Structure−Affinity Relationship Study on *N*-[4-(4-Arylpiperazin-1-yl)butyl]arylcarboxamides as Potent and Selective Dopamine D_3 Receptor Ligands

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Received June 4, 2002

The benzamide PB12 (*N*-[2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide) (**1**), already reported as potent and selective dopamine D_4 receptor ligand, has been modified searching for structural features that could lead to D_3 receptor affinity. Changes in the aromatic ring linked to N-1 piperazine ring led to the identification of 2-methoxyphenyl and 2,3-dichlorophenyl derivatives (compounds **6** and **13**) displaying moderate D_3 affinity (K_i = 145 and 31 nM, respectively). Intermediate alkyl chain elongation in compounds **1**, **6**, and **13** improved binding affinity for the D_3 receptor and decreased the D_4 affinity (compounds **18**−**26**). Among these latter compounds, the *N*-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butyl]-3-methoxybenzamide (**19**) was further modified with the replacement or of the 2,3-dichlorophenyl moiety (compounds **27**−**30**) or of the 3-methoxyphenyl ring (compounds **31**−**41**). In this way, we identified several high-affinity D_3 ligands (0.13 nM < K_i's < 4.97 nM) endowed with high selectivity over D_2, D_4, 5-HT_{1A}, and α_1 receptors. In addition, *N*-[4-[4-(2,3-dimethylphenyl)-piperazin-1-yl]butyl]-3-methoxybenzamide (**27**) and *N*-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]-butyl]-7-methoxy-2-benzofurancarboxamide (**41**) appear to be valuable candidates for positron emission tomography (PET) because of their affinity values, lipophilicity properties, and liability of ^{11}C labeling in the O-methyl position.

Introduction

The cloning of the gene for dopamine D_3 receptor and subsequent identification of its distribution in brain and pharmacology allowed for serious consideration of the possibility that might be a target for antipsychotic and antiparkinsonian drugs. As early as 1990, the D_3 receptor was considered a potential target for developing antipsychotic agents because dopamine (DA) antagonists used in the treatment of schizofrenia were not selective for the D_2 receptor, but they also exhibited high affinity for the D_3 receptor.[1] Because D_3 receptor is highly expressed in limbic regions of the brain, but exhibited low expression in motor divisions, it would be a target for antipsychotics potentially devoid of unwanted motor side effects.[2] Another therapeutic use of D_3 agents is for treatment of Parkinson's disease (PD) because DA agonists used in PD therapy have, in many cases, as high or higher affinity for the D_3 receptor.[3] Therefore, it remains tenable that the mesolimbic D_3 receptor could play a role in antiparkinsonian relief, and recently the D_3 preferring agonists pramipexole and ropinirole (Chart 1) have been introduced in therapy for effective treatment of PD.

The D_3 receptor subtype would also be involved in the pharmacological effects of psychostimulant drugs.[1,4] An early study on the D_3-selective agonist 7-OH-DPAT suggested that D_3 receptors played a modulatory role in the self-administration of cocaine.[5] Also, the selective D_3 partial agonist BP 897 was found to attenuate cocaine-seeking behavior,[6] although a recent study suggested that it may be the dopamine D_3 receptor antagonist properties of BP 897 which have potential in the treatment of addiction and withdrawal.[7] Despite the early encouraging results with 7-OH-DPAT, BP 897, and other D_3 agents, presently, the in vivo function of the D_3 receptor and its role in cocaine's actions remains debatable because of the lack of D_3-receptor selectivity of these agents.

Therefore, D_3 ligands having subnanomolar affinities, high receptor subtype specificity, and improved bioavailability would greatly aid in understanding the role of the D_3 receptor. Additionally, the presence in the structure of such ligands of methoxy or *N*-methyl groups would give access to ^{11}C radioligands suitable for positron emission tomography (PET).[8,9] To date, no effective D_3-preferring PET radioligand for in vivo D_3 receptor imaging has been reported.[10]

In recent years, we have been interested in SAFIR studies on D_4 ligands represented by the potent and selective PB12 (**1**) (Table 1).[11,12] From a survey of the literature dealing with D_3 ligands, it emerged that compounds structurally related to PB12 were able to bind to D_3 receptor.[13] This ability depended upon the nature of the aromatic ring linked to the piperazine N-1 position. On the basis of this observation, a first set of compounds (derivatives **6**−**17**) was designed by changing the aromatic ring linked to the piperazine ring. Some aromatic rings, such as phenyl, 2,3-diCl-phenyl, and 2-CH_3O-phenyl, were selected because they were displayed by known arylpiperazine D_3 ligands.[13−15] Among these analogues of compound **1**, only 2,3-diCl-

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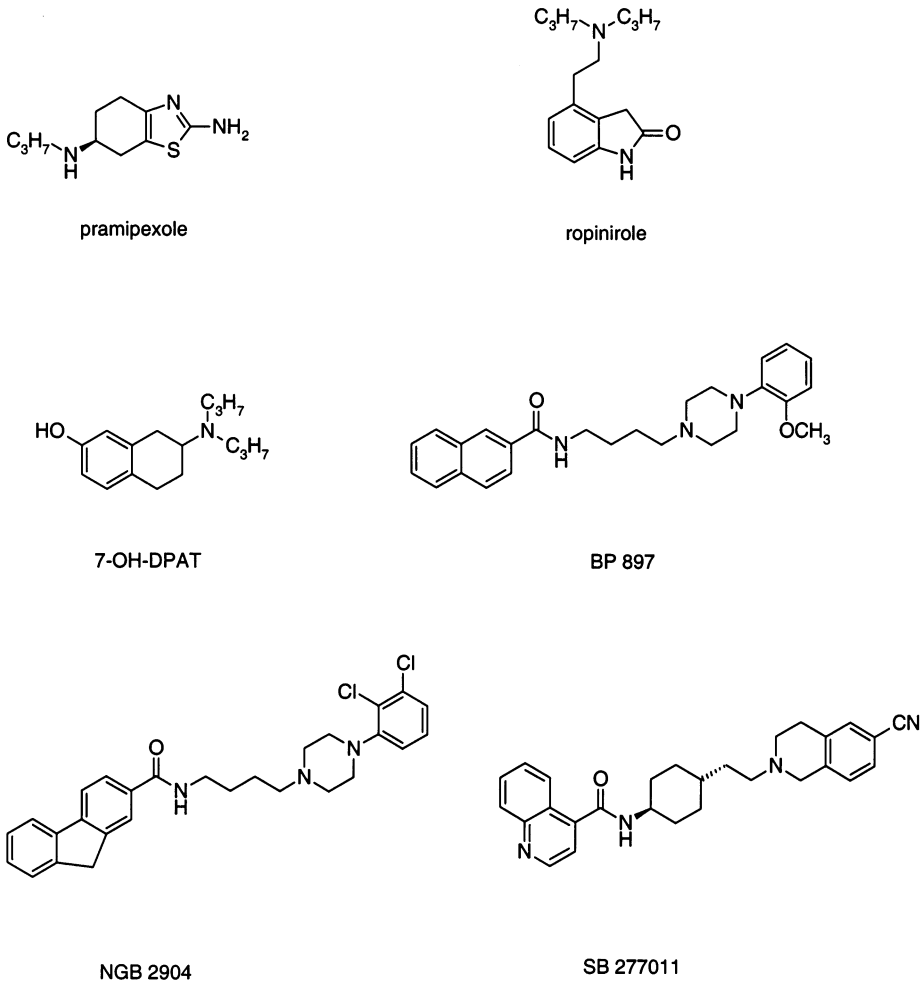
10.1021/jm020952a CCC: $22.00
Published on Web 11/22/2002

Chart 1. Dopamine D_3 Agents



phenyl and 2-CH_3O-phenyl derivatives (**6** and **13**, respectively) displayed moderate D_3 receptor affinity, along with high D_4 receptor affinity. Then, the effect of intermediate alkyl chain elongation on D_3 receptor affinity was evaluated by preparing a set of homologues of compounds **1**, **6**, and **13** (derivatives **18**−**26**). This modification was considered because three high affinity D_3 ligands (i.e., BP 897, NGB 2904,[16] and SB 277011[17]) (Chart 1) displayed the four carbon butyl chain and also because alkyl chain elongation of compound **1** resulted in a decrease in D_4 receptor affinity.[12] In line with the above considerations, D_3 affinity values of compounds **18**−**26** indicated that the four carbon alkyl chain was an important requisite for high D_3 affinity. Consequently, several *n*-butyl chain containing 1-arylpiperazine derivatives (compounds **27**−**41**) were evaluated in the search for structural features that could enhance the selectivity over the other receptors capable of binding 1-arylpiperazines (i.e., D_2, 5-HT_{1A}, and α_1 receptors). In particular, we prepared some compounds related to *N*-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]-butyl]-3-methoxybenzamide (**19**) by replacing the 2,3-dichlorophenyl group with the 2,3-dimethylphenyl group (compound **27**) or with a bicyclic aromatic nucleus (compounds **28**−**30**). Then, we also prepared *N*-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butyl]arylcarboxamides **31**−**41**, bearing an aryl group other than the 3-methoxyphenyl. These groups were chosen for their different contribution to lipophilicity (expressed as ClogP values[18]) and also among those displayed by already reported D_3 ligands (i.e., 4-bromo-1-methoxy-2-naphthalenyl,[19] 1-methoxy-2-naphthalenyl,[20] 1,1′-biphenyl,[21] 4-quinolyl[17]).

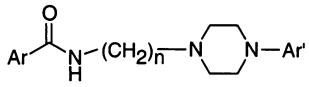
Chemistry

Benzamides **8**−**17** were prepared by reacting the appropriate 1-arylpiperazine with *N*-(2-chloroethyl)-3-methoxybenzamide (**2**),[11] as depicted in Scheme 1. Similarly, benzamide **18** was prepared by condensing 1-(2,3-dichlorophenyl)piperazine with *N*-(3-chloropropyl)-3-methoxybenzamide (**3**). This latter compound was obtained by acylating 3-chloropropylamine with 3-methoxybenzoyl chloride. The synthesis of the benzamides **19**, **20**, **22**, **23**, **27**−**41** (Scheme 2) required the intermediate amines **5a**−**j**. Among these, amines **5a**−**d** were prepared by alkylating the appropriate 1-arylpiperazine with 4-chlorobutanenitrile or 5-chloropentanenitrile and subsequent reduction of nitriles **4a**−**d** with borane-methyl sulfide complex,[22] whereas amines **5e**−**j** were synthesized according to literature methods, as detailed in Experimental Section. Final compounds were achieved by condensing the amines **5a**−**j** with appropriate acyl chloride or carboxylic acid in the presence of 1,1′-carbonyldiimidazole as condensing agent.

Results and Discussion

Affinity values of the target compounds **6**−**41** for D_3, D_4, D_2, 5-HT_{1A}, and α_1 receptors are listed in Table 2.

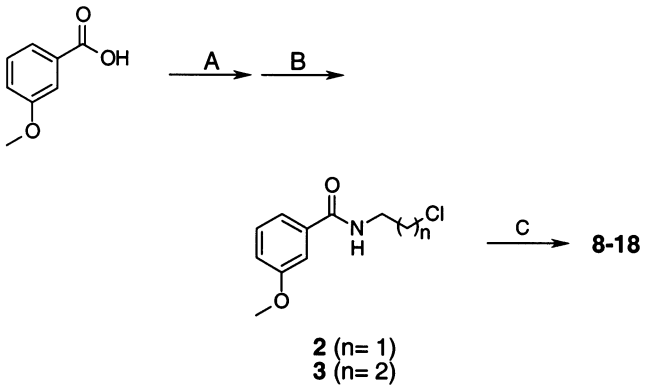
Table 1. Physical Properties of Target Compounds



compd	*n*	Ar	Ar′	formula[a]	mp, °C	CLogP
1[b] (PB12)	2	3-CH_3O-Ph	4-Cl-Ph			3.72
6[b]	2	3-CH_3O-Ph	2-CH_3O-Ph			2.86
7[b]	2	3-CH_3O-Ph	2-Py			1.89
8	2	3-CH_3O-Ph	2-Cl-Ph	$C_{20}H_{24}ClN_3O_2$	116−118	3.72
9	2	3-CH_3O-Ph	3-Cl-Ph	$C_{20}H_{24}ClN_3O_2$	147−149	3.72
10	2	3-CH_3O-Ph	4-CH_3-Ph	$C_{21}H_{27}N_3O_2$·HCl	229−231	3.33
11	2	3-CH_3O-Ph	4-CH_3O-Ph	$C_{21}H_{27}N_3O_3$·2HCl	223−225	2.71
12	2	3-CH_3O-Ph	4-F-Ph	$C_{20}H_{24}FN_3O_2$	157−159	3.15
13	2	3-CH_3O-Ph	2,3-di-Cl-Ph	$C_{20}H_{23}Cl_2N_3O_2$·HCl	254−256	4.36
14	2	3-CH_3O-Ph	Ph	$C_{20}H_{25}N_3O_2$·HCl	234−236	2.83
15	2	3-CH_3O-Ph	1-naphthalenyl	$C_{24}H_{27}N_3O_2$·$(COOH)_2$·H_2O	177−179	4.01
16	2	3-CH_3O-Ph	4-Cl-2-Py	$C_{19}H_{23}ClN_4O_2$·$(COOH)_2$	239−240	2.67
17	2	3-CH_3O-Ph	4-CH_3-2-Py	$C_{20}H_{26}N_4O_2$·2HCl	221−224	2.38
18	3	3-CH_3O-Ph	2,3-di-Cl-Ph	$C_{21}H_{25}Cl_2N_3O_2$·HCl·4/5H_2O	184−187	4.57
19	4	3-CH_3O-Ph	2,3-di-Cl-Ph	$C_{22}H_{27}Cl_2N_3O_2$·HCl	218−220	4.50
20	5	3-CH_3O-Ph	2,3-di-Cl-Ph	$C_{23}H_{29}Cl_2N_3O_2$·HCl	188−189	5.03
21[c]	3	3-CH_3O-Ph	2-CH_3O-Ph			3.08
22	4	3-CH_3O-Ph	2-CH_3O-Ph	$C_{23}H_{31}N_3O_3$·2HCl	185−186	3.00
23	5	3-CH_3O-Ph	2-CH_3O-Ph	$C_{24}H_{33}N_3O_3$·2HCl	189−191	3.53
24[c]	3	3-CH_3O-Ph	4-Cl-Ph			3.93
25[c]	4	3-CH_3O-Ph	4-Cl-Ph			3.86
26[c]	5	3-CH_3O-Ph	4-Cl-Ph			4.93
27	4	3-CH_3O-Ph	2,3-di-CH_3-Ph	$C_{24}H_{33}N_3O_2$·HCl	185−187	3.92
28	4	3-CH_3O-Ph	1-naphthalenyl	$C_{26}H_{31}N_3O_2$·HCl·1/2H_2O	184−186	4.15
29	4	3-CH_3O-Ph	1-isoquinolyl	$C_{25}H_{30}N_4O_2$·2$(COOH)_2$	163−164	3.20
30	4	3-CH_3O-Ph	1,2-benzisoxazol-3 -yl	$C_{23}H_{28}N_4O_3$·HCl	111−113	2.85
31	4	4-Br-1-CH_3O-2-naphthalenyl	2,3-di-Cl-Ph	$C_{26}H_{28}BrCl_2N_3O_2$·HCl	204−206	6.60
32	4	1-CH_3O-2-naphthalenyl	2,3-di-Cl-Ph	$C_{26}H_{29}Cl_2N_3O_2$·HCl·1/5H_2O	190−192	5.61
33	4	2-naphthalenyl	2,3-di-Cl-Ph	$C_{25}H_{27}Cl_2N_3O$·HCl	217 dec	5.28
34	4	4-quinolyl	2,3-di-Cl-Ph	$C_{24}H_{26}Cl_2N_4O$·$(COOH)_2$	150−153	4.74
35	4	1,1′-biphenyl	2,3-di-Cl-Ph	$C_{27}H_{29}Cl_2N_3O$·HCl	245 dec	6.00
36	4	2-benzofuranyl	2,3-di-Cl-Ph	$C_{23}H_{25}Cl_2N_3O_2$·HCl	236 dec	4.67
37	4	1*H*-indol-2-yl	2,3-di-Cl-Ph	$C_{23}H_{26}Cl_2N_4O$·2HCl	245 dec	4.70
38	4	1*H*-indol-3-yl	2,3-di-Cl-Ph	$C_{23}H_{26}Cl_2N_4O$·HCl	265 dec	4.36
39	4	3-indazolyl	2,3-di-Cl-Ph	$C_{22}H_{25}Cl_2N_5O$·HCl·H_2O	267 dec	4.46
40	4	2-benzo[*b*]thienyl	2,3-di-Cl-Ph	$C_{23}H_{25}Cl_2N_3OS$·HCl	228 dec	5.33
41	4	7-CH_3O-2-benzofuranyl	2,3-di-Cl-Ph	$C_{24}H_{27}Cl_2N_3O_3$·HCl	212−214	4.98

[a] All compounds were recrystallized from CH_3OH/Et_2O except **8**, **9**, **12** (from $CHCl_3$/ *n*-hexane), and **15**, **16**, **29** (CH_3OH). Analysis for C,H,N; results were within ±0.4% of the theoretical values for the formulas given. [b] See ref 11. [c] See ref 12.

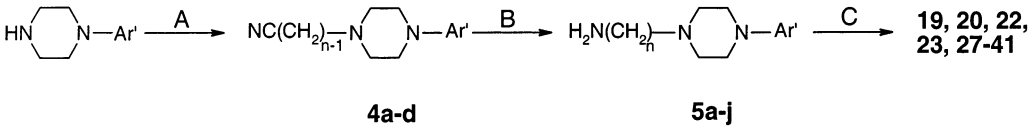
Scheme 1[a]



[a] Reagents: (A) thionyl chloride; (B) 2-chloroethylamine or 3-chloropropylamine; (C) 1-arylpiperazine.

The variation of the aromatic group linked to the piperazine ring N-1 position of compound **1** led to compounds **6**−**17** that were devoid of D_3 receptor affinity, except for compounds **6**, **8**, **13**, **15**, that showed moderate D_3 affinity (K_i's ranging between 31 and 146 nM). These compounds are characterized by a 2- or 2,3-di-substituted phenyl ring or by a 1-naphthalenyl ring. On the other hand, compounds **6**−**17** can be considered as high-affinity D_4 ligands. In particular, compounds **8**, **10**, and **13** were equipotent to **1**, showing subnanomolar D_4 affinity values (K_i's ranging between 0.018 and 0.040 nM). Compounds **6**−**17** did not bind to D_2 receptor and displayed a wide range of 5-HT_{1A} and α_1 receptor affinities. Subsequently, we evaluated the effect on D_3 affinity of alkyl chain elongation in compounds **6** and **13**. This modification was also aimed at decreasing the D_4 affinity, because in a previous study[12] we observed that elongation of the alkyl chain in **1** resulted in a decrease in D_4 affinity (compounds **24**−**26**). The results made clear different structural requirements between D_3 and D_4 receptors. In fact, the D_3 affinities of compounds **18**−**26**, that are homologues of compounds **6**, **13**, and **1**, were ranked as follows: butyl > pentyl ≥ propyl > ethyl. In particular, butyl derivatives **19**, **22**, and **25** displayed D_3 affinities ranging between 0.27 and 1.7 nM. On the other hand, D_4 affinity values are ordered oppositely: ethyl > propyl ≥ butyl > pentyl. These opposite trends resulted in an increasing in specificity for the D_3 receptor, especially in compounds **19** and **25**, which were also selective versus D_2, 5-HT_{1A}, and α_1 receptors. The observed lack of selectivity of compounds **6** and **21**−**23** over 5-HT_{1A} receptors should be mainly due to the 1-(2-methoxyphenyl)piperazine

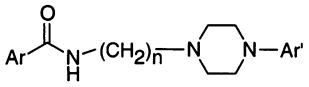
Scheme 2[a]



a (n= 5, Ar'= 2,3-di-Cl-Ph)
b (n= 4, Ar'= 2,3-di-CH_3-Ph)
c (n= 4, Ar'= 1-naphthalenyl)
d (n= 4, Ar'= 1-isoquinolyl)
e (n= 4, Ar'= 2,3-di-Cl-Ph)
f (n= 4, Ar'= 1,2-benzisoxazol-3-yl)
g (n= 4, Ar'= 2-OCH_3-Ph)
j (n= 5, Ar'= 2-OCH_3-Ph)

[a] Reagents: (A) 4-chlorobutanenitrile or 5-chloropentanenitrile; (B) borane-methyl sulfide complex; (C) acyl chloride or carboxylic acid and 1,1′-carbonyldiimidazole.

Table 2. Binding Affinities of Target Compounds



				$K_i \pm$ S.E.M., nM				
compd	*n*	Ar	Ar′	D_3	D_4	D_2	5-HT_{1A}	α_1
1 (PB12)	2	3-CH_3O-Ph	4-Cl-Ph	>1000 (28%)[a]	0.040 ± 0.002	1900 ± 250	147 ± 14	245 ± 30
6	2	3-CH_3O-Ph	2-CH_3O-Ph	145 ± 16	1.1 ± 0.3	467 ± 33	0.060 ± 0.004	180 ± 20
7	2	3-CH_3O-Ph	2-Py	>850 (16%)	0.63 ± 0.04	>1000 (35%)	27 ± 4	283 ± 15
8	2	3-CH_3O-Ph	2-Cl-Ph	146 ± 24	0.040 ± 0.007	>1000 (19%)	27 ± 4	18 ± 2
9	2	3-CH_3O-Ph	3-Cl-Ph	472 ± 30	0.26 ± 0.02	>1000 (24%)	35 ± 9	224 ± 12
10	2	3-CH_3O-Ph	4-CH_3-Ph	>850 (30%)	0.025 ± 0.007	7460 ± 320	432 ± 27	454 ± 25
11	2	3-CH_3O-Ph	4-CH_3O-Ph	>850 (18%)	22.3 ± 8.0	>1000 (15%)	>850 (27%)	5900 ± 350
12	2	3-CH_3O-Ph	4-F-Ph	>850 (33%)	11 ± 2	>1000 (13%)	313 ± 22	134 ± 15
13	2	3-CH_3O-Ph	2,3-di-Cl-Ph	31 ± 7	0.018 ± 0.007	3680 ± 120	29 ± 5	425 ± 52
14	2	3-CH_3O-Ph	Ph	674 ± 35	2.2 ± 0.8	>8300 (26%)	59 ± 8	197 ± 20
15	2	3-CH_3O-Ph	1-naphthalenyl	70 ± 5	0.21 ± 0.01	>1000 (12%)	0.60 ± 0.03	7.3 ± 0.6
16	2	3-CH_3O-Ph	4-Cl-2-Py	>1000 (22%)	3.95 ± 0.80	>1000 (17%)	433 ± 17	115 ± 19
17	2	3-CH_3O-Ph	4-CH_3-2-Py	>850 (33%)	23.9 ± 8.0	>1000 (26%)	58.6 ± 6.0	2900 ± 180
18	3	3-CH_3O-Ph	2,3-di-Cl-Ph	2.3 ± 0.2	7.3 ± 0.6	1130 ± 120	117 ± 20	66.7 ± 6.0
19	4	3-CH_3O-Ph	2,3-di-Cl-Ph	0.27 ± 0.03	9.0 ± 0.8	1410 ± 80	123 ± 15	134 ± 9
20	5	3-CH_3O-Ph	2,3-di-Cl-Ph	3.0 ± 0.4	345 ± 25	1560 ± 200	78.7 ± 7.3	92.1 ± 4.0
21	3	3-CH_3O-Ph	2-CH_3O-Ph	124 ± 20	1.8 ± 0.4	2990 ± 110	19.8 ± 2.0	61.4 ± 8.0
22	4	3-CH_3O-Ph	2-CH_3O-Ph	1.7 ± 0.5	3.1 ± 0.7	680 ± 18	7.5 ± 1.1	26.4 ± 2.2
23	5	3-CH_3O-Ph	2-CH_3O-Ph	5.3 ± 0.8	55 ± 7	253 ± 12	4.5 ± 0.7	16.2 ± 2.4
24	3	3-CH_3O-Ph	4-Cl-Ph	586 ± 37	5.4 ± 0.7	3960 ± 150	>850 (23%)	437 ± 31
25	4	3-CH_3O-Ph	4-Cl-Ph	0.41 ± 0.05	25 ± 2	2350 ± 270	397 ± 92	406 ± 40
26	5	3-CH_3O-Ph	4-Cl-Ph	36 ± 3	241 ± 35	>850 (22%)	>850 (44%)	470 ± 25
27	4	3-CH_3O-Ph	2,3-di-CH_3-Ph	0.17 ± 0.05	63.6 ± 8.0	77.0 ± 5.2	268 ± 12	717 ± 24
28	4	3-CH_3O-Ph	1-naphthalenyl	0.54 ± 0.02	2.3 ± 1.5	930 ± 30	0.43 ± 0.06	57 ± 3
29	4	3-CH_3O-Ph	1-isoquinolyl	9.5 ± 0.8	168 ± 18	770 ± 15	12.7 ± 3.5	1120 ± 120
30	4	3-CH_3O-Ph	1,2-benzisoxazol-3-yl	46.5 ± 6.2	7.58 ± 0.50	210 ± 24	7730 ± 220	3119 ± 125
31	4	4-Br-1-CH_3O-2-naphthalenyl	2,3-di-Cl-Ph	4.97 ± 0.30	652 ± 85	3800 ± 130	>1000 (46%)	>1000 (25%)
32	4	1-CH_3O-2-naphthalenyl	2,3-di-Cl-Ph	0.60 ± 0.02	720 ± 225	830 ± 120	575 ± 230	5100 ± 150
33	4	2-naphthalenyl	2,3-di-Cl-Ph	0.58 ± 0.02	370 ± 80	5200 ± 350	335 ± 21	5 ± 5
34	4	4-quinolyl	2,3-di-Cl-Ph	0.72 ± 0.02	604 ± 50	430 ± 12	88.5 ± 8.2	138 ± 16
35	4	1,1′-biphenyl	2,3-di-Cl-Ph	1.15 ± 0.30	283 ± 15	>1000 (32%)	>1000 (41%)	>1000 (43%)
36	4	2-benzofuranyl	2,3-di-Cl-Ph	0.62 ± 0.03	890 ± 125	5740 ± 125	126 ± 20	236 ± 24
37	4	1*H*-indol-2-yl	2,3-di-Cl-Ph	0.62 ± 0.02	>800 (24%)	135 ± 14	1660 ± 140	2050 ± 130
38	4	1*H*-indol-3-yl	2,3-di-Cl-Ph	0.94 ± 0.02	>800 (30%)	63 ± 13	1110 ± 170	1880 ± 320
39	4	3-indazolyl	2,3-di-Cl-Ph	0.18 ± 0.02	>800 (39%)	107 ± 18	621 ± 12	1120 ± 230
40	4	2-benzo[*b*]thienyl	2,3-di-Cl-Ph	0.14 ± 0.01	>800 (38%)	170 ± 10	5500 ± 220	656 ± 20
41	4	7-CH_3O-2-benzofuranyl	2,3-di-Cl-Ph	0.13 ± 0.01	720 ± 15	373 ± 20	184 ± 16	110 ± 21
haloperidol				28 ± 2	0.74 ± 0.08	0.12 ± 0.04		
clozapine					30.0 ± 0.3			
8-OH-DPAT							2.1 ± 0.4	
phentolamine								18 ± 3

[a] Full K_i not obtained, percentage inhibition at the concentration shown given in parentheses.

moiety that is often present in 5-HT_{1A} receptor ligands.[23] Therefore, we have identified the structure of *N*-[4-(4-arylpiperazin-1-yl)butyl]-3-methoxybenzamide as a framework to obtain potent D_3 ligands. At this point, a further examination of the SAFIR was carried out on compound **19** that showed the highest D_3 affinity. Changes were made by replacing either the 2,3-dichorophenyl moiety (compounds **27**−**30**) or the 3-meth-

oxyphenyl group (compounds **31**−**41**). For the first modification, we replaced the two Cl atoms with two CH_3 groups (compound **27**), or we used a bicyclic aromatic ring to mimic the 2,3-dichlorophenyl group. The 2,3-dimethylphenyl derivative **27** displayed slightly higher D_3 affinity than the parent 2,3-dichlorophenyl derivative **19** and showed at least 300-fold selectivity over D_2, D_4, 5-HT_{1A}, and α_1 receptors. Also, 1-naphthalenyl derivative **28** displayed high D_3 affinity ($K_i = 0.54$ nM), but it proved to be nonselective over D_4 and 5-HT_{1A} receptors. Isoquinoline **29** and 1,2-benzisoxazole **30** were significantly less potent than **19** at D_3 receptor. However, data concerning derivatives **27**−**30** did not provide clear information for SAFIR on that part of the molecule.

For the second modification, we replaced the 3-methoxyphenyl ring of compound **19** with a variety of bicyclic aromatic rings including 4-bromo-1-methoxy-2-naphthalenyl,[19] 1-methoxy-2-naphthalenyl,[20] 1,1′-biphenyl,[21] 4-quinolyl[17] (compounds **31**−**41**) that are present in already reported D_3 ligands. All these compounds possessed high D_3 receptor affinity (0.13 nM < K_i < 4.97 nM) and high selectivity over D_2, D_4, 5-HT_{1A}, and α_1 receptors. Therefore, it seems clear that the replacement of the 3-methoxyphenyl ring attached to the amide moiety of compound **19** with a bicyclic aromatic ring did not change the D_3 affinity but greatly increased the specificity for the D_3 receptor.

In conclusion, structural modifications of the high-affinity D_4 ligand PB12 (**1**) have led to the identification of several *N*-[4-(4-arylpiperazin-1-yl)butyl]arylcarboxamides with high affinity for D_3 receptor. Moreover, the benzamides derived from aromatic bicyclic carboxylic acid were also highly selective over D_2, D_4, 5-HT_{1A}, and α_1 receptors. Finally, the in vitro binding profiles of compounds **27**, **32**, and **41** suggest that these highly potent and selective D_3 receptor ligands may be particularly attractive potential candidates for receptor imaging with PET. Moreover, it is generally more desirable to perform PET studies with competitive receptor antagonists, and compounds **27**, **32**, and **41** should also possess this property. In fact, they are structurally closely related to the D_3 receptor antagonists NGB 2904 and NGB 2849.[16] The phenolic precursors of compounds **27**, **32**, and **41** will provide ^{11}C radiolabeled derivatives that will be tested in PET studies for their ability of in vitro imaging of primate brain D_3 receptor.

Experimental Section

Chemistry. Column chromatography was performed with 1:30 ICN silica gel 60A (63−200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses (C, H, N) were performed on Eurovector Euro EA 3000 analyzer or on a Carlo Erba model 1106 instrument; the analytical results were within ±0.4% of the theoretical values for the formula given. ^1H NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer or at 300 MHz on a Bruker AM 300 WB spectrometer or on a Varian Mercury-VX spectrometer. All chemical shift values are reported in ppm (δ). Recording of mass spectra was done on an HP6890−5973 MSD gas chromatograph/mass spectrometer; only significant *m*/*z* peaks, with their percentage of relative intensity in parentheses, are reported. All spectra were in accordance with the assigned structures. Purity of target compounds was checked by HPLC analysis on a Perkin-Elmer series 200 LC instrument using a Phenomenex Prodigy ODS-3 RP-18 column (250 × 4.6 mm, 5 μ particle size) and equipped with a Perkin-Elmer 785A UV/vis detector setting $\lambda = 254$ nm. All compounds were eluted with $CH_3OH/H_2O/Et_3N$, 4:1:0.01, v/v, at a flow rate of 1 mL/min. A standard procedure was used to transform final compounds into their hydrochloride or oxalate salts that were recrystallized as detailed in Table 1.

1-(2,3-Dichlorophenyl)piperazine was a kind gift by Clariant Life Science Molecules (Origgio, Varese, Italy). The following compounds were synthesized according to published procedures: 1-(1-naphthalenyl)piperazine,[24] 1-(4-chloro-2-pyridinyl)-piperazine,[25] 1-(4-methyl-2-pyridinyl)piperazine,[25] 1-(isoquinolin-1-yl)piperazine,[27] 4-bromo-2-methoxy-1-naphthoic acid,[28] 2-methoxy-1-naphthoic acid,[29] *N*-(2-chloroethyl)-3-methoxybenzamide (**2**),[11] 4-(2,3-dichlorophenyl)-1-piperazinebutanamine (**4e**),[16] 3-[4-(4-aminobutyl)-1-piperazinyl]-1,2-benzisoxazole (**4f**),[30] 4-(2-methoxyphenyl)-1-piperazinebutanamine (**4g**),[31] 4-(2-methoxyphenyl)-1-piperazinepentanamine (**4j**).[32]

***N*-(3-Chloropropyl)-3-methoxybenzamide (3).** To a cooled mixture containing 3-chloropropylamine hydrochloride (4.10 g, 31.5 mmol) in 1.2% aqueous NaOH (120 mL) was added dropwise under vigorous stirring a CH_2Cl_2 solution (50 mL) of 3-methoxybenzoyl chloride, prepared from the corresponding acid (5.05 g, 33.2 mmol) and $SOCl_2$ (10 mL). Then, the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_2 and evaporated to dryness under reduced pressure. The crude residue was chromatographed ($CHCl_3$ as eluent) to give pure benzamide **3** as a solid (4.53 g, 63% yield). ^1H NMR (90 MHz, $CDCl_3$): δ 1.93−2.25 (m, 2H, $CH_2CH_2CH_2$), 3.50−3.70 (m, 4H, $CH_2CH_2CH_2$), 3.83 (s, 3H, CH_3), 6.83 (br s, 1H, NH), 6.90−7.45 (m, 4H, aromatic); GC/MS *m*/*z* 229 ($M^+ + 2$, 3), 227 (M^+, 9), 192 (58), 164 (20), 135 (100).

4-(2,3-Dichlorophenyl)-1-piperazinepentanenitrile (4a). A stirred mixture of 1-(2,3-dichlorophenyl)piperazine (1.71 g, 7.4 mmol), 5-chloropentanenitrile (0.70 mL, 6.2 mmol), and an excess of anhydrous Na_2CO_3 in acetonitrile (50 mL) was refluxed overnight. After cooling, the mixture was evaporated to dryness and water was added to the residue. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL) and the collected organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was chromatographed ($CHCl_3$/AcOEt, 1:1 as eluent) to yield pure **4a** as a white semisolid (1.6 g, 86% yield). ^1H NMR (90 MHz, $CDCl_3$): δ 1.50−1.85 [m, 4H, $(CH_2)_2CH_2CN$], 2.25−2.70 [m, 8H, $(CH_2)_2NCH_2$, CH_2CN], 3.03 [br t, 4H, $ArN(CH_2)_2$], 6.80−7.25 (m, 3H, aromatic); GC/MS *m*/*z* 313 ($M^+ + 2$, 18), 312 ($M^+ + 1$, 7), 311 (M^+, 27), 245 (72), 243 (100).

4-(2,3-Dimethylphenyl)-1-piperazinebutanenitrile (4b). As above, the title compound was obtained in 38% yield starting from 1-(2,3-dimethylphenyl)piperazine and 4-chlorobutanenitrile. ^1H NMR (90 MHz, $CDCl_3$): δ 1.75−2.10 (m, 2H, CH_2CH_2CN), 2.27 and 2.33 (2 s, 6H, 2 CH_3), 2.37−2.75 [m, 8H, $(CH_2)_2NCH_2$, CH_2CN], 2.95 [br t, 4H, $ArN(CH_2)_2$], 6.85−7.25 (m, 3H, aromatic); GC/MS *m*/*z* 259 ($M^+ + 2$, 2), 258 ($M^+ + 1$, 20), 257 (M^+, 100), 217 (87), 203 (35).

4-(1-Naphthalenyl)-1-piperazinebutanenitrile (4c). Title compound was prepared as above in 85% yield starting from 1-(1-naphthalenyl)piperazine and 4-chlorobutanenitrile. ^1H NMR (90 MHz, $CDCl_3$): δ 1.80−2.07 (m, 2H, CH_2CH_2CN), 2.27−3.17 [m, 8H, $(CH_2)_2NCH_2$, CH_2CN], 3.60 [br t, 4H, $ArN(CH_2)_2$], 7.05−8.30 (m, 7H, aromatic); GC/MS *m*/*z* 281 ($M^+ + 2$, 3), 280 ($M^+ + 1$, 25), 279 (M^+, 100), 239 (49), 154 (53).

4-(1-Isoquinolyl)-1-piperazinebutanenitrile (4d). As for compound **4a**, nitrile **4d** was prepared from 1-(1-isoquinolyl)-piperazine and 4-chlorobutanenitrile. The crude residue was chromatographed with $CHCl_3$/ CH_3OH, 19:1, as eluent, in 28% yield. ^1H NMR (90 MHz, $CDCl_3$): δ 1.75−2.05 (m, 2H, CH_2CH_2CN), 2.33−2.75 [m, 8H, $(CH_2)_2NCH_2$, CH_2CN], 3.45 [br t, 4H, $ArN(CH_2)_2$], 7.17−8.20 (m, 6H, aromatic); GC/MS *m*/*z* 281 ($M^+ + 1$, 3), 280 (M^+, 11), 171 (20), 157 (100), 144 (40).

General Procedure for the Synthesis of Amines 5a−d. Borane-methyl sulfide complex as 10.0 M BH_3 in excess methyl sulfide (1.6 mL, 16 mmol) was dropped into an ice-cooled solution of nitrile (5.1 mmol) in anhydrous THF (10 mL), under stirring. After being refluxed for 4 h, the reaction mixture was cooled at −10 °C and MeOH was added dropwise very carefully until gas evolution ceased. The mixture was treated with 3 N HCl (20 mL) and was refluxed for 1 h. After cooling, the mixture was alkalized with 3 N NaOH and extracted with CH_2Cl_2 (2 × 50 mL). The collected organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give the pure amine as a colorless oil.

4-(2,3-Dichlorophenyl)-1-piperazinepentanamine (5a). Nearly quantitative yield.^{1}H NMR (90 MHz, $CDCl_3$): δ 1.25−1.80 [m, 8H, $(CH_2)_3CH_2NH_2$, 2H D_2O exchanged], 2.15−2.80 [m, 8H, $(CH_2)_2NCH_2$, CH_2NH_2], 3.15 [br t, 4H, $ArN(CH_2)_2$], 6.80−7.30 (m, 3H, aromatic); GC/MS *m*/*z* 315 (M^+, 1), 245 (68), 243 (100), 200 (29), 172 (25), 141 (76).

4-(2,3-Dimethylphenyl)-1-piperazinebutanamine (5b). 77% Yield. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.53−2.10 [m, 6H, $(CH_2)_2CH_2NH_2$, 2H D_2O exchanged], 2.27 and 2.33 (2 s, 6H, 2 CH_3), 2.50−2.80 [m, 8H, $(CH_2)_2NCH_2$, CH_2NH_2], 3.00 [br t, 4H, $ArN(CH_2)_2$], 6.90−7.30 (m, 3H, aromatic); GC/MS *m*/*z* 262 (M^+ + 1, 1), 261 (M^+, 3), 203 (79), 160 (62), 146 (78), 132 (84), 127 (100).

4-(1-Naphthalenyl)-1-piperazinebutanamine (5c). 74% Yield. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.45−1.98 [m, 6H, $(CH_2)_2CH_2NH_2$, 2H D_2O exchanged], 2.30−2.90 [m, 8H, $(CH_2)_2NCH_2$, CH_2NH_2], 3.15 [br t, 4H, $ArN(CH_2)_2$], 7.10−8.35 (m, 7H, aromatic); GC/MS *m*/*z* 284 (M^+ + 1, 2), 283 (M^+, 8), 225 (33), 182 (31), 154 (50), 127 (100).

4-(1-Isoquinolyl)-1-piperazinebutanamine (5d). 34% Yield. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.40−2.03 [m, 6H, $(CH_2)_2CH_2NH_2$, 2H D_2O exchanged], 2.33−3.00 [m, 8H, $(CH_2)_2NCH_2$, CH_2NH_2], 3.35 [br t, 4H, $ArN(CH_2)_2$], 7.10−8.15 (m, 6H, aromatic); GC/MS *m*/*z* 284 (M^+, 0.3), 157 (100).

General Procedure for the Synthesis of Benzamides 8−18. A stirred solution of the appropriate 1-arylpiperazine (6.0 mmol), chloroderivative **2** (5.0 mmol) (or compound **3** in the case of the benzamide **18**), and triethylamine (4 mL) in toluene (50 mL) was refluxed for 20 h. Then the solvent was evaporated under reduced pressure and the residue taken up with a 20% aqueous Na_2CO_3 and extracted with AcOEt. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude residue was chromatographed as detailed below to give target benzamides as pale yellow oils or solids.

***N*-[2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (8).** Eluted with $CHCl_3$/AcOEt, 1:1, in 59% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 [br t, 6H, $CH_2N(CH_2)_2$], 3.08 [br s, 4H, $(CH_2)_2NAr$], 3.57 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.84 (s, 3H, CH_3), 6.84 (br s, 1H, NH, D_2O exchanged), 6.92−7.38 (m, 8H, aromatic); GC/MS *m*/*z* 373 (M^+, 1), 211 (36), 209 (100).

***N*-[2-[4-(3-Chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (9).** Eluted with $CHCl_3$/AcOEt, 1:1, in 18% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65−2.69 [m, 6H, $CH_2N(CH_2)_2$], 3.22 [br t, 4H, $(CH_2)_2NAr$], 3.59 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.83 (s, 3H, OCH_3), 6.75−7.38 (m, 9H, aromatic, NH, 1H D_2O exchanged); GC/MS *m*/*z* 374 (M^+ + 1, 1), 373 (M^+, 4), 211 (34), 209 (100), 166 (21).

***N*-[2-[4-(4-Methylphenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (10).** Eluted with $CHCl_3$/AcOEt, 1:1, in 10% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.64−2.69 [m, 6H, $CH_2N(CH_2)_2$], 3.17 [br t, 4H, $(CH_2)_2NAr$], 3.58 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.85 (s, 3H, OCH_3), 6.84−7.39 (m, 9H, aromatic, NH, 1H D_2O exchanged); GC/MS *m*/*z* 354 (M^+ + 1, 4), 353 (M^+, 15), 189 (100).

***N*-[2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (11).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64−2.69 [m, 6H, $CH_2N(CH_2)_2$], 3.11 [br t, 4H, $(CH_2)_2NAr$], 3.58 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.77 and 3.84 (2 s, 6H, 2 CH_3), 6.83−7.38 (m, 9H, aromatic, NH, 1H D_2O exchanged); GC/MS *m*/*z* 371 (M^+ + 2, 1), 370 (M^+ + 1, 8), 369 (M^+, 35), 205 (100), 135 (20).

***N*-[2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (12).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63−2.69 [m, 6H, $CH_2N(CH_2)_2$], 3.12 [br t, 4H, $(CH_2)_2NAr$], 3.57 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.82 (s, 3H, CH_3), 6.82−7.38 (m, 9H, aromatic, NH, 1H D_2O exchanged); GC/MS *m*/*z* 358 (M^+ + 1, 2), 357 (M^+, 10), 193 (100), 150 (26).

***N*-[2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (13).** Eluted with $CHCl_3$/AcOEt, 1:1, in 11% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67 [br t, 6H, $CH_2N(CH_2)_2$], 3.07 [br s, 4H, $(CH_2)_2NAr$], 3.57 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.83 (s, 3H, CH_3), 6.82 (br s, 1H, NH, D_2O exchanged), 6.91−7.38 (m, 7H, aromatic); GC/MS *m*/*z* 409 (M^+ + 2, 1), 407 (M^+, 1), 245 (64), 243 (100).

***N*-[2-(4-Phenylpiperazin-1-yl)ethyl]-3-methoxybenzamide (14).** Eluted with $CHCl_3$/AcOEt, 1:1, in 11% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64−2.69 [m, 6H, $CH_2N(CH_2)_2$], 3.21 [br t, 4H, $(CH_2)_2NAr$], 3.58 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.83 (s, 3H, CH_3), 6.82−7.38 (m, 10H, aromatic, NH, 1H D_2O exchanged); GC/MS *m*/*z* 340 (M^+ + 1, 1), 339 (M^+, 6), 175 (100), 132 (24).

***N*-[2-[4-(1-Naphthalenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (15).** Eluted with $CHCl_3$/AcOEt, 1:1, in 10% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 [t, 2H, J = 5.9 Hz, $CH_2N(CH_2)_2$], 2.84 [br s, 4H, $CH_2N(CH_2)_2$], 3.17 [br s, 4H, $(CH_2)_2NAr$], 3.63 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.85 (s, 3H, CH_3), 6.99−8.19 (m, 12H, aromatic, NH, 1H D_2O exchanged); GC/MS *m*/*z* 391 (M^+ + 2, 1), 390 (M^+ + 1, 4), 389 (M^+, 14), 225 (100).

***N*-[2-[4-(4-Chloro-2-pyridinyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (16).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 11% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60−2.67 [m, 6H, $CH_2N(CH_2)_2$], 3.49 [br t, 4H, $(CH_2)_2NAr$] 3.58 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.83 (s, 3H, OCH_3), 6.59 (d, 1H, J = 8.7 Hz, CCl=CH), 6.89 (br s, 1H, NH, D_2O exchanged), 6.99−7.38 (m, 5H, aromatic), 8.01 (d, 1H, J = 1.8 Hz, N=CH); GC/MS *m*/*z* 375 (M^+ + 1, 1), 374 (M^+, 4), 246 (31), 221 (21), 212 (31), 210 (100), 181 (33), 155 (35).

***N*-[2-[4-(4-Methyl-2-pyridinyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (17).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 23% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.62−2.67 [m, 6H, $CH_2N(CH_2)_2$], 3.48−3.61 [m, 6H, $(CH_2)_2NAr$, $NHCH_2$], 3.84 (s, 3H, OCH_3), 6.59 (d, 1H, J = 8.4 Hz, C=CH), 6.90 (br s, 1H, NH, D_2O exchanged), 7.00−7.39 (m, 5H, aromatic), 8.01−8.02 (m, 1H, N=CH); GC/MS *m*/*z* 355 (M^+ + 1, 2), 354 (M^+, 9), 246 (74), 190 (100), 178 (22), 161 (44), 135 (99), 121 (99).

***N*-[3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl]-3-methoxybenzamide (18).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88−1.95 (m, 2H, $NHCH_2CH_2$), 2.65−2.90 [m, 6H, $CH_2N(CH_2)_2$], 3.10 [br s, 4H, $(CH_2)_2NAr$], 3.60 (q, 2H, J = 5.4 Hz, $NHCH_2$), 3.82 (s, 3H, CH_3), 6.90−7.48 (m, 7H, aromatic), 8.32 (br s, 1H, NH, D_2O exchanged); GC/MS *m*/*z* 423 (M^+ + 2, 1), 421 (M^+, 3), 386 (23), 245 (50), 243 (78), 221 (100), 192 (63).

General Procedure for the Synthesis of Benzamides 19, 20, 22, 23, 27−30, 32, 33, 35. To a cooled mixture containing the appropriate amine (5.0 mmol) in 1.2% aqueous NaOH (20 mL) was added dropwise under vigorous stirring a CH_2Cl_2 solution (50 mL) of acyl chloride, prepared from the corresponding acid (6.0 mmol) and $SOCl_2$ (5 mL). Then, the aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude residue was chromatographed as detailed below to give target benzamide as a pale yellow liquid.

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-3-methoxybenzamide (19).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63−1.71 [m, 4H, $NHCH_2(CH_2)_2$], 2.46 [t, 2H, J = 6.8 Hz, $CH_2N(CH_2)_2$], 2.61 [br s, 4H, $CH_2N(CH_2)_2$], 3.01 [br s, 4H, $(CH_2)_2NAr$], 3.45 (q, 2H, J = 6.1 Hz, $NHCH_2$), 3.83 (s, 3H, CH_3), 6.72 (br t, 1H,

NH), 6.87−7.40 (m, 7H, aromatic); GC/ MS *m/z* 436 ($M^+ + 1$, 1), 435 (M^+, 2), 261 (32), 245 (50), 243 (79), 235 (100), 135 (53).

***N*-[5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentyl]-3-methoxybenzamide (20).** Eluted with $CHCl_3$/AcOEt, 1:1, in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41−1.49 (m, 2H, $CH_2CH_2CH_2$), 1.59−1.71 (m, 4H, $CH_2CH_2CH_2$), 2.50 [t, 2H, J = 7.6 Hz, $CH_2N(CH_2)_2$], 2.71 [br s, 4H, $CH_2N(CH_2)_2$], 3.11 [br s, 4H, $(CH_2)_2NAr$], 3.47 (q, 2H, J = 6.4 Hz, $NHCH_2$), 3.84 (s, 3H, CH_3), 6.26 (br s, 1H, NH), 6.93−7.36 (m, 7H, aromatic); GC/MS *m/z* 450 ($M^+ + 1$, 1), 449 (M^+, 2), 275 (30), 263 (20), 249 (100), 245 (65), 243 (99).

***N*-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]-3-methoxybenzamide (22).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 41% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65−1.69 [m, 4H, $NHCH_2(CH_2)_2$], 2.48 [t, 2H, J = 6.5 Hz, $CH_2N(CH_2)_2$], 2.67 [br s, 4H, $CH_2N(CH_2)_2$], 3.07 [br s, 4H, $(CH_2)_2NAr$], 3.45−3.49 (m, 2H, $NHCH_2$), 3.82 and 3.85 (2 s, 6H, 2 CH_3), 6.83−7.36 (m, 9H, aromatic, NH); GC/MS *m/z* 398 ($M^+ + 1$, 8), 397 (M^+, 29), 382 (40), 235 (55), 205 (100), 190 (30).

***N*-[5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl]-3-methoxybenzamide (23).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 46% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40−1.47 (m, 2H, $CH_2CH_2CH_2$), 1.56−1.70 (m, 4H, $CH_2CH_2CH_2$), 2.44 [t, 2H, J = 7.5 Hz, $CH_2N(CH_2)_2$], 2.69 [br s, 4H, $CH_2N(CH_2)_2$], 3.11 [br s, 4H, $(CH_2)_2NAr$], 3.45 (q, 2H, J = 6.7 Hz, $NHCH_2$), 3.83 and 3.85 (2 s, 6H, 2 CH_3), 6.29 (br s, 1H, NH), 6.83−7.36 (m, 8H, aromatic); GC/MS *m/z* 412 ($M^+ + 1$, 6), 411 (M^+, 22), 396 (21), 249 (32), 205 (100), 135 (43).

***N*-[4-[4-(2,3-Dimethylphenyl)piperazin-1-yl]butyl]-3-methoxybenzamide (27).** Eluted with $CHCl_3$/AcOEt, 1:1, in 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72−1.65 [m, 4H, $NHCH_2(CH_2)_2$], 2.20 and 2.26 (2 s, 6H, 2 CH_3), 2.47 [t, 2H, J = 6.9 Hz, $CH_2N(CH_2)_2$], 2.61 [br s, 4H, $CH_2N(CH_2)_2$], 2.87 [br t, 4H, $(CH_2)_2NAr$], 3.45−3.51 (m, 2H, $NHCH_2$), 3.83 (s, 3H, OCH_3), 6.80 (br t, 1H, NH), 6.85−7.36 (m, 7H, aromatic); GC/MS *m/z* 397 ($M^+ + 2$, 1), 396 ($M^+ + 1$, 3), 395 (M^+, 13), 380 (21), 235 (100), 203 (85).

***N*-[4-[4-(1-Naphthalenyl)piperazin-1-yl]butyl]-3-methoxybenzamide (28).** Eluted with $CHCl_3$/AcOEt, 1:1, in 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75−1.68 [m, 4H, $NHCH_2(CH_2)_2$], 2.54 [t, 2H, J = 6.7 Hz, $CH_2N(CH_2)_2$], 2.75 [br s, 4H, $CH_2N(CH_2)_2$], 3.12 [br s, 4H, $(CH_2)_2NAr$], 3.52 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.83 (s, 3H, CH_3), 6.82 (br s, 1H, NH), 6.91−8.20 (m, 11H, aromatic); GC/MS *m/z* 419 ($M^+ + 2$, 2), 418 ($M^+ + 1$, 11), 417 (M^+, 38), 402 (35), 235 (100), 225 (94).

***N*-[4-[4-(1-Isoquinolyl)piperazin-1-yl]butyl]-3-methoxybenzamide (29).** Eluted with $CHCl_3$/AcOEt, 1:1, in 24% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 [br s, 4H, $NHCH_2(CH_2)_2$], 2.51 [t, 2H, J = 6.7 Hz, $CH_2N(CH_2)_2$], 2.71 [br s, 4H, $CH_2N(CH_2)_2$], 3.43 [br s, 4H, $(CH_2)_2NAr$], 3.50 (q, 2H, J = 5.6 Hz, $NHCH_2$), 3.83 (s, 3H, CH_3), 6.57 (br s, 1H, NH), 6.99−8.14 (m, 10H, aromatic); GC/MS *m/z* 418 (M^+, 2), 157 (100).

***N*-[4-[4-(1,2-Benzisoxazol-3-yl)piperazin-1-yl]butyl]-3-methoxybenzamide (30).** Eluted with $CHCl_3$/AcOEt, 1:1, in 37% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62−1.69 [m, 4H, $NHCH_2(CH_2)_2$], 2.45 [t, 2H, J = 6.9 Hz, $CH_2N(CH_2)_2$], 2.62 [br t, 4H, $CH_2N(CH_2)_2$], 3.48 (q, 2H, J = 6.2 Hz, $NHCH_2$), 3.55 [br t, 4H, $(CH_2)_2NAr$], 3.82 (s, 3H, CH_3), 6.55 (br s, 1H, NH), 6.35−7.69 (m, 8H, aromatic); GC/MS *m/z* 408 (M^+, 14), 249 (63), 216 (40), 206 (28), 161 (33), 135 (100).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-1-methoxy-2-naphthalenecarboxamide (32).** Eluted with $CHCl_3$/AcOEt, 19:1, in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67−1.77 [m, 4H, $NHCH_2(CH_2)_2$], 2.50 [t, 2H, J = 7.0 Hz, $CH_2N(CH_2)_2$], 2.65 [br s, 4H, $CH_2N(CH_2)_2$], 3.02 [br s, 4H, $(CH_2)_2NAr$], 3.55−3.61 (m, 2H, $NHCH_2$), 4.00 (s, 3H, CH_3), 6.84−8.17 (m, 10H, aromatic, NH).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-2-naphthalenecarboxamide (33).** Eluted with $CHCl_3$/AcOEt, 1:1 in 48% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66−1.79 [m, 4H, $NHCH_2(CH_2)_2$], 2.48 [t, 2H, J = 6.7 Hz, $CH_2N(CH_2)_2$], 2.62 [br s, 4H, $CH_2N(CH_2)_2$], 2.97 [br s, 4H, $(CH_2)_2NAr$], 3.54 (q, 2H, J = 6.2 Hz, $NHCH_2$), 6.71−8.33 (m, 11H, aromatic, NH).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-(1,1′-biphenyl)-4-carboxamide (35).** Eluted with $CHCl_3/CH_3OH$, 19:1, in 38% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68−1.75 [m, 4H, $NHCH_2(CH_2)_2$], 2.53 [t, 2H, J = 6.7 Hz, $CH_2N(CH_2)_2$], 2.68 [br s, 4H, $CH_2N(CH_2)_2$], 3.05 [br t, 4H, $(CH_2)_2NAr$], 3.52 (q, 2H, J = 6.0 Hz, $NHCH_2$), 6.86−7.88 (m, 13H, aromatic, NH).

General Procedure for the Synthesis of Benzamides 31, 34, 36−41. A mixture of the appropriate carboxylic acid (0.48 mmol) and 1,1′-carbonyldiimidazole (0.50 mmol) in 10 mL of anhydrous THF was stirred for 8 h. A solution of amine **5e** (0.5 mmol) in 10 mL of anhydrous THF was added and the resulting mixture was stirred for 1 h. The reaction mixture was partitioned between AcOEt and H_2O. The organic layer was washed with aqueous Na_2CO_3 solution, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was chromatographed with $CHCl_3/CH_3OH$, 19:1 to afford the pure benzamide.

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-4-bromo-1-methoxy-2-naphthalenecarboxamide (31).** 36% Yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66−1.76 [m, 4H, $NHCH_2(CH_2)_2$], 2.49 [t, 2H, J = 7.0 Hz, $CH_2N(CH_2)_2$], 2.63 [br s, 4H, $CH_2N(CH_2)_2$], 3.01 [br t, 4H, $(CH_2)_2NAr$], 3.54−3.60 (m, 2H, $NHCH_2$), 3.99 (s, 3H, CH_3), 6.82−8.38 (m, 9H, aromatic, NH).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-4-quinolinecarboxamide (34).** 49% Yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68−1.82 [m, 4H, $NHCH_2(CH_2)_2$], 2.41−2.55 [m, 10H, $CH_2N(CH_2)_2$, $(CH_2)_2NAr$], 3.52−3.58 (m, 2H, $NHCH_2$), 6.44−8.91 (m, 10H, aromatic, NH); GC/MS *m/z* 458 ($M^+ + 2$, 19), 457 ($M^+ + 1$, 9), 456 (M^+, 30), 256 (57), 245 (64), 243 (100).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-2-benzofurancarboxamide (36).** 66% Yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64−1.71 [m, 4H, $NHCH_2(CH_2)_2$], 2.49 [t, 2H, J = 6.9 Hz, $CH_2N(CH_2)_2$], 2.67 [br s, 4H, $CH_2N(CH_2)_2$], 3.09 [br s, 4H, $(CH_2)_2NAr$], 3.51 (q, 2H, J = 6.5 Hz, $NHCH_2$), 6.90−7.68 (m, 9H, aromatic, NH); GC/MS *m/z* 447 ($M^+ + 2$, 1), 446 ($M^+ + 1$, 1), 445 (M^+, 2), 271 (21), 245 (100), 243 (62).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-1H-indole-2-carboxamide (37).** 7% Yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45−1.62 [m, 4H, $NHCH_2(CH_2)_2$], 2.36 [br t, 2H, $CH_2N(CH_2)_2$], 2.51 [br s, 4H, $CH_2N(CH_2)_2$], 2.95 [br s, 4H, $(CH_2)_2NAr$], 3.36−3.42 (m, 2H, $NHCH_2$), 6.98−7.59 (m, 8H, aromatic), 8.44 (br t, 1H, NH), 11.51 (s, 1H, indole NH, D_2O exchanged); GC/MS *m/z* 446 ($M^+ + 2$, 11), 445 ($M^+ + 1$, 7), 444 (M^+, 19), 270 (24), 245 (72), 244 (100), 243 (94).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-1H-indole-3-carboxamide (38).** 11% Yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44−1.58 [m, 4H, $NHCH_2(CH_2)_2$], 2.34 [br s, 2H, $CH_2N(CH_2)_2$], 2.50 [br t, 4H, $CH_2N(CH_2)_2$], 2.92 [br s, 4H, $(CH_2)_2NAr$], 3.20−3.28 (m, 2H, $NHCH_2$), 7.00−8.10 (m, 9H, aromatic, NH), 11.50 (s, 1H, indole NH, D_2O exchanged).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-1H-indazole-3-carboxamide (39).** 39% Yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.76 [br s, 4H, $NHCH_2(CH_2)_2$], 2.15 [br s, 2H, $CH_2N(CH_2)_2$], 2.80 [br s, 4H, $CH_2N(CH_2)_2$], 3.18 [br s, 4H, $(CH_2)_2NAr$], 3.24 (br s, 2H, $NHCH_2$), 7.26−8.37 (m, 7H, aromatic), 8.52 (br s, 1H, CONH), 13.60 (s, 1H, indazole NH).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]benzo[b]thiophene-2-carboxamide (40).** 66% Yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44−1.60 [m, 4H, $NHCH_2(CH_2)_2$], 2.38 [t, 2H, J = 6.5 Hz, $CH_2N(CH_2)_2$], 2.54 [br s, 4H, $CH_2N(CH_2)_2$], 2.94 [br s, 4H, $(CH_2)_2NAr$], 3.41 (q, 2H, J = 6.0 Hz, $NHCH_2$), 6.74−7.71 (m, 8H, aromatic), 8.74 (br t, 1H, NH); GC/MS *m/z* 463 ($M^+ + 2$, 1), 462 ($M^+ + 1$, 1), 461 (M^+, 3), 287 (32), 261 (100), 245 (63), 243 (97).

***N*-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-7-methoxy-2-benzofurancarboxamide (41).** 70% Yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64−1.73 [m, 4H, $NHCH_2(CH_2)_2$], 2.48 [t, 2H, J = 6.8 Hz, $CH_2N(CH_2)_2$], 2.66 [br s, 4H, $CH_2N(CH_2)_2$], 3.08 [br s, 4H, $(CH_2)_2NAr$], 3.51 (q, 2H, J = 6.5 Hz, $NHCH_2$), 3.69 (s, 3H, CH_3), 6.87−7.45 (m, 8H, aromatic, NH); GC/MS *m/z* 477 ($M^+ + 2$, 1), 476 ($M^+ + 1$, 1), 475 (M^+, 3), 301 (30), 275 (100), 245 (57), 243 (83).

Biological Methods. 1. General. Human recombinant $D_{4.4}$ dopamine receptor expressed in CHO cells, human recombinant D_{2L} dopamine receptor expressed in Sf9 cells, and rat recombinant D_3 dopamine receptor expressed in Sf9 cells were obtained from RBI (Research Biochemicals International, Natick, MA). For receptor binding studies, the compounds were dissolved in absolute ethanol. Male Wistar Hannover rats (200−250 g) were from Harlan (S. Pietro al Natisone, Italy). The animals were handled according to internationally accepted principles for care of laboratory animals (E. E. C. Council Directive 86/609, O. J. No. L358, December 18, 1986). 8-OH-DPAT hydrobromide was from RBI (Research Biochemicals International, Natick, MA); haloperidol, phentolamine hydrochloride, and clozapine were from Sigma-Aldrich (Milan, Italy); [^{3}H]prazosin, [^{3}H]8-OH-DPAT, and [^{3}H]spiroperidol were obtained from NEN Life Science Products (Milan, Italy).

2. Radioligand Binding Assay at Rat-Cloned D_3 Dopaminergic Receptors. Binding of [^{3}H]spiroperidol at rat-cloned D_3 receptor was performed according to Swarzenski et al.[33] with minor modifications. The reaction buffer consisted of 50 mM Tris, 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, 120 mM NaCl (pH 7.4), including 100 μL of dopamine D_3 diluted membranes, 0.4 nM of [^{3}H]spiroperidol (K_d = 0.60 nM), and 100 μL of the drug solution (six to nine concentrations) for a total volume of 1 mL. Samples were incubated at 27 °C for 60 min, then the incubation was stopped by rapid filtration through Whatman GF/C glass fiber filters (presoaked in 0.3% polyethylenimine). The filters were washed twice with 1 mL of ice-cold buffer (50 mM Tris, pH 7.4). Nonspecific binding was defined in the presence of 10 μM haloperidol.

3. Radioligand Binding Assay at Human-Cloned $D_{4.4}$ Dopaminergic Receptors. Binding of [^{3}H]spiroperidol at human-cloned $D_{4.4}$ receptor was performed according to Hadley et al.[34] with minor modifications. The reaction buffer consisted of 50 mM Tris, 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$ (pH 7.4), including 500 μL of dopamine $D_{4.4}$ diluted membranes, 0.15 nM of [^{3}H]spiroperidol (K_d = 0.17 nM), and 100 μ L of the drug solution (six to nine concentrations) for a total volume of 1 mL. Samples were incubated at 25 °C for 60 min, then the incubation was stopped by rapid filtration through Whatman GF/A glass fiber filters (presoaked in 0.3% polyethylenimine). The filters were washed twice with 1 mL of ice-cold buffer (50 mM Tris, pH 7.4). Nonspecific binding was defined in the presence of 10 μM clozapine.

4. Radioligand Binding Assay at Human-Cloned D_{2L} Dopaminergic Receptors. Binding of [^{3}H]spiroperidol at human-cloned D_{2L} receptor was performed according to Hadley et al.[34] with minor modifications. The reaction buffer consisted of 50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA (pH 7.4), including 500 μL of dopamine D_{2L} receptor diluted membranes, 0.2 nM [^{3}H]spiroperidol (K_d = 0.20 nM), and 100 μL of the drug solution (six to nine concentrations) for a total volume of 1 mL. Samples were incubated at 27 °C for 60 min, then the incubation was stopped by rapid filtration through Whatman GF/C glass fiber filters (presoaked in 0.3% polyethylenimine). The filters were washed twice with 1 mL of ice-cold buffer (50 mM Tris, pH 7.4). Nonspecific binding was defined in the presence of 10 μM haloperidol.

5. Radioligand Binding Assay at Rat Hippocampal Membranes 5-HT_{1A} Receptors. Binding experiments were performed according to Borsini et al.[35] with minor modifications. Rats were killed by decapitation, the brain was quickly removed, and the hippocampus was dissected. The hippocampus (1.0 g) was homogenized with a Brinkman polytron (setting 5 for 3 × 15 s) in 25 mL of 50 mM Tris buffer, pH 7.6. The homogenate was centrifuged at 48000*g* for 15 min at 4 °C. The supernatant was discarded, and the pellet was resuspended in 25 mL of buffer, then preincubated for 10 min at 37 °C. The homogenate was centrifuged at 48000*g* for 15 min at 4 °C. The supernatant was discarded, and the final pellet was stored at −80 °C until used. Each tube received in a final volume of 1 mL of 50 mM Tris (pH 7.6) hippocampus membranes suspension and 1 nM [^{3}H]-8-OH-DPAT. For competitive inhibition experiments, various concentrations of drugs studied were incubated. Nonspecific binding was defined using 1 μM 8-OH-DPAT. Samples were incubated at 37 °C for 20 min and then filtered on Whatman GF/B glass microfiber filters. The K_d value determined for 8-OH-DPAT was 8.8 nM.

6. Radioligand Binding Assay at Rat Cortical Membranes α_1-Adrenoceptors. Binding experiments were performed according to Glossmann and Hornung[36] with minor modifications. Rats were killed by decapitation, the brain was quickly removed, and the cerebral cortex was dissected. The cerebral cortex (1.0 g) was homogenized with a Brinkman Polytron (setting 5 for 3 × 15 s) in 25 mL of buffer (50 mM Tris, 0.1 mM PMSF, pH 7.4). The homogenate was centrifuged at 1000*g* for 15 min at 4 °C. The supernatant was recovered and centrifuged at 50000*g* for 30 min at 4 °C. The final pellet was stored at −80 °C until used. Each tube received in a final volume of 1 mL of 50 mM Tris (pH 7.4) rat cerebral cortical membranes suspension and 1 nM [^{3}H]prazosin. For competitive inhibition experiments, various concentrations of drugs studied were incubated. Nonspecific binding was defined using 10 μM phentolamine. Samples were incubated at 25 °C for 50 min and then filtered on Whatman GF/B glass microfiber filters. The filters were presoaked for 50 min in Tris-polyethylenimine 0.5%. The K_d value determined for prazosin was 0.5 nM.

7. Statistical Analysis. The inhibition curves on the different binding sites of the compounds reported in Table 2 were analyzed by nonlinear curve fitting utilizing the GraphPad Prism program.[37] The value for the inhibition constant, K_i, was calculated by using the Cheng-Prusoff equation.[38]

Acknowledgment. This study was supported by Research Grant No. 2001037552-003 from Università degli Studi di Bari and MURST (Italy) for the scientific program in CHIM/08 field (2002-2003).

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JM020952A