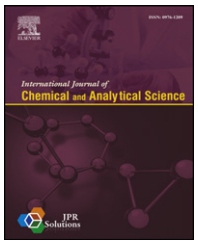
Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/ijcas



Original Article

Human sweet taste receptor: Complete structure prediction and evaluation

*Aditi Shrivastav, Sudha Srivastava**

Department of Biotechnology, Jaypee Institute of Information Technology, A-10, Sector-62, Noida, UP 201307, India

ARTICLE INFO

Article history:
Received 3 December 2012
Accepted 4 March 2013
Available online 14 March 2013

Keywords:
Homology modelling
Molecular docking
Threading
Sweet molecule
Human sweet taste receptor

ABSTRACT

Aims/Background: Human sweet taste receptor structure is predicted and was further evaluate using experimental result. This would enable receptor-based docking and pharmacophore studies since no structure, experimental or predicted model, for complete subunits of human sweet taste receptor (hSTR) is available till date.

Methods: Different homology modelling as well as threading-based tools were employed for structure prediction of individual domains (amino terminal domain (ATD), cysteine rich domain (CRD) and transmembrane domain (TMD)) and complete subunit structure. Finally, complete subunits structure was built from combinations of individual domain models. These predicted models were validated and further evaluated using docking and interaction analysis of the experimentally studied sweet molecules.

Results/Conclusion: hSTR Modelling through threading based tools was of poor quality with the exception of ITASSER software that predicted models with greater than 90% residues in energetically favourable environment. Among homology based software, CPH Model, SWISS Model and Prime predicted hSTR model of acceptable quality with more than 95% residues in energetically favourable environment. This model can be used for receptor-based pharmacophore modelling or searching newer sweet molecules.

1. Introduction

With exponentially increasing cases of diabetes and obesity an estimated 346 million people worldwide are suffering from diabetes alone. Left untreated or poorly controlled, diabetes increases the risk of cardiovascular disease, blindness, kidney failure, eye problems, nerve damage and amputations. This in the light of the fact that longer a person has the disease, the greater the risk of associated diseases needs immediate attention for the efforts to prevent it. In addition to other measures like healthy diet, regular exercise etc., decreased sugar and saturated fat intake is recommended to prevent or delay the onset of the disease. Hence search of alternate sweeteners is necessitated. Efforts in this direction led to low calorie sweeteners like aspartame, saccharin, sucralose, acesulfame-K etc that have gained wide popularity. However, there are contradictory reports regarding prolonged usage of these and associated side effects like dizziness, nausea, lung cancer, chronic respiratory disease hallucination, hypersensitivity, bladder cancer, heart failure and brain tumour etc,[1–9] etc. In view of above facts there is a need for alternate safer sweeteners with less side effects and which is easily metabolized. For instance, certain natural proteins like Brazzein, Thaumatin, Monellin, Mabinlin, Miraculin, Curculin and

* *Corresponding author*. Fax: +91 120 2400986.
E-mail address: Sudha.srivastava@jiit.ac.in (S. Srivastava).

0976-1209/$ – see front matter
http://dx.doi.org/10.1016/j.ijcas.2013.03.002

Neoculin can be an alternate. However, in many diseases where high protein diet can not be administered, these proteins can not be given. Designing newer sweet molecules desires the knowledge of pharmacophores. Whereas glucophores identification for small sweet molecules has been studied exhaustively, identification of the same for sweet proteins have not been attempted because of the complexity involved. To identify these glucophores, the primary requirement is knowledge and understanding of structure of human sweet taste receptor (hSTR). hSTR having more than 800 residues, it is difficult to find accurate structure experimentally (crystallography, NMR) or by computational modelling. Till date, most of the modelling studies are reported on amino terminal or transmembrane domain of T1R2–T1R3 subunits of hSTR. Computationally predicted model of amino terminal domain (25–483 aa) of T1R2 Q8TE23, is available at SWISS-MODEL respository.[10]

In this paper we report, complete structure prediction of both subunits of hSTR using homology and threading based software like SWISS-MODEL,[11] CPHmodels,[12] Geno3D,[13] EsyPred 3D,[14] HHpred,[15] LOOPP,[16] Phyre,[17] I-TASSER[18] and Prime.[19] The predicted models were validated in terms of stereochemical quality, packing quality and 3-D structure compatibility with the sequence. This was followed by refinement of the structure and docking of the sweet molecules (sod. cyclamate, aspartame, neotame, NHDC) and sweet taste inhibitor (lactisole) onto the predicted receptor structure. Finally, structure was evaluated by comparing the predicted results with experimentally identified residues important for eliciting sweetness.

2. Methods

2.1. *Sweet taste receptor modelling*

Query sequence for structure prediction of human sweet taste receptor (hSTR) T1R2 (Q8TE23) and T1R3 (Q7RTX0) subunits were obtained from NCBI. Templates for different

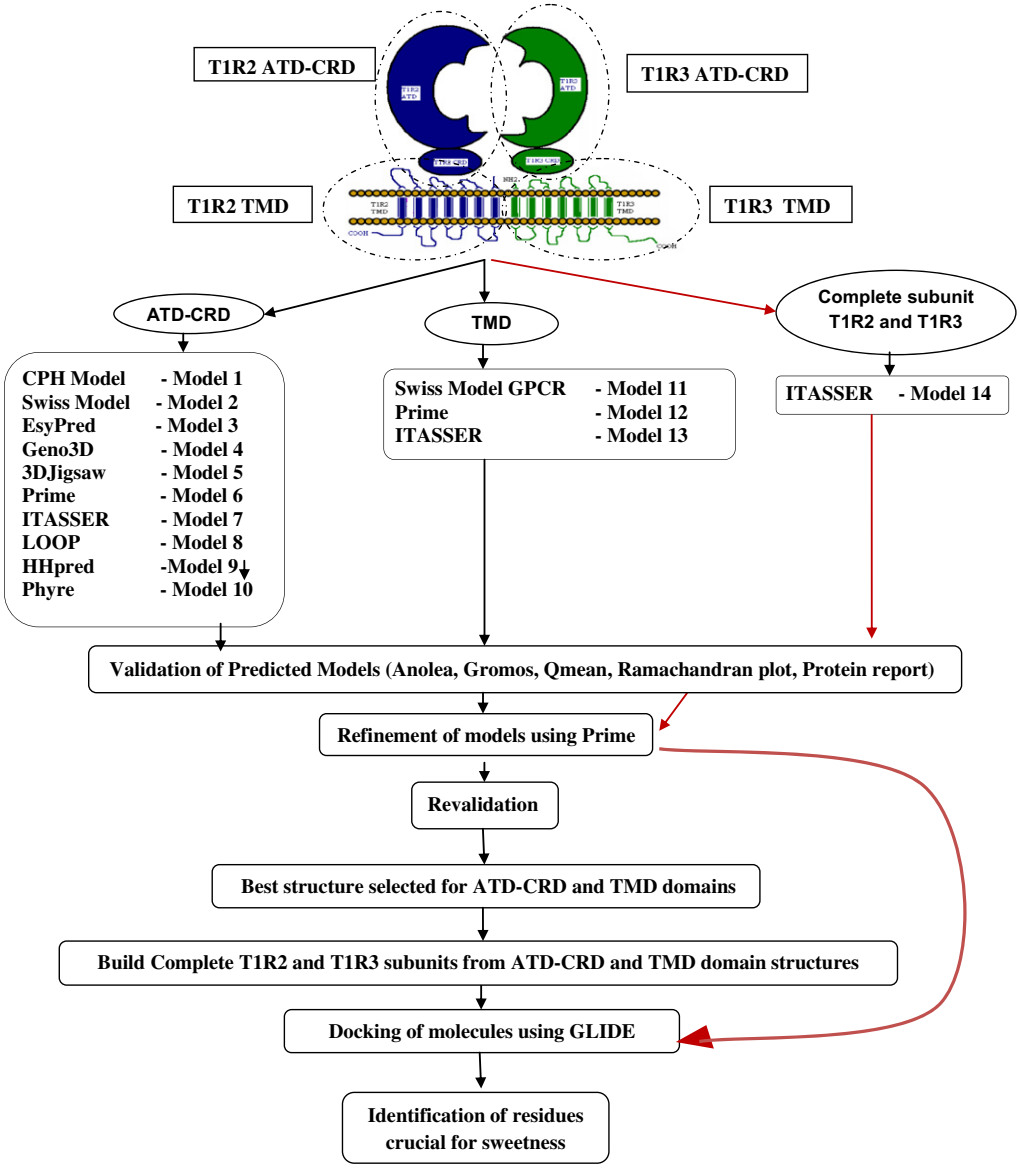


Fig. 1 – Schematic representation of the methodology.