Novel Substituted (Pyridin-3-yl)phenyloxazolidinones: Antibacterial Agents with Reduced Activity against Monoamine Oxidase A and Increased Solubility

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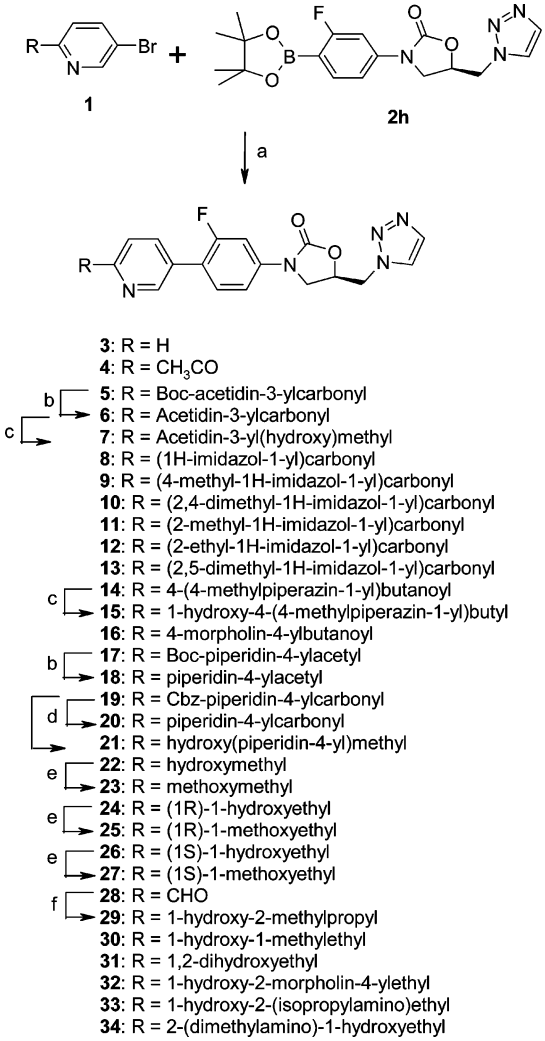
Oxazolidinones represent a new and promising class of antibacterial agents. Current research in this area is mainly concentrated on improving the safety profile and the antibacterial spectrum. Oxazolidinones bearing a (pyridin-3-yl)phenyl moiety (e.g., **3**) generally show improved antibacterial activity compared to linezolid but suffer from potent monoamine oxidase A (MAO-A) inhibition and low solubility. We now disclose the finding that new analogues of **3** with acyclic substituents on the pyridyl moiety exhibit excellent activity against Gram-positive pathogens, including linezolid-resistant *Streptococcus pneumoniae*. Generally, more bulky substituents yielded significantly reduced MAO-A inhibition relative to the unsubstituted compound **3**. The MAO-A SAR can be rationalized on the basis of docking studies using a MAO-A/MAO-B homology model. Solubility was enhanced with incorporation of polar groups. One optimized analogue, compound **13**, showed low clearance in the rat and efficacy against *S. pneumoniae* in a mouse pneumonia model.

Introduction

Oxazolidinones are a new class of antibacterial agent that show good activity against Gram-positive bacteria. Oxazolidinones target bacterial protein synthesis, probably by binding at or near the peptidyltransferase center in actively translating bacterial ribosomes.[1−3] Linezolid was the first member of this class to achieve FDA[a] approval. However, resistance against linezolid has already started to develop in *Enterococcus faecium*[4−8] and, more alarmingly, in *S. aureus*, giving rise to linezolid-resistant MRSA strains.[9] A key concern with oxazolidinones as a drug class has been inhibition of MAO, especially type A (MAO-A), because of the structural similarity to MAO inhibitors like toloxatone.[10] Inhibition of MAO-A could potentially lead to severe hypertensive crises as a result of ingesting tyramine-containing food together with an oxazolidinone drug (the "cheese effect").[11,12] It is therefore desirable to develop novel oxazolidinones that have improved activity against linezolid-resistant Gram-positive bacteria and show an improved safety profile with regard to MAO-A inhibition.[13] Pyridylphenyloxazolidinones, exemplified by the triazole derivative **3**, display excellent activity against Gram-positive bacteria. However, unsubstituted pyridyl derivatives such as **3** suffer from potent MAO-A inhibition (**3**: $K_i < 0.3\ \mu$M) and cytochrome P450 (CYP) inhibition ($K_i \approx 7\ \mu$M for **3** against both 2D6 and 3A4 isozymes). In addition, the low solubility of **3** is a problem for iv formulation. We and others have addressed these issues with varying success by appending yet another ring directly off the pyridine unit in the 6-position.[14−17] However, in our experience, this approach generally tends to confound problems with slow dissolution rates because of increased crystallinity and low solubility, and problems with formulation remain. Also, these analogues with a flat and rodlike shape, consisting of four conjoined rings, still generally retain potent MAO-A inhibition.

Scheme 1[a]



[a] Reagents: (a) Na_2CO_3, $Pd(PPh_3)_4$, DMF, 75 °C; (b) HCl, dioxane, room temp; (c) $Na(BH_4)$, THF, 0 °C; (d) H_2, Pd/C, MeOH, room temp; (e) NaH, MeI, DMF, 0 °C; (f) iprMgBr, THF, −20 °C to room temp.

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[a] Abbreviations: MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; SAR, structure−activity relationship; FDA, Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*; CyP450, cytochrome P450 enzymes; MS (ESP), mass spectroscopy (electrospray); APCI, atmospheric pressure chemical ionization.

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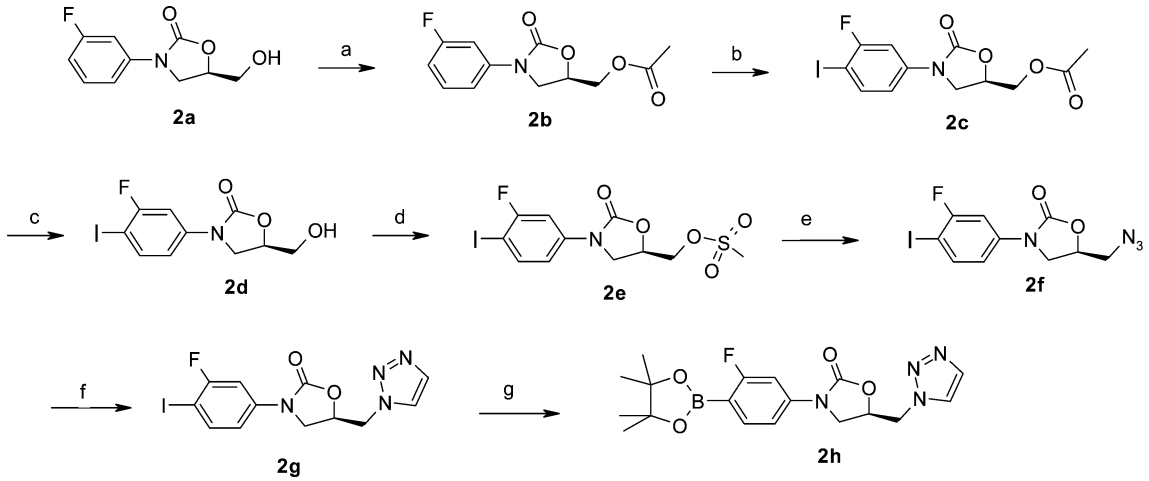
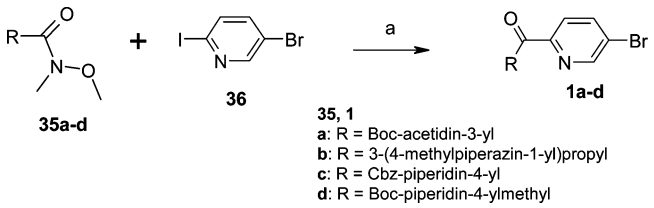
Scheme 2[a]



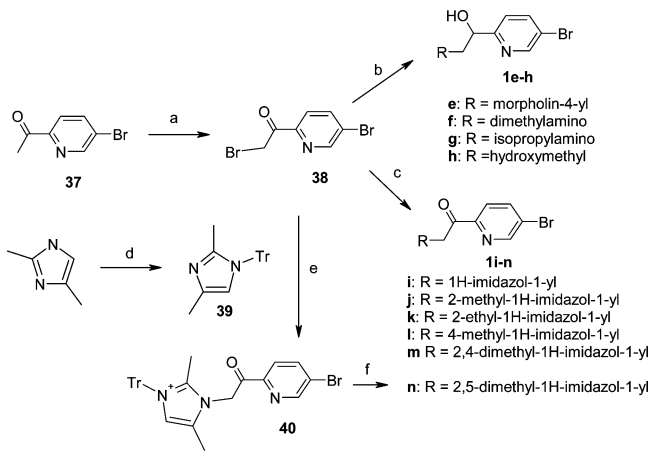
[a] Reagents: (a) NEt_3, DMAP, Ac_2O, CH_2Cl_2, room temp; (b) Ag triflate, I_2, $CHCl_3/CH_3CN$, room temp; (c) K_2CO_3, $MeOH/CH_2Cl_2$, room temp; (d) NEt_3, MsCl, CH_2Cl_2, 0 °C to room temp; (e) NaN_3, DMF, 75 °C; (f) bicyclo[2.2.1]hepta-2,5-diene, dioxane, 100 °C; (g) bis(pinacolato)diboron, KOAc, Pd(dppf)Cl_2.

Scheme 3[a]



[a] Reagents: (a) **36**, iprMgCl, THF, −10 °C, then **35**, 10 °C.

Scheme 4[a]



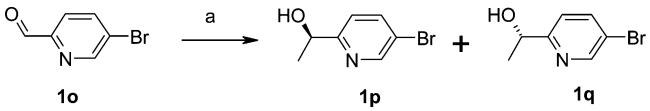
[a] Reagents: (a) Br_2, HBr, MeOH/HOAc, 0 °C to room temp; (b) amine, THF, 0 °C, then $NaBH_4$, MeOH; for **1h**, HCOONa, EtOH, 50 °C, then $NaBH_4$, MeOH, 0 °C; (c) imidazole derivative, THF, 0 °C; (d) TrCl, NEt_3, CH_2Cl_2, room temp; (e) dioxane, 75 °C; (f) TFA/CH_2Cl_2, reflux.

We now report on our studies into the SAR of 6-acyclic-substituted pyridylphenyloxazolidinones (researchers at RibX have recently published patent applications in this area as well[18−20]) that have led to new oxazolidinones with significantly reduced MAO-A inhibition and improved solubility relative to the lead **3** and with excellent Gram-positive activity, including against linezolid-resistant strains.[21,22]

Chemistry

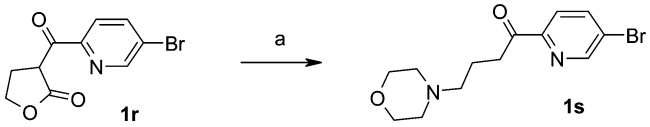
Pyridylphenyloxazolidinones were assembled by Suzuki coupling of pyridyl bromides **1a**−**s** (Schemes 3−6) with the boronic ester **2h** (Scheme 1). In some cases further modifications, including alkylations of alcohols to methoxy ethers (**23**, **25**, **27**), reduction of ketones to alcohols (**7**, **15**, **21**), and simple deprotection reactions, were performed after coupling using standard functional group manipulations. However, most transformations were carried out at the pyridyl bromide stage rather than after Suzuki coupling because of the low solubility of oxazolidinone intermediates such as **4** and **28** in most organic solvents. The boronic ester **2h** was synthesized using a silver triflate assisted iodination in the key step, as outlined in Scheme 2. Acylated pyridyl bromides **1a**−**d** were prepared by reaction of Weinreb amides **35a**−**d** with the Grignard reagent prepared from 5-bromo-2-iodopyridine (**36**) and isopropylmagnesium chloride[23] (Scheme 3). Imidazole derivatives **1i**−**n** were obtained by reaction of α-bromoketone **38** with imidazoles (Scheme 4). Compound **38** was obtained from methyl ketone **37**[17,24] by bromination with bromine/HBr. For the 2,5-dimethyl-1*H*-imidazole derivative **1n**, 2,4-dimethylimidazole was first protected on the less sterically hindered nitrogen with a trityl group and then reacted with **38**, followed by deprotection of the trityl group. Amino alcohols **1e**−**g** and 1,2-diol **1h** were prepared by nucleophilic substitution on **38** with an amine or, for **1h**, with sodium formate, followed by reduction of the α-aminoketone/α-hydroxyketone intermediates with sodium borohydride in situ. The ketone intermediates of **1e**−**h** were unstable and could not be isolated. Reaction of aldehyde **1o**[23,25] with methylmagnesium bromide gave the chiral alcohols **1p** and **1q** (Scheme 5), which were separated by chromatography on a chiral stationary phase. The hydroxymethyl and 1-hydroxy-1-methylethylpyridyl bromides needed for **22** and **30** were obtained via selective monolithiation of 2,5-dibromopyridine.[25] For **1s** (Scheme 6), ethyl 5-bromopyridine-2-carboxylate was reacted with the

Scheme 5[a]



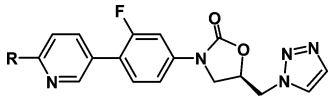
[a] Reagents: (a) MeMgBr, THF, 0 °C.

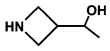
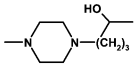
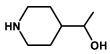
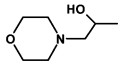
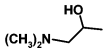
Scheme 6[a]



[a] Reagents: (a) concentrated HCl, 80 °C, then morpholine, 85 °C.

Table 1. SAR of Alcohols and Ethers Compared to Unsubstituted Lead **3**



Compd	R	S.a.[a] MIC (μg/mL)	S.p.[b] MIC (μg/mL)	S.p. LinR[c] MIC (μg/mL)	H.inf.[d] MIC (μg/mL)	*Solub.* (μM)[e]	*PPB* human[f] (%)	*MAO*–A Ki[g] (μM)
3	H	0.25	<0.06	1	2	12.5	ND	<0.3
22	$HOCH_2$	0.25	0.13	1	1	100	ND	4.8
23	CH_3OCH_2	0.5	0.13	1	4	100	ND	1.7
24	(*R*)CH_3CHOH	0.25	<0.06	1	2	>400	76	4.3
25	(*R*)CH_3CHOCH_3	1	0.25	2	8	>400	ND	3
26	(*S*)CH_3CHOH	0.5	<0.06	1	2	>400	67	5.9
27	(*S*)CH_3CHOCH_3	1	0.25	4	16	>400	ND	2.5
29	$(CH_3)_2CHCHOH$	0.5	0.25	2	16	>400	ND	11.3
30	$(CH_3)_2COH$	1	0.25	2	8	200	ND	6
31	$HOCH_2CHOH$	0.25	<0.06	1	1	>400	46	48
7		64	16	>64	64	>400	ND	58
15		2	0.25	1	8	>400	ND	41
21		64	4	32	64	>400	ND	136
32		1	0.25	2	4	>400	33	94
33		4	0.5	2	4	>400	ND	>178
34		4	0.25	2	4	>400	ND	>178

[a] Methicillin-susceptible *Staphylococcus aureus* AP601055. [b] Penicillin-susceptible *Streptococcus pneumoniae* AP671401. [c] Linezolid-resistant (LinR) *Streptococcus pneumoniae*.[43] [d] *Haemophilius influenzae* ATCC51907. Minimum inhibitory concentration (MIC): lowest drug concentration that reduced growth by 80% or more.[32] [e] Solubilities were obtained by nephelometric analysis of test compounds diluted into the MAO-A assay mixture. [f] Human plasma protein binding. ND: no data. [g] Monoamineoxidase A K_i.[35]

sodium salt of γ-butyrolactone to give the dihydrofuranone **1r**,[26] which was cleanly converted to the γ-chloride with HCl. Heating of the chloride with morpholine gave **1s**, together with the 7-bromo-1-oxo-1,2,3,4-tetrahydroquinolizinium salt.

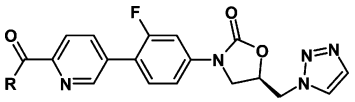
Molecular Modeling

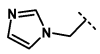
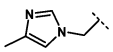
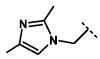
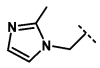
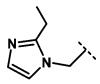
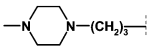
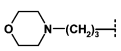
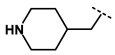
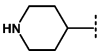
Crystal structures for human mitochondrial monoamine oxidase B (MAO-B) have been reported recently.[27−29] A simple homology model for MAO-A was built by substituting the MAO-B substrate cavity residues Leu 171, Cys 172, Ile 199, and Tyr 326 with the MAO-A residues Ile 180, Asn 181, Phe 208, and Ile 335, respectively. The accuracy of the model is supported by the similarity of the active sites of MAO-A and MAO-B.[29] Docking studies of oxazolidinones using the homology model of MAO-A were performed using the QXP/FLO software.[30] Residues in the substrate and entrance cavities were allowed full conformational flexibility in the docking studies. Figure 1 illustrates the most favorable binding mode identified for **3.** Figure 2 shows the docking of the sterically more demanding **13**, indicating less favorable binding due to crowding at the 6-position of the pyridyl moiety.

Results and Discussion

Oxazolidinones bearing a 6-substituted pyridylphenyl moiety were submitted for evaluation of antibacterial activity. For alcohols (Table 1), compounds bearing a substituent that is relatively small and nonbasic (compounds **22**, **24**, **26**, **31**) retain the excellent Gram-positive activity of the unsubstituted parent **3**, including against linezolid-resistant strains. Moreover, compounds **22** and **31** also show good activity against *Haemophilus influenzae*. Substituents that are more sterically demanding or basic yield reduced activity (**7**, **21**, **29**, **30**, **32**−**34**). Ethers (compounds **23**, **25**, **27**) were less active than the corresponding alcohols. The presence of a base may reduce permeability

Table 2. SAR of Ketones



Compd	R	S.a.[a] MIC (μg/mL)	S.p.[b] MIC (μg/mL)	S.p. LinR[c] MIC (μg/mL)	H.inf.[d] MIC (μg/mL)	*Solub.* (μM)[e]	*PPB* human[f] (%)	*MAO*–A Ki[g] (μM)
4	CH_3	0.25	<0.06	0.5	2	50	ND	0.7
6		8	1	4	16	200	ND	4.5
8		0.25	ND	0.5	2	12.5	ND	>12
9		0.5	<0.06	0.5	2	12.5	69	>5.6
10		0.25	<0.06	0.25	2	25	88	>11
11		0.5	0.13	0.5	2	200	75	>89
12		0.5	<0.06	0.5	4	100	ND	>44
13		0.25	<0.06	0.5	4	50	90	19
14		1	<0.06	0.5	8	>400	50	10.5
16		0.5	0.13	0.5	4	100	65	15
18		1	0.13	0.5	8	>400	ND	28
20		0.5	0.13	0.5	4	100	ND	>44

[a] Methicillin-susceptible *Staphylococcus aureus* AP601055. [b] Penicillin-susceptible *Streptococcus pneumoniae* AP671401. [c] Linezolid-resistant (LinR) *Streptococcus pneumoniae*.[43] [d] *Haemophilius influenzae* ATCC51907. Minimum inhibitory concentration (MIC): lowest drug concentration that reduced growth by 80% or more.[32] [e] Solubilities were obtained by nephelometric analysis of test compounds diluted into the MAO-A assay mixture. [f] Human plasma protein binding. ND: no data. [g] Monoamineoxidase A K_i.[35]

through the bacterial membrane, especially for the more polar alcohols. For ketones (Table 2) antibacterial activity was generally excellent and similar to **3** except for the azetidine analogue **6**.

With regard to the undesired MAO-A inhibition, we observed a correlation to substituent size, with rising K_i values observed for compounds with greater steric bulk next to the alcohol (**7**, **21**, **29**) or ketone (**20**), relative to unbranched derivatives (**4**, **14**− **15**, **16**, **18**, **24**, **26**). Amino alcohols **21** and **32**−**34** had no or weak MAO-A inhibition, which could be due to a combination of increased steric bulk and basic group. The MAO-A SAR of the oxazolidinones listed in Tables 1 and 2 can be largely rationalized on the basis of the docking model shown in Figures 1 and 2. The Lee and Richards molecular surface in Figure 2 indicates that substitution of the pyridyl ring in the 6-position is sterically crowded for larger and more rigid substituents.

The solubility of substituted compounds was generally enhanced relative to parent **3**, especially when ionizable groups were added. Human protein binding was low (<50%) for more soluble compounds (**14**, **31**, and **32**) but higher for the less polar ketones **10** and **13** (88% and 90%, respectively) (Tables 1 and 2).

A small substituent added to the pyridine ring in the 6-position (compound **22**) abolished moderate CYP 3A4 and 2D6 inhibition seen with compound **3** (Table 3). Potent CYP 3A4

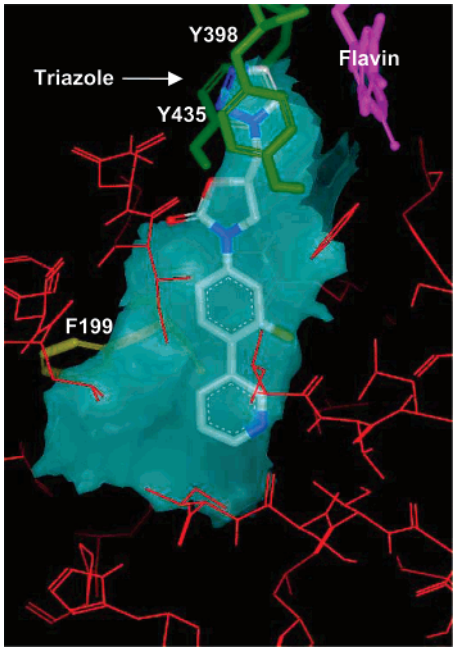


Figure 1. Model of compound **3** docked into a MAO-A homology model. The triazole ring is buried in an "aromatic cage" formed by Y398, Y435, and the flavin cofactor. Note that the binding of **3** induces a conformational change on Phe 199, the gatekeeper residue identified by Binda[27] that joins or separates the entrance and substrate cavities. A Lee and Richards molecular surface is displayed to illustrate the shape of the induced binding pocket. Residue numbers correspond to those from the MAO-B X-ray structure.[27,28]

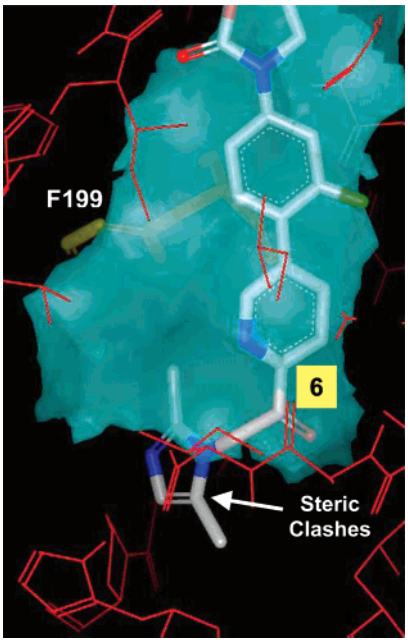
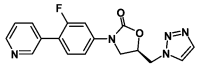
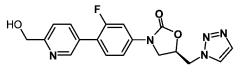
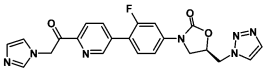
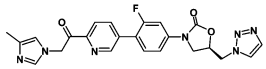
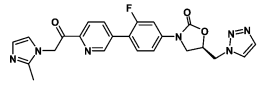
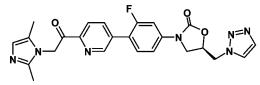


Figure 2. Close-up view of the MAO-A binding pocket surrounding the (pyridin-3yl)phenyl scaffold of **13**. The Lee and Richards molecular surface indicates that substitution of the pyridyl ring in the 6-position is sterically crowded. Small flexible substituents at the 6-position are better tolerated than larger and more rigid substituents. Compound **3** is >60 times more potent against MAO-A than **13**.

inhibition was observed with the unsubstituted imidazole analogue **8**; however, the addition of alkyl groups (**9**, **11**, **13**) on the imidazole ring removed that problem.[31]

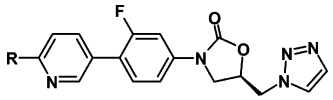
The pharmacokinetics of selected compounds were determined in the rat (Table 4). The alcohols (**26**, **31**) showed high clearance and short half-lives, with glucuronidates identified as

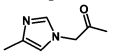
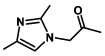
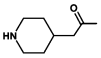
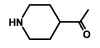
Table 3. CYP450 Inhibition: Substitution Effects on Pyridine and Imidazole[a]

		CYP450 Isoform, IC_{50} (μM)				
Compd	Structure	1A2	2C9	2C19	2D6	3A4
3		>20	>20	>20	6.6	6.8
22		>20	>20	>20	>20	>20
8		>20	8	>20	>20	0.3
9		>20	>20	>20	>20	>20
11		>20	>20	>20	>20	>20
13		>20	>20	>20	>20	10.7

[a] CYP450 inhibition using recombinant human P450 enzymes.

Table 4. Pharmacokinetics of Alcohols and Ketones in the Rat[a]



Compd	R	Clearance (ml/min/kg)	Volume (L/kg)	Half-life *(hr)*	AUC μg·h/mL	Bioavailability (%)
26	(*S*)CH_3CHOH	25	1.3	1	6.7	100
31	$HOCH_2CHOH$	43	1	0.45	3.9	ND
9		Clint >100	ND	ND	ND	ND
10		13	0.9	1	2.6	14
11		62	0.3	0.4	1.2	100
12		23	0.9	0.6	1.6	ND
13		10	1.4	1.8	3.3	73
18		196	15	2.4	0.8	ND
20		38	3.8	2.4	4	ND

[a] Pharmacokinetic parameters following administration of 2 mg/kg (compounds **10**, **12**, **13**) or 10 mg/kg (compounds **11**, **18**, **20**, **26**, **31**) iv bolus injection. Oral bioavailability was assessed following a 10 mg/kg dose.

major metabolites in rat. Ketones with less steric hindrance around the keto group were unstable in vitro in rat microsomes or showed high clearance in vivo (**9**, **11**, **18**). Imidazoles **9**−**11** exhibited the best properties overall with regard to microbiological potency, reduced MAO-A inhibition, absence of CYP inhibition, and acceptable solubility. However, high clearance remained a problem. Metabolic studies for **11** in rat, dog, and human microsomes identified one major metabolite in all species with two mass units higher than the mass of the parent drug, indicating reduction to the corresponding alcohol. The alcohol

Table 5. Exposure and Efficacy of Compound **13** Compared to Linezolid in a Mouse Pneumonia Model[a]

	compound **13**		linezolid	
	exposure (AUC, g h^{-1} mL^{-1})	log of reduction in CFU/lung vs vehicle-treated control	exposure (AUC, g h^{-1} mL^{-1})	log of reduction in CFU/lung vs vehicle-treated control
40 mg kg^{-1} day^{-1}	17.4	1.94	45.7	ND
80 mg kg^{-1} day^{-1}	31.0	2.57	105	3.89

[a] In vivo activity against *S. pneumoniae* 548 (ARC548, AstraZeneca culture collection).

and the associated glururonidate were observed as metabolites in rat plasma after iv dosing of **11**. Since both enantiomeric alcohols showed reduced antibacterial activity relative to **11** (data not shown), we tried to block this metabolism. We hypothesized that metabolic lability of the ketone functionality in the imidazole derivatives would be reduced in a 2,5-disubstituted imidazole because of increased steric hindrance. Indeed, 2,5-dimethylimidazole **13** showed lower clearance of 10 mL min^{-1} kg^{-1} in the rat, considered acceptable for further pharmacodynamic studies. Oral bioavailability of **13** in the rat was 73%. Compound **13** was orally active against *Streptococcus pneumoniae* in a mouse pneumonia model at 40 mg kg^{-1} day^{-1} (Table 5), causing a ~2 log reduction in viable counts in the lung relative to the vehicle-treated control.

Conclusions

We report the synthesis and biological evaluation of novel oxazolidinones with acyclic substituents in the 6-position of a (pyridin-3yl)phenyl moiety. We found that compounds bearing a relatively small alcohol or ketone substituent on the pyridine were potent antibacterials with good activity against Gram-positive pathogens, including linezolid-resistant strains. Many of these analogues, especially the alcohol derivatives, had significantly higher MAO-A K_i values than the unsubstituted parent, a potential advantage in the search for oxazolidinones with a better safety profile. The MAO-A SAR can largely be rationalized by docking studies using a MAO-A/MAO-B homology model. The incorporation of polar groups resulted in significantly improved solubility for some compounds, improving the potential for iv formulations.

Experimental Section

Minimum Inhibitory Concentration Testing. Minimum inhibitory concentrations were determined by broth microdilution according to the Clinical and Laboratory Standards Institute guidelines.[32] Compounds were dissolved in 100% DMSO and diluted to 2% DMSO (v/v) in culture medium from 64 to 0.06 μg/mL. Specific culture media are as follows: for *S. aureus*, Mueller Hinton broth, Difco catalog no. 275730; for *H. influenzae*, 2.2% (w/v) Mueller Hinton broth, 0.5% (w/v) yeast extract (Difco, catalog no. 288620), 15 μg/mL hematin (Sigma, catalog no. H3281-5G), and 1.5 μg/mL NAD (Sigma, catalog no. N6522-5G); for *S. pneumoniae*, 2.2% (w/v) Mueller Hinton broth, 0.65% (v/v) lysed horse blood (Hema Resource and Supply, catalog no.15-14-0100-28). Cultures were incubated at 35 °C under aerobic conditions for *S. aureus* and in a 5% CO_2 atmosphere for *S. pneumoniae* and *H. influenzae*. Microtiter plates were read by spectrophotometry at 620 nm.

MAO-A Assay. Human liver MAO-A was expressed in yeast[33] and purified according to Tan.[34] The assay was carried out adapting the method of Flaherty.[35] Specific conditions were 100 μM substrate 4-(1-methyl-2-pyrryl)-1 methyl-1,2,3,6-tetrahydropyridine, 82 nM human liver monoamine oxidase A[34] (MAO-A concentration was determined using the BioRad Protein assay reagent, catalog no. 500-0006), 100 mM potassium phosphate buffer at pH 7.4 and 25 °C; total substrate turnover was ~10%. Inhibition was reversible and competitive to the amine substrate. Reversibility of inhibition was confirmed by dialysis against 10 mM potassium phosphate, pH 7.4, and subsequent MAO-A activity determination.

K_i values were fitted using the model for MAO-A previously described.[36]

Plasma Protein Binding. Plasma protein binding was determined using the Dianorm equilibrium dialysis chamber.

Compound (10 μM) was spiked in the plasma chamber (donor side), and phosphate buffer was placed in the receiver side. The unit was rotated at 37 °C for 16 h. Drug concentration was determined for the plasma sample that represents the bound fraction and for the buffer sample that represents the free fraction. LC/MS−MS quantitative sample analysis was achieved using an Ace C18 50 mm × 4.6 mm column (MacMod, PA) and electrospray ionization MRM detection (PE Sciex API 4000 mass spectrometer, Applied Biosystems CA). Plasma samples (50 μL) or the buffer samples (100 μL) were treated with methanol (150 μL) containing an internal standard (an oxazolidinone analogue) to precipitate the protein. Concentration determination was based on a standard curve (10 nM to 10 μM), and data were processed by the Analyst, version 1.4.1, software.

P450 Inhibition Assay. The IC_{50} of CYP3A4, CYP1A2, CYP2D6, CYP2C9, and CYP2C19 was determined in 96-well plates, at 0.2−20 μM , using recombinant human P450 enzymes. The following chemicals were used as substrates: 7-methoxy-4-trifluoromethylcoumarin (2C19), 7-methoxy-4-trifluoromethylcoumarin (2C9), 7-methoxy-4-(aminomethyl)coumarin (2D6), 7-benzyloxy-4-(trifluoromethyl)coumarin (3A4), and 3-cyano-7-ethoxycoumarin (1A2). Sample preparation and detection were performed on a Tecan U.S. Genesis RSP200 robotic workstation and a Tecan Safire monochromator fluorescence detector (Durham NC).

Microsomal Incubation. Study compounds (2 μM) were incubated with rat, dog, or human liver microsomes (0.5 mg/mL protein, BD Bioscience, MA) in the presence of NADPH (2 mM) at 37 °C. Aliquots (25 μL) were withdrawn at 0, 5, 10, 20, and 30 min, mixed with methanol (100 μL) containing an oxazolidinone internal standard, prior to sample analysis.

Metabolite Identification. Rat plasma samples were taken at various time points after drug administration, or at 30 min after microsomal incubations, and treated with methanol followed by quantitative sample analysis as described for plasma protein binding. Qualitative sample analysis was performed on an Ace C18 150 mm × 4.6 mm column, and metabolites detection was achieved by full scan, precursor scan, MRM scan, and product ion scan.

Animals. Wistar Han rats for pharmacokinetic studies were obtained from Charles River Laboratories (Raleigh, NC). CD-1 mice were obtained from Charles River Laboratories (Kingston, NY). All animals were housed and acclimated in the animal facility on site before each study. All experimental procedures were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee.

Pharmacokinetic Studies. Pharmacokinetic properties of selected compounds were studied in the rat. Groups of three Wistar Han rats were administered test compound at a dose of 2 or 10 mg/kg by bolus injection into a cannulated jugular vein. Oral bioavailability was determined following a 10 mg/kg dose given by oral gavage. Serial 200 μL samples of whole blood were taken at time intervals. The concentration of compound in plasma was determined by LC−MS/MS, and pharmacokinetic parameters were estimated using a noncompartmental model in WinNonLin (Pharsight).

Exposure in CD-1 mice was determined for analysis of the efficacy studies. Compound **13** was dosed by oral gavage to groups of mice at 40 and 80 mg/kg. At timed intervals, groups of three mice were sacrificed and whole blood samples collected by cardiac puncture. Plasma samples were prepared and analyzed as described above.

***S. pneumoniae* Lung Infection Model.** Compound **13** and linezolid were studied in a mouse lung infection model. Groups of 10 mice were infected with *S. pneumoniae* 548 (AstraZeneca culture collection) at 1×10^5 cfu/lung via the intratracheal route. Treatment with test compound or with vehicle alone was given by oral gavage and commenced 18 h after infection. Efficacy was evaluated by viable counts in the lung 24 h after the start of treatment. Mice were sacrificed; lungs were removed aseptically and homogenized and serial dilutions plated on Tryptic Soy agar plates supplemented with 5% sheep blood.

General Chemical Methods. All commercially available solvents and reagents were used without further purification. All moisture-sensitive reactions were carried out under a nitrogen atmosphere in commercially available anhydrous solvents. Column chromatography was performed on 230−400 mesh silica gel 60. Aluminum-backed sheets of silica gel 60 F254 (EM Science) were used for TLC. Melting points were obtained with a Mel-TempII melting point apparatus from Laboratory Devices, Inc., and are uncorrected. ^{1}H NMR spectra were recorded at 300 or 500 MHz. Chemical shifts are reported in ppm (δ) relative to solvent. Mass spectroscopy was performed using a Micromass Quattro Micro mass spectrometer (for ESP) and an Agilent 1100 MSD instrument (for APCI). Elemental analyses were carried out by Quantitative Technology, Inc., Whitehouse, NJ.

***tert*-Butyl 3-[(5-Bromopyridin-2-yl)carbonyl]azetidine-1-carboxylate (1a).** A solution of 5-bromo-2-iodopyridine (1.09 g, 3.85 mmol) in THF (10 mL) was cooled to −10 °C and treated dropwise with a solution of iprMgCl in THF (2 M, 1.83 mL, 3.66 mmol). It was stirred for 30 min, and then a solution of **35a** (466 mg, 1.9 mmol) was added via syringe. The reaction mixture was allowed to warm to 10 °C over 2 h and was then poured into potassium phosphate buffer (1 M, pH 7, 200 mL) under stirring. It was extracted with ethyl acetate (150 mL) and dried over sodium sulfate. Chromatography on silica gel with hexanes/ethyl acetate (7:1) gave 447 mg (69%) of the product as a colorless solid. MS (ESP) *m*/*z* 341/343 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.36 (s, 9H), 3.92−4.14 (m, 4H), 4.44 (m, 1H), 7.93 (d, 1H), 8.28 (dd, 1H), 8.84 (d, 1H).

1-(5-Bromopyridin-2-yl)-4-(4-methylpiperazin-1-yl)butan-1-one (1b). 5-Bromo-2-iodopyridine (927 mg, 3.27 mmol) was reacted with isopropylmagnesium chloride (2 M in THF, 1.64 mL, 3.27 mmol) and **35b** (749 mg, 3.27 mmol) as described for **1a**. Chromatography on silica gel with dichloromethane/methanol (10:1 to 4:1) gave 582 mg (55%) of the product as a colorless oil. MS (ESP) *m*/*z* 326.47/328.47 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.80 (tt, 2H), 2.04 (s, 3H), 2.02−2.35 (m, 10H), 3.07 (t, 2H), 7.87 (d, 1H), 8.25 (m, 1H), 8.85 (m, 1H).

Benzyl 4-[(5-Bromopyridin-2-yl)carbonyl]piperidine-1-carboxylate (1c). 5-Bromo-2-iodopyridine (490 mg, 1.73 mmol) was reacted with isopropylmagnesium chloride (2 M in THF, 0.86 mL, 1.73 mmol) and **35c** (529 mg, 1.73 mmol) as described for **1a**. Chromatography on silica gel with hexanes/ethyl acetate (5:1) gave 252 mg (36%) of the product as a colorless solid. MS (ESP) *m*/*z* 403/405 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.42 (m, 2H), 1.83 (m, 2H), 2.99 (m, 2H), 3.93 (m, 1H), 4.04 (m, 2H), 5.07 (s, 2H), 7.26−7.40 (m, 5H), 7.90 (d, 1H), 8.28 (d, 1H), 8.88 (d, 1H).

***tert*-Butyl 4-[2-(5-Bromopyridin-2-yl)-2-oxoethyl]piperidine-1-carboxylate (1d).** 5-Bromo-2-iodopyridine (764 mg, 2.69 mmol) was reacted with isopropylmagnesium chloride (2 M in THF, 1.35 mL, 2.63 mmol) and **35d** (770 mg, 2.69 mmol) as described for **1a**. Chromatography on silica gel with hexanes/ethyl acetate (7:1) gave 591 mg (57%) of the product as a colorless solid. MS (ESP) *m*/*z* 383/385 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.09 (m, 2H), 1.37 (s, 9H), 1.63 (m, 2H), 2.02 (m, 1H), 2.72 (m, 2H), 3.06 (m, 2H), 3.91 (m, 2H), 7.87 (d, 1H), 8.25 (dd, 1H), 8.85 (d, 1H).

1-(5-Bromopyridin-2-yl)-2-morpholin-4-ylethanol (1e). Compound **38** (600 mg, 1.67 mmol) was suspended in dry THF (5 mL) and cooled to 0 °C. Morpholine (0.58 mL, 6.7 mmol) was added, and the mixture was vigorously stirred for 1 h at 0 °C. Sodium borohydride (190 mg, 5 mmol) was added, followed by addition of methanol (4 mL). The mixture was stirred for 30 min at 0 °C and then acidified to pH < 2 with concentrated hydrochloric acid. Solvent was removed under reduced pressure, and the pH was adjusted to pH 10 with aqueous potassium hydroxide solution (1 M). The product was extracted with dichloromethane and dried over sodium sulfate. Chromatography on silica gel with hexanes/acetone (1:1) and then with acetone gave 388 mg (81%) of the product as a pale-yellow solid. MS (ESP) *m*/*z* 287/289 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.40−2.65 (m, 6H), 3.53 (dd, 4H), 4.73 (ddd, 1H), 5.37 (d, 1H), 7.47 (m, 1H), 8.02 (m, 1H), 8.59 (m, 1H).

1-(5-Bromopyridin-2-yl)-2-(dimethylamino)ethanol (1f). 38 (500 mg, 1.8 mmol) was dissolved in methanol (20 mL) and cooled to −10 °C. Dimethylamine (0.9 mL, 2 M in THF) was added dropwise, followed by addition of triethylamine (0.25 mL). After 30 min, more dimethylamine solution (0.25 mL) was added and the mixture was stirred for 1.5 h at −10 to −5 °C. Sodium borohydride (205 mg, 5.4 mmol) was added in portions, the reaction mixture was stirred for another hour at −5 °C and then acidified to pH < 2 with concentrated hydrochloric acid. Solvent was removed under reduced pressure, and the pH was adjusted to pH 10 with aqueous potassium hydroxide solution (1 M). Chromatography on a C-18 column (RediSep, Isco Inc.) with 0−5% acetonitrile in water containing 0.1% TFA gave approximately 220 mg of the TFA salt of the product (34%) together with the TFA salts of dimethylamine and triethylamine. The product was used without further purification. MS (ESP) *m*/*z* 245/247 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.87−3.15 (m, 3H), 3.02 (s, 6H), 4.70 (m, 1H), 7.20 (d, 1H), 7.77 (dd, 1H), 8.29 (s, 1H), 9.53 (brs, 1H).

1-(5-Bromopyridin-2-yl)-2-(isopropylamino)ethanol (1g). 38 (600 mg, 1.67 mmol) was reacted with isopropylamine (0.57 mL, 6.7 mmol) as described for **1f**. Chromatography on a C-18 column (RediSep, Isco Inc.) with 0−30% acetonitrile in water, containing 0.1% TFA, gave 241 mg of the TFA salt of the product (39%) as a colorless oil. MS (ESP) *m*/*z* 259/261 (MH^+). ^{1}H NMR (MeOH-d_4) δ: 1.34 and 1.36 (2 × d, 6H), 3.22 (m, 1H), 3.38−3.55 (m, 2H), 4.98 (dd, 1H), 7.59 (d, 1H), 8.04 (dd, 1H), 8.64 (s, 1H).

1-(5-Bromopyridin-2-yl)ethane-1,2-diol (1h). 38 (700 mg, 2.51 mmol) and sodium formate (683 mg, 10.04 mmol) were mixed in 85% ethanol (5 mL) and heated to 50 °C for 3 h. It was cooled to room temperature, and most of the solvent was evaporated under reduced pressure. It was diluted with dichloromethane (50 mL) and water (5 mL). The aqueous phase was extracted three times with dichloromethane, and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure, the residue was taken up in methanol (20 mL) and cooled to 0 °C. Sodium borohydride (285 mg, 7.5 mmol) was added in portions, and the mixture was stirred for 1 h at 0 °C. The pH was adjusted to ∼pH 2 by addition of concentrated HCl, and the solvent was removed under reduced pressure. The residue was taken up with dichloromethane (100 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL), and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate. Chromatography on silica gel with hexanes/acetone (2:1) gave 223 mg (41%) of the product as a colorless solid. MS (ESP) *m*/*z* 218/220 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.47 (m, 1H), 3.65 (m, 1H), 4.55 (m, 1H), 4.71 (ddd, 1H), 5.50 (dd, 1H), 7.45 (m, 1H), 8.01 (m, 1H), 8.59 (m, 1H).

1-(5-Bromopyridin-2-yl)-2-(1*H*-imidazol-1-yl)ethanone (1i). 38 (440 mg, 1.22 mmol) was suspended in dry THF (5 mL) and cooled to 0 °C. Imidazole (330 mg, 4.85 mmol) was added, and the mixture was vigorously stirred for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, and dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol (15:1) gave 197 mg of the product (61%) as an off-white

solid. ^{1}H NMR (DMSO-d_6) δ: 5.77 (s, 2H), 6.91 (brs, 1H), 7.13 (brs, 1H), 7.59 (s, 1H), 7.93 (dd, 1H), 8.34 (dd, 1H), 8.96 (dd, 1H).

1-(5-Bromopyridin-2-yl)-2-(2-methyl-1*H*-imidazol-1-yl)ethanone (1j). 38 (650 mg, 1.8 mmol) and 2-methylimidazole (593 mg, 7.2 mmol) were reacted as described for **1i** to give 336 mg of the product (66%) as an off-white solid. MS (ESP) *m*/*z* 280/282 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.15 (s, 3H), 5.68 (s, 2H), 6.74 (d, 1H), 7.00 (d, 1H), 7.93 (d, 1H), 8.33 (dd, 1H), 8.96 (d, 1H).

1-(5-Bromopyridin-2-yl)-2-(2-ethyl-1*H*-imidazol-1-yl)ethanone (1k). 38 (400 mg, 1.81 mmol) and 2-ethylimidazole (427 mg, 4.4 mmol) were reacted as described under **1i** to give 237 mg of the product as an off-white solid. MS (ESP) *m*/*z* 294/296 (MH^+).

1-(5-Bromopyridin-2-yl)-2-(4-methyl-1*H*-imidazol-1-yl)ethanone (1l). 38 (1.2 g, 3.3 mmol) and 4-methylimidazole (1.09 g, 13.3 mmol) were reacted as for **1i**. Chromatography on silica gel with acetone/hexanes (1:1 to 2:1) gave 170 mg of the product (18%) as an off-white solid (r_f = 0.29, TLC; acetone/hexanes, 1:1; the 5-methylimidazole analogue was also formed, r_f = 0.21). MS (ESP) *m*/*z* 280/282 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.09 (s, 3H), 5.67 (s, 2H), 6.79 (s, 1H), 7.44 (s, 1H), 7.93 (d, 1H), 8.33 (dd, 1H), 8.94 (d, 1H). The assignment of the 4- and 5-methylimidazole isomers was based on HMBC (heteronuclear multiple bond correlation NMR- experiment).

1-(5-Bromopyridin-2-yl)-2-(2,4-dimethyl-1*H*-imidazol-1-yl)-ethanone (1m). 38 (400 mg, 1.81 mmol) and 2,4-dimethylimidazole (422 mg, 4.4 mmol) were reacted as described under **1i** to give 210 mg of the product as an off-white solid. MS (ESP) *m*/*z* 294/296 (MH^+).

1-(5-Bromopyridin-2-yl)-2-(2,5-dimethyl-1*H*-imidazol-1-yl)-ethanone (1n). 40 (4.75 g, 7.7 mmol) was dissolved in dichloromethane (100 mL), and trifluoroacetic acid (15 mL) was added. The mixture was heated at gentle reflux for 1.5 h. It was diluted with dichloromethane (200 mL) and washed with potassium phosphate buffer (pH 7, 1 M, ~600 mL). The aqueous phase was extracted three times with dichloromethane (3 × 100 mL), and the combined organic phases were dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol (20:1) gave 1.94 g (77%) of the product as an off-white solid. MS (ESP) *m*/*z* 294/296 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.98 (s, 3H), 2.12 (s, 3H), 5.57 (s, 2H), 6.49 (s, 1H), 7.93 (m, 1H), 8.35 (m, 1H), 8.98 (m, 1H).

(1*R*)-1-(5-Bromopyridin-2-yl)ethanol (1p) and (1*S*)-1-(5-Bromopyridin-2-yl)ethanol (1q). 5-Bromopyridine-2-carbaldehyde (**1o**)[23,25] (1.0 g, 5.4 mmol) was dissolved in dry THF (25 mL) and cooled to 0 °C. Methylmagnesium bromide (1.4 M in toluene/THF (3:1), 4.6 mL, 6.45 mmol) was added dropwise under stirring. The reaction mixture was diluted with ethyl acetate, washed with potassium phosphate buffer (1 M, pH 7), and dried over sodium sulfate. Chromatography on silica gel with hexanes/ethyl acetate (2:1) gave 1.013 g (93%) of the racemic product as a colorless oil. MS (ESP) *m*/*z* 202/204 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.33 (d, 3H), 4.68 (m, 1H), 5.45 (d, 1H), 7.48 (d, 1H), 8.01 (dd, 1H), 8.57 (d, 1H). The racemic mixture of the two products was separated on a Chiralpak AD column with 95% hexanes, 5% ethanol/methanol (1:1). The first isomer to elute from the column had an optical rotation of $[\alpha]_D^{20}$ −42.2 (*c* 1, ethanol) and was assigned the *S*-configuration. Yield: 400 mg. The second isomer to elute showed an optical rotation of $[\alpha]_D^{20}$ +38.3 (*c* 1, ethanol) and was assigned the *R*-configuration. Yield: 430 mg.

1-(5-Bromopyridin-2-yl)-4-morpholin-4-ylbutan-1-one (1s). 3-[(5-Bromopyridin-2-yl)carbonyl]dihydrofuran-2(3*H*)-one, **1r**,[26] sodium salt (1.05 g, 3.6 mmol) was heated in concentrated HCl (5 mL) for 1 h at 80 °C. The reaction mixture was cooled to room temperature and poured into saturated aqueous sodium hydrogen carbonate solution (100 mL). It was extracted with dichloromethane (3 × 100 mL) and dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude 1-(5-bromopyridin-2-yl)-4-chlorobutan-1-one intermediate was heated in morpholine (3 mL) at 85 °C for 3 h to give the product next to the 7-bromo-1-oxo-1,2,3,4-tetrahydroquinolizinium salt. Chromatography on silica gel with hexanes/acetone (5:1), followed by chromatography on RediSep C-18 with 5−20% acetonitrile in water (0.1% TFA) gave 190 mg of the trifluoroacetate (TFA) salt of the product (12%) as a colorless oil. MS (ESP) *m*/*z* 313/315 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.99 (m, 2H), 2.98−3.30 (m, 6H), 3.46 (m, 2H), 3.64 (t, 2H), 3.97 (m, 2H), 7.90 (m, 1H), 8.29 (m, 1H), 8.87 (m, 1H), 9.79 (brs, 1H).

Acetic Acid (5*R*)-3-(3-Fluorophenyl)-2-oxooxazolidin-5-ylmethyl Ester (2b). (5*R*)-3-(3-Fluorophenyl)-5-hydroxymethyloxazolidin-2-one, **2a**[37,38] (40 g, 0.189 mol), was suspended by stirring in dry dichloromethane (400 mL) under nitrogen. Triethylamine (21 g, 0.208 mol) and 4-dimethylaminopyridine (0.6 g, 4.9 mmol) were added, followed by dropwise addition of acetic anhydride (20.3 g, 0.199 mol) over 30 min, and stirring continued at ambient temperature for 18 h. Saturated aqueous sodium bicarbonate (250 mL) was added and the organic phase was separated, washed with 2% sodium dihydrogen phosphate, dried (magnesium sulfate), filtered, and evaporated to give the desired product (49.6 g) as an oil. MS (ESP) *m*/*z* 254 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 2.02 (s, 3H), 3.84 (dd, 1H), 4.16 (t, 1H), 4.25 (dd, 1H), 4.32 (dd, 1H), 4.95 (m, 1H), 6.95 (td, 1H), 7.32 (d, 1H), 7.43 (t, 1H) , 7.51 (d, 1H).

Acetic Acid (5*R*)-3-(3-Fluoro-4-iodophenyl)-2-oxooxazolidin-5-ylmethyl Ester (2c). 2b (15.2 g, 60 mmol) was dissolved in a mixture of chloroform (100 mL) and acetonitrile (100 mL) under nitrogen, and silver trifluoroacetate (16.96 g, 77 mmol) was added. Iodine (18.07 g, 71 mmol) was added in portions over 30 min to the vigorously stirred solution, and stirring continued at ambient temperature for 18 h. Because reaction was not complete, a further portion of silver trifluoroacetate (2.64 g, 12 mmol) was added and stirring continued for 18 h. After filtration, the mixture was added to sodium thiosulfate solution (3%, 200 mL) and dichloromethane (200 mL), and the organic phase was separated, washed with sodium thiosulfate (200 mL), saturated aqueous sodium bicarbonate (200 mL), and brine (200 mL), dried (magnesium sulfate), and filtered and solvent evaporated. The crude product was suspended in isohexane (100 mL) and sufficient diethyl ether added to dissolve the brown impurity while stirring for 1 h. Filtration gave the desired product (24.3 g) as a cream solid. MS (ESP) *m*/*z* 380 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.03 (s, 3H), 3.82 (dd, 1H), 4.15 (t, 1H), 4.24 (dd, 1H), 4.30 (dd, 1H), 4.94 (m, 1H), 7.19 (dd, 1H), 7.55 (dd, 1H), 7.84 (t, 1H).

(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-hydroxymethyloxazolidin-2-one (2d). 2c (30 g, 79 mmol) was treated with potassium carbonate (16.4 g, 0.119 mmol) in a mixture of methanol (800 mL) and dichloromethane (240 mL) at ambient temperature for 25 min, then immediately neutralized by the addition of acetic acid (10 mL) and water (500 mL). The precipitate was filtered, washed with water, and dissolved in dichloromethane (1.2 L), and the solution was washed with saturated sodium bicarbonate and dried (magnesium sulfate). Filtration and evaporation gave the desired product (23 g). MS (ESP) *m*/*z* 338 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.53 (m, 1H), 3.67 (m, 1H), 3.82 (dd, 1H), 4.07 (t, 1H), 4.70 (m, 1H), 5.20 (t, 1H), 7.21 (dd, 1H), 7.57 (dd, 1H), 7.81 (t, 1H).

[(5*R*)-3-(3-Fluoro-4-iodophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl Methanesulfonate (2e). 2d (25.0 g, 74.2 mmol) was stirred in dichloromethane (250 mL) at 0 °C. Triethylamine (10.5 g, 104 mmol) was added followed by methanesulfonyl chloride (11.2 g, 89 mmol), and the mixture was stirred overnight, slowly warming to room temperature. The yellow solution was diluted with sodium bicarbonate, and the compound was extracted with dichloromethane (3 × 250 mL). The organic layer was dried (magnesium sulfate), filtered, and concentrated to give the desired product as a light-yellow solid (30.3 g). MS (ESP) *m*/*z* 416 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.24 (s, 3H), 3.82 (dd, 1H), 4.17 (t, 1H), 4.43−4.52 (m, 2H), 4.99−5.03 (m, 1H), 7.21 (dd, 1H), 7.55 (dd, 1H), 7.83 (t, 1H).

(5*R*)-5-(Azidomethyl)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one (2f). 2e (6.14 g, 14.7 mmol) was dissolved in *N*,*N*-dimethylformamide (50 mL). Sodium azide (1.92 g, 29.6 mmol) was added, and the mixture was stirred at 75 °C overnight. The

yellow mixture was poured into half-saturated sodium bicarbonate and extracted using ethyl acetate. The organic layer was washed three times with water, dried (magnesium sulfate), filtered, and concentrated to give the title compound as a yellow solid (4.72 g). MS (ESP) *m*/*z* 363 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.72−3.82 (m, 3H), 4.14 (t, 1H), 4.89−4.94 (m, 1H), 7.22 (dd, 1H), 7.57 (dd, 1H), 7.83 (t, 1H).

(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (2g). 2f (30.3 g, 72.9 mmol) was stirred in 1,4-dioxane. Bicyclo[2.2.1]hepta-2,5-diene (40.3 g, 437 mmol) was added, and the mixture was heated at 100 °C overnight. The resulting brown mixture was filtered, and the desired product was obtained as a light-brown solid (14.8 g). MS (ESP) *m*/*z* 389 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.90 (dd, 1H), 4.23 (t, 1H), 4.84 (d, 2H), 5.11−5.18 (m, 1H), 7.14 (dd, 1H), 7.49 (dd, 1H), 7.76 (s, 1H), 7.82 (t, 1H), 8.17 (s, 1H).

(5*R*)-3-[3-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (2h). 2g (2 g, 5.15 mmol), bis(pinacolato)diboron (2.62 g, 10.3 mmol), potassium acetate (2.5 g, 25.5 mmol), and 1,1′-[bis-(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.38 g, 0.52 mmol) were suspended in DMSO (15 mL). The mixture was heated at 80 °C for 40 min to give a clear black solution. Ethyl acetate (150 mL) was added, and the mixture was filtered through Celite, washed with saturated brine (2 × 100 mL), dried over sodium sulfate, and evaporated. The dark residue was purified by chromatography on silica gel with 40−100% ethyl acetate in hexane, followed by 1−5% acetonitrile in ethyl acetate, to give the product as a crystalline tan solid, 1.97 g (98%). (Note: highly colored impurities elute ahead of product band, and extended elution is required to obtain product). ^{1}H NMR (DMSO-d_6) δ: 1.28 (s, 12H), 3.91 (dd, 1H), 4.23 (t, 1H), 4.83 (d, 2H), 5.14 (m, 1H), 7.27 (dd, 1H), 7.37 (dd, 1H), 7.62 (t, 1H), 7.75 (s, 1H), 8.16 (s, 1H).

(5*R*)-3-(3-Fluoro-4-pyridin-3-ylphenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (3). A mixture of 3-bromopyridine (245 mg, 1.55 mmol), **2h** (500 mg, 1.29 mmol), and sodium carbonate (430 mg, 4.05 mmol) in *N*,*N*-dimethylformamide/water (5 mL, 10:1) was degassed, and flushed with nitrogen, and tetrakis-(triphenylphosphine)palladium(0) (75 mg, 0.065 mmol) was added. The mixture was heated at 75 °C overnight and cooled to room temperature, and the solvent was evaporated. Chromatography with 5% methanol in dichloromethane gave the product as an off-white solid (220 mg). MS (ESP) *m*/*z* 340 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.96 (m, 1H), 4.31 (dd, 1H), 4.86 (d, 2H), 5.18 (m, 1H), 7.40 (dd, 1H), 7.52 (m, 2H), 7.62 (t, 1H), 7.75 (s, 1H), 7.96 (d, 1H), 8.19 (s, 1H), 8.59 (s, 1H), 8.72 (s, 1H). Anal. ($C_{17}H_{14}FN_5O_2$) C, H, N.

(5*R*)-3-[4-(6-Acetylpyridin-3-yl)-3-fluorophenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (4). 37 (2.47 g, 12.4 mmol),[17,24] **2h** (4.0 g, 10.3 mmol), sodium carbonate (3.98 g, 37.5 mmol), and tetrakis(triphenylphosphine)palladium(0) (1.2 g, 1.03 mmol) were reacted as described for **3**, but the mixture was heated for 3 h. Chromatography on silica gel with hexanes/acetone (1:1) to acetone and precipitation of the product from methanol/dichloromethane (4:1, 50 mL) by removing most of the dichloromethane under reduced pressure gave 1.98 g of product (50%) as an off-white solid, mp >210 °C (dec). MS (ESP) *m*/*z* 382 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.66 (s, 3H), 3.96 (dd, 1H), 4.30 (dd, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.43 (dd, 1H), 7.60 (dd, 1H), 7.72 (dd, 1H), 7.76 (s, 1H), 8.03 (d, 1H), 8.17 (m, 1H), 8.18 (s, 1H), 8.90 (s, 1H). Anal. ($C_{19}H_{16}FN_5O_3$) C, H, N.

***tert*-Butyl 3-[(5-{2-Fluoro-4-[(5*R*)-2-oxo-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}pyridin-2-yl)carbonyl]-azetidine-1-carboxylate (5). 1a** (447 mg, 1.31 mmol), **2h** (509 mg, 1.31 mmol), sodium carbonate (416 mg, 3.93 mmol), and tetrakis-(triphenylphosphine)palladium(0) (151 mg, 0.13 mmol) were reacted as described for **4** but using 10 mL of solvent. Chromatography on silica gel with hexanes/acetone (1:1) gave 500 mg (73%) of product as a colorless hard foam. MS (ESP) *m*/*z* 523 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.37 (s, 9H), 3.93−4.18 (m, 5H), 4.30 (dd, 1H), 4.53 (m, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.44 (dd, 1H), 7.60 (dd, 1H), 7.73 (dd, 1H), 7.77 (s, 1H), 8.10 (d, 1H), 8.18 (s, 1H), 8.20 (m, 1H), 8.88 (brs, 1H).

(5*R*)-3-{4-[6-(Azetidin-3-ylcarbonyl)pyridin-3-yl]-3-fluorophenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (6). A solution of **5** (220 mg, 0.42 mmol) in dioxane (2 mL) was treated under vigorous stirring with HCl (4 M in dioxane, 2 mL), and the mixture was stirred at room temperature for 1 h. Solvent was evaporated under reduced pressure. Chromatography was performed on C-18 RP silica (using a RediSep cartridge) with 0−20% acetonitrile (containing 0.1% TFA) in water. Fractions containing product were pooled, and solvent was removed under reduced pressure. The residue was taken up in isopropanol (20 mL), and HCl (1 M in ether, 0.2 mL) was added under vigorous stirring. The precipitated solid was collected by filtration and dried at room temperature under reduced pressure to give 44 mg (23%) of the hydrochloride salt of the product as a greenish solid, mp >90 °C (dec). MS (ESP) *m*/*z* 423 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.97 (dd, 1H), 4.17−4.34 (m, 5H), 4.70 (m, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.44 (m, 1H), 7.60 (m, 1H), 7.73 (dd, 1H), 7.77 (s, 1H), 8.11−8.27 (m, 3H), 8.81 (m, 1H), 8.90 (brs, 1H), 9.22 (m, 1H). Anal. ($C_{21}H_{19}FN_6O_3$) C, H, N.

(5*R*)-3-(4-{6-[Azetidin-3-yl(hydroxy)methyl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (7). 5 (245 mg, 0.47 mmol) was dissolved in THF (5 mL). The mixture was cooled to 0 °C, and sodium borohydride (53 mg, 1.4 mmol) was added, followed by addition of methanol (2 mL). After 2 h at 0 °C the mixture was quenched with potassium phosphate buffer (pH 7, 1 M, 5 mL) and diluted with ethyl acetate (100 mL), and the organic phase was dried over sodium sulfate and concentrated to give the crude Boc-protected alcohol. This alcohol was dissolved in 1,4-dioxane (5 mL), and HCl (4 M in dioxane, 3 mL) was added under vigorous stirring. After 1 h, the solvent was evaporated under reduced pressure and the residue was codistilled twice with water and crystallized from water/isopropanol to give 171 mg (79%) of the hydrochloride salt of the product as an off-white solid, mp >180 °C. MS (ESP) *m*/*z* 425 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.27 (m, 1H), 3.70−4.70 (m, 7H), 4.86 (d, 2H), 4.96 (m, 1H), 5.19 (m, 1H), 7.41 (dd, 1H), 7.58 (dd, 1H), 7.67 (dd, 1H), 7.72−7.85 (m, 2H), 8.16−8.25 (m, 2H), 8.74 (brs, 1H), 8.90 (brs, 1H), 9.17 (brs, 1H). Anal. ($C_{21}H_{21}FN_6O_3$) C, H, N.

(5*R*)-3-{3-Fluoro-4-[6-(1*H*-imidazol-1-ylacetyl)pyridin-3-yl]-phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (8). 1i (195 mg, 0.73 mmol), **2h** (284 mg, 0.73 mmol), sodium carbonate (233 mg, 2.2 mmol), and tetrakis(triphenylphosphine)palladium-(0) (85 mg, 0.07 mmol) were reacted as described for **4**. Chromatography was done on silica gel with dichloromethane/methanol (10:1). The free base thus obtained was dissolved in isopropanol/dichloromethane (∼20 mL, 1:1). HCl in ether (1 mL, 1 M) was added, and most of the dichloromethane was removed under reduced pressure. The residue was collected by filtration and dried to give 189 mg (59%) of the hydrochloride salt of the product as a colorless solid, mp >230 °C (dec). MS (ESP) *m*/*z* 448 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.97 (m, 1H), 4.31 (m, 1H), 4.86 (d, 2H), 5.20 (m, 1H), 6.12 (s, 2H), 7.45 (dd, 1H), 7.62 (dd, 1H), 7.70−7.82 (m, 5H), 8.11−8.20 (m, 2H), 8.29 (m, 1H), 9.05 (d, 1H), 14.62 (brs, 1H). Anal. ($C_{22}H_{18}FN_7O_3$) C, H, N.

(5*R*)-3-(3-Fluoro-4-{6-[(4-methyl-1*H*-imidazol-1-yl)acetyl]pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (9). 1l (170 mg, 0.607 mmol), **2h** (214 mg, 0.552 mmol), sodium carbonate (175 mg, 1.65 mmol), and tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.05 mmol) were reacted as described under **8** to give 155 mg (56%) of product as the hydrochloride salt, a colorless solid, mp >217 °C (dec). MS (ESP) *m*/*z* 462 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 3H), 3.97 (dd, 1H), 4.31 (dd, 1H), 4.87 (d, 2H), 5.20 (m, 1H), 6.06 (s, 2H), 7.40−7.49 (m, 2H), 7.62 (dd, 1H), 7.74−7.80 (m, 2H), 8.13 (d, 1H), 8.19 (s, 1H), 8.28 (m, 1H), 8.95 (s, 1H), 9.02 (brs, 1H), 14.57 (brs, 1H). Anal. ($C_{23}H_{20}FN_7O_3$) C, H, N.

(5*R*)-3-(4-{6-[(2,4-Dimethyl-1*H*-imidazol-1-yl)acetyl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazo-

lidin-2-one (10). 1m (210 mg, 0.714 mmol), **2h** (333 mg, 0.86 mmol), potassium carbonate (296 mg, 2.14 mmol), and tetrakis-(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol) were reacted and the product was purified as described for **4** to give 105 mg of the product as an off-white solid, mp 78 °C. MS (ESP) *m*/*z* 476 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.26 (s, 3H), 3.55 (s, 3H), 3.95 (m, 1H), 4.27 (m, 1H), 4.98 (m, 2H), 5.18−5.22 (m, 1H), 5.98 (s, 2H), 7.27 (m, 1H), 7.43−7.64 (m, 2H), 7.76 (m, 2H), 8.10 (m, 1H), 8.19 (m, 1H), 8.26−8.28 (m, 1H), 9.03 (s, 1H). Purity, >95% by HPLC.

(5*R*)-3-(3-Fluoro-4-{6-[(2-methyl-1*H*-imidazol-1-yl)acetyl]pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (11). 1j (336 mg, 1.2 mmol), **2h** (388 mg, 1.0 mmol), sodium carbonate (300 mg, 2.8 mmol), and tetrakis(triphenylphosphine)-palladium(0) (115 mg, 0.1 mmol) were reacted as described for **8** to give 276 mg (55%) of product as the hydrochloride salt, a colorless solid, mp >240 °C (dec). MS (ESP) *m*/*z* 462 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.55 (s, 3H), 3.97 (m, 1H), 4.31 (m, 1H), 4.87 (d, 2H), 5.20 (m, 1H), 6.05 (s, 2H), 7.46 (dd, 1H), 7.57−7.65 (m, 3H), 7.72−7.80 (m, 2H), 8.13 (d, 1H), 8.19 (s, 1H), 8.27 (m, 1H), 9.03 (s, 1H), 14.48 (brs, 1H). Anal. ($C_{23}H_{20}FN_7O_3$) C, H, N.

(5*R*)-3-(4-{6-[(2-Ethyl-1*H*-imidazol-1-yl)acetyl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (12). 1k (237 mg, 0.806 mmol), **2h** (376 mg, 0.97 mmol), potassium carbonate (340 mg, 2.41 mmol), and tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol) were reacted and the product was purified as described for **4**, but it was heated at 80 °C for 30 min, to give 174 mg of the product as an off-white solid, mp 77−79 °C. MS (ESP) *m*/*z* 476 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.21 (m, 3H), 2.89−2.96 (m, 2H), 3.52 (m, 2H), 3.98−3.98 (m, 1H), 4.28 (m, 1H), 4.86 (s, 2H), 5.17−5.20 (m, 1H), 6.08 (s, 2H), 7.42−7.44 (dd, 1H), 7.57−7.72 (m, 1H), 7.76 (s, 1H), 7.98−8.08 (m, 1H), 8.19 (s, 1H), 8.43−8.59 (m, 1H), 8.82 (m, 2H). Anal. ($C_{24}H_{22}FN_7O_3$) C, H, N.

(5*R*)-3-(4-{6-[(2,5-Dimethyl-1*H*-imidazol-1-yl)acetyl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (13). 1n (985 mg, 3.35 mmol), **2h** (1.30 g, 3.35 mmol), sodium carbonate (887 mg, 8.37 mmol), and tetrakis(triphenylphosphine)palladium(0) (387 mg, 0.35 mmol) were reacted as described for **4** but using 15 mL of solvent and heating at 75 °C for 6 h. Chromatography on silica gel with dichloromethane/methanol (10:1 to 8:1), followed by crystallization from ethanol, gave 658 mg (41%) of product as colorless needles, mp 112−115 °C. MS (ESP) *m*/*z* 476 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.01 (s, 3H), 2.15 (s, 3H), 3.97 (dd, 1H), 4.31 (dd, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 5.64 (s, 2H), 6.51 (s, 1H), 7.46 (dd, 1H), 7.62 (dd, 1H), 7.75 (dd, 1H), 7.77 (s, 1H), 8.10 (d, 1H), 8.19 (s, 1H), 8.25 (m, 1H), 8.99 (brs, 1H). Anal. ($C_{24}H_{22}FN_7O_3$) C, H, N.

(5*R*)-3-(3-Fluoro-4-{6-[4-(4-methylpiperazin-1-yl)butanoyl]-pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (14). 1b (580 mg, 1.8 mmol), **2h** (690 mg, 1.8 mmol), sodium carbonate (377 mg, 3.55 mmol), and tetrakis(triphenylphosphine)palladium(0) (205 mg, 0.18 mmol) were reacted as described for **4** but using 10 mL of solvent. Chromatography on silica gel with dichloromethane/methanol (5:1 to 3:1) gave 510 mg (57%) of product as a colorless hard foam. The free base of the product (310 mg, 0.61 mmol) was taken up in isopropanol (10 mL). HCl (1 M in ether, 2 mL) was added under vigorous stirring. After the mixture was stirred for 15 min, solvent was removed under reduced pressure and the residue was crystallized from water/isopropanol (~30 mL, 1:15) to give 261 mg of the bis HCl salt of the product as a colorless solid, mp >240 °C. MS (ESP) *m*/*z* 508 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.09 (m, 2H), 2.82 (s, 3H), 3.13−3.88 (m, 12H), 3.97 (dd, 1H), 4.30 (dd, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.43 (m, 1H), 7.60 (m, 1H), 7.73 (dd, 1H), 7.77 (s, 1H), 8.06 (d, 1H), 8.15−8.23 (m, 2H), 8.91 (brs, 1H). Anal. ($C_{26}H_{30}FN_7O_3$) C, H, N.

(5*R*)-3-(3-Fluoro-4-{6-[1-hydroxy-4-(4-methylpiperazin-1-yl)-butyl]pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (15). 14, bis hydrochloride salt (200 mg, 0.34 mmol), in THF (5 mL) was cooled to 0 °C. Sodium borohydride (52 mg, 1.38 mmol) was added, followed by addition of methanol (5 mL). After 30 min, the reaction was quenched with HCl (aqueous, 1 M, 5 mL), and the mixture was concentrated to dryness under reduced pressure. This material was heterogeneous by LC, with several peaks showing the desired product mass, indicating the presence of boronic ester product complexes. The residue was taken up in HCl (aqueous, 3 M, 5 mL), and the mixture was heated at 65 °C for 45 min. A homogeneous product was obtained by LC−MS. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in water (5 mL) and purified on a RP (C-18) Redi Sep cartridge with 0−20% acetonitrile in water containing 0.1% TFA. The fractions containing product were pooled and concentrated under reduced pressure. The residue was taken up in isopropanol (15 mL), and HCl (1 M in ether, 0.8 mL) was added under vigorous stirring. The precipitate was collected by filtration and dried under vacuum to give 100 mg (50%) of the bis hydrochloride salt of the product as slightly yellow solid, mp >212 °C (dec). MS (ESP) *m*/*z* 510 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.76 (m, 4H), 2.45−3.75 (m, 11H), 2.79 (s, 3H), 3.95 (dd, 1H), 4.29 (dd, 1H), 4.67 (m, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.39 (dd, 1H), 7.56 (dd, 1H), 7.60−7.66 (m, 2H), 7.77 (s, 1H), 8.02 (m, 1H), 8.18 (s, 1H), 8.67 (brs, 1H). Anal. ($C_{26}H_{32}FN_7O_3$) C, H, N.

(5*R*)-3-{3-Fluoro-4-[6-(4-morpholin-4-ylbutanoyl)pyridin-3-yl]phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (16). 1s, TFA salt (190 mg, 0.44 mmol), **2h** (173 mg, 0.44 mmol), sodium carbonate (141 mg, 1.33 mmol), and tetrakis-(triphenylphosphine)palladium(0) (51 mg, 0.044 mmol) were reacted as described for **8** to give 119 mg of the hydrochloride salt of the product (54%) as a colorless solid, mp >240 °C (dec). MS (ESP) *m*/*z* 495 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.00−2.12 (m, 2H), 3.00−4.02 (m, 13H), 4.30 (m, 1H), 4.86 (m, 2H), 5.19 (m, 1H), 7.43 (m, 1H), 7.60 (m, 1H), 7.68−7.78 (m, 2H), 8.05 (m, 1H), 8.16−8.22 (m, 2H), 8.91 (s, 1H), 10.57 (s, 1H). Anal. ($C_{25}H_{27}FN_6O_4$) C, H, N.

***tert*-Butyl 4-[2-(5-{2-Fluoro-4-[(5*R*)-2-oxo-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}pyridin-2-yl)-2-oxoethyl]-piperidine-1-carboxylate (17). 1d** (590 mg, 1.54 mmol), **2h** (598 mg, 1.54 mmol), sodium carbonate (490 mg, 4.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (178 mg, 0.154 mmol) were reacted as described for **4**. Chromatography on silica gel with hexanes/acetone (2:1) gave 691 mg (79%) of product as a colorless solid, mp >140 °C. MS (ESP) *m*/*z* 565 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.11 (m, 2H), 1.38 (s, 9H), 1.66 (m, 2H), 2.07 (m, 1H), 2.72 (m, 2H), 3.13 (m, 2H), 3.84−4.00 (m, 3H), 4.30 (dd, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.43 (dd, 1H), 7.60 (dd, 1H), 7.72 (dd, 1H), 7.77 (s, 1H), 8.05 (d, 1H), 8.15−8.21 (m, 1H), 8.18 (s, 1H), 8.90 (brs, 1H).

(5*R*)-3-{3-Fluoro-4-[6-(piperidin-4-ylacetyl)pyridin-3-yl]phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (18). A solution of **17** (630 mg, 1.12 mmol) in dioxane (5 mL) was treated under vigorous stirring with a solution of HCl in dioxane (4 M, 5 mL). The mixture was stirred overnight at room temperature and solvent was removed under reduced pressure and the residue recrystallized from water/isopropanol (33 mL, 1:10) to give 409 mg (73%) of product as the hydrochloride salt, a colorless solid, mp >196 °C (dec). MS (ESP) *m*/*z* 465 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.45 (m, 2H), 1.83 (m, 2H), 2.19 (m, 1H), 2.88 (m, 2H), 3.16−3.26 (m, 4H), 3.97 (dd, 1H), 4.30 (dd, 1H), 4.87 (d, 2H), 5.20 (m, 1H), 7.43 (dd, 1H), 7.60 (dd, 1H), 7.72 (dd, 1H), 7.77 (s, 1H), 8.05 (d, 1H), 8.16−8.21 (m, 1H), 8.19 (s, 1H), 8.70 (m, 1H), 8.87−8.98 (m, 1H), 8.90 (brs, 1H). Anal. ($C_{24}H_{25}FN_6O_3$) C, H, N.

Benzyl 4-[(5-{2-Fluoro-4-[(5*R*)-2-oxo-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}pyridin-2-yl)carbonyl]piperidine-1-carboxylate (19). 1c (250 mg, 0.62 mmol), **2h** (241 mg, 0.62 mmol), sodium carbonate (197 mg, 1.86 mmol), and tetrakis(triphenylphosphine)palladium(0) (72 mg, 0.06 mmol) were reacted as described for **4**. Chromatography on silica gel with hexanes/acetone (1:1) gave 339 mg (93%) of product as a slightly yellow hard foam. MS (ESP) *m*/*z* 585 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.47 (m, 2H), 1.87 (m, 2H), 3.01 (m, 2H), 3.93−4.12 (m, 4H), 4.30 (dd, 1H), 4.86 (d, 2H), 5.08 (s, 2H), 5.19 (m, 1H), 7.28−

7.46 (m, 6H), 7.60 (dd, 1H), 7.73 (dd, 1H), 7.77 (s, 1H), 8.06 (d, 1H), 8.15−8.23 (m, 2H), 8.93 (brs, 1H).

(5*R*)-3-{3-Fluoro-4-[6-(piperidin-4-ylcarbonyl)pyridin-3-yl]-phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (20) and (5*R*)-3-(3-Fluoro-4-{6-[hydroxy(piperidin-4-yl)methyl]pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (21). **19** (305 mg, 0.52 mmol) was hydrogenated on Pd/C (10%, wet) in methanol (10 mL, containing a few drops of acetic acid) at room temperature and normal pressure for 2 h. It was filtered through a 0.45 μm membrane, and solvent was removed under reduced pressure. Chromatography was performed on C-18 RP silica (using a RediSep cartridge) with 0−20% acetonitrile (containing 0.1% TFA) in water to give the free bases of **20** and **21**. Fractions containing **20** and **21** were separately pooled, and solvent was removed under reduced pressure. The residues were taken up in isopropanol (20 mL) and HCl (1 M in ether, 0.5 mL) was added under vigorous stirring. It was diluted with hexanes (10 mL) and the solids were collected by filtration and dried at 50 °C under reduced pressure to give 71 mg (28%) of the hydrochloride salt of **20** as a colorless solid, mp >275 °C (dec), and 44 mg (17%) of the hydrochloride salt of **21** as a colorless solid, mp >185 °C (dec).

20: MS (ESP) *m*/*z* 451 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.79 (m, 2H), 2.04 (m, 2H), 3.10 (m, 2H), 3.97 (dd, 1H), 4.12 (m, 1H), 4.30 (dd, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.44 (dd, 1H), 7.60 (dd, 1H), 7.73 (dd, 1H), 7.77 (s, 1H), 8.07 (d, 1H), 8.18 (s, 1H), 8.21 (m, 1H), 8.50 (m, 1H), 8.76 (m, 1H), 8.92 (brs, 1H). An additional 2H signal is either under the solvent or under the HDO signal. Anal. ($C_{23}H_{23}FN_6O_3$) C, H, N.

21: MS (ESP) *m*/*z* 453 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.60 (m, 4H), 2.05 (m, 1H), 2.78 (m, 2H), 3.23 (m, 2H), 3.40−3.75 (m, 1H, under HDO peak), 3.97 (dd, 1H), 4.29 (dd, 1H), 4.61 (d, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.41 (dd, 1H), 7.58 (dd, 1H), 7.67 (dd, 1H), 7.68−7.72 (m, 1H), 7.77 (s, 1H), 8.15−8.21 (m, 2H), 8.38 (m, 1H), 8.72−8.83 (m, 2H). Anal. ($C_{23}H_{25}FN_6O_3$) C, H, N.

(5*R*)-3-{3-Fluoro-4-[6-(hydroxymethyl)pyridin-3-yl]phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (22). (5-Bromopyridin-2-yl)methanol[25] (200 mg, 1.06 mmol), **2h** (413 mg, 1.06 mmol), sodium carbonate (450 mg, 4.25 mmol), and tetrakis-(triphenylphosphine)palladium(0) (122 mg, 0.106 mmol) were reacted as described for **4**. Chromatography on silica gel with dichloromethane/methanol (10:1) and precipitation from hot methanol with hexanes gave 191 mg (49%) of the product as a colorless solid, mp 177 °C. MS (ESP) *m*/*z* 370 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.95 (dd, 1H), 4.29 (dd, 1H), 4.60 (d, 2H), 4.86 (d, 2H), 5.18 (m, 1H), 5.48 (t, 1H), 7.39 (m, 1H), 7.52−7.66 (m, 3H), 7.77 (s, 1H), 7.96 (m, 1H), 8.18 (s, 1H), 8.64 (s, 1H). Anal. ($C_{18}H_{16}FN_5O_3$) C, H, N.

(5*R*)-3-{3-Fluoro-4-[6-(methoxymethyl)pyridin-3-yl]phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (23). **22** (150 mg, 0.41 mmol) and iodomethane (116 mg, 0.82 mmol) were mixed in dry DMF (3 mL) and cooled to 0 °C. Sodium hydride (14.6 mg, 0.61 mmol) was added, and the reaction mixture was slowly warmed to room temperature overnight. The reaction was quenched with a few drops of water and extracted with dichloromethane. The organic phase was dried over anhydrous magnesium sulfate, concentrated, and purified by chromatography on silica gel with 5% methanol in dichloromethane to give the product as a colorless solid (31 mg, 20%). MS (ESP) *m*/*z* 384 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 3.50 (s, 3H), 3.97 (dd, 1H), 4.17 (t, 1H), 4.60 (s, 2H), 4.80 (d, 2H), 5.05 (m, 1H), 7.17 (d, 1H), 7.38−7.50 (m, 3H), 7.70 (s, 1H), 7.81 (s, 1H), 7.82 (d, 1H), 8.70 (s, 1H). Anal. ($C_{19}H_{18}FN_5O_3$) C, H, N.

(5*R*)-3-(3-Fluoro-4-{6-[(1*R*)-1-hydroxyethyl]pyridin-3-yl}-phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (24). **1p** (430 mg, 2.13 mmol), **2h** (826 mg, 2.13 mmol), sodium carbonate (677 mg, 6.4 mmol), and tetrakis(triphenylphosphine)-palladium(0) (246 mg, 0.213 mmol) were reacted as described for **3** but heating at 70 °C for 4 h in 10 mL of solvent. Chromatography on silica gel with dichloromethane/methanol (12:1) and crystallization from ethanol/hexanes gave 421 mg (52%) of the product as a colorless solid, mp 190 °C. MS (ESP) *m*/*z* 384 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.39 (d, 3H), 3.95 (dd, 1H), 4.29 (dd, 1H), 4.76 (m, 1H), 4.85 (d, 2H), 5.18 (m, 1H), 5.42 (d, 1H), 7.38 (dd, 1H), 7.52−7.66 (m, 3H), 7.77 (s, 1H), 7.95 (m, 1H), 8.18 (s, 1H), 8.63 (s, 1H). Purity, >98% by HPLC.

(5*R*)-3-(3-Fluoro-4-{6-[(1*R*)-1-methoxyethyl]pyridin-3-yl}-phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (25). **24** (300 mg, 0.78 mmol) was dissolved in dry DMF (3 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 35 mg, 0.86 mmol) was added, and the mixture was stirred for 10 min. Then methyl iodide (0.058 mL, 0.94 mmol) was added. After 1.5 h the reaction was quenched with acetic acid (1 drop) and solvent was evaporated under reduced pressure. Chromatography on silica gel with hexanes/acetone (1:1) and crystallization from ethanol/hexanes gave 138 mg (44%) of the product as colorless solid, mp 150 °C. MS (ESP) *m*/*z* 398 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.39 (d, 3H), 3.23 (s, 3H), 3.95 (dd, 1H), 4.29 (dd, 1H), 4.42 (m, 1H), 4.85 (d, 2H), 5.18 (m, 1H), 7.39 (dd, 1H), 7.50 (d, 1H), 7.57 (dd, 1H), 7.64 (dd, 1H), 7.77 (s, 1H), 7.99 (m, 1H), 8.18 (s, 1H), 8.68 (s, 1H). Anal. ($C_{20}H_{20}FN_5O_3$) C, H, N.

(5*R*)-3-(3-Fluoro-4-{6-[(1*S*)-1-hydroxyethyl]pyridin-3-yl}-phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (26). **1r** (400 mg, 1.98 mmol), **2h** (769 mg, 1.98 mmol), sodium carbonate (630 mg, 5.9 mmol), and tetrakis(triphenylphosphine)-palladium(0) (228 mg, 0.198 mmol) were reacted as described for **24** to give 287 mg (38%) of the product as a colorless solid, mp 183 °C. MS (ESP) *m*/*z* 384 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.39 (d, 3H), 3.95 (dd, 1H), 4.29 (dd, 1H), 4.76 (m, 1H), 4.85 (d, 2H), 5.18 (m, 1H), 5.42 (d, 1H), 7.38 (dd, 1H), 7.52−7.66 (m, 3H), 7.77 (s, 1H), 7.95 (m, 1H), 8.18 (s, 1H), 8.63 (s, 1H). Anal. ($C_{19}H_{18}FN_5O_3 \cdot 0.05CH_2Cl_2$) C, H, N. H: calcd, 4.71; found, 4.27.

(5*R*)-3-(3-Fluoro-4-{6-[(1*S*)-1-methoxyethyl]pyridin-3-yl}-phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (27). **26** (220 mg, 0.57 mmol), sodium hydride (60% in mineral oil, 25 mg, 0.63 mmol), and methyl iodide (0.043 mL, 0.69 mmol) were reacted following the procedure described for **25** to give 112 mg (49%) of the product as colorless solid, mp 160 °C. MS (ESP) *m*/*z* 398 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.39 (d, 3H), 3.23 (s, 3H), 3.95 (dd, 1H), 4.29 (dd, 1H), 4.42 (m, 1H), 4.85 (d, 2H), 5.18 (m, 1H), 7.39 (dd, 1H), 7.50 (d, 1H), 7.57 (dd, 1H), 7.64 (dd, 1H), 7.77 (s, 1H), 7.99 (m, 1H), 8.18 (s, 1H), 8.68 (s, 1H). Anal. ($C_{20}H_{20}FN_5O_3$) C, H, N.

5-{2-Fluoro-4-[(5*R*)-2-oxo-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}pyridine-2-carbaldehyde (28). 1o[23,25] (450 mg, 2.42 mmol), **2h** (939 mg, 2.42 mmol), sodium carbonate (769 mg, 7.26 mmol), and tetrakis(triphenylphosphine)palladium(0) (280 mg, 0.24 mmol) were reacted as described for **3** but with 10 mL of solvent and 10 h of heating at 70 °C. Chromatography on silica gel with hexanes/acetone (1:1) gave 535 mg (60%) of the product as a colorless solid, mp >180 °C (dec). MS (ESP) *m*/*z* 368 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.97 (dd, 1H), 4.30 (dd, 1H), 4.86 (d, 2H), 5.19 (m, 1H), 7.45 (dd, 1H), 7.61 (dd, 1H), 7.75 (dd, 1H), 7.77 (s, 1H), 8.02 (d, 1H), 8.18 (s, 1H), 8.23 (d, 1H), 9.01 (s, 1H), 10.02 (s, 1H).

(5*R*)-3-{3-Fluoro-4-[6-(1-hydroxy-2-methylpropyl)pyridin-3-yl]phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (29). To a solution of **28** (150 mg, 0.37 mmol) in dry THF (10 mL) was added dropwise at −20 °C isopropylmagnesium bromide (1 M in THF, 0.74 mL, 0.74 mmol). The reaction mixture was allowed to reach room temperature over 2 h and was stirred overnight. It was quenched with a few drops of water, diluted with ethyl acetate (15 mL), washed with HCl (aqueous, 5%, 10 mL) and with brine (10 mL), and dried over sodium sulfate. Chromatography on silica gel with dichloromethane/acetone (1:1) gave 31 mg of the product as a colorless solid, mp 156−157 °C. MS (ESP) *m*/*z* 412 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 0.80 (d, 3H), 0.88 (d, 3H), 2.05 (m, 1H), 3.95 (m, 1H), 4.27 (dd, 1H), 4.37 (m, 1H), 4.82 (d, 2H), 5.17 (m, 1H), 5.27 (d, 1H), 7.41 (m, 1H), 7.50∼7.68 (m, 3H), 7.78 (s, 1H), 7.95 (d, 1H), 8.19 (s, 1H), 8.65 (s, 1H). Anal. ($C_{21}H_{22}FN_5O_3$) C, H, N.

(5*R*)-3-{3-Fluoro-4-[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]-phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (30).

2-(5-Bromopyridin-2-yl)propan-2-ol[25] (500 mg, 2.31 mmol), **2h** (900 mg, 2.32 mmol), sodium carbonate (740 mg, 7 mmol), and tetrakis(triphenylphosphine)palladium(0) (268 mg, 0.232 mmol) were reacted as described for **3** but heating at 70 °C for 7.5 h in 10 mL of solvent. Chromatography on silica gel first with dichloromethane/methanol (17:1) and then with dichloromethane/DMF (20:1) and precipitation from dichloromethane/DMF (20:1, 20 mL) with hexanes gave 247 mg (27%) of the product as a colorless solid, mp 180 °C. MS (ESP) *m*/*z* 398 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.46 (s, 6H), 3.95 (dd, 1H), 4.29 (dd, 1H), 4.85 (d, 2H), 5.18 (m, 1H), 5.27 (s, 1H), 7.38 (dd, 1H), 7.55 (dd, 1H), 7.62 (dd, 1H), 7.73 (d, 1H), 7.76 (s, 1H), 7.92 (m, 1H), 8.18 (s, 1H), 8.64 (s, 1H). Anal. ($C_{20}H_{20}FN_5O_3$) C, H, N.

(5*R*)-3-{4-[6-(1,2-Dihydroxyethyl)pyridin-3-yl]-3-fluorophenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (31). 1h (323 mg, 1.48 mmol), **2h** (575 mg, 1.48 mmol), sodium carbonate (471 mg, 4.44 mmol), and tetrakis(triphenylphosphine)palladium(0) (171 mg, 0.148 mmol) were reacted as described for **4**. Chromatography on silica gel with dichloromethane/methanol (5:1) and crystallization from ethanol/hexanes gave 388 mg of the product (66%) as a colorless solid, mp 175 °C. MS (ESP) *m*/*z* 400 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.52 (m, 1H), 3.71 (m, 1H), 3.95 (m, 1H), 4.28 (dd, 1H), 4.63 (m, 1H), 4.73 (m, 1H), 4.85 (d, 2H), 5.18 (m, 1H), 5.45 (m, 1H), 7.39 (m, 1H), 7.53−7.64 (m, 3H), 7.76 (s, 1H), 7.94 (m, 1H), 8.17 (s, 1H), 8.64 (s, 1H). Anal. ($C_{19}H_{18}FN_5O_4$) C, H, N.

(5*R*)-3-{3-Fluoro-4-[6-(1-hydroxy-2-morpholin-4-ylethyl)pyridin-3-yl]phenyl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (32). 1e (388 mg, 1.35 mmol), **2h** (525 mg, 1.35 mmol), sodium carbonate (430 mg, 4.05 mmol), and tetrakis(triphenylphosphine)palladium(0) (156 mg, 0.135 mmol) were reacted as described for **4**. Chromatography was done on silica gel with dichloromethane/methanol (10:1). The hydrochloride salt was prepared as described for **8** to give 507 mg of the hydrochloride salt of the product (74%) as a colorless solid, mp >194 °C (dec). MS (ESP) *m*/*z* 469 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 3.00−4.20 (m, 11H), 4.29 (dd, 1H), 4.86 (d, 2H), 5.14−5.40 (m, 2H), 6.61 (brs, 1H), 7.40 (m, 1H), 7.52−7.75 (m, 3H), 7.77 (s, 1H), 8.05 (d, 1H), 8.19 (s, 1H), 8.71 (s, 1H), 10.58 (brs, 1H). Anal. ($C_{23}H_{25}FN_6O_4$) C, H, N.

(5*R*)-3-(3-Fluoro-4-{6-[1-hydroxy-2-(isopropylamino)ethyl]pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (33). 1g, TFA salt (241 mg, 0.65 mmol), **2h** (361 mg, 0.93 mmol), sodium carbonate (296 mg, 2.79 mmol), and tetrakis(triphenylphosphine)palladium(0) (108 mg, 0.093 mmol) were reacted as described for **4**. Chromatography on silica gel with acetonitrile/water (6:1) and then with dichloromethane/methanol (5:1), followed by precipitation of the hydrochloride salt as described for **8**, gave 193 mg of the hydrochloride salt of the product (63%) as a colorless solid, mp >170 °C (dec). MS (ESP) *m*/*z* 441 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.27 (m, 6H), 3.12 (m, 1H), 3.37 (m, 2H), 3.96 (m, 1H), 4.30 (dd, 1H), 4.86 (d, 2H), 5.11−5.22 (m, 3H), 7.40 (m, 1H), 7.53−7.75 (m, 3H), 7.77 (s, 1H), 8.13 (d, 1H), 8.20 (s, 1H), 8.67 (brs, 1H), 8.75 (s, 1H), 9.15 (brs, 1H). Anal. ($C_{22}H_{25}FN_6O_3$) C, H, N.

(5*R*)-3-(4-{6-[2-(Dimethylamino)-1-hydroxyethyl]pyridin-3-yl}-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (34). 1f, TFA salt (200 mg, 0.56 mmol), **2h** (216 mg, 0.56 mmol), sodium carbonate (177 mg, 1.67 mmol), and tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.056 mmol) were reacted as described for **3**. Chromatography on silica gel with acetonitrile/water (5:1) and precipitation from ethanol by addition of HCl in ether (1 M, ∼0.7 mL) gave 125 mg (48%) of the hydrochloride salt of the product as a colorless solid, mp >115 °C (dec). MS (ESP) *m*/*z* 427 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 2.88 (s, 6H), 3.25−3.75 (m, 3H), 3.96 (m, 1H), 4.29 (dd, 1H), 4.86 (d, 2H), 5.12−5.20 (m, 2H), 7.39 (m, 1H), 7.52−7.75 (m, 3H), 7.75 (s, 1H), 8.05 (d, 1H), 8.20 (s, 1H), 8.69 (s, 1H), 10.20 (brs, 1H). Anal. ($C_{21}H_{23}FN_6O_3$) C, H, N.

***tert*-Butyl 3-{[Methoxy(methyl)amino]carbonyl}azetidine-1-carboxylate (35a).** To a solution of 1-(*tert*-butoxycarbonyl)-azetidine-3-carboxylic acid (0.5 g, 2.48 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.633 g, 2.48 mmol) in DMF (4 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (339 mg, 3.48 mmol), followed by diisopropylethylamine (1.3 mL, 7.45 mmol). The reaction was exothermic, and the mixture was allowed to cool to room temperature and was stirred for 2 h. Excess base was removed under reduced pressure, and the residue was diluted with ethyl acetate (100 mL), washed with potassium phosphate buffer (1 M, pH 7, 2 × 100 mL) and with water (2 × 100 mL), and dried over sodium sulfate. Chromatography on silica gel with hexanes/acetone (3:1) gave 470 mg (77%) of the product as a colorless solid. MS (ESP) *m*/*z* 267 (MNa^+). ^{1}H NMR (DMSO-d_6) δ: 1.36 (s, 9H), 3.10 (s, 3H), 3.61 (s, 3H), 3.68 (m, 1H), 3.83−4.00 (m, 4H).

***N*-Methoxy-*N*-methyl-4-(4-methylpiperazin-1-yl)butanamide (35b).** 4-Chloro-*N*-methoxy-*N*-methylbutyramide[39] (1 g, 6.04 mmol) and 1-methylpiperazine (1.2 g, 12 mmol) were mixed in DMSO (2 mL) and heated to 80 °C for 3 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate solution (∼100 mL), extracted with dichloromethane (3 × 100 mL), and dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol (18:1 to 3:1) gave 749 mg (54%) of the product as a slightly yellow oil. MS (ESP) *m*/*z* 230 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.63 (tt, 2H), 2.13 (s, 3H), 2.10−2.45 (m, 10H), 3.07 (s, 3H), 3.38 (m, 2H), 3.64 (s, 3H).

Benzyl 4-{[Methoxy(methyl)amino]carbonyl}piperidine-1-carboxylate (35c).[40] A mixture of benzyl 4-(chlorocarbonyl)-piperidine-1-carboxylate (1 g, 3.55 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (346 mg, 3.55 mmol) in dichloromethane (20 mL) was cooled to −20 °C, and pyridine (1.15 mL, 14.2 mmol) was added. The reaction mixture was allowed to reach room temperature over 30 min and was stirred for another hour. It was diluted with dichloromethane (100 mL), washed with potassium phosphate buffer (1 M, pH 7, 3 × 100 mL), and dried over sodium sulfate. Chromatography on silica gel with hexanes/ethyl acetate (1:1 to 0:1) gave 650 mg (60%) of the product as a colorless oil. MS (ESP) *m*/*z* 307 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 1.40 (m, 2H), 1.66 (m, 2H), 2.80−2.99 (m, 3H), 3.08 (s, 3H), 3.67 (s, 3H), 4.01 (m, 2H), 5.06 (s, 2H), 7.26−7.45 (m, 5H).

***tert*-Butyl 4-{2-[Methoxy(methyl)amino]-2-oxoethyl}piperidine-1-carboxylate (35d).**[41,42] To a solution of Boc-(4-carboxymethyl)-piperidine (1 g, 4.11 mmol) and bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (1.05 g, 4.11 mmol) in DMF (4 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (561 mg, 5.57 mmol), followed by diisopropylethylamine (2.15 mL, 12.3 mmol). It was stirred for 30 min, diluted with ethyl acetate (100 mL), washed with water (2 × 50 mL), and dried over sodium sulfate. Chromatography on silica gel with hexanes/ethyl acetate (2:1 to 1:2) gave 770 mg (65%) of the product as a colorless oil. MS (ESP) *m*/*z* 187 ($M - BocH^+$). ^{1}H NMR (DMSO-d_6) δ: 1.02 (m, 2H), 1.37 (s, 9H), 1.61 (m, 2H), 1.85 (m, 1H), 2.29 (m, 2H), 2.68 (m, 2H), 3.06 (s, 3H), 3.62 (s, 3H), 3.89 (m, 2H).

1-(5-Bromopyridin-2-yl)ethanone (37).[17,24] 5-Bromo-2-cyanopyridine (8 g, 43.7 mmol) was dissolved in dry THF (200 mL) and cooled to −20 °C. Methylmagnesium bromide (43.7 mL, 3 M) was added dropwise, and the temperature was held between −20 and −10 °C for 3 h. The reaction mixture was cooled to −40 °C, and concentrated HCl (4.5 mL) in water (15 mL) was added dropwise. It was stirred for 10 min at −35 °C and then poured into potassium phosphate buffer (300 mL, 1 M, pH 7), under stirring. Ethyl acetate (300 mL) was added, and the organic phase was dried over sodium sulfate. Upon concentration at room temperature under reduced pressure to ∼50 mL the product crystallized, 2.4 g, mp 112 °C. The mother liquor was further concentrated and chromatographed on silica gel with dichloromethane/ethyl acetate (100:1) to give another 3.25 g of product (65% combined yield). ^{1}H NMR (DMSO-d_6) δ: 2.60 (s, 3H), 7.88 (dd, 1H), 8.25 (dd, 1H), 8.86 (d, 1H).

2-Bromo-1-(5-bromopyridin-2-yl)ethanone (38). 37 (5.65 g, 28.2 mmol) was dissolved in methanol/acetic acid (50 mL + 70 mL) and cooled to 0 °C, and 30% HBr in acetic acid (8 mL) was added. Bromine (1.45 mL, 28.3 mmol) in acetic acid (10 mL) was

added dropwise, and the reaction mixture was allowed to reach room temperature and then was heated to 70 °C for 1 h. It was cooled to ~50 °C. More bromine (0.4 mL) in acetic acid (5 mL) and methanol (15 mL) was added, and the mixture was heated to 70 °C for another 30 min. The reaction mixture was concentrated to dryness under reduced pressure and the residue was crystallized from isopropanol to give 3.45 g (34%) of the crude hydrobromide salt of the product as a pale-yellow solid. MS (ESP) *m*/*z* 278/280/282 (MH^+). ^{1}H NMR (DMSO-d_6) δ: 4.96 (s, 2H), 7.93 (m, 1H), 8.29 (m, 1H), 8.87 (m, 1H), 9.19 (brs, 1H).

2,4-Dimethyl-1-trityl-1*H*-imidazole (39). A solution of trityl chloride (15 g, 55 mmol) in dichloromethane (50 mL) was added dropwise over 45 min to a solution of 2,4-dimethylimidazole (5 g, 52 mmol) in a mixture of dichloromethane (100 mL) and triethylamine (11.3 mL, 81 mmol) at room temperature. The mixture was stirred overnight, then quenched with methanol (4 mL) and stirred for additional 30 min. The solvent was evaporated, and the residue was taken up in toluene (600 mL), washed with potassium phosphate buffer (pH 7, 1M, 2 × 200 mL) and with water (200 mL). The organic phase was diluted with dichloromethane (200 mL), dried over sodium sulfate, and concentrated under reduced pressure to ~100 mL. Hexanes (100 mL) were added and the precipitate was collected by filtration and washed with hexanes (2 × 50 mL) to give 14.76 g (84%) of the product as a colorless solid. ^{1}H NMR ($CDCl_3$) δ: 1.62 (s, 3H), 2.16 (s, 3H), 6.40 (s, 1H), 7.10−7.40 (m, 15H).

1-[2-(5-Bromopyridin-2-yl)-2-oxoethyl]-2,5-dimethyl-3-trityl-1*H*-imidazol-3-ium bromide (40). A mixture of **39** (4.5 g, 13.4 mmol), **38** (free base) (2.5 g, 9 mmol) (the free base was generated from the hydrobromide salt by treating a suspension of the hydrobromide salt of **38** in ethyl acetate with potassium phosphate buffer (pH 7, 1 M), washing the organic phase with water and drying over sodium sulfate), and 2,6-di-*tert*-butylpyridine (3 mL, 13.35 mmol) was heated in 1,4-dioxane (50 mL) at 75 °C for 30 min. The reaction mixture was allowed to cool to room temperature and the precipitate was collected by filtration and washed with hexanes (2 × 50 mL) to give 4.75 g (86%) of the product as an off-white solid, mp >150 °C (dec). MS (ESP) *m*/*z* 536/538 (M^+). ^{1}H NMR (DMSO-d_6) δ: 1.82 (s, 3H), 2.21 (s, 3H), 5.95 (s, 2H), 7.07 (s, 1H), 7.12−7.18 (m, 6H), 7.44−7.65 (m, 9H), 7.98 (m, 1H), 8.36 (m, 1H), 8.98 (m, 1H).

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Supporting Information Available: Elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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