

## **7 Literaturverzeichnis**

- (1) Windaus, A.; Vogt, W. Synthese des Imidazolyl-ethylamins. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3691-3695.
- (2) Ackermann, D. Über den Ursprung der Basen bei der Verwesung. *Z. Physiol. Chem.* **1910**, *60*, 482-501.
- (3) Bovet, D.; Staub, A. M. Protective Action of Some Phenolic Ethers in Histamine Intoxication. *Compt. Rend. Soc. Biol. (Paris)* **1937**, *124*, 547-549.
- (4) Halpern, B. N. Synthetic Antihistamine Substances. *Arch. Int. Pharmacodyn. Ther.* **1942**, *68*, 339-352.
- (5) Ash, A. S.; Schild, H. O. Receptors Mediating Some Actions of Histamine. *Br. J. Pharmacol. Chemother.* **1966**, *27*, 427-439.
- (6) Black, J. W.; Duncan, W. A.; Durant, C. J.; Ganellin, C. R.; Parsons, E. M. Definition and Antagonism of Histamine H<sub>2</sub>-Receptors. *Nature* **1972**, *236*.
- (7) Arrang, J. M.; Garbarg, M.; Schwartz, J. C. Auto-Inhibition of Brain Histamine Release Mediated by a Novel Class (H3) of Histamine Receptor. *Nature* **1983**, *302*, 832-837.
- (8) Arrang, J. M.; Garbarg, M.; Lancelot, J. C.; Lecomte, J. M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J. C. Highly Potent and Selective Ligands for Histamine H<sub>3</sub>-Receptors. *Nature* **1987**, *327*, 117-123.
- (9) Arrang, J. M.; Garbarg, M.; Schwartz, J. C. Autoinhibition of Histamine Synthesis Mediated by Presynaptic H<sub>3</sub>-Receptors. *Neurosci.* **1987**, *23*, 149-157.
- (10) Arrang, J. M.; Garbarg, M.; Schwartz, J. C. Autoregulation of Histamine Release in Brain by Presynaptic H<sub>3</sub>-Receptors. *Neurosci.* **1985**, *15*, 553-562.
- (11) Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Jiang, X.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. Cloning and Functional Expression of the Human Histamine H<sub>3</sub>-Receptor. *Mol. Pharmacol.* **1999**, *55*, 1101-1107.
- (12) 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.
- (13) 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<sub>4</sub>) Expressed in Bone Marrow. *Mol. Pharmacol.* **2001**, *59*, 420-426.
- (14) 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.
- (15) Zhu, Y.; Michalovich, D.; Wu, H.; Tan, K. B.; Dytko, G. M.; Mannan, I. J.; Boyce, R.; Alston, 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.
- (16) Morse, K. L.; Behan, J.; Laz, T. M.; West, R. E., Jr.; 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.; Greene, J.; Bayne, M.; Monsma, F. J., Jr. Cloning and Characterization of a Novel Human Histamine Receptor. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 1058-1066.

- (17) Coge, F.; Guenin, S. P.; Rique, H.; Boutin, J. A.; Galizzi, J. P. Structure and Expression of the Human Histamine H<sub>4</sub>-Receptor Gene. *Biochem. Biophys. Res. Commun.* **2001**, *284*, 301-309.
- (18) Raible, D. G.; Lenahan, T.; Fayvilevich, Y.; Kosinski, R.; Schulman, E. S. Pharmacologic Characterisation of a Novel Histamine Receptor on Human Eosinophils. *Am. J. Respir. Crit. Care Med.* **1994**, *149*, 1506-1511.
- (19) Corbel, S.; Traiffort, E.; Stark, H.; Schunack, W.; Dy, M. Binding of Histamine H<sub>3</sub>-Receptor Antagonists to Hematopoietic Progenitor Cells. Evidence for a Histamine Transporter Unrelated to Histamine H<sub>3</sub>-Receptors. *FEBS Lett.* **1997**, *404*, 289-293.
- (20) Black, J. W.; Ganellin, C. R. Naming of Substituted Histamines. *Experientia* **1974**, *30*, 111-113.
- (21) Ganellin, C. R. The Tautomer Ratio of Histamine. *J. Pharm. Pharmacol.* **1973**, *25*, 787-792.
- (22) Durant, G. J.; Ganellin, C. R.; Parsons, M. E. Chemical Differentiation of Histamine H<sub>1</sub>- and H<sub>2</sub>-Receptor Agonists. *J. Med. Chem.* **1975**, *18*, 905-909.
- (23) Zhang, M. Q.; Leurs, R.; Timmermann, H. In *Burger's Medicinal Chemistry and Drug Discovery, Therapeutic Agents*; Wolff, M. E., Ed.; Wiley & Sons Inc.: New York, 1997; Vol. 5, p 495-559.
- (24) Schwartz, J. C.; Arrang, J. M.; Garbarg, M.; Pollard, H.; Ruat, M. Histaminergic Transmission in the Mammalian Brain. *Physiol. Rev.* **1991**, *71*, 1-51.
- (25) Prast, H.; Fischer, H. P.; Prast, M.; Philippu, A. *In Vivo* Modulation of Histamine Release by Autoreceptors and Muscarinic Acetylcholine Receptors in the Rat Anterior Hypothalamus. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1994**, *350*, 599-604.
- (26) Hill, S. J.; Straw, R. M. α<sub>2</sub>-Adrenoceptor-Mediated Inhibition of Histamine Release from Rat Cerebral Cortical Slices. *Br. J. Pharmacol.* **1988**, *95*, 1213-1219.
- (27) Cooper, D. G.; Young, R. C.; Durant, G. J.; Ganellin, C. R. In *Comprehensive Medicinal Chemistry: The Rational Design, Mechanistic Study & Therapeutic Application of Chemical Compounds*; Press, P., Ed.; Hansch, C.: Oxford, U. K., 1990, p 323-421.
- (28) Smits, R. P. J. M.; Steinbusch, H. W. M.; Mulder, A. H. Studies on the Specificity of Uptake and Release of Radiolabelled Histamine in Rat Brain Slices. *Neurochem. Int.* **1988**, *12*, 193-201.
- (29) Maslinski, C.; Fogel, W. Catabolism of Histamine. In *Handbook of Experimental Pharmacology*; Uvnäs, B., Ed.; Springer Verlag: Berlin, Heidelberg, 1991, p 165-189.
- (30) Schwartz, J. C.; Pollard, H.; Quach, T. T. Histamine as a Neurotransmitter in Mammalian Brain: Neurochemical Evidence. *J. Neurochem.* **1980**, *35*, 26-33.
- (31) Van der Vliet, A.; Van der Werf, J. F.; Bast, A.; Timmerman, H. Frequency-Dependent Autoinhibition of Histamine Release from Rat Cortical Slices: a Possible Role for H<sub>3</sub>-Receptor Reserve. *J. Pharm. Pharmacol.* **1988**, *40*, 577-579.
- (32) Arrang, J. M.; Roy, J.; Morgat, J. L.; Schunack, W.; Schwartz, J. C. Histamine H<sub>3</sub>-Receptor Binding Sites in Rat Brain Membranes: Modulations by Guanine Nucleotides and Divalent Cations. *Eur. J. Pharmacol.* **1990**, *188*, 219-227.
- (33) Zingel, V.; Schunack, W. Agonists of the H<sub>1</sub>-Receptors: Structure and Pharmacology. *Pharmazie* **1993**, *48*, 483-493.
- (34) Hill, S. J. Distribution, Properties, and Functional Characteristics of Three Classes of Histamine Receptor. *Pharmacol. Rev.* **1990**, *42*, 45-83.

- (35) Prast, H.; Heistracher, M.; Philippu, A. *In Vivo* Modulation of the Histamine Release in the Hypothalamus by Adrenoreceptor Agonists and Antagonists. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1991**, *344*, 183-186.
- (36) Gulat-Marnay, C.; Lafitte, A.; Arrang, J.-M.; Schwartz, J. C. Modulation of Histamine Release and Synthesis in the Brain Mediated by  $\alpha_2$ -Adrenoceptors. *J. Neurochem.* **1989**, *52*, 248-254.
- (37) Prast, H.; Prast, M.; Philippu, A. H<sub>3</sub>-Autoreceptors and Muscarinic Acetylcholine Receptors Modulate Histamine Release in the Anterior Hypothalamus of Freely Moving Rats. *Agents Actions* **1994**, *41*, C64-65.
- (38) Gulat-Marnay, C.; Lafitte, A.; Arrang, J. M.; Schwartz, J. C. Modulation of Histamine Release in the Rat Brain by  $\kappa$ -Opioid-Receptors. *J. Neurochem.* **1990**, *55*, 47-53.
- (39) Okakura, K.; Mochizuki, T.; Yamamoto, Y.; Horii, A.; Yamatodani, A. Endogenous GABA Modulates Histamine Release from the Anterior Hypothalamus of the Rat. *J. Neurochem.* **1996**, *67*, 171-176.
- (40) Morisset, S.; Sahm, U. G.; Traiffort, E.; Tardivel-Lacombe, J.; Arrang, J. M.; Schwartz, J. C. Atypical neuroleptics Enhance Histamine Turnover in Brain via 5-Hydroxytryptamine<sub>2A</sub> Receptor Blockade. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 590-596.
- (41) Arrang, J. M.; Gulat-Marnay, C.; Defontaine, N.; Schwartz, J. C. Regulation of Histamine Release in Rat Hypothalamus and Hippocampus by Presynaptic Galanin Receptors. *Peptides* **1991**, *12*, 1113-1117.
- (42) Prast, H.; Heistracher, M.; Philippu, A. Modulation by Dopamine Receptors of Histamine Release in the Rat Hypothalamus. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1993**, *347*, 301-305.
- (43) Okakura, K.; Yamatodani, A.; Mochizuki, T.; Horii, A.; Wada, H. Glutamatergic Regulation of Histamine Release from Rat Hypothalamus. *Eur. J. Pharmacol.* **1992**, *213*, 189-192.
- (44) Ono, J.; Yamatodani, A.; Kishino, J.; Okada, S.; Wada, H. Cholinergic Influence of K<sup>+</sup>-evoked Release of Endogenous Histamine from Rat Hypothalamic Slices *In Vitro*. *Meth. Find. Exp. Clin. Pharmacol.* **1992**, *14*, 35-40.
- (45) Itoh, Y.; Oishi, M.; Nishibori, M.; Saeki, K. Involvement of  $\mu$ -Receptors in the Opioid Induced Increase in the Turnover of Mouse Brain Histamine. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 1021-1026.
- (46) Chikai, T.; Oishi, R.; Saeki, K. Increase in the Extracellular Histamine Concentration in the Rat Striatum by  $\mu$ -Opioid Receptor Activation. *J. Neurochem.* **1994**, *62*, 724-729.
- (47) Schlicker, E.; Fink, K.; Hinterthaner, M.; Gothert, M. Inhibition of Noradrenaline Release in the Rat Brain Cortex via Presynaptic H<sub>3</sub>-Receptors. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1989**, *340*, 633-638.
- (48) Schlicker, E.; Werthwein, S.; Zentner, J. Histamine H<sub>3</sub>-Receptor-Mediated Inhibition of Noradrenaline Release in the Human Brain. *Fundam. Clin. Pharmacol.* **1999**, *13*, 120-122.
- (49) Schlicker, E.; Fink, K.; Detzner, M.; Gothert, M. Histamine Inhibits Dopamine Release in the Mouse Striatum via Presynaptic H<sub>3</sub>-Receptors. *J. Neural. Transm. Gen. Sect.* **1993**, *93*, 1-10.
- (50) Molina-Hernandez, A.; Nunez, A.; Arias-Montano, J. A. Histamine H<sub>3</sub>-Receptor Activation Inhibits Dopamine Synthesis in Rat Striatum. *Neuroreport* **2000**, *11*, 163-166.
- (51) Schlicker, E.; Betz, R.; Gothert, M. Histamine H<sub>3</sub>-Receptor-Mediated Inhibition of Serotonin Release in the Rat Brain Cortex. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 588-590.

- (52) Matsubara, T.; Moskowitz, M. A.; Huang, Z. UK-14,304, *R*(-)alpha-Methyl-histamine and SMS 201-995 Block Plasma Protein Leakage within Dura Mater by Prejunctional Mechanisms. *Eur. J. Pharmacol.* **1992**, *224*, 145-150.
- (53) Dimitriadou, V.; Rouleau, A.; Trung Tuong, M. D.; Newlands, G. J.; Miller, H. R.; Luffau, G.; Schwartz, J. C.; Garbarg, M. Functional Relationships Between Sensory Nerve Fibers and Mast Cells of Dura Mater in Normal and Inflammatory Conditions. *Neurosci.* **1997**, *77*, 829-839.
- (54) Willems, E.; Knigge, U.; Jorgensen, H.; Kjaer, A.; Warberg, J. Effect of Blockade of Postsynaptic H<sub>1</sub>- or H<sub>2</sub>-Receptors or Activation of Presynaptic H<sub>3</sub>-Receptors on Catecholamine-induced Stimulation of ACTH and Prolactin Secretion. *Eur. J. Endocrinol.* **2000**, *142*, 637-641.
- (55) Clapham, J.; Kilpatrick, G. J. Histamine H<sub>3</sub>-Receptors Modulate the Release of [<sup>3</sup>H]-Acetylcholine from Slices of Rat Entorhinal Cortex: Evidence for the Possible Existence of H<sub>3</sub>-Receptor Subtypes. *Br. J. Pharmacol.* **1992**, *107*, 919-923.
- (56) Arrang, J. M.; Drutel, G.; Schwartz, J. C. Characterization of Histamine H<sub>3</sub>-Receptors Regulating Acetylcholine Release in Rat Entorhinal Cortex. *Br. J. Pharmacol.* **1995**, *114*, 1518-1522.
- (57) Knigge, U.; Kjaer, A.; Jorgensen, H.; Warberg, J. Functional Role of H<sub>3</sub> Receptors in Peripheral Tissues. In *The Histamine H<sub>3</sub>-Receptor*; Leurs, R., Timmermann, H., Eds.; Elsevier: Amsterdam, 1998, p 41-58.
- (58) Knigge, U.; Soe-Jensen, P.; Jorgensen, H.; Kjaer, A.; Moller, M.; Warberg, J. Stress-induced Release of Anterior Pituitary Hormones: Effect of H<sub>3</sub> Receptor-mediated Inhibition of Histaminergic Activity or Posterior Hypothalamic Lesion. *Neuroendocrinology* **1999**, *69*, 44-53.
- (59) Clark, E. A.; Hill, S. J. Sensitivity of Histamine H<sub>3</sub>-Receptor Agonist-stimulated [<sup>35</sup>S]GTPγ[S] Binding to Pertussis Toxin. *Eur. J. Pharmacol.* **1996**, *296*, 223-225.
- (60) Leurs, R.; Hoffmann, M.; Wieland, K.; Timmerman, H. H<sub>3</sub> Receptor Gene is Cloned at Last. *Trends Pharmacol. Sci.* **2000**, *21*, 11-12.
- (61) Morisset, S.; Rouleau, A.; Ligneau, X.; Gbahou, F.; Tardivel-Lacombe, J.; Stark, H.; Schunack, W.; Ganellin, C. R.; Schwartz, J. C.; Arrang, J. M. High Constitutive Activity of Native H<sub>3</sub>-Receptors Regulates Histamine Neurons in Brain. *Nature* **2000**, *408*, 860-864.
- (62) Drutel, G.; Peitsaro, N.; Karlstedt, K.; Wieland, K.; Smit, M. J.; Timmerman, H.; Panula, P.; Leurs, R. Identification of Rat H<sub>3</sub> Receptor Isoforms with Different Brain Expression and Signaling Properties. *Mol. Pharmacol.* **2001**, *59*, 1-8.
- (63) Gomez-Ramirez, J.; Ortiz, J.; Blanco, I. Presynaptic H<sub>3</sub> Autoreceptors Modulate Histamine Synthesis Through cAMP Pathway. *Mol. Pharmacol.* **2002**, *61*, 239-245.
- (64) Cherifi, Y.; Pigeon, C.; Le Romancer, M.; Bado, A.; Reyl-Desmars, F.; Lewin, M. J. Purification of a Histamine H<sub>3</sub> Receptor Negatively Coupled to Phosphoinositide Turnover in the Human Gastric Cell Line HGT1. *J. Biol. Chem.* **1992**, *267*, 25315-25320.
- (65) Takeshita, Y.; Watanabe, T.; Sakata, T.; Munakata, M.; Ishibashi, H.; Akaike, N. Histamine Modulates High-voltage-activated Calcium Channels in Neurons Dissociated from the Rat Tuberomammillary Nucleus. *Neuroscience* **1998**, *87*, 797-805.

- (66) Endou, M.; Poli, E.; Levi, R. Histamine H<sub>3</sub>-Receptor Signaling in the Heart: Possible Involvement of G<sub>i</sub>/G<sub>o</sub> Proteins and N-type Ca<sup>++</sup> Channels. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 221-229.
- (67) Poli, E.; Pozzoli, C.; Coruzzi, G.; Bertaccini, G. Signal Transducing Mechanisms Coupled to Histamine H<sub>3</sub>-Receptors and alpha-2 Adrenoceptors in the Guinea Pig Duodenum: Possible Involvement of N-type Ca<sup>++</sup> Channels. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 788-794.
- (68) Nakamura, T.; Itadani, H.; Hidaka, Y.; Ohta, M.; Tanaka, K. Molecular Cloning and Characterization of a New Human Histamine Receptor, HH4R. *Biochem. Biophys. Res. Commun.* **2000**, *279*, 615-620.
- (69) Schwartz, J.-C.; Arrang, J.-M.; Garbarg, M.; Korner, M. Properties and Roles of the Three Subclasses of Histamine Receptors in Brain. *J. Exp. Biol.* **1986**, *124*, 203-224.
- (70) Onodera, K.; Yamatodani, A.; Watanabe, T.; Wada, H. Neuropharmacology of the Histaminergic Neuron System in the Brain and its Relationship with Behavioral Disorders. *Prog. Neurobiol.* **1994**, *42*, 685-702.
- (71) Schlicker, E.; Malinowska, B.; Kathmann, M.; Gothert, M. Modulation of Neurotransmitter Release via Histamine H<sub>3</sub>-Heteroreceptors. *Fundam. Clin. Pharmacol.* **1994**, *8*, 128-137.
- (72) Lovenberg, T. W.; Pyati, J.; Chang, H.; Wilson, S. J.; Erlander, M. G. Cloning of Rat Histamine H<sub>3</sub> Receptor Reveals Distinct Species Pharmacological Profiles. *J. Pharmacol. Exp. Ther.* **2000**, *293*, 771-778.
- (73) Tardivel-Lacombe, J.; Rouleau, A.; Heron, A.; Morisset, S.; Pillot, C.; Cochois, V.; Schwartz, J. C.; Arrang, J. M. Cloning and Cerebral Expression of the Guinea Pig Histamine H<sub>3</sub>-Receptor: Evidence for Two Isoforms. *Neuroreport* **2000**, *11*, 755-759.
- (74) Morisset, S.; Sasse, A.; Gbahou, F.; Heron, A.; Ligneau, X.; Tardivel-Lacombe, J.; Schwartz, J. C.; Arrang, J. M. The Rat H<sub>3</sub>-Receptor: Gene Organization and Multiple Isoforms. *Biochem. Biophys. Res. Commun.* **2001**, *280*, 75-80.
- (75) Wiedemann, P.; Bonisch, H.; Oerters, F.; Bruss, M. Structure of the Human Histamine H<sub>3</sub>-Receptor Gene (HRH3) and Identification of Naturally Occurring Variations. *J. Neural. Transm.* **2002**, *109*, 443-453.
- (76) Rouleau, A.; Ligneau, X.; Tardivel-Lacombe, J.; Morisset, S.; Gbahou, F.; Schwartz, J. C.; Arrang, J. M. Histamine H<sub>3</sub>-Receptor-mediated [<sup>35</sup>S]GTPγ[S] Binding: Evidence for Constitutive Activity of the Recombinant and Native Rat and Human H<sub>3</sub> Receptors. *Br. J. Pharmacol.* **2002**, *135*, 383-392.
- (77) Wieland, K.; Bongers, G.; Yamamoto, Y.; Hashimoto, T.; Yamatodani, A.; Menge, W. M.; Timmerman, H.; Lovenberg, T. W.; Leurs, R. Constitutive Activity of Histamine H<sub>3</sub> Receptors, Stably Expressed in SK-N-MC Cells: Display of Agonism and Inverse Agonism by H<sub>3</sub> Antagonists. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 908-914.
- (78) Airaksinen, M. S.; Paetau, A.; Paliärui, L.; Reinikainen, K.; Riekkinen, P.; Suomalainen, R.; Panula, P. Histamine Neurons in Human Hypothalamus : Anatomy in Normal and Alzheimer Diseased Brains. *Neuroscience* **1991**, *44*, 465-481.
- (79) Tardivel-Lacombe, J.; Morisset, S.; Gbahou, F.; Schwartz, J. C.; Arrang, J. M. Chromosomal Mapping and Organization of the Human Histamine H<sub>3</sub>-Receptor Gene. *Neuroreport* **2001**, *12*, 321-324.

- (80) Arrang, J. M.; Devaux, B.; Chodkiewicz, J. P.; Schwartz, J. C. H<sub>3</sub>-Receptors Control Histamine Release in Human Brain. *J. Neurochem.* **1988**, *51*, 105-108.
- (81) West, R. E., Jr.; Wu, R. L.; Billah, M. M.; Egan, R. W.; Anthes, J. C. The Profiles of Human and Primate [<sup>3</sup>H]-N<sup>ω</sup>-Methylhistamine Binding Differ from that of Rodents. *Eur. J. Pharmacol.* **1999**, *377*, 233-239.
- (82) Ligneau, X. M., S.; Tardivel-Lacombe, J.; Gbahou, F.; Ganellin, C. R.; Stark, H.; Schunack, W.; Schwartz, J. C.; Arrang, J. M. Distinct Pharmacology of Rat and Human Histamine H<sub>3</sub>-Receptors: Role of Two Amino Acids in the Third Transmembrane Domain. *Br. J. Pharmacol.* **2000**, *131*, 1247-1250.
- (83) Leurs, R.; Vollinga, R. C.; Timmerman, H. The Medicinal Chemistry and Therapeutic Potentials of Ligands of the Histamine H<sub>3</sub> Receptor. *Prog. Drug Res.* **1995**, *45*, 107-165.
- (84) Stark, H.; Schlicker, E.; Schunack, W. Developments of Histamine H<sub>3</sub>-Receptor Antagonists. *Drugs Future* **1996**, *21*(5), 507-520.
- (85) Rouleau, A.; Garbarg, M.; Ligneau, X.; Mantion, C.; Lavie, P.; Advenier, C.; Lecomte, J. M.; Krause, M.; Stark, H.; Schunack, W.; Schwartz, J. C. Bioavailability, Antinociceptive and Antiinflammatory Properties of BP 2-94, a Histamine H<sub>3</sub>-Receptor Agonist Prodrug. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1085-1094.
- (86) Krause, M.; Rouleau, A.; Stark, H.; Luger, P.; Lipp, R.; Garbarg, M.; Schwart, J. C.; Schunack, W. Synthesis, X-ray Crystallography, and Pharmacokinetics of Novel Azomethine Prodrugs of (R)-α-Methylhistamine: Highly Potent and Selective Histamine H<sub>3</sub>-Receptor Agonists. *J. Med. Chem.* **1995**, *38*, 4070-4079.
- (87) Ganellin, C. R.; Bang-Andersen, B.; Khalaf, Y. S.; Tertiuk, W.; Arrang, J. M.; Garbarg, M.; Ligneau, X.; Rouleau, A.; Schwartz, J. C. Imetit and N-Methyl Derivatives. The Transition from Potent Agonists to Antagonist at Histamine H<sub>3</sub>-Receptors. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1231-1234.
- (88) Garbarg, M.; Arrang, J. M.; Rouleau, A.; Ligneau, X.; Tuong, M. D.; Schwartz, J. C.; Ganellin, C. R. S-[2-(4-Imidazolyl)ethyl]isothiourea, a Highly Specific and Potent Histamine H<sub>3</sub> Receptor Agonist. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304-310.
- (89) Howson, W.; Parsons, M. E.; Raval, P.; Swayne, G. T. G. Two Novel, Potent and Selective Histamine H<sub>3</sub> Receptor Agonists. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 77-78.
- (90) Vollinga, R. C.; de Koning, J. P.; Jansen, F. P.; Leurs, R.; Menge, W. M.; Timmerman, H. A New Potent and Selective Histamine H<sub>3</sub>-Receptor Agonist, 4-(1H- Imidazol-4-ylmethyl)piperidine. *J. Med. Chem.* **1994**, *37*, 332-333.
- (91) Shih, N. Y.; Aslanian, R.; Lupo, A. T., Jr.; Orlando, S.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; West, R.; Tozzi, S.; Kreutner, W.; Hey, J. A. *Trans*-4-methyl-3-imidazoyl Pyrrolidine as a Potent, Highly Selective Histamine H<sub>3</sub> Receptor Agonist *in vivo*. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 243-248.
- (92) Hey, J. A.; Aslanian, R.; Bolser, D. C.; Chapman, R. W.; Egan, R. W.; Rizzo, C. A.; Shih, N. Y.; Fernandez, X.; McLeod, R. L.; West, R.; Kreutner, W. Studies on the Pharmacology of the Novel Histamine H<sub>3</sub> Receptor Agonist Sch 50971. *Arzneim.-Forsch. (Drug Res.)* **1998**, *48*, 881-888.

- (93) Shih, N. Y.; Lupo, A. T., Jr.; Aslanian, R.; Orlando, S.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Clark, M. A.; Tozzi, S.; Kreutner, W. A Novel Pyrrolidine Analogue of Histamine as a Potent, Highly Selective Histamine H<sub>3</sub>-Receptor Agonist. *J. Med. Chem.* **1995**, *38*, 1593-1599.
- (94) Sasse, A.; Stark, H.; Reidemeister, S.; Hüls, A.; Elz, S.; Ligneau, X.; Ganellin, C. R.; Schwartz, J. C.; Schunack, W. Novel Partial Agonists for the Histamine H<sub>3</sub>-Receptor with High *In Vitro* and *In Vivo* Activity. *J. Med. Chem.* **1999**, *42*, 42-69-4274.
- (95) Vollinga, R. C.; Menge, W. M.; Leurs, R.; Timmerman, H. Homologs of Histamine as Histamine H<sub>3</sub>-Receptor Antagonists: A New Potent and Selective H<sub>3</sub>-Antagonist, 4(5)-(5-Aminopentyl)-1*H*-imidazole. *J. Med. Chem.* **1995**, *38*, 266-271.
- (96) van der Goot, H.; Schepers, M. J. P.; Strek, G. J.; Timmerman, H. Isothiourea Analogues of Histamine as Potent Agonists or Antagonists of the Histamine H<sub>3</sub>-Receptor. *Eur. J. Med. Chem.* **1992**, *27*, 511-517.
- (97) Ligneau, X.; Lin, J.; Vanni-Mercier, G.; Jouvet, M.; Muir, J. L.; Ganellin, C. R.; Stark, H.; Elz, S.; Schunack, W.; Schwartz, J. C. Neurochemical and Behavioral Effects of Ciproxifan, a Potent Histamine H<sub>3</sub>-Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 658-666.
- (98) Sasse, A.; Sadek, B.; Ligneau, X.; Elz, S.; Pertz, H. H.; Luger, P.; Ganellin, C. R.; Arrang, J. M.; Schwartz, J. C.; Schunack, W.; Stark, H. New Histamine H<sub>3</sub>-Receptor Ligands of the Proxifan Series: Imoproxifan and Other Selective Antagonists with High Oral *In Vivo* Potency. *J. Med. Chem.* **2000**, *43*, 3335-3343.
- (99) Halpert, J. R.; Guengerich, F. P.; Bend, J. R.; Correia, M. R. Selective Inhibitors of Cytochrome P<sub>450</sub>. *Toxicol. Appl. Pharmacol.* **1994**, *53*, 1675-1683.
- (100) Karjalainen, A.; Kalapudas, A.; Södervall, M.; Pelkonen, O.; Lammintausta, R. Synthesis of New Potent and Selective Aromatase Inhibitors Based on Long-Chained Diarylalkylimidazole and Diarylalkyltriazole Molecule Skeletons. *Eur. J. Pharm. Sci.* **2000**, *11*, 109-131.
- (101) Yang, R.; Hey, J. A.; Aslanian, R.; Rizzo, C. A. Coordination of Histamine H<sub>3</sub>-Receptor Antagonists with Human Adrenal Cytochrome P450 Enzymes. *Pharmacology* **2002**, *66*, 128-135.
- (102) Kiec-Kononowicz, K.; Ligneau, X.; Schwartz, J. C.; Schunack, W. Pyrazoles as Potential Histamine H<sub>3</sub>-Receptor Antagonists. *Arch. Pharm. Pharm. Med. Chem.* **1995**, *328*, 469-472.
- (103) Kiec-Kononowicz, K.; Ligneau, X.; Stark, H.; Schwartz, J. C.; Schunack, W. Azines and Diazines as Potential Histamine H<sub>3</sub>-Receptor Antagonists. *Arch. Pharm. Pharm. Med. Chem.* **1995**, *328*, 445-450.
- (104) Walczynski, K.; Guryn, R.; Zuiderveld, O. P.; Timmerman, H. Non-Imidazole Histamine H<sub>3</sub>-Ligands. Part I. Synthesis of 2-(1-Piperazinyl)- and 2-(Hexahydro-1*H*-1,4-diazepin-1-yl)benzothiazole Derivatives as H<sub>3</sub>-Antagonists with H<sub>1</sub>-Blocking Activities. *Farmaco* **1999**, *54*, 684-694.
- (105) Walczynski, K.; Guryn, R.; Zuiderveld, O. P.; Timmerman, H. Non-Imidazole Histamine H<sub>3</sub>-Ligands, Part 2: New 2-Substituted Benzothiazoles as Histamine H<sub>3</sub>-Antagonists. *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 389-398.
- (106) Ganellin, C. R.; Leurquin, F.; Piripitsi, A.; Arrang, J. M.; Garbarg, M.; Ligneau, X.; Schunack, W.; Schwartz, J. C. Synthesis of Potent Non-Imidazole Histamine H<sub>3</sub>-Receptor Antagonists. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 395-404.

- (107) Meier, G.; Apelt, J.; Reichert, U.; Graßmann, S.; Ligneau, X.; Elz, S.; Leurquin, F.; Ganellin, C. R.; Schwartz, J. C.; Schunack, W.; Stark, H. Influence of Imidazole Replacement in Different Structural Classes of Histamine H<sub>3</sub>-Receptor Antagonists. *Eur. J. Pharm. Sci.* **2001**, *13*, 249-259.
- (108) Stark, H.; Hüls, A.; Ligneau, X.; Purand, K.; Pertz, H.; Arrang, J. M.; Schwartz, J. C.; Schunack, W. Development of FUB 181, a Selective Histamine H<sub>3</sub>-Receptor Antagonist of High Oral *In Vivo* Potency with 4-(ω-(Arylalkyloxy)alkyl)-1*H*-imidazole Structure. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 211-218.
- (109) Apelt, J.; Stark, H.; Reichert, U.; Grassmann, S.; Elz, S.; Ligneau, X.; Arrang, J.-M.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W. Non-Imidazole Derivatives of Reference Antagonists for the Third Histamine Receptor Subtype. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333(Suppl. 1)*, 9.
- (110) Stark, H.; Ligneau, X.; Arrang, J. M.; Schwartz, J. C.; Schunack, W. General Construction Pattern of Histamine H<sub>3</sub>-Receptor Antagonists: Change of a Paradigm. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2011-2016.
- (111) Tedford, C. E.; Hoffmann, M.; Seyedi, N.; Maruyama, R.; Levi, R.; Yates, S. L.; Ali, S. M.; Phillips, J. G. High Antagonist Potency of GT-2227 and GT-2331, New Histamine H<sub>3</sub>-Receptor Antagonists, in Two Functional Models. *Eur. J. Pharmacol.* **1998**, *351*, 307-311.
- (112) <http://www.gliatech.com/pages/corp-info/2000financials.pdf>.
- (113) Sansom, C. Histamine Control of Sleep, Learning and Memory. *Drug Discov. Today* **2000**, *5*, 94-95.
- (114) Aslanian, R.; Brown, J. E.; Shih, N. Y.; Wa Mutahi, M.; Green, M. J.; She, S.; Del Prado, M.; West, R.; Hey, J. 4-[(1*H*-Imidazol-4-yl) methyl]benzamidines and Benzylamidines: Novel Antagonists of the Histamine H<sub>3</sub>-Receptor. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2263-2268.
- (115) Aslanian, R. G.; Shih, N. Y.; Green, M. J. In *PCT WO 95/14007 USA*, 1995.
- (116) Aslanian, R. G.; McCormick, K. D.; Mutahi, M. W. In *PCT WO 99/24405 USA*, 1999.
- (117) Aslanian, R. G.; McCormick, K. D.; Piwinski, J. J. In *PCT WO 99/24406 USA*, 1999.
- (118) Aslanian, R.; Mutahi, M. W.; Shih, N. Y.; McCormick, K. D.; Piwinski, J. J.; Ting, P. C.; Albanese, M. M.; Berlin, M. Y.; Zhu, X.; Wong, S.; Rosenblum, S. B.; Jiang, Y.; West, R.; She, S.; Williams, S. M.; Bryant, M.; Hey, J. A. Identification of a Novel, Orally Bioavailable Histamine H<sub>3</sub> Receptor Antagonist Based on the 4-Benzyl-(1*H*-imidazol-4-yl) Template. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 937-941.
- (119) Soe-Jensen, P.; Knigge, U.; Garbarg, M.; Kjaer, A.; Rouleau, A.; Bach, F. W.; Schwartz, J. C.; Warberg, J. Responses of Anterior Pituitary Hormones and Hypothalamic Histamine to Blockade of Histamine Synthesis and to Selective Activation or Inactivation of Presynaptic Histamine H<sub>3</sub>-Receptors in Stressed Rats. *Neuroendocrinology* **1993**, *57*, 532-540.
- (120) Schwartz, J. C.; Arrang, J. M.; Garbarg, M.; Llorens Cotres, C.; Dam Trung Tuong, M.; Rouleau, A.; Ligneau, X.; Ganellin, C. R. Histamine H<sub>3</sub>-Receptors: Novel Ligands and Responses. In *Trends in Receptor Research*; Angeli, P., Gulini, U., Qualgia, W., Eds.; Elsevier Science: Amsterdam, 1992, p 141-152.
- (121) Lin, J. S.; Sakai, K.; Vanni-Mercier, G.; Arrang, J. M.; Garbarg, M.; Schwartz, J. C.; Jouvet, M. Involvement of Histaminergic Neurons in Arousal Mechanisms Demonstrated with H<sub>3</sub>-Receptor Ligands in the Cat. *Brain Res.* **1990**, *523*, 325-330.

- (122) Monti, J. M. Involvement of Histamine in the Control of the Waking State. *Life Sci.* **1993**, *53*, 1331-1338.
- (123) Ookuma, K.; Sakata, T.; Fukagawa, K.; Yoshimatsu, H.; Kurokawa, M.; Machidori, H.; Fujimoto, K. Neuronal Histamine in the Hypothalamus Suppresses Food Intake in Rats. *Brain Res.* **1993**, *628*, 235-242.
- (124) Fargeas, M. J.; Fioramonti, J.; Bueno, L. J. Involvement of Different Receptors in the Central and Peripheral Effects of Histamine on Intestinal Motility in the Rat. *J. Pharm. Pharmacol.* **1989**, *41*, 534-540.
- (125) Malmberg-Aiello, P.; Lamberti, C.; Ghelardini, C.; Giotti, A.; Bartolini, A. Role of Histamine in Rodent Antinociception. *Br. J. Pharmacol.* **1994**, *111*, 1269-1279.
- (126) Sakai, N.; Onodera, K.; Maeyama, K.; Yanai, K.; Watanabe, T. Effects of Thioperamide, a Histamine H<sub>3</sub>-Receptor Antagonist, on Locomotor Activity and Brain Histamine Content in Mast Cell-Deficient W/Wv Mice. *Life Sci.* **1991**, *48*, 2397-2404.
- (127) Bristow, L. J.; Bennett, G. W. Biphasic Effects of Intra-accumbens Histamine Administration on Spontaneous Motor Activity in the Rat. A Role for Central Histamine Receptors. *Br. J. Pharmacol.* **1988**, *95*, 1292-1302.
- (128) Prinz, C.; Kajimura, M.; Scott, D. R.; Mercier, F.; Helander, H. F.; Sachs, G. Histamine Secretion from Rat Enterochromaffin like Cells. *Gastroenterology* **1993**, *105*, 449-461.
- (129) Bertaccini, G.; Morini, G.; Coruzzi, G.; Schunack, W. Histamine H<sub>3</sub>-Receptors in the Guinea Pig Ileum: Evidence for a Postjunctional Location. *J. Physiol. (Paris)* **2000**, *94*, 1-4.
- (130) Bertaccini, G.; Coruzzi, G. An Update on Histamine H<sub>3</sub>-Receptors and Gastrointestinal Functions. *Dig. Dis. Sci.* **1995**, *40*, 2052-2063.
- (131) Malinowska, B.; Schlicker, E. H<sub>3</sub>-Receptor-Mediated Inhibition of the Neurogenic Vasopressor Response in Pithed Rats. *Eur. J. Pharmacol.* **1991**, *205*, 307-310.
- (132) Hey, J. A.; del Prado, M.; Egan, R. W.; Kreutner, W.; Chapman, R. W. Inhibition of Sympathetic Hypertensive Responses in the Guinea-Pig by Prejunctional Histamine H<sub>3</sub>-Receptors. *Br. J. Pharmacol.* **1992**, *107*, 347-351.
- (133) Ea Kim, L.; Javellaud, J.; Sercombe, R.; Oudart, N. A Histamine H<sub>3</sub>-Agonist Decreases the Pressor Response to Nicotine in Rats. *Pharm. Sci.* **1995**, *1*, 329-332.
- (134) Ichinose, M.; Stretton, C. D.; Schwartz, J. C.; Barnes, P. J. Histamine H<sub>3</sub>-Receptors Inhibit Cholinergic Neurotransmission in Guinea-Pig Airways. *Br. J. Pharmacol.* **1989**, *97*, 13-15.
- (135) Ichinose, M.; Barnes, P. J. Histamine H<sub>3</sub>-Receptors Modulate Nonadrenergic Noncholinergic Neural Bronchoconstriction in Guinea-Pig *In Vivo*. *Eur. J. Pharmacol.* **1989**, *174*, 49-55.
- (136) Ichinose, M.; Barnes, P. J. Histamine H<sub>3</sub>-Receptors Modulate Antigen-Induced Bronchoconstriction in Guinea Pigs. *J. Allergy Clin. Immunol.* **1990**, *86*, 491-495.
- (137) Ichinose, M.; Barnes, P. J. Inhibitory Histamine H<sub>3</sub>-Receptors on Cholinergic Nerves in Human Airways. *Eur. J. Pharmacol.* **1989**, *163*, 383-386.
- (138) Oades, R. D. Attention Deficit Disorder with Hyperactivity (ADHD): The Contribution of Catecholaminergic Activity. *Prog. Neurobiol.* **1987**, *29*, 365-391.

- (139) Arnsten, A. F. T.; Steere, J. C.; Hunt, R. D. The Contribution of  $\alpha_2$ -Noradrenergic Mechanisms of Prefrontal Cortical Cognitive Function. Potential Significance for Attention Deficit Hyperactivity Disorder. *Arch. Gen. Psychiatry* **1996**, *53*, 448-455.
- (140) Meguro, K.; Yanai, K.; Sakai, N.; Sakurai, E.; Maeyama, K.; Sasaki, H.; Watanabe, T. Effects of Thioperamide, a Histamine H<sub>3</sub>-Antagonist, on the Step-through Passive Avoidance Response and Histidine Decarboxylase Activity in Senescence-accelerated Mice. *Pharmacol. Biochem. Behav.* **1995**, *50*, 321-325.
- (141) Giovannini, M. G.; Bartolini, L.; Bacciottini, L.; Greco, L.; Blandina, P. Effects of Histamine H<sub>3</sub> Receptor Agonists and Antagonists on Cognitive Performance and Scopolamine-induced Amnesia. *Behav. Brain. Res.* **1999**, *104*, 147-155.
- (142) Panula, P.; Rinne, J.; Kuokkanen, K.; Eriksson, K. S.; Sallmen, T.; Kalimo, H.; Relja, M. Neuronal Histamine Deficit in Alzheimer's Disease. *Neuroscience* **1998**, *82*, 993-997.
- (143) Mazurkiewicz-Kwilecki, I. M.; Nsonwah, S. Changes in the Regional Brain Histamine and Histidine Levels in Postmortem Brains of Alzheimer's Patients. *Ca. J. Physiol.* **1989**, *67*, 75-78.
- (144) Miyazaki, S.; Imaizumi, M.; Onodera, K. Effects of Thioperamide on the Cholinergic System and the Step-Through Passive Avoidance Test in Mice. *Methods Find. Exp. Clin. Pharmacol.* **1995**, *17*, 653-658.
- (145) Smith, C. P.; Hunter, A. J.; Bennett, G. W. Effects of (R)- $\alpha$ -Methylhistamine and Scopolamine on Spatial Learning in the Rat Assessed Using a Water Maze. *Psychopharmacology (Berl)* **1994**, *114*, 651-656.
- (146) Miyazaki, S.; Onodera, K.; Imaizumi, M.; Timmerman, H. Effects of Clobenpropit (VUF-9153), a Histamine H<sub>3</sub>-Receptor Antagonist, on Learning and Memory, and on Cholinergic and Monoaminergic Systems in Mice. *Life Sci.* **1997**, *61*, 355-361.
- (147) Giacobini, E. From Molecular Structure to Alzheimer Therapy. *Jp. J. Pharmacol.* **1997**, *74*, 225-241.
- (148) Giacobini, E. Therapeutics against Alzheimer Disease. *Jp. J. Pharmacol.* **1997**, 235-245.
- (149) Yokoyama, H.; Sato, M.; Iinuma, K.; Onodera, K.; Watanabe, T. Centrally Acting Histamine H<sub>1</sub> Antagonists Promote the Development of Amygdala Kindling in Rats. *Neurosci. Lett.* **1996**, *217*, 194-196.
- (150) Murakami, K.; Yokoyama, H.; Onodera, K.; Iinuma, K.; Watanabe, T. AQ-0145, a Newly Developed Histamine H<sub>3</sub>-Antagonist, Decreased Seizure Susceptibility of Electrically Induced Convulsions in Mice. *Methods Find. Exp. Clin. Pharmacol.* **1995**, *17 Suppl C*, 70-73.
- (151) Yokoyama, H.; Onodera, K.; Iinuma, K.; Watanabe, T. Effect of Thioperamide, a Histamine H<sub>3</sub>-Receptor Antagonist, on Electrically Induced Convulsions in Mice. *Eur. J. Pharmacol.* **1993**, *234*, 129-133.
- (152) Yokoyama, H.; Onodera, K.; Maeyama, K.; Sakurai, E.; Iinuma, K.; Leurs, R.; Timmerman, H.; Watanabe, T. Clobenpropit (VUF-9153), a New Histamine H<sub>3</sub>-Receptor Antagonist, Inhibits Electrically Induced Convulsions in Mice. *Eur. J. Pharmacol.* **1994**, *260*, 23-28.
- (153) Vohora, D.; Pal, S. N.; Pillai, K. K. Histamine and Selective H<sub>3</sub>-Receptor Ligands: a Possible Role in the Mechanism and Management of Epilepsy. *Pharmacol. Biochem. Behav.* **2001**, *68*, 735-741.

- (154) Fischer, W.; van der Goot, H. Effect of Clobenpropit, a Centrally Acting Histamine H<sub>3</sub>-Receptor Antagonist, on Electroshock- and Pentylenetetrazol-Induced Seizures in Mice. *J. Neural. Transm.* **1998**, *105*, 587-599.
- (155) Kathmann, M.; Schlicker, E.; Gothert, M. Intermediate Affinity and Potency of Clozapine and Low Affinity of Other Neuroleptics and of Antidepressants at H<sub>3</sub> Receptors. *Psychopharmacology (Berlin)* **1994**, *116*, 464-468.
- (156) Prell, G. D.; Green, J. P.; Kaufmann, C. A.; Khandelwal, J. K.; Morrishow, A. M.; Kirch, D. G.; Linnoila, N.; Wyatt, R. J. Histamine Metabolites in Cerebrospinal Fluid of Patients with Chronic Schizophrenia: Their Relationships to Levels of Other Aminergic Transmitters and Ratings of Symptoms. *Schiz. Res.* **1995**, *14*, 93-104.
- (157) Nakai, T.; Kitamura, N.; Hashimoto, T.; Kajimoto, Y.; Nishino, N.; Mita, T.; Takana, C. Decreased Histamine H<sub>1</sub>-Receptors in the Frontal Cortex of Brains from Patients with Chronic Schizophrenia. *Biol. Psychiat.* **1991**, *30*, 349-356.
- (158) Schwartz, J. C.; Garbarg, M.; Quach, T. T. Histamine Receptors in Brains as Target for Tricyclic Antidepressant Drugs. *Trends Pharmacol. Sci.* **1981**, *2*, 122-125.
- (159) Ghi, P.; Ferretti, C.; Blengio, M. Effects of Different Types of Stress on Histamine-H<sub>3</sub>-Receptors in the Rat Cortex. *Brain Res.* **1995**, *690*, 104-107.
- (160) Ghi, P.; Ferretti, C.; Blengio, M.; Portaleone, P. Stress-Induced Changes in Histaminergic System: Effects of Diazepam and Amitriptyline. *Pharmacol. Biochem. Behav.* **1995**, *51*, 65-68.
- (161) Lamberti, C.; Ipponi, A.; Bartolini, A.; Schunack, W.; Malmberg-Aiello, P. Antidepressant-like Effects of Endogenous Histamine and of Two Histamine H<sub>1</sub>-Receptor Agonists in the Mouse Forced Swim Test. *Br. J. Pharmacol.* **1998**, *123*, 1331-1336.
- (162) Leurs, R.; Tulp, M. T.; Menge, W. M.; Adolfs, M. J.; Zuiderveld, O. P.; Timmerman, H. Evaluation of the Receptor Selectivity of the H<sub>3</sub> Receptor Antagonists, Iodophenpropit and Thioperamide: An Interaction with the 5-HT<sub>3</sub> Receptor Revealed. *Br. J. Pharmacol.* **1995**, *116*, 2315-2321.
- (163) Perez-Garcia, C.; Morales, L.; Cano, M. V.; Sancho, I.; Alguacil, L. F. Effects of Histamine H<sub>3</sub>-Receptor Ligands in Experimental Models of Anxiety and Depression. *Psychopharmacology (Berlin)* **1999**, *142*, 215-220.
- (164) Sakata, T.; Yoshimatsu, H.; Kurokawa, M. Hypothalamic Neuronal Histamine: Implications of its Homeostatic Control of Energy Metabolism. *Nutrition* **1997**, *13*, 403-411.
- (165) Yoshimatsu, H.; Hidaka, S.; Niijima, A.; Sakata, T. Histamine Neurons Down-Regulate *ob* Gene Expression in Rat White Adipose Tissue. *Inflamm. Res.* **2001**, *50*, (Suppl. 2), 72-73.
- (166) Yoshimatsu, H.; Itateyama, E.; Kondou, S.; Tajima, D.; Himeno, K.; Hidaka, S.; Kurokawa, M.; Sakata, T. Hypothalamic Neuronal Histamine as a Target of Leptin in Feeding Behavior. *Diabetes* **1999**, *48*, 2286-2291.
- (167) Machidori, H.; Sakata, T.; Yoshimatsu, H.; Ookuma, K.; Fujimoto, K.; Kurokawa, M.; Yamatodani, A.; Wada, H. Zucker Obese Rats: Defect in Brain Histamine Control of Feeding. *Brain Res.* **1992**, *590*, 180-186.
- (168) Vanni-Mercier, G.; Sakai, K.; Jouvet, M. Specific Neurons for Wakefulness in the Posterior Hypothalamus in the Cat. *C. R. Acad. Sci.* **1984**, *298*, 195-200.

- (169) Mochizuki, T. e. a. Circadian Rhythm of Histamine Release from the Hypothalamus of Freely Moving Rats. *Physiol. Behav.* **1992**, *51*, 391-394.
- (170) Monti, J. M.; Jantos, H.; Ponzoni, A.; Monti, D. Sleep and Waking During Acute Histamine H<sub>3</sub> Agonist BP 2.94 or H<sub>3</sub> Antagonist Carboperamide (MR 16155) Administration in Rats. *Neuropsychopharmacology* **1996**, *15*, 31-35.
- (171) Imamura, M.; Smith, N. C.; Garbarg, M.; Levi, R. Histamine H<sub>3</sub>-Receptor-Mediated Inhibition of Calcitonin Gene-Related Peptide Release from Cardiac C Fibers. A Regulatory Negative-Feedback Loop. *Circ. Res.* **1996**, *78*, 863-869.
- (172) Sperr, W. R.; Bankl, H. C.; Mundigler, G.; Klappacher, G.; Großschmidt, K.; Agis, H.; Simon, P.; Laufer, P.; Imhof, M.; Radaszkiewicz, T.; Glogar, D.; Lechner, K.; Valent, P. The Human Cardiac Mast Cell: Localization, Isolation, Phenotype and Functional Characterisation. *Blood* **1994**, *84*, 3876-3884.
- (173) Godlewski, G.; Malinowska, B.; Buczko, W.; Schlicker, E. Inhibitory H<sub>3</sub>-Receptors on Sympathetic Nerves of the Pithed Rat: Activation by Endogenous Histamine and Operation in Spontaneously Hypertensive Rats. *Naunyn Schmiedebergs Arch. Pharmacol.* **1997**, *355*, 261-266.
- (174) Luo, X. X.; Tan, Y. H.; Sheng, B. H. Histamine H<sub>3</sub>-Receptors Inhibit Sympathetic Neurotransmission in Guinea Pig Myocardium. *Eur. J. Pharmacol.* **1991**, *204*, 311-314.
- (175) Imamura, M.; Seyedi, N.; Lander, H. M.; Levi, R. Functional Identification of Histamine H<sub>3</sub>-Receptors in the Human Heart. *Circ. Res.* **1995**, *77*, 206-210.
- (176) Mazenot, C.; Ribouot, C.; Durand, A.; Joulin, Y.; Demenge, P.; Godin-Ribouot, D. *In Vivo* Demonstration of H<sub>3</sub>-Histaminergic Inhibition of Cardiac Sympathetic Stimulation by R- $\alpha$ -Methylhistamine and its Prodrug BP 2.94 in the Dog. *Br. J. Pharmacol.* **1999**, *126*, 264-268.
- (177) Imamura, M.; Poli, E.; Omoniyi, A. T.; Levi, R. Unmasking of Activated Histamine H<sub>3</sub>-Receptors in Myocardial Ischemia: Their Role as Regulators of Exocytotic Norepinephrine Release. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 1259-1266.
- (178) Levi, R.; Smith, N. C. Histamine H<sub>3</sub>-Receptors: A New Frontier in Myocardial Ischemia. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 825-830.
- (179) Moskowitz, M. A. Neurogenic Versus Vascular Mechanisms of Sumatriptan and Ergot-Alkaloids in Migraine. *Trends Pharmacol. Sci.* **1992**, *13*, 307-311.
- (180) De Vries, P.; Villalón, C. M.; Saxena, P. R. Pharmacological Aspects of Experimental Headache Models in Relation to Acute Antimigraine Therapy. *Eur. J. Pharmacol.* **1999**, *375*, 61-74.
- (181) Dimitriadou, V.; Rouleau, A.; Dam Trung Tuong, M.; Newlands, G. J.; Miller, H. R.; Luffau, G.; Schwartz, J. C.; Garbarg, M. Functional Relationship between Mast Cells and C-sensitive Nerve Fibres Evidenced by Histamine H<sub>3</sub>-Receptor Modulation in Rat Lung and Spleen. *Clin. Sci. (Colch)* **1994**, *87*, 151-163.
- (182) Delaunois, A.; Gustin, P.; Garbarg, M.; Ansay, M. Modulation of Acetylcholine, Capsaicin and Substance P Effects by Histamine H<sub>3</sub> Receptors in Isolated Perfused Rabbit Lungs. *Eur. J. Pharmacol.* **1995**, *277*, 243-250.

- (183) Nemmar, A.; Delaunois, A.; Beckers, J. F.; Sulon, J.; Bloden, S.; Gustin, P. Modulatory Effect of Imetit, a Histamine H<sub>3</sub>-Receptor Agonist, on C- Fibers, Cholinergic Fibers and Mast Cells in Rabbit Lungs *In Vitro*. *Eur. J. Pharmacol.* **1999**, *371*, 23-30.
- (184) Morini, G.; Grandi, D.; Bertaccini, G. (R)-α-Methylhistamine Inhibits Ethanol-Induced Gastric Lesions in the Rat: Involvement of Histamine H<sub>3</sub>-Receptors? *Digestion* **1995**, *56*, 145-152.
- (185) Morini, G.; Grandi, D.; Gentili, S.; Bertaccini, G. Rapid Onset of (R)-α-Methylhistamine Protection in Response to Ethanol-Induced Histologic Damage in Rat Gastric Mucosa. *Life Sci.* **1998**, *62*, PL13-18.
- (186) Morini, G.; Grandi, D.; Krause, M.; Schunack, W. Gastric Mucosal Injury by Non-Steroidal Anti-Inflammatory Drugs is Reduced by (R)-α-Methylhistamine and its Prodrugs in the Rat. *Inflamm. Res.* **1997**, *46* (*Suppl. I*), 101-102.
- (187) Bertaccini, G.; Coruzzi, G.; Poli, E. Functional Role of Histamine H<sub>3</sub>-Receptors in Peripheral Tissues. In *The Histamine H<sub>3</sub>-Receptor*; Leurs, R., Timmerman, H. E., Eds.; Elsevier Science B. V.: Amsterdam, 1998, p 59-111.
- (188) Vuyyuru, L.; Schubert, M. L. Histamine, Acting via H<sub>3</sub>-Receptors, Inhibits Somatostatin an Stimulates Acid Secretion In Isolated Mouse Stomach. *Gastroenterology* **1997**, *113*, 1545-1552.
- (189) Vuyyuru, L.; Harrington, L.; Arimura, A.; Schubert, M. L. Reciprocal Inhibitory Paracrine Pathways Link Histamine and Somatostatin Secretion in the Fundus of the Stomach. *Am. J. Physiol.* **1997**, *273*, G106-111.
- (190) Bado, A.; Hervatin, F.; Lewin, M. J. Pharmacological Evidence for Histamine H<sub>3</sub> Receptor in the Control of Gastric Acid Secretion in Cats. *Am. J. Physiol.* **1991**, *260*, G631-635.
- (191) Poli, E.; Pozzoli, C.; Coruzzi, G. Role of Histamine H<sub>3</sub>-Receptors in the Control of Gastrointestinal Motility. An Overview. *J. Physiol. Paris* **2001**, *95*, 67-74.
- (192) Ganellin, C. R.; Fkyerat, A.; Bang-Andersen, B.; Athmani, S.; Tertiuk, W.; Garbarg, M.; Ligneau, X.; Schwartz, J. C. A Novel Series of (Phenoxyalkyl)imidazoles as Potent H<sub>3</sub>-Receptor Histamine Antagonists. *J. Med. Chem.* **1996**, *39*, 3806-3813.
- (193) Corrie, J. E. T.; Moore, M. H.; Wilson, G. D. Product Diversity in Cyclisations of Maleamic Acids: The Imide-Isoimide Dichotomy. *J. Chem. Soc. Perkin Trans. I* **1996**, *8*, 777-782.
- (194) Sircar, S. S. G. The Influence of Groups and Associated Rings on the Stability of Certain Heterocyclic Ring Systems. Part I. The Substituted Glutarimides. *J. Chem. Soc.* **1927**, 599-605.
- (195) Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. The Synthesis of 5-Ylidenepyrrol-2(5H)-ones from Maleimides and from Pyrrol-2-(5H)-ones. *J. Chem. Soc. Perkin Trans. I* **1993**, *21*, 2567-2579.
- (196) Schreiber, K. C.; Fernandez, V. P. The Lithium Aluminum Hydride Reduction of some N-Substituted Suuccinimides. *J. Org. Chem.* **1961**, *26*, 1744-1747.
- (197) Claisen, L.; Eisleb, O. Über die Umlagerung von Phenolallylethern in die isomeren Allylphenole. *Liebigs Ann. Chem.* **1913**, *401*, 29.
- (198) Stark, H. Convenient Procedures for Synthesis of Ciproxifan, a Histamine H<sub>3</sub>-Receptor Antagonist. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 315-316.
- (199) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. An Improved Method for Reductive Alkylation of Amines using Titanium(IV)-isopropoxide and Sodium Cyanoborohydride. *J. Org. Chem.* **1990**, *55*, 2552-2554.

- (200) Brown, H. C.; Subba Rao, B. C. A New Powerful Reducing Agent-Sodium Borohydride in the Presence of Aluminum Chloride and Other Polyvalent Metal Halides. *J. Am. Chem. Soc.* **1956**, *78*, 2582-2588.
- (201) Talukdar, S.; Benerji, A. Low-Valent Titanium Mediated Reductive Deoxygenation of Carbonyls to Methylenes via Carbon-Nitrogen Bond Cleavage in *N*-(Arylmethyl)anilines. *Synth. Commun.* **1996**, *26*, 1051-1056.
- (202) Apelt, J.; Ligneau, X.; Pertz, H. H.; Arrang, J. M.; Ganellin, C. R.; Schwartz, J. C.; Schunack, W.; Stark, H. Development of a New Class of Nonimidazole Histamine H<sub>3</sub>-Receptor Ligands with Combined Inhibitory Histamine N-Methyltransferase Activity. *J. Med. Chem.* **2002**, *45*, 1128-1141.
- (203) Maggiolo, A.; Phillips, A. P. The Reaction of Alkylamines with Chloroheterocyclic Compounds II. 2-Amino-4-chloro-6-methylpyrimidine. *J. Org. Chem.* **1951**, *16*, 376-382.
- (204) Bank, C. K.; Gruhzit, O. M.; Tillitson, E. W.; Controulis, J. Arylaminoheterocycles. III. Arsenicals of Anilinotriazines. *J. Am. Chem. Soc.* **1944**, *66*, 1771-1775.
- (205) Apelt, J. Dissertation, Freie Universität Berlin, 2001.
- (206) Hüls, A. Dissertation, Freie Universität Berlin, 1995.
- (207) March, J. *Advanced Organic Chemistry*; 3 ed.; Wiley & Sons Inc.: New York, 1985, p 499-500.
- (208) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1-28.
- (209) Stark, H.; Purand, K.; Hüls, A.; Ligneau, X.; Garbarg, M.; Schwartz, J. C.; Schunack, W. [<sup>125</sup>I]-Iodoproxyfan and Related Compounds: a Reversible Radioligand and Novel Classes of Antagonists with High Affinity and Selectivity for the Histamine H<sub>3</sub>-Receptor. *J. Med. Chem.* **1996**, *39*, 1220-1226.
- (210) Stark, H.; Purand, K.; Ligneau, X.; Rouleau, A.; Arrang, J. M.; Garbarg, M.; Schwartz, J. C.; Schunack, W. Novel Carbamates as Potent Histamine H<sub>3</sub>-Receptor Antagonists with High *In Vitro* and Oral *In Vivo* Activity. *J. Med. Chem.* **1996**, *39*, 1157-1163.
- (211) Ligneau, X.; Garbarg, M.; Vizuete, M. L.; Diaz, J.; Purand, K.; Stark, H.; Schunack, W.; Schwartz, J. C. [<sup>125</sup>I]Iodoproxyfan, a New Antagonist to Label and Visualize Cerebral Histamine H<sub>3</sub> Receptors. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 452-459.
- (212) Schlicker, E.; Kathmann, M.; Reidemeister, S.; Stark, H.; Schunack, W. Novel Histamine H<sub>3</sub>-Receptor Antagonists: Affinities in an H<sub>3</sub>-Receptor Binding Assay and Potencies in Two Functional H<sub>3</sub>-Receptor Models. *Br. J. Pharmacol.* **1994**, *112*, 1043-1048.
- (213) Vollinga, R. C.; Zuiderveld, O. P.; Scheerens, H.; Bast, A.; Timmerman, H. A Simple and Rapid *In Vitro* Test System for the Screening of Histamine H<sub>3</sub>-Ligands. *Meth. Find. Exp. Clin. Pharmacol.* **1992**, *14*, 747-751.
- (214) Hirschfeld, J.; Buschauer, A.; Elz, S.; Schunack, W.; Ruat, M.; Traiffort, E.; Schwarz, J. C. Iodoaminopotentidine and Related Compounds: A New Class of Ligands with High Affinity and Selectivity for Histamine H<sub>2</sub> Receptors. *J. Med. Chem.* **1992**, *35*, 2231-2238.
- (215) Garbarg, M.; Tuong, M. D.; Schwartz, J. C.; Gros, C. Sensitive Radioimmunoassay for Histamine and Telemethylhistamine in the Brain. *J. Neurochem.* **1989**, *53*, 1724-1730.
- (216) Parker, R. B.; Waud, D. R. Pharmacological Estimation of Drug-Receptor Dissociation Constants. Statistical Evaluation. I. Agonists. *J. Pharmacol. Exp. Ther.* **1971**, *177*, 1-12.

- (217) Waud, D. R.; Parker, R. B. Pharmacological Estimation of Drug-Receptor Dissociation Constants. Statistical Evaluation. II. Competitive Antagonists. *J. Pharmacol. Exp. Ther.* **1971**, *177*, 13-24.
- (218) Cheng, Y. C.; Prusoff, W. H. Relationship Between the Inhibition Constant ( $K_i$ ) and the Concentration of Inhibitor which Causes 50% Inhibition(I<sub>50</sub>) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.
- (219) van Rossum, J. M. Cumulative Dose-Response Curves II. Technique for the Making of Dose-Response Curves in Isolated Organs and the Evaluation of Drug Parameters. *Arch. Int. Pharmacodyn. Ther.* **1963**, *143*, 299-329.
- (220) Kathmann, M.; Schlicker, E.; Marr, I.; Werthwein, S.; Stark, H.; Schunack, W. Ciproxifan and Chemically Related Compounds are Highly Potent and Selective Histamine H<sub>3</sub>-Receptor Antagonists. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1998**, *358*, 623-627.
- (221) Stark, H.; Sadek, B.; Krause, M.; Hüls, A.; Ligneau, X.; Ganellin, C. R.; Arrang, J. M.; Schwartz, J. C.; Schunack, W. Novel Histamine H<sub>3</sub>-Receptor Antagonists with Carbonyl-Substituted 4-(3-(Phenoxy)propyl)-1*H*-imidazole Structures like Ciproxifan and Related Compounds. *J. Med. Chem.* **2000**, *43*, 3987-3994.
- (222) Sasse, A.; Kiec-Kononowicz, K.; Stark, H.; Motyl, M.; Reidemeister, S.; Ganellin, C. R.; Ligneau, X.; Schwartz, J. C.; Schunack, W. Development of Chiral N-Alkylcarbamates as New Leads for Potent and Selective H<sub>3</sub>-Receptor Antagonists: Synthesis, Capillary Electrophoresis, and *In Vitro* and Oral *In Vivo* Activity. *J. Med. Chem.* **1999**, *42*, 593-600.
- (223) Stark, H.; Hüls, A.; Ligneau, X.; Arrang, J. M.; Schwartz, J. C.; Schunack, W. Search for Novel Leads for Histamine H<sub>3</sub>-Receptor Antagonists: Oxygen-Containing Derivatives. *Pharmazie* **1997**, *52*, 495-500.
- (224) Stark, H.; Ligneau, X.; Lipp, R.; Arrang, J. M.; Schwartz, J. C.; Schunack, W. Search for Novel Leads for Histamine H<sub>3</sub>-Receptor Antagonists: Amine Derivatives. *Pharmazie* **1997**, *52*, 419-423.
- (225) Hansch, C.; Maloney, P. P.; Fujita, T.; Muir, R. M. *Nature* **1962**, *194*, 178-180.
- (226) Ghose, A. K.; Crippen, G. M. Atomic Physicochemical Parameters for Three-Dimensional-Structure-Directed Quantitative Structure-Activity Relationships. 2. Modeling Dispersive and Hydrophobic Interactions. *J. Chem. Inf. Comput. Sci.* **1986**, *27*, 21-35.
- (227) Wollweber, H.; Wilms, H.; Hiltmann, R.; Stöpel, K.; Kroneberg, G. Guanidinoalkyl-azacycloalkane : Chemische Struktur und Antihypertensive Wirkung. *Arzneim.-Forsch. (Drug Res.)* **1971**, *21*, 2089-2100.
- (228) Brown, J. A.; Van Gulick, W. The Preparation of Geminally substituted 4-Bromobutylamines. II. 4-Bromo-2,2-Dialkyl- and Diarylbutylamines. *J. Am. Chem. Soc.* **1955**, *77*, 1083-1085.
- (229) Ohki, Y. Reduction of Cyclic Imides. Reduction of  $\alpha$ -Methyl- and  $\alpha$ ,  $\alpha$ -Dimethylsuccinimide by Sodium Borohydride and Synthesis of 3-Diphenylmethyleno-1,1,2,4,4-Pentamethylpyrrolidinium Iodide from its Reduction Product. *Yakugaku Zasshi* **1973**, *93*, 841-844.
- (230) Curphey, T. J.; Hung, J. C.; Chun Chian Chu, C. A Study of the Alkylation of Enamines Derived from Sterically Hindered Amines. *J. Org. Chem.* **1975**, *40*, 607-614.
- (231) Mehta, N. B.; Phillips, A. P.; Fu, F.; Brooks, R. E. Maleamic and Citraconamic Acids, Methyl Esters, and Imides. *J. Am. Chem. Soc.* **1959**, *25*, 1012-1015.

- (232) Lin, T.-Y.; Kingsbury, C. A.; Cromwell, N. H. The Synthesis of 4-Methyl-2-pyrrolidinones and 3-Methyl-1-pyrrolidines and Their Mass Spectral Study. *J. Heterocycl. Chem.* **1984**, *21*, 1871-1875.
- (233) Houlihan, W. J.; Munder, P. G.; Handley, D. A.; Cheon, S. H.; Parrino, V. A. Antitumor Activity of 5-Aryl-2,3-dihydroimidazo[2,1-a]isoquinolines. *J. Med. Chem.* **1995**, *38*-*2*, 234-240.
- (234) Valenti, P.; Fabbri, G.; Rampa, A.; Da Re, P.; Carrara, M.; Zampiron, S.; Giusti, P.; Cima, L. Basic Carbamates with Local Anaesthetic Activity. *Acta Anaesthesiol. Ital.* **1983**, *34*, 893-901.
- (235) Crombie, L.; Jamieson, S. V. Dihydrostilbenes of Cannabis. Synthesis of Canniprene. *J. Chem. Soc., Perkin Trans. 1* **1982**, *7*, 1467-1475.
- (236) Bonjean, J.; Schunack, W. Alkyl- und Alkoxy-substituierte Lamtidin-Analoga: Synthese und H<sub>2</sub>-antagonistische Aktivität. *Arzneim.-Forsch. (Drug Res.)* **1988**, *38*, 501-507.
- (237) Hirauchi, K.; Amano, T. Studies on the Phosphorimetric Determination of Amines with Halonitro Compounds. II. Substituent Effect on the Fluorescence and Phosphorescence of 4'-Substituted 4-Nitrodiphenylamines and 2-(Substituted Anilino)-5-nitropyridines. *Chem. Pharm. Bull.* **1979**, *27*, 1120-1124.
- (238) Drefahl, G.; Lückert, H.; Köhler, W. Notiz zur Spaltung der C-N Bindung tertiärer Amine durch Säureanhydride und -chloride. *J. Prakt. Chem.* **1960**, *11*, 341-344.
- (239) Buchheit, K.-H.; Engel, G.; Mutschler, E.; Richardson, B. Study of the Contractile Effect of 5-Hydroxytryptamine (5-HT) in the Isolated Longitudinal Muscle Strip from Guinea-Pig Ileum. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1985**, *329*, 36-41.
- (240) Bowsher, R. R.; Verburg, K. M.; Henry, D. P. Rat Histamine N-Methyltransferase. *J. Biol. Chem.* **1983**, *258*, 12215-12220.
- (241) Garbarg, M.; Tuong, M. D.; Gros, C.; Schwartz, J. C. Effects of Histamine H<sub>3</sub>-Receptor Ligands on Various Biochemical Indices of Histaminergic Neuron Activity in Rat Brain. *Eur. J. Pharmacol.* **1989**, *164*, 1-11.