[P34] 4D-QSAR of a set of novel β-*N*-biaryl ether sulfonamide-based hydroxamates for MMP9-inhibition

Kely M.Turra,[1] Kerly F.M. Pasqualoto,[2] Diogo P. Rivelli,[1] Silvia B.M. Barros[1]

[1]Laboratory of Pathology, Department of Clinical Chemistry and Toxicology, Faculty of Pharmaceutical Sciences, University of São Paulo, Av. Prof. Lineu Prestes, 580, Cidade Universitária, 05508-000, São Paulo, SP, Brazil;
[2]Laboratory of Biochemistry and Biophysics, Butantan Institute, Av. Vital Brasil, 1500 , Butantã, 05503-900, São Paulo, SP, Brazil
kely.turra@gmail.com

Matrix metalloproteinases (MMPs) are enzymes responsible for tissue remodeling and extracellular matrix degradation being overexpressed in several types of cancer. MMP-9 subtype promotes tumor invasion and progression by destroying the extracellular matrix (ECM) and basement membrane [1]. In this study, a *receptor-independent* (*RI*) four dimensional (4D) quantitative structure-activity relationships (QSAR) formalism was applied to a set of sixty-four novel β-*N*-biaryl ether sulfonamide-based hydroxamates, reported as potential MMP-9 inhibitor [1]. This approach can help to identify the 3D pharmacophore group and moieties related to molecular enzyme- inhibitor recognizing process. The 3D molecular models of inhibitors were constructed in their neutral forms considering a fragment (4-methoxybenzenesulfonamide) [2] bound to a MMP as reference. A geometry optimization procedure employed MM+ force field and partial atomic charges were calculated using AM1 method (HyperChem 7.51) [3]. The energy-minimized molecular models (steepest descent and conjugate gradient methods) were used as initial structures to perform molecular dynamics simulations (MDS) of 1 ns [1,000,000 steps, 1 fs step size, T 298 K] (MOLSIM 3.2) [4] to obtain the conformational ensemble profile (CEP) for each compound. The CEP of each analogue was aligned (three-ordered atoms; three distinct alignments were tested) in a cubic grid cell with 1.0 Å resolution to enclose the ligands of the training set (n = 47) and compute the grid cell occupancy descriptors (GCODs) (4D-QSAR 3.0) [5]. The partial least squares (PLS) regression was used to perform a data reduction fit. The 700 most highly weighted PLS GCODs were used to form the trial basis set for the genetic function approximation (GFA) analysis. The top ten models generated by GFA-MLR (multiple linear regression) and leave-one-out (LOO) crossvalidation method for each alignment were evaluated. The final best QSAR model (n = 47) presented 9 GCODs and was statistically significant: r^2 = 0.91; q_{LOO}^2 = 0.83; LOF = 0.35; LSE = 0.09. External validation was performed using a test set (n = 17; 26% of the total data set), and indicated a suitable power of prediction (82%).

Acknowledgments**:** The authors thank the São Paulo Research Foundation, FAPESP/Brazil and the Chem21 Group for the academic license of MOLSIM 3.2 and 4D-QSAR software.

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