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Antineoplastic Isoflavonoids Derived from Intermediate *ortho*-Quinone Methides Generated from Mannich Bases

Dr. Mykhaylo S. Frasinyuk^[a,b,c], Dr. Galyna P. Mrug^[c], Dr. Svitlana P. Bondarenko^[d], Volodymyr P. Khilya^[d] [Prof.], Dr. Vitaliy M. Sviripa^[a,b], Oleksandr A. Syrotchuk^[e], Wen Zhang^[a,f], Dr. Xianfeng Cai^[a,f], Dr. Michael V. Fiandalo^[g], James L. Mohler^[g] [Prof.], Chunming Liu^[a,f] [Prof.], and David S. Watt^[a,b,f] [Prof.]

^[a]Department of Molecular and Cellular Biochemistry, College of Medicine, University of Kentucky, Lexington, KY 40536-0596, USA

^[b]Center for Pharmaceutical Research and Innovation, College of Pharmacy, University of Kentucky, Lexington, KY 40536-0509, USA

^[c]Department of Chemistry of Bioactive Nitrogen Containing Heterocyclic Bases, Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Science of Ukraine, Kyiv 02094, Ukraine

^[d]Department of Chemistry, Taras Shevchenko Kyiv National University, Kyiv 01601, Ukraine

^[e]Central Laboratory for Quality Control of Medicines and Medical Products, Kyiv 04053, Ukraine

^[f]Lucille Parker Markey Cancer Center, University of Kentucky, Lexington, KY 40536-0093, USA

^[g]Department of Urology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA

Abstract

The regioselective condensations of various 7-hydroxyisoflavonoids with bis(N,N-dimethylamino)methane in a Mannich reaction provided C-8 N,N-dimethylaminomethyl-substituted isoflavonoids in good yield. Similar condensations of 7-hydroxy-8-methylisoflavonoids led to the C-6 substituted analogs. Thermal eliminations of dimethylamine from these C-6 or C-8 N,N-dimethylaminomethyl-substituted isoflavonoids generated *ortho*-quinone methide intermediates within isoflavonoid frameworks for the first time. Despite other potential competing outcomes, these *ortho*-quinone methide intermediates trapped dienophiles including 2,3-dihydrofuran, 3,4-dihydro-2H-pyran, 3-(N,N-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one, 1-morpholinocyclopentene, and 1-morpholinocyclohexene to give various inverse electron-demand Diels-Alder adducts. Several adducts derived from 8-N,N-dimethylaminomethyl-substituted isoflavonoids displayed good activity in the 1-10 μ M concentration range in an *in vitro* proliferation assay using the PC-3 prostate cancer cell line.

Abstract

dwatt@uky.edu, mykhaylo.frasinyuk@ukr.net.

Supporting information for this article is given via a link at the end of the document.

Keywords

isoflavonoid; Mannich reaction; *ortho*-quinone methides; inverse electron-demand Diels-Alder reaction; prostate cancer PC-3 cell line

Introduction

Androgen-deprivation therapy produces temporary palliation but fails to cure advanced prostate cancer in which tissue levels of testosterone and 5 α -dihydrotestosterone are sufficient to activate the androgen receptor.[1] Although the steroidal drug, abiraterone, interferes with the metabolism of adrenal androgens to testosterone and 5 α -dihydrotestosterone by inhibiting cytochrome 17A1 (CYP17A1),[2] its effects are only short-lived when used after the failure of androgen-deprivation therapy.[3] Prostate cancer remains the second leading cause of cancer-related mortality in men,[4] and new therapies focused on the selective inhibition of enzymes participating in the backdoor pathway[5] to dihydrotestosterone from 4-androstene-3,17-dione remain a worthy goal for enhancing the extent or duration of response to androgen-deprivation therapy.

Isoflavones, particularly daidzein (**1a**) and genistein (**1b**) (Figure 1), attracted interest as potential agents for the treatment of prostate cancer,[6] but these natural products and their metabolites have a spectrum biological effects, including those that act on androgen receptor expression and enzymes associated with androgen metabolism.[7] We selected 7-hydroxyisoflavones as candidates as part of a program to develop antineoplastic agents against *selective* biological targets. Prior work in our laboratories demonstrated that the removal or transformation of hydroxyl groups from natural products and replacement of these groups with functional groups capable of hydrogen bonding and van der Waals interactions led to new agents with singular and important biological targets.[8]

Results and Discussion

The removal of hydroxyl groups found frequently in naturally occurring isoflavones limited competitive redox processes as well as phase II metabolism (*e.g.*, sulfation or glucuronidation) and provided an opportunity to acquire a pharmacophore with a singular mechanism of action. For example, the elimination of hydroxyl groups in resveratrol, a hackneyed natural product with a multiplicity of biological effects, led to the fluorinated stilbenes.[8a, 9] These antineoplastic agents act as epigenetic regulators of a single molecular target, the catalytic subunit of methionine adenosyltransferase-2. Additional modifications of the stilbene pharmacophore led to the fluorinated 3-arylquinolines[8b] as antineoplastic agents that bind uniquely to the intermediate filament protein, vimentin, and promote the secretion of the natural tumor suppressor, Prostate apoptosis response-4 protein (Par-4). In the same fashion, we initiated a structure-activity study on semisynthetic

isoflavones using an *in vitro* proliferation assay based on the PC-3 human prostate cancer cell line to interrogate structures, identify potent analogs and provide a framework for biotinylation and target identification. This decision distanced us from the debate surrounding the naturally occurring isoflavone and allowed us to focus on developing synthetic isoflavonoids with substituent patterns not seen in natural products. As part of this effort to identify enzyme inhibitors within new, heterocyclic platforms, we explored Diels-Alder cycloadditions involving the chromone core, which appears in isoflavones. Although chromones were used previously in Diels-Alder reactions with various dienes, invariably successful Diels-Alder reactions required the presence of electron-withdrawing carbonyl- or cyano- group in position 3 of chromone ring.[10]

This limitation would appear to exclude the use of semisynthetic flavonoids or isoflavonoids in Diels-Alder reactions because they possess electron-donating phenyl substituent at positions 2 or 3, respectively. The *in situ* generation of *ortho*-quinone methides from phenolic Mannich bases,[11] hydroxybenzyl alcohol derivatives,[12] and oxygen-containing heterocycles[13] provided chromane derivatives in hetero-Diels-Alder reaction but the generation of *ortho*-quinone methides in a chromone platform was without precedent. It was unclear at the outset of this work if the reactive 1,4-benzopyrone functionality in isoflavonoids would accommodate a transitory *ortho*-quinone methides and trap dieneophiles without competitive, interfering reactions. Specifically, we wanted to synthesize substituted 3-aryl-9,10-dihydropyrano[2,3-f]chromen-4(8H)-ones **2** and 3-aryl-3,4-dihydro-2H,6H-pyrano[3,2-g]chromen-6-ones **3** (Figure 1).[14] To accomplish this aim, aminomethyl-, hydroxymethyl-, and methoxymethyl derivatives of 7-hydroxyflavones were tested as precursors to *ortho*-quinone methides and as dienes in an inverse electron-demand Diels Alder addition. Synthesis of these precursors involved the application of the Mannich reaction to 7-hydroxyisoflavonoids **4** with bis(N,N-dimethylamino)methane in isopropanol at reflux to provide regioselectively the C-8 substituted N,N-dimethylaminomethyl analogs **5** (Scheme 1) in good yields.[15] The 7-hydroxy-8-methoxyisoflavonoids **6** gave, as expected, the isomeric C-6 analogs **7**.

Heating the N,N-dimethylaminomethyl-substituted isoflavonoids **5** generated the intermediate *ortho*-quinone methides **8** (Scheme 2) that trapped various electron-rich dienophiles including 2,3-dihydrofuran, 3,4-dihydro-2H-pyran, 3-(N,N-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one, 1-morpholino-cyclopentene, and 1-morpholinocyclohexene. These reactions led to Diels-Alder adducts **11-15** (Scheme 2) in yields that varied with dienophile reactivity (Table 1). Table 1 summarizes representative combinations of dienophiles and N,N-dimethylamino-substituted isoflavonoids that led to biologically active adducts. Among the various dienophiles, dihydrofuran and dihydropyran produced the most biologically active compounds, and consequently, these dienophiles were explored in the most detail. The few adducts synthesized from other dienophiles, such as the enamines, had low activity, or in the case of 3-(N,N-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one, produced very insoluble adducts that could not be evaluated in a biological assay.

The further transformation of hemi-aminals **10** that were intermediates in some cases depended on substituents. The presence of an electron-withdrawing carbonyl group led to dimethylamine elimination (path A) with formation of **13**. In cases of 1-

morpholinocyclopentene or 1-morpholinocyclohexene, the hydrolysis of hemi-aminals **10** (path B) led to 2-substituted ketones or tautomeric hemi-ketals **14** or **15**. The yields were low (<50%) using either 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran due to dimerization and polymerization reactions but were acceptable using other dienophiles. Similar reactions with dienophiles were observed for the intermediate *ortho*-quinone methides **9** derived from 6-dimethylaminomethyl isoflavones **7**. In these cases, linear 6a,7,8,9a-tetrahydro-4*H*,6*H*-furo[2,3-*b*]pyrano[3,2-*g*]chromen-4-ones **16** and 6,8,9,10-tetrahydro-4*H*,7*H*-pyrano[3,2-*b*]xanthene-4,7-dione **17** were formed. Attempts to employ common electron-deficient dienophiles were unsuccessful.

The Diels-Alder reactions of **5** with either 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran led to a 1:1 ratio of enantiomeric, *cis*-fused adducts **11** or **12**, respectively, which was confirmed by the coupling constants ³*J* between the acetal proton at C-7a and bridgehead proton at C-10a and by chiral phase HPLC. The structures of the *cis*-fused adducts **11** and **12** were also confirmed by 2D NOESY spectra. The Diels-Alder reaction of the isomeric isoflavonoids **7** with 2,3-dihydrofuran led to the corresponding *cis*-fused adduct **16**. The 2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene skeleton within adducts **11** and **16** appears in bioactive xyloketal isolated from fungi.[14] The Diels-Alder reactions of **5** and **7** with 3-(*N,N*-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one led to initial adducts that suffered concomitant thermal eliminations of dimethylamine to give the isolated adducts **13** and **17**, respectively, in excellent yield. A study of the reaction of **5a** with the 3-(*N,N*-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one in various solvents led to the selection of refluxing *N,N*-dimethylformamide (DMF) as the optimal conditions for these reactions (Table 1). Finally, Diels-Alder reactions with 1-morpholinocyclopentene and 1-morpholinocyclohexene led to the adducts **14** and **15**, respectively. The mechanism leading to each of these adducts involved an initial cycloaddition and the subsequent hydrolysis of intermediate hemi-aminals. The adducts adopted either the open-chain tautomer **14** in the case of 1-morpholinocyclopentene or the cyclic hemiacetal **15** in the case of 1-morpholinocyclohexene.

In place of the Mannich bases as precursors to the *ortho*-quinone methides, we also investigated 8-hydroxymethyl- and 8-methoxymethyl substituted 7-hydroxyisoflavones **18a**, **18g**, **19a**, and **19g** and diacetates **20a** and **20g**[15] as intermediates for generation of *ortho*-quinone methides in model reaction with 3-(*N,N*-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one in DMF (Scheme 3). Although 8-methoxymethyl-7-hydroxyisoflavonoids gave only marginally improved yields of pyranoxanthones **13a** and **13g** than the 8-dimethylaminomethylisoflavonoids **5a** and **5g** (Table 2), the use of the Mannich bases was preferred given their ready availability. These findings suggest that other naturally occurring hydroxymethyl- or methoxymethyl hydroxychromones could be deployed in inverse electron-demand Diels-Alder reactions.

Proliferation studies using PC-3 cells revealed that Diels-Alder adducts formed from 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran with the *ortho*-quinone methide derived from C-8 *N,N*-dimethylaminomethyl-substituted isoflavonoids **6** produced the most active adducts **11** and **12** (Table 3). Adduct **12** was more active than other adducts, with a few exceptions.

Among the exceptions, adducts **11a** and **11e** were comparable in activity to **12a** and **12e**, and adduct **15g** was slightly superior in activity to **12g**. With respect to substituents on the isoflavonoid framework, those adducts bearing 3-(4'-methoxyphenyl), 3-(3',4'-dimethoxyphenyl), 3-(3',4'-methylenedioxyphenyl), or 3-(4'-chlorophenyl) substituents were most active. In a promising outcome, the adduct **13b**, which was generated using 3-(N,N-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one, displayed 86% inhibition at 10 μ M and 31% inhibition at 1 μ M.

In a preliminary study of cell toxicity, the treated cells were analyzed by Vi-Cell XR viability analyzer that took 50 images per sample and permitted the determination of cell concentrations, viability and size. The viability of each sample was greater than 95%; however, the cell numbers were significantly reduced by active compounds. The cell sizes were similar (Table 3) except for cells treated with **13b**, which was the most potent compound. Isoflavonoid **13b** significantly reduced the size of PC-3 cells, suggesting that it may inhibit PC-3 cell proliferation by inhibiting the cell cycle as well as inducing apoptosis. Additional studies will be needed to clarify this point.

Conclusions

A regioselective condensation of 7-hydroxyisoflavonoids **4** or 7-hydroxy-8-methylisoflavonoids **6** with bis(N,N-dimethylamino)methane in isopropanol at reflux provided **5** or **7**, respectively. Thermal eliminations of dimethylamine from these Mannich bases as well as elimination of methanol or water from corresponding 8-methoxymethyl- or 8-hydroxymethyl 7-hydroxyisoflavones generated *ortho*-quinone methide intermediates that trapped a variety of dienophiles to give various Diels-Alder adducts **11-17** in good yields. Some of these adducts, particularly those derived from 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran, or 3-(N,N-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one, displayed good activity in a proliferation assay using PC-3 cells. Subsequent studies will focus on identifying the biological target of these isoflavonoids.

Experimental Section

Chemicals and instruments. ^1H and ^{13}C NMR spectra were recorded on a Varian 500 spectrometer (at 500 MHz or at 125 MHz, respectively) or on a Varian 400 spectrometer (at 400 MHz or at 100 MHz, respectively) in deuteriochloroform (CDCl_3) or deuterated dimethylsulfoxide ($\text{DMSO}-d_6$). ^{13}C NMR Chemical shifts for minor isomers compounds **15** are given in brackets. IR spectra were recorded on a Bruker Vertex 70 FT/IR spectrometer. Melting points were determined in open capillarity tubes with a Buchi B-535 apparatus and were uncorrected. Mass spectra were obtained with an Agilent 1100 spectrometer under chemical ionization conditions. Column chromatography was performed using Macherey-Nagel Silica 60, 0.04-0.063 mm silica gel.

General procedure for synthesis of Mannich bases 5a-5i

To a stirred suspension of isoflavonoids **4a-4i** (2 mmol) in 10 mL of isopropanol was added 0.3 mL (2.2 mmol, 1.1 eq) of bis(N,N-dimethylamino)methane at 70°C. The mixture was heated at 80°C for 2 h and cooled to afford a precipitate that was collected by gravity

fitration. In the absence of crystallization, the residue was triturated with hexane to induce crystallization. The Mannich bases **5** were re-crystallized from isopropanol-hexane.

8-[(*N,N*-Dimethylamino)methyl]-7-hydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (**5a**)

Pale yellow solid (83% yield); mp 174-176°C; IR (KBr) $\nu_{\max}$ 3448, 2951, 1626, 1427, 1246, 1178, 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.44 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.85 (s, 3H, 4'-OCH₃), 3.99 (s, 2H, 8-CH₂), 6.90 (d, 1H, $^3J = 8.8$ Hz, 6-H), 6.97 (d, 2H, $^3J = 8.8$ Hz, 3', 5'-H), 7.50 (d, 2H, $^3J = 8.8$ Hz, 2', 6'-H), 7.89 (s, 1H, 2-H), 8.14 (d, 1H, $^3J = 8.8$ Hz, 5-H), 10.21 ppm (br s, 1H, 7-OH); ^{13}C NMR (125 MHz, CDCl_3) δ 44.41, 54.87, 55.20, 107.27, 113.80, 115.44, 116.89, 124.22, 124.32, 126.67, 130.00, 151.25, 154.96, 159.41, 163.97, 175.74 ppm; MS (CI): m/z 326.1 (MH^+ , 100). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.88; H, 5.97; N, 4.39.

3-(3,4-Dimethoxyphenyl)-8-[(*N,N*-dimethylamino)methyl]-7-hydroxy-4*H*-chromen-4-one (**5b**)

Pale yellow solid (77% yield); mp 154-155°C; IR (KBr) $\nu_{\max}$ 2948, 1636, 1602, 1517, 1266, 1145, 1024 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.44 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.91, 3.93 (2s, 6H, 3', 4'-OCH₃), 3.99 (s, 2H, 8-CH₂), 6.86-6.96 (m, 2H, 6, 6'-H), 7.00-7.07 (m, 1H, 5'-H), 7.18-7.23 (m, 1H, 2'-H), 7.92 (s, 1H, 2-H), 8.13 (d, 1H, $^3J = 8.8$ Hz, 5-H), 9.79 ppm (s, 1H, 7-OH); ^{13}C NMR (125 MHz, CDCl_3) δ 44.52, 55.04, 55.88, 55.89, 107.40, 111.04, 112.46, 115.58, 116.93, 120.90, 124.45, 124.70, 126.68, 148.64, 148.95, 151.44, 154.93, 164.05, 175.86 ppm; MS (CI): m/z 356.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.88; H, 5.97; N, 4.39.

3-(1,3-Benzodioxol-5-yl)-8-[(*N,N*-dimethylamino)methyl]-7-hydroxy-4*H*-chromen-4-one (**5c**)

Pale yellow solid (73% yield); mp 160-161°C; IR (KBr) $\nu_{\max}$ 2960, 2987, 1639, 1488, 1425, 1246, 1017 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.44 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.98 (s, 2H, 8-CH₂), 5.98 (s, 2H, 3',4'-OCH₂O), 6.80-7.00 (m, 3H, 6, 5', 6'-H), 7.06-7.13 (m, 1H, 2'-H), 7.86 (s, 1H, 2-H), 8.11 (d, 1H, $^3J = 8.8$ Hz, 5-H), 9.95 ppm (s, 1H, 7-OH); ^{13}C NMR (125 MHz, CDCl_3) δ 44.60, 55.15, 101.13, 107.49, 108.34, 109.78, 115.62, 116.94, 122.34, 124.61, 125.78, 126.78, 147.56, 147.62, 151.46, 154.97, 164.12, 175.73 ppm; MS (CI): m/z 340.3 (MH^+ , 100). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.48; H, 4.97; N, 4.39.

3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-8-[(*N,N*-dimethylamino)methyl]-7-hydroxy-4*H*-chromen-4-one (**5d**)

Pale yellow solid (68% yield); mp 179-180°C; IR (KBr); $\nu_{\max}$ 3072, 2955, 1643, 1602, 1509, 1289, 1060, 1027 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.42 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.97 (s, 2H, 8-CH₂), 4.27 (s, 4H, 3',4'-OCH₂CH₂O), 6.88 (d, 1H, $^3J = 8.7$ Hz, 6-H), 6.91 (d, 1H, $^3J = 8.4$ Hz, 8'-H), 7.02 (dd, 1H, $^3J = 8.7$ Hz, $^4J = 2.0$ Hz, 7'-H), 7.09 (d, 1H, $^4J = 2.0$ Hz, 5'-H), 7.86 (s, 1H, 2-H), 8.11 (d, 1H, $^3J = 8.7$ Hz, 5-H), 10.04 ppm (s, 1H, 7-OH); ^{13}C NMR (125 MHz, CDCl_3) δ 44.39, 54.63, 64.24, 64.38, 107.04, 115.54, 116.87, 117.16, 117.88, 122.08, 124.27, 125.10, 126.94, 143.32, 143.57, 151.46, 155.02, 164.03, 175.67 ppm; MS (CI): m/z 354.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.10; H, 5.67; N, 4.79.

3-(4-Chlorophenyl)-8-[(*N,N*-dimethylamino)methyl]-7-hydroxy-4*H*-chromen-4-one (5e)

Pale yellow solid (78% yield); mp 174-176°C; IR (KBr) $\nu_{\max}$ 3061, 2958, 2838, 1881, 1632, 1590, 1466, 1378, 1257, 1204, 1176, 1011, 824 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.43 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.97 (s, 2H, 8- CH_2), 6.90 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.36-7.41 (m, 2H, 3', 5'-H), 7.46 – 7.52 (m, 2H, 2', 6'-H), 7.89 (s, 1H, H-2), 8.11 (d, 1H, $^3J = 8.8$ Hz, 5-H), 12.48 ppm (s, 1H, 7-OH); ^{13}C NMR (100 MHz, CDCl_3) δ 44.59, 55.14, 107.55, 115.79, 116.89, 123.84, 126.75, 128.60, 130.21, 130.51, 134.01, 151.79, 155.00, 164.32, 175.37 ppm; MS (CI): m/z 330.2 (MH^+ , 100), 332.2 (MH^+ , 28). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{ClNO}_3$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.81; H, 5.07; N, 4.47.

8-[(*N,N*-Dimethylamino)methyl]-7-hydroxy-2-methyl-3-phenyl-4*H*-chromen-4-one (5f)

Pale yellow solid (81% yield); mp 168-170°C; IR (KBr) $\nu_{\max}$ 3052, 2952, 1633, 1599, 1399, 1287, 1258, 1018 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.29 (s, 3H, 2- CH_3), 2.44 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.98 (s, 2H, 8- CH_2), 6.84 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.24-7.47 (m, 5H, 3-Ph), 8.05 (d, 1H, $^3J = 8.8$ Hz, 5-H), 11.79 ppm (s, 1H, 7-OH); ^{13}C NMR (125 MHz, CDCl_3) δ 19.32, 44.41, 54.67, 106.69, 115.12, 115.83, 122.95, 126.83, 127.58, 128.24, 130.38, 133.17, 154.73, 161.90, 163.78, 176.29 ppm; MS (CI): m/z 310 (MH^+ , 100). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.92; H, 5.99; N, 4.43.

8-[(*N,N*-Dimethylamino)methyl]-7-hydroxy-3-(4-methoxyphenyl)-2-methyl-4*H*-chromen-4-one (5g)

Pale yellow solid (91% yield); mp 185-187°C decomp; IR (KBr) $\nu_{\max}$ 3450, 2958, 1626, 1603, 1255, 1176, 1016 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 2.30 (s, 3H, 2- CH_3), 2.44 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.84 (s, 3H, 4'- OCH_3), 3.98 (s, 2H, 8- CH_2), 6.85 (d, 1H, $^3J = 8.8$ Hz, 6-H), 6.97 (d, 2H, $^3J = 8.7$ Hz, 3', 5'-H), 7.20 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 8.04 (d, 1H, $^3J = 8.8$ Hz, 5-H), 11.30 ppm (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.28, 44.44, 54.85, 55.21, 106.83, 113.78, 115.03, 115.89, 122.51, 125.33, 126.74, 131.51, 154.68, 158.99, 161.76, 163.69, 176.47 ppm; MS (CI): m/z 340.1 (MH^+ , 100). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.91; H, 5.95; N, 4.33.

3-(3,4-dimethoxyphenyl)-8-[(*N,N*-dimethylamino)methyl]-7-hydroxy-2-methyl-4*H*-chromen-4-one (5h)

Pale yellow solid (87% yield); mp 150-152°C; IR (KBr) $\nu_{\max}$ 2995, 2841, 1635, 1516, 1393, 1262, 1020 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 2.31 (s, 3H, 2- CH_3), 2.45 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.87, 3.91 (2s, 6H, 3', 4'- OCH_3), 3.99 (s, 2H, 8- CH_2), 6.78-6.83 (m, 2H, 2', 6'-H), 6.85 (d, 1H, $^3J = 8.8$ Hz, 6-H), 6.92 (d, 1H, $^3J = 8.7$ Hz, 5'-H), 8.05 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (125 MHz, CDCl_3): δ 19.39, 44.62, 55.24, 55.88, 55.89, 107.14, 111.11, 113.67, 115.11, 115.94, 122.76, 122.80, 125.84, 126.64, 148.50, 148.70, 154.61, 161.89, 163.78, 176.50 ppm; MS (CI): m/z 370.3 (MH^+ , 100). Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.97; H, 6.14; N, 4.56.

3-(4-Chlorophenyl)-8-[(*N,N*-dimethylamino)methyl]-7-hydroxy-2-methyl-4*H*-chromen-4-one (5i)

Pale yellow solid (86% yield); mp 174-175°C; IR (KBr) $\nu_{\max}$ 2974, 2835, 1631, 1407, 1371, 1285, 1258, 1014 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.29 (s, 3H, 2- CH_3), 2.44 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.98 (s, 2H, 8- CH_2), 6.86 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.19-7.25 (m, 2H, 3', 5'-H), 7.36-7.42 (m, 2H, 2', 6'-H), 8.03 (d, 1H, $^3J = 8.8$ Hz, 5-H), 12.14 ppm (s, 7-OH); ^{13}C NMR (100 MHz, CDCl_3) δ 19.32, 44.63, 55.24, 107.18, 115.29, 115.80, 121.99, 126.65, 128.54, 131.76, 131.88, 133.61, 154.63, 161.76, 163.99, 176.03 ppm; MS (CI): m/z 344.3 (MH^+ , 100), 346.3 (MH^+ , 29). Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{ClNO}_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.10; H, 4.99; N, 3.85.

6-[(*N,N*-Dimethylamino)methyl]-7-hydroxy-3-(4-methoxyphenyl)-8-methyl-4*H*-chromen-4-one (7a)

To a suspension of 2 mmol of **6a** in 10 mL of 1,4-dioxane was added 1 mL (7.4 mmol) of bis(*N,N*-dimethylamino)methane at 70°C. The mixture was heated at 100°C for 16 h, cooled, and diluted with hexane. The precipitate was collected to afford 672 mg (99 %) of **7a** as a yellow solid: mp 182-183°C; IR (KBr) $\nu_{\max}$ 3069, 2954, 2831, 1627, 1512, 1461, 1369, 1290, 1223, 1176, 830 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.32 (s, 3H, 8- CH_3), 2.37 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.78 (s, 2H, 6- CH_2), 3.84 (s, 3H, 4'- OCH_3), 6.97 (d, 2H, $^3J = 8.7$ Hz, 3', 5'-H), 7.50 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 7.81 (s, 1H, 5-H), 7.97 (s, 1H, 2-H), 9.81 ppm (br s, 1H, 7-OH); ^{13}C NMR (125 MHz, CDCl_3) δ 7.81, 44.21, 55.30, 62.37, 111.80, 113.88, 116.63, 120.31, 122.69, 124.02, 124.60, 130.07, 152.01, 155.76, 159.38, 161.30, 176.30 ppm; MS (CI): m/z 340.3 (MH^+ , 100). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$: C, 70.87; H, 6.24; N, 4.13. Found: C, 70.62; H, 6.43; N, 4.11.

6-[(*N,N*-Dimethylamino)methyl]-7-hydroxy-3-(4-methoxyphenyl)-2,8-dimethyl-4*H*-chromen-4-one (7g)

The procedure described for **6a** was repeated to afford 509 mg of **7g** as white solid (72% yield); mp 176-177°C; IR (KBr) $\nu_{\max}$ 3039, 2952, 2834, 1643, 1606, 1511, 1397, 1239, 1158 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.32 (s, 6H, 2, 8- CH_3), 2.36 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.76 (s, 2H, 6- CH_2), 3.85 (s, 3H, 4'- OCH_3), 6.97 (d, 2H, $^3J = 8.7$ Hz, 3', 5'-H), 7.21 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 7.74 ppm (s, 1H, 5-H); ^{13}C NMR (125 MHz, CDCl_3) δ 7.83, 19.43, 44.20, 55.23, 62.34, 111.39, 113.77, 115.55, 119.84, 122.14, 122.62, 125.67, 131.55, 155.31, 158.87, 161.02, 162.34, 176.92 ppm; MS (CI): m/z 354.2 (MH^+ , 100). Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.46; H, 6.31; N, 4.17.

General procedure for synthesis of Diels-Alder adducts 11 and 16

To a solution of 2 mmol of **5** or **7** in 10 mL of DMF was added 2 mL (26 mmol, 13 eq) of 2,3-dihydrofuran. The use of 13 equivalents of 2,3-dihydrofuran per mmole of **5** or **7** was chosen arbitrarily and does not represent an optimized ratio. Increased equivalents, however, lowered the reflux temperature, slowed the generation of the *ortho*-quinone methide and reduced product yield. The solution was refluxed for 24-40 h. The solvent and excess 2,3-dihydrofuran were evaporated *in vacuo*, and the residue was purified by chromatography using 1:50 methanol-dichloromethane to afford adducts **11** or **16**.

3-(4-Methoxyphenyl)-9,10,10a,11-tetrahydro-4*H*,7*aH*-furo[2,3-*b*]pyrano[2,3-*f*]chromen-4-one (11a)

Pale yellow solid (70% yield); mp 201–202°C; IR (KBr) $\nu_{\max}$ 2903, 2844, 1643, 1610, 1510, 1435, 1295, 1242, 1205, 1052 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.69–1.82 (m, 1H, 10 α -CH), 2.10–2.20 (m, 1H, 10 β -CH), 2.75–2.86 (m, 1H, 10a-CH), 3.09 (dd, 1H, $^2J = 17.5$ Hz, $^3J = 6.2$ Hz, 11 α -CH), 3.19 (dd, 1H, $^2J = 17.5$ Hz, $^3J = 2.0$ Hz, 11 β -CH), 3.85 (s, 3H, 4'-OMe), 4.01–4.10 (m, 1H, 9 α -CH), 4.16–4.24 (m, 1H, 9 β -CH), 5.68 (d, 1H, $^3J = 4.2$ Hz, 7a-CH), 6.94 (d, 1H, $^3J = 8.8$ Hz, 6-H), 6.96–7.00 (m, 2H, 3', H-5'-H), 7.48–7.54 (m, 2H, 2', H-6'-H), 7.96 (s, 1H, 2-H), 8.10 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.46, 27.72, 36.27, 55.34, 68.45, 100.86, 107.02, 113.95, 115.55, 118.49, 124.19, 124.79, 125.49, 130.11, 151.74, 155.39, 157.14, 159.57, 175.95 ppm; MS (CI): m/z 351.2 (MH^+ , 100). Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{O}_5$: C, 71.99; H, 5.18. Found: C, 72.17; H, 4.92.

3-(3,4-Dimethoxyphenyl)-9,10,10a,11-tetrahydro-4*H*,7*aH*-furo[2,3-*b*]pyrano[2,3-*f*]chromen-4-one (11b)

Pale yellow solid (29% yield); mp 193–195°C; IR (KBr) $\nu_{\max}$ 2900, 2843, 1637, 1607, 1510, 1437, 1398, 1290, 1244, 1057, 1025, 840 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.681.82 (m, 1H, 10 α -CH), 2.10–2.21 (m, 1H, 10 β -CH), 2.75–2.86 (m, 1H, 10a-CH), 3.09 (dd, 1H, $^2J = 17.5$, $^3J = 6.0$ Hz, 11 α -CH), 3.14–3.24 (m, 1H, 11 β -CH), 3.92 (s, 3H, 3'-OMe), 3.93 (s, 3H, 4'-OMe), 4.01–4.12 (m, 1H, 9 α -CH), 4.15–4.24 (m, 1H, 9 β -CH), 5.68 (d, 1H, $^3J = 4.1$ Hz, 7a-CH), 6.91–6.98 (m, 2H, 6, 5'-H), 7.03–7.09 (m, 1H, 6'-H), 7.22 (d, 1H, $^4J = 1.8$ Hz, 2'-H), 7.99 (s, 1H, 2-H), 8.10 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.47, 27.71, 36.26, 55.96, 55.99, 68.46, 100.87, 107.03, 111.15, 112.52, 115.65, 118.47, 121.01, 124.62, 124.85, 125.47, 148.76, 149.10, 151.94, 155.38, 157.21, 176.00 ppm; MS (CI): m/z 381.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_6$: C, 69.46; H, 5.30. Found: C 69.21; H, 5.01.

3-(1,3-Benzodioxol-5-yl)-9,10,10a,11-tetrahydro-4*H*,7*aH*-furo[2,3-*b*]pyrano[2,3-*f*]chromen-4-one (11c)

Pale yellow solid (64% yield); mp 203–205°C; IR (KBr) $\nu_{\max}$ 2986, 2903, 1641, 1600, 1490, 1435, 1245, 1226, 1056, 1032 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.67–1.81 (m, 1H, 10 α -CH), 2.10–2.20 (m, 1H, 10 β -CH), 2.75–2.86 (m, 1H, 10a-CH), 3.09 (dd, 1H, $^2J = 17.6$, $^3J = 6.2$ Hz, 11 α -CH), 3.19 (dd, 1H, $^2J = 17.6$, $^3J = 2.0$ Hz, 11 β -CH), 4.00–4.11 (m, 1H, 9 α -CH), 4.14–4.24 (m, 1H, 9 β -CH), 5.68 (d, 1H, $^3J = 4.2$ Hz, 7a-CH), 6.00 (s, 2H, OCH_2O), 6.87 (d, 1H, $^3J = 8.0$ Hz, 7'-H), 6.94 (d, 1H, $^3J = 8.8$ Hz, 6-H), 6.98 (dd, 1H, $^3J = 8.0$, $^4J = 1.7$ Hz, 6'-H), 7.10 (d, 1H, $^3J = 1.7$ Hz, 4'-H), 7.95 (s, 1H, 2-H), 8.09 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.46, 27.71, 36.26, 68.46, 100.87, 101.16, 107.04, 108.36, 109.75, 115.63, 118.41, 122.35, 124.93, 125.50, 125.64, 147.63, 147.66, 151.91, 155.37, 157.21, 175.79 ppm; MS (CI): m/z 365.1 (MH^+ , 100). Anal. Calcd. for $\text{C}_{21}\text{H}_{16}\text{O}_6$: C, 69.23; H, 4.43. Found: C 69.52; H, 4.18.

3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-9,10,10a,11-tetrahydro-4H,7aH-furo[2,3-b]pyrano[2,3-f]chromen-4-one (11d)

Pale yellow solid (75% yield); mp 188-189°C; IR (KBr) $\nu_{\max}$ 2936, 2862, 1656, 1611, 1512, 1437, 1281, 1219, 1198, 1138 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.68-1.82 (m, 1H, 10 α -CH), 2.09-2.20 (m, 1H, 10 β -CH), 2.75-2.86 (m, 1H, 10a-CH), 3.09 (dd, 1H, $^2J = 17.4$, $^3J = 6.4$ Hz, 11 α -CH), 3.19 (dd, 1H, $^2J = 17.4$, $^3J = 2.0$ Hz, 11 β -CH), 3.99-4.09 (m, 1H, 9 α -CH), 4.14-4.23 (m, 1H, 9 β -CH), 4.25-4.32 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 5.68 (d, 1H, $^3J = 4.2$ Hz, 7a-CH), 6.90-6.96 (m, 2H, 6, 8'-H), 7.04 (dd, 1H, $^3J = 8.3$, $^4J = 2.0$ Hz, 7'-H), 7.11 (d, 1H, $^3J = 2.0$ Hz, 2'-H), 7.94 (s, 1H, 7-H), 8.09 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.45, 27.70, 36.25, 64.32, 64.46, 68.45, 100.87, 107.05, 115.55, 117.25, 117.94, 118.46, 122.13, 124.63, 125.09, 125.48, 143.42, 143.69, 151.92, 155.35, 157.15, 175.79 ppm; MS (CI): m/z 379.2 (MH^+ , 100). Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{O}_6$: C, 69.84; H, 4.79. Found: C, 70.07; H, 4.95.

3-(4-Chlorophenyl)-9,10,10a,11-tetrahydro-4H,7aH-furo[2,3-b]pyrano[2,3-f]chromen-4-one (11e)

Pale yellow solid (55% yield); mp 194-195°C; IR (KBr) $\nu_{\max}$ 2961, 2899, 1637, 1598, 1492, 1438, 1377, 1244, 1092, 1064, 1012, 819 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.70-1.82 (m, 1H, 10 α -CH), 2.12-2.21 (m, 1H, 10 β -CH), 2.77-2.86 (m, 1H, 10a-CH), 3.09 (dd, 1H, $^2J = 17.5$, $^3J = 6.3$ Hz, 11 α -CH), 3.19 (dd, 1H, $^2J = 17.5$, $^3J = 2.0$ Hz, 11 β -CH), 4.02-4.11 (m, 1H, 9 α -CH), 4.16-4.25 (m, 1H, 9 β -CH), 5.69 (d, 1H, $^3J = 4.2$ Hz, 7a-CH), 6.96 (d, 1H, $^3J = 8.9$ Hz, 6-H), 7.39-7.44 (m, 2H, 3', 5'-H), 7.49-7.55 (m, 2H, 2', 6'-H), 7.99 (s, 1H, 2-H), 8.10 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.46, 27.70, 36.22, 68.48, 100.90, 107.10, 115.83, 118.38, 124.19, 125.50, 128.65, 130.22, 130.36, 134.15, 152.27, 155.42, 157.40, 175.50 ppm; MS (CI): m/z 355.2 (MH^+ , 100), 357.1 (MH^+ , 30). Anal. Calcd for $\text{C}_{20}\text{H}_{15}\text{ClO}_4$: C, 67.71; H, 4.26. Found: C, 67.55; H, 4.43.

2-Methyl-3-phenyl-9,10,10a,11-tetrahydro-4H,7aH-furo[2,3-b]pyrano[2,3-f]chromen-4-one (11 f)

Pale yellow solid (73% yield); mp 181-182°C; IR (KBr) $\nu_{\max}$ 2966, 2900, 1634, 1607, 1579, 1510, 1437, 1398, 1244, 1057, 840 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.70-1.83 (m, 1H, 10 α -CH), 2.11-2.21 (m, 1H, 10 β -CH), 2.32 (s, 3H, 2- CH_3), 2.75-2.85 (m, 1H, 10a-CH), 3.10 (dd, 1H, $^2J = 17.4$, $^3J = 6.1$ Hz, 11 α -CH), 3.21 (dd, 1H, $^2J = 17.4$, $^3J = 2.0$ Hz, 11 β -CH), 4.01-4.10 (m, 1H, 9 α -CH), 4.16-4.23 (m, 1H, 9 β -CH), 5.68 (d, 1H, $^3J = 4.2$ Hz, 7a-CH), 6.91 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.27-7.30 (m, 2H, 2', 6'-H), 7.46-7.34 (m, 3H, 3', 4', 5', H), 8.02 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.39, 19.52, 27.76, 36.31, 68.44, 100.84, 106.71, 115.15, 117.44, 123.38, 125.40, 127.68, 128.33, 130.42, 133.20, 155.01, 157.00, 162.28, 176.34 ppm; MS (CI): m/z 335.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{O}_4$: C, 75.43; H, 5.43. Found: C 75.85; H, 5.72.

3-(4-Methoxyphenyl)-2-methyl-9,10,10a,11-tetrahydro-4H,7aH-furo[2,3-b]pyrano[2,3-f]chromen-4-one (11g)

Pale yellow solid (62% yield); mp 227-229°C; IR (KBr) $\nu_{\max}$ 2900, 2825, 1634, 1607, 1510, 1437, 1398, 1290, 1244, 1057, 1025 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.68-1.82 (m, 1H,

10 α -CH), 2.09-2.20 (m, 1H, 10 β -CH), 2.33 (s, 3H, 2-CH₃), 2.74-2.85 (m, 1H, 10 α -CH), 3.09 (dd, 1H, ²*J* = 17.4, ³*J* = 6.2 Hz, 11 α -CH), 3.19 (dd, 1H, ²*J* = 17.4, ³*J* = 1.6 Hz, 11 β -CH), 3.85 (s, 3H, 4'-OMe), 4.00-4.09 (m, 1H, 9 α -CH), 4.15-4.22 (m, 1H, 9 β -CH), 5.67 (d, 1H, ³*J* = 4.2 Hz, 7 α -CH), 6.90 (d, 1H, ³*J* = 8.8 Hz, 6-H), 6.97 (d, 2H, ³*J* = 8.7 Hz, 3', 5'-H), 7.21 (d, 2H, ³*J* = 8.7 Hz, 2', 6'-H), 8.01 ppm (d, 1H, ³*J* = 8.8 Hz, 5-H); ¹³C NMR (400 MHz, CDCl₃) δ 19.41, 19.53, 27.78, 36.33, 55.29, 68.43, 100.84, 106.69, 113.87, 115.08, 117.43, 122.92, 125.31, 125.42, 131.55, 154.98, 156.94, 159.07, 162.22, 176.55 ppm; MS (CI): *m/z* 365.1 (MH⁺, 100). Anal. Calcd for C₂₂H₂₀O₅: C, 72.51; H, 5.53. Found: C, 72.80; H, 5.82.

3-(3,4-Dimethoxyphenyl)-2-methyl-9,10,10a,11-tetrahydro-4*H*,7*aH*-furo[2,3-*b*]pyrano[2,3-*f*]chromen-4-one (11h)

Pale yellow solid (56% yield); mp 217-219°C; IR (KBr) ν_{max} 2936, 2859, 1634, 1602, 1578, 1506, 1436, 1386, 1242, 1216, 1067 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.69-1.82 (m, 1H, 10 α -CH), 2.10-2.19 (m, 1H, 10 β -CH), 2.33 (s, 3H, 2-CH₃), 2.75-2.84 (m, 1H, 10 α -CH), 3.10 (dd, 1H, ²*J* = 17.5, ³*J* = 6.1 Hz, 11 α -CH), 3.20 (dd, 1H, ²*J* = 17.5, ²*J* = 2.0 Hz, 11 β -CH), 3.88 (s, 3H, 3'-OMe), 3.92 (s, 3H, 4'-OMe), 4.02-4.10 (m, 1H, 9 α -CH), 4.15-4.23 (m, 1H, 9 β -CH), 5.68 (d, 1H, ³*J* = 4.2 Hz, 7 α -CH), 6.80-6.83 (m, 2H, 2', 6'-H), 6.90 (d, 1H, ³*J* = 8.8 Hz, 6-H), 6.93 (d, 1H, ³*J* = 8.6 Hz, 5'-H), 8.02 ppm (d, 1H, ³*J* = 8.8 Hz, 5-H); ¹³C NMR (400 MHz, CDCl₃) δ 19.45, 19.53, 27.77, 36.32, 55.90, 55.92, 68.43, 100.85, 106.68, 111.18, 113.68, 115.16, 117.42, 122.80, 123.14, 125.41, 125.73, 148.60, 148.77, 154.99, 156.99, 162.44, 176.57 ppm; MS (CI): *m/z* 395.3 (MH⁺, 100). Anal. Calcd for C₂₃H₂₂O₆: C, 70.04; H, 5.62. Found: C, 69.85; H, 5.90.

3-(4-Chlorophenyl)-2-methyl-9,10,10a,11-tetrahydro-4*H*,7*aH*-furo[2,3-*b*]pyrano[2,3-*f*]chromen-4-one (11i)

Pale yellow solid (60% yield); mp 266-268°C; IR (KBr) ν_{max} 2971, 2903, 1641, 1605, 1582, 1491, 1438, 1399, 1251, 1088, 1068 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.69-1.83 (m, 1H, 10 α -CH), 2.11-2.20 (m, 1H, 10 β -CH), 2.32 (s, 3H, 2-CH₃), 2.75-2.85 (m, 1H, 10 α -CH), 3.10 (dd, 1H, ²*J* = 17.4, ³*J* = 6.3 Hz, 11 α -CH), 3.20 (dd, 1H, ²*J* = 17.4, ²*J* = 2.1 Hz, 11 β -CH), 4.02-4.11 (m, 1H, 9 α -CH), 4.16-4.23 (m, 1H, 9 β -CH), 5.68 (d, 1H, ³*J* = 4.2 Hz, 7 α -CH), 6.91 (d, 1H, ³*J* = 8.8 Hz, 6-H), 7.19-7.25 (m, 2H, 3', 5'-H), 7.38-7.44 (m, 2H, 2', 6'-H), 8.01 ppm (d, 1H, ³*J* = 8.8 Hz, 5-H); ¹³C NMR (400 MHz, CDCl₃) δ 19.38, 19.52, 27.74, 36.28, 68.45, 100.87, 106.75, 115.32, 117.27, 122.34, 125.38, 128.59, 131.65, 131.86, 133.71, 155.01, 157.16, 162.32, 176.10 ppm; MS (CI): *m/z* 369.1 (MH⁺, 100), 371.1 (MH⁺, 29). Anal. Calcd for C₂₁H₁₇ClO₄: C, 68.39; H, 4.65. Found: C, 68.70; H, 4.87.

3-(4-Methoxyphenyl)-11-methyl-6*a*,7,8,9*a*-tetrahydro-4*H*,6*H*-furo[2,3-*b*]pyrano[3,2-*g*]chromen-4-one (16a)

Pale yellow solid (27% yield); mp 155-157°C; IR (KBr) ν_{max} 2963, 2907, 1640, 1606, 1512, 1462, 1289, 1219, 1176, 1056 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.53-1.67 (m, 1H, 7 α -CH), 2.00-2.14 (m, 1H, 7 β -CH), 2.33 (s, 3H, 11-CH₃), 2.79-2.93 (m, 2H, 6 α -CH, 6 α -CH), 3.10 (dd, ²*J* = 16.4, ³*J* = 5.9 Hz, 1H, 6 β -CH), 3.83 (s, 3H, 4'-OCH₃), 3.88-3.98 (m, 2H, 8-CH₂), 5.83 (d, 1H, ³*J* = 5.1 Hz, 9 α -CH), 6.98 (d, 2H, ³*J* = 8.8 Hz, 3', 5'-H), 7.51 (d, 2H, ³*J* = 8.8 Hz, 2', 6'-H), 7.91 (s, 1H, 5-H), 8.00 ppm (s, 1H, 2-H); ¹³C NMR (100 MHz, CDCl₃) δ 8.20, 26.53, 27.97, 37.67, 55.34, 68.33, 102.87, 113.96, 118.62, 120.49, 123.20, 124.19,

124.49, 130.11, 152.27, 154.78, 155.98, 159.49, 176.33 ppm; MS (CI): m/z 365.3 (MH^+ , 100). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.80; H, 5.35.

3-(4-Methoxyphenyl)-2,11-methyl-6a,7,8,9a-tetrahydro-4H,6H-furo[2,3-b]pyrano[3,2-g]chromen-4-one (16g)

Pale yellow solid (24% yield); mp 155–157°C; IR (KBr) ν_{max} 2933, 2837, 1635, 1608, 1513, 1462, 1238, 1932 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.52–1.62 (m, 1H, 7 α -CH), 2.02–2.12 (m, 1H, 7 β -CH), 2.33, 2.35 (2s, 3H, 3H, 2, 11-CH₃), 2.80–2.91 (m, 2H, 6 α -CH, 6 α -CH), 3.09 (dd, $^2J = 16.0$, $^3J = 5.7$ Hz, 1H, 6 β -CH), 3.84 (s, 3H, 4'-OCH₃), 3.88–3.99 (m, 2H, 8-CH₂), 5.83 (d, 1H, $^3J = 5.3$ Hz, 9a-CH), 6.97 (d, 2H, $^3J = 8.6$ Hz, 3', 5'-H), 7.21 (d, 2H, $^3J = 8.6$ Hz, 2', 6'-H), 7.82 ppm (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.24, 19.50, 26.54, 28.03, 37.76, 55.29, 68.32, 102.91, 113.60, 113.88, 117.58, 120.15, 122.38, 123.09, 125.59, 131.59, 154.37, 155.79, 159.00, 162.77, 176.94 ppm; MS (CI): m/z 365.3 (MH^+ , 100). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.80; H, 5.35.

General procedure for synthesis of Diels-Alder adducts 12

To a solution of 2 mmol of **5** in 10 mL of DMF was added 2 mL (22 mmol, 11 eq) of 2H, 3,4-dihydropyran. The solution was refluxed for 36–40 h. The solvent and excess 2H,3,4-dihydropyran were evaporated *in vacuo*, and the residue was purified by chromatography with 1:50 methanol-dichloromethane to afford **12**.

3-(4-Methoxyphenyl)-10,11,11a,12-tetrahydro-4H,7aH,9H-dipyran[2,3-b:2',3'-f]chromen-4-one (12a)

Pale yellow solid (30% yield); mp 182–183°C; IR (KBr) ν_{max} 2966, 2933, 1636, 1598, 1511, 1437, 1248, 1205, 1178, 1090, 1029 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.47–1.92 (m, 4H, 10, 11-CH₂), 2.24–2.40 (m, 1H, 11a-CH), 2.90 (dd, 1H, $^2J = 17.4$ Hz, $^3J = 4.2$ Hz, 12 α -CH), 3.01 (dd, 1H, $^2J = 17.4$, $^3J = 6.1$ Hz, 12 β -CH), 3.75–3.82 (m, 1H, 9 α -CH), 3.85 (s, 3H, 4'-OMe), 3.95–4.09 (m, 1H, 9 β -CH), 5.44 (d, 1H, $^3J = 2.0$ Hz, 7a-CH), 6.93–7.02 (m, 3H, 6, 3', 5'-H), 7.50 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 7.96 (s, 1H, 2-H), 8.10 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.17, 23.57, 24.02, 30.62, 55.33, 62.58, 96.94, 107.86, 113.94, 115.27, 118.45, 124.19, 124.79, 125.29, 130.13, 151.79, 155.37, 157.15, 159.55, 176.07 ppm; MS (CI): m/z 365.1 (MH^+ , 100). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.38; H, 5.67.

3-(3,4-Dimethoxyphenyl)-10,11,11a,12-tetrahydro-4H,7aH,9H-dipyran[2,3-b:2',3'-f]chromen-4-one (12b)

Pale yellow solid (54% yield); mp 177–178°C; IR (KBr) ν_{max} 3076, 2925, 1642, 1600, 1515, 1436, 1267, 1249, 1139, 1090, 1023 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.61–1.82 (m, 4H, 10, 11-CH₂), 2.27–2.37 (m, 1H, 11a-CH), 2.91 (dd, 1H, $^2J = 17.3$, $^3J = 4.1$ Hz, 12 α -CH), 2.99 (dd, 1H, $^2J = 17.3$, $^3J = 6.1$ Hz, 12 β -CH), 3.76–3.83 (m, 1H, 9 α -CH), 3.92 (s, 3H, 3'-OMe), 3.93 (s, 3H, 4'-OMe), 4.00–4.08 (m, 1H, 9 β -CH), 5.45 (d, 1H, $^3J = 2.0$ Hz, 7a-CH), 6.93 (d, 1H, $^3J = 8.3$ Hz, 5'-H), 6.98 (d, 1H, $^3J = 8.9$ Hz, 6-H), 7.04 (dd, 1H, $^3J = 8.3$, $^4J = 2.0$ Hz, 6'-H), 7.22 (d, 1H, $^4J = 2.0$ Hz, 2'-H), 7.99 (s, 1H, 2-H), 8.09 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.15, 23.56, 24.05, 30.64, 55.96, 55.98, 62.61,

96.97, 107.89, 111.16, 112.55, 115.34, 118.46, 121.02, 124.67, 124.83, 125.26, 148.76, 149.10, 151.96, 155.35, 157.22, 176.06 ppm; MS (CI): m/z 395.3 (MH^+ , 100). Anal. Calcd for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 70.27; H, 5.90.

3-(1,3-Benzodioxol-5-yl)-10,11,11a,12-tetrahydro-4*H*,7*aH*,9*H*-dipyran[2,3-*b*:2',3'-*f*]chromen-4-one (12c)

Pale yellow solid (25% yield); mp 179-181°C; IR (KBr) ν_{max} 2925, 1637, 1599, 1434, 1247, 1142, 1033 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.68-1.84 (m, 4H, 10, 11- CH_2), 2.25-2.37 (m, 1H, 11a-CH), 2.83-3.08 (m, 2H, 12 α , 12 β -CH), 3.75-3.85 (m, 1H, 9 α -CH), 4.00-4.09 (m, 1H, 9 β -CH), 5.44 (d, 1H, $^3J = 2.4$ Hz, 7a-CH), 6.00 (s, 2H, OCH_2O), 6.88 (d, 1H, $^3J = 8.0$ Hz, 7'-H), 6.95-7.01 (m, 2H, 6, 6'-H), 7.10 (d, 1H, $^3J = 1.7$ Hz, 4'-H), 7.95 (s, 1H, 2-H), 8.09 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.19, 23.58, 24.05, 30.63, 62.58, 96.91, 101.11, 107.82, 108.31, 109.71, 115.29, 118.30, 122.31, 124.86, 125.23, 125.56, 147.53, 147.55, 151.88, 155.25, 157.13, 175.82 ppm; MS (CI): m/z 379.2 (MH^+ , 100). Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.84; H, 4.79. Found: C, 70.07; H, 4.61.

3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-10,11,11a,12-tetrahydro-4*H*,7*aH*,9*H*-dipyran[2,3-*b*:2',3'-*f*]chromen-4-one (12d)

Pale yellow solid (36% yield); mp 160-162°C; IR (KBr) ν_{max} 2943, 2924, 2860, 1635, 1599, 1507, 1436, 1303, 1287, 1249, 1091 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.67-1.82 (m, 4H, 10, 11- CH_2), 2.27-2.35 (m, 1H, 11a-CH), 2.91 (dd, 1H, $^2J = 17.3$, $^3J = 4.1$ Hz, 12 α -CH), 2.99 (dd, 1H, $^2J = 17.3$, $^3J = 6.1$ Hz, 12 β -CH), 3.75-3.83 (m, 1H, 9 α -CH), 4.00-4.09 (m, 1H, 9 β -CH), 4.27-4.31 (m, 4H, OCH_2CH_2O), 5.44 (d, 1H, $^3J = 2.4$ Hz, 7a-CH), 6.93 (d, 1H, $^3J = 8.3$ Hz, 8'-H), 6.97 (d, 1H, $^3J = 8.9$ Hz, 6-H), 7.03 (dd, 1H, $^3J = 8.3$, $^4J = 2.1$ Hz, 7'-H), 7.10 (d, 1H, $^4J = 2.1$ Hz, 5'-H), 7.94 (s, 1H, 2-H), 8.09 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.19, 23.58, 24.01, 30.63, 62.56, 64.32, 64.46, 96.94, 107.85, 115.27, 117.28, 117.96, 118.45, 122.18, 124.67, 125.12, 125.32, 143.42, 143.68, 151.93, 155.33, 157.17, 175.90 ppm; MS (CI): m/z 393.2 (MH^+ , 100). Anal. Calcd for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.15; H, 5.40.

3-(4-Chlorophenyl)-10,11,11a,12-tetrahydro-4*H*,7*aH*,9*H*-dipyran[2,3-*b*:2',3'-*f*]chromen-4-one (12e)

Pale yellow solid (19% yield); mp 195-197°C; IR (KBr) ν_{max} 2930, 1643, 1597, 1437, 1256, 1206, 1094, 826 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.67-1.84 (m, 4H, 10, 11- CH_2), 2.28-2.38 (m, 1H, 11a-CH), 2.85-3.07 (m, 2H, 12 α , 12 β -CH), 3.76-3.85 (m, 1H, 9 α -CH), 3.99-4.11 (m, 1H, 9 β -CH), 5.45 (d, 1H, $^3J = 2.4$ Hz, 7a-CH), 6.99 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.42 (d, 2H, $^3J = 8.7$ Hz, 3', 5'-H), 7.52 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 7.99 (s, 1H, 2-H), 8.09 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.20, 23.59, 24.05, 30.61, 62.60, 96.93, 107.89, 115.47, 118.33, 124.13, 125.25, 128.60, 130.16, 130.32, 134.06, 152.16, 155.28, 157.28, 175.27 ppm; MS (CI): m/z 369.2 (MH^+ , 100), 371.2 (MH^+ , 25). Anal. Calcd for $C_{21}H_{17}ClO_4$: C, 68.39; H, 4.65. Found: C, 68.17; H, 4.43.

2-Methyl-3-phenyl-10,11,11a,12-tetrahydro-4H,7aH,9H-dipyran[2,3-b:2',3'-f]chromen-4-one (12f)

Pale yellow solid (33% yield); mp 165-167°C; IR (KBr) $\nu_{\max}$ 2927, 1626, 1600, 1440, 1400, 1255, 1139, 1090 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.66-1.81 (m, 4H, 10, 11- CH_2), 2.32 (s, 4H, 2- CH_3 , 11a-CH), 2.86-3.08 (m, 2H, 12 α , 12 β -CH), 3.75-3.86 (m, 1H, 9 α -CH), 4.01-4.11 (m, 1H, 9 β -CH), 5.45 (d, 1H, $^3J = 2.4$ Hz, 7a-CH), 6.94 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.28-7.32 (m, 2H, 2', 6'-H), 7.36 (t, 1H, $^3J = 7.3$ Hz, 4'-H), 7.44 (t, 2H, $^3J = 7.3$ Hz, 3', 5'-H), 8.02 ppm (d, 1H, $^3J = 8.9$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.43, 23.24, 23.62, 24.09, 30.72, 62.58, 96.86, 107.44, 114.77, 117.37, 123.30, 125.15, 127.59, 128.25, 130.36, 133.16, 154.87, 156.87, 162.15, 176.26 ppm; MS (CI): m/z 349.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_4$: C, 75.84; H, 5.79. Found: C, 76.01; H, 5.95.

3-(4-Methoxyphenyl)-2-methyl-10,11,11a,12-tetrahydro-4H,7aH,9H-dipyran[2,3-b:2',3'-f]chromen-4-one (12g)

Pale yellow solid (34% yield); mp 199-200°C; IR (KBr) $\nu_{\max}$ 2931, 2901, 1637, 1606, 1510, 1440, 1397, 1255, 1243, 1136, 1091, 1030 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.61-1.82 (m, 4H, 10, 11- CH_2), 2.28-2.35 (m, 4H, 2- CH_3 , 11a-CH), 2.92 (dd, 1H, $^2J = 17.3$, $^3J = 4.2$ Hz, 12 α -CH), 3.00 (dd, 1H, $^2J = 17.3$, $^3J = 6.3$ Hz, 12 β -CH), 3.76-3.83 (m, 1H, 9 α -CH), 3.85 (s, 3H, 4'-OMe), 4.00-4.10 (m, 1H, 9 β -CH), 5.44 (d, 1H, $^3J = 2.2$ Hz, 7a-CH), 6.93 (d, 1H, $^3J = 8.8$ Hz, 6-H), 6.97 (d, 2H, $^3J = 8.7$ Hz, 3', 5'-H), 7.21 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 8.01 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.41, 23.18, 23.58, 24.06, 30.69, 55.28, 62.59, 96.90, 107.48, 113.84, 114.76, 117.38, 122.88, 125.19, 125.32, 131.55, 154.94, 156.91, 159.02, 162.25, 176.63 ppm; MS (CI): m/z 379.3 (MH^+ , 100). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{O}_5$: C, 73.00; H, 5.86. Found: C, 73.18; H, 6.02.

3-(3,4-Dimethoxyphenyl)-2-methyl-10,11,11a,12-tetrahydro-4H,7aH,9H-dipyran[2,3-b:2',3'-f]chromen-4-one (12h)

Pale yellow solid (15% yield); mp 209-210°C; IR (KBr) $\nu_{\max}$ 2934, 1636, 1581, 1513, 1438, 1394, 1258, 1138 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.56-1.82 (m, 4H, 10, 11- CH_2), 2.27-2.35 (m, 4H, 2- CH_3 , 11a-CH), 2.98 (dd, 1H, $^2J = 17.2$, $^3J = 4.4$ Hz, 12 α -CH), 3.00 (dd, 1H, $^2J = 17.2$, $^3J = 6.3$ Hz, 12 β -CH), 3.75-3.83 (m, 1H, 9 α -CH), 3.88 (s, 3H, 3'-OMe), 3.92 (s, 3H, 4'-OMe), 4.00-4.10 (m, 1H, 9 β -CH), 5.44 (d, 1H, $^3J = 2.4$ Hz, 7a-CH), 6.79-6.83 (m, 2H, 2', 6'-H), 6.91-6.95 (m, 2H, 6, 5'-H), 8.02 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.45, 23.17, 23.57, 24.08, 30.69, 55.90, 55.91, 62.61, 96.93, 107.51, 111.17, 113.68, 114.86, 117.37, 122.81, 123.12, 125.19, 125.76, 148.58, 148.76, 154.97, 156.99, 162.51, 176.68 ppm; MS (CI): m/z 409.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{O}_6$: C, 70.58; H, 5.92. Found: C, 70.69; H, 6.17.

3-(4-Chlorophenyl)-2-methyl-10,11,11a,12-tetrahydro-4H,7aH,9H-dipyran[2,3-b:2',3'-f]chromen-4-one (12i)

Pale yellow solid (15% yield); mp 205-206°C; IR (KBr) $\nu_{\max}$ 2927, 1635, 1605, 1439, 1398, 1257, 1139, 1094, 895 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.82-1.64 (m, 4H, 10, 11- CH_2), 2.28-2.37 (m, 4H, 2- CH_3 , 11a-CH), 2.84-3.07 (m, 2H, 12 α , 12 β -CH), 3.75-3.84 (m, 1H, 9 α -CH), 4.00-4.10 (m, 1H, 9 β -CH), 5.44 (d, 1H, $^3J = 2.5$ Hz, 7a-CH), 6.95 (d, 1H, $^3J = 8.8$

Hz, 6-H), 7.20-7.25 (m, 2H, 2', 6'-H), 7.38-7.43 (m, 2H, 3', 5'-H), 8.01 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 19.38, 23.12, 23.51, 24.03, 30.60, 62.59, 96.90, 107.55, 115.03, 117.15, 122.27, 125.16, 128.57, 131.59, 131.83, 133.67, 154.96, 157.15, 162.44, 176.20 ppm; MS (CI): m/z 383.2 (MH^+ , 100), 385.2 (MH^+ , 25). Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{ClO}_3$: C, 72.03; H, 5.22. Found: C, 72.31; H, 5.43.

General procedure for synthesis of pyranoxanthenediones **13** and **17**

To a solution of 1 mmol of **5** or **7** was added 1.25 mmol (1.25 eq) of 3-(*N,N*-dimethylamino)-5,5-dimethylcyclohex-2-en-1-one in 10 mL of DMF. The solution was refluxed for 4 h. The mixture was diluted with 20 mL of methanol, and the precipitate was collected by filtration and re-crystallized from DMF-methanol to afford **13** or **17**.

3-(4-Methoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-4*H*,11*H*-pyrano[2,3-*a*]xanthene-4,11-dione (**13a**)

Beige solid (92% yield); mp 223-225°C; IR (KBr) ν_{max} 2949, 1647, 1606, 1511, 1438, 1237, 1032 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.10 (s, 6H, 9- CH_3), 2.33 (s, 2H, 10- CH_2), 2.53 (2, 2H, 8- CH_2), 3.52 (s, 2H, 12- CH_2), 3.81 (s, 3H, 4'- OCH_3), 7.01 (d, 2H, $^3J = 8.6$, 3', 5'-H), 7.18 (d, 1H, d , $^3J = 8.8$, 6-H), 7.54 (d, 2H, $^3J = 8.6$, 2', 6'-H), 8.00 (d, 2H, $^3J = 8.8$, 5-H), 8.50 ppm (s, 1H, 2-H); ^{13}C NMR (125 MHz, CDCl_3 and $\text{DMSO}-d_6$ 1:1) δ 16.01, 27.89, 31.67, 40.57, 50.07, 54.80, 107.61, 109.39, 113.36, 113.84, 120.34, 123.22, 124.36, 124.84, 129.51, 151.86, 152.47, 153.99, 159.01, 163.63, 174.96, 196.87 ppm; MS (CI): m/z 403.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{25}\text{H}_{22}\text{O}_5$: C, 74.61; H, 5.51. Found: C, 74.47; H, 5.27.

3-(3,4-Dimethoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-4*H*,11*H*-pyrano[2,3-*a*]xanthene-4,11-dione (**13b**)

Beige solid (75% yield); mp 196-198°C; IR (KBr) ν_{max} 2955, 1654, 1640, 1516, 1440, 1261, 1237, 1195 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.17 (s, 6H, 9- CH_3), 2.39 (s, 2H, 10- CH_2), 2.50 (s, 2H, 8- CH_2), 3.65 (s, 2H, 12- CH_2), 3.93, 3.94 (2s, 6H, 3', 4'- OCH_3), 6.94 (d, 1H, $^3J = 8.3$ Hz, 5'-H), 7.02-7.10 (m, 2H, 6, 6'-H), 7.21 (d, 1H, $^4J = 1.8$ Hz, 2'-H), 8.04 (s, 1H, 2-H), 8.15 ppm (d, 1H, $^3J = 8.3$ Hz, 5-H); ^{13}C NMR (400 MHz, CDCl_3) δ 16.51, 28.42, 32.20, 41.17, 50.60, 55.94, 55.96, 108.31, 109.99, 111.18, 112.39, 114.45, 121.02, 121.07, 124.17, 125.20, 125.60, 148.80, 149.24, 152.51, 153.12, 154.62, 164.28, 175.76, 197.69 ppm; MS (CI): m/z 433.3 (MH^+ , 100). Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{O}_6$: C, 72.21; H, 5.59. Found: C, 72.49; H, 5.22.

3-(1,3-Benzodioxol-5-yl)-9,9-dimethyl-8,9,10,12-tetrahydro-4*H*,11*H*-pyrano[2,3-*a*]xanthene-4,11-dione (**13c**)

Beige solid (80% yield); mp 258-260°C; IR (KBr) ν_{max} 2950, 2897, 1649, 1599, 1429, 1240, 1194, 1037 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.17 (s, 6H, 9- CH_3), 2.39 (s, 2H, 10- CH_2), 2.50 (s, 2H, 8- CH_2), 3.64 (s, 2H, c, 12- CH_2), 6.00 (s, 2H, OCH_2O), 6.88 (d, 1H, $^3J = 8.0$ Hz, 5'-H), 6.99 (dd, 1H, $^4J = 1.7$ Hz, $^3J = 8.0$ Hz, 6'-H), 7.05 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.10 (d, 1H, $^4J = 1.7$ Hz, 2'-H), 8.00 (s, 1H, 2-H), 8.15 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.52, 28.43, 32.21, 41.19, 50.61, 101.22, 108.33, 108.45, 109.71, 110.01, 114.46, 120.99, 122.42, 125.23, 125.32, 125.69, 147.74, 147.81, 152.49,

153.15, 154.65, 164.28, 175.62, 197.69 ppm; MS (CI): m/z 417.3 (MH^+ , 100). Anal. Calcd for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 72.29; H, 5.11.

2,9,9-trimethyl-3-phenyl-8,9,10,12-tetrahydro-4H,11H-pyrano[2,3-a]xanthene-4,11-dione (13f)

Beige solid (84% yield); mp 265-266°C; IR (KBr) ν_{max} 3047, 2947, 2885, 1646, 1590, 1390, 1235, 1215, 700 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 6H, 9-CH₃), 2.35 (s, 3H, 2-CH₃), 2.40 (s, 2H, 10-CH₂), 2.51 (s, 2H, 8-CH₂), 3.66 (s, 2H, 12-CH₂), 7.01 (d, 1H, $^3J = 8.8$ Hz, 6-H), 7.26-7.30 (m, 2H, 2', 6'-H), 7.35-7.40 (m, 1H, 4'-H), 7.41-7.47 (m, 2H, 3', 5'-H), 8.08 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.48, 19.55, 28.42, 32.20, 41.22, 50.64, 108.34, 109.56, 113.99, 120.04, 123.73, 125.56, 127.85, 128.41, 130.34, 132.82, 152.94, 154.29, 163.30, 164.46, 176.08, 197.89 ppm; MS (CI): m/z 387.3 (MH^+ , 100). Anal. Calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74. Found: C, 77.92; H, 5.88.

3-(4-Methoxyphenyl)-2,9,9-trimethyl-8,9,10,12-tetrahydro 4H,11H-pyrano[2,3--a]xanthene-4,11-dione (13g)

Beige solid (90% yield); mp 236-237°C; IR (KBr) ν_{max} 2958, 2890, 1653, 1586, 1515, 1440, 1393, 1239, 1174, 1026 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 6H, 9-CH₃), 2.32 (s, 3H, 2-CH₃), 2.36 (s, 2H, 10-CH₂), 2.47 (s, 2H, 8-CH₂), 3.62 (s, 2H, 12-CH₂), 3.82 (s, 3H, 4'-OCH₃), 6.92-6.99 (m, 3H, 6, 3', 5'-H), 7.15-7.21 (m, 2H, 2', 6'-H), 8.04 ppm (d, 1H, $^3J = 8.8$ Hz, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.47, 19.56, 28.42, 32.19, 41.23, 50.65, 55.28, 108.36, 109.52, 113.92, 113.93, 120.02, 123.28, 124.91, 125.56, 131.50, 152.90, 154.26, 159.17, 163.25, 164.46, 176.30, 197.86 ppm; MS (CI): m/z 417.3 (MH^+ , 100). Anal. Calcd for $C_{26}H_{24}O_5$: C, 74.98; H, 5.81. Found: C, 74.70; H, 6.10.

3-(4-Methoxyphenyl)-9,9,12-trimethyl-6,8,9,10-tetrahydro-4H,7H-pyrano[3,2-b]xanthene-4,7-dione (17a)

Beige solid (80% yield); mp 230-232°C; IR (KBr) ν_{max} 3079, 2958, 2835, 1645, 1612, 1514, 1463, 1391, 1296, 1220, 1179 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H, 9-CH₃), 2.35 (s, 2H, 8-CH₂), 2.39 (s, 3H, 12-CH₃), 2.52 (s, 2H, 10-CH₂), 3.62 (s, 2H, 6-CH₂), 3.84 (s, 3H, 4'-OCH₃), 6.97 (d, 2H, $^3J = 8.8$ Hz, 3', 5'-H), 7.50 (d, 2H, $^3J = 8.8$ Hz, 2', 6'-H), 7.96 (s, 1H, 5-H), 8.00 ppm (s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.32, 20.97, 28.45, 32.20, 41.29, 50.62, 55.34, 109.16, 113.99, 114.18, 118.85, 120.88, 124.05, 124.16, 124.49, 130.05, 151.43, 152.48, 153.96, 159.62, 163.91, 175.92, 197.56 ppm; MS (CI): m/z 417.3 (MH^+ , 100). Anal. Calcd for $C_{26}H_{14}O_5$: C, 74.98; H, 5.81. Found: C, 75.22; H, 5.64.

3-(4-Methoxyphenyl)-2,9,9,12-tetramethyl-6,8,9,10-tetrahydro-4H,7H-pyrano[3,2-b]xanthene-4,7-dione (17g)

Beige solid (72% yield); mp 270-272°C; IR (KBr) ν_{max} 2954, 2878, 1642, 1609, 1395, 1238, 1220, 1142 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H, 9-CH₃), 2.34 (s, 3H, 2-CH₃), 2.36 (s, 2H, 8-CH₂), 2.40 (s, 3H, 12-CH₃), 2.52 (2H, 10-CH₂), 3.61 (s, 2H, 6-CH₂), 3.85 (s, 3H, 4'-OCH₃), 6.97 (d, 2H, $^3J = 8.7$ Hz, 3', 5'-H), 7.20 (d, 2H, $^3J = 8.7$ Hz, 2', 6'-H), 7.89 ppm (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.33, 19.54, 20.95, 28.47, 32.20, 41.33, 50.63, 55.29, 109.19, 113.70, 113.91, 118.35, 119.84, 122.75, 124.08, 125.16,

131.54, 151.26, 153.58, 159.11, 163.11, 163.96, 176.53, 197.61 ppm; MS (CI): m/z 431.1 (MH⁺, 100). Anal. Calcd for C₂₇H₂₆O₅: C, 75.33; H, 6.09. Found: C, 75.52; H, 5.87.

General procedure for synthesis of Diels-Alder adducts 14 and 15

To a solution of 2 mmol of **5** in 10 mL of DMF was added 2.2 mmol (1.1 eq) of 1-morpholinocyclopentene or 1-morpholinocyclohexene. The mixture was heated at 154°C for 4 h. The solvent was evaporated in vacuo, and residue was chromatographed using 1:50 methanol-dichloromethane to afford **14** or **15**.

7-Hydroxy-3-(4-methoxyphenyl)-2-methyl-8-[(2-oxocyclopentyl)methyl]-4H-chromen-4-one (14g)

Pale yellow solid (58% yield); mp 210-211°C; IR (KBr) $\nu_{\max}$ 2960, 1735, 1631, 1580, 1512, 1436, 1291, 1244 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.62-2.25 (m, 4H, 4'', 5''-CH₂), 2.33 (s, 3H, 2-CH₃), 2.38-2.63 (m, 2H, 3''-CH₂), 3.01-3.17 (m, 2H, 8-CH₂), 3.37-3.74 (m, 1H, 1''-H), 3.84 (s, 3H, 4'-OCH₃), 6.91-7.00 (m, 3H, 6, 3', 5'-H), 7.21 (d, 2H, ³J = 8.6 Hz, 2', 6'-H), 7.99 ppm (d, 1H, ³J = 8.7 Hz, 5-H); ¹³C NMR (125 MHz, DMSO-d₆) δ 19.15, 20.05, 22.40, 28.91, 37.40, 48.03, 55.04, 113.25, 113.43, 113.69, 115.56, 121.25, 124.27, 125.31, 131.67, 155.07, 158.46, 159.94, 162.29, 175.36, 219.25 ppm; MS (CI): m/z 379.1 (MH⁺, 100). Anal. Calcd for C₂₃H₂₂O₅: C, 73.00; H, 5.86. Found: C, 73.26; H, 5.62.

3-(3,4-Dimethoxyphenyl)-7-hydroxy-2-methyl-8-[(2-oxocyclopentyl)methyl]-4H-chromen-4-one (14h)

Pale yellow solid (53% yield); mp 88-90°C; IR (KBr) $\nu_{\max}$ 2924, 1736, 1633, 1515, 1440, 1265 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 1.51-2.07 (m, 4H, 4'', 5''-CH₂), 2.27 (s, 3H, 2-CH₃), 2.66-3.16 (m, 4H, 8, 3''-CH₂), 3.36-3.60 (m, 1H, 1''-H), 3.74, 3.79 (2s, 6H, 3', 4'-OCH₃), 6.74-6.88 (m, 2H, 2', 6'-H), 6.93-7.03 (m, 2H, 6, 5'-H), 7.76 (d, 1H, ³J = 8.7 Hz, 5-H), 10.64 ppm (s, 1H, 7-OH); ¹³C NMR (125 MHz, DMSO-d₆) δ 19.63, 20.47, 29.33, 37.83, 48.43, 55.93, 55.97, 111.89, 113.68, 114.12, 114.80, 116.05, 122.01, 123.24, 124.70, 126.17, 148.54, 148.68, 155.50, 160.34, 162.85, 175.75, 219.65 ppm; MS (CI): m/z 409.2 (MH⁺, 100). Anal. Calcd for C₂₄H₂₄O₆: C, 70.58; H, 5.92. Found: C, 70.28; H, 6.18.

7a-Hydroxy-3-(4-methoxyphenyl)-8,9,10,11,11a,12-hexahydro-4H,7aH-pyrano[2,3-a]xanthen-4-one (15a)

Pale yellow solid (91% yield); mp 222-223°C; IR (KBr) $\nu_{\max}$ 2987, 1613, 1513, 1439, 1251, 1030 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.30-2.18 (m, 9H, 8, 9, 10, 11-CH₂, 11a-CH), 2.35-3.26 (m, 2H, 12-CH₂), 3.85 (s, 3H, 4'-OCH₃), 6.81-6.89 (m, 1H, 6-H), 6.98 (d, 2H, ³J = 8.6 Hz, 3', 5'-H), 7.51 (d, 2H, ³J = 8.6 Hz, 2', 6'-H), 7.96 (s, 1H, 2-H), 8.02-8.09 ppm (m, 1H, 5-H); ¹³C NMR (125 MHz, DMSO-d₆) δ 21.82 (21.73), 22.82 (23.00), 24.93 (24.30), 29.11 (28.59), 36.33 (35.45), 37.51 (37.28), 55.13, 98.10 (97.70), 111.20 (108.97), 113.58, 115.63 (115.65), 117.11 (117.33), 123.13 (123.18), 123.84, 124.16, 130.06 (130.08), 153.15, 154.26 (154.95), 156.84 (156.37), 158.96, 174.88 (174.86) ppm; MS (CI): m/z 349.2 (MH⁺, 100). Anal. Calcd for C₂₃H₂₂O₅: C, 73.00; H, 5.86. Found: C, 72.71; H, 5.98.

3-(3,4-Dimethoxyphenyl)-7a-hydroxy-8,9,10,11,11a,12-hexahydro-4H,7aH-pyrano[2,3-a]xanthen-4-one (15b)

Pale yellow solid (85% yield); mp 214-216°C; IR (KBr) $\nu_{\max}$ 2930, 1629, 1612, 1516, 1439, 1263, 1143, 1027 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 1.40-2.62 (m, 9H, 8, 9, 10, 11-CH₂, 11a-CH), 2.70-3.60 (m, 2H, 12-CH₂), 3.75 (s, 6H, 3', 4'-OCH₃), 6.84-6.99, 7.07-7.19 (2m, 4H, 6, 2', 5', 6'-H), 7.81-7.87 (m, 1H, 5-H), 8.42, 8.43 ppm (2s, 1H, 2-H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 22.22 (22.13), 23.25 (23.42), 25.35 (24.73), 29.54 (29.02), 36.76 (35.87), 37.94 (37.71), 55.96, 55.96, 98.54 (98.13), 109.39 (109.30), 111.95 (111.62), 113.17, 116.10 (116.07), 117.56 (117.78), 121.63 (121.66), 123.63 (123.63), 124.28, 124.90 (124.91), 148.68, 149.03, 153.79, 154.63 (155.32), 157.27 (156.79), 175.28 (175.26) ppm; MS (CI): m/z 409.2 (MH^+ , 100). Anal. Calcd for C₂₄H₄O₆: C, 70.58; H, 5.92. Found: C, 70.31; H, 6.21.

3-(1,3-Benzodioxol-5-yl)-7a-hydroxy-8,9,10,11,11a,12-hexahydro-4H,7aH-pyrano[2,3-a]xanthen-4-one (15c)

Pale yellow solid (76% yield); mp 197-197°C; IR (KBr) $\nu_{\max}$ 2937, 1630, 1587, 1435, 1251, 1027 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 1.23-2.62 (m, 9H, 8, 9, 10, 11-CH₂, 11a-CH), 2.70-3.60 (m, 2H, 12-CH₂), 6.05 (s, 2H, OCH₂O), 6.88-7.18 (2m, 4H, 6, 2', 5', 6'-H), 7.81-7.99 (m, 1H, 5-H), 8.41, 8.45 ppm (2s, 1H, 2-H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 22.24 (22.14), 23.24 (23.42), 25.35 (24.72), 29.53 (29.02), 36.76 (35.88), 37.95 (37.70), 98.56 (98.15), 101.45, 108.51, 109.83 (109.86), 111.65, 116.13 (116.10), 117.49 (117.72), 122.81 (122.84), 123.58 (123.63), 124.29, 126.11 (126.13), 147.34, 147.41, 153.86 (153.64), 154.64 (155.33), 157.32 (156.86), 175.16 (175.15) ppm; MS (CI): m/z 393.2 (MH^+ , 100). Anal. Calcd for C₂₃H₂₀O₆: C, 70.40; H, 5.14. Found: C, 70.14; H, 4.85.

7a-Hydroxy-3-(4-methoxyphenyl)-2-methyl-8,9,10,11,11a,12-hexahydro-4H,7aH-pyrano[2,3-a]xanthen-4-one (15g)

Pale yellow solid (69% yield); mp 212-213°C; IR (KBr) $\nu_{\max}$ 2924, 1632, 1608, 1514, 1435, 1251, 1177 cm^{-1} ; ^1H NMR (400 MHz, CDCl₃) δ 1.57-2.17 (m, 9H, 8, 9, 10, 11-CH₂, 11a-CH), 2.33 (s, 3H, 2-CH₃), 2.54-3.27 (m, 2H, 12-CH₂), 3.85 (s, 3H, 4'-OCH₃), 6.70-6.81 (m, 1H, 6-H), 6.97 (d, 2H, 3J = 8.5 Hz, 3', 5'-H), 7.21 (d, 2H, 3J = 8.5 Hz, 2', 6'-H), 7.87-7.97 ppm (m, 1H, 5-H); ^{13}C NMR (400 MHz, CDCl₃) δ 19.43 (19.44), 22.12 (21.97), 23.09 (23.34), 25.51 (24.92), 29.44 (29.13), 36.64 (38.54), 37.80 (37.85), 55.29, 97.93 (97.76), 110.68 (108.50), 113.85, 115.24 (115.21), 116.93 (117.14), 122.74 (122.77), 124.61 (124.70), 125.50 (125.51), 131.61, 154.48 (155.18), 155.81 (156.39), 159.02, 162.51 (162.51), 177.10 (177.07) ppm; MS (CI): m/z 393.2 (MH^+ , 100). Anal. Calcd for C₂₄H₂₄O₅: C, 73.45; H, 6.16. Found: C, 73.18; H, 6.42.

3-(3,4-Dimethoxyphenyl)-7a-hydroxy-2-methyl-8,9,10,11,11a,12-hexahydro-4H,7aH-pyrano[2,3-a]xanthen-4-one (15h)

Pale yellow solid (51% yield); mp 193-194°C; IR (KBr) $\nu_{\max}$ 2938, 1631, 1610, 1577, 1514, 1437, 1264, 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl₃) δ 1.30-2.16 (m, 9H, 8, 9, 10, 11-CH₂, 11a-CH), 2.34 (s, 3H, 2-CH₃), 2.53-3.28 (m, 2H, 12-CH₂), 3.88, 3.92 (2s, 6H, 3', 4'-OCH₃), 6.62-6.99 (m, 1H, 6-H), 6.78-6.86, 6.90-6.96 (2m, 3H, 2', 5', 6'-H), 7.84-7.92 ppm (m, 1H,

5-H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 19.19 (19.21), 21.76 (21.69), 22.80 (22.99), 24.96 (24.32), 29.10 (28.59), 36.36 (35.46), 37.57 (37.31), 55.47, 55.50, 97.97 (97.58), 110.87 (108.64), 111.41, 114.31, 115.20 (115.17), 116.05 (116.27), 122.02 (122.08), 122.80, 123.64, 125.65 (125.67), 148.13, 148.22, 153.81 (154.50), 156.65 (156.16), 162.53, 175.20 (175.17) ppm; MS (CI): m/z 423.2 (MH^+ , 100). Anal. Calcd for $\text{C}_{25}\text{H}_{26}\text{O}_6$: C, 71.07; H, 6.20. Found: C, 71.33; H, 6.07.

Cell Proliferation Assay

PC-3 human prostate cancer cells were grown in Dulbecco's Modified Eagle Medium Nutrient Mixture F-12 (DMEM/F-12 HAM) (Sigma D8437) with 10% Fetal Bovine Serum (Atlanta Biological S11150). For cell proliferation assays, 3.5×10^4 cells per well were placed into 12-well plates. After 1 d, $10 \mu\text{M}$ of each compound was added to each well. DMSO was used as a control. The experiments were performed in triplicate. Cell viability and number were analyzed using Vi-Cell XR Cell Viability Analyzer (Beckman Coulter) as previously described.^[8a] Inhibition data represents the mean $\pm$ SD for at least three experiments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]a). Mohler JL, Gregory CW, Ford OH, Kim D, Weaver CM, Petrusz P, Wilson EM, French FS. Clin. Cancer Res. 2004; 10:440–448. [PubMed: 14760063] b) Titus MA, Schell MJ, Lih FB, Tomer KB, Mohler JL. Clin. Cancer Res. 2005; 11:4653–4657. [PubMed: 16000557]
- [2]a). Njar VCO, Hector M, Hartmann RW. Bioorg. Med. Chem. 1996; 4:1447–1453. [PubMed: 8894102] b) Attard G, Reid AHM, A'Hern R, Parker C, Oommen NB, Folkerd E, Messiou C, Molife LR, Maier G, Thompson E, Olmos D, Sinha R, Lee G, Dowsett M, Kaye SB, Dearnaley D, Kheoh T, Molina A, de Bono JS. J. Clin. Oncol. 2009; 27:3742–3748. [PubMed: 19470933] c) Jarman M, Barrie SE, Llera JM. J. Med. Chem. 1998; 41:5375–5381. [PubMed: 9876107] d) Purushottamachar P, Khandelwal A, Vasaitis TS, Bruno RD, Gediya LK, Njar VCO. Bioorg. Med. Chem. 2008; 16:3519–3529. [PubMed: 18316193]
- [3]a). Attard G, Reid AHM, Yap TA, Raynaud F, Dowsett M, Settatre S, Barrett M, Parker C, Martins V, Folkerd E, Clark J, Cooper CS, Kaye SB, Dearnaley D, Lee G, de Bono JS. J. Clin. Oncol. 2008; 26:4563–4571. [PubMed: 18645193] b) de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Flechon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI. N. Engl. J. Med. 2011; 364:1995–2005. [PubMed: 21612468] c) Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PFA, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttman H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin M-E, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE. N. Engl. J. Med. 2013; 368:138–148. [PubMed: 23228172]

- [4]. Siegel R, Ma J, Zou Z, Jemal A. *CA Cancer J. Clin.* 2014; 64:9–29. [PubMed: 24399786]
- [5]. Fiandalo MV, Wilton J, Mohler JL. *Int. J. Biol. Sci.* 2014; 10:596–601. [PubMed: 24948872]
- [6]a). Munro IC, Harwood M, Hlywka JJ, Stephen AM, Doull J, Flamm WG, Adlercreutz H. *Nutr. Rev.* 2003; 61:1–33. [PubMed: 12638461] b) Adlercreutz H. *Scand. J. Clin. Lab. Invest.* 1990; 50:3–23.c) Andres S, Abraham K, Appel KE, Lampen A. *Crit. Rev. Toxicol.* 2011; 41:463–506. [PubMed: 21438720]
- [7]. Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. *J. Nutr.* 2007; 137:1769–1775. [PubMed: 17585029]
- [8]a). Zhang W, Sviripa V, Chen X, Shi J, Yu T, Hamza A, Ward ND, Kril LM, Vander Kooi CW, Zhan C-G, Evers BM, Watt DS, Liu C. *ACS Chem. Biol.* 2013; 8:796–803. [PubMed: 23363077] b) Burikhanov R, Sviripa VM, Hebbar N, Zhang W, Layton WJ, Hamza A, Zhan C-G, Watt DS, Liu C, Rangnekar VM. *Nat. Chem. Biol.* 2014; 10:924–926. [PubMed: 25218743]
- [9]a). Zhang W, Sviripa V, Kril LM, Chen X, Yu T, Shi J, Rychahou P, Evers BM, Watt DS, Liu C. *J. Med. Chem.* 2011; 54:1288–1297. [PubMed: 21291235] b) Sviripa VM, Zhang W, Balia AG, Tsodikov OV, Nickell JR, Gizard F, Yu T, Lee EY, Dwoskin LP, Liu C, Watt DS. *J. Med. Chem.* 2014; 57:6083–6091. [PubMed: 24950374]
- [10]a). Sandulache A, Silva AMS, Cavaleiro JAS. *Tetrahedron.* 2002; 58:105–114.b) Kamble RM, Ramana MMV. *Can. J. Chem.* 2010; 88:1233–1239.c) Valiulin RA, Arisco TM, Kutateladze AG. *J. Org. Chem.* 2011; 76:1319–1332. [PubMed: 21268619] d) Cremins PJ, Saengchantara ST, Wallace TW. *Tetrahedron.* 1987; 43:3075–3082.e) Hsung RP. *J. Org. Chem.* 1997; 62:7904–7905. [PubMed: 11671885]
- [11]a). Von Strandtmann M, Cohen MP, Shavel J. *J. Heterocyclic Chem.* 1970; 7:1311–1319.b) Osyanin VA, Ivleva EA, Klimochkin YN. *Synth. Commun.* 2012; 42:1832–1847.c) Gardner PD, Rafsanjani HS, Rand L. *J. Am. Chem. Soc.* 1959; 81:3364–3367.d) Osyanin VA, Osipov DV, Klimochkin YN. *J. Org. Chem.* 2013; 78:5505–5520. [PubMed: 23668240]
- [12]a). Kumbaraci V, Ergunes D, Midilli M, Begen S, Talinli N. *J. Heterocyclic Chem.* 2009; 46:226–230.b) Shaikh, A. k.; Cobb, AJA.; Varvounis, G. *Org. Lett.* 2012; 14:584–587. [PubMed: 22233235] c) Bray CD. *Org. Biomol. Chem.* 2008; 6:2815–2819. [PubMed: 18633540] d) René L. *Synthesis.* 1989; 1989:69–70.e) Rodriguez R, Adlington RM, Moses JE, Cowley A. *J. E. Baldwin Org. Lett.* 2004; 6:3617–3619.
- [13]. Sugimoto H, Nakamura S, Ohwada T. *Adv. Synth. Catal.* 2007; 349:669–679.
- [14]a). Wu X, Liu X, Jiang G, Lin Y, Chan W, Vrijmoed LLP. *Chem. Nat. Compd.* 2005; 41:27–29.b) Wu XY, Liu XH, Lin YC, Luo JH, She ZG, Houjin L, Chan WL, Antus S, Kurtan T, Elsässer B, Krohn K. *Eur. J. Org. Chem.* 2005; 2005:4061–4064.c) Lin Y, Wu X, Feng S, Jiang G, Luo J, Zhou S, Vrijmoed LLP, Jones EBG, Krohn K, Steingröver K, Zsila F. *J. Org. Chem.* 2001; 66:6252–6256. [PubMed: 11559170] d) Li Z-X, Chen J-W, Yuan F, Huang Y-Y, Zhao L-Y, Li J, Su H-X, Liu J, Pang J-Y, Lin Y-C, Lu X-L, Pei Z, Wang G-L, Guan Y-Y. *Marine Drugs.* 2013; 11:504–522. [PubMed: 23429283] e) Liu X, Xu F, Zhang Y, Liu L, Huang H, Cai X, Lin Y. *W. Chan, Russ. Chem. Bull.* 2006; 55:1091–1092.
- [15]. Frasinuk M, Mrug GP, Bondarenko SP, Sviripa VM, Zhang W, Cai X, Fiandalo M, Mohler JL, Liu C, Watt D. *Org. Biomol. Chem.* 2015; 13:11292–11301. [PubMed: 26416505]

Figure 1. Naturally occurring isoflavones daidzein (**1a**) and genistein (**1b**), and synthetic isoflavonoids **2** and **3**.

Figure 2.

Diels-Alder adducts **11-17** derived from thermal reactions of Mannich bases **5** or **7** with various dienophiles

Scheme 1.

Regioselective modification of 7-hydroxyisoflavones **4** and 7-hydroxy-8-methylisoflavones

6. Reagents and conditions: a) $CH_2(NMe)_2$, *i*-PrOH, 80°C, 2-4 h, 68-91% yields; b) $CH_2(NMe)_2$, dioxane, 100°C, 16 h, 72-99% yields

Scheme 2.

Diels-Alder reaction of N,N-dimethylaminoisoflavones **5** and **7** with dienophiles *Reagents and conditions*: a) 2,3-dihydrofuran, DMF, reflux; 24-40 h; b) 3,4-dihydro-2*H*-pyran, DMF, reflux; 36-40 h; c) 3-(dimethylamino)-5,5-dimethylcyclohex-2-en-1-one, DMF, reflux; 4 h; d) 4-cyclopent-1-en-1-yl morpholine, DMF, reflux; 4 h; e) 4-cyclohex-1-en-1-yl morpholine, DMF, reflux; 4 h

Scheme 3.

Regioselective modification of 7-hydroxyisoflavones **5** and 7-hydroxy-8-methylisoflavones

7. Reagents and conditions: a) CH₂(NMe)₂, *i*-PrOH, 80°C, 2-4 h; b) CH₂(NMe)₂, dioxane, 100°C, 16 h

Table 1

Isolated yields of Diels-Alder adducts **11-17** from the reaction of dienophiles and *ortho*-quinone methides derived from **5** and **7**

Substrate	Dienophile	Solvent, Temperature and Time	Diels-Alder Adduct	Isolated Yield (%)
5a	2,3-dihydrofuran	DMF, 154°C, 24 h	11a	70
5a	3,4-dihydro-2H-pyran	DMF, 154°C, 36 h	12a	30
5a		1,4-dioxane, 100°C, 12 h	13a [a]	81
5a		toluene, 110°C, 12h	13a [a]	68
5a		2-methoxyethanol, 124°C, 8 h	13a [a]	69
5a		DMSO, 160°C, 4 h	13a [a]	71
5a		DMF, 154°C, 4 h	13a [a]	92
5a		DMF, 154°C, 16 h	15a [b]	91
5b	2,3-dihydrofuran	DMF, 154°C, 40 h	11b	29
5b	3,4-dihydro-2H-pyran	DMF, 154°C, 40 h	12b	55
5b		DMF, 154°C, 4 h	13b [a]	75

Substrate	Dienophile	Solvent, Temperature and Time	Diels-Alder Adduct	Isolated Yield (%)
5b		DMF, 154°C, 4 h	15b ^[b]	85
6c	2,3-dihydrofuran	DMF, 154°C, 36 h	11c	64
5c	3,4-dihydro-2H-pyran	DMF, 154°C, 40 h	12c	25
5c		DMF, 154°C, 4 h	13c ^[a]	81
5c		DMF, 154°C, 4 h	15c ^[b]	76
6d	2,3-dihydrofuran	DMF, 154°C, 36 h	11d	75
5d	3,4-dihydro-2H-pyran	DMF, 154°C, 40 h	12d	36
6e	2,3-dihydrofuran	DMF, 154°C, 24 h	11e	55
5e	3,4-dihydro-2H-pyran	DMF, 154°C, 36 h	12e	19
5f	2,3-dihydrofuran	DMF, 154°C, 40 h	11f	73
5f	3,4-dihydro-2H-pyran	DMF, 154°C, 38 h	12f	33
5f		DMF, 154°C, 4 h	13f ^[a]	84
5g	2,3-dihydrofuran	DMF, 154°C, 24 h	11g	62
5g	3,4-dihydro-2H-pyran	DMF, 154°C, 40 h	12g	34
5g		DMF, 154°C, 4 h	13g ^[a]	81
5g		DMF, 154°C, 4 h	14g ^[b]	58

Substrate	Dienophile	Solvent, Temperature and Time	Diels-Alder Adduct	Isolated Yield (%)
5g		DMF, 154°C, 4 h	15g ^[b]	69
5h	2,3-dihydro-furan	DMF, 154°C, 30 h	11h	56
5h	3,4-dihydro-2H-pyran	DMF, 154°C, 36 h	12h	15
5h		DMF, 154°C, 4 h	14h ^[b]	53
5h		DMF, 154°C, 4 h	15h ^[b]	51
5i	2,3-dihydro-furan	DMF, 154°C, 40 h	11i	60
5i	3,4-dihydro-2H-pyran	DMF, 154°C, 40 h	12i	15
7a	2,3-dihydro-furan	DMF, 154°C, 16 h	16a	27
7a		DMF, 154°C, 4 h	17a	80
7g	2,3-dihydro-furan	DMF, 154°C, 16 h	16g	46
7g		DMF, 154°C, 4 h	17g	72

^[a]Product of elimination of dimethylamine;

^[b]Product of hydrolysis of hemi-aminals

Table 2

Isolated yields of Diels-Alder adducts **13a,g** from the reaction of 3-(N,N-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one and precursors of *ortho*-quinone methides in DMF at 154°C, 4 h

Subst- rate	Substituents on Isoflavonoid		Diels-Alder Adduct	Isolated Yield (%)
	X	Y		
5a	H	NMe ₂	13a	92
5g	H	NMe ₂	13g	81
18a	H	OH	13a	96
18g	H	OH	13g	88
19a	H	OMe	13a	84
19g	H	OMe	13g	78
20a	Ac	OAc	13a	87
20g	Ac	OAc	13g	74

Table 3

Percent inhibition of PC-3 proliferation by some isoflavonoid-based Diels-Alder adducts

Isoflavonoid Diels-Alder Adduct	Substituents on Isoflavonoid		Inhibition ^[a] at 10 μ M (%)	Cell Diameter (microns) [^{a,b}]
	C-2	C-3		
Genistein (1b)	H	C ₆ H ₄ OH-4	46 $\pm$ 4.5	17.41 $\pm$ 0.46
11a	H	C ₆ H ₄ OMe-4	62 $\pm$ 7	16.43 $\pm$ 0.19
11c	H	C ₆ H ₃ (OCH ₂ O)-3,4	47 $\pm$ 4	16.37 $\pm$ 0.34
11e	H	C ₆ H ₄ Cl-4	63 $\pm$ 10	16.50 $\pm$ 0.19
12a	H	C ₆ H ₄ OMe-4	73 $\pm$ 6	17.08 $\pm$ 0.34
12b	H	C ₆ H ₃ (OMe) ₂ -3,4	35 $\pm$ 10	16.56 $\pm$ 0.17
12c	H	C ₆ H ₃ (OCH ₂ O)-3,4	68 $\pm$ 0.5	16.39 $\pm$ 0.11
12d	H	C ₆ H ₃ (OCH ₂ CH ₂ O) -3,4	48 $\pm$ 3	16.50 $\pm$ 0.29
12e	H	C ₆ H ₄ Cl-4	44 $\pm$ 4	16.53 $\pm$ 0.08
12g	Me	C ₆ H ₄ OMe-4	62 $\pm$ 0.4	17.08 $\pm$ 0.27
12h	Me	C ₆ H ₃ (OMe) ₂ -3,4	44 $\pm$ 3	16.55 $\pm$ 0.18
12i	Me	C ₆ H ₄ Cl-4	74 $\pm$ 3	16.30 $\pm$ 0.35
13b	H	C ₆ H ₃ (OMe) ₂ -3,4	86 $\pm$ 1	13.68 $\pm$ 0.74
15a	H	C ₆ H ₄ OMe-4	30 $\pm$ 15	17.25 $\pm$ 1.03
15b	H	C ₆ H ₃ (OMe) ₂ -3,4	56 $\pm$ 5	17.11 $\pm$ 0.17
15g	Me	C ₆ H ₄ OMe-4	78 $\pm$ 1	17.11 $\pm$ 0.45
16a	H	C ₆ H ₄ OMe-4	78 $\pm$ 3	15.89 $\pm$ 0.10
16g	Me	C ₆ H ₄ OMe-4	61 $\pm$ 2	16.77 $\pm$ 0.59

^[a] mean $\pm$ SD for at least three experiments;^[b] 16.24 $\pm$ 0.34 for DMSO alone