Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 5251–5256
Bioorganic & Medicinal Chemistry Letters

Synthesis and structure–activity relationships of indole and benzimidazole piperazines as histamine H_4 receptor antagonists

Nalan Terzioglu,[a,b] Richard M. van Rijn,[b] Remko A. Bakker,[b] Iwan J. P. De Esch[b] and Rob Leurs[b,*]

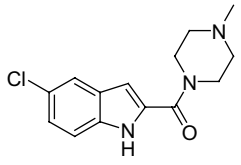
[a]*Istanbul University, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, 34452 Istanbul, Turkey*
[b]*Leiden/Amsterdam Center of Drug Research (LACDR), Division of Medicinal Chemistry, Department of Pharmacochemistry, Faculty of Chemistry, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands*

Received 11 June 2004; revised 5 August 2004; accepted 17 August 2004
Available online 16 September 2004

Abstract—We describe the structure–activity relationships for a series of ligands structurally related to the recently identified (5-chloro-1*H*-indol-2-yl)-(4-methyl-piperazin-1-yl)-methanone (**1**) as histamine H_4 receptor (H_4R) antagonists. Furthermore, we identified related benzimidazoles as novel lead compounds for the H_4R. The ligands have been evaluated by radioligand displacement studies and functional assays for their interaction with both the human histamine H_3 and H_4 receptors and exhibit pK_i values up to 7.5 at the human H_4R.

The biogenic amine histamine mediates its physiological actions via a variety of G-protein coupled receptors.[1] Recently, a novel histamine receptor subtype, the H_4 receptor (H_4R), was cloned independently by several groups.[2–6] The H_4R is preferentially expressed in various cells of the immune system and mast cells and induces the chemotaxis of for example eosinophils and mast cells.[7,8] Consequently, the H_4R is considered to be a promising new drug target[4] and initial studies have indicated that H_4R antagonists are effective in various models of inflammatory conditions.[9]

The H_4R shows considerable homology with the H_3 receptor (H_3R) and many of the known H_3R agonists and antagonists also bind the H_4R, albeit with a different pharmacological profile.[1] At this moment the development of potent and selective H_4R ligands is therefore of utmost importance as it will provide molecular tools to further characterize the H_4R and to explore the therapeutic potential of H_4R related drugs. Recently, we have reported on (−)-2-cyano-1-methyl-3-{(2*R*,5*R*)-5-[1*H*-imidazol-4(5)-yl]tetrahydrofuran-2-yl}methylguanidine as an H_4 receptor agonist with a 40-fold selectivity over the H_3R.[10] Moreover, the first nonimidazole H_4R antagonist (**1**) has recently been reported by Jablonowski et al.[11] This compound shows a good selectivity over other histamine receptors and shows interesting anti-inflammatory activities in vivo as well.[9,11] In this study we report on our efforts to convert this lead compound into a [^{125}I]-labeled derivative as pharmacological tool for H_4R studies and to obtain structure–activity relationships within this class of compounds.

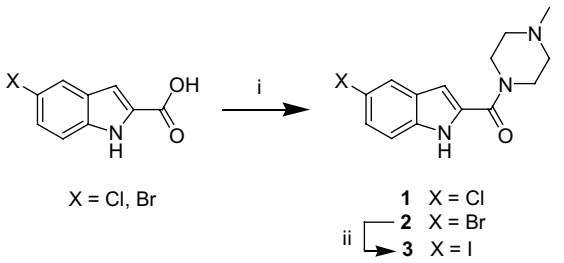


1

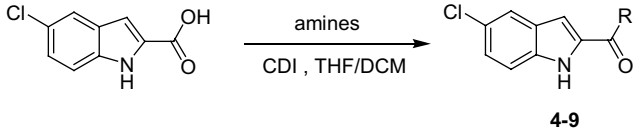
The synthesis of the indolepiperazines **1**–**3** is outlined in Scheme 1. Commercially available 5-halo-2-indolecarboxylic acids were coupled with N-methylpiperazine using N,N′-carbonyldiimidazole (CDI) as coupling agent to form compound **1** and **2**.[12] Halide exchange of compound **2** with potassium iodide and copper iodide in hexamethylphosphoric triamide (HMPA)[13,14] resulted in the iodo analogue **3**. Using the same procedure as for the synthesis of **1** and **2**, 5-chloro-2-indolecarboxylic acid was coupled to a range of amines to give analogues **4**–**9** as indicated in Scheme 2.

Keywords: Histamine H_4 receptor; Antagonists.
* Corresponding author. Tel.: +31 20 4447600; fax: +31 20 4447610; e-mail: leurs@few.vu.nl

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.08.035



Scheme 1. Synthetic pathway of **1**–**3**. Reagent and conditions: (i) 1-methylpiperazine, CDI, THF, 0 °C; (ii) KI, CuI, HMPA, 155 °C.

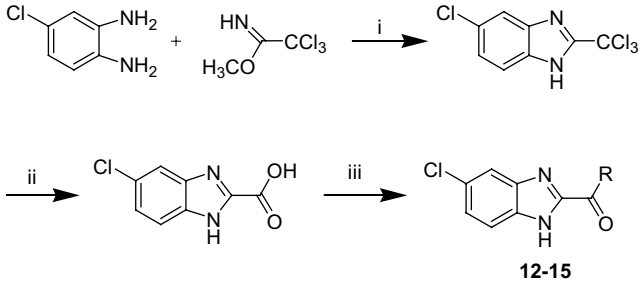


Scheme 2. Synthetic pathway of **4**–**9**.

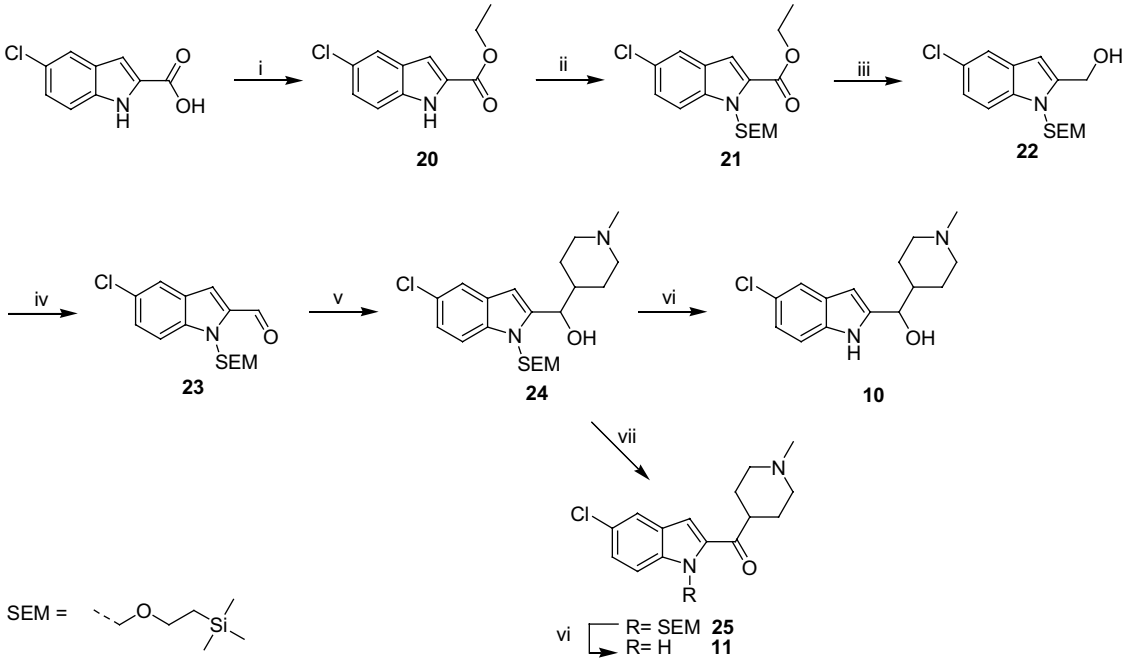
Compounds **10** and **11** were prepared according to Scheme 3. Starting from 5-chloro-2-indolecarboxylic acid, the ethyl ester **20** was readily prepared by means of an excess of absolute ethanol saturated with HCl gas. Reaction of **20** with 55% sodium hydride in THF followed by treatment with [2-(trimethylsilyl)ethoxy]methyl chloride (SEM-Cl) gave SEM-protected derivative **21**.[15,16] Reduction of the intermediate **21** using $LiAlH_4$ resulted in the alcohol **22**,[17] which was subsequently transformed into the aldehyde **23** via a Swern oxidation reaction.[18,19] The key intermediate, [5-chloro-1-(2-(trimethylsilyl)ethoxymethyl)-1H-indol-2-yl]-(1-methyl- piperidin-4-yl)-methanol **24** was easily obtained from its aldehyde analogue **23** via a Grignard reaction in the presence of 4-chloro-1-methyl-4-chloropiperidine and dibromoethane.[20] The intermediate **24** was transformed to the ketone **25** via a Swern oxidation reaction.[21] The reaction of SEM-protected intermediates **24** and **25** with tetrabutylammonium fluoride monohydrate in the presence of ethylenediamine resulted in good yields of the deprotected indoles **10** and **11**, respectively.[22]

To obtain the 5-chloro-2-benzimidazolecarboxamides **12**–**15**, 5-chloro-2-benzimidazole-carboxylic acid, which was synthesized according to literature procedures,[23,24] activated with CDI and the intermediate imidazolide was treated with different amines (Scheme 4).[25,26]

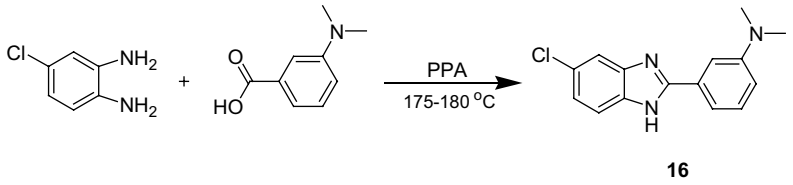
Cyclization of 4-chloro-1,2-phenylenediamine and 3-dimethylaminobenzoic acid in PPA afforded compound **16**[27] (Scheme 5). While the acetyl analogue of 2-amino-



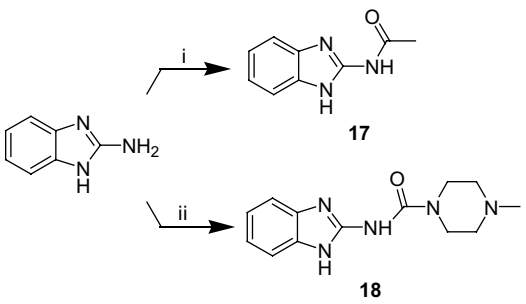
Scheme 4. Synthetic pathway of **12**–**15**. Reagents and conditions: (i) CH_3COOH; (ii) (1) 1 N NaOH, (2) 1 N HCl; (iii) amine, CDI, DMF, 0 °C.



Scheme 3. Synthetic pathway of **10**–**11**. Reagents and conditions: (i) EtOH/HCl; (ii) [2-(trimethylsilyl)ethoxy]methyl chloride, THF, 0 °C; (iii) $LiAlH_4$, THF, 0 °C; (iv) oxalyl chloride, dimethyl sulfoxide, triethylamine, DCM, −60 °C to rt; (v) 1-methyl-4-chloropiperidine, Mg, $BrCH_2CH_2Br$, THF; (vi) $TBAF{\cdot}H_2O$, ethylendiamine, DMF; (vii) oxalyl chloride, dimethyl sulfoxide, triethylamine, DCM, −78 °C to rt.



Scheme 5. Synthetic pathway of **16**.



Scheme 6. Synthetic pathway of **17** and **18**. Reagents and conditions: (i) Ac_2O; (ii) (1) 1-methylpiperazine, CDI, DCM, rt to 0 °C.

benzimidazole, compound **17**, was formed with Ac_2O,[28] its urea analogue **18** was synthesized by carbamoylation of 2-aminobenzimidazole and 1-methylpiperazine with CDI as shown in Scheme 6.[29] The evaluation of the compounds for their affinity for H_3 and H_4 receptors was performed using SK-N-MC cells, stably expressing either the human histamine H_3R or the human histamine H_4R. Cell homogenates of H_3R expressing cells (475 ± 32 fmol/mg of protein) were incubated for 40 min at 25 °C with 0.9–1.1 nM [^{3}H]-N^{α}-methylhistamine (82 Ci/mmol) in 50 mM sodium phosphate buffer (pH 7.4) with or without competing ligands whereas cell homogenates of H_4R expressing cells (620 ± 44 fmol/mg of protein) were incubated for 60 min at 37 °C with 9–11 nM [^{3}H]-histamine (23.2 Ci/mmol) in 50 mM Tris HCl (pH 7.4), with or without competing ligands. Incubations were terminated by the addition of 3 mL ice-cold wash buffer (for H_3R binging: 25 mM Tris HCl, 145 mM NaCl, pH 7.4 at 4 °C; for H_4R binding: 50 mM Tris HCl, pH 7.4 at 4 °C) and filtered through 0.3% polyethyleneimine pretreated Whatman GF/C filters. Filters were subsequently washed twice with wash buffer. Retained radioactivity was determined by liquid scintillation counting. Nonspecific binding was defined with 1 μM thioperamide as competing ligand. Competition isotherms were analyzed with the GraphPad Prism software (GraphPad, Intuitive Software for Science, San Diego, CA). K_i values were determined with the equation $K_i = IC_{50}/(1 + ([ligand]/K_d))$. Protein concentrations were determined spectrophotometrically by a Packard Argus 400 Microplate Reader using the Bradford reagent,[30] with bovine serum albumin as a standard. The functional evaluation of the compounds was performed using SK-N-MC cells stably expressing a cyclic AMP responsive element (CRE)-responsive β-galactosidase reporter-gene and either the human histamine H_3R or the human histamine H_4R were incubated for 6 h with 1 μM (hH_4R) or 1.5 μM (hH_3R) forskolin and respective ligands at 37 °C the day after the cells were seeded in 96-well plates. Thereafter, the medium was aspirated and cells were incubated overnight at 4 °C with 100 μL of assay buffer 100 mM NaH_2PO_4, 100 mM Na_2HPO_4, pH 8, 2 mM $MgSO_4$, 0.1 mM $MnCl_2$, 0.5% Triton, 40 mM β-mercaptoethanol, and 4 mM *o*-nitrophenyl-β-D-galactopyranoside (ONPG) and the absorbance at 405 nm was determined.

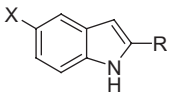
Compound **1**, 5-chloroindole-2-piperazinecarboximide, is the first described selective H_4R antagonist ($pA_2 = 8.0 \pm 0.1$).[9] In our hands, the compound also shows high affinity for the human H_4R (Table 1). In this study, SAR explorations were undertaken, using the reference compound **1**, in order to investigate if the H_4R affinity of this class of compounds can be further increased. Substitution of the chloro atom of **1** with bromine and iodine induced a small to moderate decrease in H_4R affinity ($pK_i = 7.5$ for **2** and 7.2 for **3**, respectively). The moderate H_4R affinity of compound **3** did not encourage us to synthesize a [^{125}I]-labeled analogue. Taking into account the affinity of the few known H_4R ligands, we consider an affinity <30 nM a premise for a H_4R radioligand to be useful as a powerful pharmacological tool.

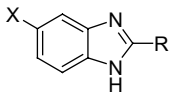
Replacement of the piperazine ring by more flexible moieties results in derivatives with a decreased H_4R affinity, while introduction of ethylenediamines (compound **4** and **5**) yielded low affinity ($pK_i = 5.5$ and 4.6, respectively), and elongation of the spacer between the two nitrogen atoms (propylenediamine, compound **6**) results in a complete loss of H_4R affinity. Conversion of piperazine **1** into the aminopiperazine **7** results in a more than 1000-fold decrease in affinity for the H_4R.

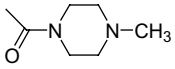
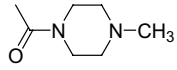
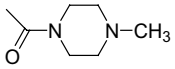
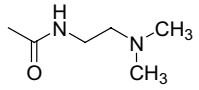
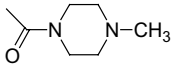
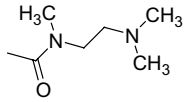
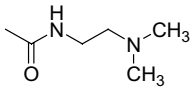
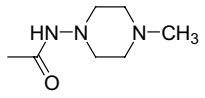
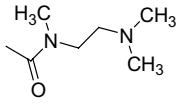
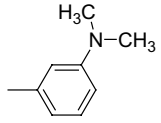
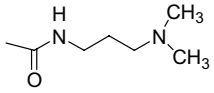
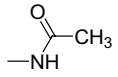
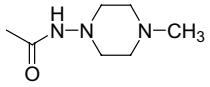
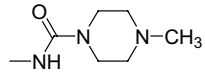
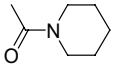
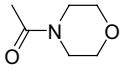
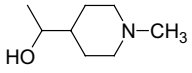
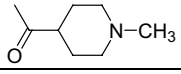
The importance of the basic nitrogen atom in the piperazine ring was confirmed by the preparation of compound **8** and **9**, which both exhibit low H_4R affinities. Removing the nitrogen atom of the amide moiety results in the ketone analogue **11** with only moderate H_4R affinity. The hydroxy intermediate **10** showed a 3-fold reduced H_4R affinity compared to the more rigid ketone compound **11**.

Next, we attempted to replace the indole system with a benzimidazole ring, resulting in compound **12**. Compound **12** exhibits considerable H_4R affinity ($pK_i = 7.1$). This ligand is only slightly less effective than the lead compound **1** and shows only moderate affinity for the H_3 receptor (Fig. 1A, Table 2). Similar to **1**, compound **12** exhibits a 50-fold selectivity in affinity for the H_4R over the H_3R. As reported before,[3,4] the H_4R

Table 1. Affinities of histamine and various indole and benzimidazole derivatives for the human histamine H_4R





No.	X	R	pK_i ± SEM[a]	No.	X	R	pK_i ± SEM[a]
Histamine			8.1 ± 0.1				
1	Cl		7.7 ± 0.1	**12**	Cl		7.1 ± 0.1
2	Br		7.5 ± 0.1	**13**	Cl		6.0 ± 0.1
3	I		7.2 ± 0.1	**14**	Cl		4.6 ± 0.1
4	Cl		5.5 ± 0.1	**15**	Cl		<4
5	Cl		4.6 ± 0.1	**16**	Cl		<4
6	Cl		<4	**17**	H		<4
7	Cl		4.6 ± 0.1	**18**	H		4.7 ± 0.1
8	Cl		5.1 ± 0.1				
9	Cl		<4				
10	Cl		5.3 ± 0.1				
11	Cl		6.7 ± 0.1				

[a] The pK_i values were measured by [^{3}H]-histamine binding to membranes of SK-N-MC cells expressing the human H_4R. The results were presented as the mean ± SEM of at least three independent experiments.

shows considerable constitutive activity and in our hands this can be inhibited by the H_3R and H_4R inverse agonist thioperamide (data not shown). In the same assay none of the tested compounds act as agonists or inverse agonists. Detailed analyses indicate that compounds **1** and **12** behave as neutral antagonists on the H_4R. As a neutral antagonist **12** is able to antagonize the effect of histamine on the H_4R in a competitive manner. The rightward shifts produced by various concentrations of **12** (Fig. 1B) give rise to a Schild plot with a slope that is not significantly different from unity and yielding a pA_2 value of 7.1 ± 0.2. For compound **1** a pA_2 value of 8.0 ± 0.1 was obtained as a neutral antagonists against histamine. Interestingly, at the H_3R both ligands act as inverse agonists (Table 2).

Replacement of the piperazine moiety of the benzimidazole derivative **12** with conformationally less constrained groups results in compounds **13** and **14** that exhibit a decreased H_4R affinity compared to **12**. A similar effect is seen for the indole derivatives (compare **1**, **4**, and **5**). The H_4R affinity of benzimidazole **15** was also decreased compared to its indole derivative **7**. Dimethylaminophenyl **16** and acetylamino **17** derivatives did not show any H_4R affinity. The urea derivative **18**, which has an NH group between carbonyl and benzimidazole ring showed a 120-fold lower H_4R affinity than compound **12**.

In conclusion, the structure–activity relationships of the indole piperazine **1** indicate that only limited variation is

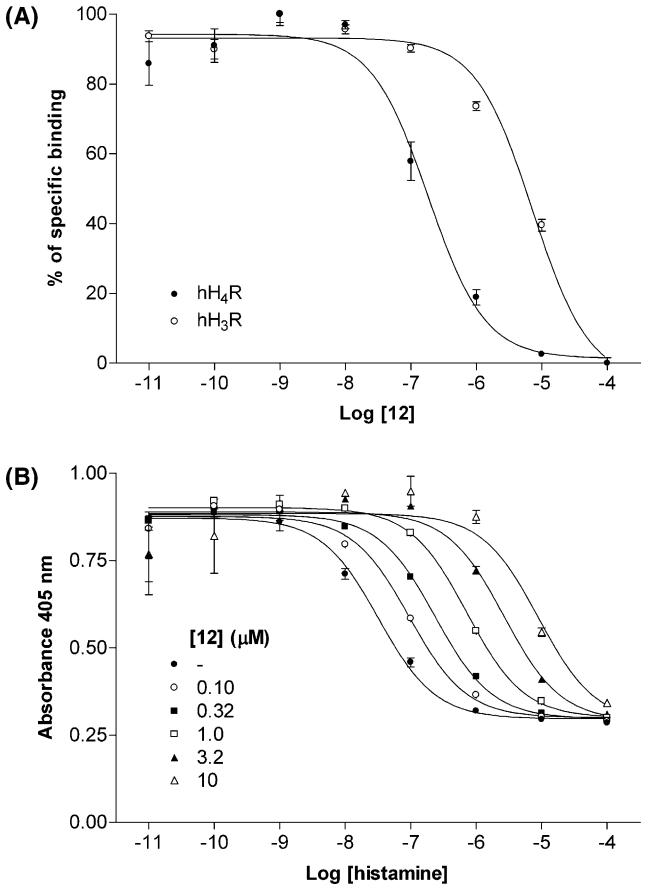


Figure 1. (A) Displacement of [^{3}H]-histamine on SK-N-MC-hH$_4$ R cells (closed circles), and displacement of [^{3}H]-N$^\alpha$-methylhistamine on SK-N-MC-hH$_3$R cells (open circles) by compound **12**. (B) The effect of compound **12** on the concentration–response curve of histamine in the SK-N-MC-hH$_4$R cells.

Table 2. Affinities and functional activities of histamine, indole and benzimidazole derivatives for the human histamine H$_3$R

No.	Human histamine H$_3$ receptor		
	pK_i ± SEM[a]	pEC$_{50}$ ± SEM[b]	Intrinsic activity (α)
1	5.7 ± 0.1	6.0 ± 0.1	−0.7
2	5.5 ± 0.1	5.8 ± 0.1	−0.7
3	5.6 ± 0.1	5.5 ± 0.3	−0.8
4	5.3 ± 0.1	—	0
8	5.2 ± 0.1	5.5 ± 0.2	−0.6
10	5.8 ± 0.1	6.0 ± 0.1	−0.5
11	5.5 ± 0.1	6.0 ± 0.1	−0.5
12	5.4 ± 0.1	5.5 ± 0.1	−1.0
13	4.6 ± 0.1	5.5 ± 0.1	−0.5

The results were presented as the mean ± SEM of at least three independent experiments.

[a] The pK_i values were measured by [^{3}H]-N^α-methylhistamine binding to membranes of SK-N-MC cells expressing the human H$_3$R.

[b] The pEC$_{50}$ values were determined by the inhibition of the cAMP-stimulated β-galactosidase transcription in SK-N-MC cell expressing the human H$_3$R.

allowed in this series of compounds. However, we have found that the indole moiety can be replaced by the benzimidazole heterocycle and novel benzimidazole-containing compounds with moderate to good H$_4$R affinity are presented. While this manuscript was in preparation, benzimidazoles, including compound **12**, were also reported as H$_4$R antagonists in a patent by Carruthers et al.[31] Since the benzimidazoles have different physiochemical properties compared to their indole analogs (e.g., improved solubility), these molecules are important new assets in the histamine H$_4$R research field.

Acknowledgements

This work was supported in part (N.T.) by Scientific Human Resources Development (BAYG NATO-B2) with financial aid from The Scientific and Technical Research Council of Turkey (TUBITAK). The cells stably expressing the human histamine H$_3$Rs and H$_4$Rs were a gift from Dr. T. Lovenberg (Johnson and Johnson Pharmaceutical Research and Development, L.L.C., San Diego, USA).

References and notes

1. Hough, L. Genomics Meets Histamine Receptors: New Subtypes, New Receptors. *Mol. Pharmacol.* **2001**, *59*, 415–419.
2. Oda, T.; Morikawa, N.; Saito, Y.; Masuho, Y.; Matsumoto, S. Molecular Cloning and Characterization of a Novel Type of Histamine Receptor Preferentially Expressed in Leukocytes. *J. Biol. Chem.* **2000**, *275*, 36781–36786.
3. 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. Cloning and Pharmacological Characterization of a Fourth Histamine Receptor H$_4$ Expressed in Bone Marrow. *Mol. Pharmacol.* **2001**, *59*, 420–426.
4. Morse, K. L.; Behan, J.; Laz, T. M.; West, R. E.; Greenfeder, S. A.; Anthes, J. C.; Umland, S.; Wan, Y.; Hipkin, R. W.; Gonsiorek, W.; Shin, N.; Gustafson, E. L.; Qiao, X.; Wang, S.; Hedrick, J. A.; Grene, J.; Bayne, M.; Monsma, F. J. Cloning and Characterization of a Novel Human Histamine Receptor. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 1058–1066.
5. Nguyen, T.; Shapiro, D. A.; George, S. R.; Setola, V.; Lee, D. K.; Cheng, R.; Rauser, L.; Lee, S. P.; Lynch, K. R.; Roth, B. L.; O'Dowd, B. F. Discovery of a Novel Member of the Histamine Receptor Family. *Mol. Pharmacol.* **2001**, *59*, 427–433.
6. Zhu, Y.; Michalovich, D.; Wu, H. L.; Tan, K. B.; Dytko, G. M.; Mannan, I. J.; Boyce, R.; Alson, J.; Tierney, L. A.; Li, X.; Herrity, N. C.; Vawter, L.; Sarau, H. M.; Ames, R. S.; Davenport, C. M.; Hieble, J. P.; Wilson, S.; Bergsma, D. J.; Fitzgerald, L. R. Cloning, Expression, and Pharmacological Characterization of a Novel Human Histamine Receptor. *Mol. Pharmacol.* **2001**, *59*, 434–441.
7. Hofstra, C. L.; Desai, P. J.; Thurmond, R. L.; Fung-Leung, W. P. Histamine H$_4$ Receptor Mediates Chemotaxis and Calcium Mobilization of Mast Cells. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 1212–1221.
8. O'Reilly, M.; Alpert, R.; Jenkinson, S.; Gladue, R. P.; Foo, S.; Trim, S.; Peter, B.; Trevethick, M.; Fidock, M. Identification of a Histamine H$_4$ Receptor on Human Eosinophils—Role in Eosinophil Chemotaxis. *J. Recept. Signal. Tr. Res.* **2002**, *22*, 431–448.
9. Thurmond, R. L.; Desai, P. J.; Dunford, P. J.; Fung-Leung, W. P.; Hofstra, C. L.; Jiang, W.; Nguyen, S.; Riley, J. P.; Sun, S.; Williams, K. N.; Edwards, J. P.; Karlsson, L. A Potent and Selective Histamine H$_4$ Receptor Antagonist with Anti-inflammatory Properties. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 404–413.

10. Hashimoto, T.; Harusawa, S.; Araki, L.; Zuiderveld, O. P.; Smit, M. J.; Imazu, T.; Takashima, S.; Yamamoto, Y.; Sakamoto, Y.; Kurihara, T.; Leurs, R.; Bakker, R. A.; Yamatodani, A. A Selective Human $H(_4)$-Receptor Agonist: (−)-2-Cyano-1-methyl-3-{(2*R*,5*R*)-5-[1H-imidazol-4(5)-yl]tetrahydrofuran-2-yl}methylguanidine. *J. Med. Chem.* **2003**, *46*, 3162–3165.
11. Jablonowski, J. A.; Grice, C. A.; Chai, W.; Dvorak, C. A.; Venable, J. D.; Kwok, A. K.; Ly, K. S.; Wei, J.; Baker, S. M.; Desai, P. J.; Jiang, W.; Wilson, S. J.; Thurmond, R. L.; Karlson, L.; Edwards, J. P.; Lovenberg, T. W.; Carruthers, N. I. The First Potent and Selective Non-Imidazole Human Histamine H_4 Receptor Antagonists. *J. Med. Chem.* **2003**, *46*, 3957–3960.
12. Romero, D. L.; Morge, R. A.; Biles, C.; Berrios-Pena, N.; May, P. D.; Palmer, J. R.; Johnson, P. D.; Smith, H. W.; Busso, M.; Tan, C.; Voorman, R. L.; Reusser, F.; Althaus, I. W.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G.; Aristoff, P. A. Discovery, Synthesis, and Bioactivity of Bis(heteroaryl)piperazines.1. A Novel Class of Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1994**, *37*, 999–1014.
13. Suziki, H.; Kondo, A.; Ogawa, T. Preparation of Aromatic Iodides from Bromides via The Reverse Halogen Exchange. *Chem. Lett.* **1985**, 411–412.
14. Sabelle, S.; Renard, P.-Y.; Pecorella, K.; Suzzoni-Dezard, S.; Creminon, C.; Grassi, J.; Mioskowski, C. Design and Synthesis of Chemiluminescent Probes for the Detection of Cholinesterase Activity. *J. Am. Chem. Soc.* **2002**, *124*, 4874–4880.
15. Bennasar, M. L.; Vidal, B.; Bosch, J. Biomimetic Total Synthesis of Ervitsine and Indole Alkaloids of the Ervatamine Group via 1,4-Dihydropyridines. *J. Org. Chem.* **1997**, *62*, 3597–3609.
16. Labadie, S. S.; Teng, E. Indol-2-yltributylstannane: A Versatile Reagent for 2-Substituted Indoles. *J. Org. Chem.* **1994**, *59*, 4250–4254.
17. Brehm, W. J. Derivatives on Indole-2-Carboxylic Acid. *J. Am. Chem. Soc.* **1949**, *71*, 3541–3542.
18. Luca, L.; Giacomelli, G.; Porcheddu, A. A Mild and Efficient Alternative to the Classical Swern Oxidation. *J. Org. Chem.* **2001**, *66*, 7907–7909.
19. Omura, K.; Swern, D. Oxidation of Alcohols by 'Activated' Dimethyl sulfoxide. A Preparative Steric and Mechanistic Study. *Tetrahedron* **1978**, *34*, 1651–1660.
20. Ashton, M. J.; Ashford, A.; Loveless, A. H.; Riddell, D.; Salmon, J.; Stevenson, G. V. W. Heterocyclic Analogues of Chlorcyclizine with Potent Hypolipidemic Activity. *J. Med. Chem.* **1984**, *27*, 1245–1253.
21. Kitbunnadaj, R.; Zuiderveld, O. P.; De Esch, I. J. P.; Vollinga, R. C.; Bakker, R.; Lutz, M.; Spek, A. L.; Cavoy, E.; Deltent, M.-F.; Menge, W. M. P. B.; Timmerman, H.; Leurs, R. Synthesis and Structure–Activity Relationships of Conformationally Constrained Histamine H_3 Receptor Agonists. *J. Med. Chem.* **2003**, *46*, 5445–5457.
22. Passarella, D.; Favia, R.; Giardini, A.; Lesma, G.; Martinelli, M.; Silvani, A.; Danieli, B.; Efange, S. M. N.; Mash, D. C. Ibogaine Analogues. Synthesis and Preliminary Pharmacological Evaluation of 7-Heteroaryl-2-azabicyclo[2.2.2]oct-7-enes. *Bioorg. Med. Chem.* **2003**, *11*, 1007–1014.
23. Louvet, P.; Lallement, G.; Pernot-Marino, I.; Luu-Duc, C.; Blanchet, G. Novel Benzimidazoles as Ligands for the Stychnine-Insensitive N-methyl-D-aspartate-Linked Glycine Receptor. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 123–129.
24. Dannhardt, G.; Kohl, B. K. Benzimidazoles as NMDA Glycine-Site Antagonists: Study on Structural Requirements in 2-Position of the Ligands. *Eur. J. Med. Chem.* **1993**, *28*, 71–75.
25. Battagliaa, S.; Boldrinib, E.; Da Settimoa, F.; Dondioc, G.; La Mottaa, C.; Marinia, A. M.; Primofiorea, G. Indole Amide Derivatives: Synthesis, Structure–Activity Relationships and Molecular Modelling Studies of a New Series of Histamine H_1-Receptor Antagonists. *Eur. J. Med. Chem.* **1999**, *34*, 93–105.
26. Ponasik, J. A.; Conova, S.; Kinghorn, D.; Kinney, W. A.; Rittschof, D.; Ganem, B. Pseudoceratidine, A Marine Natural Product with Antifouling Activity: Synthetic and Biological Studies. *Tetrahedron* **1998**, *54*, 6977–6986.
27. Lee, I. H.; Jeoung, E. H.; Kreevoy, M. M. Marcus Theory of a Parallel Effect on R for Hydride Transfer Reaction Between NAD+ Analogues. *J. Am. Chem. Soc.* **1997**, *119*, 2722–2728.
28. Ohemengt, K. A.; Roth, B. Receptor-Based Design of Novel Dihydrofolate Reductase Inhibitors: Benzimidazole and Indole Derivatives. *J. Med. Chem.* **1991**, *34*, 1383–1394.
29. Matsuno, K.; Ichimura, M.; Nakajima, T.; Tahara, K.; Fujiwara, S.; Kase, H.; Ushiki, J.; Geise, N. A.; Pandey, A.; Scarborough, R. M.; Lokker, N. A.; Yu, J.-C.; Irie, J.; Tsukuda, E.; Ide, S.; Oda, S.; Nomoto, Y. Potent and Selective Inhibitors of Platelet-Derived Growth Factor Receptor Phosphorylation. 1. Synthesis, Structure–Activity Relationship, and Biological Effect of a New Class of Quinazoline Derivatives. *J. Med. Chem.* **2002**, *45*, 3057–3066.
30. Bradford, M. A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding. *Anal. Biochem.* **1976**, *72*, 248–254.
31. Carruthers, N. I.; Dvorak, C. A.; Edwards, J. P.; Grice, C. A.; Jablonowski, J. A.; Ly, K. S.; Pio, B. A.; Shah, C. R.; Venable, J. D. Preparation of Nitrogen Containing Heterocyclic Compounds as Compounds Useful for in the Treatment of Histamine H_4 Receptor Mediated Diseases. PCT Int. Appl. (2004), 70 pp. CODEN: PIXXD2 WO 2004022060 A2 20040318 Application: WO 2003-US27461 20030904. Priority: US 2002-408569 20020906. CAN 140:270852 AN 2004:220205 CAPLUS.