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Research Article

MOLECULAR PROPERTIES AND DOCKING STUDIES ON CHROMONE PYRAZOLONES AS POTENTIAL INHIBITORS OF P38 MAP KINASE

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ABSTRACT

The p38 mitogen-activated protein (MAP) kinase plays important role in inflammatory response. Inhibitors of the p38 MAP Kinase can offer effective treatment for the inflammatory diseases. Here we report the molecular docking analysis of chromone pyrazolones derivatives as the inhibitors of p38 MAP Kinase. The docking analysis was done using Argus Lab. The molecular properties were analyzed by using simple molecular descriptors used by "Lipinski's rule of 5". Comparative study of molecular properties and the binding score obtained by docking of known inhibitor (Biphenyl amide) and synthesized chromone pyrazolones derivatives suggest that some of these derivative's can be used as the potential inhibitor of the p38 MAP kinase. The study provides the base for further in vitro and in vivo study of the synthesized derivative in the direction of p38 MAP kinase inhibition and as an antiflammatory drug.

Keywords: p38 MAP Kinase, Chromones, Pyrazolones, Molecular docking, Molecular descriptor, Lipinski's rule of 5, Inflammatory.

INTRODUCTION

The inflammatory response is mainly regulated by the proinflammatory cytokines. Increase in the level of this cytokines led to inflammatory diseses if autoimmunity. The p38 mitogen-activated protein (MAP) kinase are important in the inflammatory diseases. These belong to serine/threonine protein kinases family and are involved in cellular responses to external stress signals[1]. The p38 MAP kinase are involved in signal transduction for the stabilization of mRNA which play important role in expression if interlukins (IL-6 and IL-8). The increase in stability of the mRNA involved in proinflammatory cytokine production increase the concentration of this cytokines and thus is one of the leading cause for inflammatory disorders[2]. One of the approach to control the inflammatory disorders is to reduce this abnormal increase in the number of proinflammatory cytokines. As the p38 MAP kinase plays crucial role in the cascade for the regulation of proinflammatory cytokine production[3], it can be a good potential target for its inhibition.

The pyrazolone derivatives are organic compounds used as intermediates for synthesizing pharmaceuticals and act as anti-inflammatory and allergy inhibitors[4]. Chromones are the major classes of naturally occurring compounds in plants and they exhibit wide range biological activities like cytotoxicity (anticancer)[5-7], neuroprotective[8], HIV-inhibitory[9] and antioxidant activity[10].

In current study the chromone pyrazolones derivatives synthesized earlier by knovengeal condensation[11] were checked for their molecular descriptive properties by the "Lipinski's rule of 5"[12] and further their ability to bind in the active site region of p38 MAP kinase was identified using molecular docking approach. The active site region of p38 MAP kinase consists of conserved Asp-Phe-Gly (DFG) motif and is present in majority of Ser/Thr kinase. The DFG motif in kinase is required for binding of the inhibitor[13]. The region involved in binding of biphenyl amides (BPAs) which are novel series of p38 MAP kinase inhibitors uses the same conserved motif region[14]. In current study same region involved in biphenyl amide (BPAs), p38 MAP kinase inhibitor binding was used for docking of the chromone pyrazolones derivatives.

MATERIALS AND METHODS

Protein Molecule Preparation

The coordinate for the crystal structure of p38 MAP kinase bound with biphenyl amide inhibitor was downloaded (PDB id- 2ZB0)[14] from Protein Data Bank (http://www.rcsb.org/pdb/home.do). The region of active site and amino acids involved were identified by using Swiss PDB Viewer[15]. The 5 Angstrom region around the bound biphenyl amide inhibitor was checked and confirmed that it contains the identified DFG motif essential for binding of the inhibitor. The PDB file was prepared by only selecting the protein molecule and saving the file in the absence of the ligand. The new file generated was used for docking analysis. The hydrogen molecules were added and protein was subjected to energy minimization and geometry optimization.

Ligand Structure Preparation

The 5 derivatives earlier synthesized and the structural data identified by IR and NMR mass were used as ligand drug data set. ChemSketch[16], the chemically intelligent drawing interface freeware (http://www.acdlabs.com/download) was used to draw the structures of chromone pyrazolones derivatives (Table 1), followed by generation of 3D structure in PDB format using open Babel[17]. Later on PRODRG2 Server[16]

(http://davapc1.bioch.dundee.ac.uk/prodrg/) was used to generate 3D structure in desired .mol format required by Argus Lab software.

Docking Analysis and Calculation of Molecular Properties

The docking was performed by using the Arugus Lab 4.0.1[18] (http://www.arguslab.com) and the docking score for all the ligand molecules were calculated to identify the potential active drug against p38 MAP kinase. The molecular properties were calculated on basis of simple molecular descriptors used by "Lipinski's rule of 5"[12]. The five properties consist of Molecular weight, hydrogen donor; acceptors, LogP, and Total Polar Surface Area (TSPA) which were calculated using the online chemoinformatics tool molinspiration (http://www.molinspiration.com/)[19].

RESULT

The molecular descriptor calculation and docking study of known p38 MAP kinase inhibitor (BAP) and chromone pyrazolones derivatives on p38 MAP kinase were performed in order to estimate molecular properties for "Lipinski's rule of 5" and binding affinity respectively (Table 2).

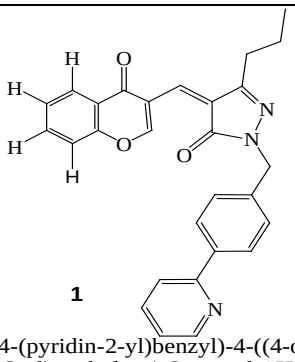
Binding site in p38 MAP kinase

The binding site for the MAP kinase inhibitor was identified by using the Swiss PDB Viewer. The crystal structure downloaded from PDB databank consisted the BAP inhibitor bound to the kinase. The predicted site comprised of VAL30, VAL38, ALA40, ARG49, ALA51, VAL52, LYS53, GLU71, LEU74, LEU75, ILE84, LEU104, THR106, HIS107, LEU108, MET109, GLY110, LEU167, ASP168, PHE169, GLY 170 and LEU171 interacting residues. This predicted site was used as the target site for docking of chromone pyrazolones derivative.

Docking analysis

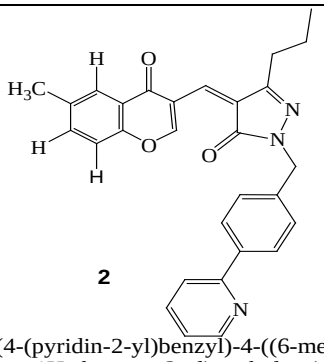
The MAP kinase protein was used as the receptor molecule against the available set of ligands. As per the docking score obtained in energy kcal/mol as shown in Table 2, the highest docking score was obtained for the derivative 2 with score of -12.9 kcal/mol followed by derivative 4 with score of -12.65 kcal/mol, derivative 1 with score of -11.22 kcal/mol, derivative 3 with score of -10.52 kcal/mol and lastly derivative 5 with docking score of – 9.78 kcal/mol. BAP showed the score of -11.31. The docked molecules into the kinase binding site were visualized using UCSF Chimera[20] (Figures 1.a to e).

Table 1: Chemical structure of Chromone pyrazolones derivatives



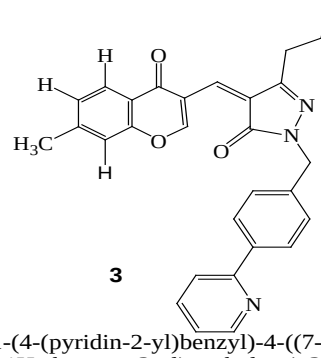
1

(4*Z*)-1-(4-(pyridin-2-yl)benzyl)-4-((4-oxo-4*H*-chromen-3-yl)methylene)-3-propyl-1*H*-pyrazol-5(4*H*)-one



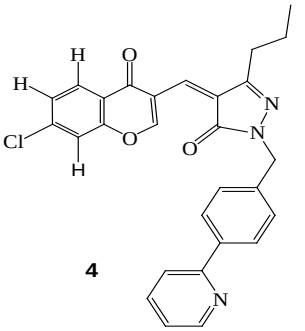
2

(4*Z*)-1-(4-(pyridin-2-yl)benzyl)-4-((6-methyl-4-oxo-4*H*-chromen-3-yl)methylene)-3-propyl-1*H*-pyrazol-5(4*H*)-one



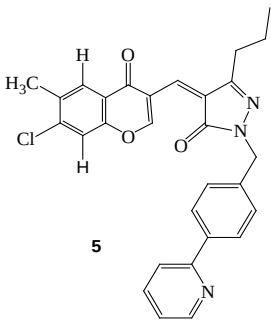
3

(4*Z*)-1-(4-(pyridin-2-yl)benzyl)-4-((7-methyl-4-oxo-4*H*-chromen-3-yl)methylene)-3-propyl-1*H*-pyrazol-5(4*H*)-one



4

(4*Z*)-1-(4-(pyridin-2-yl)benzyl)-4-((7-chloro-4-oxo-4*H*-chromen-3-yl)methylene)-3-propyl-1*H*-pyrazol-5(4*H*)-one

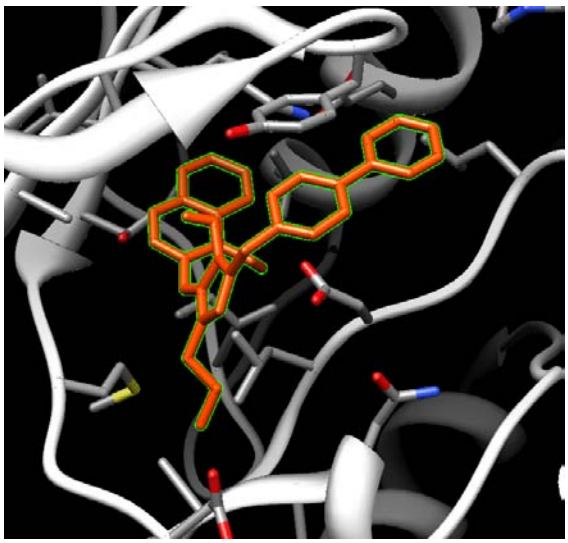


5

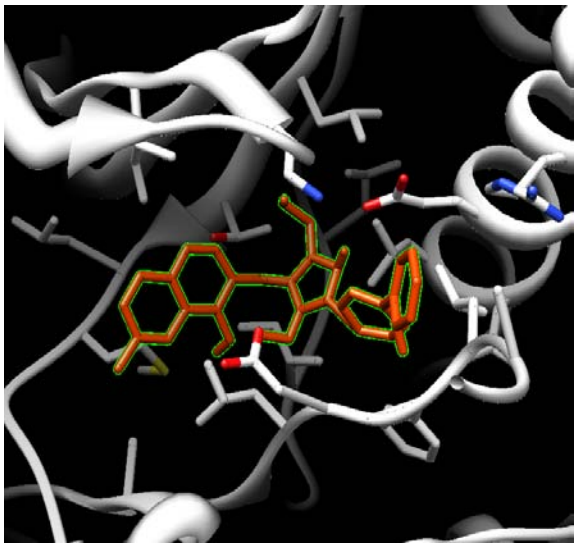
(4*Z*)-1-(4-(pyridin-2-yl)benzyl)-4-((7-chloro-6-methyl-4-oxo-4*H*-chromen-3-yl)methylene)-3-propyl-1*H*-pyrazol-5(4*H*)-one

Table 2: Binding Energy and Molecular description score of Chromone pyrozolone derivatives.

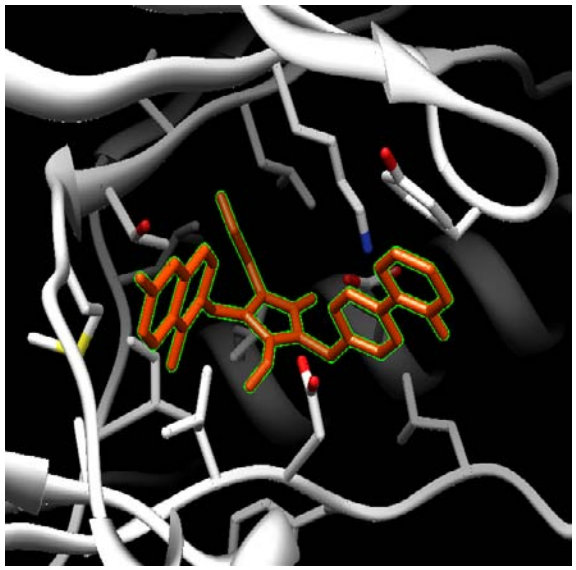
Sr. No	Chromone pyrozolones derivative.	Binding energy (kcal/mol)	LogP value	Molecular Weight	TPSA	HA ON	HD OHNH
1.	Derivative 1	-11.22	4.708	449.51	78.0	6	0
2.	Derivative 2	-12.90	5.133	463.537	78.0	6	0
3.	Derivative 3	-10.52	5.133	463.537	78.0	6	0
4.	Derivative 4	-12.65	5.362	483.955	78.0	6	0
5.	Derivative 5	– 9.78	5.739	497.982	78.0	6	0
6.	Biphenyl amide (BPA)	-11.31	3.332	402.498	88.4	6	5



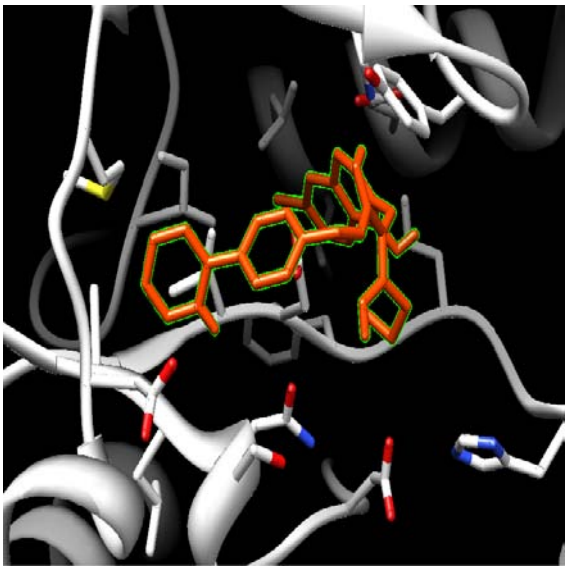
1a: Chromone pyrazolones derivative 1



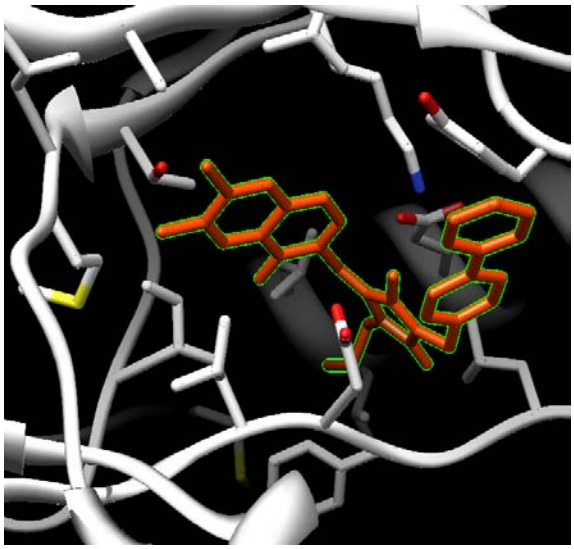
1b: Chromone pyrazolones derivative 2



1c: Chromone pyrazolones derivative 3



1d: Chromone pyrazolones derivative 4



1e: Chromone pyrazolones derivative 5

Fig. 1a-e: Chromone pyrazolones derivatives docked in p38 MAP Kinase

DISCUSSION

The p38 MAP kinase is involved in majority of immunological responses. It plays important role in innate as well as adaptive immune response. It is involved in signaling for the expression of certain NF-κB target genes which plays crucial role in the apoptosis pathways[21], majorly in the macrophages which are key cells involved in innate immune response. The p38 MAP kinase also takes part in inflammatory responses by regulating the interleukin and tumor necrosis factor expression[22]. Due to these key properties this kinase can be an excellent target for the therapy of the immunological and inflammatory[1] disorders. In the progress to identify the inhibitors of p38 MAP kinase, numbers of the compounds are identified but very few are used[23].

In current study, an approach of molecular docking was used to identify the potential inhibitor of this kinase by measuring their binding affinities. Further it is imperative to know the molecular properties related with pharmacokinetics of drug molecules which refers to the absorption, distribution, metabolism and excretion (ADME) of bioactive compounds[24]. Lipinski's "rule of five" is a heuristic approach for predicting drug-likeness stating that molecules having molecular weight >500, log P >5, hydrogen bond donors >5 and hydrogen bond acceptors >10 have poor absorption or permeation[25]. TPSA descriptor is described as a polar part of the molecule associated with the oxygen, nitrogen, sulfur atoms and also hydrogen connected to these heteroatom. For the drug the predictive value of TPSA should range in between 61 Å to 140 Å[26].

Comparing the results obtained through molecular docking of BPA and chromone pyrazolones derivatives, it becomes evident that binding energy of derivative 2 and 4 is better; followed by derivative 1. However derivative 3 and 5 exhibit poor binding affinity towards p38 MAP kinase. Derivative 1 obeys all the parameters for "Lipinski's rule of 5" while other derivatives slightly violates the rule in terms of log P value.

CONCLUSION

Form the data obtained by molecular docking as well as the molecular descriptor analysis the chromone pyrazolones derivatives 1 and 2 had the predicted data in the desired range and thus can be used for the further study in drug development for the inflammatory and immunological disorders.

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