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Fluorinated non-imidazole histamine H_3 receptor antagonists

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ABSTRACT

Fluorine substituents have become a widespread and important component in drug design and development. Here, the synthesis of fluorine containing compounds and some corresponding precursor molecules are presented for potential isotope labelling as well as their data obtained with in vitro and in vivo screenings. The compounds vary in the basic centres (piperidine or pyrrolidine) and are fluoro substituted in different positions of the basic alicyclic moiety. Pharmacological evaluation resulted in ligands with high affinities at hH$_3$ receptor in the nanomolar and subnanomolar concentration range and some with high antagonist in vivo potencies.

The histamine H_3 receptor (H_3R) is one of four different G protein-coupled histamine receptors known as H_{1-4}.[1] The H_3R was first discovered in 1983 in rats[2] and cloned in 1999.[3] As presynaptic auto- and heteroreceptor the H_3R is acting mainly in the central nervous system (CNS) controlling the synthesis and release of histamine, but also modulating the liberation of several other neurotransmitters, for example, dopamine, serotonin, γ-aminobutyric acid, noradrenaline, or acetylcholine. The abundance and localization of H_3Rs in the CNS suggests an integrative role in neuronal functions and behaviour, for example, arousal, cognition, memory or food intake.[4]

Numerous H_3R antagonists demonstrate positive effects in animal models of various CNS-related dysfunctions[5] and might be useful for the treatment of these disorders such as daytime sleepiness, attention deficit and hyperactivity, Alzheimer's disease, schizophrenia or obesity.[6]

One clinical candidate is the inverse H_3R agonist Tiprolisant, the former BF2.649 (Fig. 1), which shows high H_3R affinity.[7] The compound is now in phase II of clinical testing and targeting on narcolepsy, and epilepsy.[8]

We have exploited of the common 'amino-propyloxy' H_3R pharmacophore of Tiprolisant and others and linked it to benzyl moieties as central element to obtain our lead structures. This aromatic spacer has also been successfully used in other H_3R antagonists like UCL 2138.[9] The diamine approach in our compounds is based on previously described related benzylic derivatives like FUB 880[10] and JNJ-5207852[11] (Fig. 1). Different lead developments with such a diamine element was described, in some cases with some potential therapeutic long-term treatment drawbacks like phospholipidosis.[12,13]

We combined the phenoxy moiety with heterogeneous aliphatic mono- and difluorinated substitutions. These compounds were screened for hH$_3$R affinity displaying influence of fluoro

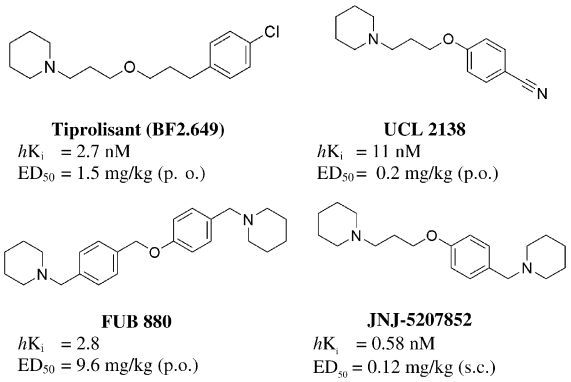

Figure 1. Non-imidazole histamine H_3 receptor antagonists.

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substitution in comparison to other halogenated derivatives or another leaving group. The high affinity hH$_3$R ligands were screened to determine their in vivo potencies after p.o. application. Novel compounds might be useful as pharmacological tools for drug development with changed basicity or for radioactive labelling eligible tool to get rapid information on receptor occupation in vivo.[14,15]

The compounds have been synthesized in two different sequential approaches, described in Figure 2 as Method A or Method B. The synthesis route in Method A has started with alkylation of a 5- or 6-membered aliphatic heterocycle (piperidine and pyrrolidine) with 3-chloropropan-1-ol under basic conditions resulting in synthon **1a** and **1b**, respectively. The alcohol group has been activated by reaction with thionyl chloride. These alkyl chlorides have been directly coupled to different phenols in a Williamson reaction. Based on this linear synthesis strategy, compounds **2**, **3**, **4a**, and **4b** have been obtained in good yields. The benzaldehydes (**4a**, **4b**) have been used as starting material for reductive amination with corresponding secondary amines to **5a–h**.

The mesylate compound **7** has not been synthesized directly by reductive amination, but it has been formed from the 4-hydroxypiperidine derivate **6** by transformation with mesyl chloride.

In Method B the central part of the structure has been built up firstly by Williamson reaction of 3-chloropropan-1-ol with 4-cyanophenol for compound **8** or 4-hydroxybenzaldehyde for compound **9**, respectively, under iodide catalysis. Afterwards, the different fluorinated aminergic rings have been linked on the corresponding functional group on either side. 4,4-Difluoropiperidine has been coupled with 4-(3-hydroxypropoxy)benzonitrile (**8**), which was previously activated by reaction with thionyl chloride, to obtain compound **10**.

For compound **12** the aldehyde functionality of **9** has been reacted with pyrrolidine in a reductive amination to give the alcohol **11**, which has been finally activated by thionyl chloride and coupled with 4-fluoropiperidine.

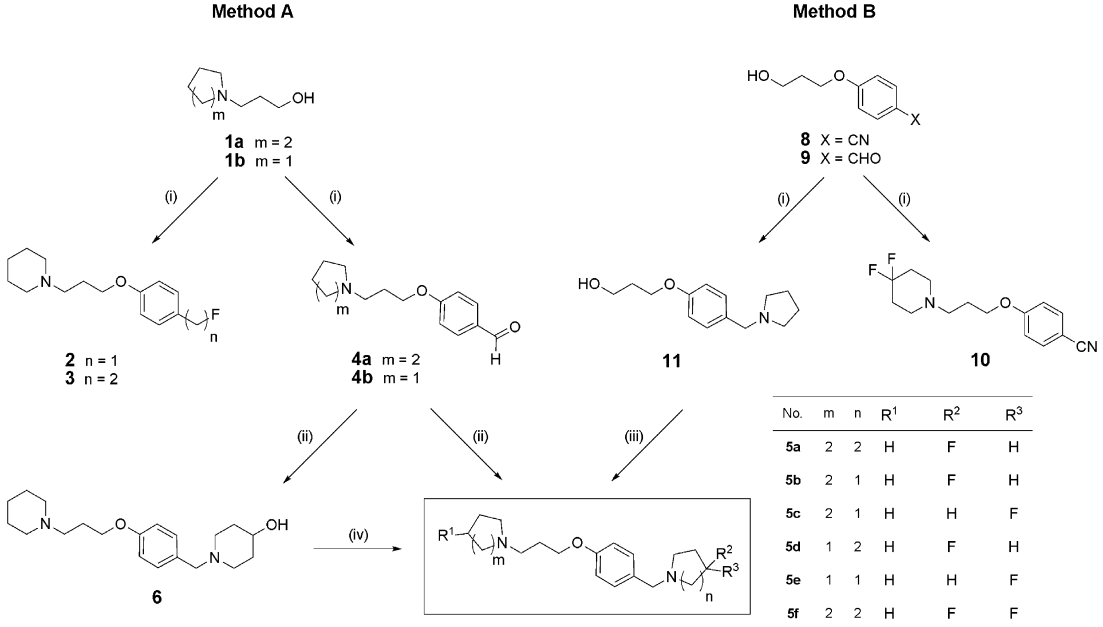
Briefly, the compounds have been pharmacologically screened for H$_3$R affinities by [^{125}I]iodoproxyfan displacement assay on HEK-293 cells stably expressing the hH$_3$R.[16] The non-specific binding was determined using imetit. Central in vivo H$_3$R potency has been determined after p.o. administration of the compounds to Swiss mice measuring the increase of N^{τ}-methylhistamine level in the cerebral cortex.[17]

Introduction of fluorine changes properties of neighbouring functional groups, especially pK_A values.[18] Thereby, it modifies pharmacodynamic and pharmacokinetic properties.[19] Fluoro substitution can be used to solve problems unique to the CNS, for example, blood brain barrier (BBB) permeation.[20] Additionally it may exert a substantial effect on the conformation of a molecule and it is used to enhance the binding affinity to the target protein.[21]

Our initial starting point was the difluorination of the piperidine of a modern monoamine non-imidazole H$_3$R antagonist (compound **10**) (Table 1). This derivatisation disappointingly caused a complete loss in affinity. Consequently, our studies mainly focused on modification and fluorination of the lipophilic pharmacophore on the right-hand part of the molecule. The monofluorination to fluorobenzyl derivate **2** resulted in moderate affinity, which even decreased with elongation of the spacer to fluoroethylphenyl derivative **3**.

The development of dibasic structures in combination of monofluorination on the right-hand basic centre (**5a–e**) involved high affinities in low subnanomolar concentration ranges. Compound **5a** fluorinated on the second piperidine moiety showed the highest affinity in this short series.

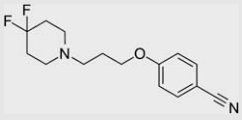
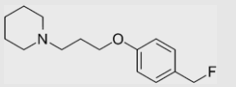
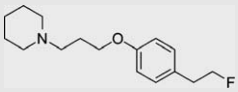
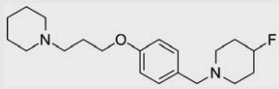
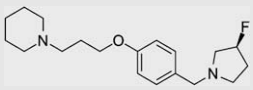
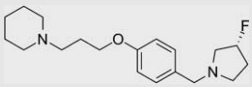
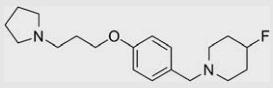
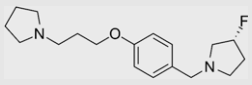
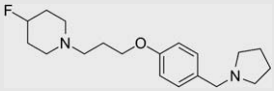
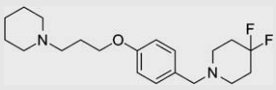
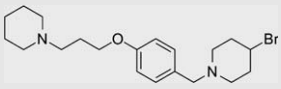
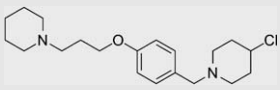
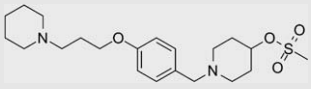
After changing piperidine to pyrrolidine fluorination in 3-position introduced a stereocenter. Stereoselective differentiation of eutomer and distomer has not been observed with the enantiomeric compounds **5b** and **5c**. Change of the left-hand basic ring system from piperidine to pyrrolidine (**5a** → **5d**, **5c** → **5e**) did not result in any improvement of affinity.



No.	m	n	R^1	R^2	R^3
5a	2	2	H	F	H
5b	2	1	H	F	H
5c	2	1	H	H	F
5d	1	2	H	F	H
5e	1	1	H	H	F
5f	2	2	H	F	F
5g	2	2	H	Br	H
5h	2	2	H	Cl	H
7	2	1	H	OSO_2CH_3	H
12	2	1	F	H	H

Figure 2. Synthesis of compounds: (i) (1) $SOCl_2$, toluene, 0 °C → 60 °C, 3 h; (2) different phenols, KI, K_2CO_3, acetone, reflux, 48 h; (ii) *sec*-amine base, $NaBH(AcO)_3$, dichloroethane, rt, 1–12 h; (iii) (1) $SOCl_2$, toluene, 0 °C → 60 °C, 3 h; (2) *sec*-amine base, KI, K_2CO_3, acetone, reflux, 48 h; (iv) for compound **7** only: CH_3SO_2Cl, DCM, 0 °C → rt.

Table 1
hH$_3$R affinities and potencies of compounds **2**, **3**, **5a–h**, **7**, **10** and **12**

No.	Structure	hH$_3$R K_i[a] (nM)	ED_{50}[b] (mg/kg)
10		>1000	
2		17.3 ± 3.4	
3		43 ± 5	
5a		0.094 ± 0.011	7.4 ± 3.9
5b		0.28 ± 0.07	3.9 ± 0.4
5c		0.28 ± 0.16	
5d		0.26 ± 0.02	12 ± 1
5e		0.31 ± 0.08	
12		0.99 ± 0.16	
5f		0.24 ± 0.05	0.40 ± 0.01
5g		0.20 ± 0.03	
5h		0.068 ± 0.004	
7		0.84 ± 0.08	

[a] HEK-293 cells expressing hH$_3$R.[16]
[b] p.o. Administration to Swiss mice.[17]

Fluorination on the left-hand side as in compound **10** is accepted by maintaining affinity (**12**) although the K_i value is about 1 nM, which constitutes the worst K_i in the diamine series. In contrast to the derivatisation of **10** the difluorination of piperidine on the right-hand moiety of compound **5f** involved an affinity in the subnanomolar concentration range.

Interestingly, the chlorinated precursor molecule **5h** for potential [^{18}F]-labelling showed the highest affinity pointing out the distinct steric demands for hH$_3$R binding pocket interaction.

Selected compounds with high affinity have been tested for their central antagonist in vivo potencies by p.o. application to mice. All tested compounds showed central antagonistic efficacies with good oral potencies. Here, the best compound is the difluorinated derivative **5f** (ED_{50} value of 0.23 mg/kg). Metabolic lability, distribution differences or other potential reasons for the related monofluorinated compound **5a** in comparison to difluoro compound **5f** might taken into account, but need additional investigations.

In addition to fluorination other halogenations (**5g, 5h**) or introduction of other leaving groups (**7**) have been introduced has also led to bioisosteric replacements. These compounds have not been tested in vivo due to their chemical reactivity.

In summary, all diamine compounds with fluorination on the right-hand side showed subnanomolar affinities at hH$_3$R. The high affinity of **5a** recommends this compound as a potential candidate for [^{18}F]-labelling to receive a novel pharmacological tool for drug discovery in CNS by means of positron emission tomography (PET)[22] or ligand-based [^{19}F]NMR binding screening.[23] With compounds **5g**, **5h**, and **7** suitable precursors are available for a convenient and last-step labelling. Further studies in this direction are in progress. In addition, all high affine fluorinated antagonists exhibit antagonist potency in vivo after p.o. administration indicating that this structural modification is a new lead element in compound optimization (cf. **5f**). This offers the possibility of a potent, orally available hH$_3$R antagonist. Further non-target studies and pharmacokinetic investigations are awaited for compound evaluation.

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Supplementary data

Supplemental material with analytical data of target compounds will be freely available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.02.110.

References and notes

1. Hill, S. J.; Ganellin, C. R.; Timmerman, H.; Schwartz, J. C.; Shankley, N. P.; Young, J. M.; Schunack, W.; Levi, R.; Haas, H. L. *Pharmacol. Rev.* **1997**, *49*, 253.
2. Arrang, J. M.; Garbarg, M.; Schwartz, J. C. *Nature* **1983**, *302*, 832.
3. Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Jiang, X.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. *Mol. Pharmacol.* **1999**, *55*, 1101.
4. Sander, K.; Kottke, T.; Stark, H. *Biol. Pharm. Bull.* **2008**, *31*, 2163.
5. Isensee, K.; Petroianu, G.; Stark, H. *J. Appl. Biosci.* **2007**, *5*, 57.
6. Celanire, S.; Lebon, F.; Stark, H. In *The Third Histamine Receptor: Selective Ligands as Potential Therapeutic Agents in CNS Disorders*; Vohora, D. S., Ed.; Taylor & Francis CRC Press: Boca Raton, Fl, 2009; p 103.
7. Ligneau, X.; Perrin, D.; Landais, L.; Camelin, J. C.; Calmels, T. P.; Berrebi-Bertrand, I.; Lecomte, J. M.; Parmentier, R.; Anaclet, C.; Lin, J. S.; Bertaina-Anglade, V.; la Rochelle, C. D.; d'Aniello, F.; Rouleau, A.; Gbahou, F.; Arrang, J. M.; Ganellin, C. R.; Stark, H.; Schunack, W.; Schwartz, J. C. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 365.
8. Raga, M. M.; Sallares, J.; Guerrero, M.; Guglietta, A.; Arrang, J. M.; Schwartz, J. C.; Lecomte, J. M.; Ligneau, X.; Schunack, W.; Ganellin, C. R.; Stark, H.; Patent WO2006/084833 A1, **2006**.
9. (a) Schwartz, J. C.; Arrang, J. M.; Garbarg, M.; Lecomte, J. M.; Ligneau, X.; Schunack, W.; Stark, H.; Ganellin, C. R.; Leurquin, F.; Sigurd, E.; Patent EP0978512 A1, **2000**.; (b) Ganellin, C. R.; Leurquin, F.; Piripitsi, A.; Arrang, J. M.; Garbarg, M.; Ligneau, X.; Stark, H.; Schunack, W.; Schwartz, J. C. In *Histamine Research in the New Millennium;*; Watanabe, T., Timmerman, H., Yanai, K., Eds.; Elsevier Science: Amsterdam, 2001; pp 25–31.
10. Mikó, T.; Ligneau, X.; Pertz, H. H.; Ganellin, C. R.; Arrang, J. M.; Schwartz, J. C.; Schunack, W.; Stark, H. *J. Med. Chem.* **2003**, *46*, 1523.
11. (a) Barbier, A. J.; Berridge, C.; Dugovic, C.; Laposky, A. D.; Wilson, S. J.; Boggs, J.; Aluisio, L.; Lord, B.; Mazur, C.; Pudiak, C. M.; Langlois, X.; Xiao, W.; Apodaca, R.; Carruthers, N. I.; Lovenberg, T. W. *Br. J. Pharmacol.* **2004**, *143*, 649; (b) Apodaca, R.; Carruthers, N. I.; Dvorak, C. A.; Rudolph, D. A.; Shah, C. R.; Xiao W. Patent WO02/12214 A2, 2001.

12. Bonaventure, P.; Letavic, M.; Dugovic, C.; Wilson, S.; Aluisio, L.; Pudiak, C.; Lord, B.; Mazur, C.; Kamme, F.; Nishino, S.; Carruthers, N.; Lovenberg, T. *Biochem. Pharmacol.* **2007**, *73*, 1084.
13. Cowart, M.; Gfesser, G. A.; Browman, K. E.; Faghih, R.; Miller, T. R.; Milicic, I.; Baranowski, J. L.; Krueger, K. M.; Witte, D. G.; Molesky, A. L.; Komater, V. A.; Buckley, M. J.; Diaz, G. J.; Gagne, G. D.; Zhou, D.; Deng, X.; Pan, L.; Roberts, E. M.; Diehl, M. S.; Wetter, J. M.; Marsh, K. C.; Fox, G. B.; Brioni, J. D.; Esbenshade, T. A.; Hancock, A. A. *Biochem. Pharmacol.* **2007**, *73*, 1243.
14. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
15. Shah, P.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527.
16. Ligneau, X.; Morisset, S.; Tardivel-Lacombe, J.; Gbahou, F.; Ganellin, C. R.; Stark, H.; Schunack, W.; Schwartz, J. C.; Arrang, J. M. *Br. J. Pharmacol.* **2000**, *131*, 1247.
17. Garbarg, M.; Arrang, J. M.; Rouleau, A.; Ligneau, X.; Tuong, M. D.; Schwartz, J. C.; Ganellin, C. R. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304.
18. Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.
19. Kirk, K. L. *Curr. Top. Med. Chem.* **2006**, *6*, 1447.
20. Sun, S.; Adejare, A. *Curr. Top. Med. Chem.* **2006**, *6*, 1457.
21. Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.
22. Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, 2853.
23. Dalvit, C. *Prog. Nucl. Mag. Reson. Spectrosc.* **2007**, *51*, 243.