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Design, Synthesis, and Biological Activities of Pyrrolylethanoneamine Derivatives, a Novel Class of Monoamine Oxidases Inhibitors

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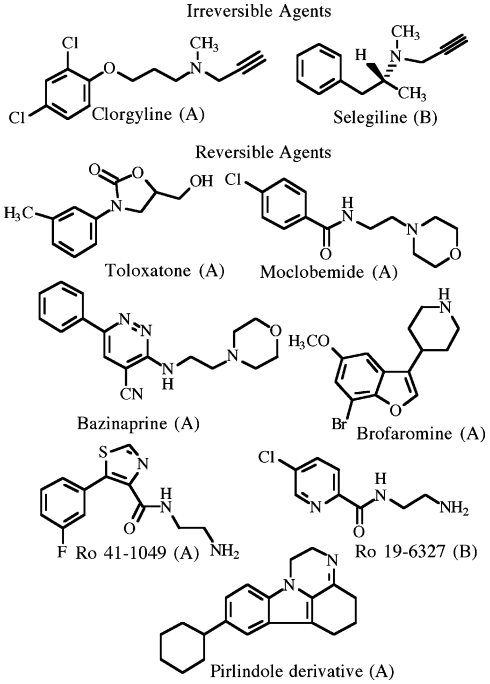
Abstract: Pyrrolylethanoneamines **1**−**12**, **18**−**23** and related amino alcohols **13**−**15**, **24**−**27** were synthesized and tested against monoamine oxidases A and B (MAO-A and MAO-B) enzymes. In general, aminoketones **1**−**12**, **18**−**23** were found to be potent and selective MAO-A inhibitors. In particular, **18** was more potent and selective against the MAO-A isoenzyme than reference drugs. Interestingly, amino alcohol **25** selectively inhibited MAO-B enzyme and could be a lead compound for designing more potent and selective MAO-B inhibitors.

Mitochondrial monoamine oxidases (MAOs, EC 1.4.3.4) are flavin-containing enzymes (FAD or FMN) that catalyze the oxidative deamination of neurotransmitters and exogenous arylalkylamines. In mammals, two different types of MAOs are present in most tissues, namely, MAO-A and MAO-B.[1] MAO-A preferentially deaminates aromatic monoamines such as the neurotransmitters serotonin (5-HT), noradrenaline (NA), and adrenaline (A), while MAO-B mainly oxidizes β-phenylethylamines (PEA) and benzylamines. Both isoforms act on dopamine (D) and tryptamine.[1] Selective MAO-A inhibitors are currently used for treating neurological disorders such as anxiety and depression,[2] while selective inhibitors of the B isoform (e.g., selegiline) are administered alone or together with L-DOPA for the treatment of Parkinson's syndrome[3] and Alzheimer's disease.[4] Chart 1 shows the structures of some MAO inhibitors (MAOIs) used in clinical practice or in clinical trials.[1,5]

More recent studies on MAOIs have been focused on reversible and selective agents. In fact, irreversible and/or nonselective inhibitors showed shortcomings including cumulative effects, loss of selectivity after chronic treatment, and interaction with tyramine-containing

Chart 1. Irreversible and Reversible MAO-A (A) and MAO-B (B) Selective Inhibitors Used in Clinical Practice or in Clinical Trials



foods (cheese effect).[6] The rational design of new agents targeted to MAOs could be based on the crystal structure of human MAO-B[7] and rat MAO-A[8] and aided with theoretical calculations.[9] The above studies have elucidated some factors responsible for selectivity against the A and B isoforms, such as the lipophilicity of the inhibitor that is important for achieving effective binding to MAO-B,[9] the presence of electron-rich aromatic moieties, typical of selective MAO-A inhibitors,[10] and the role played by some amino acid residues in the active sites, such as Tyr326 for MAO-B and Ile335 for MAO-A.[8]

The aim of the present study was the identification of novel potent, reversible, and selective MAO inhibitors that could serve as potential lead molecules for drug discovery. An examination of the chemical structures of new MAOIs of clinical interest or in clinical trials led us to identify some structural features that characterize these compounds: (i) a basic nitrogen atom sometimes incorporated in an alicyclic ring such as piperidine or morpholine (brofaromine,[11] moclobemide,[12] and bazinaprine[13]); (ii) an electron-rich aromatic moiety that plays a pivotal role in the interaction with the biological target, as shown in recent QSAR studies by Vallejos et al.[10] (brofaromine, Ro 41-1049,[14] and pirlindole derivatives[15]); (iii) a carbonyl or alcohol group (moclobemide, Ro 41-1049, Ro 19-6327,[14] and toloxatone[16]) (Chart 1). Therefore, we decided to test the activity against MAO-A and MAO-B enzymes of a series of phenylpyrrolylethanoneamines **1**−**10** (PEAs) previously reported by us, of which some showed antiphobic−anxiolitic activity.[17] In fact, **1**−**10** (Table 1, Chart 1) are characterized by (i) an amino group linked at the 2-position of the ethanone chain, (ii) a pyrrole ring as an electron-

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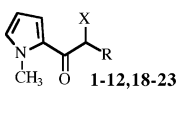
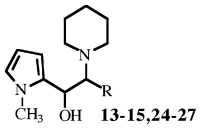
Table 1. Anti-MAO Activities of Pyrrolylethanonamines **1**−**12**, **18**−**23**, and Pyrrolylethanolamines **13**−**15**, **24**−**27**[a]



1-12,18-23



13-15,24-27

compd	R	X	stereochemistry	MAO-A K_i (μM)	MAO-B K_i (μM)	A-selectivity[b]
1	Ph	NH_2	racemic	0.095 ± 0.0005	42 ± 0.14	442
2	Ph	$N(CH_3)_2$	racemic	1.75 ± 0.045	875 ± 1	500
3	Ph	1-pyrrolidinyl	racemic	0.0075 ± 0.0015	600 ± 5	80000
4	Ph	1-piperidinyl	racemic	0.096 ± 0.005	500 ± 0.01	5208
5	Ph	4-methyl-1-piperazinyl	racemic	0.347 ± 0.006	>100 ± 0.02	>288
6	Ph	4-benzyl-1-piperazinyl	racemic	0.93 ± 0.001	10 ± 4	11
7	Ph	4-morpholinyl	racemic	0.35 ± 0.005	>100 ± 1	>286
8	Ph	4-thiomorpholinyl	racemic	0.1 ± 0.015	>100 ± 2	>1000
9	Ph	1-phthalimido	racemic	0.81 ± 0.002	>100 ± 2.1	>123
10	Ph	4-etoxyphenylamino	racemic	0.83 ± 0.01	>100 ± 3	>121
11	H	1-piperidinyl		0.007 ± 0.0009	15 ± 0.01	947
12	CH_3	1-piperidinyl	racemic	0.038 ± 0.001	36 ± 0.9	2143
13	Ph		racemic	31 ± 1.5	9.22 ± 0.15	0.29
14	Ph		racemic	1 ± 0.5	140 ± 1	140
15	H			0.51 ± 0.02	23.9 ± 1.1	47
18	Ph	1-pyrrolidinyl	(−)-(*R*)	0.0035 ± 0.0005	700 ± 1	200000
19	Ph	1-pyrrolidinyl	(+)-(*S*)	0.0095 ± 0.001	500 ± 4	52632
20	Ph	1-piperidinyl	(−)-(*R*)	0.01 ± 0.002	520 ± 4.3	5200
21	Ph	1-piperidinyl	(+)-(*S*)	0.1 ± 0.04	410 ± 2	4100
22	Ph	4-thiomorpholinyl	(−)-(*R*)	0.076 ± 0.002	400 ± 2.6	5263
23	Ph	4-thiomorpholinyl	(+)-(*S*)	0.082 ± 0.001	100 ± 0.9	1220
24	Ph		(−)-threo	55 ± 1	17.2 ± 1.5	0.31
25	Ph		(+)-threo	7 ± 0.1	1.24 ± 0.06	0.18
26	Ph		(−)-erythro	0.6 ± 0.03	46 ± 3	77
27	Ph		(+)-erythro	0.52 ± 0.06	>10 ± 2	>19
MCL[c]				11.5 ± 0.1	>100 ± 2	>8.7
TOL[d]				0.38 ± 0.023	15 ± 0.96	39.5
SEL[e]				38 ± 1	0.97 ± 0.01	0.025

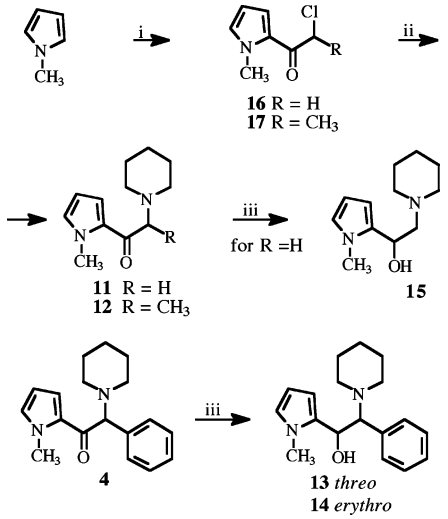
[a] Data represent mean values of at least three separate experiments. [b] Expressed as K_i(MAO-B)/K_i(MAO-A). [c] MCL: moclobemide. [d] TOL: toloxatone. [e] SEL: selegiline.

rich aromatic moiety, and (iii) a carbonyl group linked at the α-carbon of pyrrole ring. Moreover, as a preliminary study of the structure−activity relationships in this class of inhibitors, amines **11**−**15** related to **1**−**10** were designed, synthesized, and tested on both MAO isoforms.

The newly synthesized derivatives **11**−**15** were obtained as depicted in Scheme 1. 1-Methylpyrrole underwent a Friedel−Crafts reaction with 2-chloroacetyl chloride or 2-chloropropionyl chloride to give ketones **16**[18] or **17**,[19] respectively. These compounds were treated with piperidine in the presence of K_2CO_3 to afford amino derivatives **11** and **12**. Reaction of ketones **4** and **11** with lithium aluminum hydride in anhydrous ethyl ether gave the corresponding carbinols **13**−**15**. In particular, the reduction of **4** gave a mixture of threo (**13**) and erythro (**14**) isomers, with predominance of erythro couple **14**, according to Cram's rule.[20] Separation of diastereoisomers **13** and **14** was performed by preparative TLC on silica gel using a mixture of chloroform/methanol 20:1 as eluent.

Because of the well-known stereoselectivity of enantiomeric chiral MAOIs such as selegiline (SEL)[21] and oxazolidinones,[22] we decided to resolve a number of potent racemates (**3**, **4**, **8**) and aminoethanols **13**, **14** to determine the impact of chirality in biological efficacy within this novel class of MAOIs. Single enantiomers **18**−**27** were obtained by semipreparative HPLC of the racemic mixtures on a polysaccharide-based chiral stationary phase (CSP)[23] (Chiralpak AD) (the reader is referred to the Supporting Information for details of the separation methods).

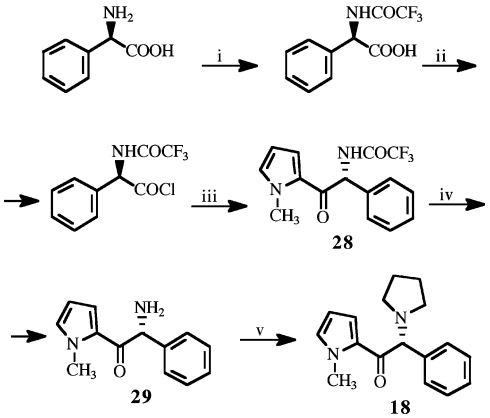
Scheme 1[a]



[a] Reagents and conditions: (i) RCH(Cl)COCl, $AlCl_3$, CH_2Cl_2, −20 °C, 15 min, **16** 26%, **17** 47%; (ii) piperidine, K_2CO_3, acetone, reflux 15 h, **11** 86%, **12** 67%; (iii) $LiAlH_4$, Et_2O, 0 °C, 40 min, **13** 13%, **14** 75%, **15** 87%.

As reported in Scheme 2, a synthesis of *R* isomer **18** was accomplished to determine the absolute configuration of the enantiomers of **3** (and related derivatives **4**, **8**), separated by chiral HPLC. Reaction of (*R*)-phenylglycine with ethyl trifluoroacetate afforded the *N*-trifluoroacetamide derivative[24] (99% ee), which was then converted to the corresponding acyl chloride with a procedure that gives high retention of stereochemical integrity.[25] The acyl chloride was immediately used in

Scheme 2[a]



[a] Reagents and conditions: (i) $CF_3COOC_2H_5$, tetramethylguanidine, MeOH, room temp, 24 h, 93%; (ii) Vilsmeier reactive, *n*-butyl acetate, −15 °C, 3 h; (iii) 1-methylpyrrole, $AlCl_3$, CH_2Cl_2, −5 °C, 2 h, 13%; (iv) concentrated HCl, MeOH, 40 °C, 15 h, 80%; (v) 1,4-dibromobutane, NaI, $KHCO_3$, reflux, 12 h, 67%.

a Friedel−Crafts reaction with 1-methylpyrrole to achieve protected amino ketone **28** (80% ee), which was then deprotected in acidic medium to afford **29**. Finally, **29** was alkylated with 1,4-dibromobutane in the presence of NaI to give the required pyrrolidine **18** (the 80% ee of the starting material **28** was nearly retained in the last two steps). The designed *R* isomer **18** and the related derivatives **20** and **22** were levorotatory, as well as the intermediates **28** and **29**. A similar procedure was performed starting from (*S*)-phenylglycine to afford **19** via intermediates (*S*)-1-(1-methyl-1*H*-pyrrol-2-yl)-2-phenyl-2-[*N*-(trifluoroacetyl)amino]ethanone (**30**) and (*S*)-2-amino-1-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylethanone (**31**) (for details, see Supporting Information).

Derivatives **1**−**15**, **18**−**27** were tested on bovine brain mitochondria isolated according to Basford,[26] used as the source of the two isoforms of MAO, in comparison with moclobemide (MCL), toloxatone (TOL), and SEL as reference drugs. MAO-A and MAO-B activities were determined by a fluorometric assay, using kinuramine as a substrate,[27] in the presence of their specific inhibitor (1 μM SEL to estimate the MAO-A activity, and 1 μM clorgyline to assay the isoform B). The K_i values against the two isoforms and the A-selectivity (expressed as K_i(MAO-B)/K_i(MAO-A) ratio) are reported in Table 1. All compounds act as reversible inhibitors. In fact, 90−100% of enzyme activity was restored by dialysis performed in a period of 24 h in a cold room against 0.1 M potassium phosphate buffer (pH 7.2).

Enzymatic assays revealed that all test compounds were weak MAO-B inhibitors, while potent activity against MAO-A was observed at low micromolar or submicromolar concentrations, with the sole exceptions of **13**, **24**, and **25**. This behavior could be ascribed to the presence of a pyrrole ring in the structure of our inhibitors. In fact, this electron-rich heterocycle could enhance the affinity for the MAO-A isoenzyme, according to literature data.[15] Moreover, the inhibitor access into the catalytic site of bovine MAO-B enzyme is possibly hindered by Phe208, which replaces Ile208 of the human enzyme.[8] Noteworthy were the A-selectivity values that ranged from 11 (**6**) to 200000 (**18**), with the exception of 0.29, 0.31, and 0.18 values obtained for derivatives **13**, **24**, and **25**, respectively. On the basis of the above remarks, in the present work, preliminary structure−activity relationships shall only be discussed for MAO-A inhibitors.

Amino derivative **1** showed potent and selective activity against MAO-A enzyme (K_i(MAO-A) = 0.095 μM, K_i(MAO-B) = 42 μM, A-selectivity = 442). It was 4- and 120-fold more potent than TOL and MCL, respectively. Methylation of **1** gave the *N*,*N*-dimethylamino derivative **2**, which was less potent than the parent compound. The presence of morpholine and piperidine moieties in certain anti-MAO-A drugs currently in clinical use (MCL, bazinaprine, and brofaromine) induced us to replace the amino group of **1** with some six-membered cyclic amines. Piperazine and morpholine gave derivatives **5**−**7** that had decreased activity. In contrast, the piperidine and thiomorpholine derivatives **4** and **8** were comparable to the lead compound **1** and proved to be 3−10 times more potent than **5**−**7**. Insertion of phthalimide and ethoxyphenylamine moieties at the 2-position of ethane chain led to **9** and **10**, endowed with lower potencies if compared to those of the alicyclic counterparts. Conversely, when the NH_2 group of **1** was replaced by a pyrrolidine ring, a potent and highly selective MAO-A inhibitor (**3**) was obtained.

In general, *R* isomers (**18**, **20**, **22**) were more active than the parent racemates (**3**, **4**, **8**) and 2−10 times more potent than the *S* counterparts (**19**, **21**, **23**). In particular, compound **18** showed the highest potency and selectivity (K_i(MAO-A) = 0.0035 μM, K_i(MAO-B) = 700 μM, and A-selectivity = 200000) among all test derivatives. **18** was 3285 and 108 times more potent and 23000 and 5060 times more A-selective than MCL and TOL.

To determine the role of the ketone group in the binding to biological target, we synthesized amino alcohols **13**−**15**, **24**−**27** related to piperidine derivative **4**. Reduction of the ketone group of **4** produced four diastereoisomers, **24**, **25** (threo isomers), and **26** and **27** (erythro isomers), which were 5−570 times less potent against MAO-A isoenzyme than the parent ketone **4**. Similar results were obtained when the ketone **11** was reduced to the corresponding alcohol **15**. In fact, an abatement of anti-MAO-A and anti-MAO-B activities was observed with a shift of A-selectivity from 2143 to 47. This led to conclude that the ketone group seems to play a pivotal role in the tight binding with the MAO-A isoenzyme.

It is worth noting that threo alcohols **13**, **24**, and **25** were the only selective MAO-B inhibitors reported in the present work, with B-selectivity (K_i(MAO-A)/K_i(MAO-B) ratio) falling in the range 3−6. In particular, **25** (K_i = 1.24 μM) was as active as SEL (K_i = 0.97 μM) but 7-fold less selective in inhibiting the MAO-B isoenzyme. The selective activity against MAO-B could be ascribed to favorable interactions of the ethanolamine moiety of threo isomers **13**, **24**, and **25** with the hydrophilic region located between Tyr398 and Tyr435 or with Tyr326 of the MAO-B catalytic cavity.[7,8] On the other hand, the lower anti-MAO-B potency of erythro diastereoisomers **14**, **26**, and **27** is probably due to different interactions of the aromatic groups with the biological target. At last, the low potency of **15** against MAO-B could be reasonably attributed to the lack of a

phenyl group, which causes a decrease of inhibitor lipophilicity.

In summary, the present work describes the first report on the identification of PEAs as a novel class of potent and highly selective MAO-A inhibitors. To our knowledge, PEAs are the first aminoketone derivatives described as inhibitors of MAO enzymes. Among the test derivatives, **18** showed the highest potency against MAO-A, with the A-selectivity value much higher than those of MCL and TOL, two clinical agents used as reference drugs. This result can be regarded as an important discovery that might be applied as a future therapeutic application. In addition, this finding lends support to expanding the chemical and biological search for novel selective inhibitors of MAO-A enzyme to other pyrrolylethanoneamines. Furthermore, pyrrolylethanolamine **25** was proven to exert significant inhibitory activity against the MAO-B isoenzyme and can be considered suitable as a lead compound in the search for novel potent and selective MAO-B inhibitors. We are currently expanding our SAR studies on arylethanoneamines and arylethanoleamines to establish the observations that the electron-rich aromatic ring and the ketone function play a role in determining the selectivity against the MAO-A isozyme. These studies will be extended to different structural classes of inhibitors containing electron-rich aromatic moieties and carbonyl groups, providing useful information for the rational design of potent MAO-A inhibitors. We will report the results of our expanded SAR studies in the near future.

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Supporting Information Available: Experimental procedures and characterization data for intermediates **16**, **17** and final compounds **11**−**15**, details on stereoselective syntheses of **18** and **19** and HPLC separations, and description of biochemical assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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