Simple, Potent, and Selective Pyrrole Inhibitors of Monoamine Oxidase Types A and B

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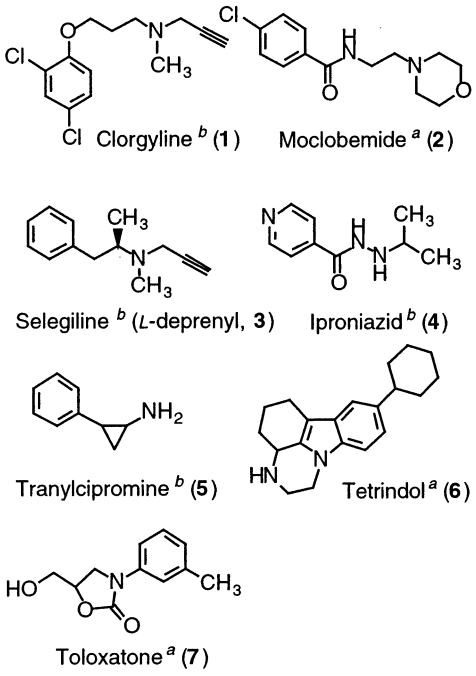
Abstract: *N*-Benzyl- and *N*-propargyl-1*H*-pyrrole-2-carboxyamides and some related methylenamines were synthesized and tested for their monoamine oxidase types A and B inhibitory activity. 2-(*N*-Methyl-*N*-propargylaminomethyl)-1*H*-pyrrole (**24**) was the most potent MAO-A inhibitor of the series [K_i(MAO-A) = 0.0054 μM], but it was not selective. Inhibitors *N*-4-fluorobenzyl-1*H*-pyrrole-2-carboxamide (**12**) and *N*-cyclohexylmethyl-1*H*-pyrrole-2-carboxamide (**25**) showed the highest MAO-A selectivity indexes (SI) corresponding to 2025 and >2500, respectively, while 2-(*N*-methyl-*N*-benzylaminomethyl)-1*H*-pyrrole (**21**) was the most selective MAO-B inhibitor, having an SI of 0.0057.

Introduction. MAO (EC 1.4.3.4) is an outer mitochondrial membrane FAD containing enzyme[1] found in nearly all tissues. On the basis of their substrate and inhibitor specificities, two major isoforms have been described, the MAO-A and the MAO-B[2,3] made up of different polypeptides.[4] The structure of human MAO-B was recently resolved,[5] and the molecular determinants required for MAO selectivity were investigated.[6,7] MAOs are responsible for the major neurotransmitter degrading in the central nervous system (CNS) and peripheral tissues.[8] MAO-A preferentially catalyzes the oxidative deamination of serotonin (5-HT), adrenaline (A), and noradrenaline (NA) and is selectively inhibited by clorgyline (**1**) and moclobemide (**2**) (Chart 1). MAO-B mainly catalyzes the oxidative deamination of β-phenetylamine and benzylamine and is selectively inhibited by selegiline (**3**). Both isoforms act either on dopamine (DA) in vitro or on tyramine. In mankind, DA is preferentially deaminated by MAO-B. Because of their role in the metabolism of monoamine neurotransmitters, MAO-A and MAO-B are thought to be involved in psychiatric and neurological disorders such as depression and Parkinson's disease, respectively.[9]

Depression is a widespread disabling disease with social and economic consequences.[10] Antidepressant drugs currently marketed fall into four main selective 5-HT uptake inhibitors (SSRIs), the MAO-A inhibitors and the atypical antidepressants.[11] All antidepressant drugs act by a modulation of the synaptic transmission of monoamines 5-HT, A, NA, or D.[12] Iproniazid (**4**) was the prototype of MAO inhibitor introduced in therapy since the 1957s.[13] Iproniazid and tranylcipromine (**5**) are irreversible and nonselective MAO inhibitors responsible for some side interactions with other drugs and certain foods. Because of their adverse actions, the therapeutic applications of first-generation MAO inhibitors have been diminished.[14,15] Modern research on the development of more reversible, selective, and safe MAO-A inhibitors led to the launch of moclobemide[16] (**2**, Roche, 1990), tetrindol[17] (**6**, Center of Chemistry of Moscow, 1992), and toloxatone[16] (**7**, Sanofi-Synthélabo, 1984). Today, a wide range of novel MAO-A inhibitors are under clinical and preclinical trials.

Chart 1. Reversible (a) and Irreversible (b) MAO Inhibitors



Parkinson's disease is a neurodegenerative syndrome for which the main therapy is the amelioration of the symptoms with L-DOPA and/or DA agonists.[18] Selegiline (**3**, L-deprenyl) is an irreversible but not highly selective MAO-B inhibitor administered to gain the L-DOPA level in Parkinson therapy as well as to reach a protective effect in patients with the pre-Parkinson syndrome.[19] In a recent survey, both **3** and L-DOPA at high doses induce neuronal apoptosis.[20] In contrast, low doses of **3** act as a neuroprotector by stopping the apoptotic event.[20]

Our decennial interest in heterocyclic bioisosters of CNS agents[21] motivated us to synthesize novel, simple, and highly selective pyrrole-containing MAO inhibitors. Investigation of structures **2** and **3** allowed the identification of some common structural features attributed to the presence of (A) an aryl ring, (B) a nitrogen-containing four-atom chain, (C) an electron-rich zone due to the tertiary amino group in **2** or a triple bond in

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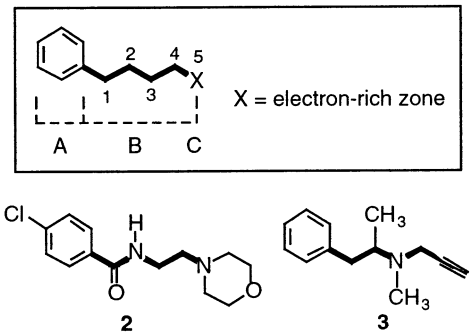
Chart 2. Reference Models for the Novel MAO Inhibitors



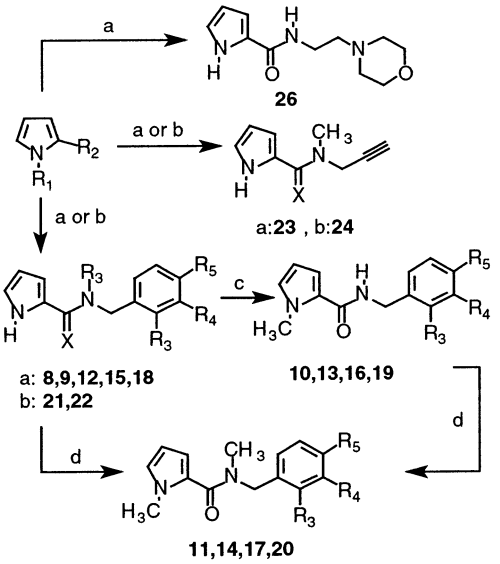
3 (Chart 2). In fact, we planned the synthesis of derivatives **8**−**26**, bearing the structural requirements A−C, after replacing the phenyl moiety with a pyrrole nucleus. Because of the presence of a C═O function in **2** but not in **3**, both amides and methylene derivatives were synthesized and tested.

Chemistry. The synthesis of the title derivatives was reached by heating 2-trichloroacetyl-1*H*-pyrrole[22] with the appropriate benzylamine *N*-methylbenzylamine, *N*-methylpropargylamine, or 4-(2-aminoethyl)morpholine in the presence triethylamine to give *N*-benzyl-1*H*-pyrrole-2-carboxamides (**8**, **12**, **15**, **18**), *N*-benzyl,*N*-methyl 1*H*-pyrrole-2-carboxamide (**9**), *N*-propargyl-*N*-methyl 1*H*-pyrrole-2-carboxamide (**23**), or *N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide (**26**), respectively. The *N*-benzyl-1-methyl-1*H*-pyrrole-2-carboxamides **10**, **13**, **16**, and **19** were obtained from *N*-benzyl-1*H*-pyrrole-2-carboxamides **8**, **12**, **15**, and **18** by a phase-transfer reaction[23] with iodomethane in benzene/50% sodium hydroxide in the presence of tetrabutylammonium hydrogensulfate (TBAS) as a catalyst. The *N*-benzyl-*N*-methyl-1-methyl-1*H*-pyrrole-2-carboxamides **11**, **14**, **17**, and **20** were obtained from *N*-benzyl-1*H*-pyrrole-2-carboxamides **8**, **12**, **15**, and **18** by a similar phase-transfer reaction by using dichloromethane as a solvent. In this way, amides **11**, **14**, **17**, and **20** were alternatively obtained starting from **10**, **13**, **16**, **19**. 2-(*N*-Methyl-*N*-benzylaminomethyl)-1*H*-pyrrole (**21**), 2-(*N*-methyl-*N*-benzylaminomethyl)-1-methyl-1*H*-pyrrole (**22**), and 2-(*N*-methyl-*N*-propargylaminomethyl)-1*H*-pyrrole (**24**) (Mannich bases) were obtained by treating pyrrole or 1-methylpyrrole with *N*-methyl-*N*-benzylamine or *N*-methyl-*N*-propargylamine, respectively, and formaldehyde in acetic acid at 0 °C (Scheme 1).

Biology. All compounds were tested on bovine brain mitochondria, isolated according to Basford,[24] and used as a source of the two isoforms of MAO. The activities of MAO-A and -B were determined by a fluorometric method using kinuramine as substrate,[25] in the presence of their specific inhibitors (L-deprenyl, 1 mM, to estimate the MAO-A activity and clorgyline, 1 mM, to assay the isoform B).

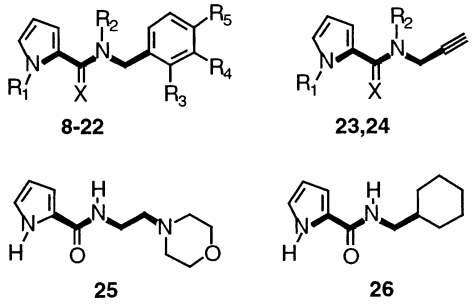
Results and Discussion. The inhibitory activities (K_i values) of test compounds **8**−**26** are reported in Table 1. All compounds act through a noncompetitive and reversible mechanism. Enzymatic assays revealed potent MAO-A or MAO-B inhibitory activity for some of the compounds examined. With the exception of the derivative **21**, all test compounds showed MAO-A inhibitory activities at a submicromolar concentration,

Scheme 1[a]



[a] (a) R_1 = H, R_2 = $COCCl_3$, amine, $(H_5C_2)_3N$, 60 °C, overnight; (b) R_1 = H, CH_3, R_2 = H, amine, HCOH, CH_3COOH, 0 °C, 1 h; (c) R_3 = H, CH_3I, TBAS, C_6H_6−50% NaOH, room temp, overnight; (d) R_1 = H, CH_3I, TBAS, CH_2Cl_2−50% NaOH, room temp, overnight.

Table 1. Structures and Monoamine Oxidase Inhibitory Activities of Derivatives **8**−26[a]



compd	R_1	R_2	R_3	R_4	R_5	X	K_i(MAOA), μM	K_i(MAOB), μM	SI[b]
8	H	H	H	H	H	O	0.25	150	600
9	H	CH_3	H	H	H	O	0.6	300	500
10	CH_3	H	H	H	H	O	0.26	150	576
11	CH_3	CH_3	H	H	H	O	0.54	300	555
12	H	H	F	H	H	O	0.4	810	2025
13	CH_3	H	F	H	H	O	0.59	8	13.5
14	CH_3	CH_3	F	H	H	O	0.18	140	750
15	H	H	H	F	H	O	0.34	200	588
16	CH_3	H	H	F	H	O	0.2	0.4	2
17	CH_3	CH_3	H	F	H	O	0.98	0.42	0.42
18	H	H	H	H	F	O	0.72	400	555
19	CH_3	H	H	H	F	O	0.4	5	12.5
20	CH_3	CH_3	H	H	F	O	0.36	0.45	1.2
21	H	CH_3	H	H	H	H_2	3.5	0.02	0.0057
22	CH_3	CH_3	H	H	H	H_2	0.15	85	572
23	H	CH_3				O	0.075	50	666
24	H	CH_3				H_2	0.0054	0.02	3.7
25							0.4	>1000	>2500
26							0.5	80	160
MCL[c]							11.5	>100	>87
CLG[d]							0.054	58	1074
SLG[e]							38	0.97	0.025

[a] Data represent mean values of at least three separate experiments. [b] SI: selectivity index = K_i(MAO-B)/K_i(MAO-A). [c] MCL: moclobemide.[14] [d] CLG: clorgyline.[17] [e] SLG: selegiline.[17]

while five of these compounds (**16**, **17**, **20**, **21**, and **24**) inhibited MAO-B in the submicromolar range. The selectivity index (SI) values [SI = K_i(MAO-B)/K_i(MAO-

A)] ranged from >2500 (**25**) to 0.0057 (**21**). The amides showed SI values between 0.42 (**17**) and >2500 (**25**). Compound **24** was the most potent MAO-A inhibitor within the series [K_i(MAO-A) = 0.0054 μM], but it was not sufficiently selective [K_i(MAO-B) = 0.02 μM, SI = 3.7]. Both amides **12** and **25** showed the most favorable selectivity toward MAO-A with SI values of 2025 and >2500, respectively. Such values were higher than those of the reference drugs clorgyline (SI = 1074) and moclobemide (SI > 87). The two derivatives **21** and **24** showed the highest anti-MAO-B activities with just the same K_i(MAO-B) = 0.02 μM. In enzymatic assays, compound **21** showed an interesting anti-MAO activity [K_i(MAO-A) = 3.5 μM, K_i(MAO-B) = 0.02 μM, and SI = 0.0057], being more active than selegiline against the MAO-A isoform. This compound displayed inhibitory potency about 50 times higher than that of reference drug selegiline against the MAO-B isoform. Thus, **21** was the most selective MAO-B inhibitor among the test derivatives.

Preliminary SARs were obtained from data of enzymatic experiments reported in Table 1.

We first examined derivatives without substituents on the phenyl ring. Data of Table 1 clearly demonstrated that in this series the N-methylation of the pyrrole did not affect the MAO-A or the MAO-B inhibitory properties. This is exemplified by a comparison of unmethylated compounds **8** and **9** with their N-methylated counterparts **10** and **11**, respectively.

We also observed that the reduction of the carbonyl group to a methylene had a dramatic effect on MAO-B activity of unmethylated pyrroles with an increase of 15 000 times (compare **9** with **21**), whereas it did not influence the activity of the related *N*-methyl analogues (compare **11** with **22**). As far as the MAO-A isoform is concerned, either the reduction of the C=O to a CH_2 (compare **9** with **21** and **11** with **22**) or the N-methylation of the pyrrole (compare **9** with **11** and compare **21** with **22**) had poor influence on the inhibitory activities of compounds **9**, **11**, **21**, and **22**.

When the phenyl ring of **8** was replaced by a cyclohexyl, a slight reduction of anti-MAO-A activity (twice) was balanced by an increase (about twice) of anti-MAO-B activity (compare **8** with **26**).

Further significant SAR indications were deduced by examination of the fluoro-substituted phenyl derivatives. In fact, the presence of a fluorine atom at the ortho, meta, or para position of the phenyl ring was a determinant for the inhibitory activities of both MAO isoforms.

Independent of its position on the phenyl ring, a fluorine atom did not remarkably influence the anti-MAO activities of compounds **12**−**20**. This is exemplified by the fluoro derivative **14**, which showed an inhibitory potency only 3-fold higher than that of the parent compound **11**. In contrast, the position of the fluorine atom on the phenyl ring was crucial for activity against the MAO-B isoform. In fact, introduction of a fluorine atom in the phenyl ring of **10** reinforced the anti-MAO-B activity from 19 to 375 times (compare **10** with **13**, **16**, and **19**).

The anti-MAO-B activities of the dimethyl derivatives **11**, **14**, **17**, and **20** were strengthened about 600−700 times by the introduction of a fluorine atom at the meta or para position (compare **11** with **17** and **20**), while a decrease of activity was observed when the fluorine was introduced at the ortho position (compare **11** with **14**). In the fluorinated series, the N-methylation of pyrrole did not affect the anti-MAO-A activity whereas the anti-MAO-B activity increased 100, 500, and 80 times going from the ortho to the meta and then to the para position (compare **12** with **13**, **15** with **16**, and **18** with **19**).

It is also worth noting that N-methylation of the NH−C=O group did not increase the inhibitory potency against the MAO-A isoform with the exception of the derivative **14** (3 times higher than **16**), whereas the anti-MAO-B activity was diminished (compare **13** with **14**) or retained (compare **16** with **17** and compare **19** with **20**).

When the benzyl group of **9** was replaced with a propargyl group (compound **23**), both anti-MAO-A (8 times) and anti-MAO-B (6 times) activities increased. Reduction of the carbonyl group of **23** to a methylene (compound **24**) caused only a slight improvement of the anti-MAO-A activity (about 14 times) but a dramatic increase (2500 times) of the anti-MAO-B activity, whereas the selectivity between MAO-A and MAO-B isoforms was lowered.

Substitution of the benzyl group of **8** with a 2-(4-morpholinyl)ethyl moiety gave **25**, a pyrrole analogue of moclobemide with higher potencies against MAO-A (about 29 times) and MAO-B (about 10 times) and the highest selectivity index (SI > 2500) within the test compounds.

In conclusion, *N*-benzyl- and *N*-propargyl-1*H*-pyrrole-2-carboxyamides and the related *N*-benzyl- and *N*-propargyl-1*H*-pyrrole-2-methylenamines were shown to be simple, potent, and effective MAO inhibitors. The biological results led us to discriminate between MAO-A and MAO-B selectivity in terms of structural differences. The best anti-MAO-A activity was reached with the *N*-propargylpyrrolylamine **24**. Unfortunately, this compound showed a low selectivity index also being very active against the MAO-B isoform. The corresponding amide **23**, although 15-fold less active against the MAO-A isoform, showed the best selectivity profile because of its lower activity against MAO-B. The maximum of selectivity was obtained when the propargyl moiety of **23** was replaced by the less lipophilic morpholinylethyl chain giving **25**, the pyrrole analogue of moclobemide. Some derivatives (**16**, **17**, **20**, and **24**) were found to be more active than the reference compounds against MAO-B, but they lacked selectivity against this isoform. The sole derivative with a selectivity index greater than selegiline (SI = 0.025) was the *N*-methyl-*N*-benzyl-2-pyrrolylmethylamine **21** (SI = 0.0057). These findings will be considered in planning novel and selective MAO-A and MAO-B inhibitors.

Our study is actually aimed at investigating more deeply the molecular determinants for the MAO selectivity through the synthesis of novel pyrrole derivatives obtained by molecular modeling aided design.

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Supporting Information Available: Preparative and chemicophysical data for compounds **8**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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