Synthesis, crystal structure, biological evaluation, and molecular docking studies of quinoline-arylpiperazine derivative as potent α_{1A} -adrenoceptor antagonist

Wei Xu ^a, Renwang Jiang ^{a,*}, Mu Yuan ^{b,*}

^a School of pharmaceutical sciences, Jinan University, Guangzhou 510632, China

^b Pharmaceutical Research Center, Guangzhou Medical University, 195# Dongfengxi Road, Guangzhou 510182, China

Corresponding author. Tel./fax: +86 020 81340727.

E-mail address: mryuanmu838@sina.com (M. Yuan); rwjiang2008@126.com (R. Jiang)

ABSTRACT

Arylpiperazine derivatives received special attention owing to their antagonist potency on α_1 -adrenoceptors (α_1 -ARs). In this work, quinoline-arylpiperazine derivative (**1**) was synthesized and its structural properties were investigated using single crystal X-ray diffraction analysis and theoretical calculations. Biological evaluation *in vitro* revealed that compound **1** exhibited a 3-fold higher selectivity for α_{1A} -AR over than α_{1B} subtype when compared to non-selective antagonist prazosin. Molecular docking studies shed light on the antagonistic activity of both **1** and prazosin on α_{1A} and α_{1B} -AR. The docking results suggested that residues Gln177, Phe86, Phe288, Phe308, Phe312 and Tyr316 were identified as the major sites for the two agents binding to the α_{1A} receptor. As depicted by pharmacophoric model, **1** was deemed to be the α_{1A} -selective antagonist on the basis of pharmacophoric features. Our present work may provide valuable information for better drug design of subtype-selective α_1 -AR antagonists.

Keywords: α_1 -Adrenoceptor; Quinoline-arylpiperazine; X-ray crystallography; Molecular docking; Pharmacophoric model

Introduction

Benign prostatic hyperplasia (BPH) is a common disease in the aging males that has attracted worldwide attention [1]. Estimates of annual pharmaceutical sales of BPH therapies range from \$US 3 to 10 billion. Emerging contenders to current therapies is focusing on drug targets which are able to relax prostatic smooth muscle in a similar way to the α_1 -adrenoceptor (AR) antagonists, as this appears to be the most effective mechanism of action [2].

Based on the distinctive structures and significant differences in pharmacology, α_1 -AR in humans is divided into three subtypes (α_{1A} , α_{1B} and α_{1D}) [3]. Blocking α_{1B} receptor was widely accepted to be the origin of side effects that result in lightheadedness, dizziness and orthostatic hypotension [2]. α_{1A} subtype, located in large abundance in prostatic tissue, was reported to play an critical role in relieving the symptoms associated with BPH. The α_{1D} -AR antagonist can improve the bladder filling to achieve the enhanced therapeutic efficacy for the treatment of BPH [4]. Highly selective α_{1A} and/or α_{1D} antagonists are thus desired owing to the minimal cardiovascular side effects [5].

Arylpiperazines including naftopidil [6], a flavone substituent [7], pyridine and 2-pyridone derivatives [8] and quinazolinone-arylpiperazine [9] represented particularly important categories of α_1 -adrenoceptor antagonists [10-12]. Arylpiperazine skeleton have attracted considerable research interests in the field of development of subtype-selective α_1 -AR antagonists.

In the present body of work, quinoline-arylpiperazine derivative (**1**) was synthesized and structural properties were characterized by NMR, single-crystal X-ray diffraction analysis and density functional theory (DFT) calculations. The crystallographic structure of compound **1** was also matched with the pharmacophore model for ideal α_1 -AR antagonists. The biological activities of **1** and prazosin behaved as positive control were evaluated by using a dual-luciferase reporter assay. Molecular docking studies were performed to investigate the binding modes of ligand- α_{1A} and ligand- α_{1B} complexes. This work provided valuable clues for the structure-based drug design.

Experimental

All reagents and solvents were of analytical grade and commercially available. Melting point was determined on SGW X-4 micro melting point apparatus (Shanghai Precision & Scientific Instrument Co., Ltd, Shanghai, China). NMR spectra were accomplished on a Bruker AVANCE-500 spectrometer in $CDCl_3$ using TMS as the internal standard, and coupling constants (J) were in Hz. X-ray diffraction data of compound **1** were collected on a R-Axis RAPID II diffractometer at room temperature. Flash column chromatography was performed with silica gel (Qing Dao Ocean Chemical Factory, 300 ~400 mesh).

Chemistry

The intermediate product 3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-amine was synthesized according to a previously reported method [13]. Quinoline-2-carboxylic acid (0.069 g, 0.40 mmol) and O-(7-azabenzotriazol-1-yl)- N,N,N',N' -tetramethyluronium hexafluorophosphate (HATU) (0.152 g, 0.40 mmol) were added to a solution of 3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-amine (0.100 g, 0.40 mmol) and N,N -diisopropylethylamine (DIEA, 0.6 mL) in CH_2Cl_2 (20 mL), see Scheme 1. The reaction

solution was stirred for 6 h until complete, as indicated by TLC. The reaction mixture was then successively washed with 5% potassium carbonate and saturated brine. The organic layer was separated and dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (3/1, v/v) as eluent to afford 0.135 g (83.2% yield) of compound **1** as a white powder. m.p. 130.0–131.0 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.08 (s, 1H), 8.33 (q, J = 8.5 Hz, 2H), 8.13 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.62 (dt, J = 15.1, 7.4 Hz, 2H), 7.07–6.99 (m, 1H), 6.99–6.92 (m, 2H), 6.89 (d, J = 7.8 Hz, 1H), 3.88 (s, 3H), 3.70 (dd, J = 12.2, 6.0 Hz, 2H), 3.26 (s, 4H), 2.76 (s, 4H), 2.66 (t, J = 6.4 Hz, 2H), 1.98–1.89 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 166.32, 156.79, 153.01, 141.10, 139.73, 133.00, 130.61, 127.87, 127.61, 127.59, 127.40, 123.55, 119.27, 119.09, 118.01, 114.69, 56.83, 55.38, 52.13, 50.67, 39.22, 26.47. HRMS (m/z): calcd for $\text{C}_{24}\text{H}_{29}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$, 405.2212; found, 405.2217.

X-ray crystallography

Suitable crystals of compound **1** were obtained by slowly evaporating a mixture of dichloromethane and n-hexane solution at ambient temperature. A colorless crystal of **1** was mounted on a glass fiber at a random orientation. The data were collected by a R-Axis RAPID II diffractometer equipped with graphite-monochromatic Cu-K α radiation (λ = 1.54178 Å) by using a ω scan mode. The structures were solved by direct methods using Olex2 software [14], and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with XL using a full-matrix least squares procedure based on F^2 [15]. The weighted R factor, wR and goodness-of-fit S values were obtained based on F^2 . The hydrogen atom positions were fixed geometrically at the calculated distances and allowed to ride on the parent atoms. Crystallographic data (CCDC-1002332) excluding structure factors have been deposited at the Cambridge Crystallographic Data Center.

Theoretical calculations

The initial conformation of compound **1** was optimized by using MM+ force fields at the molecular mechanics level of theory. The conformer was further submitted to the Gaussian 09 [16] for DFT geometry optimizations at the CAM-B3LYP/6-311G(d, p) level of theory. Harmonic vibration frequency analysis revealed that no imaginary frequencies were observed in ground states [17]. Conformational optimization of prazosin was carried out at the B3LYP/6-31G(d) level of theory in water based on the continuum polarizable continuum model (CPCM).

Biological evaluation

Antagonist activities of compound **1** and prazosin as positive control towards α_1 -AR subtypes (α_{1A} , α_{1B} and α_{1D}) were examined using a dual-luciferase reporter assay in HEK293 cells. Detailed experimental procedures were referred to our reported literature [18].

Molecular docking

The homology models of α_{1A} and α_{1B} receptors were generated by our previously reported methods [19,20]. The crystallographic structure of compound **1** was defined as stable conformation and saved in Mol format with the assistance of the program Diamond 3.0 [21]. Among the crystal structure of compound **1**, atoms C29B and C30B with higher atomic occupancy

were left. The theoretically calculated conformer of prazosin was used to perform molecular docking.

The preparation of the pdbqt files was done by standard procedure using AutoDock Tools 1.5.6. The docking procedures were performed in AutoDock Vina using the default scoring function [22]. The binding site was identified according to previous studies [19,20]. Exhaustiveness was set to 100, and number of output conformations was set to 20. The searching seed was random. The calculated geometries were ranked in terms of free energy of binding and the best poses were selected for further analysis.

Results and discussion

X-ray crystallographic structure of compound 1

The title compound **1** crystallizes in the triclinic space group *P*-1. The crystal data and structural refinement of **1** were presented in Table 1. Visualizations of crystal structure were made with the Diamond 3.0 program.

As shown in Fig. 1, the labeled C29 and C30 atoms were found to be positionally disordered. The dihedral angle between quinoline moiety and aromatic ring is $69.26(7)^\circ$. The pseudo six-membered ring formed by intramolecular H-bond [N(3)–H(3)···N(2)] result in the big torsion angles [N(2)–C(29B)–C(30B)–C(26) = $-48.8(9)^\circ$ and C(29B)–C(30B)–C(26)–N(3) = $53.6(7)^\circ$]. In addition, hydrogen bonds [C(14)–H(14a)···O(1)] and N(3)–H(3)···N(4)] can lead to the formation of non-planar six-membered and five-membered rings, respectively.

In crystal packing (Fig. 2), intermolecular hydrogen bond C(27)–H(27b)···O(2) [$d_{\text{H(27b)}\cdots\text{O(2)}} = 2.557(4) \text{ \AA}$; $d_{\text{C(27)}\cdots\text{O(2)}} = 3.509(4) \text{ \AA}$; $\theta_{\text{C(27)-H(27b)}\cdots\text{O(2)}} = 170.8(3)^\circ$; symmetry code: $-1+x, -1+y, -1+z$] was also observed to stabilize the three-dimensional structure. The framework is reinforced by C–H··· π interactions [$d_{\text{H(19a)}\cdots\text{Cg(3)}} = 2.716(3) \text{ \AA}$; $d_{\text{C(19)}\cdots\text{Cg(3)}} = 3.496(3) \text{ \AA}$; $\theta_{\text{C(19)-H(19a)}\cdots\text{Cg(3)}} = 137.9(2)^\circ$; Cg(3) is the centroid of the aromatic ring; symmetry code: $1-x, -y, 2-z$].

Basing on the crystallographic structure of compound **1**, distances between positive ionisable center (PI) and the pharmacophoric fragments corresponding to Barbaro's model [23,24,10] were calculated (Fig. 3). Results displayed that α_1 -AR antagonistic properties of **1** were limited owing to some unfavourable distances between the PI and hydrophobic fragments (HY2, HY3) and hydrogen bond acceptor (HBA). However, the aromatic moiety of arylpiperazine was in good accordance with an ideal antagonist of α_1 -AR in terms of distance between PI and HY1. The distances of compound **1** (X2, X3, X4) showed a decrease in comparison to that of ideal α_1 -AR antagonist model, which may be ascribed to the intra- and inter-molecular H-bonds, limited conformational flexibility in respect to rigid quinoline moiety and close packing in the crystal. Despite it exhibited a striking discrepancy between crystal structure of compound **1** and pharmacophore model, **1** could also exert good selectivity profile against the α_1 -AR subtypes.

DFT calculations

To investigate the structural properties of compound **1**, DFT optimization calculations were performed at the theoretical level of CAM-B3LYP/6-311G(d,p). The theoretical bond lengths and bond angles were nearly equal to that from crystallographic structure, but there were significant

differences in torsion angles along the alkyl spacer between the lowest energy conformation and solid-state crystal structure (Table 2). It was rationally explained that the theoretically calculated model cannot fully consider the weak interactions between molecules, such as intramolecular H-bonds and C–H... π interactions. Theoretical geometric parameters still presented a good approximation to the experimental results, except for torsion angles. Thus, we investigated the frontier molecular orbitals and energy gaps on the basis of the calculated structure.

Molecular orbitals, particularly highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), are very useful to characterize the chemical reactivity and kinetic stability of molecule [25]. HOMO-LUMO plots are given in Fig. 4. HOMO is mainly localized over the piperazine ring, whereas LUMO is distributed over the quinoline moiety. The HOMO–LUMO energy gap is found to be 6.697 eV, suggesting a higher kinetic stability than our previously reported indole-arylpiperazine derivatives [20].

Biological evaluation in vitro

Biological activity of compound **1** against α_1 -AR subtypes was displayed in Table 3. **1** exhibited a 3-fold higher antagonistic activity at the α_{1A} receptor and a decreased antagonistic effect on the α_{1D} receptor as comparison to non-selective antagonist prazosin. Antagonistic activity of **1** at the α_{1B} subtype associated with adverse effects in the treatment of BPH was the same to that of positive control prazosin. In comparison to control, **1** showed better selectivity over α_{1A} subtype.

Binding mechanisms studied by molecular docking

α_1 -AR is a member of the G protein-coupled receptors (GPCRs) family that are constructed by seven transmembrane (TM) helices, N- and C-terminal fragments, and intra- and extracellular loop (ECL) regions [26]. The accurate 3D structures of α_1 -AR with high resolutions had been not still obtained, and homology-modeling strategies thus provided a viable tool for structure-based α_1 -AR antagonist design [27].

To elucidate the binding mechanisms for explaining the antagonistic activities for both **1** and prazosin at α_1 -AR, we performed molecular docking studies using the homology models of α_{1A} and α_{1B} subtypes. As revealed by Fig. 5A, arylpiperazine moiety of compound **1** was engaged in hydrophobic interactions with residues Phe86, Trp102, Phe312 and Tyr316 of homology-modeled α_{1A} -AR. Quinoline part entered into the hydrophobic pocket involving TM III, V and VI. As for the proposed binding mode of prazosin with α_{1A} -AR, the protonated piperazine moiety formed a weak electrostatic interaction with Gln177 (4.1 Å between the nitrogen atom of piperazine ring and the amide oxygen atom of Gln177) [28]. The cationic nitrogen atom in the quinazoline moiety for electrostatic binding to Glu305 of TM VII (3.3 Å) was also observed. Additionally, furan group at the terminal contacted via hydrophobic interactions with Phe288 and Phe308, which had been identified as major sites for ligand binding with α_{1A} subtype [29]. Fig. 5B indicated that the two agents protruded the different binding pockets in terms of the binding sites and ligand orientations. Distinct binding modes of the two antagonists should provide a reasonable explanation for their antagonistic activities toward the α_{1A} -AR.

Arylpiperazine moiety of **1** mainly was engaged in hydrophobic interactions with Phe310, Phe311, and Trp307 residues of α_{1B} subtype (Fig. 5C). The quinoline group was placed in the

hydrophobic pocket defined by residues Trp121, Trp307, Phe330 and Tyr338. The aromatic moiety of quinoline group formed π -stacking against Phe334 of TM7. The N atom of arylpiperazine moiety was in a weak van der waal contact with residue Val197 of ECL2. As observed from prazosin- α_{1B} complex, Asp125 of TM III, reported by R. Griffith *et al.* [24], realized a H-bond (2.3 Å) with the amino substituent attached on the quinazoline ring. The oxygen atom of carbonyl group formed hydrogen bond with residue Cys195 (3.0 Å) of ECL2 which was proved to be the first contact point for the α_{1B} -AR's ligands despite for agonists [30]. Although molecular interactions with key residues of α_{1B} -AR were difference, compound **1** and prazosin shared the similar binding pockets (see Fig. 3D). Accordingly, this binding pose seemed to deduce the same biological activities for **1** and prazosin against the α_{1B} subtype.

Ligand-based pharmacophore models suggested that the α_{1A} -AR antagonists were proposed to contain four pharmacophoric features [PI, HBA, Har (hydrophobic aromatic moiety), Hai (hydrophobic aliphatic group)]; pharmacophoric features of the α_{1B} -AR antagonists were comprised of 2×HBA, Har and Hai [24]. According to the published descriptions, **1** compared very favorably to the model of α_{1A} -AR antagonists. Furthermore, the title compound **1** was classified as the α_{1A} -selective antagonist with the significant characteristics that the PI nitrogen atom was positioned 2-3 bond lengths from the benzene ring of arylpiperazine moiety.

Conclusions

Agents containing arylpiperazine skeleton show high biological potency of blocking α_1 -AR. In this work, quinoline-aryl piperazine derivative (**1**) was synthesized and structural properties were characterized by X-ray crystallography and theoretical calculations. The bent conformation of compound **1** may be attributed to intra- and inter-molecular hydrogen bonds as well as C–H $\cdots\pi$ interactions. Biological evaluation *in vitro* exhibited that compound **1** displayed a 3-fold selectivity for α_{1A} -AR over α_{1B} subtype when compared to prazosin. Molecular docking studies of both ligand- α_{1A} and ligand- α_{1B} complexes were performed to investigate the binding modes associated with their antagonistic activities. Residues Gln177, Phe86, Phe288, Phe308, Phe312 and Tyr316 were identified as the major sites for both **1** and prazosin binding to the α_{1A} receptor. On the other hand, the important sites for ligands binding with the α_{1B} subtype were involved in Asp125, Phe334, Phe330, Val197 and Cys195 residues (Table 4). Pharmacophore models also suggested that four pharmacophoric features of **1** favorably matched with the model of α_{1A} -AR antagonists. Thus compound **1** was deemed to be the α_{1A} -selective antagonist given biological activities towards α_1 -AR, binding modes for **1**- α_{1A} and **1**- α_{1B} complexes and evaluation of pharmacophore models.

Acknowledgements

This work was supported by grants from the Technological Innovation Project of Colleges and Universities in Guangdong Province (No. cx2d1127), the National Science Foundation of Guangdong Province (No. S2013040014088), the Postdoctoral Science Foundation of Guangzhou City (Q188), Guangzhou Industry-University Collaborative Innovation Major Projects (201508030016) and Guangdong Major Scientific and Technological Special Project for New Drug Development (2013A022100029).

References

- [1] A. Sarswat, R. Kumar, L. Kumar, L. Nand, S. Sharma, S.P. Yenamandra, K.P. Shailendra, L. Jawahar, V. Verma, A. Jain, P.M. Diwakar, L.S. Vishnu, *J. Med. Chem.* 54 (2011) 302–311.
- [2] S. Ventura, V.I. Oliver, C.W. White, J.H. Xie, J.M. Haynes, B. Exintaris, *Br. J. Pharmacol.* 163 (2011) 891–907.
- [3] G.K. Kinsella, I. Rozas, G.W. Watson, *J. Med. Chem.* 49 (2006) 501–510.
- [4] G. Chiu, S. Li, P.J. Connolly, V. Pulito, J. Liu, S.A. Middleton, *Bioorg. Med. Chem. Lett.* 17 (2007) 3930–3934.
- [5] K. Nanda, K.S. Naruganahalli, S. Gupta, S. Malhotra, A. Tiwari, L.G. Hegde, S. Jain, J.B. Gupta, N. Anand, A. Ray, *Eur. J. Pharmacol.* 607 (2009) 213–219.
- [6] F. Castiglione, F. Benigni, A. Briganti, A. Salonia, L. Villa, A. Nini, E. Di Trapani, U. Capitanio, P. Hedlund, F. Montorsi, *Curr. Med. Res. Opin.* 30 (2014) 719–732.
- [7] J. Jin, X.B. Wang, L.Y. Kong, *Bioorg. Med. Chem. Lett.* 21 (2011) 909–911.
- [8] M. Baran, E. Kepczyńska, M. Zylewski, A. Siwek, M. Bednarski, M.T. Cegła, *Med. Chem.* 10 (2014) 144–153.
- [9] S.M. Abou-Seri, K. Abouzid, D.A. Abou El Ella, *Eur. J. Med. Chem.* 46 (2011) 647–658.
- [10] J. Handzlik, E. Szymańska, R. Wójcik, A. Dela, M. Jastrzębska-Więsek, J. Karolak-Wojciechowska, A. Fruziński, A. Siwek, B. Filipek, K. Kieć-Kononowicz, *Bioorg. Med. Chem.* 20 (2012) 4245–4257.
- [11] M.Y. Li, H. Fang, L. Xia, *Bioorg. Med. Chem. Lett.* 15 (2005) 3216–3219.
- [12] L.A. Romeiro, M. da Silva Ferreira, L.L. da Silva, H.C. Castro, A.L. Miranda, C.L. Silva, F. Noël, J.B. Nascimento, C.V. Araújo, E. Tibiriçá, E.J. Barreiro, C.A. Fraga, *Eur. J. Med. Chem.* 46 (2011) 3000–3012.
- [13] J.J. Huang, F. He, M. Huang, X. Liu, Y. Xiong, Y. Huang, L. Zhu, Y. Yang, X. Xu, M. Yuan, *Eur. J. Med. Chem.* 96 (2015) 83–91.
- [14] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, *J. Appl. Cryst.* 42 (2009) 339–341.
- [15] G.M. Sheldrick, A short history of SHELX, *Acta. Crystallogr. A* 64 (2008) 112–122.
- [16] Gaussian 09, Revision B.01, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian Inc., Wallingford CT, 2010.
- [17] A. Nakahashi, Y. Yaguchi, N. Miura, M. Emura, K. Monde, *J. Nat. Prod.* 74 (2011) 707–711.
- [18] F. Xu, H. Chen, X. He, J. Xu, B. Xu, B. Huang, X. Liang, M. Yuan, *Molecules* 19 (2014) 12699–12709.
- [19] W. Xu, B. Shao, X. Xu, R.W. Jiang, M. Yuan, *J. Mol. Struct.* 1106 (2016) 485–490.
- [20] W. Xu, J. Huang, B. Shao, X. Xu, R.W. Jiang, M. Yuan, *Molecules* 20 (2015) 19674–19689.

- [21] K. Brandenburg, H. Putz, DIAMOND Version 3.0, Crystal Impact GbR, Bonn, Germany, 2006.
- [22] O. Trott, A.J. Olson, *J. Comput. Chem.* 31 (2010) 455–461.
- [23] J. Handzlik, A.J. Bojarski, G. Satała, M. Kubacka, B. Sadek, A. Ashoor, A. Siwek, M. Więcek, K. Kucwaj, B. Filipek, K. Kieć-Kononowicz, *Eur. J. Med. Chem.* 78 (2014) 324–339.
- [24] I.J. MacDougall, R. Griffith, *J. Mol. Graph. Model* 25 (2006) 146–157.
- [25] F.A.M. Al-Omary, Y.S. Mary, C.Y. Panicker, A. A. El-Emam, I.A. Al-Swaidan, A.A. Al-Saadi, C. V. Alsenoy, *J. Mol. Struct.* 1096 (2015) 1–14.
- [26] C. de Graaf, N. Foata, O. Engkvist, D. Rognan, *Proteins*. 71 (2008) 599–620.
- [27] A. Evers, G. Hessler, H. Matter, T. Klabunde, *J. Med. Chem.* 48 (2005) 5448–5465.
- [28] A. Pedretti, M. Elena Silva, L. Villa, G. Vistoli, *Biochem. Biophys. Res. Commun.* 319 (2004) 493–500.
- [29] X.F. Zhao, J. Wang, G.X. Liu, T.P. Fan, Y.J. Zhang, J. Yu, S.X. Wang, Z.J. Li, Y.Y. Zhang, X.H. Zheng, *RSC Adv.* 5 (2015) 57050–57057.
- [30] A.P. Campbell, I. J. MacDougall, R. Griffith, A.M. Finch, *Eur. J. Pharmacol.* 733 (2014) 90–96.

Captions of Figures and Tables

Scheme 1. Synthesis of the title compound **1**

Fig.1. Crystallographic structure of **1** in an asymmetric unit. Dashed lines show the intramolecular hydrogen bonds.

Fig.2. Crystal packing of **1** viewing along the *b* axis. Black and red dashed lines represent the intermolecular hydrogen bonds and C–H··· π interactions, respectively.

Fig.3. Visualization of pharmacophoric features of **1** based on Barbaro's model (upper) and comparison of important distances between pharmacophoric features in reported ideal α_1 -AR antagonists and **1** (below).

Fig.4 HOMO–LUMO plots of **1** by DFT/CAM-B3LYP/6-31G(d,p) level of theory.

Fig.5. (A) Binding mode of both **1** (yellow carbons) and prazosin (pink carbons) with the homology modelled α_{1A} -AR. (B) α_{1A} (surface)–ligand (stick) complex. (C) Binding mode of both **1** (yellow carbons) and prazosin (magenta carbons) with the α_{1B} subtype. (D) α_{1B} (surface)–ligand (stick) complex. These receptors are shown in cartoon representation with cyan alpha helices, green beta sheets and magenta loops, and seven transmembrane helices are labeled by I, II, III, IV, V, VI and VII, respectively. **1** and prazosin are shown in stick representation. Dashed lines represent the H-bonds or electrostatic interactions.

Table 1 The crystal data and structural refinement of compound **1**.

Table 2 Comparison between experimental and calculated geometric parameters for **1**.

Table 3 Relative antagonistic activities for **1** towards α_{1A} , α_{1B} and α_{1D} subtypes. Prazosin is non-selective α_1 -AR antagonist employed as positive control.

Table 4 The different interactions between antagonists and α_1 -AR.

Scheme 1.

Fig. 1.

Fig. 2.

	Distances X1-X4 (Å)			
	X1(PI-HY1)	X2(PI-HY2)	X3(PI-HBA)	X4(PI-HY3)
Ideal α_1 -AR antagonists	5.69	6.17	5.62	9.78
X-ray structure of 1	5.65	5.00	4.05	6.27

Fig. 3.

Fig. 4.

A)

B)

C)

D)

Fig. 5.

Table 1

Empirical formula	C ₂₄ H ₂₈ N ₄ O ₂	F(000)	431.3
Formula weight	403.51	θ range for data collection	4.16 to 68.19°
Temperature (K)	290	h , k and l range	-12–12, -13–13, -14–13
Crystal system	Triclinic	Reflections collected	19483
Space group	$P\bar{1}$	Independent reflections	3861
a , b , c (Å)	10.251(2), 10.838(2), 11.637(2)	R_{int}	0.0642
α , β , γ (°)	90.21(3), 111.82(3), 113.72(3)	Data/restraints/parameters	3861/14/272
Crystal size (mm ³)	0.3 × 0.2 × 0.2	Goodness-of-fit on F^2	1.042
Volume (Å ³), Z	1080.9(6), 2	R_1 , wR_2 [$I \geq 2\sigma(I)$]	0.0553, 0.1628
ρ_{calc} (mg/mm ³)	1.2397	R_1 , wR_2 [all data]	0.0702, 0.1800
μ (mm ⁻¹)	0.643	$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e Å ⁻³)	0.35, -0.38

Table 2

Bonds	Dist. ^a (Å)	Dist. ^b (Å)
O(1)–C(5)	1.373(2)	1.360
O(2)–C(9)	1.237(3)	1.210
N(3)–C(26)	1.454(3)	1.453
C(23)–C(24)	1.399(4)	1.414
Angle	(°)	(°)
O(2)–C(9)–C(12)	120.6(2)	122.21
O(1)–C(5)–C(4)	115.90(16)	116.05
N(1)–C(14)–C(17)	109.45(16)	109.47
N(3)–C(26)–C(30A)–C(29A)	-44.7(8)	-179.48
C(26)–C(30A)–C(29A)–N(2)	27.9(1)	-174.71

^a obtained from crystal structure^b theoretical results at DFT/CAM-B3LYP/6-31G(d,p) level of theory.

Table 3

Compound	α_{1A}	α_{1B}	α_{1D}
1	3.33	0.99	0.53
Prazosin	1.00	1.00	1.00

Table 4

	Compound 1	Prazosin
α_{1A}	Hydrophobic interactions: Phe86, Trp102, Phe312,Tyr316	Hydrophobic interactions: Phe288 and Phe308 Electrostatic interactions: Gln177, Glu305
α_{1B}	Hydrophobic interactions: Trp121, Trp307, Phe330, Tyr338 π - π stacking: Phe334 Van der waal contact: Val197	Hydrogen bond: Cys195 (3.0 Å) Asp125 (2.3 Å)