Using novel click chemistry algorithm to design D3R inhibitors as blood–brain barrier permeants

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Background

The dopamine D3 receptor (D3R) is involved in several pathological conditions, including schizophrenia, Parkinson's disease, addiction, anxiety, depression and glaucoma. Molecules selectively targeting D3R have a potential in treatment of these conditions and have been the subject of search in many studies [1].

An important obstacle in D3R ligands discovery is the high sequence similarity to D2R. An effective approach to tackle this issue is by employing bitopic molecules, bearing two pharmacophores joined by linker [1]. A commonly used template here is a substituted 4-phenylpiperazine and an extended aryl ring system, connected by butylamide linker chain (**Fig. 1a**).

As far as amide is a potential site of metabolism, a bioisosteric substitution to 1,2,3-triazole has been proposed to increase drug biostability (**Fig. 1b**). In addition, such compounds is accessible via convenient synthesis with copper-catalyzed azide-alkyne cycloaddition (CuAAC) known as click chemistry.

Goal:

The aim of the study is to screen novel D3R ligands synthesizable with click chemistry and also permeable for blood-brain barrier (BBB). 4-phenylpiperazine scaffold is employed for screening. The screening from virtual library is performed with molecular docking and molecular dynamics simulations.

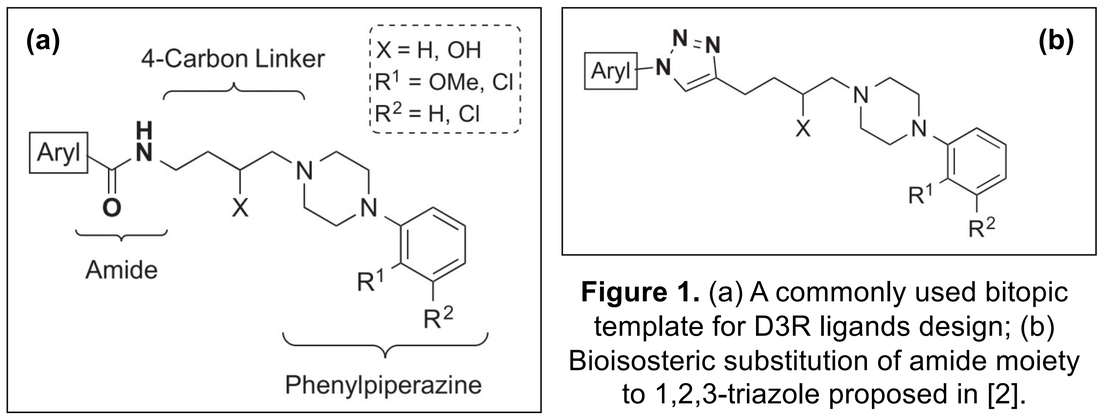

Figure 1. (a) A commonly used bitopic template for D3R ligands design; (b) Bioisosteric substitution of amide moiety to 1,2,3-triazole proposed in [2].

The screening workflow

A library of azides as SMILES strings from PunChem database (143,075 molecules)

Retained only reasonably small molecules with one azide group (9,776 molecules left)

Virtual click reaction programmed using RDKit Python package

Template alkyne [C:4/5]

Azide [N:1] [N:2] [N:3] [*:6]

both 1,4 and 1,5-isomers are generated

Filtration by Lipinski rules

A library of **18,838 molecules** (9,419 of 1,4- and 1,5-isomers)

1-phenyl-4-[4-(1H-1,2,3-triazol-5-yl)butyl]piperazine scaffold

Eticlopride, reference D3R binder

*Filtration by BBB permeability (logBB) estimated by Clark and Rishton equations (**Fig. 2a**)**

230 molecules $logBB_{Clark} > 0.3$

3062 molecules $logBB_{Rishton} > 0.3$

Molecular docking with D3R (PDB 3PBL) with Vina and iDock software

Ligand id 7000

eticlopride

D3R

Docking visualization prepared with Protein Imager

*Comparison of Vina and iDock scores (**Fig. 2b**)*

Top 10 binders identified and the best selected for MD:

id 7000

Vina: -10.16; iDock: -10.17 kJ/mol

$logBB_{Clark}$: 0.34; $logBB_{Rishton}$: 0.56

MD simulation in GROMACS for the best hit and eticlopride (**Fig. 3a**). Estimation of ΔG using the linear interaction energy method (**Fig. 3b**)

Clark and Rishton models for logBB estimation:

*$logBB_{Clark} = 0.152 \cdot ClogP - 0.0148 \cdot TPSA + 0.139$

$logBB_{Rishton} = 0.155 \cdot ClogP - 0.01 \cdot TPSA + 0.164$

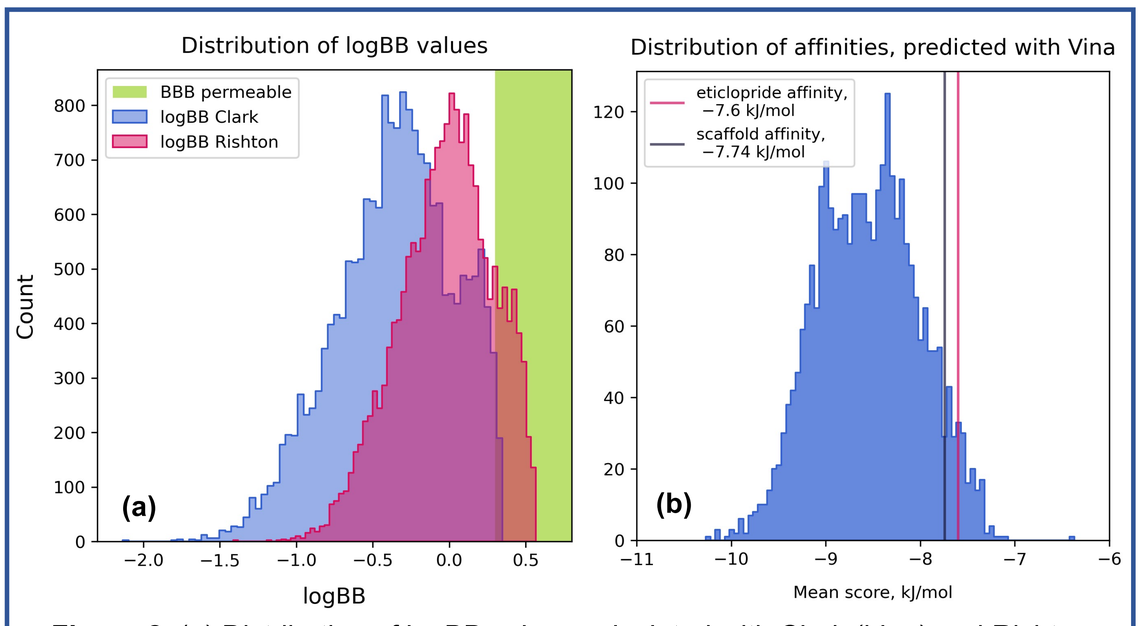

Figure 2. (a) Distribution of logBB values calculated with Clark (blue) and Rishton (red) equations indicating the difference between these models; (b) Distribution of the mean affinities predicted with Vina with mean affinities for reference compounds, eticlopride (red line) and the scaffold (balck).

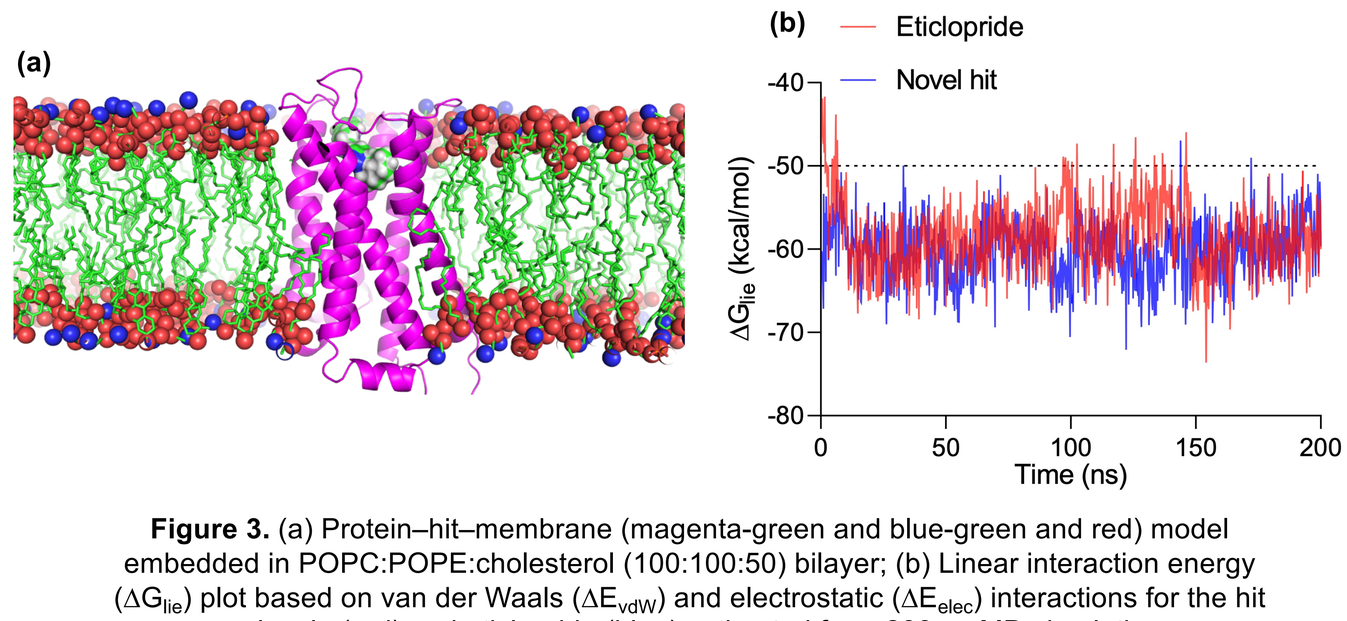

Figure 3. (a) Protein–hit–membrane (magenta-green and blue-green and red) model embedded in POPC:POPE:cholesterol (100:100:50) bilayer; (b) Linear interaction energy (ΔG_{lie}) plot based on van der Waals (ΔE_{vdW}) and electrostatic (ΔE_{elec}) interactions for the hit molecule (red) and eticlopride (blue) estimated from 200 ns MD simulation

Conclusion:

A novel hit for designing D3R ligands is discovered. Its binding superiority to eticlopride is validated via MD simulation with membrane-embedded protein. A workflow utilizing *in silico* click chemistry to screen compounds with BBB permeability is established. The proposed click reaction-based algorithm holds significant potential as a valuable tool in the screening of effective antipsychotic compounds and beyound.

References:

[1] Leggio, G. M., Bucolo, C., Platania et al (2016). Current drug treatments targeting dopamine D3 receptor. *Pharmacology & therapeutics*, 165, 164-177.

[2] Keck, T. M., Banala, A. K., Slack, R. D. et al (2015). Using click chemistry toward novel 1, 2, 3-triazole-linked dopamine D3 receptor ligands. *Bioorganic & medicinal chemistry*, 23(14), 4000-4012.