



# STRUCTURE BASED DRUG DESIGNING OF p38 MAP KINASE INHIBITORS FOR THE TREATMENT OF OSTEOARTHRITIS

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## ABSTRACT

p38 MAP kinase is one of the important targets in the treatment of osteoarthritis and inflammation. The best highly active lead compound was docked into the active site of Human p38 MAP Kinase Inhibitor Complex 11AN using Ligand fit of Cerius 2. The results demonstrate that lead compounds derived in this study could be considered to be a useful and reliable tool in identifying structurally diverse compounds with desired biological activity for the successful treatment of various types of osteoarthritis.

**Keywords:** p38 MAP kinase; Osteoarthritis; Inflammation; Ligand Fit ; Docking

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## INTRODUCTION

p38 MAP kinase is a key regulator in stress, inflammation, development, and cell death. Osteoarthritis (OA) is a common rheumatic disease that is characterized by a progressive loss of articular cartilage. Cartilage degeneration results from an imbalance between anabolic and catabolic processes due to the dedifferentiation and apoptosis of chondrocytes and increased synthesis of matrix degrading proteinases. There is increasing evidence that inflammation plays an active role in pathophysiology of osteoarthritis. Proinflammatory cytokines are secreted from the inflamed synovium and from activated chondrocytes. Cytokines such as interleukin 1 beta (IL-1 $\beta$ ) and tumor necrosis factor alpha (TNF $\alpha$ ) upregulate numerous cytokines from chondrocytes and synoviocytes as well as prostaglandin E2 and proteinases such as the matrix metalloproteinases (MMPs) and aggrecanases. The aggrecanases and the matrix metalloproteinases are thought to mediate the structural degradation of cartilage in OA<sup>1</sup>.

p38 MAP kinase plays a crucial role in regulating the production of proinflammatory cytokines, such as tumor necrosis factor and interleukin-1. Blocking this kinase may offer an effective therapy for treating many inflammatory diseases<sup>2</sup>.

## EXPERIMENTAL

### Docking studies using Ligand Fit of Cerius 2 (Accelrys)

The automatic docking of a flexible ligand into a protein active site is a critical step in the process of structure-based design. Ligand Fit provides structure-based design capabilities including binding site finding and flexible docking and scoring capabilities, allowing evaluation of compounds against a receptor site. Scores from Ligand Fit provide direct insight into the complementary features of ligands and their potential as lead candidates.

LigandFit only requires a model or an experimental structure of the protein. No natural ligand or binding-site information is required. LigandFit simplifies user intervention during docking by automatically moving the ligand, evaluating energies and checking whether the structure is acceptable. Fast flexible docking with Ligand Fit allows quickly evaluating and prioritizing series of compounds with respect to their ability to fit and bind to the receptor<sup>3</sup>.

### Steps for docking ligand in active site

1. Active site search by flood filling method.

2. Fast conformational search for ligand in protein cavity.
3. Fast grid method for evaluation of protein-ligand interactions.
4. Scoring with both protein-ligand interaction energy and ligand internal non-bonded energy.
5. Visualization of docked conformations in binding site cavity.
6. Clustering of docked conformers.
7. Multiple scoring functions.
8. Consensus scoring

Ligand fit is designed to dock a ligand or a series of ligand molecules into a protein binding site. During docking the protein is rigid while the ligand remains flexible allowing different conformations to be searched and docked within the binding site<sup>3</sup>.

The three key steps in ligand fit are-

#### **1. Site search**

The aim of the site search is to define the binding site of the protein, the position and shape of which will be used in the docking process.

#### **2. Conformational search**

The Monte Carlo method is employed in the conformational search of the ligand. During the search, bond lengths and bond angles are untouched but only torsion angles are touched.

#### **3. Ligand fitting**

After a new conformation is generated, the fitting is carried in two steps. First the non-mass weighted principle moment of inertia (PMI) of the binding site is compared with the non-mass weighted PMI of ligand<sup>3</sup>.

If the fit PMI is above the threshold or not better than fitting results previously saved, no further docking is performed, if the fit PMI is better than previously saved results, the ligand is positioned into the binding site according to the PMI. The docking score is negative value of the non-bonded intermolecular energy between the ligand and protein. After the docking score is calculated for each orientation of the ligand, it is compared with the results saved previously. If the new one is better, it is saved. The process of conformational search and ligand fitting is iterated until maximum number of trials is reached. Finally, rigid body minimization is applied to the saved conformations of the ligand to optimize their positions and docking scores<sup>3</sup>.

#### **Steps followed for docking ligand into active site for ligand fit:**

1. Potent molecules which can inhibit the action of p38 MAP kinase were taken.
2. Molecules with diversified similarities and pharmacophore features were selected from the literature.
3. The molecules which are to be docked in a receptor site were created in a SD file so as all the molecules are processed for the docking score at a time.
4. The active site of a protein is identified by the active site viewer which is processed by the flood flow algorithm.
5. The identification of the active site is located by the already docked ligand.
6. The Human p38 Map Kinase Inhibitor Complex IAN protein molecule obtained from Protein Data Bank is selected, the set of molecules in the SD file are chosen and docking score is calculated.
7. Thus the docking score for a set of molecules are calculated through ligand fit.

The training set of 3 active compounds, 3 moderately active compounds and 3 least active compounds were selected for docking into the active site of Human p38 Map Kinase Inhibitor Complex IAN obtained from Protein Data Bank<sup>4-8</sup>.

The molecular structures of all the training set compounds with their IC<sub>50</sub> values and of highly active compound 5 and least active compound 4 are represented in Table 1.

### RESULTS AND DISCUSSION

The docking score of the molecules show positive values. The Human p38 Map Kinase Inhibitor Complex IIAN obtained from Protein Data Bank receptor is shown in Fig.-1. Training sets highly active molecule compound 5 of IC<sub>50</sub> value of 0.005  $\mu$ M shows a good dock score of 68.540 as seen in Fig.-2 and Fig.-3. Training sets least active compound 4 of IC<sub>50</sub> value of 1000  $\mu$ M shows low dock score of 31.764 as seen in Fig.-4. About four molecules shows dock score more than 30. Thus, these molecules can be used as the potential ligands for the inhibition of p38 MAP kinase.

### CONCLUSION

The best highly active lead compound was docked into the active site of Human p38 Map Kinase Inhibitor Complex IIAN obtained from Protein Data Bank using Ligand fit and a good dock score of 68.540 was obtained when the ligand binded to the active site. The highly active molecules are further used to design more potent lead molecules against p38 MAP kinase inhibitors for the treatment of various types of osteoarthritis.

Thus, we hope that the lead molecules generated from this structure based drug designing of p38 MAP kinase inhibitors would be helpful in identifying structurally diverse compounds with desired biological activity for the successful treatment of various types of osteoarthritis.

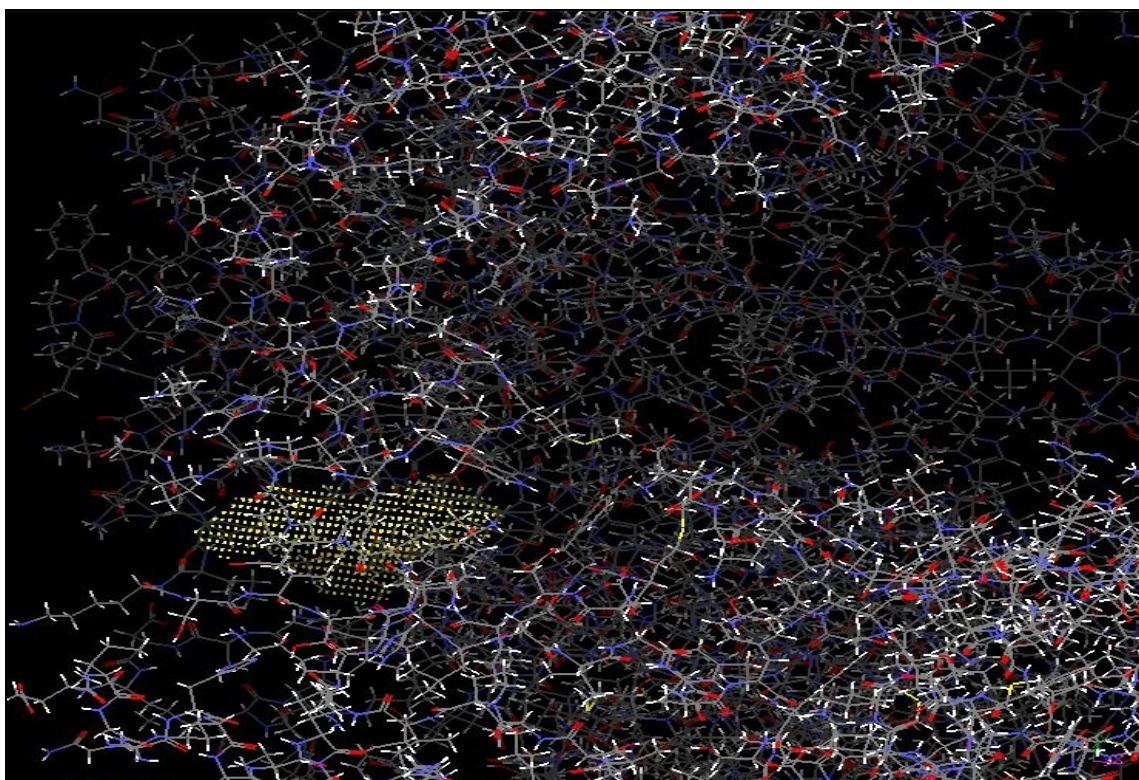


Fig.-1: Active site of p 38 MAP kinase. The Human P38 Map Kinase Inhibitor Complex IIAN obtained from Protein Data Bank receptor

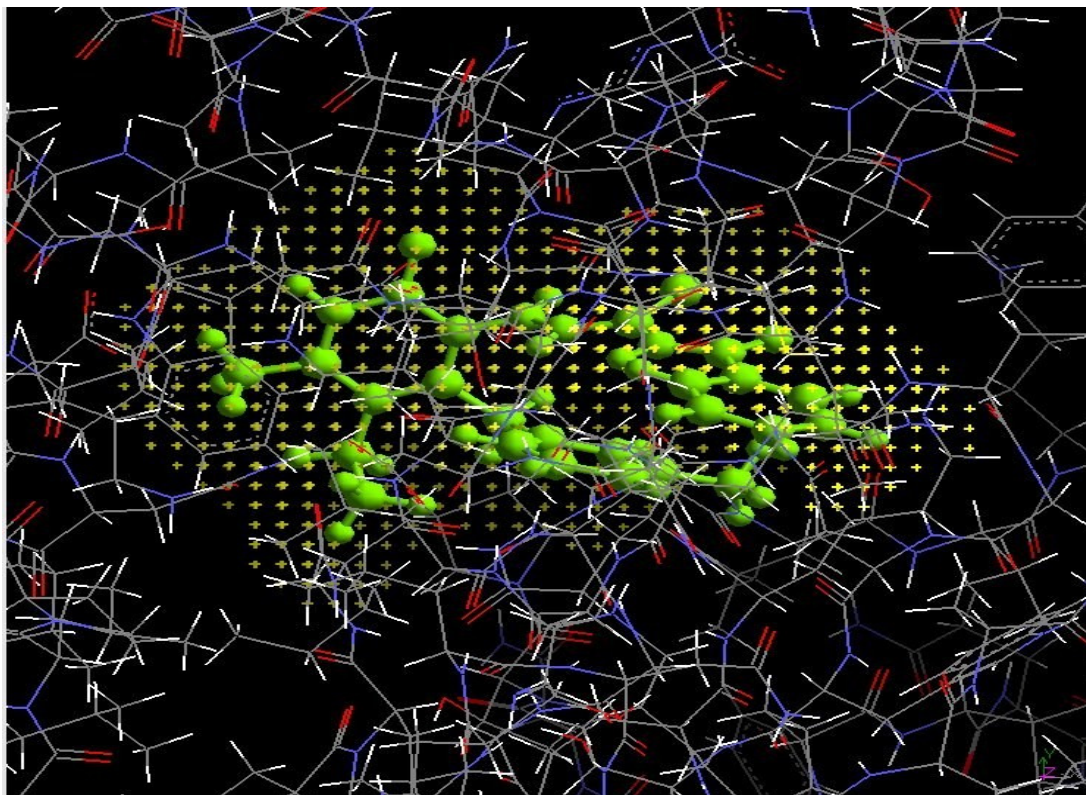


Fig.-2: High active compound docked in active site. Training set highly active molecule compound 5 shows a good dock score of 68.540.

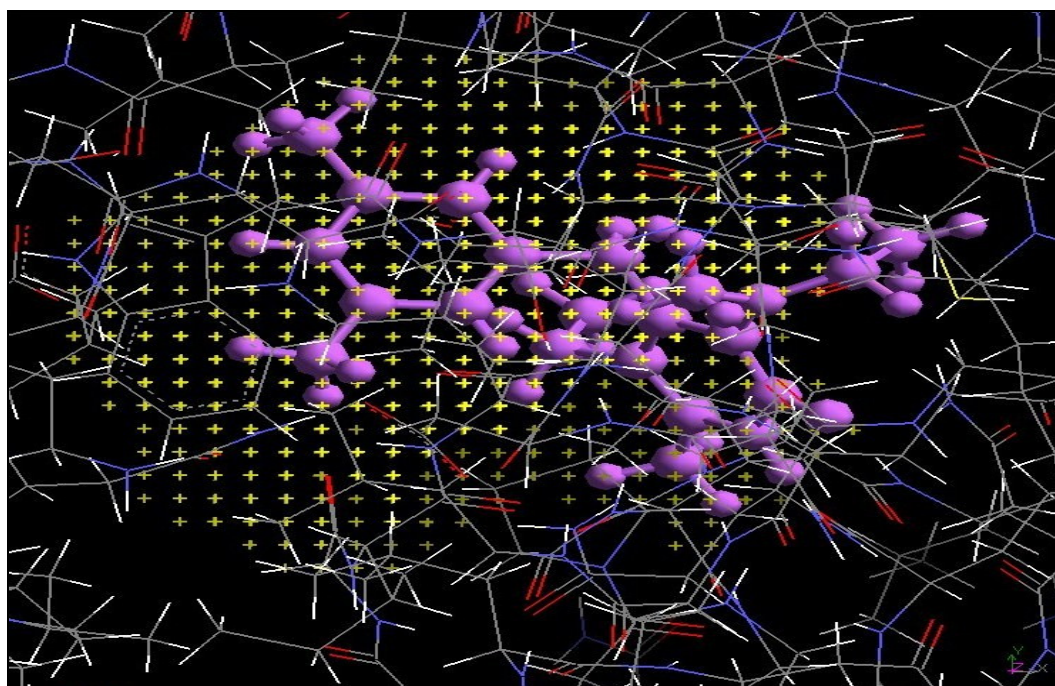


Fig.-3: High active compound 5

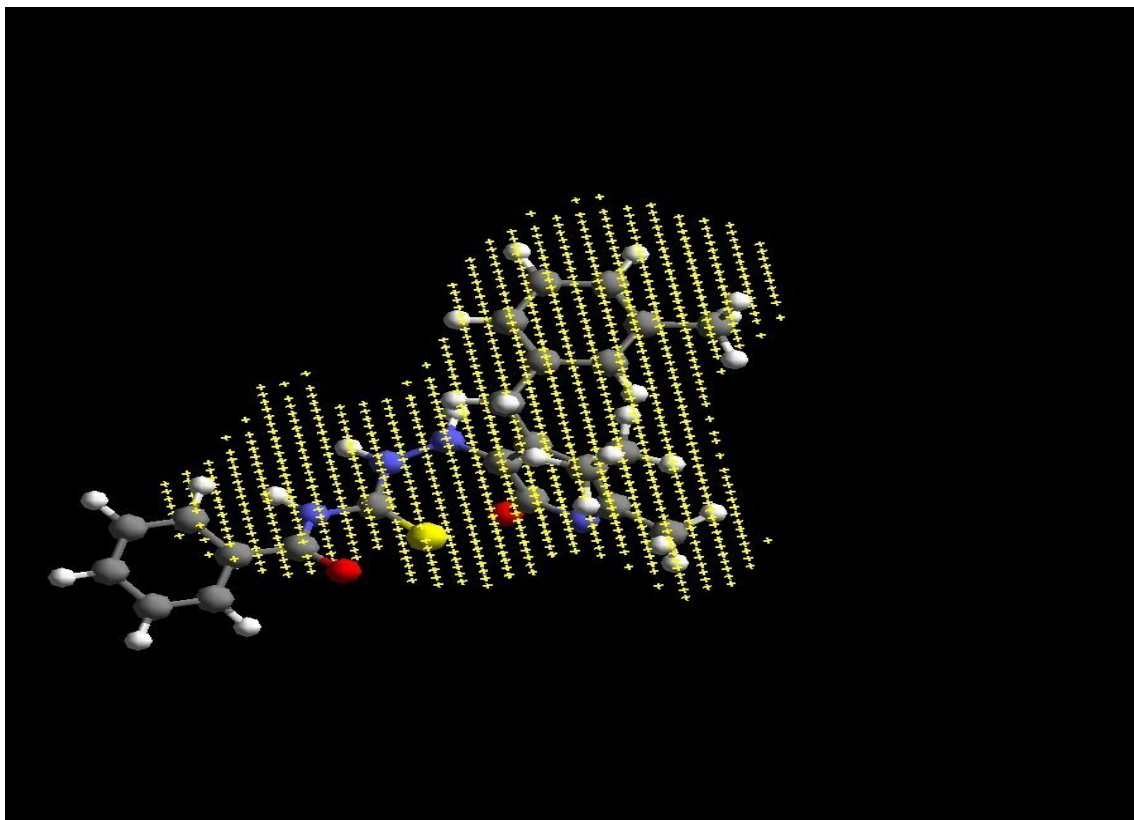
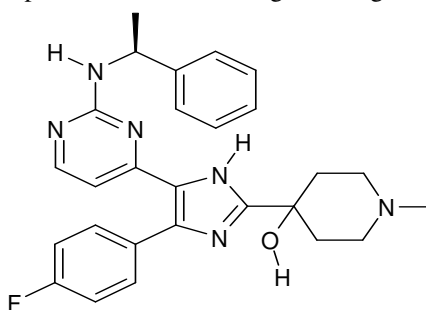


Fig.-4: Low active compound 4. Training set least active compound 4 shows low dock score of 31.764

Table-1

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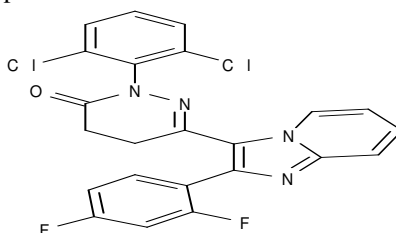
Highly Active Compound used for Docking with High Dock score of 68.540



Compound 5, IC<sub>50</sub> value of 0.005  $\mu$ M

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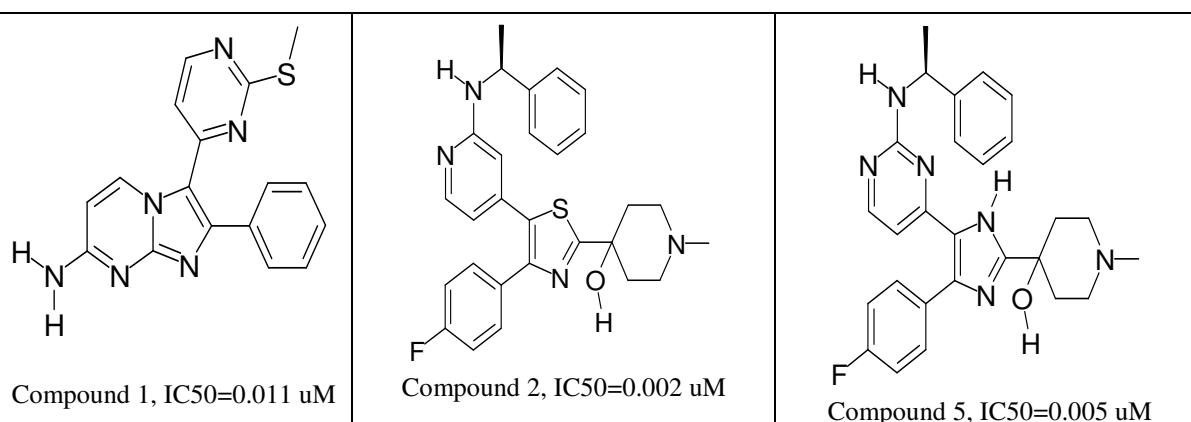
Least Active Compound with Low Dock Score of 31.764 in the Active Site



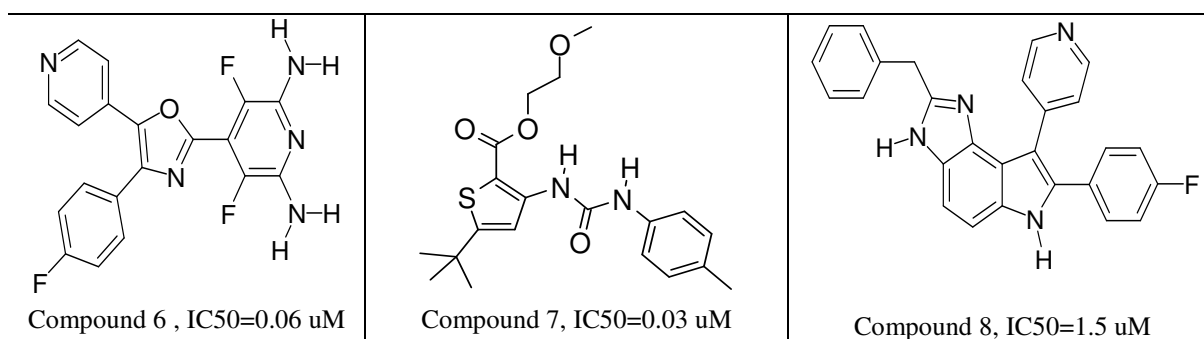
Compound 4, IC<sub>50</sub> value of 1000  $\mu$ M

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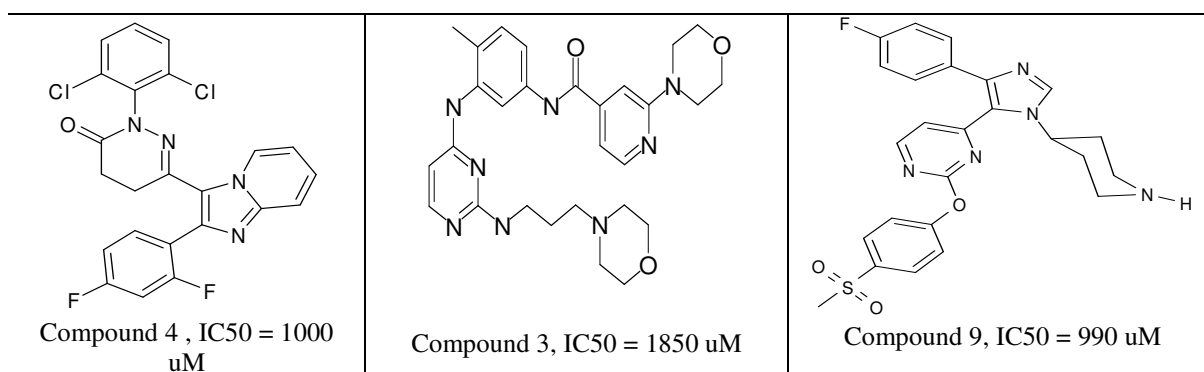
Three highly active compounds



Three moderately active compounds



Three least active compounds



### ACKNOWLEDGEMENTS

All molecular modeling works were performed on a Silicon Graphics Octane R12000 computer running Linux 6.5.12 (SGI, 1600 Amphitheatre Parkway, Mountain View, CA 94043). Ligand Fit of Cerius 2 (Accelrys software) was used for docking of molecules in active site.

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