RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 40149

Synthesis and biological evaluation of pyrano and furano fused ring isoflavene derivatives

Valerio Falasca, *[a] Eugene Yee,[a] Shekh Sabir,[a] Mohan Bhadbade,[b] Daniel S. Wenholz,[ac] David StC. Black[a] and Naresh Kumar *[a]

Received 19th August 2025
Accepted 7th October 2025

DOI: 10.1039/d5ra06129f

rsc.li/rsc-advances

Idronoxil (IDX) is a clinically tested isoflavene with anticancer and anti-inflammatory activity. While it has shown favourable safety and efficacy profiles in early trials, further optimisation is needed to improve its potency and pharmacokinetic properties. Structural modifications at the C6 and C7 positions of IDX have yielded promising leads; however, dual functionalisation of these sites remains underexplored. In this study, we report the synthesis of novel fused-ring IDX derivatives incorporating coumarin, pyran, and furan moieties *via* Pechmann and Knoevenagel condensations, Rap–Stoermer cyclisations, and [4 + 2] cycloaddition reactions involving *o*-quinone methide intermediates. A selection of analogues with differing functionality was evaluated for anticancer activity across prostate (PC-3), neuroblastoma (SKN-BE(2)C), and triple-negative breast cancer (MDA-MB-231) cell lines. These findings establish synthetic strategies for the incorporation of various fused rings to isoflavene scaffolds and offer insights for structure–activity optimisation.

1 Introduction

Isoflavonoids are a naturally occurring class of flavonoids found predominantly in soy based foods, and have garnered attention for their anti-inflammatory, anti-cancer, antioxidant and anti-microbial effects, with many having been tested in clinical trials.[1] Among them, genistein (**1**) and daidzein (**2**) (Fig. 1) have been widely studied, however, their moderate potency, low bioavailability, and promiscuity have limited their clinical translation.[2,3] Idronoxil (IDX) (**3**) (Fig. 1), a semi-synthetic isoflavene, has shown promise as an anti-inflammatory and anti-cancer agent. IDX has been tested in multiple clinical trials as both standalone and combination therapies, where it was well tolerated by patients.[4–6] However, despite improvements over other isoflavonoids, IDX's clinical efficacy is hampered by poor drug properties, stressing a need for further improvements.[2,4–7]

Various modifications of IDX, particularly on the A-ring, have been tested to improve potency, selectivity and solubility.[8–10] Previous work from the Kumar group has focused on the C6 and C7 positions of IDX, where Mannich substitutions or *O*-alkylation generated analogues with nanomolar cytotoxicity in breast cancer and neuroblastoma cell lines.[8,11] Petasis reaction at the C6 position was also successful in potentiating the anti-inflammatory potency of IDX to nanomolar levels *via* TBK1 inhibition. C4 alkylation of similar benzoxazine molecules also resulted in anticancer analogues with low micromolar IC_{50} values against PC-3 cells.[12]

Although individual modification at the C6 position and C7 phenol have yielded promising anticancer and anti-inflammatory leads, dual functionalisation of these sites remains underexplored. Chen *et al.* synthesized a series of benzoxazines *via* Mannich reaction of IDX with anticancer activity against MDA-MB-231 cells (**4**, IC_{50} = 0.7 μM, Fig. 2), however, other fused ring structures such as furan or pyran have not been incorporated into IDX. Fused ring functionalisation reduces a structure's flexibility and increases three-dimensional complexity, which can often lead to an improvement in the selectivity, potency and pharmacokinetics of lead candidates.[13–15] Furthermore, the rigid planar shape of certain isoflavonoids and flavonoids mechanistically favours cancer cytotoxicity by intercalating between DNA base pairs and/or poisoning topoisomerase I.[16] IDX is known to undergo extensive first-pass and post-absorption metabolism, with a short plasma half-life of ~45 minutes.[17] Its phenolic groups are key sites for rapid metabolic clearance, as they are readily subjected to both phase I oxidation and phase II conjugation (glucuronidation and sulfation), processes that increase polarity and promote rapid elimination.[18] Fused-ring compounds contain one fewer phenolic hydroxyl group than IDX. This modification is predicted to reduce hydrogen bond donor count and polar surface area, which can improve bioavailability while also lowering susceptibility to metabolism at that position.

Fused pyran and furan rings have played a pivotal role in the pharmacological activities of many natural and synthetic

[a]*School of Chemistry, University of New South Wales, Sydney, NSW-2052, Australia. E-mail: n.kumar@unsw.edu.au*

[b]*Solid State and Elemental Analysis Unit, Mark Wainwright Analytical Centre, The University of New South Wales, Sydney, NSW 2052, Australia*

[c]*Noxopharm Limited, Sydney, NSW, Australia*

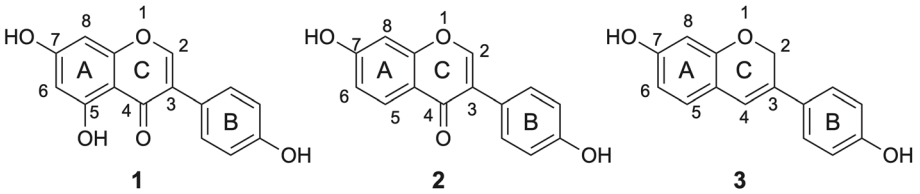


Fig. 1 Chemical structures of isoflavonoids genistein (**1**) daidzein (**2**) and IDX (**3**).

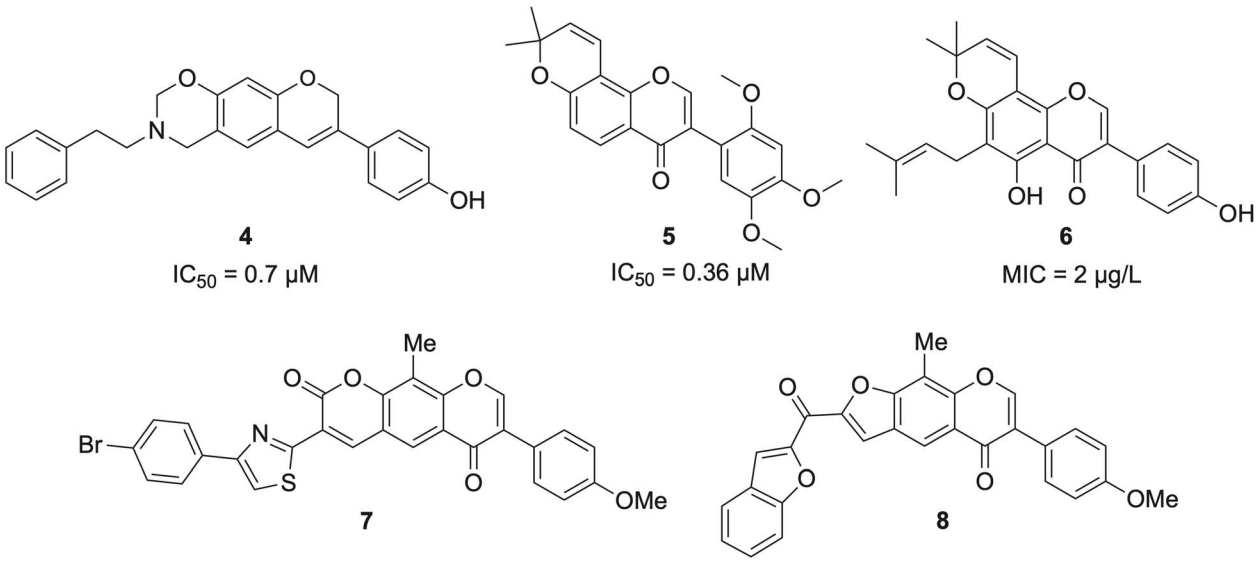


Fig. 2 Biologically active pyrano- and furano-functionalized isoflavonoids.

isoflavonoids, including their anti-inflammatory, anti-cancer, and antimicrobial effects. A flagship example is barbigerone (**5**) (Fig. 2), a natural pyranoisoflavone. Barbigerone was reported to induce apoptosis and possess nanomolar inhibition in liver and lung cancer models (IC_{50} = 0.61 μM, 0.36 μM, respectively), demonstrating superior levels of potency that are usually observed among other natural isoflavones.[19,20] Compound **5** also possesses anti-inflammatory properties through its inhibition of TNF-α at an IC_{50} of 8.5 μM.[21] Similarly, the natural pyranoisoflavone osajin (**6**) (Fig. 2), posesses highly potent antimicrobial properties (MIC against *Staphylococcus aureus* = 2 μg mL^{-1}).[22] Pyran rings can also be fused to isoflavones to form coumarins, which consist of a 2*H*-1-benzopyran-2-one core. The coumarin core is frequently present in natural products and has been used as a scaffold and pharmacophore to create clinical agents possessing antibacterial,[23] anticoagulant,[24] vasodilator,[25] anti-inflammatory[26] and anti-tumour effects[27] (Fig. 2).[27] The synthesis of coumarin (**7**) and pyrano (**8**) fused rings with isoflavones has been reported (Fig. 2), however, these compounds were not evaluated against any biological assays.[28]

Coumarins can be synthesized through many methods, including reacting an activated phenol *via* Pechmann condensation,[29] or an *ortho*-hydroxybenzaldehyde *via* Perkin,[30] Knoevenagel,[31] Wittig,[32] and Reformatsky reactions.[33] Isoflavonoids have not been reported to react under Pechmann conditions, possibly due to the harsh conditions and poor solubility associated with the C6 phenol bearing scaffolds.[34] Shokol *et al.* synthesized compounds **7** and **8** *via* formylation of an isoflavone followed by a Knoevenagel condensation. In their approach, a methyl group was introduced at the C8 position to block formylation and subsequent cyclisation at that site, which would

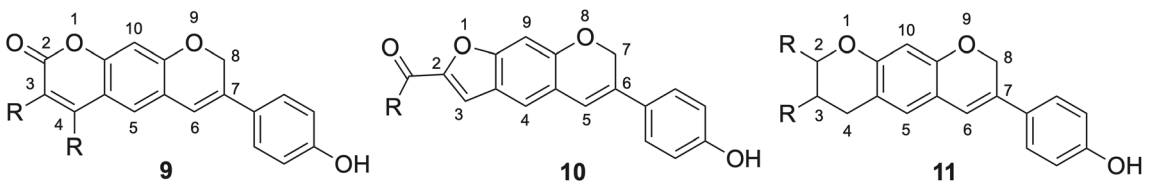


Fig. 3 Target fused-ring isoflavene structures.

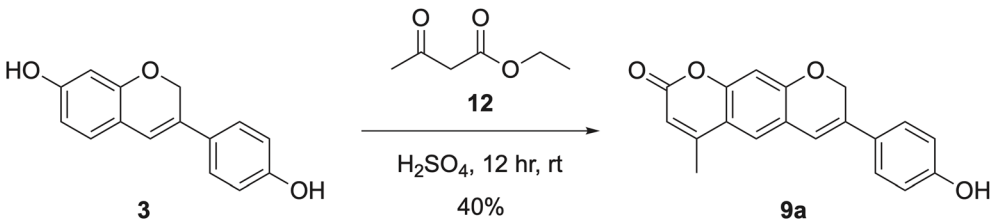
otherwise occur preferentially in isoflavones.[28,35] Unlike isoflavones, IDX can be selectively formylated at the C6 position without requiring a blocking group at C8, providing a synthetic advantage in the design of C6 and C7 fused pyrano- and furanoisoflavenes **9** and **10**, respectively (Fig. 3).[8] Pyranoisoflavonoid fused rings can also be achieved through the formation of quinone methide intermediates. This intermediate can be adopted to undergo [4 + 2] cycloaddition with a variety of dienophiles through an inverse electron-demand Diels–Alder reaction to fuse various rings onto the IDX structure **11** (Fig. 3).[36]

2 Results and discussion

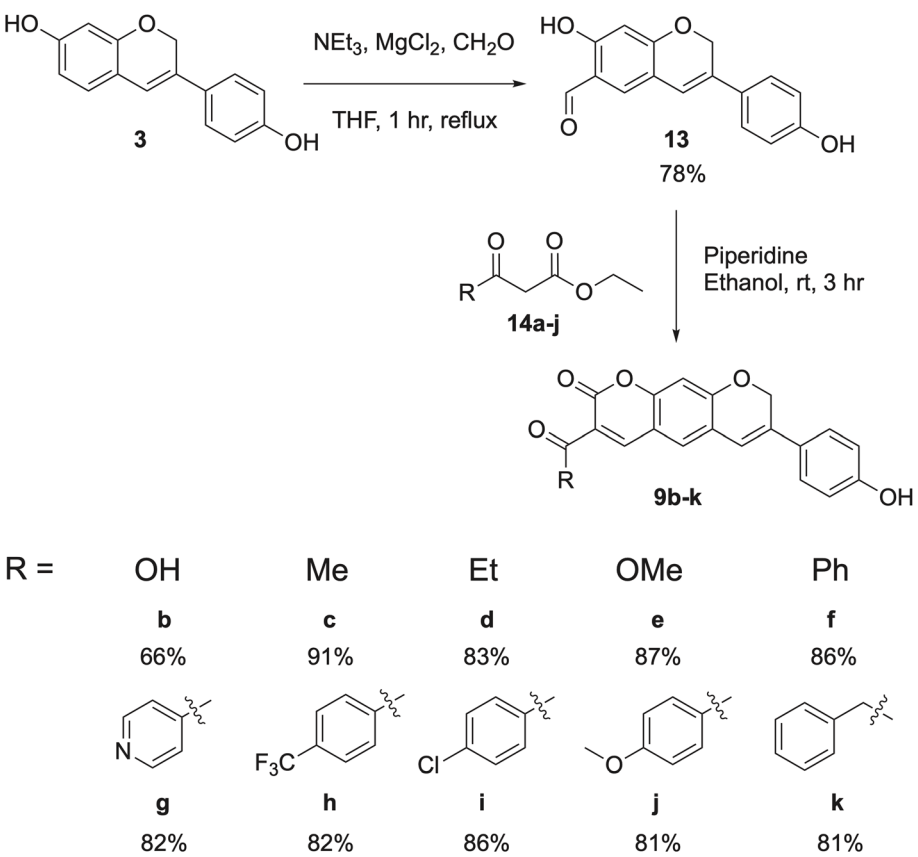
2.1 Pechmann condensation

The synthetic approach of this project began with the attempt to incorporate a coumarin core selectively onto the IDX A ring *via* a Pechmann condensation. This would result in the formation of compound **9a** in only one step using ethyl acetoacetate (**12**) (Scheme 1).

A key challenge with this reaction is the fact that IDX is often unstable under the strongly acidic conditions, and in fact decomposed when heated with various acids (Table S1, entries 1, 4 and 7).[37] To decrease the degradation of IDX, various protic and non-protic acids were investigated at lower temperatures, and the reaction time was also reduced (Table S1). The use of mild Pechmann conditions in the form of the nonprotic Lewis acid $InCl_3$ was envisaged to be ideal for minimising IDX degradation that might occur with strong acids.[38,39] Although $InCl_3$ has been a successful catalyst for Pechmann conditions in the literature,[38,39] it was ineffective at generating any product at varying temperatures and timepoints (Table S1, entries 1–3). Consequently, the more conventional strong acids HCl (Table



Scheme 1 Successful Pechmann reaction on IDX.



Scheme 2 Synthesis of fused ring coumarins *via* Knoevenagel condensation.

S1, entries 5–6) and H_2SO_4 (Table S1, entries 3b–d) were investigated at room temperature and different reaction times. Both acid-catalysed conditions did not convert a significant amount of starting material after 5 hours of stirring at room temperature (Table S1, entries 5 and 8), however, most of the starting material was consumed after 12 hours (Table S1, entries 6 and 9). Entry 9 resulted in the highest yield of 40%, which is more than double that obtained by HCl (Table S1, entry 6). This may be due to the H_2SO_4 forming fewer side products than HCl or converting IDX to the more stable coumarin form faster than HCl. A yield of 40% is low, but understandable considering that the starting material and product are unstable in strongly acidic conditions. This was corroborated by increasing the reaction time to more than 12 hours (Table S1, entry 10), which was detrimental to the yield of **9a**, likely due to decomposition under the strongly acidic conditions. Finally, the desired coumarin product **9a** was obtained in 40% yield using H_2SO_4 at room temperature for 12 hours (Scheme 1).

2.2 Knoevenagel condensation

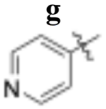
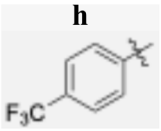
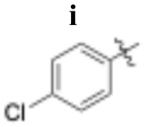
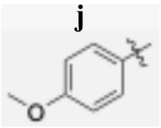
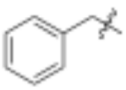
Although the Pechmann condensation offered a direct and regioselective method to annulate the A-ring of IDX, the optimized conditions still resulted in relatively low yields. To improve this limitation, a more reliable 2-step approach was adopted leveraging the selective formylation of IDX at the C6 position reported by Chen *et al.* to form the IDX aldehyde **13**.[8] The intermediate **13** was then able to undergo a Knoevenagel condensation on the A ring with different ethoxy 1,3-dicarbonyls **14a–j** enabling the synthesis of the coumarin products **9b–k** (Scheme 2) with various R groups installed at the 3 position of the fused coumarin structure, resulting in moderate 2-step yields (Table 1). The formation of products **9b–k** was confirmed by the appearance of an extra aromatic singlet around 8.80–8.42 ppm in the ^{1}H NMR spectra, and the absence of the *O*-ethyl protons in the aliphatic region. Literature conditions utilising a 2-hydroxyquinoline-3-aldehyde in neat ethyl acetoacetate and piperidine as a catalyst were initially tested, but aldehyde **13** had poor solubility in the neat reagent.[40] Instead, the conditions were adapted by introducing ethanol as a co-solvent, which assisted the dissolution of all starting materials, as well as precipitating the final products **9b–k**, which could be filtered as pure solids in high yields. This adjustment significantly improved the yield of the coumarin products **9b–k**; for example, the yield of **9c** increased from 61% to 91% when adding ethanol as a co-solvent, which equates to overall two-step yields of 48% *vs.* 71% starting from IDX, respectively.

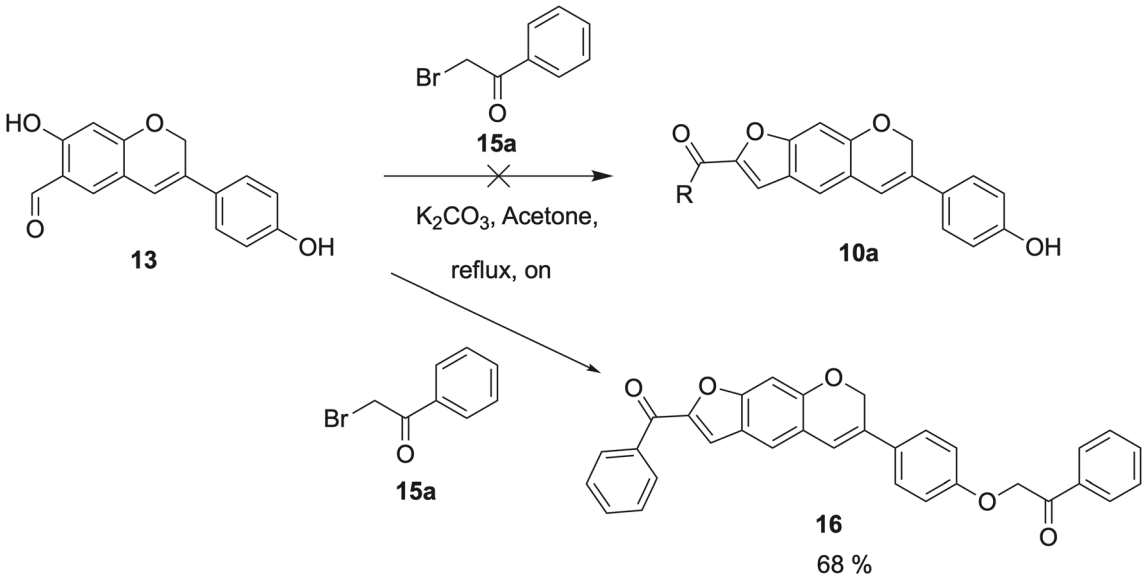
2.3 Intramolecular furan condensations

To further expand the scope of A ring cyclisations, the synthesis of similar furan fused ring structures was investigated utilising the Rap–Stoermer condensation conditions for the cyclisation of salicylaldehydes.[41] These conditions involve the cascade of nucleophilic substitution, nucleophilic addition, and elimination of water.[41] The Rap–Stoermer conditions were adapted for the reaction of IDX aldehyde **13** with an acetophenone derivative **15a** to form compound **10a** (Scheme 3).[41] However, under such conditions the cyclisation of the A-ring was coupled with the *O*-alkylation of the B ring phenol, resulting in compound **16** instead (Scheme 3). The formation of **16** was confirmed by ^{1}H NMR, by the absence of phenol peaks in the spectrum, and the appearance of an O–CH_2 peak at 5.65 ppm as well as five additional aromatic protons. Unfortunately, utilising the acetophenone **10a** as a limiting reagent did not improve the selectivity for A-ring cyclisation without alkylating the second phenol. However, the synthesis of compound **16** is useful, as it will serve as a direct comparison to **10a** to undergo the structure activity relationship (SAR) analysis of the B-ring phenol for biological activity.

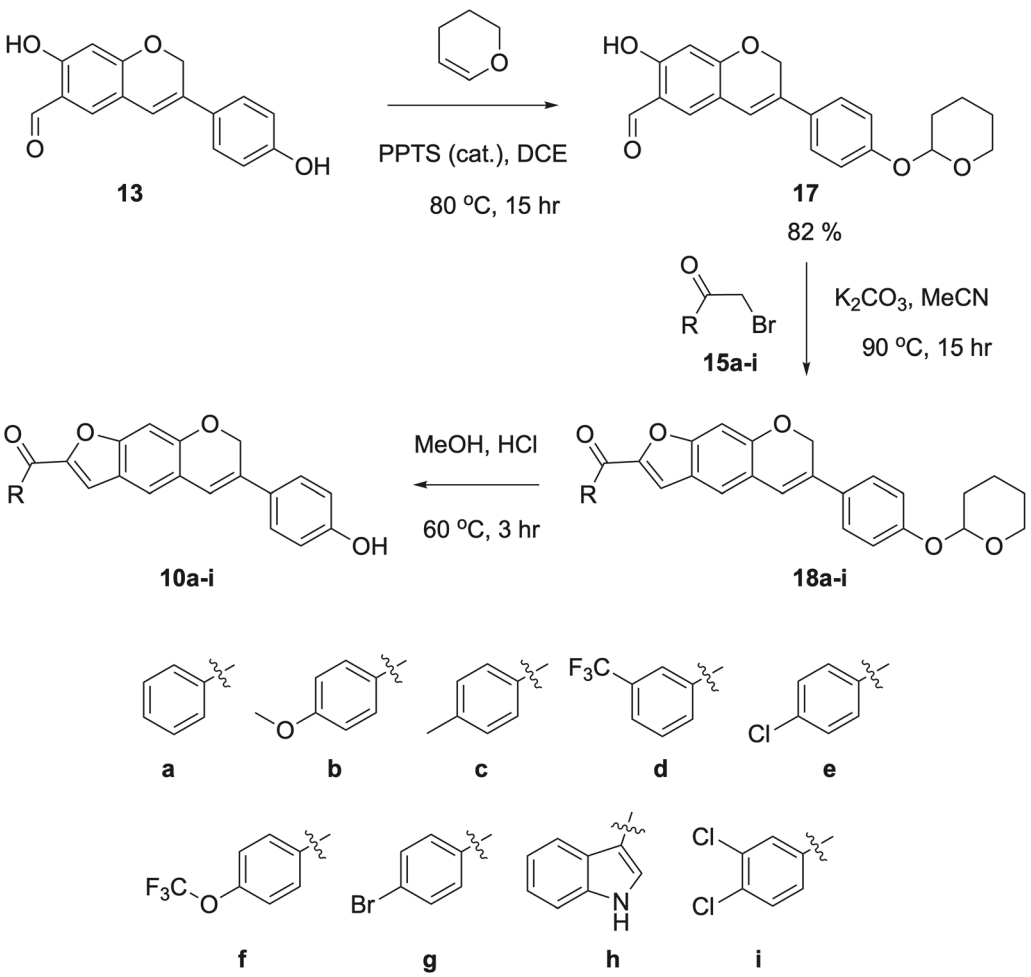
The selectivity issue with A/B ring phenol alkylation was avoided by selectively protecting the B-ring phenol with a tetrahydropyranyl (THP) group to form the protected intermediate **17** (Scheme 4). The successful addition of the THP protecting group was observed by the disappearance of an OH signal, combined with a novel hemiacetal triplet at 5.50 ppm, two OCH_2- multiplets between 3.8–3.4 ppm, and two CH_2- multiplets between 2.0–1.4 ppm. Compound **17** was reacted with 2-

Table 1 Reaction yields for the synthesis of pyrans **9b–k**

R	Yield of 9 (%)	Overall yield of 9 from IDX (%)
b –OH	66	52
c –Me	91	71
d –Et	83	65
e –OMe	87	68
f –Ph	86	67
g 	82	64
h 	82	64
i 	86	67
j 	81	63
k 	81	63

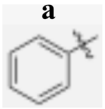
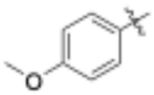
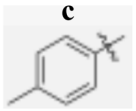
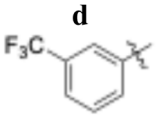
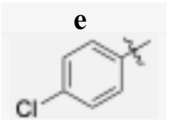
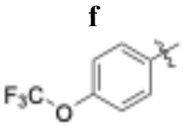
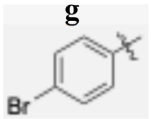
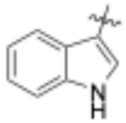
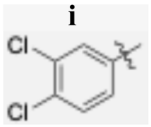


Scheme 3 Attempted selective annulation of **13** *via* Rap–Stoermer condensation.



Scheme 4 A-ring selective synthesis of fused furan rings on IDX.

Table 2 Reaction yields for the synthesis of furans **10a–i**[a]

R	Yield of 18 (%)	Yield of 10 (%)	Overall yield of 10 from IDX (%)
a 	76	94	45
b 		75*	48
c 	59	95	35
d 	54	95	32
e 	81	92	45
f 	88	95	51
g 		70	43
h 		69*	42
i 	80	92	46

[a] * = two step yield of **18** + **10**.

bromoacetophenones **15a–i** to give the THP protected fused pyran compounds **18a–i** in high yields (Scheme 4 and Table 2). The generation of the new furan ring was confirmed by the appearance of a new singlet peak between 7.9–7.7 ppm on ^{1}H NMR. Compounds **18a–i** were then deprotected to yield the desired compounds **10a–i**. The completion of the deprotection was confirmed with ^{1}H NMR by the removal of the THP OCH-, OCH_2-, and CH_2- signals, and in some cases the appearance of a broad phenol peak between 10–9 ppm.

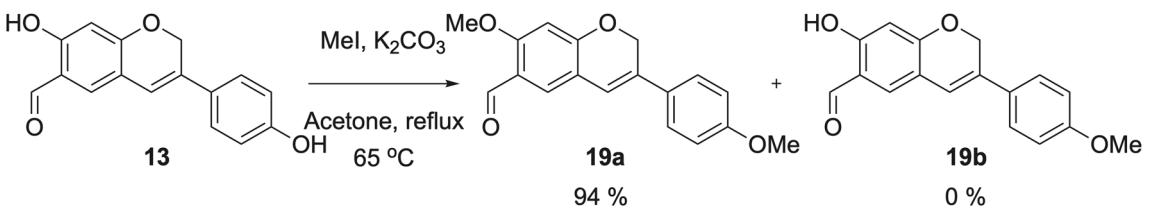
The selectivity of THP protection for the B ring phenol is likely due to steric hindrance and intramolecular hydrogen bonding between the phenolic OH and aldehyde C═O of compound **13**. This interaction may stabilise an unreactive hydrogen bonded conformation, increasing the enthalpic barrier for protection at the A-ring phenol. In comparison, protection with methyl iodide, which is smaller and highly electrophilic, showed no selectivity between the two phenols, preferentially forming the diprotected product **19a** (Scheme 5).

2.4 [4 + 2] cycloaddition reactions

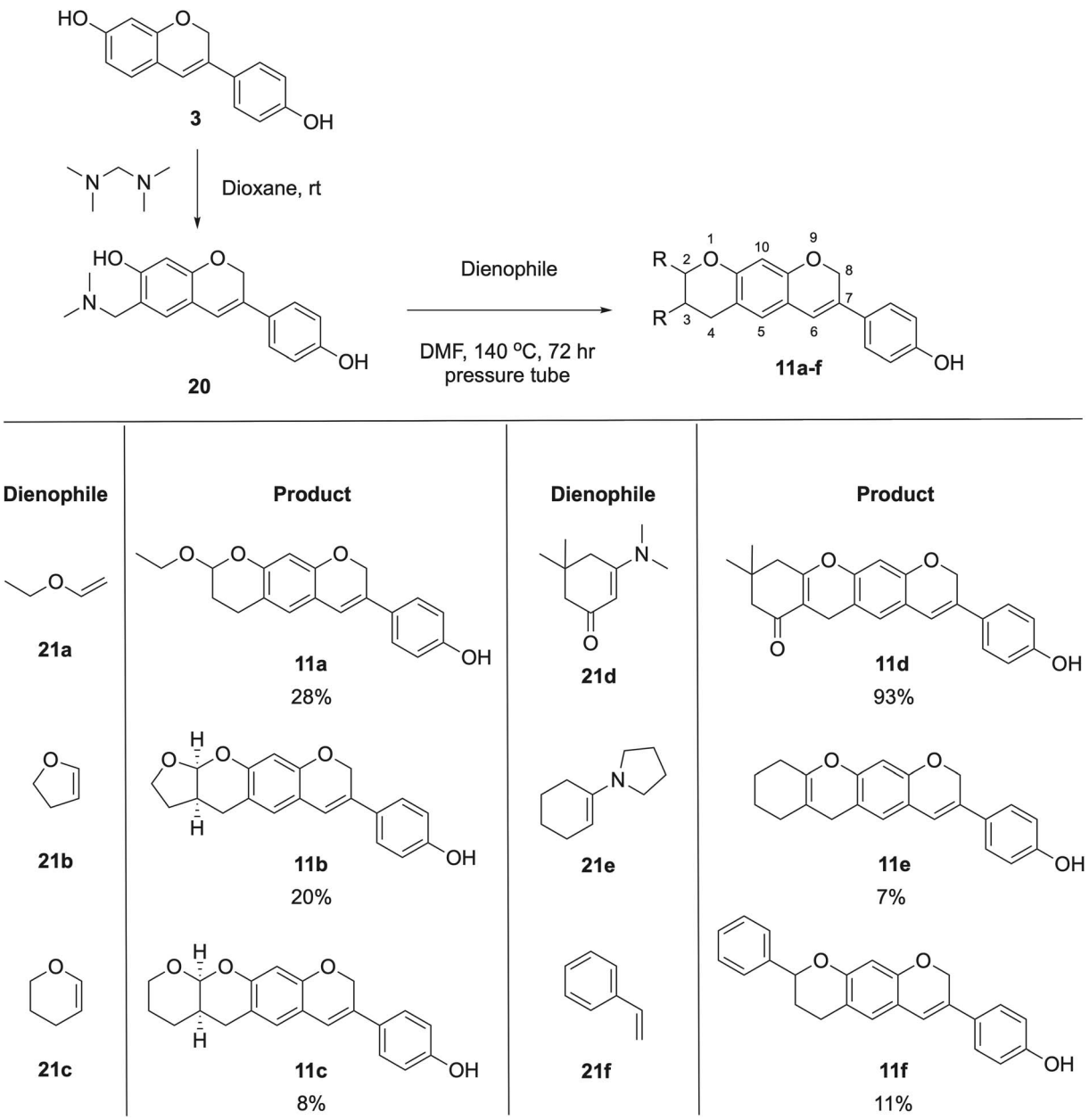
An *o*-quinone methide (*o*-QM) intermediate of IDX was explored in [4 + 2] cycloaddition reactions to construct fused-ring analogues. The *o*-QM intermediate was generated by synthesizing the Mannich precursor **20** through the reaction of IDX with bis(dimethylamino)methane. Under strong heat, **20** generated an *o*-QM intermediate, which then reacted *via* [4 + 2] cycloaddition with different dienophiles **21a–f** to yield 6 new fused ring analogues **11a–f** (Scheme 6).

While most of the cycloaddition products were obtained in low yields ranging from 8–28%, compound **11d** was an exception, being isolated in an excellent yield of 93%. This notably higher yield is likely due to the enhanced reactivity of the enaminoketone dienophile, which features a conjugated push–pull system comprising an electron-donating enamine and an electron-withdrawing carbonyl group. This electronic activation facilitates efficient addition to the *o*-QM intermediate, followed by elimination of the enamine moiety to yield the desired fused structure.

Crystals of **11b** were obtained through recrystallisation from DCM, and resulted in the determination of an X-ray crystal structure (Fig. 4). The structure indicates the non-planar orientation of the molecule, where the tetrahydrofuran ring is positioned at a 90-degree angle to the adjacent pyran ring. The asymmetric unit was the monoclinic space group P21/C.



Scheme 5 Experimentation with the selectivity of phenols across different IDX scaffolds.



Scheme 6 [4 + 2] cycloadditions *via o*-QM.

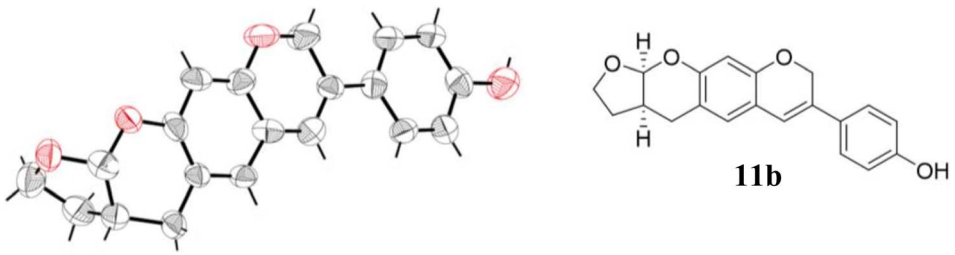


Fig. 4 ORTEP diagram of compound **11b**. CCDC = 2476513.

2.5 Biological evaluation

A selection of fused ring analogues was evaluated across an array of cancer cell lines. Fused ring coumarins **9**, **10** and **16** were screened against PC-3 prostate cancer cells at a dosage of 25 μM (Fig. 5). By comparison, the reported IC_{50} of IDX in the literature is 7.0 μM against PC-3 cells.[2,42] The results of the screen resulted

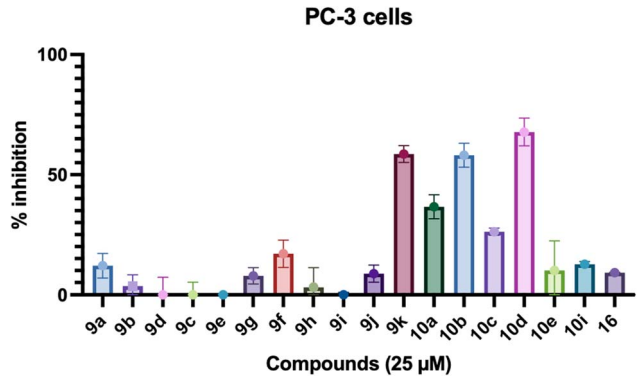


Fig. 5 Anticancer screen of fused ring analogues in PC-3 cells. Green = inhibition above 50%.

in negligible activity for most pyran compounds **9a–k**. Therefore, no SAR trend could be established between the 4-substituted coumarin (**9a**) and the 3-substituted coumarins (**9b–k**). The benzyl analogue **9k** was the only pyran-fused ring to show appreciable activity, inhibiting 58.6% of cells. The superior inhibition of the benzyl **9k** compared to a large selection of phenyl substituents (**9f–9j**) suggests that a further protruding aryl group is necessary for anticancer activity. However, at a dose of 25 μM this level of inhibition indicates relatively poor potency, with an IC_{50} of approximately 25 μM, three-fold less than IDX. The *O*-alkylated furan side product **16** displayed a three-fold lower inhibition than its counterpart **10a** with a free OH group. This result indicates a trend that B ring *O*-alkylation is detrimental for activity, however, this trend lacks biological significance due to both compounds' weak inhibition of less than 50% at 25 μM. Unlike the inactive phenyl substituents (**9f–9j**), the *para*-methoxy **10b** and *meta*-trifluoromethyl **10d** furan compounds also displayed moderate inhibitory activities of 58.1 μM and 67.8 μM. This data indicates that aryl substituents are necessary for the anticancer activity of both compounds. However, the low inhibition values at the relatively high screening dose of 25 μM provide only weak evidence for such conclusions.

A selection of [4 + 2] cycloaddition products with variation in functionality and ring size was also screened against different cancers, namely neuroblastoma (SKN-BE(2)C) and triple negative breast cancer (MDA-MB-231) (Table 3). Against MDA-MB-231 cells, compounds **11b** and **11e** (GI_{50} = 39.0–41.8 μM) possessed comparable inhibitory potency to IDX (GI_{50} = 31.3 μM). The remainder of the compounds were at least two times less active than IDX. In the case of SKN-BE(2)C cells, all compounds had more than 6-fold less potent antiproliferative activity than IDX. Overall, while some analogues retained modest activity, the [4 + 2] cycloaddition modifications did not yield improvements over IDX in either cancer model.

Table 3 Antiproliferative screen of IDX and [4 + 2] cycloaddition products in SKN-BE(2)C and MDA-MB-231 cell lines

	GI_{50} μM	
Compound	SKN-BE(2)C	MDA-MB-231
IDX	4.5 ± 0.3	31.3 ± 0.4
11b	>100	39.0 ± 4.6
11d	>100	>100
11e	29.7 ± 0.8	41.8 ± 1.2
11f	69.9 ± 0.9	73.5 ± 0.7

2.6 Conclusion

A novel library of pyran- and furan-fused isoflavenes was successfully synthesised from the IDX scaffold *via* Pechmann and Knoevenagel condensations, as well as intramolecular cyclisations and *o*-QM cycloadditions. The selective C6 formylation or Mannich reaction enabled the directed functionalisation of the A-ring of IDX through minimal synthetic steps. Challenges in selectivity during furan synthesis were addressed through selective THP protection of the C7 phenol. Biological evaluation revealed that, despite the successful synthesis of various fused ring systems, the compounds exhibited limited anticancer activity. Nonetheless, this work establishes a flexible platform for designing a variety of structurally rigid isoflavene derivatives.

3 Experimental section

3.1 Materials and methods

Melting points (uncorrected) were measured using a Mel-Temp melting point apparatus. Infrared spectra were recorded as Nujol mulls on a PerkinElmer 298 or a PerkinElmer 580B spectrometer. ^{1}H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker AC300F (400 MHz) or (600 MHz) spectrometer. ^{1}H NMR data were recorded as follows: chemical shift measured in parts per million (ppm) downfield from TMS (δ), multiplicity, observed coupling constant (J) in Hertz (Hz), proton count. Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). ^{13}C NMR chemical shifts are reported in ppm downfield from TMS and identifiable carbons are given. The EI and ES mass spectra were recorded on an AEI MS 12 mass spectrometer at 70 eV ionizing potential and 8000 V accelerating voltage with an ion source temperature of 2100C. Kieselgel 60H (Merck, Art 7736) was employed for flash chromatography. Solvents and reagents were purified by literature methods.

3.2 Cellular assays

3.2.1 Cytotoxicity screen. Cytotoxicity was determined using a CellTitre-Glo assay using PC-3 cells. A stock solution of each compound was prepared at 10 mM in DMSO. Single dose screen values were determined at 25 μM concentrations. IC_{50} values were determined by testing cell growth inhibition across 10 compound concentrations, starting at 50 μM and using 3-fold serial dilution in a 96-well plate. Each compound concentration was tested in technical duplicate. DMSO final concentration was normalised at 0.5%. PC-3 cell plates were incubated for 72 hours at 37 °C and 5% CO_2. Cell lines were obtained from Shanghai ChemPartner Co., Ltd.

3.2.2 Anti-proliferative (GI) assay. For anti-proliferative assay, SKN-BE(2)C and MDA-MB-231 cells were seeded at 2250, 3000, 3000 and 3000 cells per well in 96-well plates respectively to ensure sustained exponential growth for 4 days. Cells were treated 24 h after seeding with a range of concentrations from 1 to 300 μM of compounds. After 72 h drug incubation, 25 μL of Alamar blue was added and the cells were incubated for another 6 h. The metabolic activity was detected by spectrophotometric analysis by assessing the absorbance of Alamar blue (difference between 570 nm and 595 nm) using a Bio Rad multiplate reader. Cell viability was determined and expressed as a percentage of untreated control cells. The determination of GI_{50} values was performed using GraphPad Prism 6. Cell lines were obtained from the Children's Cancer Institute Australia, Lowy Cancer Research Centre, UNSW.

3.3 General procedures

3.3.1 General procedure A: Pechmann coumarin synthesis. IDX (**3**) (100 mg, 0.417 mmol) was added to a stirring solution of ethyl acetoacetate (67 μL, 0.52 mmol) in sulfuric acid (1.0 mL). The reaction was stirred at room temperature for 12 hours. The reaction mixture was diluted with water (5 mL) and the precipitate was collected. The crude solid was purified by column chromatography in 2.5% MeOH/DCM to afford the coumarin product as a yellow solid.

3.3.2 General procedure B: Knoevenagel coumarin synthesis. Piperidine (10 mL, 0.10 mol), was added to a stirring solution of IDX aldehyde (**13**) (100 mg, 0.350 mmol) and the corresponding ethoxy 1,3-dicarbonyls **14a–j** (67 μL, 0.52 mmol) in ethanol (1.5 mL). The reaction was stirred at room temperature for 3 hours, monitoring by TLC. Orange precipitate was collected by vacuum filtration and washed with ethanol (5 mL) to afford the coumarin product.

3.3.3 General procedure C: Rap–Stoermer reaction. The corresponding bromoacetophenone **15a–i** (0.700 mmol) was added to a suspension of THP-IDX aldehyde (**17**) (100 mg, 0.350 mmol) in acetonitrile (5 mL) at room temperature. The suspension was heated to a homogenous solution at 90 °C and stirred overnight. The cloudy reaction mixture was cooled and water (10 mL) was added. The precipitate was filtered and washed with water (5 mL) and hexane (5 mL) to afford protected products **18a–i**.

3.3.4 General procedure D: THP deprotection. Concentrated HCl (4 drops) was added to the THP-Product **18a–i** (50 mg) in methanol (3 mL) and the suspension was heated at 60 °C for 3 hours. Water (10 mL) was added and the precipitate was filtered and washed with water (5 mL) and hexane (5 mL) to afford furan products **10a–i**.

3.3.5 General procedure E: *o*-QM reactions. 6-((Dimethylamino)methyl)-3-(4-hydroxyphenyl)-2*H*-chromen-7-ol **20** (20–40 mg) was dissolved in DMF (2 mL) and the corresponding dienophiles (20 eq.) were added in a pressure tube held under an argon atmosphere. The mixture was stirred at 130–140 °C for 48 h and the reaction mixture was evaporated, purified through column chromatography (DCM/EtOAc) or prep-HPLC to obtain the desired product or as otherwise stated.

3.4 Experimental data

3.4.1 3-Acetyl-7-(4-hydroxyphenyl)-2*H*,8*H*-pyrano[3,2-*g*] chromen-2-one (16). 2-Bromoacetophenone (139 mg, 0.700 mmol) was added to a suspension of IDX aldehyde (**33**) (100 mg, 0.350 mmol) in acetonitrile (5 mL) at room temperature. The suspension was heated to a homogenous solution at 90 °C and stirred overnight. The cloudy reaction mixture was cooled and water (10 mL) was added. The precipitate was filtered and washed with water (5 mL) and hexane (5 mL) to afford **63** as a yellow solid (116 mg, 68%). M.P. 189–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07–8.00 (m, 2H), 7.98–7.93 (m, 2H), 7.74–7.68 (m, 3H), 7.62–7.56 (m, 5H), 7.55–7.51 (m, 2H), 7.22 (s, 1H), 7.11 (s, 1H), 7.07–7.00 (m(appt. d), 2H), 5.64 (s, 2H), 5.25 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.43, 182.67, 158.06, 156.11, 154.56, 151.23, 137.05, 134.37, 133.79, 132.76, 131.11, 128.93, 128.82, 128.67, 128.33, 127.85, 126.03, 121.21, 120.71, 117.82, 117.44, 114.90, 98.60, 70.16, 66.78. IR 1688, 1617, 1539 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{32}H_{22}O_5$ $(M + H)^+$ 487.1540. Found 487.1540.

3.4.2 7-Hydroxy-3-(4-((tetrahydro-2*H*-pyran-3-yl)oxy) phenyl)-2*H*-chromene-6-carbaldehyde (17). IDX aldehyde (**13**) (800 mg, 2.98 mmol), DHP (1.62 mL, 18.0 mmol) and PPTS (150 mL, 0.598 mol) were stirred in DCE (20 mL) at room temperature. The suspension was stirred overnight at 80 °C. The reaction mixture was cooled and washed with water (20 mL). The aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and solvent was removed under reduced pressure. The crude solid was purified by column chromatography (1/9 EtOAc/Hexane) to give yellow flakes of **17** (600 mg, 63%) M.P. 146–149 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.06 (s, 1H), 7.49–7.46 (m, 2H), 7.41–7.33 (m, 1H), 7.10–7.00 (m, 2H), 6.97 (s, 1H), 6.83–6.78 (m, 1H), 6.41–6.39 (m, 1H), 5.52 (t, J = 3.3 Hz, 1H), 5.24 (d, J = 1.5 Hz, 2H), 3.79–3.70 (m, 1H), 3.61–3.51 (m, 1H), 1.95–1.68 (m, 3H), 1.66–1.49 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 189.82, 162.65, 159.60, 156.40, 128.60, 127.68, 125.78, 117.04, 116.58, 115.52, 102.68, 95.62, 67.05, 61.52, 29.75, 24.67, 19.14, 18.54. IR 3237, 2938, 2847, 1685, 1600, 1512, 1490 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{21}O_5$ $(M + H)^+$ 353.1384. Found 353.1384.

3.4.3 7-Methoxy-3-(4-methoxyphenyl)-2*H*-chromene-6-carbaldehyde (19a). Methyl iodide (2.6 mL, 41.7 mmol) was added to a suspension of IDX aldehyde (**13**) (800 mg, 2.98 mmol) and K_2CO_3 (464 mg, 3.36 mmol) in acetone (600 mL, 2.24 mmol). The suspension was refluxed for 6 hours, monitoring by TLC. The solvent was evaporated under reduced pressure and the crude diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and solvent was removed under reduced pressure, resulting in a yellow solid **33** (723 mg, 82%) M.P. 164–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.85 (s, 1H), 7.12–7.03 (m, 3H), 7.02–6.99 (m, 1H), 6.77–6.70 (m, 2H), 6.50 (s, 1H), 5.29 (d, J = 1.5 Hz, 2H), 3.78 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.90, 162.42, 161.77, 158.05, 132.90, 132.11, 129.08, 126.44, 119.27, 115.60, 114.63, 113.98, 100.94, 67.62, 55.40, 48.24. IR 2931, 2840, 1668, 1605,

1554, 1513 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{17}O_4$ $(M + H)^+$ 297.1121, found 297.1121.

3.4.4 7-(4-Hydroxyphenyl)-3-methyl-2*H*,8*H*-pyrano[3,2-*g*] chromen-2-one (9a). The title compound was synthesised by following general procedure A and isolated as a yellow solid (51 mg, 40%). M.P. 220 °C, (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.50 (s, 1H), 7.43–7.36 (m, 2H), 6.96 (s, 1H), 6.85–6.78 (m, 3H), 6.20 (s, 1H), 5.25 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.97, 157.92, 155.83, 153.75, 153.24, 126.13, 122.60, 115.61, 115.14, 113.97, 111.41, 102.64, 66.96, 18.22. IR 3205, 1693, 1606 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{15}O_4$ $(M + H)^+$ 307.0965, found 307.0966.

3.4.5 7-(4-Hydroxyphenyl)-2-oxo-2*H*,8*H*-pyrano[3,2-*g*] chromene-3-carboxylic acid (9b). The title compound was synthesised by following general procedure B and isolated as an orange solid (78 mg, 66%). M.P. 197–201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 9.76 (s, 1H), 8.65 (s, 1H), 7.61 (s, 1H), 7.47–7.40 (m, 2H), 6.93 (s, 1H), 6.89 (s, 1H), 6.85–6.78 (m, 2H), 5.33 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.15, 158.29, 158.06, 157.06, 155.89, 131.81, 127.01, 126.26, 120.46, 115.57, 114.42, 114.25, 102.42, 67.30. IR 3284, 3044, 1725, 1550 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{13}O_6$ $(M + H)^+$ 337.0707. Found 337.0707.

3.4.6 3-Acetyl-7-(4-hydroxyphenyl)-2*H*,8*H*-pyrano[3,2-*g*] chromen-2-one (9c). The title compound was synthesised by following general procedure B and isolated as an orange solid (105 mg, 91%). M.P. 146–149 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.57 (s, 1H), 7.63 (s, 1H), 7.47–7.39 (m, 2H), 6.92 (s, 1H), 6.90 (s, 1H), 6.85–6.78 (m, 2H), 5.33 (s, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.18, 159.18, 159.05, 158.56, 156.65, 147.77, 132.30, 128.05, 126.72, 126.27, 121.08, 121.06, 116.06, 114.85, 113.09, 102.85, 67.86, 30.52. IR 3278, 1708, 1612, 1545 cm^{-1}; HRMS (ESI) *m*/*z* calcd. For $C_{20}H_{14}O_5Na$ $(M + Na)^+$ 357.0733. Found 357.0734.

3.4.7 7-(4-Hydroxyphenyl)-3-propionyl-2*H*,8*H*-pyrano[3,2-*g*] chromen-2-one (9d). The title compound was synthesised by following general procedure B and isolated as an orange solid (107 mg, 83%). M.P. 210–211 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.58 (s, 1H), 7.65 (s, 1H), 7.46–7.41 (m, 2H), 6.94 (s, 1H), 6.92 (s, 1H), 6.84–6.79 (m, 2H), 5.34 (s, 2H), 3.01 (q, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 197.77, 158.62, 158.48, 158.09, 156.05, 147.17, 131.85, 127.51, 126.29, 125.81, 120.60, 115.59, 114.42, 112.68, 102.39, 67.37, 40.06, 34.86, 7.99. IR 3282, 1700, 1609, 1548 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{17}O_5$ $(M + H)^+$ 349.1071. Found 349.1068.

3.4.8 Methyl 7-(4-hydroxyphenyl)-2-oxo-2*H*,8*H*-pyrano[3,2-*g*]chromene-3-carboxylate (9e). The title compound was synthesised by following general procedure B and isolated as an orange solid (107 mg, 87%). M.P. 208–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.27 (s, 1H), 7.92–7.85 (m, 2H), 7.55 (s, 1H), 7.49–7.41 (m, 2H), 7.12–7.02 (m, 2H), 6.95 (d, J = 4.8 Hz, 2H), 6.87–6.78 (m, 2H), 5.33 (d, J = 1.5 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.62, 164.14, 158.68, 158.50, 157.89, 155.72, 145.49, 132.51, 132.26, 129.61, 126.97, 126.74, 126.37, 123.68, 120.94, 116.05, 115.07, 114.44, 113.16, 103.15, 67.68, 56.13. IR 3374.8, 3045.5, 2950, 1722, 1560 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{15}O_6$ $(M + H)^+$ 351.0863. Found 351.0867.

3.4.9 3-Benzoyl-7-(4-hydroxyphenyl)-2*H*,8*H*-pyrano[3,2-*g*] chromen-2-one (9f). The title compound was synthesised by following general procedure B and isolated as an orange solid (126 mg, 86%). M.P. 120–122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.36 (s, 1H), 7.92–7.85 (m, 2H), 7.72–7.64 (m, 1H), 7.58 (s, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.48–7.42 (m, 2H), 6.95 (s, 2H), 6.85–6.79 (m, 2H), 5.34 (d, J = 1.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.33, 158.60, 158.52, 158.20, 155.97, 146.53, 137.04, 134.03, 132.31, 129.89, 129.10, 127.20, 126.75, 126.36, 123.09, 121.00, 116.07, 115.03, 113.14, 103.16, 67.75. IR 3235, 1700, 1612, 1553 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{17}O_5$ $(M + H)^+$ 419.0890. Found 419.0889.

3.4.10 7-(4-Hydroxyphenyl)-3-isonicotinoyl-2*H*,8*H*-pyrano [3,2-*g*]chromen-2-one (9g). The title compound was synthesised by following general procedure B, with heating to 50 °C and isolated as a red solid (114 mg, 82%). M.P. 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.82–8.76 (m, 2H), 8.51 (s, 1H), 7.76–7.73 (m, 2H), 7.63 (s, 1H), 7.46 (s, 2H), 6.96 (s, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.36 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.58, 158.46, 158.08, 156.08, 150.34, 148.34, 143.65, 139.96, 131.89, 127.20, 126.29, 125.78, 122.09, 121.48, 120.59, 115.58, 114.38, 112.71, 102.69, 67.37. IR 2820, 2697, 1730 cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{16}NO_5$ $(M + H)^+$ 398.1023 found 398.1018.

3.4.11 7-(4-Hydroxyphenyl)-3-(4-(trifluoromethyl)benzoyl)-2*H*,8*H*-pyrano[3,2-*g*]chromen-2-one (9h). The title compound was synthesised by following general procedure B and isolated as a red solid (133 mg, 82%). M.P. 202–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (br. s, 1H), 8.48 (s, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.61 (s, 1H), 7.48–7.41 (m, 2H), 6.96 (d, J = 2.1 Hz, 2H), 6.85–6.79 (m, 2H), 5.35 (d, J = 1.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.18, 158.16, 158.09, 158.04, 155.83, 147.57, 140.35, 132.41 (q, J = 32 Hz, CF_3), 131.82, 129.88, 126.97, 126.22, 125.76, 125.43 (q, J = 5.1 Hz), 125.10, 121.52, 120.52, 115.53, 114.39, 112.66, 102.63, 67.30. IR 3254, 1695, 1549 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{26}H_{16}F_3O_5$ $(M + H)^+$ 465.0944. Found 465.0942.

3.4.12 3-(4-Chlorobenzoyl)-7-(4-hydroxyphenyl)-2*H*,8*H*-pyrano[3,2-*g*]chromen-2-one (9i). The title compound was synthesised by following general procedure B and isolated as an orange solid (130 mg, 86%). M.P. 207–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.39 (s, 1H), 7.94–7.87 (m, 2H), 7.63–7.56 (m, 3H), 7.48–7.41 (m, 2H), 6.95 (d, J = 3.0 Hz, 2H), 6.85–6.79 (m, 2H), 5.34 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.34, 158.64, 158.53, 158.38, 156.13, 147.18, 138.85, 135.91, 132.31, 131.75, 129.19, 127.29, 126.76, 126.32, 122.62, 121.00, 116.05, 114.97, 113.17, 103.16, 67.76. IR 3223, 1689, 1610, 1552 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{16}ClO_5$ $(M + H)^+$ 431.0681. Found 431.0680.

3.4.13 7-(4-Hydroxyphenyl)-3-(4-methoxybenzoyl)-2*H*,8*H*-pyrano[3,2-*g*]chromen-2-one (9j). The title compound was synthesised by following general procedure B and isolated as a yellow solid (127 mg, 81%). M.P. 210–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (br. s, 1H), 8.27 (s, 1H), 7.92–7.85 (m, 2H), 7.55 (s, 1H), 7.47–7.41 (m, 2H), 7.09–7.03 (m, 2H), 6.95 (s,

1H), 6.94 (s, 1H), 6.85–6.78 (m, 2H), 5.32 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.62, 164.14, 158.68, 158.50, 157.89, 155.72, 145.49, 132.51, 132.26, 129.61, 126.97, 126.74, 126.37, 123.68, 120.94, 116.05, 115.07, 114.44, 113.16, 103.15, 67.68, 56.13. IR 3238, 1688, 1600, 1554 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{26}H_{19}O_6$ (M + H)$^+$ 449.0996. Found 449.0995.

3.4.14 7-(4-Hydroxyphenyl)-3-(2-phenylacetyl)-2*H*,8*H*-pyrano[3,2-*g*]chromen-2-one (9k). The title compound was synthesised by following general procedure B and isolated as an orange solid (123 mg, 81%). M.P. 267–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.61 (s, 1H), 7.64 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.34–7.28 (m, 2H), 7.26–7.20 (m, 2H), 6.92 (s, 2H), 6.82 (s, 1H), 6.80 (s, 1H), 5.34 (d, J = 1.4 Hz, 2H), 4.35 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.41, 159.14, 159.09, 158.56, 156.62, 148.26, 135.34, 132.33, 130.33, 128.68, 128.00, 126.98, 126.74, 126.23, 121.11, 120.90, 116.05, 114.81, 113.12, 102.89, 67.87, 48.02. IR 3236, 1682, 1609 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{26}H_{19}O_5$ (M + H)$^+$ 433.1046. Found 433.1040.

3.4.15 (6-(4-Hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(phenyl)methanone (10a). The title compound was synthesised by following general procedure D and isolated as a yellow/green solid (38 mg, 94%). M.P. 172–176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98–7.92 (m, 2H), 7.74–7.68 (m, 2H), 7.64–7.55 (m, 3H), 7.47–7.40 (m, 2H), 7.21 (s, 1H), 7.04 (s, 1H), 6.85–6.78 (m, 2H), 5.23 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 183.19, 158.29, 156.50, 155.01, 151.67, 137.55, 133.28, 132.00, 129.45, 129.19, 126.76, 126.62, 121.89, 121.68, 120.95, 118.38, 116.83, 116.04, 99.06, 67.31. IR 2945, 2898, 1613, 1512 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{17}O_4$ (M + H)$^+$ 369.1121. Found 369.1132.

3.4.16 (6-(4-Hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(4-methoxyphenyl)methanone (10b). The title compound was synthesised by following general procedure C and procedure D without intermediate purification. The crude solid was purified by column chromatography to afford the product as a yellow/green solid (103 mg, 75%). M.P. 167–170 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 8.07–7.98 (m, 2H), 7.70 (d, J = 1.0 Hz, 1H), 7.57 (s, 1H), 7.49–7.40 (m, 2H), 7.21 (s, 1H), 7.18–7.09 (m, 2H), 7.04 (s, 1H), 6.87–6.79 (m, 2H), 5.23 (d, J = 1.4 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 181.14, 163.09, 157.78, 155.76, 154.24, 151.58, 131.48, 129.46, 126.35, 126.15, 121.32, 121.21, 120.30, 116.69, 116.44, 115.56, 114.06, 98.59, 66.80, 55.61. IR 3203, 1682, 1611, 1554 cm^{-1} HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{18}O_5Na$ (M + Na)$^+$ 421.1046. Found 421.1044.

3.4.17 (6-(4-Hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(*p*-tolyl)methanone (10c). The title compound was synthesised by following general procedure D and isolated as a yellow solid (41 mg, 95%). M.P. 209–213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.91–7.85 (m, 2H), 7.70 (d, J = 1.0 Hz, 1H), 7.56 (s, 1H), 7.47–7.37 (m, 4H), 7.21 (s, 1H), 7.04 (s, 1H), 6.85–6.78 (m, 2H), 5.22 (d, J = 1.4 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 182.79, 158.27, 156.38, 154.88, 151.83, 143.75, 134.87, 131.97, 129.74, 129.63, 126.79, 126.62, 121.84, 121.68, 120.88, 117.86, 116.87, 116.04, 99.06, 67.29, 21.67. IR 3386, 3120, 1601, 1539 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{18}O_4Na$ (M + Na)$^+$ 405.1097. Found 405.1098.

3.4.18 (6-(4-Hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(3-(trifluoromethyl)phenyl)methanone (10d). The title compound was synthesised by following general procedure D and isolated as a yellow solid (42 mg, 95%). M.P. 196–201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.18 (s, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.58 (s, 1H), 7.47–7.40 (m, 2H), 7.22 (s, 1H), 7.04 (s, 1H), 6.85–6.78 (m, 2H), 5.23 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.82, 158.29, 156.73, 155.30, 151.27, 138.40, 132.08, 130.50, 130.08, 129.76, 129.56 (q, J = 3.0 Hz), 126.74, 126.63, 125.79 (q, J = 4.0 Hz), 122.01, 121.67, 121.06, 119.11, 116.03, 99.05, 67.35. IR 3042, 2965, 1650, 1611, 1512 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{15}F_3O_4Na$ (M + Na)$^+$ 459.0815. Found 459.0814.

3.4.19 (4-Chlorophenyl)(6-(4-hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)methanone (10e). The title compound was synthesised by following general procedure D and isolated as a yellow solid (38 mg, 92%). M.P. 181–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.02–7.95 (m, 2H), 7.76 (s, 1H), 7.70–7.63 (m, 2H), 7.57 (s, 1H), 7.47–7.40 (m, 2H), 7.22 (s, 1H), 7.04 (s, 1H), 6.85–6.78 (m, 2H), 5.24 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.47, 157.80, 156.10, 154.66, 150.98, 137.68, 135.72, 131.57, 130.91, 128.83, 126.29, 126.15, 121.49, 121.17, 120.46, 118.12, 116.34, 115.56, 98.59, 66.85. IR 3256, 3122, 1620, 1545 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{16}ClO_4$ (M + H)$^+$ 403.0732. Found 403.0731.

3.4.20 (6-(4-Hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(4-(trifluoromethoxy)phenyl)methanone (10f). The title compound was synthesised by following general procedure D and isolated as a yellow solid (42 mg, 95%). M.P. 161–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.13–8.07 (m, 2H), 7.78 (s, 1H), 7.60–7.55 (m, 3H), 7.47–7.40 (m, 2H), 7.22 (s, 1H), 7.04 (s, 1H), 6.85–6.78 (m, 2H), 5.23 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.75, 158.27, 156.62, 155.18, 151.67 (q), 151.40, 136.43, 132.05, 131.93, 129.45, 126.76, 126.63, 121.98, 121.67, 121.33, 120.97, 118.80, 116.80, 116.03, 99.06, 67.33. IR 3474, 2834, 1616, 1541 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{15}F_3O_5Na$ (M + Na)$^+$ 475.0764. Found 475.0760.

3.4.21 (4-Bromophenyl)(6-(4-hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)methanone (10g). The title compound was synthesised by following general procedure C and procedure D without intermediate purification. The crude solid was purified by column chromatography to afford the product as a yellow/green solid (110 mg, 70%). M.P. 170–173 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.93–7.90 (m, 2H), 7.83–7.80 (m, 2H), 7.76 (s, 1H), 7.58 (s, 1H), 7.46–7.43 (m, 2H), 7.22 (s, 1H), 7.05 (s, 1H), 6.84–6.81 (m, 2H), 5.24 (d, J = 1.5 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 182.12, 156.59, 151.46, 151.39, 136.55, 136.48, 132.82, 132.06, 132.01, 131.66, 130.96, 130.91, 127.13, 121.98, 121.67, 116.53, 115.50, 99.60, 98.53, 67.33. IR 3242, 3110, 1614, 1551 cm^{-1}; HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{16}O_4Br$ (M + H)$^+$ 447.0232. Found 447.0231.

3.4.22 (6-(4-Hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(1*H*-indol-3-yl)methanone (10h). The title compound was synthesised by following general procedure C and procedure D without intermediate purification. The crude solid was purified by column chromatography to afford the product as a yellow/

green solid (98 mg, 69%). M.P. 186, (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.51 (s, 1H), 8.34 (d, J = 7.0 Hz, 1H), 7.71 (s, 1H), 7.59–7.54 (m, 2H), 7.47–7.41 (m, 2H), 7.31–7.22 (m, 3H), 7.05 (s, 3H), 6.83 (d, J = 8.5 Hz, 2H), 5.22 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.61, 166.59, 155.65, 154.09, 153.88, 131.79, 130.64, 127.16, 127.01, 126.85, 126.57, 122.49, 122.01, 121.81, 121.69, 121.50, 120.25, 117.09, 116.06, 115.53, 114.69, 112.91, 112.81, 99.26, 67.21. IR 3389, 3203, 3052, 1668, 1612, 1554, 1520 cm^{-1} HRMS (ESI) m/z calcd. for $C_{26}H_{17}NO_4$ (M + H)$^+$ 408.1236. Found 408.1236.

3.4.23 (4-Chlorophenyl)(6-(4-hydroxyphenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)methanone (10i). The title compound was synthesised by following general procedure D and isolated as a yellow solid (41 mg, 92%). M.P. 146–150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.3, 2.0 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H), 7.57 (s, 1H), 7.47–7.40 (m, 2H), 7.22 (s, 1H), 7.04 (s, 1H), 6.85–6.78 (m, 2H), 5.23 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 180.72, 158.30, 156.74, 155.33, 151.15, 137.78, 135.99, 132.15, 132.09, 131.50, 131.20, 129.55, 126.75, 126.63, 122.02, 121.65, 121.02, 119.16, 116.78, 116.04, 99.05, 67.37. IR 3491, 3091, 1617, 1539 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{24}H_{16}Cl_2O_4$ (M + H)$^+$ 459.0161. Found 459.0160.

3.4.24 Phenyl(6-(4-((tetrahydro-2*H*-pyran-3-yl)oxy)phenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)methanone (18a). The title compound was synthesised by following general procedure C and isolated as a yellow solid (98 mg, 76%). M.P. 175–178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00–7.93 (m, 2H), 7.73 (s, 1H), 7.72–7.68 (m, 1H), 7.64–7.58 (m, 3H), 7.58–7.51 (m, 2H), 7.23 (s, 1H), 7.12 (s, 1H), 7.10–7.05 (m, 2H), 5.53 (t, J = 3.3 Hz, 1H), 5.26 (s, 2H), 3.80–3.71 (m, 1H), 3.60–3.51 (m, 1H), 1.93–1.70 (m, 3H), 1.69–1.46 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 183.19, 157.06, 156.62, 155.06, 151.72, 137.55, 133.29, 131.64, 129.45, 129.31, 129.19, 126.49, 121.72, 121.70, 121.26, 118.39, 118.06, 117.07, 99.14, 96.09, 67.27, 61.99, 30.22, 25.14, 19.01. IR 2933, 2863, 1614, 1512 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{29}H_{26}O_5$ (M + H)$^+$ 453.1697. Found 453.1670.

3.4.25 (6-(4-((Tetrahydro-2*H*-pyran-3-yl)oxy)phenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(*p*-tolyl)methanone (18c). The title compound was synthesised by following general procedure C and isolated as a yellow solid (78 mg, 59%). M.P. 150–154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92–7.85 (m, 2H), 7.71 (s, 1H), 7.59 (s, 1H), 7.57–7.51 (m, 2H), 7.44–7.38 (m, 2H), 7.22 (s, 1H), 7.12 (s, 1H), 7.10–7.05 (m, 2H), 5.53 (t, J = 3.2 Hz, 1H), 5.25 (s, 2H), 3.79–3.71 (m, 1H), 3.60–3.52 (m, 1H), 2.43 (s, 3H), 1.93–1.71 (m, 3H), 1.67–1.50 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 182.79, 157.06, 156.51, 154.94, 152.36, 143.77, 134.98, 131.61, 129.64, 129.32, 129.11, 126.48, 121.71, 121.19, 120.06, 118.09, 117.87, 117.08, 99.13, 96.02, 67.25, 61.99, 30.22, 25.13, 21.67, 19.00. IR 2937, 2862, 1617, 1538 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{30}H_{27}O_5$ (M + H)$^+$ 467.1853. Found 467.1853.

3.4.26 (6-(4-((Tetrahydro-2*H*-pyran-3-yl)oxy)phenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(3-(trifluoromethyl)phenyl)methanone (18d). The title compound was synthesised by following general procedure C and isolated as a yellow solid (80 mg, 54%). M.P. 172–176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 7.8 Hz, 1H), 8.19 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.79 (s, 1H), 7.61 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.24 (s, 1H), 7.12 (s, 1H), 7.08 (d, J = 8.5 Hz, 2H), 5.53 (t, J = 3.2 Hz, 1H), 5.27 (s, 2H), 3.80–3.71 (m, 1H), 3.60–3.52 (m, 1H), 1.90–1.71 (m, 3H), 1.66–1.51 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.39, 156.63, 156.39, 154.89, 150.86, 137.93, 133.02, 131.26, 130.05, 129.71, 129.12 (q, J = 3.0 Hz), 128.80, 126.04, 125.34 (q, J = 4.0 Hz), 121.86, 121.36, 121.24, 120.92, 118.66, 117.52, 116.61, 98.66, 95.63, 66.85, 61.53, 29.76, 24.67, 18.54. IR 2939, 2868, 1641, 1617, 1542 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{30}H_{24}F_3O_5$ (M + H)$^+$ 521.1570. Found 521.1572.

3.4.27 (4-Chlorophenyl)(6-(4-((tetrahydro-2*H*-pyran-3-yl)oxy)phenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)methanone (18e). The title compound was synthesised by following general procedure C and isolated as a yellow/green solid (112 mg, 81%). M.P. 226 °C, (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02–7.95 (m, 2H), 7.77 (d, J = 1.0 Hz, 1H), 7.70–7.64 (m, 2H), 7.60 (s, 1H), 7.57–7.52 (m, 2H), 7.23 (s, 1H), 7.13 (s, 1H), 7.10–7.06 (m, 2H), 5.53 (t, J = 3.4 Hz, 1H), 5.26 (d, J = 1.5 Hz, 2H), 3.79–3.71 (m, 1H), 3.59–3.53 (m, 1H), 1.97–1.69 (m, 4H), 1.69–1.46 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.95, 157.10, 156.70, 155.19, 151.53, 138.17, 136.19, 135.64, 131.70, 131.38, 129.30, 126.49, 121.78, 121.68, 121.25, 118.04, 118.56, 117.10, 99.13, 96.14, 67.31, 63.51, 30.24, 25.14, 20.49. IR 2935, 2863, 1618, 15.37 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{29}H_{25}ClO_4$ (M + H)$^+$ 487.1307. Found 487.1300.

3.4.28 (6-(4-((Tetrahydro-2*H*-pyran-3-yl)oxy)phenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)(4-(trifluoromethoxy)phenyl) methanone (18f). The title compound was synthesised by following general procedure C and isolated as a yellow solid (134 mg, 88%). M.P. 217–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17–8.05 (m, 2H), 7.79 (s, 1H), 7.63–7.49 (m, 5H), 7.24 (s, 1H), 7.13 (s, 1H), 7.11–7.05 (m, 2H), 5.53 (t, J = 3.3 Hz, 1H), 5.26 (s, 2H), 3.80–3.71 (m, 1H), 3.60–3.51 (m, 1H), 1.92–1.70 (m, 3H), 1.67–1.50 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.76, 157.08, 156.74, 155.23, 151.69 (q), 151.45, 136.42, 131.94, 131.69, 129.28, 126.49, 121.79, 121.72, 121.71, 121.34, 121.28, 118.81, 118.01, 117.07, 99.14, 96.09, 67.29, 61.98, 30.22, 25.14, 19.00. IR 2935, 1617, 1539 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{30}H_{23}F_3O_6Na$ (M + Na)$^+$ 559.1339. Found 559.1340.

3.4.29 (3,4-Dichlorophenyl)(6-(4-((tetrahydro-2*H*-pyran-3-yl)oxy)phenyl)-7*H*-furo[3,2-*g*]chromen-2-yl)methanone (18i). The title compound was synthesised by following general procedure C and isolated as a yellow solid (118 mg, 80%). M.P. 176–180 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.14 (d, J = 1.9 Hz, 1H), 7.93 (dd, J = 8.3, 2.0 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 7.60 (s, 1H), 7.57–7.52 (m, 2H), 7.25 (s, 1H), 7.13 (s, 1H), 7.10–7.06 (m, 2H), 5.54 (t, J = 3.1 Hz, 1H), 5.27 (s, 2H), 3.78–3.72 (m, 1H), 3.60–3.53 (m, 1H), 1.94–1.70 (m, 3H), 1.69–1.48 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 180.80, 157.07, 155.36, 154.89, 137.78, 135.99, 132.14, 131.72, 131.52, 131.23, 129.58, 129.24, 126.50, 121.84, 121.69, 121.34, 119.29, 117.96, 117.05, 99.16, 96.03, 67.30, 61.96, 40.49, 30.21, 25.13, 18.99. IR 3135, 2936, 1620 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{29}H_{24}Cl_2O_5$ (M + H)$^+$ 521.0917. Found 521.0912.

3.4.30 4-(8-Ethoxy-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromen-3-yl)phenol (11a). The title compound was synthesised by following general procedure E and isolated as a white powder (12 mg, 28%). M.P. 156 °C dec. ^{1}H NMR (400

MHz, CD_3CN): δ 7.33 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.79 (s, 1H), 6.71 (s, 1H), 6.27 (s, 1H), 5.23 (t, J = 6.4 Hz, 1H), 5.03 (s, 2H), 3.85–3.77 (m, 1H), 3.66–3.58 (m, 1H), 2.81–2.73 (m, 1H), 2.59–2.53 (m, 1H), 1.99–1.84 (m, 2H). 1.13 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3CN): δ 157.8, 153.5, 153.4, 130.2, 129.5, 128.0, 126.9, 117.9, 116.8, 116.5, 104.4, 98.1, 67.7, 64.5, 27.4, 20.4, 15.5. IR 3372, 2972, 1624, 1605, 1493, 1441, cm^{-1}. HRMS (ESI) m/z calcd. for $C_{20}H_{20}O_4Na$ (M + Na)$^+$ 347.1254. Found 347.1251.

3.4.31 4-(6*a*,7,8,9*a*-Tetrahydro-2*H*,6*H*-furo[2,3-*b*]pyrano [3,2-*g*]chromen-3-yl)phenol (11b). The title compound was synthesised by following general procedure E and isolated as a white powder (10 mg, 20%). M.P. 224 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.62 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.88 (s, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.76 (s, 1H), 6.24 (s, 1H), 5.59 (d, J = 5.0 Hz, 1H), 5.02 (s, 2H), 3.87–3.76 (m, 2H), 2.90 (dd, J = 5.7 and 15.8 Hz, 1H), 2.68 (m, 1H), 2.60 (dd, J = 2.6, 15.8 Hz, 1H), 2.00 (m, 1H), 1.48 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.3, 153.1, 152.1, 128.8, 126.9, 125.8, 116.8, 116.4, 115.5, 114.4, 103.3, 101.3, 67.4, 66.3, 37.1, 27.5, 24.8. IR 3361, 2949, 1620, 1514, 1445, cm^{-1}. HRMS (ESI) m/z calcd. for $C_{20}H_{18}O_4Na$ (M + Na)$^+$ 345.1097. Found 345.1095.

3.4.32 4-(6*a*,8,9,10*a*-Tetrahydro-2*H*,6*H*,7*H*-dipyrano [2,3-*b*:3′,2′-*g*]chromen-3-yl)phenol (11c). The title compound was synthesised by following general procedure E and isolated as a white powder (5 mg, 8%). M.P. 140–143 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.75 (s, 1H), 6.25 (s, 1H), 5.28 (d, J = 2.5 Hz, 1H), 5.02 (s, 2H), 3.83–3.79 (m, 1H), 3.62–3.59 (m, 1H), 2.79 (dd, J = 16.2, 5.7 Hz, 1H), 2.52 (dd, J = 16.2, 2.5 Hz, 1H), 2.10–2.05 (m, 1H), 1.63–1.43 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.2, 152.6, 151.9, 128.8, 127.0, 125.8, 116.7, 116.4, 115.5, 113.0, 102.5, 96.1, 66.3, 61.9, 34.49, 31.1, 27.2, 23.6, 22.8. IR 3311, 2929, 1621, 1513, 1452 cm^{-1}. HRMS (ESI): m/z calcd for $C_{21}H_{20}O_4Na$ (M + Na)$^+$ 359.1254; found 359.1252.

3.4.33 3-(4-Hydroxyphenyl)-9,9-dimethyl-6,8,9,10-tetrahydro-2*H*,7*H*-pyrano[3,2-*b*]xanthen-7-one (11d). The title compound was synthesised by following general procedure E and isolated as a white powder (13 mg, 93%). M.P. 201 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (s, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.00 (s, 1H), 6.81 (s, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.51 (s, 1H), 5.09 (s, 2H), 3.29 (s, 2H), 2.44 (s, 2H), 2.26 (s, 2H), 1.04 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.9, 164.2, 157.7, 151.9, 148.8, 130.7, 127.2, 126.5, 126.1, 120.1, 115.7, 115.5, 112.9, 108.1, 103.0, 66.4, 50.0, 40.3, 31.8, 27.8, 19.9. IR 2957, 2425, 2289, 1619, 1515 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{23}O_4$ (M + H)$^+$ 375.1591; found 375.1590.

3.4.34 4-(7,8,9,10-Tetrahydro-2*H*,6*H*-pyrano[3,2-*b*]xanthen-3-yl)phenol (11e). The title compound was synthesised by following general procedure E and isolated as a white powder (3 mg, 7%). M.P. 200–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.75 (s, 1H), 6.25 (d, J = 8.9 Hz, 1H), 4.99 (s, 2H), 3.16 (s, 2H), 1.65–1.24 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.1, 152.8, 152.2, 151.7, 128.3, 127.2, 126.7, 125.7, 116.6, 116.0, 115.8, 115.5, 103.0, 96.9, 66.2, 48.6, 29.2, 27.0, 25.0, 22.8. IR 3295, 2932, 2854, 1621, 1576, 1513, 1442 cm^{-1}. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{21}O_3$ (M + H)$^+$ 333.1485; found 333.1487.

3.4.35 4-(8-Phenyl-7,8-dihydro-2*H*,6*H*-pyrano[3,2-*g*] chromen-3-yl)phenol (11f). The title compound was synthesised by following general procedure E and isolated as a white powder (6 mg, 11%). M.P. 154–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 7.43–7.30 (m, 7H), 6.87 (s, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.77 (s, 1H), 6.30 (s, 1H), 5.10 (d, J = 10.0 Hz, 1H), 5.02 (s, 2H), 2.90–2.82 (m, 1H), 2.66–2.59 (m, 1H), 2.17–2.11 (m, 1H), 2.02–1.92 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.2, 154.7, 151.9, 141.4, 128.7, 128.4, 127.7, 127.2, 127.0, 126.0, 125.8, 116.4, 115.5, 114.8, 102.9, 77.0, 66.3, 29.2, 23.6. IR 3025, 2922, 2846, 1621, 1513, 1451 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{21}O_3$ (M + H)$^+$ 357.1485; found 357.1480.

Author contributions

Conceptualization: N. K. and V. F., methodology: V. F., E. Y. and S. S. software V. F., validation: V. F., formal analysis: V. F., E. Y. and S. S., investigation: V. F. and E. Y., resources: N. K., data curation, writing – original draft: V. F., writing – review & editing: V. F. and N. K., visualization: V. F. supervision: N. K. and D. S. W., project administration: N. K., funding acquisition: N. K.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

CCDC 2476513 contains the supplementary crystallographic data for this paper.[43]

All experimental data supporting the findings of this study are included in the article and its supplementary information (SI). Additional raw data are available from the corresponding author upon reasonable request. The compound characterization data, including ^{1}H and ^{13}C NMR spectra, are provided in the SI. Supplementary information is available. See DOI: **https://doi.org/10.1039/d5ra06129f**.

Acknowledgements

We thank the BMSF and NMR facilities at UNSW Mark Wainwright Analytical Centre for the structural determination of the synthesised compounds.

References

1 M. Abotaleb, S. M. Samuel, E. Varghese, S. Varghese, P. Kubatka, A. Liskova and D. Büsselberg, Flavonoids in Cancer and Apoptosis, *Cancers*, 2018, **11**, 1.

2 D. M. Brown, G. E. Kelly and A. J. Husband, Flavonoid compounds in maintenance of prostate health and

prevention and treatment of cancer, *Mol. Biotechnol.*, 2005, **30**(3), 253–270, DOI: 10.1385/mb:30:3:253.

3 Z. Yang, K. Kulkarni, W. Zhu and M. Hu, Bioavailability and pharmacokinetics of genistein: mechanistic studies on its ADME, *Anticancer Agents Med. Chem.*, 2012, **12**(10), 1264–1280, DOI: 10.2174/187152012803833107.

4 K. Kiknavelidze, M. Shavdia, N. Chikhladze, L. Abshilava, M. Messina, G. Mautner and G. Kelly, NOX66 as Monotherapy, and in Combination With Carboplatin, in Patients With Refractory Solid Tumors: Phase Ia/b Study, *Curr. Ther. Res. Clin. Exp.*, 2021, **94**, 100631, DOI: 10.1016/j.curtheres.2021.100631.

5 S. Pathmanandavel, M. Crumbaker, A. O. Yam, A. Nguyen, C. Rofe, E. Hovey, C. Gedye, E. M. Kwan, C. Hauser, A. A. Azad, *et al.*, (177)Lu-PSMA-617 and Idronoxil in Men with End-Stage Metastatic Castration-Resistant Prostate Cancer (LuPIN): Patient Outcomes and Predictors of Treatment Response in a Phase I/II Trial, *J. Nucl. Med.*, 2022, **63**(4), 560–566, DOI: 10.2967/jnumed.121.262552.

6 C. Fotopoulou, I. Vergote, P. Mainwaring, M. Bidzinski, J. B. Vermorken, S. A. Ghamande, P. Harnett, S. A. Del Prete, J. A. Green, M. Spaczynski, *et al.*, Weekly AUC2 carboplatin in acquired platinum-resistant ovarian cancer with or without oral phenoxodiol, a sensitizer of platinum cytotoxicity: the phase III OVATURE multicenter randomized study, *Ann. Oncol.*, 2014, **25**(1), 160–165, DOI: 10.1093/annonc/mdt515.

7 K. Porter, W. D. Fairlie, O. Laczka, F. Delebecque and J. Wilkinson, Idronoxil as an Anticancer Agent: Activity and Mechanisms, *Curr. Cancer Drug Targets*, 2020, **20**(5), 341–354, DOI: 10.2174/1568009620666200102122830.

8 Y. Chen, S. L. Cass, S. K. Kutty, E. M. Yee, D. S. Chan, C. R. Gardner, O. Vittorio, E. Pasquier, D. S. Black and N. Kumar, Synthesis, biological evaluation and structure-activity relationship studies of isoflavene based Mannich bases with potent anti-cancer activity, *Bioorg. Med. Chem. Lett.*, 2015, **25**(22), 5377–5383, DOI: 10.1016/j.bmcl.2015.09.027.

9 E. M. H. Yee, M. B. Brandl, D. S. Black, O. Vittorio and N. Kumar, Synthesis of isoflavene-thiosemicarbazone hybrids and evaluation of their anti-tumor activity, *Bioorg. Med. Chem. Lett.*, 2017, **27**(11), 2454–2458, DOI: 10.1016/j.bmcl.2017.04.002.

10 E. M. H. Yee, G. Cirillo, M. B. Brandl, D. S. Black, O. Vittorio and N. Kumar, Synthesis of Dextran–Phenoxodiol and Evaluation of Its Physical Stability and Biological Activity, *Front. Bioeng. Biotechnol.*, 2019, **7**, 183.

11 V. Falasca, D. S. Wenholz, T. T. Yu and N. Kumar, Synthesis of novel isoflavene derivatives with anti-tumour activity, *Bioorg. Med. Chem. Lett.*, 2025, 130350, DOI: 10.1016/j.bmcl.2025.130350.

12 X. Fu, D. Wenholz, D. S. H. Chan, D. S. Black and N. Kumar, Rational Design, Synthesis, and Anti-Proliferative Evaluation of Novel 4-Aryl-3,4-Dihydro-2H-1,4-Benzoxazines, *Molecules*, 2024, **29**, 166.

13 M. M. Hann, A. R. Leach and G. Harper, Molecular Complexity and Its Impact on the Probability of Finding Leads for Drug Discovery, *J. Chem. Inf. Comput. Sci.*, 2001, **41**(3), 856–864, DOI: 10.1021/ci000403i.

14 T. J. Ritchie and S. J. F. Macdonald, The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design?, *Drug Discov. Today*, 2009, **14**(21), 1011–1020, DOI: 10.1016/j.drudis.2009.07.014.

15 J. Hall, A. Brault, F. Vincent, S. Weng, H. Wang, D. Dumlao, A. Aulabaugh, D. Aivazian, D. Castro, M. Chen, *et al.*, Discovery of PF-06928215 as a high affinity inhibitor of cGAS enabled by a novel fluorescence polarization assay, *PLoS One*, 2017, **12**(9), e0184843, DOI: 10.1371/journal.pone.0184843.

16 M. R. Webb and S. E. Ebeler, Comparative analysis of topoisomerase IB inhibition and DNA intercalation by flavonoids and similar compounds: structural determinates of activity, *Biochem. J.*, 2004, **384**(Pt 3), 527–541, DOI: 10.1042/bj20040474.

17 A. B. Alvero, M. Kelly, P. Rossi, A. Leiser, D. Brown, T. Rutherford and G. Mor, Anti-Tumor Activity of Phenoxodiol: From Bench to Clinic, *Future Oncol.*, 2008, **4**(4), 475–482, DOI: 10.2217/14796694.4.4.475.

18 S.-M. Heinonen, K. Wähälä and H. Adlercreutz, Metabolism of isoflavones in human subjects, *Phytochem. Rev.*, 2002, **1**(2), 175–182, DOI: 10.1023/A:1022555216303.

19 H. Ye, A. Fu, W. Wu, Y. Li, G. Wang, M. Tang, S. Li, S. He, S. Zhong, H. Lai, *et al.*, Cytotoxic and apoptotic effects of constituents from Millettia pachycarpa Benth, *Fitoterapia*, 2012, **83**(8), 1402–1408, DOI: 10.1016/j.fitote.2012.08.001.

20 M. A. Selepe, Isoflavone Derivatives as Potential Anticancer Agents: Synthesis and Bioactivity Studies, *ChemMedChem*, 2024, **19**(23), e202400420, DOI: 10.1002/cmdc.202400420.

21 Z. Wei, Y. Yang, C. Xie, C. Li, G. Wang, L. Ma, M. Xiang, J. Sun, Y. Wei and L. Chen, Synthesis and biological evaluation of pyranoisoflavone derivatives as anti-inflammatory agents, *Fitoterapia*, 2014, **97**, 172–183, DOI: 10.1016/j.fitote.2014.06.002.

22 H. Dong, Y. Che, X. Zhu, Y. Zhong, J. Lin, J. Wang, W. Du and T. Song, Total Syntheses and Antibacterial Studies of Natural Isoflavones: Scandenone, Osajin, and 6,8-Diprenylgenistein, *Molecules*, 2024, **29**, 11.

23 A. Bryskier and M. Klich, Coumarin Antibiotics: Novobiocin, Coumermycin, and Clorobiocin, *Antimicrob. Agents*, 2005, 816–825.

24 A. K. Wittkowsky, Warfarin and other coumarin derivatives: pharmacokinetics, pharmacodynamics, and drug interactions, *Semin. Vasc. Med.*, 2003, **3**(3), 221–230, DOI: 10.1055/s-2003-44457.

25 M. Campos-Toimil, F. Orallo, L. Santana and E. Uriarte, Synthesis and Vasorelaxant Activity of New Coumarin and Furocoumarin Derivatives, *Bioorg. Med. Chem. Lett.*, 2002, **12**(5), 783–786, DOI: 10.1016/S0960-894X(02)00015-X.

26 B. Rostom, R. Karaky, I. Kassab and M. Sylla-Iyarreta Veitía, Coumarins derivatives and inflammation: Review of their effects on the inflammatory signaling pathways, *Eur. J. Pharmacol.*, 2022, **922**, 174867, DOI: 10.1016/j.ejphar.2022.174867.

27 V. Flores-Morales, A. P. Villasana-Ruíz, I. Garza-Veloz, S. González-Delgado and M. L. Martinez-Fierro, Therapeutic Effects of Coumarins with Different Substitution Patterns, *Molecules*, 2023, **28**(5), DOI: 10.3390/molecules28052413.

28 T. V. Shokol, N. V. Gorbulenko, M. S. Frasinyuk and V. P. Khilya, Synthesis of 7-Hydroxy-8-Methyl-4'-Methoxy-6-Formylisoflavone and Linear Hetarenochromones Based on It, *Chem. Nat. Compd.*, 2020, **56**(3), 420–422, DOI: 10.1007/s10600-020-03052-9.

29 H. Pechmann, Neue Bildungsweise der Cumarine. Synthese des Daphnetins. I, *Ber. Dtsch. Chem. Ges.*, 2006, **17**, 929–936, DOI: 10.1002/cber.188401701248.

30 W. H. Perkin, XXIII.—On the hydride of aceto-salicyl, *J. Chem. Soc.*, 1868, **21**, 181–186, DOI: 10.1039/JS8682100181.

31 E. Knoevenagel, Condensation von Malonsäure mit aromatischen Aldehyden durch Ammoniak und Amine, *Eur. J. Inorg. Chem.*, 1898, **31**, 2596–2619.

32 T. Harayama, K. Nakatsuka, H. Nishioka, K. Murakami, N. Hayashida and H. Ishii, Convenient Synthesis of a Simple Coumarin from Salicylaldehyde and Wittig Reagent. II.: Synthesis of Bromo- and Methoxycarbonylcoumarins, *Chem. Pharmaceut. Bull.*, 1994, **42**(10), 2170–2173, DOI: 10.1248/cpb.42.2170.

33 S. Reformatsky, Neue Synthese zweiatomiger einbasischer Säuren aus den Ketonen, *Ber. Dtsch. Chem. Ges.*, 1887, **20**(1), 1210–1211, DOI: 10.1002/cber.188702001268.

34 A. Shaabani, R. Ghadari and A. H. Rezayan, Synthesis of Functionalized Coumarins, *Iran. J. Chem. Chem. Eng.*, 2011, **30**(4), 19–22, DOI: 10.30492/ijcce.2011.6084.

35 T. V. Shokol, V. A. Turov, V. V. Semenyuchenko and V. P. Khilya, Azaheterocyclic derivatives of α-pyrono[2,3-f] isoflavones, *Chem. Nat. Compd.*, 2006, **42**(6), 668–672, DOI: 10.1007/s10600-006-0248-6.

36 V. A. Nuraini, V. Falasca, D. S. Wenholz, D. S. Black and N. Kumar, Synthesis of fused-ring systems and diarylmethane flavonoids via ortho-quinone methide intermediates, *RSC Adv.*, 2025, **15**(4), 2912–2929, DOI: 10.1039/D4RA08704F.

37 M. H. E. Yee, *Synthesis of Novel Flavonoid Hybrids and Development of Their Delivery Systems*, The University of New South Wales, 2017.

38 S. J. Becerra-Anaya, D. R. Merchán Arenas and V. V. Kouznetsov, A Simple and Effective Protocol for the Pechmann Reaction to Obtain 4-Methylcoumarin Derivatives Using a High-Speed Mixer Ball Mill Process, *Chemistry*, 2023, **5**, 1077–1088.

39 D. Subhas Bose, A. P. Rudradas and M. Hari Babu, The indium(III) chloride-catalyzed von Pechmann reaction: a simple and effective procedure for the synthesis of 4-substituted coumarins, *Tetrahedron Lett.*, 2002, **43**(50), 9195–9197, DOI: 10.1016/S0040-4039(02)02266-9.

40 B. Litim, A. Djahoudi, S. Meliani and A. Boukhari, Synthesis and potential antimicrobial activity of novel α-aminophosphonates derivatives bearing substituted quinoline or quinolone and thiazole moieties, *Med. Chem. Res.*, 2022, **31**(1), 60–74, DOI: 10.1007/s00044-021-02815-5.

41 M. Koca, A. S. Ertürk and O. Bozca, Rap-Stoermer Reaction: TEA Catalyzed One-Pot Efficient Synthesis of Benzofurans and Optimization of Different Reaction Conditions, *ChemistrySelect*, 2022, **7**(30), e202202243, DOI: 10.1002/slct.202202243.

42 G. E. Kelly and A. J. Husband, Flavonoid compounds in the prevention and treatment of prostate cancer, *Methods Mol. Med.*, 2003, **81**, 377–394, DOI: 10.1385/1-59259-372-0:377.

43 CCDC 2476513: Experimental Crystal Structure Determination, 2025, DOI: 10.5517/ccdc.csd.cc2p40jd.