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# Historical overview on structure–activity relationships among sweeteners

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*Abstract:* The literature on 100 years of research on the structure-activity relationships among sweeteners is reviewed. It started with information on the tastes of many compounds, which were correlated with functional groups of the molecules. In 1967 Shallenberger and Acree indicated a common AH-B moiety among sweeteners. Kier postulated the concept of the third binding site, capable of dispersion bonding, in 1972. New conceptual parameters $\alpha$, $\delta$ and $\omega$ for sweeteners were introduced by van der Heijden in 1985 in order to describe three dimensions of the third binding sites versus the AH-B moieties more precisely. In 1990 Tinti and Nofre developed a more extensive model about structure-activity of sweetness assuming the possible presence of eight recognition sites. Application of this model can explain the potency of hyperpotent sweeteners.

## INTRODUCTION

The most likely reasons for the great interest by scientists in structure-activity relationships among sweeteners are:

- the early organic chemists tasted many substances of which a great number were found to be sweet
- the discovery and successful marketing of artificial sweeteners
- the desire of scientists to explain the facts that a great diversity of molecules can induce sweetness and that sweeteners can have a large range of potencies

The main objective of this review is to present an historical overview of the pieces of scientific information produced to complete the jigsaw puzzle of the sweet taste. In the course of time a great number of review articles (ref. 1-7) and books (ref. 8-12) have been published. The most striking observations and differences among sweeteners are:

- the great diversity among the classes of (generally organic) compounds (ref. 1)
- the potencies can be as high as 200,000 times that of sucrose (ref. 1 and 7)
- some D-amino acids may taste sweet, but the corresponding L-isomers not (ref. 12)
- both D-carbohydrates and the corresponding L-isomers taste sweet (ref. 12)
- in a homologous series of compounds the lower and higher molecular weight members may be tasteless, while the intermediate members are sweet (ref. 1)
- isomers may differ completely in taste behaviour (*n*-propoxy-2-amino-4-nitrobenzene is sweet, but *n*-propoxy-2-nitro-4-aminobenzene is tasteless; ref. 1)
- there is a large range of temporal taste properties among sweeteners (ref. 12) both for appearance (4 to 16 sec) and extinction (14 to 69 sec)
- high-potency sweeteners have also other taste characteristics (ref. 9 and 12)
- carbohydrates and sugar alcohols show a *linear* concentration/response (C/R) function, while high-potency sweeteners have *hyperbolic* C/R functions (ref. 9 and 11)

The question arises whether such observations and differences can satisfactorily be explained by the theories developed in the course of time.

## EARLY OBSERVATIONS

The first extensive report on the relationships between chemical structures and sweet taste was given by Sternberg in 1898 (ref. 13). The author concluded that the hydroxyl and amino groups are responsible for sweet and bitter tastes and that sweet molecules are in principle not different from bitter molecules. No effect of 'stereogeometric configuration' (double bond position) could be established. Later on Sternberg (ref. 14) summarized his views on the sweet principle for inorganic and organic compounds.

In 1914 Cohn published a book of over 900 pages, entitled *'Die Organischen Geschmackstoffe'* (which can best be translated as *'The Organic Tastants')* with the structures of thousands of organic compounds and their associated tastes (ref. 15). He observed a large number of simple correlations between taste and chemical structures: polyhydroxy compounds and α-amino acids are often sweet and highly nitrated compounds are usually bitter. The incorporation of a chlorine atom in a molecule generally introduced sweetness. He proposed that in order to evoke a certain taste, *sapophoric groups* must be present in the molecule. It was observed that there was an inverse relationship between sweetness and molecular weight within a given series of chemical compounds. According to Cohn, two factors are responsible for this property: First, the water solubility decreases until the substances are insoluble and thus tasteless; and second, the sapophoric group is significant in the small members of a series but less significant in the larger series.

Five years later, Oertly and Myers (ref. 16) postulated that a sweet substance must contain two units, namely a glucophore and an auxogluc. This assumption was based on the Witt's theory of dyeing according to which two different groups are required to produce a dyestuff, namely a chromophore and an auxochrome. In the case of sweeteners the glucophore is a group of atoms capable of forming a sweet compound when combined with any auxogluc, which would otherwise be tasteless. The authors proposed six glucophores and nine auxoglucs.

## AH-B THEOREM

A significant step forward in the structure-activity relationships of sweeteners was the assignment of the AH-B moiety in sweeteners by Shallenberger and Acree in 1967 (ref. 17). They proposed that all sweeteners contain an AH-B moiety, of which A and B are electronegative atoms separated by a space of 0.25 - 0.40 nm and H is a hydrogen atom. Hydrogen bonding features of sweeteners and complimentary features on the taste bud receptor site allows the formation of a short-lived complex that results in the generation of a signal that is transmitted through the nervous system to the brain (Fig. 1). In the course of time attention was paid to the assignment of AH-B moieties in different series of sweeteners (ref. 7 and 12).

There is a consensus of opinion among scientists over the assignment of AH-B moieties in several sweetener series i.e. saccharins, sulfamates, acesulfames (all HN-SO) and dipeptide esters ($H_3N^+$-$COO^-$; see ref. 7 and 12).

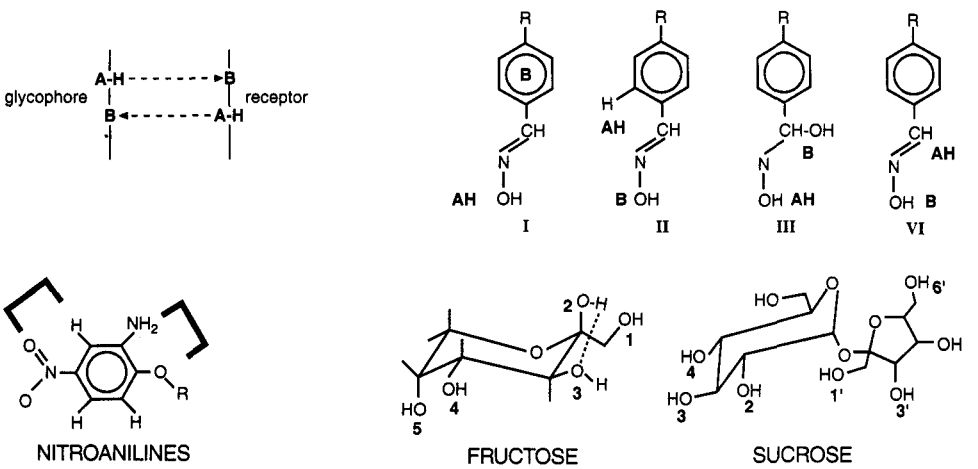


Fig. 1 The assignments of AH-B moieties in oximes, nitroanilines, fructose and sucrose.

**Oximes.** In the series of oximes there are several possibilities for the selection of the AH-B moieties (Fig. 1). Shallenberger and Acree (ref. 18) indicated the hydroxyl function of the oxime group as AH, and the π-bonding cloud of the aromatic ring as B (I in Fig. 1). Kier (ref. 19) selected an aromatic ring hydrogen ortho to the oxime group as AH and the hydroxyl oxygen of the oxime group as B (II in Fig. 1). This assignment was in accordance with several other observations published later on, such as the molecular connectivity calculations for cyclohexylaldoximes (ref. 20) and the molecular electrostatic potential recognition pattern (ref.

21). Beets (ref. 8) suggested an hydration of the oxime function and indicated the two hydroxyl groups as AH-B moieties (III in Fig. 1). However, NMR measurements could not confirm any hydration (ref. 22), so this assignment is very doubtful. Van der Heijden *et al.* (ref. 22) proposed the C-H of the oxime group as AH and the oxime hydroxyl oxygen as B (IV in Fig. 1), also because acetaldehyde oxime was found to be faintly sweet. Assignments II and IV are very similar with respect to their positions versus the third binding site (see later on).

**Nitroanilines.** Shallenberger & Acree (ref. 17) selected the ortho aromatic hydrogen atom as AH and one of the oxygen atoms of the $NO_2$ group as B; although the aromatic hydrogen cannot be considered as a favourite candidate for hydrogen bonding. The consideration was also based on the fact that nitrobenzene itself is sweet (95 times sweeter than sucrose). Several other scientists have accepted this proposal (ref. 19, 22 and 23). Crosby *et al.* (ref. 6), however, selected the ortho amino group as AH and the alkoxy oxygen atom as B. Van der Heijden *et al.* (ref. 22) did not share this view because (i) other nitro compounds are also sweet, although they lack the alkoxy group; and (ii) generally, changes in the neighbourhood of the AH-B moiety will decrease the potency, which is not the case with this nitroaniline series; on the contrary, in the homologous series there is an optimum in sweetness potency, which corroborates with the influence of the third binding site (ref. 22) as defined later on. A remarkable assignment of the AH-B moiety in the nitroaniline series came from Nofre and Tinti (ref. 24) in 1993 when they indicated several recognition sites in sweeteners. These scientists selected N-H of the amino group as AH, but no B . This is the first report on the possible absence of a complete AH-B moiety in sweeteners !

**Fructose.** It is logical that assignments of AH-B moieties in carbohydrates are very difficult as each OH group can function as AH and/or as B. The latter is also an explanation for the fact that both D- and L-carbohydrates are sweet while in the series of amino acids the L-isomers are not sweet, in contrast with the sweet D-isomers. The assignment of the AH-B unit (Fig. 1) in ß-D-fructopyranose ($^2C_5$) was based on interpretation of infrared spectra and the significance of substitution reactions. In the first instance a number of scientists (ref. 17, 25 and 26) selected OH-2 and O-1 as the AH-B moiety in fructose. This was based on the knowledge that di-fructose dianhydride (containing no free anomeric center) was tasteless (ref. 17), the hydroxyl absorption bands in ketose sugars (ref. 25) and on ab initio calculations (ref. 26). Birch *et al.* (ref. 27) proposed that the anomeric centre plays no direct role in the sweetness of sugars as a binding site but rather it is the 3,4-glycol system of pyranoses which constitutes the AH,B glycophore. Based on the fact that the synthesized 1,6-di-S-methyl-1,6-dithio-D-fructofuranose, which cannot form a bicyclic chelate ring, is 15 to 20 times sweeter than sucrose (ref. 28), it appears that O-3 is the probable B function and not O-1. Considering tripartite glycophore requirements, Shallenberger (ref. 12) concluded that OH-5 is AH and O-4 is B for the fructopyranose glycophore (the γ-glycophore is C-1 and is unimpeded by axial hydroxyl groups).
Later views on AH-B assignments for fructose strongly support either OH-1 and O-2 or OH-5 and O-3 as AH-B moieties. In 1989 Hough (ref. 29) proposed OH-1 and O-2 as the AH-B unit and validated this proposal through interaction studies on the stereomolecular interaction mechanism of sugars with a proteinaceous receptor model (ref. 30). In 1990 the research group of Szarek reversed their previous view (ref. 26) on the AH-B assignment for fructose. Their new findings were based on AM1 optimized geometries and energies of the pyranoid forms (ref. 31). They stated that OH-2 might act most effectively as a proton acceptor when it adopts an anti-exo-anomeric orientation. Summarizing, one can state that OH-1 and O-2 can be considered as the most likely AH-B moiety.

**Sucrose.** The first assignments of AH-B units in sucrose were done by Birch (ref. 4) and Shallenberger & Lindley (ref. 32). Based on observations of sweetness of sucrose derivatives, these scientists indicated OH-4 and O-3 as the most likely AH-B unit. It was observed (ref. 33) that *galacto*-sucrose (the 4-epimer of sucrose) has only trace sweetness and that methyl derivatives of sucrose varied in sweetness depending upon the specific hydroxyl groups substituted. They proposed that in concentrated solution, the O-5 oxygen and the OH-6' hydrogen may also form an AH-B system (ref. 34). This proposition was not sustained by other scientists later on. Lichtenthaler *et al.* (ref. 35 and 36) performed MOLCAD program-mediated calculations of the molecular electrostatic potential (MEP) and of the respective lipophilicity (hydrophobicity) potential (MLP) on the contact surfaces of, among others, sucrose. Based on their findings this research group proposed that the groups OH-2 and O-3 can best be assigned as the AH-B moiety. This proposition also was not followed by others, as interactions with water were not taken into account. In his article on the sweetness of sucrose and derivatives Hough (ref. 29) indicated that the most likely AH-B systems can be assigned to the following three pairs OH-1', O-2; OH-2, O-3' and OH-3', O-2. The basis for these assignments was previous NMR studies

(ref. 37, 38 and 39) and examinations of molecular models. The assignment of OH-2, O-3' was also proposed by Rohse and Belitz (ref. 40) and can be considered as the most likely one.

## THIRD BINDING SITES

In 1972 Kier (ref. 19) made another important step forward in the structure-activity relationship of sweeteners. He concluded that there must be a third component (firstly described as X) in the sweetness glycophore, which is a site capable of dispersion bonding and can explain the high potency in, for instance, nitroanilines. In all cases, the tripartite arrangement of the groups AH, B and X approximate an oblique position. This binding site was indicated later on as γ (Greek for C). This led to more attention for three dimensional structures of sweeteners and the conformation of flexible molecules.

The tripartite AH, B, γ was also assigned in other sweeteners, e.g. in glucose (the C-6 methylene carbon atom) by Shallenberger and Lindley (ref. 32) and in aspartame (phenyl group) by Van der Heijden *et al* (ref. 41). In the author's opinion the assignment in glucose was rather premature in view of the facts that this sweetener has hydrophilic substituents all over the molecule and the C-6 carbon atom cannot be considered as ***the*** hydrophobic site to impart or enhance the potency as is the case for other high potency sweeteners.

In 1985 Van der Heijden *et al.* (ref. 22 and 42) introduced *new conceptual parameters* (Fig. 2) to describe more precisely the positions of third binding sites versus the AH-B moieties. Sweeteners from a homologous series can reasonably be expected to interact with the same receptor. In such series the potency increases and decreases with chain length. When the chain length is too short or too long there may be no sweetness, while in the intermediate series a maximum of sweetness is obtained.

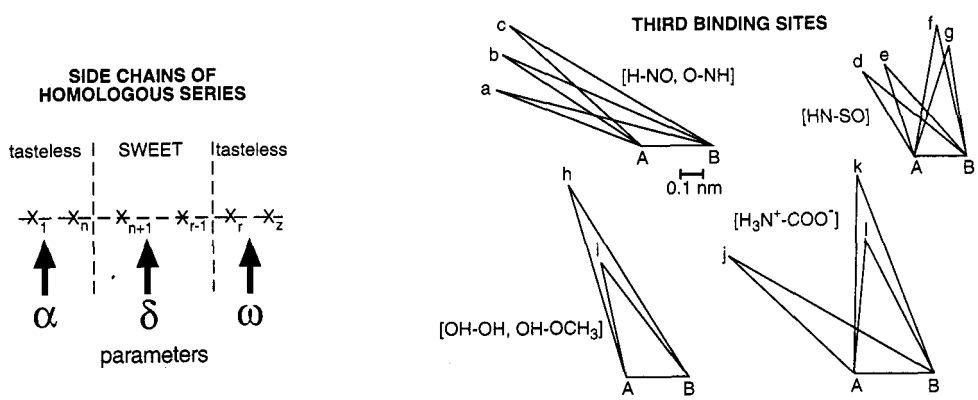


Fig. 2. The parameters α, δ and ω and the averaged positions of the third binding sites δ versus A and B atoms in 10 series of sweeteners (ref. 7, 22 and 42).

Van der Heijden *et al.* (ref. 22) introduced parameters α, δ and ω (Fig. 2) representing points (or better small areas) indicating respectively the minimum, optimal and maximum distances of the hydrophobic sites versus the AH-B moiety. The distance between an atom (belonging to α, δ and ω) and the plane formed by the AH-B moiety was designated as S. The parameters α, δ and ω can be defined as follows (Fig. 2):

- α or (ω) is the terminal *n*th (or *r*th) atom in a side chain of a tasteless compound originating from a homologous series of sweeteners in which the representative, containing a side chain with a terminal $n + 1$ ($r - 1$) atom, positively tastes sweet
- δ denotes the center (or an intermediate point) of side chains in molecules originating from a series of sweeteners with the highest sweetness potencies observed

Van der Heijden *et al.* (ref. 22 and 42) determined the positions for the parameters in 10 series of sweeteners,

which can be classified in 4 categories (ref. 7) resulting in various triangles (Fig. 2). This approach gave more information on the three dimensional character of sweeteners and dimensions involved. Researchers paid more and more attention to lengths, widths, surface areas and volumes of side chains (ref. 7 and 43). For instance, for aspartyl dipeptide esters it was found (ref. 44) that compounds are sweet provided the length parameter L is confined to certain limits (0.50 nm < L < 0.62nm) or otherwise when L exceeds these limits, the width parameter $B_5$ has to be greater than 0.45 nm (when L < 0.50nm) or smaller than 0.72 nm (when L > 0.62 nm). The maximum width of the access to reach the receptor site was found to be 1.5 nm.
Spillane and Sheahan (ref. 45) reported for a series of carbosulfamates a surface area for the receptor site of 30 $Å^2$ and a site depth of 6.2 Å. For heterosulfamates, however, the data are 46.1 $Å^2$ and 6.3 Å, respectively.

Shinoda and Okai (ref. 46) prepared the trifunctional groups in aspartame (AH, α-amino; B, ß-carboxyl; X, L-Phe residue) and observed whether or not the sweet taste is reproduced by the recombination of the components. The authors observed that the AH-X component of aspartame exhibited bitterness and the taste was changed to sweetness by the addition of the B component on the tongue. The phenomenon suggested that bitter and sweet tastes are recognized in the same taste receptor and that the receptor discriminates bitter and sweet tastes by the difference of the combination of the three units between AH-X and AH-X-B.

## QSAR

Besides the studies among particular moieties of sweeteners involved in taste chemoreception as discussed so far (*structural models*), we can correlate sweetness potencies with physico-chemical parameters (*statistical models*; commonly referred to as QSAR, Quantitative Structure-Activity Relationships). This methodology was frequently used for designing drugs. In 1993 Van der Heijden (ref. 7) summarized these QSAR studies for sweeteners done so far yielding the following parameters for the various classes of sweeteners:

| *sweeteners* | *parameters involved* | *elucidation* |
|---|---|---|
| sulfamates | P | P = parachor parameter |
| oximes | P, L, $W_1$, $W_u$ | L = length parameter |
| nitroanilines | $_2\chi$, L, $W_1$, π, $\sigma^*$ | W, B = width parameters |
| aspartyl peptides | P, $B_4$ | π = hydrophobic bonding constant |
| . acid amides | $\sigma^*$, $W_u$, $W_r$ | $\sigma^*$ = electronic parameter |
| . aminoethyl esters | $\sigma^*$, $L_2$, $W_u$, $L_1$ | $_2\chi$ = index of molecular shape |
| . aminopropionates | $\sigma^*$, $W_r$ | |
| . aminoacetates | $\sigma^*$, $L_1$, $L_2$, $W_1$ | |

From data generated in the third binding site determinations and from these QSAR studies it became clear that lengths, widths and volumes of side chains play an important role in the sweet taste chemoreception. Apparent specific and apparent molar volume (ASV and AMV) give an apparent measure of solute size and reflect displacement or disturbance of water structure. ASV values have proved to be particularly important in interpreting events in the chemoreception of tastant molecules and four appropriate ranges of ASV values have been found to be associated with the four basic tastes: salty < ≈0.33, sour ≈0.33 - ≈0.52, sweet ≈0.52 - ≈0.71 and bitter ≈0.71 - ≈0.93 (ref. 47). Good correlations were found for AMV, van der Waals and Corey-Pauling-Koltun volumes for amino acid, carbohydrate and sulfamate tastant molecules (ref. 48-50).

In recent years attention has been paid to the role of water in sweet chemoreception (ref. 51-54). Whether water will facilitate the approach of the sweeteners to the taste bud or will have a direct influence on the interaction at the site is an open question. In this context it is relevant to mention the specific studies on the hydration of monosaccharides as a function of their stereochemistry carried out by Galema (ref. 55 and 56).

## RECOGNITION SITES IN SWEETENERS

The last historical and significant step forward in the structure-activity relationships of sweeteners was the

development of hyperpotent sweeteners by Tinti and Nofre (ref. 57) and the assignment of a great number of recognition sites. The *working hypothesis* of the authors was that all the types of sweeteners could be recognized by a single type of sweet taste receptor and that therefore this receptor must contain all the recognition sites to identify all types of sweeteners. The authors compared the structures of cyanosuosan (sweetness 650 x sucrose) and aspartame (sweetness 180 x sucrose) and observed the common structural feature, the 3-aminopropionate moiety (ref. 24). Tinti and Nofre prepared the hybrid molecule of these sweeteners (called *superaspartame*) and found it to be extremely potent (8,000 x sucrose). Further optimization of the series by Tinti and Nofre yielded compounds with a potency of about 40 000 times that of sucrose. Van der Heijden (ref. 58) concluded from molecular modelling of the hybrid that the positions of some hydrophobic sites (as indicated earlier in the literature) are combined to get a highly potent sweetener. The p-nitrophenyl group of suosan lies in the same position versus the AH-B moiety as the hydrophobic groups in oximes, nitroanilines and ureas found earlier.

In the course of the work by Tinti and Nofre an outstanding class of sweeteners was discovered: guanidine sweeteners. Research in this area resulted in the synthesis of the most potent sweeteners to date, namely sucrononic acid (Fig. 3.). Based on the information from many potent sweeteners Tinti and Nofre (ref. 59) developed a receptor model with 8 recognition sites:

**AH** : an H-bond donor group such as NH or OH
**B** : an anionic group such as $CO_2$, $SO_3^-$, $CN_4^-$ groups
**G** : a hydrophobic group such as the alkyl, cycloalkyl or aryl group
**D** : an H-acceptor ligand such as CN, $NO_2$, Br or Cl, but in which hydrophobic and/or steric effects are also involved
**Y** : an H-bond acceptor ligand such as CO, SO, CN or halogens
**XH** : an H-bond donor group such as NH or OH
**$E_1$, $E_2$** : two sites often working cooperatively, which are H-bond acceptor ligands such as CO, SO, intramolecular H-bonded OH or halogens

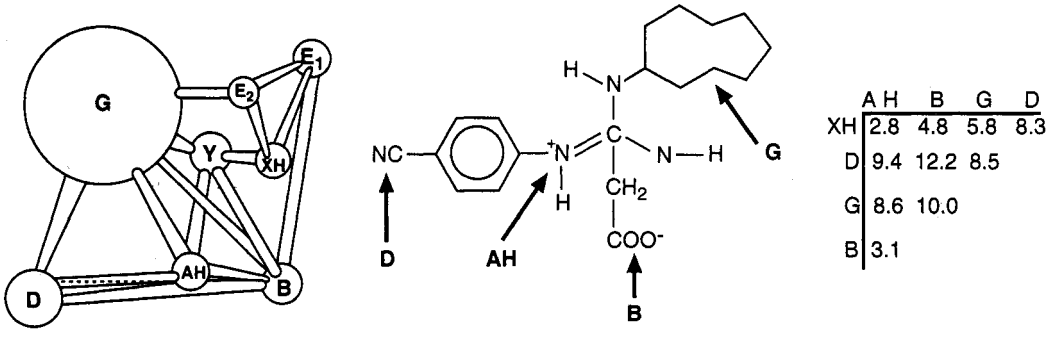


Fig. 3. The revised spatial arrangement of 8 recognition sites of sweeteners as proposed by Tinti and Nofre (ref. 57) and the distances between binding sites in sucrononic acid (ref. 60).

In the past some authors already indicated that some of the sites defined by Tinti and Nofre are relevant for sweet taste chemoreception (e.g. XH in aspartame) but they did not explicitly express the statement of recognition sites.

A series of amides of 1-amino-1-deoxy-D-glucitol and 1-deoxy-1-methylamino-D-glucitol were prepared by Ellis *et al.* (ref. 61). They conducted a study of the correlation of these compounds with the Tinti-Nofre model, but found that in the original article the position of site Y was incorrect. Upon a request by the author of this article to Tinti and Nofre the correct figure could be given here (Figure 3). Suami and Hough (ref. 60) studied the interaction of sucrononic acid with a helical proteinaceous receptor by computer graphics. These

authors found excellent fits and suggested that the model is very good model for future synthetic studies.

## FUTURE ASPECTS IN STRUCTURE-ACTIVITY RELATIONSHIPS

This review clearly demonstrates that in the course of time a very good insight into the structure-activity relationship of sweeteners has been obtained. We can now explain the potency differences within and between a great variety of classes of compounds. There are reasons to believe that high potency sweeteners have a different chemoreception mechanism than the carbohydrates and sugar alcohols. Aspects which have not yet been satisfactorily elucidated are the relation between structures on the one hand and flavour characteristics other than sweet or the differences in temporal taste properties, such as appearance and extinction on the other hand (ref. 62). A challenge for scientists in the SAR area would be to develop a superior low-cal sweetener with all properties equal to those of sucrose.

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