RESEARCH PAPER

In Silico Assessment Of Porphyrins Against Sars-Cov-2 Main Protease: Adme, Pass And Docking Studies

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Abstract

Two porphyrins, *meso*-5,10,15,20-tetrakis(p-hydroxyphenyl) porphyrin [T(*p*−OH) PP] and *meso*-5,10,15,20-tetrakis(*p*-bromophenyl) porphyrin [T(*p*−Br) PP], were investigated using integrated in silico approaches to evaluate their antiviral potential and safety profiles. Molecular docking against the COVID-19 main protease (PDB ID: 5R7Y) revealed strong binding affinities, with binding free energies of −159.06 and −163.39 kcal/mol. ADMET analysis using Swiss ADME and pkCSM demonstrated favourable pharmacokinetic properties, including good solubility, high intestinal absorption, and compliance with Lipinski's rule of five. PASS predictions indicated broad biological activity, particularly involving redox enzyme inhibition and receptor antagonism. Carcinogenicity assessment using Carcino-Pred-EL ensemble models consistently classified both compounds as non-carcinogenic. Collectively, these findings highlight the promising therapeutic potential of the studied porphyrins and support further experimental validation.

Key words: Porphyrins, COVID-19 protein, Docking, ADME-Tox, PASS, Carcinogenicity

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1. Introduction

Recent advances in the development of tetrapyrrolic photosensitizers have opened new therapeutic perspectives, particularly in chemotherapy. Porphyrin derivatives exhibit a strong affinity for tumor cells, highlighting their potential in oncology(Nyman and Hynninen 2004; Xue et al. 2019; Park et al. 2021). Their therapeutic effectiveness arises from their well-defined structural design, favorable photo-physical properties, and strong absorption within the therapeutic window, combined with their ability to generate reactive oxygen species (ROS) in the presence of light and molecular oxygen (Berbigier et al. 2024). Porphyrins are biologically important compounds with broad applications in medicine and materials sciences. In addition to their biomedical relevance, certain porphyrins function as efficient catalysts for alkene oxidation reactions (Rajora et al. 2017; Chen et al. 2021). Many essential biomolecules contain metal ions enclosed within a molecular cavity, including chlorophylls, respiratory pigments such as hemoglobin, myoglobin, hemocyanin, hemerythrin, and hemovanadin, as well as cytochromes and vitamin B12 derivatives (Kostova 2023). Owing to their structural similarity to naturally occurring tetrapyrroles and versatile coordination chemistry, porphyrins serve as effective platforms for incorporating catalytic and electronic properties (Shimizu 2017; Dar et al. 2024).

In line with these observations, computational and experimental approaches have become highly synergistic in addressing the challenges of drug discovery. Modern drug design has evolved from a largely stochastic process based on natural product screening to a rational strategy that integrates computational methods with structural-chemical analysis (Gupta et al. 2020; Wang et al. 2024).

Among these methods, molecular docking has emerged as a valuable *in silico* tool, enabling the rapid and cost-effective identification of drug molecules with high affinities for target proteins using scoring functions (Ekins et al. 2007). In addition, computational models facilitate the early-stage prediction of key pharmacokinetic parameters, including absorption, distribution, metabolism, and excretion (ADME), thereby improving the efficiency of lead selection (Wishart 2007; Ghani et al. 2025).

Beyond efficacy and pharmacokinetics, toxicity evaluation is a critical component of the drug development process. Among the various toxicological endpoints, carcinogenicity is of particular concern because of its severe implications for human health (Cohen et al. 2019). Carcinogens are substances that can induce cancer, often through genomic damage or disruption of cellular metabolic pathways. Notably, several approved drugs have been identified as carcinogenic in humans or animals and have subsequently been withdrawn from the market. To mitigate the risk of drug-induced cancer, regulatory authorities require comprehensive carcinogenicity assessments before granting marketing approval for new drug candidates.

Overall, the present study employs integrated *in silico* approaches to investigate the interaction of two porphyrins *meso*-5,10,15,20-tetrakis(p-hydroxyphenyl) porphyrin and *meso*-5,10,15,20-tetrakis(p-bromophenyl) porphyrin with the COVID-19 main protease. Molecular docking was performed to evaluate their binding affinity and interaction modes with the target protein. In addition, PASS analysis was carried out to predict the biological activity spectrum of the compounds, while ADME/T profiling was conducted to assess their drug-likeness and pharmacokinetic feasibility. Furthermore, carcinogenicity prediction using CarcinoPred-EL classified the compounds as either carcinogenic or non-carcinogenic based on their two-dimensional structural features.

2. Materials and Software Techniques Porphyrins namely, Meso-5,10,15,20-Tetrakis(*P*-hydroxyphenyl) porphyrin [T(*p*-OH) PP] and meso-5,10,15,20-Tetrakis(*p*-bromophenyl) porphyrin [T(*p*-Br) PP] were retrieved from the PubChem database in SDF format (give citation). The schematic representations of these previously reported porphyrins are illustrated in Fig.1.

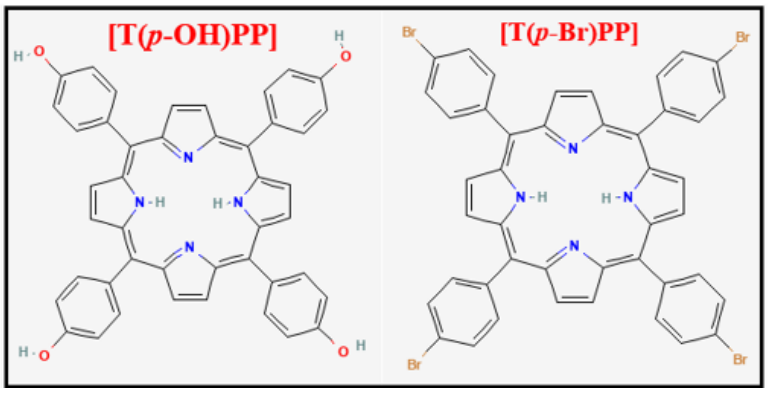

Fig. 1. The schematic representations of these previously reported porphyrins

Computational Evaluation

Below are details of the software and methods used for molecular docking, in silico ADMET, PASS, and Carcino-Pred-EL analysis.

2.1 In silico Molecular Docking Investigation

In silico molecular docking studies of selected porphyrins [T(*p*-OH) PP and T(*p*-Br) PP] were performed using HEX 8.0 software. This interactive molecular graphics system

is specifically designed to analyse protein-ligand interactions (AKBABA and KARATAŞ 2023), calculate docking free energies, and identify potential docked conformations of biomolecules. For this study, the X-ray crystal structure of the COVID-19 main protease (PDB ID: 5R7Y, resolution 1.65 Å) was obtained from the Protein Data Bank (Fearon et al., 2020).

2.2 ADME Profiling and Toxicity Prediction

The online pkCSM (Tomar et al. 2023) platform was employed for computational analysis to assess the studied compounds' pharmacokinetic properties. Absorption parameters such as Lipinski's five laws, water solubility (log mol L−1), Caco-2 permeability (log Papp in 10^{-6} cms^{-1}), human intestinal absorption (human %), skin permeability (log Kp) and P-glycoprotein interaction were evaluated. Additional properties such as apparent volume of distribution (VDss), Fraction unbound (human) (Fu), blood-brain barrier penetration (Log BBB), and central nervous system permeability were considered. Furthermore, metabolic and excretion factors were analysed. The integrated PkCSM method assessed Max. Tolerated dose (human) (log mg kg^{-1} day^{-1}), skin sensitivity, cardiotoxicity, acute oral toxicity (LD50), hepatotoxicity, T. Pyriformis toxicity (log ug/L) and antibacterial activity. (http://biosig.unimelb.edu.au/pkcsm/).

2.3 Prediction of Activity Spectra for Substances (PASS)

The biological activity spectrum of the selected porphyrins [T(*p*-OH) PP and T(*p*-Br) PP] includes various biological effects resulting from interactions with biological systems (Lagunin et al. 2000). Biological activity is classified qualitatively as "present" or "absent." This means that the biological activity spectrum is intrinsically a property of a substance, determined primarily by its structural and physicochemical properties. This is essential as no single publication comprehensively covers all the diverse facets of the biological action of porphyrins. (http://www.pharmaexpert.ru/PASSonline/predict.php).

2.4 Carcinogen Identification Using Ensemble Models

CarcinoPred-EL is a web-based platform designed to predict the carcinogenicity of compounds using ensemble learning methods. The server analyses solely the two-dimensional structures of chemicals. It categorizes them as carcinogenic or non-carcinogenic. Three novel cluster models were used. Ensemble XGBoost, Ensemble SVM, and Ensemble RF contributed to the accuracy and reliability of the forecast (Zhang et al. 2017). The platform is accessible at (http://112.126.70.33/toxicity/CarcinoPred-EL/index.html#).

3. Results and discussion

In silico evaluation of the porphyrins namely, Meso-5,10,15,20-Tetrakis (*p*-hydroxyphenyl) porphyrin [T(*p*-OH) PP] and meso-5,10,15,20-Tetrakis (o nitrophenyl) porphyrin [T(*p*-Br) PP] revealed the following results.

3.1 Molecular Docking

Molecular docking is a powerful computational approach for predicting protein–drug interactions (Kanakaveti et al. 2020), including those involving [T(*p*-OH) PP and T(*p*-Br) PP]. Understanding these interactions is crucial for evaluating drug efficacy and guiding rational drug design. Generally, lower binding free energy values indicate stronger and more stable interactions between ligands and their target proteins. To gain deeper insights into these interactions, computational models of the ligands and their corresponding target proteins were constructed (Ajay and Murcko 1995).

In this study, the receptor consisted of a selected region of the COVID-19 protein containing one or more well-defined active sites. Molecular docking was performed to evaluate ligand–receptor interactions and identify the most favorable binding orientations [20]. The resulting docked

conformations are shown in Figure 2. Among the seven docking poses generated for each ligand, the lowest-energy conformation was selected for detailed analysis to elucidate the types of interactions that can trigger a biological response.The docking results demonstrated that the investigated drug molecules could effectively access and bind within the protein's active site, highlighting their potential inhibitory activity against the COVID-19 protein. The ligand was stabilized primarily through a combination of van der Waals forces and hydrophobic interactions with the functional groups of the receptor (Schaeffer 2008). The calculated binding free energy values for [T(*p*-OH) PP and T(*p*-Br) PP] were −159.06and −163.39 kcal/mol, respectively. Overall, molecular docking analysis revealed that the selected porphyrins exhibited strong interactions with the COVID-19 protein.

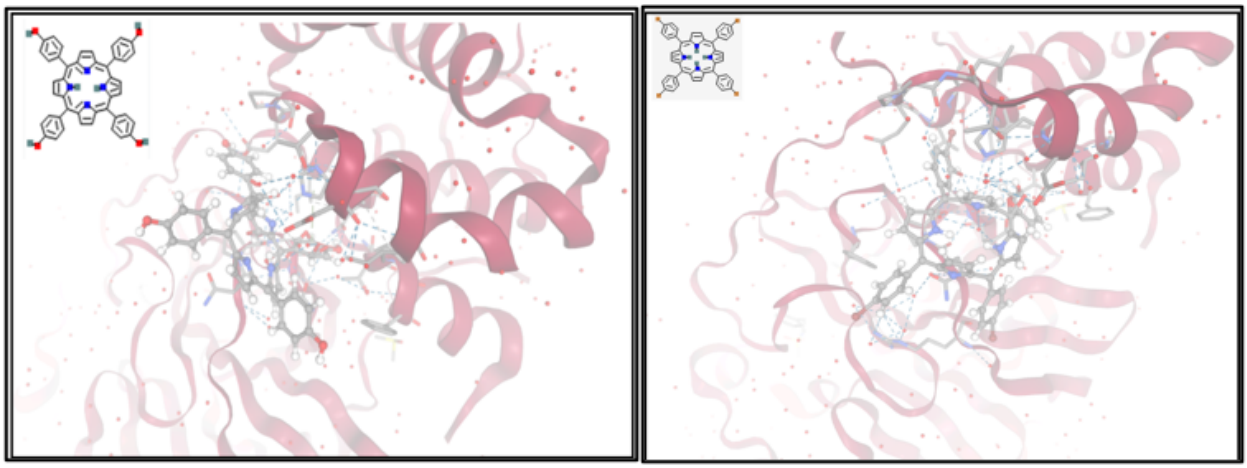

Fig. 2. Molecular docked model of [T(*p*OH)PP] and [T(*p*-Br) PP] with COVID-19 protein

3.2 ADME Profiling and Toxicity Prediction

In silico ADME and toxicity profiling were performed to evaluate the pharmacokinetic feasibility of the selected porphyrin derivatives as an alternative to early-stage animal experiments (El-Sewedy et al. 2023). The SMILES representations of [T(*p*-OH) PP] and [T(*p*-Br) PP] were generated (Table 1) and analyzed using the SwissADME and pkCSM web servers to predict their absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics. The predicted results are presented in Table 2.

Both [T(*p*-OH) PP] and [T(*p*-Br) PP] demonstrated favorable aqueous solubility, which was notably higher than that of many conventional drug molecules. Adequate solubility is a critical parameter for oral drug absorption and bioavailability. According to Lipinski's rule of five (Lipinski et al. 1997), compounds that violate no more than one criterion are generally considered to possess acceptable oral bioavailability (OB). The present analysis indicates that both porphyrins comply with Lipinski's criteria, supporting their potential suitability for oral administration.

In terms of absorption, both compounds exhibited high predicted intestinal absorption and acceptable Caco-2 permeability, suggesting efficient uptake across the intestinal epithelium. The distribution parameters revealed moderate volumes of distribution (VDss) and low fractions of unbound drugs, indicating substantial plasma protein binding. The blood-brain barrier (BBB) permeability values were predicted to be −1.137 for [T(*p*-OH) PP] and 0.294 for [T(*p*-Br) PP], suggesting limited to moderate central nervous system penetration. Metabolic profiling showed that both compounds were substrates of CYP3A4 but not substrates or inhibitors of other major

cytochrome P450 isoforms, including CYP1A2, CYP2C9, CYP2C19, and CYP2D6. This selective interaction profile reduces the likelihood of broad drug–drug interactions occurring. However, their lipophilic nature and metabolic behavior suggest a potential influence on oxidative metabolic pathways, which may contribute to oxidative stress under certain conditions. Excretion analysis indicated moderate total clearance values and no interaction with the renal OCT2 transporters. Toxicity predictions revealed that both compounds were non-mutagenic (AMES-negative), non-inhibitory toward hERG I channel, and possessed acceptable maximum tolerated doses. However, both compounds were predicted to inhibit hERG II channels, warranting further experimental validation. Overall, the ADMET profiles suggest that [T(*p*-OH) PP] and [T(*p*-Br) PP] possess promising pharmacokinetic characteristics with manageable toxicity risks, supporting their further investigation as bioactive agents in the future (Asif et al. 2024; Bhattacharya et al. 2024).

Table. 1. SMILES of a. [T(*p*-OH) PP] and b. [T(*p*-Br) PP]

a	C1=CC(=CC=C1C2=C3C=CC(=C(C4=NC(=C(C5=CC=C(N5)C(=C6C=CC2=N6)C7=CC=C(C=C7)O)C8=CC=C(C=C8)O)C=C4)C9=CC=C(C=C9)O)N3)O
b	C1=CC(=CC=C1C2=C3C=CC(=C(C4=NC(=C(C5=CC=C(N5)C(=C6C=CC2=N6)C7=CC=C(C=C7)Br)C8=CC=C(C=C8)Br)C=C4)C9=CC=C(C=C9)Br)N3)Br

Table. 2. ADMET properties of [T(*p*-OH) PP] and [T(*p*-Br)PP]

Property		[T(*p*-OH)PP]	[T(*p*-Br)PP]
Absorption	Water solubility (log mol L^{-1})	-3.222	-3.351
	Caco2 permeability (log Papp in 10^{-6} cm s^{-1})	-0.068	1.19
	Intestinal absorption (human %)	100	80.067
	Skin Permeability (log K_p)	100	-2.735
	P-glycoprotein substrate	Yes	Yes
	P-glycoprotein I inhibitor	Yes	Yes
	P-glycoprotein II inhibitor	Yes	Yes
Distribution	VDss (human)	-0.822	-0.437
	Fraction unbound (human) (Fu)	0.099	0.052
	BBB permeability (log BB)	-1.137	0.294
	CNS permeability (log PS)	-1.541	0.935
Metabolism	CYP2D6 substrate	No	No
	CYP3A4 substrate	Yes	Yes
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	No

Excretion	Total Clearance (log ml mim^{-1} kg^{-1})	0.505	-0.26
	Renal OCT2 substrate	No	No
Toxicity	AMES Toxicity	No	No
	Max. tolerated dose (human) (log mg kg^{-1} day^{-1})	0.412	0.512
	hERG I inhibitor	No	No
	hERG II inhibitor	Yes	Yes
	Oral Rat Acute Toxicity (LD50) (mol kg^{-1})	2.961	2.839
	Oral Rat Chronic Toxicity	2.18	1.082
	Hepatotoxicity	No	No
	Skin Sensitization	No	No
	T.Pyriformis toxicity (log ug/L)	0.285	0.285
	Minnow toxicity (log mM)	-0.513	-3.731
Drug Likeness	Lipinski	No; 2-Violation	No; 2-Violation

3.3 Prediction of Activity Spectra for Substances (PASS)

Prediction of Activity Spectra for Substances (PASS) is a computational tool used to estimate the potential biological activity profiles of chemical compounds based on their structural features. Such predictions are valuable during early-stage drug discovery because they help prioritize compounds with promising pharmacological potential before experimental validation (Druzhilovskiy et al. 2017). PASS provides two probability values: Pa, which represents the probability that a compound is biologically active for a given activity, and Pi, which represents the probability of a compound being inactive. Generally, biological activities with Pa > Pi, particularly Pa > 0.7, are considered to be highly reliable. In the present study, the chemical structures of the selected porphyrin derivatives were converted into SMILES format and analyzed using the online PASS software. The results indicate that these compounds exhibit a broad spectrum of predicted biological activities, extending beyond their previously reported anti-carcinogenic, antimutagenic, antiseptic, and antidyskinetic properties. Notably, the predictions suggest potential roles in antifungal activity, modulation of oxidative enzymes and alleviation of allergic and inflammatory responses. The predicted biological activities of [T(*p*-OH) PP] and [T(*p*-Br) PP] are summarized in Tables 3(a) and 3(b), respectively. Only activities with relatively high Pa values are presented to highlight their pharmacological potential (Arun 2025).

Tables 3 (a) Predicted biological activities of[T(*p*-OH) PP].

P_a	P_i	Activity
0,870	0,015	Aspulvinonedimethylallyltransferase inhibitor
0,850	0,006	Taurine dehydrogenase inhibitor
0,845	0,003	Thioredoxin inhibitor
0,851	0,024	CYP2C12 substrate

0,830	0,011	5 Hydroxytryptamine release stimulant
0,822	0,009	NADPH peroxidase inhibitor
0,802	0,016	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,795	0,010	Dehydro-L-gulonate decarboxylase inhibitor
0,787	0,006	2-Hydroxyquinoline 8-monooxygenase inhibitor
0,774	0,004	Hyponitrite reductase inhibitor
0,767	0,005	Aryl-acylamidase inhibitor
0,772	0,011	Aldehyde oxidase inhibitor
0,758	0,004	Magnesium-protoporphyrin IX monomethyl ester (oxidative) cyclase inhibitor
0,759	0,008	Nitrate reductase (cytochrome) inhibitor
0,775	0,025	Chlordecone reductase inhibitor
0,766	0,017	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,771	0,024	Antiseborrheic
0,870	0,015	Aspulvinonedimethylallyltransferase inhibitor

Tables 3(b) Predicted biological activities of [T(*p*-Br)PP]

P_a	P_i	**Activity**
0,840	0,023	Aspulvinonedimethylallyltransferase inhibitor
0,816	0,007	Prolyl aminopeptidase inhibitor
0,778	0,005	Centromere associated protein inhibitor
0,729	0,008	Thioredoxin inhibitor
0,739	0,018	Feruloyl esterase inhibitor
0,728	0,008	HMGCS2 expression enhancer
0,694	0,004	Endothelial growth factor antagonist
0,715	0,028	Taurine dehydrogenase inhibitor
0,686	0,012	Kidney function stimulant
0,681	0,040	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,671	0,033	Nicotinic alpha2beta2 receptor antagonist
0,667	0,033	NADPH peroxidase inhibitor
0,648	0,017	Chloride peroxidase inhibitor
0,637	0,014	Antihypoxic
0,637	0,038	Antineoplastic
0,612	0,015	(S)-6-hydroxynicotine oxidase inhibitor
0,647	0,050	Glycosylphosphatidylinositol phospholipase D inhibitor
0,630	0,036	Pseudolysin inhibitor

3.4. Prediction of chemical carcinogenicity using ensemble learning methods.

Carcinogenicity prediction was performed using CarcinoPred-EL, a freely accessible web-based platform designed to assess the carcinogenic potential of chemical compounds based on their two-dimensional structural descriptors (Singh et al. 2024). The server classifies compounds as either carcinogenic or non-carcinogenic using three ensemble machine-learning models: Ensemble Random Forest (RF), Ensemble Support Vector Machine (SVM), and Ensemble Extreme Gradient Boosting (XGBoost).

In this study, [T(*p*-OH)PP] and [T(*p*-Br)PP] were evaluated using CarcinoPred-EL. Each ensemble model employs multiple molecular fingerprint descriptors, including CDK, CDK-Extended (CDKExt), CDK-Graph, KR, KRC, MACCS, and PubChem. The output provides probability

scores ranging from 0 to 1 for each descriptor and model. An average probability score is calculated for each compound, which is used for final classification. Compounds with an average probability value greater than 0.5 are classified as carcinogenic, whereas those with values below 0.5 are classified as non-carcinogenic. The predicted probability values and classifications obtained from the ensemble models are presented in Table 4. All three ensemble learning approaches consistently classified both [T(*p*-OH)PP] and [T(*p*-Br)PP] as non-carcinogenic, with average probability values well below the threshold of 0.5. These findings strongly suggest that the selected porphyrin derivatives do not possess carcinogenic potential, thereby supporting their safety profile for further pharmacological and therapeutic investigations (Fadda et al. 2013).

Table. 4. Carcinogenic or non-carcinogenic nature of [T(*p*-OH)PP] and [T(*p*-Br)PP]

4(a) Carcino Pred-EL of [T(*p*-OH)PP]									
Method	CDK	CDKExt	CDKGraph	KR	KRC	MACCS	Pubchem	Average	Class
RF	0.32	0.32	0.22	0.47	0.45	0.35	0.31	0.39	Non-Carcinogen
SVM	0.60	0.62	0.29	0.67	0.54	0.55	0.37	0.48	Non-Carcinogen
XGBoost	0.07	0.19	0.47	0.45	0.89	0.63	0.76	0.47	Non-Carcinogen

4(b) CarcinoPred-EL of [T(*p*-Br)PP]									
Method	CDK	CDKExt	CDKGraph	KR	KRC	MACCS	Pubchem	Average	Class
RF	0.82	0.81	0.20	0.24	0.46	0.23	0.36	0.32	Non-Carcinogen
SVM	0.79	0.78	0.47	0.52	0.44	0.62	0.55	0.46	Non-Carcinogen
XGBoost	0.07	0.19	0.47	0.45	0.91	0.63	0.76	0.42	Non-Carcinogen

CONCLUSION

This study demonstrates, through integrated in silico analyses, that porphyrins [T(*p*-OH)PP] and [T(*p*-Br)PP] exhibit a strong binding affinity toward the COVID-19 main protease, favourable pharmacokinetic properties, broad predicted biological activity, and low carcinogenic risk. Combined docking, ADMET, PASS, and ensemble carcinogenicity predictions highlighted their potential as safe multitarget therapeutic candidates. Despite these promising findings, this study is limited by its reliance on computational predictions, which do not fully capture the complexity of biological systems. Therefore, experimental validation through in vitro enzymatic assays, antiviral activity studies and *in vivo* toxicity evaluations is required. Future studies should also focus on optimizing the structure–activity relationship and metallation effects to enhance the selectivity and efficacy. Overall, these results provide a strong computational framework for the rational development of porphyrin-based therapeutics.

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Competing interests

The authors declare no competing interests.

Data availability

The authors do not have permission to share data.

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