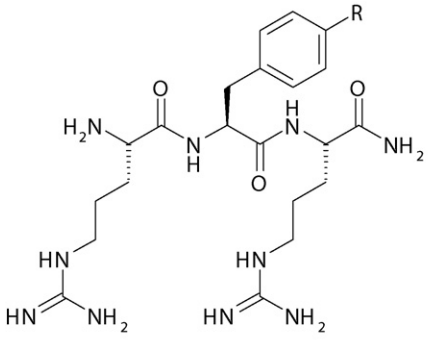
monitor

MOLECULES

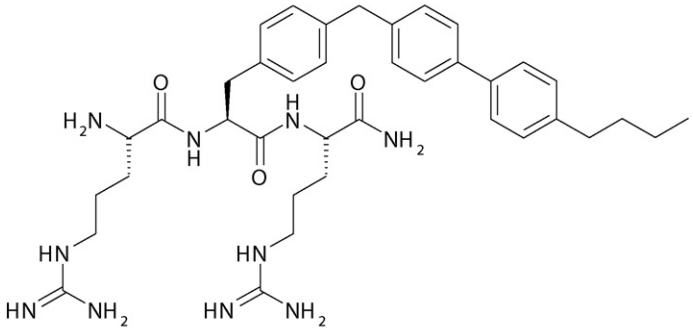
Combinatorial approaches to combating multidrug resistance

Antimicrobial peptides

The widespread use of antibiotics throughout the world has led to bacterial resistance to many commercially available antibiotics. This resistance development, coupled to the fact that only a few new classes of antibacterial agents have been introduced into the clinic during the last decades, has created a continued need for the development of novel antibiotics. To fill this need, cationic antimicrobial peptides are a promising class of future antibacterial agents [1]. Cationic antimicrobial peptides (CAPs) are believed to be less likely to induce resistance in bacteria, and this lower propensity for resistance development has been demonstrated by several research groups [2]. Reduced propensity for resistance development may arise from the unique mechanism of action of antimicrobial peptides. Although no exact mode of action has been established, most antimicrobial peptides are thought to act on, or at least to involve an action on, bacterial membranes [3]. Several models have been put forward to explain the interactions between CAPs and bacterial membranes [4], but no common view has been reached to date. A mechanism of action common to all CAPs is also highly unlikely to explain these interactions, as a wide range of biological activities have been found for different classes of CAPs. Considering the development of CAPs into drugs, several challenges exist. One approach has been the development of small molecular weight CAPs [5]. In a recent study [6], a library of tripeptide derivatives containing the unnatural amino acid 4-iodo phenylalanine has been prepared using a Rink Amide Linker [7]. These novel tripeptides were synthesized through Suzuki–Miyaura cross-coupling reactions. After synthesis, tripeptide derivatives of general formula (i) were tested for their ability to inhibit the growth of *Streptococcus pyogenes*, *S. aureus*, MRSA, and MRSE. The results obtained were expressed as the minimal inhibitory concentration (MIC in micromoles). Of the peptides synthesized and tested, generally all of the derivatives displayed significant increases in antimicrobial activity compared to the control peptides used. *S. pyogenes* was found to be the least susceptible bacterium in the test panel, while all peptides were most active against MRSE. One of the most potent peptides isolated was (ii) which possessed a MIC of 16 μM against Streptococcus pyogenes and a MIC of 4.1 μM against MRSE. Additionally, the peptides were also tested for their ability to produce hemolysis of human erythrocytes. Most of the peptides were found to be non-hemolytic within the concentration range tested (up to 500 μg/mL). In summary, the low hemolytic propensity of these peptides in combination with their high antimicrobial activity increases the chances that such entities could be developed into clinical candidates, allowing for the future development of drugs effective against multidrug resistant pathogens.



(i)



(ii)

Evaluation of new taxoids derived from 2-deacetoxytaxinine J

Paclitaxel (Taxol®) is a complex natural diterpene extracted from *Taxus brevifolia*. Paclitaxel and its derivative, docetaxel, are two of the more important anticancer agents for the treatment of ovarian and breast cancer [8]. The use in a clinical setting of anticancer drugs such as these, has

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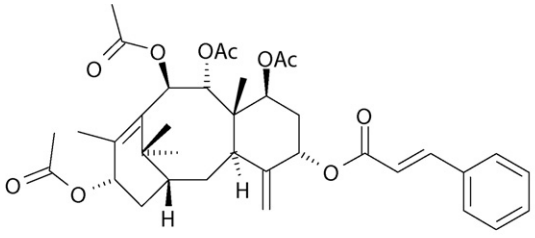
revealed a number of undesirable side effects and multidrug resistance (MDR). MDR induced by taxoid treatment in tumour cells is an obstacle to the successful application of chemotherapy in many cancer treatments. In particular, MDR is a phenomenon whereby tumour cells that have been exposed to one cytotoxic agent develop cross resistance to a range of structurally and functionally unrelated compounds. Drug resistance developed in cancer cells may be controlled by many mechanisms. One such postulated mechanism relates to the overexpression of particular proteins in cancer cells, such as *P*-glycoprotein (P-gp), which expel hydrophobic anticancer compounds and maintain their intracellular concentration below a cytotoxic level [9]. Of the natural taxoids, 2-deacetoxytaxinine J (DAT-J) (iii) has emerged as an active P-gp inhibitor with a potency higher than that of verapamil [10]. DAT-J (iii) is extracted in low amounts from several yew species, but it can be synthesised from the natural alkaloid 20-deacetoxyaustropicatine (DAS) (iv) available in multigram amounts from Taxus × media Rehd. Cv. HicKsii. Additionally, unlike other cinnamates related to taxine, (iii) does not show cardiac toxicity, and so may provide an important starting material for the synthesis of new reversal agents. For these reasons, the development of a procedure using (iii) as starting material for the preparation of new bioactive taxinine analogues, is desirable. Recent work [11] has reported on the preparation of a small library of DAT-J analogues (v) and their biological screening as new putative MDR-reversing agents against multidrug-resistant breast tumour cell lines. Biological evaluation of DAT-J analogues of general structure (v) synthesized in this work were tested *in vitro* for their MDR revertant activity in the human mammary carcinoma cell line MCF7-R; this cell line being resistant to paclitaxel. The compounds were tested at non-cytotoxic concentrations (1.0 and 0.1 μM) in combination with paclitaxel. The activity was expressed as an IC_{50} (in nM), that is, the concentration that caused 50% inhibition of cancer cell growth. One of the most potent compounds synthesized and tested was (vi) which possessed an IC_{50} of 31 nM. Further work in this area is warranted to continue development of compounds within this series to optimize for biological activity and continue to reduce any undesirable side effects and multidrug resistance.



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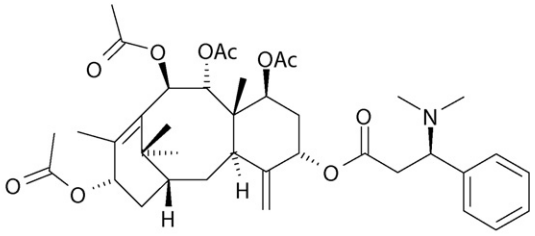

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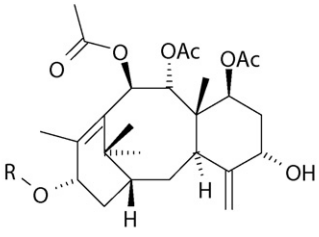

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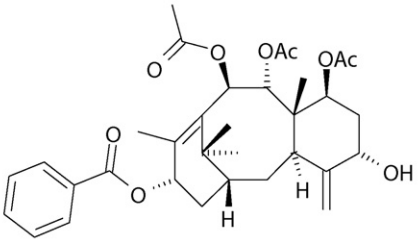

(vi)

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