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(2,2-Diphenyl-[1,3]oxathiolan-5-ylmethyl)-(3-phenyl-propyl)-amine: a Potent and Selective 5-HT$_{1A}$ Receptor Agonist

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*Starting from compound **1**, a previously reported α_{1D}-adrenoceptors antagonist, a new series of ligands acting at 5-HT$_{1A}$ serotonin receptor were identified through simple structure modifications. Among them (2,2-diphenyl-[1,3]oxathiolan-5-yl-methyl)-(3-phenyl-propyl)amine (**19**) exhibits outstanding activity (pK_i = 8.72, pD_2 = 7.67, E_{max} = 85) and selectivity (5-HT$_{1A}$/α_{1D} > 150), and represents an as yet unidentified 5-HT$_{1A}$ agonist scaffold.*

Introduction

Over the past decade, the 5-HT$_{1A}$ receptor has been a major target for neurobiological research and drug development.[1–4] Many compounds, belonging to different chemical classes, display high affinity for 5-HT$_{1A}$ receptors. Most of these ligands are agonists or partial agonists. Full antagonists, devoid of any agonistic activity at presynaptic or postsynaptic receptors, are still scarce. Agonists and partial agonists of 5-HT$_{1A}$ receptors have been proven to be effective in treating anxiety and depression.[4–8] In addition to therapeutic applications in the field of psychiatry, more recent preclinical studies have suggested that 5-HT$_{1A}$ receptor agonists also have pronounced neuroprotective properties.[9] More recently in animal models, it has been discovered that 5-HT$_{1A}$ receptor activation is a molecular mechanism involved in pain relief. Although further evidence is needed in humans, 5-HT$_{1A}$ receptor agonists may challenge the opioids in pain relief therapy.[10] Conversely, potential therapeutic applications for 5-HT$_{1A}$ receptor antagonists have been evaluated, for example, in cognition disorders.[11]

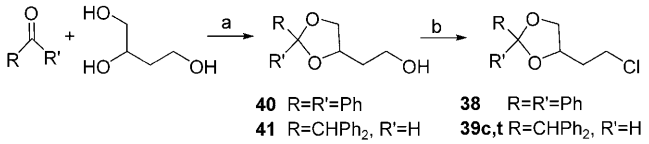
The 5-HT$_{1A}$ receptor belongs to a class of G-protein-coupled receptors (GPCRs), the members of which have a number of characteristic amino acid patterns in common. In particular, the transmembrane amino acid sequence of the 5-HT$_{1A}$ subtype is noteworthy for its high degree of homology with the α_1-adrenergic receptor (approximately 45%).[12] For this reason, a great number of ligands show high 5-HT$_{1A}$ affinity, but poor selectivity.

We have recently reported a new series of 1,3-dioxolane-based α_1-adrenoceptor antagonists,[13] among which compound **1** displayed the highest affinity and selectivity toward the α_{1D} subtype. Considering the high degree of homology of amino acid sequence between the α_1-adrenergic and 5-HT$_{1A}$ receptors, the pharmacological profile of compound **1** was investigated further. Tests on human cloned 5-HT$_{1A}$ receptors showed that, unsurprisingly, compound **1** binds to the 5-HT$_{1A}$ receptor with similarly high affinity (pK_i = 8.45). This observation prompted us to study this new class of compounds further in both receptor systems. Here, we report the synthesis of a new set of derivatives (**5**–**20**) and their pharmacological evaluation along with previously synthesized compounds (**2**, **3**, **4-*c,t***).[15]

Results and Discussion

Chemistry

Compounds **5**–**20** were synthesized by standard procedures and characterized by ^{1}H NMR and elemental analysis (see the Experimental Section). Briefly, the chloro derivatives were obtained by reacting the appropriate aldehyde/ketone with 3-chloro-1,2-propanediol (not shown), or when $n = 2$ (compounds **16** and **18 c**,**t**), in a two-step procedure involving an alcohol intermediate (Scheme 1). For compounds **6** and **7**, the



Scheme 1. Synthesis of chlorinated intermediates **38** and **39 c**,**t**. *Reagents and conditions*: a) *p*TsOH, toluene; b) $SOCl_2$, Py, benzene.

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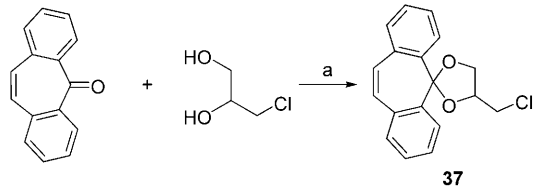
chlorinated precursor was synthesized from commercially available starting materials as shown (Scheme 2) Amination of the chlorinated precursors in 2-methoxyethanol in the presence of



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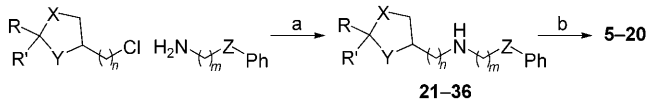
Scheme 2. Synthesis of the dibenzosuberenone-derived intermediate **37**. *Reagents and conditions*: a) *p*TsOH, toluene.

a catalytic amount of KI gave intermediates **21**–**36** (Scheme 3). The diastereomeric mixtures were separated by flash chromatography at this stage, and the *cis* and *trans* stereochemistry



21–36

Scheme 3. The general synthesis of oxalates **5**–**20**. *Reagents and conditions*: a) KI, 2-methoxyethanol; b) $C_2H_2O_4$, Et_2O.

was assigned by measurement of the nuclear Overhauser effect (NOE) between the C2 proton (or methyl group) and the C4 proton. The oxalate salts (**5**–**20**) were formed under standard conditions (Scheme 3). The commercially unavailable amines were prepared by reacting 2-chloroacetamide and the appropriate phenol followed by reduction of the amide using diborane as previously reported.[14]

Pharmacology

The pharmacological profile of compounds **1**–**20**, was determined for α1-adrenoceptors in different isolated tissues. BMY-3748 and 8-OH-DPTA were used as reference compounds. Inhibitory activity was assessed by antagonism of (−)-noradrenaline-induced contraction of rat prostatic vas deferens (α_{1A})[15] or thoracic aorta (α_{1D})[17] and by antagonism of (−)-phenylephrine-induced contraction of rat spleen (α_{1B})[16] Radioligand binding assays using [^{3}H]prazosin to label cloned human α1-adrenoceptors expressed in CHO cells,[18,19] and [^{3}H]8-OH-DPAT to label cloned human α_1-adrenoceptors expressed in HeLa cells[19] were also used. Functional characterization of some selected compounds (**1**, **12**, **19** and **20**) against the 5-HT$_{1A}$ receptor was performed according to methods of Stanton and Beer,[22] using [^{35}S]GTPγS binding in cell membrane from HeLa cells transfected with human cloned 5-HT$_{1A}$ receptor. Stimulation of [^{35}S]GTPγS binding was expressed as the percent increase in binding above the basal value, where the maximal stimulation observed with serotonin was taken as 100%. α_1/5-HT$_{1A}$ selectivity ratios of tested compounds were preliminarily calculated comparing α_1 antagonist potencies (expressed as pK_b values) with their 5-HT$_{1A}$ binding affinity data (expressed as pK_i values). The selectivity ratio of promising compounds was then evaluated more stringently by comparing the pK_i values of both the α_1 and 5-HT$_{1A}$ receptors (Table 2).

Structure–Activity and Affinity Relationship Analysis

As observed previously for α_1-adrenergic receptors, methylation (compound **2**) and quaternization (compound **3**) of the amine strongly decrease the binding affinity with 5-HT$_{1A}$ receptors (Table 1). The *cis* and *trans* diastereomers of compound **4** showed very weak binding affinities, indicating that both phenyl rings are essential for optimal binding to either α_1-adrenergic and 5-HT$_{1A}$ receptors.

Having established that among the small set of compounds studied, compound **1** shows the highest affinity for 5-HT$_{1A}$ receptors with no selectivity compared to α_1-adrenergic system, we decided to undertake a research project aimed at defining some structural elements important for binding and to address selectivity for one receptor system over the other. With this aim in mind, we designed analogues of compound **1** with simple structural modifications. Given the importance of the diphenyl substitution at position 2 of the 1,3-dioxolane ring, compound **5**, **6** and **7** were designed to verify whether these groups should be freely rotating or whether a rigid system as in the tricyclic derivatives (**5**–**7**) would be tolerated. The conformational restriction proved to be detrimental to the activity in both receptor systems indicating that the two phenyl ring should have a certain degree of conformational freedom in order to better adapt to the corresponding receptor subsite. In order to gain further insight into the topography of the binding sites, extended, sterically bulky compounds **8** and **9** were also prepared. They displayed weaker binding affinities than that of compound **1**, indicating that the region accommodating the phenoxy moiety is of limited size.

We then turned our attention to the oxygen atom of the phenoxyethylamine lateral chain. Isosteric replacement of O atom with S (compound **10**), NH (compound **11**) and CH_2 (compound **12**) causes a clear decrease in antagonism of the three α_1-adrenoceptor subtypes. A similar trend is observed for 5-HT$_{1A}$ receptors, with the exception of compound **12** for which the affinity value (pK_i = 8.56) is much the same as the lead compound **1** (pK_i = 8.45). Therefore, compound **12** is 191- and 33-fold selective for 5-HT$_{1A}$ over α_{1D}-adrenergic receptors in functional (Table 1) and binding studies (Table 2), respectively.

Intermolecular distances were also studied, such as the distance between the phenyl ring and the nitrogen atom of the lateral chain, and between the nitrogen atom and the diphenyl group on C2 of the 1,3-dioxolane ring. The latter variation may be accomplished in different ways, i.e. a) moving the nitrogen atom away from the 1,3-dioxolane ring, b) moving away the diphenyl moiety, or c) combining these two variations. Shortening or lengthening the carbon chain linking the phenyl ring and the nitrogen atom by one methylene unit (compounds **14** and **15**) decreases the binding affinity for 5-HT$_{1A}$ by approximately tenfold, which is further reduced to more than 100-fold

Table 1. Antagonist potencies (pK_b)[a] and binding affinities (pK_i)[b] for compounds **1**–**20**.[c]

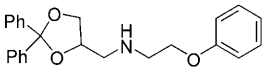
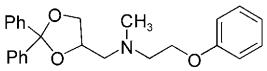
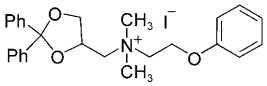
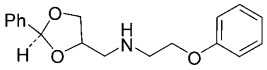
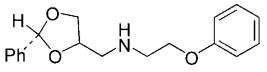
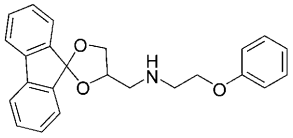
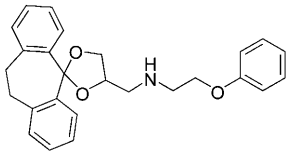
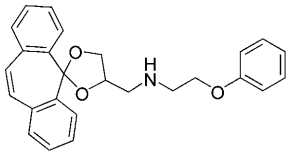
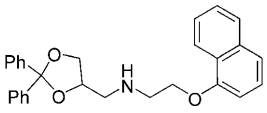
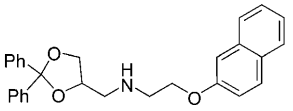
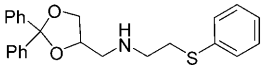
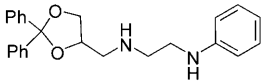
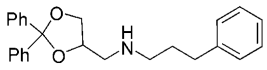
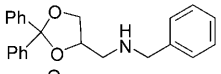
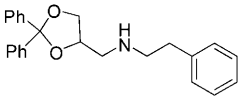
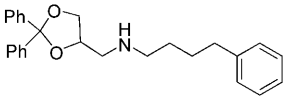
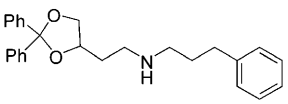
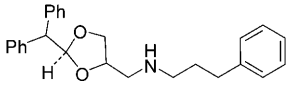
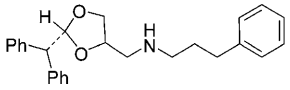
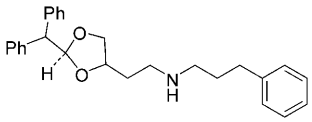
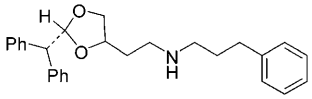
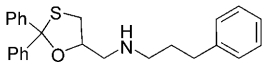
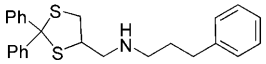
Compound	Structure	pK_b α_{1A}	pK_b α_{1B}	pK_b α_{1D}	pK_i 5-HT_{1A}	5-HT_{1A}/α_{1D}[d]
1		6.16	5.86	8.37	8.45	1
2		5.06	5.31	6.06	6.32	2
3		< 5	5.60	6.19	< 6	< 0.7
4c		5.44	6.30	7.09	5.93	0.07
4t		6.01	6.40	6.94	5.70	0.06
5		5.15	6.34	7.31	6.90	0.4
6		5.74	6.07	7.12	6.96	0.7
7		6.39	6.33	7.68	7.22	0.3
8		5.03	5.51	6.49	7.33	7
9		< 4.52	5.73	6.69	7.34	4
10		< 5	5.59	6.87	7.03	1
11		< 5	5.54	6.49	6.56	1
12		< 5	5.34	6.28	8.56	191
13		< 5.52	6.04	6.26	< 6	< 0.6
14		< 5.52	5.79	6.53	7.32	6
15		< 5.52	6.09	6.46	7.37	8
16		< 6	6.42	6.65	7.24	4

Table 1. (Continued)

Compound	Structure	pK_b α_{1A}	pK_b α_{1B}	pK_b α_{1D}	pK_i 5-HT$_{1A}$	5-HT$_{1A}$/α_{1D}[d]
17c		<6	5.43	6.37	<7	<4
17t		6.03	5.94	6.08	7.62	35
18c		5.21	6.15	6.04	<7	<9
18t		<6	6.28	6.40	7.26	7
19		5.05	5.42	6.36	8.72	229
20		5.75	5.65	6.66	8.00	22
BMY-7378		7.01	7.48	8.40	8.90	3

[a] Antagonist potencies (pK_b) for a_1-adrenoceptors in isolated rat prostatic vas deferens (a_{1A}), spleen (a_{1B}) and thoracic aorta (a_{1D}), pK_b values agreed to ±2%. [b] Binding affinities (pK_i) for human cloned 5-HT$_{1A}$ receptor, pK_i values agreed to ±10%. [c] All compounds tested as the oxalate salt except for compound **3**. [d] Selectivity ratio

Table 2. Pharmacological profile of oxalate derivatives **1**, **12**, **19** and **20**.

	Binding affinities[a]				Selectivity	[^{35}S]GTPγS-binding assay[b]	
Compound	pK_i α_{1A}	pK_i α_{1B}	pK_i α_{1D}	pK_i 5-HT$_{1A}$	5-HT$_{1A}$/α_{1D}	pD_2	E_{max}[c]
1	7.43	7.20	7.94	8.45	3	8.8	24
12	6.78	6.92	7.04	8.56	33	7.26	53
19	6.65	<6	6.54	8.72	151	7.67	85
20	7.12	<6	6.88	8.00	13	7.38	80
8-OH-DPTA	6.82	<6	<6	8.43	>270	7.83	100

[a] Binding affinities (pK_i) for human recombinant α_1-adrenoceptor subtypes and human 5-HT$_{1A}$ receptor, pK_i values agreed to ±10%. [b] Potency (pD_2) and relative effectiveness (E_{max}) values in the agonist-induced [^{35}S]GTPγS-binding assay at human 5-HT$_{1A}$ receptor. [c] Maximal stimulation expressed as a percentage of the maximal 5-HT response.

by further shortening the chain (compound **13**). Compounds **16**–**18** behave similarly. Taken together, these results show that all modifications of the above mentioned distances, while scarcely affecting the activity against α_1-adrenoceptors, are detrimental to 5-HT$_{1A}$ binding and consequently, selectivity, indicating that the intermolecular distances in compound **12** are optimal.

Thereafter, we focused our attention on the 1,3-dioxolane ring and applied the isosteric substitution strategy to the oxygen atoms. The 1,3-oxathiolane derivative **19** and the 1,3-dithiolane derivative **20** were prepared and tested. Compound **19** maintains the same pharmacological profile as compound **12** with a pK_i value of 8.72 and a selectivity ratio of 229. For compound **20**, the selectivity is significantly reduced (22) as a consequence of a decreased affinity for 5-HT$_{1A}$ and an increase for the α_{1D} subtype. The pharmacological profile of the two compounds is confirmed in radioligand binding studies (Table 2).

In a functional characterization test against the 5-HT$_{1A}$ receptor, compounds **1**, **12**, **19** and **20** increase the binding of [^{35}S]GTPγS above the basal value with a pD_2 values ranging between 7.26 (compound **12**) and 8.80 (compound **1**) and E_{max} values ranging between 24 (compound **1**) and 85 (compound **19**), defining them as partial agonists.

Although only a limited number of compounds were tested for stimulation of [^{35}S]GTPγS binding, some structure–activity relationships can be drawn. Replacing the phenoxy O atom with a CH_2 group in compound **1** (pD_2 = 8.8, E_{max} = 25) leads to a 35-fold decrease in agonism, while the efficacy (E_{max}) is more than doubled. Isosteric substitution O/S within the 1,3-dioxolane ring further increases the efficacy (85 and 80 for compound **19** and **20**, respectively) and selectivity (compound **19**).

Conclusions

In conclusion, a previously unknown class of 5-HT$_{1A}$ receptor agonists were discovered from an α_{1D}-adrenoceptor antagonist. Among these novel derivatives, compound **19** exhibits outstanding activity (pK_i = 8.72, pD_2 = 7.67, E_{max} = 85) and selectivity (5-HT$_{1A}$/α_{1D} > 150). Further structure–activity relationship

studies within this new class of compounds are in progress and will be reported in due course.

Experimental Section

Chemistry

The structural characterization was achieved using NMR and elemental analysis techniques (C, H, N Elemental Analyzer Mod. 1106, Carlo Erba Instruments). Analyses data reported were within ±0.4% of the theoretical values. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 200 Advance working at 200.13 MHz and at a temperature of 300 K. Chemical shifts are reported as δ (ppm) relative to tetramethylsilane. Silica gel TLC plates (Merck, Kieselgel 60, F_{254}) were used to monitor the progression of the reactions. Chromatographic separations were performed on silica gel columns (Kiesel gel 60, 0.040–0.063 mm, Merck) by flash chromatography. The names of compounds were generated by applying the PC software AUTONOM, version 2.1.

General procedure for the synthesis of amines 21–36 and their oxalate salts 5–20: A solution of the appropriate chloro alkyl derivative in 2-methoxyethanol was treated with a large excess of amine (5–10 equiv) and a catalytic amount of KI then refluxed (18–24 h). The solvent was concentrated in vacuo and the residue was redissolved in $CHCl_3$. The organic phase was washed with a solution of 5% NaOH (3×) and saturated NaCl (2×), dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography (cyclohexane/EtOAc, 90:10 → EtOAc, 100%) to give the desired amine (**21**–**36**) as oil.

(2-Phenoxyethyl)[2-(9*H*-fluoren-9-yl)[1,3]dioxolan-4-yl-methyl]-amine (21): 0.80 g (2.1 mmol); yield 65%; ^{1}H NMR ($CDCl_3$) δ = 1.99 (brs, 1H), 3.10 (m, 4H), 4.10 (m, 2H), 4.18 (dd, 1H), 4.53 (dd, 1H), 4.80 (m, 1H), 6.94 (m, 3H), 7.40 ppm (m, 10H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **5**: mp 180 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 3.35 (m, 4H), 4.20 (m, 3H), 4.57 (m, 1H), 4.92 (m, 1H), 6.95 (m, 3H), 7.41 (m, 8H), 7.71 ppm (m, 2H). Anal. calcd for $C_{26}H_{25}NO_7$: C 67.38, H 5.44, N 3.02, found: C 67.04, H 5.43, N 3.36.

(2-Phenoxyethyl)[2-(10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5-yl)[1,3]dioxolan-4-yl-methyl)amine (22): 0.27 g (0.67 mmol); yield 48%; ^{1}H NMR ($CDCl_3$) δ = 1.91 (brs, 1H), 2.90 (ddd, 2H), 3.05 (t, 2H), 3.37 (m, 4H), 3.86 (dd, 1H), 4.07 (t, 2H), 4.12 (dd, 1H), 4.40 (m, 1H), 6.93 (m, 3H), 7.21 (m, 8H), 7.69 (m, 1H), 7.83 ppm (m, 1H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **6**: mp 195 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 2.83 (m, 2H), 2.99 (m, 2H), 3.20 (m, 4H), 3.77 (dd, 1H), 4.08 (m, 3H), 4.21 (m, 1H), 6.92 (m, 3H), 7.20 (m, 8H), 7.57 (m, 1H), 7.72 ppm (m, 1H). Anal. calcd for $C_{28}H_{29}NO_7$: C 68.42, H 5.95, N 2.85, found: C 68.10, H 5.89, N 3.05.

(2-Phenoxyethyl)[2-(5*H*-dibenzo[a,d]cyclohepten-5-yl)[1,3]-dioxolan-4-yl-methyl)amine (23): 0.40 g (1.0 mmol); yield 71%. ^{1}H NMR ($CDCl_3$) δ = 1.93 (brs, 1H); 2.97 (m, 4H), 3.91 (m, 1H); 4.03 (t, 2H); 4.15 (m, 1H); 4.57 (m, 1H), 6.95 (m, 3H); 7.08 (s, 2H); 7.37 (m, 8H); 7.90 ppm (m, 2H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **7**: mp 234 °C. ^{1}H NMR ([D$_6$]DMSO) δ = 3.15 (m, 2H), 3.45 (m, 2H); 4.20 (m, 4H); 4.60 (m, 1H); 6.95 (m, 3H); 7.05 (s, 2H); 7.40 (m, 8H); 7.80 (m, 1H), 7.95 ppm (m, 1H). Anal. calcd for $C_{28}H_{27}NO_7$: C 68.70, H 5.56, N 2.86, found: C 68.53, H 5.57, N 3.22.

(2,2-Diphenyl-[1,3]dioxolan-4-yl-methyl)[2-(naphthalen-1-yloxy)-ethyl]amine (24): 0.55 g (1.3 mmol); yield 36%.^{1}H NMR ($CDCl_3$) δ = 1.88 (brs, 1H); 2.98 (ddd, 2H), 3.24 (t, 2H); 3.92 (dd, 1H); 4.15 (dd, 1H); 4.30 (t, 2H); 4.45 (m, 1H); 6.86 (m, 1H); 7.41 (m, 14H); 7.86 (m, 1H); 8.29 ppm (m, 1H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **8**: mp 194–195 °C. ^{1}H NMR ([D$_6$]DMSO) δ = 3.23 (ddd, 2H); 3.52 (t, 2H); 3.84 (dd, 1H); 4.09 (dd, 1H); 4.40 (t, 2H); 4.49 (m, 1H); 6.97 (m, 1H); 7.40 (m, 14H); 7.86 (m, 1H); 8.32 ppm (m, 1H). Anal. calcd for $C_{30}H_{29}NO_7$: C 69.89, H 5.67, N 2.72, found: C 70.10, H 5.54, N 3.03.

(2,2-Diphenyl-[1,3]dioxolan-4-yl-methyl)[2-(naphthalen-2-yloxy)-ethyl]amine (25): 0.93 g (2.2 mmol); yield 40% ^{1}H NMR ($CDCl_3$) δ = 1.84 (brs, 1H); 2.94 (ddd, 2H); 3.15 (t, 2H); 3.92 (dd, 1H); 4.15 (dd, 1H); 4.23 (t, 2H); 4.43 (m, 1H); 7.18 (m, 2H); 7.45 (m, 12H); 7.79 ppm (m, 3H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **9**: mp 189–190 °C. ^{1}H NMR ([D$_6$]DMSO) δ = 3.20 (m, 2H); 3.42 (t, 2H), 3.84 (dd, 1H); 4.08 (dd, 1H); 4.35 (t, 2H); 4.44 (m, 1H); 7.33 (m, 14H); 7.82 ppm (m, 3H). Anal. calcd for $C_{30}H_{29}NO_7$: C 69.89, H 5.67, N 2.72, found: C 70.01, H 5.70, N 3.07.

2,2-Diphenyl-[1,3]dioxolan-4-yl-methyl)(2-phenylsulfanyl-ethyl)-amine (26): 0.36 g (0.92 mmol); yield 26%; ^{1}H NMR ($CDCl_3$) δ = 2.41 (brs, 1H), 2.90 (m, 4H), 3.12 (t, 2H), 3.88 (dd, 1H), 4.11 (dd, 1H), 4.41 (m, 1H), 7.30 (m, 11H), 7.54 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **10**: mp 196 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 3.19 (m, 6H), 3.82 (dd, 1H), 4.08 (dd, 1H), 4.39 (m, 1H), 7.35 ppm (m, 15H). Anal. calcd for $C_{26}H_{27}NO_6S$: C 64.84, H 5.66, N 2.91, found: C 64.49, H 5.41, N 2.65.

***N*-(2,2-Diphenyl-[1,3]dioxolan-4-yl-methyl)*N*′-phenyl-ethane-1,2-diamine (27)**: 0.91 g (2.44 mmol), yield 45%; ^{1}H NMR ($CDCl_3$) δ = 2.15 (brs, 1H), 2.86 (m, 2H), 2.95 (dd, 2H), 3.24 (dd, 2H), 3.75 (brs, 1H), 3.91 (dd, 1H), 4.12 (dd, 1H), 4.39 (m, 1H), 6.71 (m, 3H), 7.30 (m, 8H), 7.53 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **11**: m.p. 187–188 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 3.25 (m, 6H), 3.85 (dd, 1H), 4.11 (dd, 1H), 4.46 (m, 1H), 6.62 (m, 3H), 7.13 (m, 2H), 7.41 ppm (m, 10H). Anal. calcd for $C_{26}H_{28}N_2O_6$: C 67.21, H 6.08, N 6.03, found: C 67.14, H 6.07, N 5.68.

(2,2-Diphenyl-[1,3]dioxolan-4-yl-methyl)(3-phenyl-propyl)amine (28): 0.56 g (1.5 mmol); yield 42%; ^{1}H NMR ($CDCl_3$) δ = 1.49 (brs, 1H), 1.80 (m, 2H), 2.64 (m, 4H), 2.78 (ddd, 2H), 3.84 (dd, 1H), 4.07 (dd, 1H), 4.33 (m, 1H), 7.26 (m, 11H), 7.49 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **12**: m.p. 192–194 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 2.02 (m, 2H), 2.75 (t, 2H), 3.19 (m, 4H),3.92 (dd, 1H), 4.19 (dd, 1H), 4.52 (m, 1H), 7.43 ppm (m, 15H). Anal. calcd for $C_{27}H_{29}NO_6$: C 69.95, H 6.31, N 3.02, found: C 70.22, H 6.45, N 3.40.

Benzyl-(2,2-diphenyl-[1,3]dioxolan-4-yl-methyl)amine (29): 0.26 g (0.75 mmol); yield 62%; ^{1}H NMR ($CDCl_3$) δ = 1.63 (brs, 1H), 2.81 (ddd, 2H), 3.83 (s, 2H), 3.86 (dd, 1H), 4.07 (dd, 1H), 4.36 (m, 1H), 7.30 (m, 11H), 7.49 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from

methanol to give compound **13**: mp 229–231 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 3.01 (ddd, 2H), 3.77 (dd, 1H), 4.06 (dd, 1H), 4.12 (s, 2H), 4.43 (m, 1H), 7.36 ppm (m, 15H). Anal. calcd for $C_{25}H_{25}NO_6$: C 68.95, H 5.79, N 3.22, found: C 68.58, H 5.79, N 3.50.

(2,2-Diphenyl-[1,3]dioxolan-4-yl-methyl)phenethylamine (30): 0.19 g (0.52 mmol); yield 43%; ^{1}H NMR ($CDCl_3$) δ = 1.55 (brs, 1H), 2.83 (m, 6H), 3.86 (dd, 1H), 4.07 (dd, 1H), 4,32 (m, 1H), 7.28 (m, 11H), 7.49 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **14**: mp 189–190 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 2.89 (m, 2H), 3.14 (m, 4H), 3.81 (dd, 1H), 4.06 (dd, 1H), 4.41 (m, 1H), 7.33 ppm (m, 15H). Anal. calcd for $C_{26}H_{27}NO_6$: C 69.47, H 6.05, N 3.12, found: C 69.11, H 6.09, N 3.45.

(2,2-Diphenyl-[1,3]dioxolan-4-yl-methyl)(4-phenylbutyl)amine (31): 0,10 g (0.27 mmol); yield 44%; ^{1}H NMR ($CDCl_3$) δ = 1.49 (brs, 1H), 1.60 (m, 4H), 2.65 (m, 4H), 2.80 (ddd, 2H), 3.86 (dd, 1H), 4.09 (dd, 1H), 4.35 (m, 1H), 7.27 (, 11H), 7.53 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **15**: mp 167–168 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 1.52 (m, 4H), 2.53 (t, 2H), 2.72 (t, 2H), 2.85 (d, 2H), 3.77 (dd, 1H), 4.02 (dd, 2H), 4.28 (m, 1H), 7.29 ppm (m, 15H). Anal. calcd for $C_{28}H_{31}NO_6$: C 70.42, H 6.54, N 3.23, found: C 70.80, H 6.19, N 3.52.

[2-(2,2-Diphenyl-[1,3]dioxolan-4-yl)ethyl](3-phenylpropyl)amine (32): 0,30 g (0.77 mmol); yield 74%; ^{1}H NMR ($CDCl_3$) δ = 1.57 (s, 1H), 1.80 (m, 4H), 2.74 (m, 6H), 3.69 (dd, 1H), 4.12 (dd, 1H), 4.22 (m, 1H), 7.28 (m, 11H), 7.50 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **16**:mp 195 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 1.87 (m, 4H), 2.60 (t, 2H), 2.97 (m, 4H), 3.68 (dd, 1H), 4.04 (dd, 1H), 4.20 (m, 1H), 7.31 ppm (m, 15H). Anal. calcd for $C_{28}H_{31}NO_6$: C 70.42, H 6.54, N 2.93, found: C 70.14, H 6.85, N 3.22.

***cis*-(2-Benzhydryl-[1,3]dioxolan-4-yl-methyl)(3-phenylpropyl)-amine (33c)**: 0.35 g (0.90 mmol); yield 95%. ^{1}H NMR ($CDCl_3$) δ = 1.46(brs, 1H), 1.72(m, 2H), 2.31(dd, 1H), 2.48(m, 3H), 2.62(t, 2H), 3.54 (dd, 1H), 3.90 (dd, 1H), 4.20 (m, 1H), 4.30 (d, 1H), 5.55 (d, 1H), 7.24 ppm (m, 15H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **17c**: mp 188 °C, ^{1}H NMR ([D$_6$]DMSO) δ = 1.82 (m, 2H), 2.55 (m, 3H), 2.78 (m, 2H), 2.93 (dd, 1H), 3.66(dd, 1H), 3.91(dd, 1H), 4.23 (d, 1H), 4.32 (m, 1H), 5.59 (d, 1H), 7.27 ppm (m, 15H). Anal. calcd for $C_{28}H_{31}NO_6$: C 70.42, H 6.54, N 2.93, found: C 70.30, H 6.60, N 3.30.

***trans*-(2-Benzhydryl-[1,3]dioxolan-4-yl-methyl)(3-phenylpropyl)-amine (33t)**: 0.16 g (0.41 mmol); yield 51%. ^{1}H NMR ($CDCl_3$) δ = 1.56 (brs, 1H), 1.80 (m, 2H), 2.70 (m, 6H), 3.56 (dd, 1H), 3.90 (dd, 1H), 4.00 (m, 1H), 4.21(d, 1H), 5.67 (d, 1H), 7.25 ppm (m, 15H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **17t**: mp 217–218 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 1.87 (m, 2H), 2.58 (t, 2H), 2.86 (m, 2H), 3.05 (m, 2H), 3.55 (dd, 1H), 3.95 (dd, 1H), 4.18 (d, 1H), 4.25 (m, 1H), 5.72 (d, 1H), 7.25 ppm (m, 15H). Anal. calcd for $C_{28}H_{31}NO_6$: C 70.42, H 6.54, N 2.93, found: C 70.35, H 6.45, N 3.23.

***cis*-[2-(2-Benzyhydryl-[1,3]dioxolan-4-yl)ethyl](3-phenylpropyl)-amine (34c)**: 0.11 g (0.28 mmol); yield 58%; ^{1}H NMR ($CDCl_3$) δ = 1.47 (brs, 1H), 1.50 (m, 2H), 1.77 (m, 2H), 2.61 (m, 6H), 3.29 (dd, 1H), 3.90 (dd, 1H), 4.11 (m, 1H), 4.22 (d, 1H), 5.53 (d, 1H), 7.26 ppm (m, 15H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **18c**: mp 173–174 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 1.76 (m, 4H), 2.62 (t, 2H), 2.78 (m, 4H), 3.45 (dd, 1H), 3.88 (dd, 1H), 4.14 (m, 1H), 4.16 (d, 1H), 5.53 (d, 1H), 7.27 ppm (m, 15H). Anal. calcd for $C_{29}H_{33}NO_6$: C 70.86, H 6.77, N 2.85, found: C 70.74, H 6.92, N 3.16.

***trans*-[2-(2-Benzyhydryl-[1,3]dioxolan-4-yl)-ethyl]-(3-phenyl-propyl)-amine (34t)**: 0.08 g (0.20 mmol); yield 42%; ^{1}H NMR ($CDCl_3$) δ = 1.65 (brs, 1H), 1.75 (m, 4H), 2.66 (m, 6H), 3.45 (dd, 1H), 3.88 (m, 1H), 3.96 (dd, 1H), 4.20 (d, 1H), 5.67 (d, 1H), 7.27 ppm (m, 15H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **18t**: mp 165 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 1.82 (m, 4H), 2.61 (t, 2H), 2.90 (m, 4H), 3.46 (dd, 1H), 3.98 (m, 2H), 4.12 (d, 1H), 5.66 (d, 1H), 7.20 ppm (m, 15H). Anal. calcd for $C_{29}H_{33}NO_6$: C 70.86, H 6.77, N 2.85, found: C 70.53, H 6.90, N 3.20.

(2,2-Diphenyl-[1,3]oxathiolan-5-yl-methyl)(3-phenylpropyl)amine (35): 0.22 g (0.57 mmol); yield 54%. ^{1}H NMR ($CDCl_3$) δ = 1.60 (brs, 1H), 1.85 (m, 2H), 2.69 (m, 4H), 2.98 (ddd, 2H), 3.14 (m, 2H), 4.32 (m, 1H), 7.29 (m, 13H), 7.61 ppm (m, 2H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **19**: mp 185–188 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 1.92 (m, 2H), 2.65 (m, 2H), 2.92 (m, 2H), 3.16 (m, 4H), 4.30 (m, 1H), 7.28 (m, 13H), 7.55 ppm (m, 2H). Anal. calcd for $C_{27}H_{29}NO_5S$: C 67.62, H 6.09, N 2.92, found: C 67.68, H 6.25, N 3.02.

(2,2-Diphenyl-[1,3]dithiolan-4-yl-methyl)(3-phenyl-propyl)amine (36): 0.20 g (0.49 mmol); yield 61%. ^{1}H NMR ($CDCl_3$) δ = 1.44 (brs, 1H), 1.83 (m, 2H), 2.65 (m, 4H), 2.95 (m, 2H), 3.27 (d, 2H), 4.08 (m, 1H), 7.23 (m, 11H), 7.60 ppm (m, 4H). The free amine was transformed into the corresponding oxalate salt, which was crystallized from methanol to give compound **20**: mp 187–192 °C; ^{1}H NMR ([D$_6$]DMSO) δ = 1.87 (m, 2H), 2.62 (t, 2H), 2.89 (m, 2H), 3.11 (dd, 1H), 3.30 (m, 2H), 3.45 (dd, 1H), 4.25 (m, 1H), 7.30 (m, 13H), 7.53 ppm (m, 2H). Anal. calcd for $C_{27}H_{29}NO_4S_2$: C 65.43, H 5.90, N 2.83, found: C 65.49, H 6.03, N 2.99.

4′-(Chloromethyl)-spiro[5*H*-dibenzo[a,d]cyclohepten-5,2′-[1,3]di-oxolane] (37): A solution of dibenzo[a,d]cyclohepten-5-one (1.0 g, 4.8 mmol) in toluene (70 mL) was treated with an excess of 3-chloro-propane-1,2-diol (5 equiv) and a catalytic amount of *p*TsOH. The reaction mixture was refluxed with a Dean–Stark apparatus, for 6 days. The reaction mixture was washed with H_2O (2×), saturated $NaHCO_3$ (2×) and saturated NaCl (2×). The organic layer was dried (Na_2SO_4) and concentrated. Purification by flash chromatography (cyclohexane/EtOAc, 99.5:0.5) gave compound **37** as oil: 0.43 g (1.5 mmol); yield 30%; ^{1}H NMR ($CDCl_3$) δ = 3.78 (ddd, 2H), 4.20 (dd, 1H), 4.44 (dd, 1H), 4.70 (m, 1H), 7.15 (s, 2H), 7.44 (m, 6H), 7.89 ppm (m, 2H).

Known compounds, 4-chloromethyl-2,2-diphenyl-[1,3]dioxolane,[13] 2-benzhydryl-4-chloromethyl-[1,3]dioxolane,[13] 4-(chloromethyl)-spiro[1,3-dioxolane-2,9′-[9*H*]fluorene],[20] 4′-(chloromethyl)-10,11-dihydro-spiro[5*H*-dibenzo[a,d]cyclohepten-5,2′-[1,3]dioxolane],[21] 5-(chloromethyl)-2,2-diphenyl-1,3-oxathiolane,[20] 4-(chloromethyl)-2,2-diphenyl-1,3-dithiolane,[20] were prepared using the procedure described above.

General procedure for the synthesis of compound 40 and 41: A solution of benzophenone or diphenylacetaldeide in toluene was

treated with an excess of 1,2,4-butanetriol (1.5–3 equiv) and a catalytic amount of *p*TsOH. The reaction mixture was refluxed with a Dean–Stark apparatus for 2 days. The reaction mixture was washed with H_2O (2×), saturated $NaHCO_3$ (2×) and saturated NaCl (2×). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (cyclohexane/EtOAc, 80:20) gave the desired alcohol as an oil.

2-(2,2-Diphenyl-[1,3]dioxolan-4-yl)-ethanol (40): 5.30 g (19.6 mmol); yield 34%; ^{1}H NMR ([D$_6$]DMSO) $\delta = 1.88$ (m, 2H), 3.77 (m, 3H), 4.15 (dd 1H), 4.35(m, 1H), 7.32 (m, 6H), 7.55 (m, 4H).

For compound **41**, a mixture of dioxane/dioxolane derivatives was obtained and no attempts at diastereomeric separation were made at this stage.

General procedure for the synthesis of compound 38 and 39c,t: A solution of the appropriate alcohol in toluene and pyridine (1.6:1) was cooled to 0 °C and treated dropwise with thionyl chloride (1.3 equiv). The reaction was warmed to RT and refluxed for 2 h. The reaction mixture was concentrated in vacuo, water was added, and the crude mixture was extracted with EtOAc (×2). The organic layer was washed with H_2O (×2) and saturated NaCl (×1), dried (Na_2SO_4) and concentrated in vacuo. Purification and separation of the diastereoisomers was achieved by flash chromatography (cyclohexane/EtOAc, 98:2).

4-(2-Chloro-ethyl)-2,2-diphenyl-[1,3]dioxolane (38): 1.27 g (4.4 mmol); yield 40%; ^{1}H NMR ($CDCl_3$) $\delta = 2.10$ (m, 2H), 3.72 (m, 3H), 4.16 (dd, 1H), 4.39 (m, 1H), 7.30 (m, 6H), 7.52 ppm (m, 4H).

***cis*-2-Benzhydryl-4-(2-chloro-ethyl)-[1,3]dioxolane (39c)**: 0.40 g (1.3 mmol); yield 17%; ^{1}H NMR ($CDCl_3$) $\delta = 1.62$ (m, 2H), 3.39 (dd, 1H), 3.45 (m, 2H), 3.96 (dd, 1H), 4.25 (m, 1H), 4.29 (d, 1H), 5.58 (d, 1H), 7.30 ppm (m, 10H).

***trans*-2-Benzhydryl-4-(2-chloro-ethyl)-[1,3]dioxolane (39t)**: 0.10 g (0.3 mmol); yield 15%; ^{1}H NMR ($CDCl_3$) $\delta = 1.88$ (m, 1H), 2.07 (m, 1H), 3.50 (dd, 1H), 3.62 (m, 2H), 3.93 (dd, 1H), 4.02 (m, 1H), 4.25 (d, 1H), 5.68 (d, 1H), 7.30 ppm (m, 10H).

Biology

Functional Antagonism in Isolated Tissues

Male Wistar rats (275–300 g) were killed by cervical dislocation, and the organs required were extracted, freed from adhering connective tissues, and set up rapidly under a suitable resting tension in 20 mL organ baths containing physiological salt solution kept at 37 °C and aerated with 5% CO_2 and 95% O_2 at pH 7.4. Concentration-response curves were constructed by cumulative addition of the test agonist. The concentration of agonist in the organ bath was increased approximately threefold at each step, with each addition being made only after the response to the previous addition had reached a maximal level and remained steady. Contractions were recorded by means of a force displacement transducer connected to a Mac Lab system PowerLab/800 and to a polygraph channel recorder (Gemini). Additionally, parallel experiments in which tissues did not receive any test compound were run in order to check any variation in sensitivity.

All animal testing was carried out according to the European Community Council Directive of November 1986 (86/609/EEC).

Vas deferens prostatic portion: This tissue was used to assess the antagonism towards α_{1A}-adrenoceptors.[15] Prostatic portions of 2 cm length were mounted under 0.5 g tension at 37 °C in Tyrode's solution (NaCl, 130; KCl, 1; $CaCl_2$, 1.8, $MgCl_2$, 0.89; NaH_2PO_4, 0.42; $NaHCO_3$, 25; glucose, 5.6 mM). Cocaine hydrochloride (0.1 μM) was added to the Tyrode's solution to prevent the neuronal uptake of (−)-noradrenaline. The preparations were equilibrated for 60 min with washing every 15 min. After the equilibration period, tissues were primed twice by addition of noradrenaline (10 μM). After another washing and equilibration period of 60 min, a noradrenaline concentration-response curve was constructed (basal response). The antagonist was allowed to equilibrate for 30 min before constructing a new concentration-response curve to the agonist. (−)-Noradrenaline solutions contained 0.05% $Na_2S_2O_5$ to prevent oxidation.

Spleen: This tissue was used to assess the antagonism towards α_{1B}-adrenoceptors.[16] The spleen was removed and bisected longitudinally into two strips, which were suspended in tissue baths containing Kreb's solution (NaCl, 120; KCl, 4.7; $CaCl_2$, 2.5, $MgSO_4$, 1.5; KH_2PO_4, 1.2; $NaHCO_3$, 20; glucose, 11; K_2EDTA, 0.01 mM). Propranolol hydrochloride (4 μM) was added to block β-adrenoceptors. The spleen strips were placed under 1 g resting tension and equilibrated for 2 h. The cumulative concentration-response curves to phenylephrine were measured isometrically and obtained at 30 min intervals, the first one being discarded and the second taken as a control. The antagonist was allowed to equilibrate for 30 min before constructing a new concentration-response curve to the agonist.

Aorta: This tissue was used to assess the antagonism towards α_{1D}-adrenoceptors.[17] Thoracic aorta was cleaned from extraneous connective tissues and placed in Kreb's solution (NaCl, 118.4; KCl, 4.7; $CaCl_2$, 1.9, $MgSO_4$, 1.2; NaH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11.7; K_2EDTA, 0.01 mM). Cocaine hydrochloride (0.1 μM) and propranolol hydrochloride (4 μM) were added to prevent the neuronal uptake of (−)-noradrenaline and to block β-adrenoceptors, respectively. Two helicoidal strips (15 mm×3 mm) were cut from each aorta beginning from the end proximal to the heart. The endothelium was removed by rubbing with filter paper. The absence of acetylcholine (100 μM) -induced relaxation in preparations contracted with (−)-noradrenaline (1 μM) was taken as an indicator that the vessels were denuded successfully. Vascular strips were then tied with surgical thread and suspended in a jacketed tissue bath containing Tyrode's solution. Strip contractions were measured isometrically. After an equilibration period of at least 2 h and under an optimal tension of 1 g, cumulative (−)-noradrenaline concentration-response curves were recorded at 1 h intervals, the first two being discarded and the third one taken as control. The antagonist was allowed to equilibrate with the tissue for 30 min before the generation of the fourth cumulative concentration-response curve to (−)-noradrenaline. (−)-Noradrenaline solutions contained 0.05% K_2EDTA in 0.9% NaCl to prevent oxidation.

Radioligand-binding assays

Human cell line (HeLa) stably transfected with genomic clone G-21 coding for the human 5-HT_{1A} serotonin receptor was used. HeLa cells were grown as monolayers in Dulbecco's Modified Eagle's Medium (DMEM), supplemented with 10% fetal calf serum and gentamicin (100 mg mL^{-1}) under 5% CO_2 at 37 °C. Cells were detached from the growth flask at 95% confluency by a cell scraper and were lysed in ice-cold Tris (5 mM) and EDTA (5 mM) buffer

(pH 7.4). Homogenates were centrifuged for 20 min at 40,000 *g*, and pellets were resuspended in a small volume of ice-cold Tris (5 mM) and EDTA (5 mM) buffer (pH 7.4), and immediately frozen and stored at −70 °C until use. On the day of the experiment, cell membranes were resuspended in binding buffer (50 mM Tris, 2.5 mM $MgCl_2$, and 10 mM pargyline, pH 7.4). Membranes were incubated in a final volume of 1 mL for 30 min at 30 °C with [^{3}H]8-OH-DPAT (1 nM), in the absence or presence of various concentrations of the competing drugs (1 pM–10 mM); each experimental condition was performed in triplicate. Nonspecific binding was determined in the presence of 5-hydroxytryptamine (5-HT, 10 mM). Binding to recombinant human α_1-adrenoceptor subtypes was performed in membranes from Chinese hamster ovary (CHO) cells transfected by electroporation with DNA expressing the gene encoding each α_1-adrenoceptor subtype. Cloning and stable expression of the human α_1-adrenoceptor genes were performed as described previously.[18] CHO cell membranes were incubated in 50 mM Tris (pH 7.4) with [^{3}H]prazosin (0.2 nM), in a final volume of 1.02 mL for 30 min at 25 °C, in the absence or presence of competing drugs (1 pM–10 mM). Nonspecific binding was determined in the presence of phentolamine (10 mM). The incubation was stopped by the addition of ice-cold Tris buffer and rapid filtration through 0.2% polyethyleneimine pretreated Whatman GF/B or Schleicher & Schuell GF52 filters.

[^{35}S]GTPγS binding: The effects of different compounds on [^{35}S]GTPγS binding in HeLa cells expressing the recombinant human 5-HT$_{1A}$ receptor were evaluated according to the method of Stanton and Beer[22] with minor modifications. On the day of the experiment, cell membranes were resuspended in buffer containing HEPES (20 mM), $MgSO_4$ (3 mM), and NaCl (120 mM) (pH 7.4). The membranes were incubated with GDP (30 mM) and different concentrations of test drugs (0.1 nM–100 mM) or 5-HT (reference curve) for 20 min at 30 °C in a final volume of 0.5 mL. Samples were cooled on ice, [^{35}S]GTPγS (200 pM) was added, and the samples were then incubated for another 30 min at 30 °C. For both procedures, nonspecific binding was determined in the presence of GTPγS (10 mM). Incubation was stopped by the addition of ice-cold HEPES buffer and rapid filtration on Schleicher & Schuell GF52 filters using a Brandel cell harvester. The filters were washed with ice-cold buffer, and the radioactivity retained on the filters was counted by liquid scintillation spectrometry at 90% efficiency.

Data analysis

In functional studies, responses were expressed as a percentage of the maximal contraction observed in the agonist concentration-response curves, taken as a control, which were analyzed by pharmacological computer programs. pK_b values were calculated according to van Rossum[23] at one or two concentrations. Binding data were analyzed using the nonlinear curve-fitting program, Allfit.[24] Scatchard plots were linear in all preparations. None of the pseudo-Hill coefficients (n^H) were significantly different from unity ($p > 0.05$). Equilibrium dissociation constants (K_i) were derived from the Cheng–Prusoff[25] equation: $K_i = IC_{50}/(1 + L/K_d)$, where L and K_d are the concentration and the equilibrium dissociation constant of the radioligand. pK_i values are the mean of 2–3 separate experiments performed in triplicate. Stimulation of [^{35}S]GTPγS binding induced by the compounds tested was expressed as the percent increase in binding above basal value, with the maximal stimulation observed with 5-HT taken as 100%. The concentration-response curves of the agonistic activity were analyzed by Allfit as reported above. The maximum percentage of stimulation of [^{35}S]GTPγS binding (E_{max}) achieved for each drug, and the concentration required to obtain 50% of E_{max} (p$D_2 = -\log_{10}$ EC$_{50}$ value), were evaluated.

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Keywords: 5-HT$_{1A}$ · biological activity · drug design · receptors · structure–activity relationships

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