Configurations and reactivity control of constrained macrocycles - Steve Archibald (s.j.archibald@hull.ac.uk)

Introduction

Macrocycles are ring type ligands that can bind to metal ions to form highly stable compounds. The nature of a ring ligand is such that the conformation will be constrained. Addition of further linking groups across the ring will increase the level of constraint and decrease the number of possible configurations [1]. The configuration (shape) will determine the properties of the compounds as drugs or biologically active moieties. The research challenge is in the design of appropriate constrained derivatives and their synthesis. Biological testing can then be carried out. Structural data is key to the design of molecules and their synthesis.

1. Chemokine receptor binding drugs

CXCR4 chemokine receptors are found on the surface of immune cells, and together with the specific natural ligand CXCL12 have been revealed to play a role in a number of disease states. For example, the CXCR4-CXCL12 signalling system has involvement in cancer progression and metastasis, and the development of rheumatoid arthritis. Also, within the last ten years the CXCR4 and CCR5 co-receptors have been revealed as the entry route for HIV into cells, generating interest in a new therapeutic approach to treatment via entry inhibitor drugs rather than the current preference for reverse transcriptase and protease inhibitors. Our aim is to synthesise new antagonists for the CXCR4 co-receptor. They are configurationally fixed macrocyclic compounds where the unrestrained equivalent is a known CXCR4 antagonist. We are attempting to gain further insights into the essential design features for this drug class through computational, spectroscopic and biological studies [2].

2. Novel radiopharmaceutical constructs incorporating macrocycles

There is much current interest in the applications of bifunctional chelators based on tetraazamacrocycles such as 1,4,8,11-tetraazacyclotetradecane (cyclam) to biology and medicine, for example, in MRI contrast agents and radioimmunotherapy [3]. In particular, a great deal of research effort in this area has been focused on 6-(4-aminobenzyl)-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid and its analogues.

Applications of structural data to research

Structure activity relationships for drugs

Examination of structural data and correlation with biological activity is just as valuable for metal based drugs as organic molecules. However accurate molecular modelling can be considerably more challenging for coordination complexes. Useful insight can frequently be gained by an analysis and examination of the structural parameters of related compounds in the Cambridge Crystallographic Database. In our work we make use of both the ConQuest software and the CrystalWeb web browser system. Both are accessed via the Chemical Database Service.

Predictions of reactivity on a structural basis

Control of reactivity in a molecule is essential to synthesising the desired product. Existing structural data can inform the synthetic process and design of...
selective routes. This is particularly true for macrocyclic compounds [4].

Formation of rigid molecules may orient some parts of the molecule for preferential reaction. For example, the rigid compound shown in figure 3, has only two reactive nitrogen positions \( (\text{exo}) \) and two non-reactive nitrogen positions \( (\text{endo}) \). This data allowed us to design a related precursor that would undergo the same selective reactions to give a novel biologically active target molecule.

Summary

The Cambridge Crystallographic Database accessed via the Chemical Database Service provides an excellent source of structural information that can be used both as a starting point for computer based modelling studies and to gather further information about structural flexibility. For example the two X-ray structures shown in figure 4, both contain copper with the same chelator, however the Jahn-Teller distortion can either occur across the macrocycle or along the axis formed by the two pendant arms. This structural flexibility goes some way to explaining the insufficient \textit{in vivo} stability of the radiopharmaceuticals based on these macrocycles.

![Figure 3: X-ray structure showing reactive positions](image)

![Figure 4: X-ray structures showing complex flexibility](image)


