Review
doi.org/10.1002/cmdc.202400420
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Isoflavone Derivatives as Potential Anticancer Agents: Synthesis and Bioactivity Studies

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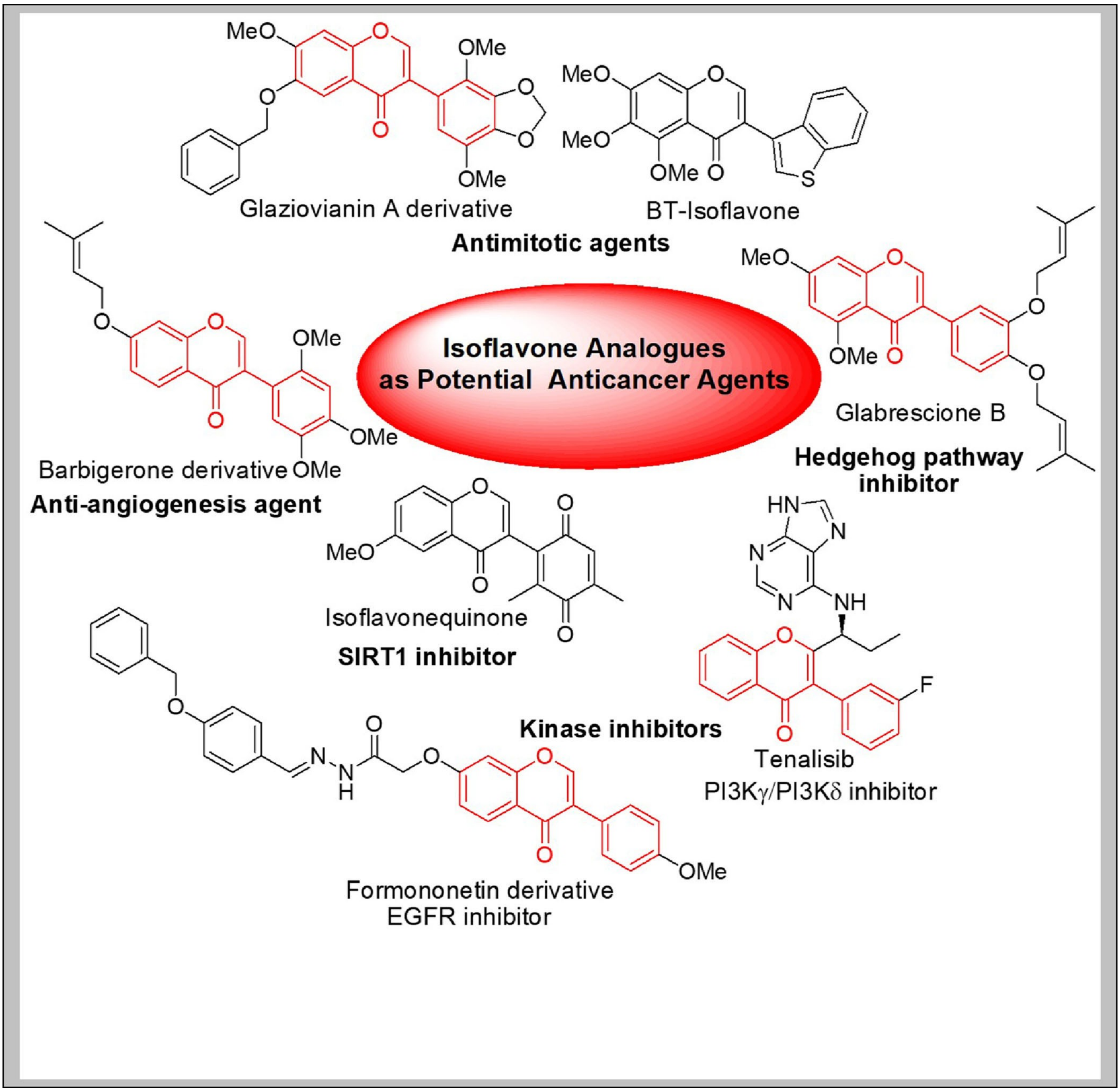

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Chemistry Europe
European Chemical Societies Publishing

Isoflavones are phenolic natural compounds with a $C_6C_3C_6$ framework. They possess a plethora of biological activities that are associated with putative benefits to human health. In particular, the cancer chemopreventive and chemotherapeutic potential of isoflavones has attracted the interest of researchers. Several isoflavone derivatives have been synthesised and probed for their anticancer activities. The isoflavone analogues are mainly synthesised by molecular hybridisation and other strategies that enable diversification through early or late-stage functionalisation of A-, B- and C-rings of the isoflavones. This has resulted in the discovery of isoflavone analogues with improved antiproliferative activities against several cancer cells and different mechanisms of action. In this review, the synthesis of isoflavone derivatives and their anticancer activity studies are discussed.

1. Introduction

Isoflavones are phenolic secondary metabolites commonly found in the Leguminosae family.[1,2] Isoflavone compounds consist of two aromatic systems, the A-ring and the B-ring adjoined to the heterocyclic pyran-4-one moiety (C-ring). They differ from other classes of flavonoids by the position of the B-ring, which is at C-3 (Figure 1). Isoflavones have been reported to exhibit a myriad of biological activities that include anti-inflammatory, anti-microbial, vasorelaxation, cardioprotective, neuroprotective, chemoprotective and antiproliferative activities.[3–9] The anticancer activities of isoflavones have been of great interest to researchers. In vivo and in vitro antiproliferative activity studies show that isoflavones attenuate the growth of different human cancer cells including breast, prostate, colon, pancreatic, lung and others.[10–13] Furthermore, isoflavones have shown the potential to block tumour invasion and metastasis and suppress cancer stem cells.[10,11,14,15] The anti-tumour activities of isoflavones are attributed to different mechanisms of action and their ability to inhibit multiple signalling pathways that are involved in tumourigenesis, invasion and migration.[11,15,16]

Although natural isoflavones offer promise for drug development, their progression in the drug discovery pipeline is hampered by several factors that include poor solubility, bioavailability and selectivity.[17,18] Therefore, isoflavone derivatives have been prepared to improve their physicochemical properties and efficacy,[19,20] as well as chemical accessibility[21] by reducing the complexity of some of the isoflavone structures, while retaining the activity.[22] In some instances, isoflavone derivatives were synthesised to confer favourable properties and reduce the toxicity of existing chemotherapeutic drugs and other potential anticancer compounds.[23–25] The isoflavone derivatives have mainly been prepared by molecular hybridisation,[26–28] whereby natural or unnatural isoflavone compounds were amalgamated with other privileged pharmacophores, other natural compounds or chemotherapeutic drugs.[19,29–32] Chemical space expansion could also be attained by the replacement of the B-ring with other heterocyclic ring structures or by key scaffolds that mimic other bioactive compounds.[33–35] Other strategies included diversity-oriented synthesis (DOS)[36,37] involving divergent transformation and elaboration of functional groups and substituents in isoflavones.[38,39] Computer-aided drug design (CADD) including scaffold hoping has also been employed to guide the synthesis of isoflavone analogues with improved properties.[40–42] These efforts have resulted in the discovery of isoflavone derivatives that exhibit enhanced antiproliferative activities than the parent isoflavones,[40,43,44] inhibit proliferation of resistant cancer cells,[34] and sensitise cells to chemotherapeutic drugs and radiation.[45,46] The isoflavone derivatives elicit their anticancer activities as mitotic,[34,47,48] kinases (EGFR, PI3Kδ, PI3 Kγ),[40,42,49–52] SIRT1,[53] and angiogenesis inhibitors.[44] Moreover, analogues that supress signalling pathways that include Hedgehog,[41] PI3 K/AKT/mTOR,[45] MAPK/Wnt,[19] EGFR/PI3 K/Akt/Bad, EGFR/ERK and EGFR/PI3 K/Akt/b-catenin[40] have been discovered. Examples of the antiproliferative isoflavone analogues are shown in Figure 1.[34,40,41,44,51,53]

This review discusses the synthesis and anticancer activity studies of isoflavone derivatives optimised through different strategies including molecular hybridisation, CADD, DOS and functional group manipulation. They consist of analogues of

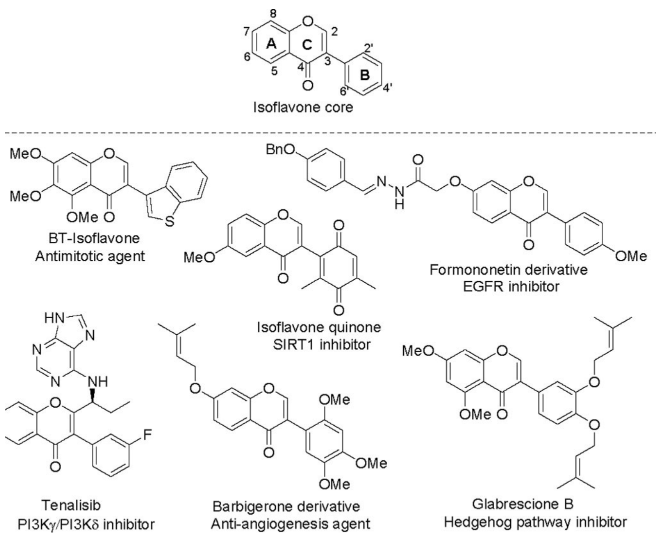

Figure 1. Isoflavone core structure and isoflavone analogues with potential anticancer activity.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/cmdc.202400420

natural isoflavones such as genistein,[23,29] formononetin,[19,24,25,40] glaziovianin A[12,47] and prenylated isoflavone derivatives, including barbigerone,[44,48] 4′-*O*-methylgrynullarin[13,22] and glabrescione B derivatives.[41] Other non-natural isoflavone analogues with structural modification at different positions on the A-, B- and C-rings are also discussed. They comprise B-ring replaced derivatives,[33,34] including antimitotic benzo[*b*]thiophene (BT) analogues.[34] Others encompass analogues inspired by isoflavone-bearing kinase inhibitors such as tenalisib, which is undergoing phaseI/II clinical trials and umbralisib, which was approved for treatment of different types of lymphoma and later withdrawn.[49,51] The final set of compounds under discussion are the isoflavone-inspired preclinical and clinical super-benzopyran analogues.[54–56] The focus is on reports published from 2012 to March 2024.

2. Genistein Derivatives

Genistein (**1**) is the main metabolite of *Glycine max* (soy).[57] Genistein (**1**) and other soy isoflavones are regarded as phytoestrogens, due to their ability to modulate estrogenic effects.[58] Apart from their potential role as phytoestrogens, soy isoflavones have also been reported to exhibit several biological activities including chemopreventive and anticancer activity.[59,60] Clinical studies have been conducted for genistein (**1**) and other soy isoflavones, daidzein and glycitein in patients with prostate and urothelial bladder cancer.[10,16]

Several derivatives that link genistein (**1**) with synthetic or natural scaffolds have been prepared and evaluated for potential anticancer activities.[18,20,61,62] Some of the synthesised derivatives exhibited improved activity than genistein (**1**).[18,61] A detailed review of the anticancer potential of genistein (**1**) and its derivatives was written by Gupta and colleagues in 2022.[62] Recent studies involved the synthesis of 5-fluorouracil-genistein hybrids,[23] triazine-genistein derivatives[29] and fluorinated genistein analogues.[63]

5-Fluorouracil-genistein analogues were prepared and evaluated for antiproliferative activity against human colon adenocarcinoma cells (SW480 and SW620) and non-malignant cell lines (HaCaT and CHO–K1).[23] Some of the synthesised derivatives showed enhanced antiproliferative activity than that of 5-fluorouracil. The synthesis commenced with the preparation of the main precursors, *N*-propargylated 5-fluorouracil **5** and genisteinalkylazides **3a–h** (Scheme 1). Compound **5** was prepared by *N*-alkylation of 5-fluorouracil (**4**) with propargyl bromide, while genisteinalkylazides **3a–h** were prepared by 7-*O*-etherification of genistein (**1**) with dibromoalkanes of different chain lengths, followed by ultrasound (US)-mediated nucleophilic substitution with sodium azide. Click reaction of genisteinalkylazides **3a–h** and propargyl **5** rendered the hybridised genistein analogues **6a-h**. Of the synthesised compounds, **6a** showed antiproliferative activity with IC_{50} values of 62.73±7.26 and 50.58±1.33 μM for SW480 and SW620 cells, respectively. This activity was greater than that of 5-fluorouracil (174.3±19.10 and 180.90±18.80 μM, for SW480 and SW620 cells, respectively) and that of genistein (**1**) (75.84±5.83 μM) against SW620.[23]

Zou and colleagues synthesised 1,3,5-triazine analogues of genistein.[29] Firstly, they reacted 2,4,6-trichloro-1,3,5-triazine (**7**) with secondary amines to give aminotriazine derivatives **8a-l** (Scheme 2). The reaction of **8a-l** with genistein (**1**) gave the 7-*O* and 4′-*O*-disubstituted analogues (**9a-l**). The triazine-genistein derivatives were assessed for antiproliferative activity against MDA-MB-231, HeLa, HCT-116 and Huh-7 cancer cell lines. Most of the synthesised compounds exhibited superior antiproliferative activity than the parent compound genistein (**1**). Compound **9i** exhibited the most potent activity against MDA-MB-231 and HeLa cell lines with IC_{50} values of 23.13±1.29 and 39.13±0.89 μM, respectively. Compound **9a** exhibited the best activity against HCT-116 cell line (IC_{50}=18.40±3.41 μM) and compound **9b** showed better activity against Huh-7 cell line (37.56±1.92 μM). Compound **9i** was subjected to further studies on cell migration, invasion and adhesion, as well as *in vivo* studies in xenograft models of MDA-MB-231 cells. The results showed that **9i** could inhibit the migration, invasion and adhesion of MDA-MB-231 cells, and also inhibit the proliferation of MDA-MB-231 tumour in xenografts.[29]

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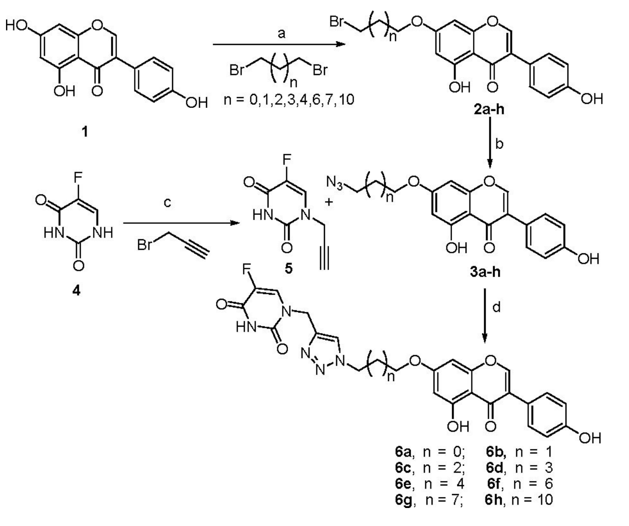
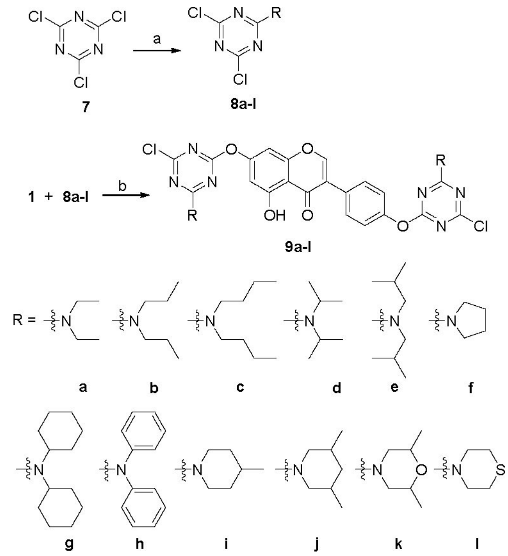


Scheme 1. Synthesis of 5-Fluorouracil-genistein analogues. Reagents and conditions: a) DIPEA, DMF, 61–71%; b) NaN_3, DMF, 40°C, US, 78–89%; c) DIPEA, KI, DMF, US, 40%; d) Ascorbic acid, $Cu(OAc)_2$, DMF-H_2O, 40°C, US, 43–93%.



Scheme 2. Synthesis of 1,3,5-triazine analogues of genistein. Reagents and conditions: a) Secondary amine, Acetone, K_2CO_3, −20 °C; b) Acetone, K_2CO_3, rt, 69–81 %.

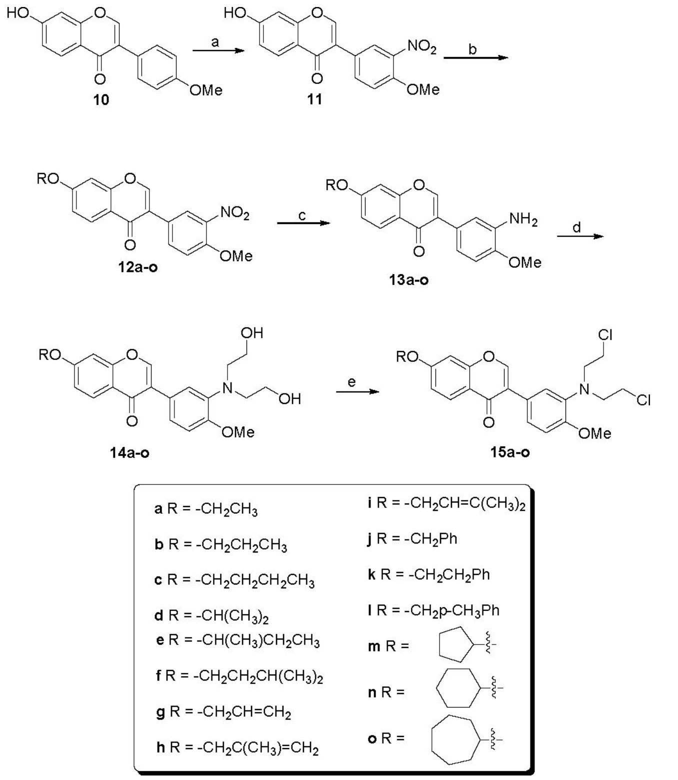
3. Formononetin Derivatives

Formononetin (**10**) is mainly found in red clover plant and is widespread in other plants of the Leguminosae family.[64] Formononetin has been reported to exhibit many biological activities that include antioxidant, antitumor, neuroprotective, antihypertensive, antibacterial and antiviral effects.[64–66] Several derivatives of formononetin have been synthesised and evaluated for their potential anticancer activities.[19,24,25,40]

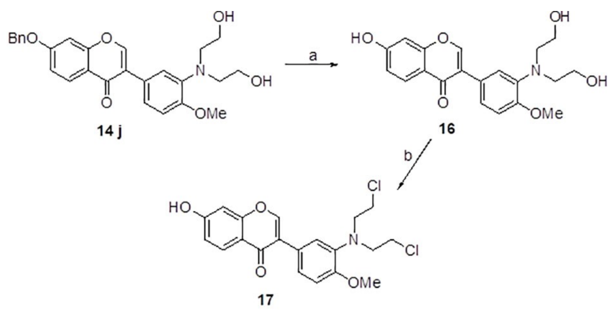
Formononetin *N*-mustard derivatives were synthesised and evaluated for cytotoxicity against a panel of cancer cell lines.[24] The synthesis is outlined in Scheme 3. B-ring nitration of formononetin (**10**) gave 3′-nitroformononetin (**11**) in a 75 % yield. Alkylation of the 7-hydroxy group with different alkyl bromides or by Mitsunobu reaction yielded 7-*O*-alkylated derivatives **12 a**-**o**. The zinc-mediated reduction of the nitro group gave 3′-aminoisoflavones **13 a**-**o** in 78–85 % yields, which were *N*-alkylated with ethylene oxide in the presence of AcOH to render compounds **14 a**-**o**. Treatment of **14a**-**o** with $SOCl_2$ in dichloromethane gave the final compounds **15 a**-**o**.

Another targeted compound **17** with a free hydroxy group at the 7 position was prepared from **14 j** as shown in Scheme 4. Benzyl deprotection of **14 j** and subsequent treatment of the resulting 7-hydroxyisoflavone **16** with $SOCl_2$ in dichloromethane gave the targeted compound **17**.[24]

The synthesised formononetin *N*-mustard hybrids were evaluated for cytotoxicity against cancer cell lines that included SH-SY5Y, HCT-116, DU-145, Hela and SGC-901.[24] All synthetic derivatives showed better antiproliferative activity against HCT-116, SH-SY5Y and DU-145 cell lines compared to formononetin (**10**). Compound **15 o** exhibited activity against SH-SY5Y cell line with IC_{50} value of 2.08 μM and compound **15 n** exhibited activity against Hela cell line with IC_{50} value of 8.29 μM. Compounds **15 d** and **17** showed almost equipotent activity against HCT-116, SH-SY5Y and SGC-7901 cell lines with IC_{50} values of 3.8, 2.17 and 9.21 μM, respectively for **15 d**; and IC_{50} values of 4.1, 2.7 and 8.2 μM, respectively for **17**. Further studies demonstrated that compounds **15 d** and **15 n** could induce cell cycle arrest at G2/M phase and cell apoptosis.[24]



Scheme 3. Synthesis of formononetin nitrogen mustard derivatives. Reagents and conditions: a) concentrated HNO_3, concentrated H_2SO_4, AcOH, 50 °C, 12 h, 75 %; b) Method A: K_2CO_3, R–Br, acetone, reflux, 3–8 h, 79–87 % (for **12 a**-**l**); Method B: DIAD, PPh_3, THF, R-OH, 0 °C to rt, overnight, 65–77 % (for **12 m**-**o**); c) Zn, EtOH, HOAc, reflux, 1–2 h, 78–85 %, d) ethylene oxide, HOAc, rt, overnight, 70–82 %; e) $SOCl_2$, DCM, reflux, 1.5 h, 66–75 %.



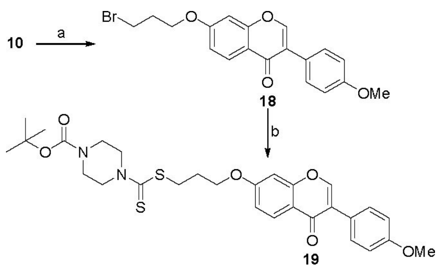
Scheme 4. Synthesis of formononetin nitrogen mustard derivative **17**. Reagents and conditions: a) H_2, 10 % Pd/C, MeOH, rt, 1 h, 90 %; b) $SOCl_2$, DCM, reflux, 1.5 h, 70 %.

Several formononetin-dithiocarbamate conjugates were synthesised and evaluated for antiproliferative activity against MGC-803, EC-109 and PC-3 cell lines. All the synthesised derivatives were more active than formononetin. Of the synthesised compounds, **19** was identified as the most potent compound against MGC-803, EC-109 and PC-3 cells (IC_{50} = 6.07 ± 0.88, 3.54 ± 1.47 and 1.97 ± 0.01 μM, respectively). In addition, compound **19** showed superior activity compared to 5-FU on all cell lines. Mechanistic studies showed that **19** induced cell cycle arrests in G1 phase and exhibited concentration-dependent downregulation of cyclin D1 and CDK4 proteins. Further studies demonstrated that **19** could reduce PC-3 cell growth and migration via MAPK/Wnt signalling pathways.[19]

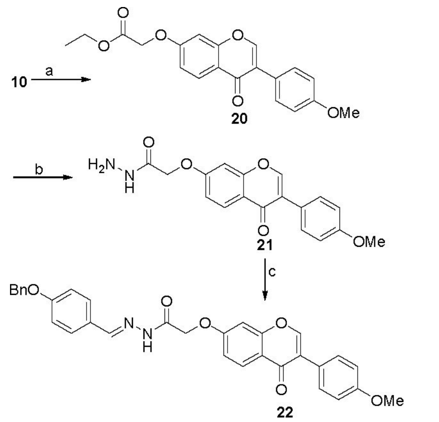
Compound **19** was prepared by alkylation of the 7-hydroxy group of formononetin (**10**) with 1,3-dibromopropane to give compound **18**. The reaction of *tert*-butyl piperazine-1-carboxylate with CS_2 followed by coupling with **18** in the presence of Na_3PO_4.12H_2O gave **19** (Scheme 5).[19]

7-*O* Derivatives of formononetin that target human epidermal growth factor receptor (EGFR) were designed based on CADD method and synthesised by Lin and colleagues.[40] The synthesised compounds were first assessed for inhibition of EGFR. All synthesised compounds showed greater potency at 150 nm than formononetin (**10**). The most active compound, **22** exhibited 87.3 % inhibition and IC_{50} value of 14.5 nm against EGFR. In vitro antiproliferative study on four cancer cells, MCF-7, MDA-MB-231, H460 and H1650, and non-cancer cells, L02 and VERO revealed **22** to be the most active compound. It showed cell growth inhibition with IC_{50} values of 11.5 ± 1.52, 5.44 ± 1.28, 6.36 ± 1.55 and 7.26 ± 1.02 μM against MCF-7, MDA-MB-231, H460 and H1650, respectively. It was less active on the non-cancer cells L02 and VERO (IC_{50} > 100 and 95.2 ± 4.72 μM, respectively). Studies on the mode of action of **22** for the observed activity in MDA-MB-231 cells showed that it induced apoptosis by regulating EGFR/PI3 K/Akt/Bad pathway, inhibited cell growth by blocking EGFR downstream Ras/Raf/MEK/ERK signalling pathway and migration by targeting EGFR/PI3 K/Akt/b-catenin pathway. Compound **22** did not induce cell cycle arrest and had no significant effect on Cyclin A, Cyclin D1, CDK4 protein expression. In vivo anti-tumour study using female nude mice showed that **22** greatly inhibited tumour growth with effectiveness similar to that of the positive control, lapatinib.[40]

The synthesis of **22** is depicted in Scheme 6. The reaction of formononetin (**10**) with ethyl bromoacetate gave compound **20**, which was converted into hydrazide **21**. The reaction of



Scheme 5. Synthesis of formononetin-dithiocarbamate conjugate **19**. Reagents and conditions: a) 1,3-dibromopropane, K_2CO_3, THF, reflux, 70–83 % yield; (b) CS_2, *tert*-butyl piperazine-1-carboxylate, Na_3PO_4·12H_2O, acetone, rt, 78–85 % yield.

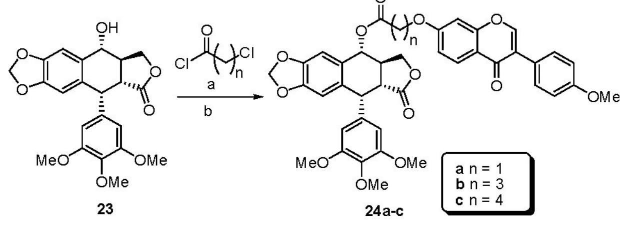


Scheme 6. Synthesis of formononetin hydrazide derivative **22**. Reagents and conditions: a) ethyl bromoacetate, acetone, K_2CO_3, reflux, 10 h, 95 %; b) hydrazine hydrate, ethanol, reflux, 10 h, 87 %; c) 4-benzyloxybenzaldehyde, glacial acetic acid, ethanol, reflux, 6 h, 69 %.

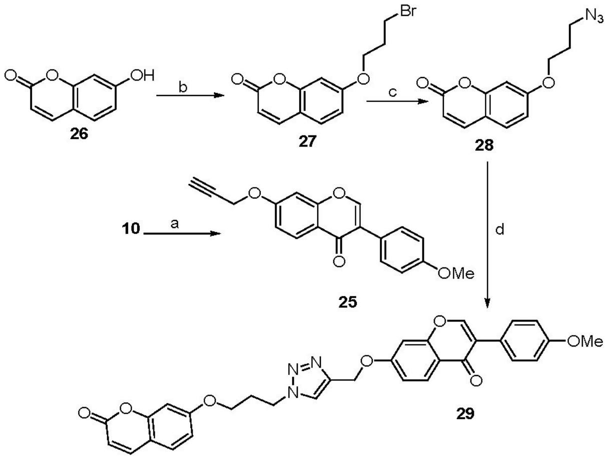
hydrazide **21** with 4-benzyloxybenzaldehyde gave the most active formononetin hydrazide derivative **22**.[40]

Three novel compounds were prepared by hybridisation of an anticancer lignan, podophyllotoxin (**23**) and isoflavone, formononetin (**10**). The target compounds were obtained by esterification of podophyllotoxin (**23**) with chloroacyl chloride and subsequent nucleophilic substitution reaction with formononetin (**10**) (Scheme 7).[25] The conjugates **24 a**-**c** were evaluated for cytotoxicity against SKOV3, MCF7, HepG2, HeLa, A549, CT26, B16f10 and HUVEC cancer cell lines. The three synthesised compounds exhibited potent cytotoxic activity than formononetin (**10**) in all cancer cell lines. Compound **24 a** exhibited improved activity against A549 human lung carcinoma cell line (IC_{50} = 0.753 ± 0.173 μM) than podophyllotoxin (**10**) (IC_{50} = 1.934 ± 0.089 μM).[25] Mechanistic studies demonstrated that **24 a** could reduce caspase-8 expression, induce apoptosis and disrupt microtubule network in A549 cells. Furthermore, **24 a** showed potential to inhibit migration and invasion of A549 cells.

Coumarin-formononetin hybrid **29** was prepared by Yao and colleagues and evaluated for antiproliferative activity against three gastric cancer cell lines (SGC7901, MKN45 and MGC803).[67] The synthesis commenced with the preparation of two main precursors, 7-*O*-propargylformononetin (**25**) and 7-*O*-alkylazide coumarin **28** (Scheme 8). Compound **25** was prepared by alkylation of **10** with propargyl bromide using NaOH



Scheme 7. Synthesis of podophyllotoxin-formononetin hybrid. Reagents and conditions: a) Et_3N, DCM; b) **10**, K_2CO_3, KI, DMF, 64–85 % over two steps.



Scheme 8. Synthesis of the formononetin-coumarin hybrid **29**. Reagents and conditions: a) propargyl bromide, NaOH, acetone, reflux; b) 1,3-dibromopropane, K_2CO_3, DCM, reflux, 50.7%; c) NaN_3, CH_3CN, reflux, 41.3%; d) intermediate **25**, $CuSO_4.5H_2O$, sodium ascorbate, DMSO:H_2O (1:1), rt, 32.9%.

as a base. Compound **28** was prepared by the reaction of coumarin (**26**) with dibromopropane to give bromoalkylcoumarin **27** and subsequent displacement of bromine with NaN_3. Click reaction of compounds **25** and **28** in the presence of $CuSO_4.5H_2O$ gave the requisite triazole bridged coumarin-formononetin hybrid **29**. The antiproliferative results of the three gastric cancer cell lines showed that **29** potently inhibited SGC7901 with IC_{50} value of 1.07 μM. Compound **29** was also evaluated for inhibition of SIRT1 activity and it exhibited inhibitory activity with IC_{50} value of 2.52 μM. Furthermore, compound **10** was reported to inhibit SGC7901 growth and migration by Wnt/β-Catenin and AKT/mTOR signalling pathways and show in vivo antitumor activity.[67]

4. Glaziovianin A Derivatives

Glaziovianin A (**30**) was isolated from the leaves of a Brazilian tree, *Ateleia glazioviana* Baillon (Leguminosae) through bioassay-guided fractionation against HL-60 leukemia cells.[12] It was determined to exhibit cytotoxic activity against HL-60 cell line with IC_{50} value of 0.29 μM.[12] It also exhibited differential cytotoxicity in a panel of 39 cell lines from the Japanese Foundation for Cancer Research[12] and was determined to be a microtubule dynamics inhibitor.[68] Owing to its biological activities, different research groups have synthesised glaziovianin A (**30**)[69–71] and its derivatives.[47,70,72–74] Hayakawa and colleagues prepared several derivatives of glaziovianin A with modifications on the A- and B-rings.[47,73,74] Some of the synthesised compounds showed improved cytotoxic activity against HeLa S3 cells than glaziovianin A (**30**).[47] Interestingly, the 6-*O*-benzyl derivative **31** was discovered to be an α,β-tubulin inhibitor,[47] while the 7-*O*-benzyl derivative, gatastatin (**32**), was determined to be a specific γ-tubulin inhibitor (Figure 2).[75] However, gatastatin (**32**) showed less potent activity against HeLa S3 cells.[47] Recently, more active derivatives of **32** were synthesised by modification at C-6.[74] These included the 6-*O*-propargyl derivative, gatastatin G2 (**33**), which showed improved activity against HeLa S3 cells and γ-tubulin, than gatastatin (**32**).

The synthesis of glaziovianin A derivatives was based on the Suzuki-Miyaura coupling reaction of halochromones with boronic esters.[76,77] As shown in Scheme 9, 6-O-benzylglaziovianin A (**31**) was prepared by coupling of iodochromone **37** with boronate ester **38**.[47] The iodochromone **37** was in turn synthesised by a sequence of steps that involved the conversion of sesamol (**34**) into an appropriately substituted acetophenone **35**,[47,78] followed by condensation with DMF-DMA to give enaminone **36**, and finally iodine-mediated cyclisation by modified Gammill procedure.[79]

Recently the synthesis of gatastatin (**32**) and other modified A- and B-ring analogues led to the discovery of the more potent specific γ-tubulin gatastatin G2 (**33**).[74] The synthesis of gatastatin analogues was initiated from isovanillin (**39**), from which the main precursors, 3-iodochromones **40** and **41** were prepared (Scheme 10). The Suzuki–Miyaura reaction of iodochromones **40** and **41** with different boronate esters and subsequent derivatisation at C-6 yielded several gatastatin analogues. Specifically, gatastatin (**32**) was synthesised by the Suzuki coupling of iodochromone **40** with boronate ester **38**, while gatastatin G2 (**33**) was synthesised by coupling iodochromone **41** with **38**, followed by deprotection of the resulting

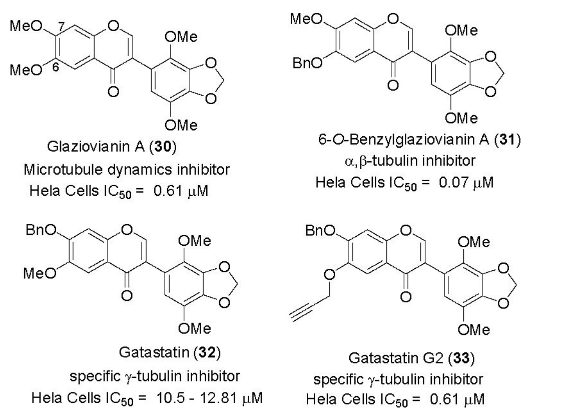
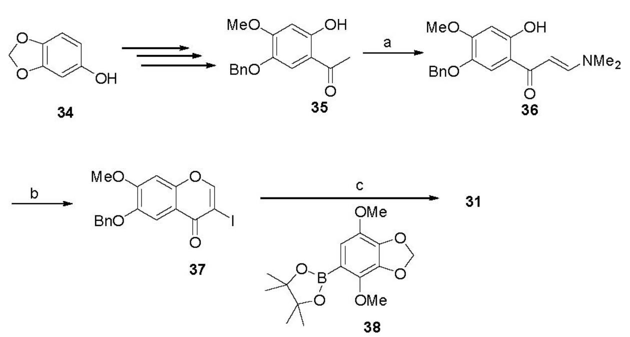
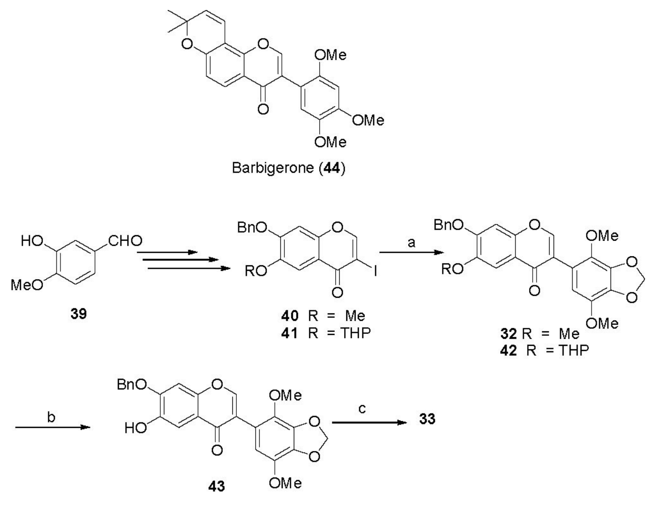


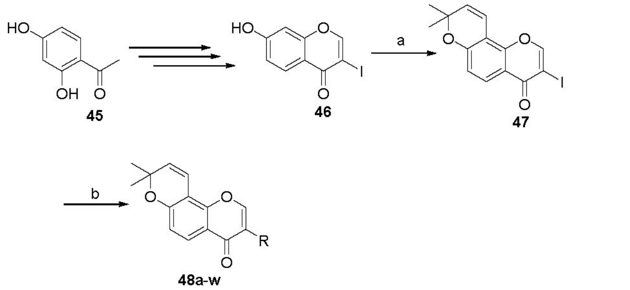
Figure 2. Glaziovianin A and derivatives.



Scheme 9. Synthesis of 6-*O*-benzylglaziovianin A (**31**). Reagents and conditions: a) DMF-DMA, 95 °C; b) I_2, py, $CHCl_3$, rt, 86% in two steps; c) **38**, $PdCl_2$(dppf).DCM, 1 M Na_2CO_3 aq, 1,4-dioxane, rt, 76%.



Scheme 10. Synthesis of gatastatin analogues. Reagents and conditions: a) **38**, $PdCl_2$(dppf)·DCM, 1 M Na_2CO_3 aq, 1,4-dioxane, rt, 61% for **32** and 97% for **42**; b) *p*-TSOH·H_2O, $CHCl_3$, MeOH, rt, 75% c) propargyl bromide, K_2CO_3, acetone, reflux, 97%.



a: R = 3-methoxyphenyl
b: R = 3,4-dimethoxyphenyl
c: R = 4-methoxyphenyl
d: R = 2,4-dimethoxyphenyl
e: R = 2benzo[*d*][1,3]dioxol-5-yl
f: R = 2,3,4-trimethoxyphenyl
g: R = 2-fluoro-3-methoxyphenyl
h: R = 4-acetylphenyl
i: R = 4-hydroxyphenyl
j: R = 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl
k: R = 4-formylphenyl
l: R = 4-cyanophenyl
m: R = 3-formylphenyl
n: R = 4-chloro-3-(trifluoromethyl)phenyl
o: R = 2-chloro-4-(trifluoromethyl)phenyl
p: R = 4-(trifluoromethyl)phenyl
q: R = 3-(trifluoromethyl)phenyl
r: R = 3,5-dimethoxyphenyl
s: R = 2-ethoxyphenyl
t: R = 2,5-dimethoxyphenyl
u: R = 3,4,5-trimethoxyphenyl
v: R = 2-methoxyphenyl
w: R = 4-ethoxyphenyl

Scheme 11. Synthesis of B-ring modified barbigerone analogues. Reagents and conditions: a) 1,1-diethoxy-3-methyl-2-butene, 3-picoline, xylene, reflux, 24 h (48.4%); b) $ArB(OH)_2$, 10% Pd/C, Na_2CO_3, H_2O, DME, 45°C, 1 h (49.6–89.7%).

isoflavone **42** and alkylation of **43** with propargyl bromide (Scheme 10).[74]

5. Derivatives of Prenylated Isoflavones

Prenylated isoflavones constitute the largest group of isoflavones.[2] They refer to isoflavones bearing a C5-isoprenoid unit and other long-chain units (geranyl, farnesyl, etc).[80] Modification of the prenyl substituents can involve reduction, hydroxylation and epoxidation of the double bond or cyclisation of prenyl chain with adjacent hydroxy groups of phenols resulting in pyrano- and furanoisoflavones.[80] Prenylated isoflavones exhibit a myriad of biological activities, including anticancer activity.[13,22,44,81,82] Owing to their interesting structures and bioactivities, several research groups have embarked on the synthesis of prenylated isoflavones and their derivatives.[22,44,83–87]

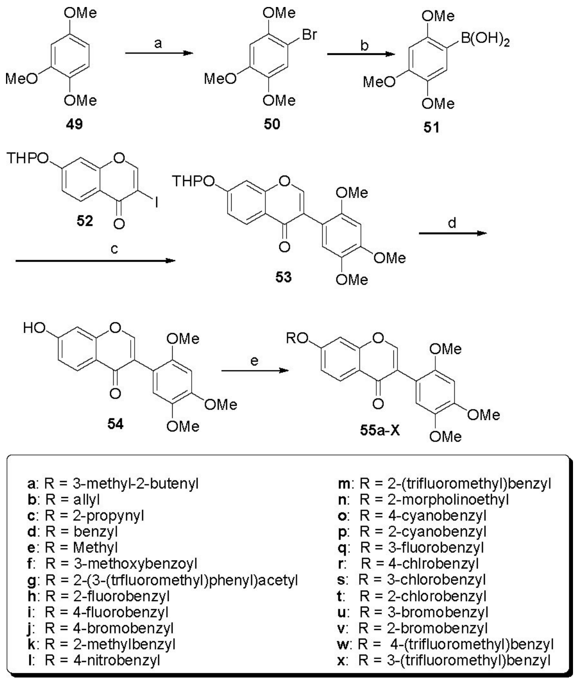
5.1. Barbigerone Derivatives

Barbigerone (**44**), an angular pyranoisoflavone first isolated from the seeds of *Tephrosia barbigera*[88] was reported to exhibit cytotoxicity against several cancer cell lines that include HepG2, C26, LL2 and B16.[81] In addition, it exhibited apoptotic-inducing effects and sensitised adriamycin (ADR)-resistant human breast carcinoma (MCF-7/ADR) cells.[81,82] Barbigerone derivatives with modifications on the A- and B-rings were synthesised by Wang and colleagues.[44] To keep the A-ring intact, 3-iododimethylpyranochromone **47** was coupled to various boronic acids leading to barbigerone derivatives **48a-w** with different substituents on the B-ring (Scheme 11). The dimethylpyranochromone **47** was prepared by the reaction of 3-iodo-7-hydroxychromone (**46**) with 1,1-diethoxy-3-methyl-2-butene in the presence of 3-picoline. The chromone **46** was derived from 2,4-dihydroxyacetophenone (**45**) (Scheme 11).[44]

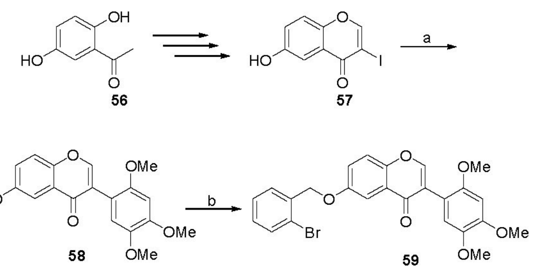
The synthesis of the A-ring modified analogues was initiated by preparing the boronic acid **51** by bromination of trimethoxybenzene **49** and subsequent treatment of the resulting bromobenzene **50** with *n*-BuLi and trimethyl borate. Suzuki-Miyaura coupling of boronic acid **51** with iodochromone **52**, followed by deprotection gave an isoflavone precursor **54**. Alkylation or esterification gave 7-*O* derivatives **55a-x** (Scheme 12).[44]

The barbigerone analogues **48a–w** and **55a–x** were evaluated for antiproliferative activity against cancer cell lines that included HepG2, A375, U251, B16, HCT116 and HUVEC. Most derivatives bearing the dimethylpyran scaffold in the A-ring showed reduced cytotoxic activity against all cancer cell lines compared to barbigerone (**44**). The exception was **48o**, which showed improved activity against U251 cell line (2.50 μM) than barbigerone (4.10 μM). Several 7-*O* derivatives exhibited antiproliferative activity with IC_{50} below 10 μM. The most active derivative **55a**, exhibited cytotoxic activity with IC_{50} values of 0.28, 1.58, 3.50, 1.09, 0.68 and 3.80 μM, against HepG2, A375, U251, B16, HCT116 and HUVEC cells, respectively. Furthermore, compound **55a** showed anti-angiogenic activities.

Following the discovery that barbigerone (**44**) inhibits tubulin polymerisation and the determination by X-ray crystal structure that it binds to colchicine-binding site, Yang and Chen's group designed and synthesised a more active barbigerone analogue **59**.[48] The compound **59** was synthesised by coupling boronic acid **51** with 3-iodochromone **57**, and subsequent reaction of resulting isoflavone **58** with bromobenzylbromide (Scheme 13). Compound **59** exhibited antiproliferative activity against H460, Ramos, HeLa and HCT116 with IC_{50} values of 0.46 ± 0.14, 0.62 ± 0.09, 0.17 ± 0.11 and 0.12 ± 0.07 μM, respectively. Furthermore, both **44** and **59** inhibited tubulin



Scheme 12. Synthesis of A-ring modified barbigerone analogues. Reagents and conditions: a) Br_2, CH_2Cl_2, 0 °C (92.3 %); b) *n*-BuLi, trimethyl borate, THF, −78 °C (37.7 %); c) 10 % Pd/C, Na_2CO_3, H_2O, DME, 45 °C, 1 h (61.4 %); d) *p*-TsOH, CH_3OH, THF, 60 °C, 1 h (87.1 %); e) RX, K_2CO_3, acetone, rt, overnight, or RCOOH, DCC, DMAP, DCM, rt, overnight (18.7–99.4 %).



Scheme 13. Synthesis of barbigerone analogue **59**. Reagents and Conditions: a) **51**, 10 % Pd/C, Na_2CO_3, H_2O, DME, 45 °C, 65.8 %; b) 1-bromo-2-(bromomethyl)benzene, K_2CO_3, MeCN, reflux, 92.2 %.

polymerisation, induced G2/M phase cell cycle arrest and apoptosis and exhibited in vivo anticancer activity in H460 xenograft model.[48] The results from the two studies by Chen's group indicate that the presence of the dimethylpyran ring is not significant for the anticancer activity of barbigerone derivatives, but keeping the substitution pattern of the B-ring intact is important for the activity of the analogues.

5.2. 4′-*O*-Methylgrynullarin Derivatives

A novel diprenylated isoflavone, 4′-*O*-methylgrynullarin (**60**) and other known prenylated isoflavones **61**–**62** with potent preferential cytotoxic activity against pancreatic cancer cell lines were isolated from *Derris scandens* flowers by Awale's group (Figure 3).[13]

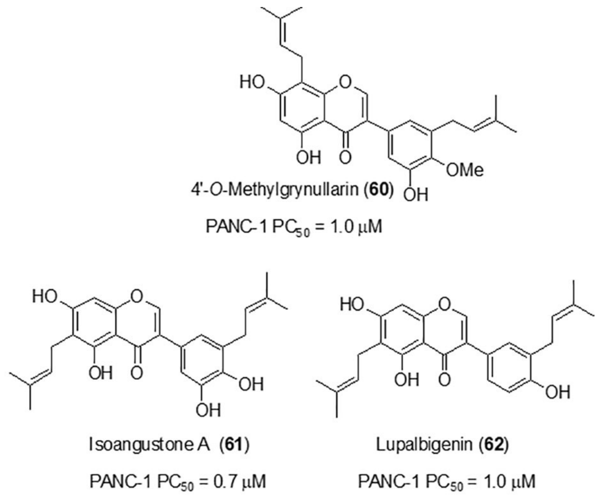


Figure 3. Natural diprenylated isoflavones with preferential cytotoxic activity against pancreatic cancer cell line.

Simpler derivatives of these compounds bearing one prenyl group in the A-ring were synthesised for structure-activity relationship study.[22] Most of the synthesised derivatives showed potent cytotoxic activity against PANC-1 cell line under nutrient-deprived conditions. The most active compounds were **69 a**, **69 b**, **74 b**, **74 f** and **74 h** with PC_{50} values of 1.5, 1.6, 0.8, 1.6 and 1.3 μM, respectively, against PANC-1 cell lines in nutrient-deprived medium (NDM). The 8-prenyl isoflavone **78** was less active (PC_{50} = 5.7 μM) than its 6-prenyl counterpart **69 a**. These results confirmed that the prenyl group at the 6 position was important for the cytotoxic activity and that the absence of the prenyl substituents in the B-ring did not negatively impact the activity of the molecules. The initial synthesis employed the deoxybenzoin intermediates **65 a**-**b** for the construction of the isoflavones **66 a**-**b**, and Claisen rearrangement of allyl ethers **67 a**-**b** followed by cross-coupling metathesis reaction for C-6 prenylation (Scheme 14). The deoxybenzoins **65 a**-**b** were prepared by acylation of phloroglucinol (**63**) with phenyl acetyl chlorides **64 a**-**b**.[22]

The low yields obtained from the acylation of phloroglucinol and limited phenylacetic acid starting materials prompted the group to synthesise additional derivatives by the Suzuki-Miyaura reaction (Scheme 15). The 6-prenylisoflavones **74 a**-**h** were prepared by late-stage prenylation of **73 a**-**h** following the established procedure. The isoflavones **73 a**-**h** were in turn synthesised by the Pd-catalysed coupling of 3-iodochromones **71 a**-**b** with various phenylboronic acids followed by selective deprotection of the resulting MOM-protected isoflavones **72 a**-**h**. The iodochromones **71 a**-**b** were obtained from acetophenones **70 a**-**b** (Scheme 15).[22]

To evaluate the effect of the prenyl side chain at the 8 position, 8-prenylisoflavone **78** was synthesised by conversion of MOM-protected acetophenone **75** into 8-prenyliodochromone **76**,[84] followed by the Suzuki reaction and deprotection of the isoflavone **77** (Scheme 16).[22]

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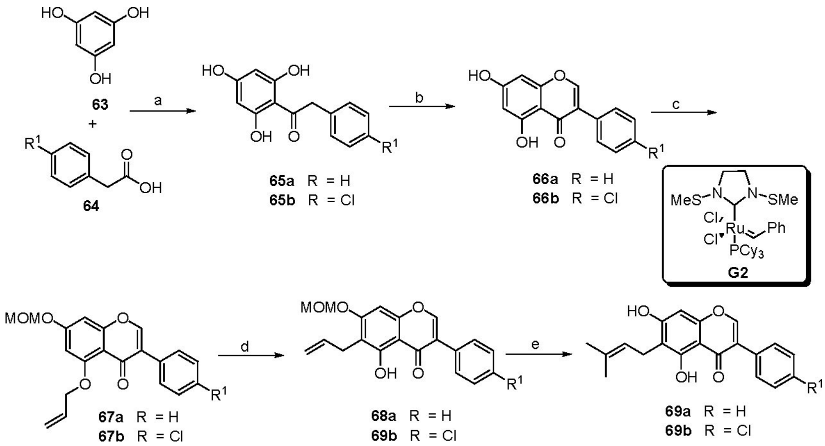
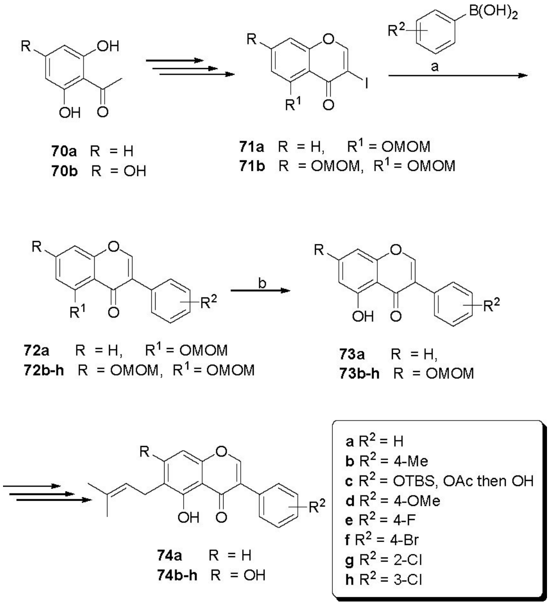
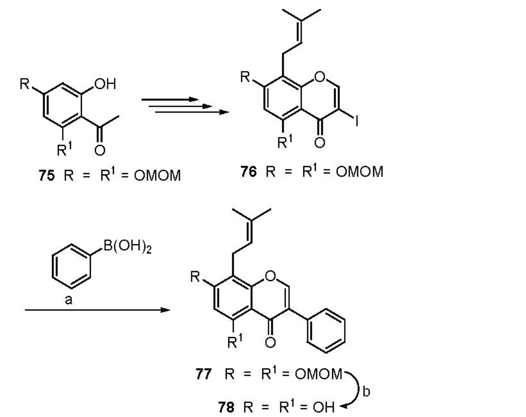


Scheme 14. Synthesis of prenylated isoflavone derivatives **69a-b**. Reagents and Conditions: a) $MeSO_3H$, 60 °C, 31 % for **65a** and **65b**; b) MsCl, BF_3·OEt_2, DMF, 80 °C, 77 % for **66a** and 69 % for **66b**; c) i: MOMCl, NaH, THF; ii) AllylBr, NaH, THF, reflux, 88 % for **67a** and 51 % for **67b**; d) $Eu(fod)_3$, $ClCH_2Cl$, 100 °C, sealed tube, 90 % for **68a** and 83 % for **68b**; e) i: isobutene, **G2**, benzene, 100 °C, sealed tube; ii: conc. HCl, MeOH, 64 % for **69a** and 51 % for **69b**.



Scheme 15. Synthesis of prenylated isoflavone derivatives **74a-h**. Reagents and Conditions: a) $(PhCN)_2PdCl_2$, dppb, Na_2CO_3, toluene/EtOH/H_2O, 70 °C, 35–98 %; b) I_2, MeOH, 72–95 %.



Scheme 16. Synthesis of 8-prenylated isoflavone derivative **77**. Reagents and Conditions: a) $(PhCN)_2PdCl_2$, dppb, Na_2CO_3, toluene/EtOH/H_2O, 70 °C, 57 %; b) 10 % HCl, MeOH, 40 °C, 40 %.

5.3. Glabrescione B derivatives

Berardozzi and colleagues designed and synthesised Hedgehog pathway inhibitors based on the prenylated isoflavone glabrescione B (**79**).[41] Glabrescione B (**79**) inhibited Gli1/DNA interaction and exhibited in vitro and in vivo activity against Hedgehog-dependent human and murine basal cell carcinoma (BCC) and medulloblastoma (MB) cells.[89] The glabrescione B derivatives were tested for Hedgehog pathway inhibitory activity using luciferase reporter assays. The experimental results together with computational studies led to the identification of compounds **80** and **81** as potential Gli1 inhibitors, while compounds **82** and **83** were identified as Smo antagonists (Figure 4).

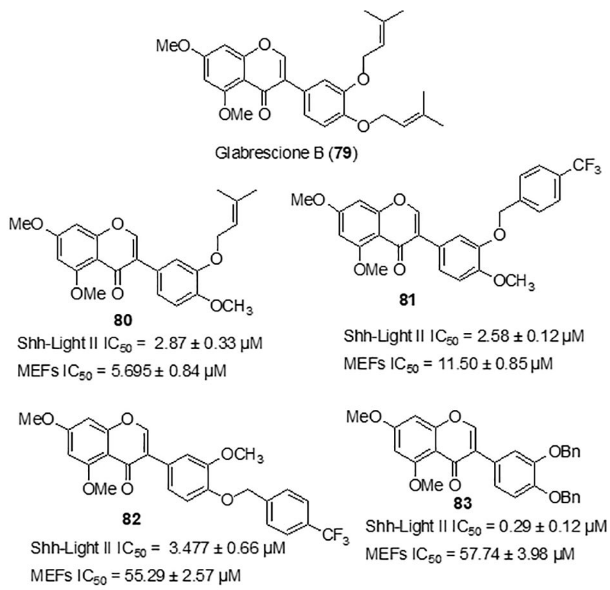


Figure 4. Glabrescione B (79) and derivatives.

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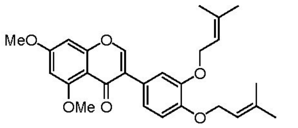
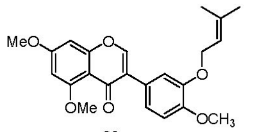
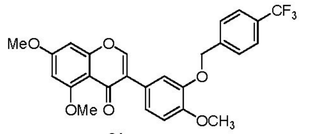


Glabrescione B (**79**)



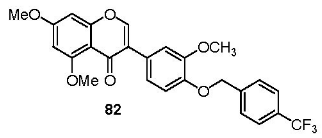
80

Shh-Light II IC_{50} = 2.87 ± 0.33 µM
MEFs IC_{50} = 5.695 ± 0.84 µM



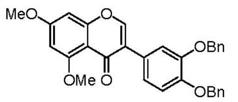
81

Shh-Light II IC_{50} = 2.58 ± 0.12 µM
MEFs IC_{50} = 11.50 ± 0.85 µM



82

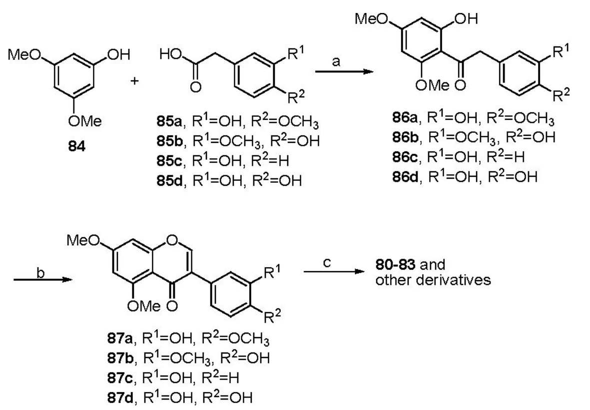
Shh-Light II IC_{50} = 3.477 ± 0.66 µM
MEFs IC_{50} = 55.29 ± 2.57 µM



83

Shh-Light II IC_{50} = 0.29 ± 0.12 µM
MEFs IC_{50} = 57.74 ± 3.98 µM

The Gli1 and Smo inhibitors, together with glabrescione B (**79**) were also evaluated for antiproliferative activity against MB cells, individually and in combination. The combination treatments showed synergistic effects between the isoflavones analogues acting as Gli1 and Smo antagonists as well as glabrescione B (**79**).The active compounds and other analogues were synthesised by BF_3·OEt_2-catalysed Friedel-Crafts acylation of dimethoxyphenol **84** with differently substituted phenylacetic acids **85 a**-**d** to give the benzylketones **86 a**-**d**. Formylation and subsequent *O*-cyclisation gave isoflavones **87 a**-**d**, which were alkylated by benzyl, prenyl and geranyl bromides to give several derivatives including **80**–**83** (Scheme 17).

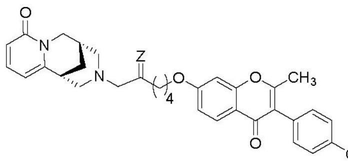


Scheme 17. Synthesis of glabrescione B derivatives. Reagents and Conditions: a) BF_3·OEt_2, 90 °C, 90 min 50–60%; b) BF_3·OEt_2, (chloromethylene)dimethyliminium chloride, DMF, rt, 2 h, 28–32%; c) alkyl- or benzylbromide, K_2CO_3, acetone, 45 °C, 17 h, 88–95%.

6. Other Isoflavone Derivatives

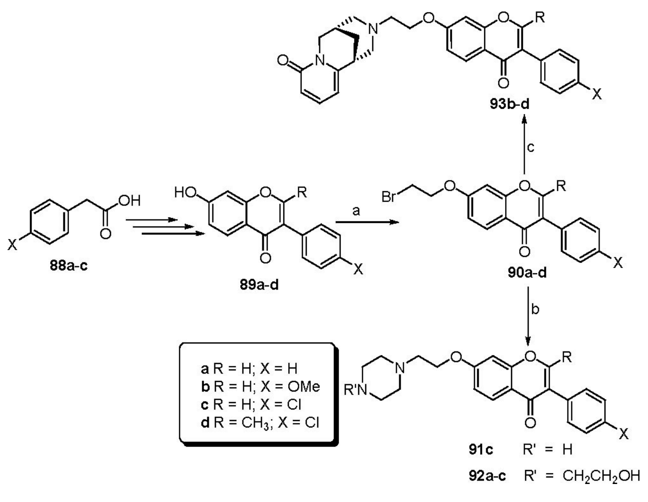
6.1. Alkaloid-Isoflavone Hybrids

Frasinyuk and colleagues synthesised several analogues of isoflavones hybridised with the alkaloid, cytisine.[30,90] These included the 7-*O* cytisine-linked derivatives,[30] as well as derivatives with cytisine at the 6 and 8 positions.[90] The 7-*O* derivatives were prepared as shown in Scheme 18. Firstly, the isoflavones **89 a**-**d** were constructed by the deoxybenzoin route starting from substituted phenylacetic acids **88 a**-**c**. Alkylation of OH-7 of isoflavones **89 a**-**d** with dibromoethane gave compounds **90 a**-**d**. The reaction of **90 a**-**d** with piperazine analogues gave compounds **91 c** and **92 a**-**c**. The cytisine-linked isoflavones **93 b**-**d** were prepared by reacting the isoflavones **90 b**-**d** with cytisine using NaI and diisopropylamine in DMF.[30]



94d Z = $NNHCO(CH_2CH_2O)_4CH_2CH_2NH$(biotin)

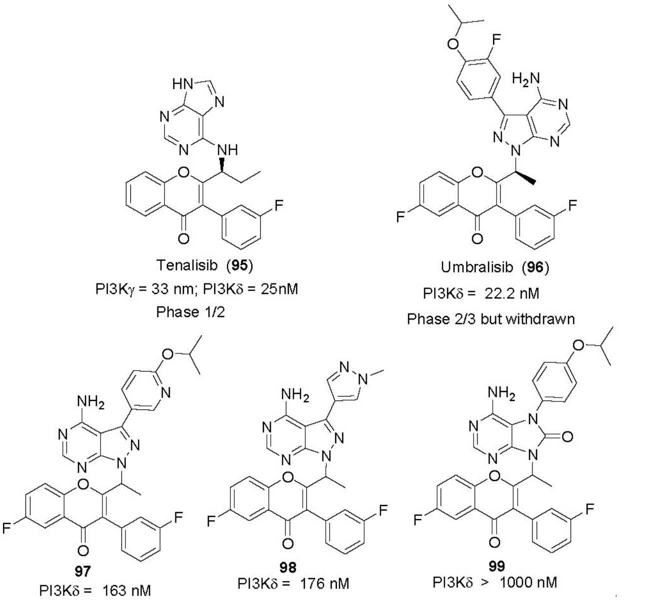
The synthesised isoflavones **89 a**-**d**, **91 c**, **92 a**-**c** and **93 b**-**d** were evaluated for antiproliferative effects on PC-3 prostate cancer cells. Compounds **91 c**, **92 b**-**c**, and **93 b**-**d** inhibited the proliferation of PC-3 cells significantly at 10 µM. The most active compound was **93 c**, which also inhibited the growth of LS174T colon cancer cells and weakly inhibited normal cell lines, BEAS-2B and BCL-299. To identify the cellular targets of **93 c**, an almost equipotent biotinylated derivative **94 d** was synthesised and subjected to a pull-down assay using streptavidin beads and subjected to enzymatic studies. The results showed that cytisine-linked isoflavones specifically bound to hydroxysteroid 17β-dehydrogenase-4 (HSD17B4) and were selective inhibitors of the enoyl CoA hydratase.



Scheme 18. Synthesis of cytisine and piperazine isoflavone analogues. Reagents and Conditions: a) K_2CO_3, $BrCH_2CH_2Br$ (62–88%); b) piperazine, NaI, K_2CO_3, DMF (79% for **91c**); or *N*-(2-hydroxyethyl)piperazine, NaI, K_2CO_3, DMF (60–74%); c) cytisine, NaI, iPr_2NH, DMF (62–76%).

6.2. Isoflavone-Anchored Aminopyrimidine Hybrids

Several purine and pyrazolo[3,4-*d*]pyrimidine derivatives have been developed for cancer treatment and progressed to clinical trials.[49,91] Some of the developed compounds include the isoflavone-anchored kinase inhibitors, umbralisib and tenalisib.[49,51,91] Umbralisib is a dual inhibitor of PI3Kδ and CK1ε.[91–93] It was approved for the treatment of marginal zone lymphoma and follicular lymphoma and later withdrawn.[49] Tenalisib is a dual PI3 Kγ/PI3Kδ inhibitor, which is currently undergoing clinical trials.[49,51,94,95] The syntheses of umbralisib and tenalisib have been patented and discussed in several reviews.[93,96,97]

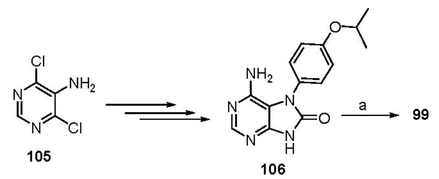


To discover new PI3Kδ inhibitors with improved water solubility, Lei and co-workers synthesised racemic derivatives of pyrazolo[3,4-*d*]pyrimidine and purinone attached to isoflavone or benzopyrimidinone skeletons.[42] The isoflavone-linked derivatives **97**, **98** and **99** were synthesised from the main precursor **100** (Scheme 19). The coupling of C-2 substituted isoflavone **100** with 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**101**), followed by the Suzuki-Miyaura coupling of **102** with boronic acids **103** and **104** rendered compounds **97** and **98**, respectively. Compound **99** was synthesised by *N*-alkylation of intermediate **106** with bromoethylisoflavone **100**. The intermediate **106** was prepared in a sequence of steps starting from 4,6-dichloropyrimidin-5-amine (**105**) (Scheme 20). Of the synthesised isoflavone analogues, **97** and **98** showed inhibitory effects against PI3Kδ with IC_{50} values of 163 and 176 nM, respectively. However, compound **99** lost activity (IC_{50} > 1000 nM).

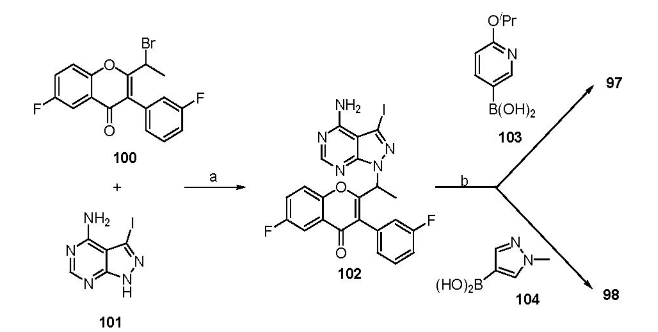
The success of this study was in the discovery of **110**, a pyrazolo[3,4-*d*]pyrimidine analogue anchored by the 3-phenylquinazolinone scaffold. Compound **110** was prepared by coupling of **101** with **107** and subsequent Suzuki cross-coupling reaction of **108** with boronic acid **109** (Scheme 21). It inhibited PI3Kδ with IC_{50} value of 72 nm and exhibited cytotoxicity against jeko-1 cancer cell line overexpressing PI3Kδ. In addition, it showed improved solubility (15 times higher than that of TGR1202/umbralisib), and diminished cytotoxicity against normal human cell lines at high concentrations. The design of compound **110** and related compounds was inspired by the realisation that the quinazolinone and the chromone rings in idelalisib and umbralisib overlapped when the two structures were superimposed.[42] Indeed, 3-phenylquinazolinone and isoflavone scaffolds possess similar frameworks, except that oxygen and carbon atoms at the 1 and 3 positions of the isoflavone nucleus are replaced by nitrogen atoms in the 3-phenylquinazolinone unit.

6.3. B-Ring Modified Analogues

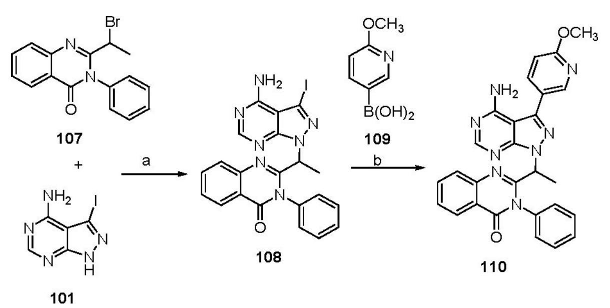
Several analogues have been synthesised by replacement of the isoflavone B-ring with other heterocyclic ring structures or by pharmacophores that mimic other bioactive compounds.[33–35] Inspired by the potential anticancer properties



Scheme 20. Synthesis of isoflavone linked purinone derivative **99**. Reagents and Conditions: a) **100**, K_2CO_3, DMF, 47.7 %.



Scheme 19. Synthesis of isoflavone linked pyrazolo[3,4-*d*]pyrimidine derivatives. Reagents and Conditions: a) K_2CO_3, DMF, rt, 83 %; b) $Pd(PPh_3)_4$, Na_2CO_3, DMF, 45.3 % for **1** and 86.9 % for **2**.



Scheme 21. Synthesis of 3-phenylquinazolinone linked pyrazolo[3,4-*d*]pyrimidine derivative **110**. Reagents and Conditions: a) K_2CO_3, DMF, rt, 72.6 %; b) $Pd(PPh_3)_4$, Na_2CO_3, DMF, 49.7 %.

and synergistic effects of genistein and curcumin,[98,99] Chen and colleagues designed and synthesised analogues with a chromone core attached to a conjugated system at the 3 position.[33] The chromone component was inspired by isoflavone and flavone natural compounds, while the conjugated moieties with heterocyclic scaffolds mimicked curcumin. Ten analogues **115 a-j** were synthesised by aldol condensation of 3-formylchromone (**114**) and imidazolylbutenones **113 a-j** (Scheme 22). The (*E*)-4-(1-alkyl-1*H*-imidazol-2-yl)but-3-en-2-ones (**113 a–j**) were prepared by the Wittig reaction of aldehydes **112 a–j** with 1-(triphenyl-phosphanylidene) propan-2-one (**111**) (Scheme 22).

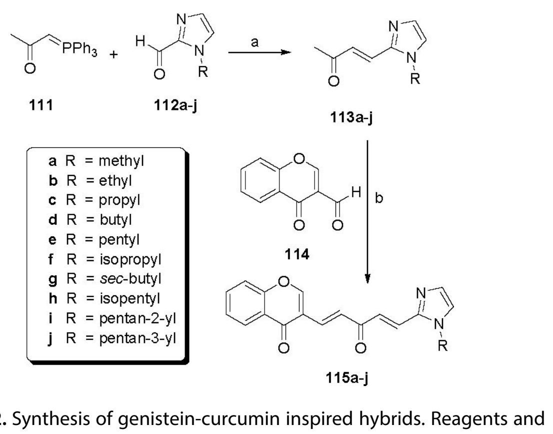
The synthesised compounds together with curcumin, genistein and quercetin were evaluated for antiproliferative activity against prostate cancer cell lines, PC-3, DU-145 and LNCaP. All the synthesised derivatives inhibited the proliferation of the cancer cells at concentrations that were significantly lower than those of curcumin, genistein, and quercetin. Compounds **115 b** and **115 j** were the most active compounds against the PC-3 cell line, with IC_{50} values of 1.8 ± 0.3 and 1.8 ± 0.4 μM, respectively. Compound **115 b** together with **115 e**, **115 f** and **115 j** exhibited good inhibitory activity against LNCaP with IC_{50} values of 1.0 ± 0.2, 1.8 ± 0.9, 1.2 ± 0.6 and 1.3 ± 0.2 μM, respectively. The most active compound against DU-145 cell line was **115 i** (IC_{50} = 1.4 ± 0.3 μM).[33]

In another example, Hirazawa and colleagues synthesised flavonoid-based derivatives with the B-ring substituted mainly by the benzo[*b*]thiophene (BT) system.[34] These included analogues of chalcones, isoflavones, and aurones. Of the synthesised isoflavone derivatives, compound **119 a** potently inhibited the proliferation of A549, MDA-MB-231, MCF-7, KB and KB-VN (the P-gp-overexpressing MDR subline of KB) with IC_{50} values of 0.64, 0.82, 0.72, 0.82 and 0.51 μM, respectively. Other active isoflavone analogues were **119 b** and **119 c**. The compounds exhibited antiproliferative activity with IC_{50} values of 2.6, 1.0, 3.1, 4.2 and 0.67 μM (**119 b**) and 4.8, 5.2, 4.0, 4.0 and 0.84 μM against A549, MDA-MB-231, MCF-7, KB and KB-VN (**119 c**), respectively. The selectivity of compounds **119 b** and **119 c** against the resistant cell line, KB-VN is worth noting. Compound **119 c** and other active derivatives were further determined to cause cell cycle arrest and induce multipolar spindle formation in the prometaphase.[34]

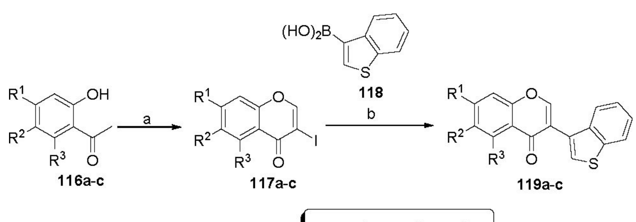
The isoflavone derivatives were synthesised by the Suzuki-Miyaura coupling of 3-iodochromones with differently substituted phenyl, naphthyl and BT boronic acids. The synthesis of active isoflavones **119 a-c** was achieved from acetophenones **116 a-c**, which were converted into 3-iodochromones **117 a-c** by condensation with DMF-DMA, followed by iodine-mediated cyclisation of the resulting enaminone. The Suzuki-Miyaura coupling reaction of 3-iodochromone **117 a-c** with BT boronic (**118**) rendered the isoflavone **119 a-c** (Scheme 23).[34]

In 2019, Selepe's group reported the unexpected conversion of methoxybenzoylbenzofurans into isoflavone derivatives through a cascade of processes that involved demethylation and oxa-Michael-type cycloaddition, leading to furan ring deconstruction and chromone reconstruction.[71] Treatment of a 2'-methoxybenzoylbenzofuran **120** with different demethylating reagents rendered either an isoflavone derivative **121** or the 2'-hydroxybenzoylbenzofuran **122** or both products depending on the reaction conditions (Table 1).

The substrate scope of the unexpected transformation using BBr_3 at 0 °C to rt was evaluated using differently substituted benzoylbenzofuran intermediates. This led to the correction of the structures of benzoylbenzofuran SIRT1 inhibitors to isoflavones.[71] A follow-up study on antiproliferative activity and SIRT1 inhibitory activity of the synthesised benzoylbenzofurans and isoflavone analogues revealed that isoflavone analogues were potent SIRT1 inhibitors and three isoflavonequinones **123 a**, **123 b**, and **123 c** exhibited significant SIRT1 inhibitory activity with IC_{50} values of 5.58 ± 0.373, 1.62 ± 0.0720, and 7.24 ± 0.823 μM, respectively.[53] The most active compound, **123 b** displayed SIRT1 inhibitory activity comparable to that of suramin. The antiproliferative effects of the SIRT1 inhibitors **123 a-c** and other compounds against the MDA-MB-231 cell line showed that both benzoylbenzofurans and isoflavone analogous potently inhibited the proliferation of the MDA-MB-231 cells.[53]



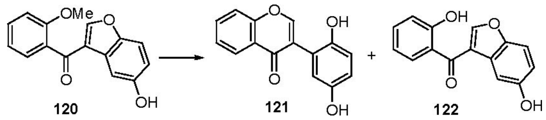
Scheme 22. Synthesis of genistein-curcumin inspired hybrids. Reagents and Conditions: a) Toluene, 70 °C, 5 h, 75–99 %; b) Toluene, PTSA, 100 °C, overnight, 11–58 %.



	R^1	R^2	R^3
a	OMe	OMe	OMe
b	OEt	OMe	OEt
c	OMe	OEt	OMe

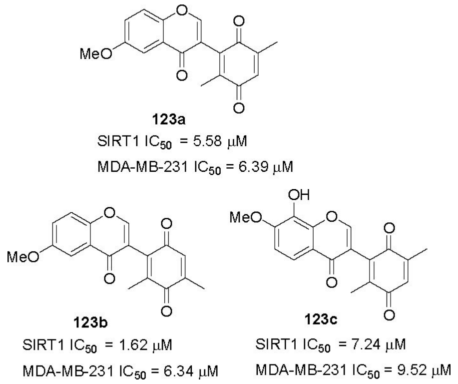
Scheme 23. Synthesis of the most active BT-isoflavone analogues. Reagents and conditions: a) i: DMF – DMA, xylene, 150 °C, 99, 87, 87 % for anaminone **a**, **b** and **c**, respectively; ii) I_2, $CHCl_3$, rt, 75, 78, 91 % for **117 a**, **b** and **c**, respectively; (b) $Pd(PPh_3)_4$, 2 M Na_2CO_3(aq), PhH, reflux, 67, 82, and 88 % for **119 a**, **b** and **c**, respectively.

Table 1. Demethylation of 2'-methoxybenzoylbenzofuran.[71]



Entry	T (°C)	Time (h)	Solvent	Demethylating Reagent	Mol Equiv	Yield (%)[a] **121**	**122**
1	−78	6	CH_2Cl_2	BBr_3	3	11	18
2	−78 −0	3	CH_2Cl_2	BBr_3	3	28	33
3	0-rt	4	CH_2Cl_2	BBr_3	3	78	-
4	0-rt	18	CH_2Cl_2	$AlCl_3$	6	-	91
5	0-rt	12	CH_2Cl_2	$AlCl_3$/EtSH	3	[b]	[b]
6	80	48	DMF	TMSI[c]	8	[d]	[d]
7	80	48	DMF	TMSI[e]	6	68	4
8	80	48	DMF	NaI/TMSCl	6	56	9

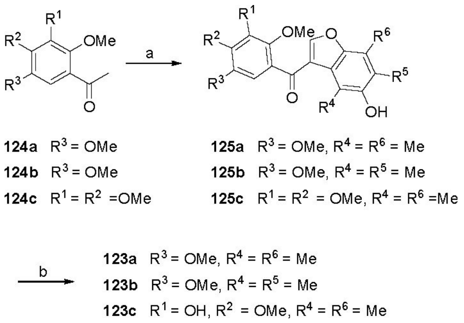
[a] Isolated yields. [b] Uncharacterized products. [c] 1 M TMSI was used. [d] No reaction. [e] 98 % TMSI was used.



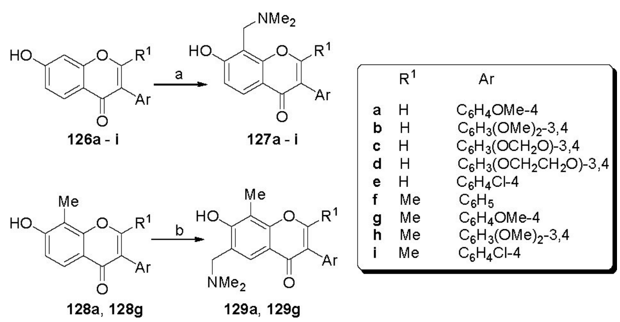
The synthesis of the active isoflavonequinones **123 a-c** is shown in Scheme 24.[71] The acetophenones **124 a-c** were converted into enaminones, which were reacted with benzoquinones in acetic acid to give methoxybenzoylbenzofurans **125 a-c**. Treatment of the benzoylbenzofurans **125 a-c** with BBr_3 rendered isoflavonequinones **123 a-c**.

6.4. A-ring Derivatives- Mannich Bases Derived C-6 and C-8 Analogues

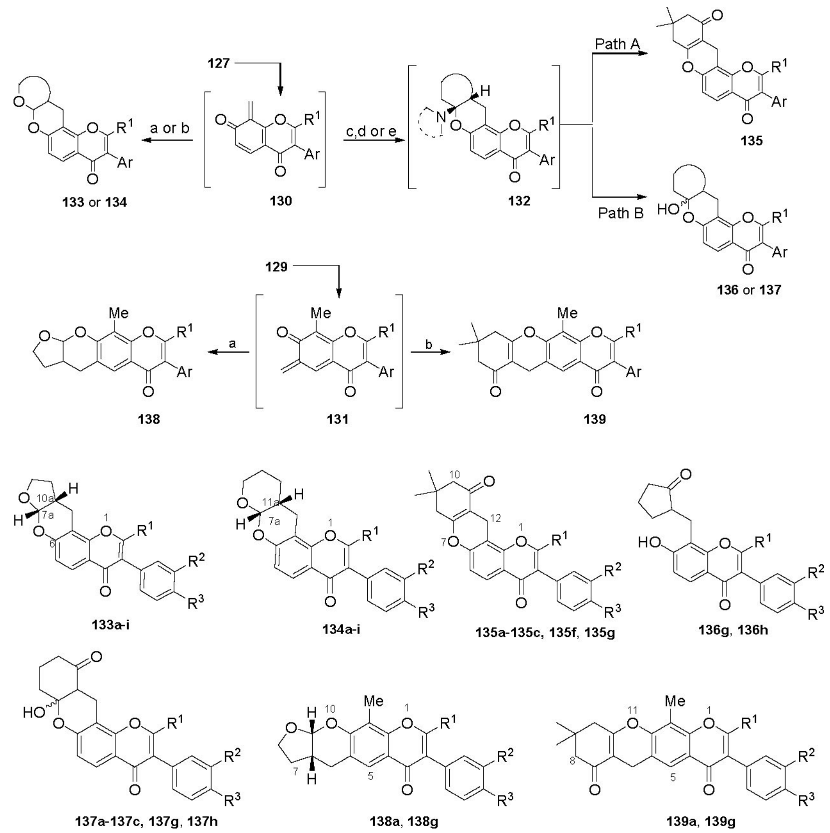
Frasinyuk and colleagues synthesised an array of C-6 and C-8 substituted isoflavone derivatives with antiproliferative activities from aminomethylated intermediates.[39,100] These included polycyclic isoflavone analogues derived from Diels–Alder reaction of *ortho*-quinone methides with dienophiles.[39] The synthesis commenced with regioselective aminomethylation of isoflavones **126 a-i**, **128 a** and **128 g** to give aminomethylated compounds **127 a-i**, **129 a** and **129 g** (Scheme 25). Transformation of aminomethylated isoflavones by *in situ* generation of ortho-quinone methides **130** and **131** and subsequent trapping with various electron-rich dienophiles rendered a diverse library of C-8 and C-6 polycyclic isoflavone derivatives **133–139** (Scheme 26). The isoflavone derivatives were evaluated for antiproliferative activity against PC-3 cell line. Some of the most active derivatives were **135 b**, **137 g** and **138 a**, which attenuated cell proliferation by 86, 78 and 78 %, respectively at 10 μM.



Scheme 24. Synthesis of isoflavonequinone SIRT1 inhibitors. Reagents and conditions: (a) i. DMF – DMA, ii. 2,5-dimethylbenzoquinone or 3,5-dimethylbenzoquinone, HOAc; (b) BBr_3 (3 equiv. per methoxy), CH_2Cl_2, 0 – rt, 66, 42, 11 % for **120 a-c**, respectively.



Scheme 25. Regioselective modification of 7-hydroxyisoflavones **126** and 7-hydroxy-8-methylisoflavones **128**. Reagents and conditions: a) $CH_2(NMe)_2$, ^{i}PrOH, 80 °C, 2–4 h, 68–91 %; b) $CH_2(NMe)_2$, dioxane, 100 °C, 16 h, 72–99 %.



Scheme 26. Diels–Alder reaction of *N*,*N*-dimethylaminoisoflavones **127** and **129** with dienophiles. Reagents and conditions: a) 2,3-dihydrofuran, DMF, reflux, 24–40 h, 27–75 %; b) 3,4-dihydro-2H-pyran, DMF, reflux, 36–40 h, 15–55 %; c) 3-(dimethylamino)-5,5-dimethylcyclohex-2-en-1-one, DMF, reflux; 4 h, 68–92 %; d) 4-cyclopent-1-en-1-yl morpholine, DMF, reflux, 4 h, 53–58 %; e) 4-cyclohex-1-en-1-yl morpholine, DMF, reflux, 4 h, 51–91 %.

6.5. Functionalised Benzopyrans

Three generations of benzopyran derivatives with anticancer activities have been developed based on the isoflavone framework.[55,56] The compounds exhibit broad anticancer activity and inhibit the proliferation of resistant cancer cells and stem cells.[54,101,102] Examples of second and third generation super-benzopyran analogues are Me-344 (**140**), Cantrixil/TRX–E-002-1 (**141**) and Trilexium/TRX–E-009-1 (**142**) (Figure 5).[55,56,101] Me-344 (**140**) underwent Phase 1 clinical trials in patients with refractory solid tumours that included colorectal, non-small cell lung, ovarian cancers and others,[102,103] while TRX–E-002-1 (**141**) was investigated for resistant or recurrent ovarian, fallopian tube and primary peritoneal cancers,[104,105] TRX–E-009-1 (**142**) is a preclinical candidate and it has been determined to be tubulin polymerisation inhibitor.[101]

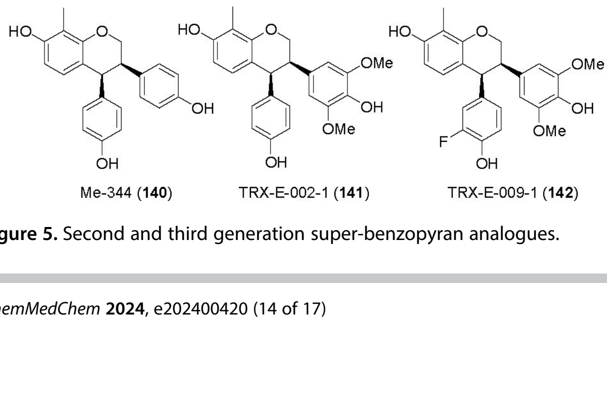


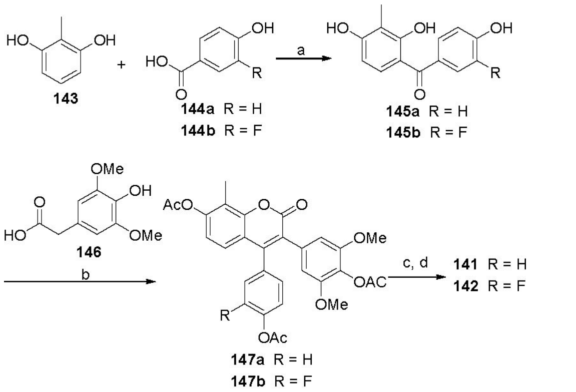
Figure 5. Second and third generation super-benzopyran analogues.

A recent study investigated the effects of TRX–E-009–1 against (diffuse intrinsic pontine gliomas) DIPG neurosphere cultures as a single agent and in combination with histone deacetylase inhibitor, SAHA and radiation. TRX–E-009-1 exhibited tumour-specific activity against DIPG neurosphere cultures. A triple combination treatment of TRX–E-009-1 with SAHA and radiation significantly enhanced survival in DIPG models.[106]

The synthesis of the benzopyran analogues was reported by Heaton and colleagues in 2015.[54] Using TRX–E-002–1 and TRX–E-009-1 as examples, the synthesis was initiated by acylation of 2-methylresorcinol (**143**) with benzoic acids **144 a**-**b** to give benzophenones **145 a**-**b** (Scheme 27). Condensation of benzophenones **145 a**-**b** with phenylacetic acid **146** rendered 3,4-diphenylcoumarins **147 a**-**b**, which underwent successive reduction to give **141** and **142** as racemic mixtures. The requisite enantiomers were obtained by chiral resolution.

7. Conclusions

Several isoflavone derivatives have been synthesised and evaluated for their potential anticancer activities. This has led to the discovery of analogues with improved in vitro and/or in vivo antiproliferative activities, selectivity, specificity and physicochemical properties. Further studies revealed that the isoflavone derivatives induce cell cycle arrest and apoptosis and act as



Scheme 27. Synthesis of third generation super-benzopyrans. Reagents and conditions: a) $ZnCl_2$, $POCl_3$, 70 °C, 2 h, 87 % (**145 a**) and 41 %(**145 b**); b) DiPEA, Ac_2O, 135 °C, 18 h, 76 % (**147 a**) and 68 % (**147 b**); c) THF, $BH_3{\cdot}Me_2S$ in THF, 35 °C, 18 h, 53 % from **147 a** and 53 % from **147 b**; d) H_2, Pd/C, EtOH, 3 bar, 40 °C, 18 h, 88 % (**141**) and 60 % (**142**).

mitotic, kinases, sirtuins and angiogenesis inhibitors. Moreover, some of the analogues were determined to block signalling pathways involved in cancer initiation and progression.

Strategies that were employed for optimisation included molecular hybridisation, CADD, DOS and functional group manipulation. Molecular hybridisation was employed in several instances and its combination with other techniques such CADD was determined to be beneficial for the development of compounds with high target binding affinity and physicochemical properties. An example includes the discovery of the formononetin derivative **22**, which potently inhibited EGFR and also suppressed MDA-MB-231 tumour growth in vivo.[40] In another example, optimisation of isoflavone-pyrazolo[3,4-*d*]pyrimidine hybrids through scaffold hopping approach led to the discovery of a 3-phenylquinazolinone-pyrazolo[3,4-*d*]pyrimidine hybrid **110** with enhanced affinity for PI3Kδ than other derivatives, low toxicity and 15 times improved solubility than umbralisib (**96**).[42] On the other hand, hybrids that involved replacement of the phenyl B-ring with electron rich heterocyclic ring resulted in improved activity and selectivity.[34] For instance, the BT-isoflavone analogues, showed improved activity compared to 3-phenylchromones and two analogues, **119 b** and **119 c** displayed selectivity for the P-gp-overexpressing MDR subline of KB (KB-VN).[34]

Derivatisation of the isoflavones by functional group manipulation also yielded more active derivatives, improved specificity and facilitated chemical accessibility of some of the complex isoflavone compounds. An Intriguing observation was in the development of GVA derivatives, whereby the 6-*O*-benzyl derivative **31** was discovered to be an α,β-tubulin inhibitor,[47] while the 7-*O*-benzyl derivative, gatastatin (**32**) and its analogue gatastatin G2 (**33**) were determined to be specific γ-tubulin inhibitors.[74,75] This showed that the position of the benzyl group influenced the specificity of the GVA derivatives. Other analogues that demonstrated specificity included glabrescione B derivatives.[41] Compounds **80** and **81** were identified as potential Gli1 inhibitors, while compounds **82** and **83** were identified as Smo antagonists.[41]

These studies affirm the importance of the isoflavone framework in the discovery and development of novel anticancer agents. Future studies could leverage a combination of optimisation techniques to facilitate efficient discovery of more active analogues with improved properties.

Acknowledgements

This research was supported by the National Research Foundation of South Africa through Thuthuka funding (grant number: 138404) and the University of Pretoria. I thank Dr Molahlehi Sonopo for proofreading the document and for the discussions.

Conflict of Interests

The author declares no conflicts of interest.

Keywords: Anticancer · Isoflavones · Derivatives · Natural compounds

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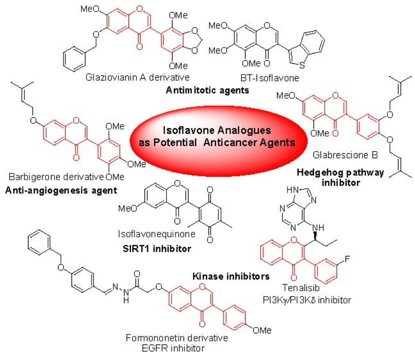
Manuscript received: May 31, 2024
Revised manuscript received: July 31, 2024
Accepted manuscript online: August 2, 2024
Version of record online: ■■, ■■

REVIEW

Several isoflavone analogues with potential anticancer activities have been discovered. They include tubulin polymerase, kinases (EGFR, PI3Kδ, PI3 Kγ) HDACs and angiogenesis inhibitors. They also block signalling pathways such as Hedgehog, PI3 K/AKT/mTOR, MAPK/Wnt, EGFR/PI3 K/Akt/Bad, EGFR/ERK and EGFR/PI3 K/Akt/b-catenin.



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