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A theoretical study on the effect of N-methylation of amino acids (Ac-X-OMe) on their electronic structure and ADMET properties

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N-Methylation has a significant impact on both improving oral bioavailability of peptide-based lead structures and their conformational states. Herein, a comprehensive electronic structure study was performed using density functional theory (DFT) with B3LYP functional and 6-311++G** basis set. The selected mono-amino acid derivatives Ac-X-OMe, where X= Asp, Cys, Gly, His, Ile, Leu, Met, Phe, Ser and Val, as well as their corresponding N-methylated analogues were investigated. Based on computational studies, this study attempted to assess how N-methylation affects the absorption-distribution-metabolism-excretion-toxicity (ADMET) properties - particularly their solubility and lipophilicity. Our results reveal that backbone single N-methylation leads to an increase of polarizibility, dipole moment, while ΔGsolv, becomes more negative; backbone N-methylation thus makes the amino acid derivatives/short peptides more soluble in water. As for lipophilicity, the Clog P values of all N-methylated cases are greater than their non-N-methylated series. This observation confirms the improvement in lipophilicity due to N-methylation. All N-methylated amino acids have higher EHOMO (less negative) in comparison to the non-methylated analogues, and in all cases N-methylation decreases EHOMO-LUMO. These results imply that N-methylation makes these compounds more polarized and potentially more reactive to exchange electrons in aqueous medium. The natural atomic charges derived by natural bond orbital analysis (NBO) of N, C and O nuclei involved in amide bond formation become more positive/ (less negative) after N-methylation. The calculated amide cis/trans energy barrier (EA) of all the N-methylated amino acid derivatives was lower than the non-methylated analogues. N-methylation of these amino acid derivatives leads to an increase in aqueous solubility, lipophilicity and lowering of the cis/trans amide energy barrier (EA).

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