



<https://ijrps.com>

ISSN: 0975-7538

Research Article

Comparison of molecular docking and molecular dynamics simulations of 1H-benzo[d]imidazole with TGF- β type I protein

Ajay Kumar T.V¹, Kabilan S², Parthasarathy V^{1*}

¹Immunology Laboratory, Annamalai University, Annamalai Nagar-608002, Tamil Nadu, India

²Drug Discovery Laboratory, Annamalai University, Annamalai Nagar-608002, Tamil Nadu, India

ABSTRACT

TGF- β type I protein is an interesting and significant molecule in the cancer progression. The altered ratios of the TGF- β type I receptor leads to oncogenic functions from its tumor suppressor activity. The present study was carried out to develop the suitable inhibitors for the treatment of cancer by targeting TGF- β type I receptor. Hence, 1H-benzoimidazole ((R)-1-(1H-benzo[d]imidazol-1-yl)-3-(cyclohexyl methoxy) propan-2-ol) molecule was screened by 3D QSAR study using "PHASE" module of Schrodinger to inhibit TGF- β type I protein and the molecular dynamics simulations of the complexes of TGF- β type I was also carried out. This study identified the binding modes of the inhibitors and the lead compound which showed an interaction with His283 of TGF- β type I and the results was similar to that of docking study. The result is crucial for inhibiting TGF- β type I receptor. The compound which was identified is a good initiation for further *in vitro* studies to develop drug molecule to treat cancer.

Keywords: Dynamics; His283; TGF- β ; TGF- β type I; 1H-benzo[d]imidazole; 3D QSAR; PHASE; Schrodinger.

INTRODUCTION

Transforming Growth Factor (TGF) is playing pivotal role in cancer progression and the members of mammalian TGF- β are namely, TGF- β 1, TGF- β 2 and TGF- β 3 (Kingsley, 1994). The TGF- β is the member of a large family of cytokines which plays a significant role in cellular differentiation, proliferation, and state of activation of various cell types including immune cells. In addition to these, TGF- β also induces the formation of a heteromeric transmembrane serine/threonine kinase receptor complex to activate their biological process. The intracellular signaling of the receptors occurs through the activation of Smad proteins and specific Smads gets phosphorylated with the association of other Smad proteins (Dennler, 2002). The antiproliferative effects of the TGF- β gets inhibited due to the inactivation or the impairment in the expressions associated signaling pathway of TGF- β type I and II will lead to the co-operation for the formation of cancer cells (De, 2000). Considering all these facts, targeting the TGF- β type I receptor as the drug target will create a protection in the TGF- β signaling pathway to treat cancer.

The derivatives of benzimidazole, a class of nitrogen containing heterocyclic compounds associated with an extensive range of therapeutic activity such as, antihis-

tamine (Wang, 2012), anticancer (Sharma, 2013), antibacterial (Jardosh, 2013), antifungal (Kucukbaya, 2003), anti-inflammatory as well as antioxidant (Kus, 2008), antianalgesic (Arora, 2014), antiulcer (Jain, 2007) and so on. The broad antitumor properties associated with benzimidazole showed continuing interest in the treatment of cancer (Patel, 2011).

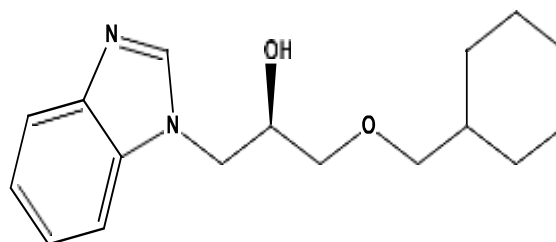


Figure 1: The structure of (R)-1-(1H-benzo[d]imidazol-1-yl)-3-(cyclohexyl methoxy) propan-2-ol used for the molecular dynamics simulation.

Hence, the present study explored the opportunity to target TGF- β type I with benzo[d]imidazole based anti-cancer compounds. Through *in silico* approach the drug design led to the development of novel 1H-benzoimidazole derivatives. The molecular dynamic simulation study of the docked complex of the ligand and the protein were carried out using "Desmond" module of Schrodinger to identify the protein ligand interactions. From the results of the above study, the ligand molecule been considered for further experimental analysis.

* Corresponding Author
Email: vapartha@yahoo.com
Contact: +91-9443512724
Received on: 18-10-2016
Revised on: 24-11-2016
Accepted on: 28-11-2016

MATERIALS AND METHODS

Molecular docking

The crystal structure of TGF- β type I receptor (PDB: ID: 1VJY) with a resolution factor of 2 Å was retrieved from Protein data bank (www.rcsb.org) (Gellibert, 2004). The biological units as well as assigned bond orders, zero-order bonds to metals, disulfide bonds were created and the missing hydrogens were added to retrieve protein using the "Protein preparation wizard" module of Schrodinger suite Ver. 2015.4 (Sastry, 2013). Then the protein was minimized by using the OPLS-2005 force field by setting the pH range at 7.0. The minimization was kept under control until the root mean square deviation (RMSD) average of the non-hydrogen atoms gets closer to 0.30 Å. The grid generation was made using the "Glide receptor grid generation" module to represent the shape and properties of the receptor at the active site in accurate scoring for the ligand poses.

Ligand preparation

The 2D structure of ((R)-1-(1H-benzo[d]imidazol-1-yl)-3-(cyclohexyl methoxy) propan-2-ol) was drawn using the ChemDraw tool (Nancy, 2006) and saved in .mol format (Figure. 1). The ligand was prepared using the LigPrep Ver.3.6 module of Schrodinger suite 2015.4. The ligand was minimized using the parameter OPLS-2005 force field and further allowed to generate its maximum conformers (Schrödinger Lig Prep, 2015).

Ligand docking

Grid-based Ligand Docking with Energetics (GLIDE) Ver. 6.9 (Small -Molecule, 2015) module of Schrodinger software was used for docking studies using the force field OPLS-2005. Glide program used a grid based technique for the ligand docking and it searches for the favorable interactions between small molecule or ligands and the receptor protein. The protein was kept fixed and the ligand was keeping flexible during the docking. The prepared ligand docked into the active site of the TGF- β type I protein using the 'extra precision' (XP) Glide algorithm (Balachandran, 2016).

Molecular dynamic simulation

Desmond Ver.4.4 (Schrödinger Desmond, 2015) module was utilized to study the thermodynamic stability of the protein-ligand arrangement. The water model TIP3P (Jorgensen, 1998) was used to simulate the water molecules using the force field OPLS2005. The boundary regions were set using the orthorhombic periodic boundary conditions, which specify the shape and size of the repeating unit buffered at 10 Å distances. In order to neutralize the system electrically, an appropriate sodium ions were added to balance the system charge and placed randomly in the solvated system. After the protein and ligand complex in the solvated system was completed it was further minimized using the protocol of Desmond module using

force field OPLS 2005. Molecular dynamic simulations were carried out with the periodic boundary conditions in the NPT (Rodrigo, 2015) by keeping the temperature and pressure at 300 K and one atmospheric pressure using Nose-Hoover temperature coupling with isotropic scaling (Puneet, 2014). The long ranges of electrostatic interactions were analyzed using "Particle Mesh Ewald" method (Essmann, 1995; Athavan, 2015).

RESULTS AND DISCUSSION

Molecular docking

The binding affinity of the compound to TGF- β type I was analyzed using the molecular study. The 4 conformers of 1H-benzoimidazole generated by the LigPrep were docked into the active site of the protein (PDB: ID: 1VJY) (Figure. 2) and the Glide XP docking score for the protein with the ligand "1H-benzoimidazole" indicates that the ligands exhibited a high binding affinity with specific residues of TGF- β type I protein (Table 1). The Glide score of the 4 conformers in the ascending order are:- 10.37, -10.26, -6.59 and -6.25 kcal/mol. The compound with low Glide score i.e -10.37 was considered as a best conformer. The Glide energy values are: 38.51, 35.31, 36.44 and 36.95 kcal/mol respectively. The evdw and eoul were also calculated to find out the Vander Waals force as well as electrostatic interactions and their corresponding values are: 32.83, 28.91, 31.68 and 32.71 and 5.6, 6.4, 4.7 and 4.2 respectively.

The ligand and the protein demonstrated the hydrogen bond interaction with the amino acid residues His283 and Ser280 respectively. The interaction also showed hydrophobic interaction with the amino acid residues Tyr282, Leu340, Leu260, Ala230, Tyr249, Leu278, Phe262, Val279, val231, Ala350, val219 and Ile211 respectively. The 2D and 3D ligand interaction with the protein TGF- β type I diagram is shown in Figure. 3.

Molecular dynamic simulations

The docked complex of ligand 1H-benzo[d]imidazole and the protein "TGF- β type I" were imported using Desmond module. The orthorhombic box with TIP3P as a water solvent model was chosen and simulated using the OPLS force field. The simulations were kept under balanced condition for 5 nano seconds using the Desmond module. The solvent water model with the prepared complex of ligand-protein is shown in Figure. 4 and the quality analysis of the molecular dynamic simulations is given in Table 2.

The root mean square deviation (RMSD) plot in Figure. 5 represents that how stable the ligand is interacted with the protein and its binding pocket. In addition to these, it also indicates that the 1H-benzo[d]imidazole derivative compounds and the TGF- β type I complex reached its stable form at 2 nano seconds (ns) and continues its stability up to 4 ns. Further chances of the complex may reach its stability after 5ns. Moreover, the interactions of the residues of molecular dynamic

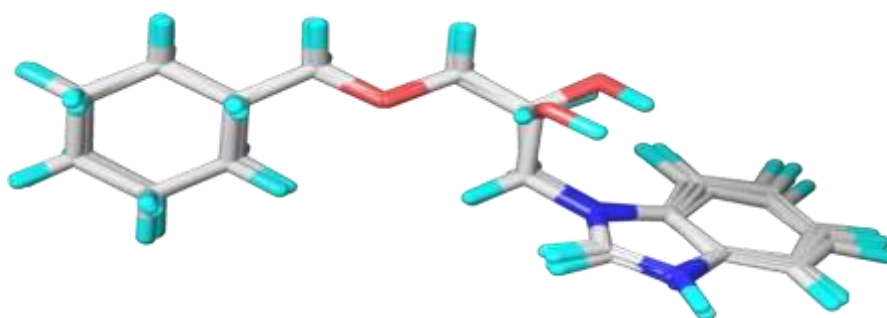


Figure 2: The four conformers of the ligand 1H-benzimidazole derivative generated using the "LigPrep" module of Schrodinger.

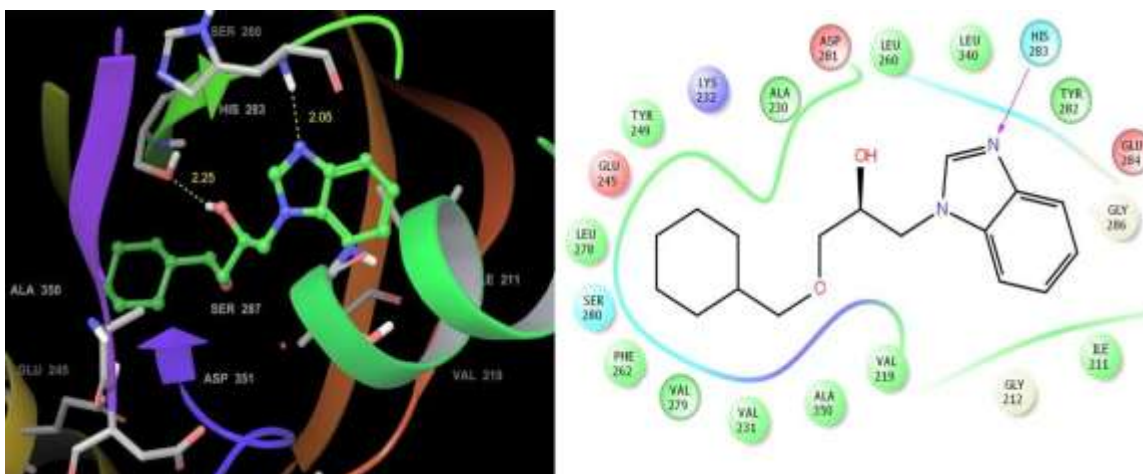


Figure 3: The 3D and 2D interaction poses from the molecular docking of 1H-benzimidazole derivative with the target protein "TGF-β type I".

Table 1: The molecular docking results of 4 conformers of 1H-benzimidazole derivatives with the protein "TGF-β type I". Where, evdw denotes "Vander Waals force of interaction energies"; ecoul represents "Coulomb interaction energies".

1H-benzimidazole derivative	Glide score	Glide evdw	Glide ecoul	Glide energy (kcal/mol)
Conformer 1	10.37	32.83	5.6	38.51
Conformer 2	10.26	28.91	6.4	35.31
Conformer 3	6.59	31.68	4.7	36.44
Conformer 4	6.25	32.71	4.2	36.95

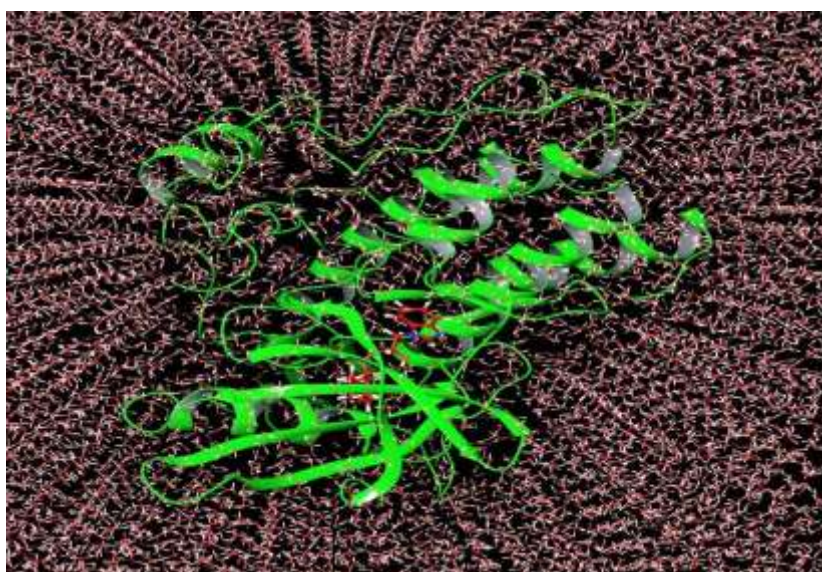


Figure 4: Prepared solvent system with the ligand-protein complex for the molecular dynamic simulations.

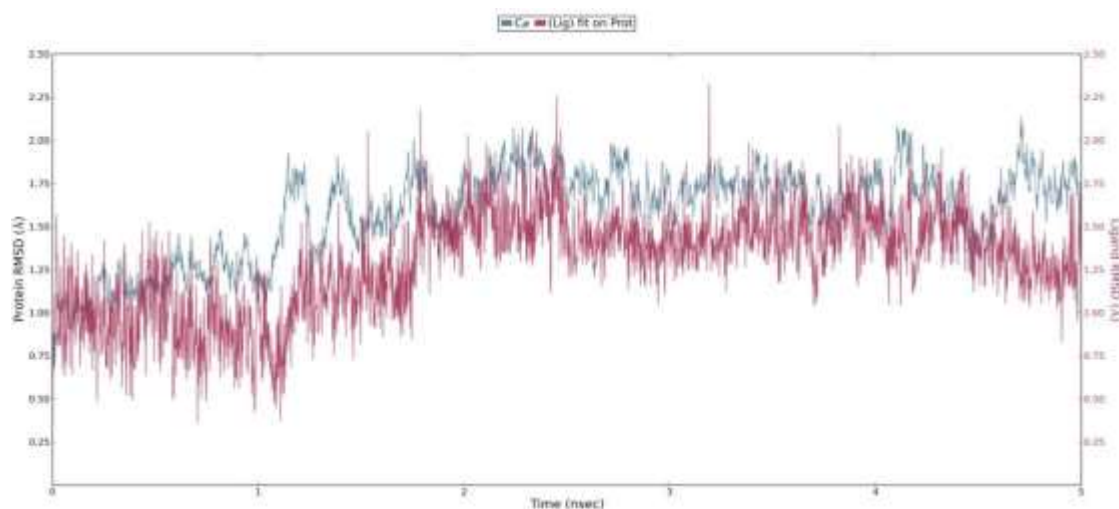


Figure 5: The root mean square deviation plot of 1H-benzoimidazole and TGF- β type I protein complex.

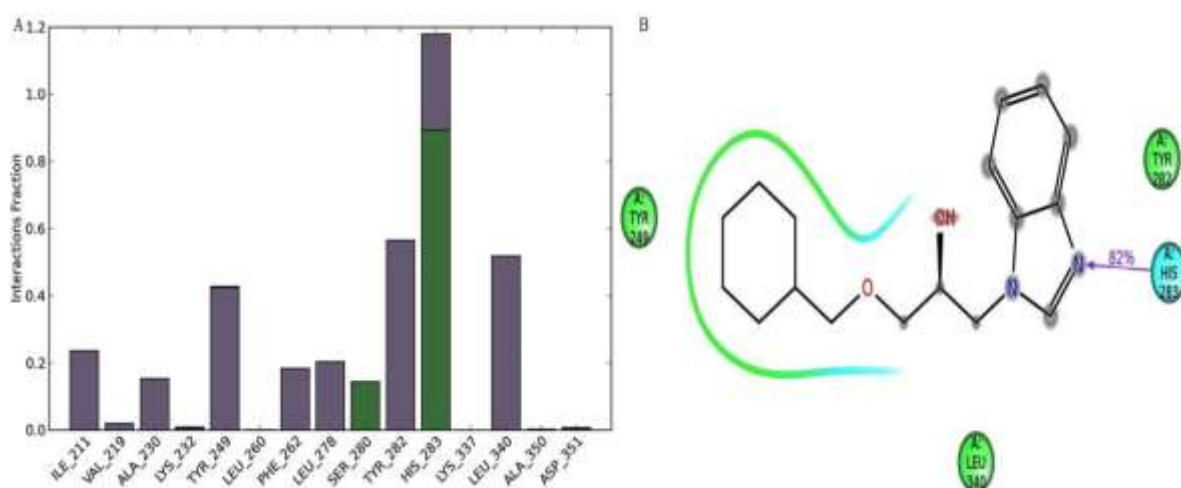


Figure 6: The histogram of fraction of interactions (A) and the 2D interaction diagram predicted using Desmond module for their molecular dynamic simulations (B).

Table 2: The quality analysis set up for the molecular dynamic simulations after equilibrium.

S.No	Properties	Statistical parameters
1	Simulation period	4. 99
2	Degrees of freedom	71813. 000
3	Number of atoms	34662. 000
4	Average total energy (kcal/mol)	96711. 284
5	Average potential energy (kcal/mol)	18494. 239
6	Pressure (bar)	0. 005
7	Volume (\AA^3)	47299. 32
8	Temperature (K)	298. 61

simulations were similar to that of the docking results. The nitrogen atom of 1H-benzo[d]imidazole ring interacted with the amino acid His283 through hydrogen bond to an extent of 82%. It indicates that the ligand showed a lead interaction with His283 by hydrogen bonding, which is necessary for the inhibitory activity of ligand against TGF- β Type I protein (Gellibert *et al.*, 2004; Fang *et al.*, 2013). The 2D interaction poses and the histogram chart of ligand interaction with the protein "TGF- β type I" is shown in Figure. 6. The 2D interaction of the simulation studies showed the hydrophobic interaction with the amino acid residues such as, Tyr249, Leu340 and Tyr282.

CONCLUSION

The molecule 1H-benzoimidazole derivative ((R)-1-(1H-benzo[d]imidazol-1-yl)-3-(cyclohexyl methoxy) propan-2-ol) were obtained from the screening protocol based on the 3D-QSAR study by targeting cancer marker protein TGF- β type I. The molecule was further studied for the comparative analysis using molecular docking and dynamics simulations with the protein "TGF- β type I" (PDB ID: 1VJY). The likely interactions of the amino acid residues with the ligand were predicted, analyzed and compared. The study reports that the significant hydrogen bond interaction achieved to an

extent of 82% with residue His283 and the same result was observed mutually in molecular docking as well as molecular dynamics simulations studies. The outcome of the study is encouraging to carry forward.

REFERENCES

- Arora, RK, Kaur, N, Bansal, Y, Bansal, G, 2014. Novel coumarin benzimidazole derivatives as antioxidants and safer antiinflammatory agents. *Acta Pharm. Sin.*, 4(5), 368- 375.
- Athavan, AAS, Loganathan, C, Saravanan, K, Kabilan S, 2016. Comparison of Molecular Docking and Molecular Dynamics Simulations of 1, 3-thiazin-4-one with MDM2 Protein. *International Letters of Chemistry, Physics and Astronomy*, 60, 161-167.
- Balachandran, P, Ajay Kumar TV, Parthasarathy V, 2016. Screening of potential anticancer compounds from *Sargassum wightii* to target breast Cancer specific HER2 receptor using in-silico analysis. *The natural products journal*, 6(2), 108-115.
- De Caestecker, MP, Piek, E, Roberts, AB, 2000. Role of transforming growth factor-beta signaling in cancer. *Journal National Cancer Inst.* 2000, 92(17):1388-402.
- Dennler, S, Goumans, MJ, Ten Dijke, P, 2002. Transforming growth factor beta signal transduction. *Journal Leukoc Biol.*, 71(5), 731-740.
- Essmann, U, Perera, L, Berkowitz, ML, Darden, T, Lee, H, Pedersen, LG, 1995. Smooth particles mesh Ewald method. *Journal Chem. Phys.* 103(1995), 8577-8859.
- Fang, Y, Chen, Y, Yu, L, Zheng, C, Qi, Y, Li, Z, Yang, Z, Zhang, Y, Shi, T, Luo, J, Liu, M, 2013. Inhibition of breast cancer metastases by a novel inhibitor of TGF- β Receptor 1. *Journal National Cancer Inst.* 105(1), 47-58.
- Gellibert, F, Woolven, J, Fouchet, MH, Mathews, N, Goodland, H, Lovegrove, V, Laroze, A, Nguyen, VL, Sautet, S, Wang, R, Janson, C, Smith, W, Krysa, G, Boullay, V, De Gouville, AC, Huet, S, Hartley, D, 2004. Identification of 1,5-Naphthyridine derivatives as a Novel Series of Potent and Selective TGF-beta Type I Receptor Inhibitors. *J.Med.Chem.* 47, 4494-4506.
- Jain, KS, Shah, AK, Bariwal, J, Shelke, SM, Kale, AP, Jagtap, JR, Bhosale, AV, 2007. Recent advances in proton pump inhibitors and management of acid-peptic disorders. *Bioorg. Med. Chem.*, 15, 1181-1205.
- Jardosh, HH, Sangani, CB, Patel, MP, Patel, RG, 2013. One step synthesis of pyrido(1,2) a benzimidazole derivatives of aryloxy pyrazole and their antimicrobial evaluation. *Chin. Chem. Lett.*, 24, 123-126.
- Jorgensen, WL, Jenson, C, 1998. Temperature dependence of TIP3P, SPC, and TIP4P water from NPT Monte Carlo simulations: Seeking temperatures of maximum density. *Journal Comput. Chem.*, 19, 1179-1186.
- Kingsley, DM, 1994. The TGF β superfamily: new members, new receptors & new genetic tests of function in different organisms. *Gen. Dev*, 8(2), 133-146.
- Kucukbaya, H, Durmaz, R, Okyucu, N, Günald, S, 2003. Antifungal activity of some bis-5-methylbenzimidazole compounds. *Folia Microbiol (praha)*, 48(5), 679-681.
- Kus, C, Kilcigil, GA, Ozbey, S, Kaynak, FB, Kaya, M, Coban, T, Can-Eke, B, 2008. Synthesis and antioxidant properties of novel N-methyl-1, 3, 4- thiadiazol-2-amine and 4-methyl-2H-1, 2, 4-triazole- 3(4H)-thione derivatives of benzimidazole class. *Bioorg. Med. Chem.*, 16, 4294-4303.
- Nancy, M, 2006. ChemDraw Ultra 10.0 CambridgeSoft, 100 CambridgePark Drive, Cambridge, MA 02140. *Journal American Chemical Society*, 128 (41), 13649-13650.
- Patel, K, Karthikeyan, C, Solomon, VR, Narayana, NSH, Lee, H, Sahu, K, Deora, DS, Trivedi, P, 2011. Synthesis of some coumarinyl chalcones and their antiproliferative activity against breast cancer cell lines. *Letters in Drug Design Discovery*, 8, 308-311.
- Puneet, KP, Baidurya, B, 2014. Nonergodicity of the Nose-Hoover chain thermostat in computationally achievable time. *Phys. Rev*, 90(4), 043304.
- Rodrigo, GM, Daniel, RR, Thomas, EC, 2015. Convergence and reproducibility in molecular dynamics simulations of the DNA duplex d (GCACGAACGAACGAACGC). *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1850(5), 1041-1058.
- Sastry, GM, Adzhigirey, M, Day, T, Annabhimoju, R, Sherman, W, 2013. Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments. *Journal of Computer-Aided Molecular Design*, 27, 221-234.
- Schrödinger Release 2015-4: Desmond Molecular Dynamics System, version 4.4, D. E. Shaw Research, New York, NY, 2015. Maestro-Desmond Interoperability Tools, version 4.4, Schrödinger, New York, NY, 2015.
- Schrödinger Release 2015-4: LigPrep, version 3.6, Schrödinger, LLC, New York, NY, 2015.
- Sharma, A, Luxami, V, Paul, K, 2013. Synthesis, single crystal and antitumor activities of benzimidazole-quinazoline hybrids. *Bioorg. Med. Chem. Lett.*, 23, 3288-3294.
- Small-Molecule Drug Discovery Suite 2015-4: Glide, version 6.9, Schrödinger, LLC, New York, NY, 2015.
- Wang, XJ, Xi, MY, Fu, JH, Zhang, FU, Cheng, GF, Yin, DL, You, QD, 2012. Synthesis, biological evaluation and SAR studies of benzimidazole derivatives as H1 - antihistamine agents. *Chin. Chem. Lett*, 23, 707-710.