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# Extended Aromatic and Heteroaromatic Ring Systems in the Chalcone-Flavanone Molecular Switch Scaffold

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*KEYWORDS – molecular switch, chemoswitchable, pH dependent switch, chalcone, flavanone, isomerism*

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**ABSTRACT:** Previous work on the o-hydroxychalcone/flavanone molecular switching scaffold showed that simple substitutions alter the pH range in which rapid interconversion occurs. Herein, more impactful structural modifications were performed via alteration of the characteristic phenyl rings to alternative aromatic systems. It was determined that the scaffold was still viable after these changes and that the range of accessible midpoint pH values was markedly increased. To further explore the switch's scope, scaffolds able to have multiple switching events were also investigated.

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A molecular switch is a molecule that can be reversibly biased between two states – usually conformational – upon exposure to an external stimulus.[1] Molecular switches are an important class of molecules to study due to their wide range of potential applications, including smart materials, protein-folding mimics, and chemical sensors.[2-5]

Molecular switches can be described as either photoswitchable[6-15] or chemoswitchable,[2-5,16-18] which refers to the stimulus that instigates the change in state (Figure 1). A defining feature of our scaffold is the incorporation of a reversible covalent bond, an area of molecular switch research that has seen significant contributions from Fischer[19] and Hirshberg,[19,20] Kelly,[21-23] Branchaud,[24,25] and Feringa.[6,7] The popular photoswitchable azobenzenes,[8-14] for example, utilize an isomeric change, from *cis* to *trans* (Figure 1A). Other switches, such as Aprahamian's hydrazone chemoswitches (Figure 1B) or Hamilton's diphenylacetylenes[2-4] stabilize each of the two interconvertible conformational states by intramolecular hydrogen bonding.

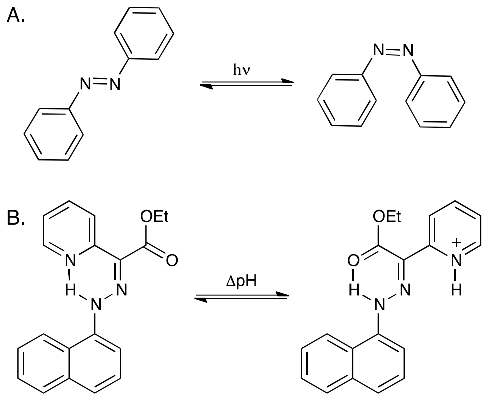

Figure 1. Examples of current molecular switches: A) photoswitchable azobenzene scaffold[8-14] and B) chemoswitchable hydrazone[5,16] based molecular switch.

*ortho*-Hydroxychalcone (1a) is a naturally occurring molecule that can undergo reversible isomerization to its flavanone isomer (2a, Figure 2). *o*-Hydroxychalcone/flavanone isomerization has been well-studied in the past,[26-34] but its utility as a covalent molecular switch scaffold has only recently been explored.[35,38] The most important feature of this scaffold is that it incorporates the reversible formation of a covalent bond. The presence of this reversible covalent bond instills rigidity to the molecule and creates a truly binary switching system. A big advantage of this easy-to-access scaffold is that starting materials are relatively low-cost and a wide range of derivatives are commercially available.

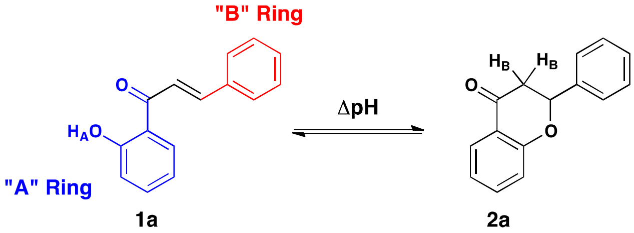

Figure 2. The reversible isomerism between *ortho*-hydroxychalcone (**1a**) and flavanone (**2a**) can be controlled through a change in pH. The acidities of protons $H_A$ and $H_B$ have a significant impact on the switching activity.

The isomerization between chalcone and flavanone is controlled by a change in pH. In aqueous solution, flavanone **2a** is favored below pH 10 and appears pale yellow. Above pH 13, the chalconate of 1a is in solution exclusively and exhibits a characteristic orange to red color.[29] Between these pH values there is rapid interconversion, with equilibrium concentrations shifting as a function as pH. The midpoint pH is defined as the pH at which there is a 1:1 ratio of chalcone and flavanone in solution, and this metric has been used to compare structural derivatives of the chalcone/flavanone switch.[35,38] The midpoint pH can be conveniently obtained by analyzing the sigmoidal curve formed by plotting the measured UV/Vis absorbance vs. pH as we have outlined in our previous works.[35]

The midpoint pH is believed to be dependent on the $pK_a$ values of key protons found at two locations on the molecule, $H_A$ and $H_B$ (Figure 2). Previous studies queried how this midpoint pH shifted as a result of mono substitution on one or both the A/B rings and how these changes were connected to the electronics of the molecule. We have shown that mono/disubstitution can be employed to predictably impact the overall midpoint pH of isomerization.

The parent scaffold has a midpoint pH of 11.46; to this point, we have been able to depress this value to as low as 10.26.[38] Ideally, the chalcone/flavanone interconversion would take place much closer to neutral pH, as this would enable the facile application of this switch in the biological realm in manners similar to existing switches. For example, Wooley's azobenzene scaffolds have been used to activate or deactivate a protein complex depending on the switch's conformation;[36] Aprahamian has used his switch as a fluorescent super-gelation material for the detection of biologically relevant amines.[37]

Our aims herein are to further probe the system by drastically altering the core scaffold to see 1) if it still undergoes reversible pH-dependent isomerization and 2) to see in what way and how significantly the midpoint pH will be affected. To achieve this, we have focused on altering the identities of the A and B rings to variable aromatic systems and synthesizing di-switch scaffolds.

*Alteration of Benzaldehyde Identity*

To determine how each ring's identity affects the overall function of the switching scaffold, the "B" ring was varied from a benzene ring to several other arenes (Figure 3). Previously, it has been shown that the addition of a functional group to the benzaldehyde ring had minor effects on the overall midpoint pH of the molecule; we now find that changing the identity of the ring has a significant influence on the midpoint pH.

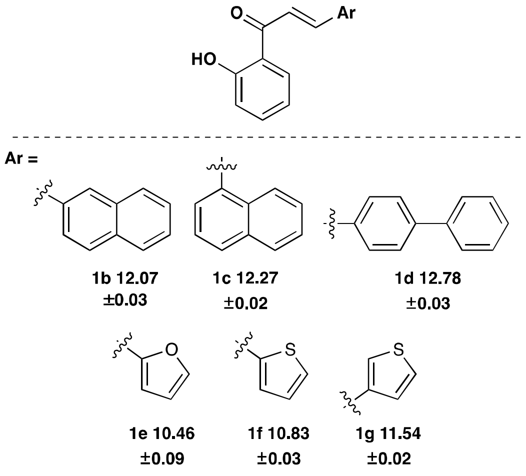

Figure 3. Synthesized 2-hydroxychalcones with alternate aromatics at "B" ring. The value below each image is the experimental midpoint pH.

When comparing the aromatic hydrocarbon moieties, larger π systems (i.e. those seen in **1b**, **1c**, and **1d**) cause the midpoint pH to rise as far as 1.32 pH units from the parent scaffold (**1a/2a**); this can be attributed to their increased electron donor capacity causing an increase in the pKa of $H_B$.[28] Replacement of the B ring with a smaller heteroarene (furan or thiophene), causes the midpoint pH of the scaffold to drastically decrease (**1e-1g**) by lowering the $pK_a$ of $H_B$ via inductive electron density withdrawal as compared to a phenyl ring.[39] The furthest shift downward is seen when using a 2-furan ring (**1e**), which results in a midpoint pH of 10.46 – one full pH unit lower than the parent chalcone (11.46). The variance in midpoint pH between the 2- and 3-thiophene derivatives (**1f, 1g**) is due to the change in proximity of the sulfur atom to the conjugated system. When the sulfur atom is closer to $H_B$, its inductive effect is greater and thus the midpoint pH is lower (10.83 vs. 11.54).

### *"B" Ring Alteration and "A" Ring Substitution*

In our previous work, we showed that the chalcone/flavanone molecular switch tolerates substitution on each of its aromatic rings and that these substitutions have a predictable effect on the midpoint pH. It was shown that chalcones with disubstitution exhibited an additive effect where the midpoint pH of each could be predicted by adding the net changes caused by each single substituent. To further examine the tolerance and predictability of functional group substitutions and with the hopes of observing a record-low midpoint pH, we produced "A"-ring substituted chalcones bearing smaller heteroaromatic "B" rings (Figure 4).

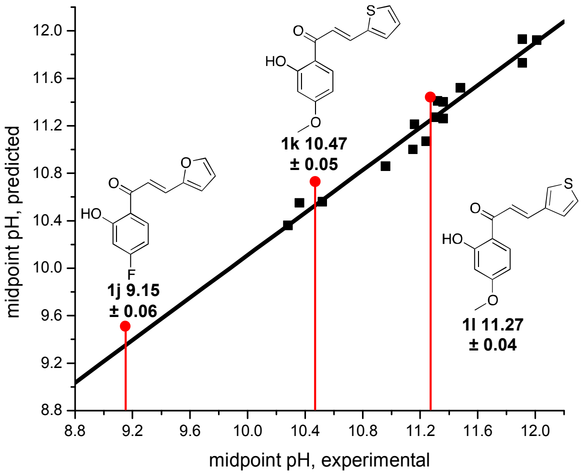

Figure 4. Experimental vs. predicted midpoint pH values of **1j-1k** are compared to previously published disubstituted chalcones. Predicted values are determined by adding the net changes caused by a single structural modification (substitution or aryl replacement).

Compounds **1j-l** are all consistent with the substitution effects observed in our previous work. It was shown that a 4'-flouro or 4'-methoxy substituent dropped the midpoint pH by approximately 0.96 and 0.10, respectively, when added to the parent compound. Introducing these same substituents to the heteroaromatic variants resulted in a similar and predicted midpoint pH shift. By exploiting these findings, we have achieved our lowest midpoint pH to date: Compound **1j** has an experimental midpoint pH of 9.15, a 2.31 pH unit decrease from **1a**. This value was achieved by incorporating the highest impact modifications found for each ring ("A" ring and "B" ring) into the same molecule.

### *Alteration of Acetophenone Identity*

In order to further gauge the ability of this molecular switch scaffold to tolerate large structural modification, compounds with an extended "A" ring system were synthesized (Figure 5). The findings show that changing the "A" ring from an acetophenone to a naphthanone does not hinder the molecule's ability to undergo interconversion. We find that the positioning of substitution causes an almost equal but opposite deviation from the parent midpoint pH value: **1i** increased by 0.33 and **1h** decreased by 0.42.

It has been our hypothesis that the pKa value for the key acidic protons, $H_A$ and $H_B$, in the chalcone/flavanone scaffold play a pivotal role in determining the midpoint pH for interconversion. The pKa values for the corresponding protons of 1-naphthol and 2-naphthol in water are 9.34 and 9.51 respectively.[40,41] The pKa of the 1'-hydroxy analogue is lower than that of the 2'-hydroxy, so it is expected that the midpoint pH will be lower and, indeed, this is the case.

To compare the midpoint pH data obtained for **1h** and **1i** to **1a**, the acidities of each phenolic proton in water are examined. Compound **1a** has an "A" ring that is comparable to the structure of phenol, **1h** similar to 1-naphthol, and **1i** similar to 2-naphthol (Figure 5). If the midpoint pH was solely dependent on the $pK_a$ of the $H_A$, the parent chalcone would have a higher midpoint pH than both of the naphthalene derivatives. This is not what is observed, supporting our hypothesis that additional factors can contribute to the switching activity of this system. Specifically in the case of **1i**, the deleterious steric interaction caused by the bulky ring system when the molecule is in the chalcone form is alleviated when the molecule adopts the flavanone form, which may explain why the midpoint pH is higher than expected.

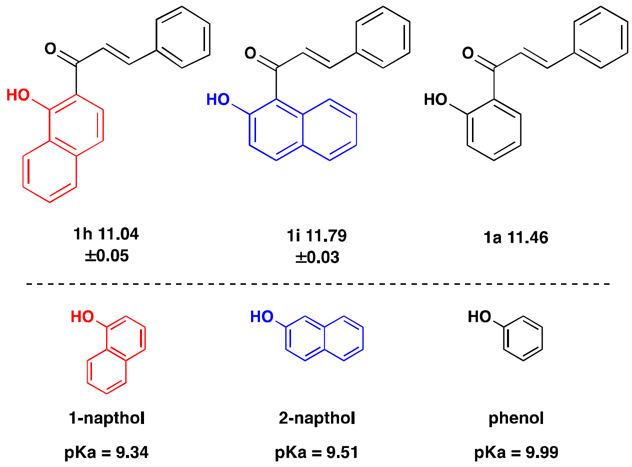

Figure 5. The A-ring substituted hydroxynapthanones' and parent compound's midpoint pHs are compared to the corresponding napthols and phenol pKa in water.[40,41]

*Multichalcone Scaffolds*

To determine whether the scaffold could undergo multiple switching events and what these events might do to the midpoint pH multichalcone scaffolds were synthesized (Figure 6). Multichalcones are structures that contain two instances of the molecular switch on the same molecule. In the same fashion as previously discussed, the midpoint pH values of these molecules were determined.

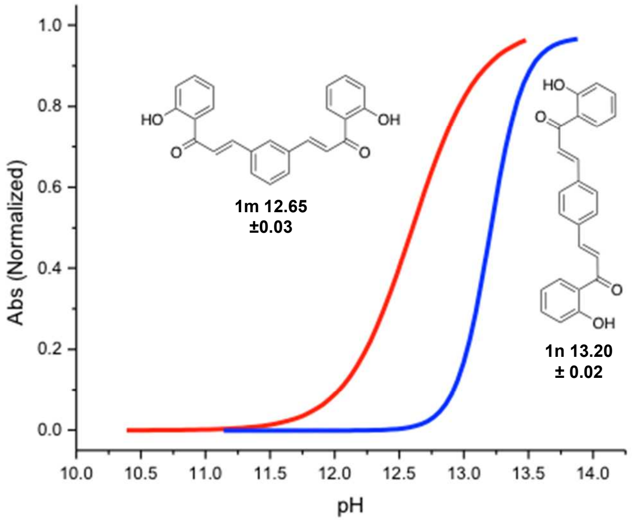

Figure 6. The normalized UV-Vis data sigmoids for each synthesized multichalcone scaffold are shown along with their experimental midpoint pH values.

It was found that both the *meta*- (**1m**) and *para*-dichalcone (**1n**) derivatives demonstrated a significantly higher midpoint pH (12.65 and 13.20, respectively) than the single switch scaffold (11.46). As seen in the extended aromatics of the B ring, this upward shift in midpoint pH is due to an overall increase in the amount of electron density in the molecule, specifically at $H_B$.

It is worth noting that when performing the UV-Vis data analysis there was no indication of partial isomerization, as we do not observe multiple steps in the overall sigmoidal curve for each instance of switching (Figure 6). This data suggests that there is no pH at which the molecule containing one chalcone and one flavanone is favorable.

This work demonstrates the versatility and robustness of the chalcone/flavanone scaffold as a chemosensitive covalent molecular switch. The molecular switch remained fully functional after incorporation of alternative aromatic rings and also tolerated expansion to a multichalcone system.  As a result of these manipulations, the achievable range of midpoint pH values has expanded in both directions, currently spanning from 9.15 (**1j**) to 13.20 (**1n**).

Our previous studies showed that a single substitution on the “B” ring had little to no effect on the overall midpoint pH of the scaffold. However, this work suggests that $H_B$ plays a much larger role in the isomerization equilibrium than previously thought. The pKa of $H_B$ is more strongly influenced by the electronics of the B ring than a simple substitution on the traditional phenyl ring; this can be seen in both the midpoint pH and in the UV/Vis spectra (Figure 7).

Finally, we have shown that the chalcone/flavanone scaffold remains predictable, tunable, and controllable after undergoing large structural changes. These findings highlight the scaffold’s potential for use as a molecular switch and we aim to exploit our findings to provide further utility.

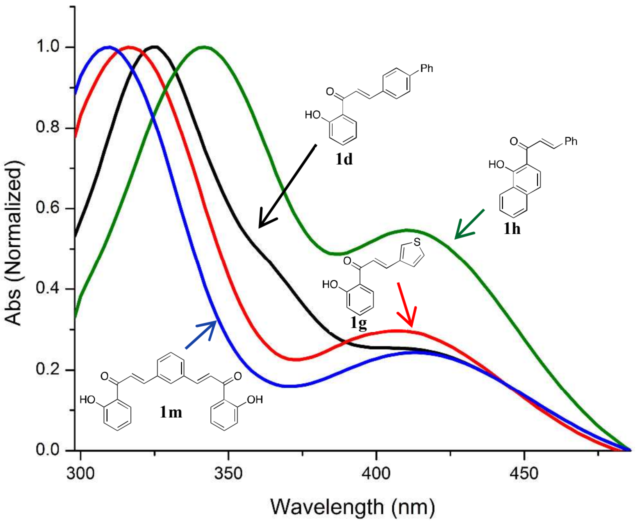

Figure 7. The normalized absorbance data for selected compounds, highlighting the impact of “B” ring alteration on UV/Vis absorbance.

## EXPERIMENTAL SECTION

### General Considerations

Chemical shifts are reported relative to residual $CHCl_3$ (δ 7.24 ppm for $^1H$, δ 77.23 ppm for $^{13}C$). Buffers for the UV/Vis studies were prepared as described in Robinson and Stokes's "Electrolyte solutions" (1970) and the pH was measured immediately prior to use. HRMS analysis was done using EI+ injection method on a magnetic sector mass analyzer.

*General Procedure A*

To a 25 mL round-bottomed flask containing a magnetic stirbar was added sequentially 1 mmol of the appropriate acetophenone, 2 mL of ethanol, 1 mmol of the required benzaldehyde, and 2 mL of 6 M aqueous NaOH. The resulting solution was allowed to stir for 24 hours at a constant temperature, after which the solution was acidified at room temperature with aqueous 1 M HCl. The mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were dried over magnesium sulfate. After filtration and concentration, the chalcones were purified via flash column chromatography using a hexane/ethyl ether eluent. Reported yields represent isolated yields from a single, unoptimized run.

*General Procedure B*

To a 10 mL round-bottomed flask containing a magnetic stirbar was added sequentially 1 mmol of the appropriate acetophenone, 2 mL of methanol, 1.1 mmol of the required benzaldehyde, and 0.3 mmol of piperidine. The resulting solution was allowed to stir at reflux (85°C) for 24 hours, after which the solution was acidified at room temperature with aqueous 1 M HCl. The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic layers were dried over magnesium sulfate. After filtration and concentration, the chalcones were purified via flash column chromatography using a hexane/ethyl acetate eluent. Reported yields represent isolated yields from a single, unoptimized run.

*General Procedure C*

To a 500 mL round-bottomed flask containing a stirbar was added sequentially 30 mg of representative chalcone, 100 mL of methanol, 50 mL of previously prepared 12.00 pH buffer solution, and 25 mL of distilled, deionized water. The resulting solution was stirred at room temperature until all chalcone was dissolved. To this stirring solution was added 0.5 mL aliquots of 1 M HCl until the final pH of the solution was 1 pH unit below the determined midpoint pH and the resulting mixture was allowed to stir overnight, after which the solution was acidified at room temperature with aqueous 1 M HCl. The methanol in solution was reduced and the resulting aqueous portion was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were dried over magnesium sulfate. After filtration and concentration, the flavanone was isolated via flash column chromatography using a hexane/ethyl acetate eluent. Reported yields represent isolated yields from a single, unoptimized run.

*General Procedure D*

To a 500 mL round-bottomed flask containing a stirbar was added sequentially 30 mg of representative flavanone, 100 mL of methanol, 50 mL of previously prepared 12.00 pH buffer solution, and 25 mL of distilled, deionized water. The resulting solution was stirred at room temperature until all chalcone was dissolved. To this stirring solution was added 0.5 mL aliquots of 1 M NaOH until the final pH of the solution was 1 pH unit above the determined midpoint pH and the resulting mixture was allowed to stir overnight, after which the solution was acidified at room temperature with aqueous 1 M HCl. The methanol in solution was reduced and the resulting aqueous portion was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were dried over magnesium sulfate. After filtration and concentration, the chalcone was isolated via flash column chromatography using a hexane/ethyl acetate eluent. Reported yields represent isolated yields from a single, unoptimized run.

*Preparation of Stock pH 12.00 Buffer Solution*

Equal parts of aqueous 0.2 M $NaHCO_3$, 0.2 M $Na_2PO_4$, and 0.2 M KCl solutions were mixed together in a large stock bottle. An aqueous solution of 0.2M NaOH was added to the mixture while stirring to increase the pH of the overall solution to 12.00 as monitored by pH meter.

***E*)-1-(2-hydroxyphenyl)-3-(naphthalen-2-yl)prop-2-en-1-one (1b)**[42] Prepared via General Procedure A, 85%, $^1H$ NMR (300 MHz, $CDCl_3$) δ 12.89 (300 MHz, $CDCl_3$) δ 12.89 (s, 1H), 8.06 (d, J = 15.7 Hz, 1H), 8.02 (s, 1H), 7.95 (dd, J = 8.1, 1.6 Hz, 1H), 7.89-7.83 (m, 3H), 7.77 (dd, J = 8.5, 1.7 Hz, 1H), 7.73 (d, J = 15.4 Hz, 1H), 7.55-7.47 (m, 3H), 7.04 (dd, J = 8.4, 1.1 Hz, 1H), 6.95 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H) $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 193.9, 163.8, 145.8, 136.6, 134.8, 133.5, 132.3, 131.3, 129.9, 129.0, 128.9, 128.0, 127.8, 127.1, 123.9, 120.4, 120.3, 119.1, 118.9; IR (Neat) 3050, 2360, 2342, 1637, 1578, 1508, 1487, 1443, 1397, 1345, 1307, 1279, 1450, 1235, 1202, 1157, 1127, 1023, 1012, 973, 914, 860, 815, 799, 774, 755, 688, 667, 602 $cm^{-1}$.

**(*E*)-1-(2-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (1c)**[43] Prepared via General Procedure A, 94%, $^1$H NMR (300 MHz, $CDCl_3$) δ 12.89 (s, 1H), 8.77 (d, J = 9.8 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 7.95-7.87 (m, 4H), 7.72 (d, J = 15.2 Hz, 1H), 7.61-7.47 (m, 4H), 7.05 (dd, J = 8.4, 1.1 Hz, 1H), 6.94 (ddd, J = 8.2, 7.2, 1.1 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 193.8, 163.9, 142.6, 136.7, 134.0, 132.2, 132.0, 131.4, 130.0, 129.0, 127.3, 126.6, 125.6, 125.5, 123.6, 123.0, 120.2, 119.1, 118.9; IR (Neat) 3056, 2366, 1637, 1606, 1567, 1488, 1437, 1393, 1355, 1335, 1304, 1276, 1200, 1174, 1155, 1127, 1027, 992, 951, 909, 857, 847, 818, 757, 728, 690, 660, 626 $cm^{-1}$.

**(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (1d)**[44] Prepared via General Procedure A, 66%, $^1$H NMR (300 MHz, $CDCl_3$) δ 12.85 (s, 1H), 7.98-7.92 (m, 2H), 7.75-7.71 (m, 3H), 7.67-7.60 (m, 5H), 7.53-7.35 (m, 4H), 7.03 (dd, J = 8.4, 1.1 Hz, 1H), 6.95 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 193.9, 163.8, 145.2, 143.9, 140.2, 136.6, 133.8, 129.9, 128.2, 120.3, 120.1, 119.0, 118.9; IR (Neat) 3057, 3033, 2360, 2342, 1637, 1583, 1557, 1520, 1487, 1450, 14340, 1409, 1362, 1345, 1324, 1309, 1284, 1273, 1237, 1203, 1157, 1129, 1078, 1025, 1006, 990, 947, 911, 869, 833, 792, 752, 717, 690, 660, 615, 590, 565, 530 $cm^{-1}$.

**(*E*)-3-(furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (1e)**[45] Prepared via General Procedure A, 85%, $^1$H NMR (500 MHz, $CDCl_3$) δ 12.87 (s, 1H), 7.90 (d, J = 8.0, 1H), 7.65 (d, J = 15.2 Hz, 1H), 7.54 (t, J = 6.3, 2H), 7.47 (t, J = 8.3 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 3.4 Hz, 1H), 6.52 (d, J = 0.9 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 193.5, 163.8, 151.7, 145.6, 136.5, 131.3, 128.8, 120.3 ,119.0, 18.7, 117.8, 117.3, 113.1; IR (Neat) 3149, 3127, 3095, 1636, 1574, 1552, 1509, 1487, 1473, 1440, 1390, 1361, 1336, 1306, 1270, 1258, 1212, 1189, 1158, 1079, 1014, 968, 929, 910, 857, 831, 829, 793, 743, 720, 695, 651, 592, 564 $cm^{-1}$.

**(*E*)-1-(2-hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (1f)**[45] Prepared via General Procedure A, 56%, $^1$H NMR (500 MHz, $CDCl_3$) δ 12.83 (s, 1H), 8.04 (d, J = 15.1 Hz, 1H), 7.87 (dd, J = 8.1, 1.6 Hz, 1H), 7.48 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 7.45 (d, J = 5.0 Hz, 1H), 7.42 (d, J = 15.2Hz, 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.11-7.09 (m, 1H) , 7.00 (dd, J = 8.4, 1.1 Hz, 1H), 6.93 (ddd, J = 8.2, 1.2 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 196.4, 163.8, 140.4, 138.1, 136.6, 133.0, 127.7, 128.7, 120.2, 119.1, 119.0, 118.8; IR (Neat) 3101, 3086, 3071, 3024, 1690, 1632, 1605, 1573, 1557, 1507, 1482, 1436, 1419, 1378, 1343, 1328, 1298, 1265, 1237, 1221, 1206, 1177, 1148, 1124, 1077, 1047, 1020, 974, 878, 848, 836, 814, 762, 722, 707, 685, 660, 597 $cm^{-1}$.

**(*E*)-1-(2-hydroxyphenyl)-3-(thiophen-3-yl)prop-2-en-1-one (1g)**[46] Prepared via General Procedure A, 48%, $^1$H NMR (500 MHz, $CDCl_3$) δ 12.83 (s, 1H), 7.92-7.87 (m, 2H), 7.64 (dd, J = 2.7, 0.9 Hz, 1H), 7.49-7.4394 (m, 2H), 7.43 (dd, J = 5.1, 1.2 Hz, 1H), 7.38 (dd, J = 4.9, 2.8 Hz, 1H), 7.01(dd, J = 8.4, 1.1 Hz, 1H), 6.92 (ddd, J = 8.2, 7.4, 1.2 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 194.1, 163.8, 139.0, 138.2, 136.5, 130.2, 129.8, 127.5, 125.4, 120.2, 120.0; IR (Neat) 3097.8, 2360, 2341, 1688, 1634, 1566, 1515, 1486, 1463, 1442, 1421, 1393, 1355, 1336, 1302, 1258, 1235, 1199, 1153, 1127, 1085, 1021, 973, 864, 829, 809, 793, 752, 696, 651, 605, 594 $cm^{-1}$.

**(*E*)-1-(2-hydroxynaphthalen-1-yl)-3-phenylprop-2-en-1-one (1h)**[49] Prepared via General Procedure D, 67%, $^1$H NMR (500 MHz, $CDCl_3$) δ 12.59 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.95 (d, 4.5 Hz, 1H), 7.93 (d, J = 2.1 Hz, 1H), 7.84-7.82 (m, 1H), 7.65-7.64 (m, 2H), 7.55 (ddd, 8.5, 6.8, 1.3 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.44-7.45 (m, 3H), 7.41-7.42 (m, 1H), 7.20 (d, J = 9.0 Hz, 1H) (76 MHz, $CDCl_3$) δ 194.8, 163.0, 143.3, 137.1, 135.0, 131.8, 130.9, 128.5, 129.3, 128.9, 128.1, 127.3, 125.4, 124.2, 119.7, 116.1; IR (Neat) 2360, 2341, 1634, 1621, 1597, 1571, 1513, 1496, 1463, 1407, 1370, 1340, 1299, 1276, 1243, 1183, 1157, 1107, 994, 973, 826, 758, 717, 684, 658, 644, 605, 581, 562, 547 $cm^{-1}$.

**(*E*)-1-(1-hydroxynaphthalen-2-yl)-3-phenylprop-2-en-1-one (1i)**[50] Prepared via General Procedure A, 57%, $^1$H NMR (500 MHz, $CDCl_3$) δ 14.82 (s, 1H), 8.49 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 15.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.76 (dd, J = 8.5, 6.5 Hz, 2H), 7.69 (dd, J = 7.0, 4.0 Hz, 2H), 7.63 (ddd, J = 8.0, 7.0, 1.5 Hz, 1H), 7.53 (ddd, J = 8.5, 7.5, 1.0 Hz, 1h) 7.44 (dd, J = 5.0, 1.5 Hz, 3H), 7.30 (d, J = 8.5 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 193.5, 164.7, 145.3, 137.6, 135.0, 130.5, 129.3, 128.9, 127.6, 126.2, 125.7, 124.8, 124.2, 120.7, 118.5, 113.7; IR (Neat) 2360, 2342, 1626, 1597, 1573, 1495, 1467, 1448, 1418, 1339, 1352, 1323, 1301, 1282, 1223, 1207, 1150, 1119, 1062, 1023, 1000, 971, 902, 854, 804, 790, 765, 742, 709, 683, 669, 651, 570 $cm^{-1}$.

**(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-(furan-2-yl)prop-2-en-1-one (1j)**[47] Prepared via General Procedure B, 63% flavanone, 8% chalcone, $^1$H NMR (300 MHz, $CDCl_3$) δ 13.26 (s, 1H), 7.91 (dd, J = 8.9, 6.5 Hz, 1H), 7.66 (d, J = 15.1 Hz, 1H), 7.54 (d, J = 1.53 Hz, 1H), 7.45 (d, J = 15.1 Hz, 1H), 6.76 (d, J = 16.9 Hz, 1H), 6.70-6.60 (m, 2H), 6.53 (dd, J = 3.4, 1.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 192.4, 169.3, 166.4, 166.2, 165.9, 151.6, 145.7, 132.2, 132.1, 131.5, 117.6, 117.6, 117.3,117.3, 113.2, 107.5, 107.2, 105.4, 105.1; IR (Neat) 1610, 1595, 1571, 1549, 1511, 1477, 1416, 1370, 1345, 1298, 1278, 1264, 1234, 1212, 1191, 1164, 1078, 1015, 974, 959, 929, 883, 853, 828, 805, 745, 716, 689, 641, 605, 590, 578 $cm^{-1}$.

**(*E*)-1-(2-hydroxy-4-methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (1k)**[48] Prepared via General Procedure A, 86%, $^1$H NMR (300 MHz, $CDCl_3$) δ 13.44 (s, 1H), 7.99 (d, J = 15.2 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 5.1 Hz, 1H) 7.36 (s, 1H), 7.33 (d, J = 12.2 Hz, 1H), 7.08 (dd, J = 5.1, 3.7 Hz, 1H), 6.49-6.45 (m, 2H), 3.84 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 191.5, 166.9, 166.4, 140.5, 137.1, 132.5, 131.3, 129.3, 128.6, 119.3, 114.2, 108.0, 101.3, 55.8; IR (Neat) 3104, 3082, 3006, 2968, 2936, 2911, 2841, 2361, 1623, 1561, 1505, 1463, 1441, 1443, 1370, 1339, 1272, 1239, 1214, 1153, 1128, 1033, 1017, 959, 854, 836, 798, 744, 707, 687, 628, 603, 582, 566 cm$^{-1}$.

**(*E*)-1-(2-hydroxy-4-methoxyphenyl)-3-(thiophen-3-yl)prop-2-en-1-one (1l)** Prepared via General Procedure A, 84%, $^1$H NMR (500 MHz, CDCl$_3$) δ 13.44 (s, 1H), 7.86 (d, J = 15.4 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 1.9 Hz, 1H, 7.41-7.35 (m, 3H), 6.48-6.45 (m, 2H), 3.84 (s, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 192.3, 166.8, 166.4, 138.3, 138.0, 131.4, 129.6, 127.3, 125.4, 120.2, 114.3, 107.9, 101.3; IR (Neat) 3106, 3018, 2843, 1629, 1572, 1507, 1459, 1437, 1376, 1352, 1308, 1272, 1248, 1215, 1167, 1149, 1127, 1086, 1018, 972, 960, 867, 823, 778, 737, 689, 645, 620, 587 cm$^{-1}$; HRMS (EI$^+$) *m/z* calculated for $C_{14}H_{12}O_3S$ (M$^+$) 260.0507, found 260.0500.

**(2*E*,2'*E*)-3,3'-(1,3-phenylene)bis(1-(2-hydroxyphenyl)prop-2-en-1-one) (1m)**[51] Prepared via General Procedure A, 6%, $^1$H NMR (500 MHz, CDCl$_3$) δ 12.72 (s, 1H), 7.94 (d, J = 15.5 Hz, 2H), 7.94 (dd, J = 8.1, 1.6 Hz, 2H), 7.90 (s, 1H), 7.73 (dd, J = 7.7, 1.7 Hz, 2H), 7.71 (d, J = 15.4 Hz, 2H), 7.53-7.50 (m, 3H), 7.04 (dd, J = 8.4, 1.0 Hz, 2H), 6.96 (ddd, J = 8.2, 7.4, 1.1 Hz, 2H); $^{13}$C (126 MHz, CDCl$_3$) δ 193.7, 163.9, 144.5, 136.9, 135.8, 130.7, 130.0, 129.8, 129.0, 121.5, 120.1, 119.2, 119.0; IR (Neat) 2952, 2924, 2856, 2360, 2341, 1734, 1696, 1643, 1601, 1574, 1469, 1422, 1360, 1339, 1308, 1272, 1223, 1205, 1186, 1129, 1101, 1056, 1030, 1020, 990, 908, 895, 859, 825, 802, 782, 761, 736, 718, 697, 670, 649 cm$^{-1}$.

**(2*E*,2'*E*)-3,3'-(1,4-phenylene)bis(1-(2-hydroxyphenyl)prop-2-en-1-one) (1n)**[51] Prepared via General Procedure A, 96%, $^1$H NMR (500 MHz, D-DMSO) δ 12.46 (s, 1H), 8.29 (dd, J = 8.6, 1.6 Hz, 2H), 8.16 (d, J = 15.5 Hz, 2H) 8.03 (s, 4H), 7.89 (d, J = 15.5 Hz, 2H), 7.61-7.57 (m, 2H), 7.05-7.03 (m, 4H); $^{13}$C (126 MHz, d-DMSO) δ; 193.5, 161.8, 143.7, 136.7, 136.4, 131.0, 129.7, 123.1, 120.9, 119.2, 117.7. IR (Neat) 2360, 2341, 1638, 1566, 1507, 1486, 1438, 1416, 1368, 1341, 1319, 1301, 1272, 1235, 1208, 1179, 1151, 1129, 1026, 980, 867, 828, 757, 687, 658, 531, 535 cm$^{-1}$.

**2-(naphthalen-2-yl)chroman-4-one (2b)**[52] Prepared via General Procedure C, 67%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.95 (dd, J = 7.9, 1.6 Hz, 1H), 7.93 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.88-7.85 (m, 2H), 7.58 (dd, J = 8.5, 1.5 Hz, 1H), 7.53-7.50 (m, 3H), 7.09-7.05 (m, 2H), 5.64 (dd, J = 13.2, 2.6 Hz, 1H), 3.18 (dd, J = 16.9, 13.3 Hz, 1H), 2.97 (dd, J = 16.9, 2.9 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 192.1, 161.8, 136.5, 136.3, 133.6, 133.4, 129.0, 128.4, 128.0, 127.3, 126.8, 125.6, 123.9, 121.9, 121.2, 118.4, 77.9, 44.9; IR (Neat) 3056, 3031, 2360, 231, 1688, 1605, 1577, 1520, 1488, 1462, 1409, 1365, 1303, 1225, 1148, 1114, 1068, 1027, 1008, 955, 907, 861, 847, 828, 762, 736, 697, 657, 628, 593, 574, 554, 528 cm$^{-1}$.

**2-(naphthalen-1-yl)chroman-4-one (2c)**[52] Prepared via General Procedure C, 65%, $^1$H NMR (500 MHz, CDCl$_3$) δ 8.04 (m, 1H), 7.99 (dd, J = 9.9, 3.6 Hz, 1H), 7.92-7.87 (m, 2H), 7.77 (d, J = 7.2 Hz, 1H), 7.56-7.50 (m, 4H), 7.10-7.07 (m, 2H), 6.22 (dd, J = 13.4, 2.7 Hz, 1H), 3.26 (dd, J = 17.0, 13.4 Hz, 1H), 3.09 (dd, J = 17.0, 2.8 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 192.5, 162.0, 136.4, 134.4, 134.1, 130.4, 129.6, 129.3, 127.4, 126.9, 126.2, 125.6, 124.1, 123.0, 122.0, 121.3, 118.4, 77.1, 44.2; IR (Neat) 3054, 2362, 1688, 1606, 1577, 1511, 1436, 1388, 1341, 1303, 1223, 1148, 1116, 1071, 1031, 9836, 956, 904, 868, 801, 767, 733, 652, 632, 592, 563, 527 cm$^{-1}$.

**2-([1,1'-biphenyl]-4-yl)chroman-4-one (2d)**[52] Prepared via General Procedure C, 50%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.95-7.93 (m, 1H), 7.66-7.64 (m, 2H), 7.60-7.58 (m, 2H), 7.56-7.54 (m, 2H), 7.53-7.49 (m, 1H), 7.46-7.43 (m, 2H), 7.38-7.34 (m, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.05 (dd, J = 7.1, 1 Hz, 1H), 5.53 (dd, J = 13.3, 2.8 Hz, 1H), 3.13 (dd, J = 16.8, 13.9 Hz, 1H), 2.93 (dd, J = 16.9, 2.9 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 192.0, 161.6, 141.8, 140.5, 137.7, 136.3, 128.9, 127.6, 127.2, 127.1, 126.7, 121.7, 121.0, 118.2, 79.4, 44.6; IR (Neat) 2360, 2337, 1690, 1608, 1577, 1462, 1303, 1224, 1149, 1114, 1065, 1035, 982, 891, 852, 832, 764, 707, 575 cm$^{-1}$.

**2-(furan-2-yl)chroman-4-one (2e)**[53] Prepared via General Procedure C, 66%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.48 (ddd, J = 8.7, 7.2, 1.8 Hz, 1H), 7.46-7.45 (m, 1H), 7.05-7.00 (m, 2H), 6.44 (d, J = 3.3 Hz, 1H), 6.38 (dd, J = 3.3, 1.9 Hz, 1H), 5.53 (dd, 11.6, 3.5 Hz, 1H), 3.25 (dd, J = 16.6, 11.6 Hz, 1H), 2.96 (dd, J = 16.9, 3.5 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 191.3, 160.8, 150.9, 143.5, 13633, 127.0, 121.7, 120.9, 118.1, 110.5, 109.4, 72.3, 40.1, 29.7; IR (Neat) 2360, 2341, 1691, 1653, 1636, 1609, 1559, 1541, 1507, 1463, 1405, 1357, 1304, 1221, 1150, 1116, 1065, 1027, 1014, 982, 957, 932, 911, 888, 865, 852, 823, 763, 680, 669, 654, 597, 571 cm$^{-1}$.

**2-(thiophen-2-yl)chroman-4-one (2f)**[53] Prepared via General Procedure C, 53%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.91 (dd, J = 8.3, 1.7 Hz, 1H), 7.49 (ddd, J = 8.3, 7.3, 1.8 Hz, 1H), 7.36 (dd, J = 5.1, 1.1 Hz, 1H), 7.12-7.11 (m, 1H), 7.06-7.01 (m, 3H), 5.73 (dd, J = 11.8, 3.3 Hz, 1H), 3.19 (dd, J = 16.9, 11.8 Hz, 1H), 3.05 (dd, J = 16.9, 3.4 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 191.4, 161.1, 141.7, 136.5, 127.2, 127.1, 126.6, 126.1, 122.0, 121.2, 118.4, 75.3, 44.6; IR (Neat) 2360, 1341, 1688, 4607, 1576, 1540, 1509, 1461, 1439, 1378, 1302, 1222, 1149, 1114, 1065, 1035, 982, 958, 891, 851, 831, 764, 706, 668, 647, 576, 532 cm$^{-1}$.

**2-(thiophen-3-yl)chroman-4-one (2g)** Prepared via General Procedure C, 70%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.91 (dd, J = 8.3, 1.7 Hz, 1H), 7.49 (ddd, J = 8.3, 7.3, 1.8 Hz, 1H), 7.35 (dd, J = 5.1, 1.2 Hz, 1H), 7.12 (m, 1H), 7.05-7.00 (m, 3H), 5.74 (dd, J = 11.8, 3.4 Hz, 1H), 3.18 (dd, J = 16.8, 11.8 Hz, 1H), 3.05 (dd, J = 16.9, 3.4 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 191.4, 161.1, 141.7, 136.5, 127.2, 127.1, 126.6, 126.1, 122.0, 121.2, 118.4, 75.3, 44.6; IR (Neat) 2360, 2341, 1688, 1635, 1607, 1576, 1461, 1439, 1378, 1302, 1222, 1149, 1114, 1065, 1034, 982, 958, 891, 851, 831, 763, 706, 668, 590, 576, 533 cm$^{-1}$.

**3-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (2h)**[55] Prepared via General Procedure B, 68%, $^1$H NMR (500 MHz, CDCl$_3$) δ 9.47 (dd, 8.6, 0.7 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.77-7.75 (m, 1H), 7.64 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.53-7.50 (m, 2H), 7.46-7.38 (m, 4H), 7.17 (d, J = 9.0 Hz, 1H), 5.59 (dd, J = 13.8, 3.0 Hz, 1H), 3.22 (dd, J = 16.6, 13.9 Hz, 1H), 2.97 (dd, 16.6, 3.1 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 193.2, 163.9, 138.7, 137.8, 131.7, 129.9, 129.5, 129.1, 129.0, 128.6, 126.4, 126.1, 125.2, 119.1, 112.8, 79.8, 46.0; IR (Neat) 3063, 3035, 2165, 2040, 1951, 1666, 1617, 1596, 1565, 1509, 1460, 1434, 1397, 1370, 1341, 1314, 1277, 1235, 1205, 1155, 1142, 1125, 1066, 1046, 1019, 1003, 950, 915, 897, 874, 852, 829, 782, 765, 747, 735, 694, 679, 654, 615, 594 cm$^{-1}$.

**2-phenyl-2*H*-benzo[*h*]chromen-4(3*H*)-one (2i)**[56] Prepared via General Procedure B, 34%, $^1$H NMR (500 MHz, CDCl$_3$) δ 8.34 (d) 8.37 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 8.2 1H), 7.64 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.63-7.59 (m, 2h), 7.55-7.44 (m, 5H), 5.71 (dd, J = 13.6, 3.1 Hz, 1H), 3.20 (dd, J = 16.9, 13.6 Hz, 1H), 3.01 (dd, J = 16.8, 3.1 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 191.8, 160.1, 139.0, 137.8, 129.9, 129.1, 129.0, 128.1, 126.5, 126.3, 125.1, 123.9, 122.0, 121.5, 115.7, 80.6, 44.3; IR (Neat) 3060, 1679, 1625, 1597, 1573, 1509, 1457, 1437, 1408, 1389, 1350, 1333, 1314, 1279, 1253, 1217, 1195, 1151, 1112, 1069, 1058, 1023, 991, 900, 871, 840, 813, 755, 740, 697, 674, 649, 633, 603, 572, 530 cm$^{-1}$.

**7-fluoro-2-(furan-2-yl)chroman-4-one (2j)** Prepared via General Procedure C, 54%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.96 (dd, J = 8.8, 6.6 Hz, 1H), 7.49 (dd, J = 1.8, 0.70 Hz, 1H), 6.78 (td, J = 16.9, 10.8, 8.4, 2.4 Hz, 1H), 6.72 (dd, J = 9.8, 2.4 Hz, 1H), 6.49 (d, J = 3.3 Hz, 1H), 6.42 (dd, J = 7.8, 1.8 Hz, 1H), 5.58 (dd, J = 11.3, 3.6 Hz, 1H), 3.26 (dd, J = 17.0, 11.3 Hz, 1H), 2.99 (dd, J = 17.0, 3.6 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 190.0, 167.8 (d, J$_{C-F}$ = 257.0 Hz), 162.6 (d, J$_{C-F}$ = 12.6 Hz), 150.7, 143.8, 129.7 (d, J$_{C-F}$ = 11.3 Hz), 118.1 (d, J$_{C-F}$ = 2.5 Hz), 110.8, 110.4 (d, J$_{C-F}$ = 22.7 Hz), 109.9, 105.2 (d, J$_{C-F}$ = 25.2 Hz), 73.0, 40.6; IR (Neat) 2360, 2341, 1692, 1613, 1588, 1492, 1440, 1359, 1329, 1284, 1252, 1210, 1176, 1140, 1108, 1060, 1015, 993, 967, 952, 932, 884, 855, 837, 811, 746, 669, 627, 599, 550 cm$^{-1}$; HRMS (EI$^+$) *m*/*z* calculated for $C_{13}H_9FO_3$ (M$^+$) 232.0536, found 232.0529.

**7-methoxy-2-(thiophen-2-yl)chroman-4-one (2k)**[54] Prepared via General Procedure C, 49%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, J = 8.9 Hz, 1H), 7.35 (dd, J = 5.0, 1.2 Hz, 1H), 7.12-7.11 (m, 1H), 7.01 (dd, J = 5.1, 3.6 Hz, 1H) 6.59 (dd, J = 8.9, 2.4 Hz, 1H) 7.47 (d, J = 2.4 Hz, 1H), 5.71 (dd, J = 11.9, 3.3 Hz, 1H), 3.81 (s, 3H), 3.13 (dd, J = 16.8, 11.9 Hz, 1H), 2.98 (dd, J = 16.8, 3.4 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 190.1, 166.5, 163.1, 141.7, 128.9, 127.1, 126.6, 126.1, 115.1, 110.7, 101.2, 75.7, 55.9, 44.2; IR (Neat) 2360, 2340, 1681, 1606, 1574, 1496, 1440, 1376, 1326, 1294, 1258, 1218, 1202, 1158, 1130, 114, 1060, 1023, 991, 9533, 838, 797, 709, 668, 647 cm$^{-1}$.

**7-methoxy-2-(thiophen-3-yl)chroman-4-one (2l)** Prepared via General Procedure C, 64%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, J = 8.9 Hz, 1H), 7.38-7.35 (m, 2H), 7.17 (dd, J = 4.8, 1.6 Hz, 1H), 6.59 (dd, J = 8.8, 2.4 Hz, 1H), 6.47 (d, J= 2.4 Hz, 1H), 5.56 (dd, J = 12.3, 3.3 Hz, 1H), 3.82 (s, 3H), 3.04 (dd, J = 16.8,12.3 Hz, 1H), 2.90 (dd, J = 16.8, 3.3 Hz, 1H); $^{13}$C (126 MHz, CDCl$_3$) δ 190.6, 166.4, 163.4, 140.1, 129.0, 127.1, 125.9, 123.0, 115.1, 110.5, 101.2, 76.1, 55.9, 43.7; IR (Neat) 3102, 2964, 2840, 1679, 1603, 1573, 1495, 1443, 1420, 1332, 1256, 1200, 1158, 1131, 1114, 1061, 1023, 996, 952, 893, 796, 778, 734, 716, 641, 615, 590, 550, 525 cm$^{-1}$.

**2,2'-(1,3-phenylene)bis(chroman-4-one) (2m)**[51] Prepared via General Procedure C, 72%, $^1$H NMR (500 MHz, CDCl$_3$) δ 7.98 (dd, J = 8.1, 1.8 Hz, 2H), 7.68 (s, 1H) 7.58-7.54 (m, 5H), 7.11-7.09 (m, 4H) 5.57 (dd, J = 13.4, 2.9 Hz, 2H), 3.14 (ddd, J = 17.0, 13.4, 4.3 Hz, 2H), 2.96 (ddd, J = 16.9, 5.6, 2.8 Hz, 2H); $^{13}$C (126 MHz, CDCl$_3$) δ 191.9, 161.6, 139.8, 136.5, 129.7,127.3, 126.7, 124.1, 122.0, 121.2, 118.4, 79.6, 45.0; IR (Neat) 2924, 2853, 2360, 2341, 1688, 1606, 1577, 1463, 1355, 1304, 1223, 1148, 1115, 1067, 1028, 991, 958, 907, 878, 849, 797, 764, 733, 703, 669, 649, 584 cm$^{-1}$.

**2,2'-(1,4-phenylene)bis(chroman-4-one) (2n)**[51] Prepared via General Procedure C, 37%, $^1$H NMR (500 MHz, CDCl3) δ 7.93 (dd, J = 8.3, 1.7 Hz, 2H), 7.55 (s, 1H), 7.51 (ddd, J = 8.9, 7.8, 1.7 Hz, 2H), 7.07-7.04 (m, 4H), 5.52 (dd, J = 13.3, 2.9 Hz, 2H), 3.08 (ddd, J = 16.8, 13.3, 1.5 Hz, 2H), 2.94-2.86 (m, 2H); $^{13}$C (126 MHz, CDCl$_3$) δ 191.9, 161.6, 139.6, 136.5, 127.3, 126.9, 122.0, 121.2, 118.3, 79.4, 44.9; IR (Neat) 2924, 2854, 2361, 1687, 1606, 1576, 1463, 1420, 1373, 1305, 1226, 1148, 1115, 1068, 1027, 991, 956, 907, 858, 823, 765, 733, 590, 535 cm$^{-1}$.

## ASSOCIATED CONTENT

Supporting Information: $^1$H and $^{13}$C NMR spectra and sigmoidal curves derived from UV/VIS equilibration assays.

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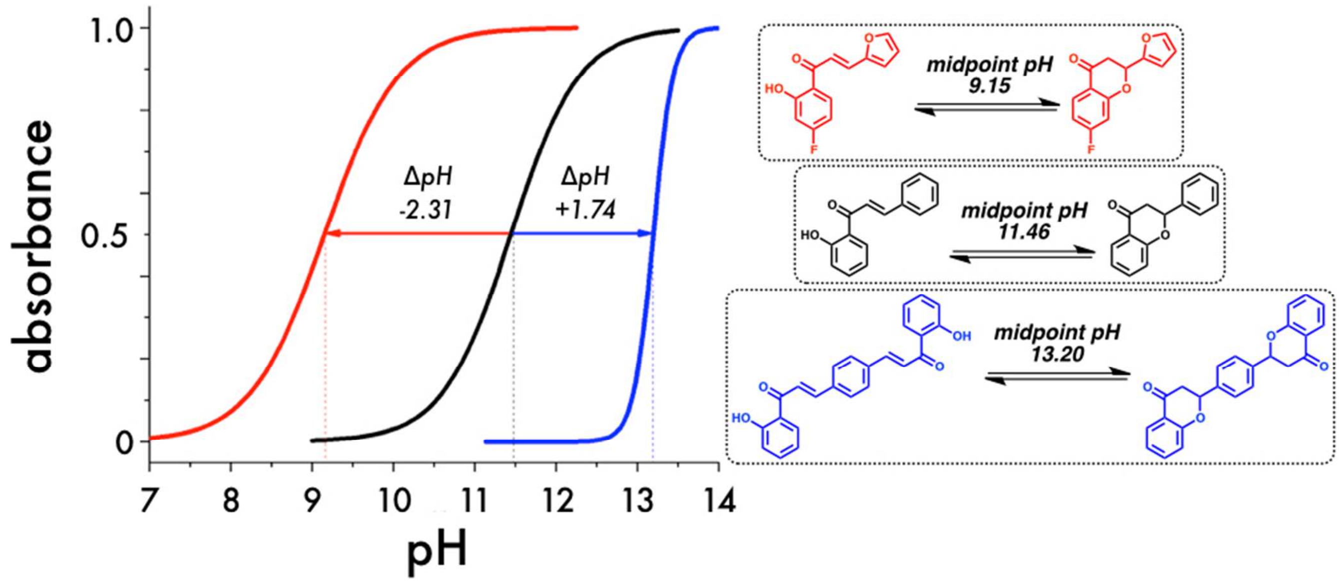
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0
7
8
9
10
11
12
13
14
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ΔpH
+1.74
midpoint pH
9.15
midpoint pH
11.46
midpoint pH
13.20
HO
F
O
OH