

# *In Silico* Drug designing Of NF- $\kappa$ B Inhibition By Curcumin Analogue “(3-((E-3-(4-METHOXY-2, 6-DIMETHYLPHENYL)ACRYLOYL) BENZENE SULFONIC-ACID)” Through Inhibiting Glycogen Synthase Kinase 3 (GSK-3 ).

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## Abstract

“(3-((E-3-(4-METHOXY- 2, 6-DIMETHYLPHENYL) ACRYLOYL)BENZENESULFONIC ACID, is our new ligand a new molecule, showing potential lead molecule of anti-Inflammation, anti-Diabetes and anti-Cancer. In pharmacophore studies, active site residues are identified as SER 203, LYS 205, ARG 96, ARG180, VAL 214 and in ligand SO<sub>3</sub> is important pharmacophore. Recent reports suggest that glycogen synthase kinase-3 (GSK-3 ) plays a key role in maintaining basal NF-  $\kappa$ B target gene expression and cell survival in pancreatic cancer cell lines. However, the mechanism of the GSK-3 facilitates constitutive NF-  $\kappa$ B signaling in pancreatic cancer regulations are maintained by IKK activity. The Lead molecule Curcumin is believed to be an inhibitor of glycogen synthase kinase-3 (GSK-3 ) in an attempt to explain some of its interesting multiple pharmacological effects, such as its anti-diabetic, anti-inflammatory, anti-cancer, anti-malarial and anti-Alzheimer's properties. The investigation included simulated docking experiments to fit Curcumin analogues within the binding pocket of GSK-3 .

**Keywords:** Curcumin, Glycogen synthase Kinase -3beta, cancer, docking, QSAR

## Introduction

Curcumin was investigated as an inhibitor of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) in an attempt to explain some of its interesting multiple pharmacological effects, such as its anti-diabetic, anti-inflammatory, anti-cancer, anti-malarial and anti-Alzheimer's properties. The investigation included simulated docking experiments to fit Curcumin within the binding pocket of GSK-3 $\beta$  followed by experimental *in-vitro* and *in-vivo* validations. Curcumin was found to optimally fit within the binding pocket of GSK-3 $\beta$  via several attractive interactions with key amino acids. Experimentally, Curcumin was found to potently inhibit

GSK-3 $\beta$  (IC<sub>50</sub> = 66.3 nM). Furthermore, our *in vivo* experiments illustrated that Curcumin significantly increases liver glycogen in fasting Balb/c mice. Our findings strongly suggest that the diverse pharmacological activities of Curcumin are at least partially mediated by inhibition of GSK-3 $\beta$ .

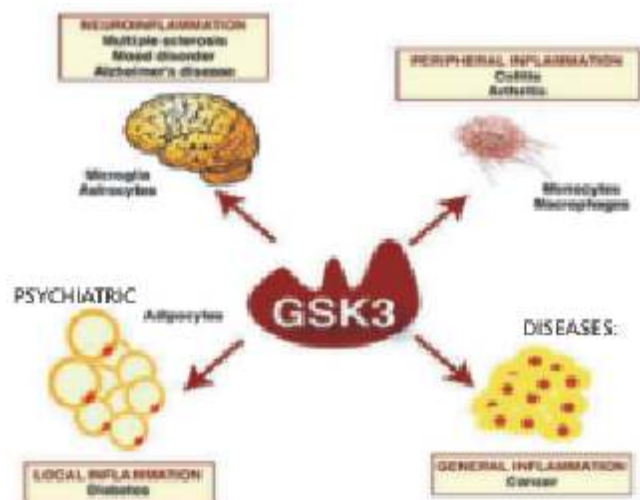
## Diseases Caused:

**Inflammation And Migration:** GSK-3 as a major regulator of peripheral inflammatory responses showed that GSK3 promotes the stimulus-induced production of several cytokines and the subsequent development of disease symptoms in animal models of inflammatory conditions. This role of GSK3 in inflammation was first established by our report that GSK3 activity is necessary for full stimulation of the production of several pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1 , and tumor necrosis factor (TNF), following stimulation of several types of Toll-like receptors in monocytes and peripheral blood mononuclear cells.

The association of glycogen synthase kinase-3 (GSK3) with psychiatric diseases is a relatively new concept, first having been raised only in 1996. At that time, it was discovered that GSK3 is a target of the mood stabilizer lithium, a primary treatment for bipolar mood disorder, an illness also referred to as manic-depression. During the intervening ten years, a wide variety of types of studies have contributed to the hypothesis that inhibition of GSK3 makes an important contribution to mood stabilizing capability.

## Neurodegenerative Diseases:

Abnormal accumulation of A $\beta$  is a critical early stage in AD neuropathology, and several studies have shown that A $\beta$  production is promoted by GSK3 and reduced by GSK3 inhibitors. Nevertheless, the mechanism whereby GSK3 promotes A $\beta$  production remains to be clarified, perhaps is being associated with the reported phosphorylation of the amyloid precursor protein by GSK3 or the binding of GSK3 to



presenilin-1, because GSK3 phosphorylates and regulates the processing of presenilin-1.

### Diabetes:

Glycogen synthase kinase-3 (GSK-3), a serine/threonine kinase, may be a factor contributing to insulin resistance and type II diabetes. The rationale of our hypothesis is based on several lines of evidence. First, GSK-3 is constitutively active in unstimulated cells and is inhibited by insulin, which characteristics suggest a role for this enzyme in suppressing the insulin signal. Second, the enzyme phosphorylates two important targets of insulin action, glycogen synthase (GS) and IRS-1, which results in inhibition of GS and impairment of insulin signaling in intact cells. Finally, studies performed in patients with type II diabetes showed that GS activity was markedly decreased in these subjects.

### Cancer:

In colon cancer cell lines and colorectal cancer patients, levels of GSK3 $\beta$  expression and amounts of its active form were higher in tumor cells than in their normal counterparts; these findings were independent of nuclear accumulation of  $\beta$ -catenin oncoprotein in the tumor cells. Inhibition of GSK3 activity by phosphorylation was defective in colorectal cancers but preserved in non-neoplastic cells and tissues. Our findings demonstrate an unrecognized role of GSK-3 in tumor cell survival and proliferation other than its predicted role as a tumor suppressor, and warrant proposing this kinase as a potential therapeutic target in colorectal cancer.

#### Mechanism of GSK-3 in NF- $\kappa$ B:

Nuclear factor- $\kappa$ B (NF- $\kappa$ B) prevents hepatocytes from undergoing apoptosis during development and liver regeneration. Mice with inactivated glycogen synthase kinase (GSK)-3 die from hepatocyte apoptosis during development due to a defect in NF- $\kappa$ B activation.

Numerous factors contribute to progression of this disease, including constitutively active NF- $\kappa$ B, which has been shown to positively influence cancer cell survival, proliferation, invasion, metastasis and chemoresistance. Recently, the cytoplasmic serine/threonine protein kinase glycogen synthase kinase-3 (GSK-3) was found to regulate NF- $\kappa$ B activation and the proliferation and survival of pancreatic cancer cells. Additionally, the study reveals that the p65 subunit of NF- $\kappa$ B is a

direct target of GSK-3 kinase activity and that an NF- $\kappa$ B-dependent gene reporter response is consequently affected by these modifications. The function of GSK-3 in signaling mechanisms activates NF- $\kappa$ B as well as the resulting effects on NF- $\kappa$ B-mediated gene expression. This is further complicated by reports that fail to acknowledge the distinction between  $\beta$ -catenin-mediated effects on NF- $\kappa$ B and direct regulation of this transcription factor via two GSK-3 isoforms.

Here, we are analyzing about the role of GSK-3 in control of NF- $\kappa$ B activation and target gene expression in mouse embryonic fibroblasts lacking GSK-3 as well as in nontransformed rat intestinal epithelial cells using a pharmacological inhibitor of GSK-3 activity.

### Existing Drugs Are:

*Olanzapine* was investigated as an inhibitor of glycogen synthase kinase-3 (GSK-3) in an attempt to evaluate its effect on blood glucose level. Side effects seen with olanzapine include akathisia (an inability to sit still), constipation, dizziness, drowsiness, insomnia, dry mouth, orthostatic hypotension, tremor, and weight gain.

*Valproic acid (VPA)* is a potent broad-spectrum anti-epileptic with demonstrated efficacy in the treatment of bipolar affective disorder. VPA inhibits both GSK-3 $\alpha$  and  $\beta$ , with significant effects observed at concentrations of VPA similar to those attained clinically. The most common complaints are: tiredness (sometimes with slower thinking), dizziness, upset stomach, vomiting and tremor (shaking of the hands or other parts of the body, hair loss, weight gain, changes in behavior (depression in adults, irritability in children)

The selected and the most powerful drug to inhibit Glycogen synthase kinase is Curcumin is taken for study. *Curcumin* is the principal Curcuminoid of the popular Indian curry spice turmeric, which is a member of the ginger family (Zingiberaceae). The other two Curcuminoids are desmethoxy Curcumin and bisdesmethoxy Curcumin. The Curcuminoids are polyphenols and are responsible for the yellow color of turmeric. Curcumin can exist in at least two tautomeric forms, keto and enol. The enol form is more energetically stable in the solid phase and in solution. Curcumin can be used for boron quantification in the so-called Curcumin method. It reacts with boric acid forming a red coloured compound, known as rosocyanine. Curcumin is brightly colored and may be used as a food coloring. Due to the potent nature of *Curcumin*, this drug is taken for our study.

### Materials and Methods

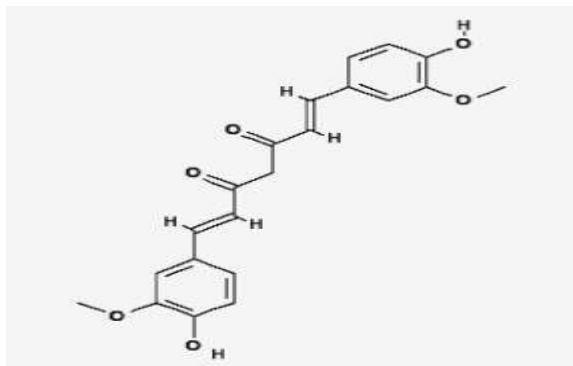
#### The information about macromolecule

The PDB is a key resource in areas of structural biology, is a key repository for 3D structure data of large molecules. The molecule which taken is Glycogen Synthase Kinase-3 (GSK-3) for our consideration. The pdb Id is 1H8F and an resolution factor is 2.80Å and the method of incorporation is X-ray diffraction method.

#### The information about drug molecule

The drug molecule information and structure is mainly collected from Pubchem literature. The compound name is curcumin and id is 969516. Its molecular weight is 368.39 g/mol. The molecular formula is  $C_{21}H_{20}O_6$ . The IUPAC name and canonical smiles were displayed (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-Dione and COC1=C(C=CC(=C1)C=CC(=O)CC(=O)C=CC2=CC(=C(C=C2)O)OC)O.

Structure of curcumin



Descriptions	Value
Compound ID:	969516
Molecular Weight	368.38 g/mol
Molecular Formula	C21H20O6
XLogP3-AA	3.2
H-Bond Donor	2
H-Bond Acceptor	6
Rotatable Bond Count	8
Tautomer Count	49
Exact Mass	368.126
Monoisotopic Mass	368.126
Topological Polar Surface Area	93.1
Heavy Atom Count	27
Formal Charge	0
Complexity	507
Isotope Atom Count	0
Defined Atom StereoCenter Count	0
Undefined Atom StereoCenter Count	0
Defined Bond StereoCenter Count	2
Undefined Bond StereoCenter Count	0
Covalently-Bonded Unit Count	1

#### Identification of Active site and Binding pocket:

The active site and the binding pocket is first identified in the target protein to be inhibited. It was clearly studied the active site and binding pocket from the research data available for the protein. The active site is the place where the protein binds. The binding pocket favourably associates with another chemical entity or compound.

#### Map of the active site:

C-terminal consists of  $\alpha$ -helical domain and N-terminal consists of  $\beta$ -strand domain and bordered by Glycine loop and the hinge. The hinge is mainly made up of TYR134 and the bottom of the active site consists of LEU188 and CYS199. The main active site of the protein taken is found to be SER203.

#### Pocket-Finder:

The Binding pocket in the protein is studied in the *Pocket-Finder* under the url [www.modelling.leeds.ac.uk/pocketfinder/](http://www.modelling.leeds.ac.uk/pocketfinder/). The *Pocket-Finder* website is opened using the url and the PDB ID is provided in the field or the protein itself is loaded using the browse button. The server clearly pictures out the binding pocket of the protein and the residues present within that pocket.

#### LigandScout:

The level of finding active site is by pharmacophore studies. This is done by using the tool *LigandScout*. The tool clearly picturize the active site present Hydrogen Bond donor, Hydrogen bond acceptor, Negative and Positive ionisable area, hydrophobic interaction, Aromatic ring, Metal Binding feature.

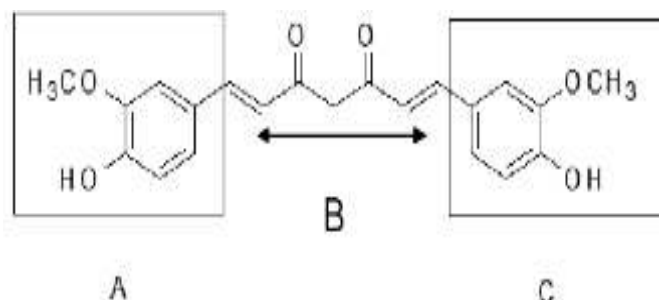
#### Energy Minimization:

The energy should be minimized before taking them for further studies. The energy can be minimized by using the *CHEM3D ULTRA 3D*. This tool can read \*.mol file.

#### Determination of Structure-Behaviour Relationship:

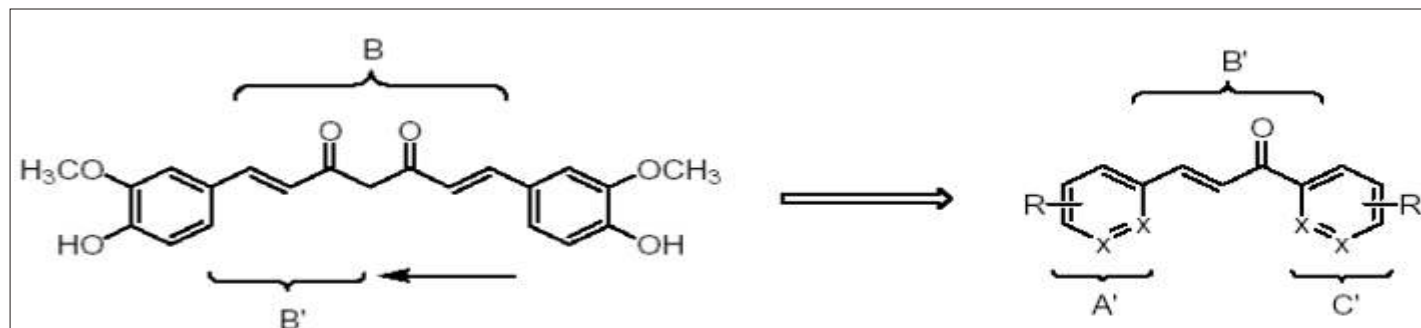
The quantitative structural activity relationship(QSAR) is done for all the test set using the training set. The QSAR is carried out by using the MDL QSAR tool. This is a 2D QSAR tool that is used to predict the pMED values for all the test set. The known structures will have the pMED50 values and using these pMED50 values of the training set, the equation is generated and with these equation the pMED50 values of the test set is predicted.

#### STRUCTURE DEVELOPMENT Construction of Analogues of Curcumin



From the above picture, there are three regions in Curcumin. A and C are regions accomodating aromatic systems. Region B is the diketone linker.

With the evidence in the research literature, ten structural analogues were explored. Curcumin has three distinct molecular regions: the two aromatic systems (R1 and R2) and the central hepta-1,6-dien-3,5-dione linker. Several structural analogues of Curcumin were designed. There is a significant increase in potency observed with these compounds. The inhibition potential ranged from 0 to 100%. These aromatic enones have a central linker, this linker is abridged to an enone system instead of having hepta-1,6-dien-3,5-dione linker found in Curcumin. This is followed by the substitution on the aromatic system with various substituent groups R1 and R2 or with heterocyclic aromatic systems. The aromatic enones Curcumin analogues were designed.



Curcumin structure and the abridged aromatic enone parent Analog. X=X represent various cyclic linkers. R represent various substituents on the two aromatic systems A' and C' respectively.

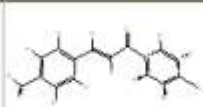
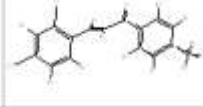
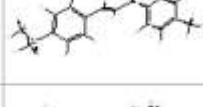
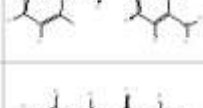
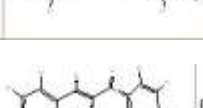
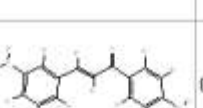

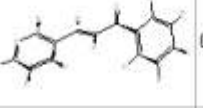
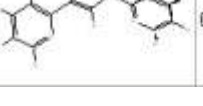
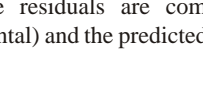
Ten such analogues are collected from literature as training set and from each set ten new test set were designed.

### TRAINING SETS

Table 1: Training set for 20 known structures given in regression analysis:

Mol_ID	Structure	Formula	MolWeight	Name	pMED50	
1		C15H12O	208.25518	chalcone	5.81	Cur_1
2		C16H12Cl2O	291.17188	[E]-3-(2,6-dichlorophenyl)-1-p-tolylprop-2-en-1-one	6.34	Cur_2
3		C17H16O	236.30834	[E]-3-(2,6-dimethylphenyl)-1-phenylprop-2-en-1-one	5.3	Cur_3
4		C17H16O	236.30834	[E]-1-(2,4-dimethylphenyl)-3-phenylprop-2-en-1-one	5.39	Cur_4
5		C16H11F3O	276.2531496	[E]-1-(3-(trifluoromethyl)phenyl)-3-phenylprop-2-en-1-one	5.76	Cur_5
6		C15H8Cl4O	346.03542	[E]-1,3-bis(2,6-dichlorophenyl)prop-2-en-1-one	5.66	Cur_6
7		C14H11NO	209.24324	[E]-1-phenyl-3-(pyridin-2-yl)prop-2-en-1-one	5.65	Cur_7
8		C15H2F10O	388.159812	[E]-1,3-bis(perfluorophenyl)prop-2-en-1-one	5.65	Cur_8
9		C15H13NO3	255.26862	[E]-3-[4-(dihydroxyamino)phenyl]-1-phenylprop-2-en-1-one	5.34	Cur_9
10		C17H12Cl2O	303.18258	[E]-2-(2,6-dichlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one	5.72	Cur_10

Table-2 Training sets for which no sets were created

11		C16H13ClO	256.72682	[E]-1-(4-chlorophenyl)-3-p-tolylprop-2-en-1-one	4.86	Cur_11
12		C16H12Cl2O	291.17188	[E]-3-(2,4-dichlorophenyl)-1-p-tolylprop-2-en-1-one	4.78	Cur_12
13		C19H20O	264.3615	[E]-3-(4-isopropylphenyl)-1-p-tolylprop-2-en-1-one	4.59	Cur_13
14		C17H15ClO	270.7534	[E]-3-(2-chlorophenyl)-1-(2,4-dimethylphenyl)prop-2-en-1-one	4.88	Cur_14
15		C15H10Cl2O	277.1453	[E]-1,3-bis(4-chlorophenyl)prop-2-en-1-one	4.35	Cur_15
16		C16H13ClO	256.72682	[E]-3-(4-chlorophenyl)-1-p-tolylprop-2-en-1-one	4.63	Cur_16
17		C15H14N2O	238.28446	[E]-3-(3-aminophenyl)-1-(4-aminophenyl)prop-2-en-1-one	4.97	Cur_17
18		C17H15ClO3	302.7522	[E]-3-(2-chlorophenyl)-1-(2,6-dimethoxyphenyl)prop-2-en-1-one	4.91	Cur_18
19		C14H11NO	209.24324	[E]-1-phenyl-3-(pyridin-3-yl)prop-2-en-1-one	4.9	Cur_19
20		C13H10N2O	210.2313	[E]-1,3-di(pyridin-2-yl)prop-2-en-1-one	2.06	Cur_20

Note: The residuals are compared manually between the actual (experimental) and the predicted biological activity values in the QSAR Model.

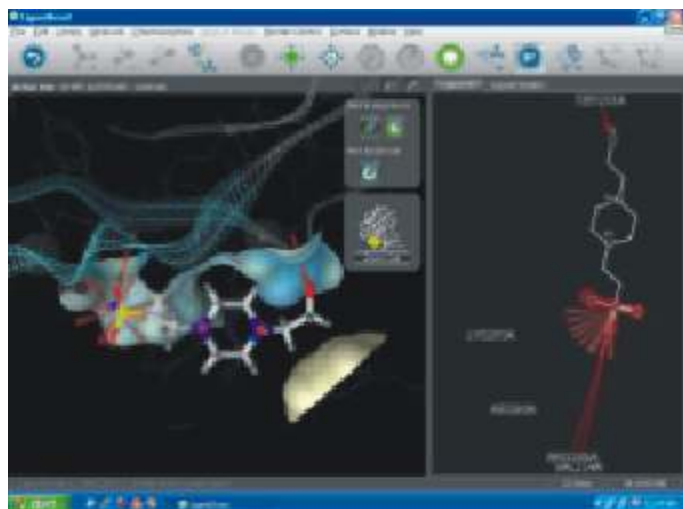
#### TEST SETS:

- The experimental pMED values of the training set is used to calculate the predicted pMED values by MDL QSAR.
- Along with the predicted values, the graph is also obtained with experimental pMED Values in the X-axis and predicted pMED values in the Y-axis.

#### Selection of the right ligand for docking

- In pharmacophore studies, active site residues are identified as SER 203, LYS 205, ARG 96, ARG180, VAL 214 and, in ligand So<sub>3</sub> is important pharmacophore in crystal structure with 4-(2-HYDROXYETHYL)-1-PIPERAZINE ETHANESULFONIC ACID.
- Therefore the compound that having SO<sub>3</sub> is selected for docking studies.
- Hence 3-((E-3-(4-Methoxy-2,6-Dimethylphenyl) Acryloyl) Benzenesulfonic acid (Cur\_3d) is chosen for the docking studies.

Pharmacophore Studies



DOCKING OF LIGAND TO THE TARGET PROTEIN:

It was done by the AUTODOCK tool

a) BINDING CONFORMATION



b) Energy Conformation

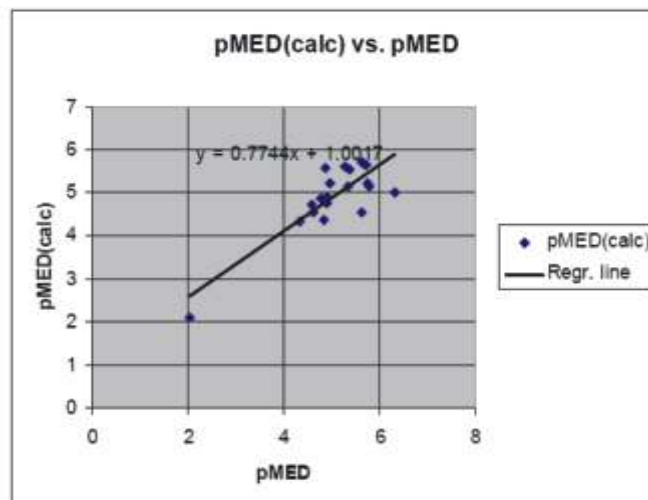
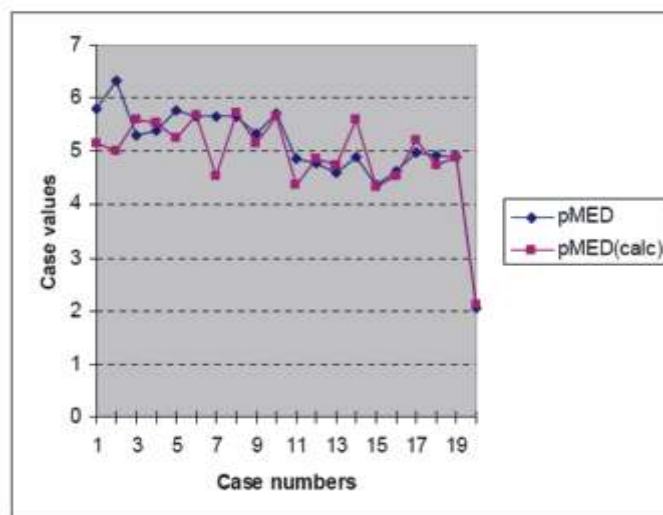


Properties	Values
Rank	1_1
Binding Energy	-8.31
KI	811.63 nM
Intermolecular Energy	-9.38
Internal Energy	-1.15
Torsional Energy	1.65
Unbounded External Energy	-0.57
Cluster RMS	0.0
Ref RMS	41.64

STRUCTURAL ACTIVITY RELATIONSHIP

The test sets are created and their structural activity relationship was determined.

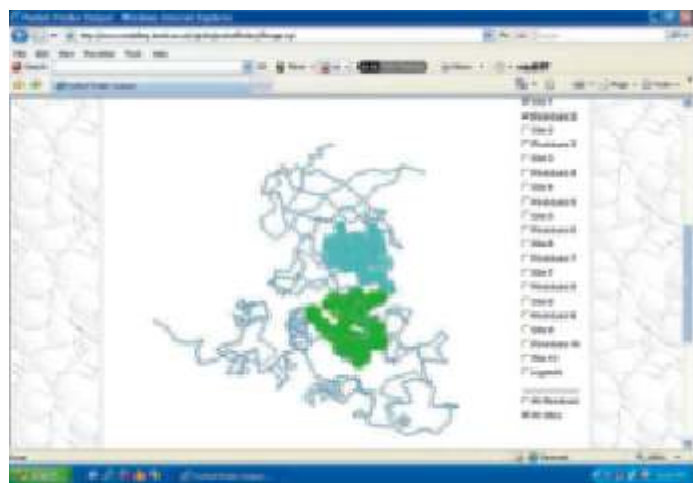
a) GRAPHS OBTAINED



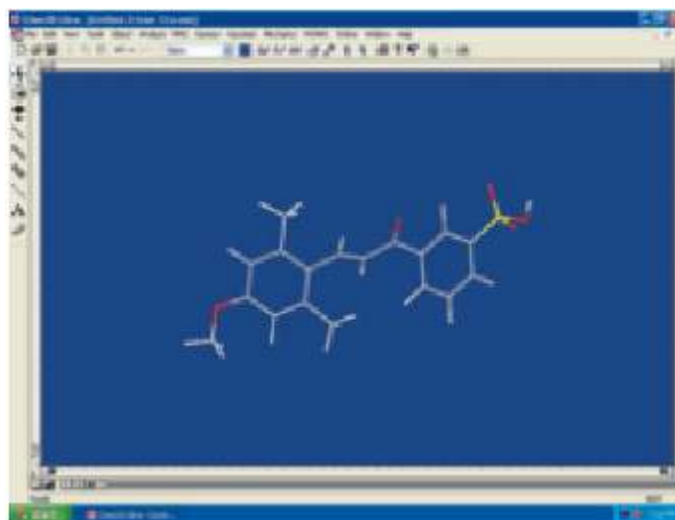
ElWakil, M.A., M.E. Abdalla and S.B. Mathur, 1998. *Fusarium oxysporum* f.sp.Lycopersici Races 1 and 2 Associated with Tomato Seeds in Egypt. *Pak. J. Biol. Sci.*, 1: 92-96.

Test Set						
Mol_ID	Structure	Formula	MolWeight	IC50	IUPAC NAME	ID provided
1		C16H18N2O4	302.32512	5.7639	(2E)-3-(1,4-dihydro-5-hydroxy-1,4-dimethylpyridin-2-yl)-1-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one	Cur_1a
2		C16H15NO5	301.294	4.53	(E)-2-(4-hydroxy-3-methoxyphenyl)imino-1-(3-hydroxy-4-methoxyphenyl)ethanone	Cur_1b
3		C17H13N3O3	307.30342	6.21	(E)-1-(3-hydroxy-2-methoxyquinolin-7-yl)-3-(pyridin-5-yl)prop-2-en-1-one	Cur_1c
4		C16H12Cl2O3	323.17068	5.28	(E)-3-(2,4-dichlorophenyl)-1-(4-hydroxy-2-methoxyphenyl)prop-2-en-1-one	Cur_1d
5		C21H25NO	307.4253	5.72	(E)-1-(3-isopropylphenyl)-3-(5-isopropylpyridin-2-yl)-2-methylprop-2-en-1-one	Cur_1e

Fig 2 Pocket DETECTION The binding pocket was detected using POCKET FINDER



ENERGY MINIMIZATION:  
The energy was minimized using Chem-3D ultra.



## Results and Discussion

**Glycogen Synthase Kinase 3 Beta.** (pdb id: 1H8F) is our protein target for drug discovery. Base ligand taken for our analysis is Curcumin, the crystal structure with 4-(2-HYDROXYETHYL)-1-PIPERAZINE ETHANESULFONIC ACID. This is used for pharmacophore studies. Potential original molecules are collected from Patents literature, and all these drawn using other tools like MDL ISIS draw followed by that it performed energy minimization techniques. The QSAR results were analyzed and it produced result as Cur\_3f e.mol is chosen for further analysis because showing higher activity. This molecule is studied for docking studies using Autodock tools. And showing, ligand fits into the grooves of protein. Below Betasheets and between 2 alpha helices. (3-((E-3-(4-Methoxy-2,6-Dimethylphenyl) Acryloyl) Benzenesulfonic acid, is our new ligand which is a new molecule, showing potential lead molecule for the treatment of Inflammation and migration, Alzheimer Disease, Diabetes and Cancer. In the pharmacophore studies, active site residues are identified as SER 203, LYS 205, ARG 96, ARG180, VAL 214 and, in ligand SO<sub>3</sub> is important pharmacophore. Our molecule is also constructed with SO<sub>3</sub> pharmacophore. This need it improved further.

FINAL HEAT OF FORMATION = -135.78451  
KCAL = -568.12238 KJ  
TOTAL ENERGY = -4347.78825 EV  
ELECTRONIC ENERGY = -28945.60808 EV  
POINT GROUP:C1  
CORE-CORE REPULSION = 24597.81983 EV  
IONIZATION POTENTIAL = 9.05628  
NO. OF FILLED LEVELS = 63  
MOLECULAR WEIGHT = 346.397

Further studies should carry about toxicity, ADME properties, and then it can be send to actual wet lab for further validations.

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