glutamate site (Table I). In fact, **4f** is 2550-fold selective for the glycine site on the basis of these ligand-binding studies. Although we have not extensively studied the structure–activity relationships of this series of compounds at the other excitatory amino acid binding site, we did establish that **4f** is highly selective toward the glycine site compared to both the kainate (IC_{50} = 418 μM) and AMPA (IC_{50} = 273 μM) sites, respectively. In retrospect, the affinity of 4a for the glutamate binding site can be rationalized on the basis of the structural relationship with the amino dicarboxylic acids, glutamic acid and aspartic acid.

In terms of structure–activity relationships, there are several important aspects which can be demonstrated from this work. Chlorine atom substitution in the 4- and 6-positions of the indole ring, but not the 5- and 7-positions, plays an important role in determining antagonist potency. Preliminary molecular modeling studies indicate that a combination of dipole effects and subtle pH changes due to chlorine substitution appear to correlate with antagonist activity.[15] The enhancing effect of the propionic acid side chain is an important discovery and suggests that there is another pocket in the receptor whose occupancy can lead to even more potent antagonists. This speculation is consistent with other reports from our group.[14] We are currently exploring the nature of this secondary binding site in an extensive structure–activity study. In conclusion, we have discovered a new series of potent antagonists of the strychnine-insensitive glycine binding site associated with the NMDA receptor complex. These compounds should allow for a more detailed understanding of the important features which define the pharmacophore for this receptor.[16]

(15) Weintraub, H. J. R.; Demeter, D. A.; et al., unpublished results.
(16) In vivo data indicate that **4f** has anticonvulsant activity against quinolinic acid induced seizures in mice (ED_{50} = 2 μg icv).

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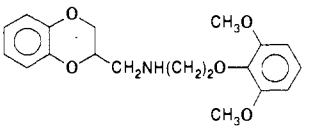
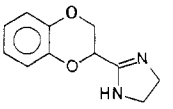
3-Phenyl Analogues of 2-[[[2-(2,6-Dimethoxyphenoxy)ethyl]amino]-methyl]-1,4-benzodioxan (WB 4101) as Highly Selective α_1-Adrenoreceptor Antagonists[1]

A benzodioxan nucleus bearing an appropriate substituent at position 2 can discriminate markedly among α-adrenoreceptor subtypes. In fact, 1 (WB 4101)[2] and 2 (idazoxan, RX 781094),[3] both carrying a 1,4-benzodioxan-2-yl moiety as a basic feature but having a different 2-substituent, are highly selective for α_1- and α_2-adrenoreceptors, respectively. A variety of 1 and 2 analogues have been studied involving a modification of the dehydrodioxane ring. Compounds in which one of the two oxygen atoms has been replaced by a methylene,[4-6] carbonyl,[4] or sulfur[4,5,7,8] and those in which the ring size has been altered to give furan,[6,9] indole,[4] and naphthalene[4,5] derivatives were investigated. All these structural modifications have shown that (a) the oxygens at positions 1 and 4 of the benzodioxan moiety play a different role in receptor binding and (b) replacement of the dehydrodioxane ring by other systems gives rise to a drop in affinity toward α_1-adrenoreceptors.[4] None of these manipulations performed on the structure of 1 has led to a significant improvement of affinity or selectivity for α-adrenoreceptors.



1 (WB 4101)



2 (Idazoxan)

Since 1 is a very potent α_1-adrenoreceptor antagonist an improvement of its affinity would not represent a major achievement unless there is also a concomitant increase in selectivity. The objectives of this study were to improve the selectivity toward α_1-adrenoreceptors by modifying the dehydrodioxane ring of 1. The starting point was the observation that replacement of a hydrogen at position 2 or 3 of **2** with a substituent such as a methyl can dramatically alter the drug–receptor interaction.[10] In fact, the 3-methyl analogue of **2** turned out to be a very weak α-antagonist compared to both **2** and its 2-methyl analogue.[10] Thus, it appears that the 3-position in 1,4-benzodioxan-bearing compounds might be crucial for the affinity toward α_2-adrenoreceptors. We thought that the introduction of a substituent such as a phenyl ring at position 3 of 1 could decrease the affinity for α_2-adrenoreceptors while leaving hopefully unaffected that for α_1-adrenoreceptors, thus giving rise to an improvement of the α_1-selectivity. To this end, we describe here the synthesis and the pharmacological profile in the isolated rat vas deferens of isomers **4** and **5**. Moreover, compound **6** was included in this study to verify whether the insertion of a phenyl ring in the structure of **3**, which displays a biological profile close to that of 1,[4] causes an effect on α-adrenoreceptor blocking activity similar to that observed

(1) Part 3 of a series entitled: Structure-Activity Relationships in 1,4-Benzodioxan-Related Compounds. For Parts 1 and 2, see, respectively, ref 4 and Giardinà, D.; Gulini, U.; Piloni, M. G.; Melchiorre, C. *Farmaco Ed. Sci.*, in press.
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(6) Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Davis, J. A.; Doxey, J. C.; Higgins, S. D.; Myers, M.; Roach, A. G.; Smith, C. F. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* **1984**, *27*, 570.
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(9) Kapur, H.; Green, P. N.; Mottram, D. R. *J. Pharm. Pharmacol.* **1979**, *31*, 188.
(10) Stillings, M. R.; Chapleo, C. B.; Butler, R. C. M.; Davis, J. A.; England, C. D.; Myers, M.; Myers, P. L.; Tweddle, N.; Welbourn, A. P.; Doxey, J. C.; Smith, C. F. C. *J. Med. Chem.* **1985**, *28*, 1054.

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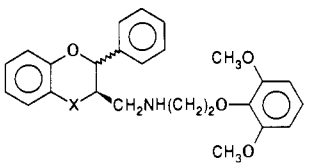
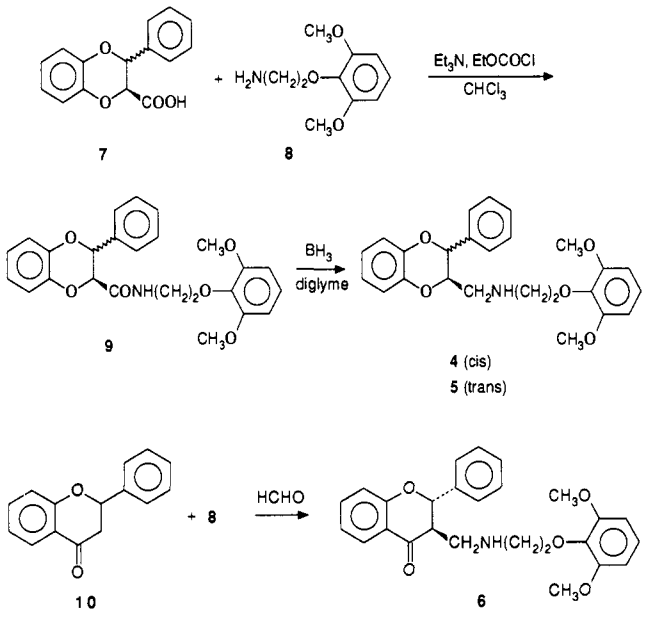
Table I. Physical Characteristics and α_1- and α_2-Adrenoreceptor pA_2 Values in the Isolated Rat Vas Deferens[a]



no.	X	mp,[b] °C	recrystn solvent	formula[c]	α_1 pA_2 against norepinephrine	α_2 pA_2 against clonidine	α_1/α_2[d] selectivity ratio
1[e]	O				9.30 ± 0.05	6.40 ± 0.10	794
3[f]	CO				8.89 ± 0.07	6.50 ± 0.06	309
4(cis)	O	158–160	2-PrOH	$C_{25}H_{27}NO_5 \cdot H_2C_2O_4$	5.29 ± 0.03[g]	4.49 ± 0.11[h]	6
5(trans)	O	150–152	EtOH	$C_{25}H_{27}NO_5 \cdot H_2C_2O_4 \cdot 0.5H_2O$	8.59 ± 0.05	4.22 ± 0.06[h]	23442
6(trans)	CO	168–170	2-PrOH	$C_{26}H_{27}NO_5 \cdot HCl$	8.27 ± 0.10	4.85 ± 0.03	2630

[a] pA_2 values plus or minus standard error of estimate were calculated according to Arunlakshana and Schild[20] constraining the slope to −1.0,[21] unless otherwise specified. When applying this method, it was always verified that the experimental data generated a line whose derived slope was not significantly different from unity. pA_2 is the positive value of the intercept of the line derived by plotting log (DR − 1) vs log antagonist concentration with the abscissa and is defined as the negative logarithm to the base 10 of that dose of antagonist that requires a doubling of the agonist dose to compensate for the action of the antagonist. The log (DR − 1) was calculated at three or four different antagonist concentrations for α_1- and α_2-activity, respectively, and each concentration was tested at least five times. Dose-ratio (DR) values represent the ratio of the potency of the agonist norepinephrine or clonidine (ED_{50}) in the presence of the antagonist and in its absence. Parallelism of dose-response curves was checked by linear regression, and the slopes were tested for significance ($p < 0.05$). [b] The heating rate was 1 °C/min. [c] Analyses for C, H, N were within ±0.4% of the theoretical value required. [d] The α_1/α_2 selectivity ratio is the antilog of the difference between pA_2 values at α_1- and α_2-adrenoreceptors. [e] Hydrochloride salt. [f] Oxalate salt. [g] This value represents the negative logarithm to the base 10 of that concentration of antagonist which inhibits 50% of the maximal response to norepinephrine (IC_{50}).[19] [h] Calculated according to van Rossum[22] at only one concentration (100 μM).

Scheme I



following the same modification in 1.

Chemistry

The compounds used in this investigation were synthesized as shown in Scheme I.[11]

Acid **7** (cis-trans mixture),[12] in chloroform, was amidated in the presence of Et_3N and EtOCOCl with amine **8**[13] to give a 75% yield of amide **9**.[14] Reduction of **9** with borane–methyl sulfide complex in dry diglyme gave a 60% yield of a mixture of **4** and **5**.[15]

The stereochemical relation between the side chain and the 3-phenyl ring in **4** and **5** was deduced on the basis of the coupling constant for the hydrogens at position 3. Thus, a trans relation was assigned to **5** since the coupling constant (J = 7.09 Hz) was greater than that found for **4** (J = 2.51 Hz) for which a cis relation should be attributed.[16]

Analogue **6** was synthesized by a Mannich reaction from **10**,[17] **8**,[13] and formaldehyde.[18] This reaction afforded only one isomer (**6**) to whom a trans relation was assigned since the coupling constant (J = 11.29 Hz) was higher than that observed for **5**, which has a trans relation.

Biology

The biological profile of compounds **4–6** at α_1- and α_2-adrenoreceptors was assessed on isolated rat vas de-

(11) IR and NMR spectra were measured for all compounds and supported the assigned structures. For the synthesis of **4–6**, the experimental procedures were similar to those described in detail in ref 4 for unsubstituted analogues.

(12) Rosnati, V.; Sannicolò, F.; Pagani, G. *Gazz. Chim. Ital.* **1968**, *98*, 1069.

(13) Woolley, D. W. *Nature (London)* **1957**, *180*, 630.

(14) This compound was purified as a cis-trans mixture by silica column chromatography eluting with cyclohexane–EtOAc (7.5:2.5).

(15) Isomers **4** and **5** were separated as the free bases by silica column chromatography eluting with chloroform–EtOAc (8:2). The first fraction was the trans isomer **5** (Phendioxan): NMR ($CDCl_3$) δ 2.45 (br s, 1 H, NH), 2.65–2.88 (m, 4 H, CH_2NCH_2), 3.85 (s, 6 H, OCH_3), 4.10 (t, 2 H, OCH_2), 4.17–4.25 (m, 1 H, 2-H), 5.02 (d, 1 H, J = 7.09 Hz, 3-H), and 6.56–7.45 ppm (m, 12 H, aromatics). The second fraction was the cis isomer **4**: NMR ($CDCl_3$) δ 2.35 (br s, 1 H, NH), 2.49–2.91 (m, 2 H, CH_2NCH_2), 3.78 (s, 6 H, OCH_3), 3.94–4.12 (m, 2 H, OCH_2), 4.61–4.67 (m, 1 H, 2-H), 5.32 (d, 1 H, J = 2.51 Hz, 3-H), and 6.52–7.43 ppm (m, 12 H, aromatics). Compounds **4** and **5** were characterized as the oxalate salts (Table I).

(16) Analogous structural assignments have been given for other 2,3-disubstituted 1,4-benzodioxan derivatives: (a) Monro, A. M.; Potter, G. W. H.; Sewell, M. J. *J. Med. Chem.* **1967**, *10*, 880. (b) Rosnati, V.; Sannicolò, F.; Zecchi, G. *Gazz. Chim. Ital.* **1971**, *101*, 344. (c) Salimbeni, A.; Manghisi, E.; Ferni, G.; Fregnan, G. B. *Farmaco Ed. Sci.* **1983**, *38*, 571.

(17) Lowenbein, A. *Chem. Ber.* **1924**, *57B*, 1515.

(18) This compound was purified as the free base in a 30% yield eluting with EtOAc–EtOH–petroleum ether (1.5:0.3:4). It was characterized as the hydrochloride salt (Table I). NMR (DMSO-d_6) δ 2.67–2.79 (m, 1 H, 3-H), 3.09–3.38 (m, 4 H, CH_2NCH_2), 3.75 (s, 6 H, OCH_3), 4.05 (t, 2 H, OCH_2), 5.75 (d, 1 H, J = 11.29 Hz, 2-H), and 6.70–7.90 ppm (m, 12 H, aromatics).

ferens with the prostatic and epididymal portions of this tissue following a protocol already described in detail.[4] In order to allow comparison of the results, we used the same techniques and statistical evaluation of the bioassays as for other benzodioxan-related compounds.[4]

The results of 4–6 are shown in Table I together with pA_2 values of parent compounds 1 and 3. It can be seen that insertion of a phenyl ring at position 3 of 1, affording 4 and 5 (Phendioxan) alters markedly both activity and selectivity toward α-adrenoreceptor subtypes. It is also evident that the stereochemical relation between the 2-side chain and the 3-phenyl ring plays a crucial role in drug–receptor interaction. In fact, both isomers 4 and 5 were very weak α_2-adrenoreceptor antagonists while trans isomer 5 (Phendioxan) was more than 3 orders of magnitude more potent than cis isomer 4 at α_1-adrenoreceptors. This finding clearly indicates that the insertion of a phenyl ring at position 3 of 1 is highly detrimental toward α_2-adrenoreceptors either in a trans or in a cis relation with respect to the 2-chain whereas the activity for α_1-adrenoreceptors is negatively affected, compared to that of 1, only for a cis relation as in 4. In fact, 4 is more than 10 000 times less active than 1 at α_1-adrenoreceptors whereas the trans isomer 5 is only five times less potent than the parent compound. Furthermore, isomers 4 and 5 not only displayed toward α_1-adrenoreceptors a markedly different activity but also a different type of antagonism, owing to the observation that 5 was a competitive antagonist over a wide range of concentrations (3–3000 μM) whereas 4 behaved as a noncompetitive antagonist.[19] However, the most stricking result of the present investigation is the selectivity toward α_1-adrenoreceptors displayed by 5 which resulted in markedly increased selectivity compared to that of the prototype 1. The high selectivity of 5 could be the result of an unfavorable binding of the 3-phenyl group with α_2-adrenoreceptors, presumably by way of a steric hindrance, while that moiety is still tolerated at the α_1-site where it produces only a slight decrease in affinity (Table I).

We demonstrated that replacement of the oxygen at position 1 of 1 with a carbonyl function, affording 3, does not alter the biological profile of the molecule.[4] Again, the insertion of a phenyl ring at position 2 of 3, affording 6, resulted in an effect which is similar to that observed above for the same structural manipulation performed on 1.

In conclusion, to our knowledge, 5 (Phendioxan) represents, until now, the most selective α_1-adrenoreceptor antagonist in in vitro experiments and it might be not only a useful tool in the characterization of α-adrenoreceptor subtypes but also a lead compound for the design of more selective and more potent antagonists.[23]

(19) This compound behaves as a noncompetitive α_1-adrenoreceptor antagonist since it caused a depression of the maximum response to norepinephrine. Thus, its activity for α_1-adrenoreceptors was expressed as the IC_{50} value that represents the concentration which produces 50% inhibition of the agonist maximal response (Table I).

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(22) van Rossum, J. M. *Arch. Int. Pharmacodyn.* **1963**, *143*, 299.
(23) Detailed pharmacological characterization of 5 shall appear elsewhere together with the results of ongoing relevant research.

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(1*R*,3*S*)-1-(Aminomethyl)-3,4-dihydro-5,6-dihydroxy-3-phenyl-1*H*-2-benzopyran: A Potent and Selective D1 Agonist

It is now generally accepted that there are two major subtypes of the dopamine receptor in the central nervous system (CNS), designated as D1 and D2.[1] Both receptors are located in postsynaptic neuronal membranes and are linked to the enzyme adenylate cyclase. The receptors differ since activation of the D1 receptor enhances the production of cyclic adenosine monophosphate (cAMP) while stimulation of the D2 receptor subtype inhibits cAMP production. A presynaptic dopamine receptor has also been characterized and is believed to be of the D2 type.[2] The D1 dopamine receptor was once thought to have no important function in the CNS. More recently, however, with the aid of selective agonists and antagonists, significant roles of the central dopamine D1 receptor have been documented.[3] Conversely, the actions of the peripheral DA1 receptor have been understood for some time.[4]

Defects in the dopaminergic neuronal systems in the brain have been implicated in a number of disease states. Parkinson's disease in particular has been widely studied and is characterized by the degeneration of the dopamine-producing neurons in the substantia nigra.[5] We believe that a selective D1 agonist could have therapeutic potential in the treatment of Parkinson's disease. A D1 agonist incapable of CNS penetration, such as fenoldopam, may also have application as a novel antihypertensive. Out of a program aimed at the development of dopaminergic compounds, A68930 [1, (1*R*,3*S*)-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-3-phenyl-1*H*-2-benzopyran] was identified as a potent and selective D1 agonist.

Compound 1 was synthesized as shown in Scheme I. The protected catechol derivative **2**[6] was lithiated with *n*-BuLi in THF and condensed with styrene oxide to afford the alcohol 3 in 50% yield. The key step was a stereo-

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