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Z1046, A NOVEL PERIPHERAL DOPAMINERGIC AGENT

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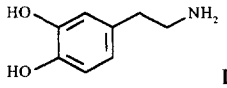
Abstract: The D_1-like, D_2-like, α_1 and α_2 *in vitro* activities of 2-aminotetraline congeners are reported. Z1046 was selected and the antihypertensive activity in rat and dog was evaluated both by intravenous and oral routes.

Introduction

Despite the fact that the death rate from heart disease has dropped 25% in the last 10 years, the number of cases of Congestive Heart Failure (CHF) has doubled over the same time period. In 1991, 39,000 Americans died from CHF and 822,000 were hospitalized. In fact, it is the leading cause of hospitalization in people over 65 years of age. The situation is similar in Europe.

For this reason, there is still a need for innovative approaches to the treatment of this severe pathology. One of the most interesting lines of research is that devoted to the discovery of dopamine receptor agonists. Dopamine (DA) is involved in a wide variety of both central and peripheral effects[1,2]. It has been demonstrated that there are two families of dopamine receptors, called D_1-like and D_2-like, with each group comprising several molecular isoforms[3]. Stimulation of these receptors induces renal and peripheral vasodilation, diuresis and natriuresis[4]. In addition, dopamine receptors are involved in the control over aldosterone and renin secretion and sympathetic tone reduction. All these neurohormonal effects are beneficial in the treatment of CHF.

DA stimulates both D_1-like and D_2-like receptors and it is used in the acute treatment of CHF by intravenous infusion.



Dopamine

However, DA and the conformationally blocked N,N-dipropyl-5,6-dihydroxy-2-aminotetraline (DP-5,6-ADTN)[5] do not show a marked specificity since they also activate α-adrenergic receptors which counteract the beneficial effects of peripheral dopamine receptor stimulation.

Our objective was to continue to investigate appropriate substitutions on the nitrogen atom in order to obtain more specific dopaminergic agents.

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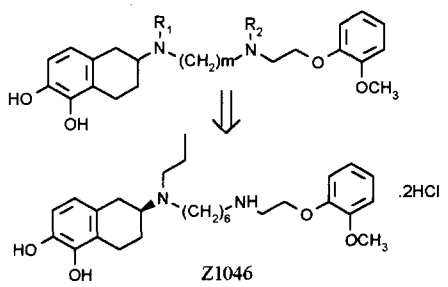
We studied the class of compounds represented by the general formula below and our structure-activity conclusions show the importance of the considered molecular modifications.



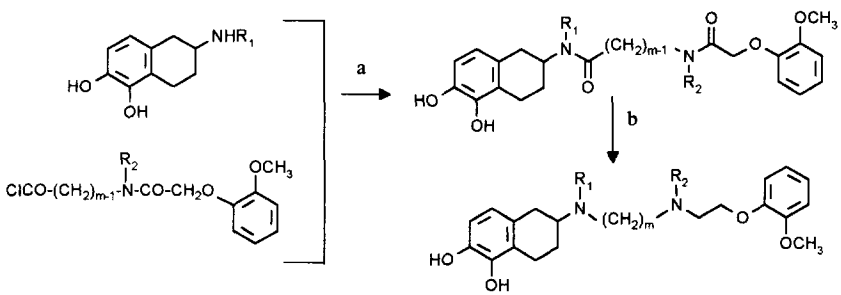
Z1046

From this study, Z1046 i.e. (*S*)-5,6,7,8-tetrahydro-6-[[6-[[2-(2-methoxyphenoxy)ethyl]amino]-hexyl]propylamino]-1,2-napththalenediol dihydrochloride emerged as the most promising compound.

Chemistry

The appropriate tetraline[6] (e.e. over 99,9% by HPCE assay[7]) (Scheme 1) was reacted with a little excess of the acid chloride of the Ω-aminoacid derivatives, obtained by conventional route, in a CH_2Cl_2/aq.K_2CO_3 mixture in a 60-80% range yield. The presence of $Na_2B_4O_7$ partially protected the catechol group from esterification by the means of acid chloride. After the work up of the reaction mixture, the diamide, without further purification, was reduced with $BH_3.S(CH_3)_2$ complex in anhydrous THF with simultaneous ester reduction. Heating the reaction mixture at reflux temperature with concentrated HCl in methanol gave the desired products. Compound **1** was obtained by the same scheme starting from N-propyldopamine.

Scheme 1



a: $Na_2B_4O_7$, K_2CO_3, CH_2Cl_2/H_2O, room temperature, 1h.
b: $BH_3.S(CH_3)_2$, anhydrous THF, reflux, 1 h then conc. HCl, MeOH, reflux, 1 h.

Discussion

The results of the investigated structural modifications are summarized in Table 1.

All the compounds were screened for their D_1-like and D_2-like activity. Furthermore, the compounds were tested for their α_1 and α_2 activity. The D_1-like activity was evaluated as $ED_{20\%}$ of Mesenteric Blood Flow increase in the anesthetized rabbit and the D_2-like activity as pD_2 on Rabbit Ear Artery.

The open derivative **1** was a selective D_2-like agonist devoid of D_1-like activity. Structure-activity considerations showed the importance of any substitution on either of the nitrogen atoms. In fact, N-alkylation of the nitrogen of the dopaminergic moiety was crucial for the dopaminergic activity: the absence of any alkyl group strongly decreased both dopaminergic activities. Moreover, the change of the N-propyl group of Z1046 for a slightly longer alkyl, i.e. n-butyl chain (compound **3**), decreased substantially both dopaminergic activities.

Also the substitution on the second nitrogen atom is important since the N-methyl derivative **4** and the N-propyl **5** were progressively less active.

The distance between the two nitrogen atoms seems to be important. A distance of six carbon atoms was optimal in comparison with a five carbon atom chain (compound **6**), and seven carbon atoms, (compound **7**). Moreover, the stereoisomer *(R)*Z1046 had a lower general activity on DA receptors than Z1046, as already reported for the stereoisomers of 5,6-ADTN[8].

At the same time, the compounds were also tested for their α_1 and α_2 activities. Concerning the α_1 activity, whilst **4** and **5** were not active on the α_1 receptor, all other compounds characterized by no substitution on the second nitrogen atom showed a comparably slight α_1 -antagonist activity.

This difference was probably due to the presence of the 2-(2-methoxyphenyloxy)ethylamino moiety common to many α_1-antagonists. On the other hand, the side chain could also have an influence on the intrinsic α-adrenergic activity of the parent tetraline, since the analogue of Z1046 without any α_1-antagonistic structure[9], i.e. (*S*)-5,6,7,8-tetrahydro-6-[[6-[[4-(2-methoxyphenyloxy)butylamino] hexyl] propylamino]-1,2-naphthalenediol, was a weak partial agonist (pD_2 5.3). No correlation with the structure was evidenced for the α_2 activity, but generally a lower activity was found than with (2S)-DP-5,6-ADTN.

Finally, with regard to α activity, it is worth noting the substantial differences between Z1046 and (2S)-DP-5,6-ADTN. In fact, Z1046 is a slight α_1-antagonist (pA_2 6.5 vs pD_2 6.1 of (2S)-DP-5,6-ADTN) and a weaker α_2-agonist (pD_2 6.7 vs pD_2 7.6 of (2S)-DP-5,6-ADTN).

From all these data taken together, Z1046 emerged as the most interesting compound and was chosen for further investigation.

In vivo experiments on different models showed that Z1046 was active both by intravenous and oral administration, reducing blood pressure and peripheral systemic and vascular resistance.

In conscious SHR rats (Fig. 1) Z1046 produced a dose-dependent and long-lasting antihypertensive effect after i.v. treatment (16 - 540 µg/kg, -40 mmHg at the highest dose, 3hrs) as well as after oral treatment (0.25 - 2.5 mg/kg, -50 mmHg at the highest dose, 5 hrs) without heart rate modifications.

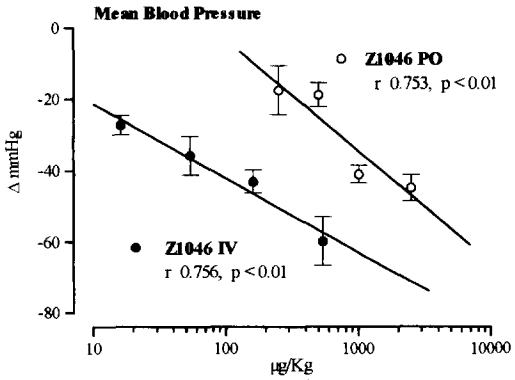


Figure 1 - Conscious SHR: antihypertensive effect of Z1046
Means ± se (n=7) are reported

In anesthetized dogs (Fig. 2) Z1046 intravenously administered (3 - 30 μg/kg) induced a dose-dependent and long-lasting decrease in blood pressure (-35% at the highest dose, more than 2 hrs) and increase in renal blood flow (40 %) without remarkable heart rate variation. At these doses Z1046 also caused a decrease in systemic vascular resistance (-25%) without cardiac output variations. A dose-dependent reduction in blood pressure and improvement in renal blood flow were also observed after intraduodenal treatment (0.125 - 0.5 mg/kg).

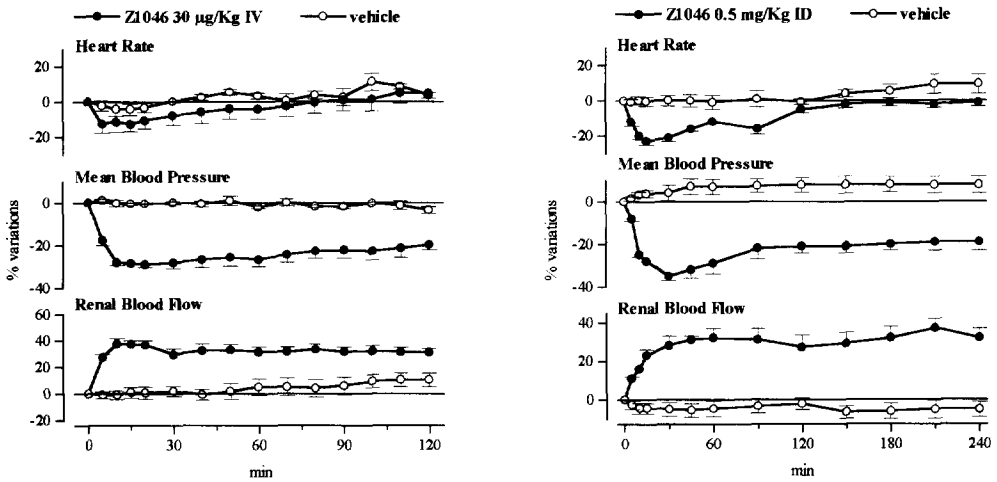
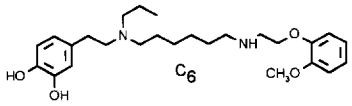
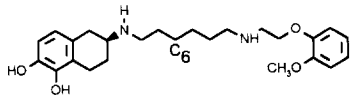
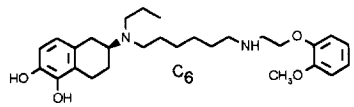
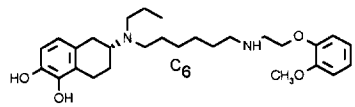
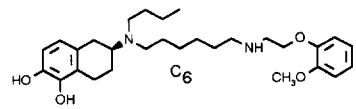
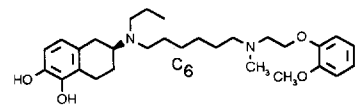
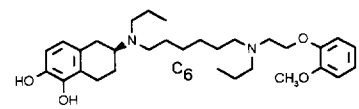
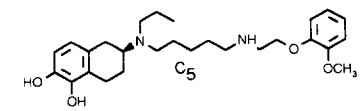
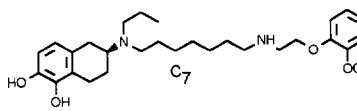


Figure 2 - Anesthetized dogs: hemodynamic effects after intravenous (IV) and intraduodenum (ID) treatment
Means ± se (3 animals/treatment) are reported

In conclusion, Z1046 elicited potent D_1-like and D_2-like activities and showed an antihypertensive effect in rat and dog by both intravenous and oral route.

Table 1: Effect of Structure Modification on Dopaminergic and Adrenergic Activity

Compound	Structure	D_1-like RMBF $ED_{20\%}$ (nmol/Kg)	D_2-like REA pD_2	α_1 RA pA_2	α_2 GPRA pD_2
1		>3000	7.56	6.5	< 5
2		>3000	6.5	7.1	< 5
Z1046		13	9.0	6.5	6.7
(*R*)Z1046		1048	6.5	6.9	< 5
3		60	7.5	6.6	< 5
4		34	8.5	< 5	6.9
5		407	7.4	< 5	6.0
6		107	8.7	6.5	6.5
7		35	8.4	6.8	5.7
Dopamine		11	7.4	pD_2 4.5	5.9
(2S)-DP-5,6-ADTN		32	9.5	pD_2 6.1	7.6
Fenoldopam		73	-	5.3	-
Phenylephrine		-	-	pD_2 6.5	-
Clonidine		-	-	-	7.8
Phentolamine				7.8	-

PD_2 = negative logarithm of molar concentration required to produce half-maximal response
PA_2 = negative logarithm of molar concentration of antagonist producing a twofold displacement to the right of an agonist dose-response curve.

Methods

D_1-like: Rabbit Mesenteric Blood Flow (RMBF). Male New Zealand rabbits (2-3 kg) were anesthetized with sodium pentobarbital and artificially ventilated with room air. Under body temperature control, the animals were catheterized for blood pressure measurement (abdominal aorta through a femoral artery) and for drug administration (jugular vein). A doppler flow probe was put around the mesenteric artery. After a period of stabilization, the animals were treated with Phenoxybenzamine 1 mg/kg i.v. and Yohimbine 1 mg/kg i.v. + 100 μg/kg/h 20 min before receiving the substance. Effects were expressed as $ED_{20\%}$ (dose that increases Mesenteric Blood Flow by 20%).

D_2-like: Rabbit Ear Artery (REA). Arterial rings were prepared using a modified method[10]. The preparations were electrically stimulated (10 Hz, 1 msec, 40-60 V, 500 msec duration) at 5 min intervals. Test substances were cumulatively administered. The agonist potency was calculated as pD_2.

α_1: Rabbit Aorta (RA). Rabbit aorta rings[11] were suspended in an organ bath containing heated (37°C) and oxygenated (95% O_2 + 5% CO_2) Krebs solution to which was added Desipramine (0.1 μM), Corticosterone (30 μM), l-Propranolol (3 μM) and EDTA (10 μM). Compounds were cumulatively administered and their contractile effect was recorded. The agonist activity was expressed as pD_2 and the antagonist activity as pA_2 (agonist Phenylephrine) calculated according to Van Rossum[12].

α_2: Guinea Pig Right Atrium (GPRA). Guinea pig right atrium[13] was suspended into an organ bath containing heated (34°C) and oxygenated (95% O_2 + 5% CO_2) Krebs solution to which was added Atropine (1 μM), Desipramine (0.1 μM) and EDTA (10 μM). The atria were electrically stimulated every 6 min. (40 v, 1 Hz, 0.5 msec for 10 sec.). Compounds were cumulatively administered and their effect on the electrically-induced tachicardia was recorded. The agonist activity was expressed as pD_2 and the antagonist activity as pA_2 vs Clonidine calculated according to Van Rossum[12].

Antihypertensive effect in conscious chronically implanted SHR rats. Male SHR rats (14-16 weeks old,) were anesthetized with Thiopental (30 mg/Kg ip) and were catheterized for recording blood pressure through the carotid artery, and for drug administration through the jugular vein. After an overnight recovery, the animals were randomly assigned to the oral or the intravenous study. Only the animals with a Mean Blood Pressure higher then 160 mmHg enter the experiments. The antihypertensive effect was expressed as maximal decrease in Mean Blood Pressure, and the ED_{40mmHg}, i.e. the dose that causes a reduction of 40 mmHg, was calculated.

Hemodynamic effects in anesthetized dogs. Beagle dogs of either sex (8-10 Kg body weight) were anesthetized with Pentobarbital 30 mg/Kg i.v. (5 mg/Kg i.v. was added when necessary during the experiment). The animals were intubated and artificially ventilated. The left jugular vein was cannulated for drug administration. Blood Pressure and Heart Rate were recorded by a catheter into the ascending aorta through the carotid artery. The left renal artery was retroperitoneally exposed and an electromagnetic flow probe was put around the artery for Renal Blood Flow measurement.

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