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Towards new 5-HT$_7$R ligands with improved metabolic stability – synthesis of LP-211 derivatives and their comprehensive evaluation *in silico* and *in vitro*

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Background: Compounds modulating activity of serotonin receptor 5-HT$_7$ are very important in terms of the therapy of disorders that are crucial from the social point of view, such as depression, cognitive disorders, anxiety and Alzheimer disease. However, the activity itself is not sufficient for a compound to constitute a promising drug candidate – not less relevant are also its physicochemical and pharmacokinetic properties, lack of toxicity and metabolic stability.
Materials and methods: A series of derivatives of the selective 5-HT$_7$R agonist: LP-211 was synthesized and evaluated *in vitro*. In order to facilitate and support the design of new stable 5-HT$_7$R ligands, *in silico* model for the metabolic stability evaluation was developed, based on the Support Vector Machines algorithm.
Results: The study led to identification of the derivative TP22 that showed affinity and selectivity profile comparable to that of LP-211, 3-fold higher *in vitro* metabolic stability, and ability to stimulate neurite outgrowth *in vitro* and to cross blood-brain barrier. The promising properties of TP22 determined its selection for further *in vivo* studies. The analysis of the accuracy predictions of the *in silico* model revealed that they strongly depended on the chemical substituents introduced to compounds and the set of descriptors used for compounds representation.
Conclusions: In further *in silico* research, it is important to focus on the provision of the proper representation of data, especially description of the compounds lipophilicity, crucial for the proper metabolic stability prediction.
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