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Communications to the Editor

2-[[[2-(2,6-Dimethoxyphenoxy)ethyl]amino]-methyl]-1,4-benzoxathian: A New Antagonist with High Potency and Selectivity toward α_1-Adrenoreceptors

Sir:

Much evidence supports the view that the α-adrenoreceptor is not a homogeneous entity. In addition to the classical postsynaptic α-adrenoreceptor, called α_1, that initiates the response of the effector organ, there is a presynaptic α-adrenoreceptor, named α_2, that modulates neurotransmitter release by a feedback mechanism.[1-3] However, this classification does not always hold true since α_1- and α_2-adrenoreceptors can be found in regions other than post- and presynaptic areas, respectively.[4-6] In order to characterize and gain further information on α-adrenoreceptor subtypes, selective ligands (either agonists or antagonists) are needed. Benzodioxans are a class of α-adrenoreceptor antagonists that has received much attention in the last few years.[7] This has led to the discovery of 2-[[[2-(2,6-dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxan (WB 4101, **2**), which is widely used for characterization of the α-adrenoreceptor owing to its high potency and selectivity toward postsynaptic α_1-adrenoreceptors.[8] Extensive structure–activity relationships have not improved either the potency or selectivity of **2**, which has remained, until now, one of the most potent and selective α_1-antagonists. We report here the synthesis and preliminary characterization of a new antagonist displaying an unprecedented potency and selectivity toward α_1-adrenoreceptors, 2-[[[2-(2,6-dimethoxyphenoxy)ethyl]-amino]methyl]-1,4-benzoxathian hydrochloride monohydrate (**1**).

Chemistry. This compound was synthesized as shown in Scheme I.[9]

Scheme I

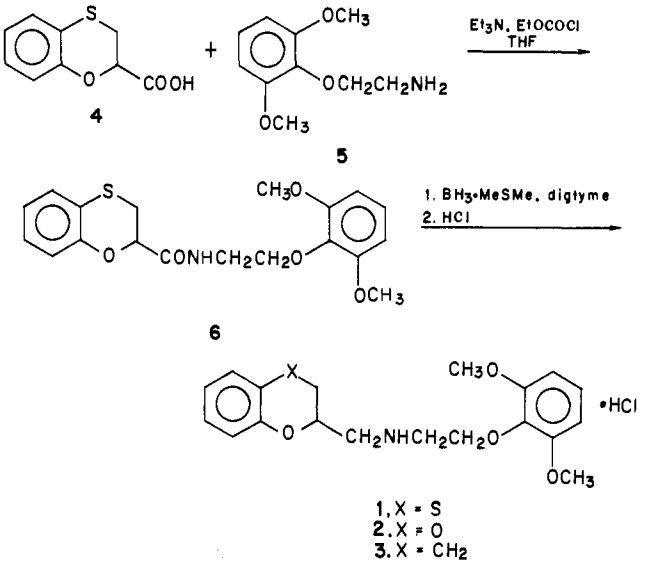

Table I. α_1- and α_2-Adrenoreceptors pA_2 Values in the Isolated Rat Vas Deferens[a]

antagonist	α_1 pA_2 value against norepinephrine	α_2 pA_2 value against clonidine	α_1/α_2[b] selectivity ratio
1	9.26 ± 0.06[c] (slope 0.99)	6.26 ± 0.08[d] (slope 1.03)	1000
2	8.83 ± 0.02	6.29 ± 0.10	347
prazosin	8.74 ± 0.16	5.81 ± 0.10	851

[a] pA_2 values plus or minus standard error of estimate of 1, 2, and prazosin were calculated according to Arunlakshana and Schild.[22] 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.[16] Parallelism of dose–response curves was checked by linear regression, and the slopes were tested for significance ($p < 0.05$). [b] The α_1/α_2 selectivity ratio is the antilog of the difference between the pA_2 values at α_1- and α_2-adrenoceptors. [c] Significantly different ($p > 0.05$) compared to **2**. [d] Not significantly different ($p < 0.05$) compared to **2**.

Treatment of ethyl 1,4-benzoxathian-2-carboxylate[10,11] with dilute NaOH gave, after acidification and extraction

(1) Langer, S. Z. *Biochem. Pharmacol.* **1974**, *23*, 1763.
(2) Starke, K. *Rev. Physiol. Biochem. Pharmacol.* **1977**, *71*, 1.
(3) Berthelsen, S.; Pettinger, W. A. *Life Sci.* **1977**, *21*, 595.
(4) Melchiorre, C. *Farmaco, Ed. Sci.* **1980**, *35*, 535.
(5) Timmermans, P. B. M. W. M.; Van Zwieten, P. *J. Med. Chem.* **1982**, *25*, 1389.
(6) McGrath, J. C. *Biochem. Pharmacol.* **1982**, *31*, 467.
(7) For example, see: Melchiorre, C.; Belleau, B. "Andrenoceptors and Catecholamine Action", Part A; Kunos, G., Ed.; Wiley: New York, 1981; pp 181–211.
(8) For example, see: U'Prichard, D. C. "Adrenoreceptors and Catecholamine Action", Part A; Kunos, G., Ed.; Wiley: New York, 1981; pp 131–179.
(9) IR and NMR spectra for all compounds were routine and supported the assigned structure. C, H, and N analyses were within 0.4%. For the synthesis of 1, the experimental procedure was similar to that described in detail in ref 16 for **2**.
(10) This compound was obtained as described in ref 11 and purified by silica column chromatography eluting with EtOAc–cyclohexane (1:9) since distillation did not yield pure material.

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with ether, followed by solvent removal, a quantitative yield of the corresponding acid **4** as a white crystalline solid, mp 115–116 °C (benzene). Acid **4**, in THF, was amidated in the presence of Et_3N and EtOCOCl with 2-(2,6-dimethoxyphenoxy)ethylamine[12] (**5**) to give a 75% yield of amide **6** as a colorless oil, which was used without further purification. Reduction of amide **6** with borane–methyl sulfide complex in dry diglyme gave 70% of **1** as a white crystalline hydrochloride, mp 104–105 °C (*i*-PrOH–EtOAc–Et_2O).

Biology. Since benzodioxans have been extensively studied in isolated rat vas deferens preparations,[7] it was thought that keeping the bioassays constant would allow a better comparison with results obtained with use of related drugs. Each vas deferens was transversely bisected in two portions of ca. 15 mm in length. Owing to their different sensitivity to agonists and their different response to electrical stimulation,[13,14] prostatic and epididymal portions of the vas deferens were used to study pre- and postsynaptic α-adrenoreceptors, respectively.[15-18]

The biological profile of compound **1** at the rat vas deferens α-adrenoreceptors is shown in Table I together with pA_2 values of the most active and selective α_1-antagonists, that is, **2** and prazosin, in order to compare potency and selectivity for α_1- and α_2-adrenoreceptors. The biological activity of **1**, **2**, and prazosin was determined simultaneously to avoid possible variations from laboratory to laboratory.

Compound **1** displays a competitive mechanism of action toward both α_1- and α_2-adrenoreceptors as revealed by the slope of Schild plots and parallelism of curves. It is also clear that **1** is a very potent antagonist at the α_1-adrenoreceptor with an unusually high pA_2 value of 9.26. It suffices to say that on the same preparation **2** and prazosin were 3 and 3.6 times, respectively, less potent compared to **1** (Table I). However, the most striking finding of the present investigation was the unprecedented selectivity toward α_1-adrenoreceptors displayed by **1** as revealed by the α_1/α_2 selectivity ratio of 1000. Under the same conditions, **2** and prazosin had an α_1/α_2 selectivity ratio of 347 and 851, respectively. This is the first time that structural manipulation of the molecule **2** has resulted in increased affinity for the α_1-adrenoreceptor. It has been reported that both benzodioxan and (2,6-dimethoxyphenoxy)ethyl moieties are essential for activity.[19] Any structural modification resulting in a pronounced difference in pharmacological activity relative to the α_1-adrenoreceptor does not significantly affect the α_2-adrenoreceptor.[16,20] The substitution of oxygen at position 4 with a methylene group[21] (**3**) caused a 1000-fold decrease in potency compared to that of **2**. Furthermore, it is interesting to note that substitution of the oxygen at position 4 with a sulfur in other antagonists of the benzodioxan class, such as prosympal and piperoxan, gave rise to compounds with agonistic instead of antagonistic activity toward the α-adrenoreceptor.[11] Taken together, these results and ours emphasize the importance of the position 4 in both the benzodioxan and benzoxathian nucleus for the interaction at α_1-adrenoreceptors. Since sulfur cannot form a productive hydrogen bond, the position 4 of antagonists bearing a benzodioxan or a benzoxathian nucleus would interact with the receptor, either increasing the electron density of the phenyl ring by a way of an electron-releasing effect or giving rise to a dipole–dipole interaction.

In conclusion, compound **1** is a potent and selective α_1-adrenoreceptor antagonist that may represent a valuable tool in the characterization of α-adrenoreceptor subtypes.[23]

Acknowledgment. Supported by the Ministry of Public Education.

(11) Tsai, C. S.; Shah, U. S.; Bhargava, H. B.; Zaylskie, R. G.; Shelver, W. H. *J. Pharm. Sci.* **1972**, *61*, 228.
(12) Woolley, D. W. *Nature (London)* **1957**, *180*, 630.
(13) Brown, C. M.; McGrath, J. C.; Summers, R. J. *Br. J. Pharmacol.* **1979**, *66*, 553.
(14) McGrath, J. C. *J. Physiol.* **1978**, *283*, 23.
(15) Compound **1** was incubated for 30 min before the initial challenge with the agonist. A 60-min incubation time gave identical results, suggesting that 30 min are sufficient to reach equilibrium conditions. Propranolol hydrochloride (1 μM), cocaine hydrochloride (10 μM), and deoxycorticosterone acetate (40 μM) were present in the Krebs solutions throughout the experiments to block β-adrenoreceptors, neuronal and extraneuronal uptake mechanisms, respectively. The experimental protocol was similar to that described in detail in ref 16 for other α-adrenoreceptor antagonists.
(16) Giardinà, D.; Angeli, P.; Brasili, L.; Guilini, U.; Melchiorre, C.; Strappaghetti, G. *Eur. J. Med. Chem.*, in press.
(17) A referee has suggested to point out the possible problems connected with the use of relatively nonselective agonists such as norepinephrine and clonidine and the rat vas deferens preparation for the overlap of prostatic and epididymal portions and nonadrenergic responses. This has given rise to the development of new procedures such as that described in ref 18. However, it is interesting to note that our results for prazosin (Table I) are in close agreement with those obtained with the newer methodology.
(18) Michel, A. D.; Whiting, R. W. *Br. J. Pharmacol.* **1981**, *74*, 256P.
(19) Kapur, H.; Mottram, D. R.; Green, P. N. *J. Pharm. Pharmacol.* **1978**, *30*, 259.
(20) Kapur, H.; Rouot, B.; Snyder, S. H. *Eur. J. Pharmacol.* **1979**, *57*, 317.
(21) Kapur, H.; Green, P. N.; Mottram, D. R. *J. Pharm. Pharmacol.* **1979**, *31*, 188.
(22) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.
(23) Detailed pharmacological characterization of **1** shall appear elsewhere together with the results of ongoing relevant research.

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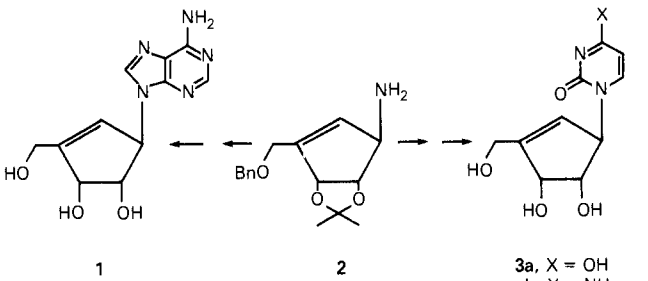
Cyclopentenyluridine and Cyclopentenylcytidine Analogues as Inhibitors of Uridine-Cytidine Kinase

Sir:

The unusual cyclopentene moiety and the antitumor properties of the antibiotic nucleoside neplanocin A[1] (**1**)



1 **2** **3a**, X = OH; **b**, X = NH_2

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