Substituent Effects on the Antibacterial Activity of Nitrogen−Carbon-Linked (Azolylphenyl)oxazolidinones with Expanded Activity Against the Fastidious Gram-Negative Organisms *Haemophilus influenzae* and *Moraxella catarrhalis*

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A series of new nitrogen−carbon-linked (azolylphenyl)oxazolidinone antibacterial agents has been prepared in an effort to expand the spectrum of activity of this class of antibiotics to include Gram-negative organisms. Pyrrole, pyrazole, imidazole, triazole, and tetrazole moieties have been used to replace the morpholine ring of linezolid **(2)**. These changes resulted in the preparation of compounds with good activity against the fastidious Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis*. The unsubstituted pyrrolyl analogue **3** and the 1*H*-1,2,3-triazolyl analogue **6** have MICs against *H. influenzae* = 4 μg/mL and *M. catarrhalis* = 2 μg/mL. Various substituents were also placed on the azole moieties in order to study their effects on antibacterial activity in vitro and in vivo. Interesting differences in activity were observed for many analogues that cannot be rationalized solely on the basis of sterics and position/number of nitrogen atoms in the azole ring. Differences in activity rely strongly on subtle changes in the electronic character of the overall azole systems. Aldehyde, aldoxime, and cyano azoles generally led to dramatic improvements in activity against both Gram-positive and Gram-negative bacteria relative to unsubstituted counterparts. However, amide, ester, amino, hydroxy, alkoxy, and alkyl substituents resulted in no improvement or a loss in antibacterial activity. The placement of a cyano moiety on the azole often generates analogues with interesting antibacterial activity in vitro and in vivo. In particular, the 3-cyanopyrrole, 4-cyanopyrazole, and 4-cyano-1*H*-1,2,3-triazole congeners **28**, **50,** and **90** had *S. aureus* MICs ≤ 0.5−1 μg/mL and *H. influenzae* and *M. catarrhalis* MICs = 2−4 μg/mL. These analogues are also very effective versus *S. aureus* and *S. pneumoniae* in mouse models of human infection with ED_{50}s in the range of 1.2−1.9 mg/kg versus 2.8−4.0 mg/kg for the eperezolid (**1**) control.

Introduction

Multi-drug-resistant Gram-positive bacterial pathogens[1−3] including methicillin-resistant *Staphylococcus aureus* (MRSA)[4] and *Staphylococcus epidermidis* (MRSE),[4] vancomycin-resistant enterococci (VRE),[5,6] and penicillin- and cephalosporin-resistant streptococci[7] have become a serious problem in hospitals and the community. Particularly alarming is the emergence of staphylococcal strains with reduced susceptibility to vancomycin, the so-called vancomycin/glycopeptide intermediate strains (VISA or GISA).[8−11] More recently, a multinational team reported high rates of resistance among aerobic Gram-negative bacilli in European intensive care units.[14] Thus, the search for novel potent broad-spectrum antibacterial agents is being fervently pursued by pharmaceutical houses worldwide.

The totally synthetic oxazolidinones typified by eperezolid **(1)** and linezolid **(2)** are one such class of antibacterial agents with potent activity against Gram-positive organisms including MRSA, MRSE, and VRE.[13] They have been shown to selectively and uniquely bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis.[14,15] In addition, single-step selection studies demonstrated that eperezolid- and linezolid-resistant mutants develop with a very low spontaneous mutation frequency of $<10^{-9}$ among selected staphylococcal bacteria.[16] Furthermore, evidence for the rapid development of bacterial resistance to both compounds could not be found via serial passage studies using spiral drug concentration gradient plates.[17] Recently, phase III clinical trials with linezolid (PNU-100766) for the treatment of Gram-positive infections have been successfully completed.

We have been interested in expanding the spectrum of activity of the oxazolidinones to include the fastidious Gram-negative bacteria *Haemophilus influenzae* and *Moraxella catarrhalis*, which are key organisms in cases of community acquired pneumonia (CAP) and otitis media. Linezolid exhibits only modest in vitro activity against these organisms (MIC_{90} = 16 μg/mL). In our efforts to improve the spectrum of activity, the (azolylphenyl)oxazolidinone subclass has been discovered wherein the morpholine ring of linezolid has been

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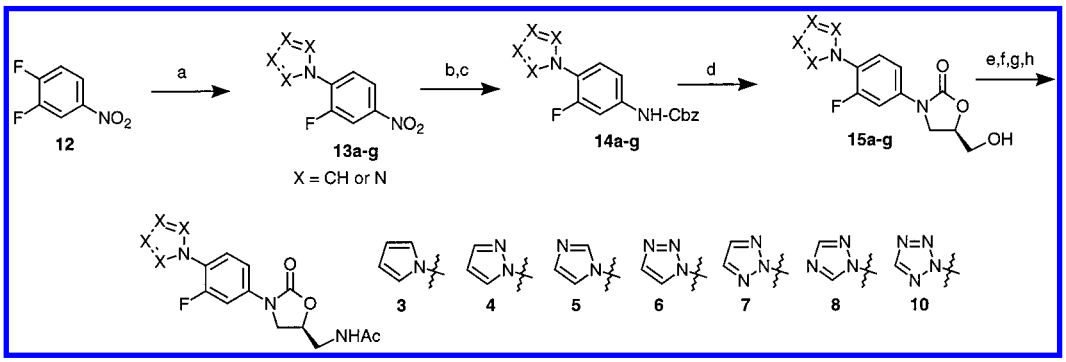
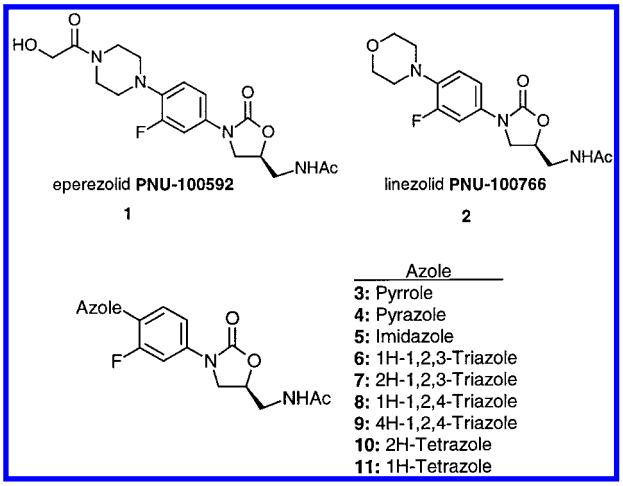
Scheme 1[a]



[a] Reagents: (a) pyrrole, NaH, THF, 66%; or pyrazole, K_2CO_3, DMSO, 90 °C, 87%; or imidazole, K_2CO_3, DMSO, 90 °C, 92%; or 1,2,3-triazole, K_2HPO_4, DMSO, 90 °C, 50% 1*H*-isomer + 43% 2*H*-isomer; or 1,2,4-triazole, K_2HPO_4, DMSO, 90 °C, 72% 1*H*-isomer; or tetrazole, NEt_3, CH_3CN, 10% 2*H*-isomer + 4% 1*H*-isomer; (b) H_2, 5% Pt/S/C, THF; or H_2, RaNi, EtOAc/MeOH; or H_2, 10% Pd/C, THF; (c) benzyl chloroformate, $NaHCO_3$, THF, rt, 37−92% for steps b + c; (d) (i) LiHMDS, THF −78 °C, (ii) *R*-(−)-glycidyl butyrate, −78 °C−rt, 48−85%; (e) MsCl, NEt_3, CH_2Cl_2; (f) NaN_3, DMF, 65 °C; (g) H_2, Pd/C, THF/MeOH; (h) Ac_2O, pyridine, 0 °C−rt, 47−66% for steps e−h.

replaced with various five-membered nitrogen-containing heterocycles (azoles). Some of these analogues have interesting levels of antibacterial activity. In particular, the pyrrole **3** and the 1*H*-1,2,3-triazole **6** analogues have excellent Gram-positive activity (MICs < 0.5−1 μg/mL), vide infra. More interesting, however, was their good activity against *H. influenzae* and *M. catarrhalis* (MICs = 2−4 μg/mL). In an effort to further increase the activity of the azolylphenyl class of oxazolidinones, we have explored the effects of various substituents on the azole rings. Previously we reported the discovery of the 3-cyanopyrrole and 4-cyanopyrazole analogues (PNU-171933 and PNU-172576) which have *S. aureus* MICs ≤ 0.5 μg/mL and *H. influenzae* and *M. catarrhalis* MICs = 2−4 μg/mL.[18] These analogues also exhibit excellent pharmacokinetics and in vivo activity.[18] We now wish to report a more extensive survey of this class in which numerous pyrrole, pyrazole, imidazole, triazole, and tetrazole analogues have been synthesized and tested for antibacterial activity.



Chemistry

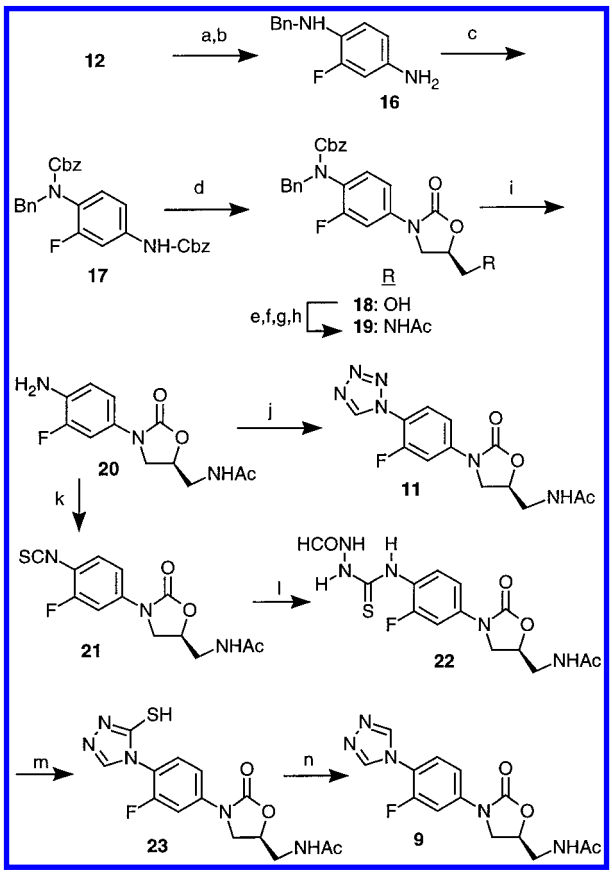
Unsubstituted Azole Analogues. The synthesis of the unsubstituted azole analogues **3**−**8** and **10** is outlined in Scheme 1. The general preparation involved nucleophilic aromatic substitution reaction between the requisite azole and 3,4-difluoronitrobenzene **(12)** to give the 3-fluoro-4-azolylnitrobenzene intermediates **13a**−**g**. Reduction of the nitro group and Cbz protection of the resulting aniline gave intermediates **14a**−**g**. Deprotonation with base followed by treatment with (*R*)-(−)-glycidyl butyrate afforded oxazolidinones **15a**−**g**.[19] The hydroxymethyl side chain was then elaborated to the final acetamide analogues **3**−**10** via standard transformations. The synthesis of the pyrrole, pyrazole, imidazole, and 1*H*-1,2,4-triazole derivatives **3**−**5** and **9** proceeded smoothly. Preparation of the 1*H*-1,2,3-triazole analogue **6** and the 2*H*-1,2,3-triazole analogue **7** was made possible by the formation of both 1*H*- and 2*H*-regioisomers in the reaction between 1,2,3-triazole and 3,4-difluoronitrobenzene.

Also shown in Scheme 1, treatment of an acetonitrile solution of 3,4-difluoronitrobenzene with tetrazole in the presence of triethylamine afforded in low yield a mixture of regioisomers, which were separable. The major 2*H*-isomer **13g** was taken on to the target 2*H*-tetrazole analogue **10**. The minor 1*H*-isomer adduct was not available in sufficient quantity for preparation of the 1*H*-tetrazole analogue **11** via this route. Thus an alternate approach was used to prepare this compound (Scheme 2). This route involved the preparation of the aniline **20**, which served as a key intermediate in the synthesis of **11** and numerous other derivatives. Reaction of **12** with benzylamine followed by bis-protection afforded **17**. Oxazolidinone ring formation and side chain elaboration gave the bis-protected aniline **19**, which was deprotected to afford **20**. Reaction of **20** with triethyl orthoformate and sodium azide afforded the desired tetrazole analogue **11** directly.[20,21]

The synthesis of the 4*H*-1,2,4-triazole analogue **9** is also shown in Scheme 2. Reaction of **20** with 1,1-thiocarbonyldi-2(1*H*)-pyridone[22] gave an excellent yield of the isothiocyanate **21** which was treated with formic hydrazide to give the thiosemicarbazide **22**.[23] Cyclization of **22** in aqueous base gave the 2-mercaptotriazole intermediate **23**.[23] Treatment of this material with nitric acid afforded the desired analogue **9**.[24]

Substituted Azole Analogues. 3-Substituted Pyrrole Analogues: Substituted pyrrole analogues were synthesized as shown in Scheme 3. The aniline **20** was condensed with dimethoxytetrahydrofurancarboxaldehyde[25] **24** to yield the 3-formylpyrrole **25** which was exploited for the preparation of **26**, **27**, **29**, and **31**−**35** via standard transformations. Dehydration of the oxime **26** with triphenylphosphine in a mixture of acetonitrile/

Scheme 2[a]



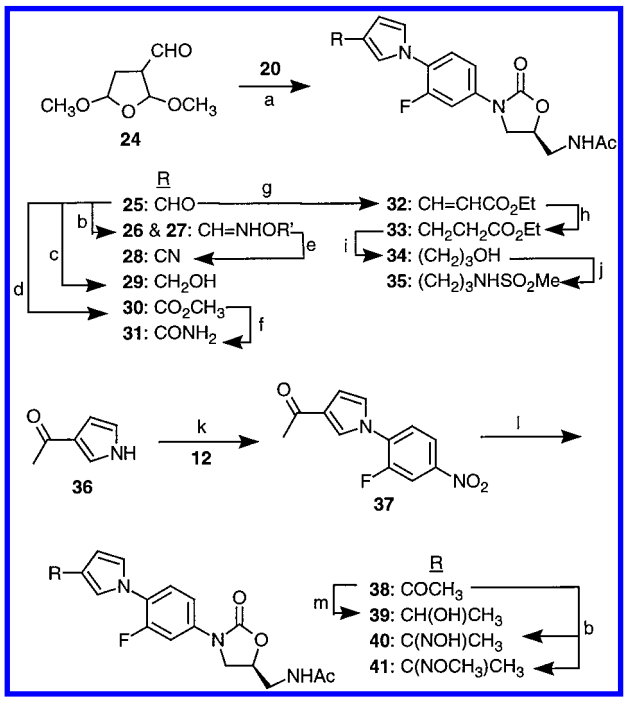
[a] Reagents: (a) $BnNH_2$, DIEA, CH_3CN, 90 °C, 84%; (b) H_2, 5% Pt/C, THF; (c) *N,N*-dimethylaniline, benzyl chloroformate, THF, 0 °C−rt, 72% for steps b + c; (d) (i) *n*-BuLi, THF, −78 °C, (ii) *R*-(−)-glycidyl butyrate, −78 °C−rt, 77%; (e) MsCl, NEt_3, CH_2Cl_2; (f) potassium phthalimide, CH_3CN, 95 °C, 93% for steps e + f; (g) hydrazine hydrate, MeOH, 80 °C, 99%; (h) Ac_2O, pyridine, 0 °C−rt, 89%; (i) H_2, 10% Pd/C, EtOH, 78%; (j) $HC(OEt)_3$, NaN_3, HOAc, reflux, 47%; (k) 1,1-thiocarbonyldi-2(1*H*)-pyridone, CH_2Cl_2, 0 °C, 94%; (l) formic hydrazide, THF, 70 °C, 91%; (m) KOH, H_2O, 98%; (n) 20% HNO_3, steam bath, NH_4OH, 77%.

CCl_4 yielded the 3-cyano analogue **28**.[26] The aldehyde **25** was oxidized to the ester **30** with manganese(IV) oxide according to the method of Corey and co-workers.[27] Analogues **38**−**41** were synthesized from 3-acetylpyrrole **36** and **12** as shown.

4-Substituted Pyrazole Analogues: Several 4-substituted pyrazole analogues were synthesized utilizing the ethyl 4-pyrazolecarboxylate analogue **47**. This material was prepared in a regioselective manner as outlined in Scheme 4. The arylhydrazine **42** was synthesized and condensed with the known (ethoxycarbonyl)malondialdehyde **(43)**[28] to give the ethyl 4-pyrazolecarboxylate **44**.[29] This material was then converted to **47** employing the azide intermediate **46** for the introduction of the acetylaminomethyl side chain. Ester **47** was further converted to **48**−**50**.

Another approach to 4-substituted pyrazoles wherein the 4-iodopyrazole **54** serves as a key intermediate was investigated. Thus, **54** was prepared in several steps as outlined in Scheme 4. Palladium-mediated carboxylation of **54** yielded an intermediate acid, which was converted to **55** via Curtius rearrangement.[30] This material was then deprotected and acylated to give **56**. The intermediate **52** was also used to prepare the terminal acetylene derivative **58** as shown.

Scheme 3[a]



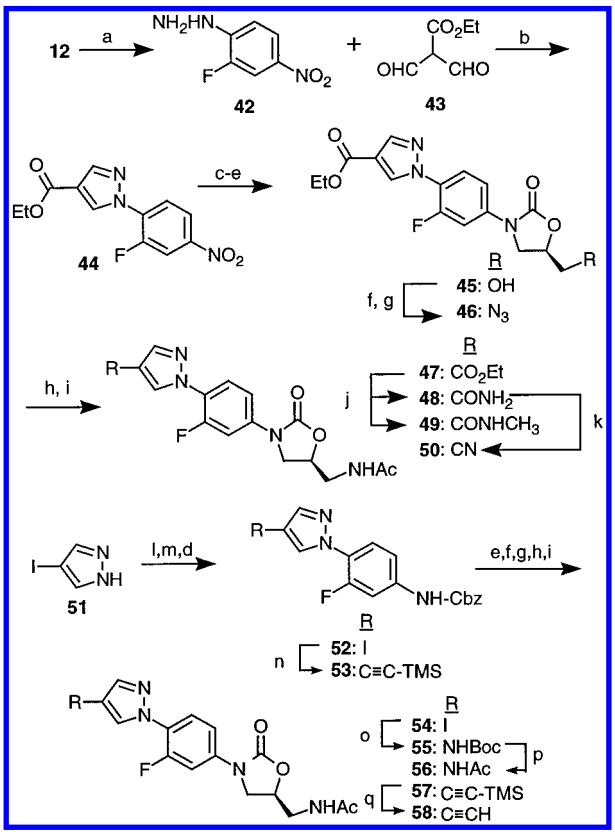
[a] Reagents: (a) **20**, HOAc, reflux, 85%; (b) NH_2OH or NH_2OMe, $MeOH/CH_2Cl_2$, K_2CO_3, 63-94% *E*/*Z* mixture; (c) $NaBH_4$, CH_2Cl_2/MeOH, 84%; (d) NaCN, MnO_2, HOAc, MeCN/MeOH, 71%; (e) PPh_3, CH_3CN/CCl_4, 72%; (f) NH_3/MeOH, KCN, 50 °C, 20%; (g) $(i\text{-PrO})_2POCH_2CO_2Et$, *t*-BuOK, −78 °C−rt, 83%; (h) CuCl, $NaBH_4$, 0 °C−rt, 99%; (i) $LiBH_4$, THF, 39%; (j) (i) MsCl, NEt_3, CH_2Cl_2, (ii) $CH_3SO_2NH_2$, NaH, DMF, 26%; (k) K_2CO_3, DMSO, 50 °C, 98%; (l) same steps as in Scheme 1, 19%; (m) $NaBH_4$, MeOH, 72%.

3-Substituted Pyrazole Analogues: The (3-aminopyrazolylphenyl)oxazolidinone **66** was targeted as a key intermediate in this series. In addition to the usual N-acylation, N-sulfonylation, and N-alkylation chemistry, we anticipated that the 3-amino derivative would allow access to the 3-cyano analogue **71** via Sandmeyer chemistry.[31] Thus, the Boc-protected (3-aminopyrazolylphenyl)oxazolidinone **65** was prepared as outlined in Scheme 5. Removal of the Boc group and functional group manipulation gave the analogues **66**−**71**. The trifluoromethyl congener **64** was synthesized in a similar fashion (Scheme 5).

It was anticipated that the arylhydrazine **72** would be a useful intermediate in azole synthesis. This material was prepared from the aniline **20** as shown in Scheme 6. Diazotization followed by reduction of the diazonium species afforded the arylhydrazine **72**.[32] Condensation of **72** with acetylacetaldehyde dimethyl acetal proceeded to give the 3- and 5-methylpyrazole analogues **73** and **74** as a 2:1 mixture (Scheme 6).[33] The hydrazine **72** was also utilized in the regiochemical synthesis of the (3-hydroxypyrazolylphenyl)oxazolidinone analogue **77**. The known ethoxyacryloyl chloride **(75)**[34] was reacted with **73** to yield the key acylhydrazine intermediate **76**. This material was cyclized in HCl to afford the desired analogue **77**,[35] which was converted to the acetoxy and methoxy analogues **78** and **79**.

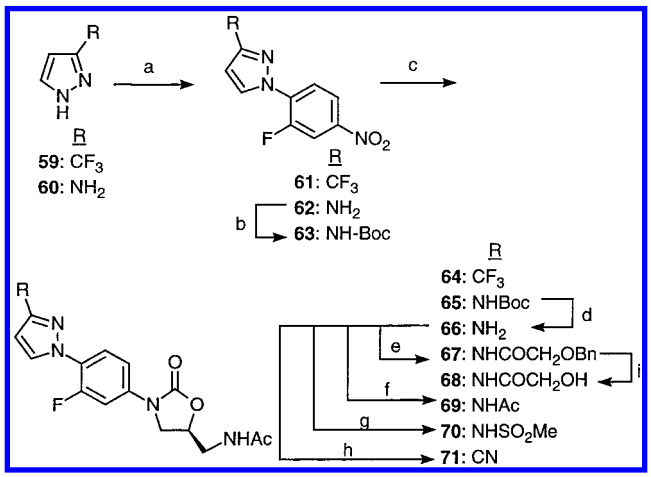
Imidazole Analogues: The synthesis of the imidazole analogues of interest is outlined in Scheme 7. The 2-hydroxymethylimidazole **(80)** was converted to the oxazolidinone derivative **83** as described above for the preparation of **3**−**8**. Removal of the silyl group yielded

Scheme 4[a]



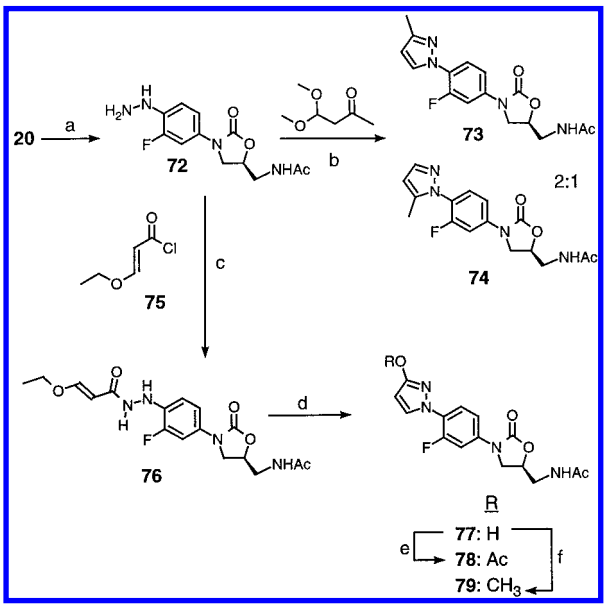
[a] Reagents: (a) hydrazine hydrate, K_2CO_3, CH_3CN, 94%; (b) NaOAc, EtOH, reflux, 65%; (c) H_2, 10% Pd/C, MeOH, 96%; (d) benzyl chloroformate, $NaHCO_3$, THF, 98%; (e) (i) *n*-BuLi, THF, −78 °C, (ii) *R*-(−)-glycidyl butyrate, −78 °C−rt, 79%; (f) MsCl, NEt_3, CH_2Cl_2, 98%; (g) NaN_3, DMF, 65 °C, 93%; (h) (i) PPh_3, THF, (ii) H_2O, 65 °C, 77%; (i) Ac_2O, pyridine, CH_2Cl_2, 99%; (j) NH_3/MeOH, KCN, 70 °C, 34%; or $MeNH_2/H_2O$/MeOH, 70 °C, 53%; (k) $SOCl_2$, DMF, 0 °C, 71%; (l) **12**, DMSO, 95 °C, 95%; (m) $SnCl_2$, EtOH, reflux, 88%; (n) $Pd(PPh_3)_2Cl_2$, CuI, 85%; (o) (i) PdOAc, dppp, CO, NEt_3, H_2O/DMF, 60%, (ii) DPPA, NEt_3, *t*-BuOH, reflux, 23%; (p) (i) TFA, CH_2Cl_2, (ii) Ac_2O, pyridine, 91%; (q) K_2CO_3, MeOH, 98%.

Scheme 5[a]



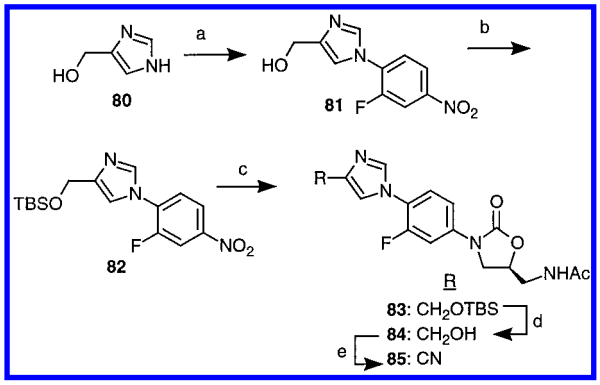
[a] Reagents: (a) **12**, 3-trifluoromethylpyrazole, DMSO, 90 °C, 94%; or 3-aminopyrazole, K_2CO_3, CH_3CN, 43%; (b) Boc_2O, THF, 77%; (c) same steps as in Scheme 6; (d) TFA, CH_2Cl_2, 83%; (e) benzyloxyacetyl chloride, NEt_3, 97%; (f) Ac_2O, NEt_3, CH_2Cl_2, 78%; (g) $MeSO_2Cl$, pyridine, 73%; (h) HCl, $NaNO_2$ then CuCN, KCN, 38%; (i) H_2, 10% Pd/C, 99%.

Scheme 6[a]



[a] Reagents: (a) $NaNO_2$, HCl then $SnCl_2$, 85%; (b) HCl, EtOH, reflux, 80%; (c) NEt_3, THF, reflux; (d) cond HCl, reflux, 65% for steps c + d; (e) Ac_2O, 89%; (f) MeI, K_2CO_3, acetone, reflux, 74%.

Scheme 7[a]



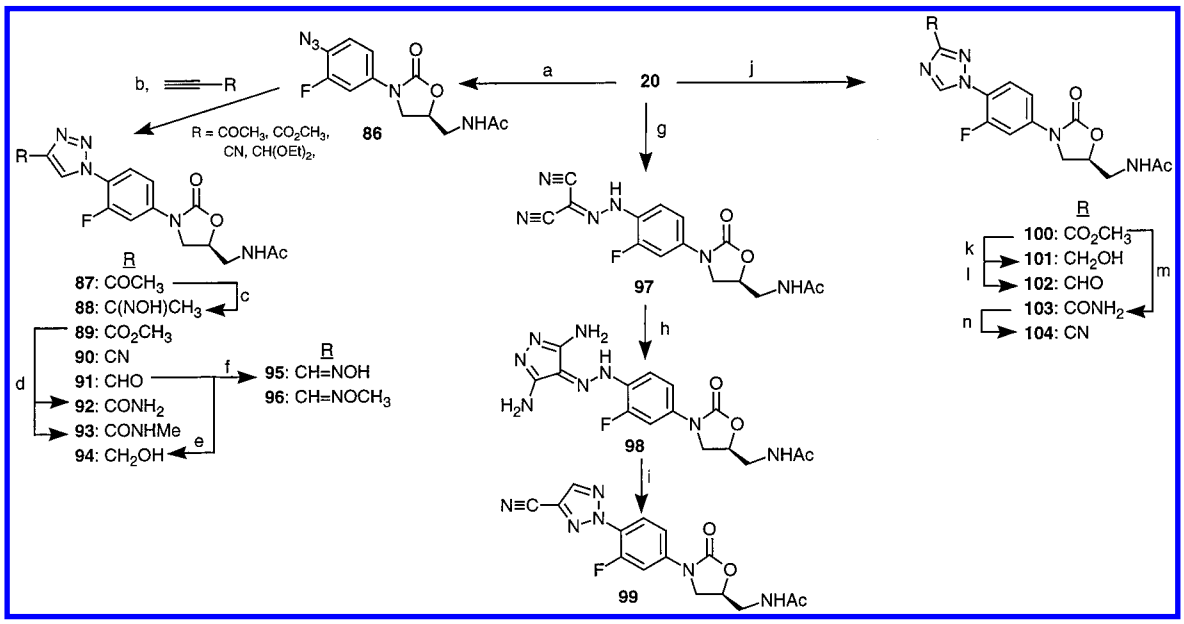
[a] Reagents: (a) K_2CO_3, DMSO, 90 °C, 47%; (b) TBDMSCl, imidazole, DMF, 64%; (c) same as in Scheme 1; (d) AcOH/THF/MeOH (98%); (e) (i) $(PhO)_2PON_3$, DBU, (ii) 2,5-dimethyl-3-hexyne-2,5-diol, 10% Pd/C, EtOH, reflux, 25%.

the hydroxymethyl congener **84** which was treated with diphenyl phosphorazidate and DBU according to the method of Mizuno and Shiori generating an intermediate azide.[36] The azide was then subjected to palladium-catalyzed decomposition to the nitrile **85** according to the method of Hayashi and co-workers.[37]

1*H*-1,2,3- and 2*H*-1,2,3-Triazole Analogues: 1*H*-1,2,3- and 2*H*-1,2,3-triazole analogues were synthesized from the aniline derivative **20** (Scheme 8). Formation of the azide **86** followed by 1,3-dipolar cycloaddition in refluxing toluene with various commercially available alkynes gave 1*H*-1,2,3-triazoles **87** and **89**−**91**.[38] These materials were converted to other analogues of interest as shown.

The primary analogue of interest in the 2*H*-1,2,3-triazole series was the cyano derivative **99**. Diazotization of aniline **20** followed by reaction of the diazonium salt with malononitrile afforded the dicyano intermediate **97**.[39] Treatment of this material with hydrazine

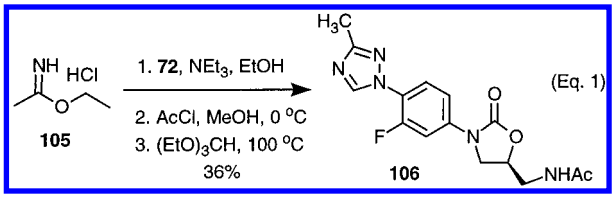
Scheme 8[a]



[a] Reagents: (a) (i) $NaNO_2$, HCl, (ii) NaN_3, NaOAc, >90%; (b) $PhCH_3$, reflux, 33−56%; (c) NH_2OH−HCl, K_2CO_3, MeOH, 20%; (d) NH_3/MeOH, KCN, 70 °C; or $MeNH_2$/MeOH 70 °C, 65−67%; (e) MeOH, $NaBH_4$, 88%; (f) NH_2OH or NH_2OMe, K_2CO_3, MeOH/THF, 72%; (g) (i) HNO_2, (ii) $CH_2(CN)_2$, 88%; (h) N_2H_4−H_2O, EtOH, reflux, 97%; (i) $Cu(OAc)_2$, pyridine, 100 °C, 7%; (j) (i) $NaNO_2$, HCl, (ii) $CNCH_2CO_2CH_3$, $NaHCO_3$, 78%; (k) $LiBH_4$, *i*-PrOH, 78%; (l) Swern, 17%; (m) NH_4OH, CH_3CN, 82%; (n) TFAA, pyridine, 83%.

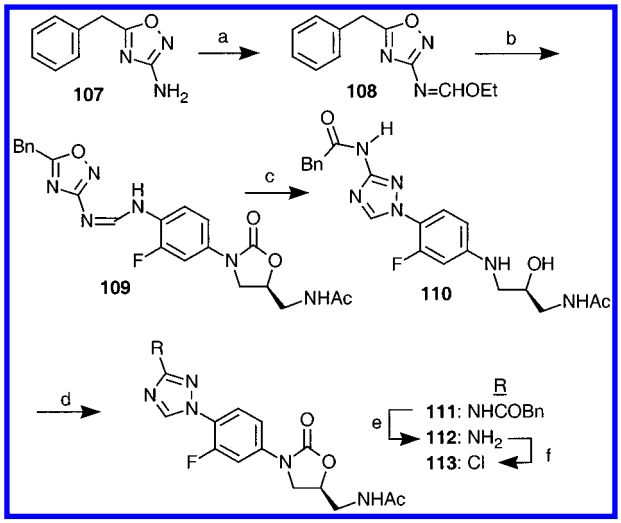
afforded the diaminopyrazolylhydrazone intermediate **98** which was cyclized with cupric acetate[40] to give the targeted cyanotriazole **99**.

1*H*-1,2,4-Triazole Analogues: Several 1*H*-1,2,4-triazoles were also prepared from the advanced aniline intermediate **20** (Scheme 8). Diazotization and condensation with methyl isocyanoacetate afforded the ester analogue **100**.[41] This material was converted to compounds **101**−**104** under standard conditions. The 3-methyl-1,2,4-triazole congener was prepared as shown in eq 1. Treatment of ethyl acetimidate with the arylhydrazine **72** in ethanol followed by addition of methanolic HCl gave an intermediate imidohydrazide, which upon refluxing in triethyl orthoformate according to the procedure of Westermann and co-workers afforded the methyltriazole **106**.[42]



Additional 1*H*-1,2,4-triazole analogues were synthesized as depicted in Scheme 9. The known aminooxadiazole **107**[43] was prepared and converted to the iminoformate intermediate **108** with triethyl orthoformate.[44] Condensation of this ethoxyformylamino derivative **108** with the aniline **20** afforded the formamidine **109** which was then cyclized to the phenylacetylaminotriazole **110**.[44] This process however cleaved the base-sensitive oxazolidinone ring to the amino alcohol. Reformation of the oxazolidinone with triphosgene yielded the protected analogue **111**. Removal of the phenylacetyl protecting group gave the amino analogue **112** which was converted to the chloro derivative **113** via diazotization and Sandmeyer reaction with copper(I) chloride.[45]

Scheme 9[a]



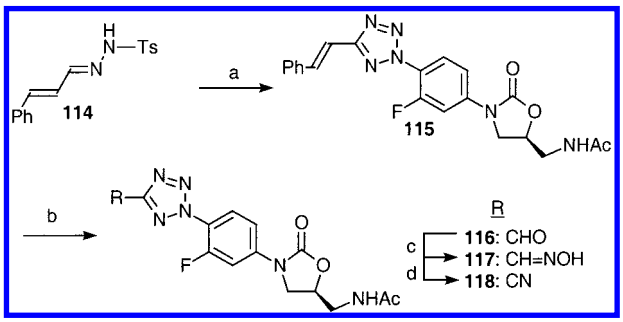
[a] Reagents: (a) $HC(OEt)_3$, reflux, 92%; (b) **20**, THF/EtOH, reflux, 82%; (c) 10% NaOH, EtOH, 89%; (d) triphosgene, CH_2Cl_2, 74%; (e) EtOH, HCl, reflux, 92%; (f) (i) $NaNO_2$, 2 N HCl, 0 °C, (ii) CuCl, rt, 22%.

2*H*-Tetrazole Analogues: Once again, the advanced aniline intermediate **20** was used for the preparation of the tetrazole analogues of interest (Scheme 10). Cycloaddition of the phenylsulfonylhydrazone **114**[46] with the diazonium salt of **20** in pyridine afforded the cinnamyltetrazole **115**.[46] Ozonolysis with reductive workup gave the aldehyde **116** that was further converted to **117** and **118**.

Results and Discussion

The oxazolidinone analogues prepared above were tested in vitro versus a panel of Gram-positive and Gram-negative bacterial isolates.[19] Minimum inhibitory concentration (MIC) values were determined using standard agar dilution methods and are shown in Tables

Scheme 10[a]



[a] Reagents: (a) (i) **20**, $NaNO_2$, HCl, H_2O, EtOH, (ii) **114**, pyridine, 35%; (b) O_3, CH_2Cl_2, −78 °C then DMS, rt, >90%; (c) NH_2OH, K_2CO_3, CH_2Cl_2, 44%; (d) PPh_3, CCl_4, CH_3CN, 69%.

1−3. Many of the analogues tested had excellent in vitro antibacterial activity several times more potent than that of linezolid, eperezolid, and vancomycin. Notably, several analogues were very potent against the fastidious Gram-negative bacteria *H. influenzae* and *M. catarrhalis*. Also, included in Tables 1−3 is in vivo efficacy data for selected analogues tested in a lethal systemic *S. aureus* infection model in mice (po administration).[19]

Considering the unsubstituted azole analogues, the pyrrolyl and 1*H*-1,2,3-triazolyl derivatives **3** and **6** emerge as the most interesting followed by the imidazolyl analogue **5**. All three have very good activity against Gram-positive and Gram-negative bacteria. It is interesting to note the profound effect on Gram-negative activity exerted by the number and location of the nitrogens of the azole rings. For example, whereas the pyrrole congener **3** is very active against *H. influenzae* and *M. catarrhalis*, the pyrazole analogue **4**, with a nitrogen in the 2-position, is not. However, moving the 2-nitrogen of the pyrazole to the 3-position to give the imidazole variant **5** results in a significant increase in the Gram-negative activity. Interestingly, replacing the 2-CH of the imidazole with a nitrogen to give the 1*H*-1,2,3-triazole **6** results in one of the most potent analogues. Thus, one can conclude that a nitrogen at the 2-position is not deleterious to activity in and of itself. Likewise, the absence of a nitrogen at the 2-position does not explain the improved activity of the imidazole **5**. It appears that the overall electronics of the azole ring play a subtle, yet important, role in the antibacterial activity of these compounds, especially when one considers the Gram-negative activity.

Several of the parent azole analogues were also tested in vivo versus a lethal systemic *S. aureus* infection in a mouse model of human infection.[19] The analogues were dosed orally and compared to either orally administered eperezolid or linezolid or subcutaneously dosed vancomycin as controls. Of the unsubstituted azoles, the 1*H*-1,2,3-triazole analogue **6** was the most efficacious with an ED_{50} = 4.7 mg/kg.

With these results in hand an extensive survey of substituted derivatives within each class was undertaken in order to increase the antibacterial activity as well as to attain and/or improve in vivo potency. This discussion will be limited to monosubstituted analogues at the 3- or 4-position of the azole rings since disubstitution generally led to decreases in activity. In addition, substitution at the 2-position (i.e. α to the phenyl ring) was not extensively explored, again due to significant losses in activity.

The pyrrole analogues were studied initially due to the excellent activity of the lead compound **3** in this series. Several 3-substituted pyrrole analogues were prepared which retain good broad-spectrum activity such as the formyl, oxime, nitrile, and hydroxymethyl derivatives **25**−**28**. Other modifications resulted in a decrease in activity across the panel of isolates. Activity against *H. influenzae* was especially sensitive to structural changes. Upon testing in vivo, the methoxime, cyano, and acetyl congeners **27**, **28**, and **38** all displayed an increase in efficacy vis-a-vis the parent pyrrole, with the cyano analogue **28** being the most efficacious (ED_{50} = 1.9 mg/kg).

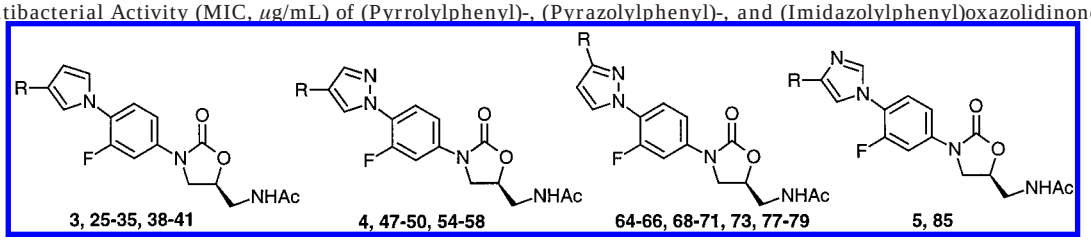
In the pyrazole series substitution at the 3- or 4-position of the ring often led to a decrease in activity. The noted exceptions to this are both the 3- and 4-cyano analogues **50** and **71** which show an increase in activity against all organisms. It is interesting to note the change in activity when moving the cyano group from the 3-position to the 4-position of the pyrazole ring. The 4-cyano congener **50** is 2−4 times more potent than the 3-cyano analogue **71**. In particular, the 4-cyano analogue has very good Gram-negative activity whereas the 3-cyano analogue has only moderate activity versus these bacteria. Furthermore, although the parent pyrazole **4** was devoid of in vivo activity, the 4-cyano-substituted compound **50** is very potent (ED_{50} = 1.2 mg/kg). The acetylene moiety was incorporated at the 4-position for a comparison to the 4-cyano congener. Although this change resulted in a reasonably active Gram-positive compound **58**, the Gram-negative activity dropped dramatically (**58** vs **50**). Because the cyano moiety imparted such interesting activity, the corresponding analogue was targeted in the imidazole series. Unfortunately, the 4-cyanoimidazole analogue **85** did not show an improvement in antibacterial activity.

Due to the very potent in vitro and in vivo activity of the unsubstituted 1*H*-1,2,3-triazole analogue **6,** a more in-depth survey of substituent effects on the various triazoles was investigated (Table 2). Several analogues in the 1*H*-1,2,3-triazole series have excellent broad-spectrum activity. Analogues **87**, **90**, **91**, and **94** are potent antibacterial agents versus both Gram-positive and Gram-negative organisms. Once again the cyano and formyl derivatives were the most active in this series, and the cyano analogue **90** maintains excellent in vivo efficacy with an ED_{50} = 1.9 mg/kg.

The 4-cyano analogue **99** was also prepared in the 2*H*-1,2,3-triazole series, and a significant increase in in vitro antibacterial activity was seen. Good broad-spectrum activity was attained, with the exception of *H. influenzae* where an MIC = 8 μg/mL was observed. This analogue is also active in vivo with an ED_{50} = 3.2 mg/kg.

The 1*H*-1,2,4-triazole series was not as interesting. Although the parent analogue **8** has good in vivo activity, it lacks Gram-negative activity. Unfortunately, the incorporation of the cyano moiety, analogue **104**, in this series did not significantly increase the Gram-negative activity. Furthermore, all other substituents explored were not beneficial. One interesting exception is the chloro derivative **113** that is equipotent with

Table 1. Antibacterial Activity (MIC, μg/mL) of (Pyrrolylphenyl)-, (Pyrazolylphenyl)-, and (Imidazolylphenyl)oxazolidinones



compd	R	*S.a.*[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.inf.*[f]	*M.cat.*[g]	ED_{50}[h]	control ED_{50}[i]
					Pyrrolyl					
3	H	1	1	≤0.5	≤0.5	1	4	2	13.2 (7.9−32.5)	2.7 (ND[j])v
25	CHO	0.25	0.25	0.125	≤0.06	0.25	2	1	>20	1.7 (0.9−2.6)v
26	CH=NOH	1	0.5	0.25	≤0.125	0.5	4	1	5.5 (3.5−9.1)	2.6 (2.2−2.9)e
27	CH=$NOCH_3$	1	1	0.5	0.25	1	16	16	7.3 (4.3−13.3)	3.5 (2.2−6.1)e
28	CN	0.5	0.25	≤0.125	≤0.125	0.25	4	1	1.9 (1.1−2.7)	4.0 (0.1−6.6)e
29	CH_2OH	1	1	0.25	0.25	1	4	2	>20	0.9 (0.5−1.5)v
30	CO_2CH_3	2	2	0.5	0.25	1	>16	16	>20	2.9 (1.8−4.4)e
31	$CONH_2$	16	8	1	0.25	4	>16	>16		
32	$CH=CHCO_2Et$	4	4	2	0.5	2	32	4	>20	2.1 (1.3−3.7)e
33	$(CH_2)_2CO_2Et$	4	4	1	0.5	2	>16	2		
34	$(CH_2)_3OH$	4	4	1	0.5	2	>16	8		
35	$(CH_2)_3NHSO_2Me$	8	4	2	0.5	2	>16	8	>20	1.8 (0.8−2.3)e
38	$COCH_3$	2	1	0.5	0.25	1	16	4	6.5 (ND)	10 (ND)e
39	$CH(OH)CH_3$	16	16	4	2	8	>16	>16		
40	$C(NOH)CH_3$	2	1	0.5	0.25	1	8	2	15 (ND)	10 (ND)e
41	$C(NOCH_3)CH_3$	4	2	1	0.5	2	>16	8		
					Pyrazolyl					
4	H	2	2	1	1	2	32	16	>20	1.8 (1.1−2.8)v
47	CO_2Et	4	4	2	1	4	>16	>16		
48	$CONH_2$	>16	>16	4	0.5	>16	>16	16		
49	CONHMe	>16	>16	2	0.5	16	>16	16		
50	CN	0.5	0.5	0.25	≤0.125	0.5	4	2	1.2 (0.8−2.0)	3.3 (1.8−7.0)e
54	I	2	2	1	0.5	2	>16	8		
55	NHBoc	8	4	2	1	8	>16	>16		
56	NHAc	>16	16	2	1	16	>16	>16		
57	CC-TMS	4	4	2	2	8	>16	>16		
58	CCH	2	2	1	0.5	2	>16	8		
64	CF_3	4	4	2	1	8	>16	>16		
65	NH−Boc	4	2	2	0.5	2	>16	8		
66	NH_2	2	4	1	0.5	4	16	16		
68	$NHCOCH_2OH$	16	16	4	1	8	>16	>16		
69	NHAc	8	8	2	0.5	4	>16	>16		
70	$NHSO_2Me$	>16	>16	4	4	>16	>16	>16		
71	CN	1	1	0.5	0.5	2	16	8		
73	CH_3	4	4	1	1	4	>16	16		
77	OH	8	8	1	1	8	16	8		
78	OAc	8	8	2	2	16	16	16		
79	OCH_3	4	4	2	2	8	>16	>16		
					Imidazolyl					
5	H	2	1	≤0.5	≤0.5	2	8	4	9.5 (5.5−22.1)	2.2 (1.43−3.5)v
85	CN	4	4	0.5	0.25	2	8	4		
linezolid		4	2	1	1	4	16	8	5.6 (2.9−8.5)	3.9 (2.5−6.4)v
eperezolid		4	1	0.5	0.5	2	16	8	1.9 (1.4−3.8)	3.9 (2.5−6.4)v
vancomycin		1	1	2	0.5	4	>32	>32	3.9 (2.5−6.4)	

[a] Methicillin-susceptible *S. aureus* UC9213. [b] Methicillin-resistant *S. aureus* UC6685. [c] Methicillin-resistant *S. epidermidis* UC12084. [d] *Str. pneumoniae* UC9912. [e] *E. faecalis* UC9217. [f] *H. influenzae* UC30063. [g] *M. catarrhalis* UC30610. Minimum inhibitory concentration (MIC): lowest concentration of drug (μg/mL) that inhibits visible growth of the organism. [h] ED_{50} is the amount of drug required after oral administration (mg/kg/day) to cure 50% of infected mice subjected to a lethal systemic infection of *S. aureus*. Numbers in parentheses are 95% confidence ranges. Data shown is from one experiment (n = 36 mice/drug). [i] v = vancomycin, e = eperezolid, l = linezolid as controls. [j] ND = not determined.

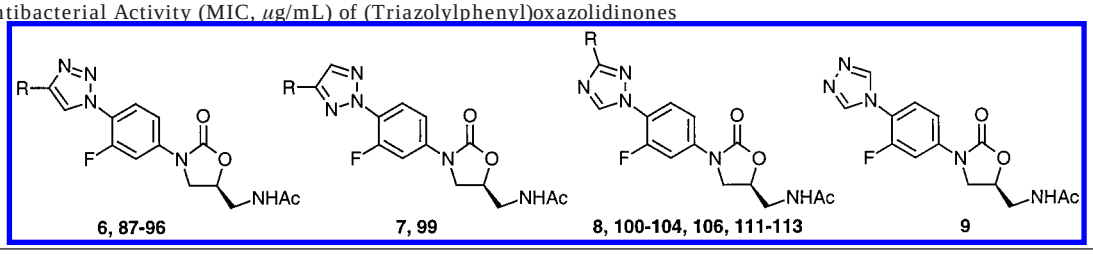
linezolid against Gram-positive bacteria and has excellent activity against *M. catharralis*.

In the tetrazole series, the 5-cyano-2*H*-tetrazole derivative **118** has good Gram-positive activity, but it is only moderately active against the Gram-negative organisms and shows no appreciable benefit over linezolid.

Conclusion

In conclusion, an effort to expand the spectrum of antibacterial activity of the oxazolidinones to include Gram-negative organisms has led to the discovery of the (azolylphenyl)oxazolidinone subclass. Certain members of this class have very potent activity versus both Gram-positive and Gram-negative organisms. Interesting differences in antibacterial activity were seen in many analogues that cannot be rationalized solely on the basis of sterics and position/number of nitrogen atoms in the azole ring. It seems that differences in activity rely strongly on subtle changes in the electronic character of the overall azole system. Electronic differences or changes in dipole may effect such characteristics as partitioning through the bacterial cell wall and/or efflux

Table 2. Antibacterial Activity (MIC, μg/mL) of (Triazolylphenyl)oxazolidinones



compd	R	*S.a.*[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.inf.*[f]	*M.cat.*[g]	ED_{50}[h]	control ED_{50}[i]
					1*H*-1,2,3					
6	H	1	1	≤0.5	≤0.5	1	4	2	4.7 (3.1−7.8)	2.0 (ND[j])v
87	$COCH_3$	1	1	1	0.5	2	8	8	8.8 (5.7−14.5)	4.4 (2.9−7.1)e
88	C(NOH)Me	4	4	2	0.5	8	16	4		
89	CO_2CH_3	4	4	2	1	4	>16	16	>20	15.3 (ND)e
90	CN	1	0.5	0.25	≤0.125	1	2	2	1.9 (1.1−3.3)	2.8 (1.7−4.5)e
91	CHO	0.5	0.25	≤0.125	0.25	0.5	4	2	>20	1.1 (0.5−1.5)e
92	$CONH_2$	4	4	1	0.5	8	>16	8		
93	$CONHCH_3$	8	4	2	1	8	>16	>16		
94	CH_2OH	4	4	0.5	0.25	2	4	2		
95	HC═NOH	8	2	1	0.5	8	>16	8		
96	HC═NOMe	4	2	1	0.5	4	>16	16	8.6 (ND)	3.8 (1.9−6.6)e
					2*H*-1,2,3					
7	H	4	2	1	1	4	>16	>16		
99	CN	0.5	0.5	≤0.125	≤0.125	0.5	8	2	3.2 (2.0−4.9)	3.8 (1.9−6.6)e
					1*H*-1,2,4					
8	H	4	4	1	1	4	32	16	5.7 (3.1−13.1)	2.4 (1.0−3.2)v
100	CO_2CH_3	>16	>16	4	4	>16	>16	>16		
101	CH_2OH	16	16	2	1	16	16	8		
102	CHO	4	2	0.5	0.5	4	8	8		
103	$CONH_2$	>16	>16	16	2	>16	>16	16		
104	CN	4	2	2	1	4	16	16		
106	CH_3	8	4	2	1	8	>16	16		
111	NHCOBn	>16	>16	>16	2	>16	>16	>16		
112	NH_2	8	4	2	1	16	>16	16		
113	Cl	4	2	0.5	≤0.125	2	16	2	9.4 (6.2−16.5)	5.0 (ND)
					4*H*-1,2,4					
9	na	16	8	4	1	8	>16	8	>20	2.0 (1.1−2.8)e
linezolid		4	2	1	1	4	16	8	5.6 (2.9−8.5)	3.9 (2.5−6.4)v
eperezolid		4	1	0.5	0.5	2	16	8	1.9 (1.4−3.8)	3.9 (2.5−6.4)v
vancomycin		1	1	2	0.5	4	>32	>32	3.9 (2.5−6.4)	

[a] Methicillin-susceptible *S. aureus* UC9213. [b] Methicillin-resistant *S. aureus* UC6685. [c] Methicillin-resistant *S. epidermidis* UC12084. [d] *Str. pneumoniae* UC9912. [e] *E. faecalis* UC9217. [f] *H. influenzae* UC30063. [g] *M. catarrhalis* UC30610. Minimum inhibitory concentration (MIC): lowest concentration of drug (μg/mL) that inhibits visible growth of the organism. [h] ED_{50} is the amount of drug required after oral administration (mg/kg/day) to cure 50% of infected mice subjected to a lethal systemic infection of *S. aureus*. Numbers in parentheses are 95% confidence ranges. Data shown is from one experiment (n = 36 mice/drug). [i] v = vancomycin, e = eperezolid, l = linezolid as controls. [j] ND = not determined.

mechanisms which have been shown to be responsible for the lack of activity of the oxazolidinones against Gram-negative bacteria.[47,48] The placement of a cyano moiety on the azole often leads to a significant increase in antibacterial activity in vitro and in vivo. In particular, the 3-cyanopyrrole, 4-cyanopyrazole, and 4-cyano-1*H*-1,2,3-triazole congeners **28**, **50,** and **90** had *S. aureus* MICs ≤ 0.5−1 mg/mL and *H. influenzae* and *M. catarrhalis* MICs = 2−4 mg/mL. Furthermore, these analogues are very effective versus *S. aureus* and *S. pneumoniae*[18] in mouse models of human infection.

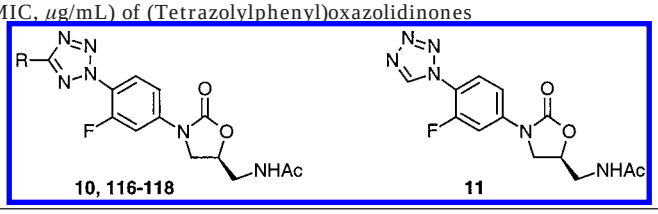
Experimental Section

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. Mass spectra and combustion analyses were obtained by the Structural, Analytical and Medicinal Chemistry Department of Pharmacia & Upjohn, Inc. Unless otherwise indicated all reactions were conducted in commercially available anhydrous solvents under a nitrogen atmosphere in oven- or flame-dried glassware. Chromatography was carried out on EM Science 230−400 mesh ASTM silica gel. Elemental analyses were within ±0.4% of calculated values. Biological assays were performed as described previously in ref 19.

3-Fluoro-1-nitro-4-(1*H*-pyrrol-1-yl)benzene (13a). Sodium hydride (630 mg of 60% in oil, 15.75 mmol) was suspended in THF (85 mL) and treated with pyrrole (1.0 g, 15 mmol), followed by warming at 50 °C for 15min. The solution was then treated with 3,4-difluoronitrobenzene (2.51 g, 15.75 mmol) and refluxed for 18 h. The mixture was cooled and treated with saturated ammonium chloride solution (10 mL). The mixture was diluted with ethyl acetate and washed with water (2×). Drying (Na_2SO_4) and concentration in vacuo afforded a dark brown solid, which was chromatographed over 75 g silica gel, eluting with 30% CH_2Cl_2/hexane. These procedures afforded 2.05 g (66%) of **13a** as a light yellow solid: mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (m, 2 H), 7.56 (t, J = 8.7 Hz, 1 H), 7.16 (m, 2 H), 6.44 (m, 2 H); HRMS (EI) calcd for $C_{10}H_7FN_2O_2$ 206.0492, found 206.0504.

General Procedure for the Preparation of 3-Fluoro-1-nitro-4-(azolyl)benzenes 13b−f, 37, 61, 62, and 81. The azole (1 equiv), K_2CO_3 or dibasic potassium phosphate (2 equiv) and 3,4-difluoronitrobenzene (1 equiv) were heated to 90 °C

Table 3. Antibacterial Activity (MIC, μg/mL) of (Tetrazolylphenyl)oxazolidinones



compd	R	*S.a.*[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.inf.*[f]	*M.cat.*[g]	ED_{50}[h]	control ED_{50}[i]
					2*H*-Tetrazolyl					
10	H	2	2	1	0.5	1	8	8		
116	CHO	8	4	2	1	16	16	16		
117	CH=NOH	4	4	1	0.5	4	16	8		
118	CN	2	1	0.5	0.5	2	16	4		
					1*H*-Tetrazolyl					
11	na	4	2	2	1	2	16	16	>20	7.8 (4.0−26.7)e
linezolid		4	2	1	1	4	16	8	5.6 (2.9−8.5)	3.9 (2.5−6.4)v
eperezolid		4	1	0.5	0.5	2	16	8	1.9 (1.4−3.8)	3.9 (2.5−6.4)v
vancomycin		1	1	2	0.5	4	>32	>32	3.9 (2.5−6.4)	

[a] Methicillin-susceptible *S. aureus* UC9213. [b] Methicillin-resistant *S. aureus* UC6685. [c] Methicillin-resistant *S. epidermidis* UC12084. [d] *Str. pneumoniae* UC9912. [e] *E. faecalis* UC9217. [f] *H. influenzae* UC30063. [g] *M. catarrhalis* UC30610. Minimum inhibitory concentration (MIC): lowest concentration of drug (μg/mL) that inhibits visible growth of the organism. [h] ED_{50} is the amount of drug required after oral administration (mg/kg/day) to cure 50% of infected mice subjected to a lethal systemic infection of *S. aureus*. Numbers in parentheses are 95% confidence ranges. Data shown is from one experiment (n = 36 mice/drug). [i] v = vancomycin, e = eperezolid, l = linezolid as controls.

in DMSO for 18 h. The reaction was cooled diluted with water (100 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layers were washed with water (5 × 100 mL) and brine (75 mL). Drying (Na_2SO_4) and concentration in vacuo afforded crude products.

3-Fluoro-1-nitro-4-(1*H*-pyrazol-1-yl)benzene (13b). Workup afforded an off-white solid which was crystallized from hot hexanes to afford 5.3 g (87%) of an off-white solid: mp 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (m, 1 H), 8.17 (m, 3 H), 7.82 (d, J = 1.4 Hz, 1 H), 6.58 (m, 1 H); MS (EI) m/z 207 (M + H); HRMS (EI) calcd for $C_9H_6FN_3O_2$ 207.0444, found 207.0454. Anal. Calcd for $C_9H_6FN_3O_2$: C, 52.18; H, 2.92; N, 20.28. Found: C, 52.01; H, 2.75; N, 20.22.

3-Fluoro-1-nitro-4-(2*H*-1,2,3,4-tetrazol-1-yl)benzene (13g). Tetrazole (15.83 g, 0.23 mol), 3,4-difluoronitrobenzene (7.19 g, 45.16 mmol) and NEt_3 (31.5 mL, 0.23 mol) in 90 mL acetonitrile was heated at reflux for 18 h, followed by cooling and concentration in vacuo. The residue was dissolved in EtOAc (250 mL) and washed with water (2 × 100 mL) and brine (100 mL). Drying (Na_2SO_4) and concentration in vacuo afforded a black oil that was chromatographed over 360 g silica gel, eluting with 3% acetone/CH_2Cl_2. These procedures afforded 0.93 g (10%) of the less polar 2*H*-regioisomer **13g** as a yellow solid and 0.38 g (4%) of the more polar 1*H*-regioisomer as a yellow-brown solid. **13g:** mp 111−115 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.71 (s, 1 H), 8.57 (dd, J = 9.6, 1.6 Hz, 1 H), 8.32 (m, 2 H); HRMS (FAB) calcd for $C_7H_4FN_5O_2$ + H 210.0427, found 210.0424. Anal. Calcd for $C_7H_4FN_5O_2$: C, 40.20; H, 1.93; N, 33.49. Found: C, 40.28; H, 1.87; N, 33.26.

1*H*-isomer: ^{1}H NMR (DMSO) δ 10.04 (s, 1 H), 8.57 (dd, J = 10.4, 2.0 Hz, 1 H), 8.34 (d, J = 8.9 Hz, 1 H), 8.23 (t, J = 8.1 Hz, 1 H).

General Procedure for the Preparation of 3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(azolyl)benzenes 14a−g. Compounds **13a−g** (1 equiv) and the indicated catalyst in THF were hydrogenated for 18 h. The mixture was filtered through Celite treated with saturated $NaHCO_3$ solution and cooled to −20 °C. Benzyl chloroformate (1.2 equiv) was added followed by warming to ambient temperature for 48 h. The mixture concentrated to ca. half the original volume diluted with EtOAc and washed with water (4×) and brine. Drying (Na_2SO_4) and concentration in vacuo afforded crude products **14a−g** which were purified as indicated.

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(1*H*-pyrrol-1-yl)benzene (14a). 5% Pt on sulfide carbon was used as catalyst and workup afforded a brown solid, which was chromatographed over 35 g silica gel, eluting with 1:3:32 to 1:3:16 CH_3OH/CH_2Cl_2/hexane gradient to yield 581 mg (77%) of **14a** as a brown solid: mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 7 H), 7.08 (d, J = 8.7 Hz, 1 H), 6.98 (m, 2 H), 6.79 (bs, 1 H), 6.35 (m, 2 H), 5.23 (s, 2 H); HRMS (EI) calcd for $C_{18}H_{15}FN_2O_2$ 310.1117, found 310.1132. Anal. Calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.32; H, 4.89; N, 9.07.

General Procedure for Oxazolidinone Ring Formation from Cbz-Protected Anilines 14a−g To Give Compounds 15a−g and 18. A solution of Cbz derivative **14a−g** (1 equiv) THF at −78 °C was treated with 1.0 M lithium bis-(trimethylsilyl)amide (1.1 equiv) followed by stirring at −78 °C for 30 min. The solution was treated with (*R*)-(−)-glycidiyl butyrate (1 equiv) followed by gradual warming to ambient temperature for 24 h. The mixture was diluted with EtOAc and washed with H_2O and brine. Drying (Na_2SO_4) and concentration in vacuo afforded crude products **15a−g**.

(*S*)-[3-[3-Fluoro-4-(1*H*-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol (15a). Workup gave a red-brown oil which was subjected to radial chromatography on a 2 mm plate, eluting with 2−5% CH_3OH/CH_2Cl_2 gradient. These procedures afforded 157 mg (59%) of **15a** as a light tan solid: mp 112−113 °C; $[\alpha]^{25}_D$ = −46° (c 0.84, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 13.2, 2.5 Hz, 1 H), 7.37 (m, 3 H), 7.00 (m, 2 H), 6.36 (m, 2 H), 4.79 (m, 1 H), 4.05 (m, 3 H), 3.79 (dd, J = 12.7, 3.7 Hz, 1 H); HRMS (EI) calcd for $C_{14}H_{13}FN_2O_3$ 276.0910, found 276.0918. Anal. Calcd for $C_{14}H_{13}FN_2O_3$: C, 60.87; H, 4.74; N, 10.14. Found: C, 60.97; H, 4.77; N, 9.84.

General Procedure for Conversion of Alcohols 15a−g to Final Acetamide Analogues 3−8 and 10. The alcohols **15a−g** (1 equiv) and NEt_3 (1.75 equiv) were cooled to 0 °C in CH_2Cl_2 and treated with methanesulfonyl chloride (1.25 equiv) followed by stirring at 0 °C for 30 min. The solution was warmed to ambient temperature, diluted with CH_2Cl_2, and washed with water (3×) and brine. Drying (Na_2SO_4) and concentration in vacuo afforded intermediate mesylates that were dissolved in DMF and treated with sodium azide (10 equiv) at 60 °C for 18 h. The mixture was cooled, diluted with EtOAc and washed with water (6×) and brine. Drying (Na_2SO_4) and concentration in vacuo afforded intermediate azides sufficiently pure for use. Then, a solution of the azide (1 equiv) in CH_3OH/THF was treated with an appropriate catalyst and hydrogenated at 1 atm for 24 h. The solution was filtered through Celite and concentrated in vacuo and the residue was dissolved in pyridine and treated with acetic anydride (1.1 equiv) followed by stirring at ambient temperature for 12 h. The solution was concentrated under high vacuum to yield crude products **3−8** and **10**.

(*S*)-*N*-[[3-[3-Fluro-4-(1*H*-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (3). Workup afforded a brown solid which was chromatographed over 50 g of silica gel, eluting with 1−2% CH_3OH/CH_2Cl_2 gradient to yield 582 mg (56%) of **3** as an off-white solid: mp 198−199.5 °C; $[\alpha]^{25}_D$ = −26° (*c* 0.93, DMSO); ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (dd, *J* = 18.3, 3.3 Hz, 1 H), 7.47 (t, *J* = 11.7 Hz, 1 H), 7.37 (dd, *J* = 11.8, 3.2 Hz, 1 H), 7.01 (m, 2 H), 6.27 (m, 2 H), 4.84 (m, 1 H), 4.18 (t, *J* = 12.1 Hz, 1 H), 3.85 (dd, *J* = 12.3, 8.5 Hz, 1 H), 3.57 (d, *J* = 6.6 Hz, 2 H), 1.97 (s, 3 H); HRMS (EI) calcd for $C_{16}H_{16}FN_3O_3$ 317.1176, found 317.1183. Anal. Calcd for $C_{16}H_{16}FN_3O_3$: C, 60.56; H, 5.08; N, 13.24. Found: C, 60.28; H, 5.10; N, 13.14.

***N*-(4-Amino-2-fluorophenyl)-*N*-benzylamine (16).** To a solution of 3,4-difluoronitrobenzene (0.7 mL, 6.29 mmol) in acetonitrile (12 mL) was added *N*,*N*-diisopropylethylamine (1.64 mL, 9.43 mmol) followed by benzylamine (0.82 mL, 7.54 mmol). After heating at 90 °C in an oil bath for 6 h the reaction was allowed to cool and stand at room temperature for 16 h and then concentrated in vacuo. The residue was treated with EtOAc and the suspended solid was removed by filtration and washed with additional EtOAc. The combined filtrates were concentrated in vacuo and the residue was chromatographed over silica gel with 5% EtOAc/hexane to yield after recrystallization from EtOAc/hexane 1.19 g (77%) of intermediate *N*-benzylnitroaniline. A solution of this material (0.50 g, 2.03 mmol) in THF (150 mL) containing of 5% platinum-on-carbon (0.1 g) was shaken with H_2 on a Parr hydrogenator for 6 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo to yield 0.54 g of **16** as a dark oil that was used as is in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (broad s, 3 H), 4.29 (s, 2 H), 6.52 (m, 3 H), 7.35 (m, 5 H).

Benzyl Benzyl(4-{[(benzyloxy)carbonyl]amino}-2-fluorophenyl)carbamate (17). To a solution of **16** (0.54 g, 4.47 mmol) in THF (36 mL) was added *N*,*N*-dimethylaniline (0.58 mL, 4.57 mmol) followed by benzyl chloroformate (0.64 mL, 4.47 mmol). After 40 min the ice bath was removed and then after stirring at room temperature for 17 h the reaction mixture was concentrated in vacuo. A solution of the residue in CH_2Cl_2 (100 mL) was washed in turn with cold 1 N HCl (3×), water, and aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel with 10−15% EtOAc/hexane gradient to yield 0.74 g (72%) of **17**: mp 105−106.5 °C. An analytical sample was recrystallized from methyl *tert*-butyl ether: mp 107−108 °C; ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.77 (broad s, 2 H), 5.16 (m, 4 H), 6.85−7.36 (m, 19 H); MS *m*/*z* 484 (M + H). Anal. Calcd for $C_{29}H_{25}FN_2O_4$: C, 71.89; H, 5.20; N, 5.78. Found: C, 71.86; H, 5.27; N, 5.74.

Benzyl 4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl(benzyl)carbamate (19). Methanesulfonyl chloride (0.16 mL, 2.05 mmol) was added dropwise to a solution of **18** (0.71 g, 1.58 mmol) and NEt_3 (0.48 mL, 3.47 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After stirring in the cold for 45 min the reaction was washed with water, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$ and concentrated in vacuo to yield 0.86 g of the mesylate as a gummy residue. This material was placed in acetonitrile (25 mL) and potassium phthalimide (0.875 g, 4.73 mmol) was added. The reaction was heated at 95 °C for 48 h and allowed to cool. A suspended solid was collected on a filter and washed well with acetonitrile. The combined filtrates were concentrated in vacuo. The residue was chromatographed over silica gel with 0.5% MeOH/CH_2Cl_2 to yield 0.85 g (93%, two steps) of the phthalimide. This phthalimide (0.85 g, 1.47 mmol) was suspended in MeOH and hydrazine monohydrate (0.075 g, 0.073 mL) was added. The mixture was heated at 80 °C for 5 h and then allowed to cool and stand at room temperature. After standing for 16 h the reaction mixture was poured into 3% aqueous sodium carbonate (25 mL) and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to give 0.65 g of the free amine as a gummy residue which was placed in pyridine (8.5 mL) at 0 °C. Acetic anhydride (2.8 mL) was added dropwise and the reaction was stirred for 18 h at room temperature and partitioned between water and EtOAc. The mixture was extracted with EtOAc (3×) and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel with 1% MeOH/0.1% NH_4OH/CH_2Cl_2 followed by 2% MeOH/0.2% NH_4OH/CH_2Cl_2 to yield 0.36 g of pure product **19** followed by 0.25 g of product mixed with a small amount of polar impurity: mp 64−66 °C; $[\alpha]_D$ −13° (*c* 0.93, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3 H), 3.64 (m, 2 H), 3.71 (m, 1 H), 3.98 (t, 1 H), 4.74 (m, 1 H), 4.81 (s, 2 H), 5.15, 5.23 (s,s, 2 H), 6.15 (broad s, 1 H), 6.95−7.52 (m, 13 H); HRMS calcd for $C_{27}H_{26}FN_3O_5$ 491.1856, found 491.1860. Anal. Calcd for $C_{27}H_{26}FN_3O_5$: C, 65.98; H, 5.33; N, 8.55. Found: C, 65.29; H, 5.41; N, 8.44.

***N*-{[(5*S*)-3-(4-Amino-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (20).** To a solution of **19** (2.381 g, 4.84 mmol) in absolute ethanol (150 mL) was added 0.5 g of 10% Pd/C catalyst. The mixture was placed on a Parr hydrogenator for 7.5 h. There was then added an additional 0.1 g of 10% Pd/C catalyst and the reaction was allowed to continue. After an additional 15.5 h the catalyst was removed by filtration through Celite. The filtrate was concentrated in vacuo and the residue was recrystallized from MeOH to yield **20**: 1.0 g (77%); mp 168−169 °C; $[\alpha]_D$ −24° (*c* 0.70, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (s, 3 H), 3.38 (m, 2 H), 3.63 (d,d, 1 H), 4.01 (t, 1 H), 4.65 (m, 1 H), 5.04 (s, 2 H), 6.76 (t, 1 H), 6.96 (d,d, 1 H), 7.30 (d,d, 1 H), 8.25 (t, 1 H); MS (EI) *m*/*z* 267 (M + H). Anal. Calcd for $C_{12}H_{14}N_3F_1O_3$: C, 53.93; H, 5.28; N, 15.72. Found: C, 53.90; H, 5.36; N, 15.66.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-1,2,3,4-tetrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (11). A slurry of **20** (500 mg, 1.87 mmol), sodium azide (182 mg, 2.81 mmol), and triethyl orthoformate (450 mg, 3.02 mmol) in acetic acid (10 mL) was refluxed for 4 h. The mixture was cooled and added to ice water (20 mL). After setting at ambient temperature for 48 h, the precipitated product was collected by filtration and washed with cold CH_3OH to yield 172 mg (29%) of **11:** mp 167−169 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.96 (s, 1 H), 8.25 (t, *J* = 5.76 Hz, 1 H), 7.89 (t, *J* = 8.7 Hz, 1 H), 7.85 (dd, *J* = 13.2, 2.4 Hz, 1 H), 4.79 (m, 1 H), 4.20 (t, *J* = 9.1 Hz, 1 H), 3.81 (dd, *J* = 9.2, 6.5 Hz, 1 H), 3.44 (t, *J* = 5.4 Hz, 1 H); HRMS (FAB) calcd for $C_{13}H_{13}FN_6O_3$ + H 321.1111, found 321.1118. Anal. Calcd for $C_{13}H_{13}FN_6O_3 \cdot 1/3CH_3OH$: C, 48.39; H, 4.37; N, 25.39. Found: C, 48.72; H, 4.29; N, 24.71.

***N*-{[(5*S*)-3-(3-Fluoro-4-isothiocyanatophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (21).** To a solution of 1,1-thiocarbonyldi-2(1*H*)-pyridone (0.96 g, 4.12 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added **20** (1.0 g, 3.74 mmol) in one portion. Over the course of 1 h **20** slowly went into solution as a second material came out. After stirring in the cold for 2.5 h and then at room temperature for 2 h, the reaction mixture was concentrated in vacuo. The residue was treated with water (15 mL) and the solid was finely divided with a spatula and collected on a filter, washed with a small amount of water and dried overnight under vacuum at 55 °C to yield 1.09 g (94%) of **21**: mp 173−176 °C; MS *m*/*z* 309 (M + H).

***N*-{[(5*S*)-3-(3-Fluoro-4-{[(2-formylhydrazino)carbothioyl]amino}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (22).** Formic hydrazide (0.23 g) was added to a mechanically stirred mixture of **21** (1.11 g, 3.6 mmol) in THF (25 mL). The mixture was heated at 70 °C and over 3.5 h a heavy precipitate came out of solution. The mixture was then allowed to cool and stir at room temperature for 1 h. The suspended solid was collected and washed well with EtOAc. The resulting solid was dried under vacuum at 60 °C to yield 1.2 g (91%) of **22** that was carried on to the next reaction without further purification.

(*S*)-*N*-[[3-[4-[3-Mercapto-4-[1,2,4]triazolyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (23). To a mechanically stirred suspension of **22** (1.10 g, 3.0 mmol) in water (22 mL) was added 1 N KOH (3.1 mL). Over 30 min the solid gradually became a finely divided suspension. After stirring for 1 h at room temperature the reaction mixture was

acidified with 1 N HCl (3 mL). The resulting precipitate was collected, washed with a little 0.1 N HCl and dried under vacuum at 60 °C to yield 1.03 g (98%) of **23**: mp 266.5−268 °C. An analytical sample was recrystallized from DMF:H_2O: mp 272−273 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84 (s, 3 H), 3.44 (m, 2 H), 3.78 (m, 1 H), 4.19 (t, 1 H), 4.78 (m, 1 H), 7.48 (d, 1 H), 7.66 (t, 1 H), 7.75 (d, 1 H), 8.29 (t, 1 H), 8.70 (s, 1 H), 14.02 (broad s, 1 H); MS *m*/*z* 351 (M + H). Anal. Calcd for $C_{14}H_{14}FN_5O_3S$: C, 47.86; H, 4.02; N, 19.93. Found: C, 48.01; H, 4.29; N, 19.70.

(*S*)-*N*-[[3-[4-[4-[1,2,4]Triazolyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (9). A mixture of **23** (0.33 g, 0.94 mmol) and 20% HNO_3 (0.6 mL) were heated on a steam bath in a test tube with vigorous effervescing. After 1 min the sides of the tube were rinsed down with an additional 0.6 mL of 20% HNO_3. Heating was continued for 7 min until the solid dissolved and then the reaction was cooled in an ice bath. The pH was adjusted to 9.5 with 1 N NH_4OH (5.7 mL) and the solution was concentrated in vacuo. The residue was chromatographed over silica gel with 5% MeOH/0.5% NH_4OH/CH_2Cl_2 to yield 0.23 g (77%) of **9**: mp 204−206 °C; $[\alpha]^{25}_D = -26°$ (*c* 0.92, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82 (s, 3 H), 3.42 (t, 2 H), 3.78 (m, 1 H), 4.16 (t, 1 H), 4.75 (m, 1 H), 7.46 (dd, 1 H), 7.72 (t, 1 H), 7.77 (dd, 1 H), 8.24, (t, 1 H), 8.90 (s, 1 H), 8.91 (s, 1 H); HRMS (FAB) calcd for $C_{14}H_{14}FN_5O_3$ + H_1 320.1159, found 320.1159. Anal. Calcd for $C_{14}H_{14}FN_5O_3$: C, 52.67; H, 4.42; N, 21.93. Found: C, 52.42; H, 4.56; N, 21.68.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-pyrrol-1-yl-3-carboxaldehyde)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (25). A solution of **20** (2.0 g, 7.5 mmol) and 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde (1.68 g, 10.5 mmol) in acetic acid (55 mL) was refluxed for 2 h. The solution was cooled and the solvent removed under high vacuum, azeotroping the residue with toluene to remove the last traces of acetic acid. The residue was chromatographed over 300 g of silica gel with 0−3% CH_3OH/CH_2Cl_2 to yield 2.21 g (85%) of **25** as a light yellow amorphous solid: mp 165−168 °C; $[\alpha]_D$ −24° (*c* 0.38, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1 H), 7.70 (dd, *J* = 13.0, 2.4 Hz, 1 H), 7.59 (q, *J* = 1.9 Hz, 1 H), 7.41 (t, *J* = 8.7 Hz, 1 H), 7.27 (d, *J* = 6.9 Hz, 1 H), 7.0 (m, 1 H), 6.80 (dd, *J* = 3.1, 1.6 Hz, 1 H), 6.07 (m, 1 H), 4.83 (m, 1 H), 4.10 (t, *J* = 9.0 Hz, 1 H), 3.85 (dd, *J* = 9.1, 6.8 Hz, 1 H), 3.70 (m, 2 H), 2.04 (s, 3 H); HRMS (EI) calcd for $C_{17}H_{16}FN_3O_4$ 345.1125, found 345.1129. Anal. Calcd for $C_{17}H_{16}FN_3O_4 \cdot 0.1H_2O$: C, 58.82; H, 4.70; N, 12.10. Found: C, 58.71; H, 4.77; N, 12.01.

General Procedure for the Preparation of Oxyimino Analogues 26, 27, 40, 41, 88, 95, 96, and 117. The aldehyde or ketone (1 equiv), hydroxyl- or methyoxylamine hydrochloride (1.5 equiv) and K_2CO_3 (1 equiv) were stirred in CH_3OH/CH_2Cl_2 (1:1). Water and EtOAc were added, the phases were separated, and the aqueous portion was extracted with EtOAc and CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated to give crude materials which were purified as indicated.

(*S*)-*N*-[[3-[3-Fluoro-4-(3-((hydroxyimino)methyl)-1*H*-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (26). The residue was purified on a 2.3 × 28 cm medium-pressure silica column with 5% MeOH/CH_2Cl_2 to give 0.116 g (72%) of **26** as a mixture of *E* and *Z* isomers: mp 216−218 °C; $[\alpha]_D$ −23° (*c* 0.47, DMSO); ^{1}H NMR (400 MHz, DMSO) δ 11.08 (s, 1 H), 10.56 (s, 1 H), 8.24 (m, 1 H), 8.01 (s, 1 H), 7.75 (m, 1 H), 7.70 (m, 1 H), 7.62 (m, 1 H), 7.40 (m, 1 H), 7.30 (m, 1 H), 7.14 (bs, 1 H), 6.63 (m, 1 H), 6.49 (m, 1 H), 4.76 (m, 1 H), 4.16 (t, *J* = 9.1 Hz, 1 H), 3.78 (dd, *J* = 9.0, 6.6 Hz, 1 H), 3.42 (t, *J* = 5.5 Hz, 2 H), 1.83 (s, 3 H); MS (EI) *m*/*z* 360 (M + H); HRMS (EI) calcd for $C_{17}H_{17}FN_4O_4$ 360.1234, found 360.1237. Anal. Calcd for $C_{17}H_{17}FN_4O_4$: C, 56.66; H, 4.75; N, 15.55. Found: C, 56.26; H, 4.85; N, 15.17.

(*S*)-[[3-[3-Fluoro-4-(3-cyanopyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (28). An acetonitrile (15 mL) solution of **26** (0.068 g, 0.19 mmol), triphenylphosphine (0.198 g, 0.75 mmol), and $CHCl_4$ (0.04 mL, 0.41 mmol) was stirred overnight. More carbon tetrachloride (2.5 mL, 25.9 mmol) was added, the reaction mixture was stirred for 4 h and partitioned between water and CH_2Cl_2. The combined organic layer was washed (H_2O), dried ($MgSO_4$), and concentrated in vacuo to give 0.254 g of crude material. This material was purified on a 2.5 × 23 cm medium-pressure silica column with 5% MeOH/CH_2Cl_2 to give 0.047 g (72%) of **28**: mp 167−168 °C; $[\alpha]^{25}_D = -26°$ (*c* 0.49, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 13.2 Hz, *J* ′ = 2.4 Hz, 1 H), 7.41 (d, *J* = 1.6 Hz, 1 H), 7.35 (t, *J* = 8.4 Hz, 1 H), 7.28 (dd, *J* = 9.6 Hz, *J* ′ = 2.4 Hz, 1 H), 6.92 (t, *J* = 3.2 Hz, 1 H), 6.58 (dd, *J* = 2.8 Hz, *J* ′ = 1.6 Hz, 1 H), 6.40 (t, *J* = 6.0 Hz, 1 H), 4.84 (m, 8 lines, 1 H), 4.09 (t, *J* = 8.8 Hz, 1 H), 3.87 (dd, *J* = 8.8 Hz, *J* ′ = 6.8 Hz, 1 H), 3.69 (dd, *J* = 6.0 Hz, *J* ′ = 4.8 Hz, 2 H), 2.03 (s, 3 H); HRMS calcd for $C_{17}H_{15}FN_4O_3$ 342.1128, found 342.1140. Anal. Calcd for $C_{17}H_{15}FN_4O_3$: C, 59.65; H, 4.42; N, 16.37. Found: C, 59.58; H, 4.57; N, 16.07.

***N*-[[(5*S*)-3-{3-Fluoro-4-[3-(hydroxymethyl)-1*H*-pyrrol-1-yl]phenyl}-2-oxo-1,3-oxazolan-5-yl)methyl]acetamide (29).** A solution of aldehyde **25** (125 mg, 0.36 mmol) in 2:1 CH_3OH/CH_2Cl_2 (6 mL) at 0 °C was treated with sodium borohydride (7 mg, 0.18 mmol) followed by warming to ambient temperature for 4 h. The solution was diluted with CH_2Cl_2, treated with saturated ammonium chloride solution, and washed. Drying (Na_2SO_4) and concentration in vacuo afforded a white solid which was crystallized from boiling EtOAc/hexane (with a few drops of methanol) to afford **29** as a white solid 106 mg (84%): mp 155−157 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(3-carbomethoxy-1*H*-pyrrol-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (30). A solution of **25** (220 mg, 0.64 mmol) in 1:1 acetonitrile−CH_3OH (10 mL) was treated with NaCN (164 mg, 0.64 mmol), activated manganese dioxide (1.15 g, 13.2 mmol), and HOAc (58 μL, 1.0 mmol). The mixture was stirred at ambient temperature for 36 h, at which point additional activated manganese dioxide (550 mg, 6.32 mmol) and HOAc (58 μL, 1.0 mmol) were added. The solution was stirred for an additional 24 h, and was filtered through Celite. The filtrate was concentrated in vacuo, diluted with EtOAc and washed with water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford a pink solid. This material was subjected to radial chromatography on a 2 mm plate, eluting with a 0−2% CH_3OH/CH_2Cl_2 gradient to afford 170 mg (71%) of **30** as a white solid: mp 134−135 °C.

General Procedure for the Amonolysis of Esters 30, 47, 89, and 100 To Give Amides 31, 48, 49, 92, and 93. A solution of the ester (1 equiv) and KCN (0.25 equiv) in saturated methanolic ammonia or 2 N $MeNH_2$/CH_3OH was heated in a sealed tube at 50 °C. The solvent was evaporated and the residue was purified as indicated.

(*S*)-*N*-[[3-[3-Fluoro-4-(3-amidopyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (31). The residue was purified on a 2.5 × 25 cm medium-pressure silica column with 5−10% MeOH/CH_2Cl_2 to give 0.029 g (20%) of **31** as a light yellow solid: mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 13.2 Hz, *J* ′ = 2.4 Hz, 1 H), 7.51 (s, 1 H), 7.35 (t, *J* = 8.4 Hz, 1 H), 7.22 (d, *J* = 9.2 Hz, 1 H), 6.90 (m, 1 H), 6.57 (m, 1 H), 4.75 (m, 1 H), 4.04 (t, *J* = 9.2 Hz, 1 H), 3.77 (dd, *J* = 9.2 Hz, *J* ′ = 6.8 Hz, 1 H), 3.58 (m, 1 H), 3.56 (m, 1 H), 3.01 (s, 3 H), 1.96 (s, 3 H); HRMS calcd for $C_{17}H_{17}FN_4O_4$ + H 361.1312, found 361.1314. Anal. Calcd for $C_{17}H_{17}FN_4O_4 \cdot 1.6H_2O$: C, 52.47; H, 5.23; N, 14.39. Found: C, 52.78; H, 5.22; N, 13.69.

(*S*)-*N*-[[3-[3-Fluoro-4-[3-(2-carbethoxyvinyl)-1*H*-pyrrol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (32). A solution of diisopropyl ethoxycarbonylmethylphosphonate (805 mg, 3.19 mmol) in THF (7 mL) at 0 °C was treated with potassium *tert*-butoxide (3.19 mL 1.0 M/THF, 3.19 mmol) and warmed to ambient temperature for 1 h. The solution was cooled to −78 °C and treated via cannula with a solution of **25** (500 mg, 1.45 mmol) in THF (4 mL). The reaction was stirred at −78 °C for 30 min, followed by warming to ambient temperature for 2 h. The solution was quenched by addition of 1 mL saturated ammonium chloride solution, diluted with EtOAc and washed with water. Drying (Na_2SO_4) and concentration in vacuo afforded a yellow solid, which was chromato-

graphed over 100 g of silica gel with 1−2% CH_3OH/CH_2Cl_2 to yield 497 mg (83%) of **32** as a light yellow solid: mp 161−163 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-[3-(2-carbethoxyethyl)-1*H*-pyrrol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (33). A solution of **32** (150 mg, 0.36 mmol) and copper[I] chloride (54 mg, 0.54 mmol) in 1:1 CH_3OH−THF (15 mL) at 0 °C was treated with $NaBH_4$ (136 mg, 3.6 mmol). The solution was stirred at 0 °C for 30 min and then warmed to ambient temperature for 1 h. The solution was treated with 2 mL saturated ammonium chloride solution and filtered through Celite. The filtrate was concentrated in vacuo and the residue was diluted with EtOAc and washed with water. Drying (Na_2SO_4) and concentration in vacuo afforded **33** 150 mg (99%) as a white solid.

(*S*)-*N*-[[3-[3-Fluoro-4-[3-(3-hydroxypropyl)-1*H*-pyrrol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (34). A solution of the ester **33** (275 mg, 0.66 mmol) in THF (15 mL) was treated with lithium borohydride (287 mg, 13.2 mmol) and stirred at ambient temperature for 18 h. The solution was treated with 1 mL of saturated ammonium chloride solution, diluted with EtOAc, and washed with water. Drying (Na_2SO_4) and concentration in vacuo afforded an oil, which was chromatographed over 20 g silica gel eluting with 2−4% CH_3OH/CH_2Cl_2 to yield 96 mg (39%) of **34** as a white solid.

(*S*)-*N*-[[3-[3-Fluoro-4-[3-(3-methanesulfonylaminopropyl)-1*H*-pyrrol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (35). A solution of the alcohol **34** (100 mg, 0.266 mmol) and NEt_3 (0.12 mL, 0.87 mmol) CH_2Cl_2 (2 mL) at 0 °C was treated with methanesulfonyl chloride (58 mL, 0.73 mmol) for 30 min. The solution was diluted with CH_2Cl_2 and washed with water and saturated sodium bicarbonate solution. Drying (Na_2SO_4) and concentration in vacuo afforded the mesylate as a solid. This was dissolved in DMF (2 mL) and added via cannula to a 0 °C solution of methanesulfonamide (38 mg, 0.40 mmol) in DMF (2 mL) that had been previously treated with NaH (17 mg of 60% in oil, 0.43 mmol). The reaction was then warmed at 60 °C for 18 h and cooled and the DMF removed in vacuo. The residue was dissolved in EtOAc and washed with water. Drying (Na_2SO_4) and concentration in vacuo afforded a solid which was subjected to radial chromatography on a 2 mm plate, eluting with 1−4% CH_3OH/CH_2Cl_2 to yield 31 mg (26%) of **35** as a white solid.

(*S*)-[[3-[3-Fluoro-4-(3-acetylpyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (38). The same procedures were used as described for the preparation of **3**−**8** above. Starting with **37** (11.612 g, 42.38 mmol) and making noncritical variations **38**, 1.12 g (19%), was isolated as a pink solid: mp 145−148 °C.

(*S*)-[[3-[3-Fluoro-4-[3-(1-hydroxyethyl)pyrrol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (39). Sodium borohydride (0.046 g, 1.21 mmol) was added to a CH_2Cl_2 (2.5 mL) and CH_3OH (2.5 mL) solution of **38** (0.101 g, 0.28 mmol). After stirring overnight, the reaction was quenched with 1 mL saturated ammonium chloride and the mixture was partitioned between water and CH_2Cl_2. The aqueous portion was extracted with CH_2Cl_2. The combined organic portions were dried ($MgSO_4$) and concentrated in vacuo to give of crude material that was purified on a preparative TLC plate (1000 μm, eluted with 5% $MeOH/CH_2Cl_2$ 2×) to give 0.073 g (72%) of the **39** as a white solid: mp 169−171 °C.

3-Fluoro-4-hydrazinonitrobenzene (42). K_2CO_3 (35 g, 251 mmol) and 3,4-difluoronitrobenzene (20 g, 126 mmol) were stirred in CH_3CN (200 mL) overnight. The solvent was removed in vacuo and the residue was partitioned between $EtOAc/H_2O$. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent in vacuo gave pure **42** as a yellow solid: 20.2 g (94%); mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (br s, 2 H), 5.97 (br s, 1 H), 7.25 (t, J = 8.7 Hz), 7.89 (dd, J = 2.3, 9.4 Hz, 1 H), 8.05 (d, J = 9.1 Hz, 1 H); MS (+ESI) m/z 172 (M + H). Anal. Calcd for $C_6H_6FN_3O_2$: C, 42.11; H, 3.53; N, 24.55. Found: C, 42.49; H, 3.52; N, 24.13.

3-Fluoro-1-nitro-4-(1*H*-4-carbethoxypyrazol-1-yl)benzene (44). The dialdehyde **43**[28] (6.5 g, 45 mmol), NaOAc (3.7 g, 45 mmol) and **42** (8.5 g,49.6 mmol) were placed in absolute EtOH and stirred at room temperature for 30 min. The reaction was then heated to reflux until complete by TLC, cooled and the solvent removed in vacuo. The residue was partitioned between $EtOAc/H_2O$. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent gave **44** as a brown solid which was crystallized from EtOAc/hexane as orange needles 11.5 g (65%): mp 127−127 °C.

(*S*)-[3-[3-Fluoro-4-(1*H*-4-carbethoxypyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol (45). The nitro compound **44** (10 g, 35.8 mmol) was hydrogenated in MeOH with 10% Pd/C (1 g) at 20 psi on a Parr shaker for 3 h. The reaction was filtered through Celite and the solvent removed in vacuo to give pure aniline as an orangish solid 8.63 g (97%). This aniline (8.36 g, 33.5 mmol) and $NaHCO_3$ (5.6 g, 67 mmol) were placed in dry THF (200 mL) and cooled to 0 °C. Benzyl chloroformate (5.3 mL, 36.9 mmol) was added and the reaction was allowed to warm to room temperature. It was partitioned between $EtOAc/H_2O$ and the organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent gave pure Cbz-aniline as an orange solid. 12.7 g (98%). The Cbz-aniline (1.23 g, 3.2 mmol) was place in dry THF at 78 °C under N_2. BuLi was added dropwise and the reaction was stirred 45 min. The *R*-(−)-glycidyl butyrate (0.48 mL, 3.4 mmol) was added dropwise and stirring was continued at −78 °C for 1 h then at room temperature overnight. The mixture was quenched with saturated $NaHCO_3$ and partitioned between H_2O and EtOAc. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent gave an orange residue which was passed through a 4 × 5 cm silica gel plug with 50%EtOAc/hexane to 100% EtOAc gradient. Product **45** was isolated as a white solid: 0.885 g (79%); mp 133−134 °C; $[\alpha]_D$ −39° (*c* 0.93, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3 H), 2.35−2.45 (br m, 1 H), 3.77−3.83 (m, 1 H), 4.02−4.10 (m, 3 H), 4.34 (q, J = 7.1 Hz, 2 H), 4.78−4.82 (m, 1 H), 7.28 (d, J = 10.7 Hz, 1 H), 7.77 (dd, J = 2.4, 11.4 Hz, 1 H), 7.88 (t, J = 8.8 Hz, 1 H), 8.11 (s, 1 H), 8.43 (d, J = 2.4 Hz, 1 H); HRMS calcd for $C_{16}H_{16}FN_3O_5$ + H 350.1152, found 350.1153. Anal. Calcd for $C_{16}H_{16}FN_3O_5$: C, 55.01; H, 4.62; N, 12.03. Found: C, 55.68; H, 4.74; N, 11.66.

(*S*)-[3-[3-Fluoro-4-(1*H*-4-carbethoxypyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl Azide (46). The alcohol **45** (0.76 g, 2.2 mmol) and NEt_3 (0.46 mL, 3.3 mmol) were placed in dry CH_2Cl_2 at 0 °C under N_2. Methanesulfonyl (0.185 mL, 2.4 mmol) was added dropwise. The reaction was allowed to stir at room temperature for 4 h at which time it was partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent gave the mesylate as an off white solid which was pure by TLC and NMR: 0.925 g (98%). The mesylate (0.74 g, 1.73 mmol) and NaN_3 (0.84 g, 13 mmol) were placed in dry DMF and heated to 65 °C overnight. The reaction was cooled, diluted with EtOAc, washed with water (2×) and brine, and dried (Na_2SO_4). Removal of solvent gave **46** as an off white solid: 0.6 g (93%); mp 128−130 °C; $[\alpha]_D$ −105° (*c* 0.96, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3 H), 3.63 (dd, J = 4.2, 13.3 Hz, 1 H), 3.76 (dd, J = 4.4, 13.2 Hz, 1 H), 3.91 (dd, J = 6.2, 8.9 Hz, 1 H), 4.13 (t, J = 8.9 Hz, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 4.82−4.87 (m, 1 H), 7.28 (d, J = 7.3 Hz, 1 H), 7.79 (dd, J = 2.4, 13.7 Hz, 1 H), 7.91 (t, J = 8.8 Hz, 1 H), 8.12 (s, 1 H), 8.45 (d, J = 2.4 Hz, 1 H); HRMS calcd for $C_{16}H_{15}FN_6O_4$ 374.1139, found 374.1143.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-4-carbethoxypyrazol-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (47). The azide **46** (0.59 g, 1.58 mmol) was placed in dry THF and a solution of triphenylphosphine (0.5 g, 1.89 mmol) in THF was added dropwise. The reaction was stirred at room temperature for 1.5 h at which time water (3 mL) was added and the temperature raised to 65 °C overnight. The reaction was cooled and the solvent removed in vacuo. The residue was partitioned between CH_2Cl_2 and water. The aqueous was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4). Removal of solvent in vacuo gave a residue which was chromatographed on a 2 × 30 cm column with 5−10% MeOH/

$CHCl_3$ gradient. The intermediate amine was isolated as a white solid: 0.43 g (77%). The amine (0.35 g, 1 mmol) and pyridine (0.243 mL, 3 mmol) were placed in CH_2Cl_2. Acetic anhydride (0.132 mL, 1.4 mmol) was added and the reaction was stirred at room temperature until complete as determined by TLC. The reaction was then diluted with CH_2Cl_2, washed with 1 N HCl (2×), saturated $NaHCO_3$, and brine, and dried (Na_2SO_4). Removal of solvent gave a residue which was chromatographed on a 2 × 35 cm column with 5% MeOH/CH_2Cl_2. Product **47** was isolated as a white solid: 0.39 g (99%); mp 160−161 °C; $[\alpha]_D$ −23° (*c* 0.47, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3 H), 2.04 (s, 3 H), 3.61−3.69 (m, 1 H), 3.70−3.79 (m, 1 H), 3.84 (dd, J = 6.8, 15.8 Hz, 1 H), 4.10 (t, J = 9.0 Hz, 1 H), 4.35 (q, J = 7.1 Hz, 2 H), 4.81−4.90 (m, 1 H), 5.95 (br t, 1 H), 7.28 (d, J = 8.8 Hz, 1 H), 7.75 (dd, J = 2.4, 13.7 Hz, 1 H), 7.91 (t, J = 8.9 Hz, 1 H), 8.12 (s, 1 H), 8.45 (d, J = 2.4 Hz, 1 H); HRMS calcd for $C_{18}H_{19}FN_4O_5$ + H 391.1418, found 391.1421. Anal. Calcd for $C_{18}H_{19}FN_4O_5 \cdot 0.25H_2O$: C, 54.75; H, 4.98; N, 14.19. Found: C, 54.67; H, 4.98; N, 14.11.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-4-cyanopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (50). The carboxamide **48** (0.23 g, 0.64 mmol) was placed in dry DMF (7.5 mL) and cooled to 0 °C under N_2. $SOCl_2$ (0.07 mL, 0.95 mmol) was added dropwise and the reaction was stirred at room temperature for 30 min. More $SOCl_2$ (0.07 mL, 0.95 mmol) was added and stirring was continued another 30 min. Saturated $NaHCO_3$ was added and the reaction was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and the solvent removed. The residue was chromatographed on a 2 × 30 cm column with 5% MeOH/CH_2Cl_2. Product **50** was isolated as a white solid: 155 mg (71%); mp 194−196 °C; $[\alpha]_D$ −27° (*c* 0.57, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 3.65−3.76 (m, 2 H), 3.86 (dd, J = 6.9, 8.9 Hz, 1 H), 4.10 (t, J = 8.9 Hz, 1 H), 4.81−4.90 (m, 1 H), 6.07 (br t, 1 H), 7.29 (d, J = 7.6 Hz, 1 H), 7.78 (dd, J = 1.9, 13.8 Hz, 1 H), 7.89 (t, J = 8.8 Hz, 1 H), 8.00 (s, 1 H), 8.38 (s, 1 H); HRMS calcd for $C_{16}H_{14}FN_5O_3$ + H 344.1159, found 344.1153. Anal. Calcd for $C_{16}H_{14}FN_5O_3 \cdot 0.5H_2O$: C, 54.55; H, 4.29; N, 19.87. Found: C, 54.66; H, 4.24; N, 19.46.

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(1*H*-4-iodopyrazol-1-yl)benzene (52). 4-Iodopyrazole (10 g, 52 mmol), 3,4-difluoronitrobenzene (8.3 g, 52 mmol) and K_2CO_3 (7.2 g, 52 mmol) were placed in dry DMSO (100 mL) and heated to 90 °C under N_2 for 24 h. The reaction was cooled and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined extracts were dried (Na_2SO_4). Removal of solvent gave a residue which was taken up in Et_2O, washed with H_2O (3×) and dried (Na_2SO_4). Removal of solvent again gave pure pyrazolylnitrobenzene intermediate as a yellow solid, 16.5 g (95%). This pyrazolylnitrobenzene (2.6 g, 7.8 mmol) and $SnCl_2$ (8.8 g, 39 mmol) were placed in absolute EtOH and heated to 75 °C for 1 h. The reaction was cooled and poured into ice. The mixture was made basic with saturated $NaHCO_3$ and filtered. The filtrate was extracted with EtOAc (3×). The combined extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave the aniline as a yellow oil 2.1 g (88%). This aniline (9.41 g, 31.05 mmol) and $NaHCO_3$ (5.2 g, 62 mmol) were placed in dry THF and benzyl chloroformate was added. The reaction was stirred at room temperature overnight, diluted with water and extracted with EtOAc (3×). The extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to give **52** as a yellow solid: 13.72 g (99% from the aniline).

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(1*H*-4-trimethylsilylacetylenylpyrazol-1-yl)benzene (53). The Cbz intermediate **52** (2.0 g, 4.6 mmol), TMS-acetylene (0.78 mL, 5.5 mmol) and diethylamine (20 mL) were place under N_2. $Pd(PPh_3)_2Cl_2$ (0.1 mmol, 70 mg) and CuI (0.005 g) were added. The reaction was stirred at room temperature under N_2 for 8 h. The reaction was evaporated to dryness and the residue was purified on a 2 × 40 cm column. Product **53** was isolated as a solid 1.6 g (85%): mp 133−136 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-4-iodopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (54). The Cbz-protected aniline **52** (3.17 g, 7.25 mmol) was reacted as above for the preparation of compound **47** making noncritical variations. The procedures afforded **54** as a white solid: 0.88 g (27%); mp 199−201 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-4-*N*-(*tert*-butoxycarbonylamino)pyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (55). The aryl iodide **54** (0.265 g, 0.6 mmol), $PdOAc_2$ (13.3 mg, 0.06 mmol), dppp (29.7 mg, 0.072 mmol), and Et_3N (0.1 mL, 0.72 mmol) were heated in 1:10 H_2O/DMF (10 mL) at 100 °C an atmosphere of CO with vigorous stirring for 2 days. The reaction was cooled, filtered and the solvent removed. The residue was triturated in hot acetone and the solid acid filtered off to give 0.2 g (92%): HRMS (FAB) calcd for $C_{16}H_{15}FN_4O_5$ 362.1104, found 362.1265. This acid (0.15 g, 0.4 mmol), DPPA (0.09 mL, 0.4 mmol), and NEt_3 (0.057 mL, 0.4 mmol) were refluxed in *t*-BuOH for 3 days. The solvent was removed and the residue was chromatographed on a 2 × 30 cm column with 5% MeOH/CH_2Cl_2 to give pure **55** as an ivory solid: 110 mg (58%); mp 177−179 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-4-*N*-(acetylamino)pyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (56). The Boc-amine **55** (20 mg, 0.05 mmol) was deprotected in 1:1 TFA/CH_2Cl_2 (4 mL) at room temperature under N_2 for 4 h. The solvent and excess TFA were removed in vacuo and the residue was triturated in Et_2O. The solvent was removed again and the solid product was placed in CH_2Cl_2 (5 mL) and NEt_3 (0.5 mL) was added followed by Ac_2O (0.5 mL). The reaction was stirred at room temperature for 2 h and evaporated to dryness in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent removed. The product **56** was purified on a 2 × 25 cm column with 10% MeOH/CH_2Cl_2 and isolated as a white solid: 15 mg (80%); mp 229−230 °C dec.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-4-trimethylsilylacetylenylpyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (57). The acetylene derivative **53** (1.2 g, 3 mmol) was reacted as described above for the preparation of compound **47** making noncritical variations. The procedures afforded **57** as a white solid: 0.35 g (28%); mp 197−199 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-4-acetylenylpyrazol-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (58). The TMS-acetylide **57** (0.31 g, 0.75 mmol) was treated with K_2CO_3 (0.1 g) in MeOH (20 mL) at room temperature for 1 h. The solvent was removed in vacuo and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and the solvent removed to give pure product as a white solid: 0.25 g (98%); mp 180−182 °C.

3-Fluoro-1-nitro-4-(1*H*-3-*tert*-butoxycarbonylamino-pyrazol-1-yl)benzene (63). The aminopyrazole derivative **62** (3 g, 13.5 mmol), di-*tert*-butyl dicarbonate (2.95 g, 13.5 mmol), NEt_3 (1.88 mL, 13.5 mmol) and (dimethylamino)-pyridine (20 mg) were placed in dry DMF and stirred under nitrogen overnight. The reaction was partitioned between water and Et_2O and the organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent gave a residue that was purified on a 3 × 30 cm column to give **63**: 2.2 g (51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 9 H), 5.97 (d, J = 2.6 Hz, 1 H), 7.12 (br s, 1 H), 8.07−8.14 (m, 4 H); MS (+ESI) m/z 322 (M + H); MS (−ESI) m/z 321 (M − H).

(*S*)-[[3-[3-Fluoro-4-(1*H*-3-trifluoromethylpyrazol-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (64). The nitro compound **61** (6.5 g, 23.6 mmol) was reacted as described above for the preparation of compound **47** making noncritical variations. The procedures afforded **64** as a white solid: 1.32 g (14%); mp 180−181 °C; $[\alpha]^{25}_D$ = −23 °C (*c* 0.95, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 3.65−3.78 (m, 2 H), 3.85 (dd, J = 6.9, 9.0 Hz, 1 H), 4.10 (t, J = 8.9 Hz, 1 H), 4.79−4.85 (m, 1 H), 6.09 (br t, 1 H), 6.73 (d, J = 2.4 Hz, 1 H), 7.24 (d, J = 10.4 Hz, 1 H), 7.77 (dd, J = 2.5, 13.7 Hz, 1 H), 7.90 (t, J = 8.8 Hz, 1 H), 8.00 (s, 1 H); MS (+ESI) m/z 387 (M + H). Anal. Calcd for $C_{16}H_{14}F_4N_4O_3$: C, 49.75; H, 3.65; N, 14.50. Found: C, 50.01; H, 3.70; N, 14.10.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-*tert*-butoxycarbonylaminopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ac-

etamide (65). The Boc intermediate **63** (1.8 g, 5.6 mmol) was reacted as described above for the preparation of compound **47**. The main variation was that 2 equiv of *n*-BuLi were used in the oxazolidinone ring forming reaction. The procedures afforded **65** as a pale yellow solid: 300 mg (12%); mp 193−194 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-aminopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (66). The Boc-protected material **65** (0.25 g, 0.58 mmol) was dissolved in CH_2Cl_2 (7 mL) and cooled to 0 °C under nitrogen. Trifluoroacetic acid (5 mL) was added and the reaction was allowed to warm to room temperature and stirred 3 h. The solvent and excess TFA were removed in vacuo and the residue was partitioned between 1 M $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with 5%MeOH/CH_2Cl_2 and the extracts were combined and dried (Na_2SO_4). Removal of solvent gave pure **66** as a pale yellow solid: 0.16 g (83%).

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-benzyloxymethylacetylaminopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (67). The arylamine **66** (25 mg, 0.075 mmol) and NEt_3 (0.012 mL, 0.082 mmol) were placed in dry methylene chloride. Benzyloxyacetyl chloride (0.013 mL, 0.082 mmol) was added and the reaction was stirred under nitrogen for 4 h and then partitioned between saturated $NaHCO_3$ solution and CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent removed to give a residue which was chromatographed on a 2 × 30 cm column with 7% MeOH/$CHCl_3$. The product **67** was isolated as a tan solid: 35 mg (97%).

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-hydroxymethylacetylaminopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (68). The intermediate **67** (30 mg, 0.062 mmol) was hydrogenated in MeOH on a Parr shaker at 30 psi with 10% Pd/C for 6 h. The reaction was filtered through Celite and evaporated to dryness. The residue was purified on a 2 × 35 cm column with 10% MeOH/$CHCl_3$ to give the product as a tan solid: 22 mg (99%); mp 129−132 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-acetylaminopyrazol-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (69). Intermediate **66** (26 mg, 0.078 mmol) and NEt_3 (0.012 mL, 0.085 mmol) were placed in dry CH_2Cl_2. Acetic anhydride (2 mL) was added and the reaction was stirred at room temperature for 2 h and evaporated to dryness. The residue was purified on a 2 × 30 cm column with 10% MeOH/$CHCl_2$ to give product as a white solid: 25 mg (78%); mp 212−214 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-methanesulfonylaminopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (70). Intermediate **66** (20 mg, 0.06 mmol) was placed in pyridine (3 mL) and cooled to 0 °C. Methanesulfonyl chloride (0.005 mL, 0.066 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and dried (Na_2SO_4). Removal of solvent in vacuo gave the product as a pale yellow foam: 18 mg (73%); mp 145−146 °C.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-cyanopyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (71). The amino derivative **67** (36 mg, 0.108 mmol) was placed in 2 N HCl (3 mL) at 0 °C. A solution of $NaNO_2$ in water (1 mL) was added and the mixture was stirred 30 min at 0 °C before being neutralized with solid $NaHCO_3$. In a separate flask CuCN (12.6 mg, 0.14 mmol), KCN (10.5 mg, 0.162 mmol), water (2 mL) and EtOAc (3 mL) were cooled to 0 °C. The diazonium salt was added to this mixture with a pipet. The reaction was stirred at 0 °C for 30 min and then at room temperature for 2 h. It was partitioned between saturated $NaHCO_3$ and $CHCl_3$ and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and evaporated to dryness. The residue obtained was purified on a 2 × 35 cm column with 5% MeOH/$CHCl_3$. Product was isolated as a yellow free flowing powder: 14 mg (38%); mp 190−192 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 3.62−3.73 (m, 2 H), 3.86 (dd, J = 6.7, 9.1 Hz, 1 H), 4.11 (t, J = 8.9 Hz, 1 H), 4.80−4.88 (m, 1 H), 5.98 (br t, 1 H), 6.88 (d, J = 2.6 Hz, 1 H), 7.27 (d, J = 6.1 Hz, 1 H), 7.80 (dd, J = 2.4, 13.8 Hz, 1 H), 7.89 (t, J = 8.8 Hz, 1 H), 8.04 (t, J = 2.5 Hz, 1 H); HRMS calcd for $C_{16}H_{14}FN_5O_3$ 343.1081, found 343.1078. Anal. Calcd for $C_{16}H_{14}FN_5O_3 \cdot 1.25CH_3OH$: C, 54.04; H, 4.99; N, 18.27. Found: C, 53.65; H, 4.35; N, 18.10.

***N*-{[(5*S*)-3-(3-Fluoro-4-hydrazinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (72).** A solution of the aniline **20** (5.34 g, 20.0 mmol) in 8 mL of methanol, 20 mL of water plus 6 mL of 37% HCl at −10 °C was treated dropwise with a solution of $NaNO_2$ (1.40 g, 20.2 mmol) in 4 mL of water over a 2 min period. After stirring for 8 min at −10° C, the contents were transferred to a dropping funnel and added over a 2 min period to a vigorously stirred solution of $SnCl_2 \cdot 2H_2O$ (10.80 g, 47.8 mmol) in 52 mL of 37% HCl at −10 °C. After stirring for an additional 40 min, the pH of the reaction mixture was adjusted to 7−8 by the dropwise addition of 10 N NaOH (80 mL) with cooling in an ice/acetone bath. The milky white aqueous suspension was concentrated and the gelatinous residue triturated (5 × 150 mL) with chloroform−methanol (9:1). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to obtain 5.2 g of crude product. Recrystallization from a methanol, methylene chloride, diethyl ether mixture afforded 4.26 g (75.5%) of analytically pure **72** as a white solid: mp 173−175 °C; $[\alpha]^{25}_D$ −26° (*c* 0.79, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (t, J = 5.77 Hz, 1 H), 7.32 (dd, J = 2.34, 14.14 Hz, 1 H), 7.11 (q, J = 8.95 Hz, 1 H), 7.04 (dd, J = 2.27, 8.87 Hz, 1 H), 6.53 (s, 1 H), 4.64 (m, 1 H), 4.01 (m, 3 H), 3.63 (m, 1 H), 3.37 (t, J = 5.54 Hz, 2 H), 1.81 (s, 3 H); MS (EI) *m*/*z* 282 (M + H). Anal. Calcd for $C_{12}H_{15}FN_4O_3$: C, 51.06; H, 5.36; N, 19.85. Found: C, 51.07; H, 5.34; N, 19.76.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-3-methylpyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (73). Acetaldehyde dimethyl acetal (0.105 mL, 0.71 mmol) and the arylhydrazine **72** (0.2 g, 0.71 mmol) were heated at reflux in ethanol for 2 h. The solvent was removed in vacuo and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified on a 2 × 35 cm column with 5% MeOH/CH_2Cl_2 to give the desired product **73** (high R_f) as a solid 110 mg (47%): mp 129−131 °C; $[\alpha]^{25}_D$ = −29° (*c* 0.74, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.35 (s, 3 H), 3.66 (dd, J = 4.6, 6.0 Hz, 2 H), 3.81 (dd, J = 6.7, 9.1 Hz, 1 H), 4.06 (t, J = 9.0 Hz, 1 H), 4.76−4.83 (m, 1 H), 6.23 (d, J = 2.4 Hz, 1 H), 6.71 (br t, J = 6.0 Hz, 1 H), 7.17 (dd, J = 1.7, 8.9 Hz, 1 H), 7.63 (dd, J = 2.4, 13.9 Hz, 1 H), 7.82 (d, J = 1.7 Hz, 1 H); HRMS (FAB) calcd for $C_{16}H_{17}FN_4O_3 + H_1$ 333.1363, found 333.1349. Anal. Calcd for $C_{16}H_{17}FN_4O_3 \cdot 0.25H_2O$: C, 57.05; H, 5.24; N, 16.63. Found: C, 57.05; H, 5.10; N, 16.44.

(*S*)-*N*-[[3-[3-Fluoro-4-(1*H*-5-methylpyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (74). In addition to the above material a lower R_f product was isolated which was found to be the 5-regioisomer by 2D NMR: 60 mg (25%); mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.20 (s, 3 H), 3.59−3.71 (m, 2 H), 3.84 (dd, J = 6.8, 9.1 Hz, 1 H), 4.08 (t, J = 9.0 Hz, 1 H), 4.76−4.83 (m, 1 H), 6.19 (s, 1 H), 6.63 (br t, J = 6.0 Hz, 1 H), 7.27 (dd, J = 1.8, 8.7 Hz, 1 H), 7.44 (t, J = 8.5 Hz, 1 H), 7.60 (d, J = 1.5 Hz, 1 H), 7.67 (dd, J = 2.4, 12.2 Hz, 1 H); HRMS (FAB) calcd for $C_{16}H_{17}FN_4O_3$ + H 333.1363, found 333.1349. Anal. Calcd for $C_{16}H_{17}FN_4O_3 \cdot 0.75H_2O$: C, 55.57; H, 5.39; N, 16.20. Found: C, 55.71; H, 5.10; N, 16.00.

***N*-{[(5*S*)-3-(4-{2-[(*E*)-3-ethoxy-2-propenoyl]hydrazino}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (76).** The arylhydrazine **72** (1.3 g, 4.6 mmol), the acryloyl chloride **75**[34] (0.42 g, 3 mmol) and triethylamine (0.42 mL, 3 mmol) were heated to reflux in dry THF for 5 h. The reaction was cooled and diluted with a large volume of Et_2O. The precipitated product was isolated as an orange solid and used without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, J = 7.0 Hz, 3 H), 1.82 (s, 3 H), 3.38 (t, 2 H), 3.65−3.70 (m, 1 H), 3.91 (q, J = 7.0 Hz, 2 H), 4.03 (t, 1 H), 4.62−4.70 (m, 1 H), 5.41 (d, 1 H), 6.72 (t, 1 H), 7.05 (d, 1 H), 7.39 (d, 1 H), 7.42 (br s, 1 H), 7.53 (br s, 1 H), 8.21 (br t, 1 H); MS (+ESI) *m*/*z* 381 (M + H); MS (−ESI) *m*/*z* 379 (M − H).

(*S*)-[[3-[3-Fluoro-4-(1*H*-3-hydroxypyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (77). The acylhy-

drazine **76** was stirred in concentrated HCl for 4 h at room temperature. An equal volume of water was added and the reaction was evaporated to dryness under Hi-vac. The residue was chromatographed on a 2 × 30 cm column with 5%MeOH/CH_2Cl_2. The product **77** was isolated as a yellow solid: 0.65 g (65% for 2 steps); mp 234−235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3 H), 3.42 (t, J = 5.5 Hz, 2 H), 3.76 (dd, J = 6.5, 9.1 Hz, 1 H), 4.12 (t, J = 9.0 Hz, 1 H), 4.70−4.78 (m, 1 H), 5.82 (d, J = 2.5 Hz, 1 H), 7.39 (d, J = 9.0 Hz, 1 H), 7.65 (dd, J = 2.4, 13.2 Hz, 1 H), 7.70 (t, J = 9.1 Hz, 1 H), 7.86 (t, J = 2.6 Hz, 1 H), 8.23 (br t, 1 H); MS (+ESI) m/z 335 (M + H); MS (−ESI) m/z 333 (M − H). Anal. Calcd for $C_{15}H_{15}FN_4O_4 \cdot 1/3H_2O$: C, 53.20; H, 4.64; N, 16.46. Found: C, 53.20; H, 4.73; N, 16.02.

(*S*)-[[3-[3-Fluoro-4-(1*H*-3-acetoxypyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (78). The alcohol **77** (20 mg, 0.06 mmol) was placed in acetic anhydride (3 mL) and pyridine (0.03 mL) was added. The reaction was stirred at room temperature for 3 h and then evaporated to dryness. The residue was purified on a 2 × 30 cm column with 3% MeOH/CH_2Cl_2 to give the product as an oil. This was crystallized from CH_2Cl_2/hexane to give 20 mg (89%): mp 125−128 °C.

(*S*)-[[3-[3-Fluoro-4-(1*H*-3-methoxypyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (79). The alcohol **77** (0.11 g, 0.33 mmol), methyl iodide (3.3 mmol) and K_2CO_3 were heated to reflux in acetone for 3 h. The reaction was cooled, filtered and evaporated to dryness. The residue was purified on a 2 × 30 cm column with 5% MeOH/CH_2Cl_2 to give the product as a gum which was solidified in CH_2Cl_2/hexane to yield a tan solid: 85 mg (74%); mp 132−133 °C.

4-({[*tert*-Butyldimethylsilyl]oxy}methyl)-1-(2-fluoro-4-nitrophenyl)-1*H*-imidazole (82). Compound **81** (5.8 g, 24.5 mmol) and imidazole (3.32 g, 48.8 mmol) were dissolved in dry DMF (40 mL) and cooled to 0 °C. TBDMSCl (5.5 g, 36.5 mmol) was added and the reaction was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was chromatographed with a 30−50% EtOAc/hexane gradient. Product was isolated as a yellow solid: 5.53 g (64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 0.94 (s, 9 H), 4.78 (s, 2 H), 7.26 (d, J = 3 Hz, 1 H), 7.34 (t, J = 8 Hz, 1 H), 7.96 (s, 1 H), 8.17 (s, 1 H), 8.20 (s, 1 H); MS (ESI+) m/z 352 (M + H); MS (ESI−) 350 (M − H).

***N*-[((5*S*)-3-{4-[4-({[*tert*-Butyldimethylsilyl]oxy}methyl)-1*H*-imidazol-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (83).** Compound **82** (5.53 g, 15.6 mmol) was reacted as described above for the preparation of compounds **3**−**8** making noncritical variations. The procedures afforded **83** as an amber solid: 1.67 g (23%).

***N*-[((5*S*)-3-{4-[4-(Hydroxymethylmethyl)-1*H*-imidazol-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-acetamide (84).** Compound **83** (1.67 g, 3.6 mmol) was dissolved in 3:1:1 AcOH/THF/H_2O (50 mL) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and diluted with Et_2O. The resulting precipitate was collected as a white solid and used as is: 1.27 g.

***N*-({(5*S*)-3-[4-(4-Cyano-1*H*-imidazol-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (85).** A slurry of **84** (1.27 g, 3.65 mmol) in CH_2Cl_2 (10 mL) was treated with DBU (1.33 mL, 8.9 mmol) followed by diphenyl phosphorazidate (1.8 mL, 8.4 mmol). The mixture was stirred at room temperature for 2 days. The solvent was removed in vacuo and the residue was purified on silica gel with 0.5−2%MeOH/CH_2Cl_2 gradient. The intermediate azide was isolated as an amber syrup: 1.17 g (86%). The azide (1.17 g, 3.14 mmol) was suspended in EtOH (80 mL). 2,5-dimethyl-3-hexyne-2,5-diol (0.58 g, 4.12 mmol) and 10% Pd/C (0.58 g) were added. The mixture was heated to reflux for 3 h. The reaction was filtered and the solvent removed in vacuo. The residue was purified on silica gel with 0.5−2%MeOH/CH_2Cl_2 gradient to give **85** as a white solid: 308 mg (28%); mp 204−205 °C; $[\alpha]^{25}_D = -25°$ (c 0.79, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 3.65−3.78 (m, 2 H), 3.88 (dd, J = 7, 9 Hz, 1 H), 4.10 (t, J = 9 Hz, 1 H), 4.84 (br m, 1 H), 6.01 (br t, 1 H), 7.34−7.43 (m, 2 H), 7.75−7.80 (m, 3 H); MS (ESI+) m/z 344 (M + H); MS (ESI−) m/z 342 (M − H). Anal. Calcd for $C_{16}H_{14}FN_5O_3$: C, 55.98; H, 4.11; N, 20.40. Found: C, 55.86; H, 3.99; N, 20.31.

***N*-{[(5*S*)-3-(4-Azido-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (86).** The aniline **20** (2 g, 7.5 mmol) was dissolved in concentrated HCl (10 mL) and water (10 mL) and cooled to 0 °C. Sodium nitrite was added and the yellow solution was stirred at 0 °C for 2 h. A solution of NaN_3 (0.97 g, 15 mmol) and NaOAc (12.3 g, 150 mmol) was added dropwise. The mixture was extracted with EtOAc and the combined extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave product as a tan solid, 2.1 g (96%), that was used without further purification.

General Procedure for the Preparation of 1,2,3-triazoles 87 and 89−91 from Azide 86 and Alkynes. The azide **86** (1 equiv) was suspended in benzene and the alkyne (3 equiv) was added and the mixture was refluxed. The reaction was cooled and the precipitated products were isolated.

***N*-({(5*S*)-3-[4-(4-Acetyl-1*H*-1,2,3-triazol-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (87):** yield 0.41 g (66%); mp 183−186 °C; $[\alpha]^{25}_D = -29°$ (c 0.73, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3 H), 2.77 (s, 3 H), 3.67−3.80 (m, 2 H), 3.88 (dd, J = 9, 7 Hz, 1 H), 4.12 (t, J = 9 Hz, 1 H), 4.81−4.90 (m, 1 H), 6.05 (br t, 1 H), 7.35 (d, J = 11 Hz, 1 H), 7.82 (dd, J = 2, 13 Hz, 1 H), 7.97 (t, J = 9 Hz, 1 H), 8.55 (d, J = 2 Hz, 1 H); MS (EI) m/z 361 (M); HRMS (EI) calcd for $C_{16}H_{16}FN_5O_4$ 361.1186, found 361.1183. Anal. Calcd for $C_{16}H_{16}FN_5O_4$: C, 53.19; H, 4.46; N, 19.38. Found: C, 53.03; H, 4.54; N, 19.13.

***N*-[((5*S*)-3-{3-Fluoro-4-[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (94).** The aldehyde **91** (100 mg, 0.29 mmol) was suspended in MeOH, $NaBH_4$ (11 mg, 0.29 mmol) was added and the mixture became homogeneous. The reaction was stirred at room temperature overnight, and a few drops of water was added and the solvent removed in vacuo. The residue was purified on silica gel with 10% MeOH/CH_2Cl_2. Product was isolated as a white solid: mp 186−188 °C.

***N*-[((5*S*)-3-{4-[2-(1-Cyano-2-nitriloethylidene)hydrazino]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (97).** A mixture of concentrated HCl (100 mL) and water (100 mL) was stirred at 25 °C and aniline **20** (20.0 g, 74.9 mmol) was added. The solution was cooled in ice and sodium nitrite (5.5 g, 79.7 mmol) added over 5 min. After 1 h of vigorous mechanical stirring, a solution of sodium acetate (12.5 g, 1.52 mole) in water (200 mL) was added. The mixture became very thick and a solution of malononitrile (5.0 g, 75.8 mmol) in ethanol (50 mL) was added. The reaction was allowed to come to room temperature then filtered. The precipitate was washed with $NaHCO_3$ solution (150 mL) and water (200 mL) and dried. The filter cake was ground up and dried in vacuo, 25 °C for 3 days, to afford a bright yellow solid (22.7 g, 88%): mp 235 °C dec; ^{1}H NMR δ (DMSO-d_6) δ 1.81 (s, 3 H), 3.40 (t, J = 5.5 Hz, 2 H), 3.73 (dd, J = 6.5, 9.1 Hz, 1 H), 4.11 (t, J = 9.0 Hz, 1 H), 4.66−4.78 (m, 1 H), 7.34 (d, J = 9.0 Hz, 1 H), 7.50 (t, J = 9.0 Hz, 1 H), 7.60 (dd, J = 2.3, 13.8 Hz, 1 H), 8.22 (t, J = 5.8 Hz, NH); MS (ESI+) m/z 345 (M + H). Anal. Calcd for $C_{15}H_{13}FN_6O_3$: C, 52.33; H, 3.81; N, 24.41. Found: C, 52.32; H, 3.84; N, 24.41.

***N*-[((5*S*)-3-{4-[2-(3,5-Diamino-4*H*-pyrazol-4-ylidene)hydrazino]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-acetamide (98).** To the dinitrile **97** (1.0 g, 2.90 mmol) suspended in ethanol (15 mL) was added hydrazine hydrate (1.0 mL). A yellow solution resulted which was heated to reflux for 2 h. After cooling, filtration afforded **98** as a caked golden solid (1.065 g, 97%): mp 256 °C dec; ^{1}H NMR δ (400 MHz, DMSO) δ 1.82 (s, 3 H), 3.40 (t, J = 5.1 Hz, 2 H), 3.75 (t, J = 7.7 Hz, 1 H), 4.14 (t, J = 9.0, Hz, 1 H), 4.64−4.78 (m, 1 H), 6.13 (bd, 3 H), 7.28 (d, J = 9.0 Hz, 1 H), 7.55 (d, J = 13.6 Hz, 1 H), 7.81 (t, J = 9.0 Hz, 1 H), 8.23 (t, J = 5.4 Hz, NH); MS (ESI+) m/z 375 (M + H). Anal. Calcd for $C_{15}H_{17}FN_8O_3$: C, 47.87; H, 4.56; N, 29.77. Found: C, 47.49; H, 4.61; N, 29.52.

***N*-({(5*S*)-3-[4-(4-Cyano-2*H*-1,2,3-triazol-2-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (99).** Cupric acetate monohydrate (4.0 g, 20 mmol) was stirred in pyridine (20 mL) to give a brilliant blue mixture. Diaminopyrazole **98** (1.88 g, 5.0 mmol) was added and the mixture heated at 100 °C for 1 h. After cooling, the solvent was removed at 40 °C/1 mm and the dark residue partitioned between chloroform (150 mL) and 1 N HCl (100 mL). The acid layer was washed with chloroform (2 × 100 mL) and the combined organics dried ($MgSO_4$), filtered and evaporated. The chloroform was evaporated and the residue chromatographed over silica gel (50 g) eluting with a 0−3% methanol−chloroform gradient. The product was obtained as a creamy yellow powder (128 mg, 7%): mp 164−5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 3.60−3.78 (m, 2 H), 3.87 (dd, J = 6.8, 9.1 Hz, 1 H), 4.11 (t, J = 9.0 Hz, 1 H), 4.80−4.90 (m, 1 H), 5.99 (t, J = 6 Hz, NH), 7.37 (d, J = 9.0 Hz, 1 H), 7.76 (dd, J = 2.4, 12.9 Hz, 1 H), 7.83 (t, J = 8.5 Hz, 1 H), 8.20 (s, 1 H); HRMS (EI) calcd for $C_{15}H_{13}FN_6O_3$ 344.1033, found 344.1022. Anal. Calcd for $C_{15}H_{13}FN_6O_3 \cdot 0.2H_2O$: C, 51.79; H, 3.88; N, 24.15. Found: C, 51.87; H, 3.99; N, 23.78.

Methyl 1-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1*H*-1,2,4-triazole-3-carboxylate (100). A mixture of **20** (5.00 g, 18.73 mmol) and 3 N HCl (26.25 mL, 78.75 mmol) at 0 °C was treated dropwise with a solution of $NaNO_2$ (1.31 g, 18.91 mmol) in 6 mL of water over a 4 min period. After stirring for 8 min, the mixture was added to an ice cooled, mechanically stirred solution of $NaHCO_3$ (20.45 g, 243.5 mmol) in 200 mL of water over a 1 min period. After stirring for an additional 5 min, a solution of methyl isocyanoacetate (2.04 g, 20.60 mmol) in 25 mL of CH_3OH was added dropwise over a 5 min period at 0−5 °C. The reation was stirred at 0−5 °C for 5 h. The mixture was diluted with $CHCl_3$−CH_3OH (9:1) and 200 mL of water, and the aqueous layer was extracted six times with $CHCl_3$−CH_3OH (9:1). The combined organics were dried with Na_2SO_4 and concentrated with 26 g of silica gel. The material was chromatographed over 350 g of silica gel, packed and eluted with EtOAc−CH_3OH (95:5) with increasing polarity gradient to 8% CH_3OH to obtain 5.50 g as an off-white solid. Trituration with 200 mL of Et_2O at room temperature gave 5.50 g (78%) of **100** as a white solid: mp 165−166.5 °C; $[\alpha]^{25}_D$ −27° (*c* 0.27, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1 H), 7.84 (t, J = 9 Hz, 1 H), 7.79 (dd, J = 2, 13 Hz, 1 H), 7.53 (dd, J = 2, 11 Hz, 1 H), 4.77 (m, 1 H), 4.17 (t, J = 9 Hz, 1 H), 3.88 (s, 3 H), 3.79 (m, 1 H), 3.43 (t, J = 5 Hz, 2 H), 1.82 (s, 3 H); MS (EI) *m*/*z* 377 (M + H). Anal. Calcd for $C_{16}H_{16}FN_5O_5$: C, 50.93; H, 4.27; N, 18.56. Found: C, 50.86; H, 4.34; N, 18.34.

***N*-[((5*S*)-3-{3-Fluoro-4-[3-(hydroxymethyl)-1*H*-1,2,4-triazol-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (101).** A mixture of lithium borohydride (0.880 g, 95% assay, 0.040 mol) in 160 mL of 2-propanol under N_2 was treated with **100** (7.54 g, 0.020 mol) at room temperature. The reaction was stirred at room temperature overnight. The mixture was treated with 30 mL of water and stirred to decompose the excess $LiBH_4$. The residuals were suspended in CH_3OH/H_2O and adsorbed onto 35 g of silica get at reduced pressure. The material was chromatographed with 400 g of silica gel packed with $CHCl_3$−CH_3OH (92:8) and eluted with increasing CH_3OH gradient to 12% to obtain 5.07 g (73%) of product. Recrystallization from EtOAc, CH_3OH and Et_2O mixture gave analytically pure **101** as white crystals: mp 180−183 °C.

***N*-({(5*S*)-3-[3-Fluoro-4-(3-formyl-1*H*-1,2,4-triazol-1-yl)-phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (102).** A mixture of **101** (0.349 g, 1.00 mmol), 4-methylmorpholine *N*-oxide (0.176 g, 1.50 mmol), tetrapropylammonium perruthenate (TPAP) (0.018 g, 0.05 mmol) and 0.50 g of flame-dried 4 Å molecular sieves in 8 mL of acetonitrile was heated at 60−65 °C for 10 h. The mixture was diluted with EtOAc and washed with 50% saturated brine (40 mL). The aqueous layer was backed extracted two times with EtOAc and the combined organics were dried over Na_2SO_4 and concentrated in vacuo. Chromatography over 50 g of silica gel, packed and eluted with acetone−methylene chloride (2:1) afforded 0.058 g (17%) of **102** as a white solid: mp 186.5−188.5 °C.

1-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1*H*-1,2,4-triazole-3-carboxamide (103). To a solution of 20 mL of 29% NH_4OH in 40 mL of CH_3CN at 50 °C was added **100** (0.500 g, 0.133 mmol). After 3.5 h, the reaction mixture was cooled to 0−5 °C for 25 min, and the white solid was collected and dried in a vacuum oven at 50 °C overnight to yield 375 mg (78%) of **103**: mp 269−270 °C dec.

***N*-({(5*S*)-3-[4-(3-Cyano-1*H*-1,2,4-triazol-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (104).** A suspension of **103** (1.20 g, 3.31 mmol) in 45 mL of CH_2Cl_2 at 0−5 °C in an ice bath was treated with pyridine (0.916 g, 11.60 mmol) followed by the dropwise addition of trifluoroacetic anhydride (2.44 g, 11.60 mmol) in 5 mL of CH_2Cl_2 over a 3 min period. The cooling bath was removed after 20 min and the contents allowed to stir overnight at room temperature. The mixture was poured into 110 mL of saturated $NaHCO_3$ and stirred to decompose the excess reagent. The contents were extracted three times with CH_2Cl_2, dried with anhydrous Na_2SO_4 and concentrated in vacuo with 6 g of silica gel. Chromatography over 55 g of silica gel, packed and eluted with acetone−methylene chloride (1:3), afforded 0.952 g (83.5%) of **104** as a white solid: mp 202−203 °C; $[\alpha]^{25}_D$ −26 (*c* 0.51, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1 H), 8.23 (t, J = 6 Hz, 1 H), 7.85 (t, J = 9 Hz, 1 H), 7.80 (dd, J = 2, 13 Hz, 1 H), 7.54 (dd, J = 2, 9 Hz, 1 H), 4.77 (m, 1 H), 4.18 (t, J = 9 Hz, 1 H), 3.79 (m, 1 H), 3.43 (t, J = 5 Hz, 2 H), 1.82 (s, 3 H); HRMS (FAB) calcd for $C_{15}H_{13}FN_6O_3$ + H 345.1111, found 345.1117. Anal. Calcd for $C_{15}H_{13}FN_6O_3$: C, 52.33; H, 3.81; N, 24.41. Found: C, 52.22; H, 3.89; N, 24.35.

***N*-({(5*S*)-3-[3-Fluoro-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)-phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (106).** To a stirred suspension of ethyl acetimidate hydrochloride **(105)** (0.492 g, 4.00 mmol) in 10 mL of absolute ethanol at room temperature under N_2 was added triethylamine (0.424 g, 4.20 mmol) and the mixture stirred for 13 min. A sample of hydrazine **72** (1.13 g, 4.00 mmol) was added with 2 mL of an additional absolute ethanol rinse. In a separate flask acetyl chloride (0.343 g, 4.40 mmol) was added to 3 mL of CH_3OH to prepare HCl in situ. After cooling to 0 °C, the methanolic HCl was added at once to the reaction mixture at 0 °C. The cooling bath was removed after addition, and the contents were stirred at ambient temperature for 10 min and concentrated in vacuo. The dry solid was treated with 15 mL of triethyl orthoformate and heated for 25 min at 100 °C, allowing the ethanol to distill off. Absolute ethanol (3 mL) was added to dissolve some insoluble material and the mixture was heated at 85 °C. The mixture was diluted with $CHCl_3$−CH_3OH (95:5) and washed successively with saturated $NaHCO_3$ (25 mL) and 50% saturated brine (30 mL) and the combined aqueous washings were back-extracted with $CHCl_3$−CH_3OH (95:5) (4 × 30 mL). The combined organics were dried with Na_2SO_4, concentrated at reduced pressure with 10 g of silica gel and chromatographed over 100 g of silica gel packed and eluted with $CHCl_3$−CH_3OH (97:3 to 96:4) to obtain 478 mg (36%) of **106** as a white solid: mp 206−208 °C; $[\alpha]^{25}_D$ −27 (*c* 0.41, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (brs, 1 H), 8.25 (m, 1 H), 7.76 (m, 2 H), 7.46 (d, J = 9 Hz, 1 H), 4.75 (m, 1 H), 4.16 (t, J = 9 Hz, 1 H), 3.77 (t, J = 9 Hz, 1 H), 3.42 (t, J = 5 Hz, 2 H), 2.34 (s, 3 H), 1.82 (s, 3 H); MS (EI) *m*/*z* 333 (M + H). Anal. Calcd for $C_{15}H_{16}FN_5O_3$: C, 54.05; H, 4.84; N, 21.01. Found: C, 54.01; H, 4.81; N, 20.92.

Ethyl 5-Benzyl-1,2,4-oxadiazol-3-yliminoformate (108). 3-Amino-5-benzyl-1,2,4-oxadiazol **(107)**[43] (12 g, 68.5 mmol) was suspended in triethyl orthoformate and refluxed overnight. The reaction was evaporated to dryness under Hi-vac to give **108** as a yellow oil which was used as is: 14.51 g (92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7 Hz, 3 H), 4.17 (s, 2 H), 4.43 (q, J = 7 Hz, 2 H), 7.28−7.37 (m, 5 H), 8.48 (s, 1 H).

***N*-({(5*S*)-3-[4-({[(5-Benzyl-1,2,4-oxadiazol-3-yl)imino]-methyl}amino)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (109).** Compound **108** (13.9 g, 60

mmol) and **20** (16 g, 60 mmol) were placed in THF (100 mL) and absolute EtOH (50 mL) and refluxed overnight. The reaction was cooled to room temperature and the precipitated product **109** was isolated as a white solid: 22 g (82%); mp 233−235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3 H), 3.43 (t, J = 5 Hz, 1 H), 3.68 (br s, 1 H), 3.78 (dd, J = 7, 9 Hz, 1 H), 4.17 (t, J = 9 Hz, 1 H), 4.99 (br m, 1 H), 7.23−7.32 (m, 6 H), 7.48 (dd, J = 2, 9 Hz, 1 H), 7.72−7.78 (m, 2 H), 8.23 (t, J = 6 Hz, 1 H), 8.81 (d, J = 2 Hz, 1 H), 10.8 (br s, 1 H).

***N*-[1-(4-{[(2*R*)-3-(Acetylamino)-2-hydroxypropyl]amino}-2-fluorophenyl)-1*H*-1,2,4-triazol-3-yl]-2-phenylacetamide (110).** The intermediate **109** (5 g, 11 mmol) was dissolved in EtOH (80 mL) and 10% NaOH (12 mL) and stirred at room temperature overnight. AcOH (11 mL) was added and the reaction was concentrated in vacuo at which time the solid product formed and was isolated, washed with cold EtOH and dried: 4.2 g (89%); mp 191−193 °C; HRMS (FAB) calcd for $C_{21}H_{23}FN_6O_3$ + H 427.1894, found 427.1886. Anal. Calcd for $C_{21}H_{23}FN_6O_3$: C, 59.15; H, 5.44; N, 19.71. Found: C, 56.13; H, 5.58; N, 18.38.

***N*-[1-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1*H*-1,2,4-triazol-3-yl]-2-phenylacetamide (111).** The amino alcohol **110** (2.3 g, 5.4 mmol) was suspended in CH_2Cl_2 (125 mL) and triphosgene (2.4 g, 8.1 mmol) was added. The reaction was stirred overnight at room temperature and concentrated and saturated $NaHCO_3$ was added. The aqueous was decanted to leave a sticky gum that was dissolved in acetone. Precipitated starting material was filtered off and the filtrate was evaporated. The residue was dissolved in MeOH and the desired product precipitated as a white solid: 0.81 g (59%); mp 204−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (s, 3 H), 3.42 (t, J = 5 Hz, 1 H), 3.68 (br s, 1 H), 3.79 (dd, J = 7, 9 Hz, 1 H), 4.17 (t, J = 9 Hz, t H), 4.77 (br m, 1 H), 7.25 (br m, 1 H), 7.3−7.33 (m, 5 H), 7.48 (d, J = 11 Hz, 1 H), 7.72−7.78 (m, 2 H), 8.23 (br t, 1 H), 8.81 (d, J = 2 Hz, 1 H), 10.85 (br s, 1 H). Anal. Calcd for $C_{22}H_{21}FN_6O_4$: C, 58.40; H, 4.68; N, 18.58. Found C, 58.09; H, 4.77; N, 18.38.

***N*-({(5*S*)-3-[4-(3-Amino-1*H*-1,2,4-triazol-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (112).** The benzoyl derivative **111** (1 g, 2.2 mmol) was suspended in EtOH and concentrated HCl (20 drops) was added. The mixture was refluxed for 3 h and the solvent was removed in vacuo. Saturated $NaHCO_3$ was added to the residue and the mixture was diluted with water. The precipitated product was isolated and dried to give a white solid: 0.68 g (92%); mp 222−224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3 H), 3.42 (t, J = 5 Hz, 2 H), 3.77 (dd, J = 7, 9 Hz, 1 H), 4.15 (t, J = 9 Hz, 1 H), 4.75 (br m, 1 H), 5.69 (s, 2 H), 7.43 (d, J = 9 Hz, 1 H), 7.68−7.73 (m, 2 H), 8.23 (br t, 1 H), 8.44 (d, J = 2 Hz, 1 H); HRMS (EI) calcd for $C_{14}H_{15}FN_6O_3$ 334.1190, found 334.1192. Anal. Calcd for $C_{14}H_{15}FN_6O_3 \cdot 1/3H_2O$: C, 49.41; H, 4.64; N, 24.69. Found: C, 49.62; H, 4.76; N, 24.37.

***N*-({(5*S*)-3-[4-(3-Chloro-1*H*-1,2,4-triazol-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (113).** The amino analogue **112** (1 g, 3 mmol) was placed in 2 N HCl (30 mL) at 0 °C and $NaNO_2$ (0.23 g, 3.2 mmol) in water was added. The yellow mixture was stirred at 0 °C for 30 min and CuCl (34 mg, 3.4 mmol) was added. The reaction was warmed to room temperature and stirred overnight. Saturated NH_4Cl was added and the mixture was extracted with EtOAc and dried (Na_2SO_4). Removal of solvent gave a residue that was purified on a silica gel column with 2% MeOH/CH_2Cl_2 to give 245 mg (22%): mp 182−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 3.67−3.74 (m, 2 H), 3.86 (dd, J = 7, 9 Hz, 1 H), 4.11 (t, J = 9 Hz, 1 H), 4.84 (br m, 1 H), 6.07 (br t, 1 H), 7.28 (d, J = 9 Hz, 1 H), 7.81 (dd, J = 2, 14 Hz, 1 H), 7.85 (t, J = 9 Hz, 1 H), 8.52 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{14}H_{13}ClFN_5O_3$: C, 47.54; H, 3.70; N, 19.80. Found: C, 47.46; H, 3.63; N, 19.63.

Cinnamaldehyde Tosylhydrazone (114). Cinnamaldehyde (3.4 mL, 26.96 mmol) was added to an ethanol (50 mL) solution of *p*-toluenesulfonyl hydrazide (5.008 g, 26.89 mmol). The reaction mixture was stirred for 1 h, then was cooled to 0 °C. The resulting yellow solid was filtered and recrystallized from boiling ethanol and water to give 7.101 g (88%) of the desired material as white needles: mp 162−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (bs, 1H), 2.43 (s, 3 H), 6.81−6.88 (m, 2 H), 7.30−7.37 (m, 5 H), 7.40−7.42 (m, 2 H), 7.57 (d, J = 8 Hz, 1 H), 7.88 (d, J = 14 Hz, 2 H); HRMS (EI) calcd for $C_{16}H_{16}N_2O_2S$ 300.0932, found 300.0938. Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.91; H, 5.42; N, 9.32.

***N*-{[(5*S*)-3-(3-Fluoro-4-{5-[(*E*)-2-phenylethenyl]-2*H*-1,2,3,4-tetraazol-2-yl}phenyl)-2-oxo-1,3-oxazolan-5-yl]methyl}acetamide (115).** A precooled (0 °C) aqueous (0.7 mL) solution of sodium nitrite (0.071 g, 1.03 mmol) was added to a solution of **20** (0.274 g, 1.03 mmol) in water (1 mL), hydrochloric acid (0.37 mL), and ethanol (1 mL). This reaction mixture was stirred at 0 °C for 10 min. Then it was added, via cannula, over 30 min, to a pyridine (8 mL) solution of **114** (0.303 g, 1.01 mmol) which had been cooled in an ice/salt bath. After stirring 2 h, chloroform and water were added to the reaction mixture. The phases were separated, and the organic portion was washed with water and brine, dried with $MgSO_4$, and evaporated. The residue was chromatographed on a 2.3 × 25 cm medium-pressure silica column with 2% MeOH/CH_2Cl_2 to give **115** (0.150 g, 35%) as a brown solid: mp 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + MeOD) δ 1.99 (s, 3 H), 3.60−3.64 (m, 2 H), 3.84 (dd, J = 9, 7 Hz, 1 H), 4.10 (t, J = 9 Hz, 1 H), 4.77−4.84 (m, 1 H), 7.19 (d, J = 16 Hz, 1 H), 7.31−7.39 (m, 5 H), 7.56 (d, J = 7 Hz, 2 H), 7.76 (dd, J = 13, 2 Hz, 1 H), 7.81 (d, J = 17 Hz, 1 H), 7.83 (dd, J = 12, 9 Hz, 1 H); HRMS (FAB) calcd for $C_{21}H_{19}FN_6O_3$ + H 423.1581, found 423.1585. Anal. Calcd for $C_{21}H_{19}FN_6O_3$: C, 59.71; H, 4.53; N, 19.90. Found: C, 59.45; H, 4.56; N, 19.77.

***N*-({(5*S*)-3-[3-Fluoro-4-(5-formyl-2*H*-1,2,3,4-tetraazol-2-yl)phenyl]-2-oxo-1,3-oxazolan-5-yl}methyl)acetamide (116).** A suspension of **115** (1.355 g, 3.21 mmol) in CH_2Cl_2 (100 mL) was cooled to −78 °C. Ozone was bubbled through the solution until it turned blue. After stirring for 20 min, nitrogen was then bubbled through the reaction mixture for about 5 min. Then dimethyl sulfide (6 mL) was added, and the mixture was stirred at −78 °C for 5 min then warmed to room temperature. The solvent was evaporated, and the crude material, a cream solid, was used in the next reaction as is: mp 230 °C dec.

***N*-({(5*S*)-3-[4-(5-Cyano-2*H*-1,2,3,4-tetraazol-2-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolan-5-yl}methyl)acetamide (118).** Acetonitrile (7.5 mL) and carbon tetrachloride (1 mL) were added to a flask containing **117** (0.052 g, 0.14 mmol) and triphenylphosphine (0.070 g, 0.27 mmol). The reaction mixture was heated at 85 °C overnight under nitrogen atmosphere. Water and CH_2Cl_2 were added to the reaction mixture. The phases were separated, and the aqueous portion was extracted with CH_2Cl_2, the combined organic portions were dried ($MgSO_4$) and evaporated. The crude material was chromatographed on a 2.3 × 26 cm medium-pressure silica column with 2−5% MeOH/CH_2Cl_2 to give 0.034 g (69%) of the desired compound **118** as a white solid: mp 199−200 °C; $[\alpha]^{25}_D = -18°$ (*c* 0.93, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3 H), 3.63 (d, J = 4 Hz, 2 H), 3.86 (dd, J = 9, 7 Hz, 1 H), 4.11 (t, J = 9 Hz, 1 H), 4.79−4.85 (m, 1 H), 7.20 (bt, 1 H), 7.42 (dt, J = 9, 1 Hz, 1 H), 7.82 (m, 1 H), 7.84 (t, J = 9 Hz, 1 H); HRMS (FAB) calcd for $C_{14}H_{12}FN_7O_3$ + H 346.1064, found 346.1078. Anal. Calcd for $C_{14}H_{12}FN_7O_3$: C, 48.70; H, 3.50; N, 28.40. Found: C, 48.68; H, 3.54; N, 28.05.

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Supporting Information Available: Full experimental descriptions and analytical data for compounds **13c,d**−**f, 14b**−**g, 15b**−**g, 18, 4**−**8, 10, 27, 37, 40, 41, 48, 49, 61, 62, 81, 88**−**93, 95, 96,** and **117** and complete analytical data for com-

pounds **29**, **30**, **32**−**35**, **38**, **39**, **44**, **52**−**58**, **65**−**70**, **78**, **79**, **83**, **94**, **101**−**103**, and **116**. This material is available free of charge via the Internet at http://pubs.acs.org.

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