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Computer modelling and optimization of the structure-activity relationship by using surface fitting methods

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Mu-opioid receptor (MOR) is an attractive target for computer modelling because it plays an important role as a pain-relieving drug. The main objective of the present work was to find a function for modelling of the structure-activity relationship (SAR) of a series of mu-opioid ligands and the results from *in silico* docking with a model of MOR (PDBid:4dkl). The relationship of the biological activity of the ligands with the optimization functions from docking experiments and with the total energies (MolDock optimization function) was modelled using a response surface methodology. Our analysis indicates that the third-order polynomial could be successfully used for modelling SAR between the biological effect of the mu-opioid ligands and results from docking. Docking studies could help to better understand the relationship between *in vitro* biological effects and docking studies and to answer whether the models of the biological macromolecules (in our case MOR) correspond to the real 3D structures.

Keywords: Computer modelling, Response surface methodology, QSAR, Docking, Ligand-receptor interaction, Mu-opioid receptor.

INTRODUCTION

Endogenous opioid systems play a critical role in modulating a large number of sensory, motivational, emotional, and cognitive functions. Endogenous opioid peptides (EOP) are small molecules that are naturally produced in the central nervous system and in various glands throughout the body. They function both as hormones and as neuromodulators. Through these mechanisms, EOP produce physiological effects as preventing diarrhea to inducing, euphoria, analgesia, etc.

Computer modelling and structure-activity relationship approaches have played an important role in the search and prediction of new biologically active ligands based on the properties of the drugs with known biological activities. The discovery of novel potent and selective ligands to MOR is related to a large amount of investigations with enkephalin and dalargin analogues [1-4]. The enkephalins are EOP and they are typically assigned to mu-, kappa-, and delta- opioid receptors. In recent years *in silico* drug design has extensive impact in the field of drug discovery and natural sciences [5,6]. Design of selective and effective ligands for MOR is related for most researchers with different enkephalin and dalargin analogues. These analogues were synthesized and biologically tested in previous studies by Pencheva *et. al* [7,8]. Computer modelling and docking experiments with investigated ligands were presented in [9,10,11].

The main purpose of this study is to investigate the relationship between the values of the biological activity of the investigated ligands and the results of the *in silico* docking and also to calculate the minimum energy conformation for each obtained ligand-receptor complex after the docking procedure. We try to find a function with two variables such as $z = f(x, y)$ from some class of polynomials, that fits given n distinct data points $\{(x_i, y_i, z_i)\}_{i=1}^{n}$ in R^3 using response surface methodology. Researches in this direction are presented in the publications [9-15].

MATERIALS AND METHODS

Objects

- *Receptor-MOR:* A model of mu-opioid receptor (MOR) with crystal structure published in RCSB Protein Data Base (www.rcsb.org) (PDBid:4dkl) was used.
- *Ligands:* A series of mu-opioid ligands investigated for their potency to MOR with *in vitro* bioassay in a previous study [7,8] were selected for docking studies with the model of MOR. The ligands are presented in Table 1.
- *Software*

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

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The total energies for the obtained ligand-receptor complexes after docking procedure in GOLD 5.2 [16,17] were calculated by the software Molegro Molecular Viewer (MMV Version 2.5) using MolDock optimization function [18].

Table 1. Ligands used in this study. The potency is the concentration which produces 50% of the maximal response of the tissue – IC_{50}) [7,8].

Ligands	IC_{50}
[Cys(O_2NH_2)^2-Met^5]-enk	1378
Dalargin	12.3
Dalarginamide	5.8
Dalarginethylamide	6
DAMGO	5.8
[L-Ala^2]-dalargin	234
[Leu^5]-enkephalin	65.3
[Met^5]-dalargin	11.9
[Met^5]-enkephalin	28.6
N-Me-[L-Phe^4]-dalarginamide	0.57

- *Surface fitted methodology:* The surface fitting of the experimental data with Curve Fitting Toolbox of MATLAB [19] can be presented as follows:

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

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

where:

- s - number of points;
- m - number of ligand-receptor complexes;
- z - dependent variable;
- x, y - independent variables;
- $z_1, z_2, \dots, z_n$ - represent the values of *in vitro* parameters;
- $x_1, x_2, \dots, x_n$ - represent the results from the docking procedure (scoring functions);
- $y_1, y_2, \dots, y_n$ - represent the total energies for the ligand-receptor complexes;
- a_{ij} - parameters of the model;
- n - 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 the degree of some polynomial functions, a set of fittings was carried out, 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 the least squares method [20] (http://www.mathworks.com/products/matlab). The following parameters were used to evaluate the goodness of fit:

- *SSE (Sum of squares due to error):*

$$(3)\quad SSE = \sum_{i=1}^{n} \omega_i (y_i - \hat{y}_i)^2$$

where: y_i is the measured value of the data, $\hat{y}_i$ is the predicted value, n - the number of performed experiments, ω_i is the relative weight of each data point, usually $\omega_i = 1$. The value of *SSE* close to 0 shows that the model has a smaller random error component and the fit will be more useful for prediction [19,20].

- *R-Square (R^2)* – the square of the correlation between the response values and the predicted response values. R^2 is the square of the multiple correlation coefficient and the coefficient of multiple determination.

$$(4)\quad R^2 = \frac{SSR}{SST} = 1 - \frac{SSE}{SST};$$

$$SSR = \sum_{i=1}^{n} \omega_i (\hat{y}_i - \bar{y}_i)^2$$

$$SST = \sum_{i=1}^{n} \omega_i (y_i - \bar{y}_i)^2$$

The values of R^2 closer to 1 indicate that a greater proportion of variance is accounted for by the model [20].

$$(5)\ Adjusted\ R^2 = 1 - \frac{SSE}{SST}$$

$Adj\ R^2$ is the best indicator of the fit quality when two models are compared. This parameter can take any value less than or equal to 1, with a value closer to 1 indicating a better fit.

- *RMSE (Root Mean Squared Error)*

$$(6)\quad RMSE = s = \sqrt{MSE}$$

RMSE represents the standard error of the regression and is an estimate of the standard deviation of the random component in the data. MSE is the mean square error or the residual mean

square. The values of *RMSE* closer to 0 indicate a fit that is more useful for prediction [21].

RESULTS AND DISCUSSION

For the purpose of the *in silico* docking the crystal structure of MOR was obtained from RCSB (PDB id:4dkl). From the literature the binding sites of MOR are known [22]. These are the residues within a radius of about 10 Å of the asparagine (Asp) acid residue located in the transmembrane helix 3 - Asp147. Computer modelling and molecular docking experiments with MOR and the investigated ligands (Table 1) were carried out with the software GOLD 5.2 and all optimization functions: ASP, ChemPLP, GoldScore, ChemScore functions [16,17]. These functions were used to rank the mu-opioid ligand conformations by evaluating the binding density of each of the probable complexes.

In order to investigate the appropriate relationship between biological activity of the mu-opioid ligands and docking results (the values of the optimization functions) the Surface Curve Fitting Toolbox in software MATLAB was applied. The total energies of the formed ligand-receptor complexes after *in silico* docking were calculated by MolDock scoring function in software MMV 2.5 [21-25].

Parametric curves used in computer graphics are often based on polynomials. For surfaces, X, Y, and Z must be matrices with the same number of elements – in our case ten data points. Sizes are compatible if X is a vector of length n, Y is a vector of length m and Z is a 2D matrix of size $[m, n]$. The Curve Fitting application expects inputs where $length\,(X) = \mathrm{n}$, $length(Y) = m$ and $size(Z) = [m, n]$. By applying the polynomial least squares surface fitting technique, a first- to a third-order polynomial was fitted to the experimental data in R^3. Experimental data were modelled by polynomials with varying degrees of x and y. The polynomial models have the following equations:

Poly11: $f(x,y) = a_{00} + a_{10}x + a_{01}y$

Poly12: $f(x,y) = a_{00} + a_{10}x + a_{01}y + a_{11}xy + a_{02}y^2$

Poly21: $f(x,y) = a_{00} + a_{10}x + a_{01}y + a_{11}xy + a_{20}x^2$

Poly22: $f(x,y) = a_{00} + a_{10}x + a_{01}y + a_{20}x^2 + a_{11}xy + a_{02}y^2$

Poly13: $f(x,y) = a_{00} + a_{10}x + a_{01}y + a_{11}xy + a_{02}y^2 + a_{12}xy^2 + a_{03}y^3$

Poly31: $f(x,y) = a_{00} + a_{10}x + a_{01}y + a_{20}x^2 + a_{11}xy + a_{30}x^3 + a_{21}x^2y$

Poly32: $f(x,y) = a_{00} + a_{10}x + a_{01}y + a_{20}x^2 + a_{11}xy + a_{02}y^2 + a_{30}x^3 + a_{21}x^2y + a_{12}xy^2$

Poly23: $f(x,y) = a_{00} + a_{10}x + a_{01}y + a_{20}x^2 + a_{11}xy + a_{02}y^2 + a_{21}x^2y + a_{12}xy^2 + a_{03}y^3$

The experimental data can be represented as follows:

1) the values of z represent the values of IC_{50};

2) the values of x represent the docking results from GOLD - the values of ASP, ChemPLP, ChemScore and GoldScore functions;

3) the values of y represent the total energies calculated from MMV for ligand-receptor complex forming after the docking - the values of MolDock function [20].

Table 2. The experimental data for the ASP function and MolDock function.

Ligands	IC_{50}	ASP Score	MolDock
[Cys(O_2NH_2)^2-Met^5]-enk	1378	42,64	272.726
Dalargin	12.3	45.69	496.613
Dalarginamide	5.8	48.04	743.587
Dalarginethylamide	6	49.94	438.743
DAMGO	5.8	45.97	77.749
[L-Ala^2]-dalargin	234	46.93	73.823
[Leu^5]-enkephalin	65.3	41.59	430.507
[Met^5]-dalargin	11.9	48.95	769.467
[Met^5]-enkephalin	28.6	46.98	439.083
N-Me-[L-Phe^4]-dalarginamide	0.57	42.61	632.829

Table 3. The experimental data for ChemPLP function and MolDock function.

Ligands	IC_{50}	ChemPLP	MolDock
[Cys(O_2NH_2)^2-Met^5]-enk	1378	85.24	-113.502
Dalargin	12.3	100.41	-162.681
Dalarginamide	5.8	97.06	-148.977
Dalarginethylamide	6	92.08	-157.038
DAMGO	5.8	80.67	-29.582
[L-Ala^2]-dalargin	234	84.69	-10.891
[Leu^5]-enkephalin	65.3	85.89	-133.004
[Met^5]-dalargin	11.9	98.6	-145.639
[Met^5]-enkephalin	28.6	87.64	-144.788
N-Me-[L-Phe^4]-dalarginamide	0.57	79.34	-76.62

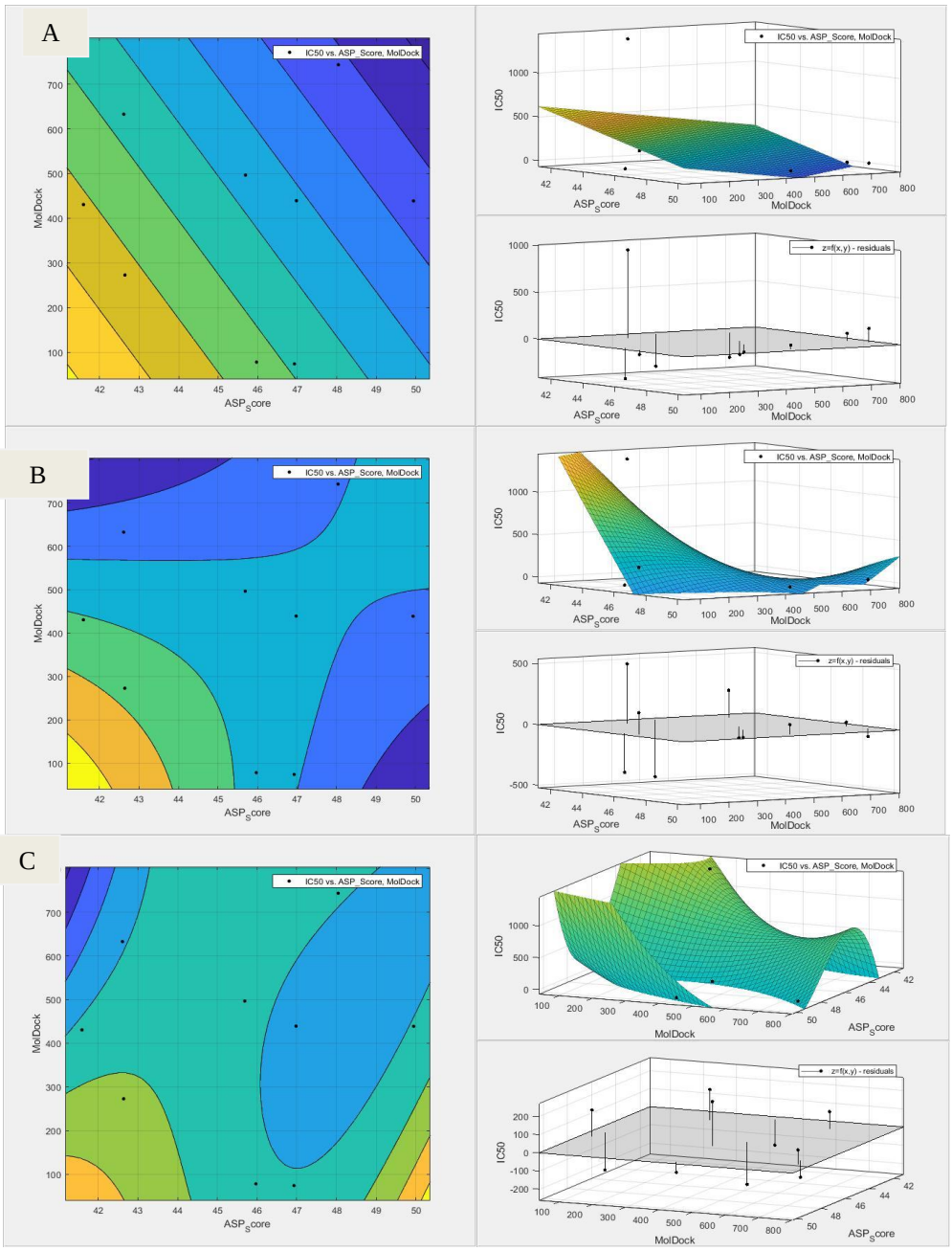

Figure 1. 3D plot of the experimental data with first to third degree of polynomials, which represent the biological activity of the ligands as a function of the values of ASP scoring function from GOLD and the values of the total energies– MolDock function. The plots represent the *Residuals Plot* and *2D contour plot* of the 3D surface for the obtained polynomial models.

Table 4. The experimental data for ChemScore function and MolDock function.

Ligands	IC_{50}	ChemScore	MolDock
[Cys(O_2NH_2)^2-Met^5]-enk	1378	19.6	-107.904
Dalargin	12.3	20.67	-135.245
Dalarginamide	5.8	28.75	-148.221
Dalarginethylamide	6	29.02	-163.106
DAMGO	5.8	14.31	-93.278
[L-Ala^2]-dalargin	234	21.28	-130.171
[Leu^5]-enkephalin	65.3	25.95	-148.483
[Met^5]-dalargin	11.9	23.27	-173.298
[Met^5]-enkephalin	28.6	25.11	-120.651
N-Me-[L-Phe^4]-dalarginamide	0.57	20.08	-107.216

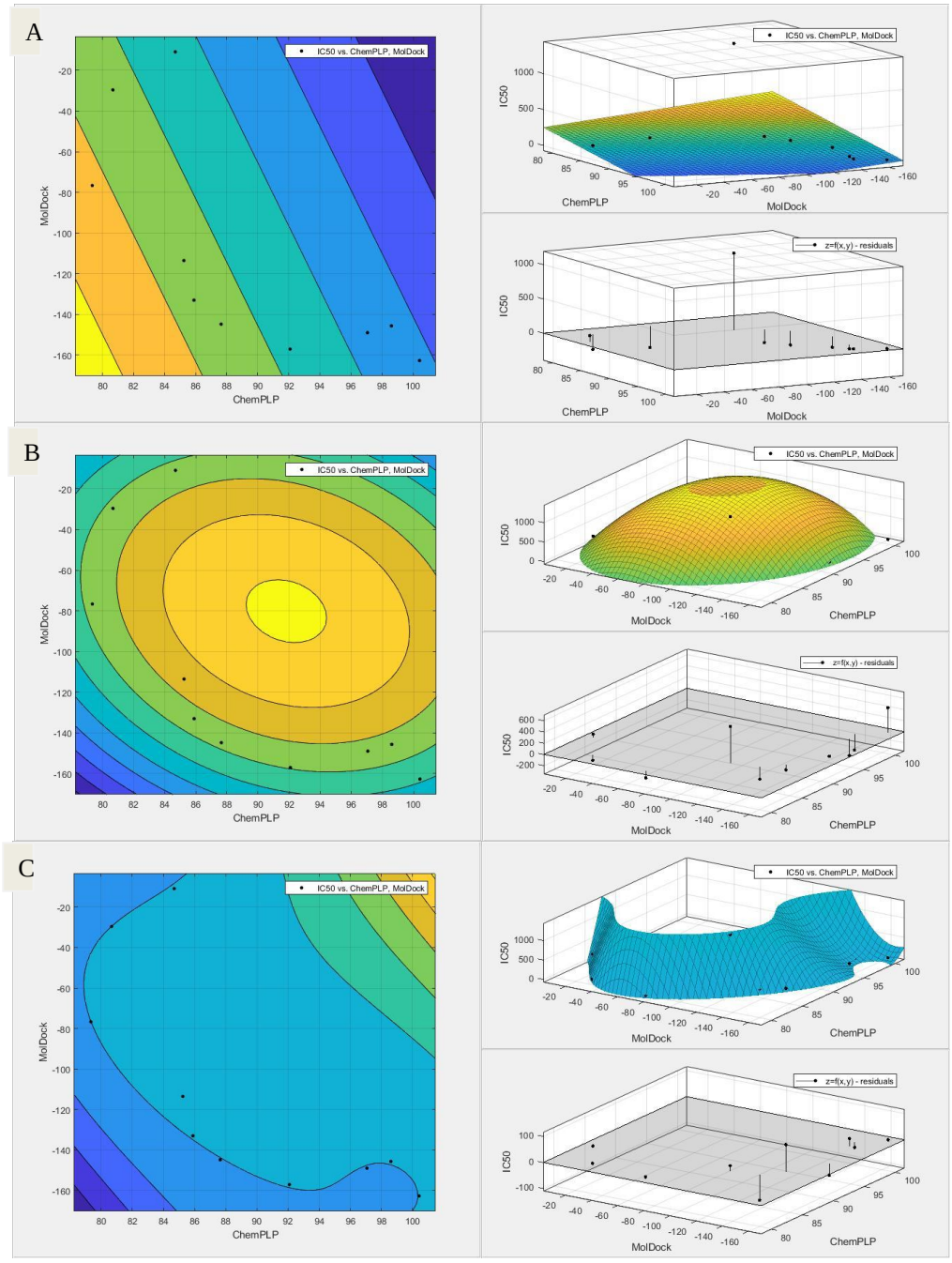

Figure 2. 3D plot of the experimental data with first to third degree of polynomials, which represent the IC_{50} of the ligands as a function of the values of ChemPLP function from GOLD and the values of the total energies – MolDock function. The plots represent the *Residuals Plot* and *2D contour plot* of the 3D surface for the obtained polynomial models.

Table 5. The experimental data for GoldScore function and MolDock function.

Ligands	IC_{50}	GoldScore	MolDock
[Cys(O_2NH_2)^2-Met^5]-enk	1378	94,39	-227,91
Dalargin	12,3	81,75	-75,84
Dalarginamide	5.8	95.4	-238.1
Dalarginethylamide	6	100.37	6.29
DAMGO	5.8	75.37	-169.4
[L-Ala^2]-dalargin	234	53.13	-96.83
[Leu^5]-enkephalin	65.3	95.27	-106.4
[Met^5]-dalargin	11.9	95.43	-146.42
[Met^5]-enkephalin	28.6	89.48	-105.67
N-Me-[L-Phe^4]-dalarginamide	0.57	77.04	-89.527

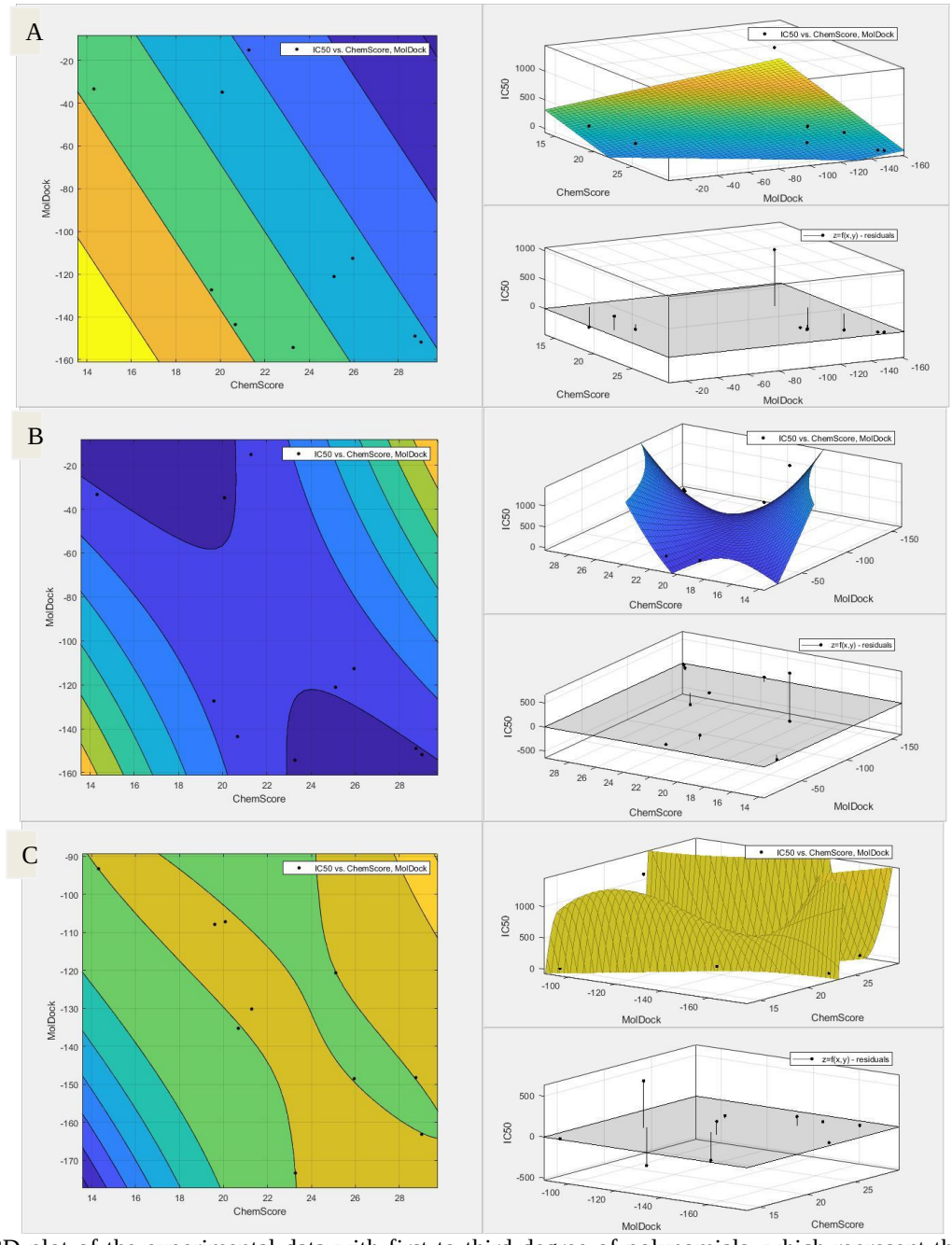

Figure 3. 3D plot of the experimental data with first to third degree of polynomials, which represent the IC_{50} of the ligands as a function of the values of ChemScore function from GOLD and the values of the total energies – MolDock function. The plots represent the *Residuals Plot* and *2D contour plot* of the 3D surface for the obtained polynomial models.

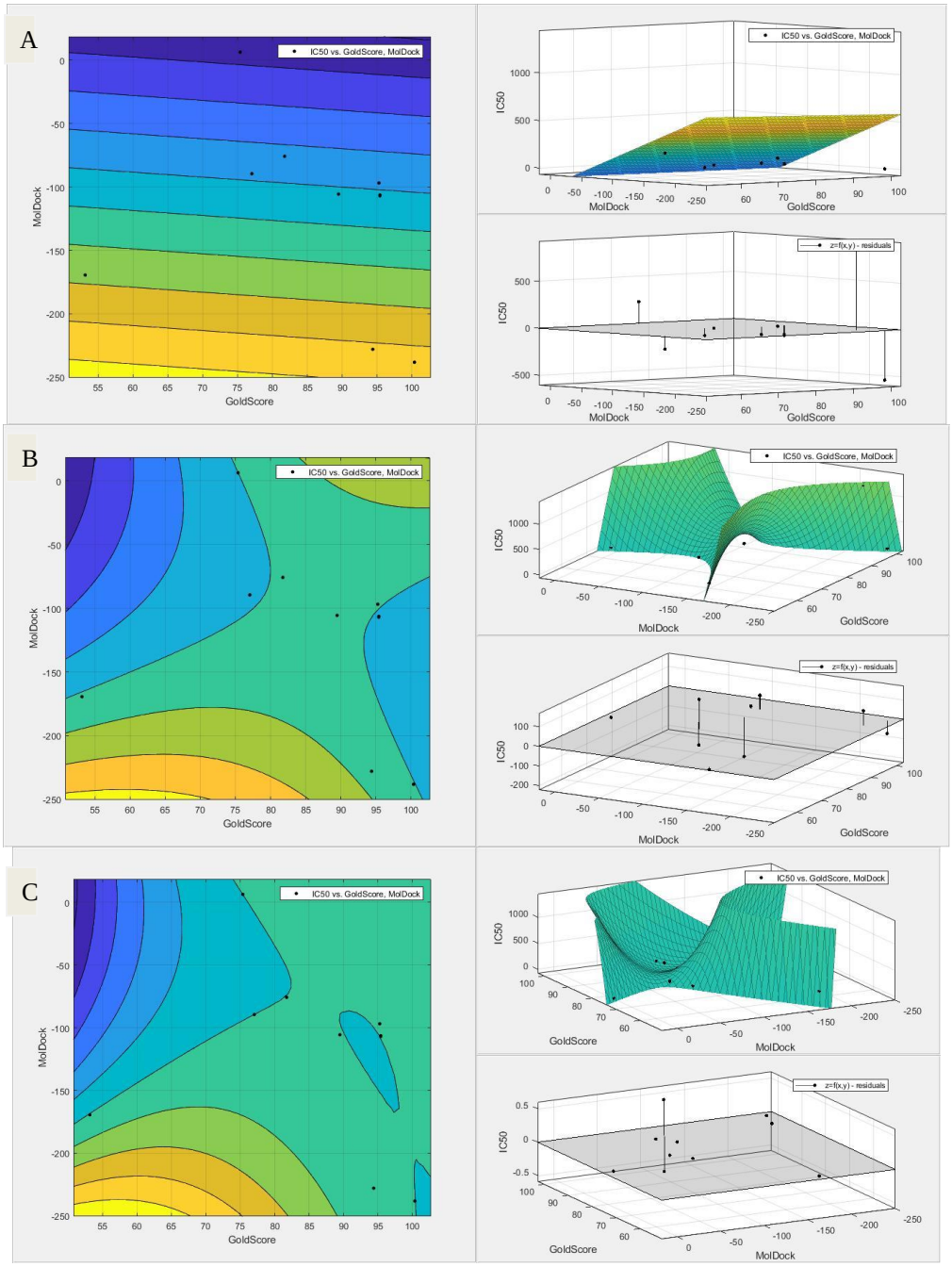

Figure 4. 3D plot of the experimental data with first to third degree of polynomials, which represent the IC_{50} of the ligands as a function of the values of GoldScore function from GOLD and the values of the total energies – MolDock function. The plots represent the *Residuals Plot* and *2D contour plot* of the 3D surface for the obtained polynomial models.

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 obtained results for the statistic parameters are presented in Table 6.nThe best results of the parameters used for surface fitting in MATLAB can be represented as follows: the values of *z* represent the values of IC_{50}, the values of x represent the values of GoldScore function from GOLD and the values of y represent the values of the total energies for ligand-receptor complexes – MolDock optimization function from MMV. As can be seen from the results in Table 6 the goodness of fit statistics shows that the obtained model for fitting of the experimental data for GoldScore with the third degree for x and the second degree for y is a good one – Poly32. This model is with the highest value of $R^2 = 1$ for MOR and the value closer to 1 indicating that a greater proportion of variance is explained by the model. The values of *SSE=0.580* for the polynomial model Poly32 are less than 1. This value shows that the model has a smaller random error component and

the fit will be more useful for prediction. The values of *Adj* R^2 for the model Poly32 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=0.761* for model Poly32 are less than 1 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, it explains a high proportion of the variability in experimental data, and is able to predict new observations with high certainty [8-15].

Table 6. The goodness of fit for the polynomial models obtained by the least squares method in MATLAB for all optimization functions from docking experiments.

Degree (x, y)	ASP function			
	SSE	R^2	*Adj* R^2	*RMSE*
11	1.268	0.233	0.01382	425.7
12	6.908	0.582	0.428	371.7
21	7.34	0.556	0.201	383.1
13	2.226	0.865	0.596	272.4
31	3.673	0.777	0.333	349.9
22	6.895	0.583	0.061	415.2
32	2.613	0.842	-0.4224	511.2
23	1.031	0.937	0.439	321
Degree (x, y)	ChemPLP function			
	SSE	R^2	*Adj* R^2	*RMSE*
11	1.551	0.061	-0.206	470.8
12	1.035	0.373	-0.126	455
21	1.242	0.248	-0.352	498.4
13	8.768	0.4697	-0.590	540.6
31	1.082	0.345	-0.963	600.6
22	9.068	0.451	-0.233	476.1
32	2.534	0.984	0.8621	159.2
23	7568	0.9954	0.9588	86.99
Degree (x, y)	ChemScore function			
	SSE	R^2	*Adj* R^2	*RMSE*
11	1.466	0.113	-0.140	457.7
12	1.402	0.152	-0.525	529.5
21	1.145	0.307	-0.246	478.6
13	1.112	0.327	-1.017	608.8
31	9.738	0.411	-0.766	569.7
22	1.142	0.309	-0553	534.3
32	7.267	0.56	-2.96	853
23	7.817	0.5273	-3.255	884.1
Degree (x,y)	GoldScore function			
	SSE	R^2	*Adj* R^2	*RMSE*
11	1.145	0.307	0.109	404.4
12	9.93	0.399	-0.081	445.6
21	9.014	0.454	0.018	424.6
13	3.349	0.979	0.939	105.7
31	7.404	0.9552	0.865	157.1
22	1.006	0.939	0.863	158.6
32	**0.580**	**1**	**1**	**0.761**
23	3.293	1	1	1.815

Table 7. The mean values (confidence bounds) of the coefficients of the polynomial models for all scoring functions.

Coefficients of the models	Mean (with 95% confidence bounds)			
Poly11	*ASP*	*ChemPLP*	*ChemScore*	*GoldScore*
a_{00}	174.8 (-143.5, 493.1)	174.8 (-177.2, 526.8)	915.5 (-1065, 2896)	174.8 (-127.6, 477.2)
a_{10}	-154.7 (-496.5, 187.1)	-145.6 (-688.6, 397.4)	-0.2719 (-122, 121.5)	-18.51 (-347, 310)
a_{01}	-111 (-452.8, 230.8)	-68.19 (-611.2, 474.8)	5.533 (-15.84, 26.9)	-241.5 (-570, 86.98)
Poly12				
a_{00}	187.1 (-261, 635.2)	821.8 (-312.4, 1956)	196 (-500.6, 892.6)	19.22 (-575.9, 614.3)
a_{10}	-204 (-560.1, 152.1)	386.4 (-658.4, 1431)	31.81 (-865.2, 928.8)	94.85 (-588.7, 778.4)
a_{01}	-247 (-623.2, 129.3)	809.3 (-805.8, 2424)	210.7 (-721.3, 1143)	-182.9 (-628.1, 262.2)
a_{11}	426.7 (-111.7, 965)	452.5 (-505.8, 1411)	133.6 (-614.1, 881.3)	248.3 (-957, 1454)
a_{02}	-95.01 (-473, 283)	-388.5 (-1310, 532.6	77.86 (-789, 944.7)	232.8 (-541.1, 1007)
Poly21				
a_{00}	60.8 (-438.2, 559.8)	462.9 (-337.5, 1263)	284.2 (-235.4, 803.7)	407.6 (-288.7, 1104)
a_{10}	-213.9 (-590.5, 162.7)	142.7 (-773.4, 1059)	127.5 (-595.6, 850.7)	-342.5 (-1152, 467.1)
a_{01}	-227.8 (-609.3, 153.6)	357.8 (-890.1, 1606)	243.7 (-422.5, 910)	-438.7 (-1033, 155.5)
a_{20}	52.29 (-375.6, 480.2)	162.3 (-928.7, 1253)	-555.3 (-1867, 755.9)	-252.4 (-853.1, 348.2)
a_{11}	390.2 (-150.5, 930.9)	660.6 (-1227, 2548)	-572 (-2195, 1051)	25.74 (-519.7, 571.2)
Poly22				
a_{00}	167.6 (-657.9, 993.1)	1167 (-640, 2974)	304.6 (-517.9, 1127)	371.2 (89.77, 652.6)
a_{10}	-200.1 (-647.3, 247)	531.2 (-764.8, 1827)	108.6 (-894.3, 1111)	-321.9 (-648.6, 4.736)
a_{01}	-249.7 (-711.8, 212.5)	1015 (-961.7, 2991)	219.9 (-796.3, 1236)	-568.3 (-816.3, -320.3)
a_{20}	16.84 (-520.2, 553.9)	-521.7 (-2446, 1403)	-577 (-2257, 1102)	-708.8 (-1039, -378.5)
a_{11}	423.3 (-234.8, 1081)	-272.7 (-3159, 2614)	-621.3 (-2965, 1722)	1382 (679.7, 2085)
a_{02}	-89.48 (-578.5, 399.5)	-780 (-2560, 1000)	-38.4 (-1042, 965.2)	824.3 (418.8, 1230)
Poly13				
a_{00}	158.8 (-276.6, 594.3)	1409 (-2429, 5247)	234.4 (-983.9, 1453)	-289.3 (-767.5, 188.8)
a_{10}	-40 (-445.3, 365.3)	1219 (-4430, 6867)	-116 (-1891, 1659)	587.6 (316.5, 858.8)
a_{01}	-1972 (-4721, 777.5)	3271 (-1.026e+04, 1.68)	970.2 (-4172, 6112)	607.7 (-549.8, 1765)
a_{11}	-348.1 (-1843, 1147)	1841 (-6129, 9810)	-630.8 (-5514, 4252)	-543 (-1274, 188.4)
a_{02}	399.2 (-314.9, 1113)	1121 (-6928, 9169)	-588 (-5994, 4818)	268.2 (-304.8, 841.2)
a_{12}	-272.4 (-1110, 565.4)	95.85 (-1828, 2020)	-45.43 (-2676, 2585)	-2563 (-3446, -1679)
a_{03}	1164 (-593.2, 2921)	-1258 (-8341, 5824)	-689 (-5876, 4498)	-1414 (-2097, -730.9)
Poly31				
a_{00}	223.2 (-428.8, 875.2)	367 (-911.6, 1646)	189 (-690.7, 1069)	366.9 (22.73, 711)
a_{10}	-703.9 (-2078, 669.9)	-341.2 (-3027, 2344)	-203.8 (-2306, 1898)	223.6 (-572, 1019)
a_{01}	-66.77 (-742.2, 608.7)	240 (-1721, 2202)	143.7 (-952, 1239)	-865.7 (-1448, -284)
a_{20}	2.19 (-491, 495.3)	66.34 (-1944, 2077)	-512.8 (-3160, 2134)	-425.5 (-1508, 657.1)
a_{11}	406.2 (-268.3, 1081)	465.3 (-3158, 4088)	-615.1 (-3491, 2261)	-374.6 (-873.3, 124.2)
a_{30}	302 (-434.4, 1038)	206.1 (-1970, 2382)	466.5 (-2046, 2979)	-495.9 (-1043, 51.49)
a_{21}	-239.9 (-1138, 658.1)	-99.04 (-3350, 3152)	435.7 (-2778, 3649)	957.6 (174.2, 1741)
Poly32				
a_{00}	107.9 (-5450, 5665)	1855 (-1383, 5093)	421.8 (-8336, 9180)	516.8 (483.2, 550.5)
a_{10}	-969.4 (-1.617e+04, 1.424)	-369.5 (-3464, 2725)	-1171 (-2.608e+04, 2.374)	-1551 (-1680, -1423)
a_{01}	212.8 (-6959, 7385)	2074 (-2484, 6632)	-331.4 (-1.373e+04, 1.307)	-1535 (-1628, -1441)
a_{20}	55.06 (-3116, 3226)	-1546 (-6211, 3119)	-2092 (-4.102e+04, 3.684)	208.9 (159.1, 258.7)
a_{11}	174.1 (-6338, 6686)	-1384 (-1.011e+04, 7343)	-3278 (-6.486e+04, 5.83)	3076 (2864, 3288)
a_{02}	198.3 (-5595, 5991)	-875.1 (-6346, 4596)	-921.5 (-2.2e+04, 2.016)	1280 (1215, 1345)
a_{30}	434.4 (-6797, 7666)	1312 (-6512, 9136)	3538 (-6.532e+04, 7.239)	1262 (1117, 1406)
a_{21}	-651.7 (-1.043e+04, 9123)	2162 (-1.636e+04, 2.068)	7456 (-1.476e+05, 1.625)	-823.7 (-1002, -645.9)
a_{12}	182 (-1.024, 1.061e+04)	2340 (-1.064e+04, 1.532)	4276 (-9.045e+04, 9.9)	-983.2 (-1124, -842.7)
Poly23				
a_{00}	248.3 (-3526, 4022)	2716 (-636.1, 6068)	587.8 (-1.111e+04, 1.228)	61.97 (5.138, 118.8)
a_{10}	-47.46 (-1995, 1900)	1669 (-3961, 7300)	475.7 (-1.723e+04, 1.818)	-110.2 (-202.6, -17.83)
a_{01}	-1997 (-1.867e+04, 1.468)	6528 (-8424, 2.148e+04)	1749 (-3.361e+04, 3.711)	-267.8 (-403.8, -131.8)
a_{20}	-94.89 (-2443, 2253)	-1277 (-4198, 1644)	-975.7 (-2.485e+04, 2.29)	-148.3 (-194, -102.7)
a_{11}	-618.2 (-8522, 7286)	1504 (-1.073e+04, 1.374)	-2601 (-5.809e+04, 5.288)	720.5 (551.5, 889.5)
a_{02}	549 (-3418, 4516)	1743 (-8543, 1.203e+04)	-1818 (-4.463e+04, 4.099)	620.3 (560.2, 680.4)
a_{21}	-349.5 (-6542, 5844)	-1636 (-4580, 1309)	-466.7 (-1.841e+04, 1.748)	482 (391.5, 572.5)
a_{12}	-211.3 (-4228, 3805)	-1099 (-5758, 3560)	-1475 (-3.462e+04, 3.167)	-676 (-929.5, -422.5)
a_{03}	1344 (-8493, 1.118e+04)	-2921 (-1.178e+04, 5941)	-1703 (-3.951e+04, 3.61)	-471.5 (-599.9, -343.1)

By using a polynomial least squares surface fitting technique, a third order for x and second order for y were fitted to the data (Poly32). The coefficients of the surface fitting for MOR by

polynomials from first to third degree for all scoring functions in 3D are presented in Table 7.

The best results for fitting of experimental data according to the results in Tables 2-5 were obtained or surface fitting by a polynomial model Poly32 in 3D for determining the relationship between biological activities and docking results of the investigated compounds. By using a polynomial least squares surface fitting technique, a polynomial model of third order for *x* and of second order for *y* was fitted to the data and it is represented as follows:

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

where: x is normalized by mean 85.76 and standard deviation 14.31 and y is normalized by mean -121 and standard deviation 72.99.

After analysing the results from Table 6 we can conclude that the best values were obtained for the potency of the mu-opioid ligands as a function of the values of GoldScore function and the values of the total energies (MolDock function) for the formed ligand-receptor complexes for a polynomial model of third order for x and of second order for y (Poly32). The established values of the statistical parameters are important because they give the best description of the fitting of the experimental data for MOR with polynomials of two variables. Surface curve fitting gives detailed account of inter-relation of dependent variable with respect to independent variables. In the present work, one dependent and two independent variables were considered to evolve the best fit model. The Curve fitting finds the values of the coefficients (parameters) which make a function match the data as closely as possible. The best values of the coefficients are known when the value of R^2 becomes 1. The fitting models and methods used here depend on the input data set.

CONCLUSIONS

In this work, two dependent variables and one independent variable data points were taken into consideration for fitting the 3D graph. The obtained model for the experimental data showed good fitting properties and significant predictive ability. Therefore, this model of a third-degree polynomial is suitable to determine the relationship structure-biological activity. The GoldScore and MolDock optimization functions could be used for describing the biological activity of newly designed compounds. This would be helpful in shortening the drug design process.

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REFERENCES

1. P. Law, Y. Wong, H. Loh, *Ann. Rev. Pharmacol.Toxicol*., **40**, 389 (2000).
2. J. Lord, A. Waterfield, J. Hughes, H. Kosterlitz, *Nature*, **267**, 495 (1977).
3. J. Froehlich, *Alcohol Health Res. World*, **21**(2), 132 (1997).
4. R. Maldonado, R. Severini, W. Hans, B. Kiefer, P. Melchiorri, L. Negri, *British Journal of Pharmacology*, **132,** 1485 (2001).
5. R. Bodnar, *J. Peptides*, **60**, 65 (2013).
6. U. Rester, *Curr. Opin. Drug Discov. Devel.*, **11**, 559 (2008).
7. N. Pencheva, P. Milanov, L. Vezenkov, T. Pajpanova, E. Naydenova, *Eur. J. Pharmacol.*, **498**, 249 (2004).
8. N. Pencheva, A. Bocheva, E. Dimitrov, C. Ivancheva, *Eur. J. Pharmacol.*, **304**, 99 (1996).
9. F. Sapundzhi, T. Dzimbova, N. Pencheva, P. Milanov, *Bulg. Chem. Commun.*, **2**, 613 (2015).
10. F. Sapundzhi, Mathematical and computer modelling of ligand-target interactions. PhD desertion. South-West University "Neofit Rilski", Blagoevgrad, Bulgaria (2015).
11. . I. Sapundzhi, Mathematical and computer modelling of drug-receptor interactions, , University Publishing house "Neofit Rilski", Blagoevgrad, ISBN 978-954-00-0190-6, 2019 (in Bulgarian).
12. F. I. Sapundzhi, Modeling of the interrelation structure – biological activity, University Publishing house "Neofit Rilski", Blagoevgrad, ISBN 978-954-00-0191-3, 2019 (in Bulgarian).
13. F. Sapundzhi, T. Dzimbova, N. Pencheva, P. Milanov, *Bulg. Chem. Commun.*, **49**, Special Issue E, 23 (2016).
14. F. Sapundzhi, T. Dzimbova, N. Pencheva, P. Milanov, *Bulg. Chem. Commun.*, **49(4)**, 768 (2017).
15. F. Sapundzhi, T. Dzimbova, P. Milanov, N. Pencheva, *Journal of Computational Methods in Molecular Design*, **5**, 98 (2015).
16. GOLD, version 5.2 UserGuide, *CCDC Software Ltd.: Cambridge*, UK, 2010.
17. G. Jones, P. Willett, R. Glen, A. Leach, R. Taylor, *J. Mol. Biol.*, **267**, 727 (1997).
18. M. Verdonk, J. Cole, M. Hartshorn, C. Murray, R. Taylor. *Proteins*, **52,** 609 (2003).
19. http://www.mathworks.com/products/matlab
20. J. Shim, A. Coop, A. MacKerell, *J. Phys. Chem. B.*, **117 (26)**, 7907 (2013).
21. F. Sapundzhi, T. Dzimbova, N. Pencheva, P. Milanov, *Der Pharma Chemica*, **8**, 118 (2016).

22. F. Sapundzhi, T. Dzimbova, N. Pencheva, P. Milanov, *Bulg. Chem. Commun.*, **50**, Special Issue B, 44 (2018).
23. F. Sapundzhi, M. Popstoilov, *Bulg. Chem. Commun.*, **50**, Special Issue B, 115 (2018).
24. F. Sapundzhi, T. Dzimbova, N. Pencheva, P. Milanov. *Bulg. Chem. Commun.*, **50**, Special Issue B, 15 (2018).
25. F. Sapundzhi, *International Journal of Online and Biomedical Engineering*, **15 (12)**, 88-96, (2019).
26. F. Sapundzhi, *International Journal of Online and Biomedical Engineering*, **15 (11),** 139-145, (2019).
27. F. Sapundzhi, T. Dzimbova, *International Journal of Online and Biomedical Engineering*, **15 (15)**, (2019), in press.
28. J. Clark, Y. Itzhak, V. Hruby, H. Yamamura, G. Pasternak, *Eur. J. Pharmacol.*, **128**, 303 (1986).
29. R. Reinscheid, H. Nothacker, A. Bourson, A. Ardati, R. Henningsen, J. Bunzow, D. Grandy, H. Langen, F. Monsma, O. Civelli, *Science*, **270**, 792 (1995).
30. R. Mavrevski, M. Traykov M., I. Trenchev, M. Trencheva, *WSEAS Transactions on Systems and Control* ,**13**, 242 (2018).
31. K. Befort, L. Tabbara, S. Bausch, C. Chavkin, C. Evans, B. Kieffer, *Mol..Pharmacol.*, **49**, 216 (1996).
32. R. Thomsen, M. Christensen, *J. Med. Chem*., **49**, 3315 (2006).
33. P. Lancaster, *Ser. C: Math. Phys. Sci*., **49**, 91 (1979).
34. D. Sun, A. Whitty, J. Papadatos, M. Newman, J. Donnelly, S. Bowes, S. Josiah, *J. Biomol. Screen*., **10**, 508 (2005).