



# INTERNATIONAL JOURNAL OF ADVANCE RESEARCH, IDEAS AND INNOVATIONS IN TECHNOLOGY

ISSN: 2454-132X

Impact factor: 4.295

(Volume3, Issue2)

Available online at [www.ijariit.com](http://www.ijariit.com)

## Insilico Studies on Taste Receptor Gene (Tas2r38) and Tas2r38 Protein Interaction with Ligands PTC and PROP Using Docking Approach

**Manisha Mathur**

Dept Of Zoology,  
Mumbai University, India  
[manishakmathurs@yahoo.co.in](mailto:manishakmathurs@yahoo.co.in)

**Parakh Sharma**

Department Of  
Bioinformatics  
Mumbai University, India  
[parakh.sehgal@gmail.com](mailto:parakh.sehgal@gmail.com)

**Faiza S.Khan**

Department Of  
Bioinformatics  
Mumbai University, India  
[kfaiza212@gmail.com](mailto:kfaiza212@gmail.com)

**Mrunmai Pednekar**

Department Of Bioinformatics  
Mumbai university, India  
[mrnunmaipednekar@gmail.com](mailto:mrnunmaipednekar@gmail.com)

**Abstract:** The G protein-coupled receptor (GPCR) Tas2r38 is a bitter taste receptor that can respond to bitter compounds such as phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). This receptor was chosen because of its haplotypes (based on three residue site polymorphism) *htas2r38pav*, *htas2r38avi* are known to have a dramatically different response to ligands *ptc* and *prop*. A docking study is performed to propose the best affinity between ligands PTC & PROP against the various active site of *tas2r38* protein. The 3D structure of *tas2r38* bitter taste receptor was predicted using GPCR-I-TASSER. The interaction of *tas2r38* protein with ligands PTC & PROP were studied, their chemical structures were drawn using Marvin Sketch and the potential ligands were optimized using PyRx. Metal Pocket tool was used to predict the binding sites for *htas2r38pav*, *htas2r38avi* bound to *ptc* & *prop* respectively. Further, the docking studies of *tas2r38* protein with *ptc* & *prop* were performed using PyRx tools and their interaction with the *tas2r38* protein was visualized using Discovery Studio. The ligand PTC & PROP was docked on the protein PAV at the active sites 108, 112, 199 & 266 which showed a docking efficiency of -4.6, -4.5, -4.7 & -5.3 respectively. Also these ligands were docked on another haplotype AVI at the active sites 198, 262, 266 which showed a docking efficiency of -4.7, -5.1, respectively. On the basis of their binding scores, it was predicted that the ligand PTC has a higher binding affinity to the haplotypes PAV and AVI as compared to the ligand PROP.

**Keywords:** PTC, PROP, TAS2R38 GENE, GPCR, DOCKING.

### I. INTRODUCTION

Bitter compounds are even more numerous and more chemically diverse than sweet molecules. Bitter substances elicit aversion leading to rejection of bitter food. It has been argued that bitter taste prevents us from ingesting potentially harmful or poisonous compounds. In fact, many bitter compounds, including food-borne substances, are toxic, although a relation of bitterness and toxicity has not been established. Bitter perception generally occurs through bitter taste receptors located on the surface of taste cells of the tongue. [1] In vertebrates, bitter compounds are detected by means of a family of specific receptors, the TAS2Rs. These receptors are encoded by T2R genes that show 25-89% amino acid sequence identity between the 60 different members of this gene family. These differences presumably allow a wide variety of different chemical shapes, sizes, and functionalities to be bound by these receptors and perceived as bitter. The human genome contains 25 TAS2R genes at four loci on chromosomes 5, 7, and 12. [2]

Based on a lack of sequence conservation with other G protein-coupled receptor genes they encode an own subfamily of G protein-coupled receptors. All members of the TAS2R family serve as oral bitter receptors, although they likely have additional functions based on the observation that the TAS2R genes are expressed at various extra-oral sites. (W. MEYERHOF) Various TAS2Rs show quite specific agonist profiles, like *ptc* & *prop*, have certain chemical substructures in common. In the formation of bitterness receptors, the human body uses "blueprints" that are saved on the 25 so-called TAS2R genes in our DNA.

TAS2R38 encodes for a seven-transmembrane G-protein-coupled receptor (GPCRs), which belongs to a TAS2R family of proteins that first sense molecules or specific stimuli outside of the cell and then trigger a certain cellular response within the cell. Essentially all GPCRs serve as a type of molecular switch, and they are referred to as seven-transmembrane receptors since the

proteins pass through the cell membrane seven times. TAS2R38 is located on the long arm of Chromosome 7 and is 1,143 base pairs long. More specifically, its cytogenetic location is 7q34 and runs from base pair 141,972,630 to base pair 141,973,772. Taste Receptor 2 member 38 is a protein that in humans are encoded by the TAS2R38 gene [2],[3].

Three common Single Nucleotide Polymorphisms (SNPs) were identified in this gene, which is at base pairs 145 (C-G), 785 (C-T) and 886 (G-A), resulting in 3 amino acid substitutions at codons P49A, A262V, and V296I. At amino acid position 49, where either a proline or an alanine is encoded, at position 262, where either an alanine or a valine is encoded, and at position 296, where either a valine or an isoleucine is encoded, giving rise to two frequent haplotypes, PAV and AVI, plus the less common haplotype AAI and PVV. The PAV haplotype associated with tasting whereas AVI associated with non-tasting. Two predominant haplotypes of the gene encode two major forms of the protein, and these PAV & AVI forms account for the majority of PTC taster and non-taster individuals in the worldwide population. Each allele codes for a bitter taste receptor protein with a slightly different shape and the shape of that receptor protein determines how strongly it can bind to the PTC [4]. The synthetic compounds, phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) have been identified as major ligands for this receptor [6],[7],[8]. TAS2R38 is the gene which is responsible for the ability to taste PTC. In particular, chemicals that resemble phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP), both contain the N-C=S group in their chemical structures and are used frequently in experiments involving TAS2R38. These two substances taste bitter to some people but are virtually tasteless to others. The ability to taste PTC shows a dominant pattern of inheritance. If one does not taste anything he or she will be homozygous recessive (tt). If one is able to taste a strong bitter flavor he or she will be homozygous dominant (TT). The third outcome of this experiment could be that one is able to taste a mildly bitter flavor and can be heterozygous (Tt). Among the tasters, some are so-called "supertaster" to whom PTC and PROP are extremely bitter. (M. Behrens et al)

This project aims to predict Tas2r38 protein structure using GPCR-I-TASSER by an homology approach, and interaction was seen using docking approach. GPCR-I-TASSER is a structural bioinformatics web-server dedicated to homology modeling of protein 3D structures. GPCR-I-TASSER is a computational method designed for 3D structure prediction of G protein-coupled receptors. Homology modeling, also known as comparative modeling of protein, refers to constructing an atomic-resolution model of the "target" protein from its amino acid sequence and an experimental three-dimensional structure of a related homologous protein [9]. A study was done in humans, based on responses to some bitter compounds. Some show a bimodal distribution that distinguishes two phenotypes, tasters and non-tasters. Phenylthiourea (PTU), is an organosulfur thiourea containing a phenyl ring. The main objective of this study was to determine the gene frequencies of dominant and recessive alleles for PTC taste sensitivity among my 20 families (relatives). The present study provides brief information on the distribution of PTC tasters and non-tasters in different populations of Mathurs in many parts of India and Abroad. Members selected were in the age range of 05-75 years, to observe taste sensitivity for Phenylthiourea. 60 individuals of this population were divided into PTC tasters (T) and non-tasters (NT) and obtained the following results from a set of 26 mathur families in my relation. According to the study, the exceptional four families with NT-NT Parents having Taster children, might possibly be because of the tt (recessive gene) of TAS2R 38 gene at 7 q. There were equally male and female tasters and non-tasters in this population, tasters (50%) males (50%) females. Individuals were divided into PTC tasters (T) and non-tasters (NT) In the first generation, 8 couples were T & NT, which had either tasters and non-tasters offsprings and two couple were NT x NT who had one taster and one T child. In the second generation, 14 couples were with phenotype T & NT, out of which all these couple had T and NT, both genes in their children except two families, which were NT x NT and had taster (T) child. No Taster- Taster couples were seen in this Mathur population. Among the 30 males and 30 females under study, 18 females were Non - tasters while 12 females came out to be tasters. In males 10 were NTs and 20 were tasters; more of females were non-tasters and more of males were tasters. [11]. The same study was extended with the comparison with PROP docking with TAS2R38 Gene.

## II.OBJECTIVES

- To model the structure of protein Tas2r38 using GPCR I-tasser and select the best model for given protein.
- To draw the structure of ligand PTC and PROP using Marvin Check.
- To predict the active site by the Metal pocket tool.
- To optimize the ligands using PyRx software to dock the PTC and PROP with the Tas2r38 protein using docking software (PyRx) and visualized in Discovery tool.
- To confirm the results, tests were performed in WetLab

## III.MATERIAL AND METHODS

- Model of Gene Sequence was derived GPCR-I TASSER Software
- UNIPROT software was used to retrieve the gene sequence Taster.
- BIOEDIT Software was used to create a sequence for NON-Taster.
- Two compounds were studied, PTC and PROP
- Structure of PTC and PROP was retrieved from PUB CHEM and drawn in MARVIN SKETCH
- The active site of protein synthesized by TAS 2R 38 Gene was detected by METAPOCKET SOFTWARE.
- DOCKING was done by PYRX
- Docking of both compounds with TAS Gene was visualized in DISCOVERY STUDIO
- Optimization was also done by PYRX
- For confirmation of results, wet lab tests were performed by tasting PTC and PROP Paper strips.

The Target Protein sequence was retrieved from UniprotKB Database. Target Protein sequence was edited in bio Editor. The Target Protein was retrieval from GPCR-I-TASSER.

TAS2R38(pav) protein's structural file was retrieved by GPCR-I-TASSER software based on C-score -0.35.

TAS2R38(avi) protein's structural file was retrieved by GPCR-I-TASSER software based on C-score -0.18.

Retrieval of similar compounds for phenylthiocarbamide(PTC) & propylthiouracil (PROP) from PubChem Database. Designing compounds of Phenylthiocarbamide & Propylthiouracil were designed using Marvin sketch. TAS2R38(pav)&TAS2R38(avi) protein was loaded on a Metal pocket server to retrieve their binding sites.

4 Binding sites of TAS2R38(pav)protein were found using Metapocket.4 Binding sites of TAS2R38(avi) protein were found using the Metal pocket.Performing docking analysis using pyrX software for finding the best binding affinity of the ligands(PTC, PROP) with protein target TAS2R38(pav)& TAS2R38(avi)

For the present study, PTC Paper stripes were tasted by 60 members of a Mathur population and they were divided into PTC tasters (T) and non-tasters (NT) and it was found that from a set of 26 mathur families (4 generations) The present study was carried out to analyze the prevalence of PTC taste sensitivity and to determine the gene frequencies among my relative Mathur population of India and Abroad, (endogenous groups). Healthy individuals of both sexes (Male-30Female-30) belonging to Mathur populations (20 families, 60 individuals) in India and Abroad were selected with the age range of 05-75 years, to observe taste sensitivity for Phenylthiourea. Individuals involved in the research were between 5 years to 75 years ages.[11].

### III.RESULTS AND DISCUSSIONS

The model of Gene Sequence was derived from GPCR-I TASSER Software and we got 10 models. PAV, as Taster and AVI as non-taster. UNIPROT software was used to retrieve the gene sequence Taster. But could not get the sequence for non-taster by this software. So, BIOEDIT Software was used to create a sequence for NON-Taster. Then, two compounds were studied, PTC and PROP. The structure of PTC and PROP was retrieved from PUB CHEM and drawn in MARVIN SKETCH. The active site of protein synthesized by TAS 2R 38 Gene was detected by METAPOCKET SOFTWARE, both for PAV and AVI, and got the result with yellow highlighted sequences. These were the active sites we used for the study. Different binding energies were obtained. Four active sites for PTC-PAV were obtained and three active sites for PTC-AVI were obtained. Four active sites for PROP -PAV AND three active sites for PROP-AVI were obtained as well. DOCKING was done by PYREX Docking of both compounds I.e., PHENYTHIOCARBAMIDE and PROP with TAS Gene was visualized in DISCOVERY STUDIO. Optimization was also done by PYREX.

After processing and analyzing through a series of above-mentioned software, we arrived at the conclusion that PHENYTHIOCARBAMIDE (PTC) shows more binding scores and less energy binding is required for docking with the TAS2R 38 Gene, as compared to PR. A protein formed by TAS2R 38 gene is Gustin And when it reacts With PTC, it forms a compound with a bitter taste, due to which, the PAV get a bitter taste. This compound is not formed in AVI , SO DO NOT GET BITTER TASTE.

The Target Protein sequence was retrieved from UniprotKB Database. Target Protein sequence was edited in bioEditor. The Target Protein was retrieval from GPCR-I-TASSER.TAS2R38 (pav) protein's structural file was retrieved by GPCR-I-TASSER software based on C-score -0.35. TAS2R38 (Avi) protein's structural file was retrieved by GPCR-I-TASSER software based on C-score -0.18.

Retrieval of similar compounds for phenylthiocarbamide (PTC) & propylthiouracil (PROP) from PubChem Database. Designing compounds of Phenylthiocarbamide & Propylthiouracil were designed using Marvin sketch. TAS2R38 (pav) &TAS2R38 (Avi) protein was loaded on Metal pocket server to retrieve their binding sites.

4 Binding sites of TAS2R38(pav)protein were found using Metapocket.4 Binding sites of TAS2R38(Avi) protein were found using Metal pocket Performing docking analysis using pyrX software for finding the best binding affinity of the ligands(PTC, PROP) with protein target TAS2R38(pav)& TAS2R38(avi)

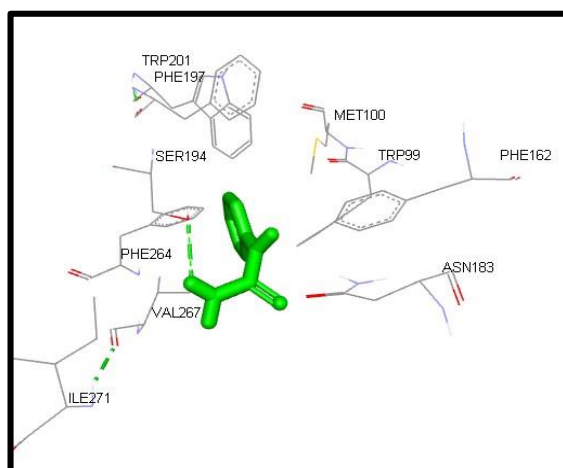


Figure 8(H): Interaction Of Ligand Ptc At The Active Site Ser 266 Of Tas2r38(Pav)

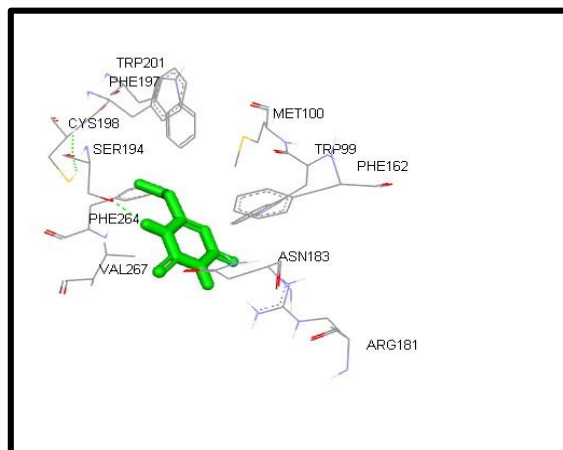


Figure 8(D): Interaction Of Ligand Prop At The Active Site Ser 266 Of TAS2R38(PAV)

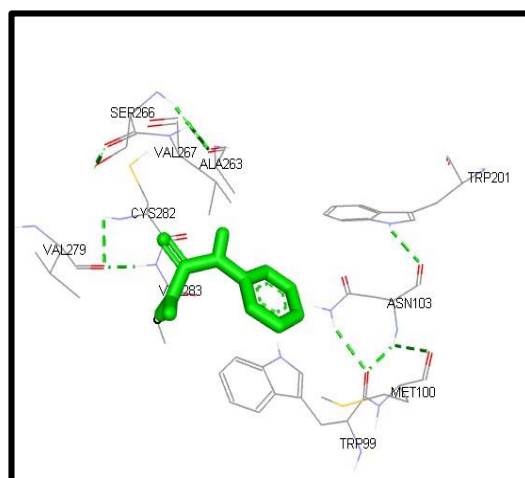


Figure 8(K):Interaction Of Ligand Ptc At The Active Site Ser 266 Of Tas2r38(Avi)

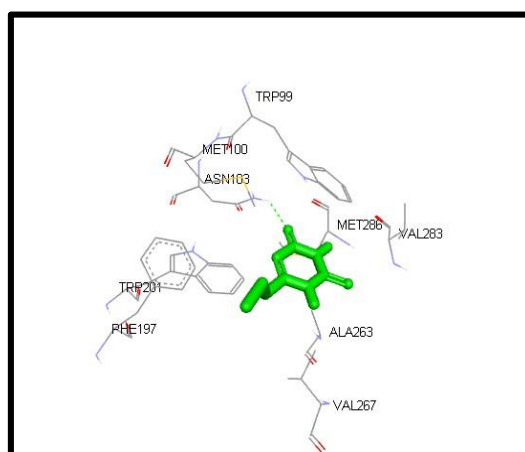


Figure 8(N): Interaction Of Ligand Prop At The Active Site Ser 266 Of Tas2r38(Avi)

These interactions explain that the ligands PTC and PROP were docked at the active sites ser 266 on the protein pav showed higher binding affinity of PTC and PROP. Also the ligands PTC & PROP were docked at the active sites cys 199, val 262 and ser 266 on the protein avi and they all showed the same binding affinity of PTC and PROP. These interactions explain that the ligands PTC and PROP were docked at the active sites ser 266 on the protein pav showed higher binding affinity of PTC and PROP. Also the ligands PTC & PROP were docked at the active sites cys 199, val 262 and ser 266 on the protein avi and they all showed the same binding affinity of PTC and PROP.

The G protein-coupled receptor(gpcr)Tas2r38 is a bitter taste receptor that can respond to bitter compounds such as phenylthiocarbamide(ptc) and 6-n-propylthiouracil(prop).This receptor was chosen because of its haplotypes (based on three

residue site polymorphism) htas2r38pav, htas2r38avi are known to have a dramatically different response to ligands ptc and prop. It was predicted that find that taster (pav) exhibited a higher affinity than nontaster (avi) exhibited a lower affinity for the ptc & prop ligands.

The phenotypic frequency of tasters was exactly the same as compared to non-tasters, and there were equally male and female tasters and tasters in my family, tasters (50%) males (50%). I divided individuals into PTC tasters (T) and non-tasters (NT) and obtained the following results from a set of 26 families, 60 individuals. In the first generation, 8 couples were T & NT, which had either tasters and non-tasters offsprings and two couple were NT x NT who had one taster and one T child (Table:1&3) In the second generation, 14 couples were with phenotype T & NT, out of which all these couples had T and NT, both genes in their children except two families, which were NT x NT and had taster (T) child. No Taster x Taster couples were seen in this population.[11].

After the results of docking of PTC and PROP with the TAS2R38 gene were obtained, it was found that most people who tasted the PTC paper strips and found it to be bitter, also found the paper strips of PROP to be bitter. However, the range of thresholds for PROP was narrower and the distribution less bimodal than for PTC, making it even more difficult to separate people into tasters and non-tasters with PROP. It was found that the association with TAS2R38 haplotypes was stronger for PTC than for PROP.

#### CONCLUSIONS

After processing and analyzing through a series of above-mentioned software, we arrived at the conclusion that PHENYTHIOCARBAMIDE (PTC) shows more binding scores and less energy binding is required for docking with the TAS2R38 Gene, as compared to PROP. A protein formed by TAS2R38 gene is Gustin and when it reacts with PTC, it forms a compound with a bitter taste, due to which, the PAV gets a bitter taste. This compound is not formed in AVI, so we do not get a bitter taste. The 3D structures haplotypes of TAS2R38 G-protein coupled receptors (GPCRs) were predicted by GPCR-ITASSER to gain a molecular-level understanding of bitter taste receptors. We used the metal pocket tool to predict the binding sites for PTC and PROP bound to hTAS2R38PAV, hTAS2R38AVI respectively. Furthermore, PyRx software was used to dock the htas2r38 with ptc and prop and visualized in Discovery tool. These interactions explain that the ligands etc & prop at the active sites were docked on the protein pav and avi, and etc was observed to have a higher binding affinity as compared to prop, on the basis of their binding scores. The bitter taste of compounds bearing a thiocarbamide but not a carbamide functional group. So, it is concluded that PTC exhibited a higher affinity.

#### ACKNOWLEDGMENT

We feel privileged to thank DR. Manisha Mathur, Asst Prof. Zoology, G.N. Khalsa College and Dr. Parakh Sharma, Asst Prof. Bioinformatics, G.N. Khalsa college Matunga, Mumbai; for their scientific contributions during the tenure of our project, without whom our research work would have been impossible. We also pay gratitude to Ms. Aparna Patil from Department of bioinformatics, Khalsa College, Matunga and Mr. Elvis Martis, from Bombay College of Pharmacy for their support during our research work.

#### REFERENCE

1. Buffer B., Hofmann T., Krautwurst D., Raguse J.D., Meyerhof W. Nat. Genet. 32: 397-401, (2002).
2. Meyerhof W. Rev. Physiol. Biochem. Pharmacol. 154: 37-72, (2005)
3. W. MEYERHOF, Expression of Multidisciplinary Flavour Science, HUMAN TASTE RECEPTORS, German Institute of Human Nutrition Potsdam-Rehbruecke, Department of Molecular Genetics, 114-116.
4. John Lee Supertaster, TAS2R38, Taste are Different-gene tool, RWappin, May 2014
5. Kim UK, Jorgenson E, Coon H, et al. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science*; 299:1221-1225, 2003.
6. Negri, Rossella; Di Feola, Mariarosaria; Di Domenico, Simone; Scala, M. Giuseppa; Artesi, Ginevra; Valente, Serena; Smarrazzo, Andrea; Turco, Francesca; Morini, Gabriella; Greco, Luigi. Taste Perception and Food Choices. - Volume 54 - Issue 5 - p 624-629, May 2012
7. M. Behrens and W. Meyerhof, Mammalian Bitter Taste Perception, German Institute of Human Nutrition Potsdam-14558 Nuthetal, Germany, 114-116
8. Harris H, Kalmus H, The measurement of taste sensitivity to phenylthiourea (PTC). *Ann Eugen* 15:32-45, (1949)
9. Adam Drewnowski and Carmen Gomez-Carneros, Bitter taste, phytonutrients, and the consumer: American Society for Clinical Nutrition, 2000
10. Alexander A. Bachmanov, Natalia P. Bosak, Cailu Lin, Ichiro Matsumoto, Makoto Ohmoto, Danielle R. Reed, and Theodore M. Nelson. Genetics of Taste Receptors. Monell Chemical Senses Center. 2014.
11. Mathur G., Study of TAS2R38 gene for bitter taste depending on heredity of Taster in three generations of Mathur Populations. *International journal of Health Sciences and Research*, Vol.6; Issue: 1; January 2016