Journal of Computational Methods in Molecular Design, 2015, 5 (2):109-114

Scholars Research Library
(http://scholarsresearchlibrary.com/archive.html)

ISSN : 2231- 3176
CODEN (USA): JCMMDA

Docking study of p-hydroxybenzohydrazide derivatives as tyrosine kinase inhibitors and anticancer agents

Prashant A. Patil*[1], Nikhil D. Amnerkar[2], Sandeep S. Pathare[1] and Kishore P. Bhusari[3]

[1]Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Bharati Vidyapeeth University, Erandawane, Pune, (MS) India
[2]Adv. V. R. ManoharInstitute of Diploma in Pharmacy, Nagpur, (MS) India
[3]Department of Pharmaceutical Chemistry, Sharad Pawar College of Pharmacy, Nagpur, (MS) India

---

ABSTRACT

Thiazole and thiazolidene derivatives of p-hydroxybenzohydrazide were found having anti cancer activity. These compounds were showed the inhibitory effect against various cancerous cell lines. An attempt was made to find the correlation in these anticancer agents as epidermal growth factor receptor (EGFR): tyrosine kinases inhibitors. N'-[4-(4-substituted-phenyl)-3-(substituted-phenyl)-1,3-thiazol-2(3H)-ylidene]-4-hydroxybenzohydrazide compounds (I-IV) and N'-[3-(substituted-phenyl)-4-oxo-1,3-thiazolidin-2-ylidene]-4-hydroxybenzohydrazide compounds (V-VIII) were used in the docking study. Compounds were evaluated in terms of GScore, Dockscore, H-bonding interactions, electrostatic interactions. In the docking study with receptor 1M17, the numbers of H-bond interactions showed crucial role in relation with activity. As standard drug was compared with the compounds (IV-VII); this showed good H-bond interactions and correlated with their anticancer activity.

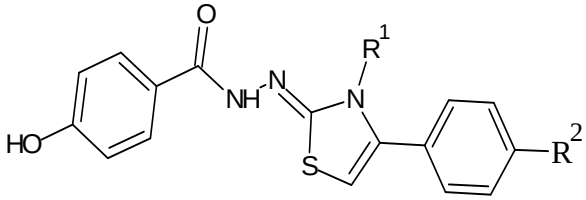
Key words: *p*-Hydroxybenzohydrazide; docking study; 1M17; anticancer activity.

INTRODUCTION

The dramatically rising prevalence of cancer in the past few years has become a serious health care problem. Cancer is uncontrolled growth of abnormal cells in the body. Cancerous cell are malignant cells. Normal cell multiply when the body needs them & die when the body does not need them. Cancer appears to when the growth of cell in the body is out of control. The rationale for targeting the epidermal growth factor receptor (EGFR) family for cancer therapy is compelling. These receptors are frequently over expressed in human tumors. It is seen when subfamily of tyrosine kinases was blocked by ligand binding, prevented activation of the receptor, and were found to have antiproliferative effects.[1,2] Increasing knowledge of the EGFR subfamily of tyrosine kinases and of their role in the initiation and progression of various cancers has, in recent years, provided the impetus for a substantial research effort aimed at developing new anticancer compounds.[3-5]

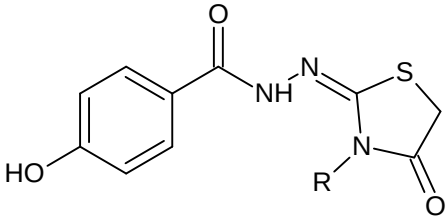
MATERIALS AND METHODS

Data set:
The compounds p-hydroxybenzohydrazide were selected from literature [6]. As they were found as promising active moieties for anticancer activity. Five compounds were selected for this study. These five compounds were showed anticancer activity against colon cancer, melanoma, breast cancer and non-small lung cancer. The anticancer activity was done at National Cancer Institute (NCI) Developmental Therapeutic Program (www.dtp.nci.nih.gov) for the in vitro cell lines.[7-9] Anticancer assays were performed according to the US, NCI protocol. The present study aim is to evaluate the biologically active compounds in comparison to standard anticancer drug, in terms of docking study.[10,11]



N'-[4-(4-substitutedphenyl)-3-(substitutedphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide

Compd.	R^1	R^2
I	2,4-Cl C6H4	4-Cl
II	2,4-OCH3 C6H4	4-Cl
III	2,4-OCH3 C6H4	4-CH3
IV	2,4-OCH3 C6H4	4-OCH3



N'-[3-(substitutedphenyl)-4-oxo-1,3-thiazolidin-2-ylidene]-4-hydroxybenzohydrazide

Compd.	R
V	4-Cl C_6H_5
VI	2,4-Cl C_6H_5
VII	3,4-Cl C_6H_5
VIII	3,5-Cl C_6H_5

Docking study

The molecular docking tool, Glide (Schrodinger Inc. U.S.A.) software was used for ligand docking studies in, (1M17) tyrosine kinase inhibitors with (PDB) site having enzyme transferase bind with ligand Erlotinib [12-14].

Molecular docking protocol

All the docking calculations were performed using "standard precision (SP) and extra precision" (XP) mode of Glide 8.5 program; Schrodinger LLC and the 2005 implementation of OPLS_2005 force field.[15] The binding site, for which the various energy grids were calculated and stored, was defined in terms of two concentric cubes; the bounding box, which was contained the center of any acceptable ligand pose, and the enclosing box, which was contained all ligand atoms of an acceptable pose. Cubes with an edge length of 12 Å and centered at the midpoint of the longest atom-atom distance in the respective co-crystallized ligand was defined the bounding box in the protein. The large enclosing box was also defined in terms of the co-crystallized ligand: an edge length of 30 Å was used. Poses with an RMSD of less than 0.3 Å was used for optimization.

The scale factor for van der Waals radii was applied to those atoms with absolute partial charges less than or equal to 0.15 (scale factor of 0.8) and 0.25 (scale factor of 1.0) electrons for ligand and protein, respectively. The max keep variable which got the maximum number of poses generated during the initial phase of the docking calculation were set to 32 and the kept best variable which got the number of poses per ligand that entered protocol included dielectric constant of 4.0 and 1000 steps of calculation, at most 100 poses per ligand were generated. The best docked structure was chosen using a glide score (Gscore) function. The g score was modified and extended version of the empirically based chemscore function. Another scoring function used by glide, which itself derived from a combination of Gscore, dock score, electrostatic and H-Bond energy contact, including PhoEnHB, were also used for docking compound. The molecules chosen from docking among them, the nine compounds showed very good glide score. These molecules were again selected for docking via standard precision method to obtain the precise results [16-18].

These molecules were then subjected for extra precision method. Both the results were noted and compared. Extra precision method was showing good results in the form of Glide score, PhobEnpair HB, Dock score and H-bond contacts [19-20].

RESULTS AND DISCUSSION

Molecular docking study of *N*'-[(3-Substituted alkyl/aryl)-4-oxo-1,3-thiazolidin-2-ylidene]-4-hydroxybenzo - hydrazide as an anti-cancer agents

The following steps were undertaken for molecular docking studies.

Ligand preparation

The selected co-crystallized ligand i.e. ligand which was already bonded to protein, consequently by opening Ligand preparation window ligand structures were taken. The force field parameter was selected as molecular mechanics force field (MMFF). The possible states of ligand generated were 32. By keeping remaining data default, ligand preparation was done.

Protein preparation

Protein preparation was done by selecting option of protein preparation wizard, from software. All hydrogen atoms were added and kept as it is. As the protein selected was the homodimer the unwanted chain from the protein is removed. Water molecules were removed from the protein and heterostates were generated and the state having lowest penalty and highest probability was selected. After going to window, Impref minimization all hydrogens and force field OPLS_2005 was selected.

Grid preparation

Grid generation was done with selection of rigid docking that is in this amino acids were not movable so scaling factor was applied up to not less than 0.7. By keeping remaining data unchanged grid was prepared [21,22].

Standard precision (SP) and extra precision (XP) mode

Standard precision docking was having precision between extra precision (XP) and high throughout screening (HTVS). XP docking was used for refining molecules which were giving good results in SP docking.

The extra precision docking was performed by using prepared ligands and preprocessed protein. The module Glide was selected from the maestro and XP docking was performed which was indicated good results in the form of dock score, glide score, H-bond contacts, PhobEnpair HB (Table 1). The comparative analysis of the docking parameters was carried out with Erlotinib (standard) (Table 1).

Viewing docking results

Using the pose-viewer module docking results visualized. The H-bonds, G score, PhobEnHB, H-Bond to the receptor were visualized using default settings to analyze the binding modes of the ligands to receptor (Figures 2 to 5).

Figure 1 Structure of 1M17 receptor

Table 1 XP Docking of Compound. (I-VIII)

Compd.	GScore	Dockscore	H-bond	Electrostatic	PhobEn Pair HB
I	**-5.51**	**-4.73**	**-0.59**	**-0.20**	**0**
II	**-5.84**	**-1.51**	**-0.64**	**-0.24**	**0**
III	**-5.82**	**-1.43**	**-0.61**	**-0.27**	**0**
IV	**-6.92**	**-1.42**	**-1.61**	**-0.26**	**0**
V	**-6.79**	**-1.39**	**-0.58**	**-0.28**	**0**
VI	**-8.01**	**-3.43**	**-1.75**	**-0.48**	**-1**
VII	**-8.01**	**-6.40**	**-1.75**	**-0.48**	**-1**
VIII	**-8.12**	**-6.42**	**-1.74**	**-0.47**	**-1**
Std. Erlotinib	**-7.12**	**-6.87**	**-2.27**	**-1.9**	**-0.93**

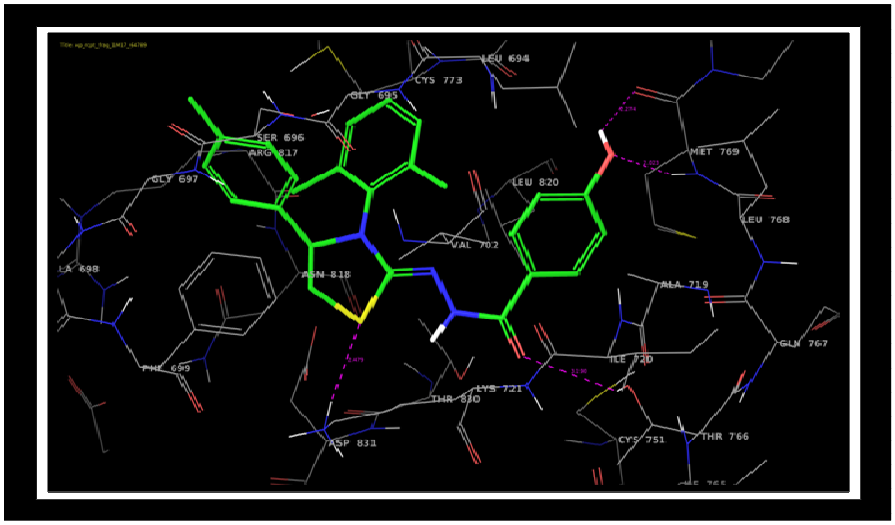


Figure 2 Compound. (IV) docked in active site of 1M17

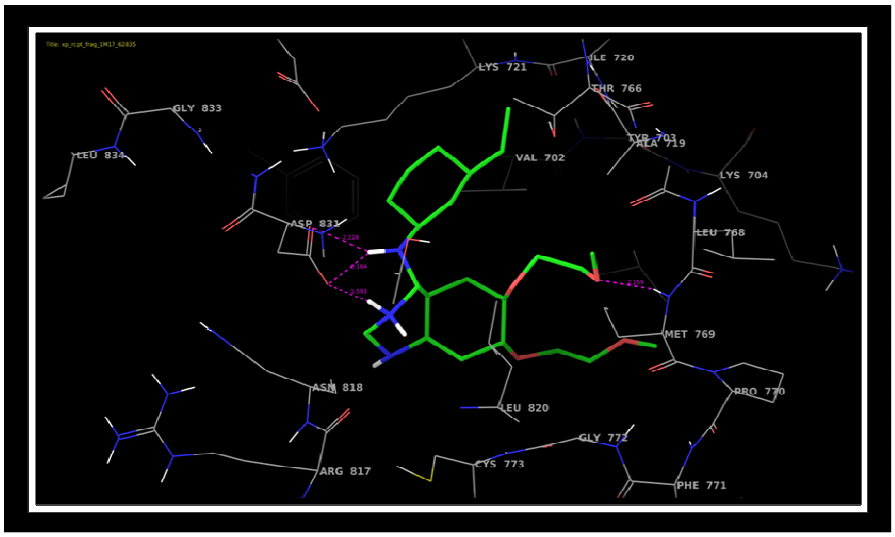


Figure 3 Compound. (VI) docked in active site of 1M17

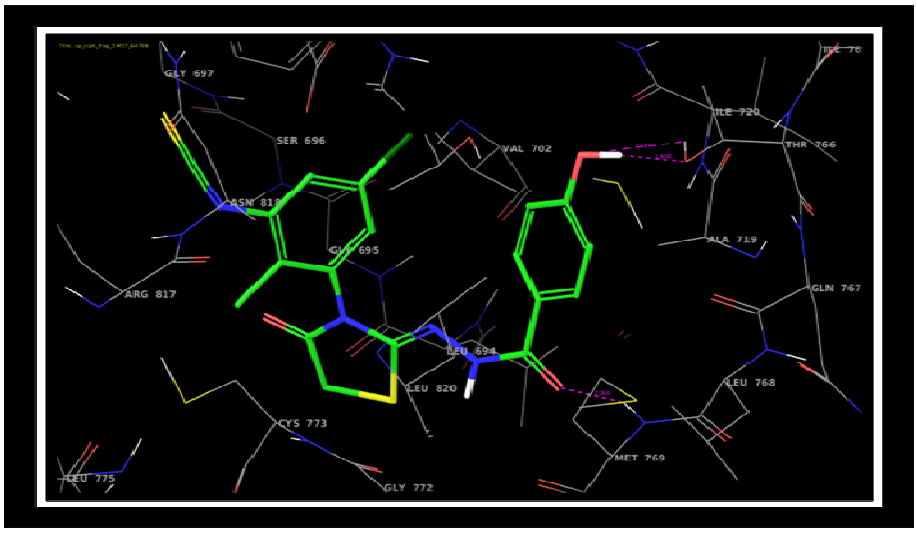


Figure 4 Compound. (VII) docked in active site of 1M17

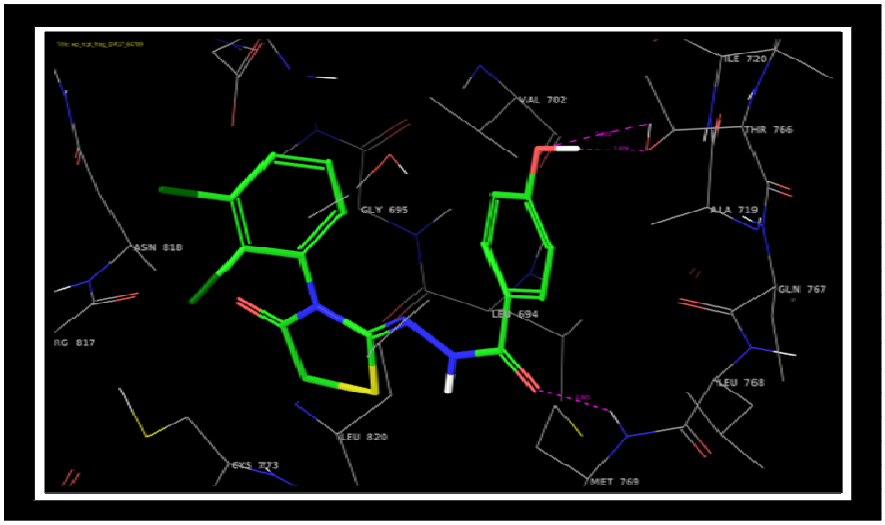


Figure 5 Compound. (VIII) docked in active site of 1M17

CONCLUSION

The molecular docking study on compounds (I-VIII), was done with 1M17 receptor which was showed good results in the form of docking score. Further docking is done using extra precision method which resulted in good docking score i.e.-3.43 to -9.12.

The docking studies were performed using standard precision mode of Glide. The results of the docking studies were generated in the form of G-score.[23-25] The more negative value of G-score indicated that the compound may be more potent and indicated the good binding potential of the compd. The G-score of the standard drug i.e. Erlotinib, in case of docking with 1M17, was found as -6.03. Close analysis of these results suggested that designed compounds were comparable with standard anticancer agent Erlotinib. Besides the G-score, other parameters like H-bond, dock score and Electrostatic .are into consideration for the evaluation of the docking results. The number of H-bond interactions in the standard compound, Erlotinib, was compared with those of the designed compounds. In case of docking with 1M17, the numbers of H-bond interactions of the standard compound, Erlotinib, was found in between -2.27. While those of compounds were found to be, -0.59,-0.64, -0.61, -0.61, -0.58,- 0.75, -0.75 and -0.74 respectively. It was well established and accepted fact the docking score is good and were considering the interaction of H-bond is close related to standard, designed compounds with 1M17 active binding site. The molecular docking study on compounds (I-VIII) was done with 1M17 receptor which was showed good results; among which compounds which was resulted in good docking score i.e.-3.43 to -9.12. Results of docking study gives hint that the activity might have increased by placing electron donating groups like methoxy/ethoxy/hydroxy. Moreover, electron withdrawing groups like chloro/nitro on possible position of phenyl ring could be retained for better activity.

Acknowledgements
Authors are thankful to All India Council for technical Education (AICTE) for their financial assistance under the Research Pramotion Sceme (F. No.: 8023/BOR/RID/RPS-190/2008-09), and Dr. Ritesh P. Bhole for providing the database for docking studies.

REFERENCES

[1] MI El-Gamal; YSPark; DY hi; KH Yoo; HO Chang, *Eur. J. Med. Chem.*, **2013**, 65, 315-322.
[2] W Xie; S Xie; Y Zhou; X Tang; J Liu; W Yang; M Qiu, *Eur. J. Med. Chem.*, **2014**, 81, 22-27.
[3] R Romagnoli; PG Baraldi; MK Salvador; M Chayah; ME Camacho; F Prencipe; E Hamel; F Consolaro; G Basso; G Viola, *Eur. J. Med. Chem.*, **2014**, 81, 394-407.
[4] R Pingaewa; P Mandi; C Nantasenamat; S Prachayasittikul; S Ruchirawat; V Prachayasittikul, *Eur. J. Med. Chem.*, **2014,** 81, 192-203.
[5] CB Sangani; JA Makawana; X Zhang; SB Teraiya; L Lin; HL Zhu, *Eur. J. Med. Chem.*, **2014**, 76, 549-557.
[6] RP Bhole; KP Bhusari, *Med. Chem. Res.*, **2011**, 20, 6, 695-705.
[7] PA Patil; ND Amnerkar; SS Pathare; KP Bhusari, *Der Pharma Chemica*, **2014**, 6, 6, 300-312.
[8] RP Bhole; PA Patil; P Agale; SP Wate, *Marmara Pharmaceutical Journal*, **2013** 17, 1-7.
[9] RP Bhole; DD Borkar; KP Bhusari; PA Patil, *J. Korean. Chem. Soc.*, **2012**, 56, 236-246.

[10] SL El-Ansary; MM Hussein; DEA Rahman; MAA Ghany, *Bioorg Chem.*, **2014**, 53, 50-66.
[11] T Chuprajob; C Changtam; R Chokchaisiri; W Chunglok; N Sornkaew; A Suksamrarn, *Bioorg. & Med. Chem. Let.*, **2014**, 24, 2839-2844.
[12] Protein data bank: www.pdb.org.
[13] Y Arun; K Saranraj; C Balachandran; PT Perumal, *Eur. J. Med. Chem.*, **2014**, 74, 50-64.
[14] AE Wakeling; AJ Barker; DH Davies; DS Brown; LR Green, SA Cartlidge; JR Woodburn, *Breast Cancer Research and Treatment*, **1996**, 38, 1, 67-80.
[15] GLIDE 2.1, Schrodinger, LLC, New York, NY, **2006**.
[16] F Meriggi; A Zaniboni. *Current Gerontology and Geriatrics Research*, **2010**, 8-19.
[17] M Ranson. *British J. Cancer*, **2004**, 90, 2250-2261.
[18] E Raymond; S Faivre; JP Armand, *Drugs*, **2000**, 60, 1, 15-28.
[19] J Baselga, *J. Clin. Oncology*, **2002**, 20, 9, 2217-2228.
[20] P Yaish; A Gazit; C Gilon; A Levitzki, *Science*, **1988**, 242, 933-942.
[21] WHJ Ward; PN Cook; AM Slater; DH Davies; GA Holdgate; LR Green, *Biochem Pharmacol.*, **1994**, 48, 659-671.
[22] I Posner; M Engel; A Levitzki, *J. Biol. Chem.*, **1992**, 267, 20638-20649.
[23] TR Burke Jr, *Drugs of the Future*, **1992**, 17, 119-127.
[24] J Schlessinger, *Trends Biochem Sci*, **1993**, 18, 273-285.
[25] Y Yarden; A Ullrich, *Ann Rev Biochem*, **1998**, 57, 443-454.