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Rational design of new antipsychotic virtual derivatives with improved ADMET properties and high binding activity

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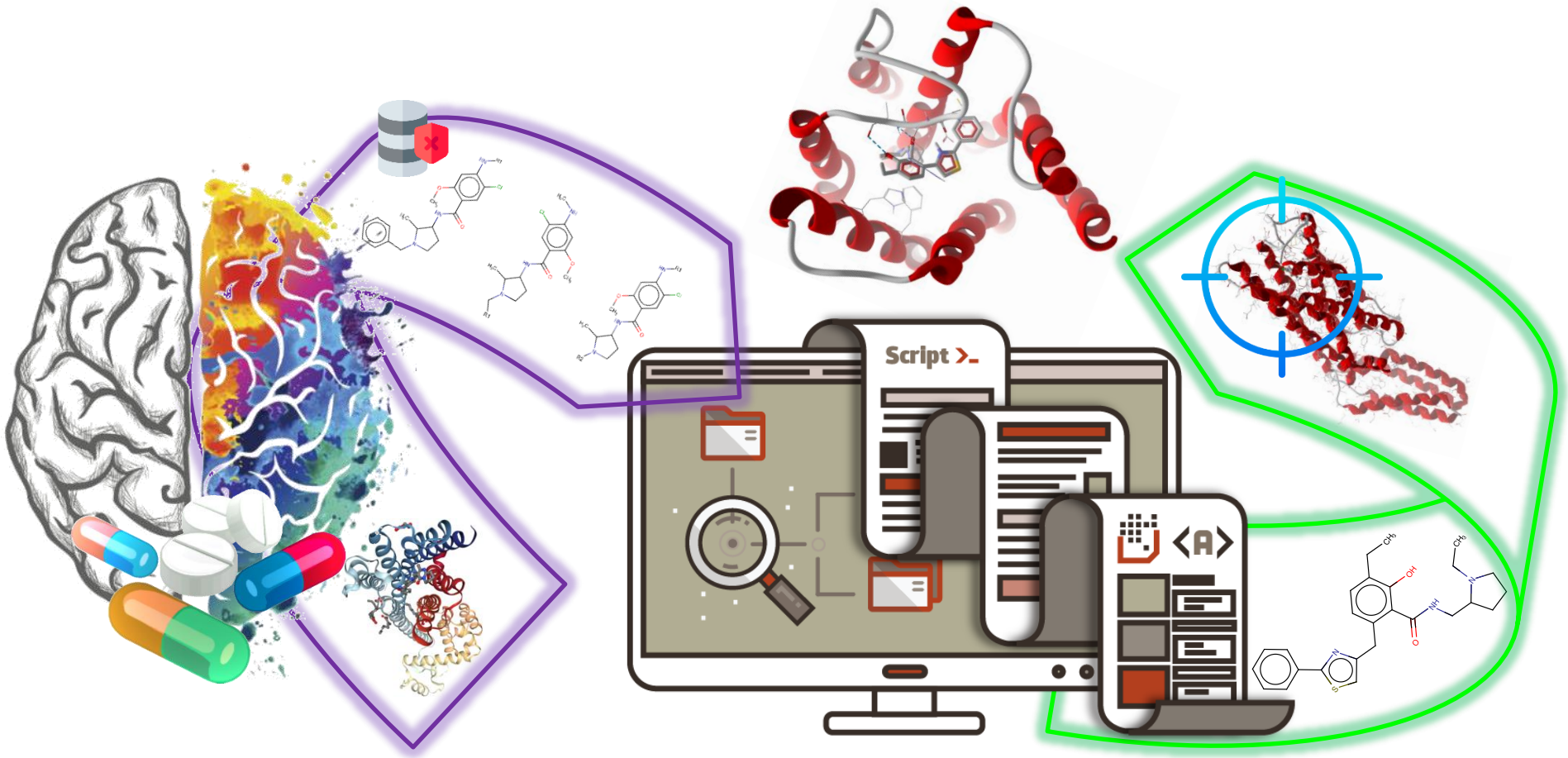

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Abstract:

Antipsychotic medications are notorious for their associations with toxicity concerns at different systemic levels and their many side effects. Our study focuses on *in silico* design of novel drug prototypes against schizophrenia, a disorder with a complex pathological mechanism involving the dysregulation of different pathways. For this particular design, the receptors of dopamine (DA) and serotonin (5-HT) were used as molecular targets. A combinatorial library was computationally generated based on scaffolds from five antipsychotics: Chlorpromazine (CHL), Risperidone (RIS), Haloperidol (HAL), Emonapride (EMO), and Eticlopride (ETI). The combinatorial library (scaffolds' donators included) was screened for lead-likeness, drug-likeness, activity at the central nervous system (CNS) and ADMET properties. Two good drug candidates (virtual derivatives of ETI) were identified, with activity at the CNS level, without any toxicity issues. One virtual derivative of HAL was found with activity at the CNS level, with an inherited low-risk toxic substructure, but without other additional toxicity concerns. With the help of molecular docking was found that the three selected virtual derivatives had better binding affinities than their scaffolds' donors against some of the DA and 5-HT receptors.

Keywords: ADMET; antipsychotics; docking

Introduction [1]

Antipsychotic medications are notorious for their associations with toxicity concerns at different systemic levels and many side effects:

- common issues (mild sedation, dry mouth);
- unpleasant issues (constipation, sexual dysfunction);
- painful (acute dystonic reactions);
- disfiguring medication-induced conditions (tardive dyskinesia, obesity);
- life-threatening disorders (myocarditis, agranulocytosis).

Introduction [2]

Our study focuses on *in silico* design of novel drug prototypes against schizophrenia, a disorder with a complex pathological mechanism involving the dysregulation of:

- Dopaminergic pathways;
- Glutamatergic pathways;
- GABAergic pathways,
- Cholinergic neurotransmitter systems…

… and their interactions.

Additional susceptibility factors for schizophrenia:

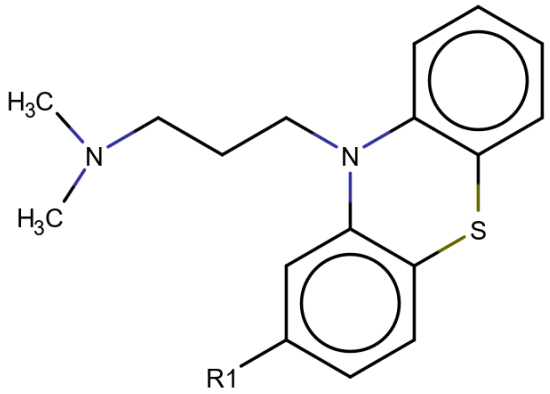
- Neuregulin 1 (Nrg1) and its receptor ErbB-4;
- Disrupted-in-Schizophrenia 1 (DISC1) gene;
- Catechol-*O*-methyl transferase (COMT);
- Brain-derived neurotrophic factor (BDNF);
- Serine/threonine-protein kinases (AKTs)…

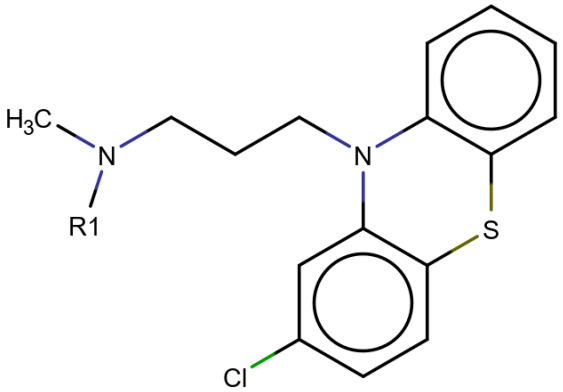
…. and their pathways, that interact with dopaminergic, glutamatergic, and GABAergic pathways.

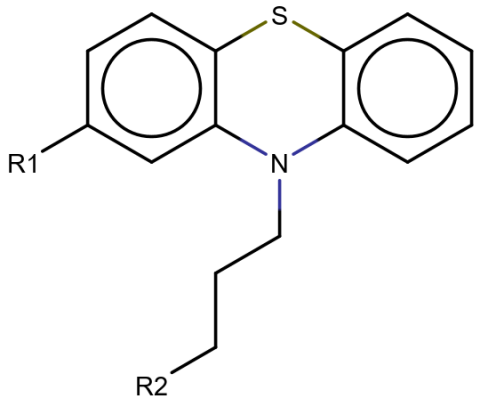
Introduction [3.1] *Rational design of novel drug prototypes against DA and 5-HT receptors based on scaffolds from four categories of compounds:*

- **one worldwide approved typical antipsychotic: CHL**

Primary Target of CHL	PBD ID: Target / Resolution [Method]
5-HT_{2A} receptor	6A93 / 3.00 Å [X-RAY DIFF]
3 x CHL's Scaffolds + Building Blocks (proprietary DB) => CHL's Virtual Derivatives	





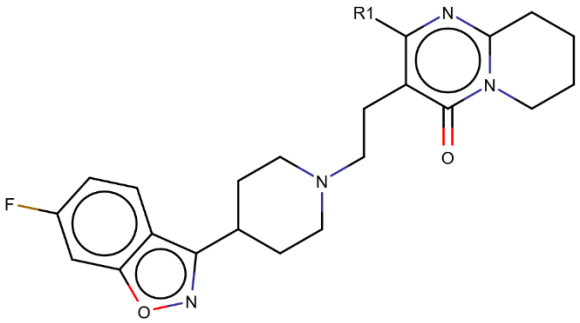


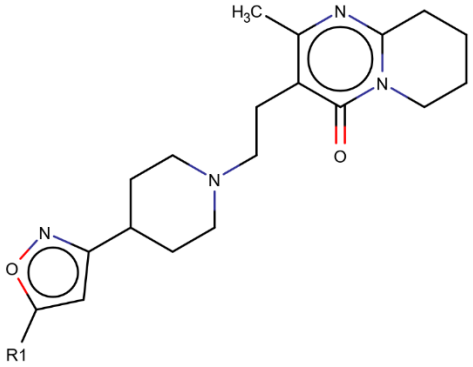
NOTE: ***All Primary Targets were selected with the help of The IUPHAR/BPS Guide to PHARMACOLOGY***

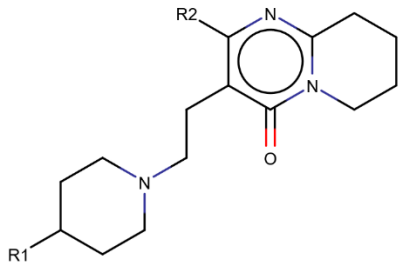
Introduction [3.2a] *Rational design of novel drug prototypes against DA and 5-HT receptors based on scaffolds from four categories of compounds:*

- **two worldwide approved atypical antipsychotics: RIS & HAL**

Primary Targets of RIS	PBD ID: Target / Resolution [Method]
5-HT_{2A} receptor	6A93 / 3.00 Å [X-RAY DIFF]
D_2 receptor	6CM4 / 2.87 Å [X-RAY DIFF]
5-HT_{1D} receptor	7E32 – Chain E / 2.90 Å [EM]
5-HT_{1B} receptor	4IAR / 2.70 Å [X-RAY DIFF]
3 x RIS's Scaffolds + Building Blocks (proprietary DB) => RIS's Virtual Derivatives	



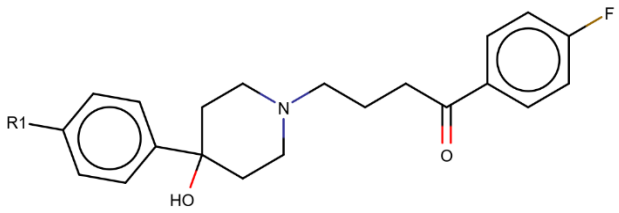


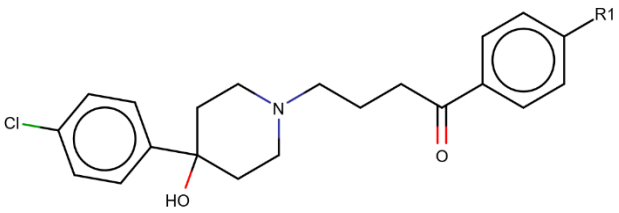


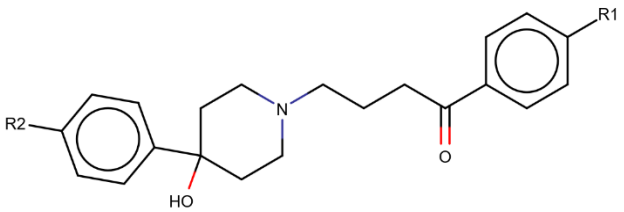
Introduction [3.2b] *Rational design of novel drug prototypes against DA and 5-HT receptors based on scaffolds from four categories of compounds:*

- **two worldwide approved atypical antipsychotics: RIS & HAL**

Primary Targets of HAL	PBD ID: Target / Resolution [Method]
D_4 receptor	5WIU / 1.96 Å [X-RAY DIFF]
D_2 receptor	6CM4 / 2.87 Å [X-RAY DIFF]
D_3 receptor	3PBL / 2.89 Å [X-RAY DIFF]
5-HT_{2A} receptor	6A93 / 3.00 Å [X-RAY DIFF]
3 x HAL's Scaffolds + Building Blocks (proprietary DB) => HAL's Virtual Derivatives	



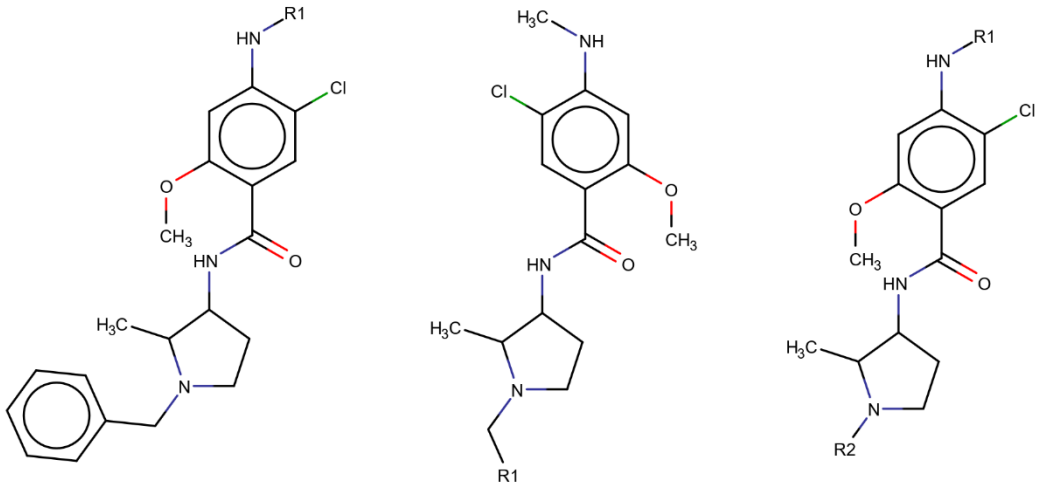




Introduction [3.3] *Rational design of novel drug prototypes against DA and 5-HT receptors based on scaffolds from four categories of compounds:*

- **one atypical antipsychotic approved only in Japan: EMO**

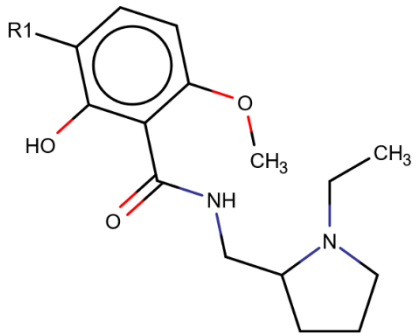
Primary Targets of EMO	PBD ID: Target / Resolution [Method]
D_4 receptor	5WIU / 1.96 Å [X-RAY DIFF]
D_3 receptor	3PBL / 2.89 Å [X-RAY DIFF]
3 x EMO's Scaffolds + Building Blocks (proprietary DB) => EMO's Virtual Derivatives	

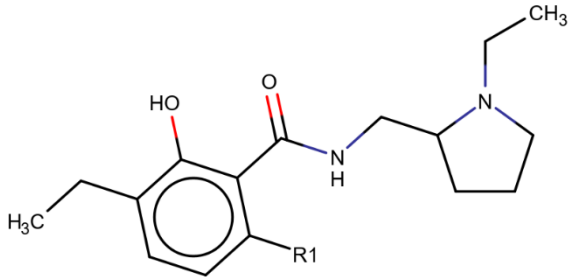


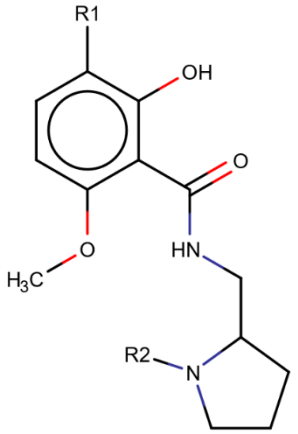
Introduction [3.4] *Rational design of novel drug prototypes against DA and 5-HT receptors based on scaffolds from four categories of compounds:*

- **one compound used in pharmacological research: ETI**

Primary Targets of ETI	PBD ID: Target / Resolution [Method]
D_2 receptor	6CM4 / 2.87 Å [X-RAY DIFF]
D_3 receptor	3PBL / 2.89 Å [X-RAY DIFF]
D_4 receptor	5WIU / 1.96 Å [X-RAY DIFF]
3 x ETI's Scaffolds + Building Blocks (proprietary DB) => ETI's Virtual Derivatives	







Results and discussion [1.a] *ADMET predictions**

- **Scaffolds' donators – computed toxicological issues**

Compound	PPI Friendly	Functional Groups	Detected Functional Groups	Phospholipidosis
CHL	No	Yes	Low_Risk_halogenure	Inducer
RIS	Yes	Yes	Low_Risk_halogenure_F	Noninducer
HAL	No	Yes	Low_Risk_halogenure Low_Risk_halogenure_F	Inducer
EMO	No	Yes	Low_Risk_halogenure	Noninducer
ETI	No	No	None	Noninducer

* Software: FAF*Drugs*4, via https://fafdrugs4.rpbs.univ-paris-diderot.fr/index.html

Setup of virtual screening (VS) included:

- lead-likeness and drug-likeness;
- activity at the central nervous system (CNS);
- ADMET properties (including PhysChem descriptors, bioavailability, detection of problematic functional groups involved in toxicity problems, phospholipidosis inducers, and non-peptidic inhibitors of Protein-Protein Interactions – iPPI);
- detection of PAINS;
- detection of covalent inhibitors;
- Compliance with rules developed by Pharmaceutical companies.

Results and discussion [1.b] *ADMET predictions*

- **Scaffolds' donators – compliance with rules developed by Pharma companies and lead-likeness rules**

Compound	GSK 4/400 rule	Pfizer 3/75 rule	Eli Lilly MedChem rules	Lead-likeness	ADMET [1.a & 1.b]
CHL	Good	Bad	Pass	Rejected (Log*P*)	Rejected (?!)
RIS	Good	Warning	Pass	Accepted	Intermediate
HAL	Good	Bad	Pass	Rejected (Log*P*)	Rejected (?!)
EMO	Good	Bad	Pass	Accepted	Rejected (?!)
ETI	Good	Warning	Pass	Accepted	Rejected (?!)

- GSK 4/400 rule: compounds with Log*P* > 4 and MW>400 Da have a less favorable safety profile.
- Pfizer 3/75 rule: relates Log*P* > 3 and tPSA < 75 $Å^2$ to adverse effect of chemical compounds.
- Eli Lilly MedChem rules: used to identify compounds that may interfere with biological assays.
- More than 50% of the nuclear receptors compounds and 45% of allosteric modulators fit in the problematic region of the Pfizer 3/75 rule while 30% and 26% of non-allosterics oral bioavailable approved drugs and iPPIs populates this region (Lagorce et al., 2017).
- Intermediate = compound which embeds low-risk structural alerts with a number of occurrences below the threshold.

Results and discussion [1.c] *ADMET predictions*

- **Lead-likeness of virtual derivatives (VDs): no good leads detected with CNS activity and without major toxicity concerns:**

CNS VDs – no good leads detected
RIS VDs – no good leads detected
HAL VDs – no good leads detected

None of VDs was selected as a good lead!

Parameter	Leads	CNS
MW	150 - 400	135 - 582
logP	-3 to 4	-0.2 to 6.1
HBA	≤ 7	≤ 5
HBD	≤ 4	≤ 3
tPSA	≤ 160	3 - 118
Rotatable Bonds	≤ 9	-
Rigid Bonds	≤ 30	
Rings	≤ 4	-
Max Size System Ring	≤ 18	-
Carbons	3 - 35	-
HeteroAtoms	1 - 15	-
H/C Ratio	0.1 to 1.1	-
Charges	≤ 4	-
Total Charge	-4 to 4	-
Stereo Centers	≤ 2	-

EMO VDs – one good lead detected:

EMO_2.1_2_9_9, without CNS activity and three toxicity issues:

- **Low_Risk_halogenure, Covalent_nitrile, Not iPPI**

ETI VDs – four good leads detected:

ETI_1.1_2_2_2, without CNS activity and two toxicity issues:

- **Covalent_nitrile, Not iPPI**

ETI_ 1.1_5_5_5, CNS active and two toxicity issues:

- **Low_Risk_halogenure_F, Not iPPI**

ETI_ 1.1_6_6_6, CNS active and two toxicity issues:

- **Low_Risk_halogenure_F, Not iPPI**

ETI_ 1.1_7_7_7, CNS active and three toxicity issues:

- **Low_Risk_thiol, Covalent_thiol, Not iPPI**

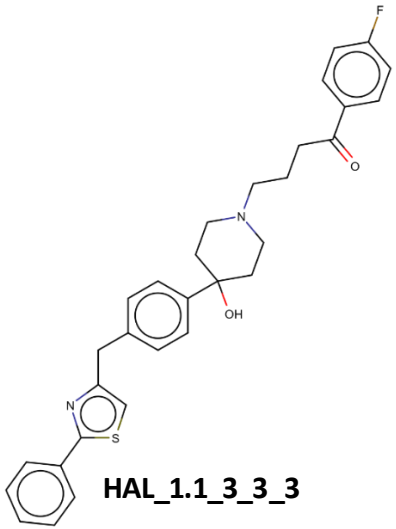
Results and discussion [1.d] *ADMET predictions*

- **Drug-likeness of VDs: only three VDs detected, with CNS activity and without problematic structural moieties:**

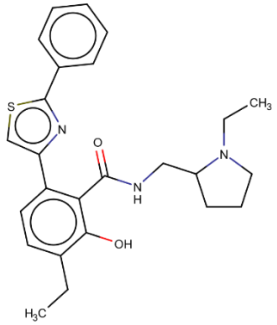
  HAL VDs – one good drug candidate detected: HAL_1.1_3_3_3 (with one inherited structural alert: Low_Risk_halogenure_F)

  ETI VDs – two good drug candidates detected (without structural alerts, and without any toxicity concerns): ETI_3.1_1_57_57 & ETI_3.1_3_59_59

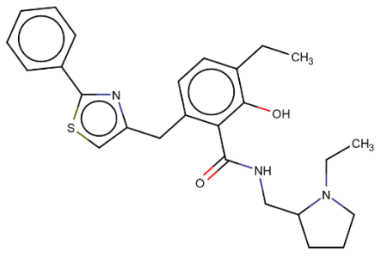
Compliance with rules developed by Pharma companies	All Selected VDs
GSK 4/400 rule	BAD
Pfizer 3/75 rule	WARNING
Eli Lilly MedChem rules	PASS



HAL_1.1_3_3_3



ETI_3.1_1_57_57



ETI_3.1_3_59_59

ADMET predictions	All selected VDs
Lipinski's RO5	PASS
Oral Bioavailability (Veber's rule)	PASS
Oral Bioavailability (Egan's rule)	PASS
Phospholipidosis inducer	NO
PPI Friendly	YES
PAINS (3 sets of filters were used)	NO
Covalent inhibitors	NO

Results and discussion [1.d] *ADMET predictions*

- **Problematic moieties (total detected chemical moieties molecules with an occurrence above 1%) found in structure of VDs who failed toxicology screening**

CHL's VDs

Low_Risk_halogenure_F: 56%
Low_Risk_thiol: 30%
Low_Risk_halogenure: 14%

RIS's VDs

Low_Risk_halogenure: 59%
Low_Risk_halogenure_F: 26%
Low_Risk_thiol: 14%

HAL's VDs

Low_Risk_halogenure_F: 60%
Low_Risk_thiol: 27%
Low_Risk_halogenure: 12%

EMO's VDs

Low_Risk_halogenure: 59%
Low_Risk_halogenure_F: 26%
Low_Risk_thiol: 14%

ETI's VDs

Low_Risk_halogenure_F: 65%
Low_Risk_thiol: 34%

Results and discussion [2.a] *Molecular docking**

Primary Target	PBD ID of Target / Resolution [Method]	Reference Ligand①	Summary of the Best Binders (BA②)
5-HT$_{1B}$ receptor	4IAR / 2.70 Å [X-RAY DIFF]	ERM③	ERM (-11.9)
5-HT$_{1D}$ receptor	7E32 – Chain E / 2.90 Å [EM]	5-HT	HAL_1.1_3_3_3 (-10.5)
5-HT$_{2A}$ receptor	6A93 / 3.00 Å [X-RAY DIFF]	RIS	HAL_1.1_3_3_3 (-11.8)
D$_2$ receptor	6CM4 / 2.87 Å [X-RAY DIFF]	RIS	RIS & HAL_1.1_3_3_3 (-11.4)
D$_3$ receptor	3PBL / 2.89 Å [X-RAY DIFF]	ETI	HAL_1.1_3_3_3 (-11.6)
D$_4$ receptor	5WIU / 1.96 Å [X-RAY DIFF]	EMO	RIS (-11.7)

All docking runs were carried out in search space lower than 27 Å (around binding site of co-crystallized ligands from experimental 3D structure of targets) and exhaustiveness was set to 200

① Co-crystallized ligand from experimental 3D structure of target
② BA = Binding Affinity in kcal/mol
③ ERM = Ergotamine (DB00696 – an alpha-1 selective adrenergic agonist vasoconstrictor)

*** Software: *AutoDock Vina* run in *PyRx – Python Prescription 0.9.5* interface**

Results and discussion [2.b] *Molecular docking*

Docking against 5-HT receptors

5-HT_{1B} receptor – Ligand Complex	BA (kcal/mol)	5-HT_{1D} receptor – Ligand Complex	BA (kcal/mol)	5-HT_{2A} receptor – Ligand Complex	BA (kcal/mol)
4IAR-ERM	-11.9	7E32-HAL_1.1_3_3_3	-10.5	6A93-RIS	-11.4
4IAR-RIS	-10.9	7E32-HAL	-9.2	6A93-HAL_1.1_3_3_3	-11.8
4IAR-HAL_1.1_3_3_3	-10.9	7E32-ETI_3.1_1_57_57	-8.9	6A93-HAL	-9.5
4IAR-ETI_3.1_3_59_59	-10.1	7E32-RIS	-8.9	6A93-ETI_3.1_3_59_59	-9.2
4IAR-ETI_3.1_1_57_57	-9.7	7E32-EMO	-8.0	6A93-ETI_3.1_1_57_57	-9.9
4IAR-HAL	-9.3	7E32-ETI_3.1_3_59_59	-8.0	6A93-ETI	-7.4
4IAR-EMO	-8.7	7E32-ETI	-7.6	6A93-EMO	-9.4
4IAR-ETI	-7.6	7E32-5-HT	-6.2	6A93-CHL	-8.4
4IAR-CHL	-7.4	7E32-CHL	-5.9	N/A	N/A

Docking against DA receptors

D_2 receptor – Ligand Complex	BA (kcal/mol)	D_3 receptor – Ligand Complex	BA (kcal/mol)	D_4 receptor – Ligand Complex	BA (kcal/mol)
6CM4-HAL_1.1_3_3_3	-11.4	3PBL-HAL_1.1_3_3_3	-11.6	5WIU-RIS	-11.7
6CM4-RIS	-11.4	3PBL-RIS	-10.7	5WIU-ETI_3.1_1_57_57	-10.5
6CM4-ETI_3.1_1_57_57	-9.7	3PBL-HAL	-9.1	5WIU-ETI_3.1_3_59_59	-10.3
6CM4-HAL	-9.5	3PBL-EMO	-8.7	5WIU-HAL_1.1_3_3_3	-9.9
6CM4-EMO	-9.3	3PBL-ETI_3.1_3_59_59	-8.4	5WIU-EMO	-9.7
6CM4-ETI_3.1_3_59_59	-8.9	3PBL-ETI_3.1_1_57_57	-8.3	5WIU-HAL	-9.5
6CM4-ETI	-7.9	3PBL-ETI	-7.9	5WIU-CHL	-8.0
6CM4-CHL	-7.1	3PBL-CHL	-7.1	5WIU-ETI	-7.8

PDB ID - Ligand	Redocking of co-crystallized ligand from experimental 3D structure of target (reference ligand)

Results and discussion [2.c] *Molecular docking*

HAL_1.1_3_3_3 showed highest binding activity from all screened molecules against:

- **5-HT_{1D} receptor**
- **D_2 receptor**
- **D_3 receptor**

Primary Targets of HAL

ETI_3.1_1_57_57 & ETI_3.1_3_59_59 are constantly better binders than ETI and, also, good binders of one of the Primary Targets of ETI:

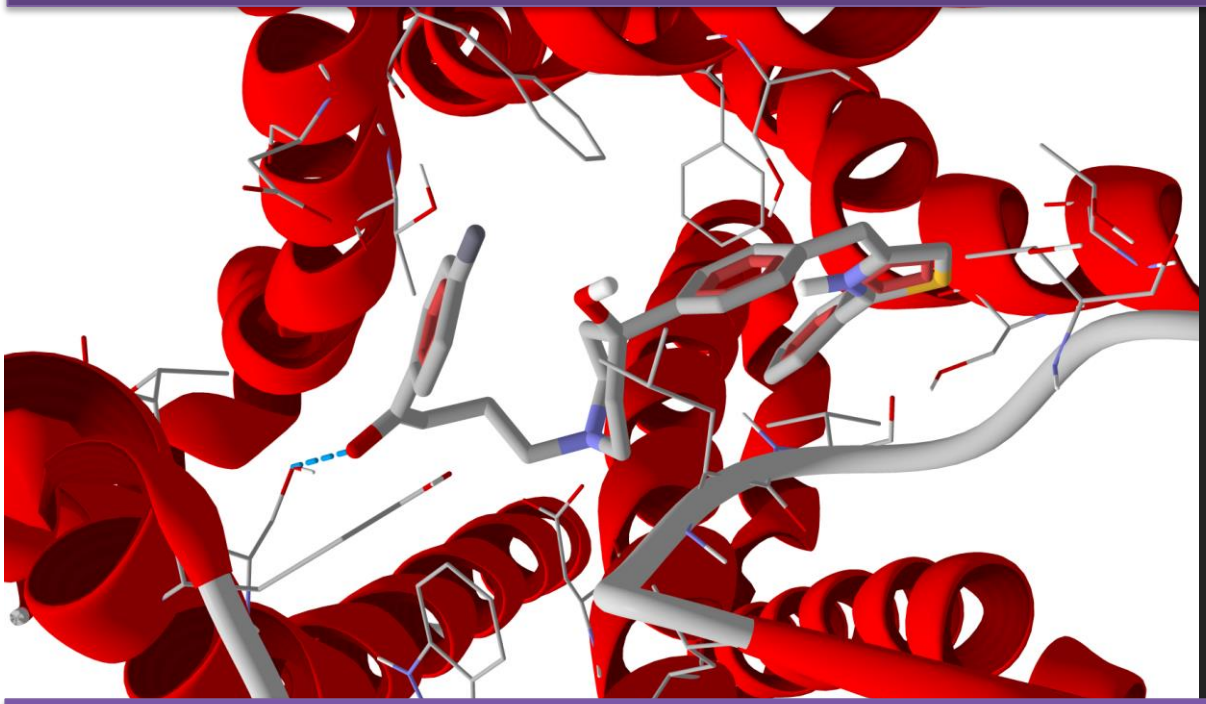
- **D_4 receptor (BA < -10.0 kcal/mol).**

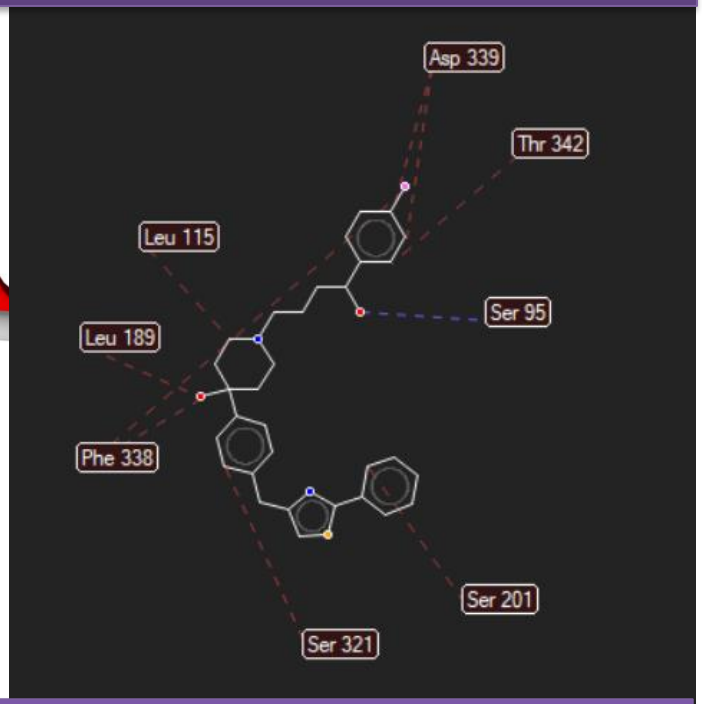
HAL_1.1_3_3_3 & ETI_3.1_3_59_59 are good binders of:

5-HT_{1B} receptor(BA < -10.0 kcal/mol).

Results and discussion [2.d] *Molecular docking*

5-HT_{1D} receptor (7E32 – Chain E) – HAL_1.1_3_3_3 complex

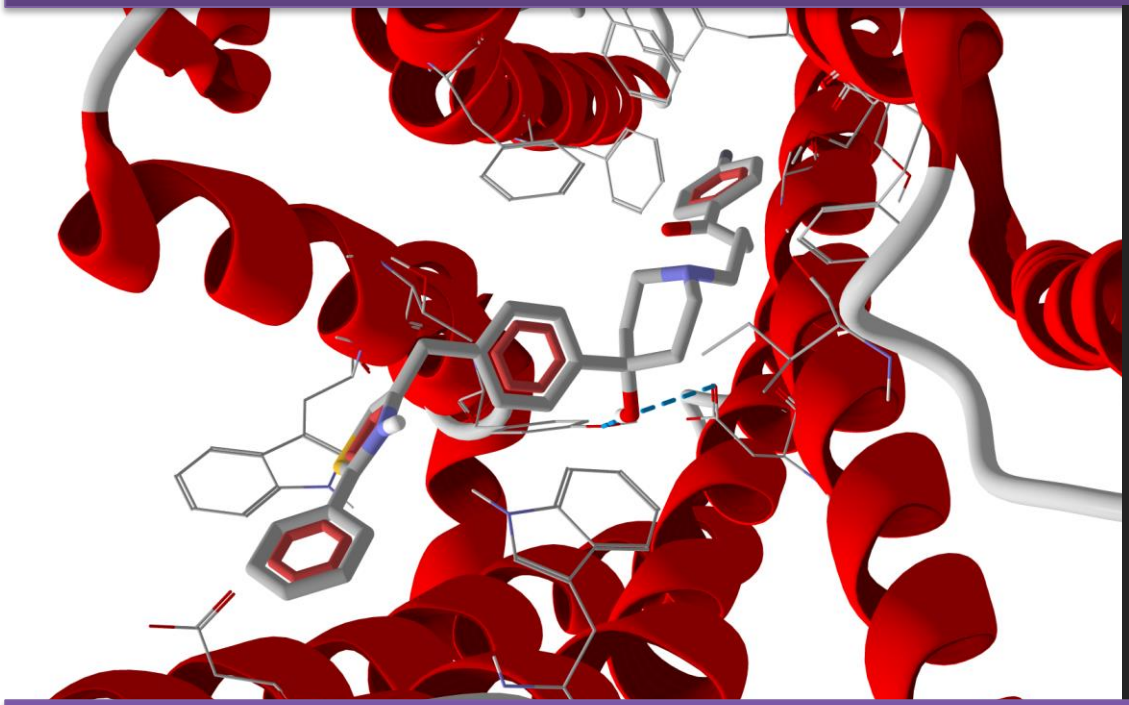


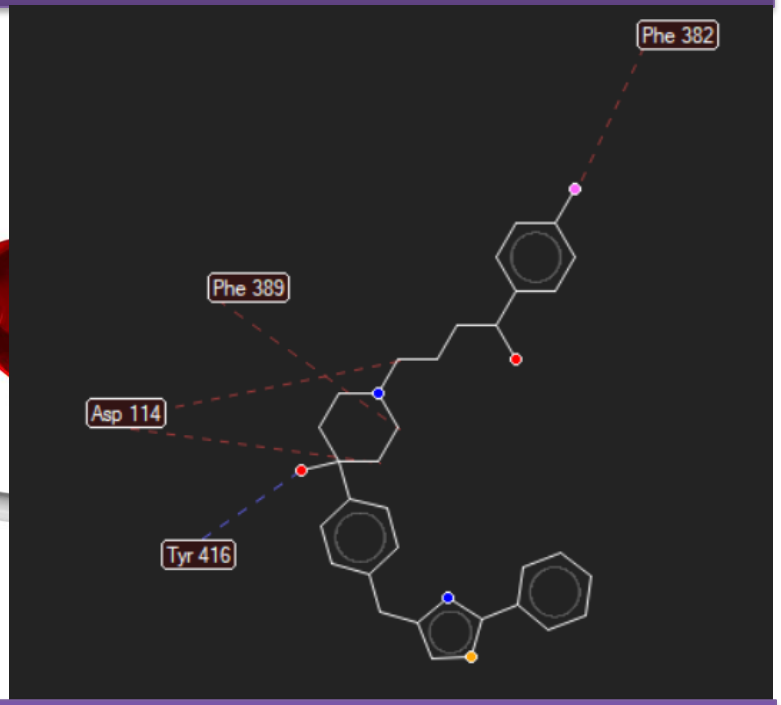


HAL_1.1_3_3_3 makes a H-bond with Ser95 from second transmembrane domain (76 – 98) and multiple steric interactions with extracellular topological domain (177 – 194) another transmembrane domains. Also, makes a steric interaction with Leu115 from agonist binding region (114 – 123). 5-HT makes H-bons with Asp118 and Ser321, electrostatic interactions with Asp118 and multiple steric interactions (common interaction sites: Ser 201, and Ser321)

Results and discussion [2.e] *Molecular docking*

D_2 receptor (6CM4) – HAL_1.1_3_3_3 complex

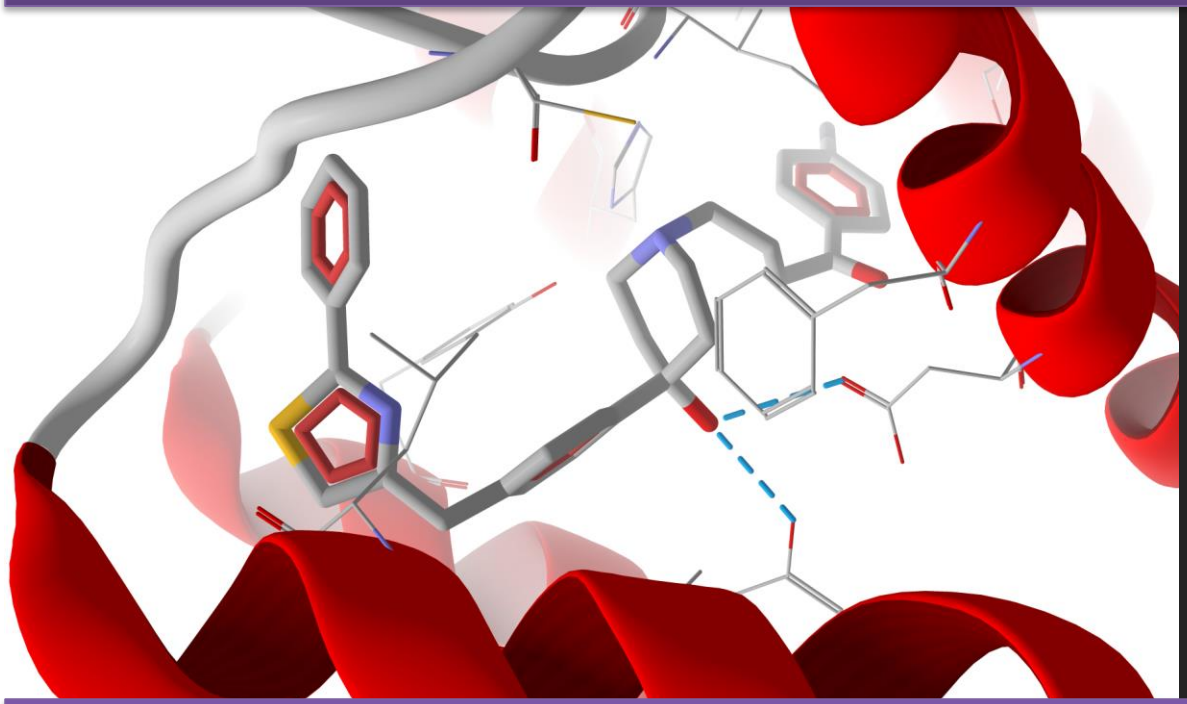


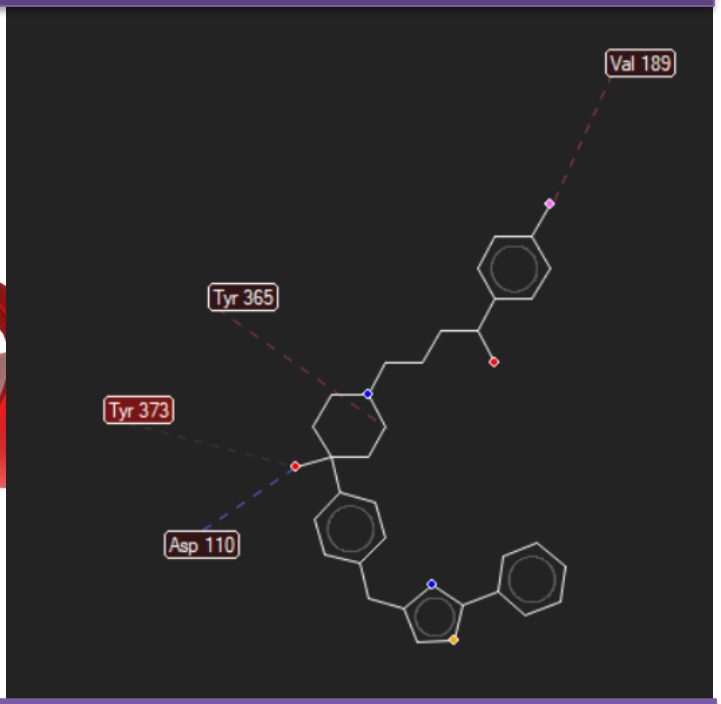


HAL_1.1_3_3_3 makes a H-bond with Tyr416 from a terminal transmembrane domain (410 – 431) – RIS, also makes a H-bond with Tyr416 in the experimental 3D structure. Also, makes steric interactions with another two transmembrane domains (109 – 130, respectively 374 – 395). Do no makes interactions with the two important sites for receptor activation (positions: 195 & 197).

Results and discussion [2.f] *Molecular docking*

D_3 receptor (3PBL) – HAL_1.1_3_3_3 complex

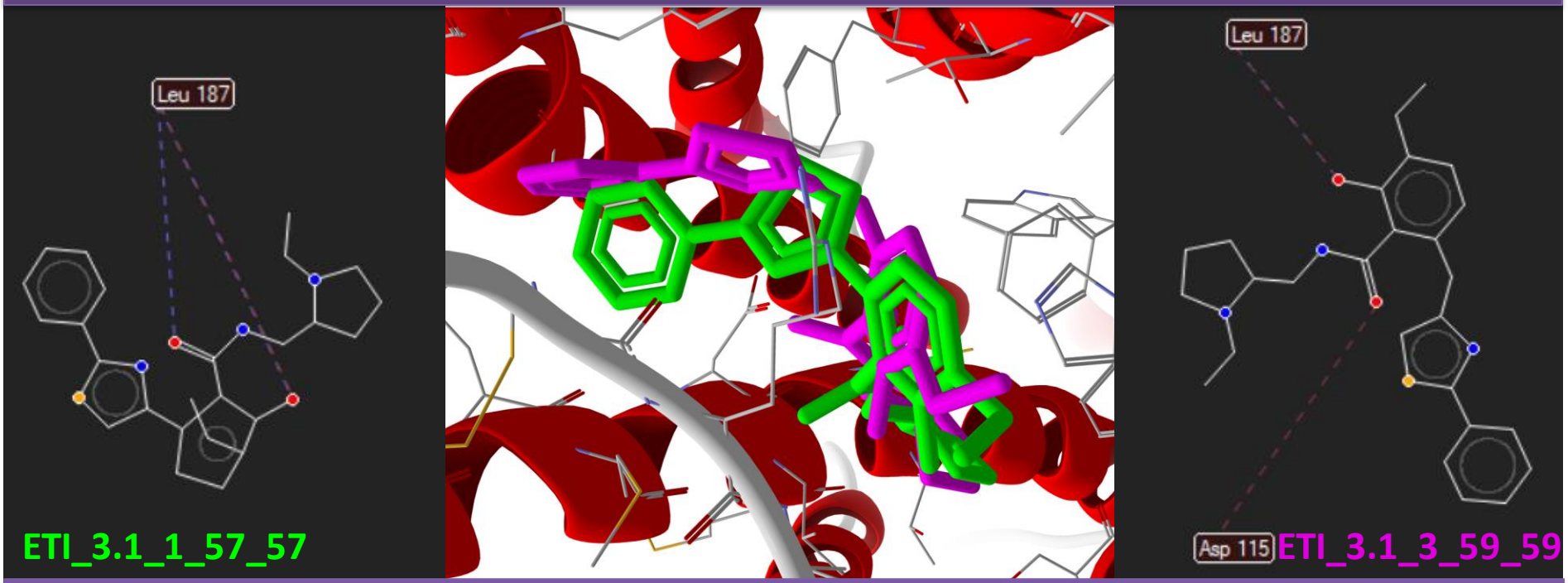




HAL_1.1_3_3_3 makes two H-bond with Asp110 (from a helical transmembrane domain) – ETI, also makes a H-bond with Asp110 in the experimental 3D structure (the other two being with His349, Tyr373). Additional, a weak H-bond (with Tyr373) and steric interactions (Val189 and Tyr365) being establish with transmembrane and topological domains.

Results and discussion [2.g] *Molecular docking*

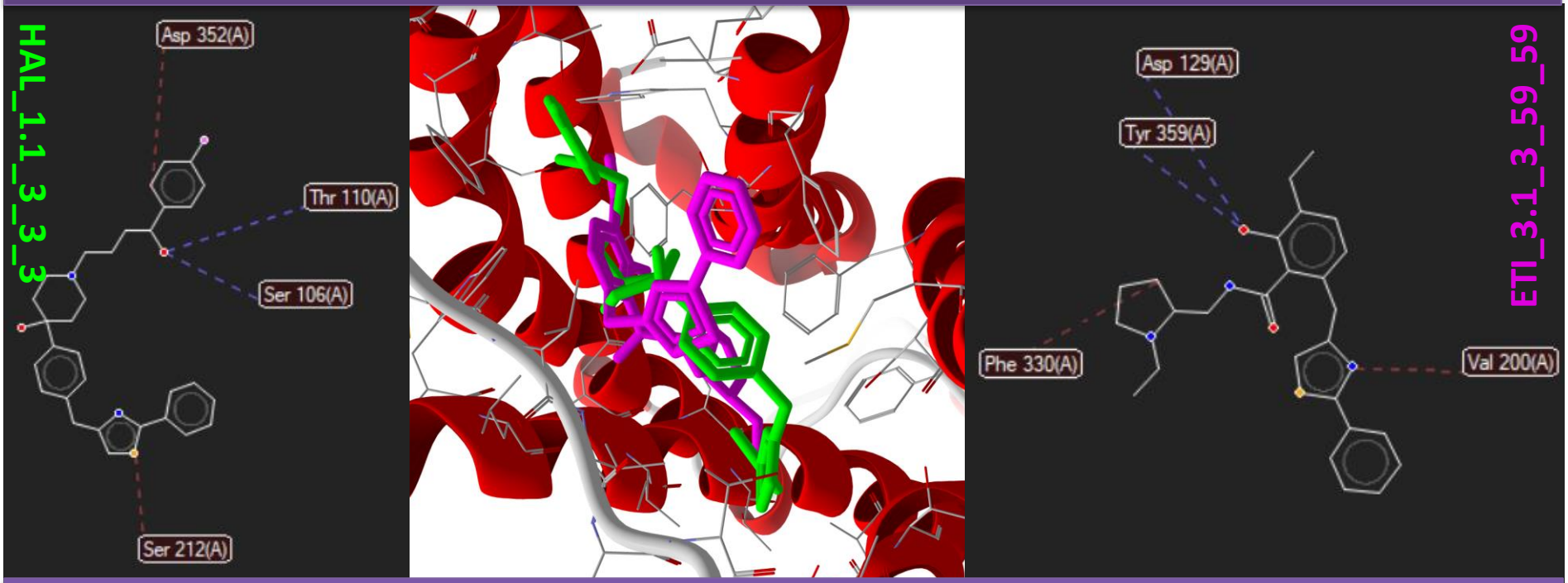
D_4 receptor (5WIU) – ETI_3.1_1_57_57 & ETI_3.1_3_59_59 complexes



Both VDs make H-bonds with Leu187 (ETI_3.1_1_57_57 – 2 H-bonds, ETI_3.1_3_59_59 - 1 H-bond) from an extracellular topological domain. Steric interactions being establish with Leu187 by both VDs, and with Asp115 only by ETI_3.1_3_59_59 (Asp115 is binding site of EMO in a transmembrane helical domain). In the experimental 3D structure, EMO establish H-bonds with Asp115 and Leu187, meanwhile steric interactions are establish only with Asp115.

Results and discussion [2.h] *Molecular docking*

5-HT_{1B} receptor (4IAR) – HAL_1.1_3_3_3 & ETI_3.1_3_59_59 complexes



HAL_1.1_3_3_3 makes two H-bonds with the second helical transmembrane domain (via Ser106 and Thr110) and two steric interactions. ETI_3.1_3_59_59 makes two H-bonds with two different helical transmembrane domains (via Asp129 and Tyr359) and two steric interactions. ERG (Ipha-1 selective adrenergic agonist vasoconstrictor) makes H-bonds with Thr134 and Val201 and steric interactions with Asp129 and Ser334.

Conclusions [1]

- Using rational design and virtual screening were found 3 VDs → promising drug prototypes

Drug Prototype	Drug-Likeness & bioavailability	CNS Activity	Toxicity Concerns	Binding Activity
HAL_1.1_3_3_3	✓	✓	INHERITED LOW RISK HALOGENURE (F)	SB: 5-HT_{1D} receptor
				SB: D_2 receptor
				SB: D_3 receptor
				GB: 5-HT_{1B} receptor
ETI_3.1_1_57_57	✓	✓	PASS	GB: D_4 receptor
ETI_3.1_3_59_59	✓	✓	PASS	GB: 5-HT_{1B} receptor
				GB: D_4 receptor

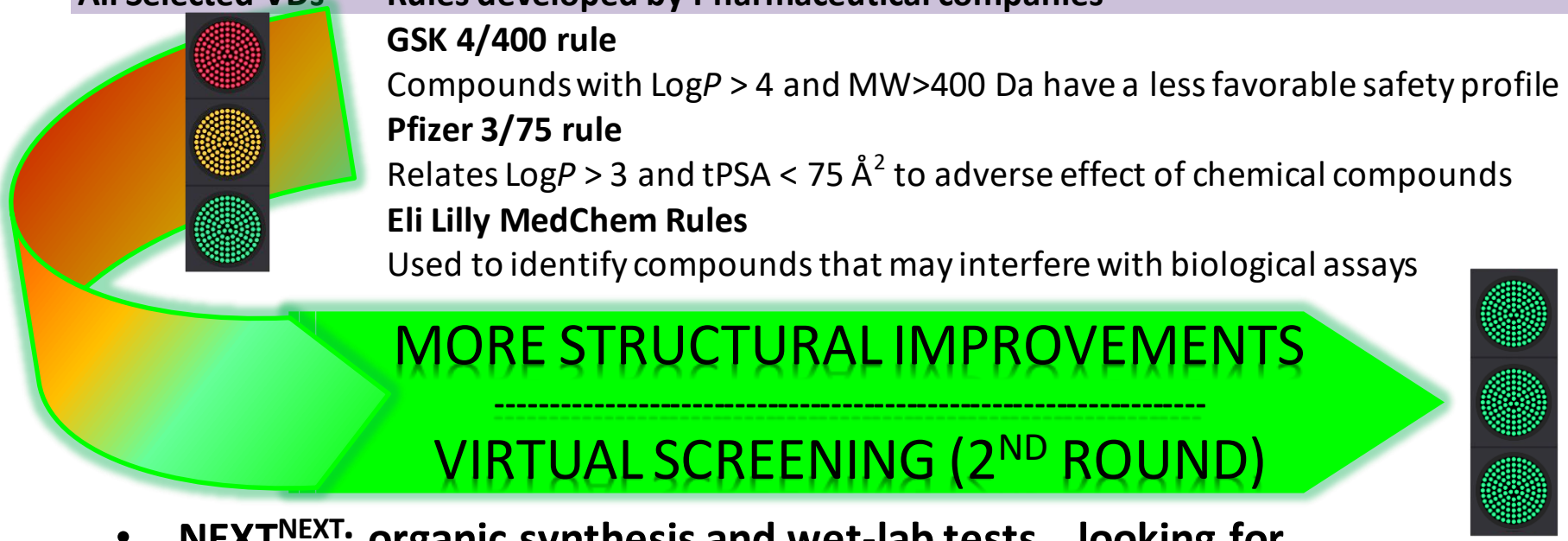
- Toxicity Concerns = cumulated results for: functional groups, PAINS, covalent inhibitors, phospholipidosis inducers, non-peptidic iPPI;
- SB = strongest binder; GB = Good binder

Conclusions [2]

NEXT: Structural improvement of selected VDs (HAL_1.1_3_3_3, ETI_3.1_1_57_57 & ETI_3.1_3_59_59) to also fully comply with all the rules developed by Pharmaceutical companies

All Selected VDs

Rules developed by Pharmaceutical companies



- **NEXT^{NEXT}: organic synthesis and wet-lab tests… looking for enthusiast collaborators!**

NO ACKNOWLEDGMENTS, BUT THANK YOU FOR YOUR ATTENTION!