Journal of Tropical Pharmacy and Chemistry

Journal homepage: https://jtpc.farmasi.unmul.ac.id

Exploring the Relationship between PheSA Scores and Ligand Efficiency in the Discovery of Potent Antimalarials: A Computational Perspective

Agede Olalekan Ayodele[1,2*], Ogunmodede James Ayodele[2], Sanni Nasiru[2], Wasagu Isa Musa[3], Oyedepo Dapo Sunday[2], Aiyedun Olawale Stephen[2], Falade Catherine Olufunke[4]

[1]Department of Pharmacology and Therapeutics, University of Ilorin, Nigeria
[2]Department of Medicine, University of Ilorin and University of Ilorin Teaching Hospital, Ilorin, Nigeria
[3]Department of Medicine, Usmanu Dan Fodiyo University Teaching Hospital, Sokoto, Nigeria
[4]Department of Pharmacology and Therapeutics, University of Ibadan, Nigeria
*Corresponding author: niffynimmy@yahoo.com & agede.oa@unilorin.edu.ng

Abstract

Pharmacophore Enhanced Shape Alignment (PheSA) compares the similarities of compounds based on their pharmacophoric and geometrical characteristics. Ligand efficiency is a notion used to maximize the potency and effectiveness of medication candidates by taking into account their molecular weight and binding affinity. This study mainly focused on Cycloguanil analogues to evaluate the association between PheSA scores and ligand efficiency in the identification of effective antimalarials. Information on 36 PfDHFR inhibitors, their structures and biological activity was retrieved from the ChEMBL database. Based on shape and pharmacophore similarity, the PheSA algorithm was used to compare the 3D structures of the inhibitors. Based on a *de novo* synthesis method, 257 new compounds with greater PheSA similarity scores that have a striking resemblance to cycloguanil were created. The PheSA score and ligand efficiency have a moderately positive link (correlation coefficient of 0.675) according to the analysis. However, the virtual screening of cycloguanil analogues based on PheSA similarity scores offers a useful initial evaluation of structural similarity, directing further experimental studies to find interesting substances for the creation of effective antimalarial drug.

Keywords: PheSA, cycloguanil analogues, ligand efficiency, antimalarial drugs

Received: 04 October 2023 **Accepted**: 02 May 2024

DOI: https://doi.org/10.25026/jtpc.v8i1.609

How to Cite:

Agede, O.A., Ogunmodede, J.A., Sanni, N., Wasagu, I.M., Oyedepo, D.S., Aiyedun, O.S., Falade, C.O., 2024. Exploring the Relationship between PheSA Scores and Ligand Efficiency in the Discovery of Potent Antimalarials: A Computational Perspective. *J. Trop. Pharm. Chem.* **8**(1). 77-85. **DOI**: https://doi.org/10.25026/jtpc.v8i1.609

1 Introduction

Malaria is still a major concern for world health, especially in areas where the disease is endemic [1]. Finding innovative and efficient treatments is a top concern since plasmodium falciparum, one of the malarial pathogens, has developed resistance to numerous widely used antimalarial medications [2]. The identification and optimization of promising antimalarial drugs has been made easier in recent years based on computational techniques [3].

One such computer method has showed promise in determining the similarity of compounds based on their pharmacophoric and shape characteristics: Pharmacophore Enhanced Shape Alignment (PheSA) [4]. PheSA can shed light on a molecule's structural similarities and potential binding interactions by assessing how closely it fits with a reference molecule or pharmacophore model [5]. This data can be used in virtual screening methods to find substances that are likely to have pharmacological properties that are comparable to those of recognized active substances.

However, ligand efficiency has drawn interest as a theory for improving the effectiveness and potency of therapeutic candidates [6]. In order to find compounds that attain high potency while having a low molecular weight, ligand efficiency is defined as the binding affinity divided by the molecular weight of a compound [7]. Researchers can enhance target specificity, decrease off-target effects, and improve the pharmacokinetic features of therapeutic candidates by increasing ligand efficiency [8].

We can better comprehend the computation of molecular similarity and its implications for drug discovery by understanding the relationship between PheSA scores and ligand efficacy. Scientists can gain additional insight into how PheSA scores can guide the selection of compounds with strong ligand efficiency, ultimately assisting in the identification of promising antimalarial possibilities, by looking into this connection. It is critical to remember that other factors may affect ligand efficiency and that correlation does not necessarily imply causation.

In order to identify effective antimalarials, the aim of this study is to look into the relationship between PheSA scores and ligand effectiveness. We can examine the extent to which PheSA scores can be utilized as a predictive tool for ligand efficiency by looking at the correlation between these two metrics and assessing their statistical significance. This computational viewpoint will offer insightful information about PheSA's ability to direct the choice and improvement of promising antimalarial drug candidates, such as cycloguanil analogues. The results of this work will advance the field of computational drug discovery and aid in the fight against malaria.

2 Methods

2.1 Collection of data and dataset groundwork

From the ChEMBL database, the insignificant name, structure, place of origin, and biological activity (Ki) of PfDHFR inhibitors were obtained. Based on chemical structures that were accessible and had linked bioactivities (Ki), ligand efficiencies, and binding efficiencies, a total of 36PfDHFR inhibitors were discovered (Figure S1). After that, bioactivities (Ki) were converted to pKi by using the formula pKi = (-

log (Ki X)). The ChEMBL database provided the chemical structures of PfDHFR inhibitors in smiles format, which Data Warrior v5.0.0 subsequently converted to (3D) SDF format [9].

2.2 Pharmacophore Enhanced Shape Alignment (PheSA)

Using datawarrior v5, the PheSA algorithm was used to the 36PfDHFR inhibitors. It begins by positioning two hard three-dimensional molecules so that the overlap of their shapes and pharmacophore features is maximized. PheSA is comparable to OpenEye's ROCS technology in this sense. The PheSA similarity, a value ranging from 0.0 to 1.0 that is composed of equal contributions from both shape and pharmacophore similarity, then quantitatively describes the optimum alignment of both molecules [10].

2.3 Drug likeness based Pharmacokinetic Evaluation

Computational technology has become a crucial tool for identifying therapeutic candidates since it has reduced the number of experimental drug trials and raised their success rate [11]. It was able to predict the drug-likeness of 36 PfDHFR inhibitors using Lipinski's Rule of 5. To set standards for novel molecular an entity (NMEs) in terms of medicine similarity, the regulation was developed [12], [13]. According to the Rule of 5, molecules are predicted to have poor molecular entity absorption or penetration if they have more than five H-bond donors, ten H-bond acceptors, a molecular weight greater than 500 Da, and a calculated Log P (Clog P) value greater than five. Therefore, it is unlikely that a molecule will be orally accessible as a drug if its properties fall outside of these ranges.

3 Results and Discussion

The findings of a virtual screening of cycloguanil analogs utilizing Pharmacophore Enhanced Shape Alignment (PheSA) to find effective antimalarials are shown in Table S2. The top-scoring compounds are shown in Table 1 alongside the associated PheSA values.

Table 1: Top hits of compounds with high PheSA scores

CHEMBL ID	PheSA score
312235	0.48703
391505	0.48359
157723	0.43697
156818	0.42073
156817	0.39551
157754	0.37235
157754	0.35463

The PheSA score evaluates how closely a given chemical resembles the well-known antimalarial drug cycloguanil. In terms of their pharmacophoric and form characteristics, drugs with higher PheSA scores are more similar to cycloguanil and may have comparable antimalarial efficacy. The compounds with the highest PheSA scores, according to the outcomes, are as follows: Based on the results, the molecules with the highest PheSA scores are as follows:

1. Molecule 312235 with a PheSA score of 0.48703
2. Molecule 391505 with a PheSA score of 0.48359
3. Molecule 157723 with a PheSA score of 0.43697

The relationship between the PheSA score and ki measures (dissociation constant) of Cycloguanil Analogues is described by the equation 1.

$$pKi = (-0.013934 * \text{PheSA score}) + 0.49032 \quad \text{(Equation 1)}$$

The correlation coefficient (Bravais-Pearson) between the PheSA score and 0.174.

A correlation coefficient of -0.174 (Figure 1) indicates a weak negative correlation between the PheSA score and ki values. This means that as the PheSA score increases, the ki values tend to slightly decrease, although the relationship is not very strong. It's important to note that a correlation coefficient close to zero suggests a weak linear relationship between the variables

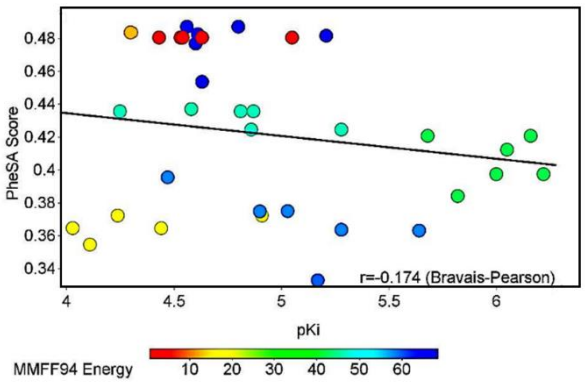

Figure 1: Relationship between PheSA score and pKi

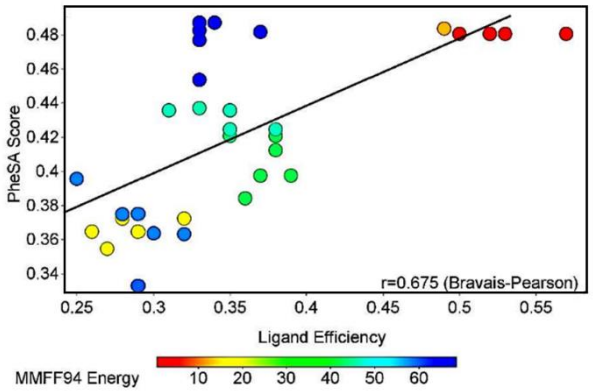

Figure 2: Relationship between PheSA score and ligand efficiency

The lack of a positive link suggests that the pKi values and the PheSA score may be related in some way. It is important to keep in mind that there may be other factors influencing the link between these variables, even though correlation does not always imply causation.

Additionally, the PheSA score and Ligand Efficiency of Cycloguanil Analogues are related according to equation 2.

$$\text{Ligand Efficiency} = (0.39435 * \text{PheSA score}) + 0.28064 \quad \text{(Equation 2)}$$

The PheSA score and Ligand Efficiency have a 0.675 Bravais-Pearson correlation coefficient.

The PheSA score and Ligand Efficiency show a somewhat positive link with a correlation coefficient of 0.675 (Figure 2). As a result, the Ligand Efficiency tends to rise along with the PheSA score. The positive connection shows that greater Ligand Efficiency values are related to higher PheSA scores.

A ligand binding affinity, in this case reflected by the PheSA score, is a measure of how effectively a ligand attaches to its target. This metric is known as ligand efficiency [14]. A more potent ligand with stronger binding characteristics will have a greater Ligand Efficiency [15].

The PheSA score and Ligand Efficiency have a positive association, which implies that compounds with higher PheSA scores are more likely to have superior binding efficiency. The fact that raising the PheSA score may improve ligand efficiency and maybe improve the therapeutic characteristics of the cycloguanil analogues makes this knowledge useful in the drug discovery and optimization processes.

Additionally, the following equation describes the link between the PheSA score and the binding efficiency of Cycloguanil analogues according to equation 3.

$$\text{Binding Efficiency} = (0.0078237 * \text{PheSA score}) + 0.28681 \quad \text{(Equation 3)}$$

The PheSA score and Binding Efficiency have a 0.664 Bravais-Pearson correlation coefficient.

The PheSA score and Binding Efficiency show a moderately positive link with a correlation coefficient of 0.664 (Figure 3). This shows that the Binding Efficiency tends to grow along with the PheSA score. According to the positive connection, greater PheSA scores correspond to higher values for binding efficiency.

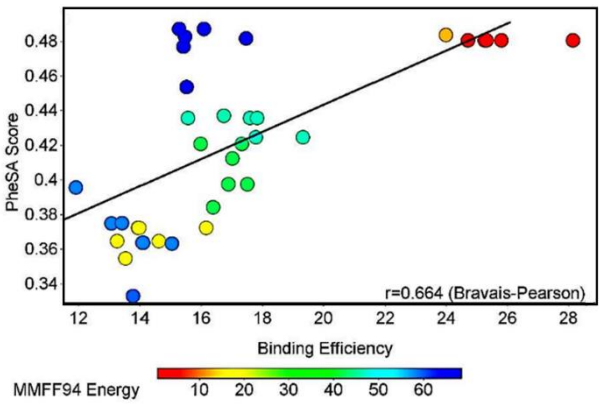

Figure 3: Relationship between PheSA score and binding efficiency

Binding Efficiency is the ligand's effectiveness in binding to its target, quantified as the binding affinity (represented by PheSA score) divided by the ligand's molecular weight [16]. Higher Binding Efficiency indicates stronger interactions and more potent compounds [17]. The positive correlation between PheSA score and Binding Efficiency suggests that increasing PheSA score could enhance binding interactions and therapeutic effects for Cycloguanil Analogues.

Finally, the relationship between the PheSA score and Surface Efficiency of Cycloguanil Analogues is described by the equation 4.

$$\text{Surface Efficiency} = (0.010995 * \text{PheSA score}) + 0.34244 \quad \text{(Equation 4)}$$

The PheSA score and Surface Efficiency show a weakly positive link with a correlation coefficient of 0.34 (Figure 4). This implies that although there isn't a particularly significant correlation, Surface Efficiency tends to rise as the PheSA score does. The positive correlation suggests a relationship between greater Surface Efficiency values and higher PheSA scores, but the connection is not very strong or constant.

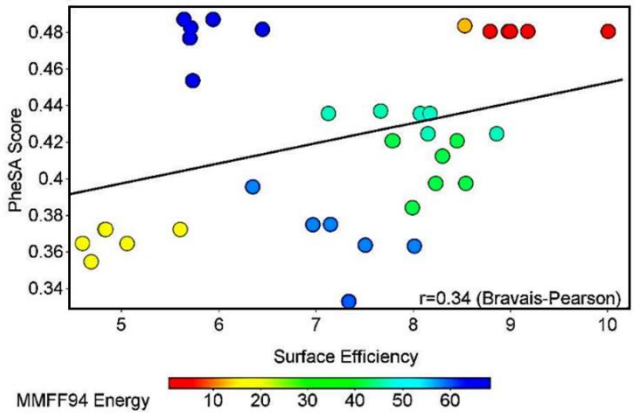

Figure 4: Relationship between PheSA score and surface efficiency

Surface Efficiency is the ligand's ability to optimize its molecular surface characteristics for efficient binding to its target [18]. It considers the ligand's surface area to molecular weight ratio, with higher values indicating optimized surface qualities for its size, potentially leading to better binding interactions [19].

The PheSA score and Surface Efficiency exhibit a small positive correlation, suggesting that compounds with higher PheSA scores tend to have slightly higher Surface Efficiency values. However, the correlation coefficient of 0.34 indicates that variations in Surface Efficiency among the Cycloguanil Analogues are influenced by factors beyond the PheSA score. Despite having slightly lower PheSA scores than the top three, these compounds still exhibit cycloguanil-like characteristics, warranting further investigation for potential antimalarial activity.

To generate new compounds with potentially superior structures, Data Warrior v5.0.0 [20] was used with a de novo design approach. DataWarrior employed an evolutionary strategy, simulating nature, by randomly modifying well-known chemical configurations with minor changes [21]. The

most advantageous structures from each generation served as starting points for subsequent generations after being evaluated for resilience using adjustable principles [22].

The mutation algorithm introduces changes like substituent migrations, ring aromatization, atom replacements, and bond order modifications [23]. Each structure undergoes a thorough assessment to gauge how changes would affect drug-likeness [24]. Mutations that align with desired directions are given greater likelihood than those diminishing drug likeness [25]. To ensure structural integrity, mutations that could result in significant ring tension are excluded. Through this process, 447 structures were created, maintaining the cycloguanil scaffold with the required fitness values (Figure S1).

The mutagenicity, tumorigenicity, reproductive effect, and irritating effects of these new structures were also tested for toxicity (Figure S2). Two hundred and fifty seven new compounds were not discovered with any related risk, for this reason.

Using the virtual screening method PheSA, the 257 new compounds were assessed for their similarity to cycloguanil (Table S2). Compounds with higher PheSA similarity scores, such as C1 to C10 (Figure S3), displayed a strong resemblance and potential as antimalarial candidates. While scores declined in C11 to C70, they still showed moderate to high similarity. Lower similarity scores were observed in C71 to C160, suggesting less resemblance but possible pharmacophoric similarities worth investigating or optimizing for future research.

Compounds C161 to C257 (Figure S3) have demonstrated lower PheSA similarity scores, indicating less structural resemblance to cycloguanil. However, it is crucial to remember that lower similarity scores do not necessarily imply inefficiency or unsuitability for antimalarial activity. These compounds may possess distinctive structural characteristics or employ various mechanisms of action that warrant investigation in the search for new drugs.

To evaluate the potential of a chemical becoming a drug candidate, drug-likeness is a crucial concept [26]. The assessment involves evaluating various physicochemical features of the molecule to determine its resemblance to well-known medications [27]. Important qualities taken into account include topological polar surface area (TPSA), number of hydrogen bond acceptors (H-Acceptors), number of hydrogen bond donors (H-Donors), and lipophilicity (cLogP). The novel compounds (Figure S3) exhibit positive cLogP values, indicating moderate lipophilicity, which is essential for drug distribution and absorption in the body [28]. Conversely, they show negative cLogS values, suggesting potential challenges in water solubility, a crucial factor for drug formulation and bioavailability [29]. The presence of three to six H-Acceptors in the new compounds (Figure S3) may imply possible interactions with target proteins but could also raise the risk of non-specific binding. Typically, the new compounds have between two and four H-Donors, indicating potential for both hydrogen bonding and binding interactions. The range of TPSA values (59.14 to 123.882) suggests increased polarity, which may facilitate interactions with biological targets. However, it is essential to acknowledge that drug-likeness assessment considers several factors beyond these characteristics, such as molecule weight, toxicity, structural warnings, and specific target requirements.

Ligand efficiency is another important consideration to enhance the effectiveness and potency of a therapeutic candidate [30]. It is determined by dividing the binding affinity by the compound's molecular weight, commonly represented by the dissociation constant, Kd [31]. Ligand efficiency seeks therapeutic candidates with high potency and low molecular weight, which can improve pharmacokinetics and minimize off-target effects [32].

Interestingly, the PheSA score and Ligand Efficiency show a strong and positive association, as indicated by the correlation coefficient (Bravais-Pearson) of 0.675. This suggests that compounds with higher PheSA scores are more likely to have higher Ligand Efficiency, offering valuable information for the search and development of effective antimalarials. However, it is essential to note that correlation does not imply causation, and Ligand Efficiency is influenced by various other factors.

While PheSA does not directly assess ligand efficiency, it can be utilized as a guide to select cycloguanil analogs with potentially advantageous ligand efficiency. For instance, if a molecule exhibits high similarity to a known active substance (e.g., Cycloguanil) according to PheSA, it indicates comparable pharmacophoric and shape aspects, suggesting potential for similar binding interactions and positive ligand efficiency.

4 Conclusions

It's crucial to realize that causality is not always implied by correlation. Ligand Efficiency may also be influenced by other factors and variables, and the PheSA score may not be the sole one, despite the statistical correlation between PheSA scores and Ligand Efficiency. The pharmacophore enhanced shape alignment (PheSA) computational method provides a useful tool for assessing the similarity of compounds based on their pharmacophoric and shape characteristics. Even while PheSA does not directly evaluate ligand efficiency, it can aid in the identification of molecules that share structural and pharmacophoric characteristics with known active substances. This might have an impact on ligand efficiency.

The main goal of virtual screening utilizing PheSA is to find molecules that are highly similar to already-known active substances. By using PheSA, scientists can give priority to Cycloguanil Analogues that resemble the reference compound closely, indicating probable shared pharmacophoric and structure properties and showing favorable ligand efficiency.

To develop a more precise and situation-specific link between PheSA and ligand efficiency, additional research and experimental studies, such as biological activity assays, are required. In spite of this, the virtual screening of cycloguanil analogs based on PheSA similarity scores offers a useful initial assessment of structural similarity, directing subsequent experimental studies towards the identification of promising substances with the potential to develop powerful antimalarial drugs.

5 Declarations

5.1 Acknowledgements

We appreciate Mrs. Agede Omolade and Mr. Oche Ambrose for their immense contribution to the success of this study.

5.2 Authors Contributions

The names of all authors listed in this work contributed equally to the conceptualization, design, manuscript writing and proof-reading.

5.3 Funding Statement

This research was not supported by any funding sources.

5.4 Conflicts of interest

The authors declare no conflict of interest.

6 Supplementary Data

Supporting information article can be accessed online.

7 References

[1] Trigg PI., Kondrachine AV. 1998. Commentary: Malaria control in the 1990s. Bulletin of the World Health Organization, 76(1), 11-16.

[2] Wells TN., Alonso PL., Gutteridge WE. 2009. New medicines to improve control and contribute to the eradication of malaria. Nature Reviews Drug Discovery, 8(11), 879-891.

[3] Na-Bangchang K., Karbwang J. 2009. Current status of malaria chemotherapy and the role of pharmacology in antimalarial drug research and development. Fundamental and Clinical Pharmacology, 23(4), 387-409.

[4] Patel AR., Patel HB., Mody SK., Singh RD., Sarvaiya VN., Vaghela SH., Tukra S. 2021. Virtual screening in drug discovery. Journal of Veterinary Pharmacology and Toxicology, 20(2), 1-9.

[5] Cavalli A., Poluzzi E., De Ponti F., Recanatini M. 2002. Toward a pharmacophore for drugs inducing the long QT syndrome: Insights from a CoMFA study of HERG K+ channel blockers. Journal of Medicinal Chemistry, 45(18), 3844-3853.

[6] Muegge I., Mukherjee, P. 2016. An overview of molecular fingerprint similarity search in virtual screening. Expert Opinion on Drug Discovery, 11(2), 137-148.

[7] Hopkins AL., Keserü GM., Leeson PD., Rees DC., Reynolds CH. 2014. The role of ligand efficiency metrics in drug discovery. Nature Reviews Drug Discovery, 13(2), 105-121.
[8] Schultes S., de Graaf C., Haaksma EE., de Esch IJ., Leurs R., Krämer O. 2010. Ligand efficiency as a guide in fragment hit selection and optimization. Drug Discovery Today: Technologies, 7(3), 157-162.
[9] Rastelli G., Pacchioni S., Sirawaraporn W., Sirawaraporn R., Parenti MD., Ferrari, AM. 2003. Docking and database screening reveal new classes of Plasmodium falciparum dihydrofolate reductase inhibitors. Journal of Medicinal Chemistry, 46(14), 2834-2845.
[10] Evbuomwan IO., Alejolowo OO., Elebiyo TC., Nwonuma CO., Ojo OA., Edosomwan E. U., 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 and Dynamics, 1-18.
[11] Gupta R., Srivastava D., Sahu M., Tiwari S., Ambasta RK., Kumar P. 2021. Artificial intelligence to deep learning: Machine intelligence approach for drug discovery. Molecular Diversity, 25, 1315-1360.
[12] El-Shamy NT., Alkaoud AM., Hussein RK., Ibrahim MA., Alhamzani AG., Abou-Krisha, MM. 2022. DFT, ADMET and Molecular Docking Investigations for the Antimicrobial Activity of 6, 6′-Diamino-1, 1′, 3, 3′-tetramethyl-5, 5′-(4-chlorobenzylidene) bis [pyrimidine-2, 4 (1H, 3H)-dione]. Molecules, 27(3), 620.
[13] Tijjani H., Olatunde A., Adegunloye AP., Ishola, AA. 2022. In silico insight into the interaction of 4-aminoquinolines with selected SARS-CoV-2 structural and nonstructural proteins in Coronavirus Drug Discovery (pp. 313-333). Elsevier.
[14] Abad-Zapatero C. 2007. Ligand efficiency indices for effective drug discovery. Expert Opinion on Drug Discovery, 2(4), 469-488.
[15] Murray CW., Carr MG., Callaghan O., Chessari G., Congreve M., Cowan, S. 2010. Fragment-based drug discovery applied to Hsp90. Discovery of two lead series with high ligand efficiency. Journal of Medicinal Chemistry, 53(16), 5942-5955.
[16] Copeland RA., Pompliano DL., Meek, T. D. 2006. Drug–target residence time and its implications for lead optimization. Nature Reviews Drug Discovery, 5(9), 730-739.
[17] Duarte AR., Cadoni E., Ressurreição AS., Moreira R., Paulo, A. 2018. Design of Modular G-quadruplex Ligands. ChemMedChem, 13(9), 869-893.
[18] Li GB., Yang LL., Wang WJ., Li LL., Yang SY. 2013. ID-Score: A new empirical scoring function based on a comprehensive set of descriptors related to protein–ligand interactions. Journal of Chemical Information and Modeling, 53(3), 592-600.
[19] Kilina S., Ivanov S., Tretiak S. 2009. Effect of surface ligands on optical and electronic spectra of semiconductor nanoclusters. Journal of the American Chemical Society, 131(22), 7717-7726.
[20] Sliwoski G., Kothiwale S., Meiler J., Lowe EW. 2014. Computational methods in drug discovery. Pharmacological reviews, 66(1), 334-395.
[21] Coghlan A., Padalino G., O'Boyle, NM., Hoffmann KF., Berriman M. 2022. Identification of anti-schistosomal, anthelmintic and anti-parasitic compounds curated and text- mined from the scientific literature. Wellcome Open Research, 7.
[22] Fedorov RG., Maletti S., Heubner C., Michaelis A., Ein-Eli Y. 2021. Molecular Engineering Approaches to Fabricate Artificial Solid-Electrolyte Interphases on Anodes for Li-Ion Batteries: A Critical Review. Advanced Energy Materials, 11(26), 2101173.
[23] Sruthi CK., Balaram H., Prakash MK. 2020. Toward developing intuitive rules for protein variant effect prediction using deep mutational scanning data. ACS Omega, 5(46), 29667-29677.
[24] Ragoza M., Masuda T., Koes DR. 2022. Generating 3D molecules conditional on receptor binding sites with deep generative models. Chemical Science, 13(9), 2701-2713.
[25] Ursu O., Rayan A., Goldblum A., Oprea TI. 2011. Understanding drug-likeness. Wiley Interdisciplinary Reviews: Computational Molecular Science, 1(5), 760-781.
[26] Daina A., Michielin O., Zoete V. 2017. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, 7(1), 42717.
[27] Chillistone S., Hardman JG. 2017. Factors affecting drug absorption and distribution. Anaesthesia & Intensive Care Medicine, 18(7), 335-339.
[28] Stegemann S., Leveiller F., Franchi D., De Jong H., Lindén, H. 2007. When poor solubility becomes an issue: From early stage to proof of concept. European Journal of Pharmaceutical Sciences, 31(5), 249-261.
[29] Corral MG., Leroux J., Stubbs KA., Mylne JS. 2017. Herbicidal properties of antimalarial drugs. Scientific Reports, 7(1), 45871.

[30] Ferenczy GG., Keserű GM. 2016. Ligand efficiency metrics and their use in fragment optimizations. Fragment-based Drug Discovery Lessons and Outlook, 75-98.
[31] Leeson PD., Young RJ. 2015. Molecular property design: Does everyone get it?. ACS Medicinal Chemistry Letters, 6(7), 722-725.
[32] Sastry GM., Dixon SL., Sherman W. 2011. Rapid shape-based ligand alignment and virtual screening method based on atom/feature-pair similarities and volume overlap scoring. Journal of Chemical Information and Modeling, 51(10), 2455-2466.