as the nitrogen source.[13,15] The MIC was recorded as the lowest concentration of drug that resulted in 5% morphologically aberant cells as visualized by microscopy after a 24-48-h incubation at 37 °C in yeast nitrogen base (Difco Labs, Detroit, MI).

Acknowledgment. This work was supported by grants from the National Institute of Allergy and Infectious Disease (AI-14387 and AI-42651) and the PSC-BHE Awards Program of City University of New York. We are grateful to David Miller who carried out many of the biological assays.

Registry No. **2**, 24695-48-5; **3A**, 112139-13-6; Cbz-**3A**, 112139-12-5; **3B**, 112139-14-7; Cbz-**3B**, 112139-26-1; 4 (diastereomer 1), 112139-17-0; 4 (diastereomer 2), 112139-18-1; 4·HCOOH (diastereomer 1), 112139-19-2; 4·HCOOH (diastereomer 2), 112139-20-5; Cbz-4 (diastereomer 1), 112139-16-9; Cbz-4 (diastereomer 2), 112139-27-2; **5A**, 112139-24-9; Cbz-**5A**, 112139-23-8; **5B**, 112139-25-0; Cbz-**5B**, 112139-28-3; (±)-α-bromooctanoic acid, 70610-87-6; (±)-α-aminooctanoic acid, 644-90-6; (±)-*N*-(benzyloxycarbonyl)-α-aminooctanoic acid, 76313-08-1; (±)-*p*-nitrophenyl *N*-(benzyloxycarbonyl)-α-aminooctanoate, 112139-11-4; (±)-α-bromododecanoic acid, 112139-15-8; (±)-α-aminododecanoic acid, 35237-37-7; (±)-*N*-(benzyloxycarbonyl)-α-aminododecanoic acid, 66398-12-7; (±)-*p*-nitrophenyl *N*-(benzyloxycarbonyl)-α-aminododecanoate, 66398-13-8; (±)-α-aminohexadecanoic acid, 98320-69-5; (±)-α-bromohexadecanoic acid, 40305-76-8; (±)-*N*-(benzyloxycarbonyl)-α-aminohexadecanoic acid, 112139-21-6; (±)-*p*-nitrophenyl *N*-(benzyloxycarbonyl)-α-aminohexadecanoate, 112139-22-7; chitin synthetase, 9030-18-6.

Development of a New Physicochemical Model for Brain Penetration and Its Application to the Design of Centrally Acting H_2 Receptor Histamine Antagonists

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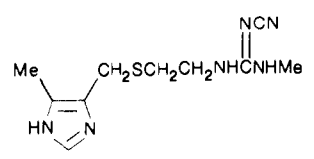
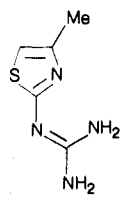
Smith Kline & French Research Ltd., The Frythe, Welwyn, Hertfordshire AL6 9AR, England. *Received February 4, 1987*

A rational approach to the design of centrally acting agents is presented, based initially upon a comparison of the physicochemical properties of three typical histamine H_2 receptor antagonists which do not readily cross the blood–brain barrier with those of the three brain-penetrating drugs clonidine (**6**), mepyramine (**7**), and imipramine (**8**). A good correlation was found between the logarithms of the equilibrium brain/blood concentration ratios in the rat and the partition parameter, Δ log *P*, defined as log *P* (1-octanol/water) − log *P* (cyclohexane/water), which suggests that brain penetration might be improved by reducing overall hydrogen-bonding ability. This model has been employed as a guide in the design of novel brain-penetrating H_2 antagonists by the systematic structural modification of representatives of different structural types of H_2 antagonists. Although marked increases in brain penetration amongst congeners of cimetidine (**1**), ranitidine (**9**), and tiotidine (**10**) were achieved, no compound was found with an acceptable combination of H_2 antagonist activity ($-\log K_B$ in the guinea pig atrium > 7.0) and brain penetration (steady-state brain/blood concentration ratio > 1.0). Conversely, structural modification of *N*-[[(piperidinylmethyl)phenoxy]propyl]acetamide (**30**) led to several potent, novel compounds which readily cross the blood–brain barrier. One of these, zolantidine (SK&F 95282, **41**), whose $-\log K_B$ is 7.46 and steady-state brain/blood ratio is 1.4, has been identified for use in studying histaminergic H_2 receptor mechanisms in brain. Comparison of Δ log *P* values with the logarithms of the brain/blood ratios for 20 structurally diverse compounds for which data became available confirms a highly significant correlation and supports the general validity of this model.

Histamine has been shown to be present in the brain of many species including humans.[1] While it does not readily cross the blood–brain barrier,[2] the occurrence of accompanying specific enzymes for its synthesis and degradation[3] and the identification of H_1 and H_2 receptors in the central nervous system (CNS)[4] all support the view that histamine has a physiological function in brain. Thus far, investigation of a possible role for central histamine H_2 receptors has been limited by the lack of potent, selective antagonists which readily penetrate the brain. Unlike histamine H_1 receptor antagonists, H_2 receptor antagonists, for example cimetidine (**1**),[5] are typically polar, hydrophilic compounds which do not readily enter the CNS.[6-8]



1



2

A compound which might be considered as a brain-penetrating H_2 antagonist from a report that it caused "CNS stimulation" in animals is ICI 17148 (**2**),[9] and we have since shown that it crosses the blood–brain barrier moderately well in a rat model (see below). The usefulness of **2** as a potential tool for studying histaminergic mechanisms in brain is, however, limited by its low H_2 antagonist activity. In the isolated guinea pig right atrium it

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(1) Green, J. P.; Johnson, C. L.; Weinstein, H. In *Psychopharmacology: A Generation of Progress*; Lipton, M. A., Dimascio, A., Killam, K. F., Eds.; Raven: New York, 1978; p 319.
(2) Schayer, R. W.; Reilly, M. A. *J. Neurochem.* **1970**, *17*, 1649.
(3) Schwartz, J.-C.; Pollard, H.; Quach, T. T. *J. Neurochem.* **1980**, *35*, 26.
(4) Schwartz, J.-C.; Barbin, G.; Duchemin, A.-M.; Garbarg, M.; Llorens, C.; Pollard, H.; Quach, T. T.; Rose, C. In *Pharmacology of Histamine Receptors*; Ganellin, C. R., Parsons, M. E., Eds.; Wright PSG: Bristol, 1982; p 351.
(5) Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E. *J. Int. Med. Res.* **1975**, *3*, 86.
(6) Ganellin, C. R.; Blakemore, R. C.; Brown, T. H.; Cooper, D. G.; Durant, G. J.; Harvey, C. A.; Ife, R. J.; Owen, D. A. A.; Parsons, M. E.; Rasmussen, A. C.; Sach, G. S. *N. Engl. Reg. Allergy Proc.* **1986**, *7*(2), 126.
(7) Cross, S. A. M. *Clin. Toxicol.* **1977**, *18*, 288.
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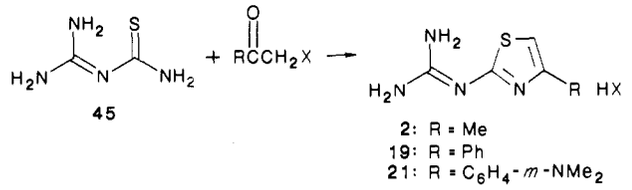
Scheme I

Method A



has been reported[9] to antagonize histamine-stimulated tachycardia with a $-\log K_B$ value of 5.4, while in the present study $-\log K_B$ was found to be 6.3 with a Schild slope of only 0.5.

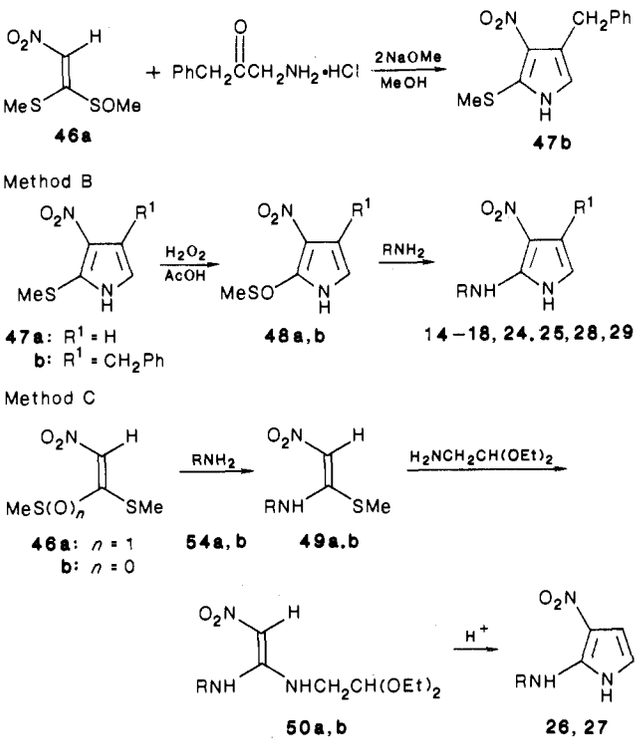
Although it is generally accepted that the rate and extent of entry of a compound into the brain are related primarily to its proton dissociation constant (K_a), partition coefficient (P), and molecular size, it is not clear from previous studies which solvent system for the measurement of partition coefficients most closely resembles the partitioning characteristics of the blood–brain barrier. In most cases, studies have been limited to comparisons between brain penetration data and partition coefficients measured in only a single solvent system, often using structurally restricted series of compounds.[10-12] In earlier studies[13,14] partition coefficients measured in the heptane/water, benzene/water, and chloroform/water solvent systems were used. More recently, several reports on the use of 1-octanol/water partition coefficients (P_{oct}) in brain-penetration studies have appeared. Linear relationships have been found[15-18] between log P_{oct}, sometimes combined with a molecular weight term, and rat brain capillary permeability for different series of compounds, and in one of these[16] it was concluded that the molecular weight limit for significant entry into the brain is between 400 and 657 daltons. Hansch[19] has suggested that, more generally, a parabolic relationship exists for the passive diffusion of neutral molecules into the CNS, with an optimum log P_{oct} value of about 2.

In this paper we consider the importance of a number of physicochemical properties in relation to brain penetration and derive a model which is used in the design of novel compounds which combine the ability to cross the blood–brain barrier with high levels of H_2 antagonist activity, a preliminary communication of which has appeared elsewhere.[20]

Chemistry

The guanidinothiazole derivative **21** was prepared by reaction of amidinothiourea (**45**) with the appropriately substituted α-halo ketone (method A) as shown in Scheme I.

Scheme II



2-Amino-3-nitropyrrole derivatives were synthesized by either of the two methods shown in Scheme II depending upon the reactivity of the respective amine precursors. Displacement of the methylsulfinyl group in **48a,b** (method B) was generally slow and gave low yields of the corresponding antagonists probably due to decomposition. In this method reactivity appeared to be limited by the ability of the leaving group to be displaced and on its acidifying effect on the pyrrole NH. Thus, methylsulfinyl was found to be superior to methylsulfonyl, while the methylthio intermediates **47a,b** were unreactive. An improved method which has been used for preparing derivatives of substituted anilines was developed (method C), using the more reactive 1,1-bis(methylthio)-2-nitroethene (**46b**)[21] or its sulfoxide (**46a**)[22] to give intermediates **49a,b**, which were then reacted with aminoacetaldehyde acetal and cyclized under mildly acidic conditions to give the respective pyrroles **26** and **27**.

In most cases, preparative methods for the amines, RNH_2, have been described elsewhere (see Tables III–V for references). The substituted anilines **54a–c** and **58** were prepared according to the routes shown in Scheme III, by using the Meerwein reaction to couple the aromatic rings, followed by introduction of the (dimethylamino)methyl group either by use of bis(dimethylamino)methane (to convert **52a–c** to **53a–c**) or via bromination (of **55**) and amination (of **56**), and finally reducing the intermediates, **53a–c** and **57**. The isoquinoline amine **60** was synthesized from isoquinoline-1-methanol (**59**) and cysteamine, by refluxing in 48% aqueous HBr.

Amine **38**[23] was used to prepare a number of amino-heterocyclic derivatives by displacement of halogen from halo-substituted heterocycles and various derivatives of amides or equivalent groups by similarly replacing a suitable leaving group (method D), as illustrated in Scheme

(10) Pardridge, W. M.; Mietus, L. J. *J. Clin. Invest.* **1979**, *64*, 145.
(11) Mellett, L. B. *Cancer Treat. Rep.* **1977**, *61*(4), 527.
(12) Evans, B. D.; Vogel, W. H. *Res. Commun. Chem. Pathol. Pharmacol.* **1977**, *17*(1), 61.
(13) Mayer, S.; Marckel, R. P.; Brodie, B. B. *J. Pharmacol. Exp. Ther.* **1959**, *127*, 205.
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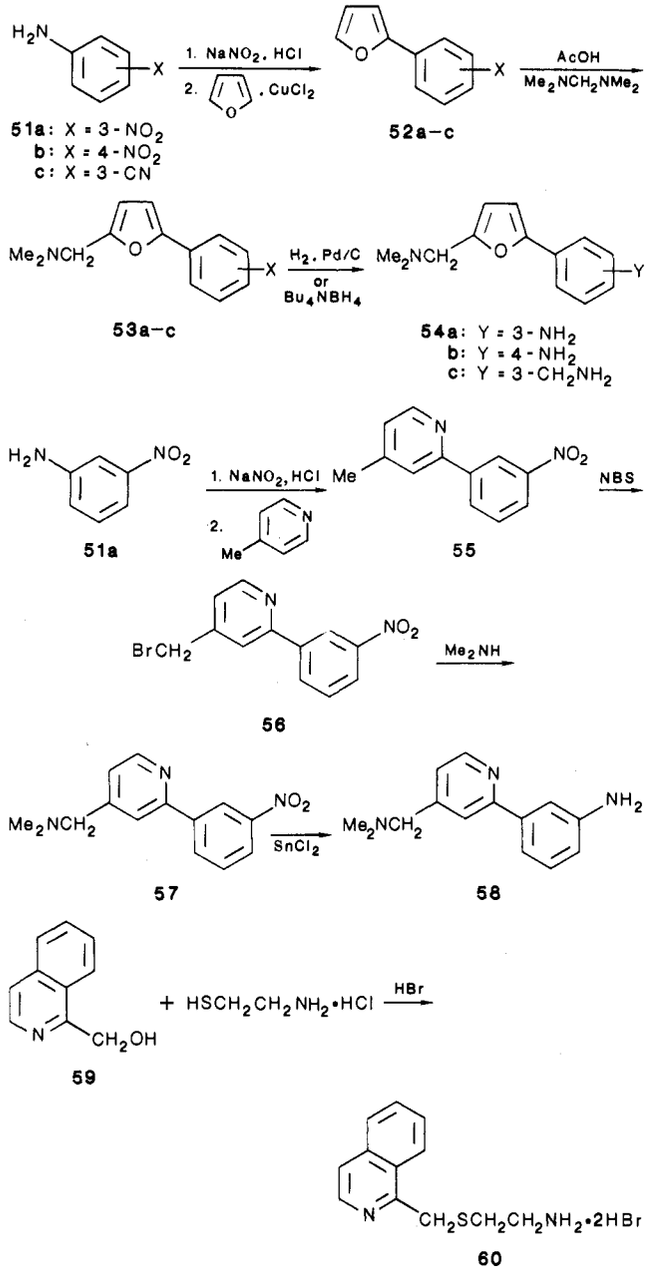
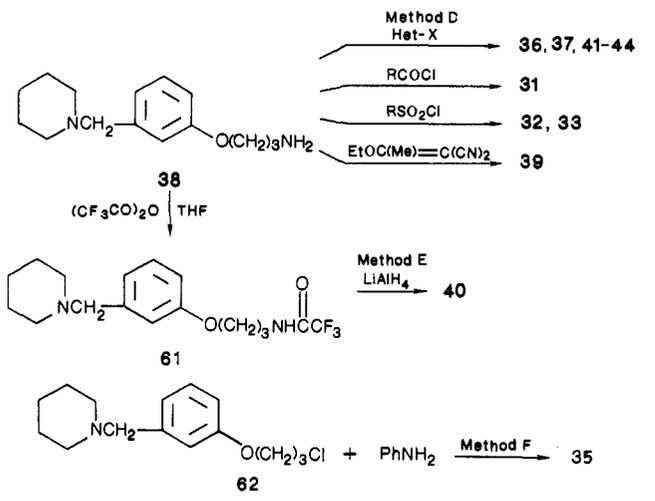
(19) Glave, W. R.; Hansch, C. *J. Pharm. Sci.* **1972**, *61*(4), 589.
(20) Ganellin, C. R.; Griffiths, R.; Mitchell, R. C.; Smith, I. R.; Young, R. C. *Br. J. Pharmacol.* **1986**, *89*, 772P.
(21) Gompper, R.; Schaefer, H. *Chem. Ber.* **1967**, *100*, 591.
(22) White, G. R. U.S. Patent 4028379, 1977.
(23) Clitherow, J. W.; Bradshaw, J.; MacFarlane, J. W.; Price, B. J.; Martin-Smith, M.; Bruce-Judd, D. GB Patent 2023133A, 1979.

Scheme III

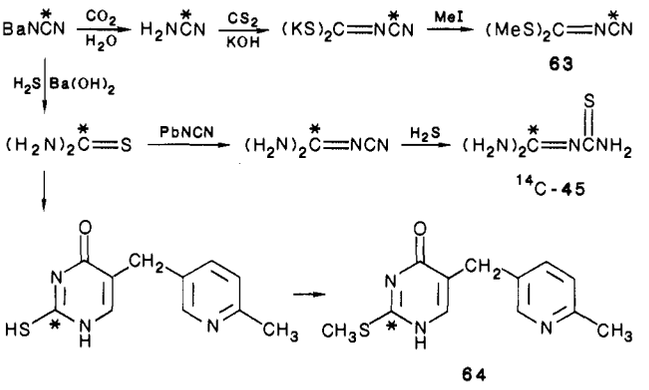


Scheme IV



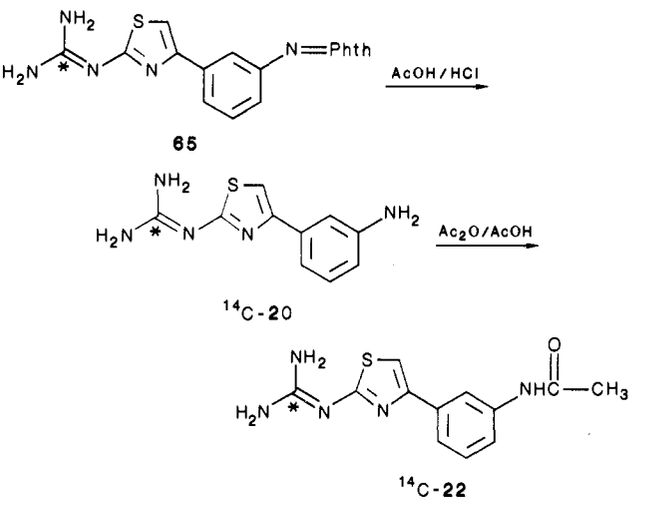
IV. The substituted aniline **35** was prepared by reacting aniline with the known alkyl chloride **62**[24] (method F), and the trifluoroacetamide **61**, made by method D, was reduced with $LiAlH_4$ to give the (trifluoroethyl)amino derivative **40**.

Scheme V[a]



[a] Asterisk denotes position of ^{14}C label.

Scheme VI[a]



[a] Asterisk denotes position of ^{14}C label.

The radiolabeled compounds were prepared either by direct tritiation of the antagonists described above (**7**, **12**, **16**, **17**, **26**, **29–31**) or by synthetic procedures utilizing common radiolabeled intermediates. Thus, barium [^{14}C]cyanamide was converted to dimethyl [*cyano*-^{14}C]-cyanodithioimidocarbonate (**63**), [*amidino*-^{14}C]amidinothiourea (^{14}C-**45**), and 5-[(6-methylpyrid-3-yl)methyl]-[2-^{14}C]-2-(methylthio)pyrimidin-4-one (**64**)[25] by the routes shown in Scheme V. Compounds ^{14}C-**1**, ^{14}C-**13**, and ^{14}C-**23** were prepared by reacting **63** with the appropriate amines by the methods described previously.[26-28] Reaction of ^{14}C-**45** with the appropriate α-halo ketones by method A gave ^{14}C-**2**, ^{14}C-**19**, and **65**. The latter was subsequently hydrolyzed to the amine ^{14}C-**20** and acetylated to give ^{14}C-**22** (Scheme VI).[28] Compounds ^{14}C-**3** and ^{14}C-**5** were both prepared from **64** by reaction with the respective amines.[29,30]

(24) Fujisawa Pharmaceutical Co. Ltd. *Jpn. Kokai Tokkyo Koho* Patent 58 90,569, 1983.
(25) Cashyap, M. M.; Mitchell, M. B.; Osborne, D. C.; Saunders, D. *J. Labelled Compd Radiopharm.* **1985**, *22*(12), 1239.
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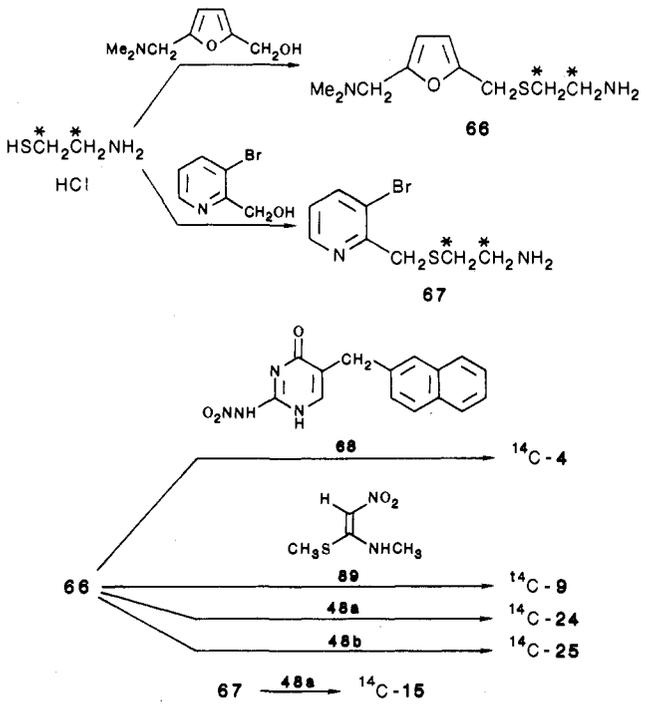
(29) Brown, T. H.; Durant, G. J.; Ganellin, C. R. U.S. Patent 4154834, 1979.

Table I. Physicochemical Properties and Brain-Penetration Data for Three H_2 Antagonists and Three Compounds That Readily Cross the Blood–Brain Barrier

		log P_n				pK_a				
compd	MW	oct	chl	cyh	Δ log P^a	1	2	3	4	log (C_{brain}/C_{blood})
3	379	2.58[b]	2.43[b]	−2.60[b]	5.18	3.15[c]	~5.6[d]	~6.1[e,f]	9.78[g]	−2.00
4	449	4.57[h]	–	0.47[i]	4.10	~3.0[e]	~8.5[e]	10.2[e]		−1.30
5	414	2.33[j]	2.64[k]	−1.48[l]	3.81	3.03[c]	6.11[f]	8.50[m]	10.20[g]	−1.06
6	230	1.59[n]	–	−0.85[o]	2.44	8.05[p]				0.11
7	285	3.30[q]	4.44[r]	2.59[s]	0.71	4.02[t]	8.92[u]			0.49
8	280	4.42[v]	6.29[w]	3.57[x]	0.85	9.5[y]				0.83

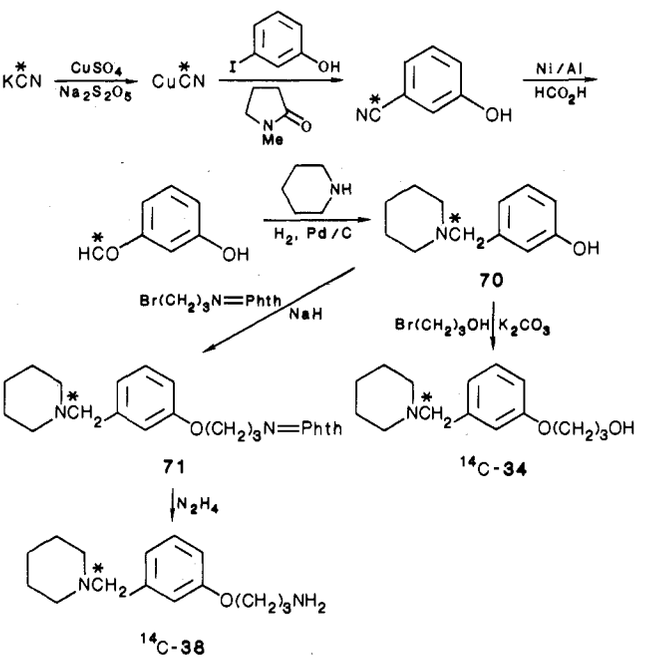
[a] log P_{oct} − log P_{cyh}. [b] Measured at pH 7.4. [c] Basic pK_a of isocytosine group. [d] Estimated value for the basic pK_a of the 3-methoxypyridyl group: pK_a = pK_a(3-methoxypyridine) + pK_a(2-methylpyridine) − pK_a(pyridine) = 4.78 + 6.00 − 5.23.[36] [e] Assumed similar to pK_a of **5**. [f] Basic pK_a of the picolyl group. [g] Acidic pK_a of the isocytosine group. [h] Estimated value: log P = log P(**5**) − log P(2-picoline)[37] + log P (naphthalene).[37] [i] Calculated from eq 1 using log P_a = 0.26 at pH 8.38; pK_a = 8.18 (pK_{a3} corrected for temperature). [j] Calculated from eq 1 using log P_a = 2.06 at pH 8.25; pK_a = 8.18. [k] Calculated from eq 1 using log P_a = 2.40 at pH 8.32; pK_a = 8.18. [l] Calculated from eq 1 using log P_a = −1.74 at pH 8.27; pK_a = 8.18. [m] Basic pK_a of the dimethylamino group. [n] Calculated from eq 1 using the data of Timmermans et al.[38,39] [o] Measured at pH 9.42. [p] Basic pK_a of the imidazoline group. [q] Measured at pH 10.7. [r] Calculated from eq 1 using log P_a = 3.94 at pH 8.32; pK_a = 8.65 (pK_{a2} corrected for temperature). [s] Measured at pH 10.78. [t] Basic pK_a of the aminopyridine group.[40] [u] Basic pK_a of the dimethylamino group.[40] [v] Value from Seiler.[41] [w] Value from Frisk-Holmberg et al.[42] [x] Calculated from the value for the dodecane/water system[41] with the solvent regression equations of Seiler.[43] [y] Basic pK_a of the dimethylamino group.[44]

Scheme VII[a]



[a] Asterisk denotes position of ^{14}C label.

Scheme VIII[a]



[a] Asterisk denotes position of ^{14}C label.

Amine **67**, labeled in the side chain, was prepared by reacting [1,2-^{14}C]cysteamine with the parent carbinol[27] by the method used for preparing **66**,[31] as shown in Scheme VII. Compounds ^{14}C-**4**, ^{14}C-**9**, ^{14}C-**24**, and ^{14}C-**25** were prepared by reacting **66** with **68** (obtained by α-formylation of ethyl β-(2-naphthyl)propionate[32] and cyclization with nitroguanidine), **69**,[22] **48a**, and **48b**, respectively, and ^{14}C-**15** was prepared from **67** and **48a** as described in method B.

Cuprous [^{14}C]cyanide was prepared from potassium [^{14}C]cyanide and used to convert 3-iodophenol to 3-[*cyano*-^{14}C]cyanophenol as shown in Scheme VIII. Subsequent reduction to 3-hydroxy[*carbonyl*-^{14}C]benzaldehyde and reductive amination with piperidine gave the intermediate, 3-(piperidin-1-yl[*methyl*-^{14}C]methyl)phenol (**70**). Reaction of **70** with 3-bromopropanol gave ^{14}C-**34**,[24] while the amine ^{14}C-**38** was prepared from **70** via the phthalimide as shown in Scheme VIII.[23] Subsequent reaction of ^{14}C-**38** with haloheterocycles by method D gave ^{14}C-**36**, ^{14}C-**37**, ^{14}C-**41**, and ^{14}C-**42**.

Results and Discussion

In attempting to establish a working model for the passage of histamine H_2 receptor antagonists across the blood–brain barrier, we initially selected six compounds for radiolabeling and measured their equilibrium brain/blood concentration ratios in anesthetized rats. Three of these compounds were the H_2 receptor antagonists icotidine (SK&F 93319, **3**),[33] **4**,[34] and lupitidine (SK&F 93479, **5**)[35] and three were compounds which were known to readily enter the brain, namely, clonidine (**6**), mepyramine

(30) Price, B. J.; Clitherow, J. W.; Bradshaw, J. GB Patent 1565966, 1980.
(31) Armitage, M. A.; Cashyap, M. M.; Saunders, D. *J. Labelled Compd Radiopharm.* **1986**, *24*(4), 431.
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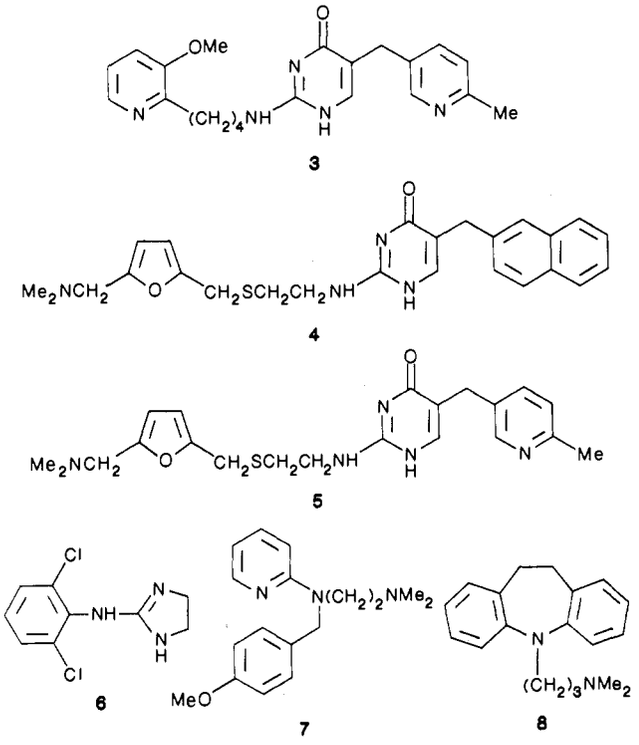
(33) Blakemore, R. C.; Brown, T. H.; Cooper, D. G.; Durant, G. J.; Ganellin, C. R.; Ife, R. J.; Parsons, M. E.; Rasmussen, A. C.; Sach, G. S. *Br. J. Pharmacol.* **1983**, *80*, 437P.
(34) Brown, T. H.; Ife, R. J. U.S. Patent 4234588, 1980.
(35) Blakemore, R. C.; Brown, T. H.; Durant, G. J.; Ganellin, C. R.; Parsons, M. E.; Rasmussen, A. C.; Rawlings, D. A. *Proc. Br. Pharmacol.* **1981**, *74*, 200P.

(7), and imipramine (8). The molecular weights (MW), log P and pK_a values of these compounds are compared with the logarithms of their brain/blood ratios (log (C_{brain}/C_{blood}), where C_{brain} and C_{blood} are the steady-state concentrations of radiolabeled compound in brain and peripheral blood) in Table I.



log P_n is the logarithm of the partition coefficient of the neutral form of the compound and is given for the 1-octanol/water (log P_{oct}), chloroform/water (log P_{chl}), and cyclohexane/water (log P_{cyh}) solvent systems. If it is assumed that only the neutral form of the compound partitions into the organic phase, then log P_n is related to the apparent partition coefficient (P_a) of the compound, measured at a pH at which the neutral and monoprotonated forms are in equilibrium in the aqueous phase, and to the dissociation constant (K_a) of a proton from the most basic site in the molecule, by eq 1. The Δ log P parameter, which was first introduced by Seiler,[43] is defined as the difference between the octanol/water and cyclohexane/water log P values and is related to the overall hydrogen-bonding ability of a compound by eq 2, where I_H denotes the additive increment to hydrogen bonding by a molecular fragment and b is a constant.

$$\log P_n = \log P_a + \log (1 + 10^{pK_a - pH}) \quad (1)$$

$$\Delta \log P = \log P_{oct} - \log P_{cyh} = \sum I_H - b \quad (2)$$

The values of log (C_{brain}/C_{blood}) for these compounds span a range of 2.83 units. Compound **3** has the lowest log (C_{brain}/C_{blood}) value in spite of the fact that it is the only compound which will be largely unionized at pH 7.4. Moreover, compound **4**, which has the highest log P_{oct} value, also has one of the lowest log (C_{brain}/C_{blood}) values.

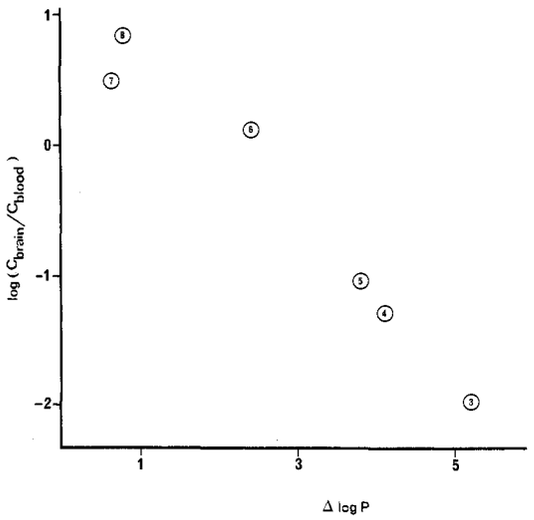


Figure 1. Relationship between brain penetration and Δ log P for clonidine, mepyramine, imipramine, and three H_2 receptor antagonists.

The results of regression analysis of the physicochemical data for the six compounds in Table I on log (C_{brain}/C_{blood}) are shown in eq 3–7. Clearly, there is no correlation between brain penetration and log P_{oct} (eq 4), while log P_{chl} and log P_{cyh} are more highly correlated (eq 5 and 6), with the latter reaching significance at the 95% level. The best correlation is given in eq 7 in which 96% of the variance in brain penetration data is accounted for by Δ log P alone.

$$\log (C_{brain}/C_{blood}) = -0.0103\ (\pm 0.0109)\mathrm{MW} + 3.02\ (\pm 3.79) \quad (3)$$

$$n = 6,\ r = 0.797,\ s = 0.760,\ F = 6.95$$

$$\log (C_{brain}/C_{blood}) = 0.150\ (\pm 1.295) \log P_{oct} - 0.96\ (\pm 4.29) \quad (4)$$

$$n = 6,\ r = 0.160,\ s = 1.241$$

$$\log (C_{brain}/C_{blood}) = 0.679\ (\pm 0.877) \log P_{chl} - 3.12\ (\pm 3.73) \quad (5)$$

$$n = 4,\ r = 0.920,\ s = 0.636,\ F = 11.08$$

$$\log (C_{brain}/C_{blood}) = 0.385\ (\pm 0.369) \log P_{cyh} - 0.598\ (\pm 0.815) \quad (6)$$

$$n = 6,\ r = 0.824,\ s = 0.713,\ F = 8.43$$

$$\log (C_{brain}/C_{blood}) = -0.604\ (\pm 0.169)\ \Delta \log P + 1.23\ (\pm 0.56) \quad (7)$$

$$n = 6,\ r = 0.980,\ s = 0.249,\ F = 98.0$$

This relationship, which is illustrated in Figure 1, suggests that brain penetration will be increased by lowering the overall hydrogen-bonding ability of a compound and is in accord with Overton's rules relating to the effects of strong hydrogen bonding groups on the ability of compounds to cross cell membranes, discussed by Wright and Diamond.[45]

It should be possible to reduce hydrogen-bonding ability either by removing polar groups not essential for H_2 antagonist activity or by reducing the polarity of groups

(36) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 3rd ed.; Chapman & Hall: London, 1984; p 154.
(37) Hansch, C.; Leo, A. J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.
(38) Timmermans, P. B. M. W. M.; van Zwieten, P. A. *Arzneim.-Forsch.* **1978**, *28*(10), 1676.
(39) Timmermans, P. B. M. W. M.; Brands, A.; van Zwieten, P. A. *Arch. Pharmacol.* **1977**, *300*(3), 217.
(40) Lordi, N. G.; Christian, J. E. *J. Am. Pharm. Assoc. Sci. Ed.* **1956**, *45*, 300.
(41) Seiler, P. *Eur. J. Med. Chem.* **1974**, *9*(6), 663.
(42) Frisk-Holmberg, M.; van der Kleijn, E. *Eur. J. Pharmacol.* **1972**, *18*, 139.
(43) Seiler, P. *Eur. J. Med. Chem.* **1974**, *9*(5), 473.
(44) Green, A. L. *J. Pharm. Pharmacol.* **1967**, *19*, 10.
(45) Wright, E. M.; Diamond, J. M. *Proc. R. Soc. London, B* **1969**, *172*, 227.

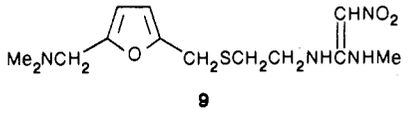
Table II. H_2 Receptor Antagonist Activities and Brain-Penetration Data for Representative Compounds of Different Structural Types

compound	$-\log K_B$ (95% limits)[a]	log (C_{brain}/C_{blood})
1 (cimetidine)	6.10 (6.04–6.17)	−1.42
9 (ranitidine)	7.05 (6.79–7.52)[b]	−1.23
10 (tiotidine)	7.52 (7.21–7.99)	−0.82
2	6.27 (5.80–6.81)[c]	−0.04
12	5.59 (4.92–6.10)[d]	−1.17

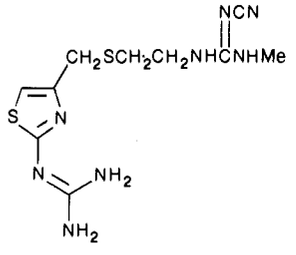
[a] H_2 receptor antagonist activity determined in vitro in the histamine-stimulated guinea pig right atrium and analyzed by Schild plot.[51] Slopes of log (X − 1) plotted against log B were not significantly different from unity (±95% limits) unless stated. [b] Slope 0.7 ± 0.2. [c] Slope 0.5 ± 0.17. [d] Slope 0.61 ± 0.23.

considered necessary for antagonist activity. The latter might be accomplished by encouraging intramolecular hydrogen bonding, shielding with nonpolar groups, or making less polar, labile derivatives (i.e., prodrugs) of an active polar compound.

Known H_2 receptor antagonists can be broadly considered[46] to fall into five principal structural categories, thus (1) compounds with simple heterocycle-containing side chains, e.g., cimetidine (1), (2) compounds with (aminomethyl)aryl-containing side chains, e.g., ranitidine (**9**),[47] (3) compounds with guanidinoheterocycle-containing side chains, e.g., tiotidine (**10**)[48] and **2**, (4) phenylformamidine derivatives, e.g., mifentidine (11),[49] and (5) biheterocyclic derivatives, e.g., **12**.[50]



9



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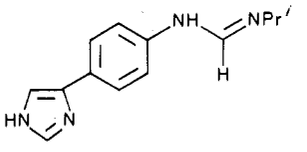

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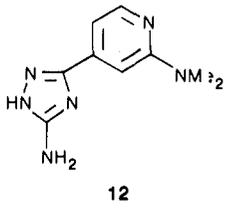
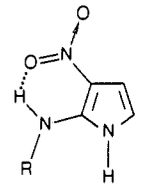


12

The logarithms of the brain/blood concentration ratios (log (C_{brain}/C_{blood}) of representative compounds of types 1–3 and 5 in the rat are shown in Table II with their H_2 antagonist activities. These compounds are all hydrophilic and possess a number of potential hydrogen-bonding sites. After peripheral iv administration, only **2** was found to enter the brain in significant amounts. In attempting to enhance the brain-penetrating ability of existing compounds, we have limited our investigation to compounds of types 1–3. These offer the advantage that a great deal is already known about the effects of structural modification on H_2 antagonist activity[46] and that similar structure–activity patterns apply.

Starting with the three lead compounds, cimetidine, ranitidine, and **2** as representatives of antagonist types 1, 2, and 3, respectively, structural modifications have been explored with the aim of reducing hydrogen-bonding ability, while maintaining or enhancing H_2 antagonist activity. Cimetidine (1) contains an imidazole and a cyanoguanidine moiety, both of which are capable of forming strong hydrogen bonds. It is known that imidazole can be replaced by other heterocycles often with retention of activity, provided that a pyridine-type nitrogen is present in a position ortho to the side chain.[46] Pyridine itself is a useful replacement as it contains just one hydrogen-bonding heteroatom and also allows antagonist activity to be retained, and even increased, as in the bromopyridyl derivative, **13** (Table III). The cyanoguanidine moiety in cimetidine can be replaced by alternative neutral, dipolar groups, and it has been proposed[52] that optimum activity can be achieved when its dipole is oriented at an angle of about 30° with respect to the last C–N bond of the side chain. The 2-amino-3-nitropyrrole moiety is perhaps the best replacement for cyanoguanidine as it appears to have a near-optimal dipole orientation[52] and is much less hydrophilic, partly due to its ability to form an intramolecular hydrogen bond between the amino and nitro groups (I).



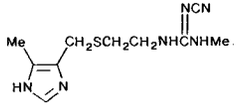
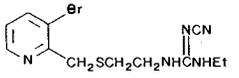
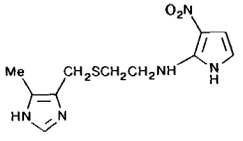
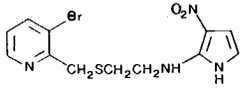
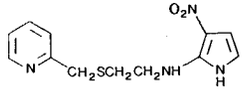
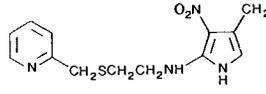
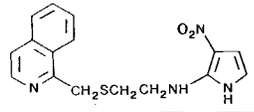
I

Some structural analogues (**13**–**18**) of cimetidine with reduced H-bonding potential are shown in Table III. Although marked improvements in brain penetration have been achieved, the highest log (C_{brain}/C_{blood}) value found was −0.12, and it was considered that the structural requirements for an antagonist of this type were sufficiently restricted to make the prospect of further modification an unattractive option.

Attempts to improve the H_2 antagonist activity of the guanidinothiazole derivative **2** have been based on structural elaboration at the thiazole 4-position. Although the cyanoguanidine-containing side chain of cimetidine has been introduced at this position to provide the very potent antagonist, tiotidine (**10**, Table IV),[48] this compound contains many potential hydrogen-bonding sites and crosses the blood–brain barrier to only a small extent. Unlike cimetidine, however, where replacement of the flexibile 4-membered chain by a benzene ring is not well tolerated,[57] the *m*-phenylene analogue of tiotidine (**23**,

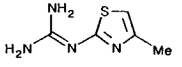
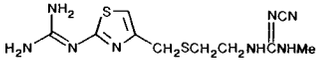
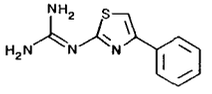
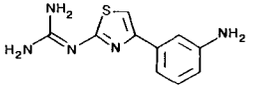
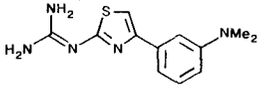
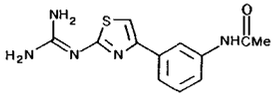
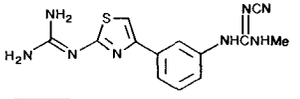
(46) Brown, T. H.; Young, R. C. *Drugs Future* **1985**, *10*(1), 51.
(47) Bradshaw, J.; Brittain, R. T.; Clitherow, J. W.; Daly, M. J.; Jack, D.; Price, B. J.; Stables, R. *Br. J. Pharmacol.* **1979**, *66*, P464.
(48) Yellin, T. O.; Buck, S. H.; Gilman, D. J.; Jones, D. F.; Wardleworth, J. M. *Life Sci.* **1979**, *25*, 2001.
(49) Donetti, A.; Cereda, E.; Bellora, E.; Gallazzi, A.; Bazzano, C.; Vanoni, P.; Del Soldato, P.; Micheletti, R.; Pagani, F.; Glachetti, A. *J. Med. Chem.* **1984**, 27(3), 380.
(50) Lipinski, C. A. *J. Med. Chem.* **1983**, *26*(1), 1.
(51) Parsons, M. E.; Owen, D. A. A.; Ganellin, C. R.; Durant, G. J. *Agents Actions* **1977**, *7*, 31.
(52) Young, R. C.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Graham, M. J.; Mitchell, R. C.; Prain, H. D.; Roantree, M. L. *J. Med. Chem.* **1986**, *29*(1), 44.
(53) Durant, G. J.; Emmett, J. C.; Ganellin, C. R. U.S. Patent 3 905 984, 1975.
(54) Beyer, H.; Hantschel, H. *Chem. Ber.* **1962**, *95*, 893.
(55) Gilman, D. J.; Jones, D. F.; Oldham, K.; Wardleworth, J. M. In *The Chemical Regulation Biological Mechanisms*; Creighton, A. M., Turner, S., Eds.; Royal Society of Chemistry Special Publication No. 42, 1982; p 58.

Table III. H_2 Receptor Antagonist Activities and Physicochemical Data for Cimetidine Analogues

compd	structure	formula[a]	mp, °C	solvent	yield,[b] %	method[c]	$-\log K_B$ (95% limits)[d]	log P_n(oct)	log P_n(cyh)	Δ log P	log (C_{brain}/C_{blood})
1		$C_{10}H_{16}N_6S$	141–143	H_2O		*e*	6.10 (6.04–6.17)	0.40[f]			−1.42
13		$C_{12}H_{16}BrN_5S$	123–124	EtOAc/pet. ether		*g*	6.50 (6.29–6.76)[h]	1.98[i]			−2.15
14		$C_{11}H_{15}N_5O_2S$	161–162	*i*-PrOH	31	B	7.31 (7.02–7.80)[j]	1.04[f]			
15		$C_{12}H_{13}BrN_4O_2S$	148–149	*i*-PrOH	6	B[k]	7.24 (6.88–7.87)[l]	1.75[m]	−1.34[n]	3.09	−0.67
16		$C_{12}H_{14}N_4O_2S$	76–78	*o*	5	B[k]	6.70 (6.49–7.07)				−0.66
17		$C_{10}H_{20}N_4O_2S$	153–154	EtOH	37	B[k]	6.97 (6.77–7.30)				−0.12
18		$C_{16}H_{16}N_4O_2S$	133–134	*i*-PrOH	11	B	6.84 (6.73–7.08)[p]	2.79[q]	−0.67[r]	3.46	

[a] All compounds were analyzed for C, H, N (and S in 1, 13–15, and 18) and are within 0.4% of theoretical values. [b] No attempts were made to optimize yields. [c] See Chemistry section. [d] See footnote *a*, Table II. [e] Durant et al.[26] [f] Measured at pH 9.0. [g] Durant et al.[27] [h] Slope 0.74 ± 0.16. [i] Estimated value: log P = log P(*N*-methyl-*N'*-cyano-*N''*-[2-[[(3-bromopyrid-2-yl)methyl]-thio]ethyl]guanidine) + $\pi(CH_3)$ = 1.48 (measured at pH 9.0) + 0.5.[37] [j] Slope 0.63 ± 0.17. [k] Using amine prepared by method of Durant et al.[53] [l] Slope 0.7. [m] Estimated value: log P = log P(2-[[2-[[(3-chloropyrid-2-yl)methyl]thio]ethyl]amino]-5-(pyrid-3-ylmethyl)pyrimidin-4-one) − log P(2-(methylamino)-5-(pyrid-3-ylmethyl)pyrimidin-4-one) + log P(2-(methylamino)-3-nitropyrrole) = 2.02 (measured at pH 7.5) − 0.36 (measured at pH 7.5) + 0.09 (measured at pH 7.3) = 1.75. [n] Value for the 3-chloropyridyl analogue (measured at pH 9.06). [o] Crystallized under Et_2O. [p] Slope 0.75 ± 0.16. [q] Estimated value: log P = log P(14) − log$P$(4-methylimidazole) + log P(isoquinoline) = 1.04 − 0.33 (measured at pH 10.15) + 2.08[37] = 2.79. [r] Measured at pH 8.38.

Table IV. H_2 Receptor Antagonist Activities and Physicochemical Data for Guanidinothiazole Derivatives

compd	structure	formula[a]	mp, °C	solvent	yield,[b] %	method[c]	$-\log K_B$ (95% limits)[d]	log P_n(oct)	log P_n(cyh)	Δ log P	log (C_{brain}/C_{blood})
2		$C_5H_8N_4S$·HCl	195–197	MeOH/Et_2O	68	A[e]	6.27 (5.80–6.81)[f]	1.24[g]	−2.79[h]	4.03	−0.04
10		$C_{10}H_{16}N_8S_2$·$C_4H_4O_4$	177–178	MeOH/EtOH		*i*	7.52 (7.21–7.99)	0.60[j]			−0.82
19		$C_{10}H_{10}N_4S$·HBr	209–211	EtOH	63	A[e]	5.93 (5.55–6.29)	2.64[k]	−1.28[l]	3.92	−0.18
20		$C_{10}H_{11}N_5S$	223–224	MeCN		*m*	7.33 (6.95–8.10)	1.41[n]	−3.19[o]	4.60	−1.15
21		$C_{12}H_{15}N_5S$·HBr[p]	>250	EtOH	22	A	<3.8				
22		$C_{12}H_{13}N_5OS$·1.25$C_2H_4O_2$	260–263	*q*		*m*	7.36 (7.08–8.07)				−1.57
23		$C_{13}H_{14}N_8S$	260–263	DMF/H_2O		*m*	7.84 (7.50–8.28)	1.60[r]	−2.66[s]	4.26	−1.54

[a] All compounds were analyzed for C, H, N (and S in **2**, **10**, **20**, and **23**) and are within 0.4% of theoretical values unless stated. [b] No attempts were made to optimize yields. [c] See Chemistry section. [d] See footnote *a*, Table II. [e] Beyer and Hantschel.[54] [f] Slope 0.50 ± 0.17. [g] Gilman et al.[55] [h] Measured at pH 9.71. [i] Yellin et al.[56] [j] Measured at pH 9.00. [k] Estimated value: log P = log P(**2**) + π(Ph) − π(Me) = 1.24 + 1.96[37] − 0.56[37] = 2.64. [l] Measured at pH 9.67. [m] Jones and Oldham.[28] [n] Estimated value: log P = log P(**19**) + $\pi(NH_2)$ = 2.64 − 1.23[37] = 1.41. [o] Measured at pH 9.80. [p] Contains 1% w/w HCl. [q] Washed with EtOAc and Et_2O. [r] Measured at pH 9.02. [s] Measured at pH 8.99.

Table IV) is a very potent H_2 receptor antagonist,[55] which we found to be slightly more active than tiotidine in the guinea pig atrium. Moreover, the possession of a benzene ring adjacent to both polar moieties should be advantageous for reducing effective hydrogen-bonding ability through its steric effect.[58] Brain penetration for this compound, however, was only marginal. Attempts to reduce the H-bonding ability of this compound still further by removal of the cyanoguanidine group led to several analogues (**19**–**22**), which are shown in Table IV. The amide **22**[55] was found to be very similar to the cyanoguanidine both in its antagonist activity and lack of brain penetration, and while further reduction of H-bonding ability led to steadily increasing brain penetration, H_2 antagonist activity fell. Because of the inherently high polarity of the guanidinothiazole moiety, it was considered unlikely that both high antagonist activity and reasonable brain penetration could easily be accommodated in a compound of this type.

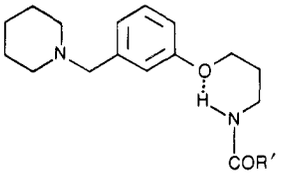
A third structural class of H_2 antagonists, represented by ranitidine (**9**), possess an aminomethylaryl group in the side chain. This group offers a useful combination of low H-bonding potential and moderately high basicity, which facilitates water solubility. Ranitidine, having a very polar nitrodiaminoethene group, does not readily enter the CNS and in this respect resembles **5** (Table V), a more potent analogue containing a substituted isocytosine group.[35]

By analogy with the cimetidine series, the 2-amino-3-nitropyrrole group has been introduced as a much less hydrophilic replacement for these two polar groups, but, in contrast, led to a slight fall in antagonist activity. Although the resulting compound, **24**, has a significantly lower $\Delta \log P$ value than **5**, its ability to cross the blood–brain barrier was not improved. A further reduction in $\Delta \log P$ can be achieved by introducing a benzene ring at an appropriate position in the molecule, and **25** and **26** (Table V) are two examples where such substitution is tolerated. In **25**, substitution of a benzyl group at the pyrrole ring 4-position results in an improvement in both antagonist activity and brain penetration, while introduction of a *m*-phenylene group in place of the (methylthio)ethyl chain in **24** led to a small reduction in antagonist activity and a marked increase in brain penetration. In both cases, steric inhibition of hydrogen-bonding ability by the benzene moiety is suggested by reductions in $\Delta \log P$. Neither **25** nor **26**, however, was thought to combine a sufficiently high level of brain penetration with adequate antagonist activity to be of biological interest.

Attempts to improve the activity of **26** met with limited success in **29** in which furan was replaced by pyridine. This compound has a slightly higher $-\log K_B$ value of 6.60 but similar ability to enter brain. The *p*-phenylene isomer of **26** (**27**) and its higher homologue (**28**) were both virtually inactive in the atrium.

A variant of the ranitidine-type side chain which has been introduced in some of the more recent H_2 antagonists, including lamtidine,[60] is the [(piperidinylmethyl)phenoxy]propyl moiety. This side chain is of particular interest as it occurs in some of the most potent H_2 receptor antagonists known, and the scope for substitution of polar groups to provide compounds with high in vitro antagonist activity appears to be wider than for any other type of aminomethylaryl derivative and includes groups possessing only a single acidic NH function. One such compound is the N-substituted acetamide **30**. This compound is one of a series of amide analogues reported to be highly effective inhibitors of gastric acid secretion[61] and combines an unusually low $\Delta \log P$ value of 1.93 with a high $-\log K_B$ value of 7.79 in the atrium. The benzamide analogue **31**, which has a comparable in vitro activity, benefits from the greater steric effect of the benzene ring compared to methyl, in terms of reduced hydrogen-bonding ability, as is evident from a small drop in $\Delta \log P$.

By far the largest contribution to the overall hydrogen-bonding ability of these two derivatives is due to the amide moiety itself, which can act as both a strong hydrogen-bond donor and acceptor. The fragmental $\Delta \log P$ value (I_H) for the NHCO moiety is quoted to be 2.56,[43] but it is possible that this might be reduced somewhat by intramolecular H-bond formation between the NH and the side chain ether oxygen via a 6-membered ring (II).



II

A minimum structural requirement for activity in antagonists of this type appears to be a hydrogen-bond-donor function, and as a way of retaining this feature while minimizing overall hydrogen-bonding ability, novel groups were selected from those described by Seiler[43] having I_H values lower than that of an amide. Three groups that satisfy these criteria are the sulfonamide, aliphatic hydroxyl, and aromatic amino groups, whose I_H values are 1.93, 1.82, and 0.61, respectively. [(Piperidinylmethyl)-phenoxy]propyl derivatives of examples of each of these are shown in Table V.

The benzenesulfonamide derivative **32**, which is structurally most analogous to the benzamide (**31**), is virtually inactive in the atrium, as is the methanesulfonamide **33**. Compound **34**, which incorporates the simple hydroxyl group as a hydrogen-bond donor, is a moderately effective H_2 receptor antagonist, and its small log (C_{brain}/C_{blood}) value is in accord with its low $\Delta \log P$ value. Even more remarkable levels of brain penetration were found amongst the amino aromatic derivatives **36**, **37**, and **41**–**44**. Although the substituted aniline **35** is a relatively weak antagonist in the atrium, the amino heterocyclic analogues exhibit a range of activities from a $-\log K_B$ of 6.09 for the 2-aminopyridine **36** to 7.72 for the 2-aminoquinazoline **44**.

Comparison of the various [(piperidinylmethyl)phenoxy]propylamine derivatives shown in Table V reveals large differences in antagonist activity, which appear to be related to the electron-withdrawing power of the attached groups. Thus, substitution of the strongly electron withdrawing benzenesulfonyl group ($\sigma_p = 0.70$) and the weakly electron withdrawing trifluoroethyl substituent ($\sigma_p = 0.09$) at the primary amino nitrogen of **38** result in two of the least effective antagonists of this type prepared (**32** and **40**, respectively), whereas those containing groups of

(56) Yellin, T. O.; Gilman, D. J.; Jones, D. F.; Wardleworth, J. M. GB Patent 2001624, 1979.
(57) Hoffman, J. M.; Pietruszkiewicz, A. M.; Habecker, C. N.; Phillips, B. T.; Bolhofer, W. A.; Cragoe, E. J.; Torchiana, M. L.; Lumma, W. C.; Baldwin, J. J. *J. Med. Chem.* **1983**, *26*(2), 140.
(58) Lumley-Jones, R. *Spectrochim. Acta* **1964**, 1879.
(59) Shibata, T.; Itaya, T.; Yamakoshi, N.; Kurata, S.; Koizumi, N.; Tarutani, M.; Sakuma, H.; Konishi, K. EP 24510, 1981.
(60) Brittain, R. T.; Daly, M. J.; Humphray, J. M.; Stables, R. *Br. J. Pharmacol.* **1982**, *76*, 195P.
(61) Shibata, T. 104th Annual Meeting, Japan Pharmacy Association, Sendai, March 1984.

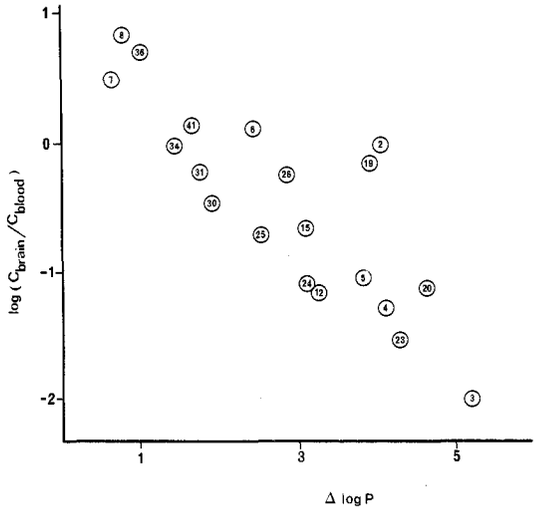


Figure 2. Relationship between brain penetration and Δ log P for 20 structurally diverse compounds.

intermediate electron-withdrawing power such as benzoyl (in **31**) and 2-benzothiazolyl (in **41**) (i.e., σ_p = 0.3 to 0.5) are the most effective. This suggests that an optimum exists for the electron density on the secondary amino group for effective interaction with the H_2 receptor, possibly through hydrogen bonding with an acceptor group (compare Young et al.[52]).

Brain penetration was measured for four of the amino heterocyclic derivatives in Table V and found to be high, comparing well with compounds such as clonidine (**6**), mepyramine (**7**), and imipramine (**8**) known for their central actions. Moreover, three of these compounds exhibit combinations of brain penetration and H_2 antagonist activity that make them suitable candidates for studying histaminergic mechanisms in the brain. Compound **41** (zolantidine, SK&F 95282) has been selected for further pharmacological investigations, the details of which are described elsewhere.[62]

Throughout this study, the Δ log P parameter, and a consideration of hydrogen-bonding ability, has been an important determinant of our synthetic strategy. A retrospective comparison of Δ log P and log (C_{brain}/C_{blood}) for 20 compounds for which the appropriate data has been derived (Table VI) reveals a highly significant correlation (eq 8) which accounts for 69% of the variance in the brain-penetration data. This relationship is shown graphically in Figure 2.

$$\log (C_{brain}/C_{blood}) = -0.485\ (\pm 0.160)\Delta \log P + 0.889\ (\pm 0.500) \quad (8)$$

$$n = 20,\ r = 0.831,\ s = 0.439,\ F = 40.23$$

$$\log (C_{brain}/C_{blood}) = 0.250\ (\pm 0.115) \log P_{cyh} - 0.471\ (\pm 0.253) \quad (9)$$

$$n = 20,\ r = 0.732,\ s = 0.538,\ F = 20.74$$

$$\log (C_{brain}/C_{blood}) = 0.266\ (\pm 0.272) \log P_{oct} - 1.22\ (\pm 0.83) \quad (10)$$

$$n = 20,\ r = 0.436,\ s = 0.711,\ F = 4.23$$

For the same 20 compounds, a rather less significant correlation was found with the log P_{cyh} parameter (eq 9), while that with log P_{oct} (eq 10) was not significant, in general agreement with eq 4, 6, and 7 found at the beginning of this study.

A literal interpretation of eq 8 might be that peripheral tissue has a greater potential for participating in hydrogen-bonding interactions with a drug molecule than does brain tissue. However, an alternative and perhaps more plausible interpretation is that log P_{oct} and log P_{cyh}, which both contribute to Δ log P, represent two different processes involved in the distribution of a drug molecule between peripheral blood and the brain. The log P_{cyh} parameter might largely reflect the partitioning process into nonpolar regions of the brain, while log P_{oct} might account for protein binding in peripheral blood,[63] which could limit the amount of free drug available for passage into the brain. In view of the structural variation encompassed by this relationship, it is believed that Δ log P might have more general utility and prove useful for the design of other potential drugs where brain penetration may need to be either improved or minimized.

Experimental Section

Clonidine hydrochloride and mepyramine maleate were commercial samples and were obtained from Boehringer Ingelheim Ltd. and May & Baker Ltd., respectively. [*phenyl*-4-^{3}H]Clonidine and [10,11-$^3H_2$]imipramine were both obtained from Amersham International plc, and [*methyl*-^{3}H]tiotidine was supplied by NEN Chemicals GmbH.

Synthesis. NMR spectra were recorded on a JEOL PFT 100P or a PMX 60 spectrometer, using Me_4Si for reference. Microanalytical data are within 0.4% of theoretical values and melting points are uncorrected. Radiochemical purities were determined with Analtech 250-μm silica gel plates with scanning on a Berthold LB2832 linear analyzer. Relevant data for all compounds used in the brain-penetration studies are given in Table VII.

α-Bromo-3-(dimethylamino)acetophenone. 3-(Dimethylamino)acetophenone (5.50 g, 0.034 mol), prepared by N-dimethylation of 3-aminoacetophenone with trimethyl phosphate,[64] was brominated by dissolving in 40% aqueous HBr (11 mL) and treating with a solution of bromine (5.40 g, 0.034 mol) in 40% aqueous HBr (8 mL) at 65 °C over 15 min. After being stirred at this temperature for 1 h, the mixture was cooled and neutralized with $NaHCO_3$ (22.0 g, 0.26 mol), extracted with $CHCl_3$, and chromatographed (SiO_2, $CHCl_3$) to give α-bromo-3-(dimethylamino)acetophenone (2.70 g, 33%) as an oil: NMR ($CDCl_3$) δ 7.38 (m, 1 H, Ph), 7.05 (m, 1 H, Ph), 6.71 (s, 1 H, Ph), 6.68 (m, 1 H, Ph), 4.53 (s, 2 H, CH_2), 2.95 (s, 6 H, 2 CH_3).

2-Guanidino-4-[3-(dimethylamino)phenyl]thiazole Hydrobromide (21). Method A. *N*-Amidinothiourea (**45**)[65] 1.39 g, 0.012 mol) and α-bromo-3-(dimethylamino)acetophenone (2.70 g, 0.011 mol) were mixed in MeOH (50 mL) and heated under reflux for 8 h. The resulting mixture was chromatographed (SiO_2, $CHCl_3$/EtOH) to give a thick, semisolid product, which was crystallized from EtOH to give **21** (0.670 g, 22%), mp >250 °C. Anal. ($C_{12}H_{15}N_5S$·HBr) C, H, N, Br.

2-(Methylsulfinyl)-3-nitro-4-benzylpyrrole (48b). A mixture of 1-amino-3-phenylpropan-2-one hydrochloride (5.30 g, 0.029 mol), prepared from phenylacetyl chloride and ethyl acetoacetate by the method of Anderson et al.,[66] and 1-(methylsulfinyl)-1-(methylthio)-2-nitroethene[22] (**46a**, 5.17 g, 0.029 mol) was treated dropwise with a solution of NaOMe (from Na, 1.31 g, 0.058 g-atom) in dry MeOH (25 mL) at 60 °C with stirring over 45 min. After being heated under reflux for a further 30 min, the mixture was cooled and poured into H_2O (1.2 L) and stirred. The resulting solid was filtered and dried to give 2-(methylthio)-3-nitro-4-benzylpyrrole (**47b**; 3.69 g, 52%), mp 175–180 °C. A sample was recrystallized from EtOAc/petroleum ether (60–80 °C): mp 190–192.5 °C; NMR (DMSO-d_6) δ 7.14 (m, 5 H, Ph), 6.55 (s, 1 H, pyrrole), 3.99 (s, 2 H, CH_2), 2.53 (s, 3 H, CH_3 + DMSO).

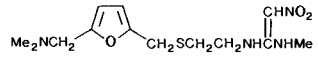
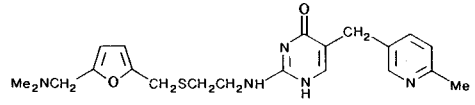
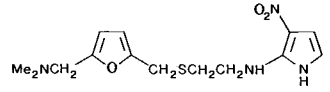
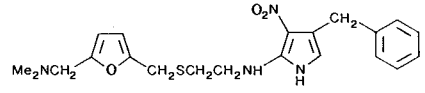
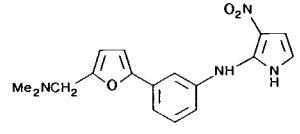
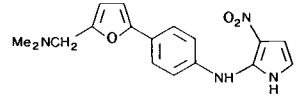
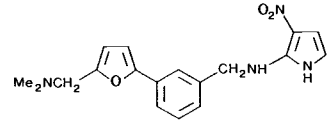
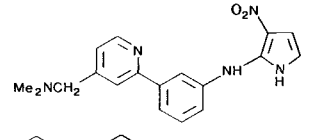
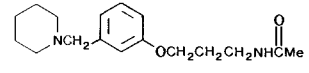
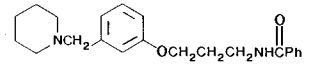
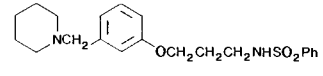
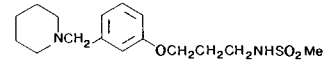
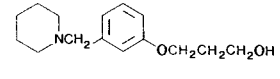
(62) Calcutt, C. R.; Ganellin, C. R.; Griffiths, R.; Leigh, B. K.; Maguire, J. P.; Mitchell, R. C.; Mylek, M. E.; Parsons, M. E.; Smith, I. R.; Young, R. C. *Br. J. Pharmacol.* **1986**, *89*, 773P.

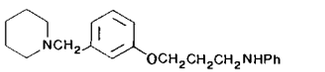
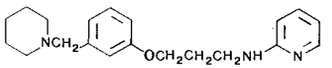
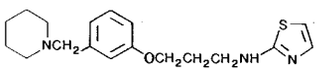
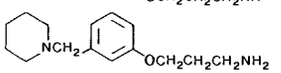
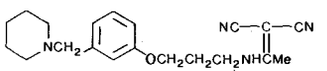
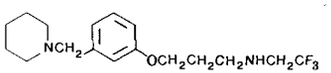
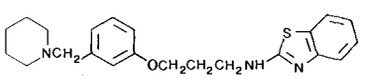
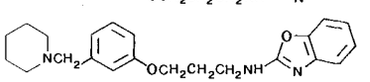
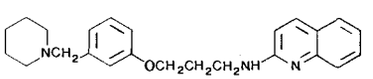
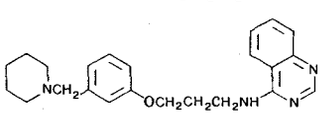
(63) Vandenbelt, J. M.; Hansch, C.; Church, C. *J. Med. Chem.* **1972**, *15*(8), 787.

(64) Grammaticakis, P. *Bull. Soc. Chim. Fr.* **1953**, 93.

(65) Kurzer, F. *J. Chem. Soc.* **1955**, 1.

Table V. H_2 Receptor Antagonist Activities and Physicochemical Data for Ranitidine Analogues

compd	structure	formula[a]	mp, °C	solvent	yield,[b] %	method[c]	−log K_B (95% limits)[d]	log P_n(oct)	log P_n(cyh)	Δ log P	log (C_{brain}/C_{blood})
9		$C_{13}H_{22}N_4O_3S$	70–73	*i*-PrOAc		*e*	7.05 (6.79–7.52)[f]	0.27[g]	<−3[h]		−1.23
5		$C_{21}H_{27}N_5O_2S$·3HCl	224–227	EtOH/HCl/H_2O		*i*	7.91 (7.08–8.51)[j]	2.33[k]	−1.48[k]	3.81	−1.06
24		$C_{14}H_{20}N_4O_3S$	67–69	*l*	24	B[m]	6.63 (6.46–6.89)	1.64[n]	−1.48[o]	3.12	−1.12
25		$C_{21}H_{26}N_4O_3S$[p]	105–106	EtOH/Et_2O	20	B[m]	7.35 (7.08–7.76)	3.65[q]	1.11[r]	2.54	−0.73
26		$C_{17}H_{18}N_4O_3$	152–153	MeCN	37[s]	C	6.02 (5.59–6.46)	3.10[t]	0.22[u]	2.88	−0.27
27		$C_{17}H_{18}N_4O_3$	>170 dec	EtOH/Et_2O	4[v]	C	<4.3				
28		$C_{18}H_{20}N_4O_3$	184–185	MeCN	7	B	<3.8				
29		$C_{16}H_{19}N_5O_2$·H_2O	101–103	*l*	11[w]	B	6.60 (6.15–7.80)[x]				−0.28
30		$C_{17}H_{26}N_2O_2$·HCl[y]	144–145	EtOH/Et_2O		*z*	7.79 (7.33–8.70)	2.15[aa]	0.22[bb]	1.93	−0.46
31		$C_{22}H_{28}N_2O_2$	123–125	*i*-PrOH	75	D	7.79 (7.27–8.45)[cc]	3.97[dd]	2.18[ee]	1.79	−0.24
32		$C_{21}H_{28}N_2O_3S$·0.9$C_2H_2O_4$	180–182	EtOH/H_2O	39	D	<4.8				
33		$C_{16}H_{26}N_2O_3S$·1.5$C_2H_2O_4$	158–160	H_2O	60	D	4.67 (4.23–9.18)				
34		$C_{15}H_{23}NO_2$·$C_4H_4O_4$	108–109	EtOAc		*ff*	6.72 (6.32–7.08)	2.78[gg]	1.31[gg]	1.47	−0.02

35		$C_{21}H_{28}N_2O \cdot 2HCl$	193.5–195.5	MeOH/Me_2CO	54	F	5.70[hh]			
36		$C_{20}H_{27}N_3O \cdot 2C_4H_4O_4$[y]	118–119	*i*-PrOH/EtOAc	25	D	6.09 (5.68–6.43)	4.29[ii]	3.23[jj]	1.06	0.69
37		$C_{18}H_{25}N_3OS \cdot 2HCl$	194–197	*i*-PrOH/EtOAc	7	D	7.41 (6.79–8.76)				0.44
38		$C_{15}H_{25}N_2O \cdot 2HCl$	213–214	EtOH/Et_2O		*kk*	5.19 (4.44–9.95)				
39		$C_{20}H_{26}N_4O \cdot C_2H_2O_4$	166–167	MeOH	48	D	<4.8				
40		$C_{17}H_{25}F_3N_2O \cdot 2C_2H_2O_4$	201–202	MeOH/EtOAc	65	E	<4.3				
41		$C_{22}H_{27}N_3OS \cdot 2.2C_4H_4O_4$	d>113	*i*-PrOH/EtOAc	80	D	7.46 (7.33–7.62)	5.41[ll]	3.72[mm]	1.69	0.14
42		$C_{22}H_{27}N_3O_2$	87–89	MeCN	64	D	7.19 (6.85–7.67)				0.22
43		$C_{24}H_{29}N_3O \cdot 2C_4H_4O_4$	148–150	EtOH	26	D	6.21 (5.31–6.74)				
44		$C_{23}H_{28}N_4O$	111	EtOAc	16	D	7.72 (7.01–8.93)				

[a] All compounds were analyzed for C, H, N (and S when present) and are within 0.4% of theoretical values unless stated. [b] No attempts were made to optimize yields. [c] See Chemistry section. [d] See footnote *a*, Table II. [e] Price et al.[30] [f] Slope 0.7 ± 0.2. [g] Measured at pH 10.5. [h] Measured at pH 8.31. [i] Brown and Ife.[34] [j] Slope 0.71 ± 0.22. [k] See Table I. [l] Crystallized under Et_2O. [m] Using amine prepared by method of Price et al.[30] [n] Estimated value: log P = log P (**9**) − log P (1,1-bis(methylamino)-2-nitroethene) + log P (2-(methylamino)-3-nitropyrrole) = 0.27 − (−1.28) (measured at pH 9.0) + 0.09 (measured at pH 7.3) = 1.64. [o] Calculated from eq 1 using log P_a = −1.7 at pH 8.37; pK_a = 8.18 (see footnote *i*, Table I). [p] % C calcd = 60.85; found = 60.38. [q] Estimated value: log P = log P (**24**) + π ($PhCH_2$) = 1.64 + 2.01[37] = 3.65. [r] Calculated from eq 1 using log P_a = 0.89 at pH 8.37; pK_a = 8.18 (see footnote *i*, Table I). [s] Overall yield from **54a**. [t] Calculated from eq 1 using log P_a = 2.88 at pH 8.37; pK_a = 8.18 (see footnote *i*, Table I). [u] Calculated from eq 1 using log P_a = 0.00 at pH 8.36; pK_a = 8.18 (see footnote *i*, Table I). [v] Overall yield from **54b**. [w] Yield based on amine used. [x] Slope 0.61 ± 0.29. [y] Contains 1% w/w H_2O. [z] Shibata et al.[59] [aa] Measured at pH 11.28. [bb] Measured at pH 11.30. [cc] Slope 0.70 ± 0.16. [dd] Calculated from eq 1 using log P_a = 2.45 at pH 7.49; pK_a = 9.0.[nn] [ee] Calculated from eq 1 using log P_a = 0.65 at pH 7.48; pK_a = 9.0.[nn] [ff] Fujisawa Pharmaceutical Co. Ltd.[24] [gg] Measured at pH 11.01. [hh] Wide confidence limits. [ii] Calculated from eq 1 using log P_a = 2.49 at pH 7.21; pK_a = 9.0.[nn] [jj] Calculated from eq 1 using log P_a = 1.44 at pH 7.22; pK_a = 9.0.[nn] [kk] Clitherow et al.[23] [ll] Calculated from eq 1 using log P_a = 1.46 at pH 5.05; pK_a = 9.0.[nn] [mm] Calculated from eq 1 using log P_a = −0.28 at pH 5.00; pK_a = 9.0.[nn] [nn] pK_a of 1-(piperidin-1-yl-methyl)-3-methoxybenzene corrected for temperature (pK_a at 25 °C = 9.34).

Table VI. Physicochemical Properties and Brain Penetration Data for 20 Compounds Used in Regression Analysis[a]

compd	log P_n oct	log P_n cyh	Δ log P	log C_{brain}/C_{blood} obsd	log C_{brain}/C_{blood} pred (eq 8)
2	1.24	−2.79	4.03	−0.04	−1.07
3	2.58	−2.60	5.18	−2.00	−1.62
4	4.57	0.47	4.10	−1.30	−1.10
5	2.33	−1.48	3.81	−1.06	−0.96
6	1.59	−0.85	2.44	0.11	−0.29
7	3.30	2.59	0.71	0.49	0.54
8	4.42	3.57	0.85	0.83	0.48
12	1.19[b]	−2.05[c]	3.24	−1.17	−0.68
15	1.75	−1.34	3.09	−0.67	−0.61
19	2.64	−1.28	3.92	−0.18	−1.01
20	1.41	−3.19	4.60	−1.15	−1.34
23	1.60	−2.66	4.26	−1.54	−1.18
24	1.64	−1.48	3.12	−1.12	−0.62
25	3.65	1.11	2.54	−0.73	−0.34
26	3.10	0.22	2.88	−0.27	−0.51
30	2.15	0.22	1.93	−0.46	−0.05
31	3.97	2.18	1.79	−0.24	−0.02
34	2.78	1.31	1.47	−0.02	0.18
36	4.29	3.23	1.06	0.69	0.37
41	5.41	3.72	1.69	0.14	0.07

[a] Data collected from Tables I–V. [b] Calculated from eq 1 using log P_a = 1.15 at pH 8.65; pK_a = 9.6.[50] [c] Calculated from eq 1 using log $P_a \simeq$ −2.1 at pH 8.67; pK_a = 9.6.[50]

Compound **47b** (3.69 g, 0.015 mol) was partially dissolved in glacial AcOH (100 mL) and H_2O_2 (30% w/w, 1.69 g, 0.015 mol) was added. The mixture was stirred at 60 °C for 4 h to give a red solution. Unreacted H_2O_2 was destroyed by stirring the cooled solution with MnO_2, and the solution was poured into H_2O (1 L). The resulting solid was filtered off, dried, and recrystallized from EtOAc to furnish **48b** (2.89 g, 73%): mp 198–200 °C; NMR (DMSO-d_6) δ 7.25 (m, 5 H, Ph), 6.82 (s, 1 H, pyrrole), 4.05 (s, 2 H, CH_2), 2.95 (s, 3 H, CH_3).

3-[2-[(Dimethylamino)methyl]furan-5-yl]aniline (54a). To a suspension of 3-nitroaniline (**51a**; 203 g, 1.5 mol) in 10% aqueous HCl (1.2 L) at 0 °C was added a solution of $NaNO_2$ (106 g, 1.5 mol) in H_2O (350 mL) while the mixture was stirred at 0 °C for 1.5 h. After 30 min the yellow solid was filtered off and the filtrate, collected in a cooled flask, was added slowly to a stirred mixture of $CuCl_2{\cdot}2H_2O$ (37.0 g, 0.21 mol) and furan (500 g, 7.3 mol) in H_2O (75 mL) over 1.5 h, while the temperature was allowed to rise steadily. The mixture was left overnight at 0 °C, extracted with $CHCl_3$ (1 L), and then chromatographed (SiO_2, C_6H_{12}/Et_2O) to yield **52a** (29.2 g, 11%), which crystallized on standing to give a solid: mp 43–45 °C; NMR ($CDCl_3$) δ 8.48 (m, 1 H, Ph), 7.89–8.12 (series of m, 2 H, Ph), 7.50 (d + t, 2 H, Ph + furan), 6.79 (d of d, 1 H, furan), 6.52 (d of d, 1 H, furan). To a solution of **52a** (16.0 g, 0.085 mol) in glacial AcOH (325 mL) cooled to below 10 °C was added portionwise, bis(dimethylamino)methane (25.9 g, 0.25 mol), while the temperature was maintained at about 12 °C. The solution was then allowed to rise to room temperature and left to stand overnight. The orange solution was poured onto crushed ice (2 L) and stirred while K_2CO_3 (400 g) was added in portions, followed by extraction with $CHCl_3$ (10 × 100 mL). Extracts were combined and back-extracted into 2% aqueous HCl (7 × 250 mL). Reneutralization to pH 10.5 with K_2CO_3, followed by extraction with $CHCl_3$, drying ($MgSO_4$), and concentration gave **53a** (18.7 g, 90%) as a yellow oil: NMR ($CDCl_3$) δ 8.49 (m, 1 H, Ph), 7.91–8.13 (m, 2 H, Ph), 7.52 (m, 1 H, Ph), 6.77 (d, 1 H, furan), 6.37 (d, 1 H, furan), 3.57 (s, 2 H, CH_2), 2.34 (s, 6 H, 2 CH_3).

A solution of **53a** (43.9 g, 0.18 mol) in EtOH (500 mL) was reduced in a Parr hydrogenator using Pd/C catalyst (10% w/w, 4.40 g) for 40 min. Filtration of the resulting mixture and concentration gave **54a** (38.3 g, 99%), which crystallized under C_5H_{12}: mp 55–57 °C; NMR ($CDCl_3$) δ 6.9–7.2 (m, 3 H, Ph), ca. 6.50 (m, 1 H, Ph), 6.50 (d, 1 H, furan), 6.23 (d, 1 H, furan), 3.66 (br s, 2 H, NH_2), 3.52 (s, 2 H, CH_2), 2.30 (s, 6 H, 2 CH_3).

4-[2-[(Dimethylamino)methyl]furan-5-yl]aniline (54b). Reaction of 4-nitroaniline (**51b**; 100 g, 0.72 mol) by the method described for **52a** using $NaNO_2$ (52.0 g, 0.75 mol), furan (183 g,

Table VII. Radiochemical and Brain-Pentration Data[a]

compd	isotope	sp act., μCi/mg	% radiochemical purity system 1	% radiochemical purity system 2	C_{brain}/C_{blood} (±SD)	n	% parent compound blood	% parent compound brain	% parent compound TLC system
1	^{14}C	23.1	97.2 A		0.0381 ± 0.0140	11	>90		A
2	^{14}C	10.9	97.4 B		0.873, 0.935	2	60		C
3	^{14}C	23.8	98.5 A	98.1 D	0.0100 ± 0.0026	3			
4	^{14}C	40.5	96.4 A	97.0 D	0.0500 ± 0.0191	6	70		A
5	^{3}H	84.3	98.6 A		0.0884 ± 0.0322	9			
6	^{3}H	90,000	90.0 A		1.30 ± 0.16	4	>90	>90	A
7	^{3}H	73.5	97.8 E		3.09 ± 1.22	8	>90		A
8	^{3}H	151	98.0 A		3.45, 10.2	2		>90	A
9	^{14}C	45.4	96.5 A	97.1 D	0.0586 ± 0.0260	9	>90	>90	A
10	^{3}H	266	99.0 B		0.110, 0.195	2			
12	^{3}H	203	98.7 A		0.0680 ± 0.0087	5	>90	>90	F
13	^{14}C	8.5	97.0 A		0.00753	1			
15	^{14}C	48.5	89.9 F		0.214	1			
16	^{3}H	100	96.9 A		0.180, 0.256	2	50		A
17	^{3}H	96.8	90.5 G		0.724, 0.780	2			
19	^{14}C	15.5	97.3 B		0.510, 0.811	2	>80		B
20	^{14}C	45.5	96.4 A	97.5 D	0.0705 ± 0.0461	4	75		H
22	^{14}C	18.8	99.6 A	99.2 D	0.0180, 0.0365	2			
23	^{14}C	40.7	97.0 A	97.4 D	0.0293 ± 0.0100	3	>90		B
24	^{14}C	42.7	95.6 A	99.0 I	0.0652, 0.0866	2	>90		H
25	^{14}C	41.7	90.4 I		0.184, 0.191	2	>90		B
26	^{3}H	409	94.1 D	95.3 J	0.545 ± 0.058	4	>90		H
29	^{3}H	94.2	96.4 D	96.0 K	0.454, 0.607	2			
30	^{3}H	3000	94.3 L		0.346 ± 0.134	5	50	>90	C
31	^{3}H	150	96.3 H		0.580 ± 0.282	3	>90		H
34	^{14}C	73.9	98.2 G	97.8 M	0.947 ± 0.414	7	>90	>90	N
36	^{14}C	126	98.5 G	98.1 O	4.85 ± 0.71	6	>90	>90	H
37	^{14}C	121	98.2 G	98.6 O	1.98, 3.54	2			
41	^{14}C	104	98.0 G	97.4 O	1.38 ± 0.44	8	>90	>90	P
42	^{14}C	53.6	97.7 G	98.0 Q	1.42, 1.88	2			

[a] A, EtOAc/MeOH/NH_4OH (5:1:1); B, EtOAc/MeOH/NH_4OH (5:2:1); C, EtOAc/MeOH/NH_4OH (10:1:1); D, n-PrOH/NH_4OH (7:3); E, MeOH/HOAc (9:1); F, CH_2Cl_2/MeOH/NH_4OH (10:1:1); G, CH_2Cl_2/MeOH/NH_4OH (90:10:1); H, $CHCl_3$/MeOH/NH_4OH (7:7:2); I, MeOH; J, $CHCl_3$/MeOH (9:1); K, CH_2Cl_2/MeOH (9:1); L, MeOH/aq HCl (9:1); M, CH_2Cl_2/MeOH/NH_4OH (20:2:1); N, MeOH/NH_4OH (6:1); O, $C_6H_{12}/CH_2Cl_2/Et_2NH$ (5:4:1); P, EtOAc/MeOH/NH_4OH (10:3:1); Q, $CHCl_3$/MeOH (4:1).

2.7 mol) and $CuCl_2 \cdot 2H_2O$ (18.0 g, 0.11 mol) gave **52b** (29.1 g, 22%), which crystallized to give a yellow solid: mp 130–132 °C; NMR ($CDCl_3$) δ 8.25 (d, 2 H, Ph), 7.80 (d, 2 H, Ph), 7.58 (s, 1 H, furan), 6.89 (d, 1 H, furan), 6.56 (m, 1 H, furan).

Subsequent reaction of **52b** (30.8 g, 0.16 mol) with bis(dimethylamino)methane (49.3 g, 0.48 mol) in glacial AcOH (1 L) gave **53b** (10.0 g, 25%), and reduction with H_2 using Pd/C furnished **54b** (8.70 g, 100%).

3-[2-[(Dimethylamino)methyl]furan-5-yl]benzylamine (54c). Reaction of 3-cyanoaniline (**51c**; 50.0 g, 0.42 mol) by the method described for **52a** using $NaNO_2$ (30.4 g, 0.44 mol), furan (107 g, 1.6 mol), and $CuCl_2 \cdot 2H_2O$ (10.6 g, 0.062 mol) gave **52c** as a yellow oil (7.81 g, 11%): NMR ($CDCl_3$) δ 7.90 (d, 1 H, furan), 7.4–7.7 (m, 4 H, Ph), 6.74 (d, 1 H, furan), 6.52 (m, 1 H, furan). Reaction of **52c** (14.8 g, 0.087 mol) with bis(dimethylamino)-methane (35.3 g, 0.35 mol) in glacial AcOH (285 mL) gave **53c** as a yellow oil (16.8 g, 85%): NMR ($CDCl_3$) δ 7.94 (s, 1 H, Ph), 7.86 (d, 1 H, Ph), 7.48 (m, 2 H, Ph), 6.69 (d, 1 H, furan), 6.32 (d, 1 H, furan), 3.53 (s, 2 H, CH_2), 2.31 (s, 6 H, 2 CH_3). Reduction of **53c** (7.50 g, 0.033 mol) was performed by heating with Bu_4NBH_4 (25.0 g, 0.097 mol) in CH_2Cl_2 under reflux overnight. After evaporation of solvent, the residue was heated under reflux with 10% aqueous HCl for 1 h, neutralized with K_2CO_3, and extracted with $CHCl_3$. Removal of solvent gave a thick oil, which was washed with H_2O, acidified with dilute HCl, washed with $CHCl_3$, and rebasified with K_2CO_3. Back-extraction into $CHCl_3$ and removal of solvent furnished **54c** as an oil (4.00 g, 52%): NMR ($CDCl_3$) δ 7.2, 7.7 (br m, 6 H, NH_2 + Ph), 6.61 (d, 1 H, furan), 6.30 (d, 1 H, furan), 3.90 (s, 2 H, CH_2Ph), 3.55 (s, 2 H, CH_2 furan), 2.30 (s, 6 H, 2 CH_3).

3-[4-[(Dimethylamino)methyl]pyrid-2-yl]aniline (58). 3-Nitroaniline (**51a**; 70.0 g, 0.51 mol) was stirred in 6% aqueous HCl (600 mL) at 0 °C and treated with a solution of $NaNO_2$ (50.0 g, 0.72 mol) in H_2O (110 mL) over 1.5 h and then stirred at 5 °C for a further 2 h. The yellow precipitate that formed was filtered off, and the filtrate was collected in a cooled flask. The resulting yellow solution was syphoned slowly into 4-picoline (480 g, 5.1 mol) stirred at room temperature, and cooling was applied to keep the temperature to below 40 °C. The mixture was heated for 1 h at 100 °C and allowed to cool overnight to produce a thick black layer under a brown aqueous phase. Aqueous NH_3 was added to bring the pH to 11 and the mixture was stirred for a further hour and allowed to settle. Removal of H_2O at 90 °C in vacuo gave a black residue, which was chromatographed (SiO_2, $CHCl_3$) and recrystallized from EtOH to give **55** (11.8 g, 11%): mp 80–83 °C; NMR ($CDCl_3$) δ 8.78 (t, 1 H, Ph), 8.1–8.6 (m, 2 H, Ph + 1 H, pyridine), 7.60 (t, 1 H, Ph), 7.58 (s, 1 H, pyridine), 7.1 (m, 1 H, pyridine), 2.5 (s, 3 H, CH_3).

A mixture of **55** (9.97 g, 0.039 mol), *N*-bromosuccinimide (6.90 g, 0.039 mol), azobisisobutyronitrile (0.500 g) and benzoyl peroxide (0.5 g) in CCl_4 was heated under reflux for 3.5 h. Further benzoyl peroxide (1.20 g) was added and the mixture refluxed for an additional 4.5 h. The solution was cooled and filtered to give crude **56** (3.63 g, 32%).

A solution of Me_2NH in EtOH (33%, 11.1 mL, 0.062 mol) was added to a solution of **56** (3.63 g, 0.12 mol) in CCl_4 (800 mL) at room temperature, and the mixture was stirred for 2 h and then left to stand overnight. The turbid solution was chromatographed (SiO_2, $CHCl_3$, $CHCl_3$/MeOH/NH_4OH (180:10:1) to give an impure product **57** (4.00 g): NMR ($CDCl_3$) δ 8.78 (m, 1 H, Ph), 8.55 (d, 1 H, pyridine), 8.22 (m, 2 H, Ph), 7.70 (m, 1 H, pyridine), 7.52 (t, 1 H, Ph), 7.20 (obscured, 1 H, pyridine), 3.50 (s, 2 H, CH_2), 2.24 (s, 6 H, 2 CH_3).

The above product (**57**) (3.50 g) was dissolved in concentrated HCl (25 mL) and a solution of $SnCl_2 \cdot 2H_2O$ (15.4 g, 0.068 mol) in concentrated HCl (50 mL) addded. The mixture was heated at 100 °C for 45 min, cooled, and concentrated in vacuo. The residue was next dissolved in H_2O (75 mL) and brought to pH 10 with aqueous K_2CO_3, and $CHCl_3$ (200 mL) was added. After filtration through Hyflo, the $CHCl_3$ layer was separated, dried ($MgSO_4$), and concentrated to furnish **58** as an oil (2.52 g, 82%): NMR ($CDCl_3$) δ 8.50 (d, 1 H, pyridine), 7.61 (m, 1 H, pyridine), 7.0–7.4 (series of res, 3 H, Ph + 1 H, pyridine), 6.64 (m, 1 H, Ph), 3.56 (br s, 2 H, NH_2), 3.22 (s, 2 H, CH_2), 2.26 (s, 6 H, 2 CH_3).

2-[(Isoquinolin-1-ylmethyl)thio]ethylamine Dihydrobromide (60). Cysteamine hydrochloride (5.40 g, 0.047 mol) was added to a solution of 1-isoquinolinemethanol[67] (7.20 g, 0.047 mol) in 48% aqueous HBr (100 mL) and the mixture was heated under reflux for 18 h. The mixture was then concentrated in vacuo to leave an oil, which was triturated with EtOH to give a white solid. Filtration and washing with Et_2O gave **60** (7.50 g, 44%): mp 198 °C dec; NMR (D_2O) δ ca. 10 (s, 2 H, NH_2), 8.0–8.7 (br m, 6 H, isoquinoline), 4.83 (s, 2 H, CH_2Ar), 3.33 (t, 2 H, CH_2N), 3.00 (t, 2 H, CH_2S).

2-[[2-[(Isoquinolin-1-ylmethyl)thio]ethyl]amino]-3-nitropyrrole (18). Method B. A mixture of **60** free base (0.670 g, 3.8 mmol) and **48a** (0.830 g, 3.8 mmol) in EtOH (20 mL) was heated under reflux for 5 days. Separation of the product by chromatography (SiO_2, CH_2Cl_2/EtOH) and crystallization from *i*-PrOH gave 18 (0.100 g, 11%): mp 133–134 °C. Anal. ($C_{16}H_{16}N_4O_2S$) C, H, N. S.

2-[[2-[[[2-[(Dimethylamino)methyl]furan-5-yl]methyl]thio]ethyl]amino]-3-nitro-4-benzylpyrrole (25). Method B. 2-[[[2-[(Dimethylamino)methyl]furan-5-yl]methyl]thio]ethylamine[68] (1.29 g, 6.1 mmol) and **48b** (0.800 g, 3.0 mmol) were mixed in EtOH (30 mL) and heated under reflux for 7 days. The resulting mixture was chromatographed (SiO_2, EtOH/EtOAc) to give a red oil, which was crystallized from *i*-PrOAc/petroleum ether (60–80 °C) and then EtOH/Et_2O to furnish **25** (0.250 g, 20%): mp 105–106 °C. Anal. ($C_{21}H_{26}N_4O_3S$) C, H, N, S.

2-[[3-[2-[(Dimethylamino)methyl]furan-5-yl]phenyl]amino]-3-nitropyrrole (26). Method C. A mixture of **54a** (30.0 g, 0.14 mol) and 1,1-bis(methylthio)-2-nitroethene[21] (**46b**; 229 g, 1.4 mol) in *n*-PrOH (1.5 L) was heated under reflux for 2 h. After being kept at 4 °C overnight, the mixture was filtered, and the solid was washed with *n*-PrOH. The resulting mother liquor was next chromatographed (SiO_2, $CHCl_3$/MeOH) to give crude **49a** (39.0 g): NMR ($CDCl_3$) δ 7.65 (m, 1 H, Ph), 7.60 (m, 1 H, Ph), 7.41 (t, 1 H, Ph), 7.16 (m, 1 H, Ph), 6.66 (d, 1 H, furan), 6.62 (s, 1 H, CH=C), 6.32 (d, 1 H, furan) 3.55 (s, 2 H, CH_2), 2.39 (s, 3 H, CH_3S), 2.30 (s, 6 H, 2 CH_3N).

The above intermediate (36.7 g, 0.11 mol) was dissolved in EtOH (500 mL) and reacted with aminoacetaldehyde diethyl acetal (29.1 g, 0.22 mol) by heating under reflux for 2 h. Purification by chromatography (SiO_2, $CHCl_3$/MeOH) gave **50a** (38.0 g): NMR (CCl_4) δ 6.9–7.5 (series of m, 4 H, Ph), 6.58 (d, 1 H, furan), 6.26 (s, 1 H, CH=C), 6.18 (d, 1 H, furan), 4.68 (br s, 1 H, OCH), 3.2–3.9 (series of res, 8 H, CH_2N + CH_2NH + 2 CH_2O), 2.20 (s, 6 H, 2 CH_3N), 1.20 (br t, 6 H, 2 CH_3C). A mixture of **50a** (21.2 g, 0.055 mol) and 0.05 N HCl (1 L) was heated to boiling with stirring for 40 min. After cooling, the mixture was basified to pH 7 with aqueous K_2CO_3 and extracted repeatedly with $CHCl_3$ and dried with anhydrous $MgSO_4$. Chromatography (SiO_2, $CHCl_3$/MeOH) yielded a crude product, which was crystallized from EtOH to furnish **26** as an ethanolate (7.90 g, 44%). A sample of this was recrystallized from MeCN to yield pure **26**, mp 152–153 °C. Anal. ($C_{17}H_{18}N_4O_3$) C, H, N.

2-[[4-[2-[(Dimethylamino)methyl]furan-5-yl]phenyl]amino]-3-nitropyrrole (27). Method C. Reaction of **54b** (5.56 g, 0.025 mol) with **46a** (4.25 g, 0.025 mol) by the method described for **26** gave **49b** as an oil (4.22 g, 50%): NMR ($CDCl_3$) δ 7.9 (br s, 1 H, NH), 7.70 (d, of d, 2 H, Ph), 7.28 (d of d, 2 H, Ph), 6.70 (s, 1 H, CH=C), 6.64 (d, 1 H, furan), 6.31 (d, 1 H, furan), 3.57 (s, 2 H, CH_2), 2.39 (s, 3 H, CH_3S), 2.32 (s, 6 H, 2 CH_3N). This intermediate (4.22 g, 0.013 mol) was then reacted with aminoacetaldehyde diethyl acetal (3.34 g, 0.024 mol) to give **50b** (3.10 g, 58%): NMR ($CDCl_3$) δ 9.34 (br s, 1 H, NH), 8.12 (br s, 1 H, NH), 7.68 (d, 2 H, Ph), 7.10 (d, 2 H, Ph), 6.65 (s, 1 H, CH=C), 6.61 (d, 1 H, furan), 6.31 (d, 1 H, furan), 4.63 (q, 2 H, CH_2NH), 3.4–4.0 (br m, 7 H, OCH + CH_2N + 2 CH_2O), 2.32 (s, 6 H, 2 CH_3N), 1.30 (t, 6 H, 2 CH_3C). Compound **50b** was subsequently cyclized and recrystallized from EtOH/Et_2O to furnish **27** (0.340 g, 14%), mp >170 °C dec. Anal. ($C_{17}H_{18}N_4O_3$) C, H, N.

***N*-Phenyl-3-[3-(piperidin-1-ylmethyl)phenoxy]propylamine Dihydrochloride (35). Method F.** The hydrochloride

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of **62**[24] (0.610 g, 2.1 mmol) was dissolved in aniline (3 mL), and the solution stirred at 85 °C for 2 h and then at 105 °C for 2.5 h. The mixture was allowed to cool and then added to 10% aqueous Na_2CO_3 (10 mL). After extraction with Et_2O (3 × 10 mL), the solution was dried over $MgSO_4$ and concentrated, with removal of excess aniline in vacuo. Purification by chromatography (SiO_2, Et_2O) afforded an oil, which was dissolved in dilute HCl/EtOH and concentrated, and the residue was crystallized from MeOH/Me_2CO to give **35** (0.430 g, 54%), mp 193.5–195.5 °C. Anal. ($C_{21}H_{28}N_2O$·2HCl) C, H, N.

1,1-Dicyano-2-[[3-[3-(piperidin-1-ylmethyl)phenoxy]propyl]amino]propene Oxalate (39). Method D. To a solution of 1-(ethoxyethylidene)malonitrile (1.10 g, 8.1 mmol) in EtOH (20 mL) was added **38**[23] (2.00 g, 8.1 mmol) in EtOH (20 mL), and the mixture was stirred at room temperature for 2 days. The mixture was evaporated to dryness and chromatographed (SiO_2, MeOH/$CHCl_3$) to give **39** free base as an oil (2.00 g, 74%). Part of this product (1.50 g, 4.4 mmol) was treated with oxalic acid (0.82 g, 9.1 mmol) in MeOH and on treatment with Et_2O gave a white solid. Recrystallization from MeOH gave **39** (oxalate) (1.10 g), mp 166–167 °C. Anal. ($C_{20}H_{26}N_4O$·$C_2H_2O_4$) C, H, N.

***N*-(2,2,2-Trifluoroethyl)-3-[3-(piperidin-1-ylmethyl)phenoxy]propylamine Dioxalate (40). Method E.** A solution of **38**[23] (2.00 g, 8.1 mmol) in dry THF (50 mL) was cooled in ice and treated with trifluoroacetic anhydride (6.77 g, 0.032 mol) in dry THF (50 mL) with stirring over 5 min. The reaction mixture was cautiously shaken with a mixture of $CHCl_3$ (100 mL) and 1% aqueous K_2CO_3 (100 mL) and the $CHCl_3$ layer quickly separated, dried ($MgSO_4$), and concentrated to give **61** (2.56 g, 96%) as an oil: NMR ($CDCl_3$) δ 7.30 (br, 1 H, NHCO), 7.23 (t, 1 H, Ph), 6.93 (m, 1 H, Ph), 6.91 (m, 1 H, Ph), 6.77 (m, 1 H, Ph), 4.11 (t, 2 H, CH_2O), 3.58 (m, 2 H, CH_2NH), 3.49 (s, 2 H, CH_2Ph), 2.42 (m, 4 H, piperidine), 2.08 (m, 2 H, CCH_2C), 1.58 (m, 4 H, piperidine), 1.45 (m, 2 H, piperidine).

To a suspension of $LiAlH_4$ (0.500 g, 0.013 mol) in dry Et_2O (20 mL) at room temperature was added a solution of **61** (0.400 g, 1.2 mmol) dropwise over 30 min. The mixture was left to stand overnight and then unreacted hydride was destroyed with aqueous Et_2O and the mixture was filtered. Chromatographic purification (SiO_2, $CHCl_3$/MeOH) gave **40** free base (0.260 g, 68%) as an oil. Treatment of this product with oxalic acid (0.152 g, 1.7 mmol) in MeOH (7 mL) furnished **40**, which recrystallized from MeOH/EtOAc with mp 201–202 °C. Anal. ($C_{17}H_{25}F_3N_2O$·$2C_2H_2O_4$) C, H, N.

2-[[3-[3-(Piperidin-1-ylmethyl)phenoxy]propyl]amino]benzothiazole Dimaleate (41). Method D. An intimate mixture of **38** (7.00 g, 0.028 mol) and 2-chlorobenzothiazole (5.26 g, 0.031 mol) was heated at 130 °C for 15 h. After being cooled, the mixture was chromatographed (SiO_2, $CHCl_3$/MeOH) to give **41** (8.50 g, 80%) as the free base. This product was dissolved in *i*-PrOH, treated with maleic acid (5.25 g, 0.045 mol), and crystallized under EtOAc. Recrystallization from *i*-PrOH/EtOAc provided **41**·dimaleate, mp >113 °C dec. Anal. ($C_{22}H_{27}N_3OS$·$2.2C_4H_4O_4$) C, H, N, S.

Dimethyl [*cyano*-^{14}C]Cyanodithioimidocarbonate (63). Barium [^{14}C]cyanamide (352 mg, 2.0 mmol, 111 mCi) was partially dissolved in H_2O (30 mL) and CO_2 gas was bubbled through until a pH of 6 was reached. The mixture was filtered and the filtrate was evaporated to leave a white solid, which was triturated with EtOH and filtered, and the ethanolic solution was evaporated to give [^{14}C]cyanamide (24.0 mg, 0.57 mmol, 32 mCi). To this product was added cyanamide (26.0 mg, 0.62 mmol), and then the mixture was dissolved in EtOH (250 μL), cooled in an ice bath, and treated with CS_2 (85 μL, 1.4 mmol) and KOH (135 mg, 2.4 mmol) in EtOH (1 mL) with stirring for 1 h. The resulting pale yellow crystals of dipotassium [*cyano*-^{14}C]cyanodithioimidocarbonate were filtered and washed with cold *i*-PrOH and then treated with MeI (2.0 mL, 32 mmol) in EtOH (2 mL), with heating under reflux for 3 h. The solution was filtered and the filtrate was evaporated to dryness. The residue was extracted with Et_2O (5 × 3 mL), and the combined extracts were evaporated to dryness to yield **63** (81.0 mg, 0.55 mmol, 15 mCi, 14% overall radiochemical yield).

[*amidino*-^{14}C]Amidinothiourea (^{14}C-45). Barium [^{14}C]-cyanamide (325 mg, 1.8 mmol, 102 mCi) and barium hydroxide octahydrate (1.02 g, 3.3 mmol) was dissolved in H_2O (40 mL), and H_2S was bubbled through for 5 h at room temperature. The resulting mixture was heated under reflux for 16 h and cooled to room temperature, and CO_2 was bubbled through for 5 h. After the mixture was allowed to stand overnight, the precipitated $BaCO_3$ was filtered off and washed with H_2O (10 mL) and EtOH (10 mL), and the filtrate and washings were combined and evaporated to dryness under reduced pressure to leave crude [^{14}C]thiourea (142 mg, 1.9 mmol).

The above product and lead cyanamide (456 mg, 1.9 mmol) were mixed in EtOH (3 mL), and the mixture was heated under reflux for 18 h. When all the [^{14}C]thiourea had reacted (TLC), the mixture was filtered hot and the filtrate allowed to cool to give crystalline [*guanidino*-^{14}C]cyanoguanidine in two crops. The combined product (156 mg, 1.9 mmol) was dissolved in H_2O (3 mL) and heated to 75 °C. A gentle stream of H_2S was passed into the solution for 18 h and the solution was allowed to cool to yield crystalline ^{14}C-**45** (162 mg, 1.4 mmol, 76 mCi, 75% overall radiochemical yield).

2-[^{14}C]Guanidino-4-(3-aminophenyl)thiazole Hydrochloride (^{14}C-20). 3-Phthalimidoacetophenone (1.35 g, 5.1 mmol; prepared from phthalic anhydride and 3-aminoacetophenone by the method of Stodola[69]) was partially dissolved in $CHCl_3$ (13 mL) and a solution of HBr in AcOH (50 μL, 48%). Bromine (203 mg, 1.3 mmol) was added dropwise with stirring at room temperature for 1 h when α-bromo-3-phthalimidoacetophenone precipitated from solution. The mixture was evaporated to dryness and dissolved in CH_3CN (6 mL). Part of this solution (1.5 mL) was added to a solution of ^{14}C-**45** (150 mg, 1.3 mmol, 66 mCi) in EtOH (2.5 mL) and the mixture was heated under reflux for 1.5 h and allowed to cool. The resulting solid, **65** (272 mg, 0.75 mmol), was filtered off. The above product was hydrolyzed by heating in a mixture of glacial AcOH (6.9 mL) and concentrated HCl (6.9 mL) at 100 °C overnight. The mixture was cooled and evaporated to dryness, azeotroping with EtOH, to give a solid, which was combined with authentic, unlabeled **20** (50.0 mg, 0.21 mmol) and recrystallized from CH_3CN to give ^{14}C-**20** in two crops (48 mg, 0.21 mmol, 2.20 mCi, 3.3% radiochemical yield).

2-(Nitroamino)-5-(2-naphthylmethyl)pyrimidin-4-one (68). A mixture of ethyl β-(2-naphthyl)propionate[32] (43.1 g, 0.19 mol) and ethyl formate (21.1 g, 0.28 mol) was added dropwise to a stirred suspension of NaH (10.6 g of a 57% dispersion, 0.25 mol) in 1,2-dimethoxyethane (130 mL) over 1.5 h, while the temperature was maintained at 5 °C. The mixture was stirred for a further 1 h at 5 °C and then allowed to warm to room temperature. The resulting brown solid was dissolved in H_2O (350 mL) and extracted with $CHCl_3$ (3 × 100 mL). The aqueous fraction was acidified with 2 N HCl to pH 4 to precipitate a brown oil, which was extracted into Et_2O (2 × 200 mL). The combined extracts were washed with H_2O, dried, and evaporated to dryness to give ethyl α-formyl-β-(2-naphthyl)propionate (42.2 g, 87%) as an oil.

Nitroguanidine (23.9 g containing 25% H_2O, 0.17 mol) was added to a solution of NaOMe (prepared from Na (5.72 g, 0.25 g-atom) in MeOH (250 mL)) and the mixture was stirred under reflux for 15 min. Ethyl α-formyl-β-(2-naphthyl)propionate (42.2 g, 0.16 mol) was added dropwise over 5 min and the mixture heated under reflux for 22 h when a buff-colored solid precipitated. The MeOH was evaporated and the residue dissolved in H_2O (500 mL) and extracted with $CHCl_3$ (3 × 100 mL). The aqueous solution was acidified with glacial AcOH to pH 4 to precipitate a solid, which was collected, washed with H_2O, and dried in vacuo to furnish **68** (36.5 g, 77%). This was recrystallized from glacial AcOH to give a white solid, mp 202–204 °C. Anal. ($C_{15}H_{12}N_4O_3$) C, H, N.

3-(Piperidin-1-yl[*methyl*-^{14}C]methyl)phenol (70). A solution of $CuSO_4$·$5H_2O$ (1.25 g, 5.0 mmol) in H_2O (4 mL) was stirred at 45 °C and treated with a solution of $Na_2S_2O_5$ (242 mg, 1.3 mmol) in H_2O (0.5 mL), followed by a solution of potassium [^{14}C]cyanide (268 mg, 4.1 mmol, 94 mCi) in aqueous KOH (112 mg, 2.0 mmol in 0.8 mL of H_2O). The mixture was stirred for 1.5 h and filtered and the precipitate washed with H_2O and dried to give cuprous [^{14}C]cyanide (315 mg, 3.6 mmol).

This product was added to 3-iodophenol (800 mg, 3.9 mmol) and *N*-methylpyrrolidone (3.5 mL), and the mixture was stirred at 180 °C for 1.5 h. The cooled reaction mixture was added to

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50% aqueous HCl (20 mL) and extracted with Et_2O. The extracts were combined and washed with 50% aqueous HCl (10 mL) and then H_2O and dried to give 3-[*cyano*-^{14}C]cyanophenol, which was used without further purification. This product was reduced with Ni/Al alloy and added in three equal portions (1.27 g of 50% dispersion) to a solution in 75% aqueous HCO_2H (2.8 mL), with heating under reflux for 6 h. The reaction mixture was then filtered, washed with 75% aqueous HCO_2H, and evaporated to dryness. The residue was extracted with Et_2O, and the extracts were dried over anhydrous $MgSO_4$. Evaporation afforded 3-hydroxy[*carbonyl*-^{14}C]benzaldehyde (310 mg, 2.5 mmol, 59 mCi).

The above product was mixed with piperidine (454 mg, 5.4 mmol) in EtOH (2.5 mL) and stirred for 45 min, followed by reduction using Pd/C catalyst (177 mg, 10% w/w) added in two portions during 5 h. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was purified by preparative TLC (SiO_2, EtOAc/MeOH/NH_4OH, 5:1:1) to give product containing unreacted aldehyde, which was subsequently removed by acid/base extraction to give **70** (203 mg, 1.1 mmol, 25 mCi, 27% overall radiochemical yield).

Tritiation of Unlabeled Materials. Compounds **7**, **12**, **16**, **17**, **26**, and **29–31** were tritiated by using the TR8 procedure by Amersham International plc, which entailed approximately 5 mg of each compound being treated with ^3H_2O of high isotopic abundance, generally under neutral conditions, in a suitable solvent such as CH_3CN or DMF. After tritiation, the compounds were diluted with unlabeled material and subjected to thin-layer chromatographic purification in a suitable system. The compounds were stored in EtOH at −25 °C.

Brain-Penetration Measurements. Brain penetration was estimated by using the method described previously.[70] An intravenous (iv) bolus of radiolabeled antagonist in saline was administered to urethane-anesthetized male rats and an iv infusion maintained for 2–3 h or until radioactivity in the blood reached a plateau. Steady-state blood concentrations in the range 1–10 μM were explored. In some cases (viz. compounds **4–6**, **8**, **30**, **37**, 41, and **42**), concentrations as low as 2.6 nM were also examined and for mepyramine a 1000-fold range of concentrations was investigated (2.4 nM–2.38 μM). In no case was a concentration-dependent difference in the measured brain/blood ratio apparent. The rat was next exsanguinated and the brain removed. Brain tissues were weighed and solubilized in Soluene-100. Aliquots of this were scintillation counted with Dimilume-30 scintillant in the presence of glacial acetic acid to prevent chemiluminescence. Dose solutions and blood samples were counted in Pico-fluor 15 scintillant in a Searle Mk III liquid scintillation counter. Samples were quench corrected by using an automated external standard method. The extent of drug entry into brain was estimated as the ratio of radioactivity in brain to that in peripheral blood at the end of infusion, and the data are given in Table VII.

The proportion of parent antagonist in the peripheral circulation and in the brain, for most of the compounds studied, was determined by thin-layer chromatography (TLC). Plasma (5 or 10 μL) and ethyl acetate brain extract (50 μL) were applied to TLC plates (Merck Kieselgel 60F_{254nm}, 20 cm × 250 μm or Camlab combination layer Kieselgel/silica gel) under an atmosphere of N_2 and allowed to dry. Elution was performed in an appropriate solvent system (see Table VII), and the proportion of radioactivity associated with the parent antagonist was quantified with use of a Berthold linear analyzer. In all cases where significant metabolism occurred, metabolites were more polar than the parent compound, as judged by their chromatographic mobility. It has been assumed that none of the circulating metabolites entered the brain and that the steady state achieved in these experiments represents an equilibrium between parent compound in the blood and the brain. The use of total radioactivity for quantifying brain penetration could therefore result in an underestimate in brain/blood ratios by as much as twofold (for compounds **16** and **30**) due to the presence of radiolabeled metabolites in the blood.

Partition Coefficients and Ionization Constants. Partition coefficients were measured by a conventional shake-flask technique[71] at 37 °C. The concentrations of the compound in the aqueous phase before and after partitioning were determined spectrophotometrically. Buffer salts were used to control the pH of the aqueous phase. The pK_a values of the isocytosine group of **3** were determined spectrophotometrically at 37 °C. The pK_a values of **5**, **6**, and 1-(piperidin-1-ylmethyl)-3-methoxybenzene[72] were determined potentiometrically at 25 °C in 0.1 M KCl. All the partition coefficients and pK_a values are the means of at least two determinations.

Pharmacology. H_2 receptor histamine antagonist activity was determined in vitro in the histamine-stimulated guinea pig right atrium by the method described by Parsons et al.[51] Dose ratios (X) were calculated as the ratio of histamine concentrations required to produce half-maximal responses in the presence and absence of different concentrations (B) of antagonist, and dissociation constants (K_B) were derived from the equation $K_B = B/(X - 1)$.

Acknowledgment. We gratefully acknowledge the contributions of M. J. Graham, C. J. Salter, and L. J. Johnson for physicochemical measurements, E. A. Brown, D. A. Knowler, and V. A. Lewis for brain-penetration measurements, D. W. Hills, P. D. Miles, and D. A. Rawlings for synthetic chemistry, M. M. Cashyap, D. C. Osborne, and J. Winster for radiochemical syntheses, R. C. Blakemore and Dr. M. E. Parsons for pharmacological data, and the Physical Organic Chemistry Department for providing the analytical data.

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Renin Inhibitors Containing ψ[CH_2O] Pseudopeptide Inserts[1]

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Renin inhibitors **2–4** with the D-Lys renin inhibitory peptide (RIP) sequence, but containing Leuψ[CH_2O]Ala (**2**), Leuψ[CH_2O]Val (**3**), and Leuψ[CH_2O]Leu (**4**) at the P_1-P_1' site, were of a comparable potency to RIP. N-Terminal Boc-protected inhibitors containing Proψ[CH_2O]Phe in positions P_4-P_3 were potent inhibitors of renin, with Boc-Phe-Proψ[CH_2O]Phe-His-Leuψ[CH(OH)CH_2]Val-Ile-(2-aminomethyl)pyridine (**17**) having an IC_{50} of 1.6×10^{-9} M.

Renin is a proteolytic enzyme whose only known function is the conversion of angiotensinogen into angiotensin I. Angiotensin I is in turn converted to the potent vasoconstrictor angiotensin II by a converting enzyme.[2] The

0022-2623/88/1831-0671$01.50/0