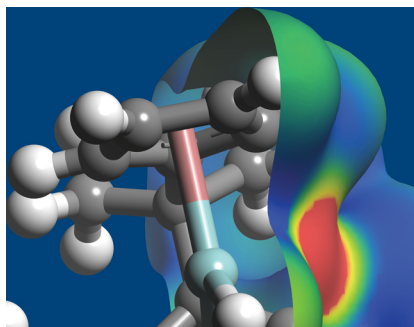


# COMBINING TARGETED SCREENING AND DIRECTED CRYSTALLIZATION EXPERIMENTS FOR POLYMORPHS OF DIFLUNISA



The ability to explore the molecular packing of potential polymorphs of an organic compound in silico can be of significant importance to the biotechnical and pharmaceutical industries, helping to guide experiments and hence save time and money.

## Industry Sector

- Pharmaceutical

## Key Products

- Materials Studio
- Polymorph
- Predictor
- Reflex Plus
- X-Cell
- COMPASS
- Discover
- DMol<sup>3</sup>

Researchers at AstraZeneca Plc (UK), the University of Manchester School of Chemical Engineering and Analytical Sciences, and Accelrys have explored a novel approach for polymorph screening of diflunisal (a fluorinated aromatic carboxylic acid used as non-steroidal anti-inflammatory drug) using a suite of crystal structure prediction software combined with subsequent specifically targeted experimental crystallization

Using a process of predicting structures, identifying and analyzing hydrogen bonding motifs, and applying the data to the rational design of crystallization experiments, the researchers were able to yield significant numbers of new, previously unsolved crystalline polymorphs of diflunisal from a limited experimental screen. The combined software/experimentation process was validated by its success. The ability to explore the molecular packing of potential polymorphs of an organic compound in silico can be of significant importance to the biotechnical and pharmaceutical industries, helping to guide experiments and hence save time and money.

Polymorphism is common in organic compounds, where, for example, variation in the hydrogen bonding of functional groups can lead to a variety of possibilities for molecular packing in the crystallized form. These polymorphic crystals each have different physical and mechanical properties such as melting point or solubility, and regulatory requirements exist for thorough exploration and testing of possible polymorphs during the development of pharmaceutical products.

Usually, this exploration is a long-drawn-out process and success is not guaranteed: traditional experimental techniques using only solvent screens (where

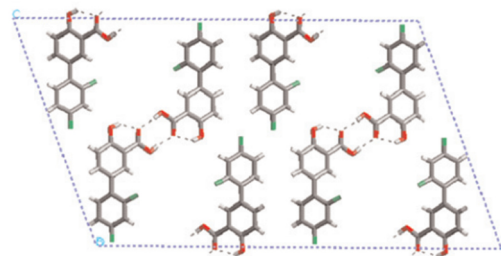
the compound is recrystallized from various solvents) may not isolate every potential variant. Therefore, anything that gives researchers the ability to explore all possible polymorphs for new molecules is invaluable. As reported in the journal *Crystal Growth and Design*<sup>1</sup>, researchers at AstraZeneca Plc, University of Manchester, and Accelrys developed something called the 'whole output strategy'. The strategy is to use software and experimentation synergistically to produce results, and began with using Polymorph Predictor<sup>TM2</sup> to predict all possible polymorphs for diflunisal in the five most common space groups,  $P_{11}$ ,  $C_2/c$ ,  $P_{21}$ ,  $P_{212121}$ , and  $P_{21}/c$ , based on the molecular structure of diflunisal. The whole output was then examined using graph set analysis<sup>3</sup> to identify common hydrogen-bonding motifs. Crystallization conditions were then manipulated via solvent selection to promote the formation of crystals containing desirable motifs. In this study, crystals were grown from acetic acid, toluene, chloroform, ethanol, and ethanol/water mixtures.

Owing to the significant difficulties involved in growing crystals of appropriate size for single crystal X-ray studies, powder diffraction data were collected to enable structure solution. The powder diffraction patterns were first indexed using X-Cell<sup>4</sup>. Geometry optimization was carried out for the diflunisal molecule with the COMPASS forcefield<sup>5</sup> in Discover. The molecular geometry was then passed on to the Reflex Plus<sup>6</sup> module for crystal structure determination.

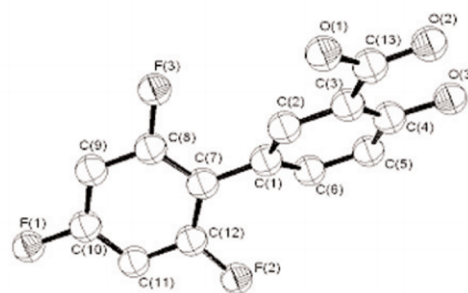
## CONCLUSION

The hydrogen-bonding motifs in the obtained crystal structures were examined carefully against the commonly found motifs identified earlier. The results validated the crystallization models put forth by the polymorph prediction and graph set analysis.

By using the new 'whole output' strategy, the researchers were able to characterize the hydrogen-bonding motifs, classify predicted structure, and guide experimental protocol, resulting in a yield of significant numbers of new, previously unsolved crystalline polymorphs of diflunisal from a limited experimental screen and so highlighting the insight offered by modeling and simulation software.



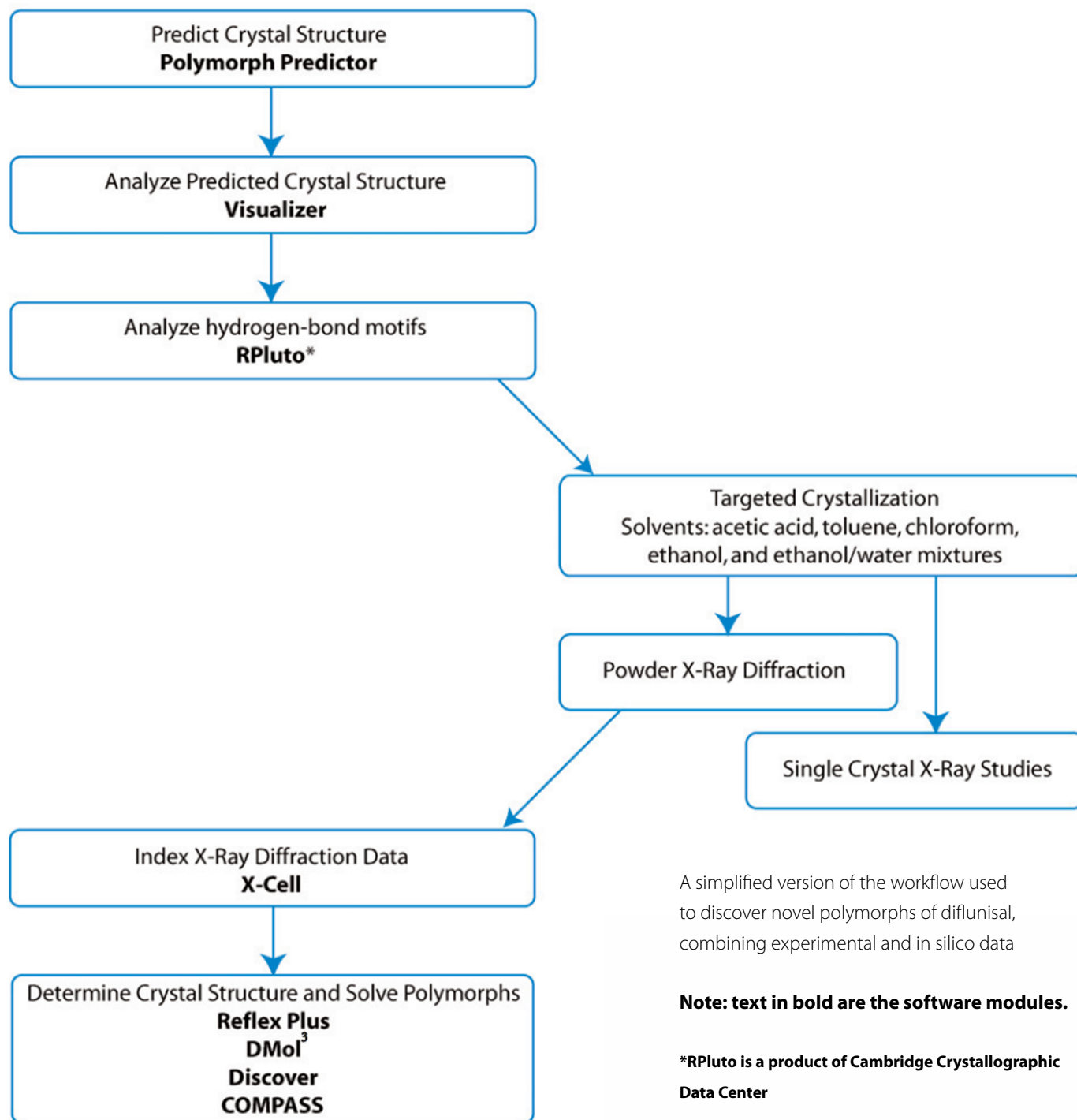
**Figure 1:** A packing diagram of polymorphic form V of diflunisal (obtained from Cambridge Structure Database)



**Figure 2:** The known molecular structure of one polymorph of diflunisal with disordered fluorine

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A simplified version of the workflow used to discover novel polymorphs of diflunisal, combining experimental and in silico data

**Note: text in bold are the software modules.**

\*RPluto is a product of Cambridge Crystallographic Data Center

To learn more about Materials Studio go to [accelrys.com/materials-studio](http://accelrys.com/materials-studio)