Synthesis and Structure−Activity Relationships of a New Model of Arylpiperazines. 1. 2-[[4-(*o*-Methoxyphenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine: A Selective 5-HT$_{1A}$ Receptor Agonist

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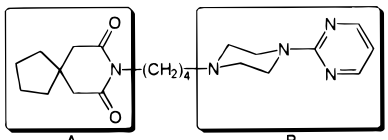
A series of new bicyclohydantoin−arylpiperazines was prepared and evaluated for affinity at 5-HT$_{1A}$, α_1, and D_2 receptors. Most of the compounds showed very low affinity for D_2 receptors, and most of them demonstrated moderate to high affinity for 5-HT$_{1A}$ and α_1 receptor binding sites. SAR observations indicated that the length of the alkyl chain between the arylpiperazine and the hydantoin moiety is of great importance for 5-HT$_{1A}$/α_1 affinity and selectivity, $n = 1$ being the optimal value. Compound **1h**, 2-[[4-(*o*-methoxyphenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine, bound at 5-HT$_{1A}$ sites with nanomolar affinity ($K_i = 31.7$ nM) and high selectivity over α_1, D_2, and 5-HT$_{2A}$ receptors (K_i > 1000, > 10 000, and >1000 nM, respectively). Preliminary studies showed that this agent is probably functioning as a partial to full 5-HT$_{1A}$ agonist, and it displayed anxiolytic activity on the social interaction test in mice.

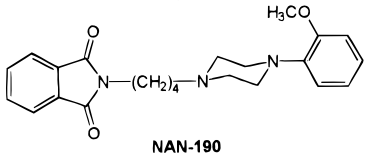
Introduction

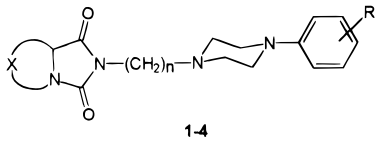
Serotonin (5-hydroxytryptamine, 5-HT) and its receptors are involved in various physiological and pathophysiological processes.[1−5] Seven 5-HT receptor classes (5-HT$_{1-7}$), including different subtypes (A, B, ...), have been described in recent years.[6−12] It is generally accepted that receptors of the 5-HT$_{1A}$ subtype are involved in psychiatric[13−15] disorders such as depression and anxiety. Buspirone, an arylpiperazine derivative with high affinity for the 5-HT$_{1A}$ receptor, was the first agent to be approved for clinical use.[16,17] However, this compound is not optimal in terms of selectivity and pharmacokinetic properties and has a slow onset of action. Several structural changes have been made on the imide (A) and arylpiperazine (B) moieties of buspirone in order to increase the selectivity for the 5-HT$_{1A}$ site. However, most of these compounds exhibit high levels of undesired affinity for the α_1 adrenoceptor [*e.g.*, NAN-190: K_i(5-HT$_{1A}$) = 0.6 nM, $K_i(\alpha_1) = 0.8$ nM], and attempts have been made to identify and eliminate the structural features that account for α_1-adrenergic binding.[18,19]

The influence of the arylpiperazine and the length of the spacer on 5-HT$_{1A}$/α_1 selectivity is clear, in contrast to the role of the cyclic imide. Some reported[18,20,21] results have demonstrated that a lipophilic character in the imide portion is needed for high 5-HT$_{1A}$ affinity, while another hypothesis[22] has suggested that steric factors play an important role.

In this paper, we have analyzed a new set of model arylpiperazines **1**−**4**, in which the imide moiety (part A) has been replaced by a bicyclohydantoin (X = $-(CH_2)_3-$, $-(CH_2)_4-$). Herein we report the synthesis







of these series and the affinities for 5-HT$_{1A}$, α_1, and D_2 receptors, obtained by radioligand binding studies. Structure−activity relationships (SAR) which are discussed afford insights for improving the selectivity for 5-HT$_{1A}$ over α_1 receptors. Several analogues with interesting 5-HT$_{1A}$-binding properties were evaluated for their ability to produce hypothermia and behavioral effects in mice.

Chemistry

The synthetic routes used in the preparation of **1**−**4** are outlined in Scheme 1. Compounds **1** ($n = 1$) were obtained by Mannich reaction of the hydantoins **5**[23,24] with formaldehyde and the corresponding arylpiperazines (method A). The desired compounds **2** ($n = 2$) (method B), **3**, and **4** ($n = 3,4$) (method C) were obtained by reaction of the intermediates **6** and **7** with the corresponding arylpiperazines in the presence of sodium carbonate and acetonitrile. The reaction of L-proline or ethyl pipecolinate with 2-chloroethyl isocyanate gave **6a,b**, respectively. The key intermediates **7a**−**d** (X =

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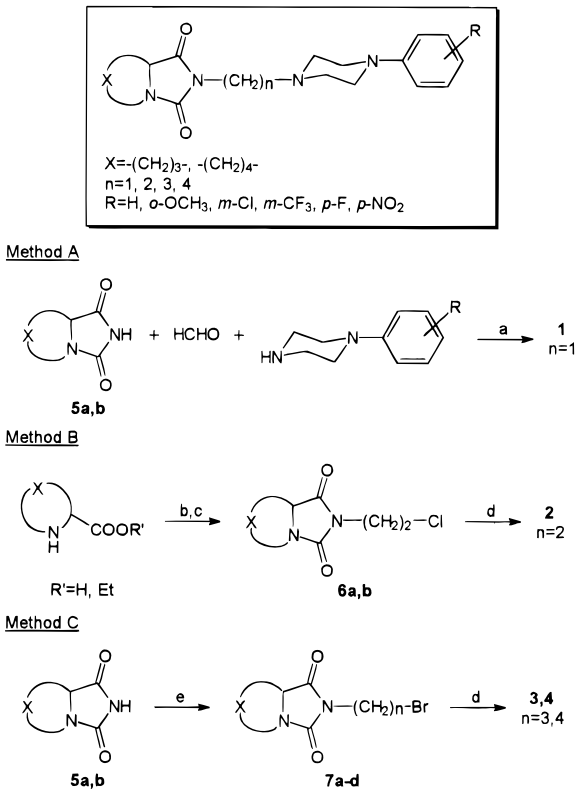
Scheme 1[a]



[a] Reagents: (a) EtOH, 100 °C, 1 h; (b) $Cl(CH_2)_2NCO$, acetone, N_2, reflux, 2 h; (c) 25% HCl, reflux, 35 min or KOH/EtOH (10%), reflux, 45 min; (d) arylpiperazine, Na_2CO_3, acetonitrile, reflux, 3−5 days; (e) HNa, DMF, N_2, 60 °C, 30 min, then $Br-(CH_2)_n-Br$, rt, 12 h.

$-(CH_2)_3-$, $-(CH_2)_4-$; $n = 3, 4$) were prepared from **5a,b**, by reaction with the appropriate dibromoalkane in the presence of NaH and *N*,*N*-dimethylformamide (DMF). Respective hydrochloride salts were prepared as samples for biological assays. All new compounds (Table 1) were characterized by IR and ^1H- and ^{13}C-NMR spectroscopy and gave satisfactory combustion analyses (C, H, N). Moreover, COSY and HETCOR experiments of the starting hydantoins **5a,b** and the final targets **3g** and **4g** were carried out, in order to assign all the protons and carbons of these new structures as well as to define the conformation of the cyclohexane ring of the hydantoin moiety. The NMR analysis and the computer modeling study[25] confirmed that this ring exists in a chair conformation.

Pharmacology

The compounds were evaluated for *in vitro* 5-HT_{1A}, α_1, and D_2 receptor affinity by radioligand binding assays. All the compounds were used in the form of hydrochloride salts and were water-soluble. The specific ligands and tissue sources used are as follows: (a) serotonin 5-HT_{1A} receptors, [^{3}H]-8-OH-DPAT, rat cerebral cortex membranes; (b) adrenergic α_1 receptors, [^{3}H]-prazosin, rat cerebral cortex membranes; (c) dopamine D_2 receptors, [^{3}H]raclopride, rat striatum membranes. The inhibition constant K_i was defined from the IC_{50} by the Cheng−Prusoff equation[26] (Table 1). Two active analogues in the 5-HT_{1A} binding screen have been evaluated for their ability to produce hypothermia in mice. The results of these assays are listed in Table 2. The social interaction assay was the behavioral paradigm selected in mice to measure a compound's anxiolytic potential (Table 3).

Results and Discussion

From the binding data, all the compounds show very low affinity for D_2 receptors except derivatives **4b**,**c**,**i**,**j**, which present moderate affinity. However, most of these compounds demonstrated moderate to high affinity for 5-HT_{1A} and α_1 receptor binding sites.

An examination of the data presented in Table 1 shows the following. (a) With respect to the phenylpiperazine substitution and in agreement with the literature studies, analogues with a methoxy group at the *ortho* position displayed the highest affinity for 5-HT_{1A} and α_1 receptors, leading to nonselective compounds. The only exception was observed in derivatives **1b**,**h** ($n = 1$, R = *o*-OCH_3). In regard to the affinity for both receptors, the same tendency was observed for *m*-chloro analogues (*e.g.*, **4c,i**). Consequently, all the compounds display poor selectivities for 5-HT_{1A} over α_1-adrenergic receptors (ranging from 0.3 to 5). Nevertheless, the presence of a trifluoromethyl group at this same position displays the best 5-HT_{1A} affinity/selectivity profile of the compounds with $n = 2-4$ [*e.g.*, **3d** and **4d** bind with high affinity (K_i = 3.8 and 2.4 nM) and 29- and 27-fold selectivity at 5-HT_{1A} sites, respectively]. The decrease in affinity of *m*-CF_3 derivatives for α_1-adrenergic receptors may be due to an unfavorable steric interaction [$E_S(Cl) = -0.97$, $E_S(CF_3) = -2.4$]. Based on this observation, further substituent variation at the *meta* position could lead to improved selectivity. The introduction of electron-withdrawing substituents in the *para* position, such as a fluoro or nitro group, reduces the binding affinity for 5-HT_{1A} receptors. Regarding the α_1-adrenergic affinity, although the presence of a *p*-nitro group clearly represents a strong detriment to the affinity (K_i > 1000−10 000 nM), the *p*-F substitution is tolerated (*e.g.*, compounds **3e**,**k** and **4k**).

(b) The length of the alkyl chain between the arylpiperazine and the hydantoin moiety is of great importance for 5-HT_{1A}/α_1 affinity and selectivity. It seems that in this series the alkyl chain is not interacting with the receptor in a hydrophobic manner but is more likely acting as a spacer.[27,28] As a general trend, maximum affinity for 5-HT_{1A} as well as α_1 receptors is reached with $n = 3$ or 4, and reduction of the hydrocarbon chain by two and one carbon atoms causes a decrease in affinity in both receptors. This decrease is especially marked for α_1 (analogues with n = 1,2) and 5-HT_{1A} (analogues with $n = 2$) receptor binding. Thus, some compounds in which $n = 1$ display significant 5-HT_{1A} receptor affinity and good 5-HT_{1A} selectivity, which is optimal in compound **1h** (5-HT_{1A}, K_i = 31.7 nM; α_1, K_i > 1000 nM). As shown in Table 4, both the arylpiperazine pharmacophore and the hydantoin moiety contribute to the 5-HT_{1A} receptor interaction of the compounds.

(c) It is known that while the presence of the amide portion (part A) is not essential for 5-HT_{1A} affinity, this moiety could contribute to increase the affinity or selectivity[18,19] over other types of G-protein-coupled receptors. In analogues **1**−**4**, the size of the hydantoin seems to have little influence on 5-HT_{1A} affinity and selectivity. For example, comparing compound **1b** with **1h**, increasing the size from a five- to six-membered ring

Table 1. Physical Properties and *in Vitro* Binding Data[a]

						K_i (nM)		
compd	X	*n*	R	mp (°C)	formula	5-HT_{1A} [^{3}H]-8-OH-DPAT	α_1 [^{3}H]prazosin	D_2 [^{3}H]raclopride
1a	$-(CH_2)_3-$	1	H	178−180	$C_{17}H_{22}N_4O_2 \cdot 2HCl \cdot {}^3/_2H_2O$	85.3 ± 3.1	1000	>10000
1b	$-(CH_2)_3-$	1	*o*-OCH_3	168−170	$C_{18}H_{24}N_4O_3 \cdot 2HCl$	34.9 ± 0.7	500 ± 65	>1000
1c	$-(CH_2)_3-$	1	*m*-Cl	146−148	$C_{17}H_{21}ClN_4O_2 \cdot 2HCl \cdot {}^1/_2H_2O$	58.4 ± 1.1	292 ± 15	>10000
1d	$-(CH_2)_3-$	1	*m*-CF_3	158−159	$C_{18}H_{21}F_3N_4O_2 \cdot 2HCl \cdot H_2O$	120 ± 10	>1000	>1000
1e	$-(CH_2)_3-$	1	*p*-F	180−182	$C_{17}H_{21}FN_4O_2 \cdot 2HCl \cdot H_2O$	500 ± 60	>1000	>10000
1f	$-(CH_2)_3-$	1	*p*-NO_2	150−152	$C_{17}H_{21}N_5O_4 \cdot HCl \cdot H_2O$	>1000	>10000	>10000
1g	$-(CH_2)_4-$	1	H	178−180	$C_{18}H_{24}N_4O_2 \cdot 2HCl \cdot H_2O$	101 ± 8	>1000	>10000
1h	$-(CH_2)_4-$	1	*o*-OCH_3	160−162	$C_{19}H_{26}N_4O_3 \cdot 2HCl \cdot H_2O$	31.7 ± 1.7	>1000	>10000
1i	$-(CH_2)_4-$	1	*m*-Cl	176−178	$C_{18}H_{23}ClN_4O_2 \cdot 2HCl \cdot 3H_2O$	57.7 ± 5.7	135 ± 5	>10000
1j	$-(CH_2)_4-$	1	*m*-CF_3	165−167	$C_{19}H_{23}F_3N_4O_2 \cdot 2HCl$	78.6 ± 7.5	>1000	>1000
1k	$-(CH_2)_4-$	1	*p*-F	170−172	$C_{18}H_{23}FN_4O_2 \cdot 2HCl \cdot H_2O$	444 ± 52	869 ± 75	>10000
1l	$-(CH_2)_4-$	1	*p*-NO_2	176−178	$C_{18}H_{23}N_5O_4 \cdot 2HCl \cdot {}^1/_2H_2O$	>1000	>10000	>10000
2a	$-(CH_2)_3-$	2	H	116−118	$C_{18}H_{24}N_4O_2$	>1000	>1000	>1000
2b	$-(CH_2)_3-$	2	*o*-OCH_3	186−188	$C_{19}H_{26}N_4O_3 \cdot 2HCl$	234 ± 20	190 ± 38	361 ± 60
2c	$-(CH_2)_3-$	2	*m*-Cl	174−176	$C_{18}H_{23}ClN_4O_2 \cdot 2HCl$	418 ± 60	500 ± 65	>1000
2d	$-(CH_2)_3-$	2	*m*-CF_3	206−208	$C_{19}H_{23}F_3N_4O_2 \cdot 2HCl$	123 ± 11	>1000	>1000
2e	$-(CH_2)_3-$	2	*p*-F	196−198	$C_{18}H_{23}FN_4O_2 \cdot 2HCl$	>10000	>1000	>10000
2f	$-(CH_2)_3-$	2	*p*-NO_2	130−132	$C_{18}H_{23}N_5O_4 \cdot 2HCl$	>10000	>10000	>10000
2g	$-(CH_2)_4-$	2	H	193−195	$C_{19}H_{26}N_4O_2 \cdot 2HCl \cdot H_2O$	>1000	>1000	>1000
2h	$-(CH_2)_4-$	2	*o*-OCH_3	178−180	$C_{20}H_{28}N_4O_3 \cdot 2HCl \cdot H_2O$	45.5 ± 4.6	131 ± 28	246 ± 13
2i	$-(CH_2)_4-$	2	*m*-Cl	224−226	$C_{19}H_{25}ClN_4O_2 \cdot HCl$	128 ± 10	375 ± 16	>1000
2j	$-(CH_2)_4-$	2	*m*-CF_3	208−210	$C_{20}H_{25}F_3N_4O_2 \cdot HCl$	65.8 ± 3.1	>1000	>1000
2k	$-(CH_2)_4-$	2	*p*-F	222−224	$C_{19}H_{25}FN_4O_2 \cdot HCl$	>10000	>1000	>10000
2l	$-(CH_2)_4-$	2	*p*-NO_2	252−254	$C_{19}H_{25}N_5O_4 \cdot HCl$	>10000	>10000	>10000
3a	$-(CH_2)_3-$	3	H	210−212	$C_{19}H_{26}N_4O_2 \cdot 2HCl$	19.2 ± 1.5	15.4 ± 3.9	>1000
3b	$-(CH_2)_3-$	3	*o*-OCH_3	212−214	$C_{20}H_{28}N_4O_3 \cdot 2HCl \cdot H_2O$	4.4 ± 0.6	3.1 ± 0.5	>1000
3c	$-(CH_2)_3-$	3	*m*-Cl	164−166	$C_{19}H_{25}ClN_4O_2 \cdot 2HCl$	55.9 ± 9.1	21.6 ± 1.1	>1000
3d	$-(CH_2)_3-$	3	*m*-CF_3	150−152	$C_{20}H_{25}F_3N_4O_2 \cdot 2HCl$	3.8 ± 0.5	109 ± 9	>1000
3e	$-(CH_2)_3-$	3	*p*-F	230−232	$C_{19}H_{25}FN_4O_2 \cdot HCl$	>1000	25.2 ± 1.1	>1000
3f	$-(CH_2)_3-$	3	*p*-NO_2	244−246	$C_{19}H_{25}N_5O_4 \cdot HCl$	>10000	>1000	>10000
3g	$-(CH_2)_4-$	3	H	213−215	$C_{20}H_{28}N_4O_2 \cdot 2HCl \cdot H_2O$	154 ± 10	11.4 ± 0.9	>1000
3h	$-(CH_2)_4-$	3	*o*-OCH_3	208−210	$C_{21}H_{30}N_4O_3 \cdot 2HCl \cdot 3H_2O$	4.1 ± 0.6	9.9 ± 1.0	>1000
3i	$-(CH_2)_4-$	3	*m*-Cl	173−175	$C_{20}H_{27}ClN_4O_2 \cdot 2HCl$	53.6 ± 1.5	17.9 ± 1.1	>1000
3j	$-(CH_2)_4-$	3	*m*-CF_3	206−208	$C_{21}H_{27}F_3N_4O_2 \cdot 2HCl \cdot 4H_2O$	5.7 ± 0.7	90.4 ± 5.1	>1000
3k	$-(CH_2)_4-$	3	*p*-F	205−207	$C_{20}H_{27}FN_4O_2 \cdot 2HCl$	598 ± 70	25.8 ± 1.1	>1000
3l	$-(CH_2)_4-$	3	*p*-NO_2	118−120	$C_{20}H_{27}N_5O_4 \cdot 2HCl$	>10000	1000	>10000
4a	$-(CH_2)_3-$	4	H	210−212	$C_{20}H_{28}N_4O_2 \cdot 2HCl$	24.8 ± 1.4	26.4 ± 1.9	416 ± 72
4b	$-(CH_2)_3-$	4	*o*-OCH_3	178−180	$C_{21}H_{30}N_4O_3 \cdot 2HCl$	5.5 ± 0.7	8.3 ± 0.3	107 ± 10
4c	$-(CH_2)_3-$	4	*m*-Cl	192−194	$C_{20}H_{27}ClN_4O_2 \cdot 2HCl$	11.3 ± 1.0	9.6 ± 0.9	151 ± 13
4d	$-(CH_2)_3-$	4	*m*-CF_3	176−178	$C_{21}H_{27}F_3N_4O_2 \cdot 2HCl$	2.4 ± 0.6	64.9 ± 2.6	>1000
4e	$-(CH_2)_3-$	4	*p*-F	194−196	$C_{20}H_{27}FN_4O_2 \cdot 2HCl \cdot 2H_2O$	89.9 ± 5.2	47.2 ± 1.8	>1000
4f	$-(CH_2)_3-$	4	*p*-NO_2	86−88	$C_{20}H_{27}N_5O_4 \cdot 2HCl$	>1000	247 ± 63	>1000
4g	$-(CH_2)_4-$	4	H	198−200	$C_{21}H_{30}N_4O_2 \cdot 2HCl \cdot H_2O$	78.5 ± 6.8	18.6 ± 3.1	>1000
4h	$-(CH_2)_4-$	4	*o*-OCH_3	199−201	$C_{22}H_{32}N_4O_3 \cdot 2HCl \cdot H_2O$	8.8 ± 0.9	8.6 ± 1.0	>1000
4i	$-(CH_2)_4-$	4	*m*-Cl	190−192	$C_{21}H_{29}ClN_4O_2 \cdot 2HCl$	7.2 ± 0.6	12.1 ± 1.2	129 ± 13
4j	$-(CH_2)_4-$	4	*m*-CF_3	140−142	$C_{22}H_{29}F_3N_4O_2 \cdot 2HCl \cdot {}^1/_2H_2O$	9.9 ± 0.9	72.4 ± 8.0	90.6 ± 8.9
4k	$-(CH_2)_4-$	4	*p*-F	168−170	$C_{21}H_{29}FN_4O_2 \cdot 2HCl \cdot 2H_2O$	57.9 ± 3.2	10.4 ± 0.6	615 ± 61
4l	$-(CH_2)_4-$	4	*p*-NO_2	200−202	$C_{21}H_{29}N_5O_4 \cdot 2HCl$	>1000	>1000	>1000

[a] All values are the mean ± SEM of two experiments performed in triplicate.

resulted in a moderate improvement of 5-HT_{1A} selectivity, whereas a similar modification in compounds **3a**,**g** caused the opposite effect.

Compound **1h** proved to be the most selective member of the series and has significantly better selectivity than reference agents such as buspirone and NAN-190 (Table 5). Two analogues (**1h** and **4j**) active as 5-HT_{1A} receptor ligands have been evaluated for their ability to produce hypothermia and for their potential anxiolytic activity in mice. Compound **1h** was selected for its selectivity in the 5-HT_{1A} receptor (similarly to 8-OH-DPAT) and **4j** for its affinity at 5-HT_{1A} and D_2 receptors (similarly to buspirone). As shown in Table 2, **1h** and **4j** decreased rectal temperature in mice following subcutaneous administration but were less potent than 8-OH-DPAT. Following oral administration only **4j** produced a slight decrease in rectal temperature.

The results of the social interaction behavioral test are shown in Table 3. Both compounds increased the number of social interactions between two mice placed together in the same cage. The maximum anxiolytic-like effect obtained after the administration of each compound was statistically significant when compared to the values for the vehicle group. The administration of 8-OH-DPAT produced a maximum behavioral effect (132.2 s) equivalent to the one obtained after the administration of **1h** (130.8 s); however, a higher dose of this compound was needed to reach the same degree of 8-OH-DPAT-induced behavioral effect. On the other hand, **4j**, although active in the social interaction test, was much less potent than 8-OH-DPAT or **1h**.

In conclusion, we have prepared a series of bicyclohydantoin−arylpiperazine derivatives related to previously described 5-HT_{1A} ligands. In this paper, we have demonstrated that two structural features seem to improve selectivity for 5-HT_{1A} receptors: (a) The trifluoromethyl group at the *meta* position of the phenylpiperazine moiety showed the best 5-HT_{1A} affinity/selectivity profile in the series with $n = 3, 4$. This position could play an important role in order to improve

Table 2. Effects of 8-OH-DPAT, **1h**, and **4j** on Rectal Temperature in Mice[a]

compd	dose (mg/kg)	route	*T* decrease (°C)
8-OH-DPAT	0.5	sc	−0.9 ± 0.24
	2.5	sc	−1.7 ± 0.55*
	5	sc	−1.66 ± 0.42*
	10	sc	−2.26 ± 0.21*
1h	0.5	sc	0.37 ± 0.3
	2.5	sc	0.06 ± 0.13
	5	sc	−0.78 ± 0.28
	10	sc	−1.46 ± 0.13*
	20	sc	−1.56 ± 0.17*
	10	po	−0.30 ± 0.29
	20	po	0.22 ± 0.27
	30	po	−0.28 ± 0.3
	40	po	−0.85 ± 0.2
4j	0.5	sc	−0.58 ± 0.3
	2.5	sc	−0.77 ± 0.31
	5	sc	−0.92 ± 0.29
	10	sc	−1.55 ± 0.34*
	20	sc	−2.73 ± 0.3*
	10	po	0.07 ± 0.03
	20	po	−0.55 ± 0.22
	30	po	−1.23 ± 0.15
	40	po	−1.00 ± 0.19

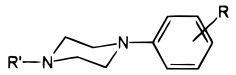
[a] Dose−response effects of sc and po administration of selected drugs on rectal temperature. Rectal temperature was measured 30 min after sc or 60 min after po administration of the vehicle or selected drugs. Values represent the means ± SEM of rectal temperature (°C) in control and drug-treated mice. *Values from drug-treated mice that are lower than 1.1 °C and significantly different (ANOVA, Student−Newmann−Keul's, $p < 0.05$) from vehicle-treated mice.

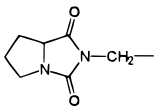
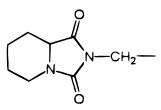
Table 3. Effects of 8-OH-DPAT, **1h**, and **4j** in the Social Interaction Behavioral Test in Mice[a]

compd	vehicle	max effect (s)	ED_{50} (mg/kg)
8-OH-DPAT	30.4	132.2*	0.58
1h	34.0	130.8*	3.58
4j	23.3	56.5*	1.25

[a] ED_{50} of selected drugs on social interaction. Social interaction was determined during a 5 min period measuring the time (s) that two mice from different cages touched each other after 30 min of the sc administration of vehicle or selected drugs. *Values from drug-treated mice that are significantly different from vehicle-treated mice (ANOVA, Student−Newmann−Keul's, $p < 0.05$).

Table 4. Affinities at 5-HT_{1A} Sites (K_i, nM)



R'/R	H[a]		
H	380	85.3	101
o-OCH_3	68	34.9	31.7
m-Cl	130	58.4	57.7
m-CF_3	175	120	78.6

[a] Data obtained from ref 27.

potency and selectivity for the 5-HT_{1A} receptor, and new substituents are the objective of future work. (b) The alkyl side chain length is a critical factor, $n = 1$ being the optimal value. Compound **1h** has substantially better selectivity than several reference agents and shows potent anxiolytic activity in the social interaction test in mice. On the basis of its *in vivo* pharmacology testing, **1h** is probably functioning as a partial to full 5-HT_{1A} agonist.

Further pharmacological properties of **1h** and the synthesis and biological evaluation of new derivatives of **1** ($n = 1$) are currently in progress, and the results will be reported in due course.

Experimental Section

Chemistry. Melting points (uncorrected) were determined on a Gallenkamp electrothermal apparatus. Infrared (IR) spectra were obtained on a Perkin-Elmer 781 infrared spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian VXR-300S or Bruker 250-AM instrument. Chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane; coupling constants (J) are in hertz. Optical rotation measurements were obtained on a Perkin-Elmer 141 polarimeter. Elemental analyses (C, H, N) were determined within 0.4% of the theoretical values. Thin-layer chromatography (TLC) was run on Merck silica gel 60 F-254 plates. For normal pressure and flash chromatography, Merck silica gel type 60 (size 70−230 and 230−400 mesh, respectively) was used. Unless stated otherwise, starting materials were used as high-grade commercial products.

The compounds **5a,b** were synthesized by published procedures. The physical data are in agreement with those given in refs 23 and 24.

General Method A. Preparation of Derivatives 1a−l. To a suspension of the hydantoins **5a,b** (9.7 mmol) and 1 mL (3.3 mmol) of formaldehyde 35% in ethanol was added the corresponding arylpiperazine (as free base). The mixture was stirred at 100 °C for 1−4 h. The reaction mixture was allowed to cool and poured into water (30 mL). The resultant precipitate was filtered, washed with water, and dried *in vacuo*. The product was converted to its hydrochloride salt.

2-[(4-Phenylpiperazin-1-yl)methyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (1a): yield 3.6 g (91%); mp 178−180 °C; IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1600, 1500 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.75 (dq, J = 12.3, 9.0 Hz, 1H, H_7), 2.00−2.14 (m, 2H, $2H_6$), 2.23−2.33 (m, 1H, H_7), 2.79 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 3.16 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 3.24 (ddd, J = 11.4, 7.8, 5.1 Hz, 1H, H_5), 3.69 (dt, J = 11.4, 7.8 Hz, 1H, H_5), 4.13 (t, J = 8.4 Hz, 1H, H_{7a}), 4.50 (s, 2H, NCH_2N), 6.83 (t, J = 8.1 Hz, 1H, H_4-phenyl), 6.91 (d, J = 8.1 Hz, 2H, H_2- and H_6-phenyl), 7.25 (t, J = 8.1 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 26.8 (C_6), 27.6 (C_7), 45.4 (C_5), 49.1 ($2CH_2$-pip), 50.2 ($2CH_2$-pip), 60.0 (NCH_2N), 63.1 (C_{7a}), 116.2 (C_2- and C_6-phenyl), 119.8 (C_4-phenyl), 129.0 (C_3- and C_5-phenyl), 151.0 (C_1-phenyl), 161.1 (C_3), 174.8 (C_1). Anal. ($C_{17}H_{22}N_4O_2 \cdot 2HCl \cdot {}^3/_2H_2O$) C, H, N.

2-[[4-(*o*-Methoxyphenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (1b): yield 3.4 g (85%); mp 168−170 °C; IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1610, 1520, 1490 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.86−2.18 (m, 4H, $2H_6$, $2H_7$), 3.20−3.61 (m, 10H, $4CH_2$-pip, $2H_5$), 3.83 (s, 3H, OCH_3), 4.36 (t, J = 8.1 Hz, 1H, H_{7a}), 4.66 (s, 2H, NCH_2N), 6.89−7.10 (m, 4H, H_3-, H_4-, H_5-, and H_6-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 26.1 (C_6), 26.5 (C_7), 45.1 (C_5), 47.2 ($2CH_2$-pip), 49.6 ($2CH_2$-pip), 55.4 (OCH_3), 61.0 (NCH_2N), 63.0 (C_{7a}), 112.1 (C_6-phenyl), 118.6 (C_3-phenyl), 120.8 (C_4-phenyl), 124.1 (C_5-phenyl), 138.0 (C_1-phenyl), 151.9 (C_2-phenyl), 158.4 (C_3), 173.8 (C_1). Anal. ($C_{18}H_{24}N_4O_3 \cdot 2HCl$) C, H, N.

2-[[4-(*m*-Chlorophenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (1c): yield 3.4 g (81%); mp 146−148 °C; IR (KBr, cm^{-1}) 1765 (CON), 1710 (NCON), 1595, 1550, 1480 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.64 (dq, J = 12.4, 9.0 Hz, 1H, H_7), 1.93−2.07 (m, 2H, $2H_6$), 2.15−2.27 (m, 1H, H_7), 2.72 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.00 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.18 (ddd, J = 11.4, 7.8, 5.1 Hz, 1H, H_5), 3.63 (dt, J = 11.4, 7.8 Hz, 1H, H_5), 4.05 (dd, J = 9.0, 7.8 Hz, 1H, H_{7a}), 4.42 (s, 2H, NCH_2N), 6.75−6.80 (m, 3H, H_2-, H_4-, and H_6-phenyl), 6.87 (t, J = 8.4 Hz, 1H, H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 26.7 (C_6), 27.6 (C_7), 45.4 (C_5), 50.1 ($2CH_2$-pip), 50.2 ($2CH_2$-pip), 60.0 (NCH_2N), 63.1 (C_{7a}), 115.2 (C_6-phenyl), 115.5 (C_2-phenyl), 117.9 (C_4-phenyl), 147.8 (C_5-phenyl), 155.5 (C_3-

Table 5. Binding Profile for **1h**, Buspirone, and NAN-190

	$K_i \pm$ SEM (nM)			
compd	5-HT_{1A} [^{3}H]-8-OH-DPAT	α_1 [^{3}H]prazosin	D_2 [^{3}H]raclopride	5-HT_{2A} [^{3}H]ketanserin
1h	31.7 ± 1.7	>1000	>10000	>1000
buspirone	20.5 ± 2.3	367 ± 32	852 ± 70	482 ± 40
NAN-190[a]	0.6	0.8	64	ND

[a] Data obtained from ref 19.

phenyl), 158.7 (C_1-phenyl), 161.1 (C_3), 174.7 (C_1). Anal. ($C_{17}H_{21}ClN_4O_2 \cdot 2HCl \cdot {}^1/_2H_2O$) C, H, N.

2-[[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]methyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (1d): yield 4.2 g (91%); mp 158−159 °C; IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1610, 1490 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.71 (dq, J = 12.6, 9.0 Hz, 1H, H_7), 1.98−2.18 (m, 2H, $2H_6$), 2.24−2.33 (m, 1H, H_7), 2.79 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 3.21 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 3.19−3.30 (m, 1H, H_5), 3.70 (dt, J = 11.1, 7.5 Hz, 1H, H_5), 4.13 (dd, J = 9.0, 7.8 Hz, 1H, H_{7a}), 4.50 (s, 2H, NCH_2N), 7.01−7.08 (m, 3H, H_2-, H_4-, and H_6-phenyl), 7.33 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 26.8 (C_6), 27.6 (C_7), 45.4 (C_5), 49.1 ($2CH_2$-pip), 50.2 ($2CH_2$-pip), 60.0 (NCH_2N), 63.1 (C_{7a}), 112.2 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 115.8 (q, $^3J_{C-F}$ = 4.0 Hz, C_4-phenyl), 118.8 (C_6-phenyl), 124.1 (q, $^1J_{C-F}$ = 272.4 Hz, CF_3), 129.4 (C_5-phenyl), 131.4 (q, $^2J_{C-F}$ = 31.9 Hz, C_3-phenyl), 151.2 (C_1-phenyl), 161.1 (C_3), 174.7 (C_1). Anal. ($C_{18}H_{21}F_3N_4O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

2-[[4-(*p*-Fluorophenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (1e): yield 3.9 g (95%); mp 180−182 °C; IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1510, 1480 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.82 (dq, J = 12.3, 9.0 Hz, 1H, H_7), 2.02−2.18 (m, 2H, $2H_6$), 2.24−2.34 (m, 1H, H_7), 2.81 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.10 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.26 (ddd, J = 11.4, 7.8, 5.1 Hz, 1H, H_5), 3.70 (dt, J = 11.4, 7.8 Hz, 1H, H_5), 4.14 (dd, J = 9.0, 7.9 Hz, 1H, H_{7a}), 4.51 (s, 2H, NCH_2N), 6.84−6.98 (m, 4H, H_2-, H_3-, H_5-, and H_6-phenyl); ^{13}C-NMR ($CDCl_3$) δ 26.8 (C_6), 27.6 (C_7), 45.4 (C_5), 50.1 ($4CH_2$-pip), 59.9 (NCH_2N), 63.1 (C_{7a}), 115.4 (d, $^2J_{C-F}$ = 22.2 Hz, C_3- and C_5-phenyl), 118.0 (d, $^3J_{C-F}$ = 7.5 Hz, C_2- and C_6-phenyl), 147.6 (C_1-phenyl), 157.2 (d, $^1J_{C-F}$ = 239.7 Hz, C_4-phenyl), 161.0 (C_3), 174.7 (C_1). Anal. ($C_{17}H_{21}FN_4O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

2-[[4-(*p*-Nitrophenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (1f): yield 4.1 g (95%); mp 150−152 °C; IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1600, 1510, 1490 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.70 (dq, J = 12.6, 9.0 Hz, 1H, H_7), 2.01−2.16 (m, 2H, $2H_6$), 2.23−2.33 (m, 1H, H_7), 2.79 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.26 (ddd, J = 11.4, 7.8, 5.1 Hz, 1H, H_5), 3.42 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.70 (dt, J = 11.4, 7.8 Hz, 1H, H_5), 4.14 (t, J = 8.4 Hz, 1H, H_{7a}), 4.50 (s, 2H, NCH_2N), 6.79 (d, J = 9.1 Hz, 2H, H_2- and H_6-phenyl), 7.27 (d, J = 9.1 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 26.8 (C_6), 27.6 (C_7), 45.4 (C_5), 46.9 ($2CH_2$-pip), 49.8 ($2CH_2$-pip), 59.9 (NCH_2N), 63.2 (C_{7a}), 112.7 (C_2- and C_6-phenyl), 125.8 (C_3- and C_5-phenyl), 138.5 (C_4-phenyl), 154.5 (C_1-phenyl), 160.8 (C_3), 174.6 (C_1). Anal. ($C_{17}H_{21}N_5O_4 \cdot HCl \cdot H_2O$) C, H, N.

2-[(4-Phenylpiperazin-1-yl)methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (1g): yield 3.0 g (76%); mp 178−180 °C; IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1640, 1600, 1500 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.24−1.56 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.71−1.76 (m, 1H, H_{6eq}), 1.96−2.04 (m, 1H, H_{7eq}), 2.20−2.40 (m, 1H, H_{8eq}), 2.79 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 2.80−2.83 (m, 1H, H_{5ax}), 3.16 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 3.79 (dd, J = 11.8, 4.3 Hz, 1H, H_{8a}), 4.16 (dd, J = 12.7, 4.2 Hz, 1H, H_{5eq}), 4.52 (s, 2H, NCH_2N), 6.84 (t, J = 7.8 Hz, 1H, H_4-phenyl), 6.90 (d, J = 7.8 Hz, 2H, H_2- and H_6-phenyl), 7.24 (dd, J = 8.4, 7.8 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.6 (C_7), 24.7 (C_6), 27.8 (C_8), 39.2 (C_5), 49.1 ($2CH_2$-pip), 50.2 ($2CH_2$-pip), 57.2(C_{8a}), 59.7 (NCH_2N), 116.1 (C_2- and C_6-phenyl), 119.7 (C_4-phenyl), 128.9 (C_3- and C_5-phenyl), 151.0 (C_1-phenyl), 154.9 (C_3), 174.1 (C_1). Anal. ($C_{18}H_{24}N_4O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

2-[[4-(*o*-Methoxyphenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (1h): yield 3.4 g (78%); mp 160−162 °C; IR (KBr, cm^{-1}) 1790 (CON), 1730 (NCON), 1620, 1490 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.16−1.56 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.72−1.77 (m, 1H, H_{6eq}), 1.97−2.02 (m, 1H, H_{7eq}), 2.19−2.24 (m, 1H, H_{8eq}), 2.78−2.87 (m, 1H, H_{5ax}), 2.86 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.05 (br t, 4H, $2CH_2$-pip), 3.80 (dd, J = 11.3, 4.2 Hz, 1H, H_{8a}), 3.84 (s, 3H, OCH_3), 4.14−4.90 (m, 1H, H_{5eq}), 4.54 (s, 2H, NCH_2N), 6.83−7.20 (m, 4H, H_3-, H_4-, H_5-, and H_6-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.6 (C_7), 24.7 (C_6), 27.6 (C_8), 39.1 (C_5), 50.3 ($2CH_2$-pip), 50.4 ($2CH_2$-pip), 55.0 (OCH_3), 57.2 (C_{8a}), 59.8 (NCH_2N), 110.6 (C_6-phenyl), 118.0 (C_3-phenyl), 120.7 (C_4-phenyl), 122.8 (C_5-phenyl), 140.9 (C_1-phenyl), 151.9 (C_2-phenyl), 155.0 (C_3), 174.2 (C_1). Anal. ($C_{19}H_{26}N_4O_3 \cdot 2HCl \cdot H_2O$) C, H, N.

2-[[4-(*m*-Chlorophenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (1i): yield 1.5 g (31%); mp 176−178 °C; IR (KBr, cm^{-1}) 1775 (CON), 1715 (NCON), 1595, 1560, 1480 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.19−1.56 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.71−1.76 (m, 1H, H_{6eq}), 1.95−2.01 (m, 1H, H_{7eq}), 2.18−2.23 (m, 1H, H_{8eq}), 2.76 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 2.82 (td, J = 12.7, 3.7 Hz, 1H, H_{5ax}), 3.14 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.79 (dd, J = 11.7, 4.3 Hz, 1H, H_{8a}), 4.14 (dd, J = 12.7, 3.7 Hz, 1H, H_{5eq}), 4.50 (s, 2H, NCH_2N), 6.74−6.81 (m, 2H, H_4- and H_6-phenyl), 6.84 (t, J = 2.2 Hz, 1H, H_2-phenyl), 7.15 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.6 (C_7), 24.7 (C_6), 27.9 (C_8), 39.2 (C_5), 48.6 ($2CH_2$-pip), 50.0 ($2CH_2$-pip), 57.2 (C_{8a}), 59.7 (NCH_2N), 113.9 (C_6-phenyl), 115.7 (C_2-phenyl), 119.2 (C_4-phenyl), 129.8 (C_5-phenyl), 134.7 (C_3-phenyl), 152.1 (C_1-phenyl), 154.9 (C_3), 174.1 (C_1). Anal. ($C_{18}H_{23}ClN_4O_2 \cdot 2HCl \cdot 3H_2O$) C, H, N.

2-[[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (1j): yield 2.0 g (45%); mp 165−167 °C; IR (KBr, cm^{-1}) 1775 (CON), 1720 (NCON), 1630, 1600, 1585 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.21−1.57 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.74−1.78 (m, 1H, H_{6eq}), 1.98−2.03 (m, 1H, H_{7eq}), 2.21−2.27 (m, 1H, H_{8eq}), 2.80 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 2.84 (td, J = 12.9, 3.3 Hz, 1H, H_{5ax}), 3.21 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.81 (dd, J = 11.8, 4.2 Hz, 1H, H_{8a}), 4.17 (dd, J = 12.6, 4.2 Hz, 1H, H_{5eq}), 4.53 (s, 2H, NCH_2N), 7.02−7.12 (m, 3H, H_2-, H_4-, and H_6-phenyl), 7.33 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.5 (C_7), 24.7 (C_6), 27.9 (C_8), 39.2 (C_5), 48.6 ($2CH_2$-pip), 50.0 ($2CH_2$-pip), 57.2(C_{8a}), 59.7 (NCH_2N), 112.2 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 115.8 (q, $^3J_{C-F}$ = 4.0 Hz, C_4-phenyl), 118.7 (C_6-phenyl), 124.2 (q, $^1J_{C-F}$ = 275.1 Hz, CF_3), 129.4 (C_5-phenyl), 131.2 (q, $^2J_{C-F}$ = 31.7 Hz, C_3-phenyl), 151.1 (C_1-phenyl), 154.9 (C_3), 174.1 (C_1). Anal. ($C_{19}H_{23}F_3N_4O_2 \cdot 2HCl$) C, H, N.

2-[[4-(*p*-Fluorophenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (1k): yield 1.9 g (46%); mp 170−172 °C; IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1620, 1600, 1510 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.11−1.48 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.63−1.68 (m, 1H, H_{6eq}), 1.88−1.92 (m, 1H, H_{7eq}), 2.13 (dd, J = 12.6, 3.0 Hz, 1H, H_{8eq}), 2.70 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 2.73 (td, J = 12.8, 3.3 Hz, 1H, H_{5ax}), 2.98 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.70 (dd, J = 11.7, 4.2 Hz, 1H, H_{8a}), 4.07 (dd, J = 13.2, 3.7 Hz, 1H, H_{5eq}), 4.42 (s, 2H, NCH_2N), 6.75 (dd, J = 9.0 Hz, $^4J_{H-F}$ = 4.8 Hz, 2H, H_2- and H_6-phenyl), 6.85 (t, J = 9.0 Hz, $^3J_{H-F}$ = 9.0 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.6 (C_7), 24.7 (C_6), 27.8 (C_8), 39.2 (C_5), 50.1 ($2CH_2$-pip), 50.2 ($2CH_2$-pip), 57.2 (C_{8a}), 59.7 (NCH_2N), 115.3 (d, $^2J_{C-F}$ = 21.9 Hz, C_3- and C_5-phenyl), 117.8 (d, $^3J_{C-F}$ = 8.3 Hz, C_2- and C_6-phenyl), 147.7 (C_1-phenyl), 154.9 (C_3), 157.0 (d, $^1J_{C-F}$ = 239.7 Hz, C_4-phenyl), 174.1 (C_1). Anal. ($C_{18}H_{23}FN_4O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

2-[[4-(*p*-Nitrophenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (1l): yield 3.2 g (72%); mp 176−178 °C; IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1600, 1520, 1490 (Ar); ^{13}H-NMR ($CDCl_3$) δ 1.30−1.51 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.74−1.76 (m, 1H, H_{6eq}), 1.98−2.02 (m, 1H, H_{7eq}), 2.21−2.25 (m, 1H, H_{8eq}), 2.77−2.85 (m, 5H, $2CH_2$-pip,

H_{5ax}), 3.41 (br t, 4H, $2CH_2$-pip), 3.83 (dd, J = 11.7, 4.2 Hz, 1H, H_{8a}), 4.16 (d, J = 12.7 Hz, 1H, H_{5eq}), 4.52 (s, 2H, NCH_2N), 6.78 (d, J = 9.0 Hz, 2H, H_2- and H_6-phenyl), 8.08 (d, J = 8.7 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 23.0 (C_7), 24.7 (C_6), 27.8 (C_8), 39.1 (C_5), 46.8 ($2CH_2$-pip), 49.7 ($2CH_2$-pip), 57.1 (C_{8a}), 59.6 (NCH_2N), 112.5 (C_2- and C_6-phenyl), 125.7 (C_3- and C_5-phenyl), 138.1 (C_4-phenyl), 154.5 (C_1-phenyl), 154.7 (C_3), 174.0 (C_1). Anal. ($C_{18}H_{23}N_5O_4 \cdot 2HCl \cdot {}^1/_2H_2O$) C, H, N.

2-(2-Chloroethyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (6a). To a stirred suspension of L-proline (5.0 g, 44.0 mmol) in acetone (50 mL) was added dropwise 2-chloroethyl isocyanate (4.0 mL, 44.0 mmol). The mixture was refluxed for 2 h under nitrogen. The L-1-[(2-chloroethyl)carbamoyl]-2-pyrrolidinecarboxylic acid was filtered and crystallized from dioxane/chloroform: yield 8.1 g (84%); mp 154−156 °C; $[\alpha]^{25}_D$ = −55.5° (c = 1, MeOH); IR (KBr, cm^{-1}) 3380 (NH), 1720 (CONH), 1600 (COOH); ^{1}H-NMR (Me_2SO-d_6) δ 1.79−2.04 (m, 4H, $2H_3$, $2H_4$), 2.05−2.50 (m, 1H, H_5), 3.19−3.39 (m, 3H, NCH_2 or CH_2Cl, H_5), 3.57 (t, J = 4.0 Hz, 2H, CH_2Cl or NCH_2), 4.17 (dd, J = 9.3, 3.0 Hz, 1H, H_2), 6.59 (t, J = 5.4 Hz, 1H, NH); ^{13}C-NMR (Me_2SO-d_6) δ 23.9 (C_4), 29.1 (C_3), 41.9, 43.4 (NCH_2, CH_2Cl), 45.5 (C_5), 58.4 (C_2), 155.9 (CONH), 174.3 (COOH). Anal. ($C_8H_{13}ClN_2O_3$) C, H, N.

A solution of L-1-[(2-chloroethyl)carbamoyl]-2-pyrrolidinecarboxylic acid (5.0 g, 23.0 mmol) in 25% hydrochloric acid (30 mL) was refluxed for 35 min. After evaporation of the solvent, the resultant oil was dissolved in acetone and dried over $MgSO_4$ to give 4.3 g (80%) of **6a**; bp 80−82 °C (0.01 mmHg); $[\alpha]^{25}_D$ = −40.6° (c = 1, MeOH); IR ($CHCl_3$, cm^{-1}) 1780 (CON), 1725 (NCON); ^{1}H-NMR ($CDCl_3$) δ 1.73 (tt, J = 12.0, 9.0 Hz, 1H, H_7), 2.03−2.16 (m, 2H, $2H_6$), 2.22−2.30 (m, 1H, H_7), 3.22−3.30 (m, 1H, H_5), 3.63−3.81 (m, 5H, H_5, NCH_2, CH_2-Cl), 4.16 (t, J = 8.1 Hz, 1H, H_{7a}); ^{13}C-NMR ($CDCl_3$) δ 26.0 (C_6), 26.6 (C_7), 39.2, 39.8 (NCH_2, CH_2Cl), 44.7 (C_5). Anal. (C_8H_{11}-ClN_2O_2) C, H, N.

2-(2-Chloroethyl)-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (6b). To a stirred suspension of ethyl pipecolinate (4.0 g, 25 mmol) was added dropwise 2-chloroethyl isocyanate (2.2 mL, 25.0 mmol). The mixture was refluxed for 2 h under nitrogen. The solvent was evaporated under reduced pressure to afford 1-[(2-chloroethyl)carbamoyl]-2-piperidinecarboxylic acid ethyl ester: yield 6.3 g (95%); bp 150−152 °C (0.7 mmHg); IR ($CHCl_3$, cm^{-1}) 3330 (NH), 1740 (COOEt), 1640, 1540 (CONH); ^{1}H-NMR ($CDCl_3$) δ 1.13−1.49 (m, 6H, CH_3, H_{3ax}, H_{4ax}, H_{5ax}), 1.66−1.70 (m, 1H, H_{5eq}), 1.90−1.95 (m, 1H, H_{4eq}), 2.12−2.17 (m, 1H, H_{3eq}), 2.77 (td, J = 12.6, 3.6 Hz, 1H, H_{6ax}), 3.45−3.56 (m, 1H, H_{6eq}), 3.64 (t, J = 5.7 Hz, 2H, NCH_2 or CH_2Cl), 3.70−3.80 (m, 4H, CH_2CH_3, CH_2Cl or NCH_2), 4.09 (dd, 1H, J = 13.5, 4.8 Hz, H_2); ^{13}C-NMR ($CDCl_3$) δ 14.0 (CH_3), 20.2 (C_4), 24.4 (C_5), 26.4 (C_3), 41.6 (C_6), 42.4, 44.3 (NCH_2, CH_2Cl), 53.5 (C_2), 60.8 (CH_2CH_3), 158.2 (CONH), 171.9 (COOEt). Anal. ($C_{11}H_{19}ClN_2O_3$) C, H, N.

To 6.0 g (28.0 mmol) of 1-[(2-chloroethyl)carbamoyl]-2-piperidinecarboxylic acid ethyl ester was added a solution of 10% KOH in ethanol until basic pH; then 25 mL of ethanol was added, and the mixture was refluxed for 45 min. After evaporation of the solvent, the resultant oil was dissolved in diethyl ether and dried over $MgSO_4$ to give 5.2 g (85%) of **6b**: bp 125 °C (0.4 mmHg); IR ($CHCl_3$, cm^{-1}) 1770 (CON), 1715 (NCON); ^{1}H-NMR ($CDCl_3$) δ 1.25−1.59 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.74−1.79 (m, 1H, H_{6eq}), 1.98−2.04 (m, 1H, H_{7eq}), 2.20−2.25 (m, 1H, H_{8eq}), 2.86 (td, J = 12.6, 3.6 Hz, 1H, H_{5ax}), 3.73 (t, J = 6.1 Hz, 2H, NCH_2 or CH_2Cl), 3.79−3.88 (m, 3H, CH_2Cl or NCH_2, H_{8a}), 4.14−4.20 (m, 1H, H_{5eq}); ^{13}C-NMR ($CDCl_3$) δ 22.4 (C_7), 24.6 (C_6), 27.5 (C_8), 39.0, 39.6, 40.3 (NCH_2, CH_2Cl, C_5), 57.1 (C_{8a}), 153.6 (C_3), 172.6 (C_1). Anal. ($C_9H_{13}ClN_2O_2$) C, H, N.

General Method B. Preparation of Derivatives 2a−l. To a suspension of **6a,b** (15.0 mmol) and Na_2CO_3 (30.0 mmol) in acetonitrile (50 mL) was added the corresponding arylpiperazine (15.0 mmol). The mixture was refluxed for 3−5 days (TLC) and hot filtered. After evaporation of the solvent, the crude oil was purified by column chromatography (eluent: ethyl acetate/ethanol, relative proportions depending upon the compound). The free base was converted to its hydrochloride salt.

2-[2-(4-Phenylpiperazin-1-yl)ethyl]-1,3-dioxoperhydropyrrolo[1,2−*c*]imidazole (2a): yield 2.0 g (40%); mp 116−118 °C (H_2O); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1610, 1510, 1460 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.72 (tt, J = 12.4, 8.6 Hz, 1H, H_7), 1.99−2.08 (m, 2H, $2H_6$), 2.16−2.26 (m, 1H, H_7), 2.65−2.66 (m, 6H, $3CH_2$-pip), 3.12−3.15 (m, 4H, CH_2-Npip, CH_2-pip), 3.18−3.22 (m, 1H, H_5), 3.61−3.80 (m, 3H, NCH_2, H_5), 4.07 (t, J = 8.0 Hz, 1H, H_{7a}), 6.83 (t, J = 7.8 Hz, 1H, H_4-phenyl), 6.92 (d, J = 7.8 Hz, 2H, H_2- and H_6-phenyl), 7.25 (t, J = 7.8 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 26.7 (C_6), 27.4 (C_7), 35.7 (NCH_2), 45.5 (C_5), 48.9 ($2CH_2$-pip), 52.7 ($2CH_2$-pip), 54.5 (CH_2-Npip), 63.1 (C_{7a}), 115.7 (C_2- and C_6-phenyl), 119.3 (C_4-phenyl), 128.8 (C_3- and C_5-phenyl), 151.0 (C_1-phenyl), 160.8 (C_3), 173.9 (C_1). Anal. ($C_{18}H_{24}N_4O_2$) C, H, N.

2-[2-[4-(*o*-Methoxyphenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (2b): yield 2.1 g (32%); mp 186−188 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1610, 1520 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.91−2.14 (m, 4H, $2H_6$, $2H_7$), 3.13−3.19 (m, 1H, H_5), 3.25 (m, 4H, $2CH_2$-pip), 3.35 (br t, 2H, CH_2-Npip), 3.50 (m, 4H, $2CH_2$-pip), 3.58−3.78 (m, 3H, NCH_2, H_5), 3.81 (s, 3H, OCH_3), 4.23 (t, J = 8.1 Hz, 1H, H_{7a}), 6.91 (t, J = 7.2 Hz, 1H, H_4-phenyl), 6.99−7.08 (m, 3H, H_3-, H_5-, and H_6-phenyl); ^{13}C-NMR (Me_2-SO-d_6) δ 26.0 (C_6), 26.9 (C_7), 33.1 (NCH_2), 45.2 (C_5), 46.8 ($2CH_2$-pip), 50.6, 51.2 ($2CH_2$-pip), 52.8 (CH_2-Npip), 55.6 (OCH_3), 63.4 (C_{7a}), 112.2 (C_6-phenyl), 118.7 (C_3-phenyl), 122.0 (C_4-phenyl), 124.2 (C_5-phenyl), 138.6 (C_1-phenyl), 151.9 (C_2-phenyl), 159.7 (C_3), 174.2 (C_1). Anal. ($C_{19}H_{26}N_4O_3 \cdot 2HCl$) C, H, N.

2-[2-[4-(*m*-Chlorophenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (2c): yield 2.0 g (30%); mp 174−176 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1610, 1510 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.90−2.10 (m, 4H, $2H_6$, $2H_7$), 3.15−3.39 (m, 7H, H_5, $2CH_2$-pip, CH_2-Npip), 3.61−3.65 (m, 1H, H_5), 3.69−3.73 (m, 2H, CH_2-pip), 3.79 (m, 2H, NCH_2), 3.84−3.93 (m, 2H, CH_2-pip), 4.25 (t, J = 7.8 Hz, 1H, H_{7a}), 6.87 (d, J = 8.1 Hz, 1H, H_6-phenyl), 6.99 (d, J = 8.1 Hz, 1H, H_4-phenyl), 7.07 (s, 1H, H_2-phenyl), 7.27 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 26.2 (C_6), 27.2 (C_7), 33.3 (NCH_2), 44.9 ($2CH_2$-pip), 45.3 (C_5), 50.2, 50.7 ($2CH_2$-pip), 52.8 (CH_2-Npip), 63.6 (C_{7a}), 114.5 (C_6-phenyl), 115.6 (C_2-phenyl), 119.6 (C_4-phenyl), 131.0 (C_5-phenyl), 134.3 (C_3-phenyl), 150.9 (C_1-phenyl), 159.9 (C_3), 174.5 (C_1). Anal. ($C_{18}H_{23}ClN_4O_2 \cdot 2HCl$) C, H, N.

2-[2-[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (2d): yield 2.9 g (42%); mp 206−208 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1610, 1460 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.92−2.10 (m, 4H, $2H_6$, $2H_7$), 3.15−3.40 (m, 7H, H_5, $2CH_2$-pip, CH_2-Npip), 3.51−3.82 (m, 5H, H_5, CH_2-pip, NCH_2), 3.98 (br t, 2H, CH_2-pip), 4.26 (t, J = 8.0 Hz, 1H, H_{7a}), 7.15 (d, J = 7.8 Hz, 1H, H_6-phenyl), 7.29 (s, 1H, H_2-phenyl), 7.32 (d, J = 7.8 Hz, 1H, H_4-phenyl), 7.48 (t, J = 7.8 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 26.1 (C_6), 27.1 (C_7), 33.2 (NCH_2), 44.7 ($2CH_2$-pip), 45.3 (C_5), 50.1, 50.7 ($2CH_2$-pip), 52.8 (CH_2-Npip), 63.5 (C_{7a}), 111.9 (q, $^3J_{C-F}$ = 3.0 Hz, C_2-phenyl), 116.0 (q, $^3J_{C-F}$ = 3.0 Hz, C_4-phenyl), 119.5 (C_6-phenyl), 124.6 (q, $^1J_{C-F}$ = 272.0 Hz, CF_3), 130.2 (q, $^2J_{C-F}$ = 26.2 Hz, C_3-phenyl), 130.4 (C_5-phenyl), 150.0 (C_1-phenyl), 159.8 (C_3), 174.4 (C_1). Anal. ($C_{19}H_{23}F_3N_4O_2 \cdot 2HCl$) C, H, N.

2-[2-[4-(*p*-Fluorophenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (2e): yield 1.9 g (30%); mp 196−198 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1520 (Ar); ^{1}H-NMR (CD_3OD) δ 1.97−2.26 (m, 4H, $2H_6$, $2H_7$), 3.26−3.50 (m, 3H, H_5, CH_2-pip), 3.56 (t, J = 5.7 Hz, 2H, CH_2-Npip), 3.60−3.82 (m, 7H, H_5, $2CH_2$-pip, NCH_2), 3.94−3.97 (m, 2H, CH_2-pip), 4.33 (dd, J = 9.3, 7.2 Hz, 1H, H_{7a}), 7.16 (t, J = 8.7 Hz, $^3J_{H-F}$ = 8.7 Hz, 2H, H_3- and H_5-phenyl), 7.35 (dd, J = 9.0 Hz, $^4J_{H-F}$ = 4.8 Hz, 2H, H_2- and H_6-phenyl); ^{13}C-NMR (CD_3OD) δ 27.5 (C_6), 28.2 (C_7), 34.4 (NCH_2), 36.2 (C_5), 49.8 ($2CH_2$-pip), 52.5 (CH_2-Npip), 55.8 ($2CH_2$-pip), 65.3 (C_{7a}), 117.2 (d, $^2J_{C-F}$ = 22.8 Hz, C_3- and C_5-phenyl), 121.4 (d, $^3J_{C-F}$ = 8.2 Hz, C_2- and C_6-phenyl), 145.0 (C_1-phenyl), 160.8 (d, $^1J_{C-F}$ = 242.3 Hz, C_4-phenyl), 161.5 (C_3), 176.0 (C_1). Anal. ($C_{18}H_{23}FN_4O_2 \cdot 2HCl$) C, H, N.

2-[2-[4-(*p*-Nitrophenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (2f): yield 2.0 g (30%);

mp 130−132 °C (ethanol); IR (KBr, cm^{-1}) 1780 (CON), 1730 (NCON), 1620, 1520, 1510 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.71−1.89 (m, 1H, H_7), 1.93−2.20 (m, 3H, $2H_6$, H_7), 3.12−3.18 (m, 1H, H_5), 3.30−3.54 (m, 11H, $3CH_2$-pip, CH_2-Npip, H_5, NCH_2), 3.73 (br t, 2H, CH_2-pip), 4.22 (t, J = 7.9 Hz, 1H, H_{7a}), 7.11 (d, J = 9.3 Hz, 2H, H_2- and H_6-phenyl), 8.09 (d, J = 9.3 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 26.5 (C_6), 26.8 (C_7), 33.2 (NCH_2), 43.8 ($2CH_2$-pip), 45.2 (C_5), 50.6 ($2CH_2$-pip), 53.0 (CH_2-Npip), 63.4 (C_{7a}), 113.8 (C_2- and C_6-phenyl), 125.7 (C_3- and C_5-phenyl), 138.8 (C_4-phenyl), 153.9 (C_1-phenyl), 159.8 (C_3), 174.1 (C_1). Anal. ($C_{18}H_{23}N_5O_4$·2HCl) C, H, N.

2-[2-(4-Phenylpiperazin-1-yl)ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (2g): yield 3.2 g (49%); mp 193−195 °C (chloroform/ethyl acetate); IR (KBr, cm^{-1}) 1760 (CON), 1700 (NCON), 1600, 1490, 1460 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.30−1.55 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.59−1.66 (m, 1H, H_{6eq}), 1.82−1.89 (m, 1H, H_{7eq}), 1.93−1.99 (m, 1H, H_{8eq}), 2.81 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.18−3.30 (m, 4H, CH_2-Npip, CH_2-pip), 3.36 (br t, 2H, NCH_2), 3.68 (t, J = 12.0 Hz, 2H, CH_2-pip), 3.80−3.83 (m, 4H, $2CH_2$-pip), 3.90−4.02 (m, 2H, H_{5eq}, H_{8a}), 6.89 (t, J = 8.1 Hz, 1H, H_4-phenyl), 7.04 (d, J = 8.1 Hz, 2H, H_2- and H_6-phenyl), 7.27 (t, J = 8.1 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (C_7), 24.4 (C_6), 26.1 (C_8), 32.5 (NCH_2), 38.9 (C_5), 45.2 ($2CH_2$-pip), 50.2, 50.4 ($2CH_2$-pip), 52.7 (CH_2-Npip), 57.0 (C_{8a}), 116.1 (C_2- and C_6-phenyl), 120.4 (C_4-phenyl), 129.2 (C_3- and C_5-phenyl), 149.2 (C_1-phenyl), 153.4 (C_3), 173.2 (C_1). Anal. ($C_{19}H_{26}N_4O_2$·2HCl·H_2O) C, H, N.

2-[2-[4-(*o*-Methoxyphenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (2h): yield 4.5 g (65%); mp 178−180 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1755 (CON), 1700 (NCON), 1620, 1600, 1510 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.47−1.61 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.74−1.76 (m, 1H, H_{6eq}), 1.99−2.02 (m, 1H, H_{7eq}), 2.14−2.18 (m, 1H, H_{8eq}), 2.90 (td, J = 12.0, 3.0 Hz, 1H, H_{5ax}), 3.53 (m, 2H, CH_2-Npip), 3.60−3.64 (m, 4H, $2CH_2$-pip), 3.94−3.99 (m, 2H, NCH_2), 4.03 (s, 3H, OCH_3), 4.10−4.17 (m, 4H, $2CH_2$-pip), 4.25−4.36 (m, 2H, H_{5eq}, H_{8a}), 7.03 (d, J = 7.8 Hz, 1H, H_6-phenyl), 7.04 (t, J = 7.8 Hz, 1H, H_4-phenyl), 7.44 (t, J = 7.8 Hz, 1H, H_5-phenyl), 8.07 (d, J = 7.8 Hz, 1H, H_3-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.6 (C_7), 24.5 (C_6), 26.2 (C_8), 32.5 (NCH_2), 39.4 (C_5), 48.5 ($2CH_2$-pip), 48.9 ($2CH_2$-pip), 54.7 (CH_2-Npip), 55.9 (OCH_3), 58.0 (C_{8a}), 113.1 (C_6-phenyl), 121.5 (C_3-phenyl), 123.3 (C_4-phenyl), 128.9 (C_5-phenyl), 131.2 (C_1-phenyl), 152.4 (C_2-phenyl), 153.4 (C_3), 173.7 (C_1). Anal. ($C_{20}H_{28}N_4O_3$·2HCl·H_2O) C, H, N.

2-[2-[4-(*m*-Chlorophenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (2i): yield 2.2 g (35%); mp 224−226 °C (ethanol); IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1600, 1560, 1490 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.37−1.58 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.68−1.70 (m, 1H, H_{6ec}), 1.93−1.95 (m, 1H, H_{7ec}), 2.10−2.14 (m, 1H, H_{8ec}), 2.89 (td, J = 12.0, 3.3 Hz, 1H, H_{5ax}), 3.10 (br t, 2H, CH_2-pip), 3.35 (br t, 2H, CH_2-Npip), 3.57−3.62 (m, 2H, CH_2-pip), 3.74−3.78 (m, 2H, CH_2-pip), 3.83−3.96 (m, 4H, NCH_2, H_{5ec}, H_{8a}), 4.05−4.09 (m, 2H, CH_2-pip), 6.86 (d, J = 8.1 Hz, 1H, H_6-phenyl), 6.93 (d, J = 8.1 Hz, 1H, H_4-phenyl), 6.97 (s, 1H, H_2-phenyl), 7.19 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.5 (C_7), 24.5 (C_6), 26.2 (C_8), 32.4 (NCH_2), 39.3 (C_5), 46.4 ($2CH_2$-pip), 51.1 ($2CH_2$-pip), 54.3 (CH_2-Npip), 57.9 (C_{8a}), 115.2 (C_6-phenyl), 117.4 (C_2-phenyl), 122.2 (C_4-phenyl), 130.4 (C_5-phenyl), 135.1 (C_3-phenyl), 149.3 (C_1-phenyl), 153.4 (C_3), 173.5 (C_1). Anal. ($C_{19}H_{25}ClN_4O_2$·HCl) C, H, N.

2-[2-[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (2j): yield 1.3 g (20%); mp 208−210 °C (ethyl acetate); IR (KBr, cm^{-1}) 1760 (CON), 1700 (NCON), 1600, 1495 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.41−1.54 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.68−1.70 (m, 1H, H_{6eq}), 1.93−1.95 (m, 1H, H_{7eq}), 2.09−2.12 (m, 1H, H_{8eq}), 2.89 (td, J = 12.6, 3.6 Hz, 1H, H_{5ax}), 2.99−3.02 (m, 2H, CH_2-pip), 3.34−3.35 (m, 2H, CH_2-Npip), 3.61−3.78 (m, 4H, $2CH_2$-pip), 3.90−3.98 (m, 4H, NCH_2, H_{5eq}, H_{8a}), 4.05−4.09 (m, 2H, CH_2-pip), 7.06 (d, J = 8.1 Hz, 1H, H_6-phenyl), 7.11 (s, 1H, H_2-phenyl), 7.15 (d, J = 8.1 Hz, 1H, H_4-phenyl), 7.36 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.5 (C_7), 24.5 (C_6), 26.3 (C_8), 32.4 (NCH_2), 39.3 (C_5), 46.0 ($2CH_2$-pip), 51.5 ($2CH_2$-pip), 54.4 (CH_2-Npip), 57.9 (C_{8a}), 113.4 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 117.8 (q, $^3J_{C-F}$ = 4.0 Hz, C_4-phenyl), 119.9 (C_6-phenyl), 123.5 (q, $^1J_{C-F}$ = 272.9 Hz, CF_3), 129.8 (C_5-phenyl), 131.5 (q, $^2J_{C-F}$ = 31.2 Hz, C_3-phenyl), 149.4 (C_1-phenyl), 153.4 (C_3), 173.5 (C_1). Anal. ($C_{20}H_{25}F_3N_4O_2$·HCl) C, H, N.

2-[2-[4-(*p*-Fluorophenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (2k): yield 1.8 g (31%); mp 222−224 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1510, 1460 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.42−1.56 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.71−1.73 (m, 1H, H_{6eq}), 1.97−1.98 (m, 1H, H_{7eq}), 2.12−2.17 (m, 1H, H_{8eq}), 2.92 (td, J = 12.3, 3.0 Hz, 1H, H_{5ax}), 3.05 (br t, 2H, CH_2-pip), 3.37 (br t, 2H, CH_2-Npip), 3.43−3.59 (m, 4H, $2CH_2$-pip), 3.92−3.98 (m, 4H, NCH_2, H_{5eq}, H_{8a}), 4.08−4.13 (m, 2H, CH_2-pip), 6.89 (dd, J = 9.0 Hz, $^4J_{H-F}$ = 4.5 Hz, 2H, H_2- and H_6-phenyl), 6.97 (t, J = 9.0 Hz, $^3J_{H-F}$ = 9.0 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.5 (C_7), 24.4 (C_6), 26.2 (C_8), 32.4 (NCH_2), 39.2 (C_5), 47.1 ($2CH_2$-pip), 51.7 ($2CH_2$-pip), 54.2 (CH_2-Npip), 57.7 (C_{8a}), 115.6 (d, $^2J_{C-F}$ = 22.1 Hz, C_3- and C_5-phenyl), 118.9 (d, $^3J_{C-F}$ = 8.0 Hz, C_2- and C_6-phenyl), 145.8 (C_1-phenyl), 153.4 (C_3), 157.8 (d, $^1J_{C-F}$ = 240.7 Hz, C_4-phenyl), 173.5 (C_1). Anal. ($C_{19}H_{25}FN_4O_2$·HCl) C, H, N.

2-[2-[4-(*p*-Nitrophenyl)piperazin-1-yl]ethyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (2l): yield 1.3 g (20%); mp 252−254 °C (H_2O/ethanol); IR (KBr, cm^{-1}) 1755 (CON), 1700 (NCON), 1600, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.30−1.51 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.62−1.67 (m, 1H, H_{6eq}), 1.82−1.88 (m, 1H, H_{7eq}), 1.92−1.98 (m, 1H, H_{8eq}), 2.81 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.16−3.20 (m, 4H, CH_2-Npip, CH_2-pip), 3.38−3.55 (m, 2H, CH_2-pip), 3.71 (br t, 2H, NCH_2), 3.80 (m, 4H, $2CH_2$-pip), 3.90−4.02 (m, 2H, H_{5eq}, H_{8a}), 7.13 (d, J = 9.3 Hz, 2H, H_2- and H_6-phenyl), 8.11 (d, J = 9.3 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (C_7), 24.5 (C_6), 26.3 (C_8), 32.8 (NCH_2), 38.9 (C_5), 43.4 ($2CH_2$-pip), 50.2 ($2CH_2$-pip), 52.9 (CH_2-Npip), 57.0 (C_{8a}), 113.6 (C_2- and C_6-phenyl), 125.7 (C_3- and C_5-phenyl), 138.0 (C_4-phenyl), 153.5, 153.9 (C_1-phenyl, C_3), 173.3 (C_1). Anal. ($C_{19}H_{25}N_5O_4$·HCl) C, H, N.

General Procedure for the Synthesis of Compounds 7a−d. To a suspension of the corresponding hydantoins **5a,b** (26.0 mmol) in anhydrous *N*,*N*-dimethylformamide (30 mL) was added 60% NaH (2.1 g, 52.0 mmol). After stirring for 30 min at 60 °C under nitrogen, a solution of the corresponding dibromoalkane (52.0 mmol) in anhydrous *N*,*N*-dimethylformamide was added dropwise. The mixture was stirred overnight under nitrogen at room temperature. Then, the solvent was evaporated under reduced pressure, and the residue was resuspended in water and extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with water and dried over $MgSO_4$. After evaporation of the solvent, the crude oil was purified by column chromatography and then distillation.

2-(3-Bromopropyl)-1,3-dioxoperhydropyrrolo[1,2−*c*]imidazole (7a): yield 5.1 g (75%); bp 79−80 °C (0.01 mmHg); IR ($CHCl_3$, cm^{-1}) 1725 (CON), 1700 (NCON); ^{1}H-NMR ($CDCl_3$) δ 1.59−1.72 (m, 1H, H_7), 1.90−2.09 (m, 4H, $2H_6$, -CH_2-), 2.16−2.25 (m, 1H, H_7), 3.21 (ddd, J = 11.1, 7.8, 5.1 Hz, 1H, H_5), 3.50 (t, J = 6.6 Hz, 2H, NCH_2 or CH_2Br), 3.58 (t, J = 6.6 Hz, 2H, CH_2Br or NCH_2), 3.61−3.68 (m, 1H, H_5), 4.05 (dd, J = 9.0, 7.5 Hz, 1H, H_{7a}); ^{13}C-NMR ($CDCl_3$) δ 26.8 (C_6), 27.2 (C_7), 30.6 (-CH_2-), 36.5 (CH_2Br), 41.8 (NCH_2), 45.2 (C_5), 63.1 (C_{7a}), 160.3 (C_3), 173.6 (C_1). Anal. ($C_9H_{13}BrN_2O_2$) C, H, N.

2-(3-Bromopropyl)-1,3-dioxoperhydroimidazo[1,5−*a*]pyridine (7b): yield 5.0 g (70%); bp 150 °C (0.7 mmHg); IR ($CHCl_3$, cm^{-1}) 1770 (CON), 1705 (NCON); ^{1}H-NMR ($CDCl_3$) δ 1.12−1.42 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.62−1.66 (m, 1H, H_{6eq}), 1.86−1.90 (m, 1H, H_{7eq}), 2.03−2.12 (m, 3H, H_{8eq}, -CH_2-), 2.79 (td, J = 12.6, 3.6 Hz, 1H, H_{5ax}), 3.28 (t, J = 6.7 Hz, 2H, NCH_2 or CH_2Br), 3.53 (t, J = 6.7 Hz, 2H, CH_2Br or NCH_2), 3.66 (dd, J = 11.7, 4.2 Hz, 1H, H_{8a}), 4.02−4.08 (m, 1H, H_{5eq}); ^{13}C-NMR ($CDCl_3$) δ 22.4 (C_7), 24.7 (C_6), 27.5 (C_8), 29.6 (-CH_2-), 31.0 (CH_2-Br), 37.2 (NCH_2), 39.1 (C_5), 57.1 (C_{8a}), 154.0 (C_3), 172.9 (C_1). Anal. ($C_{10}H_{15}BrN_2O_2$) C, H, N.

2-(4-Bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (7c): yield 5.0 g (70%); bp 77−78 °C (0.01 mmHg); IR ($CHCl_3$, cm^{-1}) 1775 (CON), 1720 (NCON); ^{1}H-NMR ($CDCl_3$) δ 1.53−1.90 (m, 5H, -$(CH_2)_2$-, H_7), 2.04−2.13 (m, 2H, $2H_6$), 2.21−2.28 (m, 1H, H_7), 3.18−3.28 (m, 1H, H_5), 3.38−3.44 (m, 4H, NCH_2, CH_2Br), 3.59−3.70 (m, 1H, H_5), 4.09−4.14 (m, 1H,

H_{7a}); ^{13}C-NMR ($CDCl_3$) δ 24.3, 25.9 (-$(CH_2)_2$-), 26.4 (C_6), 26.9 (C_7), 32.4 (CH_2Br), 37.3 (NCH_2), 45.0 (C_5), 62.7 (C_{7a}), 160.0 (C_3), 173.2 (C_1). Anal. ($C_{10}H_{15}BrN_2O_2$) C, H, N.

2-(4-Bromobutyl)-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (7d): yield 5.3 g (70%); bp 83−84 °C (0.01 mmHg); IR ($CHCl_3$, cm^{-1}) 1770 (CON), 1710 (NCON); ^{1}H-NMR ($CDCl_3$) δ 1.14−1.56 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.61−1.85 (m, 5H, H_{6eq}, -$(CH_2)_2$-), 1.90−1.96 (m, 1H, H_{7eq}), 2.11−2.16 (m, 1H, H_{8eq}), 2.77 (td, J = 12.6, 3.6 Hz, 1H, H_{5ax}), 3.36 (t, J = 6.6 Hz, 2H, NCH_2 or CH_2Br), 3.45 (t, J = 6.9 Hz, 2H, CH_2Br or NCH_2), 3.69 (dd, J = 12.0, 4.5 Hz, 1H, H_{8a}), 4.06−4.10 (m, 1H, H_{5eq}); ^{13}C-NMR ($CDCl_3$) δ 22.4 (C_7), 24.7 (C_6), 26.5 (-CH_2-), 27.5 (C_8), 29.4 (-CH_2-), 32.7 (CH_2Br), 37.3 (NCH_2), 39.0 (C_5), 57.0 (C_{8a}), 154.1 (C_3), 172.9 (C_1). Anal. ($C_{11}H_{17}BrN_2O_2$) C, H, N.

General Method C. Preparation of Derivatives 3a−l and 4a−l. To a suspension of **7** (10.9 mmol) and Na_2CO_3 (21.8 mmol) in acetonitrile (50 mL) was added the corresponding arylpiperazine (10.9 mmol). The mixture was refluxed for 3−5 days (TLC) and hot filtered. After evaporation of the solvent, the crude oil was purified by column chromatography (eluent: ethyl acetate/ethanol, relative proportions depending upon the compound). The free base was converted to its hydrochloride salt.

2-[3-(4-Phenylpiperazin-1-yl)propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (3a): yield 1.4 g (32%); mp 210−212 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1750 (CON), 1710 (NCON), 1600, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.64−1.81 (m, 1H, H_7), 1.90−2.15 (m, 5H, $2H_6$, H_7, -CH_2-), 3.11−3.34 (m, 7H, CH_2-Npip, $2CH_2$-pip, H_5), 3.43 (t, J = 6.9 Hz, 2H, NCH_2), 3.48−3.54 (m, 3H, H_5, CH_2-pip), 3.77−3.81 (m, 2H, CH_2-pip), 4.20 (t, J = 8.2 Hz, 1H, H_{7a}), 6.88 (t, J = 7.5 Hz, 1H, H_4-phenyl), 7.01 (d, J = 7.5 Hz, 2H, H_2- and H_6-phenyl), 7.27 (t, J = 7.5 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.4 (-CH_2-), 26.7 (C_6), 30.8 (C_7), 35.8 (NCH_2), 45.3 (C_5), 45.6 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 53.0 (CH_2-Npip), 63.0 (C_{7a}), 116.2 (C_2- and C_6-phenyl), 120.3 (C_4-phenyl), 129.3 (C_3- and C_5-phenyl), 149.5 (C_1-phenyl), 160.2 (C_3), 174.0 (C_1). Anal. ($C_{19}H_{26}N_4O_2$·2HCl) C, H, N.

2-[3-[4-(*o*-Methoxyphenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (3b): yield 1.6 g (31%); mp 212−214 °C (ethanol); IR (KBr, cm^{-1}) 1770 (CON), 1720 (NCON), 1620, 1530, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.63−1.78 (m, 1H, H_7), 1.94−2.17 (m, 5H, $2H_6$, H_7, -CH_2-), 3.09−3.39 (m, 7H, CH_2-Npip, $2CH_2$-pip, H_5), 3.42 (t, J = 6.6 Hz, 2H, NCH_2), 3.46−3.58 (m, 5H, H_5, $2CH_2$-pip), 3.81 (s, 3H, OCH_3), 4.22 (t, J = 8.1 Hz, 1H, H_{7a}), 6.88−7.07 (m, 4H, H_3-, H_4-, H_5-, and H_6-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.5 (-CH_2-), 26.7 (C_6), 26.8 (C_7), 35.8 (NCH_2), 45.3 (C_5), 47.0 ($2CH_2$-pip), 50.9 ($2CH_2$-pip), 53.1 (CH_2-Npip), 55.6 (OCH_3), 63.0 (C_{7a}), 112.2 (C_6-phenyl), 118.6 (C_3-phenyl), 121.0 (C_4-phenyl), 124.1 (C_5-phenyl), 138.9 (C_1-phenyl), 151.9 (C_2-phenyl), 160.3 (C_3), 174.0 (C_1). Anal. ($C_{20}H_{28}N_4O_3$·2HCl·H_2O) C, H, N.

2-[3-[4-(*m*-Chlorophenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (3c): yield 1.4 g (28%); mp 164−166 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1780 (CON), 1710 (NCON), 1460 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.56−1.85 (m, 1H, H_7), 1.86−1.99 (m, 5H, $2H_6$, H_7, -CH_2-), 2.93−3.20 (m, 7H, CH_2-Npip, $2CH_2$-pip, H_5), 3.28 (t, J = 6.6 Hz, 2H, NCH_2), 3.34−3.40 (m, 3H, H_5, CH_2-pip), 3.72−3.77 (m, 2H, CH_2-pip), 4.07 (dd, J = 9.0, 7.5 Hz, 1H, H_{7a}), 6.74 (dd, J = 8.1, 1.9 Hz, 1H, H_6-phenyl), 6.83 (dd, J = 8.1, 1.9 Hz, 1H, H_4-phenyl), 6.93 (t, J = 1.9 Hz, 1H, H_2-phenyl), 7.13 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 19.7 (-CH_2-), 24.0 (C_6), 24.2 (C_7), 33.1 (NCH_2), 42.2 ($2CH_2$-pip), 42.6 (C_5), 47.7 ($2CH_2$-pip), 50.2 (CH_2-Npip), 60.4 (C_{7a}), 111.6 (C_6-phenyl), 112.7 (C_2-phenyl), 116.7 (C_4-phenyl), 128.1 (C_5-phenyl), 131.4 (C_3-phenyl), 148.2 (C_1-phenyl), 157.6 (C_3), 171.4 (C_1). Anal. ($C_{19}H_{25}ClN_4O_2$·2HCl) C, H, N.

2-[3-[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (3d): yield 1.6 g (30%); mp 150−152 °C (ethanol); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1620, 1600, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.62−1.82 (m, 1H, H_7), 1.93−2.14 (m, 5H, $2H_6$, H_7, -CH_2-), 3.10−3.33 (m, 7H, CH_2-Npip, $2CH_2$-pip, H_5), 3.44−3.54 (m, 5H, NCH_2, H_5, CH_2-pip), 3.92−3.97 (m, 2H, CH_2-pip), 4.20 (t, J = 8.5 Hz, 1H, H_{7a}), 7.15 (d, J = 7.8 Hz, 1H, H_6-phenyl), 7.27 (s, 1H, H_2-phenyl), 7.30 (d, J = 7.8 Hz, 1H, H_4-phenyl), 7.47 (t, J = 7.8 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 18.6 (-CH_2-), 22.4 (C_6), 26.7 (C_7), 35.7 (NCH_2), 44.8 ($2CH_2$-pip), 45.2 (C_5), 50.3 (CH_2-pip), 52.9 (CH_2-pip), 56.1 (CH_2-Npip), 63.0 (C_{7a}), 111.7 (C_2-phenyl), 115.8 (C_4-phenyl), 119.4 (C_6-phenyl), 124.4 (q, $^1J_{C-F}$ = 272.0 Hz, CF_3), 129.7 (q, $^2J_{C-F}$ = 32.4 Hz, C_3-phenyl), 130.3 (C_5-phenyl), 149.9 (C_1-phenyl), 160.3 (C_3), 173.9 (C_1). Anal. ($C_{20}H_{25}F_3N_4O_2$·2HCl) C, H, N.

2-[3-[4-(*p*-Fluorophenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (3e): yield 1.5 g (35%); mp 230−232 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1520 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.64−1.77 (m, 1H, H_7), 1.92−2.13 (m, 5H, $2H_6$, H_7, -CH_2-), 3.09−3.18 (m, 7H, CH_2-Npip, $2CH_2$-pip, H_5), 3.38−3.54 (m, 5H, NCH_2, H_5, CH_2-pip), 3.69−3.73 (m, 2H, CH_2-pip), 4.20 (dd, J = 9.0, 7.5 Hz, 1H, H_{7a}), 7.01 (dd, J = 9.2 Hz, $^4J_{H-F}$ = 5.1 Hz, 2H, H_2- and H_6-phenyl), 7.10 (t, J = 9.2 Hz, $^3J_{H-F}$ = 9.2 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (-CH_2-), 26.5 (C_6), 26.6 (C_7), 35.6 (NCH_2), 45.1 (C_5), 46.0 ($2CH_2$-pip), 50.5 ($2CH_2$-pip), 52.8 (CH_2-Npip), 62.9 (C_{7a}), 115.5 (d, $^2J_{C-F}$ = 22.2 Hz, C_3- and C_5-phenyl), 117.8 (d, $^3J_{C-F}$ = 7.5 Hz, C_2- and C_6-phenyl), 146.4 (C_1-phenyl), 156.5 (d, $^1J_{C-F}$ = 236.7 Hz, C_4-phenyl), 160.1 (C_3), 173.8 (C_1). Anal. ($C_{19}H_{25}FN_4O_2$·HCl) C, H, N.

2-[3-[4-(*p*-Nitrophenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (3f): yield 1.5 g (33%); mp 244−246 °C (ethanol); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1610, 1530, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.66−1.73 (m, 1H, H_7), 1.96−2.21 (m, 5H, $2H_6$, H_7, -CH_2-), 3.10−3.19 (m, 5H, CH_2-Npip, CH_2-pip, H_5), 3.36−3.56 (m, 7H, NCH_2, $2CH_2$-pip, H_5), 4.15−4.22 (m, 3H, CH_2-pip, H_{7a}), 7.12 (d, J = 9.3 Hz, 2H, H_2- and H_6-phenyl), 8.11 (d, J = 9.3 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.4 (-CH_2-), 26.7 (C_6), 26.8 (C_7), 35.7 (NCH_2), 43.7 ($2CH_2$-pip), 45.2 (C_5), 50.2 ($2CH_2$-pip), 53.0 (CH_2-Npip), 63.0 (C_{7a}), 113.6 (C_2- and C_6-phenyl), 125.8 (C_3- and C_5-phenyl), 138.1 (C_4-phenyl), 153.9 (C_1-phenyl), 160.2 (C_3), 174.0 (C_1). Anal. ($C_{19}H_{25}N_5O_4$·HCl) C, H, N.

2-[3-(4-Phenylpiperazin-1-yl)propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (3g): yield 1.0 g (20%); mp 213−215 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1770 (CON), 1715 (NCON), 1600, 1500, 1470 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.30−1.57 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.73−1.77 (m, 1H, H_{6eq}), 1.98−2.02 (m, 1H, H_{7eq}), 2.16−2.20 (m, 1H, H_{8eq}), 2.27 (br t, 2H, -CH_2-), 2.86 (t, J = 11.5 Hz, 1H, H_{5ax}), 3.39 (br t, 2H, CH_2-Npip), 3.61−3.79 (m, 7H, NCH_2, $2CH_2$-pip, H_{8a}), 4.01−4.05 (m, 1H, H_{5eq}), 4.19 (br t, 2H, CH_2-pip), 4.70 (t, J = 11.7 Hz, 2H, CH_2-pip), 7.46−7.56 (m, 3H, H_3-, H_4-, and H_5-phenyl), 7.88 (d, J = 7.5 Hz, 2H, H_2- and H_6-phenyl); ^{1}H-NMR (Me_2SO-d_6) δ 1.28−1.53 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.67−1.71 (m, 1H, H_{6eq}), 1.84−1.90 (m, 1H, H_{7eq}), 2.00−2.06 (m, 3H, H_{8eq}, -CH_2-), 2.85 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.17−3.24 (m, 6H, CH_2-Npip, $2CH_2$-pip), 3.47 (t, J = 6.9 Hz, 2H, NCH_2), 3.53−3.57 (m, 2H, CH_2-pip), 3.81−3.84 (m, 2H, CH_2-pip), 3.93−4.02 (m, 2H, H_{5eq}, H_{8a}), 6.90 (t, J = 7.5 Hz, 1H, H_4-phenyl), 7.03 (d, J = 8.1 Hz, 2H, H_2- and H_6-phenyl), 7.29 (t, J = 7.5 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.4 (C_7), 23.1 (-CH_2-), 24.6 (C_6), 27.2 (C_8), 35.4 (NCH_2), 39.2 (C_5), 48.8 ($2CH_2$-pip), 50.9 ($2CH_2$-pip), 54.7 (CH_2-Npip), 57.3 (C_{8a}), 120.9 (C_2- and C_6-phenyl), 130.2, 130.5 (C_3-, C_5-, and C_4-phenyl), 141.0 (C_1-phenyl), 153.8 (C_3), 173.0 (C_1). Anal. ($C_{20}H_{28}N_4O_2$·2HCl·H_2O) C, H, N.

2-[3-[4-(*o*-Methoxyphenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (3h): yield 1.8 g (33%); mp 208−210 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1755 (CON), 1705 (NCON), 1605, 1510 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.26−1.50 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.63−1.68 (m, 1H, H_{6eq}), 1.82−1.86 (m, 1H, H_{7eq}), 1.98−2.07 (m, 3H, H_{8eq}, -CH_2-), 2.83 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.12 (br t, 2H, CH_2-Npip), 3.21−3.24 (m, 4H, $2CH_2$-pip), 3.44 (t, J = 6.6 Hz, 2H, NCH_2), 3.48−3.54 (m, 4H, $2CH_2$-pip), 3.81 (s, 3H, OCH_3), 3.91−4.00 (m, 2H, H_{5eq}, H_{8a}), 6.93 (t, J = 7.8 Hz, 1H, H_4-phenyl), 7.00−7.10 (m, 3H, H_3-, H_5-, and H_6-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (C_7), 22.7 (-CH_2-), 24.7 (C_6), 27.1 (C_8), 35.5 (NCH_2), 38.9 (C_5), 47.2 ($2CH_2$-pip), 50.9 ($2CH_2$-pip), 53.2 (CH_2-Npip), 55.6 (OCH_3), 56.7 (C_{8a}), 112.3 (C_6-phenyl), 118.8 (C_3-phenyl), 121.0

(C_4-phenyl), 124.5 (C_5-phenyl), 138.4 (C_1-phenyl), 152.0 (C_2-phenyl), 153.8 (C_3), 173.3 (C_1). Anal. ($C_{21}H_{30}N_4O_3 \cdot 2HCl \cdot 3H_2O$) C, H, N.

2-[3-[4-(*m*-Chlorophenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (3i): yield 1.6 g (31%); mp 173−175 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1755 (CON), 1700 (NCON), 1595, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.26−1.55 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.63−1.68 (m, 1H, H_{6eq}), 1.81−1.86 (m, 1H, H_{7eq}), 1.98−2.07 (m, 3H, H_{8eq}, -CH_2-), 2.83 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.12 (m, 4H, CH_2-Npip, CH_2-pip), 3.24 (t, J = 12.3 Hz, 2H, CH_2-pip), 3.44 (t, J = 6.6 Hz, 2H, NCH_2), 3.49−3.53 (m, 2H, CH_2-pip), 3.86−4.00 (m, 4H, CH_2-pip, H_{5eq}, H_{8a}), 6.93 (d, J = 7.8 Hz, 1H, H_6-phenyl), 6.97 (d, J = 8.4 Hz, 1H, H_4-phenyl), 7.06 (s, 1H, H_2-phenyl), 7.27 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (C_7), 22.7 (-CH_2-), 24.7 (C_6), 27.1 (C_8), 35.5 (NCH_2), 38.9 (C_5), 45.0 (2CH_2-pip), 50.4 (2CH_2-pip), 53.1 (CH_2-Npip), 56.7 (C_{8a}), 114.4 (C_6-phenyl), 115.5 (C_2-phenyl), 119.4 (C_4-phenyl), 130.8 (C_5-phenyl), 134.1 (C_3-phenyl), 151.0 (C_1-phenyl), 153.9 (C_3), 173.3 (C_1). Anal. ($C_{20}H_{27}ClN_4O_2 \cdot 2HCl$) C, H, N.

2-[3-[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (3j): yield 1.2 g (20%); mp 206−208 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1760 (CON), 1710 (NCON), 1650, 1605, 1465 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.26−1.51 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.63−1.68 (m, 1H, H_{6eq}), 1.82−1.87 (m, 1H, H_{7eq}), 1.97−2.09 (m, 3H, H_{8eq}, -CH_2-), 2.84 (td, J = 12.6, 3.3 Hz, 1H, H_{5ax}), 3.12−3.14 (m, 4H, CH_2-Npip, CH_2-pip), 3.30 (t, J = 12.0 Hz, 2H, CH_2-pip), 3.45 (t, J = 6.6 Hz, 2H, NCH_2), 3.51−3.55 (m, 2H, CH_2-pip), 3.93−4.00 (m, 4H, CH_2-pip, H_{5eq}, H_{8a}), 7.16 (d, J = 7.5 Hz, 1H, H_6-phenyl), 7.27 (s, 1H, H_2-phenyl), 7.30 (d, J = 8.4 Hz, 1H, H_4-phenyl), 7.48 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (C_7), 22.7 (-CH_2-), 24.8 (C_6), 27.1 (C_8), 35.5 (NCH_2), 38.9 (C_5), 45.0 (2CH_2-pip), 50.5 (2CH_2-pip), 53.1 (CH_2-Npip), 56.8 (C_{8a}), 111.9 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 115.9 (q, $^3J_{C-F}$ = 5.0 Hz, C_4-phenyl), 119.5 (C_6-phenyl), 124.8 (q, $^1J_{C-F}$ = 263.7 Hz, CF_3), 130.2 (q, $^2J_{C-F}$ = 32.2 Hz, C_3-phenyl), 130.4 (C_5-phenyl), 150.1 (C_1-phenyl), 153.9 (C_3), 173.3 (C_1). Anal. ($C_{21}H_{27}F_3N_4O_2 \cdot 2HCl \cdot 4H_2O$) C, H, N.

2-[3-[4-(*p*-Fluorophenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (3k): yield 1.1 g (23%); mp 205−207 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1750 (CON), 1700 (NCON), 1615, 1510, 1485 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.25−1.50 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.63−1.68 (m, 1H, H_{6eq}), 1.81−1.87 (m, 1H, H_{7eq}), 1.97−2.05 (m, 3H, H_{8eq}, -CH_2-), 2.83 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.12−3.19 (m, 4H, CH_2-Npip, CH_2-pip), 3.44 (t, J = 7.0 Hz, 2H, NCH_2), 3.51−3.53 (m, 2H, CH_2-pip), 3.70−3.73 (m, 4H, 2CH_2-pip), 3.91−3.99 (m, 2H, H_{5eq}, H_{8a}), 7.02 (dd, J = 9.2 Hz, $^4J_{H-F}$ = 3.0 Hz, 2H, H_2- and H_6-phenyl), 7.10 (t, J = 9.2 Hz, $^3J_{H-F}$ = 9.2 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (C_7), 22.6 (-CH_2-), 24.7 (C_6), 27.1 (C_8), 35.4 (NCH_2), 38.8 (C_5), 46.2 (2CH_2-pip), 50.6 (2CH_2-pip), 53.0 (CH_2-Npip), 56.7 (C_{8a}), 115.6 (d, $^2J_{C-F}$ = 22.2 Hz, C_3- and C_5-phenyl), 117.9 (d, $^3J_{C-F}$ = 7.1 Hz, C_2- and C_6-phenyl), 146.6 (C_1-phenyl), 153.8 (C_3), 156.6 (d, $^1J_{C-F}$ = 236.7 Hz, C_4-phenyl), 173.2 (C_1). Anal. ($C_{20}H_{27}FN_4O_2 \cdot 2HCl$) C, H, N.

2-[3-[4-(*p*-Nitrophenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (3l): yield 1.0 g (20%); mp 118−120 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1765 (CON), 1700 (NCON), 1600 (Ar); ^{1}H-NMR ($CDCl_3$) δ 1.22−1.51 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.67−1.72 (m, 1H, H_{6eq}), 1.92−1.98 (m, 1H, H_{7eq}), 2.06−2.10 (m, 1H, H_{8eq}), 2.24 (qt, J = 7.2 Hz, 2H, -CH_2-), 2.80 (td, J = 12.6, 3.3 Hz, 1H, H_{5ax}), 3.16 (t, J = 7.2 Hz, 2H, CH_2-Npip), 3.59 (t, J = 7.2 Hz, 2H, NCH_2), 3.59−3.69 (m, 1H, H_{8a}), 3.75−3.77 (m, 2H, CH_2-pip), 3.79−3.81 (m, 2H, CH_2-pip), 3.86 (m, 4H, 2CH_2-pip), 4.03−4.08 (m, 1H, H_{5eq}), 6.82 (d, J = 9.3 Hz, 2H, H_2- and H_6-phenyl), 8.02 (d, J = 9.3 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR ($CDCl_3$) δ 22.4 (C_7), 22.9 (-CH_2-), 24.6 (C_6), 27.3 (C_8), 35.5 (NCH_2), 39.2 (C_5), 44.2 (2CH_2-pip), 51.0 (2CH_2-pip), 54.6 (CH_2-Npip), 57.3 (C_{8a}), 113.7 (C_2- and C_6-phenyl), 125.6 (C_3- and C_5-phenyl), 139.5 (C_4-phenyl), 153.2 (C_1-phenyl), 153.9 (C_3), 173.3 (C_1). Anal. ($C_{20}H_{27}N_5O_4 \cdot 2HCl$) C, H, N.

2-[4-(4-Phenylpiperazin-1-yl)butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (4a): yield 1.6 g (34%); mp 210−212 °C (ethanol); IR (KBr, cm^{-1}) 1760 (CON), 1700 (NCON), 1600, 1500, 1470 (Ar); ^{1}H-NMR (Me_2SO-d_6/CF_3COOH) δ 1.55−1.75 (m, 5H, -(CH_2)$_2$-, H_7), 1.96−2.15 (m, 3H, 2H_6, H_7), 3.13−3.33 (m, 7H, CH_2-Npip, 2CH_2-pip, H_5), 3.40 (t, J = 6.6 Hz, 2H, NCH_2), 3.47−3.58 (m, 3H, H_5, CH_2-pip), 3.80−3.85 (m, 2H, CH_2-pip), 4.21 (t, J = 8.0 Hz, 1H, H_{7a}), 6.88 (t, J = 7.6 Hz, 1H, H_4-phenyl), 7.19 (d, J = 7.6 Hz, 2H, H_2- and H_6-phenyl), 7.32 (t, J = 7.6 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6/CF_3COOH) δ 21.5 (CH_2CH_2-Npip), 25.4 (NCH_2CH_2), 26.8 (C_6), 27.1 (C_7), 38.0 (NCH_2), 45.5 (C_5), 47.1 (2CH_2-pip), 51.2 (2CH_2-pip), 56.0 (CH_2-Npip), 63.6 (C_{7a}), 117.2 (C_2- and C_6-phenyl), 121.5 (C_4-phenyl), 129.7 (C_3- and C_5-phenyl), 149.8 (C_1-phenyl), 161.3 (C_3), 174.5 (C_1). Anal. ($C_{20}H_{28}N_4O_2 \cdot 2HCl$) C, H, N.

2-[4-[4-(*o*-Methoxyphenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (4b): yield 2.5 g (50%); mp 178−180 °C (ethanol); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1625, 1530, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.55−1.84 (m, 5H, -(CH_2)$_2$-, H_7), 1.96−2.23 (m, 3H, 2H_6, H_7), 3.11−3.33 (m, 7H, CH_2-Npip, 2CH_2-pip, H_5), 3.38 (t, J = 6.6 Hz, 2H, NCH_2), 3.43−3.52 (m, 5H, H_5, 2CH_2-pip), 3.81 (s, 3H, OCH_3), 4.20 (t, J = 8.7 Hz, 1H, H_{7a}), 6.91−7.10 (m, 4H, H_3-, H_4-, H_5-, and H_6-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 20.4 (CH_2CH_2-Npip), 24.9 (NCH_2CH_2), 26.8 (C_6, C_7), 37.7 (NCH_2), 45.3 (C_5), 47.1 (2CH_2-pip), 50.9 (2CH_2-pip), 55.0 (CH_2-Npip), 55.6 (OCH_3), 63.0 (C_{7a}), 112.3 (C_6-phenyl), 118.8 (C_3-phenyl), 121.0 (C_4-phenyl), 124.4 (C_5-phenyl), 138.5 (C_1-phenyl), 152.0 (C_2-phenyl), 160.5 (C_3), 174.1 (C_1). Anal. ($C_{21}H_{30}N_4O_3 \cdot 2HCl$) C, H, N.

2-[4-[4-(*m*-Chlorophenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (4c): yield 1.8 g (35%); mp 192−194 °C (ethanol); IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1610, 1480 (Ar); ^{1}H-NMR (Me_2SO-d_6/CF_3COOH) δ 1.58−1.88 (m, 5H, -(CH_2)$_2$-, H_7), 2.02−2.13 (m, 3H, 2H_6, H_7), 3.16−3.38 (m, 6H, CH_2-Npip, 2CH_2-pip), 3.40−3.56 (m, 5H, H_5, NCH_2, CH_2-pip), 3.60 (br t, 2H, CH_2-pip), 3.82−3.87 (m, 1H, H_5), 4.14 (t, J = 8.1 Hz, 1H, H_{7a}), 6.92 (d, J = 7.8 Hz, 1H, H_6-phenyl), 6.95 (d, J = 7.8 Hz, 1H, H_4-phenyl), 7.08 (s, 1H, H_2-phenyl), 7.27 (t, J = 7.8 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6/CF_3COOH) δ 22.9 (CH_2CH_2-Npip), 27.1 (NCH_2CH_2), 28.8 (C_6), 29.2 (C_7), 37.6 (NCH_2), 47.5 (C_5), 48.2 (2CH_2-pip), 53.3 (2CH_2-pip), 58.1 (CH_2-Npip), 65.4 (C_{7a}), 117.2 (C_6-phenyl), 118.7 (C_2-phenyl), 123.2 (C_4-phenyl), 132.9 (C_5-phenyl), 136.9 (C_3-phenyl), 152.5 (C_1-phenyl), 163.0 (C_3), 176.4 (C_1). Anal. ($C_{20}H_{27}ClN_4O_2 \cdot 2HCl$) C, H, N.

2-[4-[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (4d): yield 2.6 g (48%); mp 176−178 °C (ethanol); IR (KBr, cm^{-1}) 1775 (CON), 1710 (NCON), 1610, 1500, 1470 (Ar); ^{1}H-NMR (CD_3OD) δ 1.71−1.83 (m, 5H, -(CH_2)$_2$-, H_7), 2.07−2.24 (m, 3H, 2H_6, H_7), 3.20−3.32 (m, 7H, CH_2-Npip, 2CH_2-pip, H_5), 3.53 (br t, 2H, NCH_2), 3.57−3.71 (m, 3H, H_5, CH_2-pip), 3.92−3.95 (m, 2H, CH_2-pip), 4.21 (t, J = 7.8 Hz, 1H, H_{7a}), 7.20 (d, J = 7.5 Hz, 1H, H_6-phenyl), 7.29 (m, 2H, H_2- and H_4-phenyl), 7.47 (t, J = 7.5 Hz, 1H, H_5-phenyl); ^{13}C-NMR (CD_3OD) δ 22.2 (CH_2CH_2-Npip), 26.2 (NCH_2CH_2), 28.1 (C_6), 28.3 (C_7), 38.8 (NCH_2), 46.5 (C_5), 47.6 (2CH_2-pip), 52.9 (2CH_2-pip), 57.4 (CH_2-Npip), 64.8 (C_{7a}), 114.1 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 118.6 (q, $^3J_{C-F}$ = 4.0 Hz, C_4-phenyl), 121.3 (C_6-phenyl), 125.6 (q, $^1J_{C-F}$ = 271.9 Hz, CF_3), 131.3 (C_5-phenyl), 132.6 (q, $^2J_{C-F}$ = 31.6 Hz, C_3-phenyl), 151.3 (C_1-phenyl), 161.3 (C_3), 162.4 (C_1). Anal. ($C_{21}H_{27}F_3N_4O_2 \cdot 2HCl$) C, H, N.

2-[4-[4-(*p*-Fluorophenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (4e): yield 1.8 g (35%); mp 194−196 °C (ethanol); IR (KBr, cm^{-1}) 1780 (CON), 1720 (NCON), 1530, 1470 (Ar); ^{1}H-NMR (CD_3OD) δ 1.70−1.92 (m, 5H, -(CH_2)$_2$-, H_7), 2.09−2.27 (m, 3H, 2H_6, H_7), 3.27−3.36 (m, 5H, CH_2-Npip, CH_2-pip, H_5), 3.46 (br t, 2H, CH_2-pip), 3.57 (t, J = 6.9 Hz, 2H, NCH_2), 3.65 (dt, J = 11.1, 7.5 Hz, 1H, H_5), 3.78 (m, 4H, 2CH_2-pip), 4.25 (dd, J = 9.4, 7.3 Hz, 1H, H_{7a}), 7.16 (t, J = 8.7 Hz, $^3J_{H-F}$ = 8.7 Hz, 2H, H_3- and H_5-phenyl), 7.28−7.33 (m, 2H, H_2- and H_6-phenyl); ^{13}C-NMR (CD_3OD) δ 23.2 (CH_2CH_2-Npip), 27.2 (NCH_2CH_2), 29.1 (C_6), 29.3 (C_7), 39.8 (NCH_2), 47.5 (C_5), 50.7 (2CH_2-pip), 53.4 (2CH_2-pip), 58.4 (NCH_2), 65.9 (C_{7a}), 118.3 (d, $^2J_{C-F}$ = 22.8 Hz, C_3- and C_5-phenyl), 122.5 (d, $^3J_{C-F}$ = 8.0 Hz, C_2- and C_6-phenyl), 144.6 (C_1-phenyl), 161.1 (d, $^1J_{C-F}$ = 242.3 Hz, C_4-phenyl), 162.5 (C_3), 176.7 (C_1). Anal. ($C_{20}H_{27}FN_4O_2.2HCl \cdot 2H_2O$) C, H, N.

2-[4-[4-(*p*-Nitrophenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (4f): yield 2.0 g (38%); mp 86−88 °C (ethanol); IR (KBr, cm^{-1}) 1775 (CON), 1720 (NCON), 1610, 1520, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.56 (qt, J = 8.7 Hz, 2H, NCH_2CH_2), 1.64−1.76 (m, 3H, H_7, CH_2-CH_2-Npip), 1.92−2.16 (m, 3H, $2H_6$, H_7), 3.08−3.14 (m, 3H, CH_2-pip, H_5), 3.38 (t, J = 6.9 Hz, 2H, CH_2-Npip), 3.46−3.56 (m, 7H, NCH_2, $2CH_2$-pip, H_5), 4.14−4.22 (m, 3H, CH_2-pip, H_{7a}), 7.06 (d, J = 9.4 Hz, 2H, H_2- and H_6-phenyl), 8.02 (d, J = 9.4 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 22.3 (CH_2-CH_2-Npip), 26.5 (NCH_2CH_2), 28.2 (C_6), 28.6 (C_7), 38.8 (NCH_2), 45.6 ($2CH_2$-pip), 46.9 (C_5), 52.4 ($2CH_2$-pip), 57.4 (CH_2-Npip), 64.7 (C_{7a}), 115.3 (C_2- and C_6-phenyl), 127.2 (C_3- and C_5-phenyl), 140.6 (C_4-phenyl), 155.5 (C_1-phenyl), 162.3 (C_3), 175.7 (C_1). Anal. ($C_{20}H_{27}N_5O_4$·2HCl) C, H, N.

2-[4-(4-Phenylpiperazin-1-yl)butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (4g): yield 2.3 g (45%); mp 198−200 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1765 (CON), 1710 (NCON), 1600, 1500 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.22−1.35 (m, 2H, H_{8ax}, H_{6ax}), 1.40−1.86 (m, 7H, H_{7ax}, NCH_2CH_2, H_{6eq}, CH_2CH_2-Npip, H_{7eq}), 1.97−2.01 (m, 1H, H_{8eq}), 2.82 (td, J = 12.0, 3.3 Hz, 1H, H_{5ax}), 3.06−3.18 (m, 4H, CH_2-Npip, CH_2-pip), 3.22 (t, J = 12.3 Hz, 2H, CH_2-pip), 3.40 (t, J = 6.9 Hz, 2H, NCH_2), 3.48−3.53 (m, 2H, CH_2-pip), 3.77−3.81 (m, 2H, CH_2-pip), 3.90−3.99 (m, 2H, H_{5eq}, H_{8a}), 6.88 (t, J = 7.2 Hz, 1H, H_4-phenyl), 7.02 (d, J = 8.1 Hz, 2H, H_2- and H_6-phenyl), 7.27 (t, J = 7.7 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 20.3 (CH_2CH_2-Npip), 22.2 (C_7), 24.6 (C_6), 25.0 (NCH_2CH_2), 27.2 (C_8), 37.2 (NCH_2), 39.0 (C_5), 45.4 ($2CH_2$-pip), 50.5 ($2CH_2$-pip), 54.8 (CH_2-Npip), 56.5 (C_{8a}), 116.1 (C_2- and C_6-phenyl), 120.3 (C_4-phenyl), 129.2 (C_3- and C_5-phenyl), 149.4 (C_1-phenyl), 153.8 (C_3), 173.1 (C_1). Anal. ($C_{21}H_{30}N_4O_2$·2HCl·H_2O) C, H, N.

2-[4-[4-(*o*-Methoxyphenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (4h): yield 2.1 g (40%); mp 199−201 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1760 (CON), 1700 (NCON), 1610, 1520 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.21−1.34 (m, 2H, H_{8ax}, H_{6ax}), 1.41−1.86 (m, 7H, H_{7ax}, NCH_2CH_2, H_{6eq}, CH_2CH_2-Npip, H_{7eq}), 1.97−2.02 (m, 1H, H_{8eq}), 2.82 (td, J = 12.8, 3.3 Hz, 1H, H_{5ax}), 3.11 (m, 6H, CH_2-Npip, $2CH_2$-pip), 3.40 (t, J = 6.9 Hz, 2H, NCH_2), 3.45−3.48 (m, 4H, $2CH_2$-pip), 3.79 (s, 3H, OCH_3), 3.91−4.00 (m, 2H, H_{5eq}, H_{8a}), 6.88−7.06 (m, 4H, H_3-, H_4-, H_5-, and H_6-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 20.4 (CH_2CH_2-Npip), 22.2 (C_7), 24.7 (C_6), 25.1 (NCH_2CH_2), 27.2 (C_8), 37.3 (NCH_2), 39.0 (C_5), 46.9 ($2CH_2$-pip), 51.1 ($2CH_2$-pip), 55.0 (CH_2-Npip), 55.5 (OCH_3), 56.6 (C_{8a}), 112.1 (C_6-phenyl), 118.4 (C_3-phenyl), 120.9 (C_4-phenyl), 123.6 (C_5-phenyl), 140.0 (C_1-phenyl), 151.9 (C_2-phenyl), 153.9 (C_3), 173.2 (C_1). Anal. ($C_{22}H_{32}N_4O_3$·2HCl·H_2O) C, H, N.

2-[4-[4-(*m*-Chlorophenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (4i): yield 1.8 g (34%); mp 190−192 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1750 (CON), 1700 (NCON), 1590, 1470 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.20−1.34 (m, 2H, H_{8ax}, H_{6ax}), 1.41−1.86 (m, 7H, H_{7ax}, NCH_2CH_2, H_{6eq}, CH_2CH_2-Npip, H_{7eq}), 1.97−2.03 (m, 1H, H_{8eq}), 2.82 (td, J = 12.7, 3.0 Hz, 1H, H_{5ax}), 3.04−3.13 (m, 4H, CH_2-Npip, CH_2-pip), 3.24 (t, J = 12.3 Hz, 2H, CH_2-pip), 3.40 (t, J = 6.9 Hz, 2H, NCH_2), 3.46−3.50 (m, 2H, CH_2-pip), 3.84−3.88 (m, 2H, CH_2-pip), 3.92−3.99 (m, 2H, H_{5eq}, H_{8a}), 6.87 (dd, J = 7.8, 1.5 Hz, 1H, H_6-phenyl), 6.96 (dd, J = 8.4, 1.5 Hz, 1H, H_4-phenyl), 7.05 (t, J = 1.5 Hz, 1H, H_2-phenyl), 7.26 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 20.3 (CH_2CH_2-Npip), 22.2 (C_7), 24.7 (C_6), 25.1 (NCH_2CH_2), 27.2 (C_8), 37.2 (NCH_2), 38.8 (C_5), 44.8 ($2CH_2$-pip), 50.3 ($2CH_2$-pip), 54.8 (CH_2-Npip), 56.6 (C_{8a}), 114.2 (C_6-phenyl), 115.3 (C_2-phenyl), 119.3 (C_4-phenyl), 130.7 (C_5-phenyl), 134.0 (C_3-phenyl), 150.9 (C_1-phenyl), 153.9 (C_3), 173.2 (C_1). Anal. ($C_{21}H_{29}ClN_4O_2$·2HCl) C, H, N.

2-[4-[4-[*m*-(Trifluoromethyl)phenyl]piperazin-1-yl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (4j): yield 2.1 g (38%); mp 140−142 °C (ethanol/ethyl acetate); IR (KBr, cm^{-1}) 1760 (CON), 1695 (NCON), 1600 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.21−1.35 (m, 2H, H_{8ax}, H_{6ax}), 1.41−1.85 (m, 7H, H_{7ax}, NCH_2CH_2, H_{6eq}, CH_2CH_2-Npip, H_{7eq}), 1.97−2.01 (m, 1H, H_{8eq}), 2.82 (td, J = 12.9, 3.3 Hz, 1H, H_{5ax}), 3.07−3.13 (m, 4H, CH_2-Npip, CH_2-pip), 3.30 (t, J = 12.4 Hz, 2H, CH_2-pip), 3.40 (t, J = 6.9 Hz, 2H, NCH_2), 3.48−3.52 (m, 2H, CH_2-pip), 3.92−3.99 (m, 4H, CH_2-pip, H_{5eq}, H_{8a}), 7.16 (d, J = 7.8 Hz, 1H, H_6-phenyl), 7.27 (s, 1H, H_2-phenyl), 7.30 (d, J = 8.1 Hz, 1H, H_4-phenyl), 7.48 (t, J = 8.1 Hz, 1H, H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 20.4 (CH_2CH_2-Npip), 22.3 (C_7), 24.7 (C_6), 25.1 (NCH_2CH_2), 27.2 (C_8), 37.3 (NCH_2), 38.8 (C_5), 44.8 ($2CH_2$-pip), 50.3 ($2CH_2$-pip), 54.8 (CH_2-Npip), 56.6 (C_{8a}), 111.8 (q, $^3J_{C-F}$ = 4.1 Hz, C_2-phenyl), 115.8 (q, $^3J_{C-F}$ = 4.1 Hz, C_4-phenyl), 119.4 (C_6-phenyl), 125.4 (q, $^1J_{C-F}$ = 265.9 Hz, CF_3), 130.1 (q, $^2J_{C-F}$ = 29.2 Hz, C_3-phenyl), 130.3 (C_5-phenyl), 150.0 (C_1-phenyl), 153.9 (C_3), 173.2 (C_1). Anal. ($C_{22}H_{29}F_3N_4O_2$·2HCl·$^1/_2H_2O$) C, H, N.

2-[4-[4-(*p*-Fluorophenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (4k): yield 2.3 g (42%); mp 168−170 °C (ethanol); IR (KBr, cm^{-1}) 1770 (CON), 1710 (NCON), 1510 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.22−1.35 (m, 2H, H_{8ax}, H_{6ax}), 1.41−1.86 (m, 7H, H_{7ax}, NCH_2CH_2, H_{6eq}, CH_2CH_2-Npip, H_{7eq}), 1.97−2.02 (m, 1H, H_{8eq}), 2.83 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.10−3.14 (m, 4H, CH_2-Npip, CH_2-pip), 3.22 (t, J = 12.3 Hz, 2H, CH_2-pip), 3.40 (t, J = 6.9 Hz, 2H, NCH_2), 3.50−3.54 (m, 2H, CH_2-pip), 3.70−3.74 (m, 2H, CH_2-pip), 3.91−4.00 (m, 2H, H_{5ec}, H_{8a}), 7.04−7.16 (m, 4H, H_2-, H_3-, H_5-, and H_6-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 20.3 (CH_2CH_2-Npip), 22.3 (C_7), 24.7 (C_6), 25.1 (NCH_2CH_2), 27.2 (C_8), 37.3 (NCH_2), 38.8 (C_5), 46.3 ($2CH_2$-pip), 50.5 ($2CH_2$-pip), 54.8 (CH_2-Npip), 56.6 (C_{8a}), 115.7 (d, $^2J_{C-F}$ = 22.2 Hz, C_3- and C_5-phenyl), 118.2 (d, $^3J_{C-F}$ = 8.1 Hz, C_2- and C_6-phenyl), 146.2 (C_1-phenyl), 153.9 (C_3), 156.9 (d, $^1J_{C-F}$ = 237.7 Hz, C_4-phenyl), 173.2 (C_1). Anal. ($C_{21}H_{29}FN_4O_2$·2HCl·$2H_2O$) C, H, N.

2-[4-[4-(*p*-Nitrophenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine (4l): yield 2.0 g (38%); mp 200−202 °C (ethanol); IR (KBr, cm^{-1}) 1760 (CON), 1700 (NCON), 1595, 1490 (Ar); ^{1}H-NMR (Me_2SO-d_6) δ 1.25−1.35 (m, 2H, H_{8ax}, H_{6ax}), 1.49−1.86 (m, 7H, H_{7ax}, NCH_2CH_2, H_{6eq}, CH_2-CH_2-Npip, H_{7eq}), 1.97−2.02 (m, 1H, H_{8eq}), 2.82 (td, J = 12.6, 3.0 Hz, 1H, H_{5ax}), 3.06−3.14 (m, 4H, CH_2-Npip, CH_2-pip), 3.40 (t, J = 6.9 Hz, 2H, NCH_2), 3.47−3.55 (m, 4H, $2CH_2$-pip), 3.91−3.99 (m, 2H, H_{5eq}, H_{8a}), 4.16−4.21 (m, 2H, CH_2-pip), 7.14 (d, J = 9.6 Hz, 2H, H_2- and H_6-phenyl), 8.12 (d, J = 9.6 Hz, 2H, H_3- and H_5-phenyl); ^{13}C-NMR (Me_2SO-d_6) δ 20.3 (CH_2CH_2-Npip), 22.2 (C_7), 24.6 (C_6), 25.0 (NCH_2CH_2), 27.2 (C_8), 37.2 (NCH_2), 38.7 (C_5), 43.5 ($2CH_2$-pip), 50.1 ($2CH_2$-pip), 54.8 (CH_2-Npip), 56.5 (C_{8a}), 113.5 (C_2- and C_6-phenyl), 125.6 (C_3- and C_5-phenyl), 138.0 (C_4-phenyl), 153.8 (C_1-phenyl, C_3), 173.1 (C_1). Anal. ($C_{21}H_{29}N_5O_4$·2HCl) C, H, N.

Radioligand Binding Assays. For all receptor binding assays, male Sprague−Dawley rats (*Rattus norvegicus albinus*), weighing 180−200 g, were killed by decapitation and the brains rapidly removed and dissected.

5-HT$_{1A}$ Receptor. The receptor binding studies were performed by a modification of a previously described procedure.[30] The cerebral cortex was homogenized in 10 vol of ice-cold Tris buffer (50 mM Tris-HCl, pH 7.7 at 25 °C) and centrifuged at 28000*g* for 15 min. The membrane pellet was washed twice by resuspension and centrifugation. After the second wash the resuspended pellet was incubated at 37 °C for 10 min. Membranes were then collected by centrifugation, and the final pellet was resuspended in 50 mM Tris-HCl, 5 mM $MgSO_4$, and 0.5 mM EDTA buffer (pH 7.4 at 37 °C). Fractions of the final membrane suspension (about 1 mg of protein) were incubated at 37 °C for 15 min with 0.6 nM [^{3}H]-8-OH-DPAT [8-hydroxy-2-(di-*n*-propylamino)tetralin] (133 Ci/mmol), in the presence or absence of several concentrations of the competing drug, in a final volume of 1.1 mL of assay buffer (50 mM Tris-HCl, 10 nM clonidine, 30 nM prazosin, pH 7.4 at 25 °C). Nonspecific binding was determined with 10 μM 5-HT.

α_1 Adrenoceptor. The radioligand receptor binding studies were performed according to a previously described procedure.[31] The cerebral cortex was homogenized in 20 vol of ice-cold buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, pH 7.7 at 25 °C) and centrifuged at 30000*g* for 15 min. Pellets were washed twice by resuspension and centrifugation. Final pellets were resuspended in the same buffer. Fractions of the final membrane suspension (about 250 μg of protein) were incubated at 25 °C for 30 min with 0.2 nM [^{3}H]prazosin (23 Ci/mmol) in the presence or absence of several concentrations of the

competing drug, in a final volume of 2 mL of buffer. Nonspecific binding was determined with 10 μM phentolamine.

D_2 Dopaminergic Receptor. The receptor binding studies were performed according to a previously described procedure.[32] The corpus striatum was homogenized in 50 mM Tris-HCl buffer (pH 7.7 at 25 °C) and centrifuged at 48000*g* for 10 min. The pellet was resuspended and centrifuged as before. The final pellet was resuspended in 50 mM Tris-HCl buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.1% ascorbic acid. Fractions of the final membrane suspension (125−150 μg of protein) were incubated at 25 °C for 60 min with 0.8 nM [^{3}H]raclopride (77 Ci/mmol), in the presence or absence of the competing drug, in a final volume of 1.1 mL of the assay buffer (pH 7.4 at 25 °C). Nonspecific binding was determined with 1 μM (+)-butaclamol.

5-HT_{2A} Receptor. The receptor binding assays were performed according to a previously described procedure.[33] The frontal cortex was homogenized in 60 vol of ice-cold buffer (50 mM Tris-HCl, 0.5 mM Na_2EDTA, and 10 mM $MgSO_4$, pH 7.4 at 37 °C), and centrifuged at 30000*g* for 15 min. The membrane pellet was resuspended in buffer and incubated at 37 °C for 15 min. After centrifuging at 30000*g* for 15 min, the membranes were washed twice by resuspension and centrifugation, and the final pellet was resuspended in assay buffer (50 mM Tris-HCl, 0.5 mM Na_2EDTA, 10 mM $MgSO_4$, 0.1% ascorbic acid, and 10 μM pargyline, pH 7.4 at 37 °C). Fractions of the final membrane suspension (about 0.5 mg of protein) were incubated at 37 °C for 15 min with 0.4 nM [^{3}H]-ketanserin (77 Ci/mmol), in the presence or absence of several concentrations of the competing drug, in a final volume of 2 mL of assay buffer. Nonspecific binding was determined with 1 μM cinanserin.

For all binding assays, incubation was terminated by rapid vacuum filtration through Whatman GF/B filters, using a Brandel harvester. The filters were washed twice with 4 mL of ice-cold 50 mM Tris-HCl (pH 7.4 at 25 °C), and after drying, the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Proteins were determined by the method of Lowry *et al.*,[34] with bovine serum albumin as the standard. Competition binding isotherms were analyzed by using an iterative curve-fitting procedure (program InPlot, Graph Pad), which provided IC_{50} values for test compounds. K_i values were determined by the method of Cheng and Prusoff.[26]

Hypothermia. Rectal temperatures[35] were measured in male Swiss albino mice (Interfauna Ibérica, San Feliu de Codines, Barcelona, Spain), weighing 20−25 g, maintained in a temperature- (25 ± 1 °C) and light- (lights on between 800 and 2000 h) controlled environment; food and tap water were provided *ad libitum*. Dose−response and time course effects on rectal temperature were carried out by calculating the difference in temperature before and after the administration (sc, 0.1 mL; po, 0.2 mL) of various drugs as indicated in the legend of Table 2. A decrease of more than 1.1 °C was considered as a hypothermic response. ED_{50} was calculated according to Tallarida (Lichfield and Wilcoxon I: Confidence limits of ED_{50}). Statistical analyses were conducted by using analysis of variance followed by Student−Newman−Keul's test. Differences were considered significant if the probability of error was less than 5%.

Social Interaction. When two mice are placed together from separate cages into a small chamber in which neither has established territory, they engage in social interaction which includes a variety of behavioral patterns: sniffing, following, grooming, kicking, crawling under or over the partner, and touching or nearly touching their faces.[36,37]

Male Swiss albino mice (Interfauna Iberica, San Feliu de Codines, Barcelona, Spain), weighing 20−25 g (6 pairs/dose), were housed (12/cage) for 5 days before the experiment under a temperature- (25 ± 1 °C) and light- (lights on between 800 and 2000 h) controlled environment, and food and tap water were provided *ad libitum*. On the day of the experiment, drugs were dissolved in distilled water and sc injected. During the first 30 min of absorption time, mice remained housed in their 5-days-home cage. After this absorption time, pairs of mice from different home cages were placed together into a small plastic cage (18 × 14 cm) with a cardboard lid and fresh wood litter on the floor (no change in the light level). The time that mice touched each other was visually measured for 5 min. ED_{50} was calculated according to Tallarida (Lichfield and Wilcoxon I: Confidence limits of ED_{50}). Statistical analyses were conducted by using analysis of variance followed by Student−Newman−Keul's test. Differences were considered significant if the probability of error was less than 5%.

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