Piperazinyl Oxazolidinone Antibacterial Agents Containing a Pyridine, Diazene, or Triazene Heteroaromatic Ring

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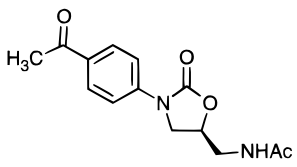
Received May 4, 1998

Oxazolidinones are a novel class of synthetic antibacterial agents active against gram-positive organisms including methicillin-resistant *Staphylococcus aureus* as well as selected anaerobic organisms. Important representatives of this class include the morpholine derivative linezolid **2**, which is currently in phase III clinical trials, and the piperazine derivative eperezolid **3**. As part of an investigation of the structure−activity relationships of structurally related oxazolidinones, we have prepared and evaluated the antibacterial properties of a series of piperazinyl oxazolidinones in which the distal nitrogen of the piperazinyl ring is substituted with a six-membered heteroaromatic ring. Compounds having MIC values ≤ 2 μg/mL vs selected gram-positive pathogens were discovered among each of the pyridine, pyridazine, and pyrimidine structural classes. Among these the cyanopyridine **17**, the pyridazines **25** and **26**, and the pyrimidine **31** exhibited in vivo potency vs *S. aureus* comparable to that of linezolid.

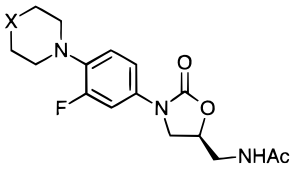
Introduction

Oxazolidinones are a new class of synthetic antibacterial agents with activity against anaerobic and gram-positive aerobic bacteria.[3] This class was discovered through broad screening and is exemplified by the erstwhile clinical candidate DuP 721 (**1**).[4−6] Early studies of DuP 721 revealed a number of attractive features, including activity against problematic resistant pathogens, a lack of cross resistance with existing antimicrobial agents, oral activity in animal models of human infection, and a unique mechanism of action involving inhibition of a very early stage of protein synthesis. Despite these attractive features the development of DuP 721 was terminated.[7]

The potential of this new antibacterial class stimulated an exploratory chemical analogue program in our discovery research laboratories. Two oxazolidinone analogues, linezolid **2** (PNU-100766) and eperezolid **3** (PNU-100592), emerged as lead compounds with the



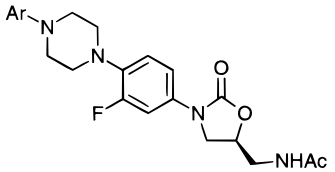
1
DuP 721



2 X = O (linezolid)
3 X = N-(C=O)CH_2OH (eperezolid)

best overall combination of positive attributes.[8−13] Linezolid and eperezolid exhibit useful levels of activity against staphylococci (including methicillin-resistant *Staphylococcus aureus* [MRSA] and methicillin-resistant *Staphylococcus epidermis* [MRSE]), enterococci (including vancomycin-resistant strains), and pneumococci (including penicillin-resistant strains).[14−18] Single-step selection studies demonstrated that eperezolid- and linezolid-resistant mutants exist with a frequency of $<10^{-9}$ among selected staphylococcal species.[15] Serial passage studies using drug gradient plates performed with these oxazolidinones failed to find evidence for the rapid development of resistance.[17] Mechanism of action studies demonstrated that eperezolid binds specifically to the 50s ribosomal subunit and prevents formation of a functional initiation complex.[19,20] The utility of linezolid in the treatment of gram-positive infections is currently being examined in phase III clinical trials.

Previous reports have described the design and synthesis of a series of oxazolidinone antibacterial agents related to linezolid by replacement of the morpholine ring with an alkyl-, acyl, or sulfonyl-substituted piperazinyl ring.[13] In the present work we describe the synthesis and antibacterial activity of a related family of compounds **A** in which the distal nitrogen of the



A

Ar = a 6-membered heterocyclic ring

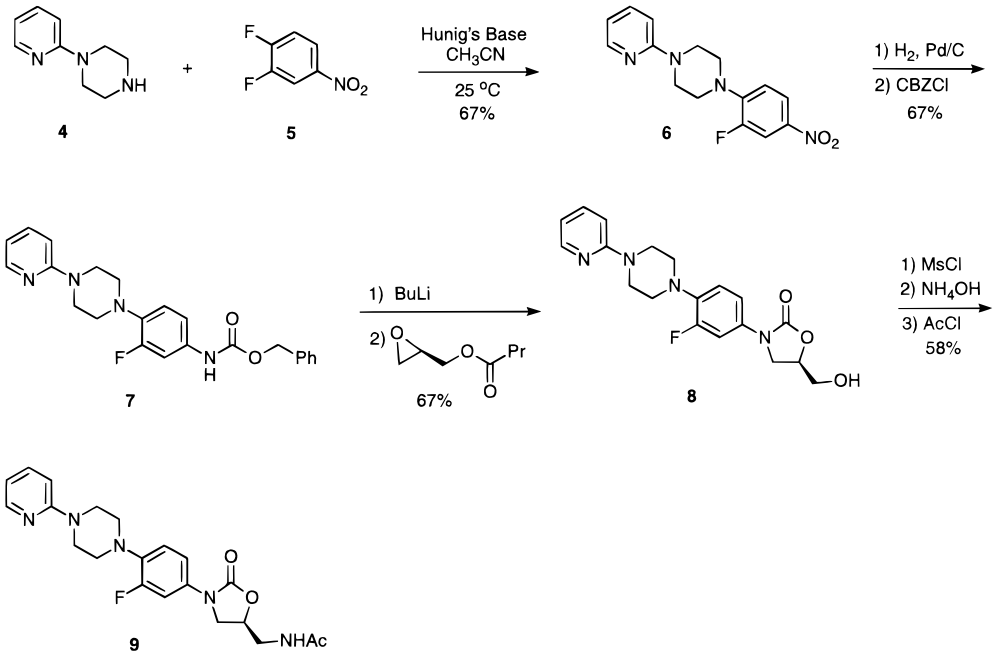
piperazinyl ring is substituted with a six-member heteroaromatic ring.

Results and Discussion

Chemistry. The first compound of this series was prepared from the commercially available piperazine derivative **4**. The chemistry involved in building up the oxazolidinone ring and its acetamidomethyl substitu-

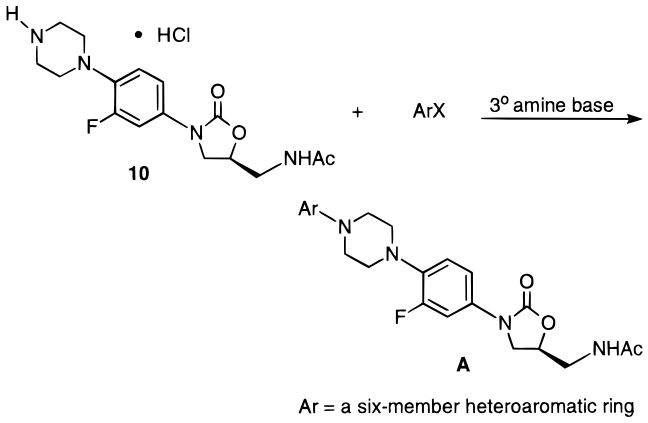
S0022-2623(98)00274-X CCC: $15.00
Published on Web 08/21/1998

Scheme 1. Synthesis of Oxazoidinone **9**

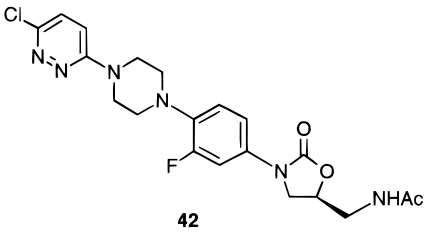


ents has been described previously.[9−13] These methods were readily applied to the preparation of compound **9** as shown in Scheme 1.

The in vitro and in vivo antibacterial activity exhibited by **9** encouraged us to develop a synthetic route which would more readily lend itself to the rapid exploration of the structure−activity relationship (SAR) of related compounds. In particular it seemed likely that at least some analogues **A** might readily be prepared in a single step by nucleophilic aromatic substitution reactions of haloaromatics with the readily available piperazine **10**.[8] In the event, a wide variety



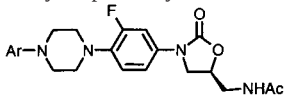
of analogues **A** in which Ar is a six-membered heteroaromatic ring were readily prepared by this method using reaction temperatures between 0 and 135 °C. Dimethylpropyleneurea (DMPU) and ethoxyethanol were especially useful solvents for these reactions. In some cases the use of dimethylformamide (DMF) led to the production of a side product which was difficult to separate from the desired product. With the exception of **9**, **25**, and **33**, all of the target compounds of the present work were prepared by nucleophilic aromatic substitution reactions. Compounds **25** and **33** were prepared by catalytic hydrogenation of **42** and **34**, respectively.



Structure−Activity Relationships. In vitro and in vivo antibacterial assays were performed following previously described methods.[8] The results of these studies are summarized in Table 1. Analogues having in vitro activity comparable to eperezolid were discovered among each of the pyridine, pyridazine, pyrazine, and pyrimidine structural classes. In the pyridine and pyrimidine classes the in vitro potency is relatively independent of whether the heteroaromatic ring is attached to the rest of the molecule through its 2- or 4-position (compounds **9** and **20**; compounds **31** and **33**). These results suggest that the binding of these analogues does not involve strong hydrogen bonds between the binding site and the heteroaromatic ring nitrogens.

The effect on in vitro activity of substituents on the heteroaromatic ring is in most cases modest and follows similar trends in each of the heterocyclic classes. Within each heterocyclic class, the unsubstituted heterocycle(s) (e.g., **9**, **20**, **25**, **31**, **33**, and **36**) exhibits activity roughly similar to that of eperezolid. Attachment of a single halogen atom (**12, 13**, **34**, and **37**), methyl group (**15**, **19**, **21**, and **26**), or cyano group (**16**, **17**, and **18**) in place of a hydrogen has little effect on potency. The presence of multiple halogen substituents exerts either a modest (**14** and **30**) or a strongly negative (**22** and **23**) effect. The activity difference between the active trihalogenated analogue **14** and the inactive tetrahalogenated analogues **22** and **23** may arise in part

Table 1. In Vitro and in Vivo Antibacterial Activity of *N*-Heteroaryl Piperazinyl Oxazolidinones



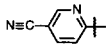
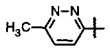
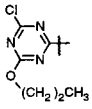
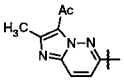
		MIC (μg/mL)[a]						
No.	Ar	*S.a.*-1	*S.a.*-2	*S.e.*	*E.f.*	*S.p.*	*S.a.-1* ED_{50} (mg/kg)[b]	(+) Control ED_{50} (mg/kg)[c]
2	(linezolid)[d]	4	2	1	2	1	5.6	3.9 (vanco)[e]
3	(eperezolid)[d]	4	1	0.5	2	0.5	1.9	3.9 (vanco)[e]
9		4	2	1	2	0.5	11.2	6.0
12		2	2	1	2	0.5		
13		2	1	0.5	1	0.5	>20	2.7
14		2	2	1	2	0.5		
15		4	2	2	2	0.5		
16		1	1	1	1	0.5		
17		2	2	0.5	1	0.5	6.8	5.8
18		2	2	0.5	1	0.5	>20	3.2
19		4	4	2	4	1		
20		4	2	0.5	2	<0.125		
21		4	2	0.5	2	0.25		
22		>16	>16	>16	>16	2		
23		>16	>16	>16	>16	>16		
24		2	2	0.5	2	0.25		
25		4	2	0.5	2	0.5	8.8	8.7
26		4	2	1	2	0.5	6.3	8.7
27		8	4	2	4	1	>20	8.7
28		>16	>16	4	>16	2		
29		>16	>16	16	>16	4		

Table 1 (Continued)

No.	Ar	MIC (μg/mL)[a] S.a.-1	S.a.-2	S.e.	E.f.	S.p.	S.a.-1 ED_{50} (mg/kg)[b]	(+) Control ED_{50} (mg/kg)[c]
30		2	2	1	2	0.5	>20	3.2
31		2	2	0.5	2	0.5	6.0	6.2
32		>16	>16	16	>16	2		
33		2	2	1	1	0.5	4.4	1.8
34		2	1	0.5	1	0.5	14.6	1.8
35		8	4	1	2	<0.5		
36		2	1	0.5	2	0.5	12.5	3.2
37		2	1	0.5	1	0.5	>20	3.2
38		4	2	1	1	0.5		
39		4	4	1	2	0.5	>20	4.4
40		16	8	8	8	2		
41		4	4	1	4	0.5		

[a] Strains: *S.a.*-1 = *Staphylococcus aureus* UC 9213 (methicillin-susceptible); *S.a.*-2 = *S. aureus* UC 6685 (methicillin-resistant); *S.e.* = *Staphylococcus epidermis* UC 12084 (methicillin-resistant); *E.f.* = *Enterococcus faecalis* UC 9217; *S.p.* = *Streptococcus pneumoniae* UC 9912. [b] PO administration; 95% confidence limits are −50% and +100% of the nominal value. [c] Positive control is eperezolid administered PO unless otherwise indicated. [d] Eperezolid and linezolid MIC and ED_{50} values taken from refs 8 and 14. [e] Positive control is vancomycin administered sc.

from conformational differences, as **22** and **23** are unique among the compounds of this report in that their heteroaromatic rings bear substituents in both postions ortho to the point of attachment to the piperazine ring. Hydrophilic substituents such as amino (compounds **35** and **39**) and acetamido (**29**) were associated with reduced potency.

Representative compounds having in vitro activity versus *S. aureus* were tested for in vivo activity against this organism in a lethal systemic mouse model. The ED_{50} values from this screen correspond the amount of drug required (mg/kg bodyweight/dose) to reduce mortality by 50%. These data are presented in Table 1 along with ED_{50} values obtained in the same trial for eperezolid as a positive control. The pyridine **17**, the pyridazines **25** and **26**, and the pyrimidine **31** each exhibited in vivo potency comparable to that of eperezolid. Several other compounds which exhibited promising in vitro activity gave disappointing results in vivo. One interesting trend is that all five of the compounds tested in vivo that have a halogen substituent attached to the heteroaromatic ring gave ED_{50} values at least 2-fold and in several cases greater than 6-fold higher than that of eperezolid.

In view of the known propensity of halogen substituents on heteroaromatic rings to undergo facile nucleophilic aromatic substitution reactions, a series of experiments was performed to determine whether the disappointing in vivo activities of representative halogenated analogues **13**, **34**, and **30** were due to facile glutathione conjugation or some other cause. No reaction was observed when compounds **13** and **34** were heated for several hours at 40 or 80 °C with glutathione (GSH) in pH 10.4 carbonate buffer. In contrast, two new

compounds were observed by HPLC when the dichloropyridazine **30** was treated with glutathione in carbonate buffer at 40 °C, and a corresponding decrease in the area of the peak corresponding to **30** was observed. Additional experiments were designed to assess the susceptibility of these compounds to *enzymatic* glutathionylation and to evaluate the effect of the halogen substituent on membrane permeability.

The Caco-2 cell line derives from a human colon adenocarcinoma. These cells spontaneously differentiate in culture, producing monolayers of cells displaying morphological and biochemical characteristics of normal intestinal absorptive cells.[21] For this reason, Caco-2 cell monolayers are frequently used to model intestinal absorption and transport.[22] Because these cells contain relatively high levels of GSH[23] and glutathione *S*-transferase (GST) enzymes[24] and exhibit little or no cytochrome P-450 activity, they also provide a useful tool for assessing susceptibility to enzymatic GSH conjugation.[25]

Compounds **13**, **34**, **30**, and their analogues **9**, **33**, and **25** which lack halogen substitution on the heteroaromatic ring were assayed for permeability across a Caco-2 cell monolayer using a previously described procedure.[26,27] Each compound was combined with phosphate-buffered saline to a target concentration of 40 μM. After sonication, the solutions were equilibrated to 25 °C and filtered. These donor solutions were used to determine permeability coefficients for transport across Caco-2 cell monolayers into a buffered receiver solution. The susceptibility of each compound to glutathione conjugation was assayed by performing each measurement in the presence and absence of the broad spectrum GST inhibitor ethacrynic acid (EA). Mass recovery was monitored by summing the total drug in the donor compartment at the end of the experiment with the total drug recovered from the receiver solutions. The ratio of this amount to the initial donor amount corresponds to the mass recovery.

Permeabilities and mass recoveries for the six compounds in the presence and absence of EA are recorded in Table 2. Mass recovery was close to 100% for all compounds except **13** and **30**. The latter compound was clearly metabolized in transit as indicated by the nearly complete restoration of mass recovery and the 2-fold increase in apparent permeability caused by the GST inhibitor EA. In addition, the same adduct peaks were observed as were seen when the compound was treated with GSH in aqueous base. Compound **13** displayed no evidence of adduct formation and neither mass recovery nor apparent permeability was affected by EA. The relatively high lipophilicity and low solution concentration of **13** (necessitated by poor solubility) may have resulted in a significant fraction of the compound being retained by the cells.[28]

All of the compounds displayed moderate to high permeability in Caco-2 monolayers, suggesting that intestinal permeability is not likely to be a significant barrier to oral absorption. Intestinal metabolism may be a problem only for **30** which undergoes facile glutathionylation. In contrast to their counterparts **9** and **33** which lack halogen substitution on the heteroaromatic ring, both **13** and **34** were significantly less soluble than 40 μM. Low solubility or slow dissolution

Table 2. Permeability Assessment of Oxazolidinones **A** across a Monolayer of Caco-2 Cells in the Presence and Absence of the GST Inhibitor Ethacrynic Acid

No.	Ar	[EA] (μM)	[A] (μM)	P_e	M. R. (%)
9		0	37	28	100
		50	37	31	100
13		0	2.6	18	70
		50	2.6	19	73
25		0	36	5.0	99
30		0	34	7.4	73
		50	34	15	96
33		0	40	13	99
		50	40	14	100
34		0	17	17	98
		50	17	18	100

[a] Abbreviations: No. = compound number, EA = ethacrynic acid, P_e = permeability coefficient (units of 10^{-6} cm/s), M.R. = mass recovery.

can also present a barrier to oral absorption by reducing the lumenal to serosal concentration gradient.[29] Taken in sum, these studies suggest that the diminished in vivo efficacy of the halogenated compounds of this report relative to their unhalogenated counterparts can be explained by either poor solubility or metabolic potential.

Conclusions. Thirty-one new piperazinyl oxazolidinone antibacterial agents substituted with a six-member heteroaromatic ring on the distal piperazine nitrogen were prepared and examined for in vitro and in vivo antibacterial activity. Several of these compounds exhibit in vitro and in vivo activity vs *S. aureus* comparable to that of eperezolid. A series of experiments designed to elucidate the factors responsible for the unexpectedly poor in vivo activity of orally dosed analogues bearing halogen substituents on the heteroaromatic ring was performed. These experiments suggest that the negative impact of halogen substituents may be related to facile glutathione conjugation or to the reduced solubility of the resulting analogues.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 300 or 400 MHz; chemical shifts are reported relative to tetramethylsilane as an internal standard at 0.00 ppm. Infrared spectroscopy was performed on mineral oil mulls. Combustion analyses were performed for each novel compound and agree within ±0.4% of the calculated theoretical value. All reactions were performed in oven-dried glassware which was flushed with nitrogen prior to cooling. DMF, DMPU, ethoxyethanol, triethylamine, and ethyldiisopropylamine were dried over

activated 3 Å molecular sieves for 24 h before use. Other solvents and reagents were used as supplied. Both the in vitro and in vivo biological screens have been described in previous publications.[8]

3-Fluoro-4-[4-(2-pyridyl)piperazin-1-yl]nitrobenzene, 6. A stirred solution of 1-(2-pyridyl)piperazine (5.00 g, 32.8 mmol), diisopropylethylamine (6.81 mL, 39.4 mmol), and 3,4-difluoronitrobenzene (3.99 mL, 36.1 mmol) in CH_3CN (300 mL) was stirred at 25 °C. After 2 days, the solvent was removed under reduced pressure. The crude yellow solid was dissolved in CH_2Cl_2, washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude orange solid was triturated with Et_2O to give 6.63 g (67%) of product as a orange solid: mp 149.5−150 °C; MS (EI) *m/z* (rel intensity) 302 (M+, 15). Anal. ($C_{15}H_{15}FN_4O_2$) C, H, N.

***N*-Benzyloxycarbonyl-3-fluoro-4-[4-(2-pyridyl)piperazin-1-yl]aniline, 7.** A vigorously stirred solution of 3-fluoro-4-[4-(2-pyridyl)piperazin-1-yl]nitrobenzene **6** (4.00 g, 13.2 mmol) in 15% aqueous THF (300 mL) was charged with 10% Pd−C (500 mg). The resulting mixture was placed under an atmosphere of H_2. After 9 h, the mixture was cooled to 0 °C and treated with $NaHCO_3$ (4.44 g, 52.8 mmol) followed by benzyloxycarbonyl chloride (2.27 mL, 15.8 mmol). After 1 h, the solvent was removed under reduced pressure. The remaining aqueous suspension was extracted with EtOAc. Purification by silica gel chromatography (5−20% EtOAc/hexanes) gave 3.57 g (67%) of the title compound as a pale yellow solid: mp 168−169.5 °C; MS (EI) *m/z* (rel intensity) 406 (M+, 8). Anal. ($C_{23}H_{23}FN_4O_2$) C, H, N.

(*R*)-[3-[3-Fluoro-4-(4-(2-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol, 8. A stirred solution of *N*-benzyloxycarbonyl-3-fluoro-4-[4-(2-pyridyl)piperazin-1-yl]-aniline **7** (3.24 g, 8.00 mmol) in anhydrous THF (80 mL) was placed under an atmosphere of N_2 and cooled to −78 °C. The cold solution was treated with *n*-BuLi (5.05 mL, 8.09 mmol). After 20 min, the solution was treated with *R*-glycidyl butyrate (1.14 mL, 8.09 mmol) and then allowed to warm to 25 °C. After 2 h, the mixture was treated with saturated aqueous ammonium chloride solution (5 mL) and concentrated under reduced pressure. The remaining material was dissolved in CH_2Cl_2, washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an amber solid. Purification by recrystallization from $CHCl_3/Et_2O$ (4:1) gave 2.57 g (86%) of the title compound as an off-white solid: mp 157−161 °C; HRMS (EI) ($C_{19}H_{21}FN_4O_3$) calcd 372.1598, found 372.1593. Anal. ($C_{19}H_{21}FN_4O_3$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(2-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide 9. A solution of (*R*)-[3-[3-fluoro-4-(4-(2-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol **8** (1.02 g, 2.74 mmol) in dry CH_2Cl_2 (55 mL) was cooled to 0 °C. The solution was treated with Et_3N (420 μL, 3.02 mmol) followed by methanesulfonyl chloride (234 μL, 3.02 mmol). After 0.5 h, the solution was washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow solid (1.19 g): mp 165.5−166.5 °C; MS (EI) *m/z* (rel intensity) 450 (M+, 8).

A mixture of this solid (870 mg, 1.93 mmol) in 1:1:1 THF/2-propanol/14 M aqueous ammonium hydroxide solution (12 mL) was heated in a heavy walled sealed tube to 95 °C for 16 h. After this time the solvent was removed under reduced pressure. The remaining crude solid was dissolved in CH_2Cl_2 (40 mL), treated with pyridine (328 mL, 4.05 mmol) followed by Ac_2O (201 μL, 2.12 mmol), and allowed to stir at 25 °C for 0.5 h. Then the reaction solution was washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (1.5−3.5% MeOH/$CHCl_3$) gave 476 mg (60%) of the title compound as a off-white solid: mp 190−192 °C; MS (EI) *m/z* (rel intensity) 413 (M+, 11). Anal. ($C_{21}H_{24}FN_5O_3$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(3-cyano-2-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide 18. To a mixture of 200 mg (0.54 mmol) of **10**, 84.6 mg (0.61 mmol) of 2-chloro-3-cyanopyridine, and 0.300 mL (1.7 mmol) of diisopropylethylamine was added 20 mL of EtOH. The solution was transferred to a sealed tube and heated to 110 °C for 7 days. After cooling to 25 °C the white solid precipitate was collected by filtration to yield 75.3 mg (28%) of the title compound: mp 190−192 °C; MS (EI) *m/z* (rel intensity) 438 (M+, 46). Anal. ($C_{22}H_{23}FN_6O_3 \cdot 0.3H_2O$) C, H, N.

General Procedure A. The appropriate pyridine (1.1 mmol), **10** (1.2 mmol), and diisopropylethylamine (2.1 mmol) were stirred in *n*-butanol (10 mL) for 2−3 days at 100−110 °C. Upon cooling, a precipitate formed and was collected by filtration.

(*S*)-*N*-[(3-{4-[4-(5-Cyano-2-pyridinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 17. According to procedure A, 2-chloro-5-carbonitrilepyridine was heated to 110 °C for 2 days in *n*-butanol. The title compound was recrystallized from 10 mL of 1-propanol to give 75.0 mg (28%) of a yellow solid: mp 175−177 °C. MS (EI) *m/z* (rel intensity) 438 (M+, 41). Anal. ($C_{22}H_{23}FN_6O_3 \cdot 1.1H_2O$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(3-Cyano-4,6-dimethyl-2-pyridinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 19. According to procedure A, 2-chloro-4,6-dimethyl-3-carbonitrilepyridine was heated to 110 °C for 2 days. The precipitate was recrystallized from EtOH to give 61.2 mg (12%) of the title compound: mp 221.5−222 °C. HRMS (EI) ($C_{24}H_{27}FN_6O_3$) calcd 466.2129, found 466.2117. Anal. ($C_{24}H_{27}FN_6O_3 \cdot 0.5H_2O$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(2,3,5,6-tetrachloro-4-pyridyl)-piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 23. This compound was made using pentachloropyridine according to procedure A except that 1-propanol was the solvent. The reaction mixture was refluxed at 100 °C for 3 days. The crude product was then suspended in 50 mL of EtOAc, and the mixture was stirred for 24 h. After filtration this process was repeated in 20 mL of EtOAc for 2 days to yield 83.5 mg (15%) of the desired product as a solid: mp 219−220 °C; MS (EI) *m/z* (rel intensity) 549 (M+, 16). Anal. ($C_{21}H_{20}Cl_4FN_5O_3 \cdot 0.75H_2O$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(6-Bromo-2-pyridinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidn-5-yl)methyl]acetamide, 13. This compound was prepared by applying procedure A to 2,6-dibromopyridine in refluxing ethoxyethanol as the solvent with a reaction time of 26 h. The product was purified by silica gel chromatography (3.5% MeOH in CH_2Cl_2). The title compound was obtained as 230 mg (29%) of a yellow-green powder: mp 173−175 °C; MS (ESI+): *m/z* 492 ($M + H^+$), 494 ($M + H^+ + 2$). Anal. ($C_{21}H_{23}BrFN_5O_3$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(2,3,5,6-tetrafluoro-4-pyridyl)-piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 22. To a mixture of 200 mg (0.54 mmol) of **10** and 0.187 mL (1.07 mmol) of diisopropylethylamine was added 10 mL of EtOH. The suspension was cooled to 0 °C. Pentafluoropyridine (0.059 mL, 0.536 mmol) was added to 5 mL of EtOH, and the resulting solution was cooled to 0 °C. The suspension of **10,** diisopropylethylamine, and EtOH was added to the cold pentafluoropyridine solution. This mixture was stirred in an ice bath for 1.5 h. The mixture was allowed to stir at room temperature for 24 h, during which a white precipitate formed and was collected to give the desired product: mp 205−206 °C; MS (EI) *m/z* (rel intensity) 485 (M+, 99). Anal. ($C_{21}H_{20}F_5N_5O_3$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(6-methyl-2-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 15. To 1.6 mL of ethoxyethanol were added 0.300 g (0.80 mmol) of **10**, 0.410 g (3.69 mmol) of 2-fluoro-6-methylpyridine, and 0.31 mL (1.78 mmol) of diisopropylethylamine. The mixture was refluxed for 27 h. A light brown solid precipitated upon cooling. It was recrystallized from butanol to yield 100 mg (11%) of the title compound: MS (ES+) *m/z* 428.2 (M + H). Anal. ($C_{22}H_{26}FN_5O_3 \cdot 0.5H_2O$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(4-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 20. A mixture

of 3.2 mL of ethoxyethanol, 0.600 g (1.61 mmol) of **10**, 0.266 g (1.77 mmol) of 4-chloropyridine hydrochloride, and 0.925 mL (5.31 mmol) of diisopropylethylamine was refluxed for 21 h. The mixture was partitioned between excess aqueous potassium carbonate solution and a 1:1 mixture of EtOAc and EtOH. The organic layer was dried ($MgSO_4$) and filtered. After the solution stood for 3 days at 25 °C, the product precipitated from this solution and it was recovered by filtration. The product was purified by silica gel chromatography eluting with 8% ammonia-saturated EtOH in CH_2Cl_2 to give 127 mg (53% yield): MS (ES+) *m/z* 414 $(M + H)^+$. Anal. ($C_{22}H_{24}FN_5O_3$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(2-methyl-4-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 21. A mixture of 1.0 g (2.68 mmol) of **10**, 0.408 g (3.21 mmol) of 4-chloro-2-methylpyridine, and 1.40 mL (8.04 mmol) of Hunig's base was refluxed for 1 h in 6 mL of ethoxyethanol. The product precipitated out of solution upon adddition of 10 mL of H_2O. The solid was collected by filtration, washed with H_2O, and dried to give the title compound: mp 188−189 °C; MS (ESI−) for *m/z* 426.2 $(M-H)^-$. Anal. ($C_{22}H_{26}FN_5O_3 \cdot H_2O$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(2-quinolinyl)piperazin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 24. A mixture of 1.0 g (2.86 mmol) of **10**, 0.53 g (3.21 mmol) of 4-chloroquinoline, and 1.40 mL (8.04 mmol) of Hunig's base was refluxed for 1 h in 6 mL of ethoxyethanol. The reaction mixture was partitioned between EtOAc and 3 N NaOH. During this procedure, a precipitate formed and was collected by filtration. The solid was washed with H_2O followed by EtOAc and dried. The solid was recrystallized from H_2O to give 0.538 g of the title compound as a tan powder: mp 138−141 °C; HRMS (FAB) ($C_{25}H_{26}FN_5O_3+H_1$) calcd 464.2098, found 464.2105. Anal. ($C_{25}H_{26}FN_5O_3 \cdot 0.6H_2O$) C, H, N.

(*S*)-*N*-[(3-{4-[4-[(4-Cyano-2-pyridinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 16. A mixture of 5.4 mL of ethoxyethanol, 0.600 g (1.61 mmol) of **10**, 0.245 g (1.81 mmol) of 2-chloropyridine-4-carbonitrile, and 0.620 mL (3.56 mmol) of diisopropylethylamine was refluxed for 21 h. Upon cooling, brown crystals formed. The crystals were washed with two portions of butanol to yield 351 mg (50%) of the title compound as a tan powder: mp > 200 °C; MS (ES+) *m/z* 461.3 (M + Na). Anal. ($C_{22}H_{23}FN_6O_3 \cdot 0.2H_2O$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(3,5,6-trifluoro-2-pyridyl)-piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 14. A mixture of 5.4 mL of EtOH, 0.600 g (1.61 mmol) of **10**, 0.267 g (1.77 mmol) of 2,3,5,6-tetrafluoropyridine, and 0.620 mL (3.56 mmol) of diisopropylethylamine was refluxed for 48 h. Upon cooling, a light brown solid formed. The solid was collected by filtration to yield 450 mg (60%) of the title compound as a tan powder: mp 176−178 °C; HRMS ($C_{21}H_{21}F_4N_5O_3$) calcd 467.1581, found 467.1599. Anal. ($C_{21}H_{21}F_4N_5O_3 \cdot 0.5H_2O$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-(6-fluoro-2-pyridyl)piperazin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, 12. A mixture of 5.4 mL of ethoxyethanol, 0.60 g (1.61 mmol) of **10**, 0.204 g (1.77 mmol) of 2,6-difluoropyridine, and 0.620 mL (3.56 mmol) of diisopropylethylamine was refluxed for 16 h. A light brown solid precipitated upon cooling. The solid was collected by filtration and recrystallized from EtOH. The title compound was isolated as 0.23 g (33% yield) of a tan solid: mp 183−185 °C; MS (ES+) *m/z* 432.3 (M + H). Anal. ($C_{21}H_{23}F_2N_5O_3 \cdot 0.2H_2O$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-[4-(2-pyrimidinyl)]-1-piperazinyl]-phenyl-2-oxo-5-oxazolidinyl]methyl]acetamide, 31. A solution of 0.50 g (1.34 mmol) of **10**, 0.153 g (1.34 mmol) of 2-chloropyrimidine, and 0.55 mL (4.0 mmol) of triethylamine in 5.0 mL of absolute EtOH was refluxed for 5.5 h and then stirred 21 h at 25 °C. The mixture was then partitioned between 50 mL of CH_2Cl_2 and 50 mL of a saturated aqueous solution of sodium bicarbonate. The solvent was evaporated at reduced pressure, and the residue was dissolved in 50 mL of CH_2Cl_2 and treated with 15 g of silica gel. The mixture was filtered, and the solvent was evaporated at reduced pressure. The residue was recrystallized from 2-propanol to give the title compound as 0.20 g (33%) of a white solid: mp 197−198 °C; MS (EI) *m/z* (rel intensity) 414 (M+, 48). Anal. ($C_{20}H_{23}FN_6O_3$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-[4-(4-pyridazinyl)]-1-piperazinyl]-phenyl-2-oxo-5-oxazolidinyl]methyl]acetamide, 33. A suspension of **34** (150 mg) in 15 mL of 2:1 absolute EtOH/EtOAc was agitated and treated with 0.3 mL of 3.0 N hydrochloric acid. Approximately 50 mg of 5% palladium on carbon was added to the resulting clear solution, and the mixture was agitated under an atmosphere of 50 psi hydrogen gas for 3 days. The catalyst was removed by filtration, and the solvent was evaporated at reduced pressure. The residue was partitioned between 20 mL of EtOAc and 20 mL of 1 M dipotassium hydrogen phosphate solution. The solvent was evaporated at reduced pressure. The residue was chromatographed on 10 g of silica gel eluting with 93:7 CH_2Cl_2/absolute EtOH. The white solid thus obtained was washed with hexanes and dried to give 52 mg (36%) of the title compound: mp 145−147 °C; HRMS (EI) ($C_{20}H_{23}FN_6O_3$) calcd 414.1816, found 414.1808. Anal. ($C_{20}H_{23}FN_6O_3 \cdot 0.15C_6H_{14} \cdot 0.75H_2O$) C, H, N. The presence of 0.15 equiv of hexane, not readily removed by heating under vacuum, was confirmed by ^1H NMR.

General Procedure B. A mixture of triethylamine (5 mmol), **10** (1.4 mmol), and the appropriate aryl halide (1.5 mmol) was stirred in DMF (5−12 mL) overnight. The mixture was partitioned between EtOAc and H_2O. The organic phase was dried ($MgSO_4$), and the solvent was evaporated at reduced pressure.

(*S*)-*N*-[(3-{4-[4-(2-Chloro-4-pyrimidinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 34. According to procedure B, 2,4-dichloropyrimidine was stirred in DMF for 16 h at 25 °C. The residue was triturated with toluene and dried in a stream of air to give 0.499 g (83%) of the title compound as a white powder: mp 189−191 °C; MS (EI) *m/z* (rel intensity) 448 (M+, 6). Anal. ($C_{20}H_{22}ClFN_6O_3 \cdot 0.15H_2O$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 38. Procedure B was applied to 2-chloro-4,6-dimethoxy-1,3,5-triazine. The crude product was recrystallized from EtOAc and hexanes to give 0.419 g (65%) of the title compound as a white solid: mp 206.5−207 °C; HRMS (EI) ($C_{21}H_{26}FN_7O_5$) calcd 475.1979, found 475.1987. Anal. ($C_{21}H_{26}FN_7O_5$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(4-Chloro-6-propoxy-1,3,5-triazin-2-yl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 40. Procedure B was applied to 2,4-dichloro-6-*n*-propoxy-1,3,5-triazine. The crude product was purified by silica gel chromatography (3−5% MeOH/CH_2Cl_2) to give 0.298 g (41%) of material. This material was recrystallized from EtOAc to give 0.143 g (20%) of the title compound as a white solid: HRMS (EI) ($C_{22}H_{27}ClFN_7O_4$) calcd 507.1797, found, 507.1797. Anal. ($C_{22}H_{27}ClFN_7O_4$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-[4-(3-pyridazinyl)]-1-piperazinyl]-phenyl-2-oxo-5-oxazolidinyl]methyl]acetamide, 25. Procedure B was applied to 3,6-dichloropyridazine in 15 mL of 70 °C DMF using a reaction time of 7 days. The crude product was purified by silica gel chromatography (3−10% MeOH/CH_2Cl_2) to give a light yellow solid. The combined product from two such preparations was hydrogenated in 1:1 MeOH/EtOAc using palladium black as a catalyst at 1 atm hydrogen pressure. The crude material was purified on a preparative TLC plate (4−8% MeOH/CH_2Cl_2) to give 0.114 g (54%) of the desired material as a cream solid: mp 207−208 °C; HRMS (EI) ($C_{20}H_{23}FN_6O_3$) calcd 414.1815, found 414.1818. Anal. ($C_{20}H_{23}FN_6O_3 \cdot 0.5H_2O$) C, H, N.

(*S*)-*N*-[[3-[3-Fluoro-4-[4-[2-[4-(trifluoromethyl)-pyrimidinyl]]]-1-piperazinyl]phenyl-2-oxo-5-oxazolidinyl]-methyl]acetamide, 32. A mixture of 0.50 g (1.34 mmol) of **10** and 0.37 mL (2.68 mmol) of triethylamine in 5 mL of DMF was treated with 0.16 mL (1.34 mmol) of 2-chloro-4-(trifluoromethyl)pyrimidine. The mixture was stirred at 25 °C for 4

days, and then it was poured into 50 mL of distilled H_2O. The precipitate was collected by filtration and recrystallized from 95% aqueous EtOH to give 0.42 g (65%) of the title compound: mp 189−192 °C (dec); MS (EI) *m*/*z* (rel intensity) 482 (M+, 73). Anal. ($C_{21}H_{22}F_4N_6O_3$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(4,6-Diamino-1,3,5-triazin-2-yl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride, 39. A mixture of 0.50 g (1.34 mmol) of **10**, 0.195 g (1.34 mmol) of 4,6-diamino-2-chlorotriazene, 0.276 mL (2.0 mmol) of triethylamine, and 15 mL of 95:5 EtOH/H_2O was refluxed for 48 h. The white solid precipitate that formed upon cooling was collected by filtration. The solid was dissolved in a warm mixture of 25 mL of 95:5 EtOH/H_2O and treated with 8 mL of 1.0 N hydrogen chloride in Et_2O. The solvent was evaporated at reduced pressure. The residue was recrystallized from absolute EtOH to give 116 mg (19%) of the title compound as a pale yellow solid: mp 172−174 °C; MS (FAB) *m*/*z* (rel intensity) 446 (M + H, 99). Anal. ($C_{19}H_{24}FN_9O_3 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(2,6-Diamino-4-pyrimidinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 35. A mixture of 0.30 g (0.80 mmol) of **10**, 0.116 g (0.80 mmol) of 2,6-diamino-4-chloropyrimidine, 2.0 mL of ethylene glycol, and 0.52 mL (3.0 mmol) of diisopropylethylamine was stirred at 100 °C for 18 h. The mixture was cooled and then partitioned between 3.0 N aqueous sodium hydroxide solution and EtOAc, and the organic phase was dried ($MgSO_4$). The volume of the organic phase was reduced to 2 mL by evaporation at reduced pressure. The resulting solution was diluted with 18 mL of diethyl ether. The tan solid precipitate was collected by filtration to give 83 mg (23%) of the title compound: mp 215 °C (dec); MS (EI) *m*/*z* (rel intensity) 444 (M+, 1). Anal. ($C_{20}H_{25}FN_8O_3 \cdot 0.5H_2O$) C, H, N.

General Procedure C. The remaining compounds were made using this general procedure: A solution of triethylamine (5 mmol), **10** (1.5 mmol), and the aryl halide (1.8 mmol) in DMF (9 mL) or DMPU (3 mL) was stirred 1−7 days at 40−110 °C. The solvent was removed via bulb-to-bulb distillation, and the crude material was purified by silica gel chromatography (3% MeOH/CH_2Cl_2).

(*S*)-*N*-{[3-(4-{4-[5-(Acetylamino)-6-chloro-3-pyridazinyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 29. According to procedure C, 4-acetamido-3,6-dichloropyridazine stirred with **10** in DMF at 55 °C for 7 days. The product was then recrystallized from MeOH to give 0.190 g (27%) of cream-colored amorphous solid: IR (mull, cm^{-1}) 3350 (m), 3259 (m), 3206 (m), 3171 (m), 3143 (m), 3126 (m), 3104 (m), 3091 (m), 3063 (m), 3044 (m), 1743 (sh), 1734 (s), 1712 (m), 1653 (s), 1543 (s), 1531 (s), 1516 (s), 1483 (s), 1224 (s); HRMS (FAB) ($C_{22}H_{25}ClFN_7O_4$ + H^+) calcd 506.1718, found 506.1715. Anal. ($C_{22}H_{25}ClFN_7O_4$) C, H, N, Cl.

(*S*)-*N*-[(3-{4-[4-(6-Chloro-5-methyl-3-pyridazinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 27. According to procedure C, a DMF solution 3,6-dichloro-4-methylpyridazine was heated with **10** at 55−95 °C for 7 days. Trituration with MeOH gave 0.135 g (19%) of pure material as a white solid: HRMS (FAB) ($C_{21}H_{24}ClFN_6O_3 + H^+$) calcd 463.1660, found 463.1667. Anal. ($C_{21}H_{24}ClFN_6O_3$) C, H, N, Cl.

(*S*)-*N*-[(3-{4-[4-(5,6-Dichloro-4-pyridazinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 30. According to procedure C, 3,4,5-trichloropyridazine and **10** were stirred at 40 °C overnight. The reaction yielded 0.139 g (21%) of the title compound as a light tan solid: mp 132−134 °C; ^1H and ^{13}C chemical shift assignments were made using 2D heteronuclear one-bond (HMQC) and multiple-bond (HMBC) NMR experiments conducted at 500 MHz (^1H). Identification of the regioisomer was accomplished using single-frequency irradiation nuclear Overhauser effect (NOE) difference experiments conducted at 500 MHz. A strong NOE observed between four downfield methylene protons on the piperazine ring and the single proton of the pyridazine ring shows that attachment of the pyridazine ring occurs at the 5-position: HRMS (EI) ($C_{20}H_{21}Cl_2FN_6O_3$) calcd 482.1036, found 482.1032. Anal. ($C_{20}H_{21}Cl_2FN_6O_3 \cdot 0.5H_2O$) C, H, N, Cl. Hydrogenation of this substance gave a compound which is isomeric to **25** (^1H NMR, MS).

(*S*)-*N*-[(3-{4-[4-(6-Chloro-4,5-dimethyl-3-pyridazinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 28. According to procedure C, a DMPU solution of 3,6-dichloro-4,5-dimethylpyridazine and **10** was stirred at 60 °C for 3 days and at 110 °C for 2 days. The reaction yielded 0.148 g (21%) of the desired material as a tan solid: mp 253−254 °C; HRMS (EI) ($C_{22}H_{26}ClFN_6O_3$) calcd 476.1739, found 476.1732. Anal. ($C_{22}H_{26}ClFN_6O_3$) C, H, N, Cl.

(*S*)-*N*-[[3-[3-Fluoro-4-[4-(2-pyrazinyl)]-1-piperazinyl]-phenyl-2-oxo-5-oxazolidinyl]methyl]acetamide, 36. According to procedure C, a DMPU solution of **10** with chloropyrazine was stirred at 60 °C for 3 days and at 110 °C for 1 day. The reaction yielded 0.360 g (52%) of the desired material as a yellow solid: mp 193−194.5 °C; HRMS ($C_{20}H_{23}FN_6O_3$) calcd 414.1815, found 414.1816. Anal. ($C_{20}H_{23}FN_6O_3 \cdot 0.4H_2O$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 37. A DMPU solution of **10** with 2,6-dichloropyrazine was heated at 100 °C overnight. The reaction yielded 0.174 g (27%) of the desired material as a light orange solid: mp 160−164 °C; HRMS (EI) ($C_{20}H_{22}ClFN_6O_3$) calcd 448.1426, found 448.1418. Anal. ($C_{20}H_{22}ClFN_6O_3 \cdot 0.4H_2O$) C, H, N, Cl.

(*S*)-*N*-[[3-[3-Fluoro-4-[4-[3-(6-methylpyridazinyl)]]-1-piperazinyl]phenyl-2-oxo-5-oxazolidinyl]methyl]acetamide, 26. According to procedure C, a DMPU solution of **10** with 3-chloro-6-methylpyridazine was stirred 2 days at 90 °C. This material was further purified on a preparative TLC plate (4% MeOH/CH_2Cl_2) to give 0.060 g (10%) of the title compound as a light tan solid: mp 237−238 °C; HRMS (EI) ($C_{21}H_{25}FN_6O_3$) calcd 428.1972, found 428.1954. Anal. ($C_{21}H_{25}FN_6O_3$) C, H, N.

(*S*)-*N*-[(3-{4-[4-(3-Acetyl-2-methylimidazo[1,2-*b*]pyridazin-6-yl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 41. According to procedure C, a DMPU solution of **10** and 3-acetyl-6-chloro-2-methylimidazo[1,2-*b*]pyridazine[30] was stirred at 100 °C for 4 days. The material was further purified by preparative TLC (4−8% MeOH/CH_2Cl_2) to give 0.101 g (26%) of the desired material as a light yellow solid: mp 217−218 °C; HRMS (FAB) ($C_{25}H_{28}FN_7O_4 + H^+$) calcd 510.2265, found 510.2264. Anal. ($C_{25}H_{28}FN_7O_4 \cdot 0.5H_2O$) C, H, N.

Caco-2 Permeability Studies. Solid test compounds were weighed out and combined with phosphate-buffered saline (containing 15 mM HEPES, 0.1% glucose, pH 7.2) to a target concentration of 40 μM. After sonication the solutions were equilibrated at 25 °C and filtered. Half of each solution was supplemented with 50 μM EA. These donor solutions, with and without EA, were used to determine permeability coefficients across Caco-2 cell monolayers. The cell monolayers were prepared and absorptive permeability was determined as previously described.[26,27] Briefly, 1.5 mL of solution was placed on top of buffer-washed confluent Caco-2 monolayers which had been grown on Costar Transwell filters. The Transwell filters were placed in six well tissue culture plates containing 2.5 mL buffer per well and were moved at regular time intervals to wells containing fresh buffer. The appearance of the test compound in these receiver solutions as a function of time was used to calculate permeability coefficients. Mass recovery was monitored by summing total drug in the donor solution at the end of the experiment with total drug recovered from receiver solutions. The ratio of this amount to the initial donor solution amount yields percent mass recovery.

A gradient HPLC system was used to determine solution concentrations of the test compounds. A BDS-Hypersil-C18 column (150 × 4.6 mm^2) from Keystone Scientific was used with a gradient ranging from 10 to 45% acetonitrile. Peaks were detected by UV absorbance at 254 nm.

Acknowledgment. The authors thank John W. Allison, Ronda D. Schaadt, and Betty Yagi for the in vitro data; Judith C. Hamel and Douglas Stapert for the in vivo data. The personnel of Pharmacia and Upjohn's Structural, Analytical, and Medicinal Chemistry unit are thanked for elemental analysis and mass spectral data.

Supporting Information Available: NMR spectral data for each of the new compounds of this report (5 pages). Ordering information is given on any current masthead page.

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JM980274L