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Density functional theory calculations and molecular docking of 2-phenylbenzimidazoles with estrogen receptor for quantitative structure–activity relationship studies

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Abstract: Benzimidazole derivatives, especially 2-phenylbenzimidazole with various substituents on the C-5, C-2 and C-6 positions, are so important in pharmaceutical chemistry. Multiple linear regression was applied to predict the activity of 27 novel 2-phenylbenzimidazole derivatives as anticancer agents. At first, we made an effort to create a QSAR model for a selected series of novel 2-phenylbenzimidazole with density functional theory and molecular docking descriptors. Then, we tried to investigate the nature of the interactions between 2-phenylbenzimidazole derivatives and the estrogen receptor using the molecular docking method. Six descriptors of MATS4e, GATS5e, R6v, R1v+, dipole moment, and torsional free energy were selected for modelling. Due to docking results, increase in the binding energy, and decrease in the dipole moment could increase inhibitor activity.

Keywords: dipole moment; torsional free energy; breast cancer; biological activity.

INTRODUCTION

Cancer is one of the most serious diseases created by unusual cell growth invading and spreading to different organs of the human body. Estrogen receptor (ER) is a therapeutic target and crucial prognostic sign of breast cancer.[1] Estrogen advances breast cancer propagation through several appointed paths. Binding estrogen with estrogen receptors irritates the estrogen responsive element of DNA. This complex causes duplication of cells and result in breast cancer.[2] Many studies have been performed in design and discovery research of novel selective estrogen receptor modulators. Thus, the design and synthesis of novel anticancer agents with further improvement and fewer side effects is necessary.

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Benzimidazole is aromatic heterocycle found in extensive number of natural and biologically active moleculs and considered to be significant pharmacophore.[3] Derivatives of novel benzimidazole replaced with various functional groups can be used as an antibacterial,[4] antimicrobial,[5] anti-inflammatory,[6] analgesic,[7] anthelmintic[8] and antitumor [9] agents. The benzimidazole is particularly one of the most effective compounds used in therapy of several cancer cell lines. The existence of substituents, such as hydroxyl groups and carbonyl in the C-5 position, besides substituents in the C-2 position, could remarkably increase the novel compounds' anticancer activity.[10] Huynh and co-workers synthesized several new derivatives of 2-phenylbenzimidazole with a various range of substituents on the C-5, C-2 and C-6 positions of 2-phenylbenzimidazole with the condensation of o-phenylenediamines and different aldehydes and afterwards illustrated their structure–activity relationship (SAR) upon three cancer cell lines: PC3, MDA-MB-231 and A54.[11]

On the other hand, quantitative structure–activity relationship studies have obtained a fundamental position within medicine chemistry. In QSAR analysis, one or more molecular descriptors described the molecular activity using statistical analysis. The basic goal of this analysis is the development of statistical models for prediction of the biological activity of novel compounds that have not been synthesized or their biological activity have not been determined. Several statistical methods suitable for chemometric analysis include multiple linear regression, partial least squares regression, principal component regression, and different types of artificial neural networks,[12] which can be used to create a correlation model between molecular descriptors and the related properties. Molecular descriptors can be calculated with molecular docking and DFT calculations.

Molecular docking may be a simulation approach for planning drug which can predict the compliance of a receptor–ligand complex. The receptor is regularly a protein or a nucleic acid molecule (DNA or RNA) and the ligand could be a small particle or drug.[13] Besides, molecular docking is one of main instruments for virtual screening strategies. Docking research and examination of the larvicidal action of some 2-phenylbenzimidazole derivatives were handled by Escal *et al*.[14] Novel benzimidazole subsidiaries as cholinesterase inhibitors were synthesized by Yoon *et al*. and their docking examination were explored.[15] Mizuno *et al.* explored docking atomic of novel benzimidazoles for the treatment of metabolic disorder.[16] Molecular docking research on a set of bisphenylbenzimidazole derivatives have been examined to identify the compounds binding orientations inside the HIV-1 reverse transcriptase non-nucleoside binding pocket.[17] A suitable correlation between the computed binding free energies and the experimental inhibitory activities proposes that the distinguished binding conformations of these inhibitors are reputable. This model may be utilized for a new non-nucleoside HIV-1 reverse transcriptase inhibitors due to the 1-benzyl-2-arylbenzim-

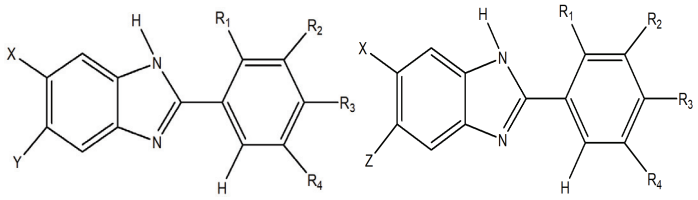
idazole scaffold. An appropriate QSAR model due to radial distribution performance descriptors and docking have been displayed for a few 4-anilinoquinazoline derivatives as potent EGFR inhibitors by Beglari *et al.*[18]

We investigated the binding mode of new 2-phenylbenzimidazole derivatives (chemical structures are shown in Table I) with estrogen receptor offering a QSAR model which could predict the biological activity of novel 2-phenylbenzimidazole. Multiple linear regressions were used to predict the activities of novel 2-phenylbenzimidazole. At first, we made an effort to create a QSAR for a selected series of novel 2-phenylbenzimidazole with DFT and molecular docking descripttors. Then, we attempted to investigate the nature of interactions between 2-phenylbenzimidazole derivatives and estrogen receptor using the molecular docking method.

EXPERIMENTAL

The dataset, involving 2-phenylbenzimidazole derivatives with inhibitory activity IC_{50} was provided from the literature. The structure of studying compounds is indicated in Table I.

TABLE I. Structures of the compounds used in inhibitory activity modelling and their IC_{50}[11]



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Compd.	X	Y	Z	R1	R2	R3	R4	IC_{50} / μM
15	H	Cl	–	OH	H	H	H	>100
16	H	Cl	–	H	OH	H	H	18.20
17	H	Cl	–	H	H	OH	H	36.56
19	H	Cl	–	OCH_3	H	H	OCH_3	85.11
20	H	Cl	–	H	OCH_3	OCH_3	OCH_3	21.88
21	H	Cl	–	H	H	$N(CH_3)_2$	H	18.62
22	H	Cl	–	NO_2	H	H	H	33.11
23	H	Cl	–	CF_3	H	H	H	6.92
24	H	Cl	–	H	OCH_3	OH	I	39.26
25	H	Cl		H	H	OCH_2Ph	H	19.95
28	Cl	Cl	–	H	H	OH	H	60.26
30	Cl	Cl	–	OCH_3	H	H	OCH_3	69.18
31	Cl	Cl		H	OCH_3	OCH_3	OCH_3	>100
32	Cl	Cl	–	H	H	$N(CH_3)_2$	H	60.26
34	Cl	Cl		CF_3	H	H	H	>100
36	Cl	Cl	–	H	H	–O–CH_2–Ph	H	52.48
37	H	Ph–CO–		OH	H	H	H	>100
38	H	Ph–CO–	–	H	OH	H	H	5.50
40	H	Ph–CO–		H	H	OCH_3	H	>100

TABLE I. Continued

Compd.	X	Y	Z	R1	R2	R3	R4	IC_{50} / μM
41	H	Ph–CO–	–	H	OCH_3	OCH_3	OCH_3	>100
45	H	Ph–CO–	–	H	OCH_3	OH	I	54.95
47	H	–	Ph–CH(OH)–	OH	H	H	H	17.78
48	H	–	Ph–CH(OH)–	H	OH	H	H	17.38
49	H	–	Ph–CH(OH)–	H	H	OH	H	33.88
50	H	–	Ph–CH(OH)–	H	H	OCH_3	H	53.70
51	H	–	Ph–CH(OH)–	H	OCH_3	OCH_3	OCH_3	>100
53	H	–	Ph–CH(OH)–	CF_3	H	H	H	47.86

Drawing of the structure of pharmaceutical derivatives was done with Gauss View software. The computation of optimization and frequency of the structure of 2-phenylbenzimidazole derivatives as ligand were with density functional hypothesis (DFT) approach[19] utilizing G09 software.[20] In these calculations, the B3LYP level of theory[21] and with 6-311G* standard basis set for all atoms except iodine (I) atom with LANDL2Z, basis set[22] has been used. Some of the computed descriptors used in this research consisted the lowest unoccupied molecular orbital and the highest occupied molecular orbital energies, electron affinity, and dipole moment, enthalpy, and log *P* and electrophilicity index. Frontier molecular orbitals of HOMO and LUMO were acquired from the population analysis calculations and visualized using Gauss View. These parameters play an influential and important role in illustrated ligands interaction in the binding pocket of the Estrogen receptor. Using the analytic second derivatives, harmonic vibrational wavenumbers were computed to corroborate the convergence to minima on the potential surface.

Docking calculations between new 2-phenylbenzimidazole derivatives as ligand and estrogen receptor have been performed using Auto Dock 4.2.[23] Estrogen receptor crystal structure (PDB ID: 3OS8) has been gained from Protein Data Bank (www.rcsb.org). This receptor has four chains A, B, C, and D but three B, C and D were omitted. Then, molecular docking was accomplished using the lamarckian genetic algorithm.[13] To identify the binding sites in estrogen receptor, blind docking has been done, by the grid size set to 60, 60, and 60 Å^3 along with *X*-, *Y*- and *Z*-axis with 9.526, 22.699 and –23.362 Å grid space. The conformation with the lowest binding free energy and low inhibition constants was employed for better analysis. Dragon, Gaussian and Auto Dock softwares were utilized to create molecular descriptors. By stepwise MLR approach, the linear relationship between a dependent variable, pIC_{50} (–log IC_{50}), and independent variables, like electronic, constitutional, topological, and steric descriptors, is displayed as a linear equation, which makes it a potent method for QSAR modelling.

RESULTS AND DISCUSSION

The reactivity of compounds was foretold, and several energy descriptors were investigated in detail. In usual, the frontier molecular orbitals are utilized to study the interactions 2-phenylbenzimidazole derivatives. In addition, HOMO and LUMO orbitals indicate the reactivity of 2-phenylbenzimidazole derivatives and their possible interactions with estrogen receptor.[24] HOMO and LUMO orbitals of one of the foremost biological activity are indicated in Fig. 1.

HOMO–LUMO's red and green colours, respectively, indicate positive and negative orbitals. HOMO is delocalized over the complete molecule, whereas

LUMO is delocalized but within the monosubstituted phenyl ring. It shows the charge transfer inside the molecules. Electronic descriptors are revealed in Tables II and III. The energy gap values were computed for these compounds which build up the stability and bioactivity of the molecules. For all molecules, energy gap over 3eV and chemical potentials are equal or higher than –3.9 eV. The computed higher hardness value, moreover, shows the stability of the molecules. All the molecules have high electrophilicity index values for the sake of which are assessed as dynamic biological system. For the foremost portion, the higher electronegative potential surface was found over C=O, which illustrates that it ought to be susceptible to nucleophilic attacks.

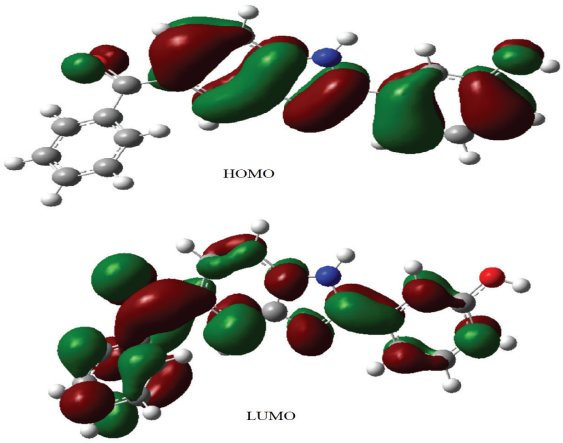

Fig. 1. Frontier orbitals of 2-phenylbenzimidazole derivatives (**38**).

TABLE II. Values of the descriptors of HOMO, LUMO, energy gap, ionization potential (I = = $-E_{HOMO}$), electron affinity (A = $-E_{LUMO}$) global hardness (η = (I–A)/2) and softness (S = = 1/η) at the B3L Y P/6-31G level

Comp.	HOMO, eV	LUMO, eV	Energy gap, eV	I / eV	A / eV	η / eV	S / eV
15	–6.1613	–1.6491	–4.5122	6.1613	1.6491	2.2561	163.9640
16	–6.3158	–1.7791	–4.5366	6.3158	1.7791	2.2683	163.0793
17	–6.1112	–1.6192	–4.4920	6.1112	1.6192	2.2460	164.6987
19	–5.9200	–1.6167	–4.3033	5.9200	1.6167	2.1516	171.9233
20	–5.9750	–1.5533	–4.4216	5.9750	1.5533	2.2108	167.3228
21	–5.4443	–1.3610	–4.0832	5.4443	1.3610	2.0416	181.1883
22	–6.7023	–3.6883	–3.0140	6.7023	3.6883	1.5070	245.4652
23	–6.6471	–2.2714	–4.3756	6.6471	2.271	2.1878	169.0806
24	–6.2105	–1.7756	–4.4349	6.2105	1.7756	2.2174	166.8199
28	–6.2568	–1.8376	–4.4191	6.2568	1.8376	2.2095	167.4155
30	–6.0566	–1.8196	–4.2369	6.0566	1.8196	2.1184	174.6164
32	–5.4897	–1.5074	–3.9823	5.4897	1.5074	1.9911	185.7796
36	–6.1439	–1.7614	–4.3824	6.1439	1.7614	2.1912	168.8182
38	–6.2565	–1.9263	–4.3302	6.2565	1.9263	2.1651	170.8542

TABLE II. Continued

Comp.	HOMO, eV	LUMO, eV	Energy gap, eV	I / eV	A / eV	η / eV	S / eV
45	–6.1648	–1.9507	–4.2140	6.1648	1.9507	2.1070	175.5631
25	–1.5297	–4.4588	5.9886	–0.0562	6.0231	0.0830	–2.9661
31	–1.8765	–4.2820	6.1586	–0.0689	6.2003	0.08064	–3.0448
34	–2.2714	–5.9619	8.2334	–0.0835	8.2669	0.0604	–4.0749
37	–1.8248	–4.2793	6.1042	–0.0670	6.1382	0.08145	–3.0185
40	–1.8528	–4.1088	5.9616	–0.0681	5.9967	0.08337	–2.9467
41	–1.9094	–4.1020	6.0114	–0.0702	6.0114	0.08317	–2.9706

TABLE III. Values of the descriptors of chemical potential ($\mu = -(I + A)/2$), electronegativity ($\chi = -\mu$), electrophilicity index ($\omega = 2\mu/2\eta$), enthalpy, dipole moment and solubility (log P) at the B3LY P/6-31G level

Comp.	μ / eV	χ / eV	$\omega = 2\mu/2\eta$	log P	Enthalpy, kcal* mol^{-1}	Dipole moment, D
15	–3.9052	3.9052	0.0232	–0.61	–1145.5221	7.8058
16	–4.0474	4.0474	0.0251	–0.61	–1145.5151	5.9407
17	–3.8652	3.8652	0.0226	–0.61	–1145.5152	7.1983
19	–3.7684	3.7684	0.0206	–1.57	–1299.2709	6.6226
20	–3.7642	3.7642	0.0211	–2.56	–1413.7352	3.9989
21	–3.4027	3.4027	0.0159	–0.53	–1204.1882	8.7549
22	–5.1953	5.1953	0.0274	–2.33	–1274.7754	4.0937
23	–4.4593	4.4593	0.0294	0.99	–1407.3609	4.7797
24	–3.9930	3.9930	0.0238	–1.08	–1270.7727	5.2597
28	–4.0472	4.0472	0.0244	–0.83	–1605.1209	7.5822
30	–3.9381	3.9381	0.0222	–1.79	–1758.8770	7.4367
32	–3.4986	3.4986	0.0164	–0.75	–1663.7944	10.1408
36	–3.9527	3.9527	0.0231	0.22	–1875.3535	8.3441
38	–4.0914	4.0914	0.0244	0.7	–1030.1764	5.6543
45	–4.0578	4.0578	0.0234	0.22	–1155.4341	5.1256
25	2.9661	–1.5297	–4.4588	0.44	–1415.7479	7.1679
31	3.0448	–1.8765	–4.2820	–2.78	–1873.3408	4.893
34	4.0749	–2.2714	–5.9619	0.99	–1407.3609	6.8421
37	3.0185	–1.824	–4.2793	0.7	–1030.1834	4.5896
40	2.9467	–1.852	–4.1088	0.73	–1069.4472	3.1936
41	2.9706	–1.9094	–4.1020	–1.26	–1298.3963	3.8498

For this research, interactions among 2-phenylbenzimidazole derivatives as ligand and estrogen receptor were performed by docking approach. As shown in Table III, docking descriptors involve binding energy, inhibition constant, Van der Waals energy, hydrogen bond and dehydration, total internal energy, ultimate intra-molecular energy, torsional free energy, and nonbinding energy. The inhibitory activity of ligands **38**, **19** and **30** is great. The inhibitory activity of ligands **17** and **15** is small. As shown in Fig. 2, docking of medicinal ligand **38** with estrogen receptor (3OS8) were detailed with Discovery Studio visualizer 4.1

* 1 kcal = 4184 J

(2014) software. For the protein 3OS8 (A), the exchanges are the residues of estrogen inhibitor; Arg 394, Met 357 and Glu 353 form π-sigma exchange with OH and C=O for ligand **38**. The ligand forms stable complex and has good binding affinity values (–9.2 kcal/mol for the complex with 3OS8 (A), all derivatives give high binding energy values, –8.9, –8.6, –9.6 and –9.02 kcal/mol for ligands of **48**, **53**, **49** and **37**, respectively. Therefore, the 2-phenylbenzimidazole derivatives display activity against estrogen inhibitor. Ligands of **17** and 15 displayed the maximum of inhibition constant (k_i) which have least activity because they have only OH substituent on the benzene ring.

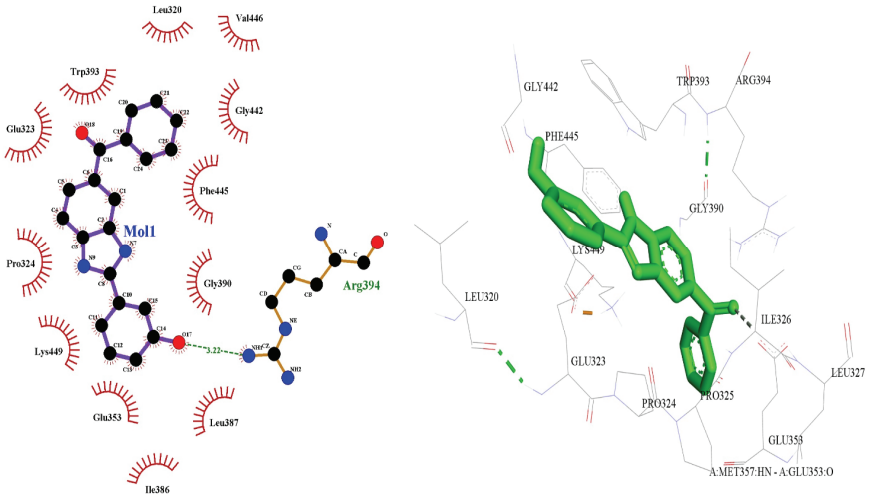

Fig. 2. Docking of ligand **38** with protein 3OS8 (A).

Ligands of **38** and **20** displayed the least of inhibition constant for they have Ph-C=O functional group. This evidence indicated that appropriate functional groups on the benzene ring were necessary for increases and better antibacterial activities in drug design. Therefore, these results indicate that electron-withdrawing groups play an important role in the anticancer activities of 2-phenylbenzimidazole derivatives.

The data set composed of 27 molecules is offered to an advanced multiple regression analysis until designing a MLR model. This method used the coefficients R, R^2 and the standard deviation to select the best regression performance. The correlation coefficient is R = 0.931, R^2 = 0.866, and F = 14.047. These values are related to assess the best model. The values of pIC_{50} of training and test sets, were predicted using MLR model. Statistical parameters of the best QSAR model, are shown in Table IV.

QSAR methods were performed on 2-phenylbenzimidazole derivatives to predict their biological activities. The values of predicted pIC_{50}, calculated with

statistical parameters and the graph of experimental pIC_{50} values against calculated pIC_{50} values using MLR method are seen in Fig. 3.

TABLE IV. Values of the chemical descriptors were obtained using molecular docking

Compd.	Energy, kcal mol^{-1}							k_i μM
	Binding	Torsional free	Final total internal	Final intermolecular	Unbound systems	Electrostatic	vdW + Hbond + desolv	
15	–6.5	0.6	–0.78	–7.13	–0.78	–0.3	–6.84	16.2
16	–7	0.6	–0.17	–7.63	–0.17	–0.37	–7.63	7.01
17	–6.4	0.6	–0.2	–6.97	–0.2	–0.1	–6.86	21.2
19	–7.9	0.89	–0.31	–8.75	–0.31	–0.37	–8.38	1.76
20	–7.1	1.19	–0.63	–8.33	–0.63	–0.13	–8.2	5.86
21	–6.7	0.6	–0.32	–7.32	–0.32	–0.1	–7.22	11.8
22	–7.8	0.6	–0.94	–8.43	–0.94	–1.14	–7.29	1.81
23	–6.7	0.6	–0.56	–7.28	–0.56	–0.02	–7.26	12.6
24	–7.2	0.89	–0.99	–8.07	–0.99	0	–8.07	5.53
28	–6.6	0.6	–0.19	–7.18	–0.19	–0.12	–7.06	15
30	–7.8	0.89	–0.31	–8.73	–0.31	–0.33	–8.39	1.82
32	–6.9	0.6	–0.32	–7.5	–0.32	–0.1	–7.4	8.71
36	–8.7	1.19	–0.84	–9.86	–0.84	0.09	–9.94	0.45
38	–9.2	1.19	–0.62	–10.4	–0.62	–0.4	–10.03	0.17
45	–9	1.49	–1.44	–10.5	–1.44	–0.01	–10.52	0.24
47	–8.7	1.49	–1.11	–10.2	–1.11	–0.34	–9.81	0.45
48	–8.9	1.49	–0.61	–10.4	–0.61	–0.39	–10	0.3
49	–9.6	1.49	–0.54	–9.81	–0.54	–0.19	–9.61	0.8
50	–8.7	1.49	–0.58	–10.2	–0.58	–0.23	–9.96	0.42
51	–8.7	2.09	–0.99	–10.8	–0.99	–0.29	–10.52	0.41
53	–8.6	1.49	–0.96	–10.1	–0.96	–0.19	–9.93	0.47
25	–8.42	1.19	–0.86	–9.61	–0.86	0.07	–9.68	0.67
31	–7.03	1.19	–0.65	–8.22	–0.65	–0.13	–8.09	7.05
34	–6.68	0.6	–0.56	–7.28	–0.56	–0.02	–7.26	12.60
37	–9.02	1.19	–1.23	–10.21	–1.23	–0.38	–9.83	0.24
40	–8.45	1.19	–0.69	–9.64	–0.69	–0.03	–9.61	0.64
41	–8.49	1.79	–1.08	–10.28	–1.08	–0.09	–10.2	0.59

This study proposed the role of atomic features (mass, van der Waals volume and Sanderson electronegativities) due to weighted 2D-autocorrelations (MATS4e and GATS5e) and descriptors due to the elements of leverage matrix obtained by centered atomic coordinates considering weighted by van der Waals volume (GETAWAY descriptors: R6v and R1v+). In MLR models (Table V), R6V descriptor has a negative correlation with pIC_{50}. The small values of dipole moment indicate a high degree of anticancer activity, *e.g.*, compounds **20** and **38** (8.7549 and 5.6543 D) compared to the compounds **32** (10.1408 D). As a result, ligands **38** and **20** have better inhibitory activity than the ligands **32**. R1v+ and MATS4e descriptors have a positive correlation with pIC_{50}.

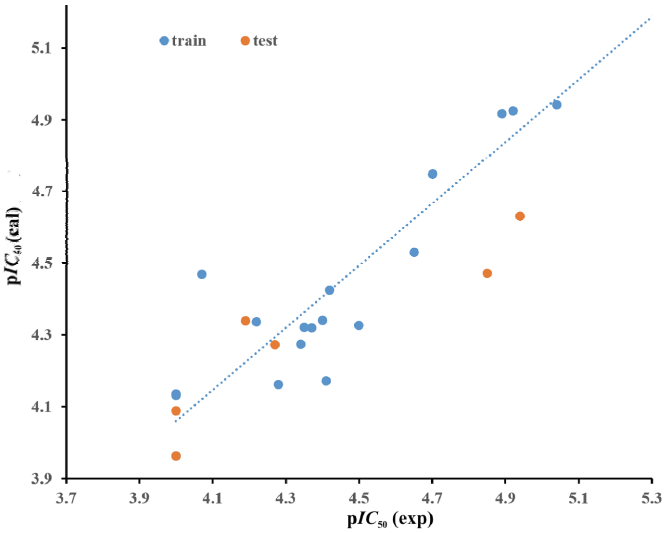

Fig. 3. Plot of experimental pIC_{50} of 2-phenylbenzimidazole derivatives against the calculated values of pIC_{50} using MLR model.

TABLE V. MLR model for of 2-phenylbenzimidazoles

Descriptor definition	Descriptor type	Regression coefficient	Standard deviation
Dipole moment	Electronic	0.065	0.033
Torsional free energy	Docking property	0.077	0.121
MATS4e	2D-autocorrelations	3.001	0.609
GATS5e	2D-autocorrelations	0.675	0.228
R6v	GETAWAY descriptors	-7.976	1.190
R1v+	GETAWAY descriptors	14.295	3.604
Constant	–	5.430	0.495

CONCLUSION

Regarding the results of QSAR, the prediction of 2-phenylbenzimidazole derivatives data in MLR method was acceptable. Hydrogen and hydrophobic interactions were investigated by molecular docking. Results showed that raising binding energy values and decreasing the constant inhibition reduce the inhibitory activity of 2-phenylbenzimidazole derivatives. Arg 394, Met 357 and Glu 353 amino acids of estrogen receptor have an important role in interaction. These results could prepare an important structural intuitions required to optimize 2-phenylbenzimidazole-sensitive inhibitors of the estrogen receptor. Considering DFT calculation compound **38** is susceptible to nucleophilic attacks due to higher electronegative potential surface. Ligands **20** and **38** are introduced for later research because they displayed the minimum value of inhibition constant and the highest electronegative surface potential.

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ИЗВОД

ТЕОРИЈА ФУНКЦИОНАЛА ГУСТИНЕ И МОЛЕКУЛСКИ ДОКИНГ ЗА ПРОУЧАВАЊЕ КВАНТИТАТИВНЕ РЕЛАЦИЈЕ СТРУКТУРА–АКТИВНОСТ У ИНТЕРАКЦИЈИ 2-ФЕНИЛБЕНЗИМИДАЗОЛА И РЕЦЕПТОРА ЕСТРОГЕНА

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Деривати бензимидазола, нарочито 2-фенилбензимидазола са разним супституентима на положајима C-5, C-2 и C-6, су веома значајни у фармацеутској хемији. Примењена је вишеструка линеарна регресија за предвиђање активности 27 нових 2-фенилбензимидазолских деривата као антиканцерских агенаса. Направљен је QSAR модел за одабрану серију нових 2-фенилбензимидазола помоћу дескриптора из теорије функционала густине и молекулског докинга. За природу интеракција између деривата 2-фенил+бензимидазола и рецептора естрогена, коришћен је метод молекулског докинга. За моделовање је одабрано шест дескриптора: MATS4e, GATS5e, R6v, R1v+, диполни моманат и торзиона слободна енергија. Према резултатима доковања, пораст енергије везивања и опадање диполног момента може повећати активност инхибитора.

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