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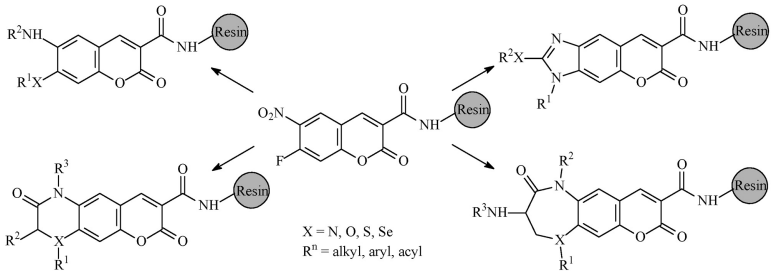

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Synthesis and Reactions of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid: A Novel Scaffold for Combinatorial Synthesis of Coumarins

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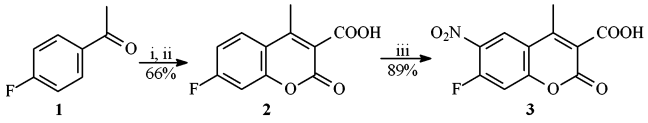
7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid has been prepared as a novel scaffold for combinatorial synthesis of coumarins. The scaffold has three points of diversity. The optimal conditions for its reactions with different nucleophiles in solid phase were obtained. Sixteen coumarin derivatives with different structures were designed and synthesized in solid phase to demonstrate its application as a scaffold for combinatorial synthesis of coumarins. Thirteen of these derivatives were obtained in high yields. Many of these model compounds fluoresce. Combinatorial libraries constructed with this novel scaffold may have interesting biological or physical properties.

Introduction

Natural products have played and continue to play an invaluable role in the drug discovery process. Many current drugs are either natural products or their derivatives.[1,2] By combining the drug quality of natural products with the efficiency of combinatorial chemistry, the synthesis and screening of small molecule libraries based on natural products as templates has attracted growing attention in the past few years. The great interest in this field is shown by an increasing number of original papers and reviews.[2,3] Thus, the search for novel scaffolds for combinatorial synthesis of natural products and libraries is a relevant and timely pursuit.

Coumarins (2*H*-1-benzopyran-2-ones) are well-known natural products displaying a broad range of biological activities.[4] Coumarin derivatives have been extensively used as therapeutic agents,[5] active media for tunable dye lasers,[6] optical bleaching agents,[7] luminescent probes,[8] and triplet sensitizers.[9] Although a solid-phase approach for coumarin synthesis has been reported,[10] the method is not suitable for library synthesis because of the lack of diversity sites. Recently, Schiedel et al. have developed synthetic protocols for solution-phase synthesis of coumarin derivatives by C−C cross-coupling reactions at the 3-position.[11] A 151-membered library was successfully made from eight 3-bromocoumarin scaffolds using this approach. However, only one functional group is available for derivatization on the scaffold, and additional diversity has to come from different scaffolds. To address this problem, we designed and synthesized a novel scaffold containing three points of diversity for combinatorial synthesis of coumarins, 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid (7-fluoro-4-methyl-6-nitrocoumarin-3-carboxylic acid). The chemical structure is shown in Scheme 1, **3**. The scaffold can be readily coupled to a solid support through the 3-carboxyl group. The *ortho*-nitro aryl fluoride is known to undergo facile aromatic nucleophilic substitution with nucleophiles. After the reduction of the nitro group, a heterocyclic ring with additional diversity can be readily constructed on the coumarin structure.

Scheme 1. Synthesis of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid[a]



[a] Reagents and conditions: (i) 7 M ammonia in methanol, rt, overnight; (ii) 1.2 equiv of Meldrum's acid in ethanol, reflux, 5 h; (iii) 1:1 HNO_3/H_2SO_4, rt, 5 h.

Result and Discussion

Synthesis of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid. The synthesis of scaffold **3** was started with commercially available 4′-fluoro-2′-hydroxyacetophenone (Scheme 1, **1**). 7-Fluoro-4-methyl-2-oxo-2*H*-1-benzopyran-3-carboxylic acid (**2**) was prepared using our previously published procedure.[12] 4′-Fluoro-2′-hydroxyacetophenone was reacted with ammonia solution in methanol (MeOH) to form a ketimine intermediate, which was subsequently condensed with Meldrum's acid to generate intermediate **2**. The nitration of intermediate **2** occurred smoothly at room temperature using the mixed acid route. During the reaction, a small amount of reaction mixture was taken out every half hour, neutralized with aqueous sodium carbonate solution, and then analyzed by HPLC. The nitration was done in 5 h. The reaction mixture was then poured into crushed ice. Since the product is partially soluble in strongly

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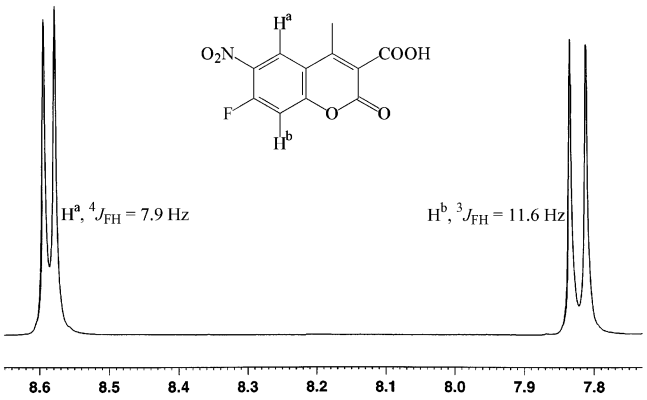


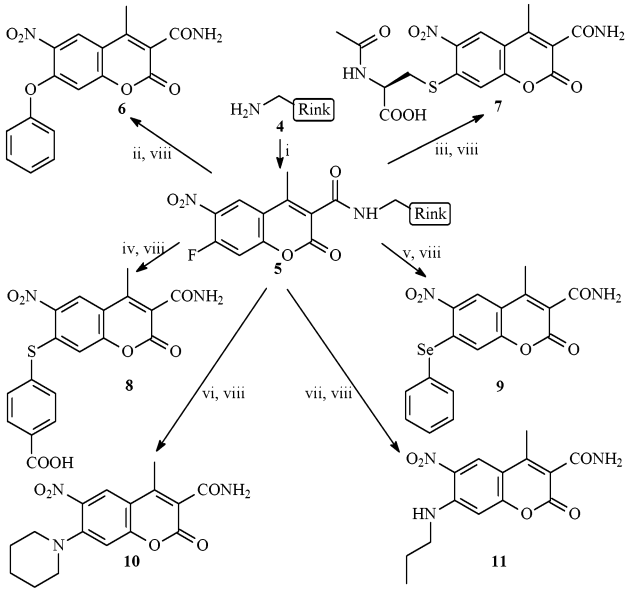
Figure 1. ^{1}H NMR spectrum of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid (7.7−8.7 ppm, other hydrogens not shown).

acidic solution, the pH of the mixture was adjusted to 2−3 with aqueous sodium hydroxide solution in an ice bath to complete the precipitation. Scaffold **3** was obtained as the major product with excellent yield. ^{1}H NMR spectrum confirmed that the nitro group was introduced to the 6-position, because no spin−spin coupling between the two hydrogens on the benzene ring was observed (Figure 1). A trace amount of 7-fluoro-4-methyl-8-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid was observed as the byproduct in the ^{1}H NMR spectrum of the crude product and was readily removed by recrystallization from aqueous acetone.

Reactions of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid with Nucleophiles in Solid Phase. The reactivity of the fluoride in scaffold **3** to nucleophilic attack was studied in solid phase (Scheme 2). Scaffold **3** was readily ligated to Rink amide resin via its 3-carboxyl group using 1,3-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) as the activating system. The concentration of the reagents and reaction time can be reduced by using stronger condensation reagents, such as *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU)/*N*,*N*-diisopropylethylamine (DIEA). Six nucleophiles were examined for the solid-phase aromatic nucleophilic substitution under various reaction conditions. To verify the extent of aromatic substitution, small portions of the resins were treated with trifluoroacetic acid (TFA). The cleaved products were separated from the resins and concentrated. The crude products were analyzed by HPLC and mass spectrometry (MS).

All six of the nucleophiles used in our experiment reacted readily with the resin-linked scaffold except phenol. Incubation of the resin-linked scaffold **5** with five equivalents of piperidine (secondary amine), Ac-Cys-OH and 4-mercaptobenzoic acid (sulfur-nucleophiles), or benzeneselenol in 5% DIEA/*N*,*N*-dimethylformamide (DMF) at room-temperature overnight gave clean products after TFA cleavage. The carboxyl group of the sulfur-nucleophiles did not interfere with the aromatic substitution. For compound **11**, 2 equiv of propylamine (primary amine) in 5% DIEA/DMF was found to be optimal. Higher concentrations of propylamine led to complicated side reactions, probably as a result of its attack on the pyran ring. Because of the low nucleophilicity of phenol, higher concentration of the reagent and a stronger

Scheme 2. Reactions of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid with Nucleophiles in Solid Phase[a]

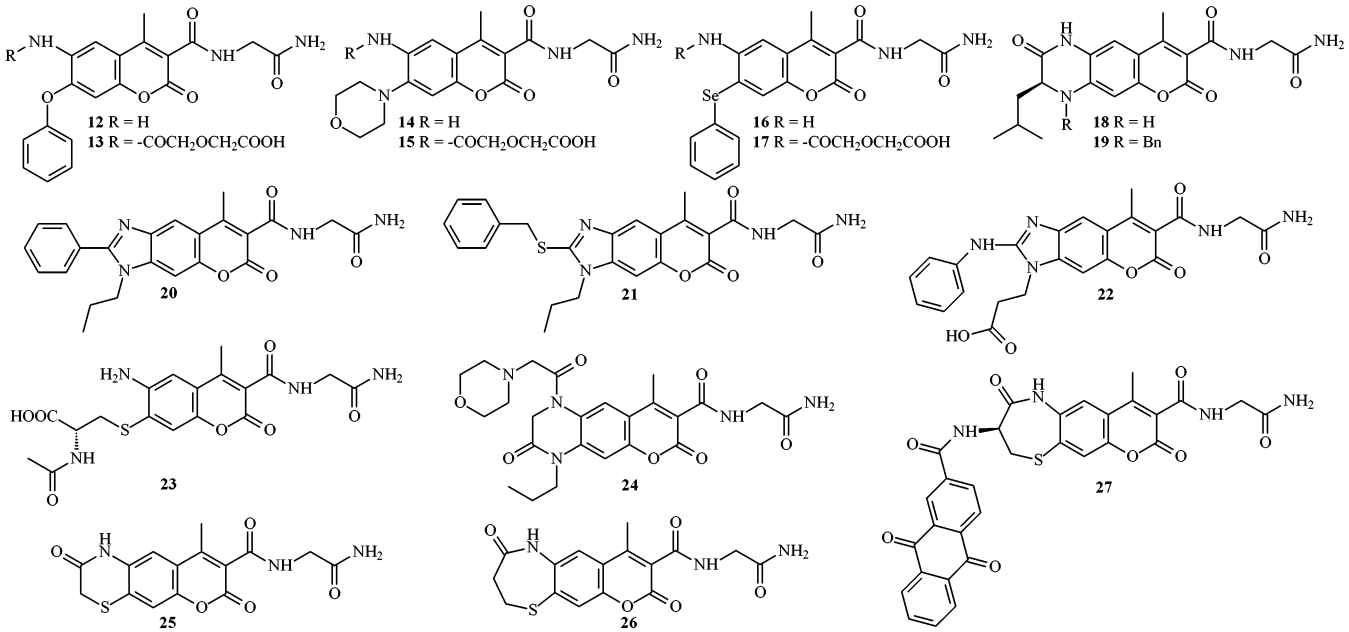


[a] Reagents and conditions: **4**, Rink amide resin; (i) 3 equiv of 7-fluoro-4-methyl-6-nitro-coumarin-3-carboxylic acid, 3 equiv of DIC and 3 equiv of HOBt in DMF, rt, 5 h; or 2 equiv of 7-fluoro-4-methyl-6-nitro-coumarin-3-carboxylic acid, 2 equiv of HBTU and 2 equiv of DIEA in DMF, rt, 2 h; (ii) 1 M phenol in 25% DIEA/DMF, rt, overnight; (iii) 5 equiv of Ac-Cys-OH in 5% DIEA/DMF, rt, overnight; (iv) 5 equiv of 4-mercaptobenzoic acid in 5% DIEA/DMF, rt, overnight; (v) 5 equiv of benzeneselenol in 5% DIEA/DMF, rt, overnight; (vi) 5 equiv of piperidine in 5% DIEA/DMF, rt, overnight; (vii) 2 equiv of propylamine in 5% DIEA, rt, overnight; (viii) 95% TFA/H_2O, rt, 2 h.

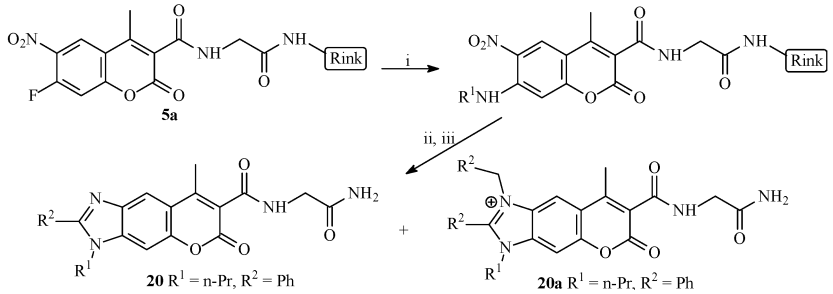
base were needed for the solid-phase aromatic substitution. Various combinations of different phenol concentrations and different bases, including DIEA, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), and sodium methoxide, were tested. After extensive optimization of the reaction conditions for compound **6**, the best conditions were determined to be 1 M phenol solution in 25% DIEA/DMF. Under the optimized reaction conditions, substitution of the fluoride in the resin-supported scaffold **5** with all the six nucleophiles (Scheme 2) was almost quantitative.

Design and Synthesis of Model Compounds. A number of small molecule libraries based on 4-fluoro-3-nitrobenzoic acid scaffold have been reported by several groups.[13−20] To demonstrate the potential of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid as the scaffold for combinatorial synthesis of coumarin derivatives, 16 model compounds with different structures have been designed and synthesized by simply applying the chemistry of 4-fluoro-3-nitrobenzoic acid to this scaffold (Chart 1). Glycine was coupled to Rink amide resin prior to the scaffold attachment to introduce the first diversity. After aromatic substitution of the *ortho*-nitro fluoride, the nitro group was reduced and subsequently modified. An additional heterocyclic ring can be readily constructed on the coumarin template to introduce interesting biological or physical properties. For example, benzimidazole moiety is an important structural element in drug discovery, and several solid-phase synthesis methods for benzimidazoles have been developed.[14,15] In the present study, we chose the "one-pot" synthetic route developed by Wu et al. for the synthesis of imidazocoumarins (Scheme

Chart 1. Structures of Model Compounds Synthesized from the 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid Scaffold

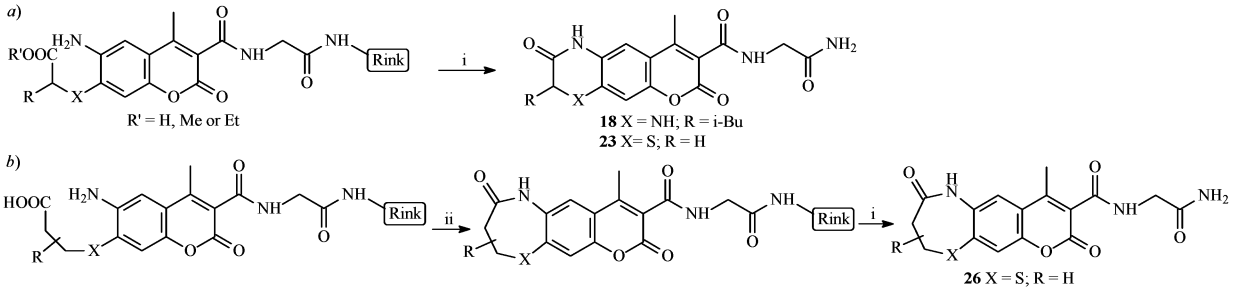


Scheme 3. "One-Pot" Solid-Phase Synthesis of Imidazocoumarins[a]



[a] Reagents and conditions: (i) 2 equiv of R^1NH_2 in 5% DIEA, rt, overnight; (ii) 2 equiv of R^2CHO and 0.75 M $SnCl_2 \cdot 2H_2O$ in DMF, 60 °C, 3 h; (iii) 95% TFA/H_2O, rt, 2 h.

Scheme 4. Formation of Six- and Seven-Member Lactams on the Coumarin Template[a]



[a] Reagents and conditions: (i) 95% TFA/H_2O, rt, 2 h; (ii) 4 equiv of HATU and 8 equiv of DIEA in DMF, rt, overnight.

3).[15] At the beginning of synthesis, the resin-supported scaffold **5a** was incubated with 2 equiv of a primary amine to form an *o*-nitroaniline intermediate. The reduction of nitro group and the formation of imidazole ring was achieved in a single step by heating the resin-supported *o*-nitroaniline intermediate with 2 equiv of an aldehyde and 0.75 M $SnCl_2 \cdot 2H_2O$ solution in DMF at 60 °C for 3 h. The desired model compound **20** was obtained in good yield (82%) after TFA cleavage along with a side-product **20a** (9%), which has an imidazolium structure according to MS and NMR analysis.

As one might expect, six-member heterocyclic rings are much easier to form, as compared to seven-member rings, because of the optimal ring size. In the synthesis of model compounds **18** and **25**, after the reduction of nitro group, the ring closure occurred automatically during the TFA cleavage, despite the esterization of the carboxyl group (Scheme 4a). In contrast, a strong coupling reagent was needed to form the seven-member ring in the synthesis of compounds **26** and **27** (Scheme 4b). Various activation systems, including DIC, DIC/HOBt, HBTU/DIEA, HBTU/HOBt, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)/1-hydroxy-7-azabenzotriazole (HOAt), and HATU/DIEA were tested. HATU/DIEA was found to be the most effective.

Table 1. Synthesis and Spectral Properties of Model Compounds Based on the 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid Scaffold

entry	yield[a] (%)	purity[b] (%)	λ_{abs}[c] (nm)	λ_{em}[c] (nm)	Φ[d]
12	91	95	376	555	0.052
13	87	90	338	448	0.113
14	92	93	388	564	0.046
15	82	91	346	459	0.054
16	93	94	387	568	0.029
17	81	88	351	460	0.003
18	78	86	388	475	0.741
19	21	41	388	479	0.723
20	82	88	340	451	0.068
21	86	93	350	458	0.103
22	53	73	367	475	0.031
23	92	94	386	571	0.014
24	78	82	375	464	0.799
25	86	93	359	469	0.032
26	83	90	345	472	0.101
27	45	54	329	465	0.011

[a] Yields were calculated on the basis of the purified products. [b] Purity was determined by HPLC analysis (UV detection at 254 nm) of crude products. [c] λ_{abs} and λ_{em} represent the maximum absorption and fluorescence wavelength, respectively. [d] Φ is the fluorescence quantum yield of coumpounds in methanol, and was determined using 7-amino-4-methylcoumarin as the standard reference.

Model compounds **12**−**27** were cleaved from the solid support by treatment with TFA after the synthesis was finished. The crude products were analyzed and purified by HPLC, followed by spectral characterization. All of these 16 compounds have at least two points of diversity. Thirteen of them were obtained in good yields and purity without further optimization of the literature methods (Table 1). More interestingly, all of these compounds fluoresce except compound **17**. Compounds **18**, **19**, and **24** exhibit very strong fluorescence. Synthesis and screening of combinatorial libraries based on these heterocylic structures may lead to the discovery of novel fluorescent coumarin derivatives with interesting biological or physical properties.

Fluorescence Quenching in a Dyad of Coumarin and Anthraquinone. Photoinduced energy and electron transfer reactions have been intensively investigated as a method of converting and storing solar energy.[21] Covalently linked multicomponent models have been reported. Since various energy and electron donors or acceptors can be used as the building blocks for library synthesis, scaffold **3** can also be used for the construction of covalently linked multicomponent systems in the study of photoinduced intramolecular interactions. A simple dyad of coumarin and anthraquinone **27** was designed and synthesized as a model. Anthraquinone is a well-known electron acceptor in the photoinduced electron transfer study. In dyad **27**, an anthraquinone moiety is linked to the coumarin structure via an amide bond. Compared to compound **26**, the fluorescence of the coumarin moiety in compound **27** is strongly quenched by the anthraquinone moiety as a result of the photoinduced intramolecular electron transfer.

Conclusion

In summary, we have developed a novel scaffold for combinatorial synthesis of coumarins. This scaffold has three points of diversity and can be readily attached to a solid support. The optimal conditions for its reactions with different nucleophiles in solid phase were obtained. Resin-supported or solution-phase coumarin libraries with high diversity can be easily prepared on the basis of this scaffold. Sixteen coumarin derivatives with different structures were designed and synthesized in solid phase, and 13 of them were obtained in high yields. Many of these compounds fluoresce. Work is currently underway in our laboratory to fully characterize the spectral properties of these novel compounds and to prepare libraries of coumarin derivatives. Combinatorial libraries constructed with this novel scaffold may have interesting biological or physical properties. Since various energy and electron donors or acceptors can be used as the building blocks, this scaffold can also be used for the construction of covalently linked multicomponent systems in the study of photoinduced intramolecular interactions.

Experimental Section

Materials and Instruments. Rink amide MBHA resin (0.45 mmol/g), amino acid derivatives, and HOBt were purchased from GL Biochem (Shanghai, China). All solvents and other chemical reagents were purchased from Aldrich (Milwaukee, WI) and were analytical grade. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer (Billerica, MA) at 25 °C. UV−vis absorption spectra were recorded on a Beckman DU 640B spectrophotometer (Fullerton, CA). Fluorescence spectra were recorded on a FluoroMax-2 spectrofluorometer from Instrument S.A., Inc. (Edison, NJ). 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 media (0.1% TFA) to 100% CH_3CN (0.1% TFA); 214, 220, 254, and 280 nm) and preparative HPLC purification (Vydac column, 20 mm × 250 mm, 5 μm, 300 Å, C_{18}, 7.0 mL/min, 45-min gradient from 100% aqueous media (0.1% TFA) to 100% CH_3CN (0.1% TFA), 254 nm) were performed on a Beckman System Gold HPLC system (Fullerton, CA). All of the experiments are carried out at room temperature unless otherwise noted.

General Procedure for Fmoc (*N*-(9-Fluorenylmethoxycarbonyl)) Deprotection. To each 100 mg of the resin was added 2 mL of 20% piperidine solution in DMF. The mixture was shaken for 15 min, and the supernatant was removed. This process was repeated once. The resin was then washed thoroughly with DMF, MeOH, and DMF.

General Procedure for TFA Cleavage. The resin was washed thoroughly with DMF, dichloromethane (DCM), MeOH, DCM, and MeOH and dried in vacuo prior to the TFA treatment. To each 100 mg of the resin was added 2 mL of 95% TFA solution in water at ice-bath temperature. The mixture was slowly warmed to room temperature and allowed to mix for 2 h. The supernatant was then removed, and the resin was washed with DCM (3 × 1 mL). The combined supernatants were concentrated to dryness under a stream of nitrogen and further dried in vacuo. The crude products were analyzed and purified by HPLC.

Synthesis of 7-Fluoro-4-methyl-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid (2). A 7.71-g (50 mmol) portion of 4′-fluoro-2′-hydroxyacetophenone was shaken with 30 mL of 7 M ammonia solution in methanol overnight. The mixture

was then concentrated in vacuo to dryness. Meldrum's acid (8.65 g, 60 mmol) and ethanol (25 mL) were added to the residue. The mixture was refluxed for 5 h and then allowed to cool to room temperature. After complete precipitation, the product was filtered and recrystallized from aqueous acetone. A total of 7.33 g of **2** was obtained as white needles (yield, 66%): mp 205−206 °C; ^{1}H NMR (DMSO-d_6) δ 7.84 (m, 1H), 7.34 (m, 1H), 7.26 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.3, 163.3 (d, $^1J_{CF}$ = 249.5 Hz), 157.8, 153.0 (d, $^3J_{CF}$ = 7.3 Hz), 144.0, 127.8 (d, $^3J_{CF}$ = 11.1 Hz), 116.8, 113.3, 112.1 (d, $^2J_{CF}$ = 22.0 Hz), 103.9 (d, $^2J_{CF}$ = 25.9 Hz), 15.9; ESI-MS *m*/*z* 223.1 (MH^+).

Synthesis of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid (3). A mixture of 10 mL of 70% nitric acid and 10 mL of concentrated sulfuric acid was chilled in an ice bath. A 5.55-g (25 mmol) portion of 7-fluoro-4-methyl-2-oxo-2*H*-1-benzopyran-3-carboxylic acid was added in batches under magnetic stirring. The ice bath was removed after 1 h. The mixture was stirred at room temperature for 5 h and was then poured into 100 g of granulated ice. The pH of the mixture was adjusted to 2−3 with 10 M aqueous NaOH solution. After complete precipitation, the precipitate was filtered and recrystallized from aqueous acetone. A total of 5.94 g of **3** was obtained as yellow needles (yield, 89%): mp 216−217 °C; ^{1}H NMR (DMSO-d_6) δ 13.9 (s, broad, 1H), 8.59 (d, 1H, J = 7.9 Hz), 7.82 (d, 1H, J = 11.6 Hz), 2.49 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.0, 156.6 (d, $^1J_{CF}$ = 264.9 Hz), 156.2 (d, $^2J_{CF}$ = 15.4 Hz), 156.1, 148.1, 134.0 (d, $^3J_{CF}$ = 8.5 Hz), 125.0, 122.4, 116.2, 107.1 (d, $^2J_{CF}$ = 25.1 Hz), 16.2; ESI-MS *m*/*z* 268.0 (MH^+).

Attachment of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid (3) to Rink Amide MBHA Resin. A 1-g (0.45 mmol) portion of Rink amide MBHA resin was swollen in DMF overnight, followed by Fmoc deprotection. A mixture of 361 mg (1.35 mmol) of **3**, 182 mg (1.35 mmol) of HOBt, 211 μL (1.35 mmol) of DIC, and 10 mL of DMF was added to the resin. The resulting mixture was shaken until the ninhydrin test was negative.[22] The supernatant was removed. The resin-linked scaffold **5** was washed with DMF, DCM, MeOH, and DCM and dried in vacuo.

Synthesis of Scaffold(3)−Gly−Rink Amide MBHA Resin (5a). For the synthesis of model compounds **12**−**27**, glycine was ligated to the resin as a linker prior to the scaffold attachment. In this case, 1 g (0.45 mmol) of Rink amide MBHA resin was swollen in DMF overnight, followed by Fmoc deprotection. A mixture of 401 mg (1.35 mmol) of Fmoc-Gly-OH, 182 mg (1.35 mmol) of HOBt, 211 μL (1.35 mmol) of DIC, and 10 mL of DMF was added to the resin. The resulting mixture was shaken until the ninhydrin test was negative. The supernatant was removed. The resin was washed with DMF, MeOH, and DMF, followed by Fmoc deprotection. The scaffold **3** was then attached to the resin using the procedure described above.

Synthesis of Compound 6. A 100-mg (0.045 mmol) portion of resin-linked scaffold **5** was shaken with 2 mL of 1 M phenol solution in 25% DIEA/DMF overnight. The supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 14 mg of **6** was obtained as a yellow solid (yield, 91%): ^{1}H NMR (DMSO-d_6) δ 8.71 (s, 1H), 7.84 (s, 1H), 7.77 (m, 3H), 7.66 (m, 1H), 7.60 (m, 2H), 6.63 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.5, 157.2, 155.2, 147.5, 142.3, 140.4, 137.8, 131.5, 131.4, 127.9, 125.8, 125.4, 118.4, 117.2, 16.3; ESI-MS *m*/*z* 341.1 (MH^+).

Synthesis of Compound 7. To 100 mg (0.045 mmol) of resin-linked scaffold **5** was added a solution of 36.7 mg (0.225 mmol) of Ac-Cys-OH in 2 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 17 mg of **7** was obtained as a yellow solid (yield, 92%): ^{1}H NMR (DMSO-d_6) δ 13.1 (s, broad, 1H), 8.59 (s, 1H), 8.47 (d, 1H, J = 8.0 Hz), 7.90 (s, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 4.51 (m, 1H), 3.61 (dd, 1H, J = 13.8, 4.7), 3.37 (dd, 1H, J = 13.8, 4.7), 2.45 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.2, 170.3, 165.6, 157.6, 155.3, 147.5, 142.8, 141.3, 125.7, 125.2, 117.0, 115.2, 51.3, 34.1, 23.0, 16.3; ESI-MS *m*/*z* 410.1 (MH^+).

Synthesis of Compound 8. To 100 mg (0.045 mmol) of resin-linked scaffold **5** was added a solution of 34.7 mg (0.225 mmol) of 4-mercaptobenzoic acid in 2 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 17 mg of **8** was obtained as a yellow solid (yield, 94%): ^{1}H NMR (DMSO-d_6) δ 13.3 (s, broad, 1H), 8.66 (s, 1H), 8.10 (d, 2H, J = 8.3 Hz), 7.86 (s, 1H), 7.78 (d, 2H, J = 8.3 Hz), 7.77 (s, 1H), 6.68 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.3, 165.5, 157.2, 155.1, 147.3, 142.1, 141.8, 135.9, 135.7, 133.3, 131.9, 125.9, 125.2, 118.0, 116.1, 16.3; ESI-MS *m*/*z* 401.0 (MH^+).

Synthesis of Compound 9. To 100 mg (0.045 mmol) of resin-linked scaffold **5** was added a solution of 23.9 μL (0.225 mmol) of benzeneselenol in 2 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 17 mg of **9** was obtained as a yellow solid (yield, 94%): ^{1}H NMR (DMSO-d_6) δ 8.56 (s, 1H), 7.88 (s, 1H), 7.76 (s, 1H), 7.50 (t, 2H, J = 7.9 Hz), 7.31 (t, 1H, J = 7.9 Hz), 7.21 (t, 2H, J = 7.9 Hz), 6.98 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.6, 157.6, 156.0, 155.3, 153.2, 147.6, 138.1, 131.3, 126.3, 125.1, 125.0, 120.1, 115.6, 107.8, 16.5; ESI-MS *m*/*z* 405.0 (MH^+).

Synthesis of Compound 10. To 100 mg (0.045 mmol) of resin-linked scaffold **5** was added a solution of 22.3 μL (0.225 mmol) of piperidine in 2 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 14 mg of **10** was obtained as a yellow solid (yield, 94%): ^{1}H NMR (DMSO-d_6) δ 8.23 (s, 1H), 7.83 (s, 1H), 7.66 (s, 1H), 7.12 (s, 1H), 3.10 (t, 4H, J = 3.9 Hz), 2.37 (s, 3H), 1.5−1.7 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 166.1, 158.2, 155.9, 148.9, 148.2, 138.0, 125.6, 122.9, 111.6, 106.8, 52.2, 25.8, 24.0, 16.2; ESI-MS *m*/*z* 332.1 (MH^+).

Synthesis of Compound 11. To 100 mg (0.045 mmol) of resin-linked scaffold **5** was added a solution of 7.4 μL (0.090 mmol) of propylamine in 2 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 13 mg of **11** was obtained as an orange solid (yield, 95%): ^{1}H NMR (DMSO-d_6) δ 8.47 (s, 1H), 8.39 (t, 1H, J = 5.3 Hz), 7.81 (s, 1H), 7.66 (s, 1H), 6.93 (s, 1H), 3.36 (m, 2H), 2.38 (s, 3H), 1.65 (m, 2H), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.1, 158.1, 157.8, 148.5, 147.7, 129.9, 126.5, 122.0, 109.3, 99.9, 45.0, 22.0, 16.1, 11.9; ESI-MS m/z 306.1 (MH^+).

Synthesis of Compounds 12 and 13. A 400-mg (0.18 mmol) portion of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was shaken with 8 mL of 1 M phenol solution in 25% DIEA/DMF overnight. The supernatant was removed, and the resin was washed with DMF, DCM, MeOH, and DMF. An 8-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. After the resin was washed with DMF, DCM, MeOH, and DCM, it was divided into two aliquots. One portion of the resin was treated with TFA cleavage, and the crude product was analyzed and purified by HPLC. A total of 30 mg of **12** was obtained as a yellow solid (yield, 91%): ^{1}H NMR (DMSO-d_6) δ 8.70 (t, 1H, J = 5.7 Hz), 7.43 (t, 2H, J = 7.8 Hz), 7.34 (s, 1H), 7.20 (t, 1H, J = 7.8 Hz), 7.17 (s, 2H), 7.08 (d, 2H, J = 7.8 Hz), 6.69 (s, 1H), 3.78 (d, 2H, J = 5.7 Hz), 2.38 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.3, 165.1, 159.7, 156.3, 149.7, 147.9, 145.1, 137.6, 130.9, 124.9, 122.6, 119.5, 116.0, 110.1, 106.0, 42.7, 16.5; ESI-MS m/z 368.1 (MH^+).

To the remaining portion of the resin was added a mixture of 208.9 mg (1.8 mmol) of diglycolic anhydride, 78.4 μL (0.45 mmol) of DIEA, and 4 mL of DCM. The resulting mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 38 mg of **13** was obtained as an off-white solid (yield, 87%): ^{1}H NMR (DMSO-d_6) δ 12.8 (s, broad, 1H), 8.71 (t, 1H, J = 5.7 Hz), 8.56 (s, 1H), 7.48 (t, 2H, J = 7.8 Hz), 7.34 (s, 1H), 7.29 (t, 1H, J = 7.8 Hz), 7.18 (m, 3H), 6.76 (s, 1H), 4.22 (s, 2H), 4.19 (s, 2H), 3.80 (d, 2H, J = 5.7 Hz), 2.42 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.2, 171.2, 168.9, 164.7, 159.1, 155.3, 152.2, 150.1, 149.6, 131.1, 126.1, 126.0, 123.0, 120.6, 119.4, 114.9, 105.0, 70.9, 68.6, 42.7, 16.5; ESI-MS m/z 484.1 (MH^+).

Synthesis of Compounds 14 and 15. To 400 mg (0.18 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 157.0 μL (1.80 mmol) of morpholine in 8 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. An 8-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. After the resin was washed with DMF, DCM, MeOH, and DCM, it was divided into two aliquots. One portion of the resin was treated with TFA cleavage, and the crude product was analyzed and purified by HPLC. A total of 30 mg of **14** was obtained as a yellow solid (yield, 92%): ^{1}H NMR (DMSO-d_6) δ 8.70 (t, 1H, J = 5.7 Hz), 7.36 (s, 1H), 7.17 (s, 2H), 7.10 (s, 1H), 6.96 (s, 1H), 3.61−3.77 (m, 6H), 2.93 (t, 4H, J = 5.3 Hz), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.4, 165.3, 160.0, 149.9, 146.6, 144.5, 138.7, 122.1, 115.4, 110.0, 107.3, 66.9, 50.8, 42.7, 16.4; ESI-MS m/z 361.2 (MH^+).

To the remaining portion of the resin was added a mixture of 208.9 mg (1.8 mmol) of diglycolic anhydride, 78.4 μL (0.45 mmol) of DIEA, and 4 mL of DCM. The resulting mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 35 mg of **15** was obtained as a yellow solid (yield, 82%): ^{1}H NMR (DMSO-d_6) δ 12.7 (s, broad, 1H), 8.73 (t, 1H, J = 5.7 Hz), 8.46 (s, 1H), 7.95 (s, 1H), 7.34 (s, 1H), 7.16 (s, 1H), 7.14 (s, 1H), 4.09 (s, 4H), 3.80 (d, 2H, J = 5.7 Hz), 3.76 (t, 4H, J = 5.3 Hz), 2.99 (t, 4H, J = 5.3 Hz), 2.38 (s, 3H); ^{13}C NMR (D_2O) δ 172.4, 171.4, 167.4, 165.2, 161.5, 151.2, 150.1, 127.3, 120.6, 120.2, 117.8, 115.5, 108.1, 70.9, 70.2, 67.0, 51.2, 42.6, 15.9; ESI-MS m/z 477.2 (MH^+).

Synthesis of Compounds 16 and 17. To 400 mg (0.18 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 95.6 μL (0.90 mmol) of benzeneselenol in 8 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. An 8-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. After the resin was washed with DMF, DCM, MeOH, and DCM, it was divided into two aliquots. One portion of the resin was treated with TFA cleavage, and the crude product was analyzed and purified by HPLC. A total of 36 mg of **16** was obtained as a yellow solid (yield, 93%): ^{1}H NMR (DMSO-d_6) δ 8.71 (t, 1H, J = 5.7 Hz), 7.40−7.45 (m, 2H), 7.32−7.38 (m, 4H), 7.23 (s, 1H), 7.17 (s, 1H), 7.16 (s, 1H), 5.33 (s, broad, 2H), 3.79 (d, 2H, J = 5.7 Hz), 2.36 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.2, 164.9, 159.1, 149.1, 145.5, 144.6, 132.9, 130.5, 129.9, 128.5, 124.7, 122.4, 121.3, 121.0, 110.0, 42.6, 16.3; ESI-MS m/z 432.1 (MH^+).

To the remaining portion of the resin was added a mixture of 208.9 mg (1.8 mmol) of diglycolic anhydride, 78.4 μL (0.45 mmol) of DIEA and 4 mL of DCM. The resulting mixture was shaken overnight, and the supernatant was removed. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 40 mg of **17** was obtained as a red solid (yield, 81%): ^{1}H NMR (DMSO-d_6) δ 12.8 (s, broad, 1H), 9.82 (s, 1H), 8.69 (t, 1H, J = 5.7 Hz), 8.02 (s, 1H), 7.56 (m, 2H), 7.40−7.48 (m, 3H), 7.33 (s, 1H), 7.15 (s, 1H), 7.13 (s, 1H), 4.23 (s, 2H), 4.21 (s, 2H), 3.80 (d, 2H, J = 5.7 Hz), 2.40 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.1, 171.1, 169.2, 164.6, 158.7, 150.2, 149.2, 135.2, 133.8, 130.8, 129.7, 129.0, 124.5, 122.2, 120.0, 119.4, 70.7, 68.6, 42.6, 16.3; ESI-MS m/z 548.1 (MH^+).

Synthesis of Compounds 18 and 19.[16] To 400 mg (0.18 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 65.4 mg (0.36 mmol) of L-leucine methyl ester hydrochloride in 8 mL of 5% DIEA/DMF. The mixture

was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. An 8-mL portion of 2 M $SnCl_2 \cdot H_2O$ solution in DMF was added to the resin. The mixture was shaken for 24 h, and the supernatant was removed. After the resin was washed with DMF, DCM, MeOH, and DCM, it was divided into two aliquots. One portion of the resin was treated with TFA cleavage, and the crude product was analyzed and purified by HPLC. A total of 27 mg of **18** was obtained as a yellow solid (yield, 78%): ^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1H), 8.65 (t, 1H, J = 5.7 Hz), 7.35 (s, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 7.04 (s, 1H), 6.64 (s, 1H), 3.97 (t, 1H, J = 5.9 Hz), 3.76 (d, 2H, J = 5.7 Hz), 2.31 (s, 3H), 1.82 (m, 1H), 1.50 (m, 2H), 0.89 (d, 3H, J = 2.7 Hz), 0.88 (d, 3H, J = 2.7 Hz); ^{13}C NMR (DMSO-d_6) δ 171.5, 167.5, 165.4, 160.1, 150.8, 150.6, 139.5, 123.9, 118.7, 110.3, 109.9, 99.4, 53.9, 42.8, 42.5, 24.1, 23.7, 22.5, 16.3; ESI-MS m/z 387.2 (MH^+).

The remaining portion of the resin was washed thoroughly with acetone. To the resin were added 248.8 mg (1.80 mmol) of K_2CO_3, 3 mL of acetone, 214.1 μL (1.80 mmol) of benzyl bromide, and 313.5 μL (1.80 mmol) of DIEA. The resulting mixture was heated at 55 °C overnight, and the supernatant was removed. The resin was washed thoroughly with acetone, water, DMF, MeOH, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 9 mg of **19** was obtained as a yellow solid (yield, 21%): ^{1}H NMR (DMSO-d_6) δ 10.70 (s, 1H), 8.63 (t, 1H, J = 5.7 Hz), 7.31−7.39 (m, 5H), 7.28 (t, 1H, J = 6.9 Hz), 7.19 (m, 1H), 7.14 (s, 1H), 6.73 (s, 1H), 4.84 (d, 1H, J = 15.0 Hz), 4.44 (d, 1H, J = 15.0 Hz), 3.96 (m, 1H), 3.76 (d, 2H, J = 5.7 Hz), 2.33 (s, 3H), 1.60 (m, 1H), 1.35−1.50 (m, 2H), 0.84 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.4, 166.8, 165.2, 159.9, 150.7, 150.3, 139.1, 137.4, 129.4, 129.0, 128.3, 125.2, 119.6, 110.6, 110.5, 100.4, 60.4, 52.2, 42.7, 39.1, 25.0, 23.9, 22.5, 16.3; ESI-MS m/z 477.2 (MH^+).

Synthesis of Compound 20.[15] To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 17.8 μL (0.18 mmol) of propylamine in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. To the resin were added 2 mL of 0.75 M $SnCl_2 \cdot 2H_2O$ solution in DMF and 18.3 μL (0.18 mmol) of benzaldehyde. The resulting mixture was heated at 60 °C for 3 h. The supernatant was removed, and the resin was washed thoroughly with DMF, DCM, MeOH, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 31 mg of **20** was obtained as an off-white solid (yield, 82%): ^{1}H NMR (DMSO-d_6) δ 8.79 (t, 1H, J = 5.7 Hz), 8.21 (s, 1H), 7.95 (s, 1H), 7.83 (m, 2H), 7.64 (m, 3H), 7.39 (s, 1H), 7.20 (s, 1H), 4.34 (t, 2H, J = 7.3 Hz), 3.83 (d, 2H, J = 5.7 Hz), 2.57 (s, 3H), 1.69 (m, 2H), 0.73 (t, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 171.3, 165.1, 159.5, 156.1, 150.7, 149.8, 138.5, 138.1, 131.5, 130.0, 129.7, 129.2, 122.6, 116.4, 115.9, 99.4, 46.9, 42.7, 23.0, 16.9, 11.5; ESI-MS m/z 419.2 (MH^+).

Synthesis of Compound 21.[17] To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 17.8 μL (0.18 mmol) of propylamine in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. A 4-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. To the resin washed with DMF, DCM, MeOH, DMF, and tetrahydrofuran (THF), a solution of 160.4 mg (0.90 mmol) of 1,1′-thiocarbonyldiimidazole in 4 mL of THF was added. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with THF, DCM, MeOH, and DMF. To the resin were added 3.5 mL of DMF, 214.1 μL (1.80 mmol) of benzyl bromide, and 313.5 μL (1.80 mmol) of DIEA. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 36 mg of **21** was obtained as an off-white solid (yield, 86%): ^{1}H NMR (DMSO-d_6) δ 8.75 (t, 1H, J = 5.7 Hz), 8.08 (s, 1H), 7.71 (s, 1H), 7.49 (d, 2H, J = 7.4 Hz), 7.37 (s, 1H), 7.33 (t, 2H, J = 7.4 Hz), 7.27 (t, 1H, J = 7.4 Hz), 7.20 (s, 1H), 4.66 (s, 2H), 4.11 (t, 2H, J = 6.8 Hz), 3.82 (d, 2H, J = 5.7 Hz), 2.54 (s, 3H), 1.71 (m, 2H), 0.83 (t, 3H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 171.4, 165.2, 159.8, 155.4, 151.1, 149.2, 140.7, 139.8, 137.8, 129.7, 129.3, 128.3, 122.0, 115.0, 114.8, 97.8, 46.0, 42.7, 36.4, 22.8, 16.9, 11.6; ESI-MS m/z 465.2 (MH^+).

Synthesis of Compound 22.[18] To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 32.7 mg (0.18 mmol) of β-alanine *tert*-butyl ester hydrochloride in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. A 4-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. To the resin washed with DMF, DCM, MeOH, and DMF, 4 mL of 1 M phenyl isothiocyanate and 1 M DIC solution in DMF was added. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 22 mg of **22** was obtained as a yellow solid (yield, 53%): ^{1}H NMR (CD_3OD) δ 7.72 (d, 2H, J = 7.8 Hz), 7.52−7.62 (m, 4H), 7.46 (m, 1H), 4.61 (t, 2H, J = 5.9 Hz), 4.02 (s, 2H), 3.04 (t, 2H, J = 5.9 Hz), 2.54 (s, 3H); ^{13}C NMR (CD_3OD) δ 174.6, 173.9, 167.1, 160.9, 152.4, 151.4, 136.9, 135.9, 131.4, 129.2, 129.0, 125.5, 122.9, 117.5, 109.4, 100.2, 43.2, 40.7, 32.9, 16.5; ESI-MS m/z 464.2 (MH^+).

Synthesis of Compound 23. To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 73.4 mg (0.45 mmol) of Ac-Cys-OH in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. A 4-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. The resin was washed with DMF, DCM, MeOH, and DCM. After TFA

cleavage, the crude product was analyzed and purified by HPLC. A total of 36 mg of **23** was obtained as a yellow solid (yield, 92%): ^{1}H NMR (DMSO-d_6) δ 8.73 (t, 1H, J = 5.7 Hz), 8.38 (d, 1H, J = 7.8 Hz), 7.34 (s, 2H), 7.17 (s, 1H), 7.09 (s, 1H), 4.44 (s, broad, 2H), 4.35 (m, 1H), 3.78 (d, 2H, J = 5.7 Hz), 3.31 (dd, 1H, J = 13.8, 4.7 Hz), 3.13 (dd, 2H, J = 13.8, 8.5 Hz), 2.37 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.5, 171.3, 165.0, 159.4, 149.2, 144.9, 144.7, 124.9, 124.2, 119.7, 119.2, 109.5, 52.2, 42.6, 34.9, 23.1, 16.3; ESI-MS m/z 437.1 (MH^+).

Synthesis of Compound 24.[19] To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 17.8 μL (0.18 mmol) of propylamine in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. A 4-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. To the resin washed with DMF, DCM, MeOH, and DCM, a solution of 307.8 mg (1.80 mmol) of chloroacetic anhydride and 73.4 μL (0.45 mmol) of DIEA in 4 mL of DCM was added. The mixture was shaken overnight, and the supernatant was removed. After the resin was washed with DCM, MeOH, and DMF, it was shaken with 3.6 mL of 10% DIEA solution in DMF for 5 h, and 400 μL (4.59 mmol) of morpholine was then added. The resulting mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 35 mg of **24** was obtained as a yellow solid (yield, 78%): ^{1}H NMR (DMSO-d_6) δ 8.72 (t, 1H, J = 5.7 Hz), 7.52 (s, 1H), 7.41 (s, 1H), 7.18 (s, 1H), 6.56 (s, 1H), 4.17 (s, 2H), 3.4−4.0 (m, 12H), 3.14 (t, 2H, J = 6.4 Hz), 2.31 (s, 3H), 1.57 (m, 2H), 0.93 (t, 3H, J = 6.4 Hz); ^{13}C NMR (DMSO-d_6) δ 171.8, 171.4, 165.6, 164.7, 160.3, 154.1, 151.2, 148.5, 124.8, 119.5, 117.9, 108.0, 95.6, 63.7, 57.7, 52.9, 44.9, 42.7, 42.6, 36.6, 22.1, 16.2, 11.6; ESI-MS m/z 500.2 (MH^+).

Synthesis of Compound 25. To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 49.3 μL (0.45 mmol) of ethyl 2-mercaptoacetate in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. A 4-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. The resin was washed with DMF, DCM, MeOH, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 27 mg of **25** was obtained as an off-white solid (yield, 86%): ^{1}H NMR (DMSO-d_6) δ 10.91 (s, 1H), 8.74 (t, 1H, J = 5.7 Hz), 7.63 (s, 1H), 7.58 (s, 1H), 7.34 (s, 1H), 7.16 (s, 1H), 3.81 (d, 2H, J = 5.7 Hz), 3.80 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 164.6, 161.5, 158.8, 149.3, 148.4, 137.1, 127.3, 124.4, 118.5, 115.7, 111.5, 42.6, 30.3, 16.4; ESI-MS m/z 348.1 (MH^+).

Synthesis of Compound 26. To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 39.2 μL (0.45 mmol) of 3-mercaptopropionic acid in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. A 4-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. To the resin washed with DMF, DCM, MeOH, and DCM, a solution of 136.9 mg (0.36 mmol) of HATU and 125.4 μL (0.72 mmol) of DIEA in 4 mL of DMF was added. The resulting mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 27 mg of **26** was obtained as an off-white solid (yield, 83%): ^{1}H NMR (DMSO-d_6) δ 9.86 (s, 1H), 8.73 (t, 1H, J = 5.7 Hz), 7.63 (s, 1H), 7.50 (s, 1H), 7.35 (s, 1H), 7.16 (s, 1H), 3.81 (d, 2H, J = 5.7 Hz), 3.52 (t, 2H, J = 6.5 Hz), 3.45 (t, 2H, J = 6.5 Hz), 2.40 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.6, 171.1, 164.5, 158.7, 149.4, 148.9, 139.4, 132.3, 125.2, 122.4, 120.6, 120.2, 42.6, 34.4, 33.9, 16.3; ESI-MS m/z 362.1 (MH^+).

Synthesis of Compound 27.[20] To 200 mg (0.090 mmol) of scaffold(**3**)−Gly−Rink amide MBHA resin **5a** was added a solution of 154.5 mg (0.45 mmol) of Fmoc-Cys-OH in 4 mL of 5% DIEA/DMF. The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. A 4-mL portion of 2 M $SnCl_2 \cdot 2H_2O$ solution in DMF was added to the resin. The mixture was shaken for 3 h. The supernatant was removed, and the reduction process was repeated. To the resin washed with DMF, DCM, MeOH, and DCM, a solution of 136.9 mg (0.36 mmol) of HATU and 125.4 μL (0.72 mmol) of DIEA in 4 mL of DMF was added. The resulting mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF, followed by Fmoc-deprotection. A mixture of 68.1 mg (0.27 mmol) of anthraquinone-2-carboxylic acid, 102.7 mg (0.27 mmol) of HATU, 94.1 μL (0.54 mmol) of DIEA, and 5 mL of DMF was added to the resin. The reaction was allowed to proceed overnight. The supernatant was removed, and the resin was washed with DMF, DCM, MeOH, DMF, and DCM. After TFA cleavage, the crude product was analyzed and purified by HPLC. A total of 25 mg of **27** was obtained as a brown solid (yield, 45%): ^{1}H NMR (DMSO-d_6) δ 10.28 (s, 1H), 9.41 (d, 1H, J = 7.4 Hz), 8.74 (t, 1H, J = 5.7 Hz), 8.67 (s, 1H), 8.31 (m, 2H), 8.25 (m, 2H), 7.96 (m, 2H), 7.76 (s, 1H), 7.63 (s, 1H), 7.36 (s, 1H), 7.17 (s, 1H), 4.74 (m, 1H), 3.83 (d, 2H, J = 5.7 Hz), 3.75 (dd, 1H, J = 11.9, 6.5 Hz), 3.45 (t, 2H, J = 11.9 Hz), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 182.9, 171.3, 171.1, 165.1, 164.4, 158.7, 149.7, 148.8, 139.0, 138.8, 135.7, 135.4, 133.9, 133.8, 131.6, 127.9, 127.7, 127.6, 126.5, 125.5, 122.8, 121.2, 120.4, 50.4, 42.6, 37.5, 16.3; ESI-MS m/z 611.1 (MH^+).

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