Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 437–440

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

α_1-Adrenoceptor Antagonists. Rational Design, Synthesis and Biological Evaluation of New Trazodone-like Compounds

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Received 4 September 2001; revised 29 October 2001; accepted 14 November 2001

Abstract—A rational design approach has been applied to synthesize a novel class of compounds with affinity for α_1 adrenergic receptors (AR). Molecular structures are characterized by a benzimidazolylpyridazinone or an imidazolylpyridazinone moiety, an original fragment in the field of the arylpiperazine compounds with α_1-AR blocking properties. A 1.1 nM affinity toward α_1-AR was found for compound **3**, the most active of this series. © 2002 Elsevier Science Ltd. All rights reserved.

The α_1-AR are comprised of multiple subtypes characterized by both pharmacological and binding studies into α_{1A}, α_{1B}, and α_{1D} and the corresponding cloned counterparts termed α_{1a}, α_{1b}, and α_{1d}, respectively. Similarly, α_2-AR have been classified into four subtypes, termed α_{2A}–α_{2D}, respectively.[1]

As benign prostatic hyperplasia (BPH) is the most common benign tumor in men, combined with the fact that α_1 blockers have been employed in the treatment of BPH for more than two decades, in recent years the search for new selective α_1-AR antagonists has increased. In this context, the goal of our research was the discovery and development of novel adrenoceptor antagonists characterized by high affinity for α_1-AR and, possibly, selectivity toward α_1 receptors with respect to α_2-AR.

For this purpose, we have used the results derived from a database search performed by means of a three-dimensional pharmacophore model of α_1-AR antagonists previously reported by our research group (Fig. 1).[2] This study resulted in the identification of trazodone (Scheme 1) as a structure characterized by chemical features able to (partially) satisfy the spatial constraints imposed by the pharmacophore model. In particular, while the positive ionizable group (corresponding to PI of the pharmacophore model) and the hydrogen bond acceptor feature (HBA of the model) are perfectly fitted by the piperazine N1 atom and the carbonyl group of trazodone, respectively, two peripheral hydrophobic regions (HY1–HY2 and HY3 of the pharmacophore) are only partially matched by the *m*-chlorophenyl moiety and the condensed pyridine ring of this compound, respectively.

It was shown that the isosteric change of the carbonyl groups in a hydantoin moiety into methylene groups decreased the affinity for α_1-AR in compounds structurally similar to trazodone,[3] suggesting a direct interaction between the carbonyl moiety and the receptor. On the contrary, compounds with nitrogen atoms at different positions in the terminal heteroaromatic ring system possess enhanced α_1-AR affinity. As an example, trazodone derivatives bearing an unsubstituted benzimidazole moiety as the terminal heterocyclic group are characterized by a very interesting affinity.[4] These data are in agreement with the pharmacophore model requiring a hydrogen bond acceptor group in the region of space occupied by the above mentioned heteroaromatic ring.

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0960-894X/02/$ - see front matter
PII: S0960-894X(01)00772-7

Moreover, it was previously reported by us that the *o*-methoxyphenylpiperazinyl moiety linked to a pyridazin-3(2*H*)-one through an appropriate polymethylene spacer is a key element for α_1 affinity.[2]

Based on this experimental evidence, in an effort to obtain compounds with enhanced α_1-AR binding affinity, we decided to perform three types of structural modifications on the trazodone molecule (Scheme 1): (i) as suggested by the partial fit of trazodone to our pharmacophore model for α_1-AR antagonists, the overall length of the molecule was increased by intercalation of a pyridazinone ring between the alkyl spacer and the terminal heterocyclic fragment of trazodone, also providing chemical moieties able to be hydrogen bond acceptors (i.e., the carbonyl group of pyridazinone); (ii) the *m*-chlorophenyl ring was substituted by *o*-chlorophenyl or *o*-methoxyphenyl groups, reported as more appropriate substituents to fill the hydrophobic region (HY1–HY2) close to the piperazine ring of trazodone; (iii) the condensed heterocyclic ring of trazodone was in turn replaced by benzimidazole, according to the literature reports, or imidazole; (iv) the length of the *n*-propyl chain has been increased.

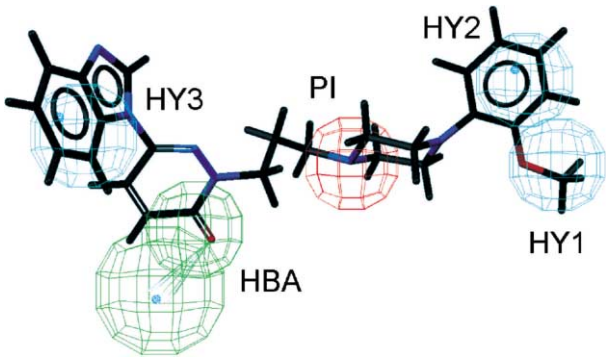
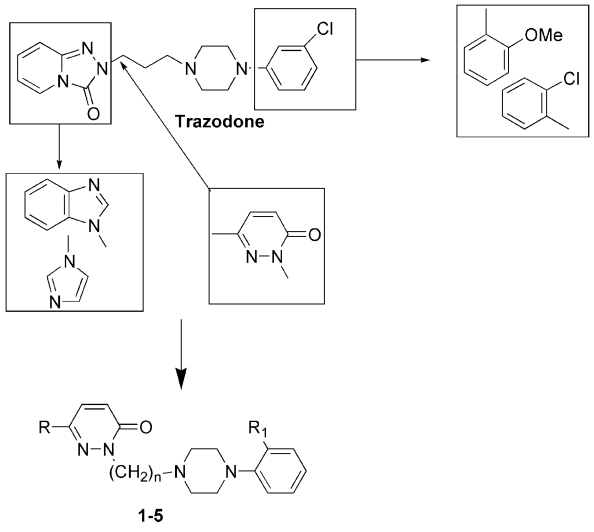


Figure 1. Compound **2**, taken as a representative example of the new α_1-AR antagonists, superposed to the pharmacophore model for α_1-adrenoceptors. Pharmacophoric features are color-coded: cyan for hydrophobic regions (HY1, HY2, and HY3), red for a positive ionizable feature (PI), and green for a hydrogen bond acceptor (HBA).



Scheme 1.

We therefore designed the hybridized molecules **1** and **2** (Table 1) that would allow a better fit with respect to trazodone to the terminal (opposite) hydrophobic features (HY1–HY2 and HY3, respectively; see Fig. 1) of the pharmacophore model by the *o*-chlorophenyl (or *o*-methoxyphenyl) and benzimidazole substituents, respectively. As a consequence, the new molecules should be characterized by the essential structural elements identified by our previous work in this field,[2,5] corresponding to an extended hydrophobic system (the *o*-methoxyphenyl group), a positive ionizable group within the piperazine ring, a hydrogen bond acceptor group within the pyridazinone nucleus, and, finally, an additional hydrophobic portion corresponding to the heterocyclic ring (i.e., benzimidazole). Prior to synthesis, we have submitted compounds **1** and **2** to a computational procedure (by means of the program Catalyst)[6] aimed at evaluating the goodness of their fit to the pharmacophore model and predicting their α_1-AR affinity. As a result, we found that all the pharmacophore features are well fitted by the chemical groups of **2**, taken as a representative example. Figure 1 shows that the (*o*-methoxy)phenylpiperazine overlaps the HY1–HY2–PI pharmacophoric system, the pyridazinone carbonyl group corresponds to the hydrogen bond acceptor feature of the model, and, finally, the benzimidazole moiety serves as additional hydrophobic portion filling HY3. Superposition of **2** to the pharmacophore model led to a predicted affinity value of 4.2 nM (as a consequence of the good fit to the pharmacophoric features). Accordingly, **1** and **2** represent very interesting synthetic targets.

In addition, taking into account that the polymethylene chain linking the arylpiperazine moiety to the pyr-

Table 1. Chemical and physical data of compounds **1**–**5**

Compd	*n*	R	R_1	Formula	mp (°C)	Yield (%)
1	3	1-Benzimidazolyl	Cl	$C_{24}H_{25}ClN_6O$[a]	200–205	40
2	3	1-Benzimidazolyl	OMe	$C_{25}H_{28}N_6O_2$[b]	175–180	40
3	4	1-Benzimidazolyl	OMe	$C_{26}H_{30}N_6O_2$[c]	165–170	60
4	3	1-Imidazolyl	OMe	$C_{21}H_{26}N_6O_2$[d]	180–185	30
5	3	1-Imidazolyl	Cl	$C_{20}H_{23}ClN_6O$[d]	175–180	50

[a]As dihydrochloride.
[b]As trihydrochloride dihydrate.
[c]As dihydrochloride dihydrate.
[d]As trihydrochloride.

Table 2. α_1- and α_2-Adrenoceptor binding affinities of the studied compounds

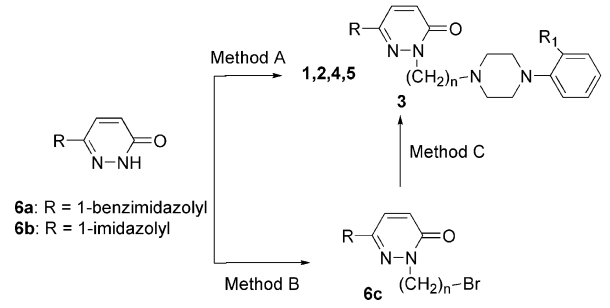
Compd	*n*	R	R_1	K_i, nM[a]		
				α_1-AR	α_2-AR	α_2/α_1
T[b]				281[c]		
1	3	1-Benzimidazolyl	Cl	15.2±1.7 (8.5)	44.7±5.0	3
2	3	1-Benzimidazolyl	OMe	6.5±0.5 (4.2)	158.3±15.3	24
3	4	1-Benzimidazolyl	OMe	1.1±0.1 (1.3)	16.0±1.9	14
4	3	1-Imidazolyl	OMe	115.4±22.4 (190)	673.4±55.5	6
5	3	1-Imidazolyl	Cl	48.3±6.3 (28)	436.6±36.7	9
P[b]				0.24±0.05		
R[b]					4.0±0.3	

[a]Values are means±standard deviation of three binding experiments. Predicted affinity values as calculated by Catalyst are given in parentheses.
[b]**T**, **P** and **R** represent trazodone, prazosin and rauwolscine, respectively.
[c]Expressed as IC_{50}; see ref 11.

idazinone ring has been demonstrated to be a critical structural element in determining both affinity and selectivity towards α_1-AR, we also planned to synthesize compound **3** having a four carbon atom alkyl chain, suggested to be the optimal spacer in compounds bearing the phenylpiperazinylpyridazinone system.[2] Finally, in order to define the requirements (in terms of size and electronic properties) of the terminal heterocyclic portion of the molecule, the imidazole derivatives **4** and **5** were also synthesized.

The synthetic pathways to compounds **1**–**5** are shown in Scheme 2. Alkylation of 6-(benzimidazol-1-yl)pyridazin-3(2*H*)-one (**6a**) (obtained by condensation of benzimidazole, 3,6-dichloropyridazine in DMF/NaH and subsequent hydrolysis with CH_3COOH/CH_3COOK) with 1-(2-chlorophenyl)-4-(3-chloropropyl)piperazine[7] or 1-(2-methoxyphenyl)-4-(3-chloropropyl)piperazine[7] in K_2CO_3/acetone (Method A) afforded compounds **1** and **2**, respectively, in moderate yield. The same method has been used for the synthesis of compounds **4** and **5** starting from 6-(imidazol-1-yl)pyridazin-3(2*H*)-one (**6b**) prepared according to reported procedures.[8,9] Alternatively, **6a** was alkylated with 1,4-dibromobutane in K_2CO_3/acetone (Method B) to give intermediate **6c**, which in turn was converted to compound **3** by reaction with 1-(2-methoxyphenyl)piperazine in Na_2CO_3 and isoamyl alcohol (Method C). Chemical and physical data of compounds **1**–**5** are reported in Table 1.[10]

The pharmacological profile of the new compounds was evaluated by radioligand binding assays (ability to displace [^{3}H]prazosin or [^{3}H]rauwolscine from α_1- and α_2-AR, respectively) on rat cerebral cortex. While benzimidazole derivatives all exhibited a good affinity toward α_1-AR (Table 2), with values ranging from 1.1 to 15.2 nM, the remaining compounds are characterized by higher K_i values for α_1-AR (48.3 and 115.4 nM for the chloro and methoxy derivatives **4** and **5**, respectively). None of the studied compounds has been found very selective toward α_1-AR with respect to α_2-AR, the highest α_2/α_1 ratio, associated with compound **2**, being 24.



Scheme 2.

In conclusion, a new class of potent α_1-AR antagonists has been synthesized based on the suggestions derived from both a database search performed by means of a 3D pharmacophore model and an exhaustive literature survey. These new compounds share a benzimidazolylpyridazinone or imidazolylpyiridazinone as a common structural feature, which represents an element of novelty in the SAR of arylpiperazinyl compounds acting toward α_1-AR. A preliminary SAR consideration also led to the suggestion that a heterocyclic terminal fragment bigger than an aromatic five-membered ring is required for best activity. Moreover, the optimal length of the alkyl spacer seems to be corresponding to a tetramethylene chain, as previously demonstrated for other classes of α_1-AR antagonists.[2] Further studies are under way to plan the synthesis of new compounds and will be reported in due course.

Acknowledgements

Financial support provided by the Italian Ministero dell'Istruzione dell'Università e della Ricerca (Project 'Progettazione e Sintesi di Agenti Neuroprotettivi') and Italian Research National Council (CNR) 'Progetto Finalizzato Biotecnologie' (CNR Target Project on 'Biotechnology') is acknowledged.

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