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*Abstract*

# Application of the 3D-QSAR Methods for the Development of Novel, More Potent $D_2$ Receptor Antagonists †

**Agata Zieba, Dariusz Matosiuk, Agnieszka A. Kaczor**

[1] Department of Synthesis and Chemical Technology of Pharmaceutical Substances with Computer Modeling Laboratory, Faculty of Pharmacy, 4A Chodzki St, PL-20059 Lublin, Poland; agatazieba@umlub.pl (A.Z.); dariusz.matosiuk@umlub.pl (D.M.); agnieszkakaczor@umlub.pl (A.A.K.)

[2] School of Pharmacy, University of Eastern Finland, Yliopistonranta 1, P.O. Box 1627, FI-70211 Kuopio, Finland

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20 million - this refers to the number of people who suffer from schizophrenia worldwide [1]. Hallucinations, distortions in thinking, abnormal motor behavior are the symptoms that impair the everyday life of people with schizophrenia and their families. Although numerous medications are available for this condition, many of them cause serious side effects, including agranulocytosis, sedation, or increased serum lipid concentration [2]. Extensive research has been carried out on dopamine $D_2$ receptors. Results of these studies suggest that there are links between the impaired dopaminergic neurotransmission and the presence of characteristic symptoms of the disease [3,4]. Thus providing this group of patients with potent dopamine $D_2$ receptor antagonists may benefit their treatment. Although multi-target ligands of aminergic G protein-coupled receptors (GPCRs) are most efficient as drugs for schizophrenia treatment, it should be emphasized that all marketed drugs against this disease are dopamine $D_2$ receptor antagonists or partial/biased agonists. Computer-Aided Drug Design (CADD) techniques, in particular 3D-QSAR methods, are vital in developing novel ligands. Proper understanding of the structure-activity relationship can assist the design of novel drugs characterized by low toxicity and high efficacy [5]. The CoMFA method is a widely used 3D-QSAR approach that can be implemented to correlate the steric and the electrostatic properties of a series of molecules with their pharmacological activities. Identification of a pharmacological gap in the treatment of schizophrenia became an incentive to thoughtfully examine the structure-activity relationship among a series of dopamine $D_2$ receptor antagonists. In our opinion, the constructed CoMFA model, characterized by good statistical parameters: ($Q^2$=0.76, $R^2$=0.92, F-value=338.9), will assist further drug design and enable to obtain ligands characterized by low toxicity and high bioactivity [6].