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Benzo[*b*]thiophene-2-carboxamides and benzo[*b*]furan-2-carboxamides are potent antagonists of the human H_3-receptor

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Abstract—Benzo[*b*]thiophene-2-carboxamides and benzo[*b*]furan-2-carboxamides have been found to be antagonists on the human histamine-3-receptor, showing a K_i value of as low as 4 nM.

The H_3-receptor was first discovered in 1983 in rats.[1] and subsequently a human variant (hH_3) has been identified and cloned.[2] It is a presynaptic receptor located on histaminergic neurons, and it has been suggested that a functional H_3-antagonist could be beneficial for the treatment of, for example, attention deficit hyperactivity disorder, epilepsy, obesity, or Alzheimer's disease.[3] For this reason a number of projects have been initiated in several pharmaceutical companies to identify compounds, which ultimately could be used as potential drugs against these ailments.[4]

In recent years, a number of non-imidazole-containing H_3-antagonists have been developed.[5–19] One of them was **NNC 0038-0000-1202** (Fig. 1),[20] which was studied both in vitro and in vivo.[21] In order to expand our knowledge about the structure–activity relationship (SAR) of compounds of this type, we wondered whether a ring closure over the cinnamic double bond could lead to equally potent H_3-antagonists. In this context, we considered benzo[*b*]thiophene-2-carboxylic acids, benzo[*b*]furan-2-carboxylic acids, or quinoline-3-carboxylic acid to be ring-closed analogues of cinnamic acids as used in **NNC 0038-0000-1202**.

Besides a number of commercially available benzo[*b*]-thiophene-2-carboxylic acids and benzo[*b*]furan-2-carboxylic acids, we also wanted to incorporate trifluoromethyl- and trifluoromethoxy-substituted acids. These

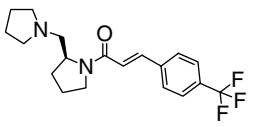

Figure 1. NNC 0038-0000-1202, K_i = 4.7 (±0.4) nM.

types of substituents have proven to influence the hepatic metabolic stability of compounds[22–24] and have been used successfully in **NNC 0038-0000-1202** and its analogues.[20] Aldehydes **3a**–**c** were used as key intermediates in the preparation of this type of compounds. Employing the described synthesis strategy for aldehyde **3a**.[25] we prepared the other two aldehydes **3b** and **3c** as depicted in Scheme 1. Starting with commercially available phenols **1b**,**c**, tetrahydropyran moieties (THP) were attached to the hydroxyl-groups. The THP moieties on compounds **2a**–**c** were utilized as directing groups in directed metallation reactions with *n*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). The intermediates were quenched with DMF to provide the aldehydes **3a**–**c**.[25] It is noteworthy that the reaction with THP-ether **2b** yielded only small amounts of the desired aldehyde because the lithiated species was not stable at −10 °C. Interestingly, starting with THP-ether **2c**, only one of the two possible regioisomeric aldehydes was isolated. Cyclization with diethyl bromomalonate[26] furnished esters **4a**–**c** and the corresponding carboxylic acids **5a**–**c**[27] were obtained after saponification employing standard conditions. 5-Cyanobenzo[*b*]furan-2-carboxylic acid was prepared as described in the literature.[28,29]

Having a number of acids available, we turned our attention to the amine part of the possible H_3-antago-

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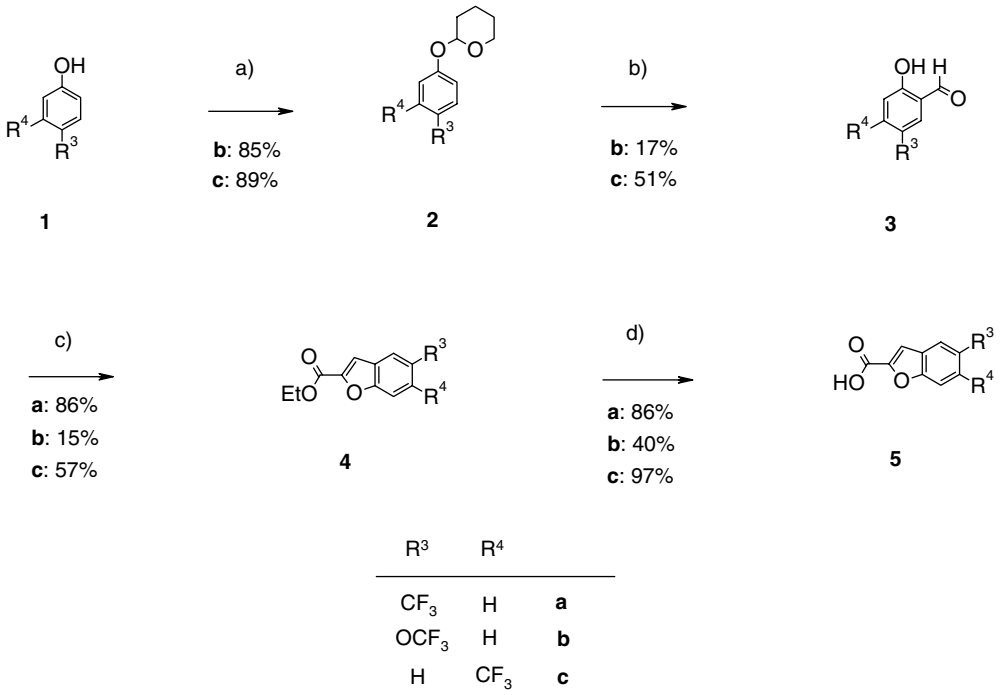


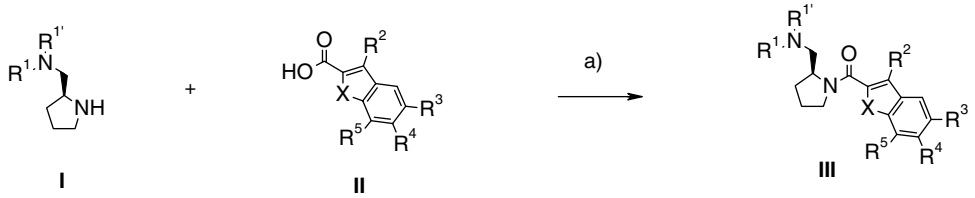
Scheme 1. Reagents and conditions: (a) 3,4-dihydro-2*H*-pyrane, anhydrous HCl, CH_2Cl_2; (b) i—*n*-BuLi, TMEDA; ii—DMF; (c) EtOOCCHBr-COOEt, K_2CO_3, MEK, Δ; (d) LiOH dioxane/H_2O.

nists. We selected the (*S*)-2-aminomethylpyrrolidines,[30] which already had been used for the series of cinnamic amides, and which were prepared as described in the literature[20] from proline. The coupling of acids and amines was easily accomplished by reaction with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) in the presence of 3,4-dihydro-3-hydroxy-1,2,3-benzotriazin-4-one (DHOBt) and DIPEA, as depicted in Scheme 2. Hence in a few steps, the compounds **5**–**16** were isolated and subsequently screened for antagonism at the hH_3-receptor, utilizing a [^{35}S]GTPγS-assay.[2,31]

As indicated in Table 1, all prepared benzo[*b*]thiophene and benzo[*b*]furan derivatives proved to be highly potent antagonists at the hH_3 receptor. Benzo[*b*]thiophene carboxamides, for example, compound **5**, which comprises the unsubstituted benzo[*b*]thiophene carboxamide scaffold, exhibited a K_i value of 4 nM. Substitution with chlorine in the 3-position reduced the potency only very slightly, as can be seen from the results of compound **6**.

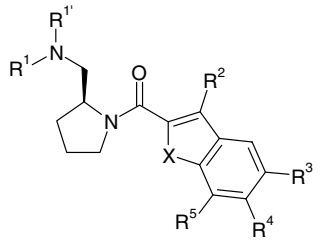
Also, several benzo[*b*]furan-2-carboxamides prepared in the series were at least equipotent to the lead compound **NNC 0038-0000-1202** that showed a K_i value of 11 nM.[20] Generally, all compounds which were substituted at the 5-position with trifluoromethyl (compounds **8**–**10**), trifluromethoxy (compound **11**) or cyano (compound **12**) were highly potent hH_3-antagonists with K_i values between 4 and 14 nM. On the other hand, compounds substituted at the 6-position were less potent than the corresponding 5-substituted analogues. This becomes obvious when the potency of the respective pairs of amides **8/13**, **9/14**, and **10/15** is compared to each other. The 7-ethoxy-substituted benzo[*b*]furan-2-carboxamide **16** exhibits, with a K_i of 17 nM, a similar potency to the 5-trifluoromethyl-substituted compound **13**.

However, somewhat surprising was the influence of the amine moiety on the potency of the compounds. A comparison of potency within the series of compounds **8**–**10** which differ only in the amino moiety and all bear a trifluoromethyl group in the 5-position of the benzo[*b*]furan moiety, and within the regioisomerical series of compounds **13**–**15** reveals that in both series the amides of (pyrrolidinomethyl)pyrrolidine are the most potent ones, but with rather little difference between the potency of all tested compounds. In part, this had been expected: in the cinnamic amide series, no significant



Scheme 2. –X– = –O–, –S–, and –CH=N–. Reagents: (a) EDAC, DHOBt, DIPEA.

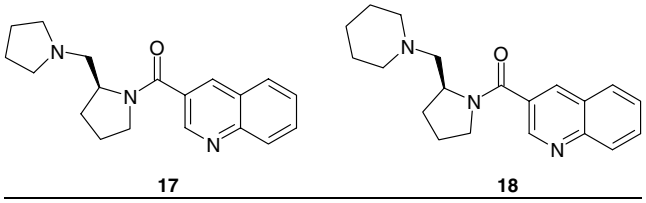
Table 1. hH_3-potency of compounds **5**–**16**



Compound	R^1	$R^{1'}$	R^2	R^3	R^4	R^5	X	K_i[a] (nM)
5	$-(CH_2)_4-$		H	H	H	H	S	4 (±0.44)
6	$-(CH_2)_4-$		Cl	H	H	H	S	12 (±0.88)
7	$-(CH_2)_4-$		H	Cl	H	H	O	5 (±0.64)
8	$-(CH_2)_4-$		H	CF_3	H	H	O	4 (±0.81)
9	$-(CH_2)_5-$		H	CF_3	H	H	O	7 (±1.1)
10	Et	Et	H	CF_3	H	H	O	14 (±0.58)
11	$-(CH_2)_4-$		H	OCF_3	H	H	O	11 (±0.70)
12	$-(CH_2)_4-$		H	CN	H	H	O	5 (±0.50)
13	$-(CH_2)_4-$		H	H	CF_3	H	O	15 (±1.5)
14	$-(CH_2)_5-$		H	H	CF_3	H	O	22 (±2.9)
15	Et	Et	H	H	CF_3	H	O	46 (±12)
16	$-(CH_2)_4-$		H	H	H	OEt	O	7 (±1.1)

[a] [^{35}S]GTPγS-assay, mean of three experiments.

Table 2. hH_3-potency of quinoline-3-carboxamides



17 **18**

Entry	**17**	**18**
K_i[a] (nM)	>150	>150

[a] [^{35}S]GTPγS-assay, mean of three experiments.

difference was found between (pyrrolidinomethyl)pyrrolidino- and the (piperidinomethyl)pyrrolidino-analogues either. However, the strong potency of the amides of ((diethylamino)methyl)pyrrolidine **10** and **15** would not have been predicted from the rather weakly potent analogues in the cinnamic amide series.

In general, we concluded that the compounds in the benzo[*b*]thiophene and in the benzo[*b*]furan series all showed quite interesting potency, independently of the nature of the substitutent, acknowledging, that only a very narrow variety of substituents were investigated.

A different scenario was found for the quinoline-3 carboxamides **17** and **18** (Table 2). These compounds were not potent toward the hH_3-receptor. The reason for this dramatic drop in potency can be explained in two possible ways. One explanation could be the ring size, having enlarged the ring from a five-membered ring in compounds **5**–**16** to a six-membered ring in compounds **17** and **18**. Another possibility could be the added polarity of the nitrogen in the quinoline ring, which was not present in compounds of the cinnamic amide series, such as in lead compound **NNC 0038-0000-1202**, or in the ring-closed benzo[*b*]thiophene or benzo[*b*]furan analogues **5**–**16**.

We have synthesized new substituted benzo[*b*]furan-2-carboxylic acids, which were incorporated in the amide template as ring-closed analogues of the cinnamic amide lead compound **NNC 0038-0000-1202**. The compounds exhibited competitive potencies as antagonists on the hH_3-receptor. Substitutions with electron-withdrawing groups such as trifluoromethyl or a trifluoromethoxy group were tolerated at positions 5 and 6 of the benzo[*b*]furan-scaffold. In contrast to what had been predicted from the results of the cinnamic amides, compound **10**, which is an amide of (*R*)-2-((diethylamino)methyl)pyrrolidine exhibited with a K_i of 14 nM a quite interesting potency on the hH_3-receptor in the [^{35}S]GTPγS-assay. However, amides of quinoline-3-carboxylic acid did not yield potent hH_3-antagonists.

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