3-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-furan-2-yl]phenylamine (Amifuraline), a Promising Reversible and Selective Peripheral MAO-A Inhibitor

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Received May 22, 2006

On the basis of the observation that the central side effects of MAO inhibitors may represent a major limit for their use in pathological processes involving peripheral MAOs, we investigated the possibility of generating novel inhibitors able to target specifically peripheral MAOs. To address this issue, we designed compounds **7**−**28**. From biological results, the 2-(5-phenyl-furan-2-yl)-4,5-dihydro-1*H*-imidazole (Furaline, **17**) proved to be a suitable lead. In fact, in enzyme assays on homogenate preparation from rat liver and HEK cells expressing MAO-A or MAO-B, compounds possessing the frame of **17** behaved as selective and reversible MAO-A inhibitors. Interestingly, in in vivo studies the amino derivative **21** (Amifuraline), endowed with good hydrophilic character, was able to significantly inhibit liver but not brain MAO-A.

Introduction

Monoamine oxidases (MAOs) are FAD-containing enzymes catalyzing the oxidation of endogenous (e.g. norepinephrine, dopamine, serotonin) and exogenous amines to the corresponding aldehyde and ammonia.[1] Currently, two MAO isoforms, encoded by separate genes sharing a common intron/exon organization,[1−3] have been identified based on substrate specificity: MAO-A preferentially metabolizes serotonin and kynuramine, whereas MAO-B has a greater affinity for phenylethylamine and benzylamine.[4] The two MAO isoforms can be also differentiated according to their inhibition by synthetic compounds: clorgyline and moclobemide for MAO-A and selegiline and lazabemide for MAO-B.[5]

Although MAOs are widely distributed in various organs, most of the studies concerning their functional properties and involvement in pathological processes have been mainly focused on the central nervous system. These studies showed that MAOs play a major role in regulating brain concentrations of biogenic amines, and their abnormalities have been involved in various psychiatric and neurodegenerative disorders.[6] In the periphery, MAO-A and MAO-B are differently expressed in a variety of organs: MAO-A is predominant in heart, adipose tissue, and skin fibroblasts, MAO-B is the major form found in platelet and lymphocytes, whereas both isoenzymes are expressed in kidney and liver.[7]

We and other authors have shown that the kidney displays one of the highest MAO activities.[8,9] As reported for the central nervous system, MAOs regulate the availability of renal dopamine and serotonin and, consequently, their activity on renal function. We have recently identified an additional MAO mechanism of action involving reactive oxygen species (ROS) production and the consequent induction of intracellular oxidative stress.[10,11]

Hydrogen peroxide (H_2O_2) is one of the reaction products generated by MAOs during substrate degradation. Except for the potential cytotoxic effect of H_2O_2 in nigral cells in Parkinson's disease,[12] the cell events following MAO-dependent H_2O_2 production in physiological conditions are still unknown. In a first series of results, we showed that in various peripheral living cells, including renal mesangial and proximal tubule cells, degradation of small quantities of substrate by MAO-A or MAO-B induces H_2O_2 production that was not fully scavenged by intracellular antioxidants and therefore may behave as an intracellular messenger.[13] This possibility was confirmed by further experiments showing that, depending on concentrations, H_2O_2 produced by MAOs is responsible for the receptor-independent proliferative and apoptotic effects of dopamine.[10,11] The relevance of this novel MAO mechanism of action in vivo was demonstrated in a model of renal ischemia-reperfusion in which animal treatment with a MAO inhibitor largely prevented the post-reperfusion oxidative stress and renal damage.[14] These findings, along with other results showing the important role of ROS generated by MAOs in heart,[15] adipose tissue,[16] macrophages,[17] and skeletal muscle,[18] pointed to the relevance of peripheral MAOs in various pathological processes and their potentiality as pharmacological targets.

Monoamine oxidase inhibitors (MAOIs) have been extensively used in the therapy of psychiatric and neurodegenerative disorders including Parkinson's disease, Alzheimer's dementia, depression syndrome, and panic disorders.[19] However, the use of these drugs has been limited by some centrally mediated side effects such as the serotonin syndrome,[20] dizziness, lightheadedness, blurred vision, and weakness. In addition, it has been reported that MAOIs may potentiate the effects of alcohol and other drugs that slow the central nervous system, such as antihistamines, cold medicine, allergy medicine, sleep aids, medicine for seizures, tranquilizers, some pain relievers, and muscle relaxants.[21−23]

These central side effects of MAOIs may represent a major limit for their use in pathological processes involving peripheral MAOs. On the basis of this observation, we decided to design a strategy to synthesize novel MAOIs able to target specifically peripheral MAOs. In the absence of any accurate SAR studies which might lead us to suppose structural deviations between the peripheral and central isoenzymes, our strategy was inspired

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10.1021/jm060605r CCC: $33.50
Published on Web 08/01/2006

Chart 1. Structural Formulas of MAO Inhibitors **1**−**5** and Dopamine (**6**)

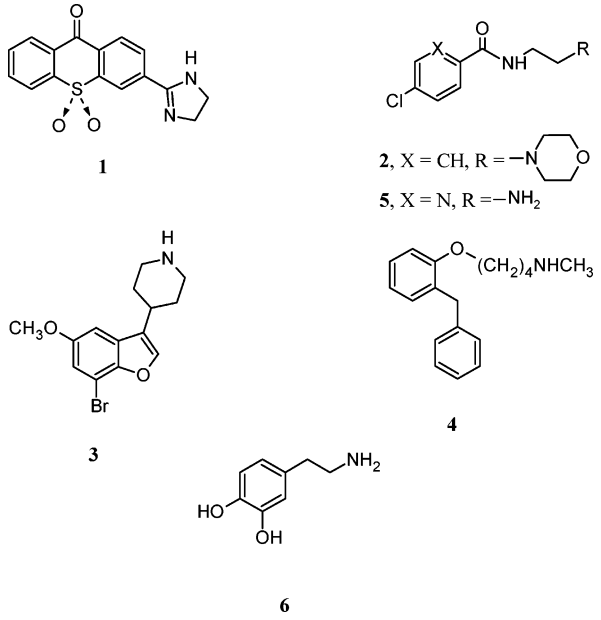
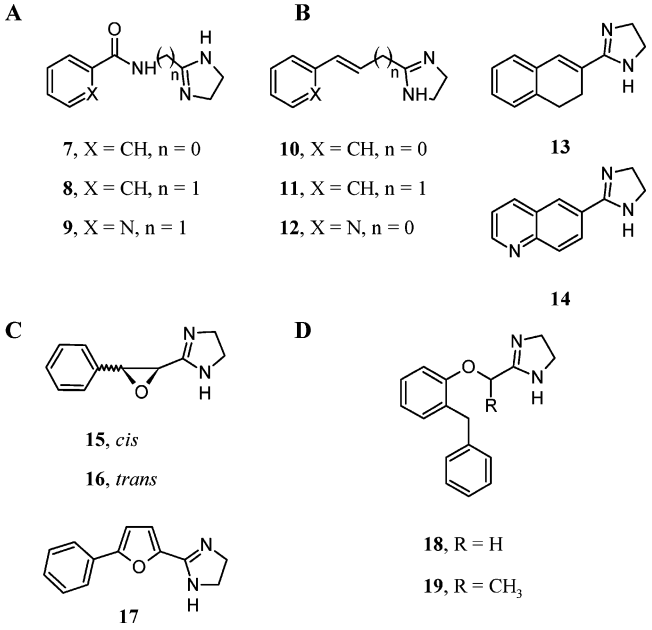


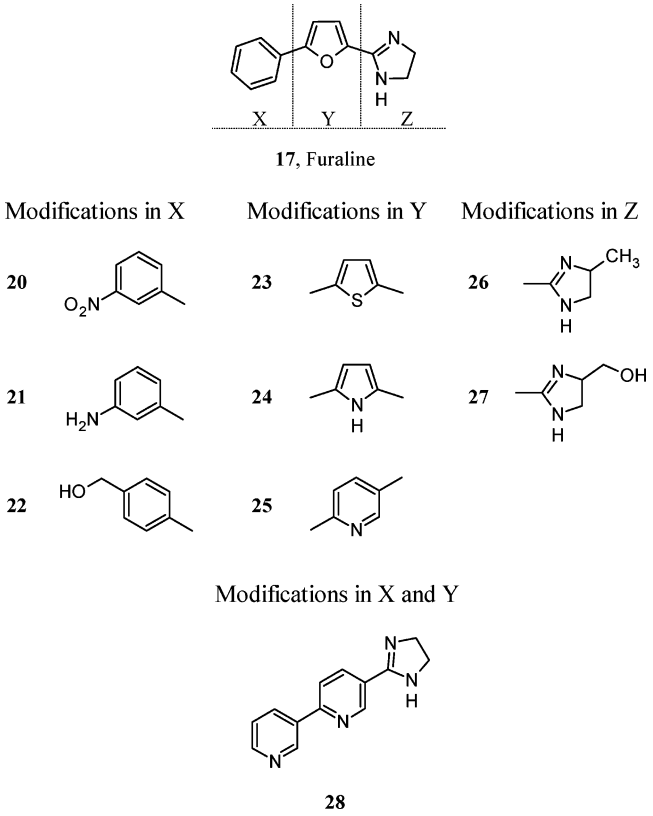
Chart 2. Imidazoline Derivatives Designed as MAO Inhibitors



by known compounds which displayed low toxicity and relative selectivity, such as 3-(imidazolin-2-yl)thioxanthen-9-one 10,10-dioxide (**1**), moclobemide (**2**), brofaromine (**3**), bifemelane (**4**), and lazabemide (**5**).[24] These inhibitors share a common pharmacophore, represented by a basic group and a suitably spaced aryl ring.[25] The same structural features are found in dopamine (**6**), a MAO-A and MAO-B substrate (Chart 1).

As our major goal was to obtain a novel lead compound, we designed, prepared, and tested compounds **7**−**19** (Chart 2, panels A−D), in which the basic function that supports the primary interaction at the catalytic site, was simulated by the imidazoline ring. This choice was made for two reasons: first because this ring is present in some efficacious MAOIs as, for example, the already mentioned compound **1**,[26] and second because the I_2-imidazoline binding sites (I_2-IBS) seem allosterically connected with the MAO isoforms.[27] To perform an adequate structure−activity relationship (SAR) investigation, the compounds of this

Chart 3. Furaline Modifications

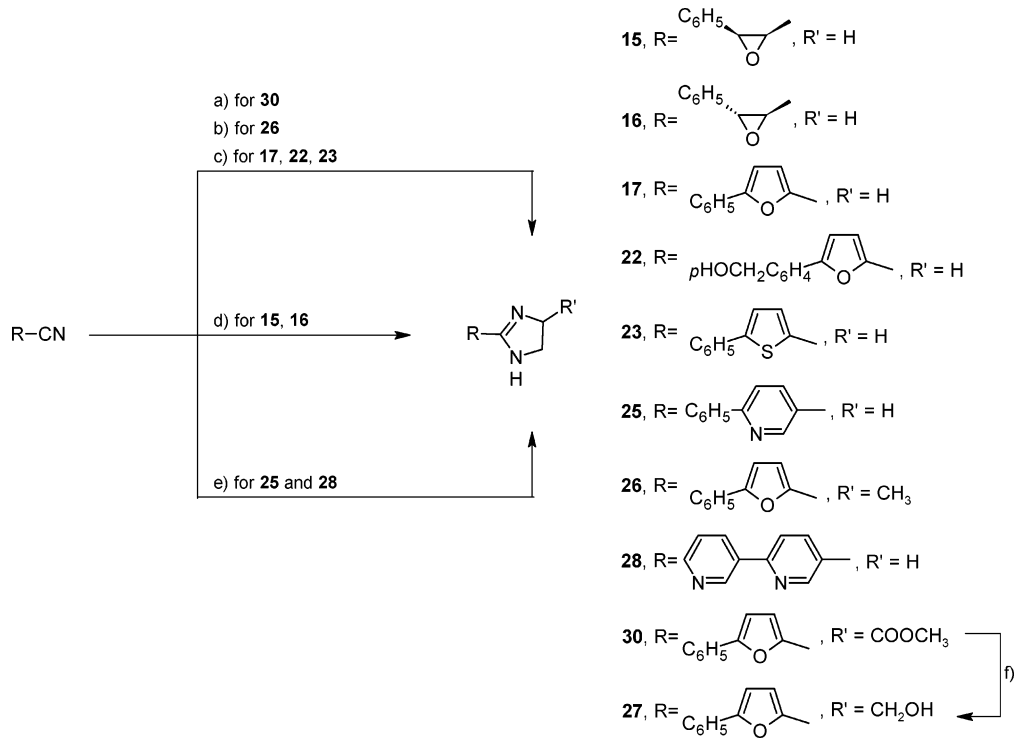


first series (**7**−**19**) showed great differences in the kind of substituent inserted at position 2 of the imidazoline ring. In fact, the aromatic function has been represented either by the simple phenyl, dihydronaphthalene, or the more hydrophilic azaryl (pyridine or quinoline) nuclei that, hindering the hemato-encephalic barrier crossing, prevented central side effects; the central spacer was represented by alkylic, amidic, as in moclobemide, and oxygenated (epoxydic or furanic), as in brofaromine, functions. In particular, the molecules shown in panel A, clearly inspired by moclobemide (**2**), allowed us to evaluate the effects of the distance between the aromatic and imidazoline functions (compounds **7** and **8**) and the increase of hydrophilicity by substitution of the phenyl with the pyridyl ring (compound **9**). The electronic effects promoted by the amidic function were partly simulated by a single double bond (compounds **10**−**12**) or a constraint structure (**13** and **14**), as reported in panel B. Instead, the epoxides **15** and **16**, and the furan-2,5-derivative **17**, shown in panel C, were inspired by brofaromine (**3**). Finally, bifemelane (**4**) was the model for the derivatives of panel (D) (compounds **18** and **19**).

Subsequently, on the basis of the obtained results, we designed, synthesized, and tested the second series of compounds **20**−**28** (Chart 3). Compounds **7**,[28] **8**,[29] **10** and **13**,[30] **12**,[31] **18**,[32] and **19**[33] were already known, but their potential inhibitory properties toward MAOs had never been described. In addition, compounds **21**, **22** and **25** were carefully studied in vitro and in vivo assays.

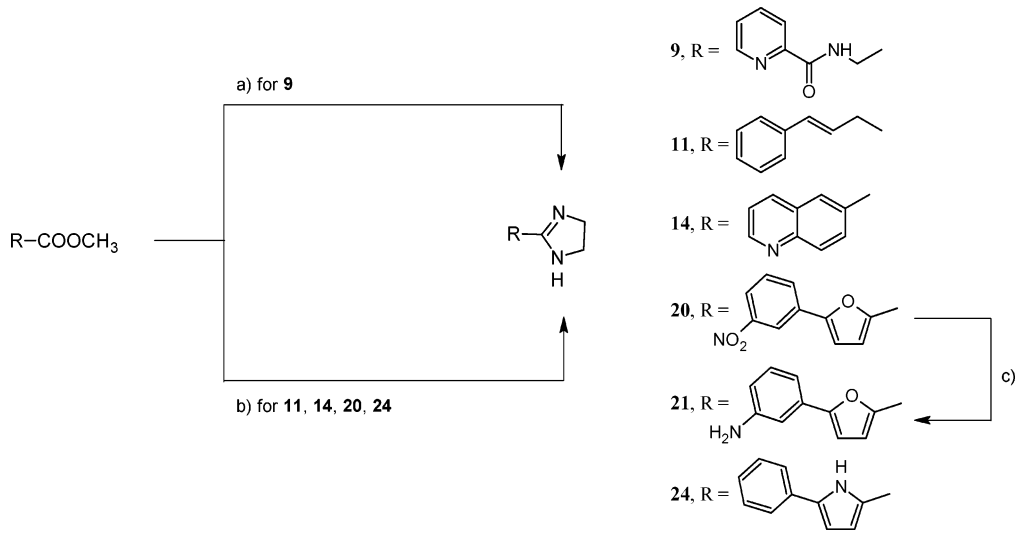
Chemistry. Compounds **15**−**17**, **22**, **23**, **25**, **26**, **28**, and **30** were synthesized according to standard methods by condensation of suitable nitriles with ethylenediamine, 1,2-diaminopropane, or 2,3-diamino-propionic acid methyl ester. [2-(5-Phenyl-furan-2-yl)-4,5-dihydro-1*H*-imidazol-4-yl]-methanol (**27**) was obtained through a $NaBH_4$ reduction of the corresponding carbomethoxy derivative **30** (Scheme 1).

Scheme 1[a]



[a] Reagents: (a) HCl_g/MeOH; $H_2NCH(COOCH_3)CH_2NH_2$; (b) HCl_g/MeOH; $H_2NCH(CH_3)CH_2NH_2$; (c) HCl_g/MeOH; $H_2NCH_2CH_2NH_2$; (d) CH_3ONa/CH_3OH, $H_2NCH_2CH_2NH_2$; (e) $H_2NCH_2CH_2NH_2$/TsOH, Δ, (f) $NaBH_4$, EtOH.

Scheme 2[a]



[a] Reagents: (a) $H_2NCH_2CH_2NH_2/\Delta$; (b) $Al(CH_3)_3$, toluene, Δ, $H_2NCH_2CH_2NH_2$; (c) H_2, Pd/C.

Imidazolines **9**, **11**, **14**, **20**, and **24** were synthesized from suitable methyl esters by treatment with ethylenediamine alone (compound **9**) or in the presence of trimethylaluminum (compounds **11**, **14**, **20**, and **24**). 3-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-furan-2-yl]phenylamine (**21**) was obtained through catalytic hydrogenation over Pd/C of the corresponding nitro-derivative **20** (Scheme 2).

Results and Discussion

To select a potential lead, we performed a first screening in vitro on homogenates from rat liver, a tissue containing MAO-A and MAO-B, using [^{14}C]tyramine, a common substrate for both MAO isoenzymes, at two compound concentrations (0.1 and 10 μM). In Table 1 the inhibitory properties, expressed as % of inhibition of [^{14}C]tyramine oxidation, of compounds **7**−**19** and their calculated hydrophilicity (Clog P)[34] are reported. Within this series a significant activity was observed for compounds **13** (40% inhibition at 10 μM) and **17** (50% inhibition at 10 μM). As shown by CLog P, compound **17** displayed a lipophilicity about 20-fold lower than that calculated for compound **13**. These observations proposed compound **17** (Furaline) as a possible lead for the design of peripheral MAO inhibitors.

Moreover, the I_2-IBS affinity value of furaline (**17**), determined following previously described procedures,[35] was pK_i = 7.68. Therefore, the more interesting compounds such as **13** (pK_i I_2 7.95)[36] and **17** showed high I_2-IBS affinity. Nevertheless, since some compounds such as **10** (pK_i I_2 8.72)[36] and **16** (pK_i

Table 1. MAO Inhibition of Imidazolines **7**−**19**[a]

compd	% inhib of [^{14}C]tyramine oxidation 0.1 μM	% inhib of [^{14}C]tyramine oxidation 10 μM	calcd Log P[b]	ref
7	0	0	0.00	28
8	25	25	1.30	29
9	0	0	0.22	-
10	10	25	1.54	30
11	0	5	2.90	-
12	0	5	0.18	31
13	10	40	2.49	30
14	0	0	0.48	-
15	25	25	1.41	-
16	5	15	0.94	-
17	5	50	1.14	-
18	5	15	4.13	32
19	10	10	4.47	33

[a] Experiments were performed in liver homogenate preparations. Values are the means of two experiments performed in triplicate. [b] Data from ACD/Labs 7.00 Release. Product Ver. 7.09, 03 Nov. 2003.[34]

Table 2. MAO Inhibition of Imidazolines **17**, **20**−**28**[a]

compd	% inhib of [^{14}C]tyramine oxidation 0.1 μM	% inhib of [^{14}C]tyramine oxidation 10 μM	calcd Log P[b]
17	5	50	1.14
20	10	15	0.67
21	30	60	−0.42
22	0	90	−0.04
23	5	50	2.05
24	10	55	0.74
25	10	50	1.28
26	10	55	1.64
27	15	25	0.40
28	0	0	−0.03

[a,b] See Table 1.

I_2 7.55) displayed high I_2-IBS affinity but negligible inhibitory properties, we suggest that peripheral MAO inhibitory properties are not necessarily linked to I_2-IBS affinity, contrary to what was observed for the central MAO inhibition produced by BU series compounds.[37]

On the basis of our results, to confirm the lead validity, to enhance possibly its potency and selectivity, and to highlight the potential interactions with ancillary enzymatic proteins sites, we performed some conservative structural modifications at the three portions X, Y, and Z of furaline (**17**) (Chart 3). These modifications included (i) introduction in the meta and para positions of the phenyl ring of substituents with different hydrophilic and electronic contributions[38] such as NO_2 (**20**) or NH_2 (**21**) and CH_2OH (**22**) (modifications in X); (ii) isosteric substitution of the furan ring with thiophene (**23**), pyrrole (**24**) and pyridine (**25**) nuclei (modification in Y); (iii) introduction of CH_3 (**26**) or CH_2OH (**27**) groups in position 4 of the imidazoline nucleus (modification in Z); (iv) simultaneous isosteric substitutions of portions X and Y with the pyridine nuclei (**28**). Instead, the imidazoline nucleus modifications, such as N-methylation, enlargement, or oxidation to the imidazole ring, that in the previous studies of Harfenist et al. proved to be unfavorable,[26] have not been designed.

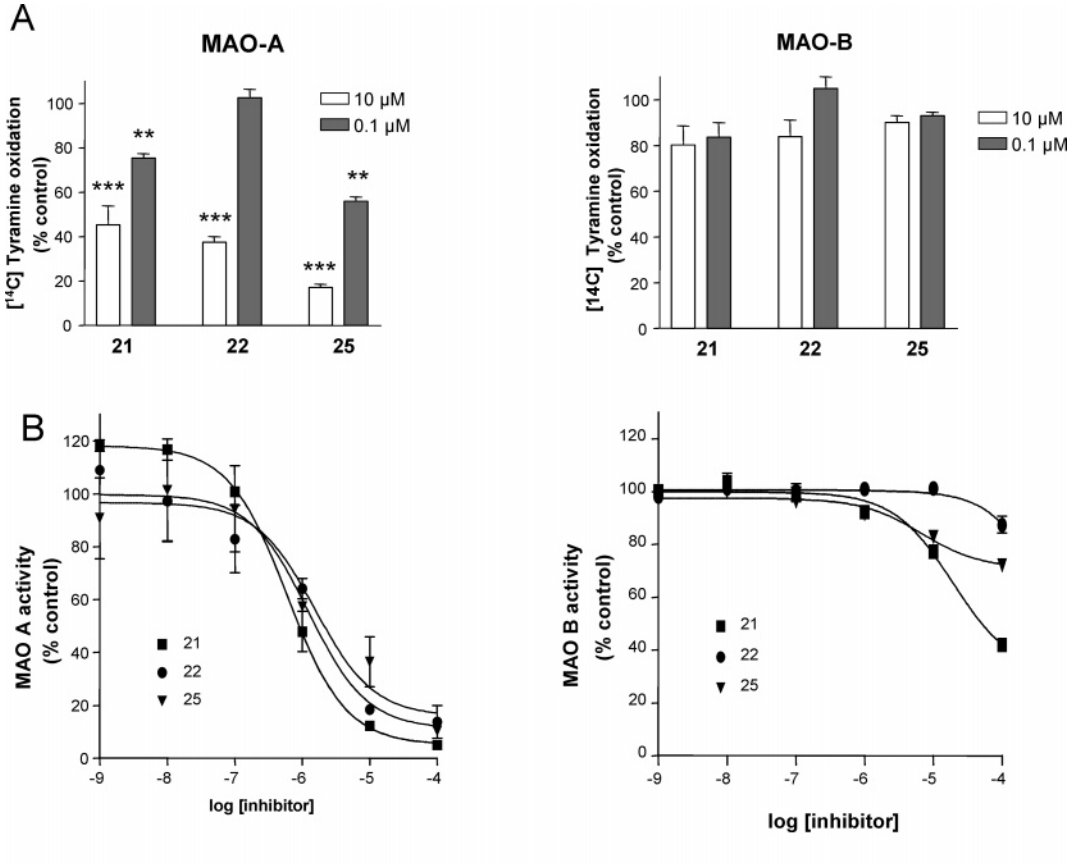
As reported in Table 2, most of the new derivatives (compounds **21**−**26**), displayed similar and significant inhibitory properties on homogenates from rat liver, comparable to that of lead. This result confirmed that furaline (**17**), selected as a model, represents a really suitable new template and an important basis for future work on peripheral MAO inhibitors.

Nevertheless, for the design of new derivatives inspired by **17,** Table 2 allows several useful considerations. The aromaticity of portion X of the ligand is critical for activity: substituents with electron-withdrawing effects ($+\sigma$) in this portion (Chart 3), probably weakening the charge-transfer interaction with the isoalloxazine nucleus of the flavin cofactor,[39] might decrease inhibitory activity, as observed for the NO_2 group (**20**). Analogously, the substitution of the phenyl group of furaline (**17**) with the pyridine nucleus (**28**) appears to be unfavorable. In fact, it is known that the nitrogen atom of the pyridine ring and the NO_2 group of the phenyl ring possess similar polarities and electron-withdrawing effects. On the contrary, substituents with null or negative σ values (CH_2OH or NH_2 group, respectively), are compatible with the activity (compounds **21** and **22**). According to known analogies among pentatomic systems (furane, thiophene, and pyrrole), the inhibitory activity does not appear affected by the type of heteroatom of the spacer (portion Y) (compounds **23** and **24**); also the replacement of the furan ring of the model **17** with the pyridine nucleus, endowed with basic character, proved to be acceptable (compound **25**). Finally, the good activity displayed by **26** allows us to hypothesize the presence in the enzymatic protein of a little lipophilic pocket near the site interacting with portion Z of the ligand.

Then, with the aim of defining the role played by new template **17** in the reversible and selective MAO-A and MAO-B inhibition of preferential peripheral character, its most hydrophilic derivatives, compounds **21** and **22** (ClogP − 0.42 and −0.04, respectively) were selected for an in-depth study. In this study, was also included compound **25** that, even if it showed a more lipophilic character than **21** and **22** (ClogP 1.28), allowed us to evaluate the effects induced by additional interactions between basic pyridine nitrogen of the spacer (portion Y) and enzymatic protein.

Their MAO inhibition properties were measured in HEK-transfected cell extracts expressing selectively MAO-A (HEK-MAO-A) or MAO-B (HEK-MAO-B) (Figure 1A) and were further confirmed on homogenate preparations from rat liver using [^{14}C]5-hydroxytryptamine ([^{14}C]5-HT) and [^{14}C]phenylethylamine ([^{14}C]PEA) as substrates for MAO-A and MAO-B, respectively (Figure 1B). The results in Figure 1A show that compounds **21**, **22**, and **25** reduced [^{14}C]tyramine oxidation obtained on HEK-MAO-A significantly. Conversely, [^{14}C]-tyramine oxidation obtained on HEK-MAO-B was poorly affected in the presence of these compounds. In liver membranes, the IC_{50} of **21**, **22**, and **25** for inhibition of [^{14}C]5-HT oxidation was 0.6 ± 0.15 μM, 1.2 ± 1.1 μM, and 1.8 ± 1.6 μM, respectively (Figure 1B). Studies on inhibition of liver homogenate [^{14}C]PEA oxidation were performed in the presence of 0.1 μM of clorgyline to prevent the metabolism of PEA by MAO-A as previously reported in rat mesangial cells or rat heart.[40,41] As shown in Figure 1B, compounds **21**, **22**, and **25** poorly inhibited [^{14}C]PEA oxidation at concentrations up to 10 μM. These results show that compounds **21**, **22**, and **25** display MAO-A selectivity in vitro.

Next we evaluated whether compounds **21**, **22**, and **25** behaved as reversible or irreversible inhibitors. This is a crucial point in view of their potential clinical development, as it is well-known that irreversible MAOIs have severe side effects (i.e. the "cheese effect") that preclude their use in therapy. In attempting this, we incubated liver homogenates with 10 μM of compounds **21**, **22** or **25** for 20 min and then we washed the homogenates by sequential dilution and centrifugation. After 20 min incubation with compounds **21**, **22** or **25**, [^{14}C]5-HT oxidation was reduced by 85%, 79%, and 53%, respectively, as compared to untreated membranes. After membrane washing,



	IC50 µM		
	21	**22**	**25**
MAO-A	0.6 +/- 0.15	1.2 +/- 1.1	1.8 +/-1.6
MAO-B	19.1 +/- 8	ND	ND

Figure 1. Inhibitory properties of compounds **21**, **22**, and **25** toward MAO-A and MAO-B. Effect of two concentrations of compounds, 0.1 μM, 10 μM, on measured MAO-A or MAO-B activity in stably transfected HEK cells expressing MAO-A or MAO-B cDNA (A). Deamination of 200 μM 5-HT (MAO-A) or 20 μM PEA (MAO-B) by the rat liver homogenates was determined in the presence of increasing concentrations of compounds **21** (squares), **22** (circles), and **25** (triangles). Symbols represent the means of three experiments per group, and vertical lines show SEM. ND: not determined (less than 50% inhibition). The table of IC_{50} values determined using GraphPad PRISM software (B). *** $P < 0.001$, ** $P < 0.01$, between MAO activity in vehicle and inhibitor-treated HEK cells homogenates.

about 80% of the enzyme activity was recovered for each condition, indicating that MAO-A inhibition by these three compounds (**21**, **22**, and **25**) was reversible (Figure 2).

To define the ability of **21**, **22**, and **25** to inhibit MAOs in vivo, we treated rats with three intraperitoneal injections (50 mg/kg) of compounds, and we measured residual MAO-A and MAO-B activities present in a homogenate preparation from liver and brain. As expected from in vitro studies, rat treatment with **21** and **22** did not considerably modify MAO-B activity in brain and liver homogenates (Figure 3). In contrast, compound **25**, which did not significantly inhibit [^{14}C]PEA degradation in vitro, decreased brain MAO-B after rat treatment. This indicates that compound **25**, displaying higher lipophilicity than **21** and **22**, not only crosses the blood−brain barrier (as also demonstrated by the brain MAO-A inhibition, Figure 3) but also metabolic modification occurring in vivo may confer to this compound the ability to interact with MAO-B. On the basis of these observations, compound **25** is not suitable to specifically target peripheral MAO-A in vivo. In contrast, administration of **21** significantly decreased MAO-A activity in liver (36%). Interestingly, we did not observe any significant MAO-A inhibition in brain homogenates, indicating that, at the dose used for rat treatment, **21** prevalently inhibits liver MAO-A. Similar results were obtained using **22** although the MAO-A inhibition in liver was less relevant than that found using **21**.

Therefore, our results in vitro and in vivo, interestingly highlighted that compounds bearing the typical structure of furaline (**17**) and with appropriate physicochemical properties, such as the promising amino derivative **21** (Amifuraline), could target prevalently peripheral MAO-A. This peculiarity could be extremely interesting in pathological situations in which it is suitable to selectively inhibit peripheral MAO-A and avoid central side effects. For example, this could be the case of the post-ischemia-reperfusion syndromes responsible for organ failure (liver, kidney, and heart) occurring after transplantation, angioplasty, or hypovolemic shock. Indeed, we showed that cardiac and renal damage after reperfusion was greatly prevented by animal pretreatment with MAO inhibitors. It is conceivable that the use of selective peripheral MAO-A inhibitors could be expanded to other peripheral pathologies in which this enzyme may be involved.

In conclusion, our study opens new perspectives for the design of a novel subclass of MAO-A inhibitors, with more selective peripheral effects and less centrally evoked side effects.

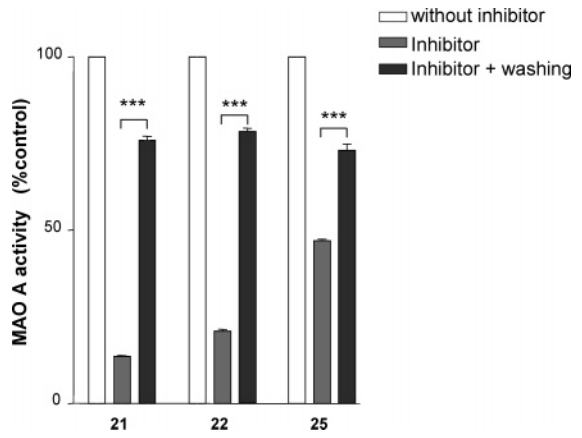


Figure 2. Reversible effect of compounds **21**, **22**, and **25** on MAO activity inhibition. MAO-A activity recovered in liver homogenate following incubation with 10 μM of compound **21**, **22**, or **25** before and after washing. Vehicle-treated homogenate was submitted to the same washing protocol and used as control for MAO-A activity recovered in compounds treated liver homogenate after washing. Activity measured in the presence of 10 μM compounds was compared to unwashed vehicle-treated homogenates. Values are from duplicate experiments and are presented as percentage of vehicle-treated liver homogenates. *** $P < 0.001$ between % of MAO activity remaining in inhibitor-treated homogenates before and after washing.

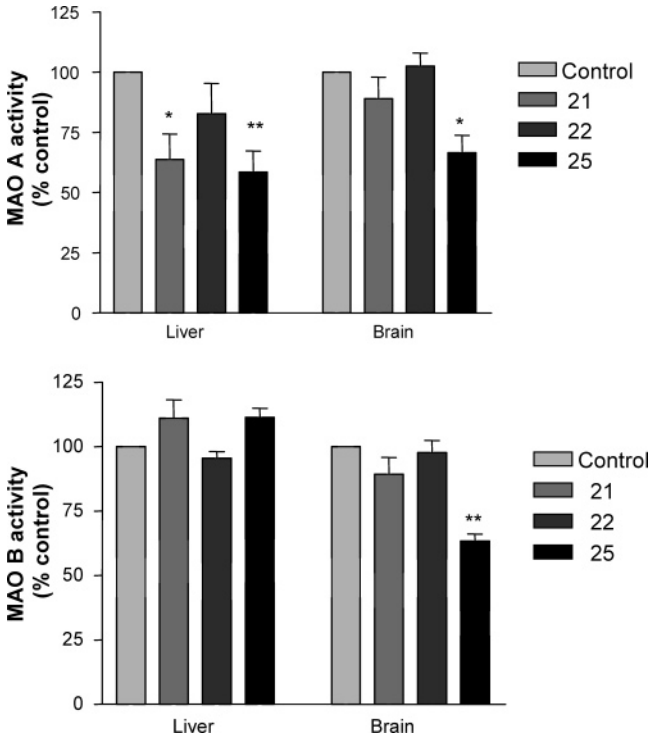


Figure 3. MAO activity on liver and brain homogenate preparation from rats treated, as reported in experimental protocol, with compounds **21**, **22**, and **25**. MAO-A was measured with 200 μM [^{14}C] 5HT and MAO-B with 20 μM [^{14}C] PEA in the presence of 0.1 μM clorgyline. An asterisk indicates groups that differed significantly from vehicle-treated animals: *$P < 0.05$, **$P < 0.01$.

Experimental Protocols

Chemistry. Melting points were taken in glass capillary tubes in a Büchi SMP-20 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian EM-390 instruments, respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). IR spectral data (not shown because of the lack of unusual features) were obtained for all compounds reported and are consistent with the assigned structures. The microanalyses were performed by the Microanalytical Laboratory of our department. The elemental composition of the compounds agreed to within ±0.4% of the calculated value. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040−0.063 mm, Merck) by flash chromatography. The term "dried" refers to the use of anhydrous sodium sulfate. Compounds were named following the IUPAC rules proposed by Beilstein-Institut AutoNom (version 2.1), a software for systematic names in organic chemistry.

Pyridine-2-carboxylic Acid (4,5-Dihydro-1*H*-imidazol-2-yl-methyl)-amide (9). To a solution of [(pyridine-2-carbonyl)-amino]-acetic acid methyl ester[42] (1.79 g, 9.22 mmol) in absolute EtOH (9 mL) was added a solution of ethylenediamine (6.21 mL, 92.2 mmol) in EtOH dry (9 mL). The mixture was refluxed for 4 h. The evaporation of the solvent gave pyridine-2-carboxylic acid [(2-amino-ethylcarbamoyl)-methyl]-amide (1.5 g, 73% yield) that, dissolved in xylene (30 mL), was refluxed with vigorous stirring and water removal for 25 h. Evaporation of the solvent gave a residue which was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (2:5:1:0.1) as eluent. The free base (0.5 g, 36% yield) was transformed into the oxalate salt, which was recrystallized from MeOH, mp 192.5−193.5 °C. ^{1}H NMR (DMSO) δ 3.82 (s, 4, NCH_2CH_2N), 4.38 (d, 2, CH_2), 7.18−8.23 (m, 4, ArH), 9.42 (t, 1, CONH, exchangeable with D_2O) 10.13 (s br, 1, NH, exchangeable with D_2O). Anal. ($C_{10}H_{12}N_4O\cdot H_2C_2O_4$) C, H, N.

2-((*E*)-3-Phenyl-allyl)-4,5-dihydro-1*H*-imidazole (11). A solution of ethylenediamine (0.505 mL, 7.5 mmol) in dry toluene (2.6 mL) was added dropwise to a mechanically stirred solution of 2 M trimethylaluminum (3.76 mL, 7.52 mmol) in dry toluene (6.3 mL) at 0 °C in nitrogen atmosphere. After being stirred at room temperature for 1 h, the solution was cooled to 0 °C and a solution of (*E*)-4-phenyl-but-3-enoic acid methyl ester[43] (0.70 g; 3.78 mmol) in dry toluene (5 mL) was added dropwise. The reaction mixture was heated to 110 °C for 8 h, cooled to 0 °C, and quenched cautiously with MeOH (1.8 mL) followed by H_2O (0.4 mL). After addition of $CHCl_3$ (14 mL), the mixture was left for 30 min at room temperature to ensure the precipitation of the aluminum salts. The mixture was filtered, and the organic layer was evaporated. The residue was purified by flash chromatography using cyclohexane/$CHCl_3$/MeOH/33% NH_4OH (8:8:2.5:2.5) as eluent (0.1 g, 13% yield) and then transformed into the oxalate salt which was recrystallized from EtOH/Et_2O, mp 151−152 °C. ^{1}H NMR (DMSO) δ 3.48 (d, 2, CH_2), 3.85 (s, 4, NCH_2CH_2N), 6.36 (dd, 1, CH_2CH), 6.68 (d, 1, CH), 7.28−7.51 (m, 5, ArH), 9.15 (br, 1, NH, exchangeable with D_2O). Anal. ($C_{12}H_{14}N_2\cdot H_2C_2O_4$) C, H, N.

6-(4,5-Dihydro-1*H*-imidazol-2-yl)-quinoline (14). It was prepared from quinoline-6-carboxylic acid methyl ester[44] via the procedure described for **11**. The free base (45% yield) was transformed into the oxalate salt which was recrystallized from MeOH−EtOH (3:7), mp 228.5−229 °C. ^{1}H NMR (D_2O) δ 4.06 (s, 4, NCH_2CH_2N), 7.68−8.99 (m, 6, ArH). Anal. ($C_{12}H_{11}N_3\cdot H_2C_2O_4$) C, H, N.

***cis*-2-(3-Phenyl-oxiranyl)-4,5-dihydro-1*H*-imidazole (15).** A mixture of *cis*-3-phenyl-oxirane-2-carbonitrile[45] (0.44 g, 3.0 mmol), sodium methoxide (0.014 g, 0.26 mmol), and MeOH (2 mL) was stirred for 4 h. On cooling to 0−10 °C, a solution of ethylenediamine (0.22 mL, 3.36 mmol) in MeOH (1 mL) was added dropwise with stirring; after a few minutes a solution of HCl in MeOH (1.043 mL of 3 N solution, 3.13 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 48 h, the solvent was evaporated and the residue was taken up in AcOEt. The organic solution was washed with H_2O, dried over Na_2SO_4, and evaporated to give a residue that was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (7:4:1:0.1) as eluent (0.2 g, 36% yield), mp 105−106 °C. ^{1}H NMR ($CDCl_3$) δ 3.37 (m, 4, NCH_2CH_2N), 4.03 (d, 1, CH), 4.30 (d, 1, ArCH), 7.31−7.42 (m, 5, ArH), 4.38 (s, 1, NH, exchangeable with D_2O). Anal. ($C_{11}H_{12}N_2O$) C, H, N.

***trans*-2-(3-Phenyl-oxiranyl)-4,5-dihydro-1*H*-imidazole (16).** It was prepared from *trans*-3-phenyl-oxirane-2-carbonitrile[46] via the procedure described for **15**. The free base was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (7:4:1:0.1) as eluent. The free base (42% yield) was transformed into the oxalate salt, which was recrystallized from 2-PrOH/Et_2O, mp 139−140 °C. ^1H NMR (DMSO) δ 3.87 (s, 4, NCH_2CH_2N), 4.26 (d, 1, CH), 4.42 (d, 1, ArCH), 7.38−7.52 (m, 5, ArH), 8.48 (s, 1, NH, exchangeable with D_2O). Anal. ($C_{11}H_{12}N_2O\cdot H_2C_2O_4$) C, H, N.

2-(5-Phenyl-furan-2-yl)-4,5-dihydro-1*H*-imidazole (Furaline) (17). HCl was bubbled through a stirred and cooled (0 °C) solution of 5-phenyl-furan-2-carbonitrile[47] (0.71 g, 4.14 mmol) and MeOH (0.35 mL, 8.29 mmol) in dry $CHCl_3$ (7 mL) for 45 min. After 12 h at 0 °C, dry ether was added to the reaction mixture to give the intermediate imidate, which was filtered (0.76 g; 77.8% yield). This solid (0.76 g, 3.22 mmol) was added to a cooled (0 °C) and stirred solution of ethylenediamine (0.26 mL, 3.99 mmol) in absolute EtOH (15.5 mL). After 1 h, concentrated HCl (a few drops) in abs EtOH (7 mL) was added to the reaction mixture, which was stored overnight in the refrigerator. It was then diluted with abs EtOH (13 mL) and heated at 75 °C for 5 h. After cooling, the solid was collected and discarded and the filtrate was concentrated and filtered again. The filtrate was evaporated to dryness to give a residue that was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (7:3:1:0.1) as eluent. The free base (0.57 g; 65% yield) was then transformed into the oxalate salt which was recrystallized from MeOH, mp 179−180 °C. ^1H NMR (DMSO) δ 4.00 (s, 4, NCH_2CH_2N), 7.37 (d, 1, J = 3.5 Hz, PhCCHC*H*), 7.78 (d, 1, J = 3.5 Hz, PhCC*H*), 7.49−8.04 (m, 5, ArH), 4.58 (br, 1, NH) exchangeable with D_2O). Anal. ($C_{13}H_{12}N_2O\cdot H_2C_2O_4$) C, H, N.

2-[5-(3-Nitro-phenyl)-furan-2-yl]-4,5-dihydro-1*H*-imidazole (20). It was prepared from 5-(3-nitro-phenyl)-furan-2-carboxylic acid methyl ester[48] via the procedure described for **11**. The free base (40% yield) was transformed into the oxalate salt which was recrystallized from H_2O, mp 249−249.5 °C. ^1H NMR (DMSO) δ 3.35 (s, 4, NCH_2CH_2N), 7.08 (d, 1, J = 3.5 Hz, PhCCHC*H*), 7.38 (d, 1, J = 3.5 Hz, PhCC*H*), 7.74−8.60 (m, 4, ArH), 7.13 (br, 1, NH, exchangeable with D_2O). Anal. ($C_{13}H_{11}N_3O_3\cdot H_2C_2O_4$) C, H, N.

3-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-furan-2-yl]-phenylamine (21). Imidazoline **20** (1 g, 3.89 mmol) was hydrogenated in MeOH for 12 h at room temperature under pressure (40 psi) using 10% Pd on charcoal as catalyst. Following catalyst removal, the evaporation of the solvent gave a residue that was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (4:6:1:0.1) as eluent. The free base (0.35 g, 40% yield) was transformed into the oxalate salt which was recrystallized from EtOH/Et_2O, mp 178.6−179.8 °C. ^1H NMR (DMSO) δ 4.00 (s, 4, NCH_2CH_2N) 4.48 (s br, 2, NH_2, exchangeable with D_2O) 6.67 (d, 1, J = 3.5 Hz, PhCCHC*H*), 7.13 (d, 1, J = 3.5 Hz, PhCC*H*), 7.09−7.72 (m, 4, ArH), 10.68 (br, 1, NH, exchangeable with D_2O). Anal. ($C_{13}H_{13}N_3O\cdot 1.5H_2C_2O_4$) C, H, N.

{4-[5-(4,5-Dihydro-1*H*-imidazol-2-yl)-furan-2-yl]-phenyl}-methanol (22). It was prepared from **29** via the procedure described for **17**. The free base was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (5:4:1:0.1) as eluent (67% yield) and transformed into the oxalate salt which was recrystallized from 2-PrOH, mp 219.5−220 °C. ^1H NMR (DMSO) δ 3.77 (s, 4, NCH_2CH_2N), 4.71 (s, 2, CH_2), 6.72 (d, 1, J = 3.5 Hz PhCCHC*H*), 7.03 (d, 1, J = 3.5 Hz, PhCC*H*), 7.38−7.67 (2 d, 4, ArH), 9.58 (s, 1, OH, exchangeable with D_2O), 10.35 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{14}H_{14}N_2O_2\cdot H_2C_2O_4$) C, H, N.

2-(5-Phenyl-thiophen-2-yl)-4,5-dihydro-1*H*-imidazole (23). It was prepared from 5-phenyl-thiophene-2-carbonitrile[49] via the procedure described for **17**. The free base was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (3:5:1:0.1) as eluent (65% yield) and transformed into the oxalate salt which was recrystallized from MeOH, mp 223−223.5 °C. ^1H NMR (DMSO) δ 3.97 (s, 4, NCH_2CH_2N), 7.48−7.76 (m, 5, ArH), 7.75 (d, 1, J = 4 Hz, PhCCHC*H*), 8.05 (d, 1, J = 4 Hz, PhCC*H*), 4.98 (br, 1, NH, exchangeable with D_2O). Anal. ($C_{13}H_{12}N_2S\cdot H_2C_2O_4$) C, H, N.

2-(5-Phenyl-1*H*-pyrrol-2-yl)-4,5-dihydro-1*H*-imidazole (24). It was prepared from 5-phenyl-1*H*-pyrrole-2-carboxylic acid methyl ester[50] via the procedure described for **11**. The free base was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (4:6:1:0.1) as eluent (35% yield) and then transformed into the oxalate salt which was recrystallized from MeOH/Et_2O, mp 220.8−222°C. ^1H NMR (DMSO) δ 3.95 (s, 4, NCH_2CH_2N), 6.82 (d, 1, J = 3.82 Hz, PhCCHC*H*), 7.31 (d, 1, J = 3.82 Hz, PhCC*H*), 7.39−7.92 (m, 5, ArH), 10.38 (br, 1, $NHCH_2$, exchangeable with D_2O), 12.88 (s br, 1, NH, exchangeable with D_2O). Anal. ($C_{13}H_{13}N_3\cdot 2H_2C_2O_4$) C, H, N.

5-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-phenyl-pyridine (25). A mixture of 2-aminoethylammonium toluene-*p*-sulfonate (6.79 g, 27.6 mmol) and 6-phenyl-nicotinonitrile[45] (0.5 g, 2.76 mmol) was heated at 200 °C for 2 h. After cooling and addition of MeOH, the solvent was evaporated to give a residue that was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (6:4:1:0.1) as eluent. The free base (0.25 g, 42% yield) was transformed into the oxalate salt which was recrystallized from EtOH, mp 236.5−236.6 °C. ^1H NMR (DMSO) δ 4.05 (s, 4, NCH_2-CH_2N), 7.52 (m, 8, ArH), 10.35 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{14}H_{13}N_3\cdot H_2C_2O_4$) C, H, N.

4-Methyl-2-(5-phenyl-furan-2-yl)-4,5-dihydro-1*H*-imidazole (26). It was prepared from 5-phenyl-furan-2-carbonitrile[47] and 1,2-diaminopropane via the procedure described for **17**. The free base (57% yield) was then transformed into the oxalate salt which was recrystallized from EtOH/Et_2O, mp 223.8−224 °C. 1H NMR (DMSO) δ 1.39 (d, 3, CH_3), 3.55 (dd, 1, NCH), 4.04−4.43 (m, 2, NCH_2), 7.33 (d, 1, J = 3.5 Hz PhCCHC*H*), 7.72 (d, 1, J = 3.5 Hz, PhCC*H*) 7.45−7.95 (m, 5, ArH), 10.55 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{14}H_{14}N_2O\cdot H_2C_2O_4$) C, H, N.

[2-(5-Phenyl-furan-2-yl)-4,5-dihydro-1*H*-imidazol-4-yl]-methanol (27). A mixture of **30** (0.38 g; 1.41 mmol) and $NaBH_4$ (0.059 g; 1.55 mmol) in dry EtOH (10 mL) was stirred at room temperature for 1 h under nitrogen atmosphere. The solvent was evaporated, and the residue was purified by flash chromatography using cyclohexane/$CHCl_3$/MeOH/33% NH_4OH (4:5:1:0.1) as eluent. The free base (0.3 g, 86% yield) was transformed into the oxalate salt which was recrystallized from MeOH/Et_2O, mp 216−216.5 °C. ^1H NMR (DMSO) δ 3.51−4.11 (m, 4, NCH_2, CH_2OH), 4.42 (m, 1, CH), 4.80 (s, 1, OH, exchangeable with D_2O), 7.34 (d, 1, J = 3.5 Hz PhCCHC*H*), 7.79 (d, 1, J = 3.5 Hz, PhCC*H*), 7.48−8.03 (m, 5, ArH), 10.82 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{14}H_{14}N_2O_2\cdot H_2C_2O_4$) C, H, N.

5-(4,5-Dihydro-1*H*-imidazol-2-yl)-[2,3′]bipyridinyl (28). It was prepared from [2,3′]bipyridyl-5-carbonitrile[51] via the procedure described for **25**. The free base was purified by flash chromatography using $CHCl_3$/MeOH/33% NH_4OH (9:1:0.1) as eluent (65% yield) and transformed into the oxalate salt which was recrystallized from EtOH/Et_2O, mp 232.5−236 °C. ^1H NMR (DMSO) δ 4.05 (s, 4, NCH_2CH_2N), 7.58−9.38 (m, 7, ArH), 10.45 (br s, 1, NH, exchangeable with D_2O). Anal. ($C_{13}H_{12}N_4\cdot H_2C_2O_4$) C, H, N.

Acetic Acid 4-(5-Cyano-furan-2-yl)-benzyl Ester (29). 5-(4-Hydroxymethyl-phenyl)-furan-2-carbaldehyde[52] (2.5 g; 12.4 mmol), hydroxylamine hydrochloride (1.75 g; 25 mmol), and sodium acetate (2.05 g; 25 mmol) in a stirred mixture of ethanol (7 mL) and water (0.7 mL) were heated under reflux for 5 h and then poured into cold water and extracted with $CHCl_3$; the organic phase was washed with H_2O. Removal of dried solvent gave 5-(4-hydroxymethyl-phenyl)-furan-2-carbaldehyde oxime (2.53 g; 94% yield). ^1H NMR (DMSO) δ 4.52 (s, 2, CH_2), 4.50 (s, 1, OH), 7.11 (d, 1, J = 3.5 Hz PhCCHC*H*), 7.28 (d, 1, J = 3.5 Hz PhCC*H*), 7.42−7.75 (2 d, 4, ArH), 11.9 (s, 1, N−OH).

5-(4-Hydroxymethyl-phenyl)-furan-2-carbaldehyde oxime (2.53 g; 11.65 mmol) was stirred under reflux for 3 h in acetic anhydride (25 mL). The cooled solution was poured into ice water and extracted with $CHCl_3$; the organic phase was washed with H_2O. Removal of dried solvent gave a residue which was purified by

flash chromatography using cyclohexane/EtOAc (9:1) as eluent to give **29** (2.53 g; 90% yield). ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3, CH_3), 5.15 (s, 2, CH_2), 6.75 (d, 1, J = 3.5 Hz PhCCHC*H*), 7.18 (d, 1, J = 3.5 Hz PhCC*H*), 7.45−7.71 (2 d, 4, ArH).

2-(5-Phenyl-furan-2-yl)-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid Methyl Ester (30). It was prepared from 5-phenyl-furan-2-carbonitrile[47] and 2,3-diamino-propionic acid methyl ester via the procedure described for **17**. The free base was purified by flash chromatography using cyclohexane/AcOEt/MeOH/33% NH_4OH (6:4:1:0.1) as eluent (42% yield) and transformed into the oxalate salt which was recrystallized from EtOH, mp 208−210 °C. ^{1}H NMR (DMSO) δ 3.78 (s, 3, CH_3), 4.18 (m, 2, NCH_2), 5.15 (dd, 1, NCH), 7.35 (d, 1, J = 3.5 Hz PhCCHC*H*), 7.78 (d, 1, J = 3.5 Hz PhCC*H*), 7.47−8.03 (m, 5, ArH), 9.95 (br, s, 1, NH, exchangeable with D_2O). Anal. ($C_{15}H_{14}N_2O_3 \cdot H_2C_2O_4$) C, H, N.

Biological Experiments. Treatment of Animals. Experimental procedures were carried out in accordance with national law and the European Community guidelines for the use of experimental animals. Male Sprague Dawley rats, weighing approximately 250 g, were housed in groups under a controlled light/dark cycle and had free access to standard food and tap water. Compounds **21**, **22**, and **25** were dissolved in 64% DMSO/36% saline (0.9% NaCl) or 100% saline or 30% DMSO/70% saline respectively at 10 mg/mL. Rats received three intraperitoneal injections of compounds at 50 mg/kg or vehicle, 20 h, 4 h 30 min, and 1 h 30 min before sacrifice. Four animals were treated in each group except for the control group where three rats were treated for each vehicle. Liver and brain were rapidly removed, briefly rinsed in cool phosphate buffer, and stocked at −80 °C before MAO activity analysis.

MAO Activity. Rat liver tissues or HEK stably transfected with MAO-A (HEK-A) or MAO-B (HEK-B)[11] were homogenized in a Dounce homogenizer (pestel A) in sodium phosphate buffer (50 mM, pH 7.5) supplemented with protease inhibitors (0.1 mM phenylmethylsulfonyl fluoride, 10 μg/mL bacitracin, 2 μg/mL soybean trypsin inhibitor, (Sigma Chemical, St. Louis, MO). Tissues were filtered through two layers of cheesecloth mesh to remove non homogenized parts. Crude extracts of proteins (10−20 μg) were incubated at 37 °C for 20 min, in sodium phosphate buffer with 200 μM of [^{14}C]serotonin, 20 μM of [^{14}C]β-phenylethylamine, or 200 μM of [^{14}C]tyramine (NEN Life Science Products, Boston, MA). The reaction was ended by the addition of 0.1 mL of HCl, 4 N at 4°C. The reaction product was extracted (efficiency 92%) with 1 mL of ethyl acetate/toluene (v/v), and the radioactivity contained in the organic phase was counted in a liquid scintillation spectrometer at 97% efficiency. Proteins were measured according to Lowry's method (Biorad) using bovine γ-globulin as standard. Activity in the presence of a compound was expressed as a percentage of that of the control. Assays were performed in triplicate. Sigmoid curves of MAO inhibition and IC_{50} values were carried out using GraphPad "Prism" software.

Reversibility of MAO Inhibition. Liver homogenate preparations, containing MAO-A and MAO B (0.5 mg/mL), in 50 mM phosphate buffer (pH 7.4) were incubated at 37 °C for 20 min with 10 μM of compound or vehicle. A half of each reaction mixture was used to measure MAO-A activity. The other half was centrifuged (40 000 *g*) for 20 min at 4 °C to pellet membrane proteins, washed with 50 mM phosphate buffer (pH 7.4), centrifuged, and resuspended in 50 mM phosphate buffer (pH 7.4) Then, an aliquot was used to measure MAO-A activity using 200 μM of [^{14}C]serotonin as substrate. Protein content was determined in each preparation after centrifugation. The enzymatic activities obtained were compared with their appropriate controls incubated with vehicle and submitted or not to the same washing protocol.

Statistical Analysis. All data are reported as mean ± SEM for each group. The significance of differences among different treatment groups was calculated using the one-way ANOVA analysis followed by Tukey test. The data are presented as a percentage of control, as specified in the individual figures.

Acknowledgment. We would like to thank SERVIER and the University of Camerino for financial support.

Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM060605R