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Short communication

Effect of 1,4-dioxanyl substitution on the adrenergic activity of some standard α-adrenoreceptor agents

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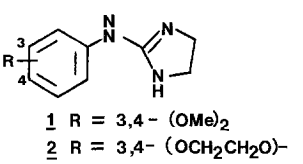
Summary – A preliminary communication reported on the pharmacology of the potent partial α_2-agonist (2-(1,4-benzodioxan-6-ylamino)-2-imidazoline, a 1,4-dioxan derivative of clonidine. Its degree of agonism / antagonism depended upon the peripheral or central α_2-adrenoreceptor system studied. It was of interest to discover whether a similar substitution of the 1,4-dioxan moiety in other standard α-adrenergic agents would similarly produce high affinity compounds of complex pharmacological profile. The same substitution when introduced into guanfacine, fenmetazole and tolazoline resulted in unpredictable changes in profile with a reduction in α-affinity.

Résumé — **Effet d'une substitution dioxanyl-1,4 sur l'activité adrénergique de quelques adrénorécepteurs classiques.** *Une communication préliminaire a décrit la pharmocologie d'un puissant α_2-agoniste partiel la (1,4-benzodioxan-6-ylamino)-2-imidazoline)* ***2****, un dérivé 1,4-dioxane de la clonidine. Le degré d'agonisme / antagonisme de* ***2*** *(dépendait du système α_2-adrénorécepteur étudié, central ou périphérique. Il était intéressant de savoir si une substitution semblable de l'entité 1,4-dioxane dans d'autres agents α-adrénergiques classiques produirait des composés à haute affinité de profil pharmacologique complexe. La même substitution a été faite sur la guanfacine, la fenmétazole et la tolazoline et a conduit à des modifications imprévisibles dans le profil, avec une réduction de l'affinité α.*

α_2-adrenoreceptors / antagonism / agonism / clonidine derivatives / 1,4-dioxan derivatives

Introduction

In a previous communication [1] the pharmacological profiles of 2 oxygenated arylaminoimidazolines, the 3,4-dimethoxy derivative **1** (RX 77171) and the corresponding 1,4-dioxan derivative **2** (RX 801074) of clonidine were compared with that of clonidine (**3**). Whereas **1** consistently displayed prejunctional α_2-adrenoreceptor antagonist properties, the dioxan compound **2** was found to possess a complex profile. Although a partial agonist at α_2-receptors, its degree of agonism / antagonism depended upon the peripheral or central α_2-adrenoreceptor system studied. Thus in the rat isolated vas deferens preparation it possessed predominantly α_2-agonist properties whereas in the guinea pig ileum preparation and after central administration compound **2** was a competitive antagonist. In view of the interesting profile of **2** and the importance of the dioxan ring in the α_2-antagonist idazoxan [2] (**4**), we undertook an investigation of 1,4-dioxan derivatives of some standard α-adrenergic agents. We report here the synthesis, including that of **1** and **2** and pharmacological evaluation of derivatives **5, 7** and **9** of guanfacine (**6**), fenmetazole (**8**) and tolazoline (**10**). A bromo derivative, **11** of **2** is also reported.



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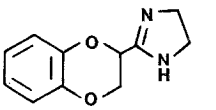
2 R = 3,4- (OCH_2CH_2O)-
3 R = 2,6-Cl_2



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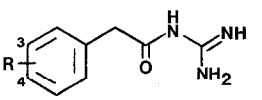

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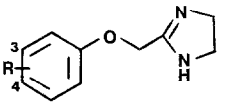
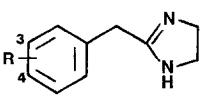
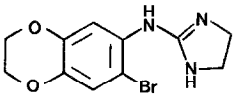
6 R = 2,6-Cl_2



7 R = 3,4-(OCH_2CH_2O)-
8 R = 3,4-Cl_2



9 R = 3,4-(OCH_2CH_2O)-
10 R = H



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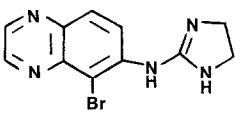

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Chemistry

All the compounds were synthesised, utilising standard literature procedures, from the appropriately substituted 1,4-benzodioxan or, in the example of **1** from 3,4-dimethoxy aniline as shown in Scheme 1. Direct bromination of **2** gave the mono-bromo derivative **11** in a good yield. An alternative route to **11** has recently been reported [3] involving bromination of 6-amino-1,4-benzodioxan, although this required protection (acylation), followed by deprotection of the amine function.

Results and Discussion

All compounds were examined for α_1- and α_2-adrenoreceptor agonist and antagonist properties by using standard testing procedures previously reported [4]. The results are summarised in Table I with the values being quoted as potencies relative to the standards as indicated.

The partial α_2-agonist **2** has previously been shown to possess high affinity for the α_2-receptor [1]; in the rat vas deferens (Table I) it is a potent α_2-agonist but in the guinea pig ileum it was shown to be a potent α_2-antagonist (pA$_2$

SCHEME I

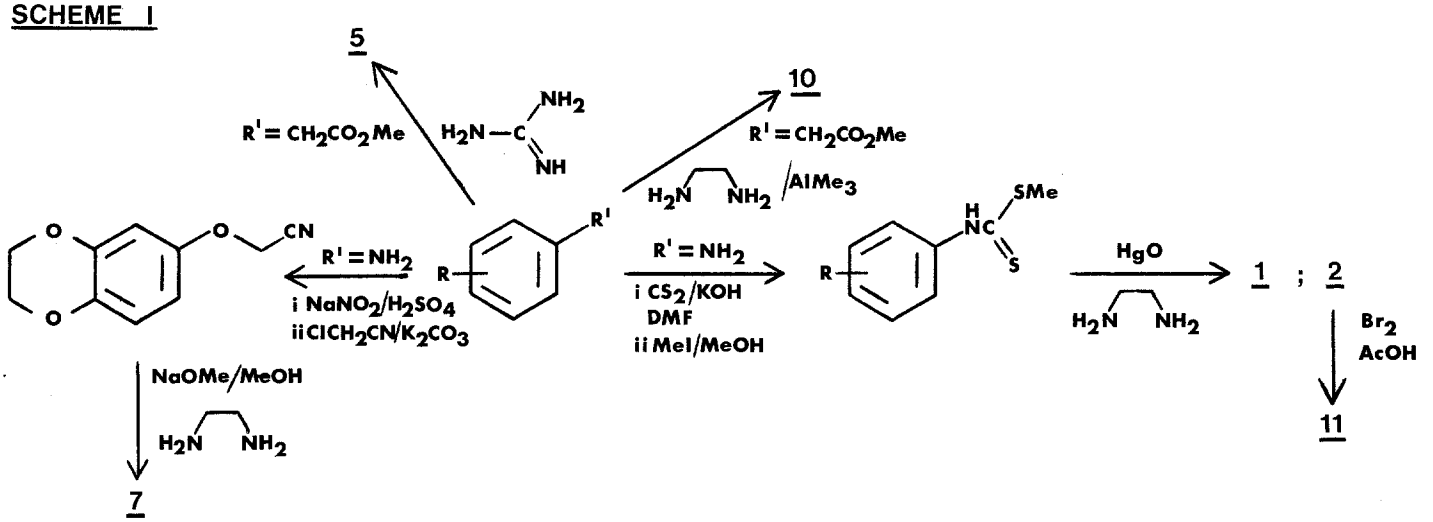

Table I. Pharmacological testing results [a] of compounds examined for α_1 and α_2-adrenoreceptor agonist and antagonist properties.

Compound		mp, °C	Formula	α_2-Agonist	α_2-Antagonist	α_1-Agonist	α_1-Antagonist
				potency[b] (*p*-aminoclonidine = 1)[d]	potency[b] (idazoxan = 1)[e]	potency[b] (phenylephrine = 1)[f]	potency[c] (idazoxan = 1)[g]
1	RX 77171	153–154	$C_{11}H_{15}N_3O_2$·HCl	0	0.007	0.07	Ag
2	RX 801074	157–159	$C_{11}H_{13}N_3O_2$·Maleate	1.5	Ag	0.01	Ag
3	Clonidine	–	–	0.49	Ag	0.8	Ag
5		194–195	$C_{11}H_{13}N_3O_3$·HCl·1/2 H_2O	0	0.0009	0	0.018
6	Guanfacine	–	–	0.69	Ag	0.42	Ag
7		243–250	$C_{12}H_{14}N_2O_3$·HCl	0.0001	0.018	0.008	Ag
8	Fenmetazole	–	–	0.004	0.021	0.17	Ag
9		190–194	$C_{12}H_{14}N_2O_2$·HCl·1/4 H_2O	0.006	Ag	0.017	Ag
10	Tolazoline	–	–	0	0.043	0	0.35
11		243–244	$C_{11}H_{12}BrN_3O_2$·HBr	0.013	0.05	0.3	Ag
12	UK 14,304	–	–	1.1	0	0.3	Ag

[a]Results are expressed as potencies which were compared directly with that of the standard in the same experiment: Ag = Agonist. [b]Dose–response curves of the standards were obtained before and after the dose–response curve of the analogue. There was no significant difference between the 2 dose–response curves of the standards. [c]Post-junctional α_1-antagonism concentration giving a dose response equal to 2 *vs* phenylephrine. A minimum of 5 dose–response curves were obtained for phenylephrine alone, followed by a minimum of 4 dose response curves in the presence of the analogue. [d]*p*-Aminoclonidine IC_{40} = 1.99 ± 0.04 nm. [e]**4** α_2–pA$_2$ = 7.98. [f]Phenylephrine IC_{50} = 78 ± 21 nm. [g]**4** α_1–pA$_2$ = 6.30.

= 7.77) [1]. Thus replacement of the 2,6-dichloro substituents in clonidine (**3**) by a 1,4-dioxan substituent (fused at positions 3,4) maintained the high affinity for the α_2-receptor, but in addition introduced a considerable and interesting variability between tissues (*i.e.*, agonism *vs* antagonism). The results shown in Table I reveal that the introduction of a 1,4-dioxan ring into other α-adrenergic agents did not produce the same effects as observed in the clonidine example. The same substitution change (2,6-Cl_2-3,4-(OCH_2CH_2O-) in the α_2-agonist guanfacine surprisingly resulted in an antagonist with very low affinity for the α_2-receptor; compare **5** with **6**. The low affinity compound fenmetazole is claimed to be an α_2-antagonist [5], although in this study it was found to possess a mixed α_1/α_2-profile. In this example the 1,4-dioxan substituent had no effect on the pharmacological profile but reduced affinity at the α_1-receptor; compare **7** with **8**. In contrast, the α-antagonist tolazoline was converted into an α-agonist, **9**, although both compounds were only weakly active.

A number of known α_2-agonists possess at least one ortho halo substituent; in the example of UK 14,304, **12**, the substituent is bromine. The mono-bromo derivative of **2** was prepared with the expectation that the resultant compound **11** would possess high affinity for the α_2-receptor but with predominantly agonist properties. Contrary to these expectations, bromination considerably reduced the α_2-affinity ($\approx$ 100-fold) and weak antagonist properties become evident. Interestingly, this low affinity compound **11** has been claimed to be of potential in the treatment of glaucoma [3].

In summary, although the presence of a 1,4-dioxan substituent in the clonidine structure produced a high affinity compound possessing an interesting pharmacological profile, the same substitution pattern when introduced into other α-adrenergic agents resulted in unpredictable changes in profile and a reduction in α-affinity.

Experimental protocols

Chemistry

Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. IR, NMR and MS spectra were recorded on Perkin–Elmer 700, Varian Associates T-60 and LKB-2091 instruments, respectively, and were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ± 0.4% of the theoretical values.

2-(1,4-Benzodioxan-6-ylamino)-2-imidazoline maleate ***2***
To a stirred solution of 90% KOH (12.6 g, 0.2 mol) and 6-amino-1,4-benzodioxan (Aldrich (30.2 g, 0.2 mol) in DMF (100 ml) at 0°C was added carbondisulfide (135 ml, 0.2 mol) over 5 min and the solution was then allowed to warm to room temperature. After 16 h, the solution was poured into a mixture of EtOAc (600 ml) and Et_2O (200 ml) and the resultant solid was collected by filtration to give the highly hygroscopic potassium salt of the thiocarbamate: yield 52 g (98%). A solution of methyl iodide (27 g, 0.19 mol) in MeOH (50 ml) was added to a stirred suspension of the thiocarbamate salt (52 g, 0.2 mol) in MeOH (100 ml). After 15 min, the mixture was evaporated to dryness and the residue dissolved in water and extracted with EtOAc. The extracts were dried and evaporated to leave a solid which was triturated with EtOH to give the *S*-methylthiocarbamate which was used directly with no purification: yield 26 g (55%). A mixture of the above thiocarbamate (9.6 g, 0.04 mol), ethylenediamine (2.6 g, 0.044 mol), and yellow mercuric oxide (8.6 g, 0.04 mol) in *n*-BuOH (120 ml) was stirred under reflux for 10 h under a nitrogen atmosphere. After cooling, the mixture was filtered and the residue washed twice with hot EtOH. The combined filtrates were evaporated and the resultant solid was triturated with cold EtOH (25 ml) and then Et_2O. The dried solid (5.3 g) was dissolved in EtOH (300 ml) and treated with a solution of maleic acid (2.8 g, 0.024 mol) in EtOH (20 ml) with stirring. After 0.5 h the precipitated maleate salt was collected by filtration and recrystallised from MeOH / Et_2O to give **2**: yield 5.1 g (38%); mp 157–159°C. Anal. $C_{11}H_{13}N_3O_2$·maleate (C, H, N). Compound **1** was also prepared using this procedure, but was isolated as its hydrochloride salt.

N-Amidino-2-(1,4-benzodioxan-6-yl) acetamide hydrochloride ***5***
1,4-Benzodioxan-6-acetic acid (Aldrich) was converted to methyl 1,4-benzodioxan-6-acetate with methanolic HCl. A solution of this ester (2.6 g, 0.013 mol) in *i*-PrOH (10 ml) was added to a freshly prepared solution of guanidine free base (0.013 mol) (generated from 1.53 g guanidine nitrate and 0.29 g sodium in 25 ml *i*-PrOH) and the mixture was left at room temperature for 16 h. The solvent was removed and water then added to the residue. The resultant solid was collected by filtration and dissolved in *i*-PrOH. A solution of ethereal HCl was then added and the precipitated hydrochloride salt was collected and dried to leave **5**: yield 0.17 g (5%); mp 194–195°C. Anal. $C_{11}H_{13}N_3O_3$ HCl·1/2 H_2O (C, H, N).

2-(1,4-Benzodioxan-6-yloxymethyl)-2-imidazoline hydrochloride ***7***
A stirred suspension of 6-amino-1-4, benzodioxan (30.2 g, 0.2 mol) in 1 N H_2SO_4 (300 ml) at 0°C was treated dropwise with a solution of $NaNO_2$ (13.8 g, 0.2 mol) in water (45 ml) maintaining the temperature at 0–5°C. After completion of the addition the solution was stirred a further 1/2 h and was then added dropwise over 1 h to a boiling solution of conc. H_2SO_4 (67 ml) in water (67 ml). After 1/2 h the mixture was cooled and extracted with CH_2Cl_2. The product was then extracted into 2 N NaOH and this aqueous phase was washed with CH_2Cl_2. Acidification with 5 N HCl was followed by extraction with CH_2Cl_2 and these extracts were dried and evaporated to leave a red oil (20.7 g). Distillation gave 6-hydroxy-1,4-benzodioxan: yield 12.6 g (41%); bp 117–120°C/0.8 mm. To a stirred mixture of the above phenol (12.5 g, 0.08 mol), acetone (50 ml), potassium iodide (0.17 g) and potassium carbonate (9.3 g) was added chloroacetonitrile (5.4 ml, 0.09 mol). The mixture was heated under reflux with stirring for 6 h. After 16 h at room temperature, evaporation gave a residue which was partitioned between water and Et_2O. The combined extracts were washed with 2 N NaOH and water, dried and evaporated to leave a solid (13.4 g). Trituration with *n*-hexane gave (1,4-benzodioxan-6-yloxy) acetonitrile: yield 12.95 g (82%); MS, 191 M^+ $C_{10}H_9NO_3$ requires M^+ 191). A solution of the above acetonitrile (1.91 g, 0.01 mol) in MeOH (9 ml) containing a catalytic amount of NaOMe (50 mg) was cooled at 0°C and a solution of ethylene diamine (0.72 g, 0.012 mol) in MeOH (2 ml) was added dropwise. After 10 min a saturated methanolic HCl solution (0.7 ml) was added and the solution was then left for 16 h at 0°C. After removal of the solvent, the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with water and dried and then treated with ethereal HCl solution. After removal of solvent the residue was recrystallised from EtOH to give **7**: yield 1.3 g (48%); mp 243–250°C. Anal. $C_{12}H_{14}N_2O_3$·HCl (C, H, N).

2-(1,4-Benzodioxan-6-ylmethyl)-2-imidazoline hydrochloride ***9***
A solution of methyl 1,4-benzodioxan-6-acetate (6.7 g, 0.032 mol) in anhydrous toluene (15 ml) was added at room temperature to a previously prepared solution of trimethylaluminium (13.4 ml of a 2 M solution in hexane) and ethylenediamine (1.93 g, 0.032 mol) in anhydrous toluene (35 ml) under an atmosphere of argon. The solution was heated under reflux for 3 h. On cooling, water (12 ml) was added followed by MeOH (33 ml) and CH_2Cl_2 (33 ml), and the mixture heated under reflux for 15 min. Evaporation gave an oily residue (4.6 g) which was partitioned between 2 N HCl and CH_2Cl_2 and then basified with aqueous $NaHCO_3$. The product was extracted with CH_2Cl_2 and the extracts dried and evaporated to leave an oil (3.2 g) which was dissolved in EtOH and treated with ethereal HCl. The resultant solid was collected and recrystallised from EtOH / Et_2O to give **9**: yield 2.42 g (29%); mp 190–194°C. Anal. $C_{12}H_{14}N_2O_2$·HCl. 1/4 H_2O (C, H, N).

2-(7-Bromo-1,4-benzodioxan-6-ylamino)-2-imidazoline hydrobromide **11**
A solution of bromine (1.46 g, 0.0091 mol) in AcOH (20 ml) was added to a stirred solution of **2** (free base) (1 g, 0.0046 mol) in AcOH (20 ml).

After 48 h the solvent was removed and $CHCl_3$ added to the residue. The resultant solid (1.7 g) was collected and recrystallised from $EtOH/Et_2O$ to give **11**: yield 1.32 g (76%); mp 243–244°C. Anal $C_{11}H_{12}BrN_3O_2 \cdot HBr$ (C, H, N).

Pharmacology

The evaluation of compounds *in vitro* was carried out using already described procedures [4].

Acknowledgments

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