PHYSICOCHEMISTRY SHAPES BIOACTIVITY LANDSCAPE OF PAN-ABC TRANSPORTER MODULATORS: ANCHOR POINT FOR INNOVATIVE ALZHEIMER'S DISEASE THERAPEUTICS

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Introduction: Alzheimer's disease (AD) is a devastating neurological disorder characterized by the pathological accumulation of macromolecular Aβ and tau leading to neuronal death. Drugs approved to treat AD may ameliorate disease symptoms, however, no curative treatment exists. Aβ peptides were discovered to be substrates of adenosine triphosphate-(ATP)-binding cassette (ABC) transporters. Activators of these membrane-bound efflux proteins that promote binding and/or translocation of Aβ could revolutionize AD medicine. The knowledge about ABC transporter activators is very scarce, however, the few molecules that were reported contain substructural features of multitarget (pan-)ABC transporter inhibitors. A cutting-edge strategy to obtain new drug candidates is to explore and potentially exploit the recently proposed multitarget binding site of pan-ABC transporter inhibitors as anchor point for the development of innovative activators to promote Aβ clearance from the brain. Molecular associations between functional bioactivities and physicochemical properties of small-molecules are key to understand these processes. This contribution will provide an analysis of a recently reported unique multitarget dataset for the correlation between multitarget bioactivity and physicochemistry. Six novel pan-ABC transporter inhibitors were validated containing substructural features of ABC transporter activators, which underpins the relevance of the multitarget binding site for the targeted development of novel AD diagnostics and therapeutics.

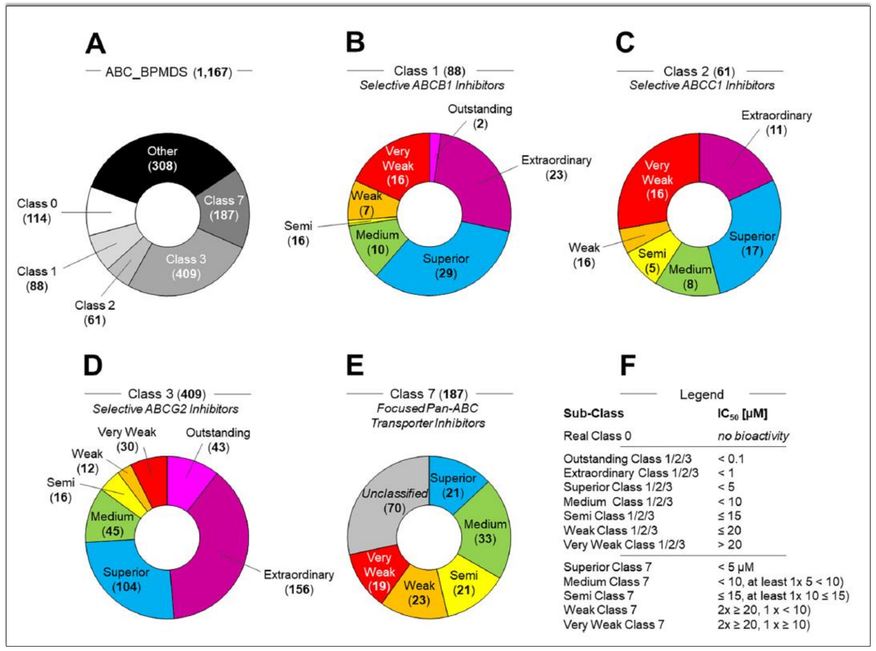

Figure 1. (Sub-)classification of compounds of the ABC_BPMDS (**A–E**) and simplified legend of sub-classification (**F**).

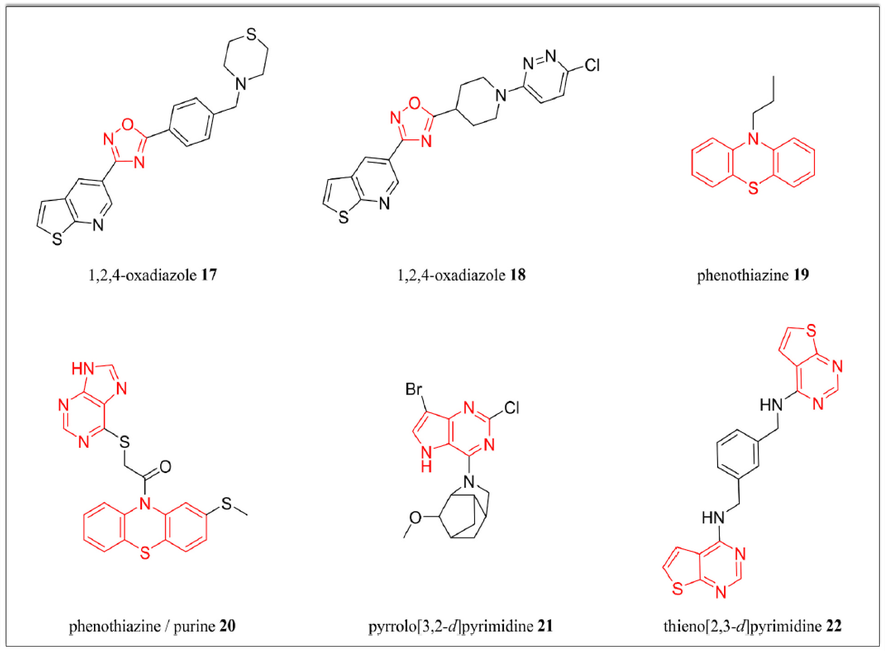

Figure 2. Depiction of biologically evaluated pan-ABC transporter inhibitors including their substructural features (red) relevant in terms of ABC transporter activation.

Table 1. Bioactivity values expressed as IC50 ± SEM of biologically evaluated focused pan-ABC transporter inhibitors **17–22.**

Compd.	Substructural Feature	ABCB1 IC_{50} ± SEM [μM] (pIC_{50} ± SEM)	ABCC1 IC_{50} ± SEM [μM] (pIC_{50} ± SEM)	ABCG2 IC_{50} ± SEM [μM] (pIC_{50} ± SEM)	CLogP	MW	MR	TPSA
17	1,2,4-Oxadiazole	117 ± 9 (3.933 ± 0.051)	25.8 ± 4.2 (4.607 ± 0.108)	105 ± 10 (3.984 ± 0.064)	3.63	394.52	11.2	55.05
18	1,2,4-Oxadiazole	27.8 ± 1.6 (4.558 ± 0.039)	22.3 ± 4.3 (4.675 ± 0.125)	47.1 ± 9.7 (4.354 ± 0.134)	4.00	398.88	10.6	80.83
19	Phenothiazine	31.3 ± 6.5 (4.550 ± 0.135)	48.5 ± 7.8 (4.347 ± 0.105)	46.2 ± 7.5 (4.369 ± 0.106)	4.63	241.36	7.45	3.24
20	Phenothiazine/Purine	9.72 ± 3.10 (5.055 ± 0.205)	11.5 ± 2.9 (4.968 ± 0.163)	16.7 ± 3.9 (4.800 ± 0.152)	3.66	437.57	12.0	74.77
21	Pyrrolo[3,2-*d*]pyrimidine	22.9 ± 3.4 (4.650 ± 0.097)	18.7 ± 12.8 (4.893 ± 0.407)	13.8 ± 0.9 (4.864 ± 0.042)	3.26	383.68	8.74	54.04
22	Thieno[2,3-*d*]pyrimidine	43.9 ± 12.8 (4.411 ± 0.188)	21.2 ± 5.2 (4.724 ± 0.158)	59.1 ± 17.7 (4.303 ± 0.193)	3.46	404.52	11.5	75.62

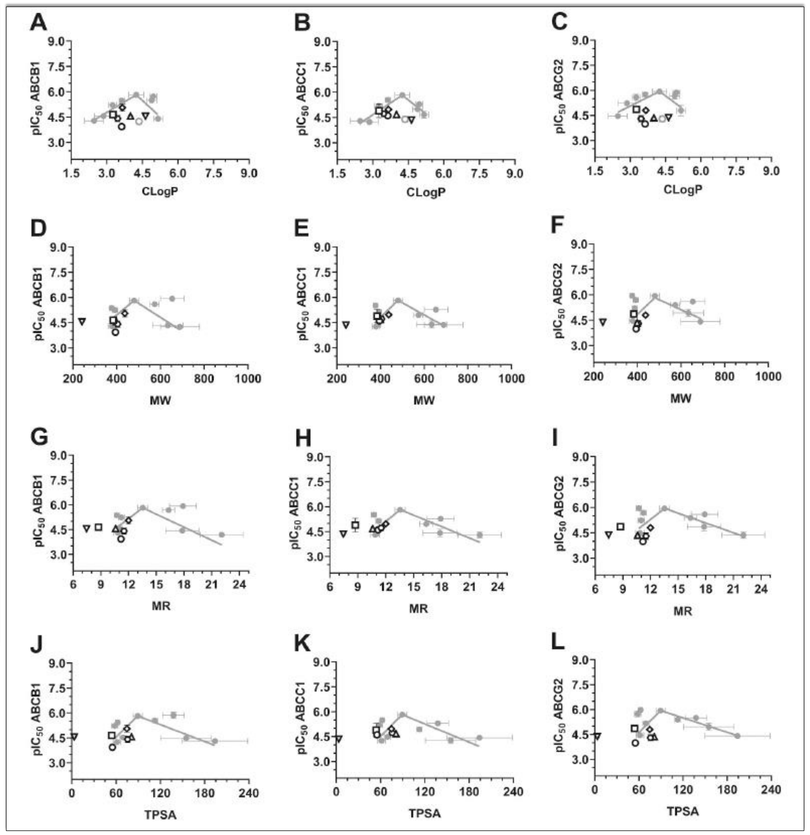

Figure 3. Bioactivity-physicochemistry plots of the 117 sub-classified focused pan-ABC transporter inhibitors of ABCB1 (**A**, **D**, **G**, and **J**), ABCC1 (**B**, **E**, **H**, and **K**), and ABCG2 (**C**, **F**, **I**, and **L**) with respect to CLogP (**A**, **B**, and **C**), MW (**D**, **E**, and **F**), MR (**G**, **H**, and **I**), as well as TPSA (**J**, **K**, and **L**). The multidirectional two-phase linear correlations are depicted with grey closed circles (outliers: open circles) and grey lines which are compared to compounds **17** (black open circles), **18** (black upward open triangles), **19** (black downward open triangles), **20** (black open routes), **21** (black open squares), and **22** (black open hexagons).

Conclusion:

- This study analyzes a unique multitarget dataset recently reported, focusing on the correlation between multitarget bioactivity and physicochemistry
- **six novel** pan-ABC transporter inhibitors were validated containing substructural features of ABC transporter activators
- these modulators could serve as anchor points for developing **innovative therapeutics for Alzheimer's disease**, particularly in targeting Aβ clearance from the brain

V. Namasivayam et al., Int. J. Biol. Macromol. (2022) 775-791. doi: 10.1016/j.ijbiomac.2022.07.062

Acknowledgement: Study was supported by the EEA and Norway Grants 2014–2021 and state budget of the Czech Republic within the TARIMAD project sponsored by TACR Kappa programme (Iceland, Liechtenstein, Norway, and Czech Republic; No. TO01000078), and the EU Joint Programme - Neurodegenerative Disease Research (JPND) project PETABC (MSMT No. 8F21002).