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In-Silico Molecular Docking Studies of Some Imidazole Based Derivatives on Mapk Inhibitor (PDB ID- 1a9u) Against Inflammation

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KEYWORDS

P38 MAPK, inflammation

Abstract

Introduction: In the present work, molecular docking analysis was conducted on proposed protein derivatives from the protein data bank using the Auto Dock for Docking programme. study on protein binding affinity using imidazole derivatives and the MAPKs. Target-oriented virtual screening of ligands under investigation with adaptable molecular docking techniques.

Methods: In the present work, molecular docking analysis was conducted on proposed protein derivatives from the protein data bank using the Auto Dock for Docking programme. study on protein binding affinity using imidazole derivatives and the MAPKs.

Objective: Target-oriented virtual screening of ligands under investigation with adaptable molecular docking techniques. Using the AutoDock 4.2 programme, a number of molecules associated with imidazole were investigated for molecular docking, acute prediction, and ADMET analysis.

Results: According to docking research, these molecules have at least one hydrogen bond stabilising them. Docking score, ADMET analysis, acute toxicity prediction, and structural location of ligands in the active MAPKs site enzyme was found to positively correlate, supporting the viability of target-based virtual screening as a way to expedite pharmacological screening. By meticulously replicating the prior pharmacological experiment's circumstances.

Conclusions:**:** we are able to compare the outcomes and talk about certain commonalities in how molecule fragments affect inflammation action. Docking score, ADMET analysis, acute toxicity prediction, and structural location of ligands in the active MAPKs site enzyme were found to positively correlate, supporting the viability of target-based virtual screening as a way to expedite pharmacological screening.

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1. Introduction

The host initiates inflammation as a vital, targeted, and self-regulating defence mechanism in response to a microbial infection, tissue damage, or trauma (1). On the other hand, inflammation can be linked to a dysregulation of regular physiological processes when the triggering events are not controlled, and the heightened response can result in major chronic inflammatory illnesses (2,3). The aetiology of arthritis, stroke, cancer, neurological illnesses, and cardiovascular disorders can all be influenced by inflammation (4). One of the main regulators of the inflammatory response is prostaglandins (PGs). The most prevalent PG in the body is prostaglandin E2 (PGE2), which supports all of the mechanisms behind the traditional symptoms of inflammation, including pain, swelling, and redness (5,6). It causes redness and oedema by increasing blood flow to the inflammatory region through microvascular permeability and arterial dilatation. The mitogen-activated protein kinases (MAPKs), a member of the tyrosine kinase receptor family, is involved in a number of physiological processes, such as cellular migration, adhesion, proliferation, differentiation, and death (7,8,9). A novel strategy for mitogen-activated protein kinases (MAPKs) targeting and inhibition to reduce inflammation was recently put forth. Non-steroidal anti-inflammatory medications (NSAIDs), which target the two isoforms of cyclooxygenases, COX-1 and COX-2, to exhibit anti-inflammatory activities, now make up the majority of anti-inflammatory therapies in clinical use. However, some adverse effects include thrombosis, gastrointestinal bleeding, renal failure, and bronchospasm restrict the use of NSAIDs (10,11). As a result, a lot of research is being done to find and create natural compounds that have anti-inflammatory and antioxidant properties. Unchecked acute inflammation leads to chronic inflammation, degenerative diseases like osteoarthritis and rheumatoid arthritis, and even cancer (12). It also gradually damages tissues and organs and hinders their functions. mitogen-activated protein kinases (MAPKs) is a critical signalling molecule that regulates the synthesis of many inflammatory mediators. Consequently, a multitude of pharmaceutical businesses and academic establishments have undertaken extensive research on the mitogen-activated protein kinases (MAPKs) The mitogen-activated protein kinases (MAPKs) family of serine/threonine kinases is characterised by a shared overall structure and activation mechanism (14,15), whereby upstream activators such as EGFR, alternately, phosphorylate the kinases at the activation loop. All four isoforms of the mitogen-activated protein kinases (MAPKs) are present worldwide, with inflammatory cells expressing the p38 isoform most commonly lipopolysaccharide (LPS), proinflammatory cytokines, and other compounds produced by bacteria. It has been recently shown that phosphorylation of the epidermal growth factor receptor (EGFR) at the docking crease may both increase and reduce the activity of the receptor by inhibiting the binding of downstream targets and kinases (16). To that end, we performed a fictitious screening of a chemical library to find potentially interesting inhibitors of the mitogen-activated protein kinases (MAPKs) that may target the docking groove. Acute inflammation brought on by a persistent injury or unique conditions (such as diabetes, obesity, corticosteroid usage, blood problems, etc.) can progress to chronic inflammation. Pain and inflammation are frequently treated with nonsteroidal anti-inflammatory medications (NSAIDs). The involvement of MAPK in inflammation renders them appealing candidates for novel therapeutic interventions, and endeavours to discover more advanced, tailored inhibitors for inflammatory ailments persist.

2. Materials and methods

Hardware and Software

Both Software and Hardware, it was a pre-owned PC with an Intel® CoreTM i9-10900 CPU clocked at 2.80 GHz and 64.00 GB of RAM running Windows 10 64-bit. Software like Swiss Target Prediction (STP; www.swisstargetprediction.ch) provides an additional choice.

Ligand Structure Preparation:

The ligand drug data set consisted of the five previously synthesised derivatives and the structural information determined by IR and NMR mass. The structures of the derivatives of chromone pyrazolones were drawn using ChemSketch16, a freeware chemically intelligent drawing interface (http://www.acdlabs.com/download). Open Babel17 was then used for ligand preparation. The 3D structure was later generated using PRODRG2 Server1 (http://davapc1.bioch.dundee.ac.uk/prodrg/) in

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the required. mol format needed by the Argus Lab programme.

Docking Analysis and Molecular Property Calculation:

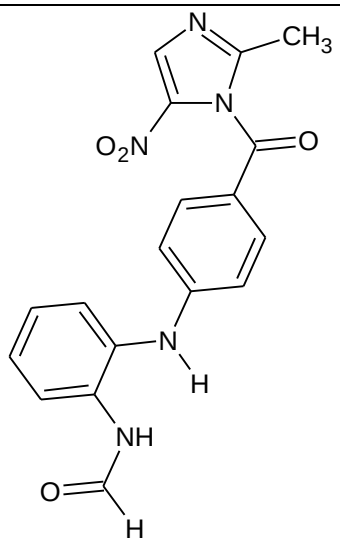
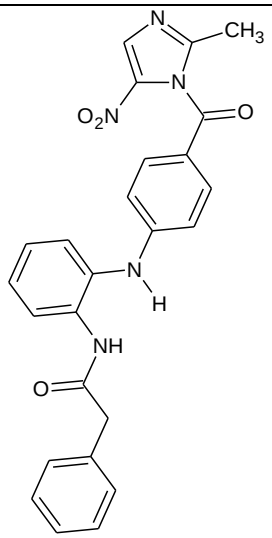
To find the possible active medication against p38 MAP kinase, docking was done using Arugus Lab 4.0.118 (http://www.arguslab.com), and the docking scores for each ligand molecule were computed. The molecular parameters were computed using Lipinski's rule of five, which makes use of basic molecular descriptors (http://www.molinspiration.com). The five parameters were determined using the online chemoinformatics tool molinspiration and include molecular weight, hydrogen donor acceptors, and LogP.

Ligand used for Docking:

Table 1: Docking Ligand information

Parameters	Details	Standards
Protein Id and method of experiment	1A9U X-RAY Diffraction	- X-RAY Diffraction
Mutation	No	No
Resolution	2.60 Å	Near about 2.00 A^0
wwPDB Validation	Blue side	Better
Ramchandran Plot (by PROCHECK server) Residues in favoured + Allowed regions	100%	>88.3 %

Table 2: Derivatives of designed compound of imidazole

Label	Structure	Label	Structure
S1a		**S1c**	

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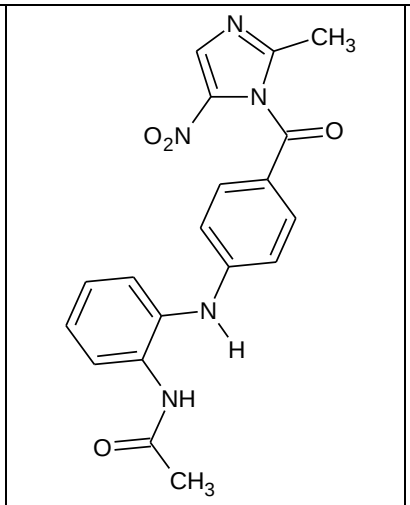
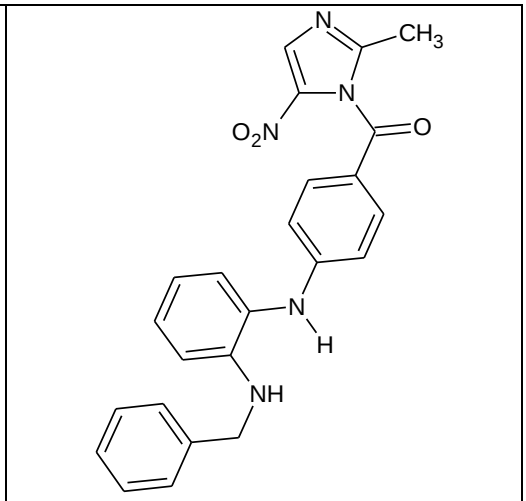
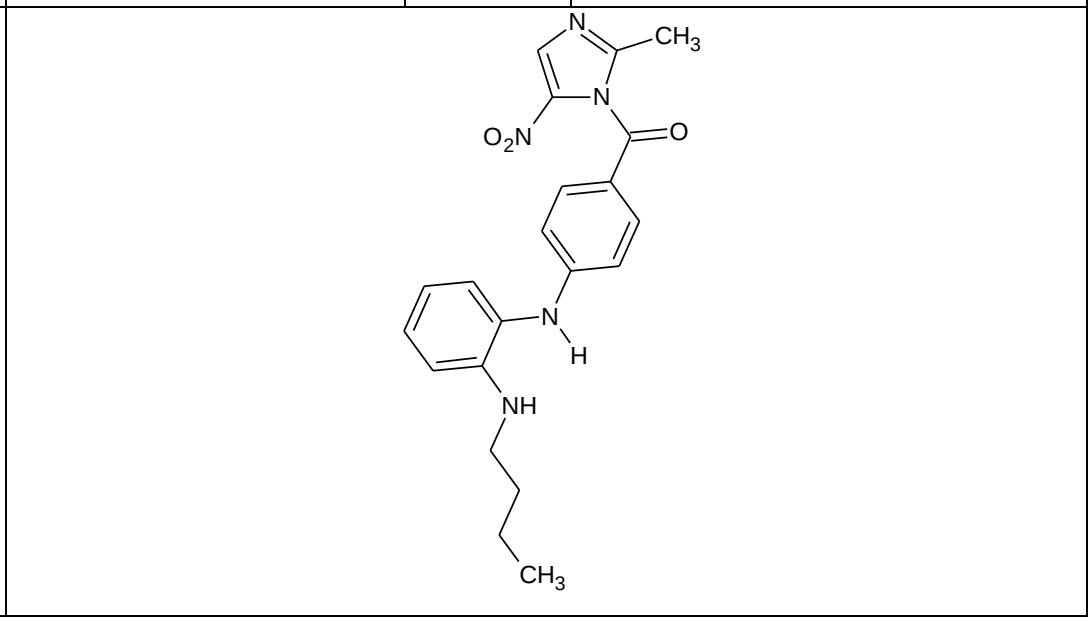
S1b		**S1d**	
S1e			

3. Results:

Table 3: Calculations of Lipinski's rule of Five and Druglikeness

Comp.	Molecular weight (g/mol)	CMC rule violation	Lipinski's rule violation	Mol Log P	H bond donor	H bond acceptor	No. of rotatable bonds	TPSA (Å2)
S1a	381.39 g/mol	3	Yes	2.15	2	5	7	121.84 Å²
S1b	379.37 g/mol	3	Yes	1.74	2	5	7	121.84 Å²

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S1c	455.47 g/mol	3	Yes	2.84	2	5	9	121.84 Å²
S1d	427.46 g/mol	3	Yes	3.07	2	4	8	104.77 Å²
S1e	393.44 g/mol	3	Yes	2.64	2	4	9	104.77 Å²

Table 4: In silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity)

Comp.	**Absorption**		**Distribution**			**Metabolism**				
	Caco2 permeability (log Papp in 10-6 cm/s)	**GI absorption**	**BBB perm. (logBB)**	**BBB Permeant**	**PPB (%)**	**CYP3A4 substrate**	**CYP1A2 inhibitor**	**CYP2C9 inhibitor,**	**CYP3A4 inhibitor**	**CYP2C19 inhibitor**
S1a	22.2815	High	1.49973	No	90.68	Non	No	Yes	No	No
S1b	22.2815	High	1.49973	No	91.54	Non	No	Yes	No	No
S1c	22.2815	Low	1.49973	No	91.88	Non	No	Yes	Yes	Yes
S1d	22.2815	High	1.49973	No	91.84	Non	No	Yes	Yes	Yes
S1e	22.2815	High	1.49973	No	92.27	Non	No	Yes	Yes	Yes

Table 5: Pharmacokinetics and drug-likeness properties of compounds

Compound codes	**Pharmacokinetics**									**Drug-likeness**			
	GI abs.	**BBB pen.**	**P-gp sub.**	**CYP 1A2**	**CYP2 C19**	**CYP 2C9**	**CYP 2D6**	**CYP 3A4**	**Log K_p (skin permeation, cm/s)**	**Ghose**	**Egan**	**Muegge**	**Bioavailability Score**
S1a	High	No	No	Yes	Yes	No	Yes	Yes	-4.60	No	No	No	0.55
S1b	Low	No	No	No	Yes	No	Yes	No	-4.61	No	No	No	0.55

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S1c	High	No	Yes	Yes	Yes	No	No	Yes	-4.74	No	Yes	No	0.55
S1d	High	No	Yes	Yes	Yes	No	No	Yes	-4.74	No	Yes	No	0.55
S1e	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.67	Yes	Yes	Yes	0.55

Table 6: Predicted acute toxicity of molecules

Compound codes	**Parameters**							
	LD_{50} (mg/kg)	**Toxicity class**	**Prediction accuracy (%)**	**Hepatotoxicity**	**Carcinogenicity**	**Immunotoxicity**	**Mutagenicity**	**Cytotoxicity**
				(Probability)				
S1a	1830	4	67.38	A (0.58)	A (0.79)	I (0.89)	A (0.71)	I (0.68)
S1b	3000	5	54.26	A (0.59)	A (0.72)	A (0.69)	A (0.96)	I (0.60)
S1c	1830	4	67.38	I (0.51)	A (0.70)	I (0.92)	A (0.66)	I (0.61)
S1d	1830	4	67.38	I (0.51)	A (0.70)	I (0.92)	A (0.66)	I (0.61)
S1e	3000	5	67.38	A (0.59)	A (0.70)	A (0.52)	A (0.59)	I (0.65)

Table 7: The active amino residues, bond length, bond category, bond type, ligand energies, and docking scores.

Active Amino acid	**Bond length**	**Bond Type**	**Bond Category**	**Docking score**
Compound: S1a				
ASP168	2.1188	Hydrogen Bond	Salt Bridge	**-7.8**
GLU71	4.29455	Electrostatic	Attractive Charge	
TYR35	3.07098	Hydrogen Bond	Conventional Hydrogen Bond	
LYS53	2.44576	Hydrogen Bond	Conventional Hydrogen Bond	
ARG67	2.11663	Hydrogen Bond	Conventional Hydrogen Bond	
ARG67	2.39002	Hydrogen Bond	Conventional Hydrogen Bond	
ASP168	2.73969	Hydrogen Bond	Conventional Hydrogen Bond	
GLU71	3.55155	Electrostatic	Pi-Anion	
ASP168	3.77571	Hydrophobic	Pi-Sigma	
TYR35	4.79017	Hydrophobic	Pi-Alkyl	
LEU75	5.4368	Hydrophobic	Pi-Alkyl	
ALA34	4.63232	Hydrophobic	Pi-Alkyl	
Compound: S1b				
LYS53	2.26012	Hydrogen Bond	Conventional Hydrogen Bond	**-8.0**

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UNL1	2.35974	Hydrogen Bond	Conventional Hydrogen Bond	
LYS53	3.92867	Electrostatic	Pi-Cation	
THR106	3.60757	Hydrophobic	Pi-Sigma	
MET109	5.30983	Hydrophobic	Alkyl	
VAL38	4.86466	Hydrophobic	Pi-Alkyl	
ALA51	4.27623	Hydrophobic	Pi-Alkyl	
LYS53	4.88503	Hydrophobic	Pi-Alkyl	
LEU104	4.97457	Hydrophobic	Pi-Alkyl	
S1c				
LYS53	2.41369	Hydrogen Bond	Conventional Hydrogen Bond	
MET109	2.2719	Hydrogen Bond	Conventional Hydrogen Bond	
LYS53	3.92616	Electrostatic	Pi-Cation	
GLU71	3.90558	Electrostatic	Pi-Anion	
ASP168	3.72908	Electrostatic	Pi-Anion	
THR106	3.61202	Hydrophobic	Pi-Sigma	**-10.2**
LEU167	5.17915	Hydrophobic	Pi-Alkyl	
LYS53	4.88992	Hydrophobic	Pi-Alkyl	
LEU104	4.9674	Hydrophobic	Pi-Alkyl	
LEU75	5.33573	Hydrophobic	Pi-Alkyl	
ALA172	5.38115	Hydrophobic	Pi-Alkyl	
S1d				
TYR35	2.73367	Hydrogen Bond	Conventional Hydrogen Bond	
ARG173	2.33741	Hydrogen Bond	Conventional Hydrogen Bond	
ASP168	2.6217	Hydrogen Bond	Conventional Hydrogen Bond	
ASP168	2.10763	Hydrogen Bond	Conventional Hydrogen Bond	
LYS53	2.51996	Hydrogen Bond	Hydrogen Bond	
GLU71	3.51816	Electrostatic	Pi-Anion	**-8.8**
ASP168	3.81634	Hydrophobic	Pi-Sigma	
ARG173	3.59993	Hydrophobic	Pi-Sigma	
TYR35	4.81576	Hydrophobic	Pi-Pi T-shaped	
UNL1	5.63231	Hydrophobic	Pi-Pi T-shaped	
VAL38	5.45181	Hydrophobic	Pi-Alkyl	

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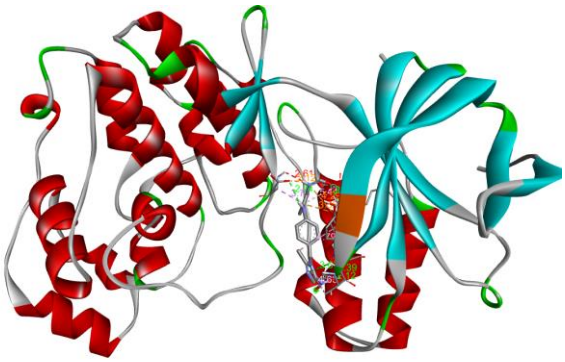
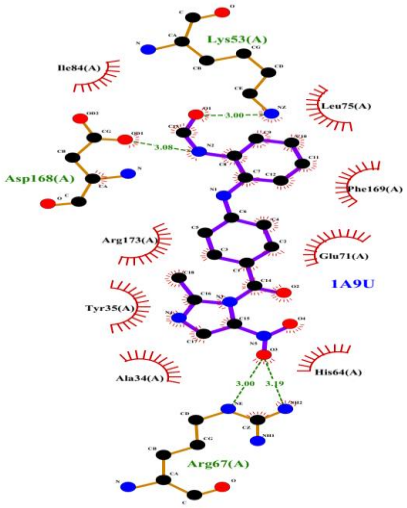
LYS53	4.5488	Hydrophobic	Pi-Alkyl	
ARG173	4.9804	Hydrophobic	Pi-Alkyl	
S1e				
LYS53	2.63552	Hydrogen Bond	Conventional Hydrogen Bond	**-7.7**
UNL1	2.21307	Hydrogen Bond	Conventional Hydrogen Bond	
LYS53	2.94653	Hydrogen Bond	Hydrogen Bond	
ARG67	3.9409	Electrostatic	Pi-Cation	
LEU75	4.75341	Hydrophobic	Alkyl	
ARG173	4.60045	Hydrophobic	Alkyl	
VAL38	5.13941	Hydrophobic	Pi-Alkyl	
ALA51	5.3172	Hydrophobic	Pi-Alkyl	
LYS53	4.7233	Hydrophobic	Pi-Alkyl	
ALA172	4.97669	Hydrophobic	Pi-Alkyl	
ARG173	5.13106	Hydrophobic	Pi-Alkyl	
LYS53	2.63552	Hydrogen Bond	Conventional Hydrogen Bond	

Table 8: Docking Poses 2D and 3D:

3D-docking poses	**2D-docking poses**
	
Compound: S1a	

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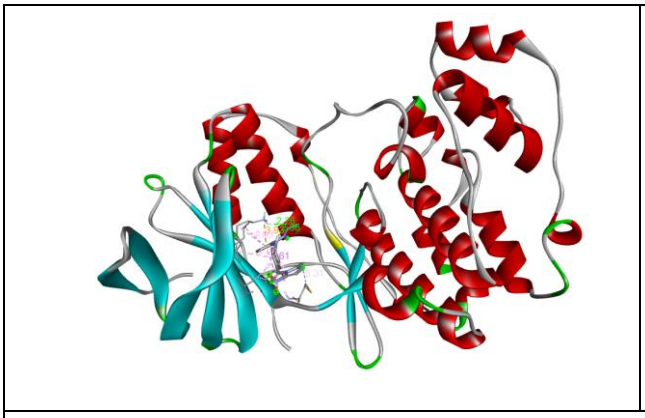
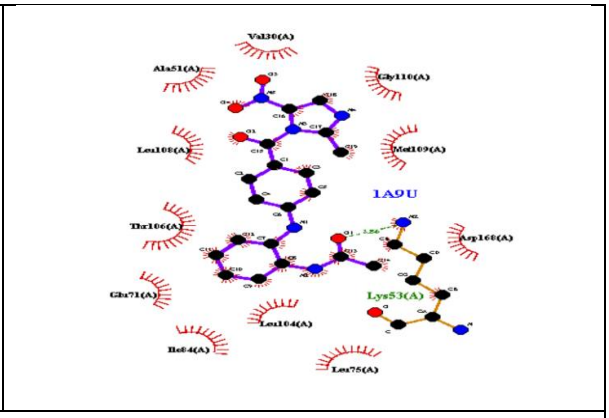
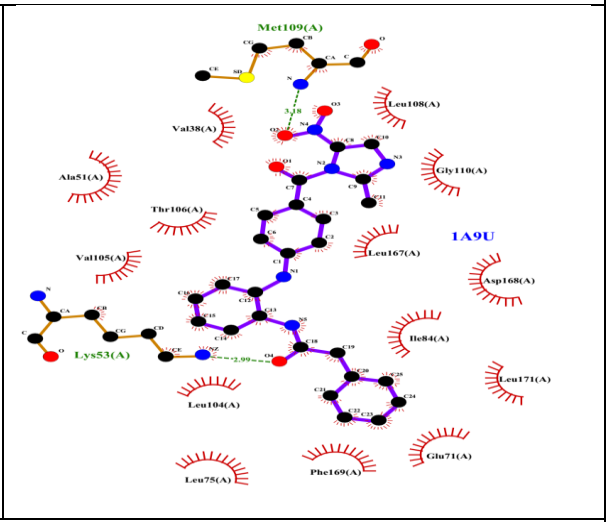
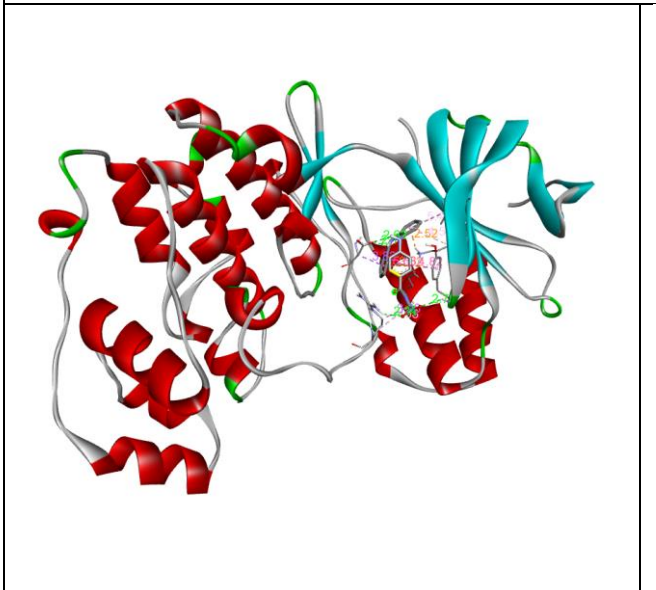


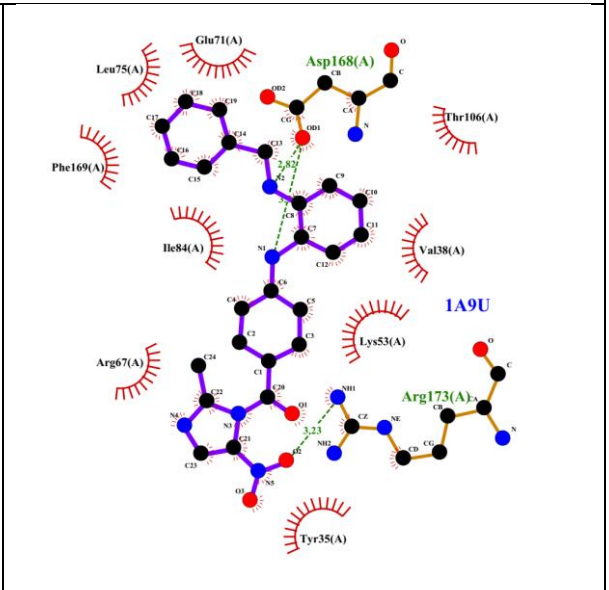


Compound: S1b



Compound: S1c





Compound: S1d

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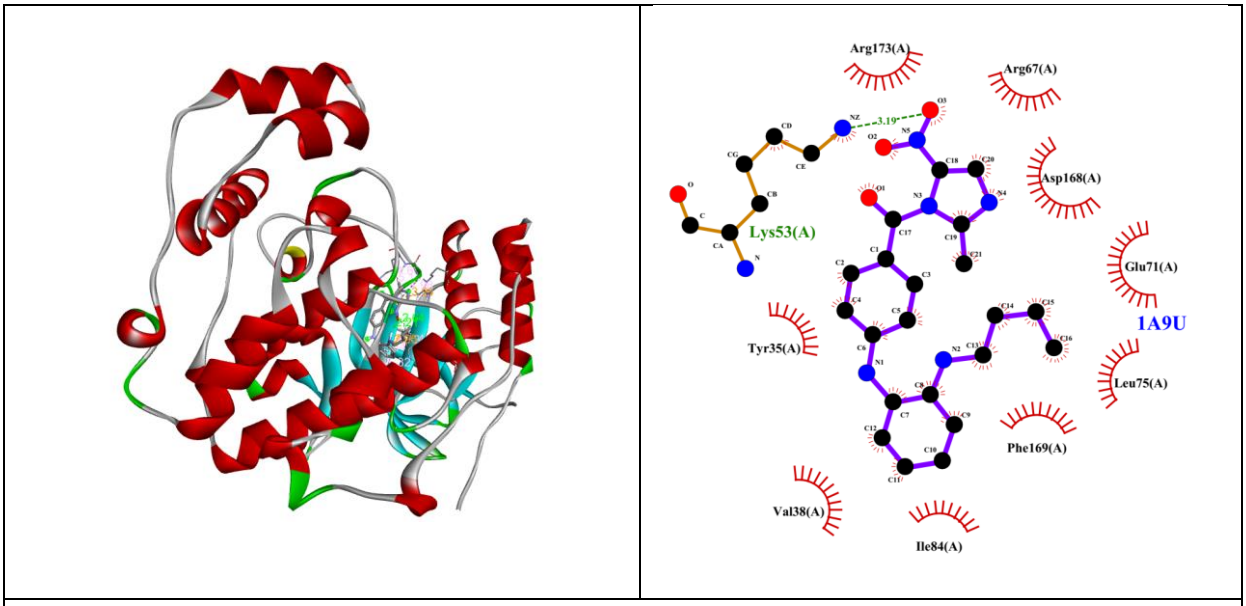

Compound: S1e

4. Discussion:

Docking Analysis of p38 MAP Kinase Inhibitors

The purpose of the docking investigation was to find out how well the new 1H-imidazole derivative bound to the p38 alpha MAP kinase protein's binding site. Table 1 and 7 displays the docking scores of five freshly synthesised compounds (S1a through S1e) and 2D and 3D Docking Posses. Based on the docking score, we provide here the docking analysis of the 3 most powerful compounds or derivatives (S1c, S1d, and S1e). It was discovered that the structures of all three powerful chemicals had one or two methyl groups. At −7.7 kcal/mol, S1e had the highest dock score, followed by S1d and S1c at −8.8 and −10.2 kcal/mol, respectively (S1d > S1e > S1c). When compared to molecules with a single methyl group, those containing two methyl groups in their structures exhibited greater binding interactions with receptors (S1d). All of the compounds exhibited hydrogen bond interactions with amino acid residues including some amino acids as well as comparable molecular interactions with the p38 MAP kinase active site.

ADME Studies

All of the synthesised compounds (S1a to S1e) were determined to be orally active medicines in this investigation (Table 3,4,5). Swiss ADME software was used to evaluate the ADME characteristics of substances. Lipinski's rule of five states that substances with a molecular weight of less than 500 have adequate oral bioavailability. Every chemical complied with the guideline. Swiss ADME software was also used to perform the gastrointestinal safety profile. These online web servers received the list of SMILES, and the necessary properties of the targeted compounds were generated.

Predicted acute toxicity of molecules.

The goal of acute toxicity studies is to identify the amount that, whether administered once or over a few administrations, will result in death or major toxicological consequences (Table 6). They also function as a source of knowledge on dosages that ought to be used in later research. These investigations offer an additional chance to ascertain compound-induced effects as shown by clinical chemistry, morphology, or other assessments. Additionally, acute investigations may provide an early indicator of the potential target organ or organs. This is a section of the acute toxicity studies. The median lethal dose (LD50) is defined as the dosage at which 50% of exposed animals die. This discovery has been useful in comparing the acute toxicity of different substances and served as the basis for the environmental and industrial toxicant categorization. Pharmaceutical development used to begin with a formal LD50 evaluation. Experience showed that the LD50 (Table 4)

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used much too many animals and provided little useful information for the creation of pharmacological products.

5. Conclusion

To sum up, several 1H-imidazole compounds were created in order to provide enhanced p38α MAP kinase inhibitors with notable anti-inflammatory properties. With significant p38α MAP kinase inhibitory activity, compounds S1a to S1e have emerged as the most powerful in the series. Moreover, compound S1d molecular docking investigation revealed a favourable orientation within the p38α MAP kinase active binding region, and its docking score was similar to kinase inhibitor. All of the synthetic compounds were found to be oral active medicines using ADME tests, which were based on Ergan's egg graph and Lipinski's rule of five. Within the allowable range, the compounds also showed excellent gastrointestinal absorption.

6. Acknowledgement

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7. Conflict of interest

The authors declare no conflict of interest.

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