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Modeling of the relationship between biological activity of delta-selective enkephalin analogues and docking results by polynomials

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One of the areas of bioinformatics is the development of fast and reliable methods for predicting the biological activity of compounds. This will facilitate the design of new compounds and reduce costs. The process of creating selective ligands of a delta opioid receptor (DOR) was directed towards the synthesis of enkephalin analogues. Their biological activity was determined by using *in vivo* and *in vitro* methods, which allows establishing the relationship between structure and biological activity. The relationship between the values of the ChemScore scoring function from the docking procedure in GOLD 5.2 and the values of the total energy of the ligand-receptor complex in Molegro was modeled with first- to third-degree polynomials and a surface fitted method. The polynomial surface of third degree displayed the best fit, assessed by the least squares method. In our previous study with the theoretical model of DOR (PDBid:1ozc) the relationship between the values of efficacy of the compound, the values of the GoldScore scoring function from the docking procedure in GOLD 5.2 and the values of the total energy of the ligand-receptor complex in Mollegro was established. This relationship was modeled with a third-degree polynomial in software MATLAB. The aim of the present work was to find an optimal fitting polynomial function modeling the relationship between the quantitative parameters of *in vitro* bioassay and the values of the scoring functions from molecular docking with crystal structure of DOR (PDBid:4ej4) and delta-opioid ligands using the least squares method. The third-degree polynomial was successfully used for modeling the relationship between the efficacy of delta-selective enkephalin analogues and docking results. It was described by a polynomial surface of third degree.

Keywords: Computer modelling, QSAR, Surface fitting, Scoring functions, Molecular docking, Delta opioid receptor.

INTRODUCTION

Morphine produces a large diversity of pharmacological responses by interacting with the opioid receptors in the nervous system. It is an agonist ligand for μ-, δ- and κ-opioid receptors and that is why most of its effects are due to particular ligand-receptor interactions. The delta-opioid receptor (DOR) is part of the G-protein-coupled receptors (GPCR) and plays an important role in the perception of pain.

The design of selective and effective ligands for DOR is related with a lot of experiments with different enkephalin analogues. These analogues were synthesized and biologically tested in previous *in vitro* studies [1, 2]. According to the *in vitro* results and the mathematical model of a partial agonism [3], the potency (concentration which produces 50 % of the maximal response of the tissue, IC_{50}), could be calculated with the explicit formulas of the affinity (reciprocal of the dissociation constant, K_A) of the respective analogues, and the relative efficacy (e_{rel}).

In silico experiments are very helpful in drug design, because of their major role in reducing the time and the costs of the studies and they can be used as viable alternatives to animal trials. The structure-based drug design methods which include three-dimensional structural information from biological targets are an important component of modern medicinal chemistry [4]. Molecular docking and structure-based virtual screening are often used in structure-based drug design because of their applications in the analysis of molecular recognition such as binding, energetic, molecular interactions and conformational changes [5]. The molecular docking of ligands with a protein structure (in our case DOR with crystal structure) aims to predict the ligand-protein complex structure by exploring the conformational space of the ligands within the binding site of the protein. The scoring functions are then used to approximate the free energy of binding between the protein and the ligand in each docking pose.

The aim of the present study was to investigate the relationship between the values of the quantitative parameters of *in vitro* tests e_{rel}, K_A, IC_{50} and the results of the molecular docking - the minimum energy conformation for each ligand-receptor complex, the scoring functions to calculate

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binding affinities of protein-ligand complexes based on experimental structure and the data from *in vitro* bioassay.

To this purpose the following tasks should be solved: 1) implementation of the molecular docking calculations of the model of DOR with crystal structure (PDBid:4ej4) and the delta-selective enkephalin analogues, and calculation of the total energies of the formed ligand-receptor complex after the docking procedure and 2) finding a function $z = f(x, y)$ from some class of polynomials, that fits given *n* distinct data points $\{(x_i, y_i, z_i)\}_{i=1}^{n}$ in R^3 by the least squares method.

MATERIALS AND METHODS

Receptor – DOR (PDBid:4ej4)

The model of the delta-opioid receptor with crystal structure published in the RCSB Protein Data Base (PDBid: 4ej4) was used (http://www.rcsb.org). This protein is long 461 amino acids [6].

Ligand - delta-selective enkephalin analogues and related compounds

The ligands used in this study were tested for their values of IC_{50}, K_A, e_{rel} in an *in vitro* test in previous research [1-3]. The results from the *in vitro* bioassay of Cys^2-containing and related analogues of enkephalins on their inhibitory effects of the mouse *vas deferens* tissue are presented in Table 1.

Docking procedure and scoring functions

The docking procedure was performed with the software GOLD 5.2 and all four scoring functions available in the program: GoldScore, ChemScore, ChemPLP, ASP scoring functions [7- 10]. In this paper we examined the ChemScore function as a scoring function for the protein-ligand docking program GOLD 5.2 and its benefits to carry out accurate docking, to predict the binding energies, and to realise the biological effects of the tested compounds.

The ChemScore scoring function is an empirical function which contains angular terms for hydrogen bond interactions and emphasizes these directed interactions more strongly. It was trained by regression against measured affinity data. The ChemScore function estimates the total free energy change that occurs on ligand binding [7].

The binding site of DOR is known from the literature [11]: it comprises the residues within 10 Å around an aspartic acid residue, Asp128.

The total energies of binding of the formed ligand-receptor complexes were calculated by the Ligand Energy Inspector Tool and MolDock scoring function in software Molegro Molecular Viewer (http://molegromolecular-viewer.software.xinformer.com), (MMV Version 2.5) [12,13]. This tool allows getting detailed information about the energy interactions for the protein-ligand complex.

Fitting methods

The fitting of the experimental data for DOR (PDBid: 4ej4) is performed by the polynomial function (Eqn.1), where z is a dependent variable, x and y are independent variables. The values of z_1, z_2…, z_n represent the values of the *in vitro* parameters IC_{50}, K_A or e_{rel}; the values of x_1, x_2…, x_n represent the results from the docking procedure, i.e. the values of GoldScore, ChemScore, ChemPLP, and ASP scoring functions; the values of y_1, y_2…, y_n represent the total energies for the formed ligand-receptor complex; a_{ij} are the parameters of the model; *n* is the degree of the polynomial ($0 \leq i + j \leq n$). The coefficients of Eqn.1 were determined by the least squares method (Eqn.2), where *m* is the number of ligand-receptor complexes (data points).

Table 1. The eleven ligands used in this study

Primary structure	Ligand	Mouse *vas deferens*		
		IC_{50} (nM)	K_A (nM)	e_{rel}
Tyr-D-Pen-Gly-Phe-D-Pen	DPDPE	6.18±1.17	180±35	30.2±10.0
Tyr-Gly-Gly-Phe-Leu	[Leu^5]-enk	11.45±2.06	54.9±13.1	5.8±1.0
Tyr-Gly-Gly-Phe-Met	[Met^5]-enk	18.91±2.15	48.4±7.5	3.6±0.3
Tyr-Cys(Bzl)-Gly-Phe-Leu	[$Cys(Bzl)^2$, Leu^5]-enk	8.30±1.40	68.5±29.7	9.3±3.2
Tyr-Cys(Bzl)-Gly-Phe-Met	[$Cys(Bzl)^2$, Met^5]-enk	9.53±1.20	23.8±3.0	3.5±0.3
Tyr-Cys(O2NH2)-Gly-Phe-Leu	[$Cys(O_2NH_2)^2$, Leu^5]-enk	1.29±0.31	36.4±16.4	29.2±9.5
Tyr-Cys(O2NH2)-Gly-Phe-Met	[$Cys(O_2NH_2)^2$, Met^5]-enk	2.22±0.45	14.1±5.4	7.3±2.0
Tyr-D-Cys(O2NH2)-Gly-Phe-Leu	[$DCys(O_2NH_2)^2$, Leu^5]-enk	11.40±2.01	73.4±12.7	7.4±1.9
Tyr-D-Cys(O2NH2)-Gly-Phe-Met	[$DCys(O_2NH_2)^2$, Met^5]-enk	75.96±11.67	463±161	7.1±1.8
Tyr-HCys(O2NH2)-Gly-Phe-Leu	[$HCys(O_2NH_2)^2$, Leu^5]-enk	31.92±5.10	76.4±7.1	3.4±0.2
Tyr-HCys(O2NH2)-Gly-Phe-Met	[$HCys(O_2NH_2)^2$, Met^5]-enk	16.09±1.90	55.7±6.1	4.5±0.3

$$(1)\quad z = f(x,y) = \sum_{0\le i+j\le k} a_{ij} x^i y^j$$

$$(2)\quad \underset{(a_{00},\dots,a_{0k})}{\text{minimize}} F(a_{00},\dots,a_{0k}) = \sum_{s=1}^{t}\left(z_s - \sum_{0\le i+j\le k} a_{ij} x_s^i y_s^j\right)^2$$

In order to explore the fitting behavior of some polynomial degree functions, a series of fittings was carried out by a polynomial with two variables from a first to a third order. The Surface Fitting Tool of MATLAB (http://www.mathworks.com/products/matlab) [14] was applied and the individual model could be interpreted as a surface fitting function of the experimental data by the least squares method. This tool provides descriptive statistics, including: *R-square (R^2), adjusted R^2 (adj R^2), sum of squares due to errors (SSE), root mean squared error (RMSE)*, etc. The goodness of fit of a statistical model describes how well it fits into a set of observations: 1) *SSE* is a quantity used in describing how well a model represents the data being modeled, where the values of *SSE* near to 0 show that the model has a smaller random error component and then the fit will be useful for prediction; 2) R^2 measures how successful the fit is in explaining the variation of the data and it is defined as the ratio of the sum of squares of the regression and the total sum of squares about the mean, where the values of R^2 closer to 1 indicate that a greater proportion of variance is accounted for by the model; 3) *Adj R^2* is a modified version of R^2 for the number of predictors in a model and it gives the percentage of variation explained by those independent variables only that in reality affect the dependent variable. It can take on any value less than or equal to 1, with a value closer to 1 indicating a better fit; 4) *RMSE* is a measure of the difference between values predicted by a model and the values actually observed from the environment that is being modeled. The values of *RMSE* closer to 0 indicate a fit that is more useful for prediction.

RESULTS AND DISCUSSION

The molecular docking calculations with the model of DOR with crystal structure (PDBid:4ej4) and the 11 ligands from Table 1 were carried out with software GOLD 5.2. The program for docking generated several probable ligand binding conformations at the active site around the protein target - DOR (PDBid: 4ej4). The active site of the DOR (PDBid: 4ej4) includes the residues within 10 Å around an Asp128 [19]. All four scoring functions embedded in the program in GOLD 5.2 (GoldScore, ChemScore, ChemPLP and ASP scoring functions) were used to rank the conformations of the opioid ligands by evaluating the binding density of each of the probable complexes.

An example of the ligand-receptor interaction between DOR (PDBid:4ej4) and an endogenous ligand [Leu^5]-enkephalin around the active site - Asp128 residue - is presented in Fig. 1.

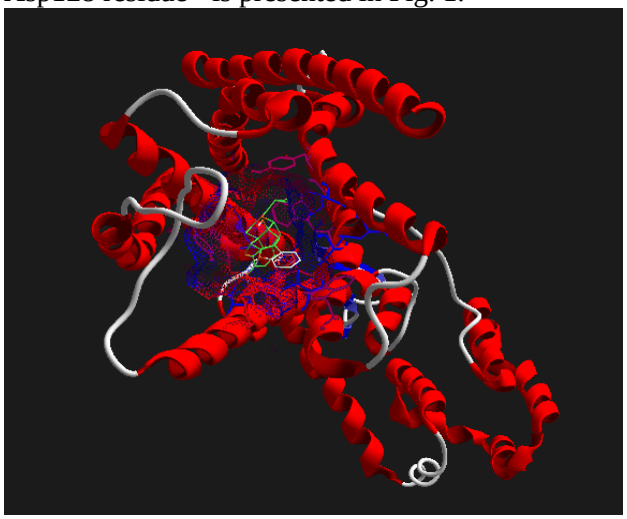

Fig. 1. Diagram of the ligand-receptor complex between DOR (PDBid:4ej4) and an endogenous ligand [Leu^5]-enkephalin. The receptor is presented in ribbons and helixes. The ligand is presented in yellow circles (picture generated by Molegro Molecular Viewer).

In order to assess the suitable relationship between biological activity of the delta opioid ligands and the docking results (the values of the scoring functions in GOLD 5.2) the Surface Curve Fitting Toolbox in the software MATLAB was applied [14].

The total energies of the ligand-receptor complexes formed after molecular docking in GOLD 5.2 with the model of the DOR (PDBid: 4ej4) and the best pose of the ligands were calculated in software MMV 2.5 [12,13].

The aim of the curve fitting was to find the parameters of a mathematical model that describes the data by minimizing the difference between the model and the set of data. By using polynomial least squares surface fitting methods, polynomials of a first to a third order were used for fitting of the experimental data in both *X*-axis and *Y*-axis. These data can be represented as follows: 1) the values of z

represent the values of the *in vitro* parameters e_{rel}, K_A or IC_{50} [2]; 2) the values of x represent the docking results (the values of scoring functions GoldScore, ChemScore, ASP and ChemPLP calculated by GOLD 5.2); 3) the values of y represent the total energies for the ligand-receptor complex formed after docking with the corresponding scoring functions (the values of MolDock scoring function calculated by MMV).

The best results of the parameters used for surface fitting in MATLAB for DOR (PDBid:4ej4) can be presented as follows: the values of z represent the values of e_{rel} from *in vitro* parameters [1-3], the values of x represent the values of the ChemScore function and the values of y represent the values of the total energies for the ligand-receptor complexes. The modeling of the relationship between efficacies of enkephalin analogues, total energies calculated by MMV and ChemScore scoring function calculated by GOLD 5.3 was carried out with methods described in Section 2. The results are presented in Table 2.

The polynomial models from the first to the third degree were estimated with the statistical criteria of goodness of fit – *SSE, R^2, adjusted R^2, RMSE*. The obtained results for the statistic parameters are presented in Table 3. The goodness of fit statistics shows that the obtained model for fitting the experimental data for DOR (PDBid: 4ej4) with the third degree for *x* and the third degree for *y* is a good one.

As it can be seen from Table 3 the model of third degree is with the highest values of R^2 and the values closer to 1 show that a greater proportion of variance is explained by the model. The values of *SSE* for the cubic polynomial are close to 0, which indicates that the model of third degree has a smaller random error component and the fit will be more useful for prediction. The values of *Adj R^2* for the cubic polynomial are less than 1. It is a good indicator of the fit quality when two models are compared and a value closer to 1 shows a better fit. The values of *RMSE* for the third degree of polynomial for DOR are closer to 0 and demonstrate a fit that is more useful for prediction.

After analysing the results from Table 3 we found that the polynomial model of third degree for the surface fitting data is a good model which explains a high proportion of the variability in experimental data, and it is able to predict new observations with high certainty [21]. This model is represented as the following Eqn.(3) and the coefficients are given in Table 4.

$$(3)\quad f(x,y) = a_{00} + a_{10} * x + a_{01} * y + a_{20} * x^2 + a_{11} * x * y + a_{02} * y^2 + + a_{30} * x^3 + a_{21} * x^2 * y + a_{12} * x * y^2 + a_{03} * y^3$$

The surface fitting by the first to the third degree of the polynomial of the experimental data from Table 2 for the DOR (PDBid:4ej4) is presented in Fig. 2 (A,B,C). A graphic representation of the relationship between the three numeric variables in 2D is presented in Fig. 3 (A, B, C). The values of the ChemScore function and the values of total energy are for *X* and *Y* axes, and the values of the potency – IC_{50} are for contour levels. Fig. 4 (A, B, C) represents the residual plot for the polynomial models from the first to the third degree. These diagrams provide visual displays for assessing how well the model fits the data. They are used to evaluate the distribution of the residuals and identify influential observations [14].

Table 2. Values of the parameters used for surface fitting: ChemScore scoring function calculated by GOLD 5.2, total energy calculated by MMV and e_{rel} obtained by *in vitro* bioassay

Ligand	ChemScore	Total energy	e_{rel}
[Cys(Bzl)^2, Leu^5]-enk	38.91	-170.657	9.3
[Cys(Bzl)^2, Met^5]-enk	35.19	-125.108	3.5
[Cys(O_2NH_2)^2, Leu^5]-enk	28.48	-118.805	29.2
[Cys(O_2NH_2)^2, Met^5]-enk	25.82	-87.343	7.3
[DCys(O_2NH_2)^2, Leu^5]-enk	31.84	-136.187	7.4
[DCys(O_2NH_2)^2, Met^5]-enk	31.55	-139.449	7.1
[HCys(O_2NH_2)^2, Leu^5]-enk	32.75	-100.702	30.2
[HCys(O_2NH_2)^2, Met^5]-enk	26.55	-112.164	3.4
DPDPE	29.23	896.877	4.5
[Leu^5]-enk	31.62	-119.009	5.8
[Met^5]-enk	32.22	-106.792	3.6

Table 3. Assessing the goodness of fit for the polynomial models obtained by the least squares method

Degree	*SSE*	*R^2*	*Adj R^2*	*RMSE*	*Coefficient*
First	443.5817	0.5446	0.4308	7.4463	3
Second	167.1000	0.8285	0.6569	5.7810	6
Third	0.0092	1.0000	0.9999	0.0960	10

Table 4. Mean values (confidence bounds) of the coefficients of the third-order polynomial model.

Coefficients	Mean (with 95% confidence bounds)	
a_{00}	-188.4	(-705.4; 373.7)
a_{10}	1855	(-17.99; 3279)
a_{01}	-828.1	(-4019; 2363)
a_{20}	740.8	(48.93; 1433)
a_{11}	1.3	(-397.5; 2.639)
a_{02}	839.8	(-1929; 3609)
a_{30}	83.1	(29.72; -136.5)
a_{21}	2506	(119.9, 4892)
a_{12}	2.3	(-1630; 4.563)
a_{03}	4556	(-1526; 1.065)

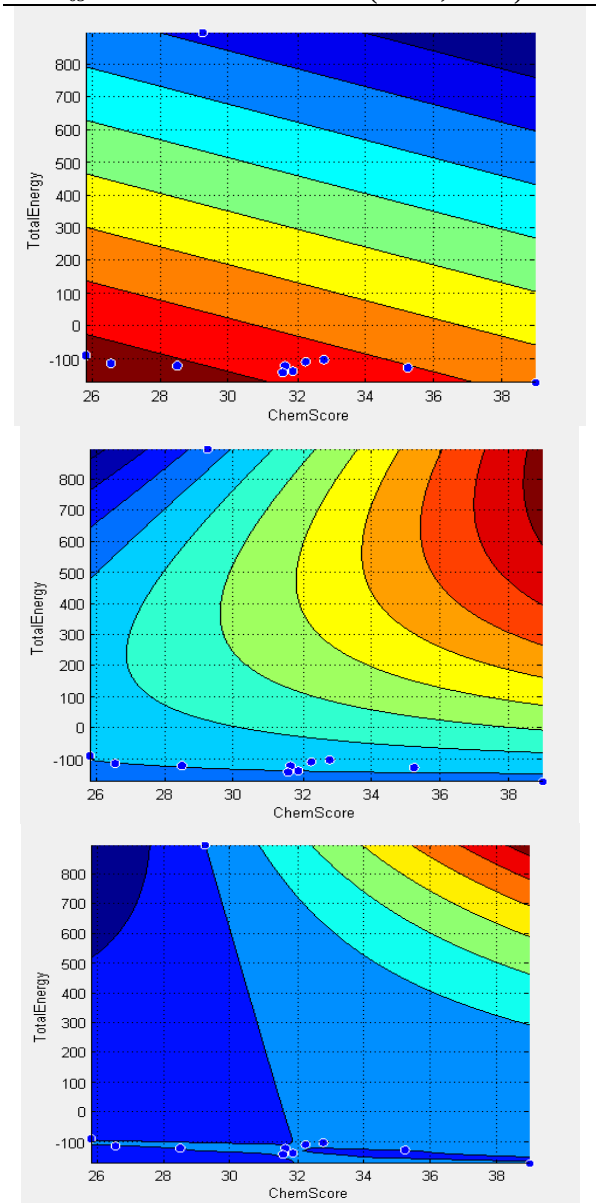

Fig.3. 2D contour plot of the 3D surface in Fig. 2 for the model of DOR (PDBid:4ej4). The first degree polynomial fitting is presented in (A); the second degree in (B); the third degree in (C). The diagrams were generated with MATLAB.

The top plot of the residual plot presented in Fig. 4 (A, B, C) shows that the residuals are calculated as the vertical distance from the data point to the fitted curve [14]. The bottom plot presented in Fig. 4 (A, B, C) displays the residuals relative to the fit which is the zero line.

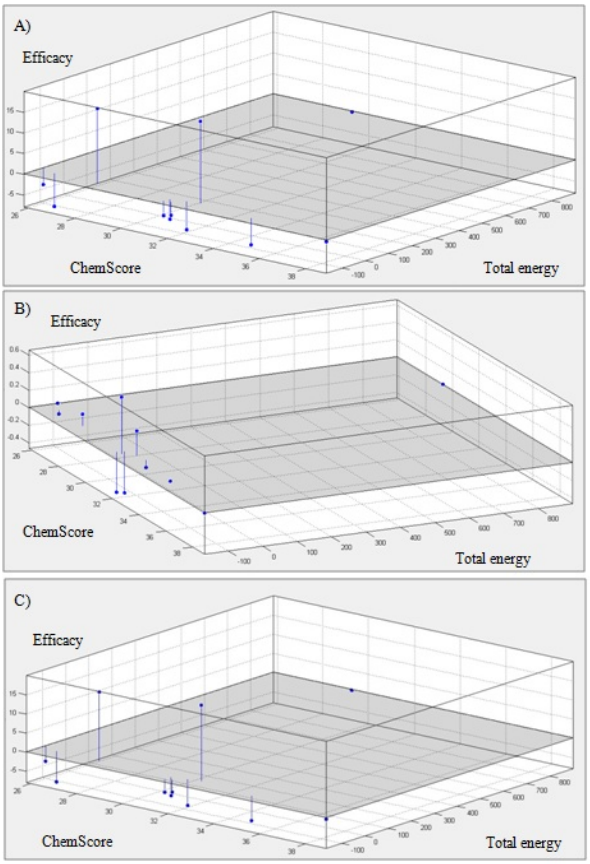

Fig. 4. The residuals plot for the obtained polynomial models of the first degree is presented in (A); the second degree in (B); the third degree in (C). The diagrams were generated with MATLAB.

Several studies were performed in this direction with other two models of DOR: 1) a theoretical model of DOR (PDBid:1ozc) and 2) a model of DOR obtained by homology modeling, named *Model B* [15-26].

A relationship between the values of the efficacy e_{rel} from *in vitro* parameters [1,2,3] and the values of GoldScore scoring function from docking procedure in GOLD 5.2 and the values of total energies of formed ligand-receptor complexes was established for the theoretical model of DOR (PDBid:1ozc). The polynomial surface of the 3rd order has the best fit, assessed by the method of least squares ($R^2 = 1.0$, $SSE = 0.009207$, $adjusted\ R^2 = 0.9999$, $RMSE = 0.096$) [15].

A relationship between the values of the potency IC_{50} from *in vitro* parameters [1,2,3] and the values of ASP scoring function from docking procedure in GOLD 5.2 and the values of total energies of formed ligand-receptor complexes was found for the *Model*

B of DOR, obtained by homology modeling [16-18]. The best fitting of experimental data for the *Model B* of DOR was obtained for a polynomial surface of the 3rd order again ($R^2 = 1.0,\ SSE = 0.2460,\ adjusted\ R^2 = 0.9999,\ \mathrm{RMSE} = 0.1568$).

According to the established relationships for the three models of DOR we suggest that the polynomial surface of the 3rd order has the best fit, assessed by the least squares method [21]. This polynomial order could be successfully used for modeling of the relationship between the efficacy of delta-selective enkephalin analogues and the results from the docking procedure. Furthermore, the ligand-based and the structure-based approaches of virtual screening are a hopeful and effective search of effective δ-selective enkephalin candidates.

The number of these parameters is determined exactly from the degree of the found "optimal" polynomial.

Usually we solve the fitting problem by the least squares method for polynomials of second, third, fourth, etc. degree and choose the best.

CONCLUSIONS

Analysis of the data from *in vitro* bioassay and *in silico* docking studies may help to better understand the relationship between *in vitro* biological effects and molecular docking results; the docking studies are in good agreement with the *in vitro* studies.

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МОДЕЛИРАНЕ НА ВРЪЗКАТА МЕЖДУ БИОЛОГИЧНАТА АКТИВНОСТ НА ДЕЛТА-СЕЛЕКТИВНИ ЕНКЕФАЛИНОВИ АНАЛОЗИ И РЕЗУЛТАТИ ОТ МОЛЕКУЛЕН ДОКИНГ С ПОЛИНОМИ

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(Резюме)

Една от областите на биоинформатиката е разработването на бързи и надеждни методи за предсказване на биологична активност на съединения. Това ще улесни дизайнът на нови съединения и ще намали разходите по експерименталната дейност. Процесът на създаване на селективни лиганди на делта опиоиден рецептор (ДОР) е насочен към синтезата на енкефалинови аналози. Тяхната биологична активност се определя чрез използване на *in vivo* и *in vitro* методи, които позволяват да се установи връзка между структурата и биологичната активност на съединенията.

Целта на представеното изследване е да се намери функция, която да моделира връзката между стойностите на количествените параметри от *in vitro* изследванията и стойностите на скоринг функциите от молекулния докинг, проведен с делта-опиоидни лиганди и ДОР (PDBid: 4ej4) с кристална структура.

Връзката между стойностите на ефикасността на изследваните съединения, стойностите на скоринг функцията - ChemScore от молекулния докинг проведен в GOLD 5.2 и стойностите на общата енергия на лиганд-рецепторните комплекси, изчислена в Molegro беше моделирана с полиноми от първа до трета степен в тримерното пространство в Matlab. Най-доброто фитване на данните беше установено за полином от трета степен, оценено по метода на най-малките квадрати.

Получените резултати показват, че полиномът от трета степен в тримерното пространство може да се прилага успешно за моделиране на връзката между ефикасността на делта-селективните енкефалинови аналози и резултати от молекулен докинг.