Bioorganic & Medicinal Chemistry Letters 20 (2010) 5713–5717

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of potent and selective histamine H_3 receptor inverse agonists based on the 3,4-dihydro-2*H*-pyrazino[1,2-*a*]indol-1-one scaffold

H. G. F. Richter [a,*], C. Freichel [a], J. Huwyler [b], T. Nakagawa [c], M. Nettekoven [a], J.-M. Plancher [a], S. Raab [a], O. Roche [a], F. Schuler [a], S. Taylor [a], C. Ullmer [a], R. Wiegand [a]

[a] *F. Hoffmann-La Roche Ltd, Pharmaceutical Research, Grenzacherstrasse, CH-4070 Basel, Switzerland*
[b] *University of Applied Sciences Northwestern Switzerland, Institute of Pharma Technology, CH-4132 Muttenz, Switzerland*
[c] *Chugai Pharmaceutical Co. Ltd, 1-135 Komakado, Gotemba, Shizuoka 412-8513, Japan*

ARTICLE INFO

Article history:
Received 21 June 2010
Revised 2 August 2010
Accepted 3 August 2010
Available online 6 August 2010

Keywords:
Histamine
Histamine H3 receptors
Histamine H3 inverse agonists

ABSTRACT

A novel series of potent histamine H_3 receptor inverse agonists based on the 3,4-dihydro-2*H*-pyrazino[1,2-*a*]indol-1-one scaffold has been discovered. Several compounds display high selectivity over other histamine receptor subtypes and have favorable physicochemical properties, low potential for CYP450 enzyme inhibition and high metabolic stability in microsomal preparations. (*R*)-2-Cyclopropylmethyl-8-(1-isopropyl-piperidin-4-yloxy)-3-methyl-3,4-dihydro-2*H*-pyrazino[1,2-*a*]indol-1-one (**8t**) showed good in vivo efficacy after per os application in an acute rat dipsogenia model of water intake.

The neurotransmitter histamine exerts its physiological effects through four distinct G-protein coupled histamine receptor subtypes known as H_1-, H_2-, H_3- and H_4-R. Both histamine H_1- and H_2 receptors have already proven to be excellent drug targets leading to the discovery of important therapeutic agents for the treatment of allergic reactions (H_1R antagonists, 'antihistamines')[1] and gastric ulcers (H_2R antagonists),[2] respectively.

The H_4 receptor, the youngest member of the histamine receptor family, is less well studied but there is preclinical evidence for its involvement in the immune response and inflammatory processes.[3]

The histamine H_3 receptor, cloned in 1999,[4] is primarily located in the central nervous system (CNS). It functions as a presynaptic autoreceptor controlling the synthesis and release of histamine. In addition, it serves as a heteroreceptor that upon activation inhibits or stimulates the release of other neurotransmitters such as serotonin, dopamine, noradrenaline, acetylcholine or γ-aminobutyric acid. These actions together with positive results from pre-clinical animal studies make the histamine H_3 receptor a promising therapeutic target for the treatment of several CNS disorders such as cognitive impairment, narcolepsy, attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease and obesity.[5]

Early histamine H_3R ligands such as ciproxifan,[6] clobenpropit[7] or thioperamide[8] (Fig. 1) were based on the imidazole core present in the endogenous substrate. However, issues like cytochrome P450 (CYP450) inhibition,[9] lack of selectivity[10] or suboptimal brain penetration[11] precluded further development of these compounds.

Over the last years focus was given to non-imidazole based histamine H_3 receptor antagonists in order to overcome the liabilities

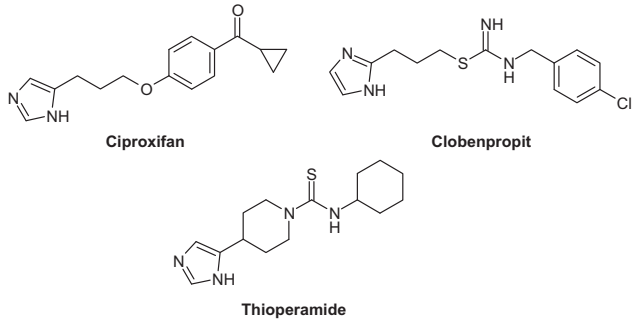


Figure 1. Selected examples of imidazole-based histamine H_3-R antagonists.

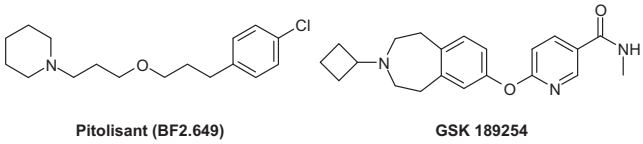


Figure 2. Selected examples of non-imidazole histamine H_3-R antagonists.

* Corresponding author. Tel.: +41 61 688 1330; fax: +41 61 688 6459.
E-mail address: hans.richter@roche.com (H.G.F. Richter).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.08.009

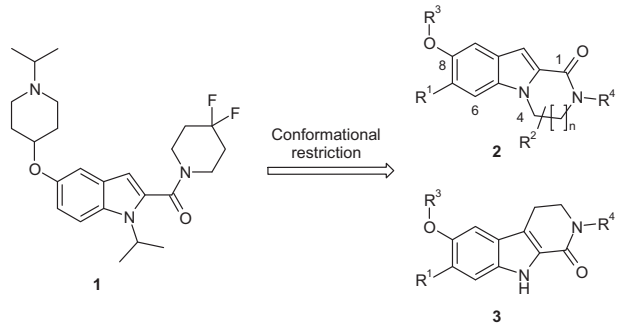


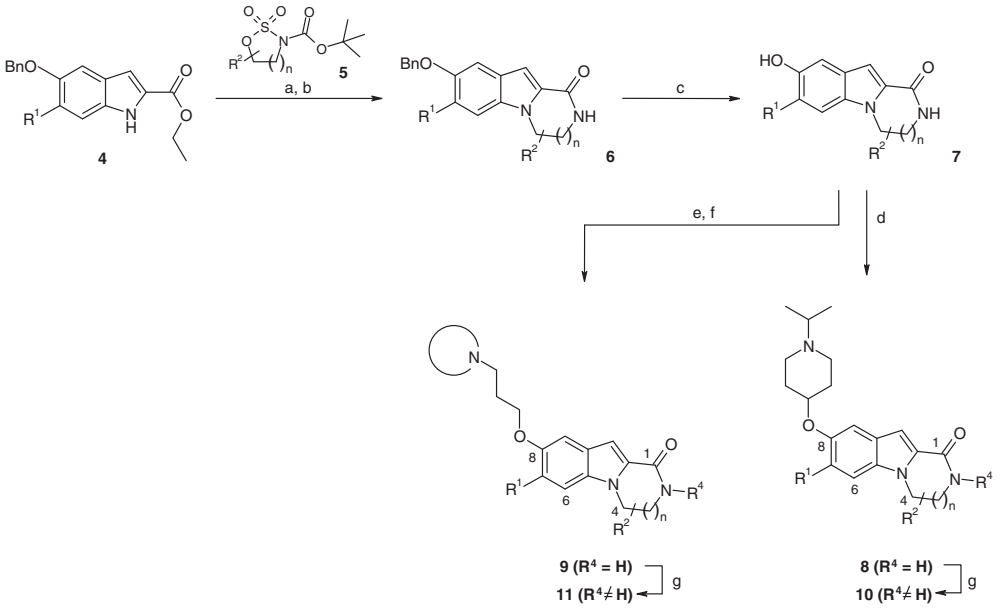
Figure 3. Conformational restriction around indole-2-carboxamide lead structure **1**.

of the earlier ligands and several analogues such as Pitolisant (BF2.649)[12] or GSK189254[13] have advanced into clinical trials (Fig. 2).[14]

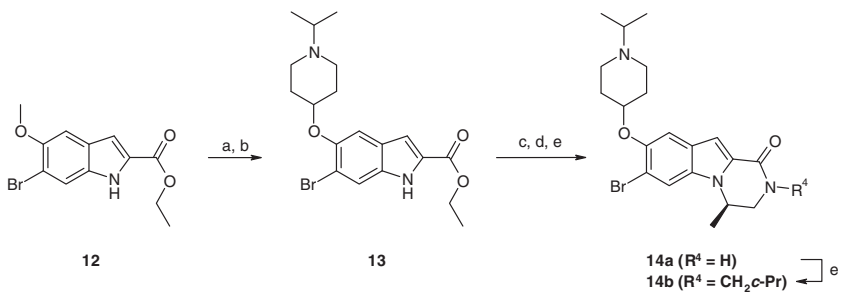
As a part of our lead optimization program around the indole lead structure **1**[15] we sought new chemical starting points for the development of novel histamine H_3 receptor inverse agonists. Herein, we report the synthesis, structure–activity relationship and evaluation of a novel series of conformationally constrained indole-2-carboxamide analogues containing a tricyclic amide core structure.

Based on the very good match with our recently published H_3R pharmacophore model,[16] we reasoned that incorporation of the amide bond of **1** into 3,4-dihydro-2*H*-pyrazino[1,2-*a*]indol-1-ones **2** may provide such a new lead series. In order to extend the structural diversity and to further validate our pharmacophore model we also investigated the constitutionally isomeric 2,3,4,9-tetrahydro-beta-carbolin-1-ones **3** (Fig. 3).

The synthesis of this new class of tricyclic amides was accomplished as outlined in Schemes 1 and 2. Alkylation of commercially available 5-benzyloxy-1*H*-indole-2-carboxylic acid ethyl ester **4** with 2,2-dioxo[1,2,3]oxathiazolidine-3-carboxylic acid *tert*-butyl esters (**5**, $n = 1$)[17] proceeded in high yields. In case of chiral 5-substituted sulfamidates the alkylation reaction proceeded under inversion of configuration with an enantiomeric excess of more than 98% ee.[18] Removal of the Boc protective group under acidic conditions and cyclization of the liberated amine onto the ester group afforded the pyrazino-indolines **6**. Cleavage of the benzyl protective group by hydrogenolysis gave the phenol intermediate **7** that underwent Mitsunobu coupling with commercially available 1-isopropyl-piperidine-4-ol to the secondary amides **8**. Alternatively, alkylation of **7** with 1-bromo-3-chloro-propane and subsequent reaction with secondary amines afforded compounds **9**.



Scheme 1. Reagents and conditions: (a) **5**, KO*t*-Bu, DMF, 0 °C to rt; (b) TFA, CH_2Cl_2, 0 °C to rt, then K_2CO_3, MeOH (45–70% over three steps); (c) H_2, Pd/C, MeOH (70–100%); (d) 1-isopropyl-piperidine-4-ol, di-*tert*-butyl-azodicarboxylate, PPh_3, THF, rt (20–45%); (e) 1-bromo-3-chloro-propane, K_2CO_3, 2-butanone (50–60%); (f) amine, K_2CO_3, KI, CH_3CN (16–75%); (g) R^4-X, NaH, DMF, rt (5–100%).



Scheme 2. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 °C to rt (79%); (b) 1-isopropyl-piperidine-4-ol, di-*tert*-butyl-azodicarboxylate, PPh_3, THF, 0 °C to rt (76%); (c) **5** (5-*S*-Me), KO*t*-Bu, DMF, 0 °C to rt (53%); (d) TFA, CH_2Cl_2, 0 °C to rt, then K_2CO_3, MeOH (31% over two steps); (f) *c*-$PrCH_2Br$, NaH, DMF (55%).

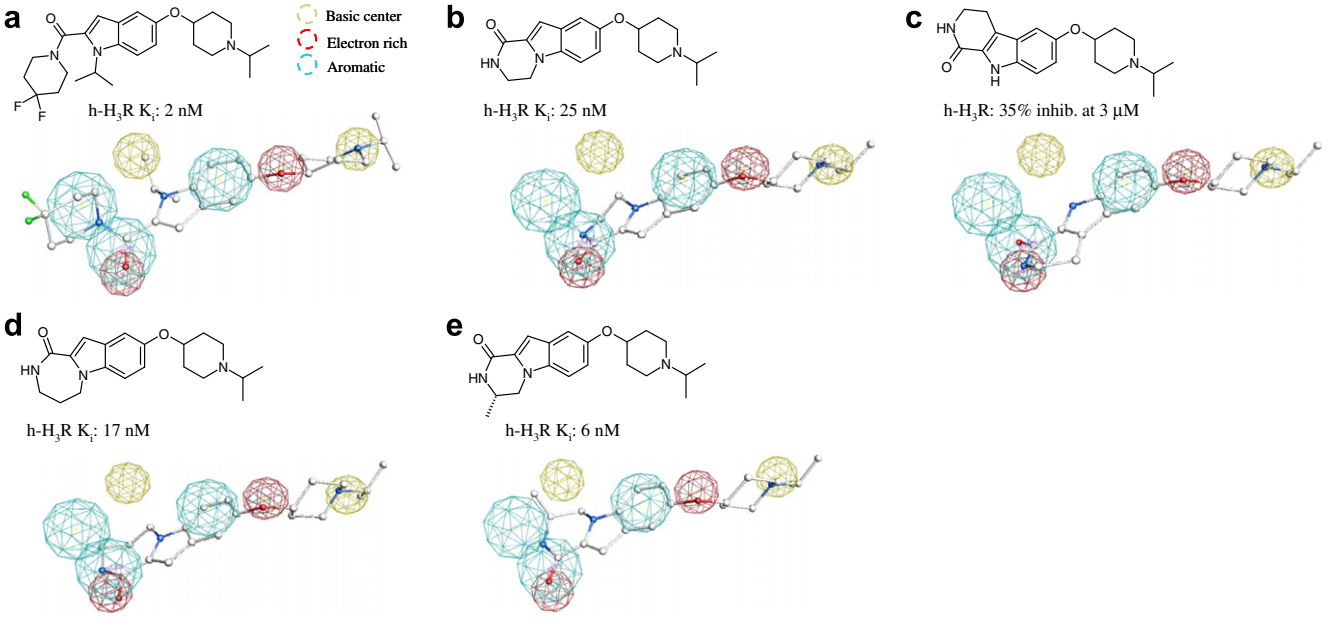
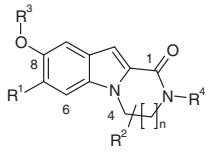


Figure 4. Docking of compound **1** (a), **8a** (b), **3** (c), **8b** (d), **8q** (e) on pharmacophore model.

Table 1
Structure–activity relationship at human H_3 receptor and selectivity over other histamine receptor sub-types



Ex	*n*	R^1	R^2 (config.)	R^3	R^4	K_i[a] hH_3-R (nM)	EC_{50}[b] hH_3-R (nM)	Inhibition[c] hH_1-R (%)	Inhibition[d] hH_2-R (%)	Inhibition[e] hH_4-R (%)
1	See Figure 3					2	2	9	−6	7
3	See Figure 3 (R^1 = R^4 = H, R^3 = N*i*-Pr-piperidin-4-yl)					>3000	NT[f]	NT	NT	NT
8a	1	H	H	N*i*-Pr-piperidin-4-yl	H	25	38	1	−17	6
8b	2	H	H	–//–	H	17	26	3	9	−3
8c	1	H	H	–//–	Me	31	48	−4	11	0
8d	1	H	H	–//–	*i*-Pr	27	25	−6	−2	−6
8e	1	H	H	–//–	CH_2*c*-Pr	9	28	−15	6	7
8f	1	H	H	–//–	CH_2CF_3	34	40	−1	−6	−4
8g	1	H	H	–//–	CH_2-(o-F-Ph)	6	28	16	6	1
8h	1	H	H	–//–	CH_2-(m-F-Ph)	14	23	24	21	4
8i	1	H	H	–//–	CH_2-(*p*-F-Ph)	7	14	17	−3	1
8j	1	H	H	–//–	CH_2-(o-Py)	6	14	6	4	−3
8k	1	H	H	–//–	CH_2-(m-Py)	5	13	3	3	3
8l	1	H	H	–//–	CH_2-(*p*-Py)	5	12	4	−14	3
8m	1	H	H	–//–	CH_2CH_2OH	46	56	−1	14	−5
8n	1	H	H	–//–	CH_2CH_2OMe	19	51	−26	6	0
8o	2	H	H	–//–	CH_2*c*-Pr	17	36	5	15	−7
8p	1	H	3-Me (*R*)	–//–	H	9	46	2	13	7
8q	1	H	3-Me (*S*)	–//–	H	6	14	−2	26	15
8r	1	H	4-Me (*R*)	–//–	H	26	29	−4	10	9
8s	1	H	4-Me (*S*)	–//–	H	42	94	11	9	10
8t	1	H	3-Me (*R*)	–//–	CH_2*c*-Pr	5	18	3	8	12
14a	1	Br	4-Me (*S*)	–//–	H	4	4	−16	18	−10
14b	1	Br	4-Me (*S*)	–//–	CH_2*c*-Pr	2	2	10	−3	1
8u	1	H	H	1-Cyclopropylmethyl-piperidin-4-yl	H	129	N.d.[f]	−4	9	3
9a	1	H	H	(Piperidin-1-yl)-propyl	H	18	74	33	45	8
9b	1	H	H	((*S*)-2-Me-pyrrolidin-1-yl)-propyl	H	21	140	11	10	4
9c	1	H	H	((*R*)-2-Me-pyrrolidin-1-yl)-propyl	H	7	4	13	4	−4
9d	1	H	H	((2*S*,5*S*)-2,5-Dimethyl-pyrrolidin-1-yl)-propyl	H	11	24	16	17	6

[a] Radioligand displacement of [3H]-RAMH (*n* = 1).
[b] GTPγ35S binding to human recombinant H_3 receptor (inverse agonist) (*n* = 1).
[c] Radioligand displacement of [3H]-mepyramine (*n* = 1).
[d] Radioligand displacement of [3H]-tiotidine (*n* = 1).
[e] Radioligand displacement of [3H]-histamine (*n* = 1).
[f] Not determined.

Alkylation of the secondary amide function in **8** and **9** furnished the *N*-alkylated products **10** and **11**, respectively.

2,3,4,5-Tetrahydro-[1,4]diazepino[1,2-*a*]indol-1-ones (**8**–**11**, *n* = 2) could be synthesized using the 2,2-dioxo[1,2,3]-oxathiazinane-3-carboxylic acid *tert*-butyl ester (**5**, *n* = 2, R^1 = H).[19] Following the same protocol, the 7-bromo analogues **14a** and **14b** (from 6-bromo-5-methoxy-1*H*-indole-2-carboxylic acid ethyl ester **12**,[20] Scheme 2) and 2,3,4,9-tetrahydro-beta-carbolin-1-ones **3** (from 6-hydroxy-2,3,4,9-tetrahydro-beta-carbolin-1-one[21]) were obtained.

In accordance with our pharmacophore model, the 2,3-annulated analogue **3** was much less active than its 1,2-annulated counterpart **8a**. The loss of activity can be rationalized by the sub-optimal positioning of the carbonyl acceptor (Figs. 4b and c). The ring size of the lactam ring (**8a/8b** and **8e/8o**, respectively) did not have a significant impact on the binding affinity, likely due to the comparable space filling properties of the six and seven membered ring (Fig. 4d). Alkylation at the lactam nitrogen especially with cyclopropylmethyl (**8e**) or pyridylmethyl substituents (**8j–8l**) led to a 3–5-fold increase in binding affinity as compared to **8a**. As a next step we examined the effects of substitutions at the lactam ring of **8a** on binding affinity. Whereas the introduction of a methyl group in the 4-position of **8a** did not significantly alter binding affinity (**8r**, **8s**), the introduction of a methyl group in the 3-position of **8a** led to a three and fourfold increase in binding affinity for the *R* and *S* enantiomer **8p** and **8q**, respectively. The highest activity resided with the 3-Me (*S*) analogue **8q** (Fig. 4e), although the higher potency is difficult to rationalize based on the pharmacophore model which indicates a significant distance of the chiral methyl group at either position 3 or 4 to the basic and aromatic pharmacophoric features, respectively.

The impact of different amine side-chains at the indole core on binding affinity (**8u**, **9a**–**9d**) was also investigated. From these analogues, the (*R*)-1-(3-methoxy-propyl)-2-methyl-pyrrolidine derivative **9c** exhibited the highest binding affinity. Finally we introduced a bulky bromo substituent in the so far unexplored position-7 of the indole core. This variation led to a further substantial increase of binding affinity resulting in the identification of the most potent compounds from this series **14a** and **14b**, respectively. All compounds were tested in a functional GTPγS assay and were characterized as potent full inverse agonists at the human H_3 receptor (Table 1) with comparable potency at the rat H_3 receptor (data not shown).

With the exception of **8h**, **9a** and **9d** that showed residual activity at hH_1 and hH_2 receptor subtypes and **8q** that showed some moderate activity against hH_2 and hH_4 receptors, all compounds were highly selective against the other histamine receptor subtypes (Table 1).

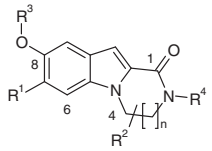
Several representative compounds were tested for their physicochemical properties and were characterized by low to moderate lipophilicity (log *D* −0.25 to 2.32) and high aqueous solubility (Table 2).

In rat liver microsomes, compounds generally tended to be less metabolically stable than in human microsomes where they were characterized by low and comparable clearance values. With the exception of **8m** that showed sub-micromolar inhibition of CYP 2D6, compounds displayed no significant CYP450 inhibition (Table 2) indicating a low drug–drug interaction potential.

Based on the promising data obtained so far for this compound class we investigated the effects of **8t** (K_i rat H_3R 12 nM, EC_{50} rat H_3R 18 nM) in a rat dipsogenia model measuring reversal of a selective H_3R agonist ((*R*)-α-methyl histamine)-induced increased water intake.[22] In addition, the animals were observed during one hour and potential behavioral side-effects were recorded according to a modified Irwin protocol. In this paradigm, compound **8t** did not lead to notable side-effects and significantly inhibited the water intake by 64% at a dose of 10 mg/kg after oral dosing, without affecting water intake when given alone. This result indicates functional antagonism of **8t** at brain H_3 receptors.

In summary, we identified a novel and conformationally rigid series of potent histamine H_3 inverse agonists derived from our indole lead structure **1**. Several compounds from this new series displayed high selectivity over other histamine receptor sub-types, low CYP450 inhibition potential and were endowed with excellent physicochemical properties. Following oral administration compound **8t** reduced water intake in a dipsogenia model after oral administration, indicating good absorption and brain penetration.

Table 2
Solubility, lipophilicity, CYP450 inhibition and microsomal clearance for selected 3,4-dihydro-2*H*-pyrazino[1,2-*a*]indol-1-ones



Ex.	*n*	R^1	R^2 (config.)	R^3	R^4	Solubility[a] (μg/mL)	log *D*[b]	CYP IC_{50} (μM) 3A4, 2D6, 2C9	Cl_{int} (h/r)[c] ((μL/min)/mg)
1	See Figure 3					>589	1.67	>50, 5, >50	4/12
8a	1	H	H	N*i*-Pr-piperidin-4-yl	H	>436	−0.05	>50, 4, >50	1/70
8b	2	H	H	–//–	H	>455	0.07	>50, >50, >50	0/28
8c	1	H	H	–//–	Me	>455	0.13	>50, 15, >50	1/23
8e	1	H	H	–//–	CH_2*c*-Pr	>508	1.09	>50, >50, >50	14/9
8i	1	H	H	–//–	CH_2-(*p*-F-Ph)	382	2.06	>50, 35, >50	5/17
8l	1	H	H	–//–	CH_2-(*p*-Py)	>456	0.64	6, >50, >50	8/27
8m	1	H	H	–//–	CH_2CH_2OH	>406	−0.25	>50, 0.9, >50	9/11
8p	1	H	3-Me (*R*)	–//–	H	284	0.28	>50, >50, >50	7/10
8q	1	H	3-Me (*S*)	–//–	H	>455	0.23	>50, >50, >50	3/0
8r	1	H	4-Me (*R*)	–//–	H	>455	0.23	>50, 22, >50	0/29
8s	1	H	4-Me (*S*)	–//–	H	345	0.28	26, >50, >50	4/0
8t	1	H	3-Me (*R*)	–//–	CH_2*c*-Pr	>441	1.4	>50, >50, >50	6/10
14a	1	Br	4-Me (*R*)	–//–	H	>526	1.13	>50, >50, >50	1/12
14b	1	Br	4-Me (*R*)	–//–	CH_2*c*-Pr	506	2.32	>50, >50, >50	7/20
9c	1	H	H	((*R*)-2-Me-pyrrolidin-1-yl)-propyl	H	>436	0.13	>50, >50, >50	0/37

[a] Aqueous solubility in phosphate buffer at pH 6.5 in 0.05 M phosphate buffer.
[b] pH 7.4.
[c] Intrinsic clearance in human (h) and rat (r) liver microsomes.

Conformational restriction did not lead to a further improvement of potency or in vitro ADME properties compared to the indole lead structure **1**.

Acknowledgements

The work of Martin Ritter and Kersten Klar is gratefully acknowledged.

References and notes

1. (a) Ash, A. S. F.; Schild, H. O. *Br. J. Pharmacol.* **1966**, *27*, 427; (b) Simons, F.; Estelle, R. *Am. J. Med.* **2002**, *113*, 38S.
2. (a) Gantz, I.; Munzert, G.; Tashiro, T.; Schaffer, M.; Wang, L.; DelValle, J.; Yamada, T. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 1386; (b) Feldman, M.; Burton, M. E. *N. Eng. J. Med.* **1990**, *323*, 1672.
3. (a) Liu, C.; Ma, X.; Jiang, X.; Wilson, S. J.; Hofstra, C. L.; Blevitt, J.; Pyati, J.; Li, X.; Chai, W.; Carruthers, N.; Lovenberg, T. W. *Mol. Pharmacol.* **2001**, *59*, 420; (b) Zhang, M.; Thurmond, R. L.; Dunford, P. J. *Pharmacol. Ther.* **2007**, *113*, 594.
4. 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.
5. Wijtmans, M.; Leurs, R.; de Esch, I. *Exp. Opin. Invest. Drugs* **2007**, *16*, 967.
6. Ligneau, X.; Lin, J.-S.; Vanni-Mercier, G.; Jouvet, M.; Muir, J. L.; Ganellin, C. R.; Stark, H.; Elz, S.; Schunack, W.; Schwartz, J.-C. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 658.
7. Van der Goot, H.; Schepers, M. J. P.; Sterk, G. J.; Timmerman, H. *Eur. J. Med. Chem.* **1992**, *27*, 511.
8. Arrang, J.-M.; Garbarg, M.; Lancelo, J.-C.; Lecomte, J.-M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. *Nature* **1987**, *327*, 117.
9. (a) LaBella, F. S.; Queen, G.; Glavin, G.; Durant, G.; Stein, D.; Brandes, L. J. *Br. J. Pharmacol.* **1992**, *107*, 161; (b) Yang, R.; Hey, J. A.; Aslanian, R.; Rizzo, C. A. *Pharmacology* **2002**, *66*, 128.
10. Stark, H.; Kathmann, M.; Schlicker, E.; Schunack, W.; Schlegel, B.; Sippl, W. *Mini-Rev. Med. Chem.* **2004**, *4*, 965.
11. Ganellin, C. R.; Leurquin, F.; Piripitsi, A.; Arrang, J.-M.; Garbarg, M.; Ligneau, X.; Schunack, W.; Schwartz, J.-C. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 395.
12. (a) Meier, G.; Apelt, J.; Reichert, U.; Grassmann, S.; Ligneau, X.; Elz, S.; Leurquin, F.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. *Eur. J. Pharm. Sci.* **2001**, *13*, 249; (b) Lin, J.-S.; Dauvilliers, Y.; Arnulf, I.; Bastuji, H.; Anaclet, C.; Parmentier, R.; Kocher, L.; Yanagisawa, M.; Lehert, P.; Ligneau, X.; Perrin, D.; Robert, P.; Roux, M.; Lecomte, J.-M.; Schwartz, J.-C. *Neurobiol. Dis.* **2008**, *30*, 74.
13. (a) Bamford, M. J.; Dean, D. K.; Sehmi, S. S.; Wilson, D. M.; Witherington, J. WO2004056369, 2004; (b) Bamford, M. J.; Dean, D. K.; Sehmi, S. S.; Wilson, D. M.; Witherington, J. *Chem. Abstr.* **2004**, *141*, 106391; (c) Medhurst, A. D.; Atkins, A. R.; Beresford, I. J.; Brackenborough, K.; Briggs, M. A.; Calver, A. R.; Cilia, J.; Cluderay, J. E.; Crook, B.; Davis, J. B.; Davis, R. K.; Davis, R. P.; Dawson, L. A.; Foley, A. G.; Gartlon, J.; Gonzalez, M. I.; Heslop, T.; Hirst, W. D.; Jennings, C.; Jones, D. N. C.; Lacroix, L. P.; Martyn, A.; Ociepka, S.; Ray, A.; Regan, C. M.; Roberts, J. C.; Schogger, J.; Southam, E.; Stean, T. O.; Trail, B. K.; Upton, N.; Wadsworth, G.; Wald, J. A.; White, T.; Witherington, J.; Woolley, M. L.; Worby, A.; Wilson, D. M. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 1032.
14. Sander, K.; Kottke, T.; Stark, H. *Biol. Pharm. Bull.* **2008**, *31*, 2163.
15. Pierson, P. D.; Fettes, A.; Freichel, C.; Gatti-McArthur, S.; Hertel, C.; Huwyler, J.; Mohr, P.; Nakagawa, T.; Nettekoven, M.; Plancher, J.-M.; Raab, S.; Richter, H.; Roche, O.; Rodriguez Sarmiento, R. M.; Schmitt, M.; Schuler, F.; Takahashi, T.; Taylor, S.; Ullmer, C.; Wiegand, R. *J. Med. Chem.* **2009**, *52*, 3855.
16. Roche, O.; Nettekoven, M.; Vivian, W.; Rodriguez Sarmiento, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4377.
17. (a) Bentley, J. M.; Hebeisen, P.; Muller, M.; Richter, H.; Roever, S.; Mattei, P.; Taylor, S. WO2002010169, 2002.; (b) Bentley, J. M.; Hebeisen, P.; Muller, M.; Richter, H.; Roever, S.; Mattei, P.; Taylor, S. *Chem. Abstr.* **2002**, *136*, 167392; (c) Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164.
18. Enantiomeric excess in the S_N2 reaction was determined by means of chiral HPLC using 40% isopropanol in *n*-heptane as mobile and Chiralpak-AD as stationary phase. The absolute configuration was assigned as previously shown by two X-ray structures on analogous substrates: (a) Roever, S.; Adam, D. R.; Benardeau, A.; Bentley, J. M.; Bickerdike, M. J.; Bourson, A.; Cliffe, I. A.; Coassolo, P.; Davidson, J. E. P.; Dourish, C. T.; Hebeisen, P.; Kennett, G. A.; Knight, A. R.; Malcolm, C. S.; Mattei, P.; Misra, A.; Mizrahi, J.; Muller, M.; Porter, R. H. P.; Richter, H.; Taylor, S.; Vickers, S. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3604; (b) Richter, Hans G. F.; Adams, D. R.; Benardeau, A.; Bickerdike, M. J.; Bentley, J. M.; Blench, T. J.; Cliffe, I. A.; Dourish, C.; Hebeisen, P.; Kennett, G. A.; Knight, A. R.; Malcolm, C. S.; Mattei, P.; Misra, A.; Mizrahi, J.; Monck, N. J. T.; Plancher, J. -M.; Roever, S.; Roffey, J. R. A.; Taylor, S.; Vickers, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1207.
19. Boehringer, M.; Hunziker, D.; Kuehne, H.; Loeffler, B. M.; Sarabu, R.; Wessel, H. P. WO2003037327, 2003.; Boehringer, M.; Hunziker, D.; Kuehne, H.; Loeffler, B. M.; Sarabu, R.; Wessel, H. P. *Chem. Abstr.* **2003**, *138*, 368754.
20. Hino, T.; Hasegawa, A.; Liu, J. J.; Nakagawa, M. *Chem. Pharm. Bull.* **1990**, *38*, 59.
21. Popelak, A.; Stach, K.; Thiel, M.; Bartsch, W.; Dietmann, K. Ger. Offen. DE2353996, 1975.; Popelak, A.; Stach, K.; Thiel, M.; Bartsch, W.; Dietmann, K. *Chem. Abstr.* **1975**, *83*, 97251.
22. Fox, G. B.; Pan, J. B.; Esbenshade, T. A.; Bitner, R. S.; Nikkel, A. L.; Miller, T.; Kang, C. H.; Bennani, Y. L.; Black, L. A.; Faghih, R.; Hancock, A. A.; Decker, M. W. *Pharmacol. Biochem. Behav.* **2002**, *72*, 741.