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Synthesis, anti-cancer and anti-inflammatory activity of novel 2-substituted isoflavenes

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ABSTRACT

Fifteen novel 2-substituted isoflavenes were synthesised via nucleophilic addition to isoflavylium salts. Twelve of the newly synthesised isoflavenes, along with the unsubstituted parent isoflavene, were tested in cell viability assays against the SHEP neuroblastoma and MDA-MB-231 breast adenocarcinoma cell lines. While the 2-substituted isoflavenes displayed a range of anti-proliferative activities, in most cases they were less active that the unsubstituted isoflavene (IC_{50} = 9.9 μM vs SHEP; IC_{50} = 33 μM vs MDA-MB-231). However, compound **7f**, derived from the reaction between isoflavylium salt **5** and *para*-methoxyacetophenone, showed improved anti-proliferative activity against breast cancer cells (IC_{50} = 7.6 μM). Furthermore, compound **7f**, as well as analogues **7a**, **7c**, **11d** and **14**, inhibited the production of interleukin-6 in LPS-activated RAW 264.7 cells.

1. Introduction

Isoflavonoid compounds are the subject of considerable research interest due to their range of biological activities in humans. These include agonistic and antagonistic interactions with estrogen receptors,[1–6] as well as anti-inflammatory[7–13] and anti-cancer activity.[14–20] The isoflav-3-ene **1** (Fig. 1) has demonstrated cytotoxic, anti-proliferative and anti-angiogenic activity against a variety of cancer types, notably ovarian and prostate cancers.[15,16] Isoflavene **1** is also highly selective in its mode of action, exhibiting minimal toxicity against normal cells. More recently, a series of oxazinyl isoflavenes and isoflavans were shown to inhibit the growth of several cancer cell lines in vitro.[17] Furthermore, isoflavonoid compounds have been shown to induce apoptosis in ovarian cancer stem cells via inhibition of the mammalian target of rapamycin.[18–20] Cancer stem cells are implicated in the development of recurrent and chemoresistant tumours and are resistant to conventional chemotherapies.[21] The development of isoflavonoid anti-cancer agents therefore represents a promising new strategy for cancer treatment.

The anti-inflammatory properties of isoflavonoid compounds have been reported in a variety of in vitro and in vivo models of conditions such as asthma,[7] arthritis,[8] UV-induced skin damage[9] and cardiovascular disease.[10] Isoflavonoid compounds have been reported to inhibit the production of a variety of inflammatory signalling molecules, such as interleukin (IL)-6, tumour necrosis factor (TNF)-α and nitric oxide.[8,9,11] In addition to these modes of action, isoflavonoid compounds can prevent tissue damage via their antioxidant capability.[3,12,13] The polyphenolic character of many isoflavenes facilitates both free radical scavenging[12] and the chelation of transition metals.[13]

Many biologically active isoflavonoid compounds bear one or more aryl substituents on the pyran ring. The 4-aryl isoflavan **2** is a potent cytotoxic and anti-proliferative agent currently under investigation as a treatment for pancreatic and bile duct cancers.[22] The 2-aryl isoflavene **3** is a selective estrogen receptor modulator developed for the treatment of hormone-dependent breast cancer.[23,24] The 2,3-diarylbenzopyran motif is shared by a number of other biologically active species.[25–27] The aim of the present study was to explore the chemistry, anti-cancer activity and anti-inflammatory activity of a variety of 2-substituted isoflavenes, with a particular focus on those with aryl moieties on the C2 substituent.

Several synthetic routes to 2-substituted isoflavonoid compounds have previously been reported. Some of the strategies

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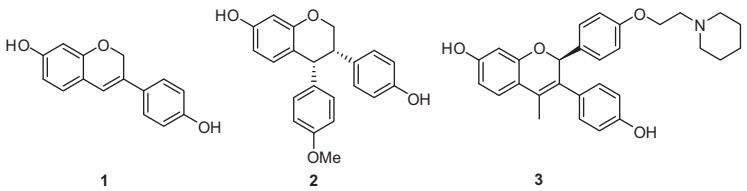


Figure 1. Structures of some biologically active isoflavonoid compounds.

employed include the cyclisation of deoxybenzoins,[28,29] condensation of enamines with salicylaldehydes[30] and Grignard addition to coumarins.[31] The treatment of isoflavylium salts with nucleophiles has been established as a versatile route to 2-substituted isoflavenes. Previously, isoflavylium salts have been reported to react with a variety of nucleophiles including amines,[32] thiols,[33] alcohols and trimethylsilanes.[34] We have expanded upon this chemistry to generate a variety of novel products. Herein, we report the synthesis, characterisation and in vitro biological activities of a series of newly synthesised 2-substituted isoflavenes.

2. Results and discussion

2.1. Synthesis of 2-substituted isoflavenes

An isoflavylium hexafluorophosphate salt was prepared using the hydride abstraction strategy employed by Faragalla et al.[34] Isoflavene **1** was acetylated to give compound **4**, which was treated with tritylium hexafluorophosphate in CH_2Cl_2 at room temperature to generate salt **5** in a yield of 91% (Scheme 1). The formation of the salt was confirmed by ^{1}H NMR spectroscopy. In the isoflavene, the two protons at C2 gave rise to a signal at δ 5.15 which appeared as a fine doublet (J = 1.4 Hz) due to allylic coupling with H4. The H4 proton appeared as a broad singlet at δ 6.76. In the isoflavylium salt, H2 and H4 appeared as doublets (J = 2.0 Hz) at δ 9.93 and 9.85.

Salt **5** was treated with a series of α-methyl ketones (Scheme 2). These reactions proceeded in the absence of any added base, indicating that the isoflavylium salt itself may have initiated the formation of the reactive enolate species. The yield of **6b** was significantly lower than those of the other analogues. This is thought to have been the result of a side reaction at the second α-carbon on the methyl butyl ketone. The structure of analogue **6a** was established via ^{1}H NMR spectroscopy. The H2 proton appeared at δ 5.93, which is downfield of the corresponding signal (δ 5.15) in the spectrum of the parent isoflavene **4**. The H2 proton appeared as a doublet of doublets, due to coupling with the diastereotopic protons of the neighbouring methylene group. The methylene protons appeared as doublets of doublets at δ 3.16 and 2.36. Similar chemical shifts and splitting patterns were observed for analogues **6b–i** and the deacetylated products **7a–i**, which were obtained by treatment with methanolic potassium hydroxide.

The carbonyl group in isoflavenes **6a–i** and **7a–i** provides a starting point for further chemical elaboration. One facile example is the formation of a hydrazone. Isoflavene **6a** was treated with 2,4-dinitrophenylhydrazine at reflux in ethanol to give the hydrazone **8** in 67% yield (Scheme 3). The phenolic analogue **9** was obtained in 91% yield by deacetylation of compound **8** with potassium hydroxide.

When the isoflavylium salt **5** was treated with 2-acetylpyrrole, the reaction occurred not at the α-methyl group, but at position 4 on the pyrrole ring, to give product **10a** (Scheme 4). In the ^{1}H NMR spectrum of **10a**, H2 appeared as a broad singlet at δ 6.19. The protons on the pyrrole ring appeared as two multiplets (each integrating for one proton) at δ 6.93 and 6.87. The methyl group appeared as a singlet at δ 2.25. In a similar manner, the isoflavylium salt **5** reacted with 3-substitued indoles and 2,6-dimethylaniline to generate 2-arylisoflavenes **10b–d**. Compounds **10a–d** were treated with aqueous potassium hydroxide to give the phenolic isoflavenes **11a–d**.

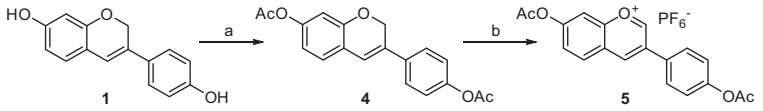
As 4-substituted isoflavonoid compounds are known to possess anti-cancer properties,[22] the synthesis of a 4-substituted isoflavylium salt was investigated. Attempts to form the isoflavylium salt of 4-substituted isoflavene **12** under the hydride abstraction conditions described in Scheme 1 were complicated by the failure of the salt to precipitate from the reaction mixture. A complex mixture of products was observed, believed to have been the result of reactions between the isoflavylium salt and the isoflavene **12**. Instead, isoflavene **12** was treated with thallium trifluoroacetate in trifluoroacetic acid, followed by concentrated HCl to give the isoflavylium chloride salt **13** in 50 % yield (Scheme 5). The TBDMS groups were cleaved during the synthesis of **13**, as indicated by the absence of signals at <2 ppm in the ^{1}H NMR spectrum. Salt **13** was treated with acetone to generate the 2,4-disubstituted isoflavene **14**.

2.2. Biological activity

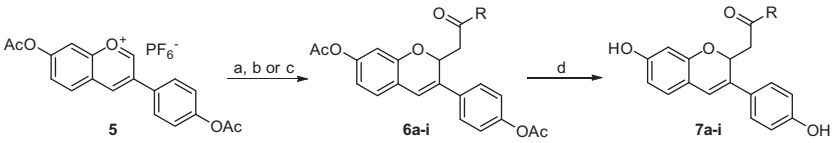
2.2.1. Anti-cancer activity

The anti-proliferative properties of isoflavenes **7a–i**, **9**, **11d**, and **14** were assessed in vitro using MDA-MB-231 breast adenocarcinoma cells and SHEP neuroblastoma cells. As shown in Figure 2, all compounds inhibited cell proliferation in a dose-dependent manner.

The newly synthesised 2-substituted isoflavenes exhibited IC_{50} values ranging from 33 μM to 377 μM against SHEP cells (Table 1), and were therefore less active than the parent isoflavene **1** (IC_{50} = 9.9 μM). The most active of the 2-substituted compounds were **7f** and **7g**, derived from *para*-methoxy- and *para*-bromoacetophenone, respectively. The substituent on the phenyl ring in compounds **7c–h** has a significant impact on anti-proliferative activity. For example, substitution of chlorine (**7h**) for bromine

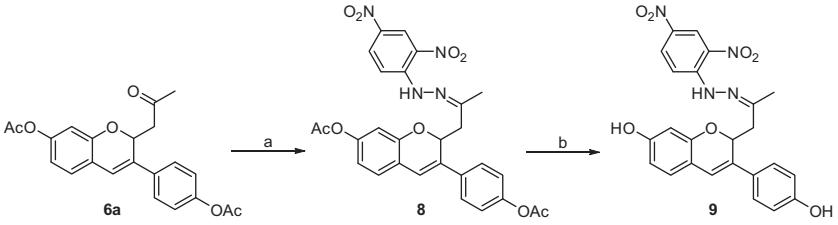


Scheme 1. Reagents and conditions: (a) Ac_2O, K_2CO_3, acetone, reflux; (b) Ph_3CPF_6, CH_2Cl_2, rt.

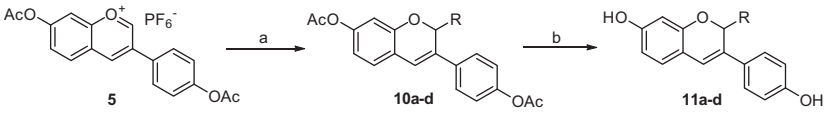


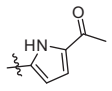
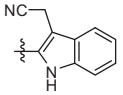
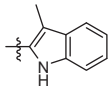
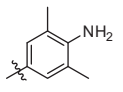
	R =	Conditions	% Yield **6**	% Yield **7**
a	Me	a	68	72
b	$CH_2CH(CH_3)_2$	b	27	88
c	Ph	b	73	83
d	*p*-MePh	c	73	83
e	*p*-EtPh	c	75	85
f	*p*-MeOPh	c	52	85
g	*p*-BrPh	c	67	94
h	*p*-ClPh	c	63	89
i	1-Naphthyl	c	49	84

Scheme 2. Reagents and conditions: (a) CH_3COR, rt; (b) CH_3COR, EtOAc, reflux; (c) CH_3COR, CH_2Cl_2, rt; (d) KOH(aq), MeOH, rt.

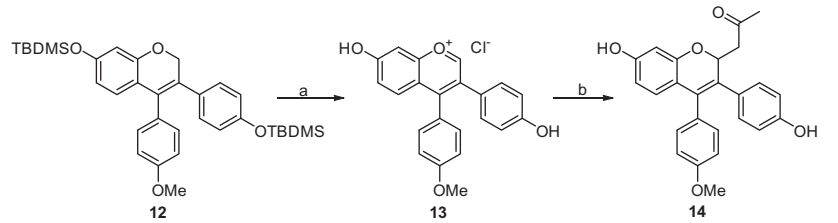


Scheme 3. Reagents and conditions: (a) 2,4-dinitrophenylhydrazine, EtOH, reflux; (b) KOH(aq), MeOH, rt.



	R =	% Yield **10**	% Yield **11**		R =	% Yield **10**	% Yield **11**
a		38	65	**c**		42	59
b		36	59	**d**		52	64

Scheme 4. Reagents and conditions: (a) RH, CH_2Cl_2, rt; (b) KOH(aq), MeOH, rt.



Scheme 5. Reagents and conditions: (a) (i) thallium trifluoroacetate, trifluoroacetic acid, rt, (ii) HCl, EtOAc, rt; (b) acetone, rt.

(**7g**) resulted in a five-fold decrease in activity. The analogue **7e**, which bears an ethyl substituent, was the least active of all 2-substituted isoflavenes.

In the MDA-MB-231 breast cancer cell line, the methoxyacetophenone derivative **7f** (IC_{50} = 7.6 μM) was significantly more active than isoflavene **1** (IC_{50} = 33 μM). Three more analogues, the bromoacetophenone derivative **7g** (IC_{50} = 37 μM), hydrazone **9** (IC_{50} = 36 μM) and 4-arylisoflavene **14** (IC_{50} = 39 μM), exhibited similar anti-proliferative activity to the parent compound. As in neuroblastoma cells, the ethylacetophenone derivative **7e** was the least active compound, followed by the chloro analogue **7h**.

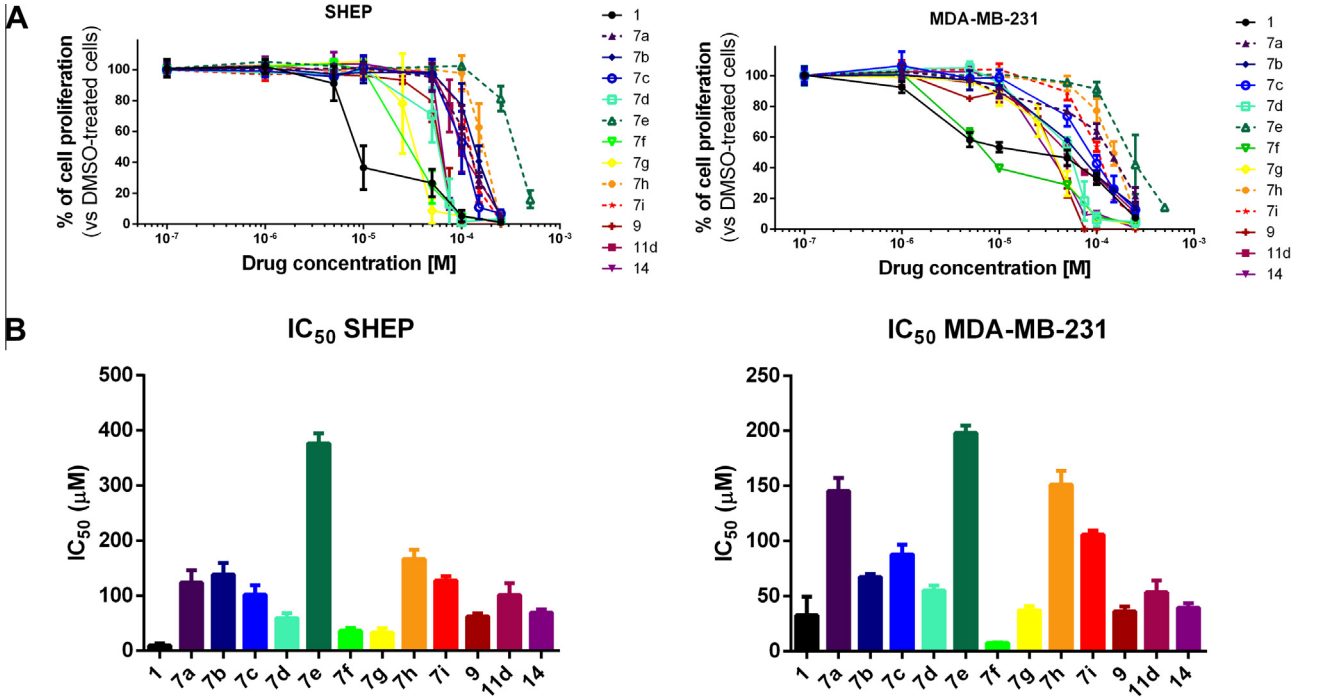
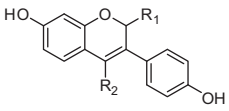
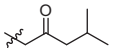
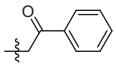
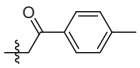
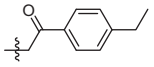
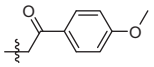
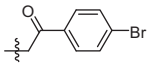
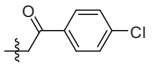


Figure 2. In vitro anti-proliferative properties of isoflavone **1** and compounds **7a–i**, **9**, **11d**, and **14** against SHEP neuroblastoma and MDA-MB-231 breast cancer cells. (A) Growth inhibition assay performed on SHEP and MDA-MB-231 cells using Alamar Blue after 72 h incubation with a range of drug concentrations. *Points*: % of cell proliferation as compared to untreated control cells, means of at least three individual experiments; *bars*: SD; log scale for *x* axis. (B) Histogram representation of the micromolar concentration of the compounds required to inhibit 50% of SHEP and MDA-MB-231 cell proliferation after 72 h drug incubation (IC_{50}). *Columns*: means of at least three individual experiments; *bars*: SD.

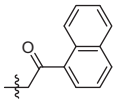
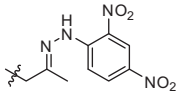
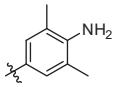
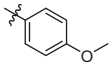
Table 1
Anti-proliferative activity of isoflavenes



Compound	R_1	R_2	IC50[a] (μM)		$\log P_{calc}$
			SHEP	MDA-MB-231	
1	H	H	9.9 ± 3.5	33 ± 17.1	2.71
7a		H	124 ± 22.7	145 ± 11.9	2.75
7b		H	139 ± 20.7	67 ± 2.7	4.16
7c		H	102 ± 17.5	88 ± 8.8	3.90
7d		H	60 ± 8.6	55 ± 4.7	4.39
7e		H	377 ± 17.8	198 ± 6.67	4.80
7f		H	37 ± 4.9	7.6 ± 0.49	3.77
7g		H	33 ± 7.8	37 ± 3.6	4.73
7h		H	167 ± 16.7	151 ± 12.6	4.46

(*continued on next page*)

Table 1 (*continued*)

Compound	R_1	R_2	IC50[a] (μM)		$\log P_{calc}$
			SHEP	MDA-MB-231	
7i		H	128 ± 7.84	106 ± 3.84	4.90
9		H	62 ± 5.3	36 ± 4.5	4.09
11d		H	102 ± 21.8	53 ± 11	4.59
14			69 ± 5.9	39 ± 4.3	4.01

[a] Reported mean ± SD.

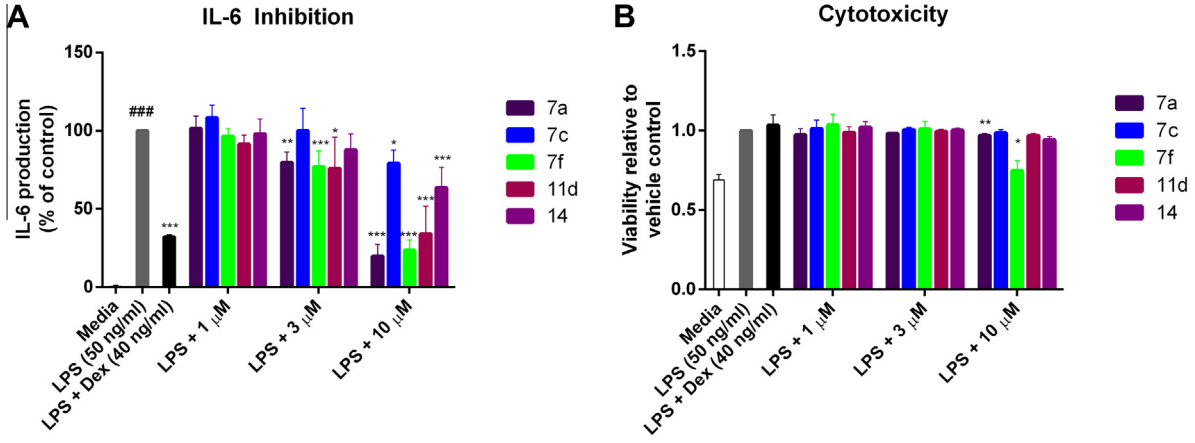


Figure 3. In vitro IL-6 inhibitory activity and cytotoxicity of compounds **7a**, **7c**, **7f**, **11d**, and **14** against LPS-stimulated RAW 264.7 murine macrophages. Dexamethasone (40 ng/mL) was used as a positive control. (A) IL-6 production was analysed using a commercial ELISA from culture supernatants of RAW 264.7 cells after 16 h incubation with LPS (50 ng/mL) and a range of drug concentrations. *Columns*: % of IL-6 production as compared to control cells treated with LPS and vehicle (0.1% DMSO), means of three individual experiments; *bars*: SEM; $^{###}P$ <0.001 relative to media alone; $^{*}P$ <0.05, $^{**}P$ <0.01 and $^{***}P$ <0.001 relative to vehicle control. (B) Viability of RAW 246.7 cells determined by CCK-8 assay. *Columns*: Cell viability as compared to vehicle control, means of three individual experiments; *bars*: SEM. $^{*}P$ <0.05 and $^{**}P$ <0.01 relative to vehicle control.

The lipophilicity ($\log P_{calc}$) of the isoflavenes was also examined (Table 1). It was observed that isoflavene **1**, which exhibited the greatest anti-proliferative activity against SHEP and was the second most active most compound against MDA-MB-231, had the lowest $\log P_{calc}$ value (2.71), while the two compounds with the highest $\log P_{calc}$, **7i** (4.90) and **7e** (4.80), were among the least active analogues. However, there was no clear correlation between lipophilicity and anti-proliferative activity overall. Compound **7a** has an almost identical $\log P_{calc}$ to isoflavene **1**, yet was considerably less active than isoflavene **1** against both SHEP and MDA-MB-231 cells. Compound **7g** has a relatively high $\log P_{calc}$ of 4.73, yet was one of the most active compounds against both cell lines.

2.2.2. Anti-inflammatory activity

The anti-inflammatory properties of compounds **7a**, **7c**, **7f**, **11d**, and **14** were assessed in vitro by measuring their effect on the production of the pro-inflammatory cytokine interleukin (IL)-6 by LPS-activated RAW 264.7 murine macrophages. All five of the compounds tested inhibited cytokine production to some extent, as shown in Figure 3a. **7a**, **7f** and **11d** were particularly active, achieving >50% inhibition of IL-6 production at 10 μM.

The toxicity of the isoflavenes towards the RAW cells was also evaluated (Fig. 3b). After removal of the supernatant for the measurement of IL-6, the viability of the cells remaining on the plate was determined using a CCK-8 assay. Only compounds **7a** and **7f** significantly decreased cell viability relative to the control. This effect was only observed at the highest concentration tested (10 μM). The cytotoxicity of **7f** at 10 μM may have contributed to the decrease in IL-6 production observed at this concentration.

3. Conclusion

This study has shown that isoflavylium salts such as compound **5** undergo nucleophilic addition reactions with α-methyl ketones, aromatic and heteroaromatic compounds to generate a variety of 2-substituted products. In most cases, the introduction of the substituent at C2 decreased the anti-proliferative activity against cancer cells relative to the parent isoflavene, **1**. However, compound **7f**, derived from the reaction between salt **5** and *p*-methoxyacetophenone, exhibited a 4-fold increase in activity against breast cancer cells. This analogue could serve as a lead compound for the development of anti-cancer agents. Furthermore, analogues **7a**

and **11d**, exhibited promising in vitro anti-inflammatory activity, indicating that 2-substituted isoflavenes may warrant further investigation as potential anti-inflammatory drugs.

4. Experimental Section

4.1. Chemistry

Commercially available reagents were purchased from Fluka, Aldrich, Acros Organics, Alfa Aesar and Lancaster and used without further purification. Isoflavenes **1** and **12** were obtained from Novogen, Sydney and used without further purification. ^{1}H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker DPX 300 spectrometer. Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar Series FTIR spectrophotometer as KBr disks. Ultraviolet spectra were measured using a Varian Cary 100 spectrophotometer in the designated solvents and data reported as wavelength (λ) in nm and adsorption coefficient (ε) in cm^{-1} M^{-1}. High-resolution [+ESI] mass spectra were recorded by the Bioanalytical Mass Spectrometry Facility, UNSW on an Orbitrap LTQ XL ion trap mass spectrometer using a nanospray (nano-electrospray) ionization source.

4.1.1. 4-(7-Acetoxy-2*H*-chromen-3-yl)phenyl acetate (4)

Isoflavene **1** (20.69 g, 86.12 mmol) and potassium carbonate (22.32 g, 161.5 mmol) were dissolved in acetone (200 mL). Acetic anhydride (32 mL, 340 mmol) was added. The mixture was heated to reflux for 90 min. The cooled reaction mixture was poured into water (600 mL). The precipitate was collected to give product **4** as a white powder. Yield: 27.67 g, 99 %. Mp 184–187 °C. Lit.[30] 192–193 °C. ^{1}H NMR (300 MHz, CDCl3): δ 7.42 (d, J = 8.8 Hz, 2H, H2′,6′), 7.12 (d, J = 8.8 Hz, 2H, H3′,5′), 7.06 (d, J = 8.1 Hz, 1H, H5), 6.76 (br s, 1H, H4), 6.65 (dd, J = 2.3 Hz, 8.1 Hz, 1H, H6), 6.61 (d, J = 2.3 Hz, 1H, H8), 5.15 (d, J = 1.4 Hz, 2H, H2), 2.31 (s, 3H, $COCH_3$), 2.29 (s, 3H, $COCH_3$).

4.1.2. 7-Acetoxy-3-(4-acetoxyphenyl)chromenylium hexafluorophosphate(V) (5)

Isoflavene **4** (5.01 g, 15.4 mmol) and tritylium hexafluorophosphate (6.57 g, 16.9 mmol) were dissolved in CH_2Cl_2 (250 mL). The mixture was stirred at room temperature for 45 min, under nitrogen. Filtration afforded product **5** as a bright yellow powder. Yield: 6.53 g, 91%. Mp 124–126 °C. ^{1}H NMR (300 MHz, d-TFA): δ 9.92 (d, J = 2.0 Hz, 1H, H2), 9.84 (d, J = 2.0 Hz, 1H, H4), 8.59 (d, J = 9.3 Hz, 1H, H5), 8.42 (d, J = 1.8 Hz, 1H, H8), 8.01 (dd, J = 1.8 Hz, 9.3 Hz, 1H, H6), 7.86 (d, J = 8.4 Hz, 2H, H2′,6′), 7.46 (d, J = 8.4 Hz, 2H, H3′,5′), 2.57 (s, 3H, $COCH_3$), 2.49 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, d-TFA): δ 177.4, 173.9, 173.4, 168.7, 159.1, 156.2, 136.1, 135.3, 133.4, 131.2, 127.3, 125.8, 115.4, 114.1, 104.8, 21.8, 21.6. IR (KBr): ν_{max} 3435, 3128, 1778, 1753, 1625, 1589, 1505, 1434, 1369, 1308, 1289, 1276, 1244, 1206, 1174, 1111, 1007, 942, 917, 896, 839 cm^{-1} UV–vis (CH_3CN): λ_{max} 318 nm (ε 6,954 cm^{-1} M^{-1}), 206 (8,558). HRMS (+ESI): Found m/z 323.0914, [M]$^{+}$; $C_{19}H_{15}O_5$ required 323.0914.

4.1.3. Synthesis of diacetoxyisoflavenes 6a–i

4.1.3.1. 4-(7-Acetoxy-2-(2-oxopropyl)-2*H*-chromen-3-yl)phenyl acetate (6a). The isoflavylium salt **5** (7.20 g, 15.4 mmol) was dissolved in acetone (250 mL). The mixture was stirred at room temperature for 18 h. Solvent was evaporated in vacuo and the crude product recrystallised from ethyl acetate to give product **6a** as an off-white solid. Yield: 3.98 g, 68%. Mp 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, J = 8.7, 2H, H2′,6′), 7.12 (d, J = 8.7 Hz, 2H, H3′,5′), 7.10 (d, J = 8.3 Hz, 1H, H5), 6.76 (br s, 1H, H4), 6.70 (dd, J = 2.4 Hz, 8.3 Hz, 1H, H6), 6.62 (d, J = 2.4 Hz, 1H, H8), 5.93 (dd, J = 2.1 Hz, 10.2 Hz, 1H, H2), 3.16 (dd, J = 10.2 Hz, 16.5 Hz, 1H, C*H*^{a}$COCH_3$), 2.36 (dd, J = 2.1 Hz, 16.5 Hz, 1H, C*H*^{b}$COCH_3$), 2.32 (s, 3H, $COCH_3$), 2.29 (s, 3H, $COCH_3$), 2.17 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 169.4, 169.2, 151.5, 151.4, 150.6, 133.6, 133.2, 127.4, 126.4, 122.2, 120.1, 119.4, 115.1, 110.4, 72.6, 45.9, 31.1, 20.1. IR (KBr): ν_{max} 3415, 3057, 2961, 1765, 1715, 1629, 1607, 1584, 1511, 1496, 1431, 1368, 1258, 1227, 1207, 1194, 1173, 1141, 1115, 1066, 1014, 949, 905, 849, 750 cm^{-1}. UV–vis (MeOH): λ_{max} 330 nm (ε 10,093 cm^{-1} M^{-1}), 240 (10,169), 205 (14,544). HRMS (+ESI): Found m/z 403.1154, [M+Na]$^{+}$; $C_{22}H_{20}O_6Na$ required 403.1152.

4.1.3.2. 4-(7-Acetoxy-2-(4-methyl-2-oxopentyl)-2*H*-chromen-3-yl)phenyl acetate (6b). General procedure A: 4-methylpentan-2-one (0.20 mL, 1.6 mmol) was added to a suspension of isoflavylium salt **5** (500 mg, 1.07 mmol) in ethyl acetate (10 mL). The mixture was heated at reflux for one hour. Solvent was evaporated in vacuo and the crude product recrystallised from aqueous methanol to give product **6b** as off-white crystals. Yield: 183 mg, 27 %. Mp 97–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, J = 8.8 Hz, 2H, H2′,6′), 7.11 (d, J = 8.8 Hz, 2H, H3′,5′), 7.09 (d, J = 8.4 Hz, 1H, H5), 6.75 (br s, 1H, H4), 6.68 (dd, J = 2.3 Hz, 8.4 Hz, 1H, H6), 6.58 (d, J = 2.3 Hz, 1H, H8), 5.97 (dd, J = 2.3 Hz, 10.1 Hz, 1H, H2), 3.14 (dd, J = 10.1 Hz, 16.3 Hz, 1H, C*H*^{a}CO), 2.35–2.22 (m, 3H, C*H*^{b}$COCH_2$), 2.31 (s, 3H, $COCH_3$), 2.28 (s, 3H, $COCH_3$), 2.17–2.03 (m, 1H, $CH_2CH(CH_3)_2$), 0.90 (d, J = 6.5 Hz, 3H, $CHCH_3$), 0.88 (3H, d, J = 6.5 Hz, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.6, 169.3, 169.2, 151.5, 151.3, 150.6, 133.5, 133.2, 127.3, 126.3, 122.1, 120.1, 119.3, 115.0, 110.3, 72.6, 53.0, 45.3, 24.3, 22.5, 22.4, 21.1. IR (KBr): ν_{max} 3413, 3065, 2959, 2871, 1759, 1710, 1610, 1585, 1509, 1495, 1467, 1431, 1369, 1312, 1259, 1205, 1170, 1140, 1116, 1072, 1043, 1014, 979, 961, 909, 847, 752 cm^{-1}. UV–vis (MeOH): λ_{max} 331 nm (ε 10,322 cm^{-1} M^{-1}), 240 (10,083), 205 (16,899). HRMS (+ESI): Found m/z 445.1610, [M+Na]$^{+}$; $C_{25}H_{26}O_6Na$ required 445.1622.

4.1.3.3. 4-(7-Acetoxy-2-(2-oxo-2-phenylethyl)-2*H*-chromen-3-yl)phenyl acetate (6c). Following general procedure A, acetophenone (0.02 mL, 0.03 mmol) was added to a suspension of isoflavylium salt **5** (100 mg, 0.214 mmol) in ethyl acetate (2 mL) to give the product **6c** as a white crystalline solid. Yield: 68 mg, 73%. Mp 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (dd, J = 1.4 Hz, 7.9 Hz, 2H, H2″,6″), 7.56 (d, J = 8.7 Hz, 2H, H2′,6′), 7.52 (tt, J = 1.4 Hz, 7.6 Hz, 1H, H4″), 7.42 (dd, J = 7.6 Hz, 7.9 Hz, 2H, H3″,5″), 7.15–7.10 (m, 3H, H3′,5′, H5), 6.83 (br s, 1H, H4), 6.69 (dd, J = 2.2 Hz, 8.2 Hz, 1H, H6), 6.49 (d, J = 2.2 Hz, 1H, H8), 6.18 (dd, J = 2.2 Hz, 9.6 Hz, 1H, H2), 3.82 (dd, J = 9.6 Hz, 16.5 Hz, 1H, C*H*^{a}COPh), 2.76 (dd, J = 2.2 Hz, 16.5 Hz, 1H, C*H*^{b}COPh), 2.31 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 169.4, 169.2, 151.7, 151.4, 150.6, 136.8, 133.6, 133.4, 133.3, 128.6, 127.4, 126.4, 122.2, 120.2, 119.5, 115.1, 110.6, 72.9, 41.2, 21.1, 21.1. IR (KBr): ν_{max} 3438, 3061, 2930, 1762, 1673, 1630, 1599, 1582, 1509, 1494, 1449, 1431, 1371, 1348, 1314, 1289, 1270, 1256, 1211, 1170, 1138, 1115, 1043, 1013, 976, 961, 903, 847, 758 cm^{-1}. UV–vis (MeOH): λ_{max} 328 nm (ε 9,513 cm^{-1} M^{-1}), 293 (7,459), 241 (15,929), 203 (25,473). HRMS (+ESI): Found m/z 465.1297, [M+Na]$^{+}$; $C_{27}H_{22}O_6Na$ required 465.1309.

4.1.3.4. 4-(7-Acetoxy-2-(2-oxo-2-(p-tolyl)ethyl)-2*H*-chromen-3-yl)phenyl acetate (6d). General procedure B: 4-methylacetophenone (0.31 mL, 2.3 mmol) was added to a suspension of isoflavylium salt **5** (1.00 g, 2.14 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 18 h. Solvent was evaporated in vacuo and the crude product recrystallised from aqueous ethanol to give the product **6d** as a yellow-green powder.

Yield: 713 mg, 73%. Mp 126–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 2H, H2″,6″), 7.55 (d, J = 8.8 Hz, 2H, H3″,5″), 7.21 (d, J = 8.8 Hz, 2H, H2′,6′), 7.15–7.09 (m, 3H, H3′,5′, H5), 6.82 (br s, 1H, H4), 6.69 (dd, J = 2.4 Hz, 8.2 Hz, 1H, H6), 6.49 (d, J = 2.4 Hz, 1H, H8), 6.17 (dd, J = 2.2 Hz, 9.6 Hz, 1H, H2), 3.79 (dd, J = 9.6 Hz, 16.5 Hz, 1H, C*H*^{a}COAr), 2.73 (dd, J = 2.1 Hz, 16.5 Hz, 1H, C*H*^{b}COAr), 2.39 (s, 3H, CH_3), 2.31 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 169.5, 169.3, 151.7, 151.3, 150.6, 144.3, 134.4, 133.6, 133.4, 129.3, 128.5, 127.4, 126.4, 122.1, 120.2, 119.4, 115.1, 110.6, 72.9, 41.0, 21.7, 21.2, 21.1. IR (KBr): ν_{max} 3473, 3048, 2978, 2941, 1755, 1743, 1672, 1640, 1603, 1573, 1510, 1493, 1430, 1371, 1347, 1314, 1288, 1259, 1201, 1169, 1138, 1110, 1042, 1013, 978, 958, 907, 886, 847, 824 cm^{-1}. UV–vis (MeOH): λ_{max} 329 nm (ε 13,272 cm^{-1} M^{-1}), 294 (10,362), 247 (20,713), 208 (25,872). HRMS (+ESI): Found m/z 457.1636, $[M+H]^+$; $C_{28}H_{25}O_6$ required 457.1646.

4.1.3.5. 4-(7-Acetoxy-2-(2-(4-ethylphenyl)-2-oxoethyl)-2*H*-chromen-3-yl)phenyl acetate (6e). Following general procedure B, 4-ethylacetophenone (0.35 mL, 2.4 mmol) was added to a suspension of isoflavylium salt **5** (1.03 g, 2.20 mmol) in CH_2Cl_2 (40 mL) to give the product **6e** as a pale green powder. Yield: 847 mg, 75%. Mp 118–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H, H2″,6″), 7.55 (d, J = 8.8 Hz, 2H, H3″,5″), 7.23 (d, J = 8.8 Hz, 2H, H2′,6′), 7.14–7.10 (m, 3H, H3′,5′, H5), 6.82 (br s, 1H, H4), 6.69 (dd, J = 2.4 Hz, 8.2 Hz, 1H, H6), 6.48 (d, J = 2.4 Hz, 1H, H8), 6.17 (dd, J = 2.2 Hz, 9.7 Hz, 1H, H2), 3.79 (dd, J = 9.4 Hz, 16.4 Hz, 1H, C*H*^{a}COAr), 2.74 (dd, J = 2.1 Hz, 16.4 Hz, 1H, C*H*^{b}COAr), 2.66 (q, J = 7.4 Hz, 2H, CH_2CH_3), 2.31 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$), 1.23 (q, J = 7.4 Hz, 2H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.8, 169.4, 169.2, 151.7, 151.3, 150.4, 144.5, 134.7, 133.6, 133.4, 128.6, 128.1, 127.3, 126.4, 122.2, 120.2, 119.4, 115.1, 110.6, 72.9, 41.1, 29.2, 21.2, 21.1, 15.2. IR (KBr): ν_{max} 3392, 3048, 2968, 2930, 2871, 1745, 1668, 1604, 1567, 1511, 1494, 1455, 1431, 1370, 1343, 1313, 1287, 1260, 1203, 1169, 1138, 1110, 1039, 1015, 979, 959, 949, 908, 890, 874, 846, 803 cm^{-1}. UV–vis (MeOH): λ_{max} 328 nm (ε 16,277 cm^{-1} M^{-1}), 248 (24,769), 209 (29,149). HRMS (+ESI): Found m/z 493.1606, $[M+Na]^+$; $C_{29}H_{26}O_6Na$ required 493.1622.

4.1.3.6. 4-(7-Acetoxy-2-(2-(4-methoxyphenyl)-2-oxoethyl)-2*H*-chromen-3-yl)phenyl acetate (6f). Following general procedure B, 4-methoxyacetophenone (311 mg, 2.4 mmol) was added to a suspension of isoflavylium salt **5** (1.02 g, 2.18 mmol) in CH_2Cl_2 (40 mL) to give the product **6f** as a brownish green powder. Yield: 536 mg, 52%. Mp 116–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 8.8 Hz, 2H, H2″,6″), 7.56 (d, J = 8.8 Hz, 2H, H2′,6′), 7.15–7.10 (m, 3H, H3′,5′, H5), 6.89 (d, J = 8.8 Hz, 2H, H3″,5″), 6.83 (br s, 1H, H4), 6.69 (dd, J = 2.3 Hz, 8.3 Hz, 1H, H6), 6.44 (d, J = 2.3 Hz, 1H, H8), 6.16 (dd, J = 2.1 Hz, 9.4 Hz, 1H, H2), 3.85 (s, 3H, OMe), 3.78 (dd, J = 9.4 Hz, 16.4 Hz, 1H, C*H*^{a}COAr), 2.72 (dd, J = 2.1 Hz, 16.4 Hz, 1H, C*H*^{b}COAr), 2.31 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 169.4, 169.2, 163.7, 151.7, 151.3, 150.6, 133.6, 133.5, 130.8, 130.1, 127.3, 126.4, 122.2, 120.3, 119.3, 115.0, 113.8, 110.7, 73.1, 55.5, 41.1, 21.1, 21.1. IR (KBr): ν_{max} 3441, 1750, 1666, 1650, 1642, 1631, 1602, 1580, 1510, 1495, 1433, 1371, 1312, 1289, 1258, 1232, 1212, 1170, 1142, 1113, 1046, 1027, 934, 845 cm^{-1}. UV–vis (MeOH): λ_{max} 327 nm (ε 8,009 cm^{-1} M^{-1}), 284 (14,033), 243 (10,844), 208 (15,828). HRMS (+ESI): Found m/z 495.1398, $[M+Na]^+$; $C_{28}H_{24}O_7Na$ required 495.1414.

4.1.3.7. 4-(7-Acetoxy-2-(2-(4-bromophenyl)-2-oxoethyl)-2*H*-chromen-3-yl)phenyl acetate (6g). Following general procedure B, 4-bromoacetophenone (480 mg, 2.4 mmol) was added to a suspension of isoflavylium salt **5** (1.00 g, 2.14 mmol) in CH_2Cl_2 (40 mL) to give the product **6g** as a pale yellow powder. Yield: 748 mg, 67%. Mp 128–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8.7 Hz, 2H, H2″,6″), 7.56 (d, J = 8.7 Hz, 2H, H3″,5″), 7.54 (d, J = 8.8 Hz, 2H, H2′,6′), 7.15–7.10 (m, 3H, H3′,5′, H5), 6.82 (br s, 1H, H4), 6.70 (dd, J = 2.0 Hz, 8.2 Hz, 1H, H6), 6.44 (d, J = 2.0 Hz, 1H, H8), 6.13 (dd, J = 2.2 Hz, 9.6 Hz, 1H, H2), 3.76 (dd, J = 9.6 Hz, 16.3 Hz, 1H, C*H*^{a}COAr), 2.72 (dd, J = 2.2 Hz, 16.3 Hz, 1H, C*H*^{b}COAr), 2.32 (s, 3H, $COCH_3$), 2.27 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3, 169.4, 169.2, 151.5, 151.4, 150.7, 135.6, 133.5, 133.2, 132.0, 130.0, 128.7, 127.4, 126.4, 122.2, 120.1, 119.5, 115.2, 110.6, 73.0, 41.1, 21.1, 21.1. IR (KBr): ν_{max} 3433, 3060, 2933, 1755, 1670, 1612, 1585, 1510, 1493, 1432, 1396, 1371, 1289, 1261, 1209, 1170, 1141, 1114, 1071, 1045, 1011, 962, 908, 844 cm^{-1}. UV–vis (MeOH): λ_{max} 324 nm (ε 13,243 cm^{-1} M^{-1}), 247 (15,406), 204 (27,424). HRMS (+ESI): Found m/z 543.0404, $[M+Na]^+$; $C_{27}H_{21}BrO_6Na$ required 543.0414.

4.1.3.8. 4-(7-Acetoxy-2-(2-(4-chlorophenyl)-2-oxoethyl)-2*H*-chromen-3-yl)phenyl acetate (6h). Following general procedure B, 4-chloroacetophenone (0.30 mL, 2.3 mmol) was added to a suspension of isoflavylium salt **5** (1.01 g, 2.16 mmol) in CH_2Cl_2 (40 mL) to give the product **6h** as a pale yellow powder. Yield: 649 mg, 63%. Mp 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J = 8.8 Hz, 2H, H2″,6″), 7.54 (d, J = 8.8 Hz, 2H, H2′,6′), 7.40 (d, J = 8.8 Hz, 2H, H3″,5″), 7.15–7.10 (m, 3H, H3′,5′, H5), 6.82 (br s, 1H, H4), 6.70 (dd, J = 2.3 Hz, 8.2 Hz, 1H, H6), 6.44 (d, J = 2.3 Hz, 1H, H8), 6.13 (dd, J = 2.3 Hz, 9.6 Hz, 1H, H2), 3.78 (dd, J = 9.6 Hz, 16.1 Hz, 1H, C*H*^{a}COAr), 2.72 (dd, J = 2.3 Hz, 16.1 Hz, 1H, C*H*^{b}COAr), 2.32 (s, 3H, $COCH_3$), 2.26 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 169.4, 169.2, 151.5, 151.4, 150.7, 139.9, 135.3, 133.5, 133.2, 129.8, 129.0, 127.4, 126.4, 122.2, 120.1, 119.5, 115.2, 110.6, 73.0, 41.1, 21.1, 21.1. IR (KBr): ν_{max} 3441, 1755, 1670, 1611, 1585, 1510, 1497, 1432, 1398, 1371, 1337, 1313, 1289, 1261, 1211, 1169, 1142, 1113, 1093, 1045, 1013, 962, 950, 907, 844, 826, 796 cm^{-1}. UV–vis (MeOH): λ_{max} 327 nm (ε 13,449 cm^{-1} M^{-1}), 294 (10,791), 246 (22,462), 208 (25,670). HRMS (+ESI): Found m/z 499.0908, $[M+Na]^+$; $C_{27}H_{21}ClO_6Na$ required 499.0919.

4.1.3.9. 4-(7-Acetoxy-2-(2-(naphthalen-1-yl)-2-oxoethyl)-2*H*-chromen-3-yl)phenyl acetate (6i). 1-Acetylnapthalene (0.65 mL, 4.3 mmol) was added to a suspension of isoflavylium salt **5** (1.48 g, 3.16 mmol) in CH_2Cl_2 (75 mL). The reaction mixture was stirred at room temperature for 18 h. Water (100 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over $MgSO_4$ Solvent was evaporated in vacuo to give the product **6i** as a dark yellow amorphous solid. Yield: 772 mg, 49%. Mp 46–50 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (dd, J = 1.2 Hz, 8.2 Hz, 1H, H8″), 8.03–7.93 (m, 1H, H4″), 7.90–9.84 (m, 1H, H5″), 7.71 (dd, J = 1.2 Hz, 7.2 Hz, 1H, H2″), 7.64–7.50 (m, 4H, H6″, H7″, H2′,6′), 7.45 (dd, J = 7.2 Hz, 8.2 Hz, 1H, H3″), 7.14 (d, J = 8.9 Hz, 2H, H3′,5′), 7.11 (d, J = 8.3 Hz, 1H, H5), 6.81 (br s, 1H, H4), 6.69 (dd, J = 2.3 Hz, 8.2 Hz, 1H, H6), 6.50 (d, J = 2.3 Hz, 1H, H8), 6.23 (dd, J = 2.3 Hz, 9.8 Hz, 1H, H2), 3.85 (dd, J = 9.8 Hz, 16.1 Hz, 1H, C*H*^{a}COAr), 2.91 (dd, J = 2.3 Hz, 16.1 Hz, 1H, C*H*^{b}COAr), 2.32 (s, 3H, $COCH_3$), 2.27 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 169.4, 169.1, 151.7, 151.3, 150.6, 135.7, 133.9, 133.6, 133.3, 133.0, 128.4, 128.3, 128.1, 127.4, 126.5, 126.0, 125.8, 124.4, 122.2, 121.9, 120.2, 119.5, 115.1, 110.5, 73.4, 44.9, 21.1, 21.1. IR (KBr): ν_{max} 3433, 3047, 2930, 1756, 1677, 1611, 1508, 1496, 1461, 1432, 1369, 1311, 1280, 1201, 1169, 1141, 1115, 1044, 1014, 947, 907, 846, 804, 778 cm^{-1}. UV–vis (MeOH): λ_{max} 322 nm (ε 14,222 cm^{-1} M^{-1}), 214 (35,326). HRMS (+ESI): Found m/z 515.1452, $[M+Na]^+$; $C_{31}H_{24}O_6Na$ required 515.1465.

4.1.4. Synthesis of isoflavenes 7a–i

4.1.4.1. 1-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl) propan-2-one (7a). General procedure C: the isoflavene **6a** (370 mg, 0.97 mmol) was suspended in methanol (10 mL). Aqueous KOH (1 M, 3.0 mL, 3.0 mmol) was added dropwise. The mixture was stirred at room temperature for 48 h before being neutralised with 1 M HCl. Water (15 mL) was added. Filtration afforded the product **7a** as a greenish yellow powder. Yield: 218 mg, 72%. Mp 174–177 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.59 (br s, 1H, OH), 9.57 (br s, 1H, OH), 7.35 (d, J = 8.8 Hz, 2H, H2′,6′), 6.97 (d, J = 8.4 Hz, 1H, H5), 6.77 (br s, 1H, H4), 6.76 (d, J = 8.8 Hz, 2H, H3′,5′), 6.34 (dd, J = 2.3 Hz, 8.4 Hz, 1H, H6), 6.18 (d, J = 2.3 Hz, 1H, H8), 6.74 (dd, J = 2.3 Hz, 10.1 Hz, 1H, H2), 2.89 (dd, J = 10.1 Hz, 15.9 Hz, 1H, C*H*^{a}COCH$_3$), 2.36 (dd, J = 2.3 Hz, 15.9 Hz, 1H, C*H*^{b}COCH$_3$), 2.13 (s, 3H, COCH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 205.9, 158.4, 157.2, 151.2, 130.0, 127.5, 126.6, 126.0, 116.6, 115.7, 114.4, 108.9, 103.3, 71.8, 45.7, 30.3. IR (KBr): ν_{max} 3359, 3038, 2960, 1704, 1619, 1584, 1517, 1506, 1459, 1447, 1372, 1356, 1336, 1288, 1269, 1232, 1186, 1159, 1148, 1114, 1063, 1043, 1006, 952, 916, 874, 845, 836, 816, 792, 736 cm^{-1}. UV–vis (MeOH): λ_{max} 333 nm (ε 12,813 cm^{-1} M^{-1}), 242 (8,629), 211 (14,176). HRMS (+ESI): Found m/z 297.1117, [M+H]$^+$; $C_{18}H_{17}O_4$ required 297.1121.

4.1.4.2. 1-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)-4-methylpentan-2-one (7b). Following general procedure C, the isoflavene **6b** (30 mg, 0.071 mmol) was dissolved in ethanol (5 mL) and treated with aqueous KOH (1 M, 0.3 mL, 0.3 mmol) The mixture was stirred at room temperature for 18 h before being neutralised to give the *title compound* **7b** as a dark brown solid. Yield: 21 mg, 88%. Mp 92–96 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.59 (br s, 1H, OH), 9.57 (br s, 1H, OH), 7.36 (d, J = 8.8, 2H, H2′,6′), 6.98 (d, J = 8.4 Hz, 1H, H5), 6.81–6.76 (m, 3H, H3′,5′, H4), 6.36 (dd, J = 2.3 Hz, 8.4 Hz, 1H, H6), 6.17 (d, J = 2.3 Hz, 1H, H8), 5.75 (dd, J = 2.5 Hz, 9.9 Hz, 1H, H2), 2.91 (dd, J = 9.9 Hz, 15.8 Hz, 1H, C*H*^{a}CO), 2.33 (d, J = 7.1 Hz, 2H, COCH_2 CH(CH$_3$)$_2$), 2.31–2.20 (m, 3H, C*H*^{b}COCH$_2$C*H*(CH$_3$)$_2$), 0.86 (d, J = 6.5 Hz, 3H, CHCH_3), 0.84 (d, J = 6.5 Hz, 3H, CHCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 207.5, 158.4, 157.1, 151.1, 130.0, 127.5, 126.5, 125.9, 116.7, 115.6, 114.4, 108.9, 103.1, 72.1, 51.5, 45.2, 23.7, 22.4, 22.2. IR (KBr): ν_{max} 3426, 3952, 1658, 1640, 1619, 1612, 1513, 1502, 1462, 1444, 1224, 1150, 1112, 909 cm^{-1}. UV–vis (MeOH): λ_{max} 271 nm (ε 15,651 cm^{-1} M^{-1}), 203 (14,890). HRMS (+ESI): Found m/z 339.1582, [M+H]$^+$; $C_{21}H_{23}O_4$ required 339.1591.

4.1.4.3. 2-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)-1-phenylethanone (7c). Following general procedure C, the isoflavene **6c** (50 mg, 0.11 mmol) was dissolved in ethanol (15 mL) and treated with aqueous KOH (1 M, 1.0 mL, 1.0 mmol) to give the product **7c** as a tan solid. Yield: 31 mg, 83%. Mp 231–234 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.59 (br s, 1H, OH), 9.50 (br s, 1H, OH), 7.85 (dd, J = 1.3 Hz, 8.0 Hz, 2H, H2″,6″), 7.63 (tt, J = 1.3 Hz, 7.5 Hz, 1H, H4″), 7.48 (dd, J = 7.6 Hz, 7.9 Hz, 2H, H3″,5″), 7.39 (d, J = 8.7 Hz, 2H, H2′,6′), 7.01 (d, J = 8.3 Hz, 1H, H5), 6.85 (br s, 1H, H4), 6.79 (d, J = 8.7 Hz, 2H, H3′,5′), 6.35 (dd, J = 2.3 Hz, 8.3 Hz, 1H, H6), 6.03 (d, J = 2.3 Hz, 1H, H8), 5.91 (dd, J = 2.1 Hz, 9.9 Hz, 1H, H2), 3.63 (dd, J = 9.6 Hz, 16.4 Hz, 1H, C*H*^{a}COPh), 2.82 (dd, J = 2.1 Hz, 16.4 Hz, 1H, C*H*^{b}COPh). ^{13}C NMR (75 MHz, CDCl$_3$): δ 197.2, 158.4, 157.2, 151.2, 136.7, 133.4, 129.9, 128.7, 128.1, 127.6, 126.6, 126.0, 116.9, 115.7, 114.4, 109.0, 103.2, 72.1, 40.8. IR (KBr): ν_{max} 3432, 1743, 1612, 1513, 1448, 1370, 1263, 1214, 1172, 1112, 1041, 1014, 836 cm^{-1}. UV–vis (MeOH): λ_{max} 278 nm (ε 11,194 cm^{-1} M^{-1}). HRMS (+ESI): Found m/z 381.1091, [M+Na]$^+$; $C_{23}H_{18}O_4Na$ required 381.1097.

4.1.4.4. 2-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)-1-(*p*-tolyl)ethanone (7d). Following general procedure C, the isoflavene **6d** (50 mg, 0.11 mmol) was dissolved in ethanol (10 mL) and treated with aqueous KOH (1 M, 0.5 mL, 0.5 mmol) to give the product **7d** as an orange solid. Yield: 34 mg, 83%. Mp 114–118 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.60 (br s, 1H, OH), 9.50 (br s, 1H, OH), 7.75 (d, J = 8.8 Hz, 2H, H2″,6″), 7.39 (d, J = 8.8 Hz, 2H, H2′,6′), 7.28 (d, J = 8.8 Hz, 2H, H3″,5″), 7.01 (d, J = 8.3 Hz, 1H, H5), 6.84 (br s, 1H, H4), 6.79 (d, J = 8.8 Hz, 2H, H3′,5′), 6.35 (dd, J = 2.4 Hz, 8.3 Hz, 1H, H6), 6.03 (d, J = 2.4 Hz, 1H, H8), 5.89 (dd, J = 2.1 Hz, 9.8 Hz, 1H, H2), 3.61 (dd, J = 9.8 Hz, 16.2 Hz, 1H, C*H*^{a}COAr), 2.75 (dd, J = 2.1 Hz, 16.2 Hz, 1H, C*H*^{b}COAr), 2.36 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.8, 158.4, 156.9, 151.3, 134.4, 129.9, 129.3, 128.3, 127.7, 126.7, 126.0, 116.1, 115.7, 114.6, 114.2, 109.1, 103.6, 72.5, 31.1, 21.3. IR (KBr): ν_{max} 3376, 3026, 2956, 2922, 1643, 1619, 1602, 1578, 1514, 1460, 1441, 1406, 1384, 1365, 1335, 1290, 1277, 1253, 1228, 1181, 1173, 1152, 1118, 1036, 1017, 1007, 832, 817, 802 cm^{-1}. UV–vis (MeOH): λ_{max} 277 nm (ε 14,152 cm^{-1} M^{-1}). HRMS (+ESI): Found m/z 395.1245, [M+Na]$^+$; $C_{24}H_{20}O_4Na$ required 395.1254.

4.1.4.5. 1-(4-Ethylphenyl)-2-(7-hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)ethanone (7e). Following general procedure C, the isoflavene **6e** (50 mg, 0.11 mmol) was dissolved in ethanol (15 mL) and treated with aqueous KOH (1 M, 0.5 mL, 0.5 mmol) to give the product **7e** as a dark yellow solid. Yield: 36 mg, 85%. Mp 129–131 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.60 (br s, 1H, OH), 9.50 (br s, 1H, OH), 7.78 (d, J = 8.8 Hz, 2H, H2″,6″), 7.39 (d, J = 8.8 Hz, 2H, H2′,6′), 7.32 (d, J = 8.8 Hz, 2H, H3″,5″), 7.01 (d, J = 8.3 Hz, 1H, H5), 6.84 (br s, 1H, H4), 6.79 (d, J = 8.8 Hz, 2H, H3′,5′), 6.35 (dd, J = 2.4 Hz, 8.3 Hz, 1H, H6), 6.03 (d, J = 2.4 Hz, 1H, H8), 5.90 (dd, J = 2.1 Hz, 9.7 Hz, 1H, H2), 3.61 (dd, J = 9.7 Hz, 16.3 Hz, 1H, C*H*^{a}COAr), 2.75 (dd, J = 2.1 Hz, 16.3 Hz, 1H, C*H*^{b}COAr), 2.66 (q, J = 7.7 Hz, 2H, CH_2 CH$_3$) 1.18 (t, J = 7.7 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.8, 158.3, 157.1, 151.3, 150.1, 140.4, 134.7, 129.9, 128.3, 128.1, 127.6, 126.0, 116.9, 115.7, 114.5, 108.6, 100.6, 72.4, 28.2, 20.2, 15.1. IR (KBr): ν_{max} 3415, 2925, 2848, 1693, 1657, 1620, 1556, 1514, 1498, 1462, 1440, 1389, 1371, 1266, 1226, 1166, 1154, 1117, 1092, 1024, 834 cm^{-1}. UV–vis (MeOH): λ_{max} 282 nm (ε 9,056 cm^{-1} M^{-1}), 203 (18,846). HRMS (+ESI): Found m/z 409.1406, [M+Na]$^+$; $C_{25}H_{22}O_4Na$ required 409.1410.

4.1.4.6. 2-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)-1-(4-methoxyphenyl)ethanone (7f). Following general procedure C, the isoflavene **6f** (13 mg, 0.027 mmol) was dissolved in ethanol (15 mL) and treated with aqueous KOH (1 M, 0.5 mL, 0.5 mmol) to give the product **7f** as a brown solid. Yield: 9 mg, 85%. Mp 196–200 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.66 (br s, 2H, OH), 7.91 (d, J = 9.0 Hz, 2H, H2″,6″), 7.47 (d, J = 8.8 Hz, 2H, H2′,6′), 7.04 (d, J = 8.5 Hz, 1H, H5), 7.00 (d, J = 9.0, 2H, H3″,5″), 6.89 (d, J = 8.8 Hz, 2H, H3′,5′), 6.86 (br s, 1H, H4), 6.45 (dd, J = 2.3 Hz, 8.1 Hz, 1H, H6), 6.16 (d, J = 2.3 Hz, 1H, H8), 6.03 (dd, J = 2.1 Hz, 9.6 Hz, 1H, H2), 3.89 (s, 3H, OCH$_3$), 3.77 (dd, J = 9.6 Hz, 16.3 Hz, 1H, C*H*^{a}COAr), 2.72 (dd, J = 2.1 Hz, 16.3 Hz, 1H, C*H*^{b}COAr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 195.5, 163.5, 158.3, 157.1, 151.3, 130.4, 130.0, 129.6, 127.9, 126.6, 125.9, 119.1, 116.8, 115.7, 114.4, 113.8, 103.6, 72.4, 55.8, 37.8. IR (KBr): ν_{max} 3374, 3016, 2933, 2830, 1642, 1621, 1589, 1514, 1457, 1442, 1368, 1335, 1290, 1265, 1231, 1171, 1152, 1117, 1037, 1023, 983, 962, 867, 834, 800 cm^{-1}. UV–vis (MeOH): λ_{max} 327 nm (ε 15,595 cm^{-1} M^{-1}), 283 (16,935), 203 (26,800). HRMS (+ESI): Found m/z 411.1196, [M+Na]$^+$; $C_{24}H_{20}O_5Na$ required 411.1203.

4.1.4.7. 1-(4-Bromophenyl)-2-(7-hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)ethanone (7g). Following general procedure C, the isoflavene **6g** (50 mg, 0.11 mmol) was dissolved in ethanol (5 mL) and treated with aqueous KOH (1 M, 0.2 mL, 0.2 mmol) to give the product **7g** as a beige powder. Yield: 45 mg, 94%. Mp 132–136 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60 (br s, 1H, OH), 8.51 (br s, 1H, OH), 7.86 (d, J = 8.8 Hz, 2H, H2″,6″), 7.68 (d, J = 8.8 Hz, 2H, H3″,5″), 7.45 (d, J = 8.8 Hz, 2H, H2′,6′), 7.03 (d, J = 8.4 Hz, 1H, H5), 6.88 (d, J = 8.8 Hz, 2H, H3′,5′), 6.85 (br s, 1H, H4), 6.44 (dd, J = 2.4 Hz, 8.1 Hz, 1H, H6), 6.44 (d, J = 2.4 Hz, 1H, H8), 6.13 (dd, J = 2.4 Hz, 9.8 Hz, 1H, H2), 3.76 (dd, J = 9.8 Hz, 16.3 Hz, 1H, C*H*^{a}COAr), 2.84 (dd, J = 2.4 Hz, 16.3 Hz, 1H, C*H*^{b}COAr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.5, 158.3, 157.1, 151.2, 135.6, 131.7, 130.1, 129.8, 127.6, 127.5, 126.6, 126.0, 116.9, 115.7, 114.4, 109.0, 103.3, 72.1, 40.9. IR (KBr): ν_{max} 3406, 1754, 1745, 1731, 1668, 1643, 1613, 1584, 1568, 1556, 1515, 1485, 1461, 1454, 1433, 1396, 1370, 1332, 1289, 1267, 1243, 1223, 1178, 1158, 1114, 1071, 1032, 1006, 984, 958, 833 cm^{-1}. UV–vis (MeOH): λ_{max} 330 nm (ε 13,720 cm^{-1} M^{-1}), 252 (17,027), 205 (25,390). HRMS (+ESI): Found m/z 459.0195, [M+Na]$^+$; $C_{23}H_{17}BrO_4Na$ required 459.0202.

4.1.4.8. 1-(4-Chlorophenyl)-2-(7-hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)ethanone (7h). Following general procedure C, the isoflavene **6h** (30 mg, 0.063 mmol) was dissolved in ethanol (5 mL) and treated with aqueous KOH (1 M, 0.3 mL, 0.3 mmol) to give the product **7h** as a red powder. Yield: 22 mg, 89%. Mp 224–227 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.62 (br s, 1H, OH), 9.53 (br s, 1H, OH), 7.88 (d, J = 8.8 Hz, 2H, H2″,6″), 7.57 (d, J = 8.8 Hz, 2H, H2′,6′), 7.40 (d, J = 8.8 Hz, 2H, H3″,5″), 7.03 (d, J = 8.2 Hz, 1H, H5), 6.86 (br s, 1H, H4), 6.81 (d, J = 8.8 Hz, 2H, H3′,5′), 6.37 (dd, J = 2.3 Hz, 8.2 Hz, 1H, H6), 6.04 (d, J = 2.3 Hz, 1H, H8), 5.91 (dd, J = 2.0 Hz, 9.7 Hz, 1H, H2), 3.62 (dd, J = 9.7 Hz, 16.3 Hz, 1H, C*H*^{a}COAr), 2.86 (dd, J = 2.0 Hz, 16.3 Hz, 1H, C*H*^{b}COAr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.3, 158.4, 157.1, 151.1, 138.3, 135.3, 130.0, 129.8, 128.8, 127.6, 126.6, 126.0, 116.9, 115.7, 114.4, 109.0, 103.3, 72.1, 40.9. IR (KBr): ν_{max} 3434, 1651, 1615, 1589, 1557, 1539, 1514, 1456, 1398, 1372, 1268, 1216, 1173, 1114, 1092, 1012, 833 cm^{-1}. UV–vis (MeOH): λ_{max} 278 nm (ε 10,174 cm^{-1} M^{-1}). HRMS (+ESI): Found m/z 415.0704, [M+Na]$^+$; $C_{23}H_{17}ClO_4Na$ required 415.0708.

4.1.4.9. 2-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)-1-(naphthalen-1-yl)ethanone (7i). Following general procedure C, the isoflavene **6i** (200 mg, 0.41 mmol) was dissolved in ethanol (15 mL) and treated with aqueous KOH (1 M, 1.0 mL, 1.0 mmol) to give the product **7i** as a tan solid. Yield: 141 mg, 84%. Mp 95–98 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.64 (br s, 1H, OH), 9.55 (br s, 1H, OH), 8.44 (dd, J = 1.5 Hz, 8.2 Hz, 1H, H8″), 8.19–8.11 (m, 1H, H4″), 8.06–7.99 (m, 1H, H5″), 7.88 (dd, J = 1.1 Hz, 7.2 Hz, 1H, H2″), 7.71–7.58 (m, 2H, H6″, H7″), 7.54 (dd, J = 7.2 Hz, 8.3 Hz, 1H, H3″), 7.42 (d, J = 8.9 Hz, 2H, H2′,6′), 7.01 (d, J = 8.3 Hz, 1H, H5), 6.86–6.81 (m, 3H, H4, H3′,5′), 6.36 (dd, J = 2.3 Hz, 8.2 Hz, 1H, H6), 6.07 (d, J = 2.3 Hz, 1H, H8), 5.90 (dd, J = 2.4 Hz, 10.1 Hz, 1H, H2), 3.53 (dd, J = 10.1 Hz, 15.8 Hz, 1H, C*H*^{a}COAr), 3.12 (dd, J = 2.4 Hz, 15.8 Hz, 1H, C*H*^{b}COAr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 201.5, 158.4, 157.2, 151.1, 135.7, 133.4, 132.4, 129.8, 129.3, 128.5, 127.7, 127.6, 126.6, 126.5, 126.4, 126.0, 125.3, 124.8, 116.9, 115.7, 114.3, 109.0, 103.2, 72.8, 44.8. IR (KBr): ν_{max} 3404, 2924, 1691, 1664, 1649, 1612, 1553, 1513, 1460, 1452, 1357, 1268, 1232, 1169, 1117, 1046, 987, 957, 833, 803, 776 cm^{-1}. UV–vis (MeOH): λ_{max} 318 nm (ε 15,256 cm^{-1} M^{-1}), 212 (47,013). HRMS (+ESI): Found m/z 431.1245, [M+Na]$^+$; $C_{27}H_{20}O_4Na$ required 431.1254.

4.1.5. 4-(7-Acetoxy-2-(2-(2-(2,4-dinitrophenyl)hydrazono)propyl)-2*H*-chromen-3-yl)phenyl acetate (8)

A solution of the isoflavene **6a** (299 mg, 0.768 mmol) in ethanol (200 mL) was added dropwise to a solution of 2,4-dinitrophenylhydrazine (178 mg, 0.898 mmol) in ethanol (100 mL). The mixture was heated at reflux for 19 h. Solvent was evaporated in vacuo and the crude product recrystallised from ethyl acetate to afford the product **8** as orange-red needles. Yield: 288 mg, 67%. Mp 192–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.02 (br s, 1H, NH), 9.14 (d, J = 2.6 Hz, 1H, H3″), 8.33 (dd, J = 2.6 Hz, 9.6 Hz, 1H, H5″), 7.89 (d, J = 9.6 Hz, 1H, H6″), 7.51 (d, J = 8.7, 2H, H2′,6′), 7.15–7.11 (m, 3H, H3′,5′, H5), 6.80 (br s, 1H, H4), 6.72 (dd, J = 2.2 Hz, 8.1 Hz, 1H, H6), 6.49 (d, J = 2.2 Hz, 1H, H8), 5.69 (dd, J = 3.1 Hz, 9.7 Hz, 1H, H2), 2.95 (dd, J = 9.7 Hz, 14.5 Hz, 1H, C*H*^{a}CN), 2.36 (dd, J = 3.1 Hz, 14.5 Hz, 1H, C*H*^{b}CN), 2.33 (s, 3H, $COCH_3$), 2.28 (s, 3H, $COCH_3$), 2.11 (s, 3H, $CNCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 169.3, 153.7, 151.5, 150.6, 145.1, 138.0, 134.0, 133.5, 130.1, 129.8, 129.3, 127.5, 126.5, 123.4, 122.4, 120.3, 119.4, 116.7, 115.2, 110.5, 74.7, 42.1, 21.2, 21.1, 16.6. IR (KBr): ν_{max} 3431, 3316, 3110, 2923, 1769, 1754, 1618, 1594, 1508, 1423, 1369, 1336, 1314, 1291, 1259, 1195, 1170, 1137, 1116, 1097, 1045, 1013, 958, 943, 922, 910, 877, 839, 743 cm^{-1}. UV–vis (MeOH): λ_{max} 338 nm (ε 15,904 cm^{-1} M^{-1}), 276 (8,674), 239 (15,862), 208 (17,600). HRMS (+ESI): Found m/z 583.1431, [M+Na]$^+$; $C_{28}H_{24}N_4O_9Na$ required 583.1435.

4.1.6. 2-(2-(2-(2,4-Dinitrophenyl)hydrazono)propyl)-3-(4-hydroxyphenyl)-2*H*-chromen-7-ol (9)

Following general procedure C, the isoflavene hydrazone **8** (50 mg, 0.089 mmol) was dissolved in ethanol (15 mL) and treated with aqueous KOH (1 M, 1.0 mL, 1.0 mmol) to give the product **9** as a dark red solid. Yield: 39 mg, 91%. Mp 228–230 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.80 (br s, 1H, NH), 8.89 (d, J = 2.5 Hz, 1H, H3″), 8.35 (dd, J =2.5 Hz, 9.6 Hz, 1H, H5″), 7.78 (d, J = 9.6 Hz, 1H, H6″), 7.45 (d, J = 8.7, 2H, H2′,6′), 7.14 (d, J = 8.8 Hz, 2H, H3′,5′), 7.01 (d, J = 8.2 Hz, 1H, H5), 6.86 (br s, 1H, H4), 6.39 (dd, J = 2.2 Hz, 8.1 Hz, 1H, H6), 6.23 (d, J = 2.2 Hz, 1H, H8), 5.73 (dd, J = 3.1 Hz, 9.6 Hz, 1H, H2), 2.77 (dd, J = 9.6 Hz, 14.5 Hz, 1H, C*H*^{a}CN), 2.59 (dd, J = 3.1 Hz, 14.5 Hz, 1H, C*H*^{b}CN), 2.12 (s, 3H, $CNCH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.7, 156.5, 151.2, 145.1, 138.0, 134.0, 133.5, 130.1, 129.8, 129.3, 127.6, 126.4, 123.0, 122.4, 119.8, 115.7, 114.3, 109.0, 103.2, 75.0, 41.9, 16.8. IR (KBr): ν_{max} 3428, 2927, 1748, 1618, 1592, 1536, 1515, 1462, 1422, 1365, 1334, 1312, 1284, 1211, 1173, 1116, 1096, 1061, 1040, 1014, 920, 833, 741 cm^{-1}. UV–vis (MeOH): λ_{max} 341 nm (ε 10,839 cm^{-1} - M^{-1}), 211 (16,684). HRMS (+ESI): Found m/z 499.1222, [M+Na]$^+$; $C_{24}H_{20}N_4O_7Na$ required 499.1224.

4.1.7. Synthesis of 2-arylisoflavenes 10a–d

4.1.7.1. 4-(7-Acetoxy-2-(5-acetyl-1*H*-pyrrol-2-yl)-2*H*-chromen-3-yl)phenyl acetate (10a). Following general procedure B, 2-acetylpyrrole (27 mg, 0.25 mmol) was added to a suspension of isoflavylium salt **5** (100 mg, 0.21 mmol) in CH_2Cl_2 (10 mL) to give the product **10a** as small beige crystals. Yield: 34 mg, 38%. Mp 255–259 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (br s, 1H, NH), 7.44 (d, J = 8.8 Hz, 2H, H2′,6′), 7.14 (d, J = 8.2 Hz, 1H, H5), 7.07 (d, J = 8.8 Hz, 2H, H3′,5′), 6.98 (br s, 1H, H4), 6.95–6.91 (m, 1H, H4″), 6.88–6.85 (m, 1H, H5″), 6.66 (dd, J = 2.2 Hz, 8.2 Hz, 1H, H6), 6.57 (d, J = 2.3 Hz, 1H, H8), 6.19 (br s, 1H, H2), 2.36 (s, 3H, $COCH_3$), 2.30 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 187.1, 169.1, 168.9, 151.7, 151.0, 150.1, 133.8, 132.2, 132.1, 127.4, 126.4, 124.7, 122.7, 122.1, 120.7, 118.9, 114.7, 110.2, 93.4, 70.7, 25.6, 20.1. IR (KBr): ν_{max} 3441, 3277, 1758, 1641, 1562, 1509, 1493, 1433, 1397, 1370, 1248, 1212, 1190, 1168, 1137, 1112, 1022, 946, 851, 733 cm^{-1}. UV–vis (MeOH): λ_{max} 333 nm (ε 5,393 cm^{-1} M^{-1}), 291 (6,471), 205

(11,110). HRMS (+ESI): Found *m*/*z* 432.1434, $[M+H]^+$; $C_{25}H_{22}NO_6$ required 432.1442.

4.1.7.2. 4-(7-Acetoxy-2-(3-methyl-1*H*-indol-2-yl)-2*H*-chromen-3-yl)phenyl acetate (10b). Following general procedure B, 3-methylindole (31 mg, 0.24 mmol) was added to a suspension of isoflavylium salt **5** (100 mg, 0.21 mmol) in CH_2Cl_2 (10 mL) to give the product **10b** as small, pale orange crystals. Yield: 34 mg, 36%. Mp 205–206 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (br s, 1H, NH), 7.57 (d, *J* = 8.0 Hz, 1H, indole ArH), 7.36 (d, *J* = 8.7 Hz, 2H, H2′,6′), 7.21 (d, *J* = 8.4 Hz, 1H, H5), 7.17–7.13 (m, 2H, indole ArH), 7.12–7.07 (m, 2H, H4, indole ArH), 7.01 (d, *J* = 8.7 Hz, 2H, H3′,5′), 6.70 (dd, *J* = 2.3 Hz, 8.3 Hz, 1H, H6), 6.55 (d, *J* = 2.3 Hz, 1H, H8), 6.51 (br s, 1H, H2), 2.49 (s, 3H, CH_3), 2.28 (s, 3H, $COCH_3$), 2.23 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 168.9, 152.0, 151.1, 150.1, 135.4, 133.8, 131.4, 129.2, 128.4, 128.0, 126.3, 122.1, 121.9, 121.0, 119.8, 118.5, 114.7, 111.7, 109.4, 109.0, 69.8, 20.8, 8.4. IR (KBr): ν_{max} 3411, 3031, 2919, 1764, 1651, 1611, 1584, 1510, 1495, 1455, 1428, 1370, 1334, 1306, 1267, 1257, 1207, 1172, 1141, 1116, 1017, 977, 936, 910, 886, 842, 739 cm^{-1}. UV–vis (MeOH): λ_{max} 294 nm (ε 6,893 cm^{-1} M^{-1}), 224 (14,013), 208 (13,741). HRMS (+ESI): Found *m*/*z* 454.1645, $[M+H]^+$; $C_{28}H_{24}NO_5$ required 454.1649.

4.1.7.3. 4-(7-Acetoxy-2-(3-(cyanomethyl)-1*H*-indol-2-yl)-2*H*-chromen-3-yl)phenyl acetate (10c). Following general procedure B, indole-3-acetonitrile (36 mg, 0.23 mmol) was added to a suspension of isoflavylium salt **5** (100 mg, 0.21 mmol) in CH_2Cl_2 (20 mL) to give the product **10c** as a light brown powder. Yield: 42 mg, 42%. Mp 206–208 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (br d, *J* = 8.5 Hz, 1H, indole ArH), 7.58 (ddd, *J* = 0.8 Hz, 1.1 Hz, 8.0 Hz, 1H, indole ArH), 7.42 (ddd, *J* = 1.1 Hz, 7.1 Hz, 8.0 Hz, 1H, indole ArH), 7.39 (br s, 1H, NH), 7.34–7.26 (m, 5H, H4, H5, H2′,6′, indole ArH), 7.04 (d, *J* = 8.8 Hz, 2H, H3′,5′), 7.00 (br s. 1H, H2), 6.79 (dd, *J* = 2.3 Hz, 8.3 Hz, 1H, H6), 6.59 (d, *J* = 2.3 Hz, 1H, H8), 3.66 (s, 2H, CH_2CN), 2.28 (s, 3H, $COCH_3$), 2.22 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 168.8, 151.5, 150.5, 150.4, 135.5, 132.7, 128.5, 127.4, 126.5, 126.3, 123.5, 123.2, 122.9, 122.4 (C3′, 5′), 120.8, 119.0, 118.7, 118.6, 110.1, 106.4, 77.7, 20.8, 13.1. IR (KBr): ν_{max} 3435, 1755, 1612, 1585, 1512, 1496, 1458, 1432, 1410, 1371, 1351, 1258, 1213, 1198, 1174, 1140, 1113, 1045, 1021, 978, 906, 851, 743 cm^{-1}. UV–vis (MeOH): λ_{max} 283 nm (ε 4,546 cm^{-1} M^{-1}), 219 (7,417). HRMS (+ESI): Found *m*/*z* 479.1595, $[M+H]^+$; $C_{29}H_{23}N_2O_5$ required 479.1601.

4.1.7.4. 4-(7-Acetoxy-2-(4-amino-3,5-dimethylphenyl)-2*H*-chromen-3-yl)phenyl acetate (10d). 2,6-Dimethylaniline (0.75 mL, 6.6 mmol) was added to a suspension of isoflavylium salt **5** (1.44 g, 3.08 mmol) in CH_2Cl_2 (100 mL) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 15 min, during which time it became clear and colourless, then pale purple and cloudy. The pale purple precipitate was collected by filtration. The crude product was recrystallised from ethyl acetate to give the product **10d** as small purple crystals. Yield: 711 mg, 52%. Mp 220–222 °C. ^{1}H NMR^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.7 Hz, 2H, H2′,6′), 7.12 (d, *J* = 8.3 Hz, 1H, H5), 7.04 (br s, 1H, H4), 7.03–6.97 (m, 4H, H3′,5′, H2″,6″), 6.62 (dd, *J* = 2.2 Hz, 8.3 Hz, 1H, H6), 6.49 (d, *J* = 2.2 Hz, 1H, H8), 6.09 (br s, 1H, H2), 3.48 (br s, 2H, NH_2), 2.28 (s, 3H, $COCH_3$), 2.23 (s, 3H, $COCH_3$), 2.09 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 169.4, 152.5, 151.5, 150.3, 143.6, 135.2, 131.8, 129.2, 127.4, 127.3, 126.8, 121.9, 121.8, 120.8, 120.3, 114.4, 110.2, 78.6, 21.3, 18.0. IR (KBr): ν_{max} 3481, 3394, 3075, 2966, 2930, 2850, 1757, 1655, 1625, 1609, 1513, 1492, 1431, 1368, 1306, 1257, 1207, 1193, 1180, 1153, 1137, 1111, 1019, 984, 961, 907, 875, 849 cm^{-1}. UV–vis (MeOH): λ_{max} 333 nm (ε 7,908 cm^{-1} M^{-1}), 295 (7,462), 246 (13,304), 209 (20,179). HRMS (+ESI): Found *m*/*z* 444.1797, $[M+H]^+$; $C_{27}H_{26}NO_5$ required 444.1805.

4.1.8. Synthesis of 2-arylisoflavenes 11a–d

4.1.8.1. 1-(5-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)-1*H*-pyrrol-2-yl)ethanone (11a). Following general procedure C, the isoflavene **10a** (25 mg, 0.058 mmol) was suspended in methanol (5 mL) and treated with aqueous KOH (1 M, 0.4 mL, 0.4 mmol) to give the product **11a** as a light brown powder. Yield: 13 mg, 65%. Mp 142–145 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.67 (br s, 1H, NH), 9.52 (br s, 1H, OH), 9.44 (br s, 1H, OH), 7.33 (d, *J* = 8.7 Hz, 2H, H2′,6′), 7.00 (d, *J* = 8.3 Hz, 1H, H5), 6.93 (br s, 1H, H4), 6.85–6.81 (m, 2H, H4″, H5″), 6.72 (d, *J* = 8.7 Hz, 2H, H3′,5′), 6.29 (dd, *J* = 2.3 Hz, 8.3 Hz, 1H, H6), 6.20 (br s, 1H, H2), 6.13 (d, *J* = 2.3 Hz, 1H, H8), 2.24 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 187.0, 158.2, 156.9, 152.0, 133.8, 132.0, 132.1, 129.8, 126.1, 124.5, 122.6, 116.5, 115.8, 115.4, 114.4, 109.8, 103.3, 70.7, 25.5. IR (KBr): ν_{max} 3417, 2924, 1703, 1697, 1614, 1556, 1514, 1504, 1462, 1454, 1402, 1368, 1286, 1265, 1177, 1152, 1115, 1025, 965, 944, 834 cm^{-1}. UV–vis (MeOH): λ_{max} 333 nm (ε 9,292 cm^{-1} M^{-1}), 294 (11,515), 251 (7,850), 203 (14,745). HRMS (+ESI): Found *m*/*z* 348.1225, $[M+H]^+$; $C_{21}H_{18}NO_4$ required 348.1230

4.1.8.2. 3-(4-Hydroxyphenyl)-2-(3-methyl-1*H*-indol-2-yl)-2*H*-chromen-7-ol (11b). Following general procedure C, the isoflavene **10b** (25 mg, 0.055 mmol) was suspended in methanol (5 mL) and treated with aqueous KOH (1 M, 0.4 mL, 0.4 mmol) to give the product **11b** as a light brown powder. Yield: 12 mg, 59%. Mp 168–172 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (br s, 1H, NH), 9.49 (br s, 1H, OH), 9.45 (br s, 1H, OH), 7.42 (br d, *J* = 7.7 Hz, 1H, indole ArH), 7.29 (d, *J* = 8.8 Hz, 2H, H2′,6′), 7.23 (br d, *J* = 7.7 Hz, 1H, indole ArH), 7.07–6.97 (m, 3H, H4, H5, indole ArH), 6.95–6.89 (m, 1H, indole ArH), 6.68 (d, *J* = 8.8 Hz, 2H, H3′,5′), 6.57 (br s, 1H, H2), 6.31 (dd, *J* = 2.3 Hz, 8.2 Hz, 1H, H6), 6.09 (d, *J* = 2.3 Hz, 1H, H8), 2.31 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.9, 154.6, 151.9, 145.4, 143.6, 141.8, 138.3, 132.9, 130.0, 128.5, 126.1, 122.9, 121.1, 118.1, 117.8, 115.3, 109.5, 106.8, 72.4, 8.8. IR (KBr): ν_{max} 3389, 2928, 1612, 1556, 1515, 1504, 1487, 1454, 1382, 1359, 1335, 1238, 1174, 1151, 1114, 1025, 976, 835, 747 cm^{-1}. UV–vis (MeOH): λ_{max} 287 nm (ε 5,702 cm^{-1} M^{-1}), 203 (16,947). HRMS (+ESI): Found *m*/*z* 392.1259, $[M+H]^+$; $C_{24}H_{19}NO_3Na$ required 392.1263.

4.1.8.3. 2-(2-(7-Hydroxy-3-(4-hydroxyphenyl)-2*H*-chromen-2-yl)-1*H*-indol-3-yl)acetonitrile (11c). Following general procedure C, the isoflavene **10c** (25 mg, 0.052 mmol) was suspended in methanol (5 mL) and treated with aqueous KOH (1 M, 0.4 mL, 0.4 mmol) to give the product **11c** as a pinkish brown powder. Yield: 12 mg, 59%. Mp 167–169 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.67 (br s, 1H, OH), 9.59 (br s, 1H, OH), 8.04 (br d, *J* = 8.3 Hz, 1H, indole ArH), 7.68 (br s, 1H, NH), 7.56 (br d, *J* = 7.9 Hz, 1H, indole ArH), 7.41 (br s, 1H, H4), 7.38–7.27 (m, 3H, H2′,6′, indole ArH), 7.25–7.16 (m, 2H, H5, indole ArH), 7.03 (br s, 1H, H2), 6.70 (d, *J* = 8.8 Hz, 2H, H3′,5′), 6.44 (dd, *J* = 2.3 Hz, 8.2 Hz, 1H, H6), 6.12 (d, *J* = 2.3 Hz, 1H, H8), 3.92 (br s, 2H, CH_2CN). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.9, 156.6, 151.8, 145.3, 143.9, 141.6, 137.6, 131.1, 130.0, 128.2, 126.6, 123.1, 119.7, 116.6, 116.1, 114.9, 109.8, 105.5, 73.9, 17.1. IR (KBr): ν_{max} 3434, 2963, 2916, 2845, 1753, 1736, 1701, 1676, 1655, 1638, 1629, 1618, 1561, 1545, 1509, 1439, 1411, 1370, 1262, 1213, 1174, 1141, 1112, 1095, 1023, 905, 852, 802, 741 cm^{-1}. UV–vis (MeOH): λ_{max} 346 nm (ε 5,028 cm^{-1} M^{-1}), 265 (4,733), 205 (16,271). HRMS (+ESI): Found *m*/*z* 395.1388, $[M+H]^+$; $C_{25}H_{19}N_2O_3$ required 395.1390.

4.1.8.4. 2-(4-Amino-3,5-dimethylphenyl)-3-(4-hydroxyphenyl)-2*H*-chromen-7-ol (11d). Following general procedure C, the isoflavene **10d** (100 mg, 0.23 mmol) was suspended in methanol (10 mL) and treated with aqueous KOH (1 M, 2.0 mL, 2.0 mmol) to give the product **11d** (53 mg, 64%) as a pale purple powder. Mp 208–212 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.46 (br s, 2H, OH), 7.26 (d, J = 8.7 Hz, 2H, H2′,6′), 7.01 (br s, 1H, H4), 6.99 (d, J = 8.3 Hz, 1H, H5), 6.82 (s, 2H, H2″,6″), 6.68 (d, J = 8.8 Hz, 2H, H3′,5′), 6.26 (dd, J = 2.3 Hz, 8.3 Hz, 1H, H6), 6.04 (br s, 1H, H2), 6.03 (d, J = 2.3 Hz, 1H, H8), 4.59 (br s, 2H, NH_2), 1.96 (s, 6H, CH_3). ^{13}C NMR (75 MHz, d_6-Acetone) δ 159.2, 157.8, 153.9, 143.6, 130.7, 130.1, 129.1, 128.2, 127.8, 127.3, 121.9, 118.7, 116.9, 116.2, 109.0, 104.3, 79.0, 18.1. IR (KBr): ν_{max} 3395, 2959, 2923, 2852, 1655, 1618, 1591, 1561, 1516, 1487, 1460, 1376, 1274, 1242, 1182, 1157, 1118, 1028, 984, 875, 832, 810, 744 cm^{-1}. UV–vis (MeOH): λ_{max} 337 nm (ε 13,100 cm^{-1} M^{-1}), 245 (12,957), 207 (28,591). HRMS (+ESI): Found m/z 360.1587, [M+H]$^+$; $C_{23}H_{22}NO_3$ required 360.1594.

4.1.9. 7-Hydroxy-3-(4-hydroxyphenyl)-4-(4-methoxyphenyl)chromenylium chloride (13)

7,4′-Di(*tert*-butyldimethylsilyl)oxy-4-(4-methoxyphenyl)-isoflav-3-ene **12** (1.02 g, 1.77 mmol), was suspended in trifluoroacetic acid (40 mL) and stirred at room temperature for ten minutes. Thallic trifluoroacetate (1.43 g, 2.63 mmol) was added and the mixture was stirred at room temperature for a further 30 min. Water (60 mL) was added and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were neutralised by washing with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated in vacuo to give a dark red oil, with was redissolved in ethyl acetate (40 mL). To this solution 36% HCl (10 mL) was added slowly, resulting in the formation of a precipitate. Filtration afforded the product **13** as a dark red solid. Yield: 337 mg, 50%. Mp 179–181 °C (decomp.). ^{1}H NMR (300 MHz, d-TFA): δ 9.02 (br s, 1H, H4), 9.44 (d, J = 2.1 Hz, 1H, H2), 8.18 (d, J = 9.3 Hz, 1H, H5), 7.78 (dd, J = 2.1 Hz, 9.3 Hz, 1H, H6), 7.64 (d, J = 1.8 Hz, 1H, H8), 7.33 (d, J = 8.7 Hz, 2H, H2″,6″) 7.16–7.01 (m, 8H, ArH), 4.01 (br s, 3H, OMe). ^{13}C NMR (75 MHz, d-TFA): δ 180.1, 171.4, 170.8, 164.7, 162.8, 157.4, 135.3, 135.0, 133.9, 126.4, 125.7, 122.9, 119.2, 117.8, 116.9, 114.1, 105.1, 57.2. IR (KBr): ν_{max} 3136, 2837, 2687, 2560, 1796, 1606, 1510, 1462, 1462, 1429, 1416, 1382, 1332, 1288, 1227, 1258, 1176, 1112, 1062, 1026, 834 cm^{-1}. UV–vis (CH_3CN): λ_{max} 312 nm (ε 10,463 cm^{-1} M^{-1}), 201 (33,512). HRMS (+ESI): Found m/z 345.1117, [M]$^+$; $C_{22}H_{17}O_4$ required 345.1121.

4.1.10. 1-(7-Hydroxy-3-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-2*H*-chromen-2-yl)propan-2-one (14)

The isoflavylium salt **13** (50 mg, 0.13 mmol) was dissolved in acetone (25 mL) and stirred at room temperature for 3 days. Solvent was evaporated in vacuo to a volume of approximately 5 mL. Filtration afforded the product **14** as a dark green solid. Yield: 38 mg, 72%. Mp 99–104 °C (decomp.). ^{1}H NMR (300 MHz, d_6-acetone): δ 8.56 (br s, 1H, OH), 8.35 (br s, 1H, OH), 7.05 (d, J = 8.4 Hz, 2H, H2″,6″), 6.98 (d, J = 8.7, 2H, H2′,6′), 6.86 (d, J = 8.4 Hz, 2H, H3″,5″), 6.66 (d, J = 8.4 Hz, 1H, H5), 6.64 (d, J = 8.7 Hz, 2H, H3′,5′), 6.39–6.30 (m, 3H, H4, H6, H8), 5.56 (dd, J = 2.5 Hz, 10.2 Hz, 1H, H2), 3.78 (s, 3H, OMe), 3.19 (dd, J = 10.2 Hz, 15.8 Hz, 1H, C*H*^{a}COCH$_3$), 2.57 (dd, J = 2.5 Hz, 15.8 Hz, 1H, C*H*^{b}COCH$_3$), 2.15 (s, 3H, COCH$_3$). ^{13}C NMR (75 MHz, d_6-acetone): δ 205.6, 159.5, 159.3, 156.9, 153.4, 132.2, 131.6, 131.3, 130.4, 130.3, 130.1, 127.9, 117.8, 115.6, 114.3, 109.1, 104.4, 76.5, 55.3, 46.4, 30.6. IR (KBr): ν_{max} 3384, 3033, 2932, 2835, 1701, 1608, 1510, 1455, 1367, 1246, 1172, 1117, 1030, 1012, 971, 832, 794 cm^{-1}. UV–vis (MeOH): λ_{max} 285 nm (ε 4,165 cm^{-1} M^{-1}), 204 (12,073). HRMS (+ESI): Found m/z 425.1350, [M+Na]$^+$; $C_{25}H_{22}O_5Na$ required 425.1359.

4.2. Biological Experiments

4.2.1. Anti-cancer activity

4.2.1.1. Cell biology techniques. The human neuroblastoma cell line, SHEP, and human breast cancer cell line, MDA-MB-231, were cultured in DMEM medium (Invitrogen) supplemented with 10% FCS, 1% PSG. The cell lines were maintained at 37 °C in 5% CO_2 as an adherent monolayer and were passaged upon reaching confluence by standard cell culture techniques.

4.2.1.2. Cell viability assays. SHEP and MDA-MB-231 cells were seeded at 3000 cells per well in 96-well plates to ensure sustained exponential growth for 4 days. Cells were treated 24 h after seeding with a range of concentrations from 1.0 to 500 μM of compounds **4a–i**, **6**, **8d** and **11**. After 72 h drug incubation, the metabolic activity was detected by spectrophotometric analysis by assessing the absorbance of Alamar blue as described previously.[35] Cell proliferation was determined and expressed as a percentage of untreated control cells. The determination of IC_{50} values was performed using GraphPad Prism 6 (San Diego, CA, USA).

4.2.1.3. Statistical analysis. All in vitro experiments were performed in at least triplicate and statistical significance was determined using the two-sided Student's *t*-test. All statistical analyses were performed using GraphPad Prism 6.

4.2.2. Anti-inflammatory activity

4.2.2.1. Interleukin-6 assay. RAW 264.7 cells were seeded at 15,000 cells per well in a 96 well plate in 100 μL of complete media (RPMI-1640, 10% FCS, Pen/Strep, L-Glutamine). After 24 h, the media was replaced with 100 μL of media containing 0.1% DMSO (vehicle control), dexamethasone (40 ng/mL) or compounds **7a**, **7c**, **7f**, **11d** or **14** in DMSO (1, 3 and 10 μM final concentration). Cells were incubated at 37 °C for 1 h after which an additional 100 μL of each test media containing LPS (100 ng/mL) was added. Cells were incubated for 16 h after which the media was collected. Interleukin-6 in cell culture supernatant was measured using an ELISA according to the manufacturer's specifications (R&D Systems, Minneapolis, MN, USA).

4.2.2.2. Cell viability assay. Immediately after the supernatant was collected, cell viability was determined using a colorimetric viability assay (CCK-8 assay; Dojindo Molecular Technologies, Rockville, MD, USA) as described previously.[36] In brief, 100 μL of complete media containing 10 μL of CCK-8 reagent was added to each well. Cells were incubated for 2 h and the absorbance at 450 nm was measured using a SpectraMax M3 plate reader (Molecular Devices, Sunnyvale, CA, USA).

4.2.2.3. Statistical analysis. The production of IL-6 and viability of drug-treated cells was reported relative to vehicle-treated controls. Data reported are the means +/− SEM of 3 independent experiments and results were analysed using a one-way ANOVA followed by a Holm-Sidak multiple comparison test. Graphs were prepared using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA).

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