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Ureas with histamine H_3-antagonist receptor activity—A new scaffold discovered by lead-hopping from cinnamic acid amides

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Abstract—A group of tri and tetrasubstituted urea derivatives have been found to be hH_3-antagonists. The most potent compounds were found in the class of (piperazine-1-yl)-(piperidine-1-yl)-methanones which in addition showed negligible hERG inhibition.
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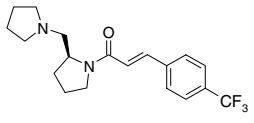
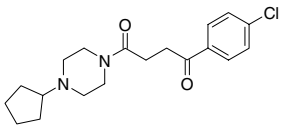
During the past few years, a plethora of novel structures with histamine H_3-interactions have been published.[1] In contrast to early generations of H_3-ligands which are derived from histamine itself and still contain an imidazole moiety, these new compounds are much more drug-like and hold some promise to also be of use in a clinical setting, for indications such as obesity and cognitive disorders.[2]

However, while the H_3-receptor is a target, for which selective and in vitro potent ligands have been detected quite readily, overcoming ADMET-issues is still a challenge for many of these substances,[3] and only a few candidates have yet reached clinical phases of development.

An earlier detected structural class of H_3-antagonists, the cinnamic acid amides, exemplified by NNC 0038-0000-1202,[4] bears the potential risk of chemical and metabolic instability due to the reactivity of the double bond. Moreover, many of these compounds have shown substantial hERG-channel inhibition.



0038-0000-1202
K_i hH3 = 4.7 nM (± 0.4)



0038-0000-1049
K_i hH3 = 1.2 nM (± 0.1)

In an attempt to overcome the hERG-channel inhibition related to the cinnamic acid amides, we decided to explore the possibilities of scaffold-hopping from this series. Information about the SAR from the old series provided a good basis for the design of new compounds. Since hERG inhibition is known to correlate with lipophilicity[5,6] we proposed the replacement of the C=C in the cinnamic acid amide with an N–C fragment leading to a more polar scaffold possessing a urea moiety.

Previously, urea containing H_3-antagonists were reported. However, the presence of the imidazole moiety was crucial for H_3-activity.[7] During the preparation of this manuscript two patent applications describing imidazole-free urea derivatives as H_3-antagonists were published.[8]

To facilitate high throughput chemistry, a solid-phase parallel synthesis protocol was developed to generate libraries of trisubstituted ureas, bearing similar substitution as the original cinnamic acid amides.[9] Commercially available 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene was treated with a variety of amines under standard reductive amination conditions[10] to give the resin bound secondary amine **1** (Scheme 1). Subsequent treatment with triphosgene and base followed by reaction with a secondary amine yielded the resin bound urea **2**. The products were cleaved from the resin using trifluoroacetic acid, to give the crude urea derivatives **3** in an average purity of 92%.[11] The crude products were purified by preparative HPLC to give the final products as their respective triflu-

Keywords: Histamine H_3 receptor; hH_3-receptor; Urea; hERG.
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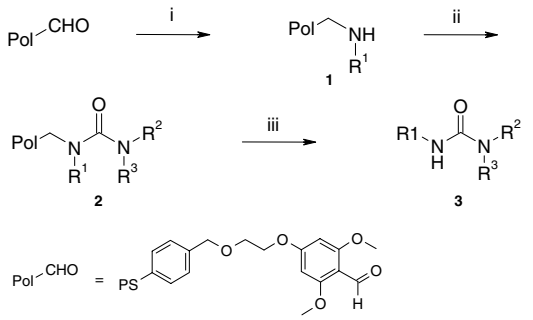


Scheme 1. Reagents and conditions: (i) 10 equiv R^1NH_2, 15 equiv $NaBH_3CN$, NMP/MeOH, 10% AcOH; (ii) a—3 equiv $CO(OCCl_3)_2$, DIPEA, DCM; b—10 equiv HNR^2R^3, NMP (iii) TFA/DCM (1:1).

oroacetic acid salts in overall yields typically between 35 and 75%.

Already in the first library, compounds with moderate H_3-potency[12] were found. Early indications after comparison of the ureas and cinnamic acid amides data showed the generally poorer potency of the ureas. Hence, the most potent urea derivative **3d** (K_i = 87 nM) is 24 times less potent than the corresponding cinnamic amide analog **9** (K_i = 3.7 nM) (Table 1).

We were however encouraged by the relative low hERG-channel inhibition of the 4-trifluoromethyl substituted urea derivative **3a** (20%)[13] compared to the respective cinnamic acid amide analog NNC-0038-0000-1202 (73%), therefore it was decided to further explore this new series of H_3-antagonists.

More than 300 trisubstituted urea derivatives were made but only minor improvement in H_3-potency was obtained. The SAR suggests a slight preference of 3- versus 4-substituted benzyl groups as exemplified by the 3-methoxy-, 3-aminomethyl-, and 3-trifluoromethylbenzyl derivatives that are all slightly more potent than the corresponding 4-substituted analogs (Table 2).

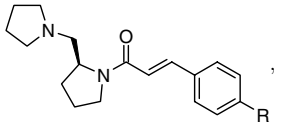
The presence of the aromatic ring is essential in this series, as most of the H_3-potency is lost when benzyl is replaced by a cyclohexyl methyl group in **3m**. Replacing the benzyl (**3e**, 196 nM) with a 2-phenylethyl substituent (**3n**, 226 nM) did not change the H_3-potency significantly, but constraining the phenylethyl group as in the indanyl analog **3o** gives rise to a more potent compound (K_i = 52 nM). The most potent ureas of pyrrolidinylmethylpyrrolidines were compounds **3k** and **3l** with K_i of 34 and 47 nM, respectively. Unfortunately, both showed unacceptable high inhibition of the hERG-channel, which was assessed to be 62 and 40%, respectively.

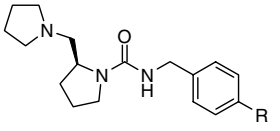
We have previously been working on a series of piperazine amides[14] represented by 0038-0000-1049. This prompted us to incorporate an alkylpiperazine moiety instead of the pyrrolidinylmethylpyrrolidine building block. Representative examples of the second series of ureas, bearing alkylpiperazine instead of pyrrolidinylmethylpyrrolidine, are shown in Table 3. A comparison of these two series shows that the alkylpiperazines generally are slightly more potent than their equally substituted counterparts. Hence, the two 3,4-dichlorobenzyl substituted cyclopentyl- and isopropylpiperazine derivatives **3x** and **3y** (15 and 20 nM, respectively) are more potent than the pyrrolidinylmethylpyrrolidine bearing the same 3,4-dichloro-benzyl group (47 nM). Another observation was that in all the piperazine ureas investigated, the potency is only minimally affected by various alkyl substitutions on the piperazine ring.

To further explore the scope of urea derivatives as H_3-antagonists, a parallel protocol for the synthesis of tetrasubstituted ureas was established (Scheme 2). A secondary amine was treated with CDI in DCM to give the carbamoylimidazole **4**.[15] Methylation using methyliodide gave the reactive intermediate **5** that subsequently was treated with a secondary amine to give the tetrasubstituted urea derivative **6**. Purification by HPLC yielded the final products as their trifluoroacetate salts in yields typically between 70 and 75%.[16]

The simple introduction of an *N*-methyl group gave less potent compounds, as exemplified by entry **6a** (281 nM) (Table 4) versus the non-methylated analog **3d** (87 nM). However, incorporation of both urea nitrogens in rings showed promising results, especially in the piperazine series. Consequently, efforts were concentrated around

Table 1. Comparison of hH_3-potency and hERG inhibition of cinnamic acid amides and the corresponding urea analogs[20]

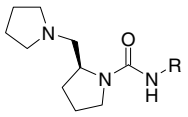


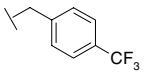
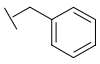
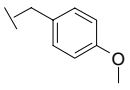
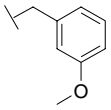
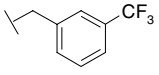
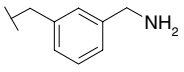
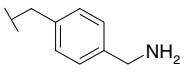
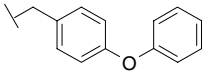
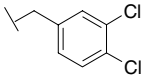
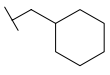
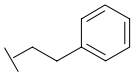
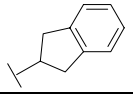


R	Entry	K_i (nM) ± SEM[a]	hERG-inhibition[b] (%)	Entry	K_i (nM) ± SEM[a]	hERG-inhibition[b] (%)
$-CF_3$	**NNC 0038-0000-1201**	4.7 (±0.4)	73	**3a**	162 (±14)	20
–Cl	**7**	11.2 (±1.4)	n.d.	**3b**	165 (±24)	n.d.
$-OCF_3$	**8**	13.4 (±1.9)	n.d.	**3c**	121 (±17)	n.d.
–Ph	**9**	3.7 (±1.3)	n.d.	**3d**	87 (±15)	n.d.

[a] hH_3-[^{35}S]GTPγ[S] binding assay (n = 3).
[b] Astemizol binding, % inhibition (mean, n = 3) at 10 μM.

Table 2. hH_3-potency of pyrrolidinylmethylpyrrolidine-ureas[20]

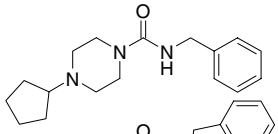
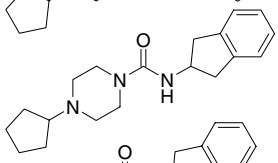
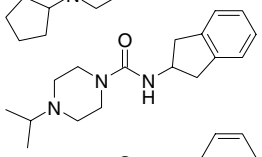
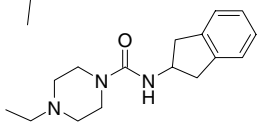
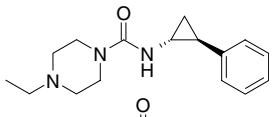
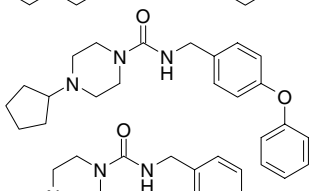
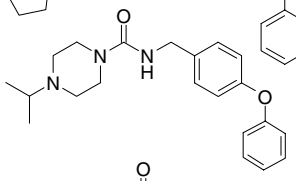
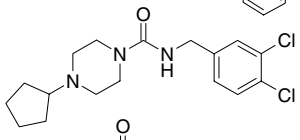
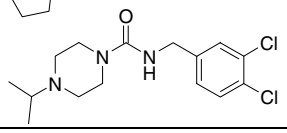


Entry	R	K_i[a] (nM)
3a		162 (±14)
3e		196 (±29)
3f		295 (±19)
3g		188 (±31)
3h		117 (±11)
3i		78 (±9)
3j		109 (±10)
3k		34 (±4)
3l		47 (±7)
3m		458 (±23)
3n		226 (±8)
3o		52 (±10)

[a] hH_3-[^{35}S]GTPγ[S] binding assay.

this scaffold. A small series of compounds bearing a dihydroindole moiety, entries **6d**, **6e**, and **6f**, showed notable increase in potency when incorporating the alkylpiperazine moiety. H_3-potency is highest with the more lipophilic cyclopentyl substituted derivative **6f**, but much more important is the finding, that the cyclopropyl group causes **6e** to be the one with the lowest hERG-channel inhibition (16% inhibition). Since hERG

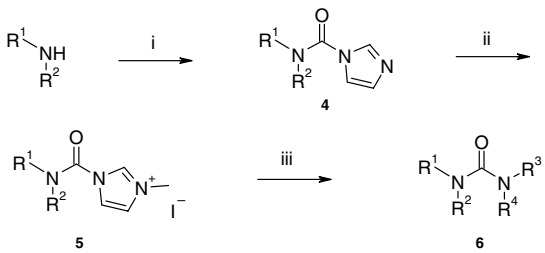
Table 3. hH_3-potency of alkylpiperazine-ureas[20]

Entry		K_i[a] (nM)
3p		94 (±3)
3q		29 (±4)
3r		30 (±6)
3s		44 (±10)
3t		40 (±9)
3u		38 (±6)
3v		34 (±8)
3x		15 (±4)
3y		20 (±2)

[a] hH_3-[^{35}S]GTPγ[S] binding assay.

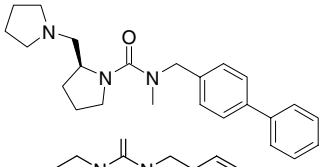
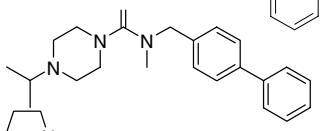
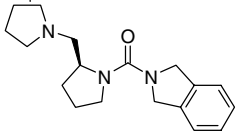
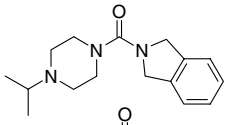
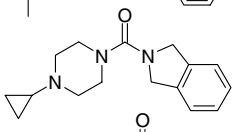
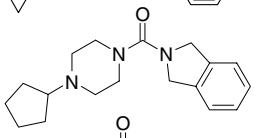
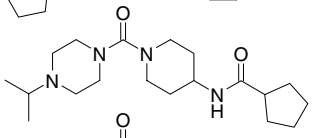
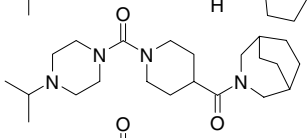
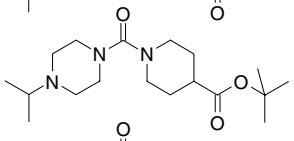
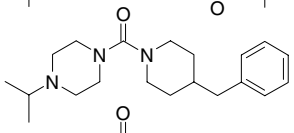
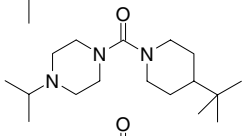
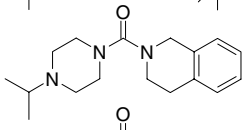
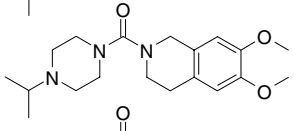
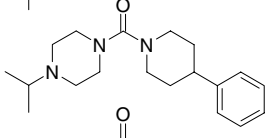
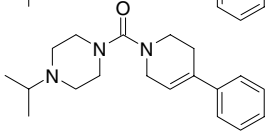
inhibition is also known to decrease with decreasing basicity the observed effect is probably caused by the lower basicity of the *N*-cyclopropylpiperazine.[17,18]

A group of quite potent ureas were the (piperazine-1-yl)-(piperidine-1-yl)-methanones. Surprisingly some of these show potent H_3-activity despite the lack of an aromatic group, as exemplified in entries **6h** and **6i** (K_i = 17 and



Scheme 2. Reagents and conditions: (i) 1.1 equiv CDI, DCM; (ii) 10 equiv MeI, MeCN, (iii) 1 equiv HNR^3R4, DIPEA, DCM.

Table 4. hH_3-potency and hERG inhibition of tetrasubstituted ureas[20]

Entry		K_i[a] (nM)	hERG % inhibition[b]
6a		281 (±49)	66
6b		37 (±8)	55
6c		94 (±14)	26
6d		59 (±11)	34
6e		45 (±5)	16
6f		23 (±5)	45
6h		17 (±3)	6
6i		14 (±3)	8
6j		25 (±5)	9
6k		14 (±3)	21
6l		47 (±10)	13
6m		73 (±18)	8
6n		16 (±3)	8
6o		86 (±16)	16
6p		27 (±7)	31

[a] hH_3-[^{35}S]GTPγ[S] binding assay ($n = 3$).
[b] Astemizol binding, % inhibition (mean, $n = 3$) at 10 μM.

14 nM, respectively). Moreover, all aliphatic derivatives had a low propensity of hERG- as well as CYP-inhibition. Hence the aliphatic derivatives **6h**, **6i**, **6j**, and **6l** show 6, 8, 9, and 13% hERG-channel inhibition, respectively, at 10 μM. The same compounds all gave IC_{50} values >25 μM on CYP1A2, CYP3A4, and CYP2D6.[19] The only exceptions were **6h** and **6l** that gave IC_{50} values of 17 and 7 μM, respectively, on CYP2D6.

In conclusion, we have developed a new series of urea H_3-antagonists. The most potent compounds are found in the class of (piperazine-1-yl)-(piperidine-1-yl)-methanones which in addition give negligible hERG interaction.

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9. General procedure for the solid-phase parallel synthesis of trisubstituted ureas exemplified with the synthesis of the trifluoroacetate salt of (4-ethyl-piperazin-1-yl)-(indane-2-amine-yl)-methanone (**3s**). A solution of 2-aminoindane (200 mg, 1.5 mmol) in NMP (1.0 mL) was added to 2-(3,5-dimethoxy-4-formyl-phenoxy)-ethoxymethyl polystyrene resin (100 mg, 0.12 mmol) pre-swollen in NMP followed by a solution of $NaBH_3CN$ (94 mg, 1.5 mmol) in MeOH (0.5 mL). After addition of AcOH (150 μL), the mixture was agitated for 18 h at room temperature. Excess reagent and solvent were removed by filtration and the resin was washed with NMP (3×1 mL), MeOH (1×1 mL), DCM (1×1 mL), and DCM/DIPEA (9:1, 1 mL). DIPEA (204 μL, 1.2 mmol) in DCP (0.5 mL) was added to the resin and the mixture was shaken for 5 min before triphosgene (107 mg, 0.36 mmol) in DCP (1.0 mL) was added and the reaction mixture was agitated for 16 h before the excess reagent and solvent were removed by filtration. The resin was washed with DCM (3×1 mL) before *N*-ethyl-piperazine (137 mg, 1.2 mmol) was added. The mixture was agitated for 18 h before it was filtered and washed in sequence with NMP (3×1 mL), DCM (3×1 mL), MeOH (1×1 mL), and DCM (3×1 mL). The resin was subsequently cleaved with TFA/DCM (1:1, 1 mL) for 1 h at room temperature before the cleavage mixture was filtered. The resin was washed with DCM (1 mL) and filtered. The filtrates were combined and concentrated in vacuo. The crude product was purified by preparative HPLC to give the trifluoroacetate salt of (4-ethyl-piperazin-1-yl)-(indane-2-amine-yl)-methanone (**3s**). Yield 23 mg (50%). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.61 (br s, 1H), 7.22–7.17 (m, 2H), 7.16–7.10 (m, 2H), 6.92 (d, 1H, $J = 6.7$ Hz), 4.43–4.32 (m, 1H), 4.18–4.03 (m, 2H), 3.53–3.35 (m, 2H), 3.19–3.07 (m, 4H), 3.06–2.94 (m, 2H), 2.94–2.85 (m, 2H), 2.85–2.76 (2H), 1.21 (t, 3H, $J = 6.9$ Hz) ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (ppm) 158 (q, $^1J_{CF} = 31.5$ Hz), 156.6, 141.3, 126.2, 124.3, 51.7, 50.7, 50.1, 40.6, 39.1, 8.8 HPLC–MS: $m/z = 274$ (M+1) MA; calcd for $C_{16}H_{23}N_3O \cdot C_2HF_3O_2$: C 55.81%; H 6.24%; N 10.85%, found: C 55.74%; H 5.97%; N 10.71%.
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12. For a detailed description of determination of H_3-binding using a hH_3-[^{35}S]GTPγ[S] binding assay ($n = 3$), see Ref. 4.
13. The ability of test compounds to bind to the hERG-channel was assessed by [^{3}H]Astemizole binding to hERG transfected HEK293 cell membranes essentially as described by Chiu et al. (*J. Pharmacol. Sci.* **2004**, *95*, 311–319). All binding assays were performed in a total volume of 100 μL: 60 μL buffer (10 mM Hepes, 5 mM KCl, 130 mM NaCl, 0.8 mM $MgCl_2$, 1 mM EGTA, 10 mM glucose, and 0.01% BSA, pH 7.4) containing 10 μg membrane, 20 μL test drug or vehicle (in buffer containing 5% DMSO), and 20 μL [^{3}H]Astemizole (15 nM in buffer). Non-specific binding (NSB) was defined by 10 μM Astemizole (FAC). Incubation was conducted in 96-well polypropylene plates at 25°C for 60 min. Binding was terminated by rapid filtration using a FilterMate Harvester (Packard) onto GF/B filters, presoaked with 0.3% polyethyleneimine, followed by rapid washing with 10 × 300 μL ice-cold washing buffer (25 mM Tris–HCl, 5 mM KCl, 130 mM NaCl, 0.8 mM $MgCl_2$, 0.05 mM $CaCl_2$, and 0.01% BSA, pH 7.4). After drying of plates and addition of 50 μL MicroScint 0 (Perkin-Elmer), captured radiolabel was detected using a Perkin-Elmer TopCount NXT. Results are presented as percent inhibition of [^{3}H]Astemizole binding at 10 μM. Using the conditions described above the IC_{50} values of the following compounds were determined; Bepridil 444 (±39) nM; Pimozide 42 (±2) nM; Haloperidol 512 (±72) nM, and Thioridazine 869 (±170) nM.
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16. General procedure for the parallel synthesis of tetrasubstituted ureas exemplified with the synthesis of the trifluoroacetate salt of (4-isopropyl-piperazin-1-yl)-(4-phenyl-piperidin-1-yl)-methanone (**6o**). 4-Phenyl-piperi-

dine (81 mg, 0.5 mmol) in DCM (5 ml) in a test tube with magnetic stirring was added CDI (89 mg, 0.55 mmol). The reaction mixture was stirred for 18 h at room temperature before it was washed with water (2×2 mL). The phases were separated using phase separation tubes from Radley. The volatiles were removed in vacuo and the residue was re-dissolved in MeCN (10 ml). MeI (5 mmol, 709.7 mg) was added and the reaction mixture was stirred for 18 h at room temperature. The volatiles were removed in vacuo and the residue was re-dissolved in DCM (10 ml) whereupon 1-isopropyl-piperazine (64 mg, 0.5 mmol) and triethylamine (70 ml, 0.5 mmol) were added. The reaction mixture was stirred for 18 h at room temperature before the solvent was removed in vacuo. THF (3 mL) and water 300 μL were added and the mixture was purified on preparative HPLC to give the trifluoroacetate salt of (4-isopropyl-piperazin-1-yl)-(4-phenyl-piperidin-1-yl)-methanone (**6o**). Yield 144 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36–7.27 (m, 2 H), 7.25–7.16 (m, 3H), 3.92–3.70 (m, 4H), 3.68–3.27 (m, 5H), 3.00–2.80 (m, 4H), 2.77–2.61 (m, 1H), 1.93–1.83 (m, 2H), 1.75–1.57 (m, 2H), 1.36 (d, 6H, $J = 6.8$) ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 162.7 (q, $^{1}J_{CF} = 35.1$ Hz), 162.8, 145.2, 128.6, 126.7, 126.5, 57.8, 47.4, 47.0, 43.8, 42.7, 33.0, 16.5 HPLC–MS: $m/z = 316$ (M+1) MA; calcd for $C_{19}H_{29}N_3O \cdot C_2HF_3O_2$: C 58.73%; H 7.04%; N 9.78%, found: C 58.69%; H 6.99%; N 9.69%.

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