

**Original Article**

**MICROWAVE ASSISTED SYNTHESIS OF TETRAHYDROPYRIMIDINE AND *IN SILICO* SCREENING OF ANTIDIABETIC DRUG**

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**ABSTRACT**

**Objective:** To detect the microwave-assisted synthesis of Tetrahydropyrimidine derivative and its molecular docking studies for Diabetes.

**Methods:** The Bignelli condensation method was used for Tetrahydropyrimidine derivative synthesis. The docking studies made in Argus Lab software.

**Results:** The Tetrahydropyrimidine is synthesized using the microwave. The Tetrahydropyrimidine derivative is found to be attack the insulin receptor, as it the tendency of binding with insulin receptor showed in Argus lab. Further, the good binding site of Tetrahydropyrimidine derivative with insulin receptor was predicted.

**Conclusion:** From the research work, The Tetrahydropyrimidine derivative shows its affinity to bind with the insulin receptor. The binding value is averagely 7 which indicates it can attraction with the receptor, so it can control Diabetic mellitus by altering insulin secretion in blood plasma.

**Keywords:** Tetrahydropyrimidine, Microwave-assisted synthesis, Molecular docking study, Antidiabetic activity

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**INTRODUCTION**

Diabetes mellitus is characterised by abnormally high levels of glucose in the blood due to an abnormal level of insulin secretion [1]. The diabetes shows the combined effect of hyperglycaemic with long period damage or malfunction or death of some organ [2]. Several pathogenic process are involved in the development of diabetes. Diabetes affected more 425 million people in the world, In India more than 742,946,400 case were studied in adult [3]. Diabetes is mainly classified as two types; 1) Type- Diabetes which is complete destruction of insulin, 2) Type- Diabetes which is inadequate supply of insulin [4]. Diabetes is treated by oral medication and lifestyle modification, oral medication is based on providing blood glucose lowering drug [5].

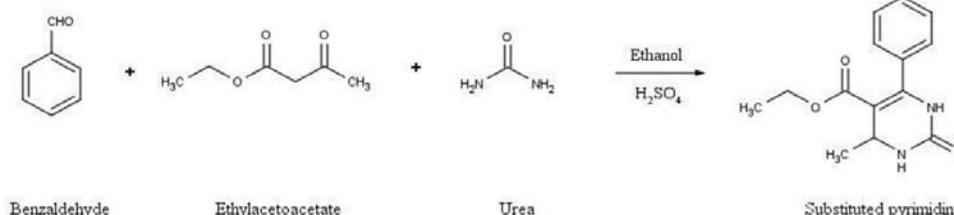
Tetrahydropyrimidine derivative synthesis based on the bignelli condensation prepared on microwave assistant [6]. Tetrahydropyrimidine derivatives can act as anthelmintics [7], antiparasitic [8], antibacterial [9] and show muscarinic activity [10]. The concept of green synthesis principle have made more attention of fine chemicals and pharmaceutical industries on preparation of

organic products. The green synthesis produce less toxic and safe reagents. Green synthesis has been identified as eco-friendly technique of formulations [11]. Microwave assisted synthesis comparatively beneficial than conventional synthesis, in conventional method need of large solvent, long time taken to get heated, spread bad odour where these can be reduced in microwave assisted synthesis [12].

Molecular docking studied are mainly made to find the interaction of ligand receptor binding by the computational method [13]. Molecular docking study helps to design and discover the drug and to study the binding in DNA/RNA site [14]. Ligand fitting into binding site due to hydrophobic and electrostatic interaction gives the free binding energy [15].

**Synthesis**

It is based on the Bignelli Condensation. The equimolar mixture of aromatic aldehyde (benzaldehyde), ethyl acetoacetate and urea were taken in a round bottom flask. To the mixture concentrated hydrochloride acid is added, converted into china dish kept in microwave 180watts for 1 minute, recrystallized by ethanol [16].



**MATERIALS AND METHODS**

**Preparation of ligand**

The green synthesis of Tetrahydropyrimidine derivative namely Ethyl 4-methyl-2-oxo-6-phenyl-3, 4-dihydro-1H-pyrimidine-5-carboxylate [17] is chosen as the ligand. The ligand structure is

initially drawn in Chemscketch software, and its 3d structure is viewed in Argus lab.

**Preparation of protein**

The crystal structure of phosphorylated insulin receptor tyrosine kinase in complex with peptide substrate and ATP analogue

receptor was downloaded from RCSB PDB (<http://www.rcsb.org>), it consists of code 1IR3 [18]. The downloaded receptor is viewed in chimera 1.13.1.

#### Molecular docking

The Ethyl 4-methyl-2-oxo-6-phenyl-3, 4-dihydro-1H-pyrimidine-5-carboxylate ligand is viewed in Argus lab, and selected as ligand group. The phosphorylated insulin receptor tyrosine kinase in complex with peptide substrate and ATP analogue receptor is

viewed in chimera, remove the complexed compound present in the receptor, further view it in Argus lab and add hydrogen to the receptor so as to increase affinity. The amino acid binding site were selected from earlier literature and the binding sites namely 1079 MET, 1150 ASP, 1006SER, 1083 ASP, 1081 HIS, 1108 GLU, 1077 GLU [19]. The docking of receptor-ligand was made on Argus lab software [20]. The binding made with grid dimension (x, y, z) = (39×39×39). The best ligand pose energy was found and for every binding site and viewed in Pymol viewer.

#### RESULTS AND DISCUSSION

Table 1: Docking score and binding site

S. No.	Rank	Binding site	Best ligand pose energy (kcal/mol)	Cluster poses
1	1	1079 MET	-9.13544	50
2	2	1150 ASP	-8.03805	24
3	3	1006 SER	-7.62575	60
4	4	1083 ASP	-7.58741	68
5	5	1081 HIS	-7.51747	50
6	6	1108 GLU	-5.44869	63
7	7	1077 GLU	-5.00426	18

Ligand: Tetrahydropyrimidine

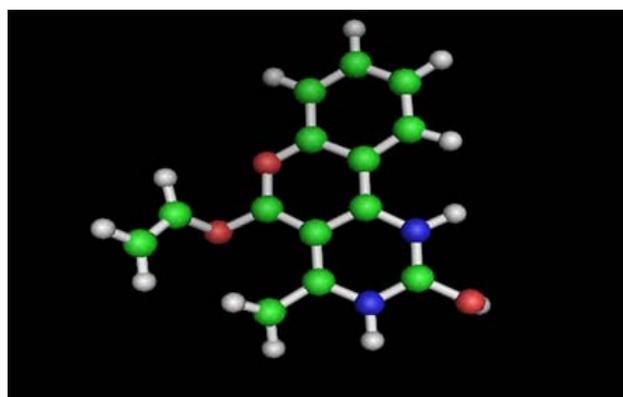


Fig. 1: Ethyl 4-methyl-2-oxo-6-phenyl-3, 4-dihydro-1H-pyrimidine-5-carboxylate

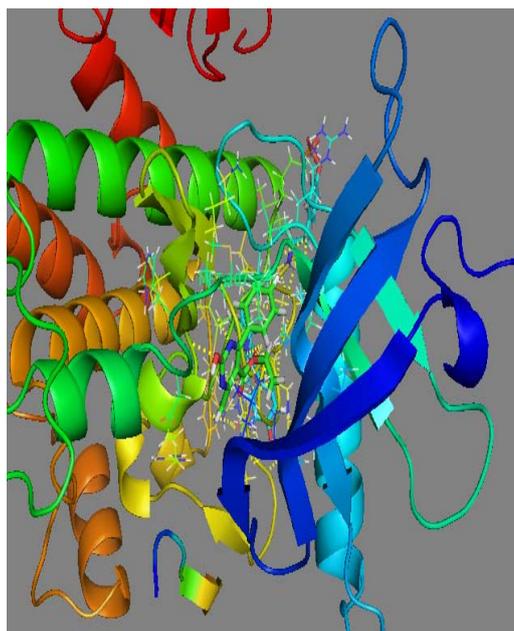


Fig. 2: 1079MET

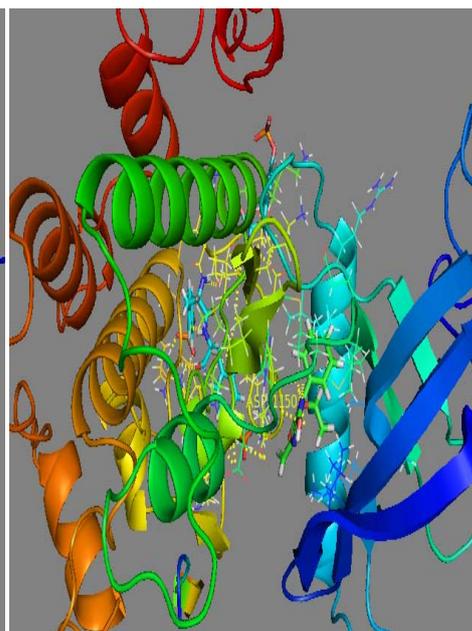


Fig. 3: 1150ASP

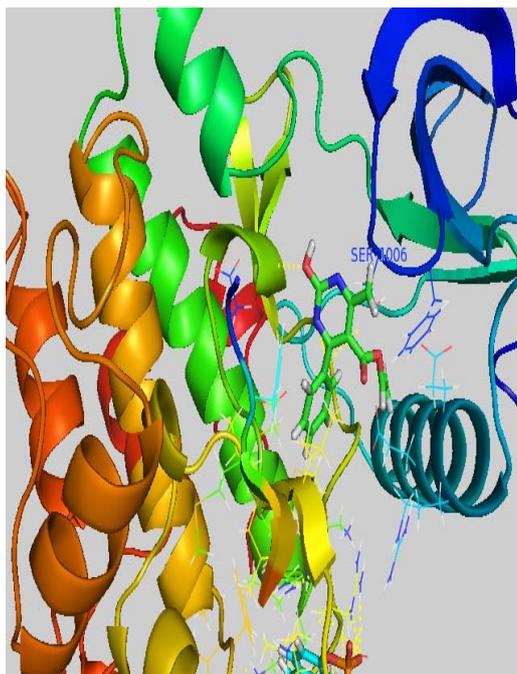


Fig. 4: 1006SER

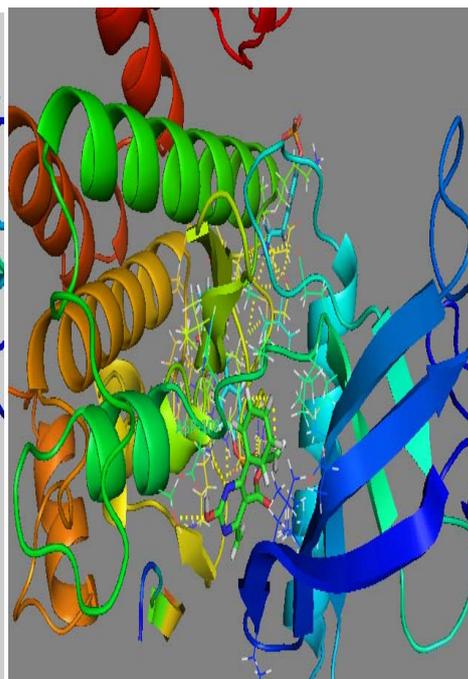


Fig. 5:1083ASP

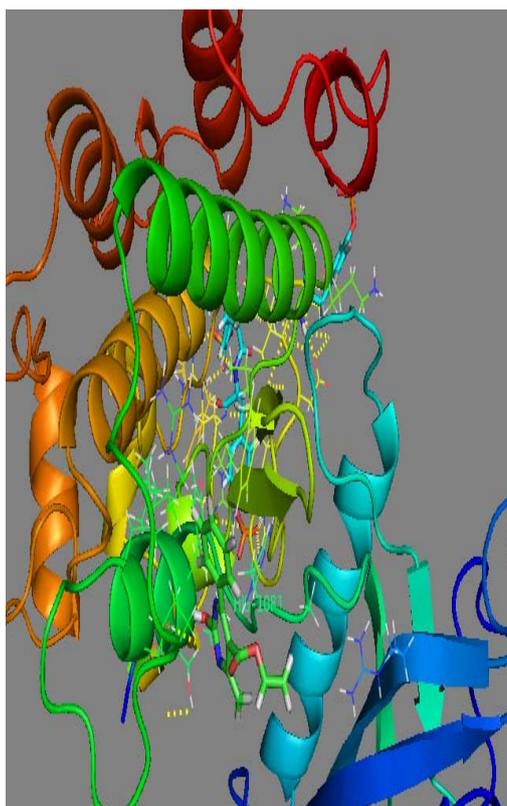


Fig. 6: 1081HIS

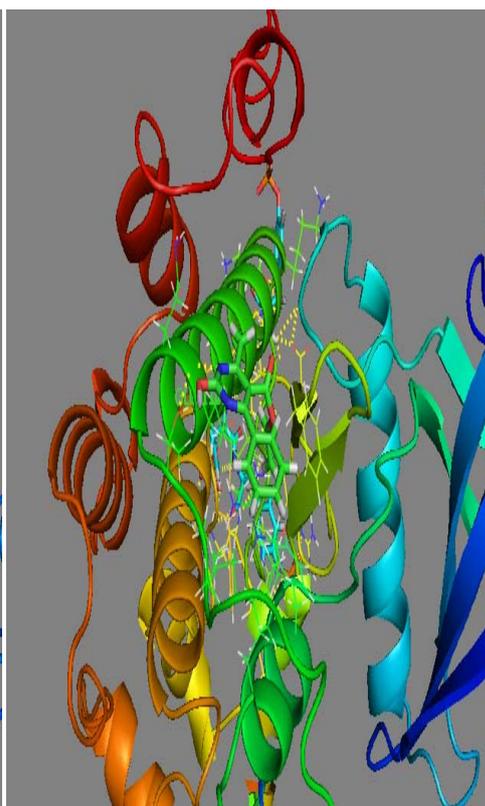


Fig. 7: 1108GLU

The docking study made to determine protein and ligand binding energy and capacity [20]. The main reason for the study is to determine the Tetrahydropyrimidine derivative compound can attach to insulin receptor and can increase insulin production, hence the Tetrahydropyrimidine compound forms interaction with insulin. Argus lab docking reports gives the best ligand pose energy and

these energy values are arranged in lower value order. The ligand binded with amino acid namely 1079 MET, 1150 ASP, 1006 SER, 1083 ASP, 1081 HIS, 1108 GLU, 1077 GLU and possess energy-9.13544,-8.03805,-7.62575,-7.58741,-7.51747,-5.44869,-5.00426 respectively. It shows that the tetrahydropyrimidine derivative can be used for insulin secretion.

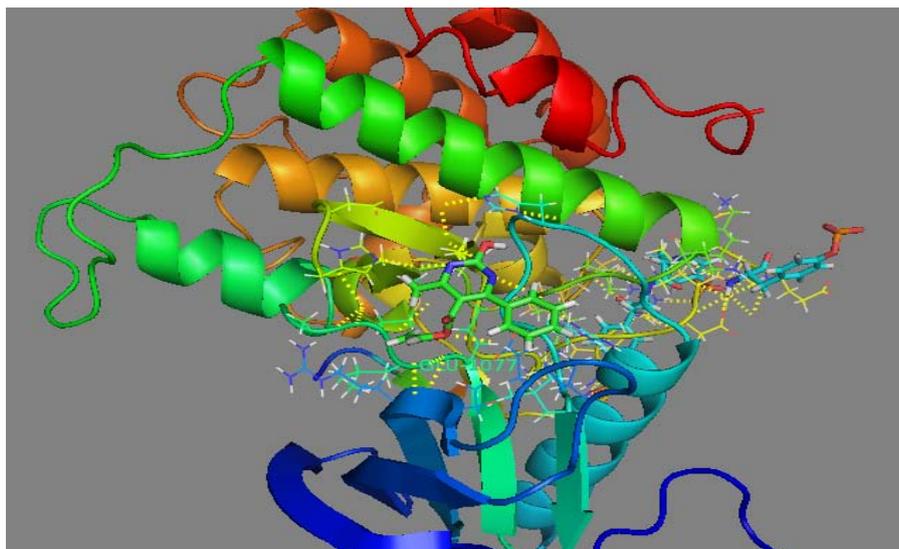


Fig. 8: 1077GLU

## CONCLUSION

The docking study shows that tetrahydro pyrimidone derivative produced by green synthesis preparation is can use for the treatment of diabetic as it can increase insulin secretion.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONCLUSION OF INTERESTS

The authors confirm that this article content has no conflict of interest.

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