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Benzylpiperidine variations on histamine H_3 receptor ligands for improved drug-likeness

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ABSTRACT

Several hH_3R antagonists/inverse agonists entered clinical phases for a broad spectrum of mainly centrally occurring diseases. Nevertheless, many promising candidates failed due to their pharmacokinetic profile, mostly because of their strong lipophilicity and their dibasic character. Analysis of previously, as potential PET ligands synthesized compounds (ST-889, ST-928) revealed promising results concerning physicochemical properties and drug-likeness. Herein, the synthesis, the evaluation of the binding properties at the hH_3R and the estimation of different physicochemical and drug-likeness properties of further novel benzylpiperidine variations on H_3R antagonists is described. Due to the introduction of various small hydrophilic moieties in the structure, drug-likeness parameters have been improved. For instance, compound **12** (ST-1032) showed in addition to high affinity at the H_3R (pK_i (hH_3R) = 9.3) *c*log*S*, *c*log*P*, LE, LipE, and LELP values of −2.48, 2.18, 0.44, 7.14, and 4.95, respectively. Also, the keto derivative **5** (ST-1703, pK_i (hH_3R) = 8.6) revealed LipE and LELP values of 5.25 and 6.84, respectively.

Histamine is the endogenous ligand of four G-protein coupled receptors, H_1R–H_4R, which mediates important physiological functions. Whereas the H_1R and the H_2R modulate allergic reactions and gastric acid secretion,[1,2] the H_4R regulates immune responses.[3,4] The transmembrane histamine H_3R is involved in numerous important neurotransmission processes and is therefore a promising drug target for centrally occurring diseases.[5]

Because of its integrative role in neuronal function and behavior, like for example sleep-wake-cycle, cognition, memory and food intake, the hH_3R antagonists/inverse agonists offer a high therapeutic potential for not yet curable diseases like daytime sleepiness, Alzheimer's disease, schizophrenia, epilepsy and obesity.[6]

Different hH_3R antagonists/inverse agonists with high affinities to the hH_3R have been synthesized in recent years.[7] Even though no crystal structure of the hH_3R exists, a pharmacophore consisting of a saturated nitrogen heterocycle coupled via a propoxy spacer to an aromatic core could be established.[8] A second basic moiety improves the affinity to the hH_3R.[9] Common leads of these diamine based structures are FUB880, JNJ-5207852, ST-889, and ST-928 (Fig. 1).[10–12]

JNJ-5207852 shows high affinity at the hH_3R and the rH_3R (pK_i = 9.0 and pK_i = 9.2, respectively). In in vivo studies a procognitive and provigilant effect of this compound in rats was proven.[13] However, apart from an undesirable long-half life time, there are potential therapeutic long-term treatment drawbacks like phospholipidosis, an aggregation of polar phospholipids in cells or tissues caused by the cationic amphiphilic character and the lipophilicity of the dibasic structure of JNJ-5207852.[14] This property is undesirable in a molecule that is aiming to treat chronic illnesses. Moreover, clinical studies indicated that this phospholipidosis inducing effect can lead to a pulmonary dysfunction.[15,16] Common parameters for an early estimation of the risk of the phospholipidosis inducing effect from a drug are pK_a and log*P* values, because a low pK_a reflects a low basicity and the lower the log*P* value of a compound the lower is the lipophilicity and respectively the amphiphilicity of a compound.[17,18] Hence, researchers from Abbott varied the structure of the second basic center of their H_3R antagonists to decrease the basic character of compounds to lower the phospholipidosis inducing potential.[18] Also Zulli *et al.*[19] performed a SAR study carried out with the aim to lower the pK_a value of the second basic center in the H_3R pharmacophore. Labeeuw et al.[20] introduced hydroxylic functions in their related lead structures to improve the toxicological and pharmacokinetic profile. Halogenated benzylpiperidine variations synthesized in

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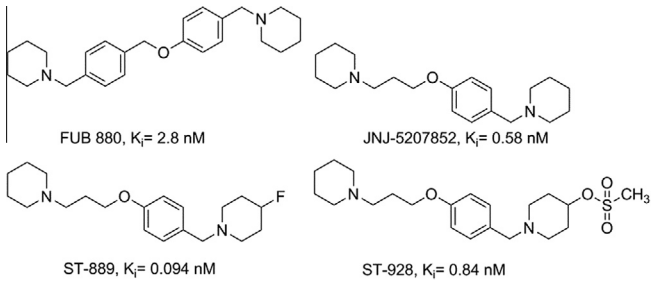

Figure 1. Reference histamine H_3R antagonists/inverse agonists and their hH_3R affinities.[11,13,14]

our working group for in vivo PET imaging studies, namely ST-889 and ST-928 (Fig. 1), showed high affinities at the hH_3R (pK_i (hH_3R) = 10.0 and 9.1, respectively).[21] Investigations of pK_a and *c*log*P* values of these compounds revealed an improved physicochemical character which maybe reduce the potential of an phospholipidosis inducing effect (Table 1). In this study, further benzylpiperidine variations were synthesized. Therefore, the aliphatic ring structure of the benzylpiperidine motif was varied preferably by introducing different electron-withdrawing functional groups at 4-position of piperidine. In addition, the hH_3R affinities and several drug-likeness parameters of the compounds were analyzed.

Starting from piperidine, compounds **1**–**4** were synthesized as described earlier (Fig. 2).[11,22,23] Compound **2** can be obtained as well as by reduction of precursor **3** or from precursor **1** by direct alkylation with 4-(hydroxymethyl)phenol. Whereas for the final products **6**–**10**, the aldehyde **3** has been reacted with different piperidine derivatives in a reductive amination, compound **5** was prepared via nucleophilic substitution of precursor **4**.

Ester **9** was the precursor for the synthesis of hydrazide **11**, the 1,3,4-oxadiazole **12**, acid **13** and the amide derivative containing compounds **14** and **15** (Fig. 3).

The preparation of compound **11** was performed by the reaction of ester **9** with hydrazine (Fig. 3). Ring formation with compound **11** to obtain compound **12** was carried out using triethyl orthoacetate. The synthesis of **13** was carried out by a basic hydrolysis. The acid **13** was not only a final product but also precursor for compounds **14** and **15**. Both compounds were obtained by an amide bond formation under microwave irradiation with EDC and HOBt as activating agents. The synthesis of **14** was carried out using as amine propargyl amine, for compound **15** methylamine hydrochloride was used.

The compounds ST-889, ST-928, **6**, **7**, **9**, **12** and **13** were tested with regard to their affinity at hH_3R as described by Ligneau et al.[24] in a [^{125}I]Iodoproxyfan displacement assay. The affinity to the hH_3R of **5**, **8**, **10**, **14** and **15** was determined in a [^{3}H]N^{α}-methylhistamine displacement assay as described by Kottke et al.[25] In both assays membrane preparations from HEK-cells stably expressing hH_3R were used. Compounds **5**, **8**, **10**, **13**, **14** and **15** revealed affinities at the H_3R in a low nanomolar concentration range. Compounds **6**, **7**, **9** and **12** provided even a subnanomolar affinity to the hH_3R (Table 1). Compounds **6** and **10** have previously been disclosed as potent H_3R antagonists by Apodaca et al.[26]

In addition to the affinities, Table 1 depicts calculated log*S*, log*P*, LE (ligand efficiency), lipophilic efficiency (LipE) and LELP (ligand efficiency-dependent lipophilicity) values of the compounds. In addition, the pK_a values of the two basic centers were calculated. The logP and the both pK_a values of the two basic centers of the compounds were calculated using the computational tool Marvin Sketch.[27] The log*P* represents the lipophilicity of a compound. The basic center in the piperidinopropyl moiety of the molecules is in Table 1 marked as (Pip), the second basic center with higher variations in the benzylpiperidine moiety of the molecule is designate with (Pip′).

Aside from compound **10**, the new compounds are less lipophilic than JNJ-5207852. In addition, the analogues show lower calculated pK_a values at both basic centers.

The ester **9** maintained the highest potency of the new compounds in binding to the hH_3R (pK_i = 9.64). Only the reference ligand ST-889 reaches a higher affinity at the hH_3R (pK_i = 10.03). The basicity (pK_a = 9.29/ 7.86) of compound **9** is lower than that of JNJ-5207852 and ST-889. Nevertheless, ST-889 is less lipophilic (*c*log*P* = 2.90). Interestingly the amide bond analogue **15** of compound **9** displays a lower affinity (pK_i = 8.53), less lipophilicity (c log*P* = 2.53) but more basicity (pK_a = 9.34/8.45). Even though **9** revealed a very high affinity at the hH_3R and also the *c*logP value of the compound is in an acceptable range (c log*P* <5, Rule of

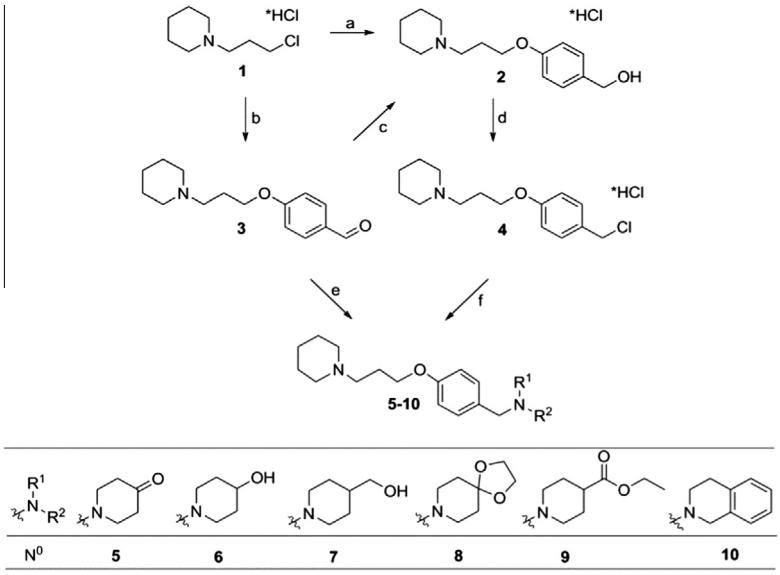

Figure 2. Synthesis of compounds **2**–**10**: (a) 4-(Hydroxymethyl)phenol, KI, K_2CO_3, acetone, reflux, 72 h; (b) 4-Hydroxybenzaldehyde, KI, K_2CO_3, acetone, reflux, 48 h; (c) $NaBH_4$, THF, 0 °C → rt, 30 min; (d) $SOCl_2$, toluene, 0 °C → 60 °C, 3 h; (e) sec. amine, $NaBH(OAc)_3$, 1,2-dichloroethane, rt, 5–12 h, (for **6**–**10**); (f) 4-piperidone, K_2CO_3, KI, acetone, reflux, 12 h (for **5**).

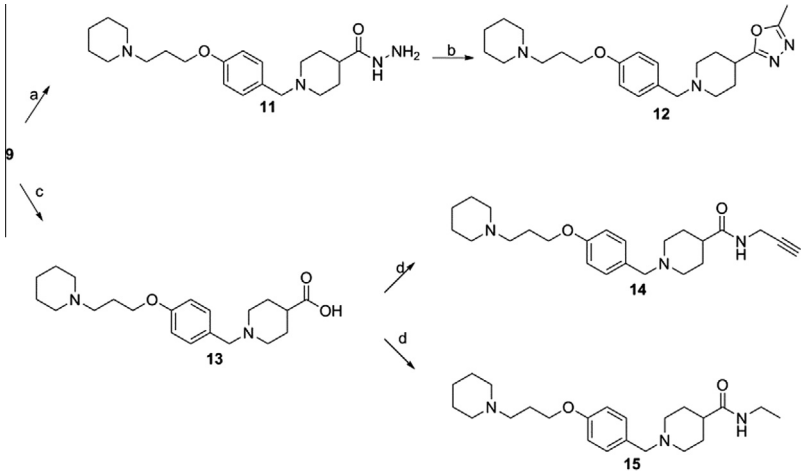

Figure 3. Synthesis of compounds **11**–**15**: (a) hydrazine, reflux, 48 h; (b) (1) triethyl orthoacetate, 120 °C, 3 h; (2) distillation; (3) 140 °C, 2 h; (c) 5 N KOH, THF/ethanol, reflux, 12 h; (d) amine, EDC/HOBt, methylene chloride, μW, 100 °C, 10 min.

Table 1
H_3R affinities, physicochemical properties and drug-likeness properties of compounds **5**–**15** and references

Compound	H_3R affinity	Basicity		Lipophilicity		Drug-likeness properties		
	pK_i	cpK_a[a,b] (Pip)	cpK_a[a,c] (Pip′)	*c*Log*S*[d]	*c*Log*P*[a]	LE	LipE	LELP
JNJ-5207852	9.24[e]	9.43	8.75	−2.75	3.54	0.55	5.70	6.44
ST-889	10.03[f]	9.32	8.35	−2.49	2.90	0.57	7.13	5.09
ST-928	9.08[f]	9.28	7.70	−2.71	1.94	0.44	7.14	4.41
5 (ST-1703)	8.60[g]	9.27	6.30	−2.44	3.35	0.49	5.25	6.84
6	9.23[f,h]	9.32	8.30	−2.35	2.00	0.53	7.23	3.77
7	9.17[f]	9.35	8.49	−2.41	2.46	0.50	6.71	4.92
8	8.69[g]	9.33	8.41	−2.41	2.67	0.44	6.02	6.07
9	9.64[f]	9.29	7.86	−2.82	3.26	0.47	6.38	6.94
10	8.53[g,h]	9.29	7.98	−3.47	4.45	0.43	4.08	10.35
12 (ST-1032)	9.32[f]	9.29	8.03	−2.48	2.18	0.44	7.14	4.95
13	7.89[f]	—	—	−2.39	0.03[i]	0.42	7.86	0.07
14	7.96[g]	9.34	8.45	−3.00	2.40	0.38	5.56	6.32
15	8.53[g]	9.34	8.45	−2.68	2.53	0.42	6.00	6.02

[a] Calculation with Marvin Sketch.[27]
[b] pK_a of the basic center of the piperidinopropyl moiety.[25]
[c] pK_a of the basic center of the benzylpiperidine moiety.
[d] Calculation with Osiris property explorer.[29]
[e] Barbier et al.[13]
[f] Experiments were performed as described by Ligneau et al.[24]
[g] Experiments were performed as described by Kottke et al.[25]
[h] Compounds **6** and **10** have been disclosed previously with comparable pK_i values of 9.13 and 8.77, respectively.[26]
[i] Value calculated for zwitterionic species.

5)[28], in matters of drug-likeness the metabolism of a compound is important as well. In the human metabolism esters are normally rapidly cleaved by esterases.

The remaining acid **13** revealed the lowest affinity value of all compounds in the displacement assay (pK_i = 7.89). The acid functionality decreases the affinity of the structure at the hH_3R in the range of at least one log-unit to its zwitterionic character. Therefore, the calculated *c*log*P* value of this compound is rather low (*c*log*P* = 0.03).

Nevertheless, the K_i value of **13** is in a higher nanomolar concentration range and indicates certain tolerance in the eastern binding pocket part of the hH_3R. This is in agreement with results obtained by Sander et al.[9]

The 1,3,4-oxadiazole was introduced as a bioisosteric replacement of the ester group in compound **9**. Compound **12** was found to be slightly more potent than the lead structure JNJ-5207852 (pK_i = 9.32), shows both reduced lipophilicity and improved solubility (higher *c*log*S*) and therefore, indicates superior absorption properties as to compound **9**. The basicity is in a comparable range to that of compound **9**. Compound **10** revealed a nanomolar affinity at the hH_3R. An examination of the physicochemical properties of this compound revealed a *c*log*P* value of 4.45, which is higher than that of JNJ-5207852. An enlargement with an aromatic system at the benzylpiperidine moiety does not seem to be useful in matters of potential phospholipidosis effects. Compound **14** revealed an affinity to the hH_3R in a nanomolar concentration range, similar to the acid derivative **3**. Lipophilic and basic properties of the compound are slightly better than that of JNJ-5207852. Compounds **6** and **7** show similar affinities (pK_i = 9.23 and 9.17, respectively) in comparison to that of the lead structure confirming that the hH_3R binding pocket accepts electron withdrawing and polar groups at the benzylpiperidine moiety of the ligand. The reference ligand ST-928, as well as compounds **12** and **5** revealed the best profile concerning the lipophilicity and basicity. For compound **5** the cpK_a value of the second basic center is 6.30 and therefore the center is not positively charged at physiologic pH. In addition, their affinities at the hH_3R are in a (sub)nanomolar concentration range. Although the basicity of the two basic centers

was significantly decreased, the compounds possess still some amphiphilic properties.

For an hH_3R antagonist with an optimized pharmacological profile the potentially reduced risk of a phospholipidosis inducing effect is only one among many others. To estimate the drug-likeness character of our compounds we calculated *c*log*S*, LE (ligand efficiency), LipE (lipophilic efficiency or ligand lipophilicity efficiency (LLE)) and LELP values (ligand efficiency-dependent lipophilicity).

The *c*log*S* values were calculated with the computational tool Osiris Property explorer.[29] This parameter represents the solubility of a drug candidate,[30] which influences its absorption and distribution properties. Therefore, *c*log*S* can be a useful parameter to estimate the ADME properties of a compound. Solubilities of all compounds are in an acceptable range (<−4 *c*log*S*).[28] Compounds **5**–**8**, **12**, **13**, and **15** showed lower calculated solubility values than that of JNJ-5207852.

Other useful tools to estimate the drug-likeness of a compound are the LE, LipE and LELP. LE can be defined as the binding energy per atom and described by the ratio of ΔG and number of heavy atoms.[28] ΔG is the free energy of ligand binding and defined as $\Delta G = -R * T * \ln K$. A LE value of a promising compound should be >0.4 at least. The problem of LE is the high dependency on number of heavy atoms and the excluding of lipophilicity effects.[31] Therefore, LipE has been introduced as a size independent metric parametrising the contribution of lipophilicity to potency. LipE can be defined as following: LipE = $pK_i - c\log P$.[32] For not to overweight the lipophilicity, LELP is another useful parameter, which contains LE as well as the log*P* value.[33] LELP is specified as the ratio of *c*log*P* and LE and also size-dependent like LE.

All new compounds revealed LE values lower than that of JNJ-5207852. The fluorinated substance ST-889 revealed a slightly higher value than that of JNJ-5207852. To obtain compounds with adequate drug-likeness, it seems useful to link ligand efficiency to lipophilicity. The calculated data of LipE and LELP values for promising drug candidates should be >5 and <7.5, respectively therefore the LELP and the LipE values were calculated.[32–35] In addition to the reference compound JNJ-5207852 almost all new compounds fulfill these notional requirements with the exception of **10**.

In conclusion, several structural analogues of JNJ-5207852, ST-889 and ST-928 were synthesized by varying the aliphatic ring structure of the benzylpiperidine moiety preferably in 4-position of piperidine. The affinities to the hH_3R of the new ligands were measured. All of them showed affinities to the hH_3R in nanomolar or subnanomolar concentration range comparable to that of the lead structures. The high affinities of the new compounds at the hH_3R confirm the postulated affinity-reinforcing effect of a second basic center in the hH_3R pharmacophore and the tolerance of the hH_3R binding pocket in the eastern part. A calculation of physicochemical properties may give a good prediction to an enhanced drug-likeness of most of the compounds. Especially compounds **5** (ST-1703) and **12** (ST-1032) with high affinities at hH_3R (pK_i = 8.60 and pK_i = 9.32) reflect reduced basicity and lipophilicity as compared to those calculated properties of JNJ-5207852. Pooling these results, these two compounds revealed promising LipE and LELP values.

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Supplementary data

Supplementary data (synthetic procedures, analytical data and assay descriptions) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.03.098.

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