Supplementary Information

Design, synthesis, and biological evaluation of small molecule-based PET radioligands for the 5-hydroxytryptamine 7 receptor

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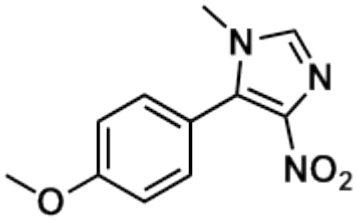
Content:

Supplementary Information

Supplemental Figure 1.

CADD analysis



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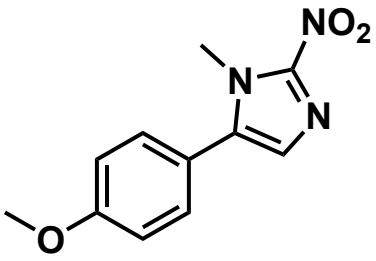

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All possible substitution has been studied for 1,2 1,3 and 1,4 substituted azoles below the molecular weight 300. Fifteen molecule having good XP Gscore values (more than -10) were selected and evaluated for binding free energy estimates using MM-GBSA. Among them two structurally diverse hits were selected on the basis of binding free energy estimates, XP Gscore and visual inspection of binding pattern. The docked complex of these final two with 5-HT_7 receptor was subjected to MD simulations for 5ns in NPT ensemble. The RMSD values for the αC atoms in 5-HT_7 receptor has attained the equilibrium after the 2ns simulations around the value of 3.2Å. The RMSF values of αC atoms was found to be highly fluctuating in the region of residues 200-250 including important residues such as Phe289 and Phe290 which is found to be involved in π-π stacking throughout the simulation in terms of largest hydrophobic interactions contribution in the stability of ligand at binding pocket of 5-HT_7 receptor.

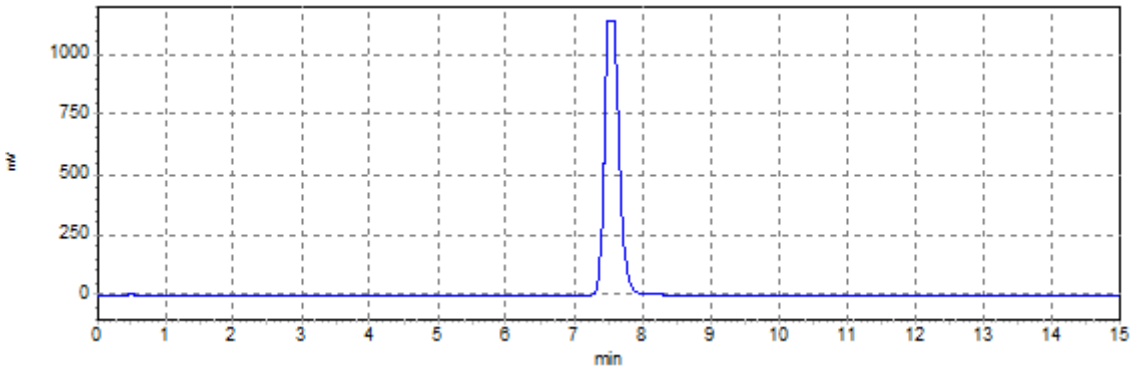
One of the important interactions which is known to be conserved in all the 5-HT7 binding ligands is hydrogen bonding with Ser203 which is present throughout the simulation with the largest contribution in the form of hydrogen bonding interactions. In similar terms other all the interactions in static flexible docking were found to be present during the 5ns simulations with very few water bridges. The vicinity of hydrophobic residues; Val114, Cys117, and Leu312 along with charged interaction with Asp113 was present with significant contribution throughout the simulations.

Supplementary Information

Supplementry Figure 2

Seperation chart of **1**

HPLC (Capcell Pack UG80 C_{18} column (10.0 mm i.d. × 250 mm). MeCN/H_2O/ Et_3N, 6.0/4.0/0.01 (v/v/v), flow rate = 4.0 mL/min, λ_{uv}= 254 nm)



Supplementary Information

Supplemetry Figure 3

Radio analytical HPLC chart of [^{11}C]**1**

HPLC (Capcell Pack UG80 C_{18} column (4.6 mm i.d. × 250 mm). MeCN/H_2O/ Et_3N, 4.0/6.0/0.01 (v/v/v), flow rate = 1.0 mL/min, λ_{uv}= 254 nm)

(Red denotes RI detector measurements and blue for UV detector)