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# Structure–affinity relationships of berbines or 5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizines at α-adrenoceptors

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**Summary** — The synthesis of some derivatives of tetrahydro-8*H*-dibenzo[*a,g*]quinolizines or berbines is described. A pharmacological study was carried out at $\alpha_1$ and $\alpha_2$-adrenoceptors using radioligand binding techniques. This study has shown that the aromatic ring A is responsible for the $\alpha_2$-affinity of berbines. Furthermore, the aromatic ring D is important for $\alpha_1$-affinity. However, in this case, it seems that the planarity of the molecule is a very important structural parameter for affinity. The role of the nitrogen atom is also discussed. A conformational analysis of the partial saturated berbines was established by a $^{13}C$ NMR study.

**Résumé — Relations structure–affinité vis-à-vis des récepteurs α-adrénergiques des berbines ou 5,6,13,13a-tétrahydro-8*H*-dibenzo[*a,g*]quinolizines.** *Ce travail décrit la synthèse de dérivés de la tétrahydro-8*H*-dibenzo[a,g]quinolizine ou berbine dans le but d'établir des relations structure–activité vis-à-vis des récepteurs $\alpha_1$ et $\alpha_2$-adrénergiques. Une étude pharmacologique a été effectuée à l'aide de la méthode des liaisons spécifiques. Ces études ont montré que le noyau aromatique A est responsable de l'affinité de ces composés pour les récepteurs $\alpha_2$-adrénergiques et que le noyau aromatique D est impliqué dans l'affinité pour les récepteurs $\alpha_1$-adrénergiques. Le rôle de l'atome d'azote est également discuté. De plus, une étude conformationnelle par RMN du $^{13}C$ de ces dérivés a été réalisée.*

**berbines / berbinanes / $\alpha_1/\alpha_2$-adrenoceptor selectivity / α-antagonists / structure–affinity relationships**

## Introduction

Dibenzo[*a,g*]quinolizines or berbines are a group of well-known agents acting on α-adrenoceptors [1]. Their 'adrenolytic' properties in anesthetized dogs were first described by Hamet [2] and their antihypertensive effects in man were reported soon after by Facquet *et al* [3].

Previous studies in our laboratory have shown that the affinities of the (+) and (–) enantiomers for $\alpha_1$ and $\alpha_2$ binding sites were different and were also differently modified by substituents added to the berbine nuclei, leading to $\alpha_1$ and $\alpha_2$ selective compounds [4, 5].

Nevertheless, the rigid tetracyclic structure of berbines provides a basic nitrogen atom, common to all adrenergic ligands, and simultaneously enforces a favorable topographical relationship among this basic nitrogen and the 2 aromatic moieties.

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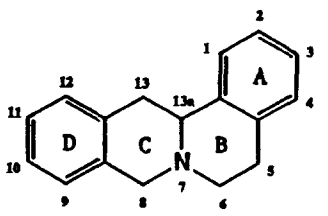
### *Berbine*

Previous studies concerning structure–affinity relationships of α-adrenergic ligands have noted the importance of these structural features [6–9]. In a further extension of our studies in this area, our aim was to gain a better understanding of the structure–affinity relationships of berbines. On this basis, we attempted to acquire some insight into the relative contribution made by the 2 aromatic rings, as well as the nitrogen atom of these molecules, to $\alpha_1$ and $\alpha_2$-adrenoceptor binding.

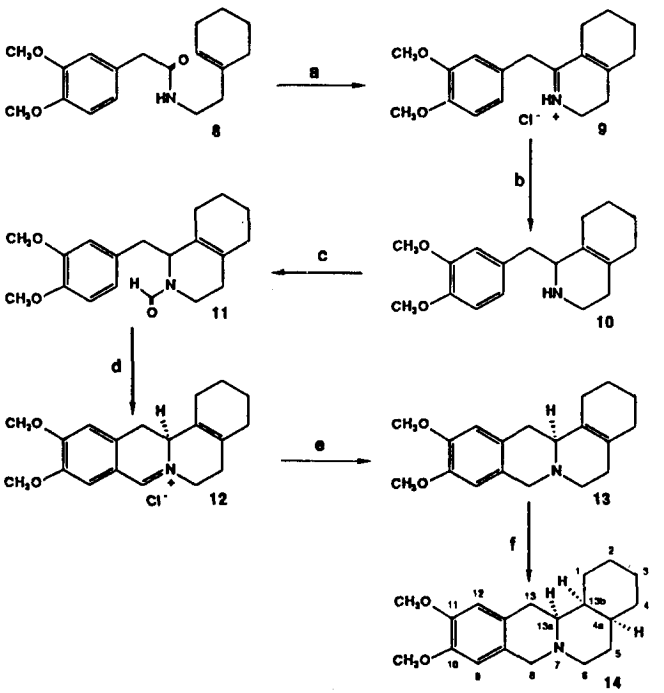


## Chemistry

The derivatives of berbine **1–6** (table II) substituted in the aromatic rings, were obtained according to our previous synthetic work [10, 11]. Conformational analysis of these berbines by $^1H$ NMR [12, 13] and IR spectroscopy [14], showed that all these compounds possess a *trans* configuration at the B/C junction.

The synthesis of derivatives of berbine **13**, **14**, saturated in ring A is reported here for the first time; we called them 'berbinanes' (scheme 1). They were prepared according to the classical synthetic strategy [15, 16] using amide **8** as starting material.

The catalytic hydrogenation over Raney Ni (at 85°C, 80 bar) of compounds **13** afforded the decahydro-8*H*-dibenzo[*a*,*g*]quinolizine **14** as a mixture of *cis*/*trans* isomers at the A/B junction. The major stereoisomer which was isolated after successive recrystallizations possesses the *cis* configuration at the A/B junction as indicated by the $^{13}C$ NMR spectra (table I). In fact, C-1 C-3, C-5 and C-13 carbons show an upfield shielding due to γ-steric effects [17]. Furthermore, both **13** and **14** have a *trans* configuration at the B/C junction according to the $^{13}C$ NMR spectra (table I; see in particular the chemical shifts of C-6, C-8, C-13 and C-13a) [18, 19].



**Scheme 1.** Reagents: a = $PCl_5/CHCl_3$; b = $NaBH_4CN/CH_3OH$; c = $HCO_2H/180°C$; d = $PCl_5/CHCl_3$; e = $NaBH_4/CH_3OH$; f = $H_2$/Ni Raney.

**Table I.** $^{13}C$ NMR chemical shifts of berbine compounds (δ ppm).

| CARBON | COMPOUND | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 13 | 14 | 20 | 24 cis | 24 trans |
| C-1 | 125.4 | 25.9 | 21.2 | 108.3 | | |
| C-2 | 126.0 | 22.6 | 25.0 | 147.2 | | |
| C-3 | 126.0 | 22.9 | 20.9 | 14.2 | | |
| C-4 | 128.8 | 30.0 | 31.7 | 111.2 | | |
| C-4a | 134.5 | 127.5 | 36.6 | 127.0 | | |
| C-5 | 29.4 | 30.2 | 26.8 | 29.4 | 23.5 | 23.8 |
| C-6 | 51.2 | 50.9 | 57.5 | 51.2 | 51.8 | 60.6 |
| C-8 | 58.6 | 58.1 | 58.9 | 59.2 | 63.4 | 65.1 |
| C-8a | 134.4 | 126.7 | 126.3 | 126.6 | | |
| C-9 | 125.8 | 108.9 | 108.7 | 27.3 | | |
| C-10 | 126.1 | 147.1 | 147.4 | 22.7 | | |
| C-11 | 126.1 | 147.2 | 147.0 | 22.0 | | |
| C-12 | 128.7 | 111.4 | 110.7 | 29.0 | | |
| C-12a | 134.4 | 126.5 | 125.7 | 126.4 | | |
| C-13 | 36.6 | 33.5 | 32.1 | 38.2 | 34.5 | 29.5 |
| C-13a | 59.8 | 61.3 | 61.9 | 59.5 | 65.5 | 66.3 |
| C-13b | 137.8 | 128.4 | 40.3 | 130.2 | | |
| $CH_3O$ | | 55.9(X2) | 55.9(X2) | 56.0(X2) | | |
| $CH_3N$ | | | | | 49.8 | 39.2 |

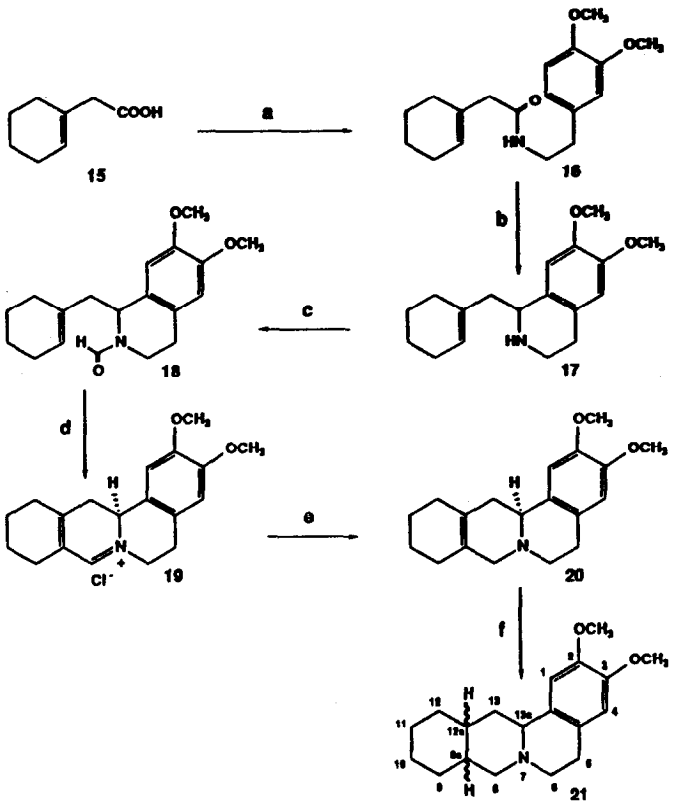
The derivatives of berbine saturated in ring D are known in the literature as 'berbanes' and different methods have been reported for their synthesis [20–22]. In this study the method employed is described in scheme 2. The starting compound **15** was prepared according to the literature [23–25].

The compound **16** was submitted to a Bischler–Napieralski reaction in the presence of phosphorus pentoxide in toluene, rather than phosphorus pentachloride in chloroform, because in the latter case hydrogen chloride is added to the ethylenic double bond. Compound **20** has a *trans* configuration at the B/C junction (see IR, NMR data), while **21** is a mixture of 2 isomers (junction C/D) which could not be separated by using different methods.

The complete reduction of the 2 aromatic rings of **1** was achieved by catalytic hydrogenation over Raney Ni (at 170°C, 150 bar) to afford the perhydroberbine **22**. Compounds **23**, **24**, **25** in which the nitrogen is present in a charged ammonium form, were prepared according to standard literature procedures. However, **23** and **25** are planar structures, while in the case of **24** both *cis* and *trans* isomers were isolated separately (table I) [26].

## Biological assays and discussion

Relative affinities of the berbines for central α-adrenoceptors were determined by measuring radioligand displacement from membrane binding sites of rat cerebral cortex.



**Scheme 2.** Reagents: a = 3,4-dimethoxyphenethylamine/ 180–200°C; b = $P_2O_5$/toluene then Zn/AcOH; c = $HCO_2H$/ 180°C; d = $PCl_5/CHCl_3$; e = $NaBH_4/CH_3OH$; f = $H_2$/Ni Raney.

Displacement of [$^3$H]-yohimbine served as a measure of interaction with $\alpha_2$-adrenoceptors while [$^3$H]-prazosin displacement was used as an assay for $\alpha_1$-adrenoceptor affinity. The results are shown in table II.

Initial inspection of this data indicates that the introduction of large substituents, like carbamate (**7**), into aromatic ring D had no significant influence on $\alpha_1$ and $\alpha_2$ affinity, while introducing the same substituent into ring A (**4**) produced a 15-fold decrease for both $\alpha_1$ and $\alpha_2$ affinity compared to those of compound **3**.

Total saturation of the ring A (**14**) produced a 16-fold decrease for both $\alpha_1$ and $\alpha_2$-affinity compared to those of compound **3**. These results indicate that the aromatic moity A of berbines can be recognized by both $\alpha_1$ and $\alpha_2$-adrenoceptor sites.

However, the introduction of chloro (**6**) substituents into aromatic ring A reduced affinity for $\alpha_2$-sites some 50-fold, compared to the parent compound **1**. By contrast, affinity for $\alpha_1$-sites remains unchanged. Partial saturation of this ring A of compound **3** gave **13**, in which the $\alpha_1$-adrenoceptors affinity was preserved, while $\alpha_2$-affinity was 8-fold reduced. Furthermore, the partial saturation of the ring D of **2** gave compound **20**, which showed no change in potency for $\alpha_1$ and $\alpha_2$-sites, while its total saturation (**21**) increased $\alpha_1/\alpha_2$-adrenoceptor selectivity by decreasing $\alpha_1$-affinity only.

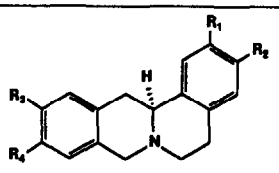
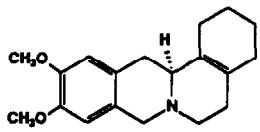
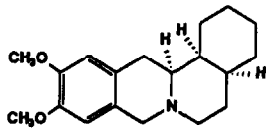
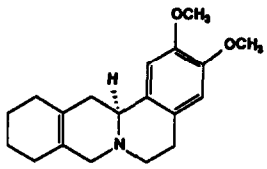
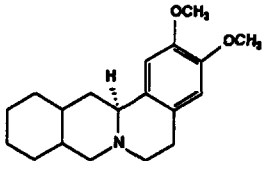
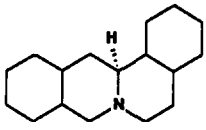
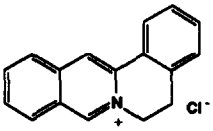
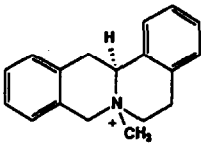
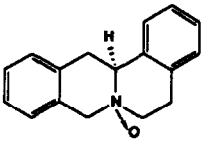
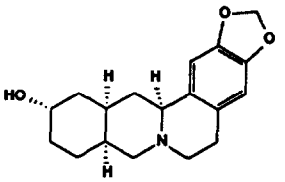
Thus, the major finding of this study is that the aromatic ring A of berbines is essential for the interaction with $\alpha_2$-sites, while the ring D could be replaced by a cyclohexane one without causing a significant effect on $\alpha_2$-affinity. Otherwise it is known that berbanes, analogues of **21**, show a high degree of affinity and selectivity for $\alpha_2$-adrenoceptors [27, 28]. A berbane derivative, CH-38083 (7,8-methylenedioxy-14-hydroxyalloberbane) in which the A ring possesses a methylenedioxy group attached to the $C_2$-$C_3$ position, has been shown to be a highly selective antagonist of $\alpha_2$-adrenoceptors (table II). This high degree of selectivity of berbanes for $\alpha_2$-adrenoceptors is apparently due to the combination of a decrease in $\alpha_1$-affinity and an increase in $\alpha_2$-affinity when compared to the berbines described in this study.

However, **14**, **21**, as well as CH-38083, do not have planar structures and therefore show an important decrease in $\alpha_1$-affinity, while **13** and **20** which have planar structures preserve $\alpha_1$-affinity. According to these results a planar structure is essential for the $\alpha_1$-affinity of berbines and berbanes independently of the aromatic ring (A or D) [29, 30].

The permanently charged quaternary analogues **24** and **25** are inactive, suggesting that the presence of a fourth substituent on the nitrogen atom does not permit the approach of the $\alpha_1$ and $\alpha_2$ receptor sites because of marked steric constraints. By contrast, **23**, which has a planar structure and a positive nitrogen atom preserved some $\alpha$-adrenergic affinity. For this compound, charge delocalization is extensive, which means that the formal positive centers would be of limited importance for direct receptor interaction, especially in the case of $\alpha_1$-adrenoceptors.

In conclusion, the results of this study show that $\alpha_2$-activity of the dibenzo[*a*,*g*]quinolizines depends only on the aromatic ring A. The lack of the aromatic ring D increases the selectivity for the $\alpha_2$-sites because this ring is implicated in the $\alpha_1$-sites. For their $\alpha_1$-activity the planarity of structure is a very important factor. The requirement of at least one aromatic ring for $\alpha$-adrenergic affinity is indicated by the inactivity of the perhydroberbine **22**. The results also indicate that the nitrogen atom is an essential structural feature of berbines and its change can profoundly affect the $\alpha$-adrenergic affinity, presumably by steric and electronic influences.

**Table II**. Structure of berbine compounds and their *in vitro* binding affinities to $\alpha_1$ and $\alpha_2$-adrenoceptors.

| N° | COMPOUND | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Ki nM [a] [$^3$H] PRAZOSIN ($\alpha_1$) | Ki nM [a] [$^3$H] YOHIMBINE ($\alpha_2$) | SELECTIVITY Ki $\alpha_1$ / Ki $\alpha_2$ |
|---|---|---|---|---|---|---|---|---|
| 1 |  | H | H | H | H | 880 ± 150 | 110 ± 14 | 8.0 |
| 2 | | $CH_3O$ | $CH_3O$ | H | H | 720 ± 130 | 615 ± 120 | 1.2 |
| 3 | | H | H | $CH_3O$ | $CH_3O$ | 230 ± 36 | 180 ± 30 | 1.3 |
| 4 | | H | $NHCO_2C_2H_5$ | $CH_3O$ | $CH_3O$ | 3000 ± 200 | 3650 ± 1050 | 0.8 |
| 5 | | H | H | $NH_2$ | $CH_3O$ | 260 ± 10 | 260 ± 20 | 1.6 |
| 6 | | Cl | Cl | $CH_3O$ | $CH_3O$ | 390 ± 60 | 5100 ± 1700 | 0.1 |
| 7 | | H | H | $NHCO_2C_2H_5$ | $CH_3O$ | 330 ± 30 | 630 ± 50 | 0.5 |
| 13 |  | | | | | 490 ± 40 | 1400 ± 300 | 0.35 |
| 14 |  | | | | | 3200 ± 670 | 3100 ± 410 | 1.0 |
| 20 |  | | | | | 920 ± 110 | 630 ± 90 | 1.5 |
| 21 |  | | | | | 5900 ± 600 | 420 ± 300 | 14.0 |
| 22 |  | | | | | > 10000 | > 10000 | - |
| 23 |  | | | | | 2200 ± 380 | 1400 ± 300 | 1.6 |
| 24 |  | | | Cis | | > 10000 | 7600 ± 800 | - |
| | | | | Trans | | > 10000 | 7230 ± 900 | - |
| 25 |  | | | | | > 10000 | > 10000 | - |
| | CH - 38083 (réf. 27)  | | | | | 2600[b] | 1.9[b] | 1368 |

[a]Values are the mean ± SEM of at least 3 separate experiments performed in triplicate.
[b]The $K_d$ values of [$^3$H]prazosin and [$^3$H]yohimbine were 0.14 ± 0.02 mmol/l and 10.2 ± 1.6 mmol/l respectively.

## Experimental protocols

*Chemistry*

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Spectroscopic data for all compounds were recorded on Beckmann 4230 (IR) and Brucker AC 200 (NMR) instruments. All the $^{13}C$ NMR spectra were obtained in $CDCl_3$ and chemical shifts were measured with respect to internal TMS: δ (TMS) = δ ($CHCl_3$) + 77.2 ppm. Analyses indicated by elemental symbols were within ± 0.4% of the theoretical values and were performed by the Central Service of Microanalysis in Vernaison and the Centre Rech Macrom in Strasbourg. All TLC were performed on Merck silica gel F-254 plates ($CHCl_3$/MeOH: 17/3).

*11-Ethoxycarbamido-10-methoxy-5,6-13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine 7*
The amine **5** (500 mg, 1.78 mmol) was dissolved in THF (100 ml) containing 0.2 ml of pyridine (anhydrous). Ethyl chloroformate (0.16 ml) was added slowly and the mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and the residue was triturated in water, filtered and recrystallized from ethanol. The white crystals (452 mg, 72%) melted at 136–138°C. IR ($CHCl_3$): 3430 (NH carbamate), 2810–2760 (Bohlmann bands), 1730 $cm^{-1}$ (C=O). $^1H$ NMR ($CDCl_3$) δ: 1.32 (t, 3H, $CH_2CH_3$), 3.35 (dd, 1H, $H_{13eq}$), 3.68 (m, 2H, $H_{8ax}$ + $H_{13a}$), 3.84 (s, 3H, $OCH_3$), 3.97 (d, 1H, $H_{8eq}$), 4.22 (q, 2H, $CH_2CH_3$), 6.56 (s, 1H, H9), 7.90 (s, 1H, $H_{12}$). Anal $C_{21}H_{24}N_2O_3$ (C, H, N).

*N-[2-(1-Cyclohexenyl)ethyl]-3,4-dimethoxyphenylacetamide 8*
A mixture of 3,4-dimethoxyphenylacetic acid (20 g, 102 mmol) and 2-(1-cyclohexenyl)ethylamine (12.82 g, 102 mmol) was heated at 180–200°C (Wood alloy) for 3 h. The solution was cooled and the crude product was crystallized from isopropanol to afford 26.3 g (85%) of white crystals, mp = 104–106°C. IR ($CHCl_3$): 3410 (NH), 1650 (C=O), 1600 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$) δ: 1.52 (m, 4H, $2CH_2$ in β of C=C), 1.80 (m, 4H, $2CH_2$ in α of C=C), 1.98 (t, 2H, $CH_2CH_2N$), 3.25 (m, 2H, $CH_2CH_2N$), 3.50 (s, 2H, $COCH_2$), 3.83 and 3.87 (2s, 6H, $2OCH_3$), 5.23 (m, 1H, CH=C), 5.32 (m, 1H, NH).

*1-(3,4-Dimethoxybenzyl)-3,4,5,6,7,8-hexahydroisoquinoline HCl 9*
The amide **8** (25 g, 82.5 mmol) was dissolved in $CHCl_3$ (125 ml) and $PCl_5$ (30 g) was cautiously added. After stirring for 6 h at room temperature, petroleum ether 40–60°C (120 ml) was added and the precipitate was filtered. Recrystallization from EtOH/$Et_2O$ gave 19.1 g (72%) of pale yellow needles, mp = 90–92°C (hygroscopic). IR ($CHCl_3$): 2700–2300 ($N^+H$, broad), 1665 ($C=N^+$), 1600 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$) δ: 1.60 (m, 4H, $2H_6$+$2H_7$), 2.25 (m, 6H, $2H_4$+$2H_5$+$2H_8$), 3.45 (m, 2H, $CH_2N$), 3.80 and 3.90 (2s, 6H, $2OCH_3$), 4.13 (s, 2H, $=C-CH_2$), 6.77 (s, 2H, $H_2$+$H_5$), 7.00 (s, 1H, $H_6$), 14.57 (m, 1H, +NH).

*1-(3,4-Dimethoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline 10*
The above hydrochloride (10 g, 31.1 mmol) was suspended in a mixture of MeOH (50 ml) and THF (200 ml). Sodium cyanoborohydride (3.4 g) was added in several portions and stirring continued for 45 min at room temperature. The solvent was evaporated and the residue was made basic with 3% aqueous NaOH solution. Extraction with $Et_2O$, washing with water, drying ($MgSO_4$) and removal of the solvent gave a liquid which was vacuum distilled (93–95°C/4 mm Hg) to afford 6.7 g (75%) of a colorless oil. IR ($CHCl_3$): 3320 (NH, weak), 1600 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$) δ: 1.65 (m, 5H, $2H_6$+$2H_7$+NH), 1.93 (m, 6H, $2H_4$+$2H_5$+$2H_8$), 2.82 (m, 5H, $NCHCH_2$+$CH_2N$+CHN), 3.90 (s, 6H, $2OCH_3$).

*1-(3,4-Dimethoxybenzyl)-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline 11*
The amine **10** (10 g, 34.8 mmol) was dissolved in a solution of anhydrous formic acid (20 ml). The mixture was heated slowly to 100–110°C (the excess of the acid distilled) and heating continued to 180–190°C for 2–3 h. After cooling the product was crystallized, filtered and recrystallized from diisopropylether/light petroleum ether(1:1) to give 7.68 g (70%) of white prisms, mp = 90–92°C. IR ($CHCl_3$): 1660 $cm^{-1}$ (HC=O). $^1H$ NMR ($CDCl_3$) δ: 3.88 (s, 6H, $2OCH_3$), 4.33 and 4.62 (2m, 1H, CHN), 7.45 and 7.93 (2s, 1H, HC=O).

*10,11-Dimethoxy-1,2,3,4,5,6,13,13a-octahydrodibenzo[a,g]-quinolizinium chloride 12*
Compound **11** (10 g, 31.7 mmol) was dissolved in $CHCl_3$ (80 ml) and $PCl_5$ (11 g) was cautiously added. After stirring for 1 h at room temperature, $Et_2O$ (160 ml) was added and the precipitate was filtered. Recrystallization from water gave 7.43 g (70%) of yellow needles, mp = 170–173°C. IR ($CHCl_3$): 1635 $cm^{-1}$ ($HC=N^+$). $^1H$ NMR ($CDCl_3$) δ: 3.99 (s, 6H, $2OCH_3$), 5.02 (m, 1H, $H_{13a}$), 6.81 (s, 1H, $H_{12}$), 7.84 (s, 1H, $H_9$), 10.50 (s, 1H, $H_8$).

*10,11-Dimethoxy-1,2,3,4,5,6,13,13a-octahydro-8H-dibenzo-[a,g]quinolizine 13*
5 g (15 mmol) of the quinolizinium salt **12** was dissolved in MeOH (200 ml) and $NaBH_4$ (2.5 g) was added in several portions. After stirring for 1 h at room temperature the solvent was removed and the solution acidified with acetic acid. After basification with diluted $NH_4OH$ solution the product was extracted with $Et_2O$, washed with water, dried($Na_2SO_4$) and evaporated. Recrystallization from cyclohexane gave 3.25 g (73%) of a white powder, mp = 117–119°C. IR ($CHCl_3$): 2810–2750 $cm^{-1}$ (Bohlmann bands). $^1H$ NMR ($CDCl_3$) δ: 2.88 (m, 3H, $H_{13ax}$+$H_{13eq}$+$H_{13a}$), 3.52 (d, $J$ = 14 Hz, 1H, $H_{8ax}$), 3.83 (d, $J$ = 14 Hz, 1H, $H_{8eq}$), 3.84 (s, 6H, $2OCH_3$), 6.53 (s, 1H, $H_{12}$), 6.59 (s, 1H, $H_9$). Anal $C_{19}H_{25}NO_2$ (C, H, N).

*10,11-Dimethoxy-1,2,3,4,4a,5,6,13,13a,13b-decahydro-8H-dibenzo[a,g]quinolizine 14*
Base **13** (2 g, 6.68 mmol) was dissolved in MeOH (100 ml) and hydrogenated over Raney Ni (0.3 g) at 85°C/80 bar for 1.5 h in a stainless steel bomb. Then the reaction mixture was filtered, the solvent evaporated and the residue dissolved in $Et_2O$. The organic phase was washed with 3% aqueous NaOH solution, then with water, dried($Na_2SO_4$) and evaporated. The product was recrystallized in a mixture of EtOH/$H_2O$ (3:1) to give only the major stereoisomer as a white powder, 1.2 g (60%), mp = 92–94°C. IR ($CHCl_3$): 2810–2750 $cm^{-1}$ (Bohlmann bands). $^1H$ NMR ($CDCl_3$) δ: 3.20 (d, $J$ = 15 Hz, 1H, $H_{8ax}$), 3.83 (s, 6H, $2OCH_3$), 3.84 (d, $J$ = 15 Hz, 1H, $H_{8eq}$), 6.50 (s, 1H, $H_{12}$), 6.56 (s, 1H, $H_9$). Anal $C_{19}H_{27}NO_2$ (C, H, N).

*N-(3,4-Dimethoxyphenethyl)-2-(1-cyclohexenyl)acetamide 16*
This compound was prepared from the acid **15** [23–25] (20 g, 0.14 mol) and 3,4-dimethoxy-β-phenethylamine (25.57 g, 0.14 mol) as described for **8**, to give white needles in 90% yield ($Et_2O$), mp = 89–91°C. IR ($CHCl_3$): 3410 (NH), 1650

(C=O), 1600 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$) δ: 1.53 (m, 4H, $2CH_2$ in β of C=C), 1.90 (m, 4H, $2CH_2$ in α of C=C), 2.75 (t, 2H, $CH_2CH_2N$), 2.82 (s, 2H, $COCH_2$), 3.50 (m, 2H, $CH_2CH_2N$), 3.88 (s, 6H, $2OCH_3$), 5.57 (m, 1H, CH=C), 5.85 (m, 1H, NH).

*1-(1-Cyclohexenyl)methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* ***17***
The above amide **16** (10 g, 33 mmol), 20 g of $P_2O_5$ and dry toluene (50 ml) were refluxed for 1 h. The solvent was decanted and ice-cold water (100 ml) was cautiously added. The aqueous layer was washed twice with $CHCl_3$ and conc HCl (100 ml) was added as well as zinc powder (10 g). The whole mixture was refluxed for 2 h and the excess Zn was filtered. After cooling diluted $NH_4OH$ solution was added slowly and the product was extracted with $CHCl_3$. The organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated to give 6.6 g (70%) of a reddish oil, which was used with no further purification. IR ($CHCl_3$): 3320 (NH, weak), 1600 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$) δ: 2.42 (m, 2H, $CH_2CHN$), 2.78 (m, 2H, $CH_2CH_2N$), 3.05 (m, 2H, $CH_2N$), 3.90 (s, 6H, $2OCH_3$), 4.00 (dd, 1H, CHN), 5.61 (s, 1H, CH=C), 6.65 (m, 2H, $H_8$+$H_5$).

*1-(1-Cyclohexenyl)methyl-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* ***18***
Using the same procedure as described for the conversion of **10** and **11**, 10 g (34.8 mmol) of **17** gave 8.34 g (76%) of white crystals (EtOH), mp = 149–151°C. IR ($CHCl_3$): 1660 (HC=O), 1600 $cm^{-1}$ (C=C). $^1H$ NMR ($CDCl_3$) δ: 3.84 (s, 6H, $2OCH_3$), 4.49 and 5.42 (2m, 1H, CHN), 5.42 (m, 1H, CH=C), 6.57 (s, 2H, arom), 8.06 and 8.13 (2s, 1H, HC=O).

*2,3-Dimethoxy-5,6,9,10,11,12,13,13a-octahydrodibenzo[a,g]quinolizinium chloride* ***19***
Using the same procedure as described for the conversion of **11** to **12**, 10 g (31.75 mmol) of **18** (except stirring was continued for 3 h), gave 7.62 g (72%) of a yellow powder (EtOH/$Et_2O$), mp = 206–210°C. IR ($CHCl_3$): 1650 (HC=N+), 1600 $cm^{-1}$ (C=C, weak). $^1H$ NMR ($CDCl_3$) δ: 3.86 (s, 6H, $2OCH_3$), 5.22 (m, 1H, $H_{13a}$), 6.66 (s, 1H, $H_4$), 6.67 (s, 1H, $H_1$), 9.25 (s, 1H, $H_8$).

*2,3-Dimethoxy-5,6,9,10,11,12,13,13a-octahydro-8H-dibenzo-[a,g]quinolizine* ***20***
Using the same procedure as described for the conversion of **12** to **13**, 5 g (15 mmol) of **19** gave 3.36 g (75%) of a white powder (*n*-hexane), mp = 89–91°C. IR ($CHCl_3$): 2810–2750 $cm^{-1}$ (Bohlmann bands). $^1H$ NMR ($CDCl_3$) δ: 3.43 (m, 2H, $H_{13a}$+$H_{8eq}$), 3.87 (s, 6H, $2OCH_3$), 6.63 (s, 1H, $H_4$), 6.72 (s, 1H, $H_1$). Anal $C_{19}H_{25}NO_2$ (C, H, N).

*2,3-Dimethoxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8H-dibenzo[a,g]quinolizine* ***21***
The title compound was prepared from **20** (2 g, 6.7 mmol), as described for **14** (reaction time 5 h), to give 1.2 g (60%) of a white powder (*n*-hexane), mp = 121–128°C [lit [22] 133°C (*cis*), 127°C (*trans*)]. IR ($CHCl_3$): 2810–2750 $cm^{-1}$ (Bohlmann bands). $^1H$ NMR ($CDCl_3$) δ: 3.82 (2s, 6H, $2OCH_3$), 6.50 (s, 1H, $H_4$), 6.62 (s, 1H, $H_1$). Anal $C_{19}H_{27}NO_2$ (C, H, N).

*Perhydrodibenzo[a,g]quinolizine* ***22***
Compound **1** (8 g, 34 mmol) was dissolved in MeOH (150 ml) and hydrogenated over Raney Ni (1.5 g) at 170°C/150 bar for 5 h in a stainless steel bomb. After filtration, the solvent was evaporated and the residue dissolved in ether. The ethereal phase was washed with 3% aqueous NaOH solution, then with water, dried ($MgSO_4$) and acidified with gaseous HCl to give white crystals of the hydrochloride. Recrystallization from EtOH/$Et_2O$ (1:10) gave 6.3 g (75%), mp = 198–205°C. $^1H$ NMR ($CDCl_3$) (base) δ: 1.48 (m, 24H, $CH_2$ cycles), 2.50 (m, 5H, CHN+$2CH_2N$). Anal $C_{17}H_{29}N$, HCl, $H_2O$ (C, H, N).

*5,6-Dihydrodibenzo[a,g]quinolizinium chloride* ***23***
1-Benzyl-2-formyl-1,2,3,4-tetrahydroisoquinoline* (1 g, 3.96 mmol) was dissolved in $CHCl_3$ (30 ml) and $PCl_5$ (1.5 g) was added. The mixture was refluxed overnight, cooled and THF (30 ml) was added. After filtration the solid was recrystallized from EtOH to give 0.557 g (52%) of a white powder, mp = 226–228°C (dec). $^1H$ NMR (DMSO–$d_6$) δ: 3.38 (m, 2H, $2H_5$), 4.96 (m, 2H, $2H_6$), 7.57 (m, 3H, $H_1$+$H_2$+$H_4$), 8.03 (t, 1H, $H_3$), 8.34 (m, 4H, $H_9$+$H_{10}$+$H_{11}$+$H_{12}$), 9.22 (s, 1H, $H_{13}$), 10.20 (s, 1H, $H_8$). Anal $C_{17}H_{14}NCl$, 2.5 $H_2O$ (C, H, N).

*7-Methyl-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizinium iodide* ***24***
This compound was prepared from **1** (1.2 g, 5.1 mmol) as described in the literature [31] to afford the *trans* isomer in colourless prisms ($H_2O$), mp = 229–231°C and the *cis* isomer in white crystals (EtOH/$Et_2O$) mp = 212–214°C. Anal $C_{18}H_{20}NI$ (C, H, N).

*5,6,13,13a-Tetrahydro-8H-dibenzo[a,g]quinolizine N-oxide* ***25***
Compound **1** (1 g, 4.25 mmol) was dissolved in MeOH (30 ml) and 3 ml of $H_2O_2$ (30%) was added. Stirring was continued at room temperature for 5 h. Then 100 mg of (5%) Pt/C was added, stirred for a few min and filtered. After evaporation of the solvent the residue was crystallized from MeOH to give 0.85 g (80%) of a white needles, mp = 165–167°C. $^1H$ NMR ($CDCl_3$) δ: 2.84 (dd, 1H, $H_{13eq}$), 3.75 (m, 5H, $2H_5$+$2H_6$+$H_{13ax}$), 4.55 (d, $J$ = 15 Hz, 1H, $H_{8ax}$), 4.67 (dd, 1H, $H_{13a}$), 4.73 (d, $J$ = 15 Hz, 1H, $H_{8eq}$), 7.20 (m, 8H, arom). Anal $C_{17}H_{17}NO$, $2H_2O$ (C, H, N).

*Pharmacology*

*Radioligand binding studies*

Rat brain membranes were prepared as described by Greengrass and Bremmer [32] with some modifications (Descombes and Stoclet) [33].

Binding studies were performed with the $\alpha_1$-selective radioligand [$^3$H]prazosin ([$^3$H]PRA specific activity 644 GBq · $mmol^{-1}$) and the $\alpha_2$-selective radioligand [$^3$H]-yohimbine ([$^3$H]YOH specific activity 3126 GBq · $mmol^{-1}$) supplied by New England Nuclear. The saturation curves were obtained by incubating various concentrations of radioligands (0.05–5 nM [$^3$H]PRA; 0.05–18 nM [$^3$H]YOH with aliquot fractions of membrane suspension (0.5 mg protein). Competition studies were performed with 0.2 nM [$^3$H]PRA or 2 nM [$^3$H]YOH. Non-specific binding was measured in presence of 10 μM phentolamine. All assays were performed in triplicate. In competition studies $IC_{50}$ (concentration displacing 50% of maximal specific binding) and the slope factor of the displacement curves were calculated using a computerised iterative non-linear curve fitting program (McPherson *et al* [34]). $IC_{50}$ values were converted to $K_i$ values using the Cheng–Prussof relation [35].

*Prepared from 1-benzyl-1,2,3,4-tetrahydroisoquinoline as described for compound **11**.

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