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Identification of FDA-approved drugs as potential inhibitors of TEM-1 β-lactamase: an integrated in silico repurposing study

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Abstract

Antimicrobial resistance driven by β-lactamase production threatens β-lactam therapy, creating a need for complementary inhibitors that can be developed efficiently. Fourteen drugs approved by the US Food and Drug Administration (FDA) were evaluated as potential repurposed inhibitors of TEM-1 β-lactamase using an integrated workflow of target prediction (SwissTargetPrediction), drug-likeness and absorption, distribution, metabolism, excretion and toxicity (ADMET) prediction (SwissADME, pkCSM) and molecular docking (SwissDock with the Attracting Cavities 2.0 and AutoDock Vina engines; Protein Data Bank [PDB] entry 4IBX), with clavulanic acid as the clinical reference. Redocking of crystallographic penicillin G (PDB ligand code PNM) from PDB entry 1FQG reproduced the experimental pose with a heavy-atom root-mean-square deviation (RMSD) of 0.77 Å across 23 atoms. Several compounds, notably troxerutin, hidrosmin and dutasteride depending on the scoring engine, scored more favourably than clavulanic acid in non-covalent docking. However, highly glycosylated flavonoids combined favourable docking with poor predicted gastrointestinal absorption, high polarity and multiple drug-likeness violations, whereas captopril and dolutegravir offered the most balanced computational profiles. Because docking scores describe predicted non-covalent interactions and no biochemical inhibition data are available, the findings are hypothesis-generating rather than evidence of efficacy.

1. Introduction

The global burden of antimicrobial resistance (AMR) is a major challenge to infectious-disease treatment, having been associated with an estimated 4.95 million deaths worldwide in 2019 alone (Murray et al. 2022). Bacterial resistance mechanisms can directly neutralise established antibiotics, and β-lactamases are among the most important of these mechanisms because they hydrolyse the β-lactam ring of penicillins, cephalosporins and related antibiotics (Bush and Bradford 2016). TEM-1 is a widely studied Class A serine β-lactamase, distinct in fold and catalytic mechanism from the metal-dependent Class B metallo-β-lactamases (Ambler 1980), and an important model for investigating strategies aimed at preserving β-lactam activity.

β-Lactamase inhibitors (BLIs) such as clavulanic acid are used clinically with susceptible β-lactam antibiotics. Continued emergence and diversification of β-lactamases nevertheless creates a need for additional inhibitory chemotypes. Drug repurposing provides a complementary strategy because compounds with established pharmacological histories can be prioritised for new mechanisms or indications, potentially shortening early development.

In silico approaches can integrate target prediction, physicochemical assessment, pharmacokinetic prediction and molecular docking before experimental testing. SwissTargetPrediction provides structure-based target hypotheses (Daina et al. 2019), while SwissADME (Daina et al. 2017) and pkCSM (Pires et al. 2015) provide computational drug-likeness and estimates of absorption, distribution, metabolism, excretion and toxicity (ADMET). Molecular docking can examine plausible ligand poses and compare

predicted non-covalent interaction energies, using engines such as SwissDock (Grosdidier et al. 2011) and AutoDock Vina (Trott and Olson 2010).

An important limitation is that a favourable docking score does not establish biochemical inhibition. Docking scores are model-dependent estimates influenced by receptor preparation, ligand state, search parameters and treatment of solvent and protein flexibility. Redocking a ligand with a known crystallographic pose provides a useful structural check. In this study, crystallographic penicillin G (ligand code PNM) from TEM-1 structure Protein Data Bank (PDB) entry 1FQG was independently redocked and gave a heavy-atom root-mean-square deviation (RMSD) of 0.77 Å. This is interpreted as pose-reproduction evidence, not as biochemical validation.

The study therefore aimed to evaluate fourteen therapeutic agents approved by the US Food and Drug Administration (FDA) as potential TEM-1 β-lactamase repurposing candidates. Objectives were to assess predicted target profiles, drug-likeness and ADMET characteristics, compare docking scores with clavulanic acid, and assess docking-pose reproduction using crystallographic PNM redocking.

2. Materials and methods

2.1. Compound selection and ligand preparation

Fourteen compounds were selected: captopril, chlorpromazine, clavulanic acid, diosmetin, diosmin, disulfiram, dolutegravir, dutasteride, hidrosmin, ketoconazole, monoxerutin, rutin, solasulfone and troxerutin. Their 2D/3D structures were retrieved from PubChem in structure-data file (SDF) and simplified molecular-input line-entry system (SMILES) formats and prepared for target-prediction, ADMET and docking analyses.

2.2. Protein structure preparation

The crystallographic TEM-1 β-lactamase structure PDB 4IBX was obtained from the RCSB Protein Data Bank. Water molecules, native ligands and cofactors were removed, polar hydrogens were added and Gasteiger charges were assigned. The docking region was defined around the catalytic Ser70-containing active site.

2.3. Target prediction

SMILES representations were submitted to SwissTargetPrediction. Predicted target profiles were examined to provide pharmacological context and identify possible polypharmacology or off-target liabilities.

2.4. Drug-likeness and ADMET prediction

SwissADME was used to assess physicochemical properties and drug-likeness, including Lipinski-related properties. pkCSM was used to evaluate gastrointestinal absorption, blood–brain barrier (BBB) permeation, P-glycoprotein substrate status, cytochrome P450 (CYP) inhibition and selected toxicity

endpoints. These are computational prioritisation tools and not substitutes for experimental pharmacokinetic or toxicological measurements.

2.5. Molecular docking

Docking was performed with SwissDock using the Attracting Cavities 2.0 and AutoDock Vina engines. The active site was defined around catalytic Ser70. Binding affinities are reported in kcal mol^{-1}, with more negative values indicating more favourable predicted non-covalent interactions within the scoring model. Clavulanic acid served as the reference comparator.

2.6. PNM redocking validation

The crystallographic PNM ligand from TEM-1 β-lactamase PDB 1FQG was extracted and independently redocked using the established docking workflow. The predicted and crystallographic PNM conformations were aligned using 23 corresponding non-hydrogen atoms and the heavy-atom RMSD was calculated. RMSD was 0.77 Å. Because the validation structure (1FQG) differs from the screening receptor (4IBX), this is interpreted as cross-structure TEM-1 pose-reproduction evidence rather than direct validation of the exact 4IBX receptor preparation. It does not establish experimental affinity, inhibition kinetics or antibacterial activity.

3. Results and discussion

3.1. Target-prediction profiles

SwissTargetPrediction produced distinct pharmacological signatures. Clavulanic acid showed strong enrichment in hydrolase/protease-associated targets, consistent with its known interaction with serine β-lactamase systems. Chlorpromazine was dominated by predicted Family A G protein-coupled receptor (GPCR) associations. Monoxerutin and dutasteride showed broader predicted target distributions, whereas captopril displayed a comparatively focused profile centred on angiotensin-converting enzyme (ACE). These results indicate that candidate selection should consider both TEM-1 docking and broader pharmacology.

3.2. Physicochemical properties and drug-likeness

Captopril, chlorpromazine, clavulanic acid, diosmetin, disulfiram and dolutegravir showed no Lipinski violations in the supplied dataset. Glycosylated flavonoids showed multiple violations, driven mainly by molecular weight and extensive hydrogen-bonding capacity. Their high polar surface areas were consistent with poor predicted gastrointestinal absorption.

Table 1
Physicochemical and drug-likeness properties of the screened compounds. Data were derived from the supplied SwissADME/pkCSM dataset.

Compound	MW	LogP	HBD	HBA	TPSA	Lipinski violations
Captopril	217.29	0.63	2	3	57.50	0
Chlorpromazine	318.86	4.29	0	3	31.78	0
Clavulanic acid	199.16	−1.10	1	5	87.91	0
Diosmetin	300.27	2.59	3	6	111.00	0
Diosmin	608.55	−1.09	8	15	242.79	3
Disulfiram	296.54	3.34	0	4	121.26	0
Dolutegravir	419.38	1.35	2	6	113.00	0
Dutasteride	528.53	5.54	2	8	58.20	2
Hidrosmin	652.60	−1.42	8	16	260.63	3
Ketoconazole	531.43	4.06	0	8	106.60	1
Monoxerutin	804.91	1.80	10	17	317.58	3
Rutin	610.52	−1.69	10	16	269.00	3
Solasulfone	654.91	−1.29	6	15	278.44	3
Troxerutin	742.68	−2.69	10	19	206.00	3

MW molecular weight (g mol^{-1}); LogP logarithm of the octanol–water partition coefficient; HBD hydrogen-bond donors; HBA hydrogen-bond acceptors; TPSA topological polar surface area ($Å^2$)

3.3. Pharmacokinetic and toxicity profiles

Captopril showed high predicted gastrointestinal absorption, no predicted BBB penetration, no P-glycoprotein substrate status and no major CYP inhibition in the supplied dataset. Dolutegravir also showed high predicted intestinal absorption and no BBB permeation, but was identified as a CYP3A4 substrate and carried a predicted hepatotoxicity flag. Diosmetin showed adequate predicted absorption but inhibition of CYP1A2, CYP2C19 and CYP2C9. The bulky glycosylated flavonoids generally showed low predicted gastrointestinal absorption and human ether-à-go-go-related gene (hERG) II flags. Disulfiram and ketoconazole showed substantial metabolic liabilities. These results demonstrate why docking rank should not alone determine repurposing priority.

Table 2
Predicted pharmacokinetic and toxicity characteristics. Predictions require experimental confirmation.

Compound	GI absorption	BBB	P-gp	CYP inhibition	Toxicity	Outlook
Captopril	High (~ 79.7%)	No	No	None	None	Primary
Chlorpromazine	High	Yes	No	Broad	hERG; sedation	Poor
Clavulanic acid	High	No	No	None	Hepatotoxicity	Reference
Diosmetin	High (~ 79.9%)	No	Yes	1A2, 2C19, 2C9	None	Plausible; DDI risk
Diosmin	Low (~ 29.3%)	No	Yes	None	hERG II	Moderate; poor PK
Disulfiram	High	Yes	No	Broad	Toxicity/alcohol interaction	Poor
Dolutegravir	High (~ 74.3%)	No	Yes	None	Hepatotoxicity	Strong candidate
Dutasteride	Low	No	Yes	CYP3A4	None	Moderate
Hidrosmin	Low (~ 21.4%)	No	Yes	None	hERG II	Low
Ketoconazole	High	No	No	Severe	Hepatotoxicity; hERG	Poor
Monoxerutin	Low	No	No	None	None	Poor
Rutin	Low (~ 23.4%)	No	Yes	None	hERG II	Poor
Solasulfone	Very low (0%)	No	No	None	None	Poor oral
Troxerutin	Low (~ 21.8%)	No	Yes	None	hERG II	Poor

GI gastrointestinal; BBB blood–brain barrier; P-gp P-glycoprotein; CYP cytochrome P450; hERG human ether-à-go-go-related gene; DDI drug–drug interaction. Percentages are predicted intestinal absorption

3.4. Molecular docking

Several compounds produced more favourable predicted non-covalent docking scores than clavulanic acid. Hidrosmin, dutasteride, dolutegravir and monoxerutin were among the stronger Vina-scoring compounds, while the SwissDock/Attracting Cavities scores produced a related but not identical ranking. This difference illustrates the dependence of absolute numerical scores on the underlying scoring function.

Table 3
Molecular docking results against TEM-1 β-lactamase (PDB 4IBX).

Compound	Vina (kcal mol^{-1})	SwissDock/AC (kcal mol^{-1})
Captopril	−4.94	−6.90
Chlorpromazine	−4.79	−6.76
Clavulanic acid	−4.51	−6.40
Diosmetin	−3.58	−8.18
Diosmin	−5.07	−9.19
Disulfiram	−3.29	−7.39
Dolutegravir	−5.73	−8.10
Dutasteride	−6.80	−8.36
Hidrosmin	−6.06	−9.19
Ketoconazole	−5.06	−9.21
Monoxerutin	−5.73	−8.02
Rutin	−5.53	−9.01
Solasulfone	−2.99	−8.83
Troxerutin	−3.38	−9.53

Vina, AutoDock Vina score; SwissDock/AC, SwissDock with the Attracting Cavities 2.0 engine. More negative values indicate more favourable predicted non-covalent binding

3.5. Redocking validation

Redocking of crystallographic PNM from PDB 1FQG produced a heavy-atom RMSD of 0.77 Å across 23 corresponding non-hydrogen atoms (Table 4). The sub-ångström RMSD indicates close reproduction of the experimentally observed PNM geometry and provides structural support for the ability of the docking workflow to reproduce a known TEM-1 ligand pose.

The validation should nevertheless be interpreted carefully. PNM was validated in PDB 1FQG, whereas the compound screen used PDB 4IBX. Thus, the experiment supports protocol performance across TEM-1 structures but is not equivalent to redocking PNM into 4IBX itself. In addition, pose reproduction is not evidence of experimental binding affinity, inhibition kinetics, covalent reactivity or antibacterial activity.

Table 4
Structural validation of the docking workflow using redocking of crystallographic PNM.

Target	PDB	Ligand	Atoms compared	RMSD	Interpretation
TEM-1 β-lactamase	1FQG	PNM	23 non-H atoms	0.77 Å	Close crystallographic-pose reproduction

PNM penicillin G; RMSD root-mean-square deviation

3.6. Integrated prioritisation

The combined analysis separates theoretical binding from translational feasibility. Highly glycosylated flavonoids showed strong docking but poor predicted gastrointestinal absorption, high molecular weight and high polarity, making systemic oral exposure uncertain. Captopril and dolutegravir offered more balanced profiles. Captopril combined favourable predicted absorption, no BBB penetration and limited CYP liability with moderate docking. Dolutegravir combined favourable drug-likeness and absorption with stronger docking, although its CYP3A4 substrate status and predicted hepatotoxicity warrant further assessment.

The relatively modest docking score of clavulanic acid should not be interpreted as evidence that it is a weak TEM-1 inhibitor. As a mechanism-based inhibitor, clavulanic acid undergoes reaction with the active-site serine, whereas conventional docking primarily evaluates a pre-reaction non-covalent complex. Consequently, docking scores should not be used to rank the clinical inhibitory potency of covalent or mechanism-based inhibitors against purely non-covalent candidates.

3.7. Limitations

The study is computational and lacks direct TEM-1 inhibition measurements, cellular assays and antibacterial combination studies. SwissTargetPrediction, SwissADME and pkCSM are model-derived estimates. Docking does not fully capture solvent, protein flexibility, induced fit or uncertainty in protonation states. The PNM redocking benchmark uses PDB 1FQG whereas screening uses PDB 4IBX, so it is a cross-structure validation rather than exact receptor-specific validation. This caution is not hypothetical: a related study screening FDA-approved drugs against a Class A serine β-lactamase (SHV-1, PDB 4ZAM) similarly identified captopril as a promising computational hit, with docking and molecular dynamics results comparable to the reference inhibitor avibactam, but found no in vitro inhibitory activity on experimental testing (Abdalla et al. 2026). This precedent reinforces that captopril's docking profile against TEM-1 should not be interpreted as evidence of genuine inhibitory potential without enzymatic validation. Finally, no conclusion can be drawn about therapeutic concentrations or clinical efficacy without experimental confirmation.

4. Conclusions

Fourteen FDA-approved compounds were evaluated as potential TEM-1 β-lactamase repurposing candidates. Several glycosylated flavonoids showed favourable predicted docking but poor predicted oral exposure, whereas captopril and dolutegravir showed the most balanced computational profiles. Redocking of crystallographic PNM from PDB 1FQG yielded a 0.77 Å heavy-atom RMSD across 23 corresponding non-hydrogen atoms, supporting the ability of the workflow to reproduce a known TEM-1 ligand pose. This structural validation strengthens confidence in the computational workflow but does not replace biochemical or microbiological validation. The identified candidates should therefore be considered priorities for experimental investigation rather than established TEM-1 inhibitors.

5. Future experimental validation

Purified-enzyme TEM-1 inhibition assays should be performed for captopril, dolutegravir and selected high-scoring compounds, using validated substrates such as nitrocefin or CENTA and clavulanic acid as a comparator. Concentration–response and kinetic experiments should determine potency and inhibition mechanism. Molecular-dynamics simulations may subsequently assess pose stability, while β-lactam combination assays in bacterial systems can determine whether candidate compounds restore antibiotic activity.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval and consent to participate

Not applicable. This study did not involve human participants or animals.

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Author Contribution

The author was responsible for conceptualization, methodology, investigation, data curation, formal analysis, and interpretation of results. The author also conducted the computational analyses, prepared the original manuscript, and performed reviewing and editing. As the corresponding author, the author takes responsibility for the integrity of the work and communication with the journal throughout the submission and publication process.

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Data availability

The data supporting the findings are contained within the manuscript and its tables. Molecular structures were obtained from publicly accessible databases as described in the Materials and methods. Docking input/output files and PNM redocking structures are available from the corresponding author upon reasonable request.

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Figures

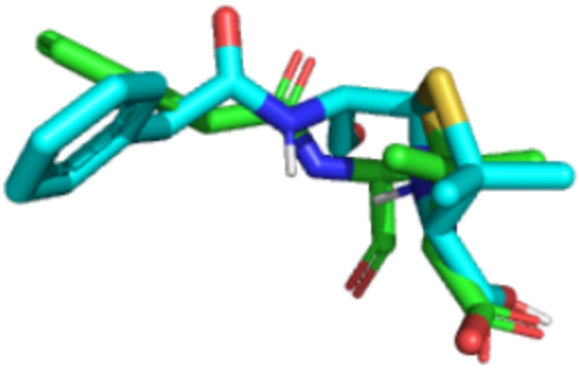


Figure 1

Structural superposition of crystallographic penicillin G (PNM; green) and its redocked pose (cyan) in the TEM-1 β-lactamase binding site (PDB 1FQG). The redocked ligand reproduced the experimental conformation with a heavy-atom RMSD of 0.77 Å

Supplementary Files

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