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1-Amino-4,4-difluorocyclohexanecarboxylic acid as a promising building block for drug discovery: design, synthesis and characterization

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ABSTRACT

1-Amino-4,4-difluorocyclohexanecarboxylic acid has been designed as a fluorinated analogue of the pharmacologically relevant 1-aminocyclohexanecarboxylic acid. The synthesis has been performed in three steps from a commercially available material in 22% overall yield. An impact of fluorine atoms on conformation, lipophilicity, acidity and fluorescent properties of the amino acid has been studied. Various practical applications of the obtained compound are suggested.

1. Introduction

1-Aminocyclohexanecarboxylic acid (**1**) is a non-proteinogenic quaternary α-amino acid, which has gained much application in peptide chemistry[1] and drug discovery.[2,3] The interest to this compound is caused by several reasons. First, amino acid **1** is intrinsically conformationally restricted due to both the cyclic ring and the quaternary α-carbon atom.[4] Conformationally restricted compounds, due to fixation of functional groups in a biologically active conformation, are often more efficient and selective ligands for various targets compared to their non-restricted analogues.[5] Second, structure **1** is symmetric and therefore achiral, so that there is no need to additionally prepare the optically active compounds in the medicinal structure–activity relationship studies. Also, the saturated cyclohexane core ensures that derivatives of **1** are lipophilic, which is an important property of oral drugs.[6] It is not surprising therefore, that ~150 pharmacologically relevant derivatives of amino acid **1** are currently known.[3] Among them are the commercialized antibiotic Cyclacillin,[7] antineoplastic Spiromustine[8] and antiosteoporosis agents Balicatib[9] and L-006235[10] (Fig. 1).

Substituted cyclohexanes are often metabolically labile due to rapid enzymatic hydroxylation at C(4) (Fig. 2).[11] This problem, however, can be solved by replacing the 4-CH_2 group with a 4-CF_2 fragment. Incorporation of fluorine atoms into the cyclohexane ring prevents its oxidative degradation, since the C–F bond (116 kcal/mol) is significantly stronger than the C–H bond (99 kcal/mol).[12,13]

Several examples of this concept are outlined in Fig. 3. Neurokinin-2 antagonist **2**,[14] antiosteoporosis agent **3**[15] and bradykinin B_1 antagonist **4**[16] recently reached the preclinical/clinical trials. In all cases, incorporation of fluorine atoms into the cyclohexane ring prevented the initially observed metabolic hydroxylation at 4-CH_2.[17] It is also worth mentioning that introduction of the difluoro-unit into the launched antiretroviral drug Maraviroc, along with improving the metabolic profile, additionally reduced the compound's toxicity.[18]

Given the high pharmaceutical potential of amino acid **1** and sensitivity of substituted cyclohexanes to metabolic hydroxylation at 4-CH_2, fluorinated building block **5** (Fig. 4) seems to be conceptually useful for drug discovery projects. Importantly, incorporation

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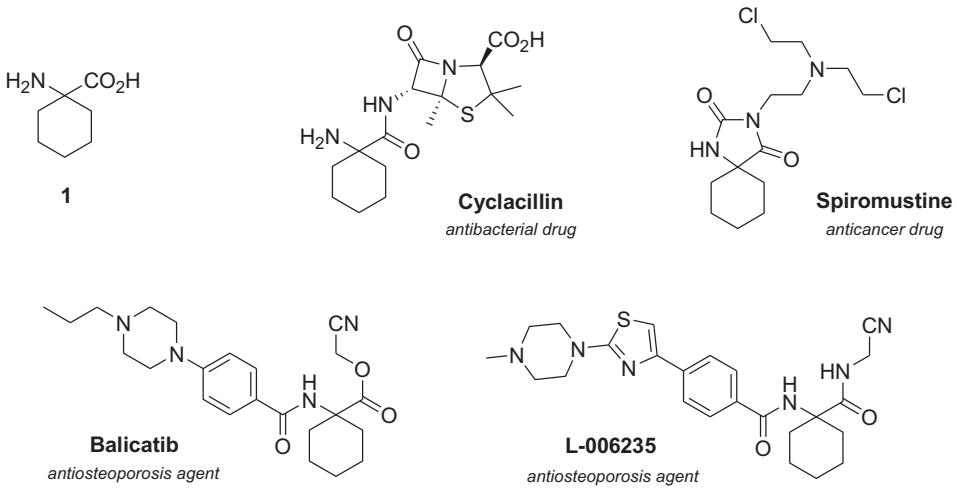

Fig. 1. 1-Aminocyclohexanecarboxylic acid (**1**) and its bioactive derivatives: Cyclacillin (antibacterial drug, *Wyeth*, 1979), Spiromustine (anticancer drug, *National Cancer Institute*, 1987), Balicatib (antiosteoporosis agent, *Novartis*, 2006), L-006235 (antiosteoporosis agent, *Merck*, 2005).[7–10]

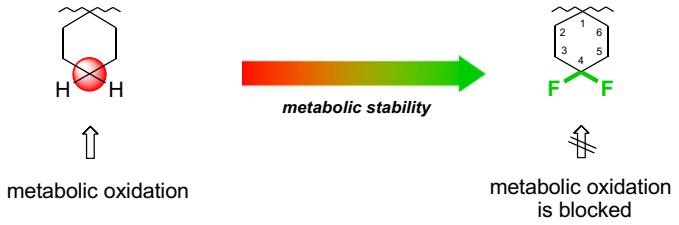

Fig. 2. Comparison of metabolic stabilities of cyclohexane and 4,4-difluorocyclohexane motifs.

of two fluorine atoms into amino acid **1** at C(4) preserves its achiral structure. Preparation of compound **5**, however, is not described in the open literature. Only the synthesis of a derivative of **5** is briefly mentioned in a recent patent[19] starting from a rather exotic non-commercially available starting material. Neither the detailed experimental procedures, nor the full compound characterizations are provided. In the present work, therefore, the practical synthesis of amino acid **5**[20] from a commercially available starting compound has been developed. An impact of fluorine atoms on the conformation, lipophilicity, acidity and fluorescent properties of the amino acid has also been studied.

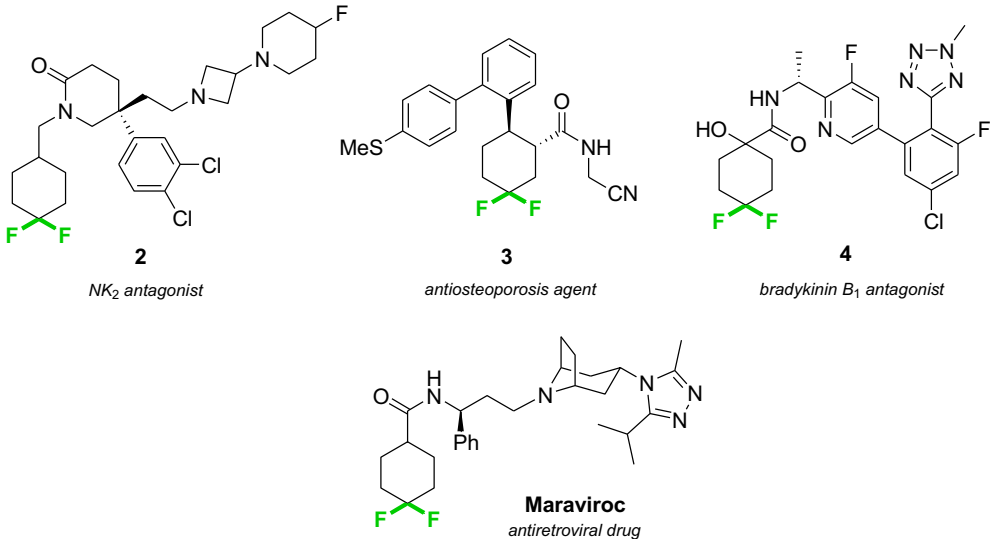

Fig. 3. Pharmacologically relevant compounds with 4,4-difluorocyclohexane motif: neurokinin-2 antagonist **2** (*Pfizer*, 2005); antiosteoporosis agent **3** (*Merck*, 2006); bradykinin B_1 antagonist **4** (*Merck*, 2008); antiretroviral drug Maraviroc (*Pfizer*, 2007).

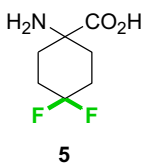

Fig. 4. 1-Amino-4,4-difluorocyclohexanecarboxylic acid (**5**).

2. Results and discussion

2.1. Retrosynthetic analysis

In a search for a convenient starting point for the synthesis of amino acid **5**, we pointed our attention to the substituted cyclohexanone **6**. This compound contained two carbonyl groups at the needed C(1) and C(4) positions of the cyclohexane ring. Moreover,