

CRYSTAL STRUCTURE SOLUTION AND REFINEMENT OF A SERIES OF D₂/β₂ RECEPTOR AGONISTS USING LABORATORY X-RAY POWDER DIFFRACTION DATA

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The crystal structures of four compounds that were developed for the potential treatment of COPD, two precursor molecules and a degradation product have been solved from laboratory XRPD data using a simulated annealing algorithm. The compounds, which span a range of conformational and crystallographic flexibility and include examples of both salts and hydrates, represent a considerable challenge to XRPD. The presence of disorder in some structures was an additional complicating factor that was overcome. Particular attention was paid to the preparation of sharply diffracting crystalline samples whenever possible and variable count time schemes were implemented where appropriate in order to maximise the chances of obtaining a successful structure determination. Although synchrotron data were collected from selected compounds, no such data were in fact required in the solution and refinement process.

The performance of the SA algorithm has been characterised principally in terms of the accuracy of the structure solution obtained with respect to the refined structure or the equivalent single-crystal structure. Overall performance in terms of accuracy was excellent, though for the more complex examples, restrained Rietveld refinement of the initially determined structure was found to be essential. Performance was also assessed in terms of the success rate in determining a crystal structure that either fitted the diffraction data extremely well or could be successfully refined to such a state. As the molecular complexity of the structures being studied increased, the introduction of torsion angle constraints, derived from related crystal structures deposited in the CSD, was found to significantly increase the chances of success.