Medications dissolve in saliva and bind to taste receptors on the tongue 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 [1]. Children have a larger number of taste buds than adults which are responsible for sensitivity toward taste. These taste buds regenerate every two weeks. Taste becomes altered as a function of the aging process which explains why most children find certain flavors to be too strong when adults do not. The American Academy of Paediatrics estimates that compliance for taking medication in children is as low as 53%. Noncompliance can lead to: (1) persistent symptoms, (2) need for additional doctor visits or even hospitalizations, (3) worsening of condition, (4) need for additional medication, (5) increased healthcare costs and (6) development of drug-resistant organisms in cases of infectious diseases [2].

In mammals, taste buds are groups of 30-100 individual elongated neuroepithelial cells which are often embedded in special structures in the surrounding epithelium known as papillae. Just below the taste bud apex, taste cells are joined by tight junctional complexes that prevent gaps between cells. Food molecules cannot squeeze between taste cells and get into the taste bud.

As taste perception fades with age, people lose about of half their taste receptors by age 20 [3]. The sensation of taste can be categorized into five basic tastes: sweetness, sourness, saltiness, bitterness, and umami. Taste buds are able to differentiate among different tastes through detecting interaction with different molecules or ions. Sweet, umami, and bitter tastes are triggered by the binding of molecules to G protein-coupled receptors on the cell membranes of taste buds. Saltiness and sourness are perceived when alkali metal or hydrogen ions enter taste buds, respectively [4]. As taste senses both harmful and beneficial substances, all basic tastes are classified as either aversive or appetitive [5]. Sweetness helps to identify energy-rich foods, while bitterness serves as a warning sign of poisons [6]. For a long period of time, it was commonly accepted that there was a finite and small number of basic tastes of which all complex tastes were composed. As of the early twentieth century, physiologists and psychologists believed of the early twentieth century, physiologists and psychologists believed there were four basic tastes: sweetness, sourness, saltiness, bitterness. At that time umami was not proposed as a fifth taste but now a large number of authorities recognize it as the fifth taste. In Asian countries within the sphere of mainly Chinese and Indian cultural influence, pungency (piquancy or hotness) had traditionally been considered a sixth basic taste [7]. Today, the consensus is that sweet, umami (amino acid), and bitter taste converge on a common transduction channel, the transient receptor potential channel TRPM5, via Phospholipase C (PLC). TRPM5 is a newly discovered TRP related to other channels in sensory signaling systems. It has been shown that PLC, a major signaling effector of G-Protein Coupled Receptors (GPCRs), and TRPM5 are co expressed with T1Rs and T2Rs and are vital for sweet, amino acid, and bitter taste transduction. Activation of T1R or T2R receptors by their respective taste molecules stimulate G proteins and in turn PLC (PLC-ß2). The activation of PLC generates two intracellular messengers, IP3 and di-acyl glycerol (DAG), from the hydrolysis of Phosphatidylinositol-4,5-bisphosphate (PIP2) and opens the TRPM5 channel, resulting in the generation of a depolarizing receptor potential. Other additional pathways may modulate sweet, umami, or bitter taste reception but do not trigger a taste response themselves. It is not currently known how PLC activates. TRPM5 or whether DAG is involved [8-18]. There are numerous pharmaceutical and Over the Counter (OTC) preparations that contain active ingredients that are bitter in taste. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. Among commonly used drugs with bitter taste are: (1) pseudoephedrine, a sympathomimetic drug of the phenylethylamine and amphetamine chemical classes. It may be used as a nasal/sinus decongestant, as a stimulant, or as a wakefulness-promoting agent, (2) dextromethorphan, an antitussive (cough suppressant) drug. It is one of the active ingredients in many over-the-counter cold and cough medicines and has had uses ranging from pain relief to psychological applications. It is sold in syrup, tablet, spray, and lozenge forms. In its pure form, dextromethorphan occurs as a white powder, (3) diphenhydramine, also known as diprophylamine, is a xanthine derivative with bronchodilator and vasodilator effects. It is used in the treatment of respiratory disorders like asthma, cardiac dyspnea, and bronchitis. It acts as an adenosine receptor antagonist and phosphodiesterase inhibitor. (4) phenylephrine, is a selective α1-adrenergic receptor agonist used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure. Phenylephrine is marketed as a substitute for the decongestant pseudoephedrine, (5) chlorhexidine, a chemical antiseptic. It is effective on both Gram-positive and Gram-negative bacteria, although it is less effective with some Gram-negative bacteria. It is also useful against fungi and enveloped viruses, though this has not been extensively investigated, (6) atorvastatin, a member of the drug class known as statins, is used for lowering blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in the production of cholesterol in the body, (7) loperamide, a piperidine derivative, is an opioid drug used for diarrhea resulting from gastroenteritis or inflammatory bowel disease. (8) terfenadine, is an antihistamine formerly used for the treatment of allergic conditions, (9) prednisolone, is a synthetic glucocorticoid, a derivative of cortisol, which is used to treat a variety of inflammatory and auto-immune
conditions. It is the active metabolite of the drug prednisone and is used particularly in patients with hepatic failure, as these individuals are unable to metabolize prednisone into prednisolone, (10) salbutamol, or albuterol (USAN) is a short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease, (11) gatifloxicin or gatifloxin (former BAN), also glycyrill guaiacolate, is an expectorant drug that is usually taken orally to assist in the expectoration of phlegm from the airways in acute respiratory tract infections and (12) amoxicillin, a moderate-spectrum, bacteriolytic, β-lactam antibiotic used to treat bacterial infections caused by susceptible microorganisms. It is usually the drug of choice within the class because it is better absorbed following oral administration than other β-lactam antibiotics. Amoxicillin is one of the most common antibiotics prescribed for children. The drug became available in 1972. The most significant challenges that developers face when pursuing masking bitter tasting drugs approaches are: (i) Safety, tolerability, and efficacy of the compound which are based on non-clinical testing, and physicochemical properties such as solubility, permeability, and stability, (ii) lack of robust and reliable techniques for early taste screening of compounds with limited toxicity data, (iii) structure–taste relationships of pharmaceutically active molecules is limited, (iv) The perception of taste of pharmaceuticals has been shown to be different in adults and children and it might differ between healthy and patient children and (v) ethical concerns to perform taste studies in healthy children unless the study is a ‘swill and spit’ one with drugs known to have a good safety profile.

A variety of taste masking approaches has been used to address the patient compliance problem. Conventional taste masking methods such as the use of sweeteners, amino acids, and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs. Drugs such as macrolide antibiotics, non-steroidal anti-inflammatory drugs such as ibuprofen, quinine, celecoxib, etoricoxib, levoflaxacin, and penicillins have a pronounced bitter taste. Masking the taste of water soluble bitter drugs, especially those given in high doses, is difficult to achieve by using sweeteners alone. As a consequence, several approaches have been investigated and have resulted in the development of more efficient techniques for masking the bitter taste of active ingredients. All of the developed techniques are based on physical modification of the formulation containing the bitter tastant. Among the approaches used to mask bitter taste of pharmaceuticals are: (1) taste masking using flavors, sweeteners, and amino acids; (2) taste masking with lipophilic vehicles such as: i) lipids, lecithin, and lecithin-like substances; (3) coating; (4) microencapsulation; (5) taste suppressants and potentiate such as the Linguagen's bitter blockers; (6) ion exchange resins; (7) inclusion complexes [9]; (8) pH modifiers; (9) adsorbates; (10) chemicals; (11) solid dispersions; (12) multiple emulsions; (13) liposomes; and (14) prodrugs [19].

Although the mentioned approaches have helped to improve the taste of some drug formulations, the problem of the bitter taste of drugs in paediatric and geriatric formulations still creates a serious challenge for pharmacists. Thus, different strategies should be developed in order to overcome this problem. The novel two approaches to be addressed in this editorial are: (1) design and synthesis of bitterless prodrugs containing the parent drug by which a promoiety is attached to the active drug functional group responsible for binding to the bitter taste receptor. When the prodrug is exposed to saliva, no sensation of bitterness is detected, however, when it reaches a physiological environment such as stomach or intestine, it undergoes intramolecular conversion to the active drug and a nontoxic promoiety; and (2) synthesis of bitter tastant antagonists based on elucidation of the interactions between bitter tastants 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 could be achieved by an appropriate modification of the structure and size of the bitter compound. An adequate dose of the antagonist should be given in order to inhibit any interaction between the bitterness of the active drug and the bitter taste receptor. In continuing our study on the design and synthesis of a variety of prodrugs, we document in this editorial the findings of studies that were conducted to design bitter tasting prodrugs through linking the parent drug to (1) a di-carboxylic semi-ester (Bruice's enzyme model) [20], (2) N-alkylmaleic acid [21] and (3) an acetal (Kirby's enzyme model) [22] to produce systems that are more hydrophilic than the parent drug and are able to mask the bitterness and release the bitter drug in a chemically driven controlled manner. Thus, introducing novel prodrugs that fulfill the following requirements:

1) Enhanced water solubility
2) Improved oral bioavailability
3) Controlled release rate
4) Predicted plasma levels
5) Improved clinical activity.

In the last few years, several computational methods (such as DFT and ab initio) were used by us to investigate the factors of the rate-determining step in a large number of intramolecular processes [23-41] such as, cyclization reactions of di-carboxylic semi-esters as studied by Bruice (20), proton transfers between two oxygens in Menger's rigid hydroxy acids [42] and kirby's acetals (22), and acid-catalyzed hydrolysis of Kirby's N-alkylmaleic acids N-alkylmaleic acids (21). From these studies, it was concluded that the reaction mechanism must be unraveled in order to be able to assign the factors that play a dominant role in the reaction rate. The information obtained was then used to design an efficient chemical device to be utilized as a prodrug linker that blocks the chemical function responsible for the bitter taste of the drug. The designed linkers might have the potential to liberate the bitter tasting drug in a controlled manner (slow or fast release depending on the use of the parental drug). For example, exploring the mechanisms for proton transfer in Kirby's acetals and Bruice's S₂,2-based-cyclization reactions of di-carboxylic semi-esters has led to the design of the prodrugs paracetamol and guaiafenisen that are capable of masking the bitter taste of the corresponding parent drugs. In addition, unravelling the mechanisms for proton transfer in Menger's rigid carboxylic amides, Kirby's acetals, and Kirby's N-alkylmaleic acids has led to the design of prodrugs that mask the bitter taste of atenolol, dopamine, pseudepdrine, amoxicillin, cephalaxin, cefuroxime, and statins. The role of the linker in these prodrugs was to block the free amine group in the corresponding parental drug and to enable the release of a drug in a programmable manner [43-57]. In the past, the prodrug approach for masking bitter tasting drugs was used for a very small number of drugs. The palmitate esters of chloramphenicol and clindamycin were made to mask the bitter taste of the corresponding drugs, and the diacetate ester of triamcinolone was synthesized to mask the bitter taste of triamcinolone. Nowadays, the modern computational approach considers using a design of linkers with bitter tasting drugs to release the parental drugs in a programmable manner. With the possibility of designing prodrugs that have different linkers, the rate of...
release of the parental bitter tasting drugs will be controlled.

In the second novel structure-based approach, the details of the interactions were utilized for virtual screening of additional binders, followed by modification of known agonists that were designed based on the computationally predicted structures of the complexes between known binders and receptors. On the other hand, in the ligand-based approach, Quantitative Structure-Activity Relationships (QSAR) were developed based on different tantastic activities and this information was used to identify additional potential strong binders with the hope of finding strong binders that do not activate the bitter taste receptor and can be utilized as antagonists for those receptors.

Many successful examples of prodrug discovery to improve the oral availability of drugs have been well documented. There are still unmet needs that should be addressed, and this will take hard work and creativity by scientists venturing into this area of research. I hope that the selected prodrug design examples discussed in this editorial and the references provided will encourage future scientists to venture on.

If this goal is accomplished, the lives of geriatric and pediatric patients can be improved along with many others in the future.

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