



## Molecular Docking of Triazine analogues

Biswajit Das<sup>1</sup>, Uttam Kumar Mondal<sup>1</sup>, Shyamal Sharma<sup>1</sup>, Pranab Ghosh<sup>2</sup>  
and Asim Kumar Bothra<sup>1\*</sup>

<sup>1</sup>Cheminformatics Bioinformatics Lab, Department of Chemistry, Raiganj College (University College), Raiganj, Uttar Dinajpur, West Bengal, INDIA

<sup>2</sup>Department of Chemistry, University of North Bengal, Rajarammohunpur, Darjeeling, West Bengal, INDIA

---

### ABSTRACT

The mitogen-activated protein (MAP) kinases a group of serine/threonine kinases function as critical mediators of signal transduction. MAP kinase causes several diseases, such as asthma osteoarthritis, rheumatoid arthritis, and chronic inflammatory autoimmune disease. Triazine analogues are inhibitor of p38 MAP kinase. Docking of MAP inhibitors are performed using AutoDock and binding energy for the inhibitors are calculated and regression equation is formed using HT29. Effect of substitution is analyzed. It is found presence of morpholino or anilino ring is essential. Some compounds are designed and their binding energy is calculated. It is seen that designed compound also inside the binding pocket.

**Keywords:** p38 MAPkinase, Molecular docking, rheumatoid arthritis, triazine derivatives, QSAR.

---

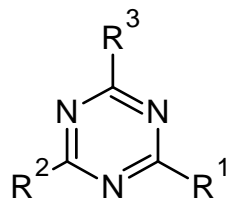
### INTRODUCTION

Mitogen- activated protein kinases (MAPK) are group of serine/threonine protein kinases that play an important role in signal transduction in many cellular process including growth, differentiation, cell death, and survival [1-5]. There are at least six different groups of MAPK that have been identified in humans cells: the extracellular signal-regulated protein kinases (ERK1, ERK2); c-Jun N-terminal kinases (JNK1, JNK2, JNK3) p38s (p38a, p38b, p38g, p38d); ERK5; ERK3s (ERK3, p97 MAPK, MAPK4); ERK7s (ERK7, ERK8) [6-8]. Each group of MAPKs can be simulated by a separate signal transduction pathway in response to different extracellular stimuli. MAP kinase plays a fundamental role to generate several diseases, such as asthma, osteoarthritis, rheumatoid arthritis, and chronic inflammatory autoimmune disease. The inhibition of MAP kinase would potentially prevent the underlying pathophysiology in the inflammatory diseases [9-11]. Rheumatoid arthritis causes damage of cartilage and deformation of bones [12]. The injury inflammation caused by inflammatory mediators such as Tumor necrosis factor- $\alpha$  and Interleukin-1 $\beta$  [13]. Biosynthesis of these two proinflammatory cytokins regulated by p38 and these two cytokins are associated with the progression of rheumatoid arthritis [14].

Triazine derivatives (T) show wide spectrum of biological activities in antimicrobial effect, Erm(erythromycin-resistance methylase)methyl transferase inhibition, anti-trypanosomal activity, VLA-4(integrin very late antigen-4) antagonism, estrogenreceptor modulation, cytotoxic activity [15-17]. Hexamethyl melamine, a triazine derivative possesses various pharmacological actions against breast, lung and ovarian cancers, severe adverse effect nausea, vomiting, abdominal cramps, and anorexia [18].

Leftheris et al. reported triaminotriazine aniline amide as potent inhibitor of p38 MAPkinase [19]. Zheng et al introduced various aryl amino groups in to the triazine scaffold and determined their biological activity [20]. Taking

the experimental activity from the work of “Zheng *et al.*” as dependent variable, we formulate a mathematical model, based on quantum chemical parameters to design numbers of potent triazine scaffold-based inhibitor (Figure 1).

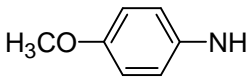
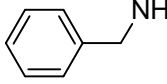
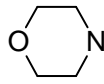
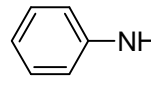
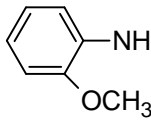
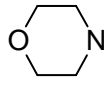
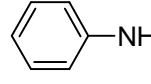
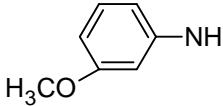
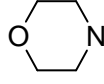
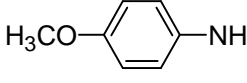
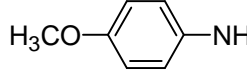
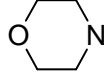
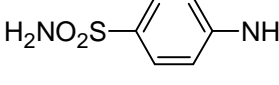
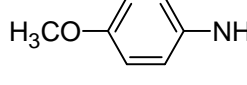
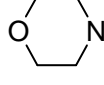
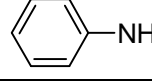
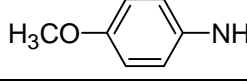
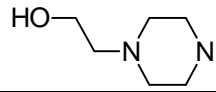


**Fig 1. Triazine analogue (T)**

In the present study the multilinear regression analysis has been applied for QSAR study. The relationship has been worked out between the values of compounds and free energy of binding. Auto Dock 4.2 simulation program was performed to determine the free energy of binding of several experimentally tested p-38 MAP kinase inhibitor [21]. Some chemically feasible compounds are designed and free energy of binding of the designed inhibitors was calculated through Auto Dock 4.2. Finally theoretical activity of designed set has been calculated.

**Table1: Chemical structures and inhibitory activities against HT-29 cells of triazine derivatives by substituting R1, R2, R3 of T**

Com	R1	R2	R3	%Inhibition at $\mu\text{M}^a$ ln(HT29)
1				4.3883
2				4.5053
3				4.4427
4				4.4671
5				4.336
6				4.4716
7				4.4751
8				4.3994
9				4.332
10				4.387
11				4.3121

12				4.4819
13				4.492
14				4.4705
15				4.3895
16				4.4212
17				4.3477

\*ln(HT29) – Natural logarithm of HT29

## EXPERIMENTAL SECTION

**Preparation of Ligand:** Triazine inhibitors and their HT29 values were collected from the published work of Zheng *et al* is shown in Table 1. For docking experiments with Autodock, ligand molecules were drawn by Chemscketch and the ligands are optimized and saved as in pdb format with the aid of Arguslab 4.01 [22]. In the next step prepared ligands were used as input files for AutoDock4.2

**Protein Setup:** The X- ray crystal structure of P38 MAP kinase was downloaded from the Protein Data Bank as PDB file (PDB entry code 1kv2) [23].

**Docking:** Docking studies were performed with AutoDock4.2 using Lamarckian genetic algorithm [24]. The flexible docking procedure was used for a P38 MAP kinase protein and a flexible ligand. A grid of 94, 78, 62 points in x,y, and z direction was constructed. A grid spacing of 0.375Å and distance- dependent function of the dielectric constant was used for the calculation of the energy map. The defaults settings were used for all other parameters. At the end of docking, ligand with most favorable free energy of binding were noted. The entire calculations were carried out on PC based machines running Linux as operating system.

**Table 2: Actual and predicted activities of the training set molecules**

Compound	Free energy of Binding (kcal/mol)	% Inhibition at $\mu\text{M}^{\alpha}$ ln(HT-29)	Predicted %Inhibition at $\mu\text{M}^{\alpha}$ ln(HT-29)
	-8.34	4.3883	4.4288
1			
2	-9.03	4.5053	4.4224
3	-8.67	4.4427	4.4258
4	-8.77	4.4671	4.4248
5	-8.9	4.336	4.4236
6	-6.95	4.4716	4.4418
7	-8.18	4.4751	4.4303
8	-8.67	4.3994	4.4258
9	-19	4.332	4.3297
10	-8.88	4.387	4.4238
11	-9.74	4.3121	4.4158
12	-9.44	4.4819	4.4186
13	-9.32	4.492	4.41972
14	-9.15	4.4705	4.4213
15	-9.11	4.3895	4.4217
16	-9.66	4.4212	4.4166
17	-8.33	4.3477	4.4289

## RESULTS AND DISCUSSION

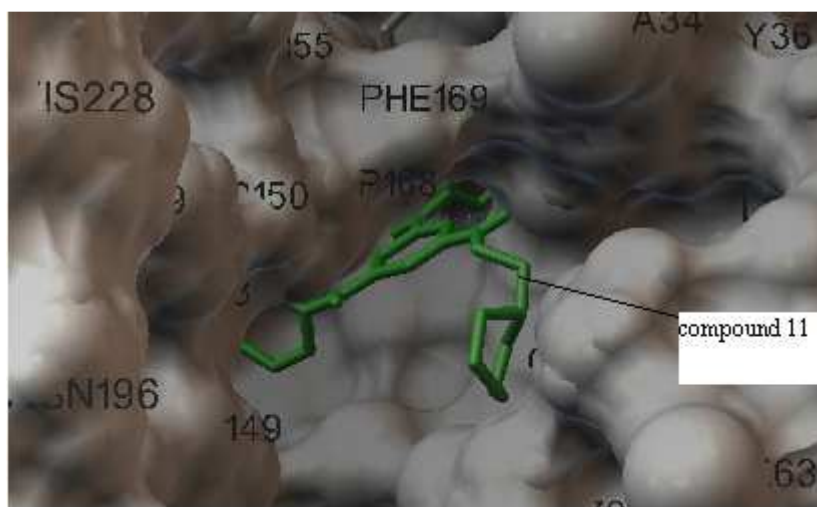
Molecules were successfully docked on to the active site of P38 MAP according to the above docking analysis. Results of the docking experiments we calculated free energy of binding for each complex with triazine analogues and P38 MAP kinase.

Total 17 compounds were used for regression analysis. A regression equation was performed using one index, free energy of binding.

$$\ln HT29 = 4.507487 + (0.0090) \text{ binding energy}$$

By this equation we calculated predicted  $\ln HT29$  activity (Table2).

A repressive figure containing one of the inhibitor (11) in the binding site of P38 MAP kinase is presented in Figure 2. From the Figure 2, it is clear that the inhibitor is well inside binding cavity.

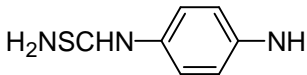
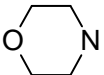
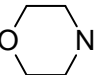
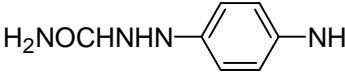
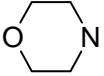
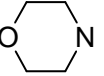
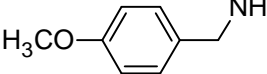
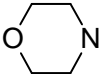
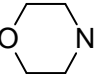
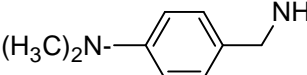
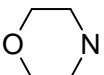
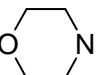
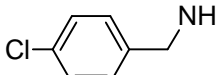
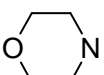
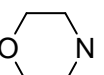
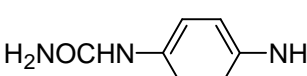
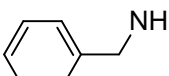
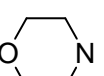
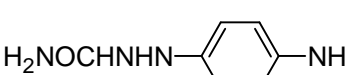
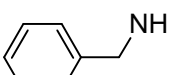
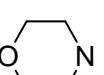
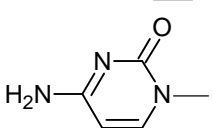
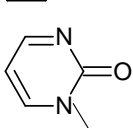
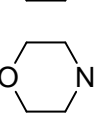
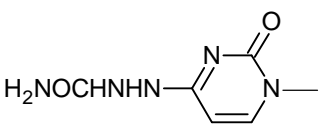
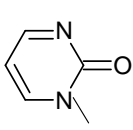
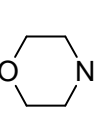
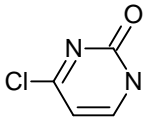
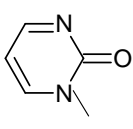
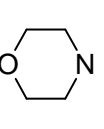
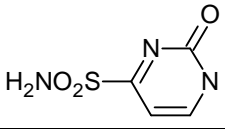
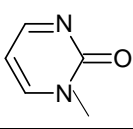
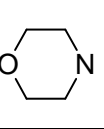


**Fig. 2: Docking result of triazine inhibitor (11)**

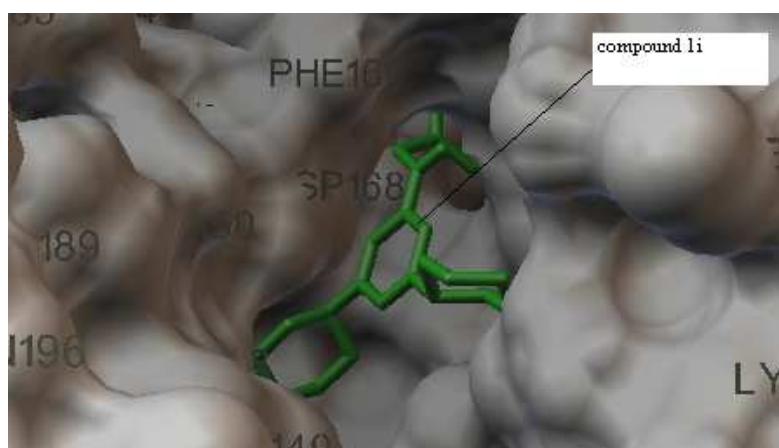
It is seen that presence of one morpolino or anilino ring is essential for the activity of triazine derivatives. Also introduced pyrimidine ring in triazine scaffold gives very high predicted activity. Basis of this finding we designed several triazine analogues as more potent p38 MAP kinase inhibitors and Docking simulation was performed. Structures of Triazine analogue and their corresponding Docking energy are shown in Table 3.

**Table 3: Chemical structures of designed triazine derivatives by substituting R1, R2, R3 of E and their Docking energies.**

Compound	R1	R2	R3	Docking Energy (kcal/mol)
1a				-8.75
1b				-7.96
1c				-9.03
1d				-9.07
1e				-8.51

1f				-9.29
1h				-8.83
1i				-9.40
1j				-9.31
1k				-9.30
1l				-9.36
1m				-8.1
1n				-9.26
1o				-8.15
1p				-7.13
1q				-8.0

One of the designed compound (1i) docked with p38 MAP kinase is presented in Figure 3. It is observed that designed compound is also inside the binding cavity.



**Fig. 3: Docking result of triazine inhibitor (1i)**

## REFERENCES

- [1] AJ Whitmarsh; RJ Davis. *J. Mol. Med.*, **1996**, 74, 589- 607.
- [2] TP Garrington; GL Johnson. *Curr. Opin. Cell Biol.*, **1999**, 11, 211-218.
- [3] P Cohen. *Trends. Cell Biol.*, **1997**, 7, 353–361.
- [4] YT Ip. RJ Davis. *Curr. Opin. Cell Biol.*, **1998**, 10, 205–21.
- [5] RJ Davis. *Curr. Opin. Cell Biol.*, **1998**, 10, 205–219.
- [6] FA Gonzalez; D L Raden; MR Rigby; RJ Davis, *FEBS Lett.*, **1992**, 304, 170-178.
- [7] MK Abe; MP Saelzler; R Espinosa; KT Kahle; MB Hershenson; BMM Le; M R Rosner. *J. Biol. Chem.*, **2002**, 277, 16733-16743.
- [8] S Kant; S Schumacher; MK Singh; A Kispert; A kotlarov, M Gaestel. *Biol Chem.*, 2006, 281 (46), 355111-355119.
- [9] EHS Choy; GS Panayi. *N Eng J Med.*, **2001**, 344, 907-916.
- [10] CA Dinarello. *Curr Opin Immunol.* **1991**, 3, 941-948.
- [11] MA Palladino; FR Bahjat; EA Theodorakis; LL Moldawer. *Nat Rev Drug Disc.* **2003**, 2, 736-741.
- [12] E Chen; EC Keystone; EN Fish. *Arthritis and Rheum.*, **1993**, 36(7), 901-910.
- [13] FG Salituro; UA Germann; KP Wilson; GW Bemis; T Fox; MS Su. *Curr Med Chem.*, **1999**, 6(9), 807-823.
- [14] J Harada; M Sugimoto. *Japan J Pharmacol.*, **1999**, 79, 369-378.
- [15] JL Silen; AT Lu; DW Solas; MA Gore; D Maclean; NH Shah; JM Coffin; NS Bhinderwala; YW Wang; KT Tsutsui; G C Look; DA Campbell; RL Hale; M Navre; FC Deluca. *Antimicrob. Agents Chemother.* **1998**, 42, 1447.
- [16] B Klenke; M Stewart; MP Barrett; R Brun; IH Gilbert. *J. Med. Chem.*, **2001**, 44, 3440.
- [17] R Menicagli; S Samaritani; G Signore; F Vaglini; LD Via. *J. Med. Chem.*, **2004**, 47, 4649.
- [18] BJ Foster; BJ Harding; JB Leyland; D Hoth. *Cancer Treat. Rev.*, **1986**, 38, 197.
- [19] K Leftheris; G Ahamed; R Chan; AJ Dyckman; Z Hussain; J Hynes; W Li; S Lin; A Metzger; K Moriarty; C Riviello; Y Shimshock; J Wen; J Wityak; ST Wroblewski; H Wu; J Wu; M Desai; KM Gillooly; TH Lin; ZR Loo; D Diller; A Doweyko; J Sack; J Baldwin; J Barrish; J Dodd; I Henderson; S Kanner; GL Schieven; M Webb. *J. Med. Chem.*, **2004**, 47, 6283.
- [20] M Zheng; C Xu; J Ma; Y Sun; F Du; H Liu; L Lin; C Li; J Ding; K Chen; H Jiang. *Bioorganic & Medicinal Chemistry*. **2007**, 15, 1815-1827.
- [21] G Morris; D Goodsell; R Huey; W Hart; S Halliday; R Belew; A Olson, *Autodock 3.0.5 User's Guide*, **1998**, 86. (<http://www.scripps.edu/pub/olson-web/doc/Autodock>)
- [22] <http://www.seanet.com/~mthompson/Arguslab>.
- [23] C Pargellis; L Gilmore; AG Graham; PM Grob; ER Hickey; N Moss; S Pav; *J Regan Nat. Struct. Biol.*, **2002**, 9, 268-272.
- [24] V Priya; RK Jannaie; K Vijayalakshmi. *J. Chem. Pharm.Res.*, **2011**, 3(4), 129-139.