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Structural manipulation on the catecholic fragment of dopamine D_1 receptor agonist 1-phenyl-*N*-methyl-benzazepines

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ABSTRACT

A series of new benzazepines with modification on the catecholic fragment were designed. The 8-hydroxyl group, other than the 7-hydroxyl was confirmed crucial to the interaction with the dopamine D_1 receptor. Subsequent replacement of the 7-hydroxyl with benzylamino groups was found tolerable. 7-(*m*-Chlorophenyl)methylamino- and 7-(*m*- or *o*-tolyl)methylamino-substituted benzazepines **13b**–**d** displayed K_i values of 270–370 nM at the D_1 receptor, which were slightly more potent than that of parent compound **1**. In addition, 7-(arylmethyl)amino-benzazepines **13a**–**c** were found possessing high binding affinities less than 10 nM at the 5-HT_{2A} receptor. Among them, the non-substituted 7-benzylamino analogue **13a** was the most potent showing a K_i values of 4.5 nM at the 5-HT_{2A} receptor and a 5-HT_{2A}/D_1 selectivity of 147.

1. Introduction

Dopamine (DA) is one of the major cerebral neurotransmitters and plays an essential role in the pathophysiology of many neurobehavioral and neuropsychiatric disorders. DA exerts its agonistic actions primarily through its five major DA receptors (D_1–D_5), among which, D_1,–D_3 receptors are the most studied DA receptors [1–3] and are the primary targets of current clinically prescribed dopaminergic drugs [4,5]. Although the D_1 receptor was discovered very early with high abundance in the mammalian brains, clinically useful D_1 receptor agonists and antagonists are very limited [4–6]. Among the reported D_1 receptor-targeting agents, the skeleton of 1-aryl-*N*3-benzazepines remains the most reliable structural scaffold in terms of the affinity and selectivity against the D_1 receptor. Many widely used D_1 receptor tool drugs (e.g. D_1 agonist SKF-38393, D_1 antagonist SCH-23390, Fig. 1) were born from this series [6–8]. Unfortunately, most of these compounds eventually failed as drug candidates due to their limited in vivo efficacy, poor pharmacokinnetics (PK) and several other unwanted side effects [6,9,10].

Since the catechol fragment in the 1-aryl-*N*3-benzazepine framework is an essential feature for effective binding to the amino acid residues of the D_1 receptor, most of the reported structural modification is focused on other sites, especially the 1-aryl, azepine ring, and C6 [11–13]. A few early reports also discussed the possibility of replacing the catecholic component, but only lower alkyls and halogens (especially 7-Cl) were investigated as the replacement of 7-OH [14–19]. As a continuation of our structure–activity relationship (SAR) study [12,13,20–23] on the 1-aryl-*N*3-benzazepine skeleton, here we report our structural manipulation on the catecholic fragment and the binding affinity and selectivity of the new compounds at the DA (D_1–D_3) receptors.

2. Chemistry

Although the *R*-enantiomers of benzazepines 1–4 are generally more active than corresponding *S*-enantiomers, there is no significant difference between the racemates and their *R*-enantiomers at the DA receptor binding level [6,12,13]. Therefore, to quickly

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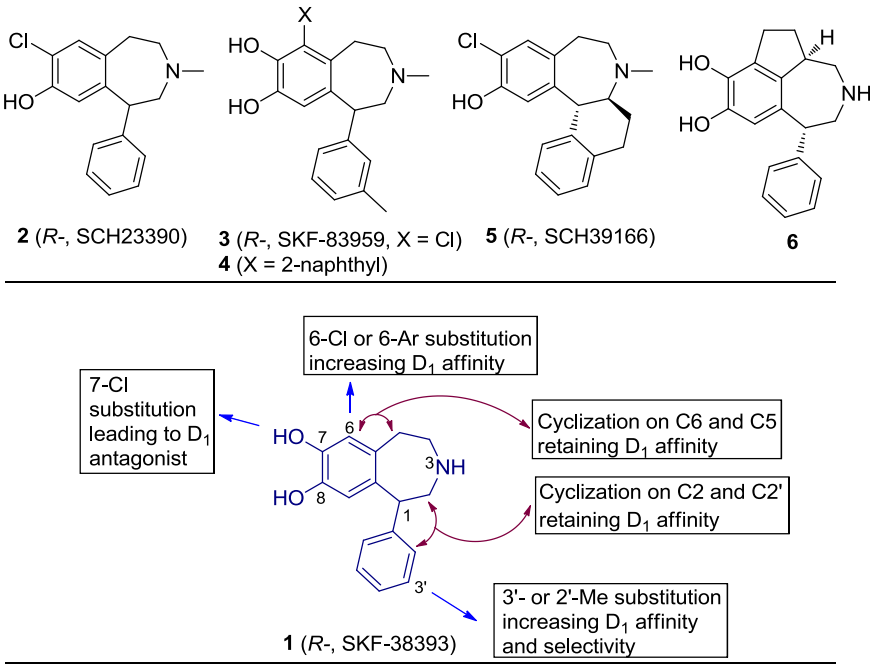
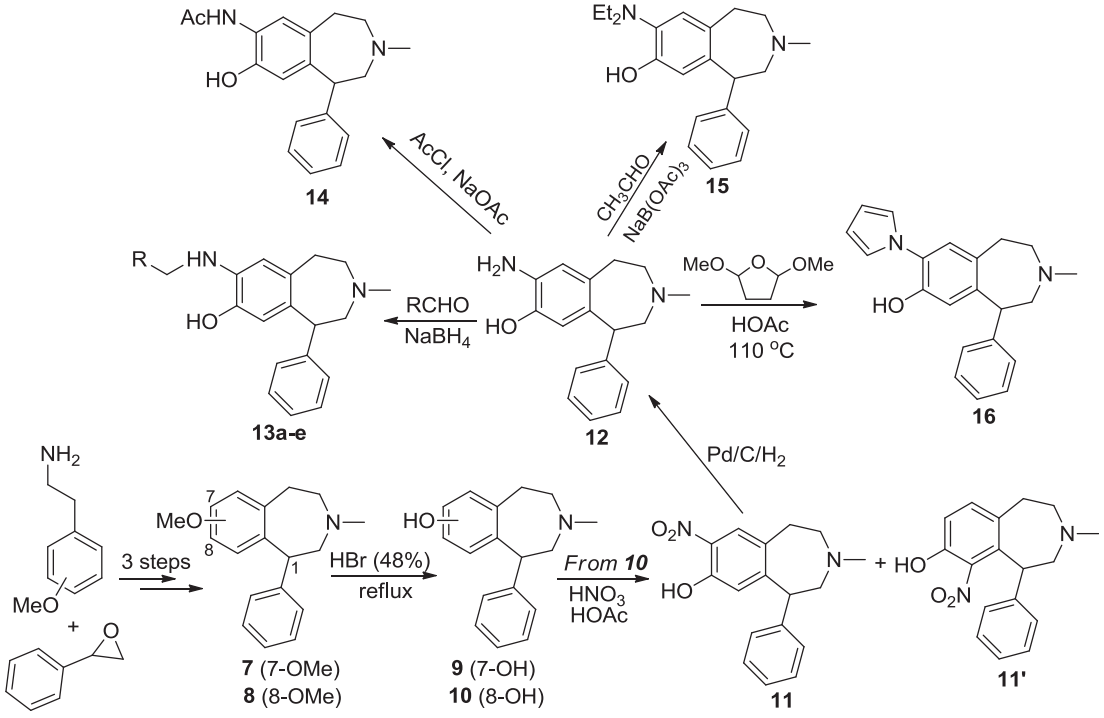


Fig. 1. Established SAR and representative 1-aryl-3-benzazepines.

identify new compounds for further study, all compounds in current report were prepared and evaluated as racemates. As shown in Scheme 1, by following a literature procedure [12,13,22,23], 7- and 8-methoxy-*N*-methyl-1-benzazepines 7 and 8 were prepared from corresponding 3- or 4-methoxyphenyl ethanamine and 2-phenyloxirane in three steps [18,19]. Removal [23] of the *O*-methyl group by refluxing in 48% HBr aqueous solution led to monohydroxyl benzazepines 9 and 10 in 90% yield. Nitration of 8-hydroxy-*N*-methyl-1-phenylbenzazepine 10 with fuming HNO_3 and HOAc provided compounds 11 and 11′ in 96% overall yield, with nearly no regioselectivity (1.1/1). Reduction of nitrobenzene 11 with Pd/C gave 7-amino-8-hydroxybenzazepine 12 in 96% yield. Reductive amination [13] of 12 by treating with aryl aldehydes followed by $NaBH_4$ yielded corresponding benzylamines 13a–e in 80–91% yields. Acylation of amine 12 led to benzazepine 14 in 41% yield, and diethylamino-substituted benzazepine 15 was prepared in 81% yield by treating 12 with acetaldehyde and $NaBH(OAc)_3$. Meanwhile, treatment [24] of 12 with 2,5-dimethoxy-



Scheme 1. Synthesis of compounds **7**–**16**.