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In Silico Pharmacokinetic and Toxicological studies of Novel Trizole Derivatives as Potential Antifungal drug candidates

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Abstract

Given the growing problem of invasive mycoses and the emergence of antifungal drug resistance, new agents with improved in vivo properties and safety are needed. In the past, potent scaffolds were previously identified by preforming quantitative structure-activity relationship (QSAR) and docking analysis. Their pharmacokinetic and toxicity properties were evaluated in this study by ADMET profiling. The selected analogues were comprehensively assessed in silico for their pharmacokinetic and toxicity characteristics using the SwissADME and ADMETlab 3.0 web platforms. The water solubility, lipophilicity, physicochemical parameters, and pharmacokinetic parameters, drug likeliness, medicinal chemistry parameters and toxicity of the compounds were systematically studied to identify the potential leads for antifungal development. The investigated compounds were found to have molecular weights ranging from 402.42 to 475.29 g/mol, topological polar surface area (TPSA) ranging from 81.65Å^2 to 109.89Å^2, and consensus LogP between 2.68 and 4.23, which are good physicochemical properties of orally active compounds. SwissADME predicted high gastrointestinal absorption for all compounds and none to traverse the blood-brain barrier. All the compounds met the Lipinski, Ghose, Veber, Egan and Muegge drug-likeness criteria, had a bioavailability score of 0.55 and were devoid of PAINS and Brenk structural alerts indicating good medicinal chemistry properties. Analysis of water solubility showed that compounds 37 and 38 had relatively high-water solubility compared to the other compounds. The toxicity prediction in ADMETlab 3.0 showed satisfactory safety profiles with relatively low predicted hERG inhibition and no serious acute toxicity issues. Compounds 33 and 37 were selected as potential antifungal lead compounds based on the comprehensive evaluation of the pharmacokinetic and medicinal chemistry parameters and toxicity profile.

1. INTRODUCTION

As invasive fungal infections and the emergence of antifungal treatment resistance in immunocompromised patients have become a large health problem around the world, fungal infections are now a serious global health threat. The World Health Organisation (WHO) has focussed on the development of new, effective and safer antifungal drugs, recognizing this threat [1-3]. Cryptococcus neoformans is an opportunistic fungus which causes cryptococcosis, a potentially fatal lung and central nervous system infection, among the priority pathogens. Current antifungal treatments have their drawbacks, such as toxicity, long-term usage, and the development of resistant strains, making the need for new treatments more pressing [4,5]. Computer-aided drug design (CADD) has become a successful approach to speed up discovery of antifungals. Using the technique of QSAR, the characteristics among the molecules which are correlated with biological activity are identified, and molecular docking serves to predict the activity of a molecule on a target, which is key to the rational drug design and refinement of candidate antifungal compounds [6-8]. It is just as significant to assess the absorption, distribution, metabolism, excretion and toxicity (ADMET) attributes at an early stage to

minimize the attrition of drugs during late stages. Platforms like SwissADME and ADMETlab allow for a fast evaluation of physicochemical characteristic's, pharmacokinetics profile, drug-likeness and toxicity, helping to choose compounds with good pharmacological profiles [21].

In our previous research [13], we have previously evaluated some triazole derivatives via docking and QSAR analysis. In that study, structurally interesting scaffolds with good binding affinity towards the fungi targets were identified, and important physicochemical properties related to antifungal properties were identified. The docking results gave indications of the interactions between the docked molecules, and the QSAR modeling gave indications to the correlation between structural descriptors and biological activity. These results provided a rational approach for screening compounds with increased antifungal activity.

The present study was aimed to screen a library of potential antifungal lead compounds against Sgl1 of C. neoformans using the integrated CADD approach, building on this basis. The derivatives of the triazole were designed to be a continuation of our previous design and optimization studies in the series of previously reported antifungal compounds. The activity and binding potential are crucial, but the efficacy of any candidate as a therapeutic agent relies on its pharmacokinetics and safety profile. As a result, the in-silico assessment of ADMET properties was conducted as well as the aforementioned QSAR and docking.

The information generated by ADMET profiling is vitally important for drug likeness, bioavailability and risk of toxicity for lead optimization. These parameters can be computed and the drug's liability can be detected early in pharmaceutical development, which decreases the attrition rate at a subsequent phase. The present study aimed to evaluate to build a comprehensive framework that combines the evaluation of the ADMET properties with prior activity and binding data in order to assess the therapeutic potential of triazole derivatives against Sgl1. This would enhance the translational significance of identified compounds, and help towards the wider aim of developing effective antifungal agents that are safer and have better PK properties [9-12].

2. MATERIAL AND METHODOLOGY

2.1 Data Set selection and preparation

Based on our previous work reported in the study, the current study was designed to screen the library of possible antifungal lead compounds against sterylglucosidase (Sgl1) of Cryptococcus neoformans using the integrated computer aided drug design (CADD) approach [13]. The shortlisted 30 triazole derivatives based on the docking were tested for ADMET. The molecular structures of the selected compounds were redrawn in 2D form to ensure the accuracy and consistency of the structures using the ChemDraw Ultra version 8.0.3 [14]. The three Dimension molecular structures were then created and geometrically optimized by the help of Chem 3D Ultra version 8.0.3 [15]. The energy minimization was performed to find the structural conformation for the stable one that can be used for computation. All subsequent pharmacokinetic and toxicity prediction studies were performed with the optimized molecular structures. using computer software, namely SwissADME. Determination of the drug's pharmacological properties

2.2 In Silico Pharmacokinetic Evaluation Using SwissADME

All compounds were molecularly optimized and then subjected to comprehensive evaluation of the physicochemical, pharmacokinetic, drug-likeness, medicinal chemistry and toxicity properties using the freely available SwissADME web server and ADMETlab 3.0 [9,21]. As the main in silico evaluation tool, SwissADME was used to prioritize compounds with good oral drug-like properties, which was helpful for identifying a total of potential therapeutic candidates for the fungi. Physicochemical properties: MW, HBA, HBD, TPSA, RB, and molar refractivity (MR). The water dissolution capacity was estimated employing ESOL, Ali, and SILICOS-IT models, and its lipophilicity was assessed using the Consensus LogP model, which is based on five independent models: iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT. GI, BBB barrier penetration, log Kp, and P-gp substrate status displayed also estimated, as were the ability to CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 inhibit this enzymes. The drug-likeness was analysed with the aid of drug likeness criteria, medicinal chemistry filters, bioavailability score, synthetic accessibility were also discussed. In addition, the suitability of the studied compounds and their possible drug-like features were examined by the assessment of the above-mentioned toxicity endpoints on the ADMETlab 3.0 platform. These computational parameters were all combined to determine compounds with desirable PK properties and reasonable medicinal chemistry features to pursue further in the development of antifungal drugs.

2.3 Toxicity Prediction Using ADMETlab 3.0

In combination with the pharmacokinetic assessment, toxicity prediction was carried out using the comprehensive online systematic prediction platform ADMETlab 3.0, which uses machine learning methods [12]. The construction of the original ADMETlab platform to the present version has enhanced the platform with a wider range of chemicals, greater prediction accuracy, API functionality and decision-support capabilities [10]. The toxicity assessment comprised prediction of DILI, hepatotoxicity, Ame's test prediction, skin sensitization, LD50 and hERG potassium channel inhibition. These parameters were employed to estimate the overall Safety Profiles of the designed compounds and together with the SwissADME predictions were included in the Lead Identification.

2.4 The ADMET parameters were accessed

In silico ADMET analysis tools were used to evaluate the studied compounds for their physicochemical and pharmacokinetic profiles – TPSA, HBA and HBD, LogP models, Water solubility property- (ESOL, Ali and SILICOS-IT), GI Absorption, BBB, medicinal resemblance, cheminformatics rules and ability to interact with P-gp and CYP450 enzymes.
The molecular information for the selected compounds including molecular formula and SMILES representation is shown in table 1 [13].

Table 1: Molecular Details of the Promising Compound

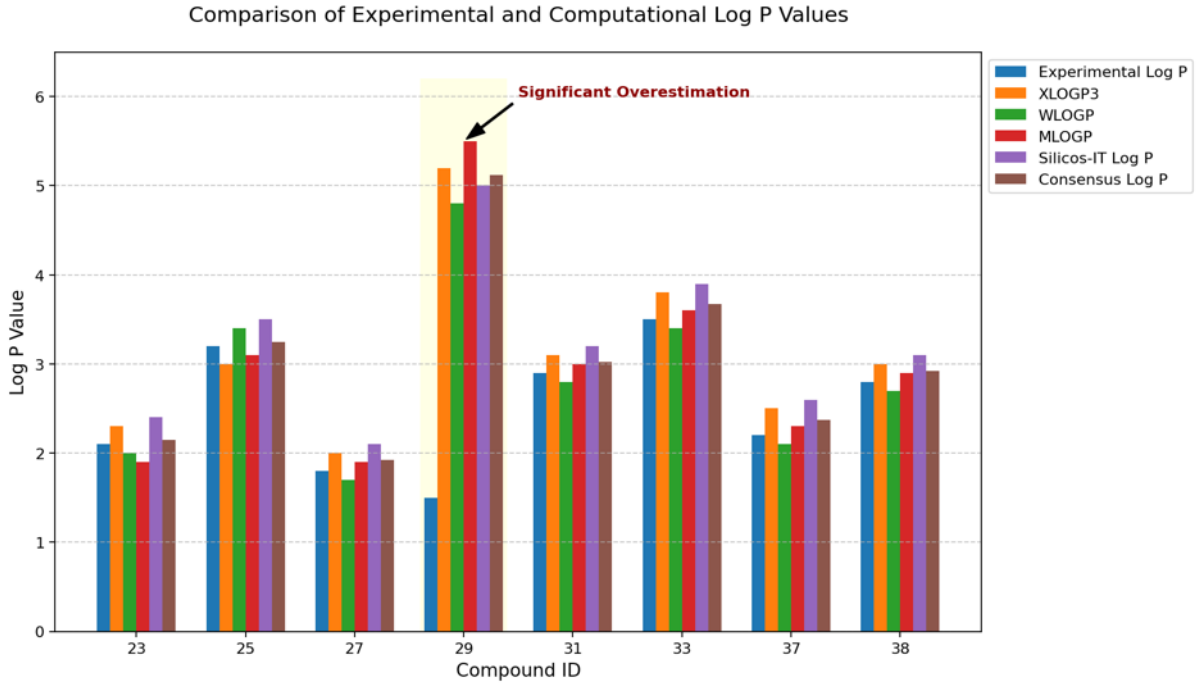
S. No.	Compound no (as per previously reported paper)	Molecular Formula	Canonical Smiles Notation
1	23	C21H21F2N6O	Cc1ccc(-c2cn([C@@H] (C)[C@] (O)(Cn3cncn3) c3ccc(F)cc3F) nn2) cc1
2	25	C25H29F2N6O	CCCCc1ccc(-c2cn([C@@H] (C)[C@@] (O) (Cn3cncn3) c3ccc(F)cc3F) nn2) cc1

3	27	C19H18F3N6O	C[C@@H] (n1cc(-c2cccc(F)cc2) nn1) [C@] (O)(Cn1cncn1) c1ccc(F)cc1F
4	29	C19H18F3N6O	C[C@@H] (n1cc(-c2ccccc2F) nn1) [C@] (O)(Cn1cncn1) c1ccc(F)cc1F
5	31	C19H18ClF2N6O	C[C@@H] (n1cc (-c2cccc (Cl)c2) nn1) [C @] (O)(Cn1cncn1) c1ccc(F)cc1F
6	33	C19H18BrF2N6O	C[C@@H] (n1cc (-c2ccc (Br)cc2) nn1) [C @] (O)(Cn1cncn1) c1ccc(F)cc1F
7	37	C17H17F2N6OS	C[C@@H] (n1cc(-c2cccs2) nn1) [C@] (O)(Cn1cncn1) c1ccc(F)cc1F
8	38	C17H17F2N6OS	C[C@@H] (n1cc(-c2ccsc2) nn1) [C@] (O)(Cn1cncn1) c1ccc(F)cc1F

3. RESULTS

3.1 Lipophilicity Analysis

Lipophilicity is an essential factor of membrane permeability, metabolic stability, and toxicity. The Consensus LogP values of the designed eight triazole derivatives (Compounds 23, 25, 27, 29, 31, 33, 37, 38) were predicted by SwissADME and plotted in Graph 1. The lipophilicity values were found to be in the range of 2.68 to 4.23 and all the compounds have moderate lipophilicity which is favourable for oral drug candidates. Moderate lipophilicity results in passive diffusion across biological membranes with a satisfactory aqueous solubility/membrane permeability balance. Compound 25 had the highest Consensus LogP value (4.23) indicating higher membrane permeability but higher lipophilicity can also lead to higher metabolic liability, which might decrease the aqueous solubility. Compounds 27, 29 and 31 had Consensus LogP values around 3.0, which is an optimum hydrophilic/hydrophobic balance, and can be correlated to good drug-like properties. Importantly, all the derivatives complied with Rule of Five criteria (LogP < 5), which suggests favourable oral absorption and appropriate for further development of antifungal drugs. The overall, the lipophilicity profile reveals that the compounds designed have physicochemical characteristics suitable for successful oral bioavailability and further pharmacokinetic and biological assessment of the compounds are warranted [9,11,16-18].



Graph 1. The designed triazole derivatives were designed with the lipophilicity (Consensus LogP) profile.

3.2 Physicochemical Properties

The designed compounds have been shown in the physicochemical properties in the hexagonal diagram (Figure 1) and a tabulated summary (Table 2) of the quantitative data. The parameters examined are MW, HBD, HBA, TPSA, RB. All the compounds fulfilled standard oral drug likeness criteria and thus showed good drug-like characteristics. The compounds exhibited Molecular weights ranging from 402 - 475 g/mol which was within the acceptable range for orally active molecules. All derivatives had one HBD = 1,

HBA= 7-8 within the recommended spanned for the number of HBA of H- bonding capacity. The TPSA values (81.65–109.89 Å²) were smaller than 140 Å², which indicated that the intestinal absorption of the compounds was promising, and the number of RB was moderate, showing a moderate degree of flexibility in the molecule. In general, the physicochemical parameters shown in the hexagonal diagram indicate that all the designed compounds are druglike and would be suitable for further pharmacokinetic characterization in terms of their favourable oral bioavailability properties, as they pass medicinal chemistry screening standards [9].

Table 2: Physicochemical and Molecular Characteristics of the Selected Compound

Compound	MW	RB	HBA	HBD	TPSA	MR
23	410.42	6	7	1	81.65	105.92
25	452.5	9	7	1	81.65	120.34
27	414.38	6	8	1	81.65	100.91
29	414.38	6	8	1	81.65	100.91
31	430.84	6	7	1	81.65	105.96
33	475.29	6	7	1	81.65	108.65
37	402.42	6	7	1	81.65	98.83
38	402.42	6	7	1	109.89	98.83

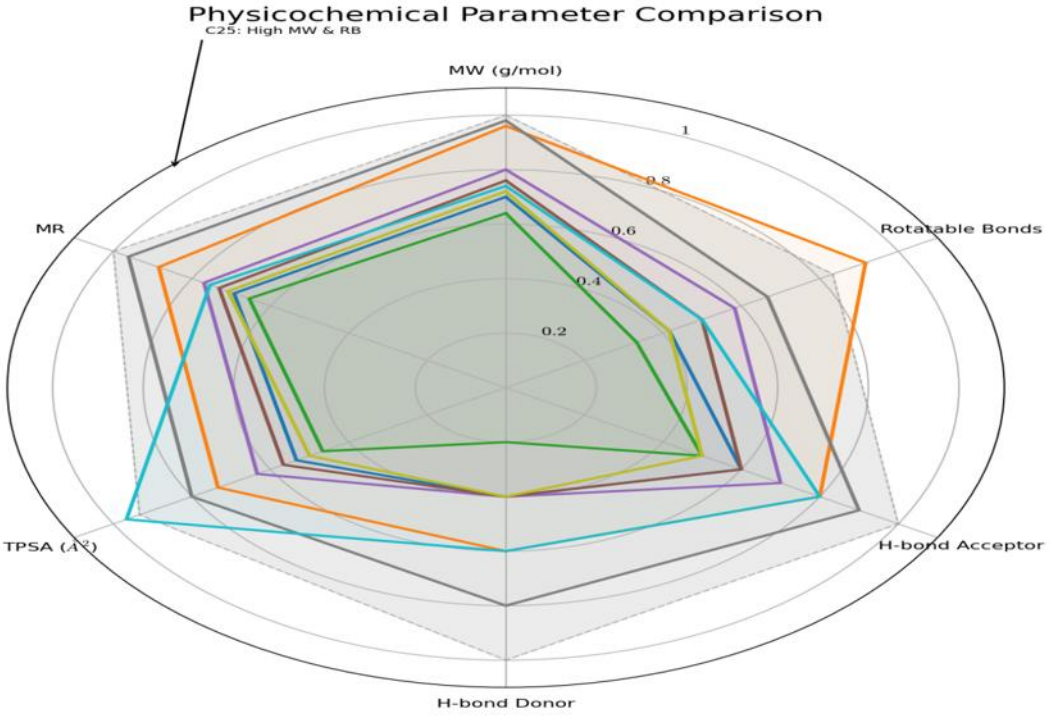
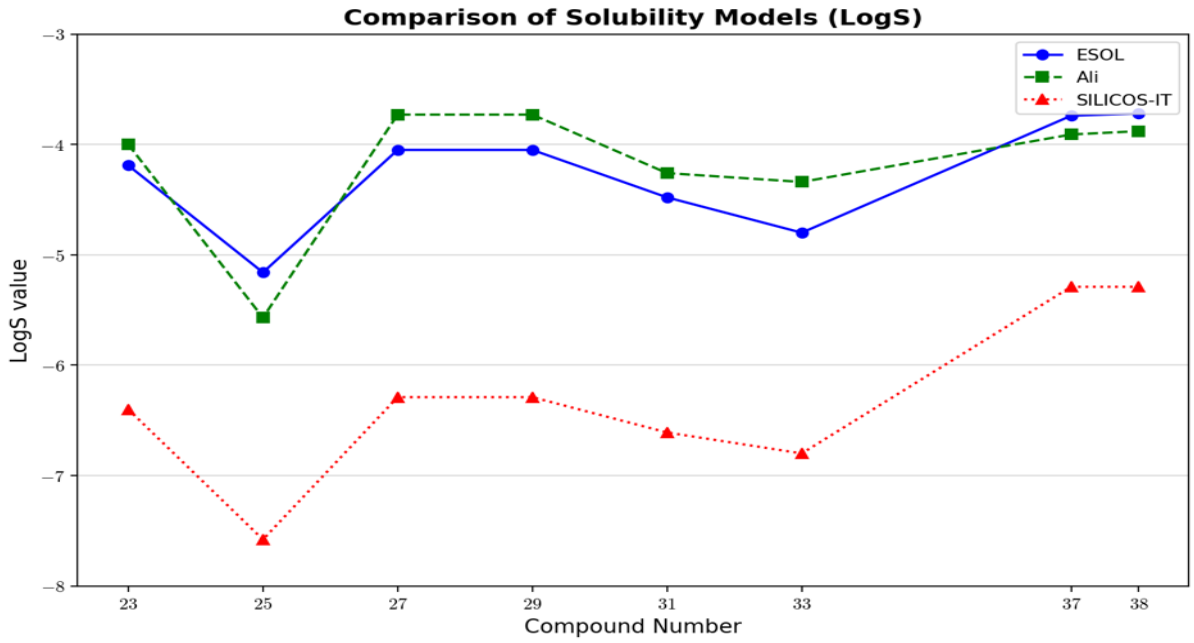


Figure 1. The physicochemical properties of the designed triazole derivatives were presented in the hexagonal form

3.3 Water Solubility Assessment

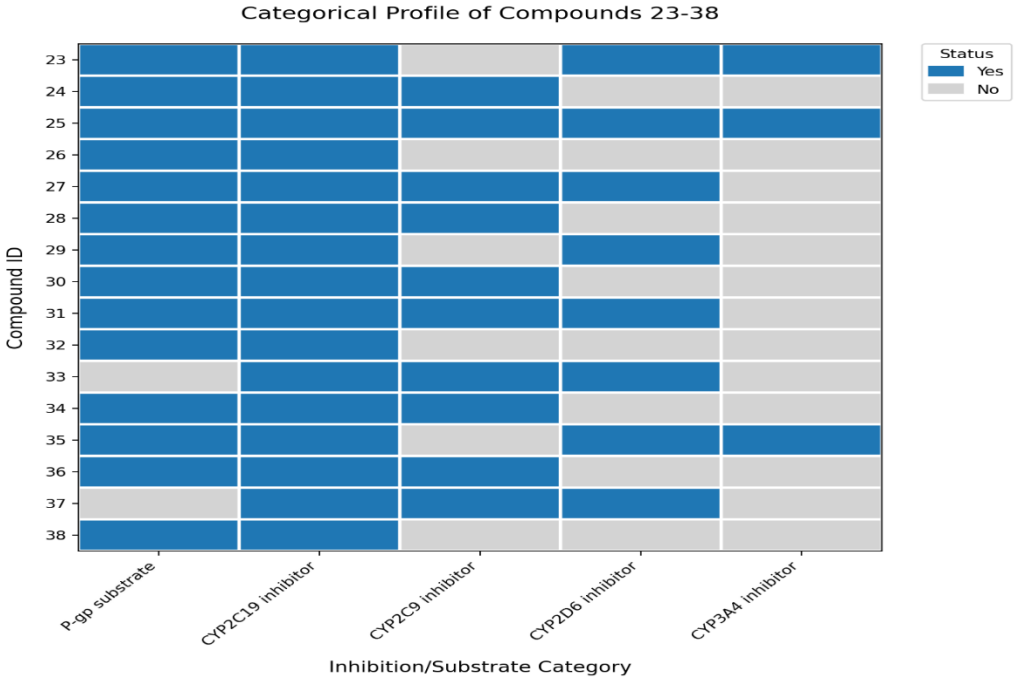
The water solubility profiles of designed triazole derivatives (23, 25, 27, 29, 31, 33, 37, and 38) were predicted using the ESOL, Ali, and SILICOS-IT prediction models, and depicted in Graph 2. This result revealed marked variations across the aqueous solubility of compounds. The ESOL model predicted that compounds 37 and 38 would be soluble while compounds 23, 25, 27, 29, 31, and 33 would be moderately soluble. In the same way, Ali predicted the compounds 23, 27, 29, 37, and 38 as soluble, while compounds 25, 31, and 33 were predicted as moderately soluble. The SILICOS-IT model classified compounds 23, 25, 27, 29, 31 and 33 as poorly soluble, and compounds 37 and 38 as moderately soluble. The aqueous solubility predictions of all the derivatives showed the lowest predicted value for compound 25, which has a higher lipophilicity, and the highest predicted value for compounds 37 and 38. Graph 2 confirms the inverse correlation between water solubility and lipophilicity which is common in the physicochemical properties of compounds, and that a compound's lower lipophilicity is associated with an improved aqueous solubility profile, which could lead to improved dissolution properties for oral drug delivery.



Graph 2. Prediction of the water solubility profile of the designed triazole derivatives using the models ESOL, Ali and SILICOS-IT

3.4 Pharmacokinetic Prediction

The designed triazole derivatives predicted pharmacokinetic properties are GI absorption, BBB permeability, P-gp substrate potential, CYP450 inhibitory activity, and log Kp as shown in Graph 3. The GI absorption for the investigated compounds were estimated to be high, which means that they have favourable oral bioavailability. None of the derivatives was predicted to be BBB permeant indicating less chance for central nervous system exposure. As for P-gp substrate prediction, compounds 33 and 37 were determined to not be P-gp substrates, while the other derivatives were all predicted to act as P-gp substrates propensity. All of the chemical entities were predicted as to supress CYP2C19, and none were predicted to inhibit CYP1A2, by means of cytochrome P450 inhibition profiling. Compound 25 was the widest range of CYP enzymes and was found to supress CYP450 isoenzymes, suggesting the potential for significant metabolism mediated pharmacological interactions. In contrast, compounds 27, 29, 31, 33, 37 and 38 only inhibited CYP2C19, which indicated a low risk of CYP-mediated interaction. The log Kp values predicted for the derivatives ranged from −6.11 to −7.37 cm/s which implies low skin permeability for all the derivatives. In general, Graph 3 shows that the compounds designed in this study have desirable pharmacokinetic characteristics, including high oral absorption, poor BBB-permeability, and the dissimilarities in the CYP inhibition properties will facilitate the prediction of the metabolic behaviour for the compounds.

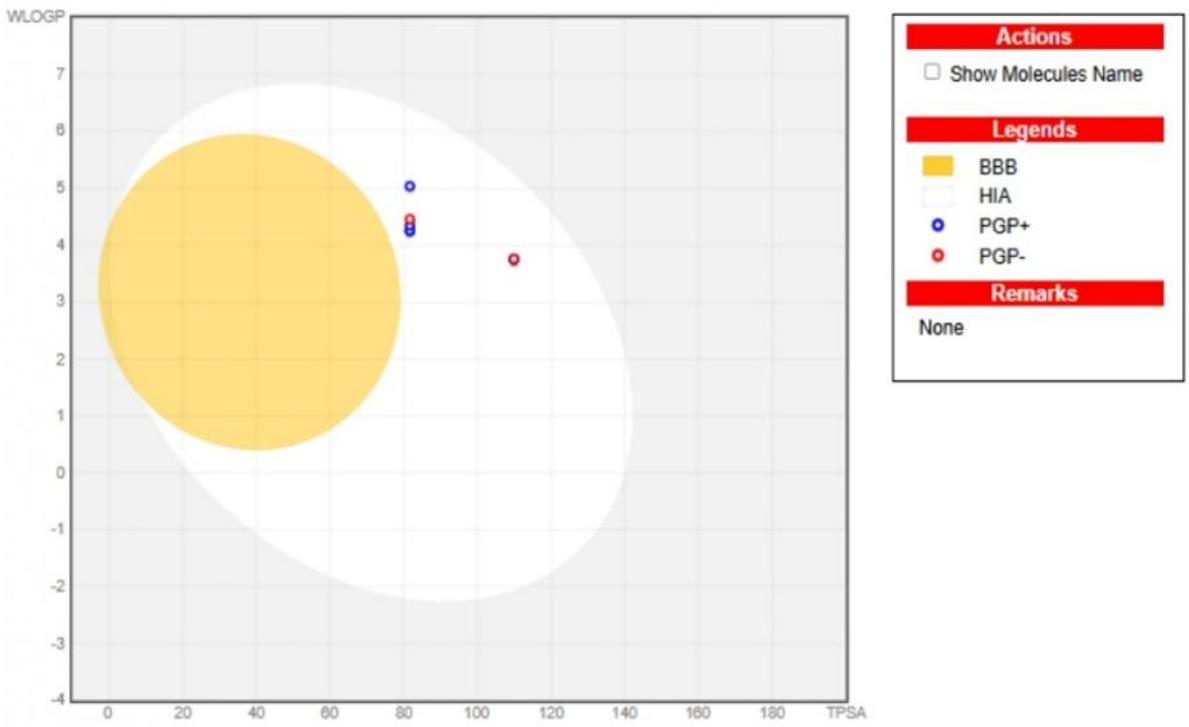


3.5 BOILED-Egg diagram analysis

BOILED-Egg diagram generated using SwissADME showing all compounds, the compounds were localized in the white area,

which exhibits high possibility of passive GI absorption and the absence of localization in the yolk area was a sign of non-permeability of the BBB. These results indicate favourable oral absorption with limited central nervous system penetration, reducing potential CNS-related adverse effects [9].

Figure 2. Boiled Egg diagram of the compound 23,25,27,29,31,33,37,38



3.6 Analysis of Bioavailability radar diagram

The bioavailability radar was constructed using SwissADME software for evaluating the oral drug-likeness profile of the investigated compounds based on 6 important physicochemical properties: LIPO, SIZE, POLAR, INSOLU, INSATU and molecular FLEX. The highlighted region displays the desirable range of the physicochemical properties that lead to favourable oral pharmacokinetic profile, with the highlighted polygonal region showing the features for each individual compound. Molecules with most of their radar plot in the pink area are more likely to have good oral absorption and acceptable pharmacokinetics. The bioavailability radar profiles for compounds 23, 25, 27, 29, 31, 33, 37, and 38 were similar and covered the major part of the optimal physicochemical space (see Figure 3). All the compounds exhibited MW, XLOGP3, TPSA, conformational flexibility and water solubility within the recommended ranges for potential oral therapeutics potential, meeting that established drug-likeness guidelines. The results from the designed molecules indicate a proper balance between membrane permeable and aqueous soluble properties which are both necessary for a good gastrointestinal absorption.

The deviation was seen in some compounds especially in 29, 31 and 38 compounds with lower percentage of sp^3 hybridized carbons than their optimal range, which is the parameter of INSATU (saturation). This is due to the multiple aromatic rings present in the molecular structures, which give them relatively higher molecular planarity. The difference in saturation may affect aqueous solubility or metabolic stability to some degree, but this is often seen in aromatic heterocyclic drug candidates and is not a major concern if the other physicochemical parameters are within the optimal region with respect to bioavailability. The results of overall bioavailability radar analysis indicated that the synthesized compounds have good physicochemical properties suitable for oral drug delivery. The close similarity of the radar profiles to optimal bioavailability space indicates that these molecules exhibit desirable drug-like characteristics and have been predicted to exhibit adequate absorption and pharmacokinetic properties. Thus, the designed compounds are potential lead compounds for subsequent biological evaluation and refinement.

Figure 3

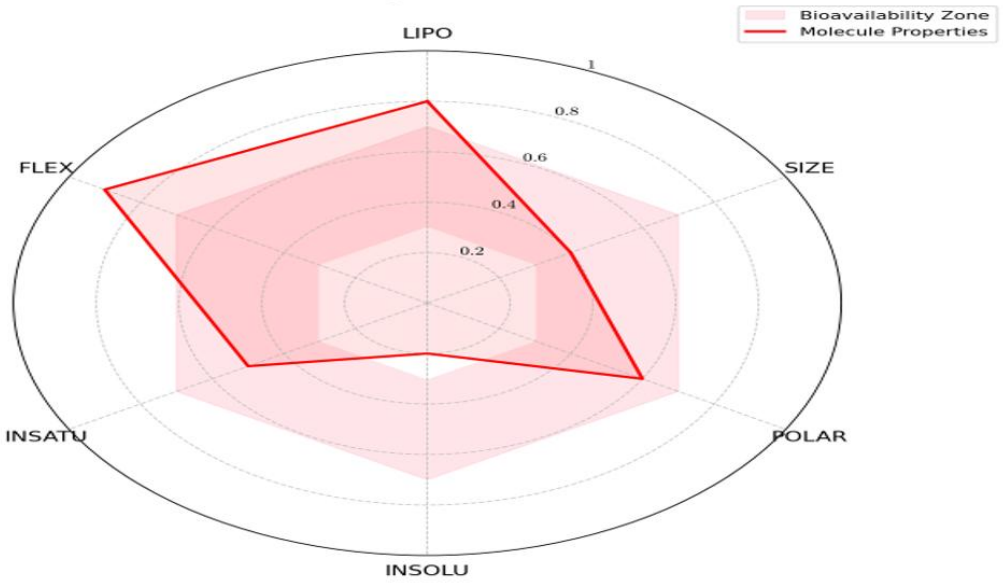
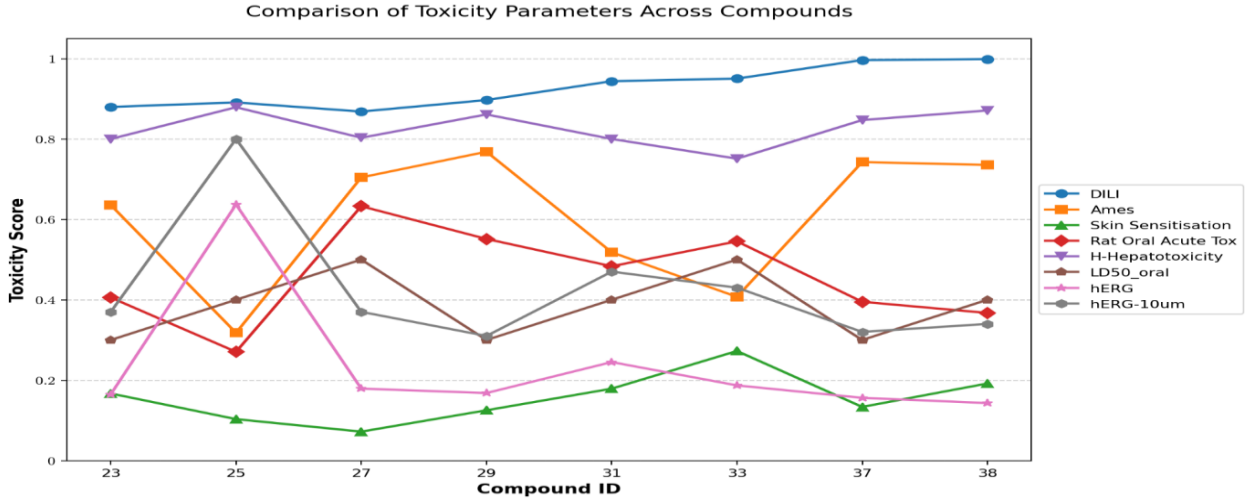


Figure 3. depicts the bioavailability radar profiles of compounds 23,25,27,29,31,33,37,38 illustrating their oral drug-likeness based on six key physiochemical parameters

3.7 Toxicological Risk Evaluation

The designed triazole derivatives toxicity profiles are predicted by Graph 4, which includes the following toxicity categories: DILI, Ame's mutagenicity, Skin sensitisation, Hepatotoxicity, LD50, hERG inhibition. The hepatotoxicity risk for the compounds was predicted using different probabilities of DILI (0.8682 to 0.9987). The lowest DILI predicted probabilities were found for compounds 27 and 23, while compounds 37 and 38 had the highest values. All derivatives were not mutagenic in the Ames test, indicating low potential for mutagenicity. Likewise, all compounds were predicted to be low skin sensitiser and low hepatotoxic, confirming as safe compounds. The rat oral acute toxicity (LD_{50}) values were predicted and ranged from 0.751 to 0.879, which is acceptable. In evaluating for hERG inhibition, compound 25 was found to have the highest hERG inhibition (0.637) making it a comparatively higher risk for QT interval prolongation and cardiac adverse effects. Compounds 27, 29, 31, 33, 37 and 38, on the other hand, had lower hERG inhibition values, suggesting a lower risk of cardiotoxicity. Overall, the designed triazole derivatives have a promising predicted toxicity profile as shown in Graph 4, including low mutagenicity, low skin sensitisation potential, low acute toxicity and generally low cardiotoxic potential, making them suitable for further preclinical evaluation.

Graph 4. Toxicity Prediction of the Novel Triazole Derivatives



3.8 Assessment of Drug-Likeness and Medicinal Chemistry Characteristic's

The designed drug-like triazole derivatives drug-likeness coverage and bioavailability hexagon is shown in figure 4. There were no violations found for the major filters of drug-likeness for all that compounds. Moreover, the entire set of derivatives showed bioavailability score of 0.55 which is a good score for favourably oral bioavailability and these are good candidates for orally active drug candidates. The relationship of lead-likeness violations vs. synthetic accessibility of designed compounds is shown in Graph 5. None of the derivatives had any PAINS or any of the structural

alerts found in the Brenk database, which are commonly linked to false-positive biological activity or toxicity. The average number of violations of lead-likeness was found to be 1 in most compounds while compound 25 had 3 lead-likeness violations and indicated comparatively lower lead-likeness. The compounds exhibited synthetic accessibility values spanned 4.07 - 4.55, which means all the compounds are moderately complex and are considered as laboratory synthesis.

The comparison of the synthetic accessibility scores for the designed triazole derivatives are shown in Graph 6. The score difference was very small, ranging from 4.07 to 4.55, which indicates the synthetic feasibility of the compounds were also similar. The highest synthetic accessibility score was obtained for compound 25 (4.55) which means that it has higher synthetic complexity while the lowest score was obtained for compound 38 (4.07) which means that the synthesis of this compound is comparatively easier. In summary, the designed triazole derivatives exhibit moderate synthetic accessibility, favourable drug-likeness profiles, acceptable bioavailability scores, and the absence of PAINS and Brenk alerts suggest their suitability for further optimization and experimental testing.

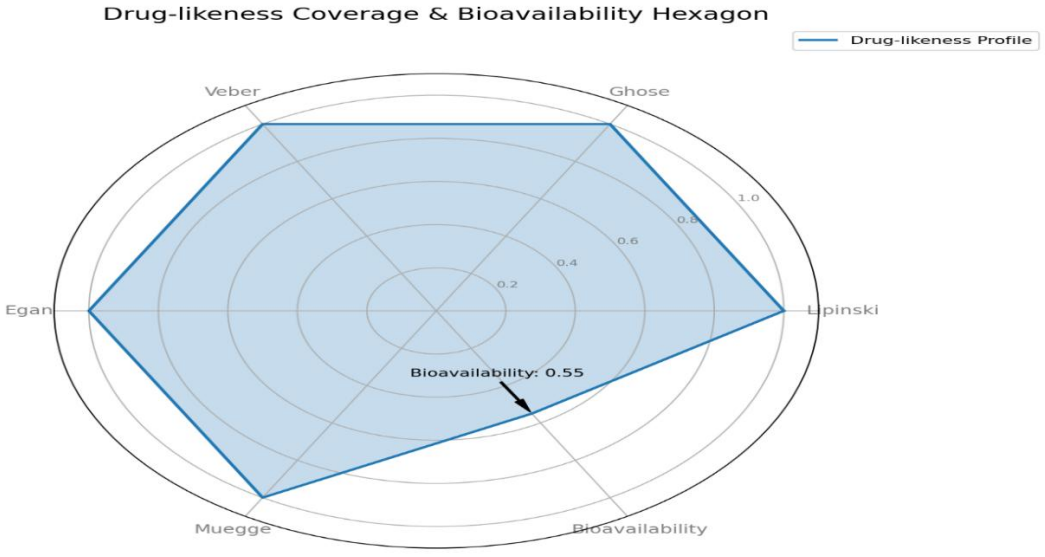
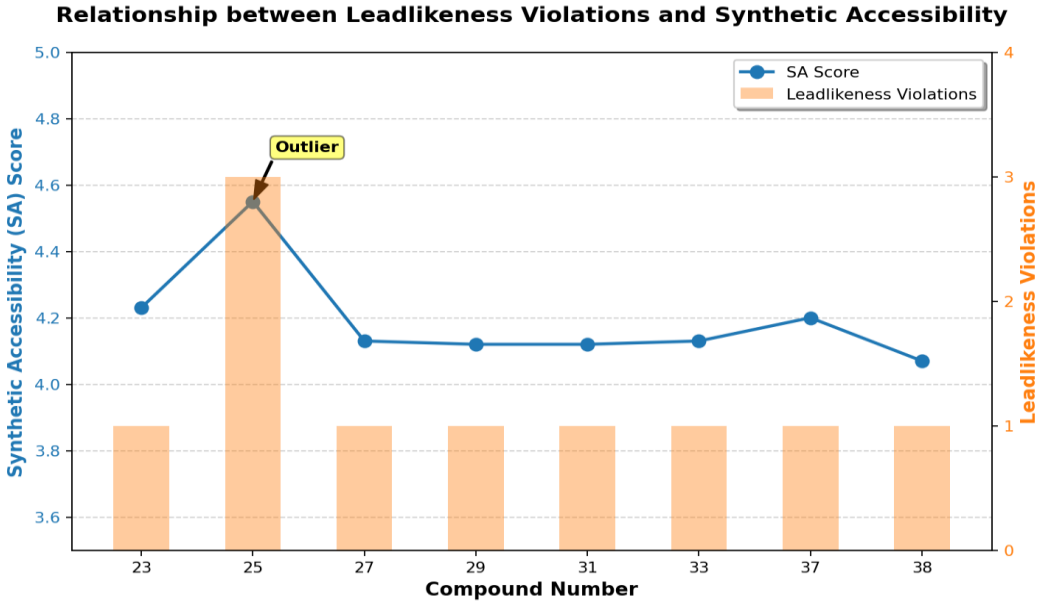
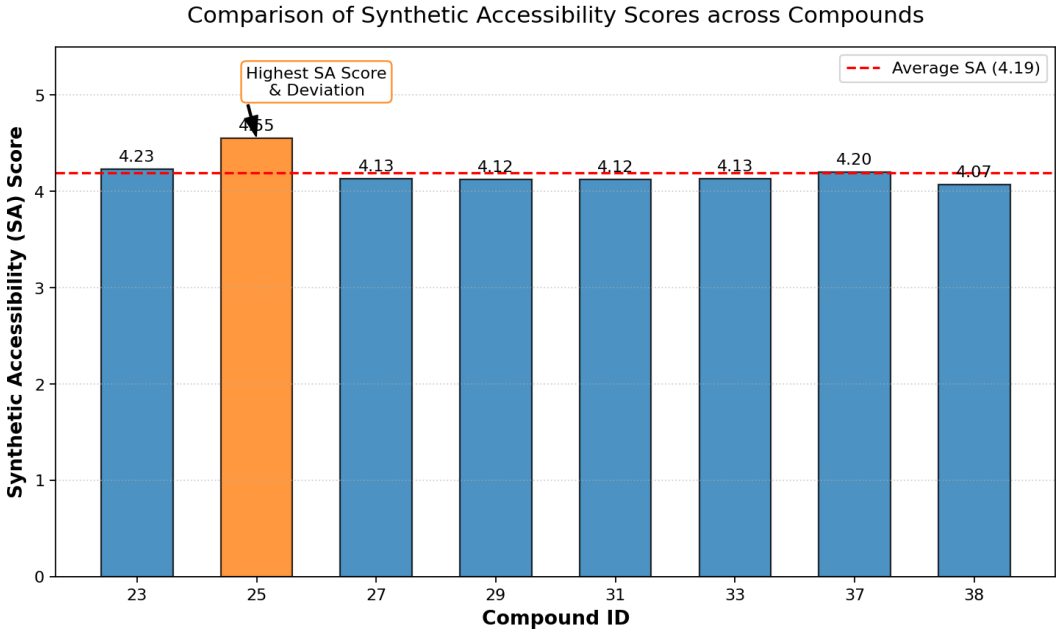


Figure 4. Designed Triazole Derivatives Hexagon of the Drug-Likeness Coverage and Bioavailability



Graph 5. The relationship between lead-likeness violation and synthetic accessibility of designed triazole derivatives



Graph 6. The Synthetic Accessibility Scores for the Designed Triazole Derivatives were compared

The evaluation of designed Antifungal compounds through ADME and ADMET studies using in silico approaches

Computer aided assessment of ADME and toxicity has become an integral part of the drug discovery within the pharmaceutical research today, allowing the compound to be evaluated for its pharmacokinetic properties, drug-likeness, and toxicity before experimental testing takes place. Minimizing the risk of late-stage failure, cutting down development costs and speeding up lead optimization with early computational assessments of compounds that have desirable ADMET properties. In the current study, two computational platforms, SwissADME and ADMETlab 3.0, were used as complementary tools for the complete assessment of the designed antifungal agents. Physicochemical properties, lipophilicity, aqueous solubility, pharmacokinetic parameters and drug-likeness parameters were predicted by SwissADME while advanced machine learning-based models of ADMETlab 3.0 were applied to estimate the ADMET endpoints. These in computational tools were combined in an integrated manner, allowing systematic prioritization of compounds with desirable properties for drug-like behaviour and safety for further biological and experimental study as potential lead candidates for use in the development of antifungal drugs.

4. LEAD IDENTIFICATION

Physicochemical, pharmacokinetic, pharmaceutical likeness, therapeutic chemistry and toxicity traits predicted by SwissADME and ADMETlab 3.0 were integrated to identify lead. The candidates were selected according to the molecular weight, consensus lipophilicity, aqueous solubility, GI absorption, BBB permeability, CYP450 interaction profile, drug-likeness criteria, medicinal chemistry properties, synthetic accessibility scores, and predicted toxicity. The molecule 37 showed the best overall profile and was the most investigated. It had a molecular weight of 402.42 g/mol, a Consensus LogP value of 2.82 and it was predicted to be soluble in both the ESOL and Ali solubility models. SwissADME was observed to have enhanced intestinal uptake, no BBB-permeability, comply with all of the main favourable drug-likeness profiles, a bioavailability score reaching 0.55 and an absence of PAINS and Brenk structural alerts. In addition, the ADMETlab 3.0 had shown lower hERG inhibition (0.156), acceptable hepatotoxicity, Ame's mutagenicity, skin sensitization and acute oral toxicity profile [9,12]. Compound 33 also showed promising pharmacokinetic properties: Consensus LogP 3.42, high gastrointestinal absorption, no P-glycoprotein substrate prediction, all major drug-likeness criteria fulfilled, and no medicinal chemistry alerts. Its predicted aqueous solubility was lower than compound 37 but its overall ADMET was still favourable making it a potential antifungal lead compound.

In general, the compounds 33 and 37 were found to be the most attractive lead compounds based on the integrated computational assessment, including their physicochemical properties, pharmacokinetic profiles, medicinal chemistry properties and acceptable toxicity. These results pave the way for their further investigation using molecular docking and experimental antifungal investigation, much like this computational lead optimization strategies reported in earlier antifungal studies [6-8].

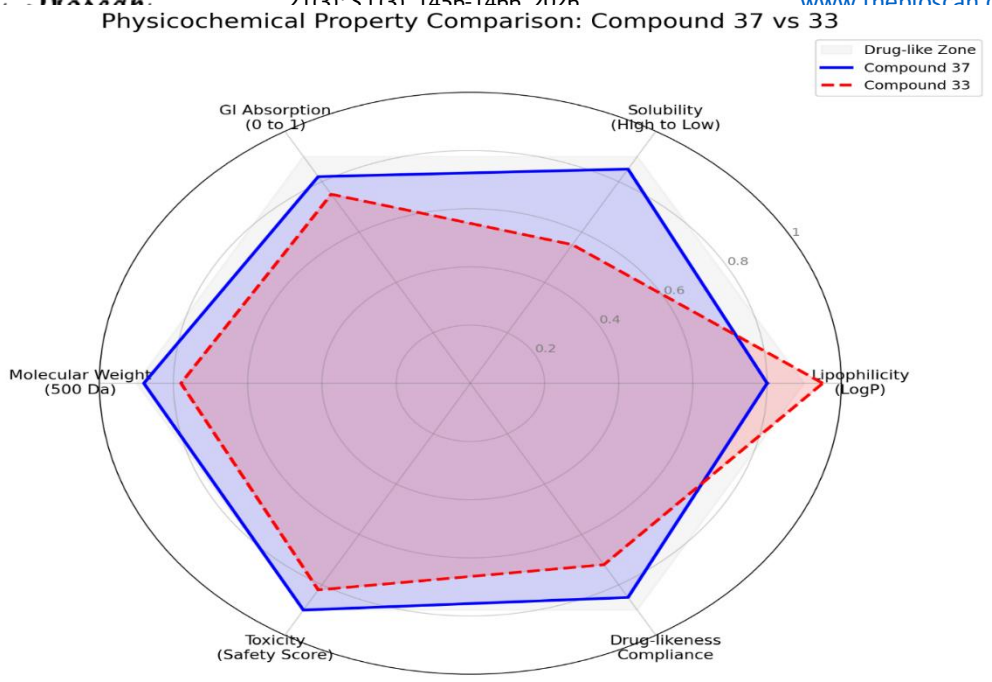


Figure 5. Comparative analysis of physiochemical properties of compound 33 and 37

5. CONCLUSION

In the current work, the designed antifungal compounds have been exhaustively evaluated using the complementary in silico platforms SwissADME and ADMETlab 3.0 to assess their physicochemical characteristic's, pharmacokinetic profiles, drug-likeness, medicinal chemistry features, and toxicity profiles. Assessment of ADMET parameters is an essential aspect of development of therapeutic agents and is useful for gather data regarding the behaviour of drug candidates during the development process and their possible safety of the modern drug discovery process since many promising drug candidates are not developed in the preclinical or clinical stages because of poor pharmacokinetic properties or unacceptable toxicity. As a result, ADMET prediction at the early lead identification stage can help to lower the attrition rate at this stage, cut down on development expenses, and increase the chances of discovering safe and effective drug candidates.

The integrated computational workflow showed that all the compounds under consideration had the desired key physicochemical parameters such as MW, lipophilic character, TPSA, and thus they could be considered suitable for oral drug application. The suitability of the designed molecules for the antifungal drug development was further emphasized by their high gastrointestinal absorption, moderate aqueous solubility for majority of the molecules, good drug-likeness criteria, absence of significant medicinal chemistry alerts and generally low predicted toxicity.

Compounds 37 and 33 showed the most well-balanced pharmacokinetic and safety profiles among the compounds evaluated, having good solubility, high drug-likeness, and low predicted toxicity levels. These results suggest that compounds 33 and 37 have the best combination of efficacy and safety parameters, and deserve to be developed as lead compounds for further optimization. In conclusion, the study showed that SwissADME and ADMETlab 3.0 can serve as a computational strategy for early design-process screening and prioritisation of antifungal candidates, providing a very efficient and reliable approach. Comprehensive ADMET prediction allows the identification of compounds having desired pharmacokinetic and toxicological properties pre-experimental testing, thus speeding up drug discovery. From the present findings, compounds 33 and 37 are recommended for further investigation via molecular docking and experimental biological profiling against antifungal protein sterylglucosidase (Sgl1) of Cryptococcus neoformans for their promising antifungal activity for developing new antifungal medicine.

This work is based on the extension of our previous work in designing antifungal drugs and the profiling of the pharmacokinetic and toxicological properties of triazole derivatives against sterylglucosidase (Sgl1) of Cryptococcus neoformans. Whereas the molecular docking and QSAR studies had previously described the structural activity and binding affinity of these compounds, the present study of ADMET profile gives a different perspective of the drug likeness, bioavailability and safety profile for these compounds. Here, the integrated CADD approach allowed such identification of favourable pharmacokinetic properties in early stages, which will limit the risk of attrition in the subsequent stages of development, and also allowed the identification of potential liabilities.

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