MOL2NET, International Conference Series on Multidisciplinary Sciences
CHEMINFOUNC-01: Chemoinformatics Workshop, *UNC Chape Hill, USA, 2019*

In silico studies for bioactive proposal against human retinoblastoma from 3,4,5-trihydroxycinnamic acid derivatives

Alex France Messias Monteiro[1,4], Érika Paiva de Moura[1], Natália Ferreira de Sousa[1], Eugene Muratov[1,2], Maria Aparecida Brilhante Damasceno[4], Marcus Tullius Scotti[1], Luciana Scotti[1,3]

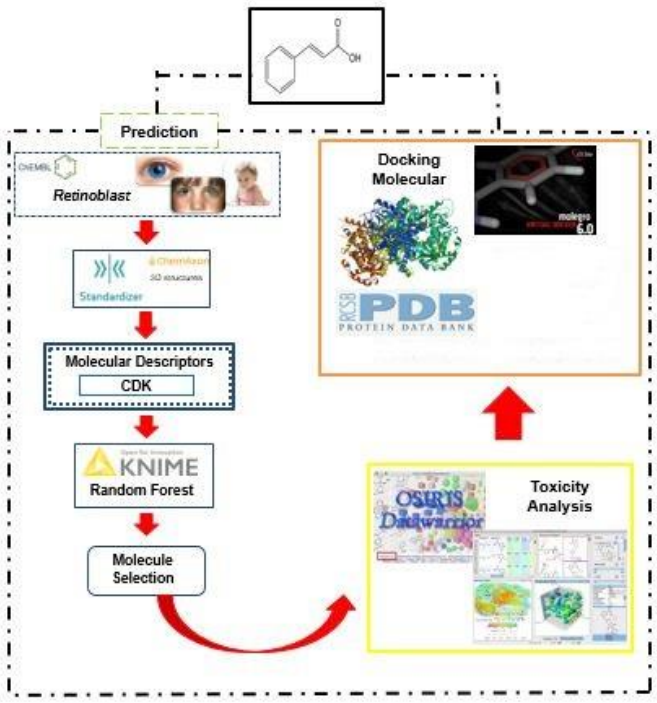
1 Postgraduate Program in Natural and Synthetic Bioactive Products, Federal University of Paraíba, Health Science Center. Campus I, 50670-910, João Pessoa, PB, Brazil;

2 Laboratory for Molecular Modelling, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599, EUA;

3 Teaching and Research Management - University Hospital, Federal University of Paraíba, João Pessoa, PB, Brazil;

4 Specialization Course in Aesthetics and Cosmetics – Integrated Technology and Research Center – CINTEP, Rua Deputado Geraldo Mariz, 849, Tambauzinho, João Pessoa - PB, CEP 58042-060;

Graphical Abstract



Abstract

Retinoblastoma is a pediatric malignant tumor, common in children up to 5 years old. It is a disease commonly developed from retinoblasts [1], therefore the eye presents as the primary symptom the leukocoria (white reflex that occurs when the retina is exposed), this signal occurs due to displacement of the retina caused by tumor growth. The disease can affect only one eye (unilateral) or both eyes (bilateral). Depending on the region in which the tumor develops, the optic nerve and central nervous system may be compromised. Phenylpropanoids are widely studied anti-tumor bioactives in medicinal chemistry, which are present in several studies with good results against brain, breast, prostate and other tumors. This research aims to present, through in silico tools, bioactive with antitumor profile for retinoblastoma of 3,4,5-trihydroxycinnamic acid derivatives.

Materials and Methods

In this research, 128 molecules derived from 3,4,5-trihydroxycinnamic acid were used, including ethers, amides, thionoesters and thionoamides. Initially ,these molecules were drawn and the energies were minimized through Molecular Mechanics (MM+) and also by the semiempirical method (AM1) in software HyperChem 7.5^{TM} (RMS 0.1 kcal.Å^{-1}.mol^{-1} in 800 cycles) [2].

After energy minimization, the molecules were imported into a biological activity prediction model in the statistical software KNIME Analytics Platform 3.6, using the classifier Random Forest and the predictor Weka 3.7. The software CDK Descriptor Calculator v1.4.8 was used to generate the molecular descriptors. After this, the molecules were imported into the software OSIRIS DataWarrior 5.0 to estimate the risks of cytotoxicity based on four parameters: mutagenicity (MUT), carcinogenicity (CAR), toxic effect on the reproductive system (ESR) and skin irritability (IRR) [3,4,5,6].

Finally, the molecules approved in the model and those presenting no risk of cytotoxicity were submitted to molecular docking. The crystallographic protein chosen was PDB ID 6BGY (histone lysine demethylase 5A)[7].

Results and Discussion

The molecules were subjected to the generated biological activity prediction model, where the ROC curve for the test group was 0.832 and for cross-validation was 0.859. In both groups, the Matthews coefficient showed a value above 0.500, high sensitivity (above 0.800), good accuracy (above 0.700) and precision above 0.800.

Thus, it can be deduced that the model created has good predictive capacity for protein histone lysine demethylase A5, where the prediction data of the active compounds of 3,4,5-trihydroxycinnamic acid derivatives can be seen below:

Table 01. Results of the *in silico* analyzes of this work.

ID	ATV	%ATV	PDB ID 6BGY [kcal.mol^{-1}]	MUT	CAR	ESR	IRR	TOX
RET004	A	58.21	-88.09	none	none	none	none	NO
RET005	A	60.42	-99.76	none	none	none	none	NO
RET008	A	63.96	-90.08	none	none	none	none	NO
RET009	A	59.58	-98.74	none	none	none	none	NO
RET011	A	54.33	-104.61	none	none	none	none	NO
RET012	A	58.96	-88.01	none	none	none	none	NO
RET013	A	57.79	-96.86	none	none	none	none	NO
RET014	A	60.08	-106.67	none	none	none	none	NO
RET015	A	56.00	-98.81	none	none	none	none	NO
RET016	A	55.04	-96.95	none	none	none	none	NO
RET017	A	55.33	-101.85	none	none	none	high	YES
RET018	A	55.08	-98.48	low	none	none	none	NO
RET019	A	52.17	-116.23	none	none	none	high	YES
RET020	A	51.67	-76.64	none	none	none	none	NO
RET021	A	56.47	-93.60	low	none	none	low	YES

RET022	A	52.38	-101.04	none	none	none	none	NO
RET024	A	53.13	-93.69	none	none	none	none	NO
RET025	A	51.88	-120.07	none	none	none	high	YES
RET029	A	56.67	-116.63	none	none	high	low	YES
RET030	A	54.17	-107.64	none	none	none	none	NO
RET031	A	52.08	-103.46	none	none	none	low	YES
RET032	A	59.33	-112.08	none	none	none	none	NO
RET033	A	56.33	-87.48	high	none	none	none	YES
RET034	A	52.83	-88.25	none	none	none	none	NO
RET036	A	55.83	-101.21	none	none	none	none	NO
RET037	A	54.42	-102.56	none	none	none	none	NO
RET040	A	59.58	-111.16	none	none	none	none	NO
RET041	A	57.33	-117.26	none	none	none	high	YES
RET044	A	57.50	-93.31	none	none	none	none	NO
RET048	A	60.33	-94.02	none	none	none	none	NO
RET049	A	51.50	-117.79	none	none	none	none	NO
RET052	A	55.63	-102.58	none	none	none	none	NO
RET088	A	50.25	-103.29	none	none	none	none	NO
Carboplatine	-	-	-52.01	-	-	-	-	-
Ciclofosfamide	-	-	-68.74	-	-	-	-	-
Doxorrubicine	-	-	-92.27	-	-	-	-	-
Etoposide	-	-	-132.01	-	-	-	-	-
Topotecane	-	-	-38.14	-	-	-	-	-
Vincristine	-	-	-42.03	-	-	-	-	-
Inhibitor	-	-	-117.81	-	-	-	-	-

ATV = Biological Activity
%ATV = Probability of Activity
MUT = Mutagenicity; CAR = Carcinogenicity; ESR = Toxic Effect on the Reproductive System; IRR = Skin Irritability and TOX = Risks of General Cytotoxicity.

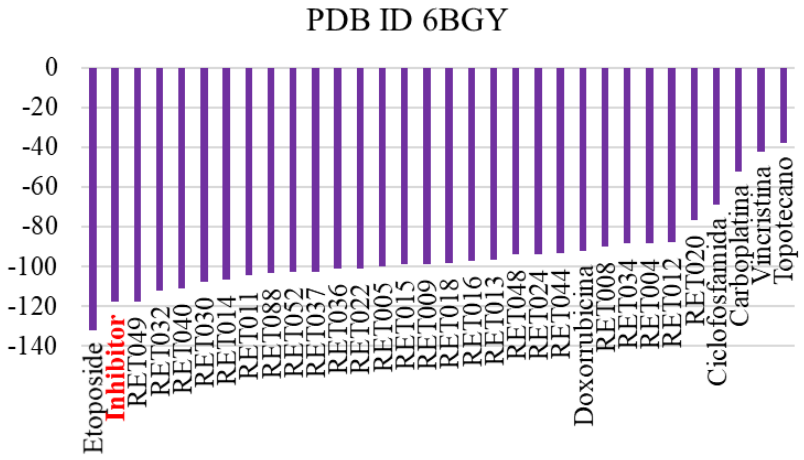


Figure 01. Ranking between co-crystallized inhibitor, controls and compounds subjected to *in silico* analysis.

As can be seen from the previous table, 33 of the 128 compounds demonstrated activity according to the model created. Therefore, the active molecules were imported into the software

OSIRIS for cytotoxicity prediction, resulting in 25 compounds without cytotoxicity risks. Thus, the active molecules that did not present *in silico* toxicity were anchored with the human retinoblastoma histone lysine demethylase 5A protein, as well as the 6 chemotherapeutic drugs used to treat the disease under discussion, as shown in figure 01.

The compound RET049 showed ligand-receptor interaction energy equal to -117.79 kcal.mol^{-1} which is similar to the interaction energy of the co-crystallized inhibitor (-117.81 kcal.mol^{-1}), becoming the most promising molecule for a possible chemotherapy prototype for retinoblastoma treatment. 20 of the 25 compounds that were approved by the model and that did not present cytotoxicity risks had lower energies than five of the six control drugs, except for etoposide control (-132.01 kcal.mol^{-1}).

Conclusions

According to the data presented in this research, corroborating the results of previous research using phenylpropanoids to evaluate possible antitumor activity, the tested compounds derived from 3,4,5-trihydroxycinnamic acid showed good results *in silico* against human retinoblastoma, with the possibility of presenting activity and low cytotoxicity. These data are expected to encourage research groups to obtain organic compounds (synthetic or natural products) from this series.

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