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Carbon–Carbon-Linked (Pyrazolylphenyl)oxazolidinones with Antibacterial Activity Against Multiple Drug Resistant Gram-Positive and Fastidious Gram-Negative Bacteria

Chi Sing Lee,[a] Debra A. Allwine,[a] Michael R. Barbachyn,[a] Kevin C. Grega,[a] Lester A. Dolak,[b] Charles W. Ford,[c] Randy M. Jensen,[b] Eric P. Seest,[b] Judith C. Hamel,[c] Ronda D. Schaadt,[c] Douglas Stapert,[c] Betty H. Yagi,[c] Gary E. Zurenko[c] and Michael J. Genin[a,*]

[a]*Combinatorial and Medicinal Chemistry Research, Pharmacia Corporation, Kalamazoo, MI 49001, USA*
[b]*Structural Analytical and Medicinal Chemistry Research, Pharmacia Corporation, Kalamazoo, MI 49001, USA*
[c]*Infectious Diseases Research, Pharmacia Corporation, Kalamazoo, MI 49001, USA*

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Abstract—In an effort to expand the spectrum of activity of the oxazolidinone class of antibacterial agents to include Gram-negative bacteria, a series of new carbon–carbon linked pyrazolylphenyl analogues has been prepared. The α-*N*-substituted methyl pyrazole (**10**α) in the C3-linked series exhibited very good Gram-positive activity with MICs ≤0.5–1 μg/mL and moderate Gram-negative activity with MICs = 2–8 μg/mL against *Haemophilus influenzae* and *Moraxella catarrhalis*. This analogue was also found to have potent in vivo activity with an $ED_{50} = 1.9$ mg/kg. β-Substitution at the C3-linked pyrazole generally results in a loss of activity. The C4-linked pyrazoles are slightly more potent than their counterparts in the C3-linked series. Most of the analogues in the C4-linked series exhibited similar levels of activity in vitro, but lower levels of activity in vivo than **10**α. In addition, incorporation of a thioamide moiety in selected C4-linked pyrazole analogues results in an enhancement of in vitro activity leading to compounds several times more potent than eperezolid, linezolid and vancomycin. The thioamide of the *N*-cyanomethyl pyrazole analogue (**34**) exhibited an exceptional in vitro activity with MICs of ≤ 0.06–0.25 μg/mL against Gram-positive pathogens and with MICs of 1 μg/mL against fastidious Gram-negative pathogens. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

The number of life-threatening infections caused by multi-drug-resistant Gram-positive pathogens has reached an alarming level in hospitals and the community.[1–3] Several clinical reports in the United States and worldwide have independently described the emergence of vancomycin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) isolates.[4–7] Infections caused by these organisms pose a serious challenge to the medical community and the need for an effective therapy has led to a search for novel antibacterial agents.

The oxazolidinones are a totally synthetic class of antibacterial agents effective against sensitive and multi-drug-resistant Gram-positive bacterial pathogens.[8] The recently approved oxazolidinone linezolid (**1**, PNU-100766) and a derivative eperezolid (**2**) exhibit potent activity against several important human pathogens including MRSA[9] and *Staphylococcus epidermidis*,[9] vancomycin-resistant enterococci,[10,11] and penicillin- and vancomycin-resistant streptococci.[12] This new class of antibiotics gives physicians a powerful new tool for the treatment of infections caused by these organisms.

These compounds have been shown to inhibit bacterial translation at the initiation phase of protein synthesis by binding to the 50S ribosomal subunit.[13–16] In recent years there has been a significant effort placed on discovering the exact molecular target within the ribosome complex. A review by Shinabarger discusses the mechanism of action of the oxazolidinones in more detail.[17] It is suggested that the oxazolidinones act by disrupting the processing of *N*-formylmethionyl-tRNA by the ribosome.

*Corresponding author. Tel.: +1-616-833-9869; fax: +1-616-833-2516; e-mail: michael.j.genin@pharmacia.com

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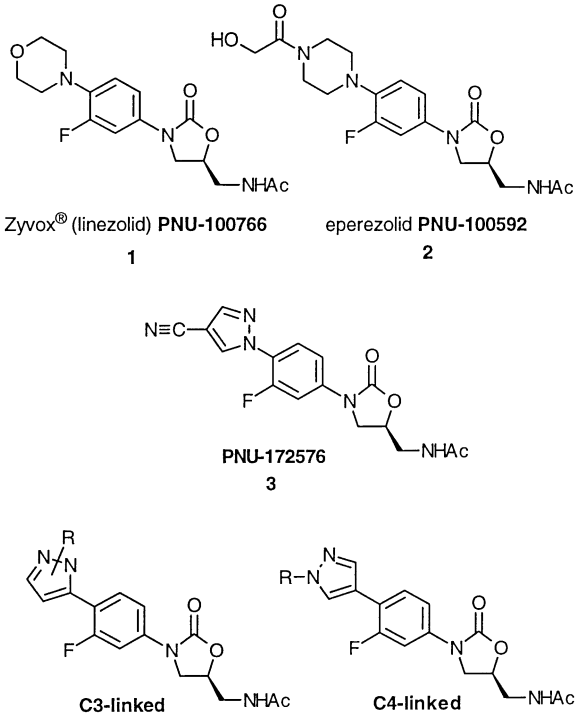
Given that a large number of upper respiratory tract infections including otitis media are caused by the fastidious Gram-negative pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*, we have targeted these organisms in our efforts to expand the spectrum of antibacterial activity of the oxazolidinones. To this end we have replaced the morpholine ring moiety of linezolid with various five-membered nitrogen-containing heterocycles (azoles).[18,19] From this effort, the nitrogen–carbon linked pyrazole derivatives were found to have very interesting activity profiles. In particular, the 3-cyano derivative **3** (PNU-172576) has excellent in vitro activity against a broad spectrum of Gram-positive organisms with MICs ≤ 0.125–$0.5\,\mu g/mL$ as well as good activity against fastidious Gram-negative bacteria with MICs = 2–4 μg/mL.[19] This analogue also shows very good in vivo activity with an $ED_{50} = 1.2\,mg/kg$ against *S. aureus* in a mouse model.[19] In light of these observations, we explored the structure–activity relationships of carbon–carbon linked pyrazole derivatives.



Results and Discussion

Chemistry

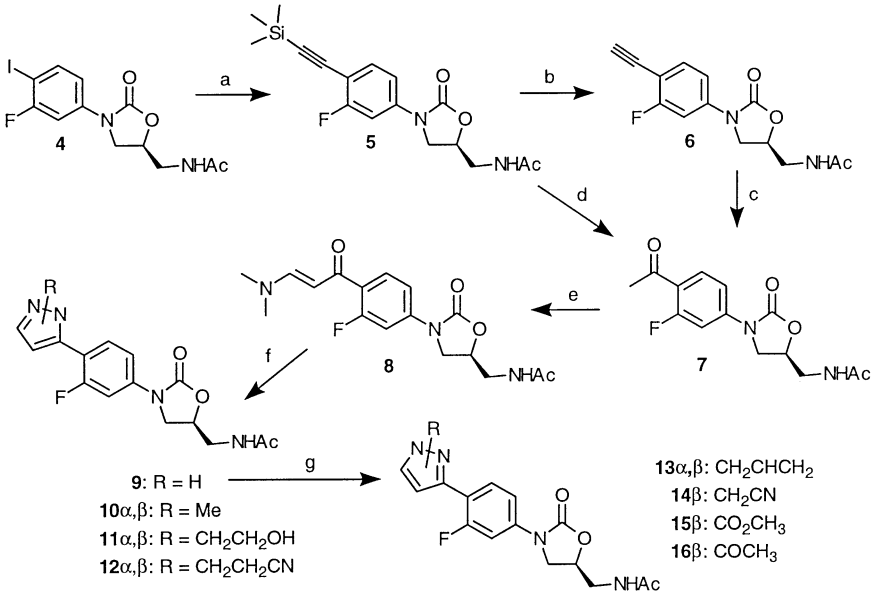
***N*-Substituted C3-linked pyrazole analogues.** The vinylogous amide **8** was used as a key intermediate in the synthesis of the *N*-substituted C3-linked pyrazole oxazolidinones (Scheme 1). Palladium mediated coupling of the known iodophenyloxazolidionone derivative **4**[20] and trimethylsilylacetylene resulted in the formation of **5**. Initially, preparation of the acetyl intermediate **7** was problematic. Removal of the trimethylsilyl group of **5** with potassium carbonate gave **6**. The acetylene was then treated with mercury oxide and Nafion to afford the ketone **7** in very poor yields. In an attempt to improve this transformation and avoid the use of mercury, compound **6** was treated with formic acid to give ketone **7**. Unfortunately, this sequence gave variable results and the yields were not reproducible. Thus, **5** was treated with formic acid which resulted in the direct formation of ketone **7** in good yield. The ketone was then condensed with *N*,*N*-dimethylformamide dimethylacetal to give the key intermediate **8**.

With **8** prepared, the vinylogous amide moiety was converted to the pyrazole using hydrazine hydrate in ethanol.[21] This transformation gave the unsubstituted C3-linked pyrazole (**9**) in good yield. The methyl (**10**), hydroxyethyl (**11**) and cyanoethyl (**12**) derivatives were also obtained from **8** via treatment with the corresponding substituted hydrazine. These conditions gave mixtures of regioisomers with the α-isomers as the primary products. The isomers were separated on a chiral HPLC column and the regiochemistry was determined via NMR (Table 1). Due to the close proximity of the α-substituent to the phenyl hydrogen *ortho* to the pyrazole ring, an interaction is observed between these two groups in a difference NOE experiment.[22] However, no NOE is seen between the α-substituent and the pyrazole-5-H. In the case of the β-isomers the opposite is true. Irradiation of the β-substituent results in an NOE with the pyrazole-5-H but not with the *ortho*-hydrogen of the phenyl ring. In addition, the hydrogens (H-4 and H-5) of the pyrazole are shifted down field by 0.18–0.22 ppm (H-4) and 0.23–0.56 ppm (H-5), respectively, in the β-isomers relative to the α-substituted analogues (α-isomers: δ H-4 = 6.34-6.41, H-5 = 7.46–7.56 ppm; β-isomers: δ H-4 = 6.55–6.61, H-5 = 7.76–7.90 ppm).

The β-*N*-substituted pyrazole analogues **13**–**16** were obtained via direct functionalization of pyrazole **9**, also shown in Scheme 1. Treatment of **9** with two equivalents of sodium hydride followed by the addition of an appropriate alkylating/acylating agent gave allyl (**13**), cyanomethyl (**14**), methoxycarbonyl (**15**), and acetate (**16**) derivatives. Formation of the β-isomers was favored under these conditions.

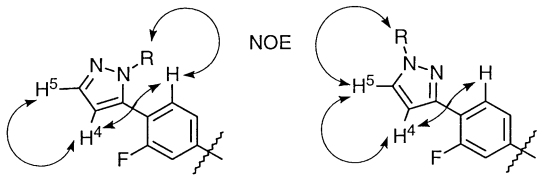
***N*-substituted C4-linked pyrazole analogues.** We initially targeted the synthesis of **22** as the key intermediate in the C4-linked pyrazole series. As shown in Scheme 2, Stille coupling between trimethylstanane **17** and tritylated 4-iodopyrazole **19** using $Pd_2(dba)_3$ in NMP afforded inconsistent yields of the desired coupling product (**21**) along with inseparable side-products. Removal of the trityl protecting group using trifluoroacetic acid facilitated the purification process and gave pyrazole **22** in very poor yields. Addition of copper(I) catalyst did not improve the yield and using $Pd(OAc)_2$, PPh_3 and *n*-BuLi to generate Pd(0) in situ did not afford any coupling product. In addition, coupling between **17** and iodide **20** also gave low yields of the desired product (**23**).

In order to optimize the yield of **22**, the utility of the one-pot Suzuki coupling[23] using pinacol diborane ester to generate the arylboronic acid in situ was investigated. The optimal conditions are shown in Scheme 2. Boronic ester formation with iodide **19** proceeded smoothly with



Scheme 1. Reagents: (a) TMSCCH, $Pd(PPh_3)_2Cl_2$,CuI, Et_3N, DMF, 45 °C, 99%; (b) K_2CO_3, CH_3OH, 60% (c) HgO, Nafion, H_2O, CH_2Cl_2, reflux, 20% or formic acid, 85 °C, 57%; (d) formic acid, 95 °C, 69%; (e) $Me_2NCH(OMe)_2$, EtOH, reflux, 76%; (f) H_2NNHR, EtOH reflux to yield 62–97% of **9**, **10** (α/β = 6:1), **11** (α/β = 7:1), **12** (α/β = 10:1); (g) NaH, DMF, 0 °C then RBr or RCOCl to yield 26–94% of **13** (α/β = 1:8), **14**β, **15**β and **16**β.

Table 1. Determination of the regiochemistry of α- and β-isomers of analogues **10**–**16**



Compound	R	δ H-4 (ppm) α-isomer	δ H-5 (ppm) α-isomer	δ H-4 (ppm) β-isomer	δ H-5 (ppm) β-isomer
10	CH_3	6.37	7.50	6.55	7.76
11	CH_2CH_2OH	6.34	7.55	6.56	7.78
12	CH_2CH_2CN	6.41	7.46	6.61	7.90
13	Allyl	6.39	7.56	6.60	7.79
14	CH_2CN			6.68	7.92
15	CO_2CH_3			6.90	8.43
16	Ac			6.94	8.48

pinacol diborane ester, potassium acetate and $Pd(PPh_3)_4$ in DMF at 100 °C. Base hydrolysis followed by coupling with iodide **4** afforded good yields of the intermediate *N*-tritylated pyrazole **21**. Finally, removal of the trityl protecting group using trifluoroacetic acid afforded **22** in good yield.

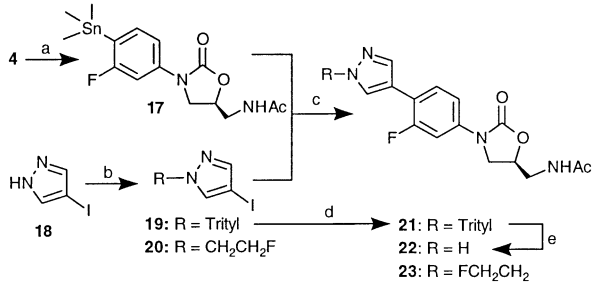
Compound **22** was useful for the synthesis of substituted C4-linked analogues **24**–**34** via alkylation conditions shown in Scheme 3. The thioamides of four analogues were also prepared. Thus, **22** and **27**–**29** were converted to the corresponding thioamides **31**–**34** using Lawesson's reagent in refluxing THF in moderate to good yields.

Antibacterial activity

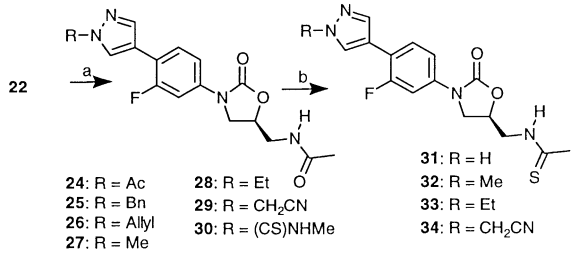
The oxazolidinone analogues prepared above were tested for antibacterial activity in vitro against a panel of Gram-positive and fastidious Gram-negative bacterial isolates. Minimum inhibitory concentration (MIC) values were determined using agar dilution methodology.[24] Selected analogues were also tested for in vivo activity by a *S. aureus* infection model in mice.[24] The MIC and ED_{50} values are shown in Tables 2 and 3.

The C3-linked unsubstituted pyrazole analogue (**9**) exhibited similar levels of in vitro activity to that of linezolid (**1**) and eperezolid (**2**). The Gram-positive MICs are <0.5–4 μg/mL for **9** and 1–4 μg/mL for linezolid (Table 2). Switching the connectivity of the pyrazole to the C4-linked analogue (**22**) led to an improvement in the in vitro activity against MRSA, *E. faecalis* and *H. influenzae* (Table 3); however the compound has only moderate in vivo activity ($ED_{50} = 11.4$ mg/kg).

The C3-linked pyrazole series showed interesting sub-



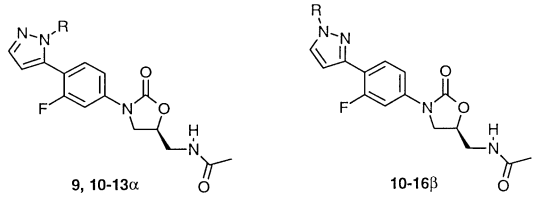
Scheme 2. Reagents: (a) $(Me_3Sn)_2$, $PdCl2(PPh_3)_2$, dioxane, reflux, 99%; (b) Trityl-Cl, Et_3N, DMF, >90% or NaH, DMF; $BrCH_2CH_2F$, 80%; (c) **19** or **20**, $Pd_2(dba)_3$, TFP, LiCl, NMP, 90 °C (0–40%); (d) Diboron pinacol ester, KOAc, $Pd(PPh_3)_4$, DMF, 100 °C then **4**, $Pd(PPh_3)_4$, Na_2CO_3, 100 °C; (e) TFA, CH_2Cl_2, 53–76% for steps d and e to give **22**.



Scheme 3. Reagents: (a) RBr or RCOCl, base, THF or acetone, reflux, 21–94%, or NaH, DMF, 0 °C then CH_3NCS, 43%; (b) Lawesson's reagent, THF, reflux, 32–94%.

stituent effects (Table 2). Changing the hydrogen at the α-position of the pyrazole (**9**) to a methyl group (**10**α) led to enhancement of in vitro activity against all organisms with the exception of *S. pneumoniae*. The Gram-positive MICs are <0.5–1 μg/mL, and the MICs versus *H. influenzae* and *M. catarrhalis* are 8 μg/mL and 2 μg/mL, respectively. Moreover, **10**α was also found to be very potent in vivo with an $ED_{50} = 1.9$ mg/kg which is comparable to that of linezolid (3.5 mg/kg). It is interesting to note the drop in antibacterial activity by simply moving the methyl group from the α- to the β-position (**10**α vs **10**β). The Gram-positive MICs increase from <0.5–1 μg/mL for **10**α to 2–>64 μg/mL for **10**β. This effect is quite profound when considering *S. pneumoniae* and *H. influenzae* where **10**β was completely inactive at 64 μg/mL, and **10**α has MICs of <0.5 μg/mL and 8 μg/mL, respectively, against these organisms. Replacement of the methyl group with the hydroxyethyl (**11**α,β), cyanoethyl (**12**α,β) or allyl (**13**α,β) moieties results in analogues with poor to moderate Gram-positive activity and little or no activity against the fastidious Gram-negative organisms. The exception to this trend was the cyanomethyl derivative (**14**β), which has essentially the same level of Gram-positive activity as linezolid; Gram-positive MICs of 14β are <0.5–4 μg/mL versus 1–4 μg/mL for linezolid.

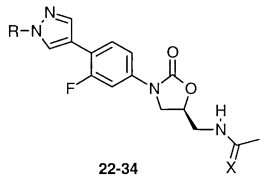
Table 2. Antibacterial activity (MIC, μg/mL) of the *N*-substituted C3-linked pyrazolylphenyl oxazolidinones



Compound	R	*S.a.*[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.inf.*[f]	*M.cat.*[g]	ED_{50}[h]	Control ED_{50}[i]
9	H	4	4	1	<0.5	4	32	8		
10α	CH_3	1	<0.5	<0.5	<0.5	<0.5	8	2	1.9(1.3–2.5)	3.5(2.8–4.8)l
11α	CH_2CH_2OH	16	16	8	8	32	>64	64		
12α	CH_2CH_2CN	16	8	4	4	16	>64	32		
13α	Allyl	8	16	4	4	16	>64	64		
10β	CH_3	8	8	2	>64	8	>64	16		
11β	CH_2CH_2OH	16	16	8	4	16	>64	32		
12β	CH_2CH_2CN	4	8	2	2	8	>64	32		
13β	Allyl	8	8	2	2	16	>64	32		
14β	CH_2CN	2	2	1	<0.5	4	32	8		
15β	CO_2CH_3	8	8	2	1	8	>64	32		
16β	Ac	4	4	2	1	8	64	16		
Linezolid		4	2	1	1	4	16	8	5.6(2.9–8.5)	3.9(2.5–6.4)v
Eperezolid		4	1	0.5	0.5	2	16	8	1.9(1.4–3.8)	3.9(2.5–6.4)v
Vancomycin		1	1	2	0.5	4	>32	>32	3.9(2.5–6.4)	

[a]Methicillin-susceptible *S. aureus* UC®9213.
[b]Methicillin-resistant *S. aureus* UC®12673.
[c]Methicillin-resistant *Staphylococcus epidermidis* UC®12084.
[d]*Streptococcus pneumoniae* UC®9912.
[e]*Enterococcus faecalis* UC®9217.
[f]*Haemophilus influenzae* UC®30063.
[g]*Moraxella catarrhalis* UC®30610. Minimum inhibitory concentration (MIC): lowest concentration of drug (μg/mL) that inhibits visible growth of the organism.
[h]ED_{50} is the amount of drug required after oral administration (mg/kg/day) to cure 50% of infected mice subjected to a lethal systemic infection of *S. aureus*. Numbers in parentheses are 95% confidence ranges. Data shown is from one experiment ($n = 36$ mice/drug).
[i]v = vancomycin, e = eperezolid, l = linezolid as controls.

Table 3. Antibacterial activity (MIC, μg/mL) of the *N*-substituted C4-linked pyrazolylphenyl oxazolidinones



22-34

Compound	R	X	*S.a.*[a]	*S.a.*[b]	*S.e.*[c]	*S.p.*[d]	*E.f.*[e]	*H.inf.*[f]	*M.cat.*[g]	ED_{50}[h]	Control ED_{50}[i]
22	H	O	2	1	0.5	0.25	1	8	4	11.4(0.0–22)	2.5(1.5–4.1)l
23	CH_2CH_2F	O	2	2	0.5	0.5	2	>16	8	>20	6.0(3.9–9.7)e
24	Ac	O	2	2	1	0.5	2	16	8		
25	Benzyl	O	8	4	2	2	4	>64	8		
26	Allyl	O	4	4	0.5	0.5	2	>16	8		
27	CH_3	O	1	1	0.5	0.25	1	8	4	3.7(2.2–6.6)	2.5(1.5–4.1)l
28	CH_2CH_3	O	4	4	2	1	4	64	8		
29	CH_2CN	O	2	1	0.25	0.25	1	8	2		
30	(CS)NHMe	O	1	1	0.5	0.25	2	>16	>16		
31	H	S	0.5	0.5	0.25	0.125	0.5	4	1	>20	3.4(2.3–5.3)l
32	CH_3	S	0.5	0.25	0.25	0.125	0.25	8	0.5	16(10.9–19)	4.5(2.9–7.3)l
33	CH_2CH_3	S	1	1	0.5	0.25	0.5	16	1		
34	CH_2CN	S	0.25	0.25	0.125	<0.06	0.25	1	1	>17.5	5.0(4.4–5.5)l
Linezolid			4	2	1	1	4	16	8	5.6(2.9–8.5)	3.9(2.5–6.4)v
Eperezolid			4	1	0.5	0.5	2	16	8	1.9(1.4–3.8)	3.9(2.5–6.4)v
Vancomycin			1	1	2	0.5	4	>32	>32	3.9(2.5–6.4)	

[a]Methicillin-susceptible *S. aureus* UC®9213.
[b]Methicillin-resistant *S. aureus* UC®12673.
[c]Methicillin-resistant *Staphylococcus epidermidis* UC®12084.
[d]*Streptococcus pneumoniae* UC®9912.
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[g]*Moraxella catarrhalis* UC®30610 or UC®30607. Minimum inhibitory concentration (MIC): lowest concentration of drug (μg/mL) that inhibits visible growth of the organism.
[h]ED_{50} is the amount of drug required after oral administration (mg/kg/day) to cure 50% of infected mice subjected to a lethal systemic infection of *S. aureus*. Numbers in parentheses are 95% confidence ranges. Data shown is from one experiment ($n = 36$ mice/drug).
[i]v = vancomycin, e = eperezolid, l = linezolid as controls.

The substituted C4-linked pyrazole analogues are slightly more potent than the α- or β-substituted C3-linked counterparts (Table 3). Again, the methyl and cyanomethyl pyrazoles **27** and **29** in this series proved the most interesting. The methyl derivative **27** has Gram-positive MICs of 0.25–1 μg/mL, slightly better than the 1–4 μg/mL for linezolid. In addition, this congener has similar in vivo activity with an $ED_{50} = 3.7$ mg/kg.

Of particular interest is the dramatic increase in antibacterial activity seen when converting the acetamides (**22**, **27**–**29**) to the thioamides (**31**–**34**).[25,26] This modification alters both the electronic character as well as the lipophilicity of the molecules. In some cases the thioamides display exceptional antibacterial activity and are up to 8 times more potent than the corresponding acetamide (Table 3). This increase, however, is not seen for all compounds against all organisms. For example, the unsubstituted pyrazole **31** has a significant increase of two dilutions in activity against only two strains, *S. aureus* and *M. catarrhalis*. However, the cyanomethyl analogue **34** is significantly more potent than its acetamide counterpart in five of the seven organisms, exhibiting Gram-positive MICs ≤ 0.06–0.25 μg/mL versus 0.25–2 μg/mL for the acetamide counterpart **29**. This compound also has excellent activity against the fastidious Gram-negative bacteria *H. influenzae* and *M. catarrhalis* with MICs = 1 μg/mL. Three thioamides (**31**, **32** and **34**) were selected for in vivo evaluation. Unfortunately, all of these compounds have little or no in vivo activity at the highest doses. The difference in in vivo activity is striking when comparing the acetamide **27** to the corresponding thioamide **32**. The ED_{50} of the acetamide **27** is 3.7 mg/kg whereas the ED_{50} of the thioamide **32** is 16 mg/kg. The unsubstituted analogue **31** and the cyanomethyl congener **34** were both inactive at the levels tested, ED_{50}s = >20 mg/kg and >17.5 mg/kg, respectively.

Several years ago workers at Pharmacia reported that deletion of the *E. coli* acrAB efflux pump confers susceptibility to oxazolidinones, thus it is likely that efflux is playing a role in the spectrum of activity of these molecules. However it is not clear what structural modifications will lead to compounds that are able to bypass these efflux mechanisms. Furthermore, the good Gram-negative activity of some of the analogues reported here and elsewhere does not necessarily imply that they are poor substrates for the pumps. It could be a matter of potency or it may simply mean that they are better able to cross the membrane and the pumps are unable to keep up with the rapid influx of drug.[27,28]

Conclusion

In summary, a series of new carbon–carbon-linked pyrazole oxazolidinones have been prepared and tested for antibacterial activity. The unsubstituted C3- and C4-

linked pyrazoles (**9** and **22**) both exhibited good in vitro activity against Gram-positive pathogens (MICs = 0.25–4 μg/mL), but moderate to poor activity against Gram-negative organisms (MICs = 8–32 μg/mL). The analogues in the C4-linked series were slightly more potent than the corresponding C3-linked analogues. Substitution on the pyrazole generally led to a loss of antibacterial activity, except in the cases of the α-*N*-methyl C3-linked pyrazole (**10**α) and the *N*-cyanomethyl C4-linked pyrazole (**29**) analogues. In addition, the activity was increased remarkably by incorporating the thioamide moiety. The most active analogue, the thioamide of the cyanomethylpyrazolylphenyloxazolidinone (**34**), was found to be several times more potent than linezolid, eperezolid and vancomycin for in vitro Gram-positive activity. More importantly, this analogue was also very potent against *H. influenzae* and *M. catarrhalis* with MICs = 1 μg/mL. Unfortunately, it was not active in the in vivo mouse model at the highest doses tested.

Experimental

General

Melting points were determined on a Fisher–Johns or a Thomas–Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Bruker AM-300 or ARX-400 spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Mass spectra and combustion analysis were obtained by the Structural, Analytical and Medicinal Chemistry Department of the Pharmacia Corporation. Unless otherwise indicated all reactions were conducted in commercially available anhydrous solvents under nitrogen atmosphere in oven- or flame-dried glassware. Chromatography was carried out on EM Science 230–400 mesh ASTM silica gel. Elemental analysis were within ±0.4% of calculated values. Biological assays were performed as described previously in ref 24.

***N*-[((5S)-3-{3-Fluoro-4-[2-(trimethylsilyl)ethynyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (5).** (Trimethylsilyl)acetylene (5.0 g, 50.91 mmol), copper iodide (0.097 g, 0.51 mmol), and bistriphenylphosphine dichloropalladium (0.594 g, 0.85 mmol) were added to a solution of iodide **4**[20] (15.871 g, 41.97 mmol) in *N,N*-dimethylformamide (60 mL) and triethylamine (60 mL). The reaction mixture was heated at 45 °C overnight under nitrogen atmosphere. The solvents were evaporated, and the resulting residue was purified on a 5.2×37 cm medium pressure silica column with 35–50% acetone/hexanes to give 14.5 g (99%) of the desired product as an off-white solid: mp 139–140.5 °C; $[\alpha]_D^{25} = -28°$ (*c* 0.88, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 9 H), 2.02 (s, 3 H), 3.63 (dt, *J* = 15, 6 Hz, 1H), 3.70 (ddd, *J* = 15, 6, 3 Hz, 1H), 3.78 (dd, *J* = 9, 7 Hz, 1H), 4.05 (t, *J* = 3 Hz, 1H), 4.79 (m, 1H), 6.13 (t, *J* = 7 Hz, 1H), 7.14 (dd, *J* = 9, 2 Hz, 1H), 7.43 (t, *J* = 8 Hz, 1H), 7.46 (dd, *J* = 11, 2 Hz, 1H); MS (−ESI) *m/z* 347 (M−H); Anal. calcd for $C_{17}H_{21}FN_2O_3Si$: C, 58.60; H, 6.07; N, 8.04; found: C, 58.45; H, 6.05; N, 7.97.

***N*-{[(5S)-3-(4-Ethynyl-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (6).** Potassium carbonate (11.479 g, 83.05 mmol) was added to a methanol (100 mL) solution of **5** (14.536 g, 41.71 mmol). After stirring the reaction mixture for 45 min, the solvent was evaporated. The residue was dissolved in methylene chloride and water, the phases were separated, and the aqueous portion was extracted with methylene chloride. The combined organic portions were dried ($MgSO_4$) and evaporated. The crude material was purified on a 5.2×30 cm medium pressure silica column with 35–80% acetone/hexanes to give 8.7 g of improved quality material which was further purified on a second medium pressure silica column (5.2×36 cm) with 2–5% methanol/methylene chloride to give 6.9 g (60%) of the desired material as a white solid: mp 162.5–164 °C; $[\alpha]_D^{25} = -36°$ (*c* 0.95, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.29 (s, 1H), 3.64 (dt, *J* = 15, 6 Hz, 1H), 3.70 (ddd, *J* = 15, 6, 3 Hz, 1H), 3.79 (dd, *J* = 9, 7 Hz, 1H), 4.06 (t, *J* = 9 Hz, 1H), 4.81 (m, 1H), 6.14 (bt, *J* = 7 Hz, 1H), 7.16 (dd, *J* = 9, 2 Hz, 1H), 7.47 (t, *J* = 8 Hz, 1H), 7.50 (dd, *J* = 11, 2 Hz, 1H); MS (+ESI) *m/z* 277 (M+H), anal. calcd for $C_{14}H_{13}FN_2O_3$: C, 60.87; H, 4.74; N, 10.14; found: C, 61.01; H, 4.88; N, 10.07.

***N*-{[(5S)-3-(4-Ethynyl-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (7).** Formic acid (100 mL) was added to a flask containing **5** (15.85 g, 45.49 mmol). The solution was heated at 95 °C under nitrogen atmosphere for 1.5 h. Then it was poured onto ice and sodium bicarbonate. Sodium bicarbonate was added until the solution pH was 8. The reaction mixture was then extracted with CH_2Cl_2. The combined organic portions were dried ($MgSO_4$) and evaporated. The crude material was purified on a 5.2×36 cm medium pressure silica column with 2–10% CH_3OH/CH_2Cl_2 to give 11.0 g (69%) of the desired material as a white solid: mp 174–175 °C; $[\alpha]_D^{25} = -33°$ (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (s, 3H), 2.54 (d, *J* = 4 Hz, 3H), 3.42 (t, *J* = 6 Hz, 2H), 3.78 (dd, *J* = 9, 7 Hz, 1H), 4.16 (t, *J* = 9 Hz, 1H), 4.76 (m, 1H), 7.43 (dd, *J* = 9, 2 Hz, 1H), 7.56 (dd, *J* = 14, 2 Hz, 1H), 7.87 (t, *J* = 9 Hz, 1H), 8.22 (t, *J* = 4 Hz, 1H); HRMS calcd for $C_{14}H_{15}FN_2O_4$ 294.1016; found 294.1016; anal. calcd for $C_{14}H_{15}FN_2O_4$: C, 57.14; H, 5.14; N, 9.52; found: C, 56.98; H, 5.20; N, 9.49.

***N*-[((5S)-3-{4-[(E)-3-(Dimethylamino)-2-propenoyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (8).** An ethanol (180 mL) solution of ketone **7** (9.977 g, 33.90 mmol) and *N,N*-dimethylformamide dimethyl acetal (25.0 mL, 181.90 mmol) was refluxed under nitrogen atmosphere for 4 h. The mixture was allowed to cool to room temperature as it stirred overnight. The solvent was then evaporated, and the resulting residue was purified on a 5.2×54 cm medium pressure silica column with 2–5% CH_3OH/CH_2Cl_2 to give 8.3 g (70%) of the desired material as a light orange solid: mp 124–125.5 °C; $[\alpha]_D^{25} = 18°$ (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.91 (bs, 3H), 3.14 (bs, 3H), 3.65 (m, 2H), 3.79 (dd, *J* = 9, 7 Hz, 1H), 4.05 (t, *J* = 9 Hz, 1H), 4.79 (m, 1H), 5.65 (d, *J* = 11 Hz, 1H), 6.64 (t, *J* = 6 Hz, 1H), 7.14 (dd, *J* = 9, 2 Hz, 1H),

7.48 (dd, $J=13$, 2 Hz, 1H), 7.80 (m, 2H); MS (+ESI) m/z 350 (M+H); anal. calcd for $C_{17}H_{20}FN_3O_4 \cdot 0.25H_2O$: C, 57.70; H, 5.84; N, 11.87; found: C, 57.73; H, 5.73; N, 11.72.

***N*-({(5S)-3-[3-Fluoro-4-(1H-pyrazol-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-acetamide (9).** Hydrazine hydrate (1.0 mL, 20.61 mmol) was added to an ethanol (100 mL) solution of **8** (1.75 g, 5.01 mmol). The reaction mixture was stirred for 2 days then the solvent was evaporated to give 1.548 g (97%) of **9** as a cream solid: mp 208–209 °C; $[\alpha]_D^{25}=-26°$ (c 0.54, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.30 (bs, 1H), 3.42 (t, $J=6$ Hz, 2H), 3.77 (dd, $J=9$, 7 Hz, 1H), 4.15 (t, $J=9$ Hz, 1H), 4.75 (m, 1H), 6.60 (dd, $J=4$, 2 Hz, 1H), 7.36 (d, $J=7$ Hz, 1H), 7.57 (d, $J=14$ Hz, 1H), 7.81 (bs, 1H), 7.96 (bs, 1H), 8.23 (t, $J=5$ Hz, 1H); HRMS (FAB) calcd for $C_{15}H_{15}FN_4O_3+H$ 319.1206; Found 319.1197; anal. calcd for $C_{15}H_{15}FN_4O_3 \cdot 0.5H_2O$: C, 55.04; H, 4.93; N, 17.12; Found: C, 54.87; H, 4.75; N, 16.78.

***N*-({(5S)-3-[3-Fluoro-4-(1-methyl-1H-pyrazol-5-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (10α) and *N*-({(5S)-3-[3-Fluoro-4-(1-methyl-1H-pyrazol-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (10β).** An ethanol (10 mL) solution of **8** (0.241 g, 0.69 mmol) and methyl hydrazine (0.21 mL, 3.94 mmol) was stirred overnight at room temperature under nitrogen atmosphere. Then, the solvents were evaporated, and the resulting residue was purified on a 2×25.2 cm medium pressure silica column with 2% CH_3OH/CH_2Cl_2 to give 0.177 g (77%) of the desired material as a mixture of the two regioisomers. After HPLC purification, 0.070 g (31%) of **10**α as a white solid and 0.019 g (8%) of **10**β as a white solid were obtained. **10**α: mp 101–102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.43 (t, $J=5$ Hz, 2H), 3.72 (s, 3H), 3.78 (dd, $J=9$, 6 Hz, 1H), 4.17 (t, $J=9$ Hz, 1H), 4.76 (m, 1H), 6.37 (d, $J=2$ Hz, 1H), 7.44 (dd, $J=9$, 2 Hz, 1H), 7.50 (d, $J=2$ Hz, 1H), 7.51 (dd, $J=8$, 8 Hz, 1H), 7.64 (dd, $J=13$, 2 Hz, 1H), 8.23 (t, $J=6$ Hz, 1H); 367 (M+Cl), 663 (2M−H); HR-MS (FAB) calcd for $C_{16}H_{17}FN_4O_3+H$ 333.1363; found 333.1330; anal. calcd for $C_{16}H_{17}FN_4O_3 \cdot 0.25H_2O$: C, 57.05; H, 5.24; N, 16.63; found: C, 57.16; H, 5.13; N, 16.43. **10**β: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.42 (t, $J=6$ Hz, 2H), 3.76 (dd, $J=9$, 7 Hz, 1H), 3.89 (s, 3H), 4.14 (t, $J=9$ Hz, 1H), 4.73 (m, 1H), 6.55 (dd, $J=4$, 2 Hz, 1H), 7.35 (dd, $J=9$, 2 Hz, 1H), 7.54 (dd, $J=14$, 2 Hz, 1H), 7.76 (d, $J=2$ Hz, 1H), 7.91 (t, $J=9$ Hz, 1H), 8.22 (t, $J=6$ Hz, 1H); HR-MS (FAB) calcd for $C_{16}H_{17}FN_4O_3$ +H 333.1363; found 333.1368.

***N*-[((5S)-3-{3-Fluoro-4-[1-(2-hydroxyethyl)-1H-pyrazol-5-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (11α) and *N*-[((5S)-3-{3-Fluoro-4-[1-(2-hydroxyethyl)-1H-pyrazol-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (11β).** 2-Hydroxyethylhydrazine (0.3 mL, 4.43 mmol) was added to an ethanol (5 mL) solution of **8** (0.113 g, 0.32 mmol). The reaction mixture was heated at 105 °C for 2 h under nitrogen atmosphere, then was allowed to cool to room temperature as it stirred overnight. The solvent was evaporated, and the resulting residue was purified on a 3×26 cm medium pressure silica column with 2–20% CH_3OH/CH_2Cl_2 to give 0.100 g (85%) of the desired material as a mixture of regioisomers. After HPLC purification, 0.084 g (72%) of **11**α as a yellow solid and 0.012 g (10%) of 11β as a yellow solid were obtained.

11α: mp 70–71 °C; $[\alpha]_D^{25}=-24°$ (c 0.46, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.42 (m, 2H), 3.67 (dd, $J=12$, 6 Hz, 2H), 3.78 (dd, $J=9$, 6 Hz, 1H), 4.00 (t, $J=6$ Hz, 2H), 4.07 (dd, $J=10$, 5 Hz, 1H), 4.17 (t, $J=9$ Hz, 1H), 4.77 (m, 1H), 6.34 (d, $J=1$ Hz, 1H), 7.43 (dd, $J=9$, 2 Hz, 1H), 7.55 (m, 2H), 7.63 (dd, $J=13$, 2 Hz, 1H), 8.23 (t, $J=5$ Hz, 1H); HR-MS(FAB) calcd for $C_{17}H_{19}FN_4O_4$: 362.1390; found: 362.1395; anal. calcd for $C_{17}H_{19}FN_4O_4 \cdot 0.25H_2O$: C, 55.66; H, 5.36; N, 15.27; found: C, 55.76; H, 5.59; N, 14.94. **11**β: mp: 110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.42 (t, $J=5$ Hz, 2H), 3.76 (m, 3H), 4.14 (t, $J=9$ Hz, 1H), 4.19 (t, $J=6$ Hz, 2H), 4.74 (m, 1H), 4.90 (t, $J=5$ Hz, 1H), 6.56 (dd, $J=4$, 2 Hz, 1H), 7.36 (dd, $J=9$, 2 Hz, 1H), 7.54 (dd, $J=14$, 2 Hz, 1H), 7.78 (d, $J=2$ Hz, 1H), 7.92 (t, $J=9$ Hz, 1H), 8.22 (t, $J=5$ Hz, 1H); HR-MS (FAB) calcd for $C_{17}H_{19}FN_4O_4$ 362.1390; found 362.1392.

***N*-[((5S)-3-{3-Fluoro-4-[1-(3-nitrilopropyl)-1H-pyrazol-5-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (12α) and *N*-[((5S)-3-{3-Fluoro-4-[1-(3-nitrilopropyl)-1H-pyrazol-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (12β).** An ethanol (5 mL) solution of **8** (0.100 g, 0.29 mmol) and 3-hydrazinopropanenitrile (0.040 g, 0.47 mmol) was stirred under nitrogen atmosphere for 2 days. The reaction was not complete, therefore, the mixture was refluxed for 24 h, then more 3-hydrazinopropanenitrile (0.060 g, 0.70 mmol) was added. After 4 h, the mixture was allowed to cool to room temperature, the solvents were evaporated, and the resulting residue was purified on a 3×24 cm medium pressure silica column with 2% methanol/methylene chloride to give 0.078 g (73%) of the desired material as a mixture of regioisomers. After HPLC purification, 0.060 g (57%) of **12**α as a cream solid and 0.006 g (6%) of **12**β as a tan solid were obtained. **12**α: mp: 183–184 °C; $[\alpha]_D^{25}=-23°$ (c 0.44, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84 (s, 3H), 2.99 (t, $J=6$ Hz, 2H), 3.43 (t, $J=6$ Hz, 2H), 3.79 (dd, $J=9$, 6 Hz, 1H), 4.17 (t, $J=9$ Hz, 1H), 4.22 (t, $J=6$ Hz, 2H), 4.77 (m, 1H), 6.41 (d, $J=2$ Hz, 1H), 7.46 (m, 2H), 7.65 (m, 2H), 8.24 (t, $J=6$ Hz, 1H); HR-MS (FAB) calcd for $C_{18}H_{18}FN_5O_3+H$ 372.1472; found 372.1479; anal. calcd for $C_{18}H_{18}FN_5O_3$: C, 58.22; H, 4.89; N, 18.86; found: C, 58.00; H, 5.00; N, 18.57. **12**β: mp 137–138 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.11 (t, $J=6$ Hz, 2H), 3.42 (t, $J=5$ Hz, 2H), 3.77 (dd, $J=9$, 7 Hz, 1H), 4.15 (t, $J=9$ Hz, 1H), 4.45 (t, $J=6$ Hz, 2H), 4.74 (m, 1H), 6.61 (dd, $J=4$, 2 Hz, 1H), 7.38 (dd, $J=9$, 2 Hz, 1H), 7.56 (dd, $J=14$, 2 Hz, 1H), 7.90 (d, $J=2$ Hz, 1H), 7.93 (t, $J=9$ Hz, 1H), 8.23 (t, $J=6$ Hz, 1H); HR-MS (FAB) calcd for $C_{18}H_{18}FN_5O_3+H$ 372.1472; found 372.1486.

General procedure for the conversion of pyrazole 9 to analogues 13–16. *N,N*-Dimethylformamide (8 mL) was added to a flame-dried flask which contained **9** (1

equiv). The solution was cooled to 0 °C under nitrogen atmosphere. Then sodium hydride (60%, 2 equiv) was added. After stirring 20 min, the appropriate alkylating agent (1.2 equiv) was added. The reaction mixture was stirred for 30 min, then water and CH_2Cl_2 were added. The phases were separated, and the aqueous portion was extracted with CH_2Cl_2 and ethyl acetate. The combined organic portions were dried ($MgSO_4$) and evaporated. The resulting residue was purified as described.

***N*-({(5S)-3-[4-(1-Allyl-1H-pyrazol-5-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (13α) and *N*-({(5S)-3-[4-(1-Allyl-5-methyl-1H-pyrazol-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (13β).** Alkylation with allyl bromide gave a residue that was purified on a 40 g Biotage column with 0–5% CH_3OH/CH_2Cl_2 to give 0.073 g (28%) of monoallylated material and 0.172 g (61%) of bisallylated material. After HPLC purification, 0.007 g (3%) of **13**α as a yellow solid, 0.058 g (23%) of **13**β as a cream solid. **13**α: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (s, 3 H), 3.42 (t, J = 5 Hz, 2H), 3.78 (dd, J = 9, 6 Hz, 1H), 4.16 (t, J = 9 Hz, 1H), 4.64 (d, J = 5 Hz, 2H), 4.75 (m, 1H), 4.77 (d, J = 12 Hz, 1H), 5.05 (dd, J = 11, 2 Hz, 1H), 5.88 (m, 1H), 6.39 (d, J = 1 Hz, 1H), 7.43 (m, 2H), 7.56 (d, J = 2 Hz, 1H), 7.63 (dd, J = 15, 2 Hz, 1H), 8.23 (t, J = 6 Hz, 1H); HR-MS (FAB) calcd for $C_{18}H_{19}FN_4O_3$ + H 359.1519; found 359.1528. **13**β: mp 144–146 °C; $[\alpha]_D^{25} = -25°$ (*c* 0.58, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.42 (t, J = 5 Hz, 2H), 3.76 (dd, J = 9, 7 Hz, 1H), 4.14 (t, J = 9 Hz, 1H), 4.75 (m, 1H), 4.81 (d, J = 6 Hz, 2H), 5.20 (m, 2H), 6.10–6.00 (m, 1H), 6.60 (dd, J = 4, 2 Hz, 1H), 7.35 (dd, J = 9, 2 Hz, 1H), 7.55 (dd, J = 14, 2 Hz, 1H), 7.79 (d, J = 2 Hz, 1H), 7.91 (t, J = 9 Hz, 1H), 8.23 (t, J = 6 Hz, 1H); HR-MS (FAB) calcd for $C_{18}H_{19}FN_4O_3$ + H 359.1519; found 359.1524; anal. calcd for $C_{18}H_{19}FN_4O_3 \cdot 0.25H_2O$: C, 59.58; H, 5.42; N, 15.44; found: C, 59.66; H, 5.42; N, 15.08.

***N*-[((5S)-3-{4-[1-(Cyanomethyl)-1H-pyrazol-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (14β).** Alkylation with bromoacetonitrile gave a residue that was purified on a 3×24 cm medium pressure silica column with 2–5% CH_3OH/CH_2Cl_2 to give 0.143 g of material, which was a mixture of regioisomers. After HPLC purification, 0.102 g (91%) of **14**β as a white solid: mp 168–169 °C; $[\alpha]_D^{25} = -25°$ (*c* 0.47, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.42 (t, J = 5 Hz, 2H), 3.78 (dd, J = 9, 7 Hz, 1H), 4.15 (t, J = 9 Hz, 1H), 4.75 (m, 1H), 5.55 (s, 2H), 6.68 (dd, J = 4, 2 Hz, 1H), 7.40 (dd, J = 9, 2 Hz, 1H), 7.58 (dd, J = 14, 2 Hz, 1H), 7.92 (t, J = 9 Hz, 1H), 7.94 (d, J = 2 Hz, 1H), 8.23 (t, J = 6 Hz, 1H); HR-MS (FAB) calcd for $C_{17}H_{16}FN_5O_3$ + H 358.1315; found 358.1319; anal. calcd for $C_{17}H_{16}FN_5O_3$: C, 57.14; H, 4.51; N, 19.60; found: C, 56.81; H, 4.24; N, 19.21.

Methyl 3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1H-pyrazole-1-carboxylate (15β). Acylation with methyl chloroformate gave a residue that was purified on a 3×24 cm medium pressure silica column with 2–5% CH_3OH/CH_2Cl_2 to give 0.101 g (85%) of **15**β as a white solid: mp 184–185 °C; $[\alpha]_D^{25} = -26°$ (*c* 0.51, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.43 (t, J = 5 Hz, 2H), 3.79 (dd, J = 9, 7 Hz, 1H), 4.01 (s, 3H), 4.16 (t, J = 9 Hz, 1H), 4.76 (m, 1H), 6.89 (t, J = 3 Hz, 1H), 7.44 (dd, J = 9, 2 Hz, 1H), 7.62 (dd, J = 14, 2 Hz, 1H), 7.99 (t, J = 9 Hz, 1H), 8.23 (t, J = 6 Hz, 1H), 8.43 (d, J = 3 Hz, 1H); HR-MS (FAB) calcd for $C_{17}H_{17}FN_4O_5$ + H 402.1465; found 402.1470; anal. calcd for $C_{17}H_{17}FN_4O_5 \cdot 0.25H_2O$: C, 53.61; H, 4.63; N, 14.71; Found: C, 54.06; H, 4.51; N, 14.72.

***N*-({(5S)-3-[4-(1-Acetyl-1H-pyrazol-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (16β).** Acylation with acetyl chloride gave a residue that was purified on a 3×25 cm medium pressure silica column with 2–5% CH_3OH/CH_2Cl_2 to give 0.052 g (46%) of **16**β as a white solid: mp 181–183 °C; $[\alpha]_D^{25} = -26°$ (*c* 0.43, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 2.71 (s, 3H), 3.43 (t, J = 5 Hz, 2H), 3.79 (dd, J = 9, 7 Hz, 1H), 4.17 (t, J = 9 Hz, 1H), 4.76 (m, 1H), 6.94 (t, J = 3 Hz, 1H), 7.45 (dd, J = 9, 2 Hz, 1H), 7.62 (dd, J = 14, 2 Hz, 1H), 8.03 (t, J = 9 Hz, 1H), 8.24 (t, J = 6 Hz, 1H), 8.48 (d, J = 3 Hz, 1H); HR-MS (FAB) calcd for $C_{17}H_{17}FN_4O_4$ + H 361.1312; found 361.1310; anal. calcd for $C_{17}H_{17}FN_4O_4 \cdot 0.25H_2O$: C, 55.96; H, 4.83; N, 15.36; found: C, 55.99; H, 4.88; N, 15.06.

***N*-({(5S)-3-[3-fluoro-4-(trimethylstannyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (17).** A solution of iodide **4** (0.83 g, 2.2 mmol) in 1,4-dioxane (15 mL) was treated with $Pd_2Cl_2(PPh_3)_2$ (77 mg, 0.11 mmol) and hexamethylditin (0.86 g, 2.6 mmol). The slurry was heated under reflux for 2 h and then concentrated in vacuo. Chromatography (1–4% CH_3OH in CH_2Cl_2) of the residue afforded **17** (0.91 g, 2.2 mmol, 100%) as an amber glassy solid which was used as is.

1-(2-fluoroethyl)-4-iodo-1H-pyrazole (20). A solution of 4-iodo-1H-pyrazole (1.16 g, 6.00 mmol) in anhydrous DMF (30 mL) was treated with NaH (264 mg of a 60% dispersion in mineral oil, 6.60 mmol) and stirred at ambient temperature for 20 min. The solution was then treated with 1-bromo-2-fluoroethane (0.50 mL, 6.6 mmol) and stirred at ambient temperature for 14 h. The solution was diluted with distilled water (300 mL) and extracted with ethyl acetate (300 mL×3). The combined extracts were washed with distilled water, brine and dried over Na_2SO_4. Filtration, concentration and chromatography (5–15% ethyl acetate in hexanes) afforded iodide **20** (1.15 g, 4.79 mmol, 80%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.53 (s, 1H), 4.73 (dt, J = 4, 73 Hz, 2H), 4.42 (dt, J = 4, 27 Hz, 2H); MS (+ESI) m/z 240 (M + H); anal. calcd for $C_5H_6FIN_2$: C, 25.02; H, 2.52; N, 11.67; found: C, 24.90; H, 2.42; N, 11.56.

***N*-({(5S)-3-[3-fluoro-4-(1H-pyrazol-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-acetamide (22).** Stille Protocol: a solution of $Pd_2(dba)_3$ (0.17 g, 0.18 mmol) in NMP (100 mL) was treated with TFP (0.17 g, 0.72 mmol) and stirred at ambient temperature for 15 min. The solution was treated with iodide **19** (3.14 g, 7.2 mmol) followed by **17** (3.6 g, 7.2 mmol) and lithium chloride (1.53 g,

36 mmol). The resulting mixture was stirred at 90 °C for 24 h, then cooled to ambient temperature and diluted with distilled water (600 mL). The aqueous phase was extracted with ethyl acetate (700 mL×3). The combined extracts were washed with distilled water, brine and dried over Na_2SO_4. Filtration, concentration and chromatography (5% CH_3OH in CH_2Cl_2) afforded **21** along with side-products. The mixture was dissolved in CH_2Cl_2 (20 mL) and treated with trifluruoacetic acid (10 mL). The solution was stirred at ambient temperature for 30 min and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL×2) and concentrated to remove any remaining acid. Then the residue was dissolved in CH_2Cl_2 and treated with triethylamine (1 mL). Concentration and chromatography (5% CH_3OH in CH_2Cl_2) afforded **22** (0.91 g, 2.9 mmol, 40%) as a white solid: mp 192–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (br s, 1H), 7.83–8.15 (br m, 2H), 7.74 (t, J=9 Hz, 1H), 7.54 (d, J=14 Hz, 1H), 7.31 (d, J=9 Hz, 1H), 4.71–4.75 (m, 1H), 4.13 (t, J=9 Hz, 1H), 3.75 (dd, J=7, 9 Hz, 1H), 3.42 (t, J=5 Hz, 2H), 1.83 (s, 3H); MS (+ESI) m/z 319 (M+H); anal. calcd for $C_{15}H_{15}FN_4O_3$: C, 56.60; H, 4.75; N, 17.60; found: C, 56.35; H, 4.82; N, 17.45.

***N*-({(5S)-3-[3-fluoro-4-(1H-pyrazol-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide trifluoroacetate (22).** Suzuki Protocol: a solution of **19** (1.0 g, 2.3 mmol) in dry DMF (10 mL) was treated with potassium acetate (675 mg, 6.9 mmol), diboron pinacol ester (1.2 g, 4.7 mmol) and terakis(triphenylphosphine)palladium(0) (130 mg, 0.11 mmol). The mixture was heated under reflux for 2 h, then cooled to ambient temperature and treated with iodide **4** (870 mg, 2.3 mmol), terakis(triphenylphosphine)palladium(0) (130 mg, 0.11 mmol) and aqueous Na_2CO_3 (5.8 mL of a 2 M solution, 11.6 mmol). The resulting mixture was stirred at 100 °C overnight. Then the solution was cooled to ambient temperature, diluted with distilled water (20 mL) and treated with 10% aqueous HCl (10 mL). The aqueous phase was extracted with ethyl acetate (50 mL×3). The combined extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Chromatography (0–10% methanol in CH_2Cl_2) of the residue afforded **21** along with side-products (1.414 g). The mixture was dissolved in CH_2Cl_2 (20 mL) and treated with TFA (10 mL) slowly at ambient temperature. The solution was stirred at ambient temperature for 2 h, then concentrated with a stream of N_2 and dried in vacuo overnight. The residue was treated with $CHCl_3$ (10 mL) and product (755 mg, 1.7 mmol, 76%) was collected by vacuum filtration. A sample of the product was treated with triethylamine and concentrated in vacuo. Chromatography (5% CH_3OH in CH_2Cl_2) of the residue afforded **22** as the free base: mp 192–195 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (br s, 1H), 7.83–8.15 (br m, 2H), 7.74 (t, J=9 Hz, 1H), 7.54 (d, J=14 Hz, 1H), 7.31 (d, J=9 Hz, 1H), 4.71–4.75 (m, 1H), 4.13 (t, J=9 Hz, 1H), 3.75 (dd, J=7, 9 Hz, 1H), 3.42 (t, J=5 Hz, 2H), 1.83 (s, 3H); MS (+ESI) m/z 319 (M+H); anal. calcd for $C_{15}H_{15}FN_4O_3$: C, 56.60; H, 4.75; N, 17.60; found: C, 56.35; H, 4.82; N, 17.45.

***N*-[((5S)-3-{3-fluoro-4-[1-(2-fluoroethyl)-1H-pyrazol-4-yl]-phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (23).** The aryl stannane **17** was dissolved in NMP (13 mL) and treated with pyrazole **20** (0.48 g, 2.0 mmol), $Pd_2(dba)_3$ (92 mg, 0.10 mmol) and TFP (93 mg, 0.40 mmol). The resulting mixture was stirred at 95 °C for 14 h, then diluted with distilled water (100 mL) and extracted with ethyl acetate (100 mL×3). The combined extracts were treated with CH_3OH to dissolve any precipitate. The resulting solution was washed with water, brine and dried over Na_2SO_4. Filtration, concentration and chromatography (1.5–4% CH_3OH in CH_2Cl_2) afforded **23** (138 mg, 0.38 mmol, 19%) as a light pink solid: mp 196–198 °C; $[\alpha]_D^{25}=-38°$ (c 0.98, DMF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 2H), 7.48–7.55 (m, 2H), 7.22 (dd, J=2, 9 Hz, 1H), 6.06 (br s, 1H), 4.81 (dt, J=2, 47 Hz, 2H) 4.80 (br s, 1H), 4.47 (dt, J=2, 26 Hz, 2H), 4.07 (t, J=9 Hz, 1H), 3.80 (dd, J=7, 9 Hz, 1H), 3.60–3.73 (m, 2H), 2.04 (s, 3H); HR-MS (EI) calcd for $C_{17}H_{18}F_2N_4O_3$ 364.1347; found 364.1345; anal. calcd for $C_{17}H_{18}F_2N_4O_3$: C, 56.04; H, 4.98; N, 15.38; found: C, 54.60; H, 5.11; N, 14.73.

***N*-({(5S)-3-[4-(1-acetyl-1H-pyrazol-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (24).** A solution of **21** (1.18 g, 2.11 mmol) in CH_2Cl_2 (25 mL) was treated with trifluoroacetic acid (2.0 mL, 26 mmol) at 0 °C. The solution was warmed to ambient temperature, stirred for 2 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and treated with aqueous NaOH (1.5 mL of a 1 N solution) with vigorous stirring. The resulting precipitate was filtered, dried in vacuo and dissolved in pyridine (20 mL). The solution was treated with acetic anhydride (0.5 mL, 5 mmol) at ambient temperature, stirred for 1 h and concentrated in vacuo. Chromatography (1–4% CH_3OH in CH_2Cl_2) of the residue afforded **24** with remaining free pyrazole (69 mg). The mixture was then resubmitted to the above acetylation conditions, stirred for 16 h and concentrated in vacuo. Chromatography (1–4% CH_3OH in CH_2Cl_2) of the residue afforded **24** (38 mg, 0.11 mmol, 5% for 2 steps) as an off-white solid: mp 230–231 °C; ^{1}H NMR (400 MHz, DMF-d_7) δ 8.83 (s, 1H), 8.49 (s, 1H), 8.43–8.46 (m, 1H), 8.10 (t, J=9 Hz, 1H), 7.85 (d, J=14 Hz, 1H), 7.58 (d, J=9 Hz, 1H), 5.02 (br s, 1H), 4.42 (t, J=9 Hz, 1H), 4.09 (dd, J=7, 9 Hz, 1H), 3.73–3.76 (br s, 2H), 2.88 (s, 3H), 2.09 (s, 3H); HR-MS (FAB) calcd for $C_{17}H_{17}FN_4O_4$+H 361.1312; found 361.1307; anal. calcd for $C_{17}H_{17}FN_4O_4$·0.1 H_2O: C, 56.38; H, 4.79; N, 15.47; found: C, 56.24; H, 4.49; N, 15.19.

General procedure for the conversion of pyrazole 22 to analogues 25–29. A solution of **22** (1 equiv) in dry THF or acetone (5 mL) was treated with K_2CO_3 or $NaHCO_3$ (10–50 equiv) and an appropriate alkylating agent (10 equiv). The mixture was heated under reflux overnight, then cooled to ambient temperature and treated with distilled water (10 mL). The aqueous phase was extracted with ethyl acetate (20 mL×3). The combined extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Chromatography (2.5–5% CH_3OH in CH_2Cl_2) of the residue afforded the desired products.

***N*-({(5S)-3-[4-(1-benzyl-1H-pyrazol-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (25).** Alkylation with benzyl bromide afforded **25** (0.16 g, 0.39 mmol, 90%) as a white solid: mp 169–170 °C dec.; $[\alpha]_D^{25} = -20°$ (*c* 0.96, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.78 (d, $J = 2$ Hz, 1H), 7.51 (dd, $J = 9$, 12 Hz, 1H), 7.49 (dd, $J = 3$, 14 Hz, 1H), 7.29–7.39 (m, 5H), 7.20 (dd, $J = 2$, 9 Hz, 1H), 5.93–6.00 (m, 1H), 5.36 (s, 2H), 4.76–4.83 (m, 1H), 4.07 (t, $J = 9$ Hz, 1H), 3.79 (dd, $J = 7$, 9 Hz, 1H), 3.73 (ddd, $J = 4$, 7, 16 Hz, 1H), δ 3.60–3.66 (m, 1H), 2.03 (s, 3H); HR-MS (FAB) calcd for $C_{22}H_{21}FN_4O_3 + H$ 409.1676; found 409.1682; anal. calcd for $C_{22}H_{21}FN_4O_3 \cdot 0.35\ H_2O$ C, 63.71; H, 5.27; N, 13.51; found: C, 64.08; H, 5.36; N, 12.62.

***N*-({(5S)-3-[4-(1-allyl-1H-pyrazol-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (26).** Alkylation with allyl bromide afforded **26** (0.24 g, 0.67 mmol, 22%) as a tan solid: mp 162–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.76 (d, $J = 2$ Hz, 1H), 7.45–7.52 (m, 2H), 7.17 (dd, $J = 2$, 9 Hz, 1H), 6.44 (br s, 1H), 6.01–6.11 (m, 1H), 5.31 (d, $J = 10$ Hz, 1H), 5.27 (d, $J = 17$ Hz, 1H), 4.78 (m, 3H), 4.05 (t, $J = 9$ Hz, 1H), 3.80 (dd, $J = 7$, 9 Hz, 1H), 3.63–3.70 (m, 2H), 2.03 (s, 3H); HR-MS (FAB) calcd for anal. calcd for $C_{18}H_{19}FN_4O_3 + H$ 359.1519; found 359.1529; $C_{18}H_{19}FN_4O_3 \cdot 0.3\ H_2O$: C, 59.43; H, 5.43; N, 15.40; Found: C, 59.15; H, 5.33; N, 15.16.

***N*-({(5S)-3-[3-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (27).** Alkylation with iodomethane afforded **27** (0.078 g, 0.23 mmol, 76%) as a white solid: mp 224–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.75 (s, 1H), 7.48–7.52 (m, 2H), 7.20 (d, $J = 9$ Hz, 1H), 6.07 (br s, 1H), 4.81 (br s, 1H), 4.07 (t, $J = 9$ Hz, 1H), 3.96 (s, 3H), 3.80 (t, $J = 7$ Hz, 1H), 3.66–3.77 (m, 2H), 2.04 (s, 3H); MS (+ESI) *m*/*z* 333 (M + H); anal. calcd for $C_{16}H_{17}FN_4O_3$: C, 57.83; H, 5.16; N, 16.86; found: C, 57.69; H, 5.23; N, 16.63.

***N*-({(5S)-3-[4-(1-ethyl-1H-pyrazol-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (28).** Alkylation with iodoethane afforded **28** (0.20 g, 0.58 mmol, 92%) as a white solid: mp 192–193 °C; $[\alpha]_D^{25} = -25°$ (*c* 0.79, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.75 (d, $J = 2$ Hz, 1H), 7.48 (dd, $J = 9$, 12 Hz, 1H), 7.46 (dd, $J = 4$, 15 Hz, 1H), 7.16 (dd, $J = 2$, 9 Hz, 1H), 6.54 (t, $J = 6$ Hz, 1H), 4.76–4.83 (m, 1H), 4.20 (q, $J = 7$ Hz, 2H), 4.05 (t, $J = 9$ Hz, 1H), 3.80 (dd, $J = 7$, 9 Hz, 1H), 3.61–3.72 (m, 2H), 2.03 (s, 3H), 1.52 (t, 3H); HR-MS (FAB) calcd for $C_{17}H_{19}FN_4O_3 + H$ 347.1519; found 347.1523; anal. calcd for $C_{17}H_{19}FN_4O_3$: C, 58.95; H, 5.53; N, 16.18; found: C, 58.65; H, 5.58; N, 16.00.

***N*-[((5S)-3-{4-[1-(cyanomethyl)-1H-pyrazol-4-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (29).** Alkylation with bromoacetonitrile afforded **29** (138 mg, 0.39 mmol, 82%) as a white solid: mp 130–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20–8.25 (m, 2H), 8.06 (s, 1H), 7.76 (t, $J = 9$ Hz, 1H), 2.57 (d, $J = 16$ Hz, 1H), 7.35 (d, $J = 9$ Hz, 1H), 5.53 (s, 2H), 4.70–4.78 (m, 1H), 4.14 (t, $J = 9$ Hz, 1H), 3.76 (t, $J = 7$ Hz, 1H), 3.42 (t, $J = 5$ Hz, 2H), 1.83 (s, 3H); HR-MS (EI) calcd for $C_{17}H_{16}FN_5O_3$ 357.1237, found 357.1233; anal. calcd for $C_{17}H_{16}FN_5O_3 \cdot 0.6H_2O$: C, 55.46; H, 4.71; N, 19.02; found: C, 55.45; H, 4.84; N, 18.90.

***N*-{[(5S)-3-(3-fluoro-4-{1-[(methylamino)carbothioyl]-1H-pyrazol-4-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (30).** A solution of **22** (0.125 g, 0.39 mmol) in dry DMF (5 mL) was treated with NaH (32 mg of a 60% dispersion in mineral oil, 0.80 mmol). The mixture was stirred at ambient temperature for 15 min, then treated with methyl thioisocyanate (58 mg, 0.79 mmol) and stirred at ambient temperature for 5 h. The mixture was treated with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Chromatography (5% CH_3OH in CH_2Cl_2) of the residue afforded **30** (67 mg, 0.17 mmol, 44%) as a white solid: mp = 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 8.97 (s, 2H), 7.50–7.56 (m, 2H), 7.24 (dd, $J = 2$, 11 Hz, 1H), 6.16 (br s, 1H), 4.82 (m, 1H), 4.08 (t, $J = 9$ Hz, 1H), 3.82 (dd, $J = 7$, 9 Hz, 1H), 3.65–3.75 (m, 2H), 3.34 (d, $J = 5$ Hz, 3H), 2.04 (s, 3H); HR-MS (FAB) calcd for $C_{17}H_{18}FN_5O_3S + H$ 392.1192; found 392.1189.

General procedure for the conversion of acetamides 22 and 27–29 to thioamides 31–34. A solution of the starting acetamide (1 equiv) in dry THF was treated with Lawesson's reagent (2.5 equiv) and refluxed overnight. After removal of THF in vacuo, the residue was chromatographed on silica gel with 0–5% CH_3OH/CH_2Cl_2 to afforded the indicated analogues.

***N*-({(5S)-3-[3-fluoro-4-(1H-pyrazol-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (31).** Compound **31** (97 mg, 0.29 mmol, 94%) was isolated as a white solid: mp 188–190 °C (dec.); $[\alpha]_D^{25} = 8°$ (*c* 0.78, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34–10.38 (m, 1H), 8.12 (br s, 1H), 7.91 (br s, 1H), 7.75 (t, $J = 9$ Hz, 1H), 7.55 (dd, $J = 2$, 14 Hz, 1H), 7.32 (dd, $J = 2$, 9 Hz, 1H), 4.91–4.98 (m, 1H), 4.18 (t, $J = 9$ Hz, 1H), 3.92 (dd, $J = 4$, 10 Hz, 2H), 3.85 (dd, $J = 7$, 9 Hz, 1H), 2.44 (s, 3H); HR-MS (FAB) calcd for $C_{15}H_{15}FN_4O_2S + H$ 335.0978; found 335.0985; anal. calcd for $C_{15}H_{15}FN_4O_2S$: C, 53.88; H, 4.52; N, 16.76; found: C, 54.27; H, 5.02; N, 14.88; HPLC shows purity of the product >95%.

***N*-({(5S)-3-[3-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (32).** Compound **32** (98 mg, 0.28 mmol, 58%) was isolated as a white solid: mp 175–176 °C; $[\alpha]_D^{25} = 9°$ (*c* 0.82, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34–10.38 (m, 1H), 8.09 (s, 1H), 7.85 (s, 1H), 7.72 (t, $J = 9$ Hz, 1H), 7.55 (dd, $J = 2$, 14 Hz, 1H), 7.32 (dd, $J = 2$, 9 Hz, 1H), 4.93–4.99 (m, 1H), 4.18 (t, $J = 9$ Hz, 1H), 3.91 (dd, $J = 5$, 10 Hz, 2H), 3.88 (s, 3H), 3.84 (dd, $J = 7$, 9 Hz, 1H), 2.44 (s, 3H); HR-MS (FAB) calcd for $C_{16}H_{17}FN_4O_2S + H$ 349.1134; found 349.1141; anal. calcd for $C_{16}H_{17}FN_4O_2S$: C, 55.16; H, 4.92; N, 16.08; found: C, 55.08; H, 5.00; N, 15.93.

***N*-({(5S)-3-[4-(1-ethyl-1H-pyrazol-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (33).** Compound **33** (120 mg, 0.33 mmol, 72%) was isolated as a white solid: mp 162–164 °C; $[\alpha]_D^{25} = 7°$ (*c* 0.78, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33–10.38 (m, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 7.72 (t, $J = 9$ Hz, 1H), 7.55 (dd, $J = 2$, 14 Hz, 1H), 7.32 (dd, $J = 2$, 9 Hz, 1H), 4.93–4.98 (m, 1H), 4.17 (m, 3H), 3.92 (dd, $J = 5$, 10 Hz, 2H), 3.84 (dd, $J = 7$, 9 Hz, 1H), 2.44 (s, 3H), 1.39 (t, $J = 7$ Hz, 3H); HR-MS (FAB) calcd for $C_{17}H_{19}FN_4O_2S + H$ 363.1291; found 363.1293; anal. calcd for $C_{17}H_{19}FN_4O_2S \cdot 0.45\ H_2O$: C, 55.11; H, 5.41; N, 15.12; found: C, 55.42; H, 5.37; N, 14.73.

***N*-[((5S)-3-{4-[1-(cyanomethyl)-1H-pyrazol-4-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]ethanethioamide (34).** Compound **34** (74 mg, 0.20 mmol, 32%) was isolated as a pale yellow solid: mp 72–75 °C; $[\alpha]_D^{25} = 5°$ (*c* 0.71, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33–10.38 (m, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 7.77 (t, $J = 9$ Hz, 1H), 7.58 (dd, $J = 2$, 14 Hz, 1H), 7.36 (dd, $J = 2$, 9 Hz, 1H), 5.54 (s, 2H), 4.93–5.00 (m, 1H), 4.19 (t, $J = 9$ Hz, 1H), 3.91 (dd, $J = 4$, 10 Hz, 2H), 3.85 (dd, $J = 7$, 9 Hz, 1H), 2.44 (s, 3H); HR-MS (FAB) calcd for $C_{17}H_{16}FN_5O_2S + H$ 374.1087; found 374.1086; anal. calcd for $C_{17}H_{16}FN_5O_2S \cdot 0.5CH_3OH$: C, 53.98; H, 4.66; N, 17.98; found: C, 54.09; H, 4.49; N, 17.82.

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