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New Classes of Antibacterial Oxazolidinones with C-5, Methylene *O*-Linked Heterocyclic Side Chains

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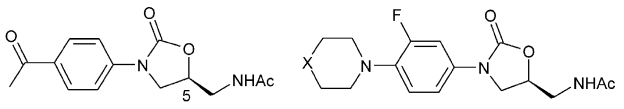
Abstract—Exploration of the structure–activity relationships of the traditional C-5 acetamidomethyl side chain of the oxazolidinone antibacterials has yielded new, potent series of compounds of which the first examples, the *O*-linked iosoxazoles are described in detail, leading to the selection of the pre-clinical candidate AZD2563.

The emergence of multidrug-resistant strains of Gram-positive pathogens presents an increasingly urgent clinical problem.[1,2] Resistance to β-lactam antibiotics in *Streptococcus pneumoniae* strains now ranges from 20 to 80% world-wide. In addition to the widely encountered methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin-resistant enterococci (VRE) have been a significant and increasing threat for some years to patients in the USA and Europe.[3] Yet more alarming is the appearance in recent years of staphylococcal strains with reduced susceptibility to vancomycin and related glycopeptides (GISA).[4] Until recently, these antibiotics represented the agents of last resort in some clinical situations.[5] When the oxazolidinone class of anti-Gram-positive agents were identified by Dupont workers in the early 80's,[6] they represented the first truly new class of synthetic antibacterial agents for nearly 30 years. Studies[7] on the first candidate drug DuP 721 **1** revealed many attractive features, including good oral activity and a novel mode of action via inhibition of the initiation of protein synthesis.[8] However, this and other early compounds were poorly tolerated in animals, and DuP 721 did not progress through development (Fig. 1).

The attractive drug-like traits of the oxazolidinone series encouraged further work in the area, for example the patents by Pharmacia-Upjohn,[9] Bayer[10] and AstraZeneca[11] amongst others. This work led to the clinical candidates eperezolid **2** and linezolid **3** having improved potency and tolerability over the early compounds.[12] The first drug in this class, linezolid was approved for sale as Zyvox™ in the USA in 2000.

In keeping with their novel site of action, the oxazolidinones are effective against all Gram-positive strains, and show no cross resistance with other classes of protein synthesis inhibitor. The target sites on the 50S ribosome have been recently identified.[13–15]

The many attractive traits of the oxazolidinone series has encouraged further work in the area, and the patent literature reveals extensive chemical programs exist. However, some *linezolid*-resistant enterococcal isolates have recently already been isolated after intensive linezolid



1 (DuP 721)

2 X = $NCOCH_2OH$ (Eperezolid)
3 X = O (Linezolid)

Figure 1. Oxazolidinone clinical candidates with C-5 acetamidomethyl side chains.

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therapy[16] and the first reports of resistant *S. aureus* strains have been made.[17] This unexpectedly early resistance development (although only isolated examples of such strains at present) emphasises the need for further exploration of features of the oxazolidinone series to overcome these deficiencies. In our work reported here,[18] we describe the first of several fundamental changes to the oxazolidinone C-5 side chain which may give promise for such improvements.

The SAR around the oxazolidinone C-5 side chain group was extensively explored[19] by the DuPont group in their early studies, mostly with the acetyl group of DuP 721 as the aryl substituent. They showed that even minor changes of the acetylaminomethyl side chain to formylamino or cyanoacetylamino, or to the methyl carbamate and simple urea, caused a 4- to 8-fold increase in MICs against *S. aureus* strains. Bulkier groups as in the isobutyramide, or *tert*-butyl carbamate analogues, caused an even greater loss of potency. The conclusion was drawn that there are both specific and sterically restricted requirements in the vicinity of the oxazolidinone side chain binding site. In contrast, these early studies[20] revealed much greater flexibility in the variation allowed on the *N*-aryl ring. The outcome of this early SAR was to direct much subsequent and more recent work to the examination of the permitted variation of the *N*-aryl function, while leaving the acetamide side chain relatively unexplored. The only major exceptions were the discovery by workers at Bayer, Pharmacia-Upjohn and others that sulfur isosteres of the acetamidomethyl side chain such as thioamides, thioureas or thiocarbamates can also give high potency compounds,[21] often exceeding that of the acetamide analogues.

As part of the AstraZeneca oxazolidinone discovery programme, we were interested in the nature of the H-bond and steric interactions which were apparently optimised in the acetamidomethyl group. In particular we were intrigued by the observation, noted in passing in the first Dupont publication,[19] that substitution of the amide hydrogen by methyl abolishes activity. Similarly, methylation of the adjacent methylene to the NH function also abolishes activity.[22] On first sight, this suggests a critical need for an H-bond donor residue on the side chain. An alternative explanation is that alkylation at either position may give rise to an important change in the conformation of the amide side chain, which might agree with the earlier findings of very limited allowable alterations to the amide substituents.[19]

In order to re-examine these effects we prepared various oxazolidinone side chain amide analogues using initially

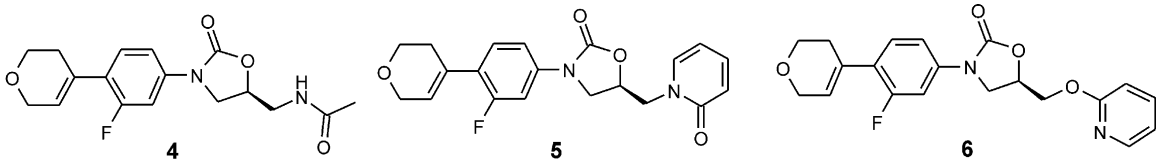
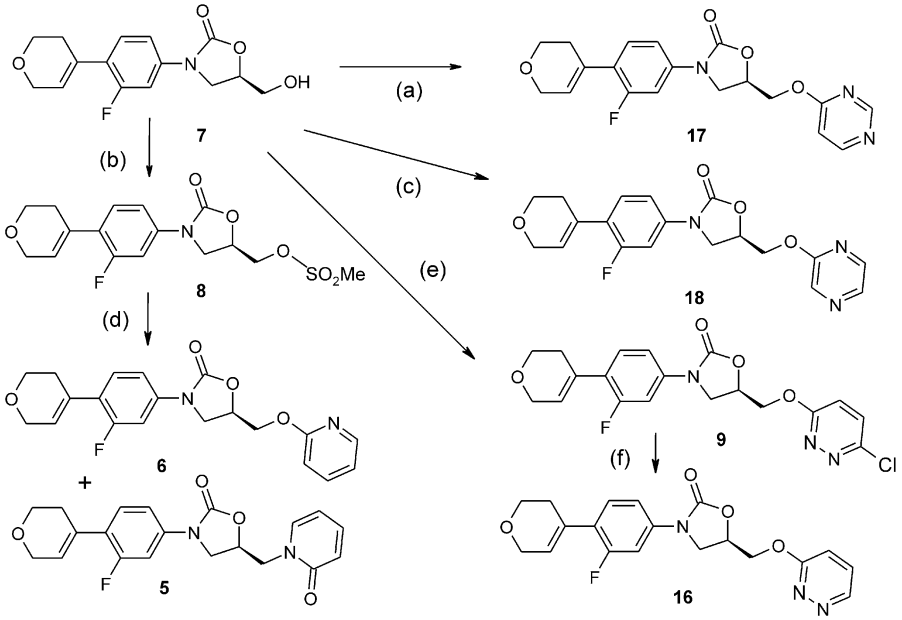


Figure 2. Dihydropyranyl oxazolidinones with alternate side chains.

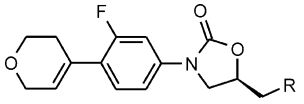


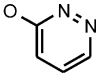
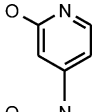
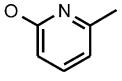
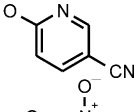
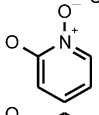
Scheme 1. Preparation of dihydropyranyl oxazolidinones: (a) DIAD, Ph_3P, 4-hydroxypyrimidine, 49%; (b) $MeSO_2Cl$, Et_3N, 85%; (c) NaH, DMF, 2-chloropyrazine, 45%; (d) NaH, DMF, 2-hydroxypyridine, **5**—29% + **6**—15%; (e) NaH, DMF, 3-chloropyridazine, 21%; (f) 30% Pd/C, ammonium formate, ethanol, rt, 41%.

the aryl oxazolidinone with a known active 4-(dihydropyranyl)-aryl substituent. Thus, our first target was the cyclic amide **5**. A simple alkylation of pyridine to give **5** also yielded the *O*-alkylation product **6** (cf. Table 1). The target pyridone **5** had poor MICs against *S. aureus* strains (mean values of 32 μg/mL) compared with the acetamide **4** (mean 0.13 μg/mL), but the *O*-linked pyridine **6** unexpectedly had MICs of 1 μg/mL, close to that of linezolid (Fig. 2).

This result was surprising for two reasons. It conflicted with the expected spacial limitations of the side chain-binding region for the oxazolidinones and also demonstrate that substituents without an H-bond donor

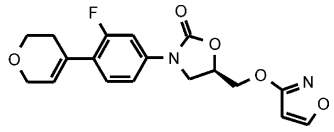
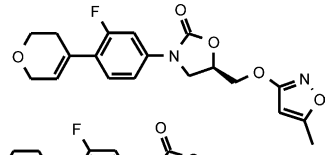
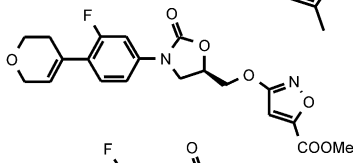
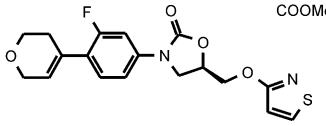
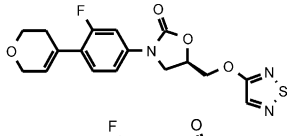
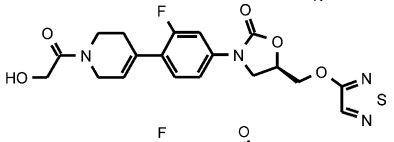
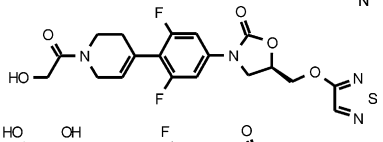
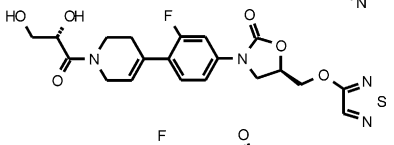
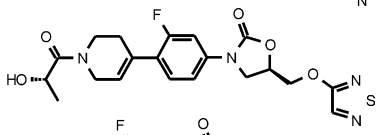
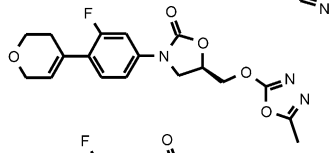
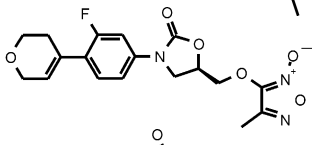
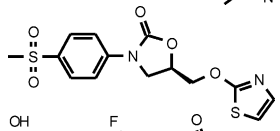
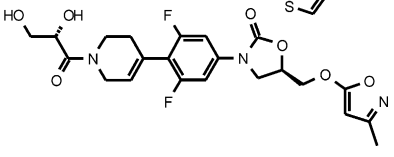
Table 1. In vitro MIC's and in vivo antibacterial activity of six-ringed heterocycles



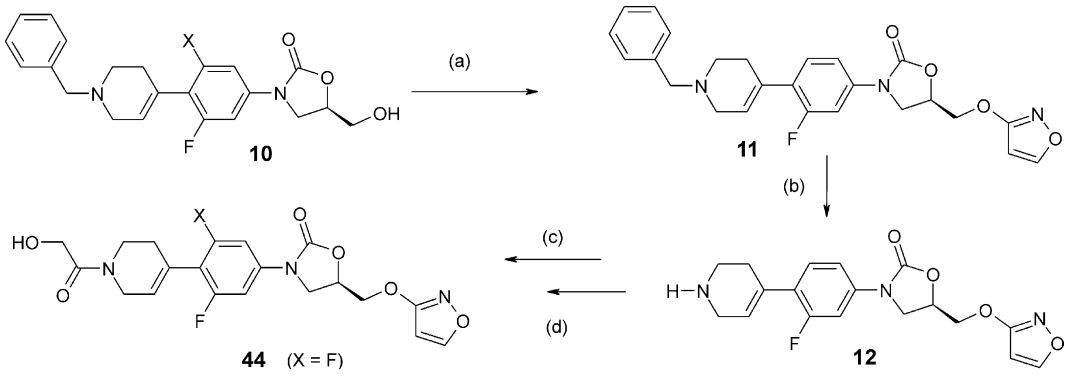
Compd	Heterocycle R	*S. aureus* Oxford	*S. aureus* MRQR	*S. aureus* CNSMR[a]	*S. pyogenes* PS.[b]	*E. faecalis*	MTT[c] 10 mg/kg	MTT[c] 5 mg/kg
4	$NHCOCH_3$	0.13	0.25	0.13	0.13	0.13	1.34	0.6
5		32	32	32	32	64		
6		0.5	1	1	2	2	0.15	0.0
14		4	4	4	8	8		
15		16	32	32	64	64		
16		2	2	2	2	4		
17		1	2	2	4	4	0.34	0.23
18		1	1	1	1	2	0.35	0.22
19		16	16	16	32	64		
20		2	2	2	4	4		
21		8	16	16	8	32		
22		> 128	> 128	> 128	> 128	> 128		
23		> 128	> 128	> 128	> 128	> 128		
24		> 128	> 128	> 128	> 128	> 128		
25		> 128	> 128	> 128	> 128	> 128		

MICs are recorded in mg/L. Results are expressed as log reductions compared to control.
[a]Coagulase −ve Staph. Methicillin resistant.
[b]Penicillin sensitive.
[c]Mouse thigh test.

Table 2. In vitro MIC's and in vivo antibacterial activity of five-ringed heterocycles

Compd	Structure	*S. aur.* Oxford	*S. aur.* MRQR	*S. aur.* CNSMR[a]	*S. pyog.* PS.[b]	*E. faec.*	MTT[c] 10 mg/kg	MTT[c] 5 mg/kg
26		0.5	0.5	0.5	0.5	1	0.06	−0.07
27		1	2	2	4	4	−0.45	
28		8	16	32	16	128		
29		0.25	0.25	0.25	0.5	0.5	0.21	0.01
30		0.25	0.25	0.25	0.25	0.5	0.45	0.11
31		0.13	0.25	0.25	0.25	0.25	1.21	0.78
32		0.13	0.25	0.25	0.25	0.5	1.72	1.05
33		0.06	0.13	0.13	0.13	0.25	1.11	0.42
34		0.25	0.5	0.5	1	1	1.14	0.43
35		4	4	8	8	8		
36		1	2	2	4	2	0.2	0.03
37		16	16	32	16	32		
38		1	2	1	2	2		

MICs are recorded in mg/L. Results are expressed as $\log_{10}$ reductions compared to control.
[a]Coagulase –ve Staph. Methicillin resistant.
[b]Penicillin sensitive.
[c]Mouse thigh test.



Scheme 2. Synthesis of 4-(tetrahydropyridinyl)-aryl oxazolidinone isoxazoles: (a) DIAD, Ph_3P, 3-hydroxyisoxazole, 75%; (b) ACE chloride, then heat/methanol; (c) acetoxyacetyl chloride, DMAP, Et_3N, DCM; (d) K_2CO_3, methanol.

function could bind with apparently similar energies to the acetamide group. We accordingly undertook to further investigate the properties of a variety of *O*-linked heterocycles at the C-5 terminous.

The preparation of the 4-(dihydropyranyl) aryl series was straight forward. From previous work, we had available[23] the alcohol **7** and its derived mesylate **8**, hence the reaction with 2-pyridone promised a quick entry to the original goal of the *N*-linked compound (**5**, Scheme 1). Having established our preferred interest in the oxygen linked series **6**, other routes were examined. Displacement of a halogen from an appropriate haloheterocycle after generation of an anion at C-5′ was possible, though low yielding, but represented a quick entry to varied substituted heterocycles such as **18** because of ready intermediate availability. The best general approach was to use the Mitsunobu reaction, exemplified by **17**. Together, these routes allowed the ready preparation of the series of pyridines and related diazines listed in Table 1; and using the latter procedure the proportion of *N*-alkylation versus *O*-alkylation was minimal. Access to the parent pyridazine **16** was achieved by dechlorination of the product **9** obtained from 3,6-dichloropyridazine. The phenoxy analogue **25** was prepared for comparison by displacement of the mesylate.

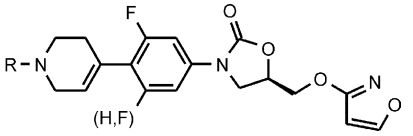
It seemed likely that five-membered heterocycles might be superior replacements for the six-membered analogues because of the presumed steric limitations at the binding site. The Mitsunobu reaction again gave ready access to the isoxazole substituted analogues, and various analogous heterocycles in analogous conditions to those in Scheme 1. Because of our findings in the acetamide series[23] at C-5′, we then switched our attention to the more versatile 4-(tetrahydropyridyl)-aryl analogues of the above compounds. Starting from the *N*-benzyl alcohols **10**, the key isoxazolyloxy amines **12** could be prepared, and then acylated by a wide variety of groups (e.g., **44**, Scheme 2). Some early indications that difluorinated compounds might be more potent led us to prepare compounds in both series. A recurrent problem with the highly crystalline oxazolidinones is poor aqueous solubility, but the availablity of **12** gave ample opportunity to introduce hydrophilic groups and vary the physical properties of the molecules. The stereoisomers of glycidic acid gave flexible access to various intermediates **13**, which were taken on to disubstituted propionamides at different oxidation levels such as **55**. The heterocycles attached at C-5′ were either available commercially, or were obtained by literature procedures.

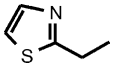
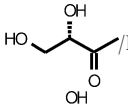
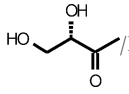
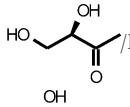
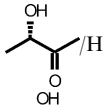
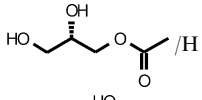
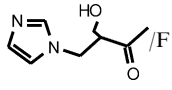
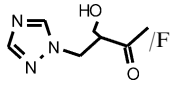
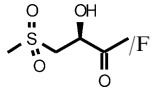
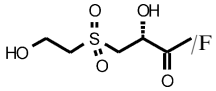
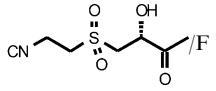
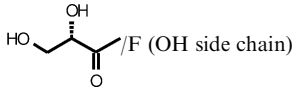
Previous structure–activity analysis of the in vitro antibacterial activity on oxazolidinones with acetamidomethyl side chains had shown that the dihydropyranyl substituent provided a sensitive probe of potential activity as other variations were made.[23] Accordingly, this substitution was used for a comparison of the effects of changing the side chain, after the initial surprise of good activity with the 2-pyridyloxy compound (**6**, Table 1). Movement of the pyridyl nitrogen to the 3-(**14**) or 4-position (**15**) led to decreases in activity, and while the diazines (**16**–**18**) were comparable in activity to the lead, there was a marked drop for the 2-pyrimidine **19**. Addition of methyl substitution to the pyridine ring of **6** led to a decline in activity as the group became closer to the ring nitrogen (**20**, **21**, **22**), suggesting an H-bond acceptor role for this atom, in line with the documented negative effect of such substituents adjacent to H-bonding centres. The similar negative effect on activity of electron withdrawing groups (**23**) supported this hypothesis, as did the loss of activity when the lone pair was absent in the *N*-oxide **24**, or the ring nitrogen was removed in the phenyloxy compound **25**. This must, however, be an over simplification, given the retention of at least some activity in the positional isomers of pyridine **14**, **15**.

Given the presumed size constraints on the amide function in the acetamidomethyl series, it was hoped that the effect of smaller five-membered heterocycles with isoxazole (a well known amide isostere) as an early choice would give improved potencies. The data of Table 2 show that it is indeed an effective replacement, with the parent dihydropyran (**26**) showing increased activity over **6**, to become comparable to linezolid. Substitution on the ring was again detrimental (**27**, **28**), and given the poor accessibility of substituted isoxazoles was not pursued.

Interestingly, given the improved antibacterial activity of thioisosteres in the amide series,[21] the same sulfur effect is observed with these heterocycles. Thus isothiazole (**29**) and thiadiazoles in particular (**30**–**34**) led

Table 3. In vitro MIC's and in vivo antibacterial activity of isoxazole series



Compd	R/(H,F)	*S. aur.* Oxford	*S. aur.* MRQR	*S. aur.* CNSMR[a]	*S. pyog.* PS.[b]	*E. faec.*	MTT[c] 10 mg/kg	MTT[c] 5 mg/kg
39	CH_3CO–/H	0.5	0.5	0.5	1	1	0.81	0.17
40	HCO–/F	0.25	0.5	0.5	0.5	1	0.43	−0.01
41	CH_3–/F	2	2	2	1	4		
42	$HOCH_2CH_2$–/H	4	8	4	2	8		
43	 /F	0.5	1	1	1	2	0.28	0.07
44	$HOCH_2CO$–/H	0.25	0.5	0.5	0.5	1	1.20	0.71
45	 /H	0.25	0.5	0.5	0.5	1	1.04	0.63
46	 /F	0.25	0.5	0.5	0.25	0.5	0.98	0.70
47	 /F	0.25	0.25	0.5	0.25	0.5	0.55	0.31
48	 /H	0.5	0.5	0.5	1	1	1.16	0.64
49		0.5	0.5	0.5	1	1	1.02	0.49
50	$HOCH_2CS$–/H	0.25	0.5	0.25	0.25	0.5	0.07	−0.01
51	$(HOCH_2)_2CHCO$–/F	0.5	0.5	0.5	0.5	1	0.41	0.37
52	 /H	0.25	0.5	0.5	0.5	1	0.48	0.27
53	 /F	1	2	2	1	2		
54	 /F	0.5	1	1	1	2	0.5	0.25
55	 /F	0.25	0.25	0.25	0.5	0.5	1.42	1.02
56	 /F	0.25	0.5	0.25	0.25	0.5	0.32	0.10
57	 /F	0.25	0.5	0.5	0.5	1		
58	 /F (OH side chain)	0.25	0.5	0.25	0.5	1	1.01	0.59
3	Linezolid	0.5	1	0.5	1	1	1.40	0.05

MICs are expressed in mg/L. Results are $\log_{10}$ reductions from control.
[a]Coagulase −ve Staph. Methicillin resistant.
[b]Penicillin sensitive.
[c]Mouse thigh test.

to exceptional potency, with **33** showing a mean MIC of 0.1 μg/mL. The parents of many of these simple five-ring hydroxythiaheterocycles are not readily accessible, so the results for substituted compounds such as **35** and **36**, taken in conjunction with those of **27** did not encourage us to pursue them further. The isomeric isoxazole **38** was very promising (compare to **27**), but the parent was too reactive towards ring opening to have further potential. The in vivo activity of these thiaheterocycles was however limited (see below) so further optimisation concentrated on the isosoxazoles in the tetrahydropyridine series.

Further isoxazole compounds are displayed in Table 3. Simple acetyl (**39**) and formyl (**40**) derivatives were roughly equivalent to the pyran in potency, but alkylated compounds (e.g., **41**–**43**) were distinctly worse. Introduction of the hydroxyacetyl motif of eperezolid (**44**), and extending the theme to dihydroxypropyl analogues (**45**–**47**) gave compounds with MICs significantly better than those found for linezolid. Stereochemistry in the side chain made no difference to activity (cf **46** and **47**, or **48** and **49**). In spite of some early indications that difluoro compounds might be more potent, this was not generally the case (cf **45**, **46**). Where good potency was found for a particular substitution pattern, both series were made in the search for what could be key differences in pharmacokinetics. The increased in vitro activity in 5′-thioacetamido-methyl compounds[21] mentioned above led us to prepare the thioamide (**50**), which had superior potency to its oxygen analogue **44,** but like the sulphur-containing heterocycles discussed above, was poor in vivo.

One of the limiting features of these compounds for in vivo work was their aqueous solubility. Incorporation of potential solubilising substituents as in **51**–**54** gave active compounds but of lesser potency. More promising were compounds with oxidised sulfur such as **55**–**57**, and these were one of several groups selected for further study.

Activity in vivo was assessed using a mouse thigh model with a localised *S. aureus* infection. The lead six-membered heterocycles **6**, **17** and **18** and the first isoxazole **26** showed at most marginal activity in this test. Dosing of these compounds in mice showed that these compounds were subject to rapid clearance. This seems to be a generic problem with the dihydropyran series, which we had also noted in earlier work with C-5′ amides. The earliest compounds with sulphur-containing heterocycles at C-5′, **29**, **30**, were also poor in vivo, but potentially suffered also from the presence of the pyranyl function **30**.

A simple example of a tetrahydropyridine **39**, gave activity in vivo, and showed an encouraging blood level profile. The hydroxylated acyl compounds **44**–**49**, **55** were even better, giving high potency in the mouse thigh test, and detectable blood levels out to the end of the pharmacokinetic assay period. In this screen, such compounds showed superior performance to the reference compound linezolid.

The thioamide **50**, though potent in vitro, was inactive in vivo, which was probably to be expected due to oxidative metabolism at sulfur. The tetrahydropyridine-containing thiadiazoles **31**–**34** showed anomalous behaviour. Some such as **32** seemed to be showing in vivo effect commensurate with their in vitro potency, but others like **33** were modest in vivo relative to their in vitro activity. When blood levels were determined, it became a surprise that any in vivo activity had been seen, since the compounds were cleared at rates comparable to dihydropyrans. Experiments involving incubation of **34** with rat hepatocytes demonstrated cleavage of the thiadiazole heterocycle to the side chain alcohol **58**, presumably via an oxidative mechanism.

Conclusions

Our efforts to understand the factors necessary for biological activity in the conventional C-5′ acetamido substituted oxazolidinones has led to the discovery that this feature can be replaced by a wide range of five- and six-membered oxygen linked heterocycles. Limited substitution of the heterocycle is possible, and five-membered rings are more potent in terms of MIC than six. The steric limitations hypothesised on the basis of work in the acetamide series were shown to be present, but to be more subtle than an effect of mere molecular volume, the detailed shape of the substituent being also important. It also becomes apparent that the loss of activity on methylating the nitrogen in the amide series is unlikely to relate to the loss of an H-bond interaction, but must relate to a steric effect, either directly from its own bulk, or indirectly by changing the conformation of the side chain to one in which other critical binding interactions are lost.

Good activity in vivo can be obtained with the correct combination of substituents on oxazolidinone and pendant phenyl rings, but some of the thioheterocycles most potent in vitro give poor or misleading in vivo results as a consequence of their rapid metabolism. Most promising are the compounds bearing aryl tetrahydropyridine substitutents. With appropriate acyl functions such as dihydroxypropanoyl and close relatives, compounds can be obtained with high in vitro and in vivo potency and excellent pharmacokinetics in mice. One such compound **46** has been taken forward to early clinical studies as **AZD2563**. A separate more detailed desciption of the properties of this compound will be given elsewhere.

Finally, related studies on NH-linked analogues[24] to the above series have shown that comparable or more potent compounds are possible. The potency increases are in the order of 2–4-fold depending on Gram-positive target strain. It seems therefore that residual hydrogen-bond acceptor bonding potential remains in this series. Further, other studies on direct, ring *N*-linked azole heterocycles,[25] show that additional potent antibacterial series are possible. Thus, all three series in total demonstrate a potential for oxazolidinone analogues with improved potencies and other properties over

linezolid, and the scope for further diversification in this important new class of antibacterials.

In vitro and in vivo assays

The bacteria used in these studies were taken from the AstraZeneca culture collection. Minimum inhibitory concentrations (MICs) were determined by an agar dilution method by the NCCLS protocol using doubling dilutions over a concentration range of 128–0.008 mg/L and incubation at 37 °C.

The mouse protection test (MTT) used female Alderly park mice (Alp/ApfCD-1) weighing 25–30 g, which were inoculated intramuscularly in the right hand thigh with 0.1 mL inoculum prepared from an overnight culture of methicillin resistant *S. aureus* 601291, diluted 1:1000 and then mixed 1:1 with cooled molten agar. At 1-h post-innoculum, groups of four mice/treatment were dosed iv using 20% hydroxypropyl-beta cyclodextrin and 5 h later the thigh tissue was removed for homogenisation and plated out to assess bacterial numbers present.

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