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1st prize at the 12th MedChem Symposium AIMECS 2019.

The poster "From single to multi-target active ligands against neurodegenerative diseases: multi-potency screening and virtual activity evaluation" has been awarded with the 1st prize at the International Symposium of Medicinal Chemistry AIMECS 2019 in Istanbul, Turkey.
For project details, see:
https://lnkd.in/eShSArh

The research has been performed within the project „Multi-target peptide-fragment hybrids for the treatment of neurodegenerative diseases", supported by the Bulgarian Scientific Fund (BNSF No. KP-06-OPR 03/8, 2019-2021). For first time, triple active molecules have been virtually screened and evaluated as first-in-class HDAC2/MAO-B/AChE inhibitors against Parkinson´s disease. The project is created and leaded by Assoc. Prof. Dr. Nikolay T. Tzvetkov from the Department of Biochemical Pharmacology and Drug Design, Institute of Molecular Biology „Roumen Tsanev" at the Bulgarian Academy of Sciences (http://www.bio21.bas.bg/imb/?id=6).

The poster is enclosed on the second page of this PDF file.

From single to multi-target active ligands against neurodegenerative diseases: multi-potency screening and virtual activity evaluation

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Introduction

Neurodegenerative diseases (NDDs), such as Alzheimer´s disease (AD) and Parkinson´s disease (PD), represent a heterogeneous group of disorders that are typically characterized by the chronic, irreversible, and progressive neuronal death in the human brain [1,2]. Therefore, to combat the multifactorial nature of NDDs, the focus is now shifted toward development of small molecules that modulate more than one therapeutic CNS target – the multi-target-directed ligands (MTDLs). Recently, an innovative project dealing with the development of novel multi-target peptide-fragment hybrids as potential drugs against NDDs was initiated [3]. A structure-based multi-step pharmacophore modelling and virtual screening (VS) were initially used to estimate a set of unique ligands acting on three NDDs-related targets, selected within the project: monoamine oxidase B (MAO-B), acetylcholinesterase (AChE), and histone deacetylase 2 (HDAC-2) (Fig. 1, see also Poster of Alov et al. "In search for multitarget leads for treating neurodegenerative disorders: structure-based pharmacophore modelling and virtual screening".

In the current study we aim at:

- Performing a combined multi-potency screening for virtual activity evaluation (step 3, Fig. 1) of a pre-screened set of small drug-like compounds using the molecular modeling platform SeeSAR/HYDE [4].
- Identifying of multi-target (triple active) acting drug-like ligands based on their predicted affinity ranges ($K_{i\,HYDE}$ scores), physicochemical and drug-like properties (see Table 1 & 2).
- Re-docking and HYDE analysis of the top-scored MTDLs using HYdrogen DEhydratation (HYDE) algorithm (consider the contribution of all non-hydrogen atom to ΔG) as embedded in SeeSAR tool that enable additional post-scoring, including generation of new poses, tautomeric and torsional analysis (see Fig. 2).

Step 1: **Initial virtual screening (VS) to generate hits (rigid receptor, no refinement)**

Step 2: **Subsequent refinement of the hits with scores above the re-docked X-ray ligands by induced fit (Protocol 2)**

Step 3: **Final VS of the identified hits after re-docking, binding affinity scoring, and torsional analysis of the best generated poses using the molecular modeling platform SeeSAR/HYDE**

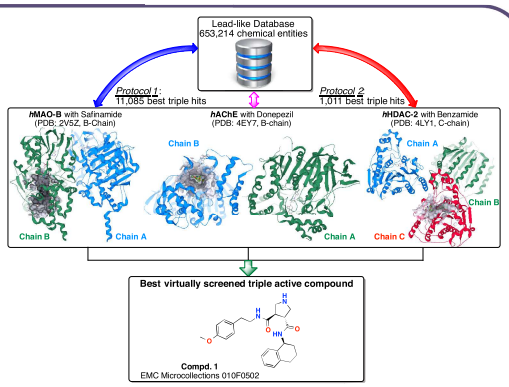


Figure 1. Three-step VS approach of 653,214 chemical entities on human MAO-B, AChE and HDAC-2 leading to the best scored compound **1.**

Multi-potency screening with SeeSAR/HYDE

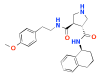
Drugs	Structure	$K_{i\,HYDE}$ ranges		
		*h*MAO-B (PDB: 2V5Z)	*h*AChE (PDB: 4EY7)	*h*HDAC-2 (PDB: 4LY1)
Safinamide (SAF)		4.06 nM < $K_{i\,HYDE}$ < 403 nM 5.18 ± 0.04 nM[1)]	69.0 nM < $K_{i\,HYDE}$ < 403 nM	2209 μM < $K_{i\,HYDE}$ < 22 mM
Compd. 1 EMC Microcollections 010F0502		0.04 nM < $K_{i\,HYDE}$ < 4.0 nM	6.89 nM < $K_{i\,HYDE}$ < 684 nM	2.36 μM < $K_{i\,HYDE}$ < 234 μM

Table 1. Estimated with HYDE/SeeSAR binding affinity ($K_{i\,HYDE}$ ranges) of reference safinamide and compound **1** towards *h*MAO-B, *h*AChE, and *h*HDAC-2 enzymes of best scored commercially available drugs. [1)] Experimental value (Ref. [5]).

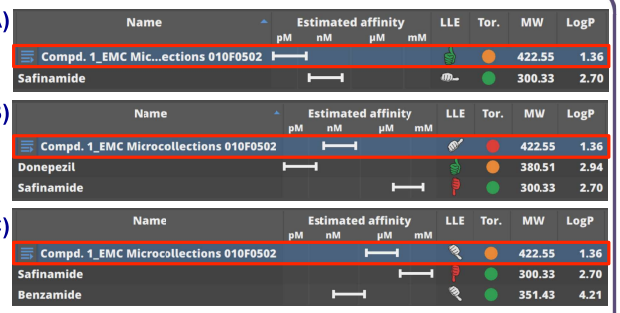


Table 2. SeeSAR representation of the estimated affinity and important parameters of X-ray ligands and compd **1** as virtually screened into *h*MAO-B (A), *h*AChE (B), and *h*HDAC-2 (C).

SeeSAR visualization and HYDE analysis of compd. 1

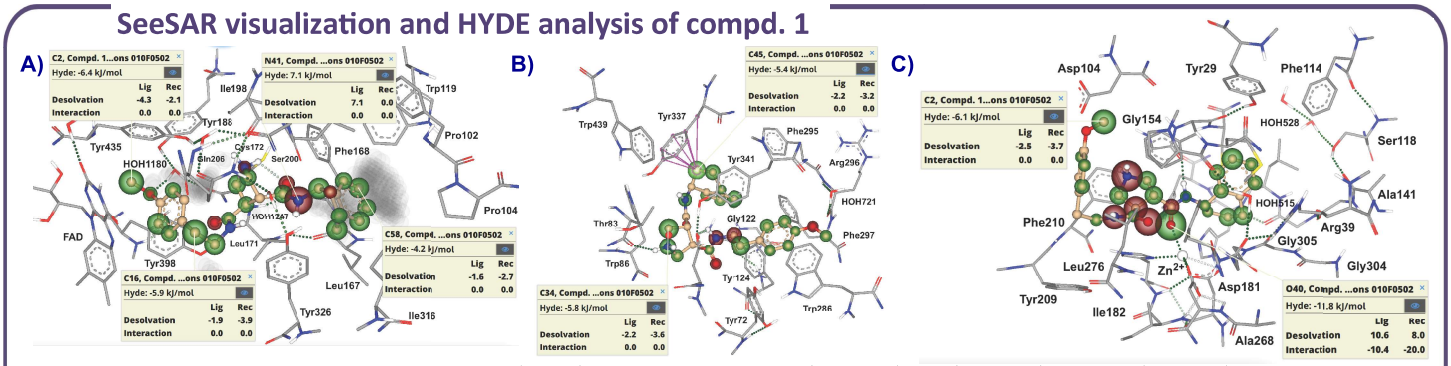


Figure 2: HYDE analysis of desolvation effects and interactions for **compd. 1** (off-white) within the binding site of *h*MAO-B (A, PDB: 2V5Z), *h*AChE (B, PDB: 4EY7), and *h*HDAC-2 (C, PDB: 4LY1). SeeSAR visualization of binding of **1** to *h*HDAC (C) is shown. HYDE coloring: **green** = good, **red** = bad for affinity.

Conclusions

- ***Multi-target concept:*** A novel mutli-target concept combining protein targets (human MAO-B, AChE, and HDAC-2 enzymes) that are related to NDDs pahtophysiology with a new molecular modeling platform SeeSAR/HYDE was used to identify a small set of multi-potent ligands (compound **1**).
- ***Proof-of-concept:*** The estimated binding affinities ($K_{i\,HYDE}$ ranges) combining both investigation of physicochemical and drug-like properties, as well as torsional and tautomeric analysis, suggested that these four compounds may be used for further exploration and creation of new peptide-fragment-based molecules with multi-target activities not only against MAO-B, AChE, and HDAC-2 enzymes, but also towards other CNS related targets. To confirm the predicted activities of the compounds, experimental evaluation of their activities is planned within the project.

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Literature

[1] S. Przedborski *Nat. Rev. Neurosci.* **2017**, 18, 251–259.
[2] (a) L.F. Burbulla et al. *Cell Death Dis.* **2014**, 5, e1180. (b) N.T. Tzvetkov and A.G. Atanasov *Future Med. Chem.* **2018**, 10, 1745–1748.
[3] https://inpst.net/multitarget-peptide-fragment-hybrids-for-the-treatment-of-neurodegenerative-diseases/
[4] www.biosolveit.de/SeeSAR (SeeSAR v.9.2, **2019**).
[5] N.T. Tzvetkov et al. *J. Med. Chem.* **2014**, 57, 6679–6703.