Synthesis and Structure−Activity Relationships of a New Model of Arylpiperazines. 4.[1] 1-[ω-(4-Arylpiperazin-1-yl)alkyl]-3-(diphenylmethylene)-2,5-pyrrolidinediones and -3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinediones: Study of the Steric Requirements of the Terminal Amide Fragment on 5-HT_{1A} Affinity/Selectivity

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In the present paper, we report the synthesis and the binding profile on 5-HT_{1A}, α_1 and D_2 receptors of a new series of 1-[ω-(4-arylpiperazin-1-yl)alkyl]-3-(diphenylmethylene)-2,5-pyrrolidinediones (**III**) (**1**−**4**) and -3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinediones (**IV**) (**1**−**4**), in which the alkyl linker contains 1−4 methylenes and the aryl group is variously substituted. The results obtained are compared to those previously reported for bicyclohydantoin (**I**) and the related bicyclic amine (**II**) series. A considerable part of the tested compounds **1**−**4** demonstrated moderate to high affinity for 5-HT_{1A} and α_1 receptor binding sites but had no affinity for D_2 receptors. The study of the length of the alkyl chain and the imide substructure has allowed us to suggest some differences between the 5-HT_{1A} and the α_1-adrenergic receptors: (i) for **III** and **IV**, affinity for the 5-HT_{1A} receptor as a function of the length of the methylene linker decreases in the order $4 > 1 \gg 3 \sim 2$, while for the α_1 receptor affinity decreases in the order $3 \sim 4 > 1 \sim 2$; (ii) the no-pharmacophoric steric pocket (receptor zone which does not hold the pharmacophore of the ligand but holds a nonessential fragment of the molecule) in the 5-HT_{1A} receptor has less restriction than the corresponding pocket in the α_1 receptor. Compounds **3a**,**e**, which are highly selective for α_1-adrenergic receptors, displayed antagonist activity. On the other hand, the best compromise between affinity and selectivity for 5-HT_{1A} receptors is reached in these new series with $n = 1$, which is in agreement with our previous results for the bicyclohydantoin derivatives **I**. Two selected compounds (**1d** and **4e**) retain agonist properties at postsynaptic 5-HT_{1A} receptors. The same 5-HT_{1A} agonist profile found in these compounds suggests the existence of two different no-pharmacophoric steric pockets in this receptor and a different interaction of compounds with $n = 1$ and $n = 4$. The information obtained from the interpretation of the energy minimization and 2D-NOESY experiments of compounds **1**−**4** together with the synthesis and binding data of new conformationally restrained analogues **4k**−**m** is in good agreement with this working hypothesis.

Introduction

The group of G-protein-coupled receptors (GPCRs) represents a protein membrane receptor class which is physiologically and pharmacologically interesting and plays an essential role in the neurotransmission processes. This receptor superfamily is characterized by its wide range of receptor subclasses and their similarity with each other, especially at tertiary and quaternary levels. So, a great number of ligands display affinity for different classes of this receptor family, and consequently, selectivity has been a problem in the design of new ligands. Research into new selective compounds is needed to improve our understanding of the transduction phenomenom and to develop ligands with higher affinity and without side effects. A particular case of this problem is represented by the ligands with affinity for both 5-HT_{1A}-serotonergic and α_1-adrenergic receptors, due to these receptors having a high degree of similarity (45%) in their amino acid sequence.[2] Thus, compounds such as buspirone,[3,4] ipsapirone,[3,5] and NAN-190[6−8] show high affinity for 5-HT_{1A} receptors, but poor selectivity. In this way, research in this area is promising since only some selective agonists, e.g., 8-OH-DPAT,[9] and antagonists, e.g., (*S*)-UH-301[10] and WAY-100635,[11] have been described.

Even for the long-chain arylpiperazines with an amide or imide moiety, which represent the class of the 5-HT_{1A} receptor ligands most thoroughly studied up to date, the structural features that decide their selectivity versus α_1-adrenergic receptor are not yet clear.[12−14] The pharmacophore interaction with the 5-HT_{1A} receptor active site has been described in detail.[15−18] The influence of

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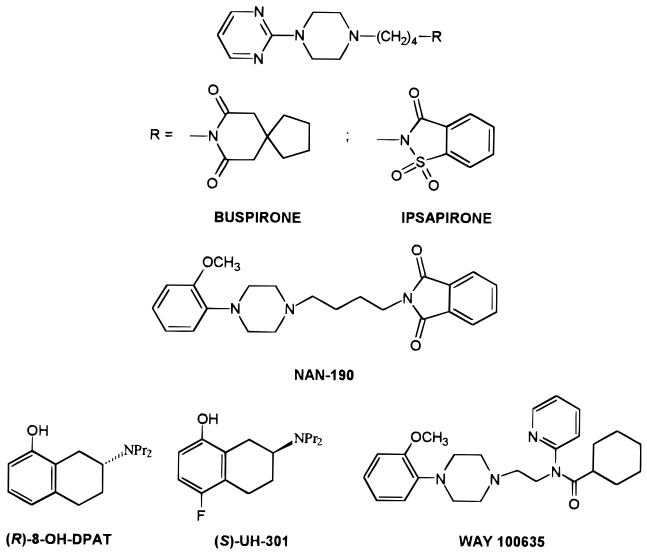
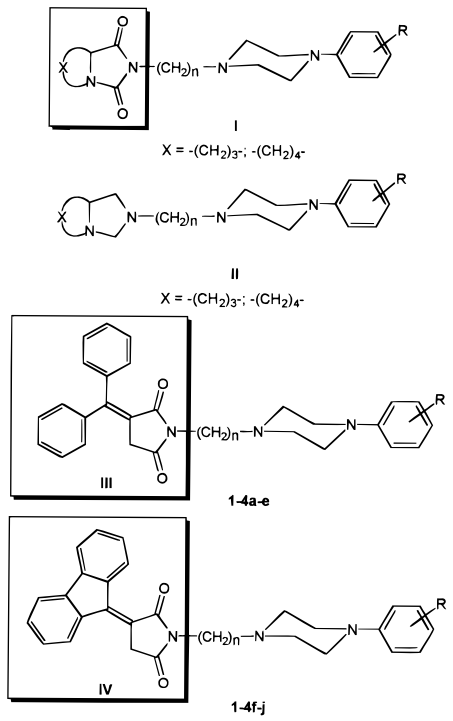


the length of the spacer on 5-HT_{1A} affinity is also well-known,[13,19,20] in contrast to the role of the amide substructure. Some authors have reported that the presence of the terminal amide fragment plays an important role in the stabilization of the 5-HT_{1A} receptor−ligand complex and that this interaction can be lipophilic,[13,18] electronic,[21−23] or steric,[24,25] while another hypothesis[7,20,26−28] has suggested that the amide function is not required for binding to the 5-HT_{1A} receptor.

In previous papers[29−31] we have reported the synthesis and quantitative structure−activity relationships (3D-QSAR) of a series of bicyclohydantoin arylpiperazines **I**, which showed affinity for 5-HT_{1A} and α_1 receptors. These studies give us a better understanding of the α_1/5-HT_{1A} selectivity of the arylpiperazine substitution and lead us to conclude that the hydantoin moiety and the side-chain length seem to modulate not only the affinity but also the selectivity α_1/5-HT_{1A}. In a recent work,[1] we described new derivatives **II** which are devoid of the terminal amide fragment present in related 5-HT_{1A} ligands but which preserve the steric requirements of this moiety (van der Waals volume about 100 Å^3). From these SAR studies we could suggest that there is influence of electronic factors on the no-pharmacophoric part (receptor zone which does not hold the pharmacophore of the ligand but holds a nonessential fragment of the molecule) of the α_1 receptor site; however, they have no influence on the stabilization of the 5-HT_{1A} receptor−ligand complex. This fact makes a slight difference between both receptors in their no-pharmacophoric sites evident. To gain insight into the role of the amide moiety of this kind of ligand in the affinity and selectivity for 5-HT_{1A} receptors, we have considered a new series of arylpiperazines **III** and **IV (1−4)**, in which we have explored some steric requirements modifying the size and the shape of the amide portion, with respect to the bicyclohydantoins **I**. We have taken into account a significant increase in the van der Waals volume of the no-pharmacophoric part (ΔV_W about 100 Å^3). The two substructures considered are 3-(diphenylmethylene)-2,5-pyrrolidinedione (series **III**; V_W = 210.07 Å^3) and 3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (series **IV**; V_W = 193.37 Å^3) which have a similar van der Waals volume but a different shape. The energy minimization of imides **5a,b** shows that while

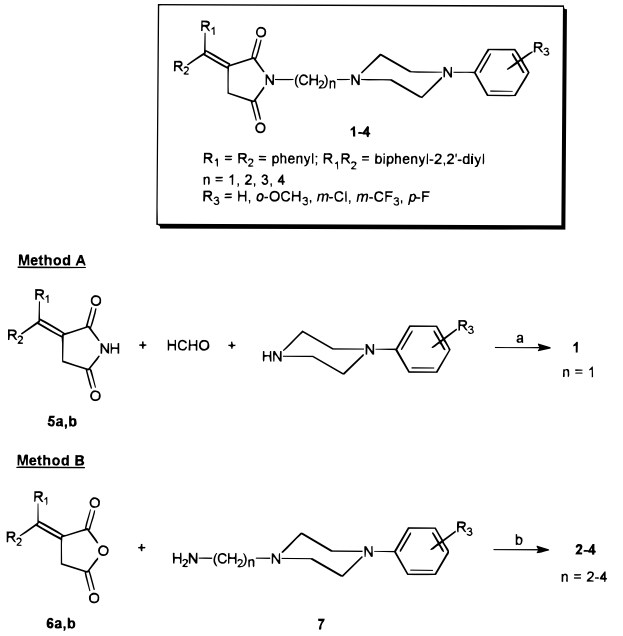


the imide **5b** has a totally coplanar conformation, **5a** has the two phenyl rings perpendicular to the plane of the imide ring. In the present paper, we report the synthesis and the binding profile on 5-HT_{1A}, α_1, and D_2 receptors of compounds **1**−**4**, where the length of the spacer is 1−4 methylenes and the arylpiperazines (R = H, *o*-OCH_3, *m*-Cl, *m*-CF_3, *p*-F) are present in compounds **I** with the highest affinity for the 5-HT_{1A} receptor. Two selected compounds with interesting 5-HT_{1A} binding were evaluated in order to determine in vitro their agonist or antagonist activity at the postsynaptic level. We also evaluated the antagonist activity for α_1-adrenergic receptors of two selective analogues.

Chemistry

Two pathways (Scheme 1) were used in order to prepare the imide derivatives **1**−**4** listed in Table 1. Compounds **1** (n = 1) were prepared by Mannich reaction of the imide **5a**[32] or **5b** with formaldehyde and the appropriate arylpiperazines (method A). The desired compounds **2**−**4** (n = 2−4) were obtained through method B, by reaction of the respective anhydride **6**[33,34] with the corresponding 1-(*ω*-aminoalkyl)-4-arylpiperazines **7** in acetic acid as solvent. The starting imide **5b** was synthesized by a condensation of fluorenone with succinonitrile using potassium *tert*-butoxide as base and in *tert*-butyl alcohol as solvent, followed by acidic hydrolysis with sulfuric acid. The 1-(*ω*-aminoalkyl)-4-arylpiperazines **7** were prepared following standard procedures[35] by reduction of the corresponding nitriles with lithium aluminum hydride in THF. The 4-(*ω*-cyanoalkyl)-1-arylpiperazines were obtained by treatment of the appropriate arylpiperazines with *ω*-chloroalkylnitriles in the presence of sodium carbonate and acetonitrile.[36] Hydrochloride salts of the target compounds **1**−**4** were prepared as samples for biological assays. All new compounds were characterized by IR and ^{1}H and ^{13}C NMR spectroscopy and gave satisfactory combustion analyses (C, H, N). Table 1 summarizes the

Scheme 1[a]



[a] Reagents: (a) EtOH, 100 °C, 1−3 h; (b) acetic acid, reflux, 24−30 h.

experimental and physical data for the desired compounds **1**−**4**.

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. The specific ligands and tissue sources used are as follows: (a) serotonergic 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) dopaminergic D_2 receptors, [^{3}H]raclopride, rat striatum membranes. The inhibition constant K_i was calculated from the IC_{50} by the Cheng−Prusoff equation[37] (Table 1). The agonist/antagonist character of compounds **1d** and **4e** at the 5-HT_{1A} receptor was evaluated by their ability to affect adenylyl cyclase activity in a rat hippocampus slice preparation. The results of these assays are shown in Figure 1. The agonist/antagonist activity of **3a**,**e** at α_1-adrenergic receptors was studied on ring segments of rat thoracic aorta contracted by phenylephrine (Table 2).

Results and Discussion

The results of the in vitro binding studies of the target compounds **1**−**4** are summarized in Table 1. Most of the compounds **1**−**4** demonstrated moderate to high affinity for 5-HT_{1A} and α_1 receptor binding sites and had no affinity for D_2 receptors.

The study of the results presented in Table 1 shows that the imide substructure together with the length of the alkyl chain plays an important role in the affinity and selectivity for the 5-HT_{1A} receptor. On the other hand, the influence of the phenyl ring substitution on the affinity at both receptors is in agreement with our previous reports.[30,31] One of the most important facts observed in Table 1 is that compounds **1** ($n = 1$) display moderate affinity for 5-HT_{1A} receptors and are almost inactive at α_1 receptors, so they show a good 5-HT_{1A} selectivity versus α_1-adrenergic receptors. Compounds **I**[29,30] with a 1-carbon atom spacer showed a similar trend, and this structural feature has become one of the few structural modulators of selectivity between 5-HT_{1A} and α_1-adrenergic receptors. Compounds **1d** (series **III**: $R_3 = m$-CF_3; K_i(5-HT_{1A}) = 59 nM; $K_i(\alpha_1) > 1000$ nM) and **1g** (series **IV**: $R_3 = o$-OCH_3; K_i(5-HT_{1A}) = 61 nM; $K_i(\alpha_1) > 1000$ nM) are the best compromise between affinity and selectivity and proved to be the most selective members of these series. On the other hand, neither the size nor the shape of the imide substructure has an important influence on 5-HT_{1A} affinity when there is a 1-carbon atom spacer in the volume range studied. Thus, compounds **1c** ($R_3 = m$-Cl) and **1h** ($R_3 = m$-Cl) are equipotent and have similar K_i values to the corresponding bicyclohydantoins **I** (X = $-(CH_2)_3-$, K_i-(5-HT_{1A}) = 58 nM; X = $-(CH_2)_4-$, K_i(5-HT_{1A}) = 57 nM), despite the fact that bicyclohydantoins have one-half the van der Waals volume.

An increase in the size of the alkyl chain to $n = 2$ leads to a marked decrease in the affinity for 5-HT_{1A} receptors and retains the inactivity for α_1 receptors. Only three compounds (**2b**,**g**,**j**) display a moderate affinity for α_1-adrenergic sites.

The influence on affinity at both receptors of the size and the shape of the imide moiety, in compounds with 3−4 methylenes in the spacer, has great importance since this structural feature could represent another selectivity modulator between 5-HT_{1A} and α_1-adrenergic receptors. So, ligands with a 3-carbon chain in the spacer display very low affinity at 5-HT_{1A} receptors, in contrast to the results we previously described,[30] since the bicyclohydantoins **I** displayed high affinity with $n = 3$. Thus, compounds **3d**,**i** ($R_3 = m$-CF_3) are inactive, while the corresponding bicyclohydantoin derivatives **I** showed high affinity (X = $-(CH_2)_3-$, K_i(5-HT_{1A}) = 3.8 nM; X = $-(CH_2)_4-$, K_i(5-HT_{1A}) = 5.7 nM). Consequently, the size of the no-pharmacophoric substructure arises as an important feature to the modulation of the affinity at 5-HT_{1A} receptors. An exception is represented by derivative **3g** with an *o*-methoxy group in the phenyl ring (K_i = 37 nM), but this compound has less affinity than the bicyclohydantoin analogue[30] (K_i = 4.1 nM). Regarding the α_1-adrenergic receptor, there is an important difference in the affinity between the two series, **III** and **IV**, when $n = 3$. While compounds **3a**−**e** (series **III**) display the highest affinity for α_1-adrenergic receptors, derivatives **3f**−**j** (series **IV**) are almost inactive. For example, the decrease in the affinity becomes 250-fold for compounds with $R_3 = m$-Cl. Thus, compounds of the series **III** have similar K_i values to the bicyclohydantoins **I**. The lack of affinity for 5-HT_{1A} receptor binding sites in derivatives with $n = 3$ leads to highly selective compounds for α_1-adrenergic receptors. Thus, analogues **3a** (R_3 = H; $K_i(\alpha_1)$ = 5.7 nM; K_i (5-HT_{1A}) > 1000 nM) and **3e** ($R_3 = p$-F; $K_i(\alpha_1)$ = 8.3 nM; K_i(5-HT_{1A}) > 1000 nM) display high affinity for α_1 receptors and are inactive at 5-HT_{1A} binding sites.

Finally, an increase in the length of the spacer to 4 carbons leads to compounds with the highest affinity at 5-HT_{1A} receptors, and we noticed that the influence of the no-pharmacophoric substructure is not clear. The structural change from a nonplanar to a planar imide portion has a different influence on the affinity for the 5-HT_{1A} receptor. Thus, when R_3 = H this change implies

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

						K_i (nM)		
compd	R_1R_2[b]	*n*	R_3	mp (°C)	formula	5-HT_{1A} [^{3}H]-8-OH-DPAT	α_1 [^{3}H]prazosin	D_2 [^{3}H]raclopride
1a	**III**	1	H	176−177	$C_{28}H_{27}N_3O_2{\cdot}2HCl{\cdot}H_2O$	98 ± 5	>1000	>1000
1b	**III**	1	*o*-OCH_3	169−170	$C_{29}H_{29}N_3O_3{\cdot}2HCl{\cdot}H_2O$	93 ± 4	>1000	>1000
1c	**III**	1	*m*-Cl	153−154	$C_{28}H_{26}ClN_3O_2$	49 ± 8	392 ± 44	>1000
1d	**III**	1	*m*-CF_3	174−175	$C_{29}H_{26}F_3N_3O_2{\cdot}2HCl{\cdot}H_2O$	59 ± 4	>1000	>1000
1e	**III**	1	*p*-F	158−159	$C_{28}H_{26}FN_3O_2$	>1000	746 ± 13	>1000
1f	**IV**	1	H	147−149	$C_{28}H_{25}N_3O_2{\cdot}2HCl$	201 ± 33	>1000	>10000
1g	**IV**	1	*o*-OCH_3	168−169	$C_{29}H_{27}N_3O_3$	61 ± 8	>1000	>10000
1h	**IV**	1	*m*-Cl	165−166	$C_{28}H_{24}ClN_3O_2{\cdot}2HCl{\cdot}H_2O$	42 ± 2	316 ± 33	>10000
1i	**IV**	1	*m*-CF_3	163−165	$C_{29}H_{24}F_3N_3O_2{\cdot}2HCl{\cdot}^5/_2H_2O$	114 ± 10	791 ± 43	>10000
1j	**IV**	1	*p*-F	161−163	$C_{28}H_{24}FN_3O_2$	>1000	>1000	>10000
2a	**III**	2	H	228−229	$C_{29}H_{29}N_3O_2{\cdot}2HCl{\cdot}H_2O$	>1000	214 ± 24	>1000
2b	**III**	2	*o*-OCH_3	210−211	$C_{30}H_{31}N_3O_3{\cdot}2HCl{\cdot}H_2O$	286 ± 5	71 ± 1	167[c]
2c	**III**	2	*m*-Cl	189−190	$C_{29}H_{28}ClN_3O_2{\cdot}2HCl{\cdot}H_2O$	>1000	>1000	>1000
2d	**III**	2	*m*-CF_3	208−209	$C_{30}H_{28}F_3N_3O_2{\cdot}2HCl{\cdot}H_2O$	>1000	>1000	>1000
2e	**III**	2	*p*-F	216−217	$C_{29}H_{28}FN_3O_2{\cdot}2HCl{\cdot}H_2O$	>1000	529 ± 19	>1000
2f	**IV**	2	H	250−252	$C_{29}H_{27}N_3O_2{\cdot}HCl$	>10000	196 ± 25	>10000
2g	**IV**	2	*o*-OCH_3	260−262	$C_{30}H_{29}N_3O_3{\cdot}HCl$	>1000	57 ± 6	>10000
2h	**IV**	2	*m*-Cl	270−272	$C_{29}H_{26}ClN_3O_2{\cdot}HCl$	>10000	>10000	>10000
2i	**IV**	2	*m*-CF_3	275−277	$C_{30}H_{26}F_3N_3O_2{\cdot}HCl$	>10000	>10000	>10000
2j	**IV**	2	*p*-F	252−253	$C_{29}H_{26}FN_3O_2{\cdot}HCl$	>10000	56 ± 1	>10000
3a	**III**	3	H	188−189	$C_{30}H_{31}N_3O_2{\cdot}2HCl{\cdot}H_2O$	>1000	5.7 ± 0.3	>1000
3b	**III**	3	*o*-OCH_3	129−130	$C_{31}H_{33}N_3O_3{\cdot}2HCl{\cdot}H_2O$	665 ± 21	8.1 ± 1.2	156[c]
3c	**III**	3	*m*-Cl	198−199	$C_{30}H_{30}ClN_3O_2{\cdot}2HCl$	127 ± 12	39 ± 7	801[c]
3d	**III**	3	*m*-CF_3	185−186	$C_{31}H_{30}F_3N_3O_2{\cdot}2HCl$	>1000	62 ± 1	>1000
3e	**III**	3	*p*-F	217−218	$C_{30}H_{30}FN_3O_2{\cdot}2HCl{\cdot}H_2O$	>1000	8.3 ± 1.1	>1000
3f	**IV**	3	H	260−262	$C_{30}H_{29}N_3O_2{\cdot}2HCl{\cdot}H_2O$	>1000	646 ± 46	>1000
3g	**IV**	3	*o*-OCH_3	212−215	$C_{31}H_{31}N_3O_3{\cdot}2HCl{\cdot}H_2O$	37 ± 4	161 ± 3	>1000
3h	**IV**	3	*m*-Cl	240−241	$C_{30}H_{28}ClN_3O_2{\cdot}HCl$	>1000	>10000	>10000
3i	**IV**	3	*m*-CF_3	215−218	$C_{31}H_{28}F_3N_3O_2{\cdot}2HCl$	>1000	>10000	>10000
3j	**IV**	3	*p*-F	295−298	$C_{30}H_{28}FN_3O_2{\cdot}HCl$	>10000	61 ± 8	>1000
4a	**III**	4	H	160−162	$C_{31}H_{33}N_3O_2{\cdot}2HCl$	125 ± 36	6.4 ± 0.9	>1000
4b	**III**	4	*o*-OCH_3	214−215	$C_{32}H_{35}N_3O_3{\cdot}2HCl$	13 ± 3	14 ± 1	>1000
4c	**III**	4	*m*-Cl	172−173	$C_{31}H_{32}ClN_3O_2{\cdot}2HCl$	39 ± 8	16 ± 1	367[c]
4d	**III**	4	*m*-CF_3	196−197	$C_{32}H_{32}F_3N_3O_2{\cdot}2HCl$	15 ± 2	60 ± 1	689[c]
4e	**III**	4	*p*-F	184−185	$C_{31}H_{32}FN_3O_2{\cdot}2HCl$	3.3 ± 0.3	51 ± 1	351[c]
4f	**IV**	4	H	198−200	$C_{31}H_{31}N_3O_2{\cdot}HCl{\cdot}H_2O$	14 ± 3	60 ± 3	397[c]
4g	**IV**	4	*o*-OCH_3	176−179	$C_{32}H_{33}N_3O_3{\cdot}2HCl{\cdot}H_2O$	9.0 ± 3.2	10 ± 4	>10000
4h	**IV**	4	*m*-Cl	185−188	$C_{31}H_{30}ClN_3O_2{\cdot}HCl{\cdot}H_2O$	72 ± 19	249 ± 30	>1000
4i	**IV**	4	*m*-CF_3	178−180	$C_{32}H_{30}F_3N_3O_2{\cdot}2HCl$	>1000	>10000	>1000
4j	**IV**	4	*p*-F	170−173	$C_{31}H_{30}FN_3O_2{\cdot}2HCl{\cdot}H_2O$	>10000	266 ± 1	>10000

[a] All values are the mean ± SEM of 2−4 experiments performed in triplicate. [b] Series **III**: $R_1 = R_2$ = phenyl. Series **IV**: R_1R_2 = biphenyl-2,2′-diyl. [c] Values taken from only one experiment.

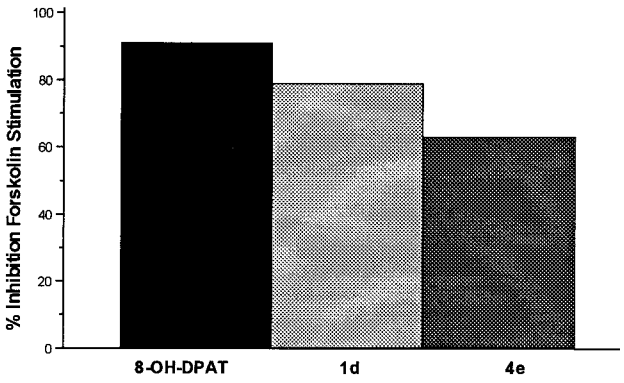


Figure 1. Effects of 8-OH-DPAT, **1d**, and **4e** on forskolin-stimulated adenylyl cyclase activity in rat hippocampal slices. Results are expressed as percentage of inhibition of the forskolin stimulation.

an 9-fold increase in the affinity, while for R_3 = *p*-F the same change leads to an approximately 3000-fold decrease. Regarding the α_1-adrenergic receptor, an increase in the length of the spacer to $n = 4$ retains the affinity with respect to analogues with $n = 3$ in the series **III** and increases the affinity for derivatives of the series **IV**. However, the affinity of compounds **4f**−**j** (series **IV**) is somewhat lower than that of the corresponding derivatives **4a**−**e** (series **III**).

Table 2. α_1-Adrenergic Receptor Antagonism[a]

compd	pA_2 ± SEM	slope	n[b]
3a	7.79 ± 0.04	0.86 ± 0.02	6
3e	8.63 ± 0.20	0.91 ± 0.08	7
prazosin	9.30 ± 0.34	1.03 ± 0.06	6

[a] Displacement of dose−response curve to phenylephrine. [b] Number of separate experiments.

These results suggest a different steric interaction of the no-pharmacophoric part with the 5-HT_{1A} and α_1-adrenergic receptors, although other factors, such as electronic contributions,[1] might be implicated in the formation of the receptor−ligand complex. We assume the existence of a restricted steric region (steric pocket) in the normal interaction ($n = 3, 4$) for both receptors that would hold the terminal imide fragment of the molecule. The data suggest that the steric restrictions are different in each case, and consequently, this pocket would have a distinct size and/or shape for these receptors. Regarding the 5-HT_{1A} receptor, these data define an optimum length of the spacer of 4 carbons, since compounds **3** with $n = 3$ are inactive. So, ligands with $n = 3$ and with a no-pharmacophoric part of about

200 Å^3 would not reach the active site of the receptor, while a decrease of this volume to about 100 Å^3 in the bicyclohydantoin derivatives **I** allows the ligand−receptor interaction, probably because part of the hydantoin portion acts as a spacer. With respect to the α_1-adrenergic receptor, the optimum spacer length is 3−4 methylene units. The fact that compounds **3f**−**j** (series **IV**: $n = 3$) are almost inactive despite having the same volume and the optimum spacer length for the α_1-adrenergic receptor could suggest that the steric pocket in this receptor could have different restrictions from the corresponding pocket in the 5-HT$_{1A}$ receptor. When derivatives have a 4-carbon chain, the length is so long that it allows the interaction with the α_1 receptor for bigger imide fragments.

On the other hand, the abnormal affinity of derivatives **1** ($n = 1$) for 5-HT$_{1A}$ receptors and the noninfluence of the imide portion on the affinity suggest an alternative manner of interaction with the receptor of this kind of ligand. This structural feature could be of great importance in order to design new selective ligands.

Compounds **3a**,**e**, which are highly selective for α_1-adrenergic receptors, were evaluated in order to determine their antagonist activity at this receptor (Table 2). Upon examination of the values of pA_2, compound **3e** (p$A_2 = 8.63$) displays high potency as an antagonist at α_1-adrenergic receptors, while **3a** (p$A_2 = 7.79$) shows a moderate potency.

Two derivatives with affinity for 5-HT$_{1A}$ receptors were selected in order to determine in vitro their agonist or antagonist activity at the postsynaptic level. Compound **1d** was selected for its selectivity at the 5-HT$_{1A}$ receptor versus α_1 and D$_2$ receptors, and **4e** was chosen since, considering all the studied compounds, it displays the highest affinity for 5-HT$_{1A}$ receptors, together with a moderate selectivity for α_1-adrenergic sites (15-fold) and high selectivity versus D$_2$ receptors (106-fold).

It is well-established that the 5-HT$_{1A}$ receptor is negatively coupled with adenylyl cyclase and that the receptor agonists inhibit the forskolin-stimulated adenylyl cyclase activity.[38] As shown in Figure 1, 100 μM 8-OH-DPAT, a 5-HT$_{1A}$ agonist, inhibited forskolin-stimulated adenylyl cyclase activity by 91%. At the same concentration (100 μM), compounds **1d** and **4e** inhibited this activity by 79% and 63%, respectively. These results indicate that both compounds retain agonist properties at postsynaptic 5-HT$_{1A}$ receptors. This fact might suggest the existence of two different no-pharmacophoric steric pockets in this receptor. To justify this hypothesis we have carried out the energy minimization[39] of compounds **1d** ($n = 1$) and **4e** ($n = 4$), as their protonated form. Both compounds were built de novo using the INSIGHT II BUILDER module and fully geometry-optimized using the standard INSIGHT II molecular mechanics force field, with a 0.001 kcal mol^{-1} energy gradient convergence. A systematic conformational search was performed on the rotable bonds using an increment at 30° in the INSIGHT II DISCOVER module, and every generated conformation was minimized up to 2000 iterations. The results of the energy minimization of compound **4e** led to a folded lowest-energy conformation (223.7 kcal mol^{-1}), wherein an intramolecular hydrogen-bonding interaction (1.78 Å) between one of the carbonyls and the protonated piperazine would be possible and a $\pi-\pi$ interaction is favored (Figure 2A). It was only possible to obtain an extended low-energy conformation of **4e** (238.0 kcal mol^{-1}), with a difference of 14 kcal mol^{-1} with respect to the folded lowest-energy conformation. Derivative **1d** has led to one-folded conformation (198.0 kcal mol^{-1}) (Figure 2B). The energy minimization of both compounds was carried out in a vacuum continuum.

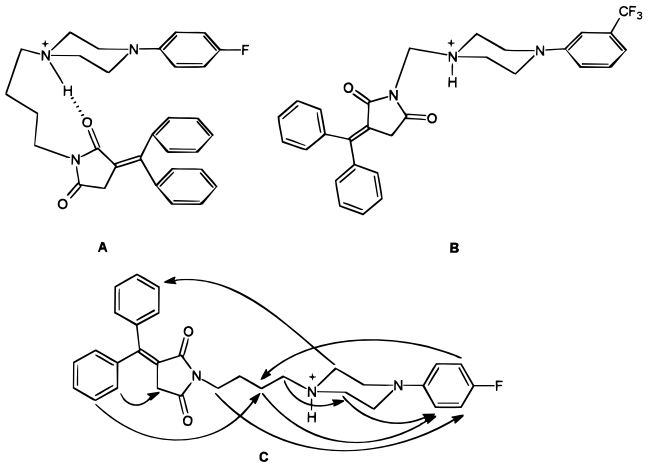


Figure 2. (A) Folded low-energy conformation of the hydrochloride salt of **4e** (223.7 kcal mol^{-1}). (B) Folded low-energy conformation of the hydrochloride salt of **1d** (198.0 kcal mol^{-1}). (C) Significant NOE signals of **4e** in deuterated dimethyl sulfoxide solution.

2D-NOESY experiments were conducted in deuterated dimethyl sulfoxide in order to obtain additional information about the conformations of compounds **1d** and **4e** in solution. Figure 2C represents the significant NOE signals which indicate that compound **4e** is in a folded conformation. If compound **4e** was in an extended conformation, the interactions between the aromatic hydrogens of the imide substructure, the phenylpiperazine protons, and the methylenes of the alkyl chain would not be possible. These results are in agreement with those described by Norman et al.[40] and Sunagawa et al.[41] for related compounds.

The superimposition of the different conformations of **1d** and **4e** were carried out via root-mean-square (rms < 0.1) using the basic nitrogen of the piperazine and the aromatic ring as a reference. If we superimpose the folded conformations of **1d** and **4e**, we can observe that the imide moiety of **1d** stays in the occupied space of the alkyl chain of **4e** (Figure 3). This fact would imply the existence of a great no-pharmacophoric steric pocket which would hold the terminal imide fragment, and it might justify the affinity of ligands with $n = 1$. Nevertheless, in this case ligands with $n = 2$, 3 would be active, and the steric pocket would not have an influence on the affinity for 5-HT$_{1A}$ receptors. Also, we have carried out the energy minimization of compounds **2d** ($n = 2$, R$_3$ = *m*-CF$_3$) and **3d** ($n = 3$, R$_3$ = *m*-CF$_3$), and we have obtained two families of conformations (extended and folded) for both compounds, with the folded conformations having a lower energy than the corresponding extended ones ($\Delta E \sim 11$ kcal mol^{-1}). The superimposition of folded conformations for all the compounds ($n = 1-4$) (Figure 4) showed that the imide moieties stay at the same distance from the pharmacophore for compounds with $n = 2-4$. This fact would

Figure 3. Superimposition of folded low-energy conformations of compounds **1d** (yellow) and **4e** (magenta) as their protonated forms.

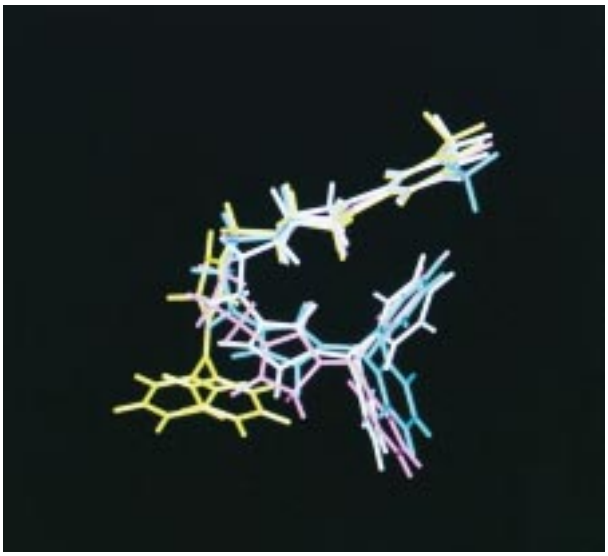


Figure 4. Superimposition of folded low-energy conformations of compounds **1d** (yellow), **2d** (white), **3d** (blue), and **4e** (magenta) as their protonated forms.

imply that compounds with $n = 2$, 3 would have the same activity as compounds with a 4-carbon chain in the spacer. On the contrary, the superimposition of the extended conformations of derivatives **2d**, **3d**, and **4e** and the folded conformation of **1d** (Figure 5) does not fit well, and these different arranges (the imide substructure of **2d** and **3d** are in the spacer zone of **4e**) might justify the different affinity observed between them. So, although the extended conformation of **4e** has a greater energy than the folded one (14 kcal mol^{-1}), this energy would be compensated with the receptor interaction energy. Then, we can assume that compounds with $n = 1$ and compounds with $n = 2-4$ adopt a different conformation in their interaction with the receptor, and this fact leads to the assumption of a second no-pharmacophoric steric pocket, placed on a shorter distance from the pharmacophore, that would hold the imide moiety of ligands with a 1-carbon spacer. The α_1-adrenergic receptor would not have this second steric pocket, and we would be able to explain the high

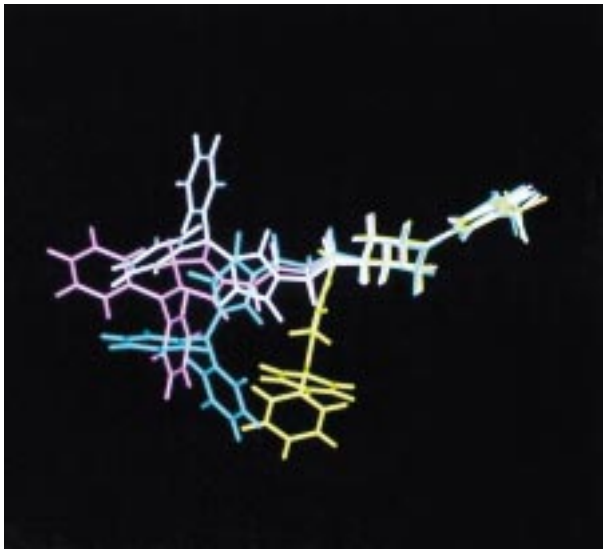
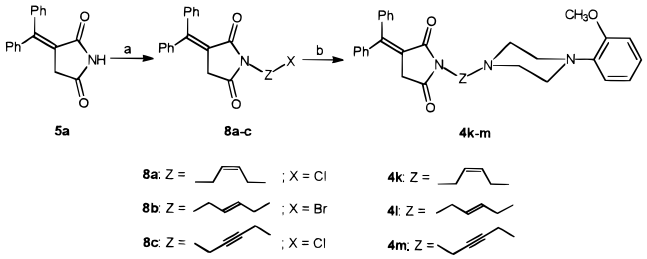


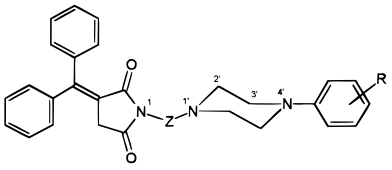
Figure 5. Superimposition of extended conformations of compounds **2d** (white), **3d** (blue), and **4e** (magenta) and the folded conformation of **1d** (yellow) as their protonated forms.

Scheme 2[a]



[a] Reagents: (a) NaH, DMF, N_2, 60 °C, 1 h, then halogenated derivative, 110 °C, 2 h; (b) 1-(*o*-methoxyphenyl)piperazine, Et_3N, acetonitrile, 60 °C, 20−24 h.

Table 3. In Vitro Binding Data[a] and Structural Parameter Values of the Extended Conformations of Compounds **4k−m** and **4e**



compd	Z	R	K_i (nM) 5-HT_{1A}	d (Å)[b]	E_{min}[c]
4k		*o*-OCH_3	237 ± 17	4.8	239.6
4l		*o*-OCH_3	27 ± 1	5.85	243.5
4m		*o*-OCH_3	6.6 ± 0.7	6.04	252.4
4e		*p*-F	3.3 ± 0.3	6.37	238.0

[a] All values are the mean ± SEM of 2−4 experiments performed in triplicate. [b] d = N1′−N1. [c] kcal mol^{-1}.

selectivity observed in compounds with 1 methylene in the alkyl chain.

To justify this hypothesis, we have synthesized new conformationally constrained unsaturated derivatives **4k−m** (Scheme 2; Table 3). All of them are characterized by a decrease of the spacer flexibility with respect to the saturated analogues. The affinity data are shown

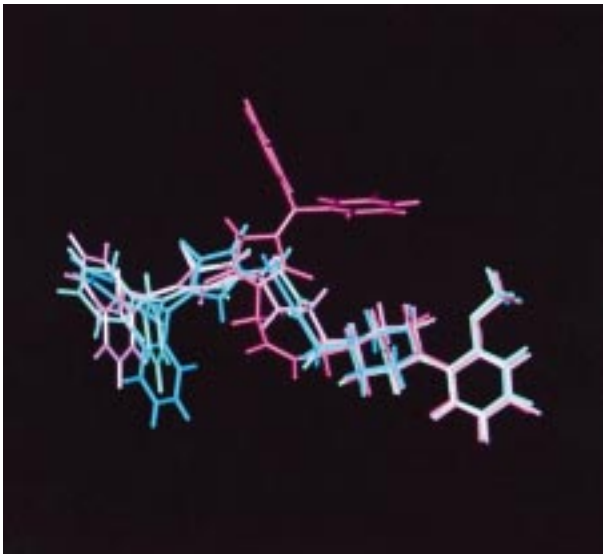


Figure 6. Superimposition of the extended conformations of compounds **4k** (dark magenta), **4l** (blue), **4m** (dark blue), and **4e** (magenta).

in Table 3. We have carried out the energy minimization of these structures following the above-described method. If we take into account the extended lower-energy conformations of restrained compounds **4k**−**m** and the saturated analogue **4e**, we could consider the distance between the piperazine basic nitrogen (N1′) and the imide nitrogen (N1) as a measure of the molecular linearity. The results in Table 3 show a clear correlation of the molecular linearity with the affinity to the 5-HT_{1A} receptor. Likewise, the superimposition of the extended conformations of saturated derivative **4e** and unsaturated compounds **4k**−**m** (Figure 6) shows an excellent fitting between analogues **4e** and **4l,m**, while the *Z* isomer **4k** does not fit well. These facts might justify the moderate decrease in the affinity of **4k**, and they confirm the hypothesis of the extended conformation of these compounds as the bioactive conformation.

Conclusion

In the present study, we have prepared a new series of imide arylpiperazines **III** and **IV (1**−**4)** in order to study the steric influence of the terminal imide fragment. The study of the length of the alkyl chain and the imide substructure allows us to suggest some differences between the no-pharmacophoric sites of both 5-HT_{1A} and α_1-adrenergic receptors, which could be of great importance in order to design new selective ligands. The optimum length of the alkyl chain for 5-HT_{1A} affinity is 4 carbon atoms since compounds **3** with $n = 3$ are inactive. With respect to the α_1-adrenergic receptor, the optimum length is 3−4 methylene units, as several compounds with $n = 3$ have shown high selectivity for this receptor. Moreover, the no-pharmacophoric pocket in the 5-HT_{1A} receptor would have less restriction than the corresponding pocket in the α_1-adrenergic receptor. On the other hand, the abnormal affinity of derivatives with $n = 1$ for 5-HT_{1A} receptors and the noninfluence of the imide portion on the affinity suggest an alternative manner of interaction of this kind of ligand with this receptor. Furthermore, the same 5-HT_{1A} agonist profile found in compounds **1d** ($n = 1$) and **4e** ($n = 4$) might justify the existence of two different no-pharmacophoric steric pockets in this receptor, to explain the affinity of both ligands. This hypothesis has been confirmed by the molecular modeling of several representative compounds and the synthesis of new conformationally constrained analogues.

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. 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 used were high-grade commercial products.

The compounds **5a** and **6a,b** were synthesized by published procedures. The physical data are in agreement with those given in refs 32−34, respectively.

3-(9*H*-Fluoren-9-ylidene)-2,5-pyrrolidinedione (5b). To a solution of potassium *tert*-butoxide (13.47 g, 120 mmol) in *tert*-butyl alcohol (40 mL) at 50 °C under nitrogen was added dropwise a solution of 9-fluorenone (18.02 g, 100 mmol) and succinonitrile (9.61 g, 120 mmol) in *tert*-butyl alcohol (40 mL). The mixture was refluxed under nitrogen for 2 h, allowed to cool, and acidified with 6 N HCl. After evaporation of the solvent, the resultant residue was washed with water and crystallized from ethanol affording the 4-(9*H*-fluoren-9-ylidene)-5-imino-2-pyrrolidone. A solution of this solid in 10% sulfuric acid (120 mL) was refluxed for 5 h. The mixture was allowed to cool; the precipitate was filtered, washed with water, and dried in vacuo to afford **5b** (14.10 g, 55%): mp 178−179 °C (ethanol); IR (KBr, cm^{-1}) 3040 (NH), 1770, 1700 (CON), 1630 (C═C); ^{1}H NMR (DMSO-d_6) δ 3.92 (s, 2H, CH_2), 7.29−7.33 (m, 2H, $H_{2'}$, $H_{7'}$), 7.36−7.41 (m, 2H, $H_{3'}$, $H_{6'}$), 7.68 (d, $J = 7.8$ Hz, 1H, $H_{8'}$), 7.76 (d, $J = 7.8$ Hz, 1H, $H_{4'}$ or $H_{5'}$), 7.79 (d, $J = 8.1$ Hz, 1H, $H_{4'}$ or $H_{5'}$), 9.24 (d, $J = 7.8$ Hz, 1H, $H_{1'}$), 11.61 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 38.4 (CH_2), 127.4 (C_3), 119.6, 120.0, 127.1, 127.9, 128.9, 130.2, 130.4, 135.3, 137.8, 140.7, 140.9, 141.3 (Ar), 171.2 (C_2), 174.7 (C_5). Anal. ($C_{17}H_{11}NO_2$) C, H, N.

General Method A. Synthesis of Derivatives 1a−**j.** To a suspension of the imides **5a,b** (9.7 mmol) and 1 mL (9.7 mmol) of 35% formaldehyde in ethanol (15 mL) was added the corresponding arylpiperazine (9.7 mmol) (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 free base was converted to its hydrochloride salt.

1-[(4-Phenylpiperazin-1-yl)methyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (1a): yield 2.56 g (50%); mp 176−177 °C (acetone); IR (KBr, cm^{-1}) 1770, 1700 (CON), 1610 (C═C); ^{1}H NMR ($CDCl_3$) δ 2.78 (t, $J = 4.8$ Hz, 4H, $2CH_2$-pip), 3.15 (t, $J = 4.8$ Hz, 4H, $2CH_2$-pip), 3.47 (s, 2H, CH_2CO), 4.57 (s, 2H, NCH_2N), 6.84−6.92 (m, 3H, ArH), 7.17−7.28 (m, 6H, ArH), 7.34−7.38 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.7 (CH_2-CO), 49.2 ($2CH_2$-pip), 50.5 ($2CH_2$-pip), 59.4 (NCH_2N), 121.0 (C_3), 116.2, 119.9, 127.8, 128.4, 128.5, 128.8, 128.9, 129.0, 138.7, 140.5, 151.0, 152.3 (Ar, Ph_2C), 169.3 (C_2), 174.5 (C_5). Anal. ($C_{28}H_{27}N_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[[4-(*o*-Methoxyphenyl)piperazin-1-yl]methyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (1b): yield 4.33 g (80%); mp 169−170 °C (acetone); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^{1}H NMR ($CDCl_3$) δ 2.77 (t, $J = 4.5$ Hz, 4H, $2CH_2$-pip), 2.92−3.01 (m, 4H, $2CH_2$-pip), 3.40 (s, 2H, CH_2CO), 3.78 (s, 3H, OCH_3), 4.54 (s, 2H, NCH_2N), 6.76−6.93 (m, 4H, ArH), 7.13−7.20 (m, 4H, ArH), 7.28−7.33 (m, 6H, ArH); ^{13}C NMR

($CDCl_3$) δ 35.6 (CH_2CO), 50.4 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 55.0 (OCH_3), 59.3 (NCH_2N), 121.1 (C_3), 110.5, 117.9, 120.6, 122.8, 127.6, 128.2, 128.3, 128.4, 128.6, 128.8, 138.7, 140.5, 140.8, 151.8, 152.0 (Ar, Ph_2C), 169.3 (C_2), 174.5 (C_5). Anal. ($C_{29}H_{29}N_3O_3 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[[4-(*m*-Chlorophenyl)piperazin-1-yl]methyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (1c): yield 3.66 g (80%); mp 153−154 °C (ethanol); IR (KBr, cm^{-1}) 1750, 1700 (CON), 1620 (C═C); ^1H NMR ($CDCl_3$) δ 2.76 (t, J = 4.5 Hz, 4H, $2CH_2$-pip), 3.15 (t, J = 4.5 Hz, 4H, $2CH_2$-pip), 3.48 (s, 2H, CH_2CO), 4.56 (s, 2H, NCH_2N), 6.75−6.85 (m, 3H, H_2-, H_4- and H_6-phenyl), 7.12−7.25 (m, 5H, ArH), 7.35−7.40 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.8 (CH_2CO), 48.7 ($2CH_2$-pip), 50.4 ($2CH_2$-pip), 59.4 (NCH_2N), 121.0 (C_3), 114.1, 115.8, 119.4, 127.8, 128.4, 128.5, 128.6, 128.9, 129.9, 134.8, 138.7, 140.5, 152.0, 152.5 (Ar, Ph_2C), 169.3 (C_2), 174.5 (C_5). Anal. ($C_{28}H_{26}ClN_3O_2$) C, H, N.

1-[[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]methyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (1d): yield 2.89 g (50%); mp 174−175 °C (acetone); IR (KBr, cm^{-1}) 1770, 1710 (CON), 1630 (C═C); ^1H NMR ($CDCl_3$) δ 3.15−3.50 (m, 4H, $2CH_2$-pip), 3.65 (bs, 6H, $2CH_2$-pip, CH_2CO), 4.85 (s, 2H, NCH_2N), 7.10−7.29 (m, 7H, ArH), 7.38−7.41 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$) δ 36.1 (CH_2CO), 46.8 ($2CH_2$-pip), 50.8 ($2CH_2$-pip), 57.1 (NCH_2N), 111.2 (q, $^3J_{C-F}$ = 3.8 Hz, C_2-phenyl), 113.9 (C_4-phenyl), 118.3 (C_6-phenyl), 120.2 (C_3), 123.9 (q, $^1J_{C-F}$ = 272.6 Hz, CF_3), 127.9, 128.0, 128.6, 128.7, 129.0, 129.1, 129.2, 129.5, 130.0, 138.4, 140.0 (Ar, C_5-phenyl), 131.8 (q, $^2J_{C-F}$ = 32.1 Hz, C_3-phenyl), 149.4 (C_1-phenyl), 155.7 (Ph_2C), 167.8 (C_2), 173.2 (C_5). Anal. ($C_{29}H_{26}F_3N_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[[4-(*p*-Fluorophenyl)piperazin-1-yl]methyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (1e): yield 3.62 g (82%); mp 158−159 °C (ethanol); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^1H NMR ($CDCl_3$) δ 2.78 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.07 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.47 (s, 2H, CH_2CO), 4.57 (s, 2H, NCH_2N), 6.82−6.98 (m, 4H, ArH), 7.19−7.26 (m, 4H, ArH), 7.36−7.39 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.8 (CH_2CO), 50.3 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 59.4 (NCH_2N), 115.4 (d, $^2J_{C-F}$ = 21.1 Hz, C_3- and C_5-phenyl), 118.0 (d, $^3J_{C-F}$ = 8.1 Hz, C_2- and C_6-phenyl), 121.0 (C_3), 127.8, 128.4, 128.5, 128.9, 129.0, 138.7, 140.5 (Ar), 147.5 (C_1-phenyl), 152.4 (Ph_2C), 156.9 (d, $^1J_{C-F}$ = 218.7 Hz, C_4-phenyl), 169.3 (C_2), 174.6 (C_5). Anal. ($C_{28}H_{26}FN_3O_2$) C, H, N.

1-[(4-Phenylpiperazin-1-yl)methyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (1f): yield 3.17 g (75%); mp 147−149 °C (chloroform/ethyl ether); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^1H NMR ($CDCl_3$) δ 2.83 (bs, 4H, $2CH_2$-pip), 3.16 (bs, 4H, $2CH_2$-pip), 3.77 (s, 2H, CH_2CO), 4.64 (s, 2H, NCH_2N), 6.80−6.89 (m, 3H, H_2-, H_4- and H_6-phenyl), 7.20−7.39 (m, 6H, H_3- and H_5-phenyl, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$), 7.43 (d, J = 7.8 Hz, 1H, $H_{8'}$), 7.55−7.60 (m, 2H, $H_{4'}$, $H_{5'}$), 9.25 (d, J = 7.5 Hz, 1H, $H_{1'}$); ^{13}C NMR ($CDCl_3$) δ 37.7 (CH_2CO), 49.3 ($2CH_2$-pip), 50.7 ($2CH_2$-pip), 59.9 (NCH_2N), 116.3 (C_2- and C_6-phenyl), 122.1 (C_3), 129.0 (C_3- and C_5-phenyl), 119.3, 119.8, 120.0, 126.5, 127.7, 128.4, 129.6, 130.6, 130.9, 135.6, 138.3, 141.5, 142.5, 144.4 (fluorene, C_4-phenyl), 151.2 (C_1-phenyl), 170.2 (C_2), 174.1 (C_5). Anal. ($C_{28}H_{25}N_3O_2 \cdot 2HCl$) C, H, N.

1-[[4-(*o*-Methoxyphenyl)piperazin-1-yl]methyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (1g): yield 3.21 g (71%); mp 168−169 °C (water); IR (KBr, cm^{-1}) 1770, 1700 (CON), 1620 (C═C); ^1H NMR ($CDCl_3$) δ 2.94 (t, J = 4.4 Hz, 4H, $2CH_2$-pip), 3.08 (bs, 4H, $2CH_2$-pip), 3.81 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2CO), 4.74 (s, 2H, NCH_2N), 6.81−6.99 (m, 4H, phenyl), 7.32−7.46 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$), 7.58 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.62−7.69 (m, 2H, $H_{4'}$, $H_{5'}$), 9.31 (d, J = 7.4 Hz, 1H, $H_{1'}$); ^{13}C NMR ($CDCl_3$) δ 37.4 (CH_2CO), 50.6 ($2CH_2$-pip), 50.9 ($2CH_2$-pip), 55.2 (OCH_3), 60.0 (NCH_2N), 110.8 (C_6-phenyl), 118.2 (C_3-phenyl), 122.2 (C_3), 123.0 (C_5-phenyl), 119.3, 120.1, 120.8, 126.6, 127.8, 128.4, 129.6, 130.7, 130.9, 135.7, 138.4, 141.1, 141.6, 142.6, 144.4 (fluorene, C_1- and C_4-phenyl), 152.1 (C_2-phenyl), 170.5 (C_2), 174.3 (C_5). Anal. ($C_{29}H_{27}N_3O_3$) C, H, N.

1-[[4-(*m*-Chlorophenyl)piperazin-1-yl]methyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (1h): yield 4.90 g (90%); mp 165−166 °C (chloroform); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^1H NMR ($CDCl_3$) δ 2.78 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.13 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.82 (s, 2H, CH_2CO), 4.63 (s, 2H, NCH_2N), 6.67−6.79 (m, 3H, H_2-, H_4- and H_6-phenyl), 7.08 (t, J = 7.8 Hz, 1H, H_5-phenyl), 7.21−7.38 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$), 7.46 (d, J = 7.8 Hz, 1H, $H_{8'}$), 7.54−7.60 (m, 2H, $H_{4'}$, $H_{5'}$), 9.24 (d, J = 7.5 Hz, 1H, $H_{1'}$); ^{13}C NMR ($CDCl_3$) δ 37.3 (CH_2CO), 48.8 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 59.9 (NCH_2N), 114.1 (C_6-phenyl), 115.9 (C_2-phenyl), 121.9 (C_3), 119.3, 119.4, 120.1, 126.6, 127.8, 128.5, 129.7, 130.0, 130.8, 131.0, 134.9, 135.7, 138.3, 141.6, 142.6, 144.7 (fluorene, C_3-, C_4- and C_5-phenyl), 152.2 (C_1-phenyl), 170.3 (C_2), 174.1 (C_5). Anal. ($C_{28}H_{24}ClN_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]methyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (1i): yield 4.70 g (78%); mp 163−165 °C (chloroform); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^1H NMR ($CDCl_3$) δ 2.86 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.23 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.95 (s, 2H, CH_2CO), 4.71 (s, 2H, NCH_2N), 7.01−7.07 (m, 3H, H_2-, H_4- and H_6-phenyl), 7.30−7.45 (m, 5H, H_5-phenyl, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$), 7.57 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.62−7.68 (m, 2H, $H_{4'}$, $H_{5'}$), 9.32 (d, J = 7.7 Hz, 1H, $H_{1'}$); ^{13}C NMR ($CDCl_3$) δ 37.4 (CH_2CO), 48.6 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 59.9 (NCH_2N), 112.3 (q, $^3J_{C-F}$ = 4.2 Hz, C_2-phenyl), 116.0 (q, $^3J_{C-F}$ = 4.2 Hz, C_4-phenyl), 118.9 (C_6-phenyl), 121.9 (C_3), 124.2 (q, $^1J_{C-F}$ = 271.9 Hz, CF_3), 131.3 (q, $^2J_{C-F}$ = 31.5 Hz, C_3-phenyl), 119.4, 120.2, 126.6, 127.8, 128.5, 129.5, 129.7, 130.8, 131.0, 135.7, 138.4, 141.7, 142.6, 144.8 (fluorene, C_5-phenyl), 151.3 (C_1-phenyl), 170.3 (C_2), 174.2 (C_5). Anal. ($C_{29}H_{24}F_3N_3O_2 \cdot 2HCl \cdot {}^5/_2H_2O$) C, H, N.

1-[[4-(*p*-Fluorophenyl)piperazin-1-yl]methyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (1j): yield 1.32 g (30%); mp 161−163 °C (acetone); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1625 (C═C); ^1H NMR ($CDCl_3$) δ 3.10−3.22 (m, 4H, $2CH_2$-pip), 3.70−3.85 (m, 4H, $2CH_2$-pip), 4.00 (s, 2H, CH_2CO), 4.75 (s, 2H, NCH_2N), 7.02−7.15 (m, 4H, phenyl), 7.31−7.39 (m, 2H, $H_{2'}$, $H_{7'}$), 7.43−7.50 (m, 2H, $H_{3'}$, $H_{6'}$), 7.78 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.81−7.89 (m, 2H, $H_{4'}$, $H_{5'}$), 9.32 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR ($CDCl_3$) δ 37.8 (CH_2CO), 45.9 ($2CH_2$-pip), 50.5 ($2CH_2$-pip), 61.5 (NCH_2N), 115.5 (d, $^2J_{C-F}$ = 22.0 Hz, C_3- and C_5-phenyl), 117.6 (d, $^3J_{C-F}$ = 6.8 Hz, C_2- and C_6-phenyl), 121.7 (C_3), 120.0, 120.2, 127.3, 128.0, 128.2, 129.1, 130.5, 130.7, 135.4, 138.1, 141.0, 141.3, 141.5 (fluorene), 146.4 (C_1-phenyl), 156.2 (d, $^1J_{C-F}$ = 235.1 Hz, C_4-phenyl), 170.1 (C_2), 174.2 (C_5). Anal. ($C_{28}H_{24}FN_3O_2$) C, H, N.

General Method B. Synthesis of Derivatives 2a−j, 3a−j, and 4a−j. A solution of the anhydrides **6a,b** (10 mmol) and the corresponding 1-(ω-aminoalkyl)-4-arylpiperazines **7** (10 mmol) in 15 mL of acetic acid was refluxed for 22−30 h. The reaction mixture was allowed to cool, the solvent was evaporated under reduced pressure, and the crude oil was purified by column chromatography (eluent: toluene/methanol, relative proportions depending upon the compound). Spectral data of title compounds **2a−e**, **3a−e**, and **4a−e** (R_1 = R_2 = phenyl) refer to the free bases, and then hydrochloride salts were prepared. When R_1R_2 was a biphenyl-2,2′-diyl group (**2f−j**, **3f−j**, and **4f−j**), spectral data refer to the hydrochloride salts.

1-[2-(4-Phenylpiperazin-1-yl)ethyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (2a): yield 1.19 g (22%); mp 228−229 °C (acetone); IR (KBr, cm^{-1}) 1770, 1710 (CON), 1640 (C═C); ^1H NMR ($CDCl_3$) δ 2.60−2.65 (m, 6H, CH_2-Npip, $2CH_2$-pip), 3.16 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.42 (s, 2H, CH_2CO), 3.72 (t, J = 6.6 Hz, 2H, NCH_2), 6.84 (t, J = 7.2 Hz, 1H, H_4-phenyl), 6.91 (d, J = 7.8 Hz, 2H, H_2- and H_6-phenyl), 7.16−7.34 (m, 12H, ArH, H_3- and H_5-phenyl); ^{13}C NMR ($CDCl_3$) δ 35.0, 35.5 (NCH_2, CH_2CO), 48.4 ($2CH_2$-pip), 52.4 ($2CH_2$-pip), 54.5 (CH_2-Npip), 121.3 (C_3), 115.4, 119.0, 127.4, 128.0, 128.2, 128.3, 128.4, 128.6, 128.8, 138.6, 140.1, 150.7, 150.8 (Ar, Ph_2C), 168.2 (C_2), 173.1 (C_5). Anal. ($C_{29}H_{29}N_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[2-[4-(*o*-Methoxyphenyl)piperazin-1-yl]ethyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (2b): yield 1.49 g (26%); mp 210−211 °C (acetone); IR (KBr, cm^{-1}) 1775, 1710 (CON), 1640 (C═C); ^1H NMR ($CDCl_3$) δ 2.64 (t, J = 6.6 Hz, 2H, CH_2-Npip), 2.68−2.74 (m, 4H, $2CH_2$-pip), 3.02−3.10 (m, 4H, $2CH_2$-

pip), 3.43 (s, 2H, CH_2CO), 3.72 (t, J = 6.6 Hz, 2H, NCH_2), 3.84 (s, 3H, OCH_3), 6.83−7.02 (m, 4H, ArH), 7.17−7.27 (m, 4H, ArH), 7.31−7.37 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.3, 35.8 (NCH_2, CH_2CO), 50.3 ($2CH_2$-pip), 53.0 ($2CH_2$-pip), 54.9 (CH_2−Npip), 55.1 (OCH_3), 121.4 (C_3), 110.9, 117.9, 120.7, 122.6, 127.6, 128.3, 128.5, 128.7, 129.0, 138.8, 140.4, 141.0, 151.2, 152.0 (Ar, Ph_2C), 168.5 (C_2), 173.4 (C_5). Anal. Calcd for $C_{30}H_{31}N_3O_3$·2HCl·H_2O: C, 62.94; H, 6.16; N, 7.34. Found: C, 62.48; H, 6.21; N, 6.98.

1-[2-[4-(*m*-Chlorophenyl)piperazin-1-yl]ethyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (2c): yield 1.79 g (31%); mp 189−190 °C (acetone); IR ($CHCl_3$, cm^{-1}) 1780, 1710 (CON), 1640 (C═C); ^{1}H NMR ($CDCl_3$) δ 2.65−2.67 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.17 (bs, 4H, $2CH_2$-pip), 3.45 (s, 2H, CH_2CO), 3.72 (t, J = 6.4 Hz, 2H, NCH_2), 6.74−6.81 (m, 2H, H_4- and H_6-phenyl), 6.86 (t, J = 2.1 Hz, 1H, H_2-phenyl), 7.12−7.25 (m, 5H, ArH), 7.31−7.38 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.3, 35.9 (NCH_2, CH_2CO), 48.3 ($2CH_2$-pip), 52.5 ($2CH_2$-pip), 54.7 (CH_2−Npip), 121.5 (C_3), 113.7, 115.6, 119.1, 121.5, 127.7, 128.4, 128.6, 128.8, 129.1, 129.9, 134.8, 138.9, 140.5, 151.5, 152.1 (Ar, Ph_2C), 168.6 (C_2), 173.5 (C_5). Anal. ($C_{29}H_{28}ClN_3O_2$·2HCl·H_2O) C, H, N.

1-[2-[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]ethyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (2d): yield 1.53 g (25%); mp 208−209 °C (acetone); IR ($CHCl_3$, cm^{-1}) 1780, 1710 (CON), 1630 (C═C); ^{1}H NMR ($CDCl_3$) δ 2.61−2.65 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.19 (bs, 4H, $2CH_2$-pip), 3.42 (s, 2H, CH_2CO), 3.71 (t, J = 6.0 Hz, 2H, NCH_2), 7.02−7.33 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.0, 35.5 (NCH_2, CH_2CO), 48.0 ($2CH_2$-pip), 52.1 ($2CH_2$-pip), 54.4 (CH_2−Npip), 111.4 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 115.1 (q, $^3J_{C-F}$ = 4.1 Hz, C_4-phenyl), 118.2 (C_6-phenyl), 121.2 (C_3), 123.9 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 127.4, 128.0, 128.2, 128.5, 128.6, 128.7, 128.9, 129.0, 138.6, 140.1 (Ar, C_5-phenyl), 130.8 (q, $^2J_{C-F}$ = 31.9 Hz, C_3-phenyl), 150.9, 151.0 (C_1-phenyl, Ph_2C), 168.2 (C_2), 173.2 (C_5). Anal. Calcd for $C_{30}H_{28}F_3N_3O_2$·2HCl·H_2O: C, 59.02; H, 5.28; N, 6.88. Found: C, 59.46; H, 5.17; N, 6.75.

1-[2-[4-(*p*-Fluorophenyl)piperazin-1-yl]ethyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (2e): yield 1.57 g (28%); mp 216−217 °C (acetone); IR ($CHCl_3$, cm^{-1}) 1780, 1710 (CON), 1640 (C═C); ^{1}H NMR ($CDCl_3$) δ 2.58−2.62 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.05 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.39 (s, 2H, CH_2CO), 3.70 (t, J = 6.3 Hz, 2H, NCH_2), 6.80−6.95 (m, 4H, ArH), 7.14−7.33 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.3, 35.6 (NCH_2, CH_2CO), 49.6 ($2CH_2$-pip), 52.6 ($2CH_2$-pip), 54.6 (CH_2−Npip), 115.1 (d, $^2J_{C-F}$ = 22.2 Hz, C_3- and C_5-phenyl), 117.2 (d, $^3J_{C-F}$ = 7.5 Hz, C_2- and C_6-phenyl), 121.4 (C_3), 127.5, 128.1, 128.2, 128.3, 128.5, 128.9, 138.7, 140.3 (Ar), 147.6 (d, $^4J_{C-F}$ = 2.0 Hz, C_1-phenyl), 150.9 (Ph_2C), 156.6 (d, $^1J_{C-F}$ = 238.7 Hz, C_4-phenyl), 168.2 (C_2), 173.1 (C_5). Anal. ($C_{29}H_{28}FN_3O_2$·2HCl·H_2O) C, H, N.

1-[2-(4-Phenylpiperazin-1-yl)ethyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (2f): yield 1.55 g (32%); mp 250−252 °C (ethanol); IR (KBr, cm^{-1}) 1770, 1700 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 3.17−3.20 (m, 4H, $2CH_2$-pip), 3.45−3.52 (m, 2H, CH_2−Npip), 3.72−3.85 (m, 4H, $2CH_2$-pip), 4.02 (t, J = 5.9 Hz, 2H, NCH_2), 4.05 (s, 2H, CH_2CO), 6.85 (t, J = 8.1 Hz, 1H, H_4-phenyl), 7.00 (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), 7.33−7.40 (m, 2H, $H_{2'}$, $H_{7'}$), 7.44−7.52 (m, 2H, $H_{3'}$, $H_{6'}$), 7.82 (d, J = 7.8 Hz, 1H, $H_{8'}$), 7.85−7.90 (m, 2H, $H_{4'}$, $H_{5'}$), 9.34 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 32.9 (NCH_2), 37.8 (CH_2CO), 45.1 ($2CH_2$-pip), 50.7 ($2CH_2$-pip), 52.4 (CH_2−Npip), 115.1 (C_2- and C_6-phenyl), 125.7 (C_3), 129.2 (C_3- and C_5-phenyl), 119.9, 120.0, 120.3, 127.4, 128.1, 128.2, 129.1, 130.6, 130.8, 135.4, 137.9, 141.1, 141.3, 141.5 (fluorene, C_4-phenyl), 149.6 (C_1-phenyl), 169.8 (C_2), 173.8 (C_5). Anal. ($C_{29}H_{27}N_3O_2$·HCl) C, H, N.

1-[2-[4-(*o*-Methoxyphenyl)piperazin-1-yl]ethyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (2g): yield 2.01 g (39%); mp 260−262 °C (ethanol); IR (KBr, cm^{-1}) 1765, 1700 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 3.12 (bs, 2H, CH_2-pip), 3.27 (bs, 2H, CH_2-pip), 3.47−3.55 (m, 4H, CH_2−Npip, CH_2-pip), 3.75 (bs, 2H, CH_2-pip), 3.83 (s, 3H, OCH_3), 4.05 (t, J = 6.1 Hz, 2H, NCH_2), 4.08 (s, 2H, CH_2CO), 6.90−7.07 (m, 4H, phenyl), 7.37−7.43 (m, 2H, $H_{2'}$, $H_{7'}$), 7.48−7.57 (m, 2H, $H_{3'}$, $H_{6'}$), 7.85 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.89−7.94 (m, 2H, $H_{4'}$, $H_{5'}$), 9.37 (d, J = 7.7 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 33.0 (NCH_2), 37.8 (CH_2CO), 48.8 ($2CH_2$-pip), 51.4 ($2CH_2$-pip or CH_2−Npip), 51.5 (CH_2−Npip or $2CH_2$-pip), 112.0 (C_6-phenyl), 118.3 (C_3-phenyl), 123.5 (C_5-phenyl), 125.8 (C_3), 120.0, 120.4, 120.9, 127.4, 128.2, 128.3, 129.1, 130.6, 130.8, 135.4, 138.0, 139.1, 141.2, 141.3, 141.5 (fluorene, C_1- and C_4-phenyl), 151.9 (C_2-phenyl), 169.9 (C_2), 173.8 (C_5). Anal. Calcd for $C_{30}H_{29}N_3O_3$·HCl: C, 69.83; H, 5.86; N, 8.14. Found: C, 69.28; H, 5.95; N, 7.94.

1-[2-[4-(*m*-Chlorophenyl)piperazin-1-yl]ethyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (2h): yield 0.73 g (14%); mp 270−272 °C (ethanol); IR (KBr, cm^{-1}) 1765, 1700 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 3.15−3.19 (m, 4H, $2CH_2$-pip), 3.44−3.50 (m, 2H, CH_2−Npip), 3.72−3.77 (m, 4H, $2CH_2$-pip), 4.00 (t, J = 5.7 Hz, 2H, NCH_2), 4.05 (s, 2H, CH_2CO), 6.86 (dd, J = 8.4, 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 = 8.4 Hz, 1H, H_5-phenyl), 7.34−7.41 (m, 2H, $H_{2'}$, $H_{7'}$), 7.45−7.52 (m, 2H, $H_{3'}$, $H_{6'}$), 7.81 (d, J = 7.8 Hz, 1H, $H_{8'}$), 7.85−7.90 (m, 2H, $H_{4'}$, $H_{5'}$), 9.32 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 33.0 (NCH_2), 37.8 (CH_2CO), 44.8 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 52.5 (CH_2−Npip), 114.2 (C_6-phenyl), 115.3 (C_2-phenyl), 125.6 (C_3), 119.2, 119.9, 120.4, 127.4, 128.1, 128.3, 129.1, 130.6, 130.7, 130.8, 134.1, 135.4, 137.9, 141.2, 141.4, 141.5 (fluorene, C_3-, C_4- and C_5-phenyl), 150.8 (C_1-phenyl), 169.8 (C_2), 173.7 (C_5). Anal. ($C_{29}H_{26}ClN_3O_2$·HCl) C, H, N.

1-[2-[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]ethyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (2i): yield 2.66 g (48%); mp 275−277 °C (ethanol); IR (KBr, cm^{-1}) 1770, 1710 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 3.17−3.19 (m, 4H, $2CH_2$-pip), 3.41−3.49 (m, 2H, CH_2−Npip), 3.61−3.78 (m, 4H, $2CH_2$-pip), 4.01 (t, J = 5.9 Hz, 2H, NCH_2), 4.07 (s, 2H, CH_2CO), 7.16 (d, J = 8.1 Hz, 1H, H_4-phenyl), 7.26 (s, 1H, H_2-phenyl), 7.28 (d, J = 8.1 Hz, 1H, H_6-phenyl), 7.33−7.40 (m, 3H, H_5-phenyl, $H_{2'}$, $H_{7'}$), 7.41−7.52 (m, 2H, $H_{3'}$, $H_{6'}$), 7.82−7.90 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{8'}$), 9.35 (d, J = 8.1 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 33.0 (NCH_2), 37.8 (CH_2CO), 45.0 ($2CH_2$-pip), 50.7 ($2CH_2$-pip), 52.5 (CH_2−Npip), 111.9 (C_2-phenyl), 116.0 (C_4-phenyl), 124.4 (q, $^1J_{C-F}$ = 273.0 Hz, CF_3), 125.6 (C_3), 119.2, 119.9, 120.3, 127.3, 128.0, 128.2, 129.0, 130.2, 130.5, 130.7, 135.4, 137.9, 141.1, 141.3, 141.4 (fluorene, C_3-, C_5- and C_6-phenyl), 150.0 (C_1-phenyl), 169.8 (C_2), 173.7 (C_5). Anal. ($C_{30}H_{26}F_3N_3O_2$·HCl) C, H, N.

1-[2-[4-(*p*-Fluorophenyl)piperazin-1-yl]ethyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (2j): yield 2.02 g (40%); mp 252−253 °C (ethanol); IR (KBr, cm^{-1}) 1765, 1700 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 3.15−3.19 (m, 4H, $2CH_2$-pip), 3.47−3.49 (m, 2H, CH_2−Npip), 3.72−3.77 (m, 4H, $2CH_2$-pip), 4.02 (t, J = 5.4 Hz, 2H, NCH_2), 4.04 (s, 2H, CH_2CO), 7.00−7.12 (m, 4H, phenyl), 7.33−7.39 (m, 2H, $H_{2'}$, $H_{7'}$), 7.44−7.51 (m, 2H, $H_{3'}$, $H_{6'}$), 7.81 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.82−7.89 (m, 2H, $H_{4'}$, $H_{5'}$), 9.34 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 32.9 (NCH_2), 37.9 (CH_2CO), 45.8 ($2CH_2$-pip), 50.7 ($2CH_2$-pip), 52.4 (CH_2−Npip), 115.6 (d, $^2J_{C-F}$ = 21.1 Hz, C_3- and C_5-phenyl), 117.8 (d, $^3J_{C-F}$ = 7.1 Hz, C_2- and C_6-phenyl), 125.8 (C_3), 120.0, 120.4, 127.4, 128.1, 128.2, 129.1, 130.6, 130.8, 135.5, 138.0, 141.1, 141.3, 141.5 (fluorene), 146.5 (C_1-phenyl), 156.6 (d, $^1J_{C-F}$ = 236.7 Hz, C_4-phenyl), 169.9 (C_2), 173.8 (C_5). Anal. ($C_{29}H_{26}FN_3O_2$·HCl) C, H, N.

1-[3-(4-Phenylpiperazin-1-yl)propyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (3a): yield 1.50 g (27%); mp 188−189 °C (acetone); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1630 (C═C); ^{1}H NMR ($CDCl_3$) δ 1.86 (qt, J = 6.9 Hz, 2H, CH_2), 2.49 (t, J = 6.9 Hz, 2H, CH_2−Npip), 2.58−2.66 (m, 4H, $2CH_2$-pip), 3.22 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.41 (s, 2H, CH_2CO), 3.73 (t, J = 7.2 Hz, 2H, NCH_2), 6.83−6.93 (m, 3H, ArH), 7.14−7.37 (m, 12H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.4 (CH_2), 35.8 (CH_2CO), 37.0 (NCH_2), 48.8 ($2CH_2$-pip), 52.8 ($2CH_2$-pip), 55.8 (CH_2−Npip), 121.4 (C_3), 116.0, 119.7, 127.8, 128.3, 128.4, 128.5, 128.7,

129.0, 138.8, 140.6, 151.0, 151.7 (Ar, Ph_2C), 168.6 (C_2), 173.5 (C_5). Anal. ($C_{30}H_{31}N_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[3-[4-(*o*-Methoxyphenyl)piperazin-1-yl]propyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (3b): yield 1.17 g (20%); mp 129−130 °C (acetone); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1630 (C═C); ^1H NMR ($CDCl_3$) δ 1.91 (qt, J = 7.2 Hz, 2H, CH_2), 2.57 (t, J = 6.9 Hz, 2H, CH_2−Npip), 2.71−2.79 (m, 4H, $2CH_2$-pip), 3.20−3.28 (m, 4H, $2CH_2$-pip), 3.43 (s, 2H, CH_2-CO), 3.63 (t, J = 6.9 Hz, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 6.88−7.03 (m, 4H, ArH), 7.17−7.39 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.1 (CH_2), 35.8 (CH_2CO), 36.7 (NCH_2), 49.8 ($2CH_2$-pip), 52.9 ($2CH_2$-pip), 55.2 (OCH_3), 55.7 (CH_2−Npip), 121.3 (C_3), 111.0, 118.1, 120.8, 123.0, 127.7, 128.3, 128.4, 128.6, 128.7, 128.9, 138.7, 140.5, 140.6, 151.6, 152.0 (Ar, Ph_2C), 168.5 (C_2), 173.4 (C_5). Anal. ($C_{31}H_{33}N_3O_3 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[3-[4-(*m*-Chlorophenyl)piperazin-1-yl]propyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (3c): yield 1.43 g (25%); mp 198−199 °C (acetone); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1630 (C═C); ^1H NMR ($CDCl_3$) δ 1.86 (qt, J = 7.1 Hz, 2H, CH_2), 2.48 (t, J = 7.1 Hz, 2H, CH_2−Npip), 2.60 (t, J = 4.6 Hz, 4H, $2CH_2$-pip), 3.21 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 3.41 (s, 2H, CH_2CO), 3.63 (t, J = 7.1 Hz, 2H, NCH_2), 6.74−6.86 (m, 3H, H_2-, H_4- and H_6-phenyl), 7.12−7.38 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.3 (CH_2), 35.8 (CH_2CO), 36.9 (NCH_2), 48.3 ($2CH_2$-pip), 52.6 ($2CH_2$-pip), 55.7 (CH_2−Npip), 121.4 (C_3), 113.8, 115.7, 119.3, 127.7, 128.3, 128.4, 128.5, 128.7, 129.0, 129.9, 134.8, 138.8, 140.5, 151.7, 152.0 (Ar, Ph_2C), 168.5 (C_2), 173.5 (C_5). Anal. ($C_{30}H_{30}ClN_3O_2 \cdot 2HCl$) C, H, N.

1-[3-[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]propyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (3d): yield 1.33 g (22%); mp 185−186 °C (acetone); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1630 (C═C); ^1H NMR ($CDCl_3$) δ 1.85 (qt, J = 6.9 Hz, 2H, CH_2), 2.48 (t, J = 6.9 Hz, 2H, CH_2−Npip), 2.61 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.24 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.41 (s, 2H, CH_2CO), 3.63 (t, J = 7.2 Hz, 2H, NCH_2), 7.02−7.39 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.2 (CH_2), 35.7 (CH_2CO), 36.7 (NCH_2), 48.2 ($2CH_2$-pip), 52.5 ($2CH_2$-pip), 55.6 (CH_2−Npip), 111.8 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 115.6 (q, $^3J_{C-F}$ = 4.0 Hz, C_4-phenyl), 118.5 (C_6-phenyl), 121.3 (C_3), 124.1 (q, $^1J_{C-F}$ = 272.4 Hz, CF_3), 127.6, 128.2, 128.3, 128.4, 128.6, 129.3, 129.9, 138.7, 140.4 (Ar, C_5-phenyl), 131.1 (q, $^2J_{C-F}$ = 31.8 Hz, C_3-phenyl), 151.0, 151.5 (C_1-phenyl, Ph_2C), 168.4 (C_2), 173.4 (C_5). Anal. ($C_{31}H_{30}F_3N_3O_2 \cdot 2HCl$) C, H, N.

1-[3-[4-(*p*-Fluorophenyl)piperazin-1-yl]propyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (3e): yield 1.26 g (22%); mp 217−218 °C (acetone); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1630 (C═C); ^1H NMR (DMSO-d_6) δ 1.98 (qt, J = 6.9 Hz, 2H, CH_2), 3.04−3.28 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.42−3.55 (m, 6H, $2CH_2$-pip, CH_2CO), 3.65−3.75 (m, 2H, NCH_2), 7.01−7.38 (m, 14H, ArH); ^{13}C NMR (DMSO-d_6) δ 24.2 (CH_2), 35.2, 35.7 (CH_2CO, NCH_2), 46.0 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 53.0 (CH_2−Npip), 115.5 (d, $^2J_{C-F}$ = 22.2 Hz, C_3- and C_5-phenyl), 117.9 (C_2- and C_6-phenyl), 122.8 (C_3), 127.7, 127.9, 128.5, 128.7, 129.2, 139.5, 140.7 (Ar), 146.4 (C_1-phenyl), 151.1 (Ph_2C), 157.3 (d, $^1J_{C-F}$ = 233.8 Hz, C_4-phenyl), 168.4 (C_2), 173.7 (C_5). Anal. ($C_{30}H_{30}FN_3O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[3-(4-Phenylpiperazin-1-yl)propyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (3f): yield 0.78 g (14%); mp 260−262 °C (ethanol); IR (KBr, cm^{-1}) 1750, 1700 (CON), 1630 (C═C); ^1H NMR (DMSO-d_6) δ 1.87 (qt, J = 7.2 Hz, 2H, CH_2), 2.58−2.70 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.08−3.22 (m, 4H, $2CH_2$-pip), 3.67 (t, J = 7.2 Hz, 2H, NCH_2), 4.06 (s, 2H, CH_2-CO), 6.78 (t, J = 7.2 Hz, 1H, H_4-phenyl), 6.90 (d, J = 7.2 Hz, 2H, H_2- and H_6-phenyl), 7.20 (t, J = 7.2 Hz, 2H, H_3- and H_5-phenyl), 7.35−7.40 (m, 2H, $H_{2'}$, $H_{7'}$), 7.45−7.52 (m, 2H, $H_{3'}$, $H_{6'}$), 7.83 (d, J = 7.8 Hz, 1H, $H_{8'}$), 7.86−7.91 (m, 2H, $H_{4'}$, $H_{5'}$), 9.38 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 24.4 (CH_2), 36.5 (NCH_2), 37.2 (CH_2CO), 48.8 ($2CH_2$-pip), 50.9 ($2CH_2$-pip), 52.1 (CH_2−Npip), 115.5 (C_2- and C_6-phenyl), 125.6 (C_3), 128.8 (C_3- and C_5-phenyl), 119.0, 119.7, 120.2, 127.2, 128.0, 128.1, 128.9, 130.4, 130.6, 135.3, 137.8, 141.0, 141.2, 141.4 (fluorene, C_4-phenyl), 148.6 (C_1-phenyl), 169.7 (C_2), 173.3 (C_5). Anal. Calcd for $C_{30}H_{29}N_3O_2 \cdot 2HCl \cdot H_2O$: C, 64.97; H, 6.00; N, 7.58. Found: C, 65.44; H, 5.70; N, 7.39.

1-[3-[4-(*o*-Methoxyphenyl)piperazin-1-yl]propyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (3g): yield 2.57 g (41%); mp 212−215 °C (ethanol); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^1H NMR (DMSO-d_6) δ 2.06−2,18 (m, 2H, CH_2), 3.12−3.20 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.46−3.53 (m, 4H, $2CH_2$-pip), 3.66 (t, J = 6.0 Hz, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 4.03 (s, 2H, CH_2CO), 6.89−7.03 (m, 4H, phenyl), 7.34−7.41 (m, 2H, $H_{2'}$, $H_{7'}$), 7.45−7.52 (m, 2H, $H_{3'}$, $H_{6'}$), 7.82 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.85−7.90 (m, 2H, $H_{4'}$, $H_{5'}$), 9.36 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 22.0 (CH_2), 35.8 (NCH_2), 37.5 (CH_2CO), 47.0 ($2CH_2$-pip), 51.1 ($2CH_2$-pip), 53.3 (CH_2−Npip), 55.5 (OCH_3), 112.1 (C_6-phenyl), 118.5 (C_3-phenyl), 123.8 (C_5-phenyl), 125.7 (C_3), 120.0, 120.4, 120.9, 127.4, 128.2, 128.3, 129.1, 130.6, 130.8, 135.5, 138.0, 139.2, 141.1, 141.2, 141.5 (fluorene, C_1- and C_4-phenyl), 151.9 (C_2-phenyl), 169.8 (C_2), 173.5 (C_5). Anal. ($C_{31}H_{31}N_3O_3 \cdot 2HCl \cdot H_2O$) C, H, N.

1-[3-[4-(*m*-Chlorophenyl)piperazin-1-yl]propyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (3h): yield 1.82 g (34%); mp 240−241 °C (ethanol); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1625 (C═C); ^1H NMR (DMSO-d_6) δ 2.07−2.18 (m, 2H, CH_2), 3.06−3.22 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.49−3.53 (m, 2H, CH_2-pip), 3.66 (t, J = 6.3 Hz, 2H, NCH_2), 3.84−3.89 (m, 2H, CH_2-pip), 4.04 (s, 2H, CH_2CO), 6.85 (d, J = 8.1 Hz, 1H, H_6-phenyl), 6.95 (d, J = 8.1 Hz, 1H, H_4-phenyl), 7.03 (s, 1H, H_2-phenyl), 7.25 (t, J = 8.1 Hz, 1H, H_5-phenyl), 7.34−7.41 (m, 2H, $H_{2'}$, $H_{7'}$), 7.44−7.52 (m, 2H, $H_{3'}$, $H_{6'}$), 7.81−7.90 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{8'}$), 9.35 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 22.3 (CH_2), 35.7 (NCH_2), 37.6 (CH_2CO), 44.8 ($2CH_2$-pip), 50.4 ($2CH_2$-pip), 53.7 (CH_2−Npip), 114.1 (C_6-phenyl), 115.2 (C_2-phenyl), 125.6 (C_3), 119.2, 119.9, 120.3, 127.3, 128.2, 129.0, 130.5, 130.7, 134.2, 135.3, 137.9, 141.1, 141.2, 141.4 (fluorene, C_3-, C_4- and C_5-phenyl), 150.8 (C_1-phenyl), 169.7 (C_2), 173.5 (C_5). Anal. ($C_{30}H_{28}ClN_3O_2 \cdot HCl$) C, H, N.

1-[3-[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]propyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (3i): yield 1.87 g (31%); mp 215−218 °C (methanol); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1625 (C═C); ^1H NMR (DMSO-d_6) δ 2.09−2.19 (m, 2H, CH_2), 3.09−3.29 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.47−3.53 (m, 2H, CH_2-pip), 3.66 (t, J = 6.0 Hz, 2H, NCH_2), 3.94−3.98 (m, 2H, CH_2-pip), 4.01 (s, 2H, CH_2CO), 7.15 (d, J = 7.8 Hz, 1H, H_4-phenyl), 7.27−7.40 (m, 5H, H_2-, H_5- and H_6-phenyl, $H_{2'}$, $H_{7'}$), 7.44−7.51 (m, 2H, $H_{3'}$, $H_{6'}$), 7.81 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.85−7.90 (m, 2H, $H_{4'}$, $H_{5'}$), 9.35 (d, J = 8.1 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 22.1 (CH_2), 35.8 (NCH_2), 37.5 (CH_2CO), 44.9 ($2CH_2$-pip), 50.5 ($2CH_2$-pip), 53.2 (CH_2−Npip), 111.8 (C_2-phenyl), 115.9 (C_4-phenyl), 124.4 (q, $^1J_{C-F}$ = 273.0 Hz, CF_3), 125.8 (C_3), 130.2 (q, $^2J_{C-F}$ = 31.7 Hz, C_3-phenyl), 119.4, 120.0, 120.4, 127.4, 128.2, 128.3, 129.2, 130.4, 130.7, 130.9, 135.5, 138.0, 141.2, 141.3, 141.6 (fluorene, C_5- and C_6-phenyl), 150.0 (C_1-phenyl), 169.8 (C_2), 173.6 (C_5). Anal. ($C_{31}H_{28}F_3N_3O_2 \cdot 2HCl$) C, H, N.

1-[3-[4-(*p*-Fluorophenyl)piperazin-1-yl]propyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (3j): yield 1.35 g (26%); mp 295−298 °C (methanol); IR (KBr, cm^{-1}) 1755, 1700 (CON), 1625 (C═C); ^1H NMR (DMSO-d_6) δ 2.09−2.18 (m, 2H, CH_2), 3.09−3.21 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.49−3.55 (m, 2H, CH_2-pip), 3.67 (t, J = 6.1 Hz, 2H, NCH_2), 3.69−3.73 (m, 2H, CH_2-pip), 4.04 (s, 2H, CH_2CO), 6.98−7.12 (m, 4H, phenyl), 7.33−7.41 (m, 2H, $H_{2'}$, $H_{7'}$), 7.45−7.52 (m, 2H, $H_{3'}$, $H_{6'}$), 7.82−7.90 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{8'}$), 9.36 (d, J = 8.1 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 22.0 (CH_2), 34.2 (NCH_2), 36.8 (CH_2CO), 46.1 ($2CH_2$-pip), 50.7 ($2CH_2$-pip), 54.5 (CH_2−Npip), 115.6 (d, $^2J_{C-F}$ = 22.1 Hz, C_3- and C_5-phenyl), 117.8 (d, $^3J_{C-F}$ = 7.8 Hz, C_2- and C_6-phenyl), 125.8 (C_3), 120.0, 120.4, 127.4, 128.2, 128.3, 128.8, 130.8, 132.1, 135.4, 138.0, 141.1, 141.2, 141.5 (fluorene), 146.5 (C_1-phenyl), 156.5 (d, $^1J_{C-F}$ = 237.5 Hz, C_4-phenyl), 169.8 (C_2), 173.6 (C_5). Anal. ($C_{30}H_{28}FN_3O_2 \cdot HCl$) C, H, N.

1-[4-(4-Phenylpiperazin-1-yl)butyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4a): yield 1.10 g (20%); mp 160−162 °C (acetone); IR (KBr, cm^{-1}) 1775, 1710 (CON), 1640 (C═C); ^1H NMR ($CDCl_3$) δ 1.40−1.62 (m, 4H, -$(CH_2)_2$-), 2.32 (t, J = 7.5 Hz, 2H, CH_2−Npip), 2.50 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.11 (t, J = 4.8 Hz, 4H, $2CH_2$-pip), 3.33 (s, 2H, CH_2CO), 3.49 (t, J = 7.2 Hz, 2H, NCH_2), 6.76−6.84 (m, 3H, ArH), 7.09−

7.31 (m, 12H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.9, 25.6 (-$(CH_2)_2$-), 35.6 (CH_2CO), 38.2 (NCH_2), 48.8 ($2CH_2$-pip), 52.9 ($2CH_2$-pip), 57.8 (CH_2−Npip), 121.3 (C_3), 115.8, 119.4, 127.7, 128.3, 128.4, 128.7, 128.8, 138.7, 140.4, 151.0, 151.5 (Ar, Ph_2C), 168.4 (C_2), 173.4 (C_5). Anal. ($C_{31}H_{33}N_3O_2$·2HCl) C, H, N.

1-[4-[4-(*o*-Methoxyphenyl)piperazin-1-yl]butyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4b): yield 1.46 g (25%); mp 214−215 °C (acetone); IR (KBr, cm^{-1}) 1770, 1710 (CON), 1640 (C═C); ^{1}H NMR ($CDCl_3$) δ 1.58−1.64 (m, 4H, -$(CH_2)_2$-), 2.52 (t, J = 6.6 Hz, 2H, CH_2−Npip), 2.70−2.82 (m, 4H, $2CH_2$-pip), 3.06−3.21 (m, 4H, $2CH_2$-pip), 3.43 (s, 2H, CH_2CO), 3.57 (t, J = 6.9 Hz, 2H, NCH_2), 3.88 (s, 3H, OCH_3), 6.84−7.00 (m, 4H, ArH), 7.18−7.36 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.1, 25.4 (-$(CH_2)_2$-), 35.6 (CH_2CO), 37.9 (NCH_2), 49.6 ($2CH_2$-pip), 52.7 ($2CH_2$-pip), 55.1 (OCH_3), 57.4 (CH_2−Npip), 121.2 (C_3), 110.9, 118.0, 120.7, 122.9, 127.6, 128.2, 128.3, 128.4, 128.6, 128.8, 138.7, 140.3, 140.5, 151.6, 152.9 (Ar, Ph_2C), 168.4 (C_2), 173.4 (C_5). Anal. ($C_{32}H_{35}N_3O_3$·2HCl) C, H, N.

1-[4-[4-(*m*-Chlorophenyl)piperazin-1-yl]butyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4c): yield 1.88 g (32%); mp 172−173 °C (acetone); IR (KBr, cm^{-1}) 1780, 1710 (CON), 1630 (C═C); ^{1}H NMR ($CDCl_3$) δ 1.48−1.69 (m, 4H, -$(CH_2)_2$-), 2.37 (t, J = 7.5 Hz, 2H, CH_2−Npip), 2.53 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.16 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.40 (s, 2H, CH_2-CO), 3.56 (t, J = 7.2 Hz, 2H, NCH_2), 6.73−6.79 (m, 2H, H_4- and H_6-phenyl), 6.85 (t, J = 1.8 Hz, H_2-phenyl), 7.10−7.38 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.9, 25.5 (-$(CH_2)_2$-), 35.6 (CH_2-CO), 38.1 (NCH_2), 48.2 ($2CH_2$-pip), 52.7 ($2CH_2$-pip), 57.7 (CH_2−Npip), 121.2 (C_3), 113.5, 115.4, 118.9, 125.0, 127.6, 128.2, 128.3, 128.4, 128.8, 129.7, 134.6, 138.7, 140.3, 151.4, 152.0 (Ar, Ph_2C), 168.4 (C_2), 173.3 (C_5). Anal. ($C_{31}H_{32}ClN_3O_2$·2HCl) C, H, N.

1-[4-[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]butyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4d): yield 1.36 g (22%); mp 196−197 °C (acetone); IR (KBr, cm^{-1}) 1780, 1720 (CON), 1630 (C═C); ^{1}H NMR ($CDCl_3$) δ 1.55−1.75 (m, 4H, -$(CH_2)_2$-), 2.48 (t, J = 7.2 Hz, 2H, CH_2−Npip), 2.62−2.74 (m, 4H, $2CH_2$-pip), 3.28 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.43 (s, 2H, CH_2CO), 3.57 (t, J = 6.6 Hz, 2H, NCH_2), 7.03−7.39 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$) δ 20.4, 24.8 (-$(CH_2)_2$-), 35.9 (CH_2-CO), 36.7 (NCH_2), 47.4 ($2CH_2$-pip), 50.9 ($2CH_2$-pip), 56.4 (CH_2−Npip), 111.5 (q, $^3J_{C-F}$ = 4.0 Hz, C_2-phenyl), 115.0 (q, $^3J_{C-F}$ = 3.6 Hz, C_4-phenyl), 120.3 (C_6-phenyl), 121.2 (C_3), 123.6 (q, $^1J_{C-F}$ = 272.6 Hz, CF_3), 127.9, 128.5, 128.6, 129.0, 129.1, 130.4, 136.2, 139.0, 140.4 (Ar, C_5-phenyl), 132.1 (q, $^2J_{C-F}$ = 31.8 Hz, C_3-phenyl), 147.7 (C_1-phenyl), 152.5 (Ph_2C), 168.9 (C_2), 173.9 (C_5). Anal. ($C_{32}H_{32}F_3N_3O_2$·2HCl) C, H, N.

1-[4-[4-(*p*-Fluorophenyl)piperazin-1-yl]butyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4e): yield 1.54 g (27%); mp 184−185 °C (acetone); IR (KBr, cm^{-1}) 1780, 1720 (CON), 1640 (C═C); ^{1}H NMR ($CDCl_3$) δ 1.44−1.56 (m, 4H, -$(CH_2)_2$-), 2.31 (t, J = 7.5 Hz, 2H, CH_2−Npip), 2.50 (t, J = 4.9 Hz, 4H, $2CH_2$-pip), 3.03 (t, J = 5.1 Hz, 4H, $2CH_2$-pip), 3.33 (s, 2H, CH_2-CO), 3.49 (t, J = 7.3 Hz, 2H, NCH_2), 6.74−6.89 (m, 4H, ArH), 7.09−7.28 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.9, 25.5 (-$(CH_2)_2$-), 35.6 (CH_2CO), 38.2 (NCH_2), 49.8 ($2CH_2$-pip), 52.9 ($2CH_2$-pip), 57.7 (CH_2−Npip), 115.2 (d, $^2J_{C-F}$ = 21.9 Hz, C_3- and C_5-phenyl), 117.5 (d, $^3J_{C-F}$ = 7.5 Hz, C_2- and C_6-phenyl), 121.3 (C_3), 127.6, 128.3, 128.4, 128.7, 128.8, 138.7, 140.4 (Ar), 147.7 (C_1-phenyl), 151.5 (Ph_2C), 156.9 (d, $^1J_{C-F}$ = 239.0 Hz, C_4-phenyl), 168.4 (C_2), 173.4 (C_5). Anal. ($C_{31}H_{32}FN_3O_2$·2HCl) C, H, N.

1-[4-(4-Phenylpiperazin-1-yl)butyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (4f): yield 1.70 g (31%); mp 198−200 °C (ethanol); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 1.66 (qt, J = 7.2 Hz, 2H, CH_2), 1.72−1.80 (m, 2H, CH_2), 3.07−3.23 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.48−3.79 (m, 4H, CH_2-pip, NCH_2), 3.75−3.79 (m, 2H, CH_2-pip), 4.01 (s, 2H, CH_2CO), 6.86 (t, J = 8.1 Hz, 1H, H_4-phenyl), 6.98 (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), 7.31−7.38 (m, 2H, $H_{2'}$, $H_{7'}$), 7.43−7.50 (m, 2H, $H_{3'}$, $H_{6'}$), 7.77 (d, J = 7.8 Hz, 1H, $H_{8'}$), 7.83−7.87 (m, 2H, $H_{4'}$, $H_{5'}$), 9.34 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 20.5 (CH_2), 24.5 (CH_2), 37.4, 37.6 (NCH_2, CH_2CO), 45.4 ($2CH_2$-pip), 50.6 ($2CH_2$-pip), 54.9 (CH_2−Npip), 116.0 (C_2- and C_6-phenyl), 125.6 (C_3), 129.2 (C_3- and C_5-phenyl), 119.9, 120.0, 120.3, 127.3, 128.1, 128.2, 129.0, 130.5, 130.7, 135.4, 137.9, 141.1, 141.2, 141.5 (fluorene, C_4-phenyl), 149.7 (C_1-phenyl), 169.7 (C_2), 173.4 (C_5). Anal. ($C_{31}H_{31}N_3O_2$·HCl·H_2O) C, H, N.

1-[4-[4-(*o*-Methoxyphenyl)piperazin-1-yl]butyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (4g): yield 3.11 g (52%); mp 176−179 °C (ethanol); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 1.61−1.73 (m, 2H, CH_2), 1.78−1.87 (m, 2H, CH_2), 3.05−3.28 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.39−3.61 (m, 6H, $2CH_2$-pip, NCH_2), 3.79 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2CO), 6.91−7.01 (m, 4H, phenyl), 7.36−7.40 (m, 2H, $H_{2'}$, $H_{7'}$), 7.44−7.49 (m, 2H, $H_{3'}$, $H_{6'}$), 7.81 (d, J = 7.5 Hz, 1H, $H_{8'}$), 7.85−7.90 (m, 2H, $H_{4'}$, $H_{5'}$), 9.36 (d, J = 8.1 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 20.6 (CH_2), 24.5 (CH_2), 37.3, 37.8 (NCH_2, CH_2CO), 48.2 ($2CH_2$-pip), 51.2 ($2CH_2$-pip), 55.1 (CH_2−Npip), 55.6 (OCH_3), 112.1 (C_6-phenyl), 118.5 (C_3-phenyl), 124.1 (C_5-phenyl), 124.8 (C_3), 120.0, 120.4, 121.0, 127.4, 128.1, 128.3, 129.1, 130.6, 130.9, 135.6, 138.0, 140.0, 141.1, 141.2, 141.5 (fluorene, C_1- and C_4-phenyl), 152.0 (C_2-phenyl), 169.6 (C_2), 173.4 (C_5). Anal. ($C_{32}H_{33}N_3O_3$·2HCl·H_2O) C, H, N.

1-[4-[4-(*m*-Chlorophenyl)piperazin-1-yl]butyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (4h): yield 1.76 g (31%); mp 185−188 °C (ethanol); IR (KBr, cm^{-1}) 1755, 1700 (CON), 1625 (C═C); ^{1}H NMR (DMSO-d_6) δ 1.59−1.70 (m, 2H, CH_2), 1.74−1.88 (m, 2H, CH_2), 3.06−3.26 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.41−3.54 (m, 2H, CH_2-pip), 3.60 (t, J = 6.9 Hz, 2H, NCH_2), 3.85−3.89 (m, 2H, CH_2-pip), 4.02 (s, 2H, CH_2CO), 6.87 (dd, J = 8.1, 1.5 Hz, 1H, H_6-phenyl), 6.96 (dd, J = 8.1, 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), 7.32−7.39 (m, 2H, $H_{2'}$, $H_{7'}$), 7.43−7.51 (m, 2H, $H_{3'}$, $H_{6'}$), 7.78 (d, J = 7.8 Hz, 1H, $H_{8'}$), 7.84−7.89 (m, 2H, $H_{4'}$, $H_{5'}$), 9.34 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 20.5 (CH_2), 24.5 (CH_2), 37.4, 37.6 (NCH_2, CH_2CO), 44.9 ($2CH_2$-pip), 50.4 ($2CH_2$-pip), 54.9 (CH_2−Npip), 114.2 (C_6-phenyl), 115.3 (C_2-phenyl), 125.6 (C_3), 119.3, 119.9, 120.3, 127.3, 128.1, 128.3, 129.1, 130.5, 130.6, 130.7, 134.0, 135.4, 137.9, 141.1, 141.2, 141.5 (fluorene, C_3-, C_4- and C_5-phenyl), 150.9 (C_1-phenyl), 169.7 (C_2), 173.4 (C_5). Anal. ($C_{31}H_{30}ClN_3O_2$·HCl·H_2O) C, H, N.

1-[4-[4-(*m*-(Trifluoromethyl)phenyl)piperazin-1-yl]butyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (4i): yield 3.15 g (51%); mp 178−180 °C (methanol); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1620 (C═C); ^{1}H NMR (DMSO-d_6) δ 1.65 (qt, J = 6.9 Hz, 2H, CH_2), 1.74−1.86 (m, 2H, CH_2), 3.07−3.30 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.51−3.55 (m, 2H, CH_2-pip), 3.60 (t, J = 6.9 Hz, 2H, NCH_2), 3.91−3.95 (m, 2H, CH_2-pip), 4.02 (s, 2H, CH_2CO), 7.14 (d, J = 8.1 Hz, 1H, H_4-phenyl), 7.26 (s, 1H, H_2-phenyl), 7.27 (d, J = 8.1 Hz, 1H, H_6-phenyl), 7.31−7.38 (m, 3H, $H_{2'}$, $H_{7'}$, H_5-phenyl), 7.42−7.50 (m, 2H, $H_{3'}$, $H_{6'}$), 7.78 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.83−7.87 (m, 2H, $H_{4'}$, $H_{5'}$), 9.33 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 20.6 (CH_2), 24.5 (CH_2), 37.4, 37.6 (NCH_2, CH_2CO), 44.8 ($2CH_2$-pip), 50.4 ($2CH_2$-pip), 54.9 (CH_2−Npip), 111.7 (C_2-phenyl), 115.8 (C_4-phenyl), 124.4 (q, $^1J_{C-F}$ = 273.0 Hz, CF_3), 125.7 (C_3), 129.9 (q, $^2J_{C-F}$ = 31.7 Hz, C_3-phenyl), 119.4, 119.9, 120.3, 127.3, 128.1, 128.2, 129.1, 130.3, 130.5, 130.7, 135.4, 138.0, 141.1, 141.2, 141.5 (fluorene, C_5- and C_6-phenyl), 150.0 (C_1-phenyl), 169.8 (C_2), 173.5 (C_5). Anal. Calcd for $C_{32}H_{30}F_3N_3O_2$·2HCl: C, 62.14; H, 5.22; N, 6.79. Found: C, 62.63; H, 5.62; N, 6.62.

1-[4-[4-(*p*-Fluorophenyl)piperazin-1-yl]butyl]-3-(9*H*-fluoren-9-ylidene)-2,5-pyrrolidinedione (4j): yield 1.88 g (32%); mp 170−173 °C (ethanol); IR (KBr, cm^{-1}) 1750, 1700 (CON), 1630 (C═C); ^{1}H NMR (DMSO-d_6) δ 1.66 (qt, J = 7.2 Hz, 2H, CH_2), 1.74−1.88 (m, 2H, CH_2), 3.11−3.14 (m, 6H, CH_2−Npip, $2CH_2$-pip), 3.40−3.53 (m, 2H, CH_2-pip), 3.61 (t, J = 6.9 Hz, 2H, NCH_2), 3.69−3.72 (m, 2H, CH_2-pip), 4.05 (s, 2H, CH_2CO), 6.99−7.13 (m, 4H, phenyl), 7.33−7.40 (m, 2H, $H_{2'}$, $H_{7'}$), 7.44−7.51 (m, 2H, $H_{3'}$, $H_{6'}$), 7.80 (d, J = 8.1 Hz, 1H, $H_{8'}$), 7.85−7.90 (m, 2H, $H_{4'}$, $H_{5'}$), 9.35 (d, J = 7.8 Hz, 1H, $H_{1'}$); ^{13}C NMR (DMSO-d_6) δ 20.6 (CH_2), 24.5 (CH_2), 37.4, 37.7 (NCH_2, CH_2CO), 46.1 ($2CH_2$-pip), 50.7 ($2CH_2$-pip), 54.9 (CH_2−Npip), 115.6 (d, $^2J_{C-F}$ = 22.1 Hz, C_3- and C_5-phenyl), 117.9 (d, $^3J_{C-F}$

= 7.1 Hz, C_2- and C_6-phenyl), 125.7 (C_3), 119.9, 120.3, 127.4, 128.1, 128.2, 129.1, 130.5, 130.8, 135.4, 138.0, 141.1, 141.2, 141.5 (fluorene), 146.6 (C_1-phenyl), 156.7 (d, $^1J_{C-F}$ = 236.7 Hz, C_4-phenyl), 169.8 (C_2), 173.5 (C_5). Anal. Calcd for $C_{31}H_{30}FN_3O_2 \cdot 2HCl \cdot H_2O$: C, 63.51; H, 5.85; N, 7.17. Found: C, 63.98; H, 6.06; N, 7.12.

General Procedure for the Synthesis of Compounds 8a−c. To a suspension of the imide **5a** (6.8 g, 26 mmol) in anhydrous *N*,*N*-dimethylformamide (30 mL) was added 60% NaH (1.0 g, 26 mmol). After the mixture stirred for 1 h at 60 °C under nitrogen, a solution of the corresponding dihalogenated derivative (52 mmol) in anhydrous *N*,*N*-dimethylformamide (25 mL) was added dropwise. The mixture was refluxed under nitrogen at 110 °C for 1−3 h. Then, the solvent was evaporated under reduced pressure, and the residue was resuspended in water (50 mL) 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 was purified by column chromatography (eluent: hexane/ethanol, 9:1).

(*Z*)-1-(4-Chloro-2-butenyl)-3-(diphenylmethylene)-2,5-pyrrolidinedione (8a): yield 5.67 g (62%); mp 131−135 °C (methanol/ethyl ether); IR (KBr, cm^{-1}) 1760, 1700 (CON), 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 2H, CH_2CO), 4.22 (d, J = 7.7 Hz, 2H, CH_2Cl), 4.24 (d, J = 7.3 Hz, 2H, NCH_2), 5.67 (dt, J = 11.4, 7.3 Hz, 1H, CH=), 5.82 (dt, J = 10.3, 7.7 Hz, 1H, CH=), 7.18−7.26 (m, 4H, ArH), 7.36−7.39 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 34.7 (CH_2Cl), 36.0 (CH_2CO), 38.8 (NCH_2), 121.3 (C_3), 126.7, 127.9, 128.6, 128.7, 129.0, 129.1, 130.1, 138.8, 140.6 (Ar, 2CH=), 152.4 (Ph_2C), 168.1 (C_2), 173.0 (C_5). Anal. ($C_{21}H_{18}ClNO_2$) C, H, N.

(*E*)-1-(4-Bromo-2-butenyl)-3-(diphenylmethylene)-2,5-pyrrolidinedione (8b): yield 3.61 g (35%); mp 115−117 °C (methanol/ethyl ether); IR (KBr, cm^{-1}) 1770, 1700 (CON), 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 2H, CH_2CO), 3.88 (d, J = 7.2 Hz, 2H, CH_2Br), 4.15 (d, J = 6.0 Hz, 2H, NCH_2), 5.75 (dt, J = 15.3, 6.0 Hz, 1H, CH=), 5.91 (dt, J = 15.0, 7.2 Hz, 1H, CH=), 7.18−7.25 (m, 4H, ArH), 7.36−7.39 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 31.4 (CH_2Br), 35.9 (CH_2CO), 39.3 (NCH_2), 121.2 (C_3), 127.7, 128.0, 128.6, 128.7, 129.0, 130.6, 138.8, 140.6 (Ar, 2CH=), 152.4 (Ph_2C), 168.1 (C_2), 173.1 (C_5). Anal. ($C_{21}H_{18}BrNO_2$) C, H, N.

1-(4-Chloro-2-butynyl)-3-(diphenylmethylene)-2,5-pyrrolidinedione (8c): yield 4.09 g (45%); oil; IR ($CHCl_3$, cm^{-1}) 2400 (C≡C), 1770, 1700 (CON), 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 2H, CH_2CO), 4.08 (bs, 2H, CH_2Br), 4.35 (bs, NCH_2), 7.19−7.27 (m, 4H, ArH), 7.36−7.39 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.7 (NCH_2), 30.2 (CH_2Br), 35.9 (CH_2CO), 77.5 (C≡), 79.6 (C≡), 120.9 (C_3), 127.9, 128.6, 128.7, 129.1, 138.7, 140.4 (Ar), 153.0 (Ph_2C), 167.3 (C_2), 172.3 (C_5). Anal. ($C_{21}H_{16}ClNO_2$) C, H, N.

General Procedure for the Synthesis of Derivatives 4k−m. To a suspension of the corresponding derivatives **8a−c** (9 mmol) and the 1-(*o*-methoxyphenyl)piperazine (3.06 g, 15 mmol) in acetonitrile (19 mL) was added 2 mL of triethylamine (1.5 g, 14.6 mmol). The mixture was refluxed for 20−24 h. Then, the solvent was evaporated under reduced pressure, and the residue was resuspended in water and extracted with dichloromethane (3 × 100 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 (eluents: hexane/ethyl acetate, ethyl acetate/ethanol, or chloroform/methanol, relative proportions depending upon the compound). Spectral data refer to the free base, and then hydrochloride salts were prepared.

(*Z*)-1-[4-[4-(*o*-Methoxyphenyl)piperazin-1-yl]-2-butenyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4k): yield 4.80 g (84%); mp 160−164 °C (methanol/ethyl ether); IR (KBr, cm^{-1}) 1770, 1700 (CON), 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.68 (bs, 4H, $2CH_2$-pip), 3.10 (bs, 4H, $2CH_2$-pip), 3.24 (d, J = 6.6 Hz, 2H, CH_2−Npip), 3.43 (s, 2H, CH_2CO), 3.86 (s, 3H, OCH_3), 4.24 (d, J = 6.3 Hz, 2H, NCH_2), 5.57 (dt, J = 11.0, 7.0 Hz, 1H, CH=), 5.72 (dt, J = 11.0, 6.6 Hz, 1H, CH=), 6.84−7.03 (m, 4H, ArH), 7.18−7.26 (m, 4H, ArH), 7.35−7.38 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.7, 36.0 (NCH_2, CH_2CO), 50.6 ($2CH_2$-pip), 53.4 ($2CH_2$-pip), 55.4 (CH_2−Npip), 55.4 (OCH_3), 121.5 (C_3), 111.2, 118.2, 121.0, 122.9, 125.7, 127.9, 128.6, 128.9, 129.1, 130.7, 138.9, 140.6, 141.4, 152.0, 152.3 (Ar, 2CH=, Ph_2C), 168.2 (C_2), 173.1 (C_5). Anal. Calcd for $C_{32}H_{33}N_3O_3 \cdot 2HCl \cdot 3H_2O$: C, 60.56; H, 6.51; N, 6.62. Found: C, 61.07; H, 6.57; N, 6.29.

(*E*)-1-[4-[4-(*o*-Methoxyphenyl)piperazin-1-yl]-2-butenyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4l): yield 2.05 g (38%); mp 111−114 °C (methanol/ethyl ether); IR (KBr, cm^{-1}) 1770, 1710 (CON), 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.54 (bs, 4H, $2CH_2$-pip), 2.95 (d, J = 5.7 Hz, 2H, $2CH_2$−Npip), 3.01 (bs, 4H, $2CH_2$-pip), 3.37 (s, 2H, CH_2CO), 3.77 (s, 3H, OCH_3), 4.08 (d, J = 4.2 Hz, 2H, NCH_2), 5.57 (dt, J = 15.6, 5.4 Hz, 1H, CH=), 5.65 (dt, J = 15.9, 5.7 Hz, 1H, CH=), 6.76−6.92 (m, 4H, ArH), 7.11−7.18 (m, 4H, ArH), 7.28−7.29 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 35.8 (CH_2CO), 39.6 (NCH_2), 50.5 ($2CH_2$-pip), 53.3 ($2CH_2$-pip), 55.2 (OCH_3), 60.1 (CH_2−Npip), 121.3 (C_3), 111.0, 118.1, 120.9, 122.8, 126.2, 127.8, 128.5, 128.8, 129.0, 130.2, 138.8, 140.5, 141.2, 151.9, 152.1 (Ar, 2CH=, Ph_2C), 168.2 (C_2), 173.1 (C_5). Anal. Calcd for $C_{32}H_{33}N_3O_3 \cdot 2HCl \cdot H_2O$: C, 64.21; H, 6.23; N, 7.02. Found: C, 63.72; H, 6.29; N, 6.79.

1-[4-[4-(*o*-Methoxyphenyl)piperazin-1-yl]-2-butynyl]-3-(diphenylmethylene)-2,5-pyrrolidinedione (4m): yield 3.04 g (55%); mp 123−126 °C (methanol/ethyl ether); IR (KBr, cm^{-1}) 1770, 1710 (CON), 1640 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.63 (bs, 4H, $2CH_2$-pip), 3.01 (bs, 4H, $2CH_2$-pip), 3.19 (t, J = 1.8 Hz, 2H, CH_2−Npip), 3.36 (s, 2H, CH_2CO), 3.75 (s, 3H, OCH_3), 4.23 (s, 2H, CH_2N), 6.77−6.90 (m, 4H, ArH), 7.07−7.16 (m, 4H, ArH), 7.24−7.27 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.8 (CH_2N), 35.8 (CH_2CO), 47.1 (CH_2−Npip), 50.4 ($2CH_2$-pip), 52.4 ($2CH_2$-pip), 55.2 (OCH_3), 78.0 (2C≡), 121.0 (C_3), 111.0, 118.1, 120.8, 122.9, 128.0. 128.4, 128.6, 128.9, 129.0, 138.7, 140.4, 141.0, 152.1, 152.5 (Ar, Ph_2C), 167.3 (C_2), 172.3 (C_5). Anal. ($C_{32}H_{31}N_3O_3 \cdot 2HCl \cdot 2H_2O$) C, H, N.

Pharmacological Methods. 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.

1. 5-HT$_{1A}$ Receptor. The receptor binding studies were performed by a modification of a previously described procedure.[42] The cerebral cortex was homogenized in 10 volumes 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 37 °C). Nonspecific binding was determined with 10 μM 5-HT.

2. α_1-Adrenoceptor. The radioligand receptor binding studies were performed according to a previously described procedure.[43] The cerebral cortex was homogenized in 20 volumes of ice-cold buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, pH 7.4 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.

3. D$_2$-Dopaminergic Receptor. The receptor binding studies were performed according to a previously described procedure.[44] 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.

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.,[45] 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.[37]

Forskolin-Stimulated Adenylyl Cyclase Assay. The assay was performed using hippocampal slices from male Sprague−Dawley rats, by a modification of a previously published procedure.[46] Briefly, the assay incubation medium contained Krebs-Henseleit buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 2.5 mM $CaCl_2$, 25 mM $NaHCO_3$, 11 mM glucose, pH 7.4), 0.5 mM 3-isobutyl-1-methylxanthine (IBMX), 0.1 μM GTP, 50 μM forskolin, 30 μg of slice protein, 0.4 μM adenine containing 2.7 μCi of [^{3}H]-adenine, and the new compound (100 μM). After 30 min of incubation at 37 °C, the reaction was stopped by the addition of the stop solution (0.08 N HCl/66% MeOH). The mixture was allowed to stand for 10 min at 4 °C, sonicated, and centrifuged for 10 min at 15000*g*. The [^{3}H]cyclic AMP formed was isolated using Dowex columns and alumina columns, and cyclic AMP production was determined by liquid scintillation spectroscopy and corrected for relative recovery.[47] Results are expressed as percentege of inhibition of the stimulation induced by forskolin.

Aorta Ring Experiments. Male Wistar rats (200−250 g) were killed by decapitation. The thoracic segment of the aorta artery was dissected free from adhering connective and fat tissues, and removed. Endothelium-denuded aorta rings (3 mm long) were mounted in a 5-mL organ bath containing Krebs-Henseleit solution (118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 2.5 mM $CaCl_2$, 25 mM $NaHCO_3$, 11 mM glucose, pH 7.4) maintained at 37 °C and bubbled with a mixture of 95% O_2 and 5% CO_2. After an equilibration period of 1 h under 1.5 g of resting tension, the contractile ability of the rings was determined by exposing them to 124 mM potassium-rich Krebs solution. Noradrenaline neuronal uptake and β-adrenergic receptors were blocked by incubating the preparations with 3 μM cocaine and 3 μM propranolol, for 30 min. Cumulative concentration−response curves of isometric contractions produced by an α_1-adrenergic-selective agonist (phenylephrine, 10^{-9}−3×10^{-4} M) were obtained before and after 30 min of exposure to each of three concentrations of the test compound. pA_2 values were determined according to Arunlakshana and Schild,[48] log(dose ratio − 1) being calculated for each concentration of the test compound.

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