New Substituted 1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl Derivatives with α₂-Adrenoceptor Antagonist Activity

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The emergence of a novel theory concerning the role of noradrenaline in the progression and the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases has provided a new impetus toward the discovery of novel compounds acting at α₂-adrenoceptors. A series of substituted 1-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl derivatives bearing an amide, urea, or imidazolidinone moiety was studied. Some members of this series of compounds proved to be potent α₂-adrenoceptor antagonists with good selectivity versus α₁-adrenergic and D₂-dopamine receptors. Particular emphasis is given to compound **33g** which displays potent α₂-adrenoceptor binding affinity in vitro and central effects in vivo following oral administration.

Introduction

Deterioration of the locus coeruleus−noradrenergic (LC−NA) system has been proposed to be a critical factor in the aetiology and progression of central neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.[1] In squirel monkeys, lesioning of the locus coeruleus, the major nucleus of noradrenergic neurones in the mammalian brain, was shown to impair spontaneous recovery of motor function following *N*-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) administration (a model of Parkinson's disease).[2] The discovery of new compounds that enhance central noradrenergic transmission may be useful to compensate the endogenous deficit of noradrenaline and thus reactivate impaired function.

Some preliminary studies with a 1-(2,3-dihydrobenzo-[1,4]dioxin-2-ylmethyl)piperidin-4-yl derivative, R 47243[3] **(1)**, in a MPTP-induced parkinsonian model in monkeys showed promising results. Colpaert et al.[3] observed a progressive reversion of MPTP-induced parkinsonian symptoms in a 20-year-old Java monkey following administration of this nonselective α₂-adrenoceptor antagonist. In particular, a normalization of blink rate and a notable reduction of rigidity, MPTP-induced hypokinesia, and resting tremor were observed. In addition, a study in patients with progressive supranuclear palsy (a motor disorder involving the nigrostriatal system)[4] described improvement in motor function following administration of the α₂-adrenoceptor antagonist idazoxan **(2)**. Based on these findings, a new interest in the discovery of novel compounds selectively acting on α₂-adrenoceptors has been generated. α₂-

Chart 1. Structure of Reference α₂-Adrenoceptor Antagonist Compounds
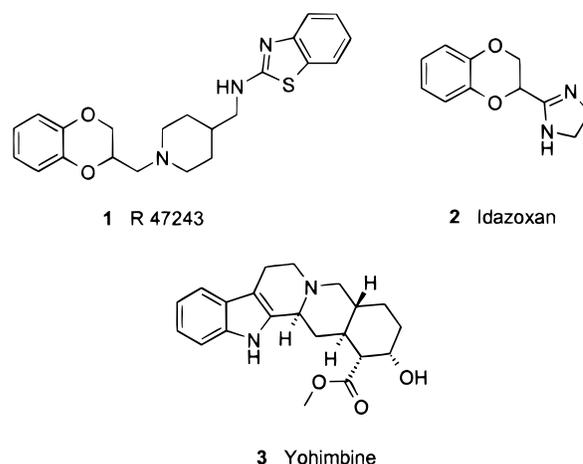
Adrenoceptor antagonists have been studied for nearly two decades for their therapeutic application in depression, owing to their noradrenergic enhancing activity in the central nervous system and their expected rapid onset of antidepressive activity in the clinic. However, the clinical development of most of them has been discontinued on account of their relative lack of efficacy. There are many types of chemically unrelated structures that have the capacity to block α₂-adrenoceptors. One group of compounds is derived from yohimbine (**3**)[5] (Chart 1), a natural plant alkaloid present in Rubiaceae and Apocynaceae families and includes synthetic analogues such as RS 15385-137[6] and MK 912.[7] Another group of α₂-adrenoceptor antagonists features idazoxan (**2**)[8] (Chart 1), whose structure merged as an hybrid between piperoxan (a weak nonselective α₂-adrenoceptor antagonist) and clonidine (a potent α₂-adrenoceptor partial agonist). This group also comprises Efaroxan,[9] RX 821002,[10] Fluparoxan,[11] and Atipamezole.[12] Our continuing research in this area has led to the design
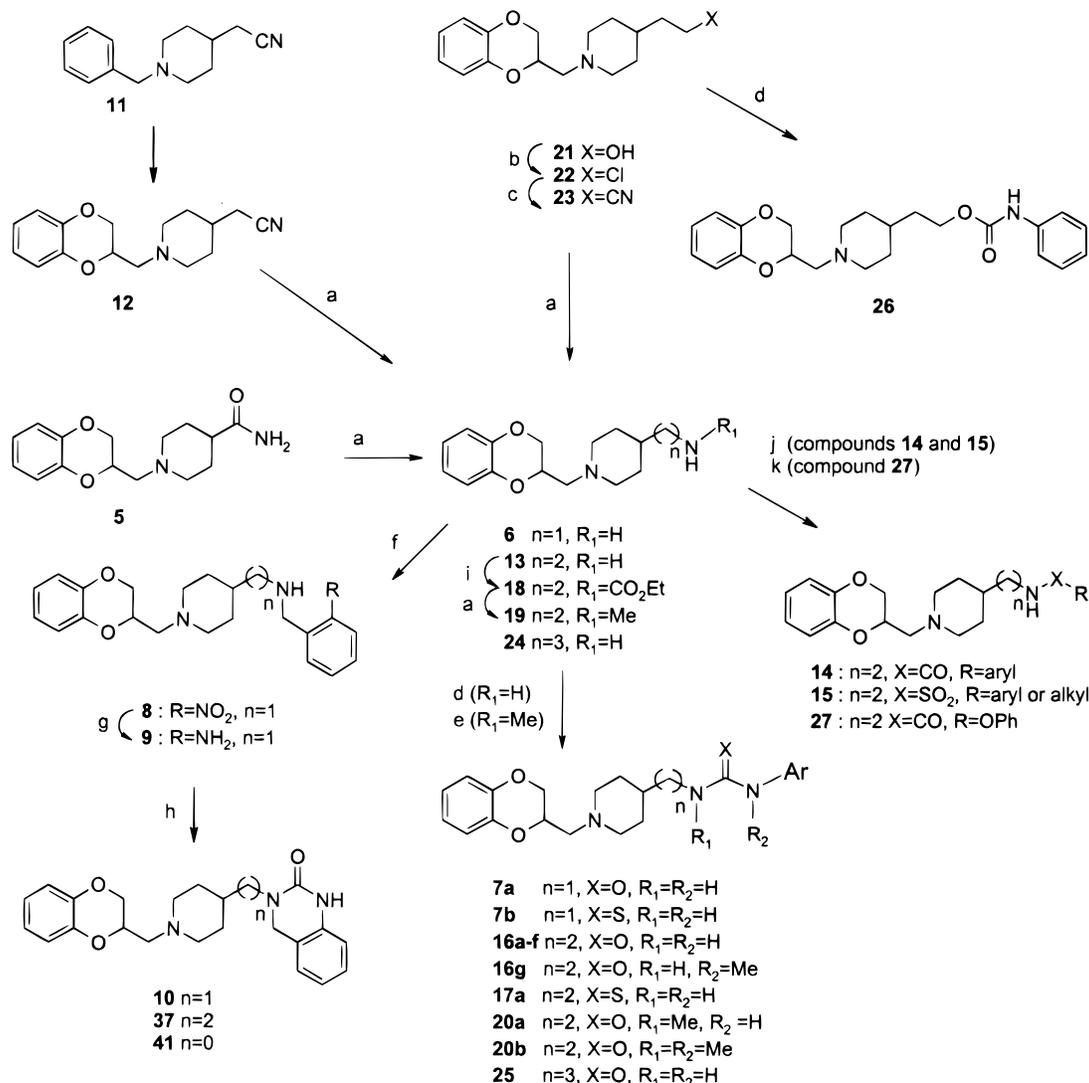
Scheme 1. Synthesis of Amides, Sulfonamides, Carbamates, Ureas, and 3,4-Dihydro-1*H*-quinazolin-2-one[a]

[a] (a) LiAlH$_4$/THF; (b) SOCl$_2$/CH$_2$Cl$_2$/reflux; (c) KCN/DMSO/120 °C; (d) ArNCO, ArNCS or PhMeNCOCl/CH$_2$Cl$_2$; (e) (i) ethyl chloroformate/Et$_3$N, (ii) LiAlH$_4$/THF, (iii) RNCO or PhMeNCOCl/CH$_2$Cl$_2$; (f) 2-nitrobenzaldehyde/NaBH$_4$/EtOH; (g) Fe/HCl; (h) urea/150 °C; (i) EtOCOCl/Et$_3$N/CH$_2$Cl$_2$; (j) RCOCl or RSO$_2$Cl/CH$_2$Cl$_2$/Et$_3$N; (k) PhOCOCl/CH$_2$Cl$_2$/Et$_3$N.

of new drugs, inspired by piperoxan as an archetypal structure of α_2-adrenoceptor antagonists and R 47243 (**1**), that reveal high binding affinities for α_2-adrenoceptors.

The two main criteria selected to evaluate the new compounds were (1) the in vitro binding affinity at α_2-adrenoceptors and their selectivity versus rat α_1-adrenoceptor and D$_2$-dopamine receptors and (2) their in vivo properties to inhibit the hypothermia induced by the centrally active α_2-adrenoceptor agonist guanabenz. α_1-Adrenoceptor affinity was evaluated as a criterion to select compounds without potential cardiovascular side effects. Furthermore, compounds were selected to be devoid of any D$_2$-receptor affinity in order to ensure specificity and to avoid potential dopamine antagonist activity. We describe here the chemical synthesis of a series of compounds of the general formula **4** (Chart 2), where modifications on parts A and B were made to determine the optimal structural requirements for α_2-adrenoceptor activity and selectivity. Variation on the piperidinylalkyl spacer (part A) concerned in particular the length of the carbon chain attached to position 4 of the piperidine ring. In vitro

Chart 2. General Formula **4**
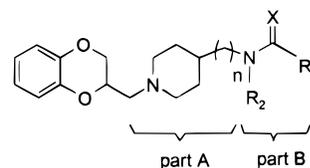
potency at α_2-adrenoceptors proved to be closely related to this moiety. The nature of the modifications on part B appeared to influence the in vivo antagonist properties of these compounds.

Chemistry

The previously described [1-(2,3-dihydrobenzo[1,4]-dioxin-2-ylmethyl)piperidin-4-yl]methylamine **(6)**[13] was synthesized according to the pathway depicted in Scheme 1, by reduction of the corresponding (piperidin-4-yl)-carboxamide **5** with lithium aluminum hydride and treated with phenyl isocyanate or phenyl isothiocyanate to give respectively **7a,b**. 2-(1*H*)-Quinazolidinone **10** was synthesized by a slightly modified literature procedure[14]

Scheme 2. Synthesis of 1-Phenylimidazolin-2-one and 1-Phenyltetrahydropyrimidin-2-one[a]
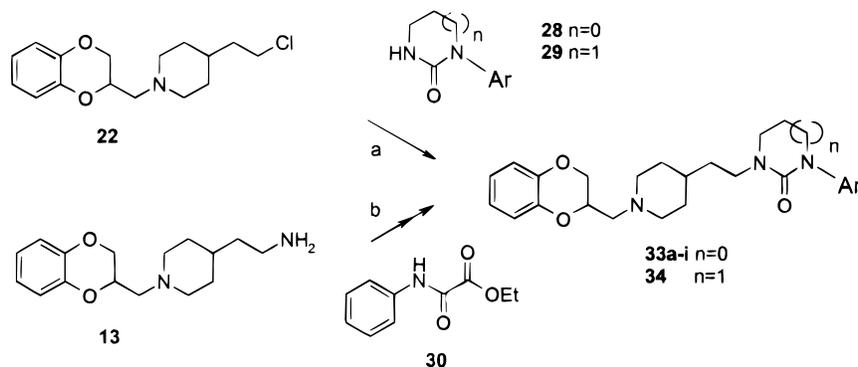
[a] (a) **28** or **29**/NaH/DMA/100 °C; (b) (i) **30**/EtOH/reflux, (ii) LiAlH$_4$/THF/reflux, (iii) Im$_2$CO/MeCN/reflux.

(Scheme 1). The (piperidin-4-yl)methylamine derivative **6** was successively treated by 2-nitrobenzaldehyde and sodium borohydride. The resulting (piperidin-4-yl)-methyl-2-nitrobenzylamine intermediate **8** was subjected to reduction with iron in hydrochloric acid. Cyclization of the resulting (piperidin-4-yl)methyl-2-aminobenzylamine compound **9** with urea at 150 °C yielded 2-(1*H*)-quinazolidinone **10** in a 35% yield. The [1-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]-2-ethylamine **(13)** was obtained as depicted in Scheme 1. Debenzylation of 1-benzyl(piperidin-4-yl)-acetonitrile **(11)** with 1-chloroethyl chloroformate[15] and reaction with 2,3-dihydro-2-tosylmethylbenzo[1,4]dioxin[16] in the presence of sodium hydroxide yielded the (piperidin-4-yl)acetonitrile **12** which reduction with lithium aluminum hydride afforded the (piperidin-4-yl)-2-ethyl-amine intermediate **13** in a 44% overall yield. Reaction of **13** with carboxylic acid chlorides or sulfonyl chlorides in the presence of triethylamine gave amides **14a–f** or sulfonamides **15a,b** (for pattern of substitution see Table 2). Reaction of **13** with phenyl isocyanates, phenyl isothiocyanates, and carbamoyl chlorides in methylene chloride yielded phenylureas **16a–h** or phenylthioureas **17a,b** (Scheme 1; for pattern of substitution see Table 2). The *N*-methyl derivatives **20a,b** were obtained via prior methylation of the (piperidin-4-yl)-2-ethylamine compound **13** in a two-step procedure: reaction of **13** with ethyl chloroformate yielded carbamate **18** which was reduced to *N*-methylamine derivative **19** with lithium aluminum hydride. Ureas **20a,b** were then obtained by action of phenyl isocyanate or *N*-methyl-*N*-phenylcarbamoyl chloride. The [1-(2,3-dihydrobenzo-[1,4]dioxin-2-ylmethyl)piperidin-4-yl]-3-propylamine **(24)** was obtained starting from (piperidin-4-yl)-2-ethanol,[17] which afforded the [1-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl]piperidin-4-yl]-2-ethanol intermediate **(21)** by reaction with 2-bromomethyl-2,3-dihydrobenzo[1,4]-dioxine in a 66% yield. Treatment of this alcohol with thionyl chloride in refluxing methylene chloride gave rise to [1-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)pip-eridin-4-yl]-2-chloroethyl hydrochloride **(22)**. The free base of **22** was reacted with potassium cyanide in dimethyl sulfoxide at 120 °C to produce the (piperidin-4-yl)propionitrile **23** in a 64% yield which was subjected to reduction by lithium aluminum hydride in tetrahydrofuran to obtain the (piperidin-4-yl)-3-propylamine derivative **24** in 96% yield. Reaction of this amine with phenyl isocyanate led to compound **25** (Scheme 1). Carbamate **26** was obtained by reaction of the (piperi-

din-4-yl)-2-ethanol derivative **21** with phenyl isocyanate. The isomeric carbamate derivative **27** was obtained by reaction of the (piperidin-4-yl)-2-ethylamine derivative **13** with phenyl chloroformate (Scheme 1).

Synthesis of the cyclic ureas **33a–i** and **34** was achieved following two different routes (Scheme 2). The first route involved the direct alkylation of the appropriate *N*-phenylimidazolidinone **28** or the *N*-phenyltet-rahydropyrimidinone **29** with the (piperidin-4-yl)-2-chloroethyl derivative **22** to render directly the target molecule. Synthesis of the cyclic ureas **28** and **29,** and their substituted analogues, was achieved by a two-step procedure: reaction of anilines with 2-chloroethyl or 3-chloropropyl isocyanate followed by a cyclization under basic conditions.[18] The second route (Scheme 2) was based on the coupling reaction of an phenyloxalamic acid ester **30** with the (piperidin-4-yl)-2-ethylamine intermediate **13**, followed by a reduction of intermediate **31** with lithium aluminum hydride. Reaction of the resulting diamino compound **32** with carbonyldiimida-zole in refluxing acetonitrile afforded the cyclic ureas **33a–i** and **34**.

Condensation of phthalic anhydride and compound **13** in refluxing acetic acid yielded the phthalimide **35** (Scheme 3). Reduction of **35** with tin in a mixture of hydrochloric and acetic acid gave the isoindolinone **36**. The 3-{2-[1-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)-piperidin-4-yl]ethyl}-3,4-dihydro-1*H*-quinazolin-2-one **(37)** was synthesized in the same way as compound **10** from the (piperidin-4-yl)-2-ethylamine intermediate **13** (Scheme 1). The benzo[*d*][1,3]diazepin-2-one derivative **40** (Scheme 3) was obtained starting from (piperidin-4-yl)-2-ethylamine **13** and the tosylate of 2-nitrophen-ylethanol.[19] The obtained 2-nitrophenyl-2-ethylamine derivative **38** was subjected to reduction by tin chloride in ethanol to afford 2-(2-{2-[1-(2,3-dihydrobenzo[1,4]-dioxin-2-ylmethyl)piperidin-4-yl]-2-ethylamino}ethyl)-phenylamine **(39)**. Cyclization with carbonyldiimidazole yielded the benzo[*d*][1,3]diazepin-2-one derivative **40**. The 3-[1-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)pip-eridin-4-yl]-3,4-dihydro-1*H*-quinazolin-2-one **(41)** (Scheme 1) was synthesized by reaction of the previously de-scribed 3-(piperidin-4-yl)-3,4-dihydro-1*H*-quinazolin-2-one[14] with 2,3-dihydro-2-tosylmethylbenzo[1,4]dioxin.[16]

Results and Discussion

Three major objectives were addressed in the present study. We first focused on the discovery of new com-

Scheme 3. Synthesis of Benzo[*d*][1,3]diazepin-2-one and 2,3-Dihydro-1*H*-isoindole Derivatives[a]
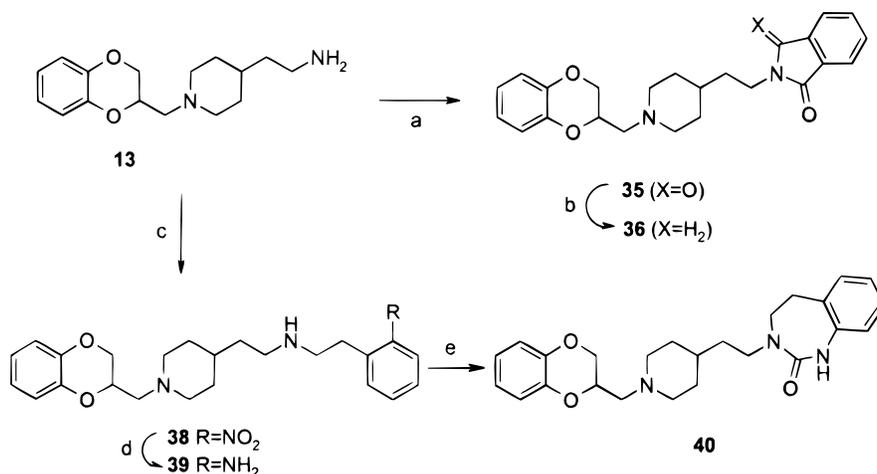
[a] (a) Phthalic anhydride/AcOH/reflux; (b) Sn/HCl/AcOH; (c) 2-(2-nitrophenyl)ethyl 4-toluenesulfonate; (d) SnCl$_2$, 2H$_2$O/EtOH; (e) Im$_2$CO/CH$_3$CN.

Table 1. In Vitro Binding Assays at α$_2$-, α$_1$-, and D$_2$-Receptors

compd (Chart 2)	n	receptor affinity IC$_{50}$ (nM)[a]		
		α$_2$	α$_1$	D$_2$
phenylureas				
7a	1	15	46	750
16a	2	1	40	10
25	3	10	62.5	90
phenylthioureas				
7b	1	13.5	100	750
17a	2	3.4	34	10
quinazolidinones				
41	0	300	30	nd
10	1	25	70	550
37	2	5	18	16

[a] IC$_{50}$ values were determined according to refs 23 and 24 and are the mean values of duplicates of one experiment. Standard deviation between duplicates is less than 10%.

pounds exhibiting high affinity at the α$_2$-adrenoceptor with an IC$_{50}$ in the nanomolar range. The most potent compounds were then tested in vivo for their ability to inhibit the hypothermia in mice induced by the α$_2$-adrenoceptor agonist guanabenz. A complete reversion of the hypothermic effect was considered as a characteristic of highly efficient α$_2$-antagonists, i.e., having little or no intrinsic agonist activity. Finally, some modifications were done on the lead molecule to improve in vitro selectivity versus α$_1$-adrenoceptor and D$_2$-dopaminergic receptors. Starting from the 1-(2,3-dihydro-[1,4]benzodioxin-2-ylmethyl)piperidine skeleton, some modifications at the part A of general formula **4** (Chart 2) were carried out and the influence of the chain length at position 4 was determined with respect to the in vitro binding profile, within the phenylurea (**7a**, **16a** and **25**), thiourea (**7b** and **17a**), and 3,4-dihydro-*1H*-quinazolin-2-one (**10**, **37** and **41**) series. Table 1 shows the α$_2$- and α$_1$-adrenoceptor and D$_2$-dopamine receptor binding affinity values.

A two-carbon atom alkyl chain (*n* = 2) led to an optimum in potency at the α$_2$-adrenoceptor in each series, i.e., compounds **16a**, **17a**, and **37**. To be emphasized is the outstanding potency of the unsubstituted phenylurea derivative **16a**, with an IC$_{50}$ of 1 nM, similar to the order of magnitude of the most potent reference compounds. Binding assays at different human α$_2$-adrenoceptor subtypes were studied on membranes

prepared from C6-glial cells transfected with the cDNA encoding α$_{2A}$-, α$_{2B}$-, or α$_{2C}$-adrenoceptors.[20] No significant subtype selectivity for any of the compounds in these series was revealed (binding affinities being in the nanomolar range; data are available as Supporting Information). The chain length modifications did not consistently alter the α$_1$-adrenoceptor potency. In contrast, high affinity at D$_2$-receptor was shown for compounds **16a**, **17a**, and **37**. Owing to the high potency at α$_2$-sites and despite the low selectivity of **16a** in the binding profile, we fixed the 4-ethylpiperidine framework as the optimum spacer and studied some 1-[(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylamine derivatives. Modifications at part B, shown in the general formula **4** (Chart 2), provide a series of amides, sulfonamides, carbamates, ureas, thioureas, and cyclic ureas. The binding profiles at α$_1$- and α$_2$-adrenoceptors and the D$_2$-receptor for these derivatives and some reference compounds are given in Table 2. As shown, all the amide derivatives **14a**−**f** exhibited high affinities for α$_2$-adrenoceptors, while sulfonamides **15a,b** are weakly potent at α$_2$-adrenoceptor. The potent affinity displayed by phenylurea **16a** at the α$_2$-adrenoceptor led to the synthesis and evaluation of some substituted aromatic ureas **16b**−**d**. The 4-MeO (**16b**) and 4-HO (**16c**) derivatives proved equipotent, while 4-NO$_2$ (**16d**) was 1 order of magnitude less potent. Other ureas **16e**−**h** showed the same potency at the α$_2$-adrenoceptor in the nanomolar range. It was noted that the thiourea **17a** was approximately equipotent, while the benzoylthiourea **17b** was 20-fold less potent than its benzoylurea analogue **16h** at the α$_2$-adrenoceptor and 50-fold less at the D$_2$-receptor. Thus an improved D$_2$/α$_2$ selectivity was not obtained with these amide, urea, and thiourea derivatives. The second main criterion of our selection was the in vivo antagonist efficacy against guanabenz-induced hypothermia in mice. The results of these experiments are given in Table 3. The potency of the studied compounds was characterized by their ED$_{50}$ which represents the dose (mg/kg) producing a significant inhibition in 50% of the animals (temperature > 36 °C). These values were established for both an intraperitoneal (ip) and a per os (po) mode of administration (see Experimental Section). This param-

Table 2. Structures and Binding Assay Results at α_2-, α_1-, and D_2-Receptors of Compounds of General Structures A and B

compd	structure	X	R_1	R_2	R_3	IC$_{50}$ (nM)^a		
						α_2	α_1	D_2
1	yohimbine					67	1580	1125
2	idazoxan					21	1650	>10000
3	R 47243					20	100	50
14a	A	O	Ph			10	27	24
14b	A	O	2-NO$_2$Ph			2	20	25
14c	A	O	2-MeOPh			1.2	20	24
14d	A	O	2-MeOPhCH$_2$			10	70	50
14e	A	O	2-NO$_2$PhCH$_2$			1	11.5	1.8
14f	A	O	Ph$_2$CH			24	170	41
15a	A	SO$_2$	4-CH$_3$Ph			30	30	30
15b	A	SO$_2$	Me			87	135	800
16a	B	O	Ph	H	H	1	40	10
16b	B	O	4-MeOPh	H	H	0.9	56	15
16c	B	O	4-OHPh	H	H	1	15	15
16d	B	O	4-NO$_2$Ph	H	H	12.5	90	11
16e	B	O	*c*-hexyl	H	H	2	42	35
16f	B	O	PhCH$_2$	H	H	3.5	62.5	45
16g	B	O	Ph	H	Me	1.1	42	11.5
16h	B	O	PhCO	H	H	2.3	17	2.6
17a	B	S	Ph	H	H	3.4	34	10
17b	B	S	PhCO	H	H	46	200	120
20a	B	O	Ph	Me	H	4.5	50	36
20b	B	O	Ph	Me	Me	27	40	32
26	OCN carbamate					1.7	34	26
27	NCO carbamate					2.9	60	52
33a	B	O	Ph	CH$_2$−CH$_2$		2	60	4.5
33b	B	O	2,6-Me$_2$Ph	CH$_2$−CH$_2$		1.8	85	80
33c	B	O	2,6-Cl$_2$Ph	CH$_2$−CH$_2$		1.6	50	2.3
33d	B	O	2,6-*i*Pr$_2$Ph	CH$_2$−CH$_2$		36	180	480
33e	B	O	2,6-MeO$_2$Ph	CH$_2$−CH$_2$		3	95	210
33f	B	O	2,6-EtO$_2$Ph	CH$_2$−CH$_2$		4	70	135
33g	B	O	2,4,6-MeO$_3$Ph	CH$_2$−CH$_2$		4.5	200	320
33h	B	O	4-FPh	CH$_2$−CH$_2$		1.5	46	<10
33i	B	O	4-pyrido	CH$_2$−CH$_2$		0.7	14	1.4
34	B	O	Ph	CH$_2$−CH$_2$−CH$_2$		1.8	105	38
35	phthalimide					11	17	10
36	isoindolidinone					1	17.5	3.8
37	quinazolidinone					5	18	16
40	benzodiazepine					4.4	50	28

^{a} IC$_{50}$ values were determined according to refs 23 and 24 and are the mean values of duplicates of one experiment. Standard deviation between duplicates is less than 10%.

eter was used to characterize potent centrally active α_2-antagonists, by determining the active dose range of the compounds as indicated in Table 3, i.e., the range of doses (mg/kg) which produced an inhibition of guanabenz-induced hypothermia in more than 80% of the animals. The range of active doses represents the propensity of the compound to be a centrally active antagonist without any intrinsic activity (agonism). While most of the compounds displayed high potency at the α_2-adrenoceptor in vitro, they antagonized guanabenz-induced hypothermia in vivo to a poor extent. Within the amide series, only **14a** exhibited in vivo antagonist activity over a wide dose range (0.16−2.5 mg/kg). Within the urea series, the phenylurea **16a** showed potent antagonism (ED$_{50}$ = 0.16 mg/kg), but the activity was maintained only at higher doses. In the same way, substitution on the phenyl ring of the urea (**16b,c**) or other ureas (**16e,f**) did not show consistent activity along with increasing doses.

A particular feature was observed with the *N*-methyl derivatives of ureas (**16g** and **20a,b**). Monomethylated
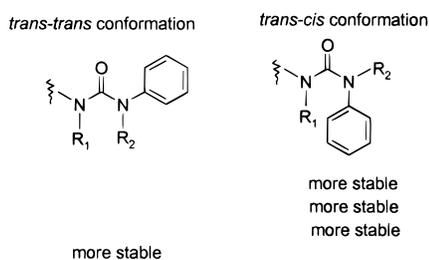
ureas **16g** and **20a** displayed an IC$_{50}$ of 1.1 and 4.5 nM, respectively, at the α_2-adrenoceptor in vitro. Potent central in vivo antagonism was shown irrespective of the route of administration with **20a** (ED$_{50}$ = 0.02 mg/kg ip) and over a wide dose range. In contrast, **16g** was less active (ED$_{50}$ = 0.56 mg/kg ip) and inactive po, which might suggest differential sensitivity to metabolism. Furthermore, a loss of α_2-adrenoceptor affinity was observed with the methylated derivative at both nitrogen atoms (compound **20b**). The hypothesis to explain such a difference in activity was based on conformational studies of phenylurea derivatives.[21] Indeed, the more stable conformer of the nonmethylated phenylurea molecule **16a** is the *trans-cis* conformer described in Chart 3 (the difference of energy between the two conformers has been calculated to be almost 2 kcal/mol). Methylation of the alkyl-linked nitrogen atom (**20a**) shifts the equilibrium toward the *trans-trans* conformation of the urea (calculations gave a difference in energy of 3 kcal/mol between the two conformers). The presence of a methyl group on the aromatic linked nitrogen (**16g**)

Table 3. In Vivo Activities in the Guanabenz-Induced Hypothermia Test in Mice

| compd | D_2/α_2 IC$_{50}$ ratio | in vivo inhib of guanabenz-induced hypothermia ED$_{50}$ (mg/kg)[a] | | range of active doses (mg/kg) | |
		ip	po	ip	po
yohimbine	17	0.56 [0.33−0.96]	1.23 [0.20−7.44]	1	10
idazoxan	79	0.31 [0.16−0.61]	0.89 [0.17−4.80]	0.63−10	10−40
R 47243	2.5	1.30 [0.71−2.37]	1.23 [0.35−4.29]	2.5−10	2.5−10
14a	20	0.11 [0.06−0.18]	0.76 [0.24−2.39]	0.16−2.5	2.5−10
14f	1.7	inactive	inactive		
16a	10	0.16 [0.06−0.40]	1.26 [0.36−4.41]	0.63−2.5	10
16b	17	0.27 [0.12−0.63]	nd	0.63	
16c	15	inactive	inactive		
16e	17.5	0.69 [0.14−3.34]	inactive	2.5	
16f	13	1.78 [0.70−4.50]	nd		
16g	8	0.56 [0.17−1.79]	nd	0.16−2.5	
16h	1	0.10 [0.03−0.34]	0.24 [0.16−0.37]	0.16−10	0.63−10
17a	3	0.02 [0.007−0.05]	nd	0.04−0.16	
17b	2.6	inactive	inactive		
20a	10	0.02 [0.005−0.07]	0.09 [0.04−0.20]	0.16−2.5	0.16−2.5
20b	1.2	0.86 [0.26−2.85]	0.29 [0.07−1.12]	2.5−10	2.5−10
26	15	0.32 [0.16−0.61]	0.34 [0.15−0.78]	0.63−2.5	0.63−10
27	18	inactive	inactive		
33a	2.3	0.02 [0.006−0.07]	0.06 [0.03−0.13]	0.16−2.5	0.16−10
33b	44	0.41 [0.17−0.98]	5.01 [2.66−9.43]	2.5−10	10−40
33c	2	0.10 [0.04−0.25]	0.69 [0.22−2.19]	0.63−10	2.5−40
33e	70	0.29 [0.12−0.73]	5.01 [1.43−17.61]	0.63−10	40
33f	33	0.89 [0.66−4.80]	0.53 [0.15−1.79]	10	2.5−40
33g	71	0.41 [0.17−0.98]	1.07 [0.46−2.47]	2.5−10	2.5−40
33h	7	2.51 [0.74−8.59]	nd	10−40	
33i	2	0.29 [0.12−0.73]	0.76 [0.24−2.39]	0.63−2.5	2.5−10
34	21	0.08 [0.04−0.15]	0.28 [0.11−0.72]	0.16−2.5	0.63−40
36	3.8	0.64 [0.19−2.13]	0.46 [0.18−1.21]	2.5−10	2.5−10
40	6	0.23 [0.08−0.64]	5.09 [0.84−30.71]	0.63−2.5	10

[a] Values in square brackets are 95% confidence limits. nd, value could not be determined.

Chart 3. Conformation of Urea Derivatives

trans-trans conformation   *trans-cis* conformation

16a R$_1$, R$_2$=H   more stable
16g R$_1$=H, R$_2$=Me   more stable
20b R$_1$=Me, R$_2$=Me   more stable
20a R$_1$=Me, R$_2$=H   more stable

or on both nitrogens (**20b**) favored again the *trans-cis* conformation (the difference in energy being 2 and 1 kcal/mol, respectively). Within this series, compound **20a**, bearing a methyl at the alkyl-linked nitrogen, displayed the most potent in vivo activity. This latter compound was the only derivative featuring the more stable *trans-trans* conformer. The *trans-cis* conformation seemed to be unfavorable within this series. Starting from this hypothesis we designed and evaluated some rigid urea analogues bearing *trans-trans* (i.e. imidazolidinones **33** and pyrimidinone **34**) or *trans-cis* blocked conformations (i.e. 3,4-dihydro-*1H*-quinazolin-2-one **37** and benzo[*d*][1,3]diazepin-2-one **40**). All these compounds retained high in vitro binding affinity for α_2-adrenoceptors in the nanomolar range. However, only the imidazolidinones **33a−i** and pyrimidinone **34** potently antagonized the guanabenz-induced hypothermia. Compound **33a** was particularly interesting owing to its wide range of active doses po (0.16−10 mg/kg). Analysis of the in vitro binding profile of the imidazolidinone **33a** showed a good selectivity for α_2- versus α_1-adrenoceptors (ratio α_1/α_2 = 30), but the affinity of this molecule for dopaminergic D$_2$-receptor remained important. This

brought us to our third criterion of selection which was the selectivity versus the D$_2$-receptor.

R 47243 (**1**), the lead structure used in the early investigations, proved to be poorly selective at both α_1-adrenoceptor and D$_2$-receptor sites with respect to the α_2-adrenoceptor. With the imidazolidinone **33a**, a series of compounds substituted at the phenyl ring was evaluated for their affinities at α_1- and D$_2$-receptors. Modification of the torsion angle between the two cyclic systems was thought to be a putative requirement to lose affinity at the D$_2$-receptor. *Ortho-ortho* substituents at the phenyl ring could break thoroughly the planarity with the imidazolidinone moiety (i.e. the rotation energy for the aromatic ring in the 2,6-dimethoxyphenylimidazolidinone has been calculated to be approximately 30 kcal/mol).[21] Interestingly, the 2,6-Me$_2$ (**33b**), 2,6-(*i*-Pr)$_2$ (**33d**), 2,6-(MeO)$_2$ (**33e**), and 2,4,6-(MeO)$_3$ (**33g**) derivatives exhibited a fair α_2- versus D$_2$-receptor selectivity. The $\alpha_2/$D$_2$ ratio reached 70 for compounds **33e**,**g**. However the 2,6-disubstitution pattern proved to be not a sufficient condition to achieve D$_2$−receptor selectivity; indeed, the 2,6-Cl$_2$-substituted derivative **33c** exhibited high affinity at both the α_2-adrenoceptor and D$_2$-receptor. Nevertheless, the in vivo profile of the trimethoxy derivative **33g** was more interesting than that of the dimethoxy analogue **33e** on account of its activity following oral administration. A balance of all the assigned criteria was fulfilled with trimethoxyphenylimidazolidinone derivative **33g**, which displayed high binding affinity at the α_2-adrenoceptor, fair selectivity versus α_1-adrenoceptor and D$_2$-dopaminergic receptor, and potent antagonist property as demonstrated by its efficacy in vivo in the guanabenz-induced hypothermia test in mice.

Conclusion

A series of substituted 1-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl derivatives was synthesized and tested in vitro and in vivo for their α_2-adrenoceptor antagonist properties. Almost all compounds exhibited very high affinity at α_2-adrenoceptors together with potent affinity for the dopaminergic D_2-receptor. Among these derivatives, the imidazolidinones **33a–i** were found to be the more potent compounds in vivo for inhibiting the guanabenz-induced hypothermia in mice. Modulation of the substituents on the phenyl group attached to the imidazolidine ring greatly influenced the affinity for the D_2-receptor.

With the discovery of 2,4,6-trimethoxyphenylimida-zolidinone compound **33g**, we attained three of the main goals of our project: high binding affinity for the α_2-adrenoceptor, potent α_2-antagonist properties evaluated by an efficient in vivo inhibition of guanabenz-induced hypothermia in mice, and fair binding selectivity versus the α_1-adrenoceptor and D_2-dopaminergic receptor. Moreover, compound **33g** displayed a long duration of action (8 h) and good bioavailability, indicated by the favorable ip/po ED_{50} ratio in vivo.

Experimental Section

General Notes. All solvents and reagents used were commercially available in 'pure for synthesis' grade and were used without further purification unless otherwise indicated. The reaction progress was monitored by TLC on silica gel plates 60F-254 (Merck art. 1.05554). Flash chromatography was run on silica gel 60-chromagel, 35–70 μm. Melting points were determined on a Electrothermal IA9300 melting point apparatus and are uncorrected. NMR spectra were recorded on a Brucker DPX400 (^{1}H, 400 MHz) spectrometer in CDCl$_3$ or in DMSO-d_6 with tetramethylsilane as internal standard. Elemental analyses were performed on a Fisons 1108 microanalyzer and were within 0.4% of the theoretical value. Salts were obtained by dissolution of the base in ethanol and addition of 1 mol equiv of the corresponding acid. The resulting salt was filtered and dried under vaccum.

1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidine-4-carboxamide (5). A mixture of isonipecotamide (10.4 g, 81 mmol) and 2,3-dihydro-2-tosylmethylbenzo[1,4]dioxine[16] (26 g, 81 mmol) was heated at 120 °C for 16 h. Cooled to room temperature, the mixture was added to ammonia water and extracted with EtOAc. The organic layer was washed with H$_2$O, brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was recrystallized from hexane to yield 12.38 g of **5** (55%) as white crystals: mp 132–134 °C; ^{1}H NMR (CDCl$_3$) δ 6.80–6.90 (m, 4H), 5.84 (s, 1H), 5.67 (s, 1H), 4.25–4.40 (m, 1H), 4.29 (dd, $J = 11.2$ and 2.1 Hz, 1H), 4.00 (dd, $J = 11.2$ and 6.9 Hz, 1H), 2.95–3.10 (m, 2H), 2.74 (dd, $J = 13.3$ and 5.9 Hz, 1H), 2.64 (dd, $J = 13.4$ and 9.9 Hz, 1H), 2.10–2.35 (m, 3H), 1.65–1.95 (m, 4H).

1-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]methylamine (6). To a mixture of LiAlH$_4$ (3.29 g, 86 mmol) in THF was added dropwise a solution of **5** (12 g, 43 mmol) in THF and then was refluxed for 4 h. The cooled reaction mixture was hydrolyzed with a solution MgSO$_4$/NaOH. After filtration, the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried (Na$_2$SO$_4$) and evaporated to dryness to yield 9.9 g of **6** (88%) as an oil: ^{1}H NMR (CDCl$_3$) δ 6.70–6.90 (m, 4H), 4.24–4.34 (m, 2H), 3.94 dd, $J = 4.1$ and 7.7 Hz, 1H), 2.90–3.04 (m, 2H), 2.64 (dd, $J = 5.6$ and 13.3 Hz, 1H), 2.52 (dd, $J = 6.1$ and 13.3 Hz, 1H), 2.32 (broad s, 2H), 2.10 (m, 2H), 1.71 (m, 2H), 1.50 (m, 2H), 1.15–1.40 (m, 3H).

1-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-ylmethyl]-3-phenylurea (7a). To a mixture of phenyl isocyanate (0.56 mL, 50 mmol) in 10 mL of CH$_2$Cl$_2$ was added

dropwise a solution of **6** (1.3 g, 50 mmol) in 5 mL of CH$_2$Cl$_2$ and was stirred at room temperature for 20 h. The cooled reaction mixture was evaporated and the residue was purified by flash chromatography CH$_2$Cl$_2$/MeOH 95/5) affording 1.35 g of **7a** (71%): ^{1}H NMR (CDCl$_3$) δ 7.31 (m, 4H), 7.09 (m, 1H), 6.96 (s, 1H), 6.84 (m, 4H), 5.26 (m, 1H), 4.26 (m, 2H), 3.96 (dd, $J = 9.7$ and 7.6 Hz, 1H), 3.13 (m, 2H), 2.93 (m, 2H), 2.67 (dd, $J = 13.3$ and 5.9 Hz, 1H), 2.54 (dd, $J = 13.4$ and 6.0 Hz, 1H), 2.06 (m, 2H), 1.67 (m, 2H), 1.47 (m, 1H), 1.29 (m, 2H). **Hydrochloride**: mp 210–212 °C. Anal. (C$_{22}$H$_{27}$N$_3$O$_3$·HCl) C, H, N.

[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-ylmethyl]-2-nitrobenzylamine (8). To a solution containing **6** (0.8 g, 3 mmol) in 15 mL of EtOH was added dropwise a solution of 2-nitrobenzaldehyde (0.47 g, 3 mmol) in 5 mL of EtOH. After stirring for 16 h NaBH$_4$ (0.15 g, 3 mmol) was added and the solution was refluxed for 1.5 h. The solvent was evaporated and the residue diluted in AcOEt. After washing with water, the organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated to dryness. The crude material was purified by flash chromatography (CHCl$_3$/MeOH 95/5). We obtained 0.5 g (50%) of pure **8** as a light yellow oil: ^{1}H NMR (CDCl$_3$) δ 7.93 (d, $J = 7.7$ Hz, 1H), 7.51–7.60 (m, 2H), 7.41 (m, 1H), 6.79–6.90 (m, 4H), 4.24–4.35 (m, 2H), 4.03 (s, 2H), 3.93 (m, 1H), 2.87–3.03 (m, 1H), 2.65 (dd, $J = 13.2$ and 5.6 Hz, 1H), 2.60 (dd, $J = 13.2$ and 5.0 Hz, 1H), 2.50 (d, $J = 6.3$ Hz, 2H), 2.00–2.15 (m, 2H), 1.65–1.80 (m, 2H), 1.45 (m, 1H), 1.20–1.40 (m, 2H).

2-{[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-ylmethyl]aminomethyl}phenylamine (9). 2.2 mL of concentrated HCl were added dropwise (26.4 mmol) to a suspension of **8** (0.6 g, 1.5 mmol) and 0.3 g iron powder (4.5 mmol) in EtOH/H$_2$O (50/50) at reflux. After 1.5 h the mixture was cooled in an ice bath and basified with an ethanolic 15% KOH solution. The solution was filtered and evaporated to dryness. The residue was dissolved in CH$_2$Cl$_2$, washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The crude material was purified by flash column chromatography (CHCl$_3$/MeOH 90/10). We obtained 0.4 g of pure **9** (73%) as an orange oil: ^{1}H NMR (CDCl$_3$) δ 7.06 (m, 2H), 6.87 (m, 4H), 6.68 (m, 2H), 4.32 (m, 2H), 3.97 (dd, $J = 11.6$ and 7.7 Hz, 1H), 2.94 (m, 2H), 2.62 (dd, $J = 13.2$ and 5.6 Hz, 2H), 2.52 (d, $J = 6.2$ Hz, 2H), 2.10 (m, 2H), 1.71 (m, 2H), 1.42 (m, 1H), 1.35 (m, 2H).

3-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-ylmethyl]-3,4-dihydro-1*H*-quinazolin-2-one (10). A mixture of 0.4 g of **9** (1.1 mmol) and 0.07 g of urea (1.1 mmol) was heated at 150 °C during 2 h. The resulting orange gum was purified by flash column chromatography (CHCl$_3$/MeOH 95/5) and crystallized from isopropyl ether/hexane. We obtained 0.1 g of **10** (23%) as beige crystals: mp 185 °C; ^{1}H NMR (CDCl$_3$) δ 7.18 (m, 1H), 7.03 (m, 1H), 6.95 (m, 1H), 6.85 (m, 4H), 6.66 (m, 1H), 4.46 (s, 2H), 4.28 (m, 2H), 3.97 (dd, $J = 11.5$ and 7.5 Hz, 2H), 3.32 (d, $J = 6.9$ Hz, 2H), 2.96 (m, 2H), 2.63 (m, 2H), 2.10 (m, 2H), 1.70 (m, 3H), 1.42 (m, 2H). **10·fumarate**: mp 225–226 °C. Anal. (C$_{23}$H$_{27}$N$_3$O$_3$·C$_4$H$_4$O$_4$) C, H, N.

Compound **37** was synthesized following the same route starting from amine **13**. **Fumarate**: mp 182–184 °C. Anal. (C$_{24}$H$_{29}$N$_3$O$_5$·C$_4$H$_4$O$_4$) C, H, N.

[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]acetonitrile (12). A mixture of 19.3 g (156 mmol) of (1-benzylpiperidin-4-yl)acetonitrile[15] **(11)** and 50 g (156 mmol) of 2,3-dihydro-2-tosylmethylbenzo[1,4]dioxine[16] was heated at 140 °C for 20 h and was treated with Na$_2$CO$_3$/CH$_2$Cl$_2$. The organic layer was washed with H$_2$O, dried (Na$_2$SO$_4$) and evaporated to dryness. The residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 98/2) affording 26.8 g (64%) of **12** as a colorless oil: ^{1}H NMR (CDCl$_3$) δ 7.00–6.78 (m, 4H), 4.34–4.16 (m, 2H), 4.00 (dd, $J = 7.6$ and 11,6 Hz, 1H), 3.12–2.84 (m, 2H), 2.70 (dd, $J = 13.3$ and 5.6 Hz, 1H), 2.56 (dd, $J = 13.4$ and 6.13 Hz, 1H), 2.28 (d, $J = 6.4$ Hz, 2H), 2.14 (m, 2H), 1.80 (m, 2H), 1.68 (m, 1H), 1.40 (m, 2H).

2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-

4-yl]-2-ethylamine (13). To a suspension of LiAlH$_4$ (3.7 g, 97 mmol) in THF was added dropwise a solution of **12** (10.5 g, 39 mmol) in 10 mL of THF. This solution was refluxed for 3 h. The cooled reaction mixture was hydrolyzed with Na$_2$SO$_4$/H$_2$O. After filtration, the organic layer was concentrated under reduced pressure to give 10.2 g (95%) of **13** as an oil: [^1]H NMR (CDCl$_3$) δ 6.81 (m, 4H), 4.26 (m, 2H), 3.94 (dd, J = 11.6 and 7.8 Hz, 1H), 2.94 (m, 2H), 2.73 (m, 2H), 2.61 (dd, J = 13.3 and 7.6 Hz, 1H), 2.53 (dd, J = 13.3 and 6.1 Hz, 1H), 2.36 (s broad, 2H), 2.08 (m, 2H), 1.64 (m, 2H), 1.50–1.07 (m, 5H).

***N*-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}benzamide (14a).** To a solution of **13** (1.9 g, 6.9 mmol), triethylamine (1.75 mL, 1.27 g, 12.6 mmol) in CH$_2$Cl$_2$ was added dropwise a solution of benzoyl chloride (0.76 g, 5.4 mmol). The mixture was stirred at 0 °C for 1 h and washed twice with H$_2$O and brine, dried over Na$_2$SO$_4$ and evaporated to dryness. The residue was recrystallized from Et$_2$O to yield 1.26 g **14a** (61%) of white crystals: mp 106–108 °C; [^1]H NMR (CDCl$_3$) δ 7.78 (m, 2H), 7.46 (m, 3H), 6.86 (m, 4H), 6.13 (m, 1H), 4.41 (m, 1H), 4.31 (dd, J = 11.3 and 2.2 Hz, 1H), 4.00 (dd, J = 11.3 and 7.0 Hz, 1H), 3.50 (m, 2H), 3.06 (m, 2H), 2.67 (m, 2H), 2.19 (m, 2H), 1.76 (m, 2H), 1.57 (m, 2H), 1.39 (m, 3H). Anal. (C$_{23}$H$_{28}$N$_2$O$_3$) C, H, N.

Compounds **14b–f** were synthesized following the same procedure. **14b (base)**: yield 55%; mp 122–124 °C. Anal. (C$_{23}$H$_{27}$N$_3$O$_5$) C, H, N. **14c·oxalate**: yield 47%; mp 175–176 °C. Anal. (C$_{24}$H$_{30}$N$_2$O$_4$·C$_2$H$_2$O$_4$) C, H, N. **14d·oxalate**: yield 60%; mp 146 °C. Anal. (C$_{25}$H$_{32}$N$_2$O$_4$·C$_2$H$_2$O$_4$) C, H, N. **14e (base)**: yield 39%; mp 135–136 °C. Anal. (C$_{24}$H$_{29}$N$_2$O$_5$) C, H, N. **14f·oxalate**: yield 57%; mp 142 °C. Anal. (C$_{30}$H$_{34}$N$_2$O$_3$·C$_2$H$_2$O$_4$) C, H, N.

***N*-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}toluene-4-sulfonamide (15a).** To a solution of **13** (1 g, 3.6 mmol) and 1.26 mL of Et$_3$N (0.9 g, 9 mmol) in 100 mL of CH$_2$Cl$_2$, cooled at 0 °C in an ice bath, was added dropwise a solution of *p*-toluenesulfonyl chloride (0.7 g, 3.7 mmol) in 10 mL of CH$_2$Cl$_2$. The solution was stirred for 1 h and then washed successively with brine and water. The organic layer was dried over Na$_2$SO$_4$ and evaporated to dryness. Purification by flash chromatography (CHCl$_3$/MeOH 95/5) yielded 1.05 g of pure **15a** (68%) as a colorless oil which crystallized from isopropyl ether: mp 94–95 °C. Anal. (C$_{23}$H$_{30}$N$_2$O$_4$S) C, H, N.

1-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-3-phenylurea (16a). To a mixture of phenyl isocyanate (0.65 g, 5.4 mmol) in CH$_2$Cl$_2$ was added dropwise a solution of **13** (1.5 g, 5.4 mmol) in CH$_2$Cl$_2$ and was stirred at room temperature for 1 h. The cooled reaction mixture was evaporated to dryness. The residue was successively purified by flash column chromatography (EtOAc/MeOH 95/5) and recrystallized from isopropyl ether to yield 1.13 g **16a** (53%) as white crystals: mp 112–114 °C; [^1]H NMR (CDCl$_3$) δ 7.29 (m, 4H), 7.08 (m, 1H), 6.87 (m, 5H), 5.04 (m, 1H), 4.30 (m, 2H), 3.96 (dd, J = 11.6 and 7.6 Hz, 1H), 3.25 (m, 2H), 2.94 (m, 2H), 2.62 (dd, J = 13.1 and 5.7 Hz, 1H), 2.60 (dd, J = 13.4 and 5.9 Hz, 1H), 2.50 (m, 2H), 1.64 (m, 2H), 1.50–1.08 (m, 5H). **Hemifumarate**: mp 186–187 °C. Anal. (C$_{23}$H$_{29}$N$_3$O$_3$·C$_2$H$_2$O$_4$) C, H, N.

Compounds **16b–f,h** were synthesized following the same procedure. **16b·oxalate**: yield 60%; mp 176 °C. Anal. (C$_{24}$H$_{31}$N$_3$O$_4$·C$_2$H$_2$O$_4$) C, H, N. **16c (base)**: yield 47%; mp 98 °C. Anal. (C$_{23}$H$_{29}$N$_3$O$_4$) C, H, N. **16d·oxalate**: yield 50%; mp 241–242 °C. Anal. (C$_{23}$H$_{28}$N$_4$O$_5$·C$_2$H$_2$O$_4$) C, H, N. **16e·oxalate**: yield 52%; mp 177–178 °C. Anal. (C$_{24}$H$_{35}$N$_3$O$_3$·C$_2$H$_2$O$_4$) C, H, N. **16f·oxalate**: yield 39%; mp 200 °C. Anal. (C$_{24}$H$_{31}$N$_3$O$_3$·C$_2$H$_2$O$_4$) C, H, N. **16h·oxalate**: yield 43%; mp 199–200 °C. Anal. (C$_{24}$H$_{29}$N$_3$O$_4$·C$_2$H$_2$O$_4$) C, H, N.

3-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-1-methyl-1-phenylurea (16g). To a solution of *N*-methyl-*N*-phenylcarbamoyl chloride (0.61 g, 3.6 mmol) in CH$_2$Cl$_2$ at 0 °C were added dropwise **13** (1 g, 3.6 mmol) and triethylamine (1.26 mL, 0.9 g, 9.1 mmol). The mixture was stirred at room temperature for 1 h and washed with H$_2$O, brine, dried over Na$_2$SO$_4$, and evaporated to dryness.

The residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH, 95/5) to yield 1.15 g of **16g** (76%): [^1]H NMR (CDCl$_3$) δ 7.40 (dd, J = 13.0 and 6.9 Hz, 2H), 7.24 (m,3H), 6.75–6.90 (m, 4H), 4.25–4.35 (m, 2H), 3.94 (dd, J = 11.6 and 7.7 Hz, 1H), 3.26 (s, 3H), 3.17 (m, 2H), 2.80–3.05 (m, 2H), 2.61 (dd, J = 13.2 and 5.6 Hz, 1H), 2.53 (dd, J = 13.3 and 6.1 Hz, 1H), 2.03 (m, 2H), 1.61 (m, 2H), 1.44–1.03 (m, broad, 5H). **Oxalate**: mp 105–106 °C. Anal. (C$_{24}$H$_{31}$N$_3$O$_3$·C$_2$H$_4$O$_4$) C, H, N.

1-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-3-phenylthiourea (17a). To a solution of phenyl isothiocyanate (0.75 g, 5 mmol) in CH$_2$Cl$_2$ was added dropwise **13** (1.5 g, 5 mmol). This mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/MeOH, 95/5) to yield 1.3 g of **17a** (65%) as white crystals: mp 145–146 °C; [^1]H NMR (CDCl$_3$) δ 7.81 (s, 1H), 7.45 (m, 2H), 7.32 (m, 1H), 7.19 (m, 2H), 6.83 (m, 4H), 5.96 (m, 1H), 4.30 (m, 2H), 3.96 (dd, J = 11.6 and 7.5 Hz, 1H), 3.64 (m, 2H), 2.98 (m, 2H), 2.64 (dd, J = 13.2 and 5.8 Hz, 1H), 2.55 (dd, J = 13.3 and 5.8 Hz, 1H), 2.08 (m, 2H), 1.68 (m, 2H), 1.50 (m,), 1.30 (m, 3H). **Hemifumarate**: mp 198–200 °C. Anal. (C$_{23}$H$_{29}$N$_3$O$_2$S·C$_2$H$_2$O$_2$) C, H, N.

Compound **17b** was synthesized following the same procedure. **Hydrochloride**: yield 61%; mp 162 °C. Anal. (C$_{24}$H$_{29}$N$_3$O$_3$S·HCl) C, H, N.

2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylcarbamic Acid Ethyl Ester (18). At 0 °C, to a solution of **13** (1.4 g, 5 mmol), triethylamine (0.8 mL, 0.6 g, 5.7 mmol) in 15 mL of THF was added dropwise a solution of ethyl chloroformate (0.55 mL, 0.62 g, 5.7 mmol). The mixture was stirred at room temperature for 30 min and was then refluxed for 4 h. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in CH$_2$Cl$_2$, and washed twice with H$_2$O. The organic layer was dried, filtered and evaporated to dryness. The residue was purified by flash column chromatography (EtOAc/MeOH, 95/5) to yield 0.9 g (52%) of **18** as a colorless oil: [^1]H NMR (CDCl$_3$) δ 6.87 (m, 4H), 4.63 (s large, 1H), 4.34 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.00 (dd, J = 11.5 and 7.4 Hz, 1H), 3.24 (m, 2H), 3.00 (m, 2H), 2.69 (dd, J = 13.2 and 5.7 Hz, 1H), 2.56 (dd, J = 13.4 and 6.2 Hz, 1H), 2.13 (m, 2H), 1.70 (m, 2H), 1.56–1.09 (m broad, 8H).

2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylmethylamine (19). Under N$_2$, to a suspension of LiAlH$_4$ (0.5 g, 13 mmol) in 10 mL of THF, was added dropwise a solution of **18** (0.9 g, 2.6 mmol) in 5 mL of THF and was then refluxed for 2.5 h. The cooled reaction mixture was hydrolyzed with 4 N MeOH/NaOH, filtered and extracted twice with EtOAc. The organic layer was washed with brine, dried, filtered and concentrated under reduced pressure to yield 0.5 g of **19** (66%) as a pale yellow oil: [^1]H NMR (CDCl$_3$) δ 6.75–6.85 (m,4H), 4.25–4.35 (m, 2H), 3.96 (dd, J = 11.6 and 7.7 Hz, 1H), 2.80–3.05 (m, 2H), 2.50–2.70 (m, 4H), 2.00–2.20 (m, 2H), 1.80 (s broad, 1H), 1.67 (m, 2H), 1.53–1.08 (m broad, 5H).

1-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-1-methyl-3-phenylurea (20a). To a solution of phenyl isocyanate (0.26 mL, 0.28 g, 2.4 mmol) in 10 mL of CH$_2$Cl$_2$ was added dropwise a solution of **19** (0.7 g, 2.4 mmol) in 10 mL of CH$_2$Cl$_2$. The mixture was stirred at room temperature for 1.5 h and evaporated to dryness. The residue was successively purified by flash column chromatography (EtOAc) and recrystallized from EtOAc/isopropyl ether to yield 0.25 g of **20a** (25%) as white crystals: mp 132–133 °C; [^1]H NMR (CDCl$_3$) δ 7.25–7.40 (m, 4H), 7.04 (tt, J = 7.1 and 1.4 Hz, 1H), 6.80–6.95 (m, 4H), 6.27 (s, 1H), 4.25–4.35 (m, 2H), 3.98 (dd, J = 11.6 and 7.7 Hz, 1H), 3.40 (dd, J = 7.7 and 7.5 Hz, 2H), 3.02 (s, 3H), 2.92 (m, 2H), 2.67 (dd, J = 13.2 and 5.6 Hz, 1H), 2.55 (dd, J = 13.3 and 6.1 Hz, 1H), 2.00–2.20 (m, 2H), 1.60–1.80 (m, 2H), 1.56 (m, 2H), 1.20–1.40 (m, 3H). **Fumarate**: mp 168–170 °C. Anal. (C$_{24}$H$_{31}$N$_3$O$_3$·C$_2$H$_2$O$_4$) C, H, N.

1-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-1,3-dimethyl-3-phenylurea (20b). To a solution of **19** (0.5 g, 1.7 mmol), triethylamine (0.25 mL, 0.18 g, 1.8 mmol) in 10 mL of CH$_2$Cl$_2$ was added dropwise a solution

of *N*-phenyl-*N*-methylcarbamoyl chloride (0.3 g, 1.8 mmol) in 10 mL of CH_2Cl_2 and was then stirred at room temperature for 18 h. The mixture was poured into H_2O, and extracted twice with CH_2Cl_2. The organic layer was washed with H_2O, dried, filtered and evaporated to dryness. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95/5) to yield 0.65 g of **20b** (90%) as a colorless oil: ^1H NMR (CDCl$_3$) δ 7.34 (dd, J = 13.7 and 7.4 Hz, 2H), 7.08 (m, 3H), 6.84 (m,4H), 4.31 (m, 2H), 3.98 (dd, J = 11.6 and 7.7 Hz, 1H), 3.10–3.30 (m, 3H), 2.80–3.05 (m, 2H), 2.50–2.70 (m, 3H), 1.90–2.20 (m, 2H), 1.64 (m, 2H), 1.50–1.04 (m broad, 5H). **Oxalate**: mp 176–178 °C. Anal. ($C_{25}H_{33}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]-2-ethanol (21). To a solution containing (piperidin-4-yl)-2-ethanol (4.1 g, 32 mmol), K_2CO_3 (4.15 g, 30 mmol), KI (5 g, 30 mmol) in 40 mL of CH_3CN was added dropwise a solution of 2-bromomethyl-2,3-dihydrobenzo[1,4]dioxine (6.9 g, 30 mmol) in 15 mL of CH_3CN. The mixture was refluxed for 3 h. The cooled reaction mixture was concentrated under reduced pressure. The residue was poured into water, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, filtered and evaporated to dryness. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 95/5) affording 5.5 g of **21** (66%) as a colorless oil: ^1H NMR (CDCl$_3$) δ 6.80–6.90 (m, 4H), 4.25–4.38 (m, 2H), 3.98 (dd, J = 11.5 and 7.5 Hz, 1H), 3.66–3.75 (m, 2H), 3.10–2.80 (m, 2H), 2.66 (dd, J = 13.5 and 5.5 Hz, 1H), 2.55 (dd, J = 13.1 and 5.9 Hz, 1H), 2.24–1.95 (m, 3H), 1.70 (m, 2H), 1.60–1.16 (m, 5H).

4-(2-Chloroethyl)-1-(2,3-dihydrobenzo[1,4]dioxin-2-yl-methyl)piperidine Hydrochloride (22). To a solution of **21** (10.5 g, 38 mmol) in 50 mL of CH_2Cl_2 was added dropwise 7 mL of $SOCl_2$ (11.4 g, 96 mmol). The mixture was refluxed for 4 h. The cooled reaction mixture was concentrated under reduced pressure. The residue was crystallized in ether to yield 10.5 g of **22** (93%): mp 174–176 °C; ^1H NMR (DMSO-d_6) δ 6.80 (m, 4H), 4.25–4.35 (m, 2H), 3.92 (dd, J = 11.7 and 7.4 Hz, 1H), 3.66 (t, J = 6.7 Hz, 2H), 2.80–3.00 (m, 2H), 2.52 (d, J = 5.8 Hz, 2H), 1.90–2.10 (m, 2H), 1.55–1.70 (m, 4H), 1.30–1.50 (m, 1H), 1.05–1.28 (m, 2H).

3-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]propionitrile (23). The hydrochloride salt **22** was quantitatively converted to its base with 1 N NaOH/CH_2Cl_2. To a solution of this base in 100 mL of DMSO were added KCN (1.3 g, 20 mmol) and KI (0.1 g, 0.6 mmol). The reaction mixture was heated at 120 °C for 6 h. The cooled solution was poured into 60 mL of H_2O, and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 95/5) to yield 1.8 g of **23** (64%) as an oil: ^1H NMR (CDCl$_3$) δ 6.80–6.90 (m, 4H), 4.25–4.35 (m, 2H), 4.00 (dd, J = 11.9 and 7.9 Hz, 1H), 2.87–3.08 (m, 2H), 2.68 (dd, J = 13.1 and 5.5 Hz, 1H), 2.56 (dd, J = 13.1 and 5.9 Hz, 2H), 2.47 (t, J = 7.4 Hz, 2H), 2.01–2.22 (m, 2H), 1.55–1.77 (m, 4H), 1.52–1.17 (m, 3H).

3-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]propylamine (24). To a suspension of LiAlH$_4$ (0.5 g, 12.6 mmol) in 20 mL of THF was added dropwise a solution of **23** (1.8 g, 6.3 mmol) in 10 mL of THF and was then refluxed for 4 h. The cooled reaction mixture was hydrolyzed with 2 N NaOH/EtOAc. The organic layer was dried, filtered and concentrated under reduced pressure to yield 1.75 g of crude **24** (96%): ^1H NMR (CDCl$_3$) δ 6.83–6.87 (m, 4H), 4.24–4.36 (m, 2H), 3.98 (dd, J = 12.0 and 7.9 Hz, 1H), 2.83–3.05 (m, 2H), 2.49–2.73 (m, 4H), 2.15 (s broad, 2H), 2.08 (m, 2H), 1.61–1.75 (m, 2H), 1.55 (m, 1H), 1.18–1.34 (m, 6H).

1-{3-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)pip-eridin-4-yl]propyl}-3-phenylurea (25). A solution of 1.7 g (6 mmol) of **24** in 5 mL of CH_2Cl_2 was added to a solution of phenyl isocyanate (0.65 mL, 0.71 g, 6 mmol) in 10 mL of CH_2-Cl_2. The solution was stirred at room temperature for 18 h and then evaporated to dryness. The residue was dissolved in HCl (2 N) and washed with EtOAc. The aqueous layer was basified with 1 N NaOH and extracted twice with CH_2Cl_2. The organic layer was washed with brine, dried, filtered and

evaporated to dryness. The residue was purified successively by flash column chromatography (EtOAc/MeOH, 95/5) and recrystallized from isopropyl ether/hexane to yield 0.55 g of **25** (22%) as white crystals: mp 126–127 °C; ^1H NMR (CDCl$_3$) δ 7.25–7.35 (m, 4H), 7.00–7.09 (m, 2H), 6.82–6.92 (m, 4H), 5.22 (m, 1H), 4.30 (m, 2H), 3.97 (dd, J = 11.5 and 7.5 Hz, 1H), 3.20 (m, 2H), 2.82–3.05 (m, 2H), 2.67 (dd, J = 13.1 and 5.2 Hz, 1H), 2.52 (dd,, J = 13.1 and 6.3 Hz, 1H), 21.96–2.18 (m, 2H), 1.62 (m, 2H), 1.50 (m, 2H), 1.40–1.04 (m large, 5H). **Oxalate**: mp 162–163 °C. Anal. ($C_{24}H_{31}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylcarbamic Acid Phenyl Ester (27). To a solution of **13** (2.76 g, 10 mmol), triethylamine (1.5 mL, 1.09 g, 11 mmol) in 25 mL of THF was added dropwise at 0 °C a solution of phenyl chloroformate (1.56 g, 10 mmol) in 5 mL of THF. The mixture was stirred at room temperature for 52 h and evaporated to dryness. The residue was dissolved in CH_2Cl_2, washed twice with H_2O, dried, filtered and evaporated to dryness. The residue was successively purified by flash column chromatography (CH_2Cl_2/MeOH 95/5) and recrystallized from isopropyl ether to yield 1.40 g of **27** (35%) as white crystals: mp 108–110 °C; ^1H NMR (CDCl$_3$) δ 7.35–7.42 (m, 2H), 7.18–7.25 (m, 1H), 7.10–7.17 (m, 2H), 6.81–6.93 (m, 4H), 5.03 (m, 1H), 4.25–4.40 (m, 2H), 4.00 (dd, J = 11.5 and 7.5 Hz, 1H), 3.32 (m, 2H), 2.85–3.10 (m, 2H), 2.67 (dd, J = 13.5 and 5.9 Hz, 1H), 2.58 (dd, J = 13.5 and 5.9 Hz, 1H), 2.02–2.25 (m, 2H), 1.73 (m, 2H), 1.45–1.61 (m, 2H), 1.25–1.45 (m, 3H). Anal. ($C_{23}H_{28}N_2O_4$) C, H, N.

Compound **26** was synthesized following the same procedure starting from **21** and phenyl isocyanate. **Oxalate**: yield 40%; mp 118–120 °C. Anal. ($C_{23}H_{28}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

1-(2,4,6-Trimethoxyphenyl)imidazolidin-2-one (28g). To a solution of 2,4,6-trimethoxyaniline (3 g, 16 mmol) in THF was added 2-chloroethyl isocyanate (1.5 mL, 1.8 g, 17 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. This mixture was evaporated to dryness, filtered through a pad of silica gel (CH_2Cl_2/MeOH 95/5) and concentrated under reduced pressure. The residue was recrystallized from Et$_2$O to yield 4 g of 1-(2′,4′,6′-trimethoxyphenyl)-3-(2′-chloroethyl)-urea (84%): ^1H NMR (CDCl$_3$) δ 6.16 (s, 2H), 3.83 (m, 9H), 3.70–3.44 (m broad, 4H). To a suspension of NaH (0.5 g, 21 mmol) in THF under N_2 was added a solution of the above compound (3 g, 10 mmol) in THF. The mixture was stirred at room temperature for 1 h and refluxed for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was poured into water, and extracted with CH_2Cl_2. The organic layer was dried, filtered and evaporated. The residue was recrystallized from isopropyl ether to yield 1.5 g of **28g** (58%) as pink crystals: mp 238 °C; ^1H NMR (CDCl$_3$) δ 6.08 (s, 2H), 3.74 (s, 6H), 3.73 (s, 3H), 3.70–3.40 (m broad, 4H).

Compounds **28b–f,h,i** were synthesized following the same procedure starting respectively from 2,6-dimethylaniline, 2,6-dichloroaniline, 2,6-diisopropylaniline, 2,6-dimethoxyaniline, 2,6-diethoxyaniline,[22] 4-fluoroaniline and 4-aminopyridine. **28b**: yield 75%; mp 172 °C. **28c**: yield 80%; mp 220 °C. **28d**: yield 75%; mp 208 °C. **28e**: yield 70%; mp 218 °C. **28f**: yield 70%; mp 149 °C. **28h**: yield 80%; mp 150 °C. **28i**: yield 40%; oil.

1-Phenyltetrahydropyrimidin-2-one (29). To a solution of aniline (3 g, 32.2 mmol) in THF was quickly added 3-chloropropyl isocyanate (3.3 mL, 3.8 g, 32.2 mmol). The mixture was stirred at room temperature for 3 h and evaporated to dryness. The residue was recrystallized with ether/isopropyl ether (1/1) to yield 6.2 g of 1-phenyl-3-(3-chloropropyl)-urea (89%) as white crystals: mp 130 °C; ^1H NMR (CDCl$_3$) δ 7.76 (s, 1H), 6.96 (d, J = 7.5 Hz, 2H), 6.81 (dd, J = 8.3 and 7.4 Hz, 2H), 6.48 (t, J = 7.3 Hz, 1H), 5.72 (s broad, 1H), 3.20 (t, J = 6.5 Hz, 2H), 2.99 (m,2H), 1.55 (m, 2H). To a suspension of NaH (1.5 g, 62.5 mmol) in THF was added a solution of the above compound (6 g, 28.2 mmol) in THF and was then stirred at room temperature for 3 h. The mixture was poured into H_2O and the THF was evaporated. The residue was dissolved in CH_2Cl_2, washed twice with H_2O, once with brine, dried over

Na$_2$SO$_4$, filtered and evaporated to dryness. The residue was recrystallized from isopropyl ether to yield 4.2 g of **29** (85%) as white crystals: ^{1}H NMR (CDCl$_3$) δ 7.22–7.39 (m, 4H), 7.15 (m, 1H), 5.90 (s, 1H), 3.62 (dd, J = 5.8 and 5.6 Hz, 2H), 3.33 (ddd, J = 8.1, 5.9 and 2.4 Hz, 2H), 2.03 (m, 2H).

N-Phenyloxalamic Acid Ethyl Ester (30). To a solution of diethyl oxalate (25.7 g, 175.8 mmol) in CHCl$_3$ was added slowly a solution of aniline (16.4 g, 176.1 mmol) in CHCl$_3$. The mixture was refluxed for 24 h and evaporated to dryness. The residue was purified successively by recrystallization from EtOH and flash column chromatography (hexane/EtOAc 90/10) to yield 13.6 g of **30** (40%): ^{1}H NMR (CDCl$_3$) δ 8.92 (s broad, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.37 (dd, J = 8.2 and 7.4 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H).

N-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-N-phenyloxalamide (31). To a solution of **13** (1.8 g, 6.5 mmol) in 30 mL of EtOH was added **30** (1.15 g, 5.9 mmol). The reaction mixture was refluxed for 3 h, cooled, diluted with EtOH and filtered. The filtered crystals were washed once with EtOH and twice with isopropyl ether. After drying 1.2 g of **31** (48%) was obtained as white crystals: ^{1}H NMR (CDCl$_3$) δ 9.28 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.57 (s, 1H), 7.40 (m,2H), 7.21 (m, 1H), 6.89 (m, 4H), 4.15 (m, 2H), 4.00 (m, 1H), 3.42 (dd, J = 13.3 and 6.3 Hz, 2H), 3.00 (m, 2H), 2.62 (m, 2H), 2.13 (m, 2H), 1.94–1.13 (m broad, 7H).

N-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-N-phenylethane-1,2-diamine (32). To a suspension of LiAlH$_4$ (0.9 g, 22.4 mmol) in 30 mL of THF was added **31** (1.2 g, 2.8 mmol) and the slurry was refluxed for 14 h under N$_2$. The cooled reaction mixture was hydrolyzed with Na$_2$SO$_4$/H$_2$O, filtered and washed with THF. The organic layer was evaporated to dryness. The residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 95/5) to yield 0.5 g of **32** (45.5%) as an oil: ^{1}H NMR (CDCl$_3$) δ 7.17 (dd, J = 8.4 and 7.3 Hz, 2H), 6.86 (m, 4H), 6.71 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 4.20 (m, 2H), 3.98 (dd, J = 11.7 and 7.7 Hz, 1H), 3.22 (dd, J = 6.1 and 5.4 Hz, 2H), 3.00 (m, 2H), 2.87 (dd, J = 6.1 and 5.4 Hz, 2H), 2.73–2.45 (m, 4H), 2.08 (m, 2H), 1.67 (m, 2H), 1.64–1.15 (m, 5H).

1-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-3-phenylimidazolidin-2-one (33a). To a solution of **32** (0.5 g, 1.3 mmol) in 20 mL of CH$_3$CN was added carbonyldiimidazole (0.25 g, 1.3 mmol) and was refluxed for 3 h. The cooled reaction mixture was evaporated to dryness. The residue was purified successively by recrystallization from EtOH/isopropyl ether and flash chromatography (EtOAc/MeOH, 90/10) to yield 0.1 g of **33a** (18.8%) of white crystals: ^{1}H NMR (CDCl$_3$) δ 7.56 (d, J = 6.6 Hz, 2H), 7.31 (dd, J = 8.6 and 7.4 Hz, 2H), 7.04 (t, J = 7.3 Hz, 1H), 6.80–6.95 (m, 4H), 4.25–4.35 (m, 2H), 4.00 (dd, J = 11.6 and 7.7 Hz, 1H), 3.83 (m, 2H), 3.48 (m, 2H), 3.33 (t, J = 7.5 Hz, 2H), 2.80–3.05 (m, 2H), 2.67 (dd, J = 13.2 and 5.4 Hz, 1H), 2.54 (dd, J = 13.3 and 6.2 Hz, 1H), 2.00–2.20 (m, 2H), 1.76 (m, 2H), 1.50 (m, 2H), 1.20–1.40 (m, 3H). **Fumarate**: mp 155–156 °C. Anal. (C$_{25}$H$_{31}$N$_3$O$_3$·C$_4$H$_4$O$_4$) C, H, N.

1-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-3-(2,4,6-trimethoxyphenyl)imidazolidin-2-one (33g). To a suspension of NaH (0.1 g, 4 mmol) in DMA was added dropwise a solution of **28g** (0.5 g, 2 mmol) in DMA. The mixture was stirred at room temperature for 30 min. To this mixture was added dropwise a solution of **22** (0.5 g, 2 mmol). The mixture was heated at 100 °C for 4 h. The cooled reaction mixture was washed with water, and extracted twice with EtOAc. The organic layer was dried, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 90/10) to yield 0.25 g of **33g** (25%) as white crystals: mp 110–112 °C; ^{1}H NMR (CDCl$_3$) δ 6.76–6.89 (m, 4H), 6.10 (s, 2H), 4.25–4.35 (m, 2H), 3.94 (dd, J = 11.5 and 7.6 Hz, 1H), 3.76 (m, 9H), 3.60–3.44 (m broad, 4H), 3.25 (m, 2H), 3.06–2.80 (m broad, 2H), 2.64 (dd, J = 13.2 and 5.7 Hz, 1H), 2.55 (dd, J = 13.3 and 6.0 Hz, 1H), 1.98–2.17 (m, 2H), 1.74 (m, 2H), 1.49 (m, 2H), 1.30 (m, 3H). Anal. (C$_{28}$H$_{37}$N$_3$O$_6$) C, H, N.

Compounds **33b–f,h,i** were synthesized following the same procedure. **33b·oxalate**: yield 31%; mp 141–142 °C. Anal. (C$_{27}$H$_{35}$N$_3$O$_3$·C$_2$H$_2$O$_4$·0.5 H$_2$O) C, H, N. **33c·hydrochloride**: yield 28%; mp 216–218 °C. Anal. (C$_{25}$H$_{29}$N$_3$O$_3$·HCl) C, H, N. **33d (base)**: yield 43%; mp 138–140 °C. Anal. (C$_{31}$H$_{43}$N$_3$O$_3$) C, H, N. **33e (base)**: yield 20%; mp 108–109 °C. Anal. (C$_{27}$H$_{35}$N$_3$O$_5$) C, H, N. **33f (base)**: yield 28%; mp 95–96 °C. Anal. (C$_{29}$H$_{39}$N$_3$O$_5$) C, H, N. **33h (base)**: yield 25%; mp 148–150 °C. Anal. (C$_{25}$H$_{30}$FN$_3$O$_3$) C, H, N. **33i·hemioxalate**: yield 22%; mp 198–200 °C. Anal. (C$_{24}$H$_{30}$N$_3$O$_3$·0.5C$_2$H$_2$O$_4$·H$_2$O) C, H, N.

1-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-3-phenyltetrahydropyrimidin-2-one (34). To a suspension of NaH (0.18 g, 7.5 mmol) in DMA was added a solution of **29** (1 g, 5.7 mmol). To this mixture was added dropwise a solution of **22** (0.7 g, 2.7 mmol) and then it was heated at 100 °C for 4 h. The cooled slurry was poured into H$_2$O and extracted with EtOAc. The organic layer was washed with H$_2$O, brine, dried over Na$_2$SO$_4$ and evaporated to dryness. The residue was recrystallized from isopropyl ether to yield 0.7 g of **34** (43%) as white crystals: mp 130 °C; ^{1}H NMR (CDCl$_3$) δ 7.20–7.38 (m, 4H), 7.13 (m, 1H), 6.75–6.95 (m, 4H), 4.20–4.35 (m, 2H), 3.96 (dd, J = 11.5 and 7.7 Hz, 1H), 3.66 (dd, J = 5.7 and 5.5 Hz), 3.30–3.50 (m, 4H), 2.80–3.05 (m, 2H), 2.65 (dd, J = 13.2 and 5.6 Hz, 1H), 2.52 (dd, J = 13.3 and 6.1 Hz, 1H), 1.95–2.20 (m, 2H), 1.65–1.85 (m, 2H), 1.52 (m, 2H), 1.18–1.38 (m, 3H). Anal. (C$_{26}$H$_{33}$N$_3$O$_3$) C, H, N.

2-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}isoindole-1,3-dione (35). To a solution of **13** (2.45 g, 8.8 mmol) in 15 mL of AcOH was added phthalic anhydride (1.35 g, 8.8 mmol). The mixture was refluxed for 5 h. The cooled reaction mixture was evaporated to dryness. The residue was taken up in Na$_2$CO$_3$ 10%, and extracted twice with CH$_2$Cl$_2$. The organic layer was washed with brine, dried, filtered and evaporated to dryness. The residue was purified successively by flash column chromatography (CH$_2$Cl$_2$/MeOH 95/5) and recrystallization with EtOH to yield 0.7 g **35** (20%) as white crystals: mp 120 °C; ^{1}H NMR (CDCl$_3$) δ 7.84 (dd, J = 5.7 and 3.1 Hz, 2H), 7.73 (dd, J = 5.6 and 3.1 Hz, 2H), 4.25–4.35 (m, 2H), 3.96 (dd, J = 11.6 and 7.7 Hz, 1H), 3.70 (m, 2H), 2.90–3.05 (m, 2H), 2.64 (dd, J = 13.3 and 5.7 Hz, 1H), 2.54 (dd, J = 13.4 and 6.1 Hz, 1H), 2.09 (m, 2H), 1.79 (m, 2H), 1.61 (m, 2H), 1.25–1.35 (m, 3H). **Hydrochloride**: mp 185–186 °C. Anal. (C$_{24}$H$_{26}$N$_2$O$_4$·HCl) C, H, N.

2-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-2,3-dihydroisoindol-1-one (36). To a solution of **35** (1.35 g, 3.3 mmol) in 20 mL of AcOH was added tin powder (0.95 g, 8 mmol). To this mixture was added dropwise concentrated HCl (2 mL, 22 mmol) and it was then heated at 120 °C for 20 h. The cooled reaction mixture was evaporated to dryness. The residue was poured into 1 N HCl. After neutralization with 1 N NaOH, the aqueous layer was extracted twice with CH$_2$Cl$_2$. The organic layer was washed with brine, 2 N NaOH, H$_2$O, dried, filtered and evaporated to dryness. The residue was successively purified by flash column chromatography (EtOAc/MeOH, 95/5) and recrystallized from isopropyl ether/hexane to yield 0.5 g of **36** (42.5%) as white crystals: mp 119–120 °C; ^{1}H NMR (CDCl$_3$) δ 7.85 (d, J = 6.7 Hz, 1H), 7.42–7.55 (m, 3H), 6.85 (m, 4H), 4.22–4.45 (m, 4H), 3.98 (dd, J = 11.5 and 7.9 Hz, 1H), 3.67 (m, 2H), 2.82–3.08 (m, 2H), 2.65 (dd, J = 13.5 and 5.95 Hz, 1H), 2.57 (dd, J = 13.1 and 5.95 Hz, 1H), 1.98–2.22 (m, 2H), 1.70–1.85 (m, 2H), 1.55–1.70 (m, 2H), 1.22–1.45 (m, 3H). Anal. (C$_{24}$H$_{28}$N$_2$O$_3$) C, H, N.

N-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethyl}-2-(2-nitrophenyl)ethylamine (38). To a solution of **13** (1.7 g, 6.1 mmol) in 2 mL of DMSO was added dropwise a solution of 2-(2-nitrophenyl)ethyl 4-toluenesulfonate[19] (2 g, 6.2 mmol) The mixture was heated at 140 °C for 2 h. The cooled reaction mixture was poured into a solution of concentrated NH$_4$OH and ice and extracted with EtOAc. The organic layer was washed twice with H$_2$O, dried, filtered and evaporated to dryness. The residue was purified by flash column chromatography (EtOAc/MeOH 50/50) to yield 0.5 g of **38** (19%)

as an oil: ^{1}H NMR (CDCl$_3$) δ 7.92 (dd, $J = 9.6$ and 1.6 Hz, 1H), 7.53 (dd, $J = 8.7$ and 1.3 Hz, 1H), 7.36 (m, 2H), 6.86 (m, 4H), 4.34 (m, 1H), 4.29 (m, 1H), 3.96 (dd, $J = 11.6$ and 7.7 Hz, 1H), 2.98 (m, 6H), 2.61 (m, 4H), 2.09 (m, 2H), 1.68 (m, 2H), 1.43 (m, 1H), 1.27 (m, 2H).

2-(2-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylamino}ethyl)phenylamine (39). To a solution of **38** (0.5 g, 1.17 mmol) in 20 mL of ethanol was added tin chloride dihydrate (1.35 g, 5.87 mmol) by small fractions. The solution was refluxed for 4 h and then evaporated nearly to dryness. The residue was hydrolyzed by addition of crushed ice and 10 mL of 1 N NaOH. The aqueous solution was extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and evaporated to dryness. The crude compound was subjected to the next step without further purification: ^{1}H NMR (CDCl$_3$) δ 6.92−7.09 (m, 1H), 6.76−6.92 (m, 5H), 6.60−6.75 (m, 2H), 4.34 (m, 1H), 4.25−4.40 (m, 2H), 3.96 (dd, $J = 11.7$ and 7.7 Hz, 1H), 3.40 (large s, 2H), 2.50−3.10 (m, 10H), 1.90−2.15 (m, 2H), 1.70−1.75 (m, 2H), 1.40−1.53 (m,1H), 1.20−1.35 (m, 2H).

3-{2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl]piperidin-4-yl]ethyl}-1,3,4,5-tetrahydrobenzo[*d*][1,3]diazepin-2-one (40). To a solution of crude **39** (0.4 g, 1 mmol) in 12 mL of CH$_3$CN was added carbonyldiimidazole (0.2 g, 1 mmol) and was then refluxed for 2.5 h. The cooled reaction mixture was filtered and evaporated to dryness. The residue was dissolved in CH$_2$Cl$_2$ and washed with H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH, 95/5) to yield 0.2 g of **40** (50%) as beige crystals: ^{1}H NMR (CDCl$_3$) δ 7.05−7.15 (m, 2H), 6.80−7.00 (m, 4H), 6.65−6.80 (m, 2H), 4.43 (m, 1H), 4.32 (dd, $J = 11.3$ and 2.2 Hz, 1H), 4.00 (dd, $J = 11.3$ and 7.0 Hz, 1H), 3.45−3.55 (m, 4H), 2.90−3.15 (m, 4H), 2.67 (m, 2H), 2.02−2.30 (m, 2H), 1.60−1.90 (m, 2H), 1.50−1.60 (m, 2H), 1.25−1.50 (m, 3H). **Fumarate**: mp 188−190 °C. Anal. (C$_{25}$H$_{31}$N$_3$O$_3$·C$_4$H$_4$O$_4$) C, H, N.

Receptors Binding Assays. α_1- and α_2-adrenoceptor binding experiments were performed according to Mallard et al.[23] using rat cortex membrane preparations. IC$_{50}$ refers to the in vitro concentration (in nM) of compound required to inhibit 50% of the specific binding of [^{3}H] RX 821002 to α_2-adrenoreceptor sites and [^{3}H]prazosin to α_1-adrenoceptor sites in rat brain membranes. D$_2$-Receptor binding experiments were performed by inhibition of [^{3}H]YM 09151-2[24] binding in rat striatal tissue. IC$_{50}$ values are expressed as the mean of duplicates of one experiment. Standard deviation between duplicates is less than 10%. The obtained values were sufficient for a screeening purpose.

Binding experiments for α_{2A}-, α_{2B}- and α_{2C}-adrenoceptors subtypes were performed on C6-glial cellular membranes stably expressing each of the α_2-adrenoceptor subtype, as previously described.[20]

In Vivo Pharmacology − Antagonism of Hypothermia Induced by Guanabenz in Mice. Male NMRI mice (Iffa Credo, France) weighing 30−32 g were housed in groups of 15 with free access to food and water in a room maintained at 21 ± 1 °C and $60 \pm 5\%$ humidity. There was a 12 h/12 h light/dark cycle with lights on from 07.00 h. The animals were given vehicle or drug by either the intraperitoneal (ip) or oral (po, by gavage) route. 5 min after ip injection or 35 min after po administration, animals received an ip injection of 1 mg/kg of guanabenz. 25 min after the administration of guanabenz, the rectal temperature was measured to the nearest 0.1 °C by insertion of a thermistor probe (Ellab, type DM 852) approximately 1.5 cm into the rectum for 3−5 s until a stable temperature reading was obtained. Experiments were conducted between 9:00 a.m. and 1:00 p.m. The number of animals tested per dose was 5. The inhibitory potency of a tested drug was estimated by an ED$_{50}$ value, representing the dose which produced an inhibitory effect (temperature >36 °C) in 50% of the animals. In this study, the temperature of all mice treated by guanabenz was lower than 36 °C (incidence of false positive = 0%). ED$_{50}$ value and their 95% confidence limits were

obtained by means of the method of Lichfield and Wilcoxon[25] using the PHARM/PCS program no. 46 of Tallarida and Murray.[26]

Molecular Modeling. Structures were built using standard bond lengths and angles in SYBIL (version 6.5) developed and distributed by Tripos Associates Inc., St. Louis, MO. Geometry optimizations were carried out using the semiempirical AM1 method in the MOPAC program (version 6 from QCPE).[21]

Supporting Information Available: Elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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