# Chapter 2
# Aims and Objectives

## 2.1 Aims

Control of crystal structure by crystallisation to deliver chemically and physically pure substances is of significant importance in the manufacture of safe, effective and high quality pharmaceutical products. The overall aim of this work is to investigate a range of experimental and computational approaches for the discovery and better understanding of the key factors underpinning solid-state structure and diversity of pharmaceuticals. A range of crystallisation techniques and analytical tools has been applied in combination with statistical modelling approaches, CSP, and a number of semi-empirical and quantum-mechanical approaches to study the molecular and crystal structures.

The work reported in this thesis has focussed on discovery of physical forms and exploration of the relationship between molecular structure and crystallisability. It has also concentrated on two groups each comprising of two structurally related molecules to investigate the influence of changes in the molecular structures and substituents on the conformation, intermolecular interactions, packing motifs in the crystal lattice, and overall extent of solid form diversity and to probe how predictions can aid in the interpretation of the experimental crystal energy landscape. The compounds studied are: olanzapine (OZPN) and clozapine (CZPN) in group 1, and loxapine (LXPN) and amoxapine (AXPN) in group 2 (Fig. 2.1).



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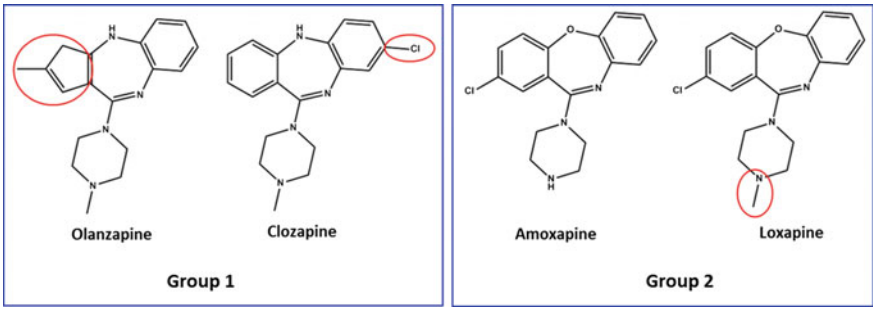


**Fig. 2.1** The four compounds studied in this thesis. The differences in the chemical structures within a group are highlighted in *red*

## 2.2 Objectives

- Development and validation of high throughput crystallisation and analysis (HTCAA) methodology for physical form screening using quartz 96/48-well plates with an automated system for collecting high quality Raman spectra.
- Development of a statistical model for prediction of the crystallisability of a set of organic molecules based on calculated physicochemical descriptors.
- Comprehensive experimental physical form screening of molecules in group 1 (OZPN and CZPN) as well as in group 2 (AXPN and LXPN) by employing multiple crystallisation techniques to identify novel physical forms and determine their crystal structures using X-ray powder diffraction (XRPD) or single crystal X-ray diffraction (SXD).
- Exploitation of predicted crystal energy landscapes to aid the accurate interpretation of the experimental physical form screening results.
- Application of molecular packing analysis tools to the crystal structures of target molecules to identify key packing motifs and structural relationship amongst them.
- Use of computational techniques such as statistical modelling approaches and PIXEL calculations to develop a comprehensive understanding of the structural and thermodynamic factors directing crystal packing in different physical forms.
- Application of geometry optimisation calculations using CASTEP to obtain accurate H-atoms position and verification of the accuracy of the crystal structures solved by XRPD.

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