CD studies gave mirro-image curves to those described for the 1*S*,3*R* and 1*R*,3*R* compounds.

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N,*N*-Di-*n*-propylserotonin: Binding at Serotonin Binding Sites and a Comparison with 8-Hydroxy-2-(di-*n*-propylamino)tetralin

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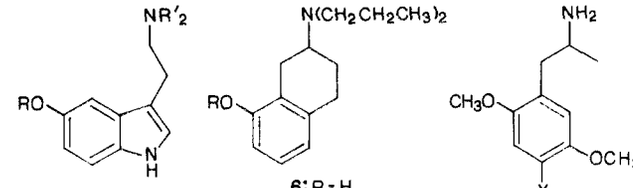
8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) is a serotonergic agonist with high affinity and selectivity for a particular population of central serotonin (5-HT) binding sites (i.e., 5-HT_{1A} sites). Because the selectivity of 8-OH-DPAT may be due to the terminal amine substituents, the di-*n*-propyl analogue of 5-HT (i.e., **4**) and of 5-methoxytryptamine (i.e., **5**) were prepared and compared with 8-OH-DPAT with respect to their binding profile. Unlike 8-OH-DPAT, neither compound **4** nor **5** displays selectivity for 5-HT_{1A} vs 5-HT_2 sites. Consistent with these results, stimulus generalization occurs with **5** both in rats trained to discriminate 8-OH-DPAT from saline and in rats trained to discriminate the 5-HT_2 agonist DOM from saline. The results of this study suggest that it is not the *N*,*N*-dipropyl groups that account for selectivity, but, rather, it is some feature associated with the pyrrole portion of the indolylalkanamines that is important.

Several different populations of central serotonin (5-hydroxytryptamine; 5-HT) binding sites have been identified in mammalian brain; these include 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 sites.[1] There is now evidence to suggest that members of a new class of anxiolytic agents (i.e., second generation anxiolytics) act as 5-HT_{1A} agonists and that both thermoregulation and appetite control may also involve a 5-HT_{1A} mechanism (see ref 1 for a review). These findings have focused considerable attention on this particular population of sites. The most potent and selective 5-HT_{1A} agonist is 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; **6**);[1-3] 8-OH-DPAT binds at 5-HT_{1A} sites with high affinity (K_i = ca. 2 nM[1]), and [^{3}H]-8-OH-DPAT is now commonly used to label these sites.[1] An early report by Hoyer and co-workers[4] showed that the di-*n*-propyl portion of 8-OH-DPAT makes a significant (>50-fold) contribution to its affinity for 5-HT_{1A} sites. The affinity of 5-HT (**1**) for 5-HT_{1A} sites is essentially identical with that of 8-OH-DPAT; however, 5-HT does not enjoy the selectivity displayed by 8-OH-DPAT. Arvidsson and coworkers[5] demonstrated that the two *n*-propyl groups of 8-OH-DPAT are necessary for optimal activity in a biochemical measure of serotonergic activity (i.e., receptor-mediated feedback inhibition of 5-hydroxytryptophan accumulation). Aminotetralin analogues with alkyl groups smaller than *n*-propyl are less active whereas those with larger substituents are essentially inactive.[5] They have also argued that 5-HT and 8-OH-DPAT share common aromatic and terminal amine sites in their binding to serotonin receptors.[5] If this is the case, it may be possible to enhance the affinity and/or selectivity of 5-HT for 5-HT_{1A} sites by incorporating the two *n*-propyl substituents onto its terminal amine. Consequently, *N*,*N*-di-*n*-propyl-2-[(5-hydroxyindol-3-yl)amino]ethane (i.e., *N*,*N*-di-*n*-propylserotonin; DiPS) (**4**) and its *O*-methyl ether, **5**, were synthesized and evaluated.

Chemistry. Compound **4** has been previously mentioned in the literature;[6-8] however, details of its synthesis and characterization of the intermediates involved were not provided.[6] Compound **4** was prepared by the Speeter–Anthony method.[9] 5-(Benzyloxy)indole was acylated with oxalyl chloride, and the resultant glyoxylyl chloride was allowed to react with di-*n*-propylamine to afford the di-*n*-propylglyoxylamide; reduction of the glyoxylamide with $LiAlH_4$ provided the benzyl-protected derivative of **4** which was isolated as the hydrochloride salt (i.e., **9**). Deprotection of **9** to **4** was achieved by catalytic hydrogenolysis.



1: R = R′ = H
2: R = Me; R′ = H
3: R = R′ = Me
4: R = H; R′ = *n*-Pr
5: R = Me; R′ = *n*-Pr

6: R = H
7: R = Me

8

Binding Studies. Binding data for 5-HT (**1**), DiPS (**4**), 8-OH-DPAT (**6**), and their *O*-methyl ethers (i.e., **2**, **5**, and **7**, respectively) at 5-HT_{1A}, 5-HT_{1B}, [^{3}H]ketanserin-labeled 5-HT_2, and [^{3}H]DOB-labeled 5-HT_2 sites are shown in Table I. Data for the *N*,*N*-dimethyl derivative of the

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Table I. Affinities at Central 5-HT Binding Sites[a]

agent	K_i, nM			
	5-HT_{1A}	5-HT_{1B}	5-HT_2 (K)	5-HT_2 (D)
5-HT (1)	1.7 (±0.3)	5.4 (±0.5)	930 (±70)	7.8 (±0.8)
5-OMeT (2)	3.2 (±0.2)	4.0 (±0.3)	305 (±20)	4.8 (±1.0)
5-OMe-DMT (3)	7.8 (±0.8)	350 (±15)	620 (±40)	15.0 (±3.0)
8-OH-DPAT (6)	1.2 (±0.1)	>10000	5350 (±460)	635 (±110)
8-OMe-DPAT (7)	1.3 (±0.3)	>1000	3050 (±520)	280 (±60)
DiPS (4)	7.1 (±0.3)	4300 (±400)	450 (±40)	1.0 (±0.2)
O-Me-DiPS (5)	4.0 (±0.7)	1800 (±80)	655 (±15)	7.1 (±1.0)
DOM	5125 (±140)	2070 (±115)	100 (±15)	8.0 (±0.4)

[a] K_i values are reported for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 binding; both [^{3}H]ketanserin (K) and [^{3}H]-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (D) were used to label 5-HT_2 sites. In all cases, Hill coefficients (n) were between 0.78 and 1.01, except that at 5-HT_{1B} sites n = 0.70 (±0.02) and 0.75 (±0.02) for 5-HT and 5-OMeT, respectively. Binding data for DOM are included for comparison.

O-methyl ether of 5-HT (i.e., **3**) and for DOM (**8**, R = CH_3) are also included for comparative purposes. The reason that two different radioligands were used to label 5-HT_2 sites is that 5-HT agonists display a higher affinity for agonist-labeled (i.e., [^{3}H]DOB-labeled) sites than for antagonist-labeled (i.e., [^{3}H]ketanserin-labeled) sites.[10,11] 5-HT displays less than a 5-fold difference in affinity (K_i) for (agonist-labeled) 5-HT sites. The selectivity of its *O*-methyl ether **2** is essentially no different from that of 5-HT. Whereas the affinity of **3** is similar to that of 5-HT at 5-HT_{1A} and 5-HT_2 sites, there is nearly a 50-fold difference in the affinity of **3** for 5-HT_{1A} vs 5-HT_{1B} sites. Apparently, dialkyl substitution on the terminal amine is not well tolerated at 5-HT_{1B} sites. The affinity of 8-OH-DPAT (**6**) and its *O*-methyl ether **7** for 5-HT_{1A} sites is also similar to that of 5-HT. Again, substitution on the terminal amine (in this case with the larger propyl groups) results in a very low affinity for 5-HT_{1B} sites. As already demonstrated by others,[1] 8-OH-DPAT is selective for 5-HT_{1A} sites relative to 5-HT_2 sites; similar results were obtained with **7** (Table I).

DiPS (**4**) and its ether, **5**, bind at 5-HT_{1A} sites and 5-HT_2 sites with high affinity but with little to no selectivity. However, the effect of the dialkyl substituents on 5-HT_{1B} binding is still evident; the affinity of **4** and **5** for 5-HT_{1B} sites is intermediate between that of **3** and 8-OH-DPAT (**6**) (Table I).

Drug Discrimination Studies. Because certain 5-hydroxyindole analogues (e.g., 5-HT, bufotenine) penetrate the blood–brain barrier with difficulty,[12] and due to the limited supply of DiPS (**4**), compound **5** (and not **4**) was selected for evaluation in the drug-discrimination paradigm. In these studies, doses of **5** were administered to groups of rats that had been previously trained to discriminate either 1.0 mg/kg of DOM or 0.2 mg of 8-OH-DPAT from saline. Both the DOM stimulus and the 8-OH-DPAT stimulus generalized to **5** (Table II). In both cases, however, response rates were reduced by greater than 50% (as compared to control values) at those doses where stimulus generalization occurred.

Discussion

As shown in Table I, DiPS (**4**) and its *O*-methyl ether **5** bind at 5-HT_{1A} and 5-HT_2 sites with very high affinity. Serotonin antagonists tend to show little difference in their affinity for 5-HT_2 sites regardless of whether [^{3}H]ketanserin or [^{3}H]DOB is employed as the radioligand.[10,11] Serotonin agonists, however, display a significantly higher affinity for [^{3}H]DOB-labeled sites than for [^{3}H]ketanserin-labeled sites. Thus, the data in Table I would suggest that **4** and **5** are serotonin agonists. Agonist activity can also be examined in drug-discrimination studies with tests of stimulus generalization. In such tests, the DOM stimulus has been shown to generalize to agents with high affinity for 5-HT_2 sites, and the 8-OH-DPAT stimulus generalizes to agents with high affinity for 5-HT_{1A} sites.[13] In addition, animals trained to a site-selective agent do not normally recognize agents that are selective for a different site; for example, the DOM stimulus does not generalize to 8-OH-DPAT and visa versa.[13] As shown in Table II, both the DOM stimulus and the 8-OH-DPAT stimulus generalize to *O*-Me-DiPS (**5**), suggesting that the agent, consistent with its binding properties, can produce both types of stimulus effects.

On the basis of the findings of Hoyer and co-workers,[4] it was anticipated that DiPS (**4**) would possess an affinity for 5-HT_{1A} sites greater than that of 5-HT; some selectivity for 5-HT_{1A} sites might also have been expected. This was not found to be the case (Table I). Thus, although the propyl groups may contribute to the affinity of 8-OH-DPAT for 5-HT_{1A} sites, those of DiPS (**4**) and **5** certainly have little effect on 5-HT_{1A}-site affinity when compared to 5-HT (**1**) and 5-OMeT (**2**). 8-OH-DPAT is known to be selective for 5-HT_{1A} sites relative to 5-HT_2 sites.[1,2] The data in Table I for 8-OH-DPAT (**6**) and 8-OMe-DPAT (**7**) are consistent with these findings regardless of which radioligand is used to label the 5-HT_2 sites. But again, the lack of selectivity of DiPS (**4**) and *O*-Me-DiPS (**5**) for 5-HT_{1A} vs 5-HT_2 sites, as compared with 5-HT (**1**) and 5-OMeT (**2**), argue against a role for the propyl groups in imparting 5-HT_{1A} vs 5-HT_2 selectivity. The propyl groups of compounds **4**–**7** do, however, seem to contribute to selectivity in that, relative to 5-HT, these agents bind at 5-HT_{1A} sites with a significantly higher affinity than they display for 5-HT_{1B} sites.

How can the selectivity of 8-OH-DPAT (**6**) and 8-OMe-DPAT (**7**), relative to that of DiPS (**4**) and *O*-Me-DiPS (**5**), for 5-HT_{1A} sites vs 5-HT_2 sites be accounted for? There are several potential explanations. The aminotetralins (i.e., **6** and **7**) and the indolealkylamines (i.e., **4** and **5**) may bind in a different fashion; in this case, it may be argued that different conformations or terminal amine sites are involved. However, certain ergolines (which contain both aminotetralin and indolylalkaneamine fragments within their tetracyclic framework) display very high affinity and little to no selectivity for 5-HT_{1A} vs 5-HT_2 sites. For example, (+)-lysergic acid diethylamide binds both at 5-HT_{1A} sites (K_i = 0.4 nM) and at [^{3}H]DOB-labeled 5-HT_2 sites (K_i = 0.5 nM).[14] This would suggest that a common conformation, such as that found in the ergolines, is important.

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Table II. Results of Stimulus Generalization Study

	dose[a]	*N*[b]	drug-appropriate responding, % (±SEM)	resp/min (±SEM)	ED50,[c] mg/kg
		A. DOM-Trained Animals			
O-Me-DiPS (5)	0.6	5/5	21 (5)	10.2 (1.8)	
	1.5	5/5	49 (18)	12.3 (2.8)	
	2.0	4/5	51 (12)	12.0 (1.5)	
	5.0	4/5	74 (12)	10.3 (2.5)	
	6.0	3/5	91 (5)	5.2 (2.0)	1.68 (0.75–3.76)
5-OMe-DMT (3)					1.43[d]
DOM	1.0	5/5	92 (4)	12.8 (1.8)	
saline (1.0 mL/kg)		5/5	12 (3)	13.5 (1.3)	
		B. 8-OH-DPAT-Trained Animals			
O-Me-DiPS (5)	0.4	4/5	15 (10)	13.6 (2.7)	
	0.8	3/4	56 (12)	9.2 (2.6)	
	0.9	4/7	56 (13)	13.6 (4.5)	
	1.0	4/5	67 (16)	5.6 (1.6)	
	1.1	4/5	81 (8)	4.1 (0.8)	0.75 (0.49–1.13)
	1.2	2/5	*e*		
8-OMe-DPAT (7)					0.22[f]
8-OH-DPAT (6)	0.2	7/7	88 (6)	16.8 (2.3)	0.08[f]
saline (1.0 mL/kg)		7/7	16 (4)	16.0 (2.4)	

[a] Dose in mg/kg. [b] Number of animals responding/number receiving drug. [c] ED50 followed by 95% confidence limits. [d] ED50 value previously published.[13] [e] No responding (i.e., disruption of behavior). [f] ED50 previously published.[13]

Another possible explanation for the observed selectivity is that the pyrrole portion, or some feature (e.g. electron density) associated with the pyrrole portion, of the indolylalkaneamines is important for affinity at 5-HT_2 sites but not for affinity at 5-HT_{1A} sites. Thus, 8-OH-DPAT (6) and 8-OMe-DPAT (7), which lack this feature, display a low affinity for 5-HT_2 sites. There are several other lines of evidence to support this argument: (a) simple tryptamine derivatives generally display a high affinity but low selectivity for 5-HT_2 sites,[4,15] (b) other 5-HT_{1A}-selective agonists such as buspirone and gepirone lack a pyrrole ring,[1] and (c) fusion of a pyrrole ring to the aminotetralin structure results in agents (i.e., 4-aminobenz[*cd*]indole derivatives) with little to no selectivity for 5-HT_{1A} vs 5-HT_2 sites.[16] A further analogy may be drawn with the bromo counterpart of DOM (i.e., DOB; 8, R = Br). We have proposed that these types of compounds interact with 5-HT_2 sites in such a manner that the meta methoxy group might interact with that portion of the receptor that normally accommodates the pyrrole portion of the indolealkylamines.[15] DOB displays a very high affinity and selectivity for 5-HT_2 sites; removal of the meta methoxy group reduces 5-HT_2-site affinity by nearly 2 orders of magnitude.[17]

Thus, the *n*-propyl groups of 4–7 appear to account for the low affinity of these agents for 5-HT_{1B} sites but, at least in the case of the indolealkylamines 4 and 5, have little effect on affinity at 5-HT_{1A} sites and selectivity for 5-HT_{1A} vs 5-HT_2 sites. The selectivity of 8-OH-DPAT (6) and 8-OMe-DPAT (7) for 5-HT_{1A} sites, and the lack of selectivity of DiPS (4) and *O*-Me-DiPS (5), seems to be related more to the absence or presence of a pyrrole-ring feature, which appears to be important for binding at 5-HT_2 sites. However, the binding of these agents to different subsites cannot be ruled out at this time.

Experimental Section

Synthesis. Proton magnetic resonance spectra were obtained with a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard; infrared spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Spectral data are consistent with the assigned structures. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. 8-OH-DPAT·HBr was purchased from RBI (Natick, MA), and all of the remaining agents were synthesized in our laboratory and were available from earlier studies.

***N,N*-Di-*n*-propyl-2-[5-(benzyloxy)indol-3-yl]ethanamine Hydrochloride (9).** Under a nitrogen atmosphere, a solution of oxalyl chloride (254 mg, 2 mmol) in N_2-purged anhydrous ether (5 mL) was added in a dropwise manner to a stirred solution of 5-(benzyloxy)indole (250 mg, 1.12 mmol) in N_2-purged anhydrous ether (10 mL) at 0 °C. After the addition was complete, the orange solution was allowed to stir for 1 h at 0 °C. The orange precipitate was collected and washed with N_2-purged anhydrous ether. The precipitate was added portionwise to a stirred aqueous solution of di-*n*-propylamine (405 mg, 4 mmol in 20 mL of water) at 0 °C. After complete addition, the solution was allowed to stir at room temperature for 30 h. The resulting white precipitate was collected to afford 312 mg (74%) of the glyoxylamide, mp 138–141 °C. A solution of this glyoxylamide (360 mg, 0.96 mmol) in dry THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (350 mg, 10 mmol) in dry THF (15 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was heated at reflux for 3.5 h and then allowed to stir at 40 °C for 10 h. The mixture was cooled to 0 °C, and the following were added successively in a dropwise manner to the stirred suspension: H_2O (0.35 mL), aqueous NaOH (15%, 0.35 mL), H_2O (3 mL). The mixture was filtered through Celite, and the filter cake was resuspended in warm THF and filtered. The combined filtrates were dried (Na_2SO_4, $MgSO_4$), and the solvent was evaporated in vacuo to yield an orange-red oil, which solidified upon trituration with anhydrous Et_2O. The solid was dissolved in absolute EtOH to which an anhydrous ethereal HCl solution was added in a dropwise manner until acidic to litmus. The solution was stored for 48 h at 10 °C after which time 178 mg (50%) of the title compound was collected by filtration, mp 198–201 °C. The product was recrystallized from an absolute EtOH/Et_2O mixture without change in the melting point.

***N,N*-Di-*n*-propyl-2-(5-hydroxyindol-3-yl)ethanamine Hydrochloride (*N,N*-Di-*n*-propylserotonin Hydrochloride) (4).** A methanolic solution (60 mL) of 9 (100 mg, 0.26 mmol) and 10% Pd/C (100 mg) was subjected to 1 atm of hydrogen at 42 psi for 24 h. The hydrogenation mixture was filtered through Celite and the filtrate was concentrated in vacuo to a final volume of 3 mL. This solution was layered with 2-butanone, and after the mixture stood for 2 days at 10 °C, yellow crystals were collected by filtration. Recrystallization from an EtOH/2-butanone mixture

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provided 50 mg (65%) of the title compound (as off-white prismatic crystals), mp 197–199 °C (lit.[6] mp 204–205 °C).

Binding Studies. The radioligand binding assay was conducted in essentially the same manner as reported earlier.[11,18] Following decapitation, the brains of male Sprague–Dawley rats (ca. 220 g) were removed and placed in 0.9% ice-cold saline and dissected over ice until the tissue was prepared. Tissues were stored in ice-cold saline for no longer than 1 h and, following blot drying and weighing, were prepared and frozen at −30 °C until used. Freshly dissected tissue was homogenized (Polytron setting 6 for 20 s) in 30 volumes of ice-cold buffer containing 50 mM Tris·HCl (pH 7.4 at 37 °C; pH 8.0 at 4 °C), 0.5 mM Na_2EDTA, and 10 mM $MgSO_4$, and centrifugated at 30000*g* for 15 min. The supernatant was discarded, and the pellet was resuspended and preincubated for 15 min at 37 °C. The pellet was washed twice by centrifugation and resuspension. The final assay buffer contained 50 mM Tris·HCl (pH 7.7), 10 μM pargyline, 0.1% ascorbate, 10 mM $MgSO_4$, and 0.5 mM Na_2EDTA. The agonist high-affinity state of the 5-HT_2 receptor was labeled with 0.4 nM [^{3}H]DOB (40 Ci/mmol; New England Nuclear) with 20 mg wet weight of tissue prepared from rat frontal cortex. Cinanserin (1 μM) was used to define nonspecific binding. 5-HT_2 sites were also labeled with [^{3}H]ketanserin (76 Ci/mmol; New England Nuclear) and 3 mg wet weight of rat frontal cortex tissue. The 5-HT_{1A} receptor was labeled with 0.1 nM [^{3}H]8-OH-DPAT (120 Ci/mmol; New England Nuclear) and 6 mg wet weight of rat hippocampal tissue. 8-OH-DPAT (1 μM) was used to determine nonspecific binding. The 5-HT_{1B} receptor was labeled with 2 nM [^{3}H]serotonin (23 Ci/mmol; New England Nuclear) and 8 mg wet weight of rat striatum. Serotonin (10 μM) was used to define nonspecific binding; 8-OH-DPAT (100 nM) and mesulergine (100 nM) were used to block 5-HT_{1A} and 5-HT_{1C} sites, respectively. Eleven concentrations of nonradioactive competing drugs were made fresh daily in assay buffer. Following incubation with membranes and radioligand at 37 °C for 15 min (5-HT_2 assays) or for 30 min (5-HT_1 assays), samples were rapidly filtered with glass-fiber filters and were washed with 10 mL of ice-cold 50 mM Tris·HCl buffer. Individual filters were inserted into vials and equilibrated with 5 mL of scintillation fluid for 6 h before counting at 45% efficiency in a Beckman 3801 counter. Results were analyzed with RS1 (BBN Software).

Discrimination Studies. The present study used male Sprague–Dawley rats that had been previously trained[17,19] to discriminate either 1.0 mg/kg of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride (DOM) or 0.2 mg/kg of 8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT) from 0.9% saline. The studies were conducted with use of standard two-lever operant chambers (Coulbourn Instruments Model E10-10), a variable-interval 15-s schedule of reinforcement for food (sweetened milk) reward, and a 15-min presession injection interval. Details of the training and testing procedures have been previously reported.[17,19] Briefly, in the tests of stimulus generalization (during which maintenance of the original DOM/saline or 8-OH-DPAT/saline discrimination was insured by continuation of training sessions throughout the studies), the animals were allowed 2.5 min to respond under extinction conditions and were then returned to their individual home cages. An odd number of training sessions (usually five, but never less than three) separated any two test sessions. During the test sessions, doses of the challenge drugs were administered by intraperitoneal injection in a random order to, routinely, groups of five animals. Once disruption of behavior occurred, only lower doses of the compound would be investigated. A 15-min presession injection interval was used throughout. Stimulus generalization was said to have occurred when the animals made ≥80% of their total responses on the drug-appropriate (i.e., either DOM-appropriate or 8-OH-DPAT-appropriate) lever. Animals making less than five total responses during the entire 2.5-min extinction session were reported as being disrupted. Where stimulus generalization occurred, ED50 values (i.e., doses at which the animals would be expected to make approximately 50% of their responses on the drug-appropriate lever) were calculated from the dose–response data.

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Peptide Derivatives of Primaquine as Potential Antimalarial Agents

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Three peptide derivatives of primaquine were synthesized. The compounds were tested for radical curative antimalarial activity against *Plasmodium cynomolgi* in rhesus monkeys and blood schizonticidal antimalarial activity against *Plasmodium berghei* in mice. All three peptide derivatives showed activity against *P. cynomolgi* greater than that expected for the primaquine content of each prodrug. The toxicity of one of the peptide derivatives was less than that of primaquine in mice.

Malaria is caused by more than 50 different species of the protozoa *Plasmodium*.[1] However, only four species attack humans: *P. faciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. If not treated properly, *vivax* malaria may subside spontaneously, only to recur at a later date. Primaquine (*1*) is the drug of choice for the radical cure of *vivax* malaria, or in combination with other antimalarial drugs such as chloroquine for prophylaxis. The major drawback of primaquine is its low therapeutic index. The drug is known to cause hemolytic lesions, particularly in patients deficient in glucose-6-phosphate dehydrogenase. Many analogues of **1** have been prepared, some less toxic than **1**.[2,3] Recently, reduced toxicity was achieved by encapsulating primaquine in liposomes[4] or by linking **1** to a macromolecular protein.[5,6] Interestingly, Trouet and co-

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