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Doxazosin-Related α_1-Adrenoceptor Antagonists With Prostate Antitumor Activity

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Doxazosin analogues **1**−**3** and **1a** were synthesized and investigated at α_1-adrenoceptors and PC-3, DU-145, and LNCaP human prostate cancer cells. Compound **1** (cyclodoxazosin) was a potent α_{1B}-adrenoceptor antagonist displaying antiproliferative activity higher than that of doxazosin in cancer cells in vitro and in vivo, respectively. Because of its antitumor efficacy at low concentrations, lower apoptotic activity in NHDF vs tumor cells, and antiangiogenetic effect, **1** showed a better therapeutic profile relative to doxazosin.

Introduction

Doxazosin is a potent and selective α_1-adrenoceptor antagonist displaying effective antihypertensive activity.[1] Because of its relaxant activity and increased apoptosis on prostate smooth muscle,[2,3] it is also used to treat the obstructive and irritative symptoms of BPH[a] disease.[4] Doxazosin exerts, via an apoptotic-induced mechanism, a potent antigrowth effect in vitro against the PC-3, DU-145, and LNCaP human prostate cancer cells, independently of its α_1-adrenoceptor antagonism or the hormone sensitivity status of cells.[5,6] The antitumor activity of doxazosin was confirmed in mice bearing PC-3-induced prostate cancer, where it displayed a significant inhibition of tumor growth.[5] These properties point to a therapeutic significance for the quinazoline-based compounds both in managing human BPH and in the antitumor treatment of prostate cancer,[6] with a possible role in the prevention of tumor development.[7]

In our continuing search for quinazoline-based α_1-adrenoceptor antagonists, we developed cyclazosin, a racemic compound known to possess high antagonist affinity and selectivity for α_{1d}- and α_{1b}-adrenoceptors relative to the α_{1a} subtype.[8,9] Here, we report on two novel cyclazosin analogues, 2-[4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)-*cis*-octahydroquinoxalin-1(2*H*)-yl]-6,7-dimethoxyquinazolin-4-amine (**1**, cyclodoxazosin) and 2-[4-(2,3-dihydro-1,4-benzodioxin2-ylcarbonyl)-*trans*-octahydroquinoxalin-1(2*H*)-yl]-6,7-dimethoxyquinazolin-4-amine (**2**), incorporating a 2,3-dihydro-1,4-benzodioxine-2-carbonyl moiety instead of the 2-furoyl group, and on the related, previously described,[10] open analogue *N*-{6-[(4-amino-6,7-dimethoxyquinazolin-2-yl) (methyl)amino]hexyl}-*N*-methyl-2,3-dihydro-1,4-benzodioxine-2-carboxamide (**3**), in order to assess the role, if any, of the decahydroquinoxaline nucleus on the α_1-adrenoceptor subtypes antagonism and the antitumor activity. In addition, because **1** is more potent than the relative trans isomer **2**, to evaluate the effect of the stereochemistry of the *cis*-octahydroquinoxalin nucleus on the antiproliferative activity (−)-2-[(4a*S*,8a*R*)-4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)-octahydroquinoxalin-1(2*H*)-yl]-6,7-dimethoxyquinazolin-4-amine (**1a**), a couple of the four stereoisomers of **1**, was included in the study. The stereochemistry of the 1,4-benzodioxine moiety was not investigated because doxazosin was less potent than **1**. The structures of the studied compounds are reported in Figure 1.

Results and Discussion

Chemistry. The synthesis of compounds **1** and **2** was achieved by reaction of 2,3-dihydro-1,4-benzodioxine-2-carbonyl chloride (**4**)[11] with *cis*-(**5**)[12] or *trans*-6,7-dimethoxy-2-[octahydroquinoxalin-1(2*H*)-yl]quinazolin-4-amine (**7**), obtained from 2-chloro-6,7-dimethoxyquinazolin-4-amine and *cis*- or *trans*-decahydroquinoxaline,[13] respectively (Scheme 1). Similarly, **1a** was obtained from **4** and (−)-6,7-dimethoxy-2-[(4a*S*,8a*R*)-octahydroquinoxalin-1(2*H*)-yl]quinazolin-4-amine (**6**).[14] Compound **3** was obtained by reaction of **4** with 6,7-dimethoxy-*N*-methyl-*N*-[6-(methylamino)hexyl]quinazoline-2,4-diamine, as reported.[10] Compounds **1** and **2** are mixtures of four stereoisomers because of the three chiral centers present in their structures. Compound **1** was isolated as mixture of two racemates, in a proportion of 28% and 72%, as shown by the HPLC/DAD analysis, whereas **2** was not analyzed. (see Supporting Information).

α_1-Adrenoceptor Antagonist Activity and Binding Affinity. Compounds **1**−**3** and cyclazosin were studied in rat isolated prostatic vas deferens, aorta, and spleen to assess their antagonist activity and selectivity at α_1-adrenoceptor subtypes.[15−17] The antagonist potency of cyclazosin at α_{1A}, α_{1B}, and α_{1D} subtypes and of **1** at the α_{1D} subtype was expressed as pA_2 values, according to Arunlakshana and Schild.[18] For **2**, **3**, and for **1** at α_{1A}, and α_{1B} adrenoceptors, as the slope of

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[a]Abbrevations: BPH, benign prostatic hyperplasia; NHDF, normal human dermal fibroblasts.

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the Schild plot was significantly different from unity, the potency was expressed by pK_B values, according to van Rossum.[19] In this latter case, the pK_B value was calculated at the lowest antagonist concentration, giving a significant rightward shift of the agonist concentration−response curve [log (concentration ratio −1) ≥ 0.5].

The affinity profile of **1**−**3** and **1a** was also evaluated in radioreceptor binding assays on membranes of Chinese hamster ovary (CHO) cells expressing human α_{1a}, α_{1b}, and α_{1d} adrenoceptor subtypes.[20] Binding affinities were expressed as pK_i values derived using the Cheng−Prusoff equation.[21] The results are reported in Table 1 in comparison with cyclazosin and doxazosin, the reference compounds.

In functional assays, **3** was more potent than **1** and **2** at all α_1-adrenoceptor subtypes with the exception of **1** at the α_{1B} subtype. Clearly, the insertion of the piperazine ring of doxazosin into a *cis*- and *trans*-decahydroquinoxaline nucleus to give **1** and **2**, respectively, is detrimental for the affinity at tissutal α_1-adrenoceptors. However, the cis isomer **1** was more potent than the trans **2** at all the subtypes. This is in agreement with the reported higher affinity of cyclazosin relative to its trans isomer at the epididymal rat vas deferens α_1-adrenoceptors.[8] Notably, unlike **3**, **1** was significantly more potent at the α_{1B} subtype relative to α_{1A} and α_{1D} adrenoceptors (12- and 8-fold, respectively), whereas **2** was more potent at α_{1B} and α_{1D} subtypes with respect to the α_{1A} (18- and 10-fold, respectively).

In the present study, cyclazosin did not display any significant selectivity in functional experiments, in contrast to the results in binding assays.[9,12] Furthermore, in binding assays, the affinity of **1**−**3** and cyclazosin at α_1-adrenoceptor subtypes did not parallel the affinity observed in functional experiments as already found for a number of other prazosin-related compounds.[22]

In Vitro Cytotoxic Activity. The antiproliferative effects of **1**−**3**, **1a**, and doxazosin were evaluated in vitro in PC-3, DU-145, and LNCaP human prostate cancer cells as well as in normal human dermal fibroblasts (NHDF) (Table 1).

Compounds **1** and **3** displayed antiproliferative activity in all tested cancer cells. In particular, **1** exhibited the highest effect, at submicromolar concentrations, whereas **3** was about 10-fold less potent than **1**. The trans isomer **2** was 17-fold less potent than **1** at LNCaP cells, and no effect was observed in the other cells up to the maximal tested concentration (10 μM). Compound **1** was 39−49-fold and 8−10-fold more potent on prostate malignant cells than doxazosin and **3**, respectively. Interestingly, **1a** was almost as active as **1**

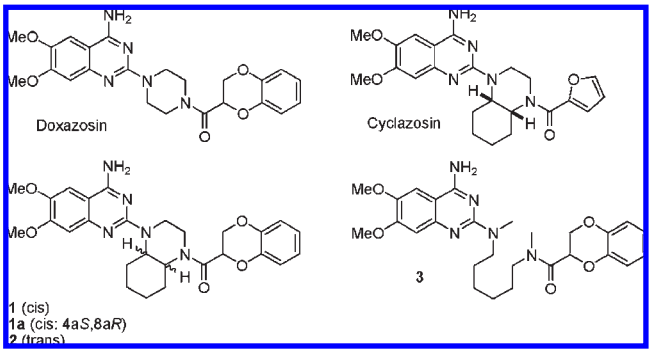
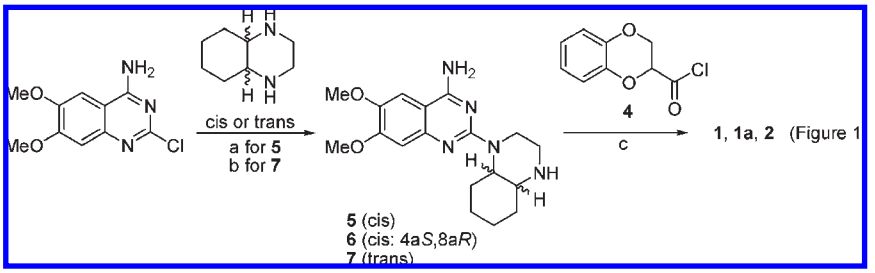


Figure 1. Chemical structures of doxazosin, cyclazosin, **1**−**3**, and **1a**.

Scheme 1[a]



[a] Reagents: (a) *i*-AmOH, reflux; (b) *i*-AmOH, triethylamine, DMAP, reflux; (c) dry CH_2Cl_2.

Table 1. Binding (pK_i) and Functional Affinity (pA_2 or pK_B) Constants and in Vitro Antiproliferative Activity (IC_{50}) of **1**−**3**, **1a**, Cyclazosin, and Doxazosin at Cloned Human α_1-Adrenoceptors, Isolated Rat Tissues α_1-Adrenoceptors, and PC-3, DU-145, and LNCaP Human Prostate Cancer Cells and NHDF Cells[a]

	p*Ki* [a]			pA_2 [b] or pK_B [c]			IC_{50} (μM)[d]			
no.	α_{1a}	α_{1b}	α_{1d}	α_{1A}	α_{1B}	α_{1D}	PC-3	DU-145	LNCaP	NHDF
1	8.55	9.38	9.77	7.21 ± 0.07[c]	8.30 ± 0.05[c]	7.39 ± 0.06[b]	0.85	0.96	0.57	1.46
1a	8.47	8.85	9.31				1.02			
2	7.09	7.65	7.58	5.88 ± 0.18[c]	7.14 ± 0.07[c]	6.88 ± 0.10[c]	> 10[g]	> 10[g]	9.75	> 10[g]
3	8.73	9.03	8.80	8.51 ± 0.07[c]	8.35 ± 0.10[c]	8.64 ± 0.13[c]	8.40	9.25	4.61	9.80
cyclazosin	8.26[e]	9.49[e]	9.77[e]	8.91 ± 0.04[b]	9.18 ± 0.03[b]	9.21 ± 0.02[b]				
doxazosin	9.27[f]	9.09[f]	9.09[f]	8.69 ± 0.70[b,f]	9.51 ± 0.41[b,f]	8.97 ± 0.23[b,f]	38.60	37.44	28.11	43.00

[a] Equilibrium dissociation constants (p*Ki*) were calculated from IC_{50} values using the Cheng−Prusoff equation. The affinity estimates, derived from displacement of [^{3}H]prazosin binding from α_1-adrenoceptors, were from two to three experiments performed in triplicate, which agreed within ±20%. [b] The α_1-adrenoceptor blocking activity was assessed by antagonism of (−)-NE-induced contractions of rat vas deferens (α_{1A}) or thoracic aorta (α_{1D}) and by antagonism of (−)-phenylephrine-induced contractions of rat spleen (α_{1B}). pA_2 values are means ± SEM of three different concentrations, each tested at least four times. [c] pK_B values (±SEM) were calculated according to van Rossum. [d] The activity was determined by using a CellTiter-Glo luminescent cell viability assay (Promega). The data, expressed as percentage of control, are reported as IC_{50} values, which represents the concentration (μM) of compounds required for inhibition of 50% of cell growth. Each value is the mean of two independent experiments performed in duplicate, with the standard deviation ranging from 2.4 to 33.5%. [e] Data from ref 12. [f] Data from ref 24. [g] These data indicate that no antiproliferative activity was observed until at least the maximal tested dose (10 μM).

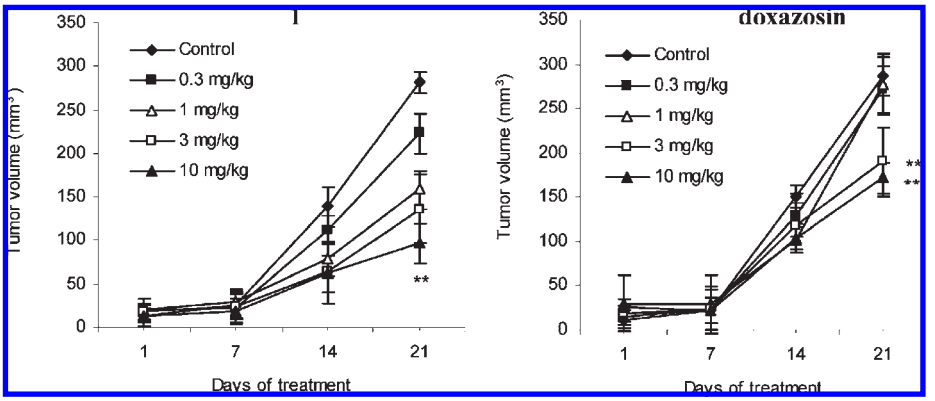


Figure 2. Effect of treatment with **1** and doxazosin on the growth of subcutaneous tumor implanted in male nude mice by human prostate PC-3 cancer cells. Each drug was administered orally and daily, for 21 consecutive days, at specific concentrations to five groups of mice (six animals/group, $n = 6$), under treatment and control. Data represent the mean ± SEM. Statistical analysis was done by analysis of variance (Anova) and Student *t*-test; **: significantly different from control, $p < 0.01$.

in PC-3 cells, suggesting that the stereochemistry, at least in these cells, may not have a relevant role in the antiproliferative activity. Concerning **2**, its activity was slightly higher than that of doxazosin in LNCaP cells (3-fold), but not comparable in the others. Like doxazosin, **1**−**3** displayed an antiproliferative effect at NHDF cells that was close to that shown in prostate cancer lines.

Apoptosis study. Different studies indicated that quinazoline-based α_1-adrenoceptor antagonists, such as doxazosin, suppress prostate tumor growth via a plurality of mechanisms, including receptor-mediated apoptosis.[7] Thus, given the structural similarity with doxazosin, the effect of **1**−**3** on apoptosis was evaluated in PC-3, DU-145, and LNCaP human prostate cancer cells and in NHDF cells through the evaluation of their ability in activation of effector caspases. The level of apoptosis was estimated by measuring in cells the activity of caspase-3 and caspase-7 that are considered the key effector of apoptosis in mammalians.[23]

Compound **1** was the most effective in caspase induction in cancer cells relative to **2**, **3**, and doxazosin (see Figure 1 of Supporting Information). This finding is in agreement with the higher antiproliferative effect observed for **1** (Table 1). Interestingly, **1**, unlike **2** and **3**, was, at the least, 4−7-fold less effective in inducing caspase activation and apoptosis in NHDF cells ($EC_{50} > 10\ \mu M$) than in tumoral PC-3, DU-145, and LNCaP cells ($EC_{50} = 1.86$, 2.60, and 1.42 μM, respectively). On the contrary, the effect of doxazosin at NHDF ($EC_{50} = 40.4\ \mu M$) was similar to that on LNCaP cells but, at the least, 2.5-fold higher than in PC-3 and DU-145 cells ($EC_{50} > 100\ \mu M$).

In Vivo Antitumor Activity. Given its interesting caspase induction ability and antiproliferative activity, **1** was chosen for further in vivo investigation in male nude mice bearing a subcutaneous tumor implanted in the left flank by injection of PC-3 cells. Figure 2 shows the course of tumor inhibition by **1** and doxazosin. A graphical representation of the different efficacy, at each tested concentration at the end of treatment, displayed by **1** and doxazosin, is reported in Figure 2 of Supporting Information.

Compound **1** inhibited the growth of the PC-3 induced tumor in a concentration-dependent fashion, which was significant at the minimal tested dose (21% decrease at 0.3 mg/kg vs control). In contrast, doxazosin gave a significant inhibition only at higher concentrations (3 and 10 mg/kg) (Figure 2 and Figure 2 of Supporting Information).

To confirm the in vitro observed apoptosis induced by **1** and doxazosin, this effect was also investigated in the removed subcutaneous tumor. At the same time, the tumor samples were employed to assess a possible antiangiogenetic effect by **1** and doxazosin. The apoptotic effect of **1** and doxazosin was determined by a DNA fragmentation assay in which, through an electrophoretic analysis, a typical DNA ladder pattern was observed on tumor treated with drugs (see Figure 3 of Supporting Information). Again, **1** was more active than doxazosin because, approximately, in tumor treated with **1**, the characteristic pattern was observed at a concentration lower than in doxazosin-treated tumor (0.3 mg/kg vs 3 mg/kg).

The antiangiogenetic activity of **1** and doxazosin was determined through immunohistochemical analysis by using the endothelial cell marker rat antimouse CD31 monoclonal antibody. Both drugs affected angiogenesis (see Figure 4 of Supporting Information). At a dose of 3 mg/kg, the drugs reduced blood vessel development. However, tumors treated with **1** were less vascularized than those treated with doxazosin and the effects of **1** on the tumors angiogenesis were also evident at dose of 0.3 and 1 mg/kg.

Conclusions

A few doxazosin analogues (**1**−**3** and **1a**) were investigated to assess their α_1-adrenoceptor antagonism and antitumoral effects. Compound **1** displayed a better biological profile than doxazosin and hence a preferential position in potential therapeutic treatment. In particular, **1** was a potent and moderately selective α_{1B}-adrenoceptor antagonist, showing in vitro antiproliferative activity in PC-3, DU-145, and LNCaP human prostate cancer cells, at submicromolar concentrations, and also in vivo antitumor activity in mice PC-3-induced subcutaneous tumor. Although the results do not provide an explanation for the relationship between the α_1-adrenoceptor antagonism and antitumor activity, compound **1**, bearing a *cis*-octahydroquinoxaline moiety, might be a useful lead compound for designing new compounds with improved biological profile.

Experimental Section

2-[4-(2,3-Dihydro-1,4-benzodioxin-2-ylcarbonyl)-*cis*-octahydroquinoxalin-1(2*H*)-yl]-6,7-dimethoxyquinazolin-4-amine hydrochloride (1). A solution of **4** (1.10 g, 5.54 mmol) in dry CH_2Cl_2

(25 mL) was added dropwise, under nitrogen, to a stirred and cooled (0 °C) solution of **5** (4.20 g, 12.20 mmol) in dry CH_2Cl_2 (75 mL), whereupon the stirring was continued at room temperature for 24 h. Removal of the solvent gave a residue that was purified by silica column chromatography eluting with petroleum ether−ethyl acetate−methanol−14% ammonia (4:4:1:0.1). The obtained free base was transformed into the hydrochloride salt (see Supporting Information for analytical characterization).

(-)-2-[(4a*S*,8a*R*)-4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)-octahydroquinoxalin-1(2*H*)-yl]-6,7-dimethoxyquinazolin-4-amine hydrochloride (1a). It was obtained from **4** and **6**[14] following a procedure similar to that described for **1** (see Supporting Information).

2-[4-(2,3-Dihydro-1,4-benzodioxin-2-ylcarbonyl)-*trans*-octahydroquinoxalin-1(2*H*)-yl]-6,7-dimethoxyquinazolin-4-amine hydrochloride (2). It was obtained from **4** and **7** following the procedure described for **1** (see Supporting Information).

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Supporting Information Available: Analytical characterization of **1**, synthetic procedures and analytical characterization of **1a**, **2**, and **7**, elemental analyses, biological methods, in vitro caspase induction and in vivo antitumor efficacy and, apoptotic and antiangiogenetic effects of **1** and doxazosin. This material is available free of charge via the Internet at http://pubs.acs.org.

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