Synthesis of Flavonoid Analogues as Scaffolds for Natural Product-Based Combinatorial Libraries

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The design and synthesis of flavonoid analogues as combinatorial scaffolds is reported. Using commercially available materials, we synthesized chalcones with fluoro and carboxy groups. Nitration of these compounds generated highly functionalized flavonoid scaffolds with an *o*-fluoronitrobenzene template. Subsequent cyclizations of these chalcones resulted in the formation of several flavone and flavonone scaffolds. One of the flavonones was chosen as the scaffold to synthesize flavonoid derivatives on the solid phase. A series of flavonoid derivatives were obtained in high yields, which demonstrates that these highly functionalized scaffolds can be used in the synthesis of natural product-based combinatorial libraries for drug discovery.

Introduction

Natural products play an important role in drug development and drug discovery.[1] Many current drugs, especially anticancer and anti-infective agents, either have natural structures or mimic naturally occurring molecules.[2] Combinatorial chemistry has a great impact on the drug discovery process because it enables rapid synthesis and high-throughput screening of a large number of compounds in a relatively short time.[3] There has been increasing interest in the design and synthesis of natural-product-like molecules using combinatorial approaches.[4] However, there is a lack of functionalized natural-product-like chemical scaffolds for such efforts.[5]

Flavonoids have a broad distribution in the plant kingdom and are found in many foodstuffs (e.g., fruits, vegetables, and drinks).[6] Flavonoids display diverse biological and pharmacological properties (e.g., antioxidant, anticancer, antiviral, and anti-inflammatory).[7] Therefore, flavonoids are a promising class of potentially useful pharmacologically active compounds, and their synthesis has found widespread application in organic chemistry.[8] Small molecule heterocycles have long been the important pharmacophores of many drugs.[9] A wide range of heterocycles can be generated from 4-fluoro-3-nitrobenzoic acid, typically via an N-, O-, or S-involved S_N2 replacement of fluorine, followed by reduction of the nitro group.[10] On the basis of a variety of biological and pharmacological activities exhibited by flavonoids and small molecule heterocycles and inspired by the *o*-fluornitrobenzene template, we designed and synthesized several new flavonoid scaffolds that are highly functionalized. Using one of the flavones as a molecular scaffold, we were able to synthesize a series of flavonoid derivatives on the solid phase with high yields.

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Results and Discussion

Design and Synthesis of Flavonoid Analogues as Scaffold. Our synthetic strategy for new flavonoid analogues is based on a Claisen condensation[11] to form chalcone, which was then nitrated with mixed acids, followed by intramolecular cyclization to generate various flavonoid analogues (Figure 1).

5′-Fluoro-2′-hydroxy-acetophenone and 4-carboxybenzaldehyde were initially selected as starting materials for the synthesis of chalcone **1** by Claisen condensation (Scheme 1).[11] Because **1** has a hydroxyl group attached directly to the aromatic ring, which is prone to oxidation in mixed nitric and sulfuric acids, **1** was first converted into flavone **2** via oxidative cyclization with I_2/DMSO.[12] However, nitration of **2** with mixed acids[13] proved to be difficult. Therefore, nitration of **1** was directly carried out in mixed acids to generate flavone **3** as the major product. ^{1}H NMR study confirmed that the nitro group was introduced to the meta position of the fluoro group. However, in this case, the fluoro group is difficult to replace by S_NAr substitution.

Therefore, we turned our attention to the employment of 4′-fluoro-2′-hydroxy-acetophenone as starting material (Scheme 2). The corresponding chalcone **4** was synthesized in the presence of KOH. The Claisen condensation reaction was carried out in 8% KOH aqueous ethanol to give **4** as major product, and the crude product was purified by recrystalization. Subsequent oxidative cyclization of **4** with I_2/DMSO gave flavone **5.** Intermediate **4** was then subjected to nitration with mixed acids (70% HNO_3 and 98% H_2SO_4). We have found that the optimal ratio of the two acids (1.5 mol equiv 70% HNO_3 and 98% H_2SO_4) is critical for nitration of **4** to form **6** and **7.**[14] The relative amounts of the para and ortho isomers to hydroxyl group varied with the concentration of sulfuric acid used. Nitration of **4** in 98% H_2SO_4 gave 70% para isomer and 30% ortho isomer (Figure 2A), in comparison with 45% para isomer and 55% ortho isomer in 82%

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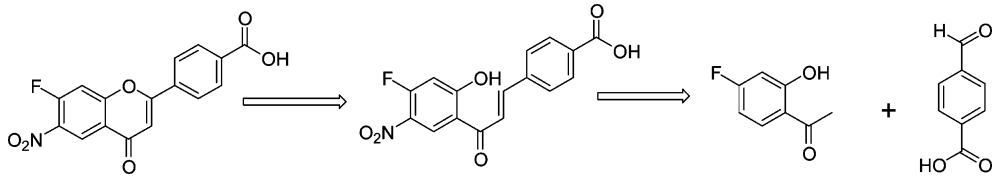
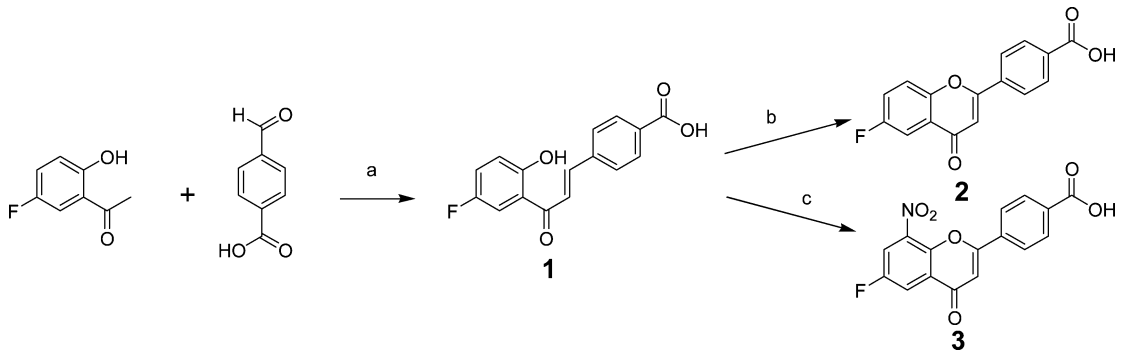


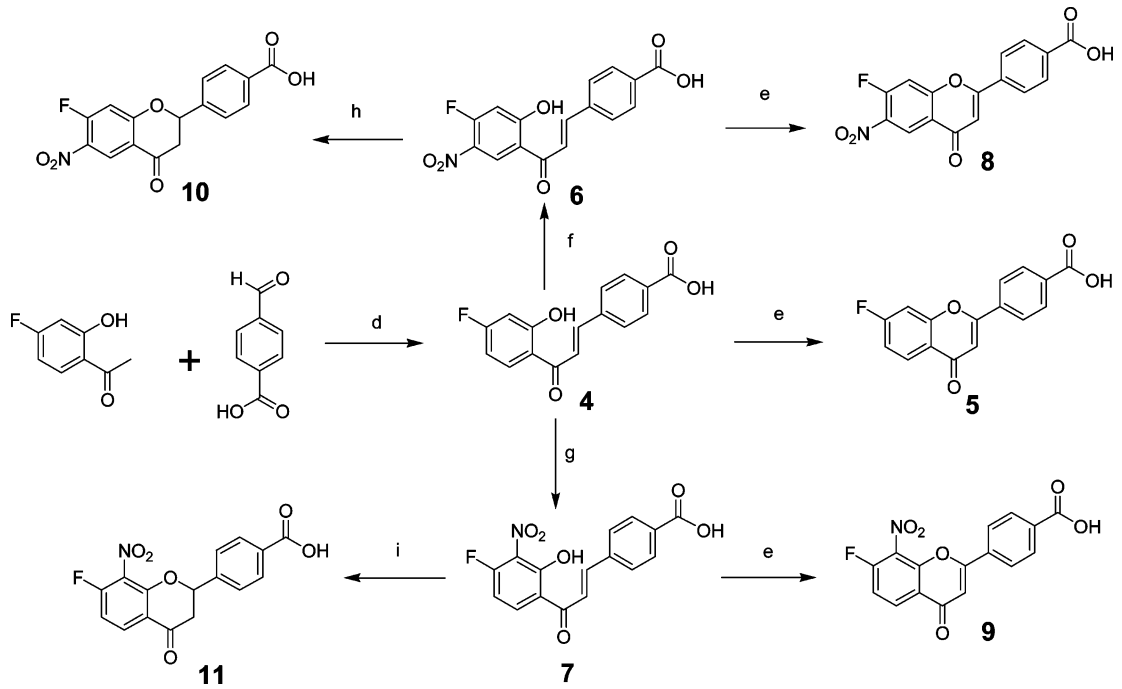
Figure 1. Proposed strategy for the synthesis of a flavonoid analogue.

Scheme 1. Synthesis of Flavonoids **1**−**3**[a]



[a] Reagents and conditions: (a) EtOH/4% KOH in H_2O (1:1), room temp, 7 days; (b) I_2, DMSO, reflux, 30 min; (c) 70% HNO_3, 98% H_2SO_4, 0 °C, 30 min.

Scheme 2. Synthesis of Flavonoids **4**−**11**[a]



[a] Reagents and conditions: (d) EtOH/8% KOH in H_2O (1:1), room temp, 7 days; (e) I_2, DMSO, reflux, 30 min; (f) 70% HNO_3, 98% H_2SO_4, 0 °C, 30 min; (g) 70% HNO_3, 82% H_2SO_4, 0 °C, 30 min; (h) 10% H_2SO_4, THF, reflux, 24 h; (i) 10% H_2SO_4, THF, reflux, 72 h.

H_2SO_4 (Figure 2B). After the reaction was completed, it was quenched with crushed ice, and the products were then precipitated. Crude products were recrystalizated in a THF/H_2O mixed solvent to give chalcone **6**. Chalcone **7**, on the other hand, could be easily separated by silca gel column chromatography.

The intramolecular oxidative cyclization of chalcone to flavone was carried out with the iodine−DMSO system. Chalcone **6** and a catalytic amount of I_2 (0.05 equiv) were refluxed in DMSO for 30 min. The products were poured into crushed ice. After the products were filtered and washed with water, flavone **8** was obtained in high yield and purity. It is interesting to note that excess I_2 led to a decrease in yield and purity. In a similar fashion, chalcone **7** was easily converted into flavone **9**.

Cyclization of chalcones to flavanones was traditionally carried out in ethanol in the presence of a mineral acid. Chalcones **6** was treated with 10% sulfuric acid in THF, instead of an alcohol,[15] because the carboxyl group of **6** was directly converted into an ester when heated with an alcohol in presence of sulfuric acid. After reflux for 24 h, HPLC showed that the reaction equilibrium was reached. Flavanone **10** was easily separated from **6** by silca gel column chromatography. Additionally, it took 72 h for cyclization

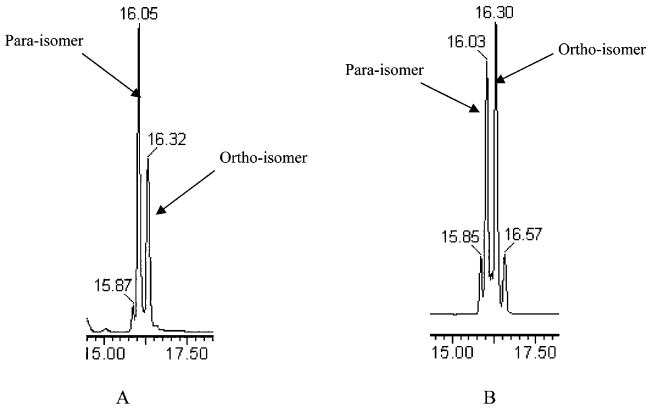


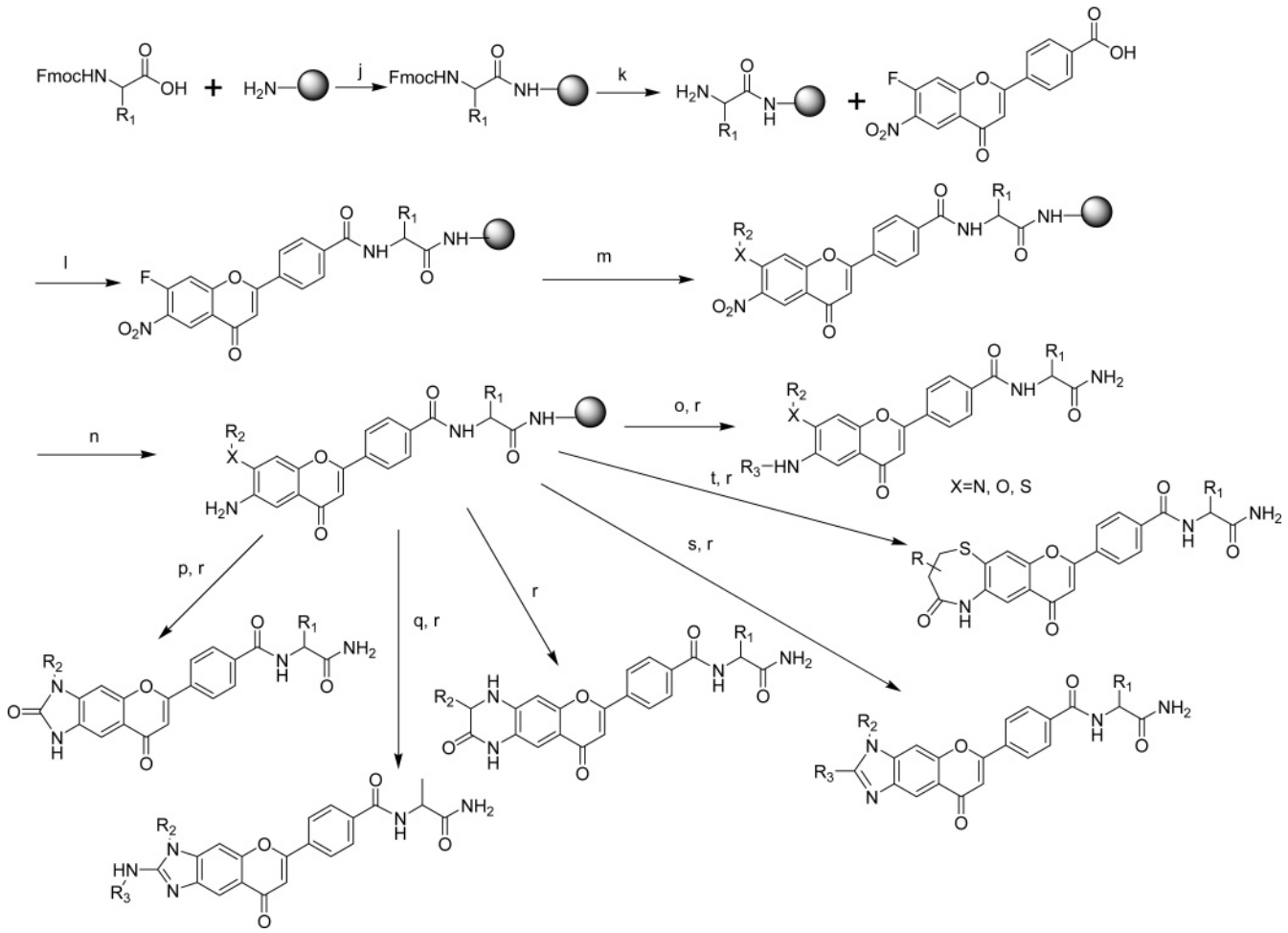
Figure 2. HPLC chromatography for nitration of **4** showing isomer ratios produced under different acid concentrations: (A) 70% HNO_3, 98% H_2SO_4 and (B) 70% HNO_3, 82% H_2SO_4.

of chalcone **7** to flavanone **11** in a similar fashion, which suggested that the chelation of the ortho nitro group with hydroxyl group retarded the cyclization of 7.[16]

Design and Synthesis of Model Compounds Based on Flavone 8. To demonstrate the potential use of the flavonoid analogues shown in Scheme 2 as scaffolds for the synthesis of combinatorial libraries, a series of flavonoid derivatives were synthesized in solid phase. A Fmoc amino acid was first coupled onto the Rink resin as the diversity point before the flavone **8** was coupled to the solid support. The synthetic route is outlined in Scheme 3. Fmoc-glycine was coupled to the resin by standard Fmoc peptide chemistry methods.[17] Following Fmoc deprotection, flavone **8** was readily attached to the resin using 1,3-diisopropylcarbodiimide (DIC) as a condensation reagent. The subsequent aromatic nucleophilic substitution proved to be problematic at lower concentrations of nucleophiles and base (DIPEA). After intensive optimization, we found that the *ortho*-nitro fluoride in the resin-bound flavone **8** was quantitatively replaced with 1 M phenols, mercaptans, or secondary amines in 25% DIPEA/DMF. The aryl nitro group was then reduced to an aryl amine with tin(II) chloride.[18] To introduce the third diversity element, the resin bound aniline was reacted with an anhydride in the presence of a base to generate flavonoid derivatives **12**, **13**, and **14** (Figure 3) with high yield and purity in each case.

Treatment of the resin bound flavone **8** with a primary amine, followed by tin(II) chloride reduction, afforded the common *o*-phenylenediamine intermediate. Different heterocyclic rings can be readily constructed on the *o*-phe-

Scheme 3. Design and Synthesis of Flavonoid Derivatives Based on Flavone **8**[a]



[a] Reagents and conditions: (j) amino acid (3 equiv), HOBt/DIC (3 equiv), DMF, room temp, 2 h; (k) 20% piperidine/DMF, 15 min, twice; (l) **8** (2.5 equiv), HOBt/DIC (3 equiv), DMF, room temp, 3 h; (m) 1 M phenol, mercaptan, or amine, 25% DIPEA/DMF, room temp, overnight; (n) 2 M $SnCl_2$/DMF, room temp, overnight; (o) Ac_2O (10 equiv), pyridine (20 equiv), room temp, overnight; (p) CDI (10 equiv), DCM, room temp, overnight; (q) isothiocyanate (1 M), DIC (1 M), DMF, room temp, overnight; (r) 95% TFA, room temp, 3 h; (s) aldehyde (10 equiv), 5% HOAc/DMF, room temp, overnight; (t) PyBrop (5 equiv), DIPEA (10 equiv), room temp, overnight.

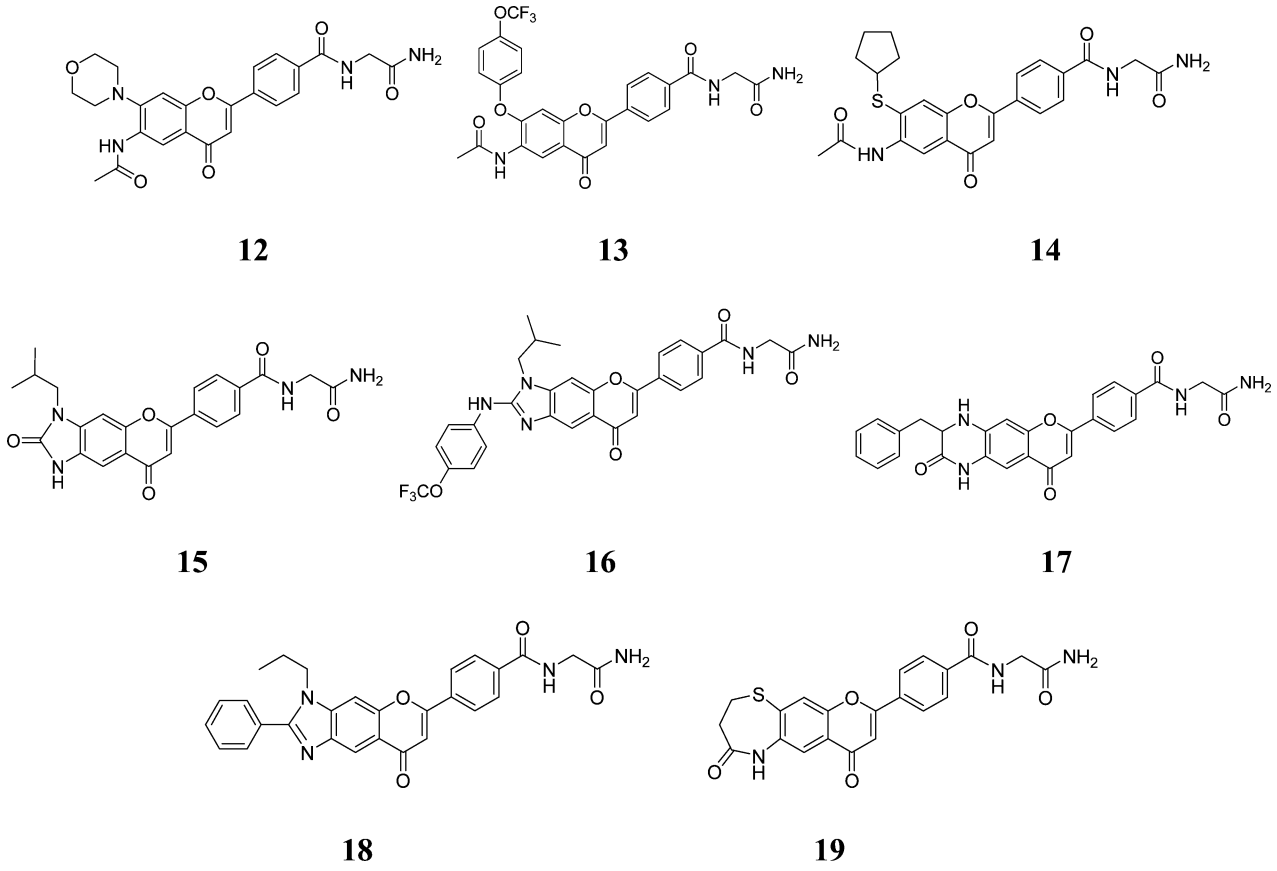


Figure 3. Structures of model compounds from flavonoid **8**.

nylenediamine templates. The resin bound *o*-phenylenediamine flavonoid was treated with 1,1′-carbonyldiimidazole (CDI) to give benzimidazolone flavonoid **15**.[19] In addition, the resin bound *o*-phenylenediamine flavonoid was exposed to isothiocyanates in the presence of 1,3-diisopropylcarbodiimide (DIC). Reaction overnight in DMF at ambient temperature provided 2-arylaminobenzimidazoles flavonoid **16** in high yield. A number of solid-phase strategies for the benzimidazole have been reported.[20] Here, the resin bound *o*-phenylenediamine flavonoid was treated with excess aldehyde in a weakly acidic solution (5% HOAc in DMF).[21] Under these conditions, benzimidazole flavonoid **18** was easily obtained in high yield.

Displacement of the resin bound aryl-fluoro group on flavone **8** with an α-amino acid ester (L-phenylalanine methyl ester hydrochloride) was accomplished in the presence of DIPEA. After the reduction of nitro group, cyclization occurred spontaneously to give quinoxanlinon flavonoid **17.** To introduce a seven-member ring to flavone **8**, the resin-bound flavone **8** was treated with a *β*-mercapto acid. Aromatic substitution of the activated aryl fluoride with 3-mercaptopropionic acid (sulfur nucleophiles) was achieved in 25% DIPEA in DMF at room temperature. Following the reduction of nitro group, subsequent cyclization was carried out with a strong coupling reagent (PyBrop). Flavonoid **19** was obtained as the major product.

Conclusions

In summary, we have developed efficient and high-yielding methods for the synthesis of a series of flavonoid analogues. Claisen condensation, mixed acid nitration, and oxidative cyclization reaction with iodine-DMSO were used in these methods. Each of these flavonoid analogues has three diversification points and can be readily transformed into a variety of chemical templates. In addition, a series of flavonoid derivatives with different chemical structures were designed and synthesized in solid phase, using one of the flavonone scaffolds. Most of them were achieved in very high yield, which indicates that these scaffolds can be used to develop natural-product-like combinatorial flavonoid libraries with large amounts of diversity.

Experimental Section

General Method. Rink amide MBHA resin (0.5 mmol/g), amino acid derivatives, HOBt, DIC, and PyBrop were purchased from GL Biochem (Shanghai, China). All solvents and other chemical reagents were purchased from Aldrich (Milwaukee, WI) and were analytical grade. All infrared spectra were determined on a Genesis II Mattson FT-IR. NMR was recorded on a Bruker DRX spectrometer (Billerica, MA) in DMSO-d_6 at 25 °C (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR spectra). HRMS was performed with Finnigan LTQ FT. MS was performed with Finnigan LCQ. Analytical HPLC analyses (Vydac column; 4.6 mm × 250 mm; 5 μm; 300 Å; C_{18}; 1.0 mL/min; 25 min gradient from 100% aqueous H_2O (0.1% TFA) to 100% CH_3CN (0.1% TFA); 214, 220, 254, and 280 nm) were performed on a Beckman System Gold HPLC system (Fullerton, CA) or on Waters 2996 photodiode array detector, a Waters 2525 binary gradient module, and a Waters 2767 sample manager

equipped with a 4.6 × 150 mm Waters Xterra MS C_{18} 5.0 μm column employing a 20 min gradient from 100% aqueous H_2O (0.1% TFA) to 100% CH_3CN (0.1% TFA) at a flow rate of 1.0 mL/min. Column chromatography was performed on silica gel using a mixture of hexane and ethyl acetate with 1% HOAc as the eluent.

4-[3-(5-Fluoro-2-hydroxy-phenyl)-3-oxo-propenyl]-benzoic Acid (1). Potassium hydroxide (4%) in water (150 mL) was added to a stirring suspension of 5′-fluoro-2′-hydroxy-acetophenone (4.624 g, 30 mmol) and 4-carboxybenzaldehyde (5.405 g, 36 mmol) in ethanol (150 mL). The reaction mixture was stirred for 7 days, and then it was acidified with 2 N HCl. The precipitate was filtered, washed with water, and dried to give a yellow solid, which was recrystalized from the mixture solvent (THF/H_2O, 4:1) to give **1** (7.3 g, yield 85%) as an orange solid. mp: 301−303 °C. UV λ_{max} (nm): 316. IR (neat, selected peaks): ν 3369, 1679, 1578, 1566, 1480, 1420 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ11.99 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.07 (d, J = 15.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 15.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.04 (dd, J = 8.5 Hz, 4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.1, 167.5, 158.3, 155.5 (d, J = 235 Hz), 144.2, 139.1, 133.1, 130.4, 129.9, 125.0, 124.2 (d, J = 27 Hz), 122.1 (d, J = 6.5 Hz), 119.9 (d, J = 8 Hz), 116.6 (d, J = 24 Hz). HR ESI-FTMS [M − H]$^-$ Calcd for $C_{16}H_{11}FO_4$: 286.06414. Found: 285.06307.

4-(6-Fluoro-4-oxo-4H-chromen-2-yl)-benzoic Acid (2). A mixture of **1** (858 mg, 3 mmol) and iodine (38.1 mg, 0.05 equiv) in DMSO (5 mL) was refluxed for 30 min and then carefully poured into crushed ice. The precipitate was filtered, washed with water, and dried to give a light yellow solid, which was recrystallized from THF to give **2** as white needles (809 mg, yield 95%). mp: 330−331 °C. UV λ_{max} (nm): 265, 302. IR (neat, selected peaks): ν 1688, 1634, 1626, 1580, 1566, 1479, 1427 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.25 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 7.94 (dd, J = 9 Hz, 4 Hz, 1H), 7.75 (m, 2H), 7.18 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 177.2, 167.3, 162.5, 159.8 (d, J = 243 Hz), 152.9, 135.5, 134.2, 130.5, 127.4, 125.2 (d, J = 7.6 Hz), 123.3 (d, J = 22 Hz), 122.2 (d, J = 7.6 Hz), 110.2 (d, J = 22 Hz), 108.1. HR ESI-FTMS [M − H]$^-$ Calcd for $C_{16}H_9FO_4$: 284.04849. Found: 283.04739.

4-(6-Fluoro-8-nitro-4-oxo-4*H*-chromen-2-yl)-benzoic Acid (3). Compound **1** (572 mg, 2 mmol) was dissolved in 98% H_2SO_4 (6 mL), and then the mixture was chilled in an ice bath; 70% HNO_3 (1.3 mL) was added dropwise under magnetic stirring. The mixture was stirred in ice bath for 30 min, and then it was poured into granulated ice. After complete precipitation, the precipitate was filtered, washed with water, and dried to give brown solid, which was recrystallized from the mixture solvent (THF/H_2O, 1:1) to give **3** (559 mg, yield 85%) as brown crystals. mp: 327−329 °C. UV λ_{max} (nm): 228, 254, 309. IR (neat, selected peaks): ν 1655, 1620, 1610, 1542, 1473, 1426, 1359 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (dd, J = 8.5 Hz, 3 Hz, 1H), 8.23 (d, J = 8.0 Hz, 2H), 8.16 (dd, J = 7.5 Hz, 3 Hz, 1H), 8.13 (d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.6, 167.2, 162.4, 157.6 (d, J = 247 Hz), 145.6, 139.9 (d, J = 8.6 Hz), 134.7, 134.6, 130.6, 127.5, 127.0 (d, J = 7.0 Hz), 119.8 (d, J = 28.8 Hz), 117.1 (d, J = 23.6 Hz), 108.6. HR ESI-FTMS[M − H]$^-$ Calcd for $C_{16}H_8FNO_6$: 329.03357. Found: 328.03338.

4-[3-(4-Fluoro-2-hydroxy-phenyl)-3-oxo-propenyl]-benzoic Acid (4). Potassium hydroxide (8%, 300 mL) was added to a stirring suspension of 4′-fluoro-2′-hydroxy-acetophenone (9.248 g, 60 mmol) and 4-carboxybenzaldehyde (10.81 g, 72 mmol) in ethanol (300 mL). The reaction mixture was stirred for 7 days, and then it was acidified with 2 N HCl. The precipitate was filtered, washed with water, and dried to give a yellow solid, which was recrystallized from the mixture solvent (THF/H_2O, 4:1) to give **4** (15.4 g, yield 90%) as yellow needles. mp: 323−324 °C. UV λ_{max} (nm): 318. IR (neat, selected peaks): ν 3356, 1686, 1603, 1563, 1506, 1414 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.81 (s, 1H), 8.37 (t, J = 7.5 Hz, 1H), 8.10 (d, J = 15.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 15.5 Hz, 1H), 6.88 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.0, 167.5, 167.3 (d, J = 252 Hz), 164.9 (d, J = 14 Hz), 144.0, 139.1, 134.6 (d, J = 11.8 Hz), 130.4, 130.3, 129.8, 124.8, 118.8, 108.9 (d, J = 21.6 Hz), 105.0 (d, J = 23.5 Hz). HR ESI-FTMS [M − H]$^-$ Calcd for $C_{16}H_{11}FO_4$: 286.06414. Found: 285.06309.

4-(7-Fluoro-4-oxo-4*H*-chromen-2-yl)-benzoic Acid (5). The procedure for the synthesis of **2** was modified as follows to produce compound **5**. The mixture of **4** (858 mg, 3 mmol) and iodine (38.1 mg, 0.05 equiv) in DMSO gave **5** (766 mg, yield 90%) as white needles. mp: 306−307 °C. UV λ_{max} (nm): 236, 302. IR (neat, selected peaks): ν 1674, 1637, 1623, 1436, 1413 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (d, J = 8.5 Hz, 2H), 8.11 (t, J = 8.5 Hz, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8 Hz, 1H), 7.74 (t, J = 8.5 Hz, 1H), 7.15 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 177.0, 167.3, 165.8 (d, J = 250), 162.5, 157.5 (d, J = 14 Hz), 135.4, 134.1, 130.5, 128.4 (d, J = 11 Hz), 127.3, 121.2, 115.0 (d, J = 24 Hz), 108.9, 106.3 (d, J = 14 Hz). HR ESI-FTMS [M − H]$^-$ Calcd for $C_{16}H_9FO_4$: 284.04849. Found: 283.04737.

4-[3-(4-Fluoro-2-hydroxy-5-nitro-phenyl)-3-oxo-propenyl]-benzoic Acid (6). Compound **4** (4 g) was dissolved in 98% sulfuric acid (20 mL), and then the mixture was chilled in an ice bath. HNO_3 (70%, 0.9 mL) was added dropwise under magnetic stirring. The mixture was stirred in an ice bath for 30 min and then poured into granulated ice. After complete precipitation, the precipitate was filtered, washed with water, and dried to give a yellow solid (3.98 g), which was recrystallized from the mixture solvent (THF/H_2O 1:1) to give **6** (2.6 g, yield 57%) as yellow needles. mp: 277−279 °C. UV λ_{max} (nm): 319. IR (neat, selected peaks): ν 1695, 1644, 1583, 1484, 1425, 1342 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.73 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H), 7.91 (d, J = 15.5 Hz, 1H), 7.79 (d, J = 15.5 Hz, 1H), 7.07 (d, J = 13 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 190.8, 167.4, 166.5 (d, J = 13.4 Hz), 159.3 (d, J = 266.2 Hz), 144.3, 139.0, 133.1, 130.6, 130.4, 130.1(d, J = 7.4 Hz), 129.8, 126.1, 120.8, 107.0

(d, $J = 21.6$ Hz). HR ESI-FTMS $[M - H]^-$ Calcd for $C_{16}H_{10}FNO_6$: 331.04922. Found: 330.04906.

4-[3-(4-Fluoro-2-hydroxy-3-nitro-phenyl)-3-oxo-propenyl]-benzoic Acid (7). In the same manner as **6**, **4** (4 g) was dissolved in 82% sulfuric acid (20 mL), and then the mixture was chilled in an ice bath. HNO_3 (70%, 0.9 mL) was added dropwise under magnetic stirring. The mixture was stirred in an ice bath for 30 min to give a yellow solid (4.1 g), which was subjected to silica gel column chromatography using a mixture of hexane and ethyl acetate with 1% HOAc as the eluent to give **7** as a brown solid (2.2 g, yield 48%). mp: 275−277 °C. UV λ_{max} (nm): 328. IR (neat, selected peaks): ν 1695, 1644, 1583, 1484, 1425, 1342 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.69 (dd, $J = 9$, 6.5 Hz, 1H), 8.12 (d, $J = 15.5$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 2H), 8.01 (d, $J = 8.5$ Hz, 2H), 7.94 (d, $J = 15.5$ Hz, 1H), 7.26 (t, $J = 9$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.2, 167.4, 157.7 (d, $J = 262$ Hz), 156.4, 145.7, 138.8, 136.4 (d, $J = 11.8$ Hz), 133.4, 130.4, 130.2, 123.8, 120.0, 108.0 (d, $J = 14.7$ Hz), 107.9 (d, $J = 12.2$ Hz). HR ESI-FTMS $[M - H]^-$ Calcd for $C_{16}H_{10}FNO_6$: 331.04922. Found: 330.04902.

4-(7-Fluoro-6-nitro-4-oxo-4*H*-chromen-2-yl)-benzoic Acid (8). A mixture of **6** (662 mg, 2 mmol) and iodine (25.4 mg, 0.05 equiv) in DMSO (4 mL) was refluxed for 30 min and then carefully poured onto crushed ice. The precipitate was filtered, washed with water, and dried to give a light yellow solid, which was recrystallized from THF to give **8** as white needles (631 mg, yield 96%). mp: 302−303 °C. UV λ_{max} (nm): 236, 302. IR (neat, selected peaks): ν 1701, 1645, 1619, 1538, 1450, 1343 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.69 (d, $J = 8.0$ Hz, 1H), 8.26 (d, $J = 8.5$ Hz, 2H), 8.20 (d, $J = 11.5$ Hz, 1H), 8.12 (d, $J = 8.5$ Hz, 2H), 7.30 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.2, 167.2, 163.1, 159.5, 158.1(d, $J = 264$ Hz), 134.8, 134.5, 130.5, 127.5, 124.9, 123.3, 120.7, 109.8 (d, $J = 24$ Hz), 109.1 (d, $J = 16$ Hz). HR ESI-FTMS $[M - H]^-$ Calcd for $C_{16}H_8FNO_6$: 329.03357. Found: 328.03337.

4-(7-Fluoro-8-nitro-4-oxo-4*H*-chromen-2-yl)-benzoic Acid (9). In the same manner as for flavone **8**, a mixture of **6** (662 mg, 2 mmol) and iodine (25.4 mg, 0.05 equiv) in DMSO (4 mL) was refluxed for 30 min to give a light yellow solid, which was recrystallized from THF to give **9** as white needles (625 mg, yield 95%). mp: 298−300 °C. UV λ_{max} (nm): 236, 302. IR (neat, selected peaks): ν 1720, 1623, 1593, 1545, 1442, 1351 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.37 (dd, $J = 9.0$. 6.0 Hz, 1H), 8.11 (s, 4H), 7.73 (t, $J = 9.0$ Hz, 1H), 7.33 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.7, 167.2, 162.4, 157.6 (d, $J = 262.6$ Hz), 149.1, 134.6 (d, $J = 14$ Hz), 131.5 (d, $J = 11.4$ Hz), 130.7, 127.3, 121.8, 115.4 (d, $J = 17.2$ Hz), 109.5 (d, $J = 20.2$ Hz). HR ESI-FTMS $[M - H]^-$ Calcd for $C_{16}H_8FNO_6$: 329.03357. Found: 328.03338.

4-(7-Fluoro-6-nitro-4-oxo-chroman-2-yl)-benzoic Acid (10). A mixture of **6** (662 mg, 2 mmol) in THF (10 mL) and aqueous H_2SO_4 (5 mL, 10%) was refluxed for 24 h in an oil bath, and then distilled to remove the THF. The precipitate was filtered to give a light yellow solid, which was subjected to silica gel column chromatography using a mixture of hexane and ethyl acetate with 1% HOAc as the eluent to give **10** (403 mg, yield 61%) as a light yellow solid. mp: 305−307 °C. UV λ_{max} (nm): 239, 283. IR (neat, selected peaks): ν 1714, 1652, 1616, 1545, 1444, 1347 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.49 (d, $J = 8.5$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 2H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.48 (d, $J = 12.5$ Hz, 1H), 6.03 (dd, $J = 13$, 2.5 Hz, 1H), 3.43 (dd, $J = 13$, 16.5 Hz, 1H), 3.03 (dd, $J = 16.5$, 2.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.6, 167.6, 166.3 (d, $J = 13.6$ Hz), 159.9 (d, $J = 266.6$ Hz), 143.0, 132.5 (d, $J = 8.4$ Hz), 131.9, 130.4, 129.8, 127.5, 126.3, 118.0, 108.6 (d, $J = 6.5$ Hz), 80.4, 43.2. HR ESI-FTMS $[M - H]^-$ Calcd for $C_{16}H_{10}FNO_6$: 331.04922. Found: 330.04903.

4-(7-Fluoro-8-nitro-4-oxo-chroman-2-yl)-benzoic Acid (11). In the same manner as for flavanone **10**, a mixture of **5** (662 mg, 2 mmol) in THF (10 mL) and aqueous H_2SO_4 (5 mL, 10%) was refluxed for 72 h to give **11** as a light yellow solid (417 mg, yield 63%). mp: 278−279 °C. UV λ_{max} (nm): 239, 283. IR (neat, selected peaks): ν 1696, 1684, 1588, 1535, 1445, 1357 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.11 (dd, $J = 9$, 6.5 Hz, 1H), 8.01 (d, $J = 8.5$ Hz, 2H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.33 (t, $J = 9$ Hz, 1H), 6.09 (dd, $J = 12.5$, 2.5 Hz, 1H), 3.41 (dd, $J = 12.5$, 17 Hz, 1H), 3.06 (dd, $J = 17$, 2.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 189.2, 167.5, 157.9 (d, $J = 261.3$ Hz), 154.5, 142.8, 132.0 (d, $J = 11.6$ Hz), 131.9, 130.4, 130.1 (d, $J = 15.5$ Hz), 127.2 (d, $J = 23.5$ Hz), 119.7, 110.9 (d, $J = 23.8$ Hz), 81.2, 43.2. HR ESI-FTMS $[M - H]^-$ Calcd for $C_{16}H_{10}FNO_6$: 331.04922. Found: 330.04904.

Synthesis of Flavonoid 8-Gly-Rink Amide MBHA Resin. Two grams of Rink amide MBHA resin was swollen in DMF for 2 h; 20% piperidine (v/v) in DMF (2 × 15 min) was added to the resin. The resin was then thoroughly washed with DMF, MeOH, DCM, and DMF. A mixture of Fmoc-Gly-OH (891.9 mg), HOBt (405.3 mg), and DIC (464.5 μL) in DMF (20 mL) was added to the resin. The final mixture was shaken until the Kaiser test was negative. The resin was washed with DMF, MeOH, DCM, and DMF, followed by Fmoc deprotection. A solution of flavonoid **8** (822.5 mg), HOBt (405.3 mg), and DIC (464.5 μL) in DMF (20 mL) was added to the resin. The final mixture was shaken until the Kaiser test was negative. The supernatant was drained, and the resin washed with DMF, MeOH, and DCM.

Synthesis of Compound 12. A solution of morpholine (344 μL) in 25% DIPEA/DMF (3 mL) was added to flavonoid **8**-Gly-Rink amide MBHA resin (200 mg). The mixture was shaken overnight, and the supernatant was drained. The resin was washed with DMF, MeOH, and DMF; 2 M $SnCl_2$/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the resin was washed with DMF, MeOH, and DCM. A solution of Ac_2O (94 μL) and pyridine (162 μL) in DCM (3 mL) was added to the resin; the mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. Three milliliters of 95% TFA in water was added to the dried resin. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen.

The crude product was purified by HPLC. Compound **12** (39 mg, yield 87%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.17(s, 1H), 8.90(t, J = 6 Hz, 1H), 8.37(s, 1H), 8.23 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.46 (s, 1H), 7.44 (s, 1H), 7.08 (s, 2H). 3.84 (brs, 6H), 3.01 (brs, 4H), 2.15(s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.9, 171.3, 169.0, 166.0, 161.5. 136.9, 134.1, 130.0, 128.5, 126.6, 118.9, 108.8, 107.8, 66.3, 51.4, 42.9, 24.3. ESI-MS: m/z 465.3 $[M + H]^+$.

Synthesis of Compound 13. A solution of 4-trifluoromethoxy-phenol (517.6 μL) in 25% DIPEA/DMF (3 mL) was added to flavonoid **8**-Gly-Rink amide MBHA resin (200 mg). The mixture was shaken overnight, and the supernatant was drained off. The resin washed with DMF, MeOH, and DMF; 2 M $SnCl_2$/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the resin was washed with DMF, MeOH, and DCM. A solution of Ac_2O (94 μL) and pyridine (162 μL) in DCM (3 mL) was added to the resin; the mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. Three milliliters of 95% TFA in water was added to the dried resin. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen. The crude product was purified by HPLC. Compound **13 (**47 mg, yield 84%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.81 (s, 1H), 8.88 (t, J = 5.5 Hz, 1H), 8.74 (s, 1H), 8.20 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.43 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.27 (s, 1H), 7.11 (s, 1H), 7.06 (s, 1H). 3.82 (d, J = 5.5 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.8, 171.3, 169.5, 166.0, 161.8, 154.2, 153.1, 145.4, 137.0, 133.9, 128.4, 128.1, 126.7, 123.6, 122.2, 119.4, 118.1, 107.7, 106.3, 42.9, 24.2. ESI-MS: m/z 556.4 $[M + H]^+$.

Synthesis of Compound 14. To flavonoid **8**-Gly-Rink amide MBHA resin (200 mg) was added a solution of cyclopentyl mercaptan (428 μL) in 25% DIPEA/DMF (3 mL). The mixture was shaken overnight, and the supernatant was drained. The resin was washed with DMF, MeOH, and DMF; 2 M $SnCl_2$/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the resin was washed with DMF, MeOH, and DCM. A solution of Ac_2O (94 μL) and pyridine (162 μL) in DCM (3 mL) was added to the resin; the mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. To the dried resin was added 3 mL 95% TFA in water. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen. The crude product was purified by HPLC. Compound **14** (41 mg, yield 86%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.50 (s, 1H), 8.91 (t, J = 5.5 Hz, 1H), 8.27 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H), 7.93 (s, 1H), 7.78 (s, 1H), 7.45 (s, 1H), 7.11 (s, 1H), 7.08 (s, 1H), 3.90 (m, J = 6.5 Hz, 1H), 3.85 (d, J = 5.5 Hz, 2H), 2.26 (m, 2H), 1.75 (m, 2H), 1.67 (m, 2H), 1.59 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.9, 171.3, 169.4, 166.0, 161.7, 153.9, 143.4, 137.1, 134.0, 132.8, 128.4, 126.8, 121.7, 120.5, 116.0, 107.9, 43.6, 42.9, 33.3, 25.1, 23.6. ESI-MS: m/z 480.3 $[M + H]^+$.

Synthesis of Compounds 15 and 16. A solution of isobutylamine (596 μL) in 25% DIPEA/DMF (6 mL) was added to flavonoid **8**-Gly-Rink amide MBHA resin (400 mg). The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DMF; 2 M $SnCl_2$/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the resin was washed with DMF, MeOH, and DMF. A solution of CDI (256.2 mg) in DCM (3 mL) was added to one portion of the resin (200 mg). The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. Three milliliters of 95% TFA in water was added to the dried resin. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen. The crude product was purified by HPLC. Compound **15** (35 mg, yield 80%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H), 8.90 (t, J = 5.5 Hz, 1H), 8.23 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H), 7.69 (s, 1H), 7.78 (s, 1H), 7.48 (s, 1H), 7.44 (s, 1H), 7.08 (s, 2H), 3.85 (d, J = 5.5 Hz, 2H), 3.70 (d, J = 7.5 Hz, 2H), 2.19 (m, 1H), 0.92 (d, J = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 177.2, 171.3, 166.0, 161.2, 155.5, 136.9, 134.3, 128.5, 127.6, 126.8, 126.5, 118.0, 115.9, 107.1, 102.2, 97.5, 48.1, 42.9, 27.6, 20.2. ESI-MS: m/z 435.4 $[M + H]^+$.

A solution of 4-trifluoromethoxyphenyl isothiocyanate (487 μL) and DIC (464 μL) in DMF (3 mL) was added to the remaining portion of the resin (200 mg). The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. Three milliliters of 95% TFA in water was added to the dried resin. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen. The crude product was purified by HPLC. Compound **16** (49 mg, yield 82%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.89(t, J = 6.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 2H), 8.07(d, J = 8.0 Hz, 2H), 7.99 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.89 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.44 (s, 1H), 7.10 (s, 1H), 7.07 (s, 1H), 4.21 (d, J = 7.5 Hz, 2H), 3.85 (d, J = 6.0 Hz, 2H), 2.27 (m, 1H), 0.96 (d, J = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 177.7, 171.3, 166.0, 161.4, 159.3, 152.7, 152.3, 138.9, 136.9, 134.3, 128.5, 126.6, 122.4, 119.2, 109.2, 106.8, 99.6, 98.7, 93.4, 49.4, 42.9, 28.0, 19.9. ESI-MS: m/z 594.4 $[M + H]^+$.

Synthesis of Compound 17. A solution of L-phenylalanine methyl ester hydrochloride (647 mg) in 25% DIPEA/DMF (3 mL) was added to flavonoid **8**-Gly-Rink amide MBHA resin (200 mg). The mixture was shaken overnight, and the supernatant was decanted. The resin was washed with DMF, MeOH, and DMF; 2 M $SnCl_2$/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the resin

was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. Three milliliters of 95% TFA in water was added to the dried resin. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen. The crude product was purified by HPLC. Compound **17** (42 mg, yield 88%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.6 (s, 1H), 8.86 (s, 1H), 8.13 (d, J = 7.0 Hz, 2H), 8.04 (d, J = 7.0 Hz, 2H), 7.43 (s, 1H), 7.31 (s, 1H), 7.24 (s, 1H), 7.22 (m, 3H), 7.17 (m, 2H), 7.07 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 4.40 (m, 1H), 3.85 (d, J = 4.5 Hz, 2H), 3.03 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.3, 171.5, 166.4, 166.2, 160.6, 154.3, 140.8, 137.2, 136.8, 134.7, 130.6, 128.8, 128.7, 127.2, 126.5, 124.8, 114.5, 108.7, 107.7, 98.9, 56.8, 43.1, 40.8. ESI-MS: m/z 483.4 $[M + H]^+$.

Synthesis of Compound 18. A solution of propylamine (246 μL) in 25% DIPEA/DMF (3 mL) was added to flavonoid **8**-Gly-Rink amide MBHA resin (200 mg). The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DMF; 2 M $SnCl_2$/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the resin was washed with DMF, MeOH, and DMF. A solution of benzaldehyde (101 μL) in 5%HOAc/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. Three milliliters of 95% TFA in water was added to the dried resin. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen. The crude product was purified by HPLC. Compound **18** (41 mg, yield 85%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.90 (t, J = 5.5 Hz, 1H), 8.31 (d, J = 8.0 Hz, 2H), 8.28 (d, J = 3.0 Hz, 2H), 8.10 (d, J = 8.0 Hz, 2H), 7.85 (m, 2H), 7.64 (m, 3H), 7.44 (s, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 4.36 (t, J = 7.5 Hz, 3H), 3.86 (d, J = 5.5 Hz, 2H), 1.77 (m, J = 7.5 Hz, 2H), 0.79 (t, J = 6.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 178.2, 171.3, 166.0, 161.9, 157.4, 152.7, 140.2, 140.0, 137.0, 134.3, 131.1, 129.7, 129.6, 129.4, 128.5, 126.7, 119.9, 114.4, 106.6, 100.4, 46.7, 42.9, 22.7, 11.3. ESI-MS: m/z 481.4 $[M + H]^+$.

Synthesis of Compound 19. A solution of 3-mercaptopropionic acid (261 μL) in 25% DIPEA/DMF (3 mL) was added to flavonoid **8**-Gly-Rink amide MBHA resin (200 mg). The mixture was shaken overnight, and the supernatant was decanted. The resin was washed with DMF, MeOH, and DMF; 2 M $SnCl_2$/DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the resin was washed with DMF, MeOH, and DMF. A solution of PyBrop (233 mg) and DIPEA (174 μL) in DMF (3 mL) was added to the resin. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, MeOH, and DCM. The resin was further dried in vacuum. Three milliliters of 95% TFA in water was added to the dried resin. The mixture was shaken at room temperature for 2 h. The supernatant was removed, and the resin was washed with DCM. The combined supernatants were dried under a stream of nitrogen. The crude product was purified by HPLC. Compound **19** (15 mg, yield 35%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.07 (s, 1H), 8.91 (t, J = 5.5 Hz, 1H), 8.26 (d, J = 8.0 Hz, 2H), 8.12 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.45 (s, 1H), 7.18 (s, 1H), 7.09 (s, 1H), 3.86 (d, J = 5.5 Hz, 2H), 3.48 (t, J = 7.0 Hz, 2H), 2.55 (t, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 177.7, 172.4, 171.3, 166.0, 162.2, 152.6, 140.0, 137.2, 134.5, 133.8, 128.5, 126.8, 124.9, 124.2, 118.0, 108.0, 42.9, 33.9, 33.7. ESI-MS: m/z 424.3 $[M + H]^+$.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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