STRUCTURAL ANALOGUES OF HISPOLON AS FLAVOUR MODIFIERS

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Abstract

Starting from the previous structure-activity relationships for bitter-masking molecules based on homoeriodictyol we have investigated into the promising class of hispolon (i.e. 1-(3,4-dihydroxyphenyl)-hex-1-en-3,5-dione) derivatives as well as dihydrochalcones. In contrast to the mostly bitter-sweet tasting phloridzin the only very weak sweet-tasting aglycon phloretin showed strong masking effects against different bitter compounds such as caffeine, salicin, and quinine. Besides their masking effects phloretin and some hispolon derivatives such as the 1-(3-hydroxy-4-methoxyphenyl)-hexan-3,5-dione ([2]-isogingerdione) show remarkably strong sweet enhancing properties.

Introduction

Due to the increasing importance of healthier products, frequently ingredients are added which are good for health but poor in taste. On the other hand, some common ingredients such as sucrose or other bulk carbohydrates are used in reduced amounts or omitted totally to lower the caloric intake. Unfortunately, in most cases the taste of the products is sacrificed and therefore a high demand for flavour modifiers with low intrinsic taste such as bitter maskers (1) or umami or sweet taste enhancers (e.g. 2) has developed during the past years. Some potent new bitter masking molecules such as the 1-carboxymethyl-5-hydroxy-2-hydroxymethylpyridinium inner salt (3) and some derivatives related to the flavanone homoeriodictyol (Figure 1) (4) were developed: hydroxybenzoic acid vanillylamides (5), hydroxylated deoxybenzoins (6), and short chain gingerdiones (7) related to hispolon (8). Some of the latter derivatives showed additional sweet enhancing properties (9) without being sweet and may be used in flavours to increase preference for low-carbohydrate applications which occasionally contain also high-intensity sweeteners as well.

In the present study we have extended our previous structure-activity concepts (5, 9) starting from homoeriodictyol leading to several interesting relatives with new flavour modifying properties.

Experimental

Synthesis. Phloretin and Phloridzin were obtained from Kaden Biochemicals (Hamburg). All other chemicals were purchased from Sigma-Aldrich (Steinheim, Germany) or Acros Organics (Geel, Belgium). The syntheses of gingerdiones and dehydrogingerdiones were performed via condensation of the corresponding hydroxylated benzaldehydes with a boron complex of the acylacetonate as described
earlier (6, 7). Dihydrochalcones were prepared starting using base catalyzed aldol condensation of the appropriately substituted and protected (as benzyl derivatives) acetophenones and benzaldehydes, respectively, by subsequent combined debenzylation and reduction of the intermediate chalcones by catalytic hydrogenation similar to the described procedures (e.g. 10). All compounds were verified by $^1$H- and $^{13}$C-NMR and LC-MS spectroscopic methods following to purification via flash chromatography up to 95 % (HPLC).

Sensory studies. Masking and enhancing studies were done using the duo-comparison method with a panel of 12-16 trained, healthy persons without any reported taste disorder. Samples were blinded, coded and presented in randomized order. Panellist had to rate the intensity of the basic taste quality on a scale of 1 (nothing) to 10 (extremely strong). Modifying effects were calculated relative to the blind sample by $\text{modifying effect} = \left(\frac{\text{rating(test)}}{\text{rating(blind)}}\right) - 1$.

Intrinsic sweetness was determined by comparing the blinded test concentrations to a series of dilutions of sucrose (0%, 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 2.0%, 3.0%, 4.0%, 5.0%).

The sweetness ratings of a series of dilutions of sucrose (0.25 % – 90 %) were determined using the 1-10 scale by the panel and the dose response plot was used to normalize the enhancing ratings into sucrose equivalents (SE) (7).

For the determination of synergistic effects, for each test compound-concentration the normalized SE of the 5 % sucrose solution was added to the intrinsic sweetness (expressed as SE) of the test compound at this concentration. The sum was
Expression of Multidisciplinary Flavour Science

compared to the SE of the experimental sweetness of 5% sucrose solution containing the test compound.

**Results**

Starting from the previously described structure-activity relationships (4, 5) we have investigated into the promising class of hispolon derivatives (7) as well as tasteless dihydrochalcones to find new taste modulating molecules (Figure 1). Besides their bitter masking effects (6) some hispolon derivatives and dihydrochalcones show remarkable sweet enhancing properties without being sweet. At higher concentrations, certain dihydrochalcones such as hesperetin dihydrochalcone and especially their glycosides (e.g. neohesperidin dihydrochalcone, NHDC) are already known as sweet molecules (10) but most of the aglycons we have synthesised and tested are generally tasteless. Phloretin, in contrast to the bitter-sweet tasting phloridzin, shows strong masking effects towards different bitter compounds such as caffeine, salicin, and quinine but not for the tested bitter peptide Leu-Trp (see Figure 2). Therefore, phloretin may be a valuable tool for elucidation of bitter receptor characterization.

![Figure 2. Masking activity of phloretin against different bitter compounds (relative expression).](image)

Phloretin and [2]-isogingerdione exhibit both intrinsic sweetness near to or lower than 1% sucrose equivalent at 100 ppm (see Figure 3A, 3B) and show much higher sweet enhancing effects as expected by simple addition.

Thus, we conclude that the new flavour modifiers exhibit a clear synergistic effect which cannot be explained simply by competitive binding to one active site on the sweet receptor couple. Further studies considering the receptor level will be performed to elucidate the mechanism.
Figure 3. Comparison of intrinsic sweetness of neat phloretin (A) and neat [2]-isoging (B) as well as calculated and found sweet intensities of sucrose/phloretin and sucrose/[2]-isogingerdione mixtures, respectively, normalized as sucrose % equivalents.

References