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# Function oriented de-risking and de-convoluting of the natural product discodermolide

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Natural medicinal compounds are typically complex, making their synthesis long and expensive. Discodermolide is a marine natural product found in deep sea sponges, shown to outperform Taxol as a microtubule stabilizer. Taxol is the first-line chemotherapy for breast and ovarian cancer, patients taking it to have a 75% chance of relapse and sadly, almost one million women will die every year from these cancers. The Novartis gram-scale total synthesis is best performing, producing a 0.65% yield over 33 steps. I applied function-oriented synthesis to recapitulate the biological activity of discodermolide with a simplified structure. Discodermolide failed a phase I trial due to cases of pneumonitis, thought to be due to chemotherapy-induced senescence (CIS). By analysing the structure-activity-relationship of discodermolide, the key moieties that interact with tubulin were identified and the groups pointing out into solvent were removed to derive the minimum effective skeleton. This structure was docked in Auto dock Vina to ensure a similar binding pose was adopted to discodermolide. Five positions on the structure were identified and selected to add fragments from the ZINC library and from the library of 500 R groups compiled by Takeuchi. This generated a massive virtual library of 100,000 analogues, from which a virtual screening was performed. This successfully identified analogues that interact with distant loops in the binding site, not encountered by native discodermolide. The WHALES algorithm developed by Schneider was employed to scaffold hop to synthetically accessible mimetics of the ten best ligands identified in the screening, the best of which 'DSC011' adopts a consistent binding pose consistent with the discodermolide crystal structure. The proposed retrosynthesis for this structure is 10 steps, significantly shorter than the Novartis route. An analogue adducted to beta-galactoside was designed to afford cytotoxicity to senescent cells, presenting a route to overcome the CIS that held back discodermolide.

## References

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## Biography

Joshua graduated from Imperial College London with a First in MSc Chemistry in 2020. In 2024 he will graduate from the University of Cambridge Medical School (MBChB). He has published structural biology papers in Angewandte Chemie cited many times and has written papers on immunotherapy for the BMJ. Joshua developed an interest in marine natural products after writing a total synthesis review of discodermolide with Professor Don Craig. Outside of his studies, Joshua works part-time as a computational chemist at Cambridge Psychopharma and as a clinical consultant at Everna. His background in both drug discovery and clinical medicine allows him to understand the development of drugs from benchtop to bedside.

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