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Cinnamic amides of (*S*)-2-(aminomethyl)pyrrolidines are potent H_3 antagonists

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Abstract—New imidazole-free H_3 antagonists have been found in a series of cinnamic amides of (*S*)-(aminomethyl)pyrrolidines. The influence of the substituent on the aromatic moiety on the potency and the inhibition of three cytochrome P450 subtypes are also described.

1. Introduction

Histamine plays an important role in a variety of biological processes[1,2] ranging from effects as a neurotransmitter in the central nervous system (CNS) to peripheral effects on, for example inflammatory conditions, gastric acid secretion and smooth muscle contraction. Due to its importance selective ligands have been developed for H_1, H_2 and H_3 receptors,[3] and also for the H_4 receptor,[4,5] that was recently discovered.[2]

The H_3 receptor is a presynaptic histamine receptor, which was first characterized in rats by Arrang et al.[6] in 1983. The human H_3 receptor was cloned in 1999 by Lovenberg et al.[7] Information in the literature[8] suggests that a functional antagonist of the H_3 receptor could lead to therapeutics in connection with for example, attention-deficit hyperactivity disorder, epilepsy, obesity, or Alzheimer's disease. Therefore we were interested in identifying functional H_3 receptor antagonists that are active in the CNS after oral administration.

Since its discovery selective ligands for the H_3 receptor have been found.[9] All the early ligands, such as thioperamide,[10] GT-2331,[11] FUB 470,[12] or ciproxifan[13] contained an imidazole-moiety. Only very recently, a number of new, imidazole-free H_3 antagonists have been reported,[14–24] some of them showing oral in vivo potency and favorable pharmacokinetic properties. Similarly to the reported observations in the literature, we found that imidazole-free H_3 antagonists were superior lead compounds for an orally available drug candidate,[25] compared to our previously prepared imidazole-containing H_3 antagonists.

The successful discovery of monoamides of piperazine[25] as selective and potent H_3 antagonists, inspired us to explore the possibility of including diversity in the amine part. Since the lead compounds had shown, that the constrained piperazine was highly suited, when searching for H_3 antagonists, we wanted to apply other, differently constrained diamines, rather than open-chain diamines. As a consequence of the changed topography of these amines, we expected that a change in the topography in the acid part would be necessary in order to obtain new types of H_3 antagonists.

2. Results and discussion

Two different strategies for the synthesis of the amine part were employed. In the first approach BOC-protected

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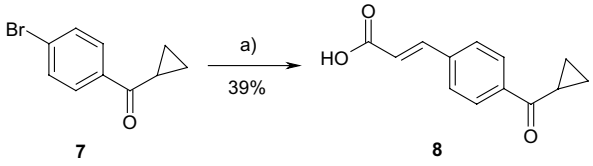
amino alcohols **I** were oxidized by Swern oxidation to the corresponding aldehydes **II**. Reductive amination with a secondary amine, followed by deprotection furnished diamines **III**, which were used for coupling with selected cinnamic acids. However, when starting from enantiomerically pure amino alcohol derivatives, this route yielded partially racemized diamines, with enantiomeric excesses of about 90% ee. Therefore, another reaction sequence was used in these examples. After forming amides **V** from BOC-protected amino acids **IV** with the corresponding amines by reaction with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) and 3-hydroxybenzotriazin-4-one (DHOBt), and removal of the BOC group, the final reduction with lithium aluminum hydride gave rise to the diamines **III** without detectable racemization.[26–30] Using either of these reaction sequences, diamines **1**, **2**, and **3** were obtained (Scheme 1).

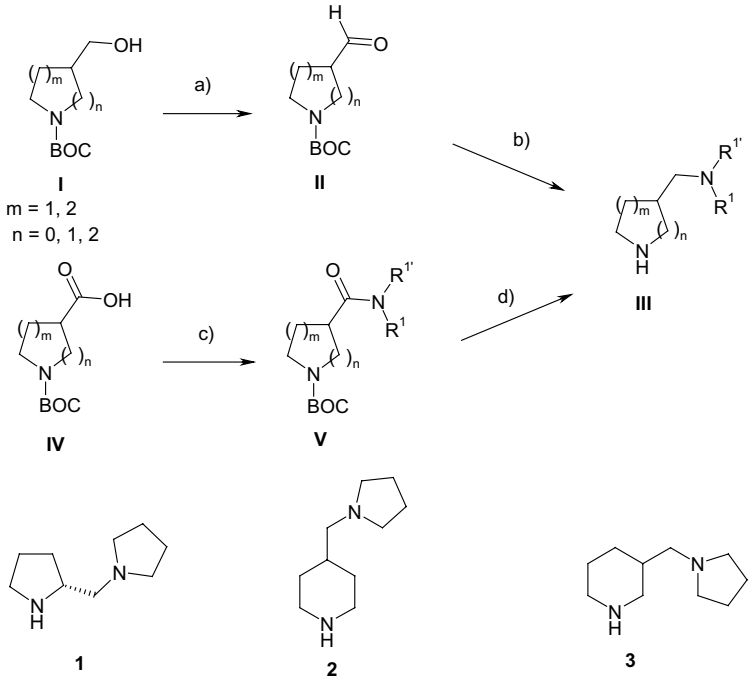
Most of the cinnamic acids were either purchased or were prepared from the corresponding aldehydes or ketones by Knoevenagel reaction with malonic acid according to the literature procedures.[31–34] All aldehydes and the ketone employed were commercially available or known.[35] Acid **6**[36] was prepared analogously from malonic acid (**4**), utilizing aldehyde **5** (Scheme 2).

A different strategy, shown in Scheme 3, was chosen for the synthesis of the cyclopropylcarbonyl-substituted cinnamic acid **8**. Starting from commercially available bromide **7**, a Heck-reaction was performed,[37] yielding a cinnamic ester, which, upon saponification with lithium hydroxide furnished cinnamic acid **8**.

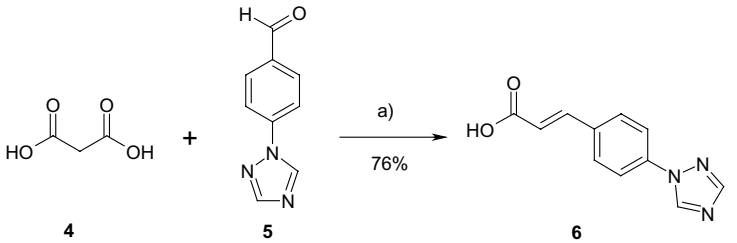
The coupling of amines **III** and cinnamic acids **VI** were performed in all cases utilizing EDAC and DHOBt as



Scheme 3. (a) (i) $Pd(PPh_3)_4$, $CH_2{=}CHCOOEt$, NEt_3; (ii) LiOH, dioxane/water.



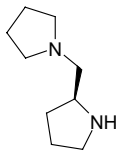
Scheme 1. (a) DMSO, $(COCl)_2$, Et_3N; (b) (i) $HNR^1\ R^{1\prime}$, $NaBH(OAc)_3$, HOAc (ii) TFA; (c) EDAC, DHOBt, Et_3N; (d) (i) TFA, (ii) $LiAlH_4$.



Scheme 2. (a) Pyridine, piperidine.

coupling reagent in the presence of an amine base, typically triethylamine, yielding cinnamic amides **VII** as depicted in Scheme 4. In cases where none racemic chiral amines had been used, enantiomerical excesses of 90–99% ee have been found in the experiments, where it was determined by capillary electrophoreses. The ^{1}H NMR characterization of the compounds **VII**, proved in most cases to be difficult, because unsymmetrically *N*,*N*-disubstituted amides resulted in two sets of signals, reflecting the two possible rotamers, which are separable on the NMR time scale. In summary, the syntheses of all test compounds **10**–**41** were accomplished in few steps, beginning with readily available starting materials. This easy access resulted in a high number of prepared amides.

Starting with the commercially available (*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidine (**9**) as a first example for a possible amine, we prepared compounds **10**–**13** by acylation with the respective acids. We chose only a limited number of acids, which we considered to be a suitable test set, in order to elucidate whether amides of amine **9** could give compounds with similar biological activity to our lead compounds from the piperazine series.[25] We were delighted to see, that amides, derived from cinnamic acids, namely amides **11** and **13**, showed potencies at the human H_3 receptor of 10 and 11 nM, respectively, in the [^{35}S]GTPγ[S] binding assay.[38] As a consequence of these positive results a further investigation based on the above amides was initiated (Fig. 1).



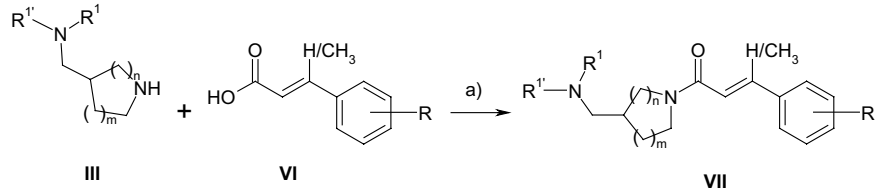
9

Figure 1.

Initially, we investigated the influence of a variation in the amine moiety on the biological potency of cinnamic amides **14**–**26**. The results of which showed, that the (pyrrolidin-1-yl)methyl side chain could be replaced by a (piperidin-1-yl)methyl side chain, as demonstrated by compounds **11**, **14**, or **15** on one hand and compounds **16**, **17**, or **18** on the other hand. An open-chain side chain as found in amides **19** or **20**, did not, however, give highly potent compounds. Similarly, a change of the core pyrrolidine ring resulted in most cases in less potent compounds: The compounds with (*R*)-configuration showed consistently lower activity than their respective (*S*)-enantiomers as shown by compounds **11**, **14**, and **17** versus compounds **21**, **22**, or **23**. Also, compound **24**, which is a racemic mixture, has a surprisingly low potency, even though the only change in comparison with amide **11** is the incorporation of a piperidine-scaffold instead of a pyrrolidine scaffold. Compounds **25** and **26** are examples of cinnamic amides derived from the two other racemic regioisomeric ((pyrrolidinyl)methyl)piperidines. Whereas amide **26** has almost no activity at the human H_3 receptor, as one might expect from a very different distance between the amide moiety and the free amino group, it is surprising, that compound **25** exhibits high antagonist potency in the [^{35}S]GTPγ[S] binding assay.

Our next approach was to investigate the influence of the substitution pattern of the aromatic moiety on the activity as H_3-ligands of the final amides. The results of which indicated that substitution with bromine is allowed in all positions. The regioisomeric compounds **11**, **27**, and **28** all show very similar activities at the hH_3 receptor. A combination of two halogen-substitutions, for example, in the 2-fluoro-4-bromocinnamic amide **41**, resulted in highly potent H_3 antagonists. A similar broad tolerance was found for the position of substitution, when investigating other types of substituents: both electron withdrawing substituents like cyano—as shown in amide **30**—or alkanoyl—as in the cyclopropylketone **31**, as well as electron-donating substituents like methoxy groups—as demonstrated with amide **32**—could be found in very potent antagonists. Especially the potency of dimethoxy-substituted derivatives as in amides **29** or **33** suggest, that electron-rich cinnamic amides are well accepted by the hH_3 receptor. It should be noted, however, that amide **33** was chemically unstable in acidic solutions, forming the inactive *Z*-double bond isomer, and hence making this compound useless as a drug candidate. The screening did not indicate any activity as H_3 antagonist for the *Z*-isomer. With respect to this isomerization the stabilities of compounds **14**, **17**, and **18** have been investigated, showing no sign of rearrangement. For all other compounds no isomerization was observed either.

This large variety of possible substitutents on the aromatic moiety of the cinnamic amides, gave us the opportunity to choose substituents, which we considered to be advantageous for the optimization of other important parameters, such as lack of CYP inhibition, plasma half life, or blood–brain barrier penetration.



Scheme 4. (a) EDAC, DHOBt, Et_3N.

In this context, we speculated, that the introduction of trifluoromethyl groups or trifluoromethoxy groups may have a positive influence on the plasma half life of the test compounds. Both trifluoromethyl—as in amides **14** or **17**—and trifluoromethoxy—as in amides **15** or **18**—were substituents that can be found in compounds with interestingly high in vitro potency at the hH_3 receptor.

On the other hand, we had concerns about the relatively high hydrophobicity of these compounds, which may give problems with unwanted pharmacokinetic properties such as low solubility or high distribution volume.[39] As a consequence of the previous considerations alternative compounds were investigated. We were looking for polar groups, which should not be too abundant in nature, since we hoped this would enhance the probability of being inert to degradation by enzymes, and thereby exhibit a prolonged plasma half life. Another demand on these groups was that despite their polarity, hydrogen-bonding capacity should be as low as possible, which is considered to be a necessity for a reasonable blood–brain barrier penetration.[40–42] Keeping all these considerations in mind, we thought that sulfones and sulfonates could be good candidates as substitutents. In fact the sulfonates **34** and **35** showed high potencies between 6 and 8 nM as antagonists at the hH_3 receptor. Also the sulfone **36** gave encouraging results.

Another possibility for a group with low polar surface area (PSA) seemed to be heterocyclic substituents, such as the 1,2,4-triazol-1-yl group in **37**. This very potent compound was found to be equipotent to its analogue **38**, where the heterocyclic ring was exchanged with a phenyl ring.

Having investigated the influence of substitution on the aromatic moiety, we finally turned our interest toward the double bond. Substitution on the double bond of the cinnamic amide is tolerated with small substituents at the β-carbon: The methyl-substituted analogue **39** is equipotent with the unsubstituted acryl amide **14**. This knowledge could be helpful, if metabolism at the double bond should become a serious problem, and shielding of the double bond is required.

In summary, we have identified a group of moderately potent hH_3 antagonists in the class of cinnamic amides of (aminomethyl)pyrrolidines. Interestingly, the potency is widely independent of the substituent on the aromatic moiety. However, when the aromatic group is omitted, as in acrylamide **40**, the potency drops significantly (Table 1).

With such a high number of potent antagonists toward the hH_3 receptor, we investigated the ability of these compounds to inhibit a number of cytochrome P450 enzymes as a counter-screen. We had observed inhibition with some of our early imidazole-containing compounds as well as with some of the imidazole-free H_3 antagonists, described in the literature.[25] An inhibition,

Table 1. hH_3-[^{35}S]GTPγ[S] binding assay

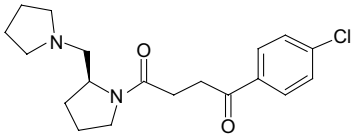
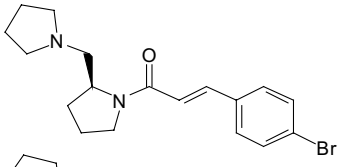
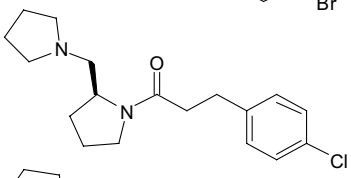
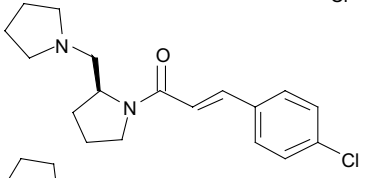
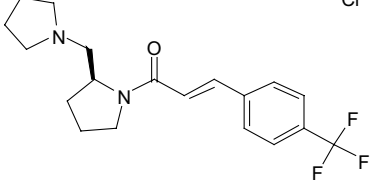
Entry		K_i (nM)
10		2148(±627)
11		10.0(±0.9)
12		196(±65)
13		11.2(±1.4)
14		4.7(±0.4)

Table 1 (*continued*)

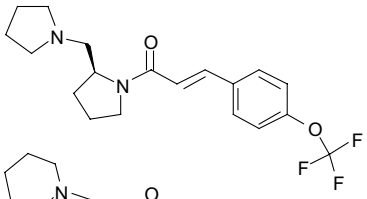
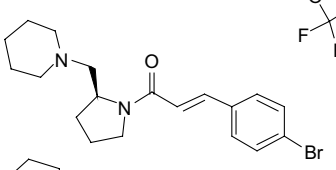
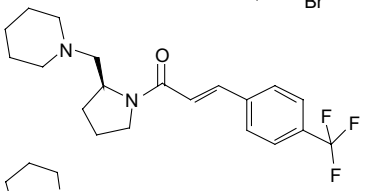
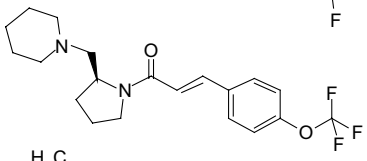
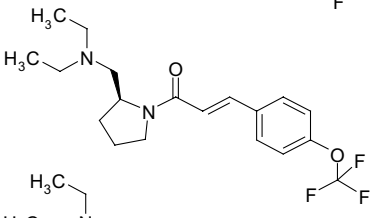
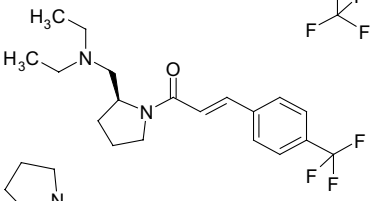
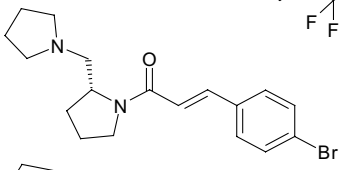
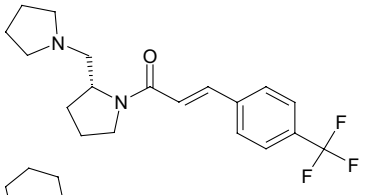
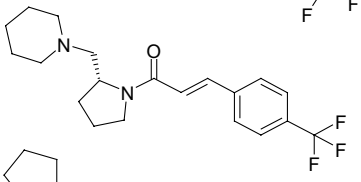
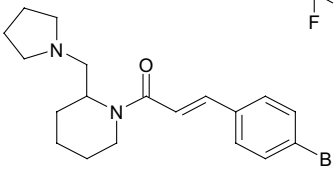
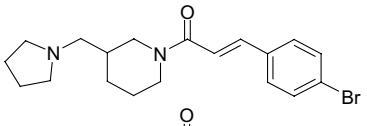
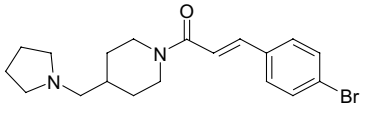
Entry		K_i (nM)
15		13.4(±1.9)
16		5.9(±1.0)
17		11.8(±2.6)
18		14.2(±3.0)
19		80(±32)
20		111(±11)
21		57(±16)
22		64(±11)
23		114(±20)
24		250(±55)
25		34.3(±5.7)
26		1099(±517)

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Table 1 (*continued*)

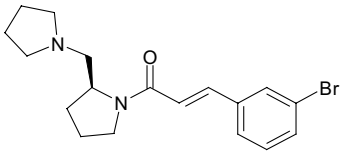
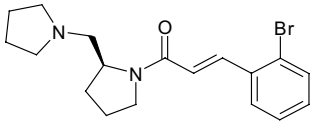
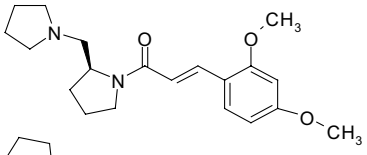
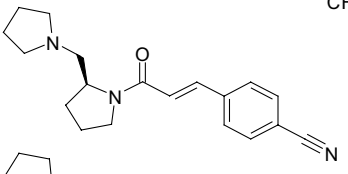
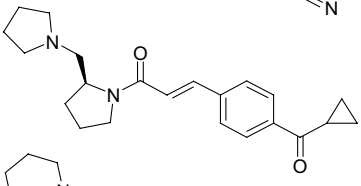
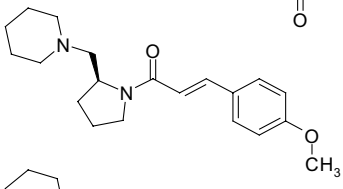
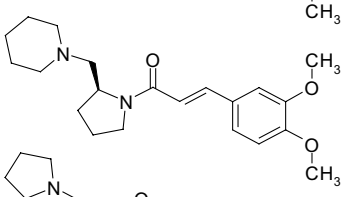
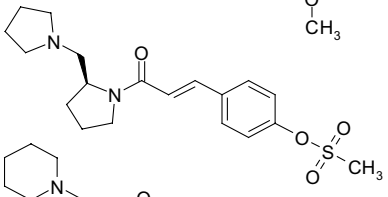
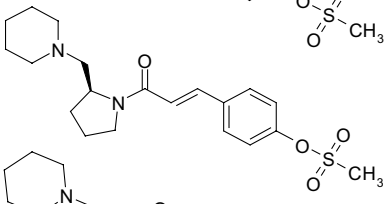
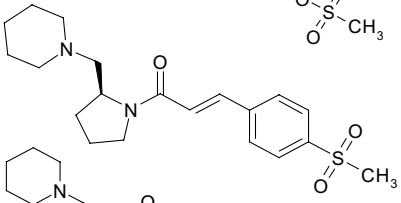
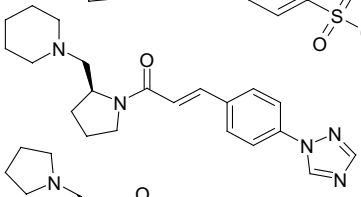
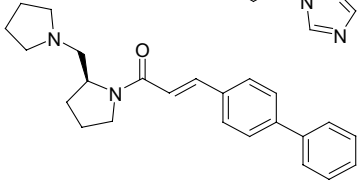
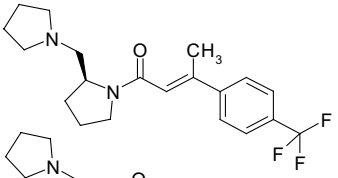
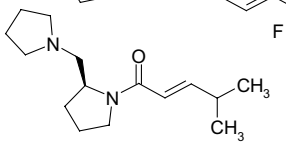
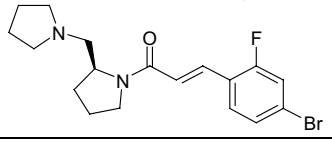
Entry		K_i (nM)
27		39.3(±13.5)
28		37.3(±10.1)
29		5.5(±2.4)
30		6.1(±1.0)
31		2.8(±0.7)
32		15.9(±7.2)
33		12.5(±3.1)
34		7.7(±1.4)
35		6.2(±0.8)
36		10.2(±1.1)
37		3.4(±0.3)
38		3.7(±1.3)

Table 1 (*continued*)

Entry		K_i (nM)
39		6.7(±2.0)
40		363(±183)
41		10.9(±5.5)

resulting either from a real inhibitor or from a competitive substrate behaving as a pseudoinhibitor, of some of the cytochrome P450 subtypes can result in serious problems in patients due to for example drug–drug interactions. Since our goal was to discover potent H_3 antagonists to be used for clinical purposes, for example for the treatment of attention deficit disorder, Alzheimer's disease or appetite regulation, we can expect that these patients would typically take more than one kind of drug. For this reason we wanted to address this issue as early as possible in our research. Hence, the compounds, which looked most promising in the potency screening, were subjected to a test where the inhibition values of three cytochrome P450 subtypes (CYP2D6, CYP3A4, and CYP1A2) were determined at a concentration of 20 μM. The observed data for the inhibition are shown in Table 2. Four compounds, namely amides **17**, **30**, **34**, and **36**, inhibit all three tested subtypes only very little or not at all. Looking for a common feature in these compounds, we concluded that electron withdrawing substituents, such as trifluoromethyl, cyano, or methylsulfonyl, in the *para*-position of the aromatic moiety might be beneficial for obtaining low CYP inhibition. On the other hand, compounds with a different common feature seem to be strong CYP2D6 and CYP1A2 inhibitors: compounds like amides **15** or **41**, which both inhibit both of these two subtypes more than 50%, bear lipophilic side chains on the aromatic moiety. In general, halogen substitution on the aromatic moiety results in compounds, which inhibit CYP2D6 and CYP1A2 moderately, independently from the position of substitution. This is shown in the series of compounds **11**, **13**, **16** and **27**. An interesting feature was found for methoxy substitution. While amide **32**, bearing a methoxy group in the *para*-position inhibits CYP2D6 with 36%, CYP3A4 with 28% and CYP1A2 with 7%, compound **29** and compound **33**, with two methoxy groups, are both weaker inhibitors with inhibition values of 22%, 19%, and 4% for compound **29** and of 12%, 18% and 0% for compound **33**, respectively. The sulfonate **34** shows only limited inhibitory effect.

Table 2. CYP-Inhibition

Entry	CYP2D6-inhibition (%)	CYP3A4-inhibition (%)	CYP1A2-inhibition (%)
11	24	2	72
13	28	23	44
14	30	31	66
15	62	20	58
16	22	22	64
17	3	12	46
18	44	18	38
19	61	8	39
21	67	35	35
22	56	9	15
27	32	24	21
29	22	19	4
30	0	0	9
32	36	28	7
33	12	18	0
34	15	6	0
36	2	6	0
37	37	7	30
38	20	11	4
39	42	[a]	[a]
41	52	10	78

[a] Not determined.

The very lipophilic phenyl substituent in compound **38** results in a relatively low inhibitory values, whereas the triazole **37** exhibits much higher the effects on CYP2D6 and CYP1A2.

These observations cannot, however, describe the complete picture: A comparison of amide **14** with amide **17** on one hand and amides **22** and **39** on the other hand reveals large differences in the inhibition data despite the same substituent on the aromatic moiety. One issue is the stereochemistry on the acylated pyrrolidine ring. The (*S*)-configured derivatives **11** and **14** are less potent inhibitors than the (*R*)-configured analogues **21** and **22** for the CYP2D6. Surprisingly the order is just the opposite for the inhibition of CYP1A2. The influence of the ring size of the amine is unpredictable: In the pair of the amides **11** and **16** almost no difference in inhibition of CYP2D6 and CYP1A2 can be seen, whereas there is a huge difference in the inhibition of CYP3A4. On the other hand the piperidine analogue **17** shows in all three tested cytochrome P450 subtypes a much more favorable profile than the pyrrolidine analogue **14**. A

comparison of compounds **15**, **18**, and **19** further shows, that also the open chain amines, such as in amide **19** do not influence the inhibitory effects in either direction dramatically.

In summary, we concluded, that it was not possible to develop a clear SAR for cinnamic amides with respect to CYP inhibition. However, by combination of the screening results for potent H_3 antagonists with the CYP inhibition data, we had the possibility to identify a number of very interesting candidates for further screening. Examples of such as compounds are **14**, **17**, **18**, **30**, **34**, and **36**.

3. Conclusion

The cinnamic amides of (*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidines and (*S*)-2-((pyrrolidin-2-yl)methyl)-piperidines are potent antagonists at the hH_3 receptor. The fact, that the effects on the hH_3 receptor is only influenced moderately by substituents on the aromatic moiety, gave us the unique opportunity to optimize further, in order to obtain compounds, that do not inhibit three important CYP subtypes. It has to be stressed, however, that a predictive understanding of the inhibitory effects of the synthesized compounds on three CYP subtypes could not be established. Despite these problems we were able to identify amides **14**, **17**, **30**, and **36** as very promising H_3 antagonists. The in vitro ADME parameters of some of these compounds will be characterized further, as will their behavior in various animal models. Surprisingly, the compounds that had been identified by the described screening procedure showed only moderate potency at the rat H_3 receptor, the receptor of the standard animal models (Table 3). Large species differences have been described in the literature.[43] However the reported compounds exhibited greater potency toward the rat receptor than on the human receptor. At this point it remains unclear, whether the compounds are active enough at the rat-H_3 receptor in order to use rat-animal-models. On the other hand, the observed selectivity seems to be quite promising: As shown in Table 3, no effects on the H_1-, H_2-, or H_4-receptor could be found for compounds **14** or **17**. Furthermore a screening for 75 different receptors or enzymes at a concentration of 10 μM showed almost exclusive selectivity for the H_3 receptor for compound **14** (IC_{50} values >10 μM). At the $5HT_{1A}$ receptor, the σ-receptor and at the sodium channel, compound **14** inhibited the binding of the reference compounds by 77%, 86% and 73%, respectively, at a concentration of 10 μM, whereas for the desired binding to the hH_3 receptor a K_i of 4.7 nM had been found.

Table 3. Binding to other histamine receptors

Entry	rH_3 K_i (nM)[a]	H_1 K_i (nM)[b]	H_2 K_i (nM)[c]	H_4 K_i (nM)[d]
14	53	>1000	>1000	>1000
17	131	>1000	>1000	>1000
30	61	[e]	[e]	[e]
36	45	[e]	[e]	[e]

[a] rH_3-[^{35}S]GTPγ[S] binding-assay.
[b] H_1 binding-assay, using ^{3}H-pyrilamine as radioligand.
[c] H_2 binding-assay, using ^{125}I-aminopentidine as radioligand.
[d] H_4 binding-assay, using [2,5-^{3}H]histamine as radioligand.
[e] Not determined.

4. Experimental

4.1. [^{35}S]GTPγ[S] binding assay

CHO cells, stably expressing the human histamine H_3 receptor as described in the literature,[7,44] were harvested and membranes were prepared by threefold homogenization in a 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) buffer (20 mM HEPES, 0.1–10 mM EDTA; pH 7.4). The functional, antagonist potency of hH_3 antagonists was measured as their ability to inhibit the binding of [^{35}S]GTPγ[S] in the presence of 10 nM (*R*)-α-methylhistamine (RAMHA). The test compound was diluted in assay buffer (20 mM HEPES, 120 mM NaCl, 10 mM $MgCl_2$, pH 7.4) at various concentrations followed by addition of 10 nM RAMHA, 3 μM GDP, 2.5 μg membranes, 0.5 mg SPA beads, and 0.1 nM [^{35}S]GTPγ[S]. After 2 h incubation at room temperature with gentle shaking of the plate, the plate was centrifuged at 370 RCF for 10 min and subsequently the radioactivity was counted in a Cobra II auto gamma topcounter. A number of 4–5 experiments were run for each test compound.

4.2. Data analysis

The IC_{50} values of H_3 antagonists were calculated by nonlinear regression analysis using GraphPad Prism (GraphPad Software, Inc.). The functional K_i values for the H_3 antagonists were calculated from the IC_{50} values using the Cheng–Prusoff relationship: $K_i = IC_{50}/(1 + (S/EC_{50}))$ where S represents the concentration of RAMHA used (10 nM) and EC_{50} represents the mean EC_{50} value (±SEM) of RAMHA in more than 60 separate agonist [^{35}S]GTPγ[S] binding experiments (i.e. 2.70 ± 0.15 nM).

4.3. CYP Inhibition assay

The in vitro CYP subtype activity in the absence and presence of a test compound (the potential CYP subtype inhibitor) was determined using a CYP subtype selective substrate (dextromethorphan for CYP2D6, erythromycin for CYP3A4, and phenacetin for CYP1A2, respectively). Incubations were utilized (200 μL, 37 °C, 10 min) containing human liver microsomes (HLM, 0.1 mg), [*O*-methyl-^{14}*C*]-dextromethorphan in the CYP2D6-assay (total conc.: 3 μM = K_m), [*N*-methyl-^{14}*C*]erythromycin and erythromycin in the CYP3A4 assay (total conc.: 20 μM = K_m), or [*O*-ethyl-^{14}*C*]phenacetin and phenacetin in the CYP1A2-assay (total conc.: 40 μM = K_m), the co-factor NADPH (1 mM) and the test compound (20 μM). All incubations were performed in triplicate. The HLM preparations used, were a pool of ⩾15

donors in order to obtain an average concentration of CYP subtypes, which is known to differ markedly between individuals.

The metabolic conversion of [*O*-methyl-^{14}C]-dextromethorphan, [*N*-methyl-^{14}C]erythromycin, or [*O*-ethyl-^{14}C]phenacetin, respectively, were assessed by activated charcoal extraction followed by liquid scintillation counting of the supernatant. The thereby measured ^{14}C-formaldehyde reflected the metabolism of the selective substrate by CYP subtype.

4.4. Chemistry

(*S*)-1-((Pyrrolidin-2-yl)methyl)piperidine,[27] (*S*)-2-((*N*,*N*-diethylamino)methyl)pyrrolidine,[26] (*R*)-2-((pyrrolidin-1-yl)methyl)pyrrolidine,[28] ((pyrrolidin-1-yl)methyl)piperidine,[29] (methanesulfonic acid 4-formylphenyl ester,[35] (*E*)-3-(4-trifluoromethylphenyl)but-2-enoic acid,[31] (*E*)-4-(methylsulfonyloxy)cinnamic acid,[32] and (*E*)-4-(methylsulfonyl)cinnamic acid[33,33,34] were prepared as described in the literature.

4.5. (*R*)-1-((pyrrolidin-2-yl)methyl)piperidine (1)

(*R*)-1-((pyrrolidin-2-yl)methyl)piperidine (**1**) was prepared analogously to the method described in the literature[27] for (*S*)-1-((pyrrolidin-2-yl)methyl)piperidine.

^{1}H NMR ($CDCl_3$) δ 1.30 (m, 1H); 1.40 (m, 2H); 1.55 (m, 4H); 1.70 (m, 3H); 1.85 (m, 1H); 2.25–2.60 (m, 6H); 2.80 (m, 1H); 3.00 (m, 1H); 3.25 (m, 1H).

4.6. 4-((Pyrrolidin-1-yl)methyl)piperidine (2)

At 0 °C, sodium triacetoxyborohydride[45] (22.3 g, 105 mmol) was added to a mixture of 4-formylpiperidine-1-carboxylic acid *tert*-butyl ester (7 g, 35 mmol), pyrrolidine (3.23 mL, 39 mmol) and 4 Å molsieves in dichloromethane (100 mL). Acetic acid (4 mL, 70 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. The solids were removed by filtration. The filtrate was diluted with *tert*-butyl methyl ether (100 mL) and washed with an 1 N aqueous solution of sodium hydroxide (100 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (90 g), using ethyl acetate/heptane (1:1) and 5% triethylamine as eluent, to give 1.97 g of 4-((pyrroidin-1-yl) methyl)piperidine carboxylic acid *tert*-butyl ester. This was dissolved in ethyl acetate. A 2.8 M solution of hydrochloric acid in ethyl acetate (60 mL) was added. The reaction mixture was stirred for 1 h, to give compound **2** as a hydrochloride salt, which was used for the amide coupling without further purification.

^{1}H NMR (dihydrochloride salt, $CDCl_3$) δ 1.30–1.50 (m, 2H); 1.80–2.10 (m, 6H); 2.70–3.10 (m, 5H); 3.15–3.30 (m, 4H); 3.55 (m, 2H); 8.75 (br, 1H); 8.95 (br, 1H); 10.05 (br, 1H).

4.7. *rac*-3-((Pyrrolidin-1-yl)methyl)piperidine (3)

Compound **3** was prepared as described for compound **2**, starting with *rac*-3-formylpiperidine 1-carboxylic acid *tert*-butyl ester[46] as starting material.

^{1}H NMR (HCl salt, $CDCl_3$) δ 1.80–2.20 (m, 6H), 2.4–3.2 (m, 9H); 3.50 (m, 3H); 3.75 (m, 1H); 9.30–9.90 (m, 2H).

4.8. (*E*)-3-(4-(1,2,4-Triazol-1-yl)phenyl)acrylic acid (6)

A mixture of 4-(1,2,4-triazol-1-yl)benzaldehyde (2.0 g, 11 mmol), malonic acid (1.8 g, 17 mmol) and piperidine (0.159 mL, 1.6 mmol) in pyridine (12 mL) was heated to 90 °C for 2.5 h. It was cooled to room temperature. A mixture of concd hydrochloric acid and ice (1:4, 200 mL) was added. The precipitate was collected by filtration. It was recrystallized from methanol to give 1.9 g (76%) of compound **6**.

^{1}H NMR (DMSO-d_6) δ 6.60 (d, 1H); 7.65 (d, 1H); 7.90 (AB, 4H); 8.30 (s, 1H); 9.40 (s, 1H); 12.50 (br, 1H).

4.9. (*E*)-3-(4-(Cyclopropylcarbonyl)phenyl)acrylic acid (8)

A mixture of commercially available (4-bromophenyl)-(cyclopropyl)methanone (**7**, 0.450 g, 2.00 mmol), palladium acetate 49 mg, 0.220 mmol), triphenylphosphine (55 mg, 0.21 mmol), methyl acrylate (0.43 g, 2.50 mmol) and triethylamine (10 mL, 72 mmol) was heated to 100 °C for 48 h in a closed reaction vial. The reaction mixture was cooled to room temperature. The solid was removed by filtration. A mixture of ice and 1 N hydrochloric acid was added to the liquid. The mixture was stirred for 1 h at room temperature. It was extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogencarbonate (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (40 g) using a mixture of dichloromethane–ethyl acetate–heptane (1:1:1) as eluent, to give 217 mg of (*E*)-3-(4-(cyclopropylcarbonyl)phenyl)acrylic acid methyl ester.

^{1}H NMR ($CDCl_3$) δ 1.05 (m, 2H); 1.25 (m, 2H); 2.65 (m, 1H); 3.85 (s, 3H); 6.55 (d, 1H); 7.62 (d, 2H); 7.75 (d, 1H); 8.05 (d, 2H).

A solution of lithium hydroxide (27 mg, 1.1 mmol) in water (2.00 mL) was added to a solution of (*E*)-3-(4-(cyclopropylcarbonyl)phenyl)acrylic acid methyl ester (217 mg, 0.94 mmol) in 1,4-dioxane (2.00 mL). 1,4-Dioxane was added until a clear solution was obtained. The reaction mixture was stirred for 16 h at room

temperature. It was diluted with an 1 N aqueous solution of sodium hydroxide (50 mL) and washed with *tert*-butyl methyl ether (2×40 mL). The aqueous solution was acidified with a 10% aqueous solution of sodium hydrogen sulfate until pH 3 was obtained. It was extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo to give 170 mg (39% over two steps) of crude compound **8**, which was used in the next step without further purification.

^{1}H NMR (DMSO-d_6) δ 1.05 (m, 4H); 2.95 (m, 1H); 6.70 (d, 1H); 7.65 (d, 1H); 7.85 (d, 2H); 8.05 (d, 2H); 12.60 (br, 1H).

4.10. Typical procedure for amide formation: 1-(4-chlorophenyl)-4-((2*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)butane-1,4-dione (10)

At 0 °C, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride salt (EDAC, 420 mg, 2.20 mmol) was added to a solution of 3-(4-chlorobenzoyl)propionic acid (470 mg, 2.20 mmol) and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (DOHBt, 360 mg, 2.20 mmol) in *N*,*N*-dimethylformamide (2 mL) and dichloromethane (2 mL). The reaction mixture was stirred for 20 min at 0 °C. A solution of the crude dihydrochloride salt of (*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidine (500 mg, 2.20 mmol) in *N*,*N*-dimethylformamide (2 mL) and triethylamine (2.15 mL, 15.4 mmol) were added successively. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (100 mL) and washed with brine (100 mL). The aqueous phase was dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (40 g), using a mixture of dichloromethane–methanol–25% aqueous ammonia (100:10:1) as eluent, to give 120 mg of compound **10**.

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.80–2.20 (m, 8H); 2.40–2.90 (m, 8H); 3.20–4.40 (m, 4H); 4.10 and 4.25 (both t, together 1H); 7.40 (d, 2H); 7.95 (d, 2H).

MS: calcd for $[M+H]^+$: 349; found: 349.

Compound **10** was transferred into its hydrochloride salt, by dissolving it in ethanol (50 mL). 1 N hydrochloric acid (12 mL) was added. The solvent was removed in vacuo. The residue was dissolved in ethanol (50 mL). The solvent was removed in vacuo. $C_{19}H_{25}ClN_2O_2{\cdot}HCl{\cdot}3H_2O$ (348.88·36.46 3·18.02). Calcd: C, 51.94; H, 7.34; N, 6.38. Found: C, 51.31; H, 7.60; N, 7.08.

4.11. (*E*)-3-(4-Bromophenyl)-1-((2*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (11)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.70–2.20 (m, 8H); 2.45–2.80 (m, 6H); 3.60 and 3.70 (both m, together 2H); 4.20 and 4.40 (both m, together 1H); 7.70 and 7.90 (both d, together 1H); 7.40 (m, 2H); 7.50 (m, 2H); 7.65 (d, 1H); MS: calcd for $[M+H]^+$: 363; found: 363.

4.12. 3-(4-Chlorophenyl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propan-1-one (12)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.70–2.20 (m, 8H); 2.30–2.80 (m, 6H); 2.90–3.05 (m, 4H); 3.20–3.60 (m, 2H); 3.80 and 4.25 (both m, together 1H); 7.10 (d, 2H); 7.25 (d, 2H). MS: calcd for $[M+H]^+$: 321; found: 321.

4.13. (*E*)-3-(4-Chlorophenyl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (13)

^{1}H NMR (HCl salt, DMSO-d_6, two sets of signals) δ 1.80–2.15 (m, 8H); 3.10, 3.20, 3.30, 3.45, and 3.55–3.85 (m, together 8H); 4.40 and 4.75 (both m, together 1H); 7.05 and 7.15 (both d, together 1H); 7.50 (m, 3H); 7.80 and 7.90 (both d, together 2H); 10.2 (br, 1H). MS: calcd for $[M+H]^+$: 319; found: 319.

4.14. (*E*)-1-((*S*)-2-((Pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propenone (14)

^{1}H NMR (HCl salt, DMSO-d_6, two sets of signals) δ 1.80–2.15 (m, 8H); 3.10, 3.25, 3.30, 3.45, and 3.55–3.80 (all m, together 8H); 4.40 and 4.80 (both m, together 1H); 7.20 and 7.30 (both d, together 1H); 7.70 and 7.75 (both d, together 1H); 7.75 and 7.80 (both d, together 2H); 7.95 and 8.10 (both d, together 2H); 10.25 (br, 1H).

MS: calcd for $[M+H]^+$: 353; found: 353.

Elemental analysis for HCl salt: $C_{19}H_{23}N_2OF_3Cl{\cdot}HCl{\cdot}0.5H_2O$ (353.40·36.46·0.5 18.02). Calcd: C, 57.36; H, 6.33; Cl, 8.91; N, 7.04. Found: C, 57.56; H, 6.30; Cl, 8.95; N, 7.07.

4.15. (*E*)-1-((*S*)-2-((Pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-(trifluoromethoxy)phenyl)propenone (15)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.80 (m, 4H); 1.85–2.20 (m, 4H); 2.40–2.80 (m, 6H); 3.55–3.75 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.70 and 6.85 (both d, together 1H); 7.20 (d, 2H); 7.55 (d, 2H); 7.65 (d, 1H). MS: calcd for $[M+H]^+$: 369; found: 369.

4.16. (*E*)-3-(4-Bromophenyl)-1-((*S*)-2-((piperidin-1-yl)methyl)pyrrolidin-1-yl)propenone (16)

1H NMR ($CDCl_3$, two sets of signals) δ 1.45 (m, 2H); 1.55 (m, 4H); 2.85–2.10 (m, 4H); 2.15–2.70 (m, 6H); 3.55–3.75 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.70 and 6.95 (both d, together 1H); 7.40 (d, 2H); 7.50 (d, 2H); 7.60 (d, 1H). MS: calc. for [M + H]+: calcd 377; found: 377.

4.17. (*E*)-1-((*S*)-2-((Piperidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propenone (17)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.40 (m, 2H); 1.55 (m, 4H); 1.80–2.10 (m, 4H); 2.15–2.70 (m, 6H); 3.55–3.75 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.80 and 7.05 (both d, together 1H); 7.60 (m, 4H); 7.70 (d, 1H). MS: calcd for $[M+H]^+$: 367; found: 367.

4.18. (*E*)-1-((*S*)-2-((Piperidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-(trifluoromethoxy)phenyl)propenone (18)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.45 (m, 2H); 1.55 (m, 4H); 1.85–2.10 (m, 4H); 2.15–2.70 (m, 6H); 3.50–3.75 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.70 and 6.90 (both d, together 1H); 7.20 (d, 2H); 7.55 (d, 2H); 7.65 (d, 1H). MS: calcd for $[M+H]^+$: 383; found: 383.

4.19. (*E*)-1-((*S*)-2-(Diethylaminomethyl)pyrrolidin-1-yl)-3-(4-(trifluoromethoxy)phenyl)propenone (19)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.05 (m, 6H); 1.85–2.15 (m, 4H); 2.15–2.80 (m, 6H); 3.50–3.75 (m, 2H); 4.10 and 4.30 (both m, together 1H); 6.70 and 6.90 (both d, together 1H); 7.20 (d, 2H); 7.55 (d, 2H); 7.65 and 7.66 (both d, together 1H). MS: calcd for $[M+H]^+$: 371; found: 371.

4.20. (*E*)-1-((*S*)-2-(Diethylaminomethyl)pyrrolidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propenone (20)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.00 (m, 6H); 1.85–2.15 (m, 4H); 2.20–2.80 (m, 6H); 3.60 and 3.70 (both m, together 2H); 4.10 and 4.30 (both m, together 1H); 6.80 and 7.00 (both d, together 1H); 7.60 (AB, 2H); 7.70 and 7.71 (both d, together 1H). MS: calcd for $[M+H]^+$: 355; found: 355.

4.21. (*E*)-3-(4-Bromophenyl)-1-((*R*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (21)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.70–2.20 (m, 8H); 2.45–2.80 (m, 6H); 3.60 and 3.70 (both m, together 2H); 4.15 and 4.40 (both m, together 1H); 7.70 and 7.90 (both d, together 1H); 7.40 (m, 2H); 7.50 (m, 2H); 7.65 (d, 1H); MS: calcd for $[M+H]^+$: 363; found: 363.

4.22. (*E*)-1-((*R*)-2-((Pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-trifluoromethylphenyl)propenone (22)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.80 (m, 4H); 1.90–2.20 (m, 4H); 2.45–1.85 (m, 6H); 3.60 and 3.70 (both m, together 2H); 4.15 and 4.40 (both m, together 1H); 6.80 and 7.00 (both d, together 1H); 7.65 (AB, 4H); 7.70 (d, 1H); MS: calcd for $[M+H]^+$: 353; found: 353.

4.23. (*E*)-1-((*R*)-2-((Piperidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propenone (23)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.45 (m, 2H); 1.55 (m, 4H); 1.85–2.10 (m, 4H); 2.15–2.70 (m, 6H); 3.50–3.75 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.80 and 7.05 (both d, together 1H); 7.65 (AB, 4H); 7.70 (d, 1H). MS: calcd for $[M+H]^+$: 367; found: 367.

4.24. (*E*)-3-(4-Bromophenyl)-1-(2-((pyrrolidin-1-yl)methyl)piperidin-1-yl)propenone (24)

^{1}H NMR ($CDCl_3$, two sets of signals) 1.35–1.90 (m, 10H); 2.40–2.90 (m, 7H); 3.90 and 4.25 (both m, together 1H); 4.60 and 5.05 (both m, together 1H); 6.95 (d, 1H); 7.35 (d, 2H); 7.45–7.65 (m, 3H). MS: calcd for $[M+H]^+$: 377; found: 377.

4.25. (*E*)-3-(4-Bromophenyl)-1-(3-((pyrrolidin-1-yl)methyl)piperidin-1-yl)propenone (25)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.20–4.25 (m, 19H); 4.35 and 4.55 (both d, together 1H); 6.90 and 7.20 (both d, together 1H); 7.30–7.55 (m, 4H); 7.60 (d, 1H). MS: calcd for $[M+H]^+$: 377; found 377.

4.26. 3-(4-Bromophenyl)-1-(4-((pyrrolidin-1-yl)methyl)piperidin-1-yl)propenone (26)

^{1}H NMR ($CDCl_3$) δ 1.20 (m, 2H); 1.80 (m, 5H); 1.90 (m, 2H); 2.35 (d, 2H); 2.50 (m, 4H); 2.80 (t, 1H); 3.10 (t, 1H); 4.10 (d, 1H); 4.70 (d, 1H); 6.90 (d, 1H); 7.35 (d, 2H); 7.50 (d, 2H); 7.55 (d, 1H). MS: calcd for $[M+H]^+$: 377; found: 377.

4.27. (*E*)-3-(3-Bromophenyl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (27)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.70–1.85 (m, 4H); 1.90–2.20 (m, 5H); 2.40–2.75 (m, 6H); 3.60 (t, 1H); 4.15 and 4.40 (both m, together 1H); 6.70 and 6.95 (both d, together 1H); 7.45 (m, 2H); 7.60 (d, 1H); 7.80 (t, 1H); MS: calcd for $[M+H]^+$: 363; found: 363.

4.28. (*E*)-3-(2-Bromophenyl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (28)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.50–1.90 (m, 4H); 1.90–2.20 (m, 4H); 2.50–2.85 (m, 6H); 3.55–3.80 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.65 and 6.85 (both d, together 1H);7.10–7.40 (m, 2H); 7.50–7.70 (m, 2H); 8.05 (d, 1H); MS: calcd for $[M+H]^+$: 363; found: 363.

4.29. (*E*)-3-(2,4-Dimethoxyphenyl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (29)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.75 (m, 4H); 1.85–2.20 (m, 4H); 2.45–2.75 (m, 6H); 3.50–3.75 (m, 2H); 3.82 (s, 3H); 3.85 (s, 3H); 4.15 and 4.40 (both m, together 1H); 6.45 (m, 2H); 6.75 and 6.90 (both d, together 1H); 7.45 (dd, 1H); 7.85 and 7.90 (both d, together 1H). MS: calcd for $[M+H]^+$: 345; found: 345.

4.30. 4-[(*E*)-3-Oxo-3-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenyl]benzonitrile (30)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.75 (m, 4H); 1.85–2.20 (m, 4H); 2.40–2.75 (m, 6H); 3.55–3.75 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.80 and 7.00 (both d, together 1H); 7.55–7.70 (m, 5H). MS: calcd for $[M+H]^+$: 310; found: 310.

4.31. (*E*)-3-(4-(Cyclopropanecarbonyl)phenyl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (31)

^{1}H NMR ($CDCl_3$, two sets of signals, broad signals) δ 1.05 (m, 2H); 1.25 (m, 2H); 1.80 (m, 4H); 1.90–2.15 (m, 4H); 2.40–2.80 (m, 6H); 3.60 and 3.70 (both m, together 2H); 4.15 and 4.40 (both m, together 1H); 6.85 and 7.00 (both d, together 1H); 7.40 (d, 2H); 7.75 (d, 1H); 8.00 (m, 2H). MS: calcd for $[M+H]^+$: 353; found: 353. $C_{22}H_{28}N_2O_2{\cdot}HCl{\cdot}0.2H_2O$. Calcd: C, 67.32; H, 7.55; N, 7.14. Found: C, 67.28; H, 7.57; N, 7.12.

4.32. (*E*)-3-(4-Methoxyphenyl)-1-((*S*)-2-((piperidin-1-yl)methyl)pyrrolidin-1-yl)propenone (32)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.45 (m, 2H); 1.55 (m, 4H); 1.85–2.10 (m, 4H); 2.15–2.70 (m, 6H); 3.55–3.75 (m, 2H); 3.85 (s, 3H); 4.15 and 4.40 (both m, together 1H); 6.60 and 6.75 (both d, together 1H); 6.90 (m, 2H); 7.50 (d, 2H); 7.65 (d, 1H). MS: calcd for $[M+H]^+$: 329; found: 329.

4.33. (*E*)-3-(3,4-Dimethoxyphenyl)-1-((*S*)-2-((piperidin-1-yl)methyl)pyrrolidin-1-yl)propenone (33)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.40 (m, 2H); 1.55 (m, 4H); 1.80–2.10 (m, 4H); 2.15–2.70 (m, 6H); 3.50–3.75 (m, 2H); 3.90 (s, 6H); 4.15 and 4.40 (both m, together 1H); 6.55 and 6.75 (both d, $J = 15.2$ Hz, together 1H); 6.85 (m, 1H); 7.10 (AB, 2H); 7.65 (d, $J = 15.2$ Hz, 1H). MS: calcd for $[M+H]^+$: 359; found. 359.

The hydrochloride salt of compound **33** was dissolved in water (pH 5 for the solution) and left at room temperature. After one week only 18% of compound **33** was left, while (*Z*)-3-(3,4-dimethoxyphenyl)-1-((*S*)-2-((piperidin-1-yl)methyl)pyrrolidin-1-yl)propenone was found.

4.33.1. (*Z*)-3-(3,4-Dimethoxyphenyl)-1-((*S*)-2-((piperidin-1-yl)methyl)pyrrolidin-1-yl)propenone. ^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.40 (m, 2H); 1.50–1.70 (m, 4H); 1.70–2.70 (m, 10H); 3.25 (m, 1H); 3.55 (m, 1H); 3.75 and 4.35 (both m, together 1H); 3.85, 3.87, 3.88 and 3.91 (all s, together 6H); 5.93 and 6.10 (both d, $J = 12.7$ Hz, together 1H) 6.50 and 6.51 (both d, $J = 12.7$ Hz, together 1H); 6.80 (m, 1H); 6.95 and 7.00 (both dd, together 1H) 7.10 and 7.15 (both d, together 1H). MS: calcd for $[M+H]^+$: 359; found: 359.

4.34. Methanesulfonic acid 4-[(*E*)-3-oxo-3-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenyl]phenyl ester (34)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.75 (m, 4H); 1.85–2.20 (m, 4H); 2.40–2.80 (m, 5H); 3.15 (s, 3H); 3.50–3.75 (m, 2H); 4.15 and 4.40 (m, 1H); 6.70 and 6.85 (both d, together 1H); 7.30 (m, 2H); 7.55 (d, 2H); 7.65 (d, 1H). MS: calcd for $[M+H]^+$: 379; found: 379.

4.35. Methanesulfonic acid 4-[(*E*)-3-oxo-3-((*S*)-2-((piperidin-1-yl)methyl)pyrrolidin-1-yl)propenyl]phenyl ester (35)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.45 (m, 2H); 1.55 (m, 4H); 1.70–2.15 (m, 4H); 2.15–2.70 (m, 6H);3.15 (s, 3H); 3.60 and 3.70 (both m, together 2H); 4.15 and 4.35 (both m, together 1H); 6.70 and 6.90 (both d, together 1H); 7.30 (d, 2H); 7.55 (d, 2H); 7.65 (d, 1H). MS: calcd for $[M+H]^+$: 393, found: 393.

4.36. (*E*)-3-(4-(Methylsulfonyl)phenyl)-1-((*S*)-2-((piperidin-1-yl)methyl)pyrrolidin-1-yl)propenone (36)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.45 (m, 2H); 1.50–1.70 (m, 4H); 1.85–2.15 (m, 4H); 2.15–2.70 (m, 6H); 3.10 (s, 3H); 3.65 and 3.75 (both m, together 2H); 4.20 and 4.40 (both m, together 1H); 6.85 and 7.10 (both d, together 1H); 7.70 (m, 3H); 7.95 (d, 2H). MS: calcd for $[M+H]^+$: 377; found: 377.

4.37. (*E*)-1-((*S*)-2-((Piperidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-(1,2,4-triazol-1-yl)phenyl)propenone (37)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.40 (m, 2H); 1.55 (m, 4H); 1.80–2.15 (m, 4H); 2.15–2.70 (m, 6H); 3.60 and 3.70 (both m, together 2H); 4.20 and 4.40 (both m, together 1H); 6.75 and 7.00 (both d, together 1H); 7.70 (m, 5H); 8.10 (s, 1H); 8.60 (s, 1H). MS: calcd for $[M+H]^+$: 366; found: 366.

4.38. (*E*)-3-(Biphenyl-4-yl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (38)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.70–2.20 (m, 8H); 2.45–2.80 (m, 6H); 3.60 and 3.70 (t and m, together 2H); 4.20 and 4.40 (both m, together 1H); 6.75 and 6.90 (both d, together 1H); 7.30–7.50 (m, 3H); 7.60 (m, 6H); 7.75 (d, 1H). MS: calcd for $[M+H]^+$: 361; found: 361.

4.39. (*E*)-1-(((*S*)-2-((Pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)-3-(4-(trifluoromethyl)phenyl)but-2-en-1-one (39)

^{1}H NMR ($CDCl_3$, two sets of signals, broad signals) δ 1.65–1.85 (m, 4H); 1.85–2.15 (m, 4H); 2.35–2.80 (m, 6H); 2.50 (s, 3H); 3.40–3.70 (m, 2H); 4.05 and 4.40 (both m, together 1H); 6.25 and 6.50 (both s, together 1H); 7.55 (m, 2H); 7.65 (d, 2H). MS: calcd for $[M+H]^+$: 367; found: 367.

4.40. (*E*)-4-Methyl-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)pent-2-en-1-one (40)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.05 (t, 6H); 1.75 (m, 4H); 1.85–2.15 (m, 5H); 2.35–2.70 (m, 6H); 3.40–3.60 (m, 2H); 4.05 and 4.30 (both m, together 1H); 6.05 and 6.15 (both d, together 1H); 6.90 and 6.92 (both t, together 1H). MS: calcd for $[M+H]^+$: 251; found: 251.

4.41. (*E*)-3-(4-Bromo-2-fluorophenyl)-1-((*S*)-2-((pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)propenone (41)

^{1}H NMR ($CDCl_3$, two sets of signals) δ 1.75 (m, 4H); 1.85–2.20 (m, 4H); 2.35–2.75 (m, 6H); 3.50–3.75 (m, 2H); 4.15 and 4.40 (both m, together 1H); 6.85 and 7.05 (both d, together 1H); 7.25–7.45 (m, 3H); 7.65 and 7.70 (both d, together 1H). MS: calcd for $[M+H]^+$: 381; found: 381.

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