ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 10 | October - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

IN-SILICO STUDIES OF ANTI-PROLIFERATIVE CURCUMIN ANALOGS

Pharmaceutical

Monu Kumar Shukla*
Postgradute, Department Of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, India - 462026 *Corresponding Author

ABSTRACT

Prostate cancer affects males more than women. Curcumin, a bioactive component of turmeric, reported to have anticancer properties on several cancer cell lines. Researchers utilised molecular docking to generate new curcumin analogues, quantify their characteristics, and anticipate its mode of action. In this research article QSAR studies were performed on 40 curcumin analogues using V-life MDS 3.5 software. The physicochemical characteristics were computed using Molinspiration Cheminformatics software. The best QSAR model for 2D and 3D QSAR was selected. Then ten compounds were designed and improved based on model results directly linked to activity. The *in-silico* approach predicted the good biological activity of compounds. Docking studies were performed using Akt1 as a probable target. Among the developed compounds, MKS50 has the best docking score (-7.175 kcal/mol). This study will provide a new path for the design, synthesis, and biological evaluation of novel curcumin analogues.

KEYWORDS

Anticancer agents, Akt1, curcumin, molecular docking.

1. INTRODUCTION

Cancer of the prostate (adenocarcinoma) is the most frequent kind in men. In the United States alone, 191,930 men had prostate cancer. It's a chronic inflammatory response is related to high-grade or aggressive tumors and metastatic prostate cancer (Risbridger et al., 2010). Angiogenesis and metastasis are aided by oncocytokines that change the tumor microenvironment in prostate gland. In the progression of prostate cancer, nuclear factor-κB (NFκB) pathway plays an important role by promoting cell survival, proliferation and invasion. NFκB activity is controlled by Akt kinase. It is possible to inhibit the NF-κB pathway by inhibiting Akt's phosphorylation and degradation (Heinrich et al., 2012; McLafferty et al., 2014).

Curcumin (diferuloylmethane), a polyphenol found in Curcuma longa, has showed promise in treating prostate cancer. Curcumin regulates the NFB pathway, according to studies. Curcumin also dephosphorylates Akt1 kinase (Lin et al., 2006).

In this research, the main goal is to build a QSAR model for optimizing the curcumin analogues described by Lin et al. and to identify the structural features that contribute to their activity. Ten more compounds were developed to identify a new cancer therapy target. A molecular docking study also confirmed the binding affinity with the receptors.

2. MATERIALS AND METHODS

2.1. Data Set

The QSAR models used in this research were based on 40 curcumin derivatives published by Li Lin and colleagues (Lin et al., 2006).

2.2. Generation of 2D QSAR Equation

2.2.1. Molecular Structure Generation

ACD/ChemSketch 12.0 was used to draw molecules. Structures were converted from 2D to 3D using V-Life MDS 3.5. Then the MMFF technique was utilized to minimize structural energy and compute descriptors (physicochemical & AI).

2.2.2. Statistical Analysis

The dataset was manually split into training and test sets for model validation. With IC50 values as dependent variables and computed descriptors as independent variables. PLS regression was utilized to construct QSAR equation (Gohate & Mehta, 2020).

2.3. Generation of 3D QSAR Equation

The field was calculated using electrostatic, steric, and hydrophobic descriptors, yielding 7113 descriptors. The data were divided into test and training sets via sphere exclusion and regression by kNN.

2.4. Designing of New Molecules

The descriptors of model were utilized to create new compounds based on the curcumin structure. Then activity of the compounds was predicted.

2.5 ADMET Properties

Molinspiration program used to calculate physicochemical properties.

2.6. Molecular Docking

Molecular docking studies of the designed curcumin analogs were performed using Glide extra precision mode of Schrödinger suite. The crystal structure of IκBα (PDB ID: 1NFI, chain E) and Akt1 (PDB ID: 4GV1) were downloaded from RCSB protein data bank. For docking studies, the proteins were prepared using protein preparation wizard and the ligands were prepared with LigPrep module of Schrödinger suite.

3. RESULTS

3.1. Generation of 2D QSAR Equation

QSAR models were developed via PLS method and the equation was obtained by using the optimal combination of descriptors. The descriptors were selected for the final equation having correlation matrix below 0.5.

3.2. 2D QSAR Model

The generated equation and values for the model were as follow;

$pIC50 = 0.0292\,T\_2\_2\_7 + 0.3082\,T\_N\_O\_6 + 4.7032$
$n=23, r^2=0.5502, q^2=0.4372, pred\_r^2=0.2361$, F-test = 25.6899, $r^2\_se=0.2864$, $q2\_se=0.3204$, $pred\_r^2\_se=0.5723$
Where, the r^2-value accounts for variance in observed activity value. This equation shows the descriptors T_2_2_7 and T_N_O_6 having positive contribution.

The best model among all generated models, found to be the best equation in the QSAR study. The fitness plot between actual activity and predicted activity of compounds were also generated. Plot that was generated by PLS indicated that all the points lay within. The best fit of the contribution of each descriptor, activity distribution graph of model and the relative error of the predicted activity were also reported.

3.3. 3D QSAR

To generate 3D QSAR equation, all the optimized structures were aligned by template-based alignment by taking (3*Z*,5*E*)-4-hydroxyhepta-3,5-dien-2-oneas the template. Conformers were generated and aligned for the structures **(Figure 1)**.

3D model was generated by kNN method which fulfilled all the selection criteria for selection. The q2 value 0.7397 shows good correlation between electrostatic, steric and hydrophobic properties and biological activities.

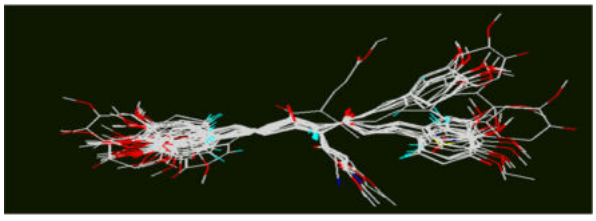


Figure 1: Alignment of structures using template based method.

in the fitness plot, test set structures were near to the best fit line but some structures of the training set deviated from the best fit line.

The actual activity along with predicted activity and residual value was calculated. The show points showed the site where the structural modification has to be done.

The best model generated from 2D QSAR studies comprised of the descriptors T_2_2_7 and T_N_O_6 with statistical significance exemplified by n = 23, r^2 = 0.5502, q^2 = 0.4372, pred_r^2 = 0.2361, r^2_se = 0.2864, q^2_se = 0.3204, pred_r^2se = 0.5723 (standard errors). Thus, these descriptors were important for anticancer activity. In 3D QSAR studies, molecular field analysis was used to construct the model using kNN method which showed good correlative and predictive capabilities in terms of n = 21, q^2 = 0.7397, pred_r^2 = 0.3749, q^2_se = 0.2731, pred_r^2se = 0.2972 (standard errors), kNN= 3 and degree of freedom = 18.

3.4. Interpretation of 3D Model

The descriptors (E_2189 and E_1198) showed correlation with the activity among all descriptors which provided the knowledge to increase the electrostatic potential. The model also suggested point of alteration on lead molecules.

3.5. Designing of New Compounds

Total 10 compounds (MKS41-MKS50) were designed from the lead via modification was done at the phenyl rings **(Table 1)**.

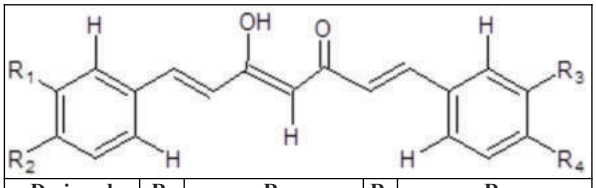
3.6. Method of Optimization

3D structures of the designed compounds were batch optimized by using MMFF force field method and the energy was calculated.

3.7. Activity Prediction of Designed Compounds

The biological activities of designed compounds were predicted for anticancer activity and exhibited moderate to good values in comparison to reported compounds chosen for QSAR studies from the series. The ADMET properties (physicochemical properties) of the compounds were also calculated.

Table 1: Structures of Designed Compounds



Designed Compounds	R_1	R_2	R_3	R_4
MKS41	OH	OCH_3NH_2	OH	OCH_3NH_2
MKS42	OH	$O(CH_2)_2NH_2$	OH	$O(CH_2)_2NH_2$
MKS43	OH	OCH_2NHNH_2	OH	OCH_2NHNH_2
MKS44	OF	OCH_2NHNH_2	OF	OCH_2NHNH_2
MKS45	OH	OCH_2F	OH	OCH_2F
MKS46	OH	OCH_2CH_2F	OH	OCH_2CH_2F
MKS47	OH	$O(CH_2)_5OH$	OH	$O(CH_2)_5OH$
MKS48	OH	$OC=C(CH_2)_3C=CH_2$	OH	$OC=C(CH_2)_3C=CH_2$
MKS49	OH	$OC=C(CH_2)_4NH2$	OH	$OC=CCH_2NHCH_2CH_3$
MKS50	OH	$OC=C(CH_2)_4NH_2$	OH	$OC=C(CH_2)_2NH_2$

3.8. Molecular Docking

The designed compound showed better docking score with Akt1 than IκBα. Therefore, Akt1 can be proposed as a target for designed curcumin analogs. Among all the designed molecules, compound MKS50 showed the highest docking score (-7.177 kcal/mol), where the co-crystallized ligand and curcumin showed the docking scores -10.111 and -6.919 kcal/mol respectively.

The co-crystallized ligand (0XZ) interacts to Akt1 via forming hydrogen bonds with Glu228, Ala230, Glu234 and Glu278. Like co-crystallized ligand, compound MKS50 also forms hydrogen bond with Glu234 and Glu278. The complex is further stabilized by additional hydrogen bonds with Glu191, Lys276, Asp292 and salt bridges with Glu191, Glu234 and Asp292 **(Figure 2).** Glu234 is considered as pivotal amino acid residues for Akt1 functioning. Glu234 interacts with ribose of ATP, thus binding of compound with this amino acid hinders the binding with ATP. Therefore, designed ligand may inhibit Akt1 activity by limiting ATP binding and phosphorylation.

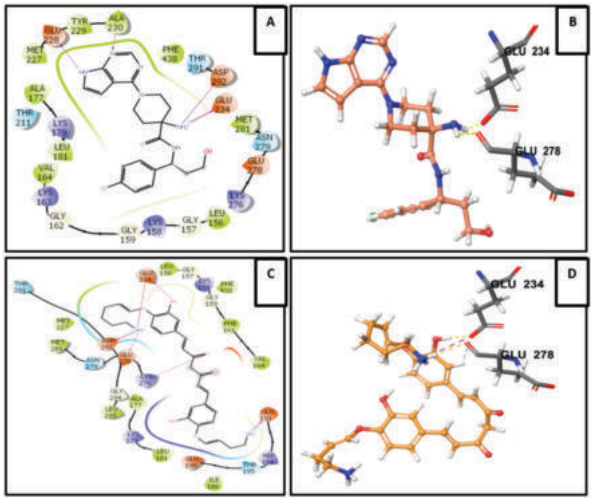


Figure 2: Binding pose and interaction diagram of co-crystallize ligand (0XZ) (A & B) and MKS50 (C & D) with Akt1.

4. DISCUSSION

Most men get prostate cancer, which is situated in front of rectum, between the bladder and the penis. The data used in this research came from Lin et al., who reported on the biological activities of PC-3 cells. This data was used to create a 2D QSAR equation using PLS regression.

The created model correctly predicted the biological activity of novel compounds. 2D-QSAR model exhibited fitness plot, contribution chart of descriptors, activity distribution graph, and relative error of predicted activity.

For 3D QSAR equation, the optimized structures were aligned using a template. Alignment was performed on conformers with low activity and improved alignment.

The data was utilized to build a 3D model using the kNN technique. 3D model was interpreted using two generated descriptors with activity among all descriptors, resulting in higher electrostatic potential. This model also indicated the lead molecule's modification site. 2D and 3D QSARs were used to build compounds from the lead moiety and the activity was predicted. The ADMET characteristics of designed compounds were calculated.

The proposed compound showed better activity with Akt1. Akt1 is reported as a target for curcumin analogues. Among all developed compounds, MKS50 outperformed than the co-crystallized ligand and curcumin in docking. MKS50 and co-crystallized ligand (0XZ) interact with Akt1 through hydrogen bonding. Additional hydrogen bonds and salt bridges stabilize the complex. Glu234 is an essential amino acid for Akt1 activity. The ligand would restrict ATP binding and phosphorylation via inhibiting Akt1 activity.

5. CONCLUSION

The designed compounds may be used to develop novel anticancer drugs. The compounds exhibited acceptable molecular characteristics. Molecular docking suggested Akt1 as a possible target for the compounds. This study may be expanded to include synthesis and bioevaluation for prostate cancer and other malignancies.

Conflicts of Interest

The authors have declared that there is no conflict of interests.

Acknowledgements

Author acknowledged Department of Pharmacy, Barkatullah University, Madhya Pradesh for providing the software and other online program for research tools.

REFERENCES

[1] Gohate, D., & Mehta, P. (2020). 2D and 3D QSAR Analysis of Imidazole Derivatives as Heme Oxygenase Inhibitor. Current Research in Pharmaceutical Sciences, 10(2), 19-29.
[2] Heinrich, E. L., Walser, T. C., Krysan, K., Liclican, E. L., Grant, J. L., Rodriguez, N. L.,

& Dubinett, S. M. (2012). The inflammatory tumor microenvironment, epithelial mesenchymal transition and lung carcinogenesis. Cancer Microenvironment, 5(1), 5-18.

[3] Lin, L., Shi, Q., Nyarko, A. K., Bastow, K. F., Wu, C. C., Su, C. Y., ... & Lee, K. H. (2006). Antitumor agents. 250. Design and synthesis of new curcumin analogues as potential anti-prostate cancer agents. Journal of medicinal chemistry, 49(13), 3963-3972.

[4] McLafferty, E., Johnstone, C., Hendry, C., & Farley, A. (2014). Male and female reproductive systems and associated conditions. Nursing Standard, 28(36).

[5] Risbridger, G. P., Davis, I. D., Birrell, S. N., & Tilley, W. D. (2010). Breast and prostate cancer: more similar than different. Nature Reviews Cancer, 10(3), 205-212.