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A theoretical study of the colchicine binding site of tubulin—a molecular modelling study

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In the treatment of cancer, anti-mitotic compounds have proved to be highly successful. For example, Taxol achieves its effect through the stabilisation of the microtubule polymers. Other compounds also exist, for example, the colchicine type compounds (Figure 1), which are believed to exert their effect through the inhibition of polymerisation of tubulin into microtubules, thereby blocking mitosis.

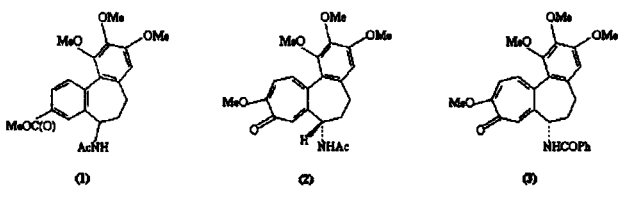

Figure 1. Derivatives of Colchicine considered.

In an attempt to gain further information regarding the receptor-colchicine interaction(s), we have initiated a line of research involving the use of molecular modelling in the development of a model which can be used in the design of novel anti-tumour agents. In particular, we believe that the consideration of the derivatives of colchicine, and their low energy conformers, would aid the drug design process.

The molecular structures of the colchicine derivatives were all constructed and minimised (using the fastest minimisation routine available - cycles of 300 iterations were attempted until the gradient dropped below 10^{-3}) within the CACHE molecular modelling software. The structures were refined under Mopac using PM3 parameters. Conformational analysis was also undertaken within CACHE using multiple pass procedure (calculations were performed in Mechanics using Augmented MM2 parameters). For the superimpositioning study, Alchemy III molecular modelling software was used.

From an initial consideration of the 2D structure of the colchicine derivatives, we hypothesised that the differences in biological activity within these compounds did' not reside within the trimethoxy substituted phenyl ring and this was therefore used in the superimpositioning process.

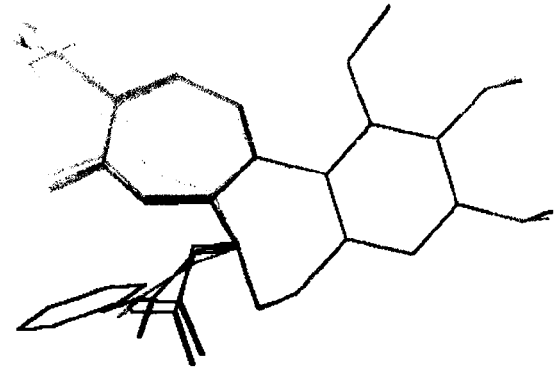

Figure 2. Superimposition of derivatives of colchicine.

The superimpositioning of the conformers of colchicine shows two distinct areas taken up by the derivatives considered (Figure 2) : one which involves the tropone ring, and; the other the cycloheptyl ring.

The results would therefore appear to suggest that there are 'two sides' of colchicine (and its derivatives) : one binding to the receptor site via hydrogen bonding about the tropone and cycloheptyl rings (and where derivatisation may take place); whilst the alternative side is involved in hydrophobic interactions with the binding site (and where derivatisation is not easily accommodated, i.e. the area about the trimethoxy phenyl group. In conclusion, we believe that the hypotheses obtained from this study can be used in the design of novel anti-mitotic compounds.