ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Review

Piperidine: A Versatile Heterocyclic Ring for Developing Monoamine Oxidase Inhibitors

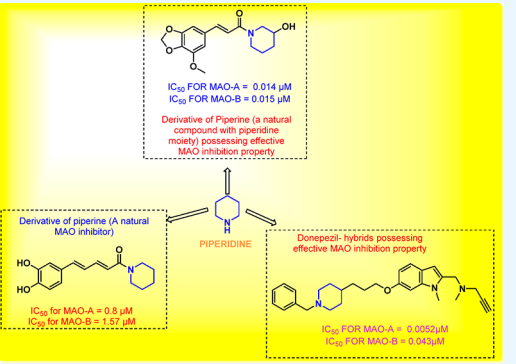
Jayalakshmi Jayan, Namitha Chandran, Amrutha Chandran Thekkantavida, Mohamed A. Abdelgawad, Mohammed M. Ghoneim, Mohamed E. Shaker, Prerna Uniyal, Feba Benny, Subin Mary Zachariah, Sunil Kumar, Hoon Kim,* and Bijo Mathew*

Cite This: *ACS Omega* 2023, 8, 37731−37751

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: The monoamine oxidase enzyme (MAO), which is bound on the membrane of mitochondria, catalyzes the oxidative deamination of endogenous and exogenous monoamines, including monoamine neurotransmitters such as serotonin, adrenaline, and dopamine. These enzymes have been proven to play a significant role in neurodegeneration; thus, they have recently been researched as prospective therapeutic targets for neurodegenerative illness treatment and management. MAO inhibitors have already been marketed as neurodegeneration illness treatments despite their substantial side effects. Hence, researchers are concentrating on developing novel molecules with selective and reversible inhibitory properties. Piperine, which is a phytochemical component present in black pepper, has been established as a potent MAO inhibitor. Piperine encompasses a piperidine nucleus with antibacterial, anti-inflammatory, antihypertensive, anticonvulsant, antimalarial, antiviral, and anticancer properties. The current Review focuses on the structural changes and structure−activity relationships of piperidine derivatives as MAO inhibitors.



1. INTRODUCTION

Neurodegeneration is the primary pathophysiological alteration in most brain illnesses.[1] Neurodegenerative diseases (NDDs) can be categorized following their fundamental clinical characteristics (such as dementia, parkinsonism, or motor neuron disease), anatomical illness distribution (such as frontotemporal degenerations, extrapyramidal disorders, or spinocerebellar degenerations), or primary molecular aberrations.[2] The most prevalent of these illnesses are Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, and Huntington's disease. These illnesses are referred to as NDDs, which are associated with the atrophy of the central nervous system (CNS) components.[3] A NDD is characterized by memory loss, problem-solving or planning difficulties, mood or personality changes, and declined judgment or decision-making.[4] AD is the predominant reason for dementia globally. The number of patients with AD is quickly increasing, and this neuronal impairment has no cure.[5] PD is another neurological illness that is characterized by tremors, muscular stiffness, and sluggish movement. This disorder is brought on by the loss of certain dopamine-producing neurons.[6] Monoamine oxidase-A (MAO-A) inhibitors cure various types of depression and other nervous system diseases, such as panic disorder, social phobia, and depression with atypical symptoms, in contrast to conventional antidepressants.[7]

Genetic, environmental, and endogenous aging-related factors are considered to be the principal basic mechanisms causing neurodegeneration. However, their pathogenic significance and fundamental molecular mechanisms remain largely unknown.[8] There are numerous uncommon NDDs with known genetic origins. Mutations cause the early onset of severe neurological illnesses by impairing the function of genes essential for neuronal or glial cell functioning.[9] Other factors responsible for neurodegeneration include epigenetics, toxins, protein misfolding, impaired protein clearance, altered cell signaling, impaired energy metabolism, oxidative stress, DNA damage, impaired cytoskeleton axonal transport, neuroinflammation, demyelination, and induced cell death.[10]

Monoamine oxidases (MAOs) are proteins on the mitochondrial outer membrane that catalyze the breakdown of numerous amines in the body. MAO isozymes, namely, MAO-A and MAO-B, are each coded by respective genes on the X chromosome.[11] Ammonia, aldehyde, and hydrogen peroxide

Received: August 10, 2023
Accepted: September 4, 2023
Published: October 3, 2023

are the three main intermediates produced through MAO-accelerated oxidative deamination.[12,13] MAO-A inhibitors are regarded as efficient therapeutic medicines for the treatment of neurological diseases, including anxiety and depression.[14] MAO-B is one of the isozymes of MAO that is associated with neurodegeneration because its activity is markedly elevated in the brains of patients with AD.[15] MAO inhibitors, which are involved in the oxidative deamination pathway, might diminish the buildup of oxidative stress mediators, such as hydrogen peroxide, aldehydes, and ammonia, possibly slowing the progression of AD.[16] These enzymes catalyze the oxidative deamination of neurochemicals, including dopamine (DA), serotonin, phenylethylamine, adrenaline, and noradrenaline.[17,18] MAO-A substrates include serotonin (5-HT), norepinephrine (NE), and DA, whereas MAO-B substrates include phenylethylamine (PEA) and benzylamine.[19]

The anatomical areas exhibiting neuronal dysfunction, biochemical and conformational changes in protein indicators, and pathologies of neuronal cells such as protein deposition, as well as differences in genetics and epigenetics, can all be used to distinguish between NDDs.[20] The diagnosis of NDDs is frequently associated with measurements of their particular receptor binding, cellular metabolism modifications, or anatomical structure alterations.[21,22] Structural neuroimaging methods, such as computed tomography and magnetic resonance imaging, are no longer used for diagnosis due to their extremely low specificity. Instead, new methods, such as positron emission tomography and single-photon emission computed tomography, have taken their place. Another more recent method for NDD diagnosis and prognosis is the metabolomic application.[23] However, brain mapping techniques may be used to characterize the regional anatomical alterations in pathological states.[24]

The first MAO antagonist used in the treatment of depression was iproniazid, which was initially used in tuberculosis therapy.[25−27] While unsuccessful, it was seen to have "psycho-energizing" effects on patients and also suppressed MAO.[28] Several analogs of hydrazine that are MAO inhibitors, including phenelzine, were later developed as antidepressants.[29] However, several MAO inhibitors were removed from the clinic after the increased incidences of liver damage, hypertensive crises, hemorrhage, and, in some cases, death.[30] Creating nonhydrazine inhibitors, such as tranylcypromine and pargyline, helped prevent liver damage, which was significantly associated with inhibitors generated from hydrazine.[31,32] However, hypertensive crises persist as an issue. Tyramine and other adrenergic amines contained within fermented foods, such as cheese, enter circulation and increase sympathetic cardiovascular activity by producing noradrenaline, resulting in the adverse impact known as the "cheese response".[26,33] Selective irreversible MAO-B inhibitors do not have these effects because intestinal MAO successfully metabolizes tyramine and MAO-B is minimal in the gut.[34−36] The creation of reversible MAO-A inhibitors, such as moclobemide and lazabemide, also prevented this issue, since these drugs may block enough MAO-A in the brain to have an antidepressant effect. Still, dietary tyramine can displace the inhibitor from peripheral MAO-A, permitting its metabolism.[37,38]

Piperidine is a nonaromatic heterocyclic nucleus with a six-membered ring with five methylene groups (−CH_2−) and one secondary amine group (−NH−) (Figure 1). Using a secondary amine, ketones are transformed into enamines, which can then be used in the Stork enamine alkylation procedure.[39] Piperidine

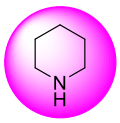


Figure 1. Structure of piperidine.

is a major heterocyclic unit that is present in piperine, which is the active ingredient in black pepper (*Psilocaulon absimile* [Aizoaceae] and *Petrosimonia monandra*).[11,16]

Numerous biological actions, including antibacterial, anti-inflammatory, antihypertensive, anticonvulsant, antimalarial, antiviral, and anticancer effects, have been established for piperidine and its derivatives.[40] Two piperidine-containing anaplastic lymphoma kinase (ALK) inhibitors, ceritinib and alectinib, were made into a series of radiolabeled fluoroanalogs by Piwnica-Worms et al. They obtained enhanced CNS pharmacokinetic characteristics for all the drugs.[41,42] Pyridine is hydrogenated to make piperidine in the industrial setting, typically using a molybdenum disulfide catalyst.[43] A modified Birch reduction using sodium in ethanol can also reduce pyridine to piperidine. Figure 2 explains some important reactions for the synthesis of piperidine nuclei from different sources.[41,44−46] Hence, numerous efforts have been made over the years to create new techniques for the synthesis of piperidine-containing molecules.[47]

Currently, Food and Drug Administration (FDA)-approved drugs, such as antipsychotics, include haloperidol,[48] benperidol,[49] risperidone,[50] and thioridazine[51] for the symptomatic management of schizophrenia; droperidol, a dopamine antagonist used to prevent and treat postoperative nausea and vomiting;[52] and anticholinesterases, including donepezil[53] for treating AD (Figure 3).[26]

Recently, many structural scaffolds, such as chalcones,[54] conjugated dienones,[55] isatins,[56] chromones,[57] coumarins,[58] pyrazolines,[59] quinazolines,[60] β-carbolines,[61] and benzyloxy-derived molecules,[62] are used to develop MAO inhibitors. In search for newer MAO inhibitors, researchers have identified the inevitable role of halogens in selective and potent MAO-B inhibition.[63] The introduction of a specific halogen, such as fluorine and bromine, will enable the compounds to optimize the pharmacokinetic properties and thereby improves the biological activities.[63] The current Review focuses on piperidine-containing MAO inhibitors and their detailed structure−activity relationships (SARs).

2. NATURAL ANALOGS FOR PIPERIDINE AS MAO INHIBITORS

Kong et al. (2004) established the inhibitory activity of piperine (Figure 4) on both types of MAO enzymes isolated from rat brains. They investigated the MAO inhibitory action of 17 naturally occurring compounds, including alkaloids, phenols, and anthraquinones, and revealed that piperine showed dose-dependent MAO inhibitory activity on both types, with half-maximal inhibitory concentration (IC_{50}) values of 49.3 and 91.3 μM for types A and B, respectively. Here, the MAO-A and MAO-B inhibitory activity experiments used clorgyline and deprenyl as positive controls, respectively. Piperine inhibits MAO-A in a mixed-type manner, while MAO-B is inhibited competitively according to the Lineweaver−Burk plot. The pyrroline analogue stachydrine, the monoterpenic indole strychnine, and the benzylisoquinoline derivatives sinomenine and fangchinoline that were also evaluated in the study did not

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

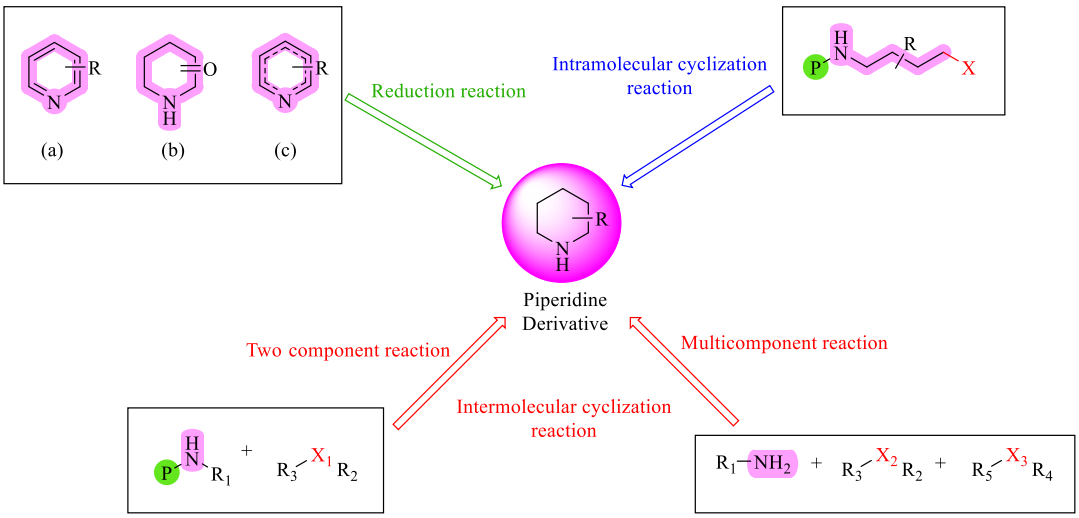


Figure 2. Different synthetic routes adopted for the production of piperidine derivatives.

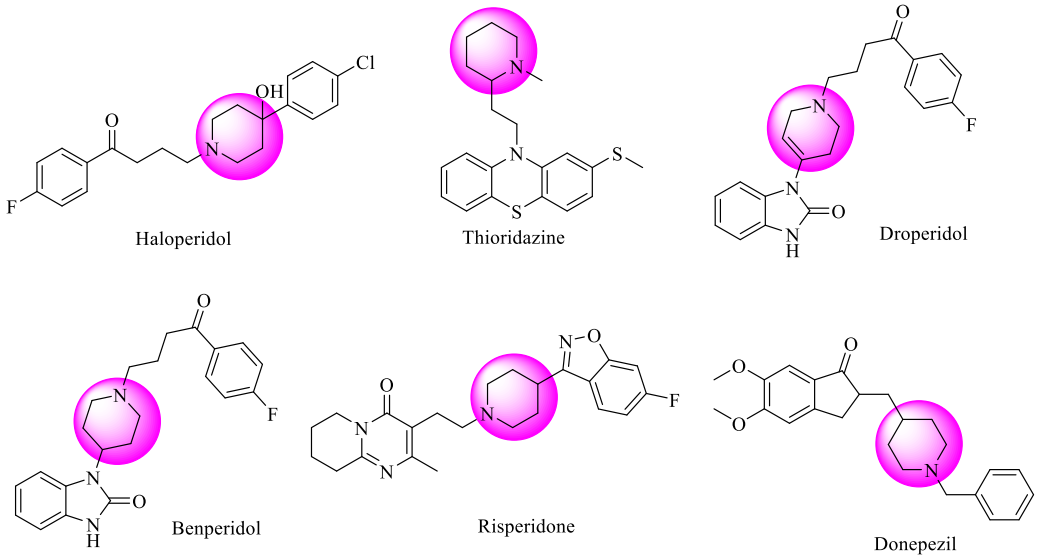


Figure 3. Structures of FDA-approved drugs containing a piperidine nucleus.

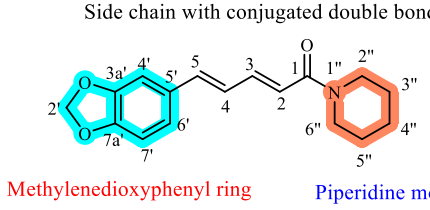


Figure 4. Structure of piperine.

have any inhibitory effects on any MAO subtype. Piperine (1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]piperidine), which is the sole piperidine derivative, was found to be active against both types of MAO enzymes, with a greater potency for MAO-A compared to the seven examined alkaloids. The compound's exposed amide group, which may create hydrogen bonds between functional protons, such as −NH−, −OH−, and −SH within the active regions of MAO enzymes, may cause the observed suppression according to a scientific theory.[64]

Lee et al. (2005) performed the extraction and activity-guided isolation of piperine from the *Piper longum* and analyzed its MAO inhibitory activity. They investigated the MAO inhibitory activity using the enzyme that was isolated from mouse brain mitochondrial fractions and iproniazid as the positive control. Piperine was found to have an IC_{50} threshold of 11.1 μM, with 38.0% MAO activity suppression at a concentration of 8 μM. Additionally, piperine has a stronger inhibitory effect on MAO-B than MAO-A, with IC_{50} values of 7.0 and 20.9 μM, respectively. Moreover, kinetic studies were conducted to consider the piperine-induced inhibition pattern of MAO, revealing that MAO-A and MAO-B demonstrated competing inhibition, with K_i concentrations of 19.0 ± 0.9 and 3.19 ± 0.5 μM, respectively. The tail suspension test is also resistant to *in vivo* antidepressant-like effects of piperine.[65]

A study by Li et al. (2007) used two depression models, including the tail suspension test and the forced swimming test, to examine the antidepressant-like effects of piperine and its derivative, antiepilepsirine (AES) (Figure 5). Additional measurements were made to clarify the mechanisms underlying the mouse brain monoamine concentrations and the functioning of MAO-A and MAO-B. Piperine and AES demonstrated marginally effective MAO-inhibiting actions according to the

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

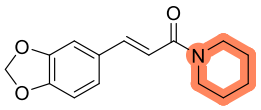


Figure 5. Structure of anti-epilepsirine.

MAO activity assay. This study revealed that piperine and AES both have marginally effective MAO-suppressing effects.[66]

Lee et al. (2008) performed the activity-guided fractionation of methylene chloride-soluble extracts of fruits of *P. longum* and obtained three piperine derivatives, namely methylpiperate, piperlonguminine, and guineensine (Figure 6). This study was

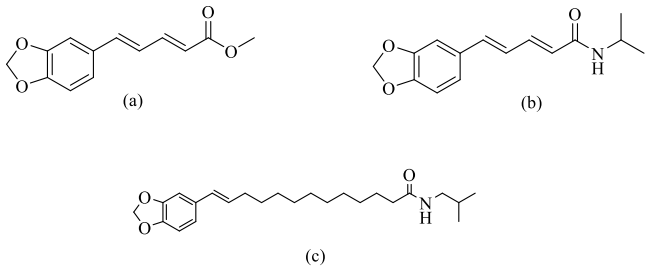


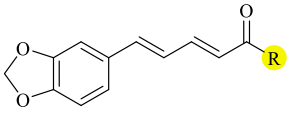
Figure 6. Structures of (a) methylpiperate, (b) piperlonguminine, and (c) guineensine.

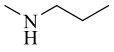
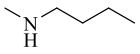
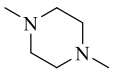
based on their previous work on naturally occurring MAO inhibitors, and the ability of piperine to hinder the MAO-A and MAO-B was already established.[67] They evaluated the inhibitory activity of extracted derivatives using mouse-brain-isolated MAO enzymes by fluorometric analysis using kynuramine as substrate. The study revealed that piperlonguminine has no inhibitory activity on MAO, and methylpiperate demonstrated a stronger inhibitory effect against MAO-B than MAO-A. Methylpiperate, guineensine, and piperlonguminine, from the three piperine derivatives, were found to possess potent, intermediate, and no inhibitory activity, respectively.[67]

The *in silico* research conducted by Rahman and Rahmatullah (2010) determined the molecular processes of piperine and its related molecules. They selected the MAO-A and MAO-B crystal structures (PDB 2Z5X[68] and 2V5Z,[69] respectively), from the Protein Data Bank, for the computational studies. The ligands for the study were obtained from the PubChem database, and the authors performed molecular dynamic simulation (MD) concerning flexible docking using NAMD version 2.7b1 and AutoDock 4.0. Figure 4 explains the different groups that make up the body of piperine. The piperine molecule interacts with Tyr69, Ile180, Asn181, Ile207, Gln215, Cys323, Ile335, Leu337, and Tyr407, as well as the isoalloxazine ring of the FAD residues at the active site of MAO-A. The methylenedioxyphenyl (MDP) ring's oxygen atoms make hydrogen bonds with water molecules (726th, 746th, and 805th in 2Z5X), while the carbonyl oxygen present in the carbonyl amide binds to the thiol group of Cys323; these hydrogen bonds are essential for keeping the molecule at the active site.[70]

MAO-B features a precursor interaction space and a single-entrance space, in contrast to MAO-A, and docking studies established that piperine can bind to both sites mainly through hydrophobic interactions. The binding fashion of piperine within those sites was such that the MDP ring interacts with the substrate cavity (Tyr398, Tyr435, Tyr188, Gln206, Gly434, Cys172, and the isoalloxazine ring of FAD) and the piperidine heterocyclic ring binds to the entrance cavity through interacting with Ileu199, Tyr326, Leu171, Thr201, Phe168, Leu164, and Leu167 residues. Two hydrogen bonds are also observed due to the water molecules present in the active site (the water molecule at the 1155th position in 2V5Z to which Cys172 and Tyr188 make hydrogen bonds and the connection of the carbonyl oxygen present in the carbonyl amide of piperine with a different water molecule [1229th position in 2V5Z] to which Ileu199, Tyr326, Thr201, and Gln206 seem to engage in comparable interactions). The piperidine moiety in the structure is what causes piperine to be MAO-B specific, but notably MAO-A-selective action is minimally impacted by its

Table 1. *r*MAO Inhibitory Activity of Piperine Derivatives



COMPOUND	R	IC_{50} MAO-A (μM)	IC_{50} MAO-B (μM)	SI VALUE[a]
1		0.404	0.26	1.553
6		3.66	0.045	81.33
7		>100	0.33	> 303.030
8		3.82	0.078	48.974
9		2.04	0.96	2.125

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

absence. Piperidine alone has some MAO-antagonistic effects, suggesting that the piperidine group in the molecule and its derivatives may be a crucial constitutional component for the overall MAO suppression. The authors investigated molecules that are similar to piperine, such as the shorter counterpart of piperine, antiepilepserine (Figure 5) and concluded that shortening the piperine scaffold can boost MAO-B affinity while maintaining MAO-A potency.[70]

A study to ascertain the effect of piperine on depressive disorder brought on by pilocarpine-induced status epilepticus in rats was conducted by Pal et al. (2011). The monoaminergic transference of noradrenergic, dopaminergic, and serotonergic signals is improved by piperine, which is an MAO inhibitor. The research established that piperine and its derivative, antiepilepsirine, efficiently trigger serotonin generation. The impact of piperine in MAO and γ-aminobutyric acid is responsible for the antidepressive function of piperine in post-SE rats.[71]

Huang et al. studied the probable mechanisms underlying the combined antidepressant-like effects of piperine and *trans*-resveratrol in mice. Results revealed that *trans*-resveratrol affects serotonergic signaling as well as hypothalamic−pituitary−adrenal axis functioning. The findings further revealed that the compound's biological availability is poor and its duration of action is short, which hinder its effectiveness in treating neurological illnesses. Piperine seems to have a potent ability to enhance bioavailability with a wide range of structurally and therapeutically diverse drugs due to its contribution to enhancing the systemic absorption of other drugs. Earlier studies have revealed that resveratrol has an antidepressant-like effect on the brain by boosting monoaminergic neurotransmitter levels. These results prompted the researchers to experiment with combining *trans*-resveratrol and piperine. The findings revealed that the combination of piperine and resveratrol causes highly specific MAO-A inhibition. Simultaneously, MAO-B activity was observed only at a concentration of 20 mg/kg resveratrol with 2.5 mg/kg piperine. The MAO antagonism property of the combination is due to the antagonistic activity of piperine on MAO.[71]

3. SYNTHETIC ANALOGS FOR PIPERIDINE AS MAO INHIBITORS

Mu et al. (2012) designed and synthesized 19 piperine derivatives by modifying the amide linkage and evaluated their activity potential against the MAO enzyme (Table 1). The property of MAO-B inhibition was present in all the compounds, and only compound **10** (Figure 7) was observed to be more

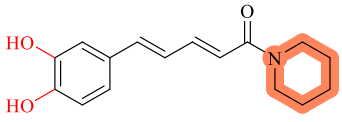


Figure 7. Structure of compound **10**.

active for MAO-A, with inhibitory concentrations of 0.8 and 1.57 μM for the A and B isoforms of MAO, respectively, and a selectivity index for MAO-B of 0.5095. The compound **6** (5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienoic acid *n*-propyl amide) was discovered as particularly effective against MAO-B (IC_{50} = 0.045 μM and SI value of 81.33 for MAO-B) and more potent than piperine, and the same was observed with comparable activity for MAO-A (IC_{50} = 3.66 μM). Therefore, piperine derivatives with a small amine moiety are effective toward MAO-B with high selectivity.[72]

Compounds with substituents of −*N*-propyl and −*N*-diethyl groups were discovered to be potent derivatives, with activity greater than that of piperine. Substituting the piperidine ring with small amino functional groups yields compounds with comparatively higher activity in the series for MAO-B inhibition. Only compound **10** (Figure 7) exhibited MAO-A inhibitory properties out of all the analogs that were synthesized. It is noted that caution must be paid to the possible inhibition of MAO-A because it depends on which spectrophotometric assay is used. Further, compounds lacking the piperidine ring become less active toward the enzyme, in contrast to the MAO-A-suppressive activity of all the synthesized compounds. The findings indicate the importance of the carbonyl group and conjugation of piperine derivatives for the ability to inhibit MAO.[72] The SAR of the derivatives is depicted in Figure 8.

In 2012, Al-Baghdadi et al. created and synthesized several substances with structural similarities with piperine and revealed that all the compounds have MAO-antagonistic activity, with comparable selectivity toward MAO-B (Table 2). The selectivity of compounds toward MAO-B increased with the butylamino side chain in the R position, reaching >303.030. Substituting R with a diethylamino group gives a compound with less selectivity than that with an *n*-butylamino group. The most potent compound was compound **14** with an inhibitory concentration of 0.497 μM toward MAO-B, where the piperidine ring's fourth position was substituted with a methyl moiety.[73]

The optimal length of the linker between the MDP ring and the nitrogen-containing heterocyclic ring for the MAO-B suppressive activity is 2−5 carbons, which should be conjugated. The maximum inhibitory activity is observed when the heterocyclic ring is a six-membered one. The inhibitory activity is drastically reduced when the amide linkage is turned into a thioamide link. The most potent derivative of piperine was compound **14** with a three-membered amide linkage and a 4-methyl-substituted piperidine ring, showing high inhibitory activity for MAO-B with a selectivity value greater than 201.207. Compound **12** shows good antagonistic activity against MAO-B, with a SI value greater than 151.515; in **12**, the piperidine ring is changed to the cyclohexanamine group, and the activity is reduced significantly whenever oxygen is introduced instead of the 4-position carbon (Figure 9).

Piperine is an established compound reported with diverse biological benefits, such as analgesic, anti-inflammatory, insecticidal, and antidepressant activity. Prashanth et al. designed a collection of substances derived from the *trans*-isoform of piperine because the (*Z*)-form of the compound was discovered to have biological activity. All the synthesized compounds were evaluated for antibacterial, antidepressant, and antioxidant activity, and selected compounds underwent the enzyme inhibitory assay against MAO-A and MAO-B using mouse brain homogenate as a source of MAO. The three tested compounds were found to possess lower inhibitory concentrations than that of the standard drug used (Table 3). Compound **20** was the most potent, and compounds **19** and **21** were more potent than clorgyline, which is the standard drug used in the study.[74]

The compound with a *para*-hydroxy piperidine ring substitution demonstrated maximum inhibitory activity, with IC_{50} values of 0.01446 ± 0.00183 and 0.01572 ± 0.00192 μM for MAO-A and MAO-B, respectively. The findings revealed that

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

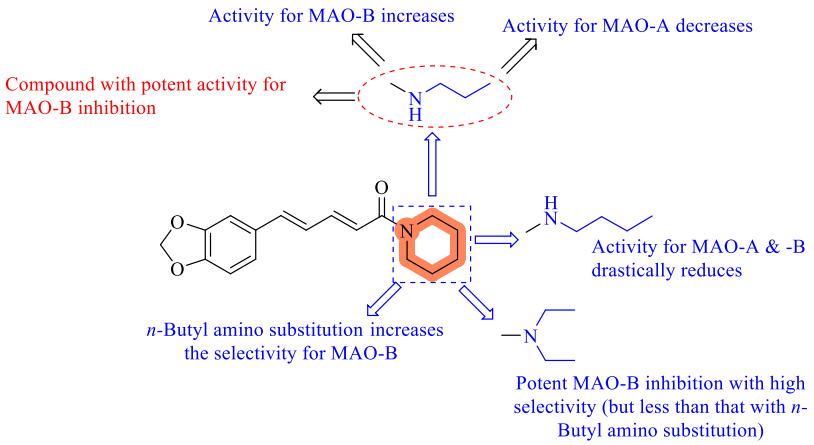
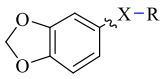
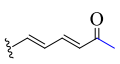
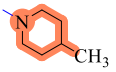


Figure 8. Structure−activity relationships (SARs) of the piperine derivatives.

Table 2. Inhibitory Activity of Structurally Similar Piperine Derivatives against *h*MAO (A and B)



COMPOUND	X	R	IC_{50} FOR MAO-A (μM)	IC_{50} FOR MAO-B (μM)	SI VALUE[a]
1			58.98	0.483	122.111
11			>100	15.39	>6.497
12			>100	0.66	>151.515
13			>100	6.39	>15.649
14			>100	0.497	>201.207
15			>100	4.89	>20.449
16			>100	3.18	>31.446
17			>100	3.43	>29.154
18			>100	>100	1

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

the *para*-substitution of piperidine is preferable to the *meta*-substitution and the addition of a hydroxyl function increases the MAO inhibitory effect (Figure 10).

By combining Tables 2 and 3, we can draw another SAR (Figure 11). The introduction of a methoxy group on the benzodioxazole ring increases the MAO inhibitory activity. Selecting an allyl group for linking the carbonyl group and benzodioxazole ring increases the MAO inhibition. A 4-methyl piperidine substituent as the R group produces high MAO-B inhibition.

Pettersson et al. assessed the impact of a series of 4-phenylpiperidines and 4-phenylpiperazines with substitutions on the *para*-position of the phenyl ring on antagonist activity against the MAO enzyme. They synthesized a set of *para*-substituted 4-phenylpiperidines and 4-phenylpiperazines and tested their compatibility with recombinant rat cerebral cortex MAO-A and MAO-B. The pK_i value for the synthesized derivatives and the K_i calculations, including confidence intervals from IC_{50}, were calculated using the Cheng Prusoff equation ($K_i = IC_{50}/(1 + (L/KD))$, where L is the concentration of radioligand in the assay and KD is the affinity of the

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

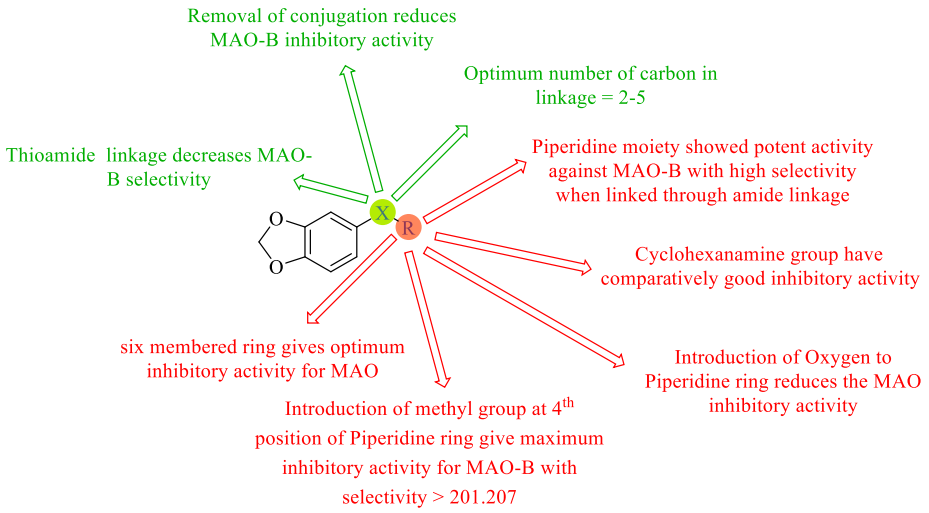
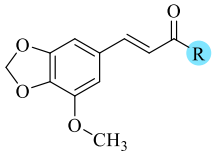
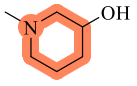
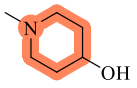


Figure 9. SAR of structurally similar piperine derivatives.

Table 3. *In Vitro h*MAO Inhibition Activity of Derivatives of the *trans*-Form of Piperine



COMPOUND	R	IC_{50} FOR MAO-A (μM)	IC_{50} FOR MAO-B (μM)	SI VALUE[a]
19		0.01709 ± 0.00226	0.01801 ± 0.00327	0.948
20		0.01446 ± 0.00183	0.01572 ± 0.00192	0.9198
21		0.01663 ± 0.00349	0.01733 ± 0.00218	0.9596

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

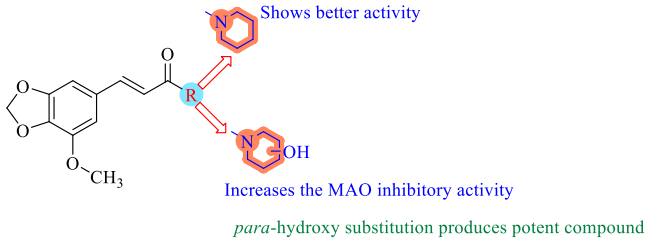


Figure 10. SAR of derivatives of the *trans*-form of piperine.

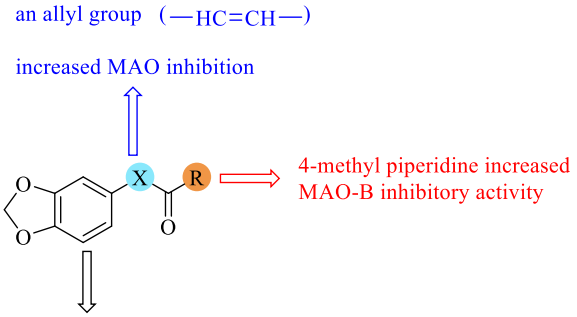


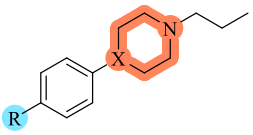
Figure 11. SAR of benzodioxazole-coupled piperidine derivatives.

radioligand for the enzyme (Table 4). Furthermore, they evaluated the SAR for 4-phenylpiperidines and 4-phenylpiperazines with substitutions on the *para*-position and looked at the equivalent analogs with substitutions at the fourth position of the dopamine receptor stabilizer pridopidine. The presence of methyl sulfone at an aromatic position of pridopidine generated a molecule in which changing the substituent position from *meta* to *para* did not affect the striatal DOPAC.[75]

Methoxy compounds displayed a strong affinity for MAO-A. In contrast, compounds with substituents with high dipole moments, such as the cyano group, yielded molecules with negligible or only minimal MAO-A affinity. The MAO-A affinity slightly decreased for each of the unsubstituted compounds (**22** and **30**) and the compounds modified with the methoxy group

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

Table 4. *r*MAO Inhibitory Activity of *para*-Substituted 4-Phenylpiperidines and 4-Phenylpiperazines



compound	X	R	pK_i (MAO-A) (mM)	p_Ki (MAO-B) (mM)
22	−CH	−H	5.01	NT
23	−CH	−Cl	5.82	4.42
24	−CH	$-CF_3$	5.16	4.89
25	−CH	−morpholine	5.92	4.89
26	−CH	−OMe	6.62	3.66
27	−CH	−O-*n*-Bu	6.43	5.80
28	−CH	−CN	4.03	3.23
29	−CH	$-SO_2Me$	3.23	3.23
30	−N	−H	4.33	NT
31	−N	−OMe	5.85	3.23
32	−N	$-OSO_2CF_3$	4.77	7.48

[a] p_K: negative logarithm of binding affinities. NT: not tested.

(**26** and **31**) when the piperidine ring was converted to piperazines, as seen in Figure 12.[75]

The substances were better blockers of MAO-A than MAO-B, although those methoxy-substituted analogs were more efficient MAO-B antagonists. The substance with the trifluoromethanesulfonate substitution was discovered as an effective antagonist of MAO-B. Generally, −CH substitution at the X position led to more effective and specific MAO-A inhibitors. The electron-donating groups, such as methoxy and butoxy, were shown to be more effective at inhibiting MAO-A than electron-donating halogens and morpholine. In contrast, the alkoxy compounds in the series followed a somewhat different pattern, with *n*-butoxy (**27**) exhibiting a lower affinity than methoxy (**26**).[75]

4. DONEPEZIL HYBRIDS AS MAO INHIBITORS

Bolea et al. generated a collection of unique hybrid compounds by linking the benzyl piperidine moiety of donepezil and the [(1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine moiety of *N*-[(5-benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine through an oligomethylene bond, hoping that they would be potent against both MAO and AChE enzymes (Figure 13). The benzyl piperidine component of the effective AChE inhibitor donepezil is thought to best interact with the receptor's catalytic and middle sites, whereas the [(1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine functional part in *N*-[(5-benzyloxy-1-methyl-1H-indol-2-yl)-methyl]-*N*-methylprop-2-yn-1-amine is a promising binder for the MAO enzyme's substrate binding site.[76]

Here, the hybrid molecules were tested for MAO and AChE/BuChE inhibitory action. Each of the molecules has been tested for its antagonism effect on A and B isozymes of MAO that were retrieved from the mitochondrial membrane of rat liver, and the results were then compared to those of the standard donepezil and *N*-[(5-benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine (Table 5). The investigation revealed that all the 1-benzylpiperidin-4-yl derivatives **33**−**36** are potent for MAO-A but have lower potency for MAO-B except compound **35**, which was the most potent one toward both types of enzymes, with IC_{50} values of 5.2 ± 1.1 and 43 ± 8.0 nM for MAO-A and MAO-B, respectively.[76]

The potency of 1-benzylpiperidin-4-yl-substituted compounds is higher than that of 4-benzylpiperidin-1-yl-substituted compounds. The resulting compound **8**, which is the most effective for both MAO-A and MAO-B, is created when the 1-benzylpiperidin-4-yl group is combined with [(1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine through an alkyl chain with $n = 2$. Potent compounds against MAO-A are produced when the X group is replaced with a tertiary amine group (Figure 14).

Previous investigations by Marco-Contelles et al. designed and synthesized 16 donepezil−pyridyl hybrids and evaluated them for their antagonistic activity toward cholinesterase and MAO. Further, the authors incorporated the benzyl piperidine group present in the donepezil and compound **ASS234** and the propargylamine moiety of **ASS234** in the second and sixth positions of the pyridine nucleus containing a six-membered aromatic ring, respectively(Figure 15).

The biological assessment revealed that the majority of the synthesized compounds were almost inactive (**49**−**51** and **54**−**55**) or moderate inhibitors (**44**, **48**, **52**, and **53**) (Table 6).

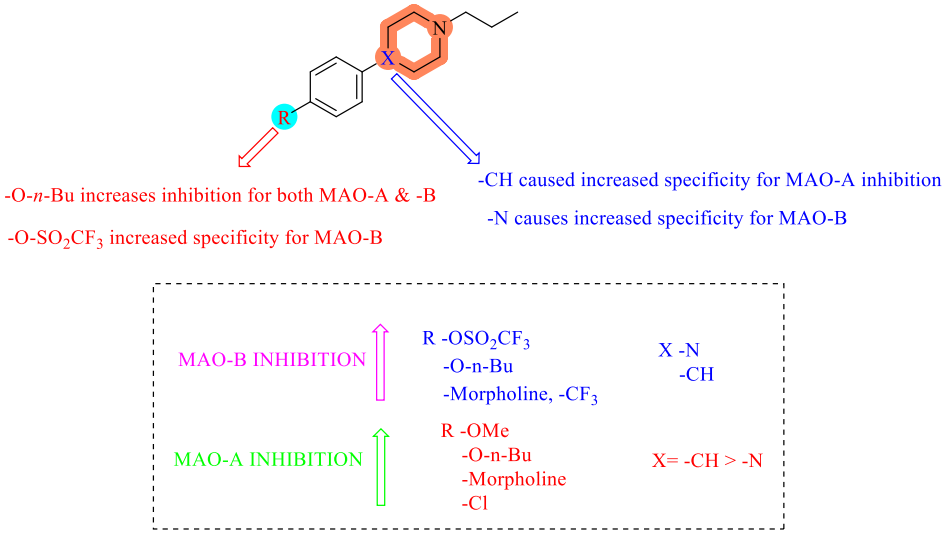


Figure 12. SAR of *para*-substituted 4-phenylpiperidines/piperazines.

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

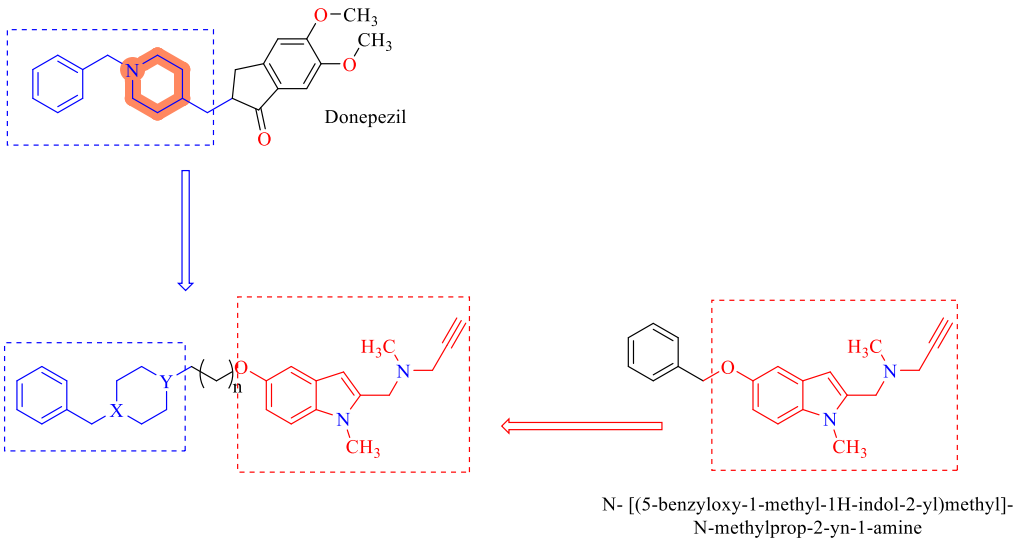
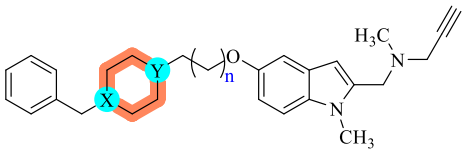


Figure 13. Design strategy of donepezil−*N*[(5-benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine hybrids.

Table 5. Rat Liver Mitochondrial MAO (*r*MAO) Enzyme Inhibitory Activity of Donepezil−*N*-[(5-Benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine Hybrids



compound	X	Y	n	IC_{50} for MAO-A (μM)	IC_{50} for MAO-A (μM)	SI value[a]
33	N	CH	0	0.082 ± 0.003	0.750 ± 0.0020	0.1093
34	N	CH	1	0.0067 ± 0.0018	0.130 ± 0.041	0.0515
35	N	CH	2	0.0052 ± 0.0011	0.043 ± 0.008.0	0.1209
36	N	CH	3	0.010 ± 0.0040	2.700 ± 0.110	0.00370
37	CH	N	1	0.140 ± 0.044	1.400 ± 0.500	0.1
38	CH	N	2	0.065 ± 0.017	11.000 ± 2.400	0.0059
39	N	N	2	0.031 ± 0.014	1.600 ± 0.710	0.0193

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

Compounds **48** and **53** exhibited stronger inhibition of MAO-A and MAO-B, respectively, with IC_{50} values of 5.7 ± 2.1 and 3.95 ± 0.94 μM. Further, compound **52** demonstrated a moderate selectivity for MAO-B and had an IC_{50} value of 6.11 ± 1.4 μM. The selective inhibition of MAO-B was demonstrated by compounds with *N*-methyl propargylamine. Removing the phenyl ring from the fourth position of the pyridine nucleus is directly linked to a change in the discernment of the compounds from MAO-A to MAO-B. Compound **53** was the most appropriate suppressor of MAO, with a MAO-B/MAO-A selectivity index of <0.039.[77]

Wang et al. developed novel molecules for AD management by clubbing the structural features of donepezil, propargylamine, and 8-hydroxyquinoline. Here, the design of new molecules was based on the structural features of some already reported molecules, including donepezil, **M30**, **M30A**, **M30B**, **HLA20A**, and **ASS234**. All seven derivatives they synthesized were evaluated for their inhibitory activity toward MAOs (Table 7). The racemic mixture of compound **61** was the most active one, with an irreversible type of antagonism against both MAO-A and MAO-B. Blood−brain barrier (BBB) permeability, toxicity, and binding ability with both isoforms of MAO were evaluated for the effective compound **61**. All the results indicate that the compound has good CNS permeation, low toxicity, and better binding scores for MAO-A and MAO-B.[78]

Outcomes of the enzyme inhibitory assay indicate that compounds substituted with the cyano group had potent inhibitory activity against both MAO-A and MAO-B when compared with unsubstituted derivatives. Selective and potent MAO-B inhibition was produced by the unsubstituted piperidine derivative with a methylene linker, and the selectivity index was calculated to be 4.402. The number of alkyl groups between the benzyl piperidine moiety and the propargylamine moiety has an important role, *i.e.*, an increase in MAO inhibition was observed with an increase in the number of carbons in the linker (Figure 16).[78]

In 2016, Li et al. developed several molecules with structural similarities with the donepezil molecule, which is an effective acetylcholinesterase inhibitor, and some MAO inhibitors, including lazabemide, Ro16-6491 (MAO-B inhibitor), and moclobemide (MAO-A inhibitor). They have been designed by preserving the benzyl piperidine moiety in both donepezil and picolinamide, which is a common feature of MAO inhibitors, and these are connected through the alkyl chain (Figure 17). The suppressive potency toward MAO isoenzymes was studied for each of the developed molecules, and a majority of them

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

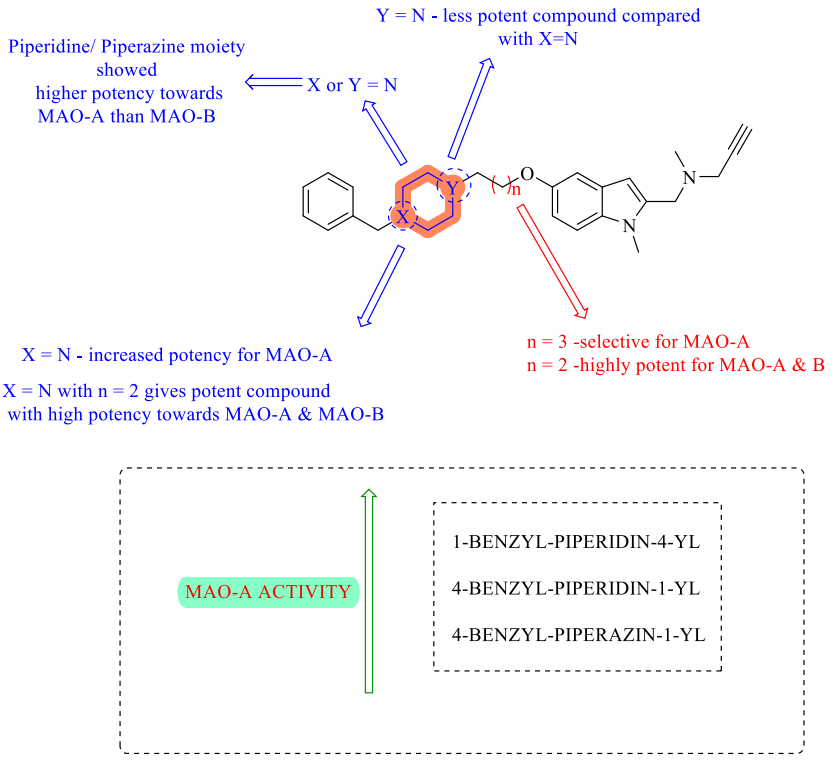


Figure 14. SAR of donepezil-*N*−[(5-benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine hybrids.

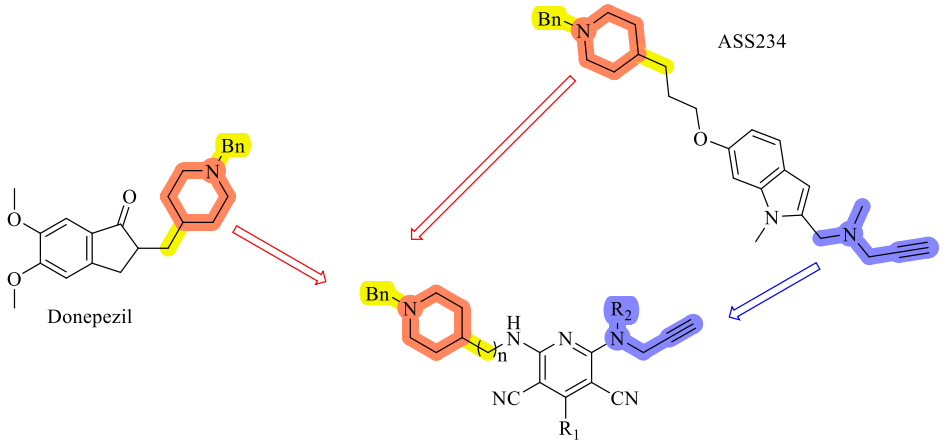


Figure 15. Design strategy of donepezil−**ASS234** hybrids.

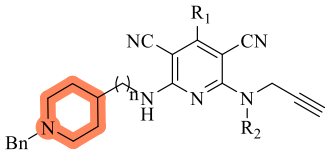
possess antagonistic activity for MAO-B and MAO-A with high potency.[79]

The SAR analysis revealed two carbons in the linker between the benzyl piperidine moiety and the amide functional moiety was optimal for MAO inhibitory activity (Figure 18). Substituting the R group with a pyridine or a thiophene nucleus containing electronegative atoms, such as chlorine and bromine, at the fifth position gives potent compounds with selective inhibition of MAO-B. The strongest compound obtained from the series is compound **69**, with inhibitory concentrations of 13.4 ± 0.9 and 3.14 ± 0.27 μM for MAO-A and MAO-B, respectively. From the series, compound **70** was discovered as an effective molecule against MAO-B, with an IC_{50} value 2.53 ± 1.4 μM, and was found to have greater selectivity toward MAO-B, with a selectivity index of >39.5. Substituted five-membered heterocyclic aromatic rings (such as thiophene) increase the selectivity toward MAO-B inhibition compared to other substituted heterocyclic aromatic rings. The substituted pyridine ring produced potent compounds for MAO inhibition compared to the activity of the substituted thiophene ring. A methyl-substituted aromatic or heteroaromatic ring system gives selective inhibition toward MAO-B.[79]

Xie et al. designed a series of molecules for targetting ChE and MAO by combining the *N*-benzyl piperidine moiety of donepezil with the coumarin nucleus. Based on their previous work, the researchers were trying to replace the acridine-based tacrine structure from the molecule that was obtained from their research. In this work, they incorporated the benzyl piperidine nucleus of donepezil (which is more potent than tacrine and has no hepatotoxic effects) instead of the tacrine structure. They synthesized and evaluated 15 derivatives of donepezil−coumarin hybrids. The study revealed that no compounds have an effect on MAO-A at a concentration of 100 μM, and

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

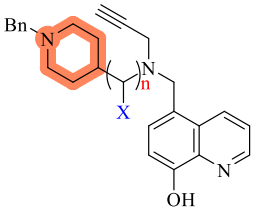
Table 6. *h*MAO Enzyme Inhibitory Activity of Donepezil−ASS234 Hybrids



compound	*n*	R_1	R_2	IC_{50} for MAO-A (μM)	IC_{50} for MAO-B (μM)	SI value[a]
40	0	−Ph	−Me	>100	>100	1
41	1	−Ph	−Me	>100	>100	1
42	2	−Ph	−Me	>100	>100	1
43	3	−Ph	−Me	>100	>100	1
44	0	−Ph	−H	14.1 ± 3.8	>100	0.141
45	2	−H	−Me	>100	>100	1
46	0	−H	−H	>100	>100	1
47	2	−H	−H	>100	>100	1
48	4	−Ph	−Me	5.7 ± 2.1	>100	0.057
49	2	−Ph	−H	>100	>100	1
50	3	−Ph	−H	>100	>100	1
51	4	−Ph	−H	>100	>100	1
52	3	−H	−Me	>100	6.11 ± 1.4	16.366
53	4	−H	−Me	>100	3.95 ± 0.94	25.316
54	3	−H	−H	>100	>100	1
55	4	−H	−H	>50	>50	1

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

Table 7. Rat Liver-Isolated MAO (*r*MAO) Inhibitory Activity of Donepezil−Propargylamine−8-Hydroxyquinoline Derivatives



compound	X	*n*	IC_{50} for MAO-A (μM)	IC_{50} for MAO-B (μM)	SI value[a]
56	H	0	≥100	≥100	1
57	CN	1	22.1 ± 0.7	39.5 ± 1.4	0.559
58	H	1	85.4 ± 3.7	19.4 ± 3.2	4.402
59	CN	2	9.7 ± 1.5	12.4 ± 2.5	0.782
60	H	2	≥100	50.1 ± 5	1.996
61	CN	3	6.2 ± 0.7	10.2 ± 0.9	0.607
62	H	3	≥100	34.5 ± 3.5	2.898

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

most of the compounds show inhibition toward MAO-B at the same concentration range (Table 9).

All the compounds with an electron-donating group, such as the methyl group at either R1 or R2, produce stronger MAO-B inhibition, whereas substitution with electron-donating groups (such as −Cl, $-OCH_3$, and $-OCF_3$) will largely reduce the MAO-B inhibition activity. A potentially effective and specific MAO-B blocker was obtained by substituting R1 with H and R2 with CH_3, and the length of carbons in the alkyl linker between the benzyl piperidinyl ring and the secondary amino group was set at two. The ether linker between the coumarin ring and the benzyl piperidinyl alkylamine is unnecessary for MAO-B inhibition because the inhibitory activity is retained with the removal of the linker (Figure 19). Alkyl substitution of the coumarin ring in the case of compound **85** is where R1 and R2 are connected to form another ring, and **85** exhibited the third most potent inhibitory activity against MAO-B.[80] Pisani et al. studied the coumarin derivatives with 1,3- and 1,4-substituted piperidinyl compounds and determined that the position of substituents at the piperidine ring strongly influenced the MAO-B inhibition activity. Compounds with a 1,3-substituted

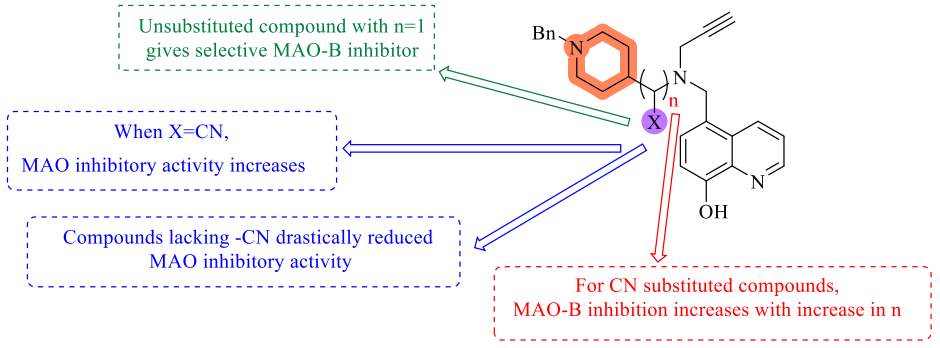
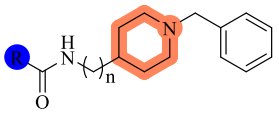


Figure 16. SAR of donepezil−propargylamine−8-hydroxyquinoline derivatives.

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

Table 8. *h*MAO Enzyme Inhibition Activity of Donepezil–Picolinamide Hybrids



compound	R	*n*	IC_{50} FOR MAO-A (μM)	IC_{50} FOR MAO-B (μM)	SI value[a]
63	2-Br-Ph-CH_2	2	NA	46.8 ± 2.2	
64	3-NO_2–Ph	2	92.4 ± 7.1	26.2 ± 1.5	3.526
65	4-NO_2–Ph	2	22.6 ± 1.8	68.3 ± 4	0.330
66	4-CH_3–Ph	2	NA	94.1 ± 4.9	
67	4-Cl-Ph	2	23.2 ± 1.8	9.27 ± 1.3	2.502
68	2-quinoline	2	24.5 ± 2.3	48.6 ± 3.3	0.504
69	5-Cl-2-pyridine	2	13.4 ± 0.9	3.14 ± 0.27	4.267
70	6-CH_3-2-pyridine	2	NA	2.53 ± 1.4	
71	5-Cl-2-thiophene	2	76.4 ± 5.4	11.5 ± 0.9	6.643
72	5-Br-2-thiophene	2	96.2 ± 4.8	9.47 ± 0.54	10.158

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

piperidine ring showed better activity, with IC_{50} values <0.25 μM.[81]

Joubert et al. developed derivatives of coumarin by substituting benzyl, piperidine, *N*-benzyl piperidine, or *p*-bromo-*N*-benzyl piperidine at the seventh position connected by an alkyl ether linkage to evaluate their anti-MAO effect. They performed the biological study using kynuramine as a combination MAO-A/B substrate (Table 10). The inhibitory concentrations of all of the compounds show their higher selectivity toward MAO-B than MAO-A. Compounds **88–95** possessed a higher inhibition on MAO-B than that produced by the reference standard selegiline. Bromobenzyl derivatives (**88–91**) exhibited better activity than unsubstituted benzyl derivatives (**92–95**). A remarkable reduction in MAO-B activity was noted when ethylpiperidine was introduced instead of the benzyl group. The results suggest no significant role for the substituent on the coumarin ring (R_2 and R_3) in MAO inhibition. Compounds with *p*-bromine substitution, from series **88–100**, have effective MAO inhibition. The compounds **92–95** and **108–112** are examples where the authors prove that the incorporation of a heterocyclic ring, such as piperazine between the coumarin and *p*-bromobenzyl group, will sharply reduce the MAO inhibition property. A piperidine ring produces increased MAO-B inhibition potency and no change in the MAO-A activity. The comparison of compounds **101** and **102** with the **103–107** series suggested that benzyl piperidinyl derivatives have higher inhibitory activity when compared with piperidinyl derivatives (Figure 20).[82] Compound **92** was the most dominant, with IC_{50} values of 0.24 and 0.0005 μM for MAO-A and MAO-B, respectively, and a selectivity of 480 toward MAO-B, followed by compounds **92**, **94**, and **93** with almost similar IC_{50} values for MAO-B and lower IC_{50} values for MAO-A (**93**, 0.05 and 0.0009 μM; **94**, 0.37 and 0.0008 μM, respectively).[82]

Cai et al. designed and developed a group of compounds by combining the structural motifs of trolox and donepezil to evaluate the multitarget effect, such as the anticholinesterase inhibitory and MAO-antagonistic effect, to develop a safer and more effective compound to control AD (Figure 21). Trolox, which is a derivative of vitamin E, is a potent antioxidant compound and has been biologically proven to reduce reactive oxygen species. The substituted benzyl piperidine functional group of donepezil is connected to this chemical structure through an amide linkage, and the ability to inhibit AChE as well as MAO was evaluated by Ellman and fluorescence-based methods, respectively. According to the results published, the compounds with a methyl amide linker (**113–125**) have a stronger inhibitory potency when compared with propyl amide-linked compounds (**126–138**) for all the molecules created.[83]

The biological evaluation and inhibitory assays revealed that compounds with an acetamide linkage between the benzyl piperidine and trolox moiety are more selective toward MAO-B than the MAO-A isoform (Table 11). The compounds with a propyl amide linkage between the benzyl piperidine and trolox moiety were nonselective MAO inhibitors. Compounds with benzyl piperidine substituted with an electronegative functional group have higher inhibitory activity those with other substitutions from all these derivatives. Fluorine group substitution is better for MAO inhibition, and the electron-donating groups have reduced potency compared with other unsubstituted derivatives (Figure 22). A highlyeffective MAO-B suppressor was compound **117**, with an IC_{50} value of 1.6 ± 0.3 μM, and compound **129** was considered the most effective compound of all the synthesized molecules, exhibiting non-selective MAO inhibition with IC_{50} values of 4.4 ± 0.2 and 4.3 ± 0.2 μM for MAO-A and MAO-B, respectively. Both the best compounds possess a fluorine on the aromatic ring of the benzyl piperidine moiety, which confirms its importance in MAO enzyme inhibition.[83]

In 2018, Cai et al. discovered novel hybrid compounds by combining donepezil and butylated hydroxytoluene (BHT). They evaluated the MAO inhibitory activity using a

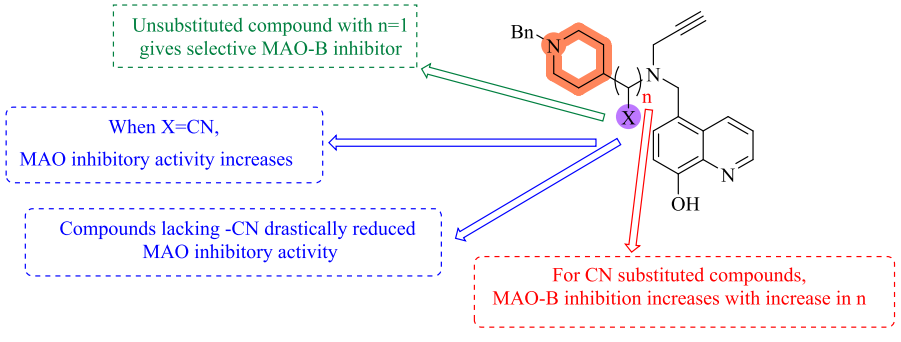


Figure 17. Design strategy of donepezil–picolinamide hybrids.

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731–37751

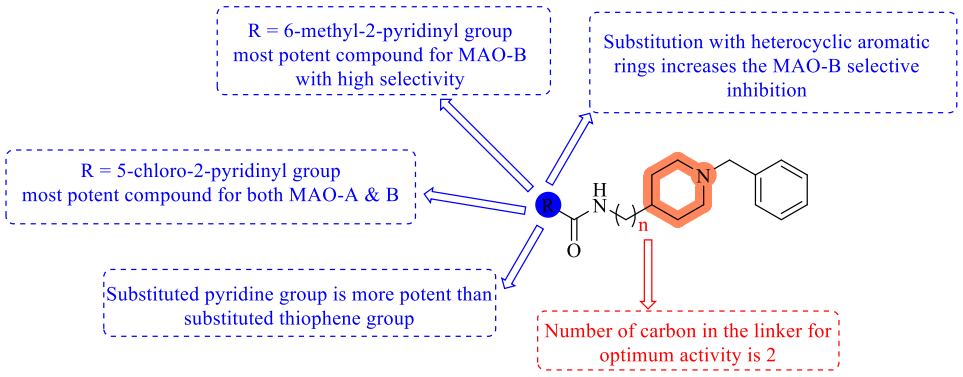
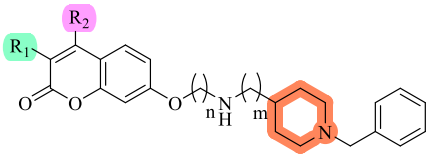
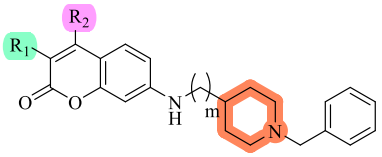


Figure 18. SAR of donepezil−picolinamide hybrids.

Table 9. Inhibitory Activity of *h*MAO Isoenzymes by Donepezil−Coumarin Hybrids



73-85



86-87

compound	R_1	R_2	*n*	*m*	IC_{50} for MAO-B (μM)
73	H	H	2	0	8.39 ± 0.91
74	H	H	3	0	12.6 ± 1.2
75	H	H	2	2	30.4 ± 2.5
76	H	Me	2	0	2.75 ± 0.22
77	H	Cl	2	0	33.9 ± 2.1
78	H	OMe	2	0	33.6 ± 0.9
79	H	OEt	2	0	31.9 ± 1.9
80	H	CF3	2	0	28.5 ± 1.7
81	H	Ph	2	0	45.6 ± 3.6
82	Me	H	2	0	2.38 ± 0.11
83	Me	Me	2	0	23.4 ± 1.1
84	Cl	Me	2	0	14.7 ± 1.5
85	$-(CH_2)_4-$		2	0	2.62 ± 0.81
86	H	Me		0	1.93 ± 0.33
87	H	Me		2	40.5 ± 4.1

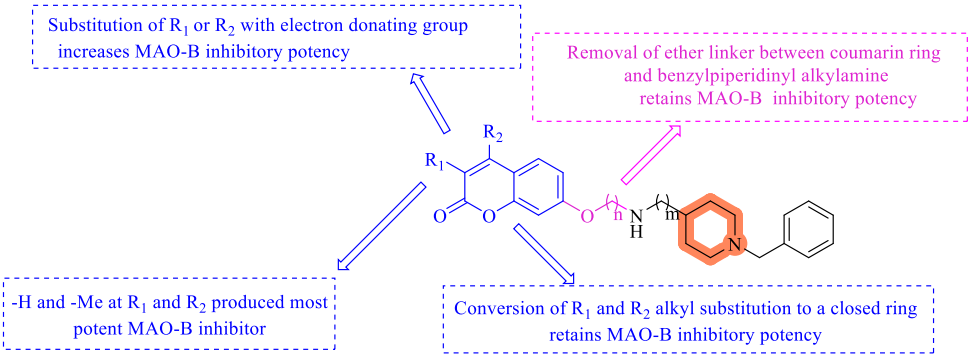


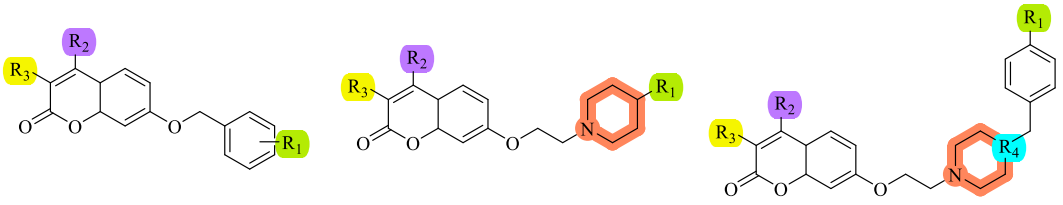
Figure 19. SAR of donepezil−coumarin hybrids.

fluorescence-based method with kynuramine as a reference molecule, which is a nonspecific MAO inhibitor. They incorporated the benzyl piperidine of donepezil with BHT and designed a series of compounds for optimizing the linker. the results that the compound with an alkene bridged amide with two methylene linkage between BHT and the piperidine ring (**139**) possessed the highest MAO inhibitory activity (Figure 23). The authors designed 13 derivatives of donepezil−BHT hybrids, each containing different substitutions on the aromatic ring of the benzyl piperidine moiety. All 13 derivatives were evaluated for inhibition activity against both the isoenzymes of MAO, revealing that all have a higher potency toward MAO-B compared with MAO-A.[84]

The evaluation of enzyme inhibition revealed compound **144** as the best molecule with specific MAO-B inhibition, with an IC_{50} value of 6.5 ± 0.2 μM, and the same molecule has a maximal

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

Table 10. ***In Vitro h*MAO Enzyme Inhibitory Activity of Coumarin Conjugates**



88-100 101-102 103-112

compound	R_1	R_2	R_3	R_4	IC_{50} for MAO-A (μM)	IC_{50} for MAO-B (μM)	SI value[a]
88	H	H	H		3.49	0.0038	930
89	H	CH_3	H		2.62	0.0020	1310
90	H	CH_3	Cl		2.13	0.0021	1024
91	H	CH_3	CN		1.38	0.0019	700
92	*p*-Br	H	H		0.24	0.0005	480
93	*p*-Br	CH_3	H		0.05	0.0009	56
94	*p*-Br	CH_3	Cl		0.37	0.0008	463
95	*p*-Br	CH_3	CN		0.05	0.0013	38
96	*p*-Br	H			>10	0.104	>96
97	*p*-F	CH_3	CN		0.60	0.0022	273
98	*p*-Cl	CH_3	CN		1.13	0.013	87
99	*o*-Br	CH_3	CN		>10	0.073	>137
100	*o*,*p*-Br	CH_3	CN		0.72	0.018	40
101	H	H	H		NA	9.21	
102	H	CH_3	H		NA	3.09	
103	H	H	H	CH	>10	0.47	>21
104	H	CH_3	H	CH	>10	0.53	>19
105	H	CH_3	C	CH	>10	0.29	>34
106	H	CH_3	CN	CH	>10	0.30	>33
107	H	CF3	H	CH	>10	5.33	>2
108	Br	H	H	N	>10	1.70	>6
109	Br	CH_3	H	N	>10	3.60	>3
110	Br	CH_3	Cl	N	>10	1.55	>7
111	Br	CH_3	CN	N	>10	1.41	>7
112	Br	CF3	H	N	>10	5.64	>2

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

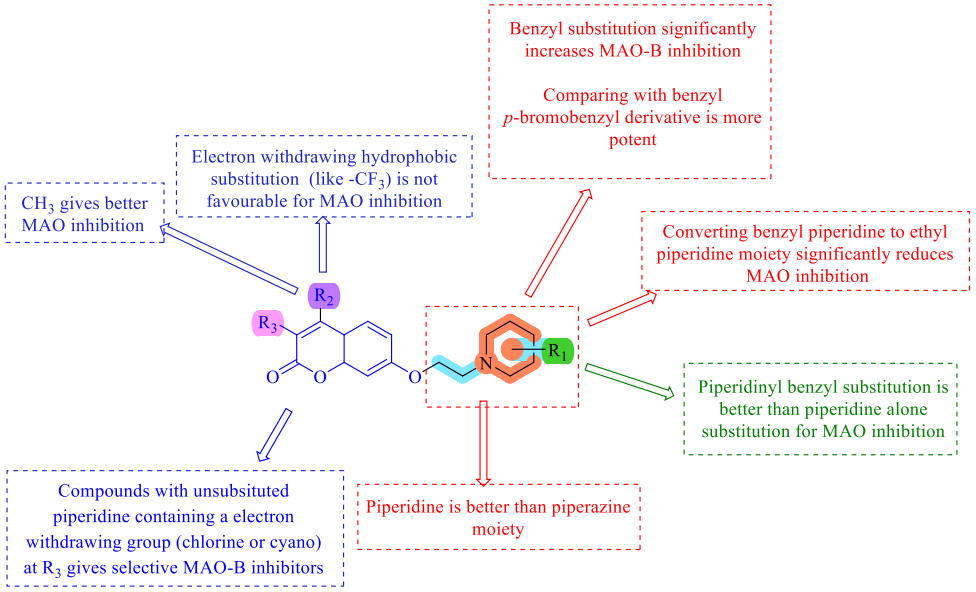


Figure 20. SAR of coumarin conjugates.

inhibitory concentration of 58.4 ± 0.5 μM against MAO-A (Table 12). The analysis of the structures and inhibitory activity of the derivatives suggested that an electron-donating group on the aromatic ring of benzyl piperidine may enhance the MAO

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

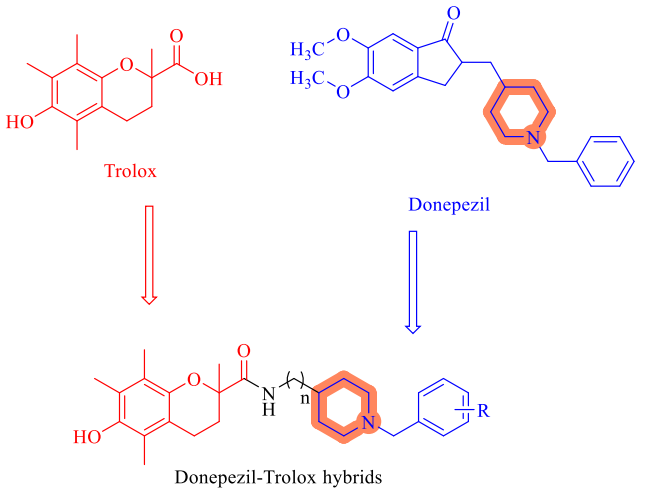


Figure 21. Design strategy of donepezil−trolox hybrids.

inhibition; simultaneously, we can say that an electron-withdrawing group can reduce the inhibition property. However, the most potent molecule **144** has a fluorine atom at the second position of the aromatic ring on the benzyl piperidine moiety (Figure 24).[84]

5. SUMMARY OF EFFECTIVE PIPERIDINE HYBRIDS AS MAO INHIBITORS

Any substitutions that make the benzyl piperidine more electron deficient, such as a halogen substitution on the benzyl group, are observed to lead to potent nonselective MAO inhibition. Piperidine analogs substituted with hydrophilic groups like hydroxyl groups were also found to be effective molecules for MAO inhibition. The highly potent hybrid compounds of piperidine with effective MAO inhibitory activity are summarized in Table 13.

6. CONCLUSION AND FUTURE PERSPECTIVES

MAO enzymes were the most significant pharmacological targets for managing and treating NDDs. Several FDA-approved drugs available for CNS activity possess the piperidine nucleus. The piperidine moiety has MAO inhibitory activity, and the piperidine in piperine is responsible for its MAO-B selective inhibition property. The *in silico* studies of the piperine molecule revealed that the piperidine nucleus interacts with the amino acid residues present in the entrance cavity of MAO. The

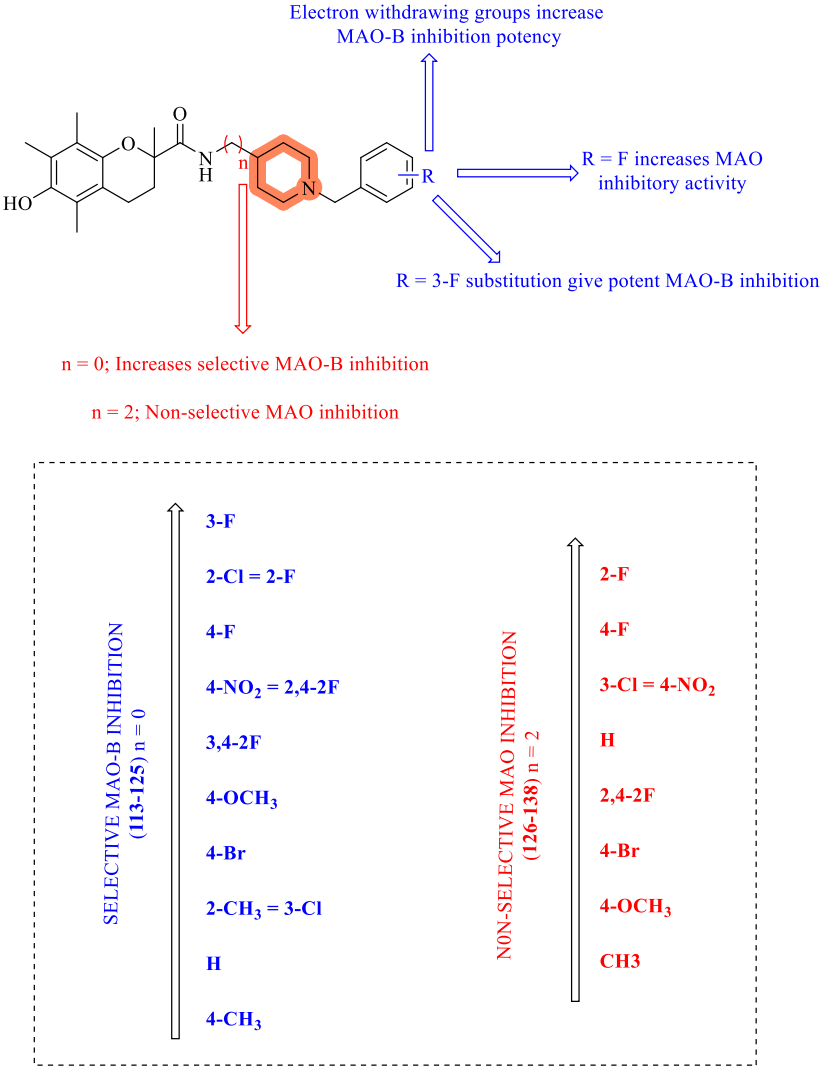
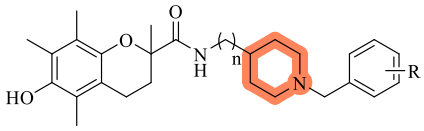


Figure 22. SAR of donepezil−trolox hybrids.

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

Table 11. *h*MAO Inhibitory Activity of Donepezil−Trolox Hybrids



compound	*n*	R	IC_{50} for MAO-A (μM)	IC_{50} for MAO-B (μM)	SI value[a]
113	0	4-OCH_3	15.3 ± 0.2	2.5 ± 0.1	6.12
114	0	2-CH_3	13.1 ± 0.3	3.1 ± 0.2	4.225
115	0	4-CH_3	12.7 ± 0.3	3.3 ± 0.2	3.848
116	0	2-F	8.9 ± 0.1	1.7 ± 0.2	5.235
117	0	3-F	9.3 ± 0.2	1.6 ± 0.3	5.812
118	0	4-F	11.4 ± 0.1	1.8 ± 0.3	6.333
119	0	2,4-2F	11.8 ± 1.2	1.9 ± 0.2	6.210
120	0	3,4-2F	12.5 ± 1.5	2.3 ± 0.5	5.434
121	0	2-Cl	12.7 ± 2.1	1.7 ± 0.3	7.470
122	0	3-Cl	13.8 ± 1.5	3.1 ± 0.1	4.451
123	0	4-Br	12.6 ± 0.3	2.7 ± 0.9	4.666
124	0	4-NO_2	13.2 ± 0.5	1.9 ± 0.3	6.947
125	0	H	11.1 ± 0.4	3.2 ± 0.3	3.468
126	2	4-OCH_3	7.8 ± 0.6	7.3 ± 0.2	1.068
127	2	2-CH_3	8.4 ± 0.1	6.9 ± 0.1	1.217
128	2	4-CH_3	8.9 ± 0.1	7.5 ± 0.1	1.186
129	2	2-F	4.4 ± 0.2	4.3 ± 0.2	1.023
130	2	3-F	5.3 ± 0.5	4.6 ± 0.2	1.152
131	2	4-F	4.8 ± 0.1	4.5 ± 0.3	1.066
132	2	2,4-2F	5.7 ± 0.3	5.8 ± 1.0	0.982
133	2	3,4-2F	8.1 ± 0.2	5.3 ± 0.7	1.528
134	2	2-Cl	7.2 ± 0.4	6.1 ± 0.4	1.180
135	2	3-Cl	5.8 ± 0.5	4.8 ± 0.3	1.208
136	2	4-Br	6.3 ± 0.2	5.7 ± 0.2	1.105
137	2	4-NO_2	5.4 ± 0.2	4.9 ± 0.1	1.102
138	2	H	5.6 ± 0.2	5.1 ± 0.2	1.098

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

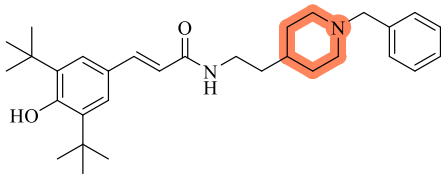
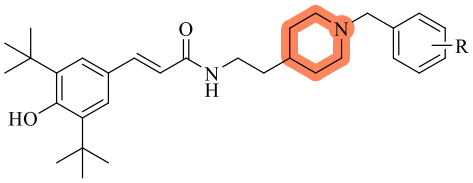


Figure 23. Structure of compound **139**

Table 12. *h*MAO Inhibition Property of Donepezil−Butylated Hydroxytoluene (BHT) Hybrids



compound	R	IC_{50} for MAO-A (μM)	IC_{50} for MAO-B (μM)	SI value[a]
139	H	62.3 ± 3.1	8.5 ± 0.3	7.329
140	4-OCH_3	72.5 ± 5.1	6.7 ± 1.2	10.820
141	2-CH_3	69.3 ± 3.2	7.2 ± 0.2	9.625
142	3-CH_3	70.1 ± 0.1	8.9 ± 0.3	7.876
143	2-F	60.2 ± 0.4	7.4 ± 0.2	8.135
144	3-F	58.4 ± 0.5	6.5 ± 0.2	8.984
145	4-F	59.6 ± 0.4	11.1 ± 0.1	5.369
146	2,4−2F	70.6 ± 0.3	12.5 ± 1.1	5.648
147	3,4−2F	64.5 ± 1.2	9.3 ± 0.2	6.935
148	2-Cl	72.1 ± 2.2	9.8 ± 0.2	7.357
149	3-Cl	65.1 ± 2.3	8.7 ± 0.1	7.482
150	4-Br	73.2 ± 1.1	13.2 ± 1.2	5.545
151	3-NO_2	70.9 ± 1.4	12.5 ± 1.1	5.672
152	4-CN	78.2 ± 1.3	13.9 ± 0.3	5.625

[a]Selectivity index for MAO-B (IC_{50} for MAO-A/IC_{50} for MAO-B).

piperidine nucleus has secondary nitrogen at its first position. By combining the whole reports, SARs of piperidine derivatives as human and rat MAO enzyme inhibitors (*h*MAO and *r*MAO, respectively) are summarized in Figures 25 and 26, respectively.

SAR of piperidine derivatives as *h*MAO inhibitors:

- Substitution of piperidine ring with an electron-withdrawing group at the third or fourth position may produce a nonselective *h*MAO inhibitor.
- For selective inhibition of *h*MAO-B inhibition, electron-donating groups such as methoxy and methyl groups can be incorporated into the piperidine ring at its third or fourth position.
- An electron-withdrawing substituent linked to the first position of piperidine was observed as an important structural feature for *h*MAO inhibition.
- A benzyl group at the first position of piperidine nucleus may produce nonselective *h*MAO inhibition.
- Any electron-withdrawing group (such as halogens) substituent at the phenyl ring of a 1-benzyl piperidine derivative may enhance selective inhibition of the *h*MAO-B isoenzyme.

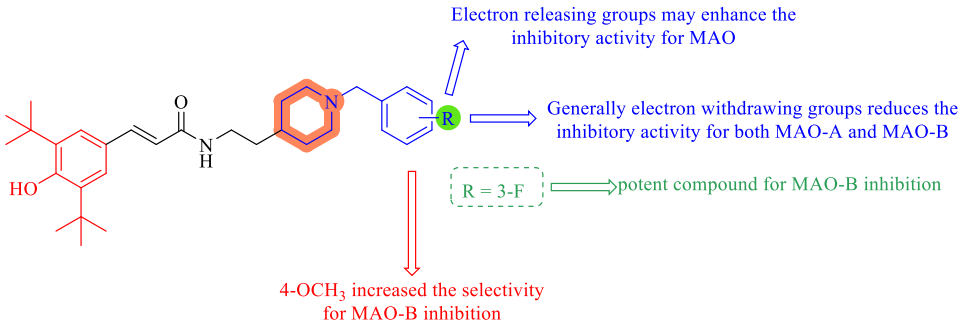
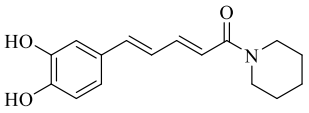
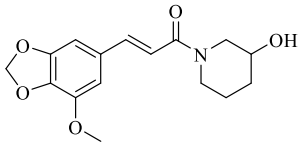
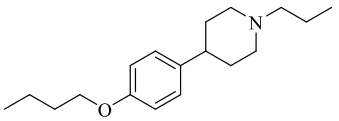
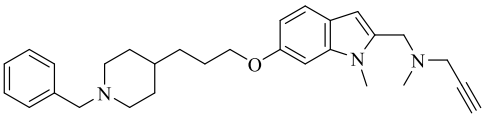
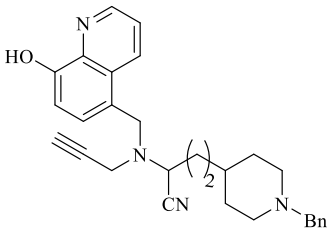
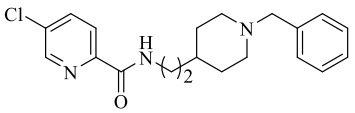
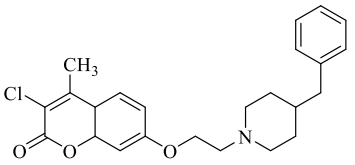
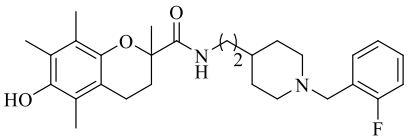
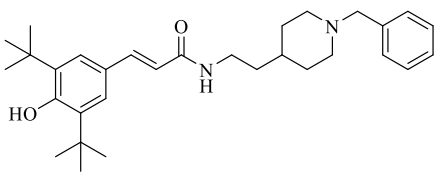


Figure 24. SAR of donepezil-BHT hybrids.

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

Table 13. Summary of Piperidine Hybrids with Effective MAO Inhibition

COMPOUND STRUCTURE	IC_{50} FOR MAO-A (μM)	IC50 FOR MAO-B (μM)
	0.8	1.57
	0.014	0.015
	6.43 (Ki value)	5.8 (Ki value)
	0.0052	0.043
	6.2	10.2
	13.4	3.14
	>10	0.29
	4.4	4.3
	6.2	8.5

- Selective *h*MAO-B inhibition may be achieved by connecting a heterocyclic ring such as coumarin or quinoline at the fourth position of piperidine ring through an amide linkage.

SAR of piperidine derivatives as *r*MAO inhibitors:

- An electron-withdrawing group at the first position may enhance the nonselective *r*MAO inhibition property of the compound.
- An electron-donating group (an alkyl group) substituent at the first position of piperidine derivative may produce selective *r*MAO-B inhibition.
- A phenyl ring at the fourth position of piperidine gives a *r*MAO-A inhibitor.
- Substituting the fourth position of the piperidine nucleus with a phenyl group with an electron-releasing group at its fourth position may enhance selective *r*MAO-B inhibition
- A benzyl substitution at the fourth position of piperidine ring may produce nonselective *r*MAO inhibition.

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

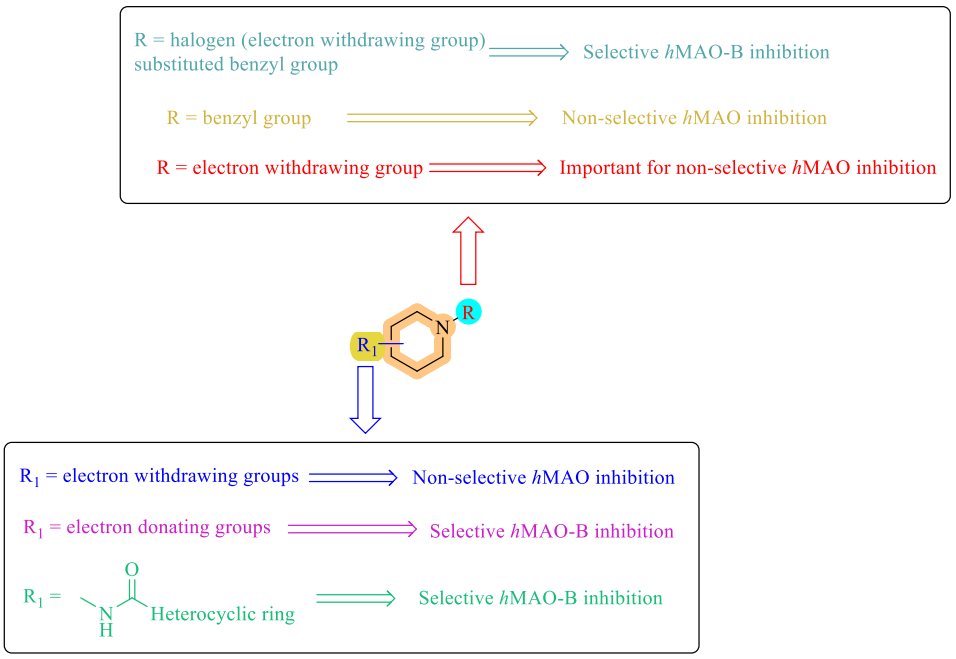


Figure 25. SAR of piperidine derivatives as *h*MAO inhibitors.

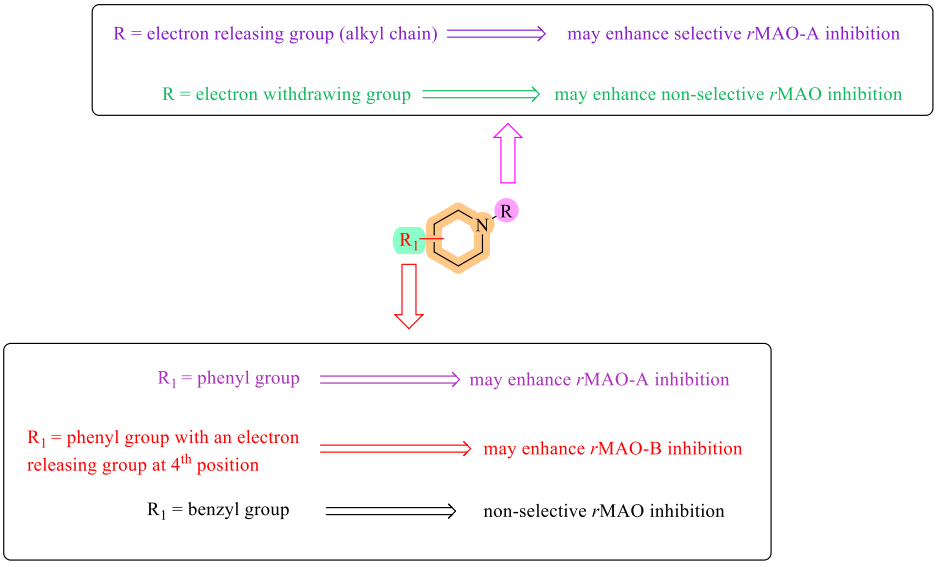


Figure 26. SAR of piperidine derivatives as *r*MAO inhibitors.

The *r*MAO-A inhibition property can be enhanced by the incorporation of an unsaturated alkyl chain to the secondary nitrogen with an amide linkage, whereas reducing the unsaturated chain to a saturated one will reduce the activity. The insertion of a benzyl group at the secondary nitrogen of the piperidine ring improves nonselective MAO inhibition in both human and rat MAO enzymes. Considering all of these facts, novel molecules can be developed in the future with potent MAO inhibition properties.

Researchers can conduct 2D- and 3D-QSAR in the future to build novel pharmacophores with substantial activity for MAO enzyme inhibition using the compounds listed in Tables 8, 11, and 12. 3D-QSAR modeling can be performed to predict the affinity and pharmacological activity of the molecules using CoMFA and CoMSIA methods. All these *in silco* methods can be utilized as tools for developing novel molecular designs for MAO inhibition activity. The essential objective of this Review is to give insight into emerging tactics that may be utilized to create novel compounds of powerful MAO inhibitors for creating medications to treat neurodegenerative diseases.

AUTHOR INFORMATION

Corresponding Authors

Bijo Mathew − *Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala 682 041, India;* orcid.org/0000-0002-6658-4497; Email: bijomathew@aims.amrita.edu, bijovilaventgu@gmail.com

Hoon Kim − *Department of Pharmacy, Research Institute of Life Pharmaceutical Sciences, Sunchon National University, Suncheon 57922, Republic of Korea;* orcid.org/0000-0002-7203-3712; Email: hoon@sunchon.ac.kr

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751

Authors

Jayalakshmi Jayan − *Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala 682 041, India*

Namitha Chandran − *Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala 682 041, India*

Amrutha Chandran Thekkantavida − *Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala 682 041, India*

Mohamed A. Abdelgawad − *Department of Pharmaceutical Chemistry, College of Pharmacy, Jouf University, Sakaka 72341, Saudi Arabia; Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Beni Suef University, Beni Suef 2722165, Egypt*

Mohammed M. Ghoneim − *Department of Pharmacy Practice, College of Pharmacy, AlMaarefa University, Ad Diriyah 13713, Saudi Arabia*

Mohamed E. Shaker − *Department of Pharmacology, College of Pharmacy, Jouf University, Sakaka 72341 Aljouf, Saudi Arabia; Department of Pharmacology and Toxicology, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt*

Prerna Uniyal − *School of Pharmacy, Graphic Era Hill University, Dehradun 248002 Uttarakhand, India*

Feba Benny − *Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala 682 041, India*

Subin Mary Zachariah − *Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala 682 041, India*

Sunil Kumar − *Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, Kerala 682 041, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c05883

Author Contributions

Conceptualization: S.M.Z., H.K., and B.M. Writing, original draft preparation: J.J., N.C., A.C.T., M.A.A., M.M.G., P.U., and F.B. Writing, review and editing: S.M.Z. Supervision: H.K. and B.M. All authors have read and agreed to the published version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We sincerely thanks to the library facility of Amrita Vishwa Vidyapeetham University for providing a digital library for the completion for this work.

■ REFERENCES

(1) Lamptey, R. N. L.; Chaulagain, B.; Trivedi, R.; Gothwal, A.; Layek, B.; Singh, J. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. *Int. J. Mol. Sci.* **2022**, *23*, 1851.

(2) Dugger, B. N.; Dickson, D. W. Pathology of Neurodegenerative Diseases. *Cold Spring Harbor Perspect. Biol.* **2017**, *9*, a028035.

(3) Choonara, Y. E.; Pillay, V.; Du Toit, L. C.; Modi, G.; Naidoo, D.; Ndesendo, V. M. K.; Sibambo, S. R. Trends in the Molecular Pathogenesis and Clinical Therapeutics of Common Neurodegenerative Disorders. *Int. J. Mol. Sci.* **2009**, *10*, 2510−2557.

(4) Kareem, R. T.; Abedinifar, F.; Mahmood, E. A.; Ebadi, A. G.; Rajabi, F.; Vessally, E. The Recent Development of Donepezil Structure-Based Hybrids as Potential Multifunctional Anti-Alzheimer's Agents: Highlights from 2010 to 2020. *RSC Adv.* **2021**, *11*, 30781−30797.

(5) Kabir, M. T.; Uddin, M. S.; Mamun, A. A.; Jeandet, P.; Aleya, L.; Mansouri, R. A.; Ashraf, G. M.; Mathew, B.; Bin-Jumah, M. N.; Abdel-Daim, M. M. Combination Drug Therapy for the Management of Alzheimer's Disease. *Int. J. Mol. Sci.* **2020**, *21*, 3272.

(6) Kumar, A.; Sudevan, S. T.; Nair, A. S.; Singh, A. K.; Kumar, S.; Jose, J.; Behl, T.; Mangalathillam, S.; Mathew, B.; Kim, H. Current and Future Nano-Carrier-Based Approaches in the Treatment of Alzheimer's Disease. *Brain Sci.* **2023**, *13*, 213.

(7) Culpepper, L. Reducing the Burden of Difficult-to-Treat Major Depressive Disorder. *Prim. Care Companion CNS Discord.* **2013**, DOI: 10.4088/PCC.13r01515.

(8) Jellinger, K. A. Basic Mechanisms of Neurodegeneration: A Critical Update. *J. Cell Mol. Med.* **2010**, *14* (3), 457−487.

(9) Tao, C. C.; Cheng, K. M.; Ma, Y. L.; Hsu, W. L.; Chen, Y. C.; Fuh, J. L.; Lee, W. J.; Chao, C. C.; Lee, E. H. Y. Galectin-3 Promotes Aβ Oligomerization and Aβ Toxicity in a Mouse Model of Alzheimer's Disease. *Cell Death Differ.* **2020**, *27* (1), 192−209.

(10) Mertens, J.; Herdy, J. R.; Traxler, L.; Schafer, S. T.; Schlachetzki, J. C. M.; Böhnke, L.; Reid, D. A.; Lee, H.; Zangwill, D.; Fernandes, D. P.; Agarwal, R. K.; Lucciola, R.; Zhou-Yang, L.; Karbacher, L.; Edenhofer, F.; Stern, S.; Horvath, S.; Paquola, A. C. M.; Glass, C. K.; Yuan, S. H.; Ku, M.; Szücs, A.; Goldstein, L. S. B.; Galasko, D.; Gage, F. H. Age-Dependent Instability of Mature Neuronal Fate in Induced Neurons from Alzheimer's Patients. *Cell Stem Cell* **2021**, *28* (9), 1533−1548.e6.

(11) Bari, A.; Iqbal, A.; Khan, Z. A.; Shahzad, S. A.; Yar, M. Synthetic Approaches toward Piperidine Related Structures: A Review. *Synth. Commun.* **2020**, *50*, 2572−2589.

(12) Nair, A. S.; Oh, J. M.; Koyiparambath, V. P.; Kumar, S.; Sudevan, S. T.; Soremekun, O.; Soliman, M. E.; Khames, A.; Abdelgawad, M. A.; Pappachen, L. K.; Mathew, B.; Kim, H. Development of Halogenated Pyrazolines as Selective Monoamine Oxidase-B Inhibitors: Deciphering via Molecular Dynamics Approach. *Molecules* **2021**, *26* (11), 3264.

(13) Ramsay, R. R. Inhibitor Design for Monoamine Oxidases. *Curr. Pharm. Des.* **2013**, *19*, 2529−2539.

(14) Benny, F.; Kumar, S.; Jayan, J.; Abdelgawad, M. A.; Ghoneim, M. M.; Kumar, A.; Manoharan, A.; Susan, R.; Sudevan, S. T.; Mathew, B. Review of B-carboline and Its Derivatives as Selective MAO-A Inhibitors. *Arch Pharm.* **2023**, 2300091 DOI: 10.1002/ardp.202300091.

(15) Kumar, S.; Manoharan, A.; J, J.; Abdelgawad, M. A.; Mahdi, W. A.; Alshehri, S.; Ghoneim, M. M.; Pappachen, L. K.; Zachariah, S. M.; Aneesh, T. P.; Mathew, B. Exploiting Butyrylcholinesterase Inhibitors through a Combined 3-D Pharmacophore Modeling, QSAR, Molecular Docking, and Molecular Dynamics Investigation. *RSC Adv.* **2023**, *13* (14), 9513−9529.

(16) Liu, G. Q.; Opatz, T. Recent Advances in the Synthesis of Piperidines: Functionalization of Preexisting Ring Systems. *Adv. Heterocycl. Chem.* **2018**, *125*, 107−234.

(17) Shih, J. C.; Chen, K.; Ridd, M. J. MONOAMINE OXIDASE: From Genes to Behavior. *Ann. Rev. Neurosci.* **1999**, *22*, 197−217.

(18) Youdim, M. B. H. Monoamine Oxidases and Their Inhibitors. In *Encyclopedia of Molecular Pharmacology*; Offermanns, S., Rosenthal, W., Eds.; Springer, 2008; pp 783−791. DOI: 10.1007/978-3-540-38918-7_191.

(19) Koyiparambath, V. P.; Prayaga Rajappan, K.; Rangarajan, T. M.; Al-Sehemi, A. G.; Pannipara, M.; Bhaskar, V.; Nair, A. S.; Sudevan, S. T.; Kumar, S.; Mathew, B. Deciphering the Detailed Structure−Activity Relationship of Coumarins as Monoamine Oxidase Enzyme Inhibitors—An Updated Review. *Chem. Biol. Drug Des.* **2021**, *98*, 655−673.

(20) Kovacs, G. G.; Budka, H. Molecular Pathology of Human Prion Diseases. *Int. J. Mol. Sci.* **2009**, *10*, 976−999.

(21) Ou, S.-H. I.; Wu, F.; Harrich, D.; Leó, L.; Garciá, L. F.; Garciá-Martińez, G.; Martińez, M.; Gaynor, R. B. *Cloning and Characterization of a Novel Cellular Protein, TDP-43, That Binds to Human Immunodeficiency Virus Type 1 TAR DNA Sequence Motifs* **1995**, *69* (6), 3584−3596.
(22) Vercruysse, P.; Vieau, D.; Blum, D.; Petersén, Å.; Dupuis, L. Hypothalamic Alterations in Neurodegenerative Diseases and Their Relation to Abnormal Energy Metabolism. *Front. Mol. Neurosci.* **2018**, *11*, No. 2, DOI: 10.3389/fnmol.2018.00002.
(23) Duyckaerts, C.; Delatour, B.; Potier, M. C. Classification and Basic Pathology of Alzheimer Disease. *Acta Neuropathologica* **2009**, *118*, 5−36.
(24) Dehay, B.; Bourdenx, M.; Gorry, P.; Przedborski, S.; Vila, M.; Hunot, S.; Singleton, A.; Olanow, C. W.; Merchant, K. M.; Bezard, E.; Petsko, G. A.; Meissner, W. G. Targeting α-Synuclein for Treatment of Parkinson's Disease: Mechanistic and Therapeutic Considerations. *Lancet Neurol.* **2015**, *14*, 855−866.
(25) Crane, G. E. Iproniazid (Marsilid) Phosphate, a Therapeutic Agent for Mental Disorders and Debilitating Diseases. *Psychiatr. Res. Rep. Am. Psychiatr. Assoc.* **1957**, *8*, 142−152.
(26) Youdim, M. B. H.; Weinstock, M. Therapeutic Applications of Selective and Non-Selective Inhibitors of Monoamine Oxidase A and B That Do Not Cause Significant Tyramine Potentiation. *Neurotoxicology* **2004**, *25* (1−2), 243−250.
(27) Hillhouse, T. M.; Porter, J. H. A Brief History of the Development of Antidepressant Drugs: From Monoamines to Glutamate. *Exp Clin Psychopharmacol* **2015**, *23* (1), 1−21.
(28) West, E. D.; Dally, P. J. Effects of Iproniazid in Depressive Syndromes. *BMJ.* **1959**, *1* (5136), 1491−1494.
(29) SCHILDKRAUT, J. J. THE CATECHOLAMINE HYPOTHESIS OF AFFECTIVE DISORDERS: A REVIEW OF SUPPORTING EVIDENCE. *American Journal of Psychiatry* **1965**, *122* (5), 509−522.
(30) Edinoff, A. N.; Swinford, C. R.; Odisho, A. S.; Burroughs, C. R.; Stark, C. W.; Raslan, W. A.; Cornett, E. M.; Kaye, A. M.; Kaye, A. D. Clinically Relevant Drug Interactions with Monoamine Oxidase Inhibitors. *Health Psychol Res.* **2022**, *10* (4), No. 39576.
(31) Da Prada, M.; Zürcher, G.; Wüthrich, I.; Haefely, W. E. On Tyramine, Food, Beverages and the Reversible MAO Inhibitor Moclobemide. *J. Neural Transm. Suppl.* **1988**, *26*, 31−56.
(32) Chaurasiya, N.; Leon, F.; Muhammad, I.; Tekwani, B. Natural Products Inhibitors of Monoamine Oxidases—Potential New Drug Leads for Neuroprotection, Neurological Disorders, and Neuroblastoma. *Molecules* **2022**, *27* (13), 4297.
(33) Knoll, J. (−)Deprenyl (Selegiline): Past, Present and Future. *Neurobiology (Bp)* **2000**, *8* (2), 179−199.
(34) Hasan, F.; McCrodden, J. M.; Kennedy, N. P.; Tipton, K. F. The Involvement of Intestinal Monoamine Oxidase in the Transport and Metabolism of Tyramine. *J. Neural. Transm. Suppl.* **1988**, *26*, 1−9.
(35) Da Prada, M.; Kettler, R.; Keller, H. H.; Cesura, A. M.; Richards, J. G.; Saura Marti, J.; Muggli-Maniglio, D.; Wyss, P. C.; Kyburz, E.; Imhof, R. From Moclobemide to Ro 19−6327 and Ro 41−1049: The Development of a New Class of Reversible, Selective MAO-A and MAO-B Inhibitors. *Nerutotransm. Act. Interact.* **1990**, *29*, 279−292.
(36) Ostadkarampour, M.; Putnins, E. E. Monoamine Oxidase Inhibitors: A Review of Their Anti-Inflammatory Therapeutic Potential and Mechanisms of Action. *Front. Pharmacol.* **2021**, *12*, No. 676239, DOI: 10.3389/fphar.2021.676239.
(37) Anderson, M. C.; Hasan, F.; Mccrodden, J. M.; Tipton, K. F. Monoamine Oxidase Inhibitors and the Cheese Effect. *Neurochem. Res.* **1993**, *18*, 1145−1149, DOI: 10.1007/BF00978365.
(38) Florvall, L.; Fagerval1, I.; Ask, A.-L.; Ross, S. B. Selective Monoamine Oxidase Inhibitors. 4. 4-Aminophenethylamine Derivatives with Neuron-Selective Action. *J. Med. Chem.* **1986**, *29*, 2250−2256, DOI: 10.1021/jm00161a020.
(39) Goel, P.; Alam, O.; Naim, M. J.; Nawaz, F.; Iqbal, M.; Alam, M. I. Recent Advancement of Piperidine Moiety in Treatment of Cancer- A Review. *Eur. J. Med. Chem.* **2018**, *157*, 480−502.
(40) Edmondson, D. E.; Binda, C.; Mattevi, A. Structural Insights into the Mechanism of Amine Oxidation by Monoamine Oxidases A and B. *Arch. Biochem. Biophys.* **2007**, *464*, 269−276.
(41) Frolov, N. A.; Vereshchagin, A. N. Piperidine Derivatives: Recent Advances in Synthesis and Pharmacological Applications. *Int. J. Mol. Sci.* **2023**, *24*, 2937.
(42) Radaram, B.; Pisaneschi, F.; Rao, Y.; Yang, P.; Piwnica-Worms, D.; Alauddin, M. M. Novel Derivatives of Anaplastic Lymphoma Kinase Inhibitors: Synthesis, Radiolabeling, and Preliminary Biological Studies of Fluoroethyl Analogues of Crizotinib, Alectinib, and Ceritinib. *Eur. J. Med. Chem.* **2019**, *182*, No. 111571.
(43) Chen, F.; Li, W.; Sahoo, B.; Kreyenschulte, C.; Agostini, G.; Lund, H.; Junge, K.; Beller, M. Hydrogenation of Pyridines Using a Nitrogen-Modified Titania-Supported Cobalt Catalyst. *Angew. Chem., Int. Ed.* **2018**, *57* (44), 14488−14492.
(44) Bourriquen, F.; Hervochon, J.; Qu, R.; Bartling, S.; Rockstroh, N.; Junge, K.; Fischmeister, C.; Beller, M. Diastereoselective Hydrogenation of Arenes and Pyridines Using Supported Ruthenium Nanoparticles under Mild Conditions. *Chem. Commun.* **2022**, *58* (63), 8842−8845.
(45) Kamesu, K.; Mohan, G. V. K.; Rajasekhar, K. SYNTHESIS OF 4-CHLORO-PIPERIDINE DERIVATIVES VIA NbCl5MEDIATED AZA-PRINS TYPE CYCLIZATION OF EPOXIDES AND HOMO-ALLYLIC AMINES. *Rasayan Journal of chemistry* **2020**, *13* (01), 494−498.
(46) Chithanna, S.; Roy, A.; Yang, D.-Y. Acid-Catalyzed, Regioselective [3 + 3] Annulation of Enaminones and α-Substituted Cinnamic Acids: Access to 3,4-Dihydropyridones and 2-Piperidinones. *Org. Biomol Chem.* **2021**, *19* (45), 9897−9905.
(47) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257−10274.
(48) Ulrich, S.; Wurthmann, C.; Brosz, M.; Meyer, F. P. The Relationship Between Serum Concentration and Therapeutic Effect of Haloperidol in Patients with Acute Schizophrenia. *Clin Pharmacokinet* **1998**, *34* (3), 227−263.
(49) Schwarz, C.; Hartung, B.; Leucht, S. Benperidol for Schizophrenia. *Cochrane Database Syst. Rev.* **2005**, No. CD003083, DOI: 10.1002/14651858.CD003083.pub2.
(50) Marder, S. R.; Meibach, R. C. Risperidone in the Treatment of Schizophrenia. *Am. J. Psychiatry* **1994**, *151*, 825−835, DOI: 10.1176/ajp.151.6.825.
(51) Fenton, M.; Rathbone, J.; Reilly, J. Thioridazine for Schizophrenia. *Cochrane Database Syst. Rev.* **2007**, No. CD001944, DOI: 10.1002/14651858.CD001944.pub2.
(52) Eberhart, L. H. J.; Morin, A. M.; Bothner, U.; Georgieff, M. Droperidol and 5-HT 3-Receptor Antagonists, Alone or in Combination, for Prophylaxis of Postoperative Nausea and Vomiting A Meta-Analysis of Randomised Controlled Trials. *Acta Anaesthesiol Scand* **2000**, *44*, 1252−1257.
(53) Seltzer, B. Donepezil: A Review. *Expert Opin. Drug Metab. Toxicol.* **2005**, *1*, 527−536.
(54) Mathew, B.; Haridas, A.; Suresh, J.; Mathew, G. E.; Uçar, G.; Jayaprakash, V. Monoamine Oxidase Inhibitory Action of Chalcones: A Mini Review. *Cent. Nerv. Syst. Agents Med. Chem.* **2016**, *16* (2), 120−136.
(55) Mathew, B.; Oh, J. M.; Abdelgawad, M. A.; Khames, A.; Ghoneim, M. M.; Kumar, S.; Nath, L. R.; Sudevan, S. T.; Parambi, D. G. T.; Agoni, C.; Soliman, M. E. S.; Kim, H. Conjugated Dienones from Differently Substituted Cinnamaldehyde as Highly Potent Monoamine Oxidase-B Inhibitors: Synthesis, Biochemistry, and Computational Chemistry. *ACS Omega* **2022**, *7* (9), 8184−8197.
(56) Kumar, S.; Nair, A. S.; Abdelgawad, M. A.; Mathew, B. Exploration of the Detailed Structure−Activity Relationships of Isatin and Their Isomers As Monoamine Oxidase Inhibitors. *ACS Omega* **2022**, *7* (19), 16244−16259.
(57) 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* (6), 522−532, DOI: 10.2174/1386207320666170227155517.
(58) Koyiparambath, V. P.; Prayaga Rajappan, K.; Rangarajan, T. M.; Al-Sehemi, A. G.; Pannipara, M.; Bhaskar, V.; Nair, A. S.; Sudevan, S. T.; Kumar, S.; Mathew, B. Deciphering the Detailed Structure−Activity Relationship of Coumarins as Monoamine Oxidase Enzyme Inhibitors—An Updated Review. *Chem. Biol. Drug Des.* **2021**, *98*, 655−673.
(59) Mathew, B.; Suresh, J.; Anbazhagan, S.; Mathew, G. Pyrazoline: A Promising Scaffold for the Inhibition of Monoamine Oxidase. *Cent Nerv Syst. Agents Med. Chem.* **2014**, *13* (3), 195−206.
(60) Rehuman, N. A.; Al-Sehemi, A. G.; Parambi, D. G. T.; Rangarajan, T. M.; Nicolotti, O.; Kim, H.; Mathew, B. Current Progress in Quinazoline Derivatives as Acetylcholinesterase and Monoamine Oxidase Inhibitors. *ChemistrySelect* **2021**, *6* (28), 7162−7182.
(61) Benny, F.; Kumar, S.; Jayan, J.; Abdelgawad, M. A.; Ghoneim, M. M.; Kumar, A.; Manoharan, A.; Susan, R.; Sudevan, S. T.; Mathew, B. Review of B-carboline and Its Derivatives as Selective MAO-A Inhibitors. *Arch Pharm.* **2023**, No. 2300091, DOI: 10.1002/ardp.202300091.
(62) Sudevan, S. T.; Rangarajan, T. M.; Al-Sehemi, A. G.; Nair, A. S.; Koyiparambath, V. P.; Mathew, B. Revealing the Role of the Benzyloxy Pharmacophore in the Design of a New Class of Monoamine Oxidase-B Inhibitors. *Arch Pharm. (Weinheim)* **2022**, *355* (8), No. 2200084.
(63) Mathew, B.; Carradori, S.; Guglielmi, P.; Uddin, Md. S.; Kim, H. New Aspects of Monoamine Oxidase B Inhibitors: The Key Role of Halogens to Open the Golden Door. *Curr. Med. Chem.* **2020**, *28* (2), 266−283.
(64) Kong, L. D.; Cheng, C. H. K.; Tan, R. X. Inhibition of MAO a and B by Some Plant-Derived Alkaloids, Phenols and Anthraquinones. *J. Ethnopharmacol* **2004**, *91* (2−3), 351−355.
(65) Lee, S. A.; Hong, S. S.; Han, X. H.; Hwang, J. S.; Oh, G. J.; Lee, K. S.; Lee, M. K.; Hwang, B. Y.; Ro, J. S. Piperine from the Fruits of Piper Longum with Inhibitory Effect on Monoamine Oxidase and Antidepressant-Like Activity. *Chem. Pharm. Bull. (Tokyo)* **2005**, *53* (7), 832−835.
(66) Li, S.; Wang, C.; Li, W.; Koike, K.; Nikaido, T.; Wang, M. W. Antidepressant-like Effects of Piperine and Its Derivative, Antiepilepsirine. *J. Asian Nat. Prod Res.* **2007**, *9* (5), 421−430.
(67) Lee, S. A.; Hwang, J. S.; Han, X. H.; Lee, C.; Lee, M. H.; Choe, S. G.; Hong, S. S.; Lee, D.; Lee, M. K.; Hwang, B. Y. Methylpiperate Derivatives from Piper Longum and Their Inhibition of Monoamine Oxidase. *Arch Pharm. Res.* **2008**, *31* (6), 679−683.
(68) Son, S.-Y.; Ma, J.; Kondou, Y.; Yoshimura, M.; Yamashita, E.; Tsukihara, T. Structure of Human Monoamine Oxidase A at 2. 2-Å Resolution: The Control of Opening the Entry for Substrates/Inhibitors. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105* (15), 5739−5744.
(69) Binda, C.; Wang, J.; Pisani, L.; Caccia, C.; Carotti, A.; Salvati, P.; Edmondson, D. E.; Mattevi, A. Structures of Human Monoamine Oxidase B Complexes with Selective Noncovalent Inhibitors: Safinamide and Coumarin Analogs. *J. Med. Chem.* **2007**, *50* (23), 5848−5852.
(70) Rahman, T.; Rahmatullah, M. Proposed Structural Basis of Interaction of Piperine and Related Compounds with Monoamine Oxidases. *Bioorg. Med. Chem. Lett.* **2010**, *20* (2), 537−540.
(71) Pal, A.; Nayak, S.; Sahu, P. K.; Swain, T. Piperine Protects Epilepsy Associated Depression: A Study on Role of Monoamines. *Eur. Rev. Med. Pharmacol Sci.* **2011**, *15* (11), 1288−1295.
(72) Mu, L. H.; Wang, B.; Ren, H. Y.; Liu, P.; Guo, D. H.; Wang, F. M.; Bai, L.; Guo, Y. S. Synthesis and Inhibitory Effect of Piperine Derivates on Monoamine Oxidase. *Bioorg. Med. Chem. Lett.* **2012**, *22* (9), 3343−3348.
(73) Al-Baghdadi, O. B.; Prater, N. I.; Van Der Schyf, C. J.; Geldenhuys, W. J. Inhibition of Monoamine Oxidase by Derivatives of Piperine, an Alkaloid from the Pepper Plant Piper Nigrum, for Possible Use in Parkinson's Disease. *Bioorg. Med. Chem. Lett.* **2012**, *22* (23), 7183−7188.
(74) Prashanth, M. K.; Revanasiddappa, H. D.; Lokanatha Rai, K. M.; Veeresh, B. Synthesis, Characterization, Antidepressant and Antioxidant Activity of Novel Piperamides Bearing Piperidine and Piperazine Analogues. *Bioorg. Med. Chem. Lett.* **2012**, *22* (23), 7065−7070.
(75) Pettersson, F.; Svensson, P.; Waters, S.; Waters, N.; Sonesson, C. Synthesis and Evaluation of a Set of Para-Substituted 4-Phenylpiperidines and 4-Phenylpiperazines as Monoamine Oxidase (MAO) Inhibitors. *J. Med. Chem.* **2012**, *55* (7), 3242−3249.
(76) Bolea, I.; Juárez-Jiménez, J.; De Los Ríos, C.; Chioua, M.; Pouplana, R.; Luque, F. J.; Unzeta, M.; Marco-Contelles, J.; Samadi, A. Synthesis, Biological Evaluation, and Molecular Modeling of Donepezil and N-[(5-(Benzyloxy)-1-Methyl-1H-Indol-2-Yl)Methyl]-N-Methylprop-2-Yn-1-Amine Hybrids as New Multipotent Cholinesterase/Monoamine Oxidase Inhibitors for the Treatment of Alzheimer's Disease. *J. Med. Chem.* **2011**, *54* (24), 8251−8270.
(77) Bautista-Aguilera, O. M.; Esteban, G.; Chioua, M.; Nikolic, K.; Agbaba, D.; Moraleda, I.; Iriepa, I.; Soriano, E.; Samadi, A.; Unzeta, M.; Marco-Contelles, J. Multipotent Cholinesterase/Monoamine Oxidase Inhibitors for the Treatment of Alzheimer's Disease: Design, Synthesis, Biochemical Evaluation, ADMET, Molecular Modeling, and QSAR Analysis of Novel Donepezil-Pyridyl Hybrids. *Drug Des Devel Ther* **2014**, *8*, 1893−1910.
(78) Wang, L.; Esteban, G.; Ojima, M.; Bautista-Aguilera, O. M.; Inokuchi, T.; Moraleda, I.; Iriepa, I.; Samadi, A.; Youdim, M. B. H.; Romero, A.; Soriano, E.; Herrero, R.; Fernández Fernández, A. P.; Ricardo-Martínez-Murillo; Marco-Contelles, J.; Unzeta, M. Donepezil + Propargylamine + 8-Hydroxyquinoline Hybrids as New Multifunctional Metal-Chelators, ChE and MAO Inhibitors for the Potential Treatment of Alzheimer's Disease. *Eur. J. Med. Chem.* **2014**, *80*, 543−561.
(79) Li, F.; Wang, Z. M.; Wu, J. J.; Wang, J.; Xie, S. S.; Lan, J. S.; Xu, W.; Kong, L. Y.; Wang, X. B. Synthesis and Pharmacological Evaluation of Donepezil-Based Agents as New Cholinesterase/Monoamine Oxidase Inhibitors for the Potential Application against Alzheimer's Disease. *J. Enzyme Inhib Med. Chem.* **2016**, *31*, 41−53.
(80) Xie, S. S.; Lan, J. S.; Wang, X.; Wang, Z. M.; Jiang, N.; Li, F.; Wu, J. J.; Wang, J.; Kong, L. Y. Design, Synthesis and Biological Evaluation of Novel Donepezil-Coumarin Hybrids as Multi-Target Agents for the Treatment of Alzheimer's Disease. *Bioorg. Med. Chem.* **2016**, *24* (7), 1528−1539.
(81) Pisani, L.; Farina, R.; Catto, M.; Iacobazzi, R. M.; Nicolotti, O.; Cellamare, S.; Mangiatordi, G. F.; Denora, N.; Soto-Otero, R.; Siragusa, L.; Altomare, C. D.; Carotti, A. Exploring Basic Tail Modifications of Coumarin-Based Dual Acetylcholinesterase-Monoamine Oxidase B Inhibitors: Identification of Water-Soluble, Brain-Permeant Neuroprotective Multitarget Agents. *J. Med. Chem.* **2016**, *59* (14), 6791−6806.
(82) 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.
(83) Cai, P.; Fang, S. Q.; Yang, X. L.; Wu, J. J.; Liu, Q. H.; Hong, H.; Wang, X. B.; Kong, L. Y. Rational Design and Multibiological Profiling of Novel Donepezil-Trolox Hybrids against Alzheimer's Disease, with Cholinergic, Antioxidant, Neuroprotective, and Cognition Enhancing Properties. *ACS Chem. Neurosci.* **2017**, *8* (11), 2496−2511.
(84) Cai, P.; Fang, S. Q.; Yang, H. L.; Yang, X. L.; Liu, Q. H.; Kong, L. Y.; Wang, X. B. Donepezil-Butylated Hydroxytoluene (BHT) Hybrids as Anti-Alzheimer's Disease Agents with Cholinergic, Antioxidant, and Neuroprotective Properties. *Eur. J. Med. Chem.* **2018**, *157*, 161−176.

https://doi.org/10.1021/acsomega.3c05883
ACS Omega 2023, 8, 37731−37751