In silico QSAR of 1-benzoyl-3-benzylurea lead and its analogue compounds as anticancer by VEGFR-2 inhibition

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ABSTRACT

VEGFR-2 plays a role in proangiogenic activity. An *in-silico* study was conducted on 1-benzoyl-3-benzylurea lead and its analogue compounds as anticancer by VEGFR-2 (PDB code: 4ASD) inhibition. The purpose of this study is to find Quantitative Structure Activity Relationship (QSAR) by designing novel compounds and predicting their bioavailability and toxicity. Structural modification was carried out by substituting some substituent with certain physicochemical properties (lipophilic, electronic, and steric) into benzoyl group. The prediction of bioavailability (F) and toxicity (LD_{50}) were performed by ACD-I/Lab. The prediction of activity (Rerank Score/RS) was carried out by Molegro Virtual Docker (MVD) 5.0. The result of regression from 1-benzoyl-3-benzylurea lead and its analogue compounds by IBM® SPSS® Statistic 20 shows that there are nonlinear relationships between modification of physicochemical properties with bioavailability prediction (F>70% oral = -1.548 ClogP + 0.198 $ClogP^2$ + 0.125 pKa – 0.168 CMR + 3.502) and modification of physicochemical properties with activity prediction (Rerank Score = 1.802 Es + 5.421 $ClogP^2$ – 44.744 ClogP – 11.152). Also, there is a linear relationship between modification of physicochemical properties and toxicity prediction (LD_{-50} Mouse = -7.422 Mw – 117.197 pKa + 260.565 π + 4342.379 and LD_{-50} Rat = 691.028 CMR – 21.453 Etot – 430.187 π – 4775.208). These quantitative equations can be used as foundations for further structural modification to discover a novel potential anticancer drug with better bioavailability, activity, and minimum toxicity.

INTRODUCTION

VEGF (endothelial growth factor) signaling is critical for blood vessel formation and is involved in all stages of angiogenesis, its inhibition is an attractive therapy target in a wide range of tumor types, and disruption of the VEGF signal has become one of the dominant strategies for the angiogenesis-related treatment of cancer (Avendano,2015).

Strategies to inhibit the VEGF pathway directed against VEGF or VEGFR. VEGFR-2, a type II transmembrane TK receptor, expressed on endothelial cells and on circulating bone marrow-derived endothelial progenitor cells, is the principal mediator of the VEGF-induced angiogenic signaling. VEGFR-2 is also a novel target. Biological and preclinical evidence suggests that the blockage of VEGFR-2 could be a promising strategy to inhibit tumor-induced angiogenesis (Fontanella C et al.,2014).

One of proved VEGFR-2 inhibitor on the market today is Sorafenib tosylate. Suhud et al. (2015) has proven that a lead compound 1-benzoyl-3-benzylurea *in- silico* inhibits Raf-kinase (PDB code 1-UWH) with Rerank Score -90,5615 Kcal/mol and *in-vitro* against MCF-7 cell line with IC_{50} 384,87 µM.

Both of sorafenib and 1- benzoyl-3-benzylurea have the same urea functional group. In order to find a novel effective angiogenesis inhibitor, the recent study on structural modification 1-benzoyl-3-benzylurea was conducted.

METHODS

1.Structural modification was carried out by substituting 22 substituents with certain physicochemical properties (lipophilic, electronic, and steric) into benzoyl group of the lead compound 1-benzoyl-3-benzylurea.

2. Molecular docking to predict activity was done to 1-benzoyl-3-benzylurea lead and its analogue compounds, also the reference hydroxyurea, 5-fluorouracil and sorafenib by Molegro Virtual Docker(MVD) 2011.5.

3. Prediction of some physicochemical properties, bioavailability and toxicity were performed by ACD/I-Lab Prediction Engine from Advances Chemistry Development.

4. Quantitative Structure- Bioavailability/ Activity/ Toxicity were analyzed using IBM® SPSS® versi 20 from IBM Corp.

RESULTS AND DISCUSSION

No.	Compound	Rerank Score (kcal/mol)
1	1-benzoyl-3-benzylurea	-96,9887
2	1-(2-chlorobenzoyl) -3-benzylurea	-97,0605
3	1- (3-chlorobenzoyl) -3-benzylurea	-100,64
4	1- (4-chlorobenzoyl) -3-benzylurea	-99,0598
5	1- (2,4-dichlorobenzoyl) -3-benzylurea	-98,7292
6	1- (3,4-dichlorobenzoyl) -3-benzylurea	-104,613
7	1- (4-chloromethylbenzoyl) -3-benzylurea	-102,067
8	1- (3-chloromethylbenzoyl) -3-benzylurea	-106,427
9	1-(2-chloromethylbenzoyl) -3-benzylurea	-102,834
10	1- (4-methylbenzoyl) -3-benzylurea	-100,401
11	1- (4-ethylbenzoyl) -3-benzylurea	-101,873
12	1- (3-ethylbenzoyl) -3-benzylurea	-109,53
13	1- (2-ethylbenzoyl) -3-benzylurea	-104,537
14	1- (4-prophylbenzoyl) -3-benzylurea	-105,938
15	1- (4-t-buthylbenzoyl) -3-benzylurea	-100,14
16	1-(4-fluorobenzoyl) -3-benzylurea	-98,4593
17	1-(2-trifluoromethylbenzoyl) -3- benzylurea	-93,2305
18	1- (3-trifluoromethylbenzoyl) -3- benzylurea	-111,711
19	1- (4-trifluoromethylbenzoyl) -3- benzylurea	-104,119
20	1-(4-bromobenzoyl) -3- benzylurea	-99,6173
21	1-(4-bromomethylbenzoyl) -3- benzylurea	-100,269
22	1- (4-nitrobenzoyl)-3- benzylurea	-104,774
23	1-(4-methoxybenzoyl) -3- benzylurea	-98,6492
24	Hydroxyurea	-41,5724
25	5-Fluorouracil	-60,7791
26	Sorafenib	-136,297

Rerank score -111,711 kcal/mol indicates that 1- (3-trifluoromethylbenzoyl)-3- benzylurea is the most stable D-R interaction and is predicted to have the best activity as VEGFR 2 inhibitor. Theoretically, trifluoromethyl ($-CF_3$) changes the electronic distribution because of its most electronegativity. Electronegativity is based on an arbitrary scale, with fluorine being the most electronegative (EN4.0). Fluorine attracts electrons strongly. Group with electronic effect induced D-R interaction and reduced electronic density (Thomas, 2003; Mc.Murry, 2011). Hydroxyurea and 5-fluorouracil showed *rerank score* -41,5724 Kcal/mol and -60,7791 kcal/mol that mean less stable D-R interaction compared to all tested compounds. Lipophilic groups like benzyl and benzoyl could stabilize D-R interaction leading to increasing activity. Moreover, other substituents with variety in lipophilic, electronic, and steric properties into benzoyl group seem to increase activity. Unfortunately, all tested compounds have higher *rerank score* (in range -93,2305 to -111,711 Kcal/mol) compared to sorafenib (-136,297 Kcal/mol). It was probably influenced by the difference of aminoacids site bonding to sorafenib and all tested compounds.

CONCLUSION

There are nonlinear relationships between modification of physicochemical properties with bioavailability prediction (F>70% oral = -1.548 ClogP + 0.198 $ClogP^2$ + 0.125 pKa – 0.168 CMR + 3.502) and modification of physicochemical properties with activity prediction (Rerank Score = 1.802 Es + 5.421 $ClogP^2$ – 44.744 ClogP – 11.152). Also, there is a linear relationship between modification of physicochemical properties and toxicity prediction (LD_{-50} Mouse = -7.422 Mw – 117.197 pKa + 260.565 π + 4342.379 and LD_{-50} Rat = 691.028 CMR – 21.453 Etot – 430.187 π – 4775.208). These quantitative equations can be used as foundations for further structural modification to discover a novel potential anticancer drug with better bioavailability, activity, and minimum toxicity.

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