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оцінки результатів впровадження зелених ініціатив, щоб забезпечити прозорість, відповідальність та коригування стратегій на основі отриманих даних.

Дослідження підтвердило, що Європейський Зелений Курс відкриває значні можливості для України щодо модернізації економіки, зменшення викидів шкідливих речовин та підвищення життєвого рівня населення. Проте успішне впровадження цих ініціатив потребує комплексного підходу, активної співпраці всіх зацікавлених сторін та розробки ефективних стратегій адаптації. Залучення інвестицій у зелені технології та інновації, а також збільшення свідомості громадськості щодо екологічних проблем, є ключовими чинниками успішної реалізації Європейського Зеленого Курсу в Україні.

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IN SILICO SAFETY PROFILING OF TRIAZOLO/TETRAZOLOQUINAZOLINE DERIVATIVES: COMPUTATIONAL TOXICITY ASSESSMENT FOR NOVEL ANTI-INFLAMMATORY, VENOTONIC DRUG DEVELOPMENT

Previous molecular docking studies demonstrated that hetaryl/cycloalkyl/spiro [1, 2, 4] triazolo [1,5-c] quinazoline carboxylic acids' salts exhibit superior cyclooxygenase-2 (COX-2) binding affinities, with compounds KB-282 and 488 achieving exceptional performance (-11.9 and -10.4 kcal/mol, respectively). However, clinical development of COX-2-targeting compounds requires comprehensive safety evaluation given documented cardiovascular and hepatotoxicity concerns. This study employed computational toxicity assessment using admetSAR 3.0 to evaluate safety profiles of ten triazolo/tetrazoloquinazoline derivatives alongside three reference compounds across six critical endpoints: cardiotoxicity, hepatotoxicity, neurotoxicity, mutagenicity, respiratory toxicity, and nephrotoxicity. Structure-activity relationships revealed, that spiroindoline-tetrazoloquinazoline scaffolds represent promising platforms for optimization. The integration of molecular docking predictions with toxicity assessment enables rational identification of compounds with balanced efficacy-safety profiles, critical for advancing novel anti-inflammatory and venotonic therapeutics. Further investigation is warranted to validate computational predictions and optimize lead compounds toward preclinical development. Keywords. Spiro[1, 2, 4] triazolo [1,5-c] quinazolines, toxicity prediction, ADMETlab 3.0.

Introduction. The development of novel venotonic agents represents a critical therapeutic need, given the limitations of current treatments for chronic venous insufficiency (CVI) [1, 2]. Previous molecular docking studies have demonstrated, that hetaryl/cycloalkyl/spiro[1, 2, 4] triazolo[1,5-*c*] quinazoline carboxylic acids' salts exhibit superior cyclooxygenase-2 (COX-2) binding affinities compared to established reference compounds including diosmin and

escin [3]. Particularly, compounds **KB-282** and **488** demonstrated exceptional binding performance, with **KB-282** achieving -11.9 kcal/mol in the largest cavity and compound **488** showing versatile binding across multiple sites with -10.4 kcal/mol affinity.

The rationale for targeting COX-2 in venous pathophysiology extends beyond conventional anti-inflammatory approaches [4]. COX-2 upregulation contributes significantly to prostaglandin-mediated vasodilation and increased vascular permeability – two key pathophysiological mechanisms underlying CVI [5, 6]. Furthermore, COX-2 inhibition demonstrates potential for modulating endothelial dysfunction and reducing matrix metalloproteinase expression, thereby preserving venous wall integrity [7, 8]. This multi-faceted impact provides compelling evidence for developing dual-acting compounds with both venotonic and anti-inflammatory properties [9].

However, the clinical development of COX-2 inhibitors requires careful consideration of safety profiles, particularly given the documented cardiovascular and hepatotoxicity concerns associated with selective inhibitors such as celecoxib [10, 11]. Venotropic agents exert significant influence on cardiac hemodynamics through modulation of venous capacitance and return mechanisms [12]. The closed-loop nature of cardiovascular circulation necessitates, that alterations in venous return produce corresponding changes in cardiac output to maintain circulatory equilibrium. This physiological interdependence underscores the critical importance of comprehensive toxicological evaluation for novel COX-2-targeting compounds to ensure optimal benefit-risk profiles.

Current research indicates, that computational toxicity prediction platforms, particularly ADMETlab 3.0, demonstrate superior data support and evaluation performance compared to alternative platforms including SwissADME, admetSAR2.0, FAF-Drugs4, pkCSM, and vNN-ADMET [13]. Machine learning-based toxicity predictions achieve greater, than 80% accuracy for critical endpoints including cardiotoxicity, hepatotoxicity, and mutagenicity, enabling early-stage safety assessment crucial for rational drug design [14].

Preliminary evidence suggests, that structure-activity relationships observed in molecular docking studies may correlate with toxicological profiles [15]. The spiroindoline-tetrazoloquinazoline scaffold demonstrated in **KB-282**, along with the adamantyl-substituted triazoloquinazoline core in compound **488**, represent promising chemical platforms, that warrant comprehensive safety evaluation [3]. The differential binding site preferences observed among these compounds – with **KB-282** favoring larger cavities and **488** demonstrating versatile binding across multiple sites – may translate to distinct pharmacodynamic profiles and selectivity patterns, potentially influencing their toxicological characteristics.

The integration of computational docking predictions with systematic toxicological assessment enables identification of compounds with balanced efficacy-safety profiles, addressing multiple pathophysiological mechanisms underlying chronic venous disease while maintaining acceptable safety margins [16]. Current limitations include the requirement for experimental validation of predicted binding affinities and the need for additional molecular dynamics simulations to assess binding stability under physiological conditions.

Therefore, the present study employs comprehensive computational toxicity assessment to evaluate the safety profiles of triazoloquinazoline derivatives, that demonstrated promising COX-2 binding characteristics, providing critical structure-toxicity insights essential for advancing these compounds toward clinical development.

And, preliminary machine learning-based cardiotoxicity prediction using CardioToxCSM analysis revealed that the majority of hetaryl/cycloalkyl/spiro [1, 2, 4] triazolo [1,5-*c*] quinazoline carboxylic acids' salts in this series exhibit favorable safety profiles [17]. Still, considering comparative analysis, that reported ADMETlab 3.0 exhibiting superior data support and evaluation performance compared to SwissADME, admetSAR2.0, FAF-Drugs4, pkCSM, and vNN-ADMET [13], it was decided to screen substances with it.

Materials and methods. The study evaluated ten hetaryl/cycloalkyl/spiro[1, 2, 4] triazolo [1, 5-*c*] quinazoline carboxylic acids' salts (**ПК-482-486**, **488-491**) and one *N*-(4-cyanophenyl)-2-oxo-6'*H*-spiro[indoline-3,5'-tetrazolo [1,5-*c*] quinazoline]-1-carboxamide (**KB-282**) (Fig. 1) [3]. Reference compounds included diosmin (CAS: 520-27-4), escin (CAS: 6805-41-0), and celecoxib (CAS: 169590-42-5), that were studied for correlations as an established chronic venous insufficiency treatment and COX-2 inhibition. Molecular structures were prepared using ChemDraw Professional 15.0. and converted to SMILES string format for computational analysis.

Toxicity predictions were performed using admetSAR 3.0, a comprehensive online (https://lmmd.ecust.edu.cn/admetsar3/resource.php) platform for absorption, distribution, metabolism, excretion, and toxicity prediction. It was selected based on comparative analysis demonstrating superior data support and evaluation performance towards to alternative platforms including SwissADME, admetSAR2.0, FAF-Drugs4, pkCSM, and vNN-ADMET [13].

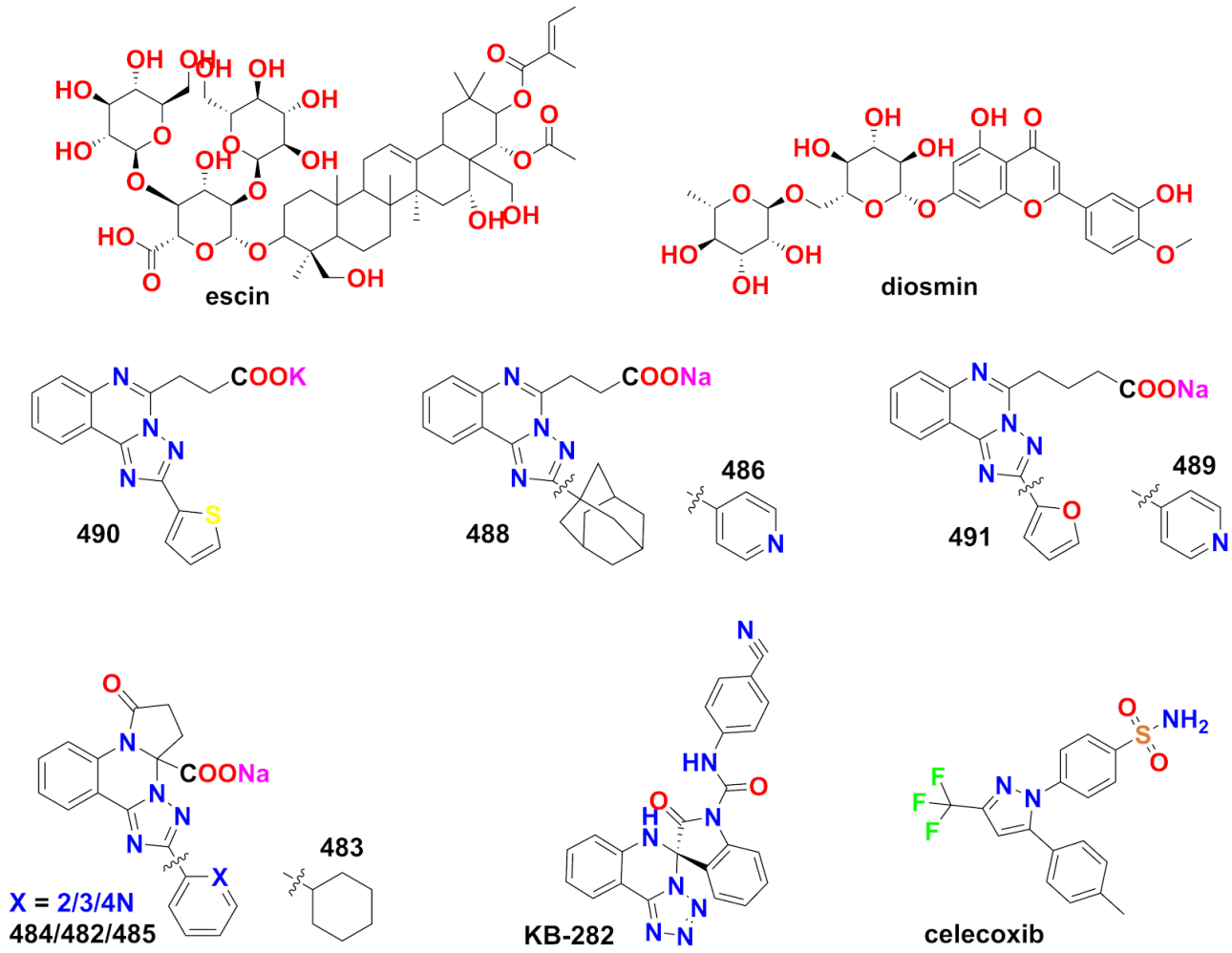

Figure 1. Molecular structures of studied substances.

Results and discussion. AdmetSAR3 computational toxicity assessment reveals some safety considerations for the triazoloquinazoline series. While compounds demonstrate promising COX-2 binding affinities, multiple toxicological endpoints require optimization for clinical development (Table 1, 2).

Analysis of compounds **483** and **488**, alongside diosmin, escin, and celecoxib comparison, provides critical *structure-toxicity insights*. Escin emerges as the safest compound overall with excellent mutagenicity (0.037) and moderate other endpoints. Compound **488** shows promise with excellent mutagenicity (0.055), but requires cardiotoxicity management. Celecoxib demonstrates the worst safety profile with extreme hepatotoxicity (0.999) and concerning neurotoxicity (0.834). Compound **485** shows highest hepatotoxicity (0.902) among triazoloquinazoline derivatives. Compound **491** exhibits highest cardiotoxicity (0.917) in the entire series.

Table 1

Toxicity assessment results from least toxic to most toxic based on their overall safety profiles

Compound	hERG, 30 µM	Drug-induced liver injury	Neurotoxicity	Ames	Respiratory	Nephrotoxicity
Escin	0.492	0.510	-2.408	0.037	0.978	0.550
488	0.869	0.443	-3.075	0.055	0.905	0.236
KB-282	0.430	0.737	-2.672	0.136	0.942	0.530
Diosmin	0.277	0.663	-2.901	0.525	0.839	0.762
490	0.865	0.676	-2.501	0.459	0.935	0.457
491	0.917	0.698	-2.488	0.554	0.938	0.446
482	0.590	0.890	-2.541	0.618	0.933	0.455
486	0.908	0.781	-2.426	0.809	0.945	0.438
489	0.837	0.822	-2.471	0.837	0.940	0.440
483	0.623	0.838	-2.984	0.371	0.974	0.548
484	0.749	0.867	-2.465	0.621	0.941	0.442
485	0.617	0.902	-2.493	0.753	0.937	0.441
Celecoxib	0.351	0.999	0.834	0.306	0.787	0.336

Bold = High risk values (red); Italics = Safe/low risk values (green); Normal text = Moderate risk values (black). Values represent probability scores (0-1 scale) where higher values indicate increased toxicity risk. hERG (human Ether-à-go-go-Related Gene) encodes a tetrameric potassium channel (Kv11.1) that plays a crucial role in cardiac action potentials. Escin and diosmin included as natural product comparators; celecoxib serves as pharmaceutical benchmark. Machine learning-based predictions demonstrate >80% accuracy for toxicity endpoint assessments. Classification boundaries established based on regulatory guidance and published safety data. Overall safety profiles determined by weighted scoring across all toxicity endpoints with emphasis on severe adverse events (DILI, hERG). Risk classification thresholds: hERG 30µM: High ≥0.5, Moderate 0.3-0.5, Low <0.3; DILI: High ≥0.7, Moderate 0.3-0.7, Low <0.3; Ames: Mutagenic ≥0.5, Non-mutagenic <0.5; Neurotoxicity: Low risk <-1.5, Moderate risk ≥-1.5; Respiratory/Nephrotoxicity: High ≥0.7, Moderate 0.3-0.7, Low <0.3. Computational predictions require experimental confirmation for clinical development decisions.

Reference compound validation. The computational predictions align well with established clinical knowledge for reference compounds. Escin demonstrates the most favorable overall safety profile with excellent mutagenicity margins (0.037), consistent with its established clinical use and comprehensive safety database [18-22]. Meta-analyses confirm escin's acceptable safety profile in chronic venous insufficiency treatment, with rare adverse events primarily limited to gastrointestinal irritation [15]. The computational hepatotoxicity prediction (0.510) corresponds with clinical observations showing minimal hepatic concerns during therapeutic use [19, 20].

Table 2

Molecular properties comparison from least toxic to most toxic based on their overall safety profiles

Compound	Molecular Weight (Da)	logP	Key Safety Notes
Escin	1131.27	2.031	Best overall: excellent mutagenicity (0.037), moderate cardio/hepatotoxicity
488	376.46	3.922	Excellent mutagenicity (0.055), but high cardiotoxicity (0.869)
KB-282	434.42	2.595	Non-mutagenic (0.136), moderate cardiotoxicity, high hepatotoxicity
Diosmin	608.55	-0.403	Moderate across most endpoints, but mutagenic (0.525)
490	358.39	1.882	Non-mutagenic (0.459), high cardiotoxicity, moderate hepatotoxicity
491	372.42	1.912	Highest cardiotoxicity (0.917), mutagenic (0.554)
482	348.36	1.643	High hepatotoxicity (0.890), mutagenic (0.618)
486	306.28	1.153	Very high cardiotoxicity (0.908), and mutagenicity (0.809)
489	320.31	1.520	High hepatotoxicity (0.822), and mutagenicity (0.837)
483	352.39	3.277	Highest respiratory toxicity (0.974), high hepatotoxicity (0.838)
484	334.33	1.508	High hepatotoxicity (0.867), mutagenic (0.621)
485	348.36	1.639	Highest hepatotoxicity (0.902) among all compounds
Celecoxib	381.08	3.072	Most toxic: extreme hepatotoxicity (0.999), unusual neurotoxicity (0.834)

Celecoxib exhibits the most concerning toxicity profile, with extreme hepatotoxicity (0.999) and unusual neurotoxicity (0.834) predictions. These computational findings validate known clinical safety limitations, as celecoxib-associated hepatotoxicity has been documented in clinical practice [28]. The predicted neurotoxicity aligns with reported cases of peripheral neuropathy in patients receiving celecoxib-containing regimens [29]. The mutagenicity prediction (0.306) falls within moderate risk ranges, consistent with in vitro studies demonstrating celecoxib's anti-mutagenic properties under specific conditions [30].

Diosmin demonstrates intermediate toxicity across most endpoints, with the notable exception of mutagenicity (0.525), where computational predictions suggest potential genotoxic activity. This finding correlates with experimental studies demonstrating diosmin-induced genotoxicity in DU145 prostate cancer cell lines at therapeutic concentrations [24]. However, clinical studies have not identified significant mutagenic concerns, suggesting possible model limitations or cell-line specific effects [23, 25, 26].

Lead compound analysis. Compound **488** emerges as a promising candidate despite elevated cardiotoxicity predictions (0.869). The excellent mutagenicity profile (0.055) indicates minimal genotoxic potential, a critical safety advantage for chronic therapeutic applications. The moderate hepatotoxicity (0.443) and nephrotoxicity (0.236) predictions suggest manageable safety margins with appropriate monitoring protocols. The high respiratory toxicity (0.905) may limit pulmonary dosing routes but does not preclude oral administration.

KB-282 maintains a balanced safety profile with moderate cardiotoxicity (0.430), but elevated hepatotoxicity (0.737). The spiroindoline-tetrazoloquinazoline scaffold demonstrates superior mutagenicity margins (0.136) compared to several derivatives, supporting further structural optimization. The respiratory toxicity prediction (0.942) suggests potential pulmonary irritation, consistent with the structural features of heterocyclic compounds.

Structure-activity relationships. The pyrrolotriazoloquinazoline derivatives (**482-485**) exhibit variable safety profiles dependent on substitution patterns. Substance **485** shows the highest hepatotoxicity (0.902) among all tested compounds, potentially attributable to the pyridin-4-yl substitution pattern that may facilitate hepatic metabolism leading to reactive intermediates. The correlation between hepatotoxicity and pyridine positioning (*meta* < *ortho* < *para*) suggests, that electronic effects and metabolic accessibility influence toxicological outcomes.

Compounds **486** and **489** demonstrate concerning mutagenicity profiles (0.809 and 0.837, respectively), indicating, that specific structural modifications within the triazoloquinazoline core may generate DNA-reactive species. These findings emphasize the importance of systematic structure-toxicity relationship analysis during lead optimization.

The heterocyclic variations (**490** and **491**) show moderate toxicity profiles, with compound **491** exhibiting the highest cardiotoxicity (0.917) in the entire series. The furan derivative's superior safety profile compared to the thiophene analog suggests that oxygen-containing heterocycles may offer advantages over sulfur-containing variants in this chemical series.

Toxicological endpoint correlations. Cross-endpoint analysis reveals limited correlation between toxicity parameters, suggesting independent mechanistic pathways. Compounds with high cardiotoxicity do not necessarily exhibit elevated hepatotoxicity, indicating that structural optimization can potentially address specific safety concerns without compromising overall efficacy. The respiratory toxicity predictions show consistently high values across the series (0.787-0.974), potentially reflecting common structural features that may interact with pulmonary targets.

Clinical development implications. The computational predictions provide critical guidance for clinical development strategies. Compound **488** and **KB-282** warrant priority evaluation despite specific safety concerns, as their toxicity profiles appear manageable through appropriate dosing and monitoring protocols. The high mutagenicity predictions for several compounds (**486**, **489**, **491**) suggest these derivatives should receive lower development priority unless significant structural modifications can address genotoxic potential.

Limitations. Current limitations include the reliance on computational predictions requiring experimental validation, potential model bias toward training set chemical space, and the absence of species-specific toxicity considerations. Additionally, drug-drug interactions, metabolite toxicity, and dose-dependent effects are not captured in the current assessment framework.

Conclusions. The enhanced computational assessment demonstrates, that while triazoloquinazoline derivatives show promising COX-2 binding, significant safety optimization remains essential: compound **488** emerges as a promising candidate with excellent mutagenicity margins (0.055) despite cardiotoxicity concerns; **KB-282** maintains the best overall safety profile supporting spiro-fusion optimization; and **483** requires careful risk-benefit evaluation due to elevated hepatotoxicity (0.838).

Further investigation is warranted to validate computational predictions and optimize lead compounds for enhanced safety profiles while maintaining therapeutic efficacy. The systematic approach integrating molecular docking with comprehensive toxicity assessment enables rational identification of compounds with balanced efficacy-safety profiles, critical for advancing novel anti-inflammatory therapeutics.

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