

FLAVOR MOLECULES

This disclosure relates to flavours, compounds for providing flavours and methods for providing flavours.

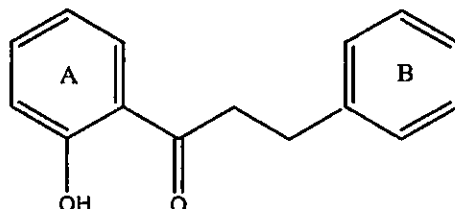
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Flavoring is added to many orally-receivable or ingestible products, such as foodstuffs, confectionery, beverages, mouthwashes, dentrifices and the like. It is preferred that these be identical to natural materials known to be safe, or to be close derivatives of such materials.

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Flavonoids are usually regarded as bitter or neutral-tasting plant constituents. However, there are flavonoids in two structural classes, which are known as sweet representative: the dihydrochalcones (DHCs) and the dihydroflavonols. Only a few dihydrochalcones have been identified from natural sources. Glycyphylin, Phloridzin and trilobatin are the

15 examples isolated from *Smilax glycyphylla* Sm. (Liliaceae), *Symplocos lancifolia* Sieb. Et Zucc., and *Symplocos microcaly*, respectively. Normally, DHCs, molecules with a basic structure according to the following formula



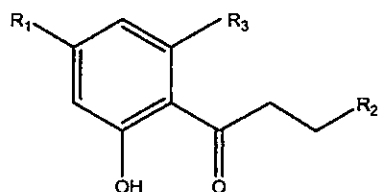
are derived from bitter flavanone glycosides in citrus fruits by catalytic reduction of the

20 chalcones. The best-known semi-synthetic DHC is neohesperidine dihydrochalcone (NDHC), which can be obtained as a by-product of citrus industry and is used in a wide variety of foodstuffs as a sweetener and flavor ingredient.

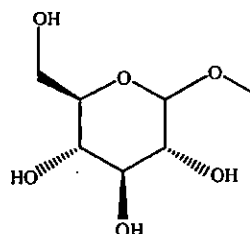
In the past 20 years there have been many attempts to produce dihydrochalcone analogs

25 with taste qualities as good as that of sucrose. It was concluded from these studies that highly sweet compounds in this series required a 3-hydroxy-4-alkoxy substitution in ring B (Whitelaw and Daniel; Journal of Agricultural and Food Chemistry (1991), 39(4), pp.663-7; and Journal of Agricultural and Food Chemistry (1991), 39(1), pp. 44-51).

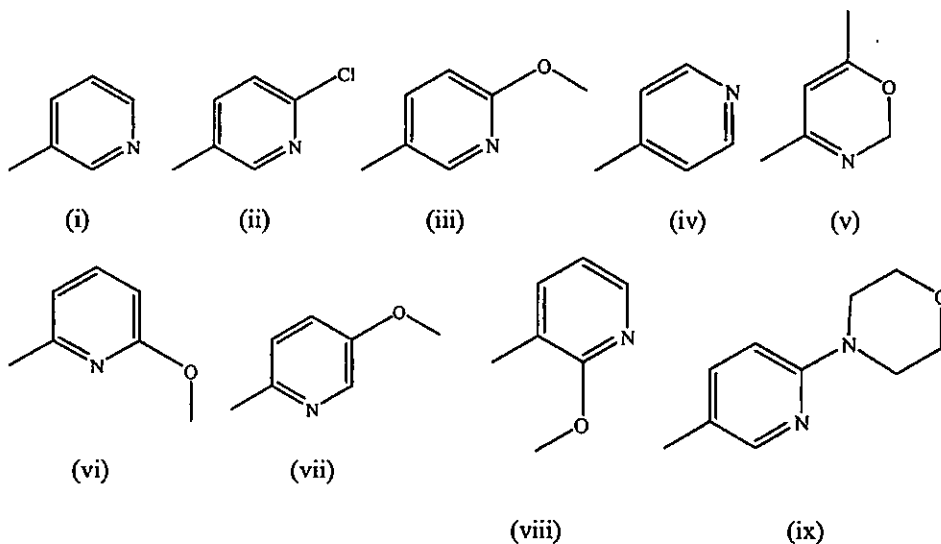
It has now been found that a range of DHC-based compounds are capable of conferring a wide variety of flavors and flavor modifications. There is therefore provided a method of providing flavor to a composition adapted to be received orally, comprising adding thereto at least one compound, including salts thereof, of the formula:



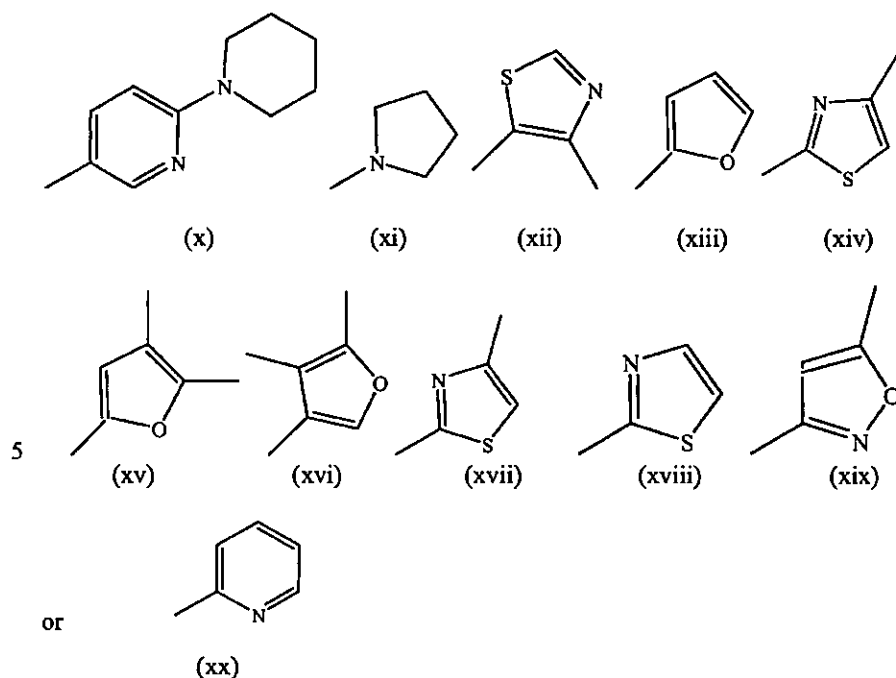
wherein R_1 comprises H, OH, $O(CH_2)_2OH$, OCH_2OCH_3 or



wherein R_2 comprises a heterocyclic species selected from



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10 and wherein R_3 comprises H or OH.

Suitable non-limiting examples of salts of the above identified compounds include K^+ , NH_4^+ , Na^+ , Ca^{2+} , Mg^{2+} , Al^{3+} , Zn^{2+} .

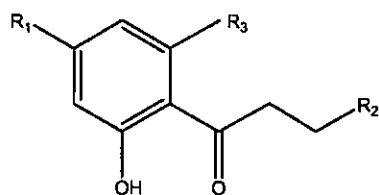
15 Certain illustrative embodiments comprise compounds comprising moieties (iii), (iv), (vii), (viii), (xiii), (xvii) and (xviii).

The compounds confer a wide variety of desirable flavors, such as sweet, sour and umami, to orally receivable or digestible products. Specific examples of these flavor
 20 characteristics are described in further detail in the examples hereinunder provided.

A number of the molecules hereinabove provided are novel materials. Some of the compounds hereinabove described are novel. There is therefore additionally provided a compound (including salts thereof) the formula:

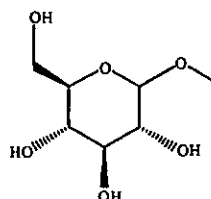
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wherein R_1 comprises H, OH, $O(CH_2)_2OH$, OCH_2OCH_3 or

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10 wherein R_3 comprises H or OH,

with the proviso that

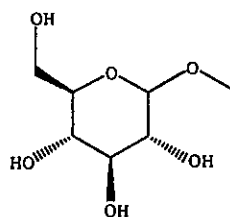
(a) when R^1 comprises H, R^2 is selected from moieties (iii), (iv), (vi), (viii), (x), (xii), (xiii),
 15 (xiv), (xvi), (xvii), (xviii), (xix) and (xx);

(b) when R^1 comprises OH, R^2 comprises a moiety selected from (iii) or (iv);

(c) when R^1 comprises $-OCH_2OCH_3$, R^2 comprises a moiety selected from (iii) or (iv);

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(d) when R^1
 comprises



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R^2 comprises a moiety selected from (iii) or (iv); and

(e) when R^1 comprises $-OCH_2CH_2OH$, R^2 comprises moiety (iii).

30 The compounds may be used in all variety of orally-receivable and ingestible products.

Non-limiting examples of such products include:

- Consumable products, including, but not limited to all food products, food additives, nutraceuticals, pharmaceuticals and any product placed in the mouth including chewing gum, oral care products, and oral hygiene products including but not limited to, cereal products, rice products, tapioca products, sago products, baker's products, biscuit products,
- 5 pastry products, bread products, confectionery products, dessert products, gums, chewing gums, flavored or flavor-coated straws, flavor or flavor-coated food/beverage containers, chocolates, ices, honey products, treacle products, yeast products, baking-powder, salt and spice products, savoury products, mustard products, vinegar products, sauces (condiments), tobacco products, cigars, cigarettes, processed foods, cooked fruits and vegetable products,
- 10 meat and meat products, jellies, jams, fruit sauces, egg products, milk and dairy products, yoghurts, cheese products, butter and butter substitute products, milk substitute products, soy products, edible oils and fat products, medicaments, beverages, carbonated beverages, alcoholic drinks such as beers, wines and spirits, non-alcoholic drinks such as soft drinks, mineral and aerated waters, fruit drinks, fruit juices, coffee, artificial coffee, tea, cocoa,
- 15 including forms requiring reconstitution including, without limitation, beverage powder, milk based beverage powder, sugar-free beverage powder, beverage syrup, beverage concentrate, instant coffee, instant tea, instant cocoa, and coffee whitener, food extracts, plant extracts, meat extracts, condiments, gelatins, pharmaceutical and non-pharmaceutical gums, tablets, lozenges, drops, emulsions, elixirs, syrups and other preparations for making
- 20 beverages, and combinations thereof.

- Oral care products, including, but not limited to, any composition applied to the oral cavity for the purposes of cleaning, freshening, healing, deodorising the cavity or any part thereof, may include, but are not limited to, toothpastes, tooth gels, tooth powders, tooth
- 25 whitening products, mouthwashes, lozenges, dental floss, toothpicks, anti-plaque and anti-gingivitis compositions, throat lozenges, throat drops, inflammatory compositions, compositions for treatment of nasal symptoms, cold symptoms and upper gastrointestinal tract distress, compositions for cold relief, for alleviating discomfort of hot flash, and gargle compositions.

The proportion of compound used will vary in every case, depending upon the end use and the nature and extent of taste required. This may be readily determined in every case by one having ordinary skill in the art by routine experimentation. Without limitation, and by way of illustration only, proportions of compound may be in the range of about 0.01 to about 600 ppm depending on the application. Typical, non-limiting examples in a beverage are from about 1 to about 50 ppm, in ice cream from about 10 to about 100 ppm, and in cereal from about 10 to about 150 ppm.

According to certain illustrative embodiments, the compounds may be used in such products with known flavor compounds, and also with all the known ancillary compounds used in flavoured products.

According to one illustrative aspect of the disclosure, it has been found that one of these compounds enhances the sweetness of a sugar-containing product in a synergistic fashion, that is, the overall sweetness is higher than the simple sum of the sweetness of two sweet substances. This compound has little sweet taste of its own, but it causes a considerable increase in the perceived sweetness of a sugar-containing product. This is of great interest, given the current interest in improved diet and the desire to decrease the sugar content of consumable products sweetness for dietary or health reasons.

According to other embodiments, also provided is a means of decreasing the sugar content of a sugar-containing consumable product, comprising adding to said sugar-containing consumable product an effective amount of 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one (hereinafter referred to as "Compound 13", the number of the Example below in which it is described).

The sweet enhancement effect of Compound 13 is illustrated in the following tables: the isointensity of Compound 13 at 20 ppm equals 0.5 % sucrose. The isointensity of 7% sucrose with 20 ppm 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one is 8% sucrose. Therefore, the perceived enhancement of sucrose is about 0.5% sucrose (8%-7.5%). This sweet enhancement effect is also observed with other natural and artificial sweeteners, for example, carbohydrates; sucrose, lactose, D-glucose, D-tagatose, D-fructose whether

naturally- or synthetically-produced, erythritol, threitol, arabitol, ribitol, xylitol, sorbitol, mannitol, maltitol, isomaltitol, dulcitol, and lactitol, thaumatin, glycin, D-phenylalanine, D-tryptophan, sodium cyclamate, acesulfam K, neohesperidine dihydrochalcone, sodium salt of saccharin, aspartame, superaspartame, neotam, alitام, sucralose, and stevioside.

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Isointensity of 20 ppm Compound 13 in water.

solutions compared	sample sweetness	R-index [%]	Critical value [%]	p-value
0.5% sucrose vs. 20 ppm Compound 13	isosweet	61%	64.61	P>0.05
1% sucrose vs. 20 ppm Compound 13	less sweet	14%	35.39	P<0.05

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Isointensity of 7% sucrose + 20 ppm Compound 13 in water.

solutions compared	sample sweetness	R-index	Critical value	p-value
7% sucrose vs. 7% sucrose + 20 ppm Cmpd 13	sweeter	66%	64.61	P<0.05
8% sucrose vs. 7% sucrose + 20 ppm Cmpd 13	isosweet	43%	35.39	P>0.05
9% sucrose vs. 7% sucrose + 20 ppm Cmpd 13	less sweet	8%	35.39	P<0.05
10% sucrose vs. 7% sucrose + 20 ppm Cmpd 13	less sweet	4%	35.39	P<0.05

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By "effective amount" is meant the amount needed to produce the desired level of sweetness, while reducing the level of sugar to the desired extent. This will naturally depend on the nature of the product and how much sweetness is desired, so no rigid limits can or should be set, but in every case a suitable level may be determined by one having ordinary skill in the art by routine experimentation. Without limitation, and by way of illustration only, proportions may be in the range of about 0.1 to about 500 ppm.

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Compound 13 may be used in conjunction with any known flavour molecule, sweetener, and sweetness enhancer such as naringen dihydro chalcone.

The disclosure is now further illustrated by the following examples, which are purely exemplary.

Example 1: 1-(2-hydroxyphenyl)-3-(6-methoxypyridin-3-yl)propan-1-one

To a stirring solution of 2-hydroxyacetophenone (2.19g, 16.1 mmol) in EtOH (30 ml) at room temperature was added 6-methoxy-3-pyridine-carboxaldehyde (1.98g, 14.4 mmol) and 10 ml solution of KOH in water (1.8g, 32.1 mmol). The solution was continuously stirred at room temperature for 5 hours, and then water was added to the reaction flask. The aqueous layer was acidified to pH=7 using 1N HCl and extracted three times with EtOAc. The organic layers combined and dried (Na₂SO₄). The solvent was removed *in vacuo* and the residue chromatographed on silica gel (5% EtOAc/Hex) to give the yellow solid which was recrystallized with hot EtOAc/hex to yield 1.2g of product (32%). ¹H NMR (300 MHz, CDCl₃): δ 12.83 (s, 1H), 8.43 (d, *J*=2.4 Hz, 1H), 7.96-7.89 (m, 2H), 7.91 (d, *J*=15.3 Hz, 1H), 7.57 (d, *J*=15.6 Hz, 1H), 7.52 (d, d, *J*=6.9, 7.2 Hz, 1H), 7.05 (d, *J*=8.4 Hz, 1H), 6.97 (d, d, *J*=6.9, 7.5 Hz, 1H), 6.84 (d, *J*=8.7 Hz, 1H), 4.01 (s, 3H). ¹³C NMR (75.5 Hz, CDCl₃) δ 193.28, 165.72, 163.64, 149.47, 141.94, 136.61, 136.39, 129.50, 124.04, 119.94, 118.88, 118.84, 118.69, 111.74, 53.92. HPLCMS (APCI+): *m/z*=256.2.

In a 100 ml round-bottom flask, 0.53g of chalcone (2.08 mmol) and 90mg of 10% Pd/C (0.86 mmol) was mixed together in 20: 10 ml THF: MeOH solution. Hydrogenation at atmospheric pressure then filtered off the catalyst. The crude was purified by chromatography on silica gel (10% EtOAc/hexane) to provide 0.35g (58%) of final compound. ¹H NMR (300 MHz, CDCl₃): δ 12.15 (s, 1H), 7.97 (d, *J*=2.4 Hz, 1H), 7.65 (d, d, *J*=1.5, 8.1 Hz, 1H), 7.41-7.36 (m, 2H), 6.91 (d, d, *J*=0.9, 8.4 Hz, 1H), 6.80 (d, d, d, *J*=1.2, 7.5, 8.4 Hz, 1H), 6.62 (d, *J*=8.7 Hz, 1H), 3.84 (s, 3H), 3.21 (t, *J*=7.5 Hz, 2H), 2.92 (t, *J*=7.5 Hz, 2H). ¹³C NMR (75.5 Hz, CDCl₃) δ 204.86, 163.00, 162.50, 146.22, 138.95, 136.43, 129.69, 128.63, 119.24, 118.95, 118.63, 110.67, 53.33, 39.74, 26.18. HPLCMS (APCI+): *m/z*=258.1.

Example 2: 1-(2-hydroxyphenyl)-3-(6-methoxypyridin-2-yl) propan-1-one.

2.35g (17.3 mmol) of 2-hydroxyacetophenone, 2.13g of 6-methoxy-2-pyridinecarboxaldehyde (15.5 mmol), and 8 ml of 25% NaOCH₃ were reacted in 70 ml dry

5 THF to give 1.2g (30%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.15 (s, 1H), 8.24 (d, J=14.7 Hz, 1H), 8.01 (d, d, J=1.2, 7.8 Hz, 1H), 7.79 (d, J=15.0 Hz, 1H), 7.65 (d, d, J=7.2, 7.2 Hz, 1H), 7.53 (d, d, J=7.2, 7.2 Hz, 1H), 7.10 (d, J=7.2 Hz, 1H), 7.06 (d, d, J=0.9, 8.1 Hz, 1H), 6.99 (d, d, J=7.2, 8.1 Hz, 1H), 6.83 (d, J=8.4 Hz, 1H), 4.08 (s, 3H).

10 ¹³C NMR (75.5 Hz, CDCl₃) δ 194.32, 163.81, 163.66, 150.24, 143.26, 139.15, 136.52, 130.03, 123.57, 120.18, 119.71, 118.88, 118.58, 113.32, 53.33.

HPLCMS (APCI+): m/z=256.0.

Hydrogenation of 1.52g of chalcone with catalytic amount of 10% Pd/C obtained 1.25g

15 (82%) of dihydrochalcone after purification on silica gel chromatography (5% EtOAc/hexane). ¹H NMR (300 MHz, CDCl₃): δ 12.39 (s, 1H), 7.83 (d, d, J=1.5, 7.8 Hz, 1H), 7.46-7.41 (m, 2H), 6.96 (d, d, J=0.9, 8.4 Hz, 1H), 6.86 (d, d, J=6.9, 7.5 Hz, 1H), 6.77 (d, J=7.2 Hz, 1H), 6.54 (d, J=8.1 Hz, 1H), 3.77 (s, 3H), 3.46 (t, J=7.2 Hz, 2H), 3.17 (t, J=7.2 Hz, 2H).

20 ¹³C NMR (75.5 Hz, CDCl₃) δ 205.86, 163.71, 162.43, 157.65, 138.79, 136.11, 129.99, 119.54, 118.83, 118.37, 115.34, 107.96, 52.95, 36.57, 31.39.

HPLCMS (APCI+): m/z=258.1.

Example 3: 1-(2-hydroxyphenyl)-3-(2-methoxypyridin-3-yl)propan-1-one.

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2.39g (17.6 mmol) of 2-hydroxyacetophenone, 2.10g of 2-methoxy-3-pyridinecarboxaldehyde (15.3 mmol), and 10 ml of 25% NaOCH₃ were reacted in 50 ml of dry THF to give 2.35g (60%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃):

δ 12.85 (s, 1H), 8.24 (d, d, J=1.8, 4.8 Hz, 1H), 8.02 (d, J=15.6 Hz, 1H), 7.94-7.86 (m, 2H),
30 7.90 (d, J=15.9 Hz, 1H), 7.52 (d, d, J=8.4, 8.7 Hz, 1H), 7.06-6.98 (m, 3H), 4.12 (s, 3H).

^{13}C NMR (75.5 Hz, CDCl_3) δ 194.06, 163.65, 162.40, 148.70, 139.84, 138.91, 136.36, 129.72, 122.69, 120.08, 118.83, 118.62, 118.23, 117.17, 53.88. HPLCMS (APCI+): $m/z=256.0$.

- 5 Hydrogenation of 0.45g of chalcone with catalytic amount of 10% Pd/C obtained 0.39g (87%) of dihydrochalcone after purification on silica gel chromatography (5% EtOAc/hexane). ^1H NMR (300 MHz, CDCl_3): δ 12.31 (s, 1H), 8.07 (d, d, $J=2.1$, 5.1 Hz, 1H), 7.78 (d, d, $J=1.8$, 8.1 Hz, 1H), 7.50-7.45 (m, 2H), 6.99 (d, d, $J=0.9$, 8.1 Hz, 1H), 6.89 (d, d, $J=7.2$, 8.1 Hz, 1H), 6.85 (d, d, $J=5.1$, 5.6 Hz, 1H), 3.98 (s, 3H), 3.32 (t, $J=7.8$ Hz, 2H), 3.02 (t, $J=7.8$ Hz, 2H).
- 10 ^{13}C NMR (75.5 Hz, CDCl_3) δ 205.66, 162.47, 162.11, 144.87, 138.32, 136.28, 129.89, 123.11, 119.34, 118.87, 118.52, 116.82, 53.32, 37.57, 25.23.
- HPLCMS (APCI+): $m/z=258.1$.

15 **Example 4: 1-(2-hydroxyphenyl)-3-(4-methylthiazol-5-yl)propan-1-one.**

- 2.21g (16.3 mmol) of 2-hydroxyacetophenone, 1.96g of 4-methylthiazole-5-carboxaldehyde (7.86 mmol), and 10 ml of 25% NaOCH_3 were reacted in 50 ml of dry THF to give 1.59g (52%) of chalcone after purification. ^1H NMR (300 MHz, CDCl_3): δ 12.73 (s, 1H), 8.76 (s, 1H), 8.05 (d, d, $J=0.9$, 15.0 Hz, 1H), 7.82 (d, d, $J=1.5$, 8.1 Hz, 1H), 7.49 (d, d, d, $J=1.5$, 7.2, 8.4 Hz, 1H), 7.31 (d, $J=15.0$ Hz, 1H), 7.00 (d, d, $J=0.9$, 8.4 Hz, 1H), 6.95-6.93 (m, 1H), 2.62 (s, 3H).
- 20 ^{13}C NMR (75.5 Hz, CDCl_3) δ 192.60, 163.62, 157.68, 153.29, 136.66, 134.28, 132.96, 129.46, 129.03, 121.63, 119.71, 119.26, 118.93, 118.66, 15.82.
- 25 HPLCMS (APCI+): $m/z=246.1$
- Hydrogenation of 0.48g (1.96 mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.15g (27%) of dihydrochalcone after purification on silica gel chromatography (25% EtOAc/hexane). ^1H NMR (300 MHz, CD_3OD): δ 8.73 (s, 1H), 7.87 (d, d, $J=1.8$, 8.4 Hz, 1H), 7.49 (d, d, d, $J=1.5$, 7.2, 8.1 Hz, 1H), 6.97-6.91 (m, 2H), 3.42 (t, $J=6.9$ Hz, 2H), 3.25 (t, $J=6.9$ Hz, 2H), 2.41 (s, 3H).
- 30 ^{13}C NMR (75.5 Hz, CD_3OD) δ 206.17, 163.24, 151.88, 149.84, 137.49, 132.31, 131.43, 120.82, 120.27, 119.05, 40.66, 21.40, 14.57. HPLCMS (APCI+): $m/z=248.0$

Example 5: 1-(2-hydroxyphenyl)-3-(6-(pyrrolidin-1-yl)pyridin-3-yl)propan-1-one.

1.85g (13.6 mmol) of 2-hydroxyacetophenone, 2.0g of 6-(pyrrolidin-1-yl)nicotinaldehyde (1.34 mmol), and 10 ml of 25% NaOCH₃ were reacted in 50 ml of dry THF to give 2.2g (65%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 13.13 (bs, 1H), 8.34 (d, J=2.4 Hz, 1H), 7.85 (d, J=15.3 Hz, 1H), 7.84 (d, J=1.5 Hz, 1H), 7.74 (d, d, J=2.4, 9.0 Hz, 1H), 7.43 (d, d, d, J=1.5, 7.2, 8.4 Hz, 1H), 7.37 (d, J=15.3 Hz, 1H), 6.98 (d, d, J=0.9, 8.4 Hz, 1H), 6.89 (d, d, d, J=0.9, 7.2, 8.1 Hz, 1H), 6.37 (d, J=9.0 Hz, 1H), 3.49 (bs, 4H), 2.05-1.96 (m, 4H).

¹³C NMR (75.5 Hz, CDCl₃) δ 193.18, 163.52, 157.88, 152.24, 143.78, 135.76, 135.03, 129.32, 120.21, 118.62, 118.46, 118.37, 114.49, 107.04, 46.97, 25.38.

HPLCMS (API-ES): m/z=295.1.

Hydrogenation of 0.65g (2.21 mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.46g (70%) of dihydrochalcone after purification on silica gel chromatography (5% EtOAc/hexane). ¹H NMR (300 MHz, CD₃OD): δ 7.89-7.85 (m, 2H), 7.50-7.43 (m, 2H), 6.94-6.89 (m, 2H), 6.43 (d, J=8.7 Hz, 1H), 3.39-3.29 (m, 6H), 2.90 (t, J=7.2 Hz, 2H), 2.02-1.98 (m, 4H).

¹³C NMR (75.5 Hz, CD₃OD) δ 205.95, 161.92, 155.96, 146.25, 137.93, 135.92, 130.13, 123.17, 119.41, 118.77, 117.62, 106.91, 46.45, 39.55, 26.03, 25.02.

HPLCMS (API-ES): m/z=297.2.

Example 6: 1-(2-hydroxyphenyl)-3-(5-methylisoxazol-3-yl)propan-1-one.

2.24g (16.5 mmol) of 2-hydroxyacetophenone, 1.65g of 5-methylisoxazole-3-carbaldehyde (14.9 mmol), and 10 ml of 25% NaOCH₃ were reacted in 50 ml of dry THF to give 1.59g (29%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.53 (s, 1H), 7.87 (d, d, J=0.6, 7.5 Hz, 1H), 7.80 (d, J=15.6 Hz, 1H), 7.69 (d, J=15.6 Hz, 1H), 7.56-7.51 (m, 1H), 7.05 (d, d, J=0.6, 8.4 Hz, 1H), 6.99-6.93 (m, 1H), 6.31 (d, J=0.3 Hz, 1H), 2.50 (s, 3H).

¹³C NMR (75.5 Hz, CDCl₃) δ 193.08, 170.59, 163.68, 159.84, 136.96, 132.03, 129.81, 126.62, 119.62, 119.02, 118.73, 99.99, 12.32. HPLCMS (APCI+): m/z=230.1.

Hydrogenation of 0.61g (2.66 mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.69g (68%) of dihydrochalcone after purification on silica gel chromatography (10% EtOAc/hexane). ¹H NMR (300 MHz, CD₃OD): δ 7.92 (d, d, *J*=1.5, 8.4 Hz, 1H), 7.51 (d, d, d, *J*=1.5, 7.2, 8.4 Hz, 1H), 6.98-6.93 (m, 2H), 6.95 (bs, 1H), 3.49 (t, *J*=7.2 Hz, 2H), 3.05 (t, *J*=7.2 Hz, 2H), 2.39 (bs, 3H).

¹³C NMR (75.5 Hz, CD₃OD) δ 206.08, 171.14, 164.76, 163.23, 137.42, 131.41, 120.75, 120.26, 119.04, 102.77, 37.30, 21.21, 11.92.

HPLCMS (API-ES): *m/z*=232.1.

10 Example 7: 1-(2-hydroxyphenyl)-3-(pyridin-3-yl)propan-1-one.

2.36g (17.3 mmol) of 2-hydroxyacetophenone, 1.7g of 3-pyridine-carboxaldehyde (15.9 mmol), and 9 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 2.05g (57%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.66 (s, 1H), 8.93 (d, *J*=1.8 Hz, 1H), 8.67 (d, d, *J*=1.5, 4.8 Hz, 1H), 8.03-8.00 (m, 1H), 7.92 (d, *J*=15.7 Hz, 1H), 7.91 (d, *J*=1.5 Hz, 1H), 7.76 (d, *J*=15.6 Hz, 1H), 7.58-7.52 (m, 1H), 7.43 (d, d, *J*=5.1, 8.1 Hz, 1H), 7.07 (d, d, *J*=0.9, 8.1 Hz, 1H), 6.99 (d, d, d, *J*=1.2, 7.2, 8.1 Hz, 1H).

¹³C NMR (75.5 Hz, CDCl₃) δ 193.11, 163.70, 151.26, 149.97, 141.47, 136.75, 134.87, 130.49, 129.64, 123.86, 122.22, 119.81, 119.00, 118.77.

HPLCMS (APCI+): *m/z*=226.1.

Hydrogenation of 0.62g (2.76 mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.31g (50%) of dihydrochalcone after purification on silica gel chromatography (10% EtOAc/hexane). ¹H NMR (300 MHz, CD₃OD): δ 8.51 (d, *J*=1.8 Hz, 1H), 8.37 (d, d, *J*=1.5, 4.8 Hz, 1H), 7.91 (d, d, *J*=1.8, 8.4 Hz, 1H), 7.81 (d, d, *J*=1.8, 7.8 Hz, 1H), 7.49 (m, 1H), 7.37 (d, d, *J*=5.1, 8.1 Hz, 1H), 6.97-6.91 (m, 2H), 3.49 (t, *J*=7.2 Hz, 2H), 3.11 (t, *J*=7.2 Hz, 2H).

¹³C NMR (75.5 Hz, CD₃OD) δ 206.61, 163.27, 150.33, 147.81, 138.92, 138.43, 137.41, 131.49, 125.14, 120.80, 120.24, 119.04, 40.28, 27.94.

HPLCMS (API-ES): *m/z*=228.1.

Example 8: 3-(furan-2-yl)-1-(2-hydroxyphenyl)propan-1-one.

2.27g (16.7 mmol) of 2-hydroxyacetophenone, 1.52g of furan-2-carbaldehyde (15.8 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 2.4g

5 (71%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.90 (s, 1H), 7.94 (d, d, J=1.5, 8.1 Hz, 1H), 7.71 (d, J=15.0 Hz, 1H), 7.58 (d, J=15.0 Hz, 1H), 7.58 (d, J=1.5 Hz, 1H), 7.51 (d, d, J=1.5, 7.2, 8.4 Hz, 1H), 7.04 (d, d, J=0.9, 8.4 Hz, 1H), 6.96 (d, d, J=8.1, 8.1 Hz, 1H), 6.79 (d, J=3.3 Hz, 1H), 6.56 (d, d, J=1.5, 3.3 Hz, 1H).

¹³C NMR (75.5 Hz, CDCl₃) δ 193.31, 163.57, 151.56, 145.41, 136.27, 131.11, 129.63,
10 120.08, 118.83, 118.54, 117.67, 117.06, 112.88.

HPLCMS (APCI+): m/z=215.1.

Hydrogenation of 0.48g (2.24mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.26g (54%) of dihydrochalcone after purification on silica gel chromatography

15 (5% EtOAc/hexane). ¹H NMR (300 MHz, CDCl₃): 12.25 (s, 1H), 7.79 (d, d, J=1.5, 8.1 Hz, 1H), 7.48 (d, d, d, J=1.5, 7.2, 8.4 Hz, 1H), 7.34-7.28 (m, 1H), 7.01 (d, d, J=0.9, 8.4 Hz, 1H), 6.92 (d, d, d, J=1.2, 7.5, 8.4 Hz, 1H), 6.32-6.30 (m, 1H), 6.09-6.08 (m, 1H), 3.39 (t, J=7.2 Hz, 2H), 3.12 (t, J=7.5 Hz, 2H).

¹³C NMR (75.5 Hz, CDCl₃) δ 204.75, 162.44, 154.27, 141.26, 136.37, 129.83, 119.28,
20 118.96, 118.53, 110.36, 105.58, 36.56, 22.55.

HPLCMS (API-ES): m/z=216.9.

Example 9: 1-(2-hydroxyphenyl)-3-(6-morpholinopyridin-3-yl)propan-1-one.

25 2.15g (15.8 mmol) of 2-hydroxyacetophenone, 2.8g of 4-morpholinobenzaldehyde (14.5 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 2.52g (56%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.99 (s, 1H), 8.43 (d, J=2.4 Hz, 1H), 7.93-7.84 (m, 3H), 7.52-7.48 (m, 2H), 7.03 (d, d, J=0.9, 8.4 Hz, 1H), 6.97-6.92 (m, 1H), 6.68 (d, J=9.0 Hz, 1H), 3.86-3.83 (m, 4H), 3.69-3.66 (m, 4H).

30 ¹³C NMR (75.5 Hz, CDCl₃) δ 193.27, 163.58, 159.87, 151.09, 142.84, 136.03, 135.90, 129.38, 120.18, 120.13, 118.70, 118.59, 116.27, 106.44, 66.58, 45.09.

HPLCMS (APCI+): m/z=311.2.

Hydrogenation of 0.341g (1.10mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.44g of dihydrochalcone after purification on silica gel chromatography (10% EtOAc/hexane). ¹H NMR (300 MHz, CD₃OD): δ 8.04 (d, J=1.8 Hz, 1H), 7.90 (d, d, J=1.5, 8.1 Hz, 1H), 7.55 (d, d, J=2.7, 8.7 Hz, 1H), 7.52-7.46 (m, 1H), 6.96-6.88 (m, 2H), 5 6.79 (d, J=7.2 Hz, 1H), 3.81-3.78 (m, 4H), 3.43-3.35 (m, 6H), 2.97 (t, J=7.2 Hz, 2H). ¹³C NMR (75.5 Hz, CD₃OD) δ 205.19, 160.51, 157.95, 146.96, 137.79, 135.95, 130.68, 125.65, 120.35, 119.17, 117.60, 106.86, 65.93, 45.42, 25.68, 0.07. HPLCMS (API-ES): m/z=313.0.

10 Example 10: 3-(4, 5-dimethylfuran-2-yl)-1-(2-hydroxyphenyl)propan-1-one.

2.0g (14.7 mmol) of 2-hydroxyacetophenone, 1.75g of 4,5-dimethylfuran-2-carbaldehyde (14.1 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 1.71g (50%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 13.07 (s, 15 1H), 7.95 (d, J=7.8 Hz, 1H), 7.61 (d, J=15.0 Hz, 1H), 7.51-7.42 (m, 2H), 7.02 (d, d, J=0.9, 8.4 Hz, 1H), 6.94 (d, d, J=1.2, 8.4, 9.0 Hz, 1H), 6.60 (s, 1H), 2.34 (s, 3H), 2.00 (s, 3H). ¹³C NMR (75.5 Hz, CDCl₃) δ 193.29, 163.52, 152.60, 148.96, 135.91, 131.22, 129.56, 121.57, 120.22, 118.67, 118.46, 118.43, 115.20, 11.88, 9.68. 20 HPLCMS (APCI+): m/z=243.1.

Hydrogenation of 1.06g (4.38 mmol) of chalcone with catalytic amount of 10% Pd/C gives the dihydrochalcone after purification on silica gel chromatography. ¹H NMR (300 MHz, CD₃OD): δ 7.91 (d, d, J=1.8, 8.4 Hz, 1H), 7.50 (d, d, d, J=1.8, 7.2, 9.0 Hz, 1H), 6.97-6.92 25 (m, 2H), 5.83 (s, 1H), 3.34 (t, J=7.8 Hz, 2H), 2.96 (t, J=7.2 Hz, 2H), 2.13 (s, 3H), 1.87 (s, 3H). ¹³C NMR (75.5 Hz, CD₃OD) δ 207.01, 163.31, 152.56, 146.67, 137.33, 131.50, 120.80, 120.18, 119.02, 115.46, 109.61, 37.88, 23.56, 11.10, 9.84. HPLCMS (APCI+): m/z=245.1.

Example 11: 1-(2-hydroxyphenyl)-3-(4-methylthiazol-2-yl)propan-1-one.

2.27g (16.7 mmol) of 2-hydroxyacetophenone, 2.0g of 4-methylthiazole-2-carbaldehyde (15.7 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give

5 0.67g (17%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.67 (s, 1H), 7.98-7.95 (m, 1H), 7.80 (d, *J*=15.3 Hz, 1H), 7.89 (d, *J*=15.0 Hz, 1H), 7.53 (d, *J*=8.4, 8.4 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J*=8.4 Hz, 1H), 6.97 (d, *J*=7.5, 7.8 Hz, 1H), 2.56 (s, 3H).

¹³C NMR (75.5 Hz, CDCl₃): δ 193.04, 163.65, 162.50, 155.71, 136.77, 135.40, 129.95,
10 123.40, 119.90, 118.99, 118.60, 117.52, 17.14.

HPLCMS (APCI+): *m/z*=246.1.

Hydrogenation of 1.2g (4.90mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.99g (81%) of dihydrochalcone after purification on silica gel chromatography

15 (10% EtOAc/hexane). ¹H NMR (300 MHz, CD₃OD): δ 7.93 (d, *J*=1.5, 8.4 Hz, 1H), 7.51 (d, *J*=1.5, 7.5, 8.4 Hz, 1H), 6.97-6.96 (m, 1H), 6.93 (s, 1H), 3.61 (t, *J*=7.2 Hz, 2H), 3.40 (t, *J*=6.9 Hz, 2H).

¹³C NMR (75.5 Hz, CD₃OD): δ 205.69, 171.34, 163.20, 153.11, 137.47, 131.42, 120.77, 120.29, 119.06, 114.50, 103.55, 38.87, 27.90, 16.65.

20 HPLCMS (API-ES): *m/z*=248.0.

Example 12: 1-(2-hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one.

2.08g (15.3 mmol) of 2-hydroxyacetophenone, 1.55g of 2-pyridine-carboxaldehyde (14.5
25 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 1.4g (43%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.76 (s, 1H), 8.73 (d, *J*=4.5 Hz, 1H), 8.29 (d, *J*=15.3 Hz, 1H), 8.06 (d, *J*=1.5, 8.1 Hz, 1H), 7.78 (d, *J*=15.0 Hz, 1H), 7.77 (d, *J*=1.8, 7.5, 9.3, 1H), 7.56-7.50 (m, 2H), 7.37-7.32 (m, 1H), 7.05 (d, *J*=8.4 Hz, 1H), 7.01-6.94 (m, 1H).

30 ¹³C NMR (75.5 Hz, CDCl₃): δ 194.12, 163.66, 152.80, 150.21, 143.14, 137.00, 136.66, 130.28, 125.83, 124.67, 124.29, 120.10, 118.94, 118.51.

HPLCMS (APCI+): *m/z*=226.1.

Hydrogenation of 1.22g (4.44mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.57g (46%) of dihydrochalcone after purification on silica gel chromatography (30% EtOAc/hexane). ¹H NMR (300 MHz, CDCl₃): δ 12.29 (s, 1H), 8.52 (d, *J*=4.8 Hz, 1H), 7.84 (d, d, *J*=1.5, 8.1 Hz, 1H), 7.61 (d, d, d, *J*=1.8, 7.5, 9.3 Hz, 1H), 7.45 (d, d, d, *J*=1.8, 8.7, 9.9 Hz, 1H), 7.25 (d, *J*=7.8 Hz, 1H), 7.13 (d, d, *J*=5.7, 7.2 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 6.92-6.86 (m, 1H), 3.56 (t, *J*=7.2 Hz, 2H), 3.25 (t, *J*=7.2 Hz, 2H). HPLCMS (API-ES): *m/z*=228.0.

Example 13: 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one.

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2.26g (16.6 mmol) of 2-hydroxyacetophenone, 1.68g of 4-pyridine-carboxaldehyde (15.7 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 1.02g (29%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.56 (s, 1H), 8.72-8.70 (m, 2H), 7.90 (d, d, *J*=1.5, 7.8 Hz, 1H), 7.80 (s, 2H), 7.56-7.48 (m, 3H), 7.05 (d, d, *J*=0.9, 8.4 Hz, 1H), 6.97 (d, d, *J*=7.2, 7.5 Hz, 1H).

15

¹³C NMR (75.5 Hz, CDCl₃) δ 193.08, 163.64, 150.62, 142.04, 141.70, 136.91, 129.74, 124.45, 122.06, 120.08, 119.05, 118.70.

HPLCMS (APCI+): *m/z*=226.1.

20 Hydrogenation of 1.4g (6.22mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.195g (14%) of dihydrochalcone after purification on silica gel chromatography (30% EtOAc/hexane). ¹H NMR (300 MHz, CDCl₃): δ 12.16 (s, 1H), 8.53-8.51 (m, 2H), 7.73 (d, d, *J*=1.5, 7.8 Hz, 1H), 7.48 (d, d, d, *J*=1.8, 7.5, 8.7 Hz, 1H), 7.19-7.17 (m, 2H), 6.99 (d, d, *J*=0.9, 8.1 Hz, 1H), 6.89 (d, d, d, *J*=1.2, 7.2, 8.1 Hz, 1H), 3.36 (t, *J*=7.2 Hz, 2H), 3.07 (t, *J*=7.5 Hz, 2H).

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¹³C NMR (75.5 Hz, CDCl₃) δ 204.18, 162.45, 149.93, 149.67, 136.55, 129.57, 123.77, 119.12, 119.00, 118.66, 38.40, 28.95.

HPLCMS (API-ES): *m/z*=228.0.

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Example 14: 1-(2-hydroxyphenyl)-3-(6-(piperidin-1-yl)pyridin-3-yl)propan-1-one.

1.72g (12.6 mmol) of 2-hydroxyacetophenone, 2.0g of 6-(piperidin-1-yl)nicotinaldehyde (10.5 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give

5 1.41g (43.5%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 13.10 (s, 1H), 8.39 (d, J=2.4 Hz, 1H), 7.93-7.89 (m, 2H), 7.80 (d, d, J=2.4, 9.0 Hz), 7.51-7.42 (m, 2H), 7.03 (d, d, J=0.9, 8.4 Hz, 1H), 6.94 (d, d, d, J=1.2, 7.2, 8.1 Hz, 1H), 6.68 (d, J=9.0 Hz, 1H), 3.71-3.67 (m, 4H), 1.75-1.67 (m, 6H).

¹³C NMR (75.5 Hz, CDCl₃) δ 193.28, 163.55, 159.69, 151.69, 143.34, 135.84, 135.60,
10 129.35, 120.23, 118.79, 118.64, 118.53, 115.07, 106.47, 45.99, 25.61, 24.64.

HPLCMS (APCI+): m/z=309.2.

Hydrogenation of 0.5g (1.62mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.33g (66%) of dihydrochalcone after purification on silica gel chromatography

15 (5% EtOAc/hexane). ¹H NMR (300 MHz, CD₃OD): δ 7.97 (d, J=0.3 Hz, 1H), 7.88 (d, d, J=1.8, 8.4 Hz, 1H), 7.51-7.45 (m, 2H), 6.95-6.89 (m, 2H), 6.75 (d, J=8.1 Hz, 1H), 3.47-3.45 (m, 4H), 3.34 (t, J=7.2 Hz, 2H), 2.92 (t, J=7.2 Hz, 2H).

¹³C NMR (75.5 Hz, CD₃OD) δ 207.28, 163.33, 160.16, 147.92, 139.59, 137.34, 131.55, 126.46, 120.83, 120.20, 119.04, 109.25, 27.34, 26.57, 25.74.

20 HPLCMS (API-ES): m/z=311.1.

Example 15: 1-(2-hydroxyphenyl)-3-(thiazol-2-yl)propan-1-one.

2.29g (16.8 mmol) of 2-hydroxyacetophenone, 1.8g of thiazole-2-carbaldehyde (15.9
25 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 0.254g (27%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.62 (s, 1H), 8.08-7.94 (m, 4H), 7.57-7.51 (m, 2H), 7.06 (d, d, J=1.2, 8.4 Hz, 1H), 6.98 (d, d, d, J=1.2, 7.2, 8.1 Hz, 1H).

¹³C NMR (75.5 Hz, CDCl₃) δ 192.97, 163.67, 163.45, 145.16, 136.89, 135.24, 129.91,
30 124.11, 122.33, 119.87, 119.06, 118.66.

HPLCMS (APCI+): m/z=232.1.

Hydrogenation of 0.27g (1.16mmol) of chalcone with catalytic amount of 10% Pd/C obtained 0.26g (27%) of dihydrochalcone after purification on silica gel chromatography (20% EtOAc/hexane). ¹H NMR (300 MHz, CD₃OD): δ 7.83 (d, d, J=1.8, 8.7 Hz, 1H), 7.63 (d, J=3.3 Hz, 1H), 7.46-7.38 (m, 2H), 6.90-6.85 (m, 2H), 3.55 (t, J=6.3 Hz, 2H), 3.39 (t, J=6.6 Hz, 2H).

¹³C NMR (75.5 Hz, CD₃OD) δ 205.56, 171.57, 163.11, 142.96, 137.58, 131.43, 120.68, 120.39, 120.37, 119.20, 38.37, 27.77.

HPLCMS (API-ES): m/z=234.0.

10 Example 16: 3-(6-chloropyridin-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one.

2.08g (15.3 mmol) of 2-hydroxyacetophenone, 2.05g of 6-chloronicotinaldehyde (14.5 mmol), and 10 ml of 25% wt NaOCH₃ were reacted in 50 ml of dry THF to give 0.55g (15%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 12.61 (s, 1H), 8.66 (d, J=2.4 Hz, 1H), 7.97-7.92 (m, 2H), 7.90 (d, J=15.9 Hz, 1H), 7.71 (d, J=15.6 Hz, 1H), 7.55 (d, d, J=1.5, 7.2, 8.7 Hz, 1H), 7.43 (d, J=8.1 Hz, 1H), 7.06 (d, d, J=0.9, 8.4 Hz, 1H), 6.98 (d, d, J=1.2, 7.5, 8.1 Hz, 1H).

¹³C NMR (75.5 Hz, CDCl₃) δ 192.84, 163.72, 153.18, 149.97, 139.93, 137.06, 136.87, 129.61, 129.42, 124.69, 122.63, 119.71, 119.05, 118.80.

HPLCMS (APCI+): m/z=260.1.

Example 17: 1-(2-hydroxy-4-(methoxy)phenyl)-3-(6-methoxypyridin-3-yl)propan-1-one.

4.18g (21.3 mmol) of 1-(2-hydroxy-4-(methoxymethoxy)phenyl)ethanone, 2.8g of 6-methoxy-3-pyridine-carboxaldehyde (20.4 mmol), and 1.8g (32.1 mmol) of KOH were reacted in 60 ml of EtOH and 20 ml of H₂O ml to give 2.18g (34%) of chalcone after purification. ¹H NMR (300 MHz, CDCl₃): δ 13.27 (s, 1H), 8.42 (d, J=2.4 Hz, 1H), 7.95-7.82 (m, 3H), 7.50 (d, J=15.6 Hz, 1H), 6.83 (d, J=8.7 Hz, 1H), 6.67 (d, J=2.7 Hz, 1H), 6.61 (d, d, J=2.4, 9.0 Hz, 1H), 5.25 (s, 2H), 4.02 (s, 3H), 3.51 (s, 3H).

¹³C NMR (75.5 Hz, CDCl₃) δ 191.62, 166.27, 165.56, 163.72, 149.14, 141.03, 136.65, 131.18, 124.21, 119.15, 114.88, 111.67, 108.26, 104.05, 94.08, 56.39, 53.92.

HPLCMS (API-ES): $m/z=316.0$.

Hydrogenation of 1.78g (5.65mmol) of chalcone with catalytic amount of 10% Pd/C obtained 1.2g (67%) of dihydrochalcone and 2-(1-hydroxy-3-(6-methoxypyridin-3-yl)propyl)-5-(methoxymethoxy)phenol after purification on silica gel chromatography (15% EtOAc/hexane).

Dihydrochalcone: ^1H NMR (300 MHz, CDCl_3): δ 12.60 (s, 1H), 8.05 (d, $J=2.4$ Hz, 1H), 7.64 (d, $J=9.0$ Hz, 1H), 7.48 (d, d, $J=2.4$, 8.7 Hz, 1H), 6.70 (d, $J=8.4$ Hz, 1H), 6.61 (d, $J=2.4$ Hz, 1H), 6.51 (d, d, $J=2.4$, 8.7 Hz, 1H), 5.21 (s, 2H), 3.92 (s, 3H), 3.48 (s, 3H), 3.22 (t, $J=7.5$ Hz, 2H), 2.99 (t, $J=7.5$ Hz, 2H).

^{13}C NMR (75.5 Hz, CDCl_3) δ 203.12, 165.00, 163.59, 162.91, 146.06, 139.06, 131.40, 128.79, 114.23, 110.66, 108.27, 103.79, 94.01, 91.26, 60.35, 56.35, 39.37, 26.39.

HPLCMS (API-ES): $m/z=318.0$.

2-(1-hydroxy-3-(6-methoxypyridin-3-yl)propyl)-5-(methoxymethoxy)phenol: ^1H NMR (300 MHz, CDCl_3): δ 7.99 (d, d, $J=0.6$, 2.4 Hz, 1H), 7.44 (d, d, $J=2.4$, 8.4 Hz, 1H), 6.83 (d, $J=8.4$ Hz, 1H), 6.70 (d, d, $J=0.6$, 9.0 Hz, 1H), 6.61 (d, $J=3.0$ Hz, 1H), 6.52 (d, d, $J=2.7$, 8.4 Hz, 1H), 5.15 (s, 2H), 4.77 (d, d, $J=5.4$, 8.1 Hz, 1H), 3.92 (s, 3H), 3.48 (s, 3H), 2.71-2.64 (m, 2H), 2.26-2.16 (m, 1H), 2.09-2.02 (m, 1H).

^{13}C NMR (75.5 Hz, CDCl_3) δ 162.72, 157.96, 156.68, 145.82, 139.21, 129.37, 127.70, 121.17, 110.62, 107.62, 105.30, 94.42, 74.17, 56.00, 53.53, 38.31, 28.05.

HPLCMS (API-ES): $m/z=320.1$.

Example 18: 1-(2,4-dihydroxyphenyl)-3-(6-methoxypyridin-3-yl)propan-1-one.

To a solution of 1-(2-hydroxy-4-(methoxymethoxy)phenyl)-3-(6-methoxypyridin-3-yl)propan-1-one (1.62g, 5.11 mmol) in CH_3CN (30 ml) at room temperature was added TFA (2 ml) dropwise, two drops of water. The reaction was stirred at same temperature for 8 h. Aqueous 1N NaOH was added to the reaction mixture until pH=7. The aqueous was extracted with 100 ml EtOAc, and the organic layers were combined. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (15% EtOAc/Hexane) to provide 0.5g (35%) of white solid.

¹H NMR (300 MHz, CD₃OD): δ 8.00 (s, 1H), 7.72 (d, *J*=9.0 Hz, 1H), 7.61 (d, *J*=2.4, 8.4 Hz, 1H), 6.72 (d, *J*=8.7 Hz, 1H), 6.33 (d, *J*=2.4, 9.0 Hz), 6.23 (d, *J*=2.4 Hz, 1H), 3.86 (s, 3H), 3.24 (t, *J*=7.2 Hz, 2H), 2.93 (t, *J*=7.2 Hz, 2H).

¹³C NMR (75.5 Hz, CD₃OD) δ 204.8, 166.4, 164.3, 147.1, 141.0, 133.6, 130.9, 114.1,
5 111.2, 109.1, 103.6, 54.1, 40.0, 27.6.
HPLCMS (APCI+): *m/z*=274.3.

Example 19: 1-(2-hydroxy-4-((3*R*, 4*S*, 5*S*, 6*R*)-3, 4, 5, -trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yloxy)phenyl)-3-(6-methoxypyridin-3-yl)propan-1-one.

- 10 To a solution of 1-(2, 4-dihydroxyphenyl-3-6-methoxypyridin-3-yl)propan-1-one (0.234g, 0.86 mmol) in 1:1 1*N* KCl: 1*N* NaHCO₃ (10 ml) at room temperature was added D-glucopyranosyl bromide (0.7g, 1.7 mmol, 10 ml in dry CH₂Cl₂) dropwise. The mixture was refluxed for 24 h under N₂. After the addition of water, the mixture was extracted 3X with CH₂Cl₂. The organic layers were combined and washed with 1*N* HCl, water, brine,
15 dried (Na₂SO₄) and concentrated. Silica gel chromatography purification (35% EtOAc/Hexane) provided 0.25g (48%) sugar dihydrochalcone, which was de-protected by NaOMe in MeOH at room temperature provided 88mg (49%) final glycosylated dihydrochalcone product.

Intermediate A: ¹H NMR (300 MHz, CDCl₃): δ 12.63 (s, 1H), 8.08 (d, *J*=2.1 Hz, 1H),
20 7.68 (d, *J*=9.0 Hz, 1H), 7.51 (d, *J*=2.7, 8.7 Hz, 1H), 6.85-6.80 (d, *J*=8.7 Hz, 1H), 6.57 (d, *J*=2.4 Hz, 1H), 6.53 (d, *J*=3.9, 6.3 Hz, 1H), 5.36-5.29 (m, 2H), 5.24-5.13 (m, 2H), 4.35-4.25 (m, 1H), 4.21-4.13 (m, 1H), 3.95 (s, 3H), 3.25 (t, *J*=7.2 Hz, 2H), 3.03 (t, *J*=7.2 Hz, 2H).
HPLCMS (APCI+): *m/z*=604.0.

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Final product: ¹H NMR (300 MHz, CD₃OD): δ 8.02 (d, *J*=1.8 Hz, 1H), 7.85 (d, *J*=9.0 Hz, 1H), 7.63 (d, *J*=2.4, 8.4 Hz, 1H), 6.74 (d, *J*=0.6, 8.4 Hz, 1H), 6.65 (d, *J*=2.4, 8.7 Hz, 1H), 6.61 (d, *J*=2.4, 1H), 4.96 (d, *J*=7.5 Hz, 1H), 3.92 (d, *J*=3.0 Hz, 1H), 3.84-3.71 (m, 4H), 3.60 (d, *J*=3.3, 9.6, Hz, 1H), 3.37-3.29 (m, 2H), 2.99 (t, *J*=7.2 Hz, 2H).

^{13}C NMR (75.5 Hz, CD_3OD) δ 205.4, 165.7, 165.2, 164.4, 147.1, 140.9, 133.2, 130.8, 115.9, 111.2, 109.5, 105.1, 101.9, 77.1, 74.7, 72.1, 70.1, 62.3, 54.0, 40.3, 27.4.
HPLCMS (ES⁺): m/z =436.1.

Example 20: 1-(2-hydroxy-4-(2-hydroxyethoxy)phenyl)-3-(6-methoxypyridin-3-yl)propan-1-one.

To a solution of 2,4 dihydroxyacetophenone (1.58g, 10.4 mmol) in dry acetone (30 ml) at room temperature was added potassium carbonate (1.56g, 27.8 mmol), (2-bromoethoxy)(*tert*-butyl)dimethylsilane. The solution was reflux for 7 hrs, then pour into water. Aqueous layer was extracted with 3X EtOAc and the organic layers were
10 combined. The organic layer was washed with 1N HCl, water, brine, dried (Na_2SO_4) and concentrated. Chromatography purification obtained 0.36g of intermediate A and 0.58g of intermediate B.

In a 100 ml round-bottom flask, 0.36g of intermediate A (1.80 mmol), 0.25g of 6-methoxynicotinaldehyde (1.80 mmol) in 10 ml EtOH was treated 0.154g of KOH (2.75
15 mmol) in 5 ml water at room temperature. The reaction was stirred at room temperature for 7 hrs and poured into water. Adjusted pH=7 by 1NHCl and extracted with EtOAc. The organic layer was washed three times with water, brine, dried (Na_2SO_4), and concentrated. The chalcone (0.18g, 0.57 mmol) was then hydrogenated in 2:1 THF:MeOH with catalytic amount of 10% Pd/C obtained 0.15g (83%) of final product.

20 Intermediate A: ^1H NMR (300 MHz, CDCl_3): δ 12.6 (s, 1H), 7.54 (d, J =9.0Hz, 1H), 6.37 (d, d, J =2.4, 9.0 Hz, 1H), 6.34 (d, d, J =2.4, 8.7 Hz, 1H), 4.02 (t, J =4.8 Hz, 2H), 3.88 (t, J =4.2 Hz, 2H), 2.46 (s, 3H).

HPLCMS (ES⁺): m/z =196.9.

Intermediate B: ^1H NMR (300 MHz, CDCl_3): δ 12.6 (s, 1H), 7.53 (d, J =8.7 Hz, 1H),
25 6.37-6.36 (m, 2H), 3.97 (t, J =4.5 Hz, 2H), 3.87 (t, J =4.5 Hz, 2H), 2.45 (s, 3H), 0.81 (s, 9H), 0.00 (s, 6H).

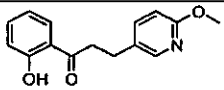
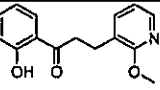
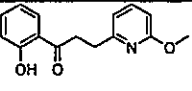
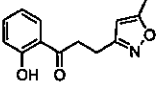
Final product: ^1H NMR (300 MHz, CD_3OD): δ 8.00 (d, $J=0.3$ Hz, 1H), 7.79 (d, $J=9.0$ Hz, 1H), 7.61 (d, d, $J=2.4$, 8.4 Hz, 1H), 6.73 (d, $J=8.4$ Hz, 1H), 6.51 (d, d, $J=2.4$, 9.0 Hz, 1H), 6.43 (d, $J=2.4$ Hz, 1H), 4.08 (t, $J=4.2$ Hz, 2H), 3.93-3.85 (m, 5H), 3.31-3.21 (t, $J=7.5$ Hz, 2H), 2.97 (t, $J=7.2$ Hz, 2H).

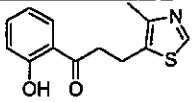
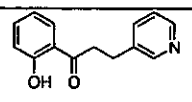
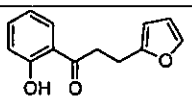
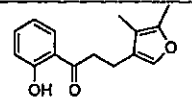
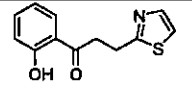
5 ^{13}C NMR (75.5 Hz, CD_3OD) δ 205.1, 166.9, 166.2, 164.4, 147.1, 140.9, 133.2, 130.9, 114.8, 111.2, 108.7, 102.5, 70.9, 61.3, 54.0, 40.1, 27.5.

HPLCMS (ES⁺): $m/z=318.0$.

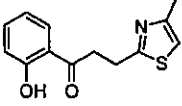
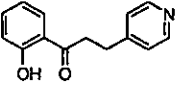
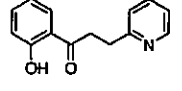
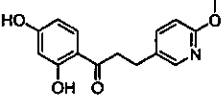
Example 21

- 10 Taste test data of some compounds are shown below. The taste testing was made by a panel of experienced tasters.

Example	Structure	Taste results in water
1		5 ppm, very weak sweet, 20 ppm weakly sweet, 100 ppm very strong sweet, weak bitter taste
3		Very weak sweet at 1 ppm, 10 ppm, 50 ppm bitter, weakly sweet and burning
2		Slightly sweet/bitter at 10 ppm, sweet, bitter, slight fruity at 100 ppm
6		0.1 ppm, slightly bitter, 1 ppm, slightly bitter, weakly sweet, 10 ppm, brothy, umami, soapy, irritating, garlic, 100 ppm, umami, bitter, soapy, garlic

4		0.1 to 1 ppm, petroleum, sulfur, 10 ppm very weak sweet, brothy, 100 ppm sweet, brothy, gassy, bitter, linger
7		0.1 ppm, nothing, 1 ppm, very weak sweet, astringent, 10 ppm, waxy, delayed sweet, astringent, 100ppm, weak sweet, chemical, bitter
8		0.01 ppm, nothing, 0.1 ppm, soap, delayed sweet, 1 ppm, soap, umami, bitter, 10 ppm, licorice aroma, soapy, weak sweet, bitter, vegetable, terpen, 100 ppm, bitter, licorice aroma, weak sweet, celery, umami, brothy
10		0.01 ppm, nothing, 0.1 ppm, floral, soapy, 1 ppm, floral, soap, astringent, piney, 10 ppm, weak bitter, vegetable, piney, astringent, 100 ppm, slightly sweet, bitter, piney, vegetable, sour
15		0.01 ppm, 0.1 ppm, delayed umami aftertaste, 1 ppm, weak plastic, soap, umami, astringent, 10 ppm, astringent, strong umami, weak soap, slight bitter, 100 ppm, bitter, umami

5

11		0.01 ppm, nothing, 0.1 ppm, very weak bitter, 1 ppm, astringent, bitter, 10 ppm, bitter, astringent, 100 ppm, bitter, terpen, weak sweet
13		0.01 ppm to 0.1 ppm, nothing, 1 ppm, weak sweet, 10 ppm, sweet, 100ppm, very sweet, licorice linger
12		1 ppm, umami, 10 ppm, high umami like taste, 100 ppm, strong umami, slightly bitter.
18		100 ppm, sweet

Example 22

Evaluation data on the compound of Example 13, showing how it modifies a flavor in water and in application.

- 10 Strawberry A= candy strawberry, Strawberry B= green strawberry, Strawberry C= floral strawberry, Strawberry D= fruity strawberry, Vanillic Flavor A= vanillic, milky, creamy flavor:

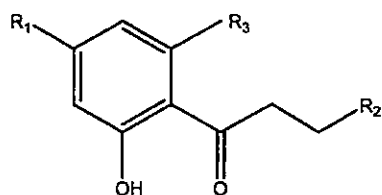
Application	Flavor	Flavorist Evaluation
water	Strawberry A @ 0.2%	Green, candy-like, moderate lactone character, overripe rotten
water	Strawberry A @ 0.2% + 20ppm compound 13	Green character remains but softer, sweeter character removing the candy-like edge associated with the flavor. Character is juicier, and more of a strawberry & cream with some plastic off-notes.
water	Strawberry B @ 0.2%	Slightly green strawberry
water	StrawberryB @0.2% + 20ppm compound 13	Sweeter, less green, jammier, maltol-like note, some plastic off-notes
water	Strawberry C @ 0.2%	Slightly green, floral, kool-aid type strawberry
water	Strawberry C @ 0.2% + 20 ppm compound 13	Less green, less floral, burnt sugar caramel note, strawberry character and coumarin-type character is intensified.
water	Sweetness Improver Flavor A in 25% sugar reduction Grape Type Drink	Sweet grape character, some of the acidic middle profile was suppressed, lingering sweet character not seen in target
water	Sweetness Improver Flavor A + 5 ppm compound 13 in 25% sugar reduction Grape Type Drink	Sweet grape character with the acidic middle regained, enhanced sweet character without the lingering, more of an abrupt sugar-like finish to the flavor profile
Vanilla ice cream 8% vegetable fat ice cream	Vanilla flavour A @ 0.5%	vanillic, milky, creamy
Vanilla ice cream 8% vegetable fat ice cream	Vanilla flavour A @ 0.5% + 10 ppm of compound 13	creamy, vanillic, sweet, slightly cooked
Vanilla ice cream 8% vegetable fat ice cream	Vanilla flavour A @ 0.5% + 15 ppm of compound 13	creamy, sweet, vanillic, lingering sweet vanilla aftertaste
Vanilla ice cream 8% vegetable fat ice cream	Vanilla flavour A @ 0.5% + 30 ppm of compound 13	sweet, vanillic, lingering sweet vanilla aftertaste
Strawberry yoghurt 3% fat, 7% sugar	Strawberry flavour D @ 0.1 %	Fruity, green, fresh, jammy, floral
Strawberry yoghurt 3% fat, 7% sugar	Strawberry flavour D @ 0.1 % + 10 ppm of compound 13	Fruity, slightly fermented, caramellic, green
Strawberry yoghurt 3% fat, 7% sugar	Strawberry flavour D @ 0.1 % + 25 ppm of compound 13	Fruity, sweet, fermented, caramellic, apple like
Strawberry yoghurt 3% fat, 7% sugar	Strawberry flavour D @ 0.1 % + 50 ppm of compound 13	Fermented, sweet, brown, caramellic, overripe banana

Application	Flavor	Panel Evaluation
water	7% sugar + 20 ppm of compound 13	Sweeter than 7% sugar, little floral, fuller, slight longer sweet character, backend slightly delayed, sweeter than 7% with a delayed onset
water	7% sugar + 50 ppm of compound 13	Sweeter than above, very close to 9% sugar-just a very small difference, slight plastic
water	7% sugar with 0.105% Citric acid + 20 ppm of compound 13	Sweeter than control, not effecting acidity, nice backend, sweeter brown notes, cotton candy
water	7% sugar with 0.105% Citric acid + 50 ppm of compound 13	Sweeter than sample at 20 ppm, musty, clean, not that lingering
2% milk	20 ppm compound 13	Slight change in profile, Sweeter than control (2% milk)
cereal	50% reduced sugar + 20 ppm of compound 13	Not lingering, more brown notes, roasted, sweeter than control
cereal	50% reduced sugar + 50 ppm of compound 13	Sweeter than 50% reduced control, better performance, sweeter than 20 ppm, maybe slight offnote, close to target
cereal	50% reduced sugar+ 20 ppm of compound 13 + 100 ppm of Sweet Flavor B	Nice, works well, more close to sugar taste, clearly sweeter than 50% red., Sweeter, close to target, higher late sweetness and longer sweetness than above

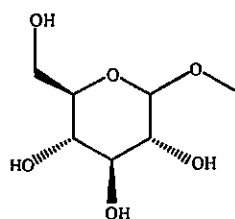
While the compounds, methods of providing flavors and orally receivable and ingestible products have been described above in connection with illustrative embodiments, it is to be understood that other similar embodiments may be used or modifications and additions may be made to the described embodiments for performing the same function without deviating therefrom. Further, all embodiments disclosed are not necessarily in the alternative, as various embodiments of the invention may be combined to provide the desired characteristics. Therefore, the compounds, methods and products should not be limited to any single embodiment, but rather construed in breadth and scope in accordance with the recitation of the attached claims.

Claims:

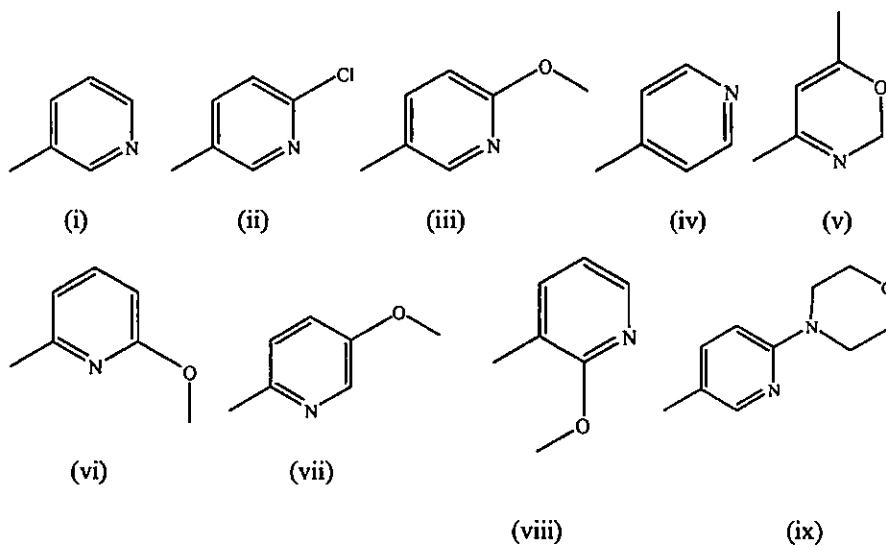
1. A method of providing flavor to a composition adapted to be received orally, comprising adding to said product at least one compound, including salts thereof, selected from compounds of the formula:



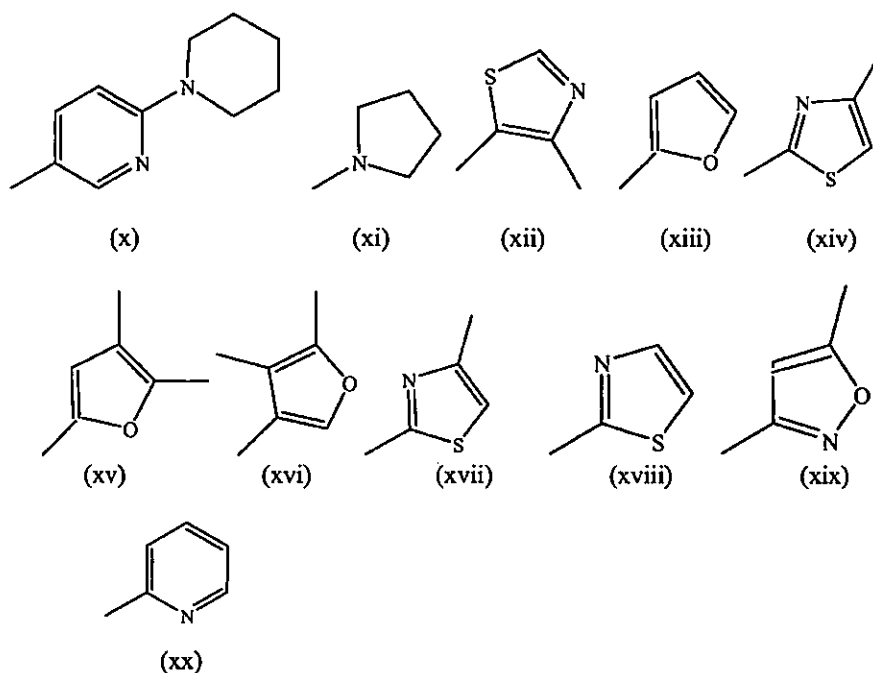
wherein R^1 comprises H, OH, $O(CH_2)_2OH$, OCH_2OCH_3 or



wherein R^2 comprises a heterocyclic moiety selected from:



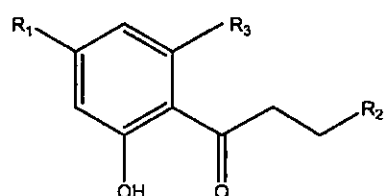
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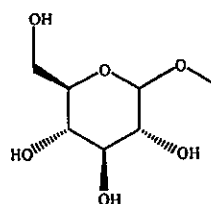
10 and wherein R_3 comprises H or OH.

2. The method according to claim 1, wherein R^2 is selected from the moieties (iii), (iv), (vii), (viii), (xiii), (xvii) and (xviii).

15 3. A compound, including salts thereof, of the formula:

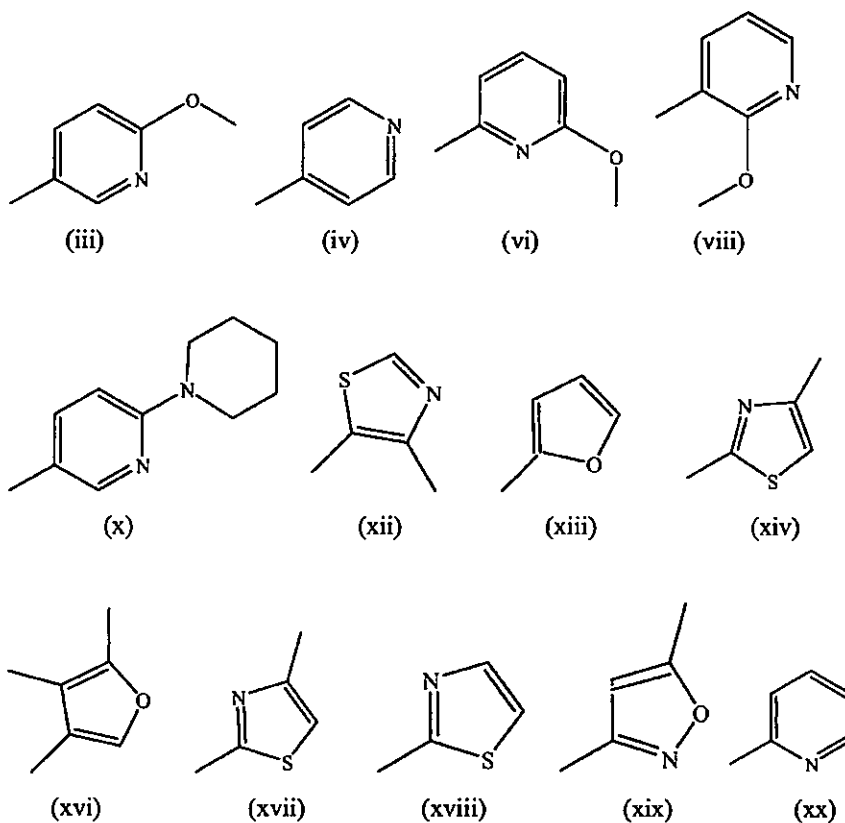


wherein R^1 comprises H, OH, $O(CH_2)_2OH$, OCH_2OCH_3 , or



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wherein R^2 comprises a moiety selected from:



and wherein R^3 comprises H or OH;

such that

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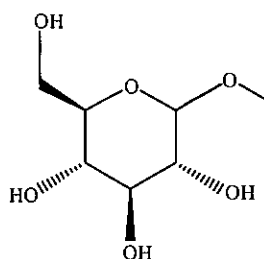
(a) when R^1 comprises H, R^2 is selected from the group consisting of the moieties (iii), (iv), (vi), (viii), (x), (xii), (xiii), (xiv), (xvi), (xvii), (xviii), (xix) and (xx);

(b) when R^1 comprises OH, R^2 comprises moiety (iii) or (iv);

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(c) when R^1 comprises $-OCH_2OCH_3$, R^2 comprises moiety (iii) or (iv);

(d) when R^1 comprises

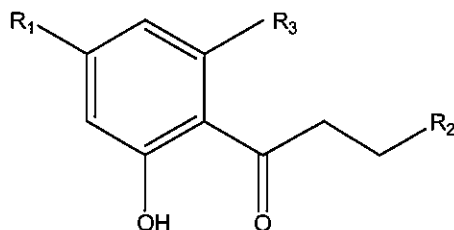


R^2 comprises moiety (iii) or (iv);

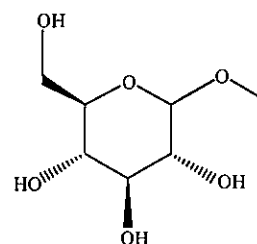
and

(e) when R^1 comprises $-OCH_2CH_2OH$, R^2 comprises moiety (iii).

4. The compound of claim 3, wherein said compound comprises 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one.
5. A method of reducing the natural or artificial sweetener content of a sweetener-containing consumable product while maintaining sweetness, comprising adding a sweetness-enhancing quantity of 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one to said product.
6. The method according to claim 5, comprising adding said 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one and at least one other sweetness-enhancing compound to said product.
7. An orally-receivable product comprising at least one flavor providing compound, including salts thereof, of the formula:

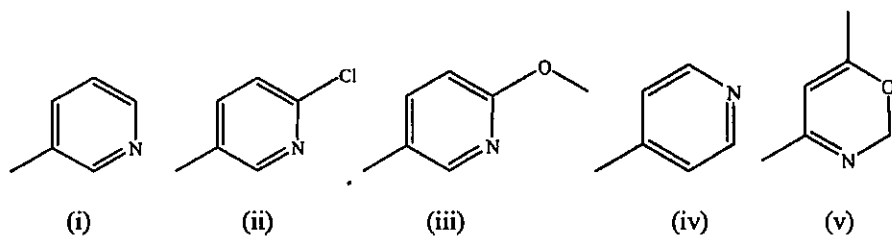


wherein R^1 comprises H, OH, $O(CH_2)_2OH$, OCH_2OCH_3 or

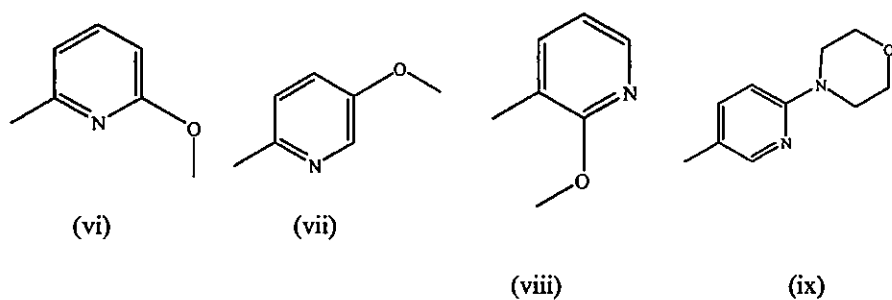


wherein R^2 comprises a heterocyclic moiety selected from:

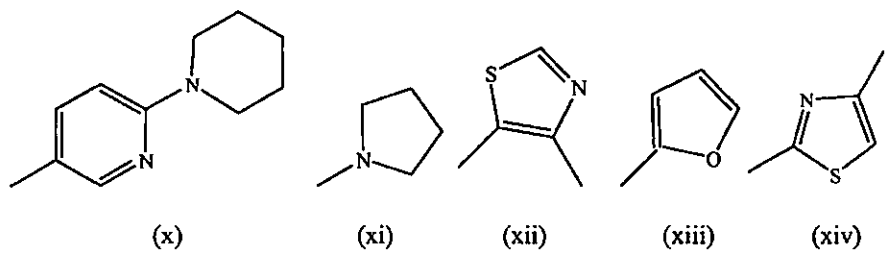
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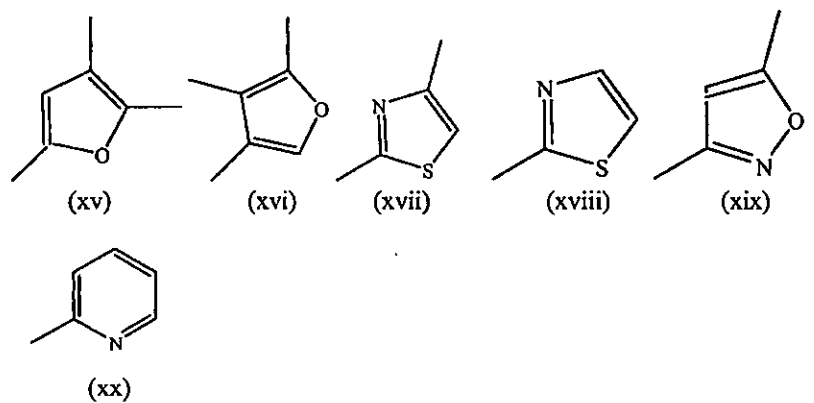
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and wherein R_3 comprises H or OH.

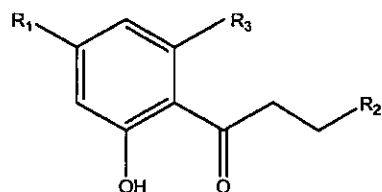
8. The orally-receivable product of claim 7, wherein said flavor-providing compound comprises 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one.

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9. The orally-receivable product of claim 8, wherein said flavor-providing compound comprises 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one and at least one other sweetness-enhancing compound.

10. A sweetener-containing consumable product comprising:

at least one flavor providing compound, including salts thereof, of the formula:

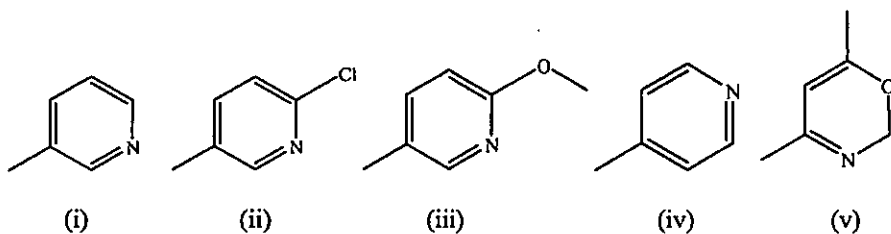
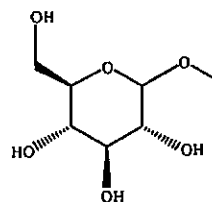


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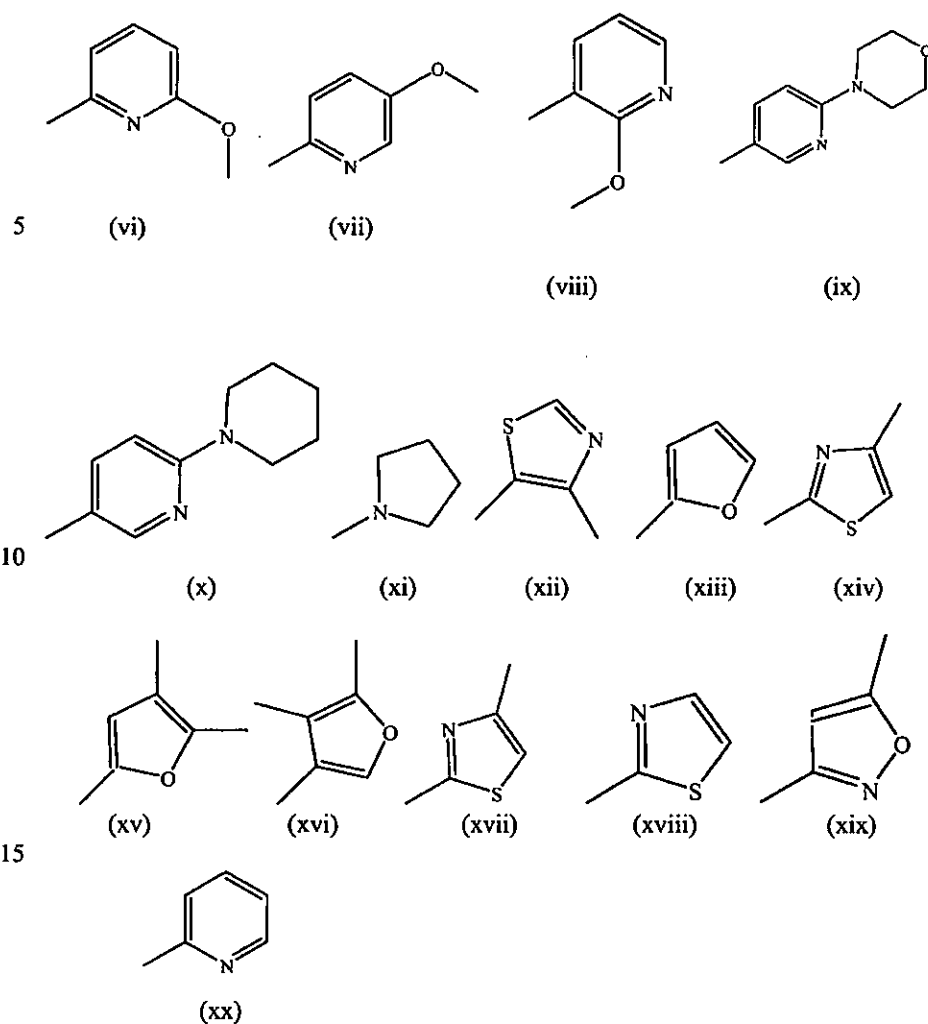
wherein R^1 comprises H, OH, $O(CH_2)_2OH$, OCH_2OCH_3 or

20

wherein R^2 comprises a heterocyclic moiety selected from:



25



and wherein R_3 comprises H or OH.

- 20 11. The sweetener-containing consumable product of claim 11, wherein said flavour-providing compound comprises 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one.

12. The sweetener-containing consumable product of claim 11, wherein said flavor providing compound comprises 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one and at least one other sweetness-enhancing compound.