Applications of synthetic organic chemistry to biological problems

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Introduction
Synthetic organic chemistry is an immensely powerful tool for Chemical Biology, which we exploit in a wide range of biological problems: from the directed evolution of enzymes for use in synthetic chemistry (using biology to control synthetic chemistry), to chemical genetic studies (using chemistry to control biology). A summary of some of our published work in 2005 is provided. You might like to browse our group webpages at www.asn.leeds.ac.uk to find out more about what we do!

Applications of conformationally diverse bisindolylmaleimides
We have used a range of experimental and theoretical approaches to determine the conformational properties of constrained bisindolylmaleimides \( \text{1} \). We have shown that the population of the limiting syn and anti conformations varies as a function of the tether length \( n \), and that this family of compounds is conformationally diverse. The family of compounds is a useful tool for comparing the active sites of the protein kinases; this chemical approach requires no structural knowledge and yet still concentrates on the comparison on the proteins’ active sites.

In other collaborations, our bisindolylmaleimides are being exploited as chemical tools for dissecting the mechanisms of stem cell differentiation and for structural studies of protein kinases.

A two-directional approach to aza-C-linked disaccharide mimetics
We have developed a two-directional approach to the synthesis of aza-C-linked disaccharide mimetics. Unusually, for a two-directional approach, the target molecules do not possess any hidden symmetry. The approach is highly general, and can be applied to the synthesis of a wide range of disaccharide mimetics; for example, complementary conditions were identified for the two-directional functionalisation of \( \text{2} \) to give the protected mimetics \( \text{3Bd’} \) and \( \text{3Ad’} \)

Fig. 2. Left panel: Conformational diversity of bisindolylmaleimide cyclophanes. Right panel: Docked bisindolylmaleimide cyclophane within the context of a kinase.
(Fig. 3). This work was published as the inaugural paper in *Beilstein Journal of Organic Chemistry*.

![Diagram](image)

**Figure 3.** Complementary two-directional synthesis of aza-C-linked disaccharide mimetics

Conditions: a) NMO, cat. OsO₄, acetone-H₂O; (b) Ac₂O, pyridine; (c) OsO₄, TMEDA, CH₂Cl₂, -78 °C

In a related synthetic study, we have also prepared a library of diverse aminoglycoside derivatives which we have exploited as powerful chemical tools for probing the functions of RNA molecules.

**Parallel synthesis of a library of sialic acid mimetics using a variant aldolase**

In collaboration with Alan Berry, we have directed the evolution of a range of aldolases with catalytic activity of value to the synthetic chemist. For example, we have evolved a variant of sialic acid aldolase with sufficiently broad substrate specificity for application in the parallel synthesis of a range of precursors of influenza A sialidase inhibitors. Ozonolysis of the alkenes 5, and variant aldolase-catalysed C-C bond formation yielded a small library of mimetics (Fig. 4). In related work, we have evolved a pair of complementary aldolases which catalyse the selective formation of either of the diastereoisomeric mimetics 6 and 7.

![Diagram](image)

**Figure 4.** Parallel synthesis of the sialic acid mimetics 6/7. Reagents and conditions: a) EDC, HOBt, R¹R²NH, CH₂Cl₂; b) 1:1 TFA-H₂O; c) O₃, MeOH then Me₂S; d) 2 x 10⁻² mol% E192N, pyruvate, pH 7.4 buffer.

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Publications


