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# *Docking and QSAR Studies of Some Quinazolinone Derivatives as Possible Inhibitors of Thyrosine Kinase*

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**Abstract:** Quinazolinones are bicyclic fused heterocyclics that have been shown cytotoxic effects through different mechanisms inparticular thyrozin kinase enzyme inhibition. Based on this, a series of quinazolinone derivatives were subjected to a quantitative structure activity relationship (QSAR) analysis, by using statistical tool, such as principal components analysis (PCA) and genetic algorithm (G.A). It was shown that GA_PLS is reliable to predict activities of new design compounds. Besides, the compounds were docked into the active site of the protein thyrozin kinase (PDB entry code:1M17) to identify the binding interactions. Among the thirty two studied compounds, five compounds showed convenient inhibitory effect. The most active compound of the studied derivatives , Q19, had a ΔGbind of -9.52kcal/mol.

***Keywords:*** *Quinazolinone; Thyrosin kinase; Docking; QSAR; GA_PLS*

## 1. Introduction

Cancer is currently the most complicated disease although great advances have been made in it 's treatment and prevention [1]. Epidermal growth factor receptor is type of membrane bound tyrosine kinase receptor which regulates proliferation, differentiation and cell death. Over expression of this receptor in some cancers, and its targeted inhibition by anticancer drugs can be a way to cancer chemotherapy [2-4].Quinazolinone scaffold has been considered as a privileged heterocycle due to diverse pharmacological properties including: antimicrobial, anticancer, anti inflammatory and anticonvulsant effects [5-11].This back bone has been used in many anticancer compounds especially thyrosinkinase receptor inhibitors. Different mechanisms have been reported for their anti cancer activity including: inhibition of the DNA repair enzyme, inhibition of EGFR [12], dihydrofolate reductase (DHFR) [9,13] or thymidylate enzyme inhibition [9,14]and inhibitory effects for tubulin polymerize [9,12] Quinazolinone derivatives with appropriate substituent mainly amine or substituted amine on4thposition promote activity against cancer cell lines [15].Derivatives of substituted quinazolinone at 2, 3 or 2, 4 positions have been reported as anticancer agents [9, 16,17]. Literature surveys have been shown many reports on cytotoxic activities of quinazolinone [9, 18-20]. Quantitative structure-activity relationship (QSAR) studies and molecular docking are key techniques in computational chemistry .Molecular docking can

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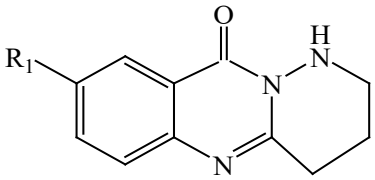
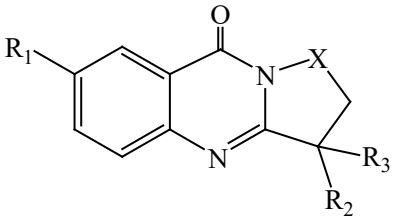
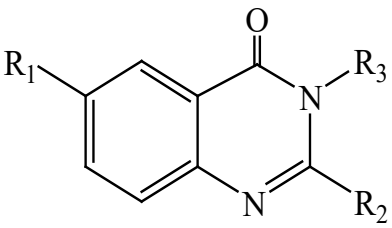
predict predominant binding conformations of a ligand with three-dimensional structure of a protein [21]. In this study, QSAR method was performed on a series of 16 quinazolinone derivatives and docking was applied to study the interactions between 32 of quinazoline derivatives with thyrosin-kinase as receptor (PDB entry code:1M17).

## 2. Computational Method

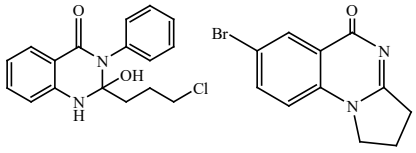
### 2.1. Data collection and calculation of molecular Descriptors

A dataset of 16 quinazolinone derivatives(Q1-Q8, Q14-Q20, Q30)with known cytotoxic activity against HeLa cell lines were used for QSAR analysis [18-20], their corresponding structures are listed in Table 1.Molecular structures were scratched by Hyperchem version 8.0. The geometries which were optimized using PM3 algorithm then the molecules were transferred into Dragon program (developed by Milano Chemometrics and QSAR Group) (Todeschini et al., 2009) used for calculating a large number of descriptors including 6 different groups, listed in Tables2 and3. As shown in Table2, total number of extracted descriptors was 438. After that, zero mean, near constant and descriptors with correlation more than 0.9 were removed. Thus, 65 descriptors were utilized in QSAR model.

**Table1.**Chemical structures of quinazolinone derivatives.

| Structure of compoiunds |  | |  | | | | |  | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | A:$Q_1$-$Q_3$ | $R_1$ | B:$Q_4$-$Q_{13}$ | R1 | R2 | R3 | X | C:$Q_{14}$-$Q_{29}$ | $R_1$ | $R_2$ | $R_3$ |
| *$Q_1$ | | H | | - | | | | | - | | |
| *$Q_2$ | | Br | | - | | | | | - | | |
| *$Q_3$ | | $NO_2$ | | | | | | | - | | |
| *$Q_4$ | - | | B | H | H | H | NH | | - | | |
| *$Q_5$ | - | | B | Br | H | H | NH | | - | | |
| *$Q_6$ | - | | B | H | H | H | C | | - | | |
| *$Q_7$ | - | | B | H | Br | Br | C | | - | | |
| *$Q_8$ | - | | B | $NO_2$ | H | H | C | | - | | |
| $Q_9$ | - | | B | Br | H | H | C | | - | | |
| $Q_{10}$ | - | | B | $CH_3$ | H | H | C | | - | | |
| $Q_{11}$ | - | | B | F | H | H | C | | - | | |
| $Q_{12}$ | - | | B | I | H | H | C | | | | |
| $Q_{13}$ | - | | B | $CH(CH_3)_2$ | H | H | C | | | | |
| *$Q_{14}$ | - | | - | | | | | C | Br | Propyl chloride | $NHCO(CH_2)_3Cl$ |

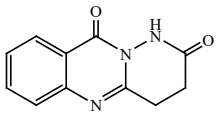
| | | | | | | |
|---|---|---|---|---|---|---|
| *$Q_{15}$ | - | - | C | H | $(CH_2)_2O$-ethyl | $NH_2$ |
| *$Q_{16}$ | - | - | C | H | propyl | $NHCOCH_2S$- 4-mehyl1,2,4- triazole |
| *$Q_{17}$ | - | - | C | H | Phenyl | $NHCOCH_2S$- 4-mehyl1,2,4-triazole |
| *$Q_{18}$ | - | - | C | H | Propyl | $NHCOCH_2S$-(4-Chlorophenyl)-1,3,4-oxadiazol |
| *$Q_{19}$ | - | - | C | H | Phenyl | $NHCOCH_2S$-(4-Chlorophenyl)-1,3,4-oxadiazol |
| *$Q_{20}$ | - | - | C | H | 4-Nitrophenyl | $NHCOCH_2S$-(4-Chlorophenyl)-1,3,4- oxadiazol |
| $Q_{21}$ | - | - | C | Br | Propyl chloride | H |
| $Q_{22}$ | - | - | C | $NO_2$ | Propyl chloride | H |
| $Q_{23}$ | - | - | C | H | Propyl chlor ide | Phenyl |
| $Q_{24}$ | - | - | C | $NO_2$ | $CH_3$ | $NH_2$ |
| $Q_{25}$ | - | - | C | H | Et | $NH\text{-}CH_3$ |
| $Q_{26}$ | - | - | C | H | $CH_2$-$CH(CH_3)_2$ | NHCOEt |
| $Q_{27}$ | - | - | C | H | Propyl | 4-chlorophenyl |
| $Q_{28}$ | - | - | C | H | $CH_2\text{-}CH(CH_3)_2$ | Phenyl |
| $Q_{29}$ | - | - | C | H | Et | $NH\text{-}CH_2CH_2$-Ph |



$Q_{30}$



$Q_{31}$



$Q_{32}$

**Table2.** The name of DRAGON blocks which descriptors were extracted

| NO. | Descriptor block | Number of descriptors |
|---|---|---|
| 1 | Constitutional descriptors | 48 |
| 2 | Topological descriptors | 119 |
| 3 | Geometrical descriptors | 74 |
| 4 | Functional group count | 154 |
| 5 | Charge descriptors | 14 |
| 6 | Molecular properties | 29 |
| | **Total descriptors** | **438** |

**Table3.**The name and block of the selected descriptors.

| NO. | Descriptor name | Meaning | Descriptor block |
|---|---|---|---|
| 1 | nN | Number of Nitrogen atom | Constitutional descriptors |
| 2 | nX | Number of Halogen atom | Constitutional descriptors |
| 3 | nR06 | Number of 6 membered rings | Constitutional descriptors |
| 4 | nR09 | Number of 9 membered rings | Constitutional descriptors |
| 5 | MSD | Mean squared distance | Topological descriptors |
| 6 | MEcc | Molecular eccentricity | Geometrical descriptors |
| 7 | ASP | Asphericity | Geometrical descriptors |
| 8 | G(O..O) | Sum of geometrical distance between O-O | Geometrical descriptors |
| 9 | Hy | Hydrophilic factor | |
| 10 | GVWAI-80 | Ghose-viswanadhan-wendoloski antidepressant-like index at 80% | Molecular properties |

## 3. Results and discussion

In order to achieve the best evaluation from the QSAR model, leave one-out internal validation and three-fold cross-validation,to partition the data randomly into 3 complementary sub samples, was applied. It is necessary to mentioned that cross validation was repeated for 3 times. In each period, one of the subsamples was saved as the test set, which using for evaluating the performance of the model, and the rest of the compounds were stored as the training set. In the test set, the aim is to predict the biological activities of molecules just based on their descriptors. All of the results extracted from three different test sets were averaged to achieve a single output. Finally, this procedure was repeated until each ligand was observed for twenty times. All twenty results were averaged to predict the molecular activities. After that, genetic algorithm, as

a subset-selection step, was utilized to extract optimum descriptors. The number of generation, population size and mutation rate were set 100, 80 and 0.2, respectively. Multiple linear regression was used as a fitness function. In the prediction step, partial least square method (PLS) was utilized.

## 3.1. Metrics

Two different standard metrics, i.e. mean squared error and Pearson correlation coefficient, were used to evaluate the performance of the 2D-QSAR model between the predicted and observed activities in the test sets.

$$MSE = \frac{\left(Y_i - \hat{Y}_i\right)^2}{n}$$

$$R = \frac{\sum(Y_i - \bar{Y})\left(\hat{Y}_i - \hat{\bar{Y}}\right)}{\sqrt{\sum(Y_i - \bar{Y})^2 \sum\left(\hat{Y}_i - \hat{\bar{Y}}\right)^2}}$$

where n, $Y$ and $\hat{Y}$ are the number of molecules, the real and predicted values, respectively.

### 3.2. Considering the best number of descriptors with GA algorithm

First of all, it was tried to find out the best number of descriptors which had to be extracted via GA algorithm. To predict survival values, MLR method was applied. The results of the model were presented for the test set in Figure 1.

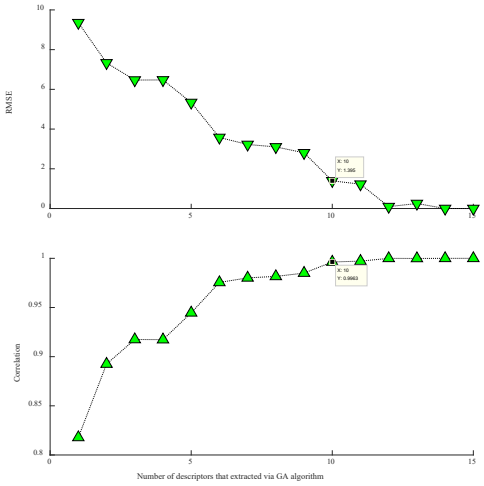



**Figure 1.** Finding out the best number of extracted descriptors via GA algorithm. As shown, according to the correlation and RMST, the best result was achieved with 16 descriptors.

As shown, according to the correlation and RMST, the best result was achieved with 10 descriptors. The list of extracted descriptors were reported in Table3.

In order to consider the relationship between selected descriptors, the correlations between them were computed (Table4).

**Table4**.The computed correlation matrix between the selected descriptors.

| | nN | nX | nR06 | nR06 | MSD | MEcc | ASP | G(O..O) | Hy | GVWAI-80 |
|---|---|---|---|---|---|---|---|---|---|---|
| nN | 1 | 0.52 | 0.36 | -0.57 | 0.01 | -0.62 | -0.02 | -0.29 | -0.09 | -0.52 |
| nX | 0.52 | 1 | -0.47 | 0.35 | 0.09 | -0.32 | 0.33 | 0.25 | -0.25 | 0.454 |
| nR06 | 0.36 | -0.47 | 1 | -0.90 | 0.14 | -0.28 | -0.29 | -0.84 | -0.01 | -0.85 |
| nR09 | -0.57 | 0.35 | -0.90 | 1 | -0.14 | 0.27 | 0.34 | 0.66 | 0.06 | 0.95 |
| MSD | 0.01 | 0.09 | 0.14 | -0.14 | 1 | 0.29 | 0.22 | -0.32 | -0.73 | 0.08 |
| MEcc | -0.62 | -0.32 | -0.28 | 0.27 | 0.29 | 1 | 0.01 | 0.18 | -0.18 | 0.32 |
| ASP | -0.02 | 0.33 | -0.29 | 0.34 | 0.22 | 0.01 | 1 | 0.20 | -0.20 | 0.36 |
| G(O..O) | -0.29 | 0.25 | -0.84 | 0.66 | -0.32 | 0.18 | 0.20 | 1 | 0.14 | 0.56 |
| Hy | -0.09 | -0.25 | -0.01 | 0.06 | -0.73 | -0.18 | -0.20 | 0.14 | 1 | -0.15 |
| GVWAI-80 | -0.52 | 0.45 | -0.85 | 0.95 | 0.08 | 0.32 | 0.36 | 0.56 | -0.15 | 1 |

### 3.3. Investigating the performance of the PLS components

As mentioned in previous section, partial least square method was utilized to estimate survival of molecules. In order to investigate performance of the PLS with respect to different components, the Pearson correlation coefitiont were sketched in the Figure 2. As shown, the best value of the error was achieved with6 components.

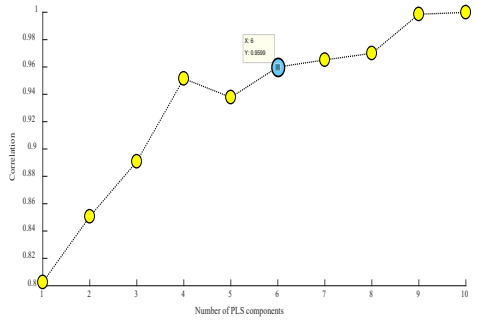



**Figure 2.** The performance of the PLS method based on different components. The best value is indicated by blue circle

### 3.4. Investigating the impact of proposed QSAR model

At the second step, it was attempted to consider impact of GA-PLS model for the survival prediction in concentration 100 µM. The results of the proposed model were presented for the training set and the test setin Figure3. The correlation of the training set and the test set were 0.87 and 0.81, respectively. Therefore, it is shown that the proposed model could be appropriate to predict the activities of the new compounds.

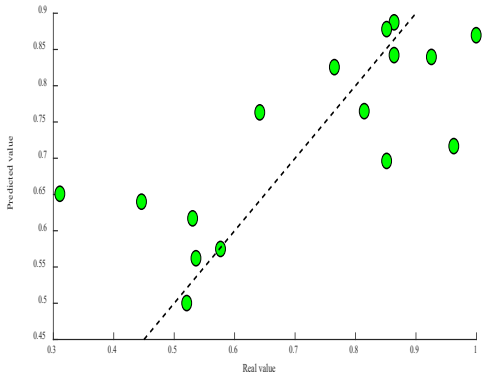



**Figure 3**. Real variable versus predicted variable of all compounds.

Since the nature of proposed model consisted two main parts, i.e. descriptor selection and activity prediction, the impact of the GA on the model output was investigated (Figure 4).Each model was run for twenty times. The results showed that extracting the optimum descriptors could be affected on the network results.

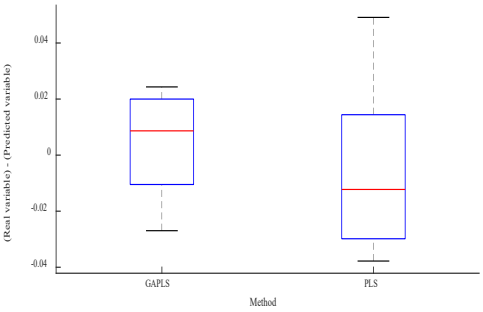



**Figure4.** Comparison between the range of PLS and GA-PLS. It is obvious that the mean and the range of GA-PLS are less than PLS. Thus, GA-PLS is more reliable than the PLS to predict molecular activity.

### 3.5. Docking results

Energy-based interactions (**ΔGb**) and inhibition constants (Ki) between quinazolinone derivatives and thyrosine kinase summarized in table 5. According to the data presented in this table ligands interact with the thyrosine kinase binding site through hydrogen bonding. Among 6- or 5 - membered ring fused quinazolinones (series A, B, $Q_{31}$, $Q_{32}$), compounds $Q_3$,$Q_7$ and $Q_8$showed the lowest binding energy and estimated inhibition constant. The conjugated oxadiazole-quinazolinone derivatives with amide linker revealed the lowest binding energy and estimated inhibition constant in the nanomolar range among 2, 3-disubstituted 4(3H)-quinazolinone derivatives ($Q_{14}$-$Q_{29}$, $Q_{30}$). Figure 5 show 3D schematic presentations of compounds$Q_3$ ,$Q_7$ ,$Q_8$ and $Q_{19}$while docked into the the thyrosine kinase binding site.

Inhibition of EGFR is one of the suggested mechanisms for anti-cancer activity of quinazolinones and over expression of this receptor in some cancers was observed [26,2,3]. According to these concepts,in this study, quinazolinone derivatives were divided into three categories based on structure including 5-membered ring-fused quinazolinones, 6-membered ring fused quinazolinones and 2, 3-disubstituted 4(3H)-quinazolinone derivatives. These analogs were docked into the active site of the thyrosin-kinase as receptor (PDB entry code:1M17)to identify the binding interactions responsible for cytotoxic activity.As shown in table 5,among tricyclic quinazolinone derivatives, (series A, B, Q31, Q32)compounds Q3 ,Q7 and Q8showed the lowest

binding energy -6.12, -6.16 and -6.10 kcal/mol respectively and the lowest estimated inhibition constant.This result is in accordance with the experimental results previously reported [18].

**Table5.**Energy-based interactions (**ΔGb**) and inhibition constants (Ki) for32 of quinazolinederivatives docked into thyrosine kinase

| No. $R_1$ | **ΔGb (kcal/mol)** | **Hydrogen bond (Distance, Å)** | Ki(μM) |
|---|---|---|---|
| $Q_1$ | -5.47 | Lys 721 (2.07) | 97.07 |
| $Q_2$ | -5.96 | Met 769(1.68) | 42.75 |
| $Q_3$ | **-6.12** | Met 769 (1.60), Lyz704 (1.86) | 32.87 |
| $Q_4$ | -5.15 | - | 168.18 |
| $Q_5$ | -5.82 | Thr 766(2.22) | 54.40 |
| $Q_6$ | -5.03 | Lyz 721(2.04) | 206.74 |
| Q7 | **-6.16** | Gln 767 | 30.78 |
| $Q_8$ | **-6.10** | Lyz 704(2.05), Met 769(2.03) | 33.58 |
| $Q_9$ | -5.59 | Met 769(1.78) | 80.38 |
| $Q_{10}$ | -5.36 | Met 769(1.78) | 116.97 |
| $Q_{11}$ | -4.95 | Met 769(1.76) | 233.55 |
| $Q_{12}$ | -5.78 | Thr766(2.04) | 57.97 |
| $Q_{13}$ | -6.05 | Met 769(1.78) | 36.79 |
| $Q_{14}$ | -8.13 | Met 769(2.15) | 1.1 |
| $Q_{15}$ | -5.92 | Lyz 721(2.02) | 45.91 |
| $Q_{16}$ | -7.39 | Lyz 721(1.90), Met 769(1.01) | 3.81 |
| $Q_{17}$ | -6.27 | Met 769(1.92) | 25.45 |
| $Q_{18}$ | -9.16 | Met 769(1.703), Cys 773(2.06) | 191.8nM |
| $Q_{19}$ | **-9.52** | Cys 773(2.1),Asp 776(2.11) | 104.93nM |
| $Q_{20}$ | -9.08 | Met 769(1.89), Asp 776(1.92) | 221.45nM |
| $Q_{21}$ | -5.76 | Gln 767 (2.08) | 60.13 |
| $Q_{22}$ | -6.07 | Met 769(1.83) | 35.71 |
| $Q_{23}$ | -7.19 | - | 5.37 |
| $Q_{24}$ | -5.97 | Met 769(2.0) | 41.94 |
| $Q_{25}$ | -5.50 | Lyz721(1.99) | 92.63 |
| $Q_{26}$ | -6.40 | Lyz721(2.12) | 20.25 |
| $Q_{27}$ | -6.95 | - | 8.09 |
| $Q_{28}$ | -7.08 | - | 6.43 |
| $Q_{29}$ | -7.54 | Met 769(2.0) | 2.95 |
| $Q_{30}$ | -6.47 | Glu738(2.15) | 18.2 |
| $Q_{31}$ | -5.86 | Met 769(1.96) | 50.97 |
| $Q_{32}$ | -5.69 | Met 769(1.63) | 67.61 |

Two compounds Q3 and Q8 can create strong hydrogenbond withLyz704via nitro electron withdrawing substitution on the phenyl ring at distance (1.86-2.05 Å) and Met 769 via carbonyl group of quinazolinone. The best result of docking studies was observed for oxadiazole-quinazolinone derivatives with amide linker (Q18-Q20) categorized in 2, 3-disubstituted 4(3H)-quinazolinone group. The lowest dock score for these series was -9.52kcal/mol for compound Q19. Rest of 2, 3-disubstituted 4(3H)-quinazolinone showed a proper dock scores ranging from -5.5 to -8.13kcal/mol. Two hydrogen binding interactions have been detected for Q19 ligand. Cys 773 and Asp 776 are the responsible amino acids for formation of hydrogen binds. Oxygens of oxadiazole ring and amid linker has been participated in a hydrogen bond interaction with Cys 773 and nitrogen atoms of the 1,3,4-oxadiazole ring has been formed hydrogen binding with Asp 776. Q18 also showed acceptable dock score and hydrogen binding with Met 769 and Cys 773residues. This compound showed the highest cytotoxic activities with the IC50value of 7.52 μM against HeLa cell line [19].

At the second step, it was attempted to model proposed structures and found out the main effective descriptors on the biological output. It seems that number of Nitrogen atom (nN), number of 6 or 5 membered rings (nR05 and nR06), mean

squared distance (MSD), molecular Eccentricity (MEcc), A sphericity (ASP), sum of geometrical distance between o-o (G(o..o)) were important on the results. Finally, the QSAR model based on the extracted descriptors was created via partial least square model. It is hope that the proposed model will be helpful on the future of design new compounds as the EGF inhibitors.

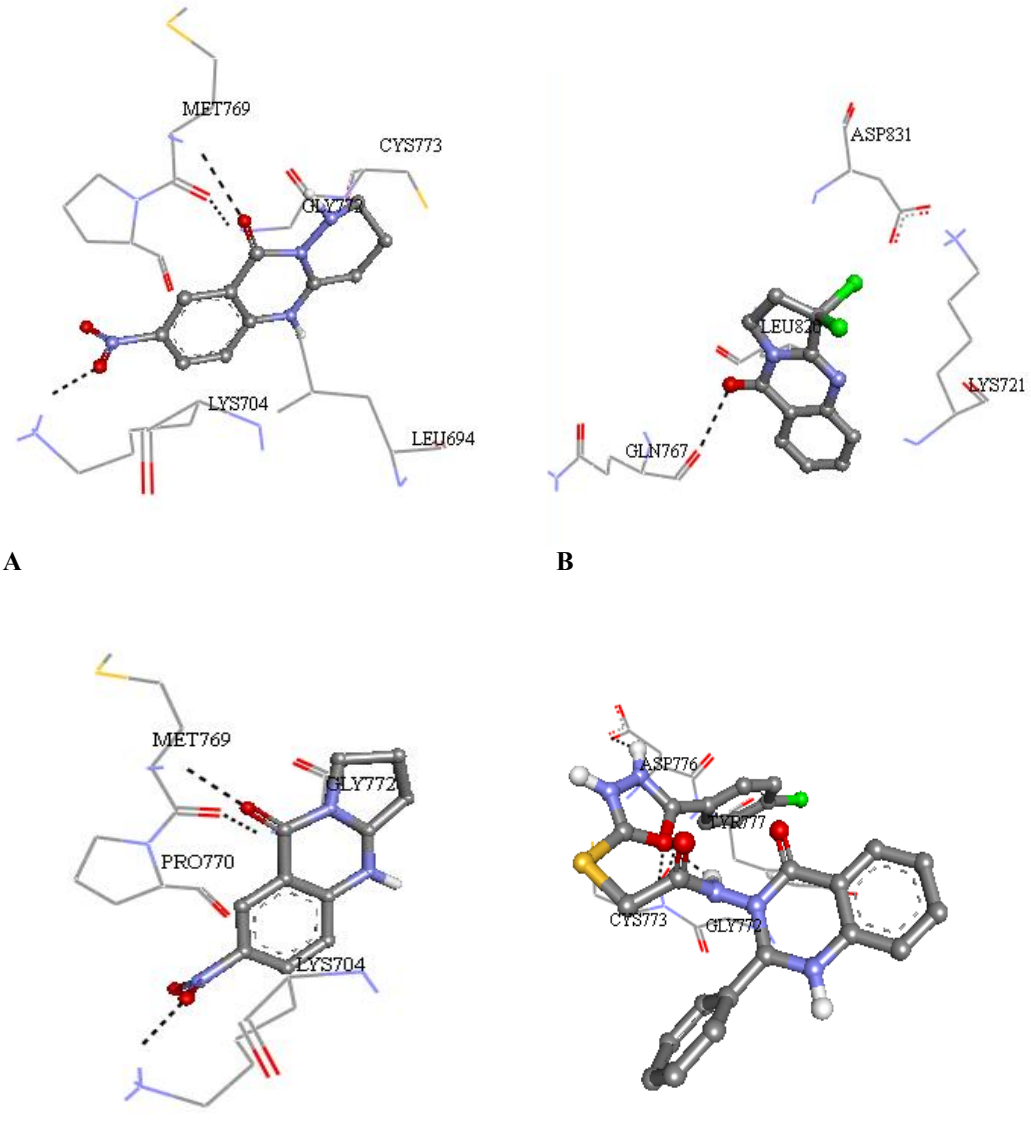



**Figure5.** Docked conformation of compounds (A)$Q_3$, (B)$Q_7$, (C) $Q_8$and (D) $Q_{19}$in the binding site of epidermal growth factorreceptor tyrosine kinase. Hydrogen bonds are shown by the black dashed line.

## 4. Conclusion

Based on the obtained results of docking and in-vitro cytotoxic assay compounds Q3 ,Q7, Q8 , Q18 and Q19could be introduced as anticancer agents via tyrosine kinase inhibition pathways. Besides, according to the QSAR model, it seems that number of Nitrogen atom and rings, centrality and geometrical distance between two oxygen are the main properties which must be noted to design new molecules in the future of work. But, in vitro inhibitory study against tyrosine kinases are necessary to complete this finding.

## Conflict of interest statement

Authors declare no conflict of interest.

## Acknowledgements

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Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.

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