Substituted 2-(2-Hydroxyphenyl)benzimidazoles as Potential Agents for the Control of Periodontal Diseases
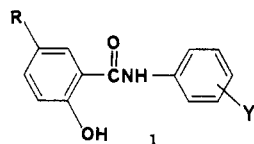
Robert A. Coburn,*[†] Michael T. Clark,[†,1] Richard T. Evans,[‡] and Robert J. Genco[‡]

Department of Medicinal Chemistry, School of Pharmacy, and Department of Oral Biology, School of Dental Medicine, State University of New York at Buffalo, Buffalo, New York 14260. Received February 19, 1986

A series of 16 substituted 2-(2-hydroxphenyl)benzimidazoles was synthesized and evaluated in vitro for antibacterial activity against bacteria associated with periodontal diseases. Several compounds demonstrated a high level of activity, in tube dilution assay, against *Actinomycetes viscosus* and *Bacteriodes gingivalis*. These results indicate that several of these compounds may serve as topical antibacterial agents for the control of acute marginal inflammatory gingivitis and periodontitis.

Topical application of antimicrobial agents for the control of human oral dental plaque, associated with caries and periodontal diseases,[2-4] appears to be a reasonable adjunct to mechanical oral hygiene as well as a superior strategy to systemic administration for chemoprophylaxis. Although specific bacteria, i.e. *Streptococcus mutans*, have been identified with caries development,[5] the role of supragingival plaque in the development of adult periodontitis is not as clearly defined. *Actinomycetes* have been associated with the development of acute marginal inflammatory gingivitis,[6] while *Bacteriodes gingivalis* may be an indicator of actively progressing periodontitis.[7]

Previous studies have revealed several 5-(n-alkyl-, 5-(n-acyl, and 5-(n-alkylsulfonyl)salicylanilides (1) that ex-

hibit high levels of in vitro activity against *Actinomycetes*.[8,9] One derivative (1a, R = n-decanoyl, Y = 4'-nitro) was more effective than 3,5,4'-tribromosalicylanilide (2) in reducing the development of gingivitis in the beagle dog, when incorporated in a mouthrinse formulation.[10] Earlier reports indicated that 2 was a component of a mouthrinse found to exhibit clinical effects against plaque[11] and gingivitis[12] in man.

In this study, bioisosteric replacements were investigated for the carboxamidophenyl moiety in 1. Several benzoxazole (3) and benzimidazole (4) analogues of 2 as well as a series of 5-n-acyl-2-(2-hydroxyphenyl)benzimidazoles (5) were prepared and examined for in vitro antibacterial
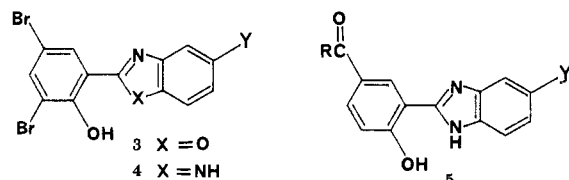

activity, in tube dilution, against several bacteria implicated in periodontal diseases. Some of the molecular features underlying this choice of isosters include hydrogen-bond acceptor and, in the case of benzimidazole, hydrogen-bond donor functionalities, potential ligand functionality for metal ion chelation, a benz ring coplanar with the amide isoster, and an electron-withdrawing effect upon the phenol ring.

Chemistry

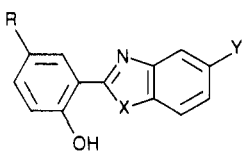The 2-(2-hydroxyphenyl)benzimidazoles 9a–d were ob-

Scheme I
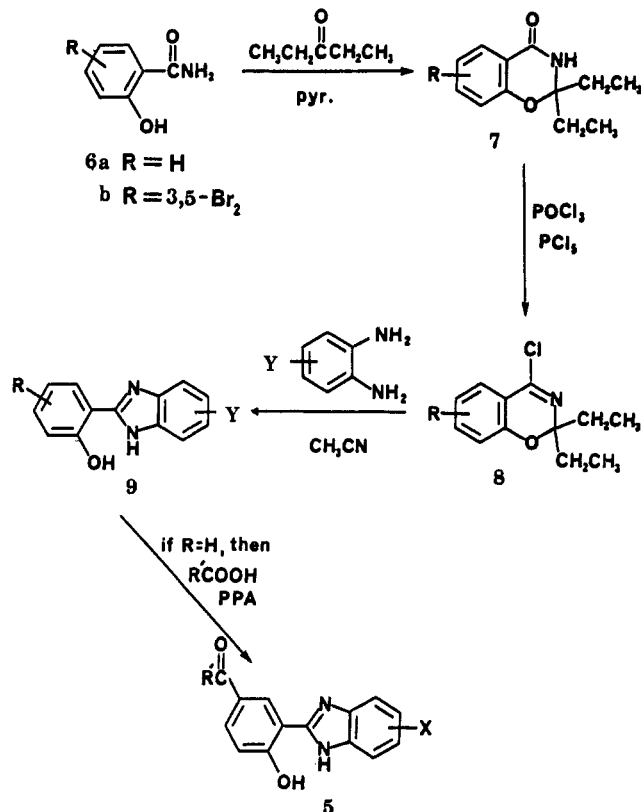
tained by the reaction of 1,2-phenylenediamines with the 4-chloro-1,3-benzoxazine 8a, which is readily obtained from

(1) Taken in part from the dissertation submitted to the Graduate School, SUNY/Buffalo, in partial fulfillment of the requirements for the Ph.D. degree.

(2) Lang, N. P. *Efficacy of Treatment Procedures in Periodontics*; Shanley, D., Ed.; Quintessence Books: Chicago, 1980; pp 57–65.

(3) Hull, P. S. *J. Clin. Periodontol.* **1980**, *7*, 431.

(4) Canfield, P. W.; Navia, J. M. *The Biologic Basis of Dental Caries*; Menaker, L., E.; Harper and Row: New York, 1980; pp 386–418.

(5) Ziekert, I.; Emilson, C. G.; Krasse, B. *Infect. Immun.* **1983**, *39*, 982.

(6) Listgarten, M.A.; Mayo, H. E.; Tremblay, R. *J. Periodontol.* **1975**, *46*, 10.

(7) Slots, J. *Host-Parasite Interactions in Periodontal Disease*; Genco, R. J., Hergenhagen, S. E., Eds.; American Society for Microbiology: Washington, DC, 1982; pp 27–45.

(8) Coburn, R. A.; Batista, A. J.; Evans, R. T.; Genco, R. J. *J. Med. Chem.* **1981**, *24*, 1245.

(9) Clark, M. T.; Coburn, R. A.; Evans, R. T; Genco, R. J. *J. Med. Chem.* **1986**, *29*, 25.

(10) Ritchey, T. W.; Lamster, J. B.; Picozzi, A. *J. Dent. Res.* **1983**, *62* 199.

†Department of Medicinal Chemistry, School of Pharmacy.
‡Department of Oral Biology, School of Dental Medicine.

Table I. Properties of 2-(2-Hydroxyphenyl)benzimidazoles and Benzoxazoles

no.	R	Y	X	mp, °C	% yield	formula[a]
3a	3,5-Br$_2$	H	O	197–199	80	C$_{13}$H$_7$NO$_2$Br$_2$
3b	3,5-Br$_2$	Cl	O	232–234	80	C$_{13}$H$_6$Br$_2$NO$_2$Cl
3c	3,5-Br$_2$	CH$_3$	O	166–168	80	C$_{14}$H$_9$NO$_2$Br$_2$
4a	3,5-Br$_2$	Cl	NH	278–279	60	C$_{13}$H$_7$Br$_2$N$_2$OCl
4b	3,5-Br$_2$	CF$_3$	NH	274–279	40	C$_{14}$H$_7$Br$_2$N$_2$OF$_3$
5a	n-C$_3$H$_7$CO	CF$_3$	NH	237–239	19	C$_{18}$H$_{15}$N$_2$O$_2$F$_3$[b]
5b	n-C$_4$H$_9$CO	CF$_3$	NH	218–219	20	C$_{19}$H$_{17}$N$_2$O$_2$F$_3$[b]
5c	n-C$_5$H$_{11}$CO	CF$_3$	NH	206–208	15	C$_{20}$H$_{19}$N$_2$O$_2$F$_3$[b]
5d	n-C$_6$H$_{13}$CO	CF$_3$	NH	203–204	14	C$_{21}$H$_{21}$N$_2$O$_2$F$_3$
5e	n-C$_6$H$_{13}$CO	CH$_3$	NH	172–174	12	C$_{21}$H$_{24}$N$_2$O$_2$
5f	n-C$_6$H$_{13}$CO	Cl	NH	211–213	13	C$_{20}$H$_{21}$N$_2$O$_2$Cl
5g	n-C$_7$H$_{15}$CO	CF$_3$	NH	197–198	15	C$_{22}$H$_{23}$N$_2$O$_2$F$_3$
5h	n-C$_7$H$_{15}$CO	CH$_3$	NH	174–176	12	C$_{22}$H$_{26}$N$_2$O$_2$
5i	n-C$_7$H$_{15}$CO	Cl	NH	203–205	18	C$_{21}$H$_{23}$N$_2$O$_2$Cl
5j	n-C$_8$H$_{17}$CO	CF$_3$	NH	188–189	21	C$_{23}$H$_{25}$N$_2$O$_2$F$_3$
5k	n-C$_8$H$_{17}$CO	CH$_3$	NH	157–159	13	C$_{23}$H$_{28}$N$_2$O$_2$
5l	n-C$_8$H$_{17}$CO	Cl	NH	223–225	13	C$_{22}$H$_{25}$N$_2$O$_2$Cl
5m	n-C$_8$H$_{17}$CO	NO$_2$	NH	161–163	17	C$_{22}$H$_{25}$N$_3$O$_4$
5n	n-C$_9$H$_{19}$CO	CF$_3$	NH	195–197	17	C$_{24}$H$_{27}$N$_2$O$_2$F$_3$
9a	H	CF$_3$	NH	266–268	85	C$_{14}$H$_9$N$_2$OF$_3$
9b	H	Cl	NH	279–281[c]	50	C$_{13}$H$_9$N$_2$OCl
9c	H	CH$_3$	NH	240–242[d]	90	C$_{14}$H$_{12}$N$_2$O
9d	H	NO$_2$	NH	298–299[e]	86	C$_{13}$H$_9$N$_3$O$_3$

[a] Elemental analyses obtained for C, H, and N were in agreement (0.4%) with theoretical values. [b] Analysis for N was not performed. [c] Literature[20] mp 279–281 °C. [d] Literature[20] mp 240–242 °C. [e] Literature[20] mp 297–299 °C.

the POCl$_3$/PCl$_3$ chlorination of 1,3-benzoxazin-4-one (**7a**),[13] as shown in Scheme I. The latter was obtained from salicylamide **6** by reaction with 3-pentanone. The 5-acyl derivatives **5a–n**, shown in Table I, were prepared by the polyphosphoric acid catalyzed condensation of the appropriate benzimidazoles **9** with an n-alkanoic acid. Several 3′,5′-dibromo derivatives **4a,b** were prepared by Scheme I, starting with 3,5-dibromosalicylic acid. The 2-(2-hydroxyphenyl)benzoxazoles **3a–c**, shown in Table I, were prepared by the reaction of substituted o-hydroxyanilines with the 6,8-dibromo derivative **8b**.

Results

Although 2-phenylbenzimidazoles are usually prepared by condensation of o-phenylenediamines, or their salts, with benzoic acids, esters, or acid chlorides, as well as benzaldehydes or benzonitriles, the method of Tachikawa et al.[13] is useful for the preparation of o-hydroxyphenyl derivatives. Failure to protect the o-hydroxy group results in very low or no yield of the desired products.

The minimum bactericidal concentrations of the benzimidazoles **4a,b** and **5a–n** are shown in Table II. The several benzoxazoles **3a–c** failed to inhibit the growth of *Actinomycetes viscosus* below 100 µg/mL and were not further evaluated. The dibromo trifluoromethyl derivatives **4a,b** were more active than salicylanilide **2** against *A. viscosus*. Of the 5′-acyl derivatives **5a–n**, all of the 5-trifluoromethyl derivatives (**5a–d, g, j**), with the single exception of **5n**, exhibited nearly identical levels of activity against *A. viscosus*. The 5′-acyl derivatives containing

(11) Fischman, S.; Picozzi, A.; Cancro, L.; Pader, M. *J. Periodontol.* **1973**, *44*, 100.
(12) Fischman, S.; Cancro, L.; Pader, M.; Bolton, S.; Picozzi, A. *J. Periodontol.* **1973**, *44*, 535.
(13) Tachikawa, R.; Kazuyuki, W.; Terada, A. *Chem. Pharm. Bull.* **1982**, *10*, 559.

Table II. In Vitro Minimum Bactericidal Concentrations of Substituted 2-(2-Hydroxyphenyl)benzimidazoles against Periopathogenic Bacteria[a]

no.	A. viscosus	B. gingivalis	A. actinomycetemcomitans
2	1.0	0.05	0.5
4a	0.5	0.05	5.0
4b	0.1	0.05	1.0
5a	0.5	0.05	5.0
5b	0.5	0.5	NE
5c	0.5	0.1	NE
5d	0.5	0.05	NE
5e	NE		
5f	NE		
5g	0.5	0.5	NE
5h	NE		
5i	NE		
5j	0.5	0.1	NE
5k	10		NE
5l	NE	NE	NE
5m	NE	NE	NE
5n	NE	NE	NE
9a	NE	50	NE
9c	NE	1.0	1.0
chlorohexidine	0.5	0.05	0.5
tetracycline	0.5	0.05	0.5

[a] Concentrations in micrograms/milliliter, consistent result for triplicate assays.

chloro- or methylbenzimidazole substituents (**5e, f, h, i, l–m**) were ineffective against *A. viscosus*. *B. gingivalis* was very sensitive to most of the agents tested with nearly uniform results. Only the salicylanilide **2** and the benzimidazoles **4a,b** and **5a** were effective against *Actinobacillus actinomycetemcomitans*. Compounds **4a,b** and **2** were found to be effective (MBC ~ 0.1–0.05 µg/mL) against the following strains and species of *Bacteriodes*: gingivalis g-14K-1, 27067, F 19M-1, 11-1-2; *intermedius* 25261, FL 8-5; *denticola*, B 45M-30.

Discussion

Most of the compounds in this class have very limited aqueous solubilities. Thus, it is not surprising to observe that a number of derivatives either are not effective or exhibit MBC values below 5 µg/mL. Among the trifluoromethyl derivatives the uniform activity against *A. viscosus* stands in sharp contrast to that observed for the salicylanilides, where activity is well correlated with apparent lipophilicities expressed as log *D* values.[8,9] It is apparent that although the halo- and 5-acylsalicylanilides possess similar structural features to these benzimidazoles, the mechanisms of action may differ. Lipophilicities of these benzimidazoles appear to be of significance only with respect to activity against *A. actinomycetemcomitans*, an anaerobic Gram-negative bacterium implicated in juvenile periodontitis.[14] Only the least lipophilic members of this series **4a,b** and **5a** were effective against this microorganism.

Other 2-phenylbenzimidazoles, lacking the 2′-hydroxy group, have been reported to be inactive below 100 µg/mL against a range of Gram-positive and Gram-negative bacteria.[15] Thiabendazole [2-(2-thiazolyl)benzimidazole] and 2-benzimidazolecarbamates are well-known fungicides. For thiabendazole, there is evidence that the mechanism of action involves inhibition of the terminal electron-transport system of fungal mitochondria.[16] Acidic benzimidazoles, possessing 2-trifluoromethyl groups, constitute a class of pesticides believed to function as uncouplers of oxidative phosphorylation.[17]

Compounds **5a** and **5j** differ in hydrophobicity by ca. 2.5 log units yet display equivalent activity against *A. viscosus*, suggesting that disruption of transport properties by cytoplasmic membrane incorporation, although likely for the salicylanilides, is unlikely for these benzimidazoles. Chelation of metal ions remains a distinct possibility for involvement in the mechanism of action. Thiabendazole strongly chelates transition-metal ions between the two nitrogen atoms.[18]

The potential effectiveness of this class of agents for use in control of plaque and periodontal diseases not only is dependent on their spectrum and levels of activity against periopathogenic bacteria but also may be dependent upon their retention properties in the oral cavity. A log *P* value of 3.63 may be estimated for the parent 2-(2-hydroxyphenyl)benzimidazole by the fragment method of Hansch and Leo.[19] The calculated log *P* values of the trifluoromethyl derivatives **4b** and **5j** are 6.92 and 7.79, respectively. Thus, the very lipophilic nature of these agents are similar to that reported for the alkyl- and acylsalicylanilides.[8] These findings suggest that these agents should be further evaluated in preclinical studies for their potential efficacy as periodontal chemoprophylactic agents.

Experimental Section

The procedures are representative for all compounds appearing in the text. Where a number of compounds are synthesized by an identical procedure, only one representative example will

appear in detail. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60A spectrometer, and chemical shift values (δ) are reported relative to internal tetramethylsilane (Me₄Si). Infrared (IR) spectra were recorded on a Nicolet 7199 FT interferometer. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and analytical results were within ±0.4% of the theoretical values. Thin-layer chromatography was performed on Uniplate thin-layer chromatography plates (Analtech) and were visualized under UV light and with iodine vapor. Melting points are uncorrected and were obtained on either a Fisher-Johns or Thomas Hoover melting point apparatus. Flash chromatography was performed by Stills procedure[20] with flash columns and flash chromatography silica gel.

2,3-Dihydro-2,2-diethyl-6,8-dibromo-4*H*-1,3-benzoxazin-4-one (7b). A mixture of 3,5-dibromosalicylamide (29.5 g, 0.1 mol), 3-pentanone (31.7 mL, 0.1 mol), and pyrrolidine (0.75 mL, 4.5 mol) in benzene (500 mL) was heated at reflux for 18 h. Water was removed during heating via a Dean–Stark trap. The reaction mixture was cooled, washed with 2 N HCl (2 × 250 mL), dried with anhydrous MgSO₄, and concentrated under reduced pressure to give a solid. The solid was recrystallized from hexane to give **7b**: yield 30 g (85%); mp 150–151 °C; ¹H NMR (CDCl₃) δ 8.65 (1 H, d), 7.65 (1 H, d), 7.8 (1 H, d), 2.0 (4 H, q), 1.1 (6 H, t); IR (KBr) 1674.8 cm⁻¹ (C=O).

4-Chloro-2,2-diethyl-6,8-dibromo-2*H*-1,3-benzoxazine (8b). 2,3-Dihydro-2,2-diethyl-6,8-dibromo-4*H*-1,3-benzoxazin-4-one (**7b**; 15 g, 40 mmol), PCl₅ (8.5 g, 4.2 mmol), and POCl₃ (3.75 mL) were stirred at room temperature for 1 h and then heated at 50 °C for 2 h. The reaction mixture was cooled, concentrated under reduced pressure to remove excess POCl₃, and distilled to give **8b**: yield 9.7 g (70%); bp 145–150 °C (3.0 mmHg); ¹H NMR (CDCl₃) δ 7.65 (2 H, m), 1.95 (4 H, q), 1.0 (6 H, t); IR (CCl₄) 1657 cm⁻¹ (C=N).

5-Chloro-2-(3,5-dibromo-2-hydroxyphenyl)benzoxazole (3b). A mixture of 3-chloro-6-aminophenol (1.14 g, 8 mmol) and 4-chloro-2,2-diethyl-6,8-dibromo-2*H*-1,3-benzoxazine (**8b**; 1.5 b, 4 mmol) was heated in 50 mL of acetonitrile at reflux for 1 h. The mixture was cooled to 0 °C and the resulting precipitate collected. Following recrystallization from ethanol there resulted 0.29 g (80%) of **3b**: mp 232–234 °C; ¹H NMR (Me₂SO-*d₆*) δ 8.25 (1 H, d), 7.85 (1 H, d), 7.25–7.80 (3 H, m); IR (KBr) 1447 cm⁻¹ (C=N).

(2-Hydroxyphenyl)benzimidazoles 9. General Procedure.[21] An appropriately substituted *o*-phenylenediamine, 4-chloro-1,3-benzoxazine, and acetonitrile were heated at reflux for 2 h. The reaction mixture was cooled to 0 °C and the precipitate collected and recrystallized to give the product.

Substituted 2-(5-Acyl-2-hydroxyphenyl)benimidazoles 5. General Procedure. A mixture of polyphosphoric acid (PPA), **9a**, and an aliphatic acid were heated over a steam bath for a period of 6 h. The reaction mixture was cooled, poured onto crushed ice, and neutralized to pH 7 with 10% KOH. The solution was extracted with CH₂Cl₂ and the extract dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to give a solid. The solid was purified by flash chromatography (flash silica gel, EtOAc/hexanes, 4:1) to give analytically pure benzimidazole **5a–n.**

Microbiological Methods. Tube dilution assays were conducted as previously described.[8] Bacterial cultures used were *A. viscosus* M100-2000, *B. gingivalis* 381, and *A. actinomycetemcomitans* Y4. All cultures were maintinaed on Trypticase Soy Broth (TBS) with an excess of calcium carbonate (stock solution). Stock solutions of test compounds were prepared at concentrations of 1 mg/100 µL of EtOH or Me₂SO and diluted 100-fold or more with growth medium to give 3-fold dilutions (1 mL) in Bacto Anerobe broth. Following inoculation with 50 µL of 10⁸ cfu/mL of log phase growth inoculum, tubes were incubated at 37 °C in an anaerobic chamber containing an atmosphere of 5% CO₂, 10% H₂, and 85% Ar. MIC values were determined visually after 24 h.

(14) Hammond, B. F.; Stevens, R. H. *Host-Parasite Interactions in Periodontal Disease*; Genco, R. J., Mergenhagen, S. E., Eds.; American Society for microbiology: Washington, DC, 1982; pp 46–59.

(15) Charles, E. S.; Rao, K. V. B.; Satyavan, S. *Pharmazie* **1982**, *37*, 413.

(16) Allen, P.; Gottlieb, D. *Appl. Microbiol.* **1970**, *20*, 919.

(17) Corbett, J. R.; Wright, B. *J. Pestic. Sci.* **1970**, *1*, 120.

(18) Kowala, C.; Murray, K.; Swan, J.; West, B. *Aust. J. Chem.* **1971**, *24*, 1369.

(19) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience: New York, 1979.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(21) Tachikawa, R.; Kazuyuki, W.; Terada, A. *Heterocycles* **1981**, *7*, 1165.

Studies on the Active Molecular Species of the H_2 Receptor Antagonists Cimetidine and Mifentidine

E. E. J. Haaksma, B. Rademaker, K. Kramer, J. Ch. Eriks, A. Bast, and H. Timmerman*

Department of Pharmacochemistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands. Received January 2, 1986

The N'-(4-1H-imidazol-4-ylphenyl)formamidines were recently introduced as a new class of active H_2 antagonists; the authors of the compounds (Donetti et al. of de Angeli, Italy) have suggested that these compounds interact with the H_2 receptor through their monocations. This is at variance with the model proposed for cimetidine by the SK&F (Smith Kline & French, UK) group who proposed the neutral molecule as the species active at the H_2 receptor. In the present study we have investigated the issue whether the neutral or charged species is the active one by measuring the pA_2 values of mifentidine and cimetidine at different pH values. Changing the pH will influence the species equilibria of both compounds and thereby affect their activity. The activity changes measured for both compounds are consistent with the proposition that cimetidine as well as mifentidine elicit their activity through their neutral species.

Recently Donetti et al.[1] introduced a new class of H_2 antagonists, the N'-(4-1H-imidazol-4-ylphenyl)form-amidines, of which mifentidine (Figure 1a) is a representative. It was shown that the predominant species present at physiological pH is the monocation, in which the amidino group of the N-isopropylformamidine is protonated and the imidazole group is uncharged. Moreover, it was suggested that (i) the charged amidino group of mifentidine upon interaction with the histamine H_2 receptor might be related to the charged imidazole of cimetidine (Figure 1b) and (ii) the imidazole ring of mifentidine might be comparable to the neutral amidine arrangement present in the cyanoguanidine group of cimetidine. That mifentidine and cimetidine occupy the same receptor site either in the classical way by assuming the same role for the imidazole groups and the amidine groups, or in the way Donetti et al. suggested might be concluded from their molecular electrostatic potentials.[2] Therefore, the speculations of Donetti et al. on the role of the imidazole moiety and the uncharged cyanoguanidine of cimetidine could lead to an interpretation on the mode of interaction of the latter molecule with the H_2 receptor different from that of Ganellin et al. The speculation of Donetti et al.[1] has important implications for studies on the interaction of histaminergic ligands at the level of the receptor and eventually for designing new active compounds. In this paper we try to answer which molecular species of the H_2 antagonists mifentidine and cimetidine interacts with the histamine H_2 receptor. The method used to get insight into this problem is based on studying the influence of pH on the binding affinity of the compounds for the H_2 receptor. This method was used previously to determine the active species of the histaminergic compounds histamine and dimaprit[3] and of two classes of

β-adrenergic compounds.[4] In this paper we apply the above-mentioned technique to cimetidine and mifentidine.

Results and Discussion

The development of H_2 antagonists was based on the notion that an antagonist on the one hand should have sufficient chemical resemblance to histamine in order to be recognized by the H_2 receptor and on the other hand should be sufficiently different as well to ensure its lack of intrinsic activity. One of the first successful compounds in this respect was the partial agonist N^α-guanylhistamine.[5] It was discovered that elongation of the side chain influences antagonistic activity positively as for example in compound SK&F 91486,[6] in which lengthening of the guanidine side chain from an N-ethyl group (N^α-guanylhistamine) to an N-propyl group enhances activity. A further increase in antagonistic activity was achieved both by reducing the basicity of the guanidine group and by changing the electronic influences on the imidazole ring in order to increase the relative amount of the N^r-H tautomer with respect to the N^π-H tautomer.[7] A favorable electronic effect could be accomplished by introducing a methyl group at position 4 in the imidazole ring and changing the side chain into N'-methyl-N-[(ethylthio)-methyl]-N''-cyanoguanidine.[8] The electron-donating character of the methyl group at position 4 and the electron-withdrawing character of the sulfur atom in the side chain increase the relative amount of N^r-H tautomer of the imidazole ring. Reduction of the basicity of the guanidine group was achieved by introduction of the strongly electron withdrawing cyano group, which reduces the pK_a of the guanidine to a value of -0.4. The conclusion

(1) Donetti, A.; Cereda, E.; Bellora, E.; Gallazi, A.; Bazzano, C.; Vanoni, P.; Del Soldato, P.; Micheletti, R.; Pagani, F.; Giochetti, A. *J. Med. Chem.* 1984, *27*, 380.

(2) Donetti, A.; Trummlitz, G.; Bietti, G.; Cereda, E.; Bazzano, C.; Wagner, H.-U. *Arzneim.-Forsch. Drug Res.* 1985, *35*, 306.

(3) Sterk, G. J.; van der Goot, H.; Timmerman, H. *Eur. J. Med. Chem.* 1984, *19*, 545.

(4) IJzerman, A. P.; Bultsma, T.; Timmerman, H.; Zaagsma, J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1984, *327*, 293.

(5) Durant, G. J.; Parsons, M. E.; Black, J. W. *J. Med. Chem.* 1975, *18*, 830.

(6) Parsons, M. E.; Blakemore, R. C.; Durant, G. J.; Ganellin, C. R.; Rasmussen, A. C. *Agents Actions* 1975, *5*, 464.

(7) Black, J. W.; Duncan, W. A. M.; Emmet, J. C.; Ganellin, C. R.; Hesselbo, T.; Parsons, M. E.; Wyllie, J. H. *Agents Actions* 1973, *3*, 133.

(8) Brimblecombe, R.; Parsons, M. E. *J. Int. Med. Res.* 1975, *3*, 86.