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Design, synthesis, crystal structure, biological evaluation and molecular docking studies of carbazole-arylpiperazine derivatives

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ABSTRACT

Subtype-selective α_1-adrenoceptor (AR) antagonists display optimum therapeutic efficacies for the treatment of benign prostatic hyperplasia (BPH). In this study, we designed and synthesized novel carbazole-arylpiperazines derivatives (**1** and **2**) on the basis of the proposed pharmacophore model for α_1-AR antagonists. Structural properties were investigated using single-crystal X-ray diffraction analysis. Comparison of crystal structures with ligand-based pharmacophore models revealed that the two agents may possess antagonistic effects on α_{1D} subtype. Tissue functional assay in vitro showed that compound **2** exerted strong antagonistic activity on α_{1B}-AR (pA_2 7.13) with a poor selectivity for α_{1A} and α_{1D} subtypes. Compound **1** exhibited enhanced antagonistic effect on α_{1D} subtype (pA_2 7.06) and excellent selectivity for α_{1D} over α_{1B} (α_{1D}/α_{1B} ratio = 79.4). To illustrate the relationship between antagonistic activity and chemical structure, molecular docking studies were performed using the homology models of α_1 receptors. Binding mechanism indicated that small hydrophobic substituents attached to the arylpiperazine moiety were essential for rational design of α_{1D}-selective antagonists.

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1. Introduction

α_1-Adrenoceptors (ARs) belong to class A of the super family of G protein-coupled receptors (GPCRs) and play a key role in contracting vascular smooth and human prostate smooth muscles.[1] Based on their distinct pharmacological properties, α_1-ARs are classified into three subtypes, namely α_{1A}, α_{1B} and α_{1D}.[2,3] In the last years, subtype-selective α_1-AR antagonists were deemed to be attractive drug candidates for the treatment of benign prostatic hyperplasia (BPH) which is a common condition that severely impairs patient's health in aging males.[4,5]

Arylpiperazine derivatives exhibited extensive bioactivities including the management of BPH progression.[6] Among this kind of compounds, arylpiperazine derivatives bearing a flavone nucleus (**I**) presented in Figure 1 showed similar antagonistic properties for α_1-AR in comparison to the reference agent prazosin.[7] Although quinazolinone-arylpiperazine derivative (**II**) displayed the α_1-blocking activity less than non-selective antagonist prazosin, the compound fitted well with the ligand-based pharmacophore model for α_1-AR antagonists which consisted of positive ionizable (PI), hydrophobic features (HY) and hydrogen bond acceptor (HBA).[8] Pyrrolidin-2-one derivative of arylpiperazine (**III**) also exhibited high affinity for the α_1-AR (pK_i = 7.30) and was further tested as α_{1A}-AR antagonist in vivo.[9] Structure–activity relationship (SAR) studies of imidazo- and indol-arylpiperazine derivatives (**IV**) validated the pharmacophore model for α_1-AR antagonists.[10] 5-arylidenehydantoin-arylpiperazine (**V**),[11] and pyridine-arylpiperazine (**VI**)[12] were also proved to possess good affinity for α_1-AR in vitro. Particularly, arylpiperazine-derived naftopidil is subtype-selective antagonist with a 15-fold selectivity for α_{1D} versus α_{1B} receptor.[13] On the other hand, carbazole derivatives displayed various biological activities, such as enzyme inhibition,[14,15] the anti-proliferation against different cancer cells lines,[16] and the 5-HT_7R blocking activity (**VII**).[17]

In this work, we designed novel α_1-AR antagonists that had a three-carbon linker between arylpiperazine moiety and carbazole fragments (see Fig. 2). The hypothesized pharmacophore model suggested that the hydrophobic regions are composed of carbazole group, the phenyl ring of the arylpiperazine moiety and the methoxyl substituent attached on the arylpiperazine, and the PI feature is the basic N atom on piperazine ring,[18] and the hydroxyl group is defined as hydrogen bond donor (HBD). Two carbazole-arylpiperazine derivatives were then synthesized, and fully characterized

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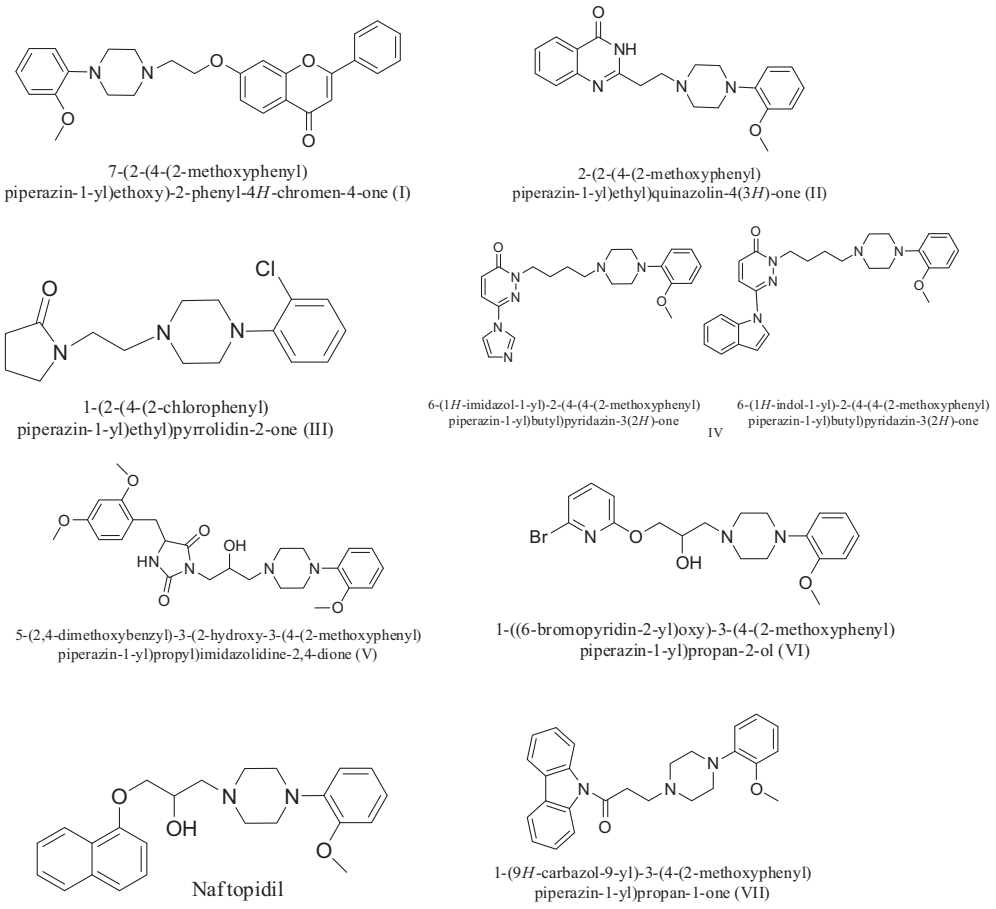

Figure 1. Chemical structures of arylpiperazine derivatives.

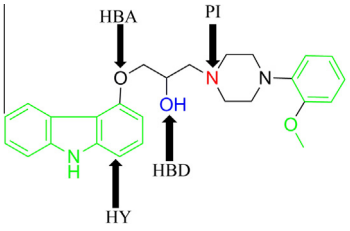

Figure 2. Visualization of pharmacophoric features for novel carbazole-arylpiperazine derivatives. Colour legend: green, hydrophobic features (HY); red, positive ionizable (PI); blue, hydrogen bond donor (HBD); black, hydrogen bond acceptor (HBA).

by NMR (^{1}H and ^{13}C), elemental analysis and single crystal X-ray diffraction analysis. The antagonistic activities towards α_1-AR were evaluated using functional assays in vitro. Molecular docking studies shed light on the relationship between antagonist structures and bioactivities against α_1-AR subtypes. The work provides valuable clues for the design of subtype-selective α_1-AR antagonists.

2. Results and discussion

2.1. Chemistry

The title compounds **1** and **2** were synthesized in two steps starting from the commercially available carbazole-4-ol and 2-(chloromethyl)oxirane, as depicted in Scheme 1. The condensation of carbazole-4-ol and 2-(chloromethyl)oxirane gave the intermediate compound 4-(oxiran-2-ylmethoxy)-9*H*-carbazole in the presence of TEBA. 1-phenylpiperazine derivatives were prepared according to a literature method.[19] The final products (**1** and **2**) were afforded under reflux conditions, and further purified by silica gel column chromatography eluted by a mixture of ethyl acetate and petroleum ether (1/5, v/v). The structures of compounds **1** and **2** were characterized by their melting points, ^{1}H NMR, ^{13}C NMR, element analysis and single-crystal diffraction.

2.2. X-ray crystallography

Compound **1** crystallizes in the monoclinic space group *Cc*. The asymmetric unit contains three crystallographically independent molecules. A representative crystal structure is presented in Figure 3. The crystal data and structural refinement of **1** are presented in Table 1. The low *R* (5.32% for **1**, 5.17% for **2**) value in X-ray crystallography validated the synthesized structures.

As depicted in Table 2, most bond lengths are within the normal ranges, e.g., the C–C single bond in the range of 1.498(8)–1.516 (8) Å, and the O–C bond lengths from 1.382(7) to 1.419(7) Å (see Table 2). The torsion angle for O(1)–C(13)–C(14)–C(15) is 62.1 (7)°, −59.3(7)° and −61.9(7)° for the three independent molecules (A, B and C), respectively, which indicates that conformation A distinctly differs from another two conformers. The carbazole ring of molecular B is almost perpendicular to [C(20), C(21), C(22), C(23), C (24), C(25)] aromatic plane with a dihedral angle of 81.44(14)°, and the corresponding dihedral angles of molecular A and C are 74.23 (16)° and 77.93(16)°, respectively.

The intra- and intermolecular interactions are of considerable interest in investigating the packing structures. Intramolecular O (2)–H···N(2) H-bond results in the formation of the pseudo-

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