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7-Hydroxy-benzopyran-4-one Derivatives: A Novel Pharmacophore of Peroxisome Proliferator-Activated Receptor α and -γ (PPARα and γ) Dual Agonists

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Design, synthesis, and in vitro bioevaluation of a new class of potential dual PPARα and γ agonists discovered through a structure-driven design paradigm are described. The 7-hydroxy-benzopyran-4-one moiety (includes flavones, flavanones, and isoflavones) is the key pharmacophore of these novel molecules, exhibiting similarity to the core structure of both fibrates and thiazolidinediones. New lead PPAR ligands were identified from "natraceuticals" and synthetic analogues. In total, 77 molecules, including chalcones, flavones, flavanones, isoflavones, and pyrazole derivatives, were screened and structure−activity relationship studies of the dual agonists undertaken. Compounds **68**, **70**, **72**, and **76** were identified as novel and potent dual PPARα and γ agonists. These novel molecules may have the potential to be the future leads in PPAR-related disorders, including type II diabetes mellitus and metabolic syndrome.

Introduction

Peroxisome proliferator-activated receptors (PPARs[a]) are nuclear receptors that function as ligand activated transcription factors regulating the expression of specific genes.[1−3] PPARs are known to act via two distinct prominent mechanisms, transrepression and transactivation. The former is a DNA independent mechanism and is associated with disruption of other transcription factor pathways while the latter is DNA dependent and involves binding to PPAR response element (PPRE) of the target genes.[2,4]

PPARs are implicated in the pathology of various disease states including type II diabetes,[5] obesity,[6] hyperlipidemia,[7] cardiovascular disease,[8] neoplastic diseases and tumors,[9] inflammatory conditions,[10] and neurodegenerative diseases.[11] PPARs are thus the target of numerous drug design and development efforts and the significant role of PPARs in regulation of inflammatory responses, development, cellular differentiation, glucose homeostasis, and lipid metabolism is the subject of many studies.[12]

Three PPAR isoforms are known to date, PPARα, γ, and β/δ.[10,13] PPARα is mainly found in liver, kidney, heart, muscle, and adipose tissue and plays a critical role in fatty acid oxidation and lipoprotein metabolism.[13,14] PPARα is the molecular target for the fibrate class of drugs,[15] fenofibrate **1**, clofibrate, bezafibrate, and similar compounds such as 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthioacetic acid (WY-14643)[16] **2**. These PPARα agonists (Figure 1) act by lowering triglycerides and elevating HDL and are most effective in the treatment of hypertriglyceridemia.[14]

PPARγ is predominately expressed in adipose tissue, macrophages, monocytes, and intestinal cells as well as skeletal muscle and endothelium. The significant role of PPARγ in lipid metabolism, adipogenesis, glucose homeostasis, and insulin sensitization is well documented. PPARγ agonists such as thiazolidinediones (TZDs, e.g. rosiglitazone **3**) and L-tyrosine analogues have been used in clinical practice to treat type II diabetes for many years and have been shown to lower blood glucose levels and improve insulin sensitivity.[17,18] However, despite their excellent potencies, several of the known PPARγ agonists (Figure 1) have presented unwanted adverse therapeutic profiles such as fluid retention, weight gain, and cardiac hypertrophy.[14,17] Troglitazone, for example, was withdrawn from therapeutic use due to liver toxicity and farglitazar **5** failed to pass phase III clinical trials due to the emergence of peripheral edema. Pioglitazone and rosiglitazone **3** are the two TZDs that are currently in clinical practice despite being linked to controversial side effects including an increased risk of cardiovascular related death.[15]

In recent years, the concept of dual PPARα and γ agonists has gained enormous attention.[14,15] It is believed that such dual agonists may exhibit enhanced effectiveness in treatment of type II diabetes and metabolic syndrome, as these drugs target hyperglycemia and insulin resistance in addition to the associated lipid abnormalities. Moreover, fibrates are well-known to alleviate weight gain and thus may reduce certain side effects induced by PPARγ activation. To date a number of dual agonists have been developed (Figure 1), including farglitazar **5**, ragaglitazar, tesaglitazar, and muraglitazar **6**,

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[a] Abbreviations: PPAR peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator-activated receptor response element; TZD, thiazolidinedione; HEK, human embryonic kidney.

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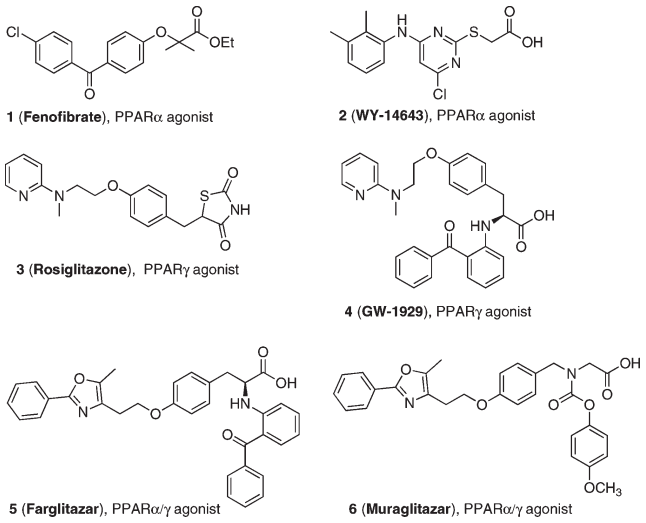


Figure 1. PPAR agonists.

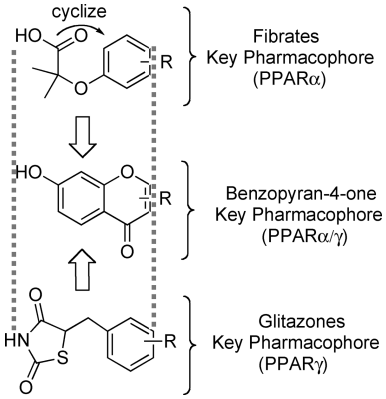


Figure 2. Graphical illustration of the key pharmacophore concept.

which despite their potencies have failed the late stages of clinical trials.[4]

Thus development of novel, efficacious, and yet safer dual PPARα and γ agonists are of considerable therapeutic value. Herein we report the design, synthesis, and in vitro bioevaluation of a new class of dual PPARα and -γ agonists that are structurally distinct from fibrates and TZDs.

Results and Discussion

Pharmacophore Design. The key pharmacophore, 7-hydroxy-benzopyran-4-one moiety (includes flavones, flavanones, and isoflavones), was designed via a proposed cyclization of 1,3-diaryl-2-propenones. 7-Hydroxy-benzopyran-4-one exhibits a high resemblance to the core structure of both fibrates and TZDs, while the key functional groups, namely the phenyl moiety and the acidic group, lie a within similar orientation and space (Figure 2).

In the search for new lead PPAR ligands that fit our key pharmacophore, it was of great importance to explore avenues that are showing much promise as potential treatments of diabetes, most importantly "natraceuticals", or natural products derived from plant and herb sources.

Flavonoids and isoflavonoids are polyphenolic compounds which have been found in plants and dietary components such as fruits, vegetables, soybeans, and red wine.

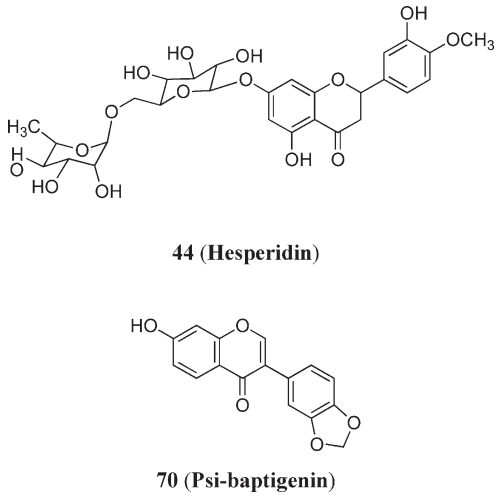


Figure 3. Lead PPARγ agonists identified by virtual screening of a natural product library.[1]

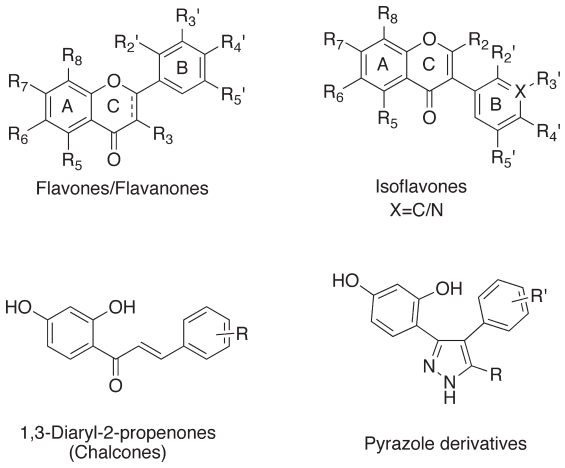
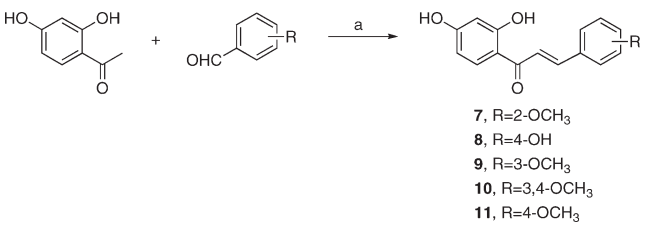


Figure 4. General structure of the flavone, flavanone, isoflavone, chalcone, and pyrazole derivatives.

Recent studies on biological evaluation revealed them to be anticancer,[19,20] antihyperglycemic,[21] antifungal,[22] antiviral,[23] anti-inflammatory,[24] antioxidant,[25] and cardiovascular agents.[26] Although the skeleton of 7-hydroxy-benzopyran-4-one pharmacophore plays an important role in biological effects of flavonoid and isoflavonoid derivatives, the nature of the peripheral substituents is also crucial. For example, isoflavones containing amine-bearing side chain are potential selective estrogen receptor modulators,[27] while substitution of the heterocyclic group of isoflavone pharmacophore enhanced aromatase inhibitory activity.[28] Recently, we have reported ψ-baptigenin **70** (isoflavone, found in plants such as red clover) and hesperidin **44** (flavanone glycoside that is mainly in citrus fruit) as two new PPARγ agonists (Figure 3).[1] This was achieved via virtual screening of an in-house natural product library consisting of 200 compounds extracted from botanical sources.[1]

Given that these two lead compounds fit our key pharmacophore perfectly, we investigated them and their analogues (in total 77 molecules) further as potential dual PPARγ and α agonists. This was achieved by initial screening of all 77 molecules for PPARγ agonist activity to highlight the potent molecules, which were subsequently bioevaluated for

Scheme 1[a]



[a] Reagents and conditions: (a) KOH, EtOH, rt, 24 h.

PPARα agonist activity to identify molecules with dual activity. Assessed molecules consisted of chalcones, 7-hydroxybenzopyran-4-one (includes flavones, flavanones, and isoflavones and their glycosylated analogues) and pyrazole derivatives including: (i) chalcones and hesperidin **44** related molecules with various substituents, (ii) flavones, which are distinguished from flavanones solely by the presence of the 2,3 double bond in the chromone ring, (iii) ψ-baptigenin derivatives (isoflavones), as well as (iv) pyrazole derivatives (Figure 4). The latter group is quite distinct from the others. This was to examine the role of the carbonyl group and the chromone ring on PPARγ agonist activity.

Chemistry. The chalcones **7**−**11** were synthesized by base catalyzed Claisen−Schmidt condensation[29] of acetophenones with appropriate benzaldehydes (Scheme 1).

Compounds **12**−**45** (95% purity or higher) were sourced from the Sigma Aldrich or Indofine Chemical Company and used as received (Table 1).

3-Iodo-7-(tetrahydropyran-2-yloxy)-benzopyran-4-one **49** (Scheme 2) was considered a key intermediate in the synthesis of the isoflavones. This was due to the excellent electrophilic properties of the iodo moiety as well as its strategic position (next to the double bond), making it an ideal substrate for palladium catalyzed Suzuki coupling. The synthesis of this intermediate was achieved from 2,4-dihydroxy acetophenone through a sequence of reactions previously described.:[30] selective protection of the 4-hydroxyl by a THP ether, condensation with *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) to give 3-(dimethylamino)-2′-hydroxyacrylophenone and cyclization using I_2 to furnish the corresponding iodobenzopyranone. Suzuki−Miyaura coupling of the intermediate with appropriate substituted boronic acids afforded **50**−**67**. Subsequent THP ether cleavage of corresponding isoflavones provided the target PPAR agonists **68**−**85** (Scheme 2).

Compounds **86**−**88** were prepared by deprotection of the methyl ether using BBr_3/CH_2Cl_3 protocol,[31] as depicted in the Scheme 3.

The isoflavones **93** and **94** were obtained by electrophilic substitution of the appropriate phenols with benzyl cyanides (Houben−Hoesch reaction).[32] Cyclization of the resultant hydroxyketones to the isoflavones was achieved using DMF as a 1-carbon electrophile in the presence of $BF_3 \cdot Et_2O$ (Scheme 4).

O-Methylation of ψ-baptigenin **70** with methyl iodide generated **95** (Scheme 5).

The intermediate **97** obtained by the previously described Houben−Hoesch reaction was used to generate compounds **98**−**103** (Scheme 6). This intermediate was cyclized to the isoflavone **98** using DMF as a 1-carbon electrophile in the presence of $BF_3 \cdot Et_2O$. The trifluoromethyl-substituted isoflavone **99** was prepared by cyclizing **97** in the presence of trifluoroacetic anhydride and pyridine. The 7-*O*-ω-carboxymethyloxy derivative **103** of ψ-baptigenin was synthesized according to the synthetic procedure depicted in Scheme 6. The intermediate **97** was converted to the corresponding isoflavone **100** via cyclization by treatment with acetic anhydride, followed by base hydrolysis, affording **101**. Subsequent alkylation of **101** with ethyl 2-bromoacetate in the presence of excess potassium carbonate in DMF yielded **102**. Base hydrolysis furnished compound **103**.

Condensation of resorcinol with the appropriate phenylacetic acid in the presence of $BF_3 \cdot Et_2O$ through the Friedel−Crafts acylation reaction[33] afforded corresponding ketones **106** and **107** (Scheme 7). The ketone **106** was cyclized to the trifluoromethyl-substituted isoflavone **108** by using trifluoroacetic anhydride and pyridine. Furthermore, the ketones **106** and **107** were cyclized to the corresponding alkylated isoflavones **109** and **110,** respectively, by using Ac_2O and K_2CO_3.

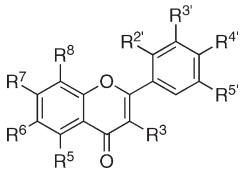
The SAR study was extended by incorporation of the pyrazole fragment into the C-ring. Compounds **111**−**115** were prepared by nucleophilic attack of hydrazine at the C(2)-atom of the corresponding isoflavones.[34] Correspondingly, we have synthesized novel 7-hydroxy-benzopyran-4-one and pyrazole derivatives (**50**, **53**−**67**, **71**, **75**, **77**−**79**, **83**−**86**, **98**−**99**, **101**, **103**, **108**, **109**, **111**−**114**) for biological evaluation to develop a preliminary set of structure−activity relationships.

Biological Evaluation. The compounds were screened for in vitro PPAR agonist activity using the human embryonic kidney (HEK) 293 cell line luciferase reporter gene assay as described previously,[35] with slight modifications. Commercially available PPAR agonists, **2** and rosiglitazone **3**, were used as positive controls for PPARγ and α activity, respectively. DMSO solution (0.1%) acted as the vehicle control. Minimum PPAR fold activation obtained with the vehicle control was defined as 1-fold activation. The results are expressed as relative luciferase activity normalized to the β-galactosidase signal (fold difference compared to vehicle control). In total, 77 compounds were tested at various concentrations. The molecules were initially evaluated for PPARγ agonist activity, and compounds showing PPARγ efficacy were then further investigated for PPARα activity. The results are summarized in Tables 2−5.

From the chalcone series, five analogues were examined (Table 2). Compound **10** demonstrated a similar PPARγ activity (3.5-fold activation) to rosiglitazone **3** (4.2-fold activation) at 25 μM. The other chalcone analogues, however, were shown to be less active. This correlates with the findings of Jung et al.[36] and highlights the importance of C-4 methoxyl group in improving the PPARγ agonistic activity. In addition, our studies demonstrate for the first time the role of C-3 methoxyl group in enhancing the PPARγ agonistic activity.

From the flavone and flavanone series, 26 and 9 compounds were examined, respectively (Table 3). Flavones **12**−**19** and **21** exhibited similar to 2-fold higher PPARγ activity (5.0−8.9-fold activation) than the positive control rosiglitazone **3** (4.2-fold activation) at 25 μM. Flavones, gossypetin **29** and robinetin trimethyl ether **33**, did not activate PPAR at the tested concentrations. Most notably, the glycosylated compounds including myricitrin **23**, linarin **24**, diosmin **25**, neodiosmin **26**, rhoifolin **27**, apiin **28**, myricetin trimethyl ether **34**, and gossypin **36** also showed no PPAR activation at the tested concentrations.

Table 1. Chemical Structures of Commercially Available Flavones and Flavanones

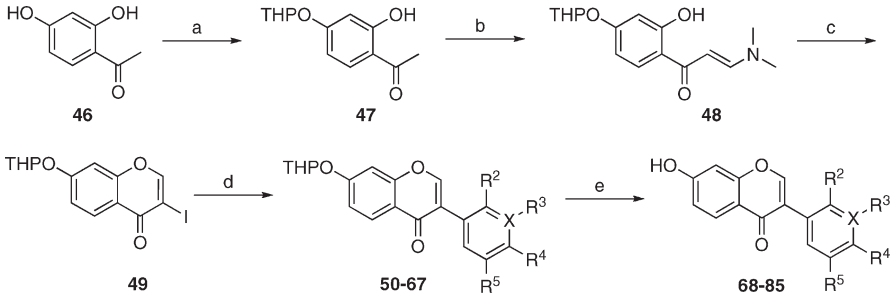


names	substitution								
	R^3	R^5	R^6	R^7	R^8	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
				(R^3: OR; R: Rhamnoside)					
12 (7,2′-dihydroxyflavone)	H	H	H	OH	H	OH	H	H	H
13 (7,3′-dihydroxyflavone)	H	H	H	OH	H	H	OH	H	H
14 (7,4′-dihydroxyflavone)	H	H	H	OH	H	H	H	OH	H
15 (6,4′-dihydroxyflavone)	H	H	OH	H	H	H	H	OH	H
16 (5,4′-dihydroxyflavone)	H	OH	H	H	H	H	H	OH	H
17 (3′,4′-dihydroxyflavone)	H	OH	H	H	H	H	H	OH	H
18 (apigenin)	H	OH	H	OH	H	H	H	OH	H
19 (acacetin)	H	OH	H	OH	H	H	H	OMe	H
20 (chrysoeriol)	H	OH	H	OH	H	H	OMe	OH	H
21 (diosmetin)	H	OH	H	OH	H	H	OH	OMe	H
22 (chrysin)	H	OH	H	OH	H	H	H	H	H
23 (myricitrin)	OR	OH	H	OH	H	H	OH	OH	OH
				(R^7: OR; R: Rutinoside)					
24 (linarin)	H	OH	H	OR	H	H	H	OMe	H
25 (diosmin)	H	OH	H	OR	H	H	H	OMe	OH
				(R^7: OR; R: Neohesperidoside)					
26 (neodiosmin)	H	OH	H	OR	H	H	H	OMe	OH
27 (rhoifolin)	H	OH	H	OR	H	H	H	OH	H
				(R^7: OR; R: Apioglucoside)					
28 (apiin)	H	OH	H	OR	H	H	H	OH	H
				(R^8: OR; R: Glucoside)					
29 (gossypetin)	OH	OH	H	OH	OH	H	OH	OH	H
30 (kaempferol)	OH	OH	H	OH	H	H	H	OH	H
31 (quercetin)	OH	OH	H	OH	H	H	OH	OH	H
32 (fisetin 3′4′-dimethyl ether)	OH	H	H	OH	H	H	OMe	OMe	H
33 (robinetin trimethyl ether)	OH	H	H	OH	H	H	OMe	OMe	OMe
34 (myricetin trimethyl ether)	OH	OH	H	OH	H	H	OMe	OMe	OMe
35 (syringetin)	OH	OH	H	OH	H	H	OMe	OH	OMe
36 (gossypin)	OH	OH	H	OH	OR	H	OH	OH	H
				(R^7: OR; R: Neohesperidoside)					
37 (naringenin)	H	OH	H	OH	H	H	H	OH	H
38 (hesperetin)	H	OH	H	OH	H	H	OH	OMe	H
39 (naringin)	H	OH	H	OR	H	H	H	OH	H
40 (neohesperidin)	H	OH	H	OR	H	H	OH	OMe	H
41 (neoeriocitrin)	H	OH	H	OR	H	H	OH	OH	H
42 (poncirin)	H	OH	H	OR	H	H	H	OMe	H
				(R^7: OR; R: Rutinoside)					
43 (narirutin)	H	OH	H	OR	H	H	H	OH	H
44 (hesperidin)	H	OH	H	OR	H	H	OH	OMe	H
				(R^7: OR; R: Glucoside)					
45 (naringeinin-7-*O*-glucoside)	H	OH	H	OR	H	H	H	OH	H

Apigenin **18**, chrysin **22**, and kaempferol **30** exhibited slightly lower PPARγ activation (Table 3) than that previously reported (8.13-, 5.6-, and 7.6-fold activation at 10 μM, respectively) using a different in vitro model (mouse macrophage RAW264.7 cell line).[37]

From the flavanone family, only compounds **37** and **38** demonstrated weak to moderate PPARγ agonist activity (Table 3). This is in contrast to studies of Liang et al.,[37] where no PPARγ activation was observed for flavanones. The glycosylated flavanones including naringin **39**, neohesperidin **40**, neoeriocitrin **41**, poncirin **42**, and narirutin **43** did not activate PPAR, except for naringeinin-7-*O*-glucoside **45**, which exhibited a slight PPARγ activation at 25 μM (1.8-fold activation). Our result for naringin **39** correlates with the studies of Liang et al.[37]

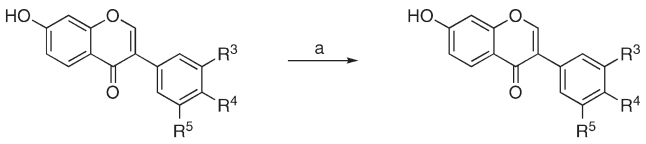
Scheme 2[a]



50, 68: X=C, R^2=H, R^3=OCH_3, R^4=H, R^5=OCH_3
51, 69: X=C, R^2=H, R^3=H, R^4=OCH_3, R^5=H
52, 70: X=C, R^2=H, R^3 and R^4=O-CH_2-O, R^5=H
53, 71: X=C, R^2=H, R^3=H, R^4=CF_3, R^5=H
54, 72: X=C, R^2=H, R^3=H, R^4=F, R^5=H
55, 73: X=C, R^2=H, R^3=OCH_3, R^4=OCH_3, R^5=H
56, 74: X=C, R^2=H, R^3 and R^4=O-CH_2-CH_2-O, R^5=H
57, 75: X=C, R^2=F, R^3=H, R^4=F, R^5=H
58, 76: X=C, R^2=H, R^3=OCH_3, R^4=H, R^5=H
59, 77: X=C, R^2=OCH_3, R^3=F, R^4=H, R^5=F
60, 78: X=C, R^2=H, R^3=F, R^4=F, R^5=F
61, 79: X=N, R^2=OCH_3, R^3=H, R^4=OCH_3, R^5=H
62, 80: X=C, R^2=H, R^3=H, R^4=Cl, R^5=H
63, 81: X=C, R^2=H, R^3=F, R^4=H, R^5=H
64, 82: X=C, R^2=OCH_3, R^3=H, R^4=H, R^5=H
65, 83: X=C, R^2=H, R^3=OCF_3, R^4=H, R^5=H
66, 84: X=C, R^2=H, R^3=OCH_2Ph, R^4=H, R^5=H
67, 85: X=C, R^2=H, R^3=OCH_3, R^4=OCH_3, R^5=OCH_3

[a] Reagents and conditions: (a) DHP, PPTS, DCM, rt for 4 h; (b) DMF-DMA, 95 °C for 3 h; (c) I_2, pyridine, $CHCl_3$, rt for 12 h; (d) $ArB(OH)_2$, 10% Pd/C, Na_2CO_3, DME/H_2O, 45 °C for 1−3 h; (e) *p*-TsOH, MeOH, THF, 60 °C for 1−2 h.

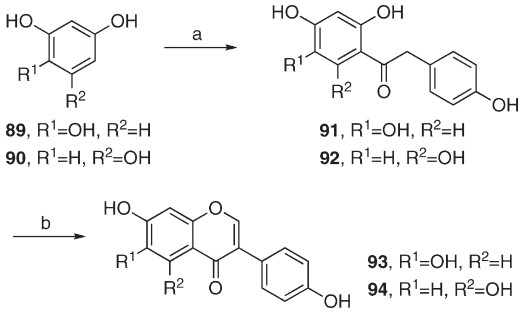
Scheme 3[a]



68, R^3=OCH_3, R^4=H, R^5=OCH_3
69, R^3=H, R^4=OCH_3, R^5=H
73, R^3=OCH_3, R^4=OCH_3, R^5=H
86, R^3=OH, R^4=H, R^5=OH
87, R^3=H, R^4=OH, R^5=H
88, R^3=OH, R^4=OH, R^5=H

[a] Reagents and conditions: (a) BBr_3, DCM, 0 °C to rt, 2−8 h.

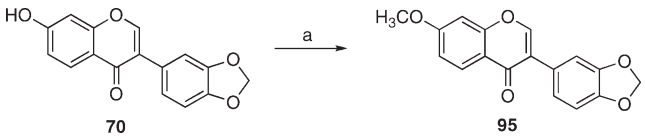
Scheme 4[a]



89, R^1=OH, R^2=H
90, R^1=H, R^2=OH
91, R^1=OH, R^2=H
92, R^1=H, R^2=OH
93, R^1=OH, R^2=H
94, R^1=H, R^2=OH

[a] Reagents and conditions: (a) 4-hydroxyphenyl acetonitrile, anhydrous HCl, $ZnCl_2$-Et_2O, then aq HCl, heat; (b) BF_3.Et_2O, DMF, $MeSO_2Cl$, 100 °C, 2 h.

Scheme 5[a]



70
95

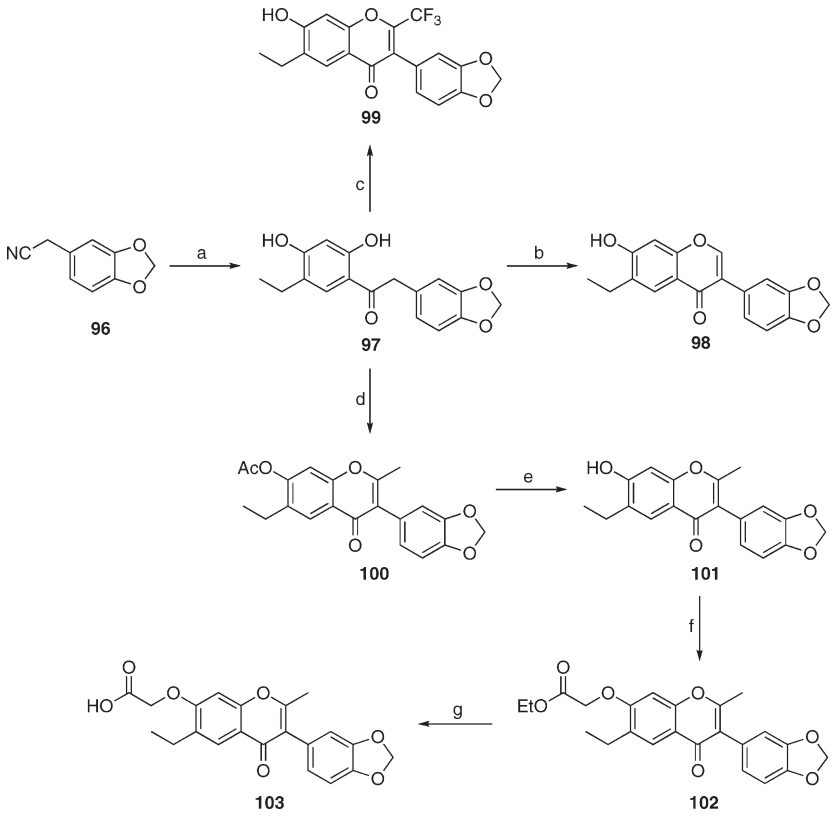
[a] Reagents and conditions: (a) MeI, K_2CO_3, DMF, rt for 3 h.

From the isoflavone and pyrazole series, 34 derivatives were examined (Table 4). Compounds **46**−**51**, **53**−**55**, **57**−**66**, **89**−**92**, **97**, **100**, **102**, **104**−**107**, and **109**−**110** were used as intermediates to derive 7-hydroxy-benzopyran-4-one analogues and therefore were not tested for PPAR activation. Compounds **79**, **84**, **85**, **99**, and **111** showed no PPAR activation at the tested concentrations. Daidzein **87** (9.6-fold activation) exhibited a substantially higher PPARγ activation compared to rosiglitazone **3** (4.2-fold activation) and genistein **94** (3.4-fold activation) at 25 μM. This is higher than the PPARγ activation in human endothelial cells by daidzein **87** (2-fold activation) but comparable to PPARγ activation by genistein **94**.[38]

Compounds **68**, **70**, **72**, and **76** (11.9, 12.1, 20.6 and 9.1-fold activation, respectively) exhibited a substantially higher PPARγ fold activation compared to rosiglitazone **3** (2.9-fold activation) at 5 μM and *N*-(2-benzoylphenyl)-*O*-[2-(methyl-2-pyridinylamino)ethyl]-L-tyrosine hydrochloride (GW1929)[39] (2.7-fold activation) at 5 μM (Table 4 and Figure 5). At a concentration of 25 μM, these compounds demonstrated remarkable PPARγ efficacy, in particular compounds **68** and **72** exhibited over 100-fold PPARγ activation. To date, rosiglitazone **3** has been considered the most efficacious "full" PPARγ agonist. We hypothesis that, as rosiglitazone **3** is a synthetic PPARγ agonist and the biologically relevant natural PPARγ agonist remains elusive, our compounds may resemble the natural full PPARγ agonists due to their very high efficacy.

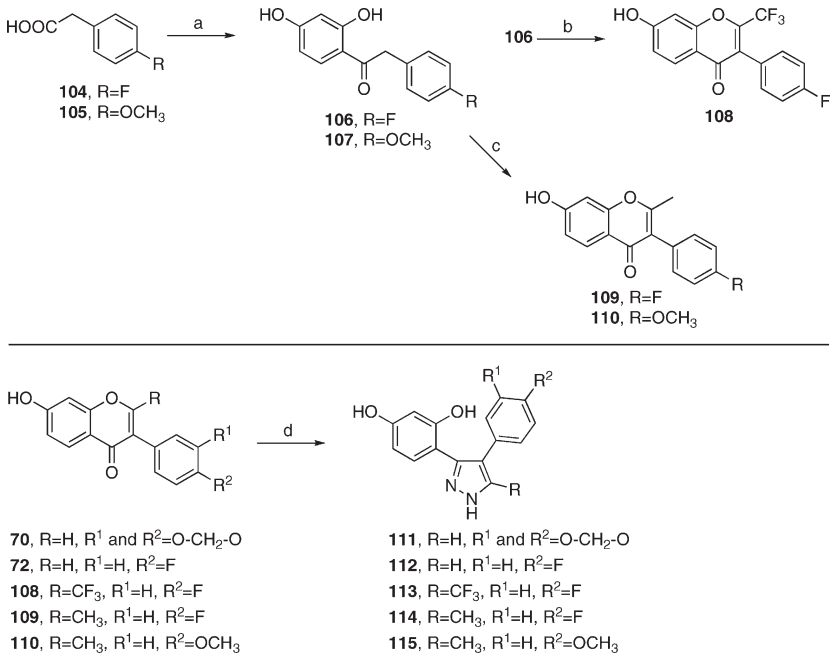
Furthermore, compounds **68**, **70**, **72**, and **76** (EC_{50} = 18.86, 26.94, 15.38, and 22.29 μM, respectively) exhibited at least nearly 2-fold more potency in activating PPARγ than the positive control, rosiglitazone **3** (EC_{50} = 43.71 μM), as shown in Table 5. The EC_{50} results obtained for rosiglitazone **3** vary from that reported in the literature.[40] This is most likely due to the different transactivation plasmid systems used in the assay, e.g., full-length hPPARγ and tk-PPREx4-Luc plasmids used in our assays versus chimeric fusion protein GAL4-PPARγ-LBD and GAL4-Luc

Scheme 6[a]



[a] Reagents and conditions: (a) 4-ethylresorcinol, anhyd HCl, $ZnCl_2$-Et_2O, then aq HCl, heat; (b) $BF_3 \cdot Et_2O$, DMF, PCl_5, 60−70 °C for 1−2 h; (c) $(CF_3CO)_2O$, pyridine, 0 °C to rt for 12 h; (d) Ac_2O, TEA, 120−130 °C for 8 h; (e) NaOH, 1 h; (f) Br-CH_2COOEt, K_2CO_3, DMF, 90 °C for 8 h; (g) NaOH, 2 h.

Scheme 7[a]



70, R=H, R^1 and R^2=O-CH_2-O
72, R=H, R^1=H, R^2=F
108, R=CF_3, R^1=H, R^2=F
109, R=CH_3, R^1=H, R^2=F
110, R=CH_3, R^1=H, R^2=OCH_3

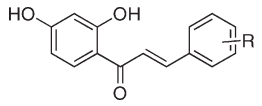
111, R=H, R^1 and R^2=O-CH_2-O
112, R=H, R^1=H, R^2=F
113, R=CF_3, R^1=H, R^2=F
114, R=CH_3, R^1=H, R^2=F
115, R=CH_3, R^1=H, R^2=OCH_3

[a] Reagents and conditions: (a) resorcinol, $BF_3 \cdot Et_2O$, 90 °C for 90 min; (b) $(CF_3CO)_2O$, pyridine, 0 °C to rt for 12 h; (c) Ac_2O, K_2CO_3, DMF, 115 °C for 2 h; (d) hydrazine hydrate, EtOH, 70 °C for 8 h.

plasmids. The transactivation plasmids used in our assay more closely correspond to the actual in vivo cellular transactivation.

The PPARγ activating flavones, flavanones, and isoflavones were subsequently tested against PPARα. Interestingly, they all demonstrated higher fold activity than the

Table 2. In Vitro PPARγ Fold Activation of Chalcones **7**−**11**



compd	PPARγ fold activation (SEM)[a] 5 μM	25 μM
3 (rosiglitazone)	2.9(0.17)	4.2(0.29)
4	2.7(0.35)	
7 (2′,4′-dihydroxy-2-methoxychalcone)	1.1(0.08)	1.1(0.04)
8 (2′,4′-dihydroxy-4-hydroxychalcone)	1.25(0.15)	1.3(0.09)
9 (2′,4′-dihydroxy-3-methoxychalcone)	1.15(0.07)	2.1(0.12)
10 (2′,4′-dihydroxy-3,4-dimethoxychalcone)	1.7(0.13)	3.5(0.12)
11 (2′,4′-dihydroxy-4-methoxychalcone)	1.8(0.11)	2.6(0.18)

[a] Fold activation compared to vehicle control, where the mean relative luciferase activity is normalized to the β-galactosidase signal of two experiments performed in triplicate.

positive controls fenofibrate **1** (1.3-fold activation) and **2** (1.7-fold activation) at 25 μM (Table 6).

Most notably, as illustrated in Figure 6, compounds **68**, **70**, **72**, and **76** demonstrated a significant dual activity, as evidenced by their additional PPARα activity (25.3-, 11.7-, 28.7-, and 43.0-fold activation, respectively) at 40 μM. To date, **2** has been considered the most efficacious "full" PPARα agonist. Similar to the PPARγ results, we hypothesis that, as **2** is a synthetic PPARα agonist and the biologically relevant natural PPARα agonist remains elusive, our compounds may resemble the natural full PPARα agonists due to their high efficacy.

Compounds **68**, **70**, **72**, and **76** (EC_{50} = 24.55, 8.90, 33.13, and 23.10 μM, respectively) exhibited similar or higher potency in activating PPARα than the positive controls fenofibrate **1** (EC_{50} = 33.51 μM) and **2** (EC_{50} = 23.33 μM) as shown in Table 5. Compound **68** and **76** showed similar potency for both PPARα and PPARγ. Compound **70** exhibited more potent PPARα activation than PPARγ activation. In contrast, compound **72** was a more potent PPARγ activator than a PPARα activator. These four molecules were therefore identified as the most potent dual PPARα and γ agonists evaluated.

To ensure that these dual active compounds (**68**, **70**, **72**, and **76**) were nontoxic to HEK 293 cell line, cytotoxicity profiles were investigated at various concentrations (0−100 μM) and compared to the cytotoxicity of fenofibrate **1**, rosiglitazone **3**, and **4**.

Compared to the commercially available PPARγ agonists rosiglitazone **3** and **4**, as illustrated in Figure 7, ψ-baptigenin **70** and compound **76** exhibited a cell viability of greater than 90% at 10 μM (comparable to **4**), while compound **68** showed a cell viability of greater than 80% at 10 μM (comparable to rosiglitazone **3**). Furthermore, ψ-baptigenin **70** and compound **76** maintained a cell viability of greater than 60% even at 100 μM, significantly less toxic than rosiglitazone **3** and **4** (46% and 33%, respectively). These ψ-baptigenin **70** results are comparable to our previous studies in macrophage THP-1 cell line.[1]

Compared to the commercially available PPARα agonist fenofibrate **1**, as shown in Figure 7, ψ-baptigenin **70** and compound **76** exhibited less toxicity with a cell viability of greater than 90% at 10 μM, while fenofibrate **1** demonstrated a cell viability of greater than 90% only at 0.1 μM. Molecules **68**, **70**, **72**, and **76** all exhibited a cell viability of more than 67% at 50 μM, however, fenofibrate **1** showed greater toxicity with a decrease in cell viability to 38% at the same concentration.

Table 3. In Vitro PPARγ Fold Activation by 7-Hydroxy-benzopyran-4-one Derivatives (Flavone and Flavanone Analogues) **12**−**22**, **30**−**32**, **35**, and **37**−**38**

name	PPARγ fold activation (SEM)[a] 5 μM	25 μM
3 (rosiglitazone)	2.9(0.17)	4.2(0.29)
4	2.7(0.35)	
12 (7,2′-dihydroxyflavone)	2.0(0.16)	6.8(0.91)
13 (7,3′-dihydroxyflavone)	1.9(0.44)	6.3(0.47)
14 (7,4′-dihydroxyflavone)	1.3(0.02)	5.0(0.34)
15 (6,4′-dihydroxyflavone)	1.7(0.46)	5.0(0.45)
16 (5,4′-dihydroxyflavone)	2.5(0.30)	8.9(0.75)
17 (3′,4′-dihydroxyflavone)	1.6(0.53)	5.0(0.66)
18 (apigenin)	1.9(0.16)	5.4(0.53)
19 (acacetin)	2.0(0.23)	7.7(0.48)
20 (chrysoeriol)	1.3(0.46)	2.2(0.34)
21 (diosmetin)	2.5(0.37)	7.3(0.25)
22 (chrysin)	1.3(0.08)	4.0(0.44)
30 (kaempferol)	NA	3.5(0.32)
31 (quercetin)	1.2(0.12)	1.3(0.22)
32 (fisetin 3′4′-dimethyl ether)	1.1(0.11)	2.4(0.14)
35 (syringetin)	1.9(0.15)	1.2(0.05)
37 (naringenin)	1.0(0.07)	1.7(0.12)
38 (hesperetin)	1.5(0.10)	3.8(0.08)

[a] Fold activation compared to vehicle control, where the mean relative luciferase activity is normalized to the β-galactosidase signal of two experiments performed in triplicate. NA: No PPAR activation was observed at the tested concentration.

In Vitro SAR Studies of Chalcones, 7-Hydroxy-benzopyran-4-one, and Pyrazole Derivatives. We have recently reported the potent in vitro PPARγ agonist activity of hesperidin **44** and ψ-baptigenin **70**. After examining the virtual screening, induced-fit docking and biological data, it became evident that in addition to the B ring required for hydrophobic interactions, such as π···π stacking, with residues Phe282, Phe363, and Phe360 of the PPARγ protein (Figure 8), all of the active flavonoids also possessed a hydroxyl at the 7-position, allowing hydrogen bond interactions with the residues Ser289, His323, and Tyr479.[1] In continuation of our efforts, this led us to further expand the structure−activity relationships to include the structural requirements for dual PPARγ and PPARα agonist activity.

In the chalcone series, introduction of a methoxyl group in positions C-3 and C-4 was shown to increase PPARγ agonist activity. This is highlighted in Table 2, as compound **10** (3, 4-dimethoxyl substituted chalcone) was found to be more efficacious than compounds **9** and **11** (3-methoxyl and 4-methoxyl substituted chalcones, respectively). This demonstrates the importance of C-3 and C-4 methoxyl groups in enhancing the PPARγ agonist activity.

The lack of PPARγ activity of flavanones indicates that the planar structure of flavones and isoflavones is a requirement for both PPARα and PPARγ agonist activity. In the case of PPARγ, hydroxyl substitution of both flavones and isoflavones is well tolerated at the 5-, 6-, and 7-position of the A-ring, with compounds **12**−**22** and most isoflavones exhibiting agonist activity at these receptors. However, the 7-hydroxy substituent substantially increases activity at PPARα receptors compared to substitution at other

Table 4. In Vitro PPARγ Fold Activation by 7-Hydroxy-benzopyran-4-one (Isoflavones) and Pyrazole Derivatives

compd	PPARγ fold activation (SEM)[a]	
	5 μM	25 μM
3 (rosiglitazone)	2.9(0.17)	4.2(0.29)
4	2.7(0.35)	
52 (3′,4′-methylenedioxy-7-(tetrahydropyran-2-yloxy)isoflavone)	3.4(0.24)	9.4(0.73)
56 (3-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-(tetrahydropyran-2-yloxy)isoflavone)	1.4(0.08)	2.0(0.15)
67 (3′,4′,5′-trimethoxy-7-(tetrahydropyran-2-yloxy)isoflavone)	1.0(0.12)	2.3(0.15)
68 (3′,5′-dimethoxy-7-hydroxyisoflavone)	11.9(0.56)	116.3(2.21)
69 (4′-methoxy-7-hydroxyisoflavone)	4.6(0.27)	12.8(0.32)
70 (ψ-baptigenin)	12.1(0.14)	38.5(1.17)
71 (4′-trifluoromethyl-7-hydroxyisoflavone)	4.7(0.34)	4.4(0.39)
72 (4′-fluoro-7-hydroxyisoflavone)	20.6(2.54)	147.8(4.21)
73 (3′,4′-dimethoxy-7-hydroxyisoflavone)	2.0(0.07)	10.5(1.05)
74 (3-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-hydroxyisoflavone)	7.1(0.95)	11.3(0.78)
75 (2′,4′-difluoro-7-hydroxyisoflavone)	2.9(0.54)	13.8(1.29)
76 (3′-methoxy-7-hydroxyisoflavone)	9.1(0.85)	57.5(2.57)
77 (2′-methoxy-3′,5′-difluoro-7-hydroxyisoflavone)	2.3(0.48)	7.5(0.94)
78 (3′,4′,5′-trifluoro-7-hydroxyisoflavone)	1.5(0.08)	1.4(0.05)
80 (4′-chloro-7-hydroxyisoflavone)	NA	2.6(0.51)
81 (3′-fluoro-7-hydroxyisoflavone)	1.8(0.14)	4.1(0.17)
82 (2′-Methoxy-7-hydroxyisoflavone)	1.0(0.06)	1.6(0.14)
83 (3′-trifluoromethoxy-7-hydroxyisoflavone)	1.8(0.12)	2.1(0.07)
86 (3′,5′,7-trihydroxyisoflavone)	2.5(0.25)	7.4(0.95)
87 (daidzein)	1.2(0.17)	9.6(1.24)
88 (3′,4′,7-trihydroxyisoflavone)	1.8(0.08)	7.5(0.87)
93 (4′,6,7,-trihydroxyisoflavone)	2.3(0.87)	4.4(0.98)
94 (genistein)	2.0(0.07)	3.4(0.35)
95 (7-methoxy-ψ-baptigenin)	8.7(0.97)	25.2(1.54)
98 (3′,4′-methylenedioxy)-6-ethyl-7-hydroxyisoflavone)	5.3(0.57)	12.7(1.08)
101 (3′,4′-methylenedioxy-2-methyl-6-ethyl-7-hydroxyisoflavone)	1.25(0.08)	5.3(0.94)
103 (2-(3-(benzo[d][1,3]dioxol-5-yl)-6-ethyl-2-methyl-4-oxo-4*H*-chromen-7-yloxy)acetic acid)	2.2(0.16)	2.3(0.11)
108 (4′-fluoro-2-trifluoromethyl-7-hydroxyisoflavone)	1.75(0.34)	3.0(0.54)
112 (3-(2,4-dihydroxyphenyl)-4-(4-fluorophenyl)-1*H*-pyrazole)	1.7(0.18)	1.7(0.10)
113 (3-(2,4-dihydroxyphenyl)-4-(4-fluorophenyl)-5-trifluoromethyl-1*H*-pyrazole)	2.25(0.72)	3.9(0.53)
114 (3-(2,4-dihydroxyphenyl)-4-(4-fluorophenyl)-5-methyl-1*H*-pyrazole)	2.2(0.05)	5.3(1.24)
115 (3-(2,4-dihydroxyphenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole)	2.4(0.27)	2.2(0.18)

[a] Fold activation compared to vehicle control, where the mean relative luciferase activity is normalized to the β-galactosidase signal of two experiments performed in triplicate. NA: no activation was observed at the tested concentration.

Table 5. In Vitro Transactivation Activity Profile of Isoflavone Derivatives

compd	transactivation EC_{50} (μM, SEM)[a]	
	hPPARγ	hPPARα
1 (fenofibrate)		33.51(1.02)
2		23.33(1.07)
3 (rosiglitazone)	43.71(1.08)	
68 (3′,5′-dimethoxy-7-hydroxyisoflavone)	18.86(1.04)	24.55(1.06)
70 (psi-baptigenin)	26.94(1.08)	8.90(1.10)
72 (4′-fluoro-7-hydroxyisoflavone)	15.38(1.02)	33.13(1.05)
76 (3′-methoxy-7-hydroxyisoflavone)	22.29(1.05)	23.10(1.04)

[a] EC_{50} values for PPARγ and α agonist activity were calculated as the concentration of the test ligand (μM) required for the half-maximal fold induction of luciferase activity. Data shown are means (SEM) from three experiments for each treatment.

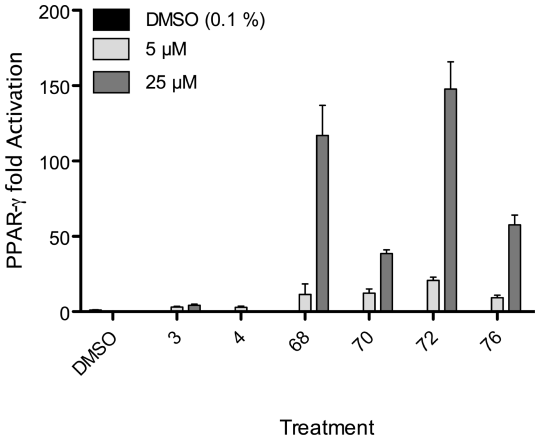


Figure 5. PPARγ luciferase reporter gene activation of the most efficacious isoflavone derivatives (5 and 25 μM) compared to the positive control rosiglitazone **3** and **4**. All values are expressed as fold activation compared to DMSO vehicle control, where the relative luciferase activity is normalized to the β-galactosidase signal, mean ± SEM of two experiments performed in triplicate.

positions of the A-ring. Changing the 7-hydroxyl group of the ψ-baptigenin **70** to the 7-OTHP (**52**) or 7-methoxyl group (**95**) is tolerated, however PPARγ activation was reduced compared to **70**. Introduction of alkyl substituents at the C-6 position of the A-ring (**98**) or the C-2 position of the C-ring (**101**) markedly reduced PPARγ agonist activity compared to the parent compounds **70** and **72**, respectively.

Introduction of alkoxy/alkyl hydrophobic substitutions at the $R^{2'}$, $R^{3'}$, $R^{4'}$, or $R^{5'}$ positions of the isoflavone B-ring showed that the presence of a H-bond acceptor on the $R^{3'}$ or $R^{5'}$ and $R^{4'}$ positions results in significantly higher PPARα and γ agonist activities, with the substituent position and H-bond acceptor capability determining activity.

Table 6. In Vitro PPARα Fold Activation of Flavones, Flavanones, and Isoflavones

compd	PPARα fold activation (SEM)[a] 25 μM	40 μM
1 (fenofibrate)	1.3(0.15)	
2	1.7(0.17)	
12 (7,2′-dihydroxyflavone)	3.6(0.27)	4.9(0.41)
13 (7,3′-dihydroxyflavone)	8.2(0.98)	14.8(0.74)
14 (7,4′-dihydroxyflavone)	1.5(0.08)	2.6(0.17)
15 (6,4′-dihydroxyflavone)	2.6(0.11)	3.5(0.15)
16 (5,4′-dihydroxyflavone)	2.4(0.21)	3.7(0.35)
17 (3′,4′-dihydroxyflavone)	2.8(0.15)	7.7(1.07)
18 (apigenin)	2.0(0.14)	2.3(0.22)
19 (acacetin)	2.3(0.31)	5.2(0.95)
20 (chrysoeriol)	1.1(0.07)	1.3(0.10)
21 (diosmetin)	2.8(0.16)	3.8(0.13)
22 (chrysin)	3.4(0.44)	5.3(0.74)
30 (kaempferol)	1.8(0.12)	2.6(0.15)
37 (naringenin)	1.2(0.09)	1.7(0.11)
38 (hesperetin)	1.9(0.25)	2.0(0.15)
56 (3-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-(tetrahydropyran-2-yloxy)isoflavone)	2.5(0.34)	3.3(0.12)
68 (3′,5′-dimethoxy-7-hydroxyisoflavone)	4.8(0.57)	25.3(1.37)
69 (4′-methoxy-7-hydroxyisoflavone)	7.5(0.52)	7.8(0.43)
70 (ψ-baptigenin)	5.6(0.95)	11.7(1.29)
72 (4′-fluoro-7-hydroxyisoflavone)	8.6(0.83)	28.7(1.85)
76 (3′-methoxy-7-hydroxyisoflavone)	16.5(0.76)	43.0(1.49)
87 (daidzein)	6.2(0.93)	13.4(1.28)
93 (4′,6,7,-trihydroxyisoflavone)	1.8(0.12)	4.0(0.38)
95 (7-methoxy-ψ-baptigenin)	2.2(0.07)	2.4(0.13)

[a] Fold activation compared to vehicle control, where the mean relative luciferase activity is normalized to the β-galactosidase signal of two experiments performed in triplicate.

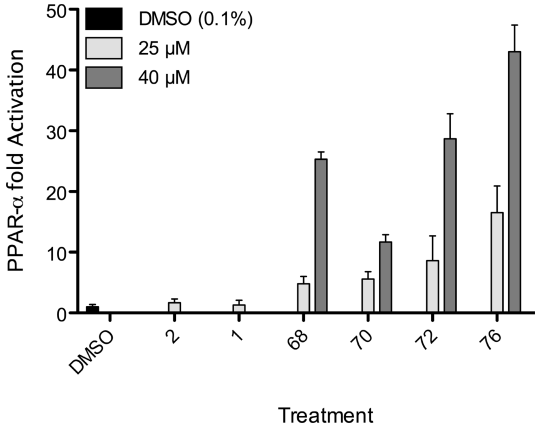


Figure 6. PPARα luciferase reporter gene activation of isoflavone derivatives with considerable PPARγ activity compared to the PPARα positive control fenofibrate **1** and **2** at 25 μM. All values are expressed as fold activation compared to DMSO vehicle control, where the relative luciferase activity is normalized to the β-galactosidase signal, mean ± SEM of two experiments performed in triplicate.

Compounds **68** (3′,5′-dimethoxy), ψ-baptigenin **70** (3′,4′-methylenedioxy), **72** (4′-fluoro), and **76** (3′-methoxy) were found to be potent dual PPARα and PPARγ agonists. Interestingly, the 4′-fluoro (**72**) exhibited the highest activity at PPARγ receptors, whereas compound **76** demonstrated the highest activity at PPARα receptors. When compared to **2** and rosiglitazone **3**, the two most widely used reference

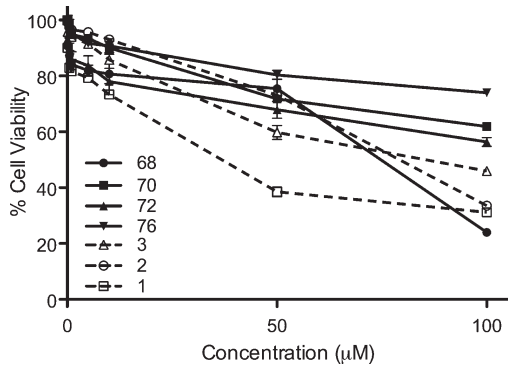


Figure 7. Cytotoxicity profile of compounds **68**, **70**, **72**, **76**, and PPAR agonists fenofibrate **1**, rosiglitazone **3**, and **4**. Cell viability was determined using the CellTiter96 Aqueous One solution cell proliferation assay. The results are expressed as % relative cell viability compared to DMSO vehicle control. All values are mean ± SEM of two experiments performed in quadruplicate.

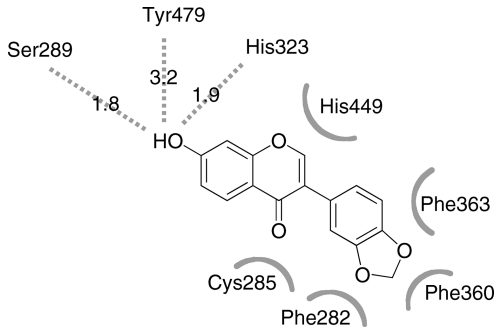


Figure 8. Two-dimensional schematic interactions of ψ-baptigenin **70** in the LBD of PPAR-γ.[1]

drugs for PPARγ and PPARα, respectively, compounds **68**, **70**, **72**, and **76** were 100 times more efficacious. A hydroxyl group in the C-7 position was shown to be vital for PPAR activity. The 4′-fluoro (**72**) exhibited the highest potency for PPARγ, whereas the 3′,4′-methylenedioxy group (**70**) was found to be the most potent PPARα activator. The methoxyl substituents at positions 3′,5′ (**68**) or 3′ (**76**) were found to exhibit similar potency for both PPARα and PPARγ. Lower PPARγ activation was observed for compounds **74**, **77**−**78**, and **84**−**85**, indicating that multiple substituents on the B-ring resulting in increased steric bulk reduces the PPARγ activation. Typical PPARα and PPARγ dual agonists usually have a carboxylic acid in a position equivalent to the C7 position of the isoflavone. Disappointingly, replacing the 7-OH group by a carboxylic acid moiety resulted in a decrease in activity. A similar decrease in activity was also reported by Guo et al.[41] in the HepG2 cell line in vitro model for CM108, a flavone derivative with 6,7-phosporothiolate moiety.

We then extended the SARs of lead compounds **70** and **72** by incorporation of the pyrazole fragment (Figure 4) into the C-ring (**112**−**115**). We were surprised to find that we were also able to see PPARγ activity from the novel pyrazole scaffold, albeit considerably weaker than the activity seen with the parent isoflavone, demonstrating the importance of the 7-hydroxy-benzopyran-4-one scaffold. Substitution of the 5-position of the pyrazole scaffold with a methyl or trifluormethyl resulted in increased PPARγ activity (Table 4).

The key SAR trends from this study are the following: (i) the 7-hydroxy-benzopyran-4-one scaffold and its orientation are an important determinant for both PPARα and γ activity, with the planar isoflavone skeleton resulting in higher activity, (ii) a hydroxyl group in the C-7 position is crucial for PPARα and γ activity, (iii) H-bond acceptors at the 3′-position and 4′-position are important for activity at PPARα and PPARγ, respectively, (iv) increased steric bulk of the isoflavone B-ring results in decreased PPAR activity, (v) a fluoro group at position 4′ is selective for PPARγ, (vi) 3′,4′-methylenedioxy group is selective for PPARα, and (vii) methoxy group at positions 3′ or 3′,5′ is selective for both PPARα and PPARγ.

Conclusion

We have discovered 7-hydroxy-benzopyran-4-one derivatives as the novel template for potential dual PPARα and γ agonists. Systematic structure-driven design led to the discovery of compounds **68**, **70**, **72**, and **76** as the most potent dual PPARα and γ agonists compared to commercially available positive controls **2** and rosiglitazone **3**. These isoflavones may have the potential to be the future leads in PPAR related disorders, including type II diabetes mellitus and metabolic syndrome. Additionally these compound exhibited significantly lower cytotoxicity than **2** and rosiglitazone **3**. This study also demonstrates the potential of structure-based drug design to fine-tune the relative activities at the different PPAR receptor subtypes to develop ligands with reduced toxicities. In particular, PPAR-δ is highly expressed in metabolic tissues such as skeletal muscle (including cardiac muscle) and brown adipose tissue (recently demonstrated in humans), where it plays a significant role in oxidative lipid metabolism and glucose homeostasis. In future studies, it might be useful to generate PPAR pan-agonists or PPARγ/δ dual agonists in order to combine antidiabetic and antiobesity effects while ameliorating cardiac toxicity. Further in vivo pharmacological evaluation of lead compounds is underway.

Experimental Section

All glass apparatus were oven-dried prior to use. All chemicals used were purchased from Aldrich Chemical Co. Ltd. (St Louis, MO) unless otherwise stated and were of highest commercially available purity. Compounds **12**−**45** (95% purity or higher) were purchased from Sigma Aldrich and Indofine Chemical Company, USA. All solvents were distilled by standard techniques prior to use. Where stated, reactions were performed under an inert atmosphere of nitrogen. ^{1}H NMR spectra were recorded at 300 MHz using a Varian (Palo Alto, CA) Gemini 300 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm), referenced externally to tetramethyl silane at 0 ppm. ^{13}C NMR spectra were recorded at 100 MHz using a Varian (USA) 400 MI spectrometer. Chemical shifts (δ) are quoted in ppm, referenced internally to $CDCl_3$ at 77.0 ppm. All coupling constants (*J*) are given in hertz. Low and high resolution electrospray ionization (ESI) MS was carried out using a Bruker (USA) Daltronics BioApexII with a 7T superconducting magnet and an analytical ESI source. All synthetic compounds for in vitro studies were ≥98% purity as determined by combustion analyses, which were performed at the Research School of Chemistry, Australian National University, Canberra. Thin layer chromatography was performed on Merck aluminum backed plates, precoated with silica (0.2 mm, $60F_{254}$), which were developed using one of the following techniques: UV fluorescence (254 nm) and iodine vapors. Flash chromatography was performed on silica gel (Merck silica gel 60H, particle size 5−40 μm). The EC_{50} is the concentration giving 50% of maximal observed activity. The EC_{50} values were calculated via nonlinear regression using GraphPad PRISM 5.02 (GraphPad software San Diego, CA). The results are expressed as means ± SEM.

General Procedure for the Synthesis of the 1,3-Diaryl-2-Propenones or Chalcones (7−11). 2′,4′-Dihydroxy-2-methoxychalcone (7). 2,4-Dihydroxyacetophenone (500 mg, 1 mmol) in EtOH (3 mL) was treated with KOH (184 mg, 1 mmol) under magnetically stirred condition for 10 min at room temperature, followed by addition of 2-methoxybenzaldehyde (447 mg, 1 mmol). The mixture was stirred magnetically for 24 h at room temperature. After the completion of the reaction, a yellow precipitate was formed and this served as indicator for monitoring the reaction visually. MeOH was removed under reduced pressure. The residue was diluted with water (5 mL), neutralized with 2% aq HCl, and extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with brine solution (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of crude product by flash chromatography (40% EtOAc/hexane) gave **7** (284 mg, 32%) as a yellow solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 12.90 (s, 1H), 8.12 (d, 1H, *J*=8.3 Hz), 7.90 (d, 1H, *J* = 15.2 Hz), 7.72 (d, 1H, *J* = 15.1 Hz), 7.56−6.60 (m, 6H), 3.97 (s, 3H). MS (ESI) *m*/*z*=271.07 [M + 1].

Compounds **8**−**11** were made using the same procedure as for the preparation of compound **7** using appropriate starting materials.

2′,4′-Dihydroxy-4-hydroxychalcone (8). Yield 41%; pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 12.40 (s, 1H), 8.98 (s, 1H), 8.03 (s, 1H), 7.86 (d, 1H, *J* = 15.1 Hz), 7.70 (d, 1H, *J* = 15.1 Hz), 7.52 (d, 1H, *J* = 3.0 Hz), 7.05 (dd, 1H, *J* = 3.0, 8.6 Hz), 6.91 (d, 2H, *J* = 8.6 Hz), 6.79 (d, 1H, *J* = 8.6 Hz). MS (ESI) *m*/*z* = 257.18 [M + 1].

2′,4′-Dihydroxy-3-methoxychalcone (9). Yield 36%; pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6): δ 12.80 (s, 1H), 8.08 (d, 1H, *J*=8.2 Hz), 7.88 (d, 1H, *J*=15.1 Hz), 7.68 (d, 1H, *J*=15.1 Hz), 7.52−6.50 (m, 6H), 3.91 (s, 3H). MS (ESI) *m*/*z* = 271.09 [M + 1].

2′,4′-Dihydroxy-3,4-dimethoxychalcone (10). Yield 38%; yellow plates. ^{1}H NMR (acetone-d_6, 300 MHz): δ 12.98 (s, 1H), 8.08 (d, 1H, *J*=8.1 Hz), 7.88 (d, 1H, *J*=15.1 Hz), 7.68 (d, 1H, *J*= 15.1 Hz), 7.52 (d, 1H, *J*=8.1 Hz), 7.01 (dd, 1H, *J*=2.1, 8.1 Hz), 7.26 (d, 1H, *J*=2.1 Hz), 6.36 (d, 1H, *J*=2.1 Hz), 6.44 (dd, 1H, *J*=2.1, 8.4 Hz), 3.87 (s, 3H), 3.85 (s, 3H). MS (ESI) *m*/*z*=301.28 [M + 1].

2′,4′-Dihydroxy-4-methoxychalcone (11). Yield 45%; yellow needles. ^{1}H NMR (300 MHz, acetone-d_6): δ 13.22 (s, 1H), 8.12 (d, 1H, *J*=8.7 Hz), 7.80 (d, 1H, *J*=15.3 Hz), 7.70 (d, 1H, *J*=15.3 Hz), 7.49 (d, 2H, *J*=8.7 Hz), 7.01 (d, 2H, *J*=8.7 Hz), 6.36 (1H, d, *J*=2.1 Hz), 6.46 (dd, 1H, *J*=2.1, 8.7 Hz), 3.84 (s, 3H). MS (ESI) *m*/*z* = 271.05 [M + 1].

General Procedure for the Synthesis of 3-Iodo-7-(tetrahydropyran-2-yloxy)-benzopyran-4-one (49). A solution of DHP (3,4-dihydro-2*H*-pyran) (18 mL, 3.0 equiv) in CH_2Cl_2 (100 mL) was added dropwise to a solution of 2,4-dihydroxy acetophenone, **46** (10 g, 3.0 equiv), and PPTS (pyridinium-*p*-toluenesulfonate) (600 mg) at room temperature. The resulting mixture was stirred for 4 h at room temperature and then washed with saturated aq $NaHCO_3$ solution and extracted with CH_2Cl_2. The collected organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was diluted with DMF/DMA (13 mL, 1.5 equiv), and the resulting mixture was stirred at 95 °C for 3 h. After evaporation of volatiles, the obtained solid was dissolved in $CHCl_3$ (100 mL) and successively treated with pyridine (5.84 mL, 1.1 equiv) and I_2 (33.36 g, 2.0 equiv). The resulting mixture was stirred at room temperature for 12 h. The reaction was hydrolyzed with saturated aq $Na_2S_2O_3$ solution and stirred for 30 min at room temperature. The aqueous phase was extracted with CH_2Cl_2. The collected organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography

(20% EtOAc/hexane then 40% EtOAc/hexane) gave **49** (22.53 g, 92% yield) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.18 (d, 1H, J = 9.6 Hz), 7.16−7.10 (m, 2H), 5.57 (m, 1H), 3.91−3.80 (m, 1H), 3.70−3.62 (m, 1H), 2.10−1.90 (m, 3H), 1.82−1.58 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.75, 161.73, 157.72, 157.37, 127.88, 116.51, 116.16, 103.15, 96.54, 86.95, 62.03, 29.93, 24.92, 18.26. MS (ESI) m/z = 273.13 [M + 1].

General Procedure of the Suzuki Coupling for the Synthesis of 50−67. To a solution of 3-iodo-7-(tetrahydropyran-2-yloxy)-benzopyran-4-one **49** (500 mg, 1.0 equiv) in DME (6 mL) and H_2O (6 mL) were added Na_2CO_3 (427 mg, 3.0 equiv), arylboronic acid (1.2 equiv), and Pd/C (71 mg, 5 mol %). The resulting mixture was stirred for 1−4 h at 45 °C and then filtered. The catalyst was washed with H_2O (3 mL) and CH_2Cl_2 (5 mL). The aqueous phase was extracted twice with CH_2Cl_2. The collected organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography to give desired products.

3′,5′-Dimethoxy-7-(tetrahydropyran-2-yloxy)isoflavone (50). Yield 84%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, 1H, J = 9.2 Hz), 7.30 (s, 1H), 6.90 (d, 1H, J = 8.3 Hz), 6.75 (t, 1H, J = 8.7 Hz), 6.63 (t, 1H, J = 7.9 Hz), 3.85 (s, 3H), 3.93 (s, 3H), 5.52 (m, 1H), 3.90−3.81 (m, 1H), 3.72−3.62 (m, 1H), 2.11-1.90 (m, 3H), 1.82−1.59 (m, 3H). MS (ESI) m/z = 383.13 [M + 1].

4′-Methoxy-7-(tetrahydropyran-2-yloxy)isoflavone (51). Yield 81%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 9.2 Hz), 7.91 (s, 1H), 7.49 (dd, 2H, J = 2.2 Hz, 6.8 Hz), 7.08 (d, 2H, J = 6.7 Hz), 6.96 (d, 2H, J = 8.8 Hz), 5.55 (m, 1H), 3.83 (s, 1H), 3.91−3.82 (m,1H), 3.71−3.62 (m, 1H), 2.06−1.89 (m, 3H), 1.80−1.59 (m, 3H). MS (ESI) m/z = 353.15 [M + 1].

3′,4′-Methylenedioxy-7-(tetrahydropyran-2-yloxy)isoflavone (52). Yield 95%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 9.3 Hz), 7.95 (s, 1H), 7.15−7.11 (m, 3H), 7.0 (dd, 1H, J = 1.5 Hz, 8.1 Hz), 6.90 (d, 1H, J = 8.1 Hz), 6.03 (s, 2H), 5.59 (m, 1H), 3.94−3.84 (m, 1H), 3.73−3.65 (m, 1H), 2.10−1.89 (m, 3H), 1.80−1.60 (m, 3H). MS (ESI) m/z = 367.20 [M + 1].

4′-Trifluoromethyl-7-(tetrahydropyran-2-yloxy)isoflavone (53). Yield 74%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27−8.23 (m, 2H), 8.03 (s, 1H), 7.73 (s, 1H), 7.18−7.14 (m, 4H), 5.61 (m, 1H), 3.94−3.85 (m, 1H), 3.74−3.65 (m, 1H), 2.09−1.90 (m, 3H), 1.83−1.60 (m, 3H). MS (ESI) m/z = 391.23 [M + 1].

4′-Fluoro-7-(tetrahydropyran-2-yloxy)isoflavone (54). Yield 85%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, 1H, J = 8.7 Hz), 8.01 (s, 1H), 7.65 (m, 2H), 7.28 (t, 2H, J = 8.7 Hz), 6.99 (dd, 1H, J = 2.1 Hz, 8.4 Hz), 6.90 (d, 1H, J = 2.4 Hz), 5.57 (m, 1H), 3.94−3.70 (m, 1H), 3.71−3.60 (m, 1H), 2.11−1.90 (m, 3H), 1.81−1.63 (m, 3H). MS (ESI) m/z = 341.14 [M + 1].

3′,4′-Dimethoxy-7-(tetrahydropyran-2-yloxy)isoflavone (55). Yield 92%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, 1H, J = 9.5 Hz), 7.94 (s, 1H), 7.22 (m, 1H), 7.11- 7.03 (m, 3H), 6.92 (d, 2H, J = 8.4 Hz), 5.57 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.94−3.70 (m, 1H), 3.71−3.60 (m, 1H), 2.11−1.90 (m, 3H), 1.81−1.63 (m, 3H). MS (ESI) m/z = 383.40 [M + 1].

3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-7-(tetrahydropyran-2-yloxy)isoflavone (56). Yield 90%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, 1H, J = 8.1 Hz), 7.94 (s, 1H), 7.14−6.93 (m, 5H), 5.59 (m, 1H), 4.33 (s, 4H), 3.92−3.84 (m, 1H), 3.70−3.65 (m, 1H), 1.97−1.92 (m, 3H), 1.75−1.66 (m, 3H). MS (ESI) m/z = 381.18 [M + 1].

2-,4′-Difluoro-7-(tetrahydropyran-2-yloxy)isoflavone (57). Yield 82%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, 1H, J = 9.1 Hz), 8.18 (s, 1H, J = 9 Hz), 6.90−7.98 (m, 5H), 5.57 (m, 1H), 3.94−3.70 (m, 1H), 3.71−3.60 (m, 1H), 2.11−1.90 (m, 3H), 1.81−1.63 (m, 3H). MS (ESI) m/z = 359.23 [M + 1].

3′-Methoxy-7-(tetrahydropyran-2-yloxy)isoflavone (58). Yield 77%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, 1H, J = 9.3 Hz), 7.98 (s, 1H), 7.40−6.92 (m, 6H), 5.58 (m, 1H), 3.86 (s, 3H), 3.93−3.80 (m, 1H), 3.74−3.60 (m, 1H), 2.08−1.85 (m, 3H), 1.80−1.59 (m, 3H). MS (ESI) m/z = 353.15 [M + 1].

2′-Methoxy-3′,5′-difluoro-7-(tetrahydropyran-2-yloxy)isoflavone (59). Yield 80%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 9.0 Hz), 8.0 (s, 1H), 7.17−7.16 (m, 2H), 6.98−6.89 (m, 2H), 5.60 (m, 1H), 3.92−3.85 (m, 1H), 3.83 (s, 3H), 3.71−3.66 (m, 1H), 2.08−1.92 (m, 3H), 1.80−1.64 (m, 3H). MS (ESI) m/z = 388.11 [M + 1].

3′,4′,5′-Trifluoro-7-(tetrahydropyran-2-yloxy)isoflavone (60). Yield 83%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, 1H, J = 9.3 Hz), 7.89 (s, 1H), 7.20−7−03 (m, 2H), 5.58 (m, 1H), 3.91−3.83 (m, 1H), 3.71−3.67 (m, 1H), 2.08−1.94 (m, 3H), 1.78−1.64 (m, 3H). MS (ESI) m/z = 377.29 [M + 1].

3-(2,6-Dimethoxypyridin-3-yl)-7-(tetrahydro-2-yloxy)-benzopyran-4-one (61). Yield 75%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, 1H, J = 8.7 Hz), 8.04 (s, 1H), 7.72 (d, 1H, J = 8.1 Hz), 7.14−7.09 (m, 2H), 6.43 (d, 1H, J = 8.1 Hz), 5.60 (m, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.97−3.84 (m, 1H), 3.70−3.66 (m, 1H), 1.97−1.91 (m, 3H), 1.79−1.63 (m, 3H). MS (ESI) m/z = 384.14 [M + 1].

4′-Chloro-7-(tetrahydropyran-2-yloxy)isoflavone (62). Yield 93%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 7.8 Hz), 7.88 (s, 1H), 7.45 (d, 2H, J = 9 Hz), 7.34 (d, 2H, J = 8.4 Hz), 7.05 (m, 2H), 5.50 (m, 1H), 3.79−3.74 (m, 1H), 3.61−3.57 (m, 1H), 1.87−1.83 (m, 3H), 1.68−1.58 (m, 3H). MS (ESI) m/z = 357.07 [M + 1].

3′-Fluoro-7-(tetrahydropyran-2-yloxy)isoflavone (63). Yield 81%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, 1H, J = 9.6 Hz), 8.01 (s, 1H), 7.44−7.34 (m, 4H), 7.16−7.08 (m, 2H), 5.60 (m, 1H), 3.89−3.85 (m, 1H), 3.71−3.68 (m, 1H), 1.97−1.92 (m, 3H), 1.80−1.64 (m, 3H). MS (ESI) m/z = 341.13 [M + 1].

2′-Methoxy-7-(tetrahydropyran-2-yloxy)isoflavone (64). Yield 78%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, 1H, J = 8.7 Hz), 7.95 (s, 1H), 7.42−7.33 (m, 3H), 7.15−7.07 (m, 3H), 5.59 (m, 1H), 3.93−3.80 (m, 1H), 3.82 (s, 3H), 3.74−3.65 (m, 1H), 1.97−1.92 (m, 3H), 1.78−1.64 (m, 3H). MS (ESI) m/z = 353.15 [M + 1].

3′-Trifluoromethoxy-7-(tetrahydropyran-2-yloxy)isoflavone (65). Yield 79%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, 1H, J = 8.1 Hz), 8.02 (s, 1H), 7.55−7.45 (m, 3H), 7.28 (d, 1H J = 8.1 Hz), 7.16 (d, 1H, J = 8.7 Hz), 7.14 (s, 1H), 5.60 (m, 1H), 3.89−3.85 (m, 1H), 3.72−3.65 (m, 1H), 1.98−1.93 (m, 3H), 1.79−1.66 (m, 3H). MS (ESI) m/z = 407.10 [M + 1].

3′-Benzyloxy-7-(tetrahydropyran-2-yloxy)isoflavone (66). Yield 88%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, 1H, J = 9.3 Hz), 7.99 (s, 1H), 7.49−7.35 (m, 7H), 7.18−7.13 (m, 1H), 7.05−7.01 (m, 1H), 6.96 (d, 1H, J = 9 Hz), 6.89 (s, 1H), 5.60 (m, 1H), 5.13 (s, 2H), 3.88−3.83 (m, 1H), 3.74−3.65 (m, 1H), 1.97−1.94 (m, 3H), 1.81−1.63 (m, 3H). MS (ESI) m/z = 429.20 [M + 1].

3′,4′,5′-Trimethoxy-7-(tetrahydropyran-2-yloxy)isoflavone (67). Yield 76%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, 1H, J = 7.8 Hz), 8.00 (s, 1H), 7.16 (s, 2H), 7.13 (d, 1H J = 8.7 Hz), 6.82 (s, 1H), 5.60 (m, 1H), 3.93 (s, 6H), 3.91 (s, 3H), 3.93−3.85 (m, 1H), 3.72−3.65 (m, 1H), 1.97−1.93 (m, 3H), 1.79−1.69 (m, 3H). MS (ESI) m/z = 413.15 [M + 1].

3′,5′-Dimethoxy-7-hydroxyisoflavone (68). To a solution of 3′,5′-dimethoxy-7-(tetrahydropyran-2-yloxy)isoflavone **50** (400 mg, 1.0 equiv) in MeOH (30 mL) and THF (30 mL) was added p-TsOH·H_2O (20 mg, 0.1 equiv) at room temperature. The resulting mixture was stirred at 60 °C for 1 h and then Et_3N (0.14 mL, 1.0 equiv) was added and volatiles were removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane then 5% MeOH/EtOAc) provided **68** (265 mg, 85% yield) as a colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 8.43 (s, 1H), 7.99 (d, 1H, J = 9.1 Hz), 6.98 (d, 1H), 6.95 (d, 1H, J = 8.2 Hz), 6.90 (d, 1H, J = 7.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 6.55 (t, 1H, J = 7.6 Hz), 3.79 (s, 6H). ^{13}C NMR (400 MHz, DMSO): δ 174.70, 163.14, 160.57, 157.78, 154.53, 134.40, 127.79, 123.74, 117.05, 115.74, 107.51, 102.60, 100.09, 55.67. MS (ESI) m/z = 299.15 [M + 1]. HRMS (ESI) calcd for ($C_{17}H_{14}O_5$ + H) 299. 0919, found 299.0914.

Compounds **69**−**85** were made using the same procedure as for the preparation of compound **70** using appropriate starting materials.

4′-Methoxy-7-hydroxyisoflavone or Formononetin (69). Yield 83%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.84 (br s, 1H), 8.34 (s, 1H), 8.0 (d, 1H, J = 8.7 Hz), 7.53 (dd, 1H, J = 2.5 Hz, 8.3 Hz), 7.01−6.87 (m, 5H), 3.79 (s, 3H). ^{13}C NMR (400 MHz, DMSO): δ 175.05, 163.00, 159.40, 157.89, 153.59, 130.51, 127.74, 124.67, 123.60, 117.06, 115.63, 114.04, 102.57, 55.59. MS (ESI) m/z = 269.12 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{12}O_4$ + H) 269.0813, found 269.0809.

3′,4′-Methylenedioxy-7-hydroxyisoflavone or ψ-baptigenin (70). Yield 80%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.82 (br s, 1H), 8.36 (s, 1H), 7.99 (d, 1H, J = 9 Hz), 7.17−6.88 (m, 5H), 6.06 (s, 2H). ^{13}C NMR (400 MHz, DMSO): δ 174.91, 163.06, 157.84, 153.89, 147.43, 147.33, 127.76, 126.19, 123.60, 122.83, 117.00, 115.68, 109.87, 108.53, 102.57, 101.47. MS (ESI) m/z = 283.09 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{10}O_5$ + H) 283. 0601, found 283.0600.

4′-Trifluoromethyl-7-hydroxyisoflavone (71). Yield 87%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.85 (s, 1H), 8.54 (s, 1H), 8.02 (d, 1H, J = 8.7 Hz), 7.82 (dd, 2H, J = 1.8 Hz, 9.3 Hz), 7.01−6.92 (m, 4H). ^{13}C NMR (400 MHz, DMSO): δ 174.50, 163.33, 157.92, 155.26, 136.94, 130.07, 128.70, 128.39, 127.79, 126.11, 125.43 (q, J = 14.8 Hz), 125.39, 123.40, 122.70, 115.92, 102.72. MS (ESI) m/z = 307.08 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_9O_3F_3$ + H) 307. 0576, found 307.0575.

4′-Fluoro-7-hydroxyisoflavone (72). Yield 85%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.84 (br s, 1H), 8.42 (s, 1H), 8.01 (d, 1H, J = 8.7 Hz), 7.65 (m, 2H), 7.28 (t, 2H, J = 8.7 Hz), 6.99 (dd, 1H, J = 2.1 Hz, 8.4 Hz), 6.90 (d, 1H, J = 2.4 Hz). ^{13}C NMR (400 MHz, DMSO): δ 174.79, 163.48, 163.17, 161.05, 157.93, 154.30, 133.44 (d, J = 832.8 Hz), 128.89, 127.76, 123.01, 166.99, 115.53 (t, J = 95.2 Hz), 102.63. MS (ESI) m/z = 257.10 [M + 1]. HRMS (ESI) calcd for ($C_{15}H_9O_3F$ + H) 257. 0603, found 269.0608.

3′,4′-Dimethoxy-7-hydroxyisoflavone (73). Yield 83%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.86 (br s, 1H), 8.38 (s, 1H), 7.98 (d, 1H, J = 8.87 Hz), 7.24−7.03 (m, 6.92 (d, 2H, J = 8.4 Hz), 5.57 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (400 MHz, DMSO): δ 175.02, 163.09, 157.84, 153.78, 149.04, 148.72, 127.74, 125.00, 123.68, 121.67, 117.04, 115.67, 113.26, 112.00, 102.55, 56.00, 55.98. MS (ESI) m/z = 299.15 [M + 1]. HRMS (ESI) calcd for ($C_{17}H_{14}$O5 + H) 299. 0841, found 269.0839.

3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-7-hydroxyisoflavone (74). Yield 88%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.84 (br s, 1H), 8.35 (s, 1H), 7.99 (d, 1H, J = 8.7 Hz), 7.13−6.87 (m, 5H), 4.26 (s, 4H). ^{13}C NMR (400 MHz, DMSO): δ 174.91, 163.01, 157.81, 153.80, 143.61, 143.36, 127.76, 125.47, 123.29, 122.22, 118.06, 117.12, 117.04, 115.63, 102.55, 64.61, 64.49. MS (ESI) m/z = 297.10 [M + 1]. HRMS (ESI) calcd for ($C_{17}H_{12}O_5$ + H) 297. 0751, found 297.0757.

2′,4′-Difluoro-7-hydroxyisoflavone (75). Yield 85%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.83 (br s, 1H), 8.39 (s, 1H), 8.18 (d, 1H, J = 9 Hz), 6.90−7.98 (m, 5H). ^{13}C NMR (400 MHz, DMSO): δ 174.02, 164.02 (d, J = 49.2 Hz), 163.32, 161.97 (d, J = 48 Hz), 159.49 (d, J = 50.8 Hz), 158.05, 155.34, 133.79 (q, J = 19.6 Hz), 127.63, 119.22, 116.97 (d, J = 64 Hz), 116.64, 115.92, 111.86 (dd, J = 13.2 Hz, 84.8 Hz), 102.77. MS (ESI) m/z = 275.08 [M + 1]. HRMS (ESI) calcd for ($C_{15}H_8O_3F_2$ + H) 275. 0514, found 275.0515.

3′-Methoxy-7-hydroxyisoflavone (76). Yield 80%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.86 (br s, 1H), 8.41 (s, 1H), 8.01 (d, 1H, J = 8.7 Hz), 7.34−6.90 (m, 5H), 6.90 (dd, 1H, J = 2.4 Hz, 8.3 Hz), 3.80 (s, 1H). ^{13}C NMR (400 MHz, DMSO): δ 174.77, 163.13, 159.43, 157.84, 154.39, 133.88, 129.56, 127.77, 123.77, 121.61, 117.07, 115.72, 115.06, 113.67, 102.61, 55.51. MS (ESI) m/z = 269.10 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{12}O_4$ + H) 269. 0813, found 269.0808.

2′-Methoxy-3′,5′-difluoro-7-hydroxyisoflavone (77). Yield 86%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.84 (br s, 1H), 8.33 (s, 1H), 7.98 (d, 1H, J = 8.7 Hz), 7.41 (t, 1H, J = 8.7 Hz), 7.10 (d, 1H, J = 9 Hz), 6.99 (d, 1H, J = 8.7 Hz), 6.92 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (400 MHz, DMSO): δ 174.24, 163.33, 158.38 (d, J = 50.4 Hz), 158.03, 156.66 (d, J = 53.2 Hz), 155.97 (d, J = 50.8 Hz), 155.06, 154.20 (d, J = 53.6 Hz), 142.97 (q, J = 44.4 Hz), 128.89 (q, J = 41.6 Hz), 127.66, 120.50, 116.75, 115.88, 114.33 (dd, J = 13.6 Hz, 92.4 Hz), 105.60 (q, J = 94 Hz), 102.76, 61.67. MS (ESI) m/z = 305.10 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{10}O_4F_2$ + H) 305. 0619, found 305.0619.

3′,4′,5′-Trifluoro-7-hydroxyisoflavone (78). Yield 78%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.83 (br s, 1H), 8.55 (s, 1H), 8.0 (d, 1H, J = 8.7 Hz), 7.63 (t, 1H, J = 9.6), 6.97 (d, 1H, J = 9 Hz), 6.91 (s, 2H). ^{13}C NMR (400 MHz, DMSO): δ 174.24, 163.41, 157.80, 155.52, 151.59 (q, J = 16.4 Hz), 149.14 (q, J = 16.4 Hz), 139.92 (t, J = 60.8 Hz), 137.43 (t, J = 182.4 Hz), 129.42 (q, J = 18 Hz), 127.78, 102.80, 116.78, 116.02, 113.87 (q, J = 22.4 Hz), 102.70. MS (ESI) m/z = 293.06 [M + 1]. HRMS (ESI) calcd for ($C_{15}H_7O_3F_3$ + H) 293. 0347, found 269.0350.

3-(2,6-Dimethoxypyridin-3-yl)-7-hydroxy-benzopyran-4-one (79). Yield 83%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.85 (br s, 1H), 8.26 (s, 1H), 7.95 (d, 1H, J = 8.7 Hz), 7.63 (d, 1H, J = 8.1 Hz), 6.97 (d, 1H, J = 9 Hz), 6.89 (s, 1H), 6.47 (d, 1H, J = 8.1 Hz), 3.91 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (400 MHz, DMSO): δ 174.65, 163.06, 162.69, 160.36, 157.95, 155.02, 143.78, 127.62, 120.24, 116.84, 115.66, 106.68, 102.65, 100.91, 53.78, 53.69. MS (ESI) m/z = 300.10 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{13}NO_5$ + H) 300. 0793, found 300.0790.

4′-Chloro-7-hydroxyisoflavone (80). Yield 85%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.85 (br s, 1H), 8.46 (s, 1H), 8.01 (d, 1H, J = 8.7 Hz), 6.64 (d, 2H, J = 8.7 Hz), 6.52 (d, 2H, J = 8.4 Hz), 6.99−6.90 (m, 2H). ^{13}C NMR (400 MHz, DMSO): δ 174.65, 163.22, 157.91, 154.58, 132.92, 131.45, 131.10, 128.57, 127.77, 122.77, 116.96, 115.82, 102.66. MS (ESI) m/z = 273.40 [M + 1]. HRMS (ESI) calcd for ($C_{15}H_9O_3Cl$ + H) 273. 0313, found 273.0315.

3′-Fluoro-7-hydroxyisoflavone (81). Yield 80%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.86 (br s, 1H), 8.49 (s, 1H), 8.01 (d, 1H, J = 8.7 Hz), 7.50−7.45 (m, 2H), 7.21−7.23 (m, 2H), 6.99−6.90 (m, 2H). ^{13}C NMR (400 MHz, DMSO): δ 174.59, 163.51, 163.26, 161.09, 157.85, 154.91, 134.95 (d, J = 43.4 Hz), 130.50 (d, J = 34 Hz), 127.79, 125.30, 122.65, 116.95, 116.19 (d, J = 88.4 Hz), 115.86, 115.02 (d, J = 83.6 Hz), 102.65. MS (ESI) m/z = 257.10 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_9O_3F$ + H) 257. 0535, found 257.0601.

2′-Methoxy-7-hydroxyisoflavone (82). Yield 84%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.81 (br s, 1H), 8.19 (s, 1H), 7.95 (d, 1H, J = 8.7 Hz), 7.39 (t, 1H, J = 8.4 Hz), 7.25 (d, 1H, J = 7.5 Hz), 7.10−6.88 (m, 4H), 3.72 (s, 3H). ^{13}C NMR (400 MHz, DMSO): δ 174.62, 162.96, 157.99, 157.89, 154.40, 132.00, 130.03, 127.64, 122.38, 121.62, 120.51, 116.98, 115.57, 11.69, 102.63, 55.93. MS (ESI) m/z = 269.33 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{12}O_4$ + H) 269. 0808, found 269.0809.

3′-Trifluoromethoxy-7-hydroxyisoflavone (83). Yield 81%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.85 (br s, 1H), 8.53 (s, 1H), 8.02 (d, 1H, J = 8.7 Hz), 7.65−7.58 (m, 3H), 7.40 (d, 1H, J = 8.4 Hz), 6.99 (d, 1H, J = 8.7 Hz), 6.92 (s, 1H). ^{13}C NMR (400 MHz, DMSO): δ 174.57, 163.35, 157.89, 155.11, 148 (d, J = 7.6 Hz), 134.87, 130.51, 128. 21, 127.78, 122.29, 121.85, 120.61, 119.30, 116.90, 115.93, 102.68. MS (ESI) m/z = 323.27 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_9O_4F_3$ + H) 323.0525, found 323.0527.

3′-Benzyloxy-7-hydroxyisoflavone (84). Yield 85%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.85 (br s, 1H), 8.42 (s, 1H), 8.01 (d, 1H, J = 9 Hz), 7.50−7.33 (m, 7H), 7.18 (d, 1H, J = 7.5 Hz), 7.05 (d, 1H, J = 8.7 Hz), 6.98 (d, 1H, J = 9 Hz), 6.90 (s, 1H), 5.14 (s, 2H). ^{13}C NMR (400 MHz, DMSO): δ 174.81, 163.11, 158.56, 157.85, 154.46, 137.49, 133.89, 129.63, 128.89, 128.29, 128.15, 127.79, 123.69, 121.89, 117.05, 115.96, 115.76,

114.44, 102.61, 69.68. MS (ESI) $m/z = 345.27$ [M + 1]. HRMS (ESI) calcd for ($C_{22}H_{16}O_4$ + H) 345.1121, found 345.1118.

3′,4′,5′-Trimethoxy-7-hydroxyisoflavone (85). Yield 77%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 10.86 (br s, 1H), 8.44 (s, 1H), 8.01 (d, 1H, J=8.7 Hz), 6.98 (d, 1H, J=8.7 Hz), 6.90 (s, 2H), 6.89 (s, 1H), 3.81 (s, 6H), 3.70 (s, 3H). ^{13}C NMR (400 MHz, DMSO): δ 174.84, 163.10, 157.80, 154.34, 152.99, 137.71, 128.03, 127.77, 123.79, 117.04, 115.73, 106.93, 102.58, 60.48, 56.38. MS (ESI) $m/z = 329.33$ [M + 1].; HRMS (ESI) calcd for ($C_{18}H_{16}O_6$ + H) 329.1019, found 329.1018.

3′,5′,7-Trihydroxyisoflavone (86). To a portion (500 mg) of 3′,5′-dimethoxy-7-hydroxyisoflavone **68** dissolved in anhyd dichloromethane (15 mL) and cooled to 0 °C, a 1 M solution of BBr_3 in dichloromethane (6 mL) was dropped slowly; the solution was stirred at room temperature for 6 h and then was diluted with iced water. The pH was arranged to 6 with 5% Na_2HPO_4, the mixture was extracted with ethyl acetate, and the organic layer was separated and washed with brine, dried, and concentrated to yield, after crystallization from dichloromethane/methanol/ethyl acetate, **86** as light-orange color solid (258 mg, 57% yield).

^{1}H NMR (300 MHz, DMSO): δ 8.30 (s, 1H), 7.99 (d, 1H, J= 8.3 Hz), 6.92 (dd, 1H, J=2.2 Hz, 8 Hz), 6.83 (d, 1H, J=2.5 Hz), 6.72 (d, 1H, J=2.2 Hz), 6.42 (d, 1H, J=2.4 Hz), 6.23 (s, 1H). ^{13}C NMR (400 MHz, DMSO): δ 174.77, 163.08, 158.48, 157.76, 153.90, 134.04, 127.77, 126.02, 124.31, 117.11, 116.97, 115.62, 102.56. MS (ESI) $m/z = 271.08$ [M + 1]. HRMS (ESI) calcd for ($C_{15}H_{10}O_9$ + H) 271.0601, found 271.0607.

Compounds **87** and **88** were made using the same procedure as for the preparation of compound **86** using appropriate starting materials.

4′,7-Dihydroxyisoflavone or Daidzein (87). Yield 65%; light-orange color solid. ^{1}H NMR (300 MHz, DMSO): δ 10.74 (brs, 1H), 9.50 (brs, 1H), 8.26 (s, 1H), 7.95 (d, 1H, J=8.7 Hz), 7.37 (dt, 2H, J=2, 8.6 Hz), 6.93 (dd, 1H, J=2.2, 8.7 Hz), 6.85 (d, 1H, J=2 Hz), 6.80 (dt, 2H, J = 2.2, 8.6 Hz). ^{13}C NMR (400 MHz, DMSO): δ 174.83, 162.78, 157.64, 157.32, 152.97, 130.21, 127.43, 123.67, 122.75, 116.84, 115.24, 115.17, 102.28. MS (ESI) $m/z = 255.10$ [M + 1].

3′,4′,7-Trihydroxyisoflavone (88). Yield 52%; light-orange color solid. ^{1}H NMR (300 MHz, DMSO): δ 8.37 (s, 1H), 7.98 (d, 1H, J=8.5 Hz), 7.63 (dd, 1H, J=2.4 Hz, 7.9 Hz), 7.60 (d, 1H, J=2.3 Hz), 7.52 (d, 1H, J=8.1 Hz), 6.90 (dd, 1H, J=2.5 Hz, 8.2 Hz), 6.83 (d, 1H, J=2.3 Hz). ^{13}C NMR (400 MHz, DMSO): δ 174.86, 163.03, 158.53, 157.77, 152.95, 134.06, 127.68, 125.98, 124.28, 117.14, 116.97, 115.67, 102.54. MS (ESI) $m/z = 271.10$ [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{10}O_5$ + H) 271. 0528, found 271.0520.

General Procedure for the Synthesis of Compound 91−94. With stirring, a rapid current of dry hydrogen chloride was passed for 10 min into a solution of 4-hydroxyphenyl acetonitrile (500 mg, 1 mmol) in dry toluene (10 mL), cooled to 0 °C, and anhyd zinc chloride (255 mg, 0.5 mmol) in dry ether (5 mL) was added. The corresponding polyhydroxybenzene (1.1 mmol) was added portionwise with constant bubbling of gaseous HCl for a further 4−6 h, and then the reaction mixture was stirred overnight at room temperature. The solvent was decanted and triturated twice with dry toluene. The hot water (50 mL) was added and the mixture was kept at 90 °C and pH 1 for 30 min. The product was separated from the hot solution and washed several times with water. The ketiminium chloride intermediate that separated as an oil after 3−4 days was washed with diethyl ether and hydrolyzed by refluxing in 5% HCl (10 mL) for 4−5 h. The corresponding ketone (**91** or **92**), which separated upon cooling, was filtered and dried under reduced pressure.

With stirring, boron trifluoride etherate (6 mmol) was added dropwise to a solution of corresponding ketone (**91** or **92**) (1 mmol) in DMF (8 mL). This solution was warmed to 50 °C, and a solution of methanesulfonyl chloride (0.5 mmol) in DMF (4 mL) was slowly added. The resulting mixture was then heated to 100 °C. After the completion of the reaction, the reaction mixture was poured into water (100 mL) and left overnight to give a precipitate, which was then stirred for 2 h in cold methanol (3 mL), filtered, and crystallized in a alcoholic solvents.

4′,6,7-Trihydroxyisoflavone (93). Crystallized in a mixture of water/ethanol. Yield 57%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 9.95 (brs, 1H), 8.37 (s, 1H), 7.48 (s, 1H), 7.43 (d, 2H, J=8.7 Hz), 6.93 (s, 1H), 6.81 (d, 2H, J=8.7 Hz), 4.53 (dd, 1H, J= 11.0 Hz, 13.2 Hz), 4.49 (dd, 1H, J=5.7 Hz, 5.9 Hz), 4.05 (dd, 1H, J = 5.5 Hz, 7.2 Hz).; ^{13}C NMR (400 MHz, DMSO): δ 174.82, 157.47, 152.82 (d, J=62.4 Hz), 151.27, 145.06, 130.50, 123.35 (d, J = 84.8 Hz), 117.02, 115.33, 108.52, 103.17. MS (ESI) m/z = 271.10 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{10}O_5$ + H) 271.0528, found 271.0523.

4′,5,7-Trihydroxyisoflavone or Genistein (94). Crystallized in ethanol. 71%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 9.95 (brs, 1H), 8.37 (s, 1H), 7.48 (s, 1H), 7.43 (d, 2H, J=8.7 Hz), 6.93 (s, 1H), 6.81 (d, 2H, J=8.7 Hz), 4.53 (dd, 1H, J=11.0 Hz, 13.2 Hz), 4.49 (dd, 1H, J=5.7 Hz, 5.9 Hz), 4.05 (dd, 1H, J=5.5 Hz, 7.2 Hz). MS (ESI) $m/z = 271.30$ [M + 1].

3′,4′-Methylenedioxy-7-methoxyisoflavone or 7-Methoxy-ψ-baptigenin (95). To a solution of (150 mg) of ψ-baptigenin **70** in dry DMF (5 mL) were added K_2CO_3 (110 mg, 1.5 mmol) and MeI (0.05 mL, 1.5 mmol). The solution was stirred at room temperature for 3 h and then was extracted with ethyl acetate, and the organic layer was separated and washed with brine, dried, and concentrated to get crude product. The crude was purified by flash chromatography (50% EtOAc/hexane) to give **95** (140 mg, 90% yield) as a colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 8.46 (s, 1H), 8.06 (d, 1H, J = 9 Hz), 7.20−6.98 (m, 5H), 6.07 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (400 MHz, DMSO): δ 174.95, 164.20, 157.85, 154.21, 147.45, 147.39, 127.41, 126.01, 123.82, 122.86, 117.98, 115.27, 109.84, 108.55, 101.50, 101.02, 56.58. MS (ESI) $m/z = 297.11$ [M + 1]. HRMS (ESI) calcd for ($C_{17}H_{12}O5$ + H) 297.0757, found 297.0752.

2-(3′,4′-Methylenedioxy)-1-(5-ethyl-2,4-dihydroxyphenyl)ethanone (97). This compound was made using the same procedure as for the preparation of compound **91** using appropriate starting materials. Crystallized in isopropyl alcohol; yield 51%; colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 1H), 6.90−6.85 (m, 3H), 6.28 (s, 1H), 5.98 (s, 2H), 4.22 (s, 2H), 2.53 (q, 2H), 1.18 (t, 3H). MS (ESI) $m/z = 301.11$ [M + 1].

3′,4′-Methylenedioxy)-6-ethyl-7-hydroxyisoflavone (98). With stirring, boron trifluoride etherate (1.30 mL, 6 mmol) was added dropwise to a solution of **97** (600 mg, 1 mmol) in DMF (2.7 mL). Then phosphorus pentachloride (384 mg, 1.1 mmol) was added at such a rate that the temperature of the reaction mixture did not rise above 60−70 °C. After the completion of the reaction, the reaction mixture was poured into water (100 mL), and the resulting mixture was kept at 70 °C for 1 h. The precipitate was filtered and crude product crystallized from isopropyl alcohol to give **98** as a white solid (452 mg, 73%). ^{1}H NMR (300 MHz, DMSO): δ 10.87 (br s, 1H), 8.33 (s, 1H), 7.81 (s, 1H), 7.13 (d, 1H, J=1.5 Hz), 7.04 (dd, 1H, J=1.5 Hz, 8.1 Hz), 6.96 (d, 1H, J=8.1 Hz), 6.88 (s, 1H), 6.04 (s, 2H), 2.64 (q, 2H), 1.17 (t, 3H). ^{13}C NMR (400 MHz, DMSO): δ 174.85, 161.14, 156.13, 153.65, 147.41, 147.28, 130.63, 126.38, 125.37, 123.52, 122.78, 116.67, 109.88, 108.53, 101.85, 101.46, 22.84, 14.24. MS (ESI) m/z = 311.15 [M + 1]. HRMS (ESI) calcd for ($C_{18}H_{14}O_5$ + H) 311.0841, found 311.0847.

3′,4′-Methylenedioxy-6-ethyl-2-(trifluoromethyl)-7-hydroxyisoflavone (99). A solution of trifluoroacetic anhydride (0.37 mL) was added to a solution of **97** (400 mg) in 2 mL of dry pyridine at 0 °C. The reaction mixture was shaken, with ice cooling, for 10−15 min, and was left overnight. On the following day, it was heated to 40−50 °C for 10−15 min and again left at room temperature for 12 h. Then it was poured into 20−30 mL cold water, and the precipitate was filtered off and crystallized from ethanol to give **99** as an off-white solid (388 mg, 77%). ^{1}H NMR

(300 MHz, DMSO): δ 11.22 (s, 1H), 7.76 (s, 1H), 6.97 (d, 1H, *J* = 8.1 Hz), 6.92 (s, 1H), 6.84 (d, 1H, *J* = 1.5 Hz), 6.71 (dd, 1H, *J* = 1.8, 8.1 Hz), 6.08 (s, 2H), 2.65 (q, 2H), 1.16 (t, 3H). ^{13}C NMR (400 MHz, DMSO): δ 175.45, 162.34, 155.14, 147.84, 147.27, 146.97 (d, *J* = 140 Hz), 131.99, 125.46, 125.01, 123.96, 123.38, 121.22, 118.47, 115.54, 110.84, 108.35, 101.82, 22.81, 14.21. MS (ESI) *m*/*z* = 379.21 [M + 1]. HRMS (ESI) calcd for ($C_{19}H_{13}O_5F_3$ + H) 379.0715, found 379.0720.

3′,4′-Methylenedioxy-6-ethyl-7-acetoxyisoflavone (100). A mixture of **97** (500 mg, 1 mmol), acetic anhydride (0.67 mL 5 mmol), and triethylamine (0.81 mL, 4 mmol) was heated at 120−130 °C for 6 h. Then the reaction mixture was added to cold water containing 0.2 mL of hydrochloric acid. The precipitate that deposited was filtered off, washed with water until free from smell, dried, and crystallized from ethyl acetate to give **100** as an off-white solid (433 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H), 7.94 (s, 1H), 7.23 (s, 1H), 7.09 (d, 1H, *J* = 2 Hz), 6.98 (dd, 2H, *J* = 7.8 Hz), 6.85 (d, 1H, *J* = 8.1 Hz), 5.99 (s, 2H), 2.66 (q, 2H), 2.38 (s, 3H), 2.26 (s, 3H), 1.26 (t, 3H). MS (ESI) *m*/*z* = 367.16 [M + 1].

3′,4′-Methylenedioxy-2-methyl-6-ethyl-7-hydroxyisoflavone (101). A hot solution of **100** (400 mg, 1 mmol) in 5 mL of ethanol was treated with a 5% NaOH (1 mL), and the mixture was boiled for 10 min. Then 5 mL water was added and boiling was continued for another 20 min, after which the mixture was neutralized with dilute hydrochloric acid to pH 7. The precipitate that deposited was filtered off and crystallized from ethanol to give **101** as a white solid (240 mg, 68%). ^{1}H NMR (300 MHz, DMSO): δ 10.78 (s, 1H), 7.70 (s, 1H), 6.95 (d, 1H, *J* = 7.8 Hz), 6.84 (s, 1H), 6.81 (d, 1H, *J* = 1.2 Hz), 6.70 (dd, 1H, *J* = 1.8, 8.1 Hz), 6.05 (s, 2H), 2.62 (q, 2H), 2.22 (s, 3H), 1.15 (t, 3H). ^{13}C NMR (400 MHz, DMSO): δ 175.30, 162.82, 160.86, 155.74, 147.35, 146.90, 130.08, 127.49, 125.25, 124.34, 122.19, 115.68, 111.45, 108.43, 101.65, 101.40, 22.79, 19.61, 14.30. MS (ESI) *m*/*z* = 325.19 [M + 1]. HRMS (ESI) calcd for ($C_{19}H_{16}O5$ + H) 325.0997, found 325.0993.

Ethyl 2-(3-(benzo[d][1,3]dioxol-5-yl)-6-ethyl-2-methyl-4-oxo-4*H*-chromen-7-yloxy)-acetate (102). To a solution of **101** (200 mg, 1 mmol)) added ethyl bromoacetate (0.07 mL, 1 mmol) and K_2CO_3 (556 mg, 3 mmol) in 5 mL ofDMF, and the mixture was stirred for 5 h at 90 °C. The reaction mixture extracted twice with CH_2Cl_2. The collected organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was crystallized from aqueous ethanol to give **102** as a light-brown solid (220 mg, 87%). ^{1}H NMR (300 MHz, DMSO): δ 7.70 (s, 1H), 6.95 (d, 1H, *J* = 8.3 Hz), 6.82 (s, 1H), 6.80 (d, 1H, *J* = 1.2 Hz), 6.74 (dd, 1H, *J* = 2.1, 8.2 Hz), 4.78 (s, 2H), 3.91 (q, 2H), 2.78 (q, 2H), 2.26 (s, 3H), 1.30 (t, 3H), 1.25 (t, 3H). MS (ESI) *m*/*z* = 411.23 [M + 1].

2-(3-(Benzo[d][1,3]dioxol-5-yl)-6-ethyl-2-methyl-4-oxo-4*H*-chromen-7-yloxy)acetic acid (103). To a solution of **102** (200 mg, 1 mmol)) added 2 mL of5% NaOH in 3 mL of ethanol and the mixture refluxed for 2 h. The reaction mixture was neutralized with 1 N hydrochloric acid. It was then diluted with water, and the precipitate that deposited was filtered off and crystallized from ethanol to give **103** as a white solid (111 mg, 60%). ^{1}H NMR (400 MHz, DMSO): δ 7.70 (s, 1H), 6.94 (d, 1H, *J* = 8.4 Hz), 6.79 (d, 1H, *J* = 8.4 Hz), 6.79 (s, 1H), 6.69 (dd, 1H, *J* = 2, 8 Hz), 6.03 (s, 2H), 4.48 (s, 2H), 2.66 (q, 2H), 2.21 (s, 3H), 1.18 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR (400 MHz, DMSO): δ 175.30, 170.89, 163.0, 161.60, 155.87, 147.36, 146.92, 131.06, 127.42, 124.41, 122.34, 116.04, 111.43, 108.44, 101.41, 99.70, 68.11, 22.97, 19.58, 14.26. MS (ESI) *m*/*z* = 383.27 [M + 1]. HRMS (ESI) calcd for ($C_{21}H_{18}O_7$ + H) 383.1052, found 383.1057.

2-(4-Fluorophenyl)-1-(2,4-dihydroxyphenyl)ethanone (106). Resorcinol (1 g, 1 mmol) and 4-fluorophenylacetic acid **104** (1.4 g, 1 mmol) in boron trifluoride etherate (5.68 mL, 0.2 mol) were heated under a nitrogen atmosphere, at 90 °C for 90 min to give a red solution. The solution was allowed to cool and poured into aq sodium acetate (10% aq; 30 mL), and the mixture stirred to give a pale-yellow precipitate. The solids were removed by filtration and washed with water (50 mL). The crude produced was extracted with ethyl acetate, and the organic layer was separated and washed with brine, dried, and concentrated to yield, after trituration with diethyl ether (50 mL) gave **106** (626 mg, 28%) as a pale-orange solid after drying in vacuo.

^{1}H NMR (300 MHz, $CDCl_3$): δ 12.11 (br s, 1H), 7.55 (d, 1H, *J* = 8.9 Hz), 7.05−6.95 (m, 4H), 6.20−6.10 (m, 2H), 3.95 (s, 2H). MS (ESI) *m*/*z* = 247.15 [M + 1].

1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenyl)ethenone (107). This compound was made using the same procedure as for the preparation of compound **106** using appropriate starting materials. Yield 20%; orange solid. ^{1}H NMR (DMSO, 300 MHz): δ 7.95 (d, 1H, *J* = 8.9 Hz), 7.22 (d, 2H, *J* = 8.7 Hz), 6.9 (d, 2H, *J* = 8.7 Hz), 6.42 (d, 1H, *J* = 9.8 Hz), 6.25 (s, 1H), 4.18 (s, 2H), 3.75 (s, 3H). MS (ESI) *m*/*z* = 259.10 [M + 1].

4′-Fluoro-2-trifluoromethyl-7-hydroxyisoflavone (108). This compound was made using the same procedure as for the preparation of compound **99** using appropriate starting materials. Yield 73%; off-white solid. ^{1}H NMR (300 MHz, DMSO): δ 11.18 (s, 1H), 7.93 (d, 1H, *J* = 8.7 Hz), 7.36−7.25 (m, 4H), 7.03 (dd, 1H, *J* = 2.4, 9 Hz), 6.95 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (400 MHz, DMSO): δ 175.47, 164.31, 163.88, 161.44, 147.20, 132.58 (d, *J* = 32.8 Hz), 127.93, 126.26, 124.50, 121.11, 118.36, 116.83, 115.82, 115.47 (d, *J* = 86.4 Hz), 102.68. MS (ESI) *m*/*z* = 325.12 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_8O_3F_4$ + H) 325.0409, found 325.0409.

4′-Fluoro-2-methyl-7-hydroxyisoflavone (109). Acetic anhydride (0.77 mL, 4 mmol) was added to a suspension of potassium carbonate (1.02 g, 4 mmol) and 2-(4-fluorophenyl)-1-(2,4-dihydroxyphenyl)ethenone **106** (500 mg, 1 mmol) in DMF (5 mL), and the resulting suspension heated at 115 °C for 120 min. The mixture was allowed to cool and poured into water (50 mL), to give an off-white precipitate. The solids were removed by filtration and washed with water (50 mL) and diethyl ether (2 × 5 mL), to give **109** (466 mg, 85%) as a white solid. ^{1}H NMR (300 MHz, DMSO): δ 11.21 (s, 1H), 7.94 (d, 1H, *J* = 8.7 Hz), 7.42−7.25 (m, 4H), 7.10−6.90 (m, 2H), 2.20 (s, 3H). MS (ESI) *m*/*z* = 271.18 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{11}O_3F$ + H) 271.0692, found 271.0697.

4′-Methoxy-2-methyl-7-hydroxyisoflavone (110). This compound was made using the same procedure as for the preparation of compound **109** using appropriate starting materials. Yield 76%; off-white solid. ^{1}H NMR (DMSO, 300 MHz): δ 7.84 (d, 1H, *J* = 8.7 Hz), 7.12 (d, 2H, *J* = 8.8 Hz), 7.05 (d, 2H, *J* = 8.8 Hz), 6.93 (d, 1H, *J* = 8.7 Hz), 6.81 (s, 1H), 3.83 (s, 3H), 2.25 (s, 3H). MS (ESI) *m*/*z* = 283.10 [M + 1]. HRMS (ESI) calcd for ($C_{17}H_{14}O_4$ + H) 283.0892, found 283.0894.

3-(2,4-Dihydroxyphenyl)-4-(3,4-methylenedioxy)-1*H*-pyrazole (111). Hydrazine hydrate (∼55% aq; 2 mL) was added to a suspension of ψ-baptigenin **70** (500 mg, 1 mmol) in ethanol (10 mL) and the mixture heated under reflux for 8 h to give a brown solution. The solution was allowed to cool and concentrated to a pale-yellow solid. The solids were washed with water to give crude product. The crude product was recrystallized from boiling toluene, washed with hexane, and dried to give **111** as colorless solid (404 mg, 77%). ^{1}H NMR (300 MHz, DMSO): δ 12.89 (s, 1H), 9.57 (s, 1H), 9.53 (s, 1H), 7.78 (s, 1H), 6.80−6−45 (m, 6H), 6.02 (s, 2H). MS (ESI) *m*/*z* = 297.23 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{12}N_2O_4$ + H 297.0797, found 297.0803.

Compounds **112**−**115** were made using the same procedure as for the preparation of compound **111** using appropriate starting materials.

3-(2,4-Dihydroxyphenyl)-4-(4-fluorophenyl)-1*H*-pyrazole (112). Yield 73%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 13.31 (s, 1H), 9.69 (s, 1H), 9.54 (s, 1H), 7.86 (s, 1H), 7.27−7.11 (m, 4H), 6.72 (d, 1H, *J* = 8.4 Hz), 6.32 (d, 1H, *J* = 2.2 Hz), 6.13 (dd, 1H, *J* = 2.3, 8.4 Hz). MS (ESI) *m*/*z* = 271.12 [M + 1]. HRMS (ESI) calcd for ($C_{15}H_{11}N_2O_2F$ + H) 271.0804, found 271.0806.

3-(2,4-Dihydroxyphenyl)-4-(4-fluorophenyl)-5-trifluoromethyl-1H-pyrazole (113). Yield 70%; colorless solid. ^{1}H NMR (300 MHz, DMSO): δ 13.51 (s, 1H), 9.76 (s, 1H), 9.57 (s, 1H), 7.22−7.12 (m, 4H), 6.74 (d, 1H, J = 8.1 Hz), 6.35 (d, 1H, J = 2.4 Hz), 6.15 (dd, 1H, J = 2.1, 8.1 Hz). ^{13}C NMR (400 MHz, DMSO): δ 162.99, 160.57, 159.73, 157.08, 140.35, 138.66 (d, J = 138.4 Hz), 132.11 (t, J = 44.4 Hz), 128.44, 126.64, 123.96, 121.28, 117.18, 115.59 (d, J = 84.8 Hz), 107.05, 106.49, 103.04, 67.46. MS (ESI) m/z = 285.08 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{13}N_2O_2F$ + H) 285.0961, found 285.0965.

3-(2,4-Dihydroxyphenyl)-4-(4-fluorophenyl)-5-methyl-1H-pyrazole (114). Yield 70%; white crystalline solid. ^{1}H NMR (300 MHz, DMSO): δ 12.94 (s, 1H), 9.51 (s, 1H), 9.40 (s, 1H), 7.24−7.13 (m, 4H), 6.74 (d, 1H, J = 8.4 Hz), 6.32−6.02 (m, 2H), 2.16 (s, 3H). MS (ESI) m/z = 239.15 [M + 1]. HRMS (ESI) calcd for ($C_{16}H_{10}N_2O_2F_4$ + H) 239.0678, found 239.0683.

3-(2,4-Dihydroxyphenyl)-4-(4-methoxyphenyl)-5-methyl-1H-pyrazole (115). Yield 75%; colorless solid. ^{1}H NMR (DMSO, 300 MHz): δ 7.21 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 6.92 (d, 1H, J = 8.6 Hz), 6.35 (s, 1H), 6.14 (d, 1H, J = 8.7 Hz), 3.85 (s, 3H), 2.25 (s, 3H). MS (ESI) m/z = 297.24 [M + 1]. HRMS (ESI) calcd for ($C_{17}H_{16}N_2O_3$ + H) 297.1160, found 297.1162.

Cell Culture. HEK 293 cell line was obtained from American Type Culture Collection (USA). All materials used for tissue culture were purchased from Invitrogen, Australia, unless specified. HEK 293 cells were grown in Dulbecco's Modified Eagle's Medium/F-12 (DMEM/F-12), containing L-glutamine supplemented with penicillin (100 U/mL), streptomycin (100 mg/mL), and 10% (v/v) heat-inactivated fetal bovine serum in a humidified atmosphere of 5% CO_2 and 95% O_2 at 37 °C.

Transfection and Luciferase Assay (PPARα and γ). The PPARα and γ transfection and luciferase procedures were performed as described previously by Bramlett et al.[35] with slight modifications. The HEK 293 cell line was transfected with either tk-PPREx4-Luc plasmid (a kind gift from Dr Teruo Kawada, Kyoto University, Japan) or tk-x3PPRE(ACO)-Luc plasmid (a kind gift from Dr Roderick Clifton-Bligh, Kolling Institute of Medical Research, Australia) plus pBI-G-hPPAR-α plasmid (a kind gift from Dr Sarah Roberts-Thomson, Queensland University, Australia) or plus pSG5-hPPAR-γ1 plasmid (a kind gift from Dr. Willa Hsueh, University of California, Los Angeles) and pSV-β-galactosidase (Promega, Australia) control plasmid. Cells were transfected with FuGENE 6 transfection reagent (Roche, Australia) in accordance with the manufacturer's instructions. After 24 h at 37 °C, cells were harvested and plated into 96-well plates at 5×10^4 cells per well in complete transfection media and allowed to attach overnight at 37 °C. The cells were then treated with fenofibrate **1** and **2** as PPARα positive controls, rosiglitazone **3** and **4** as PPARγ positive controls, DMSO (0.1%) as vehicle control, and the test samples. After 48 h, the cells were lysed and assayed for luciferase and β-galactosidase activities using the Bright-Glo luciferase assay system and Beta-Glo assay system (Promega, Australia), respectively. The results are expressed as relative luciferase activity normalized to the β-galactosidase signal (fold difference compared to vehicle control).

Cell Proliferation Assay. HEK 293 cells were seeded overnight then treated with various concentrations of fenofibrate **1**, rosiglitazone **3**, **4**, and test compounds (0−100 μM) and incubated for 48 h at 37 °C in a humidified atmosphere with 5% CO_2. MTS (tetrazolium salt) reagent (CellTiter96 Aqueous One solution cell proliferation assay, Promega, Sydney, Australia) was added and samples were incubated for a further 2 h before finally being analyzed using a BMG POLARstar Galaxy Microplate Reader (λ: 490 nm). The results are expressed as % relative cell viability compared to DMSO vehicle control.

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Supporting Information Available: Elemental analysis of compounds **68**−**85**. This material is available free of charge via the Internet at http://pubs.acs.org.

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