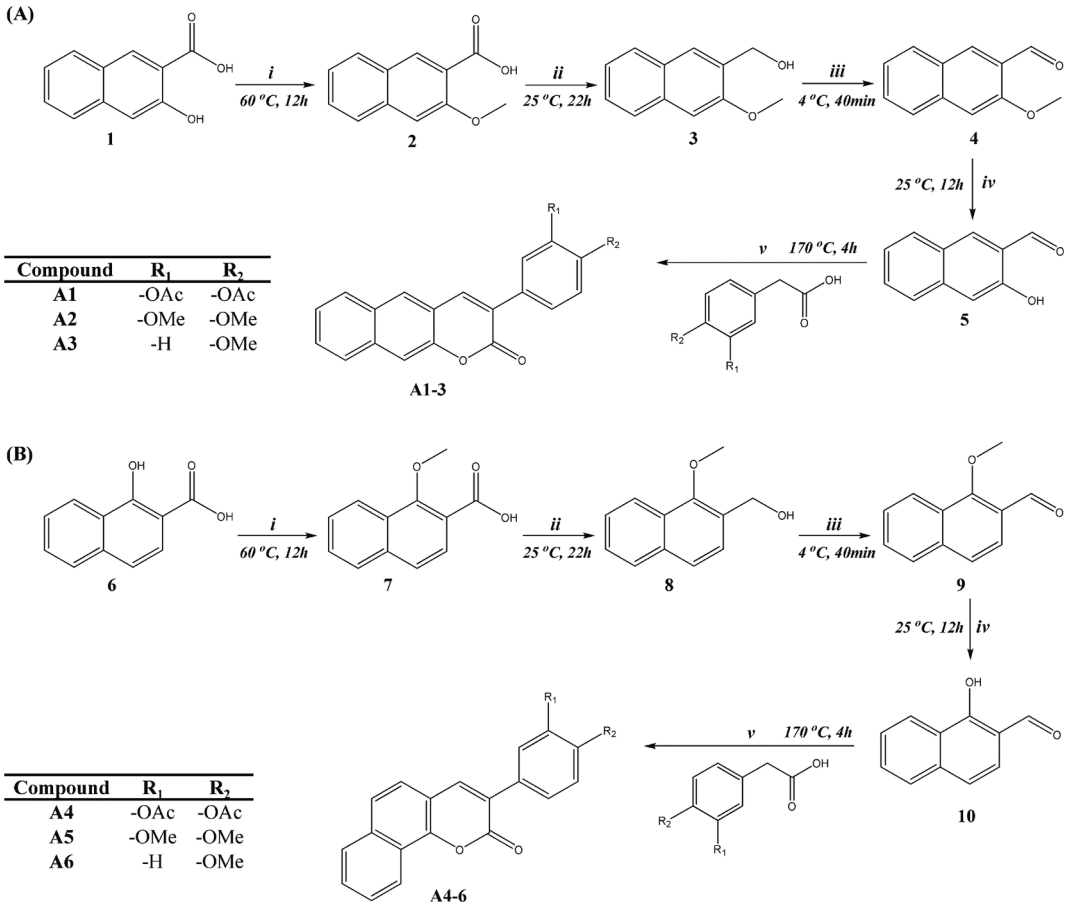
Iproniazid
Irreversible MAO-A
Case: Depression
IC_{50} = 7.690 µM, SI = 0.8

Fig. 1. The structure and biological activities of MAO inhibitors rasagiline, selegiline and iproniazid (Selectivity index: IC_{50} (hMAO-A)/IC_{50} (hMAO-B)).

synthetic origin that show a variety of pharmacological activities, such as antibacterial, antioxidant, reactive oxygen species (ROS) scavenger, anti-viral, and enzyme inhibitors.[24] Modification of coumarin substituents is a medicinal strategy to develop novel drug candidates for the treatment of neurological diseases. Some natural or synthetic coumarin derivatives are known to inhibit MAO isozymes.[25] In the literature, it is reported that substitutions of the position 3 of coumarin nucleus with methyl, phenyl, carboxylic acid, acyl chloride, or ethyl ester groups greatly increases MAO-B inhibitory activity.[26,27] Different substitutions on the phenyl ring in position 3 of the coumarin core play a crucial role in the desired MAO inhibitory activity and selectivity.[28,29] Although MAO inhibitory activity of benzocoumarin derivatives have not been published previously, to our best knowledge, various studies show that benzocoumarins have potent inhibitory effects against various enzymes such as alkaline phosphatase (*h*-TNAP),[30] carbonic anhydrase (CA),[31] acetylcholinesterase (AChE), butyrylcholinesterase (BuChE),[32] and DNA ligase I.[33].

Considering all these facts, it was planned to synthesize six novel 3-arylcoumarin derivatives bearing fused coumarin core; 6,7-benzocoumarin (benzo[*g*]coumarin) and 7,8-benzocoumarin derivatives (benzo[*h*]coumarin), as MAO-B inhibitors. The synthetic route for the synthesis of the benzo[*g*]coumarin and benzo[*h*]coumarin derivatives were given in Scheme 1..[34–37] Detailed synthesis methods and spectral characterization of the derivatives were presented in the Supplementary Material.

The MAO inhibitory activity of benzocoumarin derivatives was evaluated *in vitro* by the measurement of the enzymatic activity of MAO isoforms using a traditional fluorescent method based on the spectrofluorometric determination of the produced H_2O_2 in the reaction by Amplex Red$^{(R)}$, using *p*-tyramine as a substrate. Details of the enzymatic studies were also presented in the Supplementary Material. The IC_{50} values of the benzo[*g*]coumarin and benzo[*h*]coumarin derivatives were calculated from the non-linear regression analysis of percent inhibition vs. log concentration plots, and MAO-B selectivity indexes [IC_{50} (hMAO-A)/IC_{50} (hMAO-B)] of both newly synthesized derivatives and reference inhibitors (selegiline, rasagiline, and iproniazid) were calculated and given in Table 1. The mechanism and reversibility of the inhibition of **A6**, which is the most potent and selective inhibitor of the MAO-B isozyme were further analyzed by determining the enzyme activity at eight different substrate and three different inhibitors concentration. Detailed description of the employed method was given in the Supplementary Material. The kinetic parameters of the enzymatic reaction were calculated from the Michaelis-Menten plot (Fig. 2-A), and from the Lineweaver-Burk plot (Fig. 2-B), the reaction mechanism was predicted as mixed reversible inhibition with a K_i value of 3.274 nM. Results of the time-dependent inhibition analysis of the **A6** inhibition (Fig. 3) support the notion of reversibility for the inhibition of the enzymatic reaction, as

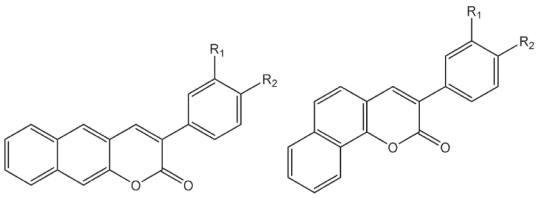


Compound	R_1	R_2
A1	-OAc	-OAc
A2	-OMe	-OMe
A3	-H	-OMe

Compound	R_1	R_2
A4	-OAc	-OAc
A5	-OMe	-OMe
A6	-H	-OMe

Scheme 1. Structures and synthetic route of newly synthesized (A) benzo[*g*]coumarin and (B) benzo[*h*]coumarin derivatives (*i* = K_2CO_3, CH_3I, Acetone, Reflux; *ii* = THF, $LiAlH_4$; *iii* = PCC, CH_3COONa, CH_2Cl_2; *iv* = BBr_3, CH_2Cl_2; *v* = Acetic anhydride, N_2 atmosphere).

Table 1
In vitro human MAO-A and MAO-B inhibitory activities of benzo[*g*]coumarin and benzo[*h*]coumarin derivatives.



Compound	R_1	R_2	hMAO-A IC_{50} (μM)[a]	hMAO-B IC_{50} (μM)[a]	Selectivity Index (SI)[b]
A1	−OAc	−OAc	97.20 ± 1.037	54.40 ± 2.163	1.79
A2	−OMe	−OMe	36.64 ± 1.872 %[c]	1.41 ± 0.371	>70.92[d]
A3	−H	−OMe	3.85 ± 0.958 %[c]	48.12 ± 1.671	>2.08[d]
A4	−OAc	−OAc	78.31 ± 0.834	13.86 ± 0.529	5.67
A5	−OMe	−OMe	24.04 ± 0.517 %[c]	0.241 ± 0.085	>414.94[d]
A6	**−H**	**−OMe**	**15.28 ± 0.723 %**[c]	**0.013 ± 0.009**	**>7693.31**[d]
Selegiline			60.13 ± 1.258	0.020 ± 0.009	3006.51
Iproniazid			5.49 ± 0.637	7.21 ± 0.685	0.76
Rasagiline			12.36 ± 0.714	0.095 ± 0.031	130.11

[a] Each IC_{50} value given as the mean ± S.D. of three replicated experiments.
[b] Selectivity index calculated from IC_{50} hMAO-A/IC_{50} hMAO-B.
[c] % inhibition measured at 100 μM.
[d] Values calculated assuming that the corresponding IC_{50} against hMAO-A is greater than the highest concentration tested (100 μM).

% inhibitory activity remains essentially constant up to 60 min of incubation time.[38].

Over the past decade, studies conducted by Matos et al. have demonstrated that 3-aryl coumarin derivatives exhibit high MAO inhibitor activity and selectivity.[39] In addition, benzocoumarins contain an extra benzene ring fused to the core, compared to coumarin compounds.[40] This ring causes the dihedral angle of the coumarin nucleus to become more planar and increases the number of pi electrons.[41] Therefore, benzocoumarins are more favorable to pi-pi stacking interactions than coumarins. We suggested that adding a benzene ring to coumarin increases the hydrophobicity of the structure, allowing the compounds to better localize to the hydrophobic pocket of MAO-B and remain stable. Because of all these reasons, we designed novel 3-aryl benzocoumarin derivatives to evaluate the effect of the additional benzene ring to the coumarin core. Furthermore, the effects of acetoxy (−OAc), and methoxy (−OMe) functional group substitutions at the 3′- and 4′-positions of the 3-aryl benzocoumarins on MAO activity were also studied. As shown in Table 1, benzo[*g*]coumarin derivatives and benzo[*h*]coumarin derivatives display MAO inhibitory activity in the micromolar range. Some of the compounds showed potent inhibitory activity below 10 μM IC_{50} values against MAO-B. Among the fused analogues, benzo[*h*]coumarins generally demonstrate higher inhibitory activity towards MAO-B than benzo[*g*]coumarins. This tendency might be explained by the more favorable conformation of the benzo[*h*]coumarins in the hydrophobic pocket of the MAO-B when compared to benzo[*g*]coumarins due to the angularity of their aromatic rings. **A1**, **A3**, and **A4** have higher IC_{50} values than all the known inhibitors tested in our study, however **A2**, **A5** and **A6** were also displayed comparatively potent inhibitory activity and selectivity against MAO-B. **A2** and **A5** derivatives bearing two methoxy substituents in the 3′- and 4′-positions (*meta* and

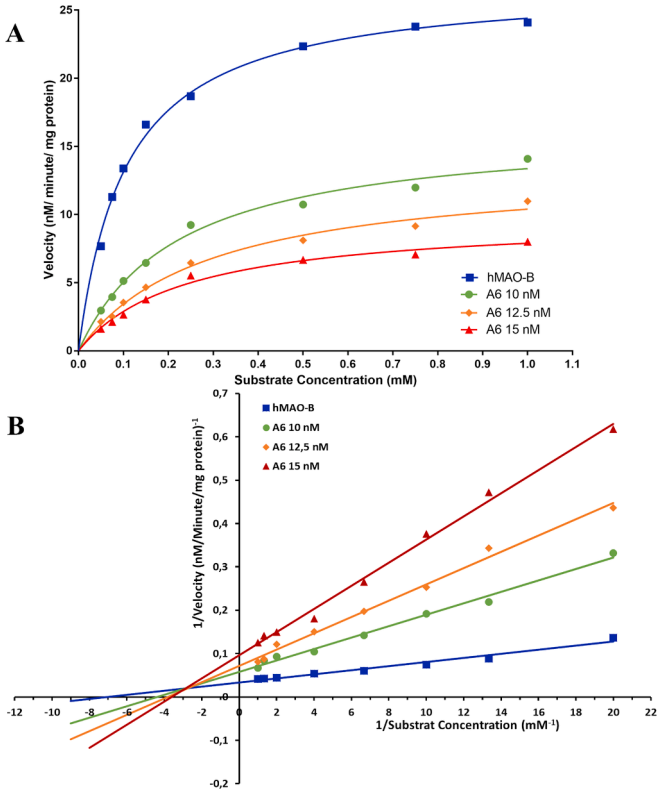


Fig. 2. Determination of the kinetic characteristics of the inhibition of human MAO-B by **A6**: (A) Michaelis-Menten plot and (B) Lineweaver-Burk plot.

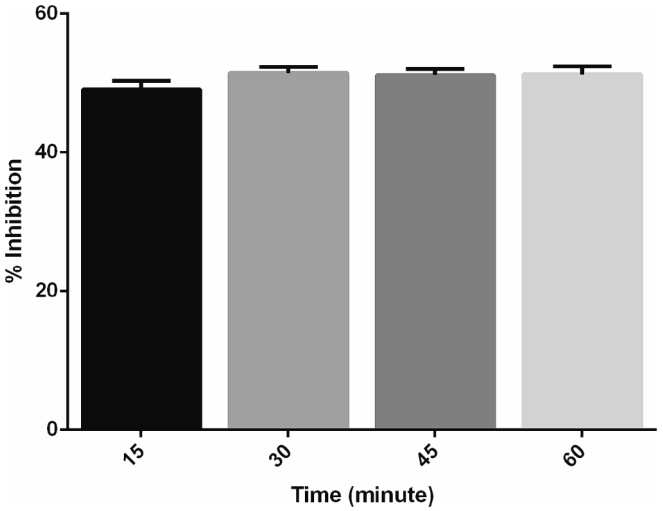


Fig. 3. Relationship of incubation time and % inhibition of hMAO-B activity by compound **A6** at 10 nM final concentration.

para position, respectively) in contrast to the derivatives that contains acetoxy substituents showed considerably higher inhibitory activity (IC_{50} = 1.41 ± 0.371 μM and IC_{50} = 0.241 ± 0.085 μM, respectively) against MAO-B. The most potent molecule was **A6**, which exhibited the highest inhibitory activity against MAO-B with an IC_{50} value of 0.013 ± 0.009 μM and a selectivity towards MAO-B (more than 7693-fold), surpassing known inhibitors and other molecules in this series. Interestingly, the **A6** compound contains a *p*-methoxy group at the 4′-position, which can modulate the affinity and selectivity for MAO-B inhibition.[42] As published in the literature, the presence of methoxy group(s) improves the pharmacological potential of 3-arylcoumarin

Table 2
Predicted pharmacokinetics and physicochemical properties of synthesized compounds as compared to selegiline, rasagiline and iproniazid.

Cmpd	MW	Fraction Csp3	RB	HBA	HBD	MR	TPSA (Å²)	log P	GI absorption	BBB perm.	Lip. V.	Bio. Sc.
A1	388.37	0.09	5	6	0	108.42	82.81	3.39	High	No	0	0.55
A2	332.35	0.10	3	4	0	98.41	48.67	3.40	High	Yes	0	0.55
A3	302.32	0.05	2	3	0	91.92	39.44	3.19	High	Yes	0	0.55
A4	388.37	0.09	5	6	0	108.42	82.81	3.34	High	No	0	0.55
A5	332.35	0.10	3	4	0	98.41	48.67	3.32	High	Yes	0	0.55
A6	302.32	0.05	2	3	0	91.92	39.44	3.17	High	Yes	0	0.55
S	187.28	0.38	4	1	0	61.31	3.24	2.80	High	Yes	0	0.55
R	171.24	0.33	2	1	1	54.45	12.03	2.51	High	Yes	0	0.55
I	179.22	0.33	4	3	2	49.65	54.02	1.38	High	Yes	0	0.55

Cmpd: Compounds, MW: Molecular weight, Fraction Csp3: The ratio of sp hybridized carbons over the total carbon count of the molecule, RB: Rotatable bonds, HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, MR: Molar refractivity, TPSA: Topological polar surface area, log P: Measure of lipophilicity, GI: Gastrointestinal, BBB perm.: Blood brain barrier permeability, Lip. V.: Lipinski violation, Bio. Sc.: Bioavailability Score, S: Selegiline, R: Rasagiline, I: Iproniazid.

derivatives,[43,44] and based on our research findings suggest that methoxy groups also important for the development of potent MAO-B inhibitors for benzocoumarin derivatives. We observed that MAO-B selectivity and inhibitory activity of the compounds decreased when the methoxy groups was replaced by acetoxy groups. Therefore, we recommended that due to its bulky nature, this substitution cannot access the active site of the enzyme, primarily due to steric hindrance.[45–47] The results are consistent with our previous publication indicating that substituted methoxy compounds have a greater effect on MAO-B inhibitory activity than substituted acetoxy.[48] Likewise, increasing the number of methoxy substituents, **A5**, compared to **A6,** seems to be reducing the enzymatic inhibitory activity. The presence of an oxygen atom shows an electron-withdrawing effect, but the unpaired electrons on the oxygen cause the exact opposite effect – the substituted methoxy on the phenyl ring acts as an electron-donating group by resonance. Consequently, **A5**, which includes two methoxy groups, donates more electrons in comparison to **A6**, which features only one methoxy group on the 3-aryl ring (Fig. S8 – Supplementary Material). The existence of a methoxy group onto the phenyl ring affects the electronic and steric properties of the ring.[49] Electron-donating methoxy substituents can increase the electron density on the phenyl ring, normally leading to enhanced resonance stabilization and potentially improving the reactivity of the ring. However, we suggested that two methoxy (**A5**) substituted into the phenyl ring, compared to one substituted methoxy (**A6**), reduces inhibitory activity by destabilizing due to increased delocalization of the ring. Two electron-donating groups increases the electron density in the molecule compared to one electron-donating group, causing an imbalance between the displaced electrons and the resonance structure.[50,51] For this reason, we suggested that because of these changes in the electronic properties of the molecule, the interaction of the enzyme with the target region becomes difficult and the inhibition effect was lower. The presence of just one methoxy substituent, especially *p*-position in the 3′-aryl ring, seems to be important to modulate and enhance the inhibitory activity of the benzo[*h*]coumarins. Therefore, we were proposed substitution of the methoxy groups instead of acetoxy, in the 3-aryl benzo[*h*]coumarins, especially at the *p*-position

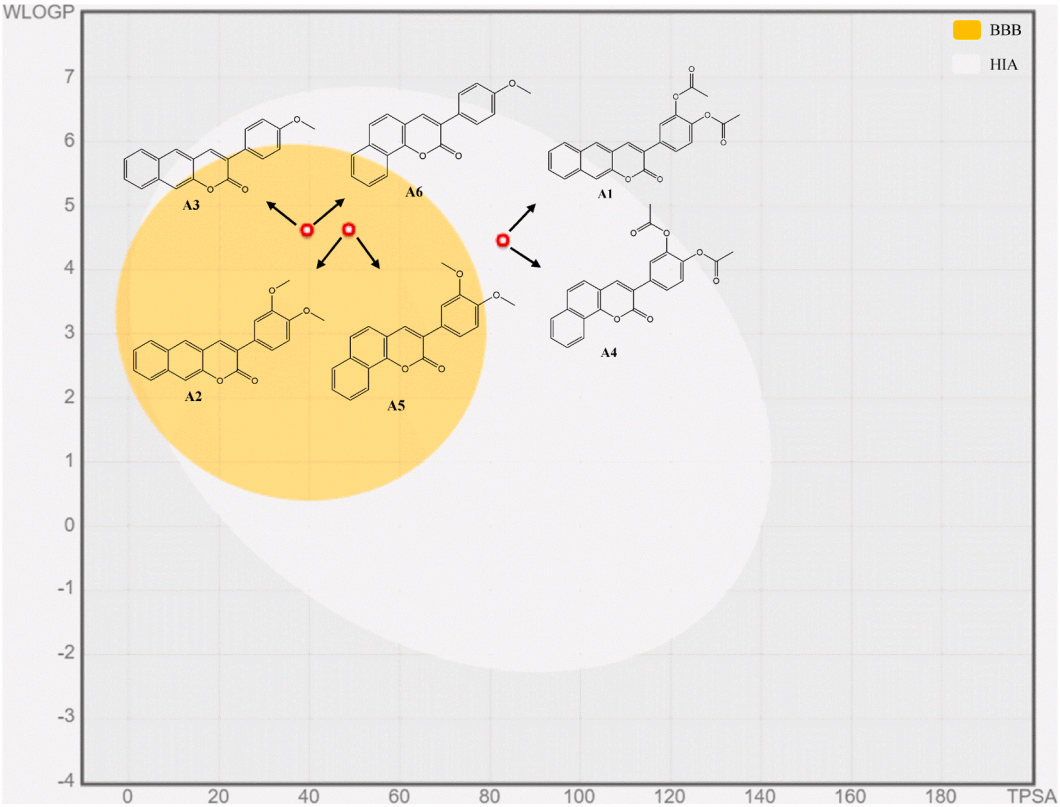


Fig. 4. Predictive human intestinal absorption (HIA) model and blood–brain barrier permeation (BBB) method (boiled-egg plot) of the **A1-6**.

Table 3
Gibbs free energy of binding of the most active coumarin derivatives for MAO-B enzyme, and calculated ligand efficiency index (LEI).

Compound	Lowest Binding Energy (ΔG, kcal/mol)	Number of heavy atoms	LEI (Δg, kcal/mol)
A5	−9.6	29	0.33
A6	−9.9	27	0.37

Δg = −(ΔG)/Non-hydrogen atoms.

could be led effectively optimized in a candidate for the treatment of the PD.

Antibacterial activity of compounds **A1-6** against Gram-negative *E. Coli* bacteria were also assessed as described in supplementary material by disc diffusion method.[52] Only compound **A4** showed a modest antibacterial activity at 30 μg/μL concentration (inhibition zone (IZ) = 1.16 cm) but it is significantly lower than the inhibition zone of both kanamycin and ampicillin (IZ = 2.28 cm and 3.35 cm, respectively).

SwissADME online server was employed to understand the ADME (absorption, distribution, metabolism and excretion) properties and the drug-like characteristics of **A1-6** (Table 2, http://www.swissadme.ch/). Drugs must be absorbed in the gastrointestinal tract and cross the blood–brain barrier in order to have high bioavailability when utilized in the central nervous system.[53,54] Hence, the boiled-egg plot was performed to better understand of pharmacokinetic parameters of the compounds. The "Boiled-Egg" model offers a straightforward and efficient approach for predicting the passive absorption in the gastrointestinal tract and the ability of small compounds to access the brain, which are crucial considerations in drug discovery and development.[55,56] The Boiled-egg analysis of six molecules (Fig. 4) has shown that compounds **A1-6** are highly absorbable in the gastrointestinal tract, whereas **A2-3** and **A5-6** are highly absorbable at the brain barrier.

In order to shed light on the hypothetical binding mode and to explain their structure–activity relationships for the most potent and selective inhibitors, **A5** and **A6**, molecular docking simulations were performed on the MAO-B crystal structure. Energy minimization of the derivatives was utilized using Avogadro version 1.2.0.[57] Binding affinities and ligand efficiency indexes (LEI) of compounds were calculated (Table 3) with crystallized MAO-B protein structure (PDB ID: 2XFN) using AutoDock Vina 1.5.6.[58] Details of the protocol of the molecular docking studies were presented in the Supplementary Material. To validate our protocol, we calculated the root mean square deviation (RMSD) between the docked pose and the co-crystallized 2-(2-benzofuranyl)-2-imidazoline structure as 0.357 Å (Fig. S7–Supplementary Material).

The validated docking procedure was utilized to the **A5** and **A6**, and the most favorable docking conformation was retrieved from the calculation. Interactions of **A5** and **A6** with MAO-B were determined by using Discovery Studio Visualizer 2021 (BIOVIA, San Diego, CA, USA). The benzene ring fused to coumarin was found to be directed towards the hydrophobic pocket in the entrance cavity establishing hydrophobic interactions for both compounds. The predominance of entry into the hydrophobic region requires the orientation of both compounds in these conformations (Fig. 5). In addition, previous work has been undertaken by our group modulating the various positions of the 3-aryl coumarin with different substituents. In our publication we observed that 3-aryl coumarins generally less potent when compared to their benzocoumarin analogues in regard to inhibition of MAO-B activity. We suggest that this difference in activity could be explained by the lack of additional benzene ring in the coumarin core of 3-arly coumarins when compared to benzo[*h*] and benzo[*g*] coumarins, which helps positioning in the hydrophobic pocket in MAO-B.[48] The methoxy substituent at position 4′ for **A6** (and at position 3′ for **A5**) is oriented towards the hydrophilic site. The methyl of methoxy group showed alkyl and π-alkyl interaction with Arg120 and Arg484 for **A5** and **A6**. But only **A6** showed π-anion interaction with Glu483, which apparently critical for the inhibitory activity (Fig. 6).

Our results indicate that due to their selective and potent MAO-B inhibitory activities and favorable ADME-related physicochemical properties, compounds **A5** and **A6** could be considered as novel scaffolds for the development of novel MAO-B inhibitor drugs in symptomatic treatment of Parkinson's disease.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

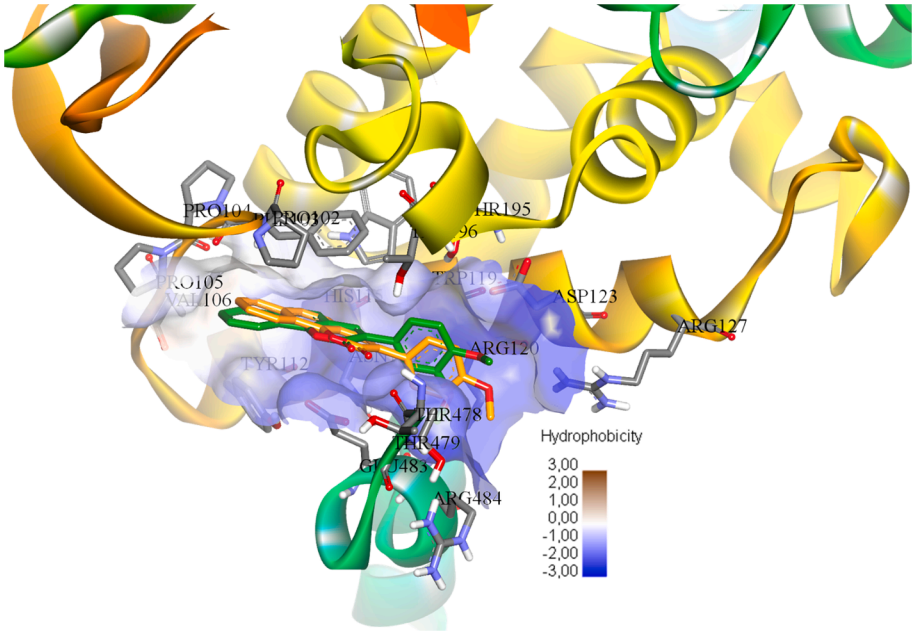


Fig. 5. Superimposition of **A5** and **A6** in the active site.

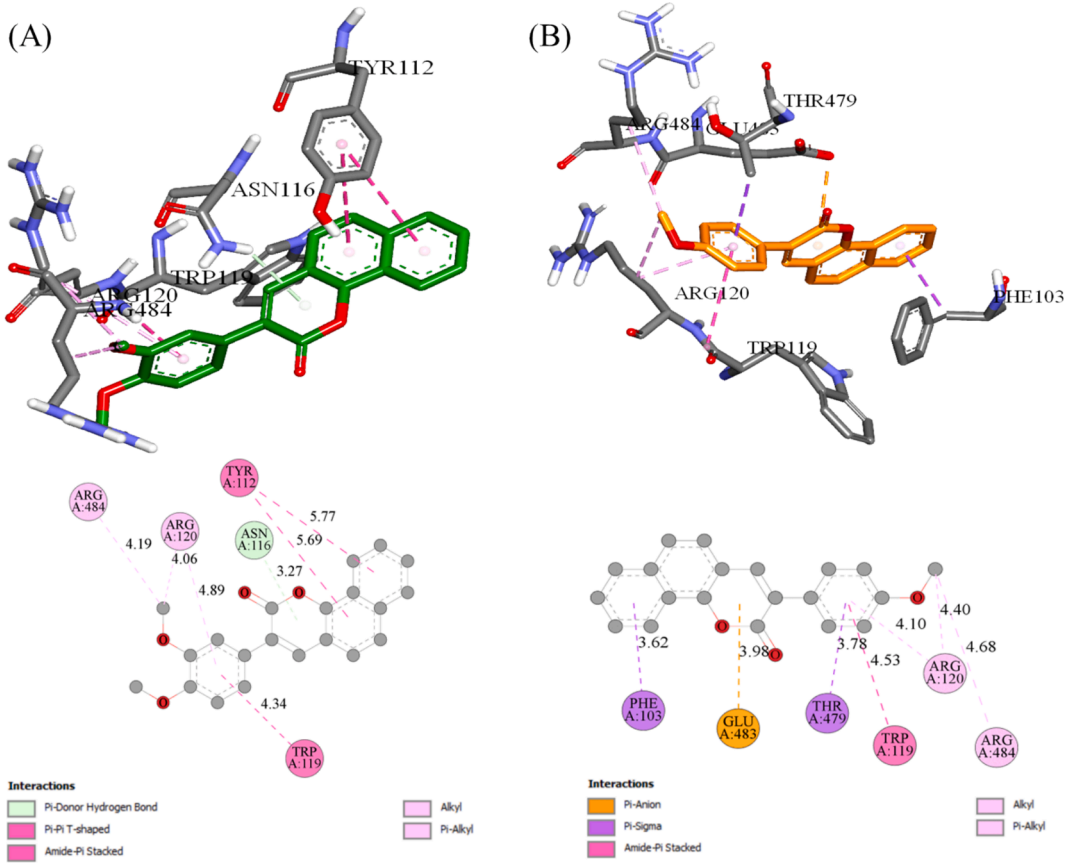


Fig. 6. Binding mode of compound (A) **A5** and (B) **A6** in MAO-B.

Data availability

Data will be made available on request.

Acknowledgments

This work was supported by Marmara University Scientific Research Fund, Türkiye through Project FEN-A-130511-0160.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2024.129984.

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