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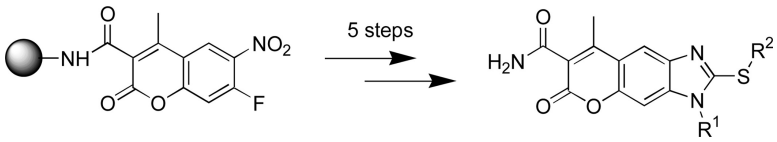

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Solid-Phase Synthesis and Spectral Properties of 2-Alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones: A Combinatorial Approach for 2-Alkylthioimidazocoumarins

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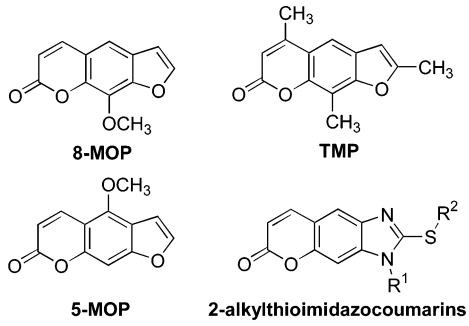
The solid-phase synthesis of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones (2-alkylthioimidazocoumarins) is described. 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid was coupled to Rink amide resin via its carboxyl group. The resin-bound scaffold then underwent aromatic nucleophilic substitution with primary amines, followed by reduction of the nitro group with tin (II) chloride. Subsequent cyclization of the *o*-dianilino intermediates with thiocarbonyldiimidazole (TCD) afforded resin-bound 1,3-dihydro-2-thioxo-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones, which were then S-alkylated with alkyl halides in the presence of *N*,*N*-diisopropylethylamine (DIEA). The desired products were obtained in good yield with high purity after trifluoroacetic acid cleavage. The unique spectral properties of 2-alkylthioimidazocoumarins indicate that they may be useful in photodynamic therapy.

Introduction

The synthesis and screening of small molecule libraries based on natural products as templates have attracted growing attention in the past few years.[1] Coumarins (2*H*-1-benzopyran-2-ones) are well-known natural products displaying a broad range of biological activities.[2] Coumarin derivatives have been used as therapeutic agents,[3] optical bleaching agents,[4] active media for tunable dye lasers,[5] triplet sensitizers,[6] and luminescent probes.[7] In particular, linear furocoumarins, commonly known as psoralens, are widely used as photosensitizing agents in photochemotherapy to treat skin diseases such as psoriasis[8] and in photopheresis to treat cutaneous T-cell lymphoma[9] and various autoimmune diseases.[10] Psoralens have also shown promise in suppression of postoperational autoimmune rejection of organ transplants.[11] Psoralen plus UVA (PUVA) photochemotherapy is one of the most common procedures performed in dermatology.[12] 8-Methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), and 4,5′,8-trimethylpsoralen (TMP) (Chart 1) are examples of compounds that have been proven highly effective in PUVA therapy. However, they also cause various side effects, such as persistent erythema,[8] carcinogenicity,[13]and genotoxicity,[14] which are attributed mostly to the DNA damage induced by psoralen sensitization.[15] Other furocoumarin analogues have been developed in an attempt to decrease adverse side effects. These analogues include pyrrolocoumarins,[16] azapsoralens,[17] furoquinolinones,[18] and triazolocoumarins.[19]

Chart 1. Structures of Psoralens for PUVA Therapy



In the present study, we describe the development of an efficient approach for the solid-phase synthesis of a series of novel psoralen analogues, 2-alkylthio-6*H*-pyrano[2,3-*f*]-benzimidazole-6-ones (2-alkylthioimidazocoumarins, Chart 1). 2-Substituted benzimidazoles represent an important structural element in drug discovery and have been shown to have a broad spectrum of biological activity, including antiulcer, antitumor, and antiviral effects.[20] By combining the benzimidazole structure with the coumarin ring in the same molecule, 2-alkylthioimidazocoumarins may exhibit interesting biological and physical properties.

Results and Discussion

Synthesis of 2-Alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones. The synthetic route for solid-phase preparation of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones **7** is illustrated in Scheme 1. We have recently reported the synthesis of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid **2** as a scaffold for solid-phase synthesis of coumarins.[21] This scaffold was used as the synthetic template. Our synthetic strategy involved a route similar to

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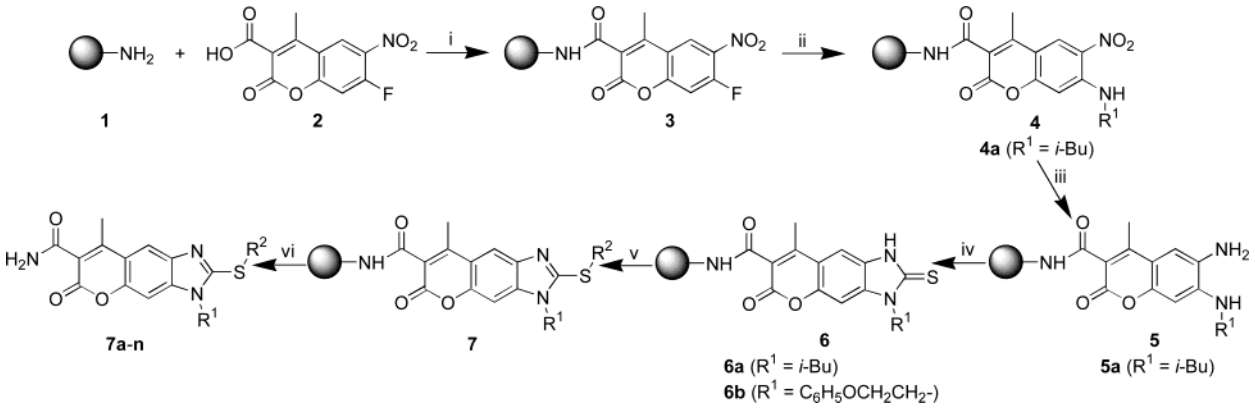
Scheme 1. Synthetic Route for Solid-Phase Preparation of 2-Alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones[a]



[a] Reagents and conditions: **1**, 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; (ii) 2 equiv of R^1NH_2 in 5% DIEA/DMF, rt, overnight; (iii) 2 M of $SnCl_2$ and 4 M of H_2O (see comment in text) in DMF, rt, 3 h × 2; (iv) 10 equiv of TCD in THF, rt, overnight; (v) 10 equiv of R^2X in 5% DIEA/DMF, rt, overnight; (vi) 95% TFA/H_2O, rt, 2 h.

the one used for the synthesis of 2-alkylthiobenzimidazoles using a 4-fluoro-3-nitrobenzoic acid scaffold.[22] The resin-bound scaffold underwent aromatic nucleophilic substitution of the aryl fluoride, followed by reduction of the nitro group and subsequent modification.

The attachment of scaffold **2** to Rink amide resin was accomplished by 1,3-diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) activation. The reaction was monitored by ninhydrin visualization[23] and proceeded to completion in 5 h. For aromatic nucleophilic substitution in solid phase, a high excess (e.g., 20 molar equiv) of amine was usually used to ensure high reaction yield.[22] However, the coumarin structure was found to be unstable toward strong bases. High concentration of primary amines resulted in complicated side reactions, probably as a result of chemical attack on the pyran ring. We examined various combinations of different amine concentrations and different bases for this reaction. After extensive optimization, best results were obtained with 2 equiv of the amine in 5% *N*,*N*-diisopropylethylamine (DIEA)/*N*,*N*-dimethylformamide (DMF). Fifty-two primary amines (see Table 1 for representative structures) were evaluated and found to react with the resin-bound scaffold **3** to give the desired products **4** after overnight incubation at room temperature under the optimized reaction conditions.

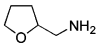
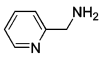
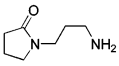
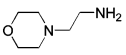
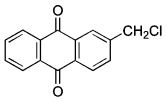
Several investigators have reported that the results of nitro reduction with tin (II) chloride were inconsistent.[24] The same phenomenon was observed in our experiments. We tested tin (II) chloride from different commercial sources using various combinations of concentration, temperature, and reaction time. The best result was achieved by incubation of **4** with a 2 M solution of anhydrous tin (II) chloride in DMF in the presence of 4 M H_2O at room temperature.[25] The reduction was completed in 6 h according to HPLC and MS analysis of **5** after trifluoroacetic acid (TFA) cleavage.

The resulting resin-bound *o*-dianilino intermediate **5** was subsequently treated with 1,1′-thiocarbonyldiimidazole (TCD, 10 equiv) in tetrahydrofuran (THF) at room temperature overnight. Complete cyclization was confirmed by HPLC, ^{1}H NMR, and MS analyses. The alkyl substituent R^1 did not adversely affect the cyclization. All of the tested intermediates **5**, including the ones with a secondary alkyl (e.g., R^1 = *sec*-butyl, cyclopentyl, or cyclohexyl), reacted with TCD to form 1,3-dihydro-2-thioxo-6*H*-pyrano[2,3-*f*]-benzimidazole-6-ones **6** in almost quantitative yield.

To introduce the second point of chemical diversity, we alkylated the resin-bound 1,3-dihydro-2-thioxo-6*H*-pyrano-[2,3-*f*]benzimidazole-6-ones **6** with a wide range of alkyl halides in the presence of DIEA. Previous studies have shown that the alkylation of benzimidazole-2-thiones gave exclusively the S-alkylated products.[22] Similar results were obtained in our experiments. In ^{13}C NMR studies, the C-2 resonance of compound **6a** was shifted upfield from 172.1 to 155.4 ppm of compound **7a** after alkylation with benzyl bromide (Figure 1). This was consistent with alkylation on the sulfur atom, as opposed to the nitrogen N-1. Furthermore, a blue shift (∼30 nm) was observed in both the absorption and fluorescence spectra of compound **7a** when compared to compound **6a** (Figure 2), indicating a significant change in the conjugated system induced by alkylation. Among the alkyl halides that we tested, primary alkyl iodides, secondary alkyl iodides, benzyl halides, allyl halides, propargyl halides, bromoacetic esters, and bromoacetonitrile reacted effectively with the resin-bound 1,3-dihydro-2-thioxo-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones **6** to form clean desired products **7**. However, 2-(bromomethyl)furans, 2-(chloromethyl)benzimidazole, and *N*-(bromomethyl)phthalimide gave complex mixtures, probably as a result of the poor stability of the heterocylic rings in a basic solution. Bromomethyl sulfones did not react at all, and the starting reactants **6** were recovered in good purity after TFA cleavage.

On the basis of these results, a small 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-one library containing 14 members with structurally diverse substituents was prepared (Table 1). The products were cleaved from the resin; analyzed and purified by HPLC; and characterized by ^{1}H NMR, ^{13}C NMR, and ESI-MS. All of the 14 compounds were obtained in high purity (79−94%) with good isolated yield (67−86%). Each of these compounds contained two points of chemical diversity. An additional diversity point could readily be introduced to the 7-carboxyl group prior to the scaffold attachment. The products were obtained in high purity and could be screened without further purification. Furthermore, this approach is especially suitable for the

Table 1. Synthesis and Spectral Properties of 2-Alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones **7** (Scheme 1)[a]

Entry	R^1NH_2	R^2X	Yield (%)	Purity (%)	λabs (nm)	λem (nm)	ϕ
7a	$(CH_3)_2CHCH_2NH_2$	$C_6H_5CH_2Br$	84	93	344	463	0.104
7b	$(CH_3)_2CHCH_2NH_2$	$2,6\text{-}Cl_2C_6H_3CH_2Br$	82	92	346	462	0.089
7c	$CH_3(CH_2)_2NH_2$	$CH_3(CH_2)_2I$	74	88	346	465	0.107
7d	$CH_3(CH_2)_2NH_2$	$(CH_3)_2CHI$	68	79	346	464	0.094
7e	$C_2H_5CH(CH_3)NH_2$	$p\text{-}O_2NC_6H_4CH_2Br$	86	94	348	466	0.041
7f	$c\text{-}C_6H_{11}NH_2$	$3,5\text{-}(CH_3O)_2C_6H_3CH_2Br$	70	83	348	464	0.081
7g	$3,4\text{-}(CH_2O_2)C_6H_3CH_2NH_2$	$C_2H_5OOCCH_2Br$	76	86	346	461	0.052
7h		$(CH_3)_2C{=}CHCH_2Br$	78	89	348	463	0.091
7i		$p\text{-}C_6H_5C_6H_4CH_2Cl$	79	87	349	462	0.082
7j	$3,5\text{-}(CH_3O)_2C_6H_3CH_2NH_2$	$HC{\equiv}CCH_2Br$	86	91	346	458	0.079
7k		$m\text{-}O_2NC_6H_4CH_2Br$	75	86	342	459	0.045
7l		$2\text{-}C_{10}H_7CH_2Br$	67	83	344	460	0.039
7m	$c\text{-}C_5H_9NH_2$	$p\text{-}CF_3C_6H_4CH_2Br$	75	88	346	462	0.092
7n	$(CH_3)_2CHCH_2NH_2$		73	90	342	—	~0

[a] Yields were calculated on the basis of the purified products. Purity was determined by HPLC analysis (UV detection at 220 nm) of crude products. λ_{abs} and λ_{em} represent the maximum absorption and fluorescence wavelength, respectively. Φ is the fluorescence quantum yield of compounds in ethanol and was determined using 7-amino-4-methylcoumarin as the standard reference (Φ = 0.88).

synthesis and screening of "one-bead one-compound" (OBOC) combinatoiral libraries[26] containing a large number of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones.

Spectral Properties of 2-Alkylthio-6*H*-pyrano[2,3-*f*]-benzimidazole-6-ones. The absorption and fluorescence properties of 14 synthesized 2-alkylthio-6*H*-pyrano[2,3-*f*]-benzimidazole-6-ones are summarized in Table 1. Figure 1 shows the absorption and fluorescence spectra of compound **7a**. All of the 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones have maximum absorption around 345 nm and maximum emission around 460 nm. Compared to 8-MOP, the most popular photosensitizer in PUVA therapy, the absorption of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones shows a red shift of ~45 nm. In addition, the molar absorptivity of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones is much higher than that of 8-MOP at 365 nm, which is the commonly used wavelength in PUVA therapy. With such spectral properties, we expect 2-alkylthio-6*H*-pyrano-[2,3-*f*]benzimidazole-6-ones to be useful sensitizers for photochemotherapy.

It appears that the substituents do not have a significant effect on the spectral properties of 2-alkylthio-6*H*-pyrano-[2,3-*f*]benzimidazole-6-ones, because these alkyl groups are not a part of the conjugated π system. Compared to other compounds, **7e**, **7g**, **7k**, and **7l** exhibited decreased fluorescence quantum yield (Table 1), while no obvious changes in their spectra were observed. A possible explanation may be that their substituents absorb excitation light at the selected wavelength (345 nm) but do not emit in the detection range (375−600 nm).

Covalently linked multicomponent compounds have been intensively investigated as models for mimicking photosynthetic electron and energy transfer.[27] By using 2-chloromethylanthraquinone as a building block, a dyad of 2-alkylthioimidazocoumarin and anthraquinone **7n** was prepared in solid phase. The fluorescence of the coumarin moiety in compound **7n** was completely quenched by anthraquinone, which is a well-known electron acceptor in the photoinduced electron transfer study. Various energy/electron donors or acceptors can be used as the building blocks for the synthesis of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones. Therefore, the synthetic method described in this paper provides a solid-phase approach to the construction of covalently linked multicomponent systems containing a 2-alkylthio-imidazocoumarin moiety as the photosensitizer.

Conclusion

In summary, we have developed an efficient solid-phase method for the parallel synthesis of 2-alkylthio-6*H*-pyrano-[2,3-*f*]benzimidazole-6-ones. The desired products were obtained in high purity with good isolated yield after five reaction steps. The methodology is ideally suited for automated application because all the synthetic reactions were carried out under mild conditions. The 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-ones prepared with this approach have two points of chemical diversity. An additional

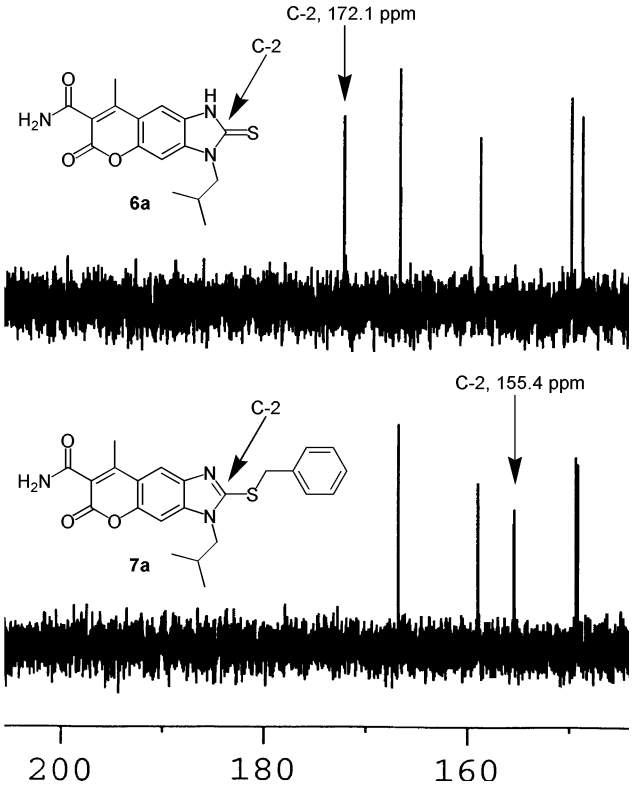


Figure 1. ^{13}C NMR spectra of compounds **6a** and **7a** (145−205 ppm; for whole spectra, please see Supporting Information).

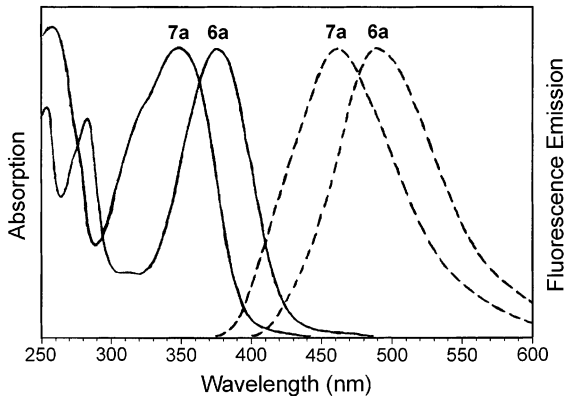


Figure 2. Normalized absorption (solid lines) and fluorescence (dashed lines) spectra of compounds **6a** and **7a**.

diversity point could be easily introduced by inserting an amino acid between the coumarin scaffold and the resin. Compared to the traditional methods for the preparation of psoralen analogues, this solid-phase approach represents a tool for the concurrent preparation and screening of a large number of 2-alkylthioimidazocoumarins. These novel psoralen analogues exhibit promising spectral properties for photochemotherapy. The synthesis and screening of 2-alkylthio-6*H*-pyrano[2,3-*f*]benzimidazole-6-one library is currently underway in our laboratory and will be reported in due course.

Experimental Section

Materials and Instruments. Rink amide MBHA resin (0.45 mmol/g) and HOBt were purchased from GL Biochem (Shanghai, China). DIC and TFA were purchased from Advanced ChemTech (Louisville, KY). 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid was prepared using our published procedure.[21] All solvents and other chemical reagents were purchased from Aldrich (Milwaukee, WI) and were of 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 Hewlett-Packard 8425A diode array spectrophotometer (Palo Alto, CA). Fluorescence spectra were recorded on a Varian Cary Eclipse fluorescence spectrophotometer (Palo Alto, CA). Fluorescence quantum yields were measured in ethanol using the literature method based on a value of $\Phi = 0.88$ for 7-amino-4-methylcoumarin.[28] 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 TFA Cleavage. The resin was washed thoroughly with DMF, dichloromethane (DCM), methanol (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 0 °C. The mixture was slowly warmed to room temperature and allowed to react 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.

Attachment of 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid 2 to Rink Amide MBHA Resin. Rink amide MBHA resin (2.0 g, 0.90 mmol) was swollen in DMF overnight. The solvent was removed, and a 20% piperidine solution in DMF (30 mL) was added to the resin. 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. A mixture of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid **2** (721 mg, 2.70 mmol), HOBt (365 mg, 2.70 mmol), DIC (423 μL, 2.70 mmol), and DMF (20 mL) was added to the resin. The resulting mixture was shaken until the ninhydrin test was negative.[23] The supernatant was removed. The resin-supported scaffold **3** was washed with DMF, DCM, MeOH, and DCM and dried in vacuo.

General Procedure for Aromatic Nucleophilic Substitution of the Resin-Supported Aryl Fluoride with Primary Amines. To the resin-supported scaffold **3** (100 mg, 0.045 mmol) was added a solution of a primary amine (0.090 mmol) in 5% DIEA/DMF (2 mL). The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DMF. Model compounds were released from the resin by TFA cleavage; analyzed and purified by HPLC; and characterized by ^{1}H NMR, ^{13}C NMR, and ESI-MS.

4-Methyl-7-[(2-methylpropyl)amino]-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxamide 4a. A total of 13 mg of **4a**

was obtained from 100 mg of resin as an orange solid (Yield, 90%). ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1H), 8.42 (t, 1H, J = 5.7 Hz), 7.81 (s, 1H), 7.64 (s, 1H), 6.94 (s, 1H), 3.25 (t, 2H, J = 6.3 Hz), 2.38 (s, 3H), 1.98 (m, 1H), 0.96 (d, 6H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 166.1, 158.1, 157.7, 148.4, 147.8, 129.9, 126.5, 122.0, 109.3, 100.1, 50.5, 27.8, 20.7, 16.1; ESI-MS m/z 320.2 $[M + H]^+$.

General Procedure for Reduction of the Aryl Nitro Group. To the resin-supported *o*-nitroaniline intermediate **4** (100 mg, 0.045 mmol) was added a 2 M $SnCl_2$ and 4 M H_2O solution in DMF (2 mL). 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, DMF, and THF. Model compounds were released from the resin by TFA cleavage; analyzed and purified by HPLC; and characterized by ^{1}H NMR, ^{13}C NMR, and ESI-MS.

6-Amino-4-methyl-7-[(2-methylpropyl)amino]-2-oxo-2*H*-1-benzopyran-3-carboxamide 5a. A total of 10 mg of **5a** was obtained from 100 mg of resin as a yellow solid (Yield, 77%). ^{1}H NMR (DMSO-d_6) δ 7.73 (s, 1H), 7.48 (s, 1H), 7.14 (s, 1H), 6.48 (s, 1H), 3.00 (d, 2H, J = 6.9 Hz), 2.30 (s, 3H), 1.92 (m, 1H), 0.97 (d, 6H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 167.3, 159.5, 151.1, 149.3, 144.0, 125.1, 118.9, 113.2, 108.5, 96.5, 51.3, 27.7, 21.1, 16.3; ESI-MS m/z 290.1 $[M + H]^+$.

General Procedure for Cyclization of the *o*-Dianilino Intermediates 5. To the resin-supported *o*-dianilino intermediate **5** (100 mg, 0.045 mmol) was added a solution of TCD (80.2 mg, 0.45 mmol) in THF (2 mL). The mixture was shaken overnight, and the supernatant was removed. The resin was washed with THF, DCM, MeOH, and DMF. Model compounds were released from the resin by TFA cleavage; analyzed and purified by HPLC; and characterized by ^{1}H NMR, ^{13}C NMR, and ESI-MS.

1,3-Dihydro-8-methyl-3-(2-methylpropyl)-6-oxo-2-thioxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6a. A total of 13 mg of **6a** was obtained from 100 mg of resin as a yellow solid (Yield, 87%). ^{1}H NMR (DMSO-d_6) δ 13.10 (s, 1H), 7.83 (s, 1H), 7.64 (s, 1H), 7.63 (s, 1H), 7.45 (s, 1H), 4.08 (d, 2H, J = 7.6 Hz), 2.44 (s, 3H), 2.36 (m, 1H), 0.90 (d, 6H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 172.1, 166.6, 158.7, 149.8, 148.7, 136.8, 128.8, 123.4, 115.3, 105.5, 98.2, 51.0, 27.8, 20.4, 16.8; ESI-MS m/z 332.1 $[M + H]^+$.

1,3-Dihydro-8-methyl-6-oxo-3-(2-phenoxyethyl)-2-thioxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6b. A total of 14 mg of **6b** was obtained from 100 mg of resin as a yellow solid (Yield, 79%). ^{1}H NMR (DMSO-d_6) δ 13.20 (s, 1H), 7.85 (1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.45 (s, 1H), 7.24 (t, 2H, J = 7.7 Hz), 6.90 (t, 1H, J = 7.3 Hz), 6.83 (d, 2H, J = 8.0 Hz), 4.68 (t, 2H, J = 5.0 Hz), 4.37 (t, 2H, J = 5.0 Hz), 2.44 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.6, 166.6, 158.7, 158.6, 149.7, 148.7, 137.0, 130.3, 128.8, 123.5, 121.6, 115.4, 115.0, 105.6, 98.7, 65.6, 44.0, 16.8; ESI-MS m/z 396.2 $[M + H]^+$.

General Procedure for the S-Alkylation. To the resin-supported intermediate **6** (100 mg, 0.045 mmol) was added a solution of an alkyl halide (0.45 mmol) in 5% DIEA/DMF (2 mL). The mixture was shaken overnight, and the supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DCM, and dried in vacuo. The final products were released from the resin by TFA cleavage; analyzed and purified by HPLC; and characterized by ^{1}H NMR, ^{13}C NMR, and ESI-MS.

2-(Benzylthio)-8-methyl-3-(2-methylpropyl)-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7a. A total of 16 mg of **7a** was obtained from 100 mg of resin as an off-white solid (Yield, 84%). ^{1}H NMR (DMSO-d_6) δ 8.06 (s, 1H), 7.84 (s, 1H), 7.68 (s, 1H), 7.62 (s, 1H), 7.48 (d, 2H, J = 7.4 Hz), 7.33 (t, 2H, J = 7.3 Hz), 7.27 (t, 1H, J = 7.2 Hz), 4.66 (s, 2H), 3.96 (d, 2H, J = 7.6 Hz), 2.44 (s, 3H), 2.13 (m, 1H), 0.85 (d, 6H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 166.8, 159.0, 155.4, 149.4, 149.2, 140.5, 139.9, 137.7, 129.7, 129.3, 128.3, 122.9, 115.0, 114.6, 98.0, 51.5, 36.5, 29.1, 20.3, 16.9; ESI-MS m/z 422.2 $[M + H]^+$.

2-[[(2,6-Dichlorophenyl)methyl]thio]-8-methyl-3-(2-methylpropyl)-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7b. A total of 18 mg of **7b** was obtained from 100 mg of resin as an off-white solid (Yield, 82%). ^{1}H NMR (DMSO-d_6) δ 8.11 (s, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 7.55 (d, 2H, J = 8.1 Hz), 7.42 (t, 1H, J = 8.1 Hz), 4.91 (s, 2H), 3.98 (d, 2H, J = 7.6 Hz), 2.50 (s, 3H), 2.13 (m, 1H), 0.85 (d, 6H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 166.8, 159.0, 154.4, 149.4, 149.3, 140.5, 139.8, 135.9, 132.3, 131.5, 129.6, 123.0, 115.2, 115.0, 98.2, 51.6, 33.7, 29.2, 20.3, 16.9; ESI-MS m/z 490.1 $[M + H]^+$.

8-Methyl-6-oxo-3-propyl-2-(propylthio)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7c. A total of 12 mg of **7c** was obtained from 100 mg of resin as an off-white solid (Yield, 74%). ^{1}H NMR (DMSO-d_6) δ 8.02 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.61 (s, 1H), 4.14 (t, 2H, J = 7.0 Hz), 3.35 (t, 2H, J = 7.1 Hz), 2.48 (s, 3H), 1.78 (m, 4H), 1.01 (t, 3H, J = 7.3 Hz), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.8, 159.0, 155.7, 149.4, 149.1, 140.6, 139.6, 122.8, 114.9, 114.4, 97.6, 45.9, 34.2, 23.2, 22.8, 16.8, 13.8, 11.6; ESI-MS m/z 360.2 $[M + H]^+$.

8-Methyl-3-(1-methylethyl)-6-oxo-2-(propylthio)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7d. A total of 11 mg of **7d** was obtained from 100 mg of resin as an off-white solid (Yield, 68%). ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.84 (s, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 4.12 (t, 2H, J = 7.0 Hz), 4.09 (m, 1H), 2.49 (s, 3H), 1.75 (m, 2H), 1.47 (d, 6H, J = 6.8 Hz), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.8, 159.0, 155.1, 149.4, 149.2, 140.8, 139.2, 122.8, 115.0, 114.6, 97.7, 46.0, 38.9, 23.8, 22.8, 16.8, 11.6; ESI-MS m/z 360.1 $[M + H]^+$.

8-Methyl-3-(1-methylpropyl)-2-[[(4-nitrophenyl)methyl]thio]-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7e. A total of 18 mg of **7e** was obtained from 100 mg of resin as a yellow solid (Yield, 86%). ^{1}H NMR (DMSO-d_6) δ 8.18 (d, 2H, J = 8.6 Hz), 8.04 (s, 1H), 7.84 (s, 1H), 7.78 (d, 2H, J = 8.6 Hz), 7.74 (s, 1H), 7.63 (s, 1H), 4.79 (s, 2H), 4.42 (m, 1H), 2.49 (s, 3H), 2.07 (m, 1H), 1.88 (m, 1H), 1.53 (d, 3H, J = 6.9 Hz), 0.62 (t, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.8, 159.0, 154.5, 149.2, 148.8, 147.5, 146.4, 141.1, 138.0, 130.9, 124.3, 123.0, 115.0, 114.8, 98.9, 55.4, 35.7, 27.6, 19.6, 16.8, 11.4; ESI-MS m/z 467.2 $[M + H]^+$.

3-Cyclohexyl-2-[[(3,5-dimethoxyphenyl)methyl]thio]-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carbox-

amide 7f. A total of 16 mg of **7f** was obtained from 100 mg of resin as an off-white solid (Yield, 70%). ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.87 (s, 1H), 7.83 (s, 1H), 7.63 (s, 1H), 6.65 (s, 1H), 6.64 (s, 1H), 6.41 (s, 1H), 4.56 (s, 2H), 3.70 (s, 6H), 3.67 (m, 1H), 2.49 (s, 3H), 2.19 (m, 2H), 1.85 (m, 2H), 1.74 (m, 2H), 1.66 (m, 1H), 1.42 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 166.8, 161.2, 159.0, 155.6, 149.2, 148.8, 141.1, 139.7, 138.0, 123.0, 114.9, 114.6, 107.8, 100.0, 99.1, 57.3, 55.9, 37.1, 30.8, 26.1, 24.9, 16.8; ESI-MS *m*/*z* 508.2 $[M + H]^+$.

Ethyl [[3-(1,3-benzodioxol-5-ylmethyl)-7-carbamoyl-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-2-yl]thio]-acetate 7g. A total of 17 mg of **7g** was obtained from 100 mg of resin as a yellow solid (Yield, 76%). ^{1}H NMR (DMSO-d_6) δ 8.00 (s, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 7.60 (s, 1H), 6.88 (d, 2H, J = 8.3 Hz), 6.81 (d, 1H, J = 7.9 Hz), 4.66 (s, 2H), 5.98 (s, 2H), 5.36 (s, 2H), 4.30 (s, 2H), 4.14 (q, 2H, J = 7.1 Hz), 2.47 (s, 3H), 1.18 (t, 3H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6) δ 168.8, 166.7, 158.9, 154.8, 149.3, 149.2, 148.3, 147.7, 140.6, 139.4, 130.1, 123.0, 121.7, 115.2, 114.8, 109.1, 108.6, 101.9, 97.9, 62.1, 47.6, 34.5, 16.9, 14.7; ESI-MS *m*/*z* 496.2 $[M + H]^+$.

8-Methyl-2-[(3-methyl-2-butenyl)thio]-6-oxo-3-[(tetrahydro-2-furanyl)methyl]-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7h. A total of 15 mg of **7h** was obtained from 100 mg of resin as an off-white solid (Yield, 78%). ^{1}H NMR (DMSO-d_6) δ 8.01 (s, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.61 (s, 1H), 5.43 (t, 1H, J = 7.8 Hz), 4.28−4.12 (m, 3H), 4.01 (d, 2H, J = 7.8 Hz), 3.74 (dd, 1H, J = 14.2, 7.3 Hz), 3.61 (dd, 1H, J = 14.2, 7.3 Hz), 2.49 (s, 3H), 2.00 (m, 1H), 1.81 (m, 2H), 1.73 (s, 3H), 1.70 (s, 3H), 1.64 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.8, 159.0, 156.0, 149.4, 149.1, 140.6, 139.8, 138.0, 122.8, 119.3, 115.0, 114.4, 98.1, 77.2, 68.1, 48.8, 31.0, 29.2, 26.1, 25.9, 18.5, 16.9; ESI-MS *m*/*z* 428.2 $[M + H]^+$.

2-[([1,1′-Biphenyl]-4-ylmethyl)thio]-8-methyl-6-oxo-3-(2-pyridinylmethyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7i. A total of 19 mg of **7i** was obtained from 100 mg of resin as an off-white solid (Yield, 79%). ^{1}H NMR (DMSO-d_6) δ 8.48 (d, 1H, J = 4.6 Hz), 8.10 (s, 1H), 7.84 (s, 1H), 7.78 (m, 1H), 7.67−7.60 (m, 5H), 7.59 (s, 1H), 7.53 (m, 2H), 7.45 (t, 2H, J = 7.7 Hz), 7.35 (t, 1H, J = 7.2 Hz), 7.31 (m, 1H), 7.26 (d, 1H, J = 7.7 Hz), 5.55 (s, 2H), 4.67 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.8, 158.9, 155.8, 155.4, 150.0, 149.4, 149.3, 140.7, 140.4, 140.1, 140.0, 138.2, 137.1, 130.3, 129.7, 128.2, 127.5, 127.3, 123.8, 122.9, 122.6, 115.2, 114.7, 98.0, 49.3, 36.2, 16.9; ESI-MS *m*/*z* 533.2 $[M + H]^+$.

3-[(3,5-Dimethoxyphenyl)methyl]-8-methyl-6-oxo-2-(2-propynylthio)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7j. A total of 18 mg of **7j** was obtained from 100 mg of resin as an off-white solid (Yield, 86%). ^{1}H NMR (DMSO-d_6) δ 8.11 (s, 1H), 7.83 (s, 1H), 7.68 (s, 1H), 7.62 (s, 1H), 6.43 (t, 1H, J = 1.4 Hz), 6.37 (d, 2H, J = 1.4 Hz), 5.37 (s, 2H), 4.24 (d, 2H, J = 2.3 Hz), 3.68 (s, 6H), 3.23 (t, 1H, J = 2.3 Hz), 2.49 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 161.5, 158.9, 154.3, 149.3, 140.6, 139.6, 138.7, 123.1, 115.4, 115.1, 106.0, 99.8, 97.9, 80.4, 74.9, 55.9, 47.8, 40.9, 21.1, 16.9; ESI-MS *m*/*z* 464.2 $[M + H]^+$.

8-Methyl-2-[[(3-nitrophenyl)methyl]thio]-6-oxo-3-[3-(2-oxo-1-pyrrolidinyl)propyl]-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7k. A total of 18 mg of **7k** was obtained from 100 mg of resin as a yellow solid (Yield, 75%). ^{1}H NMR (DMSO-d_6) δ 8.40 (s, 1H), 8.12 (dd, 1H, J = 8.2, 1.3 Hz), 8.04 (s, 1H), 7.96 (t, 1H, J = 7.6 Hz), 7.85 (s, 1H), 7.70 (s, 1H), 7.62 (m, 2H), 4.80 (s, 2H), 4.14 (t, 2H, J = 7.3 Hz), 3.20 (t, 2H, J = 7.0 Hz), 3.27 (t, 2H, J = 7.0 Hz), 2.49 (s, 3H), 2.17 (t, 2H, J = 8.0 Hz), 1.87 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 174.7, 166.8, 158.9, 154.4, 149.3, 149.2, 148.4, 140.8, 140.6, 139.4, 136.4, 130.7, 124.3, 123.1, 123.0, 115.2, 114.7, 97.8, 46.9, 42.6, 36.5, 35.3, 31.1, 27.3, 18.2, 16.9; ESI-MS *m*/*z* 536.2 $[M + H]^+$.

8-Methyl-3-[2-(4-morpholinyl)ethyl]-2-[(2-naphthalenylmethyl)thio]-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7l. A total of 16 mg of **7l** was obtained from 100 mg of resin as an off-white solid (Yield, 67%). ^{1}H NMR (DMSO-d_6) δ 8.13 (s, 1H), 8.02 (s, 1H), 7.90 (m, 4H), 7.73 (s, 1H), 7.64 (m, 2H), 7.52 (m, 2H), 4.86 (s, 2H), 4.55 (t, 2H, J = 7.0 Hz), 3.82 (m, 4H), 3.44 (t, 2H, J = 7.0 Hz), 3.32 (m, 4H), 2.52 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 163.0, 159.1, 158.9, 155.0, 149.3, 140.8, 138.9, 135.0, 133.5, 133.0, 129.0, 128.4, 128.3, 127.8, 127.2, 127.0, 123.2, 115.5, 115.0, 98.0, 64.2, 53.6, 52.3, 39.1, 37.1, 16.9; ESI-MS *m*/*z* 529.3 $[M + H]^+$.

3-Cyclopentyl-8-methyl-6-oxo-2-[[[4-(trifluoromethyl)-phenyl]methyl]thio]-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7m. A total of 17 mg of **7m** was obtained from 100 mg of resin as an off-white solid (Yield, 75%). ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.87 (s, 1H), 7.71 (m, 4H), 7.63 (s, 1H), 7.56 (s, 1H), 4.85 (m, 1H), 4.75 (s, 2H), 2.49 (s, 3H), 2.13−1.92 (m, 6H), 1.71 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 159.0, 158.9, 154.7, 149.2, 148.8, 143.1, 141.1, 137.8, 130.5, 126.1, 124.9 (q, J = 275.0 Hz), 123.0, 115.0, 114.9, 98.5, 57.6, 35.9, 30.0, 25.1, 16.8; ESI-MS *m*/*z* 502.2 $[M + H]^+$.

2-[[(9,10-Dihydro-9,10-dioxo-2-anthracenyl)methyl]thio]-8-methyl-3-(2-methylpropyl)-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 7n. A total of 18 mg of **7n** was obtained from 100 mg of resin as a brown solid (Yield, 73%). ^{1}H NMR (DMSO-d_6) δ 8.33 (s,1H), 8.18(m, 2H), 8.15 (s, 1H), 8.04 (m, 2H), 7.91 (m, 2H), 7.79 (s, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 4.87 (s, 1H), 3.98 (d, 2H, J = 7.3 Hz), 2.50 (s, 3H), 2.15 (m, 1H), 0.86 (d, 6H, J = 5.8 Hz); ^{13}C NMR (DMSO-d_6) δ 183.1, 182.8, 166.8, 159.0, 154.8, 149.3, 149.2, 145.5, 140.5, 140.0, 135.6, 135.3, 135.2, 133.8, 133.7, 132.8, 127.9, 127.7, 127.5, 127.4, 122.9, 115.1, 114.7, 98.1, 51.6, 35.8, 29.2, 20.3, 16.9; ESI-MS *m*/*z* 552.3 $[M + H]^+$.

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

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(25) In the past few years, we have purchased two tin (II) chloride dihydrate products from Aldrich. The first one was in a colorless granular crystalline form (Catalogue No. 43,150-8), which dissolved in DMF to form a clear solution. The second one came as yellowish flakes (Catalogue No. 24,-352-3), which dissolved in DMF to form a slightly turbid solution. Incomplete nitro-reduction was observed with the first tin (II) chloride preparation, even after a prolonged reaction time (2 M of $SnCl_2 \cdot 2H_2O$ in DMF, room temperature, overnight to 3 days). In contrast, complete nitro-reduction was observed after incubation with the second tin (II) chloride preparation for 4 h under the same conditions. However, item 24,352-3 purchased after early 2002 has the same physical appearance as item 43,150-8. Since then, we have encountered difficulty with nitro-reduction. We have communicated with scientists at Aldrich about our experience with the two crystalline forms of tin (II) chloride dihydrate, but we were unable to obtain a satisfactory explanation. After looking at different commercial sources of tin (II) chloride, we switched to another Aldrich product, anhydrous tin (II) chloride (Catalogue No. 20,825-6, off-white flakes). With a 2 M solution of this product in DMF, the reduction of nitro groups was complete after 6 h at room temperature in the presence of 4 M H_2O. However, it was discovered that the addition of water was not necessary if the solvent was not anhydrous.

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