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Poster presentation

Modelling the multi-target selectivity: o-phosphorylated oximes as serine hydrolase inhibitors

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Understanding, predicting and control of multi-target selectivity of bioactive compounds is an interesting problem of chemoinformatics. An important example is presented by the organophosphorus compounds that can inhibit at least four major serine hydrolase targets: acetylcholinesterase (AChE), butyrylcholinesterase (BChE), carboxylesterase (CaE) and neuropathy target esterase (NTE). The 'esterase profile' of a compound critically affects its possible application as pesticide or therapeutic agent as well as the ecotoxicity risks related to both acute and delayed toxicity in humans and warm-blooded animals.

In this paper, we present the results of the QSAR and molecular modelling analysis of inhibitory activity and selectivity with respect to AChE, BChE, CaE and NTE for a large series of O-phosphorylated oximes containing the phosphate, thiophosphate, methylphosphonate and phenylphosphonate groups [1]. The compounds of this class are studied as promising agrochemicals and the potential products of reactivation of phosphorylated cholinesterases by oximes. Using the Molecular Field Topology Analysis (MFTA) approach, [2] predictive models and activity maps for the influence of local (atomic) properties on the inhibitory activity and selectivity were obtained. The 3D QSAR models based on the Comparative Molecular Field Analysis (CoMFA) technique [3] were also derived. These models are mutually consistent, and their interpretation is in good agreement [1] with known qualitative structure-activity relationships as well as the active site structures of these serine hydrolases identified from the X-ray and molecular modelling data.

References

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