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Docking Study of Buspirone Analogues to a Serotonine Transporter Model.

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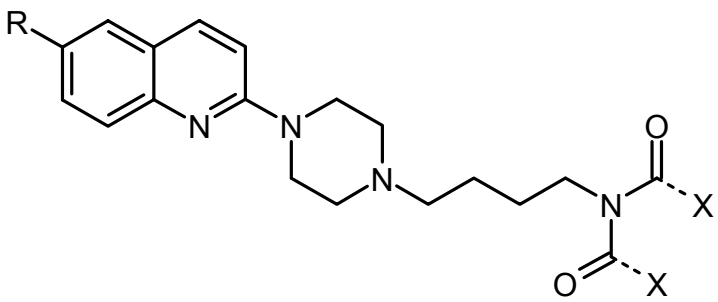
6-Nitroquipazine has been known as one of the most potent and selective inhibitors of the serotonin transporter (SERT). In the present study we examined several buspirone analogues, with known SERT affinities, containing quipazine or 6-nitroquipazine moieties in the aromatic part of a molecule. The compounds were docked to SERT and analyzed using molecular modelling methods. The SERT model was based on the crystal structure of a bacterial homologue of SERT, the leucine transporter ($LeuT_{Aa}$).



R = H; $–NO_2$

The docking indicated that the imide moieties of the high affinity ligands remained in close contacts with - SERT Tyr95 (THM1) and Ser438 (THM8). In such an orientation of nitrated (low affinity) ligands, the nitro groups were in close steric contacts with the hydrophobic amino acids Val^{343} and Lue^{344} in TMH6. It also appeared that nitro groups can occupy the binding place of imide carbonyls. Thus during docking of nitrated ligands to the SERT narrow binding site possible destabilising steric contacts between ligand's polar groups and SERT hydrophoobic amino acids were observed.

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