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CONFORMATIONAL STUDIES OF BETA-PEPTIDES THROUGH THE USE OF LMP2-COSMO AND MOLECULAR DYNAMICS

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The study of β-peptides secondary structures has gained substantial interest over the last years. Compared to α-peptides, the additional carbon in their backbone provides an extra degree of freedom due to the added torsional angle. This feature allows β-peptides to adopt a large number of distinct secondary structures with relatively low energy differences.

β-peptides seem to have an intrinsic tendency to fold into periodic structures, although the nature and relation of these interactions are not quite well understood. This appears to be related with local torsional angles as well as backbone-side chain and side chain-side chain interactions.[1] The use of local correlation methods with implicit solvent model have shown to be promising method to describe the properties of hexamers of such systems.[2]

In an attempt to characterize and better understand the β-peptides conformational landscape, several oligopeptide geometries were optimized with DFT methods in different polarity environments. The energetics were then refined through single point energy calculations carried out at the level of local second order Müller Plesset perturbation theory (LMP2)[3] in combination with the COSMO model.[4] Density-fitting approximations, which reduce the computational cost relative to the basis set size, were also applied. Molecular dynamics simulations were also carried out in order to treat the solvent explicitly and complement the quantum mechanics studies.

The results underline the applicability local correlated methods in the characterization of such systems, as well as the influence of the side chain groups.

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QSPR MODELLING OF LIPOPHILICITY AND ANTITUBERCULAR ACTIVITY OF THIOBENZANILIDE DERIVATIVES

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The search for novel drugs against bacterial infections like tuberculosis, a disease caused by *Mycobacterium tuberculosis* (*M. tb*) and other mycobacterioses, is one of the goals of present-day pharmaceutical industry, given the enormous impact of these pathologies on public health worldwide[1] and, in the case of *M. tb,* also due to the alarming spread of multi-drug resistance reported cases. Thiobenzanilides, which are relatively weakly toxic to higher organisms, have been found to show strong biological activity as anti-tubercular agents.

In this work we have analyzed a large set of thiobenzanilide derivatives (189 compounds), taken from literature, and have derived two quantitative structure-properties relationships (QSPRs) relating the lipophilicity, measured as clog*P*, and the anti-tubercular activity, measured as log(1/*MIC*), of these compounds with various computed molecular descriptors. QSPR models were generated by multiple linear regressions (MLR) using a forward stepwise variable selection.[2] The database was divided into a training set and an independent test set with similar variability. The best descriptors related to either lipophilicity (clog*P*) or biological activity (*MIC*) were selected on the basis of rigorous statistical criteria. The obtained model equations were internally and externally validated, in order to assess the robustness and predictive ability of the developed QSPR models. The best found equations showed a good interpretative ability and an effective predictive power towards test set compounds and will be used to assist us in the rational design and synthesis of new active thiobenzanilide derivatives.

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