were obtained on a Bruker WM 360-MHz variable probe NMR instrument. All NMR spectra were obtained with use of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal standard. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Sephadex G-15 (Sigma Chemical Co.) was used for column chromatography.

N^{α}-(*N*-Acetylmuramyl)-N^{ϵ}-DTAF-L-lysyl-D-isoglutamine (DTAF-Lys-MDP, 6). Lys-MDP (4) (55.2 mg, 0.10 mmol) and DTAF (2) (65.1 mg, 0.12 mmol) were added to 10 mL of a 0.25 M K_2CO_3 solution, and the reaction was stirred overnight. Amine detection on TLC ($BuOH/AcOH/H_2O$, 4:1:4; top layer) with ninhydrin showed no detectable unreacted Lys–MDP. The reaction was lyophilized to a solid and reconstituted in 2 mL of H_2O. The concentrate was eluted on a Sephadex G-15 gel filtration column (bed volume of 1.0 mg of dye to 2 mL of gel). The fastest moving band was collected, concentrated, and eluted on a second Sephadex G-15 column. Collection of the fastest moving band afforded the homogeneous fluorescent adduct DTAF-Lys-MDP (6): yield 61.8 mg (60%); NMR-LR (D_2O), integration ratio for the aromatic region (δ 6.0–8.5) to the peptide region (δ 1.0–3.0) was 1:2 (9 H to 16 h), which is consistent with a 1:1 ratio of DTAF to Lys-MDP; NMR-HR (D_2O) δ 1.36 (d, 3 H, Mur-CH_3), 1.38 (m, 2 H, $CH_2CH_2CH_2NH$), 1.97 (s, 3 H, $COCH_3$), 3.08 (m, 2 H, CH_2CH_2NH). Anal. ($C_{45}H_{49}N_9O_{16}ClK\cdot KHCO_3$) C, H, N.

***N*-(*N*-Acetylmuramyl)-L-alanyl-D-isoglutaminyl-*N*-DTAF-L-lysine (DTAF-MTP) (7).** MTP (5) (53.1 mg; 0.10 mmol) and DTAF (2) (68.2 mg, 0.13 mmol) were reacted overnight in 10 mL of 0.25 M K_2CO_3. The reaction workup was similar to the one used to purify 6. Elution of the reaction on Sephadex G 15 gave DTAF-MTP: yield 68.4 mg (61%); NMR-LR (D_2O), integration ratio for the aromatic region (δ 6.0–8.0) to the peptide region (δ 1.0–3.0) was 1:2 (9 H to 19 H), which is consistent with a 1:1 ratio of DTAF to MTP; NMR-HR (D_2O) δ 1.35 (d, 3 H, Mur-CH_3), 1.40 (d, 3 H, Ala-CH_3), 1.75 (m, 2 H, CH_2CH_2NH), 1.96 (s, 3 H, $COCH_3$), 3.07 (m, 2 H, CH_2NH). Anal. ($C_{48}H_{54}N_{10}O_{17}$,ClK·H_2O) C, H, N.

Biological Methods. Skin Testing. The immunization protocol used was previously described by Audibert et al.[15] Hartley strain guinea pigs, 400–600 g females, were obtained from CAMM and divided into groups of four animals. Each posteror footpad received an injection of 0.1 mL of a saline-incomplete Freund's adjuvant emulsion containing 0.5 mg of OA with or without MDP or its derivatives. The test group had MDP added to the emulsion at 50 μg/0.1 mL, and the various derivatives were adjusted to be at equimolar concentration to MDP. Guinea pigs were skin tested on day 14 with 0.1 mL of a saline solution containing 10 μg of OA. The skin-test response was determined by measuring the diameters of induration 48 h after intradermal injection of antigen.

Antibody Response. Guinea pigs were sacrificed by ip injection with pentobarbital 72 h after skin testing, and blood was obtained from the heart for serum antibody studies. Anti-OA activity was measured by an ELISA detection system,[16] and the activity was compared to that obtained by pooling the sera from all the guinea pigs and assigning the pool a value of 100 units/mL of activity. The lowest dilution of pooled serum that reacted in the assay was 1:265 000.

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Registry No. 2, 93265-91-9; 4, 66152-83-8; 5, 59275-09-1; 6, 115731-80-1; 7, 115705-90-3; 8, 2389-45-9; 9, 87137-45-9; 10, 66111-56-6; 11, 79701-17-0; 12, 115705-91-4; 13, 115705-92-5; 14, 115705-93-6; 15, 115705-94-7; 16, 16964-83-3; 17, 115705-95-8.

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The in Vitro Dental Plaque Inhibitory Properties of a Series of *N*-[1-Alkyl-4(1*H*)-pyridinylidene]alkylamines

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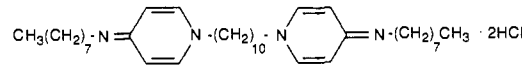
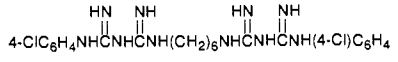
A series of novel *N*-[1-alkyl-4(1*H*)-pyridinylidene]alkylamine hydrohalides has been prepared and evaluated as inhibitors of dental plaque formation, in vitro. Several members of the series exhibited potency ca. 9-fold greater than that of chlorhexidine vs *Streptococcus sobrinus* 6715-13. The di-*n*-octyl analogue, 11 (pirtenidine), was found to be highly efficacious against several other oral plaque-forming microorganisms and is presently undergoing preclinical evaluation.

We have previously described a class of bispyridinamine antimicrobial agents that were inhibitors of dental plaque growth in vitro.[1] From this series emerged a compound, octenidine, which demonstrated clinical efficacy in inhibiting human dental plaque formation[2,3] and which has been shown in animal models to reduce caries formation[4] and improve gingival health.[5] We now report on a series of *N*-[1-alkyl-4(1*H*)-pyridinylidene]alkylamines (A) related to octenidine that have improved in vitro potency over the latter in laboratory models for inhibition of dental plaque.

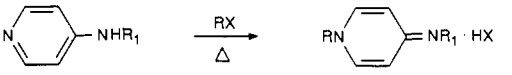


OCTENIDINE



CHLORHEXIDINE

Scheme I



A

Periodontal disease is the leading cause of tooth loss in man,[6] and dental plaque, the dense adhesive microbial mass that colonizes tooth surfaces, is strongly implicated

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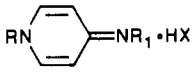
Table I. *N*-[1-Alkyl-4(1*H*)-pyridinylidene]alkylamines



compd	R	R_1	X	mp, °C	yield, %	formula[a]	minimum bactericidal concn (mM) vs *S. sobrinus* 6715-13	PBI (CC)[b] vs *S. sobrinus* 6715-13	PBI (CC)[b] vs *A. viscosus* M-100
1	n-C_8H_{13}	n-C_8H_{13}	Br	*c*			1.58	*d*	*d*
2	n-C_7H_{15}	n-C_8H_{13}	Cl	75–78	66	$C_{18}H_{33}ClN_2$	1.60	12.8 (2)	6.4 (3)
3	n-C_8H_{17}	n-C_8H_{13}	Cl	91–94	38	$C_{19}H_{35}ClN_2$	0.31	4.6 (5.6)	3.0 (6.4)
4	n-C_9H_{19}	n-C_8H_{13}	Cl	112–114	77	$C_{20}H_{37}ClN_2$	0.29	2.9 (8.8)	8.8 (2.2)
5	n-C_8H_{13}	n-C_7H_{15}	Cl	70–76	66	$C_{18}H_{33}ClN_2$	1.60	12.8 (2.0)	6.4 (3.0)
6	n-C_7H_{15}	n-C_7H_{15}	Br	88–90	36	$C_{19}H_{35}BrN_2$	1.35	8.0 (3.2)	5.4 (4)
7	n-C_8H_{17}	n-C_7H_{15}	Br	99–101	88	$C_{20}H_{37}BrN_2$	1.30	10.4 (2.5)	10.4 (1.8)
8	n-C_9H_{19}	n-C_7H_{15}	Cl	122–123	37	$C_{21}H_{39}ClN_2$	1.41	8.5 (3)	11.3 (1.7)
9	n-C_8H_{13}	n-C_8H_{17}	Br	78–80	92	$C_{19}H_{35}BrN_2$	1.35	10.8 (2.4)	13.5 (1.4)
10	n-C_7H_{15}	n-C_8H_{17}	Br	80–81	81	$C_{20}H_{37}BrN_2$	1.30	7.8 (3.3)	7.8 (2.5)
11	n-C_8H_{17}	n-C_8H_{17}	Cl	120–123	94	$C_{21}H_{39}ClN_2$	0.28	2.8 (9.1)	2.8 (6.9)
12	n-C_9H_{19}	n-C_8H_{17}	Cl	142–144	81	$C_{22}H_{41}ClN_2$	1.35	13.3 (1.9)	13.3 (1.4)
13	C_8H_{17}[e]	n-C_8H_{17}	Br	162–170	94	$C_{22}H_{39}BrN_2$	1.25	12.5 (2)	12.5 (1.5)
14	n-C_8H_{13}	n-C_9H_{19}	Cl	104–106	80	$C_{20}H_{37}ClN_2$	0.29	2.9 (8.8)	2.9 (6.6)
15	n-C_7H_{15}	n-C_9H_{19}	Br	98–101	93	$C_{21}H_{39}BrN_2$	1.25	10.0 (2.5)	10.0 (1.9)
16	n-C_8H_{17}	n-C_9H_{19}	Br	110–112	92	$C_{22}H_{41}BrN_2$	1.21	9.7 (2.6)	9.7 (1.9)
17	n-C_9H_{19}	n-C_9H_{19}	Cl	140–143	25	$C_{23}H_{43}ClN_2$	2.61	10.4 (2.5)	5.2 (4)
18	n-C_5H_{11}	n-$C_{10}H_{21}$	Cl	73–74	75	$C_{20}H_{37}ClN_2$	0.29	3.0 (8.5)	5.9 (3.2)
19	n-C_8H_{17}	C_8H_{17}[e]	Br	115–119	86	$C_{21}H_{39}BrN_2$	1.25	10.0 (2.5)	10.0 (1.9)
20	C_8H_{17}[e]	C_8H_{17}[e]	Br	152–158	81	$C_{21}H_{39}BrN_2$	1.25	20.0 (1.3)	20.0 (1.0)
21	$C_6H_5CH_2$	n-C_8H_{17}	Cl	129–130	85	$C_{20}H_{29}ClN_2$	1.50	24.0 (1.1)	12.0 (1.6)
22	4-$ClC_6H_4CH_2$	n-C_8H_{17}	Cl	115–119	43	$C_{20}H_{28}Cl_2N_2$	0.27	10.9 (2.3)	5.4 (3.6)
23	$C_6H_5CH_2$	n-$C_{12}H_{25}$	Cl	99–102	80	$C_{24}H_{37}ClN_2$	1.29	15.4 (1.7)	10.3 (1.9)
24	$C_6H_5CH_2$	n-$C_{14}H_{29}$	Cl	103–108	91	$C_{26}H_{41}ClN_2$	0.24	*d*	*d*
25[f]	CH_3	CH_3	I				*g*	*d*	*d*
26[f]	CH_3	n-$C_{12}H_{25}$	I				1.24	12.4 (2.1)	19.2 (1.0)
octenidine							3.20	25.6 (1.0)	19.2 (1.0)
chlorohexidine							3.20	25.6	19.2

[a] The compounds of Table I analyzed within ±0.4% of the calculated values for C, H, and N. [b] PBI = plaque bactericidal index = concn (mM) × duration (min) × frequency (days); CC = chlorhexidine coefficient. [c] See the Experimental Section. [d] Not bactericidal at highest concentration tested (0.2% w/v, 2 min, 5 days). [e] 2-Ethylhexyl. [f] Landquist, J. K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 454. [g] Not active at 20 mM.

in experimental models and in humans as the critical etiological factor.[7-10] Furthermore, dental plaque is also considered to be a leading contributor to the formation of caries.[11-14]

Chemistry

The target compounds were prepared by heating neat 4-(alkylamino)pyridines with the appropriate alkyl chlorides or bromides (Scheme I).[1,15-17] That the alkylation products (Table I) were indeed ring alkylated was supported by NMR evidence. For compound 11 the CH_2 adjacent to the exocyclic nitrogen appears as a quartet coupled to the neighboring CH_2 and NH, the latter appearing as a broad triplet (see the Experimental Section). Deuterium exchange with NH collapses that CH_2 quartet to a triplet.

Results and Discussion

Preliminary efficacy evaluation of test substances was conducted as previously described.[18,19] Plaques grown on standardized ceramic hydroxylapatite plates were immersed in solutions of test agent for 30 min.[20] After treatment the plaques were rinsed with sterile distilled water, transferred to fresh broth, and incubated at 37 °C under an anaerobic atmosphere. Plaque kill was judged by the cessation of culture acid production, the absence of a change in culture turbidity, and failure of 48-h post-treatment plaque samples to grow when subcultured. Each test was conducted in duplicate, and the lowest concen-

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Table II. Efficacy of Compound 11 against Selected Oral Plaque-Forming Microorganisms

microorganism	compound 11 PBI[a]	compound 11 CC[a]
S. mutans IB1600	1.4	18.3
S. mutans FA-1	1.4	18.3
S. mutans GR-5	1.4	18.3
S. mutans OMZ-61	1.4	18.3
S. sobrinus 6715-13	2.8	9.1
S. sobrinus SL-1	2.8	9.1
S. sanguis ATCC 10558	5.0	6.4
S. sanguis H7P	10.0	3.2
S. mitis 90557	5.0	6.4
S. mitis 176-A1	20	1.6
A. viscosus M-100	2.8	6.9
A. viscosus 626	1.4	13.7
A. viscosus 8A06	4.2	4.6
A. viscosus T14V	1.4	13.7
A. naeslundii 631	2.8	6.9
A. naeslundii B74	1.4	13.7
A. naeslundii N/3	1.4	13.7
A. naeslundii N/9	1.4	13.7

[a] See footnotes, Table I.

tration of test substance that completely destroyed *Streptococcus sobrinus* 6715-13 under this treatment regimen was defined as the minimum bactericidal concentration (MBC). These MBC values are shown in Table I.

In order to make a comparison between compounds that more nearly mimic clinical use of such agents, plaque bactericidal indices (PBI) and chlorhexidine coefficients (CC) were computed.[21] To calculate these parameters for *Actinomyces viscous* M100 and *S. sobrinus* 6715-13, plaques were treated once daily for 2 min with varying concentrations of test substances until the organisms were killed. Each test was conducted in duplicate. The PBI was calculated as the product of the concentration (mM), duration (exposure time in minutes), and frequency of treatment (days) required to achieve a bactericidal effect (plaque kill). The CC is calculated by dividing the PBI for chlorhexidine by that for a given test substance. These indices (PBI, CC) provide a comparator of in vitro efficacy within a chemical series and provide a comparison of those results with the standard test substance, chlorhexidine (a CC of greater that 1.0 indicates that the test substance has greater plaque bactericidal potency than chlorhexidine). Results of this testing are shown in Table I.

The MBC and PBI tests provide a useful measure of compound penetrability into a plaque matrix. This effect is necessary to kill the bacteria within the plaque, and activity in this test reveals that these compounds do, in fact, exhibit this property.

With the exception of analogue **25**, the compounds in Table I were very potent bactericidal agents vs *S. sobrinus* in the 30 min, single-exposure test with MBC's ranging from 0.24 to 2.61 mM (chlorhexidine MBC = 3.2 mM). Little correlation between structure and cidal potency was noted in this test upon varying the length or substitution of the alkyl side chains.

In general, the cidal activity noted in the single exposure test was translated into very good potency upon multiple-exposure testing. Compounds 4, 11, 14, and 18 displayed the best potency vs *S. sobrinus* with PBI's less than or equal to 3. Derivatives 1 and 24 were exceptions however; both were ineffective cidal agents in the multiple-exposure test. As was the case in the single-exposure test, a clear structure–activity relationship (SAR) was not evident from the multiple-exposure data.

Compound 11, among the most potent of the series, was evaluated against additional strains of plaque-producing organisms by using the method described above. The data from these assays are expressed in terms of PBI and CC and are found in Table II. Against these test organisms compound 11 is ca. 2–18 times as efficacious as the standard, chlorhexidine. Compound 11 (pirtenidine) is now being prepared for clinical trial.

Experimental Section

Elemental analyses performed by Galbraith Laboratories, Knoxville, TN, were obtained for all new compounds reported. Carbon, hydrogen and nitrogen analyses were within ±0.4% of the theoretical values. Melting points were taken in capillary tubes and are not corrected. All compounds were checked by proton NMR (Varian HA-100 or IBM AM-200), IR (Perkin-Elmer 467 or Nicolet 10DX), TLC (silica gel), and in most instances, mass spectrometry (JEOL JMS-01SC or HP 5980A GC/MS).

***N*-[1-Octyl-4(1*H*)-pyridinylidene]octanamine Monohydrochloride** (11). 4-(*n*-Octylamino)pyridine[1] (25.0 g, 0.12 mol) and 1-chlorooctane (18.0 g, 0.12 mol) were heated at 180 °C for 1 h. TLC (BuOH–HOAc–H_2O, 5:1:4) of an aliquot indicated a small amount of starting pyridine present. An additional 0.57 g (0.004 mol) of 1-chlorooctane was added, and heating was continued an additional 1 h. The residue was dissolved in CH_2Cl_2 and filtered (Darco). The filtrate was concentrated in vacuo, and the resulting solid was slurried in ether. Filtration of the slurry under N_2 in a dry bag provided 40.3 g (94%) of analytically pure 11, mp 120–123 °C: ^{1}H NMR (DMSO-d_6) δ 0.85 (t, 6 H), 1.24 (m, 20 H), 1.55 (m, 2 H), 1.74 (m, 2 H), 3.25 (q, 2 H), 4.14 (t, 2 H), 6.90 (d, 1 H), 7.12 (d, 1 H), 8.19 (d, 1 H), 8.35 (d, 1 H) 9.33 (br t, 1 H). Anal. ($C_{21}H_{38}N_2$·HCl) C, H, N.

With the exception of derivatives 1 and 18, the other new compounds in Table I were prepared in similar fashion.

***N*-[1-Hexyl-4(1*H*)-pyridinylidene]hexanamine Monohydrobromide** (1). A solution of 4-(*n*-hexylamino)pyridine[1] (17.2 g, 0.096 mol) and *n*-hexyl bromide (16.2 g, 0.098 mol) in 170 mL of isoamyl alcohol was refluxed for 18 h. After being cooled to ambient temperature, the mixture was diluted with acetone and chilled. A solid was filtered and discarded, and the filtrate was concentrated in vacuo. The oily residue was tritiated with ether, and a gummy solid was filtered in a dry bag under N_2. This semisolid was used for microbiological testing.

An analytically pure sample of the saccharin salt of 1 was prepared by treating an aqueous solution of the gummy HBr salt with sodium saccharinate. The water-insoluble salt was collected and recrystallized from MeOH–H_2O to provide the saccharin salt of 1, mp 40–42 °C. Anal. ($C_{17}H_{30}N_2$·$C_7H_5NO_3S$·$^1/_4H_2O$) C, H, N.

***N*-[1-Pentyl-4(1*H*)-pyridinylidene]decanamine Monohydrochloride** (18). 4-(*n*-Decylamino)pyridine[1] (13.0 g, 0.06 mol), 1-iodopentane (15.3 g, 0.08 mol), and 2,2,4-trimethylpentane (73 mL) were heated at reflux for 3 days. The mixture was cooled to ambient temperature, and the solvent was decanted. The residual solid was washed with hexane and ether and dissolved in MeOH. The resulting solution was filtered after Darco treatment and concentrated in vacuo. The remaining material was eluted with MeOH through an Amberlite IRA 400 (chloride form) ion exchange resin. The waxy solid obtained after concentration of the fractions was slurried in ether and filtered under N_2 in a dry bag to give 16.8 g (75%) of analytically pure 18, mp 73–74 °C. Anal. ($C_{20}H_{37}ClN_2$) C, H, N.

Acknowledgment. We thank the Analytical Chemistry Department of this Institute for spectral measurements and E. Cimijotti and T. Kernozek for technical assistance.

Registry No. 1, 115561-80-3; 1 (free base), 103923-52-0; 1·saccharin, 115561-93-8; 2, 115561-81-4; 2 (free base), 115561-87-0; 3, 115561-82-5; 3 (free base), 115561-88-1; 4, 115561-83-6; 4 (free base), 115561-89-2; 5, 115561-84-7; 5 (free base), 115561-90-5; 6, 103923-30-4; 6 (free base), 103923-48-4; 7, 103923-42-8; 7 (free base), 103923-60-0; 8, 103923-37-1; 8 (free base), 103923-55-3; 9, 103923-38-2; 9 (free base), 103923-56-4; 10, 103923-32-6; 10 (free

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base), 103923-50-8; 11, 100227-05-2; 11 (free base), 103923-27-9; 12, 103923-33-7; 12 (free base), 103923-51-9; 13, 103923-28-0; 13 (free base), 103923-53-1; 14, 115561-85-8; 14 (free base), 115561-91-6; 15, 103923-39-3; 15 (free base), 103923-57-5; 16, 103923-40-6; 16 (free base), 103923-58-6; 17, 103923-31-5; 17 (free base), 103923-49-5; 18, 115561-86-9; 18 (free base), 115561-92-7; 19, 103923-36-0; 19 (free base), 103923-54-2; 20, 103923-41-7; 20 (free base), 103923-59-7; 21, 103923-43-9; 21 (free base), 103944-26-9; 22, 103923-46-2; 22 (free base), 103923-63-3; 23, 103923-44-0; 23 (free base), 103923-61-1; 24, 103923-45-1; 24 (free base), 103923-62-2; 25, 96287-46-6; 25 (free base), 102635-81-4; 26, 103923-47-3; 26 (free base), 103923-64-4; $CH_3(CH_2)_6Cl$, 629-06-1; $CH_3(CH_2)_5Cl$, 544-10-5; $CH_3(CH_2)_7Br$, 111-83-1; $CH_3(CH_2)_8Cl$, 2473-01-0; $CH_3(CH_2)_6Br$, 629-04-9; $PhCH_2Cl$, 100-44-7; p-$ClC_6H_4CH_2Cl$, 104-83-6; 4-(*n*-octylamino)pyridine, 64690-19-3; 1-chlorooctane, 111-85-3; 4-(*n*-hexylamino)pyridine, 64690-14-8; *n*-hexyl bromide, 111-25-1; sodium saccharinate, 128-44-9; 4-(*n*-decylamino)pyridine, 64690-61-5; 1-iodopentane, 628-17-1; *N*-heptyl-4-pyridinamine, 35036-87-4; *N*-nonyl-4-pyridinamine, 64690-27-3; *N*-dodecyl-4-pyridinamine, 64690-59-1; *N*-tetradecyl-4-pyridinamine, 115561-94-9; *N*-(2-ethylhexyl)-4-pyridinamine, 64690-39-7; 1-bromo-2-ethylhexane, 18908-66-2.

(*S*)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-5-[^{125}I]iodo-2-methoxybenzamide Hydrochloride, a New Selective Radioligand for Dopamine D-2 Receptors

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From salicyclic acid, the two enantiomers of *N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodo-2-methoxybenzamide (**6b**) were prepared in a five-step synthesis. With use of Heindel's triazene method for introduction of the radionuclide, the iodine-125-labeled substituted benzamide was obtained with a calculated specific activity of 136 Ci/mmol and 14% radiochemical yield. For the preparation of the iodine-125-labeled benzamide with higher specific activity, this method was unsuccessful and utilization of the corresponding tri-*n*-butyltin derivative was required. Treatment of the latter in dilute hydrochloric acid with sodium iodide-125 and chloramine-T gave [^{125}I](*S*)-**6b** in 56% radiochemical yield and at least 97% radiochemical purity. The displacement of [^{125}I](*S*)-**6b** and [^{3}H](*S*)-sulpiride from their respective binding sites in striatal rat brain homogenates using various neuroleptic agents showed that (*S*)-**6b** has the same binding profile but more potent binding for dopamine D-2 receptors than has sulpiride. These experiments also indicate that the *S* enantiomer of **6b** is a specific ligand (K_D = 1.2 nM) for the D-2 receptor. Further, the octanol–water partition coefficient of (*S*)-**6b** as determined by reverse-phase high-performance liquid chromatography was found to be 40 times greater than that for sulpiride. Thus (*S*)-**6b** has a lipophilicity that will allow a relatively higher uptake into the brain compared to sulpiride. In vivo experiments with rats show that [^{125}I](*S*)-**6b** penetrates readily into the brain and is preferentially localized in the striatum as compared to the cerebellum, the ratio of uptake being 7.2 to 1, 60 min after injection. These observations of good brain penetration and high affinity and selectivity for D-2 receptors indicate that the corresponding iodine-123-labeled benzamide may be a useful ligand for the noninvasive visualization study of dopamine D-2 receptor sites in vivo by single photon emission computed tomography.

Selective, radioiodinated ligands for brain neurotransmitter binding sites may serve as pharmacological tools for the elucidation of the mechanism of action of psychotropic agents and as diagnostic agents in the investigation of patients suffering from neuropsychiatric disorders. New radioiodination techniques for small organic molecules have made this possible.[1] Several radionuclides for labeling of central dopamine receptors using various γ or positron emitting isotopes have been described: ^{125}I in autoradiography, ^{77}Br and ^{123}I in single photon emission computed tomography (SPECT),[1,2] and ^{76}Br, ^{18}F, and ^{11}C in positron emission tomography (PET).[2]

Recently the binding of the selective dopamine D-1 receptor ligand SCH 23390 [(*R*)-**1a**][3] (Chart I) and its equally selective iodinated analogue, SKF 103108 [(*RS*)-**1b**], were reported.[4] Thus, the iodine-125 form of (*R*)-**1b**, [^{125}I]SCH 23982, is considered the ligand of choice for the identification of the dopamine D-1 receptor.[4] Similarly, the butyrophenone spiperone (**2a**) has been radiolabeled in the 2′- and 4-positions (**2b** and **2c**), and these radiolabled analogues have been used for the localization of the dopamine D-2 receptor,[5,6] the receptor having been implicated in the antipsychotic action of neuroleptic agents. 4-[^{125}I]Iodospiperone (**2c**) in comparison with tritiated spiperone, however, was shown not to be a useful ligand for D-2 receptors in the central nervous system (CNS) due to aberrant binding kinetics.[7]

Substituted benzamides are also potent dopamine antagonists. Neumeyer and co-workers[8] have shown that the replacement of the chlorine atom in the substituted benzamide clebopride (**3a**) with an iodine atom (**3b**) retains binding characteristics similar to those of the butyrophenone haloperidol.[8] However, the in vivo ratio of striatal to cerebellar uptake of [^{125}I]-**3b** was 1.9 to 1,[8] which is less than optimally required for in vivo imaging. In addition, no substituted benzamide structurally related to clebopride seems to possess sufficient separation of antipsychotic activity from extrapyramidal side effects to be an effective therapeutic agent,[9] and thus, the relevance of such an agent

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