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QSAR modelling and molecular docking studies of three models of delta opioid receptor

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Delta-opioid receptor (DOR) takes part in the control of chronic pain and emotional responses. Therefore it is an interesting object for QSAR modelling and molecular docking studies with delta-opioid selective enkephalin analogues.

The purpose of this study is to find the structure-activity relationship of a series of delta-opioid selective enkephalin analogues, basing on the quantitative parameters of *in vitro* bioassay (efficacy, affinity and potency) and the results of the molecular docking with three models of DOR: (1) a theoretical model of DOR (PDBe:1ozc); (2) a model of DOR with crystal structure (PDBid:4ej4); (3) a model of DOR obtained by homology modelling (named *Model B*). The relationship of the quantitative parameters of *in vitro* bioassay with the results from the molecular docking was modelled with first to third degree polynomials and surface fitted method.

We suggest that the polynomial surface fitting of the third order has the best fit, assessed by least squares method for model of DOR obtained by homology modelling. Hence, the third order of polynomial could be used for determining the relationship structure-biological activity between the three models of DOR and a series of delta-opioid selective enkephalin analogues.

Key words: QSAR, Docking, Ligand-receptor interaction, GOLD, Delta opioid receptor.

INTRODUCTION

Computer modelling and quantitative structure-activity relationship (QSAR) approaches have played a major role in the search and prediction of new biologically active substances based on the properties of compounds with known biological activities.

This research paper discusses QSAR modelling and approaches of computer and mathematical modelling to establish relationships between molecular structure of investigated compounds and their biological effects.

By computer modelling of the ligand-receptor interactions it was analyzed relationships between virtual data analogues of endogenous opioid peptides and experimental data for the same activity in experiments on isolated tissues.

The discovery of novel potent and selective ligands to the delta-opioid receptor (DOR) is related with a large amount of investigations with enkephalin analogues. The enkephalins are endogenous opioid peptides (enkephalins, endorphins or dynorphins) [1-4] and they are typically assigned to mu-, kappa-, and delta- opioid receptors.

In the last years computer-aided drug design has extensive impact in the field of the drug design and the natural sciences [5]. The design of selective and effective ligands for DOR is related with most researchers with different enkephalin analogues. These analogues were synthesized and biologically tested in previous studies [6,7]. According to the *in vitro* results and the mathematical model of a partial agonism [8], it could be calculated with the explicit formulas the *potency* (concentration, which produce 50% of the maximal response of the tissue – IC_{50}), the *affinity* (reciprocal of the dissociation constant, K_A) of the respective analogues and relative *efficacy* (e_{rel}).

There are two broad categories of computational techniques in virtual screening: 1) a ligand-based screening uses pharmacophore maps and QSAR, which requires knowledge of some ligands that exhibit the desired bioactivity; 2) a structure-based virtual screening uses molecular docking of ligands into a protein structure by applying the scoring function to estimate the probability that the compound will bind to the biological target (in our case models of DOR) [9,10].

We would like to find a relationship between the values of 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 binding affinities of protein-ligand complexes based on experimental structure and data

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from *in vitro* bioassay, etc.) in order to predict biological activity of chemical compounds.

To achieve the goal the following tasks should be solved: 1) performance of molecular docking calculations of the models of DOR and δ-selective enkephalin analogues, and calculation of the total energies of formed ligand-receptor complex after molecular docking experiments and (2) finding a function $z = f(x,y)$ from some class polynomials, that fits given n distinct data points $\{(x_i, y_i, z_i\}^n_{i=1}$ in R^3 by the least square method.

MATERIALS AND METHODS

Objects

Receptor-DOR

Three models of DOR were used:

(1) a theoretical model of DOR (PDBe:1ozc), published in Protein Data Base (www.rcsb.org) [11];

(2) a model of DOR with crystal structure (PDBid:4ej4) [12];

(3) a model of DOR obtained by homology modelling (named *Model B*) [13];

Ligands

Eleven ligands, investigated for their potency, selectivity and efficacy to DOR with *in vitro* bioassay in previous study [6,7,8] were selected for docking studies with the models of DOR.

The primary structures of the used ligands are presented in Table 1 (including selective ligand DPDPE ([D-Pen2,5]-enkephalin, selective δ-opioid receptor agonist [14] and endogenous enkephalins ([Leu5]- and [Met5]-enkephalin) and their analogues.

Table 1. 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

Software

Docking procedure

The structures of 11 ligands were prepared for docking in the software Avogadro (open source, http://avogadro.openmolecules.net/).

All docking calculations were performed with the software GOLD (Genetic Optimisation for Ligand Docking) 5.2 using all four scoring functions available in the program: ChemPLP, GoldScore, ChemScore and ASP (Astex Statistical Potential) scoring functions, [15,16,17,18]. The DOR belong to the GPCRs, characterized by seven putative transmembrane domains. It is known from the literature that the residues within 10 Å around an aspartic acid residue at position 128 (Asp128) in transmembrane domain 3 of the DOR contributes to the conformation of the receptor binding pocket [19].

The total energies for obtained ligand-receptor complex after docking procedure in GOLD 5.2 were calculated by software Molegro Molecular Viewer (MMV Version 2.5) using MolDock scoring function [20].

Correlation and fitting methods

Finding the correlation between the quantitative parameters of the *in vitro* tests (e_{rel}, K_A, IC_{50}) and the docking results (scoring functions) for the three models of DOR was carried out in software GraphPad Prism 3.0 (http://www.graphpad.com/scientific-software/prism). In this investigation the Pearson's correlation coefficient was used, which is a measure of the

correlation (linear dependence) between normally distributed variables.

$$\min_{(a_{00},\ldots,a_{0n})} F(a_{00},\ldots,a_{0n}) = \sum_{s=1}^{m}\left(z_s - \sum_{0\le i+j\le n} a_{ij}x_s^i y_s^j\right)^2 \quad (1)$$

$$z = \sum_{0\le i+j\le n} a_{ij}x^i y^j \quad (2)$$

Where s is the number of points; m is the number of ligand-receptor complexes; z is a dependent variable, x and y are independent variables. The values of z_1, z_2…, z_n represent the values of *in vitro* parameters; the values of x_1, x_2…, x_n represent the result from the docking procedure (scoring functions); the values of y_1, y_2…, y_n represent the total energies for ligand-receptor complex; a_{ij} are the parameters of the model; n - the degree of the polynomial $(0 \le i + j \le n)$, which gives the number of coefficients to be fit and the highest power of the predictor variable.

To investigate the fitting behaviour of degree of some polynomial functions, it was carried out a set of fittings, starting from the first-degree to the third-degree polynomial. The Surface Fitting Toolbox of MATLAB was applied for analysing the behaviour of one variable which depended on more independent variables and the individual model could be interpreted as a surface fitting function of the experimental data by least squares method (http://www.mathworks.com/ products/ matlab) [21]. The following parameters are used to evaluate the goodness of fit:

SSE (Sum of squares due to error) – this parameter represents the total deviation of the response values from the curve fit to the response values, where the value of *SSE* near to 0 shows that the model has a smaller random error component and then the fit will be more useful for prediction [22, 23].

R-Square (R^2) – this parameter 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. The values of R^2closer to 1 indicate that a greater proportion of variance is accounted by the model [22, 23].

Adjusted R-square – this parameter is the best indicator of the fit quality when two models are comparing. The adj/R^2 statistic can take on any value less than or equal to 1, with a value closer to 1 indicating a better fit [22,23].

RMSE (Root Mean Squared Error) – this parameter presents the standard error of the regression and an estimate of the standard deviation of the random component in the data. The values of *RMSE* closer to 0 indicates a fit that is more useful for prediction [22,23].

The fitting of experimental data can be presented as follows (Eqns.1,2):

RESULTS AND DISCUSSION

Docking results

The molecular docking experiments with the three models of DOR ((1) a theoretical model of DOR (PDBe:1ozc), (2) a model of DOR with crystal structure (PDBid:4ej4) and (3) a model of DOR obtained by homology modelling (named Model B)) and all 11 ligands were carried out with software GOLD 5.2 and all four scoring functions embedded in the program:GoldScore, ChemScore, ASP and ChemPLP.

The active site of the DOR is the residues within 10 Å around an Asp128 residue [19]. Molecular docking with GOLD 5.2 generates several probable ligand binding conformations at the active site around the protein target - DOR. The scoring functions in GOLD 5.2 are used to rank these ligand conformations by evaluating the binding density of each of the probable complexes. Docking results show the relative pose prediction performance of GOLD 5.2 by all scoring functions the values of which are calculated by using only the best scored pose for each binding site or the solution with the highest score.

When the results were analysed we found correlation between the docking results (the values of all four scoring functions available in GOLD 5.2) and the values of *in vitro* bioassay (IC_{50}, K_A or e_{rel}). The correlation between these data was assessed by the Pearson's correlation test in GraphPad Prism 3.0 [22]. The highest values of the Pearson's correlation coefficient for the theoretical model of DOR (PDBe:1ozc) were obtained between the values of GoldScore scoring function from docking experiments and the values of e_{rel} from *in vitro* parameters (R= -0.7209) [24]. Significant correlations were obtained for the model with crystal structure of DOR (PDBid:4ej4) between the values of ASP scoring function and e_{rel} from *in vitro* parameters (R= -0.6366); and the values of ChemPLP scoring function and e_{rel} from *in vitro* parameters (R= -0.6742) [12]. The highest value of the Pearson's correlation coefficient for *Model B* of DOR was obtained between the values of ASP scoring function and the values of IC_{50} from *in vitro* parameters (R= -0.86) [5,25]. These data indicate that GOLD5.2 software gives reliable results in the

docking of the 11 delta-opioid ligands with three models of DOR [26,27,28,29].

In order to investigate the appropriate relationship between biological activity of the delta-opiod ligands and docking results (the values of all four scoring functions in GOLD 5.2 it was applied the Surface Curve Fitting Toolbox in software MATLAB.

The total energies of the ligand-receptor complexes, which are formed after molecular docking with the three models of DOR and the best pose of the corresponding ligands, were calculated by MolDock scoring function in software MMV 2.5 [20].

By using a polynomial least squares surface fitting technique, a first to a third order polynomial was fitted to the experimental data in both the *X*-axis and *Y*-axis. The experimental data can be represented as follows:1) the values of z represent the values of *in vitro* parameters (e_{rel}, K_A or IC_{50}) which were obtained by Mathematical model of partial agonism [2]; 2) the values of x represent the result from the docking procedure- the values of GoldScore, ChemScore, ChemPLP and ASP scoring functions; 3) the values of y represent the total energies for ligand-receptor complex – the values of MolDock scoring function [20] for the ligand-receptor complexes forming after the docking with corresponding scoring functions.

The best results of the parameters used for surface fitting in MATLAB of the three models of DOR can be represented as follows: 1) for DOR (PDBe:1ozc): the values of *z* represent the values of e_{rel} from *in vitro* parameters, the values of *x* represent the values of GoldScore function, the values of *y* represent the values of the total energy for ligand-receptor complexes; 2) for DOR (PDBid:4ej4): the values of z represent the values of e_{rel} from *in vitro* parameters, the values of *x* represents the values of ChemScore function and the values of *y* represents the values of the total energy for the ligand-receptor complexes; 3) for *Model B* of DOR: the values of z represent the values of IC_{50} from *in vitro* parameters, the values of *x* represents the values of ASP function and the values of *y* represents the values of the total energy for the ligand-receptor complexes. The values of the main parameters used for surface fitting in MATLAB for the three models of DOR are presented in Table 2. The surface fitting by third degree of the polynomial of the experimental data from Table 2 for the three models of DOR is presented in Fig.1 (A,B,C).

All polynomial models from first to third degree were evaluated on how well they fitted the data and how precisely they could predict. The models were estimated with the statistical criteria of goodness of fit – *SSE, R^2, adjusted R^2, RMSE.* The results obtained for the statistic parameters are presented in Table 3.

As it can be seen from the results in Table 3 the goodness of fit statistics shows that the obtained model for fitting of the data for three models of DOR with the third degree for *x* and the third degree for *y* is a good one. The polynomial model of third degree is with the highest values of R^2 for the three models of DOR and the value closer to 1 indicating that a greater proportion of variance is explained by the model.

Table 2. The values of the main parameters used for surface fitting in MATLAB for the three models of DOR ((1) a theoretical model of DOR (PDBe:1ozc), (2) a model of DOR with crystal structure (PDBid:4ej4), (3) a model of DOR obtained by homology modeling (named *Model B*)).

Ligands	**DOR (PDBe:1ozc)**				**DOR (PDBid:4ej4)**			**DOR (Model B)**	
	Values of Gold Score	*Values of Mol Dock*	*Values of e_{rel}*	*Values of Chem Score*	*Values of MolDock*	*Values of e_{rel}*	*Values of ASP score*	*Values of MolDock*	*Values of IC_{50}*
[Cys(Bzl)^2, Leu^5]-enk	64,68	-107.022	9.3	38.91	-170.657	9.3	20.26	-77.135	8.3
[Cys(Bzl)^2, Met^5]-enk	81,49	-89.091	3.5	35.19	-125.108	3.5	25.16	-98.91	9.53
[Cys(O$_2$NH$_2$)^2, Leu^5]-enk	67,72	-97.619	29.2	28.48	-118.805	29.2	22.66	-99.678	1.29
[Cys(O$_2$NH$_2$)^2, Met^5]-enk	73,91	-91.246	7.3	25.82	-87.343	7.3	26.18	-88.498	2.22
[DCys(O$_2$NH$_2$)^2, Leu^5]-enk	74,73	-84.852	7.4	31.84	-136.187	7.4	24.31	-66.115	11.4
[DCys(O$_2$NH$_2$)^2, Met^5]-enk	75,13	-86.221	7.1	31.55	-139.449	7.1	-12.82	897.265	75.96
[HCys(O$_2$NH$_2$)^2, Leu^5]-enk	57,67	-109.709	30.2	32.75	-100.702	30.2	19.58	-75.943	6.18
[HCys(O$_2$NH$_2$)^2, Met^5]-enk	68,43	-62.774	3.4	26.55	-112.164	3.4	18.87	-90.567	31.92
DPDPE	78,65	-93.301	4.5	29.23	896.877	4.5	23.84	-80.137	16.09
[Leu^5]-enk	73,42	-81.869	5.8	31.62	-119.009	5.8	22.45	-104.149	11.45
[Met^5]-enk	73,26	-118.971	3.6	32.22	-106.792	3.6	33.9	-112.752	18.91

Table 3. The goodness of fit for the polynomial models obtained by least squares method for the three models of DOR in MATLAB.

Degree	DOR (PDBid:1ozc)			
	SSE	R^2	*Adj* R^2	*RMSE*
First	443.5817	0.5446	0.4308	7.4463
Second	167.1000	0.8285	0.6569	5.7810
Third	0.0092	1.0000	0.9999	0.0960
Degree	**DOR (PDBid:4ej4)**			
	SSE	R^2	*Adj* R^2	*RMSE*
First	940.0461	0.0350	-0.2063	10.8400
Second	895.3748	0.0809	-0.8383	13.3819
Third	0.9631	0.9990	0.9901	0.9814
Degree	**DOR (Model B)**			
	SSE	R^2	*Adj* R^2	*RMSE*
First	752.844	0.8318	0.7897	9.7011
Second	287.3484	0.9358	0.8716	7.5809
Third	0.0246	1.0000	0.9999	0.1568

Table 4. The mean values (confidence bounds) of the coefficients of the third order polynomial model chosen as optimal model for the three models of DOR.

Coefficients	Mean (with 95% confidence bounds)					
	DOR (PDBe:1ozc)		DOR (PDBid:4ej4)		DOR (Model B)	
a_{00}	11.51	(9.823, 13.19)	-188.4	(-705.4; 373.7)	416.5	(319.1; 514)
a_{10}	-11.07	(-16.13, -6.008)	1855	(-17.99; 3279)	-2420	(-3089; -1751)
a_{01}	-22.37	(-33.1, -11.64)	-828.1	(-4019; 2363)	111.7	(-248.9; 472.4)
a_{20}	16.71	(14.65, 18.78)	740.8	(48.93; 1433)	-3299	(-3796; -2801)
a_{11}	3.451	(-6.742, 13.64)	1.3	(-397.5; 2.639)	-2.164	(-2.687; -1.639)
a_{02}	-0.6185	(-3.866, 2.629)	839.8	(-1929; 3609)	-1.439	(-1.829; -1.049)
a_{30}	-12.15	(-14.89, -9.411)	83.1	(29.72; -136.5)	-864.7	(-989.5; -739.8)
a_{21}	19.03	(11.96, 26.11)	2506	(119.9, 4892)	-1.301	(-1.493; -1.109)
a_{12}	44.7	(29.97, 59.43)	2.3	(-1630; 4.563)	-4.613	(-5.623; -3.602)
a_{03}	14	(7.377, 20.62)	4556	(-1526; 1.065)	-3.382	(-4.211; -2.552)

The values of *SSE* for the cubic polynomial for the three models of DOR are close to 0. Therefore this value of *SSE* shows that the model of third-degree has a smaller random error component and then the fit will be more useful for prediction. The values of *Adj* R^2 for the cubic polynomial for the DOR are closer to 0 and indicate a fit that is more useful for prediction. This shows that the obtained polynomial model for the surface fitting data is a good model and it explains a high proportion of the variability in experimental data, and it is able to predict new observations with high certainty [11,12,13].

The best results for fitting of experimental data for the three models of DOR according to the results in three models of DOR are less than 1. This statistic parameter is a good indicator of the fit quality when two models are compared and with a value closer to 1 indicating a better fit. The values of the *RMSE* for the third degree of polynomial for three models of

Table 2 were obtained for surface fitting by a cubic polynomial in three-dimensional for determining the relationship between biological activities and docking results of investigated compounds. By using a polynomial least squares surface fitting technique, a third order polynomial was fitted to the data and it is represented as the following Eqns.(3):

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

The coefficients of the surface fitting for the three models of DOR by a cubic polynomial in three-dimensions are presented in Table 4.

The efficacy as a function of the values of GoldScore function and the values of the total energy for the formed complexes for DOR (PDBe:1ozc) was presented in Fig.1A). The efficacy as a function of the values of GhemScore function and the values of the total energy for DOR (PDBid:4ej4) was presented in Fig.1B). The potency as a function of the values of ASP function and the values of the total energy for *Model B* was presented in Fig.1C).

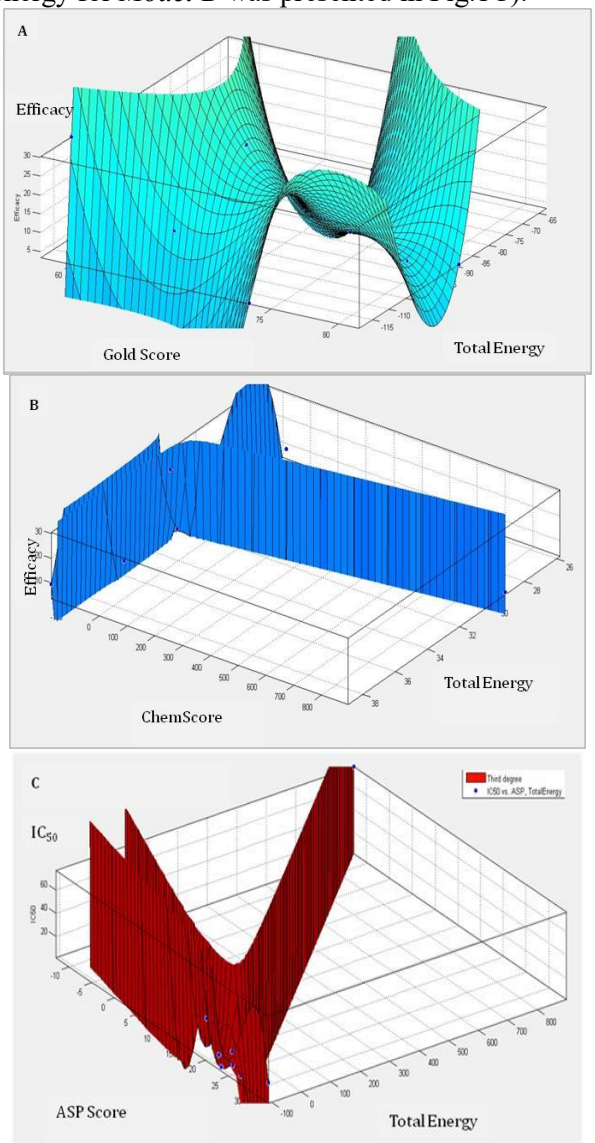

Fig. 1. A 3D surface fitting of experimental data with third degree of polynomial, which represent the biological activity of the ligands as a function of the values of scoring function from docking procedure and the values of the total energy for ligand-receptor complex: (A) Model of DOR (PDBe:1ozc); (B) Model of DOR (PDBid:4ej4); (C) Model B. The polynomial surface fitting model was obtained by Surface Fitting Toolbox in MATLAB.

Significant correlations is established between the values of ASP function and the values of IC_{50} from *in vitro* tests complexes, (R= 0.9120) for *Model B* of DOR. The established correlations between these parameters are important because they give the best description of the fitting of experimental data with polynomials of two variables. The relationship between the values of docking experiments and the values of ASP function for *Model B* of DOR is also confirmed by the fitting of experimental data with a third order polynomial with two. Therefore the model of DOR developed by homology modelling allows to optimally determining the binding affinity by ASP scoring function.

A graphic chart representation of the relationship between the three numeric variables in 2D is presented in Fig.2: 1) the values of the GoldScore function and the values of the total energy are for *X* and *Y* axes for DOR (PDBe:1ozc), where the values of e_{rel} are for contour levels; 2) the values of the ChemScore function and the values of total energy are for *X* and *Y* axes for DOR (PDBid:4ej4), where the values of e_{rel} are for contour levels; 3) the values of the ASP function and the values of total energy are for *X* and *Y* axes for *Model B*, where the values of the IC_{50} are for contour levels. For the fitting by a cubic polynomial in 3D the contour plot (Fig.2) makes it easier to see points that have the same height. The main advantage of this chart is that it allows for precise examination and analysis of the shape of the surface.

Polynomial models are commonly used as empirical models for curve fitting of data, because they have a simple form and two essential respects: a quantitative - the degrees of the polynomials (the number of parameters of model) and a qualitative - the regression function is linear in terms of the unknown parameters. Thus, we can use the polynomial models to find the optimal regression coefficients using the method of least squares.

CONCLUSION

The obtained model for the experimental data showed good fitting properties and significant predictive ability. Therefore this model of third-degree polynomial is suitable for determine the relationship structure-biological activity. The ASP scoring function and total energy obtained from docking could be used for describing the biological activity of newly designed compounds. This would be helpful in shortening the drug design process. Analysis and comparison of the data from *in vitro* tests and docking studies could help to better

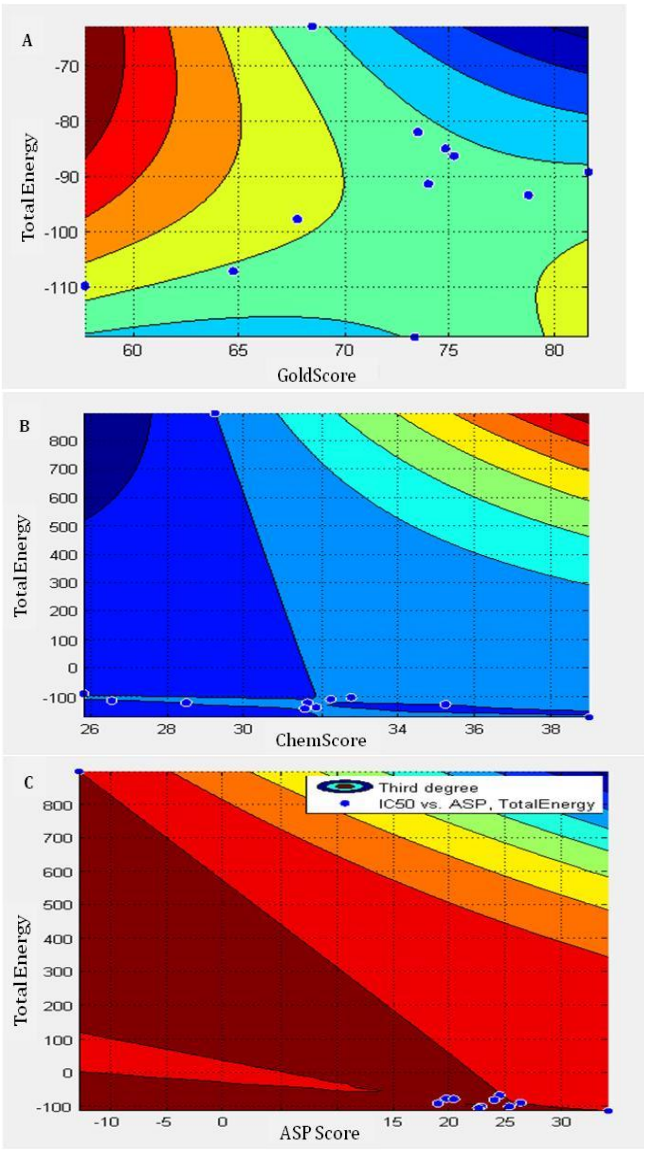

Fig. 2. A 2D contour plot of the 3D surface in the Fig.1: *X* represents the values of scoring functions from GOLD 5.2 and *Y* represents the values of total energy from MMV. (A) Model of DOR (PDBe:1ozc); (B) Model of DOR (PDBid:4ej4); (C) Model B. These diagrams were generated with the MATLAB.

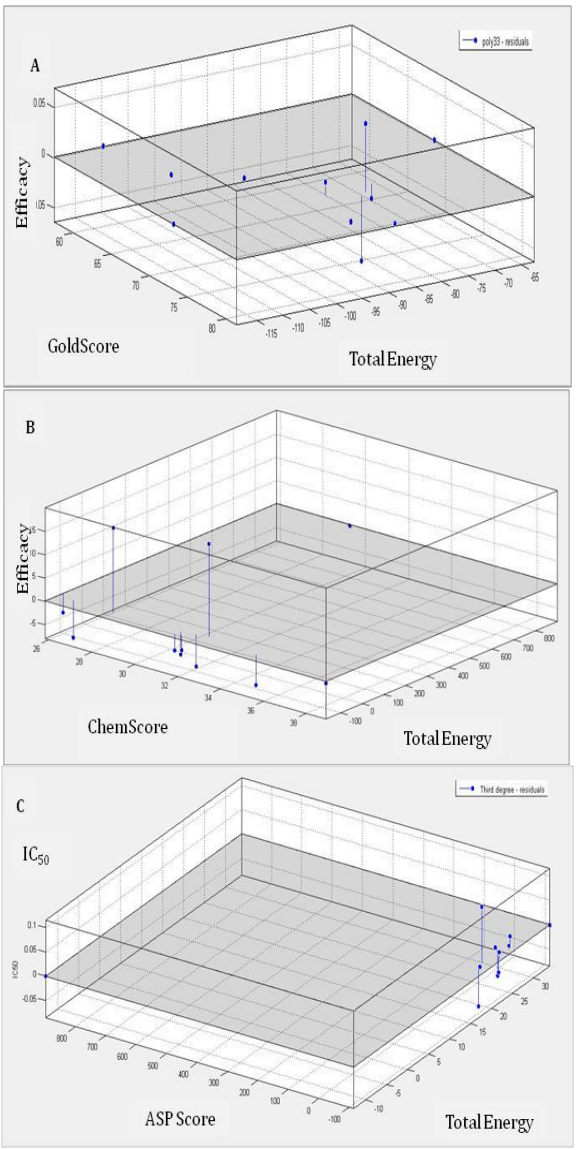

Fig. 3. The Residuals Plot for the obtained polynomial models of the third degree: A) Model of DOR (PDBe:1ozc); B) Model of DOR (PDBid:4ej4); C) *Model B* of DOR.

understand the relationship between the biological effects of ligands and docking studies and to answer whether the models of the biological macromolecules (DOR) correspond to the real 3D structure.

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QSAR МОДЕЛИРАНЕ И ДОКИНГ ЕКСПЕРИМЕНТИ С ТРИ МОДЕЛА НА δ-ОПИОИДЕН РЕЦЕПТОР

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(Резюме)

Делта-опиоидния рецептор (ДОР) участва в контрола на хроничната болка и емоционалните реакции. Ето защо ДОР е интересен обект за QSAR моделиране и докинг експерименти с делта-опиоидни селективни енкефалинови аналози.

Целта на това изследване е да се намери връзката структура-активност на серия от делта-опиоидни селективни енкефалинови аналози, базирайки се на количествените параметри от *in vitro* изследвания (ефикасност, афинитет и потентност) и резултати от молекулен докинг с три модела на ДОР: (1) теоретичен модел на ДОР (PDBe: 1ozc); (2) модел на ДОР с кристална структура (PDBid: 4ej4); (3) модел на ДОР получен чрез хомоложно моделиране (наречен *Model B*). Биологичната активност на делта-селективните енкефалинови аналози е описана чрез тримерно моделиране с полином на две променливи от трета степен, при което *in vitro* параметрите афинитет, ефикасност и потентност са представени като функции от стойностите на скоринг функцията от докинга и тоталната енергия на формираните лиганд-рецепторни комплекси. Това е един начин за определяне на QSAR.