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-Phe[1] and Cys[7] might change the orientation of D-Phe[1] and Thr[8] 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 conditions[10] or perhaps alkylated and thus offers a reactive center for producing further interesting conformational effects on peptide backbones.

Acknowledgment. We thank E. Yauger, L. Mutty, and V. Mackey for their excellent technical assistance. This research was supported by NIH Grant DK-18370-13 (to D.H.C.).

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-[CH_2NH]Cys(MeBzl)-OH, 108104-80-9; BOC-Cys(MeBzl)-[CH_2NH]Tyr-OH, 108104-81-0; BOC-Tyr[CH_2NH]D-Trp-OH, 108104-82-1; BOC-D-Trp[CH_2NH]Lys(Z)-OH, 108104-83-2; BOC-Lys(Z)[CH_2NH]Val-OH, 108104-84-3; BOC-Val[CH_2NH]-Cys(MeBzl)-OH, 108104-85-4; BOC-Cys(MeBzl)[CH_2NH]Thr-OH, 108104-86-5; H-Phe[CH_2NH]Cys-OH, 108104-87-6; H-Cys-[CH_2NH]Tyr-OH, 108104-88-7; H-Cys(SO_3H)[CH_2NH]Tyr-OH, 108104-89-8; H-Tyr[CH_2NH]D-Trp-OH, 108104-90-1; H-D-Trp-[CH_2NH]Lys-OH, 108104-91-2; H-Lys[CH_2NH]Val-OH, 108104-92-3; H-Val[CH_2NH]Cys-OH, 108104-93-4; H-Cys-[CH_2NH]Thr-OH, 108104-94-5; BOC-Val-CHO, 79069-51-5.

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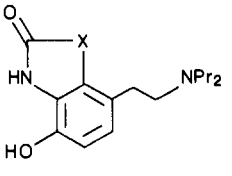
Synthesis and Evaluation of Non-Catechol D-1 and D-2 Dopamine Receptor Agonists: Benzimidazol-2-one, Benzoxazol-2-one, and the Highly Potent Benzothiazol-2-one 7-Ethylamines

Joseph Weinstock,*† Dimitri E. Gaitanopoulos,† Orum D. Stringer,† Robert G. Franz,† J. Paul Hieble,‡ Lewis B. Kinter,‡ William A. Mann,‡ Kathryn E. Flaim,§ and George Gessner§

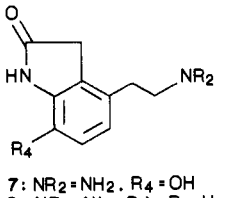
Departments of Medicinal Chemistry, Pharmacology, and Molecular Pharmacology, Research and Development Division, Smith Kline & French Laboratories, Swedeland, Pennsylvania 19479. *Received November 26, 1986*

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 (ED_{50} = 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 (DA_2)[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 (EC_{50} = 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** was inactive. This suggested that an acidic hydrogen on the 3-position of the oxindole might be required for dop-



1: X = CH_2
2: X = $CHCH_3$
3: X = $C(CH_3)_2$
4: X = S
5: X = NH
6: X = O



7: NR_2 = NH_2, R_4 = OH
8: NR_2 = N(*n*-Pr)$_2$, R_4 = H

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.
§ Department of Molecular Pharmacology.

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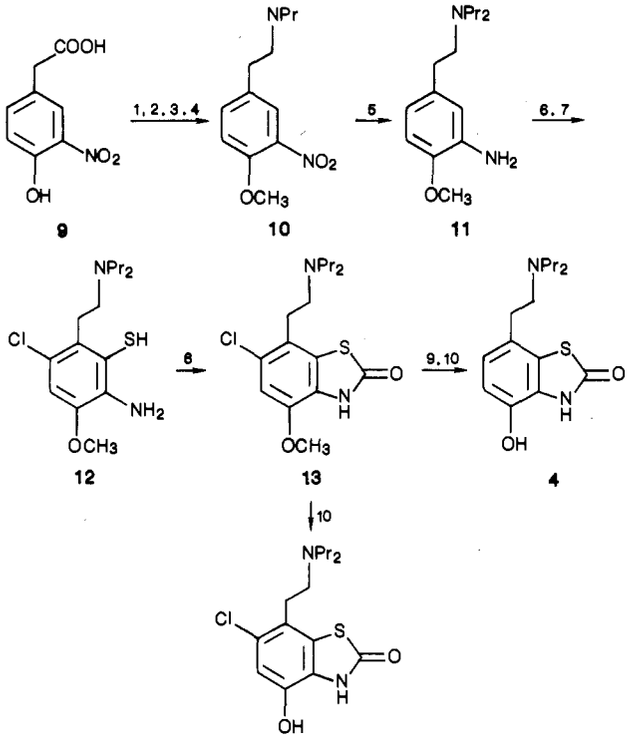
Scheme I[a]



[a] 1, $SOCl_2$; 2, $NH(CH_2CH_2CH_3)_2$; 3, K_2CO_3–$(CH_3)_2SO_4$; 4, B_2H_6; 5, H_2, Pt; 6, S_2Cl_2; 7, $Na_2S_2O_4$; 8, $COCl_2$; 9, Na, $C_5H_{11}OH$; 10, BBr_3.

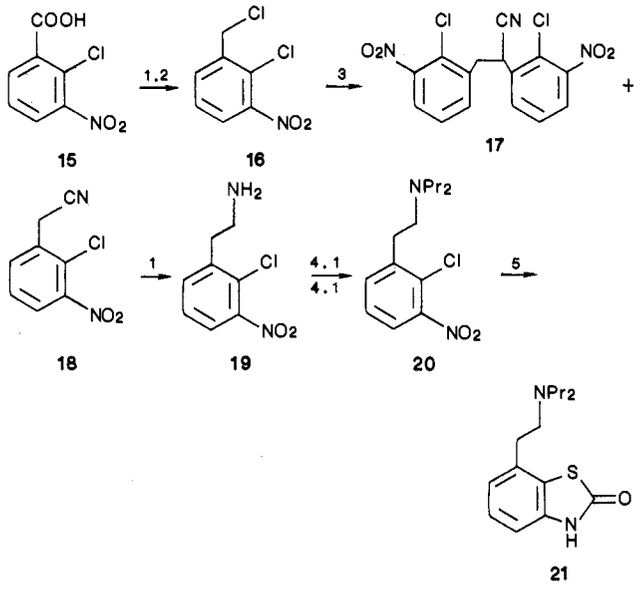
amine agonist activity. Another possibility was that the loss in activity on 3-methylation of **1** was due to a steric effect either in altering side-chain conformation or directly hindering receptor binding.

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 (DA_1) 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 (DA_1) potency.

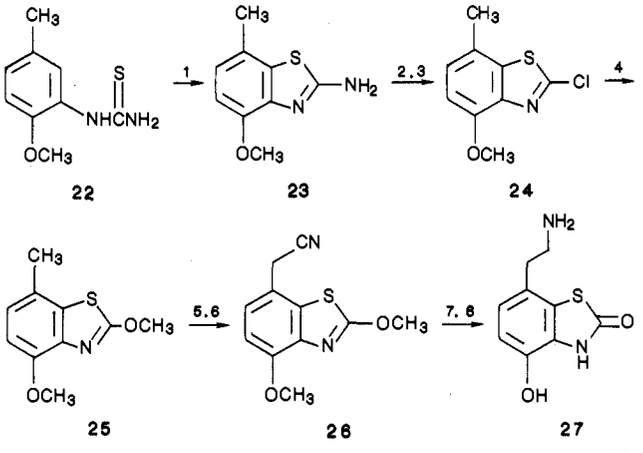
Since **8**, the des-7-hydroxy analogue of **1**, was active as a DA_2 agonist, we have also studied the corresponding analogue in the benzothiazolone series.

Scheme II[a]



[a] 1, B_2H_6; 2, $SOCl_2$, pyridine; 3, NaCN, $Bu_4N^+Br^-$, $CHCl_3$, H_2O; 4, CH_3CH_2COCl, K_2CO_3; 5, CO, S, Et_3N.

Scheme III[a]



[a] 1, Br_2; 2, H_3PO_4, $NaNO_2$; 3, NaCl, $CuSO_4$; 4, $NaOCH_3$; 5, NBS, $(C_6H_5COO)_2$, *hν*; 6, $Et_4N^+CN^-$; 7, B_2H_6; 8, 48% HBr.

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 reaction[7] 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 phenylacetonitrile **18**. Under standard conditions the major product was **17**, which arises from alkylation of **18** with **16**. However, under phase-transfer conditions[8] 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 dopmaine receptor subtypes that are differentiated by stimulation or lack of stimulation of dopamine sensitive adenylate cyclase,[2] respectively. DA_1 and DA_2 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.

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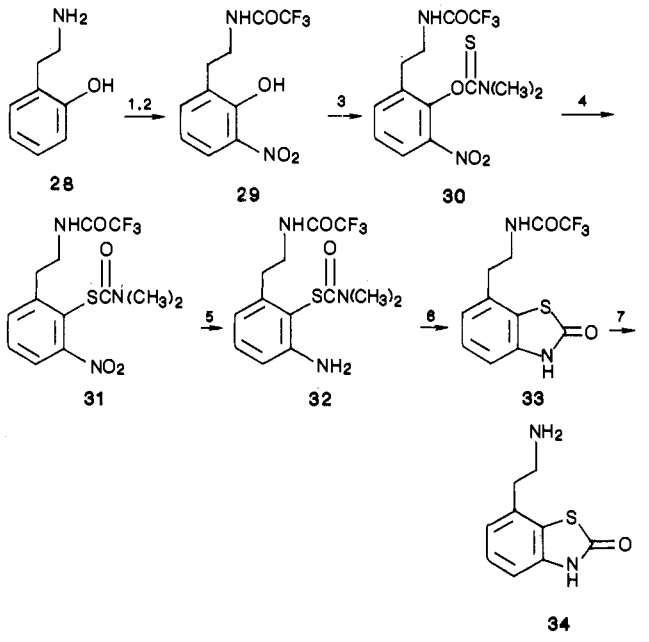
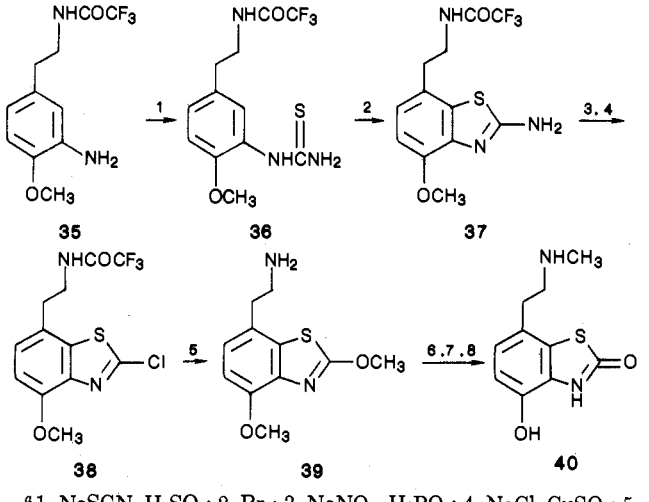
Scheme IV[a]



[a] 1, $(CF_3CO)_2O$; 2, $NaNO_3$, $La(NO_3)_3$, 6 N HCl; 3, $(CH_3)_2NCSCl$, NaOH; 4, 205 °C; 5, H_2, 10% Pd on C; 6, H_2O, 100 °C; 7, HCl, EtOH, H_2O.

Scheme V[a]

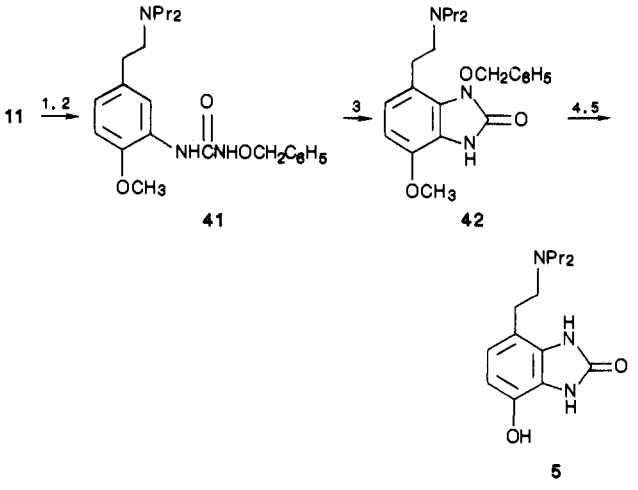


[a] 1, NaSCN, H_2SO_4; 2, Br_2; 3, $NaNO_2$, H_3PO_4; 4, NaCl, $CuSO_4$; 5, $NaOCH_3$, CH_3OH; 6, $HCOOC_2H_5$; 7, B_2H_6; 8, 48% HBr.

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**.

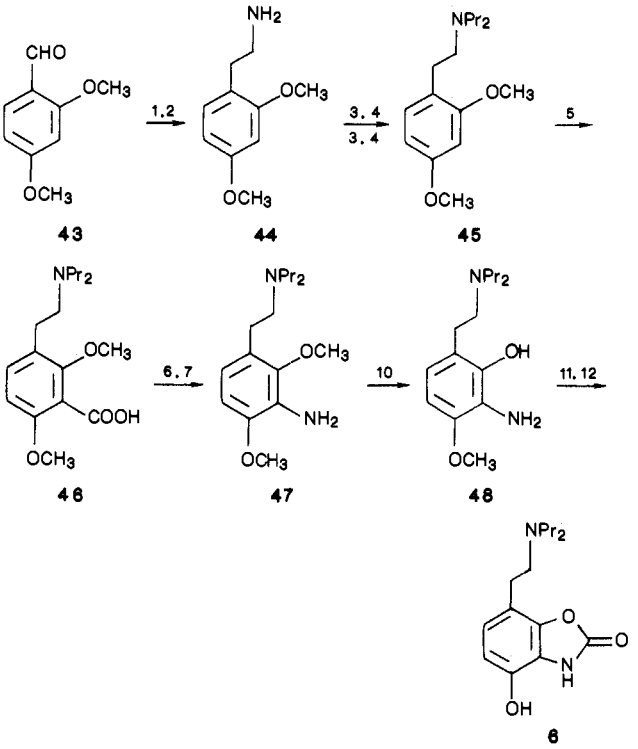
The synthesis of the deshydroxy primary amine **34** is shown in Scheme IV. The phenol **28** underwent selective ortho nitration in a lanthanum-catalyzed reaction.[11] The *o*-nitrophenol **29** was converted to the *S*-aryl thiocarbamate **31** by the Newman rearrangement.[12] Catalytic hydrogenation 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, $C_6H_5CH_2ONH_2$; 3, $Pb(OAc)_4$; 4, H_2, Raney Ni; 5, BBr_3.

Scheme VII[a]



[a] 1, CH_3NO_2; 2, $LiAlH_4$; 3, CH_3CH_2COCl; 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**.

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(11) Ouertani, M.; Girard, P.; Kagan, H. B. *Tetrahedron Lett.* **1982**, 4315.
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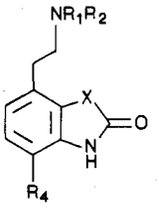
(14) Cooley, J. H.; Jacobs, P. T. *J. Org. Chem.* **1975**, *40*, 522.

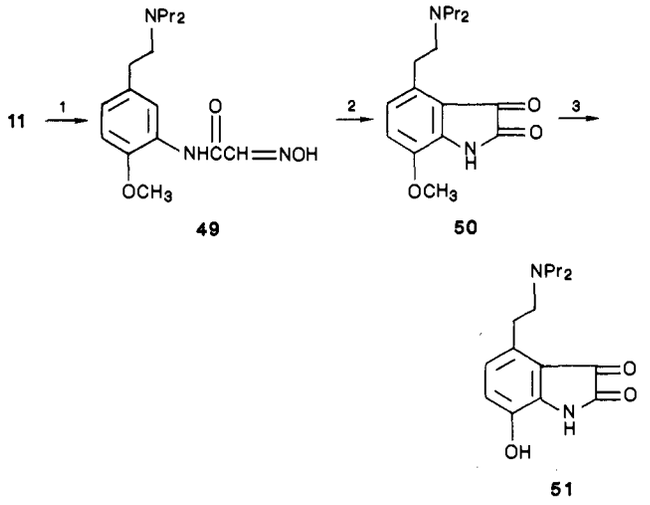
Table I. Dopaminergic Activity of 3-Heterooxindoles and Standard Compounds



no.	X	NR_1R_2	R_4	REA:[a] EC_{50}, nM (*n*)	[^{3}H]spiroperidol:[b] IC_{50}, nM (*n*)	[^{3}H]fenoldopam:[c] K_{bind}, nM (*n*)	adenylate cyclase:[c] EC_{50}, nM (*n*)
4	S	$N(n\text{-}Pr)_2$	OH	0.028 (12)	49 ± 11 (3)[d]	516 ± 82 (4)	NS[f]
14	S	$N(n\text{-}Pr)_2$	OH(6-Cl)	50			
21	S	$N(n\text{-}Pr)_2$	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	$N(n\text{-}Pr)_2$	OH	9 (3)	1000 (2)	2420 ± 190 (3)	
6	O	$N(n\text{-}Pr)_2$	OH	8 (1)	1200 (2)	6330 ± 170 (3)	
51	C=O	$N(n\text{-}Pr)_2$	OH	7	560	10000	NS[f]
1	CH_2	$N(n\text{-}Pr)_2$	OH	1.8 ± 0.3 (10)	530 ± 190[e]		20000
8	CH_2	$N(n\text{-}Pr)_2$	H	100 ± 26 (5)	6810 (2)		
7	CH_2	NH_2	OH	116 ± 43 (8)	4850 (2)	700 (1)	4650[h]
N,N-dipropyldopamine				80 ± 17 (13)			12500
dopamine				76 ± 6 (38)	4700	150 ± 25	3500
fenoldopam				1200	1580	3 ± 1	57

[a] Relaxation of the electrically stimulated rabbit ear artery. [b] Bovine pituitary. [c] Rat caudate. [d] K_{high} = 3.6 ± 1.2 nM, K_{low} = 202 ± 59 nM (*n* = 3). [e] K_{high} = 10 nM, K_{low} = 1050 nM. [f] Not significant. [g] Partial agonist, maximum effect 60% of dopamine maximum effect. [h] Partial agonist, maximum effect 59% of dopamine maximum effect.

Scheme VIII[a]



[a] 1, CCl_3CHO, H_2NOH; 2, H_2SO_4; 3, HBr or BBr_3.

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 synthesis[6] 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 [^{3}H]fenoldopam from homogenized rat striatum and the affinity for D-2 receptors by their ability to displace [^{3}H]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]

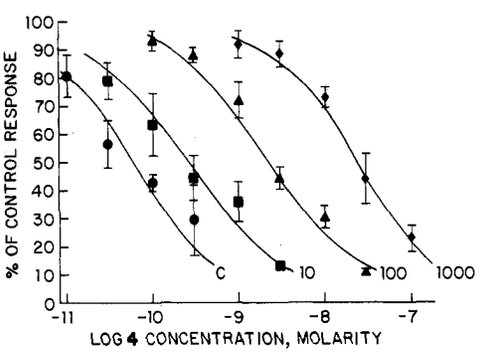


Figure 1. Neuroinhibitory effect of 4 in the isolated perfused rabbit ear artery and the blockade of this effect by (*S*)-sulpiride. Each point represents the mean ± SEM of at least four experiments. Sulpiride concentration in nM denoted adjacent to each curve.

The in vitro dopaminergic test results are shown in Table I. The benzothiazolone **4**, in which the 3-CH_2 of **1** has been replaced by sulfur, is 65 times as potent as **1** as a DA_2 agonist in the rabbit ear artery test and 11 times as potent as **1** in inhibiting [^{3}H]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

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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 [^{3}H]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*-dipropyldopamine to *N,N*-dipropyl-*m*-tyramine.[17] A similar change in the benzothiazolone series gave **21**, which is 1000 times less potent that **4** in the rabbit ear artery, but only 20 times less potent than **4** in the [^{3}H]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 [^{3}H]spiroperidol binding DA_2 and D-2 assays and more than 10 times as potent as dopamine in both the [^{3}H]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 μg/kg, but this was accompanied by emesis, presumably due to D_2 activity. In anesthetized α-blocked dogs (phenoxybenzamine pretreated) intravenous infusion of **27** at doses of 3–30 μg/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 DA_1 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 DA_2 receptor activity.

The benzothiazolone epinine analogue **40** was active in the D_2 rabbit ear artery test and the D-1 [^{3}H]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 DA_2 activity in both the rabbit ear artery and [^{3}H]spiroperidol binding assays with potencies similar to that of **1**. They showed only very weak D-1 activity in the [^{3}H]fenoldopam binding assay and thus appear to be potent selective D-2 (DA_2) agonists.

Discussion

The most striking observation of this work was that **4** is 64 times more potent than **1** as a DA_2 agonist in the rabbit ear artery test. Compound **1** is to our knowledge the most potent DA_2 agonist previously reported.[6] The related compounds with the sulfur of **4** replaced by oxygen (**6**), nitrogen (**5**), and carbonyl (**51**) are essentially equivalent 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 [^{3}H]spiroperidol binding. However, previous work[16] has suggested that as run by our procedures rabbit ear artery data may reflect high affinity binding while [^{3}H]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.

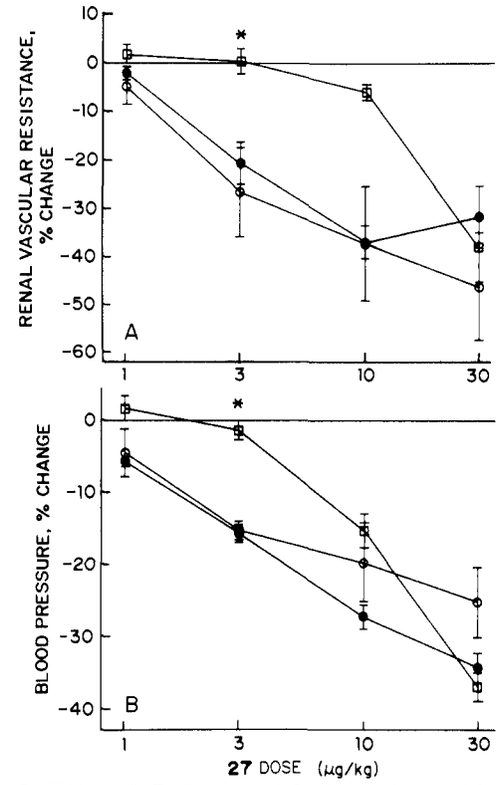

Figure 2. Effect of (*R*)-7-bromo-2,3,4,5-tetrahydro-8-hydroxy-3-methyl-1-phenyl-1*H*-3-benzazepine (SK&F R-83566), a DA-1 antagonist, and doperidone, a DA-2 antagonist, on **27** induced changes in renal vascular resistance (panel A) and blood pressure (panel B) in phenoxybenzamine-pretreated anesthetized dogs (n = 3). All dogs were given **27** intravenously by consecutive doses as indicated and the antagonists as continuous 0.5 μg kg^{-1} 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 doperidone. Asterisk indicates changes from **27** alone with $P < 0.05$.

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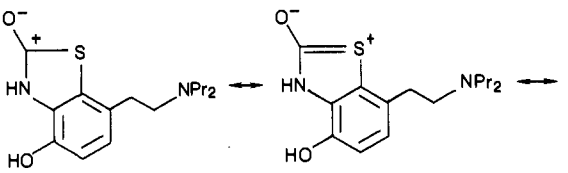
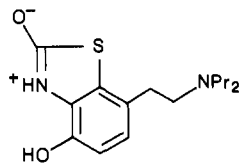
(18) Block, E. *Reactions of Organosulfur Compounds*; Organic Chemistry, A Series of Monographs; Blomquist, A. T., Wasserman, H. H., Eds.; Academic: New York, 1978; Vol. 37, p 22.



52 53



54

The activity of **4**, **6**, and **51** shows that an acidic 3-hydrogen is not necessary for potent D-2 (DA_2) 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 [^{3}H]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 DA_2 receptor stimulation.

However, the D-1 activity seen with **27** (and with **7**) does demonstrate that contrary to most previous experience[20] 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 (DA_1) 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 ^{1}H NMR spectra with a Varian EM-390 spectrometer. Compound **48** was examined for NOE with a Brucker 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 H_2O and recrystallization of the product from EtOH gave 44.3 g (69%) of **9**: mp 144–146 °C (lit.[21] mp 146–147 °C); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 3.62 (s, 2 H, CH_2), 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 $SOCl_2$ was refluxed for 3.5 h. Concentration under vacuum gave an oil, which was dissolved in $CHCl_3$ and added dropwise to a solution of 35.7 g (0.30 mol) of dipropylamine in 200 mL of $CHCl_3$. 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}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6 H, CH_3, J = 7 Hz), 1.6 (m, 4 H, CH_2CH_3), 3.30 (m, 4 H, CH_2N), 3.70 (s, 2 H, Ar CH_2), 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 H_2O and 40 mL of DMF was stirred with K_2CO_3 (36 g, 0.26 mol) and dimethyl sulfate (20 g, 0.16 mol) for 20 min and was then diluted with 250 mL of H_2O and extracted with EtOAc. The organic layer was washed with 10% NaOH, H_2O, and 10% HCl and was then dried (Na_2SO_4) 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}; ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6 H, CH_3), 1.60 (m, 4 H, CH_3CH_2), 3.35 (m, 4 H, NCH_2), 3.80 (s, 2 H, Ar CH_2), 3.95 (s, 3 H, OCH_3), 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 B_2H_6 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 $CHCl_3$. The extract was dried over Na_2SO_4 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}; ^{1}H NMR ($CDCl_3$) 1.00 (t, 6 H, CH_3, J = 7 Hz), 1.86 (m, 4 H, CH_3CH_2), 3.07 (m, 4 H, $CH_3CH_2CH_2N$), 3.25 (s, 4 H, Ar CH_2CH_2N), 3.97 (s, 3 H, OCH_3), 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 PtO_2 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 H_2 for 9 h. Filtration and concentration under vacuum gave a solid, which on recrystallization from an *i*-PrOH–Et_2O 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}; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 6 H, CH_3, J = 6 Hz), 1.90 (m, 4 H, CH_3CH_2), 3.03 (m, 8 H, CH_2N and Ar CH_2), 3.85 (s, 3 H, OCH_3), 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 H_2O, then 10% NaOH was added to achieve pH 9, and the resulting suspension was extracted with CH_2Cl_2. This extract was washed with 10% $Na_2S_2O_4$, dried over $MgSO_4$, 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 SiO_2 (CH_2Cl_2) gave white plates: mp 212–213 °C dec; IR (KBr) 3490, 3385, 2970, 1550, 1280, 1200, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 1.00 (t, 6 H, CH_3), 1.5–1.95 (m, 4 H, $CH_2CH_2CH_3$), 2.95–3.25 (m, 6 H, CH_2N), 3.4 (s, 4 H, Ar CH_2 and NH_2), 3.85 (s, 3 H, OCH_3), 5.15 (br s, 1 H, SH), 6.80 (s, 1 H, Ar H). Anal. ($C_{15}H_{25}ClN_2OS$·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

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gave 5.56 g (94%) of buff crystals, mp 251–253 °C. A sample was purified by chromatography (SiO_2–10% MeOH–$CHCl_3$) and was then recrystallized from MeOH–Et_2O: mp 202 °C dec; IR (KBr) 3400, 2960, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, Me_2SO-d_6) δ 6.82 (s, 1 H, Ar H), 3.90 (s, 3 H, OCH_3), 3.40–2.75 (m, 8 H, CH_2N and CH_2 Ar), 2.00–1.55 (m, 4 H, CH_2CH_3), 1.00 (t, 6 H, CH_3CH_2). Anal. ($C_{16}H_{23}ClN_2O_2S$·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 $CHCl_3$ 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 (Me_2SO-d_6) δ 6.96 (s, 1 H, Ar H), 3.40–2.95 (m, 8 H, CH_2N and Ar CH_2), 1.90–1.40 (m, 4 H, CH_2CH_3), 0.95 (t, 6 H, CH_2CH_3); MS, *m/e* 329 $[M + H]^+$. Anal. ($C_{15}H_{21}ClN_2O_2S$·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 ($MgSO_4$), 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 ($CDCl_3$) 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, OCH_3), 3.40–2.90 (m, 8 H, CH_2N, Ar CH_2), 1.50–2.00 (m, 4 H, CH_2CH_3), 0.98 (t, 6 H, *J* = 8 Hz, CH_2CH_3). A hydrochloride prepared from a sample purified by chromatography (SiO_2–$CHCl_3$) after recrystallization from EtOH–Et_2O 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 ($CDCl_3$, Me_2SO-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 CH_2 and CH_2N), 2.10–1.65 (m, 4 H, CH_2CH_3), 1.05 (t, 6 H, *J* = 6 Hz, CH_3CH_2). Anal. ($C_{15}H_{22}N_2O_2S$·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 (Na_2SO_4), 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. ($C_7H_5Cl_2NO_2$) C, H, N.

2-Chloro-3-nitrophenylacetonitrile (18). Method A. A solution of **16** (10.34 g, 0.050 mol) in Me_2SO (40 mL) was added over a 45-min period to a solution of NaCN (3.69 g, 0.075 mol) in 100 mL of Me_2SO. 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 $CHCl_3$. This solution was washed with water and brine and then dried (Na_2SO_4) 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 ($CDCl_3$) δ 3.43 (m, 2 H, CH_2), 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 CH_2Cl_2 and 1.96 mL of water was stirred for 18 h at room temperature. The reaction mixture was washed with water and brine, dried (Na_2SO_4), 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 $CHCl_3$–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 ($CDCl_3$) δ 3.92 (s, 2 H, CH_2CN), 7.50 (dd, H, Ar H-5), 7.80 (overlapping dd, Ar H-4,6). Anal. ($C_8H_5ClN_2O_2$·1.25H_2O) 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 B_2H_6 (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 ($CDCl_3$–Me_2SO-d_6) δ 3.00–3.45 (m, 4 H, CH_2), 7.41 (dd, H, Ar H_5), 7.72 (overlapping dd, 2 H, Ar H-4,6). Anal. ($C_8H_9ClN_2O_2$·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 K_2CO_3 (11.93 g, 0.0791 mol) in 36 mL of H_2O and 36 mL of $CHCl_3$ 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 $CHCl_3$, the $CHCl_3$ 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 Na_2SO_4. Evaporation gave the *N*-propionyl amide as a syrup (3.73 g, 98%), MS, *m/e* 257 $(M + H)^+$. Reduction with B_2H_6 in THF by the standard procedure[23] 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. ($C_{11}H_{15}ClN_2O_2$·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 ($CDCl_3$) δ 0.87 (t, *J* = 6 Hz, 6 H, CH_3), 1.25–1.63 (m, *J* = 9 Hz, 4 H, $NCH_2CH_2CH_3$), 2.47 (t, *J* = 7.5 Hz, 4 H, $NCH_2CH_2CH_3$), 2.75 (m, 2 H, CH_2CH_2N), 2.88 (m, 2 H, CH_2CH_2N), 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 $CHCl_3$–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

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(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; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 0.95 (t, J = 6 Hz, 6 H, CH_3), 1.50–1.87 (m, 4 H, $NCH_2CH_2CH_3$), 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. ($C_{15}H_{22}N_2OS$·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; ^{1}H 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. ($C_9H_{10}N_2OS$) 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 $CuSO_4$·$5H_2O$ 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: ^{1}H 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 $(M + H)^+$; ^{1}H 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 $(M + H)^+$, 208 $(M + H - HCN)^+$; ^{1}H 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(3*H*)-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(3*H*)-one hydrochloride, mp 263–266 °C, soften 256 °C, which was used without further purification: ^{1}H NMR ($CDCl_3$–Me_2SO-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 $(M + H)^+$, 208 $(M + H - NH_3)^+$, 195 $(M + H - CH_2NH_2)^+$.

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 ^{1}H NMR (Me_2SO-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 $(M + H)^+$, 194 $(M + H - NH_3)$, 181 $(M + H - CH_2NH_2)^+$. Anal. ($C_9H_{10}N_2O_2S$·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 $La(NO_3)_3$·$6H_2O$ 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. ^{1}H NMR ($CDCl_3$) δ 3.09 (t, J = 9 Hz, 2 H, CH_2CH_2N), 3.67 (dd, J = 7 Hz, 2 H, CH_2CH_2N), 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. ($C_{10}H_9F_3N_2O_4$) 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 Na_2SO_4. 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; ^{1}H NMR ($CDCl_3$) δ 2.97 (t, J = 8 Hz, 2 H, CH_2CH_2NH), 3.41 (s, 3 H, CH_3), 3.46 (s, 3 H, CH_3), 3.67 (dd, 2 H, CH_2CH_2NH), 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 Et_2O, 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; ^{1}H NMR ($CDCl_3$) δ 2.89–3.32 (br m, 8 H, CH_2CH_2NH, $N(CH_3)_2$), 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 H_2 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 Et_2O gave 3.87 g (85%) of **32**: mp 142–144 °C; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 2.90–3.30 (br m, 8 H, CH_2CH_2NH, $N(CH_3)_2$), 3.50 (br s, 2 H, CH_2CH_2NH), 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-(3*H*)-one (33). A solution of 3.65 g (0.0098 mol) of **32** in 120 mL of H_2O was heated on a stream 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(3*H*)-one Hydrochloride (34). A solution of 2.00 g (0.006 89 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}; ^{1}H NMR (D_2O) δ 2.90 (m, 3 H, CH_2N), 3.30 (t, 2 H, Ar CH_2, J = 7 Hz), 7.0–7.4 (m, 3 H, Ar H-4,5,6). Anal. ($C_9H_{10}N_2OS$·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 intially 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–H_2O 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. ($C_{12}H_{14}F_3N_3O_2S$) 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 Br_2 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 $NaHCO_3$ to give 13.85 g (89%) of **37**: mp 227–231 °C; MS, m/e 320 (M + H)$^+$; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 2.83 (t, 2 H, Ar CH_2, J = 9 Hz), 3.11 (s, 2 H), 3.47 (q, 2 H, CH_2NH, J = 9 Hz), 3.90 (s, 3 H, OCH_3), 7.75 (m, 4 H, Ar H + 2 H), on D_2O exchange, as above but 3.47 (t, 2 H, CH_2NH, 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. ($C_{12}H_{12}F_3N_3O_2S$) 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% H_3PO_4 and 9.12 g (0.132 mol) of $NaNO_2$ in 14 mL of H_2O 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 $CuSO_4$·$5H_2O$ in 380 mL of H_2O gave 14.36 g (97%) of crude **38**, mp 166–169 °C. Recrystallization from MeOH–H_2O 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}; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 2.78 (s, 1 H, NH), 3.00 (t, 2 H, Ar CH_2, J = 8 Hz), 3.61 (q, 2 H, CH_2NH, J = 7 Hz), 4.02 (s, 3 H, OCH_3), 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. ($C_{12}H_{10}ClF_3N_2O_2S$) 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 H_2O, and the solution was brought to pH 5 with acetic acid and then made basic with 14 M NH_4OH. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ was washed in turn with water and brine and then dried over Na_2SO_4. 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 − NH_3)$^+$, 209 (M − OCH_3)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 2 H, NH_2), 2.6–3.2 (m, 4 H, CH_2CH_2), 3.97 (s, 3 H, OCH_3), 4.21 (s, 3 H, OCH_3), 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(3*H*)-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 Et_2O 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 $CHCl_3$–MeOH) gave 4.89 g of a solid. Recrystallization of this from a $CHCl_3$–petroleum ether mixture gave 4.30 g (47%) of the *N*-formyl derivative: mp 150–151 °C; MS, m/e 267.2 (M + H)$^+$; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 2.87 (t, 2 H, Ar CH_2, J = 7 Hz), 3.59 (q, 2 H, CH_2NH, J = 7 Hz), 3.97 (s, 3 H, OCH_3), 4.22 (s, 3 H, OCH_3), 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, NHC*H*O); 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. ($C_{11}H_{14}N_2O_2S$·HCl·$^1/_4H_2O$) C, H, N.

A solution of 1.00 g (0.003 04 mol) of **40a** in 7 mL of 48% HBr (distilled from $SnCl_2$·H_2O) 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)$^+$; ^{1}H NMR (Me_2SO-d_6) δ 2.59 (s, 3 H, NCH_3), 2.81 (t, 2 H, Ar CH_2, J = 8 Hz), 3.09 (s, 2 H, CH_2NH), 3.34 (s, 3 H, OCH_3), 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. ($C_{10}H_{12}N_2O_2S$·HBr) C, H, N.

N-(Benzyloxy)-N'-[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 $CHCl_3$ 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 $CHCl_3$ 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 ($CDCl_3$) 0.92 (t, 6 H, CH_3CH_2, J = 7 Hz), 1.60–2.15 (m, 4 H, CH_3CH_2), 2.73–3.40 (m, 8 H, CH_2N and Ar CH_2), 3.85 (s, 3 H, OCH_3), 4.90 (s, 2 H, $OCH_2C_6H_5$), 6.70–7.05 (m, 2 H, Ar H-3,4) 7.30 (s, 1 H, Ar H-6), 7.40 (s, 5 H, $CH_2C_6H_5$), 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 $CHCl_3$ at 0 °C was treated with a solution of 16.9 g (0.038 mol) of lead tetraacetate in 200 mL of $CHCl_3$ 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 $CHCl_3$, and the combined filtrates were evaporated to dryness under vacuum. The residue was chromatographed with 400 g of silica gel, eluting with $CHCl_3$–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 ($CDCl_3$) δ 0.80 (t, 6 H, CH_3CH_2, J = 7 Hz), 1.20–1.80 (m, 4 H, CH_3CH_2), 2.05 (s, 3 H, CH_3COO), 2.52–2.80 (m, 4 H, $CH_3CH_2CH_2N$), 2.80–3.25 (m, 4 H, Ar CH_2CH_2N), 3.90 (s, 3 H, CH_3O), 5.22 (s, 2 H, $C_6H_5CH_2O$), 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, C_6H_5 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% $NaHCO_3$ was extracted three times with 50 mL of $CHCl_3$. The organic extract was dried over Na_2SO_4 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 H_2 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-(3*H*)-one (**5a**): IR (mull) 3140, 1700, 1640, 1525 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 6 H, CH_3CH_2, J = 7 Hz), 1.5 (m, 4 H, CH_3CH_2), 2.43–3.02 (m, 8 H, CH_2N and Ar CH_2), 3.90 (s, 3 H, OCH_3), 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 (0.006 29 mol) of **5a** in 100 mL of CH_2Cl_2 at −30 °C was treated with 17.5 mL of 1 M BBr_3 in $CHCl_3$ (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 ($CDCl_3$–Me_2SO-d_6) δ 1.00 (t, 6 H, CH_3CH_2, J = 6 Hz), 1.65–2.05 (m, 4 H, CH_3CH_2), 2.90–3.35 (m, 8 H, CH_2N and Ar CH_2), 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. ($C_{15}H_{23}N_3O_2$·HBr) C, H, N.

2-(2,4-Dimethoxyphenyl)ethylamine (44). 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 ($CDCl_3$) δ 3.86 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 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 $LiAlH_4$ in 400 mL of Et_2O under a N_2 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 Et_2O, which was dried over K_2CO_3, and then concentrated to give 74.3 g of a brown oil. Distillation gave 41.95 g (55%) of **44** 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 $CHCl_3$ and washed in turn with 200 mL of 10% NaOH, water, and brine and then was dried over Na_2SO_4. 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 $CHCl_3$, and the extract was washed with brine, dried over Na_2SO_4, 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 ($CDCl_3$) δ 1.05 (t, 3 H, CH_2CH_3, J = 10 Hz), 1.97 (m, 2 H, CH_2CH_3), 2.95 (m, 2 H, $CH_3CH_2CH_2NH$), 3.18 (s, 4 H, Ar CH_2CH_2N), 3.80 (s, 6 H, OCH_3), 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 ($CDCl_3$) δ 0.90 (t, 6 H, CH_3CH_2, J = 7 Hz), 1.49 (m, 4 H, CH_3CH_2), 2.42 (m, 4 H, $NCH_2CH_2CH_3$), 2.60 (s, 4 H, Ar CH_2CH_2N), 3.78 (s, 6 H, CH_3O), 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 CO_2 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 $CHCl_3$, and the $CHCl_3$ extract was dried over Na_2SO_4 and then concentrated under vacuum. The residue was recrystallized from a CH_3CN–Et_2O 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 ($CDCl_3$) δ 1.00 (t, 6 H, CH_3CH_2, J = 6 Hz), 1.84 (br m, 4 H, CH_3CH_2), 3.00 (m, 4 H, $CH_3CH_2CH_2N$), 3.18 (s, 4 H, Ar CH_2CH_2N), 3.75 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 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. ($C_{17}H_{27}NO_4$·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 $SOCl_2$ 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 NaN_3 in 45 mL of H_2O was added. The mixture was stirred for 1 h, then diluted with 400 mL H_2O, and then extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and was concentrated at 30 °C under vacuum. The residue (acid azide, IR 2140, 2020 cm^{-1}) was dissolved in 35 mL of CH_2Cl_2 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 $CHCl_3$, and the extracts were dried over Na_2SO_4

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, $CH_3CH_2CH_2N$), 2.75 (s, 4 H, Ar CH_2CH_2N), 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, $NCH_2CH_2CH_3$), 2.76 (s, 4 H, Ar CH_2CH_2N), 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 Brucker 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, $CH_3CH_2CH_2N$), 3.02 (s, 4 H, Ar CH_2CH_2N), 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–Et_2O mixture to give 0.98 g (90%) of **6**: mp 220–222 °C; IR (mull) 3300, 3160, 1820 (m), 1780, 1650, 1240, 915 cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-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 $(M + H)^+$, 114 $[(CH_3CH_2CH_2)_2N{=}CH_2]^+$. Anal. ($C_{15}H_{22}N_2O_3$·HBr) C, H, N.

2-[3-[(Hydroximinoacetyl)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 197–199 °C; IR (mull) 3380, 2600, 2540, 2480, 1690, 1600, 1550; ^1H NMR ($CDCl_3$–Me_2SO-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, $CH_3CH_2CH_2N$), 3.18 (s, 4 H, Ar CH_2CH_2N), 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 sitrred 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 Et_2O 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 167–170 °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, $CH_3CH_2CH_2N$, J = 7 Hz), 2.68 (t, 2 H, Ar CH_2CH_2N, 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 257–258 °C dec; IR (mull) 2650 (br), 1735, 1640, 1605, 1520, 1380 cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-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, $CH_3CH_2CH_2N$ and Ar CH_2CH_2N), 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. ($C_{16}H_{22}N_2O_3$·HBr·H_2O), C, H, N.

In Vitro Biological Methods. Relaxation of the electrically stimulated rabbit ear artery was carried out as previously described.[6] [^{3}H]Spiroperidol and [^{3}H]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 $\mu g\ kg^{-1}\ min^{-1}$ of SK&F R-83566-C, to establish dopamine DA-1 blockade, or 0.5 $\mu g\ kg^{-1}\ min^{-1}$ 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 $\mu g/kg$.

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 aorta[25] 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 Stathum 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 $\mu g/kg$.

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