Nonpeptide Somatostatin Agonists with sst_4 Selectivity: Synthesis and Structure−Activity Relationships of Thioureas

Shenquan Liu,[†] Cheng Tang,[†] Bin Ho,[†] Michael Ankersen,[‡] Carsten E. Stidsen,[§] and A. Michael Crider*,[†]

Division of Basic Pharmaceutical Sciences, School of Pharmacy, Northeast Louisiana University, Monroe, Louisiana 71209-0470, and MedChem Research and Molecular Pharmacology, Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

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Utilizing NNC 26-9100 (**11**) as a structural lead, a variety of nonpeptide derivatives of somatostatin were synthesized and evaluated for sst_2 and sst_4 receptor binding affinity. A novel thiourea scaffold was utilized to attach (1) a heteroaromatic nucleus to mimic the Trp^8 residue, (2) a nonheteroaromatic nucleus to mimic Phe^7, and (3) a primary amine or other basic group to mimic the Lys^9 residue of somatostatin. Displacement studies were carried out using membranes from cell lines expressing ssts [BHK cells (sst_4) and HEK 293 cells (sst_2)] utilizing [^{125}I]Tyr^{11}-SRIF as the radioligand. Several thioureas (**11**, **38**, **39**, **41**, and **42**) and the urea **66** exhibited K_i values of less than 100 nM. The thioureas **11** (K_i = 6 nM) and **41** (K_i = 16 nM) and the urea **66** (K_i = 14 nM) are believed to be the most potent nonpeptide sst_4 agonists known. Since the thiourea **11** and the urea **66** exhibit high sst_4 selectivity, these novel nonpeptide derivatives may be useful tools for studying the sst_4 receptor. Studies are currently in progress to evaluate the therapeutic potential of NNC 26-9100 (**11**) in the treatment of glaucoma.

Introduction

Somatostatin [somatotropin release-inhibiting factor (SRIF)] is a cyclic tetradecapeptide containing one internal disulfide bond between residues 3 and 14, was isolated initially from bovine hypothalamus, and is characterized as a potent inhibitor of growth hormone (GH) secretion from the anterior pituitary.[1] SRIF-14 (**1**; Figure 1) and SRIF-28, a 28-amino acid form of SRIF-14 extended from the *N*-terminal end, display similar biological activities with a different pattern of potency depending on the tissue.[2] In addition to the inhibitory effects on GH release, both peptides inhibit the release of a variety of other peptides including glucagon, insulin, and gastrin,[3] and they act as neurotransmitters and neuromodulators in the central nervous system and the periphery.[4]

SRIF exerts its potent inhibitory effects following binding to high-affinity SRIF receptors (ssts) that have been identified on target tissues. The existence of multiple receptor subtypes was first demonstrated by Reubi[5] in radioligand binding studies using rat brain cortex. The recent cloning of five sst subtypes has confirmed that the effects of SRIF are mediated by a family of G protein-coupled receptors (sst_{1-5}),[6] formerly designated SSTR 1−5.[7] These five sst isoforms have seven hydrophobic transmembrane domains (20−30-amino acid-forming helices) which are separated by stretches of hydrophilic residues. The transmembrane regions show a higher degree of homology, whereas extensive differences are seen in the amino acid sequences and the sizes of the N- and C-termini. On the basis of structural and pharmacological properties, sst_2, sst_3, and sst_5 belong to the $SRIF_1$ receptor subclass (65−75% sequence homology). The sst_1 and sst_4 subtypes comprise the $SRIF_2$ subclass[8−10] (71% sequence homology). The major difference between these two subclasses is that $SRIF_1$ receptors bind octapeptide and hexapeptide SRIF-14 analogues with high affinity, while $SRIF_2$ receptors bind these analogues with drastically reduced affinity.[11]

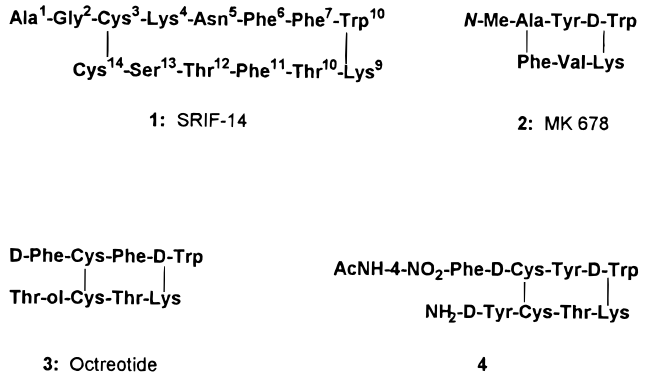

Figure 1. Chemical structures of SRIF-14 (**1**), MK 678 (**2**), octreotide (**3**), and **4**.

Due to its poor bioavailability and rapid degradation by proteases, the therapeutic utility of SRIF-14 is limited. As a result, considerable efforts have focused on the development of peptidomimetics of SRIF-14. Systematic replacement[12] of all amino acids in SRIF-14 by L-Ala revealed that Trp^8 and Lys^9 are essential for biological activity, whereas Phe^7 and Thr^{10} can undergo minor modifications. These studies showed that SRIF-14 contains a β-turn composed of the tetrapeptide Phe^7-Trp^8-Lys^9-Thr^{10}. Additional work demonstrated that the first two amino acids, Ala-Gly, are

* To whom correspondence should be addressed. Phone: (318) 342-1707. Fax: (318) 342-1606. E-mail: pycrider@alpha.nlu.edu.
[†] Northeast Louisiana University.
[‡] MedChem Research, Novo Nordisk A/S.
[§] Molecular Pharmacology, Novo Nordisk A/S.

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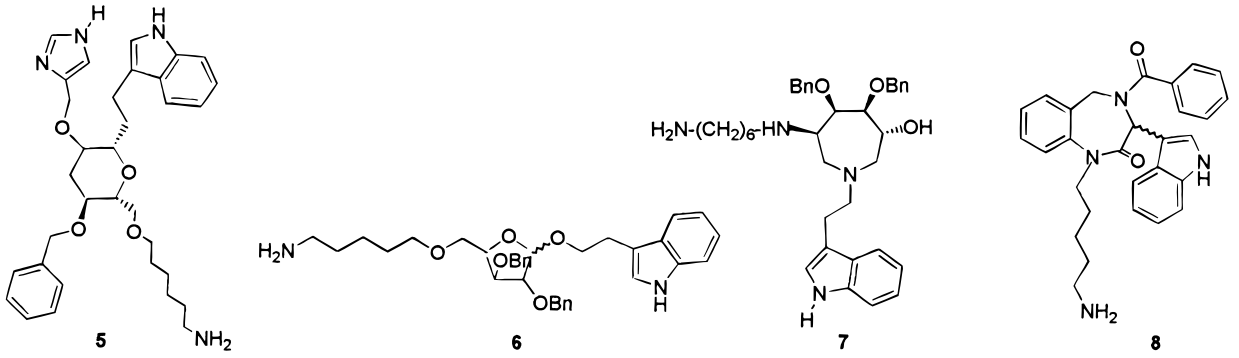


Figure 2. Chemical structures of **5**−**8**.

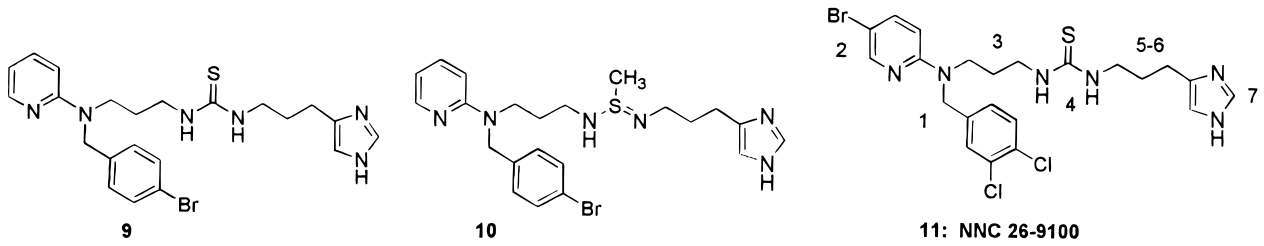


Figure 3. Chemical structures of **9**, **10**, and NNC 26-9100 (**11**).

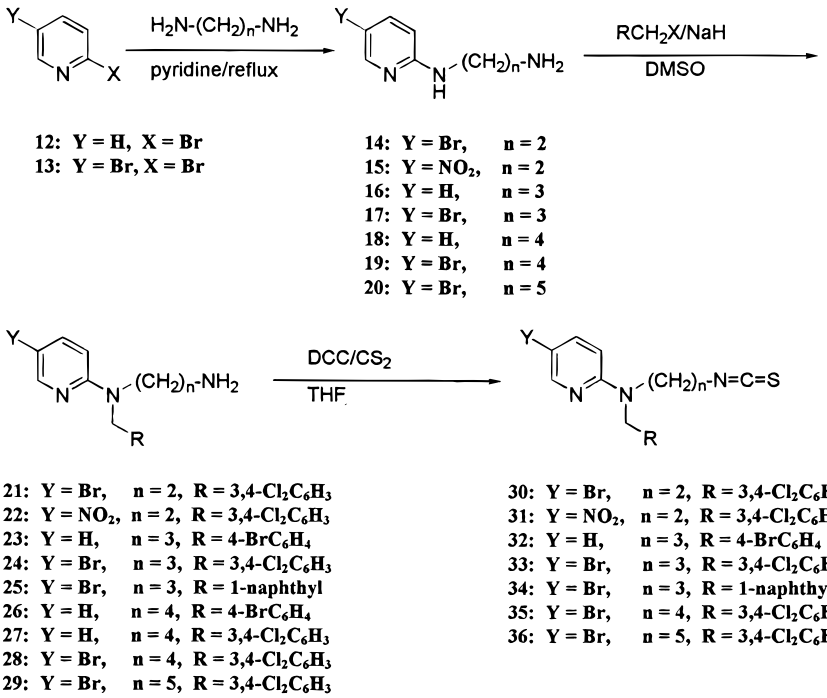
not necessary for full biological activity.[13] Using this information and structure−activity relationship (SAR) studies on hexapeptides led to the development of the hexapeptide MK 678 (**2**; Figure 1).[14] This peptide was 50−100 times more potent that SRIF-14 in the in vitro inhibition of GH release and in the in vivo release of insulin and glucagon. Due to bioavailability problems and side effects associated with a malfunction in absorption of fats, clinical trials with MK 678 were terminated. Additional studies[15] led to the discovery of octreotide (**3**; Figure 1). This octapeptide is a potent $SRIF_1$ receptor subclass agonist that has been the subject of extensive SAR studies. Long-acting preparations of octreotide are available for use in the treatment of acromegaly, neuroendocrine tumors, and gastrointestinal disorders.[16] Until recently, no full antagonist of SRIF-14 had been reported. The octapeptide **4** (Figure 1) which incorporates a D-Cys at position 2 and an 4-NO_2-L-Phe at position 1 was shown to be a full sst_2 antagonist.[17]

A number of nonpeptide derivatives (Figure 2) of SRIF have recently been reported.[18−21] In these analogues a D-sugar or heterocyclic scaffold was utilized to mimic the β-turn of SRIF. Molecular modeling studies suggested that the substituents at C_2, C_1, and C_6 of the sugar may mimic the critical Phe^7-Trp^8-Lys^9 side chains found in SRIF. Additionally, the benzyl group at C_4 may mimic the Phe^{11} residue in SRIF. Compound **5** was superimposed on the solution structure of the hexapeptide L-363,301, a sst_2 agonist, and a local minimum of the sugar derivative was found to overlap quite well with the bioactive conformation of L-363,301. The nonpeptide **5** was found to be the most potent derivative in this series, with an in vitro IC_{50} of 1.9 μM in membranes from a subclone of the AtT-20 cell line; however, this derivative also binds to β_2-adrenergic and NK-1 receptors.[19] Several tetrasubstituted xylofuranose derivatives were synthesized by Papageorgiou et al.,[20] and compound **6** exhibited an IC_{50} of 23 μM in displacement of [^{125}I]Tyr^{11}-SRIF-14 from rat whole brain homogenates. Using molecular modeling, five- to seven-membered nitrogen heterocycles were used as scaffolds to synthesize SRIF agonists. The azepine **7** was the most potent derivative with an IC_{50} of 10 μM in displacement of 3-[^{125}I]Tyr^{11}-SRIF-14 in rat brain homogenates.[21] Using the benzodiazepine skeleton as a β-turn mimetic scaffold led to the synthesis of compound **8**. This nonpeptide analogue of SRIF exhibited an IC_{50} of 7 μM in displacement of [^{125}I]Tyr^3-octreotide in rat brain homogenates.[22]

Since a nonpeptide SRIF ligand may offer therapeutic advantages[23] over peptides, a screening program was initiated to identify a lead nonpeptide with affinity for sst_{1-5} receptors. The search focused on a scaffold with the following attachments: (1) a heteroaromatic nucleus to mimic the Trp^8 residue, (2) a nonheteroaromatic nucleus to mimic Phe^7, and (3) a primary amine or other basic groups to mimic the Lys^9 residue of SRIF-14. Using these search criteria, the thiourea **9** (Figure 3) was identified as a structural lead. The key fragments in this compound are a heteroaromatic moiety (pyridine), an aromatic group, and a basic imidazole group connected through a thiourea scaffold. This compound showed moderate affinity for sst_2 with a 20-fold selectivity of sst_4 over sst_2. The *S*-methylisothiourea **10** (Figure 3) had a slightly greater affinity for sst_2 than **9**; however, this analogue exhibited about a 100-fold sst_2/sst_4 selectivity. Evaluation of additional compounds in this series led to the discovery of the thiourea **11** (NNC 26-9100) (Figure 3). To our knowledge this was the first report of the evaluation of nonpeptides at cloned ssts. Compound **11** exhibited high affinity (K_i = 6 nM) for sst_4 and sst_2/sst_4 selectivity of about 100-fold. In a functional assay based on inhibition of forskolin-induced accumulation of adenosine cyclic 3′,5′-monophosphate (cAMP) in BHK cells expressing human ssts, the thiourea **11**, like SRIF-14, potently inhibited cAMP accumulation.[24]

Using in situ hybridization techniques, Mori et al.[25] showed that the predominant expression of sst_4 is in

Scheme 1



the posterior iris epithelium and ciliary body. Since sst$_4$ activation induces inhibition of cAMP accumulation in BHK cells expressing this receptor, a similar effect may also occur in the iris/ciliary body. The fact that a decrease in cAMP levels leads to reduction in aqueous humor production suggests that an sst$_4$ agonist would likely lower intraocular pressure. Recently, a combination of SRIF-14 (0.1 μM) and acetylcholine (10 μM) was shown to induce an increase in Ca^{2+} levels in the nonpigmented cells of the rabbit ciliary body by over 25-fold. The effect was attributed to the interaction of SRIF-14 with a novel sst.[26] Thus, selective sst$_4$ agonists may have potential therapeutic utility in the treatment of glaucoma.

In an effort to increase the affinity and selectivity at sst$_4$ receptors, an extensive SAR study of the lead compound **11** was initiated. This investigation involved the following modifications of the thiourea **11**: (1) replacement of the benzyl group by an α-naphthylmethyl group, (2) replacement of the 5-bromo substituent on the pyridine ring with a 5-nitro group or a hydrogen, (3) varying the distance between the thiourea group and the two aromatic rings, (4) replacement of the thiourea group by a urea group, (5) varying the distance between the thiourea group and the imidazole ring, (6) incorporating the spacer group between the thiourea moiety and the imidazole ring into a heterocycle or an aromatic ring, and (7) replacement of the imidazole ring by other basic functionalities (Figure 3).

Chemistry

Thioureas are conveniently prepared by coupling an amine with an isothiocyanate under mild reaction conditions.[27] Reaction of the 2-bromopyridines **12** and **13** with an excess of a diaminoalkane in the presence of a catalytic amount of pyridine readily afforded the 2-(aminoalkylamino)pyridines **14**−**20** (Scheme 1). Alkylation of **14**−**20** with either a benzyl halide or α-naphthylmethyl bromide in dimethyl sulfoxide using sodium hydride as the base gave the *N*-(1,1-disubstituted)-diamines **21**−**29**. The key *N*-(1,1-disubstituted)aminoalkyl isothiocyanates **30**−**36** were prepared by reaction of *N*-(1,1-disubstituted)diamines **21**−**29** with 1 equiv of DCC in the presence of carbon disulfide in tetrahydrofuran.[28] The 2-(aminoalkylamino)pyridines **14**−**20** and the *N*-(1,1-disubstituted)diamines **21**−**29** were generally purified by column chromatography to yield nonanalytically pure oils which were utilized in the subsequent reaction without further purification.

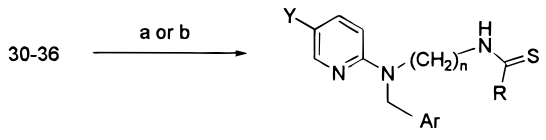
Reaction of the isothiocyanates **30**−**36** with an amine or a trityl-protected amine afforded the desired thioureas **11** and **37**−**64** after removal of the trityl protecting group with refluxing 1 N hydrochloric acid (Scheme 2, Tables 1−3). Most of the thioureas were isolated as solid foams which could not be crystallized; however, in most cases analytically pure samples could be obtained by column chromatography. Numerous attempts to prepare salts with a variety of organic and inorganic acids gave very hygroscopic oils or solids. The urea **66** was readily prepared[29] by reaction of the diamine **21** with triphosgene and 3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propylamine[24] (**65**) in the presence of triethylamine followed by removal of the trityl protecting group (Scheme 2).

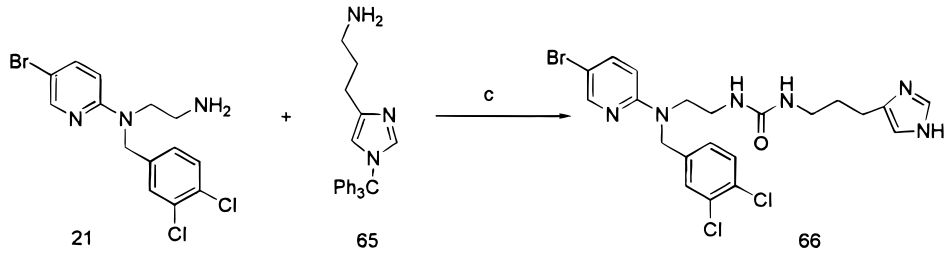
Pharmacology

Displacement studies were carried out using membranes from cell lines expressing ssts [BHK cells (sst$_4$) and HEK 293 cells (sst$_2$)] utilizing [^{125}I]Tyr^{11}-SRIF-14 as the radioligand.[24] Several of the thioureas (**11**, **38**, **39**, **41**, and **42**) and the urea **66** exhibited K_i values of less than 100 nM at sst$_4$ (Table 1).

With the exception of the aminopropyl (**59**) and the aminobutyl (**63** and **64**) derivatives, all thioureas and the urea **66** demonstrated greater affinity for sst$_4$ than for sst$_2$. Replacement of the 4-bromobenzyl group (**9**)

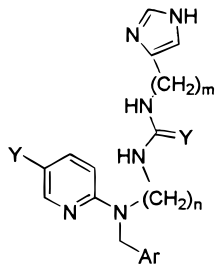
Scheme 2[a]

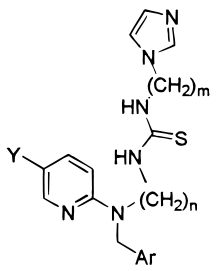


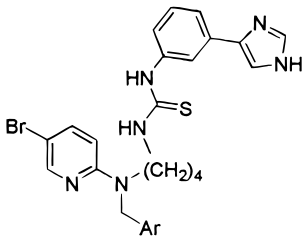


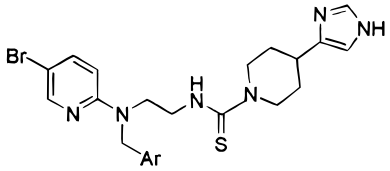
[a] (a) Amine/THF; (b) i. amine/THF, ii. refluxing 1 N HCl; (c) i. triphosgene/Et_3N/THF, ii. refluxing 1 N HCl.

Table 1. In Vitro Binding at sst_2 and sst_4 Receptors by Thioureas **11** and **37**−**50** and the Urea **66**









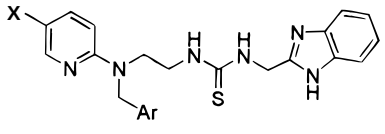
compd	Y	X	Ar[a]	*n*	*m*	sst_2[b]	sst_4[c]
37	Br	S	3,4-$Cl_2C_6H_3$	2	2	894	476
38	Br	S	3,4-$Cl_2C_6H_3$	4	2	2000	96
39	Br	S	3,4-$Cl_2C_6H_3$	2	3	310	70
66	Br	O	3,4-$Cl_2C_6H_3$	2	3	4200	14
40	NO_2	S	3,4-$Cl_2C_6H_3$	2	3	500	176
9[d]	H	S	4-BrC_6H_4	3	3	2500	118
11[d]	Br	S	3,4-$Cl_2C_6H_3$	3	3	621	6
41	Br	S	$C_{10}H_7$	3	3	778	16
42	Br	S	3,4-$Cl_2C_6H_3$	4	3	565	53
43	Br	S	3,4-$Cl_2C_6H_3$	5	3	777	132
44	Br	S	3,4-$Cl_2C_6H_3$	3	3	2200	1700
45	H	S	4-BrC_6H_4	3	3	33000	7000
46	H	S	4-BrC_6H_4	4	3	12000	7000
47	H	S	3,4-$Cl_2C_6H_3$	4	3	8000	4000
48	Br	S	3,4-$Cl_2C_6H_3$	4	3	2000	1400
49			3,4-$Cl_2C_6H_3$			1700	520
50			3,4-$Cl_2C_6H_3$			1000	413
10[d]						4600	50
SRIF[d]						0.2	1.4
octreotide[d,e]						0.3	1904
MK 678[d]						0.3	3200

[a] Ar groups: 3,4-$Cl_2C_6H_3$ (3,4-dichlorophenyl), $C_{10}H_7$ (1-naphthyl), 4-BrC_6H_4 (4-bromobenzyl). [b] K_i (nM) in transfected HEK 293 cells. [c] K_i (nM) in transfected BHK cells. [d] Reference 24. [e] SMS 201-995.

by 3,4-dichlorobenzyl (**11**) or α-methylnaphthyl (**41**) groups resulted in enhanced sst_4 affinity of 7- and 20-fold, respectively. Introduction of a 5-Br substituent on the pyridine ring enhances binding affinity at sst_4 by about 3-fold (compare compounds **47** and **48**). Decreasing the distance between the thiourea group and the 5-bromopyridyl moiety of **11** by one methylene group (compound **39**) led to a decrease in sst_4 affinity of 12-fold. Similarly, increasing the distance (n = 4 and 5, Table 1) between the 5-bromopyridyl moiety and the thiourea group of compound **11** (compounds **42** and **43**) resulted in a decrease in sst_4 affinity by 9- and 22-fold, respectively. Replacement of the thiourea group of **39** by a urea group (compound **66**) results in a compound with essentially the same sst_4 binding affinity but dramatically decreased sst_2 affinity. The urea **66** exhibited the greatest sst_2/sst_4 selectivity of any compound evaluated in this investigation.

Compounds having the 3-(imidazol-4-yl)propyl group demonstrated the greatest sst_4 affinity (compounds **11**, **38**, **39**, **41**, **42**, and **66**). These compounds all exhibited K_i values less than 100 nM at sst_4 receptors. Replace-

Table 2. In Vitro Binding at sst$_2$ and sst$_4$ Receptors by Thioureas **54**−**58**



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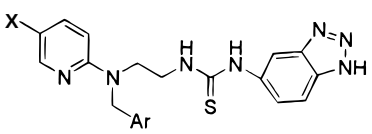

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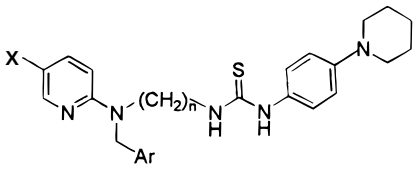

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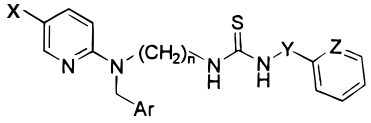
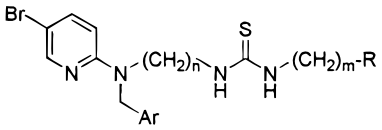


55-58

compd	X	Ar[a]	*n*	Y	Z	sst$_2$[b]	sst$_4$[c]
51	Br	3,4-$Cl_2C_6H_3$				>300000	1200
52	Br	3,4-$Cl_2C_6H_3$				3000	1000
53	Br	3,4-$Cl_2C_6H_3$	2			>300000	15000
54	Br	3,4-$Cl_2C_6H_3$	3			>300000	71000
55	Br	3,4-$Cl_2C_6H_3$	3	$(CH_2)_2$	N	74000	1700
56	H	4-BrC_6H_3	3	$(CH_2)_3NH$	N	114000	113
57	Br	3,4-$Cl_2C_6H_3$	3	$(CH_2)_3NH$	N	>300000	185
58	H	4-BrC_6H_4	4	$(CH_2)_3$	C	>300000	71000
SRIF[d]						0.2	1.4
octreotide[d,e]						0.3	1904
MK 678						0.3	3200

[a] −[e]See corresponding footnotes in Table 1.

Table 3. In Vitro Binding at sst$_2$ and sst$_4$ Receptors by Thioureas **59**−**64**



compd	Ar[a]	*n*	*m*	R	sst$_2$[b]	sst$_4$[c]
59	3,4-$Cl_2C_6H_3$	2	3	NH_2	2300	4200
60	3,4-$Cl_2C_6H_3$	2	3	$N(CH_3)_2$	2000	803
61	3,4-$Cl_2C_6H_3$	2	3	1-pyrrolidinyl	1700	477
62	3,4-$Cl_2C_6H_3$	3	3	1-pyrrolidinyl	1600	514
63	3,4-$Cl_2C_6H_3$	3	4	NH_2	830	1000
64	$C_{10}H_7$	3	4	NH_2	1000	2000
SRIF[d]					0.2	1.4
octreotide[d,e]					0.3	1904
MK 678[d]					0.3	3200

[a] −[e]See corresponding footnotes in Table 1.

ment of the 3-(imidazol-4-yl)propyl group by a 2-(imidazol-4-yl)ethyl group led to decreased sst$_4$ affinity by 2−7-fold (compare compounds **37**, **39** and **38**−**42**). Introduction of conformational constraints between the thiourea group and the imidazole ring, using either a heterocyclic system (compare compounds **39** and **50**) or a phenyl ring (compare compounds **38** and **49**), decreased sst$_4$ affinity by 6- and 10-fold, respectively.

Thioureas with high (**11** and **41**), moderate (**57**), and low (**37**, **50**, and **61**) sst$_4$ binding affinity were evaluated in a functional assay to assess inhibition of forskolin-induced adenosine cyclic 3′,5′-monophosphate (cAMP) in BHK cells expressing the human sst$_4$ receptor (Table 4 and Figure 4). The thioureas with the highest affinity for sst$_4$ receptors (compounds **11** and **41**) potently inhibited forskolin-induced cAMP accumulation with

Table 4. Inhibition by Selected Thioureas of Forskolin-Induced cAMP Accumulation in BHK Cells Expressing the Human sst$_4$ Receptor

compd	inhibition of cAMP accumulation, EC_{50} (nM)[a]
11	26 ± 6
37	2350 ± 30
41	24 ± 16
50	990 ± 340
57	154 ± 46
61	4000 ± 145

[a] EC_{50}, mean ± SEM; n = 3 or 4.

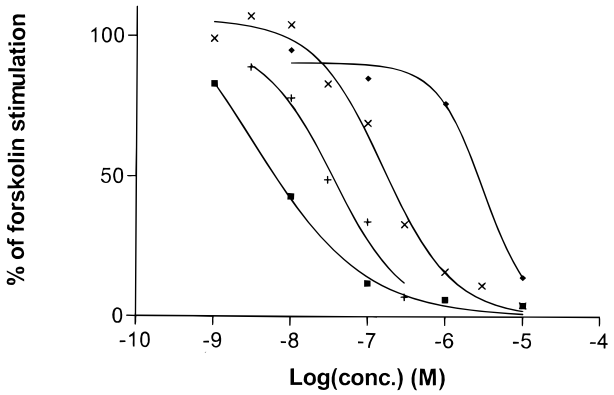


Figure 4. Inhibition by thiourea derivatives of forskolin-induced cyclic AMP accumulation in BHK cells expressing the human sst$_4$ receptor subtype. The data are from representative experiments performed in triplicate for compound **11** (+), compound **37** (◆), compound **41** (■), and compound **57** (×).

EC_{50} values of 26 and 24 nM, respectively. These data demonstrate that the thioureas act as full agonists at the human sst$_4$ receptor.

Conclusions

The amino acid sequence Phe[7]-Trp[8]-Lys[9]-Thr[10] is thought to comprise the β-turn of SRIF, and these residues appear to play an important role in the binding at ssts.[30] Additionally, the proximity of the Trp[8]-Lys[9] residues is considered essential for sst binding. Based on the results of the in vitro binding studies of the target thioureas at ssts, several conclusions can be made. The pyridine ring may mimic the Trp[8] of SRIF, and the nonheteroaromatic benzyl or naphthyl groups may mimic Phe[7] in the natural peptide. Although less basic that the ϵ-NH_2 group of Lys, the imidazoyl group, found in the most potent thioureas, may mimic the Lys[9] residue of SRIF. Hirschmann et al.[19] have shown that the Phe[8] of SRIF can be replaced by a His residue. This leads to the speculation that the imidazoyl group of the thiourea derivatives could mimic the Phe[7] of SRIF. The role of the thiourea moiety is uncertain. Perhaps, this group serves as a scaffold to properly orient the heteroaromatic, aromatic, and basic groups at ssts. The thioureas **11** (K_i = 6 nM) and **41** (K_i = 16 nM) and the urea **66** (K_i = 14 nM) are, to our knowledge, the most potent nonpeptide sst_4 agonists known. Since the thiourea **11** and the urea **66** exhibit high selectivity for sst_4 over sst_2, these compounds may be useful tools for studying the pharmacological effects of the sst_4 receptor. Selective sst_4 agonists may lead to a decrease of aqueous humor production in the iris/ciliary body.[25] This opens the possibility that these nonpeptide sst_4 agonists may represent novel therapeutic agents for the treatment of glaucoma. Studies are currently in progress to evaluate the potential utility of NNC 26-9100 (**11**) in this disorder.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are not corrected. The IR spectra were recorded as liquid films or as potassium bromide pellets on a Nicolet Impact 400D spectrometer. The NMR spectra were recorded on a JEOL FX 90Q 90-MHz spectrometer or a JEOL Eclipse 400-MHz spectrometer, and chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane. Analytical data were obtained from Oneida Research Services, Inc., Whitesboro, NY, and Desert Analytics, Tucson, AZ. Precoated plastic TLC (5- × 20-cm) 0.2-mm aluminum oxide M/UV_{254} and silica gel 0.25-mm with fluorescent indicator UV_{254} plates were purchased from the Brinkmann Instrument Co. or EM Industries, Inc. Flash chromatography was performed on Ace glass columns (i.d. = 5 cm, length = 45 cm) with 150−200 g of silica gel (40 μm) purchased from the J. R. Baker Chemical Co. All solvents which were used for recrystallizations and column chromatography were of analytical grade, and 2-(2-aminoethylamino)-5-nitropyridine (**15**) was obtained from the Aldrich Chemical Co.

Representative Procedure for the Synthesis of 2-(Aminoalkylamino)pyridines. Preparation of *N*-1-(5-Bromopyrid-2-yl)ethane-1,2-diamine (14). A mixture of 2,5-dibromopyridine (**13**; 10.0 g, 42.2 mmol) and pyridine (4.24 g, 53.6 mmol) in 1,2-diaminoethane (43 mL) was refluxed under nitrogen for 18 h. The reaction mixture was evaporated under reduced pressure and cooled, and the resulting residue was treated with THF (150 mL) to yield a white precipitate. The precipitate was filtered and washed with additional THF (100 mL). Evaporation of the filtrate afforded a brown oil which was vacuum distilled to give 6.48 g (71%) of **14** as a light-yellow oil: bp 134−142 °C (0.6 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 2 H, NH_2), 2.92 (t, 2 H), 3.29 (m, 2 H), 5.22 (br s, 1 H, NH), 6.31 (d, J = 9 Hz, 1 H, pyridine H-3), 7.44 (dd, J = 2.7 Hz, J = 9 Hz, 1 H, pyridine H-4), 8.09 (d, J = 2.5 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 41.22, 44.74, 106.72, 108.67, 139.55, 148.54, 148.70.

***N*-1-(Pyrid-2-yl)propane-1,3-diamine (16).** 2-Bromopyridine (**12**; 20.0 g, 126.7 mmol), pyridine (12.7 g, 160.8 mmol), and 1,3-diaminopropane (47.4 g, 639 mmol) afforded a dark-brown oil. Vacuum distillation gave 9.19 g (48%) of **16** as a light-yellow oil: bp 111−114 °C (0.65 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.28 (br s, 2 H, NH_2), 1.75 (m, 2 H), 2.84 (t, 2 H), 3.35 (m, 2 H), 5.00 (br s, 2 H, NH), 6.50 (m, 2 H), 7.40 (ddd, 1 H), 8.07 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 32.93, 39.92 (2×), 106.77, 112.30, 137.17, 148.00, 159.00.

***N*-1-(5-Bromopyrid-2-yl)propane-1,3-diamine (17).** 2,5-Dibromopyridine (**13**; 4.40 g, 18.6 mmol), pyridine (1.86 g, 23.6 mmol), and 1,3-diaminopropane (25 mL) yielded an oil. Vacuum distillation afforded 2.69 g (63%) of **17** as an oil: bp 135−139 °C (0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.52 (br s, 2 H, NH_2), 1.72 (m, 2 H), 2.89 (t, 2 H), 3.36 (m, 2 H), 5.30 (br s, 1 H, NH), 6.29 (d, J = 9 Hz, 1 H, pyridine H-3), 7.44 (dd, J = 2.4 Hz, J = 9 Hz, 1 H, pyridine H-4), 8.09 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 32.61, 39.98, 40.25, 106.45, 108.29, 139.50, 148.49, 157.48.

***N*-1-(Pyrid-2-yl)butane-1,4-diamine (18).** 2-Bromopyridine (**12**; 20.0 g, 126.7 mmol), pyridine (12.7 g, 160.8 mmol), and 1,4-diaminobutane (56.3 g, 639 mmol) gave 11.5 g (55%) of **18** as a light-yellow oil: bp 103−105 °C (0.05 mmHg) [lit.[32] bp 136−138 °C (2 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 1.56 (br s, 2 H, NH_2), 1.61 (m, 4 H), 2.73 (t, 2 H), 3.25 (m, 2 H), 4.73 (br s, 1 H, NH), 6.43 (m, 2 H), 7.40 (ddd, 1 H), 8.08 (m, 1 H); ^{13}C NMR δ 27.03, 31.25, 41.98, 42.09, 106.56, 112.57, 137.27, 148.22, 159.00.

***N*-1-(5-Bromopyrid-2-yl)butane-1,4-diamine (19). 13** (10.0 g, 42.2 mmol), 1,4-diaminobutane (52.6 g, 597 mmol), and pyridine (10.0 g, 42.2 mmol) gave a brown oil. Vacuum distillation afforded 7.87 g (76%) of **19** as a colorless oil: bp 165−170 °C (0.8 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.15−1.75 (m, 6 H), 2.72 (t, 2 H), 3.25 (br s, 2 H, NH_2), 4.75 (br s, 1 H, NH), 6.30 (d, J = 9 Hz, pyridine H-3), 7.47 (dd, J = 2.7 Hz, J = 9 Hz, 1 H, pyridine H-4), 8.10 (d, J = 2.4 Hz, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 26.87, 31.09, 41.87, 42.20, 108.07, 139.66, 148.71.

***N*-1-(5-Bromopyrid-2-yl)pentane-1,5-diamine (20). 13** (8.42 g, 35.5 mmol), pyridine (3.54 g, 44.8 mmol), and 1,5-diaminopentane (25.0 g, 244.7 mmol) gave an oil. Flash chromatography on silica gel using CH_2Cl_2/MeOH/concentrated NH_4OH (50:50:1) as the solvent afforded 5.50 g (60%) of **20** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 6 H), 1.85 (br s, 2 H, NH_2), 2.72 (m, 2 H), 3.25 (m, 4 H), 4.70 (br s, 1 H, NH), 6.30 (d, J = 9 Hz, 1 H, pyridine H-3), 7.47 (dd, 1 H, H-4), 8.09 (d, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 24.38, 29.40, 33.75, 41.88, 42.50, 106.88, 107.19, 140.00, 149.06, 157.50.

Representative Procedure for the Alkylation of 2-(Aminoalkylamino)pyridines Using Sodium Hydride in Dimethyl Sulfoxide. Preparation of *N*-1-(5-Bromopyrid-2-yl)-1-(3,4-dichlorobenzyl)ethane-1,2-diamine (21). A 60% mineral oil dispersion of NaH (0.584 g, 14.6 mmol) and **14** (3.00 g, 13.9 mmol) in DMSO (30 mL) was stirred for 2 h under nitrogen. The suspension was cooled to 0−5 °C and treated dropwise with 3,4-dichlorobenzyl chloride (2.71 g, 13.9 mmol) in DMSO (15 mL). After stirring overnight at room temperature, the reaction mixture was poured into 200 mL of an ice−water mixture. The mixture was extracted with ethyl acetate (3 × 75 mL), and the combined ethyl acetate extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to yield an oil. Flash chromatography on silica gel using CH_2Cl_2/MeOH/Et_3N (90:5:5) as the solvent system gave 3.5 g (67%) of **21** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 2 H, NH_2), 2.92 (t, 2 H, NCH_2), 3.57 (m, 2 H, CH_2), 4.72 (s, 2 H, $ArCH_2$), 6.39 (d, J = 9 Hz, 1 H, pyridine H-3), 7.32 (m, 4 H, ArH), 8.16 (d, J = 2 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 39.82, 51.47, 51.95, 107.00, 107.27, 126.23, 128.77, 130.62, 131.04, 132.73, 138.85, 139.77, 148.66, 156.62.

***N*-1-(5-Nitropyrid-2-yl)-1-(3,4-dichlorobenzyl)ethane-1,2-diamine (22).** **15** (3.00 g, 16.5 mmol), NaH (0.692 g, 17.3 mmol), and 3,4-dichlorobenzyl chloride (3.22 g, 16.5 mmol) in DMSO (25 mL) gave an oil. Flash chromatography on silica gel using EtOAc/MeOH/concentrated NH_4OH (60:40:1) as the solvent yielded 2.84 g (51%) of **22** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (br s, 2 H, NH_2), 3.68 (t, 2 H), 4.88 (s, 2 H), 6.55 (d, J = 9.6 Hz, 1 H, pyridine H-3), 7.30 (m, 3 H), 8.23 (dd, J = 2.7 Hz, J = 9.3 Hz, 1 H, pyridine H-4), 9.08 (d, 2.9 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 39.82, 51.47, 52.12, 104.61, 126.23, 130.83, 137.33, 146.49.

***N*-[1-(5-Bromopyrid-2-yl)-1-(naphth-1-yl)methyl]propane-1,3-diamine (25).** **17** (8.71 g, 37.9 mmol), a 60% mineral oil dispersion of NaH (1.67 g, 41.6 mmol), and 1-(bromomethyl)naphthalene[33] (9.21 g, 41.6 mmol) in DMSO (60 mL) gave an oil. Flash chromatography on silica gel using CH_2Cl_2/MeOH/concentrated NH_4OH (50:50:1) afforded 5.10 g (35%) of **25** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.43 (br s, 2 H, NH_2), 1.75 (m, 2 H), 3.67 (t, 2 H), 5.12 (s, 2 H, $ArCH_2$), 6.31 (d, J = 9 Hz, 1 H, pyridine H-3), 7.15−8.05 (m, 8 H, ArH), 8.20 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 31.31, 39.55, 45.72, 106.29, 107.54, 122.76, 123.84, 125.47, 125.85, 126.23, 127.74, 128.94,131.32, 132.24, 133.92, 139.55, 148.55, 156.94.

***N*-1-(4-Bromobenzyl)-1-(pyrid-2-yl)butane-1,4-diamine (26).** **18** (10.1 g, 30.3 mmol), a 60% mineral oil dispersion of NaH (1.27 g, 31.8 mmol), and 4-bromobenzyl bromide (7.57 g, 30.3 mmol) in DMSO (60 mL) gave an oil. Flash chromatography on silica gel using CH_2Cl_2/MeOH/Et_3N (90:5:5) yielded 4.29 g (57%) of **26** as a thick oil: ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 4 H, CH_2 and NH_2), 2.65 (t, 2 H), 3.45 (t, 2 H), 4.70 (s, 2 H, $ArCH_2$), 6.95 (m, 2 H), 7.25 (m, 5 H), 8.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.66, 31.05, 41.94, 48.39, 50.99, 105.65, 111.88, 113.01, 120.49, 128.67, 130.73, 137.23, 148.07, 157.93.

***N*-1-(3,4-Dichlorobenzyl)-1-(pyrid-2-yl)butane-1,4-diamine (27).** **18** (2.41 g, 14.6 mmol), a 60% mineral oil dispersion of NaH (613 mg, 15.3 mmol), and 3,4-dichlorobenzyl bromide (3.50 g, 14.6 mmol) gave an oil. Purification by flash chromatography on silica gel using a solvent system of CH_2Cl_2/MeOH/concentrated NH_4OH (50:50:1) afforded 0.95 g (20%) of a light-green oil: ^{1}H NMR ($CDCl_3$) δ 1.52 (m, 4 H), 2.02 (br s, 2 H, NH_2), 2.70 (t, 2 H), 3.43 (t, 2 H), 4.71 (s, 2 H, $ArCH_2$), 6.50 (m, 2 H), 7.00−7.52 (m, 4 H), 8.16 (m, 1 H).

***N*-1-(5-Bromopyrid-2-yl)-1-(3,4-dichlorobenzyl)butane-1,4-diamine (28).** **19** (7.00 g, 28.7 mmol), a 60% mineral oil dispersion of NaH (1.20 g, 30.1 mmol), and 3,4-dichlorobenzyl chloride (5.62 g, 28.7 mmol) in DMSO (75 mL) gave an oil. Flash chromatography on silica gel using a solvent system of CH_2Cl_2/MeOH/concentrated NH_4OH (50:50:1) yielded 2.32 g (20%) of **28** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 4 H, CH_2 and NH_2), 2.72 (t, 2 H), 3.45 (t, 2 H, NCH_2), 4.68 (s, 2 H, $ArCH_2$), 6.35 (d, J = 9 Hz, pyridine H-3), 7.00−7.55 (m, 4 H, ArH), 8.15 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 24.48, 30.93, 41.87, 48.81, 59.76, 106.61, 107.10, 126.28, 128.77, 130.45, 139.12, 148.60, 156.29. Anal. ($C_{16}H_{18}BrCl_2N_3$) C, H, N.

***N*-1-(5-Bromopyrid-2-yl)-1-(3,4-dichlorobenzyl)pentane-1,5-diamine (29).** **20** (5.50 g, 21.3 mmol), a 60% mineral oil dispersion of NaH (940 mg, 23.4 mmol), and 3,4-dichlorobenzyl chloride (4.60 g, 23.4 mmol) in DMSO (75 mL) afforded an oil. Purification by flash chromatography on silica gel using CH_2Cl_2/MeOH/concentrated NH_4OH (50:50:1) as the solvent gave 1.46 g (16%) of **29** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 6 H), 2.70 (m, 2 H), 3.40 (t, 2 H), 4.68 (s, 2 H, $ArCH_2$), 6.35 (d, J = 9 Hz, 1 H, pyridine H-3), 7.35 (m, 4 H, ArH), 8.15 (d, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 24.38, 27.19, 33.75, 42.20, 49.06, 50.63, 106.25, 107.50, 126.25, 127.81, 130.94, 131.25, 131.90, 140.00, 149.06, 156.56.

General Method for the Synthesis of 2-Pyridyl Isothiocyanates. Preparation of 2-[*N*-(5-Bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl Isothiocyanate (30). A mixture of DCC (2.74 g, 13.2 mmol) and CS_2 (10.1 g, 132.6 mmol) in THF (30 mL) was cooled to −10 °C in an ice−salt bath and treated dropwise with a solution of **21** (5.00 g, 13.2 mmol) in THF (20 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight under nitrogen. Removal of the solvent under reduced pressure afforded a white solid. The solid was triturated with diethyl ether (200 mL), and the dicyclohexylthiourea was removed by filtration. The filtrate was evaporated, and acetonitrile (100 mL) was added to the resulting residue. The remaining dicyclohexylthiourea was filtered, and the filtrate was evaporated under vacuum to afford an oil. Flash chromatography on silica gel using CH_2Cl_2/hexane/Et_3N (50:50:1) gave 4.31 g (78%) of a white solid. Recrystallization from Et_2O/hexane gave an analytical sample: mp 83−85 °C; ^{1}H NMR ($CDCl_3$) δ 3.84 (m, 4 H), 4.69 (s, 2 H, $ArCH_2$), 6.33 (d, J = 8.3 Hz, 1 H, pyridine H-3), 7.40 (m, 4 H), 8.20 (d, J = 2 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 43.34, 49.19, 52.71, 107.70, 108.19, 125.74, 128.34, 130.83, 140.10, 148.71, 155.65. Anal. ($C_{15}H_{12}BrCl_2N_3S$) C, H, N.

2-[*N*-(3,4-Dichlorobenzyl)-*N*-(5-nitropyrid-2-yl)amino]ethyl Isothiocyanate (31). **22** (2.80 g, 8.21 mmol), CS_2 (6.70 g, 88.0 mmol), and DCC (1.70 g, 8.21 mmol) in THF (60 mL) gave a dark-yellow solid. Flash chromatography on silica gel using CH_2Cl_2/hexane/Et_3N (50:50:1) as the solvent system gave 2.20 g (71%) of a yellow solid: mp 104−106 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (m, 4 H), 4.85 (s, 2 H, $ArCH_2$), 6.49 (d, J = 10 Hz, 1 H, pyridine H-3), 7.29 (m, 3 H, ArH), 8.23 (dd, J = 2.7 Hz, J = 9.3 Hz, 1 H, pyridine H-4), 9.08 (d, J = 2 Hz, 1 H, pyridine H-6).

3-[*N*-(4-Bromobenzyl)-*N*-(pyrid-2-yl)amino]propyl Isothiocyanate (32). **23**[24] (2.00 g, 6.24 mmol), CS_2 (5.08 g, 66.7 mmol), and DCC (1.29 g, 6.24 mmol) in THF (45 mL) yielded an oil. Flash chromatography on silica gel using hexane/EtOAc/Et_3N (70:30:1) as the solvent gave 1.35 g (60%) of **32** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 4 H), 3.55 (m, 2 H), 4.67 (s, 2 H, $ArCH_2$), 6.50 (m, 2 H), 7.25 (m, 5 H), 8.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.28, 43.01, 45.72, 51.68, 105.86, 112.57, 120.86, 128.61, 131.75, 137.49, 148.11, 157.81.

3-[*N*-(5-Bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]propyl Isothiocyanate (33). **24** (3.64 g, 9.35 mmol), CS_2 (7.62 g, 100 mmol), and DCC (1.94 g, 9.35 mmol) in THF (45 mL) gave an oil. Purification by flash chromatography on silica gel using hexane/EtOAc/Et_3N (70:30:1) as the solvent afforded 3.19 g (79%) of **33** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.06 (m, 2 H), 3.62 (m, 4 H), 4.66 (s, 2 H, $ArCH_2$), 6.40 (m, 1 H), 7.35 (m, 4 H), 8.22 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.06, 42.91, 46.10, 51.41, 107.21, 107.43, 126.17, 128.72, 130.72, 131.26, 138.31, 139.93, 148.76, 156.13; MS (CI, CH_4) 432 M^+. Anal. ($C_{16}H_{14}BrClN_3S$) C, H, N.

3-[*N*-(5-Bromopyrid-2-yl)-*N*-(naphth-1-ylmethyl)amino]propyl Isothiocyanate (34). **25** (4.00 g, 10.8 mmol), CS_2 (8.80 g, 115 mmol), and DCC (2.32 g, 10.8 mmol) in THF (140 mL) afforded an oil. Flash chromatography on silica gel using a solvent system of CH_2Cl_2/hexane/Et_3N (50:50:1) gave 2.70 g (84%) of **34** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 2 H), 3.54 (t, 2 H), 3.74 (t, 2 H), 5.11 (s, 2 H, $ArCH_2$), 6.30 (d, J = 9 Hz, 1 H, pyridine H-3), 7.15−8.02 (m, 8 H, ArH), 8.25 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 28.28, 43.01, 45.77, 50.32, 106.99, 107.59, 122.65, 123.89, 125.41, 125.90, 126.39, 128.93, 139.71, 148.60, 156.62. Anal. ($C_{20}H_{18}BrN_3S$) C, H, N.

4-[*N*-(5-Bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]butyl Isothiocyanate (35). **28** (1.68 g, 4.16 mmol), CS_2 (1.85 g, 44.2 mmol), and DCC (858 mg, 4.16 mmol) in THF (45 mL) afforded an oil. Purification by flash chromatography on silica gel using a solvent system of hexane/EtOAc/Et_3N (80:20:1) gave 1.53 g (83%) of **35** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 4 H), 3.54 (m, 4 H), 4.65 (s, 2 H, $ArCH_2$), 6.32 (d, J = 9 Hz, 1 H, pyridine H-3), 6.97−7.50 (m, 4 H), 8.16 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 24.32, 27.36, 44.80, 47.90, 51.62, 107.10, 126.18, 128.66, 130.56, 130.99, 132.67, 138.63, 139.71, 148.60, 156.18. Anal. ($C_{17}H_{16}BrCl_2N_3S$) H, N; C: calcd, 45.86; found, 46.50.

5-[*N*-(5-Bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]pentyl Isothiocyanate (36). **29** (1.46 g, 3.50 mmol), CS_2 (2.84 g, 37.3 mmol), and DCC (722 mg, 3.50 mmol) in THF

(45 mL) gave an oil. Flash chromatography using hexane/EtOAc/Et_3N (80:20:1) afforded 1.38 g (86%) of **36** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 6 H), 3.47 (m, 4 H), 4.69 (s, 2 H, $ArCH_2$), 6.35 (d, J = 9 Hz, 1 H, pyridine H-3), 7.33 (m, 4 H), 8.17 (d, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 23.99, 26.44, 29.63, 44.86, 48.65, 50.92, 106.72, 107.05, 126.33, 128.72, 130.51, 132.62, 138.90, 139.66, 148.60, 156.24.

3-[2-(1*H*-Imidazol-4-yl)ethyl]-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (37). A suspension of histamine (320 mg, 2.88 mmol) in THF (40 mL) was treated with a solution of **30** (1.20 g, 2.88 mmol) in THF (15 mL). The reaction mixture was stirred for 48 h under a nitrogen atmosphere, and the solvent was removed under reduced pressure to afford a foam. Flash chromatography on silica gel using a solvent system of EtOAc/MeOH/concentrated NH_4OH (90:5:5) gave 987 mg (67%) of a white foam: mp 72−78 °C; ^{1}H NMR ($CDCl_3$) δ 2.85 (m, 2 H), 3.68 (m, 6 H), 4.59 (s, 2 H, $ArCH_2$), 6.40 (d, 1 H, pyridine H-3), 6.80−7.50 (m, 9 H, N*H*C=SN*H* and ArH), 8.02 (d, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 27.66, 42.81, 47.74, 51.80, 107.49, 108.19, 116.16, 125.96, 130.84, 131.33, 132.95, 134.90, 135.55, 137.82, 140.32, 148.12, 156.63, 181.71. Anal. H, N; C: calcd, 45.46; found, 44.90.

3-[2-(1*H*-Imidazol-4-yl)ethyl]-1-[4-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]butyl]thiourea (38). A suspension of histamine (352 mg, 3.17 mmol) in THF (10 mL) was cooled to 0−5 °C and treated dropwise with **35** (1.41 g, 3.17 mmol) in THF (20 mL). After stirring overnight, the solvent was removed under reduced pressure to yield an oil which was purified by flash chromatography using a solvent system of EtOAc/MeOH/concentrated NH_4OH (85:15:1). Fractions homogeneous by TLC were combined and evaporated under reduced pressure to afford 1.59 g (90%) of a white foam: ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 4 H), 2.80 (m, 2 H), 3.60 (m, 8 H), 4.63 (s, 2 H, $ArCH_2$), 6.37 (s, 1 H), 6.79−7.55 (m, 7 H), 8.16 (d, J = 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.65, 26.27, 26.65, 43.94, 44.21, 48.49, 50.87, 106.72, 107.37, 115.34, 126.17, 128.61, 130.56, 130.94, 132.62, 134.68, 139.82, 148.44, 156.29, 181.59. Anal. ($C_{24}H_{25}BrCl_2N_6S$) C, H, N.

3-[3-(1*H*-Imidazol-4-yl)propyl]-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (39). A suspension of 3-[1-(triphenylmethyl)imidazol-4-yl]propylamine (**65**; 0.87 g, 2.64 mmol) in THF (40 mL) was stirred under a nitrogen atmosphere at 0−5 °C and treated dropwise with a solution of **30** (1.10 g, 2.64 mmol) in THF (15 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. TLC on silica gel using EtOAc/MeOH /Et_3N (90:5:5) indicated that considerable starting material remained. The reaction mixture was stirred for an additional 24 h, and the solvent was removed under reduced pressure to yield a white foam. Flash chromatography on silica gel using EtOAc/MeOH/Et_3N (90:5:5) as the solvent afforded 1.72 g (87%) of the trityl-protected thiourea as a colorless oil. The oil was suspended in 2 N HCl (40 mL) and was refluxed for 8 h under nitrogen. The precipitated triphenylmethanol was filtered, and the filtrate was evaporated under reduced pressure to yield a foam. The foam was suspended in 1 N NaOH (60 mL) and extracted with EtOAc (3 × 75 mL). The combined EtOAc extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to yield upon trituration with hexane 765 mg (57%) of a white hygroscopic foam: ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 2 H), 2.64 (m, 6 H), 3.55 (m, 6 H), 4.62 (s, 2 H, $ArCH_2$), 6.44 (d, J = 9 Hz, 1 H, pyridine H-3), 7.20−7.55 (m, 8 H, N*H*C=SN*H* and ArH), 8.09 (d, J = 2.5 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 23.49, 28.87, 42.42, 43.50, 47.84, 51.79, 107.51, 108.19, 115.99, 126.01, 128.50, 130.78, 131.31, 132.89, 134.35, 137.22, 137.98, 140.26, 148.04, 156.62, 181.75. Anal. ($C_{21}H_{23}BrClN_6S$) C: calcd, 46.50; found, 45.13. H: calcd, 4.28; found, 5.00. N: calcd, 15.50; found, 16.22.

3-[3-(1*H*-Imidazol-4-yl)propyl]-1-[2-[*N*-(5-nitropyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (40). A suspension of **65** (959 mg, 2.61 mmol) in THF (20 mL) was cooled to 0−5 °C in an ice−water bath and treated dropwise with **31** (1.00 g, 2.61 mmol) in THF (40 mL). After stirring overnight at room temperature under a nitrogen atmosphere, the solvent was removed under reduced pressure to yield 2.1 g of a yellow foam. The intermediate trityl-protected thiourea was suspended in 1 N HCl (35 mL) and refluxed for 1.5 h. The solution was filtered, extracted with diethyl ether (2 × 200 mL), basified with 6 N NaOH, and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with water (3 × 100 mL), dried (Na_2SO_4), and evaporated under vacuum to yield a foam. Flash chromatography on silica gel using a solvent system of CH_2Cl_2/MeOH/concentrated NH_4OH (90:10:1) yielded 500 mg (38%) of **40** as a yellow foam: ^{1}H NMR (DMSO-d_6) δ 1.72 (m, 2 H), 3.50 (m, 8 H), 4.93 (s, 2 H, $ArCH_2$), 6.75 (s, 1 H), 7.35 (m, 7 H), 8.22 (dd, 1 H, pyridine H-4), 8.97 (d, J = 2.7 Hz, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 23.14, 28.99, 42.05, 42.40, 48.01, 51.58, 105.27, 126.45, 128.89, 130.89, 133.17, 133.98, 146.28, 160.58, 181.46. Anal. ($C_{21}H_{23}Cl_2N_7O_2S$) C, H; N: calcd, 19.29; found, 18.86.

3-[3-(1*H*-Imidazol-4-yl)propyl]-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(naphth-1-ylmethyl)amino]propyl]thiourea (41). A solution of **65** (1.24 g, 3.38 mmol) was dissolved in THF (20 mL) and treated dropwise with a solution of **34** (1.40 g, 3.38 mmol) in THF (20 mL) at 0−5 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated under reduced pressure to yield an oil which was purified by flash chromatography on silica gel using a solvent system of EtOAc/MeOH/Et_3N (92:4:4). Fractions homogeneous on TLC were combined and evaporated to give 2.63 g of the trityl-protected thiourea. The oil was suspended in 1 N HCl (60 mL) and refluxed for 1.5 h. The precipitate was filtered, and the filtrate was extracted with Et_2O (2 × 100 mL). The aqueous layer was basified with 6 N NaOH and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to yield an oil. Flash chromatography on silica gel using an eluent of CH_2Cl_2/MeOH/concentrated NH_4OH (90:10:1) afforded 1.10 g (61%) of **41** as a foam: ^{1}H NMR ($CDCl_3$) δ 1.88 (m, 4 H), 2.65 (m, 2 H), 3.30−3.80 (m, 6 H), 5.02 (s, 2 H, $ArCH_2$), 6.18−8.11 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 24.06, 27.19, 29.38, 42.20, 43.75, 50.94, 108.44, 115.63, 122.50, 123.44, 125.31, 125.94, 126.56, 128.13, 129.38, 131.56, 134.75, 135.00, 138.75, 140.63, 148.44, 157.81, 181.56. Anal. ($C_{26}H_{29}BrN_6S$) C, H, N.

3-[3-(1*H*-Imidazol-4-yl)propyl]-1-[4-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]butyl]thiourea (42). A suspension of **65** (0.50 g, 1.51 mmol) in THF (20 mL) was treated dropwise with a solution of **35** (0.67 g, 1.51 mmol) in THF (10 mL) under a nitrogen atmosphere. After stirring overnight at room temperature, the solvent was removed under reduced pressure to afford an oil. Flash chromatography on silica gel using CH_2Cl_2/MeOH/Et_3N (100:2.5:2.5) afforded 0.62 g (71%) of a colorless oil. The oil was suspended in a mixture of 2 N HCl (50 mL) and EtOH (10 mL) and refluxed for 10 h. The precipitated triphenylmethanol was filtered, and the filtrate was evaporated. The residue was suspended in 2 N NaOH (40 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to give 107 mg (18%) of a hygroscopic solid: mp 63−67 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−2.00 (m, 6 H), 2.60 (m, 2 H), 3.45 (br m, 6 H), 4.63 (s, 2 H, $ArCH_2$), 5.95−7.50 (m, 9 H), 8.13 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 23.51, 24.65, 28.88, 43.39, 44.37, 48.59, 50.87, 106.72, 107.37, 115.12, 126.23, 128.66, 130.56, 130.89, 132.62, 134.14, 138.20, 148.49, 156.29, 181.65. Anal. ($C_{23}H_{27}BrCl_2N_6S$) N; C: calcd, 48.43; found, 46.41. H: calcd, 4.78; found, 4.33.

3-[3-(1*H*-Imidazol-4-yl)propyl]-1-[5-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]pentyl]thiourea (43). A solution of **65** (1.02 g, 2.77 mmol) was dissolved in THF (20 mL) and treated dropwise with a solution of **36** (1.27 g, 2.77 mmol) in THF (40 mL) at 0−5 °C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was treated with additional amine **65** (0.182 g, 0.495 mmol) and was refluxed for

24 h. Removal of the solvent afforded an oil which was purified by flash chromatography on silica gel using a solvent system of EtOAc/MeOH/Et_3N (92:4:4). Fractions homogeneous by TLC were combined and evaporated to yield 2.20 g of a foam. The trityl-protected thiourea was refluxed in 1 N HCl (50 mL) for 1.5 h, and the precipitated triphenylmethanol was removed by filtration. The filtrate was extracted with Et_2O (2 × 100 mL), and the Et_2O phase was washed with water (100 mL) and evaporated under reduced pressure. The residue was dissolved in EtOAc (300 mL), and the EtOAc phase was washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated. The resulting residue was flash chromatographed on silica gel using EtOAc/MeOH/concentrated NH_4OH (85:15:1) as the solvent. Fractions homogeneous by TLC were combined and evaporated to yield 500 mg (31%) of **43** as a solid foam: ^{1}H NMR ($CDCl_3$) δ 1.15−2.00 (m, 8 H), 2.25 (m, 2 H), 3.45 (m, 6 H), 4.64 (s, 2 H, $ArCH_2$), 6.25−8.13 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 23.86, 24.43, 26.98, 29.04, 43.61, 44.64, 48.97, 50.98, 106.78, 107.48, 126.44, 128.88, 130.67, 134.35, 139.17, 139.93, 148.65, 156.51, 181.70. Anal. ($C_{24}H_{29}BrCl_2N_6S$) C, H, N.

3-[3-(Imidazol-1-yl)propyl]-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]propyl]thiourea (44). A solution of **24** (1.00 g, 2.57 mmol) in THF (15 mL) was cooled to 0−5 °C under a nitrogen atmosphere and treated dropwise with 3-(imidazol-1-yl)propyl isothiocyanate (432 mg, 2.57 mmol) in THF (15 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. Removal of the solvent under reduced pressure afforded a semisolid. Trituration with Et_2O/petroleum ether gave a solid which was recrystallized from EtOAc/Et_2O to yield 450 mg (31%) of **44**: mp 94−97 °C; ^{1}H NMR ($CDCl_3$) δ 1.60−2.35 (m, 4 H), 3.54 (m, 5 H), 4.05 (t, 2 H), 4.57 (s, 2 H, $ArCH_2$), 6.28 (d, J = 9 Hz, 1 H), 6.99 (d, J = 4.4 Hz, 1 H), 7.19 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 27.03, 30.91, 41.01, 41.50, 44.59, 51.03, 107.05, 107.64, 119.18, 125.90, 128.39, 129.21, 130.78, 131.21, 132.89, 136.95, 137.98, 140.04, 148.33, 156.62, 182.62. Anal. ($C_{22}H_{25}BrCl_2N_6S$) C, H, N.

3-[3-(Imidazol-1-yl)propyl]-1-[3-[*N*-(4-bromobenzyl)-*N*-(pyrid-2-yl)amino]propyl]thiourea Dihydrobromide (45). A solution of **23** (616 mg, 1.92 mmol) in THF (15 mL) was treated dropwise with 3-(imidazol-1-yl)propyl isothiocyanate (323 mg, 1.92 mmol) in THF (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature, filtered, and evaporated under reduced pressure to afford a yellow oil. The oil was dissolved in MeOH and acidified with methanolic hydrogen bromide. Addition of Et_2O afforded a cloudy solution which produced a light-tan solid upon standing in the refrigerator. The solid was filtered and dried to yield 0.94 g (75%) of **45**. Recrystallization from absolute EtOH/Et_2O afforded an analytical sample: mp 199−201 °C; ^{1}H NMR (DMSO-d_6) δ 1.55−2.25 (m, 4 H, CH_2), 3.20−3.90 (m, 6 H, CH_2), 4.26 (t, 2 H), 7.00 (t, 1 H), 7.26 (d, J = 8.3 Hz, 2 H), 7.57 (d, J = 8.3 Hz, 2 H), 7.86 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 25.57, 29.09, 37.87, 39.98, 46.10, 47.40, 51.57, 111.76, 112.20, 121.78, 131.37, 134.73, 135.11, 137.44, 143.40, 151.27, 181.66. Anal. ($C_{22}H_{29}Br_3N_6S$) H, N; C: calcd, 40.69; found, 39.96.

3-[3-(Imidazol-1-yl)propyl]-1-[4-[*N*-(4-bromobenzyl)-*N*-(pyrid-2-yl)amino]butyl]thiourea (46). A solution of **26** (1.11 g, 3.34 mmol) in THF (30 mL) was treated dropwise with a solution of 3-(imidazol-1-yl)propyl isothiocyanate (559 mg, 3.34 mmol) in THF (10 mL). After stirring overnight at room temperature under nitrogen, the solvent was removed under reduced pressure to afford an oil. The oil was dissolved in absolute EtOH and acidified with ethanolic hydrogen chloride. Addition of Et_2O afforded a very hygroscopic solid. The solvents were removed under reduced pressure, and the residue was partitioned between 10% NaOH (100 mL) and CH_2Cl_2 (50 mL). The basic layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated. The resulting oil was triturated with Et_2O to yield 950 mg (57%) of a tan solid. Recrystallization from EtOAc/Et_2O afforded 691 mg (41%) of **46**: mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 4 H), 2.07 (m, 2 H), 3.55 (m, 6 H), 4.01 (t, J = 7.4 Hz, 2 H), 4.66 (s, 2 H, $ArCH_2$), 6.36−8.18 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 25.02, 26.16, 30.16, 41.28, 44.09, 44.16, 48.05, 51.19, 106.02, 112.14, 119.23, 120.64, 128.50, 129.09, 131.64, 136.95, 137.49, 147.84, 157.97, 182.89. Anal. ($C_{23}H_{29}BrN_6S$) H, N; C: calcd, 54.48; found, 55.04.

3-[3-(Imidazol-1-yl)propyl]-1-[4-[*N*-(3,4-dichlorobenzyl)-*N*-(pyrid-2-yl)amino]butyl]thiourea (47). A solution of **27** (900 mg, 2.79 mmol) in THF (20 mL) was treated dropwise with 3-(imidazol-1-yl)propyl isothiocyanate (470 mg, 2.79 mmol) in THF (15 mL). After stirring overnight under nitrogen, the solvent was removed under reduced pressure. The resulting residue was flash chromatographed on silica gel using a solvent system of CH_2Cl_2/MeOH/concentrated NH_4OH (100:10:1) to yield a yellow foam. The foam was triturated with MeOH/water to yield a white solid. Recrystallization from CH_2Cl_2/Et_2O afforded 659 mg (48%) of **47** as a white, crystalline solid: mp 112−113.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 4 H), 2.08 (m, 2 H), 3.50 (m, 6 H), 4.00 (t, 2 H), 4.63 (s, 2 H, $ArCH_2$), 7.20 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 24.97, 26.17, 30.61, 41.39, 44.10, 44.69, 48.22, 50.87, 106.02, 112.47, 126.23, 128.66, 129.21, 130.61, 137.71, 139.23, 147.95, 182.95. Anal. ($C_{23}H_{28}Cl_2N_6S$) C, H, N.

3-[3-(Imidazol-1-yl)propyl]-1-[4-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]butyl]thiourea (48). A solution of **28** (1.01 g, 2.48 mmol) in THF (20 mL) was treated dropwise with 3-(imidazol-1-yl)propyl isothiocyanate (431 mg, 2.48 mmol) in THF (15 mmol). After stirring overnight at room temperature under nitrogen, the solvent was removed under reduced pressure. The resulting residue was triturated with Et_2O/hexane to afford a solid. Recrystallization from CH_2Cl_2/Et_2O gave 1.00 g (71%) of **48** as white crystals: mp 139−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 4 H), 2.07 (m, 2 H), 3.50 (m, 6 H), 4.00 (t, 2 H), 4.62 (s, 2 H, $ArCH_2$), 6.30 (d, J = 9 Hz, 1 H, pyridine H-3), 7.15 (m, 9 H), 8.12 (d, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 24.70, 26.33, 30.44, 41.28, 43.87, 44.64, 48.43, 50.97, 106.77, 107.32, 119.23, 126.17, 128.61, 130.62, 130.99, 136.89, 138.74, 139.77, 148.54, 182.94. Anal. ($C_{23}H_{27}BrCl_2N_6S$) C, H, N.

3-[3-(1*H*-Imidazol-4-yl)phenyl]-1-[4-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]butyl]thiourea (49). A suspension of 4-(3-aminophenyl)-1*H*-imidazole dihydrochloride[34] (521 mg, 2.25 mmol) and Et_3N (455 mg, 4.49 mmol) in THF (30 mL) was stirred under nitrogen for 2 h, and the reaction mixture was treated dropwise with **35** (1.00 g, 2.25 mmol) in THF (15 mL). The reaction mixture was heated at 45 °C for 48 h and filtered, and the solvent was evaporated under reduced pressure. The residue was flash chromatographed on silica gel using CH_2Cl_2/MeOH/concentrated NH_4OH (100:10:1) to give a solid. Recrystallization from Et_2O/hexane afforded 300 mg (22%) of **49**: mp 140−160 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 4 H), 3.47 (m, 4 H), 4.51 (s, 2 H, $ArCH_2$), 6.22 (d, 1 H, pyridine H-3), 7.30 (m, 10 H), 8.00 (d, 1 H, pyridine H-6), 8.53 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.43, 26.38, 44.85, 48.48, 50.92, 106.67, 107.32, 121.51, 123.41, 126.17, 126.61, 130.18, 130.56, 130.88, 132.56, 135.11, 135.97, 137.11, 138.79, 148.43, 156.18, 180.56. Anal. ($C_{26}H_{25}BrCl_2N_6S$) C, H, N.

***N*-1-(5-Bromopyrid-2-yl)-*N*-1-(3,4-dichlorobenzyl)-*N*-2-[4-(1*H*-imidazol-4-yl)piperid-1-yl]thioxomethyl]ethane-1,2-diamine (50).** A suspension of 4-(piperidin-4-yl)-1*H*-imidazole dihydrochloride[35] (387 mg, 1.73 mmol) and triethylamine (350 mg, 3.50 mmol) in THF (30 mL) was stirred for 2 h at room temperature under nitrogen and treated dropwise with **30** (662 mg, 1.73 mmol) in THF (15 mL). After the mixture had stirred overnight, considerable starting material remained. The reaction mixture was heated at 60 °C for 24 h, cooled to room temperature, filtered, and evaporated to yield an oil. Flash chromatography on silica gel using a solvent system of EtOAc/MeOH/concentrated NH_4OH (85:15:1) afforded 700 mg (71%) of **50** as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 2 H), 2.03 (m, 2 H), 2.89 (m, 1 H), 3.09 (m, 2 H), 3.85 (t, 4 H), 4.62 (d, 4 H), 6.32−8.11 (m, 15 H); ^{13}C NMR

($CDCl_3$) δ 31.42, 34.78, 46.31, 47.67, 47.89, 51.46, 107.59, 134.67, 137.38, 140.47, 157.26, 180.99. Anal. ($C_{23}H_{25}BrCl_2N_6S$) H, N; C: calcd, 48.61; found, 49.09.

3-[(1*H*-Benzimidazol-2-yl)methyl]-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (51). A mixture of 2-(aminomethyl)benzimidazole dihydrochloride hydrate (600 mg, 2.73 mmol), Et_3N (552 mg, 5.46 mmol), and **30** (1.14 g, 2.73 mmol) in THF (45 mL) was stirred overnight under nitrogen. The mixture was filtered, and the filtrate was evaporated under reduced pressure. Flash chromatography of the residue on silica gel using CH_2Cl_2/EtOH/NH_4OH (100:5:0.5) afforded 1.00 g (66%) of a solid foam. Anal. ($C_{23}H_{21}BrCl_2N_6S$) H, N; C: calcd, 48.94; found, 48.27.

3-(1*H*-Benzotriazol-5-yl)-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (52). A solution of 5-aminobenzotriazole (312 mg, 2.28 mmol) in THF (40 mL) was stirred under nitrogen and treated with a solution of **30** (950 mg, 2.28 mmol) in THF (25 mL). After the mixture stirred overnight, a TLC [silica gel, EtOAc/MeOH/concentrated NH_4OH (9:1:0.5)] of the reaction mixture indicated that only starting material was present. The mixture was refluxed for 48 h, cooled to room temperature, and evaporated under reduced pressure to afford a brown foam. Trituration of the foam with hexane afforded a solid which was recrystallized from EtOAc/hexane to give 1.08 g (86%) of **52**: mp 189.5−191.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.67 (m, 4 H), 4.78 (s, 2 H, $ArCH_2$), 6.78−8.06 (m, 11 H), 9.86 (s, 1 H, N═N−N*H*); ^{13}C NMR (DMSO-d_6) δ 46.84, 50.01, 106.02, 108.08, 115.99, 122.92, 127.04,128.67, 129.21, 130.56, 131.00, 136.47, 139.94, 147.63, 156.24, 180.72. Anal. ($C_{21}H_{19}BrCl_2N_7S$) C, H, N.

3-[4-(Piperid-1-yl)phenyl]-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (53). A solution of *N*-(4-aminophenyl)piperidine (388 mg, 2.16 mmol) in THF (40 mL) was stirred under nitrogen and treated dropwise with **30** (0.90 g, 2.16 mmol) in THF (15 mL). The reaction mixture was stirred at 40 °C for an additional 24 h. Evaporation of the solvent afforded a dark-brown oil. Trituration with hexane gave a solid which was recrystallized from Et_2O/hexane to yield 930 mg (73%) of a light-brown solid: mp 146−147.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 6 H), 3.21 (m, 4 H), 3.80 (br s, 4 H), 4.85 (s, 2 H, $ArCH_2$), 6.32 (d, 1 H, pyridine H-3), 7.30 (m, 11 H, ArH and N*H*C═SN*H*); ^{13}C NMR ($CDCl_3$) δ 24.16, 25.67, 45.07, 47.07, 49.84, 51.30, 107.59, 116.52, 125.73, 127.36, 128.23, 130.83, 137.60, 140.04, 148.11, 151.36, 156.56, 181.37. Anal. ($C_{26}H_{28}BrClN_5S$) C, H, N.

3-[4-(Piperidin-1-yl)phenyl]-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]propyl]thiourea (54). A solution of *N*-(4-aminophenyl)piperidine (0.78 g, 4.40 mmol) in THF (50 mL) was stirred under nitrogen and treated dropwise with **33** (1.90 g, 4.40 mmol) in THF (20 mL). After stirring overnight at room temperature, the solvent was removed under reduced pressure to afford an oil. Trituration of the oil with EtOAc/hexane gave a dark-brown solid which was recrystallized from EtOAc/hexane to give 1.74 g (65%) of **54**. An analytical sample was obtained by a second recrystallization from EtOAc/hexane to give a tan solid: mp 125−127 °C; ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 8 H), 3.22 (m, 4 H), 3.63 (m, 4 H), 4.49 (s, 2 H, $ArCH_2$), 6.15 (d, J = 9 Hz, 1 H, pyridine H-3), 6.90−7.56 (m, 11 H). Anal. ($C_{27}H_{30}BrCl_2N_5S$) C, H, N.

3-[2-(Pyrid-2-yl)ethyl]-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]propyl]thiourea (55). A solution of 2-(2-aminoethyl)pyridine (0.33 g, 2.71) in THF (50 mL) was cooled to 0−5 °C under a nitrogen atmosphere and treated with a solution of **33** (1.17 g, 2.71 mmol) in THF (25 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. Removal of the solvent under reduced pressure afforded an oil which was purified by flash chromatography on silica gel using EtOAc/MeOH/concentrated NH_4OH (96:4:1) as the solvent system. Fractions homogeneous by TLC were combined and evaporated to yield 1.11 g (74%) of a foam: ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 2 H), 3.00 (t, 2 H), 3.69 (m, 6 H), 4.59 (s, 2 H, $ArCH_2$), 6.30 (d, J = 9 Hz, 1 H, pyridine H-3), 6.88−8.49 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 26.82, 36.30, 41.34, 43.34, 45.89, 50.93, 107.05, 107.59, 121.84, 123.63, 125.91, 128.40, 130.67, 131.11, 132.79, 136.96, 137.99, 139.99, 148.50, 148.93, 156.57, 159.06, 181.11. Anal. ($C_{23}H_{24}BrCl_2N_5S$) C, H, N.

3-[3-[*N*-(Pyrid-2-yl)amino]propyl]-1-[3-[*N*-(4-bromobenzyl)-*N*-(pyrid-2-yl)amino]propyl]thiourea (56). A solution of **16** (419 mg, 2.76 mmol) in THF (25 mL) was cooled to 0−5 °C under a nitrogen atmosphere and treated dropwise with **32** (1.00 g, 2.76 mmol) in THF (25 mL). After stirring overnight at room temperature, the solvent was removed under reduced pressure to afford an oil. The oil was flash chromatographed on silica gel using a solvent system of CH_2Cl_2/MeOH/Et_3N (90:5:5) to yield 9 50-mL fractions. Fractions 3−9 were combined and evaporated under reduced pressure to give 1.31 g (92%) of **56** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.82−2.40 (m, 7 H), 3.58 (m, 5 H), 4.57 (s, 2 H, $ArCH_2$), 4.75 (br m, NH), 6.35−8.14 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 27.14, 29.53, 38.63, 41.17, 45.34, 51.30, 106.40, 108.29, 112.52, 112.85, 120.86, 128.18, 131.81, 136.68, 137.39, 137.77, 147.63, 158.73, 181.05; MS (CI, CH_4) m/z 513 (M^+). Anal. ($C_{24}H_{29}BrN_6S$) C, H, N.

3-[3-[*N*-(Pyrid-2-yl)amino]propyl]-1-[3-[*N*-(3,4-dichlorobenzyl)-*N*-(5-bromopyrid-2-yl)amino]propyl]thiourea (57). A solution of **24** (352 mg, 2.32 mmol) in THF (30 mL) was cooled to 0−5 °C under nitrogen and treated dropwise with **33** (1.00 g, 2.32 mmol) in THF (20 mL). After stirring overnight at room temperature, the solvent was removed under reduced pressure to afford an oil. Flash chromatography on silica gel using a solvent system of CH_2Cl_2/MeOH/Et_3N (98:1:1) gave an oil which solidified upon trituration with hexane. Recrystallization from EtOAc/hexane gave a hygroscopic solid: mp 88 °C; ^{1}H NMR ($CDCl_3$) δ 0.90−2.10 (m, 4 H), 3.50 (m, 8 H), 4.57 (s, 2 H, $ArCH_2$), 4.90 (br s, 1 H, NH), 6.30 (d, J = 9.3 Hz, 1 H, pyridine H-3), 6.45−8.18 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 27.09, 29.64, 38.63, 41.34, 41.45, 46.05, 51.14, 107.16, 107.65, 108.57, 112.90, 125.99, 128.51, 130.78, 131.21, 132.89, 137.55, 138.15, 140.10, 147.30, 148.50, 156.62, 158.79, 181.43; MS (CI, CH_4) m/z 583 (M^+). Anal. ($C_{24}H_{27}BrCl_2N_6S$) C, H, N.

3-(3-Phenylpropyl)-1-[4-[*N*-(4-bromobenzyl)-*N*-(pyrid-2-yl)amino]butyl]thiourea (58). A solution of **26** (1.00 g, 2.99 mmol) in THF (25 mL) was treated dropwise with 3-phenylpropyl isothiocyanate (530 mg, 2.99 mmol) in THF (10 mL). After stirring overnight under nitrogen at room temperature, the solvent was evaporated under reduced pressure to afford an oil. Flash chromatography using a mobile phase of CH_2Cl_2/MeOH/Et_3N (95:2.5:2.5) afforded 817 mg (55%) of **58** as a light-yellow oil. Upon standing, a tan solid formed: mp 105−108 °C; ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 6 H), 2.67 (m, 2 H), 3.50 (m, 6 H), 4.63 (s, 2 H, $ArCH_2$), 7.22 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 25.03, 25.78, 30.50, 33.21, 43.88, 44.15, 47.94, 51.35, 106.07, 112.25, 120.70, 126.17, 128.34, 128.44, 131.64, 137.55, 141.07, 147.84, 158.02, 181.75. Anal. ($C_{26}H_{31}BrN_4S$) C, H, N.

3-(3-Aminopropyl)-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (59). A suspension of *N*-(3-aminopropyl)phthalimide hydrochloride[36] (1.11 g, 4.6 mmol) and Et_3N (1.2 g, 12 mmol) in THF (50 mL) was stirred under nitrogen for 3 h. The reaction mixture was treated dropwise with the isothiocyanate **30** (1.92 g, 4.6 mmol), stirred overnight at room temperature, filtered, and evaporated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel using EtOAc/hexane/Et_3N (60:40:1) to yield 2.44 g (85%) of the phthalimide. A portion of this compound (1.92 g, 3.09 mmol) and hydrazine hydrate (1.24 g, 25.4 mmol) in absolute EtOH (100 mL) were refluxed for 8 h, cooled, and filtered. The residue was dissolved in EtOAc (60 mL) and washed with water (10 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The resulting oil was purified by flash chromatography on silica gel using EtOAc/MeOH/concentrated NH_4OH (50:50:1) to yield 1.06 g (70%) of a solid foam: ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 6 H), 2.17 (s, 2 H, NH_2), 3.50 (m, 6 H), 4.65 (s, 2 H, $ArCH_2$), 7.03 (d, J = 6 Hz, 1 H), 7.33 (m, 6 H), 8.15 (d, J = 2.2 Hz, 1 H, pyridine H-6). Anal. ($C_{18}H_{22}BrCl_2N_5S$) C, H, N.

3-[3-(Dimethylamino)propyl]-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (60). A

solution of **21** (1.00 g, 2.67 mmol) in THF (25 mL) was cooled to 0−5 °C under a nitrogen atmosphere and treated dropwise with a solution of 3-(dimethylamino)propyl isothiocyanate (385 mg, 2.67 mmol) in THF (15 mL). After stirring overnight at room temperature, the solvent was removed under reduced pressure to afford an oil. Flash chromatography on silica gel using a solvent system of EtOAc/MeOH/concentrated NH_4OH (85:15:1) gave 900 mg (65%) of **60** as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 2 H), 1.95−2.45 (m, including s at 2.23 $N(CH_3)_2$, 8 H), 2.50−3.95 (m, 6 H), 4.68 (s, 2 H, $ArCH_2$), 6.47 (d, J = 9 Hz, 1 H), 7.20 (m, 6 H), 7.55 (d, J = 2.2 Hz, 1 H), 8.18 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.32, 43.11, 44.85, 47.67, 51.52, 57.28, 107.97, 126.06, 128.55, 130.77, 131.26, 132.89, 138.09, 140.15, 148.33, 156.72, 182.46. Anal. ($C_{20}H_{26}BrClN_5S$) C, H, N.

3-[3-(Pyrrolidin-1-yl)propyl]-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]thiourea (61). A solution of *N*-(3-aminopropyl)pyrrolidine (354 mg, 2.76 mmol) in THF (50 mL) was cooled to 0−5 °C in an ice−water bath under a nitrogen atmosphere and treated with **30** (1.19 g, 2.76 mmol) in THF (25 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. Removal of the solvent under reduced pressure afforded an oil which solidified upon trituration with hexane/EtOAc. Recrystallization from EtOAc/hexane afforded 1.03 g (66%) of **61** as a white solid: mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 6 H), 2.45 (m, 6 H), 3.50 (m, 6 H), 4.68 (s, 2 H, ArH), 6.50 (d, 1 H), 7.00−7.55 (m, 6 H), 8.16 (d, J = 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.62, 28.17, 43.07, 47.89, 51.74, 107.59, 108.08, 126.33, 128.83, 130.94, 138.47, 140.26, 148.55, 156.84, 183.0. Anal. ($C_{22}H_{28}BrCl_2N_5S$) C, H, N.

3-[3-(Pyrrolidin-1-yl)propyl]-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]propyl]thiourea (62). A solution of *N*-(3-aminopropyl)pyrrolidine (354 mg, 2.76 mmol) in THF (50 mL) was cooled to 0−5 °C under a nitrogen atmosphere and treated dropwise with a solution of **33** (1.19 g, 2.76 mmol) in THF (25 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed under reduced pressure to afford an oil which solidified upon trituration with EtOAc/hexane. Recrystallization from EtOAc/hexane gave 1.03 g (66%) of **62** as a white solid: mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 8 H), 2.57 (m, 6 H), 3.60 (m, 6 H), 4.63 (s, 2 H, $ArCH_2$), 6.33 (d, J = 9 Hz, 1 H, pyridine H-3), 7.00−7.53 (m, 6 H), 8.18 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 23.46, 27.14, 41.99, 46.16, 51.09, 53.36, 53.69, 107.05, 107.48, 126.12, 128.61, 130.72, 132.72, 132.84, 138.31, 139.99, 148.55, 156.51, 182.13. Anal. ($C_{23}H_{30}BrCl_2N_5S$) C, H, N.

3-(4-Aminobutyl)-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]propyl]thiourea (63). A suspension of *N*-(4-aminobutyl)phthalimide hydrochloride[37] (1.50 g, 5.89 mmol) and Et_3N (1.49 g, 14.7 mmol) was stirred under nitrogen for 3 h at room temperature, and a solution of **33** (2.54 g, 5.89 mmol) in THF (50 mL) was added dropwise. After stirring overnight, the precipitate was filtered, and the filtrate was evaporated under reduced pressure to yield an oil. Flash chromatography on silica gel using CH_2Cl_2/MeOH/concentrated NH_4OH (100:1:1.5) as the solvent afforded 2.06 g of the intermediate phthalimide as an oil. The oil was dissolved in a mixture of 85% hydrazine hydrate (635 mg, 12.7 mmol) and absolute EtOH (75 mL) and refluxed for 8 h. The reaction mixture was cooled, filtered, and evaporated to yield an oil. Absolute EtOH (25 mL) was added, and the solution was concentrated under reduced pressure. The resulting residue was partitioned between Et_2O (200 mL) and water (50 mL), and the Et_2O phase was separated, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Flash chromatography on silica gel using EtOAc/MeOH/concentrated NH_4OH (50:50:1.2) afforded 1.15 g (70%) of **63** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 6 H), 2.80 (t, 2 H), 3.59 (m, 6 H), 4.62 (s, 2 H, $ArCH_2$), 6.35 (d, J = 9 Hz, 1 H, pyridine H-3), 6.99−7.56 (m, 6 H), 8.18 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{13}C NMR ($CDCl_3$) δ 26.33, 27.09, 30.28, 41.44, 41.61, 43.83, 50.98, 107.75, 125.90, 128.39, 130.78, 137.87, 140.15, 148.28, 156.78, 181.11. Anal. ($C_{20}H_{26}BrCl_2N_5S$) C, H; N: calcd, 13.49; found, 12.90.

3-(4-Aminobutyl)-1-[3-[*N*-(5-bromopyrid-2-yl)-*N*-(naphth-1-ylmethyl)amino]propyl]thiourea (64). A solution of *N*-(4-aminobutyl)phthalimide hydrochloride (688 mg, 2.7 mmol) and Et_3N (547 mg, 5.4 mmol) in THF (25 mL) was stirred for 2 h at room temperature. The reaction mixture was treated dropwise with a solution of **34** (1.11 g, 2.7 mmol) in THF (20 mL), and the mixture was stirred overnight under nitrogen. The precipitated Et_3N·HCl was filtered, and the filtrate was evaporated under reduced pressure to afford an oil. Purification by flash chromatography on silica gel using a solvent system of CH_2Cl_2/MeOH/concentrated NH_4OH (100:2:1) gave 1.08 g of a yellow foam. The foam was suspended in a mixture of EtOH (20 mL) and 85% hydrazine hydrate (641 mg, 12.7 mmol), and the mixture was refluxed for 5 h. The mixture was filtered to remove the precipitated phthalhydrazide, and the solvent was removed under reduced pressure to yield an oily residue. The oil was dissolved in CH_2Cl_2 (75 mL), washed with water (3 × 50 mL), separated, dried (Na_2SO_4), filtered, and evaporated to yield 700 mg of the amine as a light-yellow foam. Flash chromatography on silica gel using EtOAc/MeOH/concentrated NH_4OH (50:50:1) as the solvent yielded 650 mg (48%) of **64** as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 10 H), 2.79 (m, 2 H), 3.70 (m, 6 H), 5.06 (s, 2 H, $ArCH_2$), 6.29 (d, J = 9 Hz, 1 H), 6.70−8.20 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 26.32, 27.18, 30.27, 41.43, 41.59, 43.71, 45.39, 49.83, 106.66, 108.34, 122.37, 123.07, 125.45, 126.00, 126.43, 127.95, 129.03, 130.82, 131.03, 133.86, 140.08, 147.99, 157.47, 181.03. Anal. ($C_{24}H_{30}BrN_5S$) H; C: calcd, 57.59; found, 56.80. N: calcd, 14.00; found, 13.58.

3-[3-(1*H*-Imidazol-4-yl)propyl]-1-[2-[*N*-(5-bromopyrid-2-yl)-*N*-(3,4-dichlorobenzyl)amino]ethyl]urea (66). The amine **21** (1.5 g, 4.0 mmol) in THF (50 mL) was cooled to 0 °C in an ice bath. Triphosgene (392 mg, 1.3 mmol) was added in one portion and stirred for 5 min. A solution of Et_3N (1.22 g, 12.0 mmol) in THF (5 mL) was added dropwise, and a white precipitate formed upon stirring. The mixture was allowed to warm to 17 °C over 15 min and cooled to 0 °C. The reaction mixture was treated dropwise with a suspension of **65** (915 mg, 2.8 mmol) in THF (20 mL) over 5 min. After stirring overnight at room temperature under a nitrogen atmosphere, the solvent was removed under reduced pressure to yield a yellow foam. The intermediate trityl-protected urea was suspended in 1 N HCl (35 mL) and refluxed for 1.5 h. The solution was filtered, extracted with Et_2O (2 × 200 mL), basified with 6 N NaOH, and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with water (3 × 100 mL), dried (Na_2SO_4), and evaporated under vacuum to yield a foam. Flash chromatography on silica gel using a solvent system of CH_2Cl_2/MeOH/concentrated NH_4OH (90:10:1) yielded 300 mg of **66** as a yellow foam which was recrystallized from $CHCl_3$/hexane to afford 200 mg (10%) of an analytical sample: mp 143−146 °C; ^{1}H NMR δ 1.60 (m, 2 H), 2.50 (m, 2 H), 3.15 (m, 4 H), 3.49 (d, 2 H), 4.75 (s, 2 H, $ArCH_2$), 6.04−7.78 (m, 10 H), 8.12 (d, J = 2.4 Hz, 1 H, pyridine H-6); ^{1}C NMR ($CDCl_3$) δ 23.84, 30.12, 38.19, 39.93, 48.60, 50.27, 106.07, 108.19, 116.90, 127.25, 128.94, 129.50, 130.72, 131.16, 134.90, 136.00, 139.77, 140.37, 147.90, 156.51, 158.41. Anal. ($C_{21}H_{23}BrCl_2N_6O$) C, H, N.

Biological Assay. Cell Lines Expressing sst Receptor Subtypes. BHK cells (tk-ts13, ATCC CRL# 1573) were grown to 20−40% confluency in a tissue dish in DMEM containing 1% penicillin/streptomycin, 10% fetal bovine serum, and 1% Glutamax. Prior to transfection, the cells were washed twice with calcium-free PBS after which 20 mL of serum-free DMEM was added to the cells.

Transfection was carried out as described previously (product description: Lipofectamin, Gibco BRL catalog no. 18324-012). Briefly, 10 μg of cDNA encoding an sst receptor subtype inserted into the mammalian vector pcDNA3 (Invitrogen) was diluted with 300 μL of sterile water. Lipofectamin (30 μg) was diluted in 300 μL of sterile water, and the cDNA and lipofectamin/cDNA mixture was added dropwise to the cells (HEK

293 cells for sst_2 and BHK cells for sst_4) while the plates were gently swirled. The cells were then incubated for 16−24 h, after which the medium was replaced with standard medium containing 1 mg/mL Geneticin (G-418 sulfate). Resistant colonies appearing after 1−2 weeks were isolated and propagated for further characterization.

Binding Assay. Cells expressing individual sst receptor subtypes were resuspended in buffer [50 mM Tris-HCl (pH 7.4), 1 mM EGTA, 5 mM $MgCl_2$] and homogenized. Membranes were washed twice in buffer by homogenization and centrifugation. Final membrane pellets were resuspended at a protein concentration of 125 μg/mL in buffer. Binding assays using 75 pM [^{125}I]Tyr-SRIF (Amersham, IM-161) were done in duplicates in minisorb polypropylene tubes in a volume of 250 μL. The assays were incubated at 30−37 °C for 30−90 min depending on the receptor subtype. Binding was terminated by filtration through Whatman GF/B glass fiber filters presoaked for 4 h in 0.5% poly(ethylenimine) and 0.1% BSA. Filters were washed three times with 5 mL of ice-cold 0.9% saline and counted in a Packard Cobra II gamma counter.

Functional Assay. Baby hamster kidney (BHK) cells expressing the human sst_4 receptor were seeded in 24-well tissue culture multidishes at 200 000 cells/well and grown for 16−20 h. The medium was removed, and fresh DMEM medium, supplemented with (1) 3-isobutyl-1-methylxanthine (IBMX), (2) forskolin (5 μM) or medium, and (3) medium, SRIF, or compound, was added. The plates were incubated for 15−30 min at 37 °C, the reaction medium was removed, and the cells were lysed with 0.1 M NaOH. Following neutralization with 0.1 M HCl, an aliquot was removed for cAMP determination using Amersham SPA RIA (RPA 538).

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