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Identification of Natural Products for the Treatment of Alzheimer's Disease: 3D Similarity Search †

Luminita Crisan *, Alina Bora and Liliana Pacureanu

"Coriolan Dragulescu" Institute of Chemistry Timisoara, 24 Mihai Viteazul Av., 300223 Timisoara, Romania; alina.bora@gmail.com (A.B.); pacureanu@acad-icht.tm.edu.ro (L.P.)

* Correspondence: lumi_crisan@acad-icht.tm.edu.ro

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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 newly discovered selective GSK-3 inhibitor with AD therapeutic potential, represents a good alternative to design future 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 (Absorption, Distribution, Metabolism, and Excretion), physicochemical parameters, and toxicity-related risk 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.

Keywords: GSK-3; SAR502250; natural products; 3D similarity search

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1. Introduction

In many studies, glycogen synthase kinase-3 (GSK-3) has arisen as a promising therapeutic target for the treatment of inflammatory disorders, diabetes, neurodegenerative diseases, different types of cancers, etc. [1–7]. GSK-3 has been proven to be a promising target for the treatment of Alzheimer's disease (AD); hence, its inhibition has been proposed as a strategy for treating AD patients [6]. The search for GSK-3 inhibitors has led to the discovery of a variety of chemical scaffolds that can be grouped into natural inhibitors, inorganic metal ions, maleimides, indirubins, paullones, purines, peptide inhibitors, etc. [8–12].

Alzheimer's is considered a chronic disease that necessitates treatment for one's entire life. Therefore, drugs must be safe and well-tolerated for long periods. In this context, attention has been focused on natural products that are considered true sources of active ingredients for medicine. They also play a key role in the drug discovery process. In the last 20 years, many drugs used in the treatment of various diseases like diabetes, cancer, cardiovascular diseases, etc. have often been natural products or their derivatives [13].

The main goal of this study was to select new natural products (NP) from the SPECS NP database [14] as possible GSK-3 inhibitors. In this light, SAR502250, a selective GSK-3 inhibitor used as a query and 3D molecular similarity search with ROCS (Rapid Overlay of Chemical Structures) [15,16], was employed to identify similar natural products with potential inhibition against GSK-3. The physicochemical parameters, toxicity-related risk profiles, and ADME (Absorption, Distribution, Metabolism, and Excretion) parameters were also explored.

2. Methods

2.1. Workflow

The workflow diagram (Figure 1) followed in this paper comprises (a) the SPECS NP download and preparation, (b) the 3D similarity search, and (c) the ADME and toxicity risk profile predictions of the selected compounds.

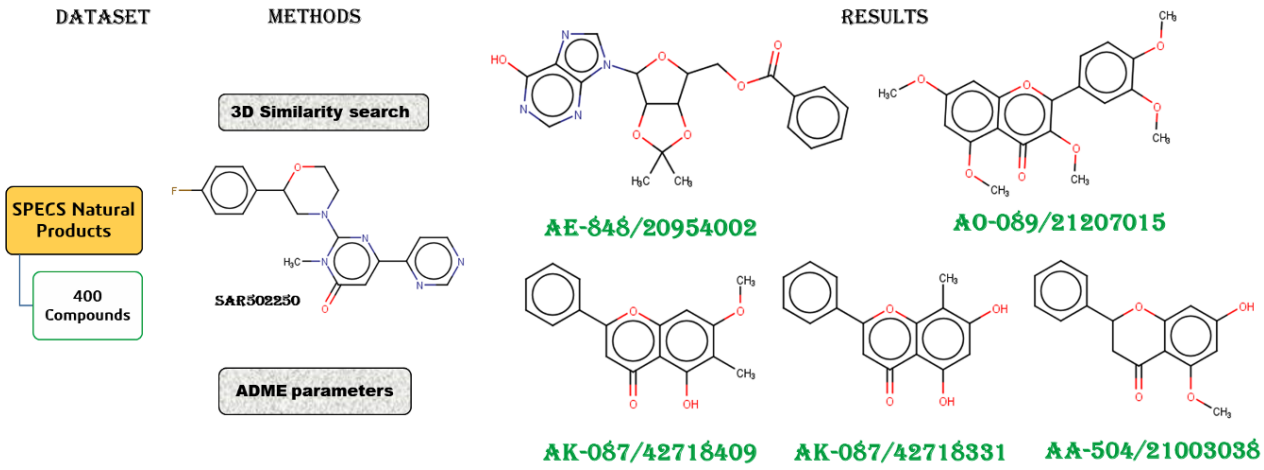

Figure 1. Workflow diagram.

2.2. Dataset Preparation

The dataset of 400 natural products [14] was prepared using LigPrep [17] from the Schrödinger suite and Omega (OMEGA v.2.5.1.4, OpenEye Scientific Software, Santa Fe, NM, USA. www.eyesopen.com (accessed on 12 February 2020)) [18,19] from the OpenEye. The ionization states and tautomers were engendered at pH = 7.2 ± 0.2, and the conformational space of each molecule was carried out, generating at most 200 conformations per ligand with an RMSD (root mean square deviation) of 0.8 Å in an energy window of 10 kcal/mol. The resulting dataset was used in the 3D similarity search process.

2.3. 3D Similarity Search

ROCS (ROCS v. 3.2.1.4, OpenEye Scientific Software, Santa Fe, NM, USA) [15,16] uses rigid conformations to evaluate shape similarity and implicit binding site complementarity. The similarity rule is based on the principle that two molecules that are structurally similar have similar biological and physical properties. When overlapping the structures, ROCS utilizes only the heavy atoms of a query, while the hydrogen atoms are ignored. This method is very often used in hit/lead identification to accelerate the speed and efficiency of the drug discovery and development process.

For 3D similarity analysis, the selective SAR502250 inhibitor (2-[2-(4-Fluorophenyl)morpholin-4-yl]-3-methyl-6-pyrimidin-4-ylpyrimidin-4-one; IC50 = 12 nM) [5] was chosen as the query molecule (Figure 2), and the SPECS NP database was engaged.

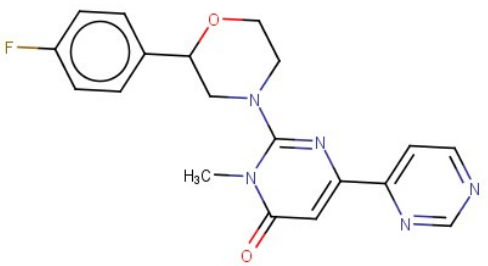

Figure 2. The structure of the query compound.

The ROCS program calculates 13 similarity coefficients as follows: TanimotoCombo, ShapeTanimoto, ColorTanimoto, ScaledColor, ComboScore, ColorScore, FitTversky-Combo, RefTverskyCombo, FitTversky, RefTversky, FitColorTversky, RefColorTversky, and Overlap. The Tanimoto similarity score is one of the most utilized coefficients in the early stage of virtual screening experiments to discover new molecules as potential drugs. ROCS quantifies and ranks the database molecules by Tanimoto coefficients (Equation (1)), based on the best shape overlap between a query molecule and a database molecule. The ROCS maximizes the volume overlap between them.

$$Tanimoto_{X,Y} = \frac{O_{X,Y}}{I_X + I_Y - O_{X,Y}} \quad (1)$$

where the I are the terms for the self-volume overlaps, and the O terms are the overlaps between molecules X and Y.

2.4. ADME and Toxicity-Related Risk Profiles

The ADME (absorption, distribution, metabolism, and excretion) properties of the selected natural products were estimated using the open-source programs, Osiris Property Explorer [20] and SwissADME [21]. Additionally, the risks of side-effects (irritation, mutagenicity, tumorigenicity, and reproduction effectivity) and the passive gastrointestinal absorption (HIA) and brain penetration (BBB) were predicted.

3. Results and Discussions

In virtual screening experiments, ROCS has been demonstrated to be robust vis-à-vis to the substitution of bioactive conformation with the lowest energy conformer [18,19]. In this respect, we investigated the SPECS NP database against the lowest energy conformation of SAR502250 (Figure 2). The minimum, maxim, and average values of the 3D similarity coefficients registered are shown in Figure 3.

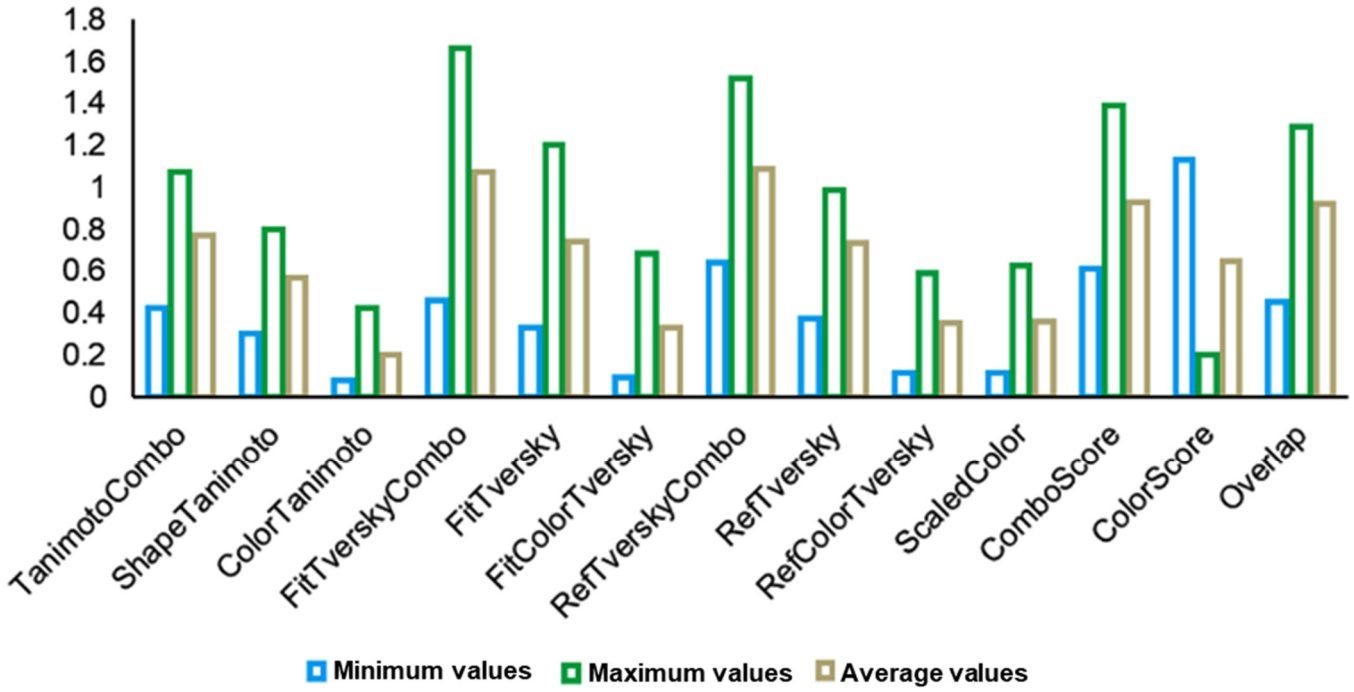

Figure 3. The minimum, maximum, and average 3D similarity coefficient values for SPECS NP concerning the SAR502250 query; for easier graphical representation, the values of the ColorScore coefficient were divided by −5, while the Overlap coefficients values were divided by −1000.

The ROCS overlays between the lowest energy conformer of SAR502250 and SPECS NP generated satisfactory results. To illustrate these observations, BIOVIA Discovery Studio v.4.5.0.15071 software was engaged (Figure 4).

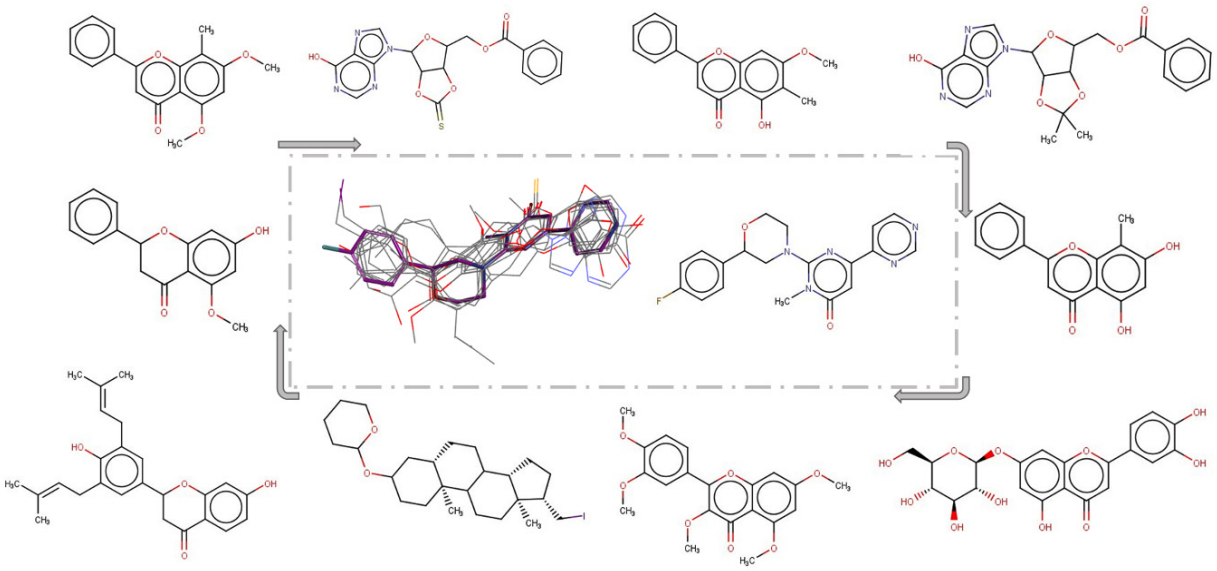

Figure 4. ROCS overlay of the top ten natural products prioritized against SAR502250, ordered by TanimotoCombo (see the gray arrow directions).

Three (TanimotoCombo, ShapeTanimoto, and ComboScore) out of 13 coefficients were used to assist the prioritization of the natural compounds (Figure 5). Natural compounds with coefficient values greater than 1 for TanimotoCombo, greater than 0.7 for ShapeTanimoto, and greater than 1.2 for ComboScore [19,22,23] were analyzed in detail.

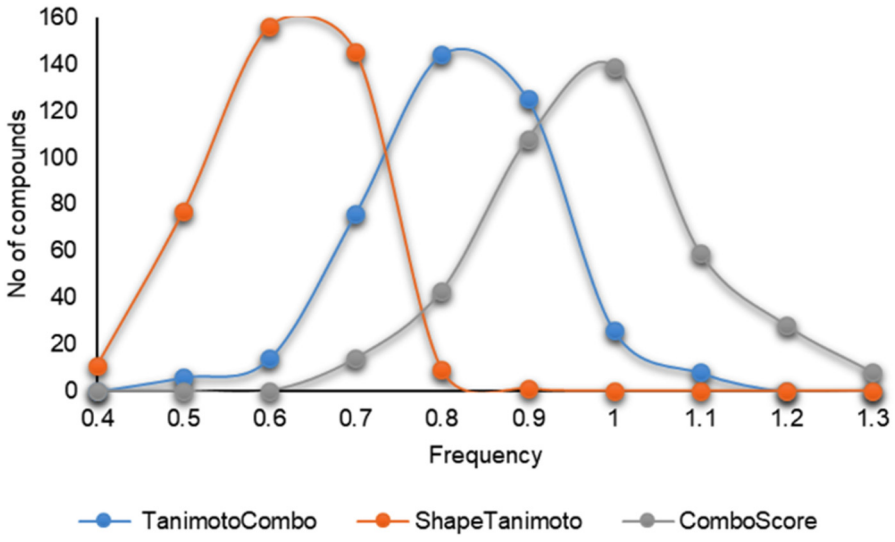

Figure 5. The distribution of 3D similarity coefficients (TanimotoCombo, ShapeTanimoto, ComboScore) values for SPECS NP against SAR502250.

The first 10 (Figures 3 and 4) compounds in the SPECS NP database ordered by TanimotoCombo values were further investigated by applying ADME and toxicity-risk filters to assess their drug-like properties (Table 1).

Table 1. Physiochemical parameters and toxicity-related risk profiles of the 10 SPECS NP predicted compounds by SwissADME and OSIRIS Property Explorer software *. The 3D similarity coefficients (TanimotoCombo, ShapeTanimoto, ComboScore) were calculated with ROCS.

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	M	M	M	M	M	M	M	M	M	M
	T	T	T	T	T	T	T	T	T	T	T
	I	I	I	I	I	I	I	I	I	I	I
	RE	RE	RE	RE	RE	RE	RE	RE	RE	RE	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; BBB (Blood Brain Barrier); MW (Molecular Weight); RBN (Rotatable Bonds); MR (Molar Refractivity); TPSA (Topological Polar Surface Area); XLOGP3 and WLOGP (lipophilicity descriptor - the partition coefficient between n-octanol and water); GI (Gastrointestinal Absorption).

The blood-brain barrier (BBB) permeation and passive gastrointestinal absorption (HIA) were predicted at the same time with SwissADME software for all 10 natural compounds. The so-called BOILED-Egg model was constructed (Figure 6). This is a simple and intuitive graph prediction of HIA and BBB as a function of apparent polarity and lipophilicity (defined by TPSA (Topological Polar Surface Area) and WLOGP (lipophilicity descriptor—the partition coefficient between n-octanol and water), respectively). Also, the bioavailability radar (Figure 7) for each selected natural compound based on size, polarity, lipophilicity, flexibility, solubility, and saturation was built. In this graph, the pink area represents 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 nine rotatable bonds, log S not higher than six, and the fraction of carbons in the sp^3 hybridization not less than 0.25.

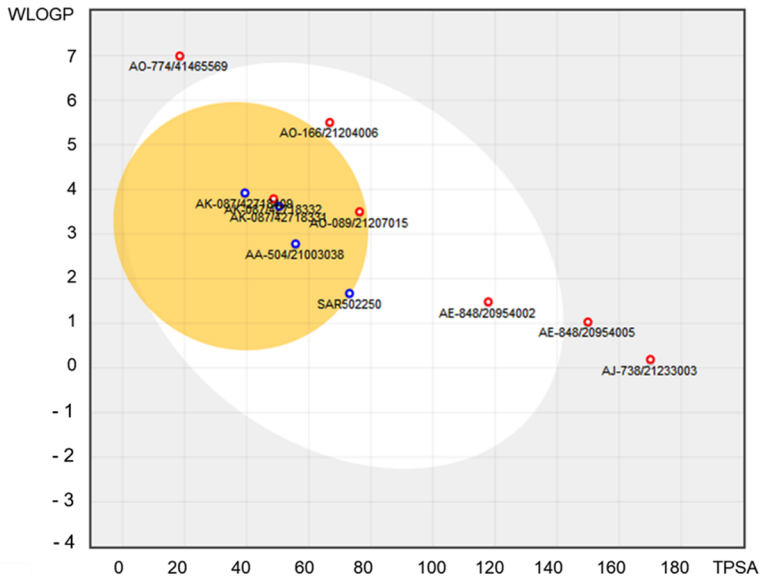

Figure 6. The WLOGP–TPSA referential for predicted SPECS NP.

Figure 7. The bioavailability radar of predicted compounds for SPECS NP and SAR502250.

The molecules plotted in the white ellipse had a high probability of good intestinal absorption, while the molecules plotted in the yellow ellipse had a high probability of a good BBB crossing. The molecules which are located in the grey area were predicted as not absorbed by the GI and as 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).

The ADME and toxicity risk profiles suggest that AK-087/42718409, AK-087/42718331, and AA-504/21003038 exhibit excellent drug-like properties, similar to those of selective inhibitor SAR202250 (Table 1, Figure 6). The AK-087/42718331 compound showed only the mutagenic effect risk. In Figure 7, we observe that AE-848/20954002 and AO-089/21207015 compounds are entirely plotted in the pink area like SAR502250 and may be considered to have drug-like properties.

4. Conclusions

In this study, a 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 13 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 analyzed in-depth 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 starting routine in the discovery of potentially selective GSK-3 inhibitors.

Author Contributions: L.C. and A.B. conceived of the presented ideas, performed the computational studies, and edited the manuscript; L.P. analyzed some resulting data. All authors discussed the outcomes, contributed to the writing of the paper, and commented on the paper. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors indicate no potential conflicts of interest.

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