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Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-003383- -00004-0000

Fecha: 2010-09-20 16:52:04 Dep 2020 DIR.NUEVASOR
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Referencia : Expediente No. 07.003.383
Asunto : SOLICITUD DE PATENTE PARA: **"PROCEDIMIENTO PARA LA PREPARACIÓN DE 3-(4-PIPERIDINIL)-2,3,4,5-TETRAHIDRO-1,3-BENZODIAZEPIN-2(1H)-ONA"**
Solicitante : BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Clase : A61K 031/055, C07D 243/004
Fecha de solicitud : Enero 15 de 2007

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, de acuerdo con las sustituciones de los poderes a mí otorgadas, me refiero al Oficio No. 10403 notificado por fijación en lista del 13 de agosto de 2010 y atentamente presento junto con este escrito el siguiente documento:

PATRICE MAYER AND COL. "New substituted 1-(2,3-Dihidrobenczo[1,4]dioxin-2-ylmethyl)piperidi-4-yl Derivatives with alfa 2 adrenoceptor Antagonist Activity". J. Med. Chem., 2000, 43 (20), pp 3653-3664. Publication Date (web): September 19, 2000. 10.1021/jm991121.

2. Puesto que se han atendido a cabalidad las peticiones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

3. Anexos:

- Presento así mismo sustitución del poder otorgado por el Doctor EMILIO FERRERO, a mi favor, y para lo cual solicito me sea reconocida personería para proseguir con el trámite de este asunto en favor de la sociedad solicitante.

Señora Directora,

Luz Clemencia de Páez
LUZ CLEMENCIA DE PÁEZ

C.C. No. 35.456.344 de Usaquén T.P.A. No. 23.555

COLO-09255-841-061-6
LMAILMAID-178706WPCL9255
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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Poderdante : BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Poder conferido el : 12/12/1995

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cédula de ciudadanía No. 35.456.344 y Tarjeta Profesional N°23.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil.

Señora Jefe,



EMILIO FERRERO

T.P.A. N° 31.929

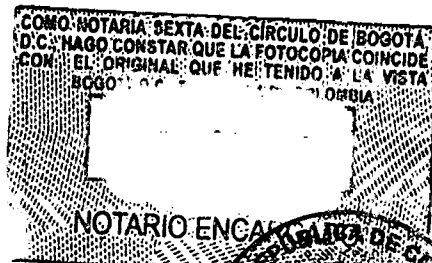
C.C. N° 438.019 de Usaquén

Acepto:


LUZ CLEMENCIA DE PAEZ

T.P.A. N° 23.555

C.C. No. 35.456.344 de Usaquén



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NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D.C.

Ante el

03 NOV 2009

NOTARIO SEXTO (E) DEL CIRCULO DE
BOGOTA D.C.

Compareció (eron)

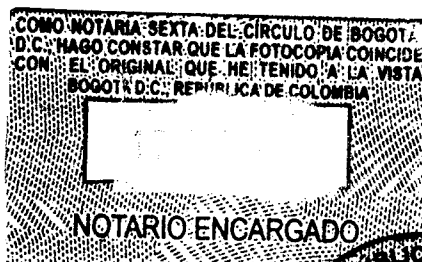
Quien(es) exhibió(aron) la(s) C.C.

*Emilio Fernando
Suarez Clemenencia de
García*
*Cc: 458 019 17 7142
Cc: 35 456 34 7027 35*

Y declaró(aron) que la(s) firma(s) que aparece(n)
en el presente documento es(son) la(s) suya(s) y
que el contenido del mismo es cierto.

En constancia se firma esta diligencia.

*Emilio Fernando
Suarez Clemenencia de
García*



New Substituted 1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl Derivatives with α_2 -Adrenoceptor Antagonist Activity

Patrice Mayer,* Pascale Brunel,* Céline Chaplain,* Christel Piedecoq,* Francis Calmel,* Philippe Schambel,† Philippe Chopin,‡ Thierry Wurch,‡ Petrus J. Pauwels,‡ Marc Marien,§ Jean-Louis Vidaluc,* and Thierry Imbert*,#

Division of Medicinal Chemistry, Department of Analytical Chemistry, Division of Neurobiology, and Department of Cellular and Molecular Biology, Centre de Recherche Pierre Fabre, 17, Avenue Jean Moulin, 81100 Castres, France

Received July 19, 1999

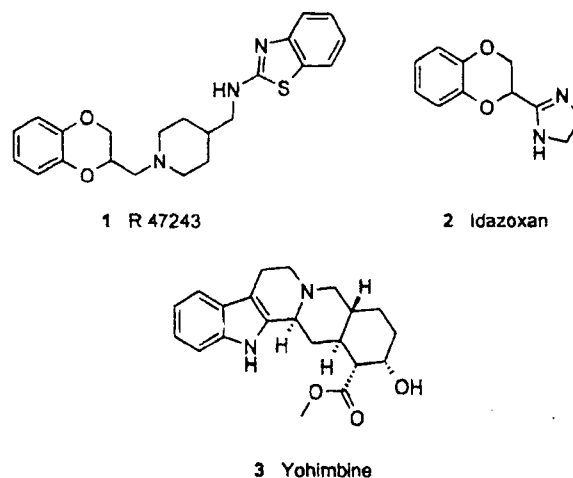
The emergence of a novel theory concerning the role of noradrenaline in the progression and the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases has provided a new impetus toward the discovery of novel compounds acting at α_2 -adrenoceptors. A series of substituted 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 α_2 -adrenoceptor antagonists with good selectivity versus α_1 -adrenergic and D₂-dopamine receptors. Particular emphasis is given to compound **33g** which displays potent α_2 -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 squirrel 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 47243³ (**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 α_2 -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 α_2 -adrenoceptor antagonist idazoxan (**2**). Based on these findings, a new interest in the discovery of novel compounds selectively acting on α_2 -adrenoceptors has been generated. α_2 -

Chart 1. Structure of Reference α_2 -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 α_2 -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 15385-137⁶ and MK 912.⁷ Another group of α_2 -adrenoceptor antagonists features idazoxan (**2**)⁸ (Chart 1), whose structure merged as an hybrid between piperoxan (a weak nonselective α_2 -adrenoceptor antagonist) and clonidine (a potent α_2 -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

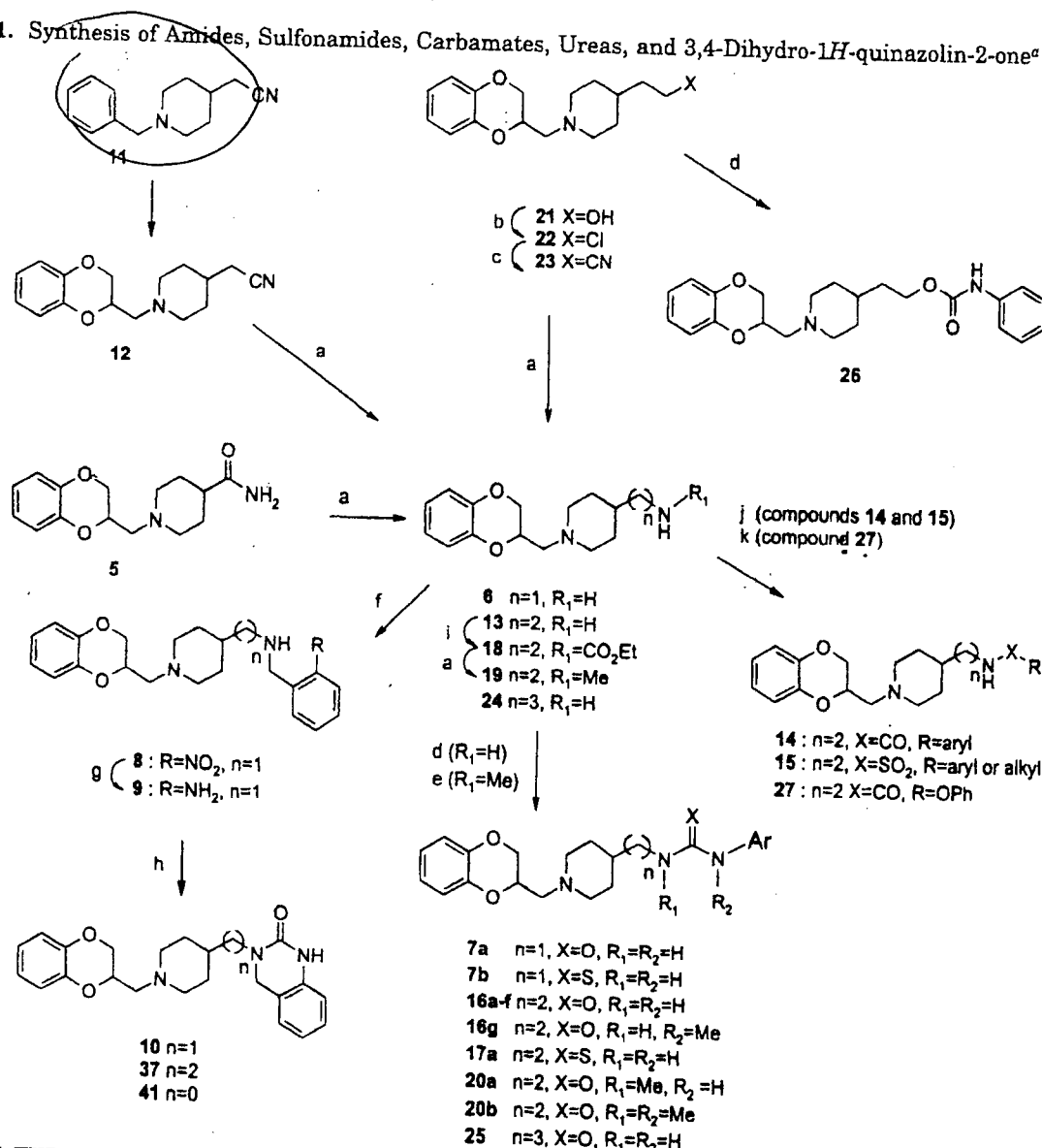
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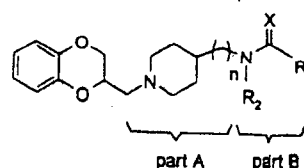
§ Department of Cellular and Molecular Biology.

Scheme 1. Synthesis of Amides, Sulfonamides, Carbamates, Ureas, and 3,4-Dihydro-1*H*-quinazolin-2-one^a

^a (a) $\text{LiAlH}_4/\text{THF}$; (b) $\text{SOCl}_2/\text{CH}_2\text{Cl}_2/\text{reflux}$; (c) $\text{KCN}/\text{DMSO}/120^\circ\text{C}$; (d) ArNCO , ArNCS or $\text{PhMeNCOC}/\text{CH}_2\text{Cl}_2$; (e) (i) ethyl chloroformate/ Et_3N , (ii) $\text{LiAlH}_4/\text{THF}$, (iii) RNCO or $\text{PhMeNCOC}/\text{CH}_2\text{Cl}_2$; (f) 2-nitrobenzaldehyde/ $\text{NaBH}_4/\text{EtOH}$; (g) Fe/HCl ; (h) urea/ 150°C ; (i) $\text{EtOCOC}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$; (j) RCOCl or $\text{RSO}_2\text{Cl}/\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$; (k) $\text{PhOCOC}/\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$.

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.

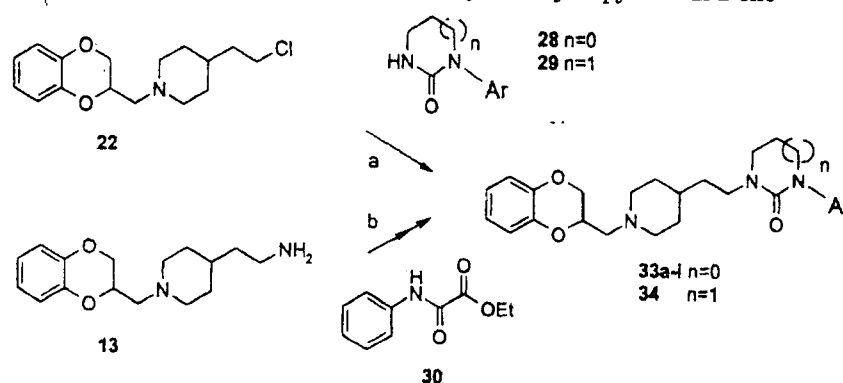
The two main criteria selected to evaluate the new compounds were (1) the in vitro binding affinity at α_2 -adrenoceptors and their selectivity versus rat α_1 -adrenoceptor and D_2 -dopamine receptors and (2) their in vivo properties to inhibit the hypothermia induced by the centrally active α_2 -adrenoceptor 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 procedure¹⁴

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) LiAlH₄/THF/reflux, (iii) Im₂CO/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 chloroformate¹⁵ and reaction with 2,3-dihydro-2-tosylmethylbenzo[1,4]dioxin¹⁶ 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-ethylamine 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)piperidin-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-

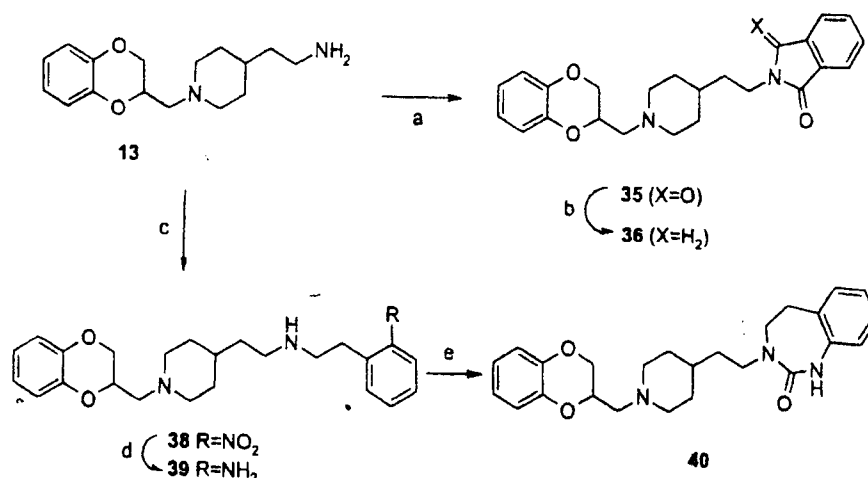
din-4-yl)-2-ethanol derivative 21 with phenyl isocyanate. The isomeric carbamate derivative 27 was obtained by reaction of the (piperidin-4-yl)-2-ethylamine derivative 13 with phenyl chloroformate (Scheme 1).

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*-phenyltetrahydropyrimidinone 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 carbonyldiimidazole 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-nitrophenylethanol.¹⁹ The obtained 2-nitrophenyl-2-ethylamine derivative 38 was subjected to reduction by tin chloride in ethanol to afford 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)piperidin-4-yl]-3,4-dihydro-1*H*-quinazolin-2-one (41) (Scheme 1) was synthesized by reaction of the previously described 3-(piperidin-4-yl)-3,4-dihydro-1*H*-quinazolin-2-one¹⁴ 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-1H-isindole Derivatives^a

^a (a) Phthalic anhydride/AcOH/reflux; (b) Sn/HCl/AcOH; (c) 2-(2-nitrophenyl)ethyl 4-toluenesulfonate; (d) SnCl₂, 2H₂O/EtOH; (e) Im₂CO/CH₃CN.

Table 1. In Vitro Binding Assays at α_2 -, α_1 -, and D₂-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
phenylthiureas				
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

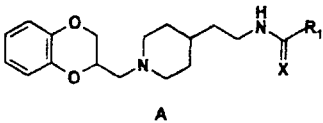
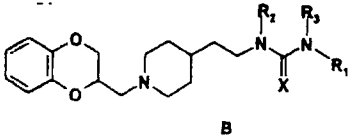
^a IC₅₀ values were determined according to refs 23 and 24 and are the mean values of duplicates of one experiment. Standard deviation between duplicates is less than 10%.

pounds exhibiting high affinity at the α_2 -adrenoceptor with an IC₅₀ 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 D₂-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 D₂-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 IC₅₀ 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-glia 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 D₂-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 D₂-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-NO₂ (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 D₂-receptor. Thus an improved D₂/ 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 ED₅₀ 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

											
		A					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	PhCH ₂			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-iPr 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 IC₅₀ 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 (ED₅₀ = 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

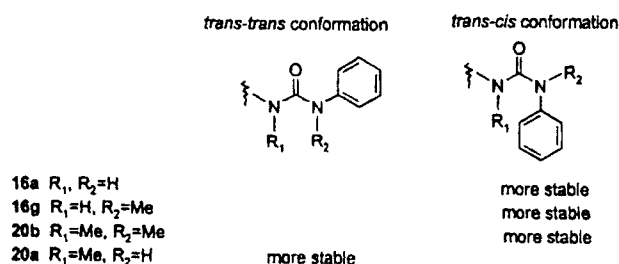
ureas 16g and 20a displayed an IC₅₀ of 1.1 and 4.5 nM, respectively, at the α_2 -adrenoceptor in vitro. Potent central in vivo antagonism was shown irrespective of the route of administration with 20a (ED₅₀ = 0.02 mg/kg ip) and over a wide dose range. In contrast, 16g was less active (ED₅₀ = 0.56 mg/kg 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



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-1*H*-quinazolin-2-one 37 and benzo[d][1,3]diazepin-2-one 40). All these compounds retained high in vitro binding affinity for α₂-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 α₂- versus α₁-adrenoceptors (ratio α₁/α₂ = 30), but the affinity of this molecule for dopaminergic D₂-receptor remained important. This

brought us to our third criterion of selection which was the selectivity versus the D₂-receptor.

R 47243 (1), the lead structure used in the early investigations, proved to be poorly selective at both α₁-adrenoceptor and D₂-receptor sites with respect to the α₂-adrenoceptor. With the imidazolidinone 33a, a series of compounds substituted at the phenyl ring was evaluated for their affinities at α₁- and D₂-receptors. Modification of the torsion angle between the two cyclic systems was thought to be a putative requirement to lose affinity at the D₂-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-Me₂ (33b), 2,6-(*i*-Pr)₂ (33d), 2,6-(MeO)₂ (33e), and 2,4,6-(MeO)₃ (33g) derivatives exhibited a fair α₂- versus D₂-receptor selectivity. The α₂/D₂ ratio reached 70 for compounds 33e,g. However the 2,6-disubstitution pattern proved to be not a sufficient condition to achieve D₂-receptor selectivity; indeed, the 2,6-Cl₂-substituted derivative 33c exhibited high affinity at both the α₂-adrenoceptor and D₂-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 α₂-adrenoceptor, fair selectivity versus α₁-adrenoceptor and D₂-dopaminergic receptor, and potent antagonist property as demonstrated by its efficacy in vivo in the guanabenz-induced hypothermia test in mice.

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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-trimethoxyphenylimidazolidinone 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 μ m. Melting points were determined on a Electrothermal IA9300 melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker DPX400 (^1H , 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 vacuum.

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]dioxine¹⁶ (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_2O , brine, dried over Na_2SO_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; ^1H 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_2SO_4) and evaporated to dryness to yield 9.9 g of **6** (88%) as an oil: ^1H 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_2Cl_2 was added

dropwise a solution of **6** (1.3 g, 50 mmol) in 5 mL of CH_2Cl_2 and was stirred at room temperature for 20 h. The cooled reaction mixture was evaporated and the residue was purified by flash chromatography $CH_2Cl_2/MeOH$ 95/5) affording 1.35 g of **7a** (71%): ^1H 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. ($C_{22}H_{27}N_3O_2 \cdot HCl$) 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_2SO_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: ^1H 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_2O (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_2Cl_2 , washed with brine, dried over Na_2SO_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: ^1H 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-1H-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; ^1H 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. ($C_{23}H_{27}N_3O_3 \cdot C_4H_4O_4$) C, H, N.

Compound **37** was synthesized following the same route starting from amine **13**. **Fumarate:** mp 182–184 °C. Anal. ($C_{24}H_{29}N_3O_5 \cdot C_4H_4O_4$) 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)acetonitrile¹⁵ (**11**) and 50 g (156 mmol) of 2,3-dihydro-2-tosylmethylbenzo[1,4]dioxine¹⁶ was heated at 140 °C for 20 h and was treated with Na_2CO_3/CH_2Cl_2 . The organic layer was washed with H_2O , dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash column chromatography ($CH_2Cl_2/MeOH$ 98/2) affording 26.8 g (64%) of **12** as a colorless oil: ^1H 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 $\text{Na}_2\text{SO}_4/\text{H}_2\text{O}$. After filtration, the organic layer was concentrated under reduced pressure to give 10.2 g (95%) of 13 as an oil: ^1H 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, 12.6 mmol) in CH_2Cl_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_2O and brine, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from Et_2O to yield 1.26 g 14a (61%) of white crystals: mp 106–108 °C; ^1H 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. ($\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_3$) C, H, N.

Compounds 14b–f were synthesized following the same procedure. **14b (base):** yield 55%; mp 122–124 °C. Anal. ($\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_5$) C, H, N. **14c-oxalate:** yield 47%; mp 175–176 °C. Anal. ($\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}_4 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N. **14d-oxalate:** yield 60%; mp 146 °C. Anal. ($\text{C}_{26}\text{H}_{32}\text{N}_3\text{O}_4 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N. **14e (base):** yield 39%; mp 135–136 °C. Anal. ($\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_5$) C, H, N. **14f-oxalate:** yield 57%; mp 142 °C. Anal. ($\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) 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_3N (0.9 g, 9 mmol) in 100 mL of CH_2Cl_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_2Cl_2 . The solution was stirred for 1 h and then washed successively with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Purification by flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 95/5) yielded 1.05 g of pure 15a (68%) as a colorless oil which crystallized from isopropyl ether: mp 94–95 °C. Anal. ($\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4\text{S}$) 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_2Cl_2 was added dropwise a solution of 13 (1.5 g, 5.4 mmol) in CH_2Cl_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; ^1H 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. ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N.

Compounds 16b–f,h were synthesized following the same procedure. **16b-oxalate:** yield 60%; mp 176 °C. Anal. ($\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_4 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N. **16c (base):** yield 47%; mp 98 °C. Anal. ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4$) C, H, N. **16d-oxalate:** yield 50%; mp 241–242 °C. Anal. ($\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_6 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N. **16e-oxalate:** yield 52%; mp 177–178 °C. Anal. ($\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N. **16f-oxalate:** yield 39%; mp 200 °C. Anal. ($\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N. **16h-oxalate:** yield 43%; mp 199–200 °C. Anal. ($\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_4 \cdot \text{C}_2\text{H}_2\text{O}_4$) 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_2Cl_2 at 0 °C were added dropwise 13 (1 g, 3.6 mmol) and triethylamine (1.26 mL, 9.1 mmol). The mixture was stirred at room temperature for 1 h and washed with H_2O , brine, dried over Na_2SO_4 , and evaporated to dryness.

The residue was purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95/5) to yield 1.15 g of 16g (76%): ^1H 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), 1.61 (m, 2H), 1.44–1.03 (m, broad, 5H). **Oxalate:** mp 105–106 °C. Anal. ($\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) 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_2Cl_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; ^1H 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. ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2\text{S} \cdot \text{C}_2\text{H}_2\text{O}_2$) C, H, N.

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

2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylcarbamate 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_2Cl_2 , and washed twice with H_2O . 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: ^1H 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: ^1H 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_2Cl_2 was added dropwise a solution of 19 (0.7 g, 2.4 mmol) in 10 mL of CH_2Cl_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; ^1H 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. ($\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) 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_2Cl_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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 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. ($\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 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-ylmethyl)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 ($\text{DMSO}-d_6$) 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 $\text{NaOH}/\text{CH}_2\text{Cl}_2$. 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 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)piperidin-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_2Cl_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), 2.19–2.18 (m, 2H), 1.62 (m, 2H), 1.50 (m, 2H), 1.40–1.04 (m large, 5H). **Oxalate**: mp 162–163 °C. Anal. ($\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N.

2-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylcarbamate 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 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. ($\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4$) 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. ($\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4 \cdot \text{C}_2\text{H}_2\text{O}_4$) 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5) and concentrated under reduced pressure. The residue was recrystallized from Et_2O 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_2SO_4 , filtered and evaporated to dryness. The residue was recrystallized from isopropyl ether to yield 4.2 g of **29** (85%) as white crystals: ^1H 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-Phenylloxalamic 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%): ^1H 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'-phenylloxalamide (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: ^1H 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 $\text{Na}_2\text{SO}_4/\text{H}_2\text{O}$, filtered and washed with THF. The organic layer was evaporated to dryness. The residue was purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5) to yield 0.5 g of **32** (45.5%) as an oil: ^1H 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_3CN 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: ^1H 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. ($\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_5 \cdot \text{C}_4\text{H}_4\text{O}_4$) 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10) to yield 0.25 g of **33g** (25%) as white crystals: mp 110–112 °C; ^1H 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, 1H), 1.74 (m, 2H), 1.49 (m, 2H), 1.30 (m, 3H). Anal. ($\text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_8$) C, H, N.

Compounds **33b–f, h, i** were synthesized following the same procedure. **33b-oxalate:** yield 31%; mp 141–142 °C. Anal. ($\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$) C, H, N. **33c-hydrochloride:** yield 28%; mp 216–218 °C. Anal. ($\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_3 \cdot \text{HCl}$) C, H, N. **33d (base):** yield 43%; mp 138–140 °C. Anal. ($\text{C}_{31}\text{H}_{43}\text{N}_3\text{O}_3$) C, H, N. **33e (base):** yield 20%; mp 108–109 °C. Anal. ($\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_5$) C, H, N. **33f (base):** yield 28%; mp 95–96 °C. Anal. ($\text{C}_{29}\text{H}_{39}\text{N}_3\text{O}_5$) C, H, N. **33h (base):** yield 25%; mp 148–150 °C. Anal. ($\text{C}_{25}\text{H}_{30}\text{FN}_3\text{O}_3$) C, H, N. **33i-hemioxalate:** yield 22%; mp 198–200 °C. Anal. ($\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}_3 \cdot 0.5 \text{C}_2\text{H}_2\text{O}_4 \cdot \text{H}_2\text{O}$) 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_2O and extracted with EtOAc. The organic layer was washed with H_2O , brine, dried over Na_2SO_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; ^1H 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. ($\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_3$) 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_2CO_3 10%, 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5) and recrystallization with EtOH to yield 0.7 g **35** (20%) as white crystals: mp 120 °C; ^1H 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. ($\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_4 \cdot \text{HCl}$) 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_2Cl_2 . The organic layer was washed with brine, 2 N NaOH, H_2O , 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; ^1H 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. ($\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3$) 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-toluenesulfonate¹⁹ (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_4OH and ice and extracted with EtOAc. The organic layer was washed twice with H_2O , 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: ^1H 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-[1-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl)piperidin-4-yl]ethylamino)ethylphenylamine (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_2SO_4 , and evaporated to dryness. The crude compound was subjected to the next step without further purification: ^1H 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_3CN 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_2Cl_2 and washed with H_2O . The aqueous layer was extracted with CH_2Cl_2 . The organic layer was washed with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95/5) to yield 0.2 g of **40** (50%) as beige crystals: ^1H 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. ($\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_5 \cdot \text{C}_4\text{H}_4\text{O}_4$) 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 [^3H] RX 821002 to α_2 -adrenoceptor sites and [^3H]prazosin to α_1 -adrenoceptor sites in rat brain membranes. D_2 -Receptor binding experiments were performed by inhibition of [^3H]YM 09151-2²⁴ 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 screening purpose.

Binding experiments for α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors subtypes were performed on C6-glia 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 Wilcoxon²⁵ 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

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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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