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Molecular docking and ADME evaluation of potential nootropics containing the pyrrolidin-2-one scaffold

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Introduction. The search for new nootropics remains relevant due to the rising prevalence of cognitive disorders, including post-COVID syndrome [1,2]. Existing racetams enhance neuronal plasticity and metabolism [3] but often show low bioavailability or moderate efficacy. Therefore, the rational molecular design of new derivatives containing a pyrrolidin-2-one fragment – the structural scaffold that underlies receptor binding and ensures favorable pharmacokinetic properties – is well justified. The modern *in silico* methods allow optimization of their nootropic activity, selectivity, and safety.
Materials and methods. The base for virtual screening was generated using the Marvin Sketch 20.5 program. ADME parameter prediction was performed using the pkCSM software. For receptor-oriented flexible docking, the AutoDock 4.2 software package was used.
Results and discussion. To create a library of new racetams, a base molecule with the highest antiamnestic activity – 1-benzyl-4-{4-[2-oxo-2-(piperidin-1-yl)ethyl]-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl}pyrrolidin-2-one – was modified to form S-alkyl derivatives (Fig. 1a). ADME parameters were calculated, and molecular docking with the M1 acetylcholine receptor was performed. From the computed data, 20 derivatives were selected with optimal docking scores and moderate BBB (logBB > 0**)** and CNS permeability (logPS > -2). Docking visualization of the potential prototype in the active site of the M1 receptor is shown in Fig. 1b.

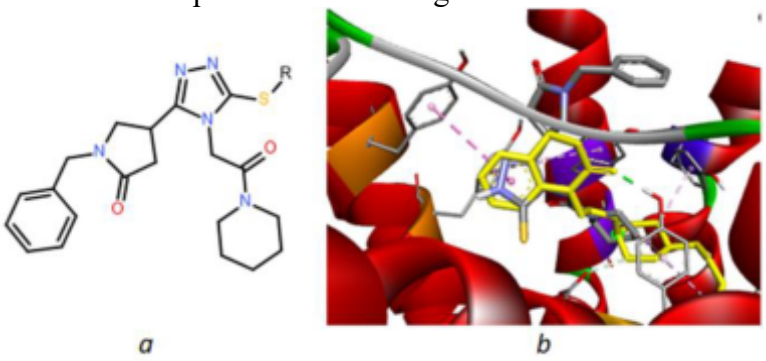

Fig. 1. Structures of the basic compounds (a) and docking visualization of the potential prototype (grey) and ligand 77LH281 (yellow) relative to the M1 receptor (b).

Conclusions. From many derivatives, 20 compounds with optimal docking and pharmacokinetic profiles were selected, indicating their potential for further synthetic and pharmacological studies.

References

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