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DESIGN OF PRODRUGS TO REPLACE COMMONLY USED DRUGS HAVING BITTER SENSATION

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ABSTRACT

As the role of taste receptors in food-intake regulation is being unraveled, agonists and antagonists of bitter taste receptors will have additional important roles in modulating food intake and metabolism. Obesity has reached epidemic proportions in many countries around the world. Modulators of food intake and appetite are therefore of immense importance to health systems worldwide. Since bitter taste receptors are present in the mammalian gastrointestinal system, the ability to control interactions between these receptors and the corresponding bitter compounds might therefore have even more direct consequences for food intake and metabolism. Replacing commonly used bitter pediatric medicines with bitterless prodrugs that upon in vivo conversion provide the bitter active drugs and improving the molecular understanding of bitterness are being currently the most important tasks for many chemists and biochemists alike. The combination of the biological, chemical and computational expertise will without any doubt lead to better understanding of the structure-function relationships of bitter taste receptors and develop candidates for bitter taste inhibition. Such inhibitors will be of great value for pharmaceutical and food industries, since they will be able to eliminate the aversive taste of medicine and foods and should therefore result in better patient compliance in taking medicines, as well as increased consumer acceptance of healthy, but bitter vegetables and fruits.

KEYWORDS: Bitter taste, Bitter taste receptors, DFT calculations, Molecular mechanics calculation, Quantum mechanics calculations, Enzyme models.

The pharmaceutical industry is undergoing dramatic change, with a shift of focus from drug discovery to development and marketing. This shift has resulted in downsizing of pharmaceuticals investment, workforce and laboratories in drug discovery research. Through this shift, the industry is relinquishing a large part of their early discovery effort to academia and biotechnology SMEs, whilst they focus on few research areas and in in-licensing promising drug candidates. The expectation of industry CEOs is that public funders and universities will generate more "Silicon valley-like" SME spin-offs to be able to fully cover the early drug discovery research and that public funders will support the more successful and entrepreneurial researchers and institutions in implementing such goals.

This editorial sheds light on the modern approaches being used to mask bitter sensation of commonly used drugs and design of efficient antagonists to some of the 25 known bitter taste receptors.

Medications dissolve in saliva and bind to taste receptors on the tongue, thus giving a bitter, sweet, salty, sour, or umami sensation. Sweet and sour taste receptors are concentrated on the tip and lateral borders of the tongue, respectively. Bitter taste is sensed by the receptors on the posterior part of the tongue and umami taste receptors are located throughout the tongue. For a short period of time after birth, infants reject substances that have a bitter taste and prefer ones that have a sweet or umami taste. Children have a larger number of taste buds, which are responsible for sensitivity toward taste, than adults. These taste buds regenerate every two weeks. The American Academy of Paediatrics estimates that compliance for taking medication in children is 53% and the noncompliance can lead to**:** (i) persistent symptoms, (ii) need for additional doctor visits or even hospitalizations, (iii) worsening of condition, (iv) need for additional medication, (v) increased healthcare costs and (vi) development of drug-resistant organisms in cases of infectious diseases.[1] Sweet, umami, and bitter tastes are triggered by the binding of molecules to G protein-coupled receptors on the cell membranes of taste buds. As taste senses both harmful and beneficial substances, all basic tastes are classified as either aversive or appetitive. Sweetness helps to identify energy-rich foods, while bitterness serves as a warning sign of poisons.[2-3] Numerous pharmaceuticals and over the counter (OTC) preparations contain active ingredients that have bitter sensation. In OTC preparations, such as cough and cold solutions or syrups, the bitterness of the preparation leads to lack of patient compliance. Among commonly used drugs with bitter taste are: (1) phenylephrine and pseudoephedrine used as decongestant, (2) guaifenesin, as an expectorant,

(3) paracetamol, as pain killer and antipyretic agent, and (4) amoxicillin, cephalexin, azithromycin and clarithromycin as antibacterial agents.[2-3] A variety of taste masking approaches has been used to address the patient compliance problem by physical means.[3-6] Although some of these approaches have helped to improve the taste of some drug formulations, the problem of the bitter taste of drugs, especially those for pain, antibacterials and anti-cough, in paediatric and geriatric formulations still creates a serious challenge to the health community. Thus, different non-physical strategies should be developed in order to overcome this problem. The two novel approaches addressed herein are: (1) a prodrug chemical approach consists of a design and synthesis of bitterless prodrugs containing the bitter parent active drug attached to a non-toxic linker. When the prodrug moiety is exposed to saliva, no sensation of bitterness is detected due to a lack of interaction between the prodrug and bitter taste receptors (prodrug molecules do not fit to the receptor's active site); however, when it reaches a physiological environment such as stomach or intestine, it undergoes intramolecular conversion to the bitter active drug and a nontoxic promoiety (Figure 1); and (2) synthesis and screening of bitter tasting antagonists based on elucidation of the interactions between bitter tastings and bitter taste receptors, using an iterative combination of computational modelling of the 3D structures of the receptor with experimental mutagenesis and functional assays. Altering the ability of the drug to interact with bitter taste receptors could reduce or eliminate its bitterness. This can be achieved by an appropriate modification of the structure and size of the bitter compound.

Recently, several quantum mechanics methods such as DFT, AM1 and ab initio were employed by us to assign the factors playing dominant role in the rate-determining step of a large number of intramolecular processes (utilized as enzyme models)[7-17] such as, cyclization reactions of di-carboxylic semi-esters,[7, 15] proton transfers between two oxygens, Kirby's acetals [8, 10,] and acid-catalysed hydrolysis of Kirby's N-alkylmaleamic acids.[14] The information obtained from these calculations was used to design efficient chemical devices to be utilized as prodrug linkers attached to the chemical functions responsible for the drug bitter sensation. Blocking such functional groups of the bitter active drug might have the potential to hinder any interaction between the drug and bitter taste receptors and expected to release the bitter active drug in a programmable manner. The conversion rate of a prodrug to its corresponding bitter active form is determined by the intramolecular reaction rate which can be programmed according to the nature of the linker attached to the parent drug.

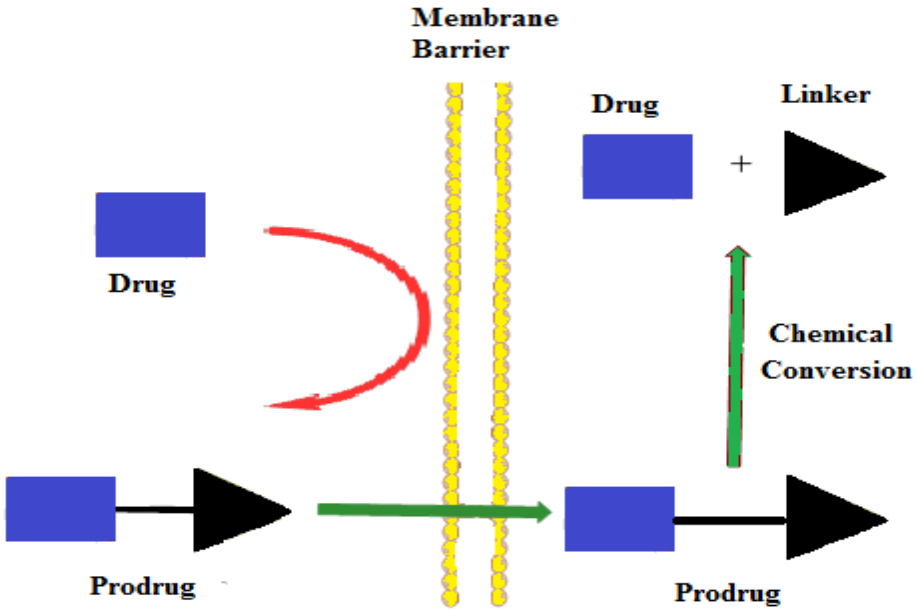

Figure 1. Schematic representation of the prodrug chemical approach.

Exploring the mechanism of intramolecular acid-catalyzed hydrolysis of Kirby's N-alkylmaleamic acids (enzyme model)[14] has led to design and synthesis of several novel prodrugs for tranexamic acid (anti- bleeding agent),[18] atenolol (anti-hypertensive agent) (Figure 2a)[19-22] and statins (cholesterol lowering agent).[23, 24] Furthermore, using the same computational tools, prodrugs for masking the bitter taste of antibacterial drugs such as amoxicillin, cefuroxime and cephalosporins were designed and synthesized[4-6] The role of the promoiety (linker) in the antibacterial prodrugs is to block the free amine of the active parent antibacterial agent which is responsible for the drug's bitter sensation, and to enable the release of the drug in a programmable manner. Prodrugs for dimethyl fumarate to treat psoriasis were also designed, synthesized and currently are under *in vitro* and *in vivo* kinetic studies.[25]

In addition, researching the mechanism of Bruice's base-catalyzed lactonization of dicarboxylic semi-esters enzyme model[7, 15] has led to design and synthesis of atovaquone prodrugs with better bioavailability than their active drug, atovaquone (anti-malarial agent) [26, 27] and bitterless paracetamol prodrugs to be formulated in aqueous preparations (solutions or syrups) for use by paediatrics and geriatrics as antipyretic and pain killer.[28]

Paracetamol, a widely used pain killer and fever-reducer found in the urine of patients who had taken phenacetin has a very unpleasant bitter taste. Phenacetin, on the other hand, lacks or has very slight bitterness. The difference in the structural features of both drugs is only in the nature of the group in the *para* position of the benzene ring, hydroxyl in paracetamol; ethoxy in phenacetin. Acetanilide has a chemical structure similar to that of paracetamol and phenacetin but lacks the group in the *para* position of the benzene ring, making it lack the bitter taste characteristic of paracetamol. These combined facts suggest that the presence of the hydroxy group on the *para* position is the major contributor for the bitter taste of paracetamol. In the designed and synthesized paracetamol prodrugs the linker is attached to the phenolic group of paracetamol (Figure 2b).[28] Binding studies on human cells revealed that while paracetamol activates bitter receptors its prodrugs lack any binding to such receptors.

Unravelling the proton transfer in of Kirby's acetals has led to a design and synthesis of novel prodrugs of aza-nucleosides for the treatment of myelodysplastic syndromes,[29] and prodrugs of phenylephrine as decongestant.[30] In these examples, the prodrug promoiety was covalently attached to the parent drug's hydroxyl group such that the drug-linker entity (prodrug) has a potential to intraconvert upon exposure into physiological environments: stomach, intestine, and/or blood circulation, with rates that are solely dependent on the structural features of the pharmacologically inactive promoiety. Furthermore, Menger's Kemp acid amide enzyme model was utilized for the design of dopamine prodrugs to treat Parkinson's disease.[31]

Bitter taste perception in humans is mediated by about 25 G protein-coupled receptors (GPCRs) of the hTAS2R gene family.[32] One of the most important questions in bitter taste research is how just 25 receptors can detect thousands of structurally diverse bitter compounds. One answer to this question is emerging from the successful identification of agonist spectra for most hTAS2Rs.[32] It appears that many hTAS2Rs are activated by a battery of structurally related and unrelated bitter compounds. In this respect, hTAS2Rs differ from many other GPCRs, such as neuropeptide or hormone receptors, which are activated by only one or a few high-affinity ligands.[33-35] Among the 25 hTAS2Rs three receptors, hTAS2R10, hTAS2R14, and hTAS2R46, stand out because of their extraordinary breadth of tuning. In a screening with 104 synthetic and natural bitter compounds each of the receptors recognized about one-third of all compounds and their combined activity accounted for the

detection of more than half of all bitter substances used in this screening.[32] Hence, determination of structure-activity relationships for these receptors is of outmost importance, because our bitter tasting ability largely depends on these three receptors.

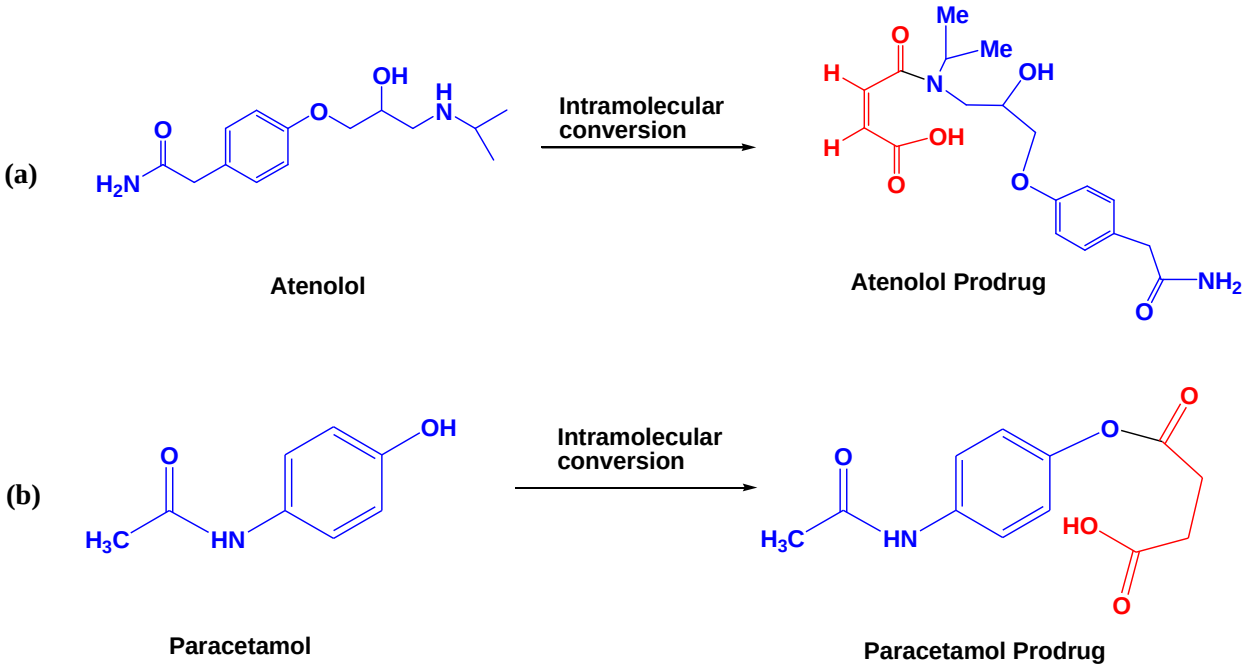

Figure 2. Intramolecular conversion of (a) atenolol prodrug and (b) paracetamol prodrug in physiological environments.

Previous efforts were devoted to the analysis of the binding pockets of the receptors TAS2R14. We demonstrated that even broadly tuned receptors possess only a single agonist binding pocket that accommodates the structurally diverse agonists. We have synthesized numerous derivatives of cognate TAS2R14 ligands and determined their activation properties in functional calcium imaging experiments. Structural modifications on the following cognate TAS2R14 ligands: guaifenesin, mefenamic acid and diclofenac have been made and the resulting derivatives were fully characterized. The ester derivatives of guaifenesin, mefenamic acid and diclofenac are examples of prodrugs that were designed and synthesized with the potential to undergo interconversion in acidic medium (stomach) to furnish the corresponding active drug and a non-toxic moiety. Based on the *in-vitro* binding and the kinetics results for guaifenesin ester we conclude that this derivative can be useful as a bitterless prodrug for the bitter expectorant drug, guaifenesin. The kinetics showed that guaifenesin ester is entirely stable in neutral pH whereas it undergoes hydrolysis in 1N HCl to provide the active drug. Formulation of the prodrug in syrup or solution having neutral pH will provide a stable expectorant dosage form, and upon administration of the prodrug, no

bitter sensation is expected. Once the prodrug reaches the stomach (pH 1-2) it undergoes acid-catalyzed hydrolysis to the active drug and the non-toxic linker, succinic anhydride.[36]

An elegant way for the application of orally administered bitter-tasting medications is to bypass bitter perception in the oral cavity by the development of prodrugs that are activated only during passage of the GI tract. Structural modifications on bitter taste drugs will elevate patients' compliance to therapy, and also represent valuable experimental tools for dissecting oral and non-oral effects of bitter taste receptors.

Disadvantages in using prodrugs that are activated by metabolic enzymes are eliminated by the better understanding of organic reaction mechanisms of certain intramolecular processes. Computational methods such as ab-initio–and molecular mechanics have the potential to provide a design of more efficient as well as bitterless paediatric and geriatric drugs.

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