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Conformational flexibility and absolute stereochemistry of (3*R*)-3-hydroxy-4-aryl-*β*-lactams investigated by chiroptical spectroscopies and TD-DFT calculations

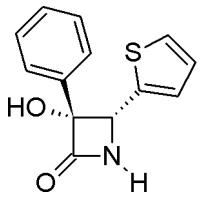
Daniele Tedesco, [a] **Carlo Bertucci,** [a] **Riccardo Zanasi,** [b] **Andrea Guerrini** [c]
[a] *Department of Pharmaceutical Sciences, University of Bologna, Italy;*
[b] *Department of Chemistry and Biology, University of Salerno, Italy;*
[c] *Institute for Organic Synthesis and Photoreactivity (ISOF), National Research Centre (CNR), Bologna, Italy*
E-mail: daniele.tedesco@unibo.it

Abstract:

β-lactam rings play a key role in medicinal chemistry: *β*-lactam derivatives are widely used in therapy as antibiotics, cholesterol absorption and prostate-specific antigen inhibitors. Stereochemical characterisation is crucial for the application of *β*-lactam rings as chiral intermediates for the asymmetric synthesis of a variety of compounds of medicinal interest, such as proteinogenic and non-proteinogenic amino acids and taxanes. [1]

The absolute stereochemistry of a series of synthetic (3*R*)-3-hydroxy-4-aryl-*β*-lactams was investigated by means of chiroptical spectroscopies, i.e. polarimetry and electronic circular dichroism (ECD), and quantum mechanical (QM) calculations using time-dependent density functional theory (TD-DFT). The absolute configuration at C3 was assigned by chemical correlation with synthetic precursors; the overall stereochemistry was assessed by application of the *β*-lactam sector rule, which relates the sign of the specific rotatory power ($[\alpha]_D$) and the lowest-energy ECD band with the absolute configuration at C4. [1] The assessed absolute configurations were then confirmed by TD-DFT calculations.

The *β*-lactam sector rule allowed a correct stereochemical characterisation of the investigated *β*-lactams, with the exception of a thienyl-substituted derivative (**1**). Conformationally-averaged TD-DFT calculations yielded accurate predictions of ECD spectra in 2-propanol and $[\alpha]_D$ values in chloroform, which allowed to assign the correct absolute configuration to compound **1**. $[\alpha]_D$ values in acetone were successfully predicted by TD-DFT calculations with explicit treatment of solvent molecules at a QM level. [2]



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A detailed analysis of the geometric features of the *β*-lactam ring for all the equilibrium conformers, as obtained by DFT geometry optimisation, helped to identify regular patterns for the arrangement of atoms around the carbonyl chromophore, which is responsible for the chiroptical properties of *β*-lactam derivatives. This study showed the importance of conformational flexibility for the definition of chiroptical properties, and highlighted strengths and weaknesses of the different methods for the stereochemical characterisation of chiral molecules in solution.

References

[1] Barbaro, G., Battaglia, A., Guerrini, A., Bertucci, C., Geremia, S., *Tetrahedron: Asymmetry 9* (**1998**), 3401-3409.
[2] Tomasi, J., Mennucci, B., Cammi, R., *Chem. Rev. 105* (**2005**), 2999-3093.