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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.

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

1. Introduction

In many studies Glycogen synthase kinase 3 (GSK-3) arises as a promising therapeutic target for the treatment of inflammatory disorders, diabetes, neurodegenerative diseases, different type of cancers, etc. [1–6]. GSK-3 has been proved 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 leads to the discovery of a variety of chemical scaffolds, that can be grouped into natural inhibitors, inorganic metal ions, maleimides, indirubins, paullones, purines, and peptide inhibitors, etc. [7–11].

Alzheimer's is considered a chronic disease that necessitates treatment for the entire life. Therefore, the 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. were often natural products or their derivatives [12].

The main goal of this study is to select new natural products from the SPECS NP database [13] as possible GSK-3 inhibitors. In this light, the SAR502250, a selective GSK-3 inhibitor used as query and 3D molecular similarity search with ROCS (Rapid Overlay of Chemical Structures) [14,15] were employed to identify similar natural products with potential inhibition against GSK-3. The physicochemical parameters, toxicity related risks profiles, and ADME parameters were also explored.

2. Methods

2.1. Workflow

The workflow diagram (Figure 1) followed in this paper comprise (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.

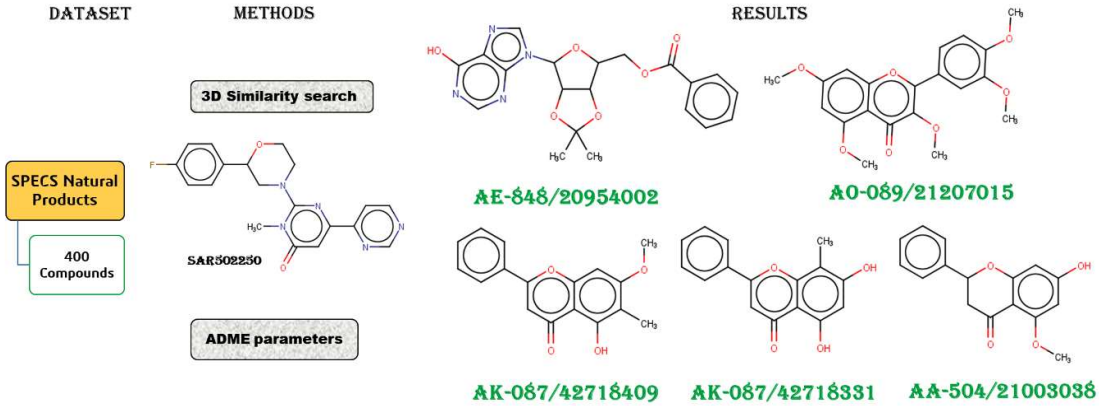

Figure 1. Workflow diagram.

2.2. Dataset Preparation

The dataset of 400 natural products [13] was prepared using LigPrep [16] from the Schrödinger suite (https://www.schrodinger.com/) and Omega (OMEGA v.2.5.1.4, OpenEye Scientific Software, Santa Fe, NM, USA. www.eyesopen.com) [17,18] from the OpenEye package (http://www.eyesopen.com). 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 resulted 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. http://www.eyesopen.com) [14,15] uses rigid conformations to evaluate shape similarity and implicitly binding site complementarity. The similarity rule is based on the principle that two molecules structurally similar have similar biological and physical properties. When overlapping the structures, ROCS utilizes only the heavy atoms of a query, 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 = 12nM) [5] chosen as query molecule (Figure 2) and SPECS NP database were engaged.

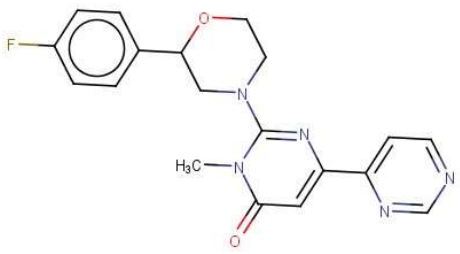

Figure 2. The structure of the query compound.

The ROCS program, calculates thirteen similarity coefficients as follows: TanimotoCombo, ShapeTanimoto, ColorTanimoto, ScaledColor, ComboScore, ColorScore, FitTverskyCombo, 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 volume overlap between them.

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

where the I is 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 [19] and SwissADME [20]. Also, 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 demonstrates to be robust vis-à-vis to the substitution of bioactive conformation with the lowest energy conformer [17,18]. 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.

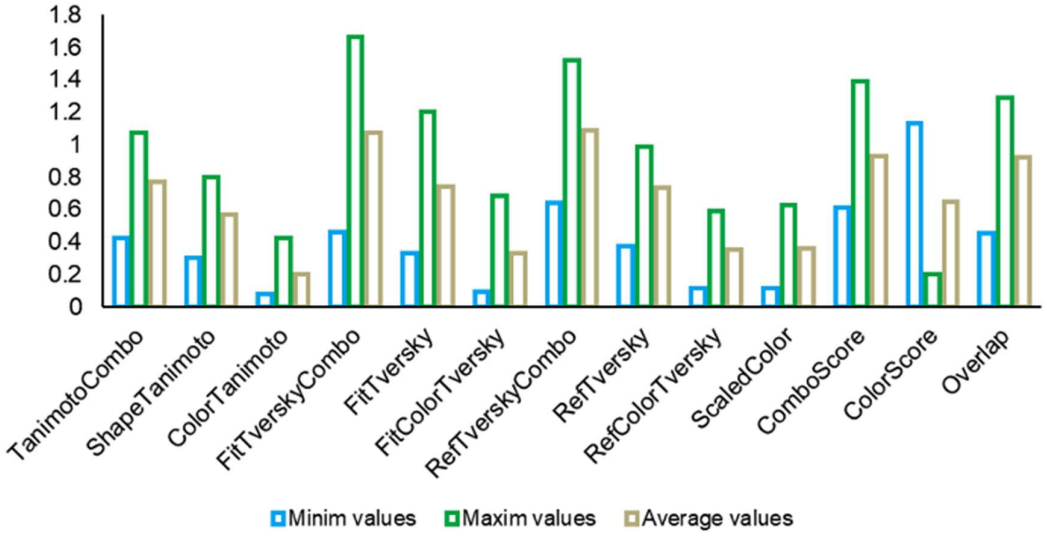

Figure 3. The minim, maxim, and average for 3D similarity coefficients values for SPECS NP concerning SAR502250 query; for easier graphical representation, the values of the ColorScore coefficient were divided by (-5) while the Overlap coefficients values were divided by (-1000).

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).

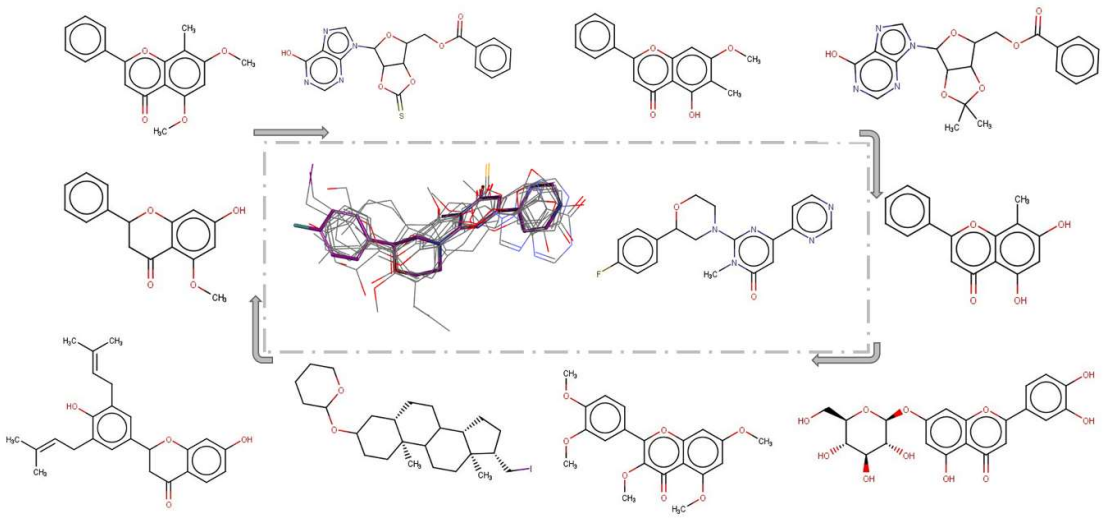

Figure 4. ROCS overly of the top ten Natural products prioritized against SAR502250 ordered by TanimotoCombo (see the gray arrows directions).

Three (TanimotoCombo, ShapeTanimoto, and ComboScore) out of thirteen 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 [18,21,22] were analyzed in detail.

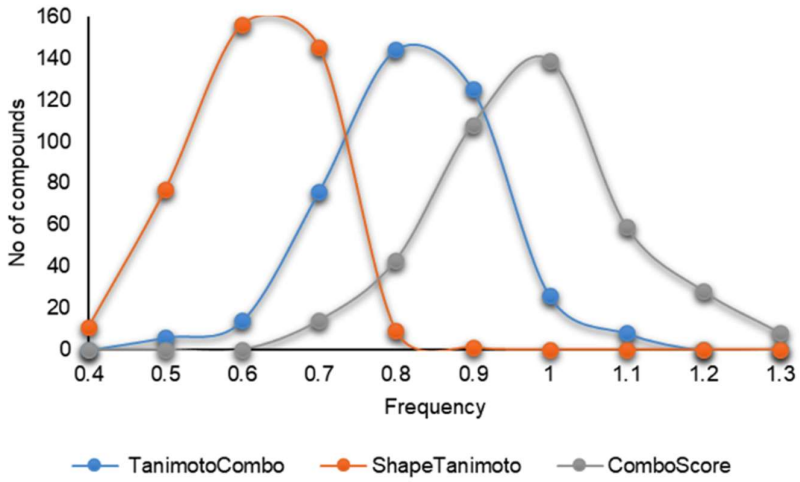

Figure 5. The distribution of 3D similarity coefficients (TanimotoCombo, ShapeTanimoto, ComboScore) values for SPECS NP against SAR502250.

The first ten (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 risks profile of the ten SPECS NP predicted compounds by SwissADME and OSIRIS Property Explorer software *. The 3D similarity coefficients (TanimotoCombo, ShapeTanimoto, ComboScore) are 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 • 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.

The blood-brain barrier (BBB) permeation and passive gastrointestinal absorption (HIA) were predicted at the same time with SwissADME software, for all ten 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 and WLOGP, 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 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, and the fraction of carbons in the sp3 hybridization not less than 0.25.

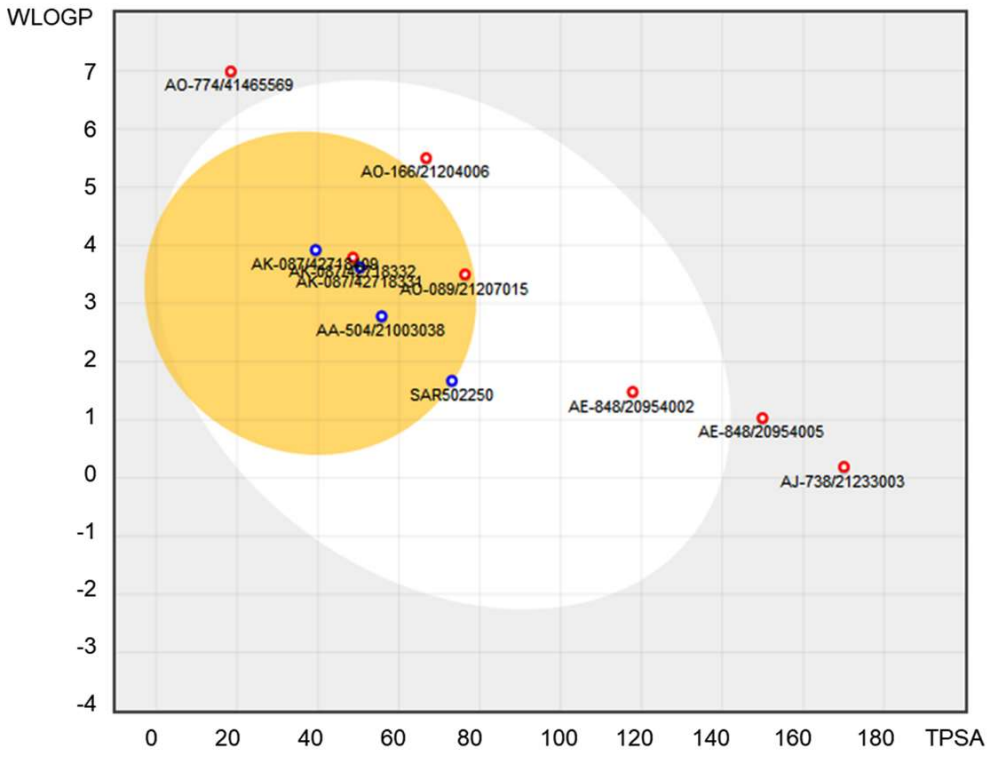

Figure 6. The WLOGP-versus-TPSA referential for predicted SPECS NP.

The molecules plotted in the white ellipse have a high probability of good intestinal absorption, while 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).

Figure 7. The Bioavailability Radar of predicted compounds for SPECS NP and SAR502250.

The ADME and toxicity risk profiles suggest that AK-087/42718409, AK-087/42718331, 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 with drug-like properties.

4. 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.

Author Contributions: L.C. and A.B. have conceived of the presented idea's, performed the computational studies and edited the manuscript; L.P. analyzed some resulted 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 conflict of interest.

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