One-Pot Access to 2-Aryl-3-(arylmethyl)chromones

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Abstract

Sodium hydroxide controlled intermolecular double aldol condensation of o-hydroxyacetophenones with 2 equivalents of arylaldehydes provides 2-aryl-3-(arylmethyl)chromones (a chimera of flavone and homoisoflavanone) in MeOH at 50 °C under mild conditions. The uses of various bases and solvents are investigated for one-pot facile and efficient transformation. A plausible mechanism is proposed.

Key words aldol condensation, o-hydroxyacetophenones, arylaldehydes, chromones, homoisoflavanone, benzopyran-4-one

The structure of a 2-aryl-3-(arylmethyl)chromone, having α-aryl methyl and β-aryl-conjugated groups, is a chimera of flavone and homoisoflavanone. On the basis of the same benzopyran-4-one skeleton (black), both flavone (blue, 2-aryl) and homoisoflavanone (red, 3-arylmethyl) possess an aryl motif and are the key members of benzofused oxacycles (Scheme 1). They are widely present in natural products and serve as multifunctionalized blocks in synthetic fields. They exhibit diversified bioactive properties, such as antioxidant, anticancer, and antimicrobial activities. 

Therefore, a number of attempts to synthesize the skeletons of flavone and homoisoflavanone have been reported via various prepared protocols. Comparing two common core skeletons, however, there are fewer studies on the related synthetic works and pharmaceutical properties of 2-aryl-3-(arylmethyl)chromones. So far, there are three main groups that have demonstrated the unique biological activities of 2-aryl-3-(arylmethyl)chromones. The Bisi group reported that 2-phenyl-3-(imidazolyl)methylchromones, e.g. 1a, are suitable to serve as flavonoid-based cytochrome P450 (CYP) inhibitors. Lee and co-workers described that 2-pyridyl-3-(pyridylmethyl)chromone 1b is an antioxidant agent.

On the other hand, two attractive examples of the synthesis of 2-aryl-3-(arylmethyl)chromones with the structural hybrid of flavone and homoisoflavanone were described as follows (Scheme 2). They included: (1) Lee and co-workers investigated the ruthenium-catalyzed one-pot C–H activation of salicylaldehydes and decarboxylative coupling of alkynoic acids (eq 1), and (2) Liu and co-workers explored the palladium-catalyzed dehydrogenation of o-acylphenols (eq 2). They both showed novel transition-metal-promoted routes in the formation of 2-aryl-3-(arylmethyl)chromones. In spite of the advancements however, some problems exist, such as complicated catalytic conditions, lack of broad substrate generality, and prefunctionalized fragments. However, an operationally easy, inexpensive, open-vessel, and high-yield route for the preparation of 2-aryl-3-(arylmethyl)chromones with potential bioactive properties had not been reported until recently. As a result of the recent findings, further investigation of efficient synthetic methods for introducing both 2-aryl and 3-arylmethyl groups into the core scaffold of benzopyran-4-one is still highly desired. Herein, we present a one-pot synthesis of 2-aryl-3-(arylmethyl)chromones via alkali-controlled intermolecular double aldol condensation of substituted o-hydroxyacetophenones with arylaldehydes under warming alcoholic reaction conditions.

Scheme 1 Structures of 2-aryl-3-(arylmethyl)chromones

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Continuing our synthetic research on the tandem aldol condensation/Michael addition of o-allylbenzaldehyde with different equivalents of substituted acetophenones (1, 2, and 3 equiv) for the preparation of diversified benzanulated molecules, a convenient route for synthesizing 2-aryl-3-(arylmethyl)chromones was explored next. Using equal equivalents of starting materials, aldol condensation of substituted o-hydroxyacetophenones (1 equiv) with arylaldehydes (1 equiv) provided o-hydroxychalcones in good yields (Scheme 3). In fact, to the best of our knowledge, so far no examples of the double aldol condensation of acetophenones with different equivalents of substituted acetophenones (1, 2, and 3 equiv) for the preparation of diversified benzanulated molecules have been reported. On the basis of these observations, initiating substrate to screen the reaction conditions since the factor of reaction concentration also affected the yield. Three alkalis with different basicity levels were examined next. Entries 10 and 11 show that no better yields were detected using LiOH and KOH (65% and 78%), respectively. Using K₂CO₃, the desired 4a could not be generated (entry 12). By controlling the combination of 50 °C and 10 h, the solvent was adjusted from MeOH to EtOH, however only a 58% yield of 4a was formed (entry 13). After elevating the temperature from 50 °C to 70 °C, the yield was still maintained at 68% (entry 14). Entries 15 and 16 show that iPrOH and tBuOH did not give better yields (37% and 12%) than MeOH (86%). By using H₂O as the solvent, no reaction was observed due to the poor solubility (entry 17). In entries 18 and 19, attempts to increase the number of equivalents (2 → 3 or 4) failed to afford higher yields (82% or 75%). Then, 1 equivalent of NaOH was tested, and only a 45% yield of 4a was formed (entry 13). After elevating the temperature to reflux (65 °C), but this reflux condition provided a 71% yield of 4a (entry 7). Furthermore, adjusting the reaction concentrations (0.033 → 0.10, 0.02 M) was examined. We found that concentrated solution (0.1 M) provided 4a in a 25% yield along with major complex unknown products (entry 8). On the other hand, the diluted solution (0.02 M) could maintain the yield at 79% (entry 9). From the phenomenon, we understood that the factor of reaction concentration also affected the yield. Three alkalis with different basicity levels were examined next. Entries 10 and 11 show that no better yields were detected using LiOH and KOH (65% and 78%), respectively. Using K₂CO₃, the desired 4a could not be generated (entry 12). By controlling the combination of 50 °C and 10 h, the solvent was adjusted from MeOH to EtOH, however only a 58% yield of 4a was formed (entry 13). After elevating the temperature from 50 °C to 70 °C, the yield was still maintained at 68% (entry 14). Entries 15 and 16 show that iPrOH and tBuOH did not give better yields (37% and 12%) than MeOH (86%). By using H₂O as the solvent, no reaction was observed due to the poor solubility (entry 17). In entries 18 and 19, attempts to increase the number of equivalents (2 → 3 or 4) failed to afford higher yields (82% or 75%). Then, 1 equivalent of NaOH was tested, and only a 45% yield of 4a was detected (entry 20). From our observations, we concluded that NaOH was the optimal alkali to yield 4a under warming methanolic reaction conditions via one-pot facile intermolecular double condensation of 2a and 3a.
Table 1 Reaction Conditions

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* Reaction conditions: 2a (1.0 mmol), 3a (2 equiv), alkali (2 equiv).
* Isolated yields of 4a.
* Unknown mixture was isolated.
* No product detected.
* 3 equiv.
* 4 equiv.
* 1 equiv.

1.3-hydride migration on F from trisubstituted exo-olefin to tetrasubstituted endo-olefin furnished the construction of 4a. On the other pathway, removal of the hydroxyl group of B provided G with a chalcone group. By intramolecular oxa-Michael annulation of G followed by intermolecular aldol

Table 2 Synthesis of 4a–4ab

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<th>Yield (%)</th>
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<tr>
<td>28</td>
<td>4ab</td>
<td>3f</td>
<td>78</td>
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* Reaction conditions: 2a–2w (1.0 mmol) 3a–3f (2 equiv), NaOH (80 mg, 2 equiv), MeOH (30 mL), 50 °C, 10 h.
* Ar is the substituted aryl ring in 2-formylarenes-1-ol (numbering shown).
* Ar’ is the substituted pyridine ring in 2-formylpyridine (numbering shown).
* Isolated yields.
* Substrate was 1-hydroxynaphthalene-2-carboxaldehyde.
* Substrate was 2-hydroxynaphthalene-1-carboxaldehyde.

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condensation of the resulting H with 3a, F was achieved. Based on the above-mentioned procedure, 4a was constructed. From the possible mechanism, we found that NaOH efficiently organized the continuous sequence of intermolecular aldol reactions and intramolecular ring-closures.

To study the scope and limitations of this approach, substituted o-hydroxyacetophenones 2a–2w and 2-formylpyridines 3a–3f were reacted with NaOH (2 equiv) to afford diversified 2-aryl-3-(arylmethyl)chromones 4a–4ab under warming methanol (50 °C/10 h) conditions, as shown in Table 2. With optimal conditions established (Table 1, entry 5) and a plausible mechanism proposed (Scheme 4), we found that this route allowed direct double aldol condensation in moderate to good yields (64–86%). Among entries 1–28, efficient formation of 4a–4ab showed that the two aryl substituents (2, Ar and 3, Ar′) did not affect the yields. The structures of 4a–4d, 4g, 4t, and 4z were determined by single-crystal X-ray crystallography. For the electronic nature of aryl substituents (Ar) of 2, not only haloaryl (bromo, chloro, dichloro) groups but also electron-neutral (methyl), electron-withdrawing (fluoro, difluoro) and electron-donating (methoxy, butoxy, benzyloxy) groups were appropriate. For the pyridyl substituents (Ar′) of 3, 6-bromo, 5-fluoro, 6-methyl, 6-chloro, and 6-methoxy groups were well-tolerated. Based on the results, after replacing the pyridyl group of 3a–3f with benzaldehyde (3g) and 2-naphthaldehyde (3h), synthesis of 4ac–4ad was examined next (Scheme 5). However, the desired 4ac and 4ad were formed in 43% and 36% yields, respectively. Next, when the monocyclic 2-formyl-heteroarenes were changed from 2-formylpyridines 3a–3f to 1-allyl-2-formyl-1H-pyrole (3i), 2-formylfuran (3j), 2-formylthiophene (3k), and 3-formylpyridine (3l), 4af and 4ag were produced with moderate results (58% and 60% yields); surprisingly, the desired 4ae could be not isolated. The structure of 4ag was determined by single-crystal X-ray crystallography. In particular, 4ah was provided in only a 27% yield. Then, changing to bicyclic 2-formylbenzofuran (3m), 2-formylbenzo[b]thiophene (3n), and 3-formyl-1-methyl-1H-indole (3o), 4ai and 4aj were obtained in 64% and 63% yields, respectively. However, the desired 4ak could be not isolated, and only 15% yield of chalcone 4ak-1 was obtained. Furthermore, 2-formylquinoline (3p) produced 63% yield of 4al.
From the results, we understand that hetero-mono cyclic 2-azaarenes could produce better yields than benzaldehyde and naphthaldehyde, especially with substituted 2-formylpyridines. The putative explanations for the differences are that the aggregated intermediate adopts a bidentate coordination of the sodium ion by the nitrogen lone-pair of 2-formylpyridine and the alkoxy anion such that this resulting complexation would necessitate the intermediate to coordinate with the second equivalent of 2-formylpyridine via the aldol reaction process.\textsuperscript{1,2}

To elongate the side arm on the pyridyl ring of 4a, Suzuki–Miyaura coupling of 4a with 3,4-dimethoxyphenylboronic acid provided 4am in a 75% yield along with a 10% yield of 4am-1, as shown in Scheme 6. With the results, we envisioned that different aryl substituents could be installed into the 6-position of pyridine ring on 4a to afford diversified aryl-pyridyl-conjugated homoisoflavonanes.

On the other hand, a macrocyclic isoflavonane was examined (Scheme 7). Under the above conditions, a one-pot NaOH-controlled reaction of 2a and 3q with the o-allyl side chain provided flavone 4an in a 40% yield. In particular, no desired homoisoflavonane was detected. The possible reason should be that the o-allyl group on 3q exhibited a bulkier steric hindrance such that the second aldol condensation could not be generated. For the formation of 4an, we thought that in situ generated 1 could trap molecular oxygen (from air) to lead II. Following, by the peroxyanion-mediated intramolecular deprotonation of II, 4an was accomplished.

In summary, we have developed an NaOH-controlled synthesis of 2-aryl-3-(aryl methyl)chromones via intermolecular double aldol condensation of o-hydroxyacetophenones with 2 equivalents of an arylaldehyde under warming MeOH reaction conditions in moderate to good yields. The process provides a cascade pathway of C–C and then, C–O bond formations. The uses of various bases and solvents are investigated for one-pot facile and efficient transformation. Related plausible mechanisms have been proposed. The structures of the key products were confirmed by X-ray crystallography. Further investigations regarding the synthetic applications of o-hydroxyacetophenones will be conducted and published in due course.

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry air with magnetic stirring. The heating mantle is used to provide a stable heat source. Products in organic solvents were dried with anhydrous MgSO\textsubscript{4} before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus.\textsuperscript{1} and \textsuperscript{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and at 100 MHz, respectively. HRMS were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

For the starting compounds 2a–2w and 3a–3r, these reagents were obtained from commercial sources and used without further purification.

### 2-Aryl-3-(aryl methyl)chromen-4-ones 4a–4ad, 4af–4aj, 4ak-1, and 4al; General Procedure

NaOH (80 mg, 2.0 mmol) was added to a solution of 2a–2w (1.0 mmol) in MeOH (30 mL) at 25 °C. The mixture was stirred at 25 °C for 10 min. Arylaldehyde 3a–3p (2.0 mmol) was added to the mixture at 25 °C and it was stirred at 50 °C for 10 h. The mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (MgSO\textsubscript{4}), filtered and evaporated to afford crude product under reduced pressure. The remaining mixture was separated by column chromatography (silica gel, hexanes/EtOAc 20:1–3:1) affording the title compounds.
2-(6-Bromopyridin-2-yl)-3-(6-bromopyridin-2-ylmethyl)-chroman-4-one (4a)

Colorless solid; yield: 404 mg (86%); mp 179–180 °C (hexanes/EtOAc).

Colorless solid: yield: 402 mg (86%); mp 190–191 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.05 (d, J = 7.2 Hz, 1 H), 7.81 (dd, J = 8.0, 3.2 Hz, 1 H), 7.71 (t, J = 8.0 Hz, 1 H), 7.55 (dd, J = 8.0, 0.8 Hz, 1 H), 7.51 (dd, J = 9.2, 4.0 Hz, 1 H), 7.43–7.36 (m, 2 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.21 (d, J = 8.0 Hz, 1 H), 4.31 (s, 2 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 177.5 (d, J = 23.6 Hz, 160, 159.5 (d, J = 245.6 Hz), 158.2, 152.0 (d, J = 1.5 Hz), 151.8, 141.4, 141.0, 139.0, 138.5, 129.4, 125.3, 123.8 (d, J = 8.6 Hz), 123.3, 122.2 (d, J = 25.7 Hz), 121.9, 120.3 (d, J = 7.6 Hz), 119.8, 110.7 (d, J = 23.5 Hz), 32.7.


Colorless solid: yield: 395 mg (76%); mp 223–224 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.05 (d, J = 8.0 Hz, 1 H), 8.19 (d, J = 8.0 Hz, 1 H), 8.15 (d, J = 8.0 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 1 H), 7.81–7.65 (m, 4 H), 7.60 (dd, J = 8.0, 0.4 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.27 (d, J = 7.6 Hz, 1 H), 7.23 (d, J = 8.0 Hz, 1 H), 4.44 (s, 2 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 177.9, 161.2, 157.7, 152.2, 141.5, 141.1, 139.1, 138.5, 137.8, 136.0, 129.4, 129.3, 128.2, 127.2, 125.5, 125.2, 123.9, 122.4, 121.90, 121.0, 119.2, 32.9.


2-(6-Bromopyridin-2-yl)-3-(6-bromopyridin-2-ylmethyl)-7-methoxychromen-4-one (4f)

Colorless solid; yield: 360 mg (72%); mp 198–199 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.12 (d, J = 8.8 Hz, 1 H), 8.07 (dd, J = 7.6, 0.8 Hz, 1 H), 7.72 (t, J = 8.0 Hz, 1 H), 7.56 (dd, J = 8.8, 2.8 Hz, 1 H), 7.46 (d, J = 8.8 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 4.31 (s, 2 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 177.4, 164.4, 161.3, 158.1, 147.7, 152.2, 141.5, 141.0, 138.9, 138.5, 129.3, 127.4, 125.2, 123.3, 122.0, 120.6, 119.9, 32.8.


2-(6-Bromopyridin-2-yl)-3-(6-bromopyridin-2-ylmethyl)-6-methoxychromen-4-one (4g)

Colorless solid; yield: 404 mg (80%); mp 177–178 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.01 (d, J = 7.6 Hz, 1 H), 7.68 (t, J = 7.6 Hz, 1 H), 7.52–7.50 (m, 2 H), 7.36 (t, J = 7.6 Hz, 1 H), 7.25 (dd, J = 8.8, 2.8 Hz, 1 H), 7.20 (d, J = 7.6 Hz, 2 H), 4.32 (s, 2 H), 3.84 (s, 3 H).
1H NMR (400 MHz, CDCl3): δ = 8.01 (d, J = 8.4 Hz, 1 H), 7.69 (t, J = 7.6 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.21 (d, J = 7.6 Hz, 1 H), 7.20 (d, J = 7.6 Hz, 1 H), 7.04 (d, J = 8.4 Hz, 1 H), 1.95–1.88 (m, 2 H), 1.60–1.50 (m, 2 H), 0.98 (t, J = 7.6 Hz, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 177.4, 161.4, 158.6, 157.9, 156.4, 152.1, 141.3, 140.9, 138.8, 138.4, 133.9, 129.1, 125.0, 123.0, 121.8, 121.3, 113.8, 109.7, 107.3, 69.3, 32.7, 31.0, 19.2, 13.8.


7-Benzoxyl-2-(6-bromopyridin-2-yl)-3-(6-bromopyridin-2-ylmethyl)chromen-4-one (4l)
Colorless solid; yield: 461 mg (80%); mp 216–217 °C (hexanes/ EtOAc).
1H NMR (400 MHz, CDCl3): δ = 8.13 (d, J = 9.2 Hz, 1 H), 8.06 (d, J = 7.6 Hz, 1 H), 7.71 (t, J = 8.0 Hz, 1 H), 7.56 (dd, J = 8.0, 0.8 Hz, 1 H), 7.37 (t, J = 7.6 Hz, 1 H), 7.26 (t, J = 7.6 Hz, 1 H), 7.21 (d, J = 8.0 Hz, 1 H), 7.07 (d, J = 8.4, 0.8 Hz, 1 H), 6.81 (d, J = 8.0 Hz, 1 H), 4.23 (s, 2 H), 3.97 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 177.7, 161.4, 159.8, 157.9, 156.8, 152.0, 141.4, 140.9, 138.9, 134.0, 129.2, 125.1, 123.3, 122.1, 121.5, 113.6, 110.1, 106.2, 56.4, 32.9.


6-Benzoxyl-2-(6-bromopyridin-2-yl)-3-(6-bromopyridin-2-yl)methylchromen-4-one (4m)
Colorless solid; yield: 420 mg (73%); mp 184–185 °C (hexanes/ EtOAc).
1H NMR (400 MHz, CDCl3): δ = 8.05 (dd, J = 7.6, 0.4 Hz, 1 H), 7.72 (t, J = 7.6 Hz, 1 H), 7.68 (d, J = 2.8 Hz, 1 H), 7.56 (dd, J = 8.0, 0.8 Hz, 1 H), 7.48–7.34 (m, 8 H), 7.24 (d, J = 7.6 Hz, 2 H), 7.06 (dd, J = 8.8, 2.4 Hz, 1 H), 6.98 (d, J = 2.4 Hz, 1 H), 5.17 (s, 2 H), 4.28 (s, 2 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 178.0, 163.4, 161.3, 158.2, 157.6, 152.1, 141.4, 141.0, 138.9, 135.6, 129.3, 128.8 (2 ×), 128.4, 127.5, 127.47 (2 ×), 125.2, 123.3, 121.9, 120.4, 117.0, 115.4, 101.1, 70.5, 32.9.


5-Benzoxyl-2-(6-bromopyridin-2-yl)-3-(6-bromopyridin-2-yl)methylchromen-4-one (4n)
Colorless solid; yield: 403 mg (70%); mp 203–204 °C (hexanes/ EtOAc).
1H NMR (400 MHz, CDCl3): δ = 8.03 (dd, J = 7.6, 0.4 Hz, 1 H), 7.70 (t, J = 8.0 Hz, 1 H), 7.57–7.53 (m, 3 H), 7.51 (t, J = 8.0 Hz, 1 H), 7.40–7.36 (m, 3 H), 7.29 (t, J = 7.2 Hz, 1 H), 7.23 (dt, J = 8.0, 0.4 Hz, 1 H), 7.07 (dd, J = 8.4, 0.4 Hz, 2 H), 6.83 (d, J = 8.0 Hz, 1 H), 5.30 (s, 2 H), 4.32 (s, 2 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 177.4, 161.5, 158.6, 157.9, 156.5, 152.1, 141.4, 140.9, 138.9, 138.6, 133.8, 129.2, 128.6 (2 ×), 128.2, 127.7 (2 ×), 125.2, 124.7, 123.4, 123.3, 121.8, 119.1, 117.9, 116.0, 106.1, 70.6, 33.0.

(2-Bromopyridin-2-yl)-3-(6-bromopyridin-2-ylmethyl)-6-methylenochromen-4-one (4q)

Colorless solid; yield: 402 mg (83%); mp 163–164 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.02 (dd, J = 7.6, 1 H), 7.97 (t, J = 0.4 Hz, 1 H), 7.70 (t, J = 7.6 Hz, 1 H), 7.53 (dd, J = 8.0, 1 H), 7.49 (dd, J = 8.4, 2.0 Hz, 1 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.35 (d, J = 7.6 Hz, 1 H), 7.22 (d, J = 8.0 Hz, 2 H), 4.32 (s, 2 H), 2.43 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 176.5 (t, J = 3.1 Hz), 160.6, 158.3 (dd, J = 9.8, 24.79 Hz), 158.0, 151.6, 151.4 (dd, J = 11.4, 256.2 Hz), 141.4 (d, J = 2.3 Hz), 141.3, 141.1, 139.1, 138.5, 129.7, 125.3, 125.0, 124.0, 123.9 (dd, J = 8.3 Hz, 12.3), 123.1, 121.8, 120.6, 109.3 (dd, J = 20.5, 28.8 Hz, 106.2 (dd, J = 4.6, 23.5 Hz), 32.5.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C_{24}H_{16}Br_{2}FN_{2}O_{2}: 506.9153; found: 506.9151.

(2-Bromopyridin-2-yl)-3-(6-bromopyridin-2-ylmethyl)-6-(4-methoxyphenyl)chromen-4-one (4t)

Colorless solid; yield: 449 mg (78%); mp 162–163 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.36 (dd, J = 2.4 Hz, 1 H), 8.07 (d, J = 7.2 Hz, 1 H), 7.89 (dd, J = 8.4, 2.4 Hz, 1 H), 7.72 (t, J = 7.6 Hz, 1 H), 7.60–7.53 (m, 4 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.24 (t, J = 7.6 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 4.36 (s, 2 H), 3.85 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 178.2, 161.3, 159.8, 154.2, 152.1, 141.3, 141.0, 138.9, 138.4, 135.23, 135.20, 129.2, 125.2, 125.1, 123.2, 122.4, 121.7, 120.2, 117.8, 32.9, 20.9.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C_{26}H_{18}Br_{2}F_{2}N_{2}O_{2}: 564.9563; found: 564.9557.

Single-crystal X-ray diagram: crystal of compound 4t was grown by slow diffusion of EtOAc into a solution of compound 4t in CHCl3 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P T, a = 7.4786(8) Å, b = 10.0187(8) Å, c = 15.9674(13) Å, V = 1079.68(15) Å³, Z = 2, d_{calc} = 1.742 g/cm³, F(000) = 560, 20 range 1.315–26.402°, R indices (all data) R1 = 0.0221, wR2 = 0.0517.
6-(Biphenyl-4-yl)-2-(6-bromopyridin-2-yl)-3-(6-bromopyridin-2-ylmethyl)chromen-4-one (4w)

Colorless solid; yield: 460 mg (74%); mp 212–213 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.47 (d, J = 7.6, 1 H), 8.08 (d, J = 7.6, 1 H), 7.98 (dd, J = 8.8, 2.4 Hz, 1 H), 7.74–7.75 (m, 9 H), 7.48–7.35 (m, 4 H), 7.26 (t, J = 7.6 Hz, 1 H), 7.25 (t, J = 8.0 Hz, 1 H), 4.38 (s, 2 H).

13C{1H} NMR (100 MHz, CDCl3): 128.8 (2 ×), 127.6 (2 ×), 127.5, 127.4 (2 ×), 127.0 (2 ×), 125.2, 123.6, 123.3, 123.2, 122.9, 121.9, 120.5, 118.7, 32.9.


Single-crystal X-ray diagram: crystal of compound 4w was grown by slow diffusion of EtOAc into a solution of compound 4z in CH2Cl2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P1̅21̅1̅21̅, α = 10.8551(5) Å, b = 10.7878(6) Å, c = 11.1421(6) Å, β = 81.563.8(8) Å, γ = 2, Z = 2, dcalc = 1.560 g/cm3, F(000) = 392, 2θ range 2.043–26.470°, R indices (all data) R1 = 0.0404, wR2 = 0.1033.

2-(6-Fluoropyridin-2-yl)-3-(6-fluoropyridin-2-ylmethyl)chromen-4-one (4aa)

Colorless solid; yield: 249 mg (78%); mp 82–83 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.22 (dd, J = 8.0, 1.6 Hz, 1 H), 7.76 (dd, J = 8.0, 0.4 Hz, 1 H), 7.68 (t, J = 7.6 Hz, 1 H), 7.65 (dd, J = 8.4, 0.8 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 7.39 (t, J = 8.0 Hz, 1 H), 7.20 (d, J = 7.6 Hz, 1 H), 6.96 (d, J = 8.0 Hz, 1 H), 6.88 (d, J = 7.6 Hz, 1 H), 4.30 (s, 2 H), 2.49 (s, 3 H), 2.46 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 178.6, 160.4, 159.4, 158.4, 157.2, 156.0, 150.9, 136.7, 136.4, 133.6, 126.0, 124.9, 124.2, 123.0, 121.3, 120.4, 119.1, 118.0, 136.3, 24.4, 24.3.


2-(6-Methoxy-2-pyridyl)-3-(6-methoxy-2-pyridylmethyl)chromen-4-one (4ad)

Colorless solid; yield: 192 mg (43%); mp 82–83 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.27 (dd, J = 8.0, 1.6 Hz, 1 H), 7.87 (d, J = 8.0 Hz, 1 H), 7.58–7.61 (m, 3 H), 7.52 (d, J = 8.4, 0.8 Hz, 1 H), 7.28 (dt, J = 8.0, 0.8 Hz, 1 H), 6.76 (d, J = 6.8 Hz, 1 H), 6.45 (d, J = 8.4 Hz, 1 H), 4.53 (s, 2 H), 3.73 (s, 3 H), 3.65 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 178.2, 163.2, 163.1, 159.2, 157.7, 155.8, 149.3, 138.8, 138.5, 133.6, 126.0, 124.8, 122.8, 120.2, 117.8, 116.9, 114.7, 112.6, 10.3, 53.4, 52.9, 32.6.


3-Benzyl-2-phenylchromen-4-one (4ac)

Colorless solid; yield: 134 mg (43%); mp 82–83 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl3): δ = 8.25 (dd, J = 8.0, 1.6 Hz, 1 H), 7.71–7.62 (m, 3 H), 7.51 (d, J = 8.4, 0.4 Hz, 1 H), 7.38 (dt, J = 8.0, 0.8 Hz, 1 H), 6.76 (d, J = 6.8 Hz, 1 H), 6.45 (d, J = 8.4 Hz, 1 H), 4.53 (s, 2 H), 3.73 (s, 3 H), 3.65 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 178.2, 163.2, 163.1, 159.2, 157.7, 155.8, 149.3, 138.8, 138.5, 133.6, 126.0, 124.8, 122.8, 120.2, 117.8, 116.9, 114.7, 112.6, 10.3, 53.4, 52.9, 32.6.

**2-(Furan-2-yl)-3-(furan-2-ylmethyl)chromone-4-one (4af)**

Colorless solid; yield: 194 mg (60%); mp 138–139 °C (hexanes/EtOAc).

**1H NMR (400 MHz, CDCl3):** δ = 8.25 (dd, J = 8.0, 1.6 Hz, 1 H), 7.68 (dd, J = 7.2, 1.6 Hz, 1 H), 7.64 (dd, J = 8.0, 1.2 Hz, 1 H), 7.61 (dd, J = 8.8, 0.8 Hz, 1 H), 7.50 (dd, J = 8.0, 0.8 Hz, 1 H), 7.40 (dd, J = 8.8, 0.8 Hz, 1 H), 7.16 (dd, J = 4.8, 0.8 Hz, 1 H), 6.12 (dd, J = 4.8, 1.2 Hz, 1 H), 6.90–6.87 (m, 2 H), 4.36 (d, J = 0.8 Hz, 2 H).

**13C{1H} NMR (100 MHz, CDCl3):** δ = 177.6, 156.6, 155.7, 142.0, 134.4, 133.7, 130.6, 127.9, 126.8, 126.1, 125.0, 124.7, 123.6, 122.6, 119.0, 117.8, 26.2.


Single-crystal X-ray diagram: crystal of compound 4ag was grown by slow diffusion of EtOAc into a solution of compound 4ag in CH2Cl2 to yield colorless prisms. The crystal structures in the monoclinic crystal system, space group P21/n, a = 9.1253(10) Å, b = 9.1493(10) Å, c = 18.386(2) Å, V = 1512.1(3) Å³, Z = 4, dcalc = 1.425 g/cm³, R(000) = 672, 28 range 2.249–26.551°, R indices (all data) R1 = 0.0339, wR2 = 0.0734.

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**2-(Pyridin-3-yl)-3-(pyridin-3-ylmethyl)chromene-4-one (4ah)**

Colorless gum; yield: 85 mg (27%).

**1H NMR (400 MHz, CDCl3):** δ = 8.78 (dd, J = 1.6, 0.8 Hz, 1 H), 8.73 (dd, J = 4.8, 1.6 Hz, 1 H), 8.35 (d, J = 3.6 Hz, 1 H), 8.26 (dd, J = 1.6, 1 Hz, 1 H), 8.20 (dd, J = 8.0, 1.6 Hz, 1 H), 7.79 (dd, J = 8.0, 2.4 Hz, 1 H), 7.67 (dd, J = 8.4, 1.6 Hz, 1 H), 7.45–7.38 (m, 4 H), 7.10 (dd, J = 8.0, 0.8 Hz, 1 H), 3.91 (s, 2 H).

**13C{1H} NMR (100 MHz, CDCl3):** δ = 177.5, 160.1, 156.0, 151.4, 149.2, 144.0, 147.5, 135.8, 135.6, 135.0, 128.9, 125.9, 125.3, 123.2 (2 x), 122.7, 120.6, 117.9, 28.4.


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**2-(Benzo-furan-2-yl)-3-(benzofuran-2-ylmethyl)chromone-4-one (4ai)**

Colorless solid; yield: 251 mg (64%); mp 186–187 °C (hexanes/EtOAc).

**1H NMR (400 MHz, CDCl3):** δ = 8.27 (dd, J = 8.4, 1.6 Hz, 1 H), 7.72 (dt, J = 8.4, 1.6 Hz, 1 H), 7.69 (dd, J = 8.0, 0.8 Hz, 1 H), 7.59 (dd, J = 8.0, 0.8 Hz, 1 H), 7.56 (dd, J = 8.4, 0.8 Hz, 1 H), 7.45–7.39 (m, 4 H), 7.32 (dd, J = 8.0, 0.8 Hz, 1 H), 7.17 (dt, J = 8.8, 1.6 Hz, 1 H), 7.12 (dt, J = 8.0, 1.6 Hz, 1 H), 6.47 (d, J = 12.2 Hz, 1 H), 4.61 (d, J = 0.8 Hz, 2 H).

**13C{1H} NMR (100 MHz, CDCl3):** δ = 177.5, 156.5, 155.7, 156.4, 152.5, 148.2, 143.0, 129.7, 128.6, 128.1, 124.7, 123.1, 122.4, 122.2, 120.3, 117.8, 117.3, 111.9, 111.5, 110.8, 102.9, 23.9.

HRMS (ESI-TOF): m/z [M + H]+ calcld for C20H15N2O2: 393.1127; found: 393.1122.
The mixture was cooled to 25 °C, concentrated, and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc 8:1–2:1) afforded 4an as a colorless gum; yield: 220 mg (75%).

1H NMR (400 MHz, CDCl₃); δ = 8.24 (dd, J = 8.0, 1.6 Hz, 1 H), 7.93 (dd, J = 7.6, 0.8 Hz, 1 H), 7.85 (dd, J = 8.0, 0.8 Hz, 1 H), 7.76 (dd, J = 8.0, 0.8 Hz, 1 H), 7.70 (dt, J = 8.4, 1.6 Hz, 1 H), 7.56–7.52 (m, 4 H), 7.45–7.47 (m, 4 H), 7.17 (d, J = 7.6 Hz, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 4.70 (s, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.71 (s, 3 H), 3.70 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl₃): δ = 137.8, 151.7, 150.2, 149.0, 141.0, 138.4, 136.8, 133.9, 133.5, 126.5, 125.5, 124.5, 123.0, 121.2, 118.4, 117.9, 116.8, 111.0, 110.7, 110.0, 109.9, 55.84, 55.81, 55.7, 55.5, 33.5.


4an: Colorless solid; yield: 129 mg (40%); mp 208–210 °C.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C₂₀H₁₉BrN₂O₄: 529.0763; found: 529.0769.

4an: Colorless solid; yield: 220 mg (40%); mp 208–209 °C (hexanes/EtOAc).

1H NMR (400 MHz, CDCl₃); δ = 8.28 (dd, J = 8.0, 1.6 Hz, 1 H), 7.69 (dt, J = 8.4, 1.6 Hz, 1 H), 7.49 (dd, J = 8.4, 0.8 Hz, 1 H), 7.43 (dt, J = 8.0, 0.8 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 6.42 (s, 1 H), 5.95–5.85 (m, 1 H), 4.91–4.82 (m, 2 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 3.51 (dt, J = 6.4, 1.6 Hz, 2 H).

13C{1H} NMR (100 MHz, CDCl₃); δ = 173.2, 155.6, 154.4, 147.8, 147.7, 138.4, 136.6, 133.9, 133.5, 126.5, 125.5, 124.5, 123.0, 121.2, 118.4, 115.2, 110.2, 60.8, 55.8, 31.8.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C₂₈H₂₂BrN₂O₄: 529.0763; found: 529.0762.

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Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690760. Included are scanned photocopies of NMR spectral data for all compounds and X-ray analysis data of 4a-4d, 4g, 4i, 4z and 4ag.

References


(11) CCDC 1896972 (4a), 1896973 (4b), 1896974 (4c), 1896975 (4d), 1896977 (4g), 1896978 (4t), and 1896979 (4z) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.