Original Article

Network pharmacology and molecular docking investigation of *Curcuma xanthorrhiza* Roxb. rhizome with the mechanisms underlying as the potential drug of eczema treatment

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Abstract

A chronic inflammatory dermatosis, eczema, affects more than 12% of the pediatric population and 7.2% of adults. Clinically, it presents with erythematous, scaly, and intensely pruritic lesions. Severe forms of the disease frequently exhibit poor responsiveness to treatments aimed at a single inflammatory pathway. *Curcuma xanthorrhiza* Roxb. rhizomes possess antioxidant, anti-inflammatory, and anti-allergic activities through a multi-target mechanism. This study aimed to evaluate the secondary metabolites of *C. xanthorrhiza* Roxb. rhizomes that can be developed into eczema drugs using virtual screening *in silico.* Secondary metabolite compounds from *C. xanthorrhiza* rhizomes were evaluated for their drug-likeness properties Subsequently, the similarity of their physicochemical properties was assessed using the principal component analysis. A target search of drug candidates was performed using the Swiss Target Prediction and Gene Expression Omnibus (GEO) Omnibus. Docking was performed using Molegro by comparing the rerank scores of the drug candidates with those of the original ligands. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction was performed using the pkCSM. Carbonic anhydrase II, epidermal growth factor receptor, and the mammalian target of rapamycin came as the protein target for eczema disease. For the docking result, demethoxycurcumin (C00037023), 1,5-dihydroxy-1,7-bis (4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one (C00055412), 1,7-bis (4-hydroxy-3-methoxyphenyl)-3,5-heptanediol (C00055175), and 3′-demethoxycyclocurcumin (C00054761) had both better rerank score than the native ligand and good ADMET profiles. Four compounds derived from *C. xanthorrhiza* Roxb. rhizomes can be developed as an eczema potential treatment.

Key words: Absorption, distribution, metabolism, excretion, and toxicity, atopic dermatitis, neglected tropical disease, network analysis, virtual screening

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INTRODUCTION

Eczema, also referred to as atopic dermatitis, it is a prevalent dermatological disorder. Clinical manifestations of eczema include dry, itchy skin, and infection in the certain areas of the skin.[1,2] AD affects more than 12% of children and 7.2% of adults.[3,4] AD can often trigger other allergic events, such as food and environmental allergies (15%), asthma (25%–50%), and allergic rhinitis (34%–75%).[5] Additionally, patients with AD also often develop other infectious diseases such as ear infections (27%), streptococcal pharyngitis (8%), and urinary tract infections (8%).[6,7]

Treatment of patients with eczema is primarily concerned with restoring the skin's defenses.[5] However, the progression of eczema to more severe disease has not matched the development of new therapeutic strategies to treat the condition.[8-10] Severe eczema often fails to respond to existing treatments, including systemic immunosuppressive agents. Therefore, there is a need to identify new drug candidates that can control the disease progression.[5,11]

Curcuma xanthorrhiza Roxb.("Temulawak" or Javanese turmeric) is widely used in Indonesia as an herbal medicine.[12,13] The main compounds found in this plant are sesquiterpenoids and curcuminoids, particularly in the rhizome.[12,14] More specifically, the compounds contained in the rhizome of *C. xanthorrhiza*, such as β-sesquiphellandrene, bisacumol, bisacurol, ar-turmerone, α-turmerone, β-turmerone, xanthorrizol (1.48%–1.64%), vanillin, camphor, β-bisabolol, demethoxycurcumin, curcumin, dihydrocurcumin, etc.[13,15]

Studies focusing on the concept of "multi-compound, multi-gene, multi-pathways" will provide complex information on the relationship between compounds, targets, proteins, pathways, and diseases.[16,17] This research employed a systems pharmacology approach to screen secondary metabolites from *C. xanthorrhiza rhizomes* as potential drug candidates, utilizing compound profiling, drug–target interaction analysis, pathway mapping, molecular docking, and Absorption, distribution, metabolism, excretion, and toxicity (ADMET) property evaluation.

SUBJECTS AND METHODS

Secondary metabolites compounds extraction from *Curcuma xanthorrhiza* rhizome

Secondary metabolites from *C. xanthorrhiza* rhizomes were obtained from the Knapsack family database (www.knapsackfamily.com/KNApSAcK/) (Nara Institute of Science and Technology, Japan). The compounds were then evaluated for drug-likeness properties based on Lipinski's "Rule of Five" and Veber's theory using the SwissADME website (www.swissadme.ch) (Swiss Institute of Bioinformatics, Switzerland).[18]

Compound feature mapping

The drug candidates were analyzed using the principal component analysis (PCA) to determine the similarity of physicochemical properties using the six variables: molecular weight, log P, number of proton donors, proton acceptors, rotatable bonds, and total surface area. The PCA was performed using GraphPad Prism ver. 9.0.2 (Boston, MA, USA).

Drug target mining

A target search of drug candidates was performed using "Swiss Target Prediction" website (www.swisstargetprediction.ch) (Swiss Institute of Bioinformatics, Switzerland).[19] The selected targets were connected using the STRING database (www.string-db.org/) (String Consortium, Switzerland)[20] to identify the possible pathways contributed by the targets.

Target enrichment network, pathway analysis, compound–target–disease network

Differential gene expression of eczema disease was acquired from the GEO, which was then sorted based on a $P < 0.05$. DAVID database (www.david.ncifcrf.gov/) (National Genomic Data Center, China)[21] was used to determine the pathways through the KEGG pathway and biological processes, which were sorted by the log FDR value.

In silico molecular docking

The selected targets were docked using Molegro version 5.5. The validation was done by docking the native ligand with fix conformation position while the lowest RMSD was chosen to pick the conformation for the docking analysis. The protein structure was extracted from the Protein Data Bank database (www.rcsb.org/) (Piscataway, NJ, USA).[22] Assessing the rerank score differences between drug candidates and native ligands provides valuable insight into their potential binding interactions with the target protein.

Absorption, distribution, metabolism, excretion, and toxicity prediction

The pkCSM (www.biosig.unimelb.edu.au/pkcsm/) (Melbourne, Vic, Australia)[23] was employed to predict the pharmacokinetic behavior and potential toxicity of the proposed drug candidates.

RESULTS

Secondary metabolites compounds extraction from *Curcuma xanthorrhiza* rhizome

The results of the database extraction yielded 28 compounds that met the criteria of Lipinski's "Rule of Five" and Veber's theory. A list of these compounds is shown in Figure 1.

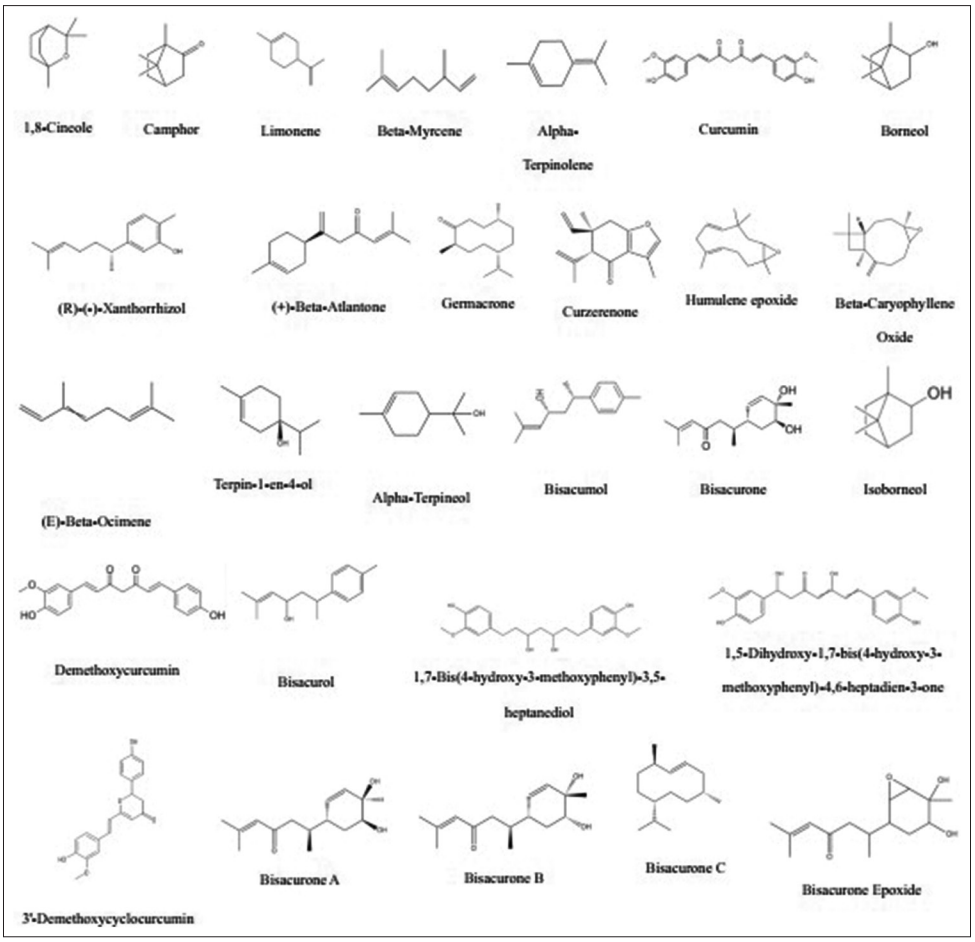

Figure 1: List of active compounds from *Curcuma xanthorrhiza* rhizomes (https://pubchem.ncbi.nlm.nih.gov/)

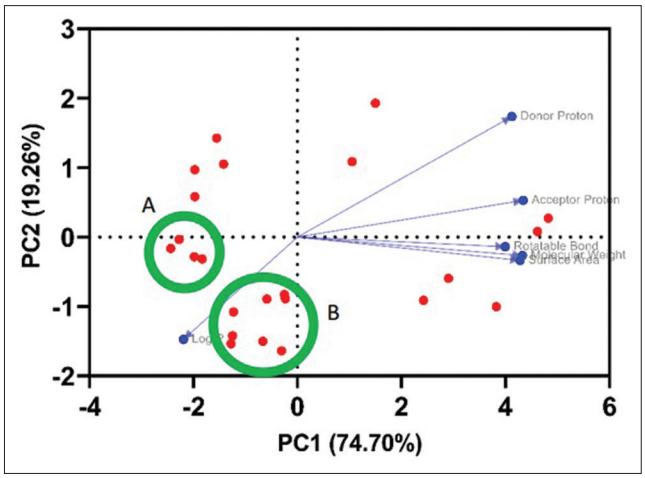

Figure 2: Relatedness distribution of the active compounds. The green circle indicates similar physicochemical features

Compound feature mapping

Each compound exhibits unique physicochemical properties. The physicochemical properties of the 28 compounds were mapped and reduced to two variables as shown in Figure 2. Some of these compounds exhibited similar physicochemical properties. This is indicated by the almost equal values of variables 1 and 2, as indicated by the green circle. Group A consists of (+)-beta-atlantone (C00011646), germacrone (C00011728), humulene epoxide (C00012443), and beta-caryophyllene oxide (C00012483). Group B consists 1,8-cineole (C00000136), camphor (C00000819), limonene (C00000823), beta-myrcene (C00000853), alpha-terpinolene (C00000861), (E)-beta-ocimene (C000029335), alpha-terpineol (C00029674), and demethoxycurcumin (C00037023).

Drug target mining

A search for possible receptors on the 28 compounds was performed to identify a list of receptors that bind well to the drug candidates. Several pathways were identified from the protein interactions, including nitrogen metabolism (strength: 1.72), steroid biosynthesis (strength: 1.39), regulation of lipolysis in adipocytes (strength: 1.26), prostate cancer (strength: 1.22), serotonergic synapses (strength: 1.19), steroid hormone biosynthesis (strength: 1.18), and central carbon metabolism in cancer (strength: 1.16).

Target enrichment network, pathway analysis, Compound–Target–Disease network

Protein interactions that are observed can be known pathways involved in the interaction of these proteins.

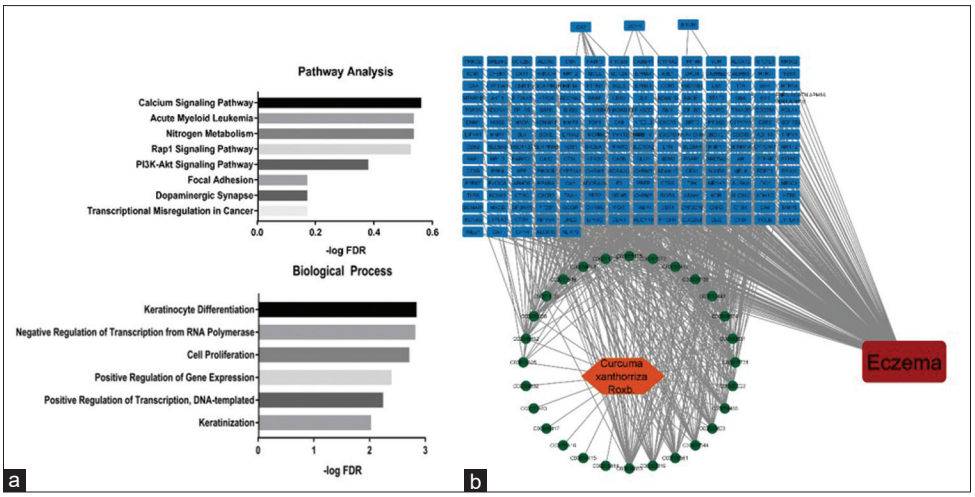

Figure 3: (a) Pathways and biological processes involved in eczema and (b) Compound–target–disease relationships of *Curcuma xanthorrhiza* rhizome for the treatment of eczema

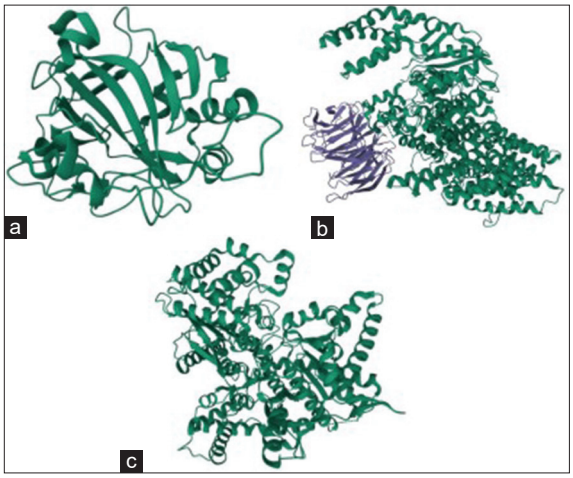

Figure 4: Cartoon representation of (a) carbonic anhydrase II; (b) epidermal growth factor receptor; (c) mammalian target of rapamycin

Based on the results of differential gene analysis of eczema, it was found that there were several dominant pathways and biological processes involved as shown in Figure 3a. While, the relationships among the compounds, targets, and diseases are shown in Figure 3b.

In silico molecular docking

In this study, three dominant proteins were identified: carbonic anhydrase II (PDB ID: 2q38), epidermal growth factor receptor (EGFR) (PDB ID: 4jt5), and the mammalian target of rapamycin (mTOR) (PDB ID: 1xkx) are shown in Figure 4. The results of the rank score and interaction of compounds and receptors after docking the three receptors are shown in Supplementary Table 1 and Figure 5. From the results of the rerank score value, four compounds have better value than the native ligand, namely demethoxycurcumin (C00037023), 1,5-dihydroxy-1,7-bis (4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one (C00055412, 1,7-bis (4-hydroxy-3-methoxyphenyl)-3,5-heptanediol (C00055175), and 3′-demethoxycyclocurcumin (C00054761).

Absorption, distribution, metabolism, excretion, and toxicity prediction

Predicting ADMET properties at the initial stage of drug development helps lower the risk of pharmacokinetic failure in later phases and is crucial for confirming target receptor-binding potential. ADMET prediction results showed that the four compounds had good pharmacokinetic parameters and safety index. These results are shown in Supplementary Table 2.

DISCUSSION

Plant-derived secondary metabolites exhibit a wide range of structural and physicochemical properties that influence their pharmacological potential. Lipinski's Rule of Five and Veber's criteria remain the most widely applied to predict a compound's suitability as a drug candidate, particularly in terms of oral bioavailability and pharmacokinetics.[24,25] Lipinski's rule focuses on molecular weight, lipophilicity, and hydrogen-bonding capacity, while Veber emphasizes molecular flexibility and polarity. Applying these rules allowed the initial selection of compounds with desirable pharmacokinetic characteristics.[25,26]

Subsequent molecular docking simulations revealed that four compounds exhibited strong binding affinities to key eczema-related proteins: carbonic anhydrase II, EGFR, and mTOR. Binding interaction between drug candidates and native ligand with carbonic anhydrase II forms several hydrogen, electrostatic, and sterical bonds. C00055412 bound with His64 as sterical bond, C00037023 bound with Gly63 as sterical bond, His64 as hydrogen bond, C00055175 bound with Asn11, Gly63, His64 as hydrogen bonds, and C00054761 bound with Gly63, His64 as sterical bonds.

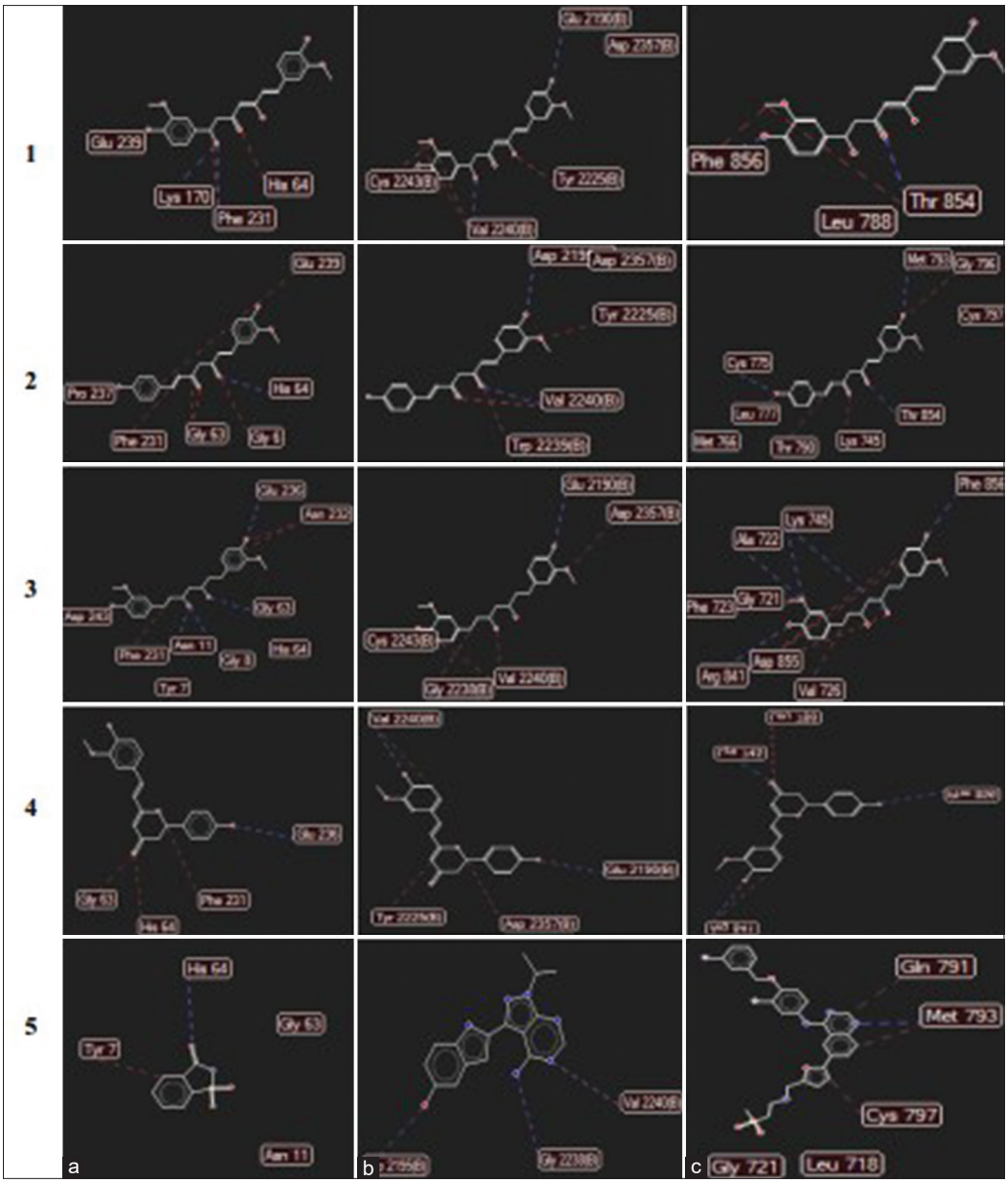

Figure 5: Interaction of compounds with receptors (a) carbonic anhydrase II; (b) epidermal growth factor receptor; and (c) mammalian target of rapamycin with (1) C00055412, (2) C00037023, (3) C00055175, (4) C00054761, and (5) their native ligands

The binding interaction between the drug candidates with EGFR forms several bonds. C00055412, C00037023, and C00054761 bound with Val2240 as hydrogen and sterical bonds, and C00055175 bound with Gly2238, Val2240 as sterical bonds. Meanwhile, the binding interaction to mTOR, C00037023 bound with Met793 as hydrogen bond, Cys797 as sterical bond, and C00055175 bound with Gly721 as sterical bond. Four previous compounds do not only have a lower rerank score than the native ligands and its inhibitor, but also have the same amino acid bound with certain functional group presented in their structure.

To complement the docking analysis, the drug candidate's pharmacokinetic behavior and toxicity potential were predicted using in silico ADMET modeling. All four compounds demonstrated high intestinal absorption rates (>75%), with C00037023 and C00054761 exceeding 90%, indicating good oral bioavailability. Permeability studies using Caco-2 cell models further confirmed that the compounds could effectively cross epithelial barriers, a key requirement for systemic drug delivery.[27,28] During the distribution phase, the blood–brain barrier (BBB) which is advantageous for minimizing central nervous system side effects, particularly for drugs not intended to target the brain.[29,30] The BBB permeability results obtained for all the compounds were negative, indicating that a minimum amount of the compound penetrated to the brain.

Drug metabolism is primarily mediated by cytochrome P450 enzymes, with CYP2D6 and CYP3A4 being the two

predominant isoforms involved.[31,32] In the metabolic phase, C00037023 is a CYP3A4 inhibitor.[33,34] In the elimination phase, C00055175 has a total clearance value that is significantly different from that of the other three compounds. Finally, in the prediction of toxicity, it was found that the four compounds were not predicted to cause toxic symptoms in the fetus and liver organs.[23,35]

CONCLUSION

Secondary metabolites from *C. xanthorrhiza* rhizomes – C00037023, C00055412, C00055175, and C00054761 – demonstrated strong predicted binding to key eczema-related targets (carbonic anhydrase II, EGFR, and mTOR). *In silico* ADMET analysis indicated favorable pharmacokinetic properties and low toxicity. These findings support their potential as drug candidates for eczema therapy.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Rerank score of compound interaction with the receptor

Receptor	C_ID	Rerank score
Carbonic anhydrase II	C00055412	−107.282
	C00037023	−106.996
	C00055175	−105.116
	C00054761	−95.2264
	Ligand	−66,8846
Epidermal growth factor receptor	C00055412	−122.922
	C00037023	−113.089
	C00054761	−112.050
	C00055175	−109.699
	Ligand	−107,491
Mammalian target of rapamycin	C00037023	−120.700
	C00055412	−114.915
	C00054761	−112.024
	C00055175	−111.728
	Ligand	−171.504

Supplementary Table 2: Absorption, distribution, metabolism, excretion, and toxicity prediction for *Curcuma xanthorrhiza* Roxb. in the treatment of eczema

C_ID	Absorption			Distribution		Metabolism		Excretion	Toxicity	
	Intestinal absorption (%)	Skin permeability (log Kp → log cm/h)	Caco-2 permeability (log Papp → log cm/s)	Distribution volume (log VDss → log L/kg)	BBB permeability (logBB)	CYP2D6 inhibitor	CYP3A4 inhibitor	Total clearance (log Cl total → log mL/min/kg)	Ames toxicity	Hepatotoxicity
C00037023	91.393	−2.768	1.023	−0.075	−0.337	No	Yes	0.026	No	No
C00055412	78.198	−2.756	0.647	0.225	−1.199	No	No	0.173	No	No
C00055175	76.622	−2.735	0.829	0.508	−1.066	No	No	1.048	No	No
C00054761	91.670	−2.798	1.152	0.07	−0.159	No	No	0.105	No	No

BBB: Blood–brain barrier