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New flavonoid glycosides conjugates: synthesis, characterization, and evaluation of their cytotoxic activities

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New flavonoid glycosides conjugates: synthesis, characterization, and evaluation of their cytotoxic activities

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Abstract: A series of novel halogenated 3-hydroxyflavones (3HF) were prepared by reacting halogenated hydroxyacetophenones with the appropriate aromatic aldehyde. Glycosylation of 3HFs with acetobromoglucose and deprotection of the acetyl protective groups afforded the desired 3-*O*-flavonoids glycosides in satisfactory yields. All the prepared compounds were tested for their cytotoxic activity against HCT-116, MCF-7, and OVCAR-3 human cancer cell lines. The 3HFs exhibited higher cytotoxic activities compared with the glycosylated flavonoids. Overall, the structure-activity relationship study showed that the introduction of glycoside moiety at the C-3 OH position does not improve the bioactivity.

Key words: Halogenated 3-hydroxyflavones, glycosylation, cytotoxic activity

1. Introduction

Flavonoids and their derivatives have attracted tremendous attention from biologists and chemists as they are among the important classes of compounds that play a key role in nature. Flavonoids are oxygenated heterocycles that, in recent years, have found, alongside other nitrogen- and sulfur-containing aryls, applications in synthesis, biology, and therapies.^{1,2} They often exist in glycosylated forms, containing sugar units and an aglycone core, and they mainly occur in plants and the human diet in the form of their *O*- and *C*-glycosides.^{3–6} Recent interest in the *O*-glycoside and/or *C*-glycoside forms has been stimulated by the potential health benefits arising from the hugely diverse bioactivities of these flavonoid derivatives. The specific properties of these flavonoid derivatives might be due to the presence of aromatic and glycoside moieties and many hydroxyl groups. However, the dietary flavonoid *C*-glycosides have received less attention than their corresponding *O*-glycosides.⁷

Among the flavonoid derivatives of pharmacological and biological interest, the 3-hydroxyflavones (3HFs) or flavonols constitute a major class as they are endowed with various biological activities such as antiinflammatory,⁸ antiacetylcholinesterase,⁹ antioxidant,^{10,11} anticancer,^{12,13} antidepressant,^{14,15} antidiabetic,¹⁶ antimicrobial,¹⁷ antihypertensive,¹⁸ anti-HIV,¹⁹ and antiallergic.²⁰ On the other hand, it has been found that almost all the dietary flavonoids, especially flavonols, exist in nature as α - or β -glycoside forms such as flavonoid glucosides, rhamnosides, galactosides, arabinosides, and rutinosides.^{3,21} As a special type of flavonoid *O*-glycoside, flavonol

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O-glycosides are often found in nature and so far more than 1500 of them have been isolated and characterized, mostly from higher plants,²² and the majority of these compounds (~80%) have a sugar linkage at the 3-OH. Moreover, flavonol *O*-glycosides have been proven to have promising pharmaceutical activities.²³ The high rate of occurrence and the importance of flavonol glycosides have attracted attention to synthetic studies of this group of natural products.

It was further reported that natural flavonols are frequently substituted at variable positions, mainly by hydroxyl, methoxyl, isoprenyl, and glycosyl groups, and it was also thought that biological activities of flavonols are due to the presence of these substituents.²⁴ Nevertheless, it has been demonstrated that halogenated organic derivatives also exhibit significant biological activities.²⁵

Since halogenated substituted flavonols are not found in nature and since glycosylation of flavonoids improves their solubility, stability, and bioavailability relative to flavonoid aglycones, and as a part of our general program in the continued search for new bioactive molecules, it was considered appropriate to synthesize, in the present study, some novel 3HF derivatives that are halogen-substituted and able to be used as lead structures for the development of new flavonol *O*-glucosides with improved biological activities.

The 3HF derivatives were previously synthesized in our laboratory as part of Znati's thesis and evaluated for their cytotoxic effect against three human cancer cell lines (HCT-116, IGROV-1, and OVCAR-3).²⁶ From this previous series, many compounds showed very encouraging results as they exhibited IC₅₀ values below 10 μ M. In the present work, we continue our efforts in the search for more potent and selective flavonoids by changing the substituent groups on rings A and B (Figure) and by adding a glucose moiety through *O*-alkylation.

All new compounds were then evaluated for anticancer activity against three human cancer cell lines: HCT-116 (human colon), MCF-7 (human breast), and OVCAR-3 (human ovarian).

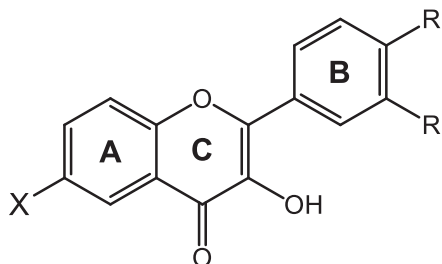
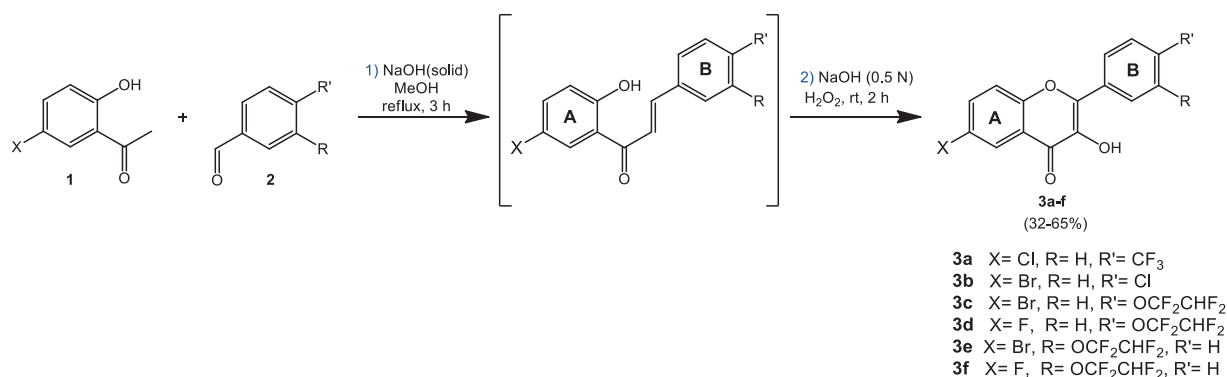


Figure. The structure of flavonol.

2. Results and discussion

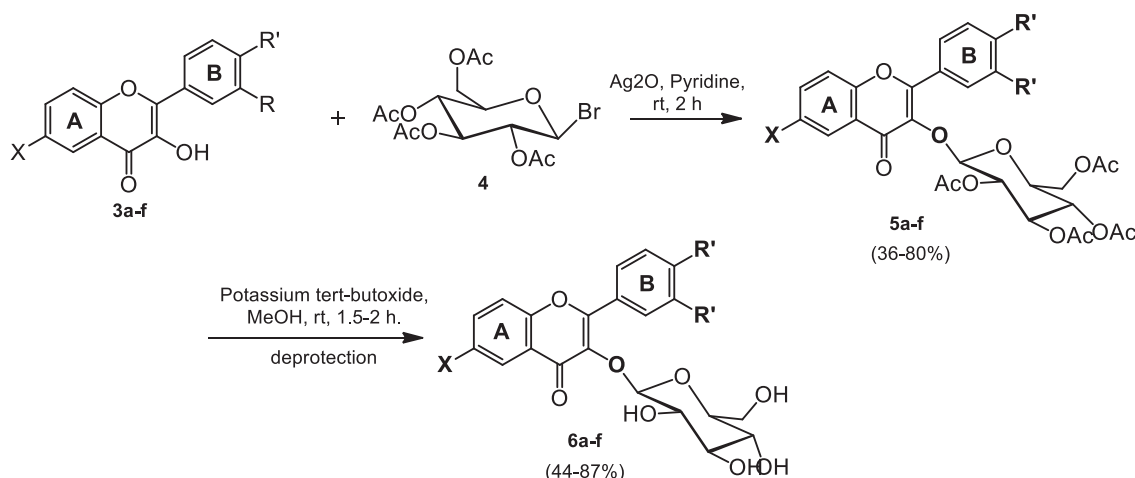
The key step of our synthetic strategy for new flavonol 3-*O*-glycosides relied on the preparation of substituted 3HF derivatives **3a–3f** as outlined in Scheme 1. The target compounds were synthesized from the condensation of halogenated 2-hydroxyacetophenone **1** with the appropriate aromatic aldehyde **2**, using typical procedures for the aldol condensation.²⁷ The reaction involves only two steps and was carried out in refluxing methanol in the presence of solid sodium hydroxide, followed by in situ oxidative cyclization with hydrogen peroxide in an aqueous base at room temperature. The syntheses were performed with moderate yields (from 32% to 65%) and quite short reaction times (2 h). The desired 3HFs were easy to isolate by simple filtration, with no intermediate or side products such as chalcones and aurone, and were used without further purification. A literature survey revealed that none of the synthesized 3HFs had been reported so far.

In the next step, and according to previously published methods,²⁸ the free hydroxyl group of obtained



Scheme 1. Synthesis of the 3HF derivatives (**3a-3f**).

derivatives **3a-3f** was reacted with acetobromoglucose **4** under the action of silver oxide to provide corresponding compounds **5a-5f**, with yields from 36% to 82% (Scheme 2). Finally, the removal of the acetyl protective groups was achieved using potassium *tert*-butoxide in methanol at room temperature affording conveniently flavonol 3-*O*-glucosides **6a-6f** in moderate to good yields (44%–87%). All the synthesized flavonol 3-*O*-glucosides derivatives are original compounds.



Scheme 2. Synthesis of compounds **6a-6f**.

The structures of the synthesized compounds were confirmed on the basis of ¹H NMR, ¹³C NMR, IR, and mass spectral data.

The eighteen synthesized compounds, six 3HFs (**3a-3f**) and twelve *O*-glucosylated compounds, with protected (**5a-5f**) and free (**6a-6f**) hydroxyl groups, were evaluated for their *in vitro* cytotoxicity against three human cancer cell lines, namely human breast adenocarcinoma (MCF-7), human colorectal carcinoma (HCT-116), and human ovarian carcinoma (OVCAR-3), using the standard MTT assay. These compounds were treated with one primary cytotoxic assay dose of 100 μM for 48 h. The results are expressed in terms of IC₅₀ values (μM) and are summarized in the Table.

Compound **3a**, bearing a chlorine at C6 and a CF₃ group at the 4' position on the phenyl ring, was both highly active and selective against the HCT-116 cell line (IC₅₀ = 8.0 ± 1.0 μM).

Compound **3b** (6-Br and 4'-Cl) also exhibited interesting activity against OVCAR-3 (IC₅₀ = 11.5 ± 0.6 μM).

Table. The *in vitro* cytotoxic activity (IC_{50} , μ M)^a of all target compounds.

Compounds	MCF-7	HCT-116	OVCAR-3
3a	63.1 \pm 5.3	8.0 \pm 1.0	28.0 \pm 2.0
3b	28.2 \pm 1.6	40.0 \pm 7.0	11.5 \pm 0.6
3c	70.0 \pm 6.0	62.0 \pm 7.0	76.0 \pm 10.0
3d	33.1 \pm 3.3	31.6 \pm 2.3	32.1 \pm 3.3
3e	44.7 \pm 2.9	18.0 \pm 1.0	42.0 \pm 3.0
3f	12.6 \pm 1.4	9.0 \pm 1.0	50.0 \pm 3.0
5a	>100	72.0 \pm 9.0	78.0 \pm 6.0
5b	94.0 \pm 6.0	74.0 \pm 5.0	75.0 \pm 8.0
5c	98.0 \pm 5.0	72.0 \pm 7.0	75.0 \pm 9.0
5d	100.0 \pm 8.0	57.0 \pm 4.0	69.0 \pm 5.0
5e	99.0 \pm 6.0	70.0 \pm 9.0	66.0 \pm 5.0
5f	92.0 \pm 7.0	72.0 \pm 8.0	91.0 \pm 7.0
6a	96.0 \pm 11.0	11.6 \pm 4.0	69.0 \pm 4.0
6b	58.0 \pm 7.0	61.0 \pm 4.0	57.0 \pm 4.0
6c	100.0 \pm 11.0	77.0 \pm 9.0	56.0 \pm 7.0
6d	31.6 \pm 4.2	58.0 \pm 7.0	62.0 \pm 6.0
6e	35.0 \pm 5.0	44.0 \pm 7.0	49.0 \pm 4.0
6f	95.0 \pm 8.0	71.0 \pm 6.0	67.0 \pm 8.0
Tamoxifen	0.38 \pm 0.03	0.36 \pm 0.03	0.52 \pm 0.04

^aMTT method.

Also, compound **3f** was cytotoxic with selectivity for HCT-116 and MCF-7 (IC_{50} = 9.0 \pm 1.0 μ M and 12.6 \pm 1.4 μ M, respectively). Compound **3e** (IC_{50} = 18.0 \pm 1.0 μ M) showed significant activity against the HCT-116 cell line. The remaining compounds possessed moderate levels of cytotoxicity against the tested cell lines.

Overall, our results are in accordance with a previously reported study that showed that the presence of chloro group on the chroman ring was favorable for cytotoxic activity of the flavanones.²⁹ Likewise, our results showed that compounds **3e** and **3f** with bromine or fluorine at the 6-position of the A-ring and tetrafluoroethoxy fragment at the 3'-position of the aromatic B-ring are more active against the HCT-116 cell line than those substituted at the 4'-position (compounds **3c** and **3d**). Thus, the presence of tetrafluoroethoxy moiety may enhance the cytotoxic activity since the inhibitory potency is higher when this fragment is at the 3'-position of the B-ring, whether with bromine or fluorine.

On the other hand, it seems that the replacement of the halogen group (ring A) from fluorine (compounds **3f** and **3d**) to bromine (compounds **3e** and **3c**) reduced the potency by nearly half, meaning that the nature of the halogen attached to ring A at the 6-position and hence the mesomerism effect exerted by each one could be a key factor for cytotoxic activity.^{30,31} These results clearly indicate the importance of halogens as substituents in 3HFs to get interesting cytotoxic activity. The findings above led us to investigate the influence of halogen substituents on the biological properties of this class of flavonoids. It was reported that the substituent's size, in addition to electronic characteristics, could affect the biological activity spectrum.^{32,33} Overall, the 3HFs (**3a**–**3f**) displayed promising cytotoxic activity, especially against the HCT-116 cell line. However, this effect is lost when the 3-OH is alkylated, either by a protected or a free glucose group. Indeed, the glycosylated derivatives **5a**–**5f** and **6a**–**6f** are generally weakly active with IC_{50} values from 31.6 to >100 μ M. The only exception is compound **6a**, which displayed considerable activity against HCT-116 cells. The starting flavonol **3a** was active

and selective against this cell line ($IC_{50} = 8.0 \pm 1.0 \mu M$). This activity was lost after *O*-alkylation with the protected glucose ring (**5a**, $72.0 \pm 9.0 \mu M$) but was restored after deprotection of acetyl groups (**6a**, $IC_{50} = 11.6 \pm 4.0 \mu M$).

From the structure-activity relationships (SARs), we may conclude that, except for compound **6a**, the introduction of glucoside moiety has a negative impact on the cytotoxic activity of 3HF.

In summary, six halogenated 3HFs, **3a–3f**, and their glucosylated counterparts **5a–5f** and **6a–6f** have been designed and synthesized with good yields and their chemical structures were confirmed by IR, 1H NMR, ^{13}C NMR, and HR-MS spectra. All these original compounds were inspected for their cytotoxic activity. Most halogenated 3HFs exhibited promising cytotoxic activities against HCT-116, MCF-7, and OVCAR-3 cell lines, especially compounds **3a** and **3f** possessing Cl/F at the 6-position of ring A. However, most of glucosylated flavonoids **5a–5f** and **6a–6f** were weak or inactive against those cell lines. From the SARs, we may conclude that using an electron-withdrawing group (especially fluorine), whether in the A-ring or B-ring, can enhance the cytotoxicity activities. On the other hand, the replacement of the OH at C-3 by glucoside moiety leads to a significant decrease of biological activity.

3. Experimental

3.1. General procedures

Melting points were measured on a DSC-50 Shimadzu apparatus (Kyoto, Japan). IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer (Waltham, MA, USA) at $4000\text{--}400\text{ cm}^{-1}$ in KBr. Flash chromatography was performed for purification of the compounds on silica gel 60 (SiGel 60, 220–240 mesh, Sigma-Aldrich). 1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a DPX 300 spectrometer (Brüker Biosciences, USA), using $CDCl_3$ and $DMSO-d_6$ as solvents and a nondeuterated residual solvent as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hertz. Haute resolution mass spectra were acquired with a DSQ Thermo Fisher Scientific mass spectrometer and signals were given as m/z .

3.2. General procedure for the synthesis of 3HFs (**3a–3f**)

A mixture of substituted 2-hydroxyacetophenone (14.6 mmol) and aromatic aldehydes (14.6 mmol) was stirred in methanol (100 mL) and then sodium hydroxide (44 mmol) was added. The pale yellow mixture was refluxed until the color turned orange (about 3 h). After cooling to room temperature, sodium hydroxide solution (0.5 N, 88 mL) and then hydrogen peroxide (6 mL) were added. After 2 h of stirring, the mixture was poured into ice-water and the resulting precipitate was filtered off and washed with water successively, and then was dried to afford the corresponding compounds.

3.2.1. 6-Chloro-3-hydroxy-2-(4-(trifluoromethyl)phenyl)-4H-chromen-4-one (**3a**)

Yield = 65%; m.p. $>260\text{ }^\circ\text{C}$; IR (KBr, cm^{-1}): 3398, 1614, 1594, 1326, 1108, 1069; 1H NMR (300 MHz, $DMSO-d_6$) (δ , ppm): 7.58 (dd, $J_1 = 9$, $J_2 = 2.5$ Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 9$ Hz, 1H), 7.93 (d, $J = 2.5$ Hz, 1H), 8.85 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $DMSO-d_6$) (δ , ppm): 120.6, 121.9, 123.4, 124.1, 124.3, 124.4, 124.5, 126.2, 131.0, 139.2, 141.4, 152.1, 154.7, 179.3; HR-MS $[M+H]^+$ calcd. for ($C_{16}H_8ClF_3O_3$): 341.0192, found: 341.0187.

3.2.2. 6-Bromo-2-(4-chlorophenyl)-3-hydroxy-4H-chromen-4-one (3b)

Yield = 57%; m.p. >260 °C; IR (KBr, cm^{-1}): 3446, 1595, 1568, 1482, 1394, 1224, 811; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 7.39 (d, $J = 9$ Hz, 2H), 7.59 (d, $J = 8.8$ Hz, 1H), 7.66 (dd, $J_1 = 8.8$, $J_2 = 2.4$ Hz, 1H), 8.07 (d, $J = 2.4$ Hz, 1H), 8.73 (d, $J = 9$ Hz, 2H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 114.0, 120.7, 122.5, 125.9, 126.5, 127.5, 129.2, 133.0, 134.4, 142.1, 152.1, 154.2, 179.0; HR-MS $[\text{M}+\text{H}]^+$ calcd. For ($\text{C}_{15}\text{H}_8\text{BrClO}_3$): 350.9423, found: 350.9423.

3.2.3. 6-Bromo-3-hydroxy-2-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one (3c)

Yield = 53%; m.p. >260 °C; IR (KBr, cm^{-1}): 3450, 1595, 1486, 1200, 1125; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 6.80 (tt, $J_1 = 51.6$, $J_2 = 3.3$ Hz, 1H), 7.26 (d, $J = 9$ Hz, 2H), 7.60 (d, $J = 9$ Hz, 1H), 7.69 (dd, $J_1 = 9$, $J_2 = 2.4$ Hz, 1H), 8.09 (d, $J = 2.4$ Hz, 1H), 8.74 (d, $J = 9$ Hz, 2H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 107.2, 114.3, 116.4, 120.7, 120.7, 122.5, 126.2, 126.5, 133.4, 133.8, 142.4, 145.7, 152.2, 152.7, 178.6; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{17}\text{H}_9\text{BrF}_4\text{O}_4$): 432.9698, found: 432.9706.

3.2.4. 6-Fluoro-3-hydroxy-2-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one (3d)

Yield = 43%; m.p. >260 °C; IR (KBr, cm^{-1}): 3436, 1600, 1567, 1491, 1208, 1126; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 6.80 (tt, $J_1 = 51.9$, $J_2 = 3$ Hz, 1H), 7.26 (d, $J = 9$ Hz, 2H), 7.46 (td, $J_1 = 9$, $J_2 = 3$ Hz, 1H), 7.63 (dd, $J_1 = 9$, $J_2 = 3$ Hz, 1H), 7.68 (dd, $J_1 = 9$, $J_2 = 3.9$ Hz, 1H), 8.80 (d, $J = 9$ Hz, 2H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 107.9, 108.2, 116.4, 119.3, 120.5, 120.7, 121.6, 125.9, 132.0, 134.3, 149.9, 153.4, 155.5, 158.6, 179.8; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{17}\text{H}_9\text{F}_5\text{O}_4$): 373.0499, found: 373.0497.

3.2.5. 6-Bromo-3-hydroxy-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one (3e)

Yield = 51%; m.p. >260 °C; IR (KBr, cm^{-1}): 3451, 1621, 1593, 1470, 1201, 1117; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 6.81 (tt, $J_1 = 51.9$, $J_2 = 3$ Hz, 1H), 7.16 (dd, $J_1 = 8.1$, $J_2 = 1.2$ Hz, 1H), 7.52 (t, $J = 8.1$ Hz, 1H), 7.67 (d, $J = 9$ Hz, 1H), 7.76 (dd, $J_1 = 9$, $J_2 = 2.4$ Hz, 1H), 8.10 (d, $J = 2.4$ Hz, 1H), 8.32 (br d, $J = 8.1$ Hz, 1H), 8.71 (br s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 107.8, 116.4, 118.2, 121.0, 122.5, 123.8, 126.6, 127.2, 128.7, 129.7, 133.6, 134.8, 135.2, 142.7, 147.9, 152.8, 175.7; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{17}\text{H}_9\text{BrF}_4\text{O}_4$): 432.9698, found: 432.9664.

3.2.6. 6-Fluoro-3-hydroxy-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one (3f)

Yield = 32%; m.p. >260 °C; IR (KBr, cm^{-1}): 3435, 1607, 1575, 1486, 1202, 1117; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 6.88 (tt, $J_1 = 51.9$, $J_2 = 3.3$ Hz, 1H), 7.21 (dd, $J_1 = 8.2$, $J_2 = 1.2$ Hz, 1H), 7.52–7.59 (m, 2H), 7.68 (dd, $J_1 = 9$, $J_2 = 3.3$ Hz, 1H), 7.78 (dd, $J_1 = 9.3$, $J_2 = 4.2$ Hz, 1H), 8.31 (br d, $J = 8.2$ Hz, 1H), 8.64 (br s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 108.8, 109.1, 116.4, 119.4, 119.4, 119.5, 121.5, 121.6, 124.1, 130.1, 136.4, 142.8, 148.5, 150.9, 156.9, 159.3, 178.5; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{17}\text{H}_9\text{F}_5\text{O}_4$): 373.0499, found: 373.0491.

3.3. General procedure for synthesis of glucosylated flavonoids 5a–5f and 6a–6f

3.3.1. General procedure for synthesis of glucosylated flavones (5a–5f)

To a solution of compounds **3a–3f** (1 mmol) and acetobromoglucose (1.5 mmol) **4** in dry pyridine (25 mL) was added 2.2 mmol silver oxide. The reaction mixture was stirred at room temperature for 1 h, and then the silver salts were removed by filtration over Celite and silica. The solvent was evaporated to dryness and the crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane) to give the desired products in good yields.

3.3.1.1. 6-Chloro-2-(4-(trifluoromethyl)phenyl)-3-tetraacetylglucosyl flavone (5a)

Yield = 61%; m.p. 152 °C; IR (KBr, cm^{-1}): 3469, 1755, 1647, 1324, 1227, 1069; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 1.85 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.13 (s, 3H), 3.62 (m, 1H), 3.91 (dd, $J_1 = 12.3$, $J_2 = 2.4$ Hz, 1H), 4.01 (dd, $J_1 = 12.3$, $J_2 = 3.9$ Hz, 1H), 5.06 (dd, $J_1 = 9.9$, $J_2 = 9.3$ Hz, 1H), 5.20 (dd, $J_1 = 9.6$, $J_2 = 7.8$ Hz, 1H), 5.29 (dd, $J_1 = 9.9$, $J_2 = 9$ Hz, 1H), 5.73 (d, $J = 8.1$ Hz, 1H), 7.52 (d, $J = 9$ Hz, 1H), 7.66 (dd, $J_1 = 9$, $J_2 = 2.4$ Hz, 1H), 7.76 (d, $J = 8.1$ Hz, 2H), 8.16 (d, $J = 8.1$ Hz, 2H), 8.19 (d, $J = 2.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) (δ , ppm): 20.3–20.8, 61.0, 68.0, 71.4, 71.8, 72.4, 98.8, 119.8, 124.9, 125.0, 125.1, 129.5, 131.3, 132.2, 132.7, 133.6, 134.3, 136.7, 153.5, 155.7, 169.4–170.2, 172.7; HR-MS $[\text{M} + \text{H}]^+$ calcd. for ($\text{C}_{30}\text{H}_{26}\text{ClF}_3\text{O}_{12}$): 671.1143, found: 671.1146.

3.3.1.2. 6-Bromo-2-(4-chlorophenyl)-3-tetraacetylglucosyl flavone (5b)

Yield = 54%; m.p. 123 °C; IR (KBr, cm^{-1}): 3467, 1753, 1645, 1369, 1227, 1037; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 1.89 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.13 (s, 3H), 3.61 (m, 1H), 3.91 (dd, $J_1 = 12.3$, $J_2 = 2.4$ Hz, 1H), 4.00 (dd, $J_1 = 12.3$, $J_2 = 4.2$ Hz, 1H), 5.06 (dd, $J_1 = 9.9$, $J_2 = 9.3$ Hz, 1H), 5.18 (dd, $J_1 = 9.6$, $J_2 = 7.8$ Hz, 1H), 5.29 (dd, $J_1 = 9.6$, $J_2 = 7.5$ Hz, 1H), 5.69 (d, $J = 7.8$ Hz, 1H), 7.44 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 7.9$ Hz, 1H), 7.77 (dd, $J_1 = 7.9$, $J_2 = 2.2$ Hz, 1H), 7.99 (d, $J = 8.7$ Hz, 2H), 8.34 (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) (δ , ppm): 20.4–20.8, 61.1, 68.1, 71.4, 71.7, 72.5, 98.8, 118.5, 120.0, 125.3, 128.2, 128.5, 130.4, 131.5, 136.3, 136.8, 137.2, 153.9, 156.4, 169.4–170.3, 172.5; HR-MS $[\text{M} + \text{H}]^+$ calcd. for ($\text{C}_{29}\text{H}_{26}\text{BrClO}_{12}$): 681.0374, found: 681.0377.

3.3.1.3. 6-Bromo-2-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-tetraacetylglucosyl flavone (5c)

Yield = 80%; m.p. 130 °C; IR (KBr, cm^{-1}): 3446, 2959, 1754, 1645, 1228, 1193; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 1.88 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 3.63 (m, 1H), 3.93 (dd, $J_1 = 12.3$, $J_2 = 2.7$ Hz, 1H), 4.02 (dd, $J_1 = 12.3$, $J_2 = 3.9$ Hz, 1H), 5.08 (dd, $J_1 = 9.9$, $J_2 = 9.3$ Hz, 1H), 5.19 (dd, $J_1 = 9.6$, $J_2 = 7.8$ Hz, 1H), 5.30 (dd, $J_1 = 9.6$, $J_2 = 9.3$ Hz, 1H), 5.72 (d, $J = 7.8$ Hz, 1H), 5.95 (tt, $J_1 = 53.1$, $J_2 = 3$ Hz, 1H), 7.35 (d, $J = 9$ Hz, 2H), 7.44 (d, $J = 9$ Hz, 1H), 7.78 (dd, $J_1 = 9$, $J_2 = 2.4$ Hz, 1H), 8.11 (d, $J = 9$ Hz, 2H), 8.34 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) (δ , ppm): 19.9–20.4, 60.7, 67.7, 71.0, 71.4, 72.1, 98.4, 107.1, 116.7, 118.1, 119.6, 120.5, 124.9, 127.8, 127.9, 130.4, 135.9, 136.4, 150.3, 153.5, 155.7, 169.0–169.8, 172.1; HR-MS $[\text{M} + \text{H}]^+$ calcd. for ($\text{C}_{31}\text{H}_{27}\text{BrF}_4\text{O}_{13}$): 763.0649, found: 763.0653.

3.3.1.4. 6-Fluoro-2-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-tetraacetylglucosyl flavone (5d)

Yield = 62%; m.p. 129 °C; IR (KBr, cm^{-1}): 3361, 2921, 1754, 1646, 1484, 1379, 1229; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 1.88 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 3.62 (m, 1H), 3.94 (dd, $J_1=12.3$, $J_2=2.7$ Hz, 1H), 4.00 (dd, $J_1=12.3$, $J_2=4.2$ Hz, 1H), 5.08 (dd, $J_1=9.9$, $J_2=9$ Hz, 1H), 5.20 (dd, $J_1=9.6$, $J_2=7.8$ Hz, 1H), 5.29 (dd, $J_1=9.6$, $J_2=9.3$ Hz, 1H), 5.71 (d, $J=7.8$ Hz, 1H), 6.01 (tt, $J_1=53.1$, $J_2=3$ Hz, 1H), 7.35 (d, $J=9$ Hz, 2H), 7.43 (ddd, $J_1=9.3$, $J_2=7.5$, $J_3=3$ Hz, 1H), 7.55 (dd, $J_1=9.3$, $J_2=3.9$ Hz, 1H), 7.86 (dd, $J_1=8.1$, $J_2=3$ Hz, 1H), 8.11 (d, $J=9$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) (δ , ppm): 20.3–20.8, 61.2, 68.1, 71.4, 71.7, 72.5, 98.8, 107.5, 110.2, 116.2, 120.2, 120.9, 122.1, 125.1, 128.5, 130.8, 135.9, 150.7, 156.1, 157.8, 161.1, 169.4–170.3, 173.1; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{31}\text{H}_{27}\text{F}_5\text{O}_{13}$): 703.1450, found: 703.1434.

3.3.1.5. 6-Bromo-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-tetraacetylglucosyl flavone (5e)

Yield = 36%; m.p. 158 °C; IR (KBr, cm^{-1}): 3436, 1753, 1647, 1384; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 1.87 (s, 3H), 2.0 (s, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 3.63 (m, 1H), 3.91 (dd, $J_1=12.3$, $J_2=2.4$ Hz, 1H), 4.02 (dd, $J_1=12.3$, $J_2=4.2$ Hz, 1H), 5.05 (dd, $J_1=9.9$, $J_2=9.3$ Hz, 1H), 5.18 (dd, $J_1=9.9$, $J_2=7.8$ Hz, 1H), 5.29 (dd, $J_1=9.6$, $J_2=9.3$ Hz, 1H), 5.74 (d, $J=8.1$ Hz, 1H), 6.02 (tt, $J_1=53.1$, $J_2=3$ Hz, 1H), 7.37 (dt, $J_1=6.9$, $J_2=1.5$ Hz, 1H), 7.47 (d, $J=9$ Hz, 1H), 7.53 (t, $J=7.8$ Hz, 1H), 7.79 (dd, $J_1=8.7$, $J_2=2.4$ Hz, 1H), 7.94 (br s, 1H), 7.99 (dt, $J_1=7.8$, $J_2=1.5$ Hz, 1H), 8.35 (d, $J=2.4$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) (δ , ppm): 20.3–20.7, 61.3, 68.1, 71.4, 71.8, 72.5, 98.8, 107.6, 116.3, 118.6, 120.1, 122.4, 124.2, 125.3, 127.3, 128.2, 129.6, 131.9, 136.9, 136.9, 148.6, 153.9, 155.7, 169.4–170.3, 172.6; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{31}\text{H}_{27}\text{BrF}_4\text{O}_{13}$): 763.0649, found: 763.0645.

3.3.1.6. 6-Fluoro-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-tetraacetylglucosyl flavone (5f)

Yield = 45%; m.p. 125 °C; IR (KBr, cm^{-1}): 3451, 1753, 1644, 1486, 1383, 1231; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 1.87 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 3.63 (dq, $J_1=9.9$, $J_2=2.7$ Hz, 1H), 3.89–4.04 (m, 2H), 5.02–5.32 (m, 3H), 5.74 (d, $J=7.8$ Hz, 1H), 6.02 (tt, $J_1=52.8$, $J_2=3$ Hz, 1H), 7.38 (dd, $J_1=8.5$, $J_2=1.0$ Hz, 1H), 7.44 (d, $J=3$ Hz, 1H), 7.52 (d, $J=7.8$ Hz, 1H), 7.58 (dd, $J_1=8.5$, $J_2=3.9$ Hz, 1H), 7.86 (dd, $J_1=7.8$, $J_2=3$ Hz, 1H), 7.95 (s, 1H), 7.99 (t, $J=8.5$ Hz, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) (δ , ppm): 20.3–20.7, 61.3, 68.2, 71.4, 71.8, 72.5, 98.8, 107.6, 110.2, 117.5, 120.3, 122.1, 122.4, 124.1, 125.1, 127.3, 129.6, 132.0, 136.1, 148.5, 155.7, 157.8, 161.1, 169.4–170.3, 173.1; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{31}\text{H}_{27}\text{F}_5\text{O}_{13}$): 703.1450, found: 703.1463.

3.3.2. General procedure for the deacetylation of the protected glycosides (6a–6f)

To a solution of **5a–5f** (0.49 mmol) in MeOH (50 mL) was added 0.6 mmol of potassium *tert*-butoxide. The reaction mixture was stirred at room temperature for 1.5–2 h, and then H_2O was added and the water layer was extracted with ethyl acetate (3×100 mL). The solvent was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (DCM/MeOH) to provide compounds **6a–6f**.

3.3.2.1. 6-Chloro-2-(4-(trifluoromethyl)phenyl)-3-glucosyl flavone (6a)

Yield = 82%; m.p. 244 °C; IR (KBr, cm^{-1}): 3420, 2924, 1625, 1322, 1070; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 3.08–5.58 (m, 6H), 4.33 (t, $J = 5.7$ Hz, 1H), 4.98 (d, $J = 4.5$ Hz, 1H), 5.08 (d, $J = 4.8$ Hz, 1H), 5.37 (d, $J = 4.8$ Hz, 1H), 5.57 (d, $J = 7.8$ Hz, 1H), 7.83–7.93 (m, 4H), 8.06 (d, $J = 2.4$ Hz, 1H), 8.36 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): δ_C ($\text{DMSO-}d_6$, 75 MHz): 60.7, 69.7, 73.9, 76.3, 77.5, 100.4, 121.0, 123.8, 124.5, 124.9, 125.0, 129.7, 129.9, 129.9, 134.2, 134.3, 136.9, 153.3, 154.4, 172.5; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{22}\text{H}_{18}\text{ClF}_3\text{O}_8$): 503.0720, found: 503.0716.

3.3.2.2. 6-Bromo-2-(4-chlorophenyl)-3-glucosyl flavone (6b)

Yield = 79%; m.p. 230 °C; IR (KBr, cm^{-1}): 3421, 1632, 1465, 1092; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 3.08–3.58 (m, 6H), 4.32 (t, $J = 5.4$ Hz, 1H), 4.99 (s, 1H), 5.10 (d, $J = 3.6$ Hz, 1H), 5.38 (d, $J = 4.8$ Hz, 1H), 5.55 (d, $J = 7.5$ Hz, 1H), 7.62 (d, $J = 9$ Hz, 2H), 7.76 (d, $J = 9$ Hz, 1H), 7.99 (dd, $J_1 = 9$, $J_2 = 2.4$ Hz, 1H), 8.17–8.20 (m, 3H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 61.5, 70.4, 74.8, 76.9, 77.8, 101.6, 118.8, 121.9, 125.4, 127.8, 129.4, 129.6, 131.7, 137.0, 137.3, 138.0, 154.5, 156.8, 174.0; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{21}\text{H}_{18}\text{BrClO}_8$): 512.9952, found: 512.9954.

3.3.2.3. 6-Bromo-2-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-glucosyl flavone (6c)

Yield = 57%; m.p. 127 °C; IR (KBr, cm^{-1}): 3421, 2925, 1609, 1195, 1121; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 3.09–3.58 (m, 6H), 4.32 (t, $J = 5.7$ Hz, 1H), 4.98 (s, 1H), 5.09 (d, $J = 3.9$ Hz, 1H), 5.38 (d, $J = 4.5$ Hz, 1H), 5.57 (d, $J = 7.5$ Hz, 1H), 6.86 (tt, $J_1 = 51.9$, $J_2 = 3$ Hz, 1H), 7.46 (d, $J = 9$ Hz, 2H), 7.76 (d, $J = 9$ Hz, 1H), 8.01 (dd, $J_1 = 9$, $J_2 = 2.4$ Hz, 1H), 8.18 (d, $J = 2.4$ Hz, 1H), 8.74 (d, $J = 9$ Hz, 2H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 60.7, 69.7, 73.9, 76.3, 77.5, 100.4, 107.7, 116.4, 117.5, 121.0, 121.1, 124.8, 126.9, 128.9, 131.1, 136.4, 136.7, 149.6, 153.6, 154.8, 172.3; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{23}\text{H}_{19}\text{BrF}_4\text{O}_9$): 595.0227, found: 595.0229.

3.3.2.4. 6-Fluoro-2-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-glucosyl flavone (6d)

Yield = 44%; m.p. 125 °C; IR (KBr, cm^{-1}): 3421, 2926, 1625, 1484, 1188, 1119; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 3.09–3.58 (m, 6H), 4.32 (t, $J = 5.4$ Hz, 1H), 4.99 (s, 1H), 5.10 (s, 1H), 5.39 (d, $J = 4.5$ Hz, 1H), 5.57 (d, $J = 7.5$ Hz, 1H), 6.86 (tt, $J_1 = 51.9$, $J_2 = 3$ Hz, 1H), 7.46 (d, $J = 9$ Hz, 2H), 7.73–7.81 (m, 2H), 7.87 (dd, $J_1 = 9$, $J_2 = 4.2$ Hz, 1H), 8.28 (d, $J = 9$ Hz, 2H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 60.7, 69.7, 73.9, 76.3, 77.4, 100.5, 107.7, 109.2, 117.2, 121.0, 121.2, 122.3, 124.4, 129.0, 131.1, 135.9, 149.5, 154.8, 157.1, 160.3, 172.8; HR-MS $[\text{M}+\text{H}]^+$ calcd. for ($\text{C}_{23}\text{H}_{19}\text{F}_5\text{O}_9$): 535.1027, found: 535.1033.

3.3.2.5. 6-Bromo-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-glucosyl flavone (6e)

Yield = 67%; m.p. 106 °C; IR (KBr, cm^{-1}): 3445, 1632, 1559, 1467, 1196, 1122; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) (δ , ppm): 3.01–3.63 (m, 6H), 4.33 (t, $J = 5.7$ Hz, 1H), 5.04 (d, $J = 4.8$ Hz, 1H), 5.16 (d, $J = 2.7$ Hz, 1H), 5.35 (d, $J = 4.8$ Hz, 1H), 5.62 (d, $J = 7.5$ Hz, 1H), 6.84 (tt, $J_1 = 51.6$, $J_2 = 2.7$ Hz, 1H), 7.48 (d, $J = 8.1$ Hz, 1H), 7.67 (t, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 9$ Hz, 1H), 8.01 (dd, $J_1 = 9$, $J_2 = 2.4$ Hz, 1H), 8.06 (d, $J = 8.1$ Hz, 1H), 8.18 (d, $J = 2.4$ Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) (δ , ppm): 61.0, 69.9,

73.7, 76.2, 77.7, 100.2, 107.5, 115.9, 117.5, 121.2, 122.7, 124.1, 124.8, 126.9, 127.1, 130.1, 132.2, 136.4, 136.8, 147.5, 153.6, 154.6, 172.3; HR-MS $[M+H]^+$ calcd. for $(C_{23}H_{19}BrF_4O_9)$: 595.0227, found: 595.0227.

3.3.2.6. 6-Fluoro-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-glucosyl flavone (6f)

Yield = 87%; m.p. 218 °C; IR (KBr, cm^{-1}): 3411, 2925, 1639, 1485, 1206, 1111; 1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 3.01–3.64 (m, 6H), 4.36 (t, $J = 5.4$ Hz, 1H), 5.04 (d, $J = 5.4$ Hz, 1H), 5.15 (d, $J = 4.5$ Hz, 1H), 5.36 (d, $J = 4.8$ Hz, 1H), 5.62 (d, $J = 7.5$ Hz, 1H), 6.84 (tt, $J_1 = 51.9$, $J_2 = 3$ Hz, 1H), 7.48 (br dd, $J_1 = 8.2$, $J_2 = 1.5$ Hz, 1H), 7.67 (t, $J = 8.2$ Hz, 1H), 7.78 (m, 2H), 7.89 (dd, $J_1 = 8.7$, $J_2 = 3.6$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6) (δ , ppm): 61.1, 70.0, 73.7, 76.1, 77.7, 100.2, 107.7, 109.1, 116.3, 121.3, 122.3, 122.7, 123.9, 124.4, 127.1, 130.1, 132.3, 135.9, 147.5, 154.6, 157.1, 160.4, 172.7; HR-MS $[M+H]^+$ calcd. for $(C_{23}H_{19}F_5O_9)$: 535.1027, found: 535.1027.

3.4. Cytotoxicity assay

The cytotoxicity of all prepared compounds was evaluated against three human tumor cell lines according to a previously described procedure adopting the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.³⁴ Briefly, 100 μ L of each cell line was plated in a 96-well plate (10^4 cells/well) and incubated for 24 h at 37 °C. Then 100 μ L of the culture medium containing samples (100 μ M) was added and these mixtures were incubated for 48 h at 37 °C. After 48 h, the medium was removed, cells were treated with 50 μ L of MTT solution (1 mg/mL) prepared in phosphate buffered saline, and the plates were incubated for a further 40 min at 37 °C. Formazan crystals formed were dissolved in 50 μ L of DMSO and absorbance was read at a wavelength of 605 nm. The concentration that inhibited 50% of cellular growth (IC_{50} value) was determined. Tamoxifen was used as positive control. The bioassays were conducted in triplicate.

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References

1. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958-3043.
2. Zirak, M.; Eftekhari-Sis, B. *Turk. J. Chem.* **2015**, *39*, 439-496.
3. Fang, R.; Veitch, N. C.; Kite, G. C.; Porter, E. A.; Simmonds, M. S. *J. Agric. Food. Chem.* **2013**, *61*, 3868-3875.
4. Pugliese, A. G.; Tomas-Barberan, F. A.; Truchado, P.; Genovese, M. I. *J. Agric. Food. Chem.* **2013**, *61*, 2720-2728.
5. Rayyan, S.; Fossen, T.; Andersen, Ø. M. *J. Agric. Food. Chem.* **2010**, *58*, 7211-7217.
6. Zou, J. H.; Yang, J.; Zhou, L. *J. Nat. Prod.* **2004**, *67*, 664-667.
7. Brazier-Hicks, M.; Evans, K. M.; Gershater, M. C.; Puschmann, H.; Steel, P. G.; Edwards, R. *J. Biol. Chem.* **2009**, *284*, 17926-17934.
8. Le Marchand, L. *Biomed. Pharmacother.* **2002**, *56*, 296-301.
9. Jung, M.; Park, M. *Molecules* **2007**, *12*, 2130-2139.
10. Havsteen, B. H. *Pharmacol. Ther.* **2002**, *96*, 67-202.
11. Parhiz, H.; Roohbakhsh, A.; Soltani, F.; Rezaee, R.; Iranshahi, M. *Phytother. Res.* **2014**, *29*, 323-331.

12. Guardia, T.; Rotelli, A. E.; Juarez, A. O.; Pelzer, L. E. *Farmaco* **2001**, *56*, 683-687.
13. Ramos, S. *J. Nutr. Biochem.* **2007**, *18*, 427-442.
14. Fernández, S. P.; Wasowski, C.; Loscalzo, L. M.; Granger, R. E.; Johnston, G. A. R.; Paladini, A. C.; Marder, M. *Eur. J. Pharmacol.* **2006**, *539*, 168-176.
15. Yi, L. T.; Li, C. F.; Zhan, X.; Cui, C. C.; Xiao, F.; Zhou, L. P.; Xie, Y. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2010**, *34*, 1223-1228.
16. Sriram Prasath, G.; Subramanian, S. *Int. J. Pharm. Sci. Rev. Res.* **2011**, *6*, 68-73.
17. Cushnie, T. P.; Lamb, A. J. *Int. J. Antimicrob. Agents* **2005**, *26*, 343-356.
18. Perez-Vizcaino, F.; Duarte, J.; Jimenez, R.; Santos-Buelga, C.; Osuna, A. *Pharmacol. Rep.* **2009**, *61*, 67-75.
19. Pasetto, S.; Pardi, V.; Murata, R. M. *PLoS One* **2014**, *9*, e115323.
20. Narayana, K. R.; Reddy, M. S.; Chaluvadi, M. R.; Krishna, D. R. *Indian J. Pharmacol.* **2001**, *33*, 2-16.
21. Taheri, R.; Connolly, B. A.; Brand, M. H.; Bolling, B. W. *J. Agric. Food. Chem.* **2013**, *61*, 8581-8588.
22. Harborne, J. B.; Williams, C. A. *Nat. Prod. Rep.* **1995**, *12*, 639-657.
23. Harborne, J. B.; Baxter, H. *The Handbook of Natural Flavonoids, Vol. 1*; John Wiley & Sons: Chichester, UK, 1999.
24. Hasan, A.; Rasheed, L.; Malik, A. *Asian J. Chem.* **2007**, *19*, 937-948.
25. Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124-7126.
26. Znati, M. PhD, University of Toulouse III-Paul Sabatier, Toulouse, France, 2014.
27. Gunduz, S.; Goren, A. C.; Ozturk, T. *Org. Lett.* **2012**, *14*, 1576-1579.
28. Van Acker, F. A.; Hageman, J. A.; Haenen, G. R.; Van Der Vijgh, W. J.; Bast, A.; Menge, W. M. *J. Med. Chem.* **2000**, *43*, 3752-3760.
29. Safavi, M.; Esmati, N.; Ardestani, S. K.; Emami, S.; Ajdari, S.; Davoodi, J.; Shafiee, A.; Foroumadi, A. *Eur. J. Med. Chem.* **2012**, *58*, 573-580.
30. Dias, T. A.; Duarte, C. L.; Lima, C. F.; Proença, M. F.; Pereira-Wilson, C. *Eur. J. Med. Chem.* **2013**, *65*, 500-510.
31. Chouaïb, K.; Romdhane, A.; Delemasure, S.; Dutartre, P.; Elie, N.; Touboul, D.; Ben Jannet, H.; Hamza, M. A. *Ind. Crops. Prod.* **2016**, *85*, 287-299.
32. Zhu, G. X.; Cheng, P. L.; Goto, M.; Zhang, N.; Morris-Natschke, S. L.; Hsieh, K. Y.; Yang, G. Z.; Yang, Q. R.; Liu, Y. Q.; Chen, H. L. et al. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1750-1753.
33. Bahrin, L. G.; Sarbu, L. G.; Hopf, H.; Jones, P. G.; Babii, C.; Stefan, M.; Birsa, M. L. *Bioorg. Med. Chem.* **2016**, *24*, 3166-3173.
34. Kammoun El Euch, S.; Bouajila, J.; Bouzouita, N. *Ind. Crops. Prod.* **2015**, *76*, 1100-1105.