new phosphorylation method for synthesizing 5′-diphosphorylated oligoribonucleotides. This group found that 2′-*O*-methylated oligonucleotides were approximately 10 times more efficiently used as primers for transcription catalyzed by influenza-virus-RNA polymerase than were the equivalent oligonucleotides lacking the 2′-*O*-methyl group.

Dr L. Pinto, Dr D. Brassard and their co-workers (Northwestern University, Chicago, IL, USA) working with scientists at Bristol-Myers Squibb (Wallingford, CT, USA) characterized the inhibition of the influenza M2 ion channel activity by BL 1743. BL 1743 (**3**), a spirene containing compound, is a novel inhibitor of influenza A virus. However, mutant viruses that are resistant to BL 1743 are also resistant to amantadine, and all known amino acid changes that result in resistance to amantadine also confer resistance to BL 1743. But some data indicate that BL 1743 and amantadine may interact differently with the M2 transmembrane pore region because inhibition by BL 1743 is complete and reversible, while that by amantadine is irreversible within the time frame of the experiment.

Joseph M. Colacino,
Lilly Research Laboratories
Indianapolis, IN, USA
W. Graeme Laver
The John Curtin School of Medical Research, The Australia National University, Canberra, Australia

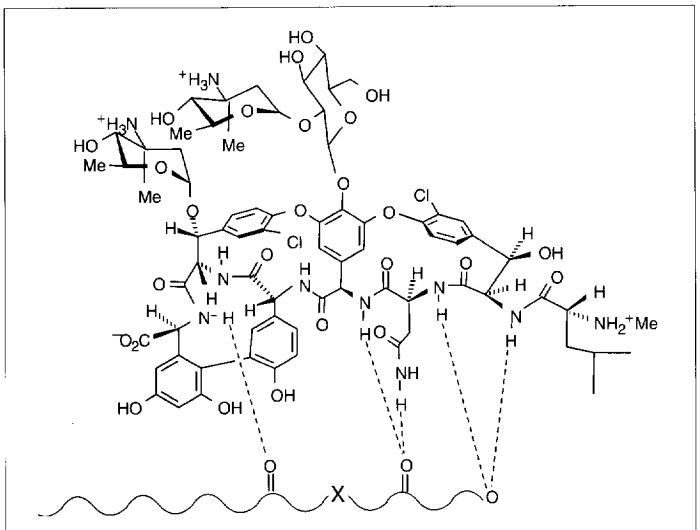
Beating superbugs with the Gulliver effect

UK researchers think they have puzzled out why an antibiotic related to vancomycin is so powerful, even though it should not bind to the vancomycin sites in bacteria any more strongly than the parent drug. According to Dr Dudley Williams of Cambridge University's Centre for Molecular Recognition the solution lies in what he calls the 'Gulliver effect'.

The glycopeptide vancomycin is often the last line of defence in a hospital's chemical weaponry against virulent strains of *Staphylococcus aureus*, which can cause lethal septicaemia. However, the increasing use of this drug in recent years has led to some bugs developing resistance to it. Williams notes that resistance follows the replacement of one D-alanine residue in the bacterial peptide overcoat with D-lactate, thus substituting a main-chain nitrogen with a oxygen. This change prevents the formation of a hydrogen bond and instead results in the repulsion of vancomycin through an unfavourable O–O interaction (see figure). Consequently, the vancomycin cannot undertake its task of killing the bacteria.

One new ally in the war against resistant bacteria is a chemical cousin of vancomycin, known as LY 264826B or chloroeremomycin. Researchers at Eli Lilly in Indianapolis have shown that a simple derivative of this compound, which contains a hydrocarbon tail, has activity against vancomycin-resistant bacteria. Williams and his team set out to elucidate the mechanism of action of this drug and find out how the new drug gets around the problem of repulsion by the altered amino acid.

In the latest issue of *Chemical Communications* (1996, 589 and 1445), Williams and his team describe evidence showing that chloroeremomycin carrying the hydrocarbon tail is likely to bind in almost exactly the same way to the bacterial cell wall, but with a clever twist that helps it avoid the effect of the repulsion. They found that vancomycin has one strong binding interaction with the bacterial cell-wall peptide, which is prevented by the amino acid swap, while the chloroeremomycin derivative is binding through surrounding groups. Many weaker adjacent bonds give rise to, what Williams calls, the 'Gulliver effect', where the hero was tied down by many weak bindings. 'An array of weak interactions is an effective way to restrict motion and ensure a strong net binding,' he explains.



Chloroeremomycin binding to the bacterial cell wall. When X is a nitrogen, a hydrogen bond is formed. When X is an oxygen, as in the resistant bacteria, repulsion results.

Whether or not bacteria develop resistance to the promising chloroeremomycin derivative, which after all works in the same way as vancomcyin but for the exact mode of binding, remains to be seen.

Williams does not wish to speculate on that point, but alludes to the fact that the new analogue would have to involve the natural selection of a new resistance mechanism – something which in thirty years of vancomycin therapy has not yet emerged.

David Bradley

  1359-6446/96/$15.00