437k Inverse-Qsar for Pharmaceutical Development Using the Signature Descriptor: Application to Γ-Secretase and Cox-II Inhibitors

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Quantitative structure-activity relationships (QSARs) provide a description of the correlation between the structure of a molecule and a specific molecular property of interest. QSARs can be employed to refine the search for molecules matching a desired property in an existing database, but ideally one would like to examine potential compounds outside the database. Here we present a novel algorithm to do just that, which involves solving the inverse-QSAR (I-QSAR) problem [1] via a powerful molecular descriptor known as Signature. [2] Focused libraries of compounds with desired predicted values are created from which a high-quality lead compound can be developed. In this study we utilize the I-QSAR technique using Signature to develop potent γ-secretase inhibitors for Alzheimer's disease (AD) treatment, and Cyclooxygenase-II (COX-II) inhibitors for potential replacement of Celebrex and Vioxx because of unwanted cardiovascular side effects.

AD is a progressive neurodegenerative disorder that is typically characterized by a cognitive and memory decline. Potential treatments of AD involve preventing cleavage of the amyloid precursor protein (APP) by inhibiting the γ-secretase enzyme. Cleavage of the APP can result in amyloid-β42 peptides that cluster together to produce the characteristic plaques in AD. A database of 61 known γ-secretase inhibitors with IC50 data was obtained to create a QSAR. From this set, the inverse QSAR technique using Signature was employed to generate potent γ-secretase inhibitors outside of the original 61 compounds. Similarly a known literature set of dozens of COX-II enzyme inhibitors and their activity in both Chinese hamster ovary cells and Human whole blood were used to create QSARs. Likewise, the I-QSAR technique with Signature was utilized to generate a focused library of compounds outside of the original set that are predicted to have an activity comparable to the most active compounds in the original data set.

[1] C. Churchwell, M. D. Rintoul, S. Martin, D. P. Visco, Jr., A. Kotu, R. S. Larson, L.O. Sillerud, D. C. Brown and J. L. Faulon , "The Signature Molecular Descriptor. 3. Inverse Quantitative Structure-Activity Relationship of ICAM-1 Inhibitory Peptides", J Molecular Graphics and Modelling, 22, 263 – 273 (2004).

[2] J. F. Faulon, D. P. Visco, Jr. and R. S. Pophale, "The Signature Molecular Descriptor. 1. Extended Valence Sequences vs. Topological Indices in QSAR and QSPR studies", J. Chem. Inf. Comput. Sci., 43, 707 – 720 (2003).