Quantitative Structure-Activity Relationship (QSAR) of *N*-Benzoyl-*N'*-Naphtylthiourea Derivative Compounds by *in Silico* as Anticancer Through Inhibition of VEGFR2 Receptors

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Abstract. Vascular endothelial growth factor receptor (VEGFR) tyrosine kinases (TKs) are clinically validated drug targets for anticancer therapy because they play an important role in the process of angiogenesis, tumor growth, and metastasis. VEGFR2 is a member of the VEGFR-Tks. VEGFR2 is an important regulator of the process of angiogenesis. Thiourea-derived compounds are known to have potential VEGFR2 inhibitors. The purpose of this study is to determine the quantitative structure-activity relationship (QSAR) of the *N*-benzoyl-*N'*-naphthylthiourea (BNTU) and its derivatives as anticancer through inhibition of the VEGFR2 receptor. The best QSAR equation model obtained can be used as a guide in designing new BNTU derivative compounds that have the best VEGFR2 inhibitory activity. The results of the analysis provide the best equation model as follows:

RS = -0.405 (±1.020) $ClogP^2$ + 1.174 (±8.709) ClogP + 5.227 (±3.273) E_{LUMO} -72.983 (±7.625) (two physicochemical parameter).

(n = 14; r = 0.971; SE = 4.519; F = 54.777; sig. = 0.000).

The Anticancer activity of BNTU compounds and their derivatives through inhibition of VEGFR2 receptors is influenced by lipophilic and electronic properties.

Keywords: VEGFR2 · BNTU · QSAR · anticancer activity

1 Introduction

Cancer is one of the major public health problems worldwide [1] and has the characteristics of excessive uncontrolled proliferation of normal cells in the body, thus forming a mass of tissue [1, 2]. Cancer cells have several abilities that are not possessed by normal cells, namely resistance to growth inhibition, proliferation without dependence

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on growth factors, unlimited replication, invasion, metastasis, anti-apoptosis, and support angiogenesis [2–4]. Angiogenesis plays an important role in cancer development because tumor cannot grow more than 1–2 mm without a vascular supply [5]. Angiogenesis (the formation of new vessels from pre-existing vasculature) is a required process in tumor growth and metastasis and plays a very important role in tumor growth and metastasis. Vascular endothelial growth factor receptor (VEGFR) tyrosine kinases (TKs) are clinically validated drug targets for anticancer therapy [6].

VEGFR2 is an important regulator of the process of angiogenesis. Mechanism of inhibition of VEGFR2 activation through inhibition of its catalytic activity to transfer ATP terminal phosphate to its tyrosine residue [6]. Inhibition of VEGFR2 activation is an attractive approach for developing targeted cancer therapies. Thiourea-derived compounds are known to be potential VEGFR2 inhibitors [5, 7]. The compound *N*-benzoyl-*N'*-naphthyl thiourea (BNTU) is a thiourea-derived compound and is predicted to have potential as a VEGFR2 inhibitor. The pharmacophore responsible for its biological activity is its thiol group.

One of the analytical methods that are often used in drug design is the study of the Quantitative Structure-Activity Relationship (QSAR). The QSAR is an important part of drug design, in an effort to get a new drug with greater activity, higher selectivity, toxicity, or side effects as small as possible, and greater convenience [8]. The QSAR is based on the assumption that the biological activity of a compound is related to its molecular properties [9]. The purpose of this study was to determine the quantitative structure-activity relationship (QSAR) of BNTU compounds and their derivatives using the Hansch method through lipophilic, electronic, and steric parameters to anticancer activity in silico. Hansch put forward the concept that the relationship between the chemical structure and biological activity of a compound derivative can be expressed quantitatively through the parameters of the physicochemical properties of the substituents, namely lipophilic (π), electronic (σ), and steric (Es) parameters [10–12].

Lipophilic parameters used in this study were ClogP (Calculated Partition Logarithmic Coefficient) and tPSA (total Polar Surface Area), electronic parameters were E_{total} (minimum energy), E_{HOMO} (Highest occupied molecular orbital), and E_{LUMO} (Lowest unoccupied molecular orbital) and steric parameters were MW (Molecular Weight) and CMR (Calculated Molar Refractivity). The quantitative relationship between structural changes, physicochemical properties parameters,and anticancer activity was analyzed statistically thr ough linear and non-linear regression equations with the help of the SPSS statistical program. The best QSAR equation model obtained can be used as a guide in designing new BNTU derivative compounds which are expected to have more potent VEGFR2 inhibitory activity than the previous compounds.

2 Methods and Procedure

2.1 Ligands Preparation

The chemical structure of the compound *N*-Benzoyl-*N'*-Naphtylthiourea and its derivatives (Table 1) was drawn in 2D and 3D using the ChemOffice 2020 program (ChemDraw 20.0 and Chem3D 20.0), then the minimum energy (Etot) was measured using the MM2 method, then stored in mol2 form [SYBYL2 (*.mol2)] and smi [SMILES (*.smi)]. The

2D) structure is used to find data on physicochemical properties (lipophilic, electronic, and steric).

2.2 Molecular Docking Studies

The structure of the compound *N*-benzoyl-*N'*-naphthylthiourea and its derivatives as well as the comparison compound sorafenib that has been stored in the form of mol2 {SYBYL2(*.mol2)} in the Chem 3D 20.0 program, the docking process for the VEGFR2 receptor target was carried out using the Molegro Virtual Docker computer program version 5.5. The results obtained are in the form of Rerank Score (RS). Crystal structure of VEGFR2 (PDB code: 4WZE) downloaded from the Protein Data Bank at RCSB (https://www.rcsb.org/). The cocrystal ligand from the VEGFR2 receptor was validated by the docking method first by measuring the RMSD (the Root Mean Square Deviation) value of the original ligand. The required RMSD value is less than 2Å [13].

2.3 QSAR Analysis of BNTU and Its Derivatives

The quantitative structure activity relationship (QSAR) was analyzed by linear and non-linear regression using the SPSS 26 computer program. The independent variables used were physicochemical descriptors of *N*-benzoyl-*N'*-naphthylthiourea derivatives which included lipophilic properties (CLogP and tPSA), electronic properties (E_{total}, E_{HOMO}, and E_{LUMO}), steric properties (CMR and MW), and docking score (Rerank score/RS). The parameters observed in the calculation of the QSAR equation using SPSS are the regression coefficient (r), standard error (SE), F value, and significance (sig.).

3 Results

3.1 Molecular Docking Studies

The validation of the docking protocol was carried out by redocking the cocrystal ligand from the VEGFR2 receptor. The accuracy of the docking protocol was evaluated by the RMSD (root mean square deviation) value, which was calculated by the difference between the original pose and the redocking pose. The obtained RMSD value is 0.462 Å. The overlay of redocking results with cocrystal ligands can be seen in Fig. 1. The parameter observed to assess the anticancer activity of BNTU compounds through inhibition of VEGFR2 receptor activation is the Rerank Score (RS) (Table 3). The lower the RS value, the lower the binding energy, which means the stability of the ligand and receptor binding is higher, and its activity can be predicted also get bigger [14, 15].

3.2 QSAR Analysis of BNTU and Its Derivatives

The results of determining the parameter values for physicochemical properties (lipophilic, electronic, steric) and the results of the anticancer activity of BNTU compounds and their derivatives through in silico inhibition of VEGFR2 activation (Rerank Score) can be seen in Table 3. Meanwhile, the results of the QSAR analysis of BNTU

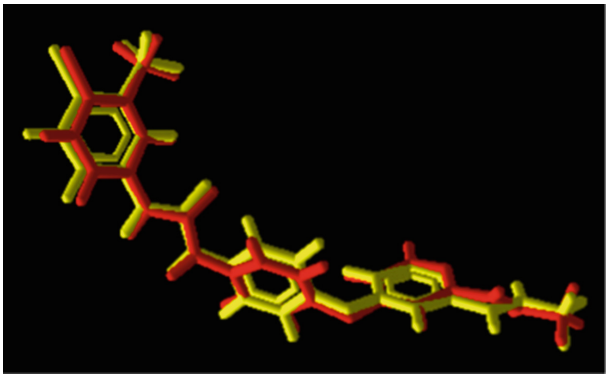
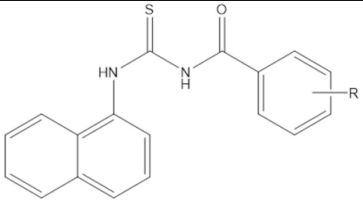


Fig. 1. Visualization of redocking results between cocrystal ligands (yellow) and redocking ligands (red)

Table 1. The chemical structure of *N*-benzoyl-*N'*-naphtylthiourea derivatives



No	Compound code	R	Compound Name
1	BNTU	H	*N*-benzoyl-*N'*-naphtylthiourea
2	2ClBNTU	2-Cl	*N*-(2-chlorobenzoyl)-*N'*-naphtylthiourea
3	3ClBNTU	3-Cl	*N*-(3-chlorobenzoyl)- *N'*-naphtylthiourea
4	4ClBNTU	4-Cl	*N*-(4-chlorobenzoyl)-*N'*-naphtylthiourea
5	34ClBNTU	3,4-Cl	*N*-(3,4-dichlorobenzoyl)-*N'*-naphtylthiourea
6	4BrBNTU	4-Br	*N*-(4-bromobenzoyl)-*N'*-naphtylthiourea
7	4FBNTU	4-F	*N*-(4-fluorobenzoyl)-*N'*-naphtylthiourea
8	3CFBNTU	3-CF_3	*N*-(3-trifluoromethylbenzoyl)-*N'*-naphtylthiourea
9	4CFBNTU	4-CF_3	N-(4-trifluoromethylbenzoyl)-*N'*-naphtylthiourea
10	3NBNTU	3-NO_2	*N*-(3-nitrobenzoyl)-*N'*-naphtylthiourea
11	4NBNTU	4-NO_2	*N*-(4-nitrobenzoyl)-*N'*-naphtylthiourea
12	4CBNTU	4-CH_3	*N*-(4-methylbenzoyl)-*N'*-naphtylthiourea
13	4OCBNTU	4-OCH_3	*N*-(4-metoxybenzoyl)-*N'*-naphtylthiourea
14	4TBBNTU	4-$C(CH_3)_3$	*N*-(4-*tert*-butylbenzoyl)-*N*'-naphtylthiourea

compounds and their derivatives as well as the resulting equations can be seen in Tables 4 and 5. The validity of the obtained QSAR equation can be seen from several statistical criteria, namely the value of r (correlation coefficient), SE (standard error), F (Fisher

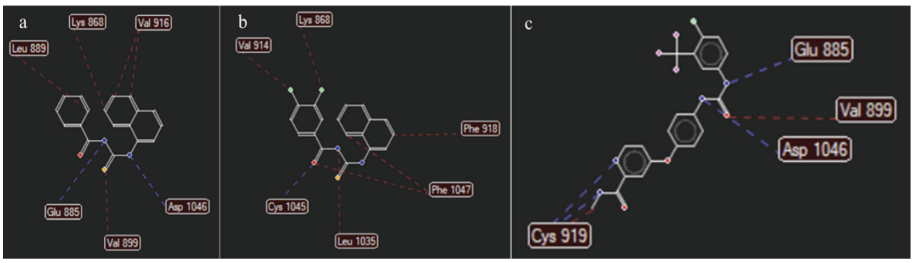


Fig. 2. Interaction of BNTU (a), 34ClBNTU (b), and sorafenib (cocrystal ligand of 3WZE) with VEGFR2 receptors

Table 2. VEGFR2 receptor amino acids (PDB ID 3WZE) involved in interaction with BNTU derivatives

No	Compound Name	Hydrogen bonds	Steric interactions
1	*N*-benzoyl-*N'*-naphtylthiourea	Glu 885, Asp 1046	Glu 885, Val 899, Asp 1046, Val 916 (2), Lys 868, Leu 889
2	*N*-(3,4-dichlorobenzoyl)-*N'*-naphtylthiourea	Cys 1045	Val 914, Lys 868, Phe 918, Phe 1047 (2), Leu 1035, Cys 1045
3	Sorafenib (cocrystal ligand)	Glu 885, Asp 1046, Cys 919 (2)	Glu 885, Val 899, Asp 1046, Cys 919

criteria/F_{count}), and Sig. (significance). In the QSAR study, trying to achieve an r value greater than 0.9, because the higher the r-value, the better this study. The SE value is the standard deviation which indicates the value of the error variation in the experiment. The greater the value of F_{count}, the greater the degree of significance of the relationship. The higher the value of F_{count}, the less likely the relationship is due to chance [8].

4 Discussion

The validation of the docking method was carried out by redocking the co-crystal of the VEGFR2 (3WZE) receptor, namely sorafenib at its binding site, thus forming a protein co-crystal complex as in the crystal structure. The validation of the docking results showed that the conformation of the re-docking results was the same as that of x-ray crystallography because the RMSD value was less than 2 Å (0.462 Å). This RMSD also proves that the docking method is valid for docking test compounds [16]. The results of the anticancer activity of BNTU compounds and their derivatives through

Table 3. Parameter values of lipophilic, electronic, steric, and inhibitory activities of BNTU and their derivatives

No	Compound code	R	Lipophilic Parameters		Electronic Parameters			Steric Parameters		RS (kcal/mol)
			CLogP	tPSA	E_{tot} (kcal/mol)	E_{HOMO} (eV)	E_{LUMO} (eV)	MW	CMR	
1	BNTU	H	3.734	41.13	27.61	-9.410	-3.883	306.38	9.4804	-89.5995
2	2ClBNTU	2-Cl	3.8186	41.13	22.74	-9.388	-3.947	340.83	9.9718	-97.2758
3	3ClBNTU	3-Cl	4.6486	41.13	20.04	-9.175	-3.368	340.83	9.9718	-89.0971
4	4ClBNTU	4-Cl	4.6486	41.13	28.78	-9.147	-3.323	340.83	9.9718	-94.1216
5	34ClBNTU	3,4-Cl	5.31216	41.13	19.78	-9.352	-4.010	375.27	10.4632	-104.651
7	4BrBNTU	4-Br	4.7986	41.13	28.92	-9.293	-3.453	385.28	10.2574	-88.756
8	4FBNTU	4-F	4.0786	41.13	27.31	-9.332	-3.470	324.37	9.4959	-94.6555
9	4CFBNTU	4-CF_3	4.9698	41.13	57.34	-9.134	-3.307	374.38	9.9907	-100.133
10	3NBNTU	3-NO_2	3.909	92.94	51.23	-9.122	-4.067	351.38	10.0919	-99.0971
11	4NBNTU	4-NO_2	3.909	92.94	63.67	-9.032	-4.212	351.38	10.0919	-96.858
12	4CBNTU	4-CH_3	4.233	41.13	26.99	-9.201	-4.077	320.41	9.9442	-92.6827
13	4OCBNTU	4-OCH_3	3.9354	50.36	33.78	-9.313	-3.488	336.41	10.0973	-96.7463
14	4TBBNTU	4-*t*-butil	5.56	41.13	42.95	-9.258	-4.060	362.49	11.3356	-97.044

molecular docking showed that BNTU derivatives had better activity than their parent compounds, except for 3ClBNTU and 4BrBNTU. The molecular docking test produces a bond energy value or Rerank Score (RS). Bond energy indicates the amount of energy required to form a bond between the ligand and the receptor. The lower the bond energy, the more stable the bond and it is predicted that the activity will also increase [14]. In other words, the more negative the bond energy value, the stronger the interaction between the ligand and protein [16]. The compound that had the highest activity based on the RS value was *N*-(3,4-dichlorobenzoyl)-*N'*-naphtylthiourea (34ClBNTU). The Cl substituent is a substituent that acts as an electron-withdrawing group, so it is predicted that an important role in this research is electronic properties.

The active site of the VEGFR2 receptor (3WZE) with co-crystal ligand sorafenib has 4 hydrogen bonds with amino acid residues Glu 885, Asp 1046, and 2 amino acids Cys 919, as well as 4 steric interactions, namely Glu 885, Val 899, Asp 1046, Cys 919. BNTU has 2 hydrogen bonds, namely hydrogen bonds with amino acid residues Glu 885 and Asp 1046. 7 steric interactions, namely Glu 885, Val 899, Asp 1046, Val 916 (2), Lys 868, and Leu 889. While 34ClBNTU has 1 Cys 1045 hydrogen bond and 7 steric interactions Val 914, Lys 868, Phe 918, Phe 1047 (2), Leu 1035, Cys 1045 (Fig. 2/Table 2).

Structure-Activity Relationship (SAR) is the study of the relationship between the chemical properties or structure of molecules and their biological activities. The QSAR model helps design new molecules and determine the chemical group responsible for enhancing the biological activity of a compound [16, 17]. QSAR analysis was carried out on one and two parameters of physicochemical properties through linear and non-linear regression equations. Lipophilic parameters play a role in drug penetration through cell membranes, so an increase in the amount of drug in receptor increases activity. Electronic

Table 4. QSAR equation of BNTU and its derivatives for one physicochemical parameter

No	Linear/non-linear regression equation	n	r	SE	F	Sig.	Correlation
1	RS = -8.753 (±0.980) ClogP – 56.322 (±4.241)	14	0.932	6.225	79.855	0.000	There is a correlation
2	RS = 1.124 (±0.375) $ClogP^2$ – 12.558 (±1.481) ClogP – 62.239 (± 3.837)	14	0.963	4.827	70.893	0.000	There is a correlation
3	RS = 0.224 (±0.233) tPSA – 102.758 (±12.814)	14	0.268	16.59	0.927	0.355	No correlation
4	RS = -0.069 (±0.018) $tPSA^2$ + 9.239 (±2.306) tPSA – 360.371 (±66.319)	14	0.783	11.198	8.693	0.005	There is a correlation
5	RS = -0562 (±0.100) E_{tot} – 74.810 (±3.782)	14	0.851	9.034	31.623	0.000	There is a correlation
6	RS = -30.560 (±40.907) E_{HOMO} – 373.823 (±378.366)	14	0.211	16.837	0.558	0.469	No correlation
7	RS = 5.175 (± 0.395) E_{LUMO} – 76.061 (±1.648)	14	0.967	4.403	171.634	0.000	There is a correlation
8	RS = -0.208 (±0.019) MW – 22.922 (±6.394)	14	0.953	5.200	119.635	0.000	There is a correlation
9	RS = -6.873 (±0.551) CMR – 26.017 (±5.371)	14	0.963	4.612	155.369	0.000	There is a correlation

parameters play a role in drug solubility in distribution. Steric parameters play a role in strengthening drug-receptor interactions [8, 15].

Based on nine QSAR equations for *N*-benzoyl-*N'*-naphthylthiourea compounds and their derivatives for one physicochemical parameter (Table 4), it is known that the anticancer activity of BNTU compounds and their derivatives is not affected by the value of tPSA (Eq. 3) and E_{HOMO} (Eq. 6), because the significance value is less than 0.05. In other words, there is no linear correlation between lipophilic properties (tPSA) and electronic properties (E_{HOMO}) on anticancer activity through inhibition of VEGFR2 receptors. In Eqs. 1 and 2, a linear and non-linear correlation is obtained between the lipophilic properties (ClogP) of BNTU compounds and their derivatives on anticancer activity through inhibition of VEGFR2 receptor activation. ClogP is a lipophilic parameter related to the absorption of pharmacokinetic properties. The drug must be lipophilic enough to penetrate the lipid bilayer, but not too lipophilic because it prevents the drug from penetrating back outside the membrane, which will cause the drug to become toxic because it stays

Table 5. QSAR equation of BNTU and its derivatives for two physicochemical parameter

No	Linear/non-linear regression equation	n	r	SE	F	Sig.	Correlation
1	RS = -6.417 (±1.349) ClogP – 0.211 (±0.095) E_{tot} -59.468 (±3.938)	14	0.954	5.397	55.609	0.000	There is a correlation
2	RS = 0.879 (± 0.412) $ClogP^2$ – 10.410 (±2.207) ClogP – 0.119 (± 0.093) E_{tot} – 62.729 (±3.748)	14	0.969	4.690	50.604	0.000	There is a correlation
3	RS = -8.712 (±1.043) ClogP – 3.123 (±16.110) E_{HOMO} – 85.371 (±149.908)	14	0.933	6.491	36.744	0.000	There is a correlation
4	RS = 1.122 (±0.394) $ClogP^2$ – 12.527 (±1.566) ClogP – 1.829 (±12.559) E_{HOMO} – 79.244 (±116.812)	14	0.963	5.057	43.064	0.000	There is a correlation
5	RS = -2.197 (±1.901) ClogP + 4.006 (±1.084) E_{LUMO} – 70.726 (±4.893)	14	0.970	4.342	88.890	0.000	There is a correlation
6	RS = -0.405 (±1.020) $ClogP^2$ + 1.174 (±8.709) ClogP + 5.227 (±3.273) E_{LUMO} -72.983 (±7.625)	14	0.971	4.519	54.777	0.000	There is a correlation
7	RS = -1.346 (± 3.424) ClogP – 0.178 (±0.080) MW – 27.508 (±13.418)	14	0.954	5.394	55.681	0.000	There is a correlation
8	RS = 0.873 (±0.432) $ClogP^2$ – 7.838 (±4.409) ClogP – 0.093 (±0.082) MW – 45.857 (±14.924)	14	0.968	4.765	48.929	0.000	There is a correlation
9	RS = 0.809 (±3.249) ClogP – 7.471 (±2.469) CMR – 23.571 (±11.307)	14	0.964	4.803	71.643	0.000	There is a correlation
10	RS = 0.610 (±0.622) $ClogP^2$ – 5.378 (±7.093) ClogP – 4.252 (±4.108) CMR – 40.897 (±20.971)	14	0.967	4.811	47.926	0.000	There is a correlation

(*continued*)

Table 5. (*continued*)

No	Linear/non-linear regression equation	n	r	SE	F	Sig.	Correlation
11	RS = 0.281 (±0.102) tPSA – 0.579 (±0.081) E_{tot} – 88.815 (±5.938)	14	0.915	7.267	28.200	0.000	There is a correlation
12	RS = -0.017 (±0.017) $tPSA^2$ + 2.509 (±2.250) tPSA – 0.489 (±0.122) E_{tot} – 154.923 (±66.935)	14	0.923	7.273	19.099	0.000	There is a correlation
13	RS = 0.414 (±0.255) tPSA – 66.144 (±44.225) E_{HOMO} – 724.306 (±415.755)	14	0.478	15.800	1.630	0.240	No correlation
14	RS = -0.066 (± 0.021) $tPSA^2$ + 8.966 (± 2.710) tPSA – 8.325 (±37.545) E_{HOMO} – 430.098 (±322.024)	14	0.784	11.716	5.311	0.019	There is a correlation
15	RS = -0.016 (±0.067) tPSA + 5.204 (±0.431) E_{LUMO} – 75.169 (±4.215)	14	0.967	4.587	79.077	0.000	There is a correlation
16	RS = 0.007 (± 0.013) $tPSA^2$ – 0.952 (±1.725) tPSA + 5.548 (± 0.774) E_{LUMO} – 47.050 (±51.967)	14	0.968	4.742	49.437	0.000	There is a correlation
17	RS = -0.027 (±0.080) tPSA – 0.211 (±0.021) MW – 20.807 (±9.118)	14	0.954	5.403	55.462	0.000	There is a correlation
18	RS = -0.002 (± 0.015) $tPSA^2$ + 0.291 (±1.944) tPSA – 0.206 (± 0.036) MW – 31.536 (±66.284)	14	0.954	5.659	33.712	0.000	There is a correlation
19	RS = - 0.055 (±0.070) tPSA – 7.032 (±0.595) CMR – 21.663 (±7.762)	14	0.965	4.686	75.551	0.000	There is a correlation
20	RS = -0.001 (± 0.013) $tPSA^2$ + 0.037 (±1.680) tPSA – 6.988 (± 1.018) CMR – 24.742 (±56.899)	14	0.965	4.914	45.803	0.000	There is a correlation

in the body for too long [18]. The lower the Etot, MW, and CMR values (Eqs. 5, 8, and 9 respectively), and the greater the E_{LUMO} value (Eq. 7), the anticancer activity increases.

E_{LUMO} plays an important role in determining the chemical stability of a molecule. LUMO (lowest unoccupied molecular orbital) indicates the ability to accept electrons from a molecule [17]. The value of E_{LUMO} (electronic parameter) is the most influential parameter on the inhibitory activity of VEGFR2. Thus, it is predicted that electronic parameters have a major contribution in determining the VEGFR2 inhibitory activity of BNTU-derived compounds compared to lipophilic and electronic parameters, but this assumption cannot be considered absolute because of other factors' influence. Therefore, the best QSAR equation for one parameter (Eq. 7) of physicochemical properties obtained from this study is:

$$\begin{aligned} &\text{RS} = 5.175(\pm 0.395)\ E_{LUMO} - 76.061(\pm 1.648) \\ &(\text{n} = 14;\ \text{r} = 0.967;\ \text{SE} = 4.403;\ \text{F} = 171.634;\ \text{sig.} = 0.000) \end{aligned}$$

From the above equation, it can be seen that there is a significant linear correlation between the electronic properties and the anticancer activity of BNTU compounds and their derivatives through inhibition of the VEGFR2 receptor. The direction of E_{LUMO} correlation is positive, this means that the greater the value of E_{LUMO}, the greater the activity of the compound.

Based on the QSAR equation for the compound *N*-benzoyl-*N'*-naphthylthiourea and its derivatives for two physicochemical parameters (Table 5), it is known that in Eq. 13 there is no linear relationship between the tPSA value which is a lipophilic parameter and the E_{HOMO} value which is an electronic parameter on the anticancer activity of the BNTU and its derivatives via VEGFR2 inhibition. The best QSAR equation is Eq. 6, where there is a nonlinear relationship between CLogP and E_{LUMO} values on the inhibitory activity of VEGFR2.

$$\begin{aligned} \text{RS} &= -0.405(\pm 1.020)\ \text{ClogP}^2 + 1.174(\pm 8.709)\ \text{ClogP} \\ &\quad +5.227(\pm 3.273)\ E_{LUMO} - 72.983(\pm 7.625) \\ &(\text{n} = 14;\ \text{r} = 0.971;\ \text{SE} = 4.519;\ \text{F} = 54.777;\ \text{sig.} = 0.000) \end{aligned}$$

Based on Eq. 6, there is a quadratic equation between activity (RS value) and lipophilic properties (ClogP). Increasing the lipophilicity of the compound will increase its activity until it reaches the optimum value. This is in line with the correlation between E_{LUMO} values and activity (RS). The greater the E_{LUMO} value, the greater the activity of the compound.

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