Synthesis of 3-aza[4.4.3]propellanes with high $\sigma_1$ receptor affinity

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Abstract

In order to obtain rigid $\sigma_1$ receptor ligands with defined orientation of pharmacophoric elements, the azapropellane scaffold was chosen. Schmidt rearrangement of propellan-8-ones 6 and 10 provided 3-aza-azapropellane-4-ones 7 and 11. Benzoylation of the secondary lactams 7 and 11 followed by LiAlH4 reduction furnished the azapropellanes 4a and 4c, respectively. A second hydrophobic element was introduced by transformation of the alcohols 4a into carbamates 4b. The $\sigma_1$ affinity of the azapropellanes 4 is strongly dependent on the stereochemistry and the substitution pattern in 12-position. anti-configured azapropellanes anti-4a and anti-4b show higher $\sigma_1$ affinity than their syn-configured counterparts syn-4a and syn-4b. Conversion of the alcohol anti-4a into the carbamate anti-4b led to increased $\sigma_1$ affinity, but complete removal of the 12-substituent resulted in the highest $\sigma_1$ affinity ($K_i(4c) = 17 \text{ nM}$). It can be concluded that the propellane scaffold alone is able to form strong lipophilic interactions and stabilize the ligand-$\sigma_1$ receptor complex as does usually the primary hydrophobic region.

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1. Introduction

The class of $\sigma$ receptors consists of two subtypes, which are termed $\sigma_1$ and $\sigma_2$ receptors. The $\sigma_1$ receptor is found in the central nervous system and in peripheral organs such as liver, lung and heart. It has been shown that ligands blocking the $\sigma_1$ receptor can be used for the treatment of neuropathic pain. The pyrazole derivative S1RA (E-52862), which is currently entering phase 3 clinical trials for the indication neuropathic pain, is currently the most advanced $\sigma_1$ ligand. Moreover, it has been reported that $\sigma_1$ antagonists have antipsychotic and antiaddiction activity. On the contrary, $\sigma_1$ agonists reveal beneficial effects in neurodegenerative and neuroinflammatory conditions (e.g. Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, stroke, Multiple sclerosis). In the field of oncology therapeutic and diagnostic applications of $\sigma$ receptor ligands are intensively discussed.

Although several reports define particular compounds as agonists and others as antagonists, the positive or negative effect of $\sigma_1$ ligands on a relevant biochemical pathway remains to be elucidated.
resulted in 2 with high σ receptor affinity but reversed selectivity. Carbamate 2 displays a 30-fold preference for the σ₂ subtype, which binds 2 in the low nanomolar range (Ki(σ₂) = 3.1 nM). The promising results with the bicyclic systems 1 and 2 led to the idea to use the [4.3.3]propellane system as conformationally rigid scaffold, which was decorated with appropriate substituents. Propel-lanes bearing the benzylamino moiety and the same carbamate as 2 displayed high σ₁ affinity only in case of syn,syn-configuration, i.e. both substituents have to be oriented towards the larger tetramethylene bridge. As a result carbamate syn,syn-3 shows moderate σ₁ affinity (Ki = 77 nM) with retaining selectivity over the σ₂ subtype. Among all diastereomers, the syn,syn-configured diastereomer syn,syn-3 has the longest distance of 11.1 Å (global energy minimum) between the basic amino moiety and the center of the phenyl ring (see Fig. 1). Compared with the lead compounds 1 and 2 this distance is rather long. Pharmacophore models also suggest a slightly shorter distance than calculated for syn,syn-3. In order to learn more about the correlation between the distances of the pharmacophoric elements and σ receptor affinity and subtype selectivity, 3-aza[4.4.3]propellanes 4 containing the basic N-atom within the framework were envisaged. In addition to reduced distances of the pharmacophoric elements, the conformational flexibility of 4 is further reduced by incorporating the N-atom into the propellane core. (Fig. 1)

Herein, we report on the synthesis and pharmacological evaluation of novel σ receptor ligands 4 based on the 3-aza[4.4.3]propellane scaffold.

2. Chemistry

The synthesis of the carbamates 4b started with propellane-8,11-dione (5), which was obtained by a Weiss-Cook reaction as previously described. In 1983 Ginsburg et al. reported their attempts to synthesize azapropellanes from diketone 5 via Beckmann rearrangement. However, all conditions to rearrange the corresponding bis-oxime failed to give an aza- or diazapropellane. Therefore, the rearrangement of propellane derivatives with only one carbonyl moiety was envisaged.

Selective reduction of only one of the keto groups of 5 with NaBH₄ led to a 1:1 mixture of diastereoisomeric alcohols syn-6 and anti-6, which could not be separated by flash chromatography. Therefore, the diastereomeric alcohols syn-6 and anti-6, were prepared by acetalization of one carbonyl moiety of diketone 5. L-Selectride reduction of the free ketone, separation of the diastereomeric alcohols and cleavage of the ethylene ketal (Scheme 1). Recrystallization of syn-7 led to colorless crystals, which were suitable for X-ray crystal structure analysis. (Fig. 2) Both enan-tiomers of syn-7 are present in the unit cell of the crystals. Pairs consisting of two molecules with the same absolute configuration are formed by two H-bonds between the NH-proton and the car-
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