ANTIBACTERIAL PROPERTIES OF DITERPENES AND THEIR DERIVATIVES

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ABSTRACT

Totarol is a diterpene isolated in large quantities from *P. totara* and a range of other plants, that has been shown to possess significant antibacterial activity against Gram positive bacteria. It has not been possible to unequivocally determine the mode of action by which this activity occurs. This research aimed to determine the mode of action of the diterpene and study a range of derivatives to elucidate a structure-function relationship for the diterpene to enable directional synthesis of future derivatives possessing increased activity and bioavailability.

The antibacterial activity of totarol and 29 derivatives was tested against *H. pylori* and *S. aureus*, two significant human pathogens, as representative Gram negative and Gram positive bacteria. Four compounds were found to possess significant activity against *S. aureus*, both MRSA and MSSA, although no significant activity was observed against *H. pylori*. The ability of the derivatives to potentiate the activity of existing β-lactam antibiotics such as methicillin was also investigated for MRSA and *E. coli*. Seven compounds including totarol were found to potentiate methicillin, one 256-fold, although no potentiation activity was exhibited against *E .coli*.

The incorporation of radiolabelled precursors was used to investigate the effect of totarol on the synthesis of three macromolecules, DNA, protein and peptidoglycan, in MRSA. No primary inhibition was detected, indicating that the mode of action of the diterpene was not inhibition of synthesis of any of these macromolecules.

The effect of totarol on the cellular respiration of MRSA was also investigated, showing 70 % inhibition of respiration at MIC levels, and complete inhibition of respiration at five times that concentration. It was therefore concluded that this was the most likely primary antibacterial effect of the compound.

The effect of totarol on the production of PBP 2a, an important protein in the β-lactam resistance mechanism of MRSA, was also investigated using a novel, non-radioactive labelling procedure to detect the protein. However, although a variety of

strategies were employed to detect the protein, none were successful, and the experiment set aside until the arrival of anti-PBP 2a antibody for use in another strategy.

Future work on this project that could be undertaken includes determination of the effect of the derivatives on cellular respiration under potentiation conditions, determination of the component(s) of the respiratory chain affected by totarol, and the investigation of the effect of the diterpene on PBP 2a production and function using antibody to detect the protein.

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