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The study of buspirone analogues docking to serotonin transporter

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It is well known that 6-nitroquipazine exhibits about 150-fold higher affinity for the serotonin transporter (SERT) than does quipazine and recently we showed quipazine buspirone analogues with high to moderate SERT affinity. Now we have designed and synthesized several 6-nitroquipazine buspirone derivatives. Unexpectedly, their SERT binding affinities were moderate, and much lower than that of the previously studied quipazine buspirone analogues. To explain these findings, docking studies of both groups of compounds into two different homology models of human SERT, was performed using a flexible target-ligand docking approach (4D-docking). The crystal structures of leucine transporters from Aquifex aeolicus in complex with leucine and with tryptophan were used as templates for the SERT models in closed and outward-facing conformations [1, 2], respectively. We found that the latter conformation represents the most reliable model for binding of buspirone analogues. Docking into that model showed that the nitrated compounds acquire a rod like shape in the binding pocket with polar groups (nitro- and imido-) at the ends of the rod. 6-Nitro substituents gave steric clashes with amino acids located at the extracellular loop 4, which may explain their lower affinity than corresponding quipazine buspirone analogues. The results from the present study may suggest chemical design strategies to improve the SERT modulators.

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