Identification of Phenylisoxazolines as Novel and Viable Antibacterial Agents Active against Gram-Positive Pathogens

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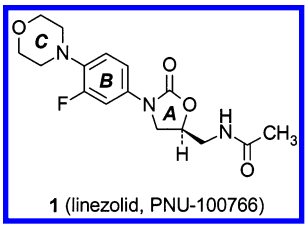
A new and promising group of antibacterial agents, collectively known as the oxazolidinones and exemplified by linezolid (PNU-100766, marketed as Zyvox), have recently emerged as important new therapeutic agents for the treatment of infections caused by Gram-positive bacteria. Because of their significance, extensive synthetic investigations into the structure−activity relationships of the oxazolidinones have been conducted at Pharmacia. One facet of this research effort has focused on the identification of bioisosteric replacements for the usual oxazolidinone A-ring. In this paper we describe studies leading to the identification of antibacterial agents incorporating a novel isoxazoline A-ring surrogate. In a gratifying result, the initial isoxazoline analogue prepared was found to exhibit in vitro antibacterial activity approaching that of the corresponding oxazolidinone progenitor. The synthesis and antibacterial activity profile of a preliminary series of isoxazoline analogues incorporating either a C−C or N−C linkage between their B- and C-rings will be presented. Many of the analogues exhibited interesting levels of antibacterial activity. The piperazine derivative **54** displayed especially promising in vitro activity and in vivo efficacy comparable to the activity and efficacy of linezolid.

Introduction

The development of bacterial resistance to currently available antibacterial agents is a growing global health problem. Of particular concern are infections caused by multidrug-resistant Gram-positive pathogens. Principal players among these problematic organisms are isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE),[1] vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VREF),[2] and also penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*.[3] These pathogens are responsible for significant morbidity and mortality in both the hospital[4] and community setting.[5]

A new and promising group of antibacterial agents, collectively known as the oxazolidinones and exemplified by linezolid (**1**, PNU-100766, marketed as Zyvox), have recently emerged as important new therapeutic agents for the treatment of infections caused by Gram-positive bacteria.[6] Importantly, linezolid's spectrum of activity includes multidrug-resistant strains of staphylococci, streptococci, and enterococci, including the recently described glycopeptide-intermediate *Staphylococcus aureus* (GISA) isolates with reduced susceptibility to vancomycin.[7] The increased prevalence of the latter organisms is particularly disturbing because aside from linezolid, quinupristin/dalfopristin (marketed as Synercid),[8] and perhaps some investigational agents, no effective treatment exists for infections caused by such strains.



1 (linezolid, PNU-100766)

Because of their significance, extensive synthetic investigations into the structure−activity relationships (SAR) of the oxazolidinones have been conducted at Pharmacia. One facet of this research effort has focused on the identification of bioisosteric replacements for the usual oxazolidinone A-ring. Earlier synthetic efforts at Pharmacia and other pharmaceutical houses explored the antibacterial potential of the dihydrofuran-2-one, tetrahydrofuran-2-one, and pyrrolidin-2-one ring systems.[9,10] In a series of racemic troponylphenyl derivatives prepared at Pharmacia,[11] it was found that the dihydrofuran-2-one ring conferred in vitro activity roughly comparable to that of its oxazolidinone congener[12] (e.g., **2** vis-à-vis **3**; see Table 1). The corresponding tetrahydrofuran-2-one analogue **4** was 4- to 16-fold less active than **2**. Interestingly, the pyrrolidin-2-one **5** was inactive at the highest level tested.

Following the premise that a suitable bioisosteric A-ring replacement requires (1) an sp^2 center (or at least substantial sp^2 character through resonance delocalization or tautomerism) adjacent to the phenyl B-ring, (2) a strategically located ring oxygen, and (3) a chiral

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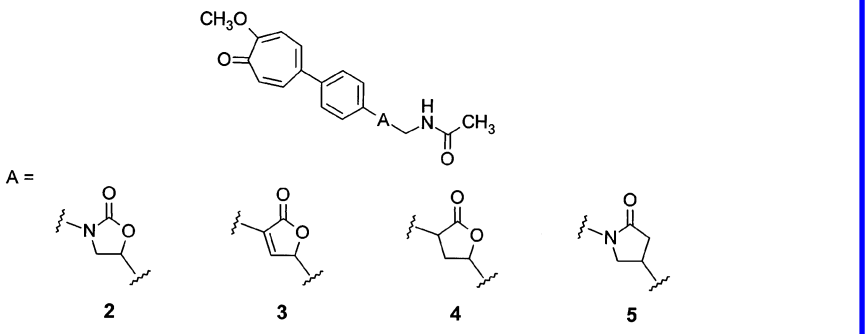
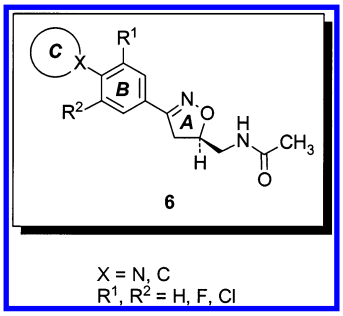
Table 1. In Vitro Antibacterial Activity of Selected Racemic Troponylphenyl A-Ring Analogues



Compound	Minimum Inhibitory Concentration[h] (μg/mL)						
	S.a.[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.i.*[f]	*M.c.*[g]
2	2	2	0.5	0.25	1	8	2
3	2	2	1	<0.5	1	16	8
4	16	16	4	2	16	>32	32
5	>64	>64	>64	>64	>64	>64	>64

[a] Methicillin-susceptible *Staphylococcus aureus* UC9213. [b] Methicillin-, ciprofloxacin-, rifampin-, imipenem-resistant *S. aureus* UC12673. [c] Methicillin-resistant *Staphylococcus epidermidis* UC12084. [d] Penicillin-susceptible *Streptococcus pneumoniae* UC9912. [e] *Enterococcus faecalis* UC9217. [f] Ampicillin-resistant *Haemophilus influenzae* UC30063. [g] *Moraxella catarrhalis* UC30610. [h] Minimum inhibitory concentration: lowest concentration of drug (μg/mL) that inhibits visible growth of the organism.

carbon of appropriate absolute configuration bearing the essential acylaminomethyl side chain leading to the conception of the isoxazoline ring system as an attractive target (see generic structure **6**).[11]



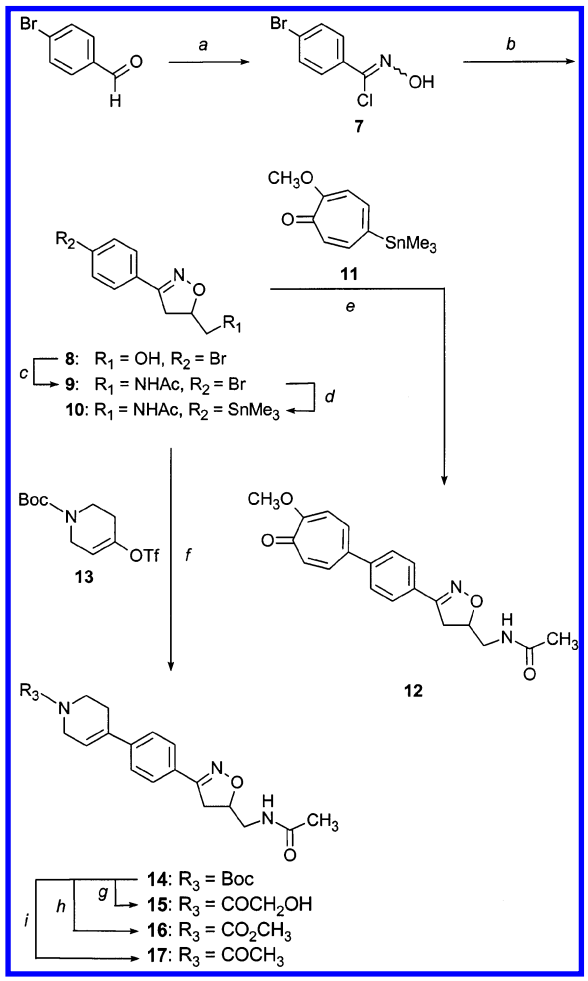
The 3-phenylisoxazoline ring system represents an appealing target from a synthetic standpoint. The isoxazoline ring is readily formed in one step from an aromatic nitrile *N*-oxide and an appropriate dipolarophile partner.[13] The nitrile *N*-oxides, in turn, can be readily generated in situ from the corresponding hydroximinoyl chloride[14] or nitromethylene precursors.[15] Finally, it was anticipated that 3-phenylisoxazolines of generic structure **6** would ultimately be available in enantiomerically enriched form via one of the known asymmetric synthetic protocols in this area.[16,17]

Chemistry

C−C Linked Phenylisoxazolines. The synthesis of initial racemic phenylisoxazolines bearing a carbon−carbon bond between their B- and C-rings is outlined in Scheme 1. The hydroximinoyl chloride **7** was prepared in good overall yield from 4-bromobenzaldehyde. In situ conversion of **7** to the corresponding nitrile oxide followed by cycloaddition with allyl alcohol as the dipolarophile generated the racemic isoxazoline **8**. Activation of the hydroxyl group of **8** as the mesylate followed by displacement with ammonia and then acetylation with acetic anhydride yielded **9** in high overall yield. Alternatively, in subsequent studies we found that allyl acetamide could be effectively employed as the dipolarophile to directly provide the isoxazoline ring system with the desired acetamidomethyl side chain (**9**). We further found that **9** could be readily converted to the corresponding stannane **10**. With the ready availability of **9** and **10** we initially targeted the isoxazoline equivalent of the troponylphenyl oxazolidinone analogue **2** (vide supra). The assumption was that it would be easy to append the requisite methoxytropone moiety through a Stille cross-coupling reaction[18] and to get a rapid determination of the antibacterial activity potential of the phenylisoxazoline class. In this event, although the Stille coupling of **9** with the troponyl stannane **11**[12] proceeded in modest yield, enough of the targeted product **12** was obtained to gather comparative antibacterial activity data. Additional C-rings known to confer potent levels of antibacterial activity to the phenyloxazolidinone pharmacophore were also targeted for attachment to the phenylisoxazoline subunit. In particular, the protected tetrahydropyridine derivative **13**[19] was coupled with the stannane derivative **10** to furnish the advanced intermediate **14**. Through subsequent deprotection and elaboration steps, **14** was converted to a variety of N-functionalized analogues such as **15**−**17**.

In the case of the phenyloxazolidinones, the absolute configuration of the C-5 chiral center plays a pivotal role in terms of imparting antibacterial activity to the pharmacophore; only the (5*S*)-enantiomer has activity.[20] As part of our effort aimed at delineating the importance of chirality in the phenylisoxazoline series, we desired to prepare a representative example of the corresponding phenylisoxazole (see Scheme 2). To this end, bromophenylhydroximinoyl chloride **7** was converted to the corresponding nitrile *N*-oxide, which then reacted with propargyl alcohol to generate the desired (hydroxymethyl)isoxazole intermediate **18**. Following the usual C-5 side chain elaboration conditions, the acetamidomethyl derivative **19** was then obtained. Compound **19** was further modified to generate the targeted phenyl-

Scheme 1[a]

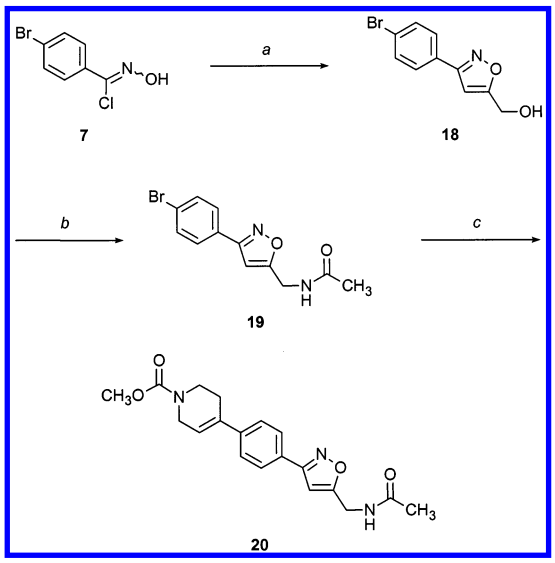


[a] Reagents: (a) (1) H_2NOH, EtOH, H_2O, (2) NCS, DMF, 0−50 °C, 55%; (b) allyl alcohol or allyl acetamide, Et_3N, CH_2Cl_2, 0 °C to room temp, 99% or 69%, respectively; (c) (1) MsCl, Et_3N, CH_2Cl_2, (2) NH_4OH, *i*-PrOH, THF, resealable pressure vessel, 100 °C, (3) Ac_2O, pyridine, CH_2Cl_2, 92%; (d) $(Me_3Sn)_2$, $(Ph_3P)_2PdCl_2$, 1,4-dioxane, 100 °C, 86%; (e) **11**, $Pd_2(dba)_3$, tri(2-furyl)phosphine (TFP), 1-methyl-2-pyrrolidinone (NMP), 90 °C, 28%; (f) **13**, $Pd_2(dba)_3$, triphenylarsine, 1-methyl-2-pyrrolidinone (NMP), room temp, 69%; (g) (1) TFA, CH_2Cl_2, (2) $AcOCH_2COCl$, Et_3N, CH_2Cl_2, (3) MeOH, K_2CO_3, 32%; (h) (1) TFA, CH_2Cl_2, (2) $ClCO_2CH_3$, K_2CO_3, acetone, H_2O, 67%; (i) TFA, CH_2Cl_2, (2) AcCl, Et_3N, CH_2Cl_2, 65%.

isoxazole analogue **20**, which incorporates the functionalized tetrahydropyridine C-ring of phenylisoxazoline congener **16**.

Intuitively, it was suspected that the isoxazolines would require the (*R*) absolute configuration at C-5 for optimal activity. This would mimic the stereochemical situation in the corresponding oxazolidinone series. To explore this notion, we targeted both the (*R*)- and (*S*)-antipodes of (±)-**15**. To facilitate this process, the racemic bromophenylisoxazoline intermedate **8** was chromatographed on a Chiralpak AD column, eluting with 25% 2-propanol in hexane, to provide, as subsequent events would indicate (vide infra), the individual enantiomers (−)-(*R*)-**21** and (+)-(*S*)-**22** (see Scheme 3). The hydroxymethyl side chains of **21** and **22** were then elaborated as described before to give the corresponding acetamidomethyl derivatives (−)-(*R*)-**23** and (+)-(*S*)-**24**, respectively. Compounds **23** and **24**, in turn, were further modified to provide the desired enantiomeric

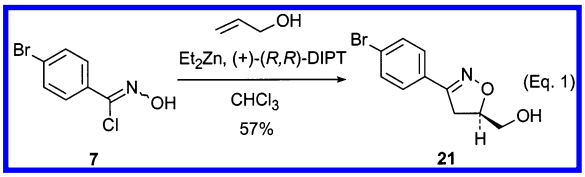
Scheme 2[a]



[a] Reagents: (a) propargyl alcohol, Et_3N, CH_2Cl_2, 76%; (b) (1) MsCl, Et_3N, CH_2Cl_2, (2) NH_4OH, *i*-PrOH, THF, resealable pressure vessel, 100 °C, (3) Ac_2O, pyridine, CH_2Cl_2, 80%; (c) (1) $(Me_3Sn)_2$, $(Ph_3P)_2PdCl_2$, 1,4-dioxane, 100 °C, (2) **13**, $Pd_2(dba)_3$, triphenylarsine, NMP, room temp, (3) TFA, CH_2Cl_2, (4) $ClCO_2CH_3$, K_2CO_3, acetone, H_2O, 14%.

isoxazoline analogues (−)-(*R*)-**25** and (+)-(*S*)-**26**, respectively.

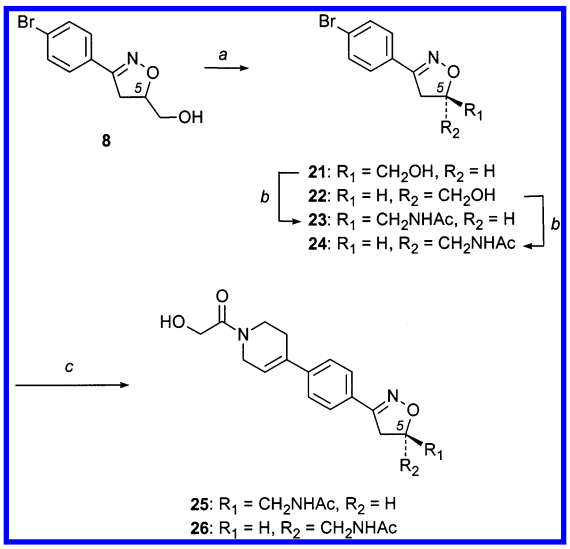
The absolute configuration of compound **21** was determined to be (*R*) by asymmetric synthesis, employing the procedure of Ukaji and co-workers.[21] Reaction of the nitrile *N*-oxide generated from bromophenylhydroximinoyl chloride **7** with allyl alcohol in the presence of diethylzinc and diisopropyl (+)-(*R*,*R*)-tartrate afforded (−)-(*R*)-**21** in an unoptimized 57% chemical yield and with an optical purity of 87% (see eq 1).



Further unequivocal confirmation of the absolute configuration of the phenylisoxazoline series was obtained by an X-ray structure determination of compound **23** (see Figure 1). With nonessential variations, compound (−)-(*R*)-**23**, like the corresponding racemate **9**, served as an important intermediate for the preparation of a range of C−C linked C-ring phenylisoxazoline derivatives in enantiomerically enriched form.

N−C Linked Phenylisoxazolines. Consideration of the positive attributes of linezolid and other N−C linked C-ring derivatives in the phenyloxazolidinone series led us to target the corresponding congeners in the isoxazoline subclass. Our initial approach, employing morpholine as a representative C-ring, is outlined in Scheme 4. Condensation of morpholine with methyl 3,4-difluorobenzoate (**28a**) or ethyl 3,4,5-trifluorobenzoate (**28b**) afforded the adducts **29a** or **29b**, respectively, in excellent yield. Reduction to the corresponding benzylic alcohols **30** was accomplished in high yield through the action of lithium aluminum hydride. We were pleased to find that the catalytic tetrapropylammonium perru-

Scheme 3[a]



[a] Reagents: (a) Chiralpak AD column, *i*-PrOH, hexane; (b) procedure, Scheme 1; (c) procedure, Scheme 1.

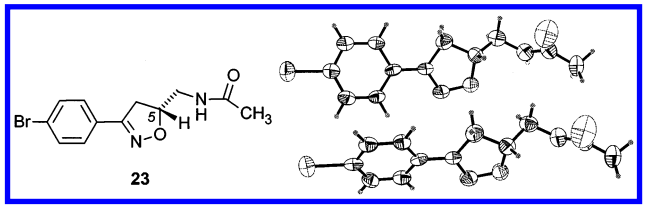
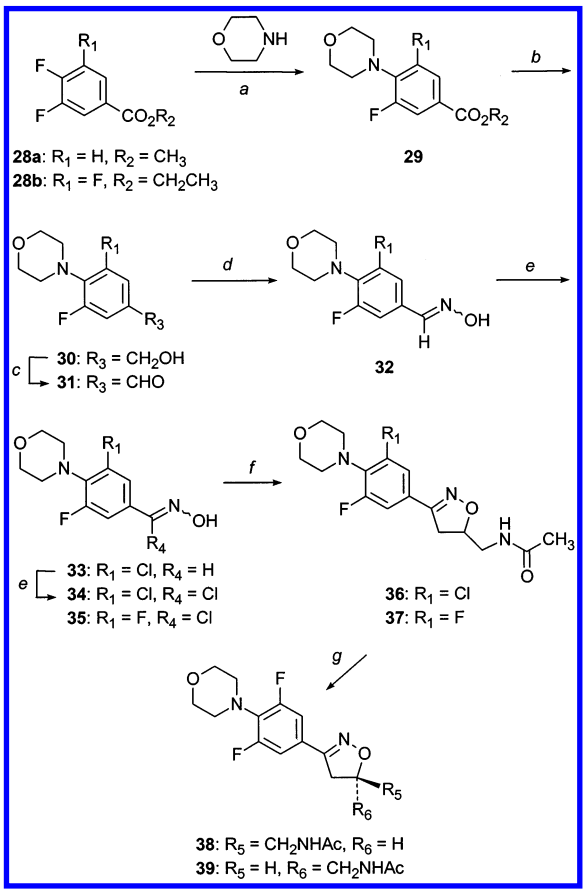


Figure 1. ORTEP diagram of phenylisoxazoline intermediate (−)-(*R*)-**23**.

thenate (TPAP) oxidation procedure[22] worked well to effect oxidation of alcohols **30a**,**b** to the substituted benzaldehydes **31a**,**b**. Treatment of aldehydes **31a**,**b** with hydroxylamine then afforded the corresponding oximes **32a**,**b** in acceptable yield. Chlorination of oxime **32a** with 1.0 equiv of NCS afforded, to our dismay, essentially a quantitative yield of the chlorobenzene derivative **33**. In an attempt to make use of this material, we added a second equivalent of NCS to generate the hydroximinoyl chloride **34**. In the case of difluoro substrate **32b**, the aforementioned untoward ring chlorination problem is neatly avoided and the hydroximinoyl chloride **35** was obtained uneventfully. Allyl acetamide then underwent 1,3-dipolar cycloaddition with the nitrile *N*-oxides generated from **34** and **35** providing the racemic phenylisoxazoline analogues **36** and **37**, respectively. Continuing a general trend in the phenylisoxazoline series, the racemate **37** could be separated into the individual enantiomers **38** and **39** by preparative chiral stationary phase HPLC.

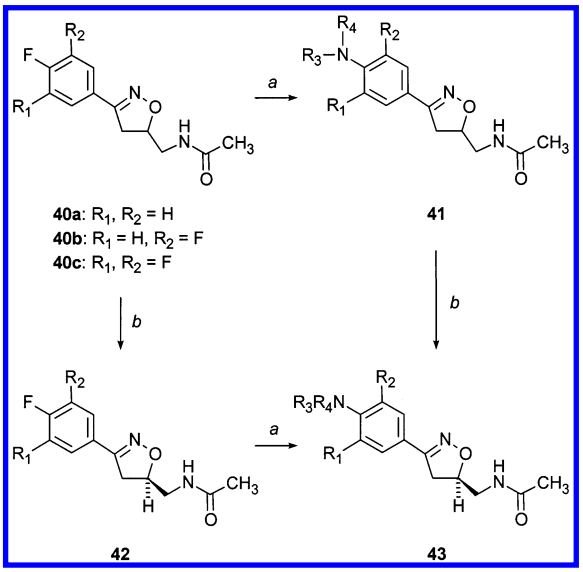
The preferred method for preparing N−C linked C-ring substituted phenylisoxazolines emerged from exploratory nucleophilic aromatic substitution studies involving halogenated phenylisoxazoline substrates. We were cognizant of the moderate electron-withdrawing ability of the isoxazoline ring, relative to its phenyloxazolidinone progenitor.[23] We speculated that the level of activation might permit nucleophilic displacement of a halogen atom in the 4-position. Initial attempts to displace a bromine substituent with primary or secondary amines failed. However, the corresponding racemic fluorinated derivatives **40a**−**c** were successfully utilized (see Scheme 5). This classical nucleophilic aromatic

Scheme 4[a]



[a] Reagents: (a) K_2HPO_4, DMSO, 81−88%; (b) $LiAlH_4$, THF, 98%; (c) TPAP, 4-methylmorpholine *N*-oxide, CH_2Cl_2, 77−83%; (d) H_2NOH, EtOH, H_2O, 69−99%; (e) NCS, DMF, 0−50 °C; (f) allyl acetamide, Et_3N, CH_2Cl_2, 0 °C to room temp, 36% for steps e and f; (g) Chiralpak AD column, *i*-PrOH, hexane.

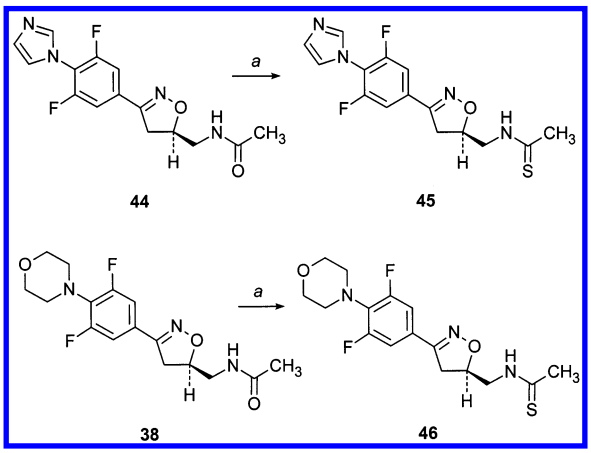
Scheme 5[a]



[a] Reagents: (a) R_3R_4NH, K_2CO_3, Δ or R_3R_4NH, K_2HPO_4, DMSO, Δ; (b) chiral HPLC separation.

substitution process facilitated the preparation of a diverse array of racemic N−C linked 4-substituted phenylisoxazolines **41**. In general, the degree of ring fluorination correlates with ease of nucleophilic displacement. It should be mentioned that in the case of

Scheme 6[a]



[a] Reagents: (a) Lawesson's reagent, 1,4-dioxane, Δ, 75−97%.

the trifluorophenyl substrate **40c**, a significant amount of side product resulting from substitution at the 3-position is obtained in some instances. Fortunately, this byproduct could be readily separated by chromatography over silica gel. The racemic starting materials **40** could also be readily separated into their individual enantiomers via preparative chiral HPLC. In this way, the desired (*R*)-enantiomers **42a**−**c** were readily isolated in enantiomerically enriched form. These intermediates could be then be reacted with amines as before to generate the targeted chiral nonracemic analogues **43**. Alternatively, the racemic amine adducts **41** could also be resolved by preparative chiral HPLC to give the desired compounds **43**. It is apparent that compound **43** is also potentially an intermediate suitable for further elaboration to alternative C-rings.

The substituted phenylisoxazoline analogues described above are amenable to further elaboration. For example, the carboxamide **44** can be readily converted to the corresponding thioamide derivative **45**, employing Lawesson's reagent (see Scheme 6). In an analogous manner the morpholine congener **38** was elaborated to the thioamide **46**.

Results and Discussion

The synthesized phenylisoxazoline analogues were submitted for a preliminary assessment of their antibacterial activity. In a gratifying result, many of the compounds exhibited potent in vitro antibacterial activity (see Table 2). The simple racemic 4-bromophenylisoxazoline intermediate **9** was inactive at the highest level tested (16 μg/mL). However, the elaborated congener bearing an appended tropone C-ring (**12**) exhibited good in vitro activity against relevant Gram-positive bacteria. Like the oxazolidinones, compound **12** was essentially devoid of activity against the Gram-negative bacterium *Escherichia coli* (MIC > 16 μg/mL). Overall, the isoxazoline **12** was approximately 2- to 4-fold less active than the corresponding oxazolidinone congener (vis-à-vis **2**, Table 1) against Gram-positive organisms. Nevertheless, the antibacterial activity levels displayed by **12** prompted an expanded evaluation of the phenylisoxazoline class.

Additional C-ring appendages previously found to impart good levels of antibacterial activity to the phenyloxazolidinone pharmacophore were adapted to the phenylisoxazoline template. Racemic C−C linked tetrahydropyridine derivatives such as **15**−**17** exhibited good in vitro activity. As expected, the corresponding achiral phenylisoxazole analogue **20** was inactive at the highest levels tested. This suggests that, like the oxazolidinones, a C-5 stereogenic center of appropriate absolute configuration is essential for antibacterial activity. This was confirmed by testing the (*R*)- and (*S*)-enantiomers **25** and **26**, respectively. Compound **25** displayed potent in vitro antibacterial activity, while **26** was inactive at the highest concentration examined. In summary, the required (*R*) absolute configuration at C-5 mimics the stereochemical situation in the corresponding oxazolidinone series.

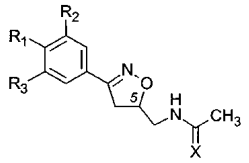
The spectrum of activity of compound **25** primarily encompasses aerobic Gram-positive bacteria. The observed level of activity was again approximately 2- to 4-fold less active than that of the corresponding oxazolidinone (data not shown). Unfortunately, the level of in vitro activity against the clinically significant fastidious Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis* remained poor with MICs greater than 16 and 8 μg/mL, respectively (corresponding oxazolidinone MICs of 4 and 2 μg/mL, respectively). A similar activity pattern was noted for the 4-pyridyl analogue **47**. The reduced level of Gram-negative activity seen for **25**, **47**, and the isoxazolines in general is an apparent limitation of this structural class.

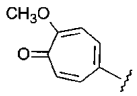
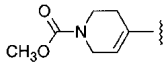
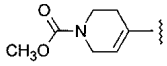
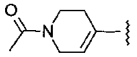
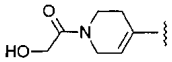
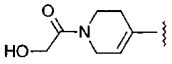
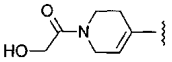
An examination of the data in Table 2 reveals that many of the N−C linked C-ring derivatives also display good in vitro antibacterial activity. Not surprisingly, the (*R*) absolute configuration at C-5 of the isoxazoline ring remains a requirement (**38** vis-à-vis **39** and **51** vis-à-vis **52**). The morpholinyl analogue (**48**) corresponding to linezolid (**1**) exhibited activity approaching that of its progenitor, with the exception of significantly weaker activity against *H. influenzae* and *M. catarrhalis*. Again, it is interesting to note the importance of the C-ring. The starting fluorinated phenylisoxazoline precursor **42b**, used to make **48** and many of the other N−C linked C-ring analogues, was devoid of antibacterial activity at the highest level tested.

One phenylisoxazoline analogue in the N−C linked series with respectable in vitro activity against *H. influenzae* (MIC = 8 μg/mL) was the piperazinyl difluorophenyl derivative **53**. Compound **53** also exhibited linezolid-like MICs against *S. aureus* and *S. pneumoniae*. Interestingly, the piperazinyl difluorophenyloxazolidinone corresponding to **53** was shown to be inactive against *S. aureus* at the highest level tested (unpublished archival data). This result apparently reflects the very different electronic character of the isoxazoline and oxazolidinone A-ring systems.[23]

A wide range of analogues bearing N−C linked azole C-rings were also prepared and evaluated. As shown in Table 2, pyrrolidin-1-yl (**55**), pyrrol-1-yl (**56**), and imidazol-1-yl (**57**) derivatives displayed interesting levels of Gram-positive antibacterial activity. In contrast, the 1,2,4-triazol-1-yl (**58**) and pyrazol-1-yl (**59**) congeners were only weakly active. In all cases a significant boost in antibacterial potency could be realized by strategically appending a cyano group to the various heterocyclic C-ring systems. For example, compounds **60** and **61**

Table 2. In Vitro Antibacterial Activity of Selected Phenylisoxazoline Analogues



Compound	R_1	X	R_2	R_3	C-5 Config.	Minimum Inhibitory Concentration (μg/mL)							
						S.a.[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.i.*[f]	*M.c.*[g]	*E.c.*[h]
9	Br	O	H	H	(±)-	>16	>16	>16	>16	>16	>16	>16	>16
12		O	H	H	(±)-	4	4	2	0.5	4	>16	16	>16
16		O	H	H	(±)-	16	16	8	4	16	>16	>16	>16
20		O	H	H	dehydro	>16	>16	>16	>16	>16	>16	>16	>16
17		O	H	H	(±)-	8	8	4	2	8	>16	>16	>16
15		O	H	H	(±)-	4	4	4	2	8	>16	>16	>16
25		O	H	H	(*R*)-	2	2	1	0.5	4	>16	8	>16
26		O	H	H	(*S*)-	>16	>16	>16	>16	>16	>16	>16	>16
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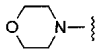
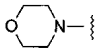
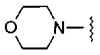
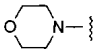
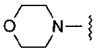
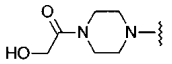
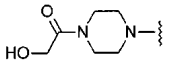
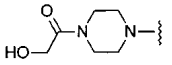
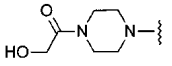
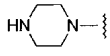
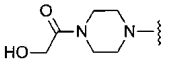
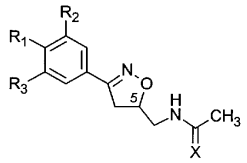
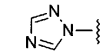
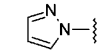
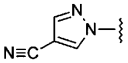
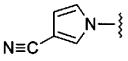
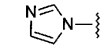
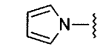
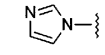
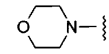
36		O	F	Cl	(±)-	8	8	8	4	16	>16	>16	>16
37		O	F	F	(±)-	8	8	4	2	8	>16	16	>16
38		O	F	F	(*R*)-	4	4	2	1	4	>16	8	>16
39		O	F	F	(*S*)-	>16	>16	>16	>16	>16	>16	>16	>16
48		O	H	F	(*R*)-	4	4	2	1	8	>16	16	>16
42b	F	O	H	F	(*R*)-	>16	>16	>16	>16	>16	>16	>16	>16
49		O	H	H	(±)-	16	8	4	4	16	>16	>16	>16
50		O	H	F	(±)-	8	8	4	2	8	>16	16	>16
51		O	H	F	(*R*)-	4	4	1	1	4	>16	8	>16
52		O	H	F	(*S*)-	>16	>16	>16	>16	>16	>16	>16	>16
53		O	F	F	(*R*)-	4	4	0.5	0.25	4	8	8	>16
54		O	F	F	(*R*)-	2	1	0.5	0.5	2	16	8	>16
55		O	H	F	(*R*)-	4	4	4	2	8	>16	>16	>16
56		O	H	F	(*R*)-	2	2	0.5	0.5	4	>16	16	>16
57		O	H	F	(*R*)-	2	2	1	1	4	>16	16	>16

Table 2. (Continued)



Compound	R_1	X	R_2	R_3	C-5 Config.	Minimum Inhibitory Concentration[i] (μg/mL)							
						S.a.[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.i.*[f]	*M.c.*[g]	*E.c.*[h]
58		O	H	F	(*R*)-	>16	16	8	4	>16	>16	>16	>16
59		O	H	F	(*R*)-	16	16	4	4	16	>16	>16	>16
60		O	H	F	(*R*)-	2	2	1	0.5	4	16	8	>16
61		O	H	F	(*R*)-	1	0.5	0.25	<0.125	1	16	4	>16
44		O	F	F	(*R*)-	8	4	2	2	8	>16	>16	>16
62		S	H	F	(*R*)-	1	1	0.5	0.5	1	>16	4	>16
45		S	F	F	(*R*)-	4	4	2	2	8	>16	>16	>16
46		S	F	F	(*R*)-	1	1	0.25	0.25	1	16	2	>16
Linezolid (**1**)						2-4	2-4	1	0.5-1	2-4	8-16	4-8	>32

[a] Methicillin-susceptible *Staphylococcus aureus* UC9213. [b] Methicillin-, ciprofloxacin-, rifampin-, imipenem-resistant *S. aureus* UC12673. [c] Methicillin-resistant *Staphylococcus epidermidis* UC12084. [d] Penicillin-susceptible *Streptococcus pneumoniae* UC9912. [e] *Enterococcus faecalis* UC9217. [f] Ampicillin-resistant *Haemophilus influenzae* UC30063. [g] *Moraxella catarrhalis* UC30610. [h] *E. coli* UC6674. [i] Minimum inhibitory concentration: lowest concentration of drug (μg/mL) that inhibits visible growth of the organism.

were found to be dramatically more active in vitro than their unsubstituted relatives.

The B-ring phenyl substituents do play a significant role in the antibacterial potency of these isoxazoline analogues. In many cases, increasing the level of ring fluorination in the positions flanking the C-ring imparts enhanced activity to this series (e.g., **50** vis-à-vis **49**, **54** vis-à-vis **51**), a trend reminiscent of the oxazolidinone situation.[24] However, there are exceptions, as can be readily seen by comparing the imidazolyl congeners **57** and **44**. It is interesting to note that the chlorofluorophenyl analogue **36b** also shows appreciable levels of in vitro antibacterial activity.

Conversion of the C-5 side chain carboxamide moiety to the corresponding thioamide was found to provide compounds with comparable or enhanced intrinsic antibacterial activity (**46** and **62** vis-à-vis **38** and **56**, respectively).

Selected phenylisoxazoline analogues were evaluated for in vivo efficacy in a lethal systemic mouse infection model, employing *S. aureus* UC9213 as the infectious organism (see Table 3). Some of the orally administered isoxazolines demonstrated efficacy comparable to that of their oxazolidinone comparators. The tropone derivative **12** exhibited good activity, especially when considering that this material was racemic and that, in principle, the individual (*R*)-enantiomer would be twice as efficacious. Efficacy closely approaching that of the oxazolidinone comparator was observed for the tetrahydropyridine analogue **25**. It is interesting to note that the morpholine C-ring congeners **38** and **48** provided disappointing results in this in vivo study, despite apparently acceptable metabolic stability and pharmacokinetic profiles (vide infra). The related thioamide analogue **46** also fared poorly in this test, despite its potent in vitro antibacterial profile, perhaps because of reduced water solubility. In contrast, the piperazine derivative **51** displayed oral efficacy similar to that of the comparator. Perhaps the most interesting isoxazoline in this preliminary panel of analogues was the difluorophenylisoxazoline **54**. Compound **54** demonstrated in vivo efficacy against *S. aureus* directly comparable to that of the clinical comparator linezolid.

Table 3. In Vivo Efficacy of Selected Phenylisoxazoline Analogues in a Systemic Mouse Infection Model

compound	administration route	*S. aureus* UC9213 ED_{50} [a] (mg/kg)
12	po	15.4 (E 6.3)
25	po	6.0 (E 4.0)
38	po	>20.0 (E 6.2)
48	po	16.5 (E 6.2)
51	po	9.1 (E 6.2)
54	po	5.0 (L 4.4)
46	po	>20.0 (L 2.9)

[a] ED_{50} is the amount of drug required to cure 50% of infected mice. Phenylisoxazoline analogues were administered orally. Orally administered control antibiotic is in parentheses: E = eperezolid; L = linezolid.

Phenylisoxazolines **48** and **51** were evaluated for metabolic stability via in vitro rat and human hepatocyte assays (Table 4). Both isoxazoline analogues exhibited stability similar to that of the oxazolidinone standards, with the piperazine derivatives in both series having the edge in stability.

The single-dose pharmacokinetic performance of phenylisoxazolines **48** and **51** in male Sprague−Dawley rats

Table 4. Hepatocyte Stability Studies on Selected Phenylisoxazoline Antibacterial Agents

compound	UV λ_{max}	% remaining at 40 min (rat)[a]	% remaining at 40 min (human)[b]
48	283	87	100
51	283	100	101
linezolid	250	97	*c*
eperezolid	250	102	*c*

[a] Rat 5E6 cells/mL at 50 μM compound concentration. [b] Human 5E6 cells/mL at 25 μM compound concentration. [c] Not determined.

is summarized in Table 5. HPLC−UV methods that utilized protein precipitation sample preparation procedures were used for the specific determination of the intact compounds in plasma samples. In general, the two isoxazolines have very good oral bioavailability, with the morpholine analogue **48** exhibiting apparent enhanced absorption presumably due to nonlinear pharmacokinetics. The isoxazolines do appear to be cleared more readily, in particular the piperazine congener **51**.

Compound **48** was investigated to evaluate its capacity to inhibit the catalytic activity of the major drug metabolizing hepatic cytochrome P-450 enzymes (CYP1A2, CYP2C9, CYP2D6, and CYP3A4) found in humans (see Table 6). It was anticipated that this information would provide a rational means to assess the potential for **48** and the phenylisoxazoline class to be involved in clinically relevant drug−drug interactions in vivo. Phenylisoxazoline **48** exhibited no appreciable inhibition of key cytochrome P-450 enzymes at therapeutically relevant concentrations.

Conclusions

In summary, we have described the genesis and preparation of antibacterially active phenylisoxazoline derivatives. The piperazine analogue **54**, in particular, exhibited a balance of in vitro activity and in vivo efficacy comparable to that of the phenyloxazolidinone clinical comparator linezolid. Taken together with earlier work on other oxazolidinone bioisosteric replacements, this research suggests that the premise (vide supra) that a suitable A-ring surrogate requires (1) an sp^2 center (or at least substantial sp^2 character through resonance delocalization or tautomerism) adjacent to the phenyl B-ring, (2) a strategically located ring oxygen, and (3) a chiral carbon of appropriate absolute configuration bearing the essential acylaminomethyl side chain has merit as a working model.[25] It is also noteworthy that the carbonyl moiety of the parent oxazolidinone A-ring is not a structural feature required for antibacterial activity. While this preliminary series of phenylisoxazolines was generally somewhat less active than the corresponding phenyloxazolidinones, especially when considering the fastidious Gram-negative organisms *H. influenzae* and *M. catarrhalis*, the possibility remains that more divergent structural modifications might improve the antibacterial activity level and/or spectrum of these agents. In connection with this notion, we point out the differential electronic and steric character of the isoxazoline ring relative to its oxazolidinone counterpart and suggest that further study of these agents is warranted.

Experimental Section

General. Melting points were determined on a Fisher-Johns or a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Bruker AM-300 or ARX-400 spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Coupling constants (J) are reported in hertz (Hz). Mass spectra and combustion analyses were obtained by the Structural, Analytical and Medicinal Chemistry Department of Pharmacia. All moisture-sensitive reactions were conducted under a nitrogen atmosphere in commercially available anhydrous solvents in oven- or flame-dried glassware. Unless specified, all commercially available solvents and reagents were used without further purification. Solvent removal was accomplished by rotary evaporation at house vacuum (40−50 Torr). Chromatography was carried out on EM Science 230−400 mesh ASTM silica gel. Silica gel plates (Analtech silica gel GF, 1 in. × 3 in., 250 μm thickness) were utilized for TLC analyses. Elemental analyses were within ±0.4% of calculated values.

4,5-Dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (8). To a flask containing 4-bromobenzaldehyde (1.00 g, 5.40 mmol) and hydroxylamine hydrochloride (410 mg, 5.94 mmol) in ethanol (20 mL) and water (40 mL) at 4 °C was added NaOH (50% (w/w), 1.08 mL). The reaction mixture was stirred for 3 h, neutralized to pH 6.0, and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with hexane/ethyl acetate (98/2). The appropriate fractions were combined (R_f = 0.43, TLC, hexane/ethyl acetate, 75/25) and concentrated in vacuo to give 1.04 g (96%) of 4-bromobenzaldoxime as a white crystalline solid with the following characteristics: mp 114−115 °C; IR (mull) 3304, 3265, 1589, 1490, 1398, 1318, 1069, 1008, 973, 954, 935, 873, 830, 819, 694 cm^{-1}; MS (EI) *m/z* (rel intensity) 199 (M^+, 99), 201 (99), 183 (21), 158 (54), 157 (34), 156 (57), 155 (33), 102 (38), 76 (24), 75 (34); HRMS (EI) calcd for C_7H_6BrNO 198.9633, found 198.9637. Anal. (C_7H_6BrNO) C, H, N.

To a flame-dried flask containing 4-bromobenzaldoxime (950 mg, 4.75 mmol) in DMF (20 mL) was added *N*-chlorosuccinimide (630 mg, 4.75 mmol) slowly at 0 °C. The reaction mixture was warmed to 50 °C for 1 h, poured over ice, diluted with H_2O (50 mL), and extracted with EtOAc (100 mL). The organic phase was washed with H_2O (2 × 50 mL) and saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with hexane/ethyl acetate (90/10). The appropriate fractions were combined (R_f = 0.62, TLC, hexane/ethyl acetate, 75/25) and concentrated in vacuo to give 630 mg (57%) of 4-bromo-*N*-hydroxybenzenecarboximidoyl chloride (**7**) as white crystals. To a flask containing 4-bromo-*N*-hydroxybenzenecarboximidoyl chloride (610 mg, 2.60 mmol) and allyl alcohol (0.14 mL, 2.08 mmol) in methylene chloride (30 mL) at 0 °C under an inert atmosphere was added triethylamine (0.36 mL, 2.60 mmol). The reaction mixture was slowly warmed to ambient temperature, stirred for 20 h, quenched with water (30 mL), and extracted with methylene chloride (2 × 50 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with chloroform/methanol (99/1). The appropriate fractions were combined (R_f = 0.06, TLC, hexane/ethyl acetate, 75/25) and concentrated in vacuo to give 529 mg (99%) of the title compound as a white crystalline solid with the following characteristics: mp 104−105 °C; IR (mull) 3322, 1593, 1431, 1401, 1352, 1101, 1054, 1043, 1037, 1012, 924, 900, 828, 809, 629 cm^{-1}; MS (EI) *m/z* (rel intensity) 255 (M^+, 69), 257 (69), 255 (69), 226 (95), 224 (99), 198 (77), 196 (79), 157 (57), 155 (58), 76 (47), 75 (45). Anal. ($C_{10}H_{10}BrNO_2$) C, H, N.

***N*-[[4,5-Dihydro-3-[4-bromophenyl]-5-isoxazolyl]methyl]-acetamide (9).** To a flame-dried flask containing (±)-4,5-dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (**8**, 520 mg, 2.03 mmol) in methylene chloride (20 mL) at 0 °C under an inert atmosphere was added triethylamine (0.43 mL, 3.05 mmol) and methanesulfonyl chloride (0.21 mL, 2.13 mmol). The reaction mixture was slowly warmed to ambient temperature, stirred for 3 h, and quenched with water (25 mL). The

Table 5. Pharmacokinetic Parameters of Selected Phenylisoxazoline Analogues in Male Sprague−Dawley Rats

compound	route	dose (mg/kg)	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}\beta$ [a] (h)	V_{ss} (L/kg)	CL/*F* (mL/min/kg)	*F* [b] (%)
48	iv	8.98	17.7 ± 1.0	*c*	0.47 ± 0.06	0.60 ± 0.03	12.4 ± 1.4	100
	po	48.9	12.2 ± 3.9	3.2 ± 1.4	0.60 ± 0.33	*d*	8.6 ± 0.6	143 ± 18
51	iv	10.1	17.7 ± 1.0	*c*	0.61 ± 0.17	0.95 ± 0.13	26.2 ± 0.7	100
	po	49.4	6.17 ± 0.9	2.5 ± 1.3	0.70 ± 0.55	*d*	30.8 ± 2.4	86 ± 7
linezolid[e]	iv	10	*c*	*c*	0.95 ± 0.08	0.72 ± 0.02	10.5 ± 1.1	100
	po	25	15.8 ± 3.3	0.31 ± 0.17	1.05 ± 0.30	*d*	*c*	109
eperezolid[e]	iv	10	20.78 ± 0.72	*c*	0.96 ± 0.14	0.99 ± 0.13	24.95 ± 2.03	100
	po	25	2.26 ± 0.59	1.33 ± 0.58	*c*	*d*	*c*	56

[a] Harmonic mean apparent terminal disposition half-life. [b] Absolute oral bioavailability. [c] Not reported. [d] Not calculated. [e] Comparative archival data.

Table 6. Inhibitory Effect of Phenylisoxazoline **48** on Specific CYP Enzyme Activities in CDNA Expressed CYP Microsomes

	% of control of P-450 marker substrate metabolism, mean ± SD[a]	
CYP enzyme	**48** [10 μM]	**48** [100 μM]
CYP1A2	100.4 ± 3.3	101.7 ± 6.6
CYP2C9	92.1 ± 5.1	95.8 ± 1.8
CYP2D6	100.9 ± 12.4	103.1 ± 16.7
CYP3A4	88.9 ± 1.9	92.1 ± 12.5

[a] Values are the mean ± SD of triplicate determinations. Incubation conditions and concentrations of CYP marker substrates are as described under Experimental Section.

organic phase was separated, washed with saturated $NaHCO_3$ (25 mL) and saline solution (25 mL), dried over sodium sulfate, and concentrated in vacuo to give crude (±)-4,5-dihydro[3-(4-bromophenyl)-5-[[(methylsulfonyl)oxy]methyl]]isoxazole. The crude (±)-4,5-dihydro[3-(4-bromophenyl)-5-[[(methylsulfonyl)-oxy]methyl]]isoxazole (680 mg, 2.03 mmol) was dissolved in tetrahydrofuran (4 mL), 2-propanol (4 mL), and concentrated ammonium hydroxide (4 mL) in a thick-wall resealable vessel and heated to 100−110 °C for 15 h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (50 mL), washed with saline solution (20 mL), dried over sodium sulfate, and concentrated in vacuo to give crude (±)-4,5-dihydro[3-(4-bromophenyl)-5-(aminomethyl)]isoxazole. The crude (±)-4,5-dihydro[3-(4-bromophenyl)-5-(aminomethyl)]isoxazole (520 mg, 2.03 mmol) was dissolved in methylene chloride (15 mL) and cooled to 0 °C under an inert atmosphere. Pyridine (0.51 mL, 6.09 mmol) and acetic anhydride (0.24 mL, 2.54 mmol) were added to the cooled solution, and the mixture was stirred for 20 h at ambient temperature. The reaction mixture was concentrated in vacuo, diluted with methylene chloride (50 mL), washed with saline solution (25 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with chloroform/methanol (98/2). The appropriate fractions were combined (R_f = 0.13, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 550 mg (92%) of the title compound as a white crystallline solid with the following characteristics: mp 198−199 °C; IR (mull) 3282, 3083, 1640, 1591, 1559, 1489, 1431, 1399, 1352, 1297, 1076, 1010, 906, 826, 806 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 297 (MH^+, 99), 451 (11), 300 (12), 299 (99), 298 (13), 297 (99), 239 (12), 237 (11), 133 (21), 60 (10), 30 (11); HRMS (FAB) calcd for $C_{12}H_{13}BrN_2O_2$ + H1 297.0239, found 297.0237. Anal. ($C_{12}H_{13}BrN_2O_2$) C, H, N.

Alternative Synthesis of (±)-*N*-[[4,5-Dihydro-3-[4-bromophenyl]-5-isoxazolyl]methyl]acetamide (9). To a flame-dried flask containing 4-bromo-*N*-hydroxybenzenecarboximidoyl chloride (**7**, 500 mg, 2.13 mmol) and allyl acetamide (210 mg, 2.13 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C was added Et_3N (300 μL, 2.13 mmol). The reaction mixture was warmed to ambient temperature, and the reaction was quenched with H_2O (50 mL). The organic phase was washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (99/1). The appropriate fractions were combined (R_f = 0.35, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 433 mg (69%) of the title compound as a white solid.

***N*-[[4,5-Dihydro-3-[4-(4-methoxy-5-oxo-1,3,6-cycloheptatrien-1-yl)phenyl]-5-isoxazolyl]methyl]acetamide (12).** To a flame-dried flask containing a prestirred slurry of 1-methyl-2-pyrrolidinone (5 mL), tris(dibenzylideneacetone)-dipalladium (60 mg, 0.07 mmol), and tri(2-furyl)phosphine (30 mg, 0.13 mmol) under an inert atmosphere was added (±)-*N*-[[4,5-dihydro-3-[4-bromophenyl]-5-isoxazolyl]methyl]-acetamide (193 mg, 0.65 mmol) and 2-methoxy-5-(trimethylstannyl)tropone[12] in 1-methyl-2-pyrrolidinone (5 mL), and the mixture was heated to 90 °C for 12 h. The reaction mixture was diluted with ethyl acetate (100 mL) and water (50 mL). The organic phase was separated, and the aqueous phase was extracted with methylene chloride (4 × 50 mL). The organic extracts were combined, dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (98/2). The appropriate fractions were combined (R_f = 0.10, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 65 mg (28%) of the title compound as a pale-yellow solid with the following characteristics: mp >230 °C; IR (mull) 3292, 3078, 1639, 1627, 1586, 1556, 1514, 1497, 1406, 1286, 1252, 1121, 1114, 911, 827 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 353 (MH^+, 99), 355 (5), 354 (26), 353 (99), 352 (13), 280 (7), 167 (7), 133 (7), 121 (8), 103 (11), 91 (6); HRMS (FAB) calcd for $C_{20}H_{20}N_2O_4$ + H1 353.1501, found 353.1516. Anal. ($C_{20}H_{20}N_2O_4$·0.30H_2O) C, H, N.

***tert*-Butyl 4-[4-[5-[(Acetylamino)methyl]-4,5-dihydro-3-isoxazolyl]phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate (14).** To a flame-dried flask containing 1,4-dioxane (15 mL), dichlorobis(triphenylphosphine)palladium(II) (50 mg, 0.07 mmol), and (±)-*N*-[[4,5-dihydro-3-[4-bromophenyl]-5-isoxazolyl]methyl]acetamide (**9**, 390 mg, 1.31 mmol) under an inert atmosphere was added hexamethylditin (470 mg, 1.44 mmol), and the mixture was heated to 100 °C for 8 h. The reaction mixture was concentrated in vacuo and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with chloroform/acetonitrile (94/6). The appropriate fractions were combined (R_f = 0.46, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 427 mg (86%) of **10** as a white foam. To a flame-dried flask containing a prestirred slurry of 1-methyl-2-pyrrolidinone (20 mL), tris(dibenzylideneacetone)dipalladium (18 mg, 0.02 mmol), and triphenylarsine (24 mg, 0.08 mmol) under an inert atmosphere was added **10** (412 mg, 1.08 mmol) and 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2*H*)-pyridinecarboxylic acid 1,1-dimethylethyl ester (**13**, 320 mg, 0.98 mmol), and the mixture was stirred for 20 h. The reaction mixture was diluted with ethyl acetate (100 mL) and water (50 mL). The organic phase was separated, extracted with water (5 × 50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with methylene chloride/methanol (99/1). The appropriate fractions were combined (R_f = 0.37, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 270 mg (69%) of the title compound as a pale-yellow solid with the following characteristics: mp 155−160 °C dec; IR (mull) 3299, 1691, 1642, 1561, 1417, 1344, 1320, 1296, 1284, 1242, 1174, 1120, 908, 813, 605 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 400 (MH^+, 99), 554 (11), 401 (25), 400 (99), 399 (23), 398 (27), 344 (51), 342 (63), 271 (15), 57 (95), 56 (16); HRMS (FAB) calcd for $C_{22}H_{29}N_3O_4$ + H1 400.2236, found 400.2242.

***N*-[[4,5-Dihydro-3-[4-[1,2,3,6-tetrahydro-1-(hydroxyacetyl)-4-pyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide (15).** To a flame-dried flask containing (±)-*tert*-butyl 4-[4-[5-[(acetylamino)methyl]-4,5-dihydro-3-isoxazolyl]phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate (**14**, 270 mg, 0.68 mmol) in methylene chloride (15 mL) at 0 °C was added trifluoroacetic acid (1.04 mL, 13.52 mmol). The reaction mixture was stirred 1 h at 0 °C and 2 h at ambient temperature. The reaction mixture was poured over a slurry of ice in saturated potassium carbonate (15 mL). The resulting aqueous phase was extracted with methylene chloride (5 × 25 mL). The extracts were dried over sodium sulfate concentrated in vacuo to give 189 mg (99%) of crude (±)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydropyridinyl]-phenyl]-5-isoxazolyl]methyl]acetamide as a pale-yellow solid: MS (ESI$^+$) for $C_{17}H_{21}N_3O_2$ *m*/*z* 300.2 $(M + H)^+$. To this material (185 mg, 0.62 mmol) in methylene chloride (20 mL) and triethylamine (0.17 mL, 1.24 mmol) was added acetoxyacetyl chloride (0.09 mL, 0.81 mmol) at 0 °C under an inert atmosphere. The reaction mixture was warmed to ambient temperature, stirred for 2 h, and concentrated in vacuo. The residue was dissolved in methanol (15 mL), and potassium carbonate (260 mg, 1.88 mmol) was added. The reaction mixture was stirred for 15 h, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (98/2). The appropriate fractions were combined (R_f = 0.10, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 72 mg (32%) of the title compound as a yellow solid with the following characteristics: mp 149−152 °C; IR (mull) 3438, 3301, 3080, 3041, 1653, 1638, 1553, 1414, 1320, 1286, 1237, 1110, 1052, 906, 814 cm^{-1}; MS (ESI$^+$) for $C_{19}H_{23}N_3O_4$ *m*/*z* 358.2 $(M + H)^+$; HRMS (EI) calcd for $C_{19}H_{23}N_3O_4$ 357.1689, found 357.1706. Anal. ($C_{19}H_{23}N_3O_4 \cdot 1.04H_2O$) C, H, N.

Methyl 4-[4-[5-[(Acetylamino)methyl]-4,5-dihydro-3-isoxazolyl]phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate (16). To a flask containing (±)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydropyridinyl]phenyl]-5-isoxazolyl]methyl]-acetamide (300 mg, 1.00 mmol) in acetone (7 mL), water (7 mL), and potassium carbonate (207 mg, 1.50 mmol) was added methyl chloroformate (0.09 mL, 1.10 mmol) at 0 °C under an inert atmosphere. The reaction mixture was warmed to ambient temperature, stirred for 15 h, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (98/2). The appropriate fractions were combined (R_f = 0.14, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 240 mg (67%) of the title compound as a pale-yellow solid with the following characteristics: mp 142−150 °C; IR (mull) 3299, 3083, 1705, 1644, 1556, 1401, 1341, 1288, 1238, 1213, 1117, 913, 817, 774, 605 cm^{-1}; MS (ESI$^-$) *m*/*z* 356.3 $(M - H)^-$; HRMS (EI) calcd for $C_{19}H_{23}N_3O_4$ 357.1689, found 357.1666. Anal. ($C_{19}H_{23}N_3O_4 \cdot 0.75H_2O$) C, H, N.

***N*-[[4,5-Dihydro-3-[4-[1,2,3,6-tetrahydro-1-(acetyl)-4-pyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide (17).** To a flask containing (±)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydropyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide (300 mg, 1.00 mmol) in methylene chloride (15 mL) and triethylamine (0.28 mL, 2.00 mmol) was added acetyl chloride (0.08 mL, 1.10 mmol) at 0 °C under an inert atmosphere. The reaction mixture was warmed to ambient temperature, stirred for 15 h, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (98/2). The appropriate fractions were combined (R_f = 0.18, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 248 mg (65%) of the title compound as a pale-yellow solid: mp 183 °C dec; IR (mull) 3303, 3082, 3042, 1657, 1638, 1590, 1553, 1434, 1322, 1294, 1281, 1236, 1027, 907, 813 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{23}N_3O_3$ 341.1739, found 341.1725. Anal. ($C_{19}H_{23}N_3O_3 \cdot 0.55H_2O$) C, H, N.

[3-(4-Bromophenyl)-5-(hydroxymethyl)]isoxazole (18). Following the similar procedure for the synthesis of (±)-4,5-dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (**8**) but substituting propargyl alcohol (220 μL, 3.84 mmol) for allyl alcohol, 817 mg (76%) of the title compound is recovered as white solid with the following characteristics: mp 114−116 °C; IR (mull) 3336, 3142, 1608, 1569, 1434, 1422, 1084, 1073, 1064, 1012, 958, 930, 827, 824, 805 cm^{-1}; MS (ESI$^+$) *m*/*z* 254.0 $(M + H)^+$. Anal. ($C_{10}H_8BrNO_2$) C, H, N.

***N*-[[3-[4-Bromophenyl]-5-isoxazolyl]methyl]acetamide (19).** Following the similar procedure for the synthesis of (±)-*N*-[[4,5-dihydro-3-[4-bromophenyl]-5-isoxazolyl]methyl]-acetamide (**9**) but substituting [3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (**18**, 650 mg, 2.56 mmol) afforded 586 mg (80%) of the title compound as a white solid: mp 171−172 °C; IR (mull) 3281, 3118, 1653, 1639, 1609, 1555, 1432, 1424, 1298, 1029, 1015, 952, 826, 606, 600 cm^{-1}; MS (ESI$^-$) *m*/*z* 293.0 $(M - H)^-$. Anal. ($C_{12}H_{11}BrN_2O_2$) C, H, N.

Methyl 4-[4-[5-[(Acetylamino)methyl]-3-isoxazolyl]phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate (20). To a flame-dried flask containing 1,4-dioxane (10 mL), dichlorobis-(triphenylphosphine)palladium(II) (60 mg, 0.08 mmol), and *N*-[[3-[4-bromophenyl]-5-isoxazolyl]methyl]acetamide (**19**, 450 mg, 1.52 mmol) under an inert atmosphere was added hexamethylditin (550 mg, 1.68 mmol), and the mixture was heated to 100 °C for 8 h. The reaction mixture was concentrated in vacuo and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/acetonitrile (94/6). The appropriate fractions were combined (R_f = 0.34, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give a quantitative yield of *N*-[[3-[4-(trimethylstannyl)phenyl]-5-isoxazolyl]methyl]acetamide. To a flame-dried flask containing a prestirred slurry of 1-methyl-2-pyrrolidinone (10 mL), tris-(dibenzylideneacetone)dipalladium (30 mg, 0.03 mmol), and triphenylarsine (40 mg, 0.12 mmol) under an inert atmosphere was added *N*-[[3-[4-(trimethylstannyl)phenyl]-5-isoxazolyl]-methyl]acetamide (580 mg, 1.52 mmol) and 3,6-dihydro-4-[[(trifluoromethyl)sulfonyl]oxy]-1(2*H*)-pyridinecarboxylic acid 1,1-dimethylethyl ester (**13**, 450 mg, 1.37 mmol), and the mixture was stirred for 20 h. The reaction mixture was diluted with ethyl acetate (100 mL) and water (50 mL). The organic phase was separated, extracted with water (5 × 50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with methylene chloride/methanol (99/1). The appropriate fractions were combined (R_f = 0.28, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 350 mg (65%) of *tert*-butyl-4-[4-[5-[(acetylamino)methyl]-3-isoxazolyl]phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate as a pale-yellow solid with the following characteristics: mp 117−120 °C; IR (mull) 3292, 1691, 1655, 1612, 1560, 1428, 1394, 1343, 1290, 1243, 1218, 1174, 1118, 1027, 810 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 398 (MH$^+$, 81), 399 (20), 398 (81), 397 (18), 396 (47), 356 (14), 342 (27), 340 (71), 296 (17), 57 (99), 41 (11); HRMS (FAB) calcd for $C_{22}H_{27}N_3O_4$ + H1 398.2079, found 398.2078. To a flame-dried flask containing this material (310 mg, 0.78 mmol) in methylene chloride (10 mL) at 0 °C was added trifluoroacetic acid (1.20 mL, 15.60 mmol). The reaction mixture was stirred for 1 h at 0 °C and for 2 h at ambient temperature. The reaction mixture was poured over a slurry of ice in saturated potassium carbonate (15 mL). The resulting aqueous phase was extracted with methylene chloride (3 × 50 mL). The extracts were dried over sodium sulfate concentrated in vacuo to give 176 mg (76%) of semipure *N*-[[3-[4-(1,2,3,6-tetrahydropyridinyl)phenyl]-5-isoxazolyl]methyl]acetamide as a brown oil. To a flask containing this material (170 mg, 0.57 mmol) in acetone (5 mL), water (5 mL), and potassium carbonate (120 mg, 0.86 mmol) was added methyl chloroformate (0.05 mL, 0.69 mmol) at 0 °C under an inert atmosphere. The reaction mixture was warmed to ambient temperature, stirred for 20 h, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (98/2). The appropriate fractions were combined (R_f = 0.31, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 60 mg (29%) of the title compound **20** as a pale-yellow solid: mp 120−124 °C; IR (mull) 3288, 3119, 3077, 1753, 1685, 1655, 1610, 1552, 1396, 1341, 1290, 1238, 1216, 1120, 951 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 356 (MH$^+$, 31), 372 (14), 371 (13), 370 (51), 356 (31), 355 (26), 354 (99), 156 (32), 92

(42), 43 (11), 30 (17); HRMS (FAB) calcd for $C_{19}H_{21}N_3O_4$ + H1 356.1610, found 356.1582. Anal. ($C_{19}H_{21}N_3O_4 \cdot 1.40H_2O$) C, H, N.

(*R*)-4,5-Dihydro[3-(4-bromophenyl)-5-(hydroxymethyl-)]isoxazole (21) and (*S*)-4,5-Dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (22). The racemate **8** (7 g) was resolved on a 5 cm × 50 cm Chiralpak AD column (Chiral Technologies) using the following conditions: 15 mL (300 mg) injections, 270 nm UV detection, 50 mL/min flow rate, 3/1 heptane/isopropyl alcohol (v/v) mobile phase. Each injection required a total run time of 120 min with two passes on the column required to obtain adequate resolution using a closed-loop recycling HPLC (EM ST140, R&S Technologies Inc.) and peak shaving for fraction collection. The (*R*)-isomer **21** was a white solid: mp 119−120 °C; $[\alpha]^{25}_D$ −137° (*c* 0.92, $CHCl_3$); IR (mull) 3393, 1594, 1442, 1401, 1108, 1076, 1052, 1010, 959, 934, 908, 823, 810, 627, 604 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 255 (M^+, 73), 257 (71), 255 (73), 226 (95), 224 (99), 198 (87), 196 (89), 157 (65), 155 (66), 76 (57), 75 (56). Anal. ($C_{10}H_{10}BrNO_2$) C, H, N. The (*S*)-isomer **22** was a white solid: mp 119−121 °C; $[\alpha]^{25}_D$ +138° (*c* 0.75, $CHCl_3$); IR (mull) 3392, 1594, 1442, 1401, 1108, 1076, 1052, 1010, 959, 933, 908, 824, 810, 627, 602 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 255 (M^+, 70), 257 (69), 255 (70), 226 (99), 224 (99), 198 (90), 196 (95), 157 (70), 155 (73), 76 (64), 75 (63). Anal. ($C_{10}H_{10}BrNO_2$) C, H, N.

Alternative Preparation of (*R*)-4,5-Dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (21). Following the procedure of Ukaji and co-workers,[21] a solution of allyl alcohol (0.23 g, 0.27 mL, 3.88 mmol) in $CHCl_3$ (7 mL) was cooled to 0 °C and treated with Et_2Zn (0.48 g, 3.92 mL of a 1 M solution in hexane, 3.92 mmol). After the mixture was stirred for 10 min more, $CHCl_3$ (7 mL) and (+)-diisopropyl tartrate (0.77 g, 0.69 mL, 3.29 mmol) were added and the mixture was then stirred at 0 °C. After 1 h, Et_2Zn (0.53 g, 4.26 mL of a 1 M solution in hexane, 4.26 mmol), $CHCl_3$ (7 mL), and 4-bromo-*N*-hydroxybenzenecarboximidoyl chloride (**7**, 1.00 g, 4.26 mmol) were added and the mixture was stirred at 0 °C. After 3 h, the reaction was quenched with saturated NH_4Cl, the mixture was transferred to a separatory funnel, and the mixture was extracted with $CHCl_3$ (2 × 25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in under reduced pressure to give a crude product. Chromatography over silica gel, eluting with 99/1 $CHCl_3$/MeOH, afforded, after concentration of appropriate fractions, 0.567 g of the title compound as a white solid with the following specific rotation: $[\alpha]^{25}_D$ −119° (*c* 0.98, $CHCl_3$).

(*R*)-*N*-[[4,5-Dihydro-3-[4-bromophenyl]-5-isoxazolyl]-methyl]acetamide (23). Following the similar procedure for the synthesis of (±)-*N*-[[4,5-dihydro-3-[4-bromophenyl]-5-isoxazolyl]methyl]acetamide (**9**), (*R*)-4,5-dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (**21**) was converted to the title compound: mp 219−220 °C; $[\alpha]^{25}_D$ −69° (*c* 0.99, $CHCl_3$); IR (mull) 3285, 1641, 1592, 1558, 1489, 1431, 1399, 1352, 1296, 1076, 1010, 906, 826, 806, 608 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 297 (MH^+, 95), 453 (9), 452 (2), 451 (10), 371 (3), 300 (3), 299 (99), 298 (4), 297 (95), 57 (7), 43 (7). Anal. ($C_{12}H_{13}BrN_2O_2$) C, H, N.

(*S*)-*N*-[[4,5-Dihydro-3-[4-bromophenyl]-5-isoxazolyl]-methyl]acetamide (24). Following the similar procedure for the synthesis of (±)-*N*-[[4,5-dihydro-3-[4-bromophenyl]-5-isoxazolyl]methyl]acetamide (**9**), (*S*)-4,5-dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (**22**) was converted to the title compound: mp 219−221 °C; $[\alpha]^{25}_D$ +71° (*c* 0.83, $CHCl_3$); IR (mull) 3285, 1641, 1591, 1558, 1489, 1431, 1399, 1352, 1296, 1076, 1010, 906, 826, 806, 608 cm^{-1}; MS (ESI^+) for $C_{12}H_{13}BrN_2O_2$ *m*/*z* 297 $(M + H)^+$. Anal. ($C_{12}H_{13}BrN_2O_2$) C, H, N.

(*R*)-*N*-[[4,5-Dihydro-3-[4-[1,2,3,6-tetrahydro-1-(hydroxyacetyl)-4-pyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide (25). Following the general procedure for (±)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydro-1-(hydroxyacetyl)-4-pyridinyl]-phenyl]-5-isoxazolyl]methyl]acetamide (**15**) but substituting (*R*)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydropyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide (280 mg, 0.94 mmol) for (±)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydropyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide, 105 mg (31%) of the title compound was recovered as a pale-yellow solid with the following characteristics: $[\alpha]^{25}_D$ = −54° (*c* 0.87, DMSO); IR (mull) 3408, 3304, 1653, 1630, 1554, 1445, 1413, 1319, 1286, 1234, 1108, 1052, 910, 816, 601 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 357 (M^+, 10), 298 (36), 296 (26), 285 (99), 241 (47), 198 (32), 183 (53), 128 (36), 115 (29), 73 (97), 56 (43); HRMS (EI) calcd for $C_{19}H_{23}N_3O_4$ 357.1689, found 357.1694. Anal. ($C_{19}H_{23}N_3O_4 \cdot 0.65H_2O$) C, H, N.

(*S*)-*N*-[[4,5-Dihydro-3-[4-[1,2,3,6-tetrahydro-1-(hydroxyacetyl)-4-pyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide (26). Following the general procedure for (±)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydro-1-(hydroxyacetyl)-4-pyridinyl]-phenyl]-5-isoxazolyl]methyl]acetamide (**15**) but substituting (*S*)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydropyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide (140 mg, 0.47 mmol) for (±)-*N*-[[4,5-dihydro-3-[4-[1,2,3,6-tetrahydropyridinyl]phenyl]-5-isoxazolyl]methyl]acetamide, 62 mg (37%) of the title compound was recovered as a pale-yellow solid: $[\alpha]^{25}_D$ = +54° (*c* 0.82, DMSO); IR (mull) 3402, 3305, 1653, 1631, 1554, 1444, 1413, 1320, 1286, 1234, 1108, 1052, 910, 816, 602 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 357 (M^+, 10), 298 (37), 296 (28), 285 (99), 283 (31), 241 (74), 198 (29), 183 (45), 128 (27), 73 (82), 56 (31); HRMS (EI) calcd for $C_{19}H_{23}N_3O_4$ 357.1689, found 357.1690. Anal. ($C_{19}H_{23}N_3O_4 \cdot 0.75H_2O$) C, H, N.

Ethyl 3,5-Difluoro-4-(4-morpholino)benzoate (29b). To a flame-dried flask containing ethyl 3,4,5-trifluorobenzoate (**28b**, 4.45 g, 21.80 mmol) in DMSO (100 mL) was added K_2HPO_4 (15.19 g, 87.20 mmol), and the mixture was heated to 75 °C for 15 h. The reaction mixture is diluted with ethyl acetate (100 mL), washed with H_2O (6 × 100 mL), washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with hexane/ethyl acetate (95/5). The appropriate fractions were combined (R_f = 0.53, TLC, hexane/ethyl acetate, 75/25) and concentrated in vacuo to give 5.19 g (88%) of the title compound as a clear colorless oil: IR (neat) 1721, 1511, 1450, 1433, 1381, 1369, 1319, 1264, 1240, 1220, 1211, 1119, 1026, 930, 767 cm^{-1}; MS (ESI^+) for $C_{13}H_{15}NO_3F_2$ *m*/*z* 272.2 $(M + H)^+$. Anal. Calcd for $C_{13}H_{15}F_2NO_3$: C, 57.56; H, 5.57; N, 5.16. Found: C, 57.33; H, 5.56; N, 5.12.

3-Fluoro-4-(4-morpholino)benzyl Alcohol (30a). A solution of methyl 3,4-difluorobenzoate (**28a**, 16.4 g, 95.2 mmol) in dry DMSO (25 mL) in a sealed tube (screw cap, O-ring, heavy wall) was heated to 95 °C for 20 h. The reaction mixture was cooled, diluted with dichloromethane (300 mL), and transferred to a separatory funnel. The organic layer was washed with water (2 × 200 mL) and brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation under reduced pressure to give a crude solid. Chromatography over silica gel, eluting with 5/1 hexane/ethyl acetate afforded, after concentration of appropriate fractions, 18.5 g (81%) of methyl 3-fluoro-4-(4-morpholino)-benzoate (**29a**) as a white solid: mp 89−90 °C. A solution of **29a** (3.35 g, 14.0 mmol) in dry THF (50 mL) was added dropwise to a slurry of lithium aluminum hydride (0.797 g, 21.0 mmol) in dry THF at 0 °C under a nitrogen atmosphere. When the addition was complete, the cooling bath was removed and the mixture was stirred at ambient temperature. After 16 h, TLC (2/1 hexane/ethyl acetate) revealed that the reaction was complete. The mixture was cooled to 0 °C, and the reaction was carefully quenched with H_2O (800 μL), 15% aqueous NaOH (800 μL), and H_2O (2.4 mL). After being stirred for 30 min, the mixture was diluted with ethyl acetate (100 mL), filtered through Celite (ethyl acetate wash), and concentrated under reduced pressure to give 3.0 g (100%) of the title compound as a white solid: mp 67−69 °C; MS (EI) for $C_{11}H_{14}FNO_2$ *m*/*z* 211 (M^+, 85), 153 (85), 69 (53), 60 (31), 57 (54), 55 (37), 45 (35), 44 (99), 43 (83), 42 (74); HRMS (EI) calcd for $C_{11}H_{14}FNO_2$ 211.1008, found 211.1011.

3-Fluoro-4-(4-morpholino)benzaldehyde (31a). To a flame-dried flask containing 4 Å sieves (235 mg, 500 mg/mmol) in CH_2Cl_2 (1 mL) was added *N*-methylmorpholine *N*-oxide (83

mg, 0.71 mmol), 3-fluoro-4-(4-morpholino)benzyl alcohol (**30a**, 100 mg, 0.47 mmol), and tetrapropylammonium perruthenate (TPAP) (7 mg, 0.02 mmol). The reaction mixture was stirred for 1 h, filtered through silica gel (70−230 mesh, 50 mL), concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 50 mL), eluting with hexane/ethyl acetate (85/15). The appropriate fractions were combined (R_f = 0.18, TLC, hexane/ethyl acetate, 75/25) and concentrated in vacuo to give 75 mg (77%) of the title compound as a white crystalline solid: mp 70−72 °C; IR (mull) 1684, 1614, 1569, 1514, 1445, 1260, 1244, 1124, 1116, 1046, 920, 878, 826, 746, 654 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 209 (M^+, 79), 210 (10), 209 (79), 208 (8), 152 (11), 151 (99), 150 (68), 122 (9), 95 (15), 75 (11), 57 (14); HRMS (EI) calcd for $C_{11}H_{12}FNO_2$ 209.0852, found 209.0855. Anal. ($C_{11}H_{12}FNO_2$) C, H, N.

3,5-Difluoro-4-(4-morpholino)benzaldehyde (31b). To a flame-dried flask containing ethyl 3,5-difluoro-4-(4-morpholino)benzoate (**29b**, 5.00 g, 18.43 mmol) in THF (40 mL) at −10 °C was added LAH (37 mL, 1 M in THF), slowly keeping the temperature less than 25 °C. The reaction mixture was cooled to 0 °C, stirred for 1 h, and quenched with H_2O (4 mL), NaOH (1.4 mL, 1 N), and H_2O (4.2 mL) slowly. The reaction mixture was diluted with ethyl acetate (100 mL), filtered through Celite, and concentrated in vacuo to give 4.13 g (98%) of semipure 3,5-difluoro-4-(4-morpholino)benzyl alcohol as a clear, pink oil. To a flame-dried flask containing 4 Å sieves (3.07 g, 500 mg/mmol) in CH_2Cl_2 (50 mL) was added *N*-methylmorpholine *N*-oxide (3.07 g, 26.17 mmol), 3,5-difluoro-4-(4-morpholino)benzyl alcohol (4.00 g, 17.45 mmol), and tetrapropylammonium perruthenate (TPAP) (310 mg, 0.87 mmol). The reaction mixture was stirred for 1.5 h, filtered through silica gel (70−230 mesh, 50 mL), concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with hexane/ethyl acetate (85/15). The appropriate fractions were combined (R_f = 0.43, TLC, hexane/ethyl acetate, 75/25) and concentrated in vacuo to give 3.27 g (83%) of the title compound as a white crystalline solid: mp 63−65 °C; IR (mull) 1694, 1683, 1612, 1568, 1514, 1400, 1393, 1312, 1303, 1265, 1231, 1112, 1047, 1021, 935 cm^{-1}; MS (ESI^+) *m*/*z* 228.2 $(M + H)^+$; HRMS (EI) calcd for $C_{11}H_{11}F_2NO_2$ 227.0758, found 227.0771. Anal. ($C_{11}H_{11}F_2NO_2$) C, H, N.

3-Fluoro-4-(4-morpholino)benzaldehydeoxime (32a). To a flask containing 3-fluoro-4-(4-morpholino)benzaldehyde (**31a**, 62 mg, 0.30 mmol) and hydroxylamine hydrochloride (23 mg, 0.33 mmol) in ethanol (5 mL) and ice (5 mL) at 4 °C was added NaOH (50% (w/w), 0.06 mL). The reaction mixture was stirred for 3 h, neutralized to pH 6.0, and extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 75 mL), eluting with hexane/ethyl acetate (90/10 to 75/25). The appropriate fractions were combined (R_f = 0.46, TLC, hexane/ethyl acetate, 50/505) and concentrated in vacuo to give 46 mg (69%) of the title compound as a tan solid. The following characteristics were noted: mp 159−161 °C; IR (mull) 3314, 1517, 1309, 1292, 1285, 1260, 1250, 1221, 1114, 1108, 976, 923, 852, 802, 647 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 224 (M^+, 74), 225 (10), 224 (74), 167 (10), 166 (99), 165 (9), 149 (8), 123 (29), 122 (12), 121 (8), 95 (10). Anal. ($C_{11}H_{13}FN_2O_2$) C, H, N.

3,5-Difluoro-4-(4-morpholino)benzaldehydeoxime (32b). To a flask containing 3,5-difluoro-4-(4-morpholino)benzaldehyde (**31b**, 3.10 g, 13.64 mmol) and hydroxylamine hydrochloride (1.04 g, 15.00 mmol) in ethanol (75 mL) and ice (50 mL) at 4 °C was added NaOH (50% (w/w), 2.73 mL). The reaction mixture was stirred for 2 h, neutralized to pH 6.0, and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, and concentrated in vacuo to give 3.27 g (99%) of semipure title compound as a pale-yellow solid: MS (ESI^+) *m*/*z* 243.1 $(M + H)^+$.

***N*-[[4,5-Dihydro-3-[3-chloro-5-fluoro-4-(4-morpholino)-phenyl]-5-isoxazolyl]methyl]acetamide (36).** To a flame-dried flask containing 3-fluoro-4-(4-morpholino)benzaldehydeoxime (**32a**, 750 mg, 3.34 mmol) in DMF (20 mL) was added *N*-chlorosuccinimide (1.34 g, 10.03 mmol) slowly at 0 °C. The reaction mixture was warmed to 50 °C for 4 h, poured over ice, diluted with H_2O (50 mL), and extracted with EtOAc (200 mL). The organic phase was washed with H_2O (6 × 50 mL) and saline solution (100 mL), dried over sodium sulfate, and concentrated in vacuo to give 980 mg (100%) of 3-chloro-5-fluoro-4-(4-morpholino)-*N*-hydroxybenzenecarboximidoyl chloride. To a flask containing this material (980 mg, 3.34 mmol) and allyl acetamide (330 mg, 3.34 mmol) in methylene chloride (30 mL) at 0 °C under an inert atmosphere was added triethylamine (0.51 mL, 3.67 mmol). The reaction mixture was slowly warmed to ambient temperature, stirred for 20 h, quenched with water (30 mL), and extracted with methylene chloride (3 × 50 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with chloroform/methanol (99.5/0.5). The appropriate fractions were combined (R_f = 0.45, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 430 mg (36%) of the title compound as a white solid: mp 121−124 °C; IR (mull) 3310, 1653, 1550, 1496, 1423, 1355, 1297, 1287, 1259, 1234, 1110, 944, 935, 908, 855 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 355 (M^+, 25), 355 (25), 285 (33), 284 (15), 283 (99), 256 (19), 225 (23), 198 (12), 183 (10), 182 (13), 73 (99); HRMS (EI) calcd for $C_{16}H_{19}ClFN_3O_3$ 355.1099, found 355.1093. Anal. ($C_{16}H_{19}ClFN_3O_3 \cdot 0.23H_2O$) C, H, N.

***N*-[[4,5-Dihydro-3-[3,5-difluoro-4-(4-morpholino)phenyl]-5-isoxazolyl]methyl]acetamide (37).** To a flame-dried flask containing 3,5-difluoro-4-(4-morpholino)benzaldehydeoxime (**32b**, 3.25 g, 13.42 mmol) in DMF (50 mL) was added *N*-chlorosuccinimide (2.24 g, 16.77 mmol) slowly at 0 °C. The reaction mixture was warmed to 50 °C for 4 h, poured over ice, diluted with H_2O (100 mL), and extracted with EtOAc (200 mL). The organic phase was washed with H_2O (6 × 50 mL) and saline solution (100 mL), dried over sodium sulfate, and concentrated in vacuo to give 3.71 g (100%) of 3,5-difluoro-4-(4-morpholino)-*N*-hydroxybenzenecarboximidoyl chloride. To a flask containing 3,5-difluoro-4-(4-morpholino)-*N*-hydroxybenzenecarboximidoyl chloride (3.71 g, 13.42 mmol) and allyl acetamide (1.33 g, 13.42 mmol) in methylene chloride (75 mL) at 0 °C under an inert atmosphere was added triethylamine (2.06 mL, 14.76 mmol). The reaction mixture was slowly warmed to ambient temperature, stirred for 20 h, quenched with water (100 mL), and extracted with methylene chloride (3 × 100 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 250 mL), eluting with chloroform/methanol (99/1). The appropriate fractions were combined (R_f = 0.30, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 1.64 g (36%) of the title compound as a white solid: mp 145−149 °C; IR (mull) 3292, 1651, 1556, 1516, 1435, 1301, 1261, 1236, 1111, 1043, 1022, 945, 900, 855, 605 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}F_2N_3O_3$ 339.1394, found 339.1386. Anal. ($C_{16}H_{19}F_2N_3O_3 \cdot 0.33H_2O$) C, H, N.

***(R)*-*N*-[[4,5-Dihydro-3-[3,5-difluoro-4-(4-morpholino)-phenyl]-5-isoxazolyl]methyl]acetamide (38) and (*S*)-*N*-[[4,5-Dihydro-3-[3,5-difluoro-4-(4-morpholino)phenyl]-5-isoxazolyl]methyl]acetamide (39).** (±)-*N*-[[4,5-Dihydro-3-[3,5-difluoro-4-(4-morpholino)phenyl]-5-isoxazolyl]methyl]-acetamide (**37**) was resolved by preparative chiral phase HPLC (5 cm × 50 cm Chiralpak AD column, Chiral Technologies) using the following conditions: 500 mg injections, 270 nm UV detection, 50 mL/min flow rate, 4/1 heptane/isopropyl alcohol (v/v) mobile phase. Each injection required a total run time of 80 min with one pass on the column required to obtain adequate resolution using a closed-loop recycling HPLC (EM ST140, R&S Technologies Inc.). The (*R*)-enantiomer (**38**) had the following characteristics: mp 153−155 °C; $[\alpha]^{25}_D$ −65° (*c* 0.94, DMSO); IR (mull) 3285, 1672, 1645, 1557, 1515, 1435, 1298, 1260, 1236, 1110, 1043, 1033, 1017, 944, 854 cm^{-1}; MS (ESI^+) *m*/*z* 340.3 $(M + H)^+$. Anal. ($C_{16}H_{19}F_2N_3O_3$) C, H, N. The (*S*)-enantiomer (**39**) had the following characteristics: mp

153−155 °C; $[\alpha]^{25}_D$ +65° (*c* 0.90, DMSO); IR (mull) 3285, 1672, 1645, 1556, 1515, 1434, 1260, 1236, 1111, 1043, 1033, 1017, 944, 899, 854 cm^{-1}; MS (ESI^+) *m/z* 340.3 $(M + H)^+$; HRMS (EI) calcd for $C_{16}H_{19}F_2N_3O_3$ 339.1394, found 339.1382. Anal. ($C_{16}H_{19}F_2N_3O_3 \cdot 0.30H_2O$) C, H, N.

***N*-[[4,5-Dihydro-3-[4-fluorophenyl]-5-isoxazolyl]methyl]-acetamide (40a).** To a flask containing 4-fluorobenzaldehyde (2.00 g, 16.12 mmol) and hydroxylamine hydrochloride (1.23 g, 5.94 mmol) in ethanol (30 mL) and ice (40 mL) at 4 °C was added NaOH (50% (w/w), 3.22 mL). The reaction mixture was stirred for 3 h, neutralized to pH 6.0, and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, and concentrated in vacuo to give a quantitative yield of 4-fluorobenzaldoxime as a white solid with the following characteristics: mp 85−86 °C; IR (mull) 3294, 3264, 3165, 3145, 3112, 3052, 3018, 1610, 1514, 1297, 1244, 972, 958, 881, 827 cm^{-1}; MS (ESI^+) *m/z* 140.1 $(M + H)^+$. Anal. Calcd for C_7H_6FNO: C, 60.43; H, 4.35; N, 10.07. Found: C, 60.25; H, 4.39; N, 9.98. To a flame-dried flask containing 4-fluorobenzaldoxime (1.00 g, 7.19 mmol) in DMF (100 mL) was added *N*-chlorosuccinimide (1.70 g, 12.73 mmol) slowly at 0 °C. The reaction mixture was warmed to 50 °C for 3 h, poured over ice, diluted with H_2O (100 mL), and extracted with EtOAc (150 mL). The organic phase was washed with H_2O (5 × 100 mL) and saline solution (100 mL), dried over sodium sulfate, and concentrated in vacuo to give a quantitative yield of 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride. To a flask containing 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (1.25 g, 7.19 mmol) and allyl acetamide (780 mg, 7.91 mmol) in methylene chloride (75 mL) at 0 °C under an inert atmosphere was added triethylamine (3.05 mL, 21.60 mmol). The reaction mixture was slowly warmed to ambient temperature, stirred for 20 h, quenched with water (100 mL), and extracted with methylene chloride (3 × 100 mL). The organic extracts were combined, washed with saline solution (50 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with chloroform/methanol (99/1). The appropriate fractions were combined (R_f = 0.26, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 386 mg (23%) of the title compound as a waxy solid: mp 167−168 °C; IR (mull) 3310, 1642, 1607, 1554, 1519, 1434, 1427, 1413, 1355, 1298, 1251, 915, 838, 800, 608 cm^{-1}; MS (ESI^+) *m/z* 237.1 $(M + H)^+$. Anal. Calcd for $C_{12}H_{13}FN_2O_2$: C, 61.01; H, 5.55; N, 11.86. Found: C, 60.97; H, 5.56; N, 11.81.

***N*-[[4,5-Dihydro-3-[3,4-difluorophenyl]-5-isoxazolyl]-methyl]acetamide (40b).** 3,4-Difluorobenzaldehyde (25 g, 176 mmol) was dissolved in 75 mL of 95% ethanol in a 500 mL one-neck round-bottom flask. The solution was treated successively with hydroxylamine hydrochloride (14.7 g, 211 mmol) in 14 mL of water and sodium hydroxide (10.6 g, 264 mmol) in 20 mL of water (exotherm). The reaction mixture was stirred over the weekend and was poured into 300 mL of ice, and the white solid was collected. The solid was washed with water, was dissolved in chloroform, and was dried over anhydrous magnesium sulfate. The dried organics were concentrated in vacuo to provide 24.5 g (89%) of 3,4-difluorobenzaldoxime as a white solid: mp 75−77 °C; IR (mull) 3333, 2294, 2242, 2043, 1911, 1523, 1436, 1329, 1290, 1214, 965, 956, 821, 817, 766 cm^{-1}; MS (EI) *m/z* (rel intensity) 157 (M^+, 4), 140 (9), 139 (99), 113 (8), 112 (22), 88 (11), 75 (6), 69 (6), 63 (6), 62 (6), 57 (11). Anal. Calcd for $C_7H_5F_2NO$: C, 53.51; H, 3.21; N, 8.91. Found: C, 53.23; H, 3.34; N, 8.82. Difluorobenzaldoxime (58.4 g, 372 mmol) was dissolved in 250 mL of dimethylformamide in a flame-dried 1000 mL three-neck round-bottom flask under nitrogen. The solution was treated with *N*-chlorosuccinimide (8 g, 59.9 mmol), and the reaction mixture was initiated by bubbling in 20 mL of the vapor from the headspace of a gallon of 12 N hydrochloric acid. The reaction mixture was allowed to exotherm to 40 °C and was maintained at that temperature via a water bath and the controlled addition of the remaining *N*-chlorosuccinimide (46.6 g, 350 mmol). The reaction mixture was stirred for 2 h at room temperature, was poured into 1 L of ice water, and was extracted with 3 × 300 mL of diethyl ether. The combined organics were washed with 4 × 250 mL of 50% saturated sodium chloride, were dried over anhydrous magnesium sulfate, and were concentrated in vacuo to give 68.8 g (96%) of 3,4-difluorobenzohydroximinoyl chloride as a pale-yellow solid. The 3,4-difluorobenzohydroximinoyl chloride (68.8 g, 359 mmol) was combined with N-allyl acetamide (33.8 g, 340 mmol) in 1300 mL of diethyl ether in a 2000 mL three-neck round-bottom flask under nitrogen equipped with a mechanical stirrer. The solution was treated dropwise with triethylamine (62.5 mL, 449 mmol) in 100 mL of diethyl ether (exotherm to gentle reflux), and the reaction mixture was stirred for 20 h at room temperature. The suspension was diluted with 750 mL of ethyl acetate and was washed with 2 × 500 mL of 50% saturated sodium chloride. The organics were dried over anhydrous magnesium sulfate and were concentrated in vacuo to a yellow pasty solid. The crude material was triturated with 250 mL of diethyl ether on the rotary evaporator at 40 °C until about 50 mL had distilled (no vacuum). The mixture was cooled and the solid was collected, washed with cold diethyl ether, and was dried to afford 71 g (82%) of the title compound as a fine white solid. An analytical sample was obtained via chromatography over silica gel (230−400 mesh), eluting with 3% methanol/dichloromethane: mp 136−137 °C; IR (mull) 3300, 1652, 1549, 1525, 1444, 1423, 1349, 1298, 1283, 1270, 1122, 929, 823, 779, 602 cm^{-1}; UV λ_{max} 261(11 800, 95% ethanol); MS (FAB) *m/z* (rel intensity) 255 (M + H, 99), 509 (14), 256 (14), 255 (99), 231 (9), 213 (15), 195 (15), 154 (41), 60 (5), 43 (6), 30 (5). Anal. ($C_{12}H_{12}F_2N_2O_2$) C, H, N.

***N*-[[3-(3,4,5-Trifluorophenyl)-4,5-dihydro-5-isoxazolyl]-methyl]acetamide (40c).** A mixture of 3,4,5-trifluorobenzaldehyde (3.0 g, 18.7 mmol) in 10 mL of 1/1 ethanol/water is cooled to 0 °C and then treated with hydroxylamine hydrochloride (1.43 g, 20.6 mmol) followed by 50% aqueous sodium hydroxide solution (4 mL) at a rate keeping the mixture at or below 20 °C. After 1.5 h, TLC analysis (2% CH_3OH/CH_2Cl_2) revealed the reaction to be complete. The solution is diluted with 10 mL of water and acidified to pH 6 by addition of concentrated HCl, resulting in a cloudy mixture. The mixture is extracted with EtOAc (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a quantitative yield of the oxime derivative as a white solid: mp 83−85 °C. A solution of the oxime derivative of step 1 (2.25 g, 12.8 mmol) in dry DMF (11 mL) is treated with *N*-chlorosuccinimide (1.72 g, 12.8 mmol) in several portions. An exotherm up to 60 °C is observed. Heating at 50 °C is maintained for 1 h, at which time TLC analysis (2% CH_3OH/CH_2Cl_2) indicated that the starting material is consumed. The mixture is diluted with EtOAc (40 mL), extracted with water (4 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude hydroximinoyl chloride derivative. The crude product is not purified further. A solution of the hydroximinoyl product of step 2 (2.68 g, 12.8 mmol) in dry CH_2Cl_2 (120 mL) is treated with *N*-allyl acetamide (1.27 g, 12.8 mmol), and the mixture is cooled to 0 °C. Triethylamine (1.3 g, 12.8 mmol) is added dropwise, and the mixture is allowed to warm to ambient temperature. After 2 h, TLC analysis (1% CH_3OH/CH_2Cl_2) revealed the reaction to be complete. The mixture is extracted with water (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 3.05 g (88%) of the title compound as a yellow solid. Recrystallization from 10% hexane/EtOAc gives 1.77 g (51%) of the title compound as a white solid with the following characteristics: mp 136−137 °C; IR (mull) 3336 (s), 2495 (w), 2288 (w), 1651 (s), 1623, 1585, 1546 (s), 1530 (s), 1441 (s), 1425, 1248, 1055, 1043 (s), 944, 756, cm^{-1}. Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$: C, 52.94; H, 4.07; N, 10.29. Found: C, 52.89; H, 4.13; N, 10.27.

***N*-[[4,5-Dihydro-3-[4-(4-morpholino)phenyl]-5-isoxazolyl]methyl]acetamide (41a, R_1 and R_2 = H, R_3R_4N = Morpholin-4-yl).** To a resealable tube containing (±)-*N*-[[4,5-dihydro-3-[4-fluorophenyl]-5-isoxazolyl]methyl]acetamide (**40a**, 340 mg, 1.44 mmol) in morpholine (1.27 mL, 14.39 mmol) was added potassium carbonate (250 mg, 1.80 mmol), and the mixture was heated to 140 °C for 30 h. The reaction mixture

was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (3 × 50 mL) and saline solution (50 mL). The organic phase was dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with methylene chloride/methanol (99/1). The appropriate fractions were combined (R_f = 0.31, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 201 mg (46%) of the title compound as a white solid with the following characteristics: mp 201−203 °C; IR (mull) 3303, 1649, 1610, 1550, 1522, 1425, 1293, 1268, 1247, 1234, 1124, 1113, 925, 906, 826 cm^{-1}; MS (ESI^+) *m*/*z* 304.1 $(M + H)^+$. Anal. ($C_{16}H_{21}N_3O_3$) C, H, N.

***N*-[[3-[3,5-Difluoro-4-(1-piperazinyl)phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (41c, R_1 and R_2 = F, R_3R_4N = Piperazin-1-yl).** A mixture of (±)-5-(acetamidomethyl)-3-(3,4,5-trifluorophenyl)isoxazoline (**40c**, 600 mg, 2.20 mmol), piperazine (1.90 g, 22.0 mmol), and dibasic potassium phosphate (1.15 g, 6.6 mmol) is slurred in dry DMSO (2.5 mL) and heated at 90 °C. After 60 h, the mixture is cooled to ambient temperature, at which point TLC analysis (8% CH_3OH/CH_2Cl_2) indicates that the starting material is consumed and two adducts formed. The waxy mixture is dissolved in water (40 mL), adjusted to pH 6 by addition of 1 N HCl, and extracted with EtOAc (3 × 30 mL) and CH_2Cl_2 (3 × 30 mL). The organic solutions are combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product is chromatographed over silica (radial chromatography, 4 mm plate), eluting with 2% CH_3OH/CH_2Cl_2 and 1% NH_4OH/5% CH_3OH/CH_2Cl_2 to give, after combination and concentration of appropriate fractions, 359 mg (48%) of the faster-eluting para isomer. Another run afforded 40% of the para isomer and 23% of the slower-eluting meta isomer. The title compound was obtained as a white solid with the following characteristics: mp 147−148 °C; IR (mull) 3298 (s), 2454 (w), 2222 (w), 1651 (s), 1556 (s), 1518 (s), 1442 (s), 1436 (s), 1298, 1247, 1238, 1140, 1024 (s), 942, 855 (s), cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}F_2N_4O_2$ 338.1554, found 338.1549. Anal. Calcd for $C_{16}H_{20}F_2N_4O_2$: C, 56.80; H, 5.96; N, 16.56. Found: C, 55.52; H, 5.98; N, 16.06.

(*R*)-5-Acetamidomethyl-3-(3,4-difluorophenyl)isoxazoline (42b) and (*S*)-5-Acetamidomethyl-3-(3,4-difluorophenyl)isoxazoline. The racemate **40b** (70 g) was resolved on a 5 cm × 50 cm Chiralpak AD column (Chiral Technologies) using the following conditions: 50 mL (500 mg) injections, 270 nm UV detection, 60 mL/min flow rate, 8/2/1.5 heptane/isopropyl alcohol/chloroform (v/v) mobile phase. Each injection required a total run time of 60 min with two passes on the column required to obtain adequate resolution using a closed-loop recycling HPLC (EM ST140, R&S Technologies Inc.) and peak shaving for fraction collection. The resolved (*R*)-enantiomer **42b** (33 g) was dissolved in 100 mL of dichloromethane in a 500 mL one-neck round-bottom flask. The solution was treated with 60 g of silica gel (230−400 mesh), and the mixture was concentrated to dryness. The plug was chromatographed over 650 g of silica gel (230−400 mesh), eluting with 5% methanol/dichloromethane and, after a 1000 mL forerun, collecting 50 mL fractions. Fractions 6−63 were combined and concentrated to provide 32 g of the title compound (*R*)-**42b** as an off-white solid: mp 125−126.5 °C; $[\alpha]^{25}_D$ −83° (*c* 0.97, DMSO); IR (mull) 3279, 2383, 2294, 2262, 2048, 1639, 1554, 1524, 1445, 1347, 1284, 1190, 826, 777, 629 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 255 (M + H, 99), 510 (4), 509 (15), 409 (5), 408 (4), 256 (14), 255 (99), 213 (9), 195 (8), 73 (2), 43 (3). Anal. ($C_{12}H_{12}F_2N_2O_2$) C, H, N. The resolved (*S*)-enantiomer (33 g) was dissolved in 100 mL of dichloromethane in a 500 mL one-neck round-bottom flask. The solution was treated with 60 g of silica gel (230−300 mesh), and the mixture was concentrated to dryness. The plug was chromatographed over 650 g of silica gel (230−400 mesh), eluting with 5% methanol/dichloromethane and, after a 1000 mL forerun, collecting 50 mL fractions. Fractions 6−63 were combined and concentrated to provide 32 g of the (*S*)-enantiomer as an off-white solid: mp 125−126.5 °C; $[\alpha]^{25}_D$ +85° (*c* 0.77, DMSO); IR (mull) 3279, 2384, 2294, 2262, 2049, 1639, 1554, 1524, 1445, 1348, 1284, 1190, 826, 777, 629 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 255 (M + H, 99), 510 (5), 509 (16), 409 (4), 256 (14), 255 (99), 231 (5), 213 (10), 195 (10), 154 (30), 43 (4). Anal. ($C_{12}H_{12}F_2N_2O_2$) C, H, N.

(−)-*N*-[[3-(3,4,5-Trifluorophenyl)-4,5-dihydro-5-isoxazolyl]methyl]acetamide (42c) and (*S*)-*N*-[[3-(3,4,5-Trifluorophenyl)-4,5-dihydro-5-isoxazolyl]methyl]acetamide. The racemate **40c** (5.94 g) was resolved on a 5 cm × 50 cm Chiralpak AD column (Chiral Technologies) using the following conditions: 40 mL (400 mg) injections, 270 nm UV detection, 60 mL/min flow rate, 8/2/1.5 heptane/isopropyl alcohol/chloroform (v/v) mobile phase. Each injection required a total run time of 50 min with two passes on the column required to obtain adequate resolution using a closed-loop recycling HPLC (EM ST140, R&S Technologies Inc.) and peak shaving for fraction collection. Another 16.9 g batch was resolved under the same conditions except that 10 mL (500 mg) injections were made and the flow rate was 50 mL/min. The separated enantiomers so obtained are further purified by column chromatography over silica gel, eluting with a gradient of 2−5% CH_2Cl_2/MeOH to give, after combination of appropriate fractions and concentration in vacuo, the separated enantiomers as white solids. The following characteristics were noted for the (*R*)-enantiomer **42c**: mp 132−133 °C; $[\alpha]^{25}_D$ −101° (*c* 0.97, DMSO); IR (mull) 3302, 2489 (w), 2262 (w), 1678 (s), 1666 (s), 1628 (s), 1581, 1548 (s), 1534 (s), 1439 (s), 1395, 1247, 1056, 1048 (s), 755, cm^{-1}. Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$: C, 52.94; H, 4.07; N, 10.29. Found: C, 52.81; H, 4.13; N, 10.24. The (*S*)-enantiomer had the following characteristics: mp 132−133 °C; $[\alpha]^{25}_D$ +100° (*c* 0.87, DMSO); ^1H NMR ($CDCl_3$, 400 MHz), identical to that of the (*R*)-enantiomer; IR (mull) 3302 (s), 2489 (w), 2262 (w), 1678 (s), 1666 (s), 1628 (s), 1582 (s), 1548 (s), 1534 (s), 1439 (s), 1422, 1395, 1247, 1056 (s), 1048 (s), cm^{-1}. Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$: C, 52.94; H, 4.07; N, 10.29. Found: C, 52.98; H, 4.10; N, 10.29.

(*R*)-*N*-[[4,5-Dihydro-3-[3-fluoro-4-(1-piperazinyl)phenyl]-5-isoxazolyl]methyl]acetamide (43b, R_1 = H, R_2 = F, R_3R_4N = Piperazin-1-yl). Following the similar procedure for the synthesis of (±)-*N*-[[4,5-dihydro-3-[3-fluoro-4-(4-morpholino)phenyl]-5-isoxazolyl]methyl]acetamide but substituting piperazine (2.03 g, 23.60 mmol) for morpholine and (*R*)-*N*-[[4,5-dihydro-3-[3,4-difluorophenyl]-5-isoxazolyl]methyl]-acetamide (**42b**, 600 mg, 2.36 mmol) for (±)-*N*-[[4,5-dihydro-3-[3, 4-difluorophenyl]-5-isoxazolyl]methyl]acetamide (**40b**), 532 mg (70%) of the title compound is recovered as a white solid. The following characteristics were noted: mp 159−163 °C; $[\alpha]^{25}_D$ −63° (*c* 0.64, DMSO); IR (mull) 3313, 3289, 1648, 1615, 1549, 1520, 1510, 1436, 1422, 1350, 1254, 917, 890, 846, 824 cm^{-1}; MS (ESI^+) *m*/*z* 321.2 $(M + H)^+$; MS (EI) *m*/*z* (rel intensity) 320 (M^+, 30), 279 (17), 278 (99), 248 (15), 179 (10), 163 (16), 137 (7), 73 (7), 57 (12), 56 (25).

(*R*)-*N*-[[3-[3,5-Difluoro-4-(1*H*-imidazol-1-yl)phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (44). A solution of imidazole (42 mg, 0.61 mmol) in dry DMF (5 mL) is treated with 60% sodium hydride dispersion in mineral oil (25 mg, 0.61 mmol), stirred for 3 min, and treated with (*R*)-5-(acetamidomethyl)-3-(3,4,5-trifluorophenyl)isoxazoline (**42c**, 150 mg, 0.55 mmol). After 18 h, the mixture is heated to 40 °C for 2 h. TLC analysis (5% CH_3OH/CH_2Cl_2) indicated the reaction to be virtually complete. The mixture is diluted with water (50 mL) and extracted with EtOAc (6 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a white solid. Chromatography over silica (radial chromatography, 2 mm plate) and eluting with CH_2Cl_2, 2% and 5% $CH_3OH-CH_2Cl_2$ give 100 mg (57%) of the title compound as a white solid with the following characteristics: mp 168−169 °C; $[\alpha]^{25}_D$ −80° (*c* 0.61, DMSO); IR (mull) 3270, 2409 (w), 2321 (w), 2260 (w), 2220 (w), 1664 (s), 1558 (s), 1540 (s), 1437 (s), 1394, 1301, 1070, 1034 (s), 723 (s), 661 cm^{-1}. Anal. ($C_{15}H_{14}F_2N_4O_2$) C, H, N.

(*R*)-*N*-[[3-[3,5-Difluoro-4-(1*H*-imidazol-1-yl)phenyl]-4,5-dihydro-5-isoxazolyl]methyl]ethanethioamide (45). A mixture of (*R*)-*N*-[[3-[3,5-difluoro-4-(1*H*-imidazol-1-yl)phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (**44**, 150 mg, 0.47 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-

2,4-disulfide (Lawesson's Reagent) (189 mg, 0.47 mmol) in 1,4-dioxane (5 mL) is heated at reflux for 1.5 h and stirred at ambient temperature. After 18 h, TLC analysis (5% CH_3OH/CH_2Cl_2) indicated the reaction to be complete. The mixture is diluted with water (50 mL), extracted with EtOAc (3 × 25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a light-yellow solid. The crude material is recrystallized from 5% CH_3OH/EtOAc to give 119 mg (75%) of the title compound as a white solid. The following characteristics were noted: mp 238−240 °C dec; IR (mull) 3034 (s), 2426 (w), 2322 (w), 2258 (w), 1572 (s), 1540 (s), 1442 (s), 1432 (s), 1393 (s), 1359 (s), 1072 (s), 1038 (s), 1031 (s), 726 (s), 662 (s) cm^{-1}; MS (ES) 337 $(M + H)^+$; HRMS (EI) calcd for $C_{15}H_{14}F_2N_4OS$ 336.0856, found 336.0862. Anal. ($C_{15}H_{14}F_2N_4OS \cdot 1.58H_2O$) C, H, N.

(*R*)-*N*-[[3-[3,5-Difluoro-4-(4-morpholinyl)phenyl]-4,5-dihydro-5-isoxazolyl]methyl]ethanethioamide (46). Following the procedure described for **45**, a sample of **38** (150 mg, 0.44 mmol) is converted to the crude title compound. Radial chromatography over silica (2 mm plate) and eluting with CH_2Cl_2 and then 2% CH_3OH/CH_2Cl_2 afforded, after combination and concentration of appropriate fractions, 152 mg (97%) of the title compound as a white solid: mp 194−195 °C; $[\alpha]^{25}_D$ −39° (*c* 0.98, DMSO); IR (mull) 3257 (s), 2473 (w), 2311 (w), 2227 (w), 2080 (w), 1965 (w), 1553 (s), 1517, 1438 (s), 1356 (s), 1262, 1237 (s), 1120 (s), 944 (s), 801 (s) cm^{-1}. Anal. ($C_{16}H_{19}F_2N_3O_2S$) C, H, N.

(*R*)-*N*-[[4,5-Dihydro-3-[4-(4-pyridinyl)phenyl]-5-isoxazolyl]methyl]acetamide (47). To a flame-dried flask containing 4-bromopyridine (950 mg, 6.01 mmol) in 1,4-dioxane (60 mL) was added hexamethylditin (2.07 g, 6.31 mmol) and dichlorobis(triphenylphosphine)palladium(II) (110 mg, 0.15 mmol), and the mixture was heated to 100 °C for 22 h. The reaction mixture was concentrated in vacuo and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform (100) and then chloroform/acetonitrile (90/10). The appropriate fractions were combined (R_f = 0.24, TLC, chloroform/acetonitrile, 90/10) and concentrated in vacuo to give 1.36 g (94%) of 4-(trimethylstannyl)pyridine. To a flame-dried flask containing a prestirred slurry of 1-methyl-2-pyrrolidinone (8 mL), tris(dibenzylideneacetone)dipalladium (490 mg, 0.54 mmol), and tri(2-furyl)phosphine (250 mg, 1.07 mmol) under an inert atmosphere was added (*R*)-4,5-dihydro[3-(4-bromophenyl)-5-(hydroxymethyl)]isoxazole (**21**, 1.38 g, 5.37 mmol) and 4-(trimethylstannyl)pyridine (1.30 g, 5.30 mmol in 1-methyl-2-pyrrolidinone (5 mL), and the mixture was heated to 90 °C for 12 h. The reaction mixture was diluted with ethyl acetate (100 mL) and water (50 mL). The organic phase was separated, and the aqueous phase was extracted with methylene chloride (4 × 50 mL). The organic extracts were combined, dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (99/1). The appropriate fractions were combined (R_f = 0.25, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 450 mg (33%) of (*R*)-4,5-dihydro[3-[4-(4-pyridinyl)phenyl]-5-(hydroxymethyl)]isoxazole: MS (ESI^+) *m/z* 255.1 $(M + H)^+$. To a flame-dried flask containing this material (440 mg, 1.73 mmol) in methylene chloride (20 mL) at 0 °C under an inert atmosphere was added triethylamine (0.36 mL, 2.60 mmol) and methanesulfonyl chloride (0.14 mL, 1.82 mmol). The reaction mixture was slowly warmed to ambient temperature, stirred for 3 h, and quenched with water (25 mL). The organic phase was separated, washed with saturated $NaHCO_3$ (25 mL) and saline solution (25 mL), dried over sodium sulfate, and concentrated in vacuo to give crude (*R*)-4,5-dihydro[3-[4-(4-pyridinyl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]isoxazole. This crude material (580 mg, 1.73 mmol) was dissolved in tetrahydrofuran (4 mL), 2-propanol (4 mL), and concentrated ammonium hydroxide (4 mL) in a thick-wall resealable vessel, and the mixture was heated to 100−110 °C for 15 h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (50 mL), washed with saline solution (20 mL), dried over sodium sulfate, and concentrated in vacuo to give crude (*R*)-4,5-dihydro[3-[4-(4-pyridinyl)phenyl]-5-(aminomethyl)isoxazole. The crude (*R*)-4,5-dihydro[3-[4-(4-pyridinyl)phenyl]-5-(aminomethyl)isoxazole (320 mg, 1.57 mmol) was dissolved in methylene chloride (15 mL) and cooled to 0 °C under an inert atmosphere. Pyridine (0.31 mL, 3.78 mmol) and acetic anhydride (0.15 mL, 1.57 mmol) were added to the cooled solution and stirred for 20 h at ambient temperature. The reaction mixture was concentrated in vacuo, diluted with methylene chloride (50 mL), washed with saline solution (25 mL), dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with chloroform/methanol (97/3). The appropriate fractions were combined (R_f = 0.14, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 196 mg (53%) of the title compound **47** as a pale-yellow solid with the following characteristics: mp 244−245 °C; $[\alpha]^{25}_D$ −78° (*c* = 0.88, DMSO); IR (mull) 3290, 3089, 1645, 1589, 1564, 1536, 1432, 1416, 1407, 1396, 1300, 918, 807, 723, 606 cm^{-1}; MS (ESI^+) *m/z* 296.3 $(M + H)^+$; HRMS *m/z* 296.3 $(M + H)^+$; HRMS (FAB) calcd for $C_{17}H_{17}N_3O_2 + H_1$ 296.1399, found 296.1382. Anal. ($C_{17}H_{17}N_3O_2 \cdot 0.17H_2O$) C, H, N.

(*R*)-*N*-[[3-[3-Fluoro-4-(4-morpholino)phenyl]-5-isoxazolyl]methyl]acetamide (48). To a resealable tube containing (±)-*N*-[[4,5-dihydro-3-[3, 4-difluorophenyl]-5-isoxazolyl]-methyl]acetamide (**40b**, 1.70 g, 6.69 mmol) in morpholine (5.83 mL, 14.39 mmol) was added potassium carbonate (1.16 g, 8.36 mmol), and the mixture was heated to 140 °C for 48 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (3 × 50 mL) and saline solution (50 mL). The organic phase was dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 200 mL), eluting with methylene chloride/methanol (98.5/1.5). The appropriate fractions were combined (R_f = 0.30, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 1.50 g (70%) of (±)-*N*-[[3-[3-fluoro-4-(4-morpholino)phenyl]-5-isoxazolyl]-methyl]acetamide as a white solid. This racemic material was resolved into individual enantiomers by preparative chiral phase HPLC (5 cm × 50 cm Chiralpak AD column, Chiral Technologies), using conditions similar to those used for isolating **38** and **39**. The (*R*)-enantiomer **48** was a white solid: mp 179−180 °C; $[\alpha]^{25}_D$ −71° (*c* 0.90, DMSO); IR (mull) 3272, 1664, 1637, 1617, 1564, 1521, 1435, 1271, 1261, 1253, 1118, 943, 882, 842, 833 cm^{-1}; MS (ESI^+) *m/z* 322.2 $(M + H)^+$. Anal. ($C_{16}H_{20}FN_3O_3$) C, H, N.

***N*-[[4,5-Dihydro-3-[4-[1-(hydroxyacetyl)-4-piperazinyl]-phenyl]-5-isoxazolyl]methyl]acetamide (49).** Following the procedure for the synthesis of (±)-*N*-[[4,5-dihydro-3-[4-(4-morpholino)phenyl]-5-isoxazolyl]methyl]acetamide but substituting piperazine (5.00 g, 58.05 mmol) for morpholine, 365 mg (57%) of (±)-*N*-[[4,5-dihydro-3-[4-(1-piperazinyl)phenyl]-5-isoxazolyl]methyl]acetamide was recovered as a tan solid: MS (ESI^+) *m/z* 303.3 $(M + H)^+$. To a flask containing this material (340 mg, 1.12 mmol) in methylene chloride (5 mL) and triethylamine (0.31 mL, 2.24 mmol) was added acetoxyacetyl chloride (0.16 mL, 1.46 mmol) at 0 °C under an inert atmosphere. The reaction mixture was warmed to ambient temperature, stirred for 2 h, and concentrated in vacuo. The residue was dissolved in methanol (10 mL), and potassium carbonate (460 mg, 1.88 mmol) was added. The reaction mixture was stirred for 15 h, concentrated in vacuo, and chromatographed on silica gel (230−400 mesh, 100 mL), eluting with chloroform/methanol (96/4). The appropriate fractions were combined (R_f = 0.07, TLC, chloroform/methanol, 95/5) and concentrated in vacuo to give 179 mg (44%) of the title compound as a blue-green solid with the following characteristics: mp 187−190 °C; IR (mull) 3426, 3304, 1658, 1608, 1540, 1522, 1444, 1426, 1396, 1283, 1242, 1219, 1115, 1021, 899 cm^{-1}; MS (ESI^+) *m/z* 361.3 $(M + H)^+$; HRMS (EI) calcd for $C_{18}H_{24}N_4O_4$ 360.1797, found 360.1806. Anal. ($C_{18}H_{24}N_4O_4 \cdot 0.24H_2O$) C, H, N.

***N*-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (50).** A mixture of (±)-*N*-[[4,5-dihydro-3-[3-fluoro-4-(1-piperazinyl)-phenyl]-5-isoxazolyl]methyl]acetamide (1.73 g, 5.4 mmol) and sodium bicarbonate (1.13 g, 13.5 mmol) in dry THF (104 mL)

at 0 °C is treated with acetoxyacetyl chloride (811 mg, 5.9 mmol) by syringe and warmed to ambient temperature overnight. After 18 h, TLC analysis (8% CH_3OH/CH_2Cl_2) indicated that the starting material is consumed. To the mixture is added methanol (75 mL), water (20 mL), and potassium carbonate (750 mg). After 2 h, TLC analysis (8% CH_3OH/CH_2Cl_2) indicates the second step is to complete. The mixture is adjusted to neutral pH by addition of 2 N HCl, extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 2.02 g (99%) of the title compound as a white solid with the following characteristics: mp 213−214 °C; IR (mull) 3282, 1657 (s), 1632, 1618, 1571, 1521, 1441, 1282, 1264, 1232, 1152, 1032, 880, 830, 622 cm^{-1}. Anal. ($C_{18}H_{23}FN_4O_4$) C, H, N.

(*R*)-*N*-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (51) and (*S*)-*N*-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (52). (±)-*N*-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (**50**, 2 g) was resolved on a 5 cm × 50 cm Chiralpak AD column (Chiral Technologies) using the following conditions: 10 mL (50 mg) injections, 300 nm UV detection, 60 mL/min flow rate, 8/8/3 heptane/isopropyl alcohol/chloroform (v/v) mobile phase. Each injection required a total run time of 60 min with three passes on the column required to obtain adequate resolution using a closed-loop recycling HPLC (EM ST140, R&S Technologies Inc.) and peak shaving for fraction collection. The separated enantiomers so obtained are further purified by column chromatography over silica gel, eluting with a gradient of 1−5% CH_2Cl_2/MeOH to give, after combination of appropriate fractions and concentration in vacuo, the enantiomeric title compounds as white solids. The following characteristics were noted for **51**: mp 228−229 °C; $[\alpha]^{25}_D$ −59° (*c* 0.96, DMSO); IR (mull) 3271, 2420, 1641 (s), 1618, 1558, 1522, 1445, 1433, 1280, 1260, 1250, 1233, 1084, 1032, 839 cm^{-1}. Anal. ($C_{18}H_{23}FN_4O_4$) C, H, N. (*S*)-**52** had the following characteristics: mp 221−223 °C; $[\alpha]^{25}_D$ +54° (*c* 0.95, DMSO); IR (mull) 3271, 2499, 2360, 1640 (s), 1618, 1558, 1522, 1445, 1433, 1280, 1233, 1032, 839 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{23}FN_4O_4$ 378.1703, found 378.1706. Anal. ($C_{18}H_{23}FN_4O_4 \cdot 0.25H_2O$) C, H, N.

(*R*)-*N*-[[3-[3,5-Difluoro-4-(1-piperazinyl)phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (53). (*R*)-5-(Acetamidomethyl)-3-(3,4,5-trifluorophenyl)isoxazoline (**42c**) is converted to the title compound by reacting it with piperazine, as described above for racemic material. The title compound (para isomer) is obtained as a white solid (45% yield) with the following characteristics: mp 149−151 °C; $[\alpha]^{25}_D$ −67° (*c* 0.79, DMSO); IR (mull) 3282 (s), 2312 (w), 2221 (w), 1996 (w), 1671, 1645 (s), 1556 (s), 1517 (s), 1435 (s), 1396 (s), 1238, 1025 (s), 1016 (s), 941 (s), 855 (s), cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}F_2N_4O_2$ 338.1554, found 338.1553. Anal. ($C_{16}H_{20}F_2N_4O_2 \cdot 0.25H_2O$) C, H, N. A small amount of the corresponding meta isomer was also observed: IR (mull) 3390, 3284, 1668 (s), 1655 (s), 1618, 1584, 1556, 1536 (s), 1517 (s), 1432 (s), 1271, 1253, 1096 (s), 1016 (s), 806 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}F_2N_4O_2$ 338.1554, found 338.1545. Anal. ($C_{16}H_{20}F_2N_4O_2$) C, H, N.

(*R*)-*N*-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-4,5-dihydro-5-isoxazolyl]methyl]acetamide (54). Following the procedure described for **50**, but starting with the (*R*)-enantiomer **53** (250 mg, 0.74 mmol), 195 mg (67%) of the title compound is obtained as a white solid: mp 220−221 °C; $[\alpha]^{25}_D$ −60° (*c* 0.94, DMSO); IR (mull) 3277, 2420 (w), 1996 (w), 1639 (s), 1557, 1433, 1429, 1277, 1232, 1083, 1038, 1029, 1023, 795, 608 cm^{-1}. Anal. ($C_{18}H_{22}F_2N_4O_4$) C, H, N.

(*R*)-5-Acetamidomethyl-3-(3-fluoro-4-pyrrolidin-1-ylphenyl)isoxazoline (55). (*R*)-5-(Acetamidomethyl)-3-(3,4-difluorophenyl)isoxazoline (**42b**, 762 mg, 3.0 mmol) was combined with 2.5 mL of pyrrolidine in a 15 mL screw cap pressure tube under nitrogen. The reaction mixture was warmed to 130 °C for 2 h, was cooled to room temperature, and was diluted with 20 mL of chloroform. The organics were washed with 1 × 25 mL of 50% saturated sodium bicarbonate, were dried over anhydrous potassium carbonate, and were concentrated in vacuo to give an off-white solid. The crude material was chromatographed over 50 g of silica gel (230−400 mesh), eluting with 5% methanol/dichloromethane while collecting 5 mL fractions. Fractions 12−31 were combined and concentrated to afford a white solid that was washed with diethyl ether and was dried to give 761 mg (83%) of the title compound **55** as a white solid: mp 165−166 °C; $[\alpha]^{25}_D$ −57° (*c* 0.76, DMSO); IR (mull) 3310, 1651, 1618, 1548, 1529, 1437, 1428, 1420, 1293, 1255, 1179, 1155, 898, 836, 809 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 305 (M^+, 63), 305 (63), 233 (99), 206 (95), 205 (21), 204 (24), 191 (20), 190 (18), 189 (22), 178 (30), 73 (26). Anal. ($C_{16}H_{20}FN_3O_2$) C, H, N.

(*R*)-5-Acetamidomethyl-3-(3-fluoro-4-(pyrrol-1-yl)phenyl)isoxazoline (56). Pyrrole (0.299 mL, 3.3 mmol) was dissolved in 7 mL of dimethylformamide in a 25 mL one-neck round-bottom flask under nitrogen. The solution was cooled to 0 °C and was treated with 60% sodium hydride (132 mg, 3.3 mmol), and the mixture was stirred for 20 min at room temperature. The solution was treated with (*R*)-5-(acetamidomethyl)-3-(3,4-difluorophenyl)isoxazoline (**42b**, 763 mg, 3.0 mmol), and the reaction mixture was stirred for 2 h at 50−60 °C. The reaction mixture was cooled, the dimethylformamide was removed under a stream of nitrogen, and the residue was washed with water followed by diethyl ether and was dried to give an off-white solid. The crude material was chromatographed over 25 g of silica gel (230−400 mesh), eluting with 5% methanol/dichloromethane while collecting 5 mL fractions. Fractions 13−30 were combined and concentrated to give 520 mg (58%) of the title compound as a white solid: mp 176−177 °C; $[\alpha]^{25}_D$ −73° (*c* 0.75, DMSO); IR (mull) 3289, 2039, 1643, 1558, 1529, 1440, 1430, 1356, 1297, 1257, 909, 825, 734, 725, 610 cm^{-1}; UV λ_{max} 285 (22 300, 95% ethanol); MS (EI) *m*/*z* (rel intensity) 301 (M^+, 5), 242 (7), 230 (15), 229 (99), 202 (9), 200 (8), 187 (8), 174 (13), 160 (8), 133 (9), 73 (50). Anal. ($C_{16}H_{16}FN_3O_2$) C, H, N.

(*R*)-5-Acetamidomethyl-3-(3-fluoro-4-(imidazol-1-yl)-phenyl)isoxazoline (57). Imidazole (225 mg, 3.3 mmol) was dissolved in 5 mL of dimethylformamide in a 25 mL one-neck round-bottom flask under nitrogen. The solution was cooled to 0 °C and was treated with 60% sodium hydride (132 mg, 3.3 mmol), and the mixture was stirred for 20 min at room temperature. The solution was treated with (*R*)-5-(acetamidomethyl)-3-(3,4-difluorophenyl)isoxazoline (**42b**, 763 mg, 3.0 mmol), and the reaction mixture was stirred for 6 h at 65 °C. The reaction mixture was cooled, was diluted with 25 mL of ethyl acetate, and was washed with 4 × 25 mL of 50% saturated 1:1 sodium chloride/sodium bicarbonate. The organics were dried over anhydrous magnesium sulfate and were concentrated in vacuo to a white solid. The crude material was chromatographed over 25 g of silica gel (230−400 mesh), eluting with 4% methanol/dichloromethane while collecting 5 mL fractions. Fractions 33−69 were combined and concentrated to give 256 mg of a white solid that was washed with ethyl acetate to afford 227 mg (25%) of the title compound as a white solid: mp 155−156 °C; $[\alpha]^{25}_D$ −76° (*c* 0.30, DMSO); IR (mull) 3279, 1935, 1665, 1554, 1531, 1515, 1442, 1287, 1259, 1064, 906, 846, 842, 718, 659 cm^{-1}; UV λ_{max} 278 (21 200, 95% ethanol); MS (FAB) *m*/*z* (rel intensity) 303 (M + H, 99), 605 (5), 457 (4), 380 (4), 379 (14), 304 (19), 303 (99), 261 (2), 243 (2), 230 (3), 188 (5); HRMS (FAB) calcd for $C_{15}H_{15}FN_4O_2$ + H1 303.1257, found 303.1253. Anal. ($C_{15}H_{15}FN_4O_2 \cdot 0.20H_2O$) C, H, N.

(*R*)-5-Acetamidomethyl-3-(3-fluoro-4-(1,2,4-triazol-1-yl)phenyl)isoxazoline (58). 1*H*-1,2,4-Triazole (228 mg, 3.3 mmol) was dissolved in 5 mL of dimethylformamide in a 25 mL one-neck round-bottom flask under nitrogen. The solution was cooled to 0 °C and was treated with 60% sodium hydride (132 mg, 3.3 mmol), and the mixture was stirred for 20 min at room temperature. The solution was treated with (*R*)-5-(acetamidomethyl)-3-(3,4-difluorophenyl)isoxazoline (**42b**, 763 mg, 3.0 mmol), and the reaction mixture was stirred for 24 h at 75 °C. The reaction mixture was cooled, was diluted with 25 mL of ethyl acetate, and was washed with 4 × 25 mL of

50% saturated 1:1 sodium chloride/sodium bicarbonate. The organics were dried over anhydrous potassium carbonate and were concentrated in vacuo to a white solid. The crude material was chromatographed over 25 g of silica gel (230−400 mesh), eluting with 4% methanol/dichloromethane while collecting 5 mL fractions. Fractions 27−48 were combined and concentrated to give 142 mg (16%) of the title compound as a white solid: mp 172−173 °C; $[\alpha]^{25}_D$ −86° (*c* 0.43, DMSO); IR (mull) 3282, 2445, 2277, 1913, 1640, 1575, 1562, 1531, 1443, 1415, 1292, 1145, 910, 833, 668 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 304 (M + H, 99), 612 (2), 607 (4), 534 (3), 459 (2), 458 (13), 457 (4), 380 (4), 305 (18), 304 (99), 244 (5). Anal. ($C_{14}H_{14}FN_5O_2$) C, H, N.

(*R*)-5-Acetamidomethyl-3-(3-fluoro-4-(pyrazol-1-yl)phenyl)isoxazoline (59). Pyrazole (150 mg, 2.2 mmol) was dissolved in 3 mL of dimethylformamide in a 25 mL one-neck round-bottom flask under nitrogen. The solution was cooled to 0 °C and was treated with 60% sodium hydride (88 mg, 2.2 mmol), and the mixture was stirred for 20 min at room temperature. The solution was treated with (*R*)-5-(acetamidomethyl)-3-(3,4-difluorophenyl)isoxazoline (**42b**, 508 mg, 2.0 mmol), and the reaction mixture was stirred for 5 h at 50−60 °C. The reaction mixture was cooled, the dimethylformamide was removed under a stream of nitrogen, and the residue was washed with water and was dried to give an off-white solid. The crude material was chromatographed over 25 g of silica gel (230−400 mesh), eluting with 4% methanol/dichloromethane while collecting 5 mL fractions. Fractions 33−69 were combined and concentrated to give a white solid that was washed with ethyl acetate to afford 303 mg (50%) of the title compound as a white solid: mp 172−173 °C; $[\alpha]^{25}_D$ −73° (*c* 0.41, DMSO); IR (mull) 3292, 2444, 2292, 2161, 1914, 1641, 1559, 1531, 1442, 1431, 1426, 1398, 907, 833, 754 cm^{-1}; UV λ_{max} 285 (25 000, 95% ethanol); MS (EI) *m*/*z* (rel intensity) 302 (M^+, 1), 243 (5), 231 (14), 230 (99), 202 (4), 201 (6), 188 (18), 175 (8), 134 (5), 107 (4), 73 (29). Anal. ($C_{15}H_{15}FN_4O_2$) C, H, N.

(*R*)-5-Acetamidomethyl-3-(3-fluoro-4-(4-cyanolpyrazol-1-yl)phenyl)isoxazoline (60). (*R*)-5-(Acetamidomethyl)-3-(3,4-difluorophenyl)isoxazoline (**42b**, 3.06 g, 12 mmol) was combined with hydrazine hydrate (2.9 mL, 60 mmol) in 6 mL of *tert*-butyl alcohol in a 48 mL screw cap pressure tube under nitrogen. The reaction mixture was warmed to 135 °C for 6 h, was cooled to room temperature, and was diluted with 30 mL of water. The solids were collected and were washed with water, and the solid was dried. The aqueous layer was washed with 6 × 50 mL of 10% methanol/chloroform, and the combined organics were dried over anhydrous potassium carbonate. The dried organics were concentrated in vacuo to a yellow oil that was combined with the white solid. The mixture was suspended in 100 mL of acetonitrile in a 200 mL one-neck round-bottom flask under nitrogen. The suspension was treated dropwise with acetic anhydride (1.01 mL, 10.75 mmol) in 5 mL of acetonitrile, and the mixture was stirred for 2 h at room temperature. The solid was collected by filtration, was washed with diethyl ether, and was dried to give 950 mg of a crude white solid. Recrystallization from methanol provided 845 mg (26%) of the hydrazinylphenyl intermediate: mp 212−214 °C; $[\alpha]^{25}_D$ −76° (*c* 0.59, DMSO); IR (mull) 3282, 1642, 1625, 1564, 1524, 1432, 1352, 1298, 1289, 1170, 1161, 914,886, 822, 607 cm^{-1}; UV λ_{max} 301 (17 500, 95% ethanol); MS (EI) *m*/*z* (rel intensity) 266 (M^+, 17), 266 (17), 195 (11), 194 (99), 167 (13), 151 (9), 150 (11), 149 (12), 139 (15), 108 (12), 73 (23); HRMS (EI) calcd for $C_{12}H_{15}FN_4O_2$ 266.1179, found 266.1183.

The (*R*)-5-acetamidomethyl-3-(3-fluoro-4-hydrazinylphenyl)-isoxazoline (400 mg, 1.5 mmol) was combined with sodium 3,3-dimethoxypropionitrile-2-formylate (273 mg, 1.65 mmol) in 6 mL of absolute ethanol in a 25 mL one-neck round-bottom flask under nitrogen. The suspension was treated with 15 drops of concentrated hydrochloric acid, and the reaction mixture was stirred at 60 °C for 30 min. The reaction mixture was cooled, the volatiles were removed in vacuo, and the residue was diluted with water and saturated sodium bicarbonate. The yellow solid was collected, washed with water, and dried to give a yellow solid. The crude material was chromatographed over 30 g of silica gel (230−400 mesh), eluting with 5% methanol/dichloromethane while collecting 5 mL fractions. Fractions 11−30 were combined and concentrated to give 365 mg (74%) of the title compound as a pale-yellow solid: mp 170−172 °C; $[\alpha]^{25}_D$ −77° (*c* 0.67, DMSO); IR (mull) 3292, 2458, 2308, 2251, 2251, 2192, 1638, 1625, 1549, 1522, 1444, 1426, 951, 884, 822 cm^{-1}; UV λ_{max} 286 (26 600, 95% ethanol); MS (FAB) *m*/*z* (rel intensity) 328 (M + H, 99), 558 (5), 482 (17), 481 (8), 329 (24), 328 (99), 286 (5), 268 (8), 75 (12), 72 (4), 30 (8). Anal. ($C_{16}H_{14}FN_5O_2$) C, H, N.

(*R*)-5-Acetamidomethyl-3-(4-(3-cyanopyrrol-1-yl)-3-fluorophenyl)isoxazoline (61). 3-Formylpyrrole (628 mg, 6.6 mmol) was dissolved in 12 mL of dimethylformamide in a 50 mL one-neck round-bottom flask under nitrogen. The solution was cooled to 0 °C and was treated with 60% sodium hydride (554 mg, 13.8 mmol), and the mixture was stirred for 30 min at room temperature. The solution was treated with (*R*)-5-(acetamidomethyl)-3-(3,4-difluorophenyl)isoxazoline (**42b**, 1.52 g, 6.0 mmol), and the reaction mixture was stirred for 6 h at 65 °C. The reaction mixture was cooled, was diluted with 100 mL of ethyl acetate, and was washed with 4 × 25 mL of 50% saturated sodium chloride. The organics were dried over anhydrous potassium carbonate and were concentrated in vacuo to a yellow oil. The crude material was chromatographed over 75 g of silica gel (230−400 mesh), eluting with 3% methanol/dichloromethane and after a 200 mL forerun collecting 9 mL fractions. Fractions 48−69 were combined and concentrated to give 1.10 g (56%) of (*R*)-5-acetamidomethyl-3-(3-fluoro-4-(3-formylpyrrol-1-yl)phenyl)isoxazoline as a white solid: mp 155−156 °C; $[\alpha]^{25}_D$ −69° (*c* 0.61, ethanol); IR (mull) 3284, 1673, 1643, 1623, 1541, 1528, 1499, 1432, 1420, 1395, 1314, 1263, 1211, 929, 753 cm^{-1}; UV λ_{max} 286 (30 000, 95% ethanol); MS (EI) *m*/*z* (rel intensity) 329 (M^+, 0), 258 (17), 257 (99), 229 (18), 213 (18), 187 (18), 174 (10), 158 (10), 133 (10), 73 (74), 72 (10); HRMS (EI) calcd for $C_{17}H_{16}FN_3O_3$ 329.1176, found 329.1173.

The (*R*)-5-acetamidomethyl-3-(3-fluoro-4-(3-formylpyrrol-1-yl)phenyl)isoxazoline (329 mg, 1.0 mmol) was suspended in 4 mL of 95% ethanol in a 50 mL one-neck round-bottom flask under nitrogen. The suspension was treated with hydroxylamine (80 mg, 1.15 mmol) followed by sodium hydroxide (60 mg, 1.5 mmol) and 0.4 mL of water. The reaction mixture was stirred for 1 h at room temperature, the pH was adjusted to 7 with 5% hydrochloric acid, and the white solid was collected. The solid was collected, washed with water, and dried to give 300 mg (87%) of (*R*)-5-acetamidomethyl-3-(3-fluoro-4-(3-hydroximinopyrrol-1-yl)phenyl)isoxazoline as a white solid. Analytical material was obtained via chromatography over silica gel (230−400 mesh), eluting with 5% methanol/dichloromethane: mp 216−217 °C; $[\alpha]^{25}_D$ −67° (*c* 0.67, DMSO); IR (mull) 3209, 3158, 3142, 3081, 1637, 1571, 1542, 1526, 1440, 1294, 1281, 956, 920, 810, 793 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 344 (M^+, 11), 344 (11), 273 (14), 272 (85), 256 (11), 254 (28), 199 (9), 186 (15), 158 (14), 73 (99), 72 (13). Anal. Calcd for $C_{17}H_{17}FN_4O_3$: C, 59.30; H, 4.98; N, 16.27. Found: C, 59.30; H, 4.94; N, 16.24.

The (*R*)-5-acetamidomethyl-3-(3-fluoro-4-(3-hydroximinopyrrol-1-yl)phenyl)isoxazoline (486 mg, 1.41 mmol) was combined with triphenylphosphine (1.48 g, 5.65 mmol) and carbon tetrachloride (0.816 mL, 8.46 mmol) in 14 mL of acetonitrile in a 50 mL one-neck round-bottom flask under nitrogen. The mixture was stirred for 1 h at room temperature, and the volatiles were removed in vacuo to give a pale-yellow oil. The crude material was chromatographed over 35 g of silica gel (230−400 mesh), eluting with 4% methanol/dichloromethane while collecting 5 mL fractions. Fractions 39−50 were combined and concentrated to give 224 mg of a white solid. The solid was washed with diethyl ether and was dried to give 160 mg (33%) of the title compound as a white solid: mp 159−161 °C; $[\alpha]^{25}_D$ −72° (*c* 0.53, DMSO); IR (mull) 3300, 2422, 2227, 2227, 2185, 1647, 1569, 1553, 1537, 1531, 928, 840, 829, 799, 633 cm^{-1}. Anal. ($C_{17}H_{15}FN_4O_2$) C, H, N.

(*R*)-3-(3-Fluoro-4-(pyrrol-1-yl)phenyl)-5-thioacetamidomethylisoxazoline (62). (*R*)-5-Acetamidomethyl-3-(3-

fluoro-4-(pyrrol-1-yl)phenyl)isoxazoline (**56**, 452 mg, 1.5 mmol) was combined with Lawesson's reagent (655 mg, 1.62 mmol) in 5 mL of dioxane in a 25 mL one-neck round-bottom flask under nitrogen. The reaction mixture was warmed to reflux for 30 min and was cooled to room temperature. The insoluble material was removed by filtration, and the filtrate was concentrated in vacuo to an amber syrup. The crude material was chromatographed two times over 25 g of silica gel (230−400 mesh), eluting with 3% methanol/dichloromethane while collecting 5 mL fractions. Fractions 10−30 were combined and concentrated to provide 345 mg (73%) of the title compound **62** as an off-white solid: mp 152−153 °C; $[\alpha]^{25}_{D}$ −27° (*c* 0.60, ethanol); IR (mull) 3364, 1527, 1439, 1352, 1319, 1290, 1192, 1155, 1073, 922, 891, 806, 748, 739, 617 cm^{-1}; UV λ_{max} 273 (26 700, 95% ethanol); MS (EI) *m*/*z* (rel intensity) 317 (M^+, 10), 284 (29), 200 (37), 186 (24), 133 (28), 100 (26), 98 (99), 89 (81), 84 (18), 59 (77), 56 (51). Anal. ($C_{16}H_{16}FN_3OS$) C, H, N.

In Vitro Susceptibility Tests. Minimum inhibitory concentrations (MICs) were determined by standard broth microdilution methods.[26]

In Vivo Efficacy Tests. Effective $dose_{50}$ (ED_{50}) determinations were conducted as previously described.[27] The mice were initially inoculated intraperitoneally with sufficient *S. aureus* (approximately 100 LD_{50} values) to kill 90−100% of the infected animals. Subsequently, the antibacterial compound was administered orally at 1 and 5 h postinfection. Deaths were monitored for at least 6 days, and after this observation period the ED_{50} values were calculated by Probit Analysis.

Rat/Human Hepatocyte Stability Tests. Rat hepatocyte data are results of duplicate incubations in 5 mL of 5E6 cells/mL at 50 μM compound concentration for 40 min. Percent remaining is determined by HPLC relative to an internal standard. Human hepatocyte data are results of incubations in 10 mL of 5E6 cells/mL at 25 μM compound concentration for 40 min. Percent remaining is determined by HPLC relative to an internal standard.

P-450 Inhibition Screen. The ability of compound **48** to inhibit P-450 enzymes was investigated against different cDNA expressed human cytochrome P-450 enzyme systems (CYP1A2, CYP2C9, CYP2D6, and CYP3A4). Incubation reactions, sample workup, and quantitation of CYP marker metabolite formation using HPLC/radiochemical detection were conducted as described previously.[28]

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Supporting Information Available: NMR, combustion analyses, and selected high-resolution mass spectral data for new compounds and tables listing crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters of **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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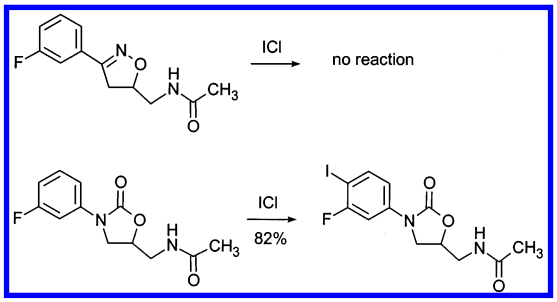

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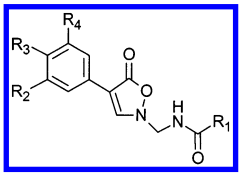

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