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α_1-Adrenoreceptor antagonists bearing a quinazoline or a benzodioxane moiety

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1. Introduction

In recent years, much effort has been directed towards characterization of receptor systems, which are composed usually of multiple subtypes. α_1-Adrenoreceptors do not represent an exception to the rule as they can be divided into at least three subtypes, namely α_{1A} (α_{1a}), α_{1B} (α_{1b}), and α_{1D} (α_{1d}), with upper and lower case subscripts being used to designate native or recombinant receptor, respectively (Bylund et al., 1994; Faure et al., 1994; Ford et al., 1994; Hieble et al., 1995). However, some functional experiments indicate that an additional α_1-adrenoreceptor subtype may exist, which was named α_{1L}-adrenoreceptor (Docherty, 1998). Efforts to clone this receptor subtype have been unsuccessful so far (Testa et al., 1997), supporting the conclusion that it may represent a different affinity state of the α_{1A}-adrenoreceptor (Ford et al., 1997; Hieble and Ruffolo, 1997).

The effort to design agents selective for each of the three α_{1A}-adrenoreceptor subtypes has been an active area of research. Whereas it has been demonstrated that α_{1A}-adrenoreceptor antagonists can be useful in the treatment of benign prostatic hyperplasia (Kenny et al., 1997; Matyus and Horvath, 1997), a potential therapeutic use for both α_{1B}- and α_{1D}-subtype antagonists has not been defined yet. Perhaps, the fact that only recently so-called selective α_1-adrenoreceptor antagonists have become available has prevented the physiological roles of α_{1B} and α_{1D}-adrenoreceptor subtypes in blood pressure control or other physiological functions from being revealed.

A vast array of structurally unrelated compounds interacts with α_1-adrenoreceptor subtypes, which makes it inherently difficult to determine the structural requirements leading to receptor subtypes selectivity (Ruffolo et al., 1995; Leonardi et al., 1996; Kenny et al., 1997). The majority of α_1-adrenoreceptor antagonists displays a competitive mechanism of action and belongs to a variety of different structural classes such as yohimbanes, ergot alkaloids, quinazolines, *N*-arylpiperazines, imidazolines, phenylalkylamines, benzodioxanes, indoles, 1,4-dihydropyridines, hetero-fused 3-benzazepines, dibenzoquinolizines.

Our research group has long been involved in designing new α_1-adrenoreceptor antagonists structurally related to prazosin (Giardinà et al., 1989, 1993, 1995, 1996a, 1997; Bolognesi et al., 1998; Minarini et al., 1998) and WB 4101 (Melchiorre et al., 1982, 1984; Giardinà et al., 1984; Pigini et al., 1988; Quaglia et al., 1990, 1993, 1996, 1999), the prototypes of quinazoline- and benzodioxane-bearing compounds, respectively, with the goal of developing high-affinity, site-selective ligands for subtypes of the α_1-adrenoreceptor.

The aim of this short review is to update the knowledge on α_1-adrenoreceptor antagonists bearing a quinazoline or a benzodioxane moiety.

2. Prazosin-related antagonists

Prazosin (**1**), the prototype of quinazoline-bearing compounds, is a selective α_1-adrenoreceptor antagonist widely used as a pharmacological tool for α-adrenoreceptor subtypes characterization and as an effective agent in the

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management of hypertension (Ruffolo et al., 1995; Kenny et al., 1997). For these reasons, prazosin represents a valid tool to explore α_1-adrenoreceptor binding site topography and a lead compound in developing new therapeutically useful agents.

The role of piperazine ring of prazosin was investigated through its replacement by an α,ω-alkanediamine chain (Giardinà et al., 1989). It turned out that the piperazine ring may not be essential for activity at α_1-adrenoreceptors and that activity and selectivity depend on the length of alkane chain and *N*-methylation of both the amide and the 2-amino functions.

The compound bearing an *N,N′*-dimethyl-1,6-hexanediamine moiety (**2**) was the most active of the series, being more potent than prazosin (Giardinà et al., 1989). The chain length effect on potency allowed us to postulate that the rat vas deferens α_1-adrenoreceptor incorporates a lipophilic area, located between the binding sites for the quinazoline and the furan rings of prazosin, which can optimally accommodate an hexane spacer.

The finding that the affinity profile of prazosin-related quinazolines can depend on the type of moiety linking the two nitrogen atoms of the piperazine ring of prazosin, prompted us to further modify the structure of analogue **2**. In particular, two types of structural modifications were performed on the structure of **2**, that is, replacement of the 1,6-hexanediamine unit with 2,3-dialkylpiperazine, 1,2-cyclohexanediamine or decahydroquinoxaline moieties, and replacement of the hexane spacer with a cystamine moiety as shown in Fig. 1.

To obtain information about the size and possible stereochemical requirements of the lipophilic area, we designed a series of compounds in which the very flexible polymethylene chain of **2** is incorporated partially or totally into a constrained structure (Giardinà et al., 1993). The objective of this structural modification was to allow compounds, in which the alkane moiety is forced, to assume a definite arrangement while keeping quinazoline and furan rings in a position likely similar to that of prazosin. It turned out that antagonist activity within *cis/trans* stereoisomeric compounds not only supported the presence of a lipophilic binding area on α_1-adrenoreceptor surface, but also suggested that the lipophilic pocket is endowed with a well-defined size and spatial orientation. Cyclazosin was the most potent and selective of the series with a significant selectivity for α_{1B} (α_{1b})-adrenoreceptors with respect to the α_{1A} (α_{1a}) and α_{1d}-subtypes, as well as an interesting long-lasting hypotensive effect, very similar to that of doxazosin (Giardinà et al., 1993, 1996a).

Since cyclazosin incorporates a decahydroquinoxaline nucleus in a cis relationship, which is responsible for the high affinity for α_1-adrenoreceptors, we have synthesized its enantiomers to investigated whether stereochemistry might increase the selectivity for α_1-adrenoreceptor subtypes (Giardinà et al., 1996b). The affinity profile displayed by the two enantiomers of cyclazosin at native α_{1A}-

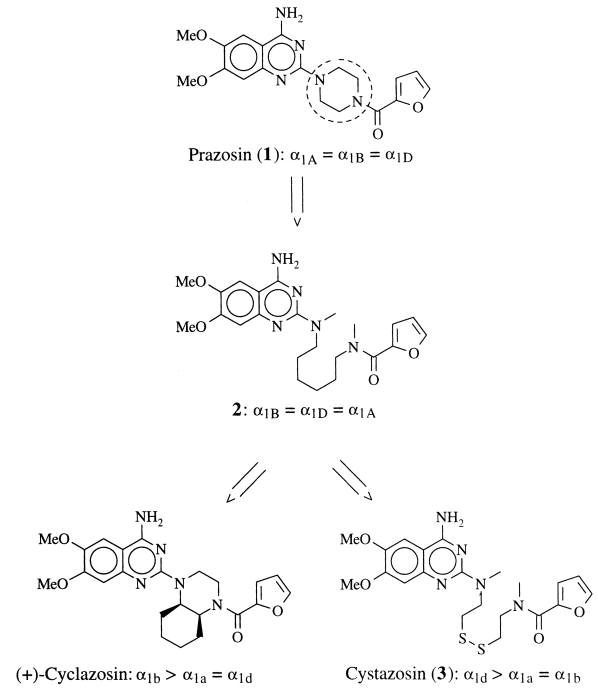


Fig. 1. Design strategy for the synthesis of prazosin (**1**)-related compounds by replacing the piperazine ring of prazosin with an α,ω-alkanediamine chain, a decahydroquinoxaline system and a cystamine moiety, affording **2**, cyclazosin and cystazosin (**3**), respectively.

and α_{1B}-, as well as at cloned α_{1a}-, α_{1b}-, and α_{1d}-adrenoreceptor subtypes, is reported in Table 1 and graphically shown in Fig. 2. (−)-Cyclazosin, although more potent than (+)-cyclazosin at all subtypes, was nearly devoid, like prazosin, of subtype selectivity with the exception of a 12-fold higher affinity at native α_{1B}-relative to α_{1A}-adrenoreceptors. On the contrary, (+)-cyclazosin displayed high affinity ($pK_i = 9.16$) at cloned α_{1b}-adrenoreceptors and a significantly lower potency at both α_{1a}- and α_{1d} subtypes ($pK_i = 7.48$ and 7.57, respectively). Furthermore, (+)-cyclazosin displayed selectivities of 1100-, 19 000-, and 12 000-fold in binding to α_{1b}-adrenoreceptors relative to α_2-adrenoreceptors and 5-HT_{1A} and D_2 receptors. Spiperone, which is considered a selective α_{1B}-adrenoreceptor antagonist, showed high affinity for other receptors as well, namely 5-HT_{1A} and D_2 receptors. Thus, (+)-cyclazosin emerges as a most interesting ligand of prazosin-related antagonists as it displayed high affinity, in the nanomolar range like prazosin, and an unprecedented selectivity for α_{1b} (α_{1B})-adrenoreceptors, which is lacking in the antagonists presently available.

Replacing the hexane chain of **2** by a cystamine moiety (Fig. 1) afforded cystazosin (**3**) which displayed an interesting selectivity profile in comparison with both (+)-cyclazosin and the carbon analogue **2**, owing to a significantly lower affinity for α_{1A}- and α_{1B}-adrenoreceptor subtypes relative to the α_{1D}-subtype (vide infra) (Minarini et al., 1998).

Table 1
Affinity estimates, expressed as pK_i, of the enantiomers of cyclazosin for native and cloned α_1-adrenoreceptor subtypes, native α_2-adrenoreceptors, and 5-HT_{1A} and D_2 receptors in comparison to prazosin and reference compound spiperone[a]

Compound	pK_i, native receptors (rat)[b]					pK_i, cloned receptors[c]		
	α_{1A}	α_{1B}	α_2	5-HT_{1A}	D_2	α_{1a}	α_{1b}	α_{1d}
(+)-Cyclazosin	7.73	9.68	6.13	4.89	5.08	7.48	9.16	7.57
(−)-Cyclazosin	8.77	9.85	5.86	5.21	< 5	8.62	9.51	9.24
(±)-Cyclazosin	8.41	9.57	6.17	5.16	< 5	8.18	9.23	9.28
Prazosin	9.03	9.44	6.83	5.63	< 5	9.14	9.34	8.96
Spiperone	7.42	8.81	6.86	7.60	9.24	7.87	8.15	7.66

[a] Data taken from Giardinà et al. (1996b).
[b] Membranes were from hippocampus + 10 μM CEC (α_{1A}), liver (α_{1B}), cerebral cortex (α_2), hippocampus (5-HT_{1A}), and striatum (D_2).
[c] Membranes were from bovine brain (α_{1a}), hamster smooth muscle (α_{1b}), and rat brain (α_{1d}).

The finding that the selectivity for α_1-adrenoreceptor subtypes can be modulated by an appropriate spacer between the two nitrogen atoms of the piperazine ring of prazosin formed the basis for further structural modifications. We thought that increasing the number of contacts between a ligand and its receptor would increase hopefully also receptor subtype selectivity. To this end, we focused our attention on the furan ring of both cystazosin and the carbon analogue **2**. The furan ring of **2** was replaced by a phenyl ring because it offered us the possibility to incorporate additional structural elements at different positions (Fig. 3). It is known that subtle and unpredictable differences in the binding pockets may account for selectivity; thus, incorporation of additional structural elements in the structure of a non-selective ligand may well lead to preferential recognition of a particular receptor subtype. Thus, a chloromethyl substituent was introduced in the aromatic ring because it can be easily functionalized affording compounds with different properties (Bolognesi et al., 1998). For example, an amine function can be protonated at physiological pH giving rise to a possible, additional interaction with a nucleophilic, complementary receptor group, which would increase the possibility to achieve receptor subtype selectivity.

The replacement of the hexane spacer or the furan ring of **2** by a cystamine moiety or a phenyl group, affording cystazosin and the phenyl analogue **8**, respectively, caused a dramatic effect in the affinity profile for α_1-adrenoreceptor subtypes as reported in Table 2 and graphically shown in Fig. 4. Clearly, **2** is a very potent α_1-adrenoreceptor antagonist but, at the same time, is not selective displaying only a slight preference for the α_{1B}-subtype. Interestingly, the structural modifications performed on **2** did not improve affinity for α_1-adrenoreceptor subtypes but, what is more important, gave rise to selectivity. Thus, cystazosin (**3**) proved to be a selective α_{1D}-adrenoreceptor antagonist owing to a slight (4.5-fold) decrease in affinity for the α_{1D}-subtype and a large drop in affinity (32- and 224-fold, respectively) for α_{1A}- and α_{1B}-subtypes in comparison with **2**. On the other hand, the phenyl analogue **8** displayed a significantly improved α_{1B}-selectivity (85- and 15-fold relative to α_{1A}- and α_{1D}-subtypes, respectively), owing to a much larger decrease in affinity for both α_{1A}- and α_{1D}-subtypes than for the α_{1B}-subtype in comparison with **2** (Fig. 4) (Bolognesi et al., 1998; Minarini et al., 1998).

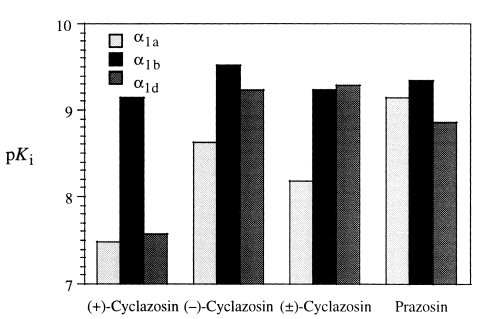


Fig. 2. Affinity estimates (pK_i) of racemic cyclazosin and its enantiomers for cloned α_1-adrenoreceptor subtypes (α_{1a}: bovine brain; α_{1b}: hamster smooth muscle; α_{1d}: rat brain) in comparison to prazosin.

The insertion of a 5-chloromethyl or a 5-*N*,*N*-dimethylaminomethyl substituent on the furan ring of **3**, affording **4** and **5**, respectively, did not improve the selectivity profile. The same structural modification performed on **2** to afford **6** and **7** caused a marked decrease in affinity which was more pronounced for 5-*N*,*N*-dimethylaminomethyl group. However, compound **6** was slightly more potent than **2** at α_{1D}-adrenoreceptors while displaying a significantly lower affinity at α_{1A}- and α_{1B}-subtypes as revealed by its pA_2 values (α_{1A}, 8.17; α_{1B}, 8.97, α_{1D}, 9.39). Clearly, this finding suggests that appropriate substituents on the aromatic moiety may have a role in achieving receptor subtype selectivity.

The insertion of a substituent on the benzene ring of **8**, affording **9**–**20**, affected differently, according to substituent type and position, the affinity and, as a consequence, the selectivity for α_1-adrenoreceptor subtypes (Table 2).

A most intriguing finding was the observation that polyamines **11**, **16** and **20** retained high affinity for α_1-adrenoreceptor subtypes which suggests clearly that a 1,6-diaminohexane chain on the benzene ring did not give rise to negative interactions with the receptor. This observation may have relevance for the development of new quinazo-

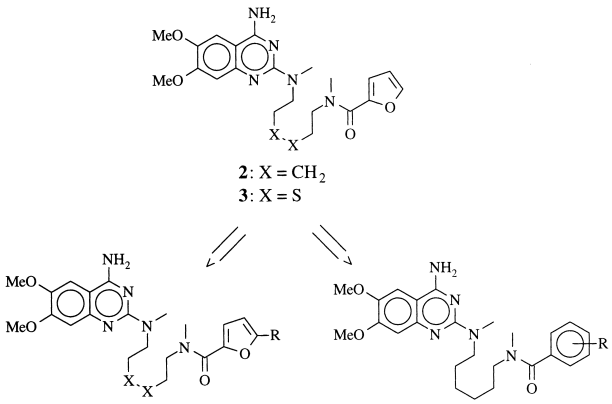
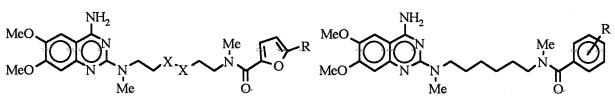


Fig. 3. Design strategy for the synthesis of prazosin-related quinazolines by inserting a substituent on the furan ring of **2** or **3** or by replacing the furan ring of **2** with an (un)substituted phenyl ring. See Table 2 for structures.

lines bearing a polyamine backbone on which additional substituents can be mounted to improve selectivity for α_1-adrenoreceptor subtypes. Clearly, the site where the terminal aromatic ring of **8** interacts does not seem to present steric hindrance and particularly stringent requirements.

The results obtained in binding experiments with selected quinazolines (Table 3) did not show the same selectivity profile observed in functional assays (Bolognesi et al., 1998). While binding affinities of prazosin (**1**), **2** and BMY-7378 are qualitatively and quantitatively comparable with pA_2 values derived from functional experiments, those observed for **3** and **14** are not in agreement at all from both a qualitative and a quantitative point of view with functional affinities. Both compounds were devoid of selectivity for α_1-adrenoreceptor subtypes in binding assays owing to a marked increase in affinity of about two orders of magnitude for α_{1a}- and α_{1b}-adrenoreceptors and of about one order of magnitude for the α_{1d}-subtype. As a matter of fact, the theory states that the affinity of an antagonist assessed in functional assays should not differ

Table 2
Antagonist affinities, expressed as pA_2 or pK_B values, of **2**–**20** at α_1-adrenoreceptors on isolated tissue from the rat, namely prostatic vas deferens (α_{1A}), spleen (α_{1B}), and thoracic aorta (α_{1D}) in comparison to prazosin (**1**) and BMY-7378[a]



2-7 8-20

No.	X	R	pA2		
			α_{1A}	α_{1B}	α_{1D}
1	(prazosin)		8.60	8.99	8.91
2	CH_2	H	9.04	9.84	9.19
3	S	H	7.53	7.49	8.54
4	S	CH_2Cl	7.78	7.37	8.03
5	S	CH_2NMe_2	6.70	7.27	8.22
6	CH_2	CH_2Cl	8.17	8.97	9.39
7	CH_2	CH_2NMe_2	7.41	8.62	8.23
8		H	7.42	9.35	8.16
9		2-CH_2Cl	6.38	8.73	8.55
10		2-CH_2NMe_2	7.04	7.88	8.26
11		2-$CH_2NH(CH_2)_6NH_2$	7.97	9.17	8.50
12		3-CH_2Cl	7.10	7.18	7.29
13		3-CH_2NH_2	7.32	8.61	8.69
14		3-CH_2NMe_2	7.26	7.43	8.26
15		3- 	7.82	8.03	8.51
16		3-$CH_2N(Me)(CH_2)_6NHMe$	8.05	7.71	7.84
17		4-CH_2Cl	7.11	9.15	7.71
18		4-CH_2NMe_2	7.14	8.53	7.86
19		4- 	7.23	8.01	8.17
20		4-$CH_2N(Me)(CH_2)_6NHMe$	6.72	9.21	8.46
BMY-7378			6.94	7.55	8.34

[a] Data taken from Bolognesi et al. (1998).

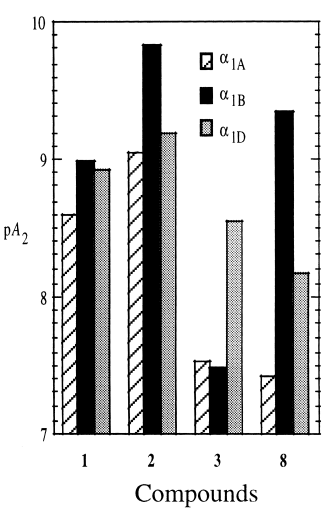


Fig. 4. Affinity constants (pA_2) in rat prostatic vas deferens (α_{1A}), spleen (α_{1B}), and aorta (α_{1D}) α_1-adrenoreceptor subtypes of cystazosin (**3**) and **8** in comparison with prazosin (**1**) and **2**.

Table 3
Affinity constants (pK_i) of **2**, **3** and **14** (see Table 2 for structures) for cloned α_1-adrenoreceptor subtypes and 5-HT_{1A} receptors in comparison with reference compounds[a]

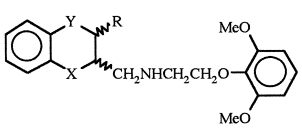
No.	pK_i, human cloned receptors[b]			
	α_{1a}	α_{1b}	α_{1d}	5-HT_{1A}
1	9.23	9.39	9.65	< 6
2	9.78	9.96	9.71	< 6
3	9.38	8.97	9.14	< 6
14	9.49	9.78	9.61	6.13
BMY-7378	6.36	7.19	8.89	8.76

[a] Data taken from Bolognesi et al. (1998).
[b] Membranes were from CHO cells expressing human cloned α_1-adrenoreceptor subtypes and HeLa cells expressing human 5-HT_{1A} receptors.

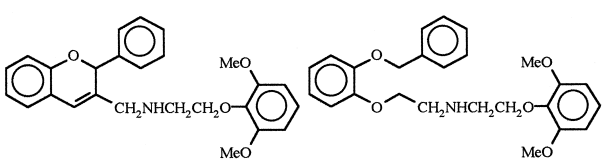
from that determined in binding experiments using both native and recombinant receptors. For this reason competitive antagonists are considered tools for receptor characterization and classification better than agonists because for the latter ones, in addition to affinity, other pharmacological parameters must be taken into account (Leff, 1995; Melchiorre et al., 1998). Consequently, there is no apparent explanation for the discrepancy observed between our functional and binding results. However, very recently we discussed the possibility that if an antagonist does not adhere perfectly to the concept of neutral antagonism in the interaction with the receptor but behaves as a negative antagonist (inverse agonist), then its affinity may not be, as assumed by theory, system-independent giving rise to affinity values which might be different according to the system employed for the determination. In other words, as pointed out by Leff (1995), the use of inverse agonists as neutral antagonists may have, like agonists, problems since their estimated affinities are system-dependent. Thus, for inverse agonists the affinity values estimated in functional assays may not necessarily be comparable with those obtained in binding experiments. Interestingly, a survey of literature has revealed that some of the so-called competitive antagonists behave as inverse agonists when tested in the appropriate model. In the field of α_1-adrenoreceptor antagonists, prazosin, WB 4101 and benoxathian were shown to be inverse agonists in a vascular model (Noguera et al., 1996). Thus, the difference, which is often observed for functional and binding affinities of antagonists, might be explained by the fact that these compounds are inverse agonists and hence their affinity is system-dependent.

3. WB 4101-related antagonists

Benzodioxanes represent one of the oldest and best known classes of α-adrenoreceptor antagonists whose chemical structure incorporates a 1,4-benzodioxan-2-yl moiety as the main feature (Melchiorre and Belleau, 1981). WB 4101 (**21**) is the prototype of α_1-adrenoreceptor antagonists bearing a benzodioxane moiety. Several investigations were devoted to improving both affinity and selectivity of **21** (Melchiorre et al., 1982, 1984; Giardinà et al., 1984; Pigini et al., 1988). As a result, a variety of analogues have been studied involving modification of the benzodioxane ring, the amine function, of the (2,6-dimethoxyphenoxy)ethyl moiety. Among these structural modifications performed on **21**, the insertion of a phenyl ring at the 3-position having a trans relationship with the 2-side chain afforded phendioxan (**22**) (Quaglia et al., 1990), which retained high affinity for α_1-adrenoreceptors while displaying only a markedly reduced affinity for α_2-adrenoreceptors. As an overall result, the presence of a 3-phenyl unit as in **22** determined a significant improvement in selectivity toward α_1-adrenoreceptors compared to the prototype **21**. It should be emphasized, however, that the majority of **21** analogues, including **22** and related compounds, were not assayed to evaluate the affinity for the three α_1-adrenoreceptor subtypes. Most of these compounds were tested only on the epididymal portion of the isolated rat vas deferens (Melchiorre et al., 1984, ; Giardinà et al., 1984; Pigini et al., 1988; Quaglia et al., 1990, 1993), which proved to be a preparation containing a mixture of α_{1A}- and α_{1L}-adrenoreceptors (Ohmura et al., 1992). Thus, the affinity for the three α_1-adrenoreceptors was not determined, which prevents to draw relevant conclusion on the structural features that determine selectivity for one α_1-adrenoreceptor subtype relative to the others. Mephendioxan, a *p*-tolyl analogue of phendioxan, represents an exception as its enantiomers were assayed at the three cloned α_1-adrenoreceptor subtypes. It turned out that, in binding experiment, (−)-2*S*,3*S*-mephendioxan is a selective antagonist for α_{1a}-adrenoreceptors (Quaglia et al., 1996).



21: R = H, X = Y = O
22: R = Ph, X = Y = O (trans)
23: R = Ph, X = CO, Y = O (trans)
24: R = Ph, X = CO, Y = S (trans)
25: R = Ph, X = CO, Y = CH_2 (trans)
26: R = Ph, X = O, Y = CH_2 (cis)
27: R = Ph, X = O, Y = CH_2 (trans)



28 29

In a recent project, the role of the dioxane unit and, in particular, of the oxygens at positions 1 and 4 of **22** in the interaction with the three different α_1-adrenoreceptors and 5-HT_{1A} receptors was investigated to get information about

Table 4
Affinity constants, expressed as pK_i ($-\log K_i$, nM), of compounds **21**, **23**–**29** and BMY-7378 for human recombinant α_1-adrenoreceptor subtypes and 5-HT_{1A} receptors[a]

No.	pK_i, human cloned receptors[b]			
	α_{1a}	α_{1b}	α_{1d}	5-HT_{1A}
21	9.37	8.0	9.29	8.68
23	9.22	6.84	7.93	6.73
24	7.42	< 6	6.37	7.36
25	8.06	6.11	6.88	6.83
26	6.78	6.51	6.86	6.76
27	8.49	6.58	7.28	6.84
28	7.14	6.84	6.95	8.08
29	9.33	9.27	10.17	7.93
BMY-7378	6.42	6.15	8.89	9.43

[a] Data taken from Quaglia et al. (1999).
[b] Membranes were from CHO cells expressing human cloned α_1-adrenoreceptor subtypes and HeLa cells expressing human 5-HT1A receptors.

the structural requirements that differentiate the binding sites of these receptors. It is known that benzodioxanes are effective ligands of 5-HT_{1A} receptors as well (Hibert et al., 1988). By taking as a starting point the prototype **21**, it was possible to observe how affinity and selectivity for α_1-adrenoreceptor subtypes can be markedly affected by inserting in the prototype structure a phenyl ring at position 3 and (a) by replacing the oxygen atom at position 1 by a carbonyl group, as in **23**, (b) by replacing the oxygen atoms at position 1 by a carbonyl function and at position 4 by a sulphur atom, as in **24**, or a methylene group, as in **25**, (c) by replacing the oxygen atom at position 4 by a methylene group, affording **26** and **27**, (d) by replacing the oxymethylene moiety by a vinyl group, as in **28**, and (e) by opening the dioxane ring through cleavage of C2–C3 bond, as in **29** (Table 4) (Quaglia et al., 1999). The insertion of a phenyl ring in a trans relationship with the 2-side chain and the replacement of an oxygen atom with a carbonyl group, leading to **23**, resulted in a marked drop in affinity at both α_{1b}- and α_{1d}-adrenoreceptors (14- and 23-fold, respectively), while not affecting the affinity at the α_{1a} subtype. Furthermore, this structural modification caused a marked drop in affinity for the other receptor systems investigated, in particular 89-fold for 5-HT_{1A} receptors relative to **21**. As an overall result, **23** proved to be a potent and selective antagonist for the α_{1a}-adrenoreceptor subtype while displaying a weak, if any, affinity for the other receptor systems. The decrease in affinity observed for **28** at all α_1-adrenoreceptor subtypes in comparison to **21** and at α_{1a}-adrenoreceptors in comparison to **23**, **25**, and **27** clearly suggests that the presence of a double bond alters the spatial orientation of the molecule in such a way that the binding with the adrenoreceptor is made difficult. Alternatively, the low affinity displayed by **28** for α_1-adrenoreceptors might indicate that the oxygen at position 1 of **21** plays a role in the binding process owing to its non bonded electrons. However, interestingly enough, unsaturated analogue **28** retained high affinity for 5-HT_{1A} receptors and turned out to be a partial agonist with an efficacy ($pD_2 = 6.44$), which was only about 10-fold lower than that of 5-hydroxytryptamine. Thus, a most intriguing finding was the observation that, whichever the kind of the oxygen-bearing ring, the presence of a phenyl ring at position 3 in a trans relationship with the side chain at position 2 imparts selective affinity for the α_{1a} subtype not only with regard to both α_{1b} and α_{1d} subtypes but also with 5-HT_{1A} receptors as well. This result may have relevance for the development of new WB 4101-related compounds having high affinity and high specificity for α_{1a}-adrenoreceptors.

Opening the dioxane ring gave **29**, which was a very potent ligand at α_1-adrenoreceptors while retaining also high affinity for 5-HT_{1A} receptors, although the affinity for the latter was 22-174-fold lower than that at the former ones. This structural modification resulted also into an inversion of the selectivity profile as **29** was more potent at α_{1d}-adrenoreceptors than at both α_{1a} and α_{1b} subtypes. Consequently, open analogue **29** may represent a lead for the design of ligands selective for this receptor subtype.

The observation that 6,7-dihydro-5-[[(*cis*-2-hydroxy-*trans*-3-phenoxycyclopentyl)amino]-methyl]-2-methylbenzo[*b*]thiophen-4(5*H*)-one (**30**) turned out to be a rather potent antagonist ($pA_2 = 8.13$) in blocking the vasoconstrictor effects of phenylephrine in rabbit aorta, while not showing any antagonism at α-adrenoreceptors in the rat vas deferens (McCarthy et al., 1985), was the starting point for the design of related compounds. An analysis of the stereomodels of compounds **21** and **30** revealed that they can be superimposed on to each other. It derives that the 6,7-dihydro-2-methylbenzo[*b*]-thiophen-4(5*H*)-one unit of **30** can be replaced by the benzodioxane moiety of **21** as the two oxygen atoms at positions 1 and 4 of **21** are not essential for affinity at α_1-adrenoreceptors and can be replaced by a carbonyl and a methylene, respectively, without affecting the potency (Pigini et al., 1988). Thus, structure I (Fig. 5), which is an hybrid structure of both prototypes **21** and **30**, was designed (Bolognesi et al.,

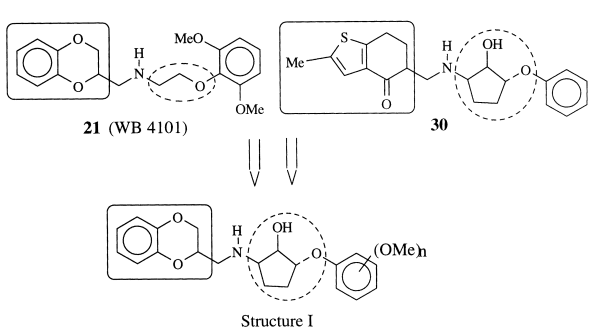
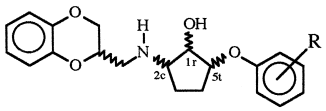


Fig. 5. Design strategy for the synthesis of compounds **31**–**36** (structure I) by replacing the oxyethylene chain of **21** with the trisubstituted cyclopentane unit of 30.

Table 5
Antagonist affinities, expressed as apparent pK_b values, of **21**, **31**–**36**, and BMY-7378 at α_1-adrenoreceptors in isolated rat prostatic vas deferens (α_{1A}), spleen (α_{1B}), and thoracic aorta (α_{1D})[a]



No.[b]	*R*	pK_b		
		α_{1A}	α_{1B}	α_{1D}
21		9.36	8.21	8.60
31	H	5.48	6.45	7.66
32	H	5.70	6.47	7.85
33	2-MeO	5.68	6.24	7.15
34	2-MeO	6.56	6.80	7.30
35	2,6-$(MeO)_2$	5.89	6.27	7.32
36	2,6-$(MeO)_2$	5.79	6.17	6.94
BMY-7378		6.94	7.55	8.34

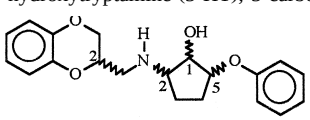
[a]Data taken from Bolognesi et al. (1999).
[b]The relationship among the substituents linked to the cyclopentane ring was always cis between the hydroxy group at position 1, taken as the reference atom (1r), and the amine function at position 2 (2c) and trans between both hydroxy and amine moieties and the phenoxy group at position 5 (5t).

1999). Since it was demonstrated that the other stereoisomers of **30**, having a different relationship among the substituents on the cyclopentane unit, were at the best less potent at α_1-adrenoreceptors (McCarthy et al., 1985), it was decided to keep constant in hybrid structure I and related compounds the same spatial arrangement as in **30** to possibly achieve the best fit with α_1-adrenoreceptor subtypes. Considering the fact that the enantiomers of **21** have different affinity for α_1-adrenoreceptors (Nelson et al., 1979; Andrisano et al., 1992), it was of interest to investigate whether the four of sixteen possible stereoisomers of structure I derived from the combination of the chiral moieties of **21** and **30** might be able to better discriminate among α_1-adrenoreceptor subtypes and 5-HT_{1A} receptors.

An inspection of the results assembled in Table 5 reveals that the inclusion of the ethylene chain separating the amine and the phenoxy moieties of **21** into a cyclopentanol unit (Fig. 5), affording **31**–**36**, caused a dramatic effect in the affinity profile for α_1-adrenoreceptor subtypes and 5-HT_{1A} receptors. The two diastereomeric racemates **31** and **32** displayed a similar selectivity profile, which was, however, remarkably different from that of **21** at α_1-adrenoreceptor subtypes. They displayed a significant selectivity toward the α_{1D}-adrenoreceptor while being weak antagonist for both α_{1A} and α_{1B} subtypes whereas prototype **21** was selective for the α_{1A} subtype. It is known that two methoxy groups at positions 2 and 6 of the phenoxy unit confer optimum affinity in prototype **21** (Melchiorre and Belleau, 1981). Surprisingly, the insertion of one, as in **33** and **34**, or two methoxy groups, as in **35** and **36**, did not modify the selectivity profile at α_1-adrenoreceptor subtypes. Instead, it caused a decrease in the affinity for the α_{1D} subtype relative to the unsubstituted compounds **31** and **32**. Clearly the methoxy groups play a different role in **21** and related cyclopentane-bearing compounds.

It has already been demonstrated that the 2*S* enantiomer of **21** is significantly more potent than the 2*R* enantiomer at α_1-adrenoreceptors (Nelson et al., 1979; Andrisano et al., 1992) and at 5-HT_{1A} receptors as well (Hibert et al., 1988). Epimers (+)-**31** and (−)-**32** have the opposite configuration at the carbon at position 2 of the benzodioxane unit, namely *R* and *S*, respectively, while having the

Table 6
Antagonist affinities and agonist efficacies, expressed as pK_b and pD_2 values, respectively, of the enantiomers of **31** and **32** at α_1-adrenoreceptors in isolated rat prostatic vas deferens (α_{1A}), spleen (α_{1B}), and thoracic aorta (α_{1D}), and at 5-HT_{1A} receptors in HeLa cells (binding [^{35}S]GTP) in comparison to 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), 5-hydroxytryptamine (5-HT), 5-carboxamidotryptamine (5-CT) and BMY-7378[a]



No.	Configuration	α_{1A}		α_{1B}		α_{1D}		5-HT_{1A}		
		pK_b	ER[b]	pK^b	ER[b]	pK_b	ER[b]	pD_2^c	ER	% max
(−)-**31**	(1*S*,2*S*,5*S*)(2*S*)	5.65		5.79		6.92		7.30		82
			3		11		7		27	
(+)-**31**	(1*R*,2*R*,5*R*)(2*R*)	6.10		6.83		7.78		5.87		23
(−)-**32**	(1*R*,2*R*,5*R*)(2*S*)	6.55		7.13		8.17		5.87		100
			> 35		49		33		123	
(+)-**32**	(1*S*,2*S*,5*S*)(2*R*)	< 5		5.44		6.65		7.96		96
8-OH-DPAT								7.60		100
5-HT								7.30		100
5-CT								8.45		96
BMY-7378		6.94		7.55		8.34		9.27		26

[a]Data taken from Bolognesi et al. (1999).
[b]The eudismic ratio (ER) is the antilog of the difference between the pK_b and pD_2 values of the eutomers and the corresponding distomers.
[c]pD_2 values are the negative logarithm of the agonist concentration required to obtain 50% of the maximal stimulation of [^{35}S]GTPγS.

same configuration at the cyclopentane nucleus. They were more potent at all α_1-adrenoreceptor subtypes and remarkably less potent at 5-HT_{1A} receptors, as compared with their corresponding enantiomers (−)-**31** and (+)-**32** (Table 6). This finding suggests clearly that the stereochemistry of the cyclopentane unit has a greater influence on affinity than that of the benzodioxane moiety. Interestingly enough, a 1*R* configuration, as in (+)-**31** and (−)-**32**, conferred higher affinity at α_1-adrenoreceptors, whereas a 1*S* configuration produced higher affinity for 5-HT_{1A} receptors, which indicates that the two receptor systems have different stereochemical requirements. Enantioselectivity was more pronounced for enantiomers (−)-**32** and (+)-**32** than for (−)-**31** and (+)-**31** at α_1-adrenoreceptors and 5-HT_{1A} receptors as well (Table 6).

It is evident that stereoisomers (−)-**31**, (+)-**31**, (−)-**32** and (+)-**32** all have, though to a different extent, the same selectivity profile, that is $\alpha_{1D} > \alpha_{1A}$, which is similar to that displayed by BMY-7378. Among them, (−)-**32** displayed a significant α_{1D} selectivity vs. the other subtypes, which was even slightly higher than that of BMY-7378. Its selectivity vs. the 5-HT_{1A} receptor is more than 2 log units. Epimers (−)-**31** and (+)-**32** proved to be agonists at 5-HT_{1A} receptors with a potency comparable to or even higher than of 5-HT as revealed by their pD_2 value (Table 6), while being 27- and 123-fold more potent than the corresponding enantiomers (+)-**31** and (−)-**32**. Enantiomers (+)-**32** and (−)-**32** behaved as full agonists, whereas (+)-**31** and (−)-**31** showed to be partial agonists, in analogy with BMY-7378.

While binding affinities of reference compound BMY-7378 were qualitatively and quantitatively comparable with pK_b values derived from functional experiments, those observed for (−)-**31**, (+)-**31**, (−)-**32** and (+)-**32** were not in complete agreement particularly for the α_{1a} subtype, where functional affinities were lower (Table 7). Prototype WB 4101 (**21**) was shown to be an inverse agonist in a vascular model containing α_{1D}-adrenoreceptors (Noguera et al., 1996). Thus, as discussed for quinazolines (see above), the 5-fold difference observed for **21** between binding and functional affinity at $\alpha_{1d/D}$-adrenoreceptors might be explained by the fact that **21** is an inverse agonist at this subtype and, as a consequence, its affinity is not system-independent. It derives that a similar explanation might apply for the discrepancy observed between binding and functional affinities for stereoisomers (−)-**31**, (+)-**31**, (−)-**32** and (+)-**32** at α_{1a}-adrenoreceptors.

Similarly to the trend observed at α_{1a}-adrenoreceptors, stereoisomers (−)-**31**, (+)-**31**, (−)-**32** and (+)-**32** displayed a radioreceptor binding affinity higher than that observed in functional assays at 5-HT_{1A} receptors. Furthermore, the eudismic ratio between (−)-**31** and (+)-**31** enantiomers was identical to that observed in functional assays whereas for (−)-**32** and (+)-**32** it was much lower. However, a difference in potency observed for the agonists in different assays is not surprising, since the affinity is system-dependent, as assumed by theory.

Table 7
Affinity constants, expressed as pK_i ($-\log K_i$, nM), of compounds **21**, the enantiomers of **31** and **32**, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and BMY-7378 for human recombinant α_1-adrenoreceptor subtypes and 5-HT_{1A} receptors[a]

No.	pK_i, human cloned receptors[b]			
	α_{1a}	α_{1b}	α_{1d}	5-HT_{1A}
21	9.37	8.0	9.29	8.68
(−)-**31**	6.41	5.74	6.70	9.08
(+)-**31**	7.11	7.03	7.79	7.65
(−)-**32**	7.44	7.33	8.10	8.26
(+)-**32**	6.02	< 6	6.03	8.43
BMY-7378	6.42	7.16	8.84	9.03
8-OH-DPAT	< 6	< 6	< 6	8.46

[a] Data taken from Bolognesi et al. (1999).
[b] Membranes were from CHO cells expressing human cloned α_1-adrenoreceptor subtypes and HeLa cells expressing human 5-HT_{1A} receptors.

With regard to the 5-HT_{1A} receptor, enantiomer (+)-**32** proved functionally the most selective, in analogy with (−)-**32** at the α_{1D} subtype.

In conclusion, the replacement of the carbon chain separating the amine and the phenoxy groups of **21** with a cyclopentane ring afforded stereoisomers (−)-**31**, (+)-**31**, (−)-**32** and (+)-**32** that retained good affinity for α_1-adrenoreceptor subtypes or 5-HT_{1A} receptors according to the configuration of cyclopentane unit. In particular for the enantiomers of **32**, a 1*R* configuration imparted high affinity and selectivity for α_{1D}-adrenoreceptors, whereas the reverse applied for high affinity and selectivity at 5-HT_{1A} receptors. The trend noted above might help in developing relevant structure-activity relationships to differentiate and to understand the structural elements which confer selective interaction at α_1-adrenoreceptor subtypes and at 5-HT_{1A} receptor.

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