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Synthesis and Dopaminergic Activity of Heterocyclic Analogues of 5,6-Dihydroxy-2-aminotetralins

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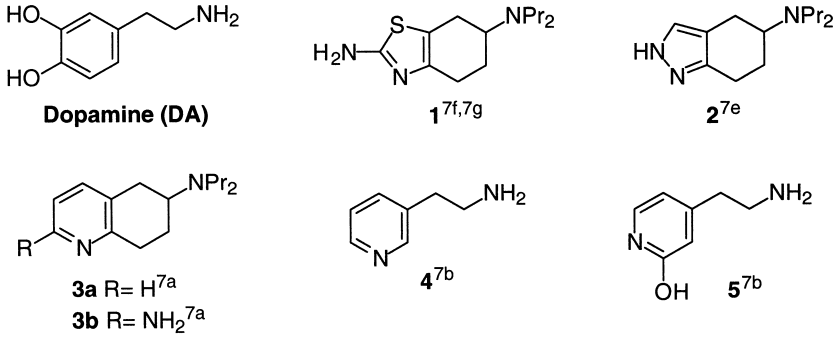
Abstract—The heterocyclic analogues of 5,6-dihydroxy-2-aminotetralins (**6**) were synthesized and their in vitro dopaminergic activity was compared to that of (−)-DP-5,6-ADTN and the novel potent agonist Z12571. The results show that changing the cathecol ring for a heterocycle decreases the D_1-like activity of the target molecules **6**. However, the D_2-like activity of tetrahydroquinoline (**6j**) was comparable to that of (−)-DP-5,6-ADTN.

Dopaminergic system disfunction in peripheral tissues has been related to congestive heart failure (CHF).[1] Pharmacological and biochemical evidence suggests the existence of two subtypes of peripheral dopamine receptors,[2] called DA_1 and DA_2. Stimulation of these receptors induces renal and peripheral vasodilation, diuresis, and natriuresis. In addition, these receptors are involved in the control of aldosterone and renin secretion and sympathetic tone reduction. So, activation of DA receptors exerts a neurohormonal control which is potentially useful in the treatment of CHF.

During the last 20 years, a number of different categories of compounds[2a] such as arylalkylamines, aminotetralins, tetrahydrobenzazepines, tetrahydroisoquinolines, and octahydrobenzoquinolines, which embody the dopamine moiety, have been synthesized and evaluated for biological activity. Unfortunately, most of them (e.g. (−)2-(dipropylamino)-5,6-dihydroxytetralin (DP-5,6-ADTN)[3]) do not show specificity for DA receptors since they also activate α adrenoreceptors, which offsets the beneficial effects of dopaminergic stimulation. However, aminotetralins **Z1046**[4] and **Z12571**[5] have been recently identified as specific dopaminergic agents. Nevertheless, the low oral bioavailability and the short duration of the effect[6] of DA agonists containing cathecol or phenol rings has stimulated the development of bioisosteres, in particular heterocyclic replacements.[7] Compounds **1**–**5** are examples of heteroaromatic systems reported as cathecol/phenol bioisosteres.

This led us to study whether replacing the cathecolic portion of **Z12571** by a heterocycle would lead to compounds with similar dopaminergic properties but a



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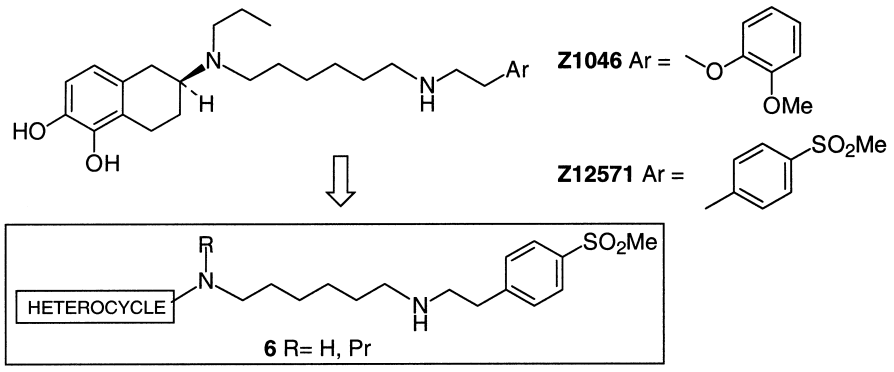
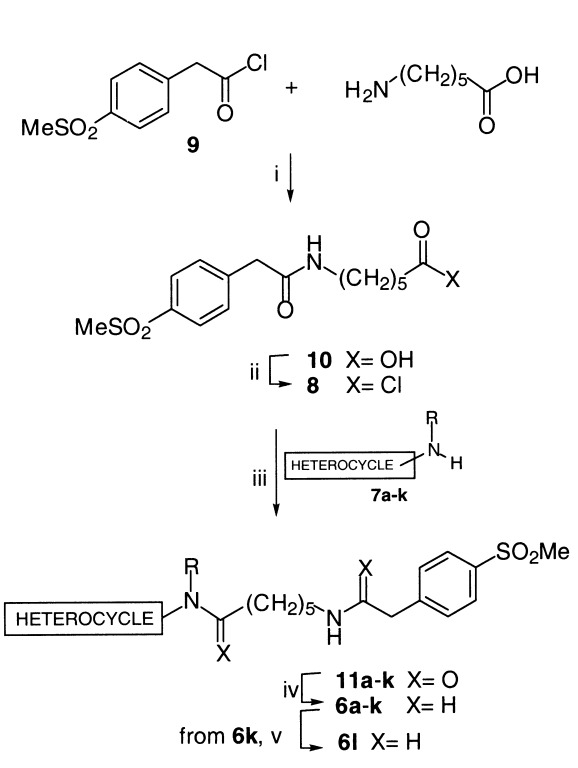


better pharmacokinetic profile. With this aim, we synthesized the class of compounds represented by the general formula below. All the compounds were screened for their D_1-like and D_2-like activities.

The target molecules **6** were synthesized by a general and efficient route, involving the acylation of an appropriate heterocyclic amine **7** with a common, easily accessible acyl chloride intermediate **8**.

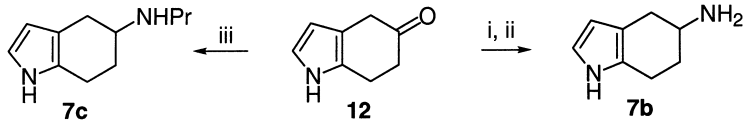
The key intermediate **8** was prepared in 82% overall yield as shown in Scheme 1, by acylation of 6-aminohexanoic acid with (4-methylsulfonylphenyl)acetyl chloride (**9**),[8] followed by treatment of the resulting carboxylic acid **10** with thionyl chloride. Treatment of the heterocyclic amines **7** with acyl chloride **8** under typical acylation conditions, followed by reduction of the resulting diamides **11** with borane–dimethylsulfide complex gave the target diamines **6a–6c** and **6e–6k**. In the case of diamide **11d** reduction by this procedure brought about concomitant reduction of the pyrrole ring. More conveniently, reduction of **11d** was achieved by using a nucleophilic reducing agent, DIBAL-H. Finally, cleavage of the methoxy group of **6k** with 48% aqueous hydrobromic acid afforded diamine **6l**.

The required heterocyclic amines **7** were prepared either as described in the literature (**7a**,[9] **7d**,[7e] **7e**,[7a,7f] **7g**,[7b]

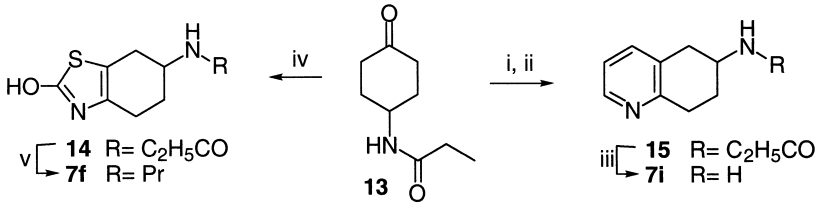


Series	R	Heterocycle
a	H	
b	H	
c	C_3H_7	
d	C_3H_7	
e	C_3H_7	
f	C_3H_7	
g	H	
h	C_3H_7	
i	H	
j	C_3H_7	
k	C_3H_7	
l	C_3H_7	

Scheme 1. i, NaOH, H_2O, CH_2Cl_2. ii, $SOCl_2$, DMF, CH_2Cl_2. iii, TEA, DMF, CH_2Cl_2. iv, $(CH_3)_2S{\cdot}BH_3$ (DIBAL-H for **11d**). v, 48% HBr.



Scheme 2. i, $NH_2OH{\cdot}HCl$. ii, H_2, Raney Ni. iii, $PrNH_2$, $NaBH(AcO)_3$.



Scheme 3. i, $H_2NOCH_2CH=CH_2$, △. ii, △, air. iii, 10% H_2SO_4. iv, I_2, $H_2NC(S)OEt$. v, $(CH_3)_2S{\cdot}BH_3$.

Table 1. Effect of structure modification on dopaminergic activity

Compound	D_1-like (pD_2)	D_2-like (pD_2)	Compound	D_1-like (pD_2)	D_2-like (pD_2)
6a	<5	—	**6i**	<5	6.3
6b	<5	<6	**6j**	<5	8.4
6c	<5	—	**6l**	<5	—
6e	6.3	8.4	**Z12571**	8.6	10.1
6g	<5	5.5	**DPDA**	5.3	7.4
6h	5.5	<6	**(−)-DP-5,6-ADTN**	6.5	9.8

7h,[7b] **7j**[7a] and **7k**[7a]) or as outlined in Schemes 2 and 3 (**7b**, **7c**, **7f** and **7i**). Reductive amination of 4,5,6,7-tetrahydro-5-oxoindole (**12**)[10] with hydroxylamine hydrochloride or propylamine provided the primary and secondary amines **7b** and **7c**, respectively. On the other hand, the thiazole derivative **7f** was prepared by Hantzsch[11] synthesis by reaction of 4-propanamidocyclohexanone (**13**)[12] with *O*-ethyl thiocarbamate[13] in the presence of iodine, followed by reduction of the propanamide **14** with borane–dimethylsulfide complex. Finally, 6-aminoquinoline (**7i**) was prepared by thermal rearrangement[14] of the *O*-allyl ether oxime of the above cyclohexanone **13**, followed by acid hydrolysis of the resulting amide **15**.

An in vitro study of the dopaminergic activity[15] of the novel compounds was carried out. The pharmacological data are summarized in Table 1. The D_1-like activity was evaluated as pD_2 (-log EC_{50}) on a superfused rabbit splenic artery, whereas the D_2-like activity was measured as pD_2 on a superfused rabbit ear artery. As can be seen in Table 1, changing the cathecol ring of **Z12571** for a heterocycle substantially decreases the D_1-like activity of the target molecules **6**. The relaxant effect of the aminothiazole derivative **6e** shown in the splenic artery test is not due to a dopaminergic activity, because it is not antagonized by SCH23390, which is the selective D_1-like dopamine antagonist used. As far as the D_2-like activity is concerned, tetrahydroquinoline **6j** and 2-aminothiazole **6e** proved to be potent agonists (pD_2 8.4).

In conclusion, the preliminary data presented suggest that, although the presence of the cathecol moiety seems to be necessary in this series to maintain a potent D_1-like activity, both the tetrahydroquinoline and the 2-aminothiazole rings are suitable cathecol bioisosteres as regards the D_2-like activity. In this context, it is worth mentioning that tetrahydroquinoline **3a** has been reported to be a relatively selective DA autoreceptor agonist.[7a]

Acknowledgement

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