IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Investigation of Antidiabetic Agents Through Molecular Dynamics and Simulation

Durgesh Kumari*, Garima Gupta, Swati Tyagi, Ranjeet Singh, Piyush Chahal

Department of Pharmacy, Monad University, Delhi Hapur Road (NH-9), Pilkhuwa, Uttar Pradesh-245304, India

ABSTRACT

Diabetes affects the routine of life, due to its potential complications such as nephropathy, neuropathy, retinopathy and stroke etc. Scientists increasingly use molecular docking for drug discovery because it provides more accurate data, helping to understand target sites, understanding and action of various enzymes, protein interactions, and selecting the best molecule from an array etc. it is a computational method for analyzing large collections of biological data which involves the interlinkage of two or more molecules to give the stable adduct. Depending upon binding properties of molecules and target site. The entire process takes place in a three-dimensional way.

Keywords: Diabetes, molecular docking, accurate data, target sites, stable adduct.

INTRODUCTION:

Diabetes is a disease in which metabolism of carbohydrates affected due to less/no synthesis of insulin in beta-cell which results in excess glucose level within the circulatory system. According to a project report of The World Health Organization approximately more than 700 million people will be suffering from diabetes by 2030. Diabetes patients spreading around the world, but is more common in developed countries (Shaw et al. 2010). Diabetes is a major cause of blindness, renal failure, cardiopulmonary arrest, stroke and amputation of the lower limbs. In modern drug discovery, molecular docking is an interesting scaffold to better-known drug size, shape, charge distribution, polarity, hydrogen bonding, and biomolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule into the preferred binding site of the target-specific region of the receptor (DNA/protein) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity via hydrophobic and or hydrogen bonding interactions (Shaw et al. 2010, Rohs et al. 2005). The data obtained from the docking technique can be used to suggest the binding energy, free energy and stability of drug-

receptor complexes. Now, the docking technique is utilized to predict the tentative drug molecule and receptor complex binding parameters beforehand. Over the last 20 years, more than 65 docking tools and programs have been invented for both academic and commercial use with improved, yielding accurate results on pose prediction such as FlexX (Rarey et al. 1996), GOLD (Jones et al. 1997), Auto-Dock (Osterberg et al. 2002), Surflex (Jain 2003), ICM (Schapira et al. 2003), Ligand-Fit (Venkatachalam et al. 2003), MC-Dock, FRED (McGann et al. 2003), Glide (Friesner et al. 2004), Auto-Dock Vina (Trott and Olson 2010), MOE-Dock (Corbeil et al. 2012), LeDock (Zhao and Caflisch 2013), rDock (Ruiz-Carmona et al. 2014), UCSF Dock (Allen et al. 2015), and many more. These software and tools greatly help in the investigation of molecules derived from synthetic as well as natural sources.

Yalamanchili et al., 2020 investigated more than twenty reported compounds from Goji were docked into both partial- and full-agonist binding sites of Peroxisome proliferator-activated receptor gamma. 24 tyramine-derivatives and three naturally occurring amides (Dihydro-N-caffeoyltyramine, trans-N-caffeoyltyramine, trans-N-feruloyloctopamine) were synthesized and screened for Peroxisome proliferator-activated receptor gamma gene induction with the cell-based assay. Three compounds showed similar or higher fold induction than the positive control, rosiglitazone. Animal studies were also performed on trans-N-feruloyloctopamine and *Lycium chinense* (21%) tyramine derivatives-enriched root bark extract. But both did not show significant antidiabetic properties in animals, due to(Lycium species) tyramine derivatives alone. The docking studies of compounds, phenylethylamide-based phytochemicals (Lyciumamide A, Dihydro-N-caffeoyltyramine, cis-N-caffeoyltyramine, trans-N-caffeoyltyramine, trans-N-feruloyloctopamine) (tyramine-derivatives) showed good docking scores and binding affinity with good interactions(Fig. 1).

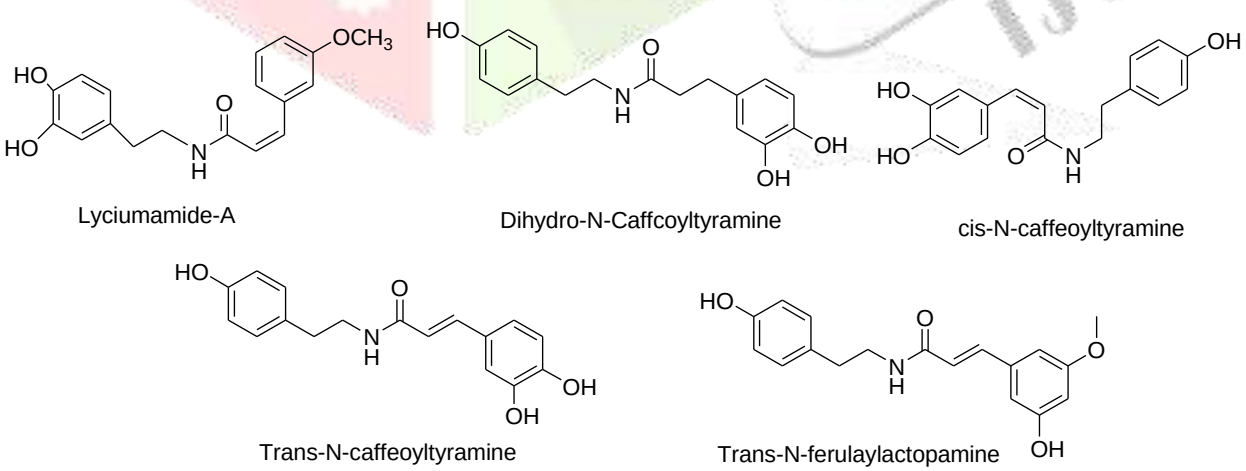
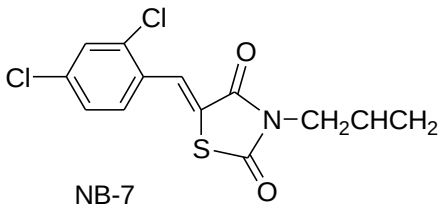


Fig. 1

Srivastava et al., 2019 synthesized a series of thirteen novel 2,4-thiazolidinedione derivatives viz. three step reaction procedure. Characterization of the synthesized novel compounds were done through IR, ^{1}H NMR, ^{13}C NMR, Mass, & elemental analysis. All the compounds were evaluated for *in vivo* anti diabetic, *in vivo* anti-

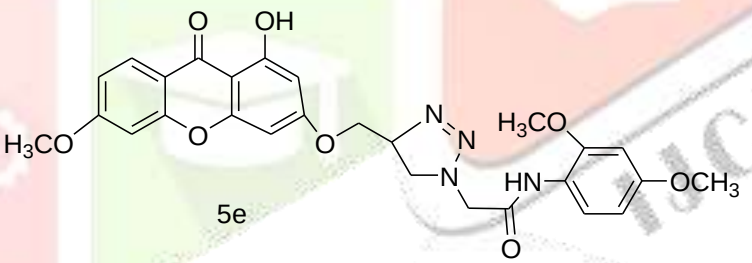
inflammatory and *in vitro* antioxidant activities. For the investigation of some possible structural insights into the potential binding patterns molecular docking was performed with most potent anti-diabetic molecules i.e. NB7,NB12 and NB13 against target PPARγ active sites using Molecular Operating Environment software. Compound NB-7 (Fig. 2) has shown great potential (0.0001 kcal/mol) in the present study. The novel derivative (NB-7**)** has grater antidiabetic activity with excellent anti-inflammatory and antioxidant activity.



NB-7

Fig. 2

Ye et al., 2019 designed and synthesized a series of novel xanthone-triazole derivatives and investigated for their *α* -glucosidase inhibitory activities and glucose uptake in HepG2 cells. Most of the compounds showed good ic_{50} values than the parental compound towards *α* -glucosidase. These compounds bind to allosteric sites away from the active site according to molecular docking i.e. Asp214, Glu276 and Asp349. The glucose uptake assays reveal that Compound 5e (Fig. 3) was the most potent inhibitor (2.06 mM. IC_{50}) 6a, 6c and 7g also have potential to promoting the glucose uptake.



5e

Fig. 3

Rammohan et al., 2019 in their current study, amino chalcones were synthesized and hydroxy chalcones were isolated from the natural source such as *Sophora interrupta*, *Clerodendrum phlomidis* and *Andrographis macrobotrys*. Structural elucidation was carried through ^{1}H, ^{13}C-NMR and Mass Spectroscopy. Animal studies reveals that compounds 3c, 3a and 3h (Fig. 5) have good antidiabetic efficacy compared with control animals. Aldose reductase, dipeptidyl peptidase, Peroxisome proliferator-activated receptor, and glucosidase were monitored during docking studies, which accomplishes that the compounds 3c, 3i, 3a and 3e (Fig. 4) have an strong binding affinity with aldose-reductase. Bioavailability of these compound was determined with the Lipinski rule of five and the design pharmacokinetic as well as pharmacodynamic properties are reliable. Therefore, chalcones were implied as antidiabetic leads for further studies and could be worthwhile for the development of new classes of effective antidiabetic agents.

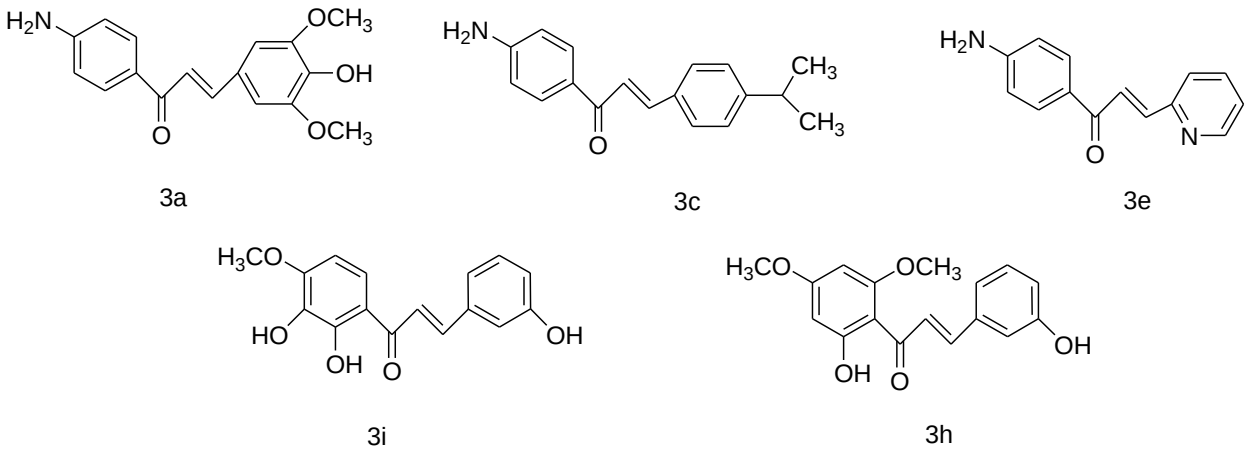


Fig. 4

Naim et al., 2018 designed and synthesized a series of novel 2,4-thiazolidinedione derivatives containing benzene sulphonyl moiety and were docked against the PPARγ target. Compounds 7b, 7d, & 7p shows significant antidiabetic potency but compound 7p exhibited most potent antidiabetic activity with 1.9 folds and increased in PPARγ gene expression due to naphthalene moiety compared with standard pioglitazone and rosiglitazone. molecular docking studies also reveled that 7p (Fig. 5) showed excellent interactions with amino acids TYR 473, SER 289, HIE 449, TYR 327, ARG 288, MET 329 and LEU 228 and did not cause hepatic injury.

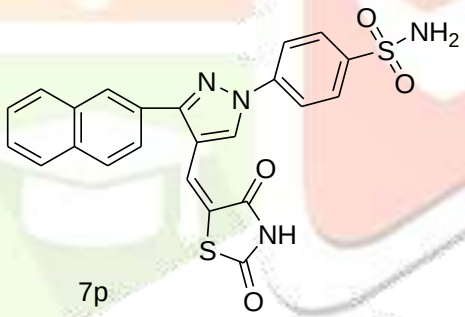
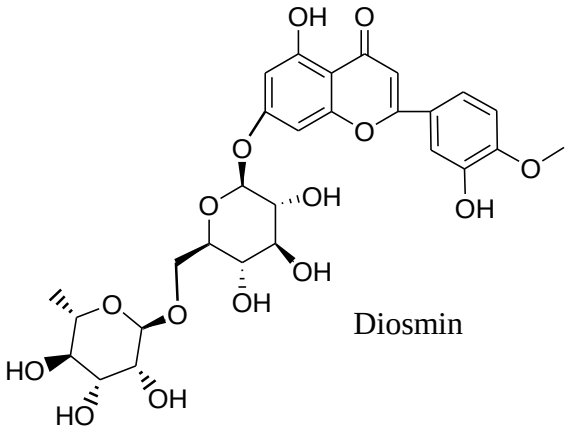
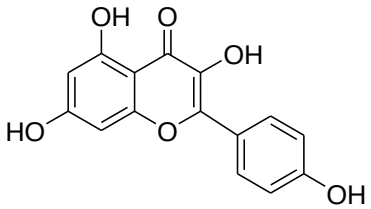


Fig.5

Tharmatt et al., 2018 reviewed, important phytoconstituents reported for antidiabetic activities. Among them, some of the phytoconstituents were selected for prediction of activity through (PASS) online software. Pa and Pi value was predicted for these phytoconstituents on different antidiabetic target sites. On the bases of PASS prediction, 5 phytoconstituents were selected for molecular docking study using AutoDock Vina 4.0. The three target sites i.e. glucagon-like peptide-1, α glucosidase, and dipeptidyl peptidase-4 were selected for prediction of probable affinities of selected phytoconstituents. In all selected phytoconstituents, diosmin showed best binding affinity with dipeptidyl peptidase-4, glucagon-like peptide-1, and α glucosidase that was −10.2 kcal/mol, −8.3 kcal/mol, and −9.7kcal/mol, followed by kaempferol (Fig. 6). The present study can be utilized for designing advanced antidiabetic studies for these phytoconstituents.



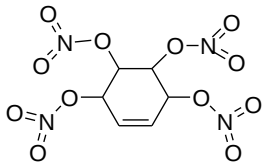
Diosmin



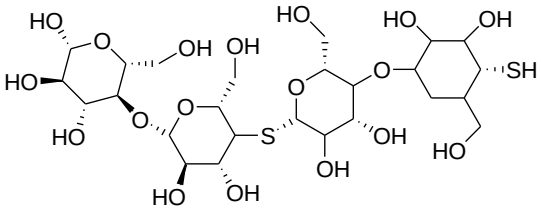
Kaempferol

Fig. 6

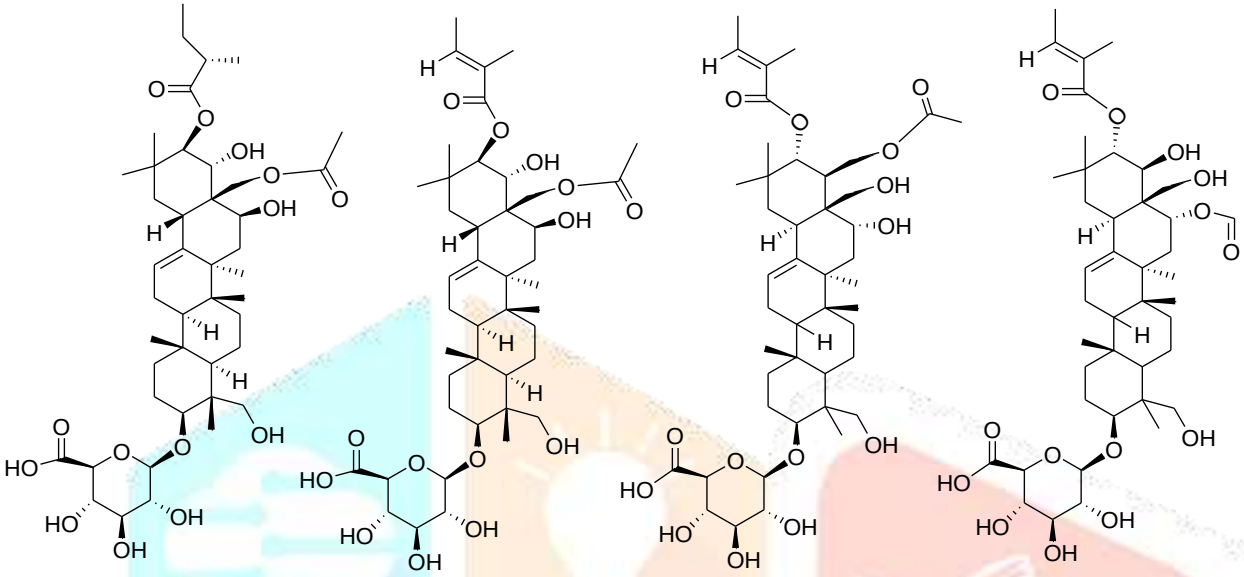
Salimullah et al., 2016 in their present study 10 bioactive small compounds derived from *Gymnema sylvestre* were chosen to determine their IR binding affinity and ADMET properties using a combined approach of molecular docking study and computational pharmacokinetic elucidation. Designing structural analogues were also performed for the compounds associated with toxicity and less IR affinity. Among the ten parent compounds, Conduritol E tetranitro, GS4, Gymnemic acid I, Gymnemic acid II, Gymnemoside A, and Gymnemoside B (Fig. 7) were found to have significant pharmacokinetic properties with a considerable binding affinity towards IR while four compounds were associated with toxicity and less IR affinity. Among the forty structural analogues, four compounds demonstrated considerably increased binding affinity towards IR and less toxicity compared with parent compounds. Finally, molecular interaction analysis revealed that six parent compounds and four analogues interact with the active site amino acids of IR. So the present study would be a way to identify new therapeutics and substituents to insulin for diabetic patients.



Condeuitol E tetranitro



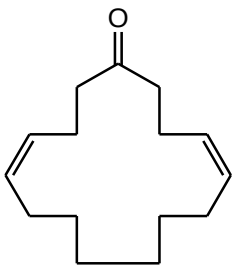
GS4



Gymnemic acid II Gymnemic acid I Gymnemoside A Gymnemoside B

Fig. 7

Sugumar et al., 2015 in their molecular docking study of ligand (4Z,12Z)-cyclopentadeca-4, 12-dienone (Fig. 8) extracted from the leaves of *G.Hirsuta* on Glycogen Synthase Kinase 3β which revealed that the oxygen atom of the compound forms hydrogen bonding with LYS-85. Strong hydrophobic interaction was observed around the Cyclopentanone ring near the ALA-83, CYS-199, PHE-67, LEU-132, LEU-188, VAL-110, and VAL-135. Polar interactions also occur with amino acids such as Asn 186 and Thr 138. It had binding energy of −6.01 and Gliding energy to be −28.72 respectively.



(4Z,12Z)-cyclopentadeca-4,12-dienone

Fig. 8

Antony et al., 2015 in their research investigated the inhibitory effects of phytochemicals present in dietary spices such as *Zingiber Officinale*, *Curcuma longa*, *Allium sativum*, and *Trigonella foenum-graecum* on aldose reductase. Molecular docking was performed on phytochemicals Gingerenones A, B and C, lariciresinol, quercetin, and calebin-A in order to determine protein-ligand interactions. All selected phytochemicals from these spices exhibited high docking scores, binding affinity and sustained protein-ligand interactions. Molecular docking revealed that natural compounds such as gingerenone-A, gingerenone-B, gingerenone-C, quercetin, lariciresinol and calebin-A (Fig. 9) from spices exhibited much better binding score and binding energy than commercially available drugs.

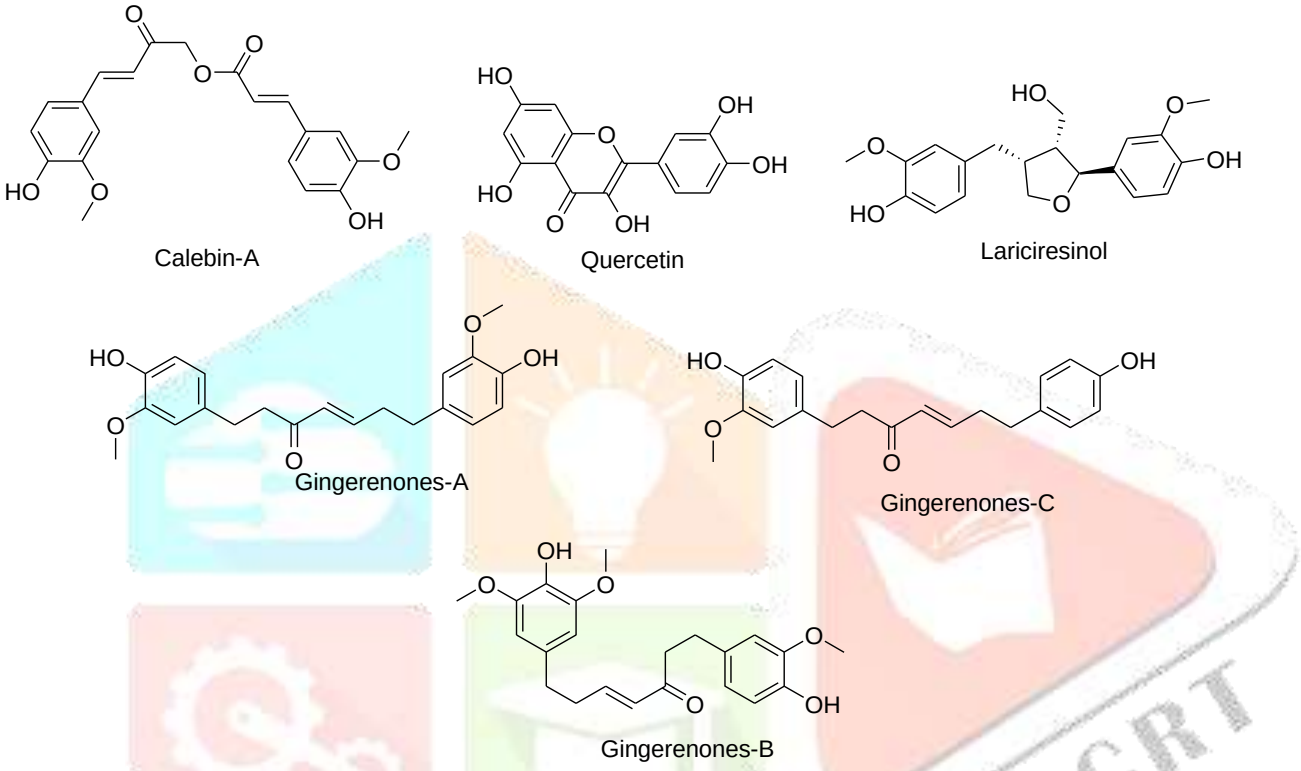


Fig. 9

Dhananjayan et al., 2014 studied molecular docking on anthraquinone derivatives for inhibition of Glycogen synthase kinase-3β. The ligands that were used for docking such as Aesculin, Aesculetin, Anthragallol, Damnacanthal, Lucidin, Morindone, Nordamnacanthal and Rubiadin(Fig.10). Among the ligands, Damnacanthal was found to possess the lowest binding energy -7.23kcal/mol, with an estimated inhibition constant of 4.98uM and Nordamnacanthal, showed lowest binding energy of -6.94 kcal/mol with double the value of estimated inhibition constant (8.25 µM). Anthragallol and Morindone have similar binding energy values (-6.68kcal/mol) and estimated inhibition constant (12.7 µM) but their conformations at the active site was found to be different. Rubiadin and Lucidin have a slight deviation in binding energy at the active site but similar inhibition constant. Aesculetin and Aesculin has binding energy and inhibition constant to be -5.42,-5.99 kcal/mol and 105.78, 40.57 µM respectively. The amino acids involved in binding with the ligands were Asn64, Ser66, Lys85, Val135, Thr138, Lys183, Asp200, and Phe201. The results revealed that the selective anthraquinone derivatives docks well and thus inhibits the activity of Glycogen synthase kinase-3β.

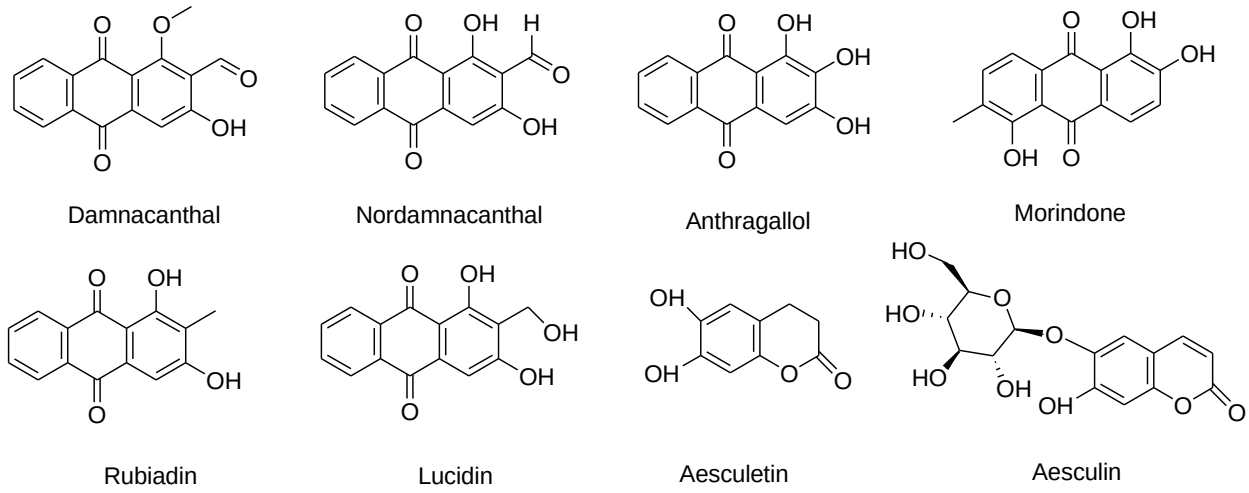


Fig.10

Rashid et al., 2013 Molecular docking of antidiabetic compounds were studied with human proteins (pdb id: 3Q6E) to evaluate the most active antidiabetic drug for high inhibitory activity. More than 50 selected compounds were screened with the active site of protein 3Q6E and the most active lead compound S21 (Fig. 11)was identified on the basis of strong binding interaction with the target protein and IC50 value from the selected compounds. The 3 types of interactions i.e. Hydrogen bonding, hydrophobic and ionic interactions were calculated with the help of Visual molecular dynamics. For the enhancement of activity 4 analogues of the lead compound(Fig. 8) were also designed and docked with protein 3Q6E by using Auto Dock Vina and all interactions showed that they could be used as antidiabetic agents and therefore could be recommended for further studies.

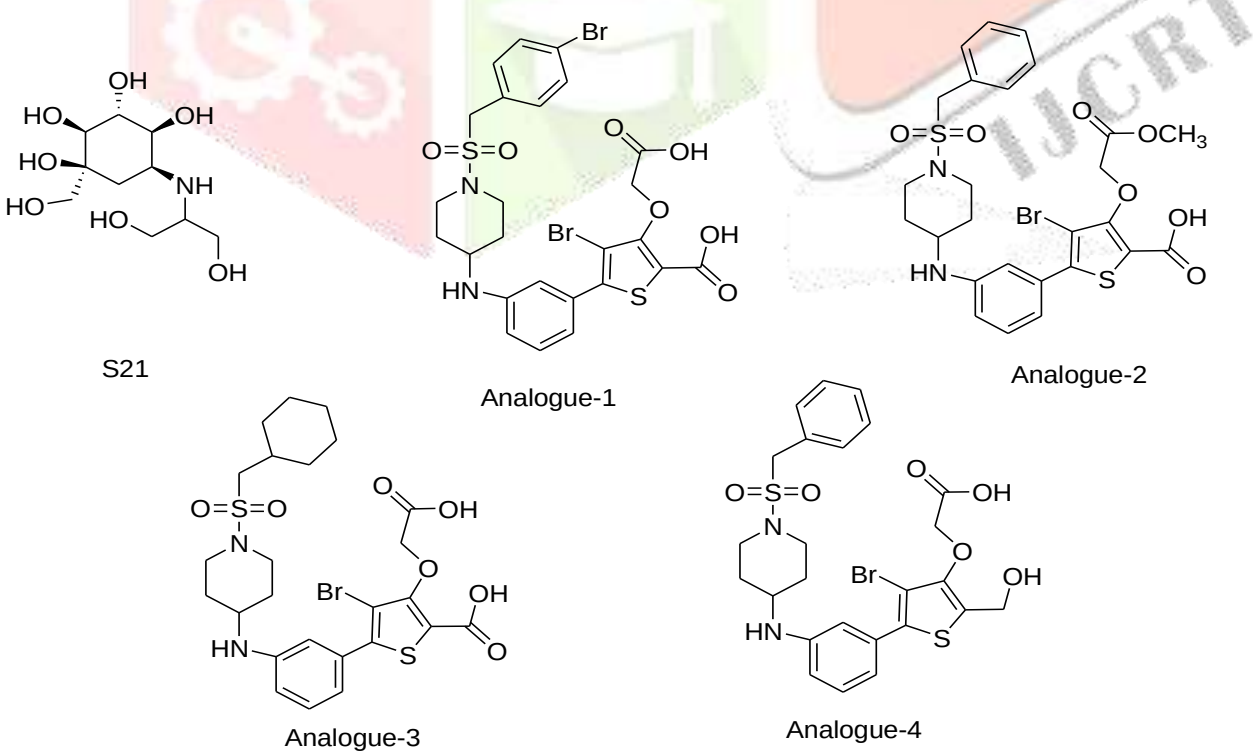
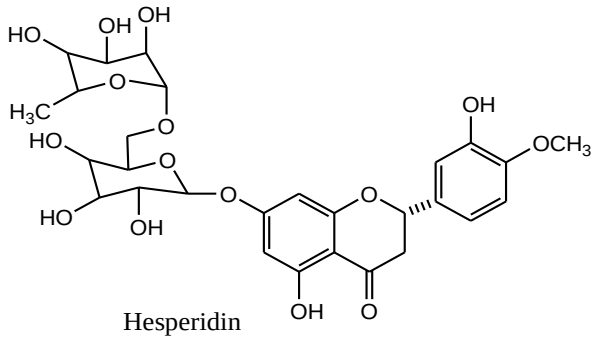


Fig. 11

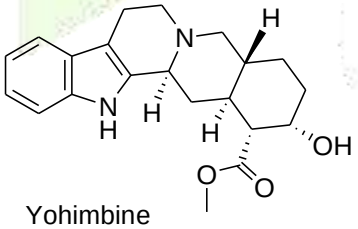
Shen et al., 2013 studied hindering the activity of Citrus flavonoids phytochemicals such as hesperidin, naringin, neohesperidin, nobiletin. with the molecular target Glycogen synthase kinase-3β. More OH functional groups in Hesperidin, neohesperidin structures promote the formation of H-bonds between ligands and protein residues. The docking studies of the four ligands with the target showed that citrus flavonoids are potent inhibitors that dock well with the protein targets related to diabetes mellitus and thus impedes its activity. Citrus flavonoids thus play a key role in blood glucose regulation, by triggering Peroxisome proliferator-activated receptor-γ, and impeding Glycogen synthase kinase-3β. The more negative binding energy revealed that Hesperidin(Fig. 12) has good hindering activity towards Glycogen synthase kinase-3β.



Hesperidin

Fig. 12

Akila et al., 2012 in their Present study screening of phytoconstituents present in *Peperomiapellucida* was done by using *in silico* approach, in order to determine the powerful phytoconstituent having antidiabetic potential. Docking analysis results clearly indicated that Yohimbine (Fig. 13) has a binding energy of -10.08cal/mol possessing excellent anti-diabetic activity compared to the standard Quercetin binding energy -9.62Kcal/mol.



Yohimbine

Fig. 13

Akhtar et al., 2012 three-dimensional inhibition studies of Glycogen synthase kinase-3β was performed by involving a novel class of 3-anilino-4-arylmaleimide derivatives. It was achieved by three mechanisms such as Adenosine triphosphate non-competitive, Adenosine triphosphate competitive and metal ion competitive. In order to develop models that understand the biological activity of derivatives. They recognized the quantitative structure-activity relationship, comparative molecular similarity index analysis and comparative molecular field

analysis models for GSK-3 inhibitors. The studies revealed the strong H-bonding interactions of the ligand with amino acid residues Val 135, Asp 133, Arg 141, and Gln185 of GSK-3. Modification in structure 49 with carboxylic moiety dd1-dd7 (Fig. 14) showed the specific interlinkage with Arg-141 which would favor greater inhibition of Glycogen synthase kinase-3β.

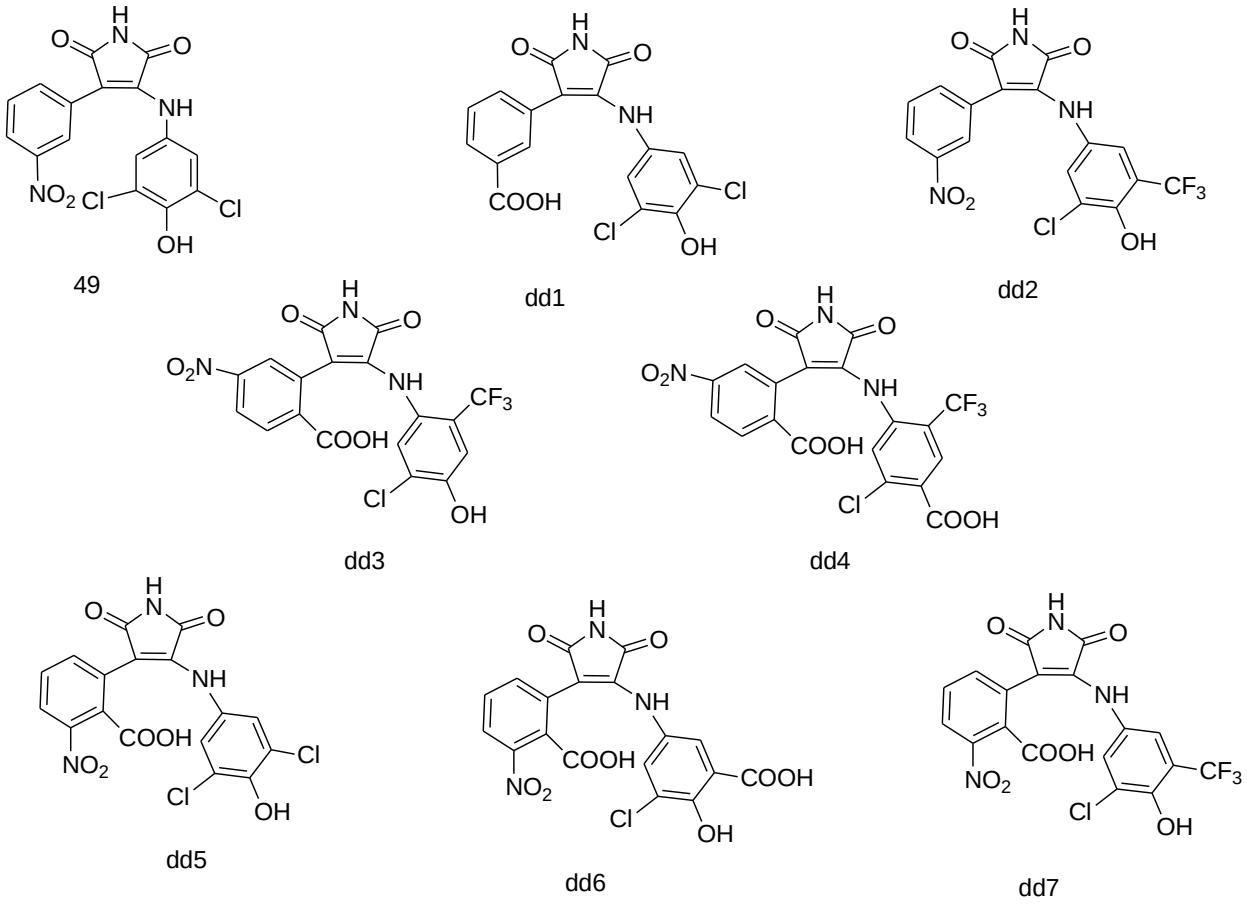
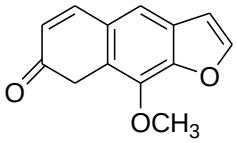


Fig. 14

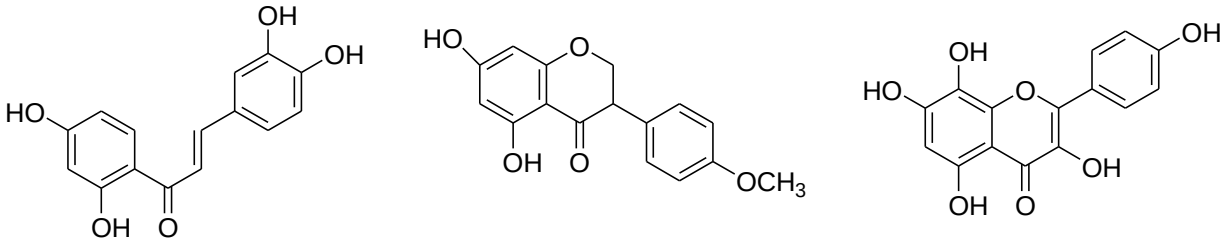
Umamaheswari et al; 2012 studied the inhibitory effect of flavonoids such as Farobin-A, Glaziovianin-A, GericudraninB, Rutin, and Xanthotoxin through molecular docking. The docking results of the standard drug (Eparestat) showed binding energy -5.59 kcal/mol and all selected flavonoids showed binding energy in the range between -7.91 to 5.08 kcal/mol. The active binding sites of the Xanthotoxin were found to be TRP 20, TYR 48, LYS 77, HIS 110, SER 159, ASN 160, GLN 183, GLU 185, TYR 209, SER 210, PRO 211, SER 214, ILE 260 and CYS 298. The binding sites of the standard was found to have amino acid residues such as GLY 18, THR 19, TRP 20, LYS 21, SER 210, PRO 211, LEU 212, SER 214, ILE 260, PRO 261, LYS 262 and SER 263 as active sites. The Ki value, binding energy and intermolecular potential energy of Xanthotoxin and Eparestat were found to be -7.25kcal/mol and -5.59 kcal/mol, 1.58 µM and 80.08 µM, -7.55 kcal/mol and -5.59 kcal/mol respectively. Finally, it was concluded that only Xanthotoxin (Fig. 15) has effective binding sites and better efficacy in the selected flavonoids as compared with the standard Eparestat.



Xanthotoxin

Fig. 15

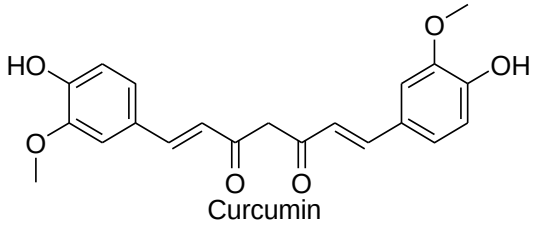
Madeswaran et al., 2012 studied the inhibitory effect of commercially available flavonoids such as biochanin, butein, esculatin, fisetin and herbacetin on aldose reductase. The docking prediction revealed that all the selected flavonoids showed binding energy ranging between -9.33 kcal/mol to -7.23 kcal/mol as compared to standard (Eparestat) (-8.73 kcal/mol). Inhibition constant (144.13 µM to 4.98 µM) and intermolecular energy (-11.42 kcal/mol to -7.83 kcal/mol) of the flavonoids also coincides with the binding energy. Butein, biochanin and herbacetin (Fig. 16) showed excellent binding interactions with aldose reductase enzyme due to the difference in the position of the functional groups in the tested compounds.



Butein Biochanin Herbacetin

Fig. 16

Bustanji et al., 2009 investigated Curcumin as an inhibitor of glycogen synthase kinase-3β and to justify some of its interesting multiple pharmacological properties, such as anti-diabetic, anti-inflammatory, anti-cancer, anti-malarial, and anti-alzheimer's, etc. molecular docking was performed to fit curcumin within the binding pocket of GSK-3β followed by its *in vitro* and *in vivo* validations. Curcumin was found to ideally fit within the binding pocket of GSK-3β via several attractive interactions with key amino acids. Experimentally, curcumin (Fig. 17) was found to be a strong inhibitor of GSK-3β with IC50 = 66.3 nM. Furthermore, their animal study illustrated that curcumin significantly increases hepatic glycogen in fasting animals. Their overall investigation strongly reviled that the pharmacological activities of curcumin are at least partially mediated by inhibition of GSK-3β.



Curcumin

Fig. 17

CONCLUSION:

With the ever-increasing stock of bio-molecular structures, nonstop up-gradation of computational potential, and improved accuracies in modeling the molecular interlinkage at the nano level, it is predicted that computation will play an even more important role in the drug discovery process in the near future. For more Better understandings of the etiology of disorder with the help of systems biology and systems pharmacology also lead to the identification of novel drug target sites and creative combinations of drug target for designing novel drugs more successfully.

REFERENCES :

Akhila S, Aleykutty NA, Manju P, "Docking studies on *Peperomiapellucida* as antidiabetic drug" *IJPPS*, 2012; *4(4)*:76-77.

Akhtar M, Bharatam P, "3D-QSAR and Molecular Docking Studies on 3-Anilino-4-Arylmaleimide Derivatives as Glycogen Synthase Kinase-β inhibitors" *CBDD*, 2012; 79(4):560-71.

Allen WJ, Balius TE, Mukherjee S, Brozell SR, Moustakas DT, Lang PT, Case DA, Kuntz ID, Rizzo RC, "DOCK 6: Impact of New Features and Current Docking Performance" J CC, 2015; 36(15):1132–1156.

Antony P,Vijayan R, "Identification of Novel Aldose Reductase Inhibitors from Spices: A Molecular Docking and Simulation Study" PLOS ONE, 2015; 10(9):1-19.

Bustanji Y, Taha MO, Almasri IM, Al-Ghussein MAS, Mohammad M K, Alkhatib HS, "Inhibition of Glycogen Synthase Kinase by Curcumin: Investigation by Simulated Molecular Docking and Subsequent *In Vitro*/*In Vivo* Evaluation" *JEIMC*, 2009; *24(3)*:771–778.

Corbeil CR, Williams CI, Labute P, "Variability in Docking Success Rates Due to Dataset Preparation" JCAMD, 2012; 26:775–786.

Dhananjayan K, Arunachalam S, Sivanandy P, "Molecular Docking Studies of Anthraquinone Derivatives on the Crystal Structure of Glycogen Synthase Kinase 3 β" *EJB*, 2014; *10(1)*:14-20.

Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, Repasky MP, Knoll EH, Shelley M, Perry JK, Shaw DE, Francis P, Shenkin PS, "Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy" JMC, 2004; 47(7):1739–1749.

Jain AN, "Surflex: Fully Automatic Flexible Molecular Docking Using a Molecular Similarity-Based Search Engine" JMC, 2003; 46(4):499–511.

Jones G, Willett P, Glen RC, Leach AR, Taylor R, "Development and Validation of a Genetic Algorithm for Flexible Docking" JMB, 1997; 267(3):727–748.

Madeswaran A, Umamaheswari M, AsokkumarK, Sivashanmugam T, Subhadradevi V, Jagannath P, "*In Silico* Docking Studies of Aldose Reductase Inhibitory Activity of Commercially Available Flavonoids" *BJP*, 2012; *7(4)*:266-271.

McGann MR, Almond HR, Nicholls A, Grant JA, Brown FK, "Gaussian Docking Functions" Biopolymers, 2003; 68(1):76–90.

Naim MJ, Alam O, Alam MJ, Hassan MQ, Siddiqui N, Naidu VGM, Alam MI, "Design, Synthesis and Molecular Docking of Thiazolidinedione Based Benzene Sulphonamide Derivatives Containing Pyrazole Core as Potential Anti-Diabetic Agents, BC, 2018; 76:98–112.

Osterberg F, Morris GM, Sanner MF, Olson AJ, Goodsell DS, "Automated Docking to Multiple Target Structures: Incorporation of Protein Mobility and Structural Water Heterogeneity in Auto Dock" Proteins, 2002; 46(1):34–40.

Rammohan A, Vijaya Bhaskar B, VenkateswarluN, Gu W, Zyryanov GV, "Design, Synthesis, Docking and Biological Evaluation of Chalcones as Promising Antidiabetic Agents" BC, 2019.

Ranjan Srivastava A, Bhatia R, Chawla P, "Synthesis, biological evaluation and molecular docking studies of novel 3,5-disubstituted 2,4-thiazolidinediones derivatives" BC, 2019; 89: 1-14.

Rarey M, Kramer B, Lengauer T, Klebe G, "A Fast Flexible Docking Method Using an Incremental Construction Algorithm" JMB, 1996; 261(3):470–489.

Rashid H,Bibi S, Kulsoom S, "In Silico Approach for Lead Identification and Optimization Of Antidiabetic Compounds" JPBS, 2013; 7(3):36-46.

Rohs R, Bloch I, Sklenar H, Shakked Z, " Molecular flexibility in ab-initio drug docking to DNA: binding-site and binding-mode transitions in all-atom Monte Carlo simulations" NAR, 2005; 33: 7048-7057.

Ruiz-Carmona, S., Alvarez-Garcia, D., Foloppe, N., Garmendia-Doval, A. B., Juhos, S., Schmidtke, P, "rDock: A Fast, Versatile and Open Source Program for Docking Ligands to Proteins and Nucleic Acids" PLOS-CB, 2014; 10(4).

Salimullah M, Hossain MU, Khan M A, Uz-Zaman SMR, Ali TM, Islam MS, Keya CA, "Treating Diabetes Mellitus: Pharmacophore Based Designing of Potential Drugs from Gymnema sylvestre against Insulin Receptor Protein" BM R I, 2016; 1-14.

Schapira M, Abagyan R, Totrov M, "Nuclear Hormone Receptor Targeted Virtual Screening" JMC, 2003; 46(14):3045–3059.

Shaw JE, Sicree RA, Zimmet PZ, "Global Estimates of the Prevalence of Diabetes for 2010 and 2030" DRCP, 2010; 87: 4–14.

Shen W, Lu YH, "Molecular Docking of Citrus Flavonoids with Some Targets Related to Diabetes" BJP, 2013; 8(2):156-170.

Sugumar S, Natarajan A, Bitragunta S, Balasubramanyan N, "Molecular Docking Studies of (4Z, 12Z)-cyclopentadeca-4, 12-dien-1-one from *Grewiahirsuta* with some targets related to Type 2 Diabetes" *BMC-CAM* , 2015; *15*:73.

Tharmatt A, Das R, Anand A, Mahajan S, Mehta M, Satija S, Sharma N, Khatik GL, Khurana N, "Identification of Molecular Targets of Potential Antidiabetic Drugs Using Prediction of Activity Spectra for Substances and Molecular Docking" IJGP, 2018; (Special issue):1-10.

Trott O, Olson AJ, "Autodock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading" JCC, 2010; 31(2):455–461.

Umamaheswari M, Aji CS, Asokkumar K, Sivashanmugam T, Subhadradevi V, Jagannath P, Madeswaran A, "*In Silico* Docking Studies of Aldose Reductase Inhibitory Activity of Selected Flavonoids" *IJDDR,* 2012; *4(3):*328-334.

Venkatachalam CM, Jiang X, Oldfield T, Waldman M, "LigandFit: A Novel Method for the Shape-Directed Rapid Docking of Ligands to Protein Active Sites" JMGM, 2003; 21(4):289–307.

Yalamanchili C, Chittiboyina AG, Haider S, Vasquez Y, Khan S, do Carmo JM, da Silva AA, Pinkerton M, Hall JE, Walker LA, Khan IA, "In Search for Potential Antidiabetic Compounds from Natural Sources: Docking, Synthesis and Biological Screening of Small Molecules from Lycium Spp. (Goji)" Heliyon, 2020; 6(1).

Ye GJ, Lan T, Huang ZX, Cheng XN, Cai CY, Ding SM, XIe ML, Wang B, "Design and synthesis of Novel Xanthone-Triazole Derivatives as Potential Antidiabetic Agents: α-Glucosidase Inhibition and Glucose Uptake Promotion" EJMC, 2019; 177:362-373.

Zhao H, Caflisch A, "Discovery of ZAP70 Inhibitors by High-Throughput Docking into a Conformation of Its Kinase Domain Generated by Molecular Dynamics" BMCL, 2013; 23(20):5721–5726.