

vivo activity was not altered. Isosteric modification of the N- or C-terminal peptide bond gave analogues (I and VII) with considerably decreased activities. For the D-Phe CO group, this is again consistent with hydrogen bond disruption. In any case, it seems likely that the lack of the two carbonyls of D-Phe¹ and Cys⁷ might change the orientation of D-Phe¹ and Thr⁸ residues, which may possibly stabilize the active conformation of the molecule as suggested for SMS-201-995 by Bauer et al.² and Wynants et al.²⁷

It can be seen that the reduced peptide bond can be a useful probe for examining structure-activity-conformation relationships in biologically active peptides. The solid-phase method for introducing it into a particular sequence now makes it possible to make this type of analogue with no more effort than normal peptides. In addition, the NH group, while not highly reactive probably due to steric hindrance, can nevertheless be acylated under forcing conditions¹⁰ or perhaps alkylated and thus offers a reactive

center for producing further interesting conformational effects on peptide backbones.

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Registry No. I, 108104-67-2; II, 108104-68-3; III, 108104-69-4; IV, 108104-70-7; V, 108104-71-8; VI, 108104-72-9; VII, 108104-73-0; VIII, 108104-74-1; IX, 108104-75-2; X, 108104-76-3; GH, 9002-72-6; BOC-D-Phe-CHO, 77119-85-8; BOC-Cys(MeBzl)-CHO, 108104-77-4; BOC-Tyr(BrZ)-CHO, 108104-78-5; BOC-D-Trp-CHO, 108104-79-6; BOC-Lys(Z)-CHO, 82689-16-5; BOC-D-Phe-[CH₂NH]Cys(MeBzl)-OH, 108104-80-9; BOC-Cys(MeBzl)-[CH₂NH]Tyr-OH, 108104-81-0; BOC-Tyr[CH₂NH]D-Trp-OH, 108104-82-1; BOC-D-Trp[CH₂NH]Lys(Z)-OH, 108104-83-2; BOC-Lys(Z)[CH₂NH]Val-OH, 108104-84-3; BOC-Val[CH₂NH]-Cys(MeBzl)-OH, 108104-85-4; BOC-Cys(MeBzl)[CH₂NH]Thr-OH, 108104-86-5; H-Phe[CH₂NH]Cys-OH, 108104-87-6; H-Cys-[CH₂NH]Tyr-OH, 108104-88-7; H-Cys(SO₃H)[CH₂NH]Tyr-OH, 108104-89-8; H-Tyr[CH₂NH]D-Trp-OH, 108104-90-1; H-D-Trp-[CH₂NH]Lys-OH, 108104-91-2; H-Lys[CH₂NH]Val-OH, 108104-92-3; H-Val[CH₂NH]Cys-OH, 108104-93-4; H-Cys-[CH₂NH]Thr-OH, 108104-94-5; BOC-Val-CHO, 79069-51-5.

(27) Wynants, C.; Van Binst, G.; Loosli, H. R. *Int. J. Peptide Protein Res.* 1985, 25, 622.

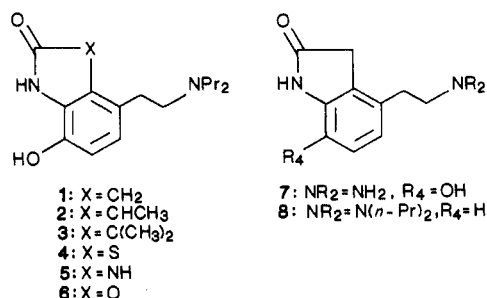
Synthesis and Evaluation of Non-Catechol D-1 and D-2 Dopamine Receptor Agonists: Benzimidazol-2-one, Benzoxazol-2-one, and the Highly Potent Benzothiazol-2-one 7-Ethylamines

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Our interest in identifying D-1 and D-2 dopamine receptor agonists that are not catechols led us to extend previous studies with oxindoles by investigating analogues of dopamine, *N,N*-dipropyldopamine, *m*-tyramine, *N,N*-dipropyl-*m*-tyramine, and epinine in which the *m*-hydroxyl is replaced by the NH portion of a thiazol-2-one, oxazol-2-one, or imidazol-2-one group fused to the 2,3-position. These compounds were evaluated for their affinity and agonist activity at D-1 and D-2 receptors by using in vitro assays. Replacement of the *m*-hydroxy in *N,N*-dipropyldopamine with the thiazol-2-one group resulted in a dramatic increase in D-2 receptor affinity and activity compared to that of *N,N*-dipropyldopamine itself or that of the corresponding oxindole, 1. The resulting compound, 7-hydroxy-4-[2-(di-*n*-propylamino)ethyl]benzothiazol-2(3*H*)-one (4), is the most potent D-2 receptor agonist reported to date in the field-stimulated rabbit ear artery (ED₅₀ = 0.028 nM). The benzoxazol-2-one (6), benzimidazol-2-one (5), and isatin (51) analogues showed D-2 receptor agonist potency similar to that of 1. The des-7-hydroxy analogue of 4 (21) also has enhanced D-2 receptor activity compared to that of the corresponding oxindole, 8. 7-Hydroxy-4-(2-aminoethyl)benzothiazol-2(3*H*)-one, 27, a non-catechol, has enhanced D-1 and D-2 receptor activity in vitro compared to that of the corresponding oxindole, 7. In vivo, 27 increased renal blood flow and decreased blood pressure in the dog. However, these effects were mediated primarily by D-2 receptor agonist activity. This may be a result of the D-1 partial agonist activity of 27 coupled with its potent D-2 receptor activity.

Previous publications from our laboratory have described the potent presynaptic D-2 (DA₂)¹ dopamine receptor agonist activity of 4-[2-(di-*n*-propylamino)ethyl]-7-hydroxy-2(3*H*)-indolone (1) and certain analogues.⁴⁻⁶ Structure-activity relationships studies showed that 1 was the most potent D-2 agonist (EC₅₀ = 1.8 nM for inhibition of vasoconstriction caused by electrical stimulation of the rabbit ear artery), while the racemic 3-methyl analogue 2 was 10 times less active and the 3,3-dimethyl analogue 3

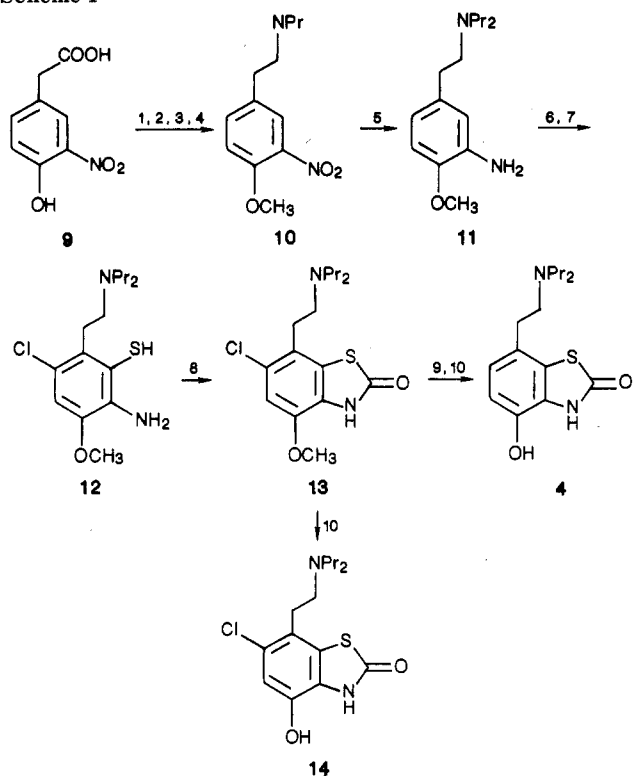


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was inactive. This suggested that an acidic hydrogen on the 3-position of the oxindole might be required for dop-

Scheme I^a

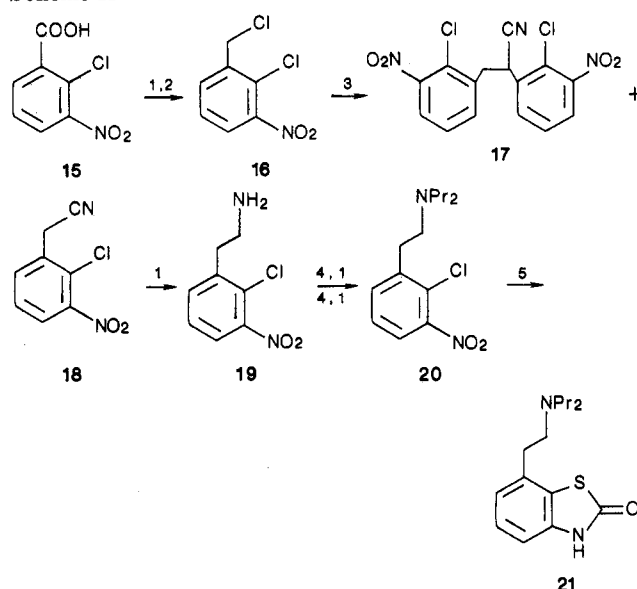
^a 1, SOCl₂; 2, NH(CH₂CH₂CH₃)₂; 3, K₂CO₃-(CH₃)₂SO₄; 4, B₂H₆; 5, H₂, Pt; 6, S₂Cl₂; 7, Na₂S₂O₄; 8, COCl₂; 9, Na, C₆H₁₁OH; 10, BBr₃.

amine agonist activity. Another possibility was that the loss in activity on 3-methylation of 1 was due to a steric effect either in altering side-chain conformation or directly hindering receptor binding.

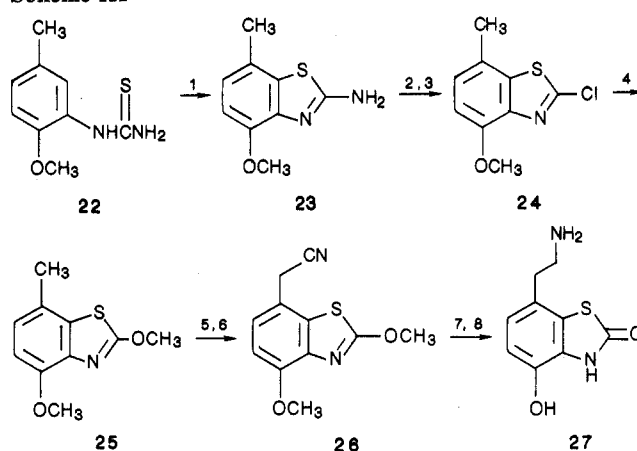
In order to test these hypotheses we prepared a series of analogues 4–6 in which the 3-carbon of 1 was replaced by a heteroatom. In 5, the 3-hydrogen is more acidic than that in 1, while in 4 and 6 this hydrogen is absent, and there are no bulky groups that could contribute steric hindrance.

Another objective of our work was to explore the possibility of developing a non-catechol postjunctional D-1 (DA₁) agonist. We confirmed previous work^{4,6} that showed that 7, the primary amine analogue of 1, had weak but reproducible activity in stimulating rat caudate adenylate cyclase. On the basis of this, since, as will be discussed below, 4 showed dramatically increased D-2 potency in comparison to 1, we investigated the possibility that the primary amine analogue of 4 might have useful D-1 (DA₁) potency.

Since 8, the des-7-hydroxy analogue of 1, was active as a DA₂ agonist, we have also studied the corresponding

Scheme II^a

^a 1, B₂H₆; 2, SOCl₂, pyridine; 3, NaCN, Bu₄N⁺Br⁻, CHCl₃, H₂O; 4, CH₃CH₂COCl, K₂CO₃; 5, CO, S, Et₃N.

Scheme III^a

^a 1, Br₂; 2, H₃PO₄, NaNO₂; 3, NaCl, CuSO₄; 4, NaOCH₃; 5, NBS, (C₆H₅COO)₂, hν; 6, Et₄N⁺CN⁻; 7, B₂H₆; 8, 48% HBr.

analogue in the benzothiazolone series.

Chemistry

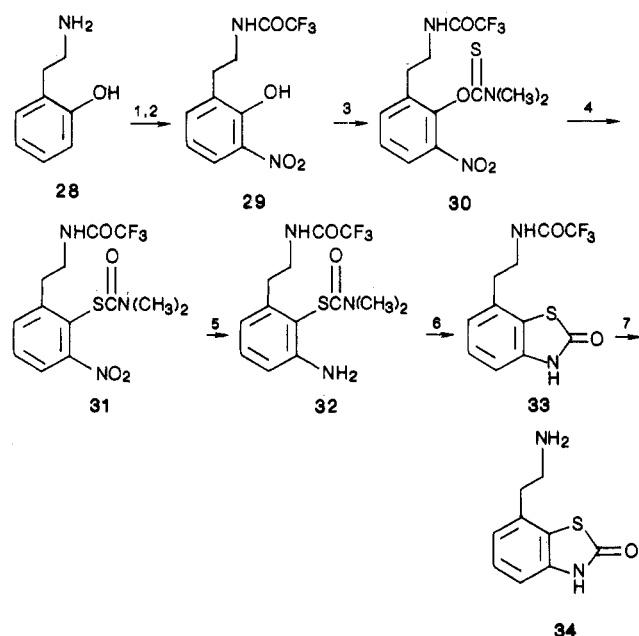
The synthesis of the compounds in Table I is outlined in Schemes I–VIII. The key reaction for the synthesis of 4 (Scheme I) was the Hertz reaction⁷ of the aniline 11, which gave the 2-mercapto-4-chloroaniline 12. This was converted to the benzothiazolone 13 with phosgene and the chlorine was removed with sodium in hot amyl alcohol. The deshydroxy analogue 21 was synthesized as shown in Scheme II. A troublesome step was the conversion of the electronegatively substituted benzyl chloride 16 to the phenylacetone 18. Under standard conditions the major product was 17, which arises from alkylation of 18 with 16. However, under phase-transfer conditions⁸ the desired product 18 was the major product. A one-pot pressure reaction using carbon monoxide, sulfur, triethylamine, and the 2-chloronitrobenzene 20 gave the desired benzothiazolone 21 in modest yield.⁹ To prepare

- (1) In this paper D-1 and D-2 refer to dopamine receptor subtypes that are differentiated by stimulation or lack of stimulation of dopamine sensitive adenylate cyclase,² respectively. DA₁ and DA₂ refer to receptor subtypes that are quite similar to D-1 and D-2, but that are differentiated by causing vasorelaxation by a direct postjunctional effect or by a prejunctional inhibition of neurotransmitter release,³ respectively.
- (2) Kebabian, J. W.; Calne, D. B. *Nature (London)* **1979**, *277*, 93.
- (3) Goldberg, L. I.; Kohlo, J. D. *Trends Pharmacol. Sci.* **1983**, *4*, 64.
- (4) Huffman, W. F.; Hall, R. F.; Grant, J. A.; Wilson, J. W.; Hieble, J. P.; Hahn, R. A. *J. Med. Chem.* **1983**, *26*, 933.
- (5) Gallagher, G.; Levanchy, P. G.; Wilson, J. W.; Hieble, J. P.; DeMarinis, R. M. *J. Med. Chem.* **1985**, *28*, 1533.
- (6) DeMarinis, R. M.; Gallagher, G.; Hall, R. F.; Franz, R. G.; Webster, C.; Huffman, W. F.; Schwartz, M. S.; Kaiser, C.; Ross, S. T.; Wilson, J. W.; Hieble, J. P. *J. Med. Chem.* **1986**, *29*, 939.

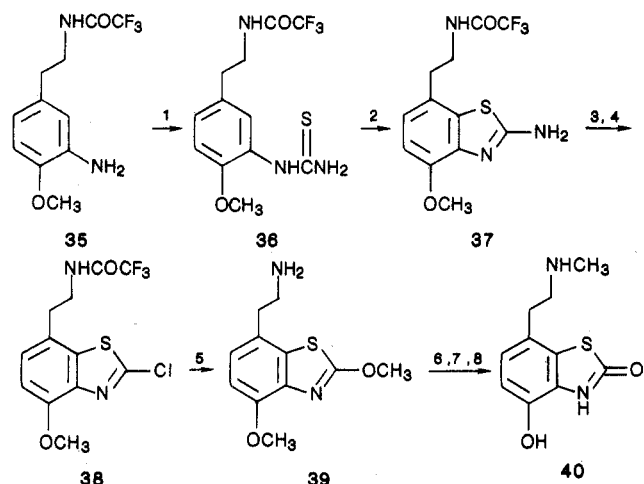
(7) Warburton, W. K. *Chem. Rev.* **1957**, *57*, 1011.

(8) Koenig, K. E.; Weber, W. P. *Tetrahedron Lett.* **1974**, *26*, 2275.

(9) Konishi, K.; Nishiguchi, I.; Hirashima, T. *Synthesis* **1984**, 254.

Scheme IV^a

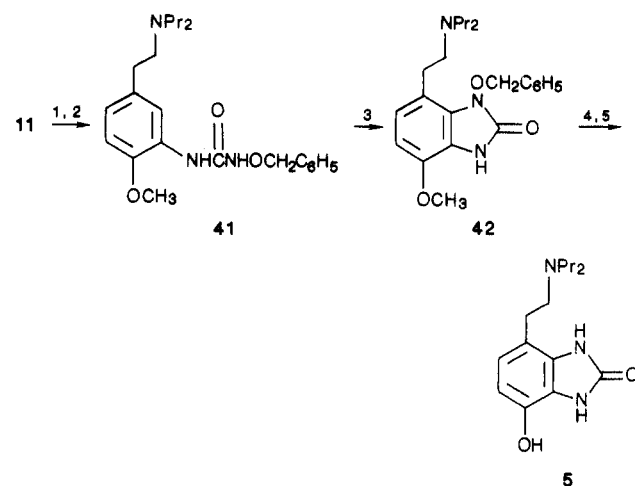
^a 1, $(\text{CF}_3\text{CO})_2\text{O}$; 2, NaNO_3 , $\text{La}(\text{NO}_3)_3$, 6 N HCl; 3, $(\text{CH}_3)_2\text{NCSCl}$, NaOH; 4, 205 °C; 5, H_2 , 10% Pd on C; 6, H_2O , 100 °C; 7, HCl, EtOH, H_2O .

Scheme V^a

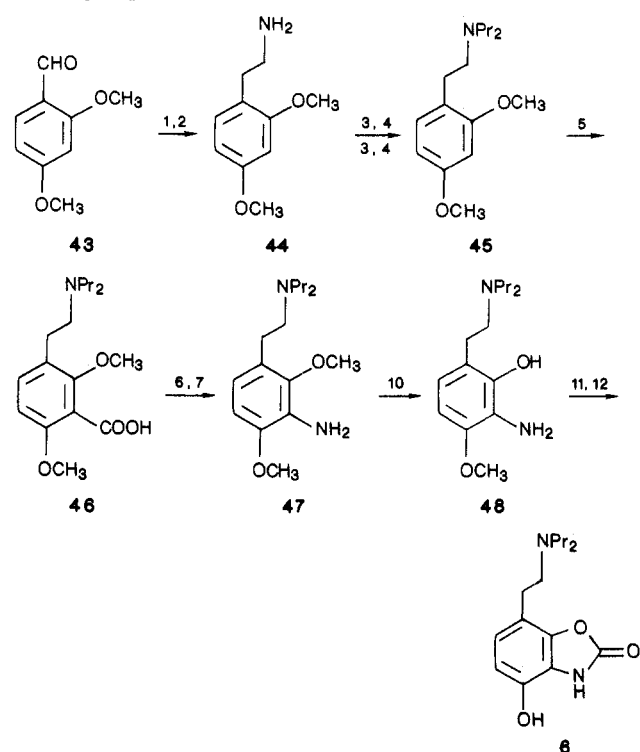
^a 1, NaSCN, H_2SO_4 ; 2, Br_2 ; 3, NaNO_2 , H_3PO_4 ; 4, NaCl, CuSO_4 ; 5, NaOCH₃, CH_3OH ; 6, HCOOC_2H_5 ; 7, B_2H_6 ; 8, 48% HBr.

the primary amine analogue 27 (Scheme III), the 2-aminobenzothiazole 23 was prepared by bromine oxidation of the *N*-arylthiourea 22.¹⁰ Compound 23 was converted to the 2-chlorobenzothiazole and then to the 2-methoxybenzothiazole 25 by established methods.¹⁰ The methoxyl was stable to conditions that allowed the conversion of the arylmethyl group of 25 to the homologated primary amine 27.

The synthesis of the deshydroxy primary amine 34 is shown in Scheme IV. The phenol 28 underwent selective ortho nitration in a lanthanum-catalyzed reaction.¹¹ The *o*-nitrophenol 29 was converted to the *S*-aryl thiocarbamate 31 by the Newman rearrangement.¹² Catalytic hydrogenation gave the aniline 32, which underwent facile cyclization to the benzothiazolone 33 in boiling water. In the

Scheme VI^a

^a 1, COCl_2 ; 2, $\text{C}_6\text{H}_5\text{CH}_2\text{ONH}_2$; 3, $\text{Pb}(\text{OAc})_4$; 4, H_2 , Raney Ni; 5, BBr_3 .

Scheme VII^a

^a 1, CH_3NO_2 ; 2, LiAlH_4 ; 3, $\text{CH}_3\text{CH}_2\text{COCl}$; 4, B_2H_6 ; 5, BuLi, CO_2 ; 6, SOCl_2 ; 7, NaN_3 ; 8, 100 °C; 9, 3 N HCl; 10, NaSC_2H_5 ; 11, COCl_2 ; 12, BBr_3 .

synthesis of the epinine analogue 40 (Scheme V), the benzothiazolone ring was formed by methodology similar to that used in the synthesis of 27.

The benzimidazolone 5 was prepared (Scheme VI) with the aniline 11 as the starting material. This was converted to an *N*-aryl isocyanate,¹³ which on reaction with *O*-benzylhydroxylamine gave the *N*-aryl-*N'*-(benzyloxy)urea 41. Oxidation of 41 with lead tetraacetate gave the *N*-(benzyloxy)benzimidazolone 42, which on Raney nickel catalyzed hydrogenolysis lost the *N*-benzyloxy group to give 5a.¹⁴ Ether cleavage with boron tribromide gave the phenol 5.

(10) Patil, D. G.; Chedekel, M. R. *J. Org. Chem.* 1984, 49, 997.

(11) Ouertani, M.; Girard, P.; Kagan, H. B. *Tetrahedron Lett.* 1982, 4315.

(12) Newman, M. S.; Hetzel, F. W. *Org. Synth.* 1971, 51, 139.

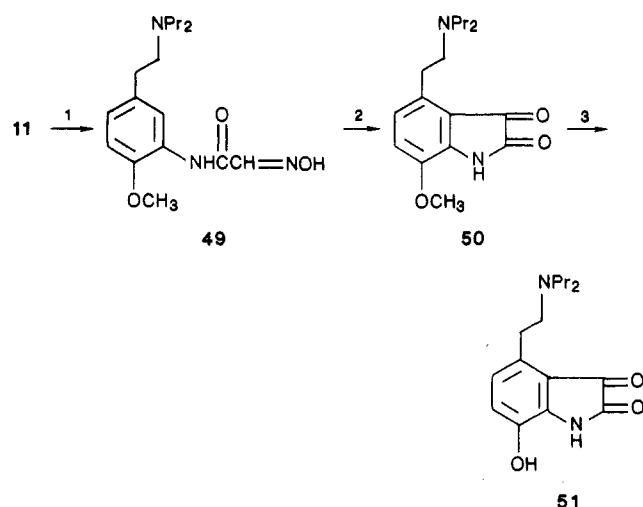
(13) Shiner, R. L.; Horne, W. H.; Cox, R. F. B. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 453.

(14) Cooley, J. H.; Jacobs, P. T. *J. Org. Chem.* 1975, 40, 522.

Table I. Dopaminergic Activity of 3-Heterooxindoles and Standard Compounds

no.	X	NR ₁ R ₂	R ₄	REA: ^a		[³ H]spiroperidol: ^b	[³ H]fenoldopam: ^c	adenylate cyclase: ^c
				EC ₅₀ , nM (n)		IC ₅₀ , nM (n)	K _{bind} , nM (n)	EC ₅₀ , nM (n)
4	S	N(<i>n</i> -Pr) ₂	OH	0.028 (12)		49 ± 11 (3) ^d	516 ± 82 (4)	NS ^f
14	S	N(<i>n</i> -Pr) ₂	OH(6-Cl)	50				
21	S	N(<i>n</i> -Pr) ₂	H	28 ± 9 (9)		1000 (2)	4700 ± 465 (3)	NS ^c
27	S	NH ₂	OH	30 (5)		2000 (2)	9 (2)	295 (2) ^g
34	S	NH ₂	H	1000 (2)		>10,000	980 ± 130 (3)	NS ^f
40	S	NHCH ₃	OH	6 (2)			30 (1)	
5	NH	N(<i>n</i> -Pr) ₂	OH	9 (3)		1000 (2)	2420 ± 190 (3)	
6	O	N(<i>n</i> -Pr) ₂	OH	8 (1)		1200 (2)	6330 ± 170 (3)	
51	C=O	N(<i>n</i> -Pr) ₂	OH	7		560	10000	NS ^f
1	CH ₂	N(<i>n</i> -Pr) ₂	OH	1.8 ± 0.3 (10)		530 ± 190 ^e		20000
8	CH ₂	N(<i>n</i> -Pr) ₂	H	100 ± 26 (5)		6810 (2)		
7	CH ₂	NH ₂	OH	116 ± 43 (8)		4850 (2)	700 (1)	4650 ^h
<i>N,N</i> -dipropyldopamine				80 ± 17 (13)				12500
dopamine				76 ± 6 (38)		4700	150 ± 25	3500
fenoldopam				1200		1580	3 ± 1	57

^aRelaxation of the electrically stimulated rabbit ear artery. ^bBovine pituitary. ^cRat caudate. ^dK_{high} = 3.6 ± 1.2 nM, K_{low} = 202 ± 59 nM (n = 3). ^eK_{high} = 10 nM, K_{low} = 1050 nM. ^fNot significant. ^gPartial agonist, maximum effect 60% of dopamine maximum effect. ^hPartial agonist, maximum effect 59% of dopamine maximum effect.

Scheme VIII^a

^a1, CCl₃CHO, H₂NOH; 2, H₂SO₄; 3, HBr or BBr₃.

The key reaction in the synthesis of the benzoxazolone 6 (Scheme VII) was the selective cleavage of the more sterically hindered methyl ether in the 2,6-dimethoxyaniline 47 by sodium mercaptide to give 48.¹⁵ The structure of 48 was established by a nuclear Overhauser enhancement experiment which showed interaction of the *O*-methyl protons and the adjacent aromatic ring proton and the lack of interaction of the *O*-methyl protons with the benzylic protons of the ethylamine side chain.

The isatin 51 was prepared by the classical Sandmeyer isatin synthesis⁶ as shown in Scheme VIII.

Biological Results

The affinity of the compounds for D-1 dopamine receptor binding sites was measured by their ability to displace [³H]fenoldopam from homogenized rat striatum and

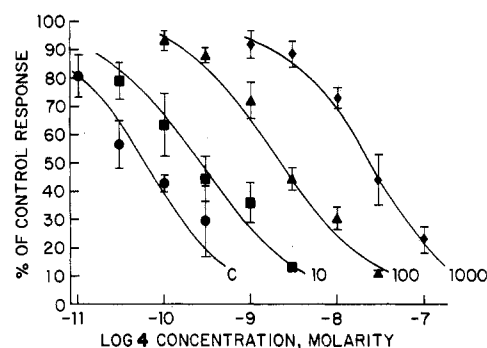


Figure 1. Neuroinhibitory effect of 4 in the isolated perfused rabbit ear artery and the blockade of this effect by (*S*)-sulpiride. Each point represents the mean ± SEM of at least four experiments. Sulpiride concentration in nM denoted adjacent to each curve.

the affinity for D-2 receptors by their ability to displace [³H]spiroperidol from homogenized bovine pituitary.¹⁶ D-1 agonist efficacy was measured with stimulation of dopamine-sensitive rat caudate adenylate cyclase.¹⁶ D-2 agonist efficacy was evaluated with the electrically stimulated isolated rabbit ear artery.¹⁶

The *in vitro* dopaminergic test results are shown in Table I. The benzothiazolone 4, in which the 3-CH₂ of 1 has been replaced by sulfur, is 65 times as potent as 1 as a DA₂ agonist in the rabbit ear artery test and 11 times as potent as 1 in inhibiting [³H]spiroperidol binding in homogenized bovine pituitary membranes. As shown in Figure 1, the activity of 4 in the rabbit ear artery could be competitively antagonized by (*S*)-sulpiride, a D-2 receptor antagonist, with a K_B of 4 nM. The extremely high potency of 4 allowed parallel shifts of the full dose-response curve to be determined over a 100-fold range of the

(16) Weinstock, J.; Gaitanopoulos, D. E.; Oh, H.-J.; Pfeiffer, F. R.; Karash, C. B.; Venslavsky, J. W.; Sarau, H. M.; Flaim, K. E.; Hieble, J. P.; Kaiser, C. J. *Med. Chem.* 1986, 29, 1615.

(15) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* 1970, 1327.

concentration of the D-2 agonist with a Schild plot slope of 1 in agreement with receptor theory for competitive receptor binding. Although **4** is about one-fourth as potent as dopamine in displacing [^3H]fenoldopam, suggesting possible D-1 activity, the absence of significant stimulation of adenylate cyclase indicates that it lacks D-1 agonist activity. The 6-chloro analogue **14** is 1800 times less potent than **4** in the rabbit ear artery test, but even so its potency is comparable to that of dopamine.

Previous work in our laboratory showed that removing the 4-hydroxyl from **1** to give **8** reduced the rabbit ear artery potency by a factor of 55, but the resulting product still has potency in a useful range. This is reminiscent of the similar D-2 potency differences seen when going from dopamine to *m*-tyramine and from *N,N*-dipropyl dopamine to *N,N*-dipropyl-*m*-tyramine.¹⁷ A similar change in the benzothiazolone series gave **21**, which is 1000 times less potent than **4** in the rabbit ear artery, but only 20 times less potent than **4** in the [^3H]spiroperidol binding assay.

Reinvestigation of the D-1 properties of **7** confirmed that it stimulated dopamine-sensitive adenylate cyclase, but was only a partial agonist. Its stimulatory effect was blocked by the D-1 antagonists SK&F R-83566 and *cis*-flupenthixol at 0.1 μM , but not by 1 μM domperidone, cinanserin, phentolamine, or 10 μM propranolol.

The benzothiazolone dopamine analogue **27** had both D-1 and D-2 agonist activity. It was about twice as potent as dopamine in the rabbit ear artery and [^3H]spiroperidol binding DA₂ and D-2 assays and more than 10 times as potent as dopamine in both the [^3H]fenoldopam and rat caudate adenylate cyclase D-1 assays. However, in the latter it was only a partial agonist with a maximum effect only 60% that of dopamine. Thus, on the basis of in vitro assays, **27** had both D-1 and D-2 agonist activity.

This nonselectivity of **27** was also seen in in vivo studies in dogs. In conscious dogs that were instrumented to measure renal blood flow, decreases in both renal vascular resistance and blood pressure were observed on intravenous infusion at doses of 1–30 $\mu\text{g}/\text{kg}$, but this was accompanied by emesis, presumably due to D₂ activity. In anesthetized α -blocked dogs (phenoxybenzamine pretreated) intravenous infusion of **27** at doses of 3–30 $\mu\text{g}/\text{kg}$ caused decreases in both blood pressure and renal vascular resistance. However, as shown in Figure 2, these responses were unchanged by the D-1 and DA₁ selective blocker SK&F 83566, but were inhibited by the D-2 selective blocker domperidone, suggesting that a major portion of the vascular responses were due to DA₂ receptor activity.

The benzothiazolone epinine analogue **40** was active in the D₂ rabbit ear artery test and the D-1 [^3H]fenoldopam binding assay. Thus, again no D-1 selectivity was seen.

The benzimidazolone (**5**), the benzoxazolone (**6**), and the isatin (**51**) analogues of **1** showed DA₂ activity in both the rabbit ear artery and [^3H]spiroperidol binding assays with potencies similar to that of **1**. They showed only very weak D-1 activity in the [^3H]fenoldopam binding assay and thus appear to be potent selective D-2 (DA₂) agonists.

Discussion

The most striking observation of this work was that **4** is 64 times more potent than **1** as a DA₂ agonist in the rabbit ear artery test. Compound **1** is to our knowledge the most potent DA₂ agonist previously reported.⁶ The related compounds with the sulfur of **4** replaced by oxygen (**6**), nitrogen (**5**), and carbonyl (**51**) are essentially equiv-

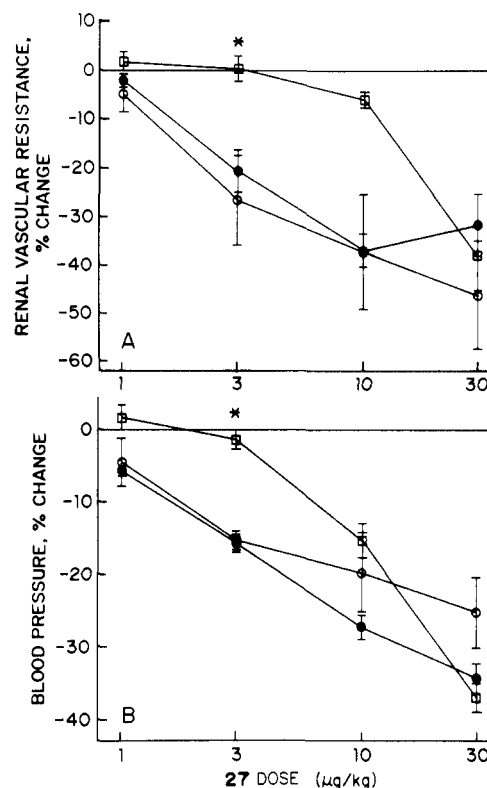


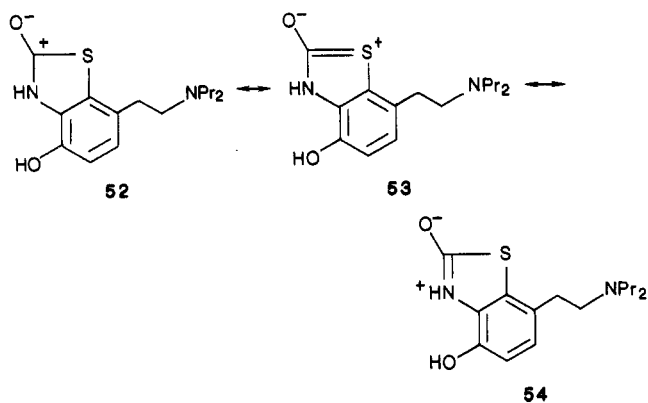
Figure 2. Effect of (*R*)-7-bromo-2,3,4,5-tetrahydro-8-hydroxy-3-methyl-1-phenyl-1*H*-3-benzazepine (SK&F R-83566), a DA-1 antagonist, and domperidone, a DA-2 antagonist, on **27** induced changes in renal vascular resistance (panel A) and blood pressure (panel B) in phenoxybenzamine-pretreated anesthetized dogs ($n = 3$). All dogs were given **27** intravenously by consecutive doses as indicated and the antagonists as continuous $0.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$ infusions starting at least 30 min prior to the first dose of **27**. Open circles, **27**; closed circles, **27** and SK&F R-83566; open squares, **27** and domperidone. Asterisk indicates changes from **27** alone with $P < 0.05$.

alent in activity to the oxindole **1** (sulfur replaced by CH_2), suggesting that in this series sulfur has a unique potency-enhancing effect. However, in the corresponding deshydroxy series, **21** (sulfur) is only 3.6 times more potent than **8** (CH_2), and in the primary amine series, **27** (sulfur) is only 3.8 times more potent than **7** (CH_2). This suggests that sulfur does have a consistent potency-enhancing effect. It appears for the large potency-enhancing effect to occur, the base molecule must be very potent, in this case having both the *N,N*-dipropyl and the hydroxyl ortho to the NH of the heterocycle. It is also remarkable that the potency-enhancing effect of sulfur is less marked when D-2 activity is determined with [^3H]spiroperidol binding. However, previous work¹⁶ has suggested that as run by our procedures rabbit ear artery data may reflect high affinity binding while [^3H]spiroperidol binding may be more indicative of lower affinity higher capacity binding, again suggesting that sulfur potentiates high affinity binding better than lower affinity binding.

Sulfur has been characterized as a "soft" atom with high polarizability and low electronegativity and possessing vacant low-lying orbitals.¹⁸ Consideration of resonance forms of **4** such as **52**–**54** suggests that the carbonyl oxygen has a high-electron density and the heterocyclic ring has a low-electron density. This charge distribution may promote binding to a complementary receptor binding site.

(17) Seeman, P.; Watanabe, M.; Grigoriadis, D.; Tedesco, J. L.; George, S. R.; Svensson, U.; Nilsson, J. L. G.; Neumeyer, J. L. *Mol. Pharmacol.* 1985, 28, 391.

(18) Block, E. *Reactions of Organosulfur Compounds*; Organic Chemistry, A Series of Monographs; Blomquist, A. T., Wasserman, H. H., Eds.; Academic: New York, 1978; Vol. 37, p 22.



The activity of 4, 6, and 51 shows that an acidic 3-hydrogen is not necessary for potent D-2 (DA₂) activity in the oxindole series, and the lack of outstanding activity of 5 suggests that an acidic 3-hydrogen is not potency enhancing.

It has been proposed that for good dopamine receptor binding potency the nitrogen of the ethylamine side chain must be within 0.6 Å of the plane of the catechol ring.¹⁹ In the 3,3-dimethyloxindole 3 the ethylamine side chain is forced away from the plane of the aromatic ring by the bulk of the *gem*-dimethyl group. Thus, a bulk-induced conformational change may explain the lack of dopaminergic activity of this compound.

The dopamine analogue 27 was prepared to test the possibility that the D-2 potency enhancing property of the thiazolone would carry over to also enhance D-1 potency. Comparison of the data for 27 and 7 shows that this did occur with respect to both receptor binding as measured by displacement of [³H]fenoldopam and the receptor event as measured by stimulation of rat caudate adenylate cyclase. However, for the latter only partial agonist activity was found. D-2 potency was also enhanced by the thiazolone ring, so although 27 does have authentic *in vitro* D-1 agonist activity, the predominant *in vivo* peripheral activity as measured by renal vasodilation in the dog is due to DA₂ receptor stimulation.

However, the D-1 activity seen with 27 (and with 7) does demonstrate that contrary to most previous experience²⁰ D-1 activity does not require a catechol and thus suggests that it may be possible to discover non-catechol dopamine agonists for which the dominant *in vivo* activity is D-1 (DA₁) mediated.

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover Unimelt apparatus and are uncorrected. When analyses are reported by symbols of the elements, results were within 0.4% of calculated values. IR spectra were determined with a Perkin-Elmer Model 683 spectrophotometer and ¹H NMR spectra with a Varian EM-390 spectrometer. Compound 48 was examined for NOE with a Bruker 360 MW spectrometer.

4-Hydroxy-3-nitrophenylacetic Acid (9). Nitric acid (100 mL of 70.5%, 1.59 mol) was added dropwise to a solution of 4-hydroxyphenylacetic acid (50 g, 0.33 mol) in 300 mL of acetic acid maintained below 15 °C, and the reaction mixture was held at that temperature for 20 min. Dilution with 1 L of H₂O and recrystallization of the product from EtOH gave 44.3 g (69%) of 9: mp 144–146 °C (lit.²¹ mp 146–147 °C); ¹H NMR (CDCl₃-

Me₂SO-*d*₆) δ 3.62 (s, 2 H, CH₂), 7.12 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 7.55 (AB q, 1 H, Ar H-6, *J* = 9, 2 Hz), 8.03 (d, 1 H, Ar H-2, *J* = 2 Hz).

2-(4-Methoxy-3-nitrophenyl)-*N,N*-dipropylethylamine Hydrochloride (10). A solution of 9 (35 g, 0.178 mol) in 100 mL of SOCl₂ was refluxed for 3.5 h. Concentration under vacuum gave an oil, which was dissolved in CHCl₃ and added dropwise to a solution of 35.7 g (0.30 mol) of dipropylamine in 200 mL of CHCl₃. Concentration under vacuum gave an oil, which crystallized from aqueous methanol and which on recrystallization from cyclohexane gave 30 g (60%) of 2-(4-hydroxy-3-nitrophenyl)-*N,N*-dipropylacetamide: mp 63–65 °C; IR (mull) 3220, 1617, 1535, 1340, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ 0.92 (t, 6 H, CH₃, *J* = 7 Hz), 1.6 (m, 4 H, CH₂CH₃), 3.30 (m, 4 H, CH₂N), 3.70 (s, 2 H, Ar CH₂), 7.13 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 7.55 (AB q, 1 H, Ar H-6, *J* = 9, 2 Hz), 8.00 (d, 1 H, Ar H-2, *J* = 2 Hz).

A suspension of 28 g (0.10 mol) of this phenol in a mixture of 40 mL of H₂O and 40 mL of DMF was stirred with K₂CO₃ (36 g, 0.26 mol) and dimethyl sulfate (20 g, 0.16 mol) for 20 min and was then diluted with 250 mL of H₂O and extracted with EtOAc. The organic layer was washed with 10% NaOH, H₂O, and 10% HCl and was then dried (Na₂SO₄) and concentrated to give 28.4 g (97%) of 2-(4-methoxy-3-nitrophenyl)-*N,N*-dipropylacetamide as an oil: IR (film) 1640, 1675, 1532, 1360, 1280, 1260 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (m, 6 H, CH₃), 1.60 (m, 4 H, CH₂CH₃), 3.35 (m, 4 H, NCH₂), 3.80 (s, 2 H, Ar CH₂), 3.95 (s, 3 H, OCH₃), 7.07 (AB q, 1 H, Ar H-5, *J* = 8 Hz), 7.52 (AB q, 1 H, Ar H-6, *J* = 8, 2 Hz), 7.80 (d, 1 H, Ar H-2, *J* = 2 Hz).

A solution of 14.7 g (0.05 mol) of the acetamide in 100 mL of THF and 100 mL (0.10 mol) of 1.0 M B₂H₆ in THF was refluxed for 2.5 h, 100 mL of 10% aqueous HCl was added, the solution was refluxed for 45 min, and the solvents were removed under vacuum. The residue was taken up in 100 mL of 10% aqueous HCl and was extracted three times with CHCl₃. The extract was dried over Na₂SO₄ and then concentrated *in vacuo* to give 16.0 g (quant) of an oil: IR (film) 3350, 2440, 1625, 1575, 1530, 1470, 1355, 1285, 1268 cm⁻¹; ¹H NMR (CDCl₃) 1.00 (t, 6 H, CH₃, *J* = 7 Hz), 1.86 (m, 4 H, CH₂CH₃), 3.07 (m, 4 H, CH₂CH₂N), 3.25 (s, 4 H, Ar CH₂CH₂N), 3.97 (s, 3 H, OCH₃), 7.10 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 7.40 (s, 1 H, NH), 7.60 (AB q, 1 H, Ar H-6, *J* = 9, 2 Hz), 7.78 (d, 1 H, Ar H-2, *J* = 2 Hz).

2-(4-Methoxy-3-aminophenyl)-*N,N*-dipropylethylamine Hydrochloride (11). A suspension of 1.0 g of PtO₂ and 57.2 g (0.181 mol) of 10 in 500 mL of MeOH was shaken in two portions in a Parr apparatus under 3 atm of H₂ for 9 h. Filtration and concentration under vacuum gave a solid, which on recrystallization from an *i*-PrOH-Et₂O mixture gave 38.1 g (73%) of crystals: mp 139–141 °C; IR (mull) 3390, 3305, 3200, 2455, 1620, 1595, 1517, 1295, 1235 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00 (t, 6 H, CH₃, *J* = 6 Hz), 1.90 (m, 4 H, CH₂CH₃), 3.03 (m, 8 H, CH₂N and Ar CH₂), 3.85 (s, 3 H, OCH₃), 6.64 (m, 3 H, Ar H).

2-(3-Amino-6-chloro-2-mercapto-4-methoxyphenyl)-*N,N*-dipropylethylamine (12). A solution of 11 (5.0 g, 17.5 mmol) in 6 mL of acetic acid was added to sulfur monochloride (9.66 mL, 120 mmol) with cooling to keep the reaction temperature below 15 °C. The mixture was stirred at ambient temperature for 1.75 h and at 55 °C for 3 h. Dilution with 200 mL of toluene gave an oil, which on trituration with ether gave 7.56 g of a purple solid. A 6.45-g portion of this solid was dissolved in 300 mL of H₂O, then 10% NaOH was added to achieve pH 9, and the resulting suspension was extracted with CH₂Cl₂. This extract was washed with 10% Na₂S₂O₄, dried over MgSO₄, and then concentrated to give a yellow solid, which on recrystallization from methanol gave 3.11 g (72%) of 12, mp 203–205 °C. Chromatography of a small portion on SiO₂ (CH₂Cl₂) gave white plates: mp 212–213 °C dec; IR (KBr) 3490, 3385, 2970, 1550, 1280, 1200, 1020 cm⁻¹; ¹H NMR (CDCl₃-Me₂SO-*d*₆) δ 1.00 (t, 6 H, CH₃), 1.5–1.95 (m, 4 H, CH₂CH₂CH₃), 2.95–3.25 (m, 6 H, CH₂N), 3.4 (s, 4 H, Ar CH₂ and NH₂), 3.85 (s, 3 H, OCH₃), 5.15 (br s, 1 H, SH), 6.80 (s, 1 H, Ar H). Anal. (C₁₅H₂₅ClN₂OS·3.5S) C, H, N.

6-Chloro-4-methoxy-7-[2-(*N,N*-dipropylamino)ethyl]-1,3-benzothiazol-2(3*H*)-one Hydrochloride (13). A solution of 7.87 g (0.080 mol) of phosgene in 80 mL of toluene was added dropwise to a suspension of 5.04 g (0.059 mol) of 12 in 125 mL of toluene, and the mixture was refluxed for 2.5 h. Chilling, filtration, and washing the resulting solid with petroleum ether

- (19) Kaiser, C. *Dopamine Receptor Agonists*; Poste, G., Crooke, S. T., Eds.; Plenum: New York, 1984; Chapter 4.
- (20) Goldberg, L. I.; Kohli, J. D. *Dopamine Receptors*; Kaiser, C., Kebabian, J. W., Eds.; American Chemical Society: Washington, DC, 1983; p 101.
- (21) Kametani, T.; Fukumoto, K.; Ro, M. *Yakugaku Zasshi* 1964, 84, 532.

gave 5.56 g (94%) of buff crystals, mp 251–253 °C. A sample was purified by chromatography (SiO₂–10% MeOH–CHCl₃) and was then recrystallized from MeOH–Et₂O: mp 202 °C dec; IR (KBr) 3400, 2960, 1490 cm⁻¹; ¹H NMR (CDCl₃, Me₂SO-*d*₆) δ 6.82 (s, 1 H, Ar H), 3.90 (s, 3 H, OCH₃), 3.40–2.75 (m, 8 H, CH₂N and CH₂Ar), 2.00–1.55 (m, 4 H, CH₂CH₃), 1.00 (t, 6 H, CH₃CH₂). Anal. (C₁₆H₂₃ClN₂O₂S·1.5HCl) C, H, N.

6-Chloro-4-hydroxy-7-[2-(*N,N*-dipropylamino)ethyl]-1,3-benzothiazol-2(3*H*)-one Hydrobromide (14). Boron tribromide (283 mg, 1.13 mmol) was added to a suspension of 400 mg (1.06 mmol) of 13 in 10 mL of CHCl₃ at –50 °C. The mixture was allowed to warm to ambient temperature and was then stirred for an additional 4 h. The volatiles were evaporated under a stream of argon, and the residue was treated with 15 mL of MeOH at –78 °C. The solution was carefully warmed to room temperature and the solvent was removed under vacuum. After several such methanol treatments, the residue was recrystallized from MeOH to give 0.17 g (39%) of 14: mp 284–286 °C; IR (mull) 2920, 2855, 1675, 1465 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 6.96 (s, 1 H, Ar H), 3.40–2.95 (m, 8 H, CH₂N and Ar CH₂), 1.90–1.40 (m, 4 H, CH₂CH₃), 0.95 (t, 6 H, CH₃CH₂); MS, *m/e* 329 [M + H]⁺. Anal. (C₁₅H₂₁ClN₂O₂S·HBr) C, H, N.

4-Hydroxy-7-[2-(*N,N*-dipropylamino)ethyl]-1,3-benzothiazol-2(3*H*)-one Hydrobromide (4). Sodium (5.76 g, 0.25 mol) was added in small portions to a stirred suspension of 13 (4.75 g, 0.0125 mol) in 135 mL of xylene and 34 mL of 1-pentanol at 105–115 °C under argon. After 1 h the heating was stopped and the reaction mixture was allowed to stand overnight. The solution was decanted from the remaining undissolved sodium, and the solution was diluted with water and brought to pH 8.5 with 10% HCl. This was extracted with EtOAc, and the organic layer was washed with brine, dried (MgSO₄), and then concentrated under vacuum. Trituration of the residue with petroleum ether gave 4-methoxy-7-[2-(*N,N*-dipropylamino)ethyl]-1,3-benzothiazol-2(3*H*)-one as off-white crystals in two crops: 1.72 g, mp 126–127 °C and 0.56 g, mp 122–124 °C (59%); IR (KBr) 3300, 2960, 1678 cm⁻¹; ¹H NMR (CDCl₃) δ 7.10 (AB q, 1 H, *J* = 9 Hz, Ar H-6), 6.87 (AB q, *J* = 9 Hz, Ar H-5), 3.90 (s, 3 H, OCH₃), 3.40–2.90 (m, 8 H, CH₂N, Ar CH₂), 1.50–2.00 (m, 4 H, CH₂CH₃), 0.98 (t, 6 H, *J* = 8 Hz, CH₃CH₂). A hydrochloride prepared from a sample purified by chromatography (SiO₂–CHCl₃) after recrystallization from EtOH–Et₂O had mp 243–246 °C.

A solution of 2.23 g of the above free base in 23 mL of 48% HBr was refluxed for 30 min. Cooling, filtration, and washing the solid product with cold water gave 2.45 g of 4, which on recrystallization from a MeOH–EtOH mixture gave 1.78 g (63%) of crystals: mp 265–267 °C; IR (KBr) 3310, 2960, 1678 cm⁻¹; ¹H NMR (CDCl₃, Me₂SO-*d*₆) δ 6.82 (AB q, 1 H, *J* = 8 Hz, Ar H-6), 6.75 (AB q, 1 H, *J* = 2.5 Hz, Ar H-5), 3.45–2.90 (m, 8, Ar CH₂ and CH₂N), 2.10–1.65 (m, 4 H, CH₂CH₃), 1.05 (t, 6 H, *J* = 6 Hz, CH₃CH₂). Anal. (C₁₅H₂₂N₂O₂S·HBr) C, H, N.

2-Chloro-3-nitrobenzyl Chloride (16). 2-Chloro-3-nitrobenzoic acid (15.39 g, 0.0764 mol) was treated with diborane in tetrahydrofuran to give 13.78 g (96%) of 2-chloro-3-nitrobenzyl alcohol: mp 69–70 °C (lit.²² mp 72–73 °C). The benzyl alcohol (9.85 g, 0.0525 mol) was added in small portions over a 5-min period to a stirred solution of thionyl chloride (11.24 g, 0.0945 mol) and a drop of pyridine in dry toluene (50 mL). The mixture was heated in a bath at 45–50 °C for 5 h and cooled in an ice bath, and ice-cold water (50 mL) was added. The mixture was stirred vigorously for a few minutes and then extracted with ether (100 mL). The organic phase was washed with 3 × 50 mL portions of water and then with 50 mL of saturated brine, dried (Na₂SO₄), and concentrated in vacuo to give 10.41 g (96%) of a clear yellowish syrup. Trituration of a portion with petroleum ether (bp 35–60 °C) gave a crystalline solid, mp 60–61 °C. Anal. (C₇H₅Cl₂NO₂) C, H, N.

2-Chloro-3-nitrophenylacetonitrile (18). **Method A.** A solution of 16 (10.34 g, 0.050 mol) in Me₂SO (40 mL) was added over a 45-min period to a solution of NaCN (3.69 g, 0.075 mol) in 100 mL of Me₂SO. The dark green reaction mixture was stirred for 30 min, diluted with 6 L of water, saturated with NaCl, and

then extracted twice with 750 mL of ether. The ether was evaporated under vacuum and the residue was dissolved in 100 mL of CHCl₃. This solution was washed with water and brine and then dried (Na₂SO₄) and on evaporation under vacuum gave 9.14 g (93%) of a brown syrup, which solidified. ¹H NMR and capillary GC analysis indicated that it was a 3:5 mixture of 17 and 18. Some 17 was isolated by trituration with ether, recrystallization of the insoluble material from methanol, and a second ether trituration: mp 148–154 °C; MS, *m/e* 366 (M + H)⁺; ¹H NMR (CDCl₃) δ 3.43 (m, 2 H, CH₂), 4.85 (m, 1 H, CH), 7.2–7.9 (m, 6 H, Ar H).

Method B.⁸ A solution of 16 (3.46 g, 0.0168 mol), NaCN (1.64 g, 0.0334 mol), and tetrabutylammonium bromide (35 mg) in 14 mL of CH₂Cl₂ and 1.96 mL of water was stirred for 18 h at room temperature. The reaction mixture was washed with water and brine, dried (Na₂SO₄), and then concentrated under vacuum to give 2.92 g (88%) of a 15:85 mixture (capillary GC analysis) of 17 and 18. Chromatography (360 g of silica gel 60, 70–230 mesh, Merck, 4:1 CHCl₃–cyclohexane) gave 2.21 g (67%) of 18: mp 102–103 °C; MS, *m/e* 197 (M + H)⁺; IR (Nujol) 2225, 1600, 1570, 1535, 1460, 1430, 1400, 1350, 1055, 975, 890, 800, 740, 730, 650 cm⁻¹; ¹H NMR (CDCl₃) δ 3.92 (s, 2 H, CH₂CN), 7.50 (dd, H, Ar H-5), 7.80 (overlapping dd, Ar H-4,6). Anal. (C₈H₅ClN₂O₂·1.25H₂O) C, H, N: calcd, 14.17; found, 13.70.

2-(2-Chloro-3-nitrophenyl)ethylamine Hydrochloride (19). A solution of 18 (3.00 g, 0.0153 mol) in 18 mL of dry THF was added dropwise to a stirred solution of B₂H₆ (31.2 mL of 0.98 M, 0.0306 mol) under argon. After 1 h of reflux, 20 mL of MeOH was added dropwise, and then dry HCl gas was added to acidify the mixture. The mixture was concentrated under vacuum, and the methanol treatment was repeated twice. The residue was dissolved in ethyl acetate and when concentrated to 30 mL gave crystals. These were collected after holding for 18 h at –15 °C to give 3.16 g (87%) of 19: mp 250–253 °C dec; IR (Nujol) 1630, 1600, 1540, 1435, 1320, 1110, 1050, 800, 790, 740, 725 cm⁻¹; ¹H NMR (CDCl₃–Me₂SO-*d*₆) δ 3.00–3.45 (m, 4 H, CH₂), 7.41 (dd, H, Ar H₅), 7.72 (overlapping dd, 2 H, Ar H-4,6). Anal. (C₈H₅ClN₂O₂·HCl) C, H, N. MS, *m/e* 201 [M + H]⁺.

2-(2-Chloro-3-nitrophenyl)-*N,N*-dipropylethylamine (20). A mixture of 19 (3.50 g, 0.0148 mol) and K₂CO₃ (11.93 g, 0.0791 mol) in 36 mL of H₂O and 36 mL of CHCl₃ was stirred for 0.5 h and then chilled to 0 °C, propionyl chloride (3.42 g, 0.0370 mol) was added, and the mixture then was stirred at ambient temperature for 30 h. The aqueous phase was extracted with 25 mL of CHCl₃, the CHCl₃ extract was combined with the organic phase, and this was washed in turn with 10% aqueous HCl (30 mL), water, and brine and dried over Na₂SO₄. Evaporation gave the *N*-propionyl amide as a syrup (3.73 g, 98%), MS, *m/e* 257 (M + H)⁺. Reduction with B₂H₆ in THF by the standard procedure²³ gave 2-(2-chloro-3-nitrophenyl)-*N*-propylethylamine hydrochloride: 3.06 g (77%); mp 186–189 °C; MS, *m/e* 243 (M + H)⁺, 207 (M + H – HCl). Anal. (C₁₁H₁₅ClN₂O₂·HCl). Repetition of this procedure gave 3.15 g (95%) of the *N*-propylpropionyl amide, which in turn gave 2.82 g (94%) of 20 as a syrup: IR (film) 2980, 2930, 2900, 1535, 1460, 1360, 1300, 1190, 1075, 820, 800, 740, 720 cm⁻¹; ¹H NMR (CDCl₃) δ 0.87 (t, *J* = 6 Hz, 6 H, CH₃), 1.25–1.63 (m, *J* = 9 Hz, 4 H, NCH₂CH₂CH₃), 2.47 (t, *J* = 7.5 Hz, 4 H, NCH₂CH₂CH₃), 2.75 (m, 2 H, CH₂CH₂N), 2.88 (m, 2 H, CH₂CH₂N), 7.19–7.62 (m, 3 H, Ar H-4,5,6); MS, *m/e* 285 (M + H)⁺.

7-[2-(*N,N*-Dipropylamino)ethyl]-1,3-benzothiazol-2(3*H*)-one Hydrochloride (21). A mixture of 20 (0.66 g, 2.3 mmol), sulfur 0.40 g (12.5 mmol), water (0.27 g, 15 mmol), and triethylamine (1.4 mL, 10 mmol) in 10 mL of THF was placed in a 45-mL stainless steel stirred Parr bomb and pressurized to 12 atm with carbon monoxide. The stirred reaction mixture was heated in an oil bath at 80–85 °C for 10 h and then cooled, the pressure was released cautiously to control frothing, and the reaction mixture was diluted with THF and filtered. Concentration of the filtrate gave a brown syrup, which on chromatography (60 g of silica gel 60, 70–230 mesh, Merck, 97:3 CHCl₃–MeOH) gave 50 mg of 21 as the free base and 180 mg of recovered 20. A total of 0.50 g of 21 as the free base was obtained from a

(22) Ricci, A.; Martani, A.; Graziani, O.; Oliva, M. L. *Ann. Chim. (Rome)* 1963, 53, 1860.

(23) Brown, H. C.; Heim, P. *J. Am. Chem. Soc.* 1964, 86, 3566.

total of five such reactions with yields of 14–30%. This was converted to 0.43 g of **21**; mp 270–272 °C; ^1H NMR (CDCl_3 - $\text{Me}_2\text{SO}-d_6$) δ 0.95 (t, J = 6 Hz, 6 H, CH_3), 1.50–1.87 (m, 4 H, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 3.00–3.30 (m, 8 H, Ar CH_2 and NCH_2), 6.98–7.33 (m, 3 H, Ar H); IR (Nujol) 1690, 1575, 1470, 1200, 790, 630 cm^{-1} ; MS, m/e 279.2. Anal. ($\text{C}_{15}\text{H}_{22}\text{N}_2\text{OS}\cdot\text{HCl}$) C, H, N.

2-Amino-4-methoxy-7-methylbenzothiazole (23). Bromine (75.0 g, 0.469 mol) was added over a 20-min period to a stirred solution of **22**¹⁰ (43.2 g, 0.220 mol) in 155 mL of CHCl_3 at 10 °C. The mixture was held at ambient temperature for 30 min and was then refluxed for 20 min. Filtration followed by washing the solid with CHCl_3 and then with ether gave 64.8 g of a yellow bromine-containing solid, mp 145–146 °C, which was suspended in 300 mL of acetone. This discharged the yellow color, and filtration followed by washing of the solid with acetone and with ether gave 43.4 g (72%) of **23**-HBr as a white solid, mp 240–242 °C. This (23.17 g) was dissolved in 1 L of hot water and the pH of the cool solution was brought to pH 9 with 14 N NH_4OH . Filtration followed by washing with water gave 21.77 g (96% recovery) of **23**: mp 165–166 °C, soften 150 °C (lit.¹⁰ mp 164–165 °C); IR (Nujol) 3360, 1640, 1590, 1530, 1500, 1460, 1335, 1320, 1280, 1260, 1215, 1175, 1110, 1030, 940, 880, 795, 775, 740, 690; ^1H NMR (CDCl_3) δ 2.34 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 5.69 (s, 2 H, NH_2), 6.72–6.89 (dd, J = 6 Hz, 2 H, Ar H-5,6). Anal. ($\text{C}_9\text{H}_{10}\text{N}_2\text{OS}$) C, H, N.

2-Chloro-4-methoxy-7-methylbenzothiazole (24). A solution of 9.91 g (0.144 mol) of sodium nitrite in 15 mL of H_2O was added over a 1.5-h period to a solution of 9.24 g (0.0476 mol) of **23** in 317 mL of 85% H_3PO_4 held at –10 to 0 °C. After being stirred an additional 30 min, the deep purple mixture was added over a 40-min period to a stirred solution of 47.6 g (0.191 mol) of $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ and 59.5 g (1.01 mol) of NaCl in 190 mL of water at –5 °C. After being stirred at –5 °C for 1 h, the solution was allowed to warm to room temperature and the resulting green suspension was extracted with three times with 100 mL of ether, and the organic extract was washed in turn with water, saturated NaHCO_3 , water, and brine, then dried over Na_2SO_4 , and concentrated under vacuum to give 9.26 g (91%) of **24**, which was used without further purification: ^1H NMR (CDCl_3) δ 2.41 (s, 3 H, CH_3), 4.00 (s, 3 H, OCH_3), 6.79–7.10 (dd, J = 9 Hz, 2 H, Ar H-5,6).

2,4-Dimethoxy-7-methylbenzothiazole (25). A suspension of **24** (5.83 g, 0.0273 mol) in a solution of 1.62 g (0.03 mol) of NaOCH_3 in 60 mL of MeOH was refluxed for 3.5 h and was then concentrated under vacuum. The residue was suspended in 25 mL of H_2O , the pH was adjusted to 4 with AcOH, and the mixture was extracted three times with 25 mL of Et_2O . The ethereal solution was washed in turn with saturated NaHCO_3 , water, and brine, then dried (Na_2SO_4), and concentrated under vacuum to give 5.00 g (88%) of **25** as a syrup. Kugelrohr distillation (120–130 °C, 0.3 mm) gave 4.51 g (79%) of material which crystallized: mp 63–64 °C; MS, m/e 210 ($\text{M} + \text{H}$)⁺; ^1H NMR (CDCl_3) δ 2.36 (s, 3 H, CH_3), 3.93 (s, 3 H, OCH_3), 4.20 (s, 3 H, Ar OCH_3), 6.72–6.94 (AB q, 2 H, Ar H-5,6); IR (Nujol) 1585, 1540, 1500, 1450, 1370, 1320, 1310, 1250, 1210, 1050, 1040, 980, 970, 880, 800, 790, 740, 660, 620, 610, 515 cm^{-1} .

2,4-Dimethoxybenzothiazole-7-acetonitrile (26). A stirred suspension of 4.45 g (0.0213 mol) of **25**, *N*-bromosuccinimide (3.75 g, 0.0213 mol), and 37 mg (0.15 mmol) of benzoyl peroxide in 300 mL of CCl_4 was irradiated with a 150-W tungsten lamp for 14 min. Filtration and concentration of the filtrate under vacuum gave a residue, which was dissolved in 20 mL of CH_2Cl_2 , 3.33 g (0.0213 mol) of tetraethylammonium cyanide was added, and the solution was refluxed for 30 min. Concentration of this solution under vacuum gave a solid, which was triturated with Et_2O , and the ether extract was concentrated to 1.55 g of a syrup. The remaining solid was shaken with a mixture of 50 mL of H_2O and 200 mL of Et_2O , and the ethereal phase was washed with H_2O and then brine. It was dried (Na_2SO_4) and then concentrated under vacuum to give 2.15 g of a syrup similar to that obtained above. Chromatography (Merck silica gel 60, 70–230 mesh, 120 g, eluted with CHCl_3) of 1.55 g of this syrup gave 0.80 g of **26**, mp 123–124 °C. Similar chromatography of 2.15 g of crude **26** gave 1.80 g of **26**: mp 127–129 °C (combined yield, 2.60 g, 52%); MS, m/e 235 ($\text{M} + \text{H}$)⁺, 208 ($\text{M} + \text{H} - \text{HCN}$)⁺; ^1H NMR (CDCl_3) δ 3.80 (s, 2 H, CH_2), 4.03 (s, 3 H, Ar OCH_3), 4.27 (s, 3 H, OCH_3),

6.85–7.21 (AB q, J = 9 Hz, 2 H, Ar H-5,6); IR (Nujol) 2220, 1595, 1580, 1500, 1460, 1420, 1400, 1385, 1335, 1280, 1255, 1245, 1230, 1210, 1190, 1180, 1030, 965, 795 cm^{-1} .

7-(2-Aminoethyl)-4-hydroxy-1,3-benzothiazol-2(3H)-one Hydrobromide (27). A solution of 2.00 g (8.54 mmol) of **26** in 30 mL of dry THF was slowly added to 20 mL (20 mmol) of 1 M borane in THF under a nitrogen atmosphere and the mixture was refluxed for 1 h. Methanol (15 mL) was added to the cooled reaction mixture, then HCl gas was added to achieve pH 1, and the solution was then refluxed on a steam bath until a white crystalline solid precipitated. The suspension was concentrated to about 20 mL by distillation and then was diluted with 60 mL of methanol to dissolve the solid. Further distillation gave 20 mL of a suspension, which was diluted with EtOAc and then was further concentrated on a steam bath to remove the MeOH. Filtration after the resulting suspension was stirred at ambient temperature for 18 h gave a solid, which was washed with EtOAc and then with Et_2O to give 2.07 g of a solid. Recrystallization from a MeOH-EtOAc mixture gave 1.88 g (80%) of 7-(2-aminoethyl)-4-methoxy-1,3-benzothiazol-2(3H)-one hydrochloride, mp 263–266 °C, soften 256 °C, which was used without further purification: ^1H NMR (CDCl_3 - $\text{Me}_2\text{SO}-d_6$) δ 2.99 (s, 4 H, CH_2CH_2), 3.91 (s, 3 H, OCH_3), 6.80–6.99 (AB q, J = 9 Hz, 2 H, Ar H-5,6); MS, m/e 225 ($\text{M} + \text{H}$)⁺, 208 ($\text{M} + \text{H} - \text{NH}_3$)⁺, 195 ($\text{M} + \text{H} - \text{CH}_2\text{NH}_2$)⁺.

A suspension of 1.65 g (6.33 mmol) of the above hydrochloride in 10 mL of 48% HBr was refluxed for 2.25 h and then cooled to ambient temperature. The resulting suspension was filtered, and the solid was washed with cold 48% HBr and then with ether to give 1.10 g (60%) of white crystals: mp 305–308 °C dec; 270-MHz ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.77 (t, 2 H, Ar CH_2 , J = 8 Hz), 2.98 (s, 2 H, CH_2NH_2), 6.74 (AB q, 1 H, Ar H-5, J = 8 Hz), 6.85 (AB q, 1 H, Ar H-6, J = 8 Hz), 7.84 (s, 2 H); IR (Nujol) 3210, 3110, 1635, 1585, 1510, 1470, 1430, 1370, 1360, 1300, 1210, 1180, 1110, 1090, 1030, 1000, 940, 930, 875, 835, 775, 730, 700, 650, 640, 610, 590, 500 cm^{-1} ; MS, m/e 211 ($\text{M} + \text{H}$)⁺, 194 ($\text{M} + \text{H} - \text{NH}_3$), 181 ($\text{M} + \text{H} - \text{CH}_2\text{NH}_2$)⁺. Anal. ($\text{C}_9\text{H}_{10}\text{N}_2\text{O}_2\text{S}\cdot\text{HBr}$) C, H, N.

2-(2-Hydroxy-3-nitrophenyl)-*N*-(trifluoroacetyl)ethylamine (29). Trifluoroacetic anhydride (141 g, 0.673 mol) was added cautiously (exothermic reaction) to a suspension of 46.1 g (0.147 mol) of 2-(2-hydroxyphenyl)ethylamine hydrobromide in 400 mL of ether. After being stirred for 1 h at ambient temperature, the clear solution was concentrated under reduced pressure, the residue was dissolved in 300 mL of MeOH, and this solution was concentrated by first distilling 200 mL on a steam bath and then removing the remaining solvent under vacuum to give 32.23 g (94%) of the *N*-trifluoroacetyl derivative as a syrup. This syrup (32.23 g, 0.142 mol) was dissolved in 427 mL of Et_2O and was added to a stirred solution of 12.11 g (0.142 mol) of NaNO_3 and 0.63 g (1.45 mmol) of $\text{La}(\text{NO}_3)_3\cdot 6\text{H}_2\text{O}$ in 228 mL of 6 N HCl.¹¹ After being stirred for 18 h at ambient temperature, the mixture was filtered and the solid was washed with Et_2O to give 13.59 g of a solid, which on TLC (SiO_2 , CHCl_3 -MeOH, 95:5) had R_f 0.6 in comparison to R_f 0.8 for the product remaining in the filtrate. The aqueous filtrate from the nitration reaction was extracted with the Et_2O washings of the above solid, and the organic layer was washed with water and then brine, dried (Na_2SO_4), and then concentrated under vacuum to give 24.3 g of a yellow-brown solid. This was suspended in 300 mL of Et_2O , stirred at ambient temperature for 1 h, and filtered to remove 4.0 g of a yellow solid, which by TLC was the same as the solid product obtained above. The filtrate was concentrated under vacuum to give 19.94 g of a brown solid, which was chromatographed (300 g of Merck silica gel 60, 70–230 mesh, eluted with 95:5 CHCl_3 -MeOH) to give 12.00 g (30%) of **29**: mp 119–121 °C. ^1H NMR (CDCl_3) δ 3.09 (t, J = 9 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{N}$), 3.67 (dd, J = 7 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{N}$), 6.59 (s, 1 H, NH), 6.95 (dd, J = 9 Hz, 1 H, Ar H-5), 7.44 (overlapping d, J = 9 Hz, 1 H, Ar H-6), 8.03 (overlapping d, J = 9 Hz, 1 H, Ar H-4); IR (mull) 3395, 3100, 1695, 1605, 1550, 1525, 1345, 1310, 1295, 1250, 1200, 1180, 1160, 1095, 1080, 1050, 1010, 930, 870, 845, 805, 740, 710, 620 cm^{-1} . Anal. ($\text{C}_{10}\text{H}_9\text{F}_3\text{N}_2\text{O}_4$) H, N; C: calcd, 43.18; found, 44.33.

O-[2-Nitro-6-[2-(trifluoroacetamido)ethyl]phenyl] *N,N*-Dimethylthiocarbamate (30). A 0.5 N NaOH solution (41 mL, 0.0205 mol) was added over a 1-h period to a stirred solution of **29** (5.56 g, 0.020 mol) in 50 mL of THF held between –10 and

0 °C. A solution of 2.59 g (0.0210 mol) of *N,N*-dimethylthiocarbamoyl chloride in 35 mL of THF was added over a 15-min period and the mixture was stirred an additional 45 min at -5 °C. The mixture was concentrated under vacuum and then extracted with 75 mL of ether, and this was washed in turn with water, 10% HCl, water, brine and then dried over Na₂SO₄. Concentration gave 7.36 g of a syrup, which crystallized on standing at ambient temperature. Trituration with light petroleum ether gave 6.81 g (93%) of **30**: mp 77–81 °C; ¹H NMR (CDCl₃) δ 2.97 (t, *J* = 8 Hz, 2 H, CH₂CH₂NH), 3.41 (s, 3 H, CH₃), 3.46 (s, 3 H, CH₃), 3.67 (dd, 2 H, CH₂CH₂NH), 6.80 (br s, 1 H, NH), 7.34 (overlapping d, *J* = 10 Hz, 1 H, Ar H-5), 7.50 (dd, *J* = 3 Hz, 1 H, Ar H-6), 8.00 (dd, *J* = 3 Hz, 1 H, Ar H-4); IR (mull) 3315, 3060, 1715, 1600, 1550, 1530, 1400, 1350, 1290, 1250, 1210, 1200, 1180, 1170, 1155, 1130, 855, 810, 800, 760, 750, 720, 680, 630 cm⁻¹.

S-[2-Nitro-6-[2-(trifluoroacetamido)ethyl]phenyl] *N,N*-Dimethylthiocarbamate (31). Neat **30** (5.80 g, 0.0159 mol) was heated at 205 °C for 0.5 h, cooled, and then mixed with 10 mL of Et₂O, and the solution was then diluted with light petroleum ether. The suspension was stirred for 15 min and the solid was collected to give 5.48 g (94%) of **31**: mp 137–139 °C; ¹H NMR (CDCl₃) δ 2.89–3.32 (br m, 8 H, CH₂CH₂NH, N(CH₃)₂), 7.40–7.67 (m, 3 H, Ar); IR (mull) 3310, 3040, 1720, 1660, 1550, 1530, 1450, 1370, 1360, 1255, 1200, 1260, 1100, 1060, 1005, 900, 860, 825, 800, 745, 740, 720, 690, 650 cm⁻¹.

S-[2-Amino-6-[2-(trifluoroacetamido)ethyl]phenyl] *N,N*-Dimethylthiocarbamate (32). A mixture of **31** (4.50 g, 0.0123 mol), 1.2 mL 12 N HCl, 1.50 g of 10% Pd-C, and 140 mL of EtOH was shaken under H₂ in a Parr apparatus for 15 min. The catalyst was removed by filtration and the filtrate was concentrated under vacuum to give 4.51 g of a light pink solid. Trituration with Et₂O gave 3.87 g (85%) of **32**: mp 142–144 °C; ¹H NMR (CDCl₃-Me₂SO-*d*₆) δ 2.90–3.30 (br m, 8 H, CH₂CH₂NH, N(CH₃)₂), 3.50 (br s, 2 H, CH₂CH₂NH), 6.90–7.40 (m, 3 H, Ar H); IR (Nujol) 3400, 3330, 2760, 2560, 2440, 1725, 1705 (m), 1650, 1550, 1520, 1250, 1210, 1185, 1140, 1105, 1055, 1020, 900, 880, 780, 720, 690 cm⁻¹.

7-[2-(Trifluoroacetamido)ethyl]-1,3-benzothiazol-2-(3H)-one (33). A solution of 3.65 g (0.0098 mol) of **32** in 120 mL of H₂O was heated on a steam bath for 2 h. Filtration of the cooled reaction mixture and washing of the solid with water gave 2.47 g (87%) of light tan crystals: mp 214–216 °C; IR (mull) 3250, 3060, 2560, 1730, 1708, 1650, 1550, 1520, 1185, 1140 cm⁻¹.

7-(2-Aminoethyl)-1,3-benzothiazol-2(3H)-one Hydrochloride (34). A solution of 2.00 g (0.00689 mol) of **33** in 40 mL of 1:1.6 N HCl-EtOH was refluxed on a steam bath for 8 h and then concentrated to about 15 mL by distillation. The resulting suspension was diluted with 50 mL of acetone and then filtered to give 1.14 g of light gray crystals, mp 303–305 °C dec. Concentration of the filtrate gave an additional 0.45 g of crystals, mp 298–300 °C dec. These were combined and recrystallized from a MeOH-EtOAc mixture to give 1.23 g of **34**: mp 303–305 °C dec; IR (mull) 1650, 1620, 1585, 1510, 1440 cm⁻¹; ¹H NMR (D₂O) δ 2.90 (m, 3 H, CH₂N), 3.30 (t, 2 H, Ar CH₂, *J* = 7 Hz), 7.0–7.4 (m, 3 H, Ar H-4,5,6). Anal. (C₉H₁₀N₂OS·HCl) C, H, N.

[3-[2-(Trifluoroacetamido)ethyl]-6-methoxyphenyl]thiourea (36). Sulfuric acid (36 N, 4.67 g, 0.0477 mol) was added over a 5-min period to a stirred solution of 25.0 g (0.0953 mol) of **35** in 70 mL of chlorobenzene at 40–60 °C. The initially formed gum turned gradually into a thick suspension, and then 10.28 g (0.126 mol) of pulverized NaSCN was added, and the mixture was heated at 110 °C for 6.5 h. After the mixture was allowed to stand at ambient temperature for 18 h, 150 mL of light petroleum ether was added, and the mixture was stirred vigorously for 0.5 h and then filtered. The solid was washed with petroleum ether and then suspended in 250 mL of water at 40–50 °C. After the mixture was stirred for 10 min, filtration gave 25 g of **36**. Recrystallization from a MeOH-H₂O mixture gave 20.62 g (84%) of **36**: mp 189–190 °C; MS, *m/e* 322 (M + H)⁺; IR (mull) 3425, 3300, 3190, 3095, 1705, 1680, 1627, 1610, 1560, 1513, 1482, 1360 cm⁻¹. Anal. (C₁₂H₁₄F₃N₃O₂S) C, H, N.

2-Amino-4-methoxy-7-[2-(trifluoroacetamido)ethyl]-benzothiazole (37). By a procedure similar to that used to obtain **23**, 15.60 g (0.0485 mol) of **36** and 16.53 g (0.103 mol) of Br₂ gave 18.07 g (93%) of **37** as the hydrobromide salt, mp 211–213 °C. This was dissolved in 250 mL of 0.5% aqueous HBr and then was

made basic with saturated NaHCO₃ to give 13.85 g (89%) of **37**: mp 227–231 °C; MS, *m/e* 320 (M + H)⁺; ¹H NMR (CDCl₃-Me₂SO-*d*₆) δ 2.83 (t, 2 H, Ar CH₂, *J* = 9 Hz), 3.11 (s, 2 H), 3.47 (q, 2 H, CH₂NH, *J* = 9 Hz), 3.90 (s, 3 H, OCH₃), 7.75 (m, 4 H, Ar H + 2 H), on D₂O exchange, as above but 3.47 (t, 2 H, CH₂NH, *J* = 9 Hz), 6.69 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 6.83 (AB q, 1 H, Ar H-6, *J* = 9 Hz); IR (mull) 3330, 3220, 3070, 1710, 1610, 1580, 1565, 1535, 1500, 1400, 1340, 1313, 1267 cm⁻¹. Anal. (C₁₂H₁₂F₃N₃O₂S) C, H, N.

2-Chloro-4-methoxy-7-[2-(trifluoroacetamido)ethyl]-benzothiazole (38). By a procedure similar to that used to prepare **24**, 14.00 g (0.0438 mol) of **37** in 288 mL of 85% H₃PO₄ and 9.12 g (0.132 mol) of NaNO₂ in 14 mL of H₂O gave the 2-diazonium salt, which on treatment with a solution of 109.5 g (1.87 mol) of NaCl and 87.6 g (0.351 mol) of CuSO₄·5H₂O in 380 mL of H₂O gave 14.36 g (97%) of crude **38**, mp 166–169 °C. Recrystallization from MeOH-H₂O gave 13.16 g (87%) of **38**: mp 171–172 °C; MS, *m/e* 339 (M + H)⁺; IR (mull) 3270, 3183, 1730, 1560, 1500, 1478, 1320, 1270, 1215 cm⁻¹; ¹H NMR (CDCl₃-Me₂SO-*d*₆) δ 2.78 (s, 1 H, NH), 3.00 (t, 2 H, Ar CH₂, *J* = 8 Hz), 3.61 (q, 2 H, CH₂NH, *J* = 7 Hz), 4.02 (s, 3 H, OCH₃), 6.89 (AB q, 1 H, Ar H-5, *J* = 8 Hz), 7.20 (AB q, 1 H, Ar H-6, *J* = 7 Hz). Anal. (C₁₂H₁₀ClF₃N₂O₂S) C, H, N.

2,4-Dimethoxy-7-(2-aminoethyl)benzothiazole (39). A suspension of 13.00 g (0.0384 mol) of **38** and sodium methoxide (prepared from 1.94 g (0.0843 g-atom) of Na) in 150 mL of MeOH was refluxed under argon for 4 h. Water (10 mL) was added and the reflux was continued for 16 h. The solvents were evaporated under vacuum, the residue was dissolved in H₂O, and the solution was brought to pH 5 with acetic acid and then made basic with 14 M NH₄OH. The mixture was extracted with CHCl₃, and the CHCl₃ was washed in turn with water and brine and then dried over Na₂SO₄. Concentration under vacuum gave 8.21 g (90%) of **39** as a syrup, which was used without further purification: MS, *m/e* 239 (M + H)⁺, 222 (M + H - NH₃)⁺, 209 (M - OCH₃)⁺; ¹H NMR (CDCl₃) δ 1.97 (s, 2 H, NH₂), 2.6–3.2 (m, 4 H, CH₂CH₂), 3.97 (s, 3 H, OCH₃), 4.21 (s, 3 H, OCH₃), 6.78 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 6.99 (AB q, 1 H, Ar H-6, *J* = 9 Hz); IR (film) 3360, 3290, 2995, 2930, 2830, 1685, 1592, 1580, 1540, 1498 cm⁻¹.

4-Hydroxy-7-[2-(*N*-methylamino)ethyl]-1,3-benzothiazol-2(3H)-one Hydrochloride (40). A suspension of 8.21 g (0.0345 mol) of **39** in 120 mL of ethyl formate was refluxed under argon for 5 h, the solvent was removed under vacuum, and the residue was stirred in 250 mL of Et₂O for 18 h. Filtration gave 5.86 g of a tan powder, which on chromatography (Merck silica gel 60, 230–400 mesh, 300 g, eluted with 97:3 CHCl₃-MeOH) gave 4.89 g of a solid. Recrystallization of this from a CHCl₃-petroleum ether mixture gave 4.30 g (47%) of the *N*-formyl derivative: mp 150–151 °C; MS, *m/e* 267.2 (M + H)⁺; ¹H NMR (CDCl₃-Me₂SO-*d*₆) δ 2.87 (t, 2 H, Ar CH₂, *J* = 7 Hz), 3.59 (q, 2 H, CH₂NH, *J* = 7 Hz), 3.97 (s, 3 H, OCH₃), 4.22 (s, 3 H, OCH₃), 6.81 (AB q, 1 H, Ar H-5, *J* = 7 Hz), 7.02 (AB q, 1 H, Ar H-6, *J* = 7 Hz), 8.11 (s, 1 H, NHCHO); IR (mull) 3280, 1645, 1597, 1580, 1533, 1499, 1425, 1390, 1250, 1045 cm⁻¹.

A solution of 1.46 g (0.0548 mol) of the *N*-formyl derivative in 10 mL of dry THF was added to a stirred solution of 1 M borane in THF (13.6 mL, 0.0136 mol) under argon. After 2.5 h of reflux, 20 mL of methanol was added to the cooled reaction mixture, and the reaction mixture was made strongly acidic with dry HCl and refluxed for 15 min. After concentration of the reaction mixture under vacuum, the residue was crystallized from a MeOH-EtOAc mixture to give 1.09 g (72%) of 2,4-dimethoxy-7-[2-(*N*-methylamino)ethyl]benzothiazole hydrochloride (**40a**): mp 244–247 °C; MS, *m/e* 239 (M + H)⁺; IR (mull) 3400, 3120, 2740, 2455, 1667, 1610, 1510, 1210, 1040 cm⁻¹. Anal. (C₁₁H₁₄N₂O₂S·HCl·1/4 H₂O) C, H, N.

A solution of 1.00 g (0.00304 mol) of **40a** in 7 mL of 48% HBr (distilled from SnCl₄·H₂O) was heated in an oil bath at 155 °C for 15 h. Chilling and filtration gave 0.98 g of **40**, which on recrystallization from a MeOH-EtOAc mixture gave 0.82 g (74%) of **40**: mp 298–300 °C; IR (mull) 3240, 2430, 1660, 1630, 1583, 1510, 1394, 1210, 658 cm⁻¹; MS, *m/e* 225 (M + H)⁺; ¹H NMR (Me₂SO-*d*₆) δ 2.59 (s, 3 H, NCH₃), 2.81 (t, 2 H, Ar CH₂, *J* = 8 Hz), 3.09 (s, 2 H, CH₂NH), 3.34 (s, 3 H, OCH₃), 6.75 (AB q, 1 H, Ar H-5, *J* = 8 Hz), 6.86 (AB q, 1 H, Ar H-6, *J* = 8 Hz). Anal. (C₁₀H₁₂N₂O₂S·HBr) C, H, N.

N-(Benzyloxy)-N¹-[2-methoxy-5-[2-(N,N-dipropylamino)ethyl]phenyl]urea (41). A mixture of 10.0 g (0.035 mol) of 11 in 100 mL of CHCl₃ and 10.40 g (0.105 mol) of phosgene in 80 mL of toluene was stirred for 18 h at ambient temperature. Concentration under vacuum gave 11.09 g of a tan solid, mp 118–120 °C. This was dissolved in a solution of *O*-benzylhydroxylamine (4.92 g, 0.040 mol) in CHCl₃ and was allowed to stand overnight at ambient temperature. Concentration under vacuum gave 17.4 g of 41 as a yellow oil, which was used without further purification. IR (film) 3400, 2970, 2940, 1690, 1600, 1540 cm⁻¹; ¹H NMR (CDCl₃) 0.92 (t, 6 H, CH₃CH₂, *J* = 7 Hz), 1.60–2.15 (m, 4 H, CH₃CH₂), 2.73–3.40 (m, 8 H, CH₂N and Ar CH₂), 3.85 (s, 3 H, OCH₃), 4.90 (s, 2 H, OCH₂C₆H₅), 6.70–7.05 (m, 2 H, Ar H-3,4), 7.30 (s, 1 H, Ar H-6), 7.40 (s, 5 H, CH₂C₆H₅), 7.85 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H).

3-(Benzyloxy)-7-methoxy-4-[2-(N,N-dipropylamino)ethyl]benzimidazol-2(3H)-one Acetate (42). A solution of unpurified 41 (17.4 g, 0.035 mol) in 100 mL of CHCl₃ at 0 °C was treated with a solution of 16.9 g (0.038 mol) of lead tetraacetate in 200 mL of CHCl₃ and then the mixture was stirred at ambient temperature for 1 h followed by reflux for 1.5 h. The inorganic solids were removed by filtration, the solids were washed with CHCl₃, and the combined filtrates were evaporated to dryness under vacuum. The residue was chromatographed with 400 g of silica gel, eluting with CHCl₃-MeOH mixtures. This gave 11.9 g of 42, which on recrystallization from a hexane-EtOAc mixture gave 5.42 g (30%) of 42: mp 92–95 °C; IR (mull) 1725 cm⁻¹; ¹H NMR (CDCl₃) δ 0.80 (t, 6 H, CH₃CH₂, *J* = 7 Hz), 1.20–1.80 (m, 4 H, CH₃CH₂), 2.05 (s, 3 H, CH₃COO), 2.52–2.80 (m, 4 H, CH₃CH₂CH₂N), 2.80–3.25 (m, 4 H, Ar CH₂CH₂N), 3.90 (s, 3 H, CH₃O), 5.22 (s, 2 H, C₆H₅CH₂O), 6.55 (AB q, 1 H, Ar H-6, *J* = 8 Hz), 6.88 (AB q, 1 H, Ar H-5, *J* = 8 Hz), 7.30–7.70 (m, 6 H, C₆H₅ and NH).

4-Hydroxy-7-[2-(N,N-dipropylamino)ethyl]benzimidazol-2(3H)-one Hydrobromide (5). A suspension of 5.0 g (0.011 mol) of 42 in 100 mL of 10% NaHCO₃ was extracted three times with 50 mL of CHCl₃. The organic extract was dried over Na₂SO₄ and concentrated under vacuum. The residue was dissolved in 250 mL of denatured EtOH, freshly activated Raney Ni was added, and the mixture was shaken under H₂ in a Parr apparatus at 50 °C for 18 h. The mixture was then filtered and the filtrate was concentrated under vacuum to give 3.1 g of a residue, which was crystallized from hexane to give 2.39 g (75%) of 4-methoxy-7-[2-(N,N-dipropylamino)ethyl]benzimidazol-2(3H)-one (5a): IR (mull) 3140, 1700, 1640, 1525 cm⁻¹; NMR (CDCl₃) δ 0.90 (t, 6 H, CH₃CH₂, *J* = 7 Hz), 1.5 (m, 4 H, CH₃CH₂), 2.43–3.02 (m, 8 H, CH₂N and Ar CH₂), 3.90 (s, 3 H, OCH₃), 6.42 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 6.70 (AB q, 1 H, Ar H-6, *J* = 9 Hz). A solution of 1.83 g (0.00629 mol) of 5a in 100 mL of CH₂Cl₂ at -30 °C was treated with 17.5 mL of 1 M BBr₃ in CHCl₃ (0.0175 mol) and then stirred at ambient temperature for 4 h. Workup as described for the preparation of 14 gave a solid, which was recrystallized from 2-propanol and then from denatured EtOH to give 1.94 g (86%) of 5: mp 240–242 °C. IR (mull) 3400, 3100, 2750, 2660, 1700, 1692, 1525 cm⁻¹; ¹H NMR (CDCl₃-Me₂SO-*d*₆) δ 1.00 (t, 6 H, CH₃CH₂, *J* = 6 Hz), 1.65–2.05 (m, 4 H, CH₃CH₂), 2.90–3.35 (m, 8 H, CH₂N and Ar CH₂), 6.40 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 6.62 (AB q, 1 H, Ar H-6, *J* = 9 Hz). Anal. (C₁₅H₂₃N₃O₂·HBr) C, H, N.

2-(2,4-Dimethoxyphenyl)ethylamine (44a). A solution of 83.0 g (0.50 mol) of 2,4-dimethoxybenzaldehyde, 94.5 g (1.55 mol) of nitromethane, and 38.5 g (0.50 mol) of ammonium acetate in 400 mL of glacial acetic acid was refluxed for 2 h and then poured into an ice-water mixture. This gave a solid, which was collected by filtration and recrystallized from EtOH to give 85.5 g (82%) of deep yellow crystals of 2-(2,4-dimethoxyphenyl)nitroethylene (44a): mp 102–104 °C; IR (mull) 1608, 1260 cm⁻¹; ¹H NMR (CDCl₃) δ 3.86 (s, 3 H, OCH₃), 3.90 (s, 3 H, OCH₃), 6.49 (s, 1 H, Ar H-3), 6.54 (dd, 1 H, *J* = 12, 1 Hz, Ar H-5), 7.40 (d, 1 H, *J* = 12 Hz, Ar H-6), 7.77 (AB q, 1 H, *J* = 12 Hz, C=CH-1), 8.10 (AB q, 1 H, *J* = 12 Hz, C=CH-2).

A solution of 88.0 g (0.421 mol) of 44a in 500 mL of THF was added slowly to a slurry of 29.7 g (0.782 mol) of LiAlH₄ in 400 mL of Et₂O under a N₂ atmosphere. After the addition was complete, the mixture was refluxed for 1.5 h and then 140 mL of 1 N NaOH was added and the mixture was filtered. The solid

was extracted with 200 mL of boiling THF. The THF extract and the filtrate were combined and concentrated under vacuum. The residue was dissolved in Et₂O, which was dried over K₂CO₃, and then concentrated to give 74.3 g of a brown oil. Distillation gave 41.95 g (55%) of 44a as a colorless oil: bp 100–110 °C (0.25 mm); IR (film) 2940, 1608, 1508, 1205 cm⁻¹.

2-(2,4-Dimethoxyphenyl)-N,N-dipropylethylamine (45). A mixture of 18.1 g (0.10 mol) of 44 and 39.0 g (0.30 mol) of propionic anhydride was heated on a steam bath for 1 h. The mixture was then dissolved in 200 mL of CHCl₃ and washed in turn with 200 mL of 10% NaOH, water, and brine and then was dried over Na₂SO₄. Concentration under vacuum and recrystallization of the residue from hexane-ethyl acetate gave 11.60 g (49%) of 45a, the propionyl amide of 44; mp 71–73 °C; IR (mull) 3310, 1640 cm⁻¹.

A solution of 11.6 g (0.049 mol) of 45a in 50 mL of THF under argon was treated dropwise with 98 mL (0.098 mol) of 1 M borane in THF. After 1 h of reflux and storage at ambient temperature for 18 h, 100 mL of 10% HCl was added and the THF was removed under vacuum. The aqueous residue was extracted with CHCl₃, and the extract was washed with brine, dried over Na₂SO₄, and concentrated. Recrystallization of the residue from 75 mL of 2-propanol gave 10.85 g (85%) of 2-(2,4-dimethoxyphenyl)-N-propylethylamine hydrochloride (45b): mp 138–139 °C dec; IR (mull) 1620, 1590, 1520, 1380, 1210 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (t, 3 H, CH₂CH₃, *J* = 10 Hz), 1.97 (m, 2 H, CH₂CH₃), 2.95 (m, 2 H, CH₃CH₂CH₂NH), 3.18 (s, 4 H, Ar CH₂CH₂N), 3.80 (s, 6 H, OCH₃), 6.38 (m, 1 H, Ar H-5), 6.40 (s, 1 H, Ar H-3), 7.10 (AB q, 1 H, Ar H-6, *J* = 9 Hz).

Reaction of 10.85 g of 45b with propionic anhydride as described above gave 10.88 g (93%) of 45c, the propionyl amide of 45b, as a colorless oil: IR (film) 2960, 2940, 2880, 2840, 1645, 1616, 1590, 1510 cm⁻¹. Reduction of 45c with borane as described above gave 8.1 g (78%) of 45 as a pale yellow oil: IR (film) 2960, 2930, 2870, 2835, 2800, 1615, 1592, 1505, 1155 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (t, 6 H, CH₃CH₂, *J* = 7 Hz), 1.49 (m, 4 H, CH₃CH₂), 2.42 (m, 4 H, NCH₂CH₂CH₃), 2.60 (s, 4 H, Ar CH₂CH₂N), 3.78 (s, 6 H, CH₃O), 6.34 (m, 1 H, Ar H-5), 6.41 (s, 1 H, Ar H-3), 7.0 (AB q, 1 H, Ar H-6, *J* = 9 Hz).

2,6-Dimethoxy-3-[2-(N,N-dipropylamino)ethyl]benzoic Acid Hydrochloride (46). *sec*-Butyllithium (100 mL of 1.4 M in cyclohexane, 0.140 mol) was added dropwise to a solution of 19.5 g (0.0736 mol) of 45 in 200 mL of ether under argon. After 2 h dry CO₂ was passed through the reaction mixture and the mixture was allowed to stand at ambient temperature for 20 h. The reaction mixture was diluted with 200 mL of ether and then extracted twice with 250 mL of water. The aqueous extract was brought to pH 7 with 12 N HCl and extracted with ether. The aqueous layer was then brought to pH 1 and extracted with CHCl₃, and the CHCl₃ extract was dried over Na₂SO₄ and then concentrated under vacuum. The residue was recrystallized from a CH₃CN-Et₂O mixture to give 8.99 g (35%) of 46 as a yellow solid: mp 176–178 °C; IR (mull) 2660, 1720, 1600, 1095 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00 (t, 6 H, CH₃CH₂, *J* = 6 Hz), 1.84 (br m, 4 H, CH₃CH₂), 3.00 (m, 4 H, CH₃CH₂CH₂N), 3.18 (s, 4 H, Ar CH₂CH₂N), 3.75 (s, 3 H, OCH₃), 3.87 (s, 3 H, OCH₃), 6.60 (AB q, 1 H, Ar H-5, *J* = 9 Hz), 7.20 (AB q, 1 H, Ar H-4, *J* = 9 Hz). Anal. (C₁₇H₂₇NO₄·HCl) C, H, N.

2,6-Dimethoxy-3-[2-(N,N-dipropylamino)ethyl]aniline (47). A mixture of 23.25 g (0.0673 mol) of 46 and 100 mL (1.37 mol) of SOCl₂ was refluxed for 2 h, and the volatiles were removed under vacuum. Toluene (150 mL) was added to the residue and then removed under vacuum three times. The residue (the acid chloride of 46 (IR (neat) 1790 cm⁻¹) was dissolved in 150 mL of acetone and held at 0–5 °C while a solution of 8.99 g (0.138 mol) of NaN₃ in 45 mL of H₂O was added. The mixture was stirred for 1 h, then diluted with 400 mL H₂O, and then extracted with CHCl₃. The CHCl₃ extract was dried over Na₂SO₄ and was concentrated at 30 °C under vacuum. The residue (acid azide, IR 2140, 2020 cm⁻¹) was dissolved in 35 mL of CH₂Cl₂ and added dropwise to refluxing toluene, and the solution was then refluxed for 1 h. The reaction mixture was concentrated under vacuum and the residue (isocyanate, IR 2140 cm⁻¹) was heated on a steam bath with 150 mL of 10% aqueous HCl for 1 h. The reaction mixture was brought to pH 12 with 40% aqueous NaOH and then extracted with CHCl₃, and the extracts were dried over Na₂SO₄.

and then concentrated under oil pump vacuum to give 13.48 g (71%) of **47** as an oil: IR (film) 2960, 2940, 2870, 2840, 2800, 1610, 1500, 1470, 1200, 1075 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.90 (t, 6 H, CH_3CH_2 , $J = 7$ Hz), 1.42 (m, 4 H, CH_3CH_2), 2.50 (m, 4 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{N}$), 2.75 (s, 4 H, Ar $\text{CH}_2\text{CH}_2\text{N}$), 3.76 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 6.50 (s, 2 H, Ar H).

2-Hydroxy-6-methoxy-3-[2-(*N,N*-dipropylamino)ethyl]-aniline (48). Sodium hydride (0.66 g of 50% in mineral oil, 0.0138 mol) was added to a solution of 1.94 g (6.93 mmol) of **47** and 0.86 g (0.0138 mol) of ethyl mercaptan in 20 mL of dry DMF. The mixture was stirred for 20 min at ambient temperature, and then it was refluxed for 1 h and poured into 30 mL of water. The pH was brought to 3 with 6 N HCl and the mixture was extracted with pentane. The pH was brought to 7 with NaHCO_3 , saturated with NaCl, and extracted with CHCl_3 . The organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was chromatographed (60 g of SiO_2 , eluting with 1–10% MeOH in CHCl_3) to give 0.87 g of **48** as an oil: ^1H NMR (CDCl_3) δ 0.90 (t, 6 H, CH_3CH_2 , $J = 6$ Hz), 1.48 (m, 4 H, CH_3CH_2), 2.60 (m, 4 H, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 2.76 (s, 4 H, Ar $\text{CH}_2\text{CH}_2\text{N}$), 3.83 (s, 3 H, CH_3O), 6.30 (AB q, 1 H, Ar H-6, $J = 7$ Hz), 6.75 (AB q, 1 H, Ar H-5, $J = 7$ Hz). In a NOE difference experiment using a 360-MHz Bruker WM 360 spectrometer, irradiation at 3.83 ppm for 3 s gave enhancement of the doublet at 6.61 ppm and did not enhance the singlet at 2.76 ppm.

4-Hydroxy-7-[2-(*N,N*-dipropylamino)ethyl]-1,3-benzoxazol-2(3*H*)-one Hydrobromide (6). A solution of 12.5% phosgene in toluene (9.58 g, 0.0116 mol) was added to a solution of 2.15 g (0.0081 mol) of **48** in 40 mL of toluene and the mixture was stirred at ambient temperature for 45 min and then was refluxed for 1 h. After concentration under vacuum, the residue was chromatographed (60 g of SiO_2 , eluting with 1–10% MeOH in CHCl_3) to give 0.71 g (30%) of 4-methoxy-7-[2-(*N,N*-dipropylamino)ethyl]-1,3-benzoxazol-2(3*H*)-one hydrochloride (**6a**): ^1H NMR (CDCl_3) δ 0.95 (t, 6 H, CH_3CH_2 , $J = 7$ Hz), 1.77 (m, 4 H, CH_3CH_2), 2.72 (m, 4 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{N}$), 3.02 (s, 4 H, Ar $\text{CH}_2\text{CH}_2\text{N}$), 3.87 (s, 3 H, CH_3O), 6.60 (AB q, 1 H, Ar H-5, $J = 7$ Hz), 6.88 (AB q, 1 H, Ar H-6, $J = 7$ Hz). A 1 M solution of BBr_3 in CH_2Cl_2 (14.64 mL, 0.0146 mol) was added to a solution of 1.2 g (0.0030 mol) of **6a** in 60 mL of CH_2Cl_2 at -30°C under a N_2 atmosphere. The reaction mixture was then stirred at ambient temperature for 20 h, the solvents were removed under vacuum, and the residue was treated five times with 30 mL of MeOH, with evaporation of the solvent under vacuum each time. The residue was recrystallized from an EtOH–Et₂O mixture to give 0.98 g (90%) of **6**: mp $220\text{--}222^\circ\text{C}$; IR (mull) 3300, 3160, 1820 (m), 1780, 1650, 1240, 915 cm^{-1} ; ^1H NMR (CDCl_3 – $\text{Me}_2\text{SO}-d_6$) δ 1.00 (t, 6 H, CH_3CH_2 , $J = 7$ Hz), 1.85 (m, 4 H, CH_3CH_2), 2.95–3.45 (m, 8 H, CH_2), 6.61 (AB q, 1 H, Ar H-5, $J = 9$ Hz), 6.81 (AB q, 1 H, Ar H-6, $J = 9$ Hz); MS, m/e 279 ($\text{M} + \text{H}$)⁺, 114 [$(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{N}=\text{CH}_2$]⁺. Anal. ($\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3\cdot\text{HBr}$) C, H, N.

2-[3-[(Hydroximinomethyl)amino]-4-methoxyphenyl]-*N,N*-dipropylethylamine Hydrochloride (49). To a solution of 40.0 g (0.14 mol) of **11** and 17.7 g (0.180 mol) of H_2SO_4 in 55 mL of water were added 24 g (0.144 mol) of chloral hydrate, 72 g (0.439 mol) of hydroxylamine sulfate, and 200 mL of H_2O . The mixture was rapidly brought to reflux and was held at reflux for 20 min before it was cooled to ambient temperature. The pH was adjusted to 8 with NaHCO_3 , the mixture was extracted with CHCl_3 , and the CHCl_3 was dried over Na_2SO_4 and then was concentrated under vacuum. The residue was dissolved in CHCl_3 and the solution was made acidic with ethereal HCl. Filtration followed by recrystallization from *i*-PrOH gave 29.8 g (60%) of tan crystals: mp $197\text{--}199^\circ\text{C}$; IR (mull) 3380, 2600, 2540, 2480, 1690, 1600, 1550; ^1H NMR (CDCl_3 – $\text{Me}_2\text{SO}-d_6$) δ 1.00 (t, 6 H, CH_3CH_2 , $J = 7$ Hz), 1.85 (m, 4 H, CH_3CH_2), 3.10 (m, 4 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{N}$), 3.18 (s, 4 H, Ar $\text{CH}_2\text{CH}_2\text{N}$), 3.90 (s, 3 H, OCH_3), 6.85 (AB q, 1 H, Ar H-5, $J = 8$ Hz), 6.90 (s, 1 H, Ar H-2), 7.00 (AB q, Ar H-6, $J = 8$ Hz).

7-Methoxy-4-[2-(*N,N*-dipropylamino)ethyl]isatin (50). A 90-mL stirred sample of 36 N H_2SO_4 was heated to 80°C and 14.9 g (0.0418 mol) of **49** was added rapidly, and the heating was continued for 16 min after dissolution. The hot solution was then poured onto 500 g of ice, and the resulting solution was brought to pH 8 with NaHCO_3 and after addition of 400 mL of H_2O was extracted four times with 200 mL of CHCl_3 . The combined CHCl_3

extracts were washed with H_2O , then dried over Na_2SO_4 , and concentrated under vacuum. The residue was extracted repeatedly with boiling Et₂O until no more crimson color was extracted, and the ether was filtered and then concentrated to give 7.35 g (58%) of **50** as a brilliant red solid: mp $167\text{--}170^\circ\text{C}$; IR (mull) 1740, 1730, 1630, 1600, 1380 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.90 (t, 6 H, CH_3CH_2 , $J = 7$ Hz), 1.46 (m, 4 H, CH_3CH_2), 2.50 (t, 4 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{N}$, $J = 7$ Hz), 2.68 (t, 2 H, Ar $\text{CH}_2\text{CH}_2\text{N}$, $J = 5$ Hz), 3.00 (t, 2 H, Ar CH_2 , $J = 5$ Hz), 3.88 (s, 3 H, OCH_3), 6.85 (AB q, 1 H, Ar H-6, $J = 6$ Hz), 7.00 (AB q, 1 H, Ar H-5, $J = 6$ Hz).

7-Hydroxy-4-[2-(*N,N*-dipropylamino)ethyl]isatin Hydrobromide (51). A solution of 0.50 g (0.0017 mol) of **50** in 2 mL of 48% HBr was held at 120°C for 7 h. Chilling gave a crystalline solid, which was collected by filtration and washed with ice water to give 0.35 g (52%) of **51**: mp $257\text{--}258^\circ\text{C}$ dec; IR (mull) 2650 (br), 1735, 1640, 1605, 1520, 1380 cm^{-1} ; ^1H NMR (CDCl_3 – $\text{Me}_2\text{SO}-d_6$) δ 1.02 (t, 6 H, CH_3CH_2 , $J = 7$ Hz), 1.90 (m, 4 H, CH_3CH_2), 2.95–3.40 (m, 8 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{N}$ and Ar $\text{CH}_2\text{CH}_2\text{N}$), 6.80 (AB q, 1 H, Ar H-6, $J = 8$ Hz), 7.08 (AB q, 1 H, Ar H-5, $J = 8$ Hz). Anal. ($\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3\cdot\text{HBr}\cdot\text{H}_2\text{O}$) C, H, N.

In Vitro Biological Methods. Relaxation of the electrically stimulated rabbit ear artery was carried out as previously described.⁶ [^3H]Spiroperidol and [^3H]fenoldopam binding studies as well as stimulation of dopamine sensitive adenylate cyclase were also carried out as previously described,²⁴ and the drugs used and their sources were also as previously described.²⁴

In Vivo Biological Methods. Anesthetized Dog. Mongrel dogs of either sex (8–15 kg) were α -blocked with 5.0 mg/kg of phenoxybenzamine intravenously 18 prior to the experiment. The dogs were anesthetized with sodium pentobarbital and prepared for direct blood pressure (BP) determination by cannulation of the left carotid artery and for renal blood flow determination by implantation of a Carolina electromagnetic flow probe on the left renal artery. RBF was monitored on a Carolina Medical Products Model 501 flow meter, and all parameters were continuously recorded on a Gould Model 200 polygraph. Mean arterial blood pressure (MABP) was calculated as 1/3 pulse pressure plus diastolic pressure. Renal vascular resistance (RVR) was calculated as MABP/RBF.

The dogs were allowed a minimum of 30 min post surgical intervention for stabilization. A continuous iv infusion was then started. Control dogs received 1.11 mL/min of 0.9% saline, and test dogs received $0.5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ of SK&F R-83566-C, to establish dopamine DA-1 blockade, or $0.5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ of domperidone, to establish dopamine DA-2 blockade. A minimum of 30 min later, the dogs received 27 iv at doses of 1, 3, 10, and 30 $\mu\text{g/kg}$.

Conscious Dogs. Female dogs (11.6–13.5 kg) were surgically prepared for measurement of arterial BP by placement of a Vascular-Access-Port (VAP) in the abdominal aorta²⁵ and for measurement of RBF by placement of a 4-mm Transonics flow probe on the left renal artery. The dogs were allowed a minimum of 2 weeks for recovery following surgery prior to drug testing. The dogs were fasted for 18 h prior to drug evaluation. On the test day the renal flow probe was connected to a Transonics T101 flow meter, and the VAP was punctured by a needle connected to a Statham P23 ID transducer. Blood pressure and RBF were continuously recorded on a Grass 200 polygraph. Renal vascular resistance was calculated as MABP/RBF. The dogs were allowed 30 min to stabilize and 27 was given iv at 0.03, 0.1, 0.3, 1.0, and 3.0 $\mu\text{g/kg}$.

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(24) Flaim, K. E.; Gessner, G. W.; Crooke, S. T.; Sarau, H. M.; Weinstock, J. *Life Sci.* **1985**, *36*, 1427.

(25) Mann, W. A.; Landi, M. F.; Horner, E.; Woodward, P.; Campbell, S.; Kinter, L. B. *Lab. Anim. Sci.* **1987**, *37*, 105.