PHARMACIA

Pharmacia 70(4): 1167–1176
DOI 10.3897/pharmacia.70.e113065

Research Article

De novo design of pimarane diterpenoid compounds as potential alternatives to sarecycline for acne vulgaris treatment

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Received 20 September 2023 ♦ **Accepted** 10 October 2023 ♦ **Published** 19 October 2023

Citation: Kola-Mustapha AT (2023) *De novo* design of pimarane diterpenoid compounds as potential alternatives to sarecycline for acne vulgaris treatment. Pharmacia 70(4): 1167–1176. https://doi.org/10.3897/pharmacia.70.e113065

Abstract

Acne vulgaris is a prevalent skin disorder that affects both adolescents and adults and has a major psychological impact. Antibiotic resistance is one issue that current therapies, including antibiotics, must address. A viable approach is to target *Cutibacterium acnes*, a crucial bacterium in the development of acne. An antibiotic of the tetracycline class called sarecycline shows efficacy despite resistance and adverse effect issues. The purpose of this study is to develop, assess, and compare the efficacy of Sandracopimar (Pimarane diterpenoids) compounds and Sarecycline in the treatment of acne by targeting the 30S ribosomal subunit of *Cutibacterium acnes*. Sarecycline's binding affinity and PheSA score were assessed at the 30S ribosomal subunit binding site of *Cutibacterium acnes*. There were distinct interactions between Sarecycline and the ribosomal subunit, including hydrophobic and hydrogen bonding. Sarecycline demonstrated a strong binding affinity (-8.2 kcal/mol) and a PheSA score of 0.53184 within the *Cutibacterium acnes* 30S ribosomal subunit binding site. Sandaracopimar-15-ene-6.beta.,8.beta.-diol exhibited a binding affinity of -7.3 kcal/mol and PheSA score of 0.37252. Compound 1, a novel compound derived from Sandaracopimar-15-ene-6.beta.,8.beta.-diol, showed a slightly higher binding affinity (-8.3 kcal/mol) than Sarecycline. The molecular dynamics simulation results reveal that Compound 1 exhibited stability during a specific phase, indicating favorable binding potential with the *Cutibacterium acnes* 30S ribosomal subunit drug target. The compound demonstrated structural flexibility, advantageous for molecular interactions. The study indicates that Sandracopimar-derived compounds, including Compound 1, show comparable parameters to Sarecycline, suggesting similar activity in targeting the *Cutibacterium acnes* 30S ribosomal subunit. These compounds may serve as a potential source of novel anti-acne compounds.

Keywords

Cutibacterium acnes, Sandracopimar, Sarecycline, PheSA score, Acne Vulgaris

Introduction

Terpenoids are one of the largest and most structurally varied classes of naturally occurring molecules. They are a group of organic compounds made up of many isoprene (C5) structural units from mevalonic acid (MVA). Terpenoids are abundant in nature and come in a variety of shapes and forms. Mainly obtained from plants, over 50 000 terpenoids have been discovered to date (Li-chao et al. 2017; Yang et al. 2020). Pimarane compounds constitute a class of diterpenoid compounds obtained from plants and fungi but are also present in insects, microorganisms and bacteria. These compounds have been highlighted for their several reported benefits in manag-

ing various conditions (Hawksworth 1984; Reveglia et al. 2018). Most especially, Pimarane diterpenoids are known for their antimicrobial activity against gram-positive and gram-negative bacteria (Pandey et al. 2022).

Cutibacterium acnes is a gram-positive bacterium that commonly causes Acne Vulgaris. Although it is mostly found in the sebum-rich pilosebaceous units, the lipophilic anaerobic bacterium is also found in nonsebaceous regions (Ahle et al. 2023). Acne Vulgaris is a common skin condition prevalent in individuals between the ages of 12 and 24 years and can also persist in ages above this age group. Characterized by the inflammation of the pilosebaceous units, it presents with various skin lesions such as comedones (blackheads and whiteheads), papules, pustules, nodules, and cysts (Asai et al. 2016; Zaenglein et al. 2016).

The *Cutibacterium acnes* 30S ribosomal subunit plays a crucial role in the development of drugs against Acne Vulgaris (Dréno et al. 2018). The 30S ribosomal subunit is an essential component of the bacterial ribosome responsible for protein synthesis. Targeting this specific subunit can disrupt bacterial protein production and ultimately inhibit bacterial growth, including *Cutibacterium acnes* (Wilson, 2014).

By targeting the 30S ribosomal subunit, drugs can specifically inhibit the protein synthesis machinery of *Cutibacterium acnes*. This leads to the suppression of bacterial growth and proliferation, reducing the population of bacteria on the skin (Eady and Cove 2003). *Cutibacterium acnes* is associated with the development of inflammation in Acne Vulgaris and has shown increasing resistance to conventional antibiotics used in acne treatment (Thiboutot et al. 2009). Targeting the 30S ribosomal subunit provides an alternative approach that may overcome antibiotic resistance mechanisms. This is because the ribosomal subunit is an essential and highly conserved component of bacterial cells, making it less prone to developing resistance (Walsh et al. 2016). By specifically targeting the *Cutibacterium acnes* 30S ribosomal subunit, drugs can disrupt bacterial growth, reduce inflammation, prevent antibiotic resistance, and provide a more targeted and effective treatment for Acne Vulgaris (Thiboutot et al. 2006). However, it is important to note that the development of such drugs requires careful research, testing, and consideration of potential side effects and resistance mechanisms.

Sarecycline is a tetracycline-class antibiotic that specifically targets the 30S ribosomal subunit of *Cutibacterium acnes* (Leyden et al. 2018). It exerts a modulatory role in the management of Acne Vulgaris by inhibiting bacterial protein synthesis and exerting anti-inflammatory effects (Moore et al. 2018). Sarecycline binds to the 30S ribosomal subunit of *Cutibacterium acnes* and prevents the attachment of transfer RNA (tRNA) to the ribosome (Swetter et al. 2019). This inhibits the synthesis of bacterial proteins, leading to a disruption in bacterial growth and replication. By targeting the ribosomal subunit, Sarecycline interferes with the essential process of protein production, ultimately reducing the population of *Cutibacterium acnes*. Sarecycline has an extended half-life compared to other tetracycline antibiotics, allowing for once-daily dosing. This prolonged presence in the body enhances its effectiveness against *Cutibacterium acnes*, leading to sustained antimicrobial activity throughout the day (Eichenfield et al. 2013; Zagórska-Dziok and Sobczak 2020).

While Sarecycline has shown potential in the management of Acne Vulgaris, it's important to consider the potential downsides associated with its use. Sarecycline is an antibiotic, and the long-term use of antibiotics in acne treatment can contribute to the development of antibiotic resistance (Bowe and Shalita 2008). Prolonged and widespread use of Sarecycline may lead to the emergence of resistant strains of *Cutibacterium acnes*, making it less effective over time. This can limit treatment options and pose challenges in managing acne in the future (Dréno et al. 2004). While Sarecycline is generally well-tolerated, like other antibiotics, it can have potential side effects. Common adverse effects include gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain. Less frequently, it may cause photosensitivity, dizziness, and headache. Patients may also experience allergic reactions or hypersensitivity to Sarecycline (Leyden et al. 2018). Hence, the need for more potent and safer alternatives in the treatment of Acne Vulgaris.

The aim of this study is to design, evaluate and compare the activity of Sandracopimar (Pimarane diterpenoids) compounds with Sarecycline in targeting *Cutibacterium acnes* 30S ribosomal subunit in the treatment of acne.

Materials and methods

Ligand selection and preparation

Sandaracopimar-15-ene-6.beta.,8.beta.-diol, a Pimarene diterpenoid compound (PUBCHEM ID: 543956) was obtained from the PubChem database and converted to the PDBQT format. The 2D SDF structure of Sarecycline was also obtained, converted to the same format and the optimization algorithm was used to minimize the energy and generate atomic coordinates at mmff94 (required) on PyRx (Suppl. material 1).

Accession and preparation of the target protein

Cutibacterium acnes 30S ribosomal subunit was prepared by retrieving its three-dimension crystal structures (PDB ID: 8CVO) from RCSB PDB (http://www.rcsb.org/pdb/home/home.do). Subsequently, the bound complex molecules within the macromolecule were removed. The non-essential water molecules and all heteroatoms were removed using Pymol tool and Discovery Studio 2017R2 respectively.

Molecular docking

Using PyRx Autodock Vina, the molecular docking between Sandaracopimar-15-ene-6.beta.,8.beta.-diol and sarecycline and the target chosen for the treatment of Acne Vulgaris was investigated. The target molecule was found by carefully examining the resolution and release time on the Protein Data Bank (PDB) (www.rcsb.org)

website. The precise binding sites and atomic separations between the macromolecule and the active chemical were determined using the Discovery Studio application.

De novo synthesis and Pharmacophore Enhanced Shape Alignment (PheSA)

To develop the retrieved hits molecules into better drug candidates with enhanced binding affinities sufficient to elicit the desired therapeutic effects, a set of new compounds from respective hits molecules via a de novo design approach using DataWarrior v5.0.0 were designed.

Conformers of hit molecule were generated while the PheSA algorithm was adopted to screen the compounds generated by De novo synthesis using Datawarrior v5. It first aligns rigid 3D molecules by maximizing their shape and pharmacophore feature overlap. In this regard, PheSA is similar to OpenEye's ROCS technology. The optimized alignment of both molecules is then quantitatively described by the PheSA similarity, a value ranging from 0.0 to 1.0 that is composed of equal contributions of both shape and pharmacophore similarity (Evbuomwan et al. 2023).

Results

Firstly, the binding affinity and pharmacophore enhanced shape alignment score of sarecycline within the binding site of the *Cutibacterium acnes* 30S ribosomal subunit is described. The binding affinity is a measure of the strength of the interaction between the ligand (Sarecycline) and the target molecule (*Cutibacterium acnes* 30S ribosomal subunit). In this case, the binding affinity is -8.2 kcal/mol. A more negative value indicates a stronger binding interaction (Ali et al. 2021).

The pharmacophore enhanced shape alignment score (PheSA score) is a measure of how well the ligand (Sarecycline) fits within the binding site of the target protein (*Cutibacterium acnes* 30S ribosomal subunit) based on its shape and pharmacophoric features (Lomakin et al. 2023). A higher score indicates a better fit and compatibility with the binding site (Evbuomwan et al. 2023). Overall, based on the given results, sarecycline demonstrates a strong binding affinity (-8.2 kcal/mol) (Table 1) within the binding site of the *Cutibacterium acnes* 30S ribosomal subunit. Additionally, it achieves a pharmacophore enhanced shape alignment score of 0.53184 (Table 1), suggesting a good fit and compatibility with the target protein's binding site.

Table 1. Binding potential and PheSA score of Sarecycline within the binding site of the target protein.

Ligand ID	Molecule name	Binding Affinity (kcal/mol)	PheSA Score
54681908	Sarecycline	-8.2	0.53184

These results indicate specific interactions between the nucleotides (G1038, C1039, A1183, G1184) of the *Cutibacterium acnes* 30S ribosomal subunit and sarecycline. The interactions are primarily hydrogen bonds, which involve the formation of weak bonds between the nucleotide and sarecycline. These hydrogen bonds contribute to the stability of the molecular complex. Additionally, there is one hydrophobic interaction between C1039 and sarecycline, where non-polar components of the molecules come into contact (Fig. 1a, b; Table 2).

Sandaracopimar-15-ene-6.beta.,8.beta.-diol (PUBCHEM ID: **543956**) has a binding affinity of -7.3 kcal/mol, although lower than sarecycline (-8.2 kcal/mol).

Sarecycline demonstrates a higher PheSA score (0.53184) compared to Sandaracopimar-15-ene-6. beta.,8. beta. -diol the (0.37252). A higher score suggests a closer structural fit and potentially more favorable ligand-receptor interactions. Therefore, a search for better analogues of Sandaracopimar-15-ene-6. beta.,8. beta. -diol as better alternatives to sarecycline became necessary. Given this, a set of new compounds from Sandaracopimar-15-ene-6. beta.,8. beta. -diol with a *de novo* design approach using DataWarrior v5.0.0 (Trif et al. 2022) were designed. DataWarrior adopted an evolutionary method that mimics nature by randomly transforming known molecular configurations having small changes to establish novel generations with possibly better structures. Each generation of molecules are tested for robustness with a set of modifiable principles and the most auspicious structures serve as a starting point for subsequent generation. The

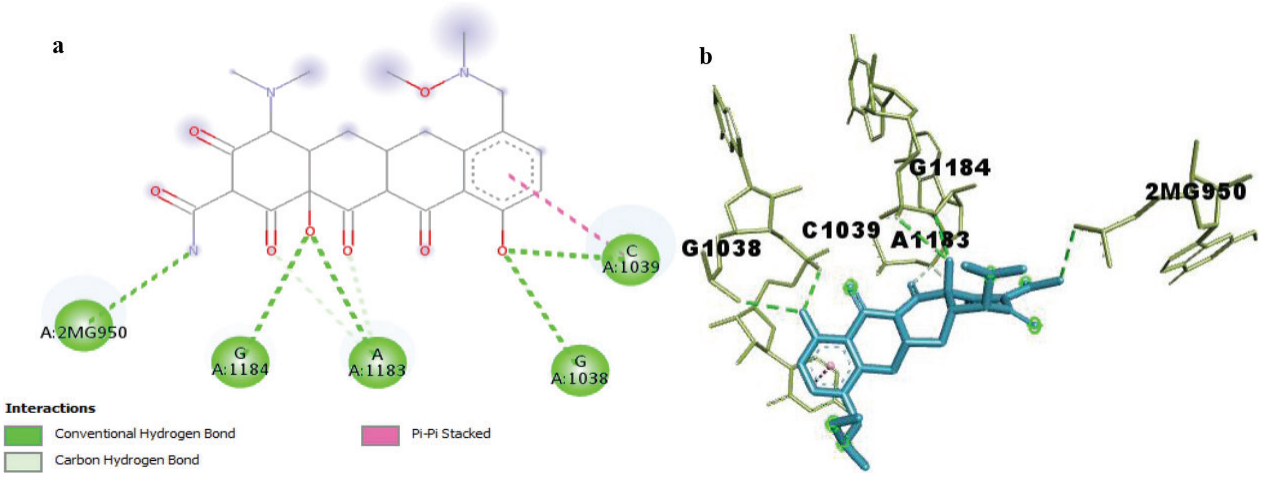

Figure 1. a 2D and **b** 3D Chemical interactions of Sarecycline within the binding site of the target protein.

Table 2. Chemical interactions of Sarecycline within the binding site of the target protein.

Interacting atoms	XYZ:X	XYZ: Y	XYZ: Z	Bond length (Å)	Category
A: V7A1601: OAX – A: G1038:OP1	176.814	234.346	117.634	3.23728	Hydrogen Bond
A: V7A1601: OAX – A: C1039:OP1	179.299	234.505	117.001	2.74369	Hydrogen Bond
A: V7A1601: NBD – A: 2MG950:OP1	187.182	236.235	125.599	2.91659	Hydrogen Bond
A: V7A1601: OBA – A: A1183:O3'	183.996	236.869	120.833	3.25236	Hydrogen Bond
A: V7A1601: OBA – A: G1184:OP1	182.717	236.93	121.044	3.01876	Hydrogen Bond
A: A1183:C5' – A: V7A1601: OAZ	184.315	234.692	118.957	2.88279	Hydrogen Bond
A: A1183:C5' – A: V7A1601: OBB	185.405	234.191	119.745	3.27422	Hydrogen Bond
A:C1039 – A: V7A1601	179.237	230.431	117.382	4.47125	Hydrophobic

mutation algorithm executes vicissitudes such as bond order changes, ring aromatisations, replacing an atom, atom insertions, substituent migrations just to mention a few (Hadi et al. 2020).

Every structure to be mutated is firstly evaluated for all possible mutations concerning how extensively the alteration will increase or decrease the drug-likeness. Mutations with alteration in the required direction are assigned a higher probability than mutations that reduce drug-likeness. Mutations that would create high ring tension are eliminated from the list. Based on this approach, 337 structures were created based on sarecycline's pharmacophores with the corresponding fitness and PheSA scores (Fig. 2).

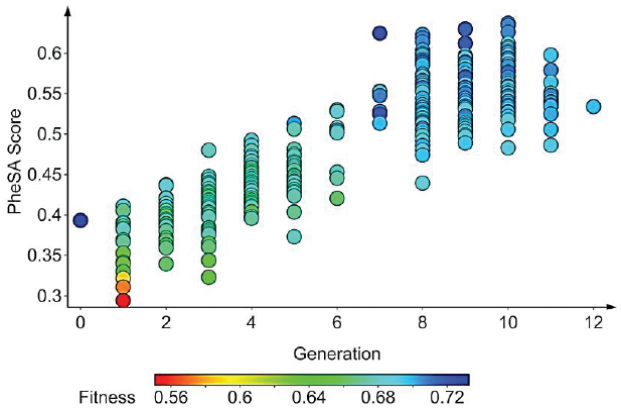

Figure 2. PheSA scores based on sarecycline's pharmacophores.

Ten compounds across different generation holds higher PheSA score, which makes them a closer structural fit and potentially more favorable ligand in its interactions with *Cutibacterium acnes* 30S ribosomal subunit when compared to sarecycline (0.53184) (Fig. 3).

Of these, only compound 1 of the 10th generation has a binding affinity (-8.3 kcal/mol) slightly higher than sarecycline's (-8.2 kcal/mol) (Table 3). This interaction is characterized by 5 hydrogen bonds with one hydrophobic interaction (Fig. 4a, b; Table 4).

Furthermore, the absorption, distribution, metabolism and excretion properties of compound 1 and sarecycline were compared based on their physicochemical properties (Table 5), lipophilicities (Table 6), water solubility (Table 7), pharmacokinetics (Table 8) and druglikeness (Table 9). Overall, the results highlight the distinct physicochemical properties of Sarecycline and Compound 1. These properties can impact the compounds' structural features, flexibility, interaction potentials, and pharmacokinetic profiles, which are crucial considerations in the development of drugs against Acne Vulgaris.

The findings from Fig. 5 provides critical insights into the behavior of Compound 1 during the molecular dynamics' simulation. During the first 100 nanoseconds of the simulation, Compound 1 exhibited RMSD values ranging from 0.0 to 0.8 Å. These values indicate that the compound maintained a relatively stable conformation with minor fluctuations. This stability is a

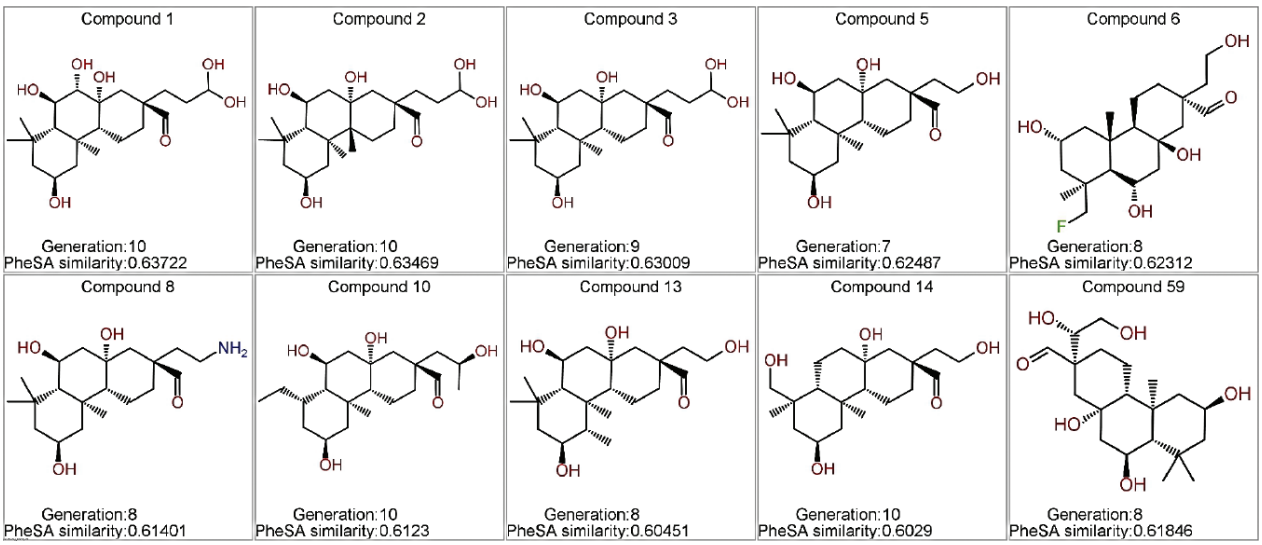

Figure 3. Ten compounds across different generation having higher PheSA score than sarecycline.

Table 3. Binding potential and PheSA score of **S**arecycline within the binding site of the target protein.

Molecule Name	Binding Affinity (kcal/mol)	PheSA Score
Compound 1	-8.3	0.63722
Compound 2	-7.8	0.6347
Compound 3	-8	0.6301
Compound 4	-7.2	0.62611
Compound 5	-8	0.62485
Compound 6	-7.8	0.62323
Compound 7	-7.8	0.61902
Compound 8	-7.3	0.61401
Compound 9	-7.8	0.6123
Compound 10	-7.7	0.61228

crucial factor when evaluating its potential as a drug candidate. Compound 1, a novel compound derived from Sandaracopimar-15-ene-6.beta.,8.beta.-diol, with unique structure and design makes it an intriguing candidate for further investigation, particularly for its potential in targeting the *Cutibacterium acnes* 30S ribosomal subunit as a drug. The statement underscores that Compound 1 is being evaluated as a drug candidate against the *Cutibacterium acnes* 30S ribosomal subunit. This bacterial ribosomal subunit is a vital target for inhibiting bacterial growth, especially in the context of Acne Vulgaris treatment.

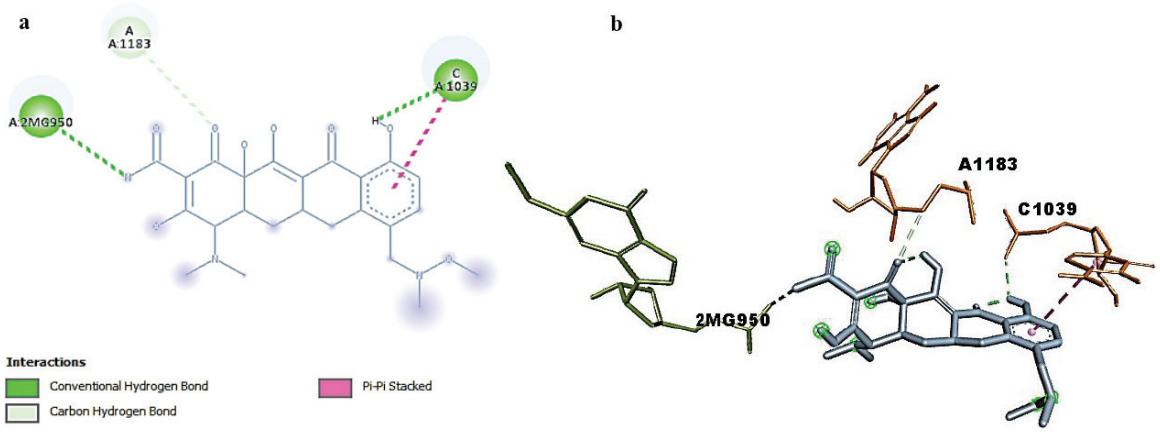

Figure 4. a 2D and **b** 3D Chemical interactions of compound 1 within the binding site of the target protein.

Table 4. Chemical interactions of **compound 1** within the binding site of the target protein.

Interacting atoms	XYZ:X	XYZ: Y	XYZ: Z	Distance	Category
A: V7A1601: NBD – A: 2MG950:OP1	187.182	236.235	125.599	2.91659	Hydrogen Bond
A: V7A1601: HAX – A: C1039:OP1	179.567	234.884	117.1	2.17528	Hydrogen Bond
A: V7A1601: HAX – A: V7A1601: OAY	179.353	234.765	118.621	1.83851	Hydrogen Bond
A: V7A1601: HAZ – A: V7A1601: OBB	184.59	234.25	120.445	2.49516	Hydrogen Bond
A: A1183:C5' – A: V7A1601: OBB	185.405	234.191	119.745	3.27422	Hydrogen Bond
A:C1039 – A: V7A1601	179.237	230.431	117.382	4.47125	Hydrophobic

Table 5. Evaluation of physicochemical properties of compound 1.

Physicochemical properties	Sarecycline	Compound 1
Formula	C24H29N3O8	C21H36O7
MW	487.5	400.51
Heavy atoms	35	28
Aromatic heavy atoms	6	0
Fraction Csp3	0.46	0.95
Rotatable bonds	5	4
H-bond acceptors	10	7
H-bond donors	5	6
MR	123.5	103.15
TPSA	173.86	138.45

Table 6. Evaluation of lipophilicity of compound 1.

Lipophilicity	Sarecycline	Compound 1
iLOGP	1.79	1.73
XLOGP3	1.06	-0.16
WLOGP	-0.19	0.33
MLOGP	-1.61	0.39
Silicos-IT Log P	-0.54	1.07
Consensus Log P	0.1	0.67

Table 7. Evaluation of water solubility of compound 1.

Water solubility	Sarecycline	Compound 1
ESOL Log S	-3.33	-1.96
ESOL Solubility (mg/mL)	2.30E-01	4.41E+00
ESOL Solubility (mol/L)	4.71E-04	1.10E-02
ESOL Class	Soluble	Very soluble
Ali Log S	-4.3	-2.29
Ali Solubility (mg/mL)	2.43E-02	2.04E+00
Ali Solubility (mol/L)	4.99E-05	5.10E-03
Ali Class	Moderately soluble	Soluble
Silicos-IT LogSw	-2.23	-1.01
Silicos-IT Solubility (mg/mL)	2.85E+00	3.93E+01
Silicos-IT Solubility (mol/L)	5.85E-03	9.82E-02
Silicos-IT class	Soluble	Soluble

Discussion

In the context of discovering drugs against Acne Vulgaris, the physicochemical properties of Sarecycline and Compound 1 are important factors to consider. Molecular

Table 8. Evaluation of pharmacokinetics of compound 1.

Pharmacokinetics	Sarecycline	Compound 1
GI absorption	Low	High
BBB permeant	No	No
Pgp substrate	Yes	Yes
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
log Kp (cm/s)	-8.52	-8.86

Table 9. Evaluation of druglikeness of compound 1.

Druglikeness	Sarecycline	Compound 1
Lipinski violations	1	1
Ghose violations	1	0
Veber violations	1	0
Egan violations	1	1
Muegge violations	1	1
Bioavailability score	0.11	0.55

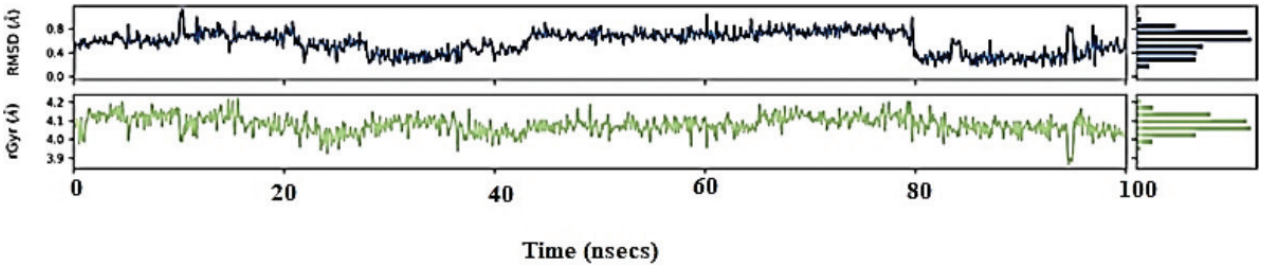

Figure 5. Behavior of Compound 1 in Molecular Dynamics Simulation. The plot shows RMSD (Root Mean Square Deviation) and rGyr (Radius of Gyration) against 100 ns window. These metrics provide insights into the stability and structural changes of Compound 1 during the simulation, making it a valuable tool for understanding its behavior in the context of potential drug development.

weight represents the sum of the atomic weights of all atoms in a molecule (Karthikeyan et al. 2017). In this case, Sarecycline has a higher molecular weight than Compound 1. A higher molecular weight can sometimes indicate larger and more complex molecules. However, it's important to note that molecular weight alone does not provide information about a compound's effectiveness or potency for acne treatment. Aromatic heavy atoms represent non-hydrogen atoms in aromatic rings. Sarecycline contains six aromatic heavy atoms, while Compound 1 does not have any. Aromatic rings are common features in many drugs and can contribute to their pharmacological properties (Stumpfe and Bajorath 2011). The presence of aromatic heavy atoms in Sarecycline suggests it may possess aromatic ring systems, potentially influencing its biological activity. The Fraction Csp3 measures the proportion of sp3-hybridized carbon atoms in a molecule (Osguthorpe et al. 2012). A higher Fraction Csp3 indicates a higher proportion of saturated carbon atoms (sp3 hybridized) in the compound's structure (Sheth and Sheth 2000). Compound 1 has a higher Fraction Csp3, suggesting it contains more saturated carbon atoms compared to Sarecycline. The level of saturation can affect the compound's lipophilicity, solubility, and other physicochemical properties, potentially influencing its pharmacokinetic profile (Nantasenamat et al. 2009). Rotatable bonds represent single bonds that can rotate freely. The number of rotatable bonds indicates the flexibility of a molecule. Sarecycline has one more rotatable bond than Compound 1 in this instance. A molecule's interaction with biological targets, such as the enzymes or receptors involved in Acne Vulgaris, may be affected by its degree of flexibility. Atoms that can receive hydrogen bonds are known as H-bond acceptors (Liu et al. 2017). These connections may be extremely important to how a medicine interacts with its target. Sarecycline has more H-bond acceptors than Compound 1, which may indicate that it has a higher propensity for establishing hydrogen bonds, which may alter its affinity for binding to the target proteins used in the treatment of acne.

The absorption, distribution, and effectiveness of a chemical are significantly influenced by its lipophilicity (Lipinski 2004). The term "lipophilicity" describes a substance's capacity to dissolve in lipids or other compounds that resemble fat. A measurement of a compound's lipophilicity based on its molecular structure is called iLOGP (intrinsic log P) (Ghose and Crippen 1987). Positive iLOGP readings for both Sarecycline and Compound 1 show some lipophilicity. Sarecycline, however, exhibits a somewhat higher iLOGP value than Compound 1, indicating that it could be marginally more lipophilic. Another indicator of lipophilicity that considers a compound's molecular makeup and three-dimensional features is called XLOGP3 (Ghose and Crippen 1987). Sarecycline has a positive XLOGP3 value, indicating some lipophilicity. In contrast, Compound 1 has a negative XLOGP3 value, suggesting it is less lipophilic and may be more hydrophilic or polar in nature. WLOGP (water/octanol log P) represents the partition coefficient between water and octanol, which is commonly used as a measure of lipophilicity (Ghose et al. 1999). In this case, Sarecycline has a negative WLOGP value, indicating it is more hydrophilic or water-soluble. Compound 1, on the other hand, has a positive WLOGP value, suggesting it is more lipophilic or soluble in organic solvents. MLOGP (modified log P) is a calculation method that estimates the log P value based on the molecular structure of a compound (Sanderson and Earnshaw 1991). Sarecycline has a negative MLOGP value, indicating higher hydrophilicity, while

Compound 1 has a positive MLOGP value, suggesting it is more lipophilic. Silicos-IT Log P is a prediction of the logarithm of the partition coefficient between octanol and water (Tetko et al. 2001). Sarecycline has a negative Silicos-IT Log P value, suggesting it has more affinity for water than octanol, indicating higher hydrophilicity. Compound 1, with a positive Silicos-IT Log P value, exhibits more affinity for octanol, indicating higher lipophilicity. Consensus Log P is an average of multiple log P prediction methods, providing a consensus value for the compound's lipophilicity (Veber et al. 2002). Both Sarecycline and Compound 1 have positive Consensus Log P values, indicating some degree of lipophilicity. Overall, the lipophilicity results suggest that both Sarecycline and Compound 1 exhibit some degree of lipophilicity, but Compound 1 may have a relatively higher lipophilicity.

Water solubility of a compound is an important factor as it affects its absorption, distribution, and bioavailability. ESOL Log S is a logarithmic measure of water solubility, with negative values indicating poor solubility (Ertl et al. 2000). Both Sarecycline and Compound 1 have negative ESOL Log S values, suggesting low water solubility. Sarecycline has a more negative value, indicating relatively lower water solubility compared to Compound 1. Sarecycline has lower solubility values, indicating poor water solubility. In comparison, Compound 1 has higher solubility values, indicating relatively better water solubility. Sarecycline is classified as soluble, indicating it has some level of solubility in water. Compound 1 is classified as very soluble, suggesting it has a higher level of solubility in water compared to Sarecycline. Ali Log S is another logarithmic measure of water solubility, with negative values indicating poor solubility (Kelder et al. 1999). Both Sarecycline and Compound 1 have negative Ali Log S values, suggesting low water solubility. Sarecycline has a more negative value, indicating relatively lower water solubility compared to Compound 1. Sarecycline has lower solubility values, indicating poor water solubility. Compound 1 has higher solubility values, indicating relatively better water solubility.

In the context of drug discovery against Acne Vulgaris, understanding the pharmacokinetic properties of a compound is crucial to assess its absorption, distribution, metabolism, and excretion. GI absorption refers to the ability of a compound to be absorbed through the gastrointestinal tract (Kerns and Di 2004). Sarecycline is characterized as having low GI absorption, indicating that it may have limited absorption from the gastrointestinal tract into systemic circulation. In contrast, Compound 1 is described as having high GI absorption, suggesting it has a higher potential for absorption from the gastrointestinal tract. Blood-Brain Barrier permeant refers to the ability of a compound to cross the blood-brain barrier (BBB) (Van de Waterbeemd et al. 1998). Both Sarecycline and Compound 1 are not considered BBB permeant, indicating that their capacity to permeate the BBB is somewhat limited. This may be useful in lowering the possibility of adverse consequences involving the central nervous system. A transporter protein called Pgp (P-glycoprotein) is involved in the efflux of substances from cells (Nigam 2015). Compound 1 and Sarecycline are both known as Pgp substrates, proving that P-glycoprotein is responsible for their transport. Their distribution and absorption in different tissues may be affected by this. In general, the pharmacokinetic findings shed light on the distribution, absorption, and possible interactions of compound 1 with sarecycline. These characteristics are crucial factors to take into account when developing new drugs since they might affect the compounds' tissue distribution, bioavailability, and potential for drug-drug interactions.

Assessing the druglikeness of a compound is crucial to determine its potential as a viable drug candidate (Wetzel et al. 2011). Lipinski's Rule of Five is a set of guidelines used to assess the druglikeness of a compound based on its physicochemical properties (Lipinski 2004). It defines four criteria related to molecular weight, lipophilicity (log P), hydrogen bond donors, and hydrogen bond acceptors (Ghose and Crippen 1987). A compound is considered to have a Lipinski violation if it fails to meet any of these criteria (Ghose et al. 1999). Both Sarecycline and Compound 1 have one Lipinski violation, suggesting they may have properties that deviate from the optimal range defined by Lipinski's Rule of Five. Alternatively, Ghose's Rule is another set of guidelines that assess the druglikeness of a compound based on its physicochemical properties (Veber et al. 2002). Sarecycline has one Ghose violation, indicating a deviation from the optimal range defined by Ghose's Rule. However, Compound 1 does not have any Ghose violations, suggesting it falls within the favorable range defined by Ghose's Rule. Also, Veber's Rule evaluates the druglikeness of a compound based on its rotatable bonds and polar surface area (PSA) (Veber et al. 2002). Compounds that meet the criteria defined by Veber's Rule are considered more likely to have good oral bioavailability (Barrero et al. 2021). Sarecycline has one Veber violation, indicating it deviates from the optimal range defined by Veber's Rule. In contrast, Compound 1 does not have any Veber violations, suggesting it falls within the favorable range. In this case, Compound 1 has a higher Bioavailability Score compared to Sarecycline, suggesting that Compound 1 may have relatively better bioavailability.

As mentioned earlier, compound 1 maintained a relatively stable conformation with minor fluctuations. The statement highlights a critical phase in the simulation where Compound 1 became stable, with an RMSD of 0.65 Å observed between 85 to 100 nanoseconds. This stability indicates that the compound's conformation remained consistent and underwent minimal structural changes during this phase. The observed stability phase suggests that Compound 1 may have established favorable interactions with the *Cutibacterium acnes* 30S ribosomal subunit drug target. A stable conformation often corresponds to an energetically favorable binding mode, which is encouraging for its role as a drug candidate (Jakhmola et al. 2021).

The measured rGyr values over 100 ns, which gradually climbed to 3.9, 4.0, 4.1, and 4.2, indicate that Compound 1 showed structural flexibility. This adaptability is helpful because it enables the chemical to modify its conformation to interact with the target in a useful way (Lee et al. 2019). Successful drug binding requires the capacity to investigate many structural conformations (Bera and Payghan 2019).

A thorough analysis of Compound 1's behavior is provided by the combination of RMSD and rGyr data. rGyr values provide information on changes in the compound's overall size and shape, whereas RMSD reveals stability and fluctuations in its conformation. These measurements provide a complete description of the structural dynamics of Compound 1.

Conclusion

The results of this study show that Sandracopimar compounds and derivatives possess comparable activity and physicochemical parameters with Sarecycline in the management of acne and may thus serve as a potential source of novel anti-acne therapies.

References

Ahle CM, Feidenhansl C, Brüggemann H (2023) *Cutibacterium acnes*. Trends in Microbiology 31(4): 419–420. https://doi.org/10.1016/j.tim.2022.10.006

Ali F, Kasry A, Amin M (2021) The new SARS-CoV-2 strain shows a stronger binding affinity to ACE2 due to N501Y mutant. Medicine in Drug Discovery 10: e100086. https://doi.org/10.1016/j.medidd.2021.100086

Asai Y, Baibergenova A, Dutil M, Humphrey S, Hull P, Lynde C, Poulin Y, Shear NH, Tan J, Toole J, Zip C (2016) Management of Acne: Canadian clinical practice guideline. CMAJ: Canadian Medical Association Journal 188(2): 118–126. https://doi.org/10.1503/cmaj.140665

Barrero JA, Cabrera F, Marcela Cruz C (2021) Gliptins vs. Milk-derived Dipeptidyl-Peptidase IV Inhibiting Biopeptides: Physicochemical Characterization and Pharmacokinetic Profiling. Vitae 28(3): 1–14. https://doi.org/10.17533/udea.vitae.v28n3a346531

Bera I, Payghan PV (2019) Use of molecular dynamics simulations in structure-based drug discovery. Current Pharmaceutical Design 25(31): 3339–3349. https://doi.org/10.2174/1381612825666190903153043

Bowe WP, Shalita AR (2008) Effective over-the-counter acne treatments. Seminars in Cutaneous Medicine and Surgery 27(4): 170–176. https://doi.org/10.1016/j.sder.2008.07.001

Dréno B, Bettoli V, Ochsendorf F, Layton A, Mobacken H, Degreef H, European Expert Group on Oral Antibiotics in Acne (2004) European recommendations on the use of oral antibiotics for acne. European Journal of Dermatology 14(6): 391–399.

Dréno B, Pécastaings S, Corvec S, Veraldi S, Khammari A, Roques C (2018) *Cutibacterium acnes* (*Propionibacterium acnes*) and Acne Vulgaris: A brief look at the latest updates. Journal of the European Academy of Dermatology and Venereology 32(Suppl 2): 5–14. https://doi.org/10.1111/jdv.15043

Eady EA, Cove JH (2003) Staphylococcal resistance revisited: Community-acquired methicillin resistant *Staphylococcus aureus* – an emerging problem for the management of skin and soft tissue infections. Current Opinion in Infectious Diseases 16(2): 103–124. https://doi.org/10.1097/00001432-200304000-00004

Eichenfield LF, Krakowski AC, Piggott C, Del Rosso J, Baldwin H, Friedlander SF, Levy ML, Lucky AW, Mancini AJ, Orlow SJ, Yan AC, Vaux KK, Webster G (2013) Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 131(Suppl 3): S163–S186. https://doi.org/10.1542/peds.2013-0490B

Ertl P, Rohde B, Selzer P (2000) Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. Journal of Medicinal Chemistry 43(20): 3714–3717. https://doi.org/10.1021/jm000942e

Evbuomwan IO, Alejolowo OO, Elebiyo TC, Nwonuma CO, Ojo OA, Edosomwan EU, Oluba OM (2023) *In silico* modeling revealed phytomolecules derived from *Cymbopogon citratus* (DC.) leaf extract as promising candidates for malaria therapy. Journal of Biomolecular Structure & Dynamics, 18 pp. https://doi.org/10.1080/07391102.2023.2192799

Ghose AK, Crippen GM (1987) Atomic physicochemical parameters for three-dimensional-structure-directed quantitative structure-activity relationships. 2. Modeling dispersive and hydrophobic interactions. Journal of Chemical Information and Computer Sciences 27(2): 21–35. https://doi.org/10.1021/ci00054a007

Ghose AK, Viswanadhan VN, Wendoloski JJ (1999) A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. Journal of Combinatorial Chemistry 1(1): 55–68. https://doi.org/10.1021/cc9900071

Hadi S, Noviany N, Suhartati T, Hadi S, Noviany N, Suhartati T (2020) The Potential Application of Organotin (IV) Carboxylate Compounds in Medicinal Chemistry. Virtual Conference on Chemistry and its Applications in Mauritius, 39–39. http://repository.lppm.unila.ac.id/25017/

Hawksworth DL (1984) Fungal Metabolites II. By W. B. Turner and D. C. Aldridge. London: Academic Press. Lichenologist 16(1): 99–101. https://doi.org/10.1017/S0024282984000219

Jakhmola S, Jonniya NA, Sk MF, Rani A, Kar P, Jha HC (2021) Identification of potential inhibitors against Epstein–Barr virus nuclear antigen 1 (EBNA1): An insight from docking and molecular dynamic simulations. ACS Chemical Neuroscience 12(16): 3060–3072. https://doi.org/10.1021/acschemneuro.1c00350

Karthikeyan M, Vyas R, Sweekar S, Shashirekha V (2017) Molecular weight. In Quantitative Structure-Activity Relationships in Drug Design, Predictive Toxicology, and Risk Assessment. Springer, Singapore, 7 pp.

Kelder J, Grootenhuis PD, Bayada DM, Delbressine LP, Ploemen JP (1999) Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs.

Pharmaceutical Research 16(9): 1514–1519. https://doi.org/10.1023/A:1018945105817

Kerns EH, Di L (2004) Physicochemical profiling: Overview of the screens. Drug Discovery Today: Technologies 1(4): 343–348. https://doi.org/10.1016/j.ddtec.2004.08.011

Lee ACL, Harris JL, Khanna KK, Hong JH (2019) A Comprehensive Review on Current Advances in Peptide Drug Development and Design. International Journal of Molecular Sciences 20(10): e2383. https://doi.org/10.3390/ijms20102383

Leyden JJ, Sniukiene V, Berk DR, Kaoukhov A (2018) Efficacy and safety of sarecycline, a novel, once-daily, narrow spectrum antibiotic for the treatment of moderate to severe facial acne vulgaris: Results of a phase 2, dose-ranging study. Journal of Drugs in Dermatology 17(3): 333–338. https://pubmed.ncbi.nlm.nih.gov/29537451/

Li-chao S, Shu-ying L, Feng-zhong W, Feng-jiao X (2017) Research progresses in the synthetic biology of terpenoids. Biotechnology Bulletin 33(1): e64. http://biotech.aiijournal.com/EN/Y2017/V33/I1/64

Lipinski CA (2004) Lead- and drug-like compounds: The rule-of-five revolution. Drug Discovery Today: Technologies 1(4): 337–341. https://doi.org/10.1016/j.ddtec.2004.11.007

Lomakin IB, Devarkar SC, Patel S, Grada A, Bunick CG (2023) Sarecycline inhibits protein translation in *Cutibacterium acnes* 70S ribosome using a two-site mechanism. Nucleic Acids Research 51(6): 2915–2930. https://doi.org/10.1093/nar/gkad103

Moore A, Green LJ, Bruce S, Sadick NS, Tschen E, Werschler P, Cook-Bolden FE, Dhawan SS, Forsha D, Gold MH, Guenthner S, Kempers SE, Kircik LH, Parish JL, Rendon MI, Rich P, Stein-Gold L, Tyring SK, Weiss RA, Nasir A, Schmitz C, Boodhoo TI, Kaoukhov A, Berk DR (2018) Once-daily oral sarecycline 1.5 mg/kg/day is effective for moderate to severe Acne Vulgaris: Results from two identically designed, phase 3, randomized, double-blind clinical trials. Journal of Drugs in Dermatology 17(9): 987–996. https://jddonline.com/articles/once-daily-oral-sarecycline-15-mgkgday-is-effective-for-moderate-to-severe-acne-vulgaris-results-fro-S1545961618P0987X

Nantasenamat C, Isarankura-Na-Ayudhya C, Naenna T, Prachayasittikul V (2009) A practical overview of quantitative structure-activity relationship. EXCLI Journal 8: 74–88. https://www.scirp.org/(S(351jmbntvnsjt1aadkozje))/reference/referencespapers.aspx?referenceid=223034

Nigam SK (2015) What do drug transporters really do? Nature Reviews. Drug Discovery 14(1): 29–44. https://doi.org/10.1038/nrd4461

Osguthorpe DJ, Sherman W, Hagler AT (2012) Exploring protein flexibility: Incorporating structural ensembles from crystal structures and simulation into virtual screening protocols. The Journal of Physical Chemistry B 116(15): 4416–4424. https://doi.org/10.1021/jp3003992

Pandey J, Hwang BY, Lee H-K, Poudel A (2022) Pimarane diterpenoids from aerial parts of *Lycopus lucidus* and their antimicrobial activity. Evidence-Based Complementary and Alternative Medicine 2022: e5178880. https://doi.org/10.1155/2022/5178880

Proschak E, Heitel P, Kalinowsky L, Merk D (2017) Opportunities and challenges for fatty acid mimetics in drug discovery. Journal of Medicinal Chemistry 60(13): 5235–5266. https://doi.org/10.1021/acs.jmedchem.6b01287

Reveglia P, Cimmino A, Masi M, Nocera P, Berova N, Ellestad G, Evidente A (2018) Pimarane diterpenes: Natural source, stereochemical configuration, and biological activity. Chirality 30(10): 1115–1134. https://doi.org/10.1002/chir.23009

Sanderson DM, Earnshaw CG (1991) Computer prediction of possible toxic action from chemical structure; the DEREK system. Human and Experimental Toxicology 10(5): 261–273. https://doi.org/10.1177/096032719101000405

Sheth M, Sheth S (2000) Fraction Csp3. Molecular Descriptors in QSAR/QSPR. Wiley-VCH Verlag GmbH and Co. KGaA, 25–43.

Stumpfe D, Bajorath J (2011) Aromatic heavy atoms. In: Chemoinformatics and Advanced Machine Learning Perspectives: Complex Computational Methods and Collaborative Techniques. IGI Global, 83–94.

Swetter SM, Tsao H, Bichakjian CK, Curiel-Lewandrowski C, Elder DE, Gershenwald JE, Guild V, Grant-Kels JM, Halpern AC, Johnson TM, Sober AJ, Thompson JA, Wisco OJ, Wyatt S, Hu S, Lamina T (2019) Guidelines of care for the management of primary cutaneous melanoma. Journal of the American Academy of Dermatology 80(1): 208–250. https://doi.org/10.1016/j.jaad.2018.08.055

Tetko IV, Tanchuk VY, Kasheva TN, Villa AE (2001) Estimation of aqueous solubility of chemical compounds using E-State indices. Journal of Chemical Information and Computer Sciences 41(5): 1488–1493. https://doi.org/10.1021/ci000392t

Thiboutot DM, Shalita AR, Yamauchi PS, Dawson C, Kerrouche N, Arsonnaud S (2006) Adapalene gel, 0.1%, as maintenance therapy for Acne Vulgaris: A randomized, controlled, investigator-blind follow-up of a recent combination study. Archives of Dermatology 142(7): 866–871. https://doi.org/10.1001/archderm.142.5.597

Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, Leyden JJ, Shalita AR, Lozada VT, Berson D, Finlay A, Goh CL, Herane MI, Kaminsky A, Kubba R, Layton A, Miyachi Y, Perez M, Martin JP, Ramos-E-Silva M, See JA, Shear N, Wolf Jr J, Global Alliance to Improve Outcomes in Acne (2009) New insights into the management of acne: An update from the Global alliance to improve outcomes in acne group. Journal of the American Academy of Dermatology 60(5, Suppl): S1–S50. https://doi.org/10.1016/j.jaad.2009.01.019

Trif C, Mihai DP, Zanfirescu A, Nitulescu GM (2022) Structural model based on genetic algorithm for inhibiting fatty acid amide hydrolase. Artificial Intelligence 3(4): 863–870. https://doi.org/10.3390/ai3040052

Van de Waterbeemd H, Camenisch G, Folkers G, Chretien JR, Raevsky OA (1998) Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. Journal of Drug Targeting 6(2): 151–165. https://doi.org/10.3109/10611869808997854

Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD (2002) Molecular properties that influence the oral bioavailability of drug candidates. Journal of Medicinal Chemistry 45(12): 2615–2623. https://doi.org/10.1021/jm020017n

Walsh TR, Efthimiou J, Dréno B (2016) Systematic review of antibiotic resistance in acne: An increasing topical and oral threat. The Lancet. Infectious Diseases 16(12): e23–e33. https://doi.org/10.1016/S1473-3099(16)30215-4

Wetzel S, Bon RS, Kumar K, Waldmann H (2011) Biology-oriented synthesis. Angewandte Chemie International Edition 50(46): 10800–10826. https://doi.org/10.1002/anie.201007004

Wilson DN (2014) Ribosome-targeting antibiotics and mechanisms of bacterial resistance. Nature Reviews. Microbiology 12(1): 35–48. https://doi.org/10.1038/nrmicro3155

Yang W, Chen X, Li Y, Guo S, Wang Z, Yu X (2020) Advances in pharmacological activities of terpenoids. Natural Product Communications 15(3): 1–13. https://doi.org/10.1177/1934578X20903555

Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, Bowe WP, Whitney P, Graber EM, Harper JC, Kang S, Keri JE, Jonette E, Leyden JJ, Reynolds RV, Silverberg NB, Gold LFS, Tollefson MM, Weiss JS, Dolan NC, Sagan AA, Stern M, Boyer KM, Bhushan, R (2016) Guidelines of care for the management of acne vulgaris. Journal of the American Academy of Dermatology 74(5): 945–973. [e33] https://doi.org/10.1016/j.jaad.2015.12.037

Zagórska-Dziok M, Sobczak M (2020) Hydrogel-based active substance release systems for cosmetology and dermatology application: A review. Pharmaceutics 12(5): e396. https://doi.org/10.3390/pharmaceutics12050396

Supplementary material 1

Grid box within which Sandaracopimar-15-ene-6.beta., 8.beta.-diol binds is 192.5686 × 260.3472 × 119.6532 along the X, Y, Z-axis

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Data type: jpg

Link: https://doi.org/10.3897/pharmacia.70.e113065.suppl1