Phenethylthiazolylthiourea (PETT) Compounds as a New Class of HIV-1 Reverse Transcriptase Inhibitors. 2. Synthesis and Further Structure−Activity Relationship Studies of PETT Analogs

Amanda S. Cantrell,[†] Per Engelhardt,[‡] Marita Högberg,*[,‡] S. Richard Jaskunas,[†] Nils Gunnar Johansson,[‡] Christopher L. Jordan,[†] Jussi Kangasmetsä,[‡] Michael D. Kinnick,[†] Peter Lind,[‡] John M. Morin, Jr.,[†] M. A. Muesing,[†] Rolf Noreén,[‡] Bo Öberg,[‡,§] Paul Pranc,[†] Christer Sahlberg,[‡] Robert J. Ternansky,[†] Robert T. Vasileff,[†] Lotta Vrang,[‡] Sarah J. West,[†] and Hong Zhang[‡]

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, Medivir AB, Huddinge, Sweden, and MTC, Center for Microbiology and Tumorbiology, The Karolinska Institute, Stockholm, Sweden

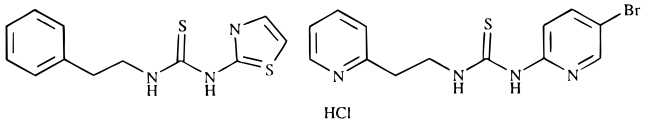
Received August 29, 1995[⊗]

Phenylethylthiazolylthiourea (PETT) derivatives have been identified as a new series of non-nucleoside inhibitors of HIV-1 RT. Structure−activity relationship studies of this class of compounds resulted in the identification of *N*-[2-(2-pyridyl)ethyl]-*N*′-[2-(5-bromopyridyl)]-thiourea hydrochloride (trovirdine; LY300046·HCl) as a highly potent anti-HIV-1 agent. Trovirdine is currently in phase one clinical trials for potential use in the treatment of AIDS. Extension of these structure−activity relationship studies to identify additional compounds in this series with improved properties is ongoing. A part of this work is described here. Replacement of the two aromatic moieties of the PETT compounds by various substituted or unsubstituted heteroaromatic rings was investigated. In addition, the effects of multiple substitution in the phenyl ring were also studied. The antiviral activities were determined on wild-type and constructed mutants of HIV-1 RT and on wild-type HIV-1 and mutant viruses derived thereof, Ile100 and Cys181, in cell culture assays. Some selected compounds were determined on double-mutant viruses, HIV-1 (Ile100/Asn103) and HIV-1 (Ile100/Cys181). A number of highly potent analogs were synthesized. These compounds displayed IC_{50}'s against wild-type RT between 0.6 and 5 nM. In cell culture, these agents inhibited wild-type HIV-1 with ED_{50}'s between 1 and 5 nM in MT-4 cells. In addition, these derivatives inhibited mutant HIV-1 RT (Ile 100) with IC_{50}'s between 20 and 50 nM and mutant HIV-1 RT (Cys 181) with IC_{50}'s between 4 and 10 nM, and in cell culture they inhibited mutant HIV-1 (Ile100) with ED_{50}'s between 9 and 100 nM and mutant HIV-1 (Cys181) with ED_{50}'s between 3 and 20 nM.

Thus far, only four antiviral drugs have been approved for use against human immunodeficiency virus (HIV) in the treatment of AIDS, namely AZT (azidothymidine), ddI (2′,3′-dideoxyinosine), ddC (2′,3′-dideoxycytidine),[1] and d4T (2′,3′-didehydro-2′,3′-dideoxythymidine).[2,3] All of these agents target the retroviral enzyme, HIV reverse transcriptase (RT). These nucleoside analogs are prodrugs and rely on cellular kinases to convert them into their active triphosphate form. Unfortunately, the utility of these agents has been limited by serious toxic side effects, emergence of resistant virus, and limited efficacy. Nonnucleoside inhibitors of this vital retroviral enzyme have also been described. A number of such agents have been, or are being, investigated in clinical trials including the dipyridodiazepinones,[4] pyridinones,[5] tetrahydroimidazobenzodiazepinethiones (TIBO),[6] bis(heteroaryl)piperazines (BHAP),[7] and anilidophenylacetamides (α-APA).[8] These agents display high anti-HIV-1 activity and relatively low toxicity, but rapid development of resistance to such agents has been a major clinical problem.[9,10]

We recently described a new class of nonnucleoside HIV-1 RT inhibitors.[11−14] These (phenethylthiazolylthioureas) (PETTs) were derived from a systematic disassemblage of the molecular architecture of the known TIBO HIV-1 RT inhibitors. The lead compound in this series, LY73497 (Scheme 1), was shown to inhibit HIV-1 RT and HIV-1 in cell culture. Through an integrated effort involving molecular modeling, chemical synthesis, and biological evaluation, modification of LY73497 led to the development of trovirdine *N*-[2-(2-pyridyl)ethyl]-*N*′-[2-(5-bromopyridyl)]thiourea hydrochloride (LY300046·HCl). This compound is currently in phase one clinical trials for potential use in the treatment of AIDS.

Scheme 1



LY 73497 **LY 300046 HCl**

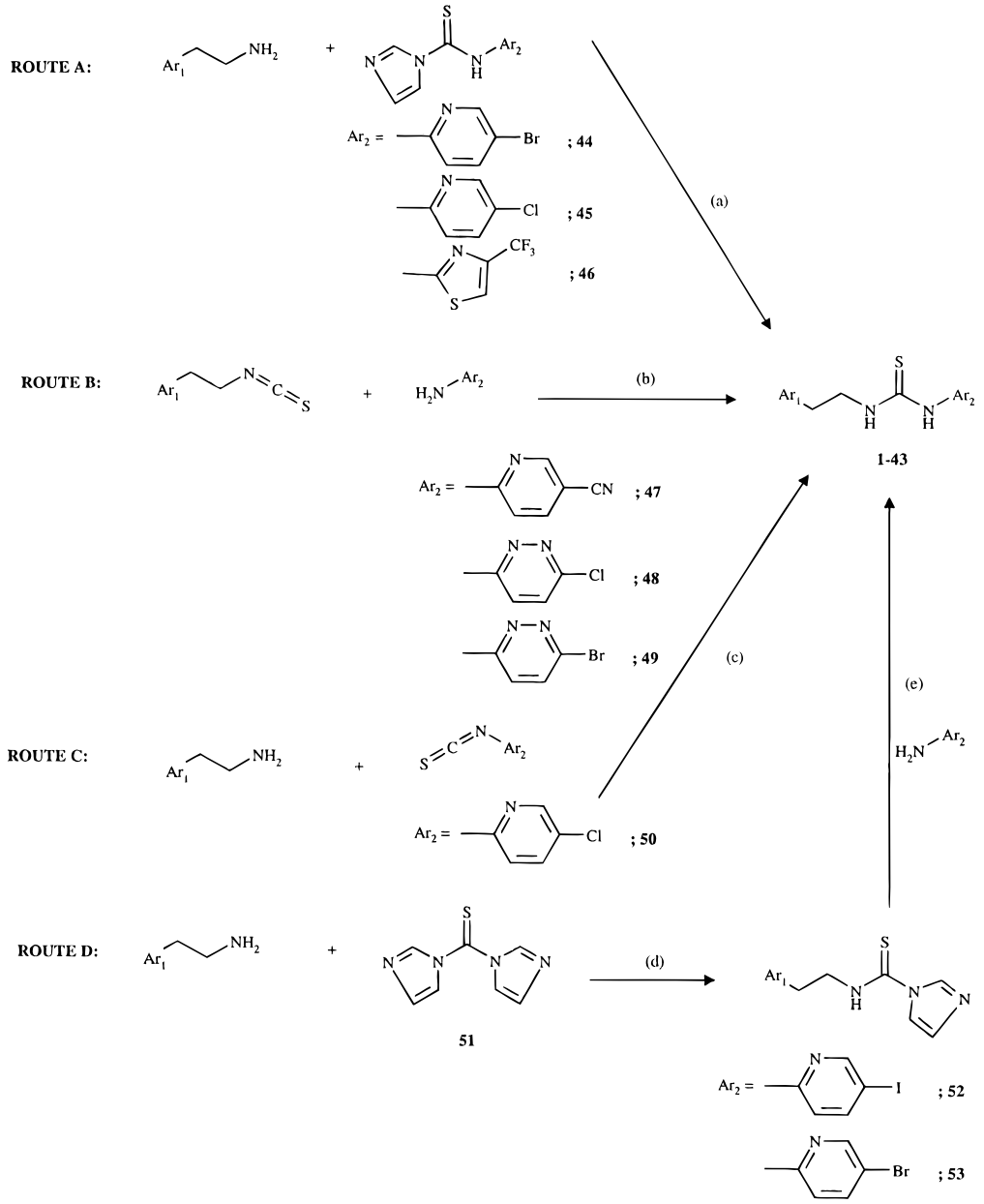
(trovirdine)

In order to further explore the potential of the PETT compounds as anti-HIV agents, we report here the synthesis and anti-HIV activities of 43 new PETT compounds. The effects of introducing alternative heteroaromatic rings and various substituents on the two aromatic and heteroaromatic moieties of LY73497 and LY300046·HCl were investigated. Inhibition assays using mutant HIV-1 RT (Ile100) and (Cys181) and virus with the Ile100 and Cys181 mutations were useful in the antiviral evaluation of these compounds.[15]

[†] Lilly Research Laboratories.
[‡] Medivir AB.
[§] The Karolinska Institute.
[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

S0022-2623(95)00639-X CCC: $12.00

Scheme 2[a]



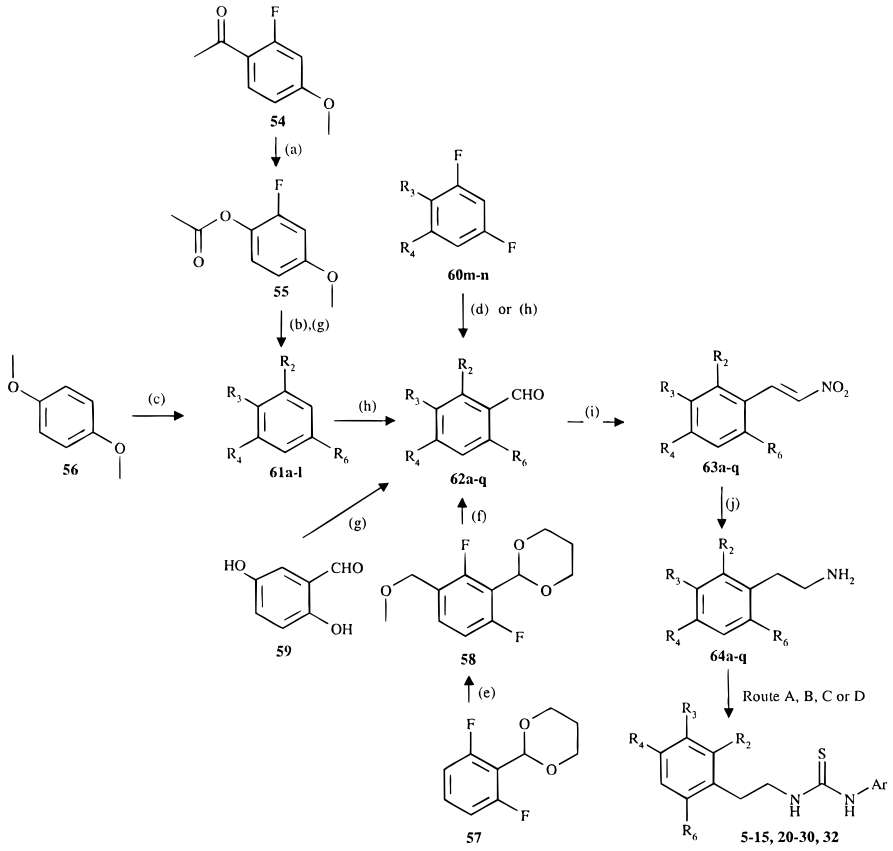
[a] Reagents and conditions: (a) acetonitrile, DMF or 1-methylpyrrolidone, 80−100 °C; (b) (1) acetonitrile, room temperature, (2) DMF, 95 °C or (1) acetonitrile, room temperature, (2) NaH, THF, 0 °C to room temperature; (c) acetonitrile, room temperature; (d) acetonitrile, 0 °C to room temperature; (e) DMF, 100 °C.

Chemistry

The compounds described in the present study, i.e. compounds **1**−**43** (Tables 1 and 2), were synthesized according to the general routes A−D depicted in Scheme 2. In route A thiocarbonyl reagents **44**−**46** derived from appropriate aminopyridines or aminothiazole and 1,1′-thiocarbonyldiimidazole **51** were condensed with appropriate phenethylamines, either commercially available or prepared according to Schemes 3 and 4. Phenethyl isothiocyanates (route B) were condensed with aminopyridine **47** (prepared by the reaction of 2-amino-5-chloropyridine with sodium cyanide) or the commercially available aminopyridazines **48** and **49**, or with the anions thereof. Isothiocyanates **50**[16] derived from 2-amino-5-chloropyridine and 1,1′-thiocarbonyldiimidazole **51** were reacted with phenethylamines (route C). A thiocarbonyl reagent (route D) which was prepared from a phenethylamine and 1,1′-thiocarbonyldiimidazole **51** was condensed with the appropriate aminopyridines, **52**[17] and **53** (commercially available).

Phenethylamines **64a**−**q** were prepared from aldehydes **62a**−**q** by condensation of the appropriate aldehyde with nitromethane[18] to give compounds **63a**−**q** followed by reduction with $LiAlH_4$ (Scheme 3). Reaction of compounds **61a**−**l** with *n*-BuLi and then DMF afforded aldehydes **62a**−**l.** Reaction of **60m,n** with $POCl_3$ or *n*-BuLi and DMF gave aldehydes **62m,n**. Aldehyde **62o** was prepared in three steps from 2,6-difluorobenzaldehyde via compounds **57** and **58**. Aldehyde **62p** was prepared from 2,5-dihydroxybenzaldehyde **59** by alkylating with EtI. Aldehyde **62q** was commercially available. Compounds **61a**−**j** were prepared from commercially available phenols by alkylation with MeI or EtI. Fluorination of 1,4-dimethoxybenzene **56** gave compound **61k**. Compound **61l** was commercially available. Compound **61f** was prepared from 2′-fluoro-4′-

Scheme 3[a]



60-64:

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q
R_2	F	Cl	Cl	F	F	F	MeO	F	F	F	F	F	F	F	F	H	H
R_3	H	EtO	EtO	EtO	F	EtO	MeO	MeO	EtO	F	MeO	H	H	$N(Me)_2$	MeOMe	EtO	MeO
R_4	H	H	Cl	H	H	H	H	H	H	H	H	F	$N(Me)_2$	H	H	H	H
R_6	EtO	F	F	Cl	EtO	MeO	F	F	F	MeO	MeO	F	F	F	F	EtO	MeO

[a] Reagents and conditions: (a) mCPBA, $NaHCO_3$, $CHCl_3$, room temperature; (b) NH_3, MeOH, room temperature (c) (1) *n*-BuLi, THF, room temperature, (2) NFSI, −70 °C; (d) DMF, $POCl_3$; (e) (1) *n*-BuLi, THF −70 °C, (2) $ClCH_2OCH_3$, −70 °C to room temperature; (f) HCl(aq) dioxane, room temperature; (g) EtI or MeI, K_2CO_3, acetone 50−60 °C; (h) (1) *n*-BuLi, THF, −65 °C, (2) DMF, −65 °C to room temperature; (i) (1) CH_3NO_2, NaOH, MeOH, −3 °C, (2) HCl or CH_3NO_2, NH_4OAc, EtOH or CH_3NO_2, NH_4OAc, CH_3COOH; (j) $LiAlH_4$, THF, reflux.

methoxyacetophenone **54**. Routes from phenethylamines **64a**−**q** to compounds **5, 7**−**15, 20**−**30**, and **32** are listed in Table 1.

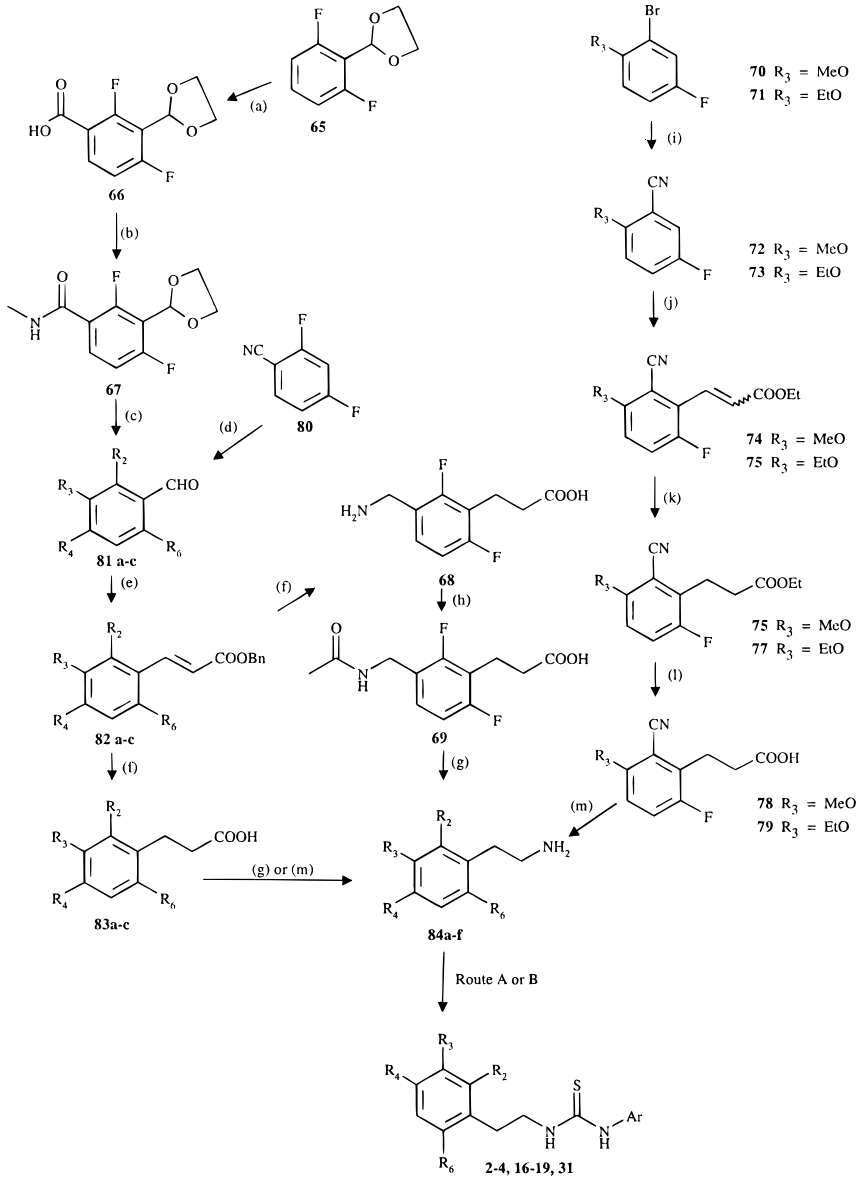
Starting amines **84a**−**f** in Scheme 4 were prepared from acids **69, 78, 79,** and **83a**−**c** via the corresponding azides followed by Curtius rearrangement. The resulting isocyanates were then hydrolyzed to the corresponding amines. Acids **69** and **83a**−**c** were obtained from aldehydes **81a**−**c** (by Wittig reactions) via benzoyl esters **82a**−**c**. Condensation of **81a**−**c** with ((benzyloxycarbonyl)methyl)triphenylphosphorane in toluene and hydrogenation−hydrolysis of intermediates **82a**−**c** gave acids **69** and **83a**−**c**. 1-Alkoxy-2-bromo-4-fluorobenzenes **70** and **71** were converted with NaCN and Ni−triphenylphosphine complex to 1-alkoxy-2-cyano-4-fluorobenzenes **72** and **73**. Reaction of compounds **72** and **73** with LDA and DMF gave aldehydes which were condensed with (carbethoxymethylene)triphenylphosphorane to afford compounds **74** and **75**. Hydrogenation and hydrolysis then gave acids **78** and **79**. Compound **65** was prepared from 2,6-difluorobenzaldehyde by conversion to the corresponding acetal with ethylene glycol, triethyl orthoformate, and *p*-TSA. Reaction of compound **65** with *n*-BuLi and CO_2 gave compound **66**, which was converted to carboxamide **67** via the acid chloride. Compound **67** was deprotected to give aldehyde **81b**. Reaction of compound **80** with LDA and DMF gave aldehyde **81a**. Aldehyde **81c** was commercially available. Compound **82a** was hydrogenated and hydrolyzed to compound **68** followed by acylation with acetic anhydride to afford acid **69**. Routes from phenethylamines **84a**−**f** to compounds **2**−**4**, **16**−**19**, and **31** are listed in Table 1.

The two furan analogs **35** and **36** were prepared by the procedure outlined in Scheme 5.[19] Heterocyclic analogs **39**, **40**, and **41** were prepared as described in Scheme 6. Compounds **33**, **34**, **37**, and **38** were prepared from commercially available amines. Phthalimidyl analogs **42** and **43** were readily prepared starting from compounds **133** and **45** as outlined in Scheme 7. Routes from phenethylamines to compounds **33**−**42** are listed in Table 2.

Biological Results and Discussion

All compounds **1**−**43** in this study were tested in HIV-1 RT enzyme assays, with wild-type and two constructed mutants, Ile100 and Cys181.[15] These de-

Scheme 4[a]



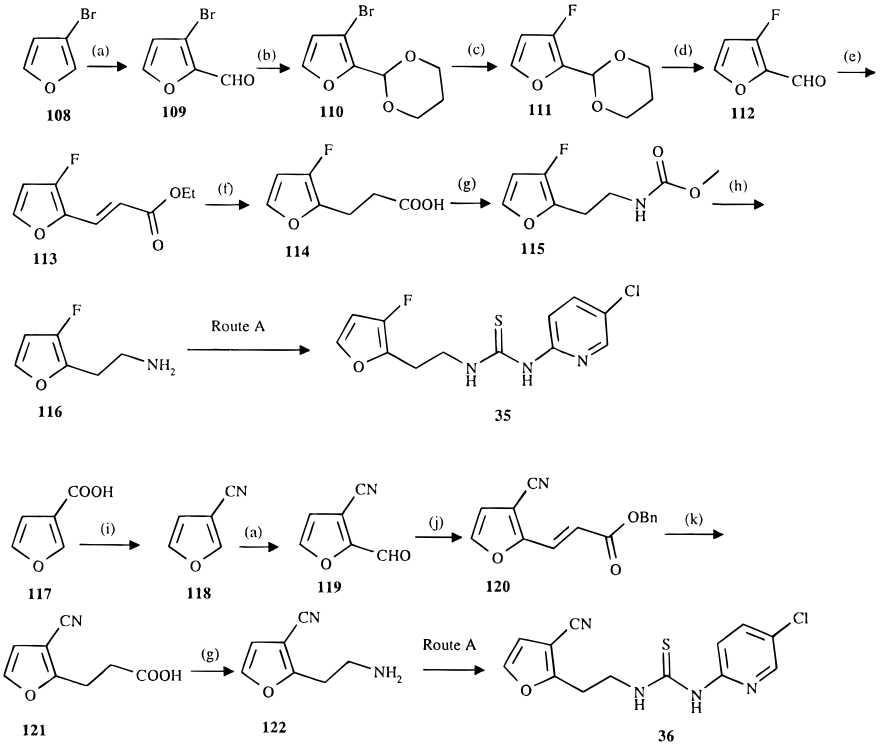
81-84:

	a	b	c	d	e	f
R_2	F	F	F	F	CN	CN
R_3	CN	(C=O)NMe	CN	CH_2NAc	MeO	EtO
R_4	H	H	$N(Me)_2$	H	H	H
R_6	F	F	H	F	F	F

[a] Reagents and conditions: (a) *n*-BuLi, THF, −70 °C, CO_2; (b) $SOCl_2$, *N*,*N*-diisopropylamine, CH_3NH_2, CH_2Cl_2, 0−20 °C; (c) *p*-TSA, H_2O, dioxane, 60 °C; (d) LDA, THF, −75 °C, DMF; (e) ((benzyloxycarbonyl)methyl)triphenylphosphorane toluene, 50 °C; (f) H_2, Pd/C, MeOH, HOAc; (g) (1) TEA, ethyl chloroformate, acetone 0 °C, NaN_3/H_2O, (2) toluene 90 °C, (3) HCl(aq), dioxane, room temperature; (h) $(AcO)_2O$, 50−60 °C; (i) NaCN, $Ni[P(Ph)_3]_4$, acetonitrile, 50−60 °C; (j) LDA, DMF, HOAc, (carbethoxymethylene)triphenylphosphorane, −70 °C; (k) H_2, Pd/C, MeOH; (l) NaOH, $EtOH/H_2O$; (m) (1) DPPA, TEA, THF, 50 °C, (2) 110 °C, toluene, (3) HCl/dioxane.

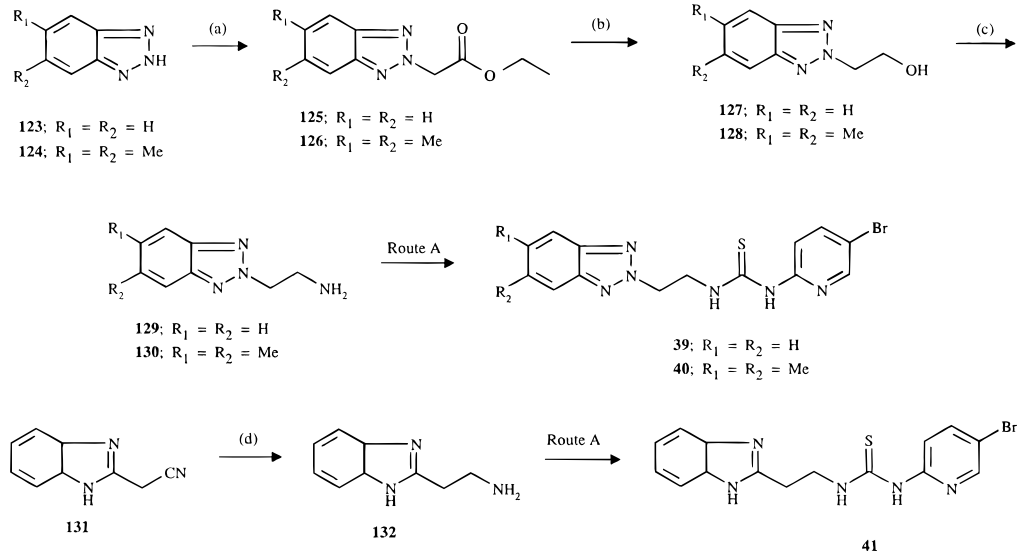
rivatives were also tested in cell culture using MT-4 cells[20] on both wild-type virus and virus containing the mutations Ile100 and Cys181. These mutations, Ile100 and Cys181, were observed at an early stage when studying PETT compounds in cell culture. It is well-known that non-nucleoside HIV-1 RT inhibitors give rise to the Cys181 mutation in both cell culture and clinic.[21] Since a clinical situation most probably will involve problems with double mutations, a selection of compounds were also tested on viruses containing the double mutations Ile100/Asn103 and Ile100/Cys181. The IC_{50} and ED_{50} values from these experiments are shown in Tables 1−3. In the original SAR studies on the PETT compounds the lead compound LY73497, *N*-(2-phenylethyl)-*N*′-(2-thiazolyl)thiourea, was segmented into four quadrants: (1) the phenyl ring, (2) the ethyl linker, (3) the thiourea moiety, and (4) the thiazole heterocycle.[14] In this study only the first and fourth quadrants were varied. Compounds **1**−**9** (Table 1) show the influence of varied substituents in position 3 of the 2,6-difluorophenyl ring on antiviral activity. The greatest effect was exhibited by carboxamido and acetamido substituents which decreased the activity in all tests. The *N*,*N*-dimethylamino substituent decreased the activity on RT mutants and in cell culture, while the HIV-1 RT (wt) activity was less affected.

Scheme 5[a]



[a] Reagents and conditions: (a) LDA, THF, −78 °C, DMF; (b) propylene glycol *p*-TSA, ambient temp; (c) *n*-BuLi, *N*-fluorobenzenesulfonimide, THF, −78 °C; (d) *p*-TSA, H_2O, dioxane, room temperature; (e) (carbethoxymethylene)triphenylphosphorane, room temperature; (f) (1) H_2, Pd/C, MeOH/H_2O, room temperature, (2) dioxane/H_2O, NaOH, 50 °C; (g) (1) TEA, toluene, DPPA, reflux, (2) MeOH, reflux or HCl/dioxane; (h) dioxane/MeOH/H_2O, reflux; (i) 1,3-dicyanobenzene, 300 °C; (j) ((benzyloxycarbonyl)methyl)triphenylphosphonium bromide; (k) (1) H_2, Pd/C, MeOH, (2) K_2CO_3.

Scheme 6[a]

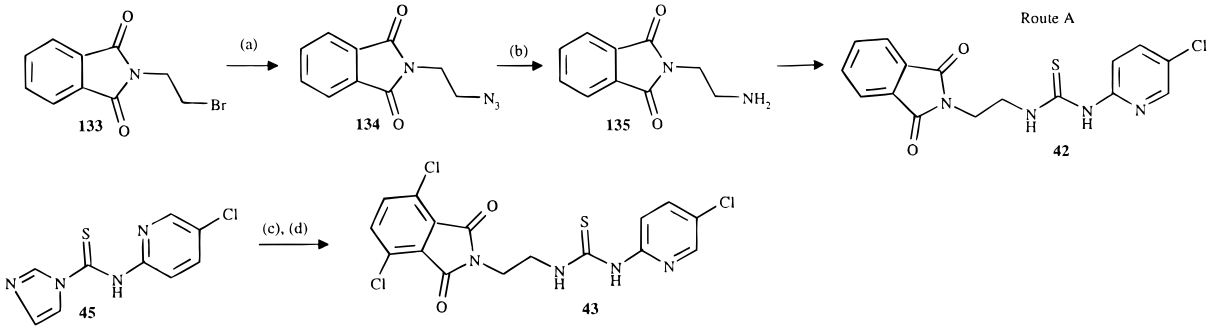


[a] Reagents and conditions: (a) ethyl bromoacetate, K_2CO_3, DMF, 40 °C; (b) $LiBH_4$, Et_2O; (c) triflic anhydride, pyridine, NH_3, −50 °C; (d) $NiCl_2$, $NaBH_4$, MeOH.

Variation of different heterocycles on the thiazole portion of the molecule, compounds **10**−**15**, is also shown in Table 1. 5-Bromopyrid-2-yl, 5-chloropyrid-2-yl, and 5-cyanopyrid-2-yl gave the highest activity when considering the effect on both RT mutants (Ile100) and (Cys181) and mutant HIV-1 (Ile100) and (Cys181). The same activity spectrum was also seen with the 2-cyano-3-methoxy-6-fluorophenethyl compounds **17** and **18**. A change from pyridyl to pyridazyl resulted in a decrease in activity against RT mutants and in the cell culture assays as evidenced from compounds **11** and **14**.

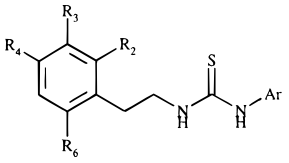
2,6-Difluoro- and 2-fluoro-6-ethoxyphenyl substitution in quadrant 1, compounds **1** and **22**, respectively, exhibited approximately equal activities, but still compound **22** was better on mutant HIV-1 strains than compound **1**. 2,5-Diethoxy substitution of the phenyl ring, compound **21,** resulted in a decrease in activity against HIV-1-RT mutants, when compared with 2,5-dimethoxy substitution on the phenyl ring of compound **20**. 2-Fluoro-3,6-dialkoxy substitution of compounds **25** and **26** compared with 2,5-dialkoxy substitution of compounds **20** and **21** gave much higher activities

Scheme 7[a]



[a] Reagents and conditions: (a) NaN_3, NaI, acetone/H_2O; (b) PPh_3, TFA, H_2O, dioxane/H_2O; (c) $H_2NCH_2CH_2NH_2$; (d) 3,6-dichlorophthalic anhydride, acetonitrile.

Table 1. Inhibition of HIV-1 (IIIB) RT and HIV-1 (IIIB) Replication

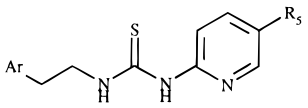


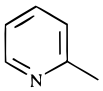
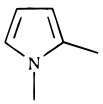
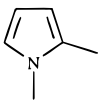
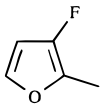
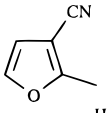
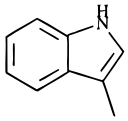
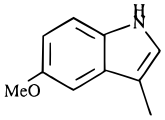
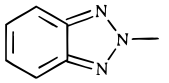
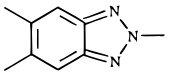
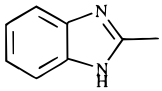
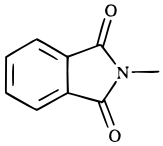
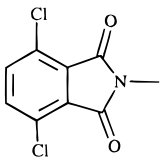
							HIV-1 RT (rCdG), IC_{50}, μM[a]			HIV-1 MT-4 cells, ED_{50}, μM[b]		
compd	R_2	R_3	R_4	R_6	Ar	route	wt	Ile100	Cys181	wt	Ile100	Cys181
1	F	H	H	F	5-bromopyrid-2-yl	D	0.001	0.05	0.030	0.013	0.60	0.150
2	F	(C═O)NMe	H	F	5-bromopyrid-2-yl	A	0.023	>2.0	>2.0	0.080	>2.0	0.300
3	F	CH_2NAc	H	F	5-bromopyrid-2-yl	A	0.045	>2.0	>2.0	0.900	>2.0	>2.0
4	F	CN	H	F	5-chloropyrid-2-yl	A	0.009	0.40	0.090	0.006	0.80	0.050
5	F	$N(Me)_2$	H	F	5-chloropyrid-2-yl	C	0.008	1.90	0.190	0.040	>2.0	0.700
6	F	$N(Me)_2$	H	F	5-bromopyrid-2-yl	A	0.007	1.90	0.170	0.040	>2.0	1.0
7	F	MeO	H	F	5-bromopyrid-2-yl	A	0.006	0.87	0.060	0.015	0.60	0.050
8	F	EtO	H	F	5-bromopyrid-2-yl	A	0.004	0.17	0.020	0.006	0.10	0.006
9	F	CH_2OMe	H	F	5-bromopyrid-2-yl	A	0.004	0.72	0.100	0.006	2.5	0.300
10	Cl	EtO	H	F	5-bromopyrid-2-yl	A	0.012	0.19	0.050	0.007	0.40	0.030
11	Cl	EtO	H	F	5-chloropyrid-2-yl	A	0.006	0.13	0.030	0.008	0.60	0.007
12	Cl	EtO	H	F	5-iodopyridin-2-yl	D	0.008	0.42	0.130	0.015	3.0	0.200
13	Cl	EtO	H	F	5-cyanopyrid-2-yl	B	0.005	0.11	0.030	0.003	0.50	0.030
14	Cl	EtO	H	F	5-chloropyridazin-2-yl	B	0.005	0.77	0.260	0.020	>2.0	1.0
15	Cl	EtO	H	F	5-(trifluoromethyl)-thiazol-2-yl	A	0.047	7.0	7.0	0.070	>2.0	>2.0
16	CN	EtO	H	F	5-bromopyrid-2-yl	A	0.002	0.14	0.210	0.004	0.04	0.005
17	CN	MeO	H	F	5-bromopyrid-2-yl	A	0.001	0.05	0.050	0.003	0.25	0.040
18	CN	MeO	H	F	5-cyanopyrid-2-yl	B	0.003	0.06	0.050	0.001	0.20	0.030
19	CN	MeO	H	F	5-chloropyrid-2-yl	B	0.005	1.10	1.10	0.011	0.40	0.100
20	H	MeO	H	MeO	5-chloropyrid-2-yl	A	0.005	0.18	0.063	0.040	>2.0	0.900
21	H	EtO	H	EtO	5-bromopyrid-2-yl	A	0.018	1.65	0.707	0.018	>2.0	0.800
22	F	H	H	EtO	5-bromopyrid-2-yl	A	0.006	0.05	0.025	0.013	0.09	0.007
23	F	F	H	EtO	5-bromopyrid-2-yl	A	0.005	0.02	0.010	0.007	1.50	0.200
24	F	F	H	MeO	5-bromopyrid-2-yl	A	0.003	0.05	0.004	0.007	0.60	0.040
25	F	MeO	H	MeO	5-chloropyrid-2-yl	C	0.001	0.08	0.054	0.002	0.009	0.003
26	F	EtO	H	MeO	5-chloropyrid-2-yl	C	0.005	0.16	0.034	0.005	0.09	0.009
27	MeO	MeO	H	F	5-bromopyrid-2-yl	A	0.007	0.43	0.085	0.012	3.0	0.200
28	F	EtO	H	Cl	5-bromopyrid-2-yl	A	0.002	0.09	0.009	0.018	0.90	0.050
29	F	H	F	F	5-chloropyrid-2-yl	C	0.002	0.81	0.290	0.010	2.0	1.50
30	F	H	$N(Me)_2$	F	5-chloro)pyrid-2-yl	C	0.020	0.27	0.130	0.018	1.50	0.900
31	F	CN	$N(Me)_2$	H	5-bromopyrid-2-yl	A	0.008	0.21	0.110	0.013	0.15	0.020
32	Cl	EtO	Cl	F	5-bromopyrid-2-yl	A	0.021	0.24	0.660	0.013	1.0	0.160
9-Cl-TIBO							0.200	32.2	13.0	0.250	>22	124
L-697,661							0.100	0.85	7.70	0.065	0.85	>11
nevirapine							0.200	11.8	201	0.150	0.62	22

[a] The HIV-1 RT assay which used (poly)rC·(oligo)dG as the template/primer is described in ref 15. [b] Anti HIV activity assay: MT-4 cells (human T cell line) grown in RPMI 1640 medium supplemented with 10% fetal calf serum, penicillin and streptomycin were seeded into 96-well microplates (2×10^4 cells/well) and infected with 10−20 $TCID_{50}$ of wt and mutant HIV-1, IIIB, per well. Test compounds in different concentrations were added. The cultures were incubated at 37 °C in CO_2 atmosphere, and the viability of cells was determined at day 5 or 6 with XTT vital dye.[20] The anti HIV-1 activity was measured as the reduction in cytopathic effect caused by the virus. Mutant HIV-1 was achieved by passaging the virus in MT-4 cells in stepwise increasing concentrations of different non-nucleoside HIV-1 RT inhibitors. When virus was growing in highest possible, nontoxic concentration of the compound it was passaged once without compound. Cellular DNA was analyzed with respect to nucleotide sequence in the HIV-1 RT gene, and the supernatant was frozen in aliquots at −70 °C for cross-resistance studies.

against mutant HIV-1 strains. In addition, compounds **29**−**32** with a substituent in the 4-position of the phenyl ring displayed diminished activity against both RT mutants and mutant HIV-1 strains. The activities of

Table 2. Inhibition of HIV-1 (IIIB) RT and HIV-1 (IIIB) Replication



Compd	Ar	R_5	Route	HIV-1 RT (rCdG) IC_{50}, μM[a] wt	Ile100	Cys181	HIV-1 MT-4 cells ED_{50}, μM[b] wt	Ile100	Cys181
LY300046·HCl		Br		0.015	0.43	2.50	0.020		
33		CN	B	0.070	3.50	1.10	0.110	>2.0	>2.0
34		Cl	C	0.090	2.70	1.40	0.250	>2.0	>2.0
35		Cl	A	0.004	0.23	0.14	0.007	0.10	0.08
36		Cl	A	0.060	2.60	2.60	0.020	0.70	0.20
37		Br	A	0.030	>2.5	0.32	0.110	3.0	0.30
38		Br	A	0.320	>2.5	2.5	0.500	>2.0	0.90
39		Br	A	0.003	2.00	0.10	0.014	2.0	1.0
40		Br	A	0.150	>2.5	0.10	0.220	>2.0	>2.0
41		Br	A	0.021	>2.5	1.86	0.120	2.5	0.9
42		Cl	A	0.001	0.28	0.13	0.005	0.2	0.04
43		Cl		0.002	0.23	0.01	0.019	>2.0	>2.0

[a,b] See footnote *a* and *b*, Table 1.

9-Cl-TIBO,[6] L-697,661,[5] and nevirapine[4] are included for reference in Table 1.

The first candidate of the PETT series chosen for clinical evaluation, trovirdine (*N*-[2-(2-pyridyl)ethyl]-*N*′-[2-(5-bromopyridyl)]thiourea hydrochloride (LY300046·HCl)), inhibited HIV-1 RT (wt) with an IC_{50} of 15 nM and had an ED_{50} of 20 nM in cell culture.[14,22] Table 2 shows the effects of different heterocycles on the left hand side of the molecule. The 2-(3-fluorofuranyl) compound **35** and phthalimidyl compound **42** had the highest activities in this series. Table 3 shows the inhibitory activity of 14 selected compounds against mutant HIV-1 (Ile100/Asn103) and (Ile100/Cys181).

In conclusion, most of these PETT compounds had a high inhibitory activity both on HIV-1 RT and against HIV-1 in cell culture, higher than the reference com-

Table 3. Inhibition of HIV-1 (IIIB) Variants in Cell Culture

	HIV-1 MT-4 cells, ED_{50}, μM[a]	
compd	Ile100/Asn103	Ile100/Cys181
4	>10	>10
8	10	1.2
16	>10	3.0
17	>10	>10
22	1.6	1.0
23	>10	>10
24	>10	>10
25	1.0	1.0
26	>10	>10
28	>10	>10
31	5.5	7.5
35	>10	>10
42	>10	15
nevirapine	8.0	>10

[a] See footnote *b*, Table 1.

pounds, 9-Cl-TIBO, L-697,661, and nevirapine. The most potent inhibitors of mutant RT (Ile100) were **1**, **17**, **22, 23**, and **24** (Table 1). These compounds contain hydrogen, fluorine, or methoxy group in the meta position of the phenyl ring in combination with a 2-(5-bromopyridyl) on the right hand side (quadrant 4) of the molecule. Compound **18** (Table 1) with a 2-(5-cyanopyridyl) moiety in quadrant 4 had comparable activity against RT (Ile100). The most potent inhibitor of mutant RT (Cys181) was compound **24**, closely followed by compounds **28** and **23**. The most potent inhibitors of mutant HIV-1 (Ile100) were compounds **16**, **25**, and **26**, and of mutant HIV-1 (Cys181), compounds **8**, **11**, **16**, **22**, **25**, and **26**. Compounds **22** and **25** gave the highest activities against double-mutant HIV-1 (Ile100/Asn103) and (Ile100/Cys181) (Table 3). 5-Bromo-, 5-chloro-, and 5-cyanopyrid-2-yl were the preferred substituents for quadrant 4. 2,3,6-Trisubstituted phenyl rings with chlorine, fluorine, ethoxy, methoxy, or cyano substituents were the preferred groups for the left hand side (quadrant 1) of the molecule.

Experimental Section

Chemistry. All melting points were determined on an Electrothermal 9100 capillary melting point apparatus and are uncorrected. Analytical results are indicated by atom symbols and are within 0.4% of theoretical values except where indicated. ^{1}H NMR spectra were recorded on Bruker AC-250 (250 MHz) and General Electric QE-300 (300 MHz) spectrometers using TMS as the internal standard. Yields were not optimized. Merck silica gel, 230−400 mesh, was used for chromatography. 9-Cl-TIBO was purchased from Pharmatech Int. Inc. L-697,661 (3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)-methyl]amino}-5-ethyl-6-methylpyridin-2(1*H*)-one) was kindly supplied by Dr. M. E. Goldman at Merck, Sharp and Dohme Research Laboratories (Rahway, NY). Nevirapine was synthesized according to published methods.[4b]

Route A. General Procedure. To a suspension of compound **44, 45**, or **46** (1.1 equiv) in acetonitrile, DMF, or 1-methylpyrrolidinone (2 mL/mmol) was added an appropriate phenyl- or pyridylethylamine (1 equiv). The reaction mixture was heated to 80−110 °C for 1−68 h and cooled to room temperature. The reaction mixture was worked up, and the crude material was purified by either recrystallization or column chromatography.

1-[[2-(5-Bromopyridyl)]thiocarbamoyl]imidazole (44). A solution of 1,1′-thiocarbonyldiimidazole (4.95 g, 25 mmol) and 2-amino-5-bromopyridine (4.46 g, 25 mmol) in acetonitrile (75 mL) was stirred at room temperature for 23 h. The resulting precipitate was collected by filtration to provide 5.42 g (76%) of the title product: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (m, 1H), 8.30 (m, 1H), 8.15 (m, 1H), 8.03 (br s, 1H), 7.75 (m, 1H), 7.15 (d, 1H), 6.80 (s, 1H).

1-[[2-(5-Chloropyridyl)]thiocarbamoyl]imidazole (45). The title compound was prepared analogously to compound **44**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 (m, 1H), 8.25 (m, 1H), 8.05 (br s, 1H), 8.03 (m, 1H), 7.65 (m, 1H), 7.15 (d, 1H), 6.80 (s, 1H).

1-[[2-(5-(Trifluoromethyl)thiazolyl)]thiocarbamoyl]-imidazole (46). The title compound was prepared analogously to compound **44**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.43 (s, 1H); MS (FAB) *m/e* 279 (M^+).

Route B. General Procedure. Alt 1. A solution of 1,1′-thiocarbonyldiimidazole (1 equiv) and phenyl- or pyridylethylamine (1 equiv) in acetonitrile (4 mL/mmol) was stirred at room temperature for 1 h. The solution was evaporated and the residue dissolved in DMF (4 mL/mmol). Aminopyridine or aminopyridazine (1 equiv) was added as a solid and the solution was stirred at 95 °C for 24 h. The reaction mixture was cooled to room temperature; poured into ethyl acetate; and washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated and the residue purified either by triturating in dichloromethane or by column chromatography.

Alt 2. A solution of phenethylamine (1 equiv) in acetonitrile (2 mL/mmol) was added to a stirred solution of 1,1′-thiocarbonyldiimidazole (1.03 equiv) in acetonitrile (3 mL/mmol) at room temperature. The solution was stirred at room temperature for 1 h, and the solvent was evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexanes, 1:1) to provide pure phenethyl isothiocyanate. Sodium hydride (1 equiv) was added to a solution of aminopyrazine or aminopyridine (1 equiv) in THF at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 30 min. Phenethyl isothiocyanate (1 equiv) in THF was added, and the reaction mixture was allowed to reach room temperature and then stirred overnight. Saturated ammonium chloride and diethyl ether was added, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The product was purified by recrystallization.

2-Amino-5-cyanopyridine (47). A mixture of $NiBr_2$ (2.18 g, 10 mmol), triphenylphosphine (10 g, 38 mmol), and zinc powder (1 g, 15.2 mmol) in 100 mL of acetonitrile was stirred under nitrogen at 60 °C for 1 h. NaCN (6.3 g, 102 mmol) and 2-amino-5-bromopyridine (17.8 g, 100 mmol) were added to the mixture which was stirred overnight at 60 °C. Then 500 mL of ethyl acetate was added to the mixture, it was filtered, and the solvent was evaporated. The product was purified on a silica gel column eluted with ethyl acetate. ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.41 (d, 1H), 7.29 (dd, 1H), 7.12 (s, 2H), 6.58 (d, 1H).

Route C. General Procedure. Phenethylamine (1 equiv) and compound **50** (1 equiv) in acetonitrile (2 mL/mmol) were stirred at room temperature for 0.5 h. The mixture was filtered. The precipitate was dried and recrystallized from acetonitrile.

2-(5-Chloropyridyl) Isothiocyanate (50).[16] 2-Amino-5-chloropyridine (10.28 g) was added in portions, with stirring, over a period of 25 min to a solution of thiocarbonyldiimidazole (14.26 g) in acetonitrile (100 mL) at room temperature. The stirring was continued, and the solution/suspension was left at room temperature for a few hours. The precipitate was filtered and washed with acetonitrile (3 × 25 mL). The solid residue was dissolved in hot acetone and filtered. The acetone solution was evaporated in vacuo, and the residue was dissolved in hot ethyl acetate and filtered through a pad of silica (diameter 7 cm × 3 cm). The silica was washed with another portion of hot ethyl acetate. The combined solutions were evaporated in vacuo to yield a crude product (5 g) of the title product: ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.54 (d, 1H), 8.17 (dd, 1H), 8.63 (d, 1H).

Route D. General Procedure. Phenethylamine (1 equiv) in acetonitrile was added dropwise to a solution of 1,1′-thiocarbonyldiimidazole in acetonitrile at 0 °C during 20 min. The reaction mixture was allowed to reach room temperature. The solvent was evaporated. Aminopyridine (1.2 equiv) in DMF was added, and the mixture was stirred at 100 °C for 15 h. The reaction mixture was cooled to room temperature and

poured into ice. The organic layer was washed with dilute HCl, water, and brine, dried over anhydrous sodium sulfate, and concentrated. The product was purified by chromatography on silica gel.

2-Amino-5-iodopyridine (52). The compound was prepared from 2-aminopyridine:[17] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.61 (q, 1H), 6.34 (d, 1H), 4.52 (br s, 2H).

***N*-[2-(2,6-Difluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]-thiourea (1).** 2,6-Difluorobenzonitrile (5 g, 33 mmol) and cobalt chloride hexahydrate (11.6 g, 49 mmol) were dissolved in 500 mL of methanol. To the solution was added $NaBH_4$ (9.3 g, 244 mmol) in portions. The reaction mixture was filtered after 3 h, and the residue was washed twice with methanol. Evaporation of the combined filtrates gave a residue which was dissolved in 1 M HCl, and this solution was washed with dichloromethane. Alkalizing with ammonia and extraction with dichloromethane gave after washing with water and evaporation of solvent 2.9 g of 2-(2,6-difluorophenethyl)amine. The title product was prepared according to route D: mp 174−175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.20 (s, 1H), 10.68 (s,1H), 8.11 (s, 1H), 7.95−7.91(m, 1H), 7.33−7.28 (m, 1H), 7.09−7.01 (m, 3H), 3.83−3.77 (m, 2H), 2.98−2.94 (m, 2H). Anal. ($C_{14}H_{12}BrF_2N_3S$)C, H, N.

***N*-[2-(2,6-Difluoro-3-(formamidomethyl)phenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (2).** 2,6-Difluorobenzaldehyde (10 g, 70.4 mmol), ethylene glycol (20 mL), triethylorthoformate (10 mL), and *p*-TSA in 1,2-dichloroethane were heated to 80 °C for 2 h. The solution was neutralized with sodium hydrogen carbonate, washed with water, dried over sodium sulfate, filtered, and evaporated.

The residual oil, compound **65**, was dissolved in THF (700 mL) under nitrogen. The solution was stirred and cooled to −70 °C, and *n*-BuLi (48 mL, 1.6 M) was added slowly. The solution was stirred for 20 min. Dry ice (20 g, 455 mmol) was added as quickly as possible. The solution was brought slowly to room temperature. Water was added, and the solution was washed with ethyl acetate, acidified with acetic acid, and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporated.

One gram of the residual solid, compound **66** (4.35 mmol), and *N*,*N*-diisopropylamine (2.0 mL) were dissolved in dichloromethane (50 mL), and the solution was cooled to 0 °C. Thionyl chloride (0.50 mL, 6.9 mmol) was added and the solution slowly heated to ambient temperature. Methylamine (3 mL) was added. The solution was stirred for 30 min, washed with water, dried over Na_2SO_4, filtered, and evaporated.

The residue, compound **67**, was dissolved in a mixture of water and dioxane (1:2, 20 mL), and *p*-TSA (0.5 g, 2.63 mmol) was added. The solution was stirred and heated to 60 °C for 2 h. The solution was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and evaporated.

The residue, compound **81b**, was dissolved in toluene, and [(benzyloxycarbonyl)methyl]triphenylphosphorane (1.5 g, 3.7 mmol) was added. The solution was stirred for 30 min at 50 °C and then put onto a silica gel column which was eluted with ethyl acetate/hexane (1:2), and the collected fractions were evaporated.

A part of the residue, compound **82b** (0.15 g), was hydrogenated in methanol (50 mL) and acetic acid (5 mL) over 10% Pd/C catalyst (100 mg), using a Parr hydrogenation apparatus at 1.0 psi for 1 h. The solution was filtered through Celite and evaporated.

A part of the residue, compound **83b** (50 mg, 0.26 mmol), was dissolved in acetone at 0 °C. Triethylamine (50 mL, 0.36 mmol) was added followed by ethyl chloroformate (30 mL, 0.32 mmol). The solution was stirred for 15 min, and sodium azide (30 mg, 0.46 mmol) in water (2 mL) was added. The solution was stirred for 15 min, diluted with ethyl acetate, and washed with water. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was dissolved in toluene (20 mL) and stirred at 90 °C for 1 h. The solution was evaporated and dissolved in a dioxane/water/hydrochloric acid (concentrated aqueous) mixture (1:3:1). The solution was stirred at room temperature for 20 min and then evaporated to give 2-(2,6-difluoro-3-(formamidomethyl)phenethyl)amine hydrochloride **84b**. The title product was prepared according to route A: mp 222.5−223.4 °C; ^{1}H NMR (250 MHz, *d*-MeOD, $CDCl_3$) δ 8.1−8.0 (s, 1H),7.8−7.7 (m, 2H), 7.0−6.9 (t, 2H), 6.9−6.8 (d, 1H), 4.1−4.0 (t, 2H), 3.2−3.1 (t, 2H), 3.0−2.9 (s, 3H). Anal. ($C_{16}H_{15}BrF_2N_4OS$) H, N; C: calc, 44.77; found, 43.70.

***N*-[2-(3-(Acetamidomethyl)-2,6-difluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (3).** Under a nitrogen atmosphere, 2,4-difluorobenzonitrile, **80** (4.6 g, 33 mmol), was dissolved in THF (200 mL) with stirring. The solution was cooled to −75 °C, and lithium diisopropylamide (25 mL, 1.5 M solution) was added. The solution was stirred for 15 min, and DMF (10 mL) was added. The cooling was withdrawn, and the solution was diluted with toluene (200 mL), washed with water, dried over Na_2SO_4, filtered, and evaporated. The residue, compound **81a** (4.76 g, 28.5 mmol), was dissolved in 250 mL of toluene, and [(benzyloxycarbonyl)methyl]triphenylphosphorane (14 g, 34 mmol) was added. The solution was stirred for 40 min at 35 °C (slightly exothermic reaction) and then put onto a silica gel column which was eluted with ethyl acetate/hexane, 1:4, and the collected fractions were evaporated.

A small part of the residue, compound **82a** (0.5 g), was dissolved in methanol (50 mL) and acetic acid (6 mL), and 5% Pd/C (300 mg) was added. The mixture was hydrogenated on a Parr hydrogenation apparatus at 1.0 psi for 1 h. The solution was filtered through Celite and evaporated.

The residue, compound **68**, was dissolved in acetic anhydride, and the solution was stirred and heated to 50 °C for 20 min. Excess reagent was evaporated, and the residue was dissolved in water. The solution was heated to 60 °C for 20 min under stirring.

The residue, compound **69** (0.29 g, 1.14 mmol), was dissolved in acetone at 0 °C. Triethylamine (0.315 mL, 2.3 mmol) was added, followed by ethyl chloroformate (0.16 mL, 1.7 mmol). The solution was stirred for 15 min, and sodium azide (220 mg, 3.3 mmol) in water (2 mL) was added. Stirring was continued for 15 min, and the solution was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated. The residue was dissolved in toluene (20 mL) and heated at 90 °C for 1 h. The solution was evaporated, and the residue was dissolved in a dioxane/water/hydrochloric acid (concentrated aqueous) mixture (50:10:1, 50 mL) and stirred at room temperature for 20 min. The solution was evaporated, to give 3-(acetamidomethyl)-2,6-difluorophenethylamine hydrochloride, **84d**. The title product was prepared according to route A: mp 180.3−181.6 °C; ^{1}H NMR (250 MHz, *d*-MeOD, $CDCl_3$) δ 8.2−8.1 (s, 1H), 7.8−7.7 (d, 1H), 7.4−7.2 (m, 1H), 6.9−6.8 (m, 2H), 4.4−4.3 (s, 2H), 4.1−3.9 (br s, 2H), 3.1−3.0 (br s, 2H), 2.0−1.9 (s, 3H). Anal. ($C_{17}H_{17}BrF_2N_4OS$) H, N; C: calc, 46.06; found, 45.20.

***N*-[2-(3-Cyano-2,6-difluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (4).** 3-Cyano-2,6-difluorophenethylamine **84a** was prepared from 3-cyano-2,6-difluorobenzaldehyde **81a** by a procedure described for compound **2**. Aldehyde **81a** was prepared from 2,4-difluorobenzonitrile **80** by a procedure described for compound **3**. The title product was prepared according to route A: mp 189.2−191.2 °C; ^{1}H NMR (250 MHz, $CDCl_3$ + CD_3OD) δ 11.4 (br s, 1H), 8.1 (d, 1H), 7.7−7.5 (m, 2H), 7.0 (t, 1H), 6.9 (d, 1H), 4.1 (q, 2H), 3.2 (t, 2H). Anal. ($C_{15}H_{11}ClF_2N_4S$) H, N; C: calc, 51.07; found, 51.9.

***N*-[2-(2,6-Difluoro-3-(dimethylamino)phenethyl)]-*N′*-[2-(5-chloropyridyl)]thiourea (5).** A mixture of 2,4-difluoroaniline (5.0 g, 38.7 mmol) and trimethyl phosphate (3.6 g, 25.8 mmol) was refluxed at 180 °C for 2 h. After the mixture was cooled to 50 °C, NaOH (3.2 g, 80.6 mmol) in 12 mL of H_2O was added to it, and it was refluxed again for 1 h. The mixture was cooled, H_2O was added to it, and it was extracted with diethyl ether, which was dried over Na_2SO_4 and evaporated. The crude material was filtrated through an Al_2O_3 column using diethyl ether as eluent to give 4.4 g (73%) of 1-(dimethylamino)-2,4-difluorobenzene, **60n**. 2,6-Difluoro-3-(dimethylamino)phenethylamine (**64n**) was prepared from this compound by using the procedure described for compound **10**. The title product was prepared according to route C: mp 167 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.32 (br s, 1H), 8.95 (s, 1H),

8.06 (d, 1H), 7.57 (dd, 1H), 6.81−6.76 (m, 3H), 4.01 (q, 2H), 3.11 (t, 2H), 2.76 (s, 6H). Anal. ($C_{16}H_{17}ClF_2N_4S$) C, H, N.

***N*-[2-(2,6-Difluoro-3-(dimethylamino)phenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (6).** The title product was prepared using the same starting amine **64n** as for compound **5** and route A: mp 175 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.33 (br s, 1H), 8.92 (br s, 1H), 8.16 (d, 1H), 7.70 (dd, 1H), 6.81−6.75 (m, 3H), 4.01 (q, 2H), 3.11 (t, 2H), 2.77 (s, 6H). Anal. ($C_{16}H_{17}BrF_2N_4S$) C, H, N.

***N*-[2-(2,6-Difluoro-3-methoxyphenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (7).** 2,6-Difluoro-3-methoxyphenethylamine (**64h**) was prepared from 2,4-difluorophenol as described for compound **10**. The title product was prepared according to route A: mp 158.5 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.35 (s, 1H), 9.16 (s, 1H), 8.12 (d, 1H), 7.68−7.72 (m, 1H), 6.82 (m, 3H), 4.00 (m, 2H), 3.86 (s, 3H), 3.12 (t, 2H). Anal. ($C_{15}H_{14}BrF_2N_3OS$) C, H, N.

***N*-[2-(2,6-Difluoro-3-ethoxyphenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (8).** 2,6-Difluoro-3-ethoxyphenethylamine (**64i)** was prepared from 2,4-difluorophenol as described for compound **10.** The title product was prepared according to route A: mp 124 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.35 (s, 1H), 9.2 (s, 1H), 8.15 (d, 1H), 7.7 (m, 1H), 6.9−6.7 (m, 3H), 4.1−3.95 (q + t, 4H), 3.1 (t, 3H), 1.38 (t, 2H). Anal. ($C_{16}H_{16}BrF_2N_3OS$) C, H, N.

***N*-[2,6-Difluoro-3-(methoxymethyl)phenethyl]-*N′*-[2-(5-bromopyridyl)]thiourea (9).** A solution of 2,6-difluorobenzaldehyde (7.05 g, 0.05 mol), propylene glycol (20 mL, 0.25 mol), and *p*-TSA (50 mg) in 300 mL of toluene was refluxed utilizing a Dean−Stark trap for 2 h. The cooled solution was washed with saturated $NaHCO_3$(aq), dried over Na_2SO_4, and concentrated in vacuo to give 2,6-difluorobenzaldehyde propylene acetal **57** as an oil (9.08 g, 92%).

To a solution of the compound **57** (7.0 g, 0.035 mol) in 100 mL of THF was added 2.5 M *n*-BuLi in hexane (16.8 mL, 0.042 mol) at −70 °C under nitrogen over a period of 10 min. The solution was stirred at −70 °C for 1 h, chloromethyl methyl ether (7.0 mL, 0.084 mol) was added, the mixture was allowed to warm to room temperature, and stirring was continued for 18 h. The mixture was diluted with Et_2O and washed with water and 25% NH_3(aq); the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel by elution with Et_2O/hexane to give 2,6-difluoro-3-(methoxymethyl)benzaldehyde propylene acetal, **58** (4.0 g, 47%).

A solution of the compound **58** (3.98 g, 0.016 mol) in 100 mL of dioxane and 50 mL of 2 M HCl was stirred for 70 h at room temperature. The solution was diluted with water, extracted with Et_2O, dried over Na_2SO_4, and concentrated in vacuo to give 2,6-difluoro-3-(methoxymethyl)benzaldehyde (**62o**) as an oil (2.77 g, 93%). From this aldehyde (**62o**), 2,6-difluoro-3-(methoxymethyl)phenethylamine (**64o)** was prepared as described for compound **10**. The title product was prepared according to route A: mp 142−143 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.31 (br s, 1H), 8.78 (br s, 1H), 8.15 (d, 1H), 7.28 (m, 1H), 7.22 (dd, 1H), 6.88 (dd, 1H), 6.69 (m, 1H), 4.44 (s, 2H), 4.00 (m, 2H), 3.39 (s, 3H), 3.10 (m, 2H). Anal. ($C_{16}H_{16}BrF_2N_3OS$) C, H, N.

***N*-[2-(2-Chloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (10).** 2-Chloro-4-fluorophenol (18.2 g, 124 mmol), ethyl iodide (30 mL, 372 mmol), and K_2CO_3 (34.3 g, 248 mmol) in 250 mL of acetone were stirred at 60 °C for 5 h. The mixture was cooled, filtered, and evaporated. The residue was stirred with hexane, cooled, filtered, and evaporated to give 20.85 g (96%) of 1-chloro-2-ethoxy-5-fluorobenzene, **61b**.

BuLi (2.5 M) in hexane (27.2 mL, 68.1 mmol) was added slowly (20 min) to a solution of compound **61b** (10.8 g, 61.9 mmol) in 220 mL of dry THF at −65 °C under nitrogen. The solution was stirred at −65 °C for 0.5 h. DMF (5.3 mL, 68.1 mmol) was added dropwise to the solution. The mixture was allowed to warm to room temperature, poured into ice (500 mL), and extracted with diethyl ether. Diethyl ether was washed with brine, dried over Na_2SO_4, and evaporated to give 2-chloro-3-ethoxy-6-fluorobenzaldehyde, **62b** (11.72 g, 94%).

NaOH (2.43 g, 60.7 mmol) in 12 mL of ice/water was added dropwise at −3 °C to a solution of compound **62b** (11.7 g, 57.8 mmol) and nitromethane (3.12 mL, 57.8 mmol) in 260 mL of methanol. The solution was stirred at −3 °C for 15 min and then added dropwise to 35 mL of 4 N HCl(aq) while stirring. The mixture was extracted with diethyl ether, and the organic layer was washed with a small volume of brine, dried over Na_2SO_4, and evaporated to give 12.1 g (85%) of 2-nitro-1-(2-chloro-3-ethoxy-6-fluorophenyl)ethene, **63b**.

Lithium aluminum hydride (6.81 g, 179.2 mmol) was added to 200 mL of dry THF. To this mixture was added dropwise compound **63b** (11.0 g, 44.8 mmol) in 200 mL of dry THF. The mixture was refluxed for 2 h, treated with 6.9 mL of H_2O, 6.9 mL of 15% NaOH(aq), and 20.7 mL of H_2O, filtered, dried over Na_2SO_4, and evaporated to give crude 2-chloro-3-ethoxy-6-fluorophenethylamine, **64b** (8.2 g, 84%). This amine using route A gave the title product (30% yield): mp 150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.30 (br s, 1H), 9.35 (s, 1H), 8.08 (d, 1H), 7.69 (dd, 1H), 6.93−6.76 (m, 3H), 4.11−4.00 (m, 4H), 3.24 (t, 2H), 1.46 (t, 3H). Anal. ($C_{16}H_{16}BrClFN_3OS$) C, H, N.

***N*-[2-(2-Chloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-chloropyridyl)]thiourea (11).** This compound was prepared as compound **10:** mp 160 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.28 (br s, 1H), 10.85 (s, 1H), 8.16 (d, 1H), 7.97 (dd, 1H), 7.29−7.15 (m, 3H), 4.18 (q, 2H), 3.98 (q, 2H), 3.24 (t, 2H), 1.44 (t, 3H). Anal. ($C_{16}H_{16}Cl_2FN_3OS$)C, H, N.

***N*-[2-(2-Chloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-iodopyridyl)]thiourea (12).** Starting amine **64b** was the same as for compound **10**. The title product was prepared according to route D: mp 170 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.27 (br s, 1H), 8.94 (s, 1H), 8.22 (d, 1H), 7.84 (dd, 1H), 6.96−6.77 (m, 2H), 6.65 (d, 1H), 4.11−3.99 (m, 4H), 3.25 (t, 2H), 1.47 (t, 3H). Anal. ($C_{16}H_{16}ClFIN_3OS$) C, H, N.

***N*-[2-(2-Chloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-cyanopyridyl)]thiourea (13).** Starting amine **64b** was the same as for compound **10**. The title product was prepared according to route B: mp 211 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.35 (br s, 1H), 11.14 (s, 1H), 8.59 (d, 1H), 8.26 (dd, 1H), 7.35−7.13 (m, 3H), 4.17 (q, 2H), 3.98 (q, 2H), 3.23 (t, 2H), 1.43 (t, 3H). Anal. ($C_{17}H_{16}ClFN_4OS$) C, H, N.

***N*-[2-(2-Chloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-chloropyridazyl)]thiourea (14).** Starting amine **64b** was the same as for compound **10.** The title product was prepared according to route B: mp 188−189 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.21(br s, 1H), 11.00 (br s, 1H), 7.93 (d, 1H), 7.64 (d, 1H), 7.21−7.13 (m, 2H), 4.15 (q, 2H), 4.00 (q, 2H), 3.21 (t, 2H), 1.41 (t, 3H). Anal. ($C_{15}H_{15}Cl_2FN_4OS$) C, H, N.

***N*-[2-(2-Chloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-(trifluoromethyl)thiazolyl)]thiourea (15).** Starting amine **64b** was the same as for compound **10**. The title product was prepared according to route A: mp 181 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.86 (br s, 1H), 8.48 (br s, 1H), 7.80 (s, 1H), 7.22−7.15 (m, 2H), 4.19 (q, 2H), 3.91 (q, 2H), 3.19 (t, 2H), 1.44 (t, 3H). Anal. ($C_{15}H_{14}ClF_4N_3OS_2$) C, H, N.

***N*-[2-(2-Cyano-3-ethoxy-6-fluorophenethyl)-*N′*-[2-(5-bromopyridyl)]thiourea (16).** 2-Bromo-4-fluorophenol (20 g, 165 mmol) was dissolved in acetone. K_2CO_3 and ethyl iodide (31 g, 200 mmol) were added. The mixture was refluxed overnight. Solid material was filtered off and rinsed with acetone. Distillation gave pure 1-bromo-2-ethoxy-5-fluorobenzene **71**. 2-Cyano-3-ethoxy-6-fluorophenethylamine (**84f**) was prepared from compound **71** as described for compound **17**. The title product was prepared according to route A: mp 184 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.29 (s, 1H), 10.87 (s, 1H), 8.22−8.21 (m, 1H), 8.12−8.07 (m,1H), 7.68−7.60 (m, 1H), 7.29−7.21 (m, 2H), 4.27 (q, 2H), 4.06 (q, 2H), 3.22 (m, 2H), 1.46 (t, 3H). Anal. ($C_{17}H_{16}BrFN_4OS$) C, H, N.

***N*-[2-(2-Cyano-6-fluoro-3-methoxyphenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (17).** A mixture of $NiBr_2$ (2.0 g, 9.2 mmol), triphenylphosphine (9.5 g, 36.2 mmol), and zinc powder (1.95 g, 30 mmol) in 100 mL of acetonitrile was stirred under nitrogen at 50 °C for 0.5 h. NaCN (23.5 g, 480 mmol) and 2-bromo-4-fluoroanisole (**70**) (95 g, 463 mmol) were added. The mixture was stirred overnight at 60 °C, and 700 mL of $CHCl_3$ was added. The mixture was then heated to the boiling point, and solids were filtered off while hot. The solvent was

removed at reduced pressure. Crystallization from dichloroethane/hexane gave 2-cyano-4-fluoroanisole, **72**.

Lithium diisopropylamide was added dropwise to a solution of compound **72** (4.65 g, 34 mmol) in 200 mL of THF at −70 °C. The reaction mixture was heated to −55 °C and kept at this temperature for 1 h. The mixture was cooled again to −70 °C, and DMF (4 mL) was added. Acetic acid (3.6 g) was added after 30 min at −55 °C, and then ((ethoxycarbonyl)-methylene)triphenylphosporane (12.0 g, 34 mmol) was added. The mixture was allowed to come to room temperature and was left overnight. Purification on a silica gel column eluted with ethyl acetate/hexane gave a cis−trans mixture of ethyl 3-(2-cyano-3-methoxy-6-fluorophenyl) propenoate, **74**.

Compound **74** was added to 100 mL of methanol, and 100 mg of 10% Pd/C was added. The stirred mixture was hydrogenated at atmospheric pressure until H_2 consumption ceased (3 h). The solution was filtered, and the solvent was evaporated. The product, ester **76**, was then hydrolyzed for 30 min in a refluxing mixture of NaOH (2 g, 50 mmol) in 50 mL of ethanol/water, 1:1. Acidification (HCl), extraction to dichloromethane, drying (Na_2SO_4), and crystallization from dichloroethane/hexane gave 2.55 g of 3-(2-cyano-3-methoxy-6-fluorophenyl)propanoic acid, **78**.

Compound **78** was dissolved in a mixture of triethylamine (30 mmol) and 30 mL of THF. Diphenyl phosphorazidate (4.125 g, 15 mmol) was added and the mixture heated to 50 °C for 1 h. The solvent was removed, and the residue was partitioned between water and dichloromethane. The organic phase was dried, and the solvent was removed. The residue was dissolved in toluene (50 mL) and heated to near reflux until N_2 evolution ceased (about 15 min). The solvent was removed, the residue was redissolved in 50 mL of dioxane, and 50 mL of concentrated HCl was added. The mixture was then refluxed for 3 h. The solvent was removed, and the residue was dissolved in 30 mL of 2 M HCl(aq) and washed with dichloromethane. The aqueous phase was made strongly basic with 40% NaOH(aq). 2-Cyano-3-methoxy-6-fluorophenethylamine (**84e**) was extracted with dichloromethane. The title product was prepared according to route A: mp 177.7 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 11.35 (t, 1H), 9.05 (s, 1H), 8.18 (m, 1H), 7.72 (m, 1H), 7.2 (m, 1H), 6.8 (m, 2H), 4.1 (q, 2H), 3.93 (s, 3H), 3.3 (t, 2H). Anal. ($C_{16}H_{14}BrFN_4OS$) C, H, N.

***N*-[2-(2-Cyano-6-fluoro-3-methoxyphenethyl)]-*N′*-[2-(5-cyanopyridyl)]thiourea (18).** Starting amine **84e** was the same as for compound **17**. The title product was prepared according to route B: mp 215 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.40 (t, 1H), 11.15 (s, 1H), 8.58 (m, 1H), 8.24 (m, 1H), 7.65 (m, 1H), 7.35 (m, 1H), 7.26 (m, 1H), 4.05 (m, 2H), 3.95 (s, 3H), 3.22 (t, 2H). Anal. ($C_{17}H_{14}FN_5OS$) C, H; N: calc, 19.61; found, 20.65.

***N*-[2-(2-Cyano-6-fluoro-3-methoxyphenethyl)]-*N′*-[2-(5-chloropyridazyl)]thiourea (19).** Starting amine **84e** was the same as for compound **17.** The title product was prepared according to route B: mp 211 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.20 (t, 1H), 11.05 (s, 1H), 7.97 (d, 1H), 7.64 (m, 2H), 7.23 (dd, 1H), 4.10 (m, 2H), 3.98 (s, 3H), 3.25 (t, 2H). Anal. ($C_{15}H_{13}ClFN_5OS$) C, N; H: calc, 3.5; found, 3.0.

***N*-[2-(2,5-Dimethoxyphenethyl)]-*N′*-[2-(5-chloropyridyl)]-thiourea (20).** 2,5-Dimethoxyphenethylamine (**64q**) was prepared from 2,5-dimethoxybenzaldehyde (**62q**) as described for compound **10**. The title product was prepared according to route A: mp 130.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.19 (br s, 1H), 8.82 (br s, 1H), 8.12 (d, 1H), 7.69 (dd, 1H), 6.83−6.67 (m, 4H), 4.00 (dd, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.00 (dd, 2H). Anal. ($C_{16}H_{18}BrN_3O_2S$) H, N; C: calc, 48.5; found, 48.0.

***N*-[2-(2,5-Diethoxyphenethyl)]-*N′*-[2-(5-bromopyridyl)]-thiourea (21).** 2,5-Diethoxyphenethylamine (**64p**) was prepared from 2,5-dihydroxybenzaldehyde (**59**) as described for compound **10.** The title product was prepared according to route A: mp 162 °C;^{1}H NMR (250 MHz, DMSO-d_6) δ 11.24 (br s, 1H), 10.80 (s, 1H), 8.26 (d, 1H), 8.07 (dd, 1H), 7.21 (d, 1H), 6.99−6.85 (m, 3H), 4.03 (t, 4H), 3.91 (q, 2H), 2.97 (t, 2H), 1.41 (t, 6H). Anal. ($C_{18}H_{22}BrN_3O_2S$) C, H, N.

***N*-[2-(2-Ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (22).** 2-Ethoxy-6-fluorophenethylamine (**64a**) was prepared from 3-fluorophenol as described for compound **10**. The title product was prepared according to route A: mp 166 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.23 (t, 1H), 10.80 (s, 1H), 8.18 (d, 1H), 8.06 (dd, 1H), 7.33 (q, 1H), 7.21 (d, 1H), 6.87 (t, 2H), 4.07 (q, 2H), 3.91 (q, 2H), 3.03 (t, 2H), 1.41 (t, 3H). Anal. ($C_{16}H_{17}BrFN_3OS$) H, N; C: calc, 48.2; found, 47.7.

***N*-[2-(2,3-Difluoro-6-ethoxyphenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (23).** 2,3-Difluoro-6-ethoxyphenethylamine (**64e**) was prepared from 2,3-difluorophenol as described for compound **10.** The title product was prepared according to route A: mp 170.7 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.22 (s, 1H), 8.20 (s, 1H), 8.13 (d, 1H), 7.73 (dd, 1H), 7.00(dd, 1H), 6.18 (d, 1H), 6.07 (m, 1H), 4.0 (m, 4H), 3.13 (m, 2H), 1.45 (t, 3H). Anal. ($C_{16}H_{16}BrF_2N_3OS$) C, H, N.

***N*-[2-(2,3-Difluoro-6-methoxyphenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (24).** 2,3-Difluoro-6-methoxyphenethylamine (**64j**) was prepared from 2,3-difluorophenol as described for compound **10.** The title product was prepared according to route A: mp 160 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.35 (s, 1H), 9.65 (s, 1H), 8.15 (d, 1H), 7.7 (m, 1H), 7.05−6.8 (m, 2H), 6.55 (m, 1H), 4.0 (s, 2H), 3.8 (s, 3H), 3.1 (m, 2H). Anal. ($C_{15}H_{14}BrF_2N_3OS$) C, H, N.

***N*-[2-(3,6-Dimethoxy-2-fluorophenethyl)]-*N′*-[2-(5-chloropyridyl)]thiourea (25).** To a solution of 1,4-dimethoxybenzene (**56**) (15.0 g, 0.109 mol) in 300 mL of dry THF was added 2.5 M *n*-BuLi (45.6 mL, 0.114 mol) at room temperature under nitrogen. After addition was complete, the solution was stirred for 1 h. The mixture was cooled to −70 °C, and *N*-fluorobenzenesulfonimide (36.0 g, 0.114 mol) in 150 mL of THF was added slowly, keeping the temperature below −60 °C. The solution was allowed to warm to room temperature overnight. Then 100 mL of saturated NH_4Cl(aq) was added and the mixture extracted with diethyl ether/THF. The organic phase was washed with 1 M NaOH (2 × 60 mL), dried over $MgSO_4$, and evaporated. Column chromatography (silica gel, *n*-hexane followed by 1, 5, and 10% EtOAc in *n*-hexane) provided 11.43 g of a mixture of 1,4-dimethoxy-2-fluorobenzene (**61k**) and 1,4-dimethoxybenzene (4.3:1). 3,6-Dimethoxy-2-fluorophenethylamine (**64k**) was prepared from 1,4-dimethoxy-2-fluorobenzene (**61k**) as described for compound **10**. The title product was prepared according to route C: mp 172−173 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.28 (s, 1H), 9.20 (s, 1H), 8.04 (d, 1H), 7.55 (dd, 1H), 6.81 (m, 2H), 6.54 (dd, 1H), 3.97 (m, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.09 (m, 2H). Anal. ($C_{16}H_{17}ClN_3O_2S$) C, H, N.

***N*-[2-(3-Ethoxy-2-fluoro-6-methoxyphenethyl)]-*N′*-[2-(5-chloropyridyl)]thiourea (26).** A suspension of 2-fluoro-4-methylacetophenone (**54**) (10.0 g, 0.059 mol), mCPBA (26.0 g, 0.128 mol), and $MgSO_4$ (30.0 g) in 500 mL of $CHCl_3$ was stirred for 12 h at room temperature. The mixture was then filtered, washed with 2 M NaOH, dried over Na_2SO_4, and concentrated in vacuo to give 1-acetyl-2-fluoro-4-methoxybenzene (**55**) as a solid (10.7 g, 98%).

A solution of the compound **55** (5.3 g, 0.029 mol) in 100 mL of MeOH and 20 mL of 25% NH_3(aq) was stirred for 1 h at room temperature. The mixture was then concentrated in vacuo, diluted with water, extracted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo to give 2-fluoro-4-methoxyphenol as an oil (3.85 g, 94%). Alkylation of this compound with EtI as described for compound **10** gave 2-ethoxy-1-fluoro-4-methoxybenzene, **61f**. 3-Ethoxy-2-fluoro-6-methoxyphenethylamine (**64f**) was prepared from compound **61f** as described for compound **10**. The title product was prepared according to route C: mp 194−196 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.24 (br s, 1H), 9.00 (br s, 1H), 8.10 (d, 1H), 7.55 (dd, 1H),6.88−6.69 (m, 2H), 6.50 (d, 1H), 4.10−3.89 (m, 4H), 3.75 (s, 3H), 3.10 (m, 2H), 1.45 (t, 3H). Anal. ($C_{17}H_{19}ClFN_3O_2S$) C, H, N.

***N*-[2-(2,3-Dimethoxy-6-fluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (27).** 2,3-Dimethoxy-6-fluorophenethylamine (**64g**) was prepared from 4-fluoroveratrole (**61g**) as described for compound **10.** The title product was prepared according to route A: mp 159−160 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.26 (s, 1H), 8.71 (s, 1H), 8.14 (d, 1H), 7.69 (dd, 1H), 6.77 (d, 2H), 6.68 (d, 1H), 3.98 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.09 (m, 2H). Anal. ($C_{16}H_{17}BrFN_3O_2S$) C, H, N.

***N*-[2-(6-Chloro-3-ethoxy-2-fluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (28).** 6-Chloro-3-ethoxy-2-fluorophenethylamine (**64d**) was prepared from 4-chloro-2-fluorophenol as described for compound **10.** The title product was prepared according to route A: mp 157−158 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.31 (s, 1H), 9.28 (s, 1H), 8.15 (d, 1H), 7.69 (dd, 1H), 7.09 (dd, 1H), 6.84−6.77 (m, 2H), 4.11−4.00 (m, 4H), 3.22 (m, 2H), 1.46 (t, 3H). Anal. ($C_{16}H_{16}BrClFN_3OS$) C, H, N.

***N*-[2-(2,3,6-Trifluorophenethyl)]-*N′*-[2-(5-chloropyridyl)]thiourea (29).** 2,3,6-Trifluorophenethylamine (**64l**) was prepared from 1,3,5-trifluorobenzene (**61l**) as described for compound **10**. The title product was prepared according to route C: mp 171−172 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.23 (t, 1H), 10.74 (s, 1H), 8.12 (d, 1H), 7.87 (dd, 1H), 7.20−7.13 (m, 3H), 3.83 (q, 2H), 2.96 (t, 2H). Anal. ($C_{14}H_{11}ClF_3N_3S$) C, H, N.

***N*-[2-(2,6-Difluoro-4-(dimethylamino)phenethyl)]-*N′*-[2-(5-chloropyridyl)]thiourea (30).** 2,6-Difluoro-4-(dimethylamino)phenethylamine (**64m**) was prepared from 3,5-difluoroaniline as described for compound **5**. The title product was prepared according to route C: mp 191.5−193 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.33 (t, 1H), 9.28 (s, 1H), 7.99 (d, 1H), 7.54 (dd, 1H), 6.84 (d, 1H), 6.21−6.10 (m, 2H), 3.92 (q, 2H), 2.98−2.90 (m, 8H). Anal. ($C_{16}H_{17}ClF_2N_4S$) C, H, N.

***N*-[2-(3-Cyano-4-(dimethylamino)-2-fluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (31).** 3-Cyano-4-(dimethylamino)-2-fluorophenethylamine (**84c**) was prepared from 3-cyano-4-(dimethylamino)-2-fluorobenzaldehyde (**81c**) as described for compound **2**. The title product was prepared according to route A: mp 190 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.28 (t, 1H), 10.84 (s, 1H), 8.27 (d, 1H), 8.07 (dd, 1H), 7.54 (t, 1H), 7.21 (d, 1H), 6.89 (d, 1H), 3.89 (q, 2H), 3.11 (s, 6H), 2.99 (t, 2H). Anal. ($C_{17}H_{17}BrFN_5S$) C, H, N.

***N*-[2-(2,4-Dichloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]thiourea (32).** 2,4-Dichloro-3-ethoxy-6-fluorophenethylamine (**64c**) was prepared from 2,6-dichloro-4-fluorophenol as described for compound **10.** The title product was prepared according to route A: mp 131 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.26 (br s, 1H), 8.99 (s, 1H), 8.15 (d, 1H), 7.72 (dd, 1H), 7.06 (d, 1H), 6.76 (d, 1H), 4.05−3.99 (m, 4H), 3.22 (t, 2H), 1.45 (t, 3H). Anal. ($C_{16}H_{15}BrCl_2FN_3OS$) C, H, N.

***N*-[2-[2-(1-Methylpyrrolyl)]ethyl]-*N′*-[2-(5-cyanopyridyl)]thiourea (33).** The title product was prepared by using 2-(2-aminomethyl)-1-methylpyrrole as starting amine and route B: mp 199−201 °C dec.; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.37 (t, 1H), 11.05 (s, 1H), 8.60 (d, 1H), 8.16 (dd, 1H), 7.25 (d, 1H), 6.64 (t, 1H), 5.93−5.90 (m, 2H), 3.81 (q, 2H), 3.56 (s, 3H), 2.90 (t, 2H). Anal. ($C_{14}H_{15}N_5S$) C, H; N: calc, 25.5; found, 24.0.

***N*-[2-[2-(1-Methylpyrrolyl)]ethyl]-*N′*-[2-(5-chloropyridyl)]thiourea (34).** The title product was prepared by using 2-(2-aminoethyl)-1-methylpyrrole as starting amine and route C: mp 169.5−171.0 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.36 (t, 1H), 10.76 (br s, 1H), 8.27 (d, 1H), 7.97 (dd, 1H), 7.32 (d, 1H), 6.74 (s, 1H), 6.03−6.00 (m, 2H), 3.93 (q, 2H), 3.67 (s, 3H), 3.01 (t, 2H). Anal. ($C_{13}H_{15}ClN_4S$) H, N; C: calc, 53.0; found, 52.1.

***N*-[2-[2-(3-Fluorofuranyl)]ethyl]-*N′*-[2-(5-chloropyridyl)]thiourea (35).** 3-Bromo-furan (**108**) (5.0 mL, 56 mmol) was dissolved in dry THF under nitrogen. The solution was cooled to −78 °C, and LDA (28 mL, 2 M, 56 mmol) was added. The solution was stirred for 20 min at −78 °C, and DMF (10 mL) was added. The solution was stirred for 5 min at −30 °C and then diluted with water and dichloromethane. The organic phase was washed with water, dried over Na_2SO_4, filtered, and evaporated with caution.

The residue, compound **109**, was dissolved in propylene glycol (100 mL), and *p*-TSA (4 g) and a 4 Å molecular sieve (20 g) were added. The mixture was stirred for 60 min at ambient temperature. The solution was neutralized with K_2CO_3(aq), diluted with ethyl acetate, washed with water, dried over Na_2SO_4, filtered, and evaporated. The residue was distilled using a small column, and the fraction with bp 95−99 °C (6 mmHg) was collected.

The product, compound **110** (7.8 g, 33.5 mmol), was dissolved in THF under nitrogen and cooled to −78 °C. *n*-BuLi (14 mL, 35 mmol) was added. The solution was stirred at −78 °C for 15 min and *N*-fluorobenzenesulfonimide (11 g, 35 mmol) dissolved in THF (40 mL) was added through a dropping funnel. The temperature was kept below −68 °C during the addition. The solution was stirred without cooling, and at −10 °C water (30 mL) and triethylamine (3 mL) were added. The solution was diluted with Et_2O, washed with water, dried over Na_2SO_4, filtered, and evaporated with caution.

The residue, compound **111,** was dissolved in dioxane/water (50 mL, 2:1), and *p*-TSA (3 g) was added. The solution was stirred for 60 min, the pH was adjusted to 8.0 with K_2CO_3, and (carbethoxymethylene)triphenylphosphorane (5.8 g, 16.6 mmol) was added. The solution was stirred for 30 min at ambient temperature, diluted with water, and extracted with dichloromethane. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified with flash chromatography by elution with ethyl acetate/*n*-hexane (1:9). The combined fractions were evaporated.

The residue, compound **113**, was dissolved in methanol/water (5:1) containing $NaHCO_3$ (200 mg) and hydrogenated over Pd/C catalyst at ambient pressure. After theoretical H_2 consumption (340 mL), the solution was filtered through Celite and evaporated. The residue was dissolved in dioxane/water (1:1), and NaOH (400 mg) was added. The solution was heated with stirring to 50 °C for 60 min. The solution was diluted with water and washed with Et_2O. The aqueous phase was acidified with acetic acid and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporated.

The residue, compound **114** (404 mg, 2.6 mmol), was dissolved in toluene, and triethylamine (0.6 mL, 4.3 mmol) and diphenyl phosphorazidate (0.6 mL, 2.8 mmol) were added. The solution was refluxed for 10 min. Hexane was added to precipitate the phosphate salt, and the solution was filtered. Methanol (20 mL) was added, and the solution was refluxed for an additional 40 min. The solution was evaporated, and the residue was purified with flash chromatography on silica gel by elution with ethyl acetate/*n*-hexane (1:4). The combined fractions were evaporated.

The residue, compound **115**, was dissolved in dioxane/methanol/water (1:1:1), NaOH (400 mg) was added, and the solution was refluxed over night. The solution was diluted with water and extracted with Et_2O. The organic phase was extracted with dilute HCl (pH 2), and the acidic water phase was evaporated to give 2-(3-fluorofuranyl)ethylamine hydrochloride, **116**. The title product was prepared according to route A: mp 153.5−154.0 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.4 (br s, 1H), 10.9 (br s, 1H), 8.3−8.2 (d, 1H), 8.0−7.9 (m, 1H), 7.6−7.5 (m, 1H), 7.3−7.2 (d, 1H), 6.6 (t, 1H), 4.0−3.9 (m, 2H), 3.1−3.0 (m, 2H). Anal. ($C_{12}H_{11}ClFN_3OS$) C, H, N.

***N*-[2-[2-(3-Cyanofuranyl)]ethyl]-*N′*-[2-(5-chloropyridyl)]thiourea (36).** 3-Furoic acid (**117**) (5.0 g, 45 mmol) and 1,3-dicyanobenzene (10.0 g, 78 mmol) were mixed and heated to 300 °C, and 2.0 g of 3-cyanofuran (**118**) was collected via a short Vigreux column equipped with a distilling head. The material was pure enough to use in the next step.

3-Cyanofuran (1.4 g, 15 mmol) was dissolved in dry THF (50 mL) and cooled to −77 °C under nitrogen. LDA (15 mmol, 2 M) was added as quickly as possible, keeping the temperature below −65 °C. The solution was stirred for 10 min, and DMF (5mL) was added rapidly. Stirring was continued for 30 s, and ((benzyloxycarbonyl)methyl)triphenylphosphonium bromide (7.3 g, 15 mmol) dissolved in MeOH (20 mL) was added rapidly. The solution was diluted with diethyl ether and washed with water. The organic phase was dried over sodium sulfate, and evaporated.

The crude residue, compound **120**, which contained some triphenylphosphine oxide as an impurity, was dissolved in MeOH, and 5% Pd/C (0.5 g) was added. The solution was hydrogenated at atmospheric pressure until about 400 mL of H_2 was consumed. The solution was filtered and diluted with water, and potassium carbonate (4 g) was added. The solution was washed with dichloromethane, acidified with acetic acid, and extracted with dichloromethane. The organic phase was dried over sodium sulfate and evaporated.

The residue, compound **121**, was dissolved in toluene and triethylamine (0.22 mL, 1.6 mmol), and diphenyl phosphorazidate (0.34 mL, 1.6 mmol) was added. The solution was

refluxed for 20 min, then diluted with diethyl ether, and filtered through Celite. The solution was mixed with 0.1 M hydrochloric acid and dioxane and stirred for 1 h. The water phase was separated, it was made basic with NH_3(aq) and extracted with dichloromethane, and the organic phase was dried over sodium sulfate and evaporated to yield 2-(3-cyanofuranyl)ethylamine (**122**) as an oil. The title product was prepared according to route A: mp 160.2−163.4 °C; ^{1}H NMR (250 MHz, *d*-MeOD, $CDCl_3$) δ 8.1 (d, 1H), 7.7−7.6 (m, 1H), 7.5 (d, 1H), 7.0−6.9(d, 1H), 6.6 (d, 1H), 4.1−4.0 (t, 2H), 3.3−3.2 (t, 2H). Anal. ($C_{13}H_{11}ClN_4OS$) C, H, N.

***N*-[2-(3-Indolyl)ethyl]-*N′*-[2-(5-bromopyridyl)]thiourea (37).** The title product was prepared by using tryptamine hydrochloride as starting amine and route A: mp 200 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.30 (s, 1H), 11.02 (s, 1H), 10.77 (s, 1H), 8.09 (s, 1H), 8.02 (d, 1H), 7.74 (d, 1H), 7.47 (d, 1H), 7.39 (s, 1H), 7.20−7.04 (m, 3H), 3.99 (q, 2H), 3.16 (t, 2H). Anal. ($C_{16}H_{15}BrN_4S$) C, H, N.

***N*-[2-[3-(5-Methoxyindolyl)]ethyl]-*N′*-[2-(5-bromopyridyl)]thiourea (38).** The title product was prepared by using 5-methoxytryptamine hydrochloride as starting amine and route A: mp 180−181 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 10.84 (s, 1H), 10.76 (s, 1H), 8.10 (s, 1H), 8.02 (dd, 1H), 7.37−7.17 (m, 4H), 6.79 (d, 1H), 3.98 (q, 2H), 3.84 (s, 3H), 3.12 (t, 2H). Anal. ($C_{17}H_{17}BrN_4OS$) H, N; C: calc, 50.4; found, 48.8.

***N*-[2-(Benzotriazol-2-yl)ethyl]-*N′*-[2-(5-bromopyridyl)]-thiourea (39).** Benzotriazole (**123**) (100 mmol) was dissolved in 600 mL of DMF, and K_2CO_3 (120 mmol) was added. Ethyl bromoacetate (100 mL) was added to the stirred mixture. The reaction mixture was stirred at 40 °C overnight and filtered, and the solvent was removed in vacuo. The two product isomers were separated by fractional crystallization from mixtures of ethanol/ethyl acetate to give pure compound **125**.

The reduction of compound **125** with lithium borohydride in Et_2O gave a mixture of two alcohols: 2-(2-hydroxyethyl)-benzotriazole (**127**) and 1-(2-hydroxyethyl)benzotriazole. 2-(2-Hydroxyethyl)benzotriazole (**127**) (4.7 g, 28.8 mmol) and pyridine (2.28 g, 28.8 mmol) were dissolved in 200 mL of Et_2O, and the mixture was cooled to −50 °C. Triflic anhydride (8.18 g, 29 mmol) was added dropwise. The mixture was heated to −30 °C. A solution of 150 mL of NH_4Cl and 50 mL of Et_2O was added to the cold solution. The mixture was heated to room temperature, and the solvent was removed. The residue was acidified with HCl and washed with dichloromethane. The mixture was alkalized with NaOH. Extraction with dichloromethane followed by evaporation gave 2-(2-aminoethyl)-benzotriazole (**129**) (2.10 g). The title product was prepared according to route A: mp 218.3 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.4 (t, 1H), 10.9 (s, 1H), 8.05 (m, 3H), 7.9 (d, 1H), 7.55 (m, 2H), 7.2 (d, 1H), 5.15 (t, 2H), 4.4 (m, 2H). Anal. ($C_{14}H_{13}BrN_6S$) C, H, N.

***N*-[2-(5,6-Dimethylbenzotriazol-2-yl)ethyl]-*N′*-[2-(5-bromopyridyl)]thiourea (40).** Starting amine **130** was prepared from 5,6-dimethylbenzotriazole (**124**) by a procedure described for compound **39**. The title product was prepared according to route A: mp 231.9 °C; ^{1}H NMR (250 MHz, DMSO-d_6/MeOD-d_4) δ 7.95 (m, 1H), 7.73 (m, 3H), 7.13 (d, 1H), 5.0 (t, 2H), 4.4 (t, 2H), 2.5 (s, 6H). Anal. ($C_{16}H_{17}BrN_6S$) H; C: calc, 47.41; found, 48.15; N: calc, 20.73; found, 19.70.

***N*-[2-(2-Benzimidazolyl)ethyl]-*N′*-[2-(5-bromopyridyl)]-thiourea (41).** 2-(2-Aminoethyl)benzimidazole (**132**) was prepared from 2-benzimidazolacetonitrile (**137**) by reduction with $NaBH_4/NiCl_2$ in MeOH. The title product was prepared according to route A: mp 203 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.43 (s, 1H), 11.61 (t, 1H), 10.83 (s, 1H), 8.06−7.98 (m, 2H), 7.8−7.5 (br d, 2H), 7.30−7.18 (m, 3H), 4.23 (q, 2H), 3.28 (t, 2H). Anal. ($C_{15}H_{14}BrN_5S$) C, H, N.

***N*-[2-(*N′*-Phthalimidyl)ethyl]-*N″*-[2-(5-chloropyridyl)]-thiourea (42).** (2-Bromoethyl)phthalimide (**133**) (6.0 g, 24 mmol), sodium azide (4.0 g, 58 mmol), and sodium iodide (0.5 g) was dissolved in acetone/water (5:1, 100 mL). The solution was refluxed for 24 h, diluted with water, and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated. The residue, compound **134**, was dissolved in dioxane/water (10:1, 200 mL), and triphenylphosphine (7.0 g, 27 mmol) and trifluoroacetic acid (25.0 mL) were added. The solution was refluxed for 60 min and diluted with water, and the aqueous phase was washed with ethyl acetate and evaporated to yield *N*-(2-aminoethyl)phthalimide **135** as trifluoroacetate salt. The title product was prepared according to route A: mp 189.5−190.0 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.3 (br s, 1H), 10.5 (br s, 1H), 8.1−7.8 (m, 6H), 7.3−7.2 (d, 1H), 4.1−3.9 (m, 4H). Anal. ($C_{16}H_{13}ClN_4O_2S$) C, H, N.

***N*-[2-[*N′*-(3,6-Dichlorophthalimidyl)]ethyl]-*N″*-[2-(5-chloropyridyl)]thiourea (43).** 1-[[2-(5-Chloropyridyl)]thiocarbamoyl]imidazole **45** (0.31 g, 1.3 mmol) and ethylenediamine (5.0 mL) were mixed, and the mixture was heated to 100 °C for 5 min. The mixture was evaporated, dissolved in water, and extracted with dichloromethane. The organic phase was dried over sodium sulfate and evaporated. The residue was dissolved in acetonitrile, and 3,6-dichlorophthalic anhydride (0.15 g, 0.7 mmol) was added. The mixture was refluxed for 12 h. The solution was cooled, and the precipitate was filtered off, suspended in water/methanol (1:2), and boiled for 5 min. The suspension was cooled to room temperature, and the solid was collected by filtration, washed with acetonitrile, and dried to yield the title product as a crystalline solid: mp 271.3−272.6 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.3 (br s, 1H), 10.5 (br s, 1H), 8.1 (s, 1H), 7.9 (m, 3H), 7.4−7.2 (d, 1H), 4.1−3.9 (m, 2H), 3.2−3.0 (m, 2H). Anal. ($C_{16}H_{11}Cl_3N_4O_2S$) H, N; C: calc, 44.7; found, 43.9.

Acknowledgment. We thank C. Rydegård and C. Åhgren for assistance with the biological assays and L. Pettersson for assistance in the preparation of the manuscript. In addition, we thank the Physical Chemistry Department of the Lilly Research Laboratories for providing analytical and spectral data.

References

(1) Sandström, E.; Öberg B. Antiviral Therapy in Human Immunodeficiency Virus Infections: Part 1. *Drugs* **1993**, *45* (4), 488−508.

(2) Accelerated Approval Recommended for D4T Treatment of HIV-Infection. *Antiviral Agents Bull.* **1994**, *7* (6), 161.

(3) Staduvine approved in the US. *Scrip* **1994**, *1937*, 23.

(4) (a) Grob, P. M.; Wu, J. C.; Cohen, K. A.; Ingraham, R. H.; Shih, C. K.; Hargrave, K. D.; Mctague, T. L.; Merluzzi, V. J. Non-nucleoside inhibitors of HIV-1 reverse transcriptase: nevirapine as a prototype drug. *AIDS Res. Hum. Retroviruses* **1992**, *8* (2), 145−52. (b) Hargrave, K. D.; Proudfood, J. R.; Grozinger, K. G.;Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridobenzo- and Dipyrido-diazepinones. *J. Med. Chem.* **1991**, *34*, 2231−2241.

(5) (a) Goldman, M. E.; O'Brien, J. A.; Ruffing, T. L.; Schleif, W. A.; Sardana, V. V.; Byrnes, V. W.; Condra, J. H.; Hoffman, J. M.; Emini, E. A. A Nonnucleoside Reverse Transcriptase Inhibitor Active on Human Immunodeficiency Virus Type 1 Isolates Resistant to Related Inhibitors. *Antimicrob. Agents Chemother.* **1993**, *37* (5), 947−949. (b) Hoffman, J. M.; Wai, J. S.; Thomas, C. M.; Levin, R. B.; O'Brien, J. A.; Goldman, M E. Synthesis and evaluation of 2-pyridinone derivatives as HIV-1-specific reverse transcriptase inhibitors. 1. Phthalimidoalkyl and -alkylamino analogs. *J. Med. Chem.* **1992**, *35*, 3784−91. (c) Saari, W. S.; Wai, J. S.; Fisher, T. E.; Thomas, C. M.; Hoffman, J. M.; Rooney, C. S.; Smith, A. M.; Jones, J. H.; Bamberger, D. L.; et al. Synthesis and evaluation of 2-pyridinone derivatives as HIV-1-specific reverse transcriptase inhibitors. 2. Analogs of 3-aminopyridin-2(1H)-one. *J. Med. Chem.* **1992,** *35*, 3792−3802. (d) Wai, J. S.; Williams, T. M.; Bamberger, D. L.; Fisher, T. E.; Hoffman, J. M.; Hudcosky, R. J.; MacTough, S. C.; Rooney, C. S.; Saari, W. S.; et al. Synthesis and evaluation of 2-pyridinone derivatives as HIV-1-specific reverse transcriptase inhibitors. 3. Pyridyl and phenyl analogs of 3-aminopyridin-2(1H)-one. *J. Med. Chem.* **1993**, *36*, 249−255. (e) Hoffman, J. M.; Smith, A. M.; Rooney, C. S.; Fisher, T. E.; Wai, J. S.; Thomas, C. M.; Bamberger, D. L.; Barnes, J. L.; Williams, T. M.; et al. Synthesis and evaluation of 2-pyridinone derivatives as HIV-1-specific reverse transcriptase inhibitors. 4. 3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1H)-one and analogs. *J. Med. Chem.* **1993**, *36*, 953−966.

(6) White, E. L.; Buckheit, R. W., Jr.; Ross, L. J.; Germany, J. M.; Andries, K.; Pauwels, R.; Janssen, P. A. J.; Shannon, W. M.; Chirigos, M. A. A TIBO derivative, R82913, is a potent inhibitor of HIV-1 reverse transcriptase with heteropolymer templates. *Antiviral Res.* **1991**, *16*, 257−266.
(7) Romero, D. L.; Morge, R. A.; Biles, C.; Berrios-Péna, N.; May, P. D.; Palmer, J. R.; Johnson, P. D.; Smith, H. W.; Busso, M.; Tan, C.-K.; Voorman, R. L.; Reusser, F.; Althaus, I. W.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G.; Aristoff, P. A. Discovery, Synthesis, and Bioactivity of Bis(heteroaryl)-piperazines. 1. A Novel Class of Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1994**, *37*, 999−1014.
(8) Pauwels, R.; Andries, K.; Debyser, Z.; Van Daele, P.; Schols, D.; Stoffels, P.; De Vreese, K.; Woestenborghs, R.; Vandamme, A.-M.; Janssen, C. G. M.; Anne, J.; Cauwenbergh, G.; Desmyter, J.; Heykants, J.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. Potent and highly selective human Immunodeficiency virus type 1 (HIV-1) inhibition by a series of alpha-anilinophenylacetamide derivatives targeted at HIV-1 reverse transcriptase. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1711−1715.
(9) Young, S. D. Non-nucleoside inhibitors of HIV-1 reverse transcriptase. *Perspect. Drug Disc. Des.* **1993**, *1*, 181−192.
(10) Smerdon, S. J.; Jäger, J.; Wang, J.; Kohlstaedt, L. A.; Chirino, A. J.; Friedman, J. M.; Rice, P. A.; Steizt, P. A. Structure of the binding site for nonnucleoside inhibitors of the reverse transcriptase of human immunodeficiency virus type 1. *Proc. Natl. Acad. Sci. U.S.A.*, **1994**, *91*, 3911−3915.
(11) Ternansky, R. J.; Morin, J. M., Jr.; Bell, F. W.; Cantrell, A.; Jaskunas, R.; Jordan, C. L.; Kinnick, M. D.; Lopez, C.; Paget, C. J., Jr.; Palkowitz, J.; Parrish, C.; Pranc, P.; Vasileff, R. T.; West, S. J.; Engelhardt, P.; Högberg, M.; Johansson, N. G.; Kangasmetsä, J.; Lind, P.; Norèen, R.; Rydegård, C.; Sahlberg, C.; Vrang, L.; Zhang, H.; Zhou, X.-X.; Åhgren, C.; Öberg, B. A Novel Class of Potent Non-nucleoside Reverse Transcriptase Inhibitors, a poster presentation, 6th ICAR, Venice, April 25−30, 1993.
(12) Johansson, N. G.; Lind, P.; Noréen, R.; Morin, J. M., Jr.; Ternansky, R. J.; et al. a poster presentation, IXth Int. Conf. AIDS, Berlin, June 6−11, 1993.
(13) Ahgren, C.; Backro, K.; Bell, F. W.; Cantrell, A. S.; Clemens, M.; Colacino, J. M.; Deeter, J. B.; Engelhardt, J. A.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kasher, J. S.; Kinnick, M. D.; Lind, P.; Lopez, C.; Morin, J. M., Jr.; Muesing, M. A.; Noreen, R.; Oberg, B.; Paget, C. J.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Rippy, M. K.; Rydergard, C.; Sahlberg, C.; Swanson, S.; Ternansky, R. J.; Unge, T.; Vasileff, R. T.; Vrang, L. West, S. J.; Zhang, H.; Zhou, X.-X. The PETT Series, a New Class of Potent Nonnucleoside Inhibitors of Human Immunodeficiency Virus Type 1 Reverse Transcriptase. *Antimicrob. Agents Chemother.* **1995**, *39*, 1329−1335.
(14) Bell, F. W.; Cantrell, A. S.; Högberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noréen, R.; Öberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. PETT Compounds, a New Class of HIV-1 Reverse Transcriptase Inhibitors. 1. Synthesis and Basic SAR Studies of PhenEthylThiazoleThiourea (PETT) Analogs. *J. Med. Chem.* **1995**, *38*, 4929−4936.
(15) Zhang, H.; Vrang, L.; Unge, T.; Öberg, B. Characterization of HIV reverse transcriptase with Tyr181→Cys and Leu 100→Ile mutations. *Antiviral Chem. Chemother.* **1993**, *4* (5), 301−308.
(16) Staab, H. A.; Walther, G. Synthese von Isothiocyanaten. *Liebigs Ann. Chem.* **1962**, *657*, 104−107.
(17) Wallingford, V. H.; Krueger, P. A.; *Organic Syntheses;* John Wiley & Sons: New York, 1957; Collect. Vol. II, pp 349−351.
(18) *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Longman: London and New York, 1978; p 796.
(19) Garst, J. E.; Wilson, B. J. Synthesis and analysis of various 3-furyl ketones from Perilla frutescens. *J. Agric. Food Chem.* **1984,** *32*, 1083−1087.
(20) Weislow, O. S.; Kiser, R.; Fine, D. L.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. New Soluble-Formazan Assay for HIV-1 Cytopathic Effects: Application to High-Flux Screening of Synthetic and Natural Products for AIDS-Antiviral Activity. *J. Nat. Cancer Inst.* **1989**, *81* (8), 577−586.
(21) Richman, D. D.; Havlir, D.; Corbeil, J.; Looney, D.; Ignario, C.; Spector, S.A.; Sullivan, J.; Cheeseman, S.; Barringer, K.; Pauletti, D.; Shih, C.-K.; Myers, M.; Griffin, J. Nevirapine Resistance Mutations of Human Immunodeficiency Virus Type 1 Selected during Therapy. *J. Virol.* **1994**, *68*, 1660−1666.
(22) Zhang, H.; Vrang, L.; Bäckbro, K.; Lind, P.; Sahlberg, C.; Unge, T.; Öberg, B. Inhibition of human immunodeficiency virus type 1 wild-type and mutant reverse transcriptases by the phenyl ethyl thiazolyl thiourea derivatives trovirdine and MSC-127. *Antiviral Res.* **1995**, *28*, 331−342.

JM950639R