**ISSN 0974-3618 (Print)**
**0974-360X (Online)**

**www.rjptonline.org**

***RESEARCH ARTICLE***

# Comparative in Silico Docking Studies of Hinokitiol with Sorafenib and Nilotinib against Proto-Oncogene Tyrosine-Protein Kinase(ABL1) and Mitogen-activated Protein Kinase (MAPK) to Target Hepatocellular Carcinoma

**Mohamed Zerein Fathima*, T.S. Shanmugarajan, S. Satheesh Kumar, B.V.Venkata Nagarjuna Yadav**

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels University (VISTAS), Pallavaram-600117, Tamilnandu, India.

*Corresponding Author E-mail: **shanmuga5@yahoo.com**

**ABSTRACT:**

Cancer is fundamentally a disease of disordered gene expression. Hepatocellular carcinoma is a well known and third most common cancer worldwide. The protein – ligand interaction plays a imporatant role in structural based drug designing for disease. Hinokitiol (HIOL) is also known as $\beta$-thujaplicin, is found in the heartwood of cupressaceous plants and naturally occurring tropolane derivative is a known biochemical target other than the fact that it induces apoptosis. The docking scores of the active constituents are compared against the standard drugs. The 3D structures of the constituents (Nilotinib, Sorafenib and Hinokitiol) are obtained from PubChem compound. The target for docking studies is selected as Proto-oncogene tyrosine-protein kinase ABL1 and Mitogen-activated protein kinase. Docking analysis is done by initially selecting the target for the disease and followed by obtaining the 3D structure of Proto-oncogene tyrosine-protein kinase ABL1 and Mitogen-activated protein kinase 14 (PDB ID:2HZI) and (PDB ID: 3LFF) respectively from protein data bank. The ABL1 and MAPK was docked with the above said drugs and based upon the lipin rule, rerank score and mol dock score we chosen the hinokitiol having good interaction with receptor molecule and docking studies has been carried out through Molegro Virtual Docker (MVD).

**KEYWORDS:** Hinokitiol, ABL1, MAPK, Hepatocellular carcinoma, Lipin rule.

## INTRODUCTION:

Natural products have been a rich source of compounds that have found many applications in the fields of medicine, pharmacy and biology. In the cancer field, a number of important new commercialized drugs have been obtained from natural sources, by structural modification of natural compounds, or by the synthesis of new compounds, designed following a natural compound as model.

The search for improved cytotoxic agents continues to be an important in the discovery of modern anticancer drugs. Hepatocellular carcinoma (HCC) ranks the fifth in frequency among common human solid tumors and the fourth leading cause of cancer-related death. And also major malignant tumor in humans and cause more than 25,00,000 deaths annually worldwide.(1)

The majority of HCC cases occur in Asia and Africa but incidence has been increasing in Western Europe and the United States in recent years. In China, HCC is now the second cancer killer. Numerous studies have been carried out in an effort to elucidate molecular mechanism of hepatocarcinogenesis (2). Hinokitiol, also known as $\beta$-thujaplicin, is a tropolone derivative found in the

Received on 18.08.2016 Modified on 26.11.2016
Accepted on 20.12.2016 
*Research J. Pharm. and Tech. 2017; 10(1): 257-262.*
**DOI: 10.5958/0974-360X.2017.00053.1**

heartwood of cupressaceous plants. Hinokitiol (HIOL) is a naturally occurring tropolane derivative is a known biochemical target other than the fact that it induces apoptosis. As an iron-chelating compound, it triggers apoptosis via activation of caspase-3 and exerts a spectrum of biological effects including differentiation-inducing, anti inflammatory, antibacterial, antifungal, and antioxidant capacities, as well as antitumor activity. Hinokitiol has also been widely used in hair tonics, tooth pastes, cosmetics, and food as an antimicrobial agent. Hinokitiol has been shown to suppress tumor growth by inhibiting cell proliferation and inducing apoptosis in various carcinoma cell lines.(3,4) .

Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed.

Molecular docking plays an important role in the rational drug design. It predicts the binding orientation of small drug targets to their protein targets. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. The drug-likeness of plant derived compounds can be predicted by Lipinski's rule of five which refers to the similarity of compounds to oral drugs. (5,6).

## MATERIALS AND METHODS:

### Preparation of Ligand:

The 3D structures of the constituents (Nilotinib, Sorafenib and Hinokitiol) are obtained from PubChem compound (7,8) and saved in .mol format. The ligands are imported to the workspace and preparation of them is done. The docking scores of the active constituents are compared against the standard drugs.

### Preparation of Enzymes:

The target for docking studies is selected as Proto-oncogene tyrosine-protein kinase ABL1 and Mitogen-activated protein kinase 14. Docking analysis is done by initially selecting the target for the disease and followed by obtaining the 3D structure of Proto-oncogene tyrosine-protein kinase ABL1 and Mitogen-activated protein kinase 14 (PDB ID:2HZI) and (PDB ID: 3LFF) respectively from protein data bank in. pdb format (9-12). It is well known that PDB files often have poor or missing assignments of explicit hydrogens, and the PDB file format cannot accommodate bond order information. Therefore, proper bonds, bond orders, hybridization and charges were assigned using the MVD. The potential binding sites of both the targets were calculated using the built-in cavity detection algorithm implemented in MVD. (13-14)

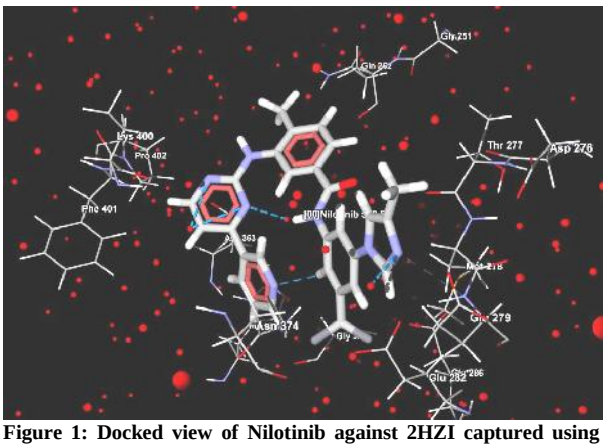


**Figure 1: Docked view of Nilotinib against 2HZI captured using Ligand Energy Inspector tool in MVD**

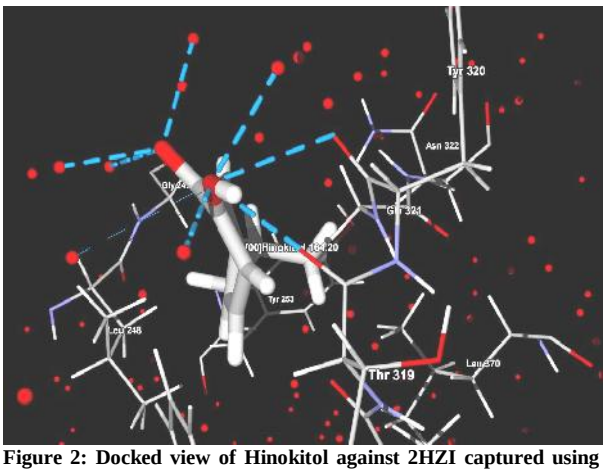


**Figure 2: Docked view of Hinokitol against 2HZI captured using Ligand Energy Inspector tool in MVD**

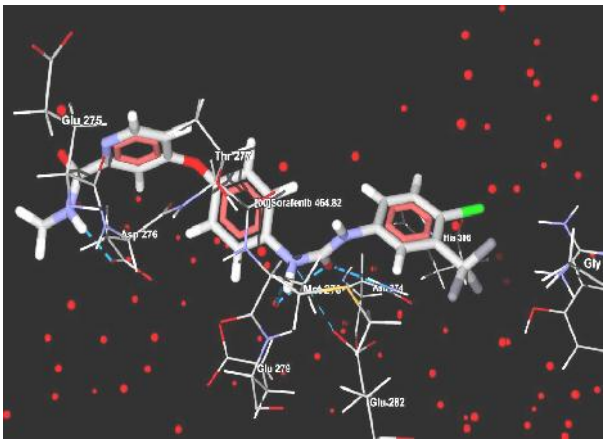


**Figure 3: Docked view of Sorafenib against 2HZI captured using Ligand Energy Inspector tool in MVD**

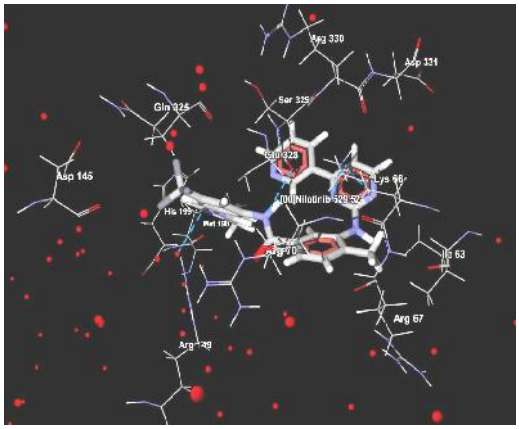


**Figure 4: Docked view of Nilotinib against 3LFF captured using Ligand Energy Inspector tool in MVD**

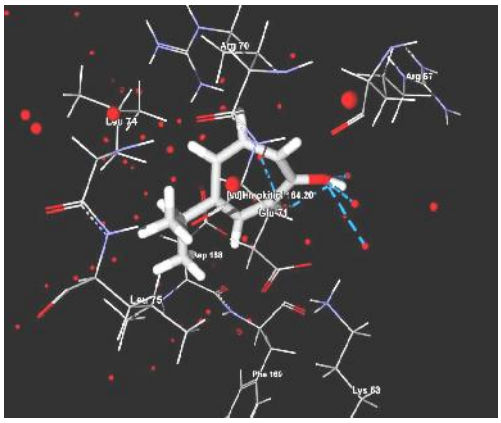


**Figure 5: Docked view of Hinokitol against 3LFF captured using Ligand Energy Inspector tool in MVD**

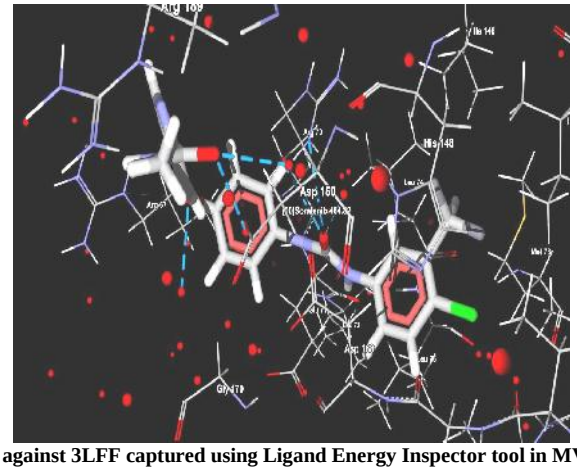


**Figure 6: Docked view of Sorafenib against 3LFF captured using Ligand Energy Inspector tool in MVD**

**Table 1.Energy overview of Nilotinib**

| Descriptors | Value | MolDock Score | Rerank Weight | Rerank Score |
|---|---|---|---|---|
| Total Energy | | -83.813 | | -55.980 |
| External Ligand interactions | | -99.148 | | -74.310 |
| Protein - Ligand interactions | | -88.319 | | -63.612 |
| Steric (by PLP) | -87.948 | -87.948 | 0.686 | -60.332 |
| Steric (by LJ12-6) | -5.601 | | 0.533 | -2.986 |
| Hydrogen bonds | -0.371 | -0.371 | 0.792 | -0.294 |
| Hydrogen bonds (no directionality) | -1.253 | | | 0.000 |
| Electrostatic (short range) | 0.000 | 0.000 | 0.892 | 0.000 |
| Electrostatic (long range) | 0.000 | 0.000 | 0.156 | 0.000 |
| Cofactor – Ligand | | 0.000 | 0.602 | 0.000 |
| Steric (by PLP) | 0.000 | 0.000 | | |
| Steric (by LJ12-6) | 0.000 | | | 0.000 |
| Hydrogen bonds | 0.000 | 0.000 | | 0.000 |
| Electrostatic | 0.000 | 0.000 | | 0.000 |
| Water - Ligand interactions | -10.828 | -10.828 | 0.988 | -10.698 |
| Internal Ligand interactions | | 15.335 | | 18.330 |
| Torsional strain | 2.994 | 2.994 | 0.938 | 2.809 |
| Torsional strain (sp2-sp2) | 0.000 | | 0.636 | 0.000 |
| Hydrogen bonds | 0.000 | | | 0.000 |
| Steric (by PLP) | 12.340 | 12.340 | 0.172 | 2.123 |
| Steric (by LJ12-6) | 96.394 | | 0.139 | 13.399 |
| Electrostatic | 0.000 | 0.000 | 0.437 | 0.000 |
| Soft Constraint Penalty | 0.000 | 0.000 | | |
| Search Space Penalty | 0.000 | 0.000 | | |

**Table 2.Energy overview of Sorafenib**

| Descriptors | Value | MolDock Score | Rerank Weight | Rerank Score |
|---|---|---|---|---|
| Total Energy | | -97.446 | | -86.584 |
| External Ligand interactions | | -113.682 | | -99.179 |
| Protein - Ligand interactions | | -92.922 | | -78.668 |
| Steric (by PLP) | -86.911 | -86.911 | 0.686 | -59.621 |
| Steric (by LJ12-6) | -26.804 | | 0.533 | -14.286 |
| Hydrogen bonds | -6.010 | -6.010 | 0.792 | -4.760 |
| Hydrogen bonds (no directionality) | -7.087 | | | 0.000 |
| Electrostatic (short range) | 0.000 | 0.000 | 0.892 | 0.000 |
| Electrostatic (long range) | 0.000 | 0.000 | 0.156 | 0.000 |
| Cofactor – Ligand | | 0.000 | 0.602 | 0.000 |
| Steric (by PLP) | 0.000 | 0.000 | | |
| Steric (by LJ12-6) | 0.000 | | | 0.000 |
| Hydrogen bonds | 0.000 | 0.000 | | 0.000 |
| Electrostatic | 0.000 | 0.000 | | 0.000 |
| Water - Ligand interactions | -20.760 | -20.760 | 0.988 | -20.511 |
| Internal Ligand interactions | | 16.235 | | 12.594 |
| Torsional strain | 1.665 | 1.665 | 0.938 | 1.562 |
| Torsional strain (sp2-sp2) | 0.000 | | 0.636 | 0.000 |
| Hydrogen bonds | 0.000 | | | 0.000 |
| Steric (by PLP) | 14.570 | 14.570 | 0.172 | 2.506 |
| Steric (by LJ12-6) | 61.342 | | 0.139 | 8.527 |
| Electrostatic | 0.000 | 0.000 | 0.437 | 0.000 |
| Soft Constraint Penalty | 0.000 | 0.000 | | |
| Search Space Penalty | 0.000 | 0.000 | | |

**Table 3. Energy overview of Hinokitiol**

| Descriptors | Value | MolDock Score | Rerank Weight | Rerank Score |
|---|---|---|---|---|
| Total Energy | | -86.527 | | -78.055 |
| External Ligand interactions | | -93.113 | | -82.072 |
| Protein - Ligand interactions | | -63.543 | | -52.857 |
| Steric (by PLP) | -58.620 | -58.620 | 0.686 | -40.213 |
| Steric (by LJ12-6) | -16.406 | | 0.533 | -8.744 |
| Hydrogen bonds | -4.923 | -4.923 | 0.792 | -3.899 |
| Hydrogen bonds (no directionality) | -4.923 | | | 0.000 |
| Electrostatic (short range) | 0.000 | 0.000 | 0.892 | 0.000 |
| Electrostatic (long range) | 0.000 | 0.000 | 0.156 | 0.000 |
| Cofactor – Ligand | | 0.000 | 0.602 | 0.000 |
| Steric (by PLP) | 0.000 | 0.000 | | |
| Steric (by LJ12-6) | 0.000 | | | 0.000 |
| Hydrogen bonds | 0.000 | 0.000 | | 0.000 |
| Electrostatic | 0.000 | 0.000 | | 0.000 |
| Water - Ligand interactions | -29.570 | -29.570 | 0.988 | -29.215 |
| Internal Ligand interactions | | 6.586 | | 4.017 |
| Torsional strain | 0.909 | 0.909 | 0.938 | 0.853 |
| Torsional strain (sp2-sp2) | 0.000 | | 0.636 | 0.000 |
| Hydrogen bonds | 0.000 | | | 0.000 |
| Steric (by PLP) | 5.677 | 5.677 | 0.172 | 0.976 |
| Steric (by LJ12-6) | 15.740 | | 0.139 | 2.188 |
| Electrostatic | 0.000 | 0.000 | 0.437 | 0.000 |
| Soft Constraint Penalty | 0.000 | 0.000 | | |
| Search Space Penalty | 0.000 | 0.000 | | |

**Table 4: In-silico docking analysis of Nilotinib, Sorafenib and Hinokitiol on Proto-oncogene tyrosine-protein kinase ABL1 (PDB ID: 2HZI) ranking based on MolDock Score**

| Name | Ligand | MolDock Score | Rerank Score | HBond |
|---|---|---|---|---|
| [00]Nilotinib | Nilotinib | -108.452 | -80.7526 | -0.371473 |
| [01]Nilotinib | Nilotinib | -105.619 | -85.4432 | -2.5 |
| [00]Sorafenib | Sorafenib | -97.4472 | -86.8339 | -6.01035 |
| [01]Sorafenib | Sorafenib | -93.4136 | -83.4473 | -3.41271 |
| [00]Hinokitiol | Hinokitiol | -84.103 | -76.4898 | -2.5 |
| [01]Hinokitiol | Hinokitiol | -77.1306 | -71.0033 | 0 |

**Table 5: In-silico docking analysis of Nilotinib, Sorafenib and Hinokitiol on Mitogen-activated protein kinase 14 (PDB ID: 3LFF) ranking based on MolDock Score**

| Name | Ligand | MolDock Score | Rerank Score | HBond |
|---|---|---|---|---|
| [00]Sorafenib | Sorafenib | -123.578 | -104.715 | -0.824235 |
| [00]Nilotinib | Nilotinib | -111.088 | -82.5973 | -8.56917 |
| [01]Sorafenib | Sorafenib | -108.344 | -79.6338 | 0 |
| [01]Nilotinib | Nilotinib | -105.295 | -81.79 | -3.59979 |
| [00]Hinokitiol | Hinokitiol | -86.4157 | -77.0637 | 0 |
| [01]Hinokitiol | Hinokitiol | -72.9071 | -64.7239 | 0 |

**Table 6.Based upon lipin rule**

| s.no | Compound | Hydrogen bond donor | Hydrogen bond acceptor | Molecular mass |
|---|---|---|---|---|
| 1. | Hinokitiol | 1 | 2 | 164.201 |
| 2. | Sorafenib | **3** | **4** | 464.825 |
| 3. | Nilotinib | **2** | **6** | 529.516 |

## RESULTS AND DISCUSSION

Hepatocellular carcinoma treatment with new improved drugs is a high priority to addressing the global problem of resistance to existing anticancer drugs. The current study highlights the importance of analogue-based designing approaches in modelling anti-cancer compounds.(15-18)

The ability of the chemical constituents to bind with the targets is given in terms of MolDock Score, Rerank score and Hydrogen bond binding Energy. The poses are ranked according to their MolDock Score, Rerank score and Hydrogen bond binding Energy.

In-silico docking analysis of Nilotinib, Sorafenib and Hinokitiol on Proto-oncogene tyrosine-protein kinase ABL1 (PDB ID: 2HZI) (19) ranking based on MolDock Score is represented in table 4. Rerank score of Nilotinib, Sorafenib and Hinokitiol are -80.7526, -86.8339 and -76.4898, respectively and the Mol Dock score of Nilotinib, Sorafenib and Hinokitiol are -108.452, -97.4472 and -84.103, respectively against ABL1.

In-silico docking analysis of Nilotinib, Sorafenib and Hinokitiol on Mitogen-activated protein kinase 14 (PDB ID: 3LFF) (20) ranking based on MolDock Score is represented in table 5. Rerank score of Nilotinib, Sorafenib and Hinokitiol are -104.715, -82.5973 and -77.0637 respectively and the Mol Dock score of Nilotinib, Sorafenib and Hinokitiol are 123.578, -111.088, -and -86.4157, respectively against MAPK.

Based on the Mol Dock score, rerank score and lipin rule hinokitiol shows best results against the hepatocellular carcinoma and hinokitiol is the most recent potent drug target for hepatocellular carcinoma.According to literature survey till now no one didn't reported that the hinokitiol docking with ABL1 and MAPK for liver cancer.This study may be the subject for further experimental validation and clinical trial to establish the hinokitiol derivatives or analogues as more potent drug for the treatment of liver cancer.

## CONCLUSION:

The Protein-Ligand interaction plays a significant role in structural based drug designing. Analysis of these docking brought in focus on some important interactions operating at the molecular level. The seven-membered ring plays a vital role in holding the molecule at place (binding) of the active site. These studies are expected to provide useful insights into the roles of various substitution patterns on the hinikitiol derivative and also help to design more potent compounds. In the present work we have docked hinokitiol with ABL 1 and MAPK and compared with the standard drugs that were used against liver Cancer. From this we can conclude that some of the modified natural drugs are better than the commercial drugs available in the market. In future research work the ADME/T (Absorption, Distribution, Metabolism, Excretion / Toxicity) properties of hinokitiol derivatives can be calculated using the commercial ADME/T tools available thus reducing the time and cost in drug discovery process and go for further experimental validation and clinical trial to establish the hinokitiol derivatives or analogues as more potent drug for the treatment of liver cancer.

## ACKNOWLEDGEMENT:

The authors are thankful to Vels University (VISTAS) and its management for providing research facilities, financial support and encouragement.

## REFERENCES:

1. Surh YJ. Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer. 2003;3:768–780.
2. Jemal A, Bray F, Center M.M. Global cancer statistics. CA Cancer Clin J, 2011; 61: 69-90.
3. Thanasekaran Jayakumar, Wen-Hsien Hsu, Ting-Lin Yen, Jun-Yun Luo,Yu-Cheng Kuo, Tsorng-Harn Fong, and Joen-Rong Sheu. Hinokitiol, a Natural Tropolone Derivative, Offers Neuroprotection from Thromboembolic Stroke in Vivo. Evidence based complementary and alternative medicine. volume 2013; article ID 840487.

4. Jong Yuh Cherng, Li Yin Chen, and Mei Fen Shih. Preventive effects of β-thujaplicin against UVB-induced MMP-1 and MMP-3 mRNA expressions in skin fibroblasts. The American Journal of Chinese Medicine 2012, 40(2): pages 387-398.
5. Computational Biology and Drug Discovery: From single – network a Drugs, Current Bioinformatics, 2006; volume 1, pages 3-13.
6. Anil M Manikrao, Pravin N Khatale, Rahul D Jawarkar, JVV yas, DT Mahajan, Vijay H Masans, Taibi ben hadda. Presuming the Probable Anti-inflammatory Mechanism of Urosolic Acid:a plant derived pentacyclic triterpenoid, using molecular docking. Journal of Computational Methods in Molecular Design 2011;1(2):9-13.
7. National Center for Biotechnology Information. PubChem Compound Database; CID=3611, https://pubchem.ncbi.nlm.nih.gov/compound/3611 (accessed Sept. 15, 2015).
8. National Center for Biotechnology Information. PubChem Compound Database; CID=644241, https://pubchem.ncbi.nlm.nih.gov/compound/644241 (accessed Sept. 15, 2015).
9. National Center for Biotechnology Information. PubChem Compound Database; CID=216239, https://pubchem.ncbi.nlm.nih.gov/compound/216239 (accessed Sept. 15, 2015).
10. Cowan-Jacob, Sandra W., et al. "Structural biology contributions to the discovery of drugs to treat chronic myelogenous leukaemia." Acta Crystallographica Section D: Biological Crystallography 63.1 (2007): 80-93. (PDB ID: 2HIZ)
11. Getlik, Matthäus, et al. "Structure-based design, synthesis and biological evaluation of N-pyrazole, N′-thiazole urea inhibitors of MAP kinase p38α." European journal of medicinal chemistry 48 (2012): 1-15. (PDB ID: 3LFF)
12. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, Gautam B, Hassanali M. Nucleic Acids Res. 2008 Jan;36 (Database issue):D901-6. PMID: 18048412
13. F.C.Bernstein, T.F.Koetzle, G.J.Williams, E.E.Meyer Jr., M.D.Brice, J.R.Rodgers, O.Kennard, T.Shimanouchi, M.Tasumi, "The Protein Data Bank: A Computer-based Archival File For Macromolecular Structures," J. of. Mol. Biol., 112 (1977): 535. http://www.rcsb.org/pdb/.
14. Thomsen R, Christensen MH: MolDock: A new technique for high-accuracy docking. J Med Chem 2006, 49:3315-3321. http://dx.doi.org/10.1021/jm051197e
15. Gehlhaar DK, Verkhivker G, Rejto PA, Fogel DB, Fogel LJ, Freer ST: Docking conformationally flexible small molecules into a protein binding site through evolutionary programming. In Proceedings of the Fourth International Conference on Evolutionary Programming: 1-3 March 1995; San Diego Edited by: John R McDonnell, Robert G Reynolds, David B Fogel. MIT Press; 1995:615-627.
16. Gehlhaar DK, Bouzida D, Rejto PA, Eds: Fully automated and rapid flexible docking of inhibitors covalently bound to serine proteases. In Proceedings of the Seventh International Conference on Evolutionary Programming: 25-27 March 1998; San Diego Edited by: William Porto V, Saravanan N, Donald E Waagen, Eiben AE. Springer; 1998:449-461.
17. Yang JM, Chen CC. Gemdock: A generic evolutionary method for molecular docking. Proteins 2004, 55:288-304.
18. Wei-Min Chen, 3D-QSAR and Molecular Docking Studies on Fused Pyrazoles as p38α Mitogen-Activated Protein Kinase Inhibitors, Ping Lan, Zhi-Jian Huang, Jun-Rong Sun, International Journal of Molecular Sciences , 2010, *11*, 3357-3374.
19. Kesavan Sabitha, Nilotinib based pharmacophore models for BCRABL Bioinformation. 2012; 8(14). 658-663.
20. Amany Belal, Dareen A. Jaiash,Mohamed A. Abdelgawad and Khaled R.A. Abdellatif. Design, Synthesis And Biological Evaluation Of New Pyrroloazepines With Potential And Selective Antitumor Activity, Acta Poloniae Pharmaceutica, 2016,Vol. 73 No 2. Pages 359-368.