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Benzyl benzoates: New phlorizin analogs as mushroom tyrosinase inhibitors

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ABSTRACT

In our research, 14 benzyl benzoates with hydroxyl(s) (**3–16**) were synthesized and their inhibitory activity on mushroom tyrosinase was tested. Results indicated that among these compounds, 4-hydroxybenzyl 3,5-dihydroxybenzoate (**3**), 4-hydroxybenzyl 2,4-dihydroxybenzoate (**5**), 4-hydroxybenzyl 2,4,6-dihydroxybenzoate (**7**), 3-hydroxybenzyl 3,5-dihydroxybenzoate (**8**), 3-hydroxybenzyl 2,4-dihydroxybenzoate (**10**) exhibited inhibitory activity with their IC_{50} less than 10 μM. Further studies showed these five compounds were competitive inhibitors of tyrosinase and their structure–activity relationships were investigated in this article.

1. Introduction

As the key enzyme of melanin biosynthesis,[1] tyrosinase (EC 1.14.18.1; polyphenol oxidase) widely exists in plants and animals. Tyrosinase is a copper-containing multifunctional oxidase that catalyzes both the hydroxylation of monophenols to diphenols and the oxidation of *o*-diphenols to *o*-quinones.[2] Quinones are highly reactive compounds, which can polymerize spontaneously to form high molecular weight compounds or melanin or can react with amino acids and proteins, thus enhance the brown color produced.[3] However, recently research demonstrated alternations in melanin synthesis results in many skin effects like hyperpigmentation, melasma and lentigo.[4] Moreover, tyrosinase may involve in neuromelanin formation in human brain and contribute to the neurodegeneration associated with Parkinson's disease.[5] In addition, browning can lead to the darkening of fruits and plants, which finally resulting in decrease on their market value.[6]

Due to the great market profits and enormous application prospects, searching for effective and proper tyrosinase inhibitors is of increasing importance. In recent decades, various tyrosinase inhibitors are extracted from natural resources or synthesized in lab, while some are applied to the pharmaceutical and cosmetic fields.[7] Overall, the majority of those inhibitors acted as competitive inhibitors, which compete with the substrate L-DOPA or tyrosine. Among the inhibitor families, flavonoids was thought to be the most effective inhibitors that already attained the IC_{50} and K_i value lower than 1 μM against mushroom tyrosinase.[8]

Phlorizin, defined as one of the flavonoids, was distributed in some fruits and vegetables such as apples and pears. It had been studied by Wang et al. in 2002.[9] The results suggested that phlorizin might act as competitive inhibitor to tyrosinase which is more effective than arbutin and kojic acid. However, their studies were quite rough and needed further research. Later its analogs, which mainly distinguished by the alkyl chain between the two aryl rings, had been prepared and studied including *N*-benzylbenzamides (the α-C in the alkyl chain was replaced by a NH group),[10] chalcones (C–C single bond between α-C and β-C were changed into C=C double bond)[11] and phenethyl gallates (the α-C in the alkyl chain was replaced by an O atom, and the alkyl chain was lengthened with a CH_2 group)[12] (Fig. 1). Both of these analogs showed exceptional inhibitory to tyrosinase. On the other hand, those researches pointed out that the inhibitory effect mainly depended on the position of the hydroxyl moieties instead of their quantity.

Based on these results, it can be concluded that phlorizin and its analogs may in a way inhibitory against tyrosinase. Hence, we designed another phlorizin analogs **3–16** and carried out on their inhibitory effect (inhibitory activity and inhibitory kinetics). Should be noted that mushroom tyrosinase is used throughout our studies. This research aimed at discovering and filtering effective compounds as tyrosinase inhibitors, which to offer potential materials on food systems, cosmetic careers and other fields to inhibit enzymatic browning.

2. Results and discussion

2.1. Effects of multisubstitute benzyl benzoate on the diphenolase activity of mushroom tyrosinase

Among the compounds reported during these years, kojic acid was widely used as a skin-whitening material, due to its high inhibitory activity to tyrosinase.[13] According to our research, nine

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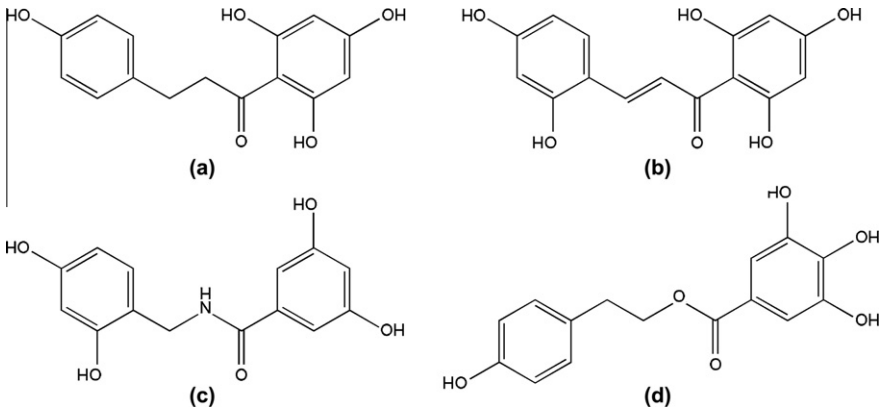


Figure 1. Phlorizin and its analogs. (a) Phlorizin; (b) chalcone, 2,2′,4,4′,6-pentahydroxychalcone as an example; (c) *N*-benzylbenzamides, *N*-(2,4-dihydroxybenzyl)-3,5-dihydroxybenzamide as an example; (d) phenethyl gallates, 4-hydroxyphenethyl 3,4,5-trihydroxybenzoate as an example.

of the 14 synthetic compounds gave the IC_{50} value lower than kojic acid, indicating these compounds were more effective tyrosinase inhibitors when compared with kojic acid. As a result, these compounds may be potential preservatives in cosmetic field or food storage.

The two aromatic rings in benzyl benzoates are asymmetric, therefore, different position of hydroxyl group(s) on ring A and B may result in different inhibitory effect on tyrosinase. All the compounds and kojic acid were tested for enzymatic inhibition. Results are listed in Table 1.

The position of hydroxyl substituted on ring B remarkably affected the inhibition, which in a way could be decisive to inhibitory activity. Compounds **3–7** with *p*-phenol on ring B revealed significant tyrosinase inhibition in general while compound **5** among them exhibited the highest inhibitory activity by IC_{50} of 4.95 μM. Compounds **8–11**, whose ring B was *m*-phenol, showed slightly lower IC_{50} values. Compounds **12–16** ranked the last owing to possessing an *o*-phenol on ring B. Especially, **5** exhibited 12-folds stronger than **14**, which possesses identical 2,4-OH moiety on ring A. The difference between compounds **3–11** and compounds **12–16** was caused by the similarity between compounds **3–16** and substrate L-DOPA (Fig. 2). While R_2 was 4′-OH or 3′-OH, the position of hydroxyl on ring B was partially the same

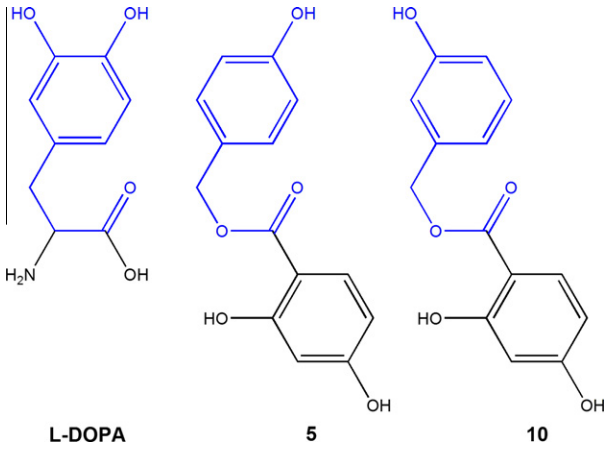


Figure 2. Similarity between L-DOPA, compounds **5** and **10**.

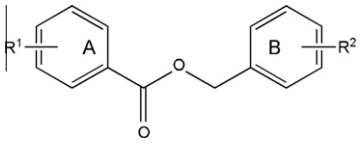
as L-DOPA, thus they exhibited high activity. The observations emphasized that 4-substituted or 3-substituted phenol subunit on B-ring was essential for the whole structure.

In contrast, the effects caused by different position of hydroxyl groups attached on ring A were not as conspicuous as on ring B. In general, ring A is likely to be a steric hindrance which prevented L-DOPA to bind with the bicopper center. Hence blocked the way DOPAchrome formed. When compared compounds **3–7** with each other, the most effective one shown an IC_{50} value just five times to the least one. The same phenomena were observed between compounds **8–11**. Interestingly, the gallyl subunit on ring A in compounds **6** and **11** were no so effective when introduced to tyrosinase, but the tendency was opposite to that subunit as on ring B.

When some of phlorizin analogs were taken into comparison, some rules could be generalized. Firstly, inhibitory activity was mainly determined by ring B. What's more 2′,4′-hydroxyl moiety was essential on ring B for binding with the active site of tyrosinase. Among these two positions 4′-OH was found to be more important to 2′-OH. As can be shown in our studies, 4′-OH on ring B resulted in higher inhibition in enzymatic oxidation. Nevertheless, while the 4′-OH was replaced by 2′-OH, inhibitory activity was unexpectedly decreased. From IC_{50} values it could infer that combination between 4′-OH and the bicopper center was stronger compared with 2′-OH.

Secondly, as described above, ring A was just a role of steric hindrance. Nonetheless, the position of hydroxyl groups on ring A somehow affected the activity of the whole compound. Among

Table 1
Inhibition effect of benzyl benzoate derivatives on mushroom tyrosinase activities



Compounds	R^1	R^2	IC_{50} (μM)
3	3,5-OH	4′-OH	5.84 ± 0.96
4	2,5-OH	4′-OH	12.29 ± 0.20
5	2,4-OH	4′-OH	4.95 ± 0.38
6	3,4,5-OH	4′-OH	25.73 ± 0.56
7	2,4,6-OH	4′-OH	8.00 ± 0.41
8	3,5-OH	3′-OH	6.11 ± 0.71
9	2,5-OH	3′-OH	24.39 ± 0.27
10	2,4-OH	3′-OH	6.23 ± 0.85
11	3,4,5-OH	3′-OH	11.47 ± 0.69
12	3,5-OH	2′-OH	19.89 ± 0.27
13	2,5-OH	2′-OH	>100
14	2,4-OH	2′-OH	66.23 ± 0.25
15	3,4,5-OH	2′-OH	>100
16	2,4,6-OH	2′-OH	19.94 ± 0.18
Kojic acid			20.99 ± 0.12

Table 2
Comparison between some best-performance inhibitions of phlorizin analogs

Constants	Phloridzin[14]	Hydroxychalcone[11]	*N*-Benzylbenzamide[10]	Phenethyl gallate[12]	Benzyl benzoate
R_1	2,4-OH-6-OGlu	2,4,6-OH	3,5-OH	3,4,5-OH	2,4-OH
R_2	4′-OH	2′,4′-OH	2′,4′-OH	4′-OH	4′-OH
IC_{50} (μM)	110	1	2.2	4.93	4.69
Inhibitory type	Competitive	Competitive	Competitive	—[a]	Competitive
K_i (μM)	64.3	3.1	1.3	—[a]	1.11

[a] No data afforded from the article.

the phlorizin analogs (Table 2), 2,4,6-OH or 2,4-OH were demonstrated to be the most effective combinations, while gallyl subunit or 3,5-OH were also proved to be efficient. However, proper size of ring A was essential. Judging from Table 2, once hydroxyl was transformed into –O(β-D-glucose), inhibitory activity was expected to be much weaker than other compounds. As –O(β-D-glucose) was extremely bulky, which resulted in difficulty in entering and binding with the active center, the IC_{50} value of phloridzin fell to 110 μM.

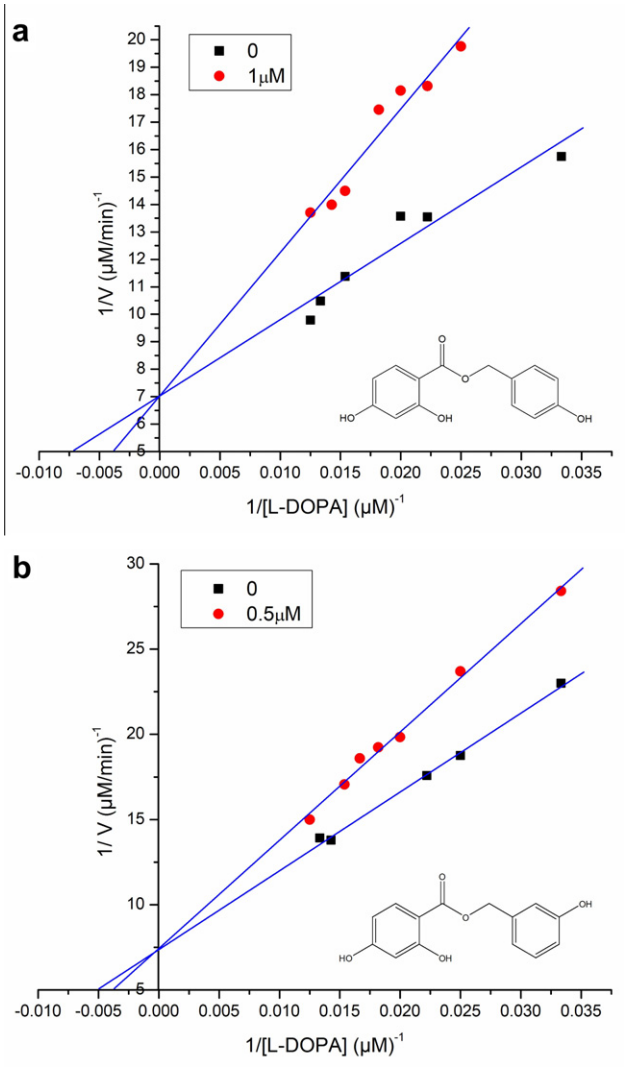


Figure 3. (a) Lineweaver–Burk plot of mushroom tyrosinase inhibition by compound **5**. Enzyme activity was measured at 475 nm in the presence of 1 μM compound **5** while the substrate. L-DOPA, varied from 30 to 80 μM. (b) Lineweaver–Burk plot of mushroom tyrosinase inhibition by compound **10**. Enzyme activity was measured at 475 nm in the presence of 0.5 μM compound **10** while the substrate. L-DOPA, varied from 30 to 80 μM.

Moreover, the alkyl chain between two aromatic rings should be another factor, in which affected by length and different atoms. We estimated that electronic effect should be considered and further studies should be carried out on those interesting phenomena.

2.2. Inhibitory types of multisubstitute benzyl benzoate on mushroom tyrosinase

Kinetic behavior of the oxidation of L-DOPA catalyzed by tyrosinase of compounds **3**, **5**, **7**, **8** and **10**, which shown exceptional tyrosinase inhibition, were further studied by method steady-state kinetic analysis. Inhibition data were then analyzed by a Lineweaver–Burk plot shown in Figure 3 (compounds **5** and **10** as an example). The plots of 1/V versus 1/[S] were characterized by a family of straight lines with different slopes, which presented different fixed substrate concentrations. All these lines were intersected each other at vertical axis, indicating that the inhibitory type of **5** was competitive manner with L-DOPA as a substrate. While its K_i reached 1.11 μM, this data strongly suggested **5** to be an effective inhibitor by binding to active site of the enzyme. After identical research was carried out on **3**, **7**, **8** and **10**, same conclusions were drawn that the four compounds were competitive inhibitors.

3. Conclusion

In summary, series of multihydroxyl benzyl benzoates were synthesized and tested. Judging from the results, position of hydroxyl moiety on ring B remarkably influenced their inhibition of tyrosinase. Compounds **3, 5, 7, 8, 10** were observed to get an IC_{50} less than 10 μM, while compound **5** was five times more potent than the positive control, kojic acid. These compounds may have potential application on food preservation or cosmetic careers.

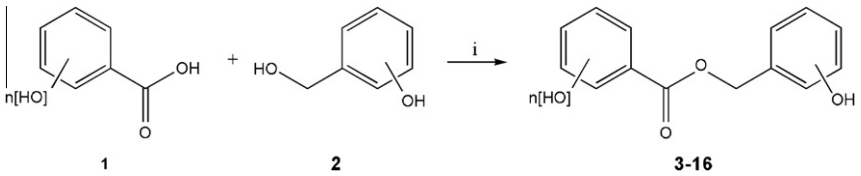
4. General experimental

Tyrosinase was purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO). 3,4-Dihydroxyphenylalanine (L-DOPA) and hydroxyphenylmethanols, 3,5-dihydroxybenzoic acid, 2,5-dihydroxybenzoic acid and 2,4,6-trihydroxybenzoic acid were purchased from Alfa Aesar. Other reagents were purchased from commercial suppliers and were dried and purified when necessary. Water used was re-distilled and ion-free.

All UV–vis absorbance were measured on a SHIMADZU UV-2501PC spectrometer without correction. Melting points were determined on a SGW X-4 melting point apparatus and were uncorrected. IR spectra were recorded as KBr flakes on a Thermo Nicolet 330FT-IR spectrometer. ^{1}H NMR spectra were recorded with a Varian Mercury-Plus 300 instrument (^{1}H, 300 MHz) in DMSO-d_6.

4.1. Chemistry

Benzyl benzoates were synthesized according to the routes in Scheme 1. Hydroxyphenylmethanol **1** was mixed with



Scheme 1. Reagents and conditions: (i) $NaHSO_4$, microwave irradiation, 93–98%.

multihydroxybenzoic acids **2** in the presence of catalyst ($NaHSO_4$) to get multisubstitute benzyl benzoates **3–16**. Microwave-assisted organic synthesis (MAOS) was carried out in consideration of green chemistry.[15,16] The reaction was found to proceed smoothly under microwave irradiation within 1–6 min. The mixture was treated with cold water and filtered. The residue was recrystallized with ethyl acetate to afford compounds **3–16**.

To afford a better yield, some factors were investigated. Basically, microwave power was 450 W and $NaHSO_4$ was 0.2 g, which took the studies of Bian et al. as reference.[16] The ratio of benzoic acid to hydroxyphenylmethanol was the main factor for the yields of this reaction. In the investigation, when the ratio decreased from 2:1 to 1:1, only slight fall occurred on the yield (Table 3). In terms of economization, we lowered the ratio to 1:1.

Irradiation time was another important factor that varied from each compound. As the time prolonged, the yield increased. Whereas, too long time would lead to the carbonization of the mixture (Table 3).

4.2. Assay of the diphenolase activity

All the synthesized compounds were screened for diphenolase inhibitory activity of tyrosinase, using L-DOPA as substrate. The inhibitors were dissolved in DMSO and prepared at concentrations of 10 mmol/L. Firstly, 20 units of mushroom tyrosinase (2000 U/mL), 10 μL of DMSO and 900 μL of phosphate buffer (pH 6.8) were mixed and pre-incubated for 20 min at 30 °C. Then, the L-DOPA (2 mg/mL) was added into this blending and the reaction was monitored for 1 min by measuring the change in absorbance at 475 nm, due to the yield of the DOPAchrome.

In subsequent experiments, DMSO was replaced by equivalent inhibitors, whose concentration would be decreased from 100 μM until the inhibition was less than 50%. The extent of inhibition by the addition of the sample was expressed as the percentage necessary for 50% inhibition (IC_{50}). As a control, the IC_{50} of kojic acid was also measured.

4.3. General procedure for the synthesis of compounds

Equivalent hydroxyphenylmethanol and multihydroxybenzoic acid (1 mmol both) were mixed with $NaHSO_4$ and grinded in mortar. The mixture was then transferred to an evaporation pan and put into the microwave oven. After irradiated for a few minutes the solid was afford with high yield. It should be noted that all yields below are isolated yield.

Table 3
Effect of the ratio of hydroxyphenylmethanol–benzoic acid and irradiation time on the reaction (compound **3** as example)

Entry	Methanol/acid (molar ratio)	Irradiation time (min)	Isolated yield (%)
1	2	5	88
2	1.5	5	86
3	1	5	85
4	1	4	75
6	1	6	87
7	1	7	73 (partly carbonized)

4.3.1. 4-Hydroxybenzyl 3,5-dihydroxybenzoate (3)

Irradiation time: 6 min, yield 85%. Yellowish brown powders; mp: 127–131 °C. IR(KBr): ν (cm^{-1}) 3396(ν_{O-H}), 1702($\nu_{C=O}$), 1608, 1509, 1475, 1436, 1201(δ_{C-O}), 1180(ν_{as}), 820, 775(τ). ^1H NMR (DMSO-d_6): δ 9.04(s, 1H), 9.00(s, 1H), 8.97(s, 1H), 7.00–6.49(m, 7H), 3.66(s, 2H).

4.3.2. 4-Hydroxybenzyl 2,5-dihydroxybenzoate (4)

Irradiation time: 5 min, yield 87%. Yellow powders; mp: 132–137 °C. IR(KBr): ν(cm^{-1}) 3331(ν_{O-H}), 1665($\nu_{C=O}$), 1609, 1508, 1474, 1441, 1227(ν_{as}), 1197(δ_{C-O}), 826, 792, 724(τ). ^1H NMR (DMSO-d_6): δ 9.13(s, 1H), 9.05(s, 1H), 9.00(s, 1H), 7.13(d, 1H, J = 3.1 Hz), 6.94(dd, 1H, J = 3.1 Hz), 6.76(d, 1H, J = 8.8 Hz), 6.62(d, 2H), 6.59(d, 2H), 3.66(s, 2H).

4.3.3. 4-Hydroxybenzyl 2,4-dihydroxybenzoate (5)

Irradiation time: 5 min, yield 84%. Yellow powders; mp: 148–150 °C. IR(KBr): ν(cm^{-1}) 3374(ν_{O-H}), 1635($\nu_{C=O}$), 1511, 1443, 1232(ν_{as}), 880, 845, 821(τ). ^1H NMR (DMSO-d_6): δ 10.33(s, 1H), 9.04(s, 2H), 7.60(d, 1H, J = 8.7 Hz), 7.00–6.46(m, 4H), 6.32(dd, 1H, J = 2.3 Hz), 6.24(d, 1H, J = 2.3 Hz), 3.66(s, 2H).

4.3.4. 4-Hydroxybenzyl gallate (6)

Irradiation time: 5 min, yield 76%. Yellow powders; mp: 141–144 °C. IR(KBr): ν(cm^{-1}) 3370(ν_{O-H}), 1702($\nu_{C=O}$), 1611, 1510, 1472, 1438, 1243(ν_{as}), 820, 771(τ). ^1H NMR (DMSO-d_6): δ 9.17(s, 1H), 9.06(s, 2H), 8.80(s, 1H), 7.00–6.50(m, 6H), 3.66(s, 2H).

4.3.5. 4-Hydroxybenzyl 2,4,6-dihydroxybenzoate (7)

Irradiation time: 5 min, yield 79%; Orange powders; mp: 153–157 °C. IR(KBr): ν(cm^{-1}) 3472(ν_{O-H}), 1649($\nu_{C=O}$), 1509, 1473, 1197(δ_{C-O}), 1164(ν_{as}), 830, 739(τ). ^1H NMR (DMSO-d_6): δ 8.96(s, 4H), 5.64(s, 2H), 7.01–6.40(m, 4H), 3.62(s, 2H).

4.3.6. 3-Hydroxybenzyl 3,5-dihydroxybenzoate (8)

Irradiation time: 1 min, yield 75%. Brown powders; mp: 153–155 °C. IR(KBr): ν(cm^{-1}) 3369(ν_{O-H}), 1695($\nu_{C=O}$), 1590, 1492, 1454, 1154(ν_{as}), 863, 774(τ). ^1H NMR (DMSO-d_6): δ 9.51(s, 1H), 9.10(s, 2H), 6.78(d, 2H, J = 2.2 Hz), 6.39(t, 1H, J = 2.3 Hz), 7.15–6.40(m, 4H), 3.67(s, 2H).

4.3.7. 3-Hydroxybenzyl 2,5-dihydroxybenzoate (9)

Irradiation time: 4 min, yield 78%. Light brown powders; mp: 167–169 °C. IR(KBr): ν(cm^{-1}) 3316(ν_{O-H}), 1669($\nu_{C=O}$), 1616, 1591, 1446, 1238(ν_{as}), 1197(δ_{C-O}), 860, 793, 754(τ). ^1H NMR (DMSO-d_6): δ 10.61(s, 1H), 9.11(s, 2H), 7.13(d, 1H, J = 3.1 Hz), 6.94(dd, 1H, J = 3.1 Hz), 6.76(d, 1H, J = 8.8 Hz), 6.64–6.31(m, 4H), 3.67(s, 2H).

4.3.8. 3-Hydroxybenzyl 2,4-dihydroxybenzoate (10)

Irradiation time: 4.5 min, yield 76%. Light brown powders; mp: 171–175 °C. IR(KBr): ν(cm^{-1}) 3374(ν_{O-H}), 1631($\nu_{C=O}$), 1446, 1153(ν_{as}), 878, 849, 774(τ). ^1H NMR (DMSO-d_6): δ 11.38(s, 1H), 10.33(s, 1H), 9.10(s, 1H), 7.60(d, 1H, J = 8.7 Hz), 6.32(dd, 1H, J = 2.3 Hz), 6.24(d, 1H, J = 2.3 Hz), 7.07–6.36(m, 4H), 3.68(s, 2H).

4.3.9. 3-Hydroxybenzyl gallate (11)

Irradiation time: 2 min, yield 73%. Light green powders; mp: 177–180 °C. IR(KBr): $\nu(cm^{-1})$ 3278(ν_{O-H}), 1700($\nu_{C=O}$), 1617, 1543, 1450, 1252(ν_{as}), 866, 767(τ). ^{1}H NMR (DMSO-d_6): δ 12.08(s, 1H), 9.14(s, 2H), 8.79(s, 1H), 6.89(s, 2H), 7.21–6.02(m, 4H), 3.67(s, 2H).

4.3.10. 2-Hydroxybenzyl 3,5-dihydroxybenzoate (12)

Irradiation time: 2 min, yield 83%. Yellow powders; mp: 143–144 °C. IR(KBr): $\nu(cm^{-1})$ 3403(ν_{O-H}), 1696($\nu_{C=O}$), 1609, 1503, 1455, 1249(ν_{as}), 755(τ). ^{1}H NMR (DMSO-d_6): δ 9.52(s, 1H), 9.22(s, 1H), 8.97(s, 1H), 6.78(d, 2H, J = 2.3 Hz), 6.39(t, 1H, J = 2.3 Hz), 7.02–6.41(m, 4H), 3.66(s, 2H).

4.3.11. 2-Hydroxybenzyl 2,5-dihydroxybenzoate (13)

Irradiation time: 3 min, yield 85%. Light yellow powders; mp: 165–168 °C. IR(KBr): $\nu(cm^{-1})$ 3311(ν_{O-H}), 1668($\nu_{C=O}$), 1618, 1501, 1447, 1236(ν_{as}), 835, 793, 745(τ). ^{1}H NMR (DMSO-d_6): δ 10.61(s, 1H), 9.50(s, 1H), 9.12(s, 1H), 7.13(d, 1H, J = 3.0 Hz), 6.94(dd, 1H, J = 3.1 Hz), 6.76(d, 1H, J = 8.8 Hz), 6.75–6.54(m, 4H), 3.75(s, 2H).

4.3.12. 2-Hydroxybenzyl 2,4-dihydroxybenzoate (14)

Irradiation time: 3 min, yield 82%. Cream powders; mp: 144–149 °C. IR(KBr): $\nu(cm^{-1})$ 3271(ν_{O-H}), 1647($\nu_{C=O}$), 1502, 1447, 1237(ν_{as}), 786, 754(τ). ^{1}H NMR (DMSO-d_6): δ 11.38(s, 1H), 10.35(s, 1H), 9.23(s, 1H), 7.59(d, 1H, J = 8.7 Hz), 7.03–6.50(m, 4H), 6.32(dd, 1H, J = 2.3 Hz), 6.24(d, 1H, J = 2.3 Hz), 3.61(s, 2H).

4.3.13. 2-Hydroxybenzyl gallate (15)

Irradiation time: 2 min, yield 85%. White powders; mp: 150–152 °C. IR(KBr): $\nu(cm^{-1})$ 3289(ν_{O-H}), 1702($\nu_{C=O}$), 1614, 1502, 1452, 1248(ν_{as}), 757(τ). ^{1}H NMR (DMSO-d_6): δ 9.16(s, 1H), 8.97(s, 1H), 8.80(s, 1H), 8.31(s, 1H), 6.90(s, 2H), 6.82–6.49(m, 4H), 3.76(s, 2H).

4.3.14. 2-Hydroxybenzyl 2,4,6-dihydroxybenzoate (16)

Irradiation time: 3 min, yield 84%. Orange powders; mp: 132–137 °C. IR(KBr): $\nu(cm^{-1})$ 3471(ν_{O-H}), 1646($\nu_{C=O}$), 1458, 1196(δ_{C-O}), 1164(ν_{as}), 831, 798, 751(τ). ^{1}H NMR (DMSO-d_6): δ 8.95(s, 4H), 7.04–6.47(m, 4H), 5.64(s, 2H), 3.65(s, 2H).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.12.051. These data include MOL files and InChiKeys of the most important compounds described in this article.

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