Identification of 4-Substituted 1,2,3-Triazoles as Novel Oxazolidinone Antibacterial Agents with Reduced Activity against Monoamine Oxidase A

Folkert Reck,*,† Fei Zhou,† Marc Girardot,† Gunther Kern,† Charles J. Eyermann,† Neil J. Hales,§ Rona R. Ramsay,‡ and Michael B. Gravestock†

AstraZeneca Discovery, AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451, and Centre for Biomolecular Sciences, University of St. Andrews, North Haugh, St. Andrews KY16 9ST, Scotland, U.K.

Received April 7, 2004

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. Many oxazolidinones, including linezolid (marketed as Zyvox), are inhibitors of monoamine oxidase A (MAO-A), which presents an undesired side effect. Recently, it was found that the 1,2,3-triazole is a good replacement for the conventional acetamide functionality found in oxazolidinones. We now disclose the finding that 1,2,3-triazoles bearing a substituent like methyl, small substituted methyl, bromo, or a linear (sp-hybridized) group at the 4 position (compounds such as **5**, **16**, **19**, and **21**) are good antibacterials with reduced or no activity, within the detection limit of the assay, against MAO-A. The results are especially promising for the development of oxazolidinones with an improved safety profile. The MAO-A SAR can be rationalized on the basis of docking studies to a MAO-A/MAO-B homology model.

Introduction

The development of bacterial resistance to existing drugs is a major problem in antibacterial therapy and necessitates continuing research into new classes of antibacterials.[1] Of particular concern are severe infections caused by multidrug-resistant Gram-positive pathogens, which cause high mortality rates especially in the hospital setting. The individual organisms responsible include methicillin-resistant *Staphylococcus aureus* (MRSA),[2,3] vancomycin-resistant *Enterococcus faecalis* (VRE),[4] and penicillin-resistant *Streptococcus pneumoniae*.[5,6] Oxazolidinones are a new class of antibacterials that are exemplified by linezolid (marketed as Zyvox)[7−9] and have resulted in important and new treatment options for infections caused by Gram-positive bacteria. Oxazolidinones target bacterial protein synthesis, probably by binding at or near the peptidyltransferase center in actively translating bacterial ribosomes.[10−12] However, resistance against linezolid has already started to develop in *Enterococcus faecium*[13−17] and, more alarmingly, in *S. aureus*, giving rise to linezolid-resistant MRSA strains.[18] A concern with oxazolidinones as a drug class has been inhibition of monoamine oxidase (MAO), especially type A (MAO-A), due to structural similarity to MAO inhibitors such as toloxatone.[19] Inhibition of MAO-A could potentially lead to severe hypertensive crises as a result of ingestion of tyramine-containing food together with an oxazolidinone drug (the "cheese effect").[20,21] It is therefore desirable to develop novel oxazolidinone drugs, which not only have improved activity against resistant Gram-positive bacteria but also show an improved safety profile with regard to MAO-A inhibition.

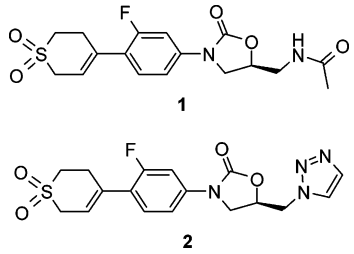


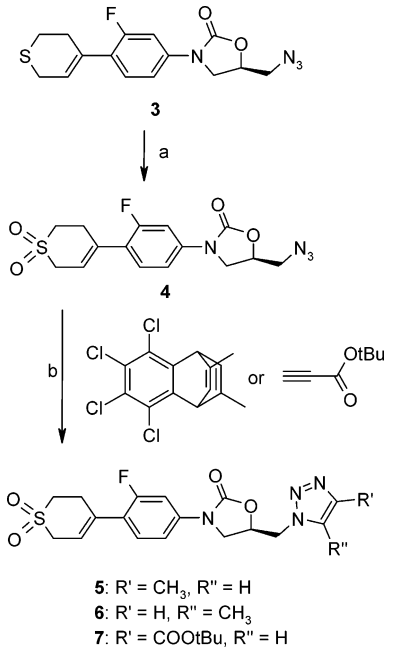
Figure 1. Thiapyran sulfone analogue of linezolid (**1**) and corresponding AstraZeneca 1,2,3-triazole lead (**2**).

We have been interested for some time in oxazolidinones bearing a thiapyran sulfone moiety because we found that structures such as **1**[22] (Figure 1) show improved potency against both Gram-positive and fastidious Gram-negative pathogens relative to linezolid. We attempted to further improve the antibacterial activity of the thiapyran sulfones by modifying the acetamido functionality in **1**. While looking for a new way of introducing diversity at this position, we saw an opportunity arising from our recent finding that the 1,2,3-triazole moiety is a good replacement for the acetamide[23] (compound **2**, Figure 1). The 4 and 5 positions of the triazole in **2** allow diversification with a different spatial arrangement compared to the conventional acetamido functionality.[24,25] Recently, Phillips et al.[26] reported a limited exploration into substituted triazole analogues of linezolid, but these efforts failed to identify new substituted triazole compounds with potent antibacterial activity. We now report on our more extensive study into the SAR in this area, which has led to the identification of potent and novel antibacterials with interesting properties.

* To whom correspondence should be addressed. Phone: 781-839-4617. Fax: 781-839-4500. E-mail: folkert.reck@astrazeneca.com.
† AstraZeneca R&D Boston.
§ Present address: AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, U.K.
‡ University of St. Andrews.

10.1021/jm0400810 CCC: $30.25
Published on Web 01/04/2005

Scheme 1[a]



[a] Reagents: (a) MCPBA, CH_2Cl_2, 0 °C to room temp; (b) dioxane, reflux.

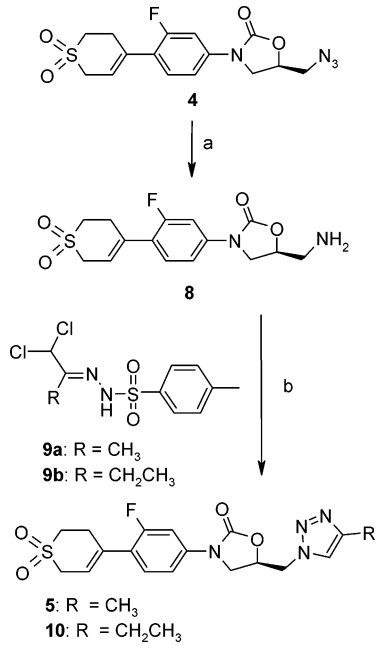
Chemistry

The synthesis of substituted 1,2,3-triazoles via Huisgen 1,3-dipolar thermal cycloaddition is outlined in Scheme 1. Cycloaddition of the azide **4** with *tert*-butyl propiolate proceeded smoothly and selectively to **7**. When 5,6,7,8-tetrachloro-1,4-dihydro-2,9-dimethyl-1,4-ethenonaphthalene[27] was employed as an alkyne equivalent, a mixture of the 4- and 5-methyl-substituted triazoles **5** and **6** was obtained (after retro-Diels–Alder reaction of the transient triazoline), which was chromatographically separated. The structural assignment of the regioisomeric triazoles was based on nuclear Overhauser effect (NOE) and heteronuclear multiple-bond correlation (HMBC) NMR experiments. In cases where both isomers were available, the proton resonance for H-5 was lower than the one for H-4 in all examples, confirming the rule by Alonso et al.[28]

Chromatographic separation of regioisomeric triazoles was tedious, and selective routes into 4-substituted triazoles were sought. Selective synthesis of the 4-methyltriazole **5** was achieved by reacting amine **8** with α,α-dichloroacetone tosylhydrazone **9a**[29] to give **5** in 64% yield (Scheme 2). Similarly, we found that the novel tosylhydrazone **9b** reacted with **8** to give cleanly the 4-ethyltriazole **10** in 72% yield. The corresponding 5-alkylated triazole species were not observed.

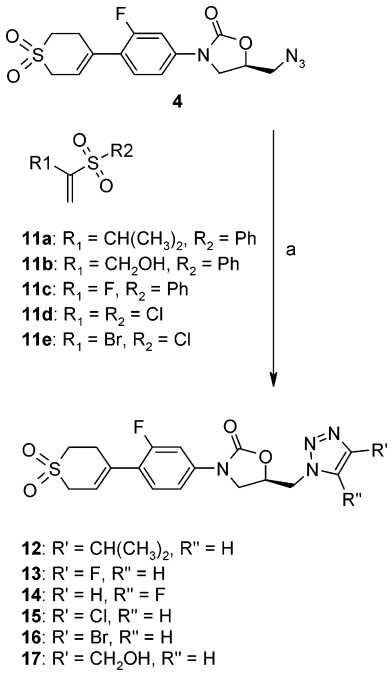
Thermal cycloaddition of vinylsulfone **11a**[30] with azide **4**, followed by elimination of phenylsulfinic acid gave the 4-isopropyltriazole **12** in 36% yield after chromatography and crystallization (Scheme 3). The corresponding 5-isopropyltriazole was not observed, and the modest yield was due to the recovery of some unreacted starting azide. Reaction of the less sterically demanding hydroxymethylvinylsulfone **11b**[31] with azide **4** gave **17** in 50% yield after chromatography. In this case the corresponding 5-hydroxymethyltriazole was observed as a minor component. We found vinyl sulfonyl reagents particularly useful for the preparation of

Scheme 2[a]



[a] Reagents: (a) $P(Ph)_3$, CH_3CN/H_2O, room temp; (b) DIEA, MeOH, 0 °C to room temp.

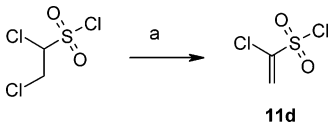
Scheme 3[a]



[a] Reagents: (a) neat or toluene or NMP, 90 or 110 °C.

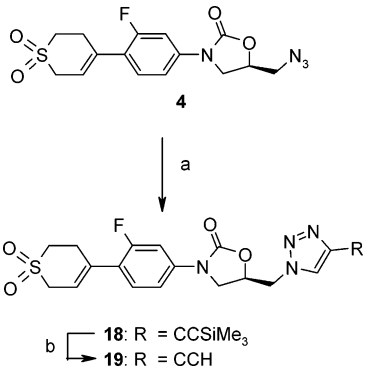
halogenated triazoles; thus, the α-bromosulfonyl chloride **11e**[32] gave selectively the 4-bromotriazole **16** in 76% yield.[33] In contrast, *p*-nitrophenyl-α-bromovinylsulfone gave the *p*-nitrophenylsulfonyl triazole as the sole product, resulting from elimination of HBr from the triazoline intermediate (result not shown). We prepared the novel α-chlorosulfonyl chloride **11d** (Scheme 4) and found that it is similarly very useful for the selective preparation of 4-chlorotriazoles, giving **15** in 64% yield. Interestingly, the regioselectivity of the addition was reversed for phenyl α-fluorovinylsulfone **11c**,[34] which gave a ~1:7 mixture of the 4- and 5-fluorotriazoles **13** and **14** in 28% yield. The lower yield was a result of

Scheme 4[a]



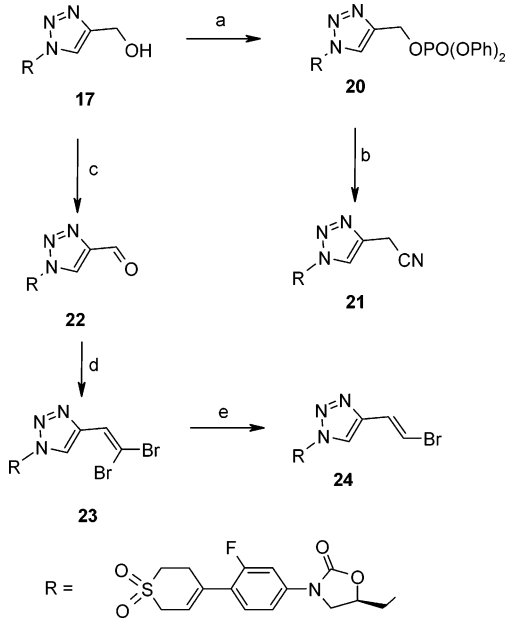
[a] Reagents: (a) (1) 2,6-lutidine, Et_2O, −60 °C to room temp, (2) H_2SO_4, 0 °C.

Scheme 5[a]



[a] Reagents: (a) buta-1,3-diynyl(trimethyl)silane, 2,6-lutidine, CuI, room temp; (b) KOH, room temp.

Scheme 6[a]



[a] Reagents: (a) diphenyl phosphorochloridate, CH_2Cl_2/pyridine, 0 °C; (b) NaCN, DMF, 60 °C; (c) (1) oxalyl chloride, DMSO, CH_2Cl_2, −50 °C, (2) DIEA, −40 to −20 °C; (d) CBr_4, $P(Ph)_3$, CH_2Cl_2, 0 °C to room temp; (e) $HPO(OEt)_2$, NEt_3, 90 °C.

unreacted starting azide; elimination of HF instead of phenylsulfinic acid was not observed.

Copper(I)-catalyzed ligation[35,36] of buta-1,3-diynyl-(trimethyl)silane[37] with **4** gave **18** in 80% yield, which was cleanly desilylated to the 4-ethynyltriazole **19** (Scheme 5). The alcohol **17** served as starting material for further modifications at the 4 position on the triazole moiety (Scheme 6). Swern oxidation gave aldehyde **22**, which was reacted with carbon tetrabromide/triphenylphosphine[38] to give the 1,1-dibromoalkene **23** in good overall yield. **23** was reduced to the *E*-bromoalkene **24** with diethyl phosphite.[39] Treatment of alcohol **17** with diphenyl phosphorochloridate gave phosphate ester

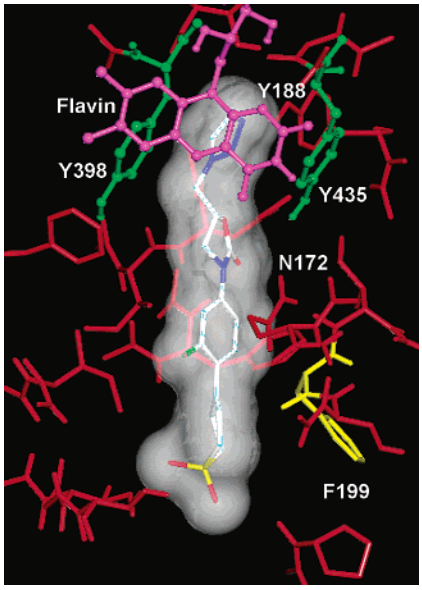


Figure 2. Model of compound **2** docked into the MAO-A homology model. Residue numbers correspond to those from the MAO-B X-ray structure.[40,41] A Connolly molecular surface is displayed for oxazolidinone **2** to illustrate the "aromatic cage" formed by Y398, Y435, and the flavin cofactor. F199 is the gatekeeper residue identified by Binda[40] that joins or separates the entrance and substrate cavities.

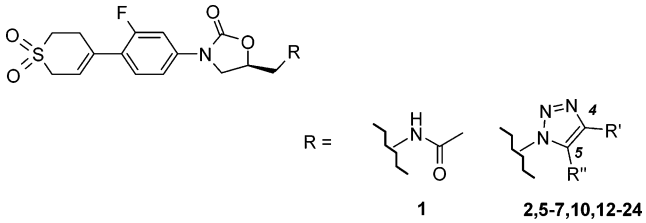
20, which was converted to the cyanide **21** with sodium cyanide in good overall yield.

Molecular Modeling

A docking model for MAO-A was constructed on the basis of homology of MAO-A to MAO-B. Crystal structures for human mitochondrial monoamine oxidase B (MAO-B) have been reported recently.[40−42] The 1.7 Å structure of MAO-B with isatin[40] was used to interpret the interaction of covalent and noncovalent inhibitors of MAO-B. Given the ∼70% sequence identity between MAO-B and MAO-A, 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. As noted by Binda et al.,[41] the different binding cavity residues in MAO-A lead to a fusion of the substrate binding cavity with the entrance cavity, thereby allowing MAO-A to bind larger substrates.

Flexible docking studies of oxazolidinones to the homology model of MAO-A were performed using the QXP/FLO software.[43] Residues in the substrate and entrance cavities were allowed full conformational flexibility in the docking studies. Figure 2 illustrates the most favorable binding mode for **2** identified by QXP. The triazolo group binds in the substrate cavity and fits exquisitely into the aromatic cage formed by Tyr 398, Tyr 435, and the flavin ring. The fluorophenyl moiety is positioned in the large hydrophobic pocket linking the substrate and entrance cavities. The mainly hydrophobic entrance cavity is occupied by the thiapyran sulfone group. Note that the gatekeeper residue F199 rotates to accommodate the longer size of this series of inhibitors (relative to small substrates such as benzylamine and dopamine).

Table 1. SAR of Substituted Triazolo Oxazolidinones, Compared to Unsubstituted Triazole and Acetamide Lead



1 **2,5-7,10,12-24**

compd	R′	R″	S.a.[a] MIC (μg/mL)	S.p.[b] MIC (μg/mL)	H.inf.[c] MIC (μg/mL)	MAO-A[d] K_i (μM)
1			1	0.25	1	5.9
2	H	H	1	0.5	2	3.4
5	CH_3	H	1	0.5	2	25
6	H	CH_3	>64	64	>64	4.5
7	COO*t*Bu	H	>64	>64	>64	3.5
10	CH_2CH_3	H	4	2	8	>200
12	$CH(CH_3)_2$	H	8	4	32	102
13	F	H	1	0.25	2	0.5
14	H	F	32	8	64	1.6
15	Cl	H	1	0.25	1	3.0
16	Br	H	2	0.5	2	16
17	CH_2OH	H	32	2	4	47
18	$CCSiMe_3$	H	>64	1	>64	>200
19	CCH	H	2	0.5	2	>200
20	$CH_2OPO(OPh)_2$	H	32	4	64	>100
21	CH_2CN	H	16	1	2	>200
22	CHO	H	16	2	16	3.2
23	$CH{=}CBr_2$	H	>64	4	>64	>100
24	CH=CHBr(E)	H	8	2	8	>200

[a] Methicillin-susceptible *Staphylococcus aureus* AP601055. [b] Penicillin-susceptible *Streptococcus pneumoniae* AP671401. [c] *Haemophilius influenzae* ATCC51907. Minimum inhibitory concentration (MIC): lowest drug concentration that reduced growth by 80% or more.[48] [d] Monoamine oxidase A K_i expressed as a mean of three experiments.[44]

Results and Discussion

Oxazolidinones bearing a substituted 1,2,3-triazole moiety were submitted for evaluation for antibacterial activity (Table 1). 5-Substituted triazoles as exemplified by the 5-methyltriazole **6** were generally inactive or only marginally active. Several other 5-substituted triazole derivatives, including the hydroxymethyl, chloromethyl, carboxymethyl, and cyclopropyl derivatives were synthesized, and these were found to show a lack of activity very similar to that of **6** (results not shown). The best compound within the 5-substituted series was the fluoride **14** with an *S. pneumoniae* MIC of 8 μg/mL. These results indicate that the loss of activity upon 5-substitution may be due to a steric effect.

However, in the case of 4-substituted triazoles it was found that many compounds showed good antibacterial activity. The best compounds had a methyl, a small substituted methyl group in the 4 position (compounds **5** and **21**), a halogen (compounds **13**, **15**, and **16**), or an ethynyl group (compound **19**). These results suggest that the effect of 4-substitution on the triazole moiety on antibacterial activity is mostly steric, with only small or linear substituents (substituent linked via an sp^3 or sp center) coming from the 4-position on the triazole moiety tolerated in the ribosomal binding site. Linking a substitutent at the 4-position via an sp^2 center (compounds **7** and **22**−**24**) was detrimental for activity. Consistent with this observation Phillips et al.[26] have found that a 4-acetyltriazole analogue of linezolid and

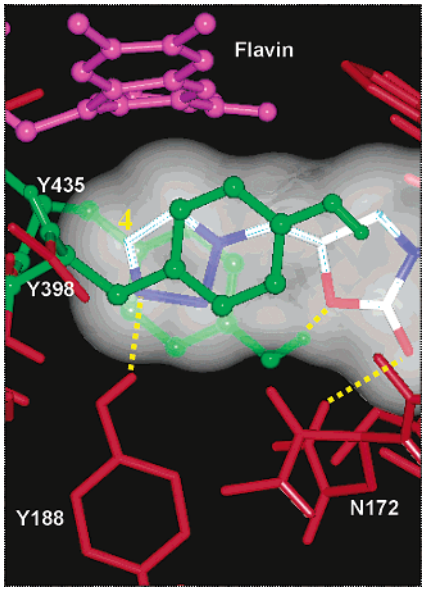


Figure 3. Close-up view on the triazole ring of **2** docked into the MAO-A homology model. The triazole ring is in van der Waals contact with the flavin, Y435, and Y398. Three putative hydrogen bonds are shown between the triazole N3 and the Y188 OH, between the N172 NH_2 group and the oxazolidinone carbonyl oxygen, and between the Y435 OH and the oxazolidinone ether oxygen. Note that the Connolly molecular surface indicates that substitution of the triazole ring is not sterically favorable, especially at the 4 position.

the corresponding methyloxime show only weak antibacterial activity. Presumably the binding site does not readily accommodate nonlinear substituents that occupy space within the plane defined by the triazole ring moiety. Even though we were not able to improve the microbiological activity of 4-substituted triazoles significantly relative to the unsubstituted triazole lead, except in the 4-chlorotriazolo compound **15**, we were pleased to find an interesting SAR against MAO-A within this series (Table 1). Increasing the bulk of substitution at the 4 position reduces MAO-A activity. This seems to be mainly a steric effect, with rising K_i values observed in the order F < Cl < Br and H < CH_3 < isopropyl < ethyl. Moreover, there seems to exist a window of opportunity in 4-substituted triazoles where MAO-A activity is abolished within the detection limit of our assay and where potent antibacterial activity is retained (compounds **10**, **19**, and **21**). The 4-methyl-, 4-bromo-, and 4-ethynyltriazoles (**5**, **16**, and **19**) show essentially the same microbiological potency as the parent triazole **2**, while showing significantly higher MAO-A K_i values (25, 16, and >200 μM compared to 3.4 μM for the parent). The rather potent inhibition by the *tert*-butyl ester **7** is difficult to explain. This compound cannot bind to the homology model without significant changes and must use a different binding mode in its interaction with MAO-A. The MAO-A SAR of the oxazolidinones listed in Table 1 can be largely rationalized on the basis of the docking model shown in Figures 2 and 3. The Connolly surface in Figure 3 suggests that 4-substituted triazoles are sterically forbidden and require the oxazolidinone to adopt a different binding mode. Further docking studies on these 4-substituted triazoles suggest that most of these analogues can still bind in the substrate cavity in a different, presumably less favorable binding mode, with

the oxazolidinone oxygens making hydrogen bonds to the Y435 OH group and to the N172 NH_2 group.

Conclusions

We report the synthesis and biological evaluation of novel oxazolidinones bearing a 4-substituted triazole moiety instead of the conventional acetamide functionality. Vinylsulfones and tosylhydrazone reagents were found to provide good selective access into this compound class, in addition to the copper(I)-catalyzed ligation of azides with alkynes. We found that compounds bearing a small substituent linked via an sp or sp^3 center to the 4 position of the triazole moiety were potent antibacterials with good Gram-positive activity. Many of these compounds had significantly higher MAO-A K_i values than the unsubstituted triazole parent or the acetamide equivalent, giving these types of compounds a potential advantage in the search for oxazolidinone drugs with a better safety profile. The MAO-A SAR can largely be rationalized by docking studies using an MAO-A/MAO-B homology model.

Experimental Section

MAO-A Assay. The assay was carried out adapting the method of Flaherty.[44] Specific conditions were 100 μM of substrate 4-(1-methyl-2-pyrryl)-1 methyl-1,2,3,6-tetrahydropyridine, 82 nM human liver monoamine oxidase A,[45] and 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. K_i values were fitted using the model for MAO-A previously described.[46]

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 spectrometry 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.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-(azidomethyl)oxazolidin-2-one (4). A solution of **3**[23] (7 g, 20.9 mmol) in dichloromethane (200 mL) was treated dropwise at 0 °C with a solution of 3-chloroperbenzoic acid (15.4 g, 70%, 62.9 mmol) in dichloromethane (100 mL). The temperature was allowed to reach room temperature over 2 h, and the reaction mixture was stirred for an additional 30 min at room temperature. It was diluted with ethyl acetate and washed with aqueous sodium thiosulfate solution and then with aqueous sodium hydrogencarbonate solution and with water, and the organic phase was dried over sodium sulfate. Chromatography on silica gel with hexanes/acetone (3:2) gave **4** (6.75 g, 88%) as a colorless solid: mp 120 °C; $[\alpha]_D$ −119° (*c* 1, acetonitrile); MS (ESP) *m/z* 367.1 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 2.98 (m, 2H), 3.35−3.40 (m, 2H), 3.71 (dd, 1H, *J* 5.6, 13.6 Hz), 3.79 (dd, 1H, *J* 3.3, 13.6 Hz), 3.82 (dd, 1H, *J* 6.0, 9.3 Hz), 3.93 (m, 2H), 4.17 (dd, 1H, *J* 9.2, 9.3 Hz), 4.93 (m, 1H), 5.84 (m, 1H), 7.37 (dd, 1H, *J* 8.7, 2.2 Hz), 7.42 (dd, 1H, *J* 8.6, 8.7 Hz), 7.54 (dd, 1H, *J* 13.7, 2.2 Hz).

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-methyl)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (5). A partial solution/suspension of **8** (2.67 g, 7.8 mmol) in dry methanol (100 mL) containing diisopropylethylamine (5.4 mL, 31 mmol) was treated with α,α-dichloroacetone tosylhydrazone[29] (2.9 g, 9.8 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. Solvent was removed under reduced pressure and the residue was taken up in dichloromethane and purified by chromatography on silica gel with acetone/hexanes (1:1 to 2:1) to give **5** (2.04 g, 64%) as a colorless solid: mp 185 °C; MS (ESP) *m/z* 407.09 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 2.24 (s, 3H), 2.97 (m, 2H), 3.32−3.38 (m, 2H), 3.89−3.92 (m, 3H), 4.25 (dd, 1H, *J* 9.1, 9.1 Hz), 4.77 (d, 2H, *J* 5.2 Hz), 5.13 (m, 1H), 5.84 (m, 1H), 7.30 (dd, 1H, *J* 1.9, 8.6 Hz), 7.41 (dd, 1H, *J* 8.6, 8.7 Hz), 7.47 (dd, 1H, *J* 1.9, 13.6 Hz), 7.89 (s, 1H). Anal. ($C_{18}H_{19}FN_4O_4S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-methyl)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (6). A solution of **4** (300 mg, 0.82 mmol) and 5,6,7,8-tetrachloro-1,4-dihydro-2,10-dimethyl-1,4-ethenonaphthalene (0.78 g, 2.44 mmol) in 1,4-dioxane (10 mL) was heated to reflux for 48 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silca gel with CH_2Cl_2/DMF (25:1), followed by crystallization from DMF/CH_2Cl_2/hexanes, to give **6** (75 mg, 23%) (TLC, R_f 0.29, dichloromethane/DMF = 20:1) as a colorless solid: mp 243 °C (**5** was formed as a minor product, R_f 0.27, not isolated); MS (ESP) *m/z* 407.09 (MH^+); ^{1}H NMR (DMSO-d_6) (300 MHz) δ 2.32 (s, 3H), 2.94 (m, 2H), 3.23−3.38 (m, 2H), 3.87−4.00 (m, 3H), 4.25 (m, 1H), 4.72 (m, 2H), 5.13 (m, 1H), 5.80 (m, 1H), 7.22−7.55 (m, 4H). Anal. Calcd for $C_{18}H_{19}FN_4O_4S\cdot 0.6H_2O$: C, 51.82; H, 4.88; N, 13.43. Found: C, 51.72; H, 4.38; N, 13.23.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-*t*-butylcarboxy)-1,2,3-triazol-1-yl)-methyl]oxazolidin-2-one (7). A solution of **4** (6.9 g, 18.83 mmol) and *tert*-butyl propiolate (4.75 g, 37.67 mmol) in dry 1,4-dioxane (15 mL) was heated to reflux for 12 h under vigorous stirring. Ethyl acetate (30 mL) was added and the resulting precipitate was collected by filtration, washed with ethyl acetate, and dried to give **7** (5 g, 54%) as a colorless solid: mp 226 °C; MS (ESP) *m/z* 493.24 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 1.53 (s, 9H), 2.95 (m, 2H), 3.31 (m, 2H), 3.92 (m, 3H), 4.25 (dd, 1H), 4.87 (d, 2H), 5.18 (m, 1H), 5.82 (m, 1H), 7.31 (m, 1H), 7.39 (m, 1H), 7.40 (m, 1H), 8.70 (s, 1H). Anal. ($C_{22}H_{25}FN_4O_6S$) C, H, N.

(5*S*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-(aminomethyl)oxazolidin-2-one (8). A solution of **4** (3 g, 8.2 mmol) and triphenylphosphine (2.6 g, 9.9 mmol) in acetonitrile/water (10:1, 50 mL) was stirred overnight with evolution of nitrogen. The reaction mixture was applied onto a silica gel column and eluted with acetonitrile/water (15:1 to 5:1) to give **8** (2.67 g, 96%) as a colorless solid: $[\alpha]_D$ −31° (*c* 1, DMSO); MS (ESP) *m/z* 341 (MH^+); ^{1}H NMR (DMSO-d_6) (300 MHz) δ 1.81 (brs, 2H), 2.81 (dd, 1H), 2.87 (dd, 1H), 2.98 (m, 2H), 3.30−3.38 (m, 2H), 3.89 (dd, 1H), 3.93 (m, 2H), 4.09 (dd, 1H), 4.65 (m, 1H), 5.84 (m, 1H), 7.37 (dd, 1H), 7.41 (dd, 1H), 7.54 (dd, 1H).

***N*′-[(1*E*)-1-(Dichloromethyl)propylidene]-4-methylbenzenesulfonohydrazide (9b).** A mixture of 1,1-dichlorobutan-2-one (210 mg, 1.49 mmol) and 4-methylbenzenesulfonohydrazide (268 mg, 1.49 mmol) was treated with propionic acid (3 mL) at 80 °C for 5 h and was then allowed to cool to room temperature overnight. Hexanes (20 mL) were added and the precipitate was filtered under nitrogen to yield **9b** (100 mg, 22%) as a colorless solid: ^{1}H NMR (DMSO-d_6) (300 MHz) δ 1.21 (m, 3H), 2.46 (m, 5H), 6.19 (s, 1H), 7.36 (m, 2H), 7.83 (m, 3H).

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-ethyl)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (10). **8** (85.5 mg, 0.25 mmol), *N*′-[(1*E*)-1-(dichloromethyl)propylidene]4-methylbenzenesulfonohydrazide (**9b**) (10 mg, 0.32 mmol), and diisopropylethylamine (0.13 mL, 0.7 mmol) were reacted as described for **5**. Chromatography on silica gel with 5% methanol in dichloromethane gave **10** (71 mg, 72%) as a colorless solid: mp 137 °C; MS (APCI) *m/z* 421.30 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 1.17 (m, 3H), 2.60 (m, 2H), 2.97 (m, 2H), 3.57 (m, 2H), 3.90 (m, 3H), 4.25 (m, 1H), 4.76 (d, 2H), 5.15 (m, 1H), 5.83 (s, 1H), 7.28 (d, 2H), 7.42 (m, 2H), 7.90 (s, 1H). Anal. ($C_{19}H_{21}FN_4O_4S$) C, H, N.

1-Chloro-1-ethenesulfonyl Chloride (11d). A stirred solution of 1,2-dichloroethanesulfonyl chloride[47] (14.54 g, 73.62 mmol) in dry ether (140 mL) was treated at −60 to −50 °C under an atmosphere of nitrogen with 2,6-lutidine (10.30 mL, 88.34 mmol). The stirred reaction mixture was allowed to warm to room temperature, cooled to 0 °C, and then treated dropwise with dilute aqueous sulfuric acid (1%, 50 mL). The ethereal phase was separated, washed with dilute aqueous sulfuric acid (1%, 2 × 60 mL) and brine (3 × 60 mL), dried over magnesium sulfate, and concentrated under reduced pressure (60 mmHg) to give an oil that was purified by distillation to give 7.2 g (61%) of **11d**: bp 26 °C/2 mmHg; ^{1}H NMR ($CDCl_3$) (300 MHz) δ 6.22 (d, 1H, *J* 3.8 Hz), 6.70 (d, 1H, *J* 3.8 Hz).

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-isopropyl)-1,2,3-triazol-1-yl)methyl]-oxazolidin-2-one (12). 4 (0.5 g, 1.36 mmol) and (2-methyl-1-methylenepropyl)phenylsulfane dioxide (0.72 g, 3.42 mmol)[30] were heated in a pressure tube to 90 °C for 5 h. The reaction mixture was diluted with dichloromethane, loaded onto a silica gel column, and eluted with hexanes/acetone (1:1). Fractions containing product were pooled, solvent was evaporated in vacuo, and precipitation from dichloromethane with hexanes gave **12** (214 mg, 36%) as a colorless solid: mp 191 °C; MS (ESP) *m/z* 435.16 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 1.20 (d, 6H, *J* 6.9 Hz), 2.93−3.00 (m, 3H), 3.31−3.37(m, 2H), 3.89−3.94 (m, 3H), 4.26 (dd, 1H, *J* 9.1, 9.1 Hz), 4.76 (d, 2H, *J* 4.8 Hz), 5.16 (m, 1H), 5.83 (m, 1H), 7.27 (dd, 1H, *J* 1.9, 8.6 Hz), 7.40 (dd, 1H, *J* 8.6, 8.8 Hz), 7.43 (dd, 1H, *J* 1.9, 13.7 Hz), 7.89 (s, 1H). Anal. ($C_{20}H_{23}FN_4O_4S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-fluoro)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (13) and (5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(5-fluoro)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (14). 4 (0.7 g, 1.9 mmol) and (1-fluoroethenyl)phenylsulfane dioxide (0.7 g, 3.8 mmol) [34] were mixted in toluene (5 mL) and heated to reflux under stirring for 2 days. The reaction mixture was cooled to room temperature, diluted with dichloromethane, washed with phosphate buffer (pH 7), and dried over sodium sulfate. Chromatography on silica gel with hexanes/acetone (1:1) gave **13** (R_f ∼0.25, TLC, hexanes/acetone, 1:1) (28 mg, 4%) and **14** (R_f ∼0.18, TLC, hexanes/acetone, 1:1) (188 mg, 24%) as colorless solids.

13: mp 139 °C; MS (ESP) *m/z* 409.19 ($M - H^-$); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 2.98 (m, 2H), 3.32−3.39 (m, 2H), 3.91−3.95 (m, 3H), 4.27 (dd, 1H, *J* 9.2, 9.2 Hz), 4.81 (d, 2H, *J* 5.3 Hz), 5.17 (m, 1H), 5.84 (m, 1H), 7.32 (dd, 1H, *J* 2.1, 8.6 Hz), 7.42 (dd, 1H, *J* 8.6, 8.8 Hz), 7.48 (dd, 1H, *J* 2.1, 13.7 Hz), 8.22 (d, 1H, *J* 7.7 Hz). Anal. Calcd for $C_{17}H_{16}F_2N_4O_4S$: C, 49.75; H, 3.93; N, 13.65. Found: C, 49.41; H, 3.58; N, 13.17.

14: mp >210 °C (dec); MS (ESP) *m/z* 409.25 ($M - H^-$); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 2.98 (m, 2H), 3.32−3.38 (m, 2H), 3.93 (m, 2H), 3.96 (dd, 1H, *J* 5.8, 9.5 Hz), 4.30 (dd, 1H, *J* 9.2, 9.5 Hz), 4.78 (m, 2H), 5.17 (m, 1H), 5.84 (m, 1H), 7.29 (dd, 1H, *J* 2.1, 8.6 Hz), 7.41 (dd, 1H, *J* 8.6, 8.8 Hz), 7.47 (dd, 1H, *J* 2.1, 13.7 Hz), 7.71 (d, 1H, *J* 7.4 Hz). Anal. Calcd for $C_{17}H_{16}F_2N_4O_4S$: C, 49.75; H, 3.93; N, 13.65. Found: C, 49.57; H, 3.64; N, 13.20.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-chloro)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (15). 4 (1.0 g, 2.7 mmol) and 1-chloro-1-ethenesulfonyl chloride (**11d**) (1.1 g, 6.8 mmol) were heated to 90 °C for 1 h under stirring in a pressure tube. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and applied onto a silica gel column. Elution with hexanes/acetone (1.5:1) gave **15** (0.745 g, 64%) as a colorless solid: mp 180 °C; MS (ESP) *m/z* 427 (MH^+); ^{1}H NMR (DMSO-d_6) (300 MHz) δ 2.96 (m, 2H), 3.29−3.43 (m, 2H), 3.90−3.95 (m, 3H), 4.25 (dd, 1H, *J* 9.2, 9.2 Hz), 4.83 (d, 2H, *J* 5.3 Hz), 5.16 (m, 1H), 5.82 (m, 1H), 7.29 (dd, 1H, *J* 2.1, 8.6 Hz), 7.40 (dd, 1H, *J* 8.6, 8.7 Hz), 7.45 (dd, 1H, *J* 2.1, 13.8 Hz), 8.45 (s, 1H). Anal. ($C_{17}H_{16}ClFN_4O_4S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-bromo)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (16). 4 (1.5 g, 4.1 mmol) and 1-bromo-1-ethenesulfonyl chloride[32] (1.8 g, 8.8 mmol) were heated to 90 °C for 1 h under stirring in a pressure tube. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and applied onto a silica gel column. Elution with hexanes/acetone (2:1 to 1:1) gave **16** (1.46 g, 76%), as a colorless solid: mp 178 °C; MS (ESP) *m/z* 471/473 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 2.98 (m, 2H), 3.34−3.38 (m, 2H), 3.92−3.96 (m, 3H), 4.27 (dd, 1H, *J* 9.2, 9.2 Hz), 4.87 (d, 2H, *J* 5.2 Hz), 5.18 (m, 1H), 5.84 (m, 1H), 7.31 (dd, 1H, *J* 2.2, 8.6 Hz), 7.42 (dd, 1H, *J* 8.6, 8.8 Hz), 7.47 (dd, 1H, *J* 2.2, 13.7 Hz), 8.49 (s, 1H). Anal. ($C_{17}H_{16}BrFN_4O_4S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-hydroxymethyl)-1,2,3-triazol-1-yl)-methyl]oxazolidin-2-one (17). A suspension of **4** (15 g, 41 mmol) in 2-(phenylsulfonyl)-2-propene-1-ol[31] (12 g, 61 mmol) and *N*-methylpyrolidone (2 mL) was heated to 90 °C under stirring. After 30 min, more NMP (2 mL) was added and the mixture was stirred for another 3.5 h. The partially solidified reaction mixture was taken up in DMF, filtered, and then concentrated under reduced pressure. Chromatography on silica gel with dichloromethane/methanol (16:1) gave **17** (TLC, R_f 0.3, chloroform/methanol = 6:1) (8.64 g, 50%) as a colorless solid: mp 168 °C (the corresponding 5-hydroxymethyl regioisomer was separated during chromatography and presented a minor product, TLC, R_f 0.4); MS (ESP) *m/z* 422.94 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 2.98 (m, 2H), 3.28−3.36 (m, 2H), 3.91−3.94 (m, 3H), 4.27 (dd, 1H, *J* 9.1, 9.1 Hz), 4.54 (d, 2H, *J* 5.7 Hz), 4.82 (d, 2H, *J* 5.4 Hz), 5.16 (m, 1H), 5.23 (dd, 1H, *J* 5.7, 5.7 Hz), 5.84 (m, 1H), 7.30 (dd, 1H, *J* 8.6, 2.2 Hz), 7.41 (dd, 1H, *J* 8.6, 8.8 Hz), 7.50 (dd, 1H, *J* 13.7, 2.2 Hz), 8.03 (s, 1H). Anal. ($C_{18}H_{19}FN_4O_5S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-((2-trimethylsilyl)ethynyl)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (18). A solution of **4** (11 g, 30 mmol), buta-1,3-diynyl(trimethyl)silane (5.8 g, 47.5 mmol),[37] 2,6-lutidine (3.53 g, 33 mmol), and copper iodide (571 mg, 10 mmol%) in dry acetonitrile (200 mL) was stirred at room temperature for 12 h. The mixture was poured into water (250 mL) and stirred for 10 min. The resulting precipitate was collected by filtration, washed with water and diethyl ether (3 × 50 mL), and dried in vacuo to give **18** (11.8 g, 80%) as a colorless solid: mp 198 °C; MS (ESP) *m/z* 489.24 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 0.01 (s, 9H), 2.96 (m, 2H), 3.34 (m, 2H), 3.91 (m, 3H), 4.28 (dd, 1H), 4.85 (m, 2H), 5.20 (m, 1H), 5.81 (m, 1H), 7.26 (m, 1H), 7.38 (m, 1H), 7.43 (m, 1H), 8.51 (s, 1H). Anal. ($C_{22}H_{25}FN_4O_4SSi$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-ethynyl)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (19). 18 (11.5 g, 23.5 mmol) was dissolved in methanol (100 mL), potassium hydroxide (1 M, 36 mL) was added, and the mixture was stirred at room temperature for 4 h. Aqueous HCl (2 M, 24 mL) was added, methanol was evaporated, and the residue was extracted with dichloromethane. The organic phase was collected and concentrated, the residue was dissolved in a mixture of 10% methanol in dichloromethane, followed by addition of hexanes, and the resulting precipitate was collected by filtration to give **19** (8.8 g, 90%) as a colorless solid: mp 244 °C; MS (ESP) *m/z* 417.24 (MH^+); ^{1}H NMR (DMSO-d_6) (500 MHz) δ 2.96 (m, 2H), 3.34 (m, 2H), 3.92 (m, 3H), 4.22 (dd, 1H), 4.38 (s, 1H), 4.82 (d, 2H), 5.18 (m, 1H), 5.81 (m, 1H), 7.22 (m, 1H), 7.38 (m, 1H) 7.42 (m, 1H), 8.51 (s, 1H). Anal. ($C_{19}H_{17}FN_4O_4S{\cdot}0.6H_2O$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-[[(diphenoxyphosphinyl)oxy]methyl]-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (20). A partial solution/suspension of **17** (0.66 g, 1.6 mmol) in dichloromethane/pyridine (10 mL, 2:1) was treated dropwise with a solution of diphenyl phosphorochloridate (0.33 mL, 1.6 mmol) in dichloromethane (2 mL) at 0 °C. After 30 min an additional 60 μL (0.29 mmol) of diphenyl phophorochloridate was added via syringe and the mixture was stirred for another hour. It was

quenched with potassium phosphate buffer (pH 7) and diluted with ethyl acetate. The organic phase was washed with water and dried over sodium sulfate. Chromatography on silica gel with acetone/hexanes (1:1) gave **20** (0.82 g (80%) as a hard foam: MS (ESP) *m/z* 655.05 (MH^+); ^1H NMR (DMSO-d_6) (500 MHz) δ 2.94 (m, 2H), 3.29−3.34 (m, 2H), 3.90 (m, 3H), 4.12 (s, 2H), 4.24 (dd, 1H, *J* 9.1, 9.1 Hz), 4.83 (m, 2H), 5.14 (m, 1H), 5.39 (m, 2H), 5.80 (m, 1H), 7.19−7.30 (m, 7H), 7.35−7.47 (m, 6H), 8.30 (s, 1H). Anal. ($C_{30}H_{28}FN_4O_8PS$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-cyanomethyl)-1,2,3-triazol-1-ylmethyl]-oxazolidin-2-one (21). Sodium cyanide (0.22 g, 4.5 mmol) was added to a solution of **20** (0.5 g, 0.76 mmol) in DMF (10 mL), and the mixture was heated to 60 °C for 1.5 h. It was diluted with ethyl acetate, washed with potassium phosphate buffer (pH 7) and with water, and dried over sodium sulfate. Chromatography on silica gel with acetone/hexanes (1:1) gave **21** (236 mg, 72%) as a colorless solid: mp 184 °C; MS (ESP) *m/z* 432.07 (MH^+); ^1H NMR (DMSO-d_6) (500 MHz) δ 2.94 (m, 2H), 3.30−3.34 (m, 2H), 3.88−3.90 (m, 3H), 4.12 (s, 2H), 4.24 (dd, 1H, *J* 9.1, 9.1 Hz), 4.82 (d, 2H, *J* 5.3 Hz), 5.14 (m, 1H). Anal. ($C_{19}H_{18}FN_5O_4S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-carboxaldehyde-1,2,3-triazol-1-yl)-methyl]oxazolidin-2-one (22). A solution of oxalyl chloride (1.36 mL, 15.6 mmol) in dichloromethane (30 mL) was treated dropwise with a solution of DMSO (1.42 mL, 20 mmol) in dichloromethane (30 mL) at −50 °C. After 10 min, a solution of **17** (5 g, 11.8 mmol) in *N*-methylpyrolidone (25 mL) was diluted with dichloromethane (25 mL) and added dropwise. The mixture was stirred vigorously for 1 h, then treated dropwise with *N*,*N*-diisopropylethylamine (10 mL, 57.4 mmol), warmed to −40 °C, and stirred for another hour. The reaction mixture allowed to warm to −20 °C slowly and held at this temperature overnight. The resulting homogeneous solution was directly applied onto a silica gel column and eluted with hexanes/acetone (1:1 to 1:2). Fractions containing product were pooled and concentrated under reduced pressure. The product was further purified by precipitation from acetone (100 mL) with hexanes (700 mL) to give **22** (4.2 g, 84%) as a colorless solid: mp 146 °C; MS (ESP) *m/z* 419.29 ($M - H^-$); ^1H NMR (DMSO-d_6) (500 MHz) δ 2.98 (m, 2H), 3.29−3.38 (m, 2H), 3.93 (s, 2H), 3.97 (dd, 1H, *J* 5.8, 9.5 Hz), 4.29 (dd, 1H, *J* 9.2, 9.5 Hz), 4.94 (d, 2H, *J* 5.4 Hz), 5.22 (m, 1H), 5.84 (m, 1H), 7.32 (dd, 1H, *J* 2.2, 8.6 Hz), 7.42 (dd, 1H, *J* 8.6, 8.8 Hz), 7.48 (dd, 1H, *J* 2.2, 13.7), 8.95 (s, 1H), 10.05 (s, 1H). Anal. ($C_{18}H_{17}FN_4O_5S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-(2,2-dibromoethenyl)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (23). To a mixture of **22** (5 g, 11.9 mmol) and carbon tetrabromide (4.34 g, 13.1 mmol) in dichloromethane (100 mL) was added triphenylphosphine (6.55 g, 25 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature. Chromatography on silica gel with toluene/ethanol (10:1 to 7:1) gave **23** (6.1 g, 89%) as an off-white solid: mp 188 °C; MS (ESP) *m/z* 575, 577, 579 (MH^+); ^1H NMR (DMSO-d_6) (500 MHz) δ 2.98 (m, 2H), 3.31−3.40 (m, 2H), 3.93−3.96 (m, 3H), 4.28 (dd, 1H, *J* 9.1, 9.1 Hz), 4.90 (d, 2H, *J* 5.2 Hz), 5.21 (m, 1H), 5.85 (m, 1H), 7.31 (dd, 1H, *J* 2.2, 8.6 Hz), 7.42 (dd, 1H, *J* 8.6, 8.8 Hz), 7.47 (dd, 1H, *J* 2.2, 13.7 Hz), 7.80 (s, 1H), 8.68 (s, 1H). Anal. ($C_{19}H_{17}Br_2FN_4O_4S$) C, H, N.

(5*R*)-3-[4-(1,1-Dioxo-3,6-dihydro-2*H*-thiopyran-4-yl)-3-fluorophenyl]-5-[(4-((*E*)-2-bromoethenyl)-1,2,3-triazol-1-yl)methyl]oxazolidin-2-one (24). A mixture of **23** (0.4 g, 0.69 mmol), diethyl phosphite (0.36 mL, 2.79 mmol), and triethylamine (0.195 mL, 1.39 mmol) in ethanol (2 mL) was heated at 90 °C for 5 h under vigorous stirring. The reaction mixture was cooled to room temperature, diluted with dichloromethane, washed with potassium phosphate buffer (pH 7), and dried over sodium sulfate. Chromatography on silica gel with dichloromethane/DMF (50:1 to 40:1) gave **24** (151 mg, 44%) as a colorless amorphous solid: MS (ESP) *m/z* 537.7/539.9 (MH^+ + 41 (acetonitrile)); ^1H NMR (DMSO-d_6) (500 MHz) δ 3.04 (m, 2H), 3.23−3.28 (m, 2H), 3.81 (brs, 2H), 3.87 (dd, 1H, *J* 5.7, 9.6 Hz), 4.22 (dd, 1H, *J* 9.3, 9.6 Hz), 4.72 (dd, 1H, *J* 6.2, 15.0 Hz), 4.78 (dd, 1H, *J* 3.7, 15.0 Hz), 5.10 (m, 1H), 5.82 (m, 1H), 7.09 (d, 1H, *J* 14.5 Hz), 7.15 (d, 1H, *J* 14.5 Hz), 7.20 (dd, 1H, *J* 2.2, 8.5 Hz), 7.33 (dd, 1H, *J* 8.5, 8.6 Hz), 7.37 (dd, 1H, *J* 2.2, 13.4 Hz), 7.97 (s, 1H). Anal. ($C_{19}H_{18}BrFN_4O_4S$) C, H, N.

Acknowledgment. The authors thank Dr. Camil Joubran, Analytical Chemistry Department of AstraZeneca R&D Boston, for performing NOE NMR experiments; Organix, Inc., Woburn, MA, for the synthesis of some intermediates and vinylsulfone reagents; Adam Mondello and Jeanette Jones, Microbiology Department, AstraZeneca R&D Boston, for the determination of MICs; and Tory Nash, Biochemistry Department, AstraZeneca R&D Boston, for the determination of MAO-A K_i values.

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

References

(1) Woodford, N. Novel agents for the treatment of resistant Gram-positive infections. *Expert Opin. Invest. Drugs* **2003**, *12*, 117−137.
(2) Khare, M.; Keady, D. Antimicrobial Therapy of Methicillin Resistant *Staphylococcus aureus* Infection. *Expert Opin. Pharmacother.* **2003**, *4*, 165−177.
(3) Hamilton-Miller, J. M. Vancomycin-resistant Staphylococcus aureus: a real and present danger? *Infection* **2002**, *30*, 118−124.
(4) Lam, S.; Singer, C.; Tucci, V.; Morthland, V. H.; Pfaller, M. A.; Isenberg, H. D. The challenge of vancomycin-resistant enterococci: a clinical and epidemiologic study. *AJIC, Am. J. Infect. Control* **1995**, *23*, 170−180.
(5) Nicolau, D. Clinical and economic implications of antimicrobial resistance for the management of community-acquired respiratory tract infections. *J. Antimicrob. Chemother.* **2002**, *50*, 61−70.
(6) Adam, D. Global antibiotic resistance in *Streptococcus pneumoniae*. *J. Antimicrob. Chemother.* **2002**, *50*, 1−5.
(7) Paladino, J. A. Linezolid: an oxazolidinone antimicrobial agent. *Am. J. Health-Syst. Pharm.* **2002**, *59*, 2413−2425.
(8) Hutchinson, D. K. Oxazolidinone Antibacterial Agents: A Critical Review. *Curr. Top. Med. Chem.* **2003**, *3*, 1021−1042.
(9) Perry, C. M.; Jarvis, B. Linezolid: a review of its use in the management of serious Gram-positive infections. *Drugs* **2001**, *61*, 525−551.
(10) Colca, J. R.; McDonald, W. G.; Waldon, D. J.; Thomasco, L. M.; Gadwood, R. C.; Lund, E. T.; Cavey, G. S.; Mathews, W. R.; Adams, L. D.; Cecil, E. T.; Pearson, J. D.; Bock, J. H.; Mott, J. E.; Shinabarger, D. L.; Xiong, L.; Mankin, A. S. Cross-linking in the living cell locates the site of action of oxazolidinone antibiotics. *J. Biol. Chem.* **2003**, *278*, 21972−21979.
(11) Aoki, H.; Ke, L.; Poppe, S. M.; Poel, T. J.; Weaver, E. A.; Gadwood, R. C.; Thomas, R. C.; Shinabarger, D. L.; Ganoza, M. C. Oxazolidinone Antibiotics Target the P Site on *Escherichia coli* Ribosomes. *Antimicrob. Agents Chemother.* **2002**, *46*, 1080−1085.
(12) Xiong, L.; Kloss, P.; Douthwaite, S.; Andersen, N. M.; Swaney, S.; Shinabarger, D. L.; Mankin, A. S. Oxazolidinone Resistance Mutations in 23S rRNA of *Escherichia coli* Reveal the Central Region of Domain V as the Primary Site of Drug Action. *J. Bacteriol.* **2000**, *182*, 5325−5331.
(13) Auckland, C.; Teare, L.; Cooke, F.; Kaufmann, M. E.; Warner, M.; Jones, G.; Bamford, K.; Ayles, H.; Johnson, A. P. Linezolid-Resistant *Enterococci*: Report of the First Isolates in the United Kingdom. *J. Antimicrob. Chemother.* **2002**, *50*, 743−746.
(14) Potoski, B. A.; Mangino, J. E.; Goff, D. A. Clinical failures of linezolid and implications for the clinical microbiology laboratory. *Emerging Infect. Dis.* **2002**, *8*, 1519−1520.
(15) Herrero, I. A.; Issa, N. C.; Patel, R. Nosocomial Spread of Linezolid-Resistant, Vancomycin-Resistant *Enterococcus faecium*. *N. Engl. J. Med.* **2002**, *346*, 867−869.
(16) Jones, R. N.; Della-Latta, P.; Lee, L. V.; Biedenbach, D. J. Linezolid-resistant *Enterococcus faecium* isolated from a patient without prior exposure to an oxazolidinone: report from the SENTRY Antimicrobial Surveillance Program. *Diagn. Microbiol. Infect. Dis.* **2002**, *42*, 137−139.
(17) Rahim, S.; Pillai, S. K.; Gold, H. S.; Venkataraman, L.; Inglima, K.; Press, R. A. Linezolid-resistant, vancomycin-resistant *Enterococcus faecium* infection in patients without prior exposure to linezolid. *Clin. Infect. Dis.* **2003**, *36*, E146−E148.

(18) Tsiodras, S.; Gold, H. S.; Sakoulas, G.; Eliopoulos, G. M.; Wennersten, C.; Venkataraman, L.; Moellering, R. C.; Ferraro, M. J. Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet* **2001**, *358*, 207−208.
(19) Ramsay, R. R.; Gravestock, M. B. Monoamine oxidases: To inhibit or not to inhibit. *Mini-Rev. Med. Chem.* **2003**, *3*, 129−136.
(20) Callingham, B. A. Drug interactions with reversible monoamine oxidase-A inhibitors. *Clin. Neuropharmacol.* **1993**, *16*, S42−S50.
(21) Anderson, M. C.; Hasan, F.; McCrodden, J. M.; Tipton, K. F. Monoamine oxidase inhibitors and the cheese effect. *Neurochem. Res.* **1993**, *18*, 1145−1149.
(22) Hutchinson, D. K.; Ennis, M. D.; Hoffman, R. L.; Thomas, R. C.; Poel, T.-J.; Barbachyn, M. R.; Brickner, S. J.; Anderson, D. J. Phenyloxazolidinones having a C−C bond to 4−8 membered heterocyclic rings, and their use as antimicrobials. PCT Int. Appl. WO 9709328, 1997 (Upjohn Co.).
(23) Gravestock, M. B.; Betts, M. J.; Griffin, D. A.; Matthews, I. R. Oxazolidinone derivatives with antibacterial activity. PCT Int. Appl. WO 0181350, 2001 (Astrazeneca U.K. Limited, Astrazeneca AB, Sweden).
(24) Gravestock, M. B.; Hales, N. J.; Reck, F.; Zhou, F.; Fleming, P. R.; Carcanague, D. R. Preparation of 5-azolylmethyl oxazolidinones and their use as antibacterial agents. PCT Int. Appl. WO 2003072576, 2003 (Astrazeneca U.K. Limited, Astrazeneca AB, Sweden).
(25) Gravestock, M. B.; Hales, N. J.; Reck, F.; Zhou, F.; Fleming, P. R.; Carcanague, D. R.; Girardot, M. M. Preparation of 3-cyclyl-5-[(nitrogen-containing 5-membered ring)methyl]oxazolidinones and their use as antibacterial agents. PCT Int. Appl. WO 2003072575, 2003 (Astrazeneca U.K. Limited, Astrazeneca AB, Sweden).
(26) Phillips, O. A.; Udo, E. E.; Ali, A. A. M.; Al-Hassawi, N. Synthesis and Antibacterial Activity of 5-Substituted Oxazolidinones. *Bioorg. Med. Chem.* **2003**, *11*, 35−41.
(27) Heaney, H.; Jablonski, J. M. Aryne Chemistry—Part XII—Some Cycloaddition Reactions of Tetrachlorobenzyne. *J. Chem. Soc. C* **1968**, 1895−1898.
(28) Alonso, G.; Garcia-Lopez, M. T.; Garcia-Munoz, G.; Madronero, R.; Rico, M. Heterocyclic *N*-Glycosides VI—The Reaction of Glycosyl Azides with Propiolic Acid and Methyl Propiolate. *J. Heterocycl. Chem.* **1970**, *7*, 1269−1272.
(29) Sakai, K.; Hida, N.; Kondo, K. Reactions of alpha-Polyhaloketone Tosylhydrazones with Sulfide Ion and Primary Amines-Cyclizations to 1,2,3-Thiadiazoles and 1,2,3-Triazoles. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179−183.
(30) Chodroff, S.; Whitmore, W. F. The Preparation of Unsaturated Sulfones by Condensation Reactions. *J. Am. Chem. Soc.* **1950**, *72*, 1073−1076.
(31) Miyamoto, N.; Inoue, S. Sulfinyl and Sulfonyl Compounds. Ger. Offen. DE2630947, 1977 (Kao Soap Co., Ltd.).
(32) Rondestvedt, C. S., Jr. Unsaturated Sulfonic Acids. IV. Preparation and Properties of α-Bromoalkenesulfonyl Chlorides. *J. Am. Chem. Soc.* **1954**, *76*, 1926−1929.
(33) Rondestvedt, C. S., Jr.; Chang, P. K. Unsaturated Sulfonic Acids. V. Addition of Diazomethane and Phenyl Azide to Derivatives of Ethylenesulfonic Acid and its Homologs. *J. Am. Chem. Soc.* **1955**, *77*, 6532−6540.
(34) Matthews, D. P.; McCarthy, J. R. Addition of α-Oxyradicals to 1-Fluoro-1-(phenylsulfonyl)ethylene. *J. Org. Chem.* **1990**, *55*, 2973−2975.
(35) Tornoe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67*, 3057−3064.
(36) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.
(37) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H. Selective Desilylation of Bis(trimethylsilyl)acetylenes. *J. Chem. Soc., Chem. Commun.* **1979**, 840−842.
(38) Corey, E. J.; Fuchs, P. L. A Synthetic Method For Formyl−Ethynyl Conversion. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.
(39) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. Reduction of *gem*-Dibromides with Diethyl Phosphite. *J. Org. Chem.* **1981**, *46*, 3745−3747.
(40) Binda, C.; Li, M.; Hubalek, F.; Restelli, N.; Edmondson, D. E.; Mattevi, A. Insights into the mode of inhibition of human mitochondrial monoamine oxidase B from high-resolution crystal structures. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 9750−9755.
(41) Binda, C.; Newton-Vinson, P.; Hubalek, F.; Edmondson, D. E.; Mattevi, A. Structure of human monoamine oxidase B, a drug target for the treatment of neurological disorders. *Nat. Struct. Biol.* **2002**, *9*, 22−26.
(42) A structure for rat monoamine oxidase A has recently been published, but the coordinates were not available to the public at the time of submission of this paper. Ma, J.; Yoshimura, M.; Yamashita, E.; Nakagawa, A.; Ito, A.; Tsukihara, T. Structure of Rat Monoamine Oxidase A and Its Specific Recognitions for Substrates and Inhibitors. *J. Mol. Biol.* **2004**, *338*, 103−114.
(43) McMartin, C.; Bohacek, R. S. QXP—Powerful, rapid computer algorithms for structure-based drug design. *J. Comput.-Aided Mol. Des.* **1997**, *11*, 333−344.
(44) Flaherty, P.; Castagnoli, K.; Wang, Y.-X.; Castagnoli, N., Jr. Synthesis and Selective Monoamine Oxidase B. Inhibiting Properties of 1-Methyl-1,2,3,6-tetrahydropyrid-4-yl Carbamate Derivatives: Potential Prodrugs of (*R*)- and (*S*)-Nordeprenyl. *J. Med. Chem.* **1996**, *39*, 4756−4761.
(45) Tan, A. K.; Weyler, W.; Salach, J. I.; Singer, T. P. Differences in substrate specificities of monoamine oxidase A from human liver and placenta. *Biochem. Biophys. Res. Commun.* **1991**, *181*, 1084−1088.
(46) Tan, A. K.; Ramsay, R. R. Substrate-specific enhancement of the oxidative half-reaction of monoamine oxidase [erratum appears in *Biochemistry* **1993** *32* (20), 5490]. *Biochemistry* **1993**, *32*, 2137−2143.
(47) Gladshtein, B. M.; Chernetskii, V. N.; Kiseleva, M. I.; Soborovskii, L. Z. Organic Compounds of Sulfur III—Properties of Haloalkane-, Alkene-, and Haloalkenesulfonyl Fluorides. *Zh. Obshch. Khim.* **1958**, *28*, 2107−2111.
(48) *)Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard*, 2nd ed.; National Committee for Clinical Laboratory Standards: Villanova, PA, 1993.

JM0400810