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Efficient Synthesis of Chromone and Flavonoid Derivatives with Diverse Heterocyclic Units

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Abstract: Chromones and flavonoids are important bioactive compounds. We envisioned that new heterocyclic-substituted chromones or flavonoids might act as new bioactive compounds. To obtain diverse molecules, we developed an efficient one-pot synthesis by Michael aldol reaction of chromone and flavonoid derivatives bearing heterocyclic units. The 2,3-heterocyclic-substituted chromones were obtained in one step. Moreover, the use of substituted benzaldehydes and subsequent addition of heterocyclic aldehydes gave 3-pyridyl-substituted flavones. We also examined these one-pot reactions in the solid phase. To introduce an additional point of diversity into the molecules, Suzuki–Miyaura coupling was performed. Furthermore, we identified the cytotoxicity of the synthesized compounds against cancer cells (PANC1 and HeLa cells). Several compounds were cytotoxic to these cancer cells.

Keywords: chromones · flavonoids · Michael aldol · one-pot synthesis · pyridine

Introduction

Natural products have a biological role, so the synthesis of small molecules based on their scaffolds would be of chemical relevance to living cells and organs,[1] binding to proteins, absorption, distribution, metabolism, and excretion. In this study, we envisioned new heterocyclic-substituted chromones or flavonoids that would act as bioactive compounds (Figure 1). Flavonoids are important bioactive compounds isolated from a wide range of plants.[2] Many studies have suggested that flavonoids have biological activity, such as antiviral action, anti-inflammatory effects, and a beneficial influence on multiple cancer-related biological pathways. In addition, pyridinyl-substituted flavanone derivatives have received attention recently.[3]

To find new bioactive chromones and flavonoids, an efficient synthesis method in which it is easy to add molecules with structural or substitutional diversity is important. Construction of small molecules with complexity and diversity would increase the number of protein-binding elements. Efficient one-pot syntheses of flavones with disubstituents at the 2- and 3-positions have yet to be developed. Chawla and Sharma reported the first one-pot synthesis of 3-arylideneflavonoids from 2′-hydroxyacetophenones with aromatic aldehydes in aqueous NaOH.[4] Dhara et al. reported an improved one-pot synthesis of 3-arylideneflavonoids and 2,3-disubstituted chromanones by using furfural or thiophen-2-aldehyde.[5] The Baker–Venkataraman rearrangement is another important one-pot method for synthesizing 3-acyl flavonoids from 2′-hydroxyacetophenones, and a 3-acyl flavonoid with pyridine units was synthesized in this manner.[6]

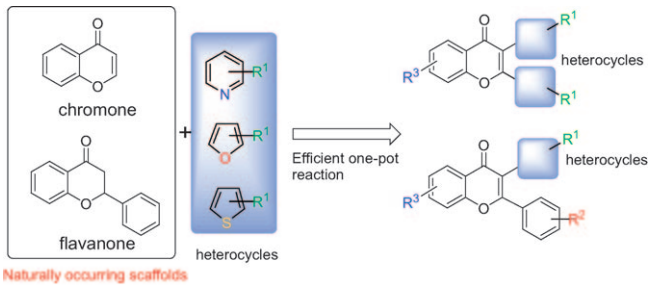

Figure 1. Synthesis of chromones and flavonoids with heterocycles.

Herein, practical, useful syntheses of heterocyclic-substituted chromones and flavonoids are described (Scheme 1). A one-pot synthesis by Michael aldol reaction of chromone and flavonoid derivatives bearing heterocycle units was developed. The 2,3-heterocyclic-substituted chromones were

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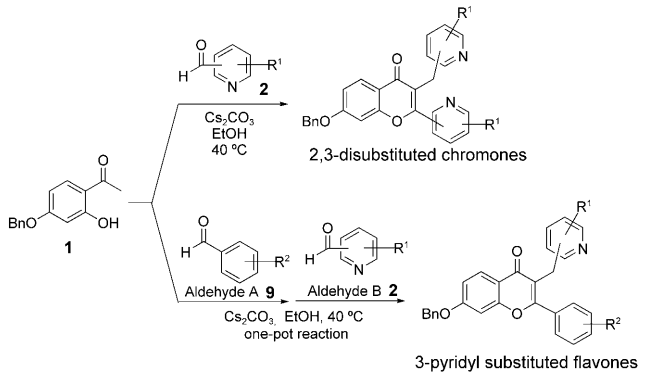


Scheme 1. One-pot synthesis by Michael aldol reaction of chromone and flavonoid derivatives bearing pyridine units.

obtained in one step. Moreover, the use of substituted benzaldehydes **9** (aldehyde A) and subsequent addition of heterocyclic aldehydes **2** (aldehyde B) gave 3-pyridyl-substituted flavones in one step. We also examined the application of these one-pot reactions to solid-phase synthesis to establish a library synthesis of diverse molecules with the naturally occurring scaffolds chromone and flavone. Suzuki–Miyaura coupling was performed to introduce an additional point of diversity into the molecules.

Results and Discussion

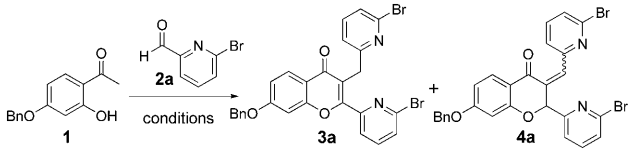
One-Pot Synthesis of Heterocyclic-Substituted Chromones and Flavonoids

The one-pot synthesis by Michael aldol reaction of chromone derivatives bearing pyridine units was optimized as shown in Table 1. 4′-Benzyloxy-2′-hydroxyacetophenone (**1**) reacted with 6-bromo-2-pyridinecarboxaldehyde (**2a**) to give 2,3-disubstituted chromone **3a** in 81% yield under KOH conditions (Table 1, entry 1). To our knowledge, there are no previously published examples of 2,3-dipyridinyl-substituted chromone scaffolds. The reaction rate was increased at 40 °C with comparable yield (Table 1, entry 2). We examined the effects of base (Table 1, entries 3–6), and Cs_2CO_3 was found to give the best yield (90%), and the reaction rate was also improved. Changing the solvent does not alter the main product, although the use of aprotic solvents such as THF and CH_2Cl_2 (Table 1, entries 9, 10) decreased the yield. Because of the Cannizzaro reaction, we decided to use excess (10 equiv) aldehyde under the final conditions.[7]

Abstract in Japanese:

天然物にて有用な活性を持つクロモンやフラボノイドの骨格を活かし、多様なヘテロ環置換基を有する化合物をMichael-aldol連続反応により、ワンポットで効率的に合成した。2,3位にヘテロ環を有するクロモン誘導体、3位にヘテロ環を有するフラボノイドを多種合成した。本法は固相合成にも適用でき、鈴木—宮浦クロスカップリングにて、化合物にさらに多様性を持たせた。これらの合成化合物の中には癌細胞毒性を有するものが見出された。

Table 1. Optimization of the reaction conditions.

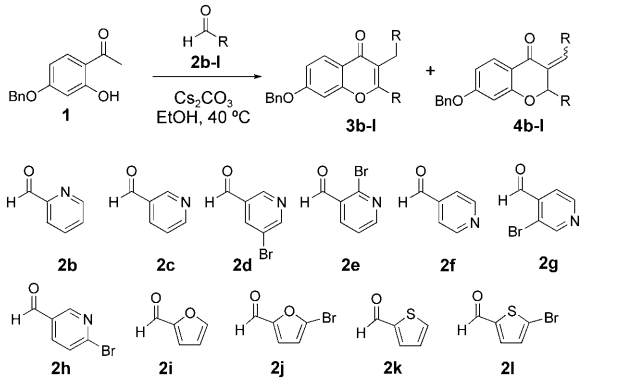


Entry[a]	Base	Solvent	T [°C]	t [h]	Yield [%][b] **3a** (*endo*)	**4a** (*exo*)
1	KOH	EtOH	RT	117	81	0
2	KOH	EtOH	40	11	80	0
3	NaOH	EtOH	40	11	75	0
4	K_2CO_3	EtOH	40	11	10	60
5[c]	$Ba(OH)_2$	EtOH	40	11	0	0
6	Cs_2CO_3	EtOH	40	8	90	0
7	Cs_2CO_3	MeOH	40	11	91	0
8	Cs_2CO_3	*i*PrOH	40	11	73	0
9	Cs_2CO_3	THF	40	11	45	0
10	Cs_2CO_3	CH_2Cl_2	40	11	53	0

[a] All reactions were carried out with **2a** (10 equiv) and base (5 equiv) in solvent (0.16 M). [b] Yields of isolated products based on **1**. [c] Only chalcone was obtained, in 49% yield.

We examined the influence of different substituents on the pyridine aldehydes (Table 2). The one-pot reaction proceeded smoothly with pyridinecarboxaldehydes **2b–h** (Table 2, entries 1–7). *Endo* olefinic products **3** were obtained in good yield in all cases apart from for **2e**. In some cases, *exo* products were obtained when the reactions were quenched after a shorter reaction time. The position of the

Table 2. Synthesis of chromones bearing heterocycles.

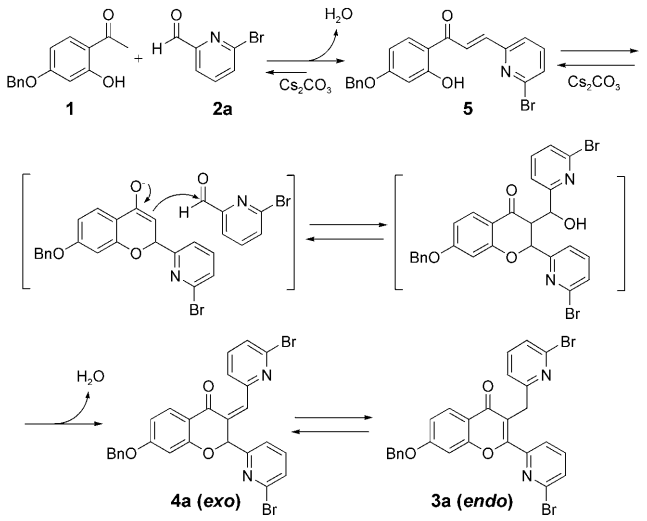


Entry[a]	Aldehyde	t [h]	Yield [%][b] **3** (*endo*)		**4** (*exo*)	
1	**2b**	47.5	**3b**	65	**4b**	0
2	**2c**	21.5	**3c**	66	**4c**	0
3	**2d**	15.5	**3d**	82	**4d**	0
4	**2e**	26	**3e**	0	**4e**	93
5	**2f**	12	**3f**	90	**4f**	0
6	**2g**	5	**3g**	84	**4g**	0
7	**2h**	42	**3h**	60	**4h**	0
8	**2i**	73	**3i**	91	**4i**	0
9	**2j**	74	**3j**	8	**4j**	71
10	**2k**	144	**3k**	90	**4k**	0
11	**2l**	63	**3l**	84	**4l**	0

[a] All reactions were carried out with **2** (10 equiv) and Cs_2CO_3 (5 equiv) in EtOH (0.16 M). [b] Yields of isolated products based on **1**.

CHO or Br group on the pyridine ring did not affect the yield. Furfural (**2i**) also gave the *endo* product in 91% yield (Table 2, entry 8), whereas its Br derivative **2j** gave mainly the *exo* product (Table 2, entry 9). The one-pot reaction with thiophen-2-aldehyde (**2k**) (Table 2, entry 10) and its Br derivative **2l** (Table 2, entry 11) gave heterocyclic-substituted chromones. In every case when heterocyclic aldehydes (**2a–l**) were used, chalcone formed spontaneously when **1** and aldehyde **2** were mixed.

A plausible mechanism based on the Michael aldol reaction is outlined in Scheme 2. In the presence of Cs_2CO_3, **1** reacts with aldehyde **2a** to produce an intermediate chalcone derivative **5**. This step is fast, and in most cases **1** was consumed within minutes. The intermediate chalcone **5** then undergoes intramolecular cyclization and subsequent aldol reaction with another aldehyde. The mono-2-substituted chromone was not obtained, revealing that the Michael aldol reaction occurs in a tandem manner. Thus, the *exo* olefin product **4a** is produced first and then isomerizes to form the *endo* olefin product **3a**.

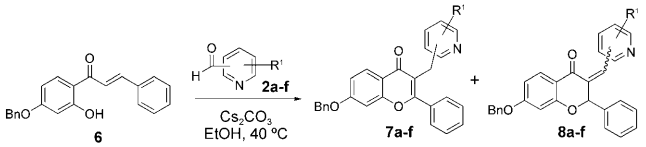


Scheme 2. Plausible mechanism for the construction of chromones from **1** and aldehydes.

Next, we studied the synthesis of flavonoids bearing different substituents (Table 3). Chalcone **6** was synthesized by the reaction of **1** and benzaldehyde with Cs_2CO_3.[8] Michael aldol reaction of **6** with pyridinecarboxaldehydes **2a–d,f** proceeded very smoothly to give the flavonoid derivatives **7** and **8**.

With these results in hand, we attempted the one-pot synthesis of 3-pyridyl-substituted flavonoids (Table 4). After chalcone formation between **1** and benzaldehyde **9a–f**, pyridinecarboxaldehyde **2** was added to the reaction mixture. The one-pot reaction proceeded smoothly to give 3-pyridyl-substituted flavonoids. Chalcone formation with **9** was slower than the reaction between **1** and **2**, and cyclization of these chalcones was very slow. However, the addition of pyridinecarboxaldehyde **2** led the chalcones to cyclize, and the Michael aldol tandem reaction proceeded. Pyridine as a base did not help the cyclization of chalcone **6** with benzaldehyde **9a**,[9] so this acceleration in cyclization might not result from the basicity of the pyridine nature of **2**. Thus, in addition to the high reactivity of pyridinecarboxaldehydes, we assume that the pyridinyl-cyclized products, 3-pyridinyl benzopyranones, are more thermodynamically stable in the subsequent Michael aldol reaction than those without a pyridine unit.

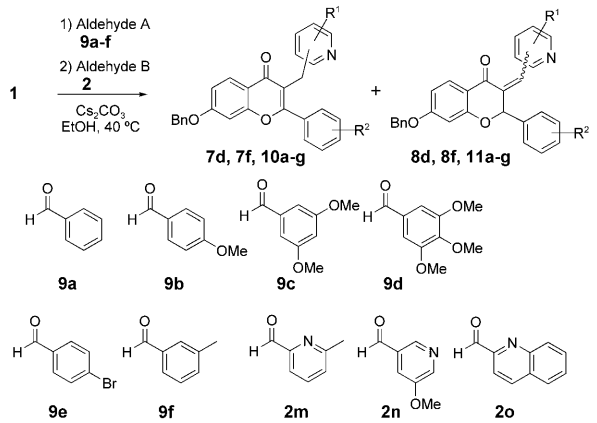
Table 3. Synthesis of flavonoids by Michael aldol reaction.



Entry[a]	Aldehyde	*t* [h]	Yield [%][b] **7** (*endo*)		**8** (*exo*)	
1	**2a**	2	**7a**	0	**8a**	82
2	**2b**	3	**7b**	26	**8b**	56
3	**2c**	29	**7c**	62	**8c**	1
4	**2d**	2	**7d**	68	**8d**	0
5	**2f**	3	**7f**	77	**8f**	0

[a] All reactions were carried out with **2** (10 equiv) and Cs_2CO_3 (5 equiv) in EtOH (0.16 M). [b] Yields of isolated products based on **6**.

Table 4. One-pot synthesis of 3-pyridyl-substituted flavonoids.



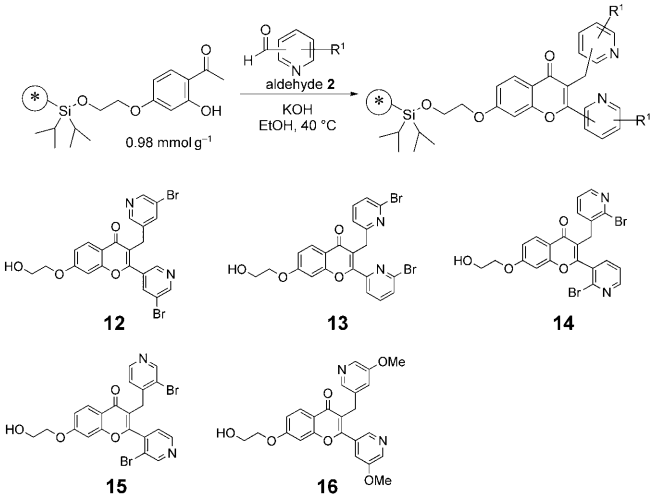
Entry[a]	Reaction with A Aldehyde A	*t* [h]	Reaction with B Aldehyde B	*t* [h]	Yield [%][b] *endo*		*exo*	
1[c]	**9a**	7.5	**2b**	4	**7b**	4	**8b**	72
2	**9a**	7.5	**2c**	34	**7c**	69	**8c**	0
3	**9a**	7.5	**2d**	2	**7d**	70	**8d**	0
4	**9a**	7.5	**2f**	2	**7f**	62	**8f**	0
5	**9b**	48	**2m**	2	**10a**	0	**11a**	79
6	**9c**	26	**2c**	7	**10b**	60	**11b**	0
7	**9d**	26	**2g**	3	**10c**	95	**11c**	0
8	**9e**	8	**2d**	5	**10d**	68	**11d**	0
9	**9f**	15	**2g**	9	**10e**	95	**11e**	0
10	**9f**	15	**2o**	4	**10f**	72	**11f**	0
11	**9f**	18	**2b**	6.5	**10g**	83	**11g**	0
12	**9d**	26	**2n**	16.5	**10h**	65	**11h**	0

[a] All reactions were carried out with **9** (3 equiv) and Cs_2CO_3 (6 equiv) in EtOH (0.16 M) at 40 °C. After chalcone formation, **2** (7 equiv) was added. [b] Yields of isolated products based on **1**. [c] Even after 36 h, the yield of *endo* **7b** did not increase.

Application to Solid-Phase Reactions

This efficient reaction was applied to solid-phase reactions for constructing small-molecule libraries. Owing to the lower solubility of Cs_2CO_3, KOH was used as the base for the solid-phase reactions (Table 5). After attaching the acetophenone derivative to (4-methoxyphenyl)diisopropylsilylpropyl polystyrene beads (novabiochem), the desired one-pot reaction smoothly proceeded with aldehyde **2d** to give the 2,3-heterocyclic-substituted chromone. The yields of all reactions were determined after cleavage of the product from the beads and are based on the weight of crude material relative to the initial loading of resin. Without neutralization of the reaction mixture, the cleaved products were obtained as HCl salts, which indicated a strong IR absorption band for N^+–H at around 2440–2480 cm^{-1} (Table 5, entries 2–5). The product was obtained in 66% yield as the free base by neutralization (Table 5, entry 1). The purity of the crude material was estimated from ^1H and ^{13}C NMR spectroscopy. Next, we tried the one-pot reaction of 3-substituted flavonoids in the solid phase.

Table 5. Synthesis of chromones by one-pot solid-phase reaction.



Entry[a]	Aldehyde	t [h]	Product	Yield [%][b]	Purity [%][e]
1	**2d**	24	**12**	66[c]	>95
2	**2a**	72	**13**	76[d]	>90
3	**2e**	72	**14**	66[d]	>95
4	**2g**	72	**15**	81[d]	>95
5	**2n**	72	**16**	47[d]	>90

[a] All reactions were carried out with **2** (20 equiv) and KOH (10 equiv). [b] Yields are based on the weight of crude material and are relative to the initial loading of resin. Only *endo* products were detected. [c] After cleavage from beads with 2% HCl/dioxane for 3 h at room temperature, then neutralization with 1 N NaOH. [d] Compound was isolated as HCl salt after cleavage without neutralization. [e] The purity of the crude material was estimated from ^1H and ^{13}C NMR spectroscopy.

In the case of the synthesis of 3-heterocyclic substituted flavonoids, we had to find the best reaction conditions for chalcone formation (Scheme 3). After optimization of the conditions, the desired products **17b** and **20b** were obtained in good yields of 74 and 82%, respectively. Furthermore, to add diverse substituents on the molecules, we examined Suzuki–Miyaura coupling on the pyridine unit of the solid-phase synthesized products. Under several reported conditions, the described combination gave coupling products in good yields. Phenyl- (**18b**), *p*-methoxyphenyl- (**19b**), or *p*-acetamidophenyl- (**21b**) attached compounds were obtained in reasonable yields.

Evaluation of Bioactivity of Synthesized Compounds

Next, the compounds synthesized by one-pot reactions were evaluated for their cytotoxicity against cancer cells.[10] Of these compounds, **8b** showed cytotoxicity against human pancreatic cancer cells (PANC1) (IC_{50} = 18.4 μM). Compounds **4b** and **10c** showed cytotoxicity against HeLa cells (IC_{50} = 8.4 and 25 μM, respectively). These compounds did not show inhibitory activity of the Wnt signaling pathway[11] or promote activity of the death receptor (DR5).[12] We very recently constructed a cell-based assay system for screening inhibitor of the hedgehog (Hh) signaling pathway.[13] Many compounds showed cytotoxicity, but in less cytotoxic compounds, we found moderate inhibitors of Hh signaling pathway (at 50 μM, **3g**; cell viability, 70%, Hh inhibition, 72%; **11a**; cell viability, 78%, Hh inhibition, 61%). We are trying to determine the actual molecular target of these compounds. We continue our search of the solid-phase library for a strong Hh inhibitor with less cytotoxicity to normal cells.

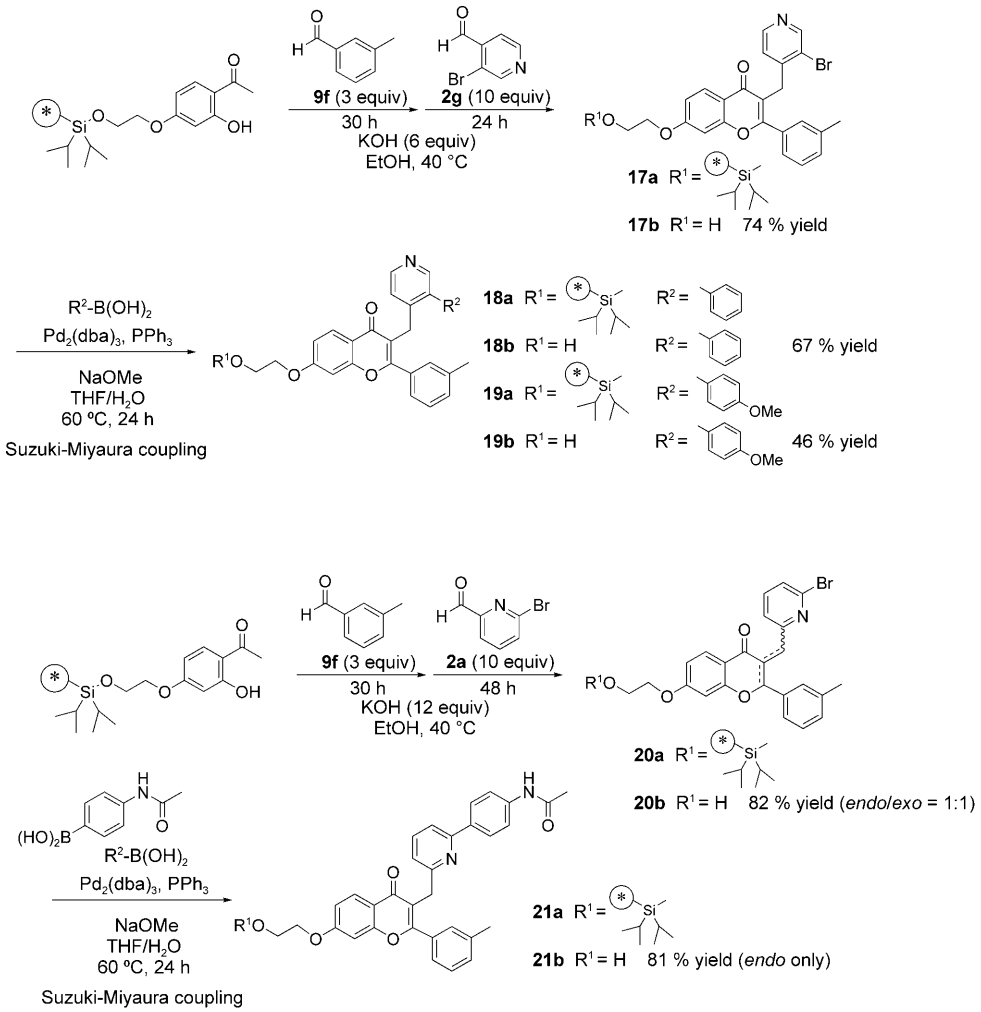
Conclusions

We have demonstrated an efficient one-pot synthesis of heterocyclic-substituted chromone and flavonoid derivatives by a Michael aldol tandem reaction. Several compounds showed cytotoxicity against cancer cells. These one-pot reactions could also be performed on the solid phase. Further application of this efficient reaction to solid-phase reactions for the construction of small-molecule libraries and bioactive evaluation of these new chromone and flavonoid derivatives are in progress.

Experimental Section

General procedure (Table 1 and 2): To a solution of 4′-bezyloxy-2′-hydroxyacetophenone (**1**) (50 mg, 0.21 mmol) in EtOH (1.3 mL; 0.16 M) was added Cs_2CO_3 (342 mg, 1.05 mmol) and 6-bromo-2-pyridinecarboxaldehyde (**2a**) (391 mg, 2.1 mmol), and the reaction mixture was stirred at 40 °C. The reaction mixture was quenched by addition of 10% AcOH in EtOH, and evaporated. The residue was dissolved in CH_2Cl_2 and H_2O, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to give the corresponding chromone derivatives (**3a**) and chromanone derivatives (**4a**). Several compounds can be separated only recrystallization with diethyl ether.

7-Benzyloxy-2-(3-bromo-2-pyridinyl)-3-(3-bromo-2-pyridinylmethyl)chromone (**3a**): IR (Attenuated Total Reflection (ATR)): $\tilde{\nu}$ = 1640, 1628,



Scheme 3. Application of the one-pot solid-phase reaction.

1609, 1579, 1552, 1435, 1425, 1381, 1173, 1119, 840, 789, 777, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.27$ (s, 2H), 5.17 (s, 2H), 6.99 (d, $J =$ 2.4 Hz, 1H), 7.07 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.22–7.26 (m, 2H), 7.36–7.46 (m, 6H), 7.58 (d, $J = 7.8$ Hz, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 8.07 (d, $J =$ 7.8 Hz, 1H), 8.14 ppm (d, $J = 8.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.4$, 163.4, 161.3, 158.2, 157.6, 152.1, 141.5, 141.0, 138.9, 138.5, 135.6, 129.3, 128.8, 128.4, 127.5, 125.2, 123.3, 121.9, 120.4, 117.1, 115.4, 101.1, 70.6, 32.9 ppm. FAB-MS $[M+H]^+$: 577. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{19}O_3N_2Br_2$ 576.9762, found 576.9758. This structure was confirmed by HMBC, HMQC, and DEPT experiments (see the Supporting Information).

7-Benzyloxy-2-(3-bromo-2-pyridinyl)-3-(3-bromo-2-pyridinylmethylene)-chromanone (**4a**): IR (ATR): $\tilde{\nu} = 1668$, 1602, 1569, 1542, 1404, 1237, 1162, 1104, 1001, 791, 757, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 5.07 (d, $J = 11.6$ Hz, 1H), 5.07 (d, $J = 11.6$ Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 6.66 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.33–7.49 (m, 10H), 7.58 (t, $J = 7.7$, 1H), 7.72 (s, 1H), 7.78 (s, 1H), 7.94 ppm (d, $J = 8.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.0$, 165.5, 161.5, 159.1, 154.3, 141.63, 141.61, 138.9, 138.7, 135.9, 135.8, 132.6, 129.5, 128.7, 128.3, 127.82, 127.81, 127.6, 126.6, 121.5, 115.8, 110.9, 102.3, 78.1, 70.3 ppm. FAB-MS $[M+H]^+$: 577. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{19}O_3N_2Br_2$ 576.9762, found 576.9753. This structure was confirmed by HMBC, HMQC, and DEPT experiments (see the Supporting Information).

7-Benzyloxy-2-(2-pyridinyl)-3-(2-pyridinylmethyl)chromone (**3b**): IR (ATR): $\tilde{\nu} = 1622$, 1601, 1447, 1366, 1239, 1186, 1110, 973, 777, 750, 714, 685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.33$ (s, 2H), 5.16 (s, 2H), 7.00 (d, $J = 2.3$ Hz, 1H), 7.04 (dd, $J = 7.7$, 1.1 Hz, 1H), 7.05 (dd, $J = 8.9$, 2.3 Hz, 1H), 7.27 (m, 1H), 7.33–7.46 (m, 6H), 7.54 (td, $J = 7.7$, 1.8 Hz, 1H), 7.81 (td, $J = 7.7$, 1.8 Hz, 1H), 8.02 (d, $J = 7.7$ Hz, 1H), 8.14 (d, $J = 8.9$ Hz, 1H), 8.45 (d, $J = 7.7$ Hz, 1H), 8.72 ppm (d, $J = 7.7$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 177.8$, 163.2, 160.1, 159.7, 157.8, 151.7, 149.6, 148.9, 136.6, 136.2, 135.7, 128.7, 128.4, 127.51, 127.47, 124.6, 124.5, 123.0, 120.9, 120.5, 117.2, 115.2, 101.1, 70.5, 33.5 ppm. FAB-MS $[M+H]^+$: 421. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{21}O_3N_2$ 421.1552, found 421.1519.

7-Benzyloxy-2-(3-pyridinyl)-3-(3-pyridinylmethyl)chromone (**3c**): IR (ATR): $\tilde{\nu} = 1627$, 1606, 1573, 1499, 1477, 1442, 1382, 1241, 1172, 1024, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.93$ (s, 2H), 5.17 (s, 2H), 6.94 (d, $J = 2.4$ Hz, 1H), 7.09 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.15 (dd, $J = 7.8$, 4.9 Hz, 1H), 7.34–7.50 (m, 7H), 7.79 (dt, $J = 8.1$, 2.0 Hz, 1H), 8.17 (d, $J = 9.0$ Hz, 1H), 8.30 (d, $J = 2.0$ Hz, 1H), 8.41 (dd, $J = 4.6$, 1.5 Hz, 1H), 8.77 (dd, $J =$ 4.9, 1.7 Hz, 1H), 8.81 ppm (d, $J = 2.2$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 176.8$, 163.6, 159.8, 157.9, 151.4, 149.6, 149.3, 147.7, 135.81, 135.80, 135.7, 135.3, 129.3, 128.8, 128.4, 127.7, 127.4, 123.28, 123.25, 121.0, 117.2, 115.4, 101.4, 70.7, 28.4 ppm. FAB-MS $[M+H]^+$: 421. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{21}O_3N_2$ 421.1552, found 421.1511.

7-Benzyloxy-2-(5-bromo-3-pyridinyl)-3-(5-bromo-3-pyridinylmethyl)chromone (**3d**): IR (ATR): $\tilde{\nu} = 1635$, 1625, 1600, 1442, 1377, 1360, 1239, 1177, 1098, 1005, 829, 727, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.90$ (s, 2H), 5.18 (s, 2H), 6.95 (d, $J = 2.4$ Hz, 1H), 7.11 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.34–7.46 (m, 5H), 7.62 (t, $J = 2.0$ Hz, 1H), 7.97 (t, $J = 2.0$ Hz, 1H), 8.16 (d, $J = 9.0$ Hz, 1H), 8.23 (d, $J = 2.0$ Hz, 1H), 8.50 (d, $J = 2.0$ Hz, 1H), 8.67 (d, $J = 2.0$ Hz, 1H), 8.84 ppm (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 176.5, 163.7, 158.2, 157.8, 152.7, 149.0, 147.5, 147.0, 138.4, 138.3, 136.7, 135.5, 130.2, 128.8, 128.5, 127.7, 127.5, 120.8, 120.8, 120.5, 116.8, 115.8, 101.1, 70.6, 28.2 ppm. FAB-MS $[M+H]^+$: 577. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{19}O_3N_2Br_2$ 576.9762, found 576.9715.

7-Benzyloxy-2-(2-bromo-3-pyridinyl)-3-(2-bromo-3-pyridinylmethylene)-chromanone (**4e**): IR (ATR): $\tilde{\nu}$ = 1632, 1608, 1556, 1498, 1440, 1381, 1241, 1171, 1100, 1048, 777, 737, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.17 (s, 2H), 6.94 (d, J = 2.4 Hz, 1H), 7.08 (dd, J = 7.6, 4.6 Hz, 1H), 7.13 (dd, J = 9.0, 2.4 Hz, 1H), 7.33 (dd, J = 7.6, 2.0 Hz, 1H), 7.36–7.45 (m, 8H), 7.49 (dd, J = 7.6, 2.0 Hz, 1H), 8.14 (dd, J = 4.6, 2.0 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.50 ppm (dd, J = 4.4, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.8, 163.8, 160.1, 158.1, 151.6, 147.8, 143.9, 142.0, 138.6, 138.2, 136.1, 135.8, 131.3, 128.8, 128.5, 127.8, 127.5, 122.7, 122.5, 121.2, 117.3, 115.7, 101.5, 70.8, 30.2 ppm. FAB-MS $[M+H]^+$: 577. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{19}O_3N_2Br_2$ 576.9762, found 576.9758.

7-Benzyloxy-2-(4-pyridinyl)-3-(4-pyridinylmethyl)chromone (**3f**): IR (ATR): $\tilde{\nu}$ = 1625, 1600, 1590, 1570, 1545, 1500, 1443, 1383, 1241, 1179, 1006, 838, 776, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 2H), 5.18 (s, 2H), 6.96 (d, J = 2.2 Hz, 1H), 7.05 (d, J = 4.4, 1.7 Hz, 2H), 7.11 (dd, J = 9.0, 2.2 Hz, 1H), 7.37–7.46 (m, 7H), 8.16 (d, J = 9.0, Hz, 1H), 8.43 (dd, J = 4.4, 1.7 Hz, 2H), 8.76 ppm (dd, J = 4.4, 1.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.8, 163.6, 159.8, 157.8, 150.5, 149.9, 148.6, 140.2, 135.5, 128.8, 128.5, 127.7, 127.4, 123.3, 122.5, 119.7, 116.8, 115.7, 101.1, 70.6, 30.5 ppm. FAB-MS $[M+H]^+$: 421. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{21}O_3N_2$ 421.1552, found 421.1519.

7-Benzyloxy-2-(2-bromo-4-pyridinyl)-3-(2-bromo-4-pyridinylmethyl)chromone (**3g**): IR (ATR): $\tilde{\nu}$ = 1635, 1610, 1440, 1397, 1382, 1241, 1176, 1085, 1019, 832, 781, 734, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 2H), 5.17 (s, 2H), 6.94 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 4.9 Hz, 1H), 7.13 (dd, J = 9.0, 2.4 Hz, 1H), 7.15 (dd, J = 4.9, 0.5 Hz, 1H), 7.34–7.46 (m, 5H), 8.20 (d, J = 9.0 Hz, 1H), 8.29 (d, J = 4.9 Hz, 1H), 8.56 (s, 1H), 8.60 (d, J = 4.9 Hz, 1H), 8.88 ppm (d, J = 0.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.4, 163.7, 159.4, 158.0, 153.0, 151.7, 148.7, 148.1, 147.2, 140.6, 135.4, 128.8, 128.5, 127.7, 127.5, 124.34, 124.27, 122.8, 120.6, 120.0, 117.0, 115.9, 101.2, 70.7, 30.1 ppm. FAB-MS $[M+H]^+$: 577. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{19}O_3N_2Br_2$ 576.9762, found 576.9758.

7-Benzyloxy-2-(4-bromo-3-pyridinyl)-3-(4-bromo-3-pyridinylmethyl)chromone (**3h**): IR (ATR): $\tilde{\nu}$ = 1628, 1606, 1577, 1498, 1441, 1381, 1241, 1173, 1120, 1083, 1019, 831, 779, 735, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 2H), 5.17 (s, 2H), 6.92 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 9.0, 2.4 Hz, 1H), 7.33–7.45 (m, 7H), 7.64–7.65 (m, 2H), 8.05 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.55 ppm (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.5, 163.8, 158.7, 157.9, 149.7, 149.5, 144.5, 140.2, 138.5, 137.9, 135.7, 134.4, 128.8, 128.5, 128.28, 128.26, 127.9, 127.8, 127.4, 120.8, 117.1, 115.7, 101.5, 70.8, 28.0 ppm. FAB-MS $[M+H]^+$: 577. FAB-HRMS $[M+H]^+$: calcd for $C_{27}H_{19}O_3N_2Br_2$ 576.9762, found 576.9758.

7-Benzyloxy-2-(2-furanyl)-3-(2-furanylmethyl)chromone (**3i**): IR (ATR): $\tilde{\nu}$ = 1615, 1606, 1570, 1498, 1444, 1358, 1248, 1182, 1097, 1006, 928, 841, 791, 743, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.28 (s, 2H), 5.17 (s, 2H), 6.04 (d, J = 3.2 Hz, 1H), 6.24 (dd, J = 3.2, 1.7 Hz, 1H), 6.60 (dd, J = 3.6, 1.7 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.9, 2.4 Hz, 1H), 7.13 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.35–7.47 (m, 5H), 7.67 (d, J = 1.7 Hz, 1H), 8.14 ppm (d, J = 8.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 163.1, 157.1, 153.2, 151.9, 146.7, 145.2, 140.9, 135.7, 128.7, 128.3, 127.5, 127.5, 116.8, 115.9, 115.0, 114.8, 112.0, 110.3, 105.8, 100.9, 70.5, 23.2 ppm. FAB-MS $[M]^+$: 398. FAB-HRMS $[M]^+$: calcd for $C_{25}H_{18}O_5$ 398.1154, found 398.1144.

7-Benzyloxy-2-(3-bromo-2-furanyl)-3-(3-bromo-2-furanylmethyl)chromone (**3j**): IR (ATR): $\tilde{\nu}$ = 1606, 1498, 1441, 1395, 1242, 1178, 1011, 785, 736, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (s, 2H), 5.18 (s, 2H), 6.05 (d, J = 3.5 Hz, 1H), 6.15 (d, J = 3.5 Hz, 1H), 6.55 (d, J = 3.6 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 9.0, 2.2 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 7.37–7.46 (m, 5H), 8.13 ppm (d, J = 9.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6, 163.4, 157.1, 155.0, 151.0, 148.1, 135.7, 128.8, 128.4, 127.6, 127.5, 126.2, 119.3, 117.1, 116.8, 115.6, 115.1, 114.1, 112.0, 108.9, 101.1, 70.6, 23.4 ppm. FAB-MS $[M+H]^+$: 555. FAB-HRMS $[M+H]^+$: calcd for $C_{25}H_{17}O_5Br_2$ 554.9443, found 554.9417.

7-Benzyloxy-2-(3-bromo-2-furanyl)-3-(3-bromo-2-furanylmethylene)chromanone (**4j**): IR (ATR): $\tilde{\nu}$ = 1667, 1602, 1440, 1299, 1254, 1206, 1139, 1106, 1017, 972, 833, 784 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.07 (d, J = 11.6 Hz, 1H), 5.08 (d, J = 11.6 Hz, 1H), 6.15 (d, J = 3.4 Hz, 1H), 6.17 (d, J = 3.4 Hz, 1H), 6.46 (d, J = 3.7 Hz, 1H), 6.49 (d, J = 2.3 Hz, 1H), 6.66 (d, J = 3.7 Hz, 1H), 6.68 (dd, J = 8.9, 2.3 Hz, 1H), 6.94 (s, 1H), 7.34–7.42 (m, 5H), 7.55 (s, 1H), 7.93 ppm (d, J = 8.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.3, 165.4, 160.8, 153.5, 152.5, 135.8, 129.3, 128.7, 128.3, 127.6, 127.2, 126.0, 123.0, 122.5, 120.8, 115.5, 114.7, 112.5, 112.1, 111.1, 102.5, 72.1, 70.3 ppm. FAB-MS $[M+H]^+$: 555. FAB-HRMS $[M+H]^+$: calcd for $C_{25}H_{17}O_5Br_2$ 554.9443, found 554.9417.

7-Benzyloxy-2-(2-thienyl)-3-(2-thienylmethyl)chromone (**3k**): IR (ATR): $\tilde{\nu}$ = 1611, 1590, 1559, 1496, 1444, 1416, 1383, 1249, 1177, 1096, 1003, 837, 786, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.33 (s, 2H), 5.18 (s, 2H), 6.86 (dd, J = 3.5, 1.2 Hz, 1H), 6.89 (dd, J = 5.1, 3.5 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 7.05 (dd, J = 8.9, 2.3 Hz, 1H), 7.11 (dd, J = 5.1, 1.2 Hz, 1H), 7.15 (dd, J = 4.6, 4.2 Hz, 1H), 7.34–7.47 (m, 5H), 7.59–7.60 (m, 2H), 8.16 ppm (d, J = 8.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9, 163.2, 157.4, 156.2, 142.2, 135.7, 134.5, 130.4, 129.8, 128.7, 128.4, 127.8, 127.6, 127.5, 126.8, 124.7, 123.6, 119.0, 116.8, 115.0, 101.0, 70.5, 26.2 ppm. FAB-MS $[M]^+$: 430. FAB-HRMS $[M]^+$: calcd for $C_{25}H_{18}O_3S_2$ 430.0697, found 430.0678.

7-Benzyloxy-2-(3-bromo-2-thienyl)-3-(3-bromo-2-thienylmethyl)chromone (**3l**): IR (ATR): $\tilde{\nu}$ = 1615, 1590, 1560, 1496, 1441, 1416, 1378, 1247, 1179, 967, 831, 784, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (s, 2H), 5.18 (s, 2H), 6.62 (d, J = 3.7 Hz, 1H), 6.84 (d, J = 3.7 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 8.9, 2.4 Hz, 1H), 7.13 (d, J = 4.1 Hz, 1H), 7.33 (d, J = 4.1 Hz, 1H), 7.37–7.47 (m, 5H), 8.14 ppm (d, J = 8.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 176.7, 163.5, 157.3, 155.1, 143.5, 135.64, 135.60, 130.9, 130.6, 129.6, 128.8, 128.5, 127.6, 127.5, 125.2, 118.3, 118.0, 116.6, 115.3, 110.0, 100.9, 70.6, 26.5 ppm. FAB-MS $[M+H]^+$: 587. FAB-HRMS $[M+H]^+$: calcd for $C_{25}H_{17}O_3S_2Br_2$ 586.8986, found 586.8950.

General procedure (Table 3): To a solution of 4′-(benzyloxy)-2′-hydroxychalcone (**6**; known compound) (50 mg, 0.15 mmol) in EtOH (0.94 mL; 0.16 M) was added Cs_2CO_3 (248 mg, 0.76 mmol) and 4-pyridinecarboxaldehyde (**2f**) (0.14 mL, 1.51 mmol), and the reaction mixture was stirred at 40 °C. The reaction mixture was quenched by addition of 10% AcOH in EtOH, and evaporated. The residue was dissolved in CH_2Cl_2 and H_2O, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to give the corresponding flavone derivatives (**7f**) (and/or flavanone derivatives **8**.)

7-Benzyloxy-3-(3-bromo-2-pyridinylmethylene)flavanone (**8a**): IR (ATR): $\tilde{\nu}$ = 1697, 1664, 1610, 1597, 1571, 1558, 1407, 1296, 1255, 1166, 1104, 1011, 985, 833, 793, 762, 714, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.05 (d, J = 11.7 Hz, 1H), 5.09 (d, J = 11.7 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.64 (dd, J = 8.8, 2.4 Hz, 1H), 7.21–7.28 (m, 3H), 7.32–7.45 (m, 9H), 7.57 (t, J = 7.7 Hz, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.88 (s, 1H), 7.91 ppm (d, J = 8.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.7, 165.7, 161.9, 154.4, 141.7, 138.8, 138.6, 137.3, 135.8, 132.0, 129.6, 128.7, 128.4, 128.3, 128.1, 127.9, 127.6, 127.4, 126.6, 115.7, 110.8, 102.4, 77.7, 70.3 ppm. FAB-MS $[M+H]^+$: 498. FAB-HRMS $[M+H]^+$: calcd for $C_{28}H_{21}O_3NBr$ 498.0705, found 498.0685.

7-Benzyloxy-3-(2-pyridinylmethylene)flavanone (**8b**): IR (ATR): $\tilde{\nu}$ = 1666, 1602, 1569, 1439, 1254, 1148, 1118, 1013, 851, 781, 737, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.11 (d, J = 11.7 Hz, 1H), 5.14 (d, J = 11.7 Hz, 1H), 6.60 (d, J = 2.3 Hz, 1H), 6.65 (dd, J = 8.8, 2.3 Hz), 7.22–7.30 (m, 3H), 7.37–7.45 (m, 8H), 7.53 (d, J = 7.8 Hz, 1H), 7.76 (td, J = 7.8, 1.6 Hz, 1H), 7.88 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 8.12 (s, 1H), 8.63 ppm (dd, J = 4.9, 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.4, 165.4, 161.8, 153.8, 149.8, 138.6, 136.6, 136.0, 135.8, 134.4, 129.6, 128.7, 128.30, 128.28, 127.9, 127.7, 127.6, 126.9, 123.4, 116.0, 110.6, 102.5, 77.3, 70.3 ppm. FAB-MS $[M+H]^+$: 420. FAB-HRMS $[M+H]^+$: calcd for $C_{28}H_{22}O_3N$ 420.1600, found 420.1599.

7-Benzyloxy-3-(3-pyridinylmethyl)flavone (**7c**): IR (ATR): $\tilde{\nu}$ = 1614, 1592, 1559, 1496, 1446, 1382, 1364, 1242, 1182, 1098, 1008, 971, 836, 773, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 2H), 5.17 (s, 2H), 6.95 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 8.9, 2.4 Hz, 1H), 7.15 (ddd, J = 7.8, 4.9,

0.7 Hz, 1H), 7.35–7.57 (m, 11H), 8.18 (d, J=8.9 Hz, 1H), 8.29 (d, J=1.9 Hz, 1H), 8.41 ppm (dd, J=4.9, 1.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.3, 163.2, 162.8, 157.8, 149.6, 147.4, 135.8, 135.7, 135.6, 132.9, 130.5, 128.71, 128.70, 128.5, 128.3, 127.44, 127.41, 123.3, 119.6, 117.0, 115.2, 101.0, 70.4, 28.5 ppm. FAB-MS $[M+H]^+$: 420. FAB-HRMS $[M+H]^+$: calcd for $C_{28}H_{21}O_3N$ 420.1600, found 420.1560.

7-Benzyloxy-3-(5-bromo-3-pyridinylmethyl)flavone (**7d**): IR (ATR): $\tilde{\nu}$=1609, 1440, 1381, 1240, 1170, 1096, 1021, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.90 (s, 2H), 5.16 (s, 2H), 6.94 (d, J=2.4 Hz, 1H), 7.08 (dd, J=8.9, 2.4 Hz, 1H), 7.33–7.57 (m, 10H), 7.61 (t, J=2.0 Hz, 1H), 8.16 (d, J=8.9 Hz, 1H), 8.18 (d, J=2.0 Hz, 1H), 8.45 ppm (d, J=2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.1, 163.3, 163.0, 157.8, 148.5, 147.7, 138.4, 137.6, 135.6, 132.7, 130.7, 128.8, 128.7, 128.42, 128.38, 127.5, 127.4, 120.6, 119.0, 117.0, 115.3, 101.1, 70.5, 28.2 ppm. FAB-MS $[M+H]^+$: 498. FAB-HRMS $[M+H]^+$: calcd for $C_{28}H_{21}O_3NBr$ 498.0705, found 498.0710.

7-Benzyloxy-3-(4-pyridinylmethyl)flavone (**7f**): IR (ATR): $\tilde{\nu}$=1630, 1600, 1444, 1385, 1362, 1241, 1180, 1102, 1002, 920, 795, 765, 721, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.92 (s, 2H), 5.17 (s, 2H), 6.95 (d, J=2.4 Hz, 1H), 7.04 (dd, J=4.4, 1.7 Hz, 2H), 7.08 (dd, J=8.9, 2.4 Hz, 1H), 7.34–7.55 (m, 10H), 8.17 (d, J=8.9 Hz, 1H), 8.43 ppm (dd, J=4.4, 1.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.2, 163.2, 163.0, 157.8, 149.7, 149.3, 135.6, 132.8, 130.6, 128.74, 128.66, 128.40, 128.38, 127.5, 127.4, 123.5, 118.7, 116.9, 115.3, 101.1, 70.5, 30.8 ppm. FAB-MS $[M+H]^+$: 420. FAB-HRMS $[M+H]^+$: calcd for $C_{28}H_{22}O_3N$ 420.1600, found 420.1560.

General procedure (Table 4): To a solution of 4′-bezyloxy-2′-hydroxyacetophenone (**1**) (20 mg, 0.083 mmol) in EtOH (0.5 mL; 0.16 M) was added Cs_2CO_3 (156 mg, 0.48 mmol) and benzaldehyde (**9a**) (26 mg, 0.25 mmol), and the reaction mixture was stirred at 40 °C for 7.5 h. After formation of chalcone, 5-bromo-3-pyridinecarboxaldehyde (**2d**) (104 mg, 0.56 mmol) was added to the reaction mixture, which was then stirred at 40 °C for 2 h, quenched by addition of 10% AcOH in EtOH, and evaporated. The residue was dissolved in CH_2Cl_2 and H_2O, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=40:1 to 5:1) to give the corresponding flavone derivatives (**7d**) (29 mg, 0.058 mmol, 70% yield) as white amorphous solids.

7-Benzyloxy-3-(3-methyl-2-pyridinylmethylene)-4′-methoxyflavanone (**11a**): IR (ATR): $\tilde{\nu}$=1666, 1599, 1573, 1508, 1440, 1244, 1161, 1101, 1007, 793, 735, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.46 (s, 3H), 3.73 (s, 3H), 5.06 (d, J=11.6 Hz, 1H), 5.07 (d, J=11.6 Hz, 1H), 6.49 (d, J=2.2 Hz, 1H), 6.62 (dd, J=8.8, 2.2 Hz, 1H), 6.77 (d, J=8.8 Hz, 2H), 7.06 (d, J=7.6 Hz, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.33–7.42 (m, 7H), 7.59 (t, J=7.6 Hz, 1H), 7.79 (d, J=1.0 Hz, 1H), 7.91 (d, J=8.8 Hz, 1H), 8.01 ppm (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=181.5, 165.4, 161.7, 159.1, 158.5, 153.0, 136.7, 135.9, 135.7, 134.3, 131.1, 129.5, 128.63, 128.59, 128.2, 127.6, 125.1, 123.0, 116.0, 113.6, 110.4, 102.5, 77.5, 70.2, 55.1, 24.5 ppm. FAB-MS $[M+H]^+$: 464. FAB-HRMS $[M+H]^+$: calcd for $C_{30}H_{26}O_4N$ 464.1862, found 464.1834.

7-Benzyloxy-3-(3-pyridinylmethyl)-3′5′-dimethoxyflavone (**10b**): IR (ATR): $\tilde{\nu}$=1627, 1594, 1569, 1440, 1379, 1245, 1207, 1156, 1057, 1025, 822, 736, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.74 (s, 6H), 3.93 (s, 2H), 5.16 (s, 2H), 6.59 (s, 3H), 6.93 (d, J=2.2 Hz, 1H), 7.07 (dd, J=8.9, 2.2 Hz, 1H), 7.15 (dd, J=8.0, 4.7 Hz, 1H), 7.34–7.45 (m, 5H), 7.53 (d, J=8.0 Hz, 1H), 8.16 (d, J=8.9 Hz, 1H), 8.34 (d, J=1.6 Hz, 1H), 8.39 ppm (dd, J=4.7, 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.3, 163.2, 162.6, 160.9, 157.8, 149.7, 147.4, 135.9, 135.8, 135.6, 134.5, 128.7, 128.4, 127.4, 123.3, 119.4, 117.0, 115.2, 106.5, 102.6, 101.1, 70.5, 55.5, 28.6 ppm. FAB-MS $[M+H]^+$: 480. FAB-HRMS $[M+H]^+$: calcd for $C_{30}H_{26}O_5N$ 480.1811, found 480.1828.

7-Benzyloxy-3-(6-bromo-4-pyridinylmethyl)-3′4′5′-trimethoxyflavone (**10c**): IR (ATR): $\tilde{\nu}$=1633, 1603, 1582, 1577, 1497, 1441, 1378, 1239, 1175, 1120, 1096, 999, 831, 779, 724, 686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.66 (s, 6H), 3.89 (s, 3H), 3.99 (s, 2H), 5.20 (s, 2H), 6.59 (s, 2H), 7.01 (d, J=2.4 Hz, 1H), 7.05 (d, J=4.9 Hz, 1H), 7.12 (dd, J=9.0, 2.4 Hz, 1H), 7.35–7.47 (m, 5H), 8.19 (d, J=9.0 Hz, 1H), 8.39 (d, J=4.9 Hz, 1H), 8.67 ppm (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.2, 163.4, 163.2, 157.8, 153.2, 151.6, 148.8, 148.5, 135.6, 128.8, 128.5, 127.60, 127.57, 127.46, 123.9, 123.1, 117.0, 116.7, 115.4, 105.5, 101.2, 70.6, 61.0, 55.9, 32.4 ppm. FAB-MS $[M+H]^+$: 588. FAB-HRMS $[M+H]^+$: calcd for $C_{31}H_{27}O_6NBr$ 588.1022, found 588.1006.

7-Benzyloxy-3-(5-bromo-3-pyridinylmethyl)-4′-bromoflavone (**10d**): IR (ATR): $\tilde{\nu}$=1624, 1609, 1440, 1379, 1240, 1172, 1011, 827, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.88 (s, 2H), 5.17 (s, 2H), 6.92 (d, J=2.4 Hz, 1H), 7.09 (dd, J=8.9, 2.4 Hz, 1H), 7.34–7.45 (m, 7H), 7.62 (t, J=2.1 Hz, 1H), 7.65 (d, J=8.8 Hz, 2H), 8.15 (d, J=8.9 Hz, 1H), 8.20 (d, J=2.1 Hz, 1H), 8.47 ppm (d, J=2.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=176.9, 163.4, 161.8, 157.7, 148.7, 147.6, 138.3, 137.3, 135.5, 132.1, 131.5, 130.0, 128.8, 128.4, 127.5, 127.4, 125.3, 120.7, 119.1, 116.9, 115.4, 101.1, 70.5, 28.2 ppm. FAB-MS $[M+H]^+$: 576. FAB-HRMS $[M+H]^+$: calcd for $C_{28}H_{20}O_3NBr_2$ 575.9810, found 575.9827.

7-Benzyloxy-3-(6-bromo-4-pyridinylmethyl)-3′-methylflavone (**10e**): IR (ATR): $\tilde{\nu}$=1623, 1600, 1440, 1379, 1241, 1174, 778, 736, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.36 (s, 3H), 3.97 (s, 2H), 5.18 (s, 2H), 6.99 (d, J=2.4 Hz, 1H), 7.03 (dd, J=4.9, 0.5 Hz, 1H), 7.10 (dd, J=8.9, 2.4 Hz, 1H), 7.20 (m, 1H), 7.23 (s, 1H), 7.29–7.47 (m, 7H), 8.17 (d, J=8.9 Hz, 1H), 8.35 (d, J=4.9 Hz, 1H), 8.66 ppm (d, J=0.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.2, 163.6, 163.3, 157.9, 151.5, 148.5, 148.3, 138.6, 135.6, 132.5, 131.5, 128.73, 128.68, 128.58, 128.4, 127.5, 127.4, 125.2, 123.9, 122.9, 117.4, 116.7, 115.3, 101.1, 70.5, 31.9, 21.4 ppm. FAB-MS $[M+H]^+$: 512. FAB-HRMS $[M+H]^+$: calcd for $C_{29}H_{23}O_3NBr$ 512.0861, found 512.0815.

7-Benzyloxy-3-(2-quinolinylmethyl)-3′-methylflavone (**10f**): IR (ATR): $\tilde{\nu}$=1611, 1570, 1502, 1440, 1380, 1239, 1172, 781, 728, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.35 (s, 3H), 4.24 (s, 2H), 5.16 (s, 2H), 6.97 (d, J=2.4 Hz, 1H), 7.05 (d, J=8.9, 2.4 Hz, 1H), 7.27–7.51 (m, 9H), 7.62–7.65 (m, 3H), 7.76 (d, J=8.1 Hz, 1H), 7.99 (d, J=8.5 Hz, 1H), 8.04 (d, J=8.5 Hz, 1H), 8.14 ppm (d, J=8.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.7, 163.3, 163.1, 160.7, 157.9, 147.9, 138.1, 136.2, 135.8, 133.0, 131.1, 129.7, 129.04, 129.01, 128.7, 128.34, 128.29, 127.47, 127.46, 127.42, 126.9, 126.0, 125.7, 121.8, 119.3, 117.1, 115.0, 101.1, 70.5, 35.2, 21.4 ppm. FAB-MS $[M+H]^+$: 484. FAB-HRMS $[M+H]^+$: calcd for $C_{33}H_{26}O_3N$ 484.1913, found 484.1891.

7-Benzyloxy-3-(2-pyridinylmethyl)-4′-methoxyflavone (**10g**): IR (ATR): $\tilde{\nu}$=2922, 2852, 1734, 1625, 1611, 1570, 1498, 1471, 1441, 1380, 1362, 1258, 1239, 1172, 1117, 1102, 997, 793, 778, 742, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.37 (s, 3H), 4.08 (s, 2H), 5.16 (s, 2H), 6.95 (d, J=2.2 Hz, 1H), 7.04 (dd, J=8.8, 2.2 Hz, 1H), 7.09 (m, 1H), 7.23–7.46 (m, 7H), 7.51–7.60 (m, 4H), 8.13 (d, J=8.8 Hz, 1H), 8.51 ppm (dt, J=4.9, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=181.5, 165.4, 161.8, 153.8, 149.8, 138.5, 138.2, 137.9, 136.5, 136.0, 135.9, 134.4, 134.3, 130.6, 129.6, 128.6, 128.25, 128.19, 127.8, 127.7, 127.5, 124.1, 123.3, 116.0, 110.5, 102.5, 70.2, 21.5, 21.2 ppm. FAB-MS $[M+H]^+$: 434. FAB-HRMS $[M+H]^+$: calcd for $C_{29}H_{24}NO_3$ 434.1756, found 434.1756.

7-Benzyloxy-3-(5-methoxy-3-pyridinylmethyl)-3′4′5′-trimethoxyflavone (**10h**): IR (ATR): $\tilde{\nu}$=1623, 1610, 1583, 1498, 1441, 1172, 1122, 1000, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.75 (s, 6H), 3.78 (s, 3H), 3.91 (s, 3H), 3.92 (s, 2H), 5.17 (s, 2H), 6.67 (s, 2H), 6.96 (d, J=2.3 Hz, 1H), 7.06 (d, J=3.0 Hz, 1H), 7.08 (dd, J=9.0, 2.3 Hz, 1H), 7.34–7.45 (m, 5H), 7.96 (s, 1H), 8.07 (d, J=3.0 Hz, 1H), 8.16 ppm (d, J=9.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=177.3, 163.2, 162.7, 157.7, 155.6, 153.3, 141.9, 136.7, 135.6, 134.9, 128.7, 128.4, 128.0, 127.5, 127.4, 120.7, 119.0, 116.9, 115.2, 105.8, 101.1, 70.5, 61.0, 56.1, 55.5, 28.7 ppm. FAB-MS $[M+H]^+$: 540. FAB-HRMS $[M+H]^+$: calcd for $C_{32}H_{30}O_7N$ 540.2022, found 540.2004.

Solid-Phase Synthesis

Loading of compound: (4-methoxyphenyl)diisopropyl-silylpropyl polystyrene (1.5 mmol g^{-1}; novabiochem) was weighed (200 mg, 0.3 mmol) into a 5 mL polypropylene Libra tube column fitted with a teflon stopcock and 5.4 mL of a 3% trifluoromethanesulfonic acid/CH_2Cl_2 solution (6 equiv of TfOH relative to Si) was added by syringe. The resin turned bright red/orange upon acid treatment. After 15 min, the solvent was drained under positive Ar pressure, followed by addition of CH_2Cl_2 (2 mL), 2,6-lutidine (0.17 mL, 5 equiv of TfOH relative to Si), and 4′-hydroxyethoxy-2′-hydroxyacetophenone (118 mg, 2 equiv of TfOH relative

to Si), which resulted in a colorless resin. The beads were then gently agitated for 24 h at room temperature. The beads were drained and washed with CH_2Cl_2 (3 mL; 3 min × 5 times). The resin was dried under reduced pressure. The weight of the dried resin was 251 mg.

Determination of loading level of compound: The resulting beads (57.1 mg) and 2% HCl in dioxane (1.0 mL) were vigorously shaken in a screw-cap sealed reaction vessel at room temperature for 3 h. The resin was filtered, washed with CH_2Cl_2, and the resulting filtrate was concentrated to dryness to yield 11.0 mg of 4′-hydroxyethoxy-2′-hydroxyacetophenone (0.98 mmol g^{-1}).

General procedure (Table 5): The above beads 50 mg (4′-hydroxyethoxy-2′-hydroxyacetophenone; 0.98 mmol g^{-1}) were swollen in EtOH (0.5 mL) into a round-bottom flask for 15 min, followed by addition of KOH (28 mg, 0.50 mmol) and 5-bromo-3-pyridinecarboxaldehyde (**2d**) (186 mg, 1.0 mmol). The reaction mixture was then heated at 40 °C for 24 h. Then, the resin was filtered, suspended, and rinsed with the sequence of solvents (3 mL) three times: AcOEt (3 min), DMF (3 min), DMF/H_2O (3 min), H_2O (3 min), DMF (3 min), EtOH (3 min), MeOH (3 min), and CH_2Cl_2 (3 min), then dried under reduced pressure. The weight of the dried resin was 65 mg.

Determination of yield: Yields of all reaction were determined after cleavage of compound from beads (10–30 mg); The resulting resin (30.3 mg) and 2% HCl in dioxane (0.5 mL) were vigorously shaken in a screw-cap sealed reaction vessel at room temperature for 3 h. The beads were filtered, washed with MeOH, and the resulting filtrate was neutralized by addition of 1 N aqueous NaOH and evaporated. The residue was dissolved in CH_2Cl_2 and H_2O, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to yield 15.3 mg of one-pot product 7-hydroxyethoxy-2-(5-bromo-3-pyridinyl)-3-(5-bromo-3-pyridinylmethyl)-chromone (**12**; 66% yield). Without neutralization: After the cleavage reaction, the beads were filtered, rinsed with AcOEt, CH_2Cl_2, and MeOH, then the resulting filtrate was concentrated. The products were obtained as HCl salts.

7-Hydroxyethoxy-2-(5-bromo-3-pyridinyl)-3-(5-bromo-3-pyridinylmethyl)chromone (**12**): IR (ATR): $\tilde{\nu}$ = 3307, 2924, 1623, 1606, 1580, 1501, 1440, 1420, 1381, 1360, 1244, 1176, 1094, 1021, 786, 727, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 2H), 4.05 (br, 2H), 4.20 (t, J = 4.3 Hz, 2H), 6.90 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 9.0, 2.2 Hz, 1H), 7.63 (br, 1H), 7.99 (t, J = 1.8 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.24 (d, J = 1.8 Hz, 1H), 8.50 (d, J = 1.8 Hz, 1H), 8.68 (d, J = 1.8 Hz, 1H), 8.85 ppm (d, J = 1.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.5, 163.7, 158.3, 157.8, 152.8, 149.0, 147.5, 147.0, 138.4, 138.3, 136.7, 130.1, 127.8, 120.84, 120.81, 120.6, 116.9, 115.5, 100.7, 70.0, 61.1, 28.2 ppm. FAB-MS $[M+H]^+$: 531. FAB-HRMS $[M+H]^+$: calcd for $C_{22}H_{17}Br_2N_2O_4$ 530.9555, found 530.9541.

7-Hydroxyethoxy-2-(3-bromo-2-pyridinyl)-3-(3-bromo-2-pyridinylmethyl)chromone (**13**): IR (ATR): $\tilde{\nu}$ = 3307, 2924, 2440, 1622, 1602, 1578, 1550, 1501, 1435, 1404, 1355, 1248, 1183, 1104, 1080, 985, 783, 733, 669 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 3.94 (t, J = 4.6 Hz, 2H), 4.21 (t, J = 4.6 Hz, 2H), 4.57 (s, 2H), 7.12 (dd, J = 9.0, 2.3 Hz, 1H), 7.23 (d, J = 2.3 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.91 (t, J = 7.8 Hz, 1H), 7.94 (t, J = 7.8 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 8.22 ppm (d, J = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 179.2, 166.1, 162.5, 159.5, 159.1, 152.8, 141.8, 141.4, 131.1, 128.3, 128.0, 124.3, 117.4, 117.1, 102.0, 71.7, 61.3, 31.9 ppm. FAB-MS $[M+H]^+$: 531, 533, and 535 (1:2:1). FAB-HRMS $[M+H]^+$: calcd for $C_{22}H_{17}{}^{79}Br_2N_2O_4$ 530.9555, found 530.9559.

7-Hydroxyethoxy-2-(2-bromo-3-pyridinyl)-3-(2-bromo-3-pyridinylmethyl)chromanone (**14**): IR (ATR): 3299, 3048, 2926, 2451, 1706, 1607, 1580, 1500, 1475, 1439, 1387, 1248, 1177, 1084, 1038, 973, 832, 729 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 3.92 (t, J = 4.6 Hz, 2H), 4.05 (s, 2H), 4.20 (t, J = 4.6 Hz, 2H), 7.16 (d, J = 2.3 Hz, 1H), 7.19 (dd, J = 8.9, 2.3 Hz, 1H), 7.90 (d, J = 5.9 Hz, 1H), 7.95 (d, J = 4.9 Hz, 1H), 8.07 (d, J = 8.9 Hz, 1H), 8.67 (d, J = 5.9 Hz, 1H), 8.85 (d, J = 4.9 Hz, 1H), 9.11 ppm (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7, 166.3, 161.6, 161.2, 159.8, 152.0, 148.4, 144.8, 144.4, 141.3, 128.3, 128.0, 127.5, 125.3, 119.7, 117.7, 117.4, 102.2, 71.8, 61.3, 33.5 ppm. FAB-MS $[M+H]^+$: 531, 533, and 535 (1:2:1). FAB-HRMS $[M+H]^+$: calcd for $C_{22}H_{17}{}^{79}Br_2N_2O_4$ 530.9555, found 530.9559.

7-Hydroxyethoxy-2-(2-bromo-4-pyridinyl)-3-(2-bromo-4-pyridinylmethyl)chromone (**15**): IR (ATR): $\tilde{\nu}$ = 3313, 2918, 2460, 1628, 1605, 1580, 1555, 1501, 1440, 1400, 1383, 1359, 1245, 1175, 1072, 1048, 780, 730 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 3.91 (t, J = 4.6 Hz, 2H), 3.91 (s, 2H), 4.18 (t, J = 4.6 Hz, 2H), 7.11 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.9, 2.4 Hz, 1H), 7.43 (dd, J = 7.8, 5.0 Hz, 1H), 7.54 (dd, J = 7.8, 5.0 Hz, 1H), 7.75 (dd, J = 7.8, 1.9 Hz, 1H), 7.94 (dd, J = 7.8, 1.9 Hz, 1H), 8.10 (d, J = 8.9 Hz, 1H), 8.28 (dd, J = 5.0, 1.9 Hz, 1H), 8.51 ppm (dd, J = 5.0, 1.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5, 166.0, 162.4, 159.7, 153.1, 147.0, 142.7, 142.4, 141.8, 141.1, 139.1, 132.5, 128.1, 125.3, 124.7, 121.2, 117.7, 117.1, 102.0, 71.7, 61.3, 31.0 ppm. FAB-MS $[M+H]^+$: 531, 533, and 535 (1:2:1). FAB-HRMS $[M+H]^+$: calcd for $C_{22}H_{17}{}^{79}Br_2N_2O_4$ 530.9555, found 530.9541.

7-Hydroxyethoxy-2-(5-methoxy-3-pyridinyl)-3-(5-methoxy-3-pyridinylmethyl) chromone (**16**): IR (ATR): $\tilde{\nu}$ = 3340, 2926, 2484, 2070, 1735, 1606, 1559, 1500, 1440, 1362, 1246, 1178, 1034, 678 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 3.92 (t, J = 4.5 Hz, 2H), 4.00 (s, 3H), 4.07 (s, 3H), 4.11 (s, 2H), 4.20 (t, J = 4.5 Hz, 2H), 7.15–7.17 (m, 2H), 8.01 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.25 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 8.67–8.77 ppm (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4, 166.1, 159.8, 142.8, 137.4, 135.3, 135.0, 132.7, 129.4, 128.0, 120.7, 117.7, 117.2, 102.2, 71.7, 61.3, 57.99, 57.94, 30.0 ppm. FAB-MS $[M+H]^+$: 435. FAB-HRMS $[M+H]^+$: calcd for $C_{24}H_{23}N_2O_6$ 435.1556, found 435.1548.

General procedure (Scheme 3): One-pot synthesis of 3-substituted flavonoids on beads: The beads (4′-hydroxyethoxy-2′-hydroxyacetophenone; 1.10 mmol g^{-1}; 50 mg, 0.048 mmol) in a round-bottom flask were swollen in EtOH (0.25 mL) for 15 min, followed by addition of KOH (16.8 mg, 0.3 mmol, 6 equiv) and *m*-tolualdehyde (0.02 mL, 0.15 mmol, 3 equiv). The reaction mixture was then heated at 40 °C for 30 h. After formation of chalcone, pyridinecarboxaldehyde (93 mg, 0.5 mmol, 10 equiv) was added to the reaction mixture, which was then heated at 40 °C for 24 h. The beads were then filtered, suspended, and rinsed with the following sequence of solvents follows three times: CH_2Cl_2 (3 mL; 3 min), AcOEt (3 mL; 3 min), MeOH (3 mL; 3 min), H_2O (3 mL; 3 min), THF (3 mL; 3 min), CH_2Cl_2 (3 mL; 3 min), and then dried under reduced pressure. The resulting resin (9.5 mg) and 2% HCl in dioxane (0.5 mL) were vigorously shaken in a screw-cap sealed reaction vessel at room temperature for 3 h. The beads were filtered, rinsed with AcOEt, CH_2Cl_2, MeOH, and the resulting filtrate was concentrated. The products were obtained as HCl salts. (**17b**, 74% yield). Suzuki–Miyaura coupling: The beads (20 mg) were swollen in THF/H_2O (10:1; 0.2 mL). The flask was purged with Ar, and phenylboronic acid (24 mg, 0.20 mmol, 10 equiv), NaOMe (22 mg, 0.40 mmol, 20 equiv), $[Pd_2(dba)_3]$ (18.3 mg, 0.02 mmol, 2 equiv Pd; dba = dibenzylideneacetone) and PPh_3 (21 mg, 0.08 mmol, 4 equiv) were added. The mixture was heated at 60 °C for 24 h. The beads were filtered, suspended, and rinsed with the following sequence of solvents three times: CH_2Cl_2 (3 mL; 3 min), AcOEt (3 mL; 3 min), EtOH (3 mL; 3 min), H_2O (3 mL; 3 min), THF (3 mL; 3 min), CH_2Cl_2 (3 mL; 3 min), and then dried under reduced pressure. The resulting beads (10.6 mg) and 2% HCl in dioxane (0.5 mL) were vigorously shaken in a screw-cap sealed reaction vessel at room temperature for 3 h. The beads were filtered, washed with MeOH, and the resulting filtrate was neutralized by added of 2 N aqueous KOH and evaporated. The residue was dissolved in CH_2Cl_2 and H_2O, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to yield 1.8 mg of product (**18b**, 74% yield).

7-Hydroxyethoxy-3-(2-bromo-4-pyridinylmethyl)-3′-methylflavone (**17b**): IR (ATR): $\tilde{\nu}$ = 3411, 2920, 2867, 1608, 1412, 1384, 1361, 1244, 1178, 1085, 1023, 780, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.97 (s, 2H), 4.04 (t, J = 4.5 Hz, 2H), 4.12 (t, J = 4.5 Hz, 2H), 6.94 (d, J = 2.4 Hz, 2H), 7.03–7.06 (m, 2H), 7.20–7.22 (m, 1H), 7.24 (s, 1H), 7.31–7.32 (m, 2H), 8.16 (d, J = 8.8 Hz, 1H), 8.35 (d, J = 5.1 Hz, 1H), 8.67 ppm (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.2, 163.7, 163.3, 157.9, 151.5, 148.6, 148.3, 138.6, 132.4, 131.6, 128.7, 128.6, 127.6, 125.2, 124.0, 123.0, 117.4, 116.8, 115.1, 100.7, 69.9, 61.1, 31.9, 21.4 ppm. FAB-MS $[M+H]^+$: 466 and

468 (1:1). FAB-HRMS $[M+H]^+$: calcd for $C_{24}H_{21}{}^{79}BrNO_4$ 466.0653, found 466.0634.

7-Hydroxyethoxy-3-(2-phenyl-4-pyridinyl)-3′-methylflavone (**18b**): IR (ATR): $\tilde{\nu}$ = 2920, 2852, 1607, 1441, 1383, 1243, 1176, 1079, 1036, 971, 835, 783, 765, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 3.87 (s, 2H), 4.04 (t, J = 4.5 Hz, 2H), 4.19 (t, J = 4.5 Hz, 2H), 6.91 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.9, 2.4 Hz, 1H), 7.14–7.17 (m, 1H), 7.20 (br s, 1H), 7.27–7.40 (m, 9H), 8.15 (d, J = 8.9 Hz, 1H), 8.41 (s, 1H), 8.42 ppm (d, J = 5.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9, 163.6, 163.3, 157.8, 152.8, 151.4, 138.8, 138.7, 135.5, 132.3, 131.5, 129.4, 128.7, 128.6, 128.3, 127.9, 127.6, 125.2, 123.5, 118.0, 116.9, 115.0, 100.8, 69.9, 61.2, 29.7, 21.4 ppm. EI-MS $[M]^+$: 463. EI-HRMS $[M]^+$: calcd for $C_{30}H_{25}NO_4$ 463.1784, found 463.1800.

7-Hydroxyethoxy-3-(2-*p*-methoxyphenyl-4-pyridinyl)-3′-methylflavone (**19b**): IR (ATR): $\tilde{\nu}$ = 2921, 2851, 1732, 1606, 1440, 1381, 1260, 1175, 1074, 1031, 790, 729, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 3.79 (s, 2H), 3.89 (s, 2H), 4.04 (m, 2H), 4.19 (m, 2H), 6.85–6.91 (m, 3H), 7.01–7.07 (m, 2H), 7.17 (m, 1H), 7.20 (br s, 1H), 8.15 (d, J = 8.9 Hz, 1H), 8.41 (s, 1H), 8.42 ppm (d, J = 5.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9, 163.5, 163.3, 159.6, 157.8, 152.6, 151.4, 150.7, 138.7, 136.7, 132.3, 131.6, 131.5, 130.9, 129.9, 129.6, 128.8, 128.7, 128.6, 127.5, 125.2, 123.5, 121.7, 115.0, 114.4, 100.8, 69.9, 61.1, 55.3, 29.7, 21.4 ppm. EI-MS $[M]^+$: 493. EI-HRMS $[M]^+$: calcd for $C_{31}H_{27}NO_4$ 493.1889, found 493.1877.

7-Hydroxyethoxy-3-(3-*p*-acetamidophenyl-2-pyridinylmethyl)-3′-methylflavanone (**21b**): IR (ATR): $\tilde{\nu}$ = 3218, 2921, 1601, 1533, 1442, 1364, 1317, 1241, 1176, 1078, 1039, 905, 782, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3H), 2.35 (s, 3H), 4.02 (m, 2H), 4.13 (s, 2H), 4.17 (m, 2H), 6.91 (d, J = 2.3 Hz, 1H), 6.98 (dd, J = 9.0, 2.3 Hz, 1H), 7.25–7.38 (m, 4H), 7.50 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.71 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 8.13 ppm (d, J = 9.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8, 168.2, 163.04, 162.97, 159.7, 157.9, 155.6, 138.4, 138.2, 137.0, 133.2, 131.1, 129.5, 128.5, 127.51, 127.50, 126.2, 121.8, 119.5, 117.3, 117.2, 114.6, 100.7, 69.8, 61.2, 34.6, 29.7, 21.5 ppm. EI-MS $[M]^+$: 520. EI-HRMS $[M]^+$: calcd for $C_{32}H_{28}N_2O_5$ 520.1998, found 520.1993.

Cytotoxic assay against cancer cells: PANC1 or HeLa cells were seeded onto 96-well microtiter plates at 1×10^4 cells per well, and were pre-incubated for 24 h at 37 °C. The medium was replaced with fresh medium containing different concentrations of each compound. The cells were then incubated at 37 °C for 24 h. After the medium was removed, cell viability was determined by fluorometric microculture cytotoxicity assay (FMCA) by using a fluorescence plate reader (Thermo). The ratio of the living cells was determined as the fluorescence in the sample wells expressed as a percentage of that in the control wells, and cytotoxic activity was indicated as an IC_{50} value.[10]

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[8] Chalcone **6** was synthesized from **1** and benzaldehyde (3 equiv) with Cs_2CO_3 (3 equiv) in EtOH at 40 °C for 25 h in 77 % yield.

[9] Cyclization between chalcone **6** and benzaldehyde **9a** (10 equiv) did not occur with pyridine (5 equiv) in EtOH at 40 °C.

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