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VIRTUAL SCREENING OF THE DRUGBANK DATABASE USING MOLECULAR DOCKING METHODS TO IDENTIFY POTENTIAL INHIBITORS OF THE HUMAN Grp94 PROTEIN

Abstract. The endoplasmic reticulum chaperone Grp94 is a promising therapeutic target for anticancer drug development due to its essential role in maintaining the stability of multiple proteins involved in tumor growth, survival, and metastasis. A total of 11 992 DrugBank compounds were docked using AutoDock Vina. The obtained docking results were subsequently re-evaluated with the machine learning-based scoring functions PLANET and OnionNet-2. A pairwise correlation analysis was performed to assess the agreement between the prediction methods, and an exponential consensus ranking (ECR) was applied to identify the most promising candidates. The consensus analysis identified the top 100 candidate compounds with the highest predicted affinity toward Grp94. Among them, DB12323 demonstrated the most consistent performance, being the only compound ranked within the top 100 by all three scoring methods and the highest-ranked compound according to the ECR. In addition, DB12983, DB20856, and DB14214 were identified as promising candidates based on the highest affinity predictions obtained with AutoDock Vina, OnionNet-2, and PLANET, respectively. The obtained results demonstrate that the combined application of multiple scoring functions and the consensus ranking improve the reliability of virtual screening and facilitate the identification of compounds with consistently high predicted affinity toward Grp94. The selected candidates represent promising targets for further molecular dynamics simulations and subsequent experimental validation.

Keywords: virtual screening, Grp94, breast cancer, small molecule inhibitors, Radotinib, Phthalocyanine, Mazokalim, Rose bengal lactone, molecular docking, AutoDock Vina, PLANET, OnionNet-2

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ВИРТУАЛЬНЫЙ СКРИНИНГ БАЗЫ ДАННЫХ DRUGBANK С ПРИМЕНЕНИЕМ МЕТОДОВ МОЛЕКУЛЯРНОГО ДОКИНГА ДЛЯ ПОИСКА ПОТЕНЦИАЛЬНЫХ ИНГИБИТОРОВ ЧЕЛОВЕЧЕСКОГО БЕЛКА Grp94

Аннотация. Шаперон эндоплазматического ретикулума Grp94 является перспективной терапевтической мишенью для разработки противоопухолевых препаратов благодаря его ключевой роли в поддержании стабильности множества белков, участвующих в росте, выживании и метастазировании опухолей. В общей сложности 11 992 соединения из базы данных DrugBank были подвергнуты молекулярному докингу с использованием программы AutoDock Vina. Полученные результаты докинга были затем переоценены с помощью оценочных функций PLANET и OnionNet-2, основанных на методах машинного обучения. Для оценки согласованности различных методов прогнозирования был проведен попарный корреляционный анализ, а для выявления наиболее перспективных соединений применено экспоненциальное консенсусное ранжирование (exponential consensus ranking, ECR). Консенсусный анализ позволил определить 100 соединений с наивысшей прогнозируемой аффинностью к Grp94. Среди них соединение DB12323 продемонстрировало наиболее стабильные результаты, оказавшись единственным соединением, вошедшим в первую сотню по всем трем методам оценки, а также занявшим первое место по результатам ECR. Кроме того, соединения DB12983, DB20856 и DB14214 были идентифицированы как наиболее перспективные кандидаты на основании наивысших прогнозируемых значений аффинности, выявленных с помощью методов AutoDock Vina, OnionNet-2 и PLANET соответственно. Полученные результаты демонстрируют, что совместное применение нескольких оценочных функций и консенсусного ранжирования повышает надежность виртуального скрининга и способствует выявлению соединений с устойчиво высокой прогнозируемой аффинностью к Grp94. Отобранные соединения представляют собой перспективные объекты для дальнейшего исследования с использованием молекулярной динамики и последующей экспериментальной валидации.

Ключевые слова: виртуальный скрининг, Grp94, рак молочной железы, низкомолекулярные ингибиторы, Radotinib, Phtalocyanine, Mazokalim, Rose bengal lactone, молекулярный докинг, AutoDock Vina, PLANET, OnionNet-2

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Introduction. *Cancer as a global public health issue.* Cancer remains one of the leading causes of death worldwide and represents one of the most significant medical and social challenges of our time. Despite significant progress in diagnosis and the development of new treatment methods, the incidence of many types of cancer continues to rise due to an aging population, environmental factors and changes in lifestyle. According to the American Cancer Society, by early 2026, approximately 2.1 million new cases of cancer had been recorded worldwide, along with nearly 630,000 deaths related to malignant tumors [1]. The global number of new cases continues to rise, highlighting the need to identify new therapeutic approaches and molecular targets for anti-tumor therapy.

Breast cancer occupies a special place among malignant diseases; it is the most commonly diagnosed malignant tumor in women and remains one of the leading causes of cancer-related mortality according to SEER, which is an authoritative source for cancer statistics in the United States (https://seer.cancer.gov/statfacts/html/breast.html). Despite the availability of surgical, radiotherapy, hormonal and targeted treatments, the development of drug resistance and the high molecular heterogeneity of tumors significantly limit the effectiveness of existing therapies. Consequently, an active search is ongoing for new molecular targets involved in maintaining the viability of tumor cells.

Heat shock proteins as promising therapeutic targets. Heat shock proteins (HSPs), which constitute a family of molecular chaperones, are one of the most important systems for maintaining cellular homeostasis. Their main function is to ensure the correct folding of proteins, prevent their aggregation, stabilize their spatial structure and participate in the degradation of damaged proteins [2]. In normal cells, HSP expression increases significantly in response to various types of cellular stress, including hypoxia, oxidative stress, exposure to toxic substances and elevated temperature [3].

Tumor cells are subject to constant physiological stress caused by a high rate of proliferation, the accumulation of mutations, metabolic disturbances and hypoxia. To maintain viability, they significantly increase the expression of genes encoding proteins that ensure the stability of a large number of oncoproteins involved in tumor growth, survival, and invasion [4]. Elevated expression of members of the HSP family has been detected in various types of malignant tumors and often correlates with a poor prognosis [5]. Owing to their ability to simultaneously regulate multiple signaling pathways, heat shock proteins are regarded as promising targets for modern anticancer therapy.

Grp94 – an endoplasmic reticulum member of the Hsp90 family. Of particular interest is the Grp94 protein (Glucose-Regulated Protein 94, Hsp90B1, gp96), a member of the Hsp90 family of molecular chaperones. Unlike the cytosolic isoforms of Hsp90, Grp94 is located in the lumen of the endoplasmic reticulum and performs specialized functions to ensure the correct maturation of secreted and membrane proteins [6].

Grp94 is involved in the folding and stabilization of a wide range of proteins, including integrins, Toll-like receptors, HER family receptors, insulin-like growth factor receptors, Wnt-signaling pathway proteins, immune receptors and other proteins essential for normal cellular function [7, 8]. Consequently, Grp94 plays a key role in maintaining cell proliferation, migration, angiogenesis and the regulation of the immune response.

Numerous studies have shown that Grp94 expression is significantly elevated in various types of malignant tumors, including breast, lung, liver, stomach, colon and prostate cancers, as well as melanoma [9, 10]. Grp94 interacts with the HER2 receptor and promotes its dimerization [11]. This dimerization is a critical step in the activation of the signaling pathway that triggers tumor cell proliferation and survival. The expression of gp96 on the surface of tumor cells correlates with the level of HER2 phosphorylation and proliferative activity. High levels of this protein's expression are often associated with increased tumor aggressiveness, the development of metastases, resistance to chemotherapy and reduced overall patient survival.

Inhibition of Grp94 as a promising strategy for anti-tumor therapy. Given the central role of Grp94 in maintaining the viability of tumor cells, the inhibition of this protein is regarded as a promising avenue for the development of new anti-tumor drugs. Unlike the inhibition of all members of the Hsp90 family, selective targeting of Grp94 has the potential to reduce the severity of side effects caused by the suppression of the functions of cytosolic Hsp90 isoforms.

In recent years, various classes of Grp94 inhibitors have been developed, most of which bind to the protein's ATP-binding domain. The best-known representatives are derivatives of purine, resorcinol, and

benzamide, as well as a number of experimental compounds that have demonstrated high selectivity for Grp94 [12, 13]. The following compounds may be used as potential experimental inhibitors of this protein: geldanamycin, radicicol (RDC), radamide (RDA) and its analogues [14]. However, most known inhibitors are currently still at the preclinical stage of research, and the challenge of identifying compounds with high efficacy, selectivity and favorable pharmacokinetic properties remains a pressing issue.

Virtual screening as a tool for discovering new inhibitors. One of the most effective modern approaches to discovering new drug compounds is virtual screening, which makes it possible to significantly reduce the scope of costly experimental research. One of the key stages of virtual screening is molecular docking, which simulates the interaction of a ligand with a protein's active site and enables the estimated binding affinity to be assessed [15], as well as allowing certain candidate compounds to be ranked and thus prioritized for further investigation using molecular dynamics and *in vitro* methods.

It should be noted that the accuracy of the prediction depends significantly on the scoring function used. Different algorithms may evaluate the contribution of individual types of intermolecular interactions differently, as a result of which the ranking of compounds may vary considerably. For this reason, modern research increasingly involves re-evaluating docking results using several independent scoring functions, which helps to improve the reliability of selecting the most promising candidates for further investigation [16].

Materials and methods. In this work, the DrugBank database (DrugBank Release Version 5.1.15: https://go.drugbank.com/releases) was screened using molecular docking methods to identify novel potential inhibitors of the human Grp94 protein.

Molecular docking. The preparation of the crystal structure of Grp94 (PDB ID: 6AOL; https://www.rcsb.org/) for molecular docking included the following steps: (i) the addition of the missing hydrogen atoms to the PDB Grp94 structure by PyMOL 3.1.6 (https://www.pymol.org), (ii) the selection of the required protein chain, and (iii) the conversion of the protein structure into a PDBQT file via AutoDock Tools 1.5.6 (https://ccsb.scripps.edu).

For the preparation of the ligand dataset, all ligand files in the DrugBank database were converted from the SDF format into PDB structures using the Python library RDKit (https://www.rdkit.org), followed by conversion into .pdbqt using MGLTools 1.5.6 (https://ccsb.scripps.edu/mgltools/1-5-6/).

At the final stage, molecular docking was carried out using AutoDock Vina 1.2.7 (https://vina.scripps.edu) with the following grid box parameters: ΔX = 20 Å, ΔY = 20 Å, ΔZ = 19 Å centered at x = –119 Å, y = 131 Å, z = 60 Å. The value of exhaustiveness parameter defining the number of individual sample runs was set to 100. The required exhaustiveness depends on the size of the docking box [17]. Moreover, highly flexible ligands require a high exhaustiveness value [18]. Consequently, the exhaustiveness value was set to 100.

A comparison of molecular docking results and affinity prediction models. Despite the widespread use of molecular docking in virtual screening, the docking score does not always accurately reflect the experimental binding affinity. This is because the built-in scoring functions of docking software use simplified physicochemical models of interactions and are primarily designed to identify the most likely ligand conformation. In this regard, a promising approach is the additional evaluation of complexes using modern machine learning models trained on experimental data regarding protein–ligand interactions. Such models are capable of more accurately predicting binding affinity, expressed in terms of pK_d. The PLANET [19] and OnionNet-2 [20] scoring functions were used to re-evaluate the results obtained using AutoDock Vina.

The energy values obtained from AutoDock Vina were converted to pK_d values to enable further valid comparisons using the following equation:

$$pK_d = -\frac{\Delta G}{RT \ln 10},$$

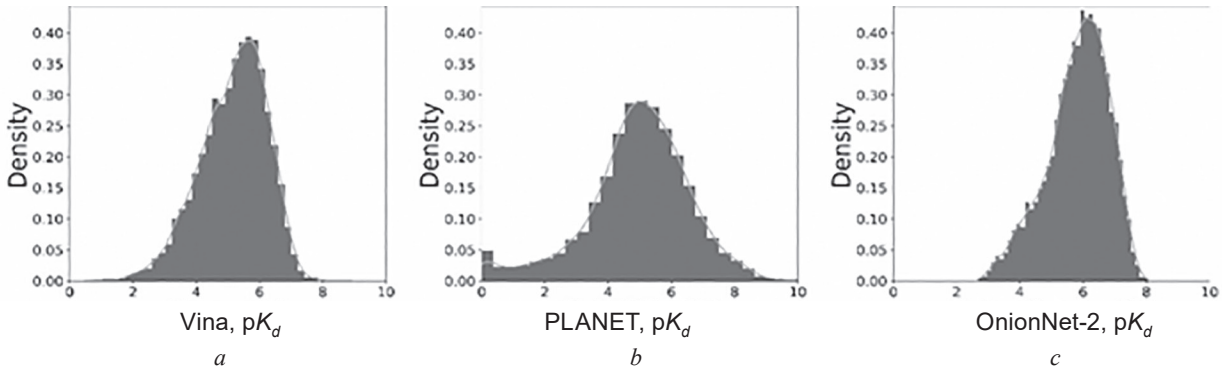
where ΔG is the Gibbs free energy, R is the gas constant (R = 0.001987 kcal/(mol·K)) and T is the temperature in Kelvin (T = 298.5 K).

Results and discussion. *Distribution of affinity and binding energy values for complexes.* During the virtual screening, 12,133 compounds from the DrugBank database were analyzed. For each compound, the binding energy was determined using molecular docking via AutoDock Vina, after which the resulting 'ligand–target' complexes were further evaluated using the deep learning models PLANET and OnionNet-2 to predict the binding affinity. A further 141 compounds were excluded from the subsequent statistical analysis as their predicted pK_d values were found to be invalid. pK_d values of 8–9 indicate a high affinity of the compound according to the method used. The main descriptive statistics parameters are shown in Table 1.

Table 1. **Descriptive statistics of the predicted pK_d values obtained using AutoDock Vina, PLANET, and OnionNet-2**

Metrics, pK_d	Vina	PLANET	OnionNet-2
Mean value	5.167	4.929	5.821
Standard deviation	1.059	1.657	0.973
Min value	0.049	0.000	2.677
Max value	8.909	15.026	8.056

The histograms of the values show a distribution that approximates a normal distribution, and are shown in Figure 1. The graphs of the distributions of the Vina pK_d and PLANET pK_d values are shifted closer to the origin of the coordinate axes, and the latter also exhibits a peak in the region where pK_d = 0.



a *b* *c*

Fig. 1. Distribution of predicted binding affinities (pK_d) estimated by AutoDock Vina, PLANET and OnionNet-2

Correlation analysis of the values obtained from molecular docking and the performance of the evaluation functionsTo carry out the correlation analysis, Pearson's and Spearman's statistical correlation coefficients were calculated. Correlation coefficients are provided in Table 2.

Table 2. **Correlation coefficients between the predicted pK_d values obtained using AutoDock Vina, PLANET, and OnionNet-2**

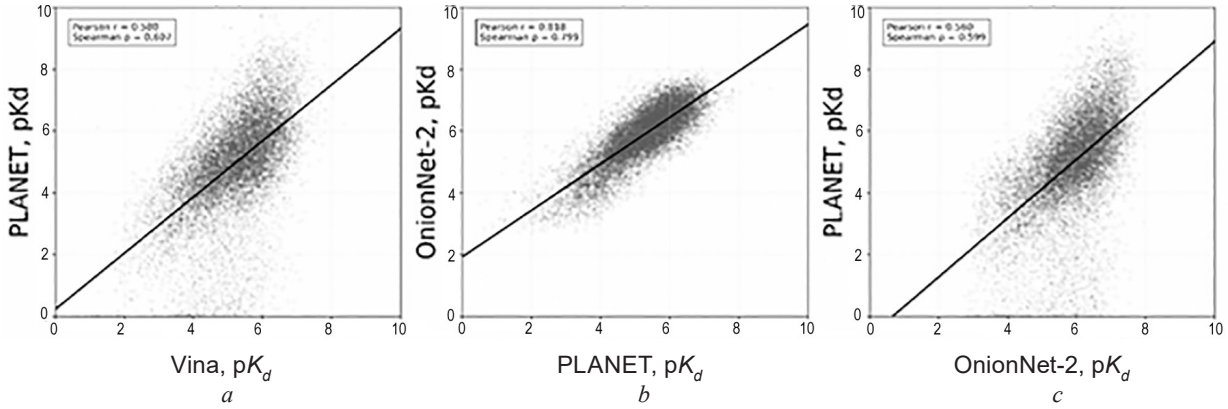
Pairs of Scoring Functions	Pearson's *r*	Spearman's ρ
Vina & PLANET	0.580	0.607
Vina & OnionNet-2	0.818	0.799
PLANET & OnionNet-2	0.560	0.599

Correlation analysis revealed a moderate positive relationship between AutoDock Vina pK_d values and pK_d values predicted by PLANET (Pearson's r = 0.580, Spearman's ρ = 0.607). A stronger positive correlation was observed between Vina scores and OnionNet-2 predictions (Pearson's r = 0.818, Spearman's ρ = 0.799), indicating greater agreement between these two approaches. Predicted pK_d values obtained using PLANET and OnionNet-2 showed a moderate positive correlation (Pearson's r = 0.560, Spearman's ρ = 0.599), suggesting that although both deep learning models identify similar trends, which is shown in Figure 2, their affinity predictions are not identical.

OnionNet-2 demonstrated a stronger agreement with docking-based ranking than PLANET.

Identification of the best compounds. To select the most promising candidates, a consensus ranking of compounds was carried out based on the ranks obtained from the binding affinity assessments performed using the AutoDock Vina, PLANET, and OnionNet-2 scoring functions. The use of a consensus approach reduces the influence of the limitations of individual scoring functions and improves the reliability of selecting compounds that demonstrate consistently high scores when assessed using several independent methods.

The final consensus rank was calculated using the exponential consensus ranking (ECR) method, which is based on an exponential transformation of the ranks of the compounds under investigation [21]. The higher the ECR value, the more promising the compound is considered to be. The general rank was calculated using the function 'rankdata' with ranking method 'average' from the Python library SciPy (https://docs.scipy.org/).



a *b* *c*

Fig. 2. Scatter plots comparing the predicted pK_d values obtained using AutoDock Vina, PLANET, and OnionNet-2. Solid lines represent linear regression fits. Pearson's (r) and Spearman's (ρ) correlation coefficients are shown for each pair of scoring functions

Table 3. **Top-10 candidate compounds selected using exponential consensus ranking (ECR)**

Generic Name	DB ID	pK_d			Rank			ECR
		Vina	Onion Net-2	PLANET	Vina	Onion Net-2	PLANET	
Radotinib	DB12323	7.3	7.9	8.6	48.5	10.0	76.0	0.002409
Nilotinib	DB04868	7.5	7.9	8.2	31.0	9.0	181.0	0.002356
Zandelisib	DB18245	7.1	7.6	9.2	143.0	75.0	30.0	0.002335
Gemnelatinib	DB21513	7.0	7.7	9.1	223.5	50.0	31.0	0.002303
Phthalocyanine	DB12983	8.9	7.4	10.1	1.0	312.0	8.0	0.002303
Adagrasib	DB15568	7.4	7.5	8.2	42.0	140.0	182.0	0.002262
Rebastinib	DB13005	7.3	7.4	8.4	51.0	199.0	119.0	0.002259
Risvodetinib	DB21602	6.9	7.7	8.6	332.0	45.0	79.0	0.002215
Umbralisib	DB14989	6.9	8.0	8.1	245.0	5.0	209.0	0.002209
L-756423	DB02009	7.2	7.6	8.0	76.0	97.0	285.0	0.002208

Despite moderate and strong correlations between the individual methods, an analysis of the overlap among the top candidates, which are presented in Table 3, revealed significant differences in their ranking. When comparing the top 100 compounds selected by each method, only one compound – Radotinib (DB12323) – appeared on all three lists simultaneously. Notably, this same compound ranked first in the consensus ranking based on the average rank from AutoDock Vina, PLANET and OnionNet-2. This result demonstrates a high degree of agreement in the evaluations of this compound by different computational approaches and allows it to be considered the most promising candidate for further experimental validation. DB12323 – the small molecule Radotinib – is a tyrosine kinase receptor inhibitor classified as 'investigational'. The compound is being investigated as a treatment for various types of cancer, in particular leukemia. Figure 3 shows the Radotinib molecule in the Grp94 protein binding site.

The second most significant candidate is the compound Phthalocyanine (DB12983) (Figure 4). It has the highest pK_d value according to Vina, and also has a high pK_d value according to PLANET. However, the pK_d value calculated using OnionNet-2 does not feature among the top 100 compounds. This discrepancy highlights differences in affinity assessment between various predictive models and points to the need for a comprehensive interpretation of results obtained using several independent scoring functions. Nevertheless, this compound can be considered as one of the potential Grp94 inhibitors. Phthalocyanine is classified in the 'investigational' group. The mechanism of action of the compound involves the inhibition of amyloid-beta precursor proteins, which are involved in the regulation of transcription and various signaling pathways necessary for cell differentiation and proliferation. It is being considered as a therapeutic compound for photodynamic therapy in patients with keratosis and skin cancer.

Two other compounds worthy of note are Mazokalim (DB20856) and Rose Bengal lactone (DB14214), which are the top-ranked compounds by pK_d, as calculated by OnionNet-2 and PLANET respectively. Mazokalim is a potassium channel activator and belongs to the group of experimental drugs, most likely classified as antihypertensive drugs according to the WHO International Nonproprietary

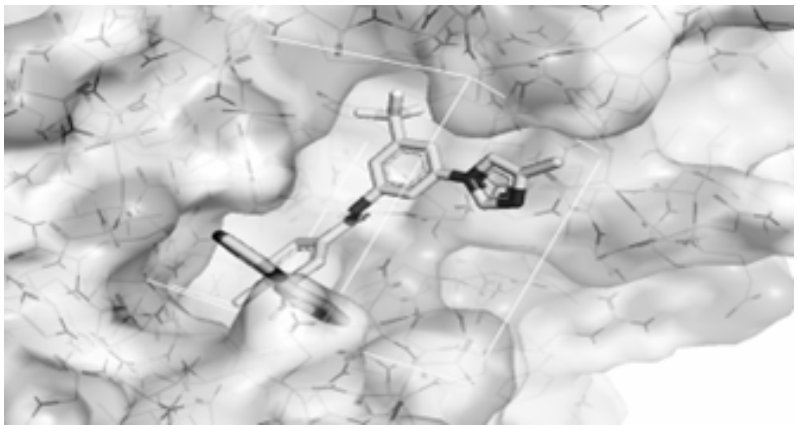


Fig. 3. Structure of the Grp94 protein with Radotinib (DB12323) in the binding site. The docking grid box is shown

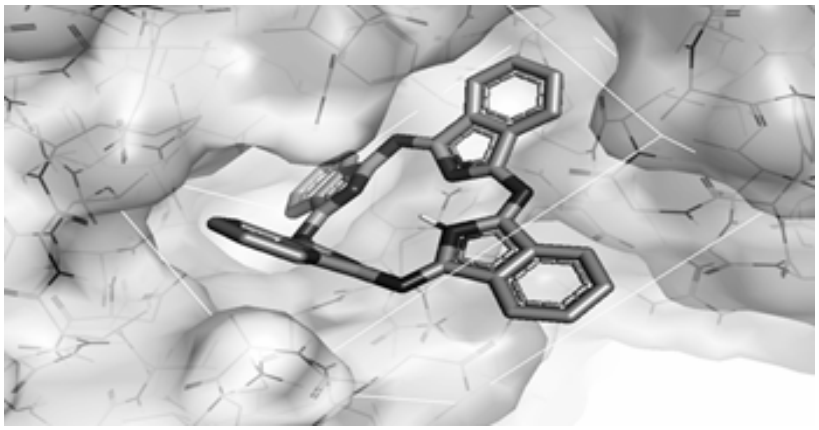


Fig. 4. Structure of the Grp94 protein with ligand DB12983 in the binding site. The docking grid box is shown

Names (INN). Rose Bengal lactone inhibits the kinesin-1 molecule and belongs to the group of experimental drug compounds. The former ranks in the top 20 by pK_d according to PLANET and OnionNet-2, but has a low rank according to Vina. The latter, in turn, has very low ranks according to both Vina and OnionNet-2. Such discrepancies between the results of different methods indicate a lack of consistent evidence for the high affinity of these compounds for Grp94. Consequently, their potential as inhibitors appears less convincing compared with compounds that have received high ratings from several independent methods simultaneously.

It should be noted that the results obtained at this stage are considered preliminary and are intended for the approximate identification of potential candidate compounds for further *in silico* investigation. The aim of this study was not to provide a definitive ranking of candidates for *in vitro* studies but to show which of the compounds can be studied in further experiments and additional computational approaches.

Conclusion. Thus, during a virtual screening of the DrugBank database of medicinal compounds, affinity values were predicted for 11,992 compounds using the AutoDock Vina, PLANET and OnionNet-2 functions. A statistical analysis of the results was carried out to identify the most likely potential inhibitors. The use of consensus ranking enabled the selection of the top 100 candidates, among which Radotinib stands out. This compound is the only one to feature in the top 100 for each affinity predicted by the functions, and is also ranked number one according to the consensus ranking. On this basis, this compound can be considered as one of the most promising inhibitors for Grp94.

In addition to this compound, Phthalocyanine, Mazokalim and Rose Bengal lactone are also candidates for further validation. All three are ranked as top-1 by pK_d values as estimated by AutoDock Vina, OnionNet-2 and PLANET, respectively.

The next stage of the research involves conducting molecular dynamics simulations to confirm the stability of the interaction between the ligands of interest and the target protein.

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