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Linear Indices Bob-Jenkins operators for development of multi-output models using multi-target inhibitors of ubiquitin-proteasome system

Gerardo Casañola-Martin * (gmaikelc@gmail.com)
Universidad Estatal Amazónica, Facultad de Ingeniería Ambiental, Paso lateral km 2 1/2 via Napo, Puyo, Ecuador
Unidad de Investigación de Diseño de Fármacos y Conectividad Molecular, Departamento de Química Física, Facultad de Farmacia, Universitat de València, Spain

Facundo Perez-Gimenez (facundo.perez@uv.es)
Unidad de Investigación de Diseño de Fármacos y Conectividad Molecular, Departamento de Química Física, Facultad de Farmacia, Universitat de València, Spain

Matilde Merino-Sanjuan (matilde.merino@uv.es)
Department of Pharmacy and Pharmaceutical Technology, University of Valencia, Valencia, Spain

Abstract: The ubiquitin-proteasome system (UPS) plays an important role in the degradation of cellular proteins and regulation of different cellular processes that include cell cycle control, proliferation, differentiation, and apoptosis. On other hand, the ChEMBL database contains >5000 experimental outcomes for >2000 compounds tested as possible proteasome inhibitors using a large number of pharmacological assay protocols. All these assays report a large number of experimental parameters of biological activity like EC50, IC50, percent of inhibition, and many others that have been determined under many different conditions, targets, organisms, etc. Although this large amount of data offers new opportunities for the computational discovery of proteasome inhibitors, the complexity of these data represents a bottleneck for the development of predictive models. In this work, we used linear molecular indices calculated with the software TOMOCOMD-CARDD (TC) and Bob-Jenkins moving average operators to develop a multi-output model that can predict outcomes for 20 experimental parameters in >450 assays carried out under different conditions. This generated multi-output model showed values of accuracy, sensitivity, and specificity above 70% for training and validation series. Finally, this model is considered multi-target and multi-scale, because it predicts the inhibition of the UPP for drugs against 22 molecular or cellular targets of different organisms contained in the ChEMBL database

Keywords: Ubiquitin-proteasome pathway inhibitors; CHEMBL; Multi-target, Multiscale and Multi-output models; Moving averages, QSAR