Monoamine Oxidases: to Inhibit or Not to Inhibit

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Abstract: Monoamine oxidase (MAO) inhibitors were developed as antidepressants but many drugs, including the novel oxazolidinone antibacterial agents, share similar molecular properties and have MAO inhibitory activity. Factors important for binding antidepressants and modifications to decrease binding of oxazolidinones to avoid undesirable vascular effects are discussed.

Although amine oxidation by tissue extracts was first described in 1928, it was the discovery that inhibition of monoamine oxidase (MAO) resulted in mood elevation that led to an appreciation of the role of MAO in the brain. Ironically, considering the current need to remove MAO inhibitory activity from anti-bacterial agents, the first inhibitor to be used as an antidepressant was discovered during screening of candidates for treating tuberculosis. The early irreversible inhibitors of MAO used as antidepressants caused undesirable vascular effects when amines were ingested, demonstrating that MAO in peripheral tissues had a protective role. A huge number of studies followed to seek the best compounds for the antidepressant market. The wealth of literature on substrate, inhibitor, and stereochemical specificities has been summarised in reviews [1-5].

Sequences for the two forms of MAO appeared in 1988 [6], completing the identification of MAO A and MAO B as separate enzymes. Monoamine oxidases are soluble only in the presence of detergents and aggregate easily, so crystallisation has been a problem until recently (see footnote). At present only a homology model of MAO A [7] has been proposed and in it the active site remains unresolved. Likewise, the mechanism of the enzyme is not fully understood despite extensive chemical and kinetic investigation [reviewed in 8].

The active sites are at once exquisitely specific and amazingly promiscuous. Clorgyline (an irreversible inhibitor preferential for MAO A) and deprenyl (an irreversible inhibitor preferential for MAO B) differentiate between the active sites giving IC50 values more than two orders of magnitude different [1]. Adding a methyl group to β-phenylethylamine turns that excellent substrate for MAO B into an inhibitor (D-amphetamine) with a preference for MAO A. Yet almost any hydrophobic amine, including many drugs, will bind to some extent [3]. A search using a pharmacophore model based on chemical features elucidated by QSAR studies generated about 3000 hits for each hypothesis [9], indicating the simplicity of the features required for generic binding to the active site. Another model was constructed from superimposed inhibitor structures to facilitate database screening and prediction of potential MAO inhibitory activity of products of combinatorial chemistry. A screen using this model identified not only known MAO inhibitors (MAOI) but also similar rigid cyclic compounds such as tipindole, a 5HT receptor agonist, and acetryptine, an anti-hypertensive drug [10].

This review will summarise recent developments in understanding the affinity of inhibitors for the active sites of MAO A. How can affinity be increased for better antidepressant activity in brain or be decreased for similar molecules where MAO inhibition is an unwanted side effect?

1. EFFECTS OF MAO INHIBITION

Mood improves with higher levels of dopamine, noradrenaline and serotonin in different brain areas. Modulation of the intersynaptic levels of serotonin can be achieved by selective serotonin reuptake inhibitors but a more general increase of amine levels is induced by MAOI. The dysfunction of the complex modulation of cortical function by catecholamines plays a role in not only depression (where the serotonin system is particularly important), but also in social phobias, obsessive-compulsive disorders, and schizophrenia. Clinical use of antidepressants has recently been reviewed [11].

Systemically, MAO inhibition also increases the levels of biogenic amines in the blood. For ingested amines, intestinal MAO deaminates sympathomimetic amines before they are absorbed into the blood stream, preventing the hypertension these amines can cause [12,13]. When the first irreversible MAOI that inhibited both MAO A and MAO B were used as antidepressants, some patients had hypertensive crises when tyramine-rich foods were ingested. Since the inhibitor was irreversibly bound to MAO, the problem disappeared only when new enzyme was synthesised. The

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half-life of MAO varies from 3-30 days depending on the tissue [14]. This response to ingestion of amines is termed the "cheese effect " because the high tyramine content of cheese is a major dietary inducer of the effect.

Tyramine is an indirectly acting sympathomimetic amine. It exerts its pharmacological actions after noradrenaline is released from storage sites in sympathetic nerve endings [15]. The released noradrenaline and dopamine cause constriction of the vascular epithelium and increased systolic blood pressure. The transmitter molecules are taken back into the presynaptic terminals via a specific carrier for return to the storage vesicles or are metabolised. When exogenous amines are present, they compete for the reuptake systems so that the hypertensive effect is prolonged. Reuptake captures exogenous amines such as tyramine as well as the catecholamine so that the storage vesicles become depleted of transmitter and orthostatic hypotension can occur when the vesicles are next discharged. To determine the risk of hypertensive side-effects, tyramine challenges have become part of the clinical development of compounds that can inhibit MAO [16].

The intestinal wall normally disposes of >80% of an oral tyramine load [12]. In rat intestine, MAO A accounts for 70 % of the total MAO activity. MAO A inhibitors decreased metabolism to 27% whereas MAO B inhibitors left the disposal rate the same as in controls (85%). Thus, MAO A in the intestine is the key to minimising tyramine absorption from an oral load at least in rats. In human intestine, MAO A accounts for 55% of the total MAO activity [17]. In the circulation, platelets which contain mainly MAO B (95%) may be involved in tyramine metabolism. Other oxidases include the copper-containing semicarbazide-sensitive amine oxidases (particularly in arterial walls) and plasma amine oxidase both of which oxidise primary amines. Thus, the cheese effect is observed when the normal mechanisms for disposal of exogenous amines both in intestine and blood are overloaded so that non-functional amines displace the neurotransmitters responsible for blood pressure modulation. It is this that makes systemic MAO inhibition an undesirable side effect of drugs with other targets.

The potential of MAOI drugs to put users at risk for hypertensive crisis can be assessed as the amount of tyramine required to induce a 30 mm mercury rise in the systolic blood pressure (see examples of Tyr30 in Table **(1)**). The first antidepressant, iproniazid (a hydrazine), inhibited both MAO A and MAO B covalently throughout the body so that tyramine intake had to be strictly limited. Selective covalent inhibitors followed in the form of the propargylic amines (acetylenic inhibitors) such as clorgyline for MAO A and deprenyl for MAO B, leaving the remaining uninhibited form to provide some protection from dietary intake. Ultimately, reversible, selective inhibitors appear to be ideal, allowing tyramine to be metabolised in the gut when it appears. To improve the efficacy of competitive inhibition *in vivo*, tight binding inhibitors were developed. As seen in Table (**1**), these MAOI have low Ki values but the tyramine potentiation is mild because they are all reversible inhibitors. Thus, it is possible to use them clinically without dietary restrictions.

2. IMPROVED BINDING: GENERAL FEATURES OF ANTIDEPRESSANT AFFINITY

Reversible inhibitors selective for MAO A (RIMA) such as moclobemide, toloxatone and pirlindole, epitomise the qualities sought for antidepressant activity without the cheese effect [reviewed in 10,11,18,19]. They are competitive inhibitors of MAO and are selective for MAO A. Their affinity for the enzyme is high and their dissociation rate is slow, so that they remain longer on the enzyme. At the molecular level, these inhibitors, like all ligands for MAO, follow a general pattern of somewhat hydrophobic heterocycles. Given the wide diversity, what can we do to predict what will make a good MAOI? Based on QSAR studies using mainly rigid or semi-rigid substrates, several models have been proposed to describe key features of the binding sites (reviewed in [5]).

The models all agree that, within a series, there is a trend with increasing lipophilicity favouring improved catalytic efficacy, particularly for MAO B. Each form of the enzyme has well defined steric limitations with the MAO A binding site being slightly larger and a different shape from MAO B [reviewed in 5]. Recently, a series of pirlindole derivatives, effective reversible antidepressants used in Russia [19], were used to define the size of the binding site for MAO A . Molecular models of the compounds with optimised

Table 1. MAO Inhibition Potency But Low Cheese Effect in Some Reversible, Selective MAOI

Compound	Ki (uM) in membrane preparations		Potency	Tyramine potentiation	Reference
	MAO A	MAO B	B/A		
Befloxatone	0.002	4	2000	Tyr_{30} = 290mg (>7 meals) No restrictions	[45]
Toloxatone	1.8	44	24	Effect observed at 400mg tyramine	[45]
Moclobemide	6	>1000	>170	Tyr_{30} = 240-300mg (>6 meals) No restrictions	[46]
Pirlindole	0.25	52	208	Mild - similar to moclobemide	[19]
Linezolid	56	170	3	Mild - no restrictions	[44, 47]

geometry were prepared and minimal box sizes derived for each inhibitor. Within the box 13x7x4.4 angstroms, no trend in IC50 with size was observed [20]. Table (**2**) illustrates the effect of the size of substituents rigidly attached to the pirlindole nucleus. When bulky groups were present at both R and X making the molecule exceed the box dimensions, the Ki value rose >100-fold. However, interactions between MAO A and the group at R are important for affinity as seen in the 5-fold advantage of the cyclohexyl over the methyl derivative. Similarly, in a study of benzylamine analogs, Van der Waals size was the most important factor particularly for MAO A [21].

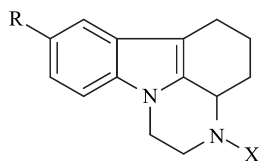
Despite the limitation in size for rigid compounds, a wide range of molecular variations can be accommodated at the active site, providing the molecule is flexible [20]. The structures of isatin and pirlindole inhibitors were superimposed with some restriction for the overlay of side groups likely to interact with functional groups on the protein to produce the shape available for molecules binding to the active site [22]. The cavity thus prepared was used to screen the Comprehensive Medicinal Chemistry database revealing fits of known inhibitors and predicting that other drugs would also have MAO A inhibitory activity [22]. A key feature of the mould is a relatively flat surface on one side. Alignment with the flavin cofactor would permit optimal stacking of the aromatic regions of the molecule with the planar flavin rings [Ramsay *et al.*, in preparation].

MAO A catalytic efficacy is also influenced by electrostatic factors [21] and electron-rich aromatic amines such as the catecholamines are good substrates. For inhibitors, the difference between 4'-pentyl-4-phenylpyridine (Ki = 35 μM) and 1-methyl-(4'-pentyl-4-phenyl)pyridinium (Ki = 0.13 μM) demonstrated that a positive charge on the nitrogen favoured binding to MAO A [23]. There was no difference between the two inhibitors with MAO B (38 and 32 μM, respectively). The efficacy of this charged inhibitor series also shows that there is no barrier to the access of polar and charged molecules to the active site. Indeed, a polar binding pocket in MAO A was revealed by studies on coumarin derivatives [24] and two polar regions in MAO B were indicated by theoretical studies on diazo heterocycles [25].

Stereochemistry is important [reviewed in 2]. MAO (both A and B) abstracts the pro-R-hydrogen from the α-carbon of a variety of substrates in contrast to plasma amine oxidase, diamine oxidase, and semicarbazide-sensitive amine oxidase which either abstract the pro-S hydrogen or are non-selective. Thus, for MAO, substitution of the pro-S hydrogen generally means better inhibition, except in the α-methylbenzylamine series. At the β-carbon it is the R-

Table 2. Inhibition of MAO A by Pirlindole Analogs

K_i values were determined as in [27] using purified MAO A with kynuramine as the substrate. Details of more substituents at R including the molecular dimensions and IC_{50} values for inhibition of both MAO A and MAO B can be found in [20]



R	X	Ki (μM)
CH_3	H	0.26
	CH_3	1.6
	CHO	7
	$COCH_3$	7
	CO-piperidine	9
	CO-admantyl	50
C_6H_{11}	H	0.05
	CHO_3	1.3
	CO-piperidine	23
	CO-admantyl	71
Admantyl	H	1.17
NH_2	H	4
OH	H	11
$(CH_3)_2CH\text{-}CH_2$ -O	H	0.17
NO_2	H	42

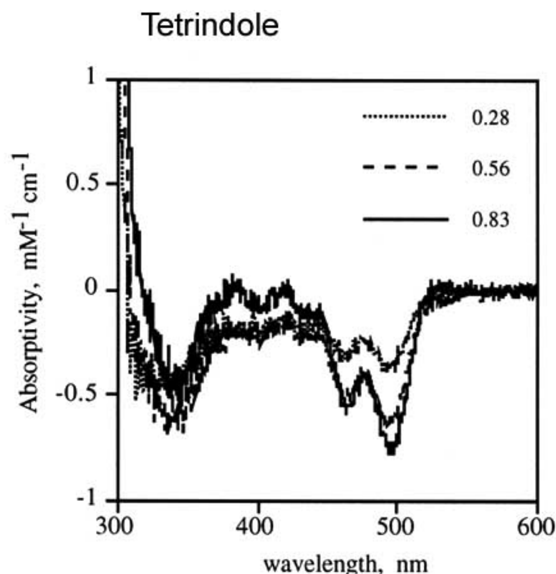


Fig. (1). Spectral changes induced by tetrindole binding to MAO A.

Purified human liver MAO A (6 μM) was titrated with tetrindole until no further change was observed. The Ki for tetrindole inhibition of MAO A is 0.05 μM, so the change in absorbance was linear with inhibitor added until saturation at approximately 1 mol tetrindole per mol MAO A. The decrease in absorbance observed at 500 nm is seen also for harmine and toloxatone binding.

enantiomer (as in noradrenaline) that is preferred. This β-carbon preference is carried through into the inhibitors, with the R-enantiomer of toloxatone (an oxazolidinone antidepressant) more than 10 fold more effective than the S form as an inhibitor of MAO A. MAO B is much less selective.

Catalysis in MAO depends on the transfer of electrons to FAD, and mechanism-based inhibitors, such as the irreversible antidepressants, modify the flavin. Thus, close proximity of the flavin and ligands in the active site would be expected. In solution, the interaction of flavin and β-carbolines indicated energetically favourable stacking of the planar molecules and stabilisation of the complex by charge transfer. Recent studies on immobilised model systems establish the basis for the thermodynamic advantages of stacking and for small electronic or spacial shifts causing changes in affinity [26]. For MAO A, the interaction of reversible inhibitors with the flavin was first demonstrated through the perturbation of the flavin spectrum in the presence of heterocyclic β-carbolines [27]. Fig. (**1**) shows the changes observed when MAO A is titrated with the pirlindole analog, tetrindole.

The electronic parameters of some planar electron-rich inhibitors have been analysed to probe their association with the isoalloxazine ring of the FAD co-factor [28,29]. The N-aryl-2-oxazolidinone antidepressant, toloxatone, and the β-carboline, harmine, both had π-orbitals delocalised over the aryl ring and heteroatoms in a way that complemented the flavin nucleus. The superimposition of the inhibitor, toloxatone, and flavin proposed from this work is shown in Fig. (**2**) left. In similar studies on pirlindole analogs, a good correlation between HOMO and IC50 was found for compounds without steric hindrance (i.e., that fit in the box described above). The HOMO of all the pirlindoles studied were π-orbitals which matched well with the delocalised electron density of the LUMO of the isoalloxazine ring. The molecular electrostatic potential maps also showed complementary matching of the two ring systems with attractive potential spread across the pyrazinocarbazole ring and repulsive potential across most of the isoalloxazine ring flanked by two large attractive zones over the carbonyls. The complementarity led to the proposal of a model for the stacking (Fig. (**2**) right allowing charge transfer bonding. Such stacking has been seen between inhibitors and the FAD cofactor in the structure of sarcosine oxidase [30]. Whether the calculated optimal stacking and the orientation of the inhibitor with the isoalloxazine ring shown in Fig. (**2**) depicts the actual relationship in the active site of MAO awaits confirmation.

None of the above considerations predict the time dependent factor that characterises the best reversible inhibitors (pirlindole, befloxatone, moclobemide). The time dependent increase in affinity does not alter the inhibitor-flavin interaction as observed in the spectral changes [27] so must be due to formation of interactions with the protein. The loss of entropy for inhibitor binding to MAO will be the same as for stacking with free flavin but in the active site of the protein there will be more enthalpy gain from hydrogen bonding and other interactions. Whether the time dependent increase in Ki is due to a slow conformational change in the protein or the formation of an metastable adduct with the enzyme is not known.

3. DECREASED BINDING: AVOIDING VASCULAR COMPLICATIONS IN OXAZOLIDINONE ANTIBACTERIAL COMPOUNDS

The oxazolidinone class of drugs has been known as inhibitors of MAO A and B for more than twenty years [31]. These compounds were of interest as potential antidepressants because they could be selective inhibitors of either the A or B isoforms and were usually reversible, in that they did not form covalently-bound enzyme-inhibitor complexes. These properties were in marked contrast to early anti-depressant drugs of the clorgyline type [5]. The first compound of the oxazolidinone class to be used clinically for depression was toloxatone [28], which is a reversible MAO A inhibitor with a Ki of 1.5 μM [29]. Structure-activity relationships for MAO A and B in the oxazolidinone series were used to develop extremely potent compounds [32]. The most recent inhibitor of this class is befloxatone which has a Ki of 2 nM and is in late stage clinical development [33].

After the antibacterial properties of this class of compounds were discovered by Dupont workers [34], it became apparent that the chiral, hydroxy- or methoxy-methyl C-5 side chain that favoured antibacterial activity in the early series, was also the favoured side chain for MAO A inhibition [32]. Further optimisation of the antibacterial

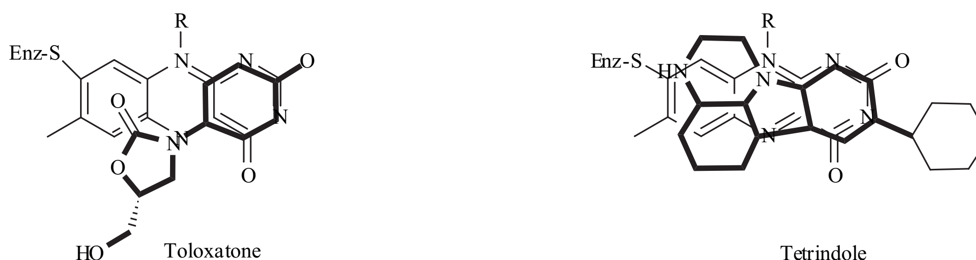


Fig. (2). Proposed model of flavin - inhibitor stacking in the active site of MAO A.

Overlay of the inhibitors, toloxatone and tetrindole with riboflavin predicted by molecular orbital calculations. The overlay of toloxatone is based on [29] and the overlay of tetrindole was prepared by R.M.G. Hynson based on the work of F. Ooms and J. Wouters. The position of the aromatic ring over the electron-poor part of the flavin is favoured in all the compounds studied.

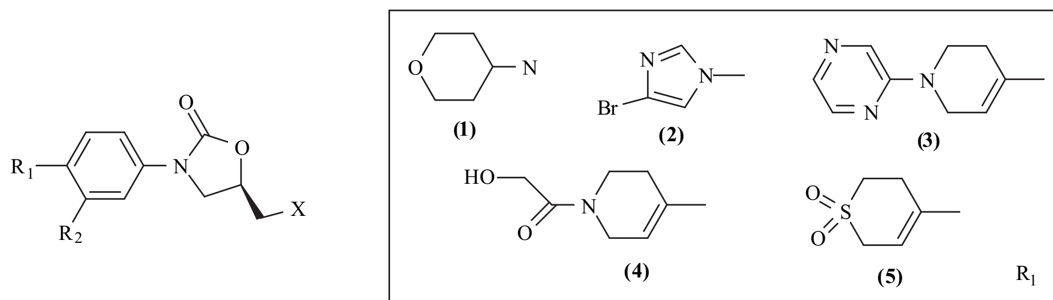
potency led to the acetamidomethyl side chain in the first clinical antibacterial candidates DuP105 and DuP721 [35]. Compounds of this type had reduced MAO-A activity but it was clear that potential *in vivo* metabolic cleavage of the acetamidomethyl function could generate the free aminomethyl group. Since the 5-aminomethyl compounds were known to be potent MAO-B isoform inhibitors [36] this was also of some concern.

Clinical development of these two particular agents was suspended due to non MAO-related toxicities [37]. However, as other research groups began to examine the antibacterial potential of the series, the relative SAR of anti-Gram positive bacterial and MAO activities was closely monitored. Features of the series which have altered or improved antibacterial potency have included changes to the aryl substituents, alternatives to the oxazolidinone ring and to the C-5 side chain. Reviews of these developments can be found elsewhere [38], but it is relevant to this account to summarise how some changes have affected the MAOI properties of the series. Most of these MAOI properties remain unpublished so only a partial picture emerges. However it is possible to combine this information together with specific binding studies of selected oxazolidinones to the MAO binding site and the FAD co-factor to draw some general conclusions about factors which may decrease binding.

The inactivation of the FAD co-factor of MAO by C-5 aminomethyl oxazolidinones has been described by Silverman [36] and Strolin-Benedetti [39]. Aminomethyl and hydroxymethyl side chain analogues can act as both substrates and inhibitors of the enzyme. Hydroxymethyl side chain inhibitors such as toloxatone have been examined by an analysis of their X-ray crystal structures, conformational and electronic properties [28]. The conclusions from this

Table 3. Comparison of MAO A Inhibition and Antibacterial Activity of Selected Oxazolidinones

K_i values were determined as in [27] using purified MAO A with kynuramine as the substrate. The antibacterial activity versus *S.pyogenes* recorded in this table was on a strain from the AstraZeneca culture collection. Minimum inhibitory concentrations (MIC) were determined by an agar dilution method using doubling dilutions over a concentration range of 128 – 0.008 µg/ml and incubation at 37° for 24h. R_1 substituents are shown in the box and numbered in column R_1



R_1	R_2	X	MAO-A (Ki) (µM)	S.pyogenes MIC (µg/ml)
H	H	NHCOCH3	117	128
N-morpholino (1)	F	OH	1.2	4
as above	F	NH2	166	256
as above	F	NHCOCH3	20	1
4-bromo-N-imidazoyl (2)	F	OH	0.34	2
as above	F	NH2	23	64
as above	F	NHCOCH3	5	0.13
N'-(2-pyrazino)-N-piperazinyl (3)	F	OH	0.16	0.5
as above	F	NH2	5.7	64
as above	F	NHCOCH3	1.6	0.13
N-(hydroxyzcetyl)-1,2,5,6-tetra-hydropyridyl (4)	F/F	OH	0.07	1
as above	F/F	NH2	0.75	32
as above	F/F	NHCOCH3	0.87	0.5
1,1 -dioxo- 1,2,5,6 tetrahydro-thiopyranyl (5)	F/F	OH	1.8	0.5
as above	F/F	NHCOCH3	2.4	0.06

latter study were that toloxatone adopts a nearly planar conformation in the crystal state. However molecular orbital calculations also showed that the planar conformation is favoured in the gas phase and is an intrinsic property of the molecule. These results were confirmed by study of three ring-bridged structures. Further studies by the same group [29] favoured the hypothesis that all members (of this class at least) exercise their inhibitory activity by close interactions with the FAD co-factor (Fig. (**2**); see also **Section 2** above).

It is of particular interest that stereospecific substitution by a methyl group on the α−carbon of the methylene side chain of methoxymethyl analogues of toloxatone produces a thousand-fold difference in MAO A potency between threo and erythro isomers [28]. This result was rationalised by the active conformation hypothesis, in other words, recognition by MAO is very sensitive to the absolute configuration of the molecules. Similar potency differences had been observed previously in the α−methyl derivatives of cimoxotone [40]. In the hydroxymethyl and aminomethyl side chain oxazolidinone series, R and S forms show both differences in reversible and irreversible binding behaviour and selectivity between MAO A and B isoforms [41].

Changes to the nature of the 4-aryl substituent have provided further insight in to the possible nature of the interaction of these compounds with MAO. It may be significant that the electrostatic interaction model described previously [29] does not predict the apparently important binding interactions for MAO B that were originally identified for extended lipophilic substituents on the aryl ring [32]. In contrast, a recent study on coumarin derivatives not only confirmed the influence of lipophilic substituents on MAO B selectivity but also identified a hydrophilic, polar binding pocket in the active site of MAO A [21]. Comparison of a selection of aryl substituents in the hydroxymethyl, aminomethyl and acetamidomethyl side chain series, Table (**3**), shows that substantial changes in the potential for interaction with MAO A can occur. The overall shape and polarity of the substituent, the nature of the linking atom to the aryl ring, the size, shape and nature of a ring (where these are present) and the overall lipophilic nature of these substituents all influence binding. It is hard to draw any general conclusions concerning other physical parameters such as log P. Perhaps the best conclusion is that substituents which extend the overall aryl and flattened-linear nature of the series give increased potency, and that more conformationally bulky substituents are disfavoured for binding.

Replacements for the oxazolidinone ring in this series which have retained good antibacterial potency have not been common. Earlier studies demonstrated that furanone and dihydrofuranone rings were successful but these substitutions retained potent MAOI activity as well [32]. More recent studies have claimed that isoxazoline bioisosteres which also have good antibacterial activity, have much reduced MAO A binding compared with their oxazolidinone analogues with comparable aryl substituents [42]. Isoxazolidinone analogues have also been claimed to have antibacterial activity [43] but their MAO inhibitory potency is not yet clear. It should be noted that Linezolid, which was approved for use in man in 2000, showed no indication of adverse events due to MAO A inhibition in clinical trials [44].

4. CONCLUSION

Designing changes for either better or poorer MAO inhibition is not a simple task. Combinatorial chemistry and large scale screening can be used to assess molecules that fulfil the minimum requirements of lipophilicity, planarity, and size. However, even when excellent inhibition of MAO A alone is found in a reversible inhibitor such as befloxatone, undesirable vascular effects are not necessarily associated. Thus, for drug safety, drugs with MAO inhibitory activity will have to be screened in a tyramine dose-response test.

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ABBREVIATIONS

MAO = Monoamine oxidase

MAOI = MAO inhibitors

QSAR = Quantitative structure activity relationships

RIMA = Reversible inhibitors of MAO A

HOMO = Highest occupied molecular orbital

LUMO = Lowest unoccupied molecular orbital

FOOTNOTE

The structure of MAO B with the inactivator pargyline covalently bound to the flavin has just appeared (Binda, C. , Newton-Vinson, P., Hubálek, F., Edmondson, D.E., and Mattevi, A. Nature Structural Biology, **2002**, *9*, 22-26, **http://structbio.nature.com**).

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