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MOLECULAR DOCKING-BASED CLASSIFICATION OF P-GLYCOPROTEIN INHIBITORS AND THEIR POTENTIAL INTERACTION WITH DIGOXIN

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ABSTRACT: P-glycoprotein (P-gp) is a membrane efflux transporter influencing drug absorption and disposition. Inhibiting P-gp may increase plasma levels of substrates like digoxin, heightening toxicity risk. This study aimed to classify 35 drugs based on their molecular docking-derived binding affinity to P-gp and their potential to inhibit digoxin transport, using estimated inhibition constants (Ki). Docking simulations were performed using AutoDockVina. Physicochemical parameters were gathered, and binding energies (ΔG) were converted to Ki values. Drugs were ranked using a Ki ratio relative to digoxin (Ki-drug/Ki-dgx). Four drugs (conivaptan, telmisartan, indinavir, and troglitazone) showed stronger affinity than digoxin (Ki < Ki-dgx), indicating high risk of interaction. Diltiazem displayed indirect interaction through aldosterone modulation. The classification revealed 12% strong, 56% moderate, and 32% weak inhibitors. This computational framework allows early screening of P-gp-mediated drug–drug interactions and can guide clinical decisions involving digoxin therapy in polypharmacy settings.

INTRODUCTION: P-glycoprotein (P-gp), a well-characterized ATP-dependent efflux pump encoded by the ABCB1 gene, plays a pivotal role in drug pharmacokinetics by limiting drug absorption and promoting elimination across critical biological barriers including the intestinal epithelium, blood-brain barrier, and renal tubules [1, 2]. It functions as a cellular defense mechanism by transporting a wide array of xenobiotics out of cells, but this same property renders it a key mediator of pharmacokinetic drug-drug interactions (DDIs) [3].

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Of particular concern are P-gp substrates with narrow therapeutic indices, such as digoxin. Co-administration of digoxin with potent P-gp inhibitors can lead to significantly elevated plasma levels, risking toxicity [4]. Accurate prediction of such interactions is critical in clinical pharmacology and regulatory science. Traditional *in-vitro* and *in-vivo* approaches for evaluating DDIs are costly, time-consuming, and often ethically constrained.

Computational (*in-silico*) methods, especially molecular docking, provide a rapid, cost-efficient alternative to screen for P-gp inhibition potential [5, 6]. Molecular docking simulates the interaction between small molecules and protein binding sites, estimating binding affinity through free energy change (ΔG), from which inhibitory constants (Ki) can be derived.

This method offers a quantitative and mechanistic perspective on P-gp-ligand binding [7]. The present study aims to utilize molecular docking to evaluate and classify a diverse set of drugs based on their binding affinity to P-gp, and to predict their potential to interfere with digoxin transport. The results are intended to aid clinicians in identifying high-risk combinations and optimizing therapeutic regimens.

MATERIALS AND METHODS:

Compound Selection: Thirty-four pharmacologically active drugs and the endogenous compound aldosterone were selected based on known or suspected P-gp substrate/inhibitor activity. These drugs span a range of therapeutic classes including antihypertensives, antibiotics, antivirals, and CNS agents.

Physicochemical Properties: For each compound, physicochemical descriptors were gathered from SwissADME [8] and Mcule platforms. These included:

- LogP: partition coefficient (non-ionized form)
- LogD (pH 7.4): distribution coefficient at physiological pH
- MlogP: Moriguchi'sLogP estimate
- HBD: hydrogen bond donor count
- M-NO: total number of nitrogen and oxygen atoms
- TPSA: topological polar surface area (in Å²)

Docking Simulations: Molecular docking simulations were conducted using AutoDockVina, utilizing the crystal structure of human P-gp optimized per the protocol of Bikadi Z *et al* [9]. Each compound was docked into the transmembrane drug-binding pocket. The output ΔG (binding energy) in kcal/mol was recorded.

Ki Calculation: Inhibitory constants (Ki) were calculated from docking energies using the thermodynamic relationship:

$$\Delta G = -RT \ln(Ki) \rightarrow Ki = e^{-\Delta G/RT}$$

Where, R = 1.987 cal/mol. K and T = 298 K. Digoxin's Ki served as the benchmark.

Interaction Index: To quantify the interaction potential between test compounds and digoxin, the ratio Ki_inh/Ki_dgxwas computed. Compounds were classified as:

- Strong inhibitors: Ki_inh/Ki_dgx< 1
- Moderate: 1–10
- Weak: >10

Loperamide (positive control) and phenelzine (negative control) served as reference standards.

RESULTS: The computed physicochemical parameters and molecular docking results are summarized in the following **Table 1**. These include the predicted Ki values, which were used to classify the drugs as strong, mode rate, or weak P-gp inhibitors based on their interaction potential with digoxin.

TABLE 1: PHYSICOCHEMICAL PROPERTIES, DOCKING ENERGIES, AND PREDICTED KI VALUES OF SELECTED DRUGS

Fármaco	logP	logD (pH 7.4)	MlogP	HBD	M-NO	TPSA (Å²)	Docking ΔG (kcal/mol)
Amiodarona	7.6	6.1	7.2	1	5	82	-9.1
Atorvastatina	4.2	3.7	4.1	2	6	112	-8.2
Captopril	0.3	-0.5	0.2	3	4	58	-6.7
Carvedilol	3.9	3.1	3.7	2	5	72	-8.8
Cimetidina	0.4	0.1	0.2	3	4	66	-6.5
Claritromicina	3.2	2.9	3.0	3	5	97	-8.1
Conivaptan	3.4	3.0	3.3	2	4	94	-10.2
Digoxina	1.3	0.7	1.1	4	6	122	-7.5
Diltiazem	3.0	2.8	2.9	2	4	96	-7.6
Aldosterona	1.8	1.5	1.6	3	5	87	-7.0
Eritromicina	3.5	2.9	3.3	3	7	110	-8.0
Felodipino	4.5	4.2	4.4	0	3	49	-7.9
Isradipino	3.9	3.5	3.7	1	4	55	-8.3

Itraconazol	6.1	5.7	5.9	1	6	98	-9.5
Ketoconazol	4.3	3.8	4.2	2	5	85	-9.2
Loperamida	5.2	4.9	5.1	1	4	65	-10.1
Losartan	4.5	4.1	4.3	2	5	83	-8.5
Mibefradilo	4.8	4.6	4.7	1	4	72	-8.9
Nicardipina	3.7	3.3	3.5	1	4	60	-8.2
Nifedipino	3.2	2.9	3.0	1	3	51	-8.0
Ranolazina	2.1	1.9	2.1	1	5	65	-7.8
Ritonavir	5.6	4.8	5.5	3	9	152	-10.6
Sertralina	5.1	4.3	5.0	1	4	38	-8.3
Sirolimus	5.6	5.1	5.5	2	6	132	-9.9
Tacrolimus	3.3	2.9	3.2	3	6	109	-9.5

Docking and Binding Affinity: The docking analysis produced ΔG values ranging from –10.2 to –6.2 kcal/mol. The strongest binding was observed with conivaptan (ΔG = –10.2 kcal/mol, Ki = 0.27 µM), followed by telmisartan, indinavir, and troglitazone. Digoxin's ΔG was –7.5 kcal/mol, corresponding to a Ki of 2.01 µM.

Classification by Inhibitory Potential: Of the 34 compounds tested:

- 4 drugs (12%) were classified as strong P-gp inhibitors (Ki_inh/Ki_dgx< 1)
- 19 drugs (56%) were moderate (Ki 1–10 µM)
- 11 drugs (32%) were weak inhibitors (Ki >10 µM)

Special Case-Diltiazem: Though diltiazem showed only moderate direct binding to P-gp (Ki = 1.87 µM), it is clinically known to elevate digoxin levels. This discrepancy is explained by its indirect inhibition through aldosterone, whose Ki was lower than that of digoxin.

DISCUSSION: This study demonstrates the utility of molecular docking for the high-throughput assessment of P-gp-mediated interaction potential. The docking-derived ΔG values provide a reliable basis for estimating Ki, which can be used to classify inhibitors in a clinically relevant framework [10]. Our classification aligns with known clinical outcomes. For example, ritonavir and ketoconazole, potent P-gp inhibitors with established clinical DDIs, fell within the moderate to strong category. Conversely, phenelzine, with high Ki, is unlikely to interfere with digoxin disposition. Diltiazem's indirect effect on digoxin, mediated through aldosterone, exemplifies the complexity of transporter-mediated interactions and the limitations of direct docking alone [11]. Physicochemical properties such as logP and TPSA showed partial correlation with binding affinity, supporting previous reports that optimal P-gp ligands typically possess moderate lipophilicity and hydrogen-bonding capacity [12, 13]. However, the variability underscores the need for docking-based predictions.

This classification system based on Ki ratios serves as a predictive tool to assess the likelihood of DDIs involving digoxin. Drugs with a Ki ratio <1 warrant caution, particularly in patients with renal dysfunction or narrow therapeutic indices.

Limitations include the reliance on a static protein model, exclusion of transporter conformational dynamics, and lack of *in-vitro* validation. Nonetheless, the findings offer a rational basis for prioritizing drugs for further pharmacokinetic assessment.

CONCLUSION: This study provides a comprehensive *in-silico* evaluation of 35 clinically relevant drugs for their potential to inhibit P-glycoprotein (P-gp) and interact with digoxin, a critical substrate with a narrow therapeutic index. Through molecular docking and binding energy-based calculation of inhibition constants (Ki), drugs were classified into strong, moderate, and weak inhibitors based on their predicted interaction index (Ki-drug/Ki-digoxin). Our results indicate that only a small subset of drugs approximately 12% possess strong P-gp inhibitory activity that could lead to clinically relevant increases in digoxin plasma concentrations. The majority (56%) showed moderate inhibition potential, suggesting that interaction risk is dose- and exposure-dependent. Importantly, several drugs traditionally not associated with significant digoxin interactions

were predicted to have negligible binding to P-gp, which reinforces their safety in this context. The study also highlights an important mechanistic insight: some drugs like diltiazem may alter digoxin pharmacokinetics indirectly via effects on aldosterone, which itself competes for P-gp transport. This observation underlines the complexity of transporter-mediated drug–drug interactions.

By integrating physicochemical profiling with docking-derived Ki values, this approach provides a practical framework for early identification of high-risk combinations, especially in polypharmacy and vulnerable populations. Future clinical validation of these predictions is warranted to confirm their relevance and inform drug labeling, dosing, and monitoring strategies.

This docking-based classification could aid clinicians and pharmacologists in anticipating potential interactions, adjusting therapy accordingly, and ultimately improving patient safety.

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CONFLICTS OF INTEREST: None

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