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Original article

Design, synthesis and receptor affinity of novel conformationally restricted σ ligands based on the [4.3.3]propellane scaffold

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ABSTRACT

A series of novel diastereoisomeric σ ligands **3** was designed, synthesized and pharmacologically evaluated. The highly rigid [4.3.3]propellane scaffold was used to fix the three dimensional orientation of the pharmacophoric moieties required for σ affinity. The *syn*,*syn*-configured aminocarbamate *syn*,*syn*-**3a** reveals the most promising σ_1 affinity (K_i = 77 nM) and selectivity over the σ_2 subtype (21-fold). The σ_2 affinity of all four diastereomers **3** was in the low micromolar range. Analysis of the distance between the hydrophobic regions (phenyl moieties) of the diastereomers **3** led to the longest range of distances (10.3 −15.2 Å) for the most potent σ_1 ligand *syn*,*syn*-**3a**, which is in good agreement with pharmacophore models.

1. Introduction

The σ receptors are singular binding sites with a specific pharmacological profile and a widespread distribution within the organism. They are classified in the σ_1 and σ_2 subtypes, which are differentiated by their pharmacological and ligand binding profile, function and molecular size [1–4]. The σ_1 receptor is well characterized at the level of DNA and amino acid sequence [5–8]. In 2011 S. Pricl et al. reported for the first time a 3D homology model of the σ_1 receptor allowing the identification of the putative ligand binding site suitable for docking and pharmacophore validation studies [9–11]. The therapeutic potential of selective σ_1 receptor agonists includes the treatment of schizophrenia, depression, Alzheimer's and Parkinson's disease as well as cancer. σ_1 receptor antagonists can be used for the treatment of neuropathic pain, cocaine, methamphetamine and alcohol dependency [12–15].

Understanding the therapeutic target σ_2 receptor is still at early stages, because it has not been cloned yet and its amino acid sequence and three dimensional structure remain to be elucidated. However, in 2011, the progesterone receptor membrane component 1 (PGRMC1), which has already been cloned [16], was suggested as the putative σ_2 receptor binding site [17]. The σ_2 receptor has attracted attention due to its overexpression in several tumor cell lines rendering it a promising biomarker for these tumors [18–20]. Therefore σ_2 selective ligands could be valuable tools in cancer diagnosis and imaging [21–23]. Moreover, σ_2 receptor agonists can trigger the death of cancer cells increasing the survival time of animals [24–28].

In recent years several structurally diverse compounds with high σ affinity have been studied, which allowed the development of some pharmacophore models [11,29–32]. These models converge on the fact that a molecule should contain at least three pharmacophoric elements in order to possess high σ affinity: a central H-bond donor group, typically a protonated secondary or tertiary amine and two hydrophobic groups. It is of particular interest that these elements should have a defined spatial orientation to each other in order to show selectivity towards the σ_1 or σ_2 subtype. The different pharmacophore models postulate slightly different distances between the pharmacophoric elements but in general agree that the distance between the two hydrophobic moieties should be approximately 3 Å longer for σ_1 ligands than for σ_2 ligands (Table 1). The distance **B** between the protonated amine (NH) and the secondary hydrophobic region (HY2) is within the range of 2.5–4.0 Å for both receptor subtypes. However the distance **A** between the protonated amine (NH) and the primary hydrophobic region (HY1) differs for potent σ_1 and σ_2 receptor ligands.

In order to learn more about the structure of the ligand binding site of σ receptors, we are interested in conformationally restricted

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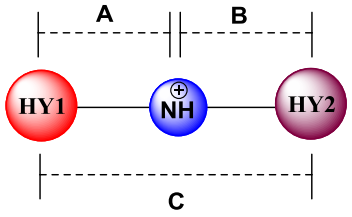
Table 1
General pharmacophore model for σ receptor ligands showing the intramolecular distances between the pharmacophoric elements NH (protonated amine), HY1 (hydrophobic region 1) and HY2 (hydrophobic region 2) in the different models.

General σ pharmacophore model



Model of receptor subtype (author)	Intramolecular distance in Å		
	A	B	C
σ_1 (Glennon) [29]	6–10	2.5–3.9	~11.2
σ_1 (Cratteri) [30]	n.r	n.r	14–16
σ_1 (Pricl) [31]	8.50	3.58	9.97
σ_1 (Pricl) [11]	9.77	4.36	13.64
σ_2 (Cratteri) [30]	11.6–13.6	n.r	10.8–13.2
σ_2 (Pricl) [32]	4.95	3.90	7.5–7.8

n.r. not reported by the author.

and stereochemically defined potent σ_1 and σ_2 receptor ligands. Recently, conformationally restricted aza-bicyclic compounds were reported exhibiting high σ affinity [28,33] (Fig. 1). The diazabicyclononane **1** showed high σ_1 affinity [33], whereas the granatane derivative **2** had a high preference for the σ_2 subtype [28]. Both compounds fulfill the structural requirements described by the pharmacophore models mentioned in Table 1.

Inspired by the σ ligands **1** and **2** and taking the general pharmacophore models for σ ligands into account, novel σ receptor ligands **3** containing the three pharmacophoric elements (NH, HY1, HY2) attached to the rigid [4.3.3]propellane scaffold [34] were envisaged. The three dimensional orientation of the pharmacophoric elements and thus their distances will be defined by the stereochemistry of the resulting propellane derivatives **3**, which will finally be responsible for the σ receptor affinity and selectivity (Fig. 1). For compounds of type **3** four achiral diastereoisomers are possible, which allows the adjustment of the desired distances

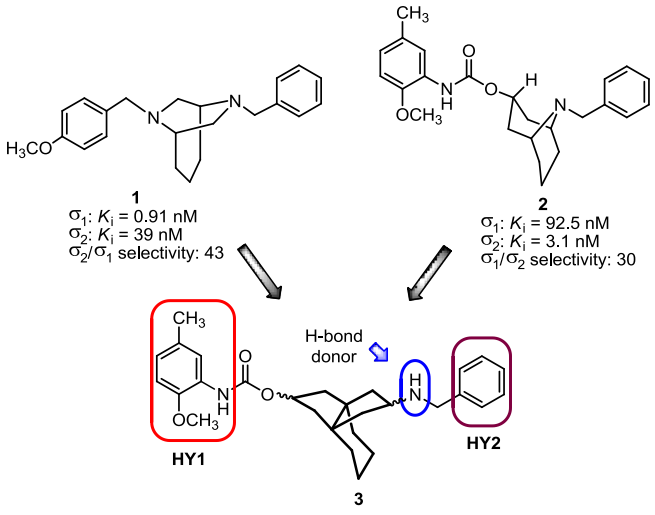


Fig. 1. Design of novel σ ligands **3** based on the conformationally restricted [4.3.3] propellane scaffold. The distances between the pharmacophoric elements NH, HY1 and HY2 are defined by the stereochemistry.

between the pharmacophoric elements. In order to explore the influence of the configuration of the propellane derivatives **3** on the σ_1 and σ_2 affinity, all four diastereoisomers should be synthesized and tested in competitive receptor binding assays.

Propellanes are defined as tricyclic hydrocarbons, in which three rings have a common carbon–carbon bond, the so called coin-joining bond [35]. The propellane chemistry was intensively developed during the 1960–1980 period. Since the mid-2000's, a renewed interest in this system has emerged, mainly in the field of material science and perfumery [36–38]. However, consideration of the propellane scaffold in the field of MedicinaChemistry is rather limited so far [39,40].

2. Chemistry

The synthesis of the key [4.3.3]propellane-8,11-dione (**6**) was achieved in two steps beginning with a modified Weiss–Cook reaction [41,42] of cyclohexane-1,2-dione (**4**) with dimethyl 3-oxoglutarate in citrate-phosphate buffer resulting in the tetraester **5** (Scheme 1). Hydrolysis of the tetraester **5** with 6 M HCl led to the diketone **6** in 61% yield over two steps. Spectroscopic and analytical data of **6** are in good accordance to reported data [42].

The next step was the selective reduction of only one of the keto groups using L-Selectride as reducing agent, which led to a 1:1 mixture of the hydroxyketones *syn*-**7a** and *anti*-**7c** (63% yield) (Scheme 1). This mixture could not be separated by flash column chromatography and therefore was reacted with 2-methoxy-5-methylphenyl isocyanate in the presence of dibutyltin diacetate as catalyst affording the diastereomeric carbamates *syn*-**8a** and *anti*-**8c**. The mixture of diastereomers was successfully separated by flash column chromatography providing *syn*-**8a** and *anti*-**8c** in 31% and 36% yields, respectively.

The configuration of the diastereoisomers *syn*-**8a** and *anti*-**8c** was determined by NOESY experiments. The NOESY spectrum of *syn*-**8a** shows a cross peak for the signals at 5.27 ppm (8-H) and 2.15 ppm (10-H *anti*, 12-H *anti*). The interaction of the protons 8-H, 10-H and 12-H of the five-membered rings is only possible when the substituent at the 8 position is *syn*-oriented toward the six-membered ring (Fig. 2). The NOESY spectrum of *anti*-**8c** shows a cross peak between the signals at 5.32 ppm (8-H) and 1.41 ppm (2-CH_2, 5-CH_2). The interaction of 8-H with the protons of the six-membered ring indicates an orientation of this proton towards the six-membered ring resulting in *anti*-configuration of the carbamate moiety (Fig. 2).

The diastereoisomeric ketones *syn*-**8a** and *anti*-**8c** were reduced with L-Selectride (Scheme 2). In case of *anti*-**8c** reduction with the bulky reducing agent L-Selectride led to the diastereoisomeric alcohols *anti*,*anti*-**9c** and *anti*,*syn*-**9d** in the ratio 8:2 determined by ^{1}H NMR spectroscopy (Fig. S1). After reduction of the diastereoisomeric ketone *syn*-**8a**, a mixture of the diastereomeric alcohols *syn*,*syn*-**9a** and *syn*,*anti*-**9b** in the ratio 1:1 was obtained (determined by ^{1}H NMR spectroscopy and HPLC analysis, Figs. S2 and S3 respectively). At that stage of the synthesis the diastereoselective alcohols were not separated by flash chromatography. The stereoselective reduction of the ketones *syn*-**8a** and *anti*-**8c** is explained by steric hindrance caused by the carbamate group at 8-position. In *anti*-**8c** the carbamate adopts the *anti*-position, which shields the *anti*-face of the ketone at C-11 leading to a selective hydride delivery to the *syn*-face. This reduction leads to the alcohol *anti*,*anti*-**9c** as the main product. However, when the carbamate at C-8 is *syn*-oriented as in *syn*-**8a**, it cannot influence the hydride attack at C-11 and thus both diastereoisomers *syn*,*syn*-**9a** and *syn*,*anti*-**9b** were formed in the ratio 1:1.

Reductive amination of the ketone *syn*-**8a** with benzylamine and $NaBH(OAc)_3$ led to both diastereoisomers *syn*,*syn*-**3a** and *syn*