Identification of natural products for the treatment of Alzheimer's disease: 3D-similarity search

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Abstract

- Glycogen synthase kinase 3 (GSK-3), one of the main tau kinases involved in a variety of cellular processes, has been evidenced as a promising target for Alzheimer's disease (AD) treatment. In recent years, great efforts have been made to discover new molecules with an enhanced profile that inhibit GSK-3 and display efficacy in AD treatment.

- SAR502250, a new discover selective GSK3 inhibitor with AD therapeutic potential, represents a good alternative to future design specific inhibitors against this condition. SAR502250 was used as a query in a 3D similarity search on the SPECS database to select new natural compounds as possible GSK-3 inhibitors.

- According to ShapeTanimoto, TanimotoCombo, and ComboScore matrics, the first 10 SPECS natural compounds were selected and structurally analyzed. The ADME, physicochemical parameters, and toxicity related risks profiles of the selected natural compounds were also investigated. The 3D-similarity results in conjunction with pharmaceutical profiles revealed the potential use of natural compounds as GSK-3 inhibitors for Alzheimer's disease therapy.

Workflow diagram

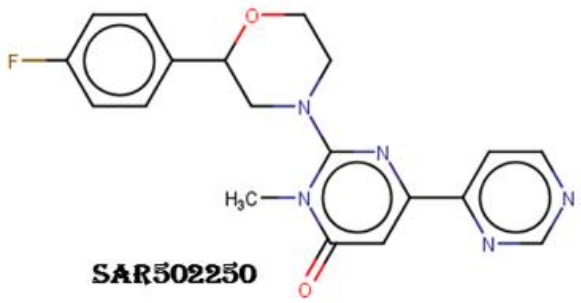
DATASET

SPECS Natural Products

400 Compounds

METHODS

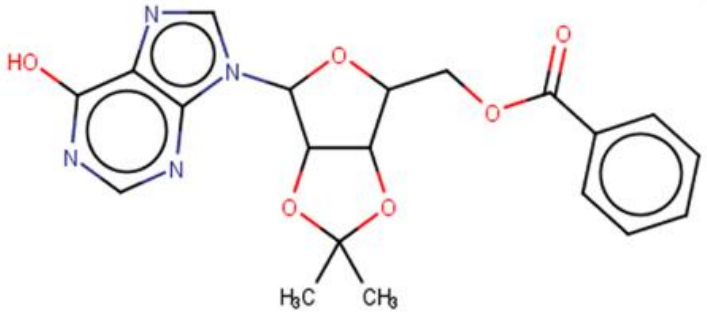
3D Similarity search



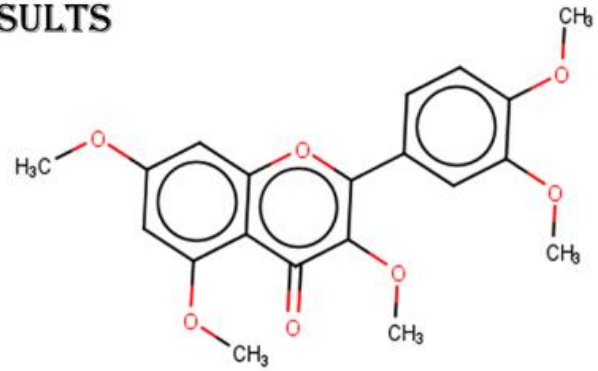
SAR502250

ADME parameters

RESULTS



AE-848/20954002



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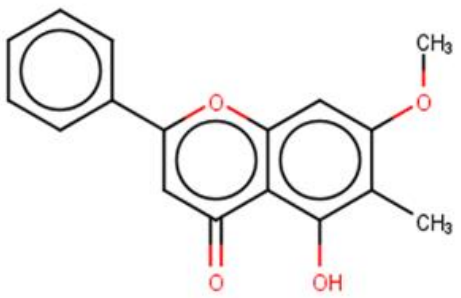
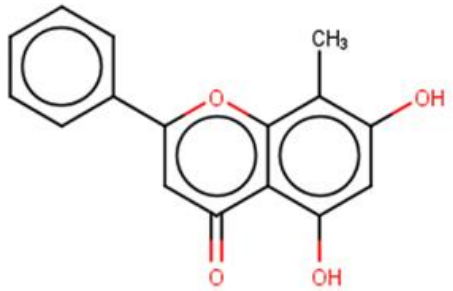


AK-087/42718409



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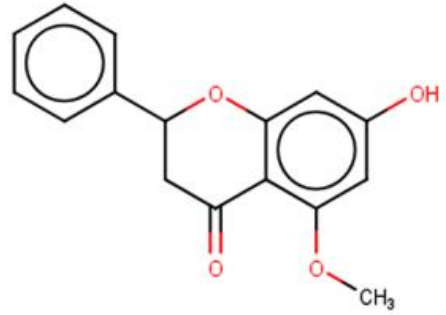


AA-504/21003038

Methods

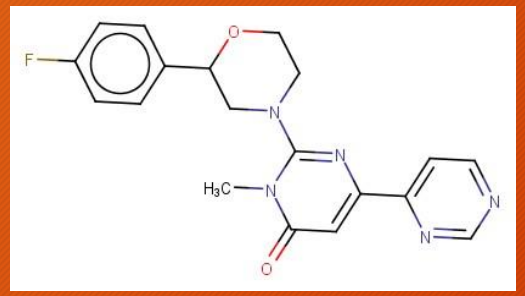
1. Dataset preparation

SPECS NP

- Ionization states and tautomers – LigPrep/Schrödinger(https://www.schrodinger.com/)
- Conformers – Omega/OpenEye (http://www.eyesopen.com).

2. 3D similarity search

- ROCS/OpenEye (http://www.eyesopen.com)
- Query - SAR502250



- TanimotoCombo coefficient

$$Tanimoto_{X,Y} = \frac{O_{X,Y}}{I_X + I_Y - O_{X,Y}}$$

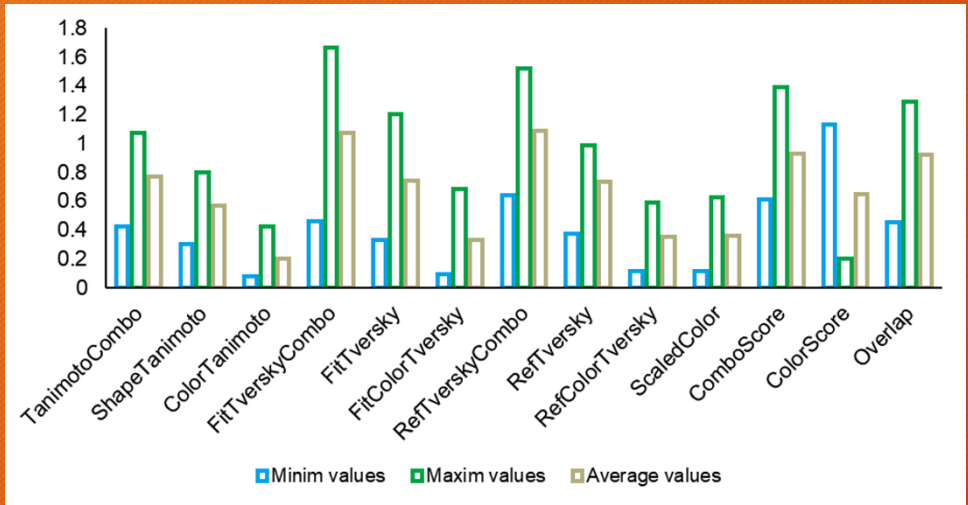
3. ADME and Toxicity related risk profiles

- The ADME (Absorption, Distribution, Metabolism, and Excretion) - SwissADME (http://www.swissadme.ch/)
- The risks of side-effects (irritation, mutagenicity, tumorigenicity, and reproduction effectivity) - Osiris Property Explorer (https://www.organic-chemistry.org/prog/peo/)

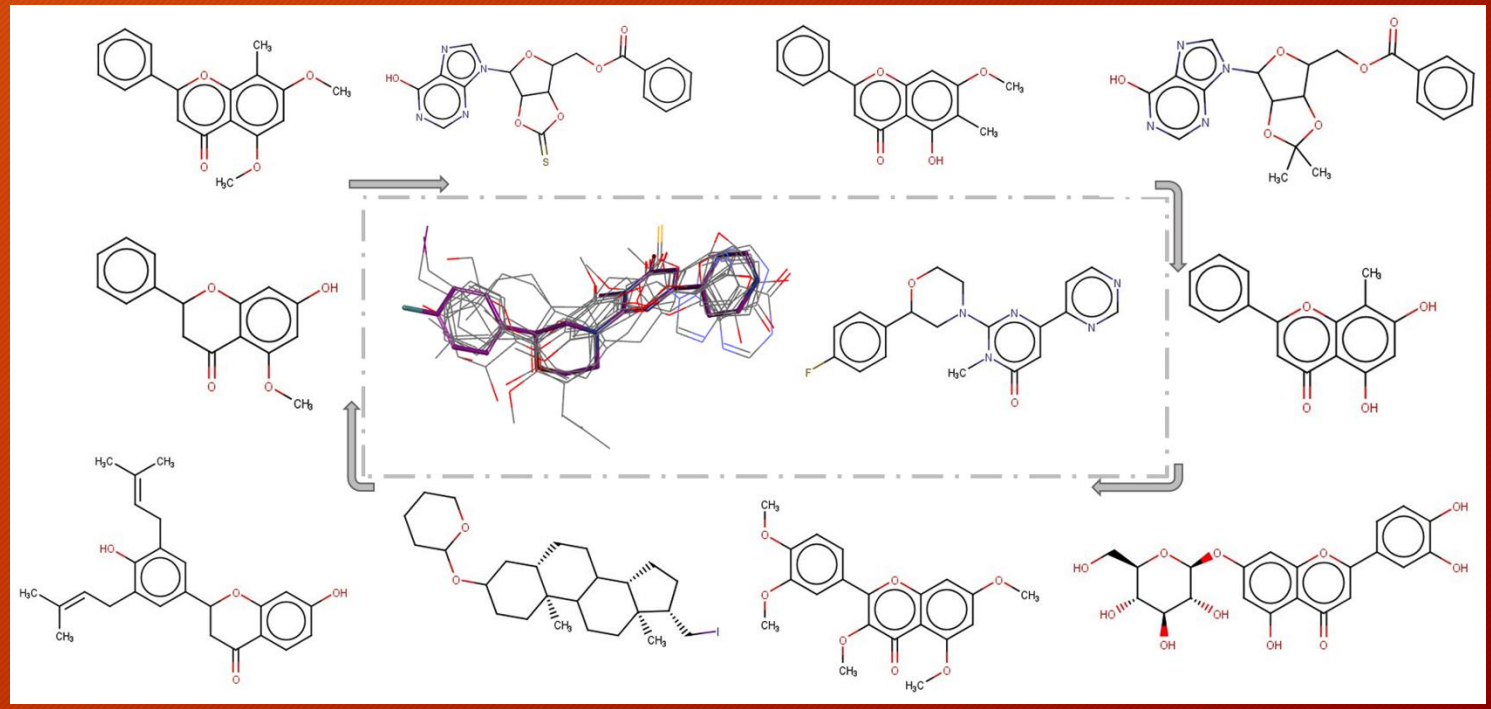
Results and Discussions

3D similarity analysis

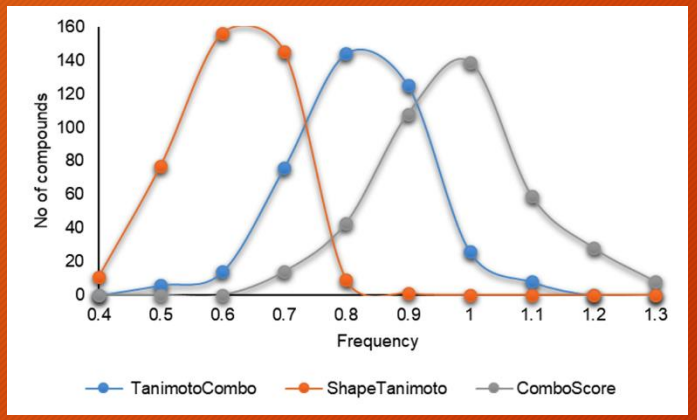
ROCS - 3D similarity coefficients



The top ten Natural products prioritized against SAR502250 ordered by TanimotoCombo



The distribution of TanimotoCombo, ShapeTanimoto, ComboScore values for SPECS NP against SAR502250



Results and Discussions

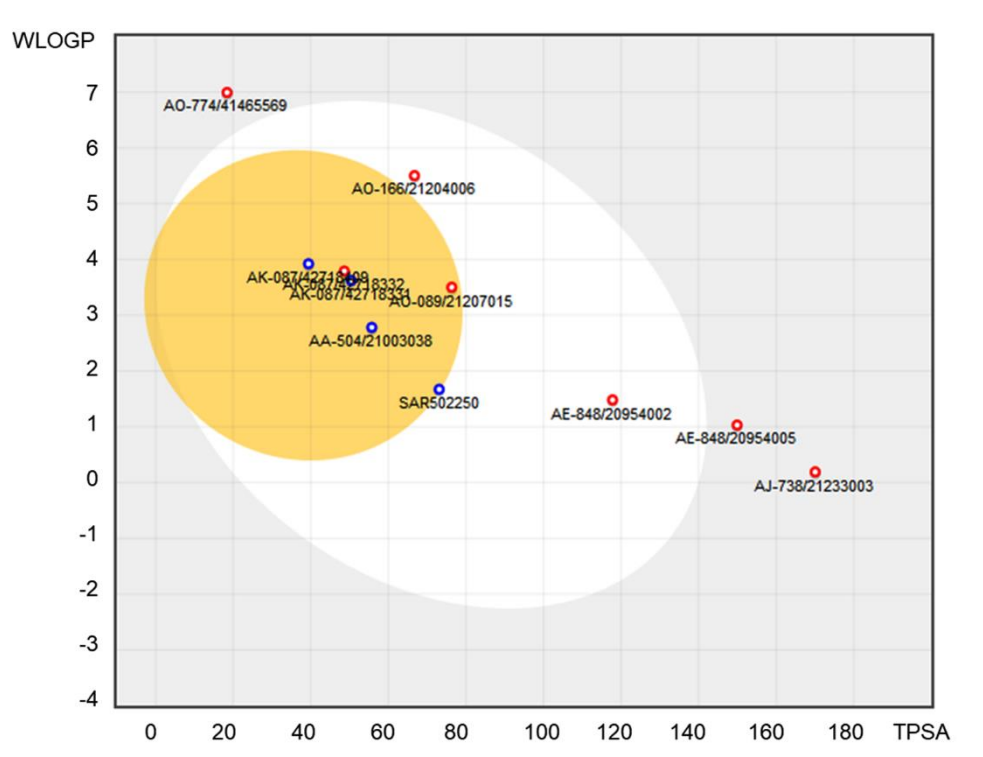
Physiochemical parameters and toxicity related risks profile of the ten SPECS NP

Molecule	AK-087/ 42718332	AE-848/ 20954005	AK-087/ 42718409	AE-848/ 20954002	AK-087/ 42718331	AJ-738/ 21233003	AO-089/ 21207015	AO-774/ 41465569	AO-166/ 21204006	AA-504/ 21003038	SAR502250
BBB permeant	Yes	No	Yes	No	Yes	No	Yes	No	No	Yes	Yes
MW	296.32	414.39	281.28	412.4	267.26	447.37	372.37	500.5	392.49	270.28	367.38
RBN	3	5	2	5	1	4	6	3	5	2	3
MR	85.87	100.26	79.51	102.12	75.04	106.24	100.38	126.33	116.99	74.02	100.96
TPSA	48.67	149.91	39.44	117.82	50.44	170.05	76.36	18.46	66.76	55.76	73.14
XLOGP3	3.49	2.14	4.21	1.66	3.88	1.46	3.25	8.3	6.15	2.65	0.68
WLOGP	3.79	1.03	3.92	1.48	3.62	0.19	3.5	6.99	5.5	2.78	1.67
GI absorption	High	Low	High	High	High	Low	High	Low	High	High	High
Lipinski #violations	0	0	0	0	0	2	0	2	0	0	0
TanimotoCombo	1.075	1.049	1.04	1.025	1.013	1.009	1.007	1.006	0.997	0.996	2
ShapeTanimoto	0.651	0.769	0.65	0.739	0.63	0.802	0.681	0.696	0.695	0.611	1
ComboScore	1.18	1.304	1.18	1.332	1.153	1.392	1.2	1.143	1.211	1.136	2
Toxicity risk*	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE	• M • T • I • RE

*M = mutagenic; T = tumorigenic; I= irritant; RE = reproductive effective; the red color circles designate properties with high risks of undesired effects like reproductive or irritant effect, or mutagenicity, while the green color circles indicate drug-like conforming behavior

Results and Discussions

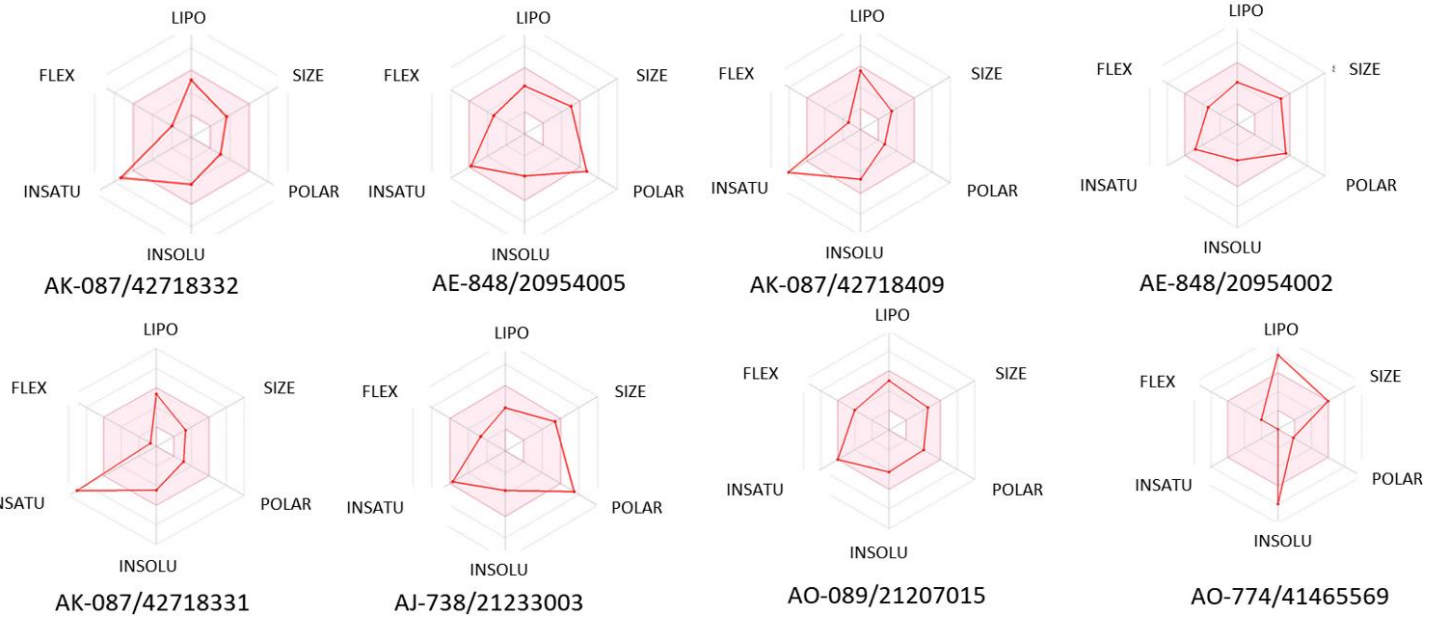
The blood-brain barrier (BBB) permeation and passive gastrointestinal absorption (HIA)



- ✓ The molecules plotted in the white ellipse have a high probability of good intestinal absorption
- ✓ The molecules plotted in the yellow ellipse have a high probability of a good BBB crossing.
- ✓ The molecules which are located in the grey area are predicted as not absorbed by the GI and BBB non-permeant.
- ✓ The red and blue circles indicate a relation to predict the active efflux by the P-glycoprotein (PGP+ code for blue circle, and PGP- for red circle).

Results and Discussions

Bioavailability Radar



The pink area is represented by the optimum range for each property:

- ✓ MW between 150 and 500 g/mol,
- ✓ TPSA between 20 and 130 Å^2,
- ✓ XLOGP3 between − 0.7 and + 5.0,
- ✓ no more than 9 rotatable bonds,
- ✓ log S not higher than 6,
- ✓ the fraction of carbons in the sp3 hybridization not less than 0.25.

Conclusions

- In this study, 3D similarity search, ADME, and toxicity related predictions were employed to identify novel natural products, from the SPECS NP database, with similar profiles compared to those of the GSK-3 selective inhibitor, SAR202250.
- Three out of thirteen 3D similarity coefficients (TanimotoCombo, ShapeTanimoto and, ComboScore) together with ADME and toxicity risk analyzed parameters indicated five SPECS natural products (AK-087/42718409, AK-087/42718331, AA-504/21003038, AE-848/20954002 and, AO-089/21207015) as displaying great predicted drug-like properties and pharmacological profiles.
- These five natural compounds are recommended to be in depth analyzed as an option for Alzheimer's disease treatment.
- We assume that the 3D-similarity search in conjunction with pharmaceutical profiles can be applied as a start routine in the discovery of potentially selective GSK-3 inhibitors.

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Acknowledgments