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Design, synthesis and biological evaluation of new arylpiperazine derivatives bearing a flavone moiety as α_1-adrenoceptor antagonists

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ABSTRACT

Elaborate study on the three-dimensional model of α_1-adrenoceptor (α_1-AR) antagonists led to the development of a series of new arylpiperazine derivatives bearing a flavone nucleus as α_1-AR antagonists. The in vitro activities were evaluated and compounds **1, 4, 10, 13** and **15** showed activities close to the reference compound (Prazosin).

In recent years, the types of α_1-adrenoceptor (α_1-AR) antagonists are established not only by pharmacological studies but also by binding studies. The α_1-ARs belong to the super family of G protein coupled seven-transmembrane helix receptors (GPCR)[1] and are comprised of multiple subtypes including α_{1A}, α_{1B} and α_{1D} which were defined in native tissues, and their corresponding cloned counterparts α_{1a}, α_{1b} and α_{1d}. Great attentions had been paid on the selective α_1-adrenoceptor antagonists due to their importance on the treatment of benign prostatic hyperplasia (BPH) for more than two decades.[2,3] In this study, the goal of our research was to discover and develop new compounds with high affinity for α_1-AR antagonists.

According to the three-dimensional pharmacophore model of α_1-AR antagonists,[4–6] an ideal α_1-AR antagonist pharmacophore consists of a positively ionizable group (PI), a polar group which provides a hydrogen bond acceptor (HBA) feature, and hydrophobic regions (HY).

Many reports had shown that heterocyclic compounds containing an arylpiperazine moiety had high affinity for α_1-ARs,[7–10] and those compounds match the pharmacophore model well. As one of the most ubiquitous families of natural products, flavonoids possess a remarkable spectrum of biological activities.[11–15] Based on the above considerations, arylperazine derivatives bearing a flavone moiety should have interesting α_1-AR antagonistic activities. The flavone compounds have phenyl rings and hydroxyl groups which can be acted as the HY and HBA of the α_1-AR antagonists. We therefore designed and synthesized a series of new arylpiperazine derivatives (**1**–**18**, Fig. 1) bearing a flavone moiety as the terminal heterocyclic molecular portion, and the two portions are linked at position 7 of 7-hydroxyflavone and position 1 of arylpiperazine moiety with polymethylene chain.

The corresponding pharmacophore of the designed compounds could be identified as following: the N-1 atom at the arylpiperazine corresponds to the PI, the phenyl of arylpiperazine and the flavone moiety serve as the HY1 and HY2 portion, respectively, and the oxygen atom from flavone as the HBA (Fig. 2).

Furthermore, to investigate the influence of the length of polymethylene chain between flavone and arylpiperazine moieties on the α_1-AR antagonistic activities, the alkyl chain was designed characterizing by 2–4 methylene units. The pharmacophore model suggests that the HY are necessary for α_1-AR antagonist,[4–6] so we conjectured that the intensification of the hydrophobicity in the hydrophobic regions will increase the activities. To assess this hypothesis, we have designed a series of compounds with an alkyl at the HY1 portion and a halogen atom at the HY2 portion. Compounds **10**–**18** with a chlorine atom at the 4′-position of the flavone moiety were synthesized. And also, compounds **4**–**9** and **13**–**18** which contain *ortho*- or *para*-substituted methyl group on the phenyl ring attached to the piperazine nucleus were

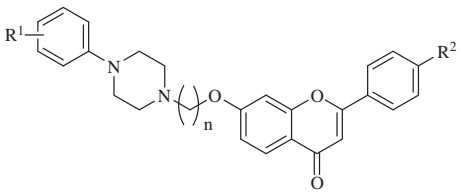

Figure 1. Structures of target compounds.

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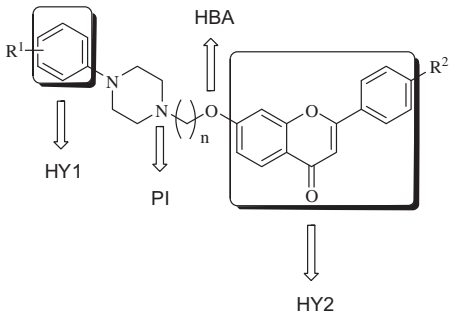


Figure 2. Target compounds superposed to the pharmacophore model for α_1-AR antagonists.

synthesized to evaluate the influence of alkyl substituents on the α_1-AR antagonistic activities.

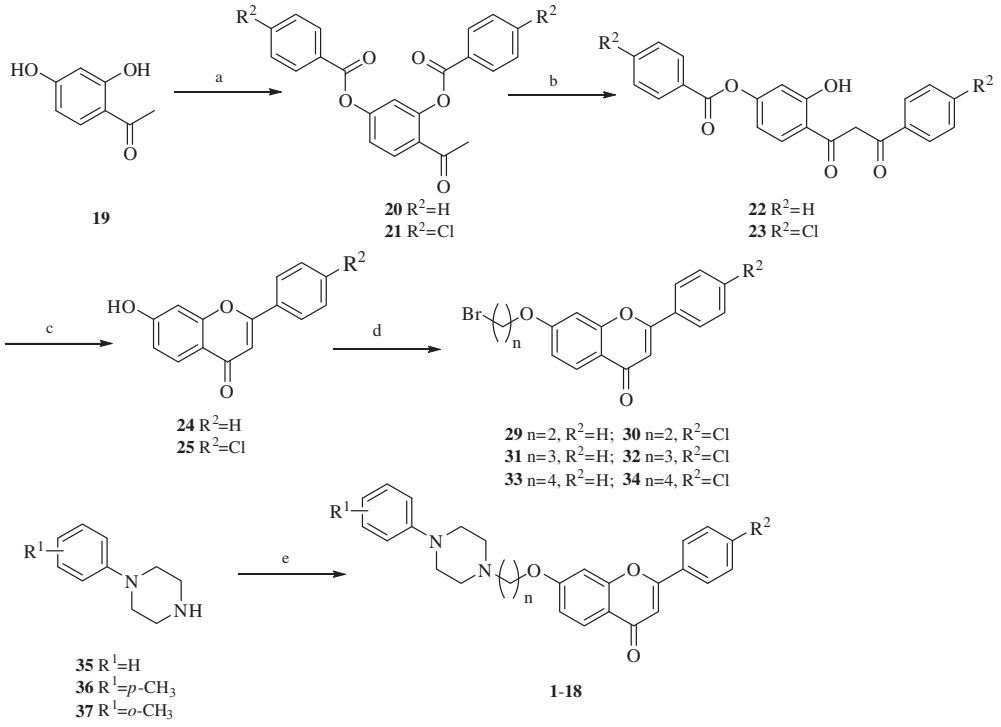
The synthesis of the target compounds, as shown in Scheme 1, is described as follows: to the solution of **19** and dry potassium carbonate in acetone, benzoyl chloride was added slowly and refluxed for 6 h. The crude product of immediate **20** was collected by filtration and then stirred with 10% aqueous glacial acetic acid and the intermediate **22** was obtained by filtration and rinsed with water. The intermediate **22** was converted to **24** by treating it with glacial acetic acid and anhydrous sodium acetate at reflux. Intermediate **29** were obtained by alkylation of **24** with 1,2-dibromoethane (**26**) in the presence of dry potassium carbonate. In turn, the final compound **1** was prepared by reacting **29** and **35** in toluene refluxing for 48 h. The other compounds **2**–**18** were prepared using the same procedure described above for compound **1**.

Compounds **1**–**18**, were tested for their in vitro α_1-AR antagonistic properties in rat anococcygeal muscles and were assessed by inhibition of phenylephrine-induced contraction. Antagonistic potency of all the compounds is expressed as pA_2. The pA_2 value was obtained from the linear regression of Schild plot and the values were taken from three repeated experiments (Table 1). All the eighteen compounds displayed lower potency (pA_2) than that of the control, Prazosin, and it can be noticed that the activities of compounds **1**, **4**, **10**, **13** and **15** are as potent as Prazosin. To illustrate the rationality and reliability of our molecular design, pA_2 value of negative controls including flavones **24, 25** and intermediates **29–34** were also obtained (Table 1). The assay showed that

Table 1
Chemical structures, physical data and α_1-AR antagonists activities of compounds **1**–**18**

Compound	*n*	R^1	R^2	Mp (°C)	Yield (%)	pA_2[a]
1	2	H	H	137–140	21.2	8.526 ± 0.126
2	3	H	H	156–158	23.1	8.177 ± 0.210
3	4	H	H	106–109	22.7	8.333 ± 0.137
4	2	*p*-CH_3	H	139–142	18.4	8.647 ± 0.098
5	3	*p*-CH_3	H	169–172	23.7	7.684 ± 0.073
6	4	*p*-CH_3	H	105–107	25.5	6.709 ± 0.128
7	2	*o*-CH_3	H	127–131	24.1	7.383 ± 0.105
8	3	*o*-CH_3	H	135–138	24.6	6.930 ± 0.210
9	4	*o*-CH_3	H	167–171	23.6	7.710 ± 0.079
10	2	H	Cl	171–175	19.7	8.579 ± 0.081
11	3	H	Cl	176–179	23.4	8.072 ± 0.112
12	4	H	Cl	161–163	20.9	7.914 ± 0.087
13	2	*p*-CH_3	Cl	190–194	19.4	8.930 ± 0.108
14	3	*p*-CH_3	Cl	188–191	23.5	8.088 ± 0.145
15	4	*p*-CH_3	Cl	145–149	20.6	8.498 ± 0.064
16	2	*o*-CH_3	Cl	152–154	20.1	8.207 ± 0.156
17	3	*o*-CH_3	Cl	152–158	22.7	7.772 ± 0.143
18	4	*o*-CH_3	Cl	125–128	24.7	7.471 ± 0.189
24			H	240–242	74.9	6.609 ± 0.201
25			Cl	275–278	72.8	6.845 ± 0.177
29	2		H	Amorphous powder	75.5	6.897 ± 0.117
30	2		Cl	Amorphous powder	76.3	6.925 ± 0.136
31	3		H	Amorphous powder	71.6	6.409 ± 0.095
32	3		Cl	Amorphous powder	75.2	6.168 ± 0.169
33	4		H	Amorphous powder	73.3	6.538 ± 0.155
34	4		Cl	Amorphous powder	76.9	6.368 ± 0.114
Prazosin						9.112 ± 0.082

[a] Values are means ± standard derivation of three repeated experiments.



Scheme 1. Reagents and conditions: (a) benzoyl chloride or 4-chlorobenzoyl chloride, dry K_2CO_3, acetone; (b) 10% glacial acetic acid solution; (c) glacial acetic acid, anhydrous sodium acetate; (d) **26** 1,2-dibromoethane, (**27** 1,3-dibromopropane, **28** 1,4-dibromobutane), dry K_2CO_3, acetone; (e) **29** (**30**–**34**), toluene.

the in vitro α_1-AR antagonistic activities of both the flavones **24, 25** and the intermediates **29–34** were far lower than that of the target compounds **1**–**18** and Prazosin.

In conclusion, a two carbon atoms which connects the flavone moieties and arylpiperazine nucleus is the best polymethylene chain for the activities for all the target compounds. With the lengthening of the carbon chain, no remarkable variation exhibited in the α_1-AR antagonistic activity. Compounds **10**–**18**, bearing a chlorine atom at the flavone nucleus, have a higher activity toward α_1-AR antagonist than those of **1**–**9**, so it suggested that a chlorine atom at the HY portion can lead to the increase of the α_1-AR antagonistic activity. Moreover, we found that whether the presence of methyl group at the *ortho*- or *para*-position of the phenyl ring attached to the piperazine or not leads to no increase on the activities, but the *ortho*-substituted derivatives are more potency than that of the *para*-substituted derivatives. Furthermore, the target compounds are more potency than that of negative controls including flavones and synthetic intermediates**,** it demonstrates that the arylpiperazine and polymethylene chain between flavone and arylpiperazine moieties are the necessary pharmacophore of the designed compounds. These results were consistent with the pharmacophore of the designed compounds and proved the reliability of the molecular design. Further studies are under way to elucidate this result and to synthesize more potency α_1-AR antagonists.

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