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SELECTIVE α-1A ADRENERGIC RECEPTOR ANTAGONISTS. EFFECTS OF PHARMACOPHORE REGIO- AND STEREOCHEMISTRY ON POTENCY AND SELECTIVITY

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Abstract: The anti-anxiety agent ipsapirone has been shown to have modest affinity for α-1 receptors. We disclose the discovery of potent α-1a receptor subtype selective antagonists based on the ipsapirone structure which possess selectivity versus the 5-HT receptors tested. These antagonists were obtained by tethering a saccharin ring to 4-phenyl-3-carboxyethyl piperidines. The design principles which led to this structural motif are discussed. The synthesis of key analogs, their SAR, as well as results of selected in vitro and in vivo studies are described.

Introduction

The three known families of G-protein coupled adrenergic receptors have been classified as the α-1, α-2, and β adrenoceptors. These receptors are distinguished based on sequence information, receptor pharmacology and signaling mechanisms. One of these receptor classes, the α-1, has recently been divided into three subclasses, the α-1a, α-1b, and α-1d.[1] Their presence in animal and human tissues was confirmed when these receptors were cloned and expressed utilizing molecular biological techniques.[2] The study of a variety of tissue preparations led to the discovery of a heterogeneous distribution of the three α-1 receptors within animal and human tissues.

Pharmacological investigations determined that nonselective α-1 antagonists were useful antihypertensive agents.[3] These α-1 antagonists were also found to be therapeutically effective for the treatment of benign prostatic hyperplasia (BPH).[4] Subsequently, it was discovered that the α-1a receptor was responsible for mediating smooth muscle contraction in the lower urinary tract.[5] While the physiological roles of the α-1b and α-1d receptors in blood pressure or other physiological functions remain undefined in human, a selective α-1a adrenergic receptor antagonist may be a suitable candidate for the treatment of BPH since it may be devoid of cardiovascular effects associated with nonselective α-1 receptor antagonists.

Rationale

Our goal at the outset of this research was to synthesize potent and selective α-1a antagonists for the treatment of BPH. Our strategy was to convert ipsapirone, **1**, an anti-anxiety agent which has modest affinity for α-1 receptors, into a potent α-1a antagonist. The approach was to replace the piperazine subunit with a variety of piperidines (Figure 1). Herein, we describe our preliminary results.

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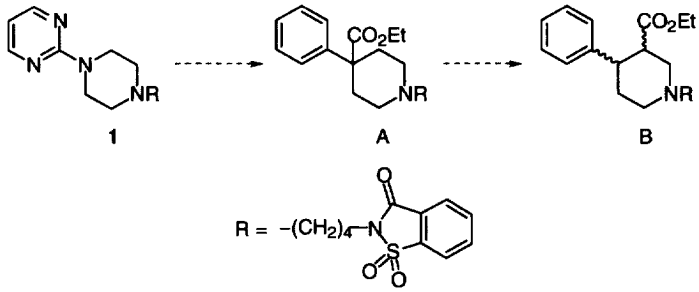
Figure 1.



Initially, we considered replacing the *N*-(2-pyrimidinyl)piperazine with a 4-carboxyethyl 4-phenyl piperidine (Figure 1, A), while maintaining the butyl saccharin moiety. However, our concern about potential metabolic generation of the known opioid ligand, normeperidine, via oxidative dealkylation of the piperidine shifted our focal point to alternative 4-phenyl piperidines. Our previous findings[6] indicated that α-1 subtype selectivity was induced by installing a carboxy group three atoms away from the biogenic amino group of a nonselective α-1 antagonist. We implemented a similar approach for dealing with α-1a antagonists containing meperidine type subunits (Figure 1, B).

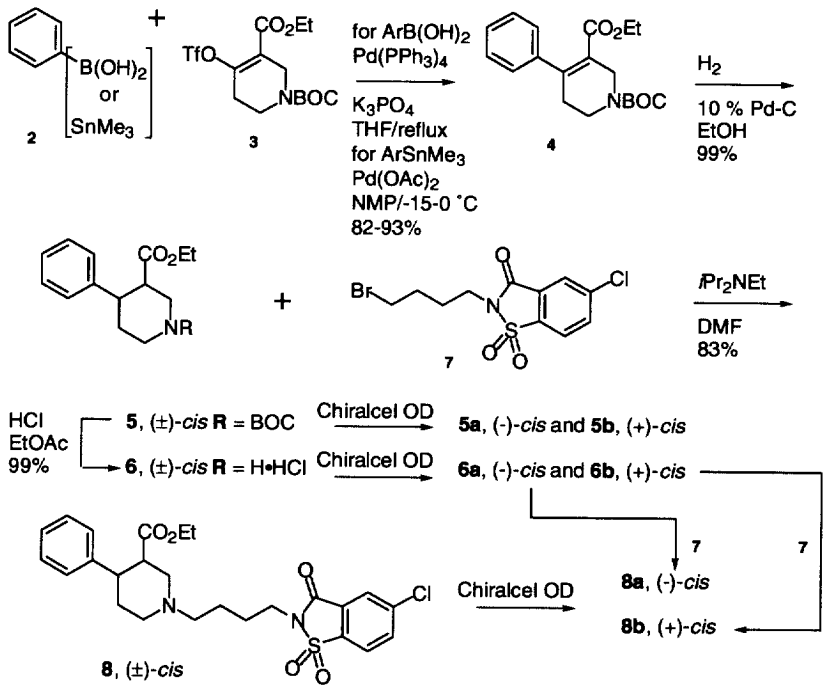
Results and Discussion

Synthesis

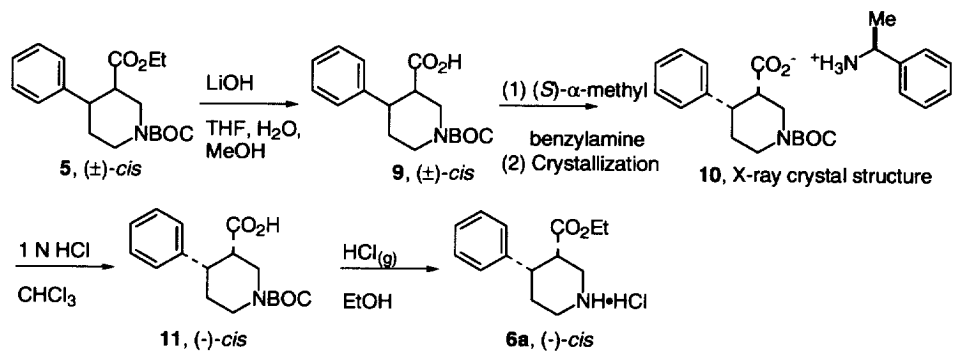
The first series of antagonists prepared were 3-carboxyethyl-4-phenyl piperidine derivatives. In this series, the saccharin ring found in ipsapirone was replaced by 5-chlorosaccharin for improved pharmacokinetic properties.[7] This substitution typically caused little change in α-1 receptor binding affinity. Their synthesis is highlighted in Scheme 1. A palladium mediated coupling[8] of either phenylboronic acid or phenyltrimethyl stannane, **2**, with enoltriflate **3** provided the 4-phenyl substituted material **4**. The enoltriflate **3** was prepared from *N*-BOC-3-carboxyethylpiperidone. Subsequent double bond reduction of **4** produced the *cis* racemate, **5**. Deprotection of **5** with HCl-EtOAc and alkylation with **7**[9] yielded the *cis* racemic antagonist, **8**. The enantiomers, (-)-*cis* **8a** and (+)-*cis* **8b**, were separated utilizing chiral HPLC (Chiralcel OD column). The (±)-*trans* analog of **8** was obtained from the base catalyzed epimerization of (±)-*cis* **5** to (±)-*trans* **5**, followed by N-BOC deprotection with HCl-EtOAc and alkylation with **7**. The racemic *cis* piperidines **5** were also separated into (-)-*cis* **5a** and (+)-*cis* **5b** and deprotected [(-)-*cis* **6a** and (+)-*cis* **6b**, respectively]. The piperidine, (+)-*cis* **6b**, was alkylated with bromide **7**, which produced (+)-*cis* **8b**.

The racemic ester, (±)-*cis* **5**, was carefully hydrolyzed to the corresponding acid (±)-*cis* **9**, which after treatment with (*S*)-α-methylbenzyl amine provided a crystalline salt **10**, which was suitable for X-ray diffraction (Scheme 2). The configuration of the salt **10** was determined to be the 3-(*S*)-carboxy-4-(*S*)-phenyl piperidine. The carboxylic acid **11** was generated by treating **10** with aqueous acid. The formation of the ethyl ester and N-BOC deprotection was accomplished by HCl-EtOH treatment, and the convergence with compound (-)-*cis* **6a** was completed. Through the use of the optical rotations of key intermediates, we have determined that the (-)-*cis* N-BOC piperidine **5a** led to the (-)-*cis* piperidine **6a** which produced **8a**, the (-)-*cis* enantiomer of antagonist **8**.

Scheme 1.

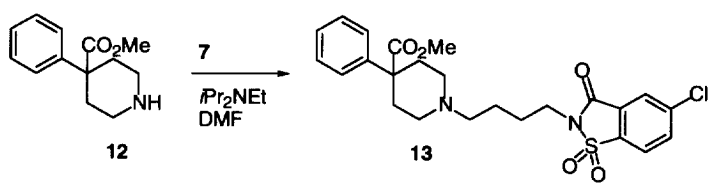


Scheme 2.



The 4-carboxymethyl-4-phenyl piperidine analog **13** was prepared via alkylation of **12** with bromide **7** (Scheme 3).

Scheme 3.



Receptor Binding Experiments

The binding affinity to the human α-1 receptors for the synthetic compounds was measured utilizing cloned receptor binding assays (Table 1).[5b] The opioid binding affinity for selected α-1a antagonists was measured utilizing ^{3}H-DAMGO as the radioligand.[10]

Figure 2.

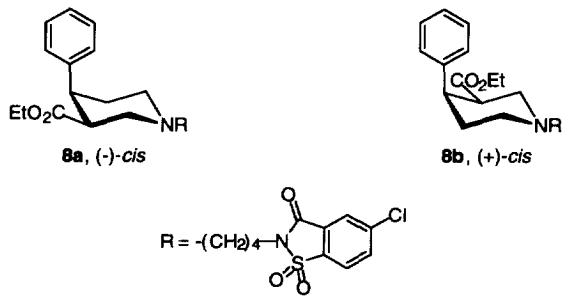


Table 1.

α-1 binding data.

	K_i (nM)		
	α-1a	α-1b	α-1d
1	87	220	46
8, (±)-*trans*	100	1400	320
8, (±)-*cis*	3.0	940	1800
8a, (-)-*cis*	0.51	170	480
8b, (+)-*cis*	98	>2000	1100
13	44	2200	2000

Structure-Activity Relationships

Replacing the *N*-(2-pyrimidinyl)piperazine present in ipsapirone, **1**, with 4-carboxymethyl 4-phenylpiperidine, **13**, led to a modest improvement in the α-1a binding affinity and enhanced α-1a receptor subtype selectivity. Relocation of the carboxyalkyl group to the 3-position of 4-phenylpiperidine caused a variety of stereochemically dependent effects. For example, the (±)-*cis* isomer of **8** has 15-fold higher affinity for the α-1a receptor than **13**. However, the (±)-*trans* isomer of **8** exhibited little change in α-1 receptor binding affinity relative to **13**. Assuming the piperidine present in (±)-*trans* **8** adopts a chair conformation, the 3,4-substituents should reside in a diequatorial arrangement. If the conformation of the piperidine ring present in (±)-*cis* **8** is consistent with that of

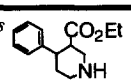
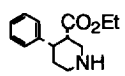
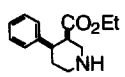
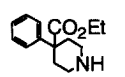
10 (determined by X-ray diffraction), the 4-phenyl group in (±)-*cis* **8** would occupy an axial position and the 3-carboxylate an equatorial post (Figure 2). In this conformation, the more potent *cis* isomer of **8** may benefit from either a unique hydrogen bond between the equatorial 3-carboxylate and the α-1a receptor or a better fit for the axial 4-phenyl group within the α-1a receptor.

The (-)-*cis* enantiomer **8a** has subnanomolar affinity for the α-1a receptor and is highly selective against the α-1b and α-1d receptors, while **8b** has much lower affinity for the α-1a receptor. Assuming that the two enantiomers of (±)-*cis* **8** bind in a similar manner, (-)-*cis* **8a** may benefit from a favorable interaction between the 3-carboxylate and the α-1a receptor and/or (+)-*cis* **8b** may suffer from steric or electrostatic interference with certain elements within the α-1a receptor binding site. Nevertheless, (-)-*cis* **8a** represents the preferred α-1a antagonist within this series based on the α-1 receptor binding profile and when counterscreened, was inactive (>30 μM) in the opioid binding assay and >500-fold selective against the other G-protein-coupled receptors (human α-2, β-1, 2, and 3, dopamine-2 and -5, and 5-HT receptors) tested. The study of the functional activity of (-)-*cis* **8a** in isolated rat prostate tissue revealed that (-)-*cis* **8a** competitively antagonizes phenylephrine induced contraction with a K_b value of 28 nM.

We also measured the opioid binding for the putative piperidine metabolites of each antagonist. These results are summarized in Table 2.

Table 2.

Opioid binding data for piperidines.

		K_i (nM) ^{3}H - DAMGO
6, (±)-*trans*		24,000
6a, (-)-*cis*		7,600
6b, (+)-*cis*		12,000
12		1,300

The relocation of the carboxyethyl group present in 4-carboxyethyl 4-phenylpiperidine, **12** to the piperidine 3-position caused a 6- to 20-fold decrease in opioid receptor binding affinity. This decrease in opioid binding activity was stereochemically dependent. The piperidine, **6a**, present in the most preferred α-1a antagonist **8a**, was approximately 6-fold less avidly bound than normeperidine, **12**.

In Vivo Study

Prior to the delineation of the stereochemistry of the preferred enantiomer of **8**, we studied the bioavailability of (±)-*cis* **8** in rats. Although reasonable plasma levels of **8** were detected its pharmacokinetic profile was poor, with 9.2% bioavailability and an 80 minute half-life.

Conclusion

The α-1a potency and selectivity of ipsapirone was increased by replacing 1-*N*-(2-pyrimidinyl)piperazine with the (-)-*cis* 3-carboxyethyl-4-aryl piperidine, (-)-*cis* **6a**, while the 5-HT activity was diminished. The (±)-*cis* 3-carboxyethyl-4-phenyl piperidine derivative, (±)-*cis* **8**, was substantially more potent and selective than the corresponding (±)-*trans* isomer, (±)-*trans* **8**. The separation of the (±)-*cis* enantiomers of **8** provided a more potent and selective isomer, (-)-*cis* **8a**, than the racemate, and a less active enantiomer, (+)-*cis* **8b**. *Therefore, the stereospecific installation of the carboxylate group at the piperidine 3-position in a relative orientation cis to the 4-phenyl substituent plays an important role in optimizing α-1a binding affinity and subtype selectivity within this class of α-1 antagonists.*

The preparation of **8a** represents yet another example of the approach to design new, potent, and selective G-protein coupled receptor antagonists from existing, low-affinity, nonselective receptor ligands.

Acknowledgment

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