A New QSPR Study on Relative Sweetness

Cristian Rojas, Instituto de Investigaciones Físicoquímicas Teóricas y Aplicadas INIFTA (CCT La Plata-CONICET, UNLP), La Plata, Argentina & Decanato General de Investigaciones, Universidad del Azuay, Cuenca, Ecuador

Piercosimo Tripaldi, Laboratorio de Química-Física de Alimentos, Facultad de Ciencia y Tecnología, Universidad del Azuay, Cuenca, Ecuador

Pablo R. Duchowicz, Instituto de Investigaciones Físicoquímicas Teóricas y Aplicadas INIFTA (CCT La Plata-CONICET, UNLP), La Plata, Argentina

ABSTRACT

The aim of this work was to develop predictive structure-property relationships (QSPR) of natural and synthetic sweeteners in order to predict and model relative sweetness (RS). The data set was composed of 233 sweeteners collected from diverse sources in the literature, which was divided into training (163) and test (70) molecules according to a procedure based on k-means cluster analysis. A total of 3763 non-conformational Dragon molecular descriptors were calculated which were simultaneously analyzed through multivariable linear regression analysis coupled with the replacement method variable subset selection technique. The established six-parameter model was validated through the cross-validation techniques, together with Y-randomization and applicability domain analysis. The results for the training set and the test set showed that the non-conformational descriptors offer relevant information for modeling the RS of a compound. Thus, this model can be used to predict the sweetness of both un-evaluated and un-synthesized sweeteners.

KEYWORDS

Dragon Software, k-Means Cluster Analysis, QSPR Theory, Relative Sweetness, Replacement Method, Sweeteners

INTRODUCTION

Sweetness is one of the most important tastes of mankind and has long been sought after as a dietary constituent to produce a pleasant sensation. Since sucrose is the most commonly used sweetener, it is the standard substance employed for measuring and comparing the Relative Sweetness (RS) of other sweet substances (Singh, Khan, & Singh, 2014). RS is defined as the ratio of a standard sucrose concentration to the iso-sweet concentration of another sweetener (Bassoli et al., 2001). In other words, a standard solution of sucrose has a sweetness perception rating of 1 (or 100), and the sweetness of whatever sweetener is being evaluated is rated relative to sucrose.

The development and search for new sweeteners is complicated. On one hand, there are multiple factors that affect sweetness; e.g., solubility, stability at wide pH and temperature ranges, clean sweet taste without post-flavor effects, sweetening effect as compared to low-cost sucrose, and finally, the most important factor is the safety of human health (Belitz, Grosch, & Schieberle, 2009). On the other hand, the measurement of sucrose has a sweetness perception rating of 1 (or 100), and the sweetness of whatever sweetener is being evaluated is rated relative to sucrose.

The development and search for new sweeteners is complicated. On one hand, there are multiple factors that affect sweetness; e.g., solubility, stability at wide pH and temperature ranges, clean sweet taste without post-flavor effects, sweetening effect as compared to low-cost sucrose, and finally, the most important factor is the safety of human health (Belitz, Grosch, & Schieberle, 2009). On the other hand, the measurement of RS involves a high cost due to the use of trained panels for the use of the “sip and spit” taste method for comparing the RS between a sweetener and the standard. Because of all these factors, there is a clear advantage to develop quantitative-structure models in order to understand the sweetness mechanism and to use these models to develop and synthesize new potent sweeteners (Yang, Chong, Yan, & Chen, 2011; Zhong, Chong, Nie, Yan, & Yuan, 2013).

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The QSAR/QSPR theory suggests that the biological activities and properties of molecules can be determined in terms of specific molecular attributes, i.e., these chemical structures can be represented theoretically although they do not offer specific details of the usually complex mechanism/path of action involved. However, the molecular structure is quantified by using a set of suitable molecular descriptors, which are numbers carrying information on the constitutional, topological, geometrical, hydrophobic, and/or electronic aspects of the chemical structure (Diudea, 2001; A. R. Katritzky, Lobanov, V. S., Karelson, M., 1995; Todeschini & Consonni, 2009; Trinajstic, 1992). Hence, the goal is to build a useful model selecting only the most representative descriptors among thousands of them. If successful, such a model can be useful to investigate and understand specific characteristics of the relationship between the molecular structure and its activity/property that is under investigation.

The first Quantitative Structure-Activity Relationship (QSAR) study of sweeteners was carried out by Edna W. Deutsch and Corwin Hansch (Deutsch & Hansch, 1966) in which they used some derivatives of 2-amino-4-nitrobenzene to model RS. They concluded that this property is well-correlated with the hydrophobicity and the Hammett constant descriptors given by the substituents. Since this pioneering study, there were several applications of the QSAR/QSPR theory to model and predict the RS for diverse sweeteners(Arnoldi, Bassoli, Merlini, & Ragg, 1991; Barker, Hattotuwagama, & Drew, 2002; Bassoli et al., 2001; Bassoli, Drew, Merlini, & Morini, 2002; Drew et al., 1998; Hansch, 1970; Iwamura, 1980, 1981; Katritzky et al., 2002; Pietrzycki, 2001; Rao & Kumar, 1986; Spillane, 1983; Spillane & McGlinchey, 1981; Spillane, McGlinchey, Muircheartaigh, & Benson, 1983; Spillane et al., 2000; William J. Spillane et al., 1996; Spillane & Sheahan, 1989; van der Heijden, Brussel, & Peer, 1979; Walters, 2002; Walters, 2006; Walters & Hinds, 1994).

Recently, Rojas et al. (Rojas, Duchowicz, Pis Diez, & Tripaldi, 2016) published a multi-criteria review of QSAR/QSPR applications for the RS during the decade 2004-2014. This period of time is remarkable for the increased application of new QSAR/QSPR theories to investigate diverse data sets of sweeteners. In this review, the authors presented in a chronological way thirteen studies regarding the synthesis of new sweeteners and their QSAR/QSPR analysis, along with the development and application of novel methodologies to perform predictive QSAR/QSPR models. The use of such models to predict the RS value of new proposed potent sweeteners was also presented. In this review, the specific term of Quantitative Structure-Relative Sweetness Relationships (QSRSR) was introduced that refers to the property of relative sweetness.

The main purpose of the present work is to use a data set of 233 diverse natural and synthetic sweeteners for the development of a predictive non-conformational QSPR model for the RS values, contemplating the principles defined by the Organization for Economic Co-operation and Development (OECD) to make it applicable. In brief, the modelled property and the mathematical algorithm should be clearly defined, the model should be accompanied by a definition of its applicability domain, the goodness-of-fit and predictivity of the model should be evaluated through appropriate strategies and, eventually, a mechanistic interpretation of model descriptors should be given, if possible. Dragon molecular descriptors and the replacement method variable subset selection were used for the first time for this purpose. The predictive ability was estimated by means of the internal and external validation procedures, and the chemical information encoded in the selected descriptors was explained. If this QSPR model shows an acceptable prediction of the relative sweetness, it may be a useful tool for scientists working on sweeteners chemistry to understand the RS mechanism, as well as to propose and synthetize new potent sweeteners.
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