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Regioselective Synthesis of Quercetin and Myricetin Derivatives

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Abstract—A regioselective method for the synthesis of esters of quercetin and myricetin at the hydroxy group in the position 3 was developed. As acids participating in the esterification reaction, 2-hydroxybenzoic (salicylic), 4-hydroxybenzoic, 2,6-dihydroxybenzoic, 3,4-dihydroxybenzoic (procatechuic), 3,4,5-trihydroxybenzoic (gallic) acids were used. A new series of quercetin and myricetin esters were obtained.

Keywords: quercetin, myricetin, esterification, Novozyme 435, PASS

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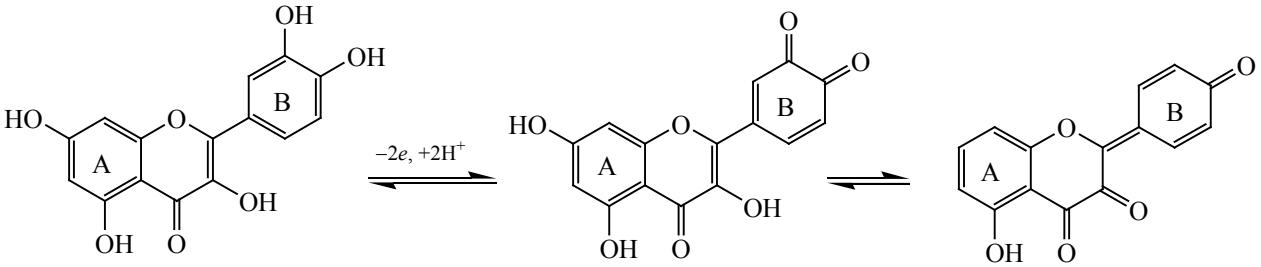
Despite more than 70 years of modern history of studying flavonoids, these secondary plant metabolites are the most studied class of natural compounds. According to the PubMed database, the number of studies devoted to flavonoids has approximately doubled over the past 10 years. In 2011, the total number of publications for the query "flavonoids" was 6394, and in 2021—12281 articles [1]. This growing interest is associated with a wide range of activity [2–5] and an increase in scientific evidence of the pharmacological properties of flavonoids [6, 7], which leads to an increase in the number of studies devoted to this class of biologically active compounds. Of particular interest are the antiviral and anticarcinogenic activity of flavonoids. Thus, epigallocatechin-3-gallate (EGCG) inhibits the development of hepatocellular carcinoma [8] and ovarian carcinoma [9]; quercetin slows down the growth and metastasis of lung adenocarcinoma, bladder and prostate cancer [10, 11]; myricetin induces apoptosis in human leukemia and hepatoma cell cultures, reduces the risk of developing skin cancer and pancreatic cancer metastasis in *in vitro* experiments [12]. The works [13, 14] provide evidence that green tea polyphenols, mainly EGCG, inhibit SARS-CoV-2 3CL protease. Previously, in an *in silico* experiment, we studied the possibility of binding 30 flavanoid ligands and the main protease of SARS-CoV-2, 3CLpro [15]. The result of the experiment showed that quercetin and myricetin have the prospect of further research in this direction. Interestingly, epicatechin (EC) is significantly less active than its natural esters with gallic acid, in particular EGCG, i.e., it is the ester with gallic acid that enhances the biological activity of EGCG [16]. We assumed that, most likely, ester modification of quercetin and myricetin would increase their antiviral and anticarcinogenic activity.

At the same time, the multifaceted study of flavonoids at the modern level [17] rarely goes beyond scientific interest and, as a rule, does not end with the creation of a new drug. This paradox is primarily due to the fact that natural flavonoids cannot be used as immediate drugs, which is often associated with a less pronounced pharmacological activity compared to synthetic compounds. Moreover, a number of pharmacokinetic properties such as low solubility, absorption and rapid metabolism cannot be considered satisfactory [18–20].

A significant part of natural flavonoids in plants are in the form of *O*-glycosides, the biological activity and bioavailability of which depend both on the nature of the carbohydrate component and on the site of attachment to the aglycone [21]. Depending on the position of the introduced sugar component, glycosidation could solve some of the problems of increasing the efficiency and bioavailability of flavonoids, but it should be taken into account that 3-*O*-glycosides are very easily hydrolyzed during the extraction process, unlike 7-*O*-glycosides [22].

Most scientists associate the antioxidant activity of flavonoids with their polyphenolic nature [23, 24], and

Scheme 1.



the antioxidant effect with their anticarcinogenic effect [19, 20]. The hydroxy groups in ring B are responsible for the most pronounced antioxidant properties, while the enol hydroxy group in position C^3, which is characterized by weak acidic properties, takes the least part in the manifestation of this type of activity. Moreover, the formation of esters at this hydroxyl practically does not reduce the antioxidant activity of the starting flavonoids [25, 26]. In this regard, it seems logical that in order to obtain esters at position C^3, it is necessary to preliminarily protect the remaining hydroxy groups, for example, positions 5,7,3′4′ for quercetin and 5,7,3′4′5′ for myricetin. An important argument in favor of the esterification of flavonoids at position C^3 is that a change in the nature of the radical in this position will not have a negative effect on pharmacophores (double bond in positions C^2–C^3 and other hydroxy groups), but at the same time, most likely, it will contribute to an increase in stability and lipophilicity of the molecule [27–30].

Another significant process that should be taken into account when modifying the structure of flavonoids is the oxidation of quercetin and its related compounds during metabolism (Scheme 1). As a result of this oxidation pathway, flavonoids lose their pharmacological activity, since the pharmacophore structure changes [31, 32].

Thus, targeted modification of the structure of flavonoids, namely ester modification of flavonoid at the C^3 position, will most likely lead to stabilization of the pharmacophore, an increase in antioxidant activity, and will have prospects for the creation of new optimized flavonoid molecules exhibiting antiviral and anticarcinogenic activity.

In order to select the initial flavonoid aglycones and acids, we preliminarily carried out a computer-aided prediction of pharmacological properties of target compounds using the PASS software (Table 1) [33].

The obtained data shows that the most promising, in terms of biological activity, should be considered esters of quercetin and myricetin with 2-hydroxybenzoic (salicylic), 4-hydroxybenzoic, 2,6-dihydroxybenzoic, 3,4-dihydroxybenzoic (protocatechic), and 3,4,5-trihydroxybenzoic (gallic) acids. The data obtained using the PASS predictive program allow us to conclude that esters based on selected starting materials will exhibit antioxidant, membrane-protective and anti-carcinogenic activity. Of particular interest are the data regarding the inhibition of the replicase polyprotein 1ab protein [33], which allows us to assume with a high degree of probability the antiviral activity of candidates against SARS-CoV-2. According to the PASS prediction results, the proposed target compounds should have low toxicity when administered orally in model experiments on rats.

Of interest are published data on the protected synthesis of rutin derivatives, in particular, 3-*O*-methylquercetin and 7-*O*-benzoylquercetin [34]. To obtain 5,7,3′,4′-benzoyl derivatives of rutin, the authors used benzoyl chloride, the reaction was carried out at room temperature for 1 h. The resulting product was dissolved in boiling ethanol, followed by acid hydrolysis of the glycoside in a water bath for 1 h in the presence of conc. hydrochloric acid. Next, the resulting ester was concentrated in acetone, methylated with dimethyl sulfate in acetone, and then the ester bonds at positions 7,5,3′,4′ were hydrolyzed in a 10% potassium hydroxide solution at a temperature of about 53°C. The synthesis product was 3-*O*-methylquercetin. The second section of this patent is the preparation of 7-*O*-benzoylquercetin, which is as follows: rutin was dissolved in a 5–10% aqueous solution of borax, an excess of benzoyl chloride was added, then the resulting

Table 1. Results of *in silico* prediction of some types of activity of quercetin and myricetin esters

Ester	Anticarcinogenic effect	SARS-CoV-2	Membrane-protective effect	Binding of free radicals	Antioxidant activity	LD_{50}, mg/kg
Quercetin-4-hydroxybenzoic acid	0.802	0.899	0.969	0.903	0.769	1878
Quercetin-2,6-dihydroxybenzoic acid	0.773	0.908	0.965	0.868	0.747	2240
Quercetin salicylic acid	0.810	0.873	0.965	0.916	0.759	2054
Quercetin protocatechuic acid	0.813	0.912	0.970	0.917	0.772	2126
Quercetingallic acid	0.835	0.935	0.965	0.933	0.831	2099
Myricetin-4-hydroxybenzoic acid	0.826	0.918	0.965	0.922	0.831	2152
Myricetin-2,6-dihydroxybenzoic acid	0.799	0.926	0.961	0.902	0.814	1952
Myricetin salicylic acid	0.832	0.896	0.961	0.931	0.821	2245
Myricetin protocatechuic acid	0.834	0.929	0.966	0.933	0.831	2415
Myricetingallic acid	0.858	0.926	0.965	0.928	0.834	2195

7-*O*-benzoylrutin was hydrolyzed in the presence of hydrochloric or sulfuric acids with heating. After cooling, 7-*O*-benzoylquercetin was separated and recrystallized from an acetone–methanol mixture. The key point of the synthesis in the patent is benzoylation in the presence of borax.

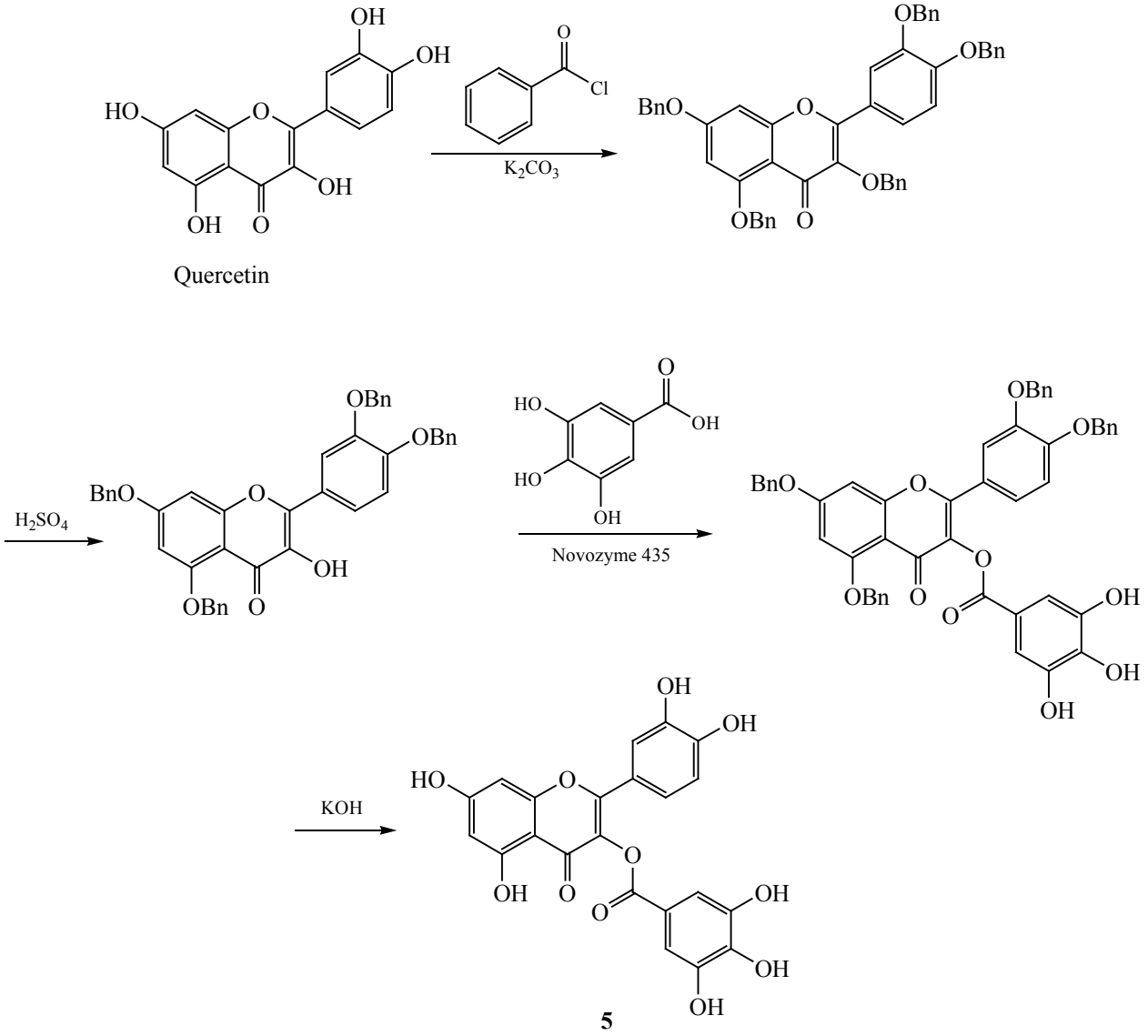
The method developed by us is based on the ester modification at position C^3 after protection of 3′,4′,5,7-hydroxy groups. At the first stage, esterification was carried out for all hydroxy groups, for which we used the Schotten–Bauman reaction and an excess of benzoyl chloride in an alkaline medium similarly procedure reported in [34]. The reaction temperature should not exceed 55°C, since at a higher temperature a hydrolysis process is observed, which reduces the yield of the target product. The pentabenzoic esters for quercetin or the hexabenzoic esters for mirecitin precipitate out and are easily separated by filtration or centrifugation. The yield of the target product at this stage was 97%.

At the second stage, the resulting ester was subjected to hydrolysis to cleave the ester bond at the C^3 position, since it is the least strong. It should be taken into account that carrying out hydrolysis under more rigid conditions will promote the cleavage of other ester bonds. We have found hydrolysis conditions that make it possible to selectively react only with the C^3-ester group, namely, acid hydrolysis in sulfuric acid when heated to no higher than 80°C in acetonitrile for no more than 2 h. Such conditions make it possible to obtain the product with a yield of 93 %.

The third step is to neutralize the acid with an alcoholic solution of potassium hydroxide to pH 6, and then add the Novozyme 435 enzyme and the appropriate acid necessary for the formation of the target ester. The reaction must be carried out at a temperature not exceeding 50°C to prevent degradation of the enzyme. This stage was previously studied by us in previous works and optimized. The use of enzyme catalysis at this stage of the synthesis makes it possible to significantly increase the yield of the product and its purity. Upon completion of the synthesis, the immobilized enzyme is removed by filtration and can be reused.

At the fourth stage of the synthesis, ester bonds in positions 3′, 4′, 5, 7 were hydrolyzed with a potassium hydroxide solution at a temperature not exceeding 70°C. In this case, the ester bond in position C^3 is not hydrolyzed if an alcoholic solution of potassium hydroxide is used in an equimolar ratio of 1 : 4 and the reaction medium is heated to no higher than 70°C for 7 min. The resulting synthesis product after cooling was acidified with sulfuric acid, washed with chloroform to remove benzoic acid, and dried. The target product was dissolved in methanol

Scheme 2.



and further purified on a column filled with silica gel. The proposed approach made it possible to regioselectively introduce substituents at the C^3 position of the pyran fragment of quercetin and myricetin with the yield of the final product for compounds **1**–**10** from 75 to 84%.

Scheme 2 shows the synthesis of an ester of quercetin and gallic acid (compound **5**). The synthesis of other esters in the reaction with all the studied acids with the participation of quercetin and myricetin occurs according to a similar way.

Structure of the synthesized compounds was proved by ^1H NMR, IR spectroscopy, and mass spectrometry data. The absence of a signal at 9.55 ppm in the ^1H NMR spectrum, which is characteristic of the hydroxy group at position C^3 for myricetin and quercetin, and the appearance of a band at 1741 cm^{-1} in the IR spectrum indicate the formation of an ester bond for both flavonoids.

In summary, a method for the regioselective preparation of esters of quercetin and myricetin at the C^3 position with aromatic acids was proposed. We believe that an additional study of the synthesized compounds

by molecular docking methods should be carried out to confirm pharmacological activity *in silico*.

EXPERIMENTAL

The follows commercial reagents (chemically pure, Sigma-Aldrich) were used: flavonoids quercetin and myricetin, 2-hydroxybenzoic (salicylic), 4-hydroxybenzoic, 2,6-dihydroxybenzoic, 3,4-dihydroxybenzoic (protocatechuic), 3,4,5-trihydroxybenzoic (gallic) acids, Novozyme 435 catalyst.

Melting points were determined on a PTP (M) instrument. ^{1}H NMR spectra were recorded on a Bruker AMXIII-400 spectrometer at 400 MHz in DMSO-d_6 relative to internal TMS. IR spectra were recorded on an FSM 1201 spectrometer (Infraspek) in potassium bromide pellets. Mass spectra were recorded on an Agilent 6420 mass spectrometer coupled to an Agilent HPLC 1260 HPLC system by atmospheric pressure chemical ionization (APCI), ion source temperature was 120°C, carrier gas was helium, CID energy was 40 eV. HPLC parameters: Phenomenex Luna C18 column (250×4.6 mm×5 μm), column temperature 30°C, UV detector, 270 nm; mobile phases: tetrahydrofuran–sodium dihydrogen phosphate solution, 15.6 g/L, adjusted to pH 3.3 with phosphoric acid (phase A), 5 : 95, and tetrahydrofuran–sodium dihydrogen phosphate solution, 15.6 g/L, adjusted to pH 3.3 with phosphoric acid (phase B)), 40:60; linear gradient: 0–15 min, phases A 40 + B 60% → A 0 + B 100%; 15 – 30 min, phases A 0 + B 100% → A 40 + B 60%; sample volume 20 μL, mobile phase rate 1.0 mL/min; the volume of the sample automatically introduced into the mass detector was 20 μL.

General procedure for the synthesis of esters. To a solution of 2 mmol of quercetin (0.604 g) or myricetin (0.636 g) in 500 mL of 10% potassium carbonate solution was added 20 mmol of benzoyl chloride (2.3 mL). The resulting mixture was stirred for 1 h at 35°C. The resulting precipitate was separated by filtration and dried at 60°C in a thermostat. The resulting product was dissolved in 200 mL of acetonitrile and 12 mL of concentrated sulfuric acid was added, the reaction mixture was stirred at a speed of 200 rpm at 80°C for 2 h. Then the solution was cooled, brought to pH 6 by adding a 10% alcoholic solution of potassium hydroxide and 0.5 g of Novozyme 435 catalyst and 2 mmol of 2-hydroxybenzoic (0.276 g), 4-hydroxybenzoic (0.276 g), 2,6-dihydroxybenzoic (0.308 g), 3,4-dihydroxybenzoic (0.308 g) or 3.4, 5-trihydroxybenzoic (0.340 g) acid. The reaction mixture was stirred for 6 h at 50°C at a speed of 120 rpm. The resulting solution was filtered, 10 mL of a 10% alcoholic solution of potassium hydroxide was added and heated at 70°C for 7 min. After cooling the reaction mixture, 10% sulfuric acid was added until the neutral (pH 6), then washed with chloroform, and the target ester was recrystallized at –10°C. The resulting product was dissolved in methanol and passed through a column filled with silica gel (5 g) using a mixture of ethyl acetate–methanol, 1:9 (v/v) as the mobile phase. The target product was dried for 2 h at a pressure of 25 mm Hg and a temperature of 60°C. The purity of the collected fraction was monitored by HPLC.

Quercetin-3-salicylate [2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl-2-hydroxybenzoate] (1). Yield 0.701 g (83%), mp 321–323°C. IR spectrum, ν, cm^{-1}: 3250 (OH), 1741 (OC=O), 1663 (C=O), 1317 (C–OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.19 d (1H, H^6, *J* 2.0), 6.41 d (1H, H^8, *J* 2.0), 6.88 d (1H, H$^{5'}$, *J* 8.4), 6.91 t (1H, H$^{5''}$, *J* 7.4), 6.97 d (1H, H$^{3''}$, *J* 7.5), 7.54 d. d (1H, H$^{6'}$, *J* 2.2, *J* 8.4), 7.58 t (1H, H$^{4''}$, *J* 7.3), 7.67 d (1H, H$^{2'}$, *J* 2.0), 8.01 d (1H, H$^{6''}$, *J* 7.7), 9.35 s (1H, C$^{3'}$OH), 9.65 s (1H, C$^{4'}$OH), 10.76 s (1H, C^{7}OH), 11.53 s (1H, C$^{2''}$OH), 12.48 s (1H, C^{5}OH). Mass spectrum, *m*/*z*: 423.04 [*M* + H]$^+$ (calcd for $C_{22}H_{15}O_9^+$: 423.06).

Quercetin-3-(4-hydroxybenzoate) [2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl-4-hydroxybenzoate] (2). Yield 0.694 g (82%), mp 321–324°C. IR spectrum, ν, cm^{-1}: 3251 (OH), 1741 (OC=O), 1663 (C=O), 1317 (C–OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.19 d (1H, H^6, *J* 2.0), 6.41 d (1H, H^8, *J* 2.0), 6.88 d (1H, H$^{5'}$, *J* 8.4), 6.90 d (2H, H$^{2'',6''}$, *J* 8.6), 7.54 d. d (1H, H$^{6'}$, *J* 2.2, *J* 8.4), 7.67 d (1H, H$^{2'}$, *J* 2.0), 7.84 d (2H, H$^{3'',5''}$, *J* 8.6), 9.35 s (1H, C$^{3'}$OH), 9.65 s (1H, C$^{4'}$OH), 10.23 s (1H, C$^{4''}$OH), 10.76 s (1H, C^{7}OH), 12.48 s (1H, C^{5}OH). Mass spectrum, *m*/*z*: 423.03 [*M* + H]$^+$ (calcd for $C_{22}H_{15}O_9^+$: 423.06).

Quercetin-3-(2,6-dihydroxybenzoate) [2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl-2,6-dihydroxybenzoate] (3). Yield 0.685 g (78%), mp 329–331°C. IR spectrum, ν, cm^{-1}: 3250 (OH), 1741 (OC=O), 1663 (C=O), 1317 (C–OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.19 d (1H, H^6, *J* 2.0), 6.41 d (1H, H^8, *J* 2.0), 6.71 d (2H, H$^{3'',5''}$, *J* 8.4), 6.88 d (1H, H$^{5'}$, *J* 8.4), 7.42 t (1H, H$^{4''}$, *J* 8.4), 7.54 d. d (1H, H$^{6'}$, *J* 2.2, *J* 8.4), 7.67 d (1H, H$^{2'}$, *J* 2.0), 9.35 s (1H, C$^{3'}$OH), 9.65 s (1H, C$^{4'}$OH), 9.94 s (2H, C$^{2'',6''}$OH), 10.76 s (1H, C^{7}OH),

12.48 s (1H, C^5OH). Mass spectrum, *m*/*z*: 439.30 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{10}^+$: 439.34).

Quercetin-3-(3,4-dihydroxybenzoate) [2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4oxo-4*H*-chromen-3-yl-3,4-dihydroxybenzoate] (4). Yield 0.691 g (79%), mp 328–331°C. IR spectrum, ν, cm^{-1}: 3250 (OH), 1741 (OC=O), 1663 (C=O), 1317 (C–OH). ^1H NMR spectrum, δ, ppm (J, Hz): 6.19 d (1H, H^6, *J* 2.0), 6.41 d (1H, H^8, *J* 2.0), 6.78 d (2H, $H^{2'',6''}$, *J* 8.4), 6.88 d (1H, $H^{5'}$, *J* 8.4), 7.40 d (2H, $H^{5''}$, *J* 8.4), 7.54 d. d (1H, $H^{6'}$, *J* 2.2, *J* 8.4), 7.67 d (1H, $H^{2'}$, *J* 2.0), 9.35 s (1H, $C^{3'}OH$), 9.65 s (1H, $C^{4'}OH$), 9.95 s (2H, $C^{3'',4''}OH$), 10.76 s (1H, C^7OH), 12.48 s (1H, C^5OH). Mass spectrum, *m*/*z*: 439.32 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{10}^+$: 439.34).

Quercetin-3-(3,4,5-trihydroxybenzoate) [2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl-3,4,5-trihydroxybenzoate] (5). Yield 0.765 g (84%), mp 333–335°C. IR spectrum, ν, cm^{-1}: 3252 (OH), 1741 (OC=O), 1663 (C=O), 1319 (C–OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.19 d (1H, H^6, *J* 2.0), 6.41 d (1H, H^8, *J* 2.0), 6.88 d (1H, $H^{5'}$, *J* 8.4), 7.05 d (2H, $H^{2'',6''}$, *J* 2.7), 7.54 d. d (1H, $H^{6'}$, *J* 2.2, *J* 8.4), 7.67 d (1H, $H^{2'}$, *J* 2.0), 8.91 s (1H, $C^{4''}OH$), 9.35 s (1H, $C^{3'}OH$), 9.45 s (2H, $C^{3'',5''}OH$), 9.65 s (1H, $C^{4'}OH$), 10.76 s (1H, C^7OH), 12.48 s (1H, C^5OH). Mass spectrum, *m*/*z*: 455.29 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{11}^+$: 455.34).

Myricetin-3-salicylate [5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-3-yl-2-hydroxybenzoate] (6). Yield 0.693 g (79%), mp 360–362°C. IR spectrum, ν, cm^{-1}: 3285 (OH), 1740 (OC=O), 1661 (C=O), 1332 (C–OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.20 d (1H, H^6, *J* 2.0), 6.39 d (1H, H^8, *J* 2.0), 6.91 t (1H, $H^{5''}$, *J* 7.4), 6.97 d (1H, $H^{3''}$, *J* 7.5), 7.29 s (1H, $H^{2',6'}$), 7.58 t (1H, $H^{4''}$, *J* 7.3), 8.01 d (1H, $H^{6''}$, *J* 7.7), 8.82 s (1H, $C^{4'}OH$), 9.48 s (2H, $C^{3',5'}OH$), 10.76 s (1H, C^7OH), 11.53 s (1H, $C^{2''}OH$), 12.48 s (1H, C^5OH). Mass spectrum, *m*/*z*: 439.29 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{10}^+$: 439.34).

Myricetin-3-(4-hydroxybenzoate) [5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-3-yl-4-hydroxybenzoate] (7). Yield 0.694 g (78%), mp 361–364°C. IR spectrum, ν, cm^{-1}: 3284 (OH), 1740 (OC=O), 1661 (C=O), 1332 (C–OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.20 d (1H, H^6, *J* 2.0), 6.39 d (1H, H^8, *J* 2.0), 6.90 d (2H, $H^{2'',6''}$, *J* 8.6), 7.29 s (1H, $H^{2',6'}$), 7.84 d (2H, $H^{3'',5''}$, *J* 8.6), 8.82 s (1H, $C^{4'}OH$), 9.48 s (2H, $C^{3',5'}OH$), 10.23 s (1H, $C^{4''}OH$), 10.76 s (1H, C^7OH), 12.48 s (1H, C^5–OH). Mass spectrum, *m*/*z*: 439.28 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{10}^+$: 439.34).

Myricetin-3-(2,6-dihydroxybenzoate) [5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-3-yl-2,6-dihydroxybenzoate] (8). Yield 0.685 g (75%), mp 369–371°C. IR spectrum, ν, cm^{-1}: 3287 (OH), 1740 (OC=O), 1661 (C=O), 1332 (C–OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.20 d (1H, H^6, *J* 2.0), 6.39 d (1H, H^8, *J* 2.0), 6.71 d (2H, $H^{3'',5''}$, *J* 8.4), 7.29 s (1H, $H^{2',6'}$), 7.42 t (1H, $H^{4''}$, *J* 8.4), 8.82 s (1H, $C^{4'}OH$), 9.48 s (2H, $C^{3',5'}OH$), 9.94 s (2H, $C^{2'',6''}OH$), 10.76 s (1H, C^7OH), 12.48 s (1H, C^5OH). Mass spectrum, *m*/*z*: 454.29 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{11}^+$: 454.34).

Myricetin-3-(3,4-dihydroxybenzoate) [5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-3-yl-3,4-dihydroxybenzoate] (9). Yield 0.691 g (77%), mp 369–371°C. IR spectrum, ν, cm^{-1}: 3287 (OH), 1740 (OC=O), 1661 (C=O), 1332 (C–OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.20 d (1H, H^6, *J* 2.0), 6.39 d (1H, H^8, *J* 2.0), 6.78 d (2H, $H^{2'',6''}$, *J* 8.4), 7.29 s (1H, $H^{2',6'}$), 7.40 d (2H, $H^{5''}$, *J* 8.4), 8.82 s (1H, $C^{4'}OH$), 9.48 s (2H, $C^{3',5'}OH$), 9.95 s (2H, $C^{3'',4''}OH$), 10.76 s (1H, C^7OH), 12.48 s (1H, C^5OH). Mass spectrum, *m*/*z*: 439.31 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{11}^+$: 454.34).

Myricetin-3-(3,4,5-trihydroxybenzoate) [5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-3-yl-3,4,5-trihydroxybenzoate] (10). Yield 0.771 g (82%), mp 373–375°C. IR spectrum, ν, cm^{-1}: 3288 (OH), 1740 (OC=O), 1661 (C=O), 1332 (C–OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.20 d (1H, H^6, *J* 2.0), 6.39 d (1H, H^8, *J* 2.0), 7.05 d (2H, $H^{2'',6''}$, *J* 2.7), 7.29 s (1H, $H^{2',6'}$), 8.82 s (1H, $C^{4'}OH$), 8.91 s (1H, $C^{4''}OH$), 9.45 s (2H, $C^{3'',5''}OH$), 9.48 s (2H, $C^{3',5'}OH$), 10.76 s (1H, C^7OH), 12.48 s (1H, C^5OH). Mass spectrum, *m*/*z*: 470.30 $[M + H]^+$ (calcd for $C_{22}H_{15}O_{12}^+$: 470.34).

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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