Supplementary Information

N-(2-hydroxyphenyl)-1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidine-4-carboxamide (D2AAK4), a multi-target ligand of aminergic GPCRs, as a potential antipsychotic

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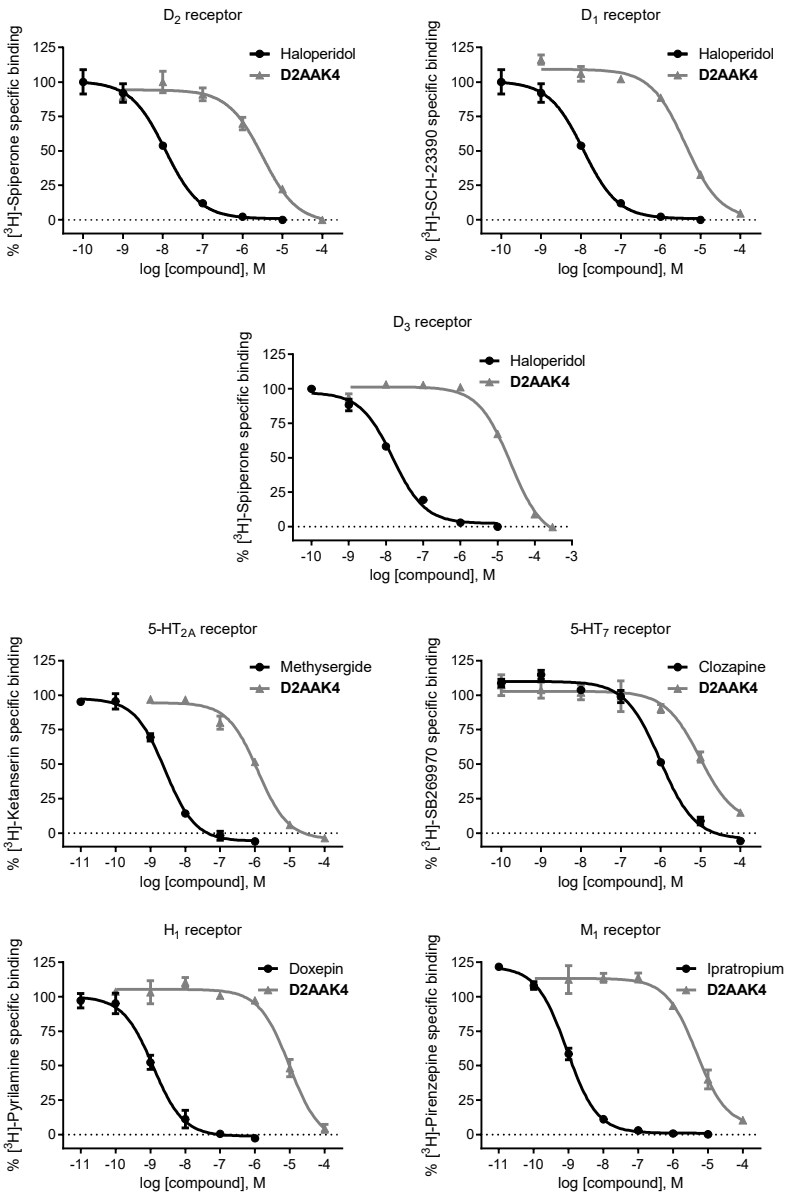

Figure S1. Competition binding curves of D2AAK4 in radioligand binding assays at the indicated receptors. Concentration-dependent displacement of the specific radioligand binding by compound D2AAK4 and the corresponding reference compound at the human cloned receptors indicated. The graphs show the data (mean ± SEM) of a representative experiment out of two (or three for 5-HT_{2A}) independent experiments performed in duplicate. pK_i (mean ± SEM; n = 3 experiments performed in duplicate) and average K_i (nM) values for reference compounds included as internal controls in the binding assays were: haloperidol (D_1) = 8.30 ± 0.07 (5.22 nM); haloperidol (D_1) = 7.93 ± 0.02 (11.8 nM); haloperidol (D_3) = 8.00 ± 0.08 (10.5 nM); 5-carboxamidotryptamine (5-CT) (5-HT_{1A}) = 9.00± 0.06 (1.04 nM); methysergide (5-HT_{2A}) = 9.29 ± 0.07 (0.53 nM); clozapine (5-HT_7) = 6.20 ± 0.05 (632 nM); doxepin (H_1) = 9.26 ± 0.18 (0.55 nM); ipratropium (M_1) = 9.27 ± 0.03 (0.53 nM).

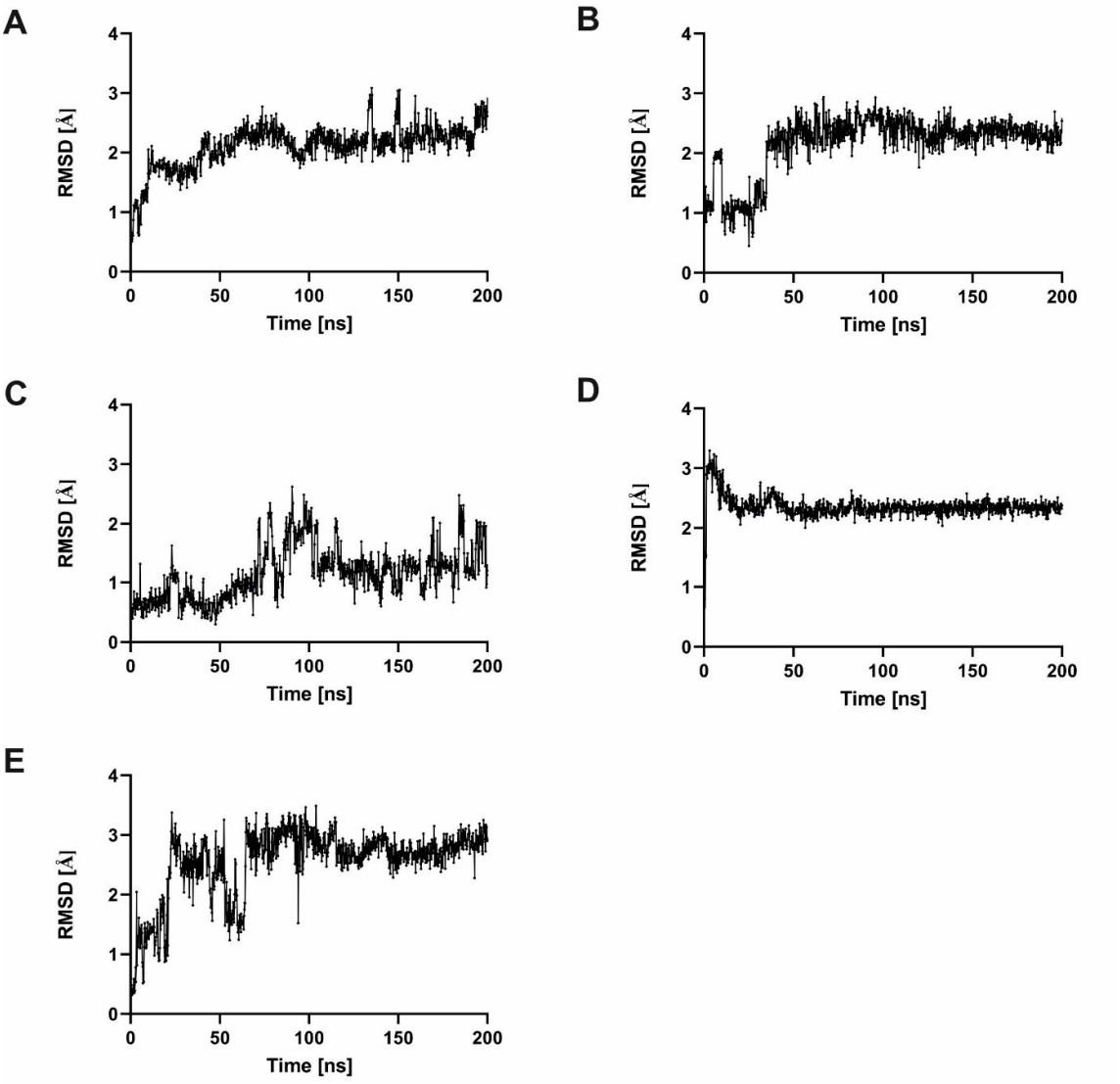

Figure S2. Ligand RMSD values during 200 ns molecular dynamics simulations for D2AAK4 in complex with dopamine D_1 (A), D_2 (B), D_3 (C) and serotonin 5-HT_{2A} (D) and 5-HT_7 receptors (E).

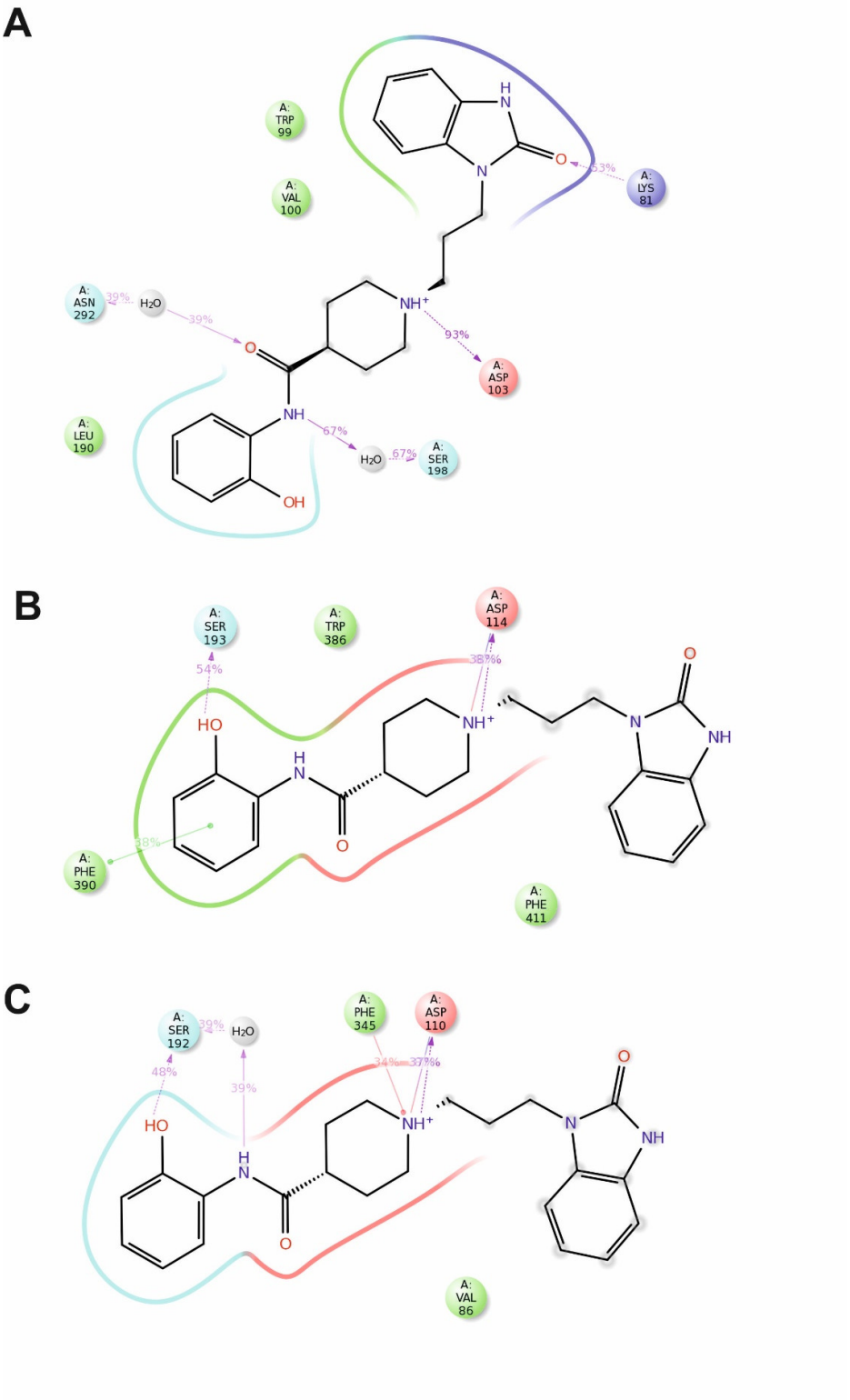

Figure S3. Molecular interactions of D2AAK4 with human dopamine D_1 (A), D_2 (B) and D_3 (C) receptor during 200 ns molecular dynamics simulations: summary of contacts. Interactions that occur more than 30% of the simulation time in the selected trajectory (0 through 200 ns) are shown.

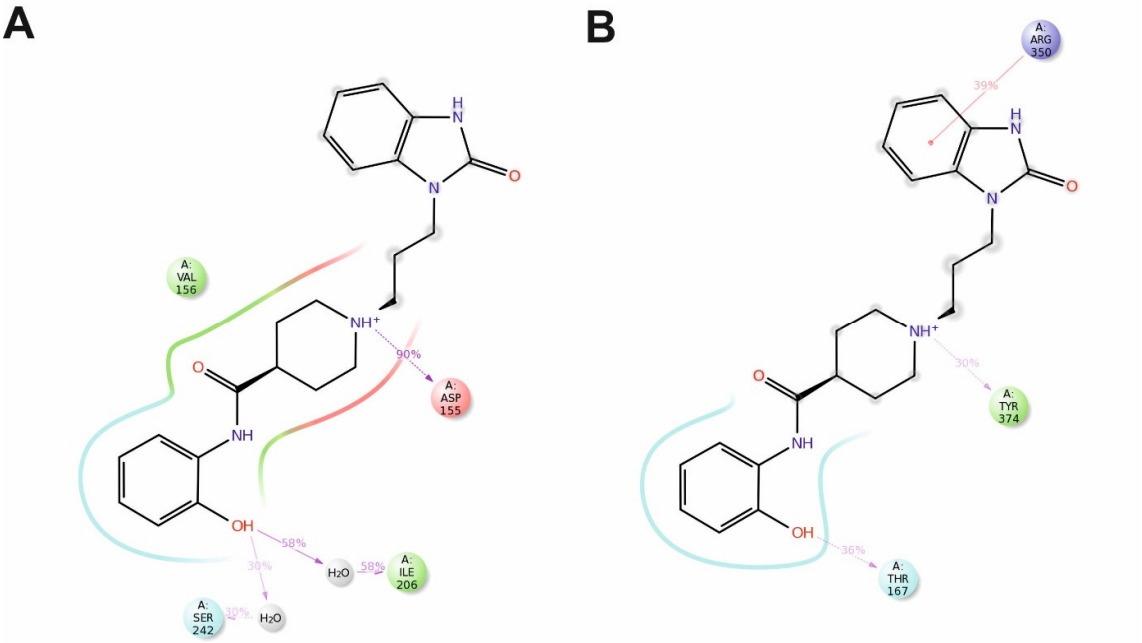

Figure S4. Molecular interactions of D2AAK4 with human serotonin 5-HT$_{2A}$ (A) and 5-HT$_7$ (B) receptor during 200 ns molecular dynamics simulations: summary of contacts. Interactions that occur more than 30% of the simulation time in the selected trajectory (0 through 200 ns) are shown.

Table S1. Results summary of the evaluation of compound D2AAK4 in *in vitro* functional assays at human cloned D$_2$ and 5-HT$_{2A}$ receptors. [a] efficacy (% inh., % of inhibition of dopamine response) as D$_2$ antagonist in cAMP assays; [b] efficacy (% inh., % of inhibition of 5-HT response) and potency (pIC$_{50}$, -log IC$_{50}$; IC$_{50}$, concentration of the compound eliciting the 50% of maximal compound response) as 5-HT$_{2A}$ antagonist in IP assays. Data are mean ± SEM of 2-3 independent experiments performed in duplicate or triplicate.

***h*D$_2$[a] [8]**		***h*5-HT$_{2A}$[b]**		
% inh. at 10 μM	**% inh. at 100 μM**	**% inh. at 10 μM**	**pIC$_{50}$**	**IC$_{50}$ [nM]**
12.1 ± 6.0%	44.1 ± 1.5%	97.4 ± 1.6%	6.15 ± 0.14	714