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Lead optimization of anti-depressive azetidine derivatives by pharmacophore model

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Depression is a common and extremely serious disease affecting about 121 million people worldwide. An important recent development in antidepressant therapy has been achieved with the investigation of triple reuptake inhibitors (TRIs) as a new target, which blocks synaptic reuptake of three neurotransmitters (5-HT, NE or DA). However, any TRI is not yet available in the market. Pharmacophore modeling, which can be used to predict the activity for new compounds or identify important features for the activity, has matured to be an important computational strategy for facilitating drug discovery. Recently, we reported syntheses and their anti-depressant activity of novel azetidine derivatives as TRIs. As a continuous our efforts of a lead optimization process we designed new nitrogen containing azetidine derivatives by the structure analysis and molecular modification of compounds which possess reuptake inhibitory activities. Herein, we will report a development of TRI 3D ligand-based pharmacophore model by the structural analyses of various training set compounds that showed TRI activities using Discovery Studio 3.5 software. Generation of the best pharmacophore model, syntheses of the compounds and their biological activities against 5-HT, NE or DA reuptake inhibition will be presented. The relationship between the biological screening results and the result of the pharmacophore mapping will be discussed also.

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