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Design and Synthesis of Novel and Potent Monoamine Oxidase Inhibitors

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Abstract. Reversible and selective monoamine oxidase-A inhibitors (RIMA's) like moclobemide (*Aurorix®*) have rehabilitated the use of MAO inhibitors as drugs of choice in depression. Starting from the structure of moclobemide, we tried to identify novel types of MAO inhibitors by bioisosteric replacement of the amide group. 2-Aminomethyl-5-phenylpyrroles retained some *in vitro* activity and served as a starting point for the construction of restricted rotation analogues. 3,4-Dihydro-6-phenylpyrrolo[1,2-*a*]pyrazines were the most interesting members of a family of 6-, 7-, and 8-phenyl-substituted pyrrolo[1,2-*a*]pyrazines and were subsequently optimized. A 'lipophilic linker' between phenyl and pyrrole ring proved exceedingly useful to improve affinity and led to the benzo[*g*]pyrazino[1,2-*a*]indole ring system. Synthetic procedures starting from substituted 1-tetralones allowed the synthesis of substituted derivatives of this ring system. Once the optimal substitution pattern had been identified, facile synthesis of derivatives was achieved from aromatic triflates by *Stille* or *Suzuki* coupling. In this series selective and reversible monoamine oxidase-A inhibitors as well as mixed MAO-A and B inhibitors were identified. Affinity of this compounds for MAO was in the nanomolar or even sub-nanomolar range (for monoamine oxidase-A). In conclusion, benzo[*g*]pyrazino[1,2-*a*]indoles have been identified as a new class of reversible and highly potent monoamine oxidase inhibitors.

1. Introduction

Early in the 1950's it was recognized that iproniazide which was then used as tuberculostatic is also an effective mood elevator [1]. Its antidepressant effect was subsequently attributed to the irreversible inhibition of monoamine oxidase (MAO, EC 1.4.3.4) [2]. Clinical use of iproniazide and other irreversible MAO inhibitors as antidepressants was, however, hampered by the innate toxicity of the hydrazides and rare but sometimes fatal hypertensive crisis following ingestion of tyramine-rich food. Tyramine is an indirect sympathomimetic and normally metabolized by MAO [3]. Progress halted until 1968 when it was shown that MAO consists of two isozymes, denoted MAO-A and MAO-B [4], and that inhibition of MAO-A suffices to exert an antidepressant effect in depressive patients [5]. Since tyramine is a substrate for both isoforms of MAO, reversible and selective MAO-A inhibitors (RIMA's) were expected to have a much better safety margin than the old irreversible inhibitors. The concept was successfully realized with moclobemide (*Aurorix®*, *Fig. 1*) [6].

This success prompted our continuing interest in new reversible MAO inhibitors with even higher potency and somewhat longer duration of action. Since modifications in the aromatic part of moclobemide's structure had been explored already [7], our focus was on rigidifying the side chain and replacement of the amide group by a suitable heterocycle.

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2. Results and Discussion

The observation that *o*-substituted moclobemide derivatives with the exception of the salicylamide derivatives have reduced potency as MAO-A inhibitors [8] suggested that the most relevant feature of the amide bond in moclobemide might be a planar transoid geometry. An analogous observation has been made with dopaminergic benzamides and led in this series to the successful replacement of the benzamide by a 2-phenylpyrrole substructure [9]. Accordingly we synthesized the 2-phenylpyrrole derivative **1** (*Scheme 1*) which contained a minimal set of structural features thought to be necessary for MAO inhibitors, and the compound showed *in vitro* MAO-A inhibition comparable to moclobemide. We tried to improve on this and chose as our strategy a further rigidification of the side chain.

Our first targets were 6-phenyl substituted pyrrolo[1,2-*a*]pyrazines **2**, **3**, and **4**. The synthesis (*Scheme 2*) utilized *Paal-Knorr* methodology for the construction of the 2-phenylpyrrole intermediate **5**, which was closed in analogy to known procedures [10] to the pyrrolo[1,2-*a*]pyrazines **2**, **3**, and **4**. Within this set of compounds the 6-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine **3** displayed the highest affinity for MAO-A (*Table 1*).

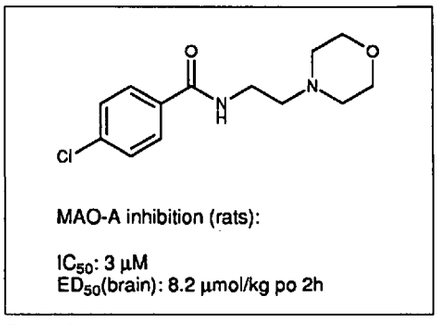
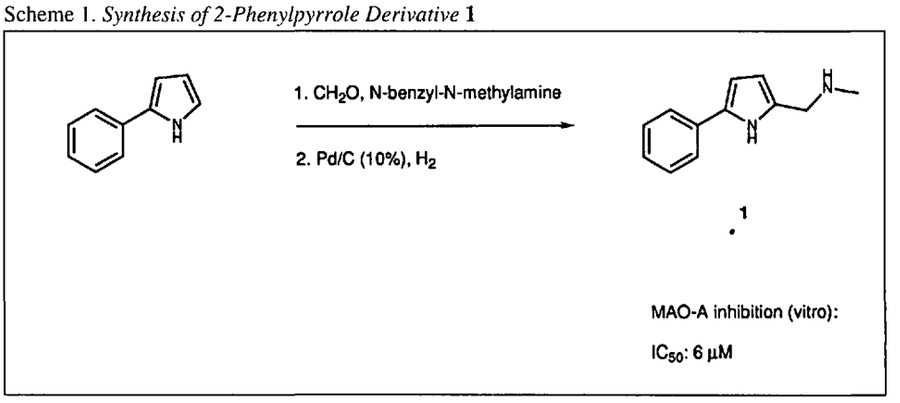
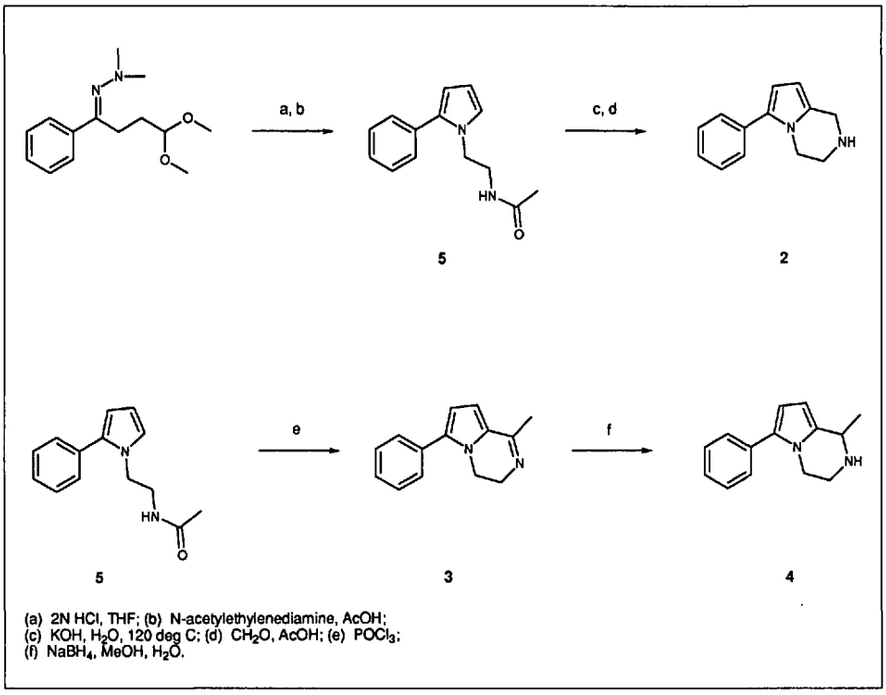


Fig. 1. *Structure and MAO-A inhibition of* Aurorix® (moclobemide)

Scheme 1. *Synthesis of 2-Phenylpyrrole Derivative* **1**



Scheme 2. *Synthesis of 6-Phenylpyrrolo[1,2-a]pyrazines* **2**, **3**, *and* **4**



Scheme 3. *Synthesis of the Regioisomeric Pyrrolo[1,2-a]pyrazines* **6** *and* **7**

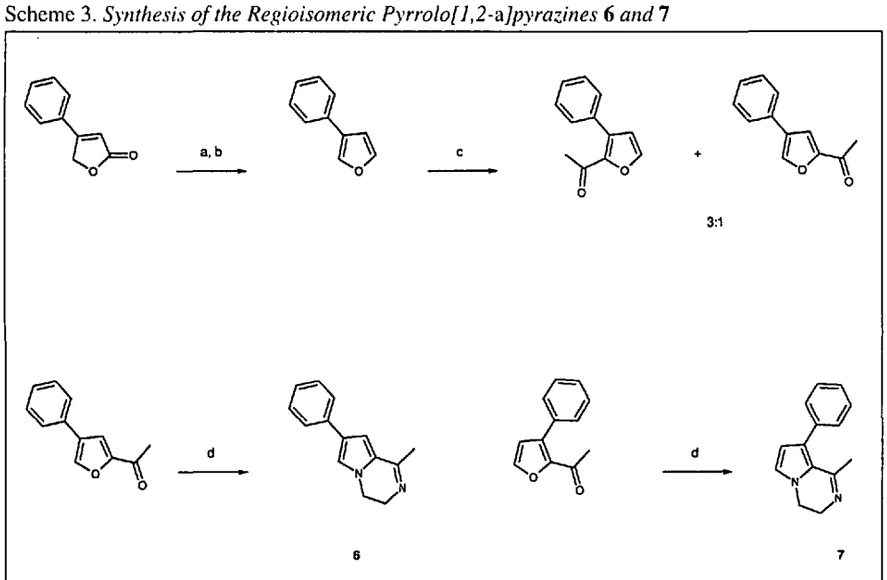


Table 1. *Potency of Pyrrolo[1,2-a]pyrazine-Type MAO Inhibitors* **2–3**, **6**, *and* **7**

No.	Preparation	IC_{50} MAO-A[a]) [nM]	IC_{50} MAO-B[a]) [nM]
2	[14]	1000	n.d.
3	[14]	300	n.d.
4	[14]	9000	n.d.
6	[14]	95	> 1000
7	[b])	inact	inact

[a]) MAO inhibition *in vitro* and *ex vivo* was assayed by standard methods [19].
[b]) *cf. Exper. Part.*

In studying the effect of the phenyl ring on the potency of 3,4-dihydropyrrolo[1,2-*a*]pyrazines as MAO inhibitors, the regioisomeric phenylpyrrolo[1,2-*a*]pyrazines as well as derivatives of **3** with substituents on the phenyl ring were synthesized.

Since 3,4-dihydropyrrolo[1,2-*a*]pyrazines can be made from 2-acetylfurans by simply heating with 1,2-diaminoethane and water [11], the regioisomeric pyrrolo[1,2-*a*]pyrazines **6** and **7** (*Scheme 3*) were synthesized from 3-phenylfuran as a common intermediate which in turn was made by DIBAL reduction followed by acidic workup from 4-phenyl-2(5*H*)-furanone. *Friedel-Crafts* acylation of 3-phenylfuran results preferentially in acylation in the 2-position. With acetyl *p*-tolylsulfonate as mild acylating agent, enough 5-acetyl-3-phenylfuran was obtained to proceed with the synthesis towards **6**.

Adapting a known synthesis of 2-arylpyrroles [12] (*Scheme 4*) we studied the effect of phenyl ring substituents on the potency of 6-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazines (*e.g.* **8–11**) as MAO-A inhibitors.

The 8-phenyl-substituted derivative **7** was inactive while the 7-phenyl-substituted derivative **6** was more potent as MAO-A inhibitor than the 6-phenyl derivative **3** (*Table 1*). The latter derivative (**3**) showed a significant increase in affinity with appropiate substitution (*Table 2*). The relative potency displayed by **3** compared to **8–11** led us to believe that electron-donating and lipophilic substituents, preferably in the *p*-position, might lead to a further increase in potency [13]. As exemplified by **12** and **13** this was the case; however, these bigger substituents in *p*-position led also to a loss of selectivity *vs.* MAO-B. This increase in affinity upon substitution with electron-donating groups might be due to transfer of electron density onto the imine nitrogen rendering it more basic. Consequently the effect of electron-donating substituents in the *o*-position on affinity and selectivity was explored. The dihedral angle between phenyl and pyrrolo[1,2-*a*]pyrazine ring will be distorted by *o*-substitution. This complicating factor may be overcome by formally incorporating the substituent into a ring connecting the *o*-position of the phenyl with the pyrrole ring. From a first set of tetracycles **14–16**, it was the benzo[*g*]pyrazino[1,2-*a*]indole **14** with the 'lipophilic linker' between phenyl and pyrrole ring that emerged as the most promising lead (*Fig. 2*). The cyclic ether **15** was less potent than expected from its electron-donating properties, and larger dihedral angles (*e.g.* **16**)

led to a loss in potency compared to the parent structure **3**.

In order to also investigate the effect of substituents at C(3) of the benzo[*g*]pyrazino[1,2-*a*]indoles on the potency of these compounds, the phenol **17** and the triflate **18** were synthesized as common precursors to facilitate the introduction of substituents (*Scheme 5*). 6-Methoxytetralone was heated with but-3-en-2-ol under acidic conditions giving in a *Claisen* rearrangement of the initially formed enol ether the corresponding but-2-enyl derivative. The latter was ozonized, deprotected to a 1,4-keto-aldehyde which yielded, after a *Paal-Knorr* cyclization with *N*-acetylethylenediamine, the intermediate **19**. Purification of the free phenol **17** proved quite difficult in the later steps of the sequence. To circumvent this, we cleaved the methyl ether with boron tribromide and reprotected as the *p*-nitro benzyl carbonate **20**. Ring closure to the corresponding benzo[*g*]pyrazino[1,2-*a*]indole was then achieved with phosphorus oxychloride under standard conditions. The phenol **17** crystallized from a methylene chloride solution of its precursor upon treatment with propylamine. *N*-Phenyltriflimide was then used as triflate source for the synthesis of **18** to avoid triflation on nitrogen and rearrangement of the imine to an enamine.

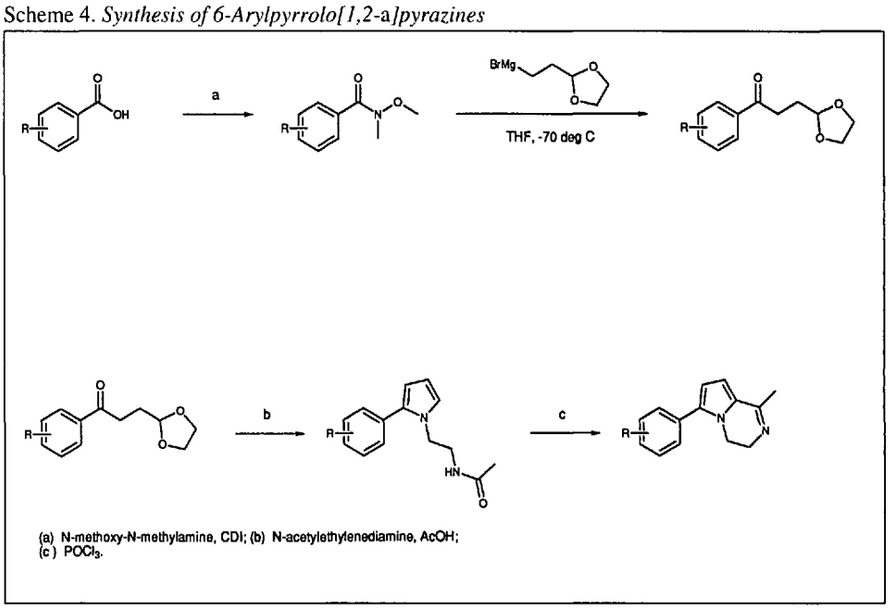
The phenol **17** served as precursor for phenol ethers (*e.g.* **21**) while the triflate **18** allowed the facile synthesis of phenyl derivatives like **22** *via Suzuki* coupling, cycloalkyl derivatives such as **23** and **24** *via Stille* coupling, and amides like **25** *via* carbonylative coupling (*Scheme 6*).

The benzo[*g*]pyrazino[1,2-*a*]indoles proved to be potent and reversible MAO inhibitors (*Table 3*). Most of them displayed remarkable selectivity for MAO-A and had, after *p. o.* administration in rats, a duration of action comparable or longer than moclobemide.

In conclusion, we have identified new potent and reversible MAO inhibitors starting with the structure of moclobemide. The design process started with bioisosteric replacement of the amide function by a pyrrole. From that point onwards classical methods of medicinal chemistry like reducing the conformational freedom of the flexible side chain and exploration of substituent effects led us on to benzo[g]pyrazino[1,2-*a*]indoles as novel, potent, and reversible inhibitors of monoamine oxidase.

The skillful assistance of *B. Frei, P. Vogel, P. Oberli, R. Mossière*, and *M. Häss* is gratefully acknowledged. The authors thank also Drs. *W. Arnold, St. Müller, W. Vetter*, and Mr. *W. Meister* for spectroscopic determinations and analysis.

Scheme 4. *Synthesis of 6-Arylpyrrolo[1,2-a]pyrazines*



Scheme 5. *Synthesis of the Intermediates* **17** *and* **18**

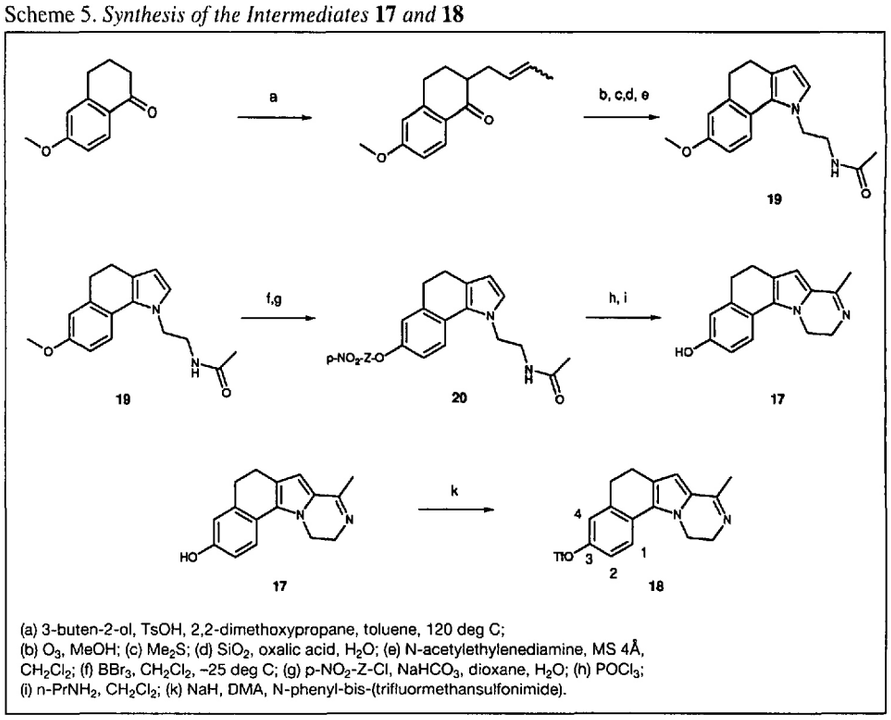
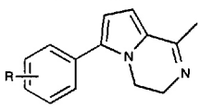


Table 2. *Effects of Substituents on the Phenyl Ring on the Potency of Pyrrolo[1,2-a]pyrazine-Type MAO Inhibitors* **3** *and* **8–13**



No.	R	Preparation	IC_{50} MAO-A[a]) [nM]	IC_{50} MAO-B[a]) [nM]
3	H	[14]	300	n.d.
8	4-OCH_3	[14]	50	> 1000
9	4-Cl	[14]	350	10000
10	4-CH_3	[14]	100	1000
11	3,4-Cl_2	[14]	> 1000	> 1000
12	4-(bicyclo[2.2.1]hept-2-yloxy)	[14]	16	3
13	4-cyclopentyloxy	[14]	10	< 1

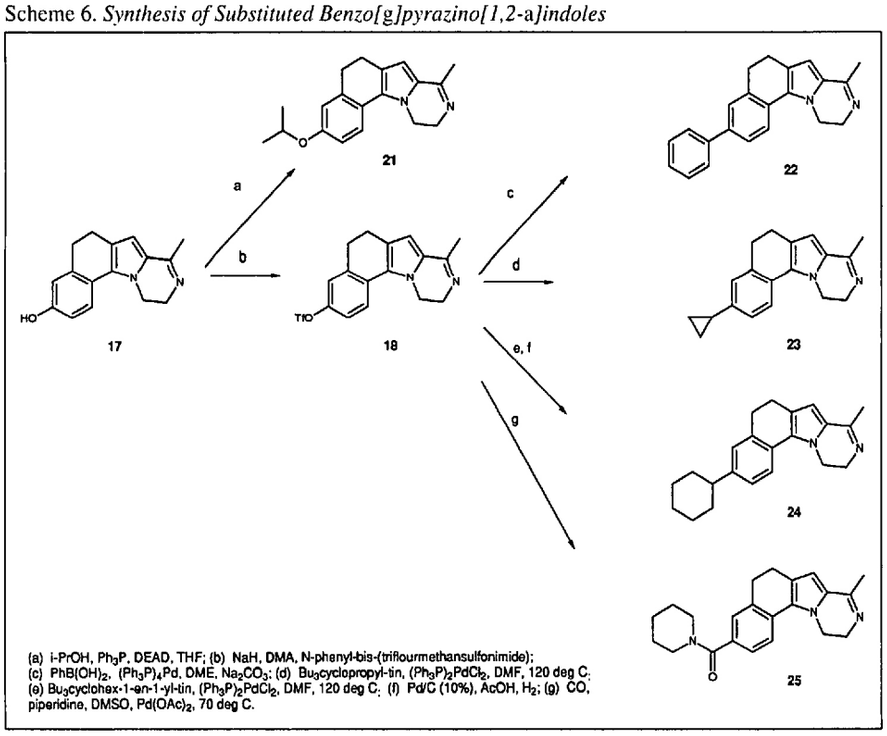
[a]) MAO inhibition *in vitro* and *ex vivo* was assayed by standard methods [19].

Table 3. *Benzo[g]pyrazino[1,2-a]indole-Type MAO Inhibitors* **14**, **17**, **18**, **21–24**

No.	Preparation	IC_{50} MAO-A[a]) [nM]	IC_{50} MAO-B[a]) [nM]	ED_{50} brain MAO-A[a]) [μmol/kg *p.o.*]	Duration of action [30 μmol/kg *p.o.*]
14	[14]	30	> 1000	> 100	n.d.
17	[14]	1000	> 1000	–	n.d.
18	[14]	160	200	100	n.d.
21	[14]	0.4	14	10	≤ 16 h
22	[14]	29	> 100	6	≤ 16 h
23	[14]	1	> 1000	8	≤ 16 h
24	[14]	1.5	160	10	≤ 16 h

[a]) MAO inhibition *in vitro* and *ex vivo* was assayed by standard methods [19]. *Ex vivo* tests were in male albino Fü-SPF rats.

Scheme 6. *Synthesis of Substituted Benzo[g]pyrazino[1,2-a]indoles*



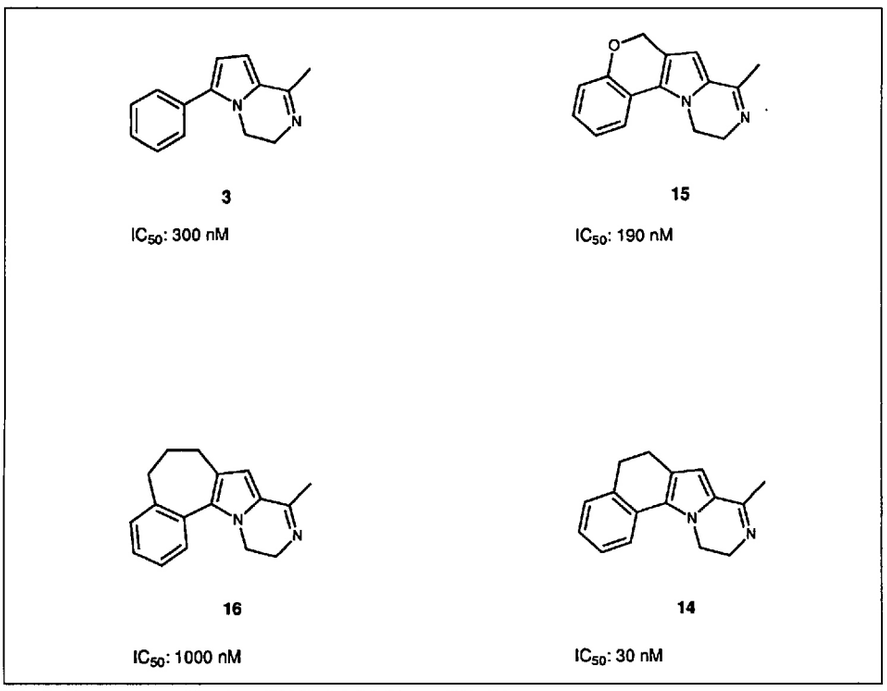


Fig. 2. *Structure and* in vitro *MAO-A inhibition of* **14–16**

3. Experimental

General. All reactions were performed under Ar. Drying of org. solns. was with $MgSO_4$, evaporation in a rotary evaporator at 40° *in vacuo* as appropriate. For chromatography, *Merck* silica gel *60* (size 70–230 mesh) was used. Thin-layer chromatography (TLC) was run on *Merck* silica gel *60 F-254* plates in CH_2Cl_2/CH_3OH/aq. NH_3 90:10:1. Starting materials were high-grade commercial products unless stated otherwise. Melting points (m.p.) are uncorrected. ^{1}H-NMR Spectra were recorded on a *Bruker-AC250* instrument in DMSO (unless noted otherwise). Chemical shifts (δ) are expressed in ppm relative to internal TMS; coupling constants (J) are in Hz. EI-MS Spectra (EI: 70 eV) were recorded on a *MS9* updated with a *VG-ZAB* console, *Finnigan* data system *SS300*, with direct sample introduction.

Methyl(5-phenyl-1H-pyrrol-2-ylmethyl)amine (**1**). To a soln. of *N*-benzyl-*N*-methylamine (6.9 ml, 0.054 mol) in EtOH (100 ml) was added aq. formaldehyde (37%; 4.1 ml, 0.053 mol). After 30 min of stirring at r.t. 2-phenylpyrrole [12] (5 g, 0.035 mol) was added and the soln. refluxed for 18 h. Evaporation of the solvent and chromatography (hexane/AcOEt 75:25) of the residue afforded crude *benzyl(methyl)(5-phenyl-1H-pyrrol-2-ylmethyl)amine* (5.1 g, 53%) as reddish oil. This was dissolved in EtOH (250 ml) and hydrogenated with Pd (10% on charcoal) as catalyst at normal pressure (10 h). TLC showed complete conversion to products. The solvent was evaporated and the residue purified by chromatography (CH_2Cl_2/CH_3OH 90:10) to afford crude **1** (1.6 g, 47%) which was characterized as its colorless fumarate salt (1:1 from EtOH): m.p. 154–156°. ^{1}H-NMR: 12.49 (br., 1 H); 11.5–10.5 (br., 3 H); 7.66 (*'d'*, J = 7.5, 2 H); 7.34 (*'t'*, J = 7.5, 2 H); 7.15 (*'t'*, J = 7.5, 1 H); 6.55 (*s*, 2 H, fumaric acid); 6.49 (*'t'*, J = 3, 1 H); 6.21 (*'t'*, J = 3, 1 H); 4.07 (*s*, 2 H); 2.50 (*s*, 3 H). EI-MS: 186 (35, M^+), 156 (100).

1-Methyl-8-phenyl-3,4-dihydropyrrolo[1,2-a]pyrazine (**7**). A soln. of 3-phenylfuran [15] (4.3 g, 0.03 mol) and acetyl *p*-tolylsulfonate [16] (8.6 g, 0.045 mol) in CH_3CN (80 ml) was stirred for 72 h. Et_2O (150 ml) was added, and acidic by-products were removed by washing with 10% $NaHCO_3$ soln. (150 ml). The ethereal soln. was dried and evaporated. Chromatography (hexane/CH_2Cl_2 50:50) of the residue afforded crude *1-(3-phenylfuran-2-yl)ethanone* (2.4 g, 43%) and the regioisomeric *1-(4-phenylfuran-2-yl)ethanone* (0.7 g, 12%) as reddish oils. A mixture of 1-(3-phenylfuran-2-yl)ethanone (1.0 g, 0.005 mol), ethylenediamine (1.1 ml, 0.016 mol), and H_2O was then refluxed for 1 h when TLC indicated complete conversion to products. H_2O was added (50 ml), and the mixture was extracted with AcOEt (3 x 50 ml). The org. layers were combined, dried, and evaporated. Chromatography of the residue (0.8 g, CH_2Cl_2/CH_3OH 95:5) afforded **7** (0.6 g, 52%) as a brownish oil. ^{1}H-NMR ($CDCl_3$): 7.35 (*m*, 5 H); 6.77 (*d*, J = 2.5, 1 H); 6.21 (*d*, J = 2.5, 1 H); 3.94 (*t*, J = 5.8, 2 H); 3.83 (*t*, J = 5.8, 2 H); 1.98 (*s*, 3H). EI-MS: 210 (100, M^+), 182 (24), 167 (22).

9-Methyl-6,7,11,12-tetrahydro-5H-benzo[6',7']cyclohepta[1',2':4,5]pyrrolo[1,2-a]pyra-

zine (**15**). A soln. of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene dimethylhydrazine [17] (34 g, 0.17 mol) and *N,N,N',N'*-tetramethylethylenediamine (30 ml, 0.20 mol) in THF (400 ml) was cooled to –70°. This temp. was maintained during the dropwise addition of BuLi (106 ml, 1.6M in hexane). After complete addition the soln. was allowed to warm to –30°, and bromoacetaldehyde dimethyl acetal (23 ml, 0.20 mol) was added. After 120 min of stirring at –30° and overnight at r.t. H_2O (500 ml) was added. The mixture was extracted with AcOEt (3 x 300 ml), the org. layers were combined and dried. Evaporation of the solvent and chromatography (hexane/AcOEt 75:25) afforded 37 g of crude *(RS)-N-[6-(2-dimethoxyethyl)-6,7,8,9-tetrahydro-5H-benzocyclohept-5-ylidene]-N',N'-dimethylhydrazine* (60%) as yellowish oil. This was then dissolved in a mixture of THF (2000 ml) and H_2O (500 ml). To the soln. were added sodium acetate (30 g, 0.37 mol) and sodium metaperiodate (82 g, 0.37 mol). The pH was adjusted to 5 with AcOH, and the mixture was stirred for 24 h at 50°. After addition of H_2O (3000 ml) and extraction with CH_2Cl_2 (1 x 3000 ml, 2 x 1000 ml) the org. layers were combined and dried. Evaporation of the solvent and chromatography of the residue (50 g) afforded crude *(RS)-6-(2-dimethoxyethyl)-6,7,8,9-tetrahydrobenzocyclohepten-5-one* (8.2 g, 20%) as a reddish oil. ^{1}H-NMR ($CDCl_3$): 7.7 (*d*, *J* = 8, 1 H); 7.25-7.05 (*m*, 3 H); 5.41 (*dd*, *J* = 2.2, *J* = 7.0, 1 H); 3.53 (*s*, 3 H); 3.49 (*s*, 3 H); 3.1 (*m*, 1 H); 2.85 (*m*, 2 H); 2.6 (*m*, 1 H); 2.4 (*m*, 2 H); 1.9 (*m*, 2 H); 1.6 (*m*, 1 H). EI-MS: 217 (8, [*M*-OCH_3)$^+$], 89 (54), 75 (100).

A homogenized mixture of oxalic acid (2.0 g), H_2O (18 ml), and silica gel (180 g, *Merck 60*, 70–230 mesh) in CH_2Cl_2 was filled into a chromatography column. *(RS)*-6-(2-Dimethoxyethyl)-6,7,8,9-tetrahydrobenzocyclohepten-5-one (8.2 g) was deprotected by chromatography (CH_2Cl_2) on this column. The eluate was evaporated and afforded crude *(RS)-(5-oxo-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)acetaldehyde* (6.2 g). To a soln. of *N*-acetylethylenediamine (3.3 g, 0.032 mol) in CH_2Cl_2 (50 ml) were added molecular sieves (50 g, 4 Å) and *(RS)*-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-yl)acetaldehyde (6.2 g, 0.03 mol). The suspension was refluxed for 16 h. The molecular sieves were removed by filtration over *Celite*®, and the filtrate was evaporated. The residue was purified by crystallization (hexane/AcOEt 2:1) and afforded *N-[2-(1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-b]pyrrol-1-yl)ethyl]acetamide* (4.0 g, 45%) as a colorless solid. M.p. 122–123°. ^{1}H-NMR ($CDCl_3$): 7.23 (*m*, 4 H); 6.67 (*d*, *J* = 2.5, 1 H); 6.12 (*d*, *J* = 2.5, 1 H); 5.23 (br., 1 H); 4.20 (*t*, *J* = 5.8, 2 H); 3.36 (*q*, *J* = 5.8, 2 H); 2.53 (*t*, *J* = 6.7, 2 H); 2.39 (*t*, *J* = 7.4, 2 H); 2.18 (*'quint.'*, *J* = 7, 2 H). EI-MS: 268 (100, *M*$^+$), 209 (37), 208 (36), 196 (65), 184 (23), 183 (52), 182 (47), 180 (25), 168 (54), 167 (32), 86 (36), 44 (27), 43 (25).

A soln. of *N*-[2-(1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*b*]pyrrol-1-yl)ethyl]acetamide (4.0 g, 0.015 mol) in phosphorus oxychloride (20 ml) was stirred for 30 min at r.t. TLC Analysis indicated complete conversion to products. The mixture was hydrolyzed with ice water (1500 g), made alkaline with conc. NaOH soln. (120 ml, 28%), and extracted with CH_2Cl_2 (3 x 200 ml). The org. layers were combined and dried. Evaporation afforded crude **15** (3.8 g, quant.) which was characterized as its colorless fumarate salt (1:1.5 from EtOH): m.p. 177–180°. ^{1}H-NMR: 13–10 (br., 3 H); 7.38 (*m*, 4 H); 6.93 (*s*, 1 H); 6.56 (*s*, 3 H); 4.14 (*t*, *J* = 6.4, 2 H); 3.80 (*t*, *J* = 6.4, 2 H); 2.51 (*t*, *J* = 5.6, 2 H); 2.40 (*m*, 5 H); 2.11 (*'quint.'*, *J* = 6, 2 H). EI-MS: 250 (100, *M*$^+$), 249 (60), 208 (22), 98 (24).

8-Methyl-10,11-dihydro-6H-[1]benzopyrano[3',4':4,5]pyrrolo[1,2-a]pyrazine (**16**). A soln. of 2,3-dihydro-3-(prop-2-enyl)-4*H*-1-benzopyran-4-one [18] (3.5 g, 0.018 mol) in CH_3OH (100 ml) was cooled to –70° and ozonized until the yellow soln. turned bluish (30 min, *ca.* 1.5 g of O_3/h). The soln. was purged with Ar. After addition of dimethylsulfide (2 ml) the soln. was allowed to reach r.t. overnight and the solvent evaporated. The residue was dissolved in CH_2Cl_2 (35 ml). To the soln. molecular sieves (40 g, 4 Å) and *N*-acetylethylenediamine (2.1 g, 0.020 mol) were added, and the soln. was refluxed for 2 d. The molecular sieves were removed by filtration over *Celite*®, and the filtrate was evaporated. The residue was purified by chromatography (AcOEt) and afforded N-*[2-(1,4-dihydro[1]benzopyrano[4,3-a]pyrrol-1-yl)ethyl]acetamide* (1.8 g, 39%) as a colorless solid. ^{1}H-NMR ($CDCl_3$): 7.37 (*d*, *J* = 8.2, 1 H); 7.04 (*'t'*, *J* = 8, 1 H); 6.97 (*m*, 2 H); 6.62 (*d*, *J* = 2.7, 1 H); 5.99 (*d*, *J* = 2.7, 1 H); 5.52 (br., 1 H); 5.17 (*s*, 2 H); 4.33 (*t*, *J* = 5.7, 2 H); 3.56 (*'q'*, *J* = 5.7, 2 H); 1.85 (*s*, 3 H). EI-MS: 256 (63, *M*$^+$), 171 (35), 170 (100), 86 (39), 44 (34), 43 (50).

A soln. of *N*-[2-(1,4-dihydro[1]benzopyrano[4,3-*a*]pyrrol-1-yl)ethyl]acetamide (1.8 g, 7.0 mmol) in phosphorus oxychloride (10 ml) was stirred for 2 h at r.t. TLC Analysis indicated complete conversion to products. The mixture was hydrolyzed with ice water (700 g), made alkaline with conc. NaOH soln. (65 ml, 28%), and extracted with CH_2Cl_2 (3 x 100 ml). The org. layers were combined and dried. Evaporation afforded crude **16** (1.6 g, 96%) which was characterized as its yellowish fumarate salt (1:1 from EtOH): m.p. 191–194°. ^{1}H-NMR: 11–9 (br., 2 H); 7.6 (*d*, *J* = 8, 1 H); 7.2 (*t*, *J* = 8, 1 H); 7.02 (*m*, 2 H); 6.66 (*s*, 1 H); 6.59 (*s*, 2 H); 5.16 (*s*, 2 H); 4.30 (*t*, *J* = 6, 2 H); 3.8 (*t*, *J* = 6, 2 H); 2.29 (*s*, 3H). EI-MS: 238 (88, *M*$^+$), 237 (100).

(8-Methyl-5,6,10,11-tetrahydrobenzo[g]pyrazino[1,2-a]indol-3-yl)(piperidin-1-yl)methanone (**25**). A mixture of trifluoromethanesulfonic acid 5,6,10,11-tetrahydro-8-methylbenzo[g]pyrazino[1,2-*a*]indol-3-yl ester [13] (1.0 g, 2.6 mmol), palladium(II) acetate (30 mg, 5 mol %), 1,3-bis(diphenylphosphino)propane (59 mg, 5 mol %), piperidine (5.5 ml), and DMSO (10 ml) in a 50-ml reaction vessel was pressurized with 10 bar CO and stirred for 17 h at 70°. TLC Analysis indicated complete conversion to products. The solvent was evaporated, the residue dissolved in AcOEt (100 ml) and extracted with 1N HCl (2 x 10 ml). The H_2O layers were combined, made alkaline with Na_2CO_3 and extracted with AcOEt (5 x 50 ml). The org. layers were combined and dried, and the solvent was evaporated. Chromatography of the residue (AcOEt/EtOH 2:1) afforded crude **25** (0.38 g, 42%) which was characterized as its fumarate salt (1:0.5 from EtOH/AcOEt): m.p. 177–180°. ^{1}H-NMR ($CDCl_3$): 7.37 (*m*, 3 H); 6.86 (*s*, 1 H); 6.75 (*s*, 1 H); 6.5–5.5 (br., 2 H); 4.41 (*t*, *J* = 7, 2 H); 4.05 (*t*, *J* = 7, 2 H); 3.7 (br., 2 H), 3.4 (br., 2 H); 2.95 (*t*, *J* = 7, 2 H); 2.70 (*t*, *J* = 7, 2 H); 2.54 (*s*, 3 H); 1.69 (br., 6 H). EI-MS: 347 (100, *M*$^+$), 346 (31), 263 (100), 235 (27), 45 (24).

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[1] J.B. O'Connor, K.S. Hawlett, R.R. Wagner, *Am. Rev. Tuberc.* **1953**, *68*, 270.

[2] a) E.A. Zeller, J. Barsky, J.R. Fouts, W.F. Kirchheimer, L.S. Van Orden, *Experientia* **1952**, *8*, 349; b) J. Delay, B. Laine, J.F. Buisson, *Ann. Med. Psychol.* **1952**, *2*, 689.

[3] B. Blackwell, E. Marley, J. Price, D. Taylor, *Br. J. Psychiatry* **1967**, *113*, 349.

[4] J.P. Johnston, *Biochem. Pharmacol.* **1968**, *17*, 1285.

[5] D.L. Murphy, S. Lipper, D. Pickar, D. Jimerson, R.M. Cohen, N.A. Garrick, I.S. Alterman, I.C. Campbell, 'Selective Inhibition of Monoamine Oxidase Type A: Clinical Antidepressant Effects and Metabolic Changes in Man', in 'Monoamine Oxidase Inhibitors – the State of the Art', Eds. M.B.H. Youdim and E.S. Paykel, J. Wiley, Chichester, 1981, p. 189.

[6] a) W. Burkard, P. Wyss, Ger. Offen. DE 2 706 179, 18 Aug. 1977, *F. Hoffmann-La Roche AG*; b) E. Moll, H. Neumann, W. Schmid-Burgk, M. Stabl, R. Amrein, *Clin. Neuropharmacol.* **1994**; *17 Suppl. 1*, S74

[7] a) R. Imhof, E. Kyburz, Ger. Offen. DE 3 530 046, 13 March 1986, *F. Hoffmann-La Roche AG*; b) W. Gassner, R. Imhof, E. Kyburz, Eur. Pat. Appl. EP 352 581, 31 Jan. 1990, *F. Hoffmann-La Roche AG*.

[8] R. Kettler, *F. Hoffmann-La Roche AG*, private communication.

[9] a) I. van Wijngaarden, C.G. Kruse, R. van Hes, J.A.M. van der Heyden, M.Th.M. Tulp, *J. Med. Chem.* **1987**, *30*, 2099; b) I. van Wijngaarden, C.G. Kruse, J.A.M. van der Heyden, M.Th.M. Tulp, *ibid.* **1988**, *31*, 1934

[10] I. Jivorsky, R. Baudy, *Synthesis* **1981**, 481.

[11] A.M. Likhosherstov, V.P. Peresada, V.G. Vinokurov, A.P. Skoldinov, *Zh. Org. Khim.* **1985**, *22*, 2610.

[12] C.G. Kruse, J.P. Bouw, R. van Hes, A. van de Kuilen, J.A.J. den Hartog, *Heterocycles* **1987**, *26*, 3141.

[13] J.G. Topliss, *J. Med. Chem.* **1977**, *20*, 463.

[14] S. Röver, Eur. Pat. Appl. EP 521 368, 7 Jan. 1993, *F. Hoffmann-La Roche AG*.

[15] A.H. Munoz, J. Tamariz, R. Jiminez, G. Garcia de la Mora, *J. Chem Res. Synop.* **1993**, 68.

[16] S.I. Pennanen, *Heterocycles* **1976**, *4*, 1021.

[17] J.P. Daub, J. Powell, B.L. Finkelstein, L. Bruce, A.D. Kleier, PCT Int. Appl. WO 93 14080, 22 Jul. 1993, *E. I. DuPont de Nemours & Co.*

[18] K.C. Santhosh, K.K. Balasubramanian, *Tetrahedron Lett.* **1991**, *32*, 7727.

[19] R.J. Wurtmann, J.A. Axelrod, *Biochem. Pharmacol.* **1963**, *12*, 1439.