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CP-MLR/PLS directed structure-activity study in modeling of the aggrecanase-1 inhibitory activity of biphenylsulfonamides

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The inhibition activity of biphenylsulfonamide derivatives on aggrecanase-1 has been determined through quantitative analysis of molecular descriptors. The resulting models account for more than 83% of the variance in observed inhibition activity and have been satisfactorily validated by test-set statistics. Molecular features such as mean square distance (MSD), polarizability weighted lag-1 (GATS1p), and electronegativity weighted lag-5 (GATS5e) have been found to be crucial for receptor site interaction, along with the presence of an H attached to CO (sp3) with no heteroatom X attached at next C (H-046). Higher values of MSD, GATS5e, and H-046, coupled with lower values of GATS1p, improve the compound's activity profile. The partial least-squares (PLS) study reveals a "single window" structure-activity model using the most significant descriptors, with two optimum components explaining 84% of the variance in observed activity values. The applicability domain (AD) study confirms the models' predictability, with all compounds except one outlier within the proposed model's AD. The AD analysis has also identified as one structurally influential compound.

Keywords: Aggrecanase-1 inhibitors, Biphenylsulfonamides, Molecular descriptors, QSAR, Combinatorial protocol in multiple linear regression (CP-MLR) analysis

Xiang *et al.*[7] found that