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Article

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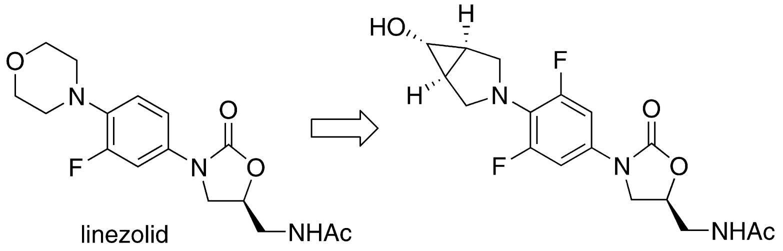

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Conformational Constraint in Oxazolidinone Antibacterials. Synthesis and Structure−Activity Studies of (Azabicyclo[3.1.0]hexylphenyl)oxazolidinones

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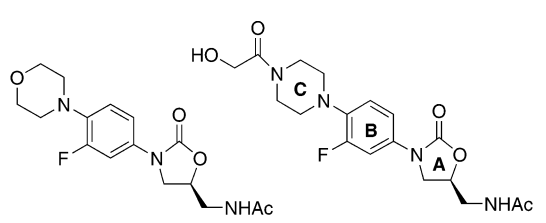
The oxazolidinones are a new class of synthetic antibacterials effective against a broad range of pathogenic Gram-positive bacteria, including multi-drug-resistant strains. Linezolid is the first drug from this class to reach the market and has become an important new option for the treatment of serious infections, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enteroccocus faecium* (VRE). In the search for novel oxazolidinones with improved potency and spectrum, we have prepared and evaluated the antibacterial properties of conformationally constrained analogues in which the morpholine ring of linezolid is replaced with various substituted azabicyclo[3.1.0]hexyl ring systems. Several classes of azabicyclic analogues were identified with activity comparable or superior to that of linezolid. These include analogues bearing hydroxyl, amino, amido, or carboxyl groups on the azabicyclic ring. The azabicyclic acid analogue **50** was 4 times more potent than linezolid against key Gram-positive and fastidious Gram-negative pathogens (*S. aureus*, *Streptococcus pneumoniae,* and *E. faecalis* MICs ≤ 1 μg/mL; *Haemophilus influenzae* MIC = 4 μg/mL).

Introduction

The emergence of bacterial pathogens resistant to existing antimicrobials is a problem of increasing significance[1−4] that has attracted the attention of the medical community and pharmaceutical scientists. The oxazolidinones,[5−7] exemplified by linezolid (**1**) and eperezolid (**2**), comprise a new class of synthetic antibacterials with activity against a broad range of Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) and vancomycin-resistant *Enterococcus faecium* (VRE). The oxazolidinones inhibit bacterial protein synthesis at the initiation phase via binding to 23S RNA of the 50S ribosomal subunit of prokaryotes.[8−11] This novel mechanism of action is not shared with any known antibiotics of natural or synthetic origin, so oxazolidinones do not exhibit cross-resistance with any of the existing classes of antibacterials.



linezolid
1

eperezolid
2

Linezolid (**1**) is the first oxazolidinone to receive regulatory approval and was launched by Pharmacia in April 2000. Linezolid exhibits an antimicrobial spectrum that encompasses a broad range of susceptible and multi-drug-resistant Gram-positive cocci. The drug displays more modest activity against the fastidious Gram-negative respiratory tract pathogens *Haemphilus influenzae* and *Moraxella catarrhalis* (MIC$_{90}$ = 16 and 4 μg/mL, respectively[5]) and is not indicated for use in infections caused by these bacteria. Not surprisingly, significant efforts have been mounted by several groups to broaden the antibacterial spectrum of the oxazolidinones in the hope of expanding the utility of this novel class of antibacterials.[12] For example, a recent report described (azolylphenyl)oxazolidinones that possess improved activity against *H. influenzae* and *M. catarrhalis*.[13]

As a part of our own efforts to develop oxazolidinone agents with improved potency and antibacterial spectrum, we chose to examine the effects of conformational constraint as applied to the saturated 4′-heterocyclic ring (C-ring) of phenyloxazolidinones. The azabicyclo[3.1.0]hexyl ring system, in particular, attracted our attention as a constrained bicyclic isostere of the piperazine C-ring of eperezolid (**2**). We expected that this structural modification would impart a rigidity in the *aliphatic* C-ring more characteristic of flat *aryl* or *heteroayl* C-ring oxazolidinones (e.g., azolylphenyl), many of which exhibit improved potency and an expanded antimicrobial spectrum. Herein, we disclose our studies on the synthesis and antibacterial activity of a new class of oxazolidinones featuring substituted azabicyclo[3.1.0]hexyl C-rings.[14]

Chemistry

Substituted Azabicyclic C-Rings. The preparation of (azabicyclohexylphenyl)oxazolidinone antibacterials (**3**) is illustrated retrosynthetically in Scheme 1. The oxazolidinone ring (A-ring) is installed at a late stage of the synthesis using known synthetic protocols.[15] Thus, reaction of an *N*-aryl carbamate **4** with (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester[16] gener-

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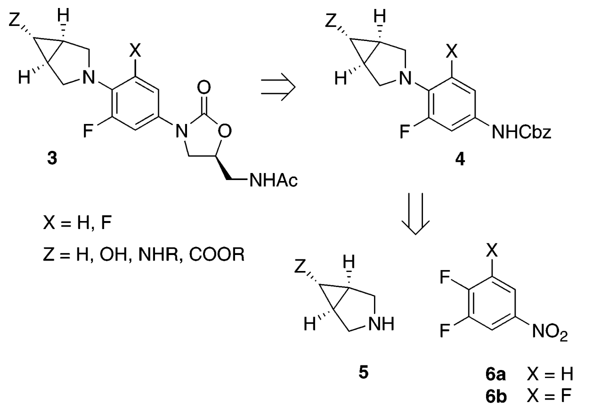
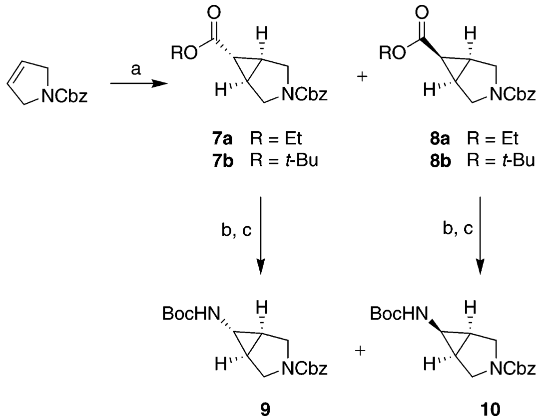
Scheme 1



Scheme 2[a]

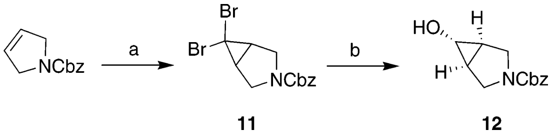


[a] Reagents: (a) N_2CHCO_2R, $Rh_2(OAc)_4$, CH_2Cl_2, 25−35%; (b) NaOH, MeOH; (c) DPPA, Et_3N, tBuOH, reflux, 50% for two steps.

ates the oxazolidinone ring in a *single step* and with the privileged acetamidomethyl side chain disposed in the biologically active (*S*)-configuration. Analogues bearing other amide side chains at C-5 are prepared using a multistep procedure, the first step involving reaction of the *N*-aryl carbamate **4** with (*R*)-(−)-glycidyl butyrate. The resulting hydroxymethyl-substituted oxazolidinone intermediate is then elaborated to generate other C-5 side chain variants.[17] The *N*-aryl carbamate intermediates **4** are derived from the corresponding nitroarenes, which are in turn produced by nucleophilic aromatic substitution reactions between the bicyclic heterocycles **5** and fluoronitroarenes **6**. The choice of fluoronitroarene starting material (**6a** or **6b**) governs the extent of B-ring fluorination in the final compounds.

The oxazolidinone analogues contemplated here required the preparation of bicyclo[3.1.0]hexylamines substituted at the 6-position with suitably protected amine, alcohol, or carboxylic acid functionality. Preparation of the amine and carboxylic acid intermediates (**7**−**10**) was accomplished according to the literature procedure[18] as illustrated in Scheme 2. Thus, rhodium-catalyzed cyclopropanation of benzyl 3-pyrroline-1-carboxylate with ethyldiazoacetate or *tert*-butyldiazoacetate provided the exo cycloadducts **7a** (R = Et) or **7b** (R = *t*-Bu) in modest yield after chromatographic separation from smaller amounts of the endo diastereomers (**8a** or **8b**) and unreacted starting material. The *tert*-butyl ester **7b** was used to prepare carboxylic acid and amide analogues, while the ethyl esters **7a** (exo) and **8a** (endo) were further converted to the protected amine intermediates **9** (exo) and **10** (endo) in two steps (ester hydrolysis followed by Curtius rearrangement). The cyclopropanol **12** was prepared from the dibromocyclopropane **11** by stereocontrolled conversion to the *exo*-cyclopropylborane followed by oxidation with alkaline hydrogen peroxide (Scheme 3).[19] The parent 3-azabicyclo[3.1.0]hexane (i.e., **5**, Z = H) was prepared using the established procedure.[20]

Scheme 3[a]



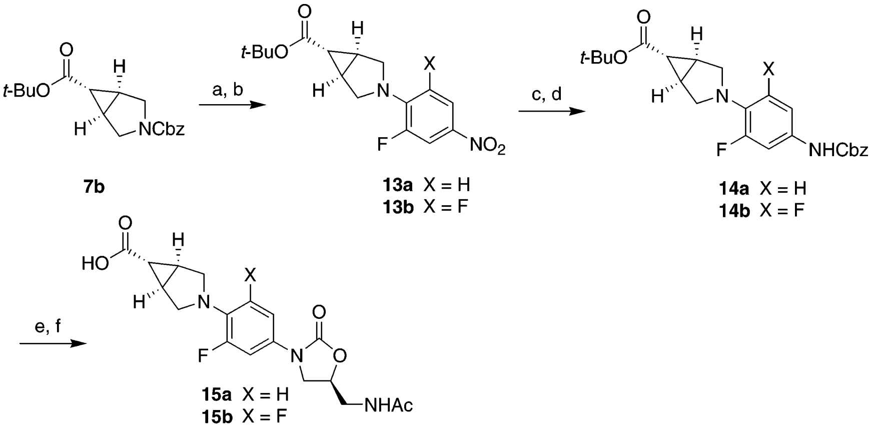
[a] Reagents: (a) $CHBr_3$, aq NaOH, CH_2Cl_2, $BnEt_3NCl$, 50%; (b) $^{n}BuLi$, THF, catecholborane, −90 to 50 °C, then H_2O_2, NaOH, 15% overall.

With the desired bicyclic building blocks **7**−**12** in hand, the stage was set for their coupling to fluoronitrobenzenes **6a** or **6b** and subsequent elaboration to oxazolidinone analogues. The synthesis of azabicyclic acid analogues **15a** and **15b** (Scheme 4) is illustrative of the general protocol used for the synthesis of (azabicyclo[3.1.0]hexylphenyl)oxazolidinone antibacterials. Removal of the benzyloxycarbonyl group in **7b** was accomplished by hydrogenolysis over Pearlman's catalyst in methanol. The resulting secondary amine was then reacted with 3,4-difluoronitrobenzene (**6a**) or 3,4,5-trifluoronitrobenzene (**6b**) in DMF or acetonitrile containing *N*,*N*-diisopropylethylamine to provide nitroarene intermediates **13**. Reduction of the nitro function was accomplished under mild conditions by heating with ammonium chloride and iron metal in ethanol−water. The resulting anilines were converted directly to benzyloxy carbamate (Cbz) derivatives **14** (CbzCl in pyridine/dichloromethane). Introduction of the oxazolidinone ring was accomplished in a single step by reaction with lithium *tert*-butoxide, (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester,[16] and methanol in DMF. A final deprotection step (trifluoroacetic acid in dichloromethane) then provided the desired azabicyclic acid analogues **15a** and **15b**.

Analogous synthetic procedures were used to convert the other azabicyclic building blocks (**9**−**12**) to oxazolidinone analogues (Schemes 5−7). Thus, azabicyclic amine analogues **18a** and **18b** were prepared as shown in Scheme 5. The bicyclic intermediate **9** was elaborated to nitro aromatic intermediates **16** and then to the Cbz-protected anilines **17**. The oxazolidinone ring was installed as before and the 6-amino group unmasked with HCl in dioxane to provide the azabicyclic amine analogues **18a** and **18b** as hydrochloride salts. The corresponding endo diastereomer **19** was prepared in an analogous fashion but starting with the endo bicyclic amine **10**.

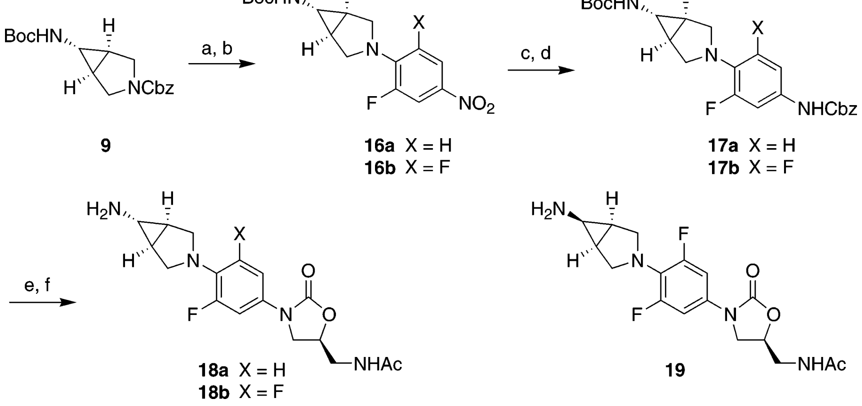
For the preparation of cyclopropanol analogue **22** (Scheme 6), protection of the hydroxy function as a *tert*-butyldimethylsilyl ether was required prior to introduction of the oxazolidinone ring (i.e., via intermediates **20** and **21**). Cleavage of the silyl ether in the final step (HF in AcOH/THF) provided the desired hydroxy analogue **22**. The unsubstituted bicyclic analogues **25a** and **25b** were prepared from azabicyclo[3.1.0]hexane[20] following the standard protocol via intermediates **23** and **24** (Scheme 7).

Scheme 4[a]



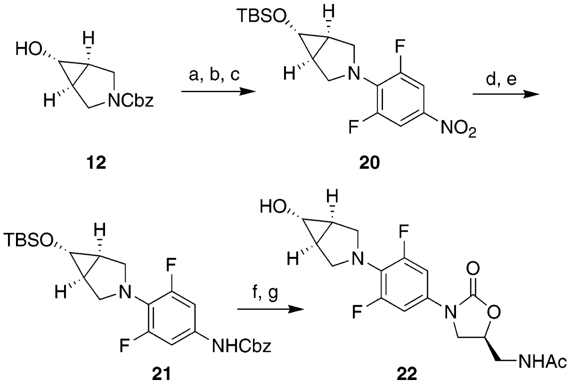
[a] Reagents: (a) H_2, $Pd(OH)_2/C$, MeOH, quant.; (b) **6a** or **6b**, DIEA, DMF, 50 °C, 80−90%; (c) Fe, NH_4Cl, EtOH−H_2O, reflux; (d) CbzCl, pyridine, CH_2Cl_2, 69% for two steps; (e) LiOtBu, MeOH, DMF, (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester; (f) TFA, CH_2Cl_2, 72% for two steps.

Scheme 5[a]



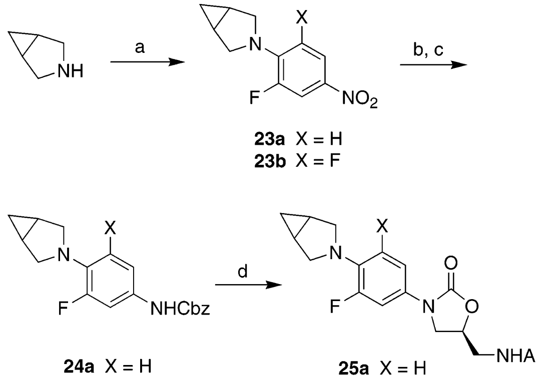
[a] Reagents: (a) H_2, $Pd(OH)_2/C$, MeOH, quant.; (b) **6a** or **6b**, DIEA, DMF, 50 °C, 84−93%; (c) Fe, NH_4Cl, EtOH−H_2O, reflux; (d) CbzCl, pyridine, CH_2Cl_2, 77−86% for two steps; (e) LiOtBu, MeOH, DMF, (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester; (f) HCl, dioxane 65% for two steps.

Scheme 6[a]



[a] Reagents: (a) H_2, $Pd(OH)_2/C$, MeOH, quant.; (b) 3,4,5-trifluoronitrobenzene, DIEA, DMF, 50 °C, 91%; (c) $tBuMe_2SiCl$, imidazole, CH_2Cl_2, 88%; (d) Fe, NH_4Cl, EtOH−H_2O, reflux; (e) CbzCl, pyridine, CH_2Cl_2, 70% for two steps; (f) LiOtBu, MeOH, DMF, (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester, 73%; (g) HF, AcOH, THF−H_2O, 85%.

Scheme 7[a]

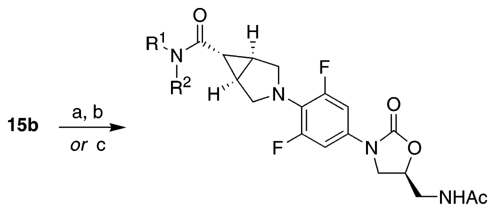


[a] Reagents: (a) **6a** or **6b**, DIEA, DMF, 50 °C, 82%; (b) Fe, NH_4Cl, EtOH−H_2O, reflux; (c) CbzCl, pyridine, CH_2Cl_2, 79−87% for two steps; (d) LiOtBu, MeOH, DMF, (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester, 62−70%.

Further elaboration of acid and amine analogues **15a**−**b** and **18a**−**b** provided amide, sulfonamide, and urea analogues. Hence, substituted carboxamide analogues **26**−**35** were prepared from the carboxylic acid analogue **15b** directly using HATU-mediated coupling reactions or via amidation of the pentafluorophenyl ester of **15b** (Scheme 8). Likewise, substituted amino bicyclic analogue **18b** could be further elaborated to amide, sulfonamide, or urea analogues (**36**−**40**) using standard methodology (Scheme 9).

C-5 Amidomethyl Modifications. The synthesis of analogues bearing C-5 side chains other than acetamidomethyl is illustrated in Schemes 10 and 11. Thus,

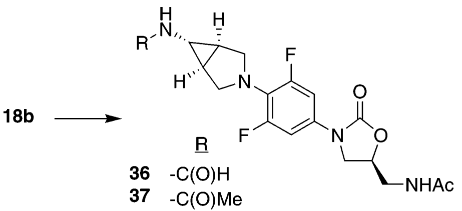
Scheme 8[a]



		R^1	R^2		R^1	R^2
	26	H	H	**31**	1,3-thiazol-2-yl	H
	27	Me	H	**32**	6-methoxypyridin-3-yl	H
	28	Me	Me	**33**	2-furylmethyl	H
d	**29**	OBn	H	**34**	pyridin-2-ylmethyl	H
	30	OH	H	**35**	1,3-benzodioxol-5-yl	H

[a] Reagents: (a) $CF_3C(=O)OC_6F_5$, pyridine, DMF; (b) R^1R^2NH, DIEA, DMF; (c) R^1R^2NH, HATU, DIEA, DMF; (d) H_2, Pd/C, EtOH.

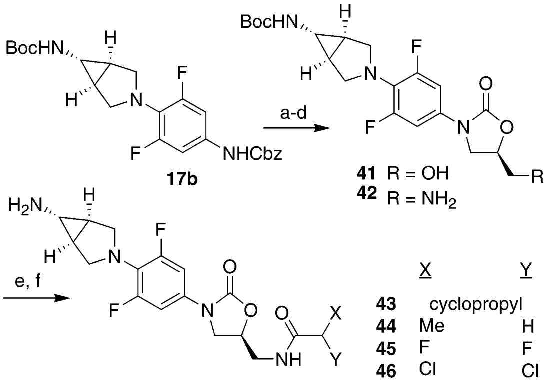
Scheme 9[a]



	R
36	-C(O)H
37	-C(O)Me
38	$-C(O)CH_2OH$
39	$-SO_2Me$
40	-C(O)NHPh

[a] Reagents: HCOOH, Ac_2O (for **36**); Ac_2O, Et_3N (for **37**), $AcOCH_2CO_2H$, HATU, DIEA, then LiOH (for **38**); $MeSO_2Cl$, Et_3N, DMF (for **39**); PhNCO, Et_3N, NMP (for **40**).

Scheme 10[a]

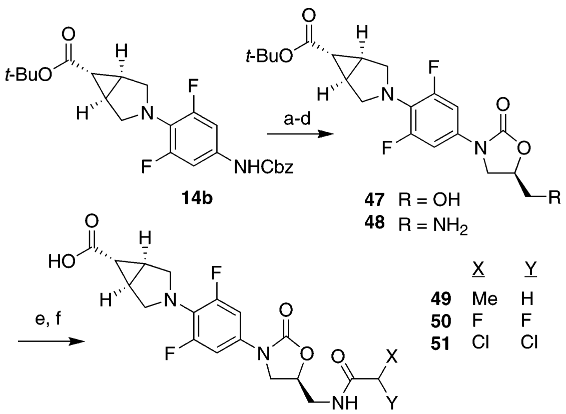


	X	Y
43	cyclopropyl	
44	Me	H
45	F	F
46	Cl	Cl

[a] Reagents: (a) LiHMDS, DMF, (*R*)-glycidyl butyrate, 81%; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (c) NaN_3, DMF, 70 °C; (d) Ph_3P, THF, then H_2O, 40 °C; 56% for three steps; (e) $(RC(=O))_2O$ or $CHF_2C(=O)OEt$, Et_3N or pyridine; (f) HCl, dioxane.

reaction of **17b** with lithium hexamethyldisilylamide and (*R*)-glycidyl butyrate produced intermediate **41** bearing a hydroxymethyl side chain at C-5. This material was elaborated via the azide to a C-5 aminomethyl intermediate (**42**) that was then acylated under standard conditions to provide dihaloacetamides, propionamides, and cyclopropyl amide intermediates. A final deprotection step employing hydrogen chloride in dioxane then provided the desired C-5 amide variants **43**–**46**. An analogous synthetic route was employed to access C-5 amide analogues in the azabicyclic acid series, starting with **14b** and proceeding through the hydroxymethyl and aminomethyl intermediates **47** and **48** (Scheme 11). Cleavage of the *tert*-butyl ester with trifluoroacetic acid in dichloromethane provided the C-5 amide variants **49**–**51**.

Scheme 11[a]



	X	Y
49	Me	H
50	F	F
51	Cl	Cl

[a] Reagents: (a) LiHMDS, DMF, (*R*)-glycidyl butyrate, 87%; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (c) NaN_3, DMF, 70 °C; (d) Ph_3P, THF, then H_2O, 40 °C; 86% for three steps; (e) $(RC(=O))_2O$ or $CHF_2C(=O)OEt$, Et_3N or pyridine; (f) TFA, CH_2Cl_2.

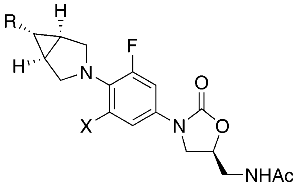
Results and Discussion

The azabicyclic phenyloxazolidinone analogues described herein were evaluated for antimicrobial activity against a panel of Gram-positive and -negative bacteria (Tables 1–4). All of the oxazolidinone analogues submitted for biological assay were ≥95% pure as judged by ^1H NMR and HPLC analysis (see Supporting Information). This level of purity is considered more than sufficient for meaningful SAR analysis, given the inherent variability of standard broth microdilution assay methods.[21]

The first compounds evaluated for antibacterial activity were the simple carboxyl (**15**), amino (**18**), hydroxyl (**22**), and unsubstituted (**25**) azabicyclic analogues shown in Table 1. Quite surprisingly, the free carboxyl- and amino-substituted analogues **15** and **18** exhibited excellent antimicrobial activity, better in some cases than linezolid itself. Fluorination of the B-ring exerted a potentiating effect, particularly within the azabicyclic acid series, where bis-fluoro B-ring analogue **15b** was 4-fold more potent than its monofluoro congener **15a**. This remarkable tolerance of either acidic or basic functionality was quite unexpected in view of previous oxazolidinone SAR. Particularly relevant to this case are earlier findings that oxazolidinone analogues bearing an acidic tetrazole substituent were devoid of antibacterial activity while nonacidic *N*-methyltetrazole derivatives were active.[22] To the best of our knowledge, analogues such as **15** represent the first active antimicrobial oxazolidinones featuring an acidic carboxylic acid function.[23] The presence of carboxylic acid functionality in a lead molecule is advantageous, as it permits the rapid generation of new analogues (vide infra) and can be used to alter solubility and membrane permeability (via ester prodrugs, alternate salt forms, etc.).

A broader range of activities was observed for analogues **15**–**25** against the Gram-negative pathogens *H. influenzae* and *Esherichia coli* (Table 1). A clear SAR trend is evident in the case of *H. influenzae*, with hydrophilic carboxyl (**15**), amino (**18**), and hydroxyl (**22**) analogues displaying better activity than more lipophilic analogues such as **25a**–**b**. B-ring fluorination was generally beneficial, with bis-fluoro analogues **15b** and **18b** exhibiting *H. influenzae* activity consistently superior to that of the monofluoro comparators and

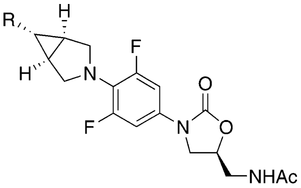
Table 1. In Vitro Antibacterial Activity of Selected (Azabicyclo[3.1.0]hexylphenyl)oxazolidinone Analogues



			minimum inhibitory concentration (μg/mL)						
compd	R	X	S.a.[a]	S.a.[b]	S.e.[c]	S.p.[d]	E.f.[e]	H.i.[f]	E.c.[g]
1	–	–	2–4	2–4	1	0.5–1	2–4	8–16	>64
15a	COOH	H	8	4	2	4	4	16	>64
15b	COOH	F	2	1	0.5–1	1	1	4–8	>64
18a	NH_2	H	2–4	4	0.5–1	1	4	8–16	32
18b	NH_2	F	2–4	2–4	0.5–1	0.5	1–2	8	16–32
19[h]	NH_2	F	8	4	1	1	4	32	>64
22	OH	F	2–4	1–2	1	1	1–2	16	>64
25a	H	H	2	2	1	1	2	32	>64
25b	H	F	2	2	1	0.5	2	64	>64

[a] Methicillin-susceptible *S. aureus* UC9213. [b] Methicillin-, ciprofloxacin-, rifampin-, imipenem-resistant *S. aureus* UC12673. [c] Methicillin-resistant *S. epidermidis* UC12084. [d] Penicillin-susceptible *S. pneumoniae* UC9912. [e] *E. faecalis* UC9217. [f] Ampicillin-reisitant *H. influenzae* UC30063. [g] *E. coli* UC6674. [h] Endo diastereomer of **18b**.

Table 2. In Vitro Antibacterial Activity of Selected (Azabicyclo[3.1.0]hexylphenyl)oxazolidinone Analogues



		minimum inhibitory concentration (μg/mL)						
compd	R	S.a.[a]	S.a.[b]	S.e.[c]	S.p.[d]	E.f.[e]	H.i.[f]	E.c.[g]
1	–	2–4	2–4	1	0.5–1	2–4	8–16	>64
26	$NH_2C(O)-$	4	4	2	1	2	32	>64
27	MeNHC(O)–	2	2	1	0.5	1	16	>64
28	$Me_2NHC(O)-$	4	4	2	2	4	64	>64
29	BnONHC(O)–	4	2	1	1	2	>64	>64
30	HONHC(O)–	4	4	2	1	2	32	>64
36	HC(O)NH–	2–4	2–4	1	0.5–1	2	32	>64
37	MeC(O)NH–	4	4	1–2	1	2–4	64	>64
38	$HOCH_2CONH-$	16	16	4	2	8	64	>64
39	$MeSO_2NH-$	4	4	1	1	2	32	>64
40	PhNHC(O)NH–	8	4	2	1	2	>64	>64

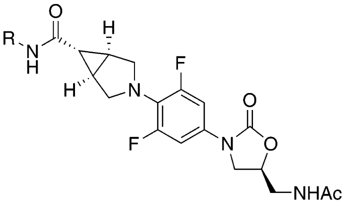
[a] Methicillin-susceptible *S. aureus* UC9213. [b] Methicillin-, ciprofloxacin-, rifampin-, imipenem-resistant *S. aureus* UC12673. [c] Methicillin-resistant *S. epidermidis* UC12084. [d] Penicillin-susceptible *S. pneumoniae* UC9912. [e] *E. faecalis* UC9217. [f] Ampicillin-reisitant *H. influenzae* UC30063. [g] *E. coli* UC6674.

linezolid itself. Hydroxy analogue **22** is structurally the most similar to linezolid and so it was no surprise that the compound exhibited antibacterial properties almost identical to its progenitor. Amino-substituted analogues **18a–b** were the only oxazolidinones in this study to display appreciable activity against the Gram-negative bacterium *Escherichia coli*.

The oxazolidinone analogue **19** features a 6-*endo*-substituted azabicyclic ring and as a result its 6-amino group is positioned quite differently than in the diastereomeric 6-*exo*-azabicyclic analogue **18b**. Comparison of these two analogues in repeated antibacterial screens revealed the inferiority of the endo configuration, with **19** consistently demonstrating 2-fold poorer Gram-positive activity than **18b** and an even greater deficiency in the case of *H. influenzae*. From a practical perspective, this result was fortuitous, since the exo cycloadduct **7** (Scheme 2) is formed preferentially in the initial cyclopropanation reaction leading ultimately to oxazolidinone analogues such as **15** and **18**. Thus, both biological and chemical considerations led us to focus our subsequent efforts exclusively on analogues possessing the exo configuration in the azabicyclic C-ring.

After being pleasantly surprised by the potency of the parent azabicyclic acid and amine analogues, we turned our attention back to the synthetic targets that initially interested us, namely various amide, urea, and sulfonamide analogues derived from azabicyclic acid **15b** and azabicyclic amine **18b**. Table 2 presents antibacterial activity for a number of these derivatives. When compared to the parent amine analogue **18b**, the corresponding acetamide (**37**), sulfonamide (**39**), and phenyl urea (**40**) analogues were less potent, particularly against the Gram-negative strains. Among the azabicyclic amine-derived analogues, only the formamide **36** and sulfonamide **39** displayed Gram-positive activity approaching that of the parent amine **18b**. Against the Gram-negative strains, all of the analogues were much less potent than **18b**. Especially surprising was the poor activity of **38** (*S. aureus* MIC = 16 μg/mL), considering

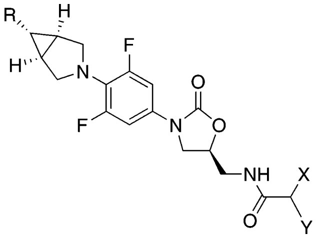
Table 3. In Vitro Antibacterial Activity of 6-Carboxamide-Substituted (Azabicyclo[3.1.0]hexylphenyl)oxazolidinone Analogues



		minimum inhibitory concentration (μg/mL)					
compd	R	S.a.[a]	S.a.[b]	S.e.[c]	S.p.[d]	E.f.[e]	H.i.[f]
1	–	2–4	2–4	1	0.5–1	2–4	8–16
31	1,3-thiazol-2-yl	2	1	0.25	0.13	0.5	>64
32	6-methoxypyridin-3-yl	2	2	1	0.5	1	>64
33	2-furylmethyl	2	2	1	0.5	1	>64
34	pyridin-2-ylmethyl	4	4	1	0.5	1	>64
35	1,3-benzodioxol-5-yl	1	1	0.5	0.5	1	>64

[a] Methicillin-susceptible *S. aureus* UC9213. [b] Methicillin-, ciprofloxacin-, rifampin-, imipenem-resistant *S. aureus* UC12673. [c] Methicillin-resistant *S. epidermidis* UC12084. [d] Penicillin-susceptible *S. pneumoniae* UC9912. [e] *E. faecalis* UC9217. [f] Ampicillin-reisitant *H. influenzae* UC30063.

Table 4. In Vitro Antibacterial Activity of (Azabicyclo[3.1.0]hexylphenyl)oxazolidinone Analogues with Various C-5 Amide Substituents



				minimum inhibitory concentration (μg/mL)					
compd	R	X	Y	S.a.[a]	S.a.[b]	S.e.[c]	S.p.[d]	E.f.[e]	H.i.[f]
1	–	–	–	2–4	2–4	1	0.5–1	2–4	8–16
18b	NH_2	H	H	2–4	2–4	0.5–1	0.5	1–2	8
43	NH_2	cyclopropyl		32	32	16	8	32	>64
44	NH_2	Me	H	4	4	1–2	0.5–1	2–4	8–16
45	NH_2	F	F	4	2	2	1	2	8
46	NH_2	Cl	Cl	4	2	2	0.5	2	4
15b	COOH	H	H	2	1	0.5–1	1	1	4–8
49	COOH	Me	H	2	1	1–2	1–2	1	8
50	COOH	F	F	1	0.5	0.5	1	0.5	4
51	COOH	Cl	Cl	1	0.5	0.5	0.5	0.5	4

[a] Methicillin-susceptible *S. aureus* UC9213. [b] Methicillin-, ciprofloxacin-, rifampin-, imipenem-resistant *S. aureus* UC12673. [c] Methicillin-resistant *S. epidermidis* UC12084. [d] Penicillin-susceptible *S. pneumoniae* UC9912. [e] *E. faecalis* UC9217. [f] Ampicillin-reisitant *H. influenzae* UC30063.

that the glycolyl side chain is often reported to impart improved antibacterial potency.[24] This finding highlights the distinct SAR profile of 6-aminoazabicyclic C-ring analogues as compared to their piperazine C-ring progenitors.

The amide and hydroxamate compounds **26**–**30** (Table 2) are derivatives of the azabicyclic acid analogue **15b**. As in the amine series, the antibacterial activity of these analogues was inferior to that of the parent acid, although some clear SAR trends were apparent. Among the *N*-alkyl amides, the *N*-methyl analogue **27** was the best, exhibiting 2-fold better activity than unsubstituted amide **26** and a 4-fold improvement over *N,N*-dimethyl amide analogue **28**. With a pK_a between that of an acid and a carboxamide, the hydroxamic acid analogue **30** displayed antibacterial activity much more similar to that of the carboxamide **26** than the acid **15b**. Surprisingly, the corresponding benzyl hydroxamate **29** was equipotent to **30** against the Gram-positive panel. This observation prompted us to consider additional amide analogues incorporating larger aromatic and heterocyclic substituents. The antibacterial activities of these extended amide analogues are shown in Table 3. These analogues (**31**–**35**) displayed quite similar Gram-positive activities, comparable and in many cases superior to that of linezolid. None of the analogues however exhibited even a hint of activity against *H. influenzae*, so this approach was not explored further.

Instead, we focused our attention on the crucial C-5 side chain of the oxazolidinone pharmacophore. Previous studies have identified various cyclic and acyclic surrogates for the privileged acetamidomethyl side chain.[25–31] In the case at hand, we chose to replace the acetamide group of linezolid with amides derived from propionic, cyclopropylcarboxylic, dichloroacetic, or difluoroacetic acids. The resulting analogues were tested for antimicrobial activity, and the results are presented in Table 4. In general, these C-5 amide modifications were well-tolerated; only the cyclopropyl amide **43** was significantly less potent than its acetamide congener.

Propionamide analogues **44** and **49** had potencies and spectrum comparable to their acetamide congeners. The dihaloacetamide modification proved the most beneficial with respect to potency, and a notable potentiating effect was observed when these side chain types were combined with the azabicyclic acid C-ring subtype. Thus, difluoroacetamide **50** and dichloroacetamide **51** displayed exceptional activity against key Gram-positive pathogens (MICs ≤ 0.5−1 μg/mL) and also exhibited respectable activity against the fastidious Gram-negative bacterium *H. influenzae* (MIC = 4 μg/mL).

Conclusions

In conclusion, we have identified a novel class of conformationally constrained (azabicyclo[3.1.0]hexylphenyl)oxazolidinones. The SAR profile of this new class is quite unusual in that free amino- and carboxyl-substituted analogues are more potent than their corresponding amido derivatives. A remarkable diversity of functionality is tolerated at C-6 of the azabicyclic C-ring, including the first potent antibacterial oxazolidinones possessing an acidic, carboxylic acid function (e.g., compounds **15a,b** and **49−51**). Nearly all of the analogues examined exhibited therapeutically useful activity against Gram-positive pathogens, whereas activity against the Gram-negative pathogen *H. influenzae* was observed only for analogues bearing compact hydrophilic groups at C-6 of the azabicyclic C-ring. The incorporation of an additional fluorine atom in the phenyl B-ring was found to be generally beneficial. Representatives of this new class possess improved potency and an expanded antibacterial spectrum as compared to linezolid. Specifically, the new compounds **15b**, **46**, **50**, and **51** are more potent than linezolid against the key fastidious Gram-negative pathogen *H. influenzae* and retain good activity against clinically relevant Gram-positive bacteria. These analogues merit further evaluation. On whole, these findings augur well for the development of second-generation oxazolidinones with an expanded antimicrobial spectrum encompassing important Gram-negative pathogens.

Experimental Section

General. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 300 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as an internal standard. Coupling constants (J) are reported in hertz (Hz). All reagents and solvents were purchased from Aldrich Chemical or Acros Organics and used as received unless otherwise indicated. Air and/or moisture sensitive reactions were carried out under a nitrogen atmosphere in oven-dried glassware using anhydrous solvents from commercial suppliers. Air and/or moisture sensitive reagents were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Solvent removal was accomplished with a rotary evaporator at ca. 10−50 Torr. Column chromatography was carried out using EM Science Silica Gel 60 (230−400 mesh). Preparative TLC purification was accomplished using Analtech Uniplate Silica Gel GF (20 × 20 cm) plates with a layer thickness of 2000 μm. Analytical TLC plates from EM Science (Silica Gel 60 F_{254}) were employed for TLC analyses.

Purity of Oxazolidinone Analogues. All oxazolidinone analogues submitted for biological assay were ≥ 95% pure as judged by ^{1}H NMR and HPLC analysis (see Supporting Information). This level of purity is more than sufficient for meaningful SAR analysis, considering the intrinsic variability of standard broth microdilution assay methods (generally considered accurate to within one dilution).

6,6-Dibromo-3-azabicyclo[3.1.0]hexane-3-carboxylic Acid Benzyl Ester (11). A solution of bromoform (0.94 mL, 10.8 mmol) in 5 mL of dichloromethane was added over 1.5 h to a stirred solution of benzyl 3-pyrroline-1-carboxylate (1.77 mL, 9.8 mmol) and benzyltriethylammonium chloride (0.055 g, 0.025 mmol) in 1:1 dichloromethane−50% aq NaOH (60 mL). The black solution was stirred for 18 h at room temperature and then diluted with dichloromethane and H_2O. The layers were separated, and the organic phase was washed with satd NH_4Cl and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−20% ethyl acetate−hexane) to afford 6,6-dibromo-3-azabicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester. Yield: 1.83 g (50%). ^{1}H NMR (300 MHz, $CDCl_3$): 2.43 (m, 2H), 3.66 (m, 4H), 5.11 (s, 2H), 7.33 (m, 5H).

(1α,5α,6α)-6-Hydroxy-3-azabicyclo[3.1.0]hexane-3-carboxylic Acid Benzyl Ester (12). *n*-BuLi (1.64 mL of a 1.6 M solution, 2.62 mmol) was added dropwise over 1 h to a cooled (−95 °C) solution of 6,6-dibromo-3-azabicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (0.85 g, 2.28 mmol) in THF (20 mL). After 10 min, a solution of catechol borane (4.56 mL of a 1.0 M solution, 4.56 mmol) was added dropwise over 30 min. The reaction mixture was allowed to warm slowly to room temperature and then heated at 50 °C for 16 h. After cooling to 0 °C, the reaction mixture was treated with 50% H_2O_2 (0.53 mL, 9.12 mmol) and 2.5 M NaOH (2.7 mL, 6.84 mmol) and stirred for 18 h. The reaction was quenched by addition of satd $Na_2S_2O_3$ and 2.5% $NaHCO_3$. The aqueous solution was concentrated to remove THF and then extracted with three portions of ethyl acetate. Combined organic phases were washed with satd $Na_2S_2O_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (20−50% ethyl acetate−hexane) to afford (1α,5α,6α)-6-hydroxy-3-azabicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester. Yield: 0.076 g (15%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.73 (m, 2H), 1.92 (s, 1H), 3.22 (s, 1H), 3.46 (m, 2H), 3.63 (m, 2H), 5.09 (s, 2H), 7.32 (m, 5H).

(1α,5α,6α)-3-(2-Fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid *tert*-Butyl Ester (13a). Diisopropylethylamine (2.3 mL, 13.2 mmol) and 3,4-difluoronitrobenzene (1.2 g, 10.8 mmol) were added to a solution of (1α,5α,6α)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester[18] (2.2 g, 12.0 mmol) in acetonitrile (20 mL). The mixture was heated at reflux for 4 h and then cooled to room temperature. The solution was concentrated; diluted with ethyl acetate (75 mL); washed with 0.1 M HCl, satd $NaHCO_3$, and brine; and dried ($MgSO_4$). The mixture was filtered and concentrated to give (1α,5α,6α)-3-(2-fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester as a yellow solid. Yield: 2.4 g (63%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.48 (s, 9H), 1.96−2.01 (m, 2H), 2.20 (s, 1H), 3.62 (d, J = 9 Hz, 2H), 3.89 (d, J = 9 Hz, 2H), 7.84−8.01 (m, 3H).

(1α,5α,6α)-3-(4-Benzyloxycarbonylamino-2-fluoro-phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid *tert*-Butyl Ester(14a). Iron metal (1.25 g, 22.3 mmol) was added in five portions over 1 h to a refluxing solution of (1α,5α,6α)-3-(2-fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (2.4 g, 7.44 mmol) and ammonium chloride (4.0 g, 74.4 mmol) in 60 mL of 2:1 ethanol−H_2O. The rust-colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O (50 mL) was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 35 mL portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine and dried ($MgSO_4$). Filtration and concentration gave the crude amine (2.2 g, 7.44 mmol), which was dissolved in 10 mL of dichloromethane. Pyridine (1.2 mL, 14.9 mmol) was added to the amine solution and after cooling to 0 °C, benzyl chloroformate (1.2 mL, 8.2 mmol) was added. The mixture was stirred for 1 h at 0 °C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane (50 mL), washed with H_2O and brine, and then dried ($MgSO_4$). Concentration gave an oil that was purified by column chromatography (0−20% EtOAc−hexane) to afford (1α,5α,6α)-3-(4-benzyloxycarbonylamino-2-fluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield: 2.2 g (69%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.43 (s, 9H), 1.74 (t, *J* = 3 Hz, 1H), 2.07 (s, 2H), 3.23 (d *J* = 9 Hz, 2H), 3.70 (d, *J* = 9 Hz, 2H), 5.15 (s, 2H), 6.45 (s, 1H), 6.54 (t, *J* = 9 Hz, 1H), 7.92 (d, *J* = 9 Hz, 1H), 7.38−7.44 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): 23.8, 25.3, 27.8, 50.9 (J_{C-F} = 5 Hz), 65.7, 79.9, 106.6 (J_{C-F} = 22 Hz), 114.4, 116.8 (J_{C-F} = 6 Hz), 127.9, 127.95, 128.2, 128.3, 131.15 (m), 136.5, 151.3 (J_{C-F} = 239 Hz), 153.1, 171.2.

(*S*)-(1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid (15a). Lithium butoxide solution (2.1 mmol of a 1.0 M THF solution, 2.1 mmol) was added to a cooled (0 °C) solution of (1α,5α,6α)-3-(4-benzyloxycarbonylamino-2-fluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.30 g, 0.7 mmol) in DMF (0.5 mL) and MeOH (0.057 mL, 1.4 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester[16] (0.27 g, 1.4 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq ammonium chloride was added, the solution was extracted with three portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by preparative TLC (5% MeOH-dichloromethane) to provide pure (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield: 0.11 g (36%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.74 (tr, *J* = 3 Hz, 1H), 2.11 (m, 2H), 2.02 (s, 3H), 3.29 (d, *J* = 9 Hz, 2H), 3.54−3.78 (m, 5H), 3.99 (tr, *J* = 9 Hz, 1H), 4.74 (m, 1H), 5.93 (br s, 1H), 6.61 (tr, *J* = 9 Hz, 1H), 7.02 (d, *J* = 9 Hz, 1H), 7.30 (dd, *J* = 18, 2 Hz, 1H). ESI-MS (*m/z*): $[M + H]^+$ = 434.

Trifluoroacetic acid (0.75 mL) was added to a solution of (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.11 g, 0.25 mmol) in 3 mL of dichloromethane. The solution was stirred for 3 h, concentrated, and lyophilized from $H_2O−CH_3CN$ to provide (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid. Yield: 0.090 g (95%). ^{1}H NMR (300 MHz, DMSO): 1.58 (tr, *J* = 3 Hz, 1H), 1.81 (s, 3H), 2.09 (m, 2H), 3.23 (d, *J* = 9 Hz, 2H), 3.38 (tr, *J* = 5 Hz, 2H), 3.60−3.68 (m, 3H), 4.03 (tr, *J* = 9 Hz, 1H), 4.67 (m, 1H), 6.76 (tr, *J* = 10 Hz, 1H), 7.08 (dd, *J* = 9, 2 Hz, 1H), 7.38 (dd, *J* = 16, 2 Hz, 1H), 8.23 (tr, *J* = 6 Hz, 1H). ESI-MS (*m/z*): $[M + H]^+$ = 378.

(1α,5α,6α)-3-(2,6-Difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid *tert*-Butyl Ester (13b). Palladium hydroxide (10% on carbon, 0.25 g) was added to a solution of (1α,5α,6α)-3-benzyloxycarbonyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.800 g, 2.52 mmol) in 15 mL of methanol. The mixture was stirred under a hydrogen atmosphere for 1.5 h. The palladium was then removed by filtration through a pad of Celite and the filtrate concentrated to give 0.423 g of (1α,5α,6α)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Diisopropylethylamine (0.55 mL, 3.15 mmol) and 3,4,5-trifluoronitrobenzene (0.372 g, 2.1 mmol) were added to a solution of (1α,5α,6α)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.423 g, 2.31 mmol) in 5 mL of DMF. The mixture was heated for 20 h at 50 °C and then cooled to room temperature. The solution was diluted with ethyl acetate; washed with 0.5 M HCl, satd. $NaHCO_3$, and brine; and dried ($MgSO_4$). The mixture was filtered and concentrated to give the product as a yellow solid. Yield: 0.791 g (92%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.60 (m, 1 H), 2.13 (m, 2H), 3.77 (d, *J* = 11 Hz, 2H), 3.99 (d, *J* = 11 Hz, 2H), 7.72 (d, *J* = 9 Hz, 2H).

(1α,5α,6α)-3-(4-Benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid *tert*-Butyl Ester (14b). Iron metal (0.39 g, 7.0 mmol) was added in five portions over 1 h to a refluxing solution of (1α,5α,6α)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.79 g, 2.32 mmol) and ammonium chloride (1.25 g, 23.2 mmol) in 50 mL of 2:1 ethanol−H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O (50 mL) was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 25 mL portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.59 g, 1.9 mmol) which was dissolved in 30 mL of dichloromethane. Pyridine (0.31 mL, 3.8 mmol) was added to the amine solution, and after cooling to 0 °C, benzyl chloroformate (0.32 mL, 2.2 mmol) was added. The mixture was stirred for 1 h at 0 °C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane, washed with H_2O and brine, and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford (1α,5α,6α)-3-(4-benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester as a yellow solid. Yield: 0.71 g (69%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.84 (m, 1H), 2.01 (m, 2H), 3.48 (s, 4H), 5.18 (s, 2H), 6.55 (s, 1 H), 6.91 (d, *J* = 11 Hz, 2H), 7.35−7.40 (m, 5 H). ESI-MS (*m/z*): $[M + H]^+$ = 445.

(*S*)-(1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid (15b). Lithium butoxide solution (3.6 mmol of a 1.0 M THF solution, 3.6 mmol) was added to a cooled (0 °C) solution of (1α,5α,6α)-3-(4-benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.53 g, 1.19 mmol) in DMF (0.8 mL) and MeOH (0.097 mL, 2.4 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester (0.457 g, 2.4 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq NH_4Cl (3 mL) was added, along with 15 mL of H_2O and 15 mL of brine. The solution was extracted with three portions of dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−2% MeOH−dichloromethane) to provide pure (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield: 0.4 g (72%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.47 (s, 9 H), 1.81 (m, 1H), 2.01 (m, 2 H), 2.02 (s, 3H), 3.49−3.72 (m, 7 H), 3.97 (tr, *J* = 9 Hz, 1H), 4.75 (m, 1H), 6.10 (tr, *J* = 6 Hz, 1H), 7.03 (d, *J* = 11 Hz, 2H). ESI-MS (*m/z*): $[M + H]^+$ = 452.

Trifluoroacetic acid (0.75 mL) was added to a solution of (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.129 g, 0.29 mmol) in 3 mL of dichloromethane. The solution was stirred for 3 h and then concentrated to give the trifluoroacetic acid salt of (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid as a tan solid. Yield: 0.148 g (99%). ^{1}H NMR (300 MHz, DMSO): 1.65 (tr, *J* = 3 Hz, 1H), 1.82 (s, 3H), 2.03 (m, 2H), 3.37−3.69 (m, 7H), 4.05 (tr, *J* = 9 Hz, 1H), 4.71 (m, 1H), 7.23 (d, *J* = 12 Hz, 2H), 8.23 (tr, *J* = 6 Hz, 1H). ESI-MS (*m/z*): $[M + H]^+$ = 396.

[(1α,5α,6α)-3-(2-Fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]-hex-6-yl]carbamic Acid *tert*-Butyl Ester (16a). Diisopropylethylamine (0.19 mL, 1.095 mmol) and 3,4-difluoronitrobenzene (0.105 g, 0.66 mmol) were added to a solution (1α,5α,6α)-6-*tert*-butoxycarbonylamine-3-azabicyclo[3.1.0]hexane (0.144 g, 073 mmol) in DMF (2 mL). The mixture was heated for 18 h at 50 °C and then cooled to room temperature. The solution was diluted with ethyl acetate; washed with 0.5 M HCl, satd $NaHCO_3$, and brine; and dried ($MgSO_4$). The mixture was filtered and concentrated to give [(1α,5α,6α)-3-(2-fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester as a yellow solid. Yield: 0.208 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.90 (s, 2H), 2.41 (s, 1H), 3.62

(d, J = 9 Hz, 2H), 3.91 (br d, J = 8 Hz, 2H), 4.75 (br s, 1H), 6.51 (tr, J = 9 Hz, 1H), 7.83−7.93 (m, 2H).

[(1α,5α,6α)-3-(4-Benzyloxycarbonylamino-2-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic Acid *tert*-Butyl Ester (17a). Iron metal (0.102 g, 1.82 mmol) was added in five portions over 1 h to a refluxing solution of [(1α,5α,6α)-3-(2-fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester (0.205 g, 0.608 mmol) and ammonium chloride (0.367 g, 6.8 mmol) in 4.5 mL of 2:1 ethanol−H_2O. The rust-colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 20 mL portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.171 g, 0.55 mmol) which was dissolved in 3.0 mL of dichloromethane. Pyridine (0.089 mL, 1.1 mmol) was added to the amine solution, and after cooling to 0 °C, benzyl chloroformate (0.090 mL, 0.63 mmol) was added. The mixture was stirred for 30 min at 0 °C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane, washed with H_2O and brine, and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [(1α,5α,6α)-3-(4-benzyloxycarbonylamino-2-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester as a yellow solid. Yield: 0.230 g (86%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 1.74 (s, 2H), 2.61 (s, 1H), 3.22 (d, J = 8.7 Hz, 2H), 3.75 (d, J = 8.4 Hz, 2H), 4.71 (br s, 1H), 5.17 (s, 2H), 6.52−6.58 (m, 2H), 6.88 (d, J = 7 Hz, 1H), 7.15−7.41 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): 23.8, 25.3, 27.8, 50.8 (J_{C-F} = 5 Hz), 65.7, 79.8, 106.6 (J_{C-F} = 25 Hz), 114.4, 116.8 (J_{C-F} = 5 Hz), 127.8, 127.9, 128.1, 128.3, 131.1 (m), 136.4, 151.3 (J_{C-F} = 238 Hz), 153.1, 171.2

(*S*)-*N*-{3-[4-((1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (18a). Lithium butoxide solution (1.15 mL of a 1.0 M THF solution, 1.15 mmol) was added to a cooled (0 °C) solution of [(1α,5α,6α)-3-(4-benzyloxycarbonylamino-2-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester (0.170 g, 0.385 mmol) in DMF (0.35 mL) and MeOH (0.031 mL, 0.771 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester[16] (0.149 g, 0.771 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq ammonium chloride (0.8 mL) was added, along with 7 mL of H_2O and 6 mL of brine. The solution was extracted with three portions of dichloromethan and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−3% MeOH−CH_2Cl_2) to provide (*S*)-((1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)carbamic acid *tert*-butyl ester. Yield: 0.115 g (66%). ESI-MS (*m*/*z*): $[M + H]^+$ = 449.

A 4.0 M solution of HCl in dioxane (1.0 mL) was added to (*S*)-((1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)carbamic acid *tert*-butyl ester (0.046 g, 0.103) in 1.0 mL of dioxane. The reaction mixture was stirred at room temperature for 2 h and then concentrated to provide (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide as the hydrochloride salt. Yield: 0.039 g (99%). ^{1}H NMR (300 MHz, DMSO): 1.82 (s, 3H), 2.02 (br s, 2H), 2.58 (br s, 1H), 3.20 (d, J = 9 Hz, 2H), 3.34−3.69 (m, 5 H), 4.05 (tr, J = 9 Hz, 1H), 4.68 (m, 1H), 6.79 (tr, J = 9 Hz, 1H), 7.10 (dd, J = 9, 2 Hz, 1H), 7.40 (dd, J = 16, 2 Hz, 1H), 8.20 (br s, 2H), 8.25 (tr, J = 6 Hz, 1H). ESI-MS (*m*/*z*): $[M + H]^+$ = 349.

[(1α,5α,6α)-3-(2,6-Difluoro-4-nitrophenyl)-3-azabicyclo-[3.1.0]hex-6-yl]carbamic Acid *tert*-Butyl Ester (16b). Diisopropylethylamine (0.17 mL, 0.96 mmol) and 3,4,5-trifluoronitrobenzene (0.113 g, 0.64 mmol) were added to a solution of (1α,5α,6α)-6-*tert*-butoxycarbonylamine-3-azabicyclo[3.1.0]-hexane (0.14 g, 0.7 mmol) in acetonitrile (3 mL). The mixture was heated for 3 h at reflux and then cooled to room temperature. The solution was concentrated, diluted with ethyl acetate, and washed with 0.5 M HCl, satd $NaHCO_3$, brine, and dried (Na_2SO_4). The mixture was filtered and concentrated to give [(1α,5α,6α)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo-[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester as a yellow solid. Yield: 0.210 g (93%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 1.80 (s, 2H), 2.47 (s, 1H), 3.75 (d, J = 10.8 Hz, 2H), 4.02 (d, J = 10.2 Hz, 2H), 4.70 (br s, 1H), 7.70 (dd, J = 9, 2 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 23.0, 28.2, 32.1, 52.4 (t, J_{C-F} = 8 Hz), 77.8, 109.2 (J_{C-F} = 30 Hz), 132.2 (t, J_{C-F} = 11 Hz), 135.4, 151.0 (dd, J_{C-F} = 244, 11 Hz), 155.6.

[(1α,5α,6α)-3-(4-Benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic Acid *tert*-Butyl Ester (17b). Iron metal (0.047 g, 0.84 mmol) was added in five portions over 1 h to a refluxing solution of [(1α,5α,6α)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester (0.10 g, 0.28 mmol) and ammonium chloride (0.148 g, 2.8 mmol) in 2.5 mL of 2:1 ethanol−H_2O. The rust-colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 15 mL portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.091 g, 0.28 mmol) which was dissolved in 1.5 mL of dichloromethane. Pyridine (0.046 mL, 0.57 mmol) was added to the amine solution, and after cooling to 0 °C, benzyl chloroformate (0.046 mL, 0.32 mmol) was added. The mixture was stirred for 30 min at 0 °C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane, washed with H_2O and brine, and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [(1α,5α,6α)-3-(4-benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo-[3.1. 0]hex-6-yl]carbamic acid *tert*-butyl ester as a yellow solid. Yield: 0.100 g (77%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 1.67 (s, 2H), 2.75 (s, 1H), 3.49 (m, 4H), 4.65 (br s, 1H), 5.18 (s, 2H), 6.56 (br s, 1H), 6.90 (d, J = 11 Hz, 2H), 7.36 (m, 5H).

(*S*)-*N*-{3-[4-((1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (18b). Lithium butoxide solution (0.61 mL of a 1.0 M THF solution, 0.61 mmol) was added to a cooled (0 °C) solution of [(1α,5α,6α)-3-(4-benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester (0.093 g, 0.203 mmol) in DMF (0.14 mL) and MeOH (0.016 mL, 0.406 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester (0.078 g, 0.406 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq ammonium chloride (0.5 mL) was added, along with 4 mL of H_2O and 3 mL of brine. The solution was extracted with three portions of dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−2% MeOH−dichloromethane) to provide (*S*)-((1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)carbamic acid *tert*-butyl ester. Yield: 0.066 g (70%). ESI-MS (*m*/*z*): $[M + H]^+$ = 467.

A 4.0 M solution of HCl in dioxane (1.5 mL) was added to (*S*)-((1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)carbamic acid *tert*-butyl ester (0.066 g, 0.142) in 1.5 mL of dioxane. The reaction mixture was stirred at room temperature for 2 h and then concentrated. The resulting solid was lyophilized from acetonitrile−water to provide (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide as the hydrochloride salt. Yield: 0.054 g (95%). ^{1}H NMR (300 MHz, $CDCl_3$−CD_3OD): 1.85 (s, 3H), 1.89 (br s, 2H), 2.60 (br s, 1H), 3.21−3.42 (m, 6H), 3.58 (tr, J = 6 Hz, 1H), 3.87 (tr, J = 3 Hz, 1H), 4.62 (m, 1H), 6.93 (d, = 11 Hz, 2H). ESI-MS (*m*/*z*): $[M + H]^+$ = 367.

(*S*)-*N*-{3-[4-((1α,5α,6*β*)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}-

acetamide (19). Lithium butoxide solution (1.53 mL of a 1.0 M THF solution, 1.53 mmol) was added to a cooled (0 °C) solution of [(1α,5α,6β)-3-(4-benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1. 0]hex-6-yl]carbamic acid *tert*-butyl ester (0.175 g, 0.38 mmol, prepared in an analogous fashion as **17b**) in DMF (0.25 mL) and MeOH (0.031 mL, 0.76 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester (0.147 g, 0.76 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq ammonium chloride (0.5 mL) was added, along with 4 mL of H_2O and 3 mL of brine. The solution was extracted with three portions of dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−3% MeOH−dichloromethane) to provide (*S*)-((1α,5α,6β)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)carbamic acid *tert*-butyl ester. Yield: 0.102 g (58%). ^1H NMR (300 MHz, $CDCl_3$): 1.46 (m, 9H), 1.72 (d, $J = 8$ Hz, 2H), 2.03 (s, 3H), 3.23 (q, $J = 8$ Hz, 1H), 3.34 (d, $J = 9$ Hz, 2H), 3.63−3.68 (m, 4H), 3.75 (dd, $J = 9, 7$ Hz, 1H), 4.00 (tr, $J = 9$ Hz, 1H), 4.78 (m, 1H), 5.48 (br s, 1H), 6.46 (br s, 1H), 7.09 (d, $J = 11$ Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 467$.

A 4.0 M solution of HCl in dioxane (2.0 mL) was added to (*S*)-((1α,5α,6β)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)carbamic acid *tert*-butyl ester (0.100 g, 0.215) in 2.0 mL of dioxane. The reaction mixture was stirred at room temperature for 2 h and then concentrated to give (*S*)-*N*-{3-[4-((1α,5α,6β)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide as the hydrochloride salt. Yield: 0.086 g (99%). ^1H NMR (300 MHz, DMSO): 1.82 (s, 3H), 1.90 (d, $J = 8$ Hz, 2H), 2.73 (tr, $J = 8$ Hz, 1H), 3.28−3.61 (m, 7H), 4.08 (tr, $J = 9$ Hz, 1H), 4.74 (m, 1H), 7.29 (d, $J = 12$ Hz, 2H), 7.96 (br s, 2H), 8.26 (tr, $J = 6$ Hz, 1H). ESI-MS (*m/z*): $[M + H]^+ = 367$.

(1α,5α,6α)-6-(*tert*-Butyldimethylsilyloxy)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane (20). Palladium hydroxide (0.030 g, 10% on carbon) was added to a solution of (1α,5α,6α)-6-hydroxy-3-azabicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (0.071 g, 0.3 mmol) in methanol (2 mL). The mixture was stirred under a hydrogen atmosphere for 3 h and then filtered through a pad of Celite and concentrated to give (1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-ol as a solid film. The amine was dissolved in DMF (0.75 mL) and treated with diisopropylethylamine (0.078 mL, 0.45 mmol) and 3,4,5-trifluoronitrobenzene (0.048 g, 0.27 mmol). The mixture was heated for 12 h at 50 °C; diluted with ethyl acetate; washed with 0.5 M HCl, satd $NaHCO_3$, and brine; and dried ($MgSO_4$). The mixture was filtered and concentrated to give (1α,5α,6α)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexan-6-ol. Yield: 0.070 g (91%).

Imidazole (0.033 g, 0.49 mmol) and *tert*-butyldimethylsilyl chloride (0.065 g, 0.43 mmol) were added to a solution of (1α,5α,6α)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]-hexan-6-ol (0.070 g, 0.27 mmol) in dichloromethane (3.0 mL). After 3 h, satd $NaHCO_3$ was added, and the layers were separated. The aqueous phase was extracted with more dichloromethane, and the combined organic phases were washed with 0.3 M HCl, satd. $NaHCO_3$, and brine and dried ($MgSO_4$). The mixture was filtered and concentrated to provide (1α,5α,6α)-6-(*tert*-butyldimethylsilyloxy)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane. Yield: 0.088 g (88%). ^1H NMR (300 MHz, $CDCl_3$): 0.12 (s, 6H), 0.90 (s, 9H), 1.73 (m, 2H), 3.19 (s, 1H), 3.74 (dd, $J = 9, 2$ Hz, 2H), 3.93 (m, 2H), 7.70 (dd, $J = 9, 2$ Hz, 2H).

{4-[(1α,5α,6α)-6-(*tert*-Butyldimethylsilanyloxy)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}carbamic Acid Benzyl Ester (21). Iron metal (0.039 g, 0.713 mmol) was added in five portions over 1 h to a refluxing solution of (1α,5α,6α)-6-(*tert*-butyldimethylsilanyloxy)-3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane (0.088 g, 0.24 mmol) and ammonium chloride (0.129 g, 2.38 mmol) in 2.5 mL of 2:1 ethanol−H_2O. The rust-colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 15 mL portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.078 g, 0.23 mmol) which was dissolved in 1.5 mL of dichloromethane. Pyridine (0.037 mL, 0.46 mmol) was added to the amine solution and after cooling to 0 °C, benzyl chloroformate (0.037 mL, 0.26 mmol) was added. The mixture was stirred for 30 min at 0 °C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane, washed with H_2O and brine, and then dried ($MgSO_4$). Concentration gave an oil that was triturated with hexane and purified by column chromatography (0−10% ethyl acetate−hexane) to afford {4-[(1α,5α,6α)-6-(*tert*-butyldimethylsilanyloxy)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-carbamic acid benzyl ester. Yield: 0.078 g (70%). ^1H NMR (300 MHz, $CDCl_3$): 0.12 (s, 6H), 0.91 (s, 9H), 1.60 (m, 2H), 3.44 (m, 5H), 5.18 (s, 2H), 6.51 (br s, 1H), 6.89 (d, $J = 12$ Hz, 2H), 7.28−7.40 (m, 5H).

(*S*)-*N*-{3-[3,5-Difluoro-4-((1α,5α,6α)-6-hydroxy-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (22). Lithium butoxide solution (0.53 mL of a 1.0 M THF solution, 0.53 mmol) was added to a cooled (0 °C) solution of {4-[(1α,5α,6α)-6-(*tert*-butyldimethylsilanyloxy)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}carbamic acid benzyl ester (0.077 g, 0.16 mmol) in DMF (0.1 mL) and MeOH (0.013 mL, 0.32 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester (0.062 g, 0.32 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq ammonium chloride (0.5 mL) was added, along with 4 mL of H_2O and 3 mL of brine. The solution was extracted with three portions of dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−2% MeOH−dichloromethane) to provide (*S*)-*N*-(3-{4-[(1α,5α,6α)-6-(*tert*-butyldimethylsilanyloxy)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxooxazolidin-5-ylmethyl)acetamide. Yield: 0.056 g (73%).

Hydrogen fluoride (2.0 μL of a 48% solution) was added to a solution of (*S*)-*N*-(3-{4-[(1α,5α,6α)-6-(*tert*-butyldimethylsilanyloxy)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxooxazolidin-5-ylmethyl)acetamide (0.027 g, 0.056 mmol) in 4 mL of acetic acid−THF−H_2O (2:1:1). The reaction mixture was stirred for 4 h at room temperature and then the THF was removed in vacuo. The aqueous solution was diluted with 2.5% $NaHCO_3$ and extracted with three portions of ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The product was triturated with hexane to provide pure (*S*)-*N*-{3-[3,5-difluoro-4-((1α,5α,6α)-6-hydroxy-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide as a white solid. Yield: 0.017 g (85%). ^1H NMR (300 MHz, CD_3OD): 1.62 (s, 2H), 1.95 (s, 3H), 3.43−3.54 (m, 7H), 3.72 (m, 1H), 4.06 (tr, $J = 9$ Hz, 1H), 4.76 (m, 1H), 7.13 (d, $J = 12$ Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 368$.

3-(2-Fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane (23a). Diisopropylethylamine (0.56 mL, 3.2 mmol) and 3,4-difluoronitrobenzene (0.184 g, 1.16 mmol) were added to a solution 3-azabicyclo[3.1.0]hexane (0.152 g of HCl salt, 1.28 mmol) in DMF (3.2 mL). The mixture was heated for 3 days at 45 °C and then cooled to room temperature. The solution was diluted with ethyl acetate; washed with 0.5 M HCl, satd $NaHCO_3$, and brine; and dried ($MgSO_4$). The mixture was filtered and concentrated to give 3-(2-fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane as a yellow solid. Yield: 0.233 g (82%). ^1H NMR (300 MHz, $CDCl_3$): 0.33 (qt, $J = 4.5$ Hz, 1H), 0.75−0.82 (m, 1H), 1.68 (m, 2H), 3.58 (d, $J = 10$ Hz, 2H), 3.80 (dd, $J = 10, 3$ Hz, 2H), 6.53 (tr, $J = 9$ Hz, 1H), 7.82−7.93 (m, 2H).

[4-(3-Azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]carbamic Acid Benzyl Ester (24a). Iron metal (0.168 g, 3.15 mmol) was added in five portions over 1 h to a refluxing solution of 3-(2-fluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane (0.233 g, 1.05 mmol) and ammonium chloride (0.566 g, 10.5 mmol) in 7.5 mL of 2:1 ethanol−H_2O. The rust-colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 20 mL portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.194 g, 0.99 mmol) which was dissolved in 8.0 mL of dichloromethane. Pyridine (0.160 mL, 2.0 mmol) was added to the amine solution, and after cooling to 0 °C, benzyl chloroformate (0.162 mL, 1.14 mmol) was added. The mixture was stirred for 30 min at 0 °C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane, washed with H_2O and brine, and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [4-(3-azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]carbamic acid benzyl ester as a yellow solid. Yield: 0.299 g (87%). ^1H NMR (300 MHz, $CDCl_3$): 0.61 (m, 2H), 1.56 (br s, 2H), 3.21 (d, J = 8.5 Hz, 2H), 3.65 (dd, J = 9, 2 Hz, 2H), 5.18 (s, 2H), 6.49 (br s, 1H), 6.63 (br s, 1H), 6.88 (d, J = 9 Hz, 1H), 7.17−7.41 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 8.5, 15.5, 51.7 (J_{C-F} = 6 Hz), 66.9, 108.4 (J_{C-F} = 30 Hz), 115.1, 116.0, 128.15, 128.17, 128.3, 128.5, 133.6 (J_{C-F} = 9 Hz), 136.0, 151.8 (J_{C-F} = 241 Hz), 153.4.

(*S*)-*N*-{3-[4-(3-Azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (25a). Lithium butoxide solution (2.5 mL of a 1.0 M THF solution, 2.5 mmol) was added to a cooled (0 °C) solution of [4-(3-azabicyclo[3.1.0]-hex-3-yl)-3-fluorophenyl]carbamic acid benzyl ester (0.267 g, 0.82 mmol) in DMF (0.6 mL) and MeOH (0.060 mL, 1.64 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester (0.316 g, 1.64 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq ammonium chloride (1.0 mL) was added, along with 9 mL of H_2O and 8 mL of brine. The solution was extracted with three portions of dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−3% MeOH−dichloromethane) to provide (*S*)-*N*-{3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide. Yield: 0.169 g (62%). ^1H NMR (300 MHz, $CDCl_3$): 0.49 (m, 1H), 0.61 (m, 1H), 1.56 (m, 2H), 2.01 (s, 3H), 3.22 (d, J = 9 Hz, 2H), 3.56−3.68 (m, 5 H), 3.97 (tr, J = 9 Hz, 1H), 4.75 (m, 1H), 6.46 (tr, J = 6 Hz, 1H), 6.59 (tr, J = 9 Hz, 1H), 6.96 (dd, J = 9, 3 Hz, 1H), 7.27 (dd, J = 15, 2 Hz, 1H). ESI-MS (*m/z*): $[M + H]^+$ = 334.

3-(2,6-Difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]-hexane (23b). Diisopropylethylamine (0.39 mL, 2.25 mmol) and 3,4,5-trifluoronitrobenzene (0.143 g, 0.81 mmol) were added to a solution 3-azabicyclo[3.1.0]hexane (0.106 g of the HCl salt, 0.9 mmol) in DMF (2 mL). The mixture was heated for 3 days at 45 °C and then cooled to room temperature. The solution was diluted with ethyl acetate; washed with 0.5 M HCl, satd $NaHCO_3$, and brine; and dried ($MgSO_4$). The mixture was filtered and concentrated to give 3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]hexane as a yellow solid. Yield: 0.177 g (82%). ^1H NMR (300 MHz, $CDCl_3$): 0.35 (q, J = 4 Hz, 1H), 0.66 (m, 1H), 1.58 (m, 2H), 3.70 (d, J = 10.5 Hz, 2H), 3.90 (d tr, J = 10.5, 2 Hz, 2H), 7.71 (dd, J = 10, 2 Hz, 2H).

[4-(3-Azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]carbamic Acid Benzyl Ester (24b). Iron metal (0.120 g, 2.15 mmol) was added in five portions over 1 h to a refluxing solution of 3-(2,6-difluoro-4-nitrophenyl)-3-azabicyclo[3.1.0]-hexane (0.172 g, 0.72 mmol) and ammonium chloride (0.385 g, 7.2 mmol) in 6.0 mL of 2:1 ethanolH_2O. The rust-colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 20 mL portions of ethyl acetate, and the combined organic phases were washed with H_2O and brine and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.145 g, 0.69 mmol) which was dissolved in 5.0 mL of dichloromethane. Pyridine (0.111 mL, 1.38 mmol) was added to the amine solution, and after cooling to 0 °C, benzyl chloroformate (0.113 mL, 0.79 mmol) was added. The mixture was stirred for 30 min at 0 °C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane, washed with H_2O and brine, and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [4-(3-azabicyclo-[3.1.0]hex-3-yl)-3,5-difluorophenyl]carbamic acid benzyl ester as a yellow solid. Yield: 0.195 g (79%). ^1H NMR (300 MHz, $CDCl_3$): 0.52 (m, 1H), 0.61 (q, J = 4 Hz, 1H), 1.45 (br s, 2H), 3.43 (m, 4H), 5.18 (s, 2H), 6.54 (br s, 1H), 6.90 (d, J = 11 Hz, 2H), 7.36 (m, 5H).

(*S*)-*N*-{3-[4-(3-Azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (25b). Lithium butoxide solution (1.6 mL of a 1.0 M THF solution, 1.6 mmol) was added to a cooled (0 °C) solution of [4-(3-azabicyclo[3.1.0]-hex-3-yl)-3,5-difluorophenyl]carbamic acid benzyl ester (0.180 g, 0.52 mmol) in DMF (0.35 mL) and MeOH (0.042 mL, 1.05 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethylethyl ester (0.203 g, 1.05 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Satd aq ammonium chloride (0.8 mL) was added, along with 7 mL of H_2O and 6 mL of brine. The solution was extracted with three portions of dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−2% MeOH-dichloromethane) to provide (*S*)-*N*-{3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide. Yield: 0.127 g (70%). ^1H NMR (300 MHz, $CDCl_3$): 0.53 (m, 2H), 1.47 (m, 2H), 2.02 (s, 3H), 3.48 (m, 4H), 3.50−3.74 (m, 3H), 3.96 (tr, J = 9 Hz, 1H), 4.74 (m, 1H), 5.98 (tr, J = 5 Hz, 1H), 7.00 (d, J = 12 Hz, 2H). ESI-MS (*m/z*): $[M + H]^+$ = 352.

(*S*)-(1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid Amide (26). Diisopropylethylamine (19 μL, 0.11 mmol) and HATU (21 mg, 0.055 mmol) were add to a solution of (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (14 mg of the TFA salt, 0.028 mmol) in 0.7 mL of DMF. Ammonium chloride (3.0 mg, 0.055 mmol) was then added and the mixture stirred at room temperature for 5 h. The reaction mixture was then concentrated and the crude product purified by preparative HPLC to provide (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid amide. Yield: 0.005 g (47%). ^1H NMR (300 MHz, DMSO): 1.76 (tr, J = 3 Hz, 1H), 1.82 (s, 3H), 1.87 (m, 2H), 3.37−3.70 (m, 7H), 4.06 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 6.81 (s, 1H), 7.23 (d, J = 12 Hz, 2H), 7.57 (s, 1H), 8.24 (tr, J = 6 Hz, 1H). ESI-MS (*m/z*): $[M + H]^+$ = 395.

(*S*)-(1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid Methylamide (27). ^1H NMR (300 MHz, DMSO): 1.74 (m, 1H), 1.82 (s, 3H), 1.88 (m, 2H), 2.57 (d, J = 5 Hz, 3H), 3.16−3.41 (m, 6H), 3.66 (tr, J = 8 Hz, 1H), 4.06 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 7.23 (d, J = 12 Hz, 2H), 8.02 (q, J = 5 Hz, 1H), 8.23 (m, 1H). ESI-MS (*m/z*): $[M + H]^+$ = 409.

(*S*)-(1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid Dimethylamide (28). Diisopropylethylamine (23 μL, 0.13 mmol) and HATU (24 mg, 0.064 mmol) were add to a solution of (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo-[3.1.0]hexane-6-carboxylic acid (17 mg of the TFA salt, 0.033 mmol) in 0.8 mL of DMF. Dimethylamine (6.3 μL of a 40% aq solution, 0.049 mmol) was then added and the mixture stirred at room temperature for 4 h. The reaction mixture was then concentrated and the crude product purified by preparative HPLC to provide (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azaicyclo[3.1.0]-hexane-6-carboxylic acid dimethylamide. Yield: 0.005 g (37%). ^1H NMR (300 MHz, DMSO): 1.82 (s, 3H), 1.94 (m, 2H), 1.97 (tr, J = 3 Hz, 1H), 2.83 (s, 3H), 3.09 (s, 3H), 3.37−4.05 (m, 8H), 4.71 (m, 1H), 7.23 (d, *J* = 13 Hz, 2H), 8.23 (tr, *J* = 6 Hz, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 423.

(*S*)-(1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid Benzyloxyamide (29). Pyridine (0.014 mL, 0.17 mmol) and then pentafluorophenyltrifluoroacetate (0.015 mL, 0.086 mmol) were added to a solution of (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.022 g, 0.055 mmol) in 0.2 mL of DMF. The mixture was stirred at room temperature for 2 h. The solution was then diluted with ethyl acetate, washed with dilute HCl and brine, dried (MgSO$_4$), filtered, and concentrated to give (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid pentafluorophenyl ester (0.031 g, 0.055 mmol) that was dissolved in 0.3 mL of DMF. Diisopropylethylamine (0.014 mL, 0.083 mmol) and *O*-benzylhydroxylamine (7 μL, 0.066 mmol) were added to this solution. After 2 h, the reaction mixture was diluted with ethyl acetate, washed with dilute HCl and brine, dried (MgSO$_4$), filtered, and concentrated. Purification by preparative TLC (5% MeOH−dichloromethane) gave pure (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid benzyloxyamide. Yield: 0.017 g (63%). ^{1}H NMR (300 MHz, DMSO): 1.64 (m, 1H), 1.82 (s, 3H), 1.95 (m, 2H), 3.33−3.45 (m, 6H), 3.67 (m, 1H), 4.05 (tr, *J* = 10 Hz, 1H), 4.71 (m, 1H), 4.79 (s, 2H), 7.23 (d, *J* = 12 Hz, 2H), 7.36−7.38 (m, 5H), 8.24 (tr, *J* = 5 Hz, 1H), 11.1 (s, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 502.

(*S*)-(1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid Hydroxyamide (30). Palladium (5 mg of 10% Pd on carbon) was added to a solution of (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid benzyloxyamide (0.013 g, 0.026 mmol) in 2 mL of ethanol. The mixture was stirred 2 h under a hydrogen atmosphere and then filtered through Celite. The filtrate was concentrated and the glassy solid obtained was lyophilized to give pure (*S*)-(1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid hydroxyamide as a white solid. Yield: 9 mg (84%). ^{1}H NMR (300 MHz, CD$_3$OD): 1.74 (tr, *J* = 3 Hz, 1H), 1.95 (s, 3H), 2.03 (m, 2H), 3.50−3.76 (m, 7H), 4.07 (tr, *J* = 9 Hz, 1H), 4.76 (m, 1H), 7.16 (d, *J* = 12 Hz, 2H). ESI-MS (*m/z*): [M + H]$^+$ = 411.

(*S*)-(1α,5α,6α)-3-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-*N*-(2-furylmethyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide (33). A solution of (*S*)-(1α,5α,6α)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.8 g, 1.57 mmol) in DMF (6 mL) and pyridine (0.51 mL, 6.28 mmol) was treated with pentafluorophenyl trifluoroacetate (0.54 mL, 3.14 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was dissolved in EtOAc; washed with 0.1 N HCl, water, and brine; dried over MgSO$_4$; and concentrated. The resulting pentafluorophenyl ester intermediate (0.075 g, 0.13 mmol) was dissolved in DMF (2 mL), and to this solution, furfurylamine (0.035 mL, 0.4 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was dissolved in EtOAc, washed with water and brine, dried over MgSO$_4$, and concentrated. The title compound was isolated by pTLC (5% MeOH/dichloromethane). Yield: 0.043 g (70%). ^{1}H NMR (300 MHz, DMSO-d_6): 1.81−1.84 (m, 4H) 1.90 (s, 2H), 3.35−3.41 (m, 6H), 3.62−3.68 (m, 1H), 4.01−4.07 (t, *J* = 9 Hz, 1H), 4.23−4.25 (d, *J* = 9 Hz, 3H), 4.67−4.72 (m, 1H), 6.21−6.23 (d, *J* = 4 Hz, 1H), 6.36−6.38 (d, *J* = 4 Hz, 1H), 7.19−7.23 (d, *J* = 9 Hz, 2H), 7.56 (s, 1H), 8.20−8.24 (t, *J* = 4 Hz, 1H), 8.53−8.57(t, *J* = 4 Hz, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 475.4.

(*S*)-(1α,5α,6α)-3-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-*N*-(pyridin-2-ylmethyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide (34). The title compound was prepared in 67% yield using the procedure described for **33**, but using 2-(aminomethyl)pyridine in reaction with the pentafluorophenyl ester intermediate. ^{1}H NMR (300 MHz, DMSO-d_6): 1.82 (br s, 2H), 1.90 (br s, 1H), 1.92 (s, 3H), 3.26−3.44 (m, 6H), 3.63−3.69 (m, 1H), 4.05 (tr, *J* = 9 Hz, 1H), 4.36 (m, 2H), 4.67−4.73 (m, 1H), 7.19−7.28 (m, 4H), 7.76 (dt, *J* = 8, 2 Hz, 1H), 8.22 (tr, *J* = 6 Hz, 1H), 8.48 (d, *J* = 3 Hz, 1H), 8.71 (tr, *J* = 3 Hz, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 486.5.

(*S*)-(1α,5α,6α)-3-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-*N*-(1,3-thiazol-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide (31). The title compound was prepared in 66% yield using the procedure described for **33**, but using 2-aminothiazole in reaction with the pentafluorophenyl ester intermediate. ^{1}H NMR (300 MHz, DMSO-d_6): 1.83 (s, 3H), 2.14 (br s, 2H), 2.25 (tr, *J* = 2 Hz, 1H), 3.40 (tr, *J* = 4 Hz, 2H), 3.50 (br s, 4H), 3.68 (dd, *J* = 7, 5 Hz, 1H), 4.07 (tr, *J* = 7 Hz, 1H), 4.72 (m, 1H), 7.18 (d, *J* = 3 Hz, 1H), 7.26 (d, *J* = 9 Hz, 2H), 7.44 (d, *J* = 3 Hz, 1H), 8.24 (tr, *J* = 6 Hz, 1H), 12.3 (s, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 478.5.

(*S*)-(1α,5α,6α)-3-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-*N*-(6-methoxypyridin-3-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide (32). The title compound was prepared using the procedure described for **33**, but using 5-amino-2-methoxypyridine in reaction with the pentafluorophenyl ester intermediate. ^{1}H NMR (300 MHz, DMSO-d_6): 1.82 (s, 3H), 2.01 (m, 1H), 2.03 (br s, 2H), 3.38 (m, 2H), 3.47 (m, 4H), 3.67 (m, 1H), 3.79 (s, 3H), 4.06 (tr, *J* = 9 Hz, 1H), 4.70 (m, 1H), 6.77 (d, *J* = 9 Hz, 1H), 7.24 (d, *J* = 12 Hz, 2H), 7.87 (dd, *J* = 9, 3 Hz, 1H), 8.23 (tr, *J* = 6 Hz, 1H), 8.33 (d, *J* = 2.5 Hz, 1H), 10.2 (s, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 502.5.

(*S*)-(1α,5α,6α)-3-(4-{(5S)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-*N*-(1,3-benzodioxol-5-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide (35). The title compound was prepared using the procedure described for **33**, but using 3,4-(methylenedioxy)aniline in reaction with the pentafluorophenyl ester intermediate. ^{1}H NMR (300 MHz, DMSO-d_6): 1.81 (s, 3H), 1.97 (m, 1H), 2.00 (br s, 2H), 3.29−3.47 (m, 6H), 3.66 (m, 1H), 4.06 (tr, *J* = 9 Hz, 1H), 4.71 (m, 1H), 5.95 (s, 2H), 6.81 (d, *J* = 8 Hz, 1H), 6.94 (dd, *J* = 8, 2 Hz, 1H), 7.24 (d, *J* = 12 Hz, 2H), 7.29 (d, *J* = 2 Hz, 1H), 8.23 (tr, *J* = 6 Hz, 1H), 10.1 (s, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 515.5.

(*S*)-*N*-{3-[3,5-Difluoro-4-((1α,5α,6α)-6-formylamino-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (36). A solution of (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide hydrochloride (0.010 g, 0.025 mmol) in formic acid (0.5 mL) and acetic anhydride (0.25 mL) was stirred at room temperature for 3 days in a sealed vial. The solution was concentrated and purified by preparative HPLC to afford (*S*)-*N*-{3-[3,5-difluoro-4-((1α,5α,6α)-6-formylamino-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide. Yield: 6 mg (61%). ^{1}H NMR (300 MHz, DMSO): 1.67 (m, 2H), 1.82 (s, 3H), 2.76 (m, 1H), 3.35−4.02 (m, 7H), 4.06 (tr, *J* = 9 Hz, 1H), 4.71 (m, 1H), 7.23 (d, *J* = 9 Hz, 2H), 7.98 (s, 1H), 8.17 (d, *J* = 3 Hz, 1H), 8.24 (tr, *J* = 6 Hz, 1H). ESI-MS (*m/z*): [M + H]$^+$ = 395.

(*S*)-*N*-{3-[4-((1α,5α,6α)-6-Acetylamino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (37). Triethylamine (0.012 mL, 0.086) and acetic anhydride (2.8 μL, 0.029 mmol) were added to a solution of (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide hydrochloride (0.010 g, 0.025 mmol) in DMF (0.2 mL), The reaction mixture was stirred for 3 h at room temperature and then diluted with ethyl acetate (10 mL). This solution was washed with 2.5% aq NaHCO$_3$ and brine and dried (Na$_2$SO$_4$). The mixture was filtered and concentrated and the crude product purified by preparative TLC (5% MeOH−dichloromethane) to afford (*S*)-*N*-{3-[4-((1α,5α,6α)-6-acetylamino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide. Yield: 6 mg (60%). ^{1}H NMR (300 MHz,

$CDCl_3-CD_3OD$): 1.59 (m, 2 H), 1.87 (s, 3H), 1.93 (s, 3H), 2.76 (m, 1H), 3.19−3.67 (m, 7H), 3.92 (tr, *J* = 9 Hz, 1H), 4.68 (m, 1H), 6.94 (dq, *J* = 10, 2 Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 409$.

(*S*)-*N*-((1α,5α,6α)-3-{4-[5-(Acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)-2-hydroxyacetamide (38). A mixture of acetoxyacetic acid (0.033 g, 0.28 mmol), diisopropylethylamine (0.131 mL, 0.75 mmol), and HATU (0.105 g, 0.28 mmol) in DMF (0.1 mL) was stirred for 15 min and then added to a solution of (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}acetamide hydrochloride (0.10 g, 0.25 mmol) in DMF (0.1 mL). After stirring for 1 h, the solution was diluted with 15 mL of ethyl acetate; washed with 10% citric acid, H_2O, and brine; dried ($MgSO_4$); filtered; and concentrated to an oil (0.08 g, 0.17 mmol). The crude acetate was dissolved in methanol (1 mL) and treated with 0.1 M LiOH in methanol (1 mL). After stirring for 30 min the solution was concentrated and the residue purified by preparative TLC (6% MeOH−dichloromethane) to provide (*S*)-*N*-((1α,5α,6α)-3-{4-[5-(acetylaminomethyl)-2-oxooxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hex-6-yl)-2-hydroxyacetamide. Yield: 0.010 g (9%). ^1H NMR (300 MHz, DMSO): 1.76 (m, 2H), 1.82 (s, 3H), 2.79 (m, 1H), 3.33−3.42 (m, 6H), 3.68 (m, 1H), 3.78 (d, *J* = 6 Hz, 2H), 4.06 (tr, *J* = 9 Hz, 1H), 4.71 (m, 1H), 5.40 (tr, *J* = 6 Hz, 1H), 7.23 (d, *J* = 9 Hz, 2H), 7.83 (d, *J* = 5 Hz, 1H), 8.23 (br tr, 1H). ESI-MS (*m/z*): $[M + H]^+ = 425$.

(*S*)-*N*-{3-[3,5-Difluoro-4-((1α,5α,6α)-6-methanesulfonylamino-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide (39). Triethylamine (8 μL, 0.057) and methanesulfonyl chloride (2.2 μL, 0.029 mmol) were added to a solution of (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo-[3.1.0]hex-3-yl)-3,5-difluoro-phenyl]-2-oxooxazolidin-5-ylmethyl}-acetamide hydrochloride (7.6 mg, 0.019 mmol) in DMF (0.2 mL). After stirring for 2 h at room temperature, the solution was diluted with ethyl acetate (10 mL) and 2.5% $NaHCO_3$ (5 mL). The layers were separated, and the aqueous solution was extracted with two portions of ethyl acetate. The combined organic phases were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated and the crude product purified by preparative TLC (5% MeOH−dichloromethane) to afford (*S*)-*N*-{3-[3,5-difluoro-4-((1α,5α,6α)-6-methanesulfonylamino-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}acetamide. Yield: 5.8 mg (70%). ^1H NMR (300 MHz, $CDCl_3-CD_3OD$): 1.84 (br s, 2H), 1.95 (s, 3H), 2.64 (br s, 1H), 2.98 (s, 3H), 3.42−3.55 (m, 6H), 3.64 (m, 1H), 3.93 (tr, *J* = 9 Hz, 1H), 4.70 (m, 1H), 6.98 (d, *J* = 11 Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 445$.

(*S*)-*N*-(3-{3,5-Difluoro-4-[(1α,5α,6α)-6-(3-phenylureido)-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxooxazolidin-5-ylmethyl)acetamide (40). Triethylamine (6.0 μL, 0.042) and phenyl isocyanate (3.3 μL, 0.029 mmol) were added to a solution of (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]-hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}-acetamide hydrochloride (8.6 mg, 0.021 mmol) in dichloromethane (0.1 mL) and NMP (0.1 mL). After stirring for 2 h at room temperature, the solution was diluted with ethyl acetate (10 mL) and 2.5% $NaHCO_3$ (5 mL). The layers were separated, and the aqueous solution was extracted with two portions of ethyl acetate. The combined organic phases were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated and the crude product purified by preparative TLC (5% MeOH−dichloromethane) to afford (*S*)-*N*-(3-{3,5-difluoro-4-[(1α,5α,6α)-6-(3-phenylureido)-3-azabicyclo[3.1.0]-hex-3-yl]phenyl}-2-oxooxazolidin-5-ylmethyl)acetamide. Yield: 8.0 mg (80%). ^1H NMR (300 MHz, $CDCl_3-CD_3OD$): 1.72 (br s, 2H), 1.96 (s, 3H), 2.73 (br s, 1H), 3.51−3.67 (m, 7H), 3.93 (tr, *J* = 9 Hz, 1H), 4.70 (m, 1H), 7.00 (d, *J* = 12 Hz, 2H), 7.21−7.32 (m, 5H). ESI-MS (*m/z*): $[M + H]^+ = 486$.

(*S*)-{(1α,5α,6α)-3-[2,6-Difluoro-4-(5-hydroxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hex-6-yl}-carbamic Acid *tert*-Butyl Ester (41). Lithium hexamethyldisilylamide (2.5 mL of a 1.0 M THF solution, 2.5 mmol) was added to a cooled (−78 °C) solution of [(1α,5α,6α)-3-(4-benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1.0]-hex-6-yl]carbamic acid *tert*-butyl ester (0.57 g, 1.24 mmol) in THF (2.5 mL). After stirring for 1.5 h, (*R*)-(−)-glycidyl butyrate (0.193 mL, 1.36 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with satd NH_4Cl (50 mL) and extracted with ethyl acetate. The organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (0−5% MeOH−dichloromethane) provided pure (*S*)-{(1α,5α,6α)-3-[2,6-difluoro-4-(5-hydroxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo-[3.1.0]hex-6-yl}carbamic acid *tert*-butyl ester. Yield: 0.43 g (81%). ^1H NMR (300 MHz, $CDCl_3$): 1.43 (s, 9H), 1.64 (s, 2H), 2.69 (s, 1H), 3.43−3.56 (m, 4H), 3.69−3.76 (m, 1H), 3.83−3.99 (m, 3H), 4.67−4.75 (m, 2H), 7.06 (d, *J* = 6 Hz, 2H).

(*S*)-{(1α,5α,6α)-3-[4-(5-Aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hex-6-yl}-carbamic Acid *tert*-Butyl Ester (42). Triethylamine (0.28 mL, 2.02 mmol) and methanesulfonyl chloride (0.078 mL, 1.01 mmol) were added to a cooled (0 °C) solution of (*S*)-{(1α,5α,6α)-3-[2,6-difluoro-4-(5-hydroxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hex-6-yl}carbamic acid *tert*-butyl ester (0.43 g, 1.01 mmol) in dichloromethane (5 mL). After 30 min, the reaction mixture was warmed to room temperature and diluted with dichloromethane (20 mL). The organic solution was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to provide crude (*S*)-methanesulfonic acid 3-[4-((1α,5α,6α)-6-*tert*-butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl ester. Yield: 0.50 g (99%).

Sodium azide (0.328 g, 5.05 mmol) was added to a solution of (*S*)-methanesulfonic acid 3-[4-((1α,5α,6α)-6-*tert*-butoxycarbonylamino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl ester (0.50 g, 1.01 mmol) in DMF (5 mL). The reaction mixture was heated at 70 °C for 15 h, cooled, and diluted with ethyl acetate. The organic solution was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to provide (*S*)-{(1α,5α,6α)-3-[4-(5-azidomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]-hex-6-yl}carbamic acid *tert*-butyl ester. Triphenylphosphine (0.618 g, 2.36 mmol) was added to a solution of the crude azide in THF (5 mL). After 3 h at room temperature, H_2O (0.3 mL) was added and the reaction mixture was heated at 40 °C for 16 h. The reaction mixture was then concentrated and the crude product purified by column chromatography (0−5% MeOH−dichloromethane) to provide (*S*)-{(1α,5α,6α)-3-[4-(5-aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hex-6-yl}carbamic acid *tert*-butyl ester. Yield: 0.24 g (56% over three steps). ^1H NMR (300 MHz, $CDCl_3$): 1.43 (s, 9H), 1.64 (s, 2H), 2.69 (s, 1H), 2.95−3.07 (m, 2H), 3.43−3.55 (m, 4H), 3.72−3.77 (m, 1H), 3.92 (t, *J* = 9 Hz, 1H), 4.59−4.65 (m, 1H), 7.06 (d, *J* = 9 Hz, 2H).

(*S*)-*N*-{3-[4-((1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}-2,2-dichloroacetamide (46). Dichloroacetic anhydride (0.20 mL, 1.36 mmol) and pyridine (0.22 mL, 2.72 mmol) were added to a solution of (*S*)-{(1α,5α,6α)-3-[4-(5-aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hex-6-yl}carbamic acid *tert*-butyl ester (0.29 g, 0.68 mmol) in DMF (5 mL). The mixture was stirred for 15 h at room temperature. The reaction mixture was then poured into ethyl acetate and washed with 5% citric acid, H_2O, and brine. The organic layer is dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (0−3% MeOH−dichloromethane) provided (*S*)-[(1α,5α,6α)-3-(4-{5-[(2,2-dichloroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]-hex-6-yl]carbamic acid *tert*-butyl ester. Yield: 0.27 g (74%).

A 4 M solution of HCl in dioxane (4 mL) was added to a solution of (*S*)-[(1α,5α,6α)-3-(4-{5-[(2,2-dichloroacetylamino)-methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo-[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester (0.27 g, 0.50 mmol) in dioxane (4 mL). The reaction mixture was stirred for 3 h and the solvent was removed in vacuo. The residue was dissolved in H_2O (5 mL) and washed with two portions of dichloromethane. The layers were separated, and the aqueous layer was frozen and lyophilized to afford the pure (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophen yl]-2-oxooxazolidin-5-ylmethyl}-2,2-dichloroacetamide. Yield: 0.22 g (99%). ^1H NMR (300 MHz, DMSO): 1.95 (m, 2H), 2.58 (m, 1H), 3.36 (m, 4H), 3.51 (tr, *J* = 6 Hz, 2H), 3.65−3.70 (m, 1H), 4.09 (tr, *J* = 9 Hz, 1H), 4.79 (m, 1H), 6.49 (s, 1H), 7.22 (d, *J* = 12 Hz, 2H), 8.18 (m, 2H), 9.01 (br tr, 1H). ESI-MS (*m/z*): $[M + H]^+ = 435$.

***N*-[((5*S*)-3-{4-[(1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarboxamide (43).** The title compound was prepared according to the procedure described above for **46** but using cyclopropane carboxylic acid in the coupling reaction. ^1H NMR (300 MHz, DMSO): 0.59−0.65 (m, 4H), 1.53−1.65 (m, 3H), 2.43 (s, 1H), 3.26−3.39 (m, 6H), 3.63−3.68 (m, 1H), 4.04 (t, *J* = 9 Hz, 1H), 4.68−4.72 (m, 1H), 7.20 (d, *J* = 9 Hz, 2H), 8.45 (t, *J* = 6 Hz, 1H). ESI-MS (*m/z*): $[M + H]^+ = 393.5$.

***N*-[((5*S*)-3-{4-[(1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanamide (44).** The title compound was prepared according to the procedure described above for **46** but using propionic acid in the coupling reaction. ^1H NMR (300 MHz, DMSO): 0.94 (tr, *J* = 8 Hz, 3H), 1.95 (s, 2H), 2.07 (q, *J* = 8 Hz, 2H), 2.57 (br s, 1H), 3.35 (br s, 4H), 3.67 (m, 2H), 4.04 (tr, *J* = 9 Hz, 1H), 4.22 (m, 1H), 4.70 (m, 1H), 7.22 (d, *J* = 12 Hz, 2H), 8.17 (tr, *J* = 6 Hz, 1H), 8.19 (br s, 2H). ESI-MS (*m/z*): $[M + H]^+ = 381.5$.

(*S*)-*N*-{3-[4-((1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}-2,2-difluoroacetamide (45). Ethyl difluoroacetate (0.50 mL, 5.0 mmol) and triethylamine (0.278 mL, 2.1 mmol) were added to a solution of (*S*)-{(1α,5α,6α)-3-[4-(5-aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hex-6-yl}carbamic acid *tert*-butyl ester (0.30 g, 0.70 mmol) in MeOH (3 mL). The solution was stirred for 15 h at room temperature and then concentrated. Purification by column chromatography (0−2% MeOH−dichloromethane) provided (*S*)-[(1α,5α,6α)-3-(4-{5-[(2,2-difluoroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester. Yield: 0.35 g (99%).

A 4 M solution of HCl in dioxane (4 mL) was added to a solution of (*S*)-[(1α,5α,6α)-3-(4-{5-[(2,2-difluoroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamic acid *tert*-butyl ester (0.34 g, 0.68 mmol) in dioxane (4 mL). The reaction mixture was stirred for 3 h and the solvent was removed in vacuo and lyophilized from H_2O and CH_3CN to afford (*S*)-*N*-{3-[4-((1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl}-2,2-difluoroacetamide. Yield: 0.27 g (99%). ^1H NMR (300 MHz, DMSO): 1.91 (m, 2H), 2.48 (m, 1H), 3.28 (m, 4H), 3.43 (m, 2H), 3.65 (m, 1H), 4.02 (tr, *J* = 9 Hz, 1H), 4.71 (m, 1H), 6.18 (tr, *J* = 54 Hz, 1H), 7.15 (d, *J* = 12 Hz, 2H), 8.31 (d, *J* = 4 Hz, 2H), 9.14 (tr, *J* = 5 Hz, 1H). ESI-MS (*m/z*): $[M + H]^+ = 403$.

(*S*)-(1α,5α,6α)-3-[2,6-Difluoro-4-(5-hydroxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid *tert*-Butyl Ester (47). Lithium hexamethyldisilylamide (9.0 mL of a 1.0 M THF solution, 9.0 mmol) was added to a cooled (−78 °C) solution of (1α,5α,6α)-3-(4-benzyloxycarbonylamino-2,6-difluorophenyl)-3-azabicyclo[3.1. 0]-hexane-6-carboxylic acid *tert*-butyl ester (2.0 g, 4.5 mmol) in THF (10 mL). After stirring for 1.5 h, (*R*)-(−)-glycidyl butyrate (0.70 mL, 4.95 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with satd NH_4Cl (50 mL) and extracted with ethyl acetate. The organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (0−5% MeOH−dichloromethane) provided pure (*S*)-(1α,5α,6α)-3-[2,6-difluoro-4-(5-hydroxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]-hexane-6-carboxylic acid *tert*-butyl ester. Yield: 1.6 g (87%). ^1H NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 1.82 (tr, *J* = 3 Hz, 1H), 2.02 (m, 2H), 3.48−3.56 (m, 4H), 3.72−4.02 (m, 4H), 4.73 (m, 1H), 7.07 (d, *J* = 12 Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 411$.

(*S*)-(1α,5α,6α)-3-[4-(5-Aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid *tert*-Butyl Ester (48). Triethylamine (0.5 mL, 5.5 mmol) and methanesulfonyl chloride (0.28 mL, 3.65 mmol) were added to a cooled (0 °C) solution of (*S*)-(1α,5α,6α)-3-[2,6-difluoro-4-(5-hydroxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.5 g, 3.65 mmol) in dichloromethane (15 mL). After 30 min, the reaction mixture was warmed to room temperature and diluted with dichloromethane (30 mL). The organic solution was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to provide (*S*)-(1α,5α,6α)-3-[2,6-difluoro-4-(5-methanesulfonyloxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield: 1.7 g (99%). ^1H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.81 (tr, *J* = 3 Hz, 1H), 2.03 (m, 2H), 3.11 (s, 3H), 3.50−3.58 (m, 4H), 3.86 (dd, *J* = 9, 6 Hz, 1H), 4.07 (tr, *J* = 9 Hz, 1H), 4.45 (dq, *J* = 12, 4 Hz, 2H), 4.91 (m, 1H), 7.05 (d, *J* = 11 Hz, 2H).

Sodium azide (1.20 g, 18.3 mmol) was added to a solution of (*S*)-(1α,5α,6α)-3-[2,6-difluoro-4-(5-methanesulfonyloxymethyl-2-oxooxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.7 g, 3.5 mmol) in DMF (5 mL). The reaction mixture was heated at 70 °C for 15 h, cooled, and diluted with ethyl acetate. The organic solution was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to provide (*S*)-(1α,5α,6α)-3-[4-(5-azidomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.5 g, 3.44 mmol). Triphenylphosphine (1.5 g, 3.8 mmol) was added to a solution of the crude azide in THF (11 mL). After 3 h at room temperature, H_2O (0.36 mL) was added and the reaction mixture was heated at 40 °C for 16 h. The reaction mixture was then concentrated and the crude product purified by column chromatography (0−7% MeOH−dichloromethane) to provide pure (*S*)-(1α,5α,6α)-3-[4-(5-aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield: 1.20 g (86%). ^1H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.83 (tr, *J* = 3 Hz, 1H), 2.03 (m, 2H), 2.95 (dd, *J* = 14, 6 Hz, 1H), 3.12 (dd, *J* = 14, 4 Hz, 1H), 3.42−3.52 (m, 4H), 3.78 (dd, *J* = 9, 7 Hz, 1H), 3.95 (tr, *J* = 9 Hz, 1H), 4.66 (m, 1H), 7.08 (d, *J* = 10 Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 410$.

(*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-Difluoroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid (50). Pyridine (0.12 mL, 1.46 mmol) and difluoroacetic acid (0.05 mL, 0.8 mmol) were added to a solution of (*S*)-(1α,5α,6α)-3-[4-(5-aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.30 g, 0.73 mmol) in DMF (3.0 mL). 1,3-Diisopropylcarbodiimide (0.125 mL, 0.8 mmol) was then added and the mixture stirred for 16 h at room temperature. The mixture was diluted with ethyl acetate, washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (0−2% MeOH−dichloromethane) to provide (*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-difluoroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield: 0.22 g (60%). ^1H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.80 (tr, *J* = 3 Hz, 1H), 2.03 (m, 2H), 3.44−3.57 (m, 4H), 3.61−3.70 (m, 2H), 3.82−3.89 (m, 1H), 4.03 (tr, *J* = 9 Hz, 1H), 4.80 (m, 1H), 5.93 (tr, *J* = 54 Hz, 1H), 6.9 (br s, 1H), 7.02 (d, *J* = 12 Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 488$.

(*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-Difluoroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.21 g, 0.4 mmol) was dissolved in trifluoroacetic acid−dichloromethane (5 mL, 1:4) and stirred for 3 h at room temperature. The solution was then concentrated and the oil lyophilized from $CH_3CN−H_2O$ to provide (*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-difluoroacetylamino)methyl]-

2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]-hexane-6-carboxylic acid. Yield: 0.18 g (99%). ^{1}H NMR (300 MHz, DMSO): 1.64 (tr, $J = 3$ Hz, 1H), 2.03 (m, 2H), 3.39−3.52 (m, 2H), 3.43 (m, 4H), 3.71 (dd, $J = 9$, 6 Hz, 1H), 4.08 (tr, $J = 9$ Hz, 1H), 4.78 (m, 1H), 6.24 (tr, $J = 54$ Hz, 1H), 7.21 (d, $J = 12$ Hz, 2H), 9.15 (tr, $J = 6$ Hz, 1H). ESI-MS (*m/z*): $[M + H]^+ = 432$.

(*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-Dichloroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo-[3.1.0]hexane-6-carboxylic Acid (51). Pyridine (0.20 mL, 2.4 mmol) and dichloroacetic anhydride (0.20 mL, 1.3 mmol) were added to a solution of (*S*)-(1α,5α,6α)-3-[4-(5-aminomethyl-2-oxooxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.25 g, 0.61 mmol) in DMF (0.75 mL) at room temperature. The mixture was stirred for 16 h, diluted with ethyl acetate, washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by preparative TLC (7% MeOH−10% CH_3CN−dichloromethane) to provide (*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-dichloroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield: 0.22 g (62%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.80 (tr, $J = 3$ Hz, 1H), 2.03 (m, 2H), 3.57 (m, 4H), 3.71−3.77 (m, 3H), 4.03 (tr, $J = 9$ Hz, 1H), 4.83 (m, 1H), 5.94 (s, 1H), 7.02 (d, $J = 12$ Hz, 2H), 7.06 (br s, 1H). ESI-MS (*m/z*): $[M + H]^+ = 521$.

(*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-Dichloroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.22 g, 0.40 mmol) was dissolved in trifluoroacetic acid−dichloromethane (5 mL, 1:4) and stirred for 3 h at room temperature. The solution was then concentrated and the oil lyophilized from CH_3CN−H_2O to provide (*S*)-(1α,5α,6α)-3-(4-{5-[(2,2-dichloroacetylamino)methyl]-2-oxooxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]-hexane-6-carboxylic acid. Yield: 0.185 g (89%). ^{1}H NMR (300 MHz, DMSO): 1.64 (tr, $J = 3$ Hz, 1H), 2.02 (m, 2H), 3.43 (m, 4H), 3.50 (m, 2H), 3.67 (dd, $J = 9$, 6 Hz, 1H), 4.09 (tr, $J = 9$ Hz, 1H), 4.78 (m, 1H), 6.47 (s, 1H), 7.21 (d, $J = 12$ Hz, 2H), 8.96 (tr, $J = 5$ Hz, 1H). ESI-MS (*m/z*): $[M + H]^+ = 521$.

(1α,5α,6α)-3-(2,6-Difluoro-4-{(5*S*)-2-oxo-5-[(propionylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-3-azabicyclo-[3.1.0]hexane-6-carboxylic Acid (49). The title compound was prepared as described above for **51** but using propionic anhydride in the acylation reaction. Yield: 0.120 g (79%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (tr, $J = 8$ Hz, 3H), 1.93 (m, 1H), 2.16 (br s, 2H), 2.25 (q, $J = 8$ Hz, 2H), 3.58 (m, 4H), 3.65−3.75 (m, 3H), 3.97 (tr, $J = 9.5$ Hz, 1H), 4.77 (m, 1H), 6.14 (tr, $J = 6$ Hz, 1H), 7.04 (d, $J = 11$ Hz, 2H). ESI-MS (*m/z*): $[M + H]^+ = 410$.

In Vitro Susceptibility Tests. Minimum inhibitory concentrations (MICs) of oxazolidinone analogues were determined by standard broth microdilution methods.[32]

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Supporting Information Available: ^{1}H NMR spectra and/or HPLC data for all new oxazolidinone analogues. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Jones, R. N.; Sader, H. S. The Clinical Impact of Enterococcal Resistance. *Challenges Infect. Dis.* **1993**, *1*, 1−5.

(2) Appelbaum, P. C. Emerging Resistance to Antimicrobial Agents in Gram-positive Bacteria: Pneumococci. *Drugs* **1996**, *51 (Suppl. 1)*, 1−5.

(3) Hiramatsu, K.; Hanaki, H.; Ino, T.; Yabuta, K.; Oguri, T.; Tenover, F. C. Methicillin-resistant *Staphylococcus aureus* Clinical Strain with Reduced Vancomycin Susceptibility. *J. Antimicrobial Chemother.* **1997**, *40*, 135−146.

(4) Sievert, D. M.; Boulton, M. L.; Stoltman, G.; Johnson, D.; Stobierski, M. G.; Dowens, F. P.; Somsel, P. A.; Rudrik, J. T.; Brown, W.; Hafeez, W.; Lundstrom, T.; Flanagan, E.; Johnson, R.; Mitchell, J.; Chang, S. *Staphylococcus aureus* Resistant to Vancomycin−United States, 2002. *Morbidity Mortality Weekly Rep.* **2002**, *51*, 565−567.

(5) Brickner, S. J. Oxazolidinone Antibacterial Agents. *Curr. Pharm. Des.* **1996**, *2*, 175−194.

(6) Barbachyn, M. R.; Ford, C. W. Oxazolidinone Structure−Activity Relationships Leading to Linezolid *Angew. Chem., Int. Ed.* **2003**, *42*, 2010−2023.

(7) Nilus, A. M. Have the oxazolidinones lived up to their billing? Future perspectives for this antibacterial class. *Curr. Opin. Invest. Drugs.* **2003**, *4*, 149−155.

(8) Shinabarger, D. Mechanism of Action of the Oxazolidinone Antibacterial Agents *Exp. Opin. Invest. Drugs* **1999**, *8*, 1195−1202.

(9) Kloss, P.; Xiong, L.; Shinabarger, D. L.; Mankin, A. S. Resistance Mutations in 23 S rRNA Identify the Site of Action of the Protein Synthesis Inhibitor Linezolid in the Ribosomal Peptidyl Transferase Center. *J. Mol. Biol.* **1999**, *294*, 93−101.

(10) Shinabarger, D. L.; Marotti, K. R.; Murray, R. W.; Lin, A. H.; Melchior, E. P.; Swaney, S. M.; Dunyak, D. S.; Demyan, W. F.; Buysse, J. M. Mechanism of Action of Oxazolidinones: Effects of Linezolid and Eperezolid on Translation Reactions. *Antimicrob. Agents Chemother.* **1997**, *41*, 2132−2136.

(11) Lin, A. H.; Murray, R. W.; Vidmar, T. J.; Marotti, K. R. The Oxazolidinone Eperezolid Binds to the 50S Ribosomal Subunit and Competes with Binding of Chloramphenicol and Lincomycin. *Antimicrob. Agents Chemother.* **1997**, *41*, 2127−2131.

(12) For a review of recent efforts, see: Hutchinson, D. K. Oxazolidinone Antibacterial Agents: A Critical Review. *Curr. Topics Med. Chem.* **2003**, *3*, 1021−1042.

(13) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. Substituent Effects on the Antibacterial Activity of Nitrogen−Carbon-Linked (Azolylphenyl)oxazolidinones with Expanded Activity Against the Fastidious Gram-Negative Organisms Haemophilus influenzae and Moraxella catarrhalis. *J. Med. Chem.* **2000**, *43*, 953−970.

(14) After our filing a patent application on this class, similar bicyclic oxazolidinone antibacterials were disclosed by another group; see Fukuda, Y. and Hammond, M. L. Bicyclo[3.1.0]hexane Containing Oxazolidinone Antibiotic and Derivatives Thereof. International Publication PCT WO 03/027083.

(15) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jeganathan, A.; Yamagata, K.; Chen, J. J.; Lu, C. V.; Herrinton, P. M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T.; Moeslein, J. A.; Greene, M. L.; Barbachyn, M. R. The Synthesis of *N*-Aryl-5(S)-aminomethyl-2-oxazolidinone Antibacterials and Derivatives in One Step from Aryl Carbamates. *Org. Process. Res. Dev.* **2003**, *7*, 533−546.

(16) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B. Process to Prepare Oxazolidinones. U.S. Patent Application Publication US 2002/0169312.

(17) Barbachyn, M. R.; Brickner, S. J.; Hutchinson, D. K. Substituted Oxazine and Thiazine Oxazolidinone Antibacterials. U.S. Patent 5,880,118, 1999.

(18) Brighty, K. E.; Castaldi, M. J. Synthesis of (1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hexane, a Novel Achiral Diamine. *Synlett* **1996**, 1097−1099.

(19) Danheiser, R. L.; Savoca, A. C. Applications of Cyclopropylboranes in Organic Synthesis 1. A Stereocontrolled Route to Substituted Cyclopropanol Derivatives. *J. Org. Chem.* **1985**, *50*, 2401−2403.

(20) Kollmeyer, W. D. 3-Benzyl-3-azabicyclo(3.1.0)hexane-2,4-dione U.S. Patent 4,183,857, 1980.

(21) Single point MIC determinations are generally considered accurate within one dilution (2-fold numerically).

(22) Jo, Y. W.; Im, W. B.; Rhee, J. K.; Shim, M. J.; Kim, W. B.; Choi, E. C. Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 5909−5915.

(23) Hybrid quinolone-oxazolidinone antibacterials with a carboxylic acid function on the quinolone ring have been reported, see Gordeev, M. F.; Hackbarth, C.; Barbachyn, M. R.; Banitt, L. S.; Gage, J. R.; Luehr, G. W.; Gomez, M.; Trias, J.; Morin, S. E.; Zurenko, G. E.; Parker, C. N.; Evans, J. M.; White, R. J.; Patel, D. V. Novel Oxazolidinone-Quinolone Hybrid Antimicrobials. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4213−4216. and Hubschwerlen, C.; Specklin, J.-L.; Sigwalt, C.; Schroeder, S.; Locher, H. H. Design, Synthesis and Biological Evaluation of Oxazolidinone-Quinolone Hybrids. *Bioorg. Med. Chem.* **2003**, *11*, 2313−2319.

(24) Johnson, P. D.; Aristoff, P. A.; Zurenko, G. E.; Schaadt, R. D.; Yagi, B. H.; Ford, C. W.; Hamel, J. C.; Stapert, D.; Moerman, J. K. Synthesis and Biological Evaluation of Benzazepine Oxazolidinone Antibacterials *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4197−4200.

(25) Riedl, B.; Haebich, D.; Stolle, A.; Ruppelt, M.; Bartel, S.; Guarnieri, W.; Endermann, R.; Kroll, H.-P. Neue Substitueirte Oxazolidinone. Ger. Offen. Patent 19604223, 1997.

(26) Hester, J. B.; Nidy, E. G.; Perricone, S. C.; Poel, T.-J. Oxazolidinone Antibacterial Agents having a Thiocarbonyl Functionality. WO 9854161, 1998.

(27) Tokuyama, R. Takahashi, Y.; Tomita, Y.; Suzuki, T.; Yoshida, T.; Iwasaki, N.; Kado, N.; Okezaki, E.; Nagata, O. Structure−Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. 1. Conversion of 5-substituent on Oxazolidinone. *Chem. Pharm. Bull.* **2001**, *49*, 347−352.

(28) Tokuyama, R. Takahashi, Y.; Tomita, Y.; Tsubouchi, M.; Iwasaki, N.; Kado, N.; Okezaki, E.; Nagata, O. Structure−Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. 3. Synthesis and Evaluation of 5-Thiocarbamate Oxazolidinones. *Chem. Pharm. Bull.* **2001**, *49*, 361−367.

(29) Gravestock, M. B. Heterocyclyl Aminomethyl Oxazolidinones as Antibacterials. International Publication WO 00/21960, 2000.

(30) Gravestock, M. B.; Hales, N. J.; Carcanague, D. R. Hydroxymethyl substituted dihydroisoxazole derivatives useful as antibiotic agents. WO04078753, 16 September, 2004**.**

(31) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. Identification of 4-Substituted 1,2,3-Triazoles as Novel Oxazolidinone Antibacterial Agents with Reduced Activity against Monoamine Oxidase A *J. Med. Chem.* **2005**, *48*, 499−506.

(32) National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*, 4th ed. (Approved Standard); NCCLS Document M7-A4; NCCLS: Wayne, Pa. 1997.

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