

ADME potential of porphyrin derivative from petroleum

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Abstract. Chlorins are tetrapyrrole pigments that are formally described as partially hydrogenated porphyrins, specifically dihydroporphyrins. This structural difference gives them distinct chemical and photophysical properties that are essential for their biological functions and applications. Chlorins are excellent photosensitizing agents. The most well-known examples of naturally occurring chlorins are the chlorophylls, which are magnesium-containing chlorin derivatives found in plants and bacteria. The structural alteration (partial hydrogenation) of the macrocycle is crucial for photosynthesis. Microbes produce two major reduced variants of the chlorin macrocycle, both of which contain two reduced pyrrole rings (tetrahydroporphyrins) and are crucial for various metabolic and photosynthetic processes: bacteriochlorins and isobacteriochlorins. The present study aims to use an *in silico* approach to predict the biological effects of a specific chlorin derivative.

1 Introduction

The discovery of porphyrins in petroleum was indeed a pivotal achievement that provided irrefutable evidence for the biological origin of crude oil, a theory first proposed in the mid-1930s. Porphyrins are complex organic molecules derived from chlorophyll (plant photosynthesis pigment) and heme (animal blood pigment). Their presence in crude oil confirmed that petroleum is not formed from inorganic deep-earth processes but rather from the thermal maturation of once-living organisms (algae, plants, and bacteria) buried in ancient sediments over millions of years [1].

Porphyrin derivatives found in petroleum are formally known as geoporphyrins or petroporphyrins. These naturally occurring compounds are critical to the petroleum industry, acting as robust biomarkers that provide a molecular fossil record of the biological origins and geological history of crude oil. A defining characteristic is their chelation with trace metals. The two most common forms are vanadyl porphyrins and nickel porphyrins. These metal-chelated structures are highly stable under geological conditions [1].

Scientists analyze these ancient molecules from the remains of extinct organisms to understand the principles of evolution. By examining variations in the porphyrin structures

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(such as side-chain alterations or the type of chelated metal) across different geological eras, researchers can infer: the types of organisms that dominated specific ancient ecosystems (e.g., algae vs. bacteria), the evolution of core metabolic functions, like photosynthesis and major shifts in past environmental conditions, such as oceanic oxygen levels, which drove evolutionary changes [1].

Porphyryns (1) are a class of intensely colored, highly stable, and biologically essential organic compounds defined by their unique molecular architecture: conjugated tetrapyrrole macrocycles linked together by methine (=CH-) bridges (Figure 1) [2]. In the standard nomenclature and depiction of the porphyrin macrocycle (porphin), the four individual pyrrole rings are assigned letters: Ring A, Ring B, Ring C, and Ring D, typically in a clockwise or counter-clockwise sequence around the structure [1]. A variety of side chains can be attached to the perimeter of the porphyrin macrocycle to form the countless porphyrin derivatives found in nature and synthesized in the lab. The most common and biologically significant side chains include: methyl, ethyl, vinyl, acetic acid, and propionic acid. The carbon atoms that form the bridges connecting the four pyrrole rings (A, B, C, and D) in the porphyrin macrocycle are known as meso-positions. They are alternatively designated as the α -, β -, δ -, and γ -positions. Isomers are traditionally identified by adding a Roman numeral at the end of the name to specify the exact arrangement of the peripheral substituents. Porphyrins possess a central cavity defined by the four inner nitrogen atoms of the pyrrole rings. This cavity acts as a highly efficient tetradentate ligand, enabling it to readily form stable complexes with a wide variety of metal cations to yield metalloporphyrins. Porphyrins can complex with numerous metal ions, with some of the most significant being: iron(II/III), magnesium(II), copper(II), and zinc(II). Numerous compounds structurally related to porphyrins exist in nature and are characterized by variations in saturation levels or the addition of extra rings fused to the core macrocycle. These derivatives possess distinct chemical and photophysical properties that are essential for their biological functions and applications. Key examples of these related structures include: chlorin (2), phorbin (3), bacteriochlorin (4), and their derivatives (Figure 1). Those are the precise structural definitions for chlorin and phorbin derivatives: chlorin (2) is 17,18-dihydroporphin [1], and phorbin (3) is a chlorin derivative containing an extra isocyclic ring between ring C and D. Bacteriochlorin (4) represents a 7,8,17,18-tetrahydroporphin derivative. If a methine bridge connecting ring A and ring D of the porphyrin macrocycle is enzymatically or chemically cleaved, the macrocyclic structure opens up, forming open-chain tetrapyrroles known as bilanes (bilanes, 5, Figure 1). The three remaining methine bridges that now link the four linear rings are designated using lowercase Greek letters to identify their specific location: a, b, and c. This classification describes their oxidation state and electronic properties: bilenes, biladienes or bilatrienes, respectively [3].

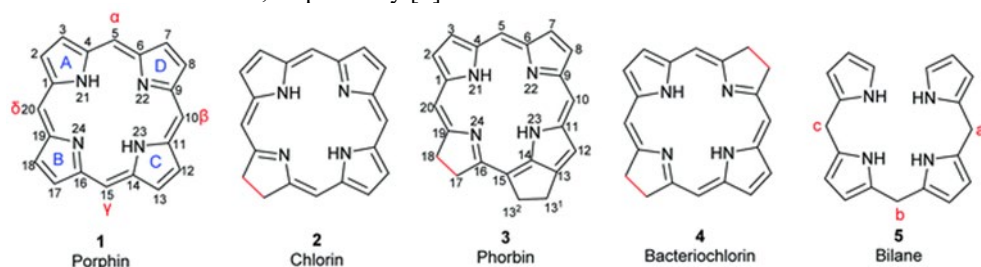


Fig. 1. The basic structures of the main tetrapyrrole macrocycles [9].

Porphyryns are indeed highly aromatic and possess a square planar geometry. The system contains 22 π -electrons in total. However, only 18 π -electrons participate in the main cyclic delocalization pathway required to satisfy Hückel's rule ($4n+2$, where $n=4$). In the free-base

form (with two inner N-H protons), the two lone pairs of the bound nitrogen atoms are oriented out of the plane and are sterically hindered from participating in the *main* aromatic circuit, effectively maintaining the 18- π electron delocalized system that confers aromatic stability. The extensive system of conjugated double bonds means porphyrins strongly absorb light at defined wavelengths, making them intensely colorful pigments [3].

The present study aims to use an *in silico* approach to predict the biological effects of a specific chlorin derivative.

2 Materials and methods

2.1 Compound data

The description is accurate: a chlorin (specifically, 7,8-Dihydro-21H,23H-porphine) is a dihydroporphyrin macrocycle that structurally contains three aromatic pyrrole rings and one partially saturated pyrroline ring (Figure 2). This structural feature is what differentiates chlorins from porphyrins, where all four rings are pyrroles. Chlorins are known for their role as photosynthetic pigments and are also used in various biomedical applications [4].

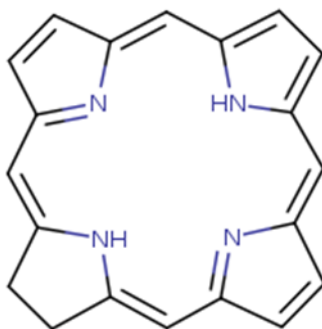


Fig 2. Structure of chlorin.

2.2 SwissADME

SwissADME is a free, web-based bioinformatics platform and computational tool used in drug discovery and medicinal chemistry to predict the physicochemical, pharmacokinetic, and drug-like properties of small molecules [5].

Lipinski's Rule of Five (Ro5) is a widely used rule of thumb in drug discovery to evaluate the "drug-likeness" of a chemical compound and predict its likelihood of being an orally active drug in humans [6]. The concept of Quantitative Estimate of Drug-likeness (QED) is widely considered more flexible and is a highly adopted method in computational drug discovery compared to the rigid, rule-based filters like Lipinski's Rule of Five (Ro5) [5, 7].

3 Results and Discussion

The specific data (physicochemical parameters and lipophilicity characteristics) of chlorin are presented in Table 1 and Table 2.

The results indicate that chlorin is a moderately lipophilic compound, with all predicted logP values being positive. The individual predictions vary significantly, from a low of 1.39

(MLOGP) to a high of 3.55 (SILICOS-IT). This wide range highlights how different computational models, based on different underlying principles (physics-based, atomistic, topological), can yield different estimations for the same molecule. The Consensus log Po/w value of 2.73 is the arithmetic mean of the five methods. It serves as a balanced, more robust estimate that mitigates the potential biases or inaccuracies of any single method. A logP value around **2.73** suggests that chlorin is significantly more soluble in non-polar solvents (like n-octanol) than in water. In a biological context, this level of lipophilicity suggests the molecule likely exhibits good membrane permeability, which is relevant for its potential use in applications like photodynamic therapy, where chlorins are commonly used as photosensitizers [5,8].

Table 1. Physicochemical properties of the chlorin.

Property	Value	Description & Implications
MW (g/mol)	312.37	Molecular Weight. This value is well below the 500 Da threshold of Lipinski's Rule of Five (≤ 500 Da), suggesting favorable oral absorption characteristics based on size alone.
Num. heavy atoms	24	The total count of non-hydrogen atoms in the molecule.
Num. arom. heavy atoms	5	While the <i>entire</i> macrocycle isn't fully aromatic (it's a dihydroporphyrin with one reduced ring), the majority of the structure retains aromatic characteristics.
Fraction Csp ³	0.1	A measure of saturation. A low fraction indicates a mostly unsaturated/rigid structure, typical of a macrocycle.
Num. rotatable bonds	0	Rigidity. This indicates a highly rigid, cyclic structure. This satisfies Veber's Rule (≤ 10), which strongly suggests good oral bioavailability due to the molecule's constrained conformation.
Num. H-bond acceptors	2	HBA count. This value is well below the Lipinski threshold of 10 (≤ 10), suggesting favorable characteristics for oral activity.
Num. H-bond donors	2	HBD count. This value is also well below the Lipinski threshold of 5 (≤ 5), suggesting favorable characteristics for oral activity.
Molar refractivity	109.05	A measure of the molecule's bulk and polarizability, often used in Ghose filters and other drug-likeness models.
TPSA (Å ²)	52.54	Topological Polar Surface Area. This measure relates directly to passive molecular transport across membranes. This value is significantly below the Veber's Rule threshold of 140 Å ² , strongly suggesting the compound has excellent potential for cell membrane permeability and oral absorption.

Table 2. Lipophilicity characteristics of the chlorin.

iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log P _{o/w}
2.71	3.48	2.52	1.39	3.55	2.73

*XLOGP3, an atomistic (or atom-additive) method that incorporates corrective factors and a knowledge-based library to improve prediction accuracy. The WLOGP method is a computational tool for predicting the octanol-water partition coefficient (logP) of a molecule, a measure of its lipophilicity. The MLOGP (Moriguchi logP) method is an archetype of a topological method used for predicting a molecule's octanol-water partition coefficient (logP). The SILICOS-IT method for predicting the octanol-water partition coefficient (logP) is characterized as a hybrid (or "mongrel") approach that combines both fragment-based and topological methodologies. The model relies on the contributions of 27 fragments and 7 topological descriptors. The iLOGP method is a physics-based approach for predicting the octanol-water partition coefficient (logP). It leans directly on the free energies of solvation in n-octanol and water, which are calculated using the Generalized Born and Solvent Accessible Surface Area (GB/SA) model [5].

The data confirms that chlorin is a lipophilic molecule, a characteristic crucial for its function and biological behavior.

The water solubility characteristics of chlorin is presented in Table 3.

Table 3. The water solubility of chlorin

ESOL				Ali et al. [8]				SILICOS-IT			
Log S (ESOL)	Solubility		Class	Log S	Solubility		Class	Log S SILI COS -IT	Solubility		Class
	mg/ml	mol/L			mg/ml	mol/L			mg/ml	mol/L	
-4.12	2.35e-02	7.53e-05	MS	-4.27	1.69e-02	5.42e-05	MS	-4.21	1.91e-02	6.12e-05	MS

*I-insoluble, PS-poorly soluble, MS-moderately soluble, S-soluble, VS-very soluble, HS-highly soluble.

The data indicate that chlorin is consistently predicted to be moderately soluble in water across all three models:

- Log S values: The Log S values (logarithm of the molar solubility) are tightly clustered around -4.2. These negative values confirm that the concentration in the saturated aqueous solution is low (less than 10⁻⁴ Molar).
- Solubility in mg/mL: The solubility is predicted to be approximately 0.02 mg/mL across all methods.
- Solubility class: All methods classify chlorin as "Moderately Soluble" (MS).

While often described as "poorly" or "sparingly" soluble in a practical sense for drug formulations, computational models classify the parent chlorin molecule as moderately soluble. The values align well with its highly lipophilic nature (high logP values from previous data). The slight variation between the methods is typical for computational predictions, and the consensus points towards a consistent, albeit low, water solubility.

The BOILED-Egg model is a simple, rapid, and effective graphical tool used in drug development to predict two crucial pharmacokinetic properties of a molecule: passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) penetration [5,9].

The pharmacokinetic parameters for chlorin are presented in Table 4, and the Bioavailability score and drug-likeness rule for chlorin are presented in Table 5.

Table 4. Pharmacokinetic parameters for the chlorin

Parameter	Value	Interpretation
GI absorption	High	The molecule is expected to be readily absorbed through the human gastrointestinal tract, likely through passive diffusion across cell membranes.
BBB permeant	Yes	The molecule is predicted to cross the blood-brain barrier, indicating potential access to the central nervous system. This aligns with its predicted lipophilicity.
P-gp substrate	No	The molecule is likely <i>not</i> actively pumped out of cells by the P-glycoprotein efflux pump. This favorable characteristic supports the "Yes" BBB permeant prediction, suggesting good retention within cells or tissues once absorbed.
CYP1A2 inhibitor	Yes	The molecule may inhibit the Cytochrome P450 1A2 enzyme, potentially affecting the metabolism of other co-administered drugs that rely on this enzyme.
CYP2C19 inhibitor	Yes	The molecule may inhibit the Cytochrome P450 2C19 enzyme.
CYP2C9 inhibitor	Yes	The molecule may inhibit the Cytochrome P450 2C9 enzyme.
CYP2D6 inhibitor	No	The molecule is not expected to inhibit the Cytochrome P450 2D6 enzyme.
CYP3A4 inhibitor	Yes	The molecule may inhibit the Cytochrome P450 3A4 enzyme, a major metabolic pathway for many drugs.
Log <i>K_p</i> (Skin Permeation) (cm/s)	-5.73	This value indicates very low skin permeability.

Table 5. Bioavailability score and drug-likeness rule for the chlorin.

Lipinski (Pfizer) filter [6]	Ghose (Amgen) method [6]	Veber (GSK) method [10]	Egan (Pharmacia) method [10]	Muegge (Bayer) method [11]	Bioavailability score
Yes; 0 violation	Yes	Yes	Yes	Yes	0.55

The results from all five drug-likeness filters are highly favorable, consistently indicating that the chlorin molecule is a potential "drug-like" candidate suitable for oral administration. The chlorin molecule passes all standard filters, including a perfect score (0 violations) on the stringent Lipinski filter. The bioavailability score of 0.55 suggests that while not exceptionally high, the molecule is likely to be orally bioavailable. The combination of these positive scores strongly suggests that the chlorin structure has a good balance of physicochemical properties (lipophilicity, polarity, size) conducive to efficient absorption and distribution within the body [12-15].

The expected medically important properties of chlorin are presented in Table 6.

Table 6. Medicinal properties of the chlorin.

Pains	0 alert	The molecule does not contain any structural fragments known to frequently interfere with biological assays, leading to false-positive results.
Brenk et al. [13]	0 alert	The molecule does not contain any structural fragments identified by the Brenk filter as having potential toxicity or metabolic liabilities.
Leadlikeness	Yes	The molecule fits within the general physicochemical property ranges defined as optimal for a "lead" compound in drug discovery, suggesting it's a good starting point for further optimization.
Synthetic accessibility (SA)	6.02	This score is likely on a scale (typically 1 to 10), where lower numbers indicate easier synthesis. A score of 6.02 suggests that the molecule is moderately complex to synthesize, potentially requiring multi-step organic synthesis, but it is feasible to produce.

The provided image of the BOILED-Egg model (Figure 3) visually confirms the prediction that the chlorin molecule is a strong candidate for high brain penetration.

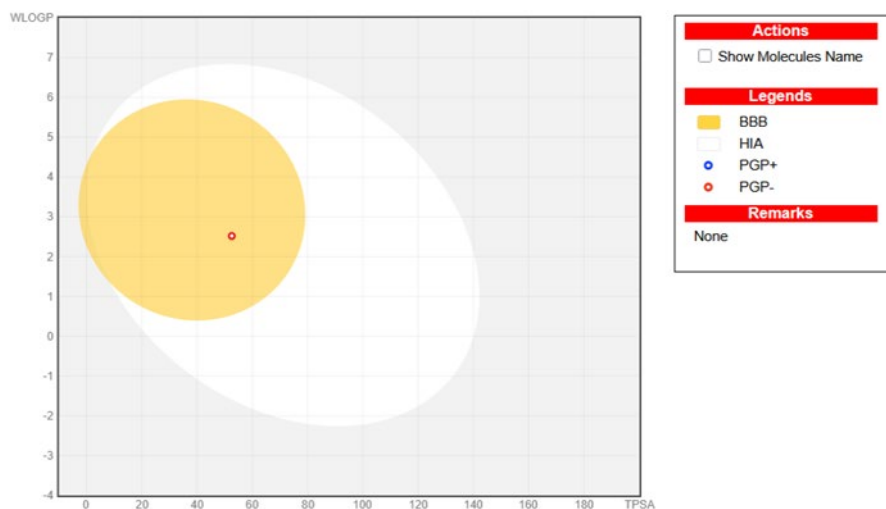


Fig 3. A schematic representation of the BOILED-Egg model, a graphical tool used for the perceptive evaluation of passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) penetration.

In the provided image, the red data point for chlorin is located within the yellow yolk area, indicating a strong prediction for both high GI absorption and brain penetration.

The Bioavailability Radar is a schematic diagram used for a rapid, visual assessment of a molecule's drug-likeness for oral administration, typically generated by tools like

SwissADME. The plot displays six key physicochemical properties on different axes to show how well a compound's values fit within an ideal range (represented by a pink or colored shaded area) (Figure 4).

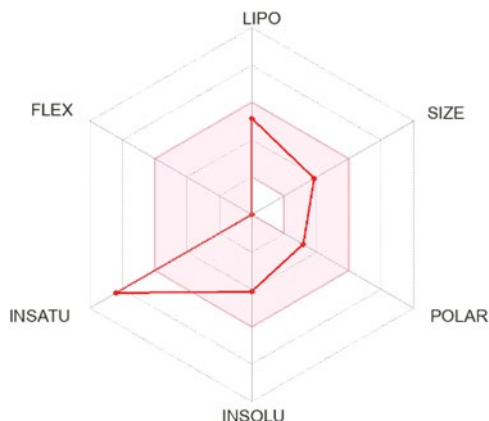


Fig. 4. Bioavailability Radar schematic diagram for drug-likeness of the chlorin.

4 Conclusion

Porphyrins do indeed play essential roles in biochemistry across many life forms. They are found widely in plants and animals. Their core tetrapyrrole structure is highly stable and resistant to decay, even during fossilization. The SwissADME computational tool is used to calculate important medical parameters (physicochemical, pharmacokinetic) of porphyrin derivatives, enabling researchers to study their potential beneficial effects and applications in medicine.

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