Articles

New (2-Methoxyphenyl)piperazine Derivatives as 5-HT_{1A} Receptor Ligands with Reduced α_1-Adrenergic Activity. Synthesis and Structure–Affinity Relationships

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New 2-(methoxyphenyl)piperazine derivatives **1** and **2** containing a terminal heteroaryl or cycloaklyl amide fragment were prepared and their 5-HT_{1A} affinities evaluated by radioligand binding assays. The influence of the alkyl chain length or the amide group on affinity was evaluated. A four-carbon chain appears to be optimal when the amide fragment is a heteroaryl group. Derivatives with a cycloalkyl moiety displayed maximum affinity in the two methylene chain series. Electronic distribution within the amide region seems to have an influence on affinity in heteroaryl derivatives. Replacement of the heteroaryl moiety by a cycloalkyl group led to compounds with enhanced affinity. Increasing the lipophilicity of the cycloalkyl derivatives by annelation and/or saturation increased their affinity for the 5-HT_{1A} sites. Compounds with *cis*-bicyclo[3.3.0]octane (**2a**, **2c**), norbornane (**2f**, **2g**), and norbornene (**2h**, **2i**) groups bind at 5-HT_{1A} sites with 2–10-fold higher affinity than NAN-190. Antagonist activity at α_1-adrenergic receptors was evaluated for compounds with high affinity at 5-HT_{1A} sites. Compounds **2a**, **2c**, **2f**, **2g**, and **2h** strongly bind (K_i = 0.12–0.63 nM) at 5-HT_{1A} receptors and are devoid of antagonist activity at α_1-adrenergic receptors.

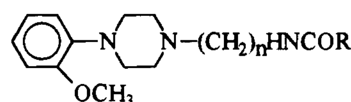
Introduction

In the last years, serotonin (5-hydroxytryptamine, 5-HT) receptors have been the subject of intense research, in part because receptor-binding studies and molecular biology have opened up new aspects of understanding but also because of the potential to find new medicines due to their possible involvement in numerous physiological and pathophysiological processes.[1–4] Multiple 5-HT receptor subtypes have been described in recent years.[5,6] Receptor-binding studies have shown that the majority of compounds with affinity for 5-HT receptors display a high to moderate affinity for more than one 5-HT receptor subtype and are often nonselective with respect to other receptors.[7]

The discovery that the anxiolytic agent buspirone, which also has antidepressant properties, binds with high affinity to 5-HT_{1A} receptors[8] has encouraged the development of 5-HT_{1A} receptor ligands as potential drugs. Several classes of agents are known to bind at 5-HT_{1A} receptor sites, such as aminotetralins, indolylalkylamines, aryloxyalkylamines, alkylpiperidines, and arylpiperazines.[9,10]

With regard to long-chain arylpiperazines,[9] they have the two structural features necessary for recognition of ligands by the 5-HT_{1A} sites: an aromatic ring and a strongly basic nitrogen atom at a distance of 5.2–5.6 Å.[11–13] The incorporation of an *o*-methoxy substituent has led to compounds with high affinity at 5-HT_{1A} binding sites.[14–18] The influence of the side chain length on 5-HT_{1A} affinity appears to be variable depending on each series of compounds.[9,18] The role of a terminal amide fragment has been extensively studied. The electron density distribution within this structural feature[19] and its hydrophobic/hydrophilic properties[20] have been considered important factors for 5-HT_{1A} affinity. However, some reported results have demonstrated that the amide moiety is not always necessary for binding.[15]

Chart 1



In general, (*o*-methoxyphenyl)piperazine derivatives are selective for 5-HT_{1A} sites over other serotonergic sites but possess an almost equal affinity for α_1-adrenergic receptors. Attempts have been made to identify and eliminate those structural features that account for α_1-adrenergic affinity.[21,15]

The aim of the present study was to develop a series of (*o*-methoxyphenyl)piperazine derivatives **1** and **2** with affinity for 5-HT_{1A} sites (Chart 1). The influence of the alkyl side chain length and the terminal amide fragment on affinity for 5-HT_{1A} binding sites was studied. For a selected number of compounds we evaluated the antagonistic activity at α_1-adrenergic receptors in order to find a high-affinity 5-HT_{1A} ligand with high selectivity for 5-HT_{1A} over α_1-adrenergic receptors.

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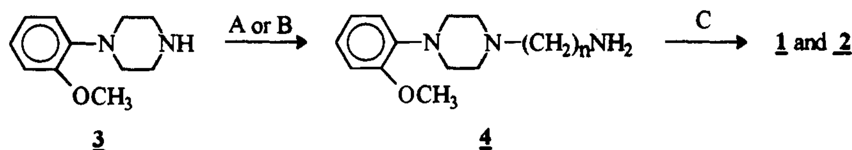
Table 1. (*o*-Methoxyphenyl)piperazine Derivatives 1 and 2

compound	*n*	R	formula[a]	% yield	mp, °C[b]
1a	2	2-pyrrolyl	$C_{18}H_{23}N_4O_2$	72	147–9
1b	3	2-pyrrolyl	$C_{19}H_{25}N_4O_2$	68	156–8
1c	4	2-pyrrolyl	$C_{20}H_{27}N_4O_2$	76	173–4
1d	2	3-pyridyl	$C_{19}H_{24}N_4O_2$	65	109–10
1e	3	3-pyridyl	$C_{20}H_{26}N_4O_2$	63	95–8
1f	4	3-pyridyl	$C_{21}H_{26}N_4O_2$	58	80–2
1g	2	3-thienyl	$C_{18}H_{23}N_3O_2S$	71	123–5
1h	4	3-thienyl	$C_{20}H_{27}N_3O_2S$	88	88–92
1i	2	5-methyl-2-thienyl	$C_{19}H_{25}N_3O_2S$	60	160–2
1j	4	5-methyl-2-thienyl	$C_{21}H_{29}N_3O_2S$	68	103–5
1k	2	3-thienylmethyl	$C_{19}H_{25}N_3O_2S$	76	86–8
1l	4	3-thienylmethyl	$C_{21}H_{29}N_3O_2S$	71	87–9
1m	2	3-methyl-2-thienyl	$C_{19}H_{25}N_3O_2S$	78	91–4
1n	4	3-methyl-2-thienyl	$C_{21}H_{29}N_3O_2S$	70	79–82
1o	2	1-methyl-2-pyrrolyl	$C_{19}H_{26}N_4O_2$	63	114–7
1p[c]	4	1-methyl-2-pyrrolyl	$C_{21}H_{30}N_4O_2{\cdot}C_4H_4O_4$	60	157–60
1q	4	2-thienyl	$C_{20}H_{27}N_3O_2S$	65	118–20
1r	4	3-chloro-2-thienyl	$C_{20}H_{26}ClN_3O_2S$	58	70–3
1s[c]	4	3-methoxy-2-thienyl	$C_{21}H_{29}N_3O_3S{\cdot}C_4H_4O_4$	50	117–9
1t[c]	4	2-furyl	$C_{20}H_{27}N_3O_3{\cdot}C_4H_4O_4$	68	125–8
2a[d]	2	*cis*-bicyclo[3.3.0]octan-2-yl	$C_{22}H_{33}N_3O_2$	60	116–8
2b[d]	3	*cis*-bicyclo[3.3.0]octan-2-yl	$C_{23}H_{35}N_3O_2$	55	84–6
2c[d]	4	*cis*-bicyclo[3.3.0]octan-2-yl	$C_{24}H_{37}N_3O_2$	60	68–70
2d	2	cyclopentanyl	$C_{19}H_{29}N_3O_2$	60	134–6
2e	4	cyclopentanyl	$C_{21}H_{33}N_3O_2$	65	115–7
2f[d]	2	norbornan-2-yl	$C_{21}H_{31}N_3O_2$	62	134–6
2g[c,d]	4	norbornan-2-yl	$C_{23}H_{35}N_3O_2{\cdot}C_4H_4O_4$	67	146–50
2h[d]	2	5-norbornen-2-yl	$C_{21}H_{29}N_3O_2$	58	123–5
2i[d]	4	5-norbornen-2-yl	$C_{23}H_{33}N_3O_2$	50	136–9

[a] Analyses for C, H, N. [b] Recrystallization solvent: hexane/EtOH. [c] Fumarate. [d] Mixture of endo and exo.

Chart 2[a]



[a]Reagents: A: (i) $Br(CH_2)_{n-1}CN$, ButOH, K_2CO_3, reflux, 2h; (ii) $LiAlH_4$, Et_2O, 20°C, 10h;

B: (i): $Br(CH_2)_n$-N-phthalimide, CH_3CN, reflux, 6h; (ii): $N_2H_4.H_2O$, EtOH, reflux, 6h;

C: RCOCl, Et_3N, THF, 20°C, 3h

Chemistry

All new compounds are shown in Table 1. The general synthetic procedure used is illustrated in Chart 2.

(Aminoalkyl)piperazines **4** were prepared following two standard procedures.[14,22] Alkylation of (*o*-methoxyphenyl)piperazine **3** with bromoalkyl nitriles in butanol in the presence of potassium carbonate afforded the corresponding nitrile derivatives, which, after reduction with lithium aluminum hydride in ether, gave **4** in 50–80% yield (Chart 2, method A). Appropriate *N*-(bromoalkyl)phthalimide was treated with **3** to yield imide derivatives which, by hydrazinolysis, were converted to **4** (Chart 2, method B). Compounds **4** were acylated with the corresponding heteroaryl or cycloalkyl acid chloride to give **1** and **2** (Chart 2, method C).

Pharmacology

All compounds were evaluated for *in vitro* 5-HT_{1A} receptor affinity by radioligand binding assay. For each compound, the ability to displace the specific ligand [^{3}H]-8-OH-DPAT from 5-HT_{1A} sites of rat brain cortex was determined. For a selected number of compounds, the antagonistic activity at α_1-adrenergic receptors was performed on ring segments of rabbit thoracic aorta contracted by noradrenaline.

Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) and K_i were calculated from two separate competition experiments with samples in triplicate using 12 different concentrations of the displacer. The negative logarithm of the molar concentration causing a 2-fold shift to the right of the concentration–response curve for noradrenaline (pA_2) was

Table 2. 5-HT_{1A} Binding Data[a]

compd	K_i (nM) (±SE)[b]	compd	K_i (nM) (±SE)[b]
1a	20.3(±1.83)	**1q**	2.34(±0.28)
1b	201(±19.1)	**1r**	3.34(±0.21)
1c	12.5(±1.36)	**1s**	32.13(±4.67)
1d	362(±32.1)	**1t**	55.71(±10.65)
1e	321(±28.8)	**2a**	0.24(±0.07)
1f	25.2(±2.05)	**2b**	11.6(±1.20)
1g	6.83(±0.67)	**2c**	0.63(±0.05)
1h	2.20(±0.19)	**2d**	4.68(±0.50)
1i	2.29(±0.27)	**2e**	1.88(±0.22)
1j	3.80(±0.23)	**2f**	0.12(±0.03)
1k	32.3(±1.73)	**2g**	0.23(±0.09)
1l	17.5(±1.07)	**2h**	0.27(±0.03)
1m	3.09(±0.25)	**2i**	0.38(±0.02)
1n	1.53(±0.14)	buspirone[c]	15.4(±1.27)
1o	1.19(±0.07)	NAN-190[d]	1.26(±0.05)
1p	0.74(±0.04)	8-OH-DPAT[e]	1.18(±0.05)

[a] Displacement of [^{3}H]-8-OH-DPAT. [b] Standard error. [c] 8-[4-[4-(2-Pyrimidinyl)butyl]-8-azaspiro[4.5]decane-7,9-dione. [d] 1-(2-Methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine. [e] 8-Hydroxy-2-(dipropylamino)tetralin.

determined according to Van Rossum[23] and expressed as a mean ± SE of data from three separate experiments.

Results and Discussion

Compounds 1 and **2** demonstrated moderate to high affinity for the 5-HT_{1A} receptor binding sites. Results are summarized in Table 2.

Increasing the two methylene chain by one carbon atom in **1d** (K_i = 362 nM) led to **1e** (K_i = 321 nM) with little affinity enhancement, whereas a similar modification led to a marked reduction in the affinity in two pairs of compounds: **1a** (K_i = 20.3 nM) and **1b** (K_i = 201 nM), **2a** (K_i = 0.24 nM) and **2b** (K_i = 11.6 nM).

In addition, increasing the length of the side chain by two methylene groups in the series **1** resulted in a significant improvement in the 5-HT_{1A} affinity; e.g., compare **1a** (K_i = 20.3 nM) with **1c** (K_i = 12.5 nM), **1d** (K_i = 362 nM) with **1f** (K_i = 25.2 nM), **1g** (K_i = 6.83 nM) with **1h** (K_i = 2.20 nM), **1k** (K_i = 32.3 nM) with **1l** (K_i = 17.5 nM), etc. Consequently, it seems that in this series a chain length of four carbon atoms is optimal for high affinity. This conclusion agrees with reported results for other arylpiperazine derivatives.[24,25] Exceptionally, the affinity of the four chain derivative **1j** (K_i = 3.80 nM) was somewhat lower in comparison to that of the two carbon chain analogue **1i** (K_i = 2.29 nM). Therefore, we have no evidence that the mode of binding might not be identical throughout the same series and the observed exception might be only fortuitous. A different trend was found in the series **2** with respect to the elongation of the alkyl chain: maximum affinity is reached in the two methylene chain derivatives; e.g., compare **2a** (K_i = 0.24 nM) with **2c** (K_i = 0.63 nM), **2f** (K_i = 0.12 nM) with **2g** (K_i = 0.23 nM), and **2h** (K_i = 0.27 nM) with **2i** (K_i = 0.38 nM).

Upon examination of compounds **1**, it is apparent that thienyl, pyrrolyl, furyl, and pyridyl groups are tolerated by 5-HT_{1A} receptors. Upon comparison of **1c** with **1q** and **1t**, it appears that sulfur is the most appropriate heteroatom in the heteroaryl moiety. Sulfur derivative **1q** (K_i = 2.34 nM) binds with more than 5 times the affinity of its nitrogen derivative analogue **1c** (K_i = 12.5 nM) and more than 20 times the affinity of the oxygen derivative **1t** (K_i = 55.71 nM). However, nitrogen-substituted derivatives **1o** (K_i = 1.19 nM) and **1p** (K_i = 0.74 nM) showed the highest affinity in the series.

Table 3. α_1-Adrenergic Receptor Antagonism[a]

compd	pA_2(±SEM)[b]	compd	pA_2(±SEM)[b]
1g	<7	**2a**	<7
1j	<7	**2c**	<7
1o	<7	**2f**	<7
1p	7.72(±0.18)	**2g**	<7
1q	9.16(±0.09)	**2h**	<7
1r	8.16(±0.16)	**2i**	8.53(±0.10)
buspirone	6.24(±0.16)	prazosin	9.42(±0.08)
NAN-190	9.18(±0.09)		

[a] Displacement of dose–response curve to noradrenaline. [b] Standard error mean.

Compounds **1k** (K_i = 32.3 nM) and **1l** (K_i = 17.5 nM), in which the carbonyl group is not directly attached to the aromatic nucleus, exhibited lower affinity than compounds **1g** (K_i = 6.83 nM) or **1h** (K_i = 2.20 nM) with conjugation within the amide fragment. The introduction of an electron-donating substituent in **1q** (K_i = 2.34 nM) led to **1s** (K_i = 32.13 nM) with a lower affinity. These results are consistent with the importance of the electronic distribution within the amide region and the electronic nature for the anchoring group–ligand interaction.[19] However, an electron-withdrawing substituent in the same position (**1r**, K_i = 3.34 nM) seems to have a small effect. Therefore, it is arguable that other factors (i.e., steric hindrance) might be implicated in this result.

On the other hand, it is known that increasing the lipophilicity of the aryl- and heteroarylpiperazinyl imides by annelation and/or saturation of the cycloalkyl moiety increases their affinity for the 5-HT_{1A} binding sites.[22] Thus, replacement of the cyclopentyl ring in **2d** (K_i = 4.68 nM) or **2e** (K_i = 1.88 nM) by a bulkier cycloalkyl moiety (**2a**, **2c**, **2f–i**) led to a higher affinity (K_i = 0.12–0.63 nM). Furthermore, saturation of the ethylene bridge in **2h** (K_i = 0.27 nM) and **2i** (K_i = 0.38 nM), which also implies an increasing in the lipophilicity, yielded **2f** (K_i = 0.12 nM) and **2g** (K_i = 0.23 nM) with higher affinity. This fact suggests that the interaction of the amide fragment with the receptor may have a hydrophobic character.

Upon examination of derivatives **1** and **2**, we conclude that replacement of heteroaryl amides by bulky cycloalkyl amides improved affinity for 5-HT_{1A} binding sites. Multiple factors seem to be implicated in ligand–receptor interactions at the level of the amide moiety, and even they might be different in each series of compounds. Since the nature of the amide participation is not quite clear, further studies are required.

Antagonistic activity at α_1-adrenergic receptors was evaluated for a selected number of compounds. Results are summarized in Table 3.

With the exception of **1q** (pA_2 = 9.16) and **1r** (pA_2 = 8.16), heteroaryl amide derivatives **1** displayed moderate to low antagonism at α_1-adrenergic receptors (pA_2 < 7.75). Comparing **1q** and **1r**, we conclude that halogen substitution is detrimental to α_1-adrenergic activity whereas the corresponding methyl analogue **1j** (pA_2 < 7) showed better selectivity for 5-HT_{1A} sites versus α_1-adrenergic receptors.

As a general trend, bulky cycloalkyl amides **2** showed low pA_2 values, although an exception was noted in compound **2i** (pA_2 = 8.53). Upon examination of **2g** (pA_2 < 7) and **2i** (pA_2 = 8.53), it seems that an increasing in

the lipophilicity improved the selectivity, but this is not a general rule; e.g., compare **2f** (pA_2 < 7) and **2h** (pA_2 < 7).

Finally, both structural features, the alkyl side chain length and the nature of the terminal amide fragment, seem to play a significant role on the binding at 5-HT_{1A} sites in (*o*-methoxyphenyl)piperazine derivatives **1** and **2**.

Compounds **1p**, **2a**, **2c**, and **2f–i** bind at 5-HT_{1A} sites with higher (2–10-fold) affinity and greater selectivity for 5-HT_{1A} versus α_1-adrenergic receptors than NAN-190 does.[14] Moreover, compounds **2a**, **2c**, **2f**, **2g**, and **2h** strongly bind (K_i = 0.12–0.63 nM) at 5-HT_{1A} receptor sites and are devoid of antagonist activity at α_1-adrenergic receptor sites. Therefore, the (*o*-methoxyphenyl)piperazines **2a**, **2g**, **2h**, and in particular **2f** display a very high affinity toward 5-HT_{1A} sites, similar to, or greater than, that of 4-[4-(1-noradamantanecarboxamido)butyl]-1-(2-methoxyphenyl)piperazine,[15] the highest affinity ligand reported to date. These derivatives have been selected for further studies in order to separate the mixture of isomers, to complete their binding profile, and to characterize their pharmacological properties.

Experimental Section

Chemistry. Commercially unavailable acid chlorides were prepared from the corresponding acids by reacting with thionyl chloride. Flash column chromatography was performed with silica gel, particle size 60 Å, mesh = 230–400 (Merck). Melting points were determined in open capillaries on a Büchi SMP-20 apparatus and are uncorrected. Elemental analyses are within 0.4% of the theoretical values. Infrared spectra were taken on a Perkin-Elmer 1310 instrument on KBr plates. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200; chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. Spectral data are consistent with assigned structures.

General Procedure for the Synthesis of Compounds Listed in Table 1. 1-(2-Methoxyphenyl)-4-[4-(2-thiophenecarboxamido)butyl]piperazine (1q). A solution of 2-thiophenecarbonyl chloride (1.47 g, 10 mmol) in dry THF (10 mL) was added dropwise to a solution of 1-(2-methoxyphenyl)-4-(4-aminobutyl)piperazine[15] (2.89 g, 11 mmol) and triethylamine (2 g, 20 mmol) in dry THF (20 mL) at 0 °C. The mixture was allowed to stir at room temperature for 3 h. The reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to yield 3.2 g of an oil, which was purified by silica gel column chromatography using a mixture of CH_2Cl_2 and MeOH (9:1) as eluent to yield 2.43 g (65%) of the desired product. ^1H NMR ($CDCl_3$): δ 1.64 (m, 4H, CCH_2C), 2.44 (br t, 2H, CH_2N), 2.64 (m, 4H, CH_2N), 3.07 (br s, 4H, CH_2N), 3.42 (br q, 2H, $NHCH_2C$), 3.83 (s, 3H, OCH_3), 6.81 (br s, 1H, NH), 6.85–7.03 (m, 5H, Ar), 7.40 (m, 1H, thiophene), 7.51 (m, 1H, thiophene). ^{13}C NMR ($CDCl_3$): δ 24.07, 27.32, 39.68, 50.28, 53.25, 55.21, 57.86, 111.05, 118.05, 120.84, 122.84, 127.37, 127.76, 129.49, 139.19, 141.01, 152.10, 161.93.

Pharmacological Methods. 5-HT_{1A} Receptor Binding Assay.[26] Adult male Wistar rats weighing 220–280 g were used. Animals were killed by decapitation, and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed, and immediately frozen at −70 °C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 10 volumes of ice-cold 0.32 M sucrose buffer and centrifuged at 900*g* for 10 min (4 °C), and the supernatant was recentrifuged at 48000*g* for 25 min (4 °C). The resulting pellet was resuspended in 10 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.5), incubated at 37 °C for 15 min and centrifuged at 48000*g* for 25 min (4 °C). The final pellet was resuspended in 4 volumes of ice-cold 50 mM Tris-HCl buffer containing 4 mM $CaCl_2$ and 0.1% ascorbate and maintained at −70 °C until required. The membranes were diluted in the same ice-cold buffer with 10 μM pargyline (final dilution 1:28, wt/vol). Competition assays were performed in triplicate, in a final volume of 1 mL. To each assay tube were added the following: 0.1 mL of the displacer drug concentration (0.1 mL of vehicle if no competing drug was added) and 0.1 mL of [^3H]-8-OH-DPAT (NEN, 148–163 Ci/mMol) in buffer (final concentration 1.5 nM). Nonspecific binding was determined using 10 μM cold 5-hydroxytryptamine. Binding experiment was initiated by addition of 0.8 mL of membrane suspension (600–800 μg of protein). After incubation for 30 min at 37 °C, tubes were filtered through Whatman GF/B glass filters, using a Brandel Cell Harvester, and washed twice with 5 mL of ice-cold 50 mM Tris-HCl (pH 7.5) buffer. Filters were placed in scintillating polyethylene vials (with 5 mL of scintillation cocktail), equilibrated and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V). IC_{50} and K_i values (± standard errors) were determined by computerized nonlinear regression methods using EBDA (McPherson).[27]

Antagonism at α_1-Adrenergic Receptors.[28] Adult male white New Zealand rabbits weighing 2.5–3.0 kg were used. Animals were anesthetized with ether and exanguinated. The thoracic aorta was carefully removed and quickly immersed in a Krebs-Henseleit solution with the following composition (mM): NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; $NaHCO_3$, 24.9; KH_2PO_4, 1.2; glucose, 12.2; ascorbic acid, 0.2% (wt/vol); and propranolol (nonspecific β-antagonist), 1 μM. The solution was equilibrated with a mixture of O_2 and CO_2 (95:5), pH 7.4. Connective tissue was removed from the thoracic aorta segments, which were cut into rings of 2–3 mm width and vertically mounted in the organ bath (20 mL, 37 °C) by stainless steel hooks. The rings were connected to a HSE force transducer (F30) for continuous recording of isometric tension and equilibrated for 2 h under a basal tension of 2 g with washes every 15 min. Three cumulative concentration–response curves to noradrenaline were constructed for each ring fragment in the presence of 30 μM cocaine (uptake inhibitor). The second concentration–response curve served as a control. Therefore, after the second cumulative curve, the tissue was washed out repeatedly and equilibrated for at least 1 h. Then the antagonist was added to the organ bath, and 15 min later a third concentration–response curve was performed again. All drugs (noradrenaline and antagonists) were added in a volume of 0.1 mL. Only one concentration of antagonist was applied to each ring preparation. The EC_{50} values with and without antagonist were graphically determined from the log concentration–response curves, and pD_2 values were calculated. The Van Rossum method[23] was used to determine the pA_2 values of the antagonists.

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Supplementary Material Available: Spectral data for compounds 1 and 2 (^1H NMR and ^{13}C NMR) (8 pages). Ordering information is given on any current masthead page.

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