Professor Charles M. Marson  
Research Summary  

1. Medicinal chemistry: synthesis of anti-cancer agents and enzyme inhibitors

1.1 Inhibitors of Histone Deacetylase (HDAC)

Histone deacetylases are hydrolases that catalyse the removal of acetyl groups from the terminally acetylated lysine residues on histones (diagram below). The resulting protonated amino groups are attracted to anionic phosphate groups of the DNA regions round which the histone protein core is assembled, leading to a compacted (chromatin) structure in which regions of DNA have become inaccessible for transcription. Since such gene repression can be associated with cancer, HDAC inhibitors are considered an important epigenetic therapy [1] but have also been proposed for use in several other diseases.

Initial studies in our group led to the synthesis of the very potent in vitro HDAC inhibitor 1 ($IC_{50} < 1 \text{ nM}$).[2] Although in vitro data were not promising, replacement of the ether linkage by a thioether gave results equipotent to Vorinostat in several in vitro tests.

Modeling of the binding of ligands 1 (magenta), 2 (yellow) and TSA (turquoise) to HDAC1.  
Left: cap region of the enzyme; Right: side-on view and coordination of inhibitors to zinc (brown sphere).
Modeling confirmed that compounds such as 3, possessing bifurcation in the cap region, could provide significant additional binding interactions with the enzyme surface. Indeed, 3 showed at least ten-fold more potency than vorinostat in several *in vitro* assays, and also showed potent activity in pre-clinical models of multiple myeloma and of non-Hodgkin's lymphoma.[3]

Although hydroxamic acids as above confer potency, off-target effects can lead to toxicity. An alternative zinc-binding group are benzamides such as mocetinostat, developed by Novartis.[4] It was of interest to see whether the potency of such benzamides could be widened by replacement of the water-solubilising pyridine ring that could be prone to metabolic degradation. Additionally, in so many HDAC inhibitors, isoform selectivity is usually poor. We asked whether variation of both rings and the introduction of stereochemistry could afford desirable features without undue loss of HDAC inhibition. Below shows the strategy and synthetic approach to the 5-membered heterocyclic replacements, prepared from a common intermediate isothiocyanate and readily available enantiopure amino alcohols.
Indeed, isoform selectivity was considerably altered, with good selectivity for HDAC3 as well as increased potency,[5] as compared to the moderate selectivity of mocetinostat for HDAC1 and HDAC2. Docking of ligand 1 in the catalytic site of HDAC3 is shown below. Further optimisation of the 5-membered ring (to give a 2-aminooxazole) and variation of its substitution and stereochemistry afforded an even more potent and selective inhibitor of HDAC.[6]

1.2 Inhibitors of Lipoxygenase (LOX) with antioxidant properties

Reactive oxygen species are associated with inflammation implicated in cancer, atherosclerosis and autoimmune diseases. Owing to the crucial role of oxidative stress and the complex nature of inflammation, multi-target agents represent a powerful approach to therapy in diseases involving reactive oxygen species. In series of substituted 2,4-diaminopteridines the compound below (docked in soybean LOX) showed potent antioxidant properties (inhibition of linoleic acid peroxidation at IC$_{50}$ = 100 nM) and potent inhibition of soybean LOX (IC$_{50}$ = 100 nM).

1.3 Inhibitors of Peptidylarginine deiminase (PAD)

PAD enzymes catalyse the hydrolysis of protein-bound arginine residues to citrulline groups. The change from a cationic group to a neutral one prevents normal protein recognition and leads to cell death in healthy cells. Compound 3 below was designed as a transition state analog and with an achiral drug-like cap region to replace the peptide
chain of the natural substrate; this compound was effective in increasing neuronal cell survival following challenge with thapsigargin.


2. Synthesis of fused and bridged scaffolds for medicinal chemistry

Natural products have been a major contributor, both as therapeutic agents and in suggesting new scaffolds for medicinal chemistry. In particular, it is increasingly being recognised that saturated compounds generally possess superior drug-like properties than those containing multiple aromatic or heteroaromatic rings.[1] Gnidilatin is an example of an alicyclic compound with anti-cancer properties. A simplified aza-analog of gnidilatin (below) was synthesised in enantiopure form via a regioselective acyliminium cyclisation, demethylation and oxidative dearomatisation.[2]
3. Catalytic asymmetric synthesis

Catalytic asymmetric processes that create more than one chiral centre, especially tandem reactions, are of much contemporary interest.\[1\]

3(2H)-Furanones can be prepared by a catalytic asymmetric protocol from enynones which if electron-rich (e.g. R = OEt) require only one reagent and involve two reactions in a single operation, a domino process.\[2\] In some cases Pd(II) catalysis has been shown to be an alternative to Hg(II). Substituted 3(2H)-furanones bearing a quaternary centre are readily obtained in high ee, as are the less robust 2-monosubstituted derivatives. Such furanones could be useful intermediates in natural product synthesis.

This reaction was used to synthesise the densely functionalised precursor 1\[3\] that could in principle be cyclised to the bridged system 2, with potential for conversion into type compounds related to zaragozic acids.

Amine catalysts that switch their enantiomeric bias simply upon N-methylation shows that possessing both enantiomeric catalysts is not always essential for preparation of a product in both enantiomeric forms.\[4\]
4. Synthetic methodology: tandem and stereocontrolled processes

4.1 Carbocyclisations

Treatment of 2,3-epoxyalcohols with Lewis acids can induce cyclisations, but the outcome depends on the relative configuration of the epoxyalcohol, and can often be rationalised in terms of a chelated intermediate. Where cyclisation of a chelated intermediate is possible (the nucleophilic and electrophilic termini being sufficiently close) this is the preferred outcome, as shown below, in which single isomers of either a six-membered ring or a seven-membered ring were isolated.
For homoallylic epoxy alcohols, which would require a six-membered ring for chelation, the fused systems obtained stereoselectively can be rationalised in terms of an epoxide rearrangement followed by a tandem cyclisation involving π-nucleophile trapping of an oxonium ion.

\[
\text{SnCl}_4 \rightarrow \text{X-ray} \quad 80\%
\]

\[
\text{SnCl}_4 \rightarrow \text{Cl}_3\text{SnO} \quad 50\%
\]


### 4.2 Synthesis of 5- and 6-membered heterocycles

#### (a) Polysubstituted furans

A catalytic cyclisation of 1-alkynyl-2,3-epoxy alcohols provides a regioselective synthesis of furans with up to three substituents. The method has been applied to the synthesis of a naturally occurring furanoid fatty acid, F\textsubscript{5}.

\[
\begin{align*}
\text{HgO (0.32 mol\%)} & \quad \text{in eq. 1.5 mM} \\
\text{H}_2\text{SO}_4 & \quad 88\%
\end{align*}
\]


#### (b) Substituted tetrahydropyran-4-ones

Tetrahydropyran rings and related systems are found in numerous natural products. A stereospecific rearrangement to substituted tetrahydropyran-4-ones was discovered in this group. A hydride shift takes place with inversion at the epoxide carbon atom; the process is highly diastereoselective, and any enantioselectivity is preserved during the reaction. The dihydropyranone products could find use as intermediates in total synthesis.

(c) Substituted piperidin-2,4-diones

In an approach to piperidine alkaloids such as anabasine, an enantioselective synthesis of piperidin-2,4-diones via regioselective Dieckmann cyclisation was achieved (as below). The β-amino ester precursors were prepared by conjugate addition according to protocols developed by Prof. S. G. Davies.

![Chemical Structure](image)


4.3 Stereocontrolled 1,2-migrations

1,2-Migrations of H and alkyl (Wagner-Meerwein rearrangements) in natural product frameworks have been long known. Using an epoxide as the electrophile to induce rearrangement, we showed that numerous groups at the 1-position of a 2,3-epoxyalcohol undergo efficient migration in the presence of Lewis acids, especially SnCl₄.[1,2] Migration of cyclopropyl is shown below (eq. 1), but other cycloalkyl, methyl, vinyl, alkynyl, aryl, and 2-furyl also migrate, among many groups, all with formation of a single diastereoisomer. In several cases, a mixture of diastereoisomeric 2,3-epoxyalcohols underwent rearrangement with inversion to give a single diastereoisomeric ketone product with a newly formed quaternary centre (evidently via unrestricted C-C bond rotation). The protocol can be applied to carbocyclic ring expansions (eq. 2), again with stereocontrol.

![Chemical Structure](image)


4.4 Tandem cyclisations via acyliminium ions

Multiple bonds can be formed with stereocontrol by generating an acyliminium cation that undergoes carbocyclisation.[1-3] Solvent can determine whether an acyliminium ion is formed, and hence the constitution of the product.[2,3]
