Bioorganic Chemistry 89 (2019) 103009

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Synthesis, molecular properties, anti-inflammatory and anticancer activities of novel 3-hydroxyflavone derivatives

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ARTICLE INFO

Keywords:
3-hydroxyflavones
DFT calculations
15-lipoxygenase inhibitory
Cytotoxic activity
Drug likeness
Molecular propreties

ABSTRACT

A new series of 3-hydroxyflavones (**1**–**46**) were synthesized according to the Claisen-Schmidt followed by Algar-Flynn-Oyamada reactions (AFO) in one step. The synthesized flavonoids were characterized by ^{1}H NMR, ^{13}C NMR and DCI-HRMS. All the synthesized compounds were tested *in vitro* for their 15-lipoxygenase inhibitory and cytotoxic activity against the human cell lines HCT-116 (Human colon carcinoma), IGROV-1 and OVCAR-3 (human ovarian carcinoma). It has been found that the derivatives **25**, **37** and **45** were the most actives against HCT-116 (IC_{50} = 8.0, 9.0 and 9.0 μM, respectively) and against IGROV-1 (IC_{50} = 2.4, 5.0 and 6.0 μM, respectively). The derivatives **14** and **21** exhibited the higher anti-inflammatory activity at 100 μM with PI values of 76.50 and 72.70%, respectively. Molecule description was performed with DFT calculations, the drug likeness and bioactivity scores. The results exhibted that some compounds are in linear correlation with Lipinski's rule of five showing good drug likeness and bioactivity score for drug targets.

1. Introduction

Flavonoids are phytochemical compounds that exist in two classes, either as free aglycones or glycosylated. Chemically, they are polyphenols and have a phenyl-benzopyrone structure (C6–C3–C6). The distinction of the subclasses of flavonoids is made according to the conformation of the central structure (benzopyrone). It is possible to distinguish in particular among the flavonoids the flavones, flavanols, isoflavones, flavonols, flavanones, flavanonols and chalcones [1]. This structural variety confers flavonoids a wide spectrum of biological activities [2], including anticarcinogenic, anti-inflammatory [3], antimicrobial [4], spasmolytic and antiviral activities [5]. Moreover, they inhibit the capillary permeability, the platelet aggregation and the lipid peroxidation. The ability of flavonoids to block the cell cycle, to induce apoptosis [6], to disturb mitotic spindle formation or to inhibit angiogenesis makes them promising agents in anti-cancer research [7,8]. The last few years, flavonoids and their synthetic analogs have been deeply investigated in the treatment of ovarian, breast, cervical, pancreatic, and prostate cancers. Flavonoids such as genistein, quercetin or flavopiridol have entered late phase clinical trials for several oncological indications [9–11]. Flavonoids have been reported to modulate several protein kinases (e.g. protein kinase-C) and to modulate epidermal growth factor receptors (EGFRs), cyclin-dependent kinases (CDKs), vascular endothelial growth factor receptors (VEGFRs) and platelet derived growth factor receptors (PDGFRs), which play important roles in cancer diseases [12]. The anti-inflammatory property of flavonoids have been investigated in *in vivo* and *in vitro* models [13]. Flavonoids are also known by their capacity to inhibit several enzymes such as lipoxygenase (LOX), xanthine oxidase and cyclooxygenase (COX) which are implicated in inflammatory diseases [14,15].

Furthermore, flavonoids are able to modulate the functional activity of several types of cells [13]. The different steps of inflammations are affected by the compounds including the formation of granulose tissue, chronic arthritis as well as the permeability of capillaries in the early stages [16], the structure-activity relationship study of 3-hydroxyflavones are of high interest [17]. However, most research on the biological activity of flavonoids has been limited on natural derivatives such as kaempferol, morin, galangin quercetin, fisetin, and myricetin [18–21].

Taking into account the biological importance (anti-inflammatory,

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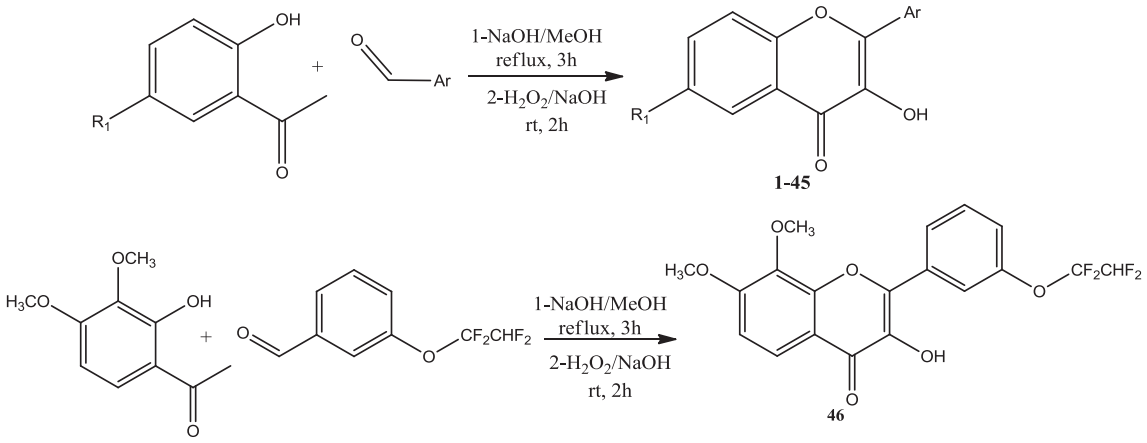
https://doi.org/10.1016/j.bioorg.2019.103009
Received 4 February 2019; Received in revised form 20 May 2019; Accepted 21 May 2019
Available online 22 May 2019
0045-2068/



Compd. No.	R1	Ar	Compd. No.	R1	Ar
1	H	4-iPr-ph	24	Cl	4-CH(OC2H5)2-ph
2	H	2,3-dihydrobenzofuran	25	Cl	4-CF3-ph
3	H	3-NO2,4-OCH3-ph	26	Cl	4'-OCH3-ph-ph
4	H	3-CH3-thiophen-ph	27	Cl	4-SCH3-ph
5	H	4'-OCH3-ph-ph	28	Cl	3-NO2,4-Eth-ph
6	H	4-morpholino-ph	29	Cl	4-morpholino-ph
7	H	3-OCF2CHF2-ph	30	Cl	3-OCF2CHF2-ph
8	Br	4-iPr-ph	31	Cl	2-F,3-CF3-ph
9	Br	4-CF3-ph	32	F	2,3-dihydrobenzofuran
10	Br	4-OBu-Ph	33	F	3-NO2,4-OCH3-ph
11	Br	2,3-dihydrobenzofuran	34	F	4-OBu-Ph
12	Br	3-NO2,4-OCH3-ph	35	F	4-SCH3-ph
13	Br	4-Cl-ph	36	F	4-morpholino-ph
14	Br	3-CH3-thiophen-ph	37	F	3-OCF2CHF2-ph
15	Br	4-CH(OC2H5)2-ph	38	OCH3	4-OBu-Ph
16	Br	4-SCH3-ph	39	OCH3	4-iPr-ph
17	Br	3-NO2,4-Eth-ph	40	OCH3	pyridine
18	Br	4-morpholino-ph	41	OCH3	4-CH(OC2H5)2-ph
19	Br	3-OCF2CHF2-ph	42	OCH3	2,3-dihydrobenzofuran
20	Br	2-F,3-CF3-ph	43	OCH3	4-Cl-ph
21	Cl	2,3-dihydrobenzofuran	44	OCH3	4-morpholino-ph
22	Cl	4-Cl-ph	45	OCH3	3-OCF2CHF2-ph
23	Cl	3-CH3-thiophen-ph			

Scheme 1. Synthetic pathway of 3-hydroxyflavones **1–46**.

anticancer…) of this family of natural compounds and in order to help enrich it with new bioactive derivatives, a series of new flavonols were synthesized using a Claisen-Schmidt and Algar-Flynn-Oyamada reactions (AFO) in one step, and a series of fourty-six compounds was tested *in vitro* for their 15-lipoxygenase inhibitory and cytotoxic activity against the human cell lines HCT-116 (Human colon carcinoma), IGROV-1 and OVCAR-3 (human ovarian carcinoma). Density functional theory (DFT) calculations were performed with the PBE (Perdew, Burke and Ernzerhof) GGA (Generalized Gradient Approximation) exchange-correlation functional method and a TZP (triple zeta) basis set. The drug likeness of all synthesized compounds as well as of their derivatives was determined and discussed.

2. Results and discussion

2.1. Synthesis

A one-step Claisen-Schmidt condensation followed by Algar-Flynn-Oyamada (AFO) reaction was used to prepare the target 3-hydroxyflavones **1–46**. As illustrated in Scheme 1, substituted aryl aldehydes with substituted 2-hydroxyacetophenones were refluxed in methanol to afford 2-hydroxychalcones, then the intramolecular cyclization of the ring C and the oxidation of the carbon 3 are carried out using (H_2O_2, NaOH) to give the desired flavonols (**1–46**) with yields ranging from 30 to 92% after precipitation in ice-water [22]. The prepared flavonols were characterized by means of spectroscopic methods (^{1}H, ^{13}C NMR and DCI-HRMS). Compound **8**, as an exemple, was obtained as a yellow solid. Its mass spectrum (DCI- HRMS) gave pseudomolecular ion peak $[M + H]^+$ at *m/z* 359.0292 in concordance with the molecular formula $C_{18}H_{16}BrO_3$. The ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound **8** has shown three signals at δ_H 8.16 (1H, d, J = 2.4 Hz), δ_H 7.87 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz) and δ_H 7.72 (1H, d, J = 9.0 Hz) attributable to H-5, H-7 and H-8, respectively of the A-ring of the flavonol skeleton. The same ^{1}H NMR spectrum displayed an AA'BB' system of the B-ring at δ_H 8.30 (2H, d, J = 8.4 Hz) and δ_H 7.39 (2H, d, J = 8.4 Hz) attributable to H-2′, H-6′ and H-3′, H-5′, respectively. The presence of two signals at δ_H 3.02 (1H, sept, J = 6.9 Hz) and δ_H 1.26 (6H, d, J = 6.9 Hz) relative to the isopropyl fragment. The ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **8** confirmed the above spectral data by the observation of signals at δ_C 174.8 (C-4) attribuable to the carbonyl group, seven quaternary carbons at δ_C 153.3 (C-9), 149.4 (C-2), 145.8 (C-4′), 135.3 (C-3), 134.1 (C-7), 126.4 (C-1′), 125.5 (C-10) and five methine carbons at δ_C 129.6 (C-5), 127.2 (C-2′, C-6′), 126.6 (C-3′, C-5′), 121.4 (C-8), 116.2 (C-6). The isopropyl fragment was also identified by the observation of the corresponding carbon atoms at δ_C 33.8 (C-7′) and 24.1 (C-8′, C-9′).

Table 1
15-lipoxygenase inhibition capacity (percent inhibition (%)) and cytotoxicity (HCT-116, IGROV-1 and OVCAR-3 cells lines) (IC_{50} (μM)) of flavonols derivatives **1–46**.

Sample	15-lipoxygenase inhibition (%) at 100 μM	Cytotoxic activity** (IC_{50} μM)		
		HCT-116	IGROV-1	OVCAR-3
1	01.1 ± 0.0 [h]	28.0 ± 3.0[d]	25.1 ± 2.3[d]	25.1 ± 2.3[d]
2	34.5 ± 2.6[e]	95.0 ± 11.0 [h]	44.7 ± 2.1[f]	60.0 ± 3.7 [g]
3	43.2 ± 5.6[d]	63.0 ± 7.0 [g]	> 100[i]	97.0 ± 4.9 [h]
4	46.4 ± 9.0[d]	> 100[i]	40.0 ± 2.6[f]	25.0 ± 0.3[d]
5	na*	26.7 ± 1.4[d]	33.0 ± 1.3[d]	25.0 ± 0.7[d]
6	na*	> 100[i]	> 100[i]	> 100[i]
7	22.5 ± 2.0[f]	51.0 ± 4.0[f]	21.0 ± 1.0[c]	94.0 ± 7.0 [h]
8	15.4 ± 0.6 [g]	25.0 ± 4.0[d]	31.6 ± 1.9[d]	40.0 ± 1.9[e]
9	01.1 ± 0.0 [h]	20.0 ± 3.0[c]	22.4 ± 1.6[c]	22.0 ± 0.8[c]
10	00.7 ± 0.0 [h]	> 100[i]	56.2 ± 3.1 [g]	63.0 ± 2.9 [g]
11	35.6 ± 8.1[e]	25.0 ± 2.0[d]	> 100[i]	22.0 ± 1.0[c]
12	20.6 ± 1.0[f]	10.0 ± 1.0[b]	25.1 ± 1.9[d]	29.0 ± 1.6[d]
13	25.9 ± 3.3[f]	40.0 ± 7.0[e]	17.8 ± 1.1[c]	11.5 ± 0.6[b]
14	76.5 ± 5.0[b]	> 100[i]	79.40 ± 7.3 [h]	63.0 ± 2.8 [g]
15	33.6 ± 4.1[e]	31.0 ± 3.0[d]	31.6 ± 1.7[d]	28.0 ± 1.4[d]
16	na*	33.0 ± 4.0[d]	> 100[i]	23.0 ± 1.0[d]
17	na*	28.0 ± 2.0[d]	17.0 ± 1.0[c]	17.0 ± 1.0[c]
18	05.6 ± 0.0 [h]	> 100[i]	> 100[i]	94.0 ± 8.0 [h]
19	44.3 ± 2.0[d]	18.0 ± 1.0[c]	10.0 ± 1.0[b]	42.0 ± 3.0[e]
20	na*	10.0 ± 0.0[b]	14.0 ± 1.0[b]	51.0 ± 4.0[f]
21	72.7 ± 3.5[b]	20.0 ± 3.0[c]	18.0 ± 1.2[c]	19.0 ± 0.8[c]
22	35.3 ± 4.6[e]	45.0 ± 3.0[e]	28.2 ± 1.7[d]	27.0 ± 1.0[d]
23	19.7 ± 3.5[f]	> 100[i]	71.0 ± 4.6 [h]	56.0 ± 1.8[f]
24	27.0 ± 1.1[f]	80.0 ± 8.0 [h]	> 100[i]	> 100[i]
25	na*	8.0 ± 1.0[b]	2.4 ± 0.02[a]	28.0 ± 2.0[d]
26	na*	> 100[i]	> 100[i]	> 100[i]
27	na*	54.0 ± 5.0[f]	> 100[i]	25.0 ± 3.0[d]
28	na*	31.0 ± 1.0[d]	20.0 ± 2.0[c]	21.0 ± 2.0[c]
29	na*	> 100[i]	> 100[i]	92.0 ± 8.0 [h]
30	24.0 ± 1.0[f]	32.0 ± 4.0[d]	24.0 ± 2.0[d]	50.0 ± 4.0[f]
31	na*	56.0 ± 4.0[f]	37.0 ± 2.0[e]	60.0 ± 5.0 [g]
32	37.0 ± 3.1[e]	40.0 ± 5.0[e]	56.0 ± 4.2 [g]	60.0 ± 2.1 [g]
33	45.3 ± 9.9[d]	50.0 ± 7.0[f]	31.6 ± 2.2[d]	33.0 ± 1.6[e]
34	21.5 ± 2.0[f]	25.0 ± 2.0[d]	39.8 ± 2.4[e]	40.0 ± 2.3[e]
35	2.9 ± 0.0 [h]	> 100[i]	> 100[i]	> 100[i]
36	3.11 ± 0.0 [h]	> 100[i]	> 100[i]	> 100[i]
37	54.9 ± 3.0[c]	9.0 ± 1.0[b]	5.0 ± 0.0[a]	50.0 ± 3.0[f]
38	13.0 ± 2.5 [g]	31.0 ± 4.0[d]	> 100[i]	> 100[i]
39	27.6 ± 1.9[f]	> 100[i]	15.8 ± 0.6[b]	20.0 ± 0.8[c]
40	24.6 ± 5.7[f]	> 100[i]	> 100[i]	> 100[i]
41	40.9 ± 2.0[d]	87.0 ± 10.0 [h]	35.5 ± 2.7[e]	18.0 ± 1.0[c]
42	na*	30.0 ± 3.0[d]	> 100[i]	> 100[i]
43	na*	95.0 ± 11.0 [h]	> 100[i]	20.0 ± 1.7[c]
44	2.7 ± 0.0 [h]	42.0 ± 2.0[e]	27.0 ± 1.0[d]	25.0 ± 2.0[d]
45	21.2 ± 1.0[f]	9.0 ± 1.0[b]	6.0 ± 0.0[a]	54.0 ± 3.0[f]
46	20.3 ± 1.0[f]	8.0 ± 0.0[b]	> 100[i]	> 100[i]
NDGA	98.0 ± 0.1[a]			
Doxorubicin		0.18 ± 0.01[a]		
Tamoxifin			2.0 ± 0.1[a]	1.3 ± 0.1[a]

* Not active.

** Cytotoxicity as IC_{50} for each cell line, is the concentration of compound that inhibits of 50% the cell multiplication after 48 h of treatment. Values in a column followed by the same letter are not significantly different at $P < 0.05$ (LSD test).

2.2. Biological assays

2.2.1. 15-lipoxygenase inhibitory

The series of 3-hydroxyflavones **1–46** were evaluated for their ability to inhibit 15-lipoxygenase enzyme and the corresponding Percent of Inhibition (PI) are given in Table 1. All derivatives were tested at 100 μM. NDGA was used as a reference compound. The results showed that this series of flavonols inhibits 5-LOX enzyme with PI values ranging from 0.7 and 76.5%. Compound **14** was found to exhibit the higher anti-5-LOX activity (PI = 76.5 ± 5.0%) followed by **21** (PI = 72.7 ± 3.5%) then **37** (PI = 54.9 ± 3.0%).

2.2.2. Cytotoxic activity

The cytotoxic activity of the synthesized compounds (**1–46**) were tested against three human cancer cell lines including HCT-116, IGROV-1 and OVCAR-3 using the MTT assay. Doxorubicin and Tamoxifen are employed as positive controls. The results expressed in IC_{50} are presented in Table 1. It was found that all the synthesized compounds displayed cytotoxic activity towards HCT-116, IGROV-1 and OVCAR-3 with IC_{50} values ranging from 2.4 to > 100 μM.

Compounds **25**, **37**, **45** and **46** exhibited the highest activity against HCT-116 cell line (IC_{50} = 8.0 − 9.0 μM). Furthermore, compounds **12** and **20** displayed an interesting activity with an IC_{50} value of 10 μM. Most of the rest of the compounds showed activity against the same cell line (HCT-116) with IC_{50} values ranging from 18.0 to 95.0 μM. Regarding the human ovarian carcinoma cell lines (IGROV-1 and OVCAR-3), compound **25** showed the most potent activity against IGROV-1 with an IC_{50} value of 2.4 μM. However, compounds **37** and **45** displayed an interesting activity against IGROV-1 with IC_{50} values of 5.0 and 6.0 μM, respectively, followed by compound **19** (IC_{50} = 10.0 μM). On the other hand, compounds **13**, **17**, **21** and **41** showed the highest activity towards OVCAR-3 with IC_{50} values of 11.5, 17.0, 19.0 and 18.0 μM, respectively. The results showed that most of the synthesized compounds have cytotoxic profile against human cancer cell lines used, some compounds are found to be more selective towards IGROV-1 than OVCAR-3. This finding can be explained by the nature of the structure of these compounds and the specific sensitivity of IGROV-1 and OVCAR-3 cell lines against them.

2.3. Bioactivity score of flavonols (1–46)

The bioactivity scores of the synthesized compounds for drug targets against G protein–coupled receptors ligands (GPCR), nuclear receptor inhibitors, ion channel modulator, kinase inhibitors and other enzyme targets based on Molinspiration software [23] are presented in Table 2. The scores let it be identified of active, inactive molecules or moderately active. A compound having bioactivity score above 0.00 is most likely to show considerable biological activities, while values −0.50 to 0.00 are expected to be moderately active and if score is less than −0.50 it is presumed to be inactive. However, G protein–coupled receptors (GPCR) ligands results exhibited all compounds were found moderately active with bioactivity scores ranged from −0.01 to −0.56. Except compounds **2**, **32**, **21** and **42** which were found to be considerably bioactive with score values of 0.04, 0.09, 0.06 and 0.04, respectively. On the other hand, the ion channel modulator and Protease inhibitor results, showed that all our molecules were found to be moderately active or inactive having bioactivity score values ranging from −0.04 to −0.56 and from −0.19 to −0.86, respectively. For the Kinase inhibitory potential, 33 molecules from the series **1–46** were found to be active with bioactivity score values of 0.01–0.30 (Table 2). A good number of synthesized compounds (27 molecules, Table 2) were found to be considerably nuclear receptor inhibitors with bioactivity scores ranging 0.01 to 0.30. However, the rest of compounds were moderately bioactive. Concerning the Enzyme inhibitory potential, only 16 molecules were found to be moderately active with bioactive score values ranging from −0.01 to −0.33, whereas 30 molecules showed good bioactivity (scores = 0.02–0.27).

2.4. Drug likeness score of flavonols (1–46)

In order to evaluate if the synthesized flavonols **1–46** present a correlation between the activity and the lipophilicity, and to better understand their overall properties, their physico-chemical properties have been assessed using Molinspiration software [23] and presented in Table 3. The LogP of compounds **4**, **5**, **7**, **8**, **9**, **10**, **14**, **17**, **19**, **20**, **23**, **26**, **30**, **31** and **45** were found greater than five, indicating that these molecules have poor permeability across the cell membrane (Table 3). The values of LogP less than five for the rest of the molecules, justify

Table 2
Bioactivity score of the flavonols derivatives according to Molinspiration cheminformatics software.

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	−0.11	−0.27	0.04	0.16	−0.31	0.14
2	0.04	−0.17	0.24	0.24	−0.23	0.27
3	−0.32	−0.52	−0.03	−0.05	−0.47	−0.04
4	−0.45	−0.56	−0.13	−0.14	−0.77	−0.04
5	−0.07	−0.26	0.12	0.13	−0.19	0.10
6	−0.06	−0.30	0.20	0.07	−0.21	0.08
7	−0.39	−0.09	0.29	−0.06	−0.46	−0.25
8	−0.23	−0.39	0.00	0.01	−0.42	0.03
9	−0.15	−0.27	0.13	0.12	−0.34	0.03
10	−0.17	−0.39	0.02	0.09	−0.32	0.05
11	−0.09	−0.30	0.20	0.09	−0.35	0.15
12	−0.44	−0.62	−0.07	−0.20	−0.59	−0.14
13	−0.18	−0.04	−0.45	−0.09	−0.40	0.02
14	−0.56	−0.69	−0.14	−0.27	−0.86	−0.14
15	−0.43	−0.37	−0.08	−0.17	−0.39	0.06
16	−0.38	−0.50	−0.09	−0.11	−0.48	−0.01
17	−0.38	−0.42	−0.16	−0.11	−0.52	−0.10
18	−0.19	−0.40	0.14	−0.08	−0.33	−0.01
19	−0.50	−0.20	0.23	−0.21	−0.58	−0.33
20	−0.15	−0.30	0.16	0.13	−0.38	0.03
21	0.06	−0.17	0.23	0.24	−0.22	0.22
22	−0.17	−0.28	0.06	0.03	−0.40	0.11
23	−0.40	−0.55	−0.09	−0.10	−0.71	−0.06
24	−0.31	−0.27	−0.05	−0.04	−0.28	0.12
25	−0.01	−0.16	0.17	0.27	−0.21	0.10
26	−0.08	−0.26	0.10	0.11	−0.21	0.06
27	−0.23	−0.37	−0.05	0.04	−0.34	0.06
28	−0.25	−0.31	−0.13	0.03	−0.40	−0.04
29	−0.07	−0.29	0.18	0.05	−0.22	0.05
30	−0.38	−0.10	0.26	−0.08	−0.47	−0.27
31	−0.02	−0.19	0.19	0.27	−0.26	0.09
32	0.09	−0.18	0.28	0.30	−0.23	0.25
33	−0.28	−0.51	0.01	−0.00	−0.47	−0.04
34	−0.01	−0.28	0.10	0.28	−0.21	0.14
35	−0.20	−0.38	0.01	0.11	−0.35	0.09
36	−0.04	−0.30	0.22	0.11	−0.22	0.08
37	−0.36	−0.10	0.30	−0.04	−0.47	−0.24
38	−0.05	−0.30	0.09	0.22	−0.20	0.13
39	−0.10	−0.32	0.06	0.19	−0.29	0.10
40	−0.16	−0.28	0.23	0.01	−0.42	0.18
41	−0.33	−0.31	−0.04	−0.02	−0.30	0.11
42	0.04	−0.22	0.26	0.26	−0.21	0.22
43	−0.17	−0.35	0.07	0.07	−0.43	0.07
44	−0.10	−0.34	0.17	0.07	−0.25	0.04
45	−0.38	−0.12	0.28	−0.07	−0.47	−0.24
46	−0.44	−0.06	0.19	−0.20	−0.52	−0.23

their good permeability and therefore are an indication of a good lipid solubility that will help the drug to interact with the membranes and to be used for generation of bioactivity. On the other hand, the molecular weight of the molecule is an important parameter in pharmaceutics drug action which acts by affecting the drug mechanisms when it increases beyond certain limit. All molecular weights of the synthesized flavonols **1–46** are less than 500 g/mol suggesting that these compounds are anticipated to be easily transported, diffused and absorbed. Polar surface area (TPSA) calculated values are between 50.439 and 105.497 $Å^2$, these resutls are a very good descriptor characterizing drug absorption with increasing molecules flexibility and facilitating their interaction with a particular binding pocket. Number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) of all the tested flavonols were found under 10 and 5, respectively and were in agreement with the Lipinski's rule of five. Interestingly, all compounds exhibited number of violation (n violations) = 1 or < 0 meaning that are easily bind to receptor. As shown, the determined molecular properties of these compounds justify their possible use as drugs.

2.5. Structure–activity relationship (SAR) analysis

The structure–activity relationship (SAR) analysis of the 5-LOX inhibition and cytotoxic activity of flavonols derivatives (**1–46**) showed that **14** (PI = 76.5%) was found to be the most active against 5-LOX enzyme. This results can be explained by the presence of the bromine atom at C-6 on ring A and methylthiopheneheterocyclic on ring B. Furthermore, Beers and their collaborators have been shown the effect of thiophene heterocyclic against 5-lipoxygenase enzyme [24]. However, the dihydrobenzofuran system on ring B (**21**) showed an interesting activity with PI value of 72.7%, which was confirmed by Janusz [25].

On the other hand, the meta 1,1,2,2-tetrafluoroethoxy on the ring B (**19**, **25**, **37**–**45** and **46**) showed the good cytotoxic activity against HCT-116 and IGROV-1 with IC_{50} values ranging from 2.4 to 9 μM. These interesting results can be explained by the effect of fluorine atom [26].

Liu *et al.* synthesized a series of novel flavone derivatives bearing chloride, isopropyl and methoxy groups to develop effective anticancer agents possess notable activity against hepatocarcinoma cells (HepG-2) [27]. SAR depicts that substitution at C-6 chloro at ring-A, is important for anticancer activity.

Forthemore, the highest activity was obtained by compounds **25** and **37** against HCT-116 and IGROV-1 due to the ability of these compounds to penetrate the cell membrane (LogP < 5).

The human genome encodes 538 protein kinases that transfer a γ-phosphate group from ATP to tyrosine, threonine or serine residues. Many of these kinases are associated with human cancer initiation and progression [28]. Significantly, protein kinases are the second most targeted group of drug targets, after the G-protein-coupled receptors [28]. Flavonoids have been reported to modulate several protein kinases [29,30]. In our study, the results of *in vitro* cytotoxicity and bioactivity testing showed that the most cytotoxic compounds (**25**, **37**, **45** and **46**) have proven to be active inhibitors of protein kinase (bioactivity scores from 0.17 to 0.30) and moderately active towards GPCR ligands. Our study suggests that flavonols could inhibit cancer cell growth by acting on protein kinase signaling pathways more than as GPCRs ligands.

Moreover, the recent development of small-molecule kinase inhibitors for the treatment of diverse types of cancer has proven successful in clinical therapy [28]. In this study, Small molecules with specific properties were investigated. Various mechanisms can lead to protein kinase inhibition. Due to their low molecular weight (340.684–432.297 g/mol) and volume (252.846–325.753 $Å^3$), these molecules can easily pass across cancer cell membranes by diffusion. Furthermore, LogP values (≤5) indicate that our compounds have the benefit of having facilitated access to cancer cells.

Finaly, analyzing the obtained data, moderate linear correlations were observed between the biological activities and the lipophilicity of the synthesized flavonol derivatives **1–46**, except compound **19** with the highest LogP value of 5.81 exhibited a good cytotoxic activity. To further exploit the dataset, Linear Discriminant Analysis was used to investigate the possible classification of the molecules in three categories (Table 4) from the 15 available descriptors (10 DFT descriptors associated with the values of LogP, MW, TPSA, *n*-ON acceptors and volume). Satisfactory results were obtained for each biologiocal activity since > 70% of the molecules were correctly classified from both the training and the cross-validated set. As an example for HCT-116, Fig. 1 represents the scatter plot of the molecules defined by the discriminant functions. F1 and F2 discriminant functions explained 93.5% and 6.5% of the variance, respectively. F1 clearly allowed discriminating classes 1 and 2, while F2 was also needed to highlight class 3. The three corresponding linear classification functions included 7 molecular descriptors: 4 variables mainly related to the electronic properties of the molecules (the molecular orbital energies LUMO and HOMO, the vertical electronic affinity A and the nucleofugality (λ_N)) (Table 5) and 3 variables related to the molecule size and their polarity (TPSA, MW and

Table 3
Calculated molecular properties of flavonols derivatives for assessment of the drug likeness.

Compound	MW[a]	TPSA[b]	Vol[c]	*n*-ON acceptors[d]	NOHNH[e]	LogP[f]	N_{vio}[g]	N_{rotlb}[h]
1	280.323	50.439	257.963	3	1	4.95	0	2
2	280.279	59.673	239.76	4	1	3.47	0	1
3	313.265	105.497	256.893	7	1	3.38	0	3
4	334.396	50.439	286.694	3	1	5.40	0	1
5	344.366	59.673	304.967	4	1	5.29	1	3
6	323.348	62.911	286.147	5	1	3.39	0	2
7	354.250	59.673	274.662	4	1	4.68	0	4
8	359.219	50.439	275.848	3	1	5.74	1	2
9	385.135	50.439	257.196	3	1	5.12	1	2
10	389.245	59.673	301.85	4	1	5.72	1	5
11	359.175	59.673	257.645	4	1	4.25	0	1
12	392.161	105.497	274.778	7	1	4.17	0	3
13	351.583	50.439	239.434	3	1	4.90	0	1
14	413.292	50.439	304.58	3	1	6.18	0	1
15	419.271	68.907	327.421	5	1	4.89	0	6
16	363.232	50.439	260.588	3	1	4.66	0	2
17	390.189	96.263	282.595	6	1	5.03	1	3
18	402.244	62.911	304.032	5	1	4.17	0	2
19	451.141	59.673	292.547	4	1	5.81	1	4
20	403.125	50.439	262.127	3	1	5.21	1	2
21	314.724	59.673	253.295	4	1	4.12	0	1
22	307.132	50.439	235.085	3	1	4.77	0	1
23	368.841	50.439	300.23	3	1	6.05	0	1
24	374.82	68.907	323.072	5	1	4.76	0	6
25	340.684	50.439	252.846	3	1	4.99	0	2
26	378.811	59.673	318.503	4	1	5.95	1	3
27	318.781	50.439	256.238	3	1	4.53	0	2
28	345.738	96.263	278.246	6	1	4.90	0	3
29	357.793	62.911	299.683	5	1	4.04	0	2
30	406.69	59.673	288.197	4	1	5.68	1	4
31	358.674	50.439	257.778	3	1	5.08	1	2
32	298.269	59.673	244.691	4	1	2.63	0	1
33	331.255	105.497	261.824	7	1	2.55	0	3
34	328.339	59.673	288.895	4	1	4.10	0	5
35	302.326	50.439	247.634	3	1	3.04	0	2
36	341.338	62.911	291.078	5	1	2.56	0	2
37	390.235	59.673	279.593	4	1	4.19	0	4
38	340.375	68.907	309.51	5	1	4.97	0	6
39	310.349	59.673	283.508	4	1	4.99	0	3
40	269.256	72.565	229.402	5	1	2.18	0	2
41	370.401	78.141	335.081	6	1	4.14	0	7
42	310.305	68.907	265.305	5	1	3.50	0	2
43	302.713	59.673	247.095	4	1	4.15	0	2
44	353.374	72.145	311.693	6	1	3.42	0	3
45	402.271	68.907	300.207	5	1	5.06	0	5
46	432.297	78.141	325.753	6	1	4.85	0	6

[a] Molecular weight.
[b] Polar surface area.
[c] Molecular volume (Å^3).
[d] Number of hydrogen-bond acceptors (O and N atoms).
[e] Number of hydrogen-bond donors (OH and NH groups).
[f] Octanol-water partition coefficient.
[g] Number of "Rule of five" violations.
[h] Number of rotatable bonds.

Table 4
The three classes defined for each measured biological activity: 15-lipoxygenase inhibitory, HCT-116, IGROV and OVCAR.

Class	15-lipoxygenase inhibition (%) at 100 µM	Cytotoxic activity** (IC_{50} µM)		
		HCT-116	IGROV-1	OVCAR-3
1	< 10	< 40	< 30	< 40
2	10 ≤ < 40	40 ≤ < 100	30 ≤ < 100	40 ≤ < 100
3	≥40	≥100	≥100	≥100

the volume). These classification functions were used to predict which class a molecule is to be assigned to using the values taken for the 7 discriminant initial variables. These predictions were used to evaluate the performance of the LDA model. Moreover, LDA model validation was carried out using a cross-validation method: 8 molecules among the 44 available molecules (~20% of the dataset) were randomly selected and used as validation set.

Results are presented in the so-called confusion matrix which gives the percentage of well classified molecules, which is the ratio of the number of well-classified molecules over the total number of molecules, for both the training and the validation sets of molecules (Tables 6 and 7). Satisfying results were obtained since about 80.6 and 75% of the molecules were correctly classified from the training and the cross-validated set, respectively.

Results of equivalent statistical quality have been obtained for 15-lipoxygenase inhibitory, OVCAR-3 and IGROV-1 activities. For 15-lipoxygenase inhibitory, the discriminant functions only involved the number of hydrogen-bond acceptors (O and N atoms) and the molecule hardness. For OVCAR-3, molecule classification was based on the

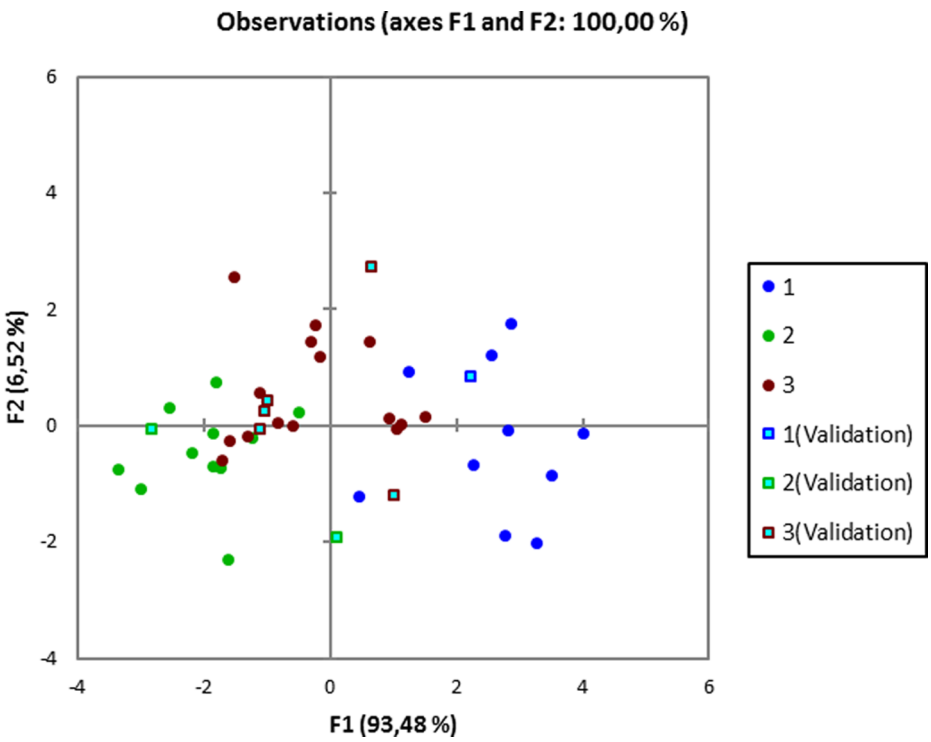


Fig. 1. LDA score plots presenting the separation of the three classes as definedfor HCT-116.

nucleofugality (λ_N), the volume and MW while for IGROV-1, it required the nucleofugality (λ_N), the dipole moment and the molecule hardness.

3. Conclusion

We synthesized Forty-six novel flavonol analogues using a Claisen-Schmidt and AFO reactions in one step and investigated their *in vitro* 15-lipoxygenase inhibitory effect and cytotoxic activity against the human cell lines HCT-116, IGROV-1 and OVCAR-3. The compounds **14**, **21** and **37** showed the higher activity against 15-lipoxygenase enzyme. Moreover, compound **14** possessing a bromine atom at C-6 on ring A and a methylthiophene group on ring B demonstrated the highest activity against 15-lipoxygenase enzyme. On the other hand, the majority of newly synthesized flavonols showed a good cytotoxicity against HCT-116. Compounds **25**, **37**, **45** and **46** showed the highest activity against HCT-116. However, compounds **25**, **37**, **45**, **13**, **17**, **21** and **41** exhibited the highest cytotoxicity against ovarian human cell lines (IGROV-1 and OVCAR-3). Furthermore, some compounds were found to be more selective towards IGROV-1 than OVCAR-3. In conclusion, the most of the synthesized compounds have cytotoxic profile against human cancer cell lines used. DFT calculations and the drug likeness of all synthesized compounds performed reinforced the biological results. Further, investigation into the mechanism of action of these flavonols derivatives is our future work.

4. Experimental section

4.1. General methods

All reagents were purchased from Aldrich. All the solvents used in the syntheses were technical grade and freshly distilled prior to use. DCI-HRMS was run in a GCT 1er Waters. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AM-300 spectrometer, using DMSO-d_6 as solvent and non deuterated residual solvent as internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hz. Melting points were determined on a Büchi 510 apparatus using capillary tubes.

4.2. General procedure for 3-hydroxyflavone syntheses

In a round-bottom flask (25 mL), equipped with magnetic stirrer 2-hydroxyacetophenone (**a**) (0.2 mL, 1.66 mmol), cumanaldehyde (**b**) (0.24 g, 1.66 mmol), sodium hydroxide (0.2 g, 5 mmol) and methanol (10 mL) were introduced. The pale yellow mixture was refluxed until the color was changed into orange (about 3 h). The reaction mixture was cooled to room temperature and sodium hydroxide (0.5 N, 10 mL) and then hydrogen peroxide (35%, 0.684 mL) were added. After stirring 2–3 h, the mixture was poured into ice-water and the formed precipitate was filtered to obtain **1** as a yellow solid (75%) [22].

The following were similarly prepared **2–46**.

4.2.1. 3-hydroxy-2-(4-isopropylphenyl)-4H-chromen-4-one (1)

Yellow solid, yield: 75%, mp: 238 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.27 (2H, d, J = 8.1 Hz, H-2′, H-6′), 8.12 (1H, dd, J_1 = 7.5, J_2 = 1.2 Hz, H-5), 7.77 (2H, m, H-6, H-7), 7.46–7.42 (3H, m, H-8, H-3′, H-5′), 2.92 (1H, sept, J = 6.9 Hz, H-7′), 1.27 (6H, d, J = 6.9 Hz, H-8′, H-9′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 175.1 (C-4), 154.7 (C-9), 149.9 (C-4′), 145.5 (C-2), 133.4 (C-3), 130.3 (C-7), 129.6 (C-1′), 127.6 (C-2′, C-6′), 126.7 (C-3′, C-5′), 125.4 (C-5), 124.4 (C-6), 121.7 (C-10), 116.2 (C-8), 33.8 (C-7′), 24.1 (C-8′, C-9′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{18}H_{17}O_3)^+$: 281.1178, found: 281.1183.

4.2.2. 2-(2,3-dihydrobenzofuran-5-yl)-3-hydroxy-4H-chromen-4-one (2)

Yellow solid, yield: 67%, mp: 255 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.71 (1H, s, H-2′), 8.51 (1H, d, J = 7.8 Hz, H-6′), 8.04 (1H, J = 7.2 Hz, H-5), 7.58 (2H, m, H-6, H-7), 7.26 (1H, d, J = 6.3 Hz, H-8), 6.81 (1H, d, J = 7.2 Hz, H-5′), 4.59 (2H, t, J = 7.2 Hz, H-7′), 3.26 (2H, t, J = 7.2 Hz, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 175.0 (C-4), 158.7 (C-4′), 153.7 (C-9), 149.6 (C-2), 135.4 (C-3), 131.3 (C-7), 128.2 (C-2′), 127.0 (C-3′), 125.1 (C-5), 125.0 (C-6′), 123.3 (C-6), 122.8 (C-1′), 121.1 (C-10), 118.0 (C-8), 109.7 (C-5′), 71.4 (C-7′),29.6 (C-8′). DCI-HRMS $[M + H]^+$ calcd. for $(C_{17}H_{13}O_4)^+$: 281.0814, found: 281.0811.

4.2.3. 3-hydroxy-2-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (3)

Yellow solid, yield: 90%, mp: 266 °C; ^{1}H NMR (300 MHz, DMSO-d_6)

Table 5
Calculated molecular DFT descriptors of flavonols derivatives.

Compound	LUMO	HOMO	Dipole moment	q_{max}	q_{min}	A	μ	η	λ_N	λ_E
1	−0.074	−0.234	6.241	2.278	−1.742	0.022	−0.154	0.264	0.317	0.265
2	−0.071	−0.229	5.511	2.358	−1.656	0.017	−0.148	0.261	0.291	0.276
3	−0.103	−0.243	9.559	2.362	−1.618	0.042	−0.168	0.251	0.498	0.245
4	−0.084	−0.236	5.926	2.273	−1.740	0.030	−0.159	0.259	0.385	0.256
5	−0.078	−0.229	6.253	2.188	−1.646	0.029	−0.150	0.242	0.419	0.278
6	−0.066	−0.216	7.117	2.362	−1.640	0.015	−0.138	0.247	0.301	0.298
7	−0.087	−0.246	5.922	2.340	−1.821	0.034	−0.166	0.265	0.398	0.244
8	−0.082	−0.239	7.647	2.409	−1.649	0.030	−0.159	0.258	0.390	0.257
9	−0.099	−0.252	4.076	2.579	−1.576	0.046	−0.174	0.256	0.522	0.233
10	−0.078	−0.234	9.154	2.194	−1.578	0.026	−0.154	0.256	0.361	0.267
11	−0.078	−0.233	7.098	2.394	−1.399	0.026	−0.154	0.255	0.365	0.267
12	−0.111	−0.252	8.507	2.315	−1.372	0.053	−0.177	0.248	0.598	0.231
13	−0.090	−0.247	5.264	2.419	−1.642	0.038	−0.167	0.257	0.453	0.244
14	−0.085	−0.244	7.311	2.130	−1.729	0.031	−0.162	0.262	0.382	0.251
15	−0.084	−0.241	7.195	1.949	−1.536	0.034	−0.162	0.257	0.416	0.253
16	−0.083	−0.233	8.110	2.356	−1.573	0.032	−0.156	0.247	0.430	0.266
17	−0.112	−0.251	8.101	2.482	−1.546	0.055	−0.178	0.246	0.623	0.230
18	−0.074	−0.220	8.735	2.535	−1.495	0.024	−0.145	0.242	0.376	0.288
19	−0.094	−0.250	6.336	2.131	−1.569	0.041	−0.171	0.258	0.474	0.238
20	−0.100	−0.254	4.012	2.557	−1.718	0.045	−0.175	0.259	0.504	0.231
21	−0.078	−0.233	7.200	1.601	−1.507	0.025	−0.154	0.257	0.355	0.267
22	−0.090	−0.247	5.302	1.486	−1.551	0.038	−0.167	0.259	0.443	0.243
23	−0.085	−0.243	7.350	1.428	−1.674	0.030	−0.162	0.264	0.372	0.250
24	−0.084	−0.241	7.660	1.236	−1.539	0.033	−0.162	0.258	0.407	0.253
25	−0.099	−0.252	4.104	1.236	−1.510	0.046	−0.175	0.258	0.512	0.232
26	−0.084	−0.233	8.093	2.028	−1.487	0.036	−0.155	0.239	0.483	0.270
27	−0.084	−0.240	7.312	2.068	−1.534	0.033	−0.160	0.253	0.424	0.258
28	−0.112	−0.252	8.140	1.185	−1.378	0.054	−0.178	0.247	0.615	0.230
29	−0.074	−0.220	8.751	1.184	−1.448	0.023	−0.144	0.243	0.368	0.289
30	−0.094	−0.250	6.375	1.618	−1.511	0.041	−0.171	0.260	0.464	0.237
31	−0.099	−0.254	4.056	1.166	−1.652	0.045	−0.175	0.261	0.494	0.230
32	−0.077	−0.233	7.136	2.380	−1.663	0.023	−0.153	0.259	0.336	0.268
33	−0.106	−0.247	9.924	2.358	−1.626	0.046	−0.172	0.251	0.534	0.238
34	−0.077	−0.233	9.138	2.244	−1.693	0.023	−0.153	0.259	0.334	0.268
35	−0.082	−0.232	8.130	2.353	−1.771	0.030	−0.155	0.250	0.403	0.267
36	−0.076	−0.225	8.436	2.380	−1.672	0.024	−0.147	0.246	0.371	0.282
37	−0.093	−0.249	6.428	2.339	−1.802	0.039	−0.170	0.263	0.443	0.237
38	−0.069	−0.223	6.925	2.765	−1.711	0.017	−0.144	0.254	0.301	0.285
39	−0.073	−0.226	6.997	2.788	−1.664	0.021	−0.148	0.254	0.333	0.277
40	−0.098	−0.237	5.494	2.772	−1.690	0.037	−0.163	0.252	0.450	0.253
41	−0.076	−0.227	8.232	2.551	−1.600	0.024	−0.151	0.252	0.359	0.274
42	−0.069	−0.223	6.038	2.827	−1.628	0.017	−0.144	0.254	0.302	0.285
43	−0.082	−0.232	5.731	2.766	−1.716	0.030	−0.156	0.253	0.395	0.264
44	−0.084	−0.241	8.506	1.257	−1.577	0.032	−0.161	0.258	0.404	0.253
45	−0.085	−0.234	7.305	2.732	−1.724	0.033	−0.159	0.253	0.420	0.259
46	−0.081	−0.237	7.004	1.331	−1.742	–	–	–	–	–

Table 6
Confusion matrix for the 36 molecules used as estimation observations.

from\to	Class 1	Class 2	Class 3	Total	% correct
Class 1	8	0	2	10	80.00
Class 2	0	10	1	11	90.91
Class 3	1	3	11	15	73.33
Total	9	13	14	36	80.56

Table 7
Confusion matrix for the 8 molecules used as validation observations.

from\to	Class 1	Class 2	Class 3	Total	% correct
Class 1	1	0	0	1	100
Class 2	0	1	1	2	50
Class 3	1	0	4	5	80
Total	2	1	5	8	**75**

δ_H: 9.55 (1H, d, J = 2.1 Hz,H-2′), 8.65 (1H, dd, J_1 = 8.4, J_2 = 2.1 Hz, H-6′), 8.04 (1H, d, J = 7.8 Hz, H-5), 7.64 (1H, d, J = 8.4 Hz, H-5′), 7.59 (1H, d, J_1 = 7.8, H-7), 7.28 (1H, dd, J_1 = 7.8 Hz, H-6), 7.40 (1H, d, J = 7.8 Hz, H-8), 3.95 (3H, s, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.4 (C-4), 153.1 (C-9), 152.3 (C-4′), 148.9 (C-2), 140.4 (C-3′), 138.7 (C-3), 130.7 (C-7), 130.7 (C-6′), 128.8 (C-2′), 128.2 (C-5), 124.5 (C-6), 121.9 (C-10), 120.9 (C-1′), 117.6 (C-8), 113.8 (C-5′), 56.2 (OCH_3). DCI-HRMS $[M + H]^+$ calcd. for $(C_{16}H_{12}NO_6)^+$: 314.0665, found: 316.0668.

4.2.4. 3-hydroxy-2-(3-methylthiophen-2-yl)-4H-chromen-4-one (*4*)

Orange solid, yield: 87%, mp: 260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.04 (1H, d, J = 7.5 Hz, H-5), 7.53 (2H, s, H-7, H-4′), 7.28 (1H, m, H-6), 7.23 (1H, m, H-8), 6.91 (1H, d, J = 4.1 Hz, H-3′),2.69 (3H, s, H-5′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 177.4 (C-4), 153.2 (C-9), 145.1 (C-2), 132.4 (C-3), 132.4 (C-7), 131.1 (C-4′), 131.0 (C-1′), 131.0 (C-2′), 129.4 (C-3′), 125.2 (C-5), 122.4 (C-10), 124.2 (C-6), 118.1 (C-8), 17.6 (C-5′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{14}H_{11}O_3S)^+$: 259.0429, found: 259.0438.

4.2.5. 3-hydroxy-2-(4′-methoxy-[1,1′-biphenyl]-4-yl)-4H-chromen-4-one (*5*)

Yellow solid, yield: 87%, mp: 195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.58 (2H, d, J = 8.7 Hz, H-2′, H-6′), 8.11 (10*H*, m, H-5, H-6, H-7, H-8, H-3′, H-5′, H-8′, H-9′, H-11′, H-12′), 3.84 (3H, s, H-13′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 173.5 (C-4), 160.3 (C-10′), 159.3 (C-9), 146.0 (C-2), 130.6 (C-3), 130.0–114.7 (11C-ar), 55.6 (C-13′). DCI- HRMS

$[M + H]^+$ calcd. for $(C_{22}H_{17}O_4)^+$: 345.1127, found: 345.1133.

4.2.6. 3-hydroxy-2-(4-morpholinophenyl)-4H-chromen-4-one (6)

Orange solid, yield: 67%, mp: 280 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.18 (2H, d, J = 8.7 Hz, H-2′, H-6′), 8.12 (1H, d, J = 7.8 Hz, H-5), 7.79 (1H, m, H-7), 7.13 (2H, d, J = 8.7 Hz, H-3′, H-5′), 6.80 (1H, dd, J_1 = 7.8, J_2 = 1.8 Hz, H-6), 6.68 (1H, dd, J_1 = 8.7, J_2 = 1.8 Hz, H-8), 3.79 (4H, m, H-8′), 3.30 (4H, m, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 172.7 (C-4), 152.1 (C-9), 151.5 (C-4′), 148.6 (C-2), 138.2 (C-3), 133.7 (C-7), 129.3 (C-2′, C-6′), 125.1 (C-5), 124.8 (C-6), 121.8 (C-10), 121.3 (C-1′), 117.8 (C-8), 114.2 (C-3′, C-5′), 66.7 (C-8′), 47.6 (C-7′). DCI-HRMS $[M + H]^+$ calcd. for $(C_{19}H_{18}NO_4)^+$: 324.1236, found: 324.1243.

4.2.7. 3-hydroxy-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one (7)

Yellow solid, yield: 43%, mp: 210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.95 (1H, s, H-2′), 8.40 (1H, d, J = 8.4 Hz, H-6′), 8.07 (1H, dd, J_1 = 8.7, J_2 = 1.2 Hz, H-5), 7.65–7.60 (2H, m, H-6, H-8), 7.52 (1H, t, J = 8.1 Hz, H-5′), 7.31 (1H, m, H-7), 7.10 (1H, m, H-4′), 6.50 (1H, s, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 180.5 (C-4), 154.1 (C-3′), 153.8 (C-9), 148.4 (C-2), 138.0 (C-3), 131.8 (C-7), 129.6 (C-5′), 129.6 (C-1′), 125.3 (C-5), 122.7 (C-6), 122.4 (C-10), 121.5 (C-4′), 118.5 (C-2′), 118.3 (C-6′), 118.3 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-7′), 108.9 (C-8), 108.4 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{11}F_4O_4)^+$: 355.0593, found: 355.0596.

4.2.8. 6-bromo-3-hydroxy-2-(4-isopropylphenyl)-4H-chromen-4-one (8)

Yellow solid, yield: 81%, mp: 228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.30 (2H, d, J = 8.4 Hz, H-2′, H-6′), 8.16 (1H, d, J = 2.4 Hz, H-5), 7.87 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.72 (1H, d, J = 9.0 Hz, H-8), 7.39 (2H, d, J = 8.4 Hz, H-3′, H-5′), 3.02 (1H, sept, J = 6.9 Hz, H-7′), 1.26 (6H, d, J = 6.9 Hz, H-8′, H-9′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 174.8 (C-4), 153.3 (C-9), 149.4 (C-2), 145.8 (C-4′), 135.3 (C-3), 134.1 (C-7), 129.6 (C-5), 127.2 (C-2′, C-6′), 126.4 (C-1′), 126.6 (C-3′, C-5′), 125.5 (C-10), 121.4 (C-8), 116.2 (C-6), 33.8 (C-7′), 24.1 (C-8′, C-9′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{18}H_{16}BrO_3)^+$: 359.0283, found: 359.0292.

4.2.9. 6-bromo-3-hydroxy-2-(4-(trifluoromethyl)phenyl)-4H-chromen-4-one (9)

Red solid, yield: 88%, mp: 270 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.87 (2H, d, J = 8.4 Hz, H-3′,5′), 8.11 (1H, d, J = 2.4 Hz, H-5), 7.71 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.71 (2H, d, J = 8.4 Hz, H-2′,6′), 7.64 (1H, d, J = 9.0 Hz, H-8). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.5 (C-4), 154.9 (C-9), 141.8 (C-2), 139.3 (C-3), 139.3 (C-1′), 133.9 (C-7), 127.0 (C-5), 125.1 (q, $^2J_{CF}$ = 31.0 Hz, C-4′), 124.9 (q, $^1J_{CF}$ = 270.1 Hz, C-7′), 124.7 (q, $^3J_{CF}$ = 3.6 Hz, C-3′,5′), 124.5 (C-2′, C-6′), 122.7 (C-10), 121.1 (C-8), 114.5 (C-6). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_9BrF_3O_3)^+$: 384.9687, found: 384.9680.

4.2.10. 6-bromo-2-(4-butoxyphenyl)-3-hydroxy-4H-chromen-4-one (10)

Yellow solid, yield: 69%, mp: 288 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.60 (2H, d, J = 8.7 Hz, H-2′, H-6′), 8.12 (1H, d, J = 2.4 Hz, H-5), 7.71 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.70 (1H, d, J_1 = 9.0 Hz, H-8), 7.00 (2H, d, J = 8.7 Hz, H-3′, H-5′), 4.03 (2H, t, J = 6.3 Hz, H-7′), 1.77 (2H, q, J = 6.3 Hz, H-8′), 1.53 (2H, six, J = 7.5 Hz, H-9′), 0.98 (3H, t, J = 7.5 Hz, H-10′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 175.9 (C-4), 158.0 (C-4′), 152.6 (C-9), 145.1 (C-2), 133.6 (C-7), 133.6 (C-3), 127.6 (C-5), 127.6 (C-6), 127.6 (C-2′, C-6′), 127.5 (C-10), 123.4 (C-1′), 121.1 (C-8), 114.3 (C-3′, C-5′), 67.5 (C-7′), 31.3 (C-8′), 19.2 (C-9′), 14.2 (C-10′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{19}H_{18}BrO_4)^+$: 389.0310, found: 389.0399.

4.2.11. 6-bromo-2-(2,3-dihydrobenzofuran-5-yl)-3-hydroxy-4H-chromen-4-one (11)

Yellow solid, yield: 67%, mp: 222 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.61 (1H, s, H-2′), 8.44 (1H, d, J = 7.8 Hz, H-6′), 8.08 (1H, d, J = 2.4 Hz, H-5), 7.68–7.44 (2H, m, H-7, H-8), 6.82 (1H, d, J = 7.2 Hz, H-5′), 4.95 (2H, t, J = 8.7 Hz, H-7′), 3.24 (2H, t, J = 8.7 Hz, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 177.4 (C-4), 159.2 (C-9), 152.5 (C-4′), 145.5 (C-2), 133.4 (C-3), 133.4 (C-7), 127.9 (C-6), 127.7 (C-5), 126.3 (C-2′), 126.2 (C-3′), 123.4 (C-6′), 123.1 (C-1′), 121.1 (C-10), 115.0 (C-8), 108.9 (C-5′), 71.6 (C-7′),29.6 (C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{12}BrO_4)^+$: 358.9919, found: 358.9903

4.2.12. 6-bromo-3-hydroxy-2-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (12)

Yellow solid, yield: 92%, mp: 280 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 9.56 (1H, d, J = 2.1 Hz, H-2′), 8.65 (1H, d, J = 9.0 Hz, H-6′), 8.08 (1H, d, J = 2.1 Hz,H-5), 7.68 (1H, dd, J_1 = 8.7, J_2 = 2.1 Hz, H-7), 7.65 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-5′),7.39 (1H, d, J = 8.7 Hz, H-8), 3.94 (3H, s,OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.7 (C-4), 153.5 (C-9), 152.5 (C-4′), 149.2 (C-2), 141.2 (C-3′), 138.9 (C-3), 133.0 (C-7), 129.0 (C-6′), 128.4 (C-5), 128.4 (C-2′), 126.5 (C-6), 126.5 (C-10), 120.7 (C-1′), 114.1 (C-8), 113.6 (C-5′), 56.5 (OCH_3). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_{11}BrNO_6)^+$: 391.9770, found: 391.9769.

4.2.13. 6-bromo-2-(4-chlorophenyl)-3-hydroxy-4H-chromen-4-one (13)

Yellow solid, yield: 69%, mp: 275 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.74 (2H, d, J = 9.0 Hz, H-2′, H-6′), 8.12 (1H, d, J = 2.4 Hz, H-5), 7.71 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.63 (1H, d, J = 9.0 Hz, H-8), 7.44 (2H, d, J = 9.0 Hz, H-3′, H-5′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.3 (C-4), 154.1 (C-9), 152.7 (C-2), 142.9 (C-7), 134.7 (C-3), 133.7 (C-5), 130.1 (C-4′), 129.8 (C-6), 128.1 (C-2′, C-6′), 127.1 (C-1′), 126.7 (C-3′, C-5′), 123.1 (C-10), 114.7 (C-8). DCI- HRMS $[M + H]^+$ calcd. for $(C_{15}H_9BrClO_3)^+$: 350.9424, found: 350.9423.

4.2.14. 6-bromo-3-hydroxy-2-(3-methylthiophen-2-yl)-4H-chromen-4-one (14)

Orange solid, yield: 77%, mp: 288 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.10 (1H, d, J = 2.4 Hz, H-5), 7.66 (1H, dd, J_1 = 8.7, J_2 = 2.4 Hz, H-7), 7.55 (1H, d, J = 8.7 Hz, H-8), 7.23 (1H, d, J = 5.1 Hz, H-4′), 6.92 (1H, d, J = 5.1 Hz, H-3′), 2.7 (3H, s, H-5′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 176.4 (C-4), 151.7 (C-9), 145.9 (C-2), 136.5 (C-3), 132.8 (C-7), 132.0 (C-4′), 131.0 (C-1′), 131.0 (C-2′), 127.0 (C-5), 124.3 (C-6), 123.9 (C-3′), 123.9 (C-10), 114.8 (C-8), 17.7 (C-5′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{14}H_{10}BrO_3S)^+$: 336.9534, found: 336.9526.

4.2.15. 6-bromo-2-(4-(diethoxymethyl)phenyl)-3-hydroxy-4H-chromen-4-one (15)

Orange solid, yield: 64%, mp: 215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.65 (2H, d, J = 8.4 Hz, H-2′, H-6′), 8.11 (1H, d, J = 2.4 Hz, H-5), 7.68 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.61 (1H, d, J = 9.0 Hz, H-8), 7.40 (2H, d, J = 8.4 Hz, H-3′, H-5′), 5.47 (1H, s, H-7′), 3.58 (4H, q, J = 7.2 Hz, H-8′), 1.16 (6H, t, J = 7.2 Hz, H-9′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.6 (C-4), 153.0 (C-9), 143.5 (C-2), 152.6 (C-4′), 136.1 (C-1′), 135.1 (C-3), 133.1 (C-7), 126.6 (C-6), 125.8 (C-5), 124.5 (C-2′, C-6′), 122.6 (C-3′, C-5′), 120.7 (C-10), 114.2 (C-8), 100.9 (C-7′),60.5 (C-8′), 15.1 (C-9′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{20}H_{20}BrO_5)^+$: 419.0494, found: 419.0498.

4.2.16. 6-bromo-3-hydroxy-2-(4-(methylthio)phenyl)-4H-chromen-4-one (16)

Yellow solid, yield: 76%, mp: 230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.70 (2H, d, J = 9.0 Hz, H-2′, H-6′), 8.12 (1H, d, J = 2.1 Hz, H-5), 7.68 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-7), 7.62 (1H, d, J = 9.0 Hz, H-8), 7.29 (2H, d, J = 9.0 Hz, H-3′, H-5′), 2.51 (3H, s, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.2 (C-4), 154.3 (C-9), 152.5 (C-4′), 143.9 (C-2), 135.1 (C-3), 133.2 (C-7), 132.8 (C-1′), 130.3 (C-6), 127.0 (C-5), 125.8 (C-2′, C-6′), 125.6 (C-3′, C-5′), 121.1 (C-10), 114.5 (C-8), 15.2 (C-7′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_{12}BrO_3S)^+$: 362.9691, found: 362.9689.

*4.2.17. 6-bromo-2-(4-ethyl-3-nitrophenyl)-3-hydroxy-4H-chromen-4-one **(17)***

Yellow solid, yield: 88%, mp: 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 9.54 (1H, d, J = 1.5 Hz,H-2′), 8.59 (1H, dd, J_1 = 8.1, J_2 = 1.5 Hz, H-6′), 8.10 (1H, d, J = 2.1 Hz, H-5), 7.73 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-7), 7.66 (1H, d, J = 9.0 Hz, H-8), 7.53 (1H, d, J = 8.1 Hz, H-5′),2.86 (2H, q, J = 7.5 Hz, H-7′), 1.26 (3H, t, J = 7.5 Hz, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.3 (C-4), 154.0 (C-9), 149.5 (C-2), 141.6 (C-3′), 135.0 (C-3), 134.5 (C-4′), 134.1 (C-7), 131.0 (C-5′), 128.1 (C-6′), 127.1 (C-5), 127.1 (C-10), 123.0 (C-6), 121.3 (C-1′), 120.3 (C-2′), 114.8 (C-8), 25.5 (C-7′), 15.4 (C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{13}BrNO_5)^+$: 389.9977, found: 389.9986.

*4.2.18. 6-bromo-3-hydroxy-2-(4-morpholinophenyl)-4H-chromen-4-one **(18)***

Orange solid, yield: 60%, mp: 215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.52 (2H, d, J = 8.4 Hz, H-2′, H-6′), 8.12 (1H, d, J = 2.1 Hz, H-5), 7.72 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.64 (1H, d, J = 9.0 Hz, H-8), 7.01 (2H, d, J = 8.4 Hz, H-3′, H-5′), 3.78 (4H, m, H-8′), 3.21 (4H, m, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 176.6 (C-4), 152.6 (C-9), 150.2 (C-4′), 149.3 (C-2), 133.7 (C-3), 133.6 (C-7), 127.4 (C-5), 127.4 (C-2′, C-6′), 126.9 (C-10), 123.5 (C-6), 121.1 (C-1′), 115.2 (C-8), 114.4(C-3′, C-5′), 66.5 (C-8′), 48.2 (C-7′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{19}H_{17}BrNO_4)^+$: 402.0341, found: 402.0341.

*4.2.19. 6-bromo-3-hydroxy-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one **(19)**.*

Yellow solid, yield: 60%, mp: 215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.86 (1H, s, H-2′), 8.37 (1H, d, J = 8.4 Hz, H-6′), 8.12 (1H, d, J = 2.4 Hz, H-5), 7.76 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.68 (1H, d, J = 9.0 Hz, H-8), 7.54 (1H, t, J = 8.1 Hz, H-5′), 7.15 (1H, m, H-4′), 6.62 (1H, m, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.6 (C-4), 152.9 (C-9), 152.9 (C-3′), 142.5 (C-2), 137.3 (C-3), 134.3 (C-7), 129.8 (C-5′), 129.8 (C-1′), 1274.1 (C-5), 123.0 (C-10), 123.0 (C-6), 121.4 (C-4′), 119.2 (C-2′), 118.7 (C-6′), 118.7 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-7′), 115.0 (C-8), 108.0 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-8′). DCI-HRMS $[M + H]^+$ calcd. for $(C_{17}H_{10}BrF_4O_4)^+$: 432.9699, found: 432.9699.

*4.2.20. 6-bromo-2-(2-fluoro-4-(trifluoromethyl)phenyl)-3-hydroxy-4H-chromen-4-one **(20)***

Red solid, yield: 40%, mp: 165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.19 (1H, d, J = 2.4 Hz, H-5), 8.13 (1H, d, J = 2.4 Hz, H-5′), 7.95 (1H, d, J = 9.0 Hz, H-2′), 7.83 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.71 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-2′), 7.49 (1H, d, J = 9.0 Hz, H-8). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.3 (C-4), 159.4 (C-2), 157.7 (C-6′), 153.7 (C-9), 145.2 (C-7), 135.2 (C-3), 134.2 (C-5), 132.5 (m, C-4′), 131.1 (d, $^1J_{CF}$ = 270.1 Hz,C-2′), 127.2 (C-10), 123.9 (d, $^2J_{CF}$ = 26.2 Hz, C-1′), 123.2 (q, $^1J_{CF}$ = 270.1 Hz, C-7′), 121.4 (m, C-3′), 116.1 (C-6), 114.7 (m, C-5′), 109.1 (C-8). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_8BrF_4O_3)^+$: 402.9593, found: 402.9606.

*4.2.21. 6-chloro-2-(2,3 dihydrobenzofuran-5-yl)-3-hydroxy-4H-chromen-4-one **(21)***

Yellow solid, yield: 60%, mp: 256 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.57 (1H, s, H-2′), 8.40 (1H, d, J = 8.7 Hz, H-6′), 7.87 (1H, d, J = 2.4 Hz, H-5), 7.61 (1H, d, J = 9.0 Hz, H-5′), 7.49 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 6.74 (1H, d, J = 8.7 Hz, H-8), 4.51 (2H, t, J = 8.4 Hz, H-7′), 3.17 (2H, t, J = 8.7 Hz, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 165.3 (C-4), 158.1 (C-9), 151.0 (C-4′), 147.3 (C-2), 136.1 (C-3), 130.6 (C-7), 129.7 (C-6), 126.8 (C-2′), 125.2 (C-5), 126.5 (C-3′), 124.1 (C-10), 122.0 (C-6′),121.1 (C-1′), 117.0 (C-8), 107.7 (C-5′), 71.4 (C-7′),30.0 (C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{12}ClO_4)^+$: 315.0424, found: 315.0427.

*4.2.22. 6-chloro-2-(4-chlorophenyl)-3-hydroxy-4H-chromen-4-one **(22)***

Yellow solid, yield: 55%, mp: 260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.70 (2H, d, J = 9.0 Hz, H-2′, H-6′), 7.97 (1H, d, J = 2.4 Hz, H-5), 7.72 (1H, d, J = 9.0 Hz, H-8), 7.63 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.46 (2H, d, J = 9.0 Hz, H-3′, H-5′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.8 (C-4), 152.5 (C-9), 143.0 (C-2), 134.3 (C-3), 131.6 (C-7), 131.4 (C-5), 130.5 (C-4′), 129.8 (C-6), 128.2 (C-2′, C-6′), 127.1 (C-1′), 126.9 (C-3′, C-5′), 123.8 (C-10), 121.1 (C-8). DCI- HRMS $[M + H]^+$ calcd. for $(C_{15}H_9Cl_2O_3)^+$: 306.9929, found: 306.9923.

*4.2.23. 6-chloro-3-hydroxy-2-(3-methylthiophen-2-yl)-4H-chromen-4-one **(23)***

Orange solid, yield: 69%, mp: 270 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 7.98 (1H, d, J = 2.4 Hz,H-5), 7.62 (1H, d, J = 9.0 Hz, H-8), 7.55 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.23 (1H, d, J = 5.1 Hz, H-4′), 6.92 (1H, d, J = 5.1 Hz, H-3′), 2.71 (3H, s, H-5′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 175.1 (C-4), 150.1 (C-9), 149.9 (C-2), 144.4 (C-2′), 135.0 (C-3), 134.6 (C-7), 130.8 (C-1′), 128.8 (C-5), 129.6 (C-4′), 127.9 (C-6), 122.8 (C-10), 121.9 (C-3′), 119.1 (C-8), 16.3 (C-5′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{14}H_{10}ClO_3S)^+$: 293.0039, found: 293.0036.

*4.2.24. 6-chloro-2-(4-(diethoxymethyl)phenyl)-3-hydroxy-4H-chromen-4-one **(24)***

Orange solid, yield: 56%, mp: 215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.57 (2H, d, J = 8.4 Hz, H-2′, H-6′), 7.95 (1H, d, J = 2.4 Hz, H-5), 7.67 (1H, d, J = 9.0 Hz, H-8), 7.55 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.39 (2H, d, J = 8.4 Hz, H-3′, H-5′), 5.46 (1H, s, H-7′), 3.52 (4H, q, J = 6.3 Hz, H-8′), 1.16 (6H, t, J = 6.3 Hz, H-9′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.4 (C-4), 152.9 (C-9), 151.2 (C-1), 142.7 (C-3),), 135.5 (C-7), 134.7 (C-4′), 129.8 (C-1′), 129.8 (C-6), 125.6 (C-5), 125.1 (C-2′, C-6′), 123.7 (C-3′, C-5′), 122.7 (C-10), 119.8 (C-8), 100.3 (C-7′),59.9 (C-8′), 14.5 (C-9′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{20}H_{20}ClO_5)^+$: 375.0999, found: 375.1002.

*4.2.25. 6-chloro-3-hydroxy-2-(4-(trifluoromethyl)phenyl)-4H-chromen-4-one **(25)***

Red solid, yield: 76%, mp: 275 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.83 (2H, d, J = 8.4 Hz, H-3′,5′), 7.95 (1H, d, J = 2.4 Hz, H-5), 7.66 (1H, d, J = 9.0 Hz, H-8), 7.66 (2H, d, J = 8.4 Hz, H-2′, H-6′), 7.57 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.6 (C-4), 154.7 (C-9), 141.9 (C-2), 139.3 (C-3), 139.3 (C-1′), 131.4 (C-7), 131.4 (C-6), 126.7 (C-5), 125.1 (q, $^2J_{CF}$ = 31.2 Hz, C-4′), 124.9 (q, $^1J_{CF}$ = 270.7 Hz, C-7′), 124.7 (q, $^3J_{CF}$ = 3.8 Hz, C-3′,5′), 124.6 (C-2′,6′), 122.1 (C-10), 120.9 (C-8). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_9ClF_3O_3)^+$: 341.0192, found: 341.0187.

*4.2.26. 6-chloro-3-hydroxy-2-(4′-methoxy-[1,1′-biphenyl]-4-yl)-4H-chromen-4-one **(26)***

Yellow solid, yield: 67%, mp: 180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.67 (2H, d, J = 8.1 Hz, H-2′, H-6′), 8.14 (1H, s, H-5), 7.72–7.63 (6H, m, H-7, H-8, H-8′, H-9′, H-11′, H-12′), 3.82 (3H, s, H-13′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 177.5 (C-4), 159.3 (C-10′), 152.9 (C-9), 144.5 (C-2), 133.2 (C-3), 130.1–114.7 (11C-ar), 55.6 (C-13′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{22}H_{16}ClO_4)^+$: 379.0737, found: 379.0729.

*4.2.27. 6-chloro-3-hydroxy-2-(4-(methylthio)phenyl)-4H-chromen-4-one **(27)***

Yellow solid, yield: 72%, mp: 210 °C; ^{1}H NMR(300 MHz, DMSO-d_6) δ_H: 8.68 (2H, d, J = 8.7 Hz, H-2′, H-6′), 7.98 (1H, d, J = 2.4 Hz, H-5), 7.70 (1H, d, J = 9.0 Hz, H-8), 7.58 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.30 (2H, d, J = 8.4 Hz, H-3′, H-5′), 2.51 (3H, s, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.0 (C-4), 153.5 (C-9), 152.2 (C-4′), 144.0 (C-2), 135.6 (C-3), 132.6 (C-7), 130.8 (C-6), 126.5 (C-5), 125.8 (C-2′, C-6′), 125.8 (C-3′, C-5′), 122.6 (C-1′), 120.9 (C-10), 120.9 (C-8), 15.2 (C-7′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_{12}ClO_3S)^+$: 319.0196, found: 319.0196.

*4.2.28. 6-chloro-2-(4-ethyl-3-nitrophenyl)-3-hydroxy-4H-chromen-4-one **(28)***

Yellow solid, yield: 76%, mp: 260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 9.58 (1H, s, H-2′), 8.60 (1H, d, J = 6.0 Hz, H-6′), 7.96 (1H, s, H-5), 7.72 (1H, d, J = 6.9 Hz, H-7), 7.52 (2H, m, H-8, H-5′), 2.83 (2H, q, J = 7.5 Hz, H-7′), 1.24 (3H, t, J = 7.5 Hz, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.8 (C-4), 155.0 (C-9), 152.4 (C-2), 149.6 (C-3′), 141.5 (C-4′), 135.2 (C-3), 134.2 (C-7), 131.4 (C-5′), 130.7 (C-6′), 130.7 (C-6), 127.8 (C-5), 126.9 (C-10), 122.2 (C-1′), 120.8 (C-2′), 120.0 (C-8), 25.5 (C-7′), 15.4 (C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{13}ClNO_5)^+$: 346.0482, found: 346.0486.

*4.2.29. 6-chloro-3-hydroxy-2-(4-morpholinophenyl)-4H-chromen-4-one **(29)***

Orange solid, yield: 56%, mp: 200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.53 (2H, d, J = 9.0 Hz, H-2′, H-6′), 7.96 (1H, d, J = 2.4 Hz, H-5), 7.72 (1H, d, J = 9.0 Hz, H-8), 7.61 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.02 (2H, d, J = 9.0 Hz, H-3′, H-5′), 3.79 (2H, m, H-8′), 3.22 (2H, m, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 176.8 (C-4), 154.6 (C-2), 152.2 (C-9), 150.2 (C-4′), 137.8 (C-3), 131.9 (C-7), 129.0 (C-6), 127.3 (C-5), 127.3 (C-2′, C-6′), 122.9 (C-10), 120.8 (C-8), 114.4 (C-3′, C-5′), 113.6 (C-1′), 66.5 (C-8′), 48.3 (C-7′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{19}H_{17}ClNO_4)^+$: 358.0846, found: 358.0853.

*4.2.30. 6-chloro-3-hydroxy-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one **(30)***

Yellow solid, yield: 66%, mp: 245 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.90 (1H, s, H-2′), 8.38 (1H, d, J = 8.1 Hz, H-6′), 7.97 (1H, d, J = 2.4 Hz, H-5), 7.75 (1H, d, J = 9.0 Hz, H-8), 7.64 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.54 (1H, t, J = 8.1 Hz, H-5′), 7.14 (1H, m, H-4′), 6.56 (1H, m, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.8 (C-4), 153.1 (C-9), 152.5 (C-3′), 148.4 (C-2), 137.5 (C-3), 131.6 (C-7), 129.7 (C-5′), 127.1 (C-5), 129.7 (C-1′), 129.7 (C-6), 122.8 (C-10), 121.1 (C-4′), 119.0 (C-2′), 118.2 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-7′), 119.0 (C-6′), 118.6 (C-8), 108.4 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{10}ClF_4O_4)^+$: 389.0204, found: 389.0209.

*4.2.31. 6-chloro-2-(2-fluoro-4-(trifluoromethyl)phenyl)-3-hydroxy-4H-chromen-4-one **(31)***

Red solid, yield: 55%, mp: 185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.05 (1H, d, J = 2.4 Hz, H-5), 7.98 (1H, d, J = 2.4 Hz, H-5′), 7.93 (1H, d, J = 9.0 Hz, H-2′), 7.72 (1H, dd, J_1 = 9.0, J_2 = 2.4 Hz, H-7), 7.64–7.52 (2H, m, H-2′, H-8). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 179.4 (C-4), 159.5 (C-2), 157.7 (C-6′), 153.9 (C-9), 145.2 (C-7), 132.6 (C-3), 131.6 (C-5), 131.1 (C-4′), 131.1 (C-2′), 128.3 (C-6), 127.0 (C-10), 124.0 (C-1′), 123.4 (C-7′), 121.2 (C-3′), 114.5 (C-5′), 109.2 (C-8). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_8ClF_4O_3)^+$: 359.0098, found: 359.0087.

*4.2.32. 2-(2,3-dihydrobenzofuran-5-yl)-6-fluoro-3-hydroxy-4H-chromen-4-one **(32)***

Yellow solid, yield: 43%, mp: 260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.55 (1H, d, J = 2.1 Hz, H-5), 8.39 (1H, dd, J_1 = 8.4, J_2 = 2.1 Hz, H-7), 7.87 (1H, d, J = 3.0 Hz, H-2′), 7.72 (1H, d, J = 9.3 Hz, H-5′), 7.66 (1H, dd, J_1 = 9.0, J_2 = 3.0 Hz, H-6′), 6.83 (1H, d, J = 8.4 Hz, H-8), 4.49 (2H, t, J = 8.7 Hz, H-7′), 3.25 (2H, t, J = 8.7 Hz, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 176.8 (C-4), 158. 7 (C-9), 157.1 (d, $^1J_{CF}$ = 227.7 Hz, C-6), 155.6 (C-4′), 148.2 (C-2), 144.6 (C-3), 126.3 (C-3′), 125.9 (C-2′), 122.6 (d, $^2J_{CF}$ = 26.0 Hz, C-7), 121.8 (C-6′),121.7 (C-8), 120.3 (C-10), 120.2 (C-1′), 119.1 (C-5′), 118.7 (d, $^2J_{CF}$ = 26.0 Hz, C-5), 70.9 (C-7′),29.0 (C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{12}FO_4)^+$: 299.0720, found: 299.0720.

*4.2.33. 6-fluoro-3-hydroxy-2-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one **(33)***

Yellow solid, yield: 75%, mp: 280 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 9.39 (1H, d, J = 2.1 Hz, H-2′), 8.63 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-6′), 7.80 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-5), 7.70 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-7), 7.56 (1H, m, H-5′),7.49 (1H, d, J = 9.0 Hz, H-8), 3.98 (3H, s, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.2 (C-4), 158.0 (d, $^1J_{CF}$ = 227.7 Hz, C-6), 156.4 (C-9), 150.7 (C-4′), 150.0 (C-2), 142.2 (C-3′), 139.5 (C-3), 130.6 (C-6′), 127.8 (C-2′), 122.8 (d, $^2J_{CF}$ = 26.0 Hz, C-7), 122.3 (C-10), 121.3 (C-1′), 120.9 (d, $^2J_{CF}$ = 26.0 Hz, C-5), 120.3 (C-8), 114.4 (C-5′), 57.1 (OCH_3). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_{11}FNO_6)^+$: 332.0570, found: 332.0573.

*4.2.34. 2-(4-butoxyphenyl)-6-fluoro-3-hydroxy-4H-chromen-4-one **(34)***

Yellow solid, yield: 40%, mp: 156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.51 (2H, d, J = 9.3 Hz, H-2′, H-6′), 7.77 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-5), 7.71 (1H, dd, J_1 = 9.0, J_2 = 3.0 Hz, H-8), 7.55 (1H, m, H-7), 7.03 (2H, d, J = 9.3 Hz, H-3′, H-5′), 4.04 (2H, t, J = 6.6 Hz, H-7′), 1.77 (2H, q, J = 6.6 Hz, H-8′), 1.53 (2H, six, J = 7.5 Hz, H-9′), 0.98 (3H, t, J = 7.5 Hz, H-10′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 176.8 (C-4), 158.6 (C-4′), 158.1 (d, $^1J_{CF}$ = 227.7 Hz, C-6), 156.5 (C-9), 147.3 (C-2), 145.4 (C-3), 128.1 (C-2′, C-6′), 126.8 (C-10), 122.6 (d, $^2J_{CF}$ = 26.0 Hz, C-7), 122.5 (C-1′), 121.1 (C-8), 119.9 (d, $^2J_{CF}$ = 26.0 Hz, C-5), 114.4 (C-3′, C-5′), 67.6 (C-7′), 31.2 (C-8′), 19.2 (C-9′), 14.2 (C-10′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{19}H_{18}FO_4)^+$: 329.1189, found: 329.1187.

*4.2.35. 6-fluoro-3-hydroxy-2-(4-(methylthio)phenyl)-4H-chromen-4-one **(35)***

Yellow solid, yield: 67%, mp: 190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.44 (2H, d, J = 8.4 Hz, H-2′, H-6′), 7.80 (1H, dd, J_1 = 9.0, J_2 = 3.0 Hz, H-5), 7.73 (1H, dd, J_1 = 8.7, J_2 = 3.0 Hz, H-8), 7.60 (1H, m, H-7), 7.37 (2H, d, J = 8.4 Hz, H-3′, H-5′), 2.54 (3H, s, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 176.1 (C-4), 158.2 (d, $^1J_{CF}$ = 227.7 Hz, C-6), 156.6 (C-9), 146.1 (C-2), 144.9 (C-4′), 138.6 (C-3), 127.1 (C-2′, C-6′), 125.7 (C-3′, C-5′), 122.6 (C-10), 122.9 (d, $^2J_{CF}$ = 26.0 Hz, C-7), 122.5 (C-1′), 121.3 (C-8), 119.1 (d, $^2J_{CF}$ = 26.0 Hz, C-5), 14.9 (C-7′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_{12}FO_3S)^+$: 303.0491, found: 303.0477.

*4.2.36. 6-fluoro-3-hydroxy-2-(4-morpholinophenyl)-4H-chromen-4-one **(36)***

Orange solid, yield: 40%, mp: 190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.52 (2H, d, J = 8.4 Hz, H-2′, H-6′), 7.78 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-5), 7.87 (1H, dd, J_1 = 9.0, J_2 = 2.1 Hz, H-7), 7.66 (1H, dd, 9.0, J_2 = 2.1 Hz, H-8), 7.10 (2H, d, J = 8.4 Hz, H-3′, H-5′), 3.78 (2H, m, H-8′), 3.27 (2H, m, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 172.0 (C-4), 157.1 (d, $^1J_{CF}$ = 227.7 Hz, C-6), 152.2 (C-9), 150.1 (C-4′), 146.1 (C-2), 137.9 (C-3), 129.4 (C-2′, C-6′), 129.4 (C-10), 121.4 (d, $^2J_{CF}$ = 26.0 Hz, C-7), 121.3 (C-1′), 121.0 (C-8), 119.4 (d, $^2J_{CF}$ = 26.0 Hz, C-5), 114.2 (C-3′, C-5′), 66.4 (C-8′), 47.6 (C-7′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{19}H_{17}FNO_4)^+$: 342.1142, found: 342.1152.

*4.2.37. 6-fluoro-3-hydroxy-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one **(37)***

Yellow solid, yield: 77%, mp: 185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.80 (1H, s, H-2′), 8.37 (1H, d, J = 8.4 Hz, H-6′), 7.80 (1H, dd, J_1 = 9.0, J_2 = 3.0 Hz, H-5), 7.80 (1H, dd, J_1 = 9.3, J_2 = 3.0 Hz, H-7), 7.70 (1H, dd, J_1 = 9.3, J_2 = 3.0 Hz, H-8), 7.54 (1H, t, J = 8.1 Hz, H-5′), 7.15 (1H, m, H-4′), 6.62 (1H, m, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 178.5 (C-4), 157.9 (d, $^1J_{CF}$ = 227.7 Hz, C-6), 156.3 (C-3′), 150.8 (C-9), 148.4 (C-2), 137.0 (C-3), 129.9 (C-5′), 123.7 (C-1′), 122.2 (d, $^2J_{CF}$ = 26.0 Hz, C-7), 121.4 (C-10), 121.2 (C-8), 120.8 (C-6′), 119.7 (C-4′), 122.9 (C-2′), 120.1 (d, $^2J_{CF}$ = 26.0 Hz, C-5), 119.0 (C-2′), 119.0 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-7′), 109.0 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0, Hz, C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{17}H_{10}F_5O_4)^+$: 373.0499, found: 373.0491.

*4.2.38. 2-(4-butoxyphenyl)-3-hydroxy-6-methoxy-4H-chromen-4-one **(38)***

Yellow solid, yield: 60%, mp: 160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.22 (2H, d, J = 9.0 Hz, H-2′, H-6′), 7.56 (1H, d, J = 3.0 Hz, H-5), 7.52 (1H, d, J = 9.0 Hz, H-8), 7.31 (1H, dd, J_1 = 9.0, J_2 = 3.0 Hz, H-7), 7.05 (2H, d, J = 9.0 Hz, H-3′, H-5′), 4.07 (2H, t, J = 6.9 Hz, H-7′), 3.91 (3H, s, OCH_3), 1.83 (2H, q, J = 6.9 Hz, H-8′), 1.56 (2H, six, J = 7.5 Hz, H-9′), 0.99 (3H, t, J = 7.5 Hz, H-10′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 172.9 (C-4), 156.1 (C-4′), 153.0 (C-9), 150.0 (C-6), 145.1 (C-2), 131.0 (C-3), 129.1 (C-2′, C-6′), 123.8 (C-1′), 123.0 (C-10), 120.8 (C-7), 119.3 (C-3′, C-5′), 114.2 (C-8), 103.5 (C-5), 68.0 (C-7′), 55.6 (OCH_3), 31.1 (C-8′), 18.5 (C-9′), 13.5 (C-10′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{20}H_{21}O_5)^+$: 341.1389, found: 341.1396.

*4.2.39. 3-hydroxy-2-(4-isopropylphenyl)-6-methoxy-4H-chromen-4-one **(39)***

Yellow solid, yield: 57%, mp: 215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.09 (2H, d, J = 8.7 Hz, H-2′, H-6′), 7.47 (1H, d, J = 3.0 Hz, H-5), 7.42 (1H, d, J = 8.7 Hz, H-8), 7.31 (2H, d, J = 8.7 Hz, H-3′, H-5′), 7.22 (1H, dd, J_1 = 8.7, J_2 = 3.0 Hz, H-7), 3.82 (3H, s, OCH_3), 2.92 (1H, sept, J = 6.9 Hz, H-7′), 1.22 (6H, d, J = 6.9 Hz, H-8′, H-9′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 172.9 (C-4), 156.7 (C-9), 150.4 (C6), 151.2 (C-4′), 145.2 (C-2), 137.8 (C-3), 128.6 (C-1′), 127.7 (C-2′, C-6′), 126.6 (C-3′, C-5′), 124.2 (C-10), 119.6 (C-7), 119.6 (C-8), 103.7 (C-5), 55.8 (OCH_3), 34.1 (C-7′),23.7 (C-8′, C-9′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{19}H_{19}O_4)^+$: 311.1283, found: 311.1289.

*4.2.40. 3-hydroxy-6-methoxy-2-(pyridin-4-yl)-4H-chromen-4-one **(40)***

Orange solid, yield: 30%, mp: 244 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.49–8.38 (4H, m, H-2′, H-3′, H-5′,H-6′), 7.57 (1H, d, J = 9.3 Hz, H-8), 7.35 (1H, d, J = 3.3 Hz, H-5), 7.24 (1H, dd, J_1 = 9.3, J_2 = 3.3 Hz, H-7), 3.82 (3H, s, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 180.4 (C-4), 155.6 (C-9), 151.2 (C-6), 149.5 (C-3′, 5′), 142.3 (C-2), 139.9 (C-3), 139.9 (C-1′), 123.7 (C-10), 121.5 (C-7), 120.2 (C-2′, C-6′), 118.1 (C-8),104.1 (C-5), 55.8 (OCH_3). DCI- HRMS $[M + H]^+$ calcd. for $(C_{15}H_{12}NO_4)^+$: 270.0766, found: 270.0768.

*4.2.41. 2-(4-(diethoxymethyl)phenyl)-3-hydroxy-6-methoxy-4H-chromen-4-one **(41)***

Orange solid, yield: 60%, mp: 122 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.59 (2H, d, J = 8.7 Hz, H-2′, H-6′), 7.62 (1H, d, J = 8.7 Hz, H-8), 7.46 (2H, d, J = 8.7 Hz, H-3′, H-5′), 7.42 (1H, d, J = 2.1 Hz, H-5), 7.27 (1H, dd, J_1 = 8.7, J_2 = 2.1 Hz, H-7), 5.52 (1H, s, H-7′), 3.86 (3H, s, OCH_3), 3.61–3.46 (4H, q, J = 6.9 Hz, H-8′), 1.20 (6H, t, J = 6.9 Hz, H-9′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 177.4 (C-4), 153.9 (C-9), 149.0 (C-6), 148.0 (C-2), 136.5 (C-4′), 136.5 (C-1′), 134.0 (C-3), 125.3 (C-2′, C-6′), 124.4 (C-3′, C-5′), 121.0 (C-10), 120.9 (C-7), 119.0 (C-8), 102.9 (C-5), 100.3 (C-7′),59.9 (C-8′), 54.8 (OCH_3), 14.0 (C-9′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{21}H_{23}O_6)^+$: 371.1495, found: 371.1500.

*4.2.42. 2-(2,3-dihydrobenzofuran-5-yl)-3-hydroxy-6-methoxy-4H-chromen-4-one **(42)***

Yellow solid, yield: 49%, mp: 180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.61 (1H, s, H-2′), 8.44 (1H, d, J = 7.8 Hz, H-6′),7.62 (1H, d, J = 8.7 Hz, H-8), 7.42 (1H, d, J = 2.1 Hz, H-5), 7.27 (1H, dd, J_1 = 8.7, J_2 = 2.1 Hz, H-7), 6.82 (1H, d, J = 7.2 Hz, H-5′), 4.61 (2H, t, J = 8.4 Hz, H-7′), 3.84 (3H, s, OCH_3), 3.26 (2H, t, J = 8.4 Hz, H-8′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 175.1 (C-4), 160.5 (C-9), 155.7 (C-6), 149.8 (C-4′), 145.7 (C-2), 136.9 (C-3), 127.8 (C-2′), 125.8 (C-3′), 124.3 (C-10), 122.6 (C-6′), 122.2 (C-7), 122.2 (C-1′),120.1 (C-9), 109.1 (C-5′), 104.1 (C-5), 71.8 (C-7′),56.0 (OCH_3), 29.4 (C-8′). DCI- HRMS $[M + H]^+$ calcd. for $(C_{18}H_{15}O_5)^+$: 311.0919, found: 311.0912.

*4.2.43. 2-(4-chlorophenyl)-3-hydroxy-6-methoxy-4H-chromen-4-one **(43)***

Yellow solid, yield: 53%, mp: 218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.50 (2H, d, J = 8.7 Hz, H-2′, H-6′), 7.62 (1H, d, J = 8.7 Hz, H-8), 7.49 (2H, d, J = 8.7 Hz, H-3′, H-5′), 7.40 (1H, d, J = 3.0 Hz, H-5), 7.29 (1H, dd, J_1 = 8.7, J_2 = 3.0 Hz, H-7), 3.84 (3H, s, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 177.2 (C-4), 155.4 (C-9), 149.5 (C-6), 147.4 (C-2), 138.9 (C-3), 133.2 (C-4′), 131.9 (C-1′), 128.5 (C-2′, C-6′), 128.0 (C-3′, C-5′), 122.7 (C-10), 122.0 (C-7), 120.5 (C-8), 113.6 (C-5), 55.9 (OCH_3). DCI- HRMS $[M + H]^+$ calcd. for $(C_{16}H_{12}ClO_4)^+$: 303.0424, found: 303.0421.

*4.2.44. 3-hydroxy-6-methoxy-2-(4-morpholinophenyl)-4H-chromen-4-one **(44)***

Orange solid, yield: 44%, mp: 180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.17 (2H, d, J = 9.0 Hz, H-2′, H-6′), 7.73 (1H, d, J = 8.7 Hz, H-8), 7.45 (1H, d, J = 3.0 Hz, H-5), 7.41 (1H, dd, J_1 = 9.0, J_2 = 3.0 Hz, H-7), 7.12 (2H, d, J = 9.0 Hz, H-3′, H-5′), 3.89 (3H, s, OCH_3), 3.78 (2H, m, H-8′), 3.30 (2H, m, H-7′). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 172.3 (C-4), 156.3 (C-9), 156.3 (C-4′), 149.7 (C-6), 146.4 (C-2), 137.9 (C-3), 129.2 (C-2′, C-6′), 123.4 (C-7), 122.4 (C-10), 121.4 (C-8), 121.4 (C-1′), 114.2 (C-3′, C-5′), 104.3 (C-5), 66.5 (C-8′), 56.1 (OCH_3), 47.6 (C-7′). DCI-HRMS $[M + H]^+$ calcd. for $(C_{20}H_{20}NO_5)^+$: 354.1341, found: 354.1346.

*4.2.45. 3-hydroxy-6-methoxy-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-4H-chromen-4-one **(45)***

Yellow solid, yield: 55%, mp: 260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.64 (1H, s, H-2′), 8.32 (1H, d, J = 8.1 Hz, H-6′), 7.68 (1H, d, J = 9.0 Hz, H-8), 7.59 (1H, t, J = 8.1 Hz, H-5′), 7.42 (1H, d, J = 2.7 Hz, H-5), 7.33 (1H, dd, J_1 = 9.0, J_2 = 3.0 Hz, H-7), 7.24 (1H, m, H-4′), 6.50 (1H, m, H-8′), 3.87 (3H, s, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 177.4 (C-4), 155.4 (C-3′), 155.4 (C-9), 149.6 (C-6), 148.5 (C-2), 136.4 (C-3), 130.2 (C-5′), 123.6 (C-1′), 122.9 (C-10), 122.0 (C-7), 120.3 (C-8), 120.1 (C-4′), 119.5 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-7′), 118.9 (C-6′), 117.0 (C-2′), 108.3(tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-8′), 104.1 (C-5), 55.9 (OCH_3). DCI- HRMS $[M + H]^+$ calcd. for $(C_{18}H_{13}F_4O_5)^+$: 385.0699, found: 385.0705.

*4.2.46. 3-hydroxy-7,8-dimethoxy-2-(3-(1,1,2,2-tetrafluoroethoxy) phenyl)-4H-chromen-4-one **(46)***

Orange solid, yield: 43%, mp: 160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 8.57 (1H, s, H-2′), 8.33 (1H, d, J = 8.1 Hz, H-6′), 7.83 (1H, d, J = 9.0 Hz, H-5), 7.62 (1H, t, J = 8.1 Hz, H-5′), 7.23 (2H, m, H-4′, H-6), 6.53 (1H, m, H-8′), 3.96, 3.94 (6H, s, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 177.4 (C-4), 155.6 (C-3′), 148.9 (C-9), 148.5 (C-7), 142.1 (C-2), 136.5 (C-3), 136.4 (C-8), 130.2 (C-5′), 130.2 (C-1′), 120.8 (C-4′), 120.1 (C-6′), 118.8 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-7′),118.8 (C-10), 117.0 (C-5), 110.2 (C-2′), 110.2 (tt, $^1J_{CF}$ = 270.1, $^2J_{CF}$ = 31.0 Hz, C-8′), 108.3 (C-6), 61.2, 56.9 (OCH_3). DCI- HRMS $[M + H]^+$ calcd. for $(C_{19}H_{15}F_4O_6)^+$: 415.0805, found: 415.0806.

4.3. 15-lipoxygenase inhibitory

The 15-lipoxygenase inhibitory of 3-hydroxyflavones derivatives (**1–46**) was determined on soybean lipoxygenase with modifications [31]. One concentration (20 µL) of each compound was mixed individually with 150 µL sodium phosphate buffer (pH = 7.4) containing (20 µL) of 5-LOX enzyme and 60 µL of linoleic acid (3.5 mM), yielding a final volume of 250 µL. The mixture was incubated at 25 °C for 10 min, and the absorbance was determined at 234 nm. Nordihydroguaiaretic acid (NDGA) was used as positive control. The percentages of enzyme activity were obtained at 100 µM. All measurements were performed in triplicate.

4.4. Cytotoxic activity

Cytotoxicity of synthesized compounds was estimated against two ovarian cancer cell lines (IGROV and OVCAR) and colon cancer cell line (HCT-116) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [32]. 100 µL of each cells at a

concentration of 104 cells/wells were distributed in 96-well plates and maintained at 37 °C during 24 h in an incubator with 5% CO_2. Then, 100 µL of each compounds (100 µM) diluted on the RPMI-1640 medium were added and the mixture was incubated for 48 h at 37 °C. Then, cells were treated with 50 µL of MTT solution, prepared in phosphate buffered saline (PBS), at a concentration of 1 mg/mL and incubated at 37 °C during 40 min. After that, MTT solution was absorbed and 50 µL of DMSO were added to dissolve insoluble formazan blue crystals. Cell growth was estimated by the determination of optical density at 605 nm. Doxorubicin and Tamoxifen were used as standard.

4.5. Molecule description

DFT is the most efficient way to calculate accurate and reliable electronic properties of molecules. Once the 3D chemical structures of the molecules built and optimized in gas phase using Amsterdam Density Functional(ADF) software [33], DFT calculations were performed with the PBE (Perdew, Burke and Ernzerhof) [34], GGA exchange-correlation functional (Generalized Gradient Approximation) method and a TZP (triple zeta) basis set [35,36]. From these, 10 molecular descriptors were obtained: the energy of the highest occupied molecular orbital (HOMO), the energy of the lowest unoccupied molecular orbital (LUMO), the maximal (q_{max}) and minimal (q_{min}) atomic Mulliken charges, the dipole moment, the vertical electronic affinity (A), the hardness (η = I-A where I is the vertical ionization potential), the electronic chemical potential (μ = -(I + A)/2)), the nucleofugality (λ_N)and electrofugality (λ_E). The results are presented in Table 1.

The physico-chemical properties of all flavonols derivatives have been assessed using Molinspiration software [23] are presented in Table 5. According to Lipinski's rule of five, used as a filter for drug-like properties to predict oral bioavailability, we describe the molecular properties of a compound in order to estimate their pharmacokinetic parameters in the human body, including their absorption, distribution, metabolism and excretion. Most "drug-like" molecules have logP ≤ 5 that means these shows good permeability across cell membrane, number of hydrogen bond acceptors ≤ 10 this measures molecular flexibility, molecular weight ≤ 500, polar surface area (TPSA) < 160 $Å^2$ which displayed to be a good descriptor characterizing drug absorption [37] and number of hydrogen bond donor's ≤ 5 is the sum of OHs and NHs [38]. Molecules violating more than one of these rules decrease the activity and selectivity of a likely drug candidate and therefore make it unlikely orally active in humans.

4.6. Statistical analysis

Data from the experiments were subjected to analysis of variance (ANOVA) using SPSS 16.0 for Windows (*SPSS Inc. Chicago, IL, USA*). The inhibition data relative to 15-lipoxygenase inhibition and cytotoxic activity have been transformed using arcsin- square root (arcsin $\sqrt{x}$) transformation before ANOVA. Means were separated at the 5% significance level by a least significant difference test (*Student's* test).

Linear Discriminant Analysis (LDA) is a multivariate technique first developed by Fisher widely used for pattern classification [39]. LDA allows determining which variables discriminate between several naturally occurring groups. Here, for each measured biological activity (15-lipoxygenase inhibitory, HCT-116, IGROV and OVCAR), the molecules were labeled so as to describe three different classes relatively balanced in size defined by taking into account the range of variation and the whole values measured for each activity (Table 2). LDA was used to investigate the possible classification of the synthesized molecules in these three categories from the available molecular descriptors. XLSTAT software was used here for LDA calculations. More precisely, LDA models were determined by using a stepwise (forward) method: the initial variables used to compute the linear discriminant functions were chosen in a stepwise manner by adding step by step the variable with the largest contribution to the discrimination between group.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

The authors acknowledge Ministry of Higher Education and Scientific Research of Tunisia for financial support (LR11ES39).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103009.

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