Synthesis, Stereochemistry, and Opioid Receptor Binding Activity of Heterocyclic Analogues of BW373U86

G. Evan Boswell*+, Robert W. McNutt+, Dulce G. Bubacz+, Ann O. Davis+, and Kwen-Jen Chang†

Division of + Organic Chemistry, †Division of Cell Biology, Burroughs Wellcome Co., Research Triangle Park, NC 27709

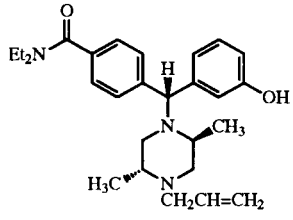
Received July 11, 1995
Revised August 31, 1995

The synthesis of a series of heterocyclic analogues of (±)-4-((α*R**)-α-((2*S**,5*R**)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethylbenzamide (BW373U86) for screening against opioid receptors is described. The intermediate α-heterocyclic benzyl alcohols **24** were synthesized either by low temperature reaction of lithioheterocycles with 3-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (**10**) or by reaction of 3-((*tert*-butyldimethylsilyl)oxy)phenylmagnesium bromide (**19**) with heterocyclic carbaldehydes. The α-heterocyclic benzyl alcohols **24** were converted to chloromethines (**25**) with thionyl chloride and used to alkylate with *trans*-1-allyl-2,5-dimethylpiperazine (**5**) to give diastereomeric pairs of the target compounds. The bromoheterocycles were then derivatized to produce amides. Compounds that are potent and selective for the δ or μ opioid receptors and some mixed δ/μ analogues are reported.

J. Heterocyclic Chem., **32**, 1801 (1995).

Introduction.

BW 373U86 (**1**) has been reported to be a potent and selective nonpeptidic δ-opioid agonist in receptor binding and isolated tissue assays [1]. Several heterocyclic compounds were prepared to gain further insight into the structure-activity relationship of compounds of this type. The synthesis of these compounds, diastereomeric assignments, and opioid receptor binding activities are reported herein.



1, BW373U86

Figure 1

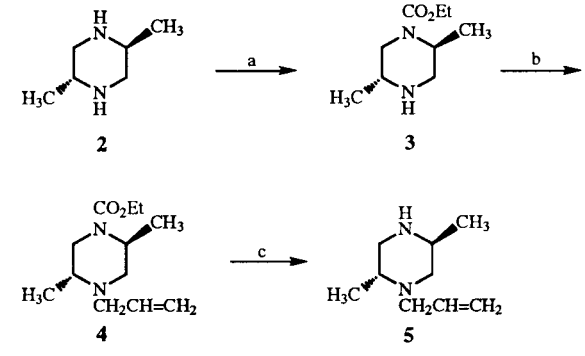
Chemistry.

trans-*N*-Allyl-2,5-dimethylpiperazine (**5**) (Scheme I) was prepared by reaction of *trans*-2,5-dimethylpiperazine (**2**) with ethyl chloroformate to form the monocarbamate **3**, which was then alkylated with allyl bromide to give **4**, and hydrolysis of the carbamate yielded **5**.

α-Heterocyclic Benzyl Alcohols.

The α-heterocyclic benzyl alcohols (**24**) were synthesized by either low temperature reaction of lithioheterocycles with 3-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (**10**) (Schemes II and III) or by reaction of 3-((*tert*-butyldimethylsilyl)oxy)phenylmagnesium bromide (**19**) with heterocyclic carbaldehydes (Scheme IV).

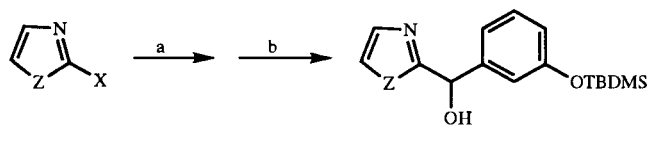
Scheme I



Conditions: (a) ethyl chloroformate, (b) allyl bromide, Na_2CO_3, CH_3CN, (c) KOH, EtOH

Thiazole analogue **8** (Scheme II) was synthesized from 3-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (**10**) by analogy to a literature procedure describing the preparation of phenylthiazolylmethanol from benzaldehyde [2]. Imidazole analogue **9** was prepared by deprotonation of 1-methylimidazole (**7**) with lithium diisopropylamide [3] and reaction of the resulting lithioheterocycle with **10** in tetrahydrofuran.

Scheme II



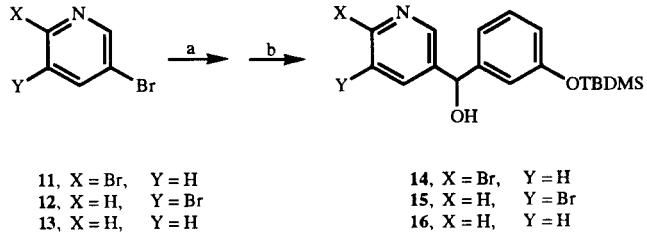
6, X = Br, Z = S
7, X = H, Z = NCH_3

8, Z = S
9, Z = NCH_3

Conditions: (a) *n*-BuLi, (b) *m*-OTBDMS-benzaldehyde (**10**)

The pyridine carbinols **14-16** (Scheme III) were prepared by low temperature lithium-halogen exchange of pyridines **11-13** in diethyl ether, followed by reaction with **10**. The 2,5-dibromopyridine (**11**) gave >99% regioselectivity at the 5-position in this reaction. A small amount of the isomer resulting from lithium-halogen exchange at the 2-position was isolated and characterized by nmr.

Scheme III



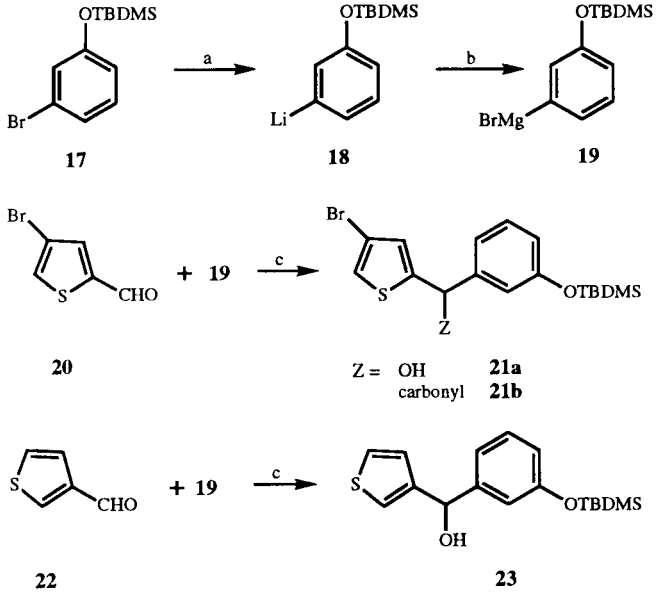
11, X = Br, Y = H
12, X = H, Y = Br
13, X = H, Y = H

14, X = Br, Y = H
15, X = H, Y = Br
16, X = H, Y = H

Conditions: (a) *n*-BuLi, Et_2O, (b) *m*-OTBDMS-benzaldehyde (**10**)

Low temperature reaction of 3-((*tert*-butyldimethylsilyl)oxy)phenyllithium (**18**) with 4-bromo-2-thiophenecarboxaldehyde (**20**) resulted in an uncharacterizable mixture, presumably due to lithium halogen exchange and α-heterodeprotonation competing with nucleophilic attack at the aldehyde. Therefore, the organolithium **18** was converted to the magnesium Grignard reagent **19** by transmetalation with magnesium bromide [4]. A solution of aldehyde **20** in tetrahydrofuran was then added to the Grignard to form alcohol **21a** (Scheme IV). The ketone **21b** was also isolated from the reaction. Using the same procedure, alcohol **23** was obtained from thiophene-3-carboxaldehyde (**22**) and **19**.

Scheme IV

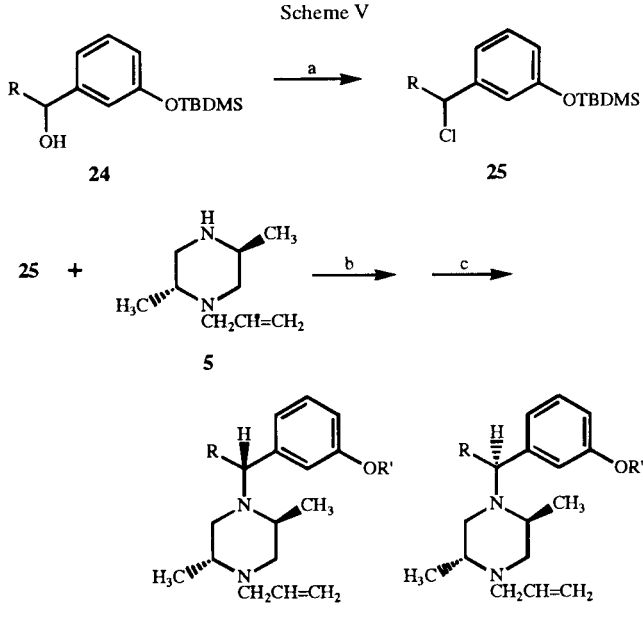


Conditions: (a) *n*-BuLi, -78°C, THF, (b) MgBr, THF, (c) THF

Conversion of α-Heterocyclic Benzyl Alcohols to Chloromethines Followed by Alkylation of *trans*-1-Allyl-2,5-dimethylpiperazine (**5**).

The alcohols **24** (Scheme V) were converted to the chloromethines **25** by treatment with an excess of thionyl chloride in dichloromethane at 25°. Crude alkyl chlorides **25** were used immediately to alkylate piperazine **5** in refluxing acetonitrile to give a mixture of the two diastereomers which are epimeric at the benzylic methine. Alternatively, a minimal amount of toluene may be used as a solvent. The diastereomeric pairs of the thiazolyl, 1-methylimidazolyl, and 3-thienyl analogues were separated by chromatography as silyl ethers. The diastereomeric pairs of the 5-bromo-3-pyridyl, 3-pyridyl, and 4-bromo-2-thienyl analogues were separated by chromatography as phenols after desilylation.

Scheme V



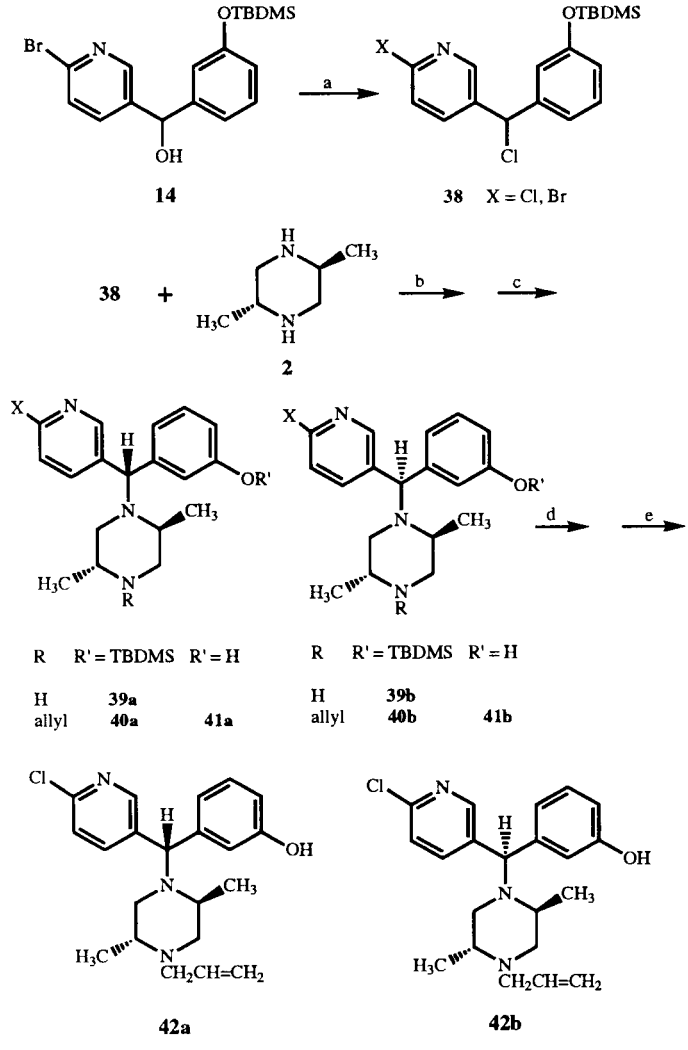
R	R' = TBDMS	R' = H	R' = TBDMS	R' = H
2-thiazolyl	**26a**	**32a**	**26b**	**32b**
N-Me-2-imidazolyl	**27a**	**33a**	**27b**	**33b**
5-Br-3-pyridyl	**28a**	**34a**	**28b**	**34b**
3-pyridyl	**29a**	**35a**	**29b**	**35b**
4-Br-2-thienyl	**30a**	**36a**	**30b**	**36b**
3-thienyl	**31a**	**37a**	**31b**	**37b**

Conditions: (a) $SOCl_2$, CH_2Cl_2, (b) CH_3CN or PhMe, Δ, (c) Et_4NF, CH_3CN

Conversion of 6-bromopyridyl alcohol **14** to the alkyl chloride with thionyl chloride was accompanied by partial halogen exchange at the 6-position to give a mixture of 6-chloro and 6-bromochloromethines **38** (Scheme VI). These were not separated but were carried through subse-

quent reactions as a mixture. The diastereomers were separated by chromatography as their silyl ethers to give bromo-chloro mixtures **40a** and **40b**, but attempts to separate the halogen congeners of **40a** or **40b**, or their corresponding phenols **41a** and **41b**, were unsuccessful. Treatment of the bromo-chloro mixture **41a** with thionyl chloride in dichloromethane did not change the halogen ratio, but treatment of diastereomers **41a** and **41b** with anhydrous hydrogen chloride drove the halogen exhange to completion to give pure chloro analogues **42a** and **42b**. Treatment of bromo-chloro mixture **41a** with anhydrous hydrogen bromide did not reverse the halogen exchange to give the 2-bromo compound.

Scheme VI

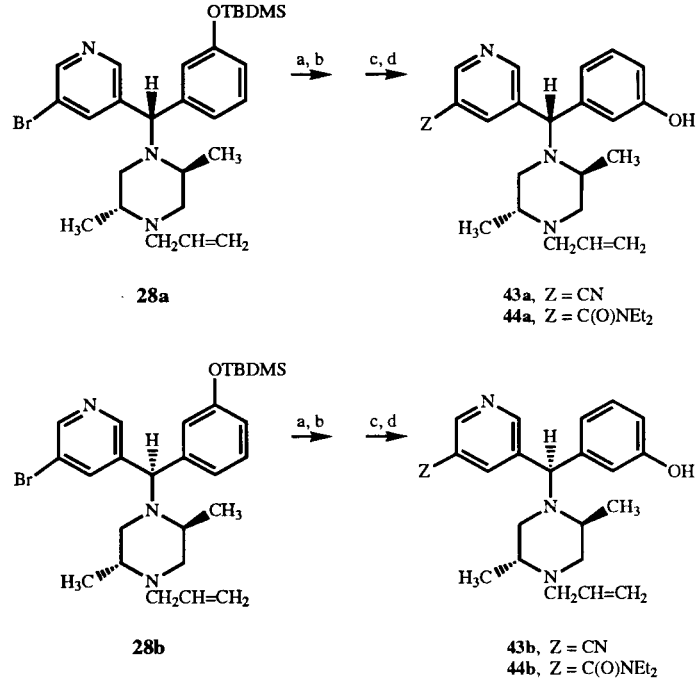


Conditions: (a) $SOCl_2$, CH_2Cl_2, (b) CH_3CN,Δ, (c) allyl bromide, Na_2CO_3, THF, (d) Et4NF, CH3CN, (e) HCl

Synthesis of Heterocyclic Amides from Bromoheterocycles.

The bromopyridine **34b** was converted to the cyano analogue **43b** with cuprous cyanide in dimethylformamide. Compound **43b** was hydrolyzed to the carboxylic acid with sodium hydroxide in ethanol. The crude acid was coupled with diethylamine in dimethylformamide using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) to form the amide **44b**.

Scheme VII

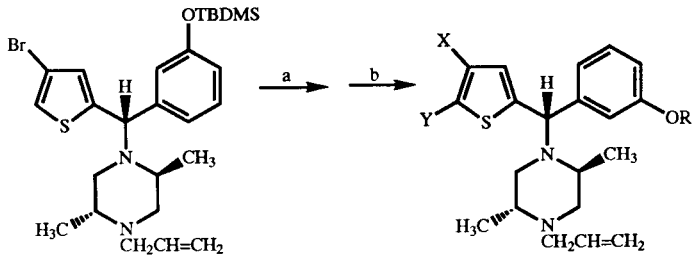


Conditions: (a) Et_4NF, CH_3CN, (b) CuCN, DMF, Δ, (c) NaOH, EtOH, (d) BOP, Et_2NH, DMF

The 4-bromothiophene **30b** (Scheme VIII) was converted to the analogous lithiothiophene by low temperature reaction with *n*-butyllithium and quenched with gaseous carbon dioxide, to give the lithium carboxylate, which was not isolated but was treated immediately with thionyl chloride to provide the acid chloride. The acid chloride also was not isolated but was treated immediately with diethylamine. This reaction sequence gave four products: the unsubstituted thiophene **45b** (21%), the 4-bromo-5-diethylamide **46b** (8.7%), the 5-diethylamide **47b** (19%), and the 4-diethylamide **48b** (16%).

The unsubstituted thiophene **45b** results from quenching of the lithiothiophene before carboxylation can take place. This product can be supressed by stringent anhydrous conditions. The bromoamide **46b** is the result of deprotonation and carboxylation at the activated thiophene 5-position. Substituting the base lithium diisopropylamide for *n*-butyllithium in this reaction sequence

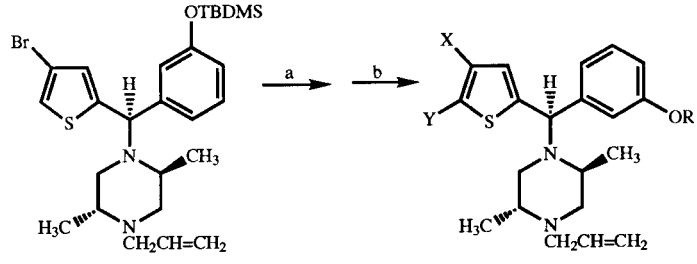
Scheme VIII



30a

R = TBDMS R = H

X = H, Y = H	**45a**	**49a**
X = Br, Y = C(O)NEt$_2$	**46a**	**50a**
X = H, Y = C(O)NEt$_2$	**47a**	**51a**
X = C(O)NEt$_2$, Y = H	**48a**	**52a**



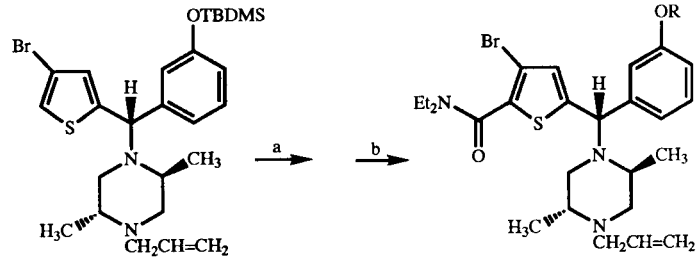
30b

R = TBDMS R = H

X = H, Y = H	**45b**	**49b**
X = Br, Y = C(O)NEt$_2$	**46b**	**50b**
X = H, Y = C(O)NEt$_2$	**47b**	**51b**
X = C(O)NEt$_2$, Y = H	**48b**	**52b**

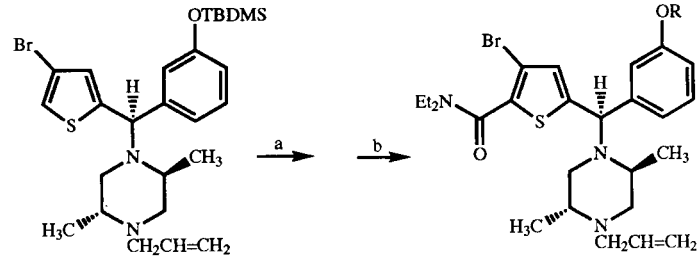
Conditions: (a) 1) *n*-BuLi, THF 2) CO_2 3) $SOCl_2$ 4) Et_2NH, (b) Et_4NF, CH_3CN

Scheme IX



30a

46a, R = TBDMS
50a, R = H



30b

46b, R = TBDMS
50b, R = H

Conditions: (a) 1) LDA, THF 2) CO_2 3) $SOCl_2$ 4) Et_2NH, (b) Et_4NF, CH_3CN

gave bromoamide **46b** in 60% yield with none of **45b** (Scheme IX). The 5-diethylamide **47b** may be the result of α-deprotonation of the quench product, thiophene **45b**. The 4-diethylamide **48b** is the normally expected regioisomer for lithium-halogen exchange followed by carbon dioxide quenching.

Desilylation with tetraethylammonium fluoride gave the target phenols **49b-52b**. The same procedure was used to prepare the other diastereomers **49a-52a** from **30a**.

Determination of Relative Stereochemistry of the Diastereomeric Pairs.

Racemate **37b** was resolved with (-)-di-*p*-toluoyl-L-tartaric acid to give the pure (-)-enantiomer **53b**. The absolute configuration was determined by X-ray crystallography (Figure 2) and shown to be the mirror image of **37b** as drawn in Scheme V. Relative stereochemistries of **37a** and **37b** are, therefore, as drawn. The positional parameters, selected bond lengths and selected bond angles of **53b** are given in Tables 1, 2, and 3.

Racemate **36b** was resolved with (-)-di-*p*-toluoyl-L-tartaric acid to give pure (+)-enantiomer **54b**. The crystallographic structure is shown in Figure 3. Relative stereochemistries of **36a** and **36b** are, therefore, as drawn. Resolution of **36b** with the antipode (+)-di-*p*-toluoyl-L-tartaric acid gave pure (-)-enantiomer **54a**. Since thiophene analogues **49a-52a** and **49b-52b** were synthesized from **36a** and **36b** respectively, their relative stereochemistries are established as drawn. The positional parameters, selected bond lengths and selected bond angles of **54b** are given in Tables 4, 5, and 6.

The pure enantiomers **54a** and **54b** were used to prepare the 2-thiophene compounds **55a** and **55b** as single enantiomers by lithium-halogen exchange followed by quenching with aqueous ammonium chloride. They were also used to prepare the bromoamides **56a** and **56b** as single enantiomers by the method of Scheme IX.

X-Ray crystallographic analyses were not performed on the thiazole, pyridine, or imidazole compounds, but the relative stereochemistry of the diastereomeric pairs of the thiazole and pyridine compounds could be assigned with some degree of confidence on the basis of an empirically observed correlation of the aromatic nmr pattern (in DMSO-d_6) with diastereomeric structure. Resonances for the phenolic aromatic protons were observed to have different characteristic patterns for the two diastereomers. For BW373U86 and analogues known to have the same

Table 1

Positional Parameters of **53b** with Estimated Standard Deviations in Parenthesis

atom	x	y	z	B(eq) [a]
S(1)	0.9042(2)	0.5657	0.0697(2)	7.8(1)
S(1A)	0.7412(4)	0.5966(2)	0.1649(3)	7.0(5)
O(1)	-0.1903(4)	0.3009(2)	-0.3568(3)	8.2(1)
N(1)	0.4632(3)	0.3366(2)	0.0740(2)	3.39(8)
N(2)	0.4906(3)	0.2553(2)	0.3740(2)	3.77(8)
C (1)	0.7866(5)	0.4819(2)	-0.0123(4)	5.6(1)
C(2)	0.7412	0.5966	0.1649	7.8(8)
C(2A)	0.9042	0.5657	0.0697	4.0(7)
C(3)	0.5746(5)	0.5320(2)	0.1128(4)	5.2(1)
C(4)	0.6093(4)	0.4690(2)	0.0167(3)	4.1(1)
C(5)	0.4771(4)	0.3956(2)	-0.0494(3)	3.7(1)
C(6)	0.2645(4)	0.4153(2)	-0.1649(3)	3.7(1)
C(7)	0.2111(5)	0.4902(2)	-0.2370(4)	5.0(1)
C(8)	0.0223(5)	0.5010(2)	-0.3547(4)	5.6(1)
C(9)	-0.1140(4)	0.4396(2)	-0.3997(4)	5.0(1)
C(10)	-0.0645(4)	0.3652(2)	-0.3251(3)	4.5(1)
C(11)	0.1244(4)	0.3537(2)	-0.2088(3)	4.2(1)
C(12)	0.3743(4)	0.3699(2)	0.1894(3)	3.6(1)
C(13)	0.3118(4)	0.3035(2)	0.2832(3)	3.8(1)
C(14)	0.5888(4)	0.2253(2)	0.2590(3)	3.9(1)
C(15)	0.6450(4)	0.2910(2)	0.1618(3)	3.7(1)
C(16)	0.7438(5)	0.2523(2)	0.0481(4)	5.2(1)
C(17)	0.2104(5)	0.3403(2)	0.3953(4)	5.3(1)
C(18)	0.4295(5)	0.1851(2)	0.4546(4)	5.4(1)
C(19)	0.6017(6)	0.1351(2)	0.5556(4)	6.1(2)
C(20)	0.6204(6)	0.0583(3)	0.5364(6)	7.3(2)

[a] B(eq) = 8/3 π^2 (U_{11}(aa*)^2 +U_{22}(bb*)^2+U_{33}(cc*)^2 + 2U_{12}aa*bb* cos γ + 2U_{13}aa*cc* cos β + 2U_{23}bb*cc* cos α)

relative stereochemistry (bromophenyl analogue **57** in Figure 4, **36a, 37a, 49a-52a**), resonances of three of the phenolic aromatic protons are overlapping at 6.7 ppm, with the fourth resonance a triplet at 7.1 to 7.2 ppm. For the benzylic epimer of BW373U86 and thienyl analogues with the same stereochemistry (**36b, 37b, 49b-52b**), resonances of the phenolic aromatic protons are distinct and

Table 2

Bond Lengths (Angstroms) of **53b** with Estimated Standard Deviations in Parenthesis

bond	distance	bond	distance
S (1)-C (1)	1.648 (4)	C (4)-C (5)	1.520 (4)
S (1)-C (2)	1.704 (3)	C (5)-C (6)	1.536 (4)
S (1A)-C (2A)	1.704 (3)	C (6)-C (11)	1.380 (4)
S (1A)-C (3)	1.539 (4)	C (6)-C (7)	1.380 (4)
O (1)-C (10)	1.352 (4)	C (7)-C (8)	1.393 (4)
N (1)-C (5)	1.473 (3)	C (8)-C (9)	1.362 (4)
N (1)-C (12)	1.455 (3)	C (9)-C (10)	1.377 (5)
N (1)-C (15)	1.464 (3)	C (10)-C (11)	1.390 (4)
N (2)-C (13)	1.478 (3)	C (12)-C (13)	1.516 (4)
N (2)-C (14)	1.478 (3)	C (13)-C (17)	1.514 (4)
N (2)-C (18)	1.490 (4)	C (14)-C (15)	1.505 (4)
C (1)-C (4)	1.375 (4)	C (15)-C (16)	1.526 (4)
C (2)-C (3)	1.539 (3)	C (18)-C (19)	1.488 (5)
C (3)-C (4)	1.405 (4)	C (19)-C (20)	1.291 (5)

Table 3

Intramolecular Bond Angles (°) of **53b** Involving the Nonhydrogen Atoms with Estimated Standard Deviations in Parenthesis

Angle	(°)	Angle	(°)
C (5)-N (1)-C (12)	113.5 (2)	C (7)-C (6)-C (11)	118.2 (2)
C (5)-N (1)-C (15)	117.2 (2)	C (6)-C (7)-C (8)	119.7(3)
C (12)-N (1)-C (15)	110.0 (2)	C (7)-C (8)-C (9)	121.7 (3)
C (13)-N (2)-C (14)	109.4 (2)	C (8)-C (9)-C (10)	119.0 (2)
C (13)-N (2)-C (18)	109.8 (2)	O (1)-C(10)-C (9)	123.9 (3)
C (14)-N (2)-C (18)	109.4 (2)	O (1)-C (10)-C (11)	116.5 (3)
S (1)-C (1)-C (4)	114.2 (3)	C (9)-C (10)-C (11)	119.5 (3)
S (1A)-C (2)-C (3)	103.1 (1)	C (6)-C(11)-C (10)	21.7 (3)
S (1A)-C (2A)-C (1)	97.7 (1)	N (1)-C (12)-C (13)	111.5 (2)
S (1A)-C (3)-C (4)	114.7 (2)	N (2)-C (13)-C (12)	108.9 (2)
C (1)-C (4)-C (3)	110.1 (3)	N (2)-C (13)-C (17)	112.2 (2)
C (1)-C (4)-C (5)	122.5 (3)	C (12)-C (13)-C (17)	109.8 (2)
C (3)-C (4)-C (5)	127.4 (3)	N (2)-C (14)-C (15)	114.1 (2)
N (1)-C (5)-C (4)	115.8 (2)	N (1)-C (15)-C (14)	108.2 (2)
N (1)-C (5)-C (6)	108.9 (2)	N (1)-C (15)-C (16)	113.1 (3)
C (4)-C (5)-C (6)	114.8 (2)	C (14)-C (15)-C (16)	108.9 (2)
C (5)-C (6)-C (7)	123.0 (3)	N (2)-C (18)-C (19)	113.5(3)
C (5)-C (6)-C (11)	118.6 (2)	C (18)-C (19)-C (20)	124.6 (4)

Table 4

Positional Parameters of **54b** with Estimated Standard Deviations in Parenthesis

atom	x	y	z	B(eq) [a]
Br(1)	0.60803(4)	0.47378(2)	0.62136(4)	6.22(2)
S(1)	0.58463(9)	0.40985(4)	0.21074(7)	4.19(3)
O(1)	0.1080(2)	0.2952(1)	0.2685(2)	4.9(1)
N(l)	0.5890(2)	0.1920(1)	0.3230(2)	2.71(9)
N(2)	0.6559(2)	0.0984(1)	0.5383(2)	3.2(1)
C(1)	0.5744(3)	0.3524(2)	0.4378(3)	3.3(1)
C(2)	0.5916(3)	0.4295(2)	0.4536(3)	3.6(1)
C(3)	0.5992(3)	0.4682(2)	0.3414(3)	4.2(1)
C(4)	0.5683(3)	0.3325(1)	0.3091(3)	2.8(1)
C(S)	0.5518(3)	0.2571(1)	0.2445(2)	2.7(1)
C(6)	0.4229(3)	0.2447(1)	0.1942(2)	2.9(1)
C(7)	0.3249(3)	0.2802(1)	0.2506(3)	3.1(1)
C(8)	0.2059(3)	0.2623(2)	0.2131(3)	3.2(1)
C(9)	0.1868(3)	0.2093(2)	0.1176(3)	4.1(1)
C(10)	0.2846(3)	0.1755(2)	0.0584(3)	4.5(2)
C(11)	0.4028(3)	0.1928(1)	0.0957(3)	3.7(1)
C(12)	0.5011(3)	0.1674(2)	0.4212(3)	3.3(1)
C(13)	0.5336(3)	0.0919(2)	0.4785(3)	3.4(1)
C(14)	0.7435(3)	0.1194(2)	0.4351(3)	3.3(1)
C(15)	0.7146(3)	0.1950(1)	0.3770(3)	3.1(1)
C(16)	0.8078(3)	0.2151(2)	0.2729(3)	4.1(1)
C(17)	0.4378(3)	0.0677(2)	0.5752(3)	4.9(2)
C(18)	0.6981(3)	0.0307(2)	0.6076(3)	4.2(1)
C(19)	0.7067(4)	-0.0385(2)	0.5271(4)	5.4(2)
C(20)	0.8075(5)	-0.0732(2)	0.5046(5)	7.9(3)

[a] B(eq) = 8/3 π^2 (U_{11}(aa*)^2 +U_{22}(bb*)^2+U_{33}(cc*)^2 + 2U_{12}aa*bb* cos γ + 2U_{13}aa*cc* cos β + 2U_{23}bb*cc* cos α)

evenly spread from 6.6 ppm to 7.1 ppm. Spectra for the epimeric pairs of thiazole analogues **32a** and **32b** and pyridine analogues **35a, 35b, 42a-44a, 42b-44b** conformed nicely to the foregoing pattern, and relative

Table 5

Bond Lengths (Angstroms) of **54b** with Estimated Standard Deviations in Parenthesis

bond	distance	bond	distance
Br (1)-C (2)	1.893 (3)	(5)-C (6)	1.522 (4)
S (1)-C (3)	1.701 (3)	(6)-C (7)	1.377 (4)
S (1)-C (4)	1.722 (3)	(6)-C (11)	1.388 (3)
O (1)-C (8)	1.351 (4)	(7)-C (8)	1.399 (4)
N (1)-C (5)	1.474 (3)	(8)-C (9)	1.377 (4)
N (1)-C (12)	1.458 (3)	(9)-C (10)	1.373 (4)
N (1)-C (15)	1.487 (3)	(10)-C (11)	1.388 (5)
N (2)-C (13)	1.480 (4)	(12)-C (13)	1.519 (4)
N (2)-C (14)	1.474 (4)	(13)-C (17)	1.506 (4)
N (2)-C (18)	1.481 (4)	(14)-C (15)	1.516 (3)
C (1)-C (2)	1.407 (4)	(15)-C (16)	1.517 (4)
C (1)-C (4)	1.359 (4)	(18)-C (19)	1.491 (4)
C (2)-C (3)	1.340 (4)	(19)-C (20)	1.292 (6)
C (4)-C (5)	1.517 (3)		

Table 6

Intramolecular Bond Angles (°) of **54b** Involving the Nonhydrogen Atoms with Estimated Standard Deviations in Parenthesis

Angle	(°)	Angle	(°)
C (3)-S (1)-C (4)	93.0 (1)	C (5)-C (6)-C (11)	119.3 (3)
C (5)-N (1)-C (12)	115.3 (2)	C (7)-C (6)-C (11)	119.2 (3)
C (5)-N (1)-C (15)	115.4 (2)	C (6)-C (7)-C (8)	120.8 (3)
C (12)-N (1)-C (15)	111.9 (2)	O (1)-C (8)-C (7)	122.0 (3)
C (13)-N (2)-C (14)	108.7 (2)	O (1)-C (8)-C (9)	118.4 (3)
C (13)-N (2)-C (18)	114.5 (2)	C (7)-C (8)-C (9)	119.6 (3)
C (14)-N (2)-C (18)	110.2 (2)	C (8)-C (9)-C (10)	119.7 (3)
C (2)-C (1)-C (4)	112.1 (3)	C (9)-C (10)-C (11)	120.9 (3)
Br (1)-C (2)-C (1)	122.0 (2)	C (6)-C (11)-C (10)	119.8 (3)
Br (1)-C (2)-C (3)	123.0 (2)	N (1)-C (12)-C (13)	112.2 (2)
C (1)-C (2)-C (3)	114.9 (3)	N (2)-C (13)-C (12)	107.5 (2)
S (1)-C (3)-C (2)	109.9 (2)	N (2)-C (13)-C (17)	112.9 (2)
S (1)-C (4)-C (1)	110.1 (2)	C (12)-C (13)-C (17)	110.1 (3)
S (1)-C (4)-C (5)	118.8 (2)	N (2)-C (14)-C (15)	111.7 (2)
C (1)-C (4)-C (5)	131.2 (2)	N (1)-C (15)-C (14)	107.9 (2)
N (1)-C (5)-C (4)	116.1 (2)	N (1)-C (15)-C (16)	112.2 (2)
N (1)-C (5)-C (6)	109.0 (2)	C (14)-C (15)-C (16)	110.1 (2)
C (4)-C (5)-C (6)	112.8 (2)	N (2)-C (18)-C (19)	116.3 (2)
C (5)-C (6)-C (7)	121.3 (2)	C (18)-C (19)-C (20)	123.6 (4)

Table 7

Positional parameters of **57** with Estimated Standard Deviations in Parenthesis

atom	x	y	z	B(eq) [a]
Br1	1.12972(7)	0.09944(4)	0.25490(6)	6.82(5)
O1	0.5294(5)	0.4761(2)	-0.2352(4)	5.4(2)
N1	0.5429(4)	0.3171(2)	0.1691(3)	3.4(2)
N2	0.3999(4)	0.3974(2)	0.3178(3)	3.8(2)
C1	0.6293(5)	0.3039(3)	0.0757(4)	3.5(2)
C2	0.7537(5)	0.2555(2)	0.1230(4)	3.4(2)
C3	0.7502(6)	0.2130(2)	0.2192(4)	4.2(2)
C4	0.8607(6)	0.1673(3)	0.2583(5)	4.6(2)
C5	0.9781(5)	0.1617(2)	0.2039(5)	4.3(2)
C6	0.9810(6)	0.2030(3)	0.1060(5)	4.7(2)
C7	0.8706(5)	0.2482(3)	0.0672(4)	4.2(2)
C8	0.6775(5)	0.3655(2)	0.0201(4)	3.4(2)
C9	0.5852(5)	0.3937(2)	-0.0850(4)	3.7(2)
C10	0.6243(5)	0.4524(2)	-0.1297(4)	3.8(2)
C11	0.7531(5)	0.4830(3)	-0.0698(4)	4.2(2)
C12	0.8459(5)	0.4557(2)	0.0349(4)	4.0(2)
C13	0.8091(6)	0.3978(2)	0.0788(5)	3.9(2)
C14	0.3905(5)	0.3415(3)	0.1176(4)	3.7(2)
C15	0.3173(6)	0.3527(3)	0.2238(5)	4.1(2)
C16	0.5497(5)	0.3707(3)	0.3708(4)	3.9(2)
C17	0.6260(5)	0.3601(3)	0.2664(4)	3.8(2)
C18	0.2955(6)	0.2938(4)	0.0275(6)	5.3(3)
C19	0.6478(7)	0.4144(3)	0.4676(6)	5.0(3)
C20	0.3139(7)	0.4070(3)	0.4124(5)	4.7(3)
C21	0.1773(6)	0.4457(3)	0.3684(5)	4.9(3)
C22	0.0435(8)	0.4315(5)	0.3794(6)	6.7(4)

[a] $B(eq) = 8/3\ \pi^2\ (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos\gamma + 2U_{13}aa^*cc^* \cos\beta + 2U_{23}bb^*cc^* \cos\alpha)$

Table 8

Bond Lengths (Angstroms) of **57** with Estimated Standard Deviations in Parenthesis

bond	distance	bond	distance
Br(1)-C (5)	1.879 (5)	C (5)-C (6)	1.393 (7)
O(1) -C (10)	1.369 (6)	C (6)-C (7)	1.368 (7)
N (1)-C (17)	1.460 (6)	C (8)-C (9)	1.392 (6)
N(1)-C (14)	1.468 (6)	C (8)-C (13)	1.395 (6)
N (1)-C (1)	1.489 (5)	C (9)-C (10)	1.391 (6)
N (2)-C (15)	1.458 (6)	C (21)-C (22)	1.306 (8)
N (2)-C (16)	1.467 (6)	C (10)-C (11)	1.362 (6)
N (2)-C (20)	1.488(6)	C (11)-C (12)	1.383 (7)
C (1)-C (2)	1.513 (6)	C (12)-C (13)	1.366 (6)
C (1)-C (8)	1.528 (6)	C (14)-C (18)	1.518 (7)
C (2)-C (7)	1.385 (6)	C (14)-C (15)	1.524(6)
C (2)-C (3)	1.393 (6)	C (16)-C (19)	1.518 (8)
C (3)-C (4)	1.376 (7)	C (16)-C (17)	1.524 (6)
C (4)-C (5)	1.375 (7)	C (20)-C (21)	1.467 (8)

Table 9

Intramolecular Bond Angles (°) of **57** Involving the Nonhydrogen Atoms with Estimated Standard Deviations in Parenthesis

Angle	(°)	Angle	(°)
C (17)-N (1)-C (14)	110.8 (4)	C (9)-C (8)-C (1)	120.7 (4)
C (17)-N (1)-C (1)	111.0 (3)	C (13)-C (8)-C (1)	120.9 (4)
C (14)-N (1)-C (1)	114.7 (3)	C (10)-C (9)-C (8)	120.5 (4)
C (15)-N (2)-C (16)	108.8 (4)	C (11)-C (10)-O (1)	123.2 (5)
C (15)-N (2)-C (20)	108.7 (4)	C (11)-C (10)-C (9)	120.0 (4)
C (16)-N (2)-C (20)	112.4 (4)	O (1)-C (10)-C (9)	116.9 (4)
N (1)-C (1)-C (2)	111.7 (3)	C (10)-C (11)-C (12)	120.3 (5)
N (1)-C (1)-C (8)	113.3 (4)	C (13)-C (12)-C (11)	120.1 (5)
C (2)-C (1)-C (8)	114.6 (4)	C (12)-C (13)-C (8)	120.9 (5)
C (7)-C (2)-C (3)	116.9 (4)	N (1)-C (14)-C (18)	111.9 (4)
C (7)-C (2)-C (1)	121.6 (4)	N (1)-C (14)-C (15)	108.5 (4)
C (3)-C (2)-C (1)	121.3 (4)	C (18)-C (14)-C (15)	108.6 (4)
C (4)-C (3)-C (2)	121.0 (5)	N (2)-C (15)-C (14)	113.8 (4)
C (5)-C (4)-C (3)	121.4 (5)	N (2)-C (16)-C (19)	113.4 (5)
C (4)-C (5)-C (6)	118.1 (5)	N (2)-C (16)-C (17)	108.4 (4)
C (4)-C (5)-Br (1)	122.3 (4)	C (19)-C (16)-C (17)	108.8 4)
C (6)-C (5)-Br (1)	119.7 (4)	N (1)-C (17)-C (16)	113.6 (4)
C (7)-C (6)-C (5)	120.2 (5)	C (21)-C (20)-N (2)	113.7 (4)
C (6)-C (7)-C (2)	122.4 (5)	C (22)-C (21)-C (20)	126.9 (7)
C (9)-C (8)-C (13)	118.2 (4)		

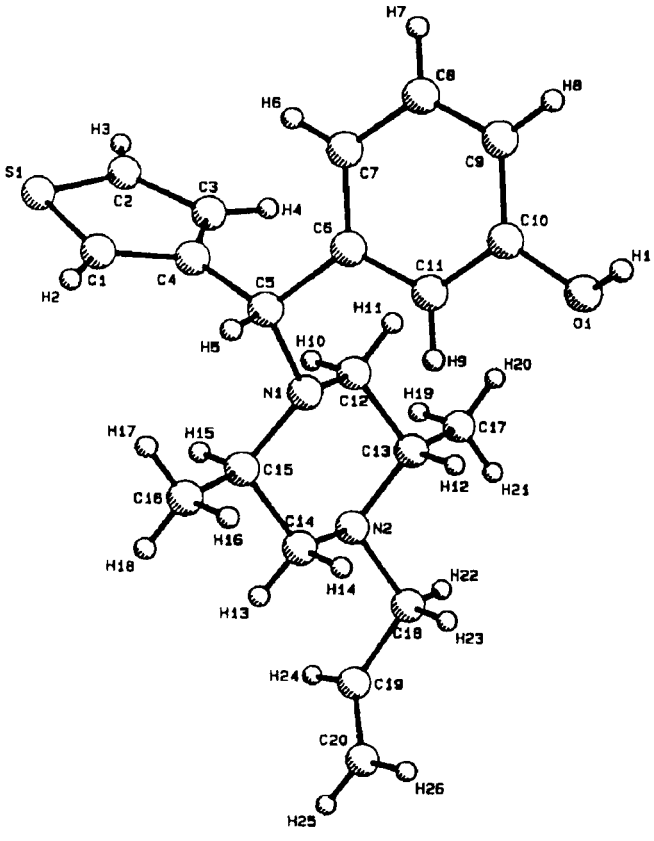


Figure 2

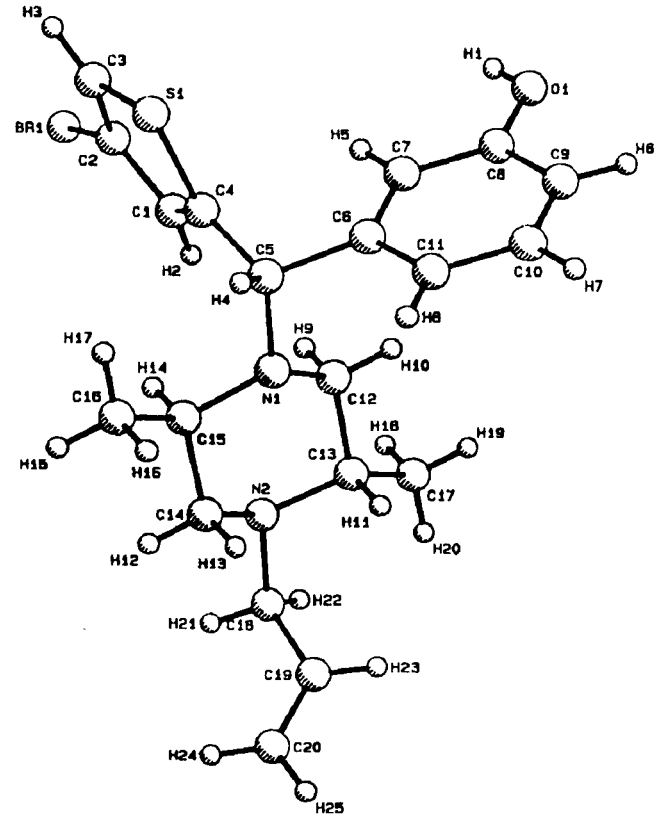


Figure 3

stereochemistry could be assigned. The nmr spectra for the pair of imidazole analogues **33a** and **33b** were ambiguous and unassignable by this method.

The relative stereochemistry of BW373U86 (Figure 1) and its bromophenyl precursor (compound **57**, Figure 4) were determined by X-ray crystallography. The positional parameters, selected bond lengths and selected bond angles of **57** are given in Tables 7, 8, and 9.

Biological Results.

Opioid receptor binding assays were performed with rat brain membrane preparations as previously described [5-7]. As reported previously [1], BW373U86 (**1**) is a potent δ-selective ligand in receptor binding assays with K_i values of 1.8 ±0.4 *nM* and 15 ±3 *nM* for the δ- and μ-receptor binding sites. In this study, all of the heterocyclic amides (except bromoamide **50a**) and chloropyridine **42a** with the same stereochemistry as BW373U86 had δ-selective receptor binding profiles similar to that of BW373U86. Compound **44a** had δ and μ K_is of 1.7 *nM* and 8.5 *nM*, **51a** had K_is of 1.4 *nM* and 25 *nM*, **52a** had K_is of 0.8 *nM* and 3.3 *nM*, and **42a** had K_is of 1 *nM* and 15 *nM*.

Some of the unsubstituted heterocyclic analogues with benzylic stereochemistry epimeric to BW373U86 were μ-selective in the potency range of morphine and fentanyl. In this assay the δ and μ K_is of morphine were 90 *nM* and

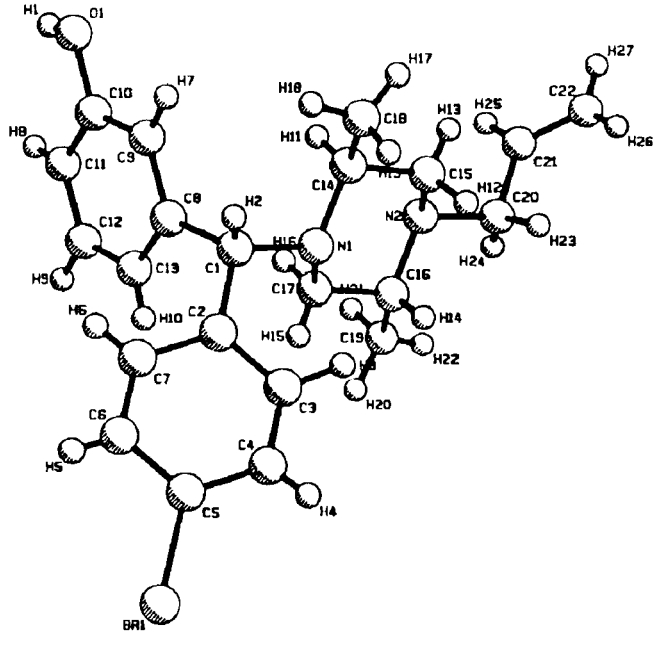


Figure 4

1 *nM*, and the δ and μ K_is of fentanyl were 400 *nM* and 1.5 *nM*. Compound **35b** had δ and μ K_is of 8 *nM* and 1.5 *nM*, **37b** had K_is of 24 *nM* and 0.76 *nM*, and **49b** had K_is of 11 *nM* and 0.78 *nM*.

The unsubstituted 3-thienyl analogue **37a**, having stereochemistry the same as BW373U86, bound equally to both receptors with δ and μ K_is of 0.7 *nM* and 0.52 *nM*. All of the remaining compounds had weak activity at either the δ or μ receptor, except the diastereomeric pair of *N*-methylimidazoles, **33a** and **33b**, which had minimal activity at both receptors. The δ K_is were 500 *nM* and 900 *nM*, and the μ K_is were 190 *nM* and 170 *nM*.

Conclusions.

Analogues of BW376U86 can be manipulated to produce either δ-selective, μ-selective, or mixed δ/μ-binding compounds of high potency by varying the relative stereochemistry and by having either unsubstituted heterocycles or the corresponding diethylcarboxamides as the nonphenolic ring.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Commercial solvents were used without further purification except tetrahydrofuran, which was distilled from potassium. Nuclear magnetic resonance (nmr) spectra were obtained with Varian XL-200 or XL-300 spectrometers. The hplc analyses were performed with a Waters liquid chromatography system equipped with a 700 Satellite WISP, 600E System Controller and a 991 Photodiode Array detector, with a β-cyclodextrin 4.6 x 250 mm Cyclobond I column (Advanced Separations Technologies, Whippany, New Jersey), at a flow rate of 1 ml/minute. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. Mass spectra were performed by Oneida Research Services, Whitesboro, New York. X-Ray crystallography was performed by Molecular Structure Corporation, College Station, Texas. Analytical thin layer chromatography was performed on Analtech glass plates pre-coated with silica gel GF (250 microns). Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia.

trans-1-Allyl-2,5-dimethylpiperazine (**5**).

A 12 l, 3-necked, round-bottom flask was charged with *trans*-2,5-dimethylpiperazine (**2**) (767 g, 6.72 moles), which had been recrystallized from toluene to mp 115-119°, and 600 ml of water. The flask was cooled in an ice bath and a solution of methanesulfonic acid (1290 g, 13.4 moles) in 600 ml of water was added slowly with stirring and cooling to maintain the temperature below 40°. The solution was cooled to 20° and 800 ml of ethanol was added. A 500 ml addition funnel was filled with 60% aqueous potassium acetate from a 2 l reservoir of the solution, and potassium acetate was added to the reaction flask to adjust the *p*H to 4.0. A second addition funnel was charged with a solution of ethyl chloroformate (642 ml, 6.71 moles) in 360 ml of tetrahydrofuran. The ethyl chloroformate and potassium acetate solutions were simultaneously added dropwise with adjustment of rate to maintain the reaction solution at *p*H 4.0 ±0.1, with cooling as necessary to maintain temperature at 25°. After addition of the ethyl chloroformate was complete, the reaction was stirred for 1 hour while the potassium acetate solution was continuously added to maintain a *p*H of 4.0. The organic solvents were removed by distillation under vacuum. The remaining aqueous solution was washed with 1500 ml of ethyl acetate to remove any biscarbamate impurity. The ethyl acetate wash was extracted with two 500 ml portions of 1 *M* hydrochloric acid to recover the desired product. The acid extracts were combined with the original aqueous solution and the *p*H was adjusted to 11 by addition of 10 *M* sodium hydroxide, while cooling to maintain temperature below 40°. The aqueous solution was extracted with two 1500 ml portions of ethyl acetate, the combined extracts were dried over magnesium sulfate, and the solvent was removed to give 927 g (74%) of ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate (**3**) as a yellow oil.

A mixture of **3** (643 g, 3.45 moles), allyl bromide (328 ml, 3.80 moles), and sodium carbonate (440 g, 4.15 moles) in 2500 ml of acetonitrile was heated at reflux for 1.5 hours. The reaction was cooled to room temperature, filtered, and the solvent removed under vacuum. The residue was dissolved in 4000 ml of dichloromethane and washed with two 500 ml portions of 1 *M* sodium hydroxide. The dichloromethane solution was dried over magnesium sulfate and the solvent was removed to give 630 g (81%) of ethyl *trans*-4-allyl-2,5-dimethyl-1-piperazinecarboxylate (**4**) as an oil.

Compound **4** (630 g, 2.78 moles) was added to a solution of 87% potassium hydroxide pellets (2970 g, 46 moles) in 4300 ml of 95% ethanol and heated at reflux for 1.5 hours. Carbon dioxide evolution was observed for the first 0.5-1 hour of heating. The reaction was cooled below reflux temperature and 2000 ml of toluene was carefully added. Ethanol was removed by azeotropic distillation at 105°, while adding an additional 4000 ml of toluene to the reaction flask during the course of the distillation. After collection of 9000 ml of distillate, the reaction was cooled to 100° and 1000 ml of toluene was carefully added. The solution was slowly cooled to 5° and maintained at 5° for 30 minutes, then filtered, washing the filter cake with an additional 1500 ml of toluene. The filtrate was washed with 1000 ml of water, dried over magnesium sulfate, and the solvent was removed to give 296 g (69%) of **5** as a dark liquid; ^1H nmr (DMSO-d_6, 300 MHz): δ 0.87 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H), 1.63 (m, 1H), 2.05 (m, 1H), 2.30 (m, 1H), 2.6-2.8 (m, 4H), 3.38 (m, 1H), 5.10-5.17 (m, 2H), 5.8 (m, 1H).

Anal. Calcd. for $C_9H_{18}N_2 \cdot 0.125H_2O$: C, 69.07; H, 11.75; N, 17.90. Found: C, 69.00; H, 11.74; N, 17.74.

α-(2-Thiazolyl)-3-((*tert*-butyldimethylsilyl)oxy)benzyl Alcohol (**8**).

A solution of 1.6 *M* *n*-butyllithium in hexane (206 ml, 0.33 mole) was cooled to -45° under nitrogen. A slurry of 2-bromothiazole (**6**) (50 g, 0.30 mole) in 75 ml of diethyl ether was added in portions, maintaining the temperature between -35° and -45°. The resulting dark brown solution was stirred an additional 15 minutes at -40° before aldehyde **10** (70.9 g, 0.30 mole) was added dropwise *via* syringe at a rate to maintain temperature between -25° and -35°. The resulting mixture was stirred an additional 30 minutes at -15°, then poured into a mixture of 1 l ice/600 ml 1 *M* hydrochloric acid. The organic phase was dried over sodium sulfate and evaporated to give a brown oil. Chromatography on silica gel with hexane:ethyl acetate (gradient

from 90:10 to 80:20) gave 25.5 g (26%) of **8** as a viscous yellow oil; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.15 (s, 6H), 0.93 (s, 9H), 5.90 (d, J = 4.5 Hz, 1H), 6.74 (m, 1H), 6.75 (d, J = 4.5 Hz, 1H), 6.91 (t, J = 1.8 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 3.2 Hz, 1H), 7.69 (d, J = 3.2 Hz, 1H).

Anal. Calcd. for $C_{16}H_{23}NO_2SSi$: C, 59.77; H, 7.21; N, 4.36; S, 9.97. Found: C, 59.72; H, 7.21; N, 4.39; S, 10.06.

3-((*tert*-Butyldimethylsilyl)oxy)-α-(1-methylimidazol-2-yl)benzyl Alcohol (**9**).

A solution of 1-methylimidazole (**7**) (20.5 g, 0.25 mole) in 350 ml of dry tetrahydrofuran under nitrogen was cooled to -70°. A solution of 1.5 *M* lithium diisopropylamide in cyclohexane (180 ml, 0.27 moles) was added dropwise at a rate to maintain a temperature below -50°. The resulting solution was stirred for 3 hours at -60°, and aldehyde **10** (63.8 g, 0.27 mole) was added dropwise at a rate to maintain a temperature below -40°. The resulting solution was washed three times with aqueous ammonium chloride, dried over sodium sulfate, and evaporated to give 95 g (119%) of crude **9** as a viscous yellow oil, which crystallized upon standing. The ^{1}H nmr of the crude product showed 93% of the desired product and 7% of the regioisomer resulting from metallation at the 5-position of the 1-methylimidazole. Two recrystallizations in hexane gave 27 g of **9** of 98% isomeric purity, which was used for the next reaction. Further recrystallization of 1.5 g from hexane:toluene/50:50 gave pure **9** as an off-white solid; mp 116-118°; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.14 (s, 6H), 0.92 (3, 9H), 3.45 (s, 3H), 5.81 (d, J = 4.2 Hz, 1H), 6.18 (d, J = 4.7 Hz, 1H), 6.70 (dd, J_1 = 7.2 Hz, J_2 = 0.7 Hz, 1H), 6.77 (m, 2H), 6.88 (d, J = 7.7 Hz, 1H), 7.03 (s, 1H), 7.19 (t, J = 8.0 Hz, 1H).

Anal. Calcd. for $C_{17}H_{26}N_2O_2Si$: C, 64.11; H, 8.23; N, 8.80. Found: C, 64.19; H, 8.24; N, 8.85.

Method A: Protection of a Phenol with the *tert*-Butyldimethylsilyl Group.

3-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde (**10**).

A mixture of 3-hydroxybenzaldehyde (142 g, 1.16 moles), *tert*-butyldimethylsilyl chloride (174.2 g, 1.16 moles), and imidazole (200.8 g, 2.95 moles) was stirred in 200 ml of dimethylformamide under nitrogen at 25° for 16 hours. The solution was poured into 1500 ml of 0.1 *N* aqueous sodium hydroxide and extracted three times with diethyl ether. The ether extracts were combined, washed with water and brine, dried over sodium sulfate, and evaporated to give 350 g of tan oil. Chromatography on silica gel with hexane gave 274.2 g (100%) of **10** as a clear oil; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 0.22 (s, 6H), 0.99 (s, 9H), 7.10 (ddd, J_1 = 7.9 Hz, J_2 = 2.5 Hz, J_3 = 1.2 Hz, 1H), 7.32 (dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.47 (ddd, J_1 = 7.6 Hz, J_2 = 1.3 Hz, J_3 = 1.3 Hz, 1H), 9.95 (s, 1H).

Anal. Calcd. for $C_{13}H_{20}O_2Si$: C, 66.05; H, 8.53. Found: C, 65.95; H, 8.56.

α-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)-6-bromo-3-pyridinemethanol (**14**).

2,5-Dibromopyridine (**11**) (20.0 g, 0.084 mole) was dissolved in 500 ml of diethyl ether under nitrogen and cooled to -70°. A solution of 1.6 *M n*-butyllithium in hexane (58 ml, 0.093 mole) was added dropwise at a rate to maintain a temperature below -65°. A fine white precipitate formed. The heterogeneous mixture was stirred for an additional 15 minutes after the addition was complete, and a solution of aldehyde **10** (22.0 g, 0.093 moles) in 50 ml of diethyl ether was added slowly at a rate to maintain a temperature below -65°. The solution turned dark and homogeneous upon completion of addition. The solution was stirred for an additional 15 minutes at -65°, then washed three times with aqueous ammonium chloride, dried over sodium sulfate, and evaporated to give 35.5 g of an orange oil. Chromatography on silica gel with hexane:ethyl acetate (gradient from 90:10 to 80:20) gave 28.3 g (85%) of **14** as a viscous yellow oil; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 8.38 (d, J = 2.3 Hz, 1H), 7.54 (dd, J_1 = 2.5 Hz, J_2 = 5.9 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.83 (s, 1H), 6.77 (m, 1H), 5.78 (s, 1H), 2.22 (br s, 1H), 0.96 (s, 9H), 0.17 (s, 6H).

Anal. Calcd. for $C_{18}H_{24}BrNO_2Si$: C, 54.82; H, 6.13; N, 3.55; Br, 20.26. Found: C, 54.75; H, 6.16; N, 3.50; Br, 20.20.

α-(5-Bromo-3-pyridyl)-3-((*tert*-butyldimethylsilyl)oxy)benzyl Alcohol (**15**).

A solution of 50.0 g (0.21 mole) of 3,5-dibromopyridine (**12**) in 600 ml of anhydrous diethyl ether was cooled to -78°. *n*-Butyllithium (131 ml of a 1.6 *M* solution in hexanes) was added at a rate to keep the temperature below -75°. After stirring for 1 hour at -78°, a solution of aldehyde **10** (49.64 g, 0.21 mole) in 600 ml of anhydrous diethyl ether was added at a rate to keep the temperature below -75°. After stirring for 1 hour at -78°, the reaction was quenched with 200 ml of saturated aqueous ammonium chloride and allowed to warm to room temperature. The aqueous layer was discarded and the ethereal layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was evaporated to give 104.3 g of a brown oil. Chromatography on silica gel with hexane:ethyl acetate gave 51.2 g (62%) of **15** as a yellow oil; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 0.1 (s, 6H), 0.9 (s, 9H), 2.8 (br s, 1H), 5.8 (s, 1H), 6.8 (m, 2H), 6.9 (d, J = 8 Hz, 1H), 7.2 (t, J = 8 Hz, 1H), 7.85 (t, J = 8 Hz, 1H), 8.5 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 2H).

Anal. Calcd. for $C_{18}H_{24}BrNO_2Si$: C, 54.82; H, 6.13; N, 3.55; Br, 20.26. Found: C, 54.73; H, 6.18; N, 3.48; Br, 20.15.

3-(Bromophenoxy)-*tert*-butyldimethylsilane (**17**).

3-Bromophenol (500 g, 2.89 moles) was protected as the silyl ether according to Method A to give 846 g (100%) of **17** as a pale yellow liquid; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 0.2 (s, 6H), 1.0 (s, 9H), 6.75 (m, 1H), 7.0 (br s, 1H), 7.1 (m, 2H).

Anal. Calcd. for $C_{12}H_{19}BrOSi$: C, 50.17; H, 6.67; N, 27.82. Found: C, 50.25; H, 6.69; N, 27.90.

α-(4-Bromo-2-thienyl)-3-((*tert*-butyldimethylsilyl)oxy)benzyl Alcohol (**21a**) and α-(4-Bromo-2-thienyl) 3-((*tert*-Butyldimethylsilyl)oxy)phenyl Ketone (**21b**).

Compound **17** (30.2 g, 0.105 mole) was dissolved in 300 ml of dry tetrahydrofuran under nitrogen and cooled to -78°. A solution of 1.6 *M n*-butyllithium in hexane (66 ml, 0.105 mole) was added dropwise at a rate to maintain a temperature below -65°. The reaction was stirred for 30 minutes after the addition was complete, and the cold solution was transferred *via* cannula to another vessel containing a room temperature solution of magnesium bromide (20.2 g, 0.11 mole) in 400 ml of dry tetrahydrofuran under nitrogen. The resulting solution was allowed to warm to 15° while stirring. After 1 hour a solution of 4-bromo-2-thiophenecarboxaldehyde (**20**) (20.0 g, 0.105 mole) in 100 ml of dry tetrahydrofuran was added slowly at a rate to maintain a temperature below 25°. The resulting solution was

stirred for 3 hours at room temperature, washed three times with aqueous ammonium chloride, dried over sodium sulfate, and evaporated to give a yellow oil. Chromatography on silica gel with dichloromethane:hexane/50:50 separated two products. Compound **21b** , 7.67 g (18%) eluted first as a clear yellow oil; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 0.23 (s, 6H), 1.00 (s, 9H), 7.61-7.06 (m, 6H).

Anal. Calcd. for $C_{17}H_{21}BrO_2SSi$: C, 51.38; H, 5.33; Br, 20.11; S, 8.07. Found: C, 51.34; H, 5.35; Br, 20.19; S, 8.12.

Compound **21a**, 20.23 g (48%) eluted second as a viscous yellow oil; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 0.19 (s, 6H), 0.97 (s, 9H), 2.38 (s, 1H), 5.92 (s, 1H), 6.77 (s, 1H), 6.80 (m, 1H), 6.90 (t, J = 1.9 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 7.15 (s, 1H), 7.23 (t, J = 7.5 Hz, 1H).

Anal. Calcd. for $C_{17}H_{23}BrO_2SSi$: C, 51.12; H, 5.80; Br, 20.00; S, 8.03. Found: C, 51.08; H, 5.80; Br, 19.93; S, 7.96.

3-((*tert*-Butyldimethylsilyl)oxy)-α-(3-thienyl)benzyl Alcohol (**23**).

Compound **17** (57.5 g, 0.20 mole) was dissolved in 300 ml of dry tetrahydrofuran under nitrogen and cooled to -78°. A solution of 1.6 *M n*-butyllithium in hexane (125 ml, 0.20 mole) was added dropwise at a rate to maintain a temperature below -70°. The reaction was stirred for 30 minutes after the addition was complete and the cold solution was transferred *via* cannula to another vessel containing a -40° solution of magnesium bromide (37.8 g, 0.205 mole) in 600 ml of dry tetrahydrofuran under nitrogen. The resulting solution was allowed to warm to -15° while stirring. After 1 hour a solution of thiophene-3-carboxaldehyde (**22**) (22.4 g, 0.20 mole) in 200 ml of dry tetrahydrofuran was added slowly at a rate to maintain a temperature below 25°. The resulting solution was stirred for 30 minutes at room temperature, then washed twice with aqueous ammonium chloride, dried over sodium sulfate, and evaporated to give a brown oil. Chromatography on silica gel with hexane:dichloromethane (gradient from 3:1 to 1:1) gave 44.1 g (69%) of **23** as a viscous yellow oil; ^{1}H nmr (DMSO-d_6, 200 MHz): δ 0.17 (s, 6H), 0.95 (s, 9H), 3.32 (s, 1H), 5.70 (d, J = 3.3 Hz, 1H), 6.70 (m, 1H), 6.86 (s, 1H), 6.97 (d, J = 6.2 Hz, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 2.9 Hz, 1H), 7.44 (dd, J_1 = 4.9 Hz, J_2 = 3.0 Hz, 1H).

Anal. Calcd. for $C_{17}H_{24}O_2SSi$: C, 63.70; H, 7.55; S, 10.00. Found: C, 63.67; H, 7.57; S, 10.08.

Method B: Conversion of a Carbinol to a Chloromethine Followed by Alkylation of Piperazine **5.**

(±)-3-((*R**)-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(2-thiazolyl)methyl)phenol (**32a**) and (±)-3-((*R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(2-thiazolyl)-methyl)phenol (**32b**).

Thionyl chloride (0.33 ml, 4.58 mmoles) was added to a solution of carbinol **8** (1.0 g, 3.27 mmoles) in 50 ml of dichloromethane. After stirring for 16 hours the solvent was evaporated, the residue was redissolved in toluene and evaporated again to drive off excess thionyl chloride.

A mixture of the crude diarylchloromethane (approximately 3.27 mmoles), piperazine **5** (1.26 g, 8.2 mmoles) and 50 ml of acetonitrile was heated to reflux under nitrogen for 16 hours. The solution was evaporated and the residue was partitioned between ethyl acetate and 0.1 *M* aqueous sodium hydroxide. The organic layer was washed twice more with 0.1 *M* aqueous sodium hydroxide and once with water, dried over sodium sulfate, and evaporated to give 1.1 g of red-black oil. Chromatography on silica gel with hexane:ethyl acetate (gradient from 80:20 to 50:50) yielded the two diastereomers in order of elution, 300 mg (20%) of **26a** and 280 mg (19%) of **26b**.

Method C: Removal of the Silyl Protecting Group.

Compound **26a** (2.65 g, 5.79 mmoles) was combined with tetraethylammonium fluoride hydrate (1.86 g, approximately 9.8 mmoles) and 200 ml of acetonitrile and stirred at room temperature for 16 hours under nitrogen. The solvent was removed by evaporation and the residue was dissolved in dichloromethane, washed three times with *p*H 8 buffer solution, dried over sodium sulfate, and evaporated to a brown glass. Chromatography on silica gel with dichloromethane:methanol/95:5 yielded 620 mg (31%) of **32a** as a tan solid; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.88 (d, J = 5.9 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.65 (m, 1H), 2.00 (m, 1H), 2.40 (m, 1H), 2.60 (m, 2H), 2.78 (m, 2H), 3.25 (m, 1H), 5.13 (m, 2H), 5.36 (s, 1H), 5.80 (m, 1H), 6.69 (m, 3H), 7.15 (t, J = 7.8 Hz, 1H), 7.63 (d, J = 3.2, 1H), 7.69 (d, J = 3.3, 1H), 9.34 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.7 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane/ethanol, then precipitated with diethyl ether to give 400 mg of the monohydrochloride salt of **32a** as a tan solid, mp 127-130°.

Anal. Calcd. for $C_{19}H_{25}N_3OS\cdot HCl\cdot 0.25H_2O$: C, 59.36; H, 6.95; N, 10.93; Cl, 9.22; S, 8.34. Found: C, 59.23; H, 6.97; N, 10.81; Cl, 9.17; S, 8.28.

Compound **26b** (1.23 g, 2.70 mmoles) was deprotected according to Method C. Chromatography on silica gel with dichloromethane:methanol/94:6 yielded 480 mg (52%) of **32b** as a tan solid; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.90 (d, J = 5.8 Hz, 3H), 1.11 (d, J = 6.1 Hz, 3H), 2.00 (m, 1H), 2.14 (m, 1H), 2.38 (m, 1H), 2.43 (m, 1H), 2.60 (m, 1H), 2.70 (m, 1H), 2.78 (m, 1H), 3.25 (m, 1H), 5.18 (m, 2H), 5.61 (s, 1H), 5.80 (m, 1H), 6.63 (dd, J = 1.1, 7.8, 1H), 6.71 (d, J = 7.8, 1H), 6.78 (s, 1H), 7.10 (t, J = 7.9 Hz, 1H), 7.74 (d, J = 3.2, 1H), 7.87 (d, J = 3.3, 1H), 9.34 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.7 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane/ethanol, then precipitated with diethyl ether to give 150 mg of the monohydrochloride salt of **32b** as a tan solid, mp 124-128°.

Anal. Calcd. for $C_{19}H_{25}N_3OS\cdot HCl\cdot 0.25H_2O$: C, 59.36; H, 6.95; N, 10.93; Cl, 9.22; S, 8.34. Found: C, 59.21; H, 6.98; N, 10.85; Cl, 9.18; S, 8.28.

(±)-3-((*R** or *S**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(1-methylimidazol-2-yl)methyl)phenol **33b** or **33a** and (±)-3-((*S** or *R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(1-methylimidazol-2-yl)methyl)phenol **33a** or **33b** .

Alcohol **9** (15.9 g, 0.05 mole) was converted to the alkyl chloride and treated with **5** according to Method B. Chromatography on silica gel with ethyl acetate yielded two products in order of elution, 7.33 g (32%) of **27b** or **27a** and 8.48 g (37%) of **27a** or **27b**.

Compound **27b** or **27a** (2.17 g, 4.8 mmoles) was desilylated according to Method C. Chromatography on silica gel with ethyl acetate:ethanol/95:5 yielded 1.35 g (83%) of **33b or 33a** as a tan solid; ^{1}H-nmr (DMSO-d_6, 300 MHz): δ 0.86 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 5.9 Hz, 3H), 1.90 (m,2H), 2.10 (m, 1H), 2.30 (m, 1H), 2.65 (m, 1H), 2.78 (m, 1H), 3.24 (m, 1H), 3.33 (d, J = 7.2 Hz, 1H), 3.66 (s, 3H), 5.13 (m, 2H), 5.26 (s, 1H), 5.80 (m, 1H), 6.67 (dd, J_1 = 1.1Hz, J_2 = 8.1Hz,1H), 6.77 (s, 1H), 6.90 (d, J =

7.5Hz, 1H), 7.03 (d, J = 0.9Hz, 1H) 7.06 (s, 1H), 7.11 (t, J = 7.8 Hz, 1H), 9.28 (s, 1H). The amine was dissolved in ethanol and converted to the dihydrochloride salt by titration to *p*H 3.7 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane/ethanol, then precipitated with diethyl ether to give 1.04 g of the dihydrochloride salt of **33b or 33a** as an off-white solid, mp 166-172°dec.

Anal. Calcd. for $C_{20}H_{28}N_4O \cdot 2HCl \cdot H_2O$: C, 55.68; H, 7.48; N, 12.99; Cl, 16.44. Found: C, 55.55; H, 7.65; N, 12.85; Cl, 16.31.

Compound **27a** or **27b** (2.49 g, 5.48 mmoles) was desilylated according to Method C. Chromatography on silica gel with ethyl acetate:ethanol/95:5 yielded 900 mg (48%) of **33a** or **33b** as an off-white foam; ^{1}H-nmr (DMSO-d_6, 300 MHz): δ 0.87 (d, J = 6.0 Hz, 3H), 0.96 (d, J = 6.1 Hz, 3H), 1.92 (m, 1H), 2.15 (m, 1H), 2.43 (m, 2H), 2.70 (m, 3H), 2.84 (m, 1H), 3.28 (m, 3H), 5.13 (m, 2H), 5.26 (s, 1H), 5.80 (m, 1H), 6.53 (d, J = 7.6 Hz, 1H), 6.62 (m, 2H), 6.87 (s, 1H), 7.07 (m,2H), 9.28 (s, 1H). The amine was dissolved in ethanol and converted to the dihydrochloride salt by titration to *p*H 3.1 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane/ethanol, then precipitated with diethyl ether to give 560 mg of the dihydrochloride salt of **33a** or **33b** as a white solid, mp 144-146°.

Anal. Calcd. for $C_{20}H_{28}N_4O \cdot 2HCl \cdot 1.5H_2O$: C, 54.55; H, 7.55; N, 12.72; Cl, 16.10. Found: C, 54.65; H, 7.56; N, 12.54; Cl, 15.92.

(±)-3-((*R**)-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(5-bromo-3-pyridyl)methyl)phenol (**34b**).

The synthesis of the free amine of **34b** is described in the experimental procedure for compound **44b**; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 0.99 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H), 1.8 (m, 1H), 2.1 (m, 1H), 2.4-2.9 (m, 5H), 3.2 (m, 1H), 5.1 (m, 3H), 5.8 (m, 1H), 6.75 (m, 2H), 6.89 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.68 (m, 1H), 8.36 (m, 1H), 8.55 (m, 1H). The amine (100 mg, 0.24 mmole) was dissolved in ethanol and converted to the hydrochloride salt by titration to *p*H 3.1 with ethanolic hydrogen chloride. The salt was precipitated with diethyl ether to give 71 mg (64%) of the monohydrochloride salt of **34b** as a white solid.

Anal. Calcd. for $C_{21}H_{26}BrN_3O \cdot HCl \cdot 0.5H_2O$: C, 54.62; H, 6.11; N, 9.10; Total halogen as bromine, 34.60. Found: C, 54.80; H, 6.16; N, 9.09; Total halogen as bromine, 34.54.

(±)-3-((*R**)-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-pyridylmethyl)phenol (**35b**) and (±)-3-((*R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-pyridylmethyl)phenol (**35a**).

3-Bromopyridine (**13**) (50.0 g, 0.316 mole) and aldehyde **10** (74.8 g, 0.316 mole) were each dissolved in 500 ml anhydrous diethyl ether under nitrogen and chilled to -78° in dry ice/acetone baths. *n*-Butyllithium (198 ml, 0.316 mole, 1.6*M* in hexanes) was added dropwise to the chilled pyridine solution at a rate that maintained the temperature below -70°. After the addition was complete, the reaction was stirred for 10 minutes. The aldehyde solution was then added to the reaction mixture *via* cannula, while the temperature was maintained below -70°. The reaction was stirred at -78° for 45 minutes, quenched with aqueous saturated ammonium chloride, allowed to warm to room temperature, and washed with water and brine. The ether layer was dried over sodium sulfate and the solvent was removed to give 98.2 g (79%) of crude alcohol **16**. The crude **16** was converted directly to the chloride and treated with piperazine **5** in toluene according to Method B. After the reaction was cooled the crude mixture was desilylated according to Method C to give a mixture of **35a** and **35b**. The solvent was removed and the product was purified by chromatography on silica gel with 0-20% ethanol in dichloromethane. The first isomer to elute was obtained as 14.7 g of a dark oil which crystallized from 100 ml of acetonitrile upon standing at room temperature to give 3.0 g (2.9%) of **35a**, mp 115-118°; ^{1}H nmr (DMSO-d_6, 200 MHz): δ 0.95 (d, J = 6 Hz, 3H), 1.09 (d, J = 6Hz, 3H), 1.84 (dd, J_1 = 7.6 Hz, J_2 = 11.7 Hz, 1H), 2.10 (dd, J_1 = 6.8 Hz, J_2 = 10.8 Hz, 1H), 2.5-2.8 (m, 4H), 2.86 (dd, J_1 = 7.2 Hz, J_2 = 14.0 Hz, 1H), 3.18 (dd, J_1 = 5.3 Hz, J_2 = 14 Hz, 1H), 5.05 (m, 3H), 5.8 (m, 1H), 6.7 (m, 3H), 7.16 (t, J = 7.6 Hz, 1H), 7.34 (dd, J_1 = 4.9 Hz, J_2 = 8.0 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 8.43 (d, J = 4.6 Hz, 1H), 8.57 (s, 1H), 9.41 (s, 1H).

Anal. Calc for $C_{21}H_{27}N_3O$: C, 74.77; H, 8.06; N, 12.45. Found: C, 74.78; H, 8.11; N, 12.47.

The second isomer to elute from the column was obtained as 6.9 g of an oil. The product was crystallized from ethyl acetate to give 2.4 g (2.3%) of **35b** as a tan solid, mp 158-160°; ^{1}H nmr (DMSO-d_6, 200 MHz): δ 0.96 (d, J = 6 Hz, 3H), 1.10 (d, J = 6 Hz, 3H), 1.79 (dd, J_1 = 7.2 Hz, J_2 = 10.6 Hz, 1H), 2.08 (dd, J_1 = 7.2 Hz, J_2 = 11.2 Hz, 1H), 2.3-2.75 (m, 4H), 2.85 (dd, J_1 = 7.0 Hz, J_2 = 13.9 Hz, 1H), 3.18 (dd, J_1 = 5.2 Hz, J_2 = 13.9 Hz, 1H), 5.08 (s, 1H), 5.10 (d, J = 9.9 Hz, 1H), 5.17 (d, J = 16.2 Hz, 1H), 5.7-5.9 (m, 1H), 6.59 (d, J = 7.8 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.82 (s, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.40 (dd, J_1 = 4.9 Hz, J_2 = 7.8 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 8.50 (d, J = 6 Hz, 1H), 8.52 (s, 1H), 9.32 (s, 1H). The free amine was dissolved in ethanol and converted to the monohydrochloride salt by titrating to a *p*H of 3.4 with ethanolic hydrogen chloride. The solvent was removed, and the residue was redissolved in dichloromethane. The salt was precipitated with ether:hexane and collected by filtration to give the monohydrochloride salt of **35b** as a white powder.

Anal. Calcd. for $C_{21}H_{27}N_3O \cdot HCl \cdot 0.75H_2O$: C, 65.10; H, 7.67; N, 10.85; Cl, 9.15. Found: C, 65.12; H, 7.68; N, 10.87; Cl, 9.20.

(±)-3-((*R**)-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(4-bromo-2-thienyl)methyl)phenol (**36a**) and (±)-3-((*R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(4-bromo-2-thienyl)methyl)phenol (**36b**).

Carbinol **21** (71.3 g, 0.18 mole) was converted to the chloride and treated with piperazine **5** according to Method B. Chromatography on silica gel with ethyl acetate removed excess *trans*-1-allyl-2,5-dimethylpiperazine to leave 86 g of black oil which was purified by chromatography on silica gel with dichloromethane:ethyl acetate/95:5 to yield 63.1 g (66%) of a mixture of **30a** and **30b** as a dark oil. The mixture of **30a** and **30b** (63.1 g, 0.118 mole) was deprotected according to Method C. The two diastereomers of the product were separated by chromatography on silica gel with dichloromethane:ethyl acetate/75:25. Elution of the first isomer gave 15.84 g (32%) of **36b**; ^{1}H-nmr (DMSO-d_6,300 MHz): δ 0.93 (d, J = 6.0 Hz, 3H), 1.09 (d, J = 6.3 Hz, 3H), 2.00 (m, 2H), 2.40 (m, 2H), 2.65-2.90 (m, 3H), 3.30 (m, 1H), 5.14 (m, 2H), 5.44 (s, 1H), 5.80 (m, 1H), 6.65 (m, 1H), 6.81 (m, 2H), 7.05 (s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.66 (s, 1H), 9.35 (s, 1H). A 500 mg portion was dissolved

in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.6 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 300 mg of the monohydrochloride salt of **36b** as a white solid, mp 128-132°.

Anal. Calcd. for $C_{20}H_{25}BrN_2OS \cdot HCl \cdot 0.25H_2O$: C, 51.96; H, 5.78; N, 6.06; Br, 17.28; Cl, 7.67, S, 6.93. Found: C, 51.94; H, 5.80; N, 6.04; total halogen Calcd. as chlorine, 15.33; S, 7.02.

Elution of the second isomer from the column gave 18.02 g (36%) of **36a**; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.90 (d, J = 6.1 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H), 1.70 (t, 1H), 1.97 (t, 1H), 2.40 (m, 2H), 2.60-2.80 (m, 3H), 3.30 (m, 1H), 5.12 (m, 2H), 5.30 (s, 1H), 5.80 (m, 1H), 6.60 (s, 1H), 6.72 (m, 3H), 7.12 (t, J = 8.2 Hz, 1H), 7.55 (s, 1H), 9.47 (s, 1H). A 500-mg portion was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.7 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 240 mg of the monohydrochloride salt of **36a** as a white solid, mp 138-141°.

Anal. Calcd. for $C_{20}H_{25}BrN_2OS \cdot HCl$: C, 52.46; H, 5.72; N, 6.12; Br, 17.45; Cl, 7.74, S, 7.00. Found: C, 52.31; H, 5.75; N, 6.07; total halogen calcd. as chlorine, 15.55; S, 7.09.

(±)-3-((*R**)-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(3-thienyl)methyl)phenol (**37a**) and (±)-3-((*R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(3-thienyl)methyl)phenol (**37b**).

Compound **23** (23.8 g, 0.074 mole) was converted to the alkyl chloride and treated with piperazine **5** according to Method B. The product was purified by chromatography on silica gel with dichloromethane:ethyl acetate/98:2 to separate, in order of elution, 12.27 g of **31a** (36%) and 11.15 g of **31b** (33%).

Compound **31a** (3.1 g, 6.79 mmoles) was deprotected according to method C. Chromatography on silica gel with dichloromethane:ethyl acetate/3:1 gave 1.6 g (69%) of **37a** as a yellow foam; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.91 (d, J = 6.2 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H), 1.79 (m, 1H), 2.00 (m, 1H), 2.45 (m, 1H), 2.62 (m, 2H), 2.80 (m, 1H), 3.21 (m, 1H), 3.32 (d, J = 7.0 Hz, 1H), 5.14 (m, 3H), 5.80 (m, 1H), 6.68 (m, 3H), 6.98 (d, J = 5.0 Hz, 1H), 7.15 (m, 2H), 7.45 (dd, J_1 = 4.9 Hz, J_2 = 3.0 Hz, 1H), 9.31 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.5 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 1.3 g of the monohydrochloride salt of **37a** as an off-white solid, mp 140-142°.

Anal. Calcd. for $C_{20}H_{26}N_2OS \cdot HCl \cdot 0.25H_20$: C, 62.65; H, 7.23; N, 7.31; Cl, 9.25; S, 8.36. Found: C, 62.49; H, 7.27; N, 7.33; Cl, 9.25; S, 8.32.

Compound **31b** (3.0 g, 6.57 mmoles) was deprotected according to method C. Chromatography on silica gel with dichloromethane:ethyl acetate/3:1 gave 1.6 g (71%) of **37b** as a white solid; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.89 (d, J = 6.1 Hz, 3H), 1.09 (d, J = 6.1 Hz, 3H), 1.79 (m, 1H), 2.01 (m, 1H), 2.34 (m, 1H), 2.50 (m, 1H), 2.70 (m, 2H), 3.25 (m, 1H), 3.31 (d, J = 7.1 Hz, 1H), 5.19 (m, 3H), 5.80 (m, 1H), 6.58 (m, 1H), 6.73 (d, J = 7.7 Hz, 1H), 6.80 (d, J = 1.0 Hz, 1H), 6.92 (dd, J_1 = 4.8 Hz, J_2 = 0.8 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 7.40 (dd, J_1 = 2.8 Hz, J_2 = 1.1 Hz, 1H), 7.51 (dd, J_1 = 4.5 Hz, J_2 = 2.9 Hz, 1H), 9.22 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.6 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 1.25 g of the monohydrochloride salt of **37b** as an off-white solid, mp 138-140°.

Anal. Calcd. for $C_{20}H_{26}N_2OS \cdot HCl \cdot 0.40H_2O$: C, 62.21; H, 7.26; N, 7.25; Cl, 9.18; S, 8.30. Found: C, 62.19; H, 7.25; N, 7.15; Cl, 9.24; S, 8.29.

(±)-3-((*R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(6-chloro-3-pyridyl)methyl)phenol (**42a**) and (±)-3-((*R**)-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(6-chloro-3-pyridyl)methyl)phenol (**42b**).

Alcohol **14** (48.0 g, 0.122 mole) was converted to the alkyl chloride and treated with piperazine **5** according to Method B. Chromatography on silica gel with ethyl acetate:triethylamine (gradient from 100:0 to 99:1) gave 22.2 g (39%) of a mixture of **39a** and **39b**.

A mixture of **39a** and **39b** (40.0 g, 0.078 mole), allyl bromide (7.1 ml, 0.082 mole), anhydrous sodium carbonate (19.1 g, 0.18 mole), and 450 ml of tetrahydrofuran was heated at reflux for 16 hours. The mixture was filtered and evaporated. The residue was partitioned between methylene chloride and water. The organic layer was washed three more times with water, dried over potassium carbonate, and evaporated to 45.1 g of a mixture of **40a** and **40b** as a viscous brown oil. Chromatography on silica gel with hexane:ethyl acetate/2:1 (0.5% triethylamine) gave 18.77 g (47%) of the first product to elute, **40a**, and 13.86 g (35%) of the second product to elute, **40b**.

Compound **40a** was desilylated according to Method C to give 15.2 g of crude **41a**. Recrystallization from acetonitrile gave 5.41 g (43%) of **41a** as a white solid.

Compound **41a** (700 mg, approximately 1.78 mmoles) was stirred in a mixture of 200 ml of dichloromethane, 200 ml of 1 *M* hydrogen chloride in diethyl ether, and 4 ml of ethanol for 96 hours under nitrogen. The solution was chilled with an ice bath, diluted with 200 ml of *p*H 8 aqueous buffer solution, treated with 10 *N* sodium hydroxide to adjust the *p*H to 8, and extracted three times with dichloromethane. The combined organic phase was dried over sodium sulfate and evaporated to give 700 mg of white foam. Two recrystallizations from acetonitrile yielded 320 mg (48%) of **42a** as a white solid; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.93 (d, J = 5.9 Hz, 3H), 1.07 (d, J = 6.2Hz, 3H), 1.76 (m, 1H), 2.07 (m, 1H), 2.5-2.6 (m, 3H), 2.71 (m, 1H), 2.83 (dd, J_1 = 7.3 Hz, J_2 = 13.7 Hz, 1H), 3.14 (dd, J_1 = 5.3Hz, J_2 = 0.7 Hz, 1H), 5.10 (m, 2H), 5.13 (s, 1H), 5.8 (m, 1H), 6.68 (m, 3H), 7.15 (t, J = 7.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.78 (dd, J_1 = 1.8 Hz, J_2 = 8.2 Hz, 1H), 8.35 (d, J = 1.5 Hz, 1H), 9.40 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.7 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 250 mg of the monohydrochloride salt of **42a** as a white solid, mp 168-175°.

Anal. Calcd. for $C_{21}H_{26}N_3ClO \cdot HCl \cdot 0.5H_2O$: C, 60.43; H, 6.76; N, 10.07; Cl, 16.99. Found: C, 60.36; H, 6.78; N, 10.02; Cl, 17.07.

(±)-3-((*R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(6-chloro-3-pyridyl)methyl)phenol (**42b**).

Compound **40b** (13.86 g, 0.027 mole) was desilylated accord-

ing to Method C to give 12.3 g of crude **41b** as a pink foam. Recrystallization from acetonitrile gave 6.95 g (65%) of **41b** as a white solid.

Compound **41b** (660 mg, approximately 1.68 mmoles) was treated with hyrogen chloride, according to the procedure used to obtain **42a,** to give 680 mg of crude **42b** as a tan foam. Recrystallization from acetonitrile yielded 430 mg (69%) of **42b** as a tan solid; ^{1}H nmr (DMSO-d_6, 300 MHz,): δ 0.94 (d, J = 6.1 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H), 1.78 (m, 1H), 2.07 (m, 1H), 2.4-2.8 (m, 5H), 3.18 (m, 1H), 5.10 (m, 3H), 5.7-5.9 (m, 1H), 6.6 (dd, J_1 = 2.0 Hz, J_2 = 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.51(d, J = 8.1 Hz, 1H), 7.70 (dd, J_1 = 2.3 Hz, J_2 = 8.2 1H), 8.34 (d, J = 2.1 Hz, 1H), 9.32 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.6 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 330 mg of the monohydrochloride salt of **42b** as a white solid, mp 160-168°.

Anal. Calcd. for $C_{21}H_{26}N_3ClO$•HCl•0.5H_2O: C, 60.43; H, 6.76; N, 10.07; Cl, 16.99. Found: C, 60.56; H, 6.74; N, 10.05; Cl, 17.05.

(±)-5-((α*R**)-α-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-3-pyridinecarboxamide (**44a**) and (±)-5-((α*R**)-α-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-3-pyridinecarboxamide (**44b**).

Compound **15** (10.00 g, 25.4 mmoles) was converted to the alkyl chloride as in Method B and treated with piperazine **5** under nitrogen in 15 ml of refluxing toluene for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with 1 *N* sodium hydroxide and saturated sodium chloride solution, dried over sodium sulfate, and the solvent was removed under vacuum. The crude diastereomeric mixture of **28a** and **28b** was purified by chromatography on silica gel (Waters Prep 500, dichloromethane with 0.1% triethylamine) to give 2.72 g (27%) of **28b**, the less mobile isomer (R_f = 0.62 on silica gel with dichloromethane:ethanol:ammonium hydroxide/90:10:1), and 3.91 g (39%) of **28a**, the more mobile isomer (R_f = 0.67), as light-brown solids.

Compound **28a** (3.91 g, 7.37 mmoles) was deprotected according to Method C to give 2.6 g (85%) of **34a** as a beige solid; ^{1}H nmr (DMSO-d_6, 200 MHz): δ 0.95 (d, J = 6 Hz, 3H), 1.1 (d, J = 6 Hz, 3H), 1.8 (m, 1H), 2.1 (m, 1H), 2.4-2.9 (m, 5H), 3.2 (m, 1H), 5.1 (m, 3H), 5.8 (m, 1H), 6.7 (m, 3H), 7.2 (m, 1H), 7.9 (s, 1H), 8.6 (s, 2H), 9.45 (s, 1H).

Starting with **34a** and following the procedures for the synthesis of **44b** , 0.18 g (7%) of **44a** was obtained as a beige solid; ^{1}H nmr (DMSO-d_6, 200 MHz): δ 0.95 (d, J = 6 Hz, 3H), 1.1 (d, J = 6 Hz, 3H), 1.1 (m, 6 H), 1.8 (m, 1H), 2.1 (m, 1H), 2.5-2.9 (m, 6H), 3.1-3.6 (br m, 4H), 5.0-5.2 (m, 2H), 5.1 (s, 1H), 5.8 (m, 1H), 6.7 (m, 3H), 7.1 (m, 1H), 7.65 (s, 1H), 8.4 (s, 1H), 8.6 (s,1H), 9.4 (s, 1H). The product was dissolved in absolute ethanol, titrated to *p*H 4 with ethanolic hydrogen chloride, and the monohydrochloride salt was precipitated with diethyl ether as a white solid (96 mg); ms: (CI-methane) m/z 437 (M+1, 95%), 436 (M^+, 18%), 283 (15%), 153 (100%).

Anal. Calcd. for $C_{26}H_{36}N_4O_2$•HCl•H_2O: C, 63.59; H, 8.00; N, 11.41; Cl, 7.22; Found: C, 63.41; H, 7.81; N, 11.43; Cl, 7.31.

Compound **28b** (1.71 g, 3.2 mmoles) was deprotected according to Method C to give 1.16 g (100%) of **34b** as a light beige solid.

A mixture of **34b** (1.03 g, 2.8 mmoles) and cuprous cyanide (0.50 g, 5.6 mmoles) was stirred in 30 ml of dimethylformamide at 150° under a nitrogen atmosphere for 24 hours. The hot reaction mixture was treated with 50 ml of 10% aqueous sodium cyanide. The resulting solution was stirred for 15 minutes and then extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed twice with 10% aqueous sodium cyanide, dried over sodium sulfate, and concentrated to a brown glass. Chromatography on silica gel with dichloromethane:ethanol (gradient from 99:1 to 97:3) yielded 400 mg (34%) of **43b**.

A mixture of **43b** (400 mg, 1.1 mmoles) and sodium hydroxide (320 mg, 8 mmoles) in 15 ml of 95% ethanol was heated at reflux for 16 hours. The solution was cooled to 25° and the *p*H was adjusted to 6 with concentrated hydrochloric acid. The solution was evaporated to dryness, and the residue was triturated with dichloromethane and filtered to give the crude carboxylic acid. The carboxylic acid was stirred in 30 ml of dimethylformamide with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (970 mg, 2.2 mmoles) and diethylamine (0.6 ml, 5.5 mmoles) for 72 hours. The solution was concentrated to dryness and the residue was dissolved in 1 *N* aqueous hydrochloric acid. The solution was washed twice with diethyl ether and the *p*H was adjusted to 8 with 10 *N* aqueous sodium hydroxide. The solution was extracted with dichloromethane. The dichloromethane extract was dried over sodium sulfate and concentrated to give 690 mg crude **44b**. Chromatography on silica gel with dichloromethane:ethanol (gradient from 99:1 to 95:5) yielded 300 mg of **44b**. The product was dissolved in absolute ethanol and titrated to *p*H 4 with ethanolic hydrogen chloride. The monohydrochloride salt (102 mg, 63%) was precipitated with diethyl ether as a white solid. A sample was converted back to the free amine for nmr; ^{1}H nmr (DMSO-d_6, 200 MHz): δ 0.95 (d, J = 6 Hz, 3H), 1.1 (d, J = 6 Hz, 3H), 1.1 (br m, 6H), 1.8 (m, 1H), 2.1(m, 1H), 2.4-3.0 (m, 5H), 3.1-3.5 (m, 5H), 5.1 (m, 3H), 5.8(m, 1H), 6.6 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz,1H), 6.85 (s, 1H), 7.1 (t, J = 8 Hz, 1H), 7.6 (s, 1H), 8.5 (s, 1H), 8.6 (s, 1H), 9.3 (s, 1H); ms: (CI-methane) m/z: 437 (M+1, 80%), 436 (M^+, 18%), 238 (13%), 153 (100%).

Synthesis of **49a,b-52a,b** (Scheme VIII).

(±)-3-((*R**)-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(2-thienyl)methyl)phenol (**49b**).

A mixture of **36b** (4.0 g, 9.5 mmoles) was protected as the *tert*-butyl dimethylsilyl ether according to Method A to give 5.4 g (100%) of **30b** as a tan oil.

A solution of **30b** (5.4 g, 9.5 mmoles) in 150 ml of dry tetrahydrofuran under nitrogen was cooled to -70°. A solution of 1.6 *M* *n*-butyllithium in hexane (6.4 ml, 10.0 mmoles) was added *via* syringe at a rate to maintain a temperature below -60°. The solution was cooled to -78° and carbon dioxide gas was introduced below the surface of the solution *via* cannula for 15 minutes. The solution was allowed to warm to room temperature with stirring. The solvent was evaporated and the residue was redissolved in toluene and evaporated again to remove butyl bromide. The resulting viscous oil was dissolved in 500 ml of dichloromethane and cooled to 0° under nitrogen. Thionyl chloride (1.0 ml, 14.0 mmoles) was added slowly *via* syringe. The resulting mixture was stirred for 2 hours at 0° before a solution of diethylamine (5.1 ml, 50 mmoles) in 60 ml of dichloromethane was added dropwise. The mixture was stirred

for 16 hours at room temperature, washed three times with water, dried over sodium sulfate, and evaporated to give an orange-brown oil. Chromatography on silica gel with dichloromethane:ethyl acetate (gradient from 90:10 to 0:100) yielded four products in order of elution; 970 mg (21%) of **45b**, 550 mg (8.7%) of **46b**, 1050 mg (19%) of **47b**, and 880 mg (16%) of **48b**.

The first material to elute, **45b** (1.06 g, 2.32 mmoles), was deprotected according to Method C. Chromatography on silica gel with dichloromethane:acetonitrile/2:1 yielded 610 mg of **49b** as a white solid; ^{1}H-nmr (DMSO-d_6, 300 MHz): δ 0.92 (d, J = 5.9 Hz, 3H), 1.10 (d, J = 5.8 Hz, 3H), 2.02 (q, 2H), 2.40 (m, 2H), 2.74 (m, 2H), 2.85 (m, 1H), 3.30 (m, 1H), 5.14 (m, 2H), 5.48 (s, 1H), 5.80 (m, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.85 (s, 1H), 7.0-7.2 (m, 3H), 7.52 (d, J = 4.9 Hz, 1H), 9.31 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.7 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 500 mg (56%) of the monohydrochloride salt of **49b** as a white solid, mp 115-121°.

Anal. Calcd. for $C_{20}H_{26}N_2OS$•HCl•0.4$H_2$0: C, 62.21; H, 7.26; N, 7.25; Cl, 9.18; S, 8.30. Found: C, 62.21; H, 7.21; N, 7.23; Cl, 9.19; S, 8.22.

(±)-5-((α*R**)-α-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-3-bromo-N,N-diethyl-2-thiophenecarboxamide (**50b**).

Compound **46b** (620 mg, 0.98 mmole) was deprotected according to Method C. Chromatography over silica gel with dichloromethane:acetonitrile/1:1 yielded 280 mg of **50b** as a colorless glass; ^{1}H-nmr (DMSO-d_6, 300 MHz,): δ 0.93 (d, J = 5.8 Hz, 3H), 1.13 (m, 9H), 1.90-2.20 (m, 2H), 2.40 (m, 2H), 2.65-3.00 (m, 3H), 3.30 (m, 5H), 5.14 (m, 2H), 5.47 (s, 1H), 5.80 (m, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.83 (s, 1H), 7.06 (s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 9.41 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.6 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 150 mg (27%) of the monohydrochloride salt of **50b** as a white solid, mp 114-124°.

Anal. Calcd. for $C_{25}H_{34}BrN_3O_2S$•HCl: C, 53.91; H, 6.33; N, 7.55; Br, 14.35; Cl, 6.37, S, 5.76. Found: C, 53.80; H, 6.38; N, 7.59; total halogen Calcd. as chlorine, 12.72; S, 5.71.

Method D (Scheme IX) for **50b.**

A solution of **30b** (2.2 g, 4.1 mmoles) in 250 ml of dry tetrahydrofuran under nitrogen was cooled to -78°. A solution of 1.5 *M* lithium diisopropylamide in cyclohexane (2.8 ml, 4.1 mmoles) was added *via* syringe at a rate to maintain a temperature below -70°. The resulting solution was stirred for 1 hour at -78° and carbon dioxide gas was introduced below the surface of the solution *via* cannula for 10 minutes. The solution was allowed to warm to room temperature with stirring. The solvent was evaporated and the residue was redissolved in toluene and evaporated again. The resulting viscous oil was dissolved in 250 ml of dichloromethane and stirred at room temperature under nitrogen. Thionyl chloride (0.42 ml, 5.75 mmoles) was added, and the resulting mixture was stirred for 1 hour at room temperature before adding diethylamine (2.1 ml, 20.6 mmoles). The mixture was stirred for 16 hours at room temperature, washed three times with water, dried over sodium sulfate, and evaporated to give a dark oil. Chromatography on silica gel with dichloromethane:ethyl acetate/9:1 gave 1.57 g (60%) of **46b**.

Compound **46b** was deprotected according to Method C. Chromatography over silica gel with dichloromethane:ethyl acetate/1:1 yielded 940 mg of **50b** as a light tan foam; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.91 (d, J = 6.0 Hz, 3H), 1.10 (m, 9H), 1.90-2.20 (m, 2H), 2.40 (m, 2H), 2.65-3.00 (m, 3H), 3.30 (m, 5H), 5.13 (m, 2H), 5.47 (s, 1H), 5.76 (m, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.82 (s, 1H), 7.04 (s, 1H), 7.13 (t, J = 7.8 Hz, 1H), 9.38 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.7 with ethanolic hydrogen chloride. The solvent was removed and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 780 mg (57%) of the monohydrochloride salt of **50b** as a white solid, mp 147-150°.

Anal. Calcd. for $C_{25}H_{34}BrN_3O_2S$•HCl: C, 53.91; H, 6.33; N, 7.55; Br, 14.35; Cl, 6.37; S, 5.76. Found: C, 53.82; H, 6.30; N, 7.50; total halogen Calcd. as chlorine, 12.72; S, 5.71.

±)-5-((α*R**)-α-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N,N*-diethyl-2-thiophenecarboxamide (**51b**).

Compound **47b** (1.2 g, 2.16 mmoles) was deprotected according to Method C. Chromatography over silica gel with acetonitrile yielded 1.03 g of **51b** as a tan glass; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.93 (d, J = 5.8 Hz, 3H), 1.20 (m, 9H), 1.90-2.20 (m, 2H), 2.40 (m, 2H), 2.60-3.00 (m, 3H), 3.30 (m, 5H), 5.15 (m, 2H), 5.47 (s, 1H), 5.80 (m, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.85 (s, 1H), 7.00 (d, J = 3.5 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 3.5 Hz, 1H), 9.35 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.9 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 200 mg (19%) of the monohydrochloride salt of **51b** as a white solid, mp 113-116°.

Anal. Calcd. for $C_{25}H_{35}N_3O_2S$•HCl•0.5 H_2O: C, 61.65; H, 7.66; N, 8.63; Cl, 7.28; S, 6.58. Found: C, 61.54; H, 7.60; N, 8.66; Cl, 7.30; S, 6.61.

(±)-5-((α*R**)-α-((2*S**,5*R**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N,N*-diethyl-3-thiophenecarboxamide (**52b**).

Compound **48b** (950 mg, 1.71 mmoles) was deprotected according to Method C. Chromatography over silica gel with acetonitrile:ethanol/95:5 yielded 440 mg of **52b** as an off-white glass; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.91 (d, J = 6.0 Hz, 3H), 1.1 (m, 9H), 1.90-2.10 (m, 2H), 2.40 (m, 2H), 2.70-2.90 (m, 3H), 3.30 (m, 5H), 5.09 (m, 2H), 5.47 (s, 1H), 5.80 (m, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.84 (s, 1H), 7.04 (s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.67 (s, 1H), 9.33 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.8 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 300 mg (36%) of the monohydrochloride salt of **52b** as a white solid, mp 108-112°.

Anal. Calcd. for $C_{25}H_{35}N_3O_2S$•HCl•0.5H_2O: C, 61.65; H, 7.66; N, 8.63; Cl, 7.28; S, 6.58. Found: C, 61.58; H, 7.63; N, 8.58; Cl, 7.33; S, 6.50.

(±)-3-((*R**)-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)(2-thienyl)methyl)phenol (**49a**).

The procedure described for compounds **45b-48b** was followed with 4.0 g (9.5 mmoles) of **36a**. Chromatography over silica gel with dichloromethane:ethyl acetate (gradient from 95:5 to 0:100) yielded four products in order of elution: 950 mg (21%) of **45a**; 480 mg (7.6%) of **46a**; 260 mg (4.7%) of **47a**; and 870 mg (16%) of **48a**.

Compound **45a** (950 mg, 2.08 mmoles) was deprotected according to Method C. Chromatography over silica gel with dichloromethane:acetonitrile/1:1 yielded 610 mg (62%) of **49a** as a white solid; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.90 (d, J = 4.0 Hz, 3H), 1.13 (d, J = 4.0 Hz, 3H), 1.76 (t, J = 9.4 Hz, 1H), 1.98 (t, J = 9.9 Hz, 1H), 2.38 (m, 2H), 2.67 (d, J = 10.9 Hz, 2H), 2.75 (m, 1H), 3.15 (m, 1H), 5.1 (m, 2H), 5.26 (s, 1H), 5.80 (m, 1H), 6.70 (m, 4H), 6.92 (dd, J_1 = 3.5 Hz, J_2 = 5.1 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 5.0 Hz, 1H), 9.38 (s, 1H). A 440-mg portion was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.8 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 330 mg of the monohydrochloride salt of **49a** as a white solid, mp 123-127°.

Anal. Calcd. for $C_{20}H_{26}N_2OS$•HCl•0.4H_2O: C, 62.21; H, 7.26; N, 7.25; Cl, 9.18; S, 8.30. Found: C, 62.07; H, 7.24; N, 7.20; Cl, 9.20; S, 8.19.

(±)-5-((α*R**)-α-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-3-bromo-*N*,*N*-diethyl-2-thiophenecarboxamide (**50a**).

A mixture of **36a** (7.25 g, 17.2 mmoles) was protected as the *tert*-butyl dimethylsilyl ether according to Method A to give 9.2 g (100%) of crude **30a** as a dark oil.

Compound **30a** (2.3 g, 4.29 mmoles) was subjected to the procedures of Method D. Chromatography on silica gel with dichloromethane:ethyl acetate/9:1 gave 1.14 g (42%) of **46a**.

Compound **46a** was deprotected according to Method C. Chromatography on silica gel with dichloromethane:ethyl acetate/1:1 gave 720 mg of **50a** as a light brown foam; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.89 (d, J = 6.0 Hz, 3H), 1.11 (m, 9H), 1.65 (m, 1H), 1.95 (m, 1H), 2.40 (m, 2H), 2.60-2.80 (m, 3H), 3.30 (m, 5H), 5.14 (m, 2H), 5.47 (s, 1H), 5.80 (m, 1H), 6.56 (s, 1H), 6.75 (m, 3H), 7.22 (t, J = 8 Hz, 1H), 9.48 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.8 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 580 mg (58%) of the monohydrochloride salt of **50a** as an off-white solid, mp 147-150°.

Anal. Calcd. for $C_{25}H_{34}BrN_3O_2S$•HCl: C, 53.91; H, 6.33; N, 7.55; Br, 14.35; Cl, 6.37; S, 5.76. Found: C, 53.69; H, 6.40; N, 7.50; total halogen Calcd. as chlorine, 12.69; S, 5.73.

(±)-5-((α*R**)-α-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethyl-2-thiophenecarboxamide (**51a**).

Compound **47a** (260 mg, 0.47 mmole) was deprotected according to method C. Chromatography over silica gel with acetonitrile yielded a tan glass; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.91 (d, J = 3.0 Hz, 3H), 1.17 (m, 9H), 1.75 (m, 1H), 2.0 (m, 1H), 2.40 (m, 2H), 2.60-2.85 (m, 3H), 3.30 (m, 1H), 3.45 (m, 4H), 5.15 (m, 2H), 5.32 (s, 1H), 5.80 (m, 1H), 6.65 (d, J = 3.1 Hz, 1H), 6.75 (m, 3H), 7.20 (m, 2H), 9.45 (s, 1H). The amine was converted to the monohydrochloride salt by titration to *p*H 3.1 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 70 mg (31%) of the monohydrochloride salt of **51a** as a white solid, mp 173-175°.

Anal. Calcd. for $C_{25}H_{35}N_3O_2S$•HCl•0.4H_2O: C, 61.87; H, 7.64; N, 8.66; Cl, 7.31; S, 6.61. Found: C, 61.93; H, 7.62; N, 8.72; Cl, 7.32; S, 6.62.

(±)-5-((α*R**)-α-((2*R**,5*S**)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethyl-3-thiophenecarboxamide (**52a**).

Compound **48a** (870 mg, 1.57 mmoles) was deprotected according to Method C. Chromatography over silica gel with acetonitrile gave an off-white glass; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 0.90 (d, J = 6.0 Hz, 3H), 1.07 (t, J = 7.0 Hz, 6H), 1.15 (d, J = 5.7 Hz, 3H), 1.74 (m, 1H), 1.97 (m, 1H), 2.35 (m, 2H), 2.60-2.80 (m, 3H), 3.30 (m, 5H), 5.15 (m, 2H), 5.29 (s, 1H), 5.80 (m, 1H), 6.66 (s, 1H), 6.73 (s, 1H), 6.74 (d, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.56 (s, 1H), 9.45 (s, 1H). The amine was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.8 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 280 mg (37%) of the monohydrochloride salt of **52a** as a white solid, mp 109-116°.

Anal. Calcd. for $C_{25}H_{35}N_3O_2S$•HCl•0.5H_2O: C, 61.65; H, 7.66; N, 8.63; Cl, 7.28; S, 6.58. Found: C, 61.58; H, 7.65; N, 8.54; Cl, 7.36; S, 6.53.

Resolutions.

(-)-3-((*S*)-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)(3-thienyl)methyl)phenol (**53b**).

Compound **37b** (2.74 g, 8.0 mmoles) was added to a solution of 6.18 g (16 mmoles) of (-)-di-*p*-toluoyl-L-tartaric acid in 20 ml of absolute ethanol. The mixture was warmed to complete solution, cooled, and allowed to crystallize at room temperature. After four recrystallizations the salt was dissolved in 20 ml of 1 *N* aqueous sodium hydroxide, and the solution was titrated to *p*H 8 with 6 *N* hydrochloric acid. The precipitated amine was collected by filtration and recrystallized from absolute ethanol to give 0.21 g (15% of theoretical for one enantiomer) of **53b** as white crystals, mp 193-194°. Absolute configuration was determined by X-ray crystallography; $[\alpha]_D^{20}$ = -3.2° (ethyl acetate, c = 1.4); hplc on β-cyclodextrin with methanol:0.1 *M* ammonium acetate/1:1 gave one peak at t_R = 7.8 minutes.

Anal. Calcd. for $C_{20}H_{26}N_2OS$: C, 70.14; H, 7.65; N, 8.18; S, 9.36. Found: C, 70.24; H, 7.69; N, 8.23; S, 9.42.

(-)-3-((*R*)-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)(4-bromo-2-thienyl)methyl)phenol (**54a**).

A solution of 6.33 g (16.4 mmoles) of (+)-di-*p*-toluoyl-D-tartaric acid in 15 ml of absolute ethanol was added to a suspension of 3.46 g of **36b** in 10 ml of absolute ethanol. The mixture was heated to boiling and the resulting clear solution was allowed to crystallize at room temperature. After five recrystallizations the salt was converted to the free amine as for **53a** and recrystallized from absolute ethanol to give 0.50 g (15% of theoretical for one enantiomer) of **54a** as white crystals, mp 183-185°; $[\alpha]_D^{20}$ = -14.0° (tetrahydrofuran, c = 2.1); hplc on β-cyclodextrin with methanol:0.1 *M* ammonium acetate/1:1 gave one peak at t_R = 8.1 minutes.

Anal. Calcd. for $C_{20}H_{25}BrN_2OS$: C, 57.00; H, 5.98; N, 6.65; Br, 18.96; S, 7.61. Found: C, 56.90; H, 6.03; N, 6.57; Br, 18.92; S, 7.52.

(+)-3-((*S*)-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)(4-bromo-2-thienyl)methyl)phenol (**54b**).

A solution of 4.22 g (11 mmoles) of (-)-di-*p*-toluoyl-L-tartaric acid in 15 ml of absolute ethanol was added to a suspension of 2.3 g (5.5 mmoles) of **36b** in 5 ml of absolute ethanol. The mixture was heated to boiling and the resulting clear solution was allowed to crystallize at room temperature. After three crystallizations the salt was converted to the free amine as for **53a** and recrystallized from absolute ethanol to give 0.490 g (43% of theoretical for one enantiomer) of **54b** as white crystals, mp 183-185°. Absolute configuration was determined by X-ray crystallography; $[\alpha]_D^{20}$ = + 14.5° (tetrahydrofuran, c = 3.3); hplc on β-cyclodextrin with methanol:0.1 *M* ammonium acetate/1:1 gave one peak at t_R = 11 minutes.

Anal. Calcd. for $C_{20}H_{25}BrN_2OS$: C, 57.00; H, 5.98; N, 6.65; Br, 18.96; S, 7.61. Found: C, 56.93; H, 5.99; N, 6.67; Br, 19.04; S, 7.67.

(-)-3-((*R*)-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)(2-thienyl)methyl)phenol (**55a**).

Compound **54a** (0.53 g, 1.3 mmoles) was dissolved in 10 ml of dry tetrahydrofuran and cooled to -78° under a nitrogen atmosphere. A solution of 1.6 *M* *n*-butyllithium (1.6 ml, 2.6 mmoles) was added *via* syringe at a rate to maintain a temperature below -60°. The resulting solution was stirred at -75° for 45 minutes and then quenched by the addition of 5 ml of a saturated aqueous solution of ammonium chloride. The solution was warmed to 25°, diluted with water, and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated to 400 mg of crude product as a pink solid. The crude product was recrystallized from acetonitrile to give 0.33 g (77%) of **55a** as beige crystals, mp 176-178°, $[\alpha]_D^{20}$ = -23.3° (ethyl acetate, c = 1.5); hplc on Cyclobond I with methanol:0.1 *M* aqueous ammonium acetate/1:1 gave one peak at t_R = 8.5 minutes.

Anal. Calcd. for $C_{20}H_{26}N_2OS \cdot 0.25 \cdot H_2O$: C, 69.23; H, 7.70; N, 8.07; S, 9.24. Found: C, 68.86; H, 7.47; N, 8.27; S, 9.06.

The product (0.30 g, 0.87 mmole) was treated with ethanolic hydrogen chloride as for **52a** to give 0.201 g (61%) of the monohydrochloride salt; $[\alpha]_D^{20}$ = -11.9° (ethanol, c = 1.05).

Anal. Calcd. for $C_{20}H_{26}BrN_2OS \cdot HCl \cdot 0.75H_2O$: C, 61.21; H, 7.32; N, 7.12; S, 8.17; Cl, 9.03. Found: C, 61.35; H, 7.01; N, 7.30; S, 8.16; Cl, 9.11.

(+)-3-((*S*)-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)(2-thienyl)methyl)phenol (**55b**).

This compound was prepared in the same manner as **55a** starting with **54b**. The product was obtained as light beige crystals, mp 179-181°; hplc on β-cyclodextrin with methanol:0.1 *M* ammonium acetate/1:1 gave one peak at t_R = 8.9 minutes; $[\alpha]_D^{20}$ = + 21.8° (ethyl acetate, c = 1.2).

Anal. Calcd. for $C_{20}H_{26}N_2OS$: C, 70.14; H, 7.65; N, 8.18; S, 9.36. Found: C, 69.89; H, 7.65; N, 8.14; S, 9.42.

(-)-3-((*R*)-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-3-bromo-*N*,*N*-diethyl-2-thiophenecarboxamide (**56a**).

Compound **54a** (1.13 g, 2.7 mmoles) was converted to 1.44 g (100%) of the silyl ether according to method A. The thiophene ring was then α-deprotonated with lithium diisopropylamide and treated sequentially with carbon dioxide, thionyl chloride, and diethylamine as for **50b**, according to Method D, to give 1.19 g (69%) of the silyl ether of **56a**. This was deprotected according to Method C to yield 0.87 g (88%) of crude **56a**. The amine (700 mg) was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.5 with ethanolic hydrogen chloride. The solution was concentrated by evaporation and the salt was precipitated with diethyl ether to give 570 mg of the monohydrochloride salt of **56a** as a white solid; $[\alpha]_D^{20}$ = -4.5° (absolute ethanol, c = 1.99).

Anal. Calcd. for $C_{25}H_{34}BrN_3O_2S \cdot HCl \cdot 0.5H_2O$: C, 53.05; H, 6.41; N, 7.42; total halogen as bromine, 28.23. Found: C, 53.21; H, 6.43; N, 7.42; total halogen as bromine, 28.35.

(+)-3-((*S*)-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-3-bromo-*N*,*N*-diethyl-2-thiophenecarboxamide (**56b**).

Compound **54b** (2.10 g, 4.99 mmoles) was converted to 2.04 g (76%) of the silyl ether according to method A. The thiophene ring was then α-deprotonated with lithium diisopropylamide and treated sequentially with carbon dioxide, thionyl chloride, and diethylamine as for **50b**, according to Method D, to give 1.04 g (43%) of the silyl ether of **56b**. This was deprotected according to Method C to yield 0.55 g (65%) of crude **56a**. The amine (480 mg, 0.92 mmole) was dissolved in ethanol and converted to the monohydrochloride salt by titration to *p*H 3.5 with ethanolic hydrogen chloride. The solvent was removed by evaporation and the salt was dissolved in dichloromethane, then precipitated with diethyl ether to give 430 mg of the monohydrochloride salt of **56b** as an off-white solid. $[\alpha]_D^{20}$ = +6.4° (absolute ethanol, c = 1.6) (free amine).

Anal. Calcd. for $C_{25}H_{34}BrN_3O_2S \cdot HCl \cdot 0.25H_2O$: C, 53.48; H, 6.37; N, 7.48; total halogen as bromine, 28.46; S, 5.71. Found: C, 53.22; H, 6.43; N, 7.37; total halogen as bromine, 28.26; S, 5.72.

X-Ray Crystallographic Analyses.

X-ray services were provided by the crystallographic staff of Molecular Structure Corporation. Measurements for all three X-ray analyses were taken with a Rigaku AFC5R diffractometer with graphite monochromated CuKα radiation and a 12KW rotating anode generator. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 400.0 mm. The intensities of three representative reflections, which were measured after every 150 reflections, remained constant throughout data collection, indicating crystal and electronic stability (no decay correction was applied). Neutral atom scattering factors were taken from Cromer and Waber [8]. Anomalous dispersion effects were included in Fcalc [9]; the values for Δf' and Δf" were those of Cromer [10]. All calculations were performed using the TEXSAN [11] crystallographic software package of Molecular Structure Corporation. Figures 2, 3, and 4 are the PLUTO [12] plots of compounds **53b**, **54b**, and **57**.

X-Ray Crystallographic Analysis of (**53b**).

A colorless prism-shaped crystal of $C_{20}H_{26}N_2OS$ having approximate dimensions of 0.500 x 0.400 x 0.300 mm was mounted on a glass fiber. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 16 carefully centered reflections

in the range $79.54 < 2\Theta < 80.07$, corresponded to a monoclinic cell with dimensions: a = 7.066 (1) Å, b = 16.508 (4) Å, c = 8.667 (2) Å, V = 952.5 (2) Å, $\beta = 109.59$ (1)°.

For z = 2 and F.W. = 342.50, the calculated density is 1.194 g/cm^3. Based on the systematic absences of:0k0: $k \neq 2n$ packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: $P2_1$ (#4).

The data were collected at a temperature of 23 ±1° using the w - 2Θ scan technique to a maximum 2Θ value of 120.6°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.34° with a take-off angle of 6.0°. Scans of (1.68 + 0.14 tan Θ)° were made at a speed of 32.0°/minute (in omega). The weak reflections ($I < 15.0\sigma$ (I)) were rescanned (maximum of 4 rescans) and the counts were accumulated to assure good counting statistics. Of the 3690 reflections that were collected, 1494 were unique (R_{int} = .066). The linear absorption coefficient for CuKα is 15.2 cm^{-1}. An empirical absorption correction, using the program DIFABS [13], was applied, which resulted in transmission factors ranging from 0.76 to 1.30. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.85643E-04).

The structure was solved by direct methods [14]. The sulfur and one of the carbon atoms on the five-membered ring are disordered. The two positions are partially occupied by both sulfur and carbon characters. Two pairs of the disordered atoms were such that the positions of the two rings overlap. That is, C(2A) is at the same position as 5(l), and 5(2A) is at the same position as C(2). The occupancies, 0.740 for 5(l) and C(2) and 0.260 for S(IA) and C(2A)1 respectively, were refined initially such that the sum of the two occupancies was equal to one. The occupancies were not refined in the final cycles. The disorder can be thought of as a rotational disorder around the C(4)-C(5) bond, where S(I) and C(2) switch places.

All non-hydrogen atoms except the two disordered carbon atoms, C(2) and C(2A), were refined anisotropically. The disordered carbon atoms were refined isotropically. The hydrogen atom attached to the oxygen atom was located from a difference Fourier map and refined isotropically. The positions of the remaining hydrogen atoms were calculated assuming ideal geometries.

Bijvoet pairs were collected and anomalous scattering terms were included to determine the absolute configuration. Two models were refined to convergence: the one presented here (with an R-value of 0.033 and a weighted R-value of 0.040) and the one related by an inversion center (with an R-value of 0.040 and a weighted R-value of 0.050). The model with the lower R-values was accepted as the absolute configuration and was used in the final refinement.

Intermolecular hydrogen bonding was observed between H(I) and N(2) with a distance of 1.98(4) Å. The N(2)-O(1) distance is 2.751 (3) Å. The N(2)..H(I) -0(l) angle is 159(4)°.

The hydrogen atoms were either refined isotropically or included in the structure factor calculation in idealized positions (d_{C-H} = 0.95Å) and were assigned isotropic thermal parameters that were 20% greater than the $B_{equivalent}$ value of the atom to which they were bonded. The final cycle of full-matrix least-squares refinement [15] was based on 1450 observed reflections ($I > 3.00\sigma$ (I)) and 223 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R = \Sigma \mid |Fo| - |Fc| \mid / \Sigma |Fo| = 0.033$ and $R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.040$.

The standard deviation of an observation of unit weight [16] was 3.85. The weighting scheme was based on counting statistics and included a factor (p = 0.01) to downweight the intense reflections. Plots of $\Sigma w (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, sin Θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum packs on the final difference Fourier map corresponded to 0.12 and -0.11 e$^-$/Å^3, respectively.

X-Ray Crystallographic Analysis of **54b**.

A colorless, irregularly cut crystal of $C_{20}H_{25}BrN_2OS$ having approximate dimensions of 0.550 x 0.500 x 0.400 mm was mounted on a glass fiber. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $103.01 < 2\Theta < 105.42°$, corresponded to an orthorhombic cell with dimensions: a = 10.991 (1) Å, b = 17.965 (2) Å, c = 10.1791 (5) Å, V = 2009.9 (3) Å. For Z = 4 and F.W. = 421.39, the calculated density is 1.393 g/cm^3. Based on the systematic absences of: h00: $h \neq 2n$, 0k0: $k \neq 2n$, 001: $l \neq 2n$ and the successful solution and refinement of the structure, the space group was determined to be: $P2_12_12_1$ (#19).

The data were collected at a temperature of 23 ±1° using the w - 2Θ scan technique to a maximum 2Θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.18° with a take-off angle of 6.0°. Scans of (1.31 + 0.30 tan Θ)° were made at a speed of 16.0°/minute (in omega). The weak reflections ($I < 10.0\sigma$ (I)) were rescanned (maximum of 4 rescans) and the counts were accumulated to assure good counting statistics.

Of the 4391 reflections which were collected, 1750 were unique (R_{int} = .037). The linear absorption coefficient for CuKα is 38.3 cm^{-1}. An empirical absorption correction, based on azimuthal scans of several reflections, was applied which resulted in transmission factors ranging from 0.73 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient - 0.57655E-05).

The structure was solved by direct methods [17,18] and refined by full-matrix least-squares and difference Fourier methods. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were either refined isotropically or included in the structure factor calculation in idealized positions (d_{C-H} = 0.95Å), and were assigned isotropic thermal parameters that were 20% greater than $B_{equivalent}$ value of the atom to which they were bonded.

Bijvoet pairs were collected and anomalous scattering terms were included to determine the absolute configuration. Two models were refined to convergence: the one presented (with both R-value and weighted R-value of 0.034) and the one related by an inversion center (with an R-value of 0.043 and weighted R-value of 0.045). The model with the lower R-values was accepted as the absolute configuration and was used in the final refinement.

Intermolecular hydrogen bonding was observed between H(1) and N(2) with a distance of 2.05(3)Å. The O(1) -H(1)...N(2) angle is 172(3)°.

The final cycle of full-matrix least-squares refinement [15] was based on 3915 observed reflections ($I > 3.00\sigma$ (I)) and 231

variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.034$ and $R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.034$.

The standard deviation of an observation of unit weight [16] was 2.04. The weighting scheme was based on counting statistics and included a factor (p = 0.01) to downweight the intense reflections. Plots of $\Sigma w (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, sin Θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.24 and -0.29 $e^-/Å^3$, respectively.

X-Ray Crystallographic Analysis of **57**.

A colorless, parallelepiped crystal of $C_{22}H_{21}BrN_2O$ having approximate dimensions of 0.200 x 0.200 x 0.400 mm was mounted on a glass fiber. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $87.73 < 2\Theta < 98.91°$, corresponded to a monoclinic cell with dimensions: a = 9.2336 (6) Å, b = 20.610 (4) Å, c = 11.1757 (8) Å, V = 2057.6 (5) $Å^3$, $\beta = 104.663$ (5)°.

For Z = 4 and F.W. = 415.37, the calculated density is 1.341 g/cm^3. Based on the systematic absences of: h01:l ≠ 2n and 0k0: k ≠ 2n and the successful solution and refinement of the structure, the space group was determined to be: $P2_1/c$ (#14).

The data were collected at a temperature of 23 ±1° using the w-2Θ scan technique to a maximum 2Θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.29° with a take-off angle of 6.0°. Scans of (1.15 + 0.30 tan Θ)° were made at a speed of 32.0°/minute (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics.

Of the 2812 reflections collected, 2678 were unique (R_{int} = .013). The linear absorption coefficient for CuKα is 30.9 cm^{-1}. An empirical absorption correction, using the program DIFABS [14], was applied which resulted in transmission factors ranging from 0.62 to 1.23. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.51877E-06).

The structure was solved by a combination of the Patterson method and direct methods [18,19]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement [15] was based on 2076 observed reflections ($I > 3.00\sigma(I)$) and 345 variable parameters and converged (largest parameter shift was 0.31 times its esd) with unweighted and weighted agreement factors of: $R = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.055$ and $R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.076$. The molecule has three chiral centers, with relative configurations of R at atom C1, S at atom C14, and R at atom C16; however, since the molecule crystallizes in a centrosymmetric space group, molecules of both hands are present in the crystal in equal numbers.

The crystal packing is influenced by intermolecular hydrogen bonding between atoms O1 and N2 (O1···N2 = 2.895(6)Å; H1···N2 = 2.24(5)Å; O1-H1···N2 = 172(6)°).

The standard deviation of an observation of unit weight [16] was 2.30. The weighting scheme was based on counting statistics and included a factor (p = 0.05) to downweight the intense reflections. Plots of $\Sigma w (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, sin Θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.43 and -0.62 $e^-/Å^3$, respectively.

REFERENCES AND NOTES

[1] K.-J. Chang, G. Rigdon, J. Howard, and R. McNutt, *J. Pharmacol. Exp. Ther.*, **267**, 852 (1993).

[2] D. A. Goff, G. A. Koolpe, A. B. Kelson, H. M. Vu, D. L. Taylor, C. D. Bedford, H. A. Musallam, I. Koplovitz, and R. N. Harris, *J. Med. Chem.*, **34**, 1363 (1991).

[3] G. Jones and H. Ollivierre, *Tetrahedron.*, **47**, 2851 (1991).

[4] A. Minato, K. Tamao, T. Hayashi, K. Suzuki, and M. Kumada, *Tetrahedron Letters*, **22**, 5319 (1981).

[5] K.-J. Chang and P. Cuatrecasas, *J. Biol. Chem.*, **254**, 2610 (1979).

[6] K.-J. Chang, B. R. Cooper, E. Hazum, and P. Cuatrecasas, *Mol. Pharmacol.*, **16**, 91 (1979).

[7] K.-J. Chang, T. E. Wei, A. Killian, and J.-K. Chang, *J. Pharmacol. Exp. Ther.*, **227**, 403 (1983).

[8] D. T. Cromer and J. T. Waber, International Tables for X-ray Crystallography, Vol **4**, The Kynoch Press, Birmingham, England, 1974, Table 2.2 A.

[9] J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, **17**, 781 (1964).

[10] D. T. Cromer, International Tables for X-ray Crystallography, Vol **4**, The Kynoch Press, Birmingham, England, 1974, Table 2.3.1.

[11] TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985.

[12] S. Motherwell and W. Clegg, PLUTO. Program for Plotting Molecular and Crystal Structures, University of Cambridge, England, 1978.

[13] N. Walker and D. Stuart, *Acta Crystallogr.*, **A39**, 158 (1983).

[14] C. J. Gilmore, University of Glasgow, Scotland, MITHRIL - An Integrated Direct Methods Computer Program, *J. Appl. Cryst.*, **17**, 42 (1984).

[15] Least-Squares:
Function minimized: $\Sigma w (|Fo| - |Fc|)^2$
where: $w = 4Fo^2/\sigma^2 (Fo^2)$
$\sigma^2 (Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$
S = Scan rate
C = Total Integrated Peak Count
R = Ratio of Scan Time to background counting time
B = Total Background Count
Lp = Lorentz-polarization factor
p = p-factor

[16] Standard deviation of an observation of unit weight:
$[\Sigma w (|Fo| - |Fc|)^2/(No - Nv)]^{1/2}$
where: No = number of observations
Nv = number of variables

[17] G. M. Sheldrick, SHELXS-86, A Program for the Solution of Crystal Structure from Diffraction Data, Institute fur Anoganische Chemie der Universitat, Tammannstrasse 4, Gottingen, Germany.

[18] P. T. Beurskens, DIRDIF; Direct Methods for Difference Structures - An Automatic Procedure for Phase Extension and Refinement of Difference Structure Factors. Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegan, Netherlands.

[19] J. C. Calbrese, PHASE; Patterson Heavy Atom Solution Extractor. University of Wisconsin-Madison, Ph. D. Thesis, 1972.