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REVIEW

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Recent developments on the structure–activity relationship studies of MAO inhibitors and their role in different neurological disorders

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Monoamine oxidase (MAO) enzyme catalyzes the oxidative deamination of xenobiotic and endogenous amines including many neurotransmitters. The MAO enzyme exists in two isoforms; MAO-A and MAO-B and these isoforms display considerable sequence similarity but differ in tissue distribution, inhibitor selectivity and specificity towards ligands. The altered concentration of the neurotransmitters in the brain is linked with the biochemical pathology of various neurological disorders including depression, Alzheimer's disease and Parkinson's disease. MAO inhibitors were the first antidepressants discovered but their irreversible binding to the enzyme resulted in a number of side effects including fatal food–drug interactions. The new generation MAO inhibitors, especially reversible and selective inhibitors, were less toxic and found to be effective against various neurological disorders. Now the MAO enzyme has been recognised as an important drug target and MAO-A selective inhibitors are being developed as drug candidates for the management of depression and anxiety disorders, whereas MAO-B selective inhibitors are found to be effective for the treatment of Parkinson's disease and Alzheimer's disease with a better safety profile as compared to nonselective MAO inhibitors. The current review article describes recent developments on the design, synthesis and screening of MAO inhibitors, structure–activity relationship studies, and their role in the etiology and treatment of various neurological disorders.

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1. Introduction

Monoamine oxidases (MAO) belong to a family of flavin adenine dinucleotide (FAD) dependent enzymes present on the outer membrane of the mitochondria.[1] MAOs are responsible for the oxidative deamination of various xenobiotic and endogenous neurotransmitters and modulate their concentration in the

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brain and peripheral tissues.[2] The enzyme is found to exist in two isoforms, MAO-A and MAO-B wherein both possess a sequence similarity of 73% but differ mainly in their substrate specificity, inhibitor selectivity and tissue distribution.[3,4] The MAO-A isoform has substrate specificity for bulkier endogenous amines like serotonin, epinephrine and norepinephrine whereas MAO-B has substrate specificity for small amines such as benzylamine, β-phenyl ethylamine.[5] Dopamine and tyramine are common substrates for both the enzyme isoforms. MAO enzyme is mostly found in the brain, however it is also reported in the gut, liver, placenta, skin, platelets and lymphocytes. The amine in the deprotonated form binds to the active site of the enzyme and is oxidised to imine with the reduction of 8α-*S*-cysteinyl FAD to its hydroquinone form.[6] The reduced FAD cofactor reacts with oxygen (O_2) to produce oxidised FAD and hydrogen peroxide which in turn generate highly toxic hydroxyl radicals responsible for the neuronal damage and death.[7,8] The imbalance in the concentration of these neurotransmitters in the brain is linked with the biochemical pathology of various neurogenic disorders[9] including depression, Alzheimer's disease (AD), and Parkinson's disease (PD). Various studies have confirmed that MAO-B is overexpressed in the brain of AD patients and is linked with the loss of cognitive functions.[10] In similar reports it has been shown that there is a correlation between the low levels of monoamine neurotransmitters associated with severe depression cases and increased concentration of MAO-A in the cortex.[11,12]

MAO inhibitors can block the catalytic activities of the enzyme and halt the catabolism process of monoamines. Inhibition of MAO enzyme, improve the concentration of the monoamine neurotransmitters (dopamine, serotonin *etc.*) stored in the nerve terminals. Thus MAO inhibitors can be developed as therapeutic agents in the disease state where MAO enzyme is overexpressed. In addition to this, MAO-catalysed metabolism of monoamine neurotransmitters generates hydrogen peroxide, toxic aldehydes and hydroxyl free radicals which are responsible for the neuronal damage and death. MAO inhibitors stop the production of these neurotoxic byproducts by halting monoamine oxidation process and hence prevent the resulting damage to the neurons. Hence, MAO inhibitors have also been proposed as potential neuroprotecting and neuro-rescue agents.

The X-ray crystal structures of human MAO-B and human MAO-A were reported in year 2002 and 2005 respectively (Fig. 1).[13,14] Crystallographic studies of the enzyme showed that human MAO-B and rat MAO-A crystallises as dimer[15,16] while human MAO-A crystallizes as monomeric unit. However, it has been observed that most of the membrane proteins are dimeric in the membrane form.[17] Andres *et al.*[18] through modeling studies and species-dependent genetic analysis concluded that the monomeric structure of human MAO-A could be due to Glu151Lys mutation near the dimer interface. The EPR data showed that rat and human MAO-A and MAO-B enzymes are dimeric in the membrane bound forms however human MAO-A crystallizes as monomer while MAO-B crystallizes as dimer.[19] The volume of human MAO-A and MAO-B cavities are ~400 $Å^3$ and ~700 $Å^3$ respectively. The MAO-B cavity is divided into two separate spaces, the active site cavity for substrate binding (~400 $Å^3$) and the entrance cavity (~300 $Å^3$).[20] Ile199 and Tyr326 side chains separate the two cavities in MAO-B isoform. Mutagenesis experiments on human MAO-B, Ile199Phe showed that bulky Phe side chain hampers conformational flexibility, reduces the space of the entrance cavity and interferes with the binding of MAO-B selective inhibitors.[21] Thus Ile199 serves as a structural determinant for substrate and inhibitor recognition. Similarly, Tyr326 exhibit its conformational changes on the inhibitor binding to human MAO-B isoform. A single Ile199Ala mutation to the MAO-B permanently open the gate and double mutations Ile199Ala–Tyr326Ala exhibit inhibitor binding properties similar to those of MAO-A than to MAO-B. This shows that the bipartite cavity structure in the MAO-B plays an important role in substrate and inhibitor

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Vinod Kumar is currently working as Assistant Professor at Centre for Pharmaceutical Sciences and Natural Products at Central University of Punjab, Bathinda, India. He has done his PhD from Institute of Himalayan Bioresource Technology, Palampur with affiliation from Guru Nanak Dev University Amritsar in 2007. Subsequently, he pursued postdoctoral studies at Siena University Italy in the research group of Prof. G. Campiani and worked there for two years. Thereafter he moved to United Kingdom and joined Professor Stephen Husbands's research group at Bath University. Currently, Dr Kumar is working on Monoamine Oxidase inhibitors and investigating their role in various neurogenic disorders.

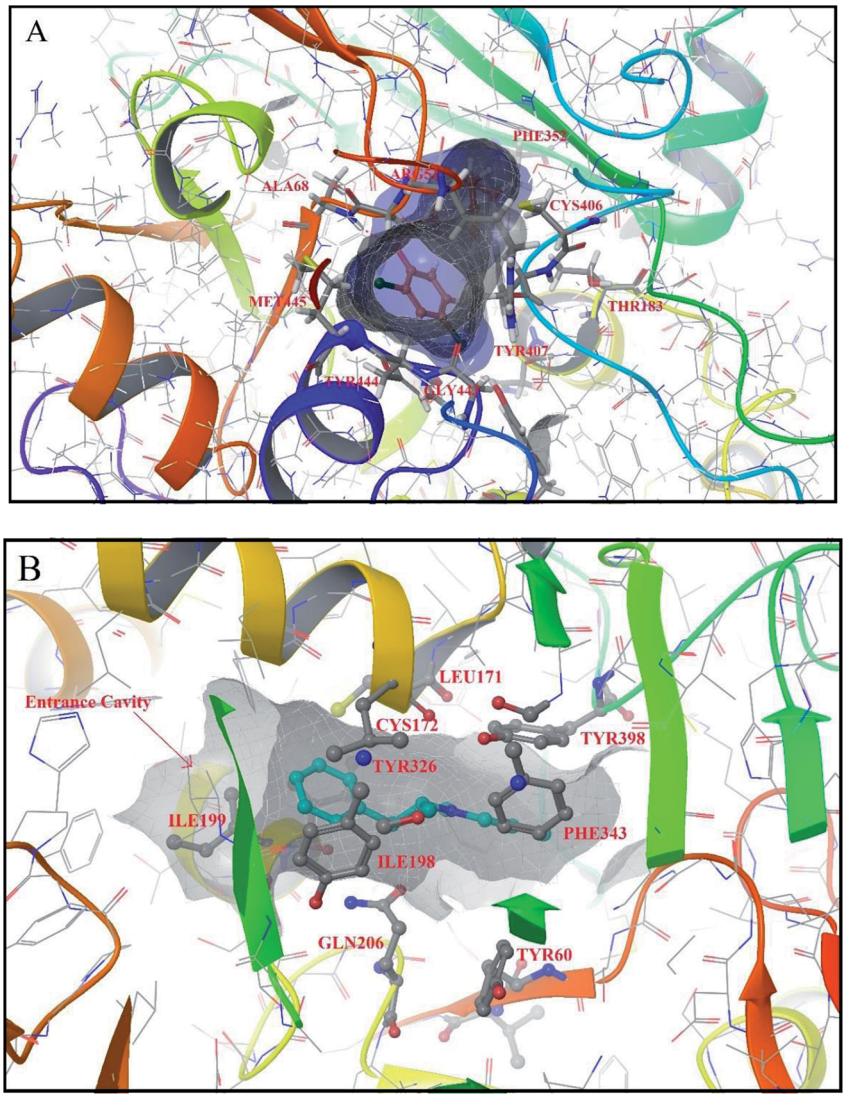


Fig. 1 (A) The co-crystallized structure of clorgyline with human MAO-A PDB ID (2Z5X).[22] The figure shows ligand interactions at the active site of MAO-A isoform with various amino acids; (B) the co-crystallized structure of human deprenyl with MAO-B (dimeric) PDB ID (2BYB).[14] In the figure entrance cavity of the MAO-B isoform is shown along with the ligand's interactions with various amino acids at the active site cavity.

recognition to distinguish its specificities from those of MAO-A. The entrance cavity may act as an allosteric binding site for the MAO-B selective inhibitors and potentiation of ligand binding to the entrance cavity of MAO-B by the ligand occupancy in the substrate cavity opens up possibilities for the design of highly specific MAO-B inhibitors that specifically target the entrance cavity space.[23] This information would be helpful in designing selective inhibitors for MAO-A and MAO-B isoforms.[20]

2. Problems with the irreversible MAO inhibitors

In the 1950's, irreversible MAO inhibitors were predominantly used for the treatment of depression but their use diminished in the following years due to their undesired side effects and fatal drug–food interactions. Various irreversible MAO inhibitors[24] are shown in Fig. 2. One of the major problems associated with the use of irreversible MAO inhibitors was their interaction with the tyramine containing foods like old cheese and wine, as a consequence of inhibition of the isoenzyme MAO-A in the intestine (cheese-effect).[25] Normally, the MAO enzyme removes excess tyramine out of the body, but in the presence of MAO inhibitors the catalytic action of MAO enzyme is halted which results in the increased level of tyramine in the blood.[26] The excess amount of tyramine present in the blood causes the release of noradrenaline from the peripheral adrenergic neurons. This may leads to severe increase in the blood pressure,[27] termed as hypertensive crisis.[28,29] In addition, irreversible MAO inhibitors were also reported to exhibit various side effects like tachycardia, photophobia, palpitation, nausea and fatal drug–drug interactions. Irreversible MAO inhibitors like isoniazid and iproniazid have been withdrawn from the market in 1961 due to their high hepatotoxicity[30,31] and research focus was shifted to new alternatives like selective

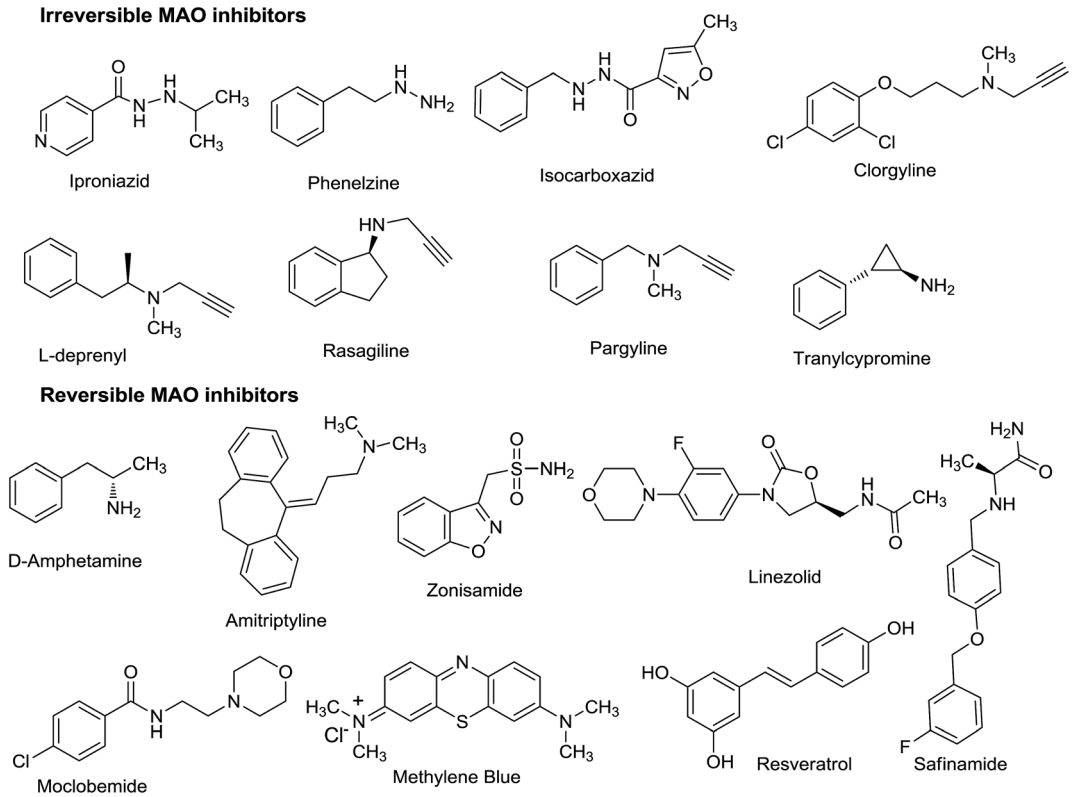


Fig. 2 Irreversible and reversible MAO inhibitors in clinical practice.

serotonin reuptake inhibitors (SSRI), serotonin nor-epinephrine reuptake inhibitors and tricyclic antidepressant. However MAO inhibitors were the only effective medication available for the management of severe and treatment-resistant depression.[32]

To address various problems associated with the first generation irreversible MAO inhibitors, new classes of compounds were developed which were not only selective for either of the MAO isoform but were also reversible in nature. Selective MAO-A inhibitors have potential to be developed as drugs for the treatment of depression and anxiety disorders,[33] whereas MAO-B selective inhibitors are effective in several neurological disorders such as PD, AD, Huntington chorea and amyotrophic lateral sclerosis.[34] The reversible and selective MAO-A inhibitors (Fig. 2) are devoid of 'cheese-effect'[35] and these ligands can inhibit the enzyme with decreased risk of tyramine reaction. The absorbed tyramine releases norepinephrine which competes with the reversible MAO-A inhibitors and reactivate the MAO-A enzyme in the intestine, liver and sympathomimetic neurons. In addition, a new delivery system has been developed in which MAO inhibitor like selegiline can be delivered directly to the blood circulation through skin patches.[36,37] This inhibits both MAO-A and MAO-B in the brain but avoid drug interactions with the MAO enzyme in the gut. These new developments reduce the risk of hypertensive crisis making MAO inhibitors comparatively safer therapeutic agents.

Many of the side effects associated with the irreversible MAO inhibitors have been curtailed with the development of selective MAO inhibitors and now the MAO enzyme has been recognised as an important and attractive drug target for the treatment of various neurogenic disorders. In addition, recent reports on the neuroprotective and neurorescue potential[38,39] of MAO inhibitors have generated enormous interests for exploring their role in the etiology of various neurogenic disorders. Since last few years, there is a surge in the number of research articles published on the synthesis and screening of selective and reversible MAO inhibitors. The PubMed data base shows more than 21 000 publications on the MAO enzyme. A variety of structurally different scaffolds have been screened for their selectivity and MAO inhibitory potential. Structure–activity relationship studies were conducted to identify important leads with an aim to develop them as potent and effective therapeutic agents for the treatment of various neurological disorders. A considerable progress has been made to understand the ligand interactions with the active site of the enzyme but it is difficult to generalize the results for MAO-A and MAO-B selectivity on the basis of chemical structure. However, through various molecular modeling studies and available crystal structures of the MAO enzymes it was concluded that the MAO-A isoform can accommodate bulkier ligands while the MAO-B isoform prefer smaller ligands due to its small entrance cavity. A number of review articles describe developments in the field of MAO inhibitors. For example, Norman *et al.*[40] investigated the role of MAO inhibitors in panic disorders. Liebowitz *et al.*[41] examined the role of reversible and irreversible MAO inhibitors in the psychiatric disorders. Similarly, Helguera *et al.*[42] have reviewed various research articles on MAO-B inhibitors containing oxygen as heterocyclic atom. Al-Nuaimi *et al.*[43] presented an

overview of the neuroprotective/neurorescue properties of MAO inhibitors and their possible neuroprotective mechanisms. Recently role of the pyrazoline moiety[44] has been explored as a promising scaffold for the inhibition of MAO enzyme. Similarly, a recent review on coumarin derivatives as MAO inhibitors highlighted the design and synthetic aspects of the coumarin based ligands and their role in the depression and AD. Patil *et al.*[45] described synthetic aspects of nitrogen heterocycles as potential MAO inhibitors. Carradori *et al.*[46] reviewed various selective MAO-B inhibitors derived from natural sources and belonging to different chemical classes. Most of these review articles are limited to discussion on a particular chemical class or describe MAO-A or MAO-B specific inhibitors and lack comprehensive discussion on compounds belonging to different chemical classes and their selectivity for either of the two MAO isoforms.

The scope of this review article is to highlight some recent developments in the field of MAO inhibitors. The current review article would focus on the synthesis, biological evaluation and relative selectivity of various ligands for the MAO-A and MAO-B enzyme isoforms and their potential role in different neurological disorders. Recent research articles on the MAO inhibitors have been reviewed in this manuscript and most of these were published in the last five years (from year 2010 onwards). The patents published on the subject were not covered in the present review article. The review article has been divided into three different sections describing selectivity of the ligands for MAO-A and MAO-B isoforms and their role in the etiology and treatment of PD, AD and depression. Although MAO inhibitors have been also linked with the etiology of many other disease states, however the scope of this review article is limited to their role in neurological disorders only, more specifically in PD, AD and depression.

3. Role of MAO inhibitors in Parkinson's disease

The MAO-B levels in the human increase four to five times on aging[47,48] and hyperactivation of MAO-B is linked with the etiology of age related neurological disorders including PD.[49] PD affects the basal ganglia region of the brain where MAO-B isoform seems to be significantly responsible for the metabolism of dopamine. Overactivation of the MAO-B isoform can diminish dopamine levels and increase the concentration of the catalytic reaction product H_2O_2 in the brain of patients suffering with PD. This promotes apoptotic signaling events resulting in the decreased levels of dopamine producing cells. Therefore inhibitors of the MAO-B isoform have been proposed as potential therapeutic agent for the management or treatment of PD.[50] Levodopa, a metabolic precursor of dopamine, and MAO-B inhibitors are given to the PD patients as combination therapy to maintain dopamine levels. MAO-B inhibitors stop the catalytic metabolism of dopamine and raise the dopamine levels in the patient's brain and hence, a reduced dose of levodopa is required for getting a therapeutic effect. In addition, the MAO enzyme is responsible for the production of hydrogen peroxide and hydroxyl free radicals in the cells that causes neuronal damage and death. MAO-B inhibition reduces the generation of these reactive oxygen species and hence limits the neurodegenerative processes associated with the PD.[51] In order to develop an effective therapeutic agent for the treatment of PD, a large number of compounds have been designed, synthesized and screened as reversible and selective MAO-B inhibitors and some of the recent reports are described below.

Fioravanti *et al.*[52] reported a series of *N*-substituted-3-[(2′-hydroxy-4′-prenyloxy)-phenyl]-5-phenyl-4,5-dihydro-(1*H*)-pyrazolines and the compounds were screened against the human MAO-A and MAO-B isoforms. In the reported series, compound **1** ($IC_{50} = 4.22$ μM) and **2** ($IC_{50} = 6.08$ μM) (Fig. 3) displayed good inhibitory activities and selectivity towards MAO-B isoform. Through structure–activity relationship studies it was found that the methoxy and chloro substitutions at the *para* position of the phenyl ring were essential for the activity. In addition, through molecular docking studies it was found that the isoprenyloxy moiety was linked with the FAD cofactor and the C5 pyrazoline substitution in the outer side of the hMAO-B cleft. The presence of different substituents like isoprenyloxy, benzyloxy, thioamide and phenolic hydroxyl group in the pyrazoline moiety improved interactions with the active site of hMAO-B. A

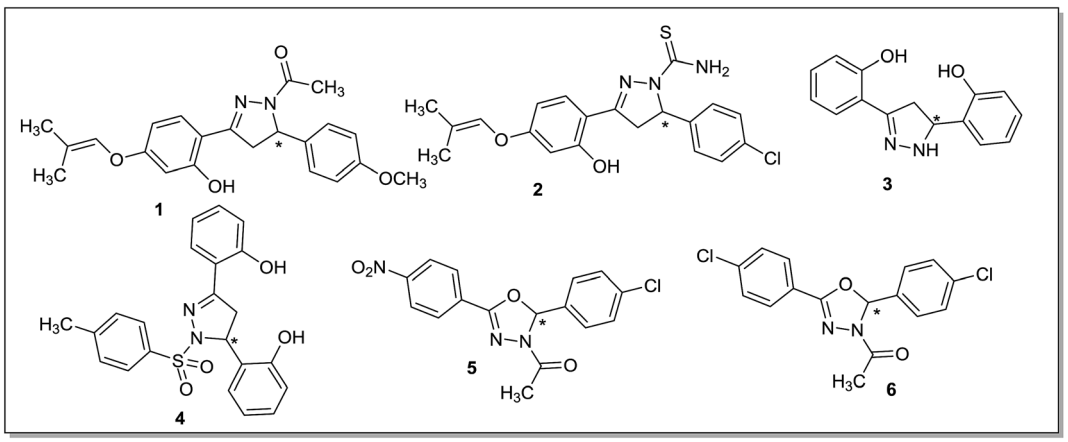


Fig. 3 Pyrazoline and oxadiazole based MAO-B selective inhibitors.

series of pyrazoline derivatives with a 3,5-diaryl substitution was also reported[53] and most of the compounds displayed reversible and selective inhibitor activities for the MAO-A or MAO-B isoform. Amongst the synthesized derivatives, compound **3** (IC_{50} = 780 nM) was found to be selective inhibitor of the MAO-B isoform while compound **4** (IC_{50} = 360 nM) was found to be selective for the MAO-A isoform. The molecular docking studies showed that compounds **3** and **4** (Fig. 3) were interacting with the enzyme through hydrogen bonding and a substitution at N1 position significantly increases the selectivity towards MAO-A isoform.

A series of 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles[54] was tested and some of the compounds were selective towards MAO-B isoform displaying IC_{50} values in the nanomolar range. Compound **5** (IC_{50} = 121.6 nM) and **6** (IC_{50} = 115.3 nM) (Fig. 3) were the most potent MAO-B inhibitors. The docking studies revealed that these compounds were stabilized by interactions between 4-chlorophenyl group at the C5 and aromatic ring of Tyr435 near the FAD cofactor. The presence of an electron withdrawing group at the aromatic ring was crucial for the hydrophobic interactions within the binding pocket of the enzyme. The electron releasing substituents at the same position induces different orientation of the molecule and led to less stable derivatives. Structure-based virtual screening of pioglitazone[55] was performed to identify novel and selective MAO-B inhibitors. The thiazolidinedione (TZD) moiety was important for binding to the MAO-B isoform. Two active compounds **7** and **8** (Fig. 4) were identified as potent MAO-B inhibitors with IC_{50} values of 82 nM and 195 nM respectively. Chimenti *et al.*[56] reported a series of [4-(3-methoxyphenyl)-thiazol-2-yl]hydrazine derivatives as MAO inhibitors. Most of them showed IC_{50} values in the nanomolar range. The most active compound (**9**) (Fig. 4) obtained in this series displayed an IC_{50} value of 3.8 ± 0.1 nM, showed high selectivity (119 times) and five times more potency than the standard drug R-(−)-deprenyl for the human MAO-B isoform. From the molecular modeling studies, it was found that C4 of the thiazole ring was responsible for the interactions between the inhibitor and FAD cofactor which control the oxidative activity of the MAO enzyme. It was concluded that even a small modification of the substituent's dimension at the C4 position could attenuate the activity of the compound. Chimenti *et al.*[57] also synthesized and evaluated 4-substituted-2-thiazolylhydrazone derivatives. Compound **10** (Fig. 4) with a C4 acetylpyridine moiety was found to be the most potent MAO-B inhibitor with IC_{50} value of 13.0 ± 1.2 nM. It was concluded that a thiazole ring as a substituent at the C4 position was required to obtain highly potent and selective hMAO-B inhibitors.

Carroll *et al.*[58] performed structure–activity relationship studies and docking experiments on the thiazolidinedione type compounds and evaluated these for the MAO inhibition activity. These compounds selectively inhibited MAO-B isoform and compound **11** (Fig. 4) was found to be the most potent with an IC_{50} value of 82 nM (MAO-B). Compounds having an aminoethyl group on the thiazolidinedione nitrogen caused the extension of the substrate cavity pushing it closer to the FAD moiety, which could be responsible for the increase in MAO-B inhibition activity.

Distinto *et al.*[59] reported on the synthesis and screening of halogenated 1-arylidene-2-(4-phenylthiazol-2-yl)hydrazines. The

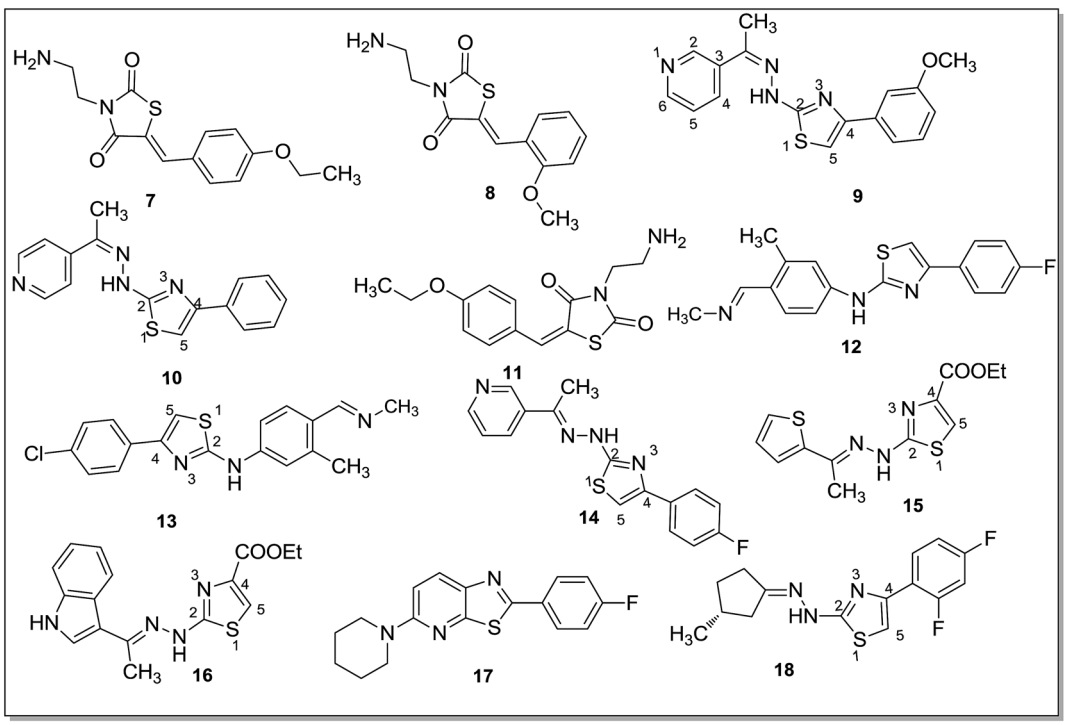


Fig. 4 Thiazole and thiazolidine derivatives as MAO-B selective inhibitors.

objective of the study was to investigate the role of 4-chloro- or 4-fluorophenyl substituents on the MAO inhibitory activity of the ligands. The fluorine as a substituent played pivotal role both in imparting activity and selectivity to the ligands towards MAO-B isoform. In the computational studies it was observed that the fluorine substituent was interacting with the water molecule close to cofactor and information about these ligand–receptor interactions could help in designing compounds with improved selectivity and potency for the MAO-B isoform. The 4-fluorophenyl (**12**) and analogous 4-chlorophenyl (**13**) (Fig. 4) derivatives were the most potent MAO-B inhibitors in the series.

A series of arylidene-(4-substituted-thiazol-2-yl)hydrazines[60] was reported as selective MAO-B inhibitors. They were mostly found to be selective for the hMAO-B isoform and displayed inhibition activity in the nanomolar range, higher than the reference drug. A pyridine ring with electron withdrawing substituents on the aryl ring at C4 of the thiazole nucleus and a substituent on the α-carbon to the N1-hydrazine moiety had a great influence on the activity and hMAO-B selectivity of the inhibitors. A methyl substituent in place of hydrogen on the α-carbon showed an improved hMAO-B inhibitory activity. Compound **14** (Fig. 4) was the most active and selective derivative with an IC_{50} value of 2.54 ± 0.22 nM and selectivity ratio more than 39 370 for the MAO-B isoform.

A series of hydrazothiazole derivatives[61] was designed by joining the hydrazine part of iproniazid and thiazole moiety of glitazones. Most of them displayed selective hMAO-B inhibitory activity. SAR studies suggested that a small or less bulky substituent at the C4 (ethyl ester) position was essential for the inhibitory activity and lead to compounds **15** and **16** (Fig. 4) with IC_{50} values of 350.0 ± 26.1 nM and 851.3 ± 64.8 nM, respectively. These compounds were found to be more selective towards MAO-B isoform than the reference drugs iproniazid and isatin with SI of 285.7 and 117.5, respectively. Oxazolopyridine and thiazolopyridine derivatives[62] were designed and evaluated against the MAO-B isoform. A series of 2-phenyloxazolopyridine derivatives was synthesized with various amino substituents and these compounds were tested against the hMAO-B isoform. Presence of a piperidino group was found essential for the activity. The phenyl ring was also substituted with a halogen atom which improved the inhibitory activity of the ligands. By replacing the basic structure from oxazolopyridine to thiazolopyridine, the activities were dramatically improved and compound **17** (Fig. 4) was the most potent in the series displaying IC_{50} value of 26.5 nM. D'Ascenzio *et al.*[63] reported a series of 4-aryl-2-cycloalkylidenhydazinylthiazoles and studied the stereochemical properties of these compounds required for the MAO inhibitory activity. The 2- and 3-methylcyclohexylidene derivatives displayed good inhibitory activity and high selectivity towards MAO-B isoform. In the biological assay studies, compound **18** (Fig. 4) was reported as the most active and selective MAO-B inhibitor. The selectivity of compound **18** was further confirmed by docking studies where it showed better docking score and interaction energy with the MAO-B as compared to MAO-A isoform. In the MAO-A isoform, **18** has shown steric hindrance with four residues, Phe352, Lys305, Tyr444 and Tyr407.

Matos *et al.*[64] synthesized a series of bromo-6-methyl-3-phenylcoumarin derivatives and evaluated these against MAO enzyme. A halogen substituent on the coumarin moiety and a bromo-substituent at C8 position of the 3-phenyl coumarin improved inhibitory activity for the MAO-B isoform. A *p*-methoxy substitution on the phenyl ring (**19**) (Fig. 5) further improved the activity and it was found to be more selective and more potent (6 times) than the reference drug R-(−)-deprenyl. Compound **19** was the most potent and selective MAO-B inhibitor in the series with IC_{50} value in low nanomolar range. The same research group[65] synthesized another series of coumarin derivatives, *i.e.*, 6-substituted 3-arylcoumarins and evaluated them, *in vitro*, as human MAO-A and MAO-B inhibitors. In this series, compound **20** (Fig. 5) was found to be the

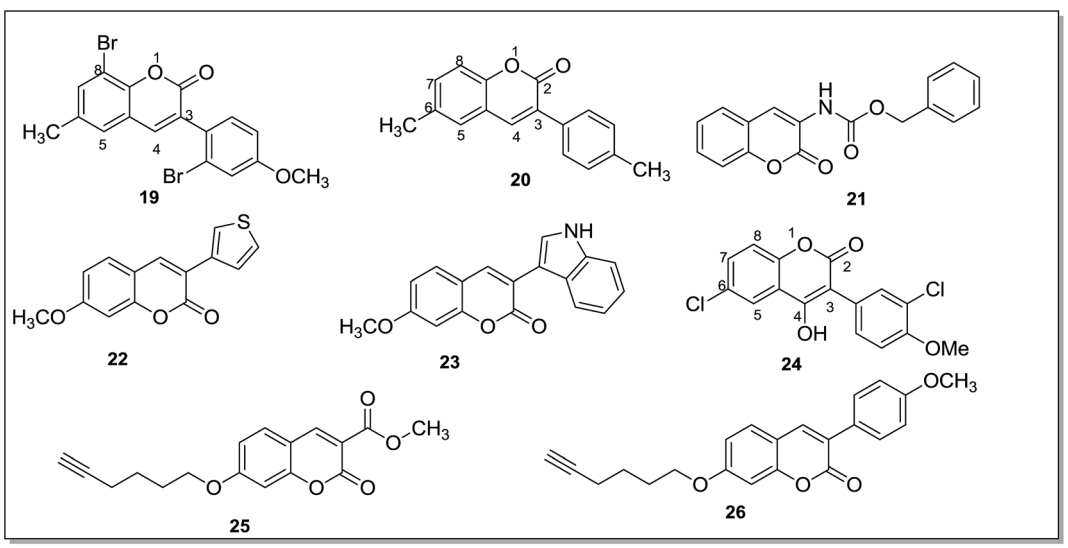


Fig. 5 Coumarin derivatives as MAO-B selective inhibitors.

most active and selective MAO-B inhibitor ($IC_{50} = 0.31 \pm 0.02$ nM) with almost 64 times more potency than the standard inhibitor selegiline. A methyl or methoxy substituent at the C6 position of the coumarin and phenyl group at the C3 position were essential for the MAO-B inhibitory activity while presence of a bulkier group at the C6 position severely decreased the MAO-B inhibitory activity. The ADME properties of a series of (coumarin-3-yl)carbamates were also evaluated[66] in order to determine the blood brain barrier permeation. In the reported series of compounds, benzyl(coumarin-3-yl)carbamate (**21**) (Fig. 5) was found to be the most active MAO-B inhibitor in the *in vitro* studies with an IC_{50} value of 45 nM which was very close to the standard inhibitor selegiline, ($IC_{50} = 20$ nM). In addition, *in vivo* assays and docking studies were also performed for the lead compound and administration of compound **21** (100 mg kg^{-1}) in mice, pretreated with the reserpine improved the motor activity, velocity and movement as done by the standard inhibitor selegiline. A series of 3-indolyl and 3-thiophenylcoumarins[67] was tested against human MAO enzyme.

The compounds showed significant inhibitory activity towards hMAO-B isoform. The position of methoxy substituent on the 3-heteroarylcoumarin ring played crucial role in the activity of compounds. In the reported series, a methoxy substituent at the C7 position of compounds **22** ($IC_{50} = 55.6$ nM) and **23** ($IC_{50} = 45.9$ nM) (Fig. 5) increased the MAO-B inhibitory activity and selectivity. In the docking studies, compounds **22** and **23** displayed good binding affinity for MAO-B isoform. A series of 3-aryl coumarin derivatives[68] was synthesized by introducing hydroxyl group at the C4 position of B ring of the coumarin skeleton. The compounds were evaluated for their affinity and selectivity for the MAO-B isoform. Structure–activity relationship studies revealed that the substitution of methoxy and chloro groups in the *para* and *meta* position of the 3-phenyl ring were crucial for the MAO-B inhibitory activities. Compound with a chloro substituent at the C6 position of coumarin ring (**24**) (Fig. 5) was the most potent inhibitor in the series with IC_{50} value of 2.79 μM and showed better selectivity (36 folds) towards MAO-B isoform. Mertens *et al.*[69] synthesized thirty one alkynyl–coumarinyl ethers as MAO-B inhibitors and the 7-hex-5-ynyloxycoumarin derivative (**25**) (Fig. 5) was identified as dual inhibitor of both MAO-A and MAO-B isoforms with IC_{50} values of 9.6 ± 0.8 nM and 1.41 ± 0.15 nM respectively whereas the 3-(4-methoxy) phenyl derivative (**26**) was found to be a selective inhibitor of MAO-B isoform with IC_{50} value of 2.96 ± 0.10 nM. It exhibited more than 3400 folds selectivity over MAO-A isoform. The compounds were found to be reversible inhibitors and it was concluded that the triple bond in these compounds was not making them an irreversible inhibitor as done by propargyl group present in the irreversible inhibitor selegiline.

Chromone moiety plays a vital role in various medicinal and biological activities such as anti-inflammatory, antitumor and antimicrobial activities. The MAO inhibitory activity of the chromone moiety was also evaluated by number of research groups. Alcaro *et al.*[70] screened two chromone isomers for their affinity towards MAO-A and MAO-B isoforms and it was found that the substitutions of an acidic group at C3 position of the heterocyclic scaffold (**27**) (Fig. 6) significantly increased the inhibitory activity towards MAO-B isoform ($IC_{50} = 48 \pm 2.6$ nM) whereas an acid group at C2 position caused no inhibition. Chromone-3-carboxylic acid was found to be the most effective and selective MAO-B inhibitor. Molecular docking studies revealed that a hydrogen donor moiety should be placed at the position three of the pyrone ring (**27**) for favorable energy minimization and selectivity towards MAO-B isoform. A number of flavones, thioflavones and flavanones were evaluated[71] as potential inhibitors of the MAO isoforms. The flavanone series was found to be most active against MAO-B isoform wherein the lead compound **28** (Fig. 6) displayed IC_{50} value of 130 ± 0.7 nM and selectivity index of about 769. The introduction of a double bond (flavones series) or of sulfur atom (thioflavones) to the flavanones led to substantial decrease in

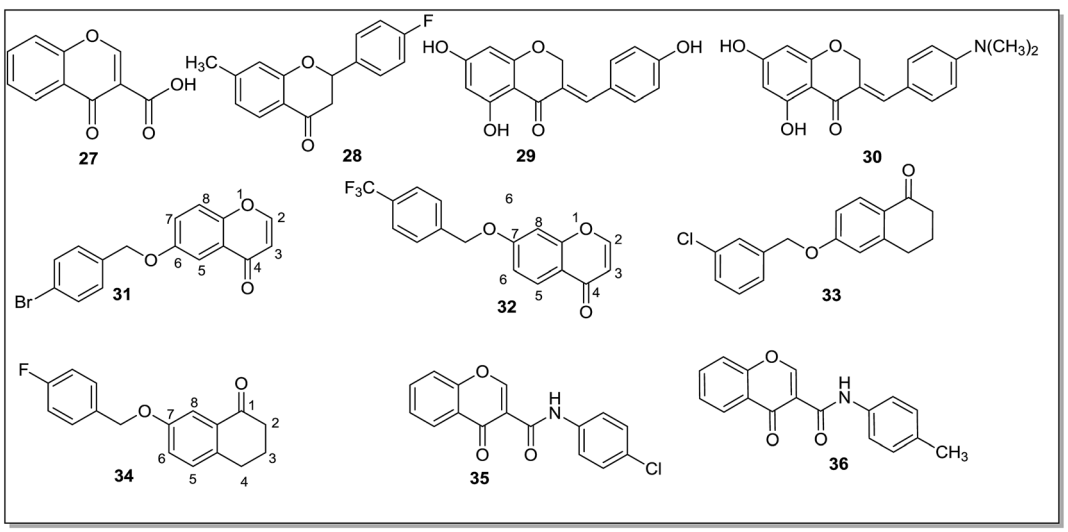


Fig. 6 Chromone and 1-tetralone based MAO-B selective inhibitors.

the MAO-B inhibitory activity. Desideri *et al.*[72] synthesized different series of chromone derivatives and evaluated these for the MAO inhibitory activity. The (*E*)-3-benzylidenechroman-4-one derivatives exhibited activity in nanomolar range and higher selectivity towards hMAO-B isoform. The compounds (*E*)-3-(4-(dimethylamino)benzylidene)chroman-4-one (**29**) (IC_{50} = 8.61 ± 0.12 nM) and (*E*)-5,7-dihydroxy-3-(4-hydroxybenzylidene)chroman-4-one (**30**) (IC_{50} = 8.15 ± 0.32 nM) (Fig. 6) were reported as the most potent MAO-B inhibitors in the series, with even better activity profile than the reference drug selegiline. Legoabe *et al.*[73] reported a series of chromone derivatives[73] substituted with alkyloxy group at C6 position and evaluated them as inhibitors of recombinant human MAO-A and MAO-B isoforms. The C6 substituted chromones were found to be potent reversible MAO-B inhibitors with IC_{50} values in sub nanomolar range. These compounds bind reversibly to MAO-A, but with less affinities when compared with MAO-B isoform and hence it was concluded that the synthesized compounds were selective MAO-B inhibitors. In the docking experiment the lead compound (**31**) (Fig. 6) exhibited differing interactions and orientation within the two isoforms. The C6 substituted chromone derivatives possessed potency against MAO-B isoform and could be used as a promising lead for the development of potent drug candidate against PD. The same research group[73] further carried out the modifications at the C7 position of the chromones and synthesized a series of C7 substituted chromone (1-benzopyran-4-one) derivatives. The compounds were evaluated for their potential to inhibit recombinant human MAO enzyme and exhibited IC_{50} values ranging from 8 nM to 370 nM for MAO-B isoform and IC_{50} values ranging from 495 nM to 803 nM for MAO-A isoform. 7-Benzyloxy substitution of chromone (**32**) (Fig. 6) was crucial for MAO-B inhibition activity. A series of fifteen α-tetralone (3,4-dihydro-2*H*-naphthalen-1-one) derivatives[74] was evaluated for MAO inhibitory activity. In the synthesized series, 6-(3-iodobenzyloxy)-3,4-dihydro-2*H*-naphthalen-1-one (**33**) (Fig. 6) was found to be the most active MAO-B inhibitor exhibiting IC_{50} value 4.5 nM with 287 folds selectivity while the cyano-analogue 6-(3-cyanobenzyloxy)-3,4-dihydro-2*H*-naphthalen-1-one exhibited greater selectivity towards MAO-A isoform with an IC_{50} value of 24 nM and 3.25 folds selectivity. Structure–activity relationship studies showed that the substitution at the C6 position was essential for the MAO inhibitory activity. A benzyloxy substitution increased the MAO-A inhibitory activity and an alkyl and halogen substitution at the *meta* and *para* position of benzyloxy, promotes MAO-B inhibitory activity. Similarly, a series of fifteen C7 substituted α-tetralone derivatives[75] was investigated for MAO inhibitory potential. Arylalkyloxy substitution on C7 position of the α-tetralone moiety improved potencies of the compounds towards hMAO-B isoform displaying IC_{50} values in submicromolar range. The synthesized α-tetralones were found to be selective for the MAO-B isoform over the MAO-A and all the compounds displayed IC_{50} values in submicromolar range (IC_{50} values < 0.47 nM). The most potent MAO-B inhibitor in the series was 7-(4-fluorobenzyloxy)-3,4-dihydro-2*H*-naphthalen-1-one (**34**), showing an IC_{50} value of 0.89 nM and SI of 13 over MAO-A. In the docking studies it was found that hydrogen bonding played relatively smaller role in inhibitor stabilization compared to the van der Waals interactions.

Gaspar *et al.*[76] synthesized two different series of chromone derivatives (substituted at 2 and 3 position) and evaluated the compounds as MAO inhibitors. The chromones with a *meta* substituent on γ-pyrone nucleus showed selectivity towards the MAO-B isoform with IC_{50} values in the micromolar to nanomolar range. Most of the chromone 3-carboxamide derivatives exhibited selectivity towards the MAO-B isoform of the enzyme. In the reported series, compound **35** (Fig. 6) with a chloro substitution at the *para* position of the exocyclic aromatic ring was the most potent and selective inhibitor of the MAO-B isoform with an IC_{50} value of 63 nM and SI greater than 1500 towards MAO-B. Docking experiments of **35** showed better stabilization of the compound in the MAO-B cavity than in the MAO-A cavity. Two different series of compounds based on chromane-2,4-dione and chromone-3-carboxamide scaffolds[77] were synthesized and most of the compounds displayed potent and selective MAO-B inhibitory activity in the micromolar to nanomolar range. The presence of C3 substituents and an amide spacer between the heterocyclic and the exocyclic ring was found to be crucial for MAO-B inhibitory activity. A *para*-chloro and a *para*-methyl group in the exocyclic ring favor activity and selectivity towards MAO-B. In this study compound **35** with an IC_{50} value of 2.9 nM and SI of more than 3400 and compound **36** with an IC_{50} value of 8.0 nM and SI of more than 1250 were found to be selective and potent MAO-B inhibitors, being more potent than the standard inhibitor deprenyl by 6.7

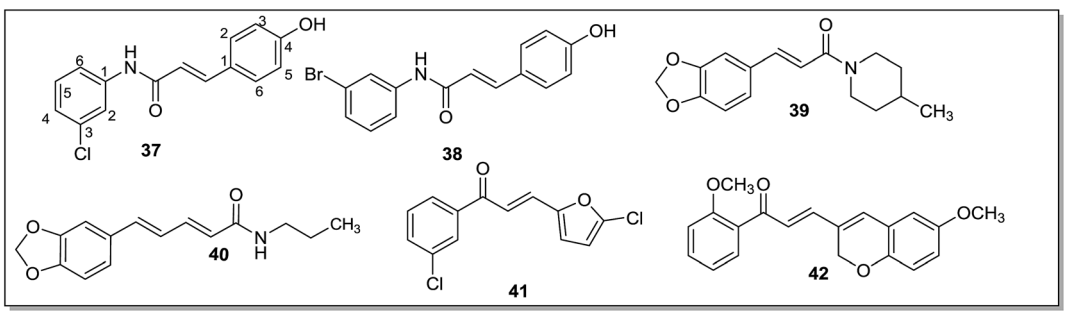


Fig. 7 Chalcone and amide derivatives as MAO-B selective inhibitors.

and 2.4-fold, respectively. Similarly, compound **36** was found to be the most potent inhibitor (hMAO-B) in another series[76] with an IC_{50} values of 68 ± 3 nM.

In a series of anilide derivatives,[78] *N*,3-diphenylpropenamides were found to be promising MAO-B inhibitors. The screening of initially synthesized compounds led to the identification of two active compounds, (2*E*)-*N*-(3-chlorophenyl)-3-phenylprop-2-enamide and (2*E*)-*N*-(3-bromophenyl)-3-phenylprop-2-enamide as reversible and selective inhibitors of the MAO-B isoform with IC_{50} values of 0.5 μM and 0.4 μM, respectively. These inhibitors were further docked with the active site models of human MAO-A and MAO-B isoforms and docking studies led to the synthesis of phenolic derivatives **37** and **38** (Fig. 7). These derivatives were found to be selective and reversible MAO-B inhibitors with IC_{50} values of 32 nM and 26 nM respectively and were almost fourteen times more potent than their parent compounds. It was suggested that the substitution of the halogen atom at C3 position of the phenyl ring of the anilide moiety and a *para* hydroxyl substitution at the aromatic ring improved MAO-B binding affinity. Piperine and antiepilepsirine derivatives[79] displayed selectivity for the MAO-B isoform and the most active compound (**39**) (Fig. 7) in the series exhibited an IC_{50} of 498 nM. The blood brain barrier permeability of the compounds was confirmed through PAMPA assays. It was noticed that the presence of a nitrogen atom in the ring reduces MAO-B inhibition potential of the compounds. The lead compound **39** was found to dock in a similar orientation to MAO-B as the parent compound, piperine. Mu *et al.*[80] evaluated a series of piperine derivatives. The amine substituent on the piperidine ring improved the potency and selectivity of the inhibitors towards MAO-B isoform. 5-(3,4-Methylenedioxyphenyl)-2*E*,4*E*-pentadienoic acid *n*-propyl amide (**40**) (Fig. 7) has shown maximum MAO-B inhibitory activity (IC_{50} = 45 nM) and good selectivity (IC_{50} MAO-A = 3660 nM). A conjugated double bond and carbonyl group of the piperine ring were found to be essential functionalities for the MAO inhibitory activities. Docking studies of compound **40** with the MAO-B isoform showed that it interacts with Tyr60, Tyr326, Tyr398 forming an aromatic cage and the aromatic ring form π–π stacking interactions with Tyr407. It was also observed that compound **40** forms more hydrogen bonds with MAO-B rather than with the MAO-A isoform. In a series of furanochalcone derivatives[81] {2*E*-3-(5-chlorofuran-2-yl)-1-(3-chlorophenyl)prop-2-en-1-one} (**41**) (Fig. 7) was identified as the most potent MAO-B inhibitor with an IC_{50} value of 174 nM. The kinetic studies revealed that the synthesized compounds were competitive and reversible inhibitors of the MAO-B isoform. It was found that furanochalcones with an electron withdrawing substituent at the phenyl ring were potent and selective MAO-B inhibitors. A series of chromenylchalcones[82] was synthesized and MAO-B inhibition potential of the compounds was evaluated using an HPLC based method and an MAO-B enzyme assay kit. Among the several synthesized derivatives, (*E*)-3-(6-methoxy-2*H*-chromen-3-yl)-1-(2-methoxyphenyl)prop-2-en-1-one (**42**) (Fig. 7) with a half-maximal inhibitory concentration of 320 nM, was reported as the most promising MAO-B inhibitor. *In silico* docking experiments indicated that the compound **42** formed ligand–protein complex *via* same residue as in case of selegiline.

Nag *et al.*[83] reported fluorine-18 labeled propargylamine derivatives as potential PET radio ligands to visualize MAO-B activity. Three ligands, (*S*)-1-fluoro-*N*,4-dimethyl-*N*-(prop-2-ynyl)-pent-4-en-2-amine (**43**), (*S*)-*N*-(1-fluoro-3-(furan-2-yl)propan-2-yl)-*N*-methylprop-2-yn-1-amine (**44**) and (*S*)-1-fluoro-*N*,4-dimethyl-*N*-(prop-2-ynyl)pentan-2-amine (**45**) (Fig. 8) were synthesized through multi-step procedures. The ligands were found to be selective for the MAO-B isoform displaying IC_{50} values of 664 ± 48.1 nM, 208.5 ± 13.4 nM and 131.5 ± 0.7 nM respectively and none of the ligand inhibited the MAO-A isoform.

Compound **45** demonstrated high selectivity for the MAO-B isoform and was selected for further investigation by PET. Compound **45** (Fig. 8) was a selective inhibitor of MAO-B isoform and in the *in vivo* studies it showed MAO-B specific binding pattern by PET in the monkeys. The compound was proposed as a candidate for further PET investigations in human. The same research group reported fluorine-18 labeled deuterium substituted analogues[84] of rasagiline as potential PET radio ligand for the study of MAO-B isoform. The compound inhibited the MAO-B activity with an IC_{50} of 9.9 ± 1.1 μM. It was found that **46** (Fig. 8) bind to MAO-B rich regions in the monkey and was blocked by MAO-B selective compound L-deprenyl. The compound was proposed as an important lead for human PET studies. A library of arylalkenylpropargylamines[85] was tested for the MAO inhibitory activities. The preliminary screening of the compounds were performed using

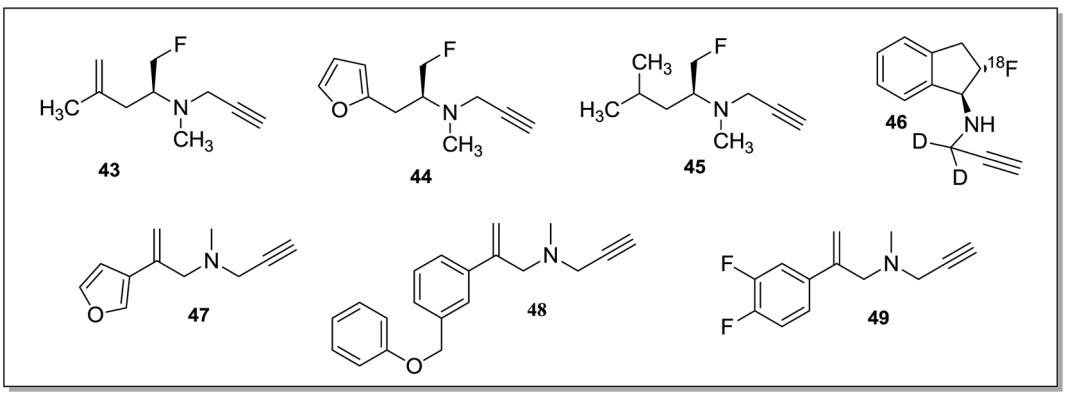


Fig. 8 Propargylamine derivatives as MAO-B selective inhibitors.

rat MAO enzymes. Potent and selective inhibitors were subsequently screened against human MAO-A and MAO-B enzyme isoforms. Amongst the four different groups of compounds synthesized, compound **47** with a furanyl ring was the most potent hMAO-B inhibitor with IC_{50} value of 0.7 nM and SI of more than 2600. In addition, selected compounds were also tested, *in vitro*, for neuroprotection (PC-12 cells treated with 6-OHDA and rotenone) and cytotoxicity (TAMH liver cell line). Some of the compounds like **48** and **49** were identified as potent lead candidates that could be developed as drugs for the treatment of PD.

Luhr *et al.*[86] designed and synthesized 2-arylthiomorpholine and 2-arylthiomorpholin-5-one derivatives as rat and human MAO inhibitors. It was found that a basic nitrogen atom in the ring was not necessary for the MAO inhibitory activity. In the docking studies it was concluded that three different interactions of ligands at the active site of receptor could modulate the bioactivity of MAO inhibitors, an aromatic ring that could participate in the π interactions with Tyr326, a heteroatom that could interact with Tyr398 and/or Tyr435 and a benzyl substituent at the opposite end of the molecule interacting at the entrance cavity which determines selectivity for the MAO-B isoform. The benzyloxy analogues **50** and **51** (Fig. 9) were found to be the most potent in the series with K_i values of 48 $\pm$ 30 nM and 38 $\pm$ 3 nM respectively for hMAO-B with SI of more than 2000 over MAO-A. Similarly for rat MAO-B compound **50** and **51** displayed K_i values of 74 $\pm$ 3 nM and 130 $\pm$ 4 nM respectively with selectivity of more than 2600 fold. Prins *et al.*[87] synthesized a series of indole and benzofuran derivatives. They showed significant MAO-B inhibitory activity and SAR studies suggested that the chloro-substituent at the C5 phenyl side chain of the indoles and benzofuranes improved both MAO-A and MAO-B inhibitory potencies. Molecular modeling studies demonstrated that the compound **52** (Fig. 9) was stabilized in the active pocket of MAO-B and showed hydrogen bonding interactions with Tyr-435 and with the water molecule in the proximity of the FAD co-factor. Compound **52** was the most effective MAO-B inhibitor in the series. It was concluded that the indole and benzofuran derivatives were selective inhibitors of MAO-B and could be developed as promising drugs for the treatment of PD. A series of 5-sulphanylpthalimide analogues[88] were screened for their affinity towards both the human MAO

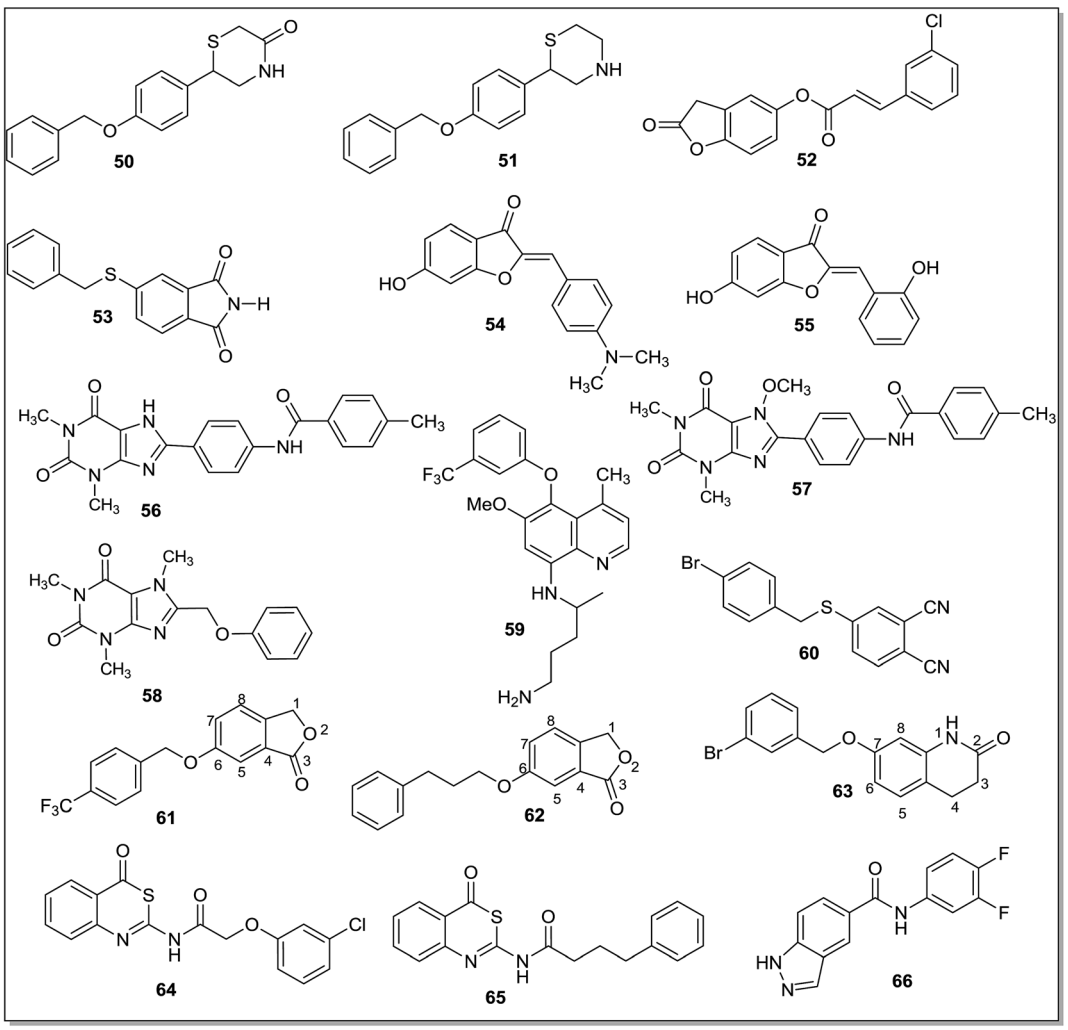


Fig. 9 Miscellaneous compounds acting as MAO-B selective inhibitors.

isoforms. Almost all the synthesized compounds exhibited MAO-B inhibitory activity with IC_{50} values in the nanomolar range. 5-(Benzylsulfanyl)phthalimide (**53**) (Fig. 9), with an IC_{50} value of 4.5 nM was the most effective MAO-B inhibitor with almost 400-fold selectivity as compared to MAO-A. Similarly, another series of thiazolidinedione (TZD) analogous[89] has been synthesized in the same laboratory and ligand based virtual screening was performed. The most active compound (**54**) (Fig. 9) obtained in the series was reported as an inhibitor of both MAO-A (IC_{50} = 268 nM) and MAO-B (IC_{50} = 99 nM) isoforms. Compound **54** is a derivative of the naturally occurring and bioactive flavonoid, sulfuretin which possesses protective activity against mitochondrial toxins in a PD model. Structure–activity relationship studies revealed that the replacement of *para* tertiary dimethylamine group (**54**) with an *ortho* hydroxyl group at the phenyl ring improved the inhibitory activity of **54** from 99 nM to 11.5 nM (**55**). A number of 8-substituted benzamido–phenylxanthine derivatives[90] were screened *in vitro* for their selectivity and MAO-B inhibition potential. Most of the compounds displayed promising activities and the *para*-substituted derivatives **56** (K_i value 0.3 μM) and **57** (K_i value 1.2 μM) (Fig. 9) were more potent than the *meta*-substituted derivatives due to steric interactions of the substituents at the binding pocket. It was concluded that caffeines can be explored as a favorable scaffold for designing potent MAO-B inhibitors. Similarly, with an aim to find out caffeine based potent MAO inhibitors, Okaecwe *et al.*[91] investigated 8-phenoxymethylcaffeines and 8-[(phenylsulfanyl)methyl]caffeine derivatives against the MAO enzyme. The 8-phenoxymethylcaffeine derivatives were found to be reversible and potent MAO-B inhibitors with IC_{50} values ranging from 0.15 μM to 5.8 μM. The second series of compounds *i.e.*, 8-[(phenylsulfanyl) methyl]caffeine derivatives were found to be weak MAO-B inhibitors with IC_{50} values ranging from 4 μM to 124 μM. In addition, both the series of compounds displayed low binding affinities for MAO-A isoform. The presence of a heteroatom at the C8 side chain of the caffeine scaffold improved the inhibitory activity and compound **58** (Fig. 9) was obtained as the most potent MAO-B inhibitor. 8-Phenoxymethylcaffeines have the potential to be developed as lead for the design of potent MAO-B selective inhibitors. Chaurasiya *et al.*[92] synthesized and treated 5-phenoxyprimaquine analogous with MAO enzymes and evaluated their potency. Bioassays results showed that these compounds displayed better inhibitory activity towards both the isoforms when compared with the standard drug primaquine and the compound 5-(4-trifluoromethylphenoxy)-4-methylprimaquine (**59**) (Fig. 9) was the most active with selectivity towards MAO-B isoform and with an IC_{50} value of 150 nM. van der Walt *et al.*[93] evaluated sulfanylphthalonitrile and sulfanylbenzonitriles analogous and most of the compounds were found to be potent and selective for MAO-B isoform with IC_{50} values in the nanomolar range. The sulfanylphthalonitriles displayed better binding affinities for MAO-B than the corresponding sulfanylbenzonitrile analogues. In the reported series, 4-[(4-bromobenzyl)sulfanyl]phthalonitrile (**60**) (Fig. 9) was the most promising MAO-B inhibitor (IC_{50} = 25 nM) with very high selectivity (8700 fold) for MAO-B over MAO-A isoform.

Strydom *et al.*[94] designed a series of C6-substituted phthalide-[2-benzofuran-1(3*H*)-one] derivatives. All the phthalide derivatives showed good binding affinities to human MAO-A and MAO-B isoforms however C6 substituted phthalide exhibited MAO-B specific inhibition. A number of *para*-phenyl substituted derivatives of 6-benzyloxyphthalide were screened and the general order of potency, *i.e.*, CF_3 > I > Br > Cl > F > CH_3 > H was observed. The most potent MAO-B inhibitor obtained in the series was a trifluoro substituted benzyloxyphthalide homologue (**61**) (Fig. 9) with an IC_{50} value of 1.4 nM while compound **62** with a phenylpropyl chain was the most active MAO-A inhibitor. The synthesized phthalides were reversible and competitive inhibitors at both isoforms and these compounds can be explored as leads for the development of new and effective drugs for the treatment of PD. A series of 3,4-dihydro-2(1*H*)-quinolinone derivatives[95] was explored for human MAO inhibition activities. They were structurally related to the coumarin-(1-benzopyran-2-one) derivatives and were found to be potent and selective MAO-B inhibitors. 7-(3-Bromobenzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (**63**) (Fig. 9) was the most potent MAO-B inhibitor with an IC_{50} value of 2.9 nM and more than 2700 folds selectivity over MAO-A. Structure–activity relationship studies suggested that a substituent at the C7 position of 3,4-dihydro-2(1*H*)-quinolinone was crucial for the MAO-B inhibitory activity. It was concluded that the C7 substituted 3,4-dihydro-2(1*H*)-quinolinone derivatives could be used as a lead for the development of drug candidate for the treatment of Parkinson's disease.

Stößel *et al.*[96] synthesized and screened benzothiazinone derivatives as dual targeting agents of adenosine A_{2A} receptors and MAO-B enzyme. In the screening studies, 2-(3-chlorophenoxy)-*N*-(4-oxo-4*H*-3,1-benzothiazin-2-yl)acetamide (**64**) (Fig. 9) has been identified as the most potent MAO-B inhibitor with an IC_{50} value of 1.6 nM but it displayed no affinity for adenosine A_{2A} receptors. However, *N*-(4-oxo-4*H*-3,1-benzothiazin-2-yl)-4-phenylbutanamide (**65**) (Fig. 9) was found to be a competitive and reversible inhibitor of the human MAO-B (IC_{50} = 34.9 nM) and human A_{2A} (K_i = 39.5 nM) receptors. These dual targeting compounds were proposed as potential candidates for the development of drugs for PD. Tzvetkov *et al.*[97] designed and synthesized indazol-5-carboxamides, indol-5-carboxamide, and (1*H*-indazol-5-yl)methenamine derivatives as new classes of MAO-B inhibitors. Structure–activity relationship studies helped in the identification of some potent and reversible MAO-B inhibitors displaying sub nanomolar potency. Molecular modelling studies assisted in the design of ligands showing high affinity and selectivity towards the MAO-B isoform. *N*-(3,4-Difluorophenyl)-1*H*-indazole-5-carboxamide (**66**) (Fig. 9) showed remarkable *in vitro* MAO-B inhibitory potential (IC_{50} = 1.6 nM and SI more than 6000 fold) and well-balanced physicochemical profile for the CNS bioavailability. The promising compounds need to be evaluated for water-solubility, bioavailability, metabolism and toxicity so that a potent drug candidate could be developed for the treatment of PD.

4. Role of MAO inhibitors in the Alzheimer's disease

Alzheimer's disease (AD) is measured as extreme loss in memory and intellectual ability convoyed by behavioral disturbances and declining ability to perform basic activities of daily life.[98] Depressive symptoms occur in patients suffering with AD and these may be associated with decrease in serotonergic and noradrenergic transmission in the limbic system.[99,100] Although the exact cause of progressive neuronal degeneration in AD is not known, evidences like oxidative stress caused by increased levels of iron, nitration of tyrosine residues, MAO-B hyperactivity in gliosis, have been reported in the literature.[101–103] The MAO inhibitor deprenyl is an anti-Parkinson drug and it has also been used to slow the progress of AD. Some clinical trials have shown that deprenyl alleviate the symptoms of AD.[104] The patients suffering with AD were also found to have low levels of cholinergic neurons causing decreased concentration of acetylcholine in the brain which in turn affects the learning and memory functions. Therefore, various acetylcholinesterase inhibitors (AChEIs) like tacrine, rivastigmine, donepezil *etc.* have been developed but these compounds exhibited partial therapeutic benefits.[105] On the other hand, the MAO enzyme is considered as an important target for the treatment of AD, as the enzyme catalyzes the oxidative deamination of a number of xenobiotic and endogenous amines with the formation of neurotoxic hydrogen peroxide and hydroxyl free radicals. Hence, the dual targeting ligands which can simultaneously inhibit MAO-B and cholinesterases are being developed as drugs for the management of AD. A number of dual targeting ligands have been reported as potential therapeutic agents for the treatment of AD. Samadi *et al.*[106] reported synthesis, biological screening and docking studies of two different series of compounds which simultaneously inhibit MAO as well as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The screening of compounds led to the identification of a lead that can act as multi-potent drug exhibiting high and selective AChE inhibitory activity ($IC_{50} = 37 \pm 4$ nM) and moderate, but selective MAO-A inhibition activity ($IC_{50} = 41 \pm 7$ μM). Molecular modeling studies of the most active compound confirmed its dual AChE inhibition activity, binding simultaneously at the catalytic active site and at the peripheric anionic site. The compound **67** (Fig. 10) was reported as the most active and selective dual AChE inhibitor, displaying a moderate and selective MAO-A inhibition activity. Compound **67** was proposed as a multi-potent lead that could be developed as a drug that simultaneously binds to two pharmacological targets and could play a role in the treatment of AD. Bolea *et al.*[107] synthesized a series of compounds using a hybrid molecular approach by combining the benzylpiperidine scaffold of the donepezil (AChE inhibitor) and indolylpropargylamino part of the MAO inhibitor *N*-[(5-benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine. The two parts of the hybrid molecule were linked through an oligomethylene linker. Molecular docking and kinetic studies showed that the most promising hybrid **68** (Fig. 10) was the inhibitor of both MAO-A ($IC_{50} = 5.2 \pm 1.1$ nM) and MAO-B ($IC_{50} = 43 \pm 8$ nM) isoforms that also exhibited potency towards AChE and BuChE. The same research group[108] designed heterocyclic substituted alkyl and cycloalkylpropargylamines as multi-targeting agents that simultaneously bind to the monoamine oxidases as well as cholinesterases. Indole derivatives reported in the series I type of compounds were well known MAO inhibitors and were investigated for their capacity to inhibit AChE and BuChE. In the series I, *N*-[(5-(benzyloxy)-1*H*-indol-2-yl)methyl]-*N*-methylbut-2-yn-1-amine has been found to be multi-potent compound that could selectively inhibit MAO-B ($IC_{50} = 31 \pm 2$ nM) and eqBuChE ($IC_{50} = 7 \pm 1$ μM) enzymes. The molecular modeling studies of this compound showed that high MAO-B inhibitory activity might be due to the presence of methyl propargyl group in the proximity of N5 of FAD in MAO-B. The series II compounds, *i.e.*, 5-amino-7-(prop-2-yn-1-yl)-6,7,8,9-tetrahydropyrido[2,3-*b*][1,6]naphthyridines were reported as weak MAO inhibitors, but displayed selective AChE inhibitory activity. 5-Amino-7-(2-propyn-1-yl)-2-(1-pyrrolidinyl)-6,7,8,9-tetrahydropyrido[2,3-*b*]-1,6-naphthyridine-3-carbonitrile (**69**) (Fig. 10) exhibited a multi-potent pharmacological profile simultaneously binding to BuChE and MAO-B and it was proposed as a lead for the design of novel and potent multi-targeting cholinesterase and MAO inhibitors. Bautista-Aguilera *et al.*[109] further designed and synthesized a series of donepezil-indolyl based amines, amides and carboxylic acid derivatives derived from *N*-((5-(3-(1-benzylpiperidin-4-yl) propoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (**68**). These were found to be multipotent inhibitors, targeting cholinesterase and MAO enzymes. The amines were more potent ChE inhibitors than the corresponding amides and carboxylic acids, showing a clear selectivity for EeChE inhibition. The most potent inhibitor obtained in the series, *i.e.* [*N*-((5-(3-(1-benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)-methyl)prop-2-yn-1-amine] (**70**) (Fig. 10) showed multi-receptor affinity profile for MAO-A ($IC_{50} = 5.5 \pm 1.4$ nM), MAO-B ($IC_{50} = 150 \pm 31$ nM), EeAChE ($IC_{50} = 190 \pm 10$ nM) and eqBuChE ($IC_{50} = 830 \pm 160$ nM). Compound **70** displayed good drug-like characteristics and ADMET properties and it could be developed as a drug candidate for the prevention and treatment of AD. Zheng *et al.*[110] designed site-activated chelators targeting both AChE and MAO. The most active compound (**71**) had only little affinity for metal (Fe, Cu, and Zn) ions. The interesting characteristic of this compound is that the iron chelation capacity becomes activated after inhibition of AChE to release the active chelators M30 (**72**) (Fig. 10). Compound **71** showed high potency, *in vitro*, against MAO-A with an IC_{50} value of 7.0 ± 0.7 nM and weak inhibition of MAO-B. It displayed lower cytotoxicity and more lipophilicity than its activated brain permeable chelator **72**. The compound **72** was able to modulate amyloid precursor protein regulation and β-amyloid reduction, suppress oxidative stress, and passivate excess metal ions (Fe, Cu, and Zn), which showed that chelators have potential to treat the underlying cause of AD.

A number of donepezil derivatives[111] were designed, synthesized and found to be potent metal chelators that target different enzyme systems related to AD (ChEs and MAO-A).

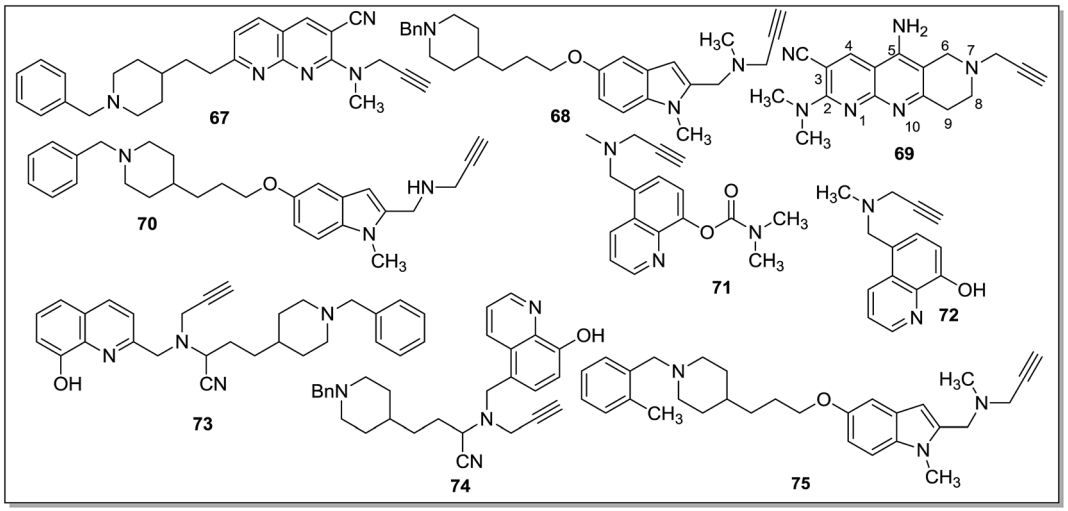


Fig. 10 Propargylamine derivatives as multireceptor inhibitors.

Compound **73** exhibited excellent ChEs and a selective MAO-A inhibition potency (*vs.* MAO-B) along with the strong complexing affinities for zinc and copper ions (involved in the progression of AD). Compound **73** has shown significant MAO-A, hrAChE and hrBuChE inhibitory activities with IC_{50} values of 10.1 ± 1.1 μM, 0.029 ± 0.003 μM and 0.039 ± 0.003 μM respectively. Compound **73** as a donepezil–hydroxyquinoline hybrid was found to be a lead with the disease modifying anti-Alzheimer's drugs (DMAAD) profile. Wang *et al.*[112] synthesized and evaluated multi target directed donepezil, propargylamine and 8-hydroxyquinoline hybrids for the treatment of Alzheimer's disease. The most active derivative obtained in the series was racemic α-aminotrile 4-(1-benzylpiperidin-4-yl)-2-(((8-hydroxyquinolin-5-yl)methyl)(prop-2-yn-1-yl)amino)butanenitrile (**74**) (Fig. 10) exhibiting affinity to MAO-A ($IC_{50} = 6.2 \pm 0.7$ μM), MAO-B ($IC_{50} = 10.2 \pm 0.9$ μM), AChE ($IC_{50} = 1.8 \pm 0.1$ μM) and BuChE ($IC_{50} = 1.6 \pm 0.2$ μM). In the docking studies compound **74** was found to be interacting simultaneously with the catalytic and peripheral site of eeAChE. Most of the compounds showed good ADMET profile and brain penetration capacity for the CNS activity. In the passive avoidance task, compound **74** significantly decreased scopolamine-induced learning deficits when tested on the mice with experimentally induced amnesia. Nineteen donepezil–indolyl hybrids[113] were designed, synthesized and evaluated as multifunctional agents binding to the MAO and ChE enzymes. Compound **75** was the most potent inhibitor in the series exhibiting irreversible hMAO-A inhibition activity with an IC_{50} value of 6.3 ± 0.4 nM and was nine times more potent than the reference drug clorgyline and 29 fold more selective towards MAO-A over MAO-B. Compound **75** also showed hAChE and hBuChE inhibition potential with IC_{50} values of 2.8 ± 0.1 μM and 4.9 ± 0.2 μM respectively. Molecular docking studies with **75** showed that *ortho* methyl group improved the ligand recognition and increased the ligand–enzyme hydrophobic interaction in the hBuChE and π–π stacking in hMAO-A, hMAO-B, and hAChE

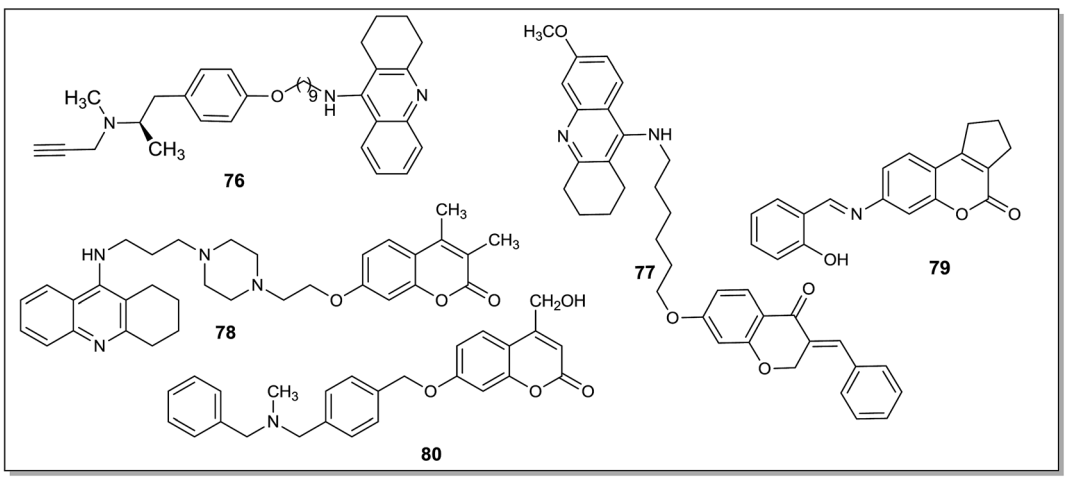


Fig. 11 Tacrine hybrids and coumarin derivatives as multireceptor inhibitors.

enzyme. Virtual ADMET analysis of compound **75** showed good drug like characteristics with better brain penetration ability as compared to the standard drug selegiline.

Lu *et al.*[114] synthesized and evaluated a series of tacrine–selegiline based hybrids as multi-potent agents with cholinesterase and MAO inhibitory activities for the treatment of AD. Compound **76** (Fig. 11) displayed an optimum inhibition profile for AChE, BuChE, hMAO-A and hMAO-B with IC_{50} values of 22.6 nM, 9.37 nM, 372.4 nM and 181 nM respectively. These types of hybrid compounds could improve patient's cognition by elevating levels of acetylcholine and protect neurons by retaining the activities of selegiline. The compounds were proposed as "one compound multi-target" drugs for the treatment of AD. Sun *et al.*[115] designed, synthesized and screened a series of tacrine–homoisoflavonoid hybrids as multifunctional compounds and most of these were found to be promising inhibitors of the cholinesterases (ChEs) and human MAOs in nanomolar range. Amongst the reported series, a compound with linker chain of six carbons between tacrine and (*E*)-7-hydroxy-3-(4-methoxybenzylidene)chroman-4-one (**77**) (Fig. 11) was found to be a potent inhibitor of AChE and MAO-B with IC_{50} values of 67.9 nM and 401 nM respectively. In the artificial membrane permeation assay, compound **77** efficiently crossed the blood–brain barrier (BBB). A series of tacrine–coumarin hybrids[116] were evaluated as multi-target ligands against AD. Most of the compounds exhibited potent inhibitory activities towards AChE, BuChE and were selective for the MAO-B isoform. The linker length connecting tacrine and coumarin fragments played a crucial role in AChE inhibition. Presence of *meta* and/or *para* substituents on the coumarins ring influenced the selectivity and inhibitory activity of ligands towards MAO enzyme. In the reported series, compound **78** (Fig. 11) was the most promising inhibitor with IC_{50} values of 0.1 μM, 16.1 μM, 112.7 μM for hMAO-B, hAChE and BuChE respectively. Compound **78** also showed good BBB permeability and exhibited low toxicity to SH-SY5Y cells. A series of coumarin derivatives[117] were evaluated as multifunctional agents for the treatment of AD and most of the compounds displayed potent hMAO-B inhibitory activity with IC_{50} values in submicromolar range and high selectivity over hMAO-A isoform. This series of compounds also showed moderate to good potencies toward inhibition of self-mediated $A\beta_{1-42}$ aggregation. In the series, compound **79** (Fig. 11) was the most potent hMAO-B inhibitor with an IC_{50} value of 81 nM and SI greater than 1200. In addition, compound **79** displayed metal chelation potential, effective blood–brain barrier (BBB) penetration and showed low cell toxicity in the rat pheochromocytoma (PC12) and SH-SY5Y cells. Farina *et al.*[118] reported structure-based design and optimization of multitarget-directed 2*H*-chromen-2-one derivatives as inhibitors of the MAO-B and cholinesterases. Flexible *N*-benzyl-*N*-alkyloxy coumarins displayed good inhibitory activities at rMAO-B, AChE and BChE, but low selectivity. However rigid inhibitors, containing *meta*- and *para*-xylyl linkers, exhibited good inhibitory activities and high rMAO-B selectivity. Similarly, polar and hydrophilic 4-hydroxymethyl derivatives showed low submicromolar activity at the three target enzymes rMAO-B, AChE, BuChE, and low or no activity at rMAO-A. Some of the promising inhibitors were screened against human MAOs and AChE and in comparison to non-human enzymes, a significant increase of inhibitory activities was observed for hMAOs with relatively high selectivity index for MAO-B isoform. The 4-hydroxymethyl coumarin derivative **80** (Fig. 11), with IC_{50} values of 10 nM, 120 nM and 930 nM for hMAO-B, AChE and BuChE respectively, was found to be a lead for further pre-clinic studies on the basis of toxicity, neuroprotection and transport data. The compound was devoid of neurotoxicity, showed moderate neuroprotective effects and good BBB permeability profile with limited P-gp affinity.

5. Role of MAO inhibitors in depression

The antidepressant effect of MAO inhibitors was a serendipitous discovery.[119] The antituberculosis drug iproniazid was found to help depression when it was administered to the tuberculosis patients who were also suffering with depression.[120] The antidepression action of the drug was due to its inhibition of mono amine oxidase enzyme. However, in addition to monoaminergic systems, many neurotransmitter systems such as noradrenergic, serotonergic, dopaminergic, neuroendocrinergic and neuropeptide systems have been reported as being involved in the pathophysiology of depression.[121–123] The etiology of the depression is linked with the suboptimal concentrations of these neurotransmitters in the central nervous system (CNS).[9] Depression can be recognized with symptoms like panic-agoraphobia syndrome, severe phobias, social anxiety disorder, and obsessive-compulsive disorder.[124] Recent advancements in the antidepressant therapeutics include use of reversible inhibitors of MAO-A including tricyclic antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin Reuptake Transporter (SERT) inhibitors. These inhibitors increase the synaptic concentration of three neurotransmitters; serotonin, norepinephrine and dopamine in the brain. SSRI and SERT inhibitors were found to be less toxic when compared with the first generation irreversible and non-selective MAO inhibitors. However, in case of severe and treatment-resistant depression, MAO inhibitors are the only available most effective drugs. The MAO enzyme can metabolize serotonin, norepinephrine and dopamine and low levels of these three neurotransmitters and the over expressed MAO enzyme is linked with the etiology of depression. In order to develop an effective and potent antidepressant, the brain MAO-A must be inhibited. One of the major limitations associated with the use of irreversible MAO inhibitors was risk of hypertensive crisis. However, with the development of reversible and selective MAO-A inhibitors, this problem has been minimized or eliminated. Thus, selective MAO-A inhibitors are being explored for the development of effective drug candidates for the treatment of severe depression.

Karuppasamy *et al.*[125] reported a series of 3,5-diarylpyrazoline derivatives and evaluated their MAO inhibitory activities. Many of the reported compounds were found to be reversible and selective inhibitors of the MAO-A isoform with selectivity

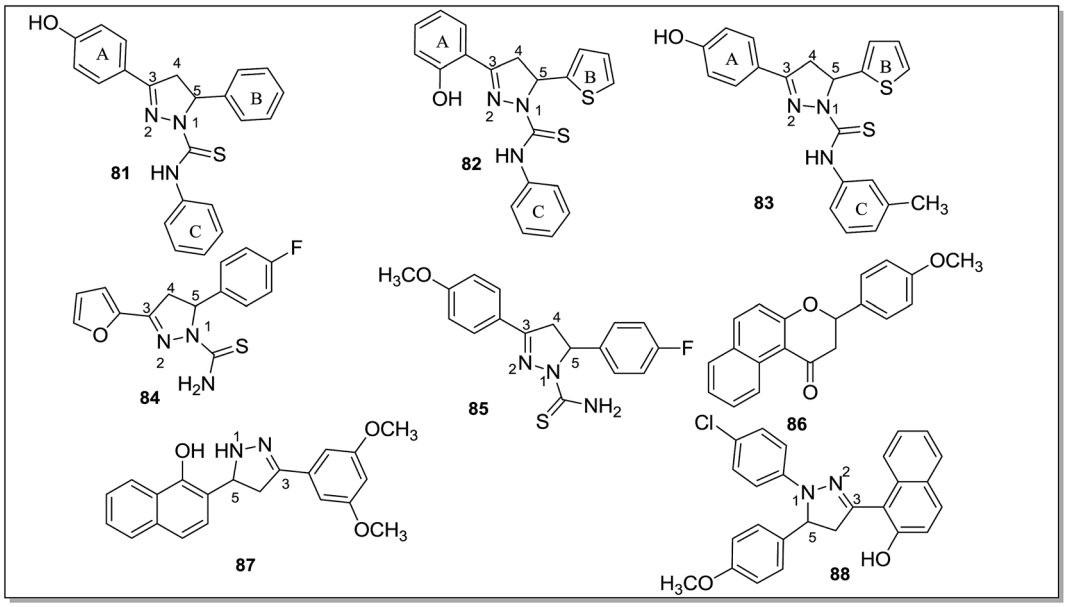


Fig. 12 Pyrazoline based MAO-A selective inhibitors.

index of 10^3 to 10^5. A 4-hydroxy substitution on ring A (**81**) (Fig. 12) improved the potency towards MAO-A isoform. The thiophen-2-yl group as ring B (**82**) (Fig. 12) caused better MOA-A inhibition than the furan-2-yl group. A methyl substituent on the ring C (**83**) was preferred for the selectivity and potency towards MAO-A isoform. Compound **83** was reported as the most potent in the series with an IC_{50} value of 150 ± 10 nM. A series of *N*1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1*H*)-pyrazoles[126] was synthesized and assayed for MAO-A and MAO-B inhibitory activities. SAR studies showed that a fluorine atom at the *para* position of the 5-phenyl substituent was essential for the activity. The presence of a hetero-aromatic substituent at 3- and 5-position of the pyrazoline ring was responsible for the decreased potency and selectivity towards MAO-B while the presence of 4′-methylphenyl and 4′-fluorophenyl at the same position of the ring retained the activity and selectivity. The compounds containing 4′-chlorophenyl substituent at 3-position had increased the activity.

*N*1-Thiocarbamoyl-3-(fur-2′-yl)-5-(4′-fluoro-phenyl)-4,5-dihydro-(1*H*)-pyrazole (**84**) (Fig. 12) was the most active candidate with an IC_{50} value of 2.7 ± 0.8 μM and selectivity ratio of 25 over MAO-B isoform. A series of 3-aryl-5-(4-fluorophenyl)-*N*-substituted-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives[127] was screened, *in vitro*, for the MAO inhibitory activities and selectivity towards MAO-A and MAO-B isoforms. 5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-*N*-methyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**85**) (Fig. 12) was the most potent MAO-A inhibitor with K_i value of 1 nM. Docking results suggested that **85** binds efficiently with the MAO-A enzyme, and a methoxy or chloro substituents at 3-phenyl ring improved the potency and selectivity towards MAO-A isoform. Jo *et al.*[128] designed, *in silico*, three MAO-A inhibitors 3-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (**86**), 2-(5-(3,5-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)naphthalen-1-ol (**87**) and 1-(1-(4-chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)naphthalen-2-ol (**88**) (Fig. 12). In the docking experiments, **86** showed stronger interactions with the MAO-A isoform as compared to the standard inhibitor clorgyline. Further, these compounds were evaluated for the MAO-A inhibition activity and compound **86** showed a similar inhibitory effect like the standard clorgyline.

A series of β-carboline derivatives[129] was synthesized and screened for MAO-A and MAO-B inhibition activities and compared with the harmine as reference drug. The presence of *ortho*-alkylated lipophilic groups like cyclohexyl, phenyl and aliphatic chains increase the MAO-A inhibitory activity but decreases activity towards MAO-B enzyme. The lead compound containing trifluorobutyloxy group (**89**) (Fig. 13) displayed maximum MAO-A inhibition with K_i of 3.6 nM. The computational studies revealed that the trifluorobutyloxy group occupies the hydrophobic pocket of the enzyme which was left vacant by harmine. The cyclohexyl bearing analogue (**90**), was also reported as the potent MAO-A inhibitor with K_i value of 4.3 nM. A series of piperamide derivatives[130] was synthesized and compounds were explored for their MAO inhibitory and antioxidant activities. The antidepressant activity of the compounds was assessed using tail suspension test and forced swim test. Compounds **91** and **92** (Fig. 13) were active in both the tests. The antioxidant activities of the compounds were determined through DPPH and superoxide radical scavenging method. Compound **92** was found to be the most potent antioxidant. Bandaruk *et al.*[131] evaluated the MAO-A inhibitory effects of quercetin and tea catechins in the mouse brain mitochondria. In different biological assays, quercetin (**93**) (Fig. 13) was less active when compared with the other antidepressant drugs but was comparatively safer as it did not show any interaction with the intestine MAO-A. Demirkiran *et al.*[132] purified and isolated four different compounds (**94–97**) (Fig. 13) from the *n*-butanol

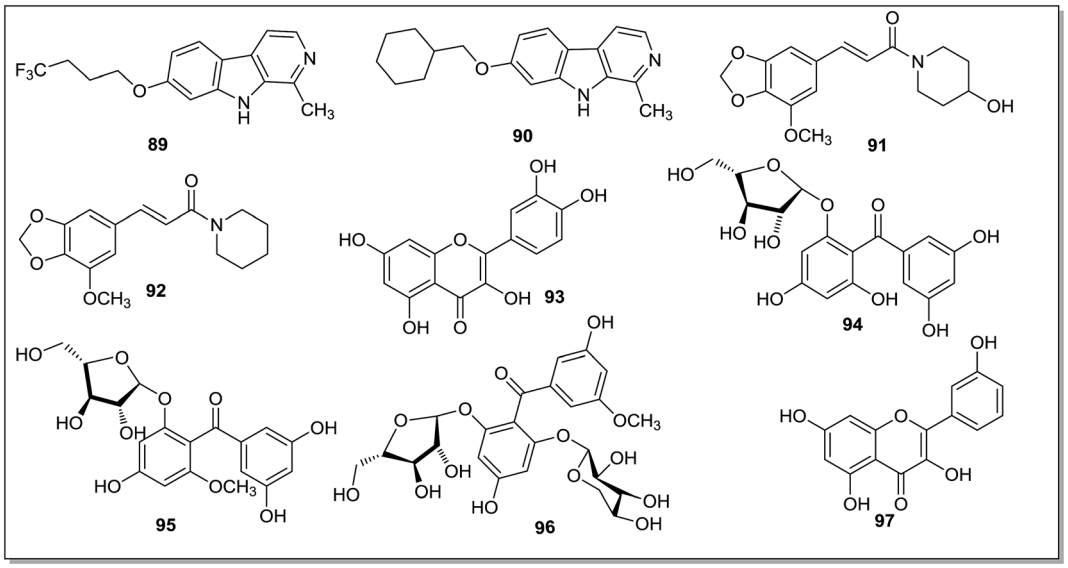


Fig. 13 Compounds acting as MAO-A selective inhibitors.

fraction of 80% ethanol extract of *Hypericum thasium* Griseb. The isolated compounds, along with kaempferol (**97**) and quercetin (**93**) were screened for MAO-A inhibitory activities. These compounds were evaluated with clorgyline as a standard inhibitor and kaempferol (**97**) was found to be the most potent compound with IC_{50} value of 17.5 μM.

Masand *et al.*[133] reported the interactions pattern of 4-propyl-2*H*-benzo[*h*]-chromen-2-one (**98**) (Fig. 14) with MAO enzyme using molecular docking studies and it was found that most of the interactions of **98** with the MAO-A crystal structure were hydrophobic and steric in nature. However, the traditional MAO-A inhibitors like clorgyline displayed hydrophobic as well as polar interactions. In the structure–activity relationship studies it was concluded that the presence of a hydrophobic group at the C4 position of **98** was favorable for the activity. Abdelhafez *et al.*[134] designed and synthesized a number of 4-methyl and 3,4-dimethyl-7-oxycoumarins which include oxadiazole, thiadiazole, triazole and thiazolidinone derivatives. Most of the reported compounds have displayed high affinity and selectivity towards MAO-A isoform with K_i values in the picomolar range. In addition, the reported series of compounds also exhibited MAO inhibitory activity when tested *in vivo*. The molecular modeling studies of the ligands provided new information about the enzyme–inhibitor interactions and potential therapeutic application of 7-oxycoumarin scaffold. The acetohydrazide derivative, **99** with a K_i of 5 pM and SI of 9.66×10^4 (MAO-A) and the diethylaminoethylthio-1,3,4-thiadiazole (**100**), with K_i of 5.18 pM, and SI of 9.58×10^4 (MAO-A) (Fig. 14) were reported as the most potent and selective MAO-A inhibitors. The same research group[135] reported a series of 7-oxycoumarin derivatives and *in vitro* studies showed that most of the compounds were potent and selective MAO-A inhibitors. In the *in vivo* studies it was found that the synthesized compounds were more active than the

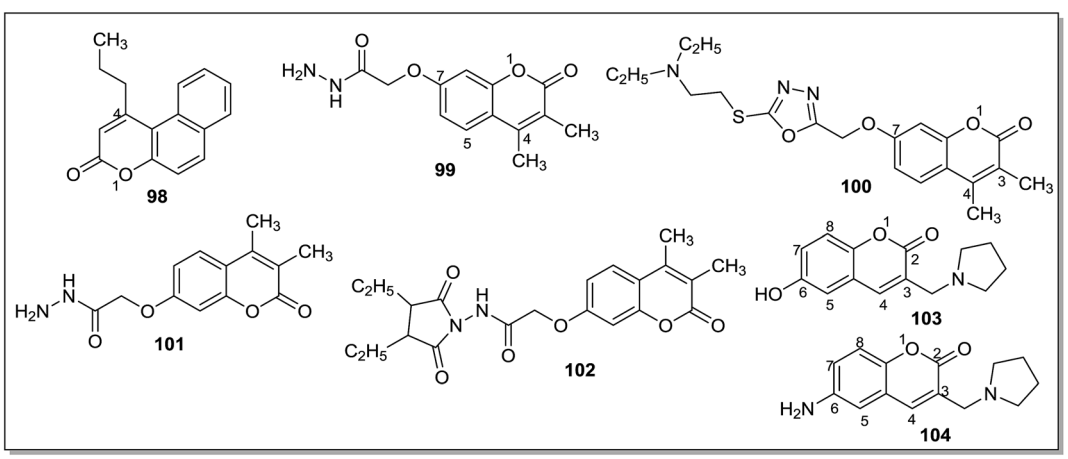


Fig. 14 Coumarin derivatives acting as MAO-A selective inhibitors.

standard inhibitor iproniazid. The most promising inhibitors obtained in the series were 2-(3,4-dimethylcoumarin-7-yloxy) acetohydrazide (**101**) (Fig. 14) with an *in vitro* K_i *i* values of 5.01 pM for MAO-A and 4.84×10^5 pM for MAO-B and *in vivo* ED_{50} of 9143 nM and 2-(3,4-dimethylcoumarin-7-yloxy)-*N*-(2,5-dioxopyrrolidin-1-yl)acetamide (**102**) (Fig. 14) with an *in vitro* K_i values of 6.34 pM for MAO-A and 5.75×10^5 pM for MAO-B and *in vivo* ED_{50} of 9.15 nM. The molecular docking studies showed a direct correlation between the binding affinities of the ligands and percentage inhibition of the MAO-A and MAO-B isoforms. A series of 6-substituted 3-(pyrrolidin-1-ylmethyl)chromen-2-ones[136] (coumarin) were evaluated for their inhibition potential against the MAO-A and MAO-B isoforms. A substituent at the C6 position of the coumarin ring and a basic amine group at C3 position produced selective inhibitors for MAO-A isoform. In the series of reported compounds, **103** ($IC_{50} = 1.46$ μM) and **104** ($IC_{50} = 3.77$ μM) (Fig. 14) were the most potent and selective MAO-A inhibitors exhibiting good aqueous solubility. In the rat brain, **104** decreased the level of 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) while increases the level of 3-methoxytyramine (5 MT). Khattab *et al.*[137] evaluated a series of 2-benzyl-3-(2-arylidenehydrazinyl) quinoxalines, 4-benzyl-1-aryl-[1,2,4]triazolo[4,3-*a*]quinoxalines and phenyl(1-aryl[1,2,4]triazolo[4,3-*a*]quinoxalin-4-yl)methanone derivatives and evaluated them for MAO-A and MAO-B inhibitory activities. They showed more activity towards MAO-A than the standard inhibitor clorgyline. The molecular modeling studies revealed that the proposed compounds showed hydrophobic interactions with Phe208 and hydrogen bonds to Ser209, Pro72, Tyr69, Tyr444, Glu74, Glu216. Compound **105** (For MAO-A $IC_{50} = 2.8 \pm 0.13$ nM) (Fig. 15) was reported as the most active analogue and found to be selective against MAO-A isoform with SI of 3×10^6. Shi *et al.*[138] evaluated *N*-(2-morpholinoethyl) nicotinamide and *N*-(2-morpholinopropyl)nicotinamide derivatives against MAO-A and MAO-B isoforms. Most of the synthesized compounds were found to be potent and MAO-A selective. The compound 5-chloro-6-hydroxy-*N*-(2-morpholinoethyl)nicotinamide (**106**) (Fig. 15) was the most potent for MAO-A isoform with an IC_{50} value of 0.04 μM.

The molecular docking studies of **106** showed that pyridine ring inside the MAO-A binding site was interacting with the 'aromatic cage' formed by Tyr197, Tyr407, Tyr444 and the FAD aromatic ring. The pyridine ring also showed π–π stacking interactions with Tyr407. The morpholine ring of **106** was implanted in a large lipophilic pocket formed by Ile180, Phe208, Asn181, Gln215 and Ile335. It was concluded that the better binding interactions of **106** with MAO-A isoform might be responsible for the higher MAO-A inhibitory potency of the compound. Valente *et al.*[139] synthesized a series of 3-(1*H*-pyrrol-3-yl)-2-oxazolidinone derivatives as reversible, potent and selective MAO-A inhibitors. The MAO-A inhibitory activity depended on the substituent at the pyrrole N1 position and replacement of methyl- and allyl- substituent with an ethyl group increased the activity from micromolar to nanomolar level. One of the potent compounds (**107**) (Fig. 15) obtained in the series displayed 2×10^5 times more selectivity towards MAO-A isoform and the compounds were proposed as promising antidepressant agents. Pettersson *et al.*[140] synthesized *para*-substituted 4-phenylpiperidines/piperazines (**108–110**) (Fig. 15) and evaluated their affinities to

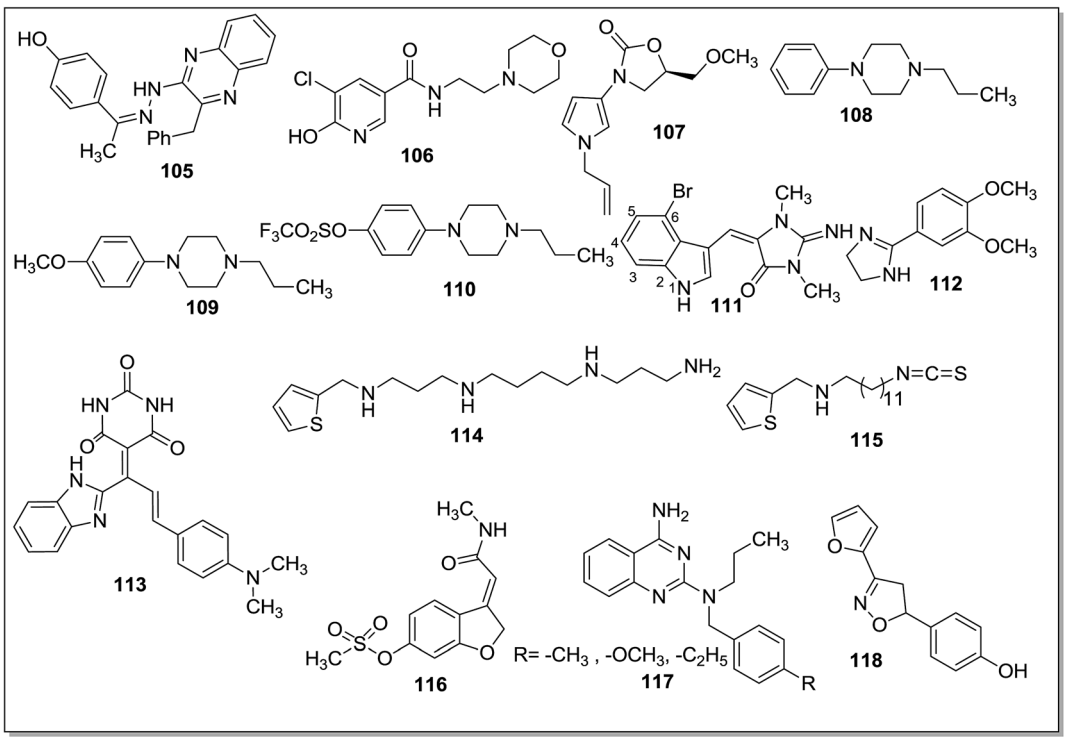
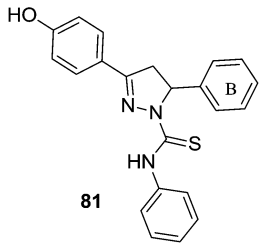
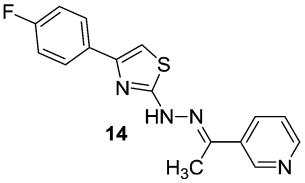
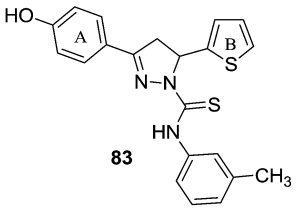
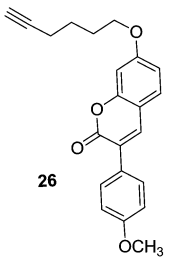
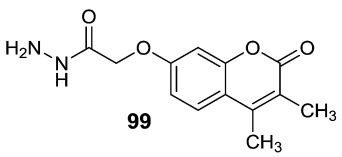
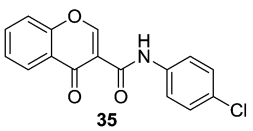
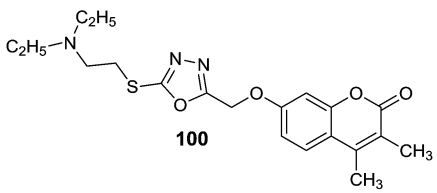
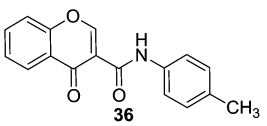
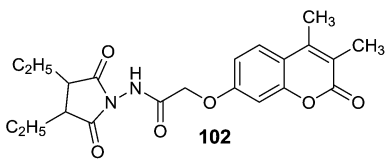
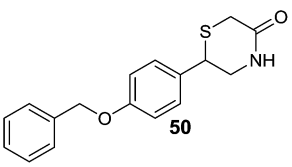
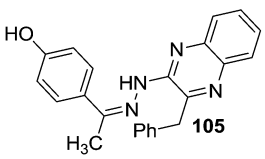
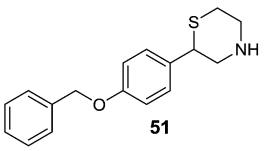
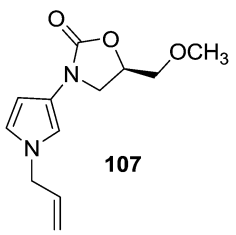
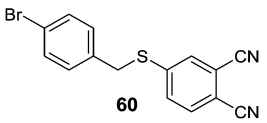
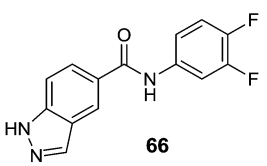


Fig. 15 Different heterocyclic compounds acting as MAO-A selective inhibitors.

Table 1 Compounds with a high selectivity index for the MAO-A and MAO-B isoform

MAO-A selective compounds		MAO-B selective compounds	
Chemical structure and compound number	Selectivity index	Chemical structure and compound number	Selectivity index
 **81**	>10 000 folds $IC_{50} = 32.1 \pm 3.0$ μM	 **14**	>39 000 folds $IC_{50} = 2.5 \pm 0.2$ nM
 **83**	>10 000 folds $IC_{50} = 150$ nM	 **26**	3400 folds $IC_{50} = 3 \pm 0.1$ nM
 **99**	9.66×10^4 folds $K_i = 5$ pM	 **35**	>3400 folds $IC_{50} = 2.9$ nM
 **100**	9.58×10^4 folds $K_i = 5.2$ pM	 **36**	>1200 folds $IC_{50} = 8$ nM
 **102**	10^5 folds $K_i = 6.3$ pM	 **50**	>2000 folds $K_i = 48 \pm 3$ nM
 **105**	3×10^6 folds $IC_{50} = 2.8 \pm 0.13$ nM	 **51**	>2000 folds $K_i = 38 \pm 3$ nM
 **107**	2×10^5 folds $K_i = 1$ nM	 **60**	>8700 folds $IC_{50} = 25$ nM
		 **66**	6×10^3 folds $IC_{50} = 1.6$ nM

recombinant rat cerebral cortex MAO-A and MAO-B. The *para* substituent on 4-phenylpiperidines/piperazines with low dipole moment increased the affinity towards MAO-A isoform while with a high dipole moment displayed no or poor affinity for the MAO-A isoform. Similarly polarity and bulk of the *para* substituents affected the MAO-B affinities and it was found that presence of a large and hydrophobic substituent increases MAO-B affinity. The compounds were examined in the freely moving rats and it was found that affinity of ligands for MAO-A was directly linked with the levels of DOPAC and 3-MT in the striatum. A series of fifty aplysinopsin analogs[141] was screened for MAO-A and MAO-B inhibitory activities. Aplysinopsins are reported to possess number of bioactivities including modulation of neurotransmission. In the reported series, three compounds exhibited significant MAO inhibition profile and (*E*)-5-[(6-bromo-1*H*-indol-3-yl)methylene]-2-imino-1,3-dimethylimidazolidin-4-one (**111**) (Fig. 15) was the most potent one with an IC_{50} value of 5.6 nM at MAO-A and with selectivity index of 80.24. SAR studies showed that *N*-methyl substituent especially at position *N*-2′ and bromine substituent at C5 or C6 were essential for the MAO-A potency and selectivity. Villarinho *et al.*[142] examined the MAO inhibitory activity and antidepressant potential of 2-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-imidazole (2-DMPI) (**112**) (Fig. 15) in the mice. 2-DMPI exhibited inhibitory activity against both the MAO isoforms but was found more selective towards MAO-A (30 times). This reversible MAO-A inhibitor showed its antidepressant-like activity by decreasing 5-HT and DA turnover without affecting the motor performance, even at high doses.

Mathew *et al.*[143] synthesized some (1*H*)benzimidazoles bearing pyrimidine-triones and screened them for selective MAO-A inhibitory activities. Molecular docking studies suggested that the lipophilic group on ring C could experience an extra hydrophobic binding region at the active site of the enzyme and could be contributing towards the CNS depressant activity. Amongst the various synthesized derivatives, compound **113** (Fig. 15) showed good antidepressant activity when compared to the standard clomipramine. The computational values obtained after the docking calculation were closely related to the experimental values. Bonaiuto *et al.*[144] reported on polyamine derivatives related to N^1,N^{12}-dibenzyldodecane-1,12-diamine (Bis-Bza-Diado) and N^1-benzylspermine (BD6) scaffolds. In the series, compound **114** (Fig. 15) was reported as a reversible mixed inhibitor with selectivity for the MAO-B ($K_{IE} = 23$ μM) isoform. Compound **115** (Fig. 15), containing 12-methylene carbon chain with an isothiocyanate (ITC) group was found as the most potent in the series acting as competitive inhibitor of MAO-B and as irreversible inhibitor of MAO-A. The amino group of Lys305 was interacting covalently with ITC group of the inhibitor resulting in irreversible inhibition of MAO-A isoform. Pisani *et al.*[145] synthesized a series of 6′-substituted-(*E*)-2-(benzofuran-3(2*H*)-ylidene)-*N*-alkylacetamides and the 6′-sulfonyloxy derivatives (**116**) (Fig. 15) showed affinities towards MAO-A, whereas 6′-benzyloxy derivatives showed potency towards MAO-B. Structure–activity relationship studies revealed the importance of rigidity in planar conformation of exocyclic double bond and indicated its role in binding with the receptor. The ligand with an exocyclic double bond in *E*-configuration exhibited more effective binding as compared to the more flexible and less active 2-(1-benzofuran-3-yl)-*N*-methylacetamide isomers and 4-*N*-methylcarboxamidomethylcoumarin analogous. The electronic and steric environment of the compound played a decisive role and influenced the activity. It was proposed that 6′-sulfonyloxy derivatives might be further developed as drug candidates for the treatment of depression, PD or other neurodegenerative diseases. Srivastav *et al.*[146] designed and synthesized 6,7-dimethoxy-N^2-(substituted benzyl)-N^2-propylquinazoline-2,4-diamine derivatives (**117**) (Fig. 15) and screened these for MAO inhibitory activities. They showed excellent antidepressant activity when compared with the imipramine (standard drug). A substitution on the phenyl ring linked with a tertiary amine group attached to the 2nd position of the quinazoline ring was essential for the MAO inhibitory activity. The presence of electron withdrawing groups like –Cl, –F and $–NO_2$ on the phenyl ring at *ortho*, *meta* or *para* position of **117** decreased the activity whereas the presence of a hydroxyl group (OH) at *ortho* position improved its antidepressant activity while hydroxyl substitution at *meta* or *para* position decreases the potency. Similarly, it was concluded that the presence of electron releasing groups like $–CH_3$, $–OCH_3$, $–C_2H_5$ and $–OC_2H_5$ at *para* position improved the antidepressant activity of the inhibitors. Kumar *et al.*[147] synthesized a series of 3-(furan-2-yl)-5-(substituted phenyl)-4,5-dihydro-1,2-oxazole derivatives and assessed their antidepressant and antianxiety activity by using force swimming test (FST) and elevated plus maze method respectively. The compounds displayed significant activity when compared with the imipramine and diazepam as standard drugs. 4-[3-(Furan-2-yl)-4,5-dihydro-1,2-oxazol-5-yl]phenol (**118**) (Fig. 15) was the most potent antidepressant agent acting through MAO inhibition. The molecular docking studies confirmed that the lead compound showed greater binding affinity with the enzyme and formed hydrogen bonding and hydrophobic interactions with the active residues.

Thus, a large number of structurally different compounds can interact with the MAO-A and MAO-B isoforms with varying degree of selectivity and potency. It is difficult to generalize a chemical scaffold for its preference for MAO-A or MAO-B isoform; however some of the compounds reported in this review article with very high selectivity index are summarized below. The compounds number **81**, **83**, **99** to **102**, **105** and **107** displayed very high selectivity for the MAO-A isoform while compounds number **14**, **26**, **35**, **36**, **50**, **51**, **60** and **66** exhibited high selectivity for the MAO-B isoform (Table 1).

6. Conclusion and future prospective

The MAO enzyme has been recognized as an important drug target for the treatment of various neurogenerative disorders. The first generation irreversible MAO inhibitors were predominantly used for the treatment of depression but now most of these were withdrawn from the clinical practice due to severe side effects and introduction of other classes of therapeutic agents. Fatal drug–drug interactions and dietary restrictions

were the main reasons cited for not prescribing first generation MAO inhibitors. The new generation of MAO inhibitors were developed which were reversible in nature and selective for either of the two isoforms making these comparatively safer as compared to irreversible inhibitors. Recently developed transdermal drug delivery systems are devoid of cheese reaction as these avoid drug–MAO-A interactions in the intestinal mucosa and hence eliminate the need of dietary tyramine restrictions. In addition, selegiline transdermal delivery system was found to be safe along with many clinically prescribed decongestants. The discovery of crystal structure of MAO-A and MAO-B isoforms contributed enormously to understand drug–receptor interactions at the molecular level. Target based rational designing of isoform selective MAO inhibitors has expedited the discovery of novel leads. A variety of structurally different scaffolds have been synthesized and investigated for their role in MAO inhibitory activities and for establishing the etiology of the neurological diseases. The structure based drug design and synthesis of novel MAO inhibitors may help in better understanding of drug–receptor interactions and in the development of effective therapeutic agents for the treatment of various neurogenic disorders. The neuroprotective potential of MAO inhibitors has also attracted interest of the researchers and neuro-scientists. However, the underlying mechanism of MAO inhibitors as neurorescue agents is not clear yet. Due to the complexity of various neurogenic disorders, now the attention is being shifted towards the development of single drug as multi-target agent. These multi-target drugs are expected to simultaneously bind to different targets and hence help in the management of complex neurological disorders. The synthetic and computational chemistry are the tools to design ligands with features for simultaneous inhibition of MAO enzyme and other receptors/enzymes such as cholinesterases. A lot of research work still needs to be done in order to establish the role of MAO inhibitors in the etiology of other disorders like ageing, cerebral ischaemia, neuroprotection/neurorescue and substance-abuse risk.

Abbreviations

MAO	Monoamine oxidase
FAD	Flavin adenine nucleotide
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
AD	Alzheimer's disease
PC	Pheochromocytoma
PD	Parkinson's disease
Glu	Glutamine
Ile	Isoleucine
Phe	Phenylalanine
TAMH	TGF-α transfected mouse hepatocyte
Tyr	Tyrosine
TGF-α	Transforming grown factor alpha
SAR	Structure activity relationship
SI	Selectivity index
μM	Micromolar
nM	Nanomolar
EPR	Electron paramagnetic resonance
K_{IE}	Enzyme–inhibitor dissociation constant/inhibition constant
pgp	P-glycoprotein

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