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# Facile solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones

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**Abstract**—We report herein the facile solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones using 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid as the scaffold. The fluorine of the resin-bound scaffold was first replaced by a primary amine. Reduction of the nitro group with tin(II) chloride afforded an *o*-dianilino intermediate that was treated with an aldehyde followed by the addition of 2,3-dichloro-5,6-dicyanoquinone (DDQ). 2,3-Disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones were obtained in high purity and good yield after cleavage.


## 1. Introduction

Natural products and their derivatives have played a major role in drug discovery and development.[1] In the past few years, significant attention has been focused on the design, synthesis and screening of natural product-based combinatorial libraries as this approach combines the 'drug-like' quality of natural products with the efficiency of combinatorial chemistry.[2] Solid-phase synthetic routes to natural products and natural product-like small molecules are of great interest for their ability to generate large combinatorial libraries in a time- and cost-effective manner.[3]

Coumarin (2*H*-1-benzopyran-2-one) derivatives constitute an important class of natural products, which are widely distributed in the plant kingdom.[4] Coumarins and related compounds have a broad range of biological activities, including antibiotic, anticoagulant, anticancer, antiinflammatory, antioxidant, and antimitotic effects.[5] A number of natural or synthetic coumarins have been widely used as therapeutic agents,[6] fluorescent probes,[7] and photosensitizers.[8] As a part of our continuing effort to construct natural product-based small molecule libraries, we recently reported the synthesis and applications of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid as a novel scaffold for combinatorial synthesis of coumarin derivatives.[9] Combinatorial libraries of 2-alkylthioimidazocoumarins[10] and 2-arylaminoimidazocoumarins[11] were prepared in solid-phase using this scaffold.

In this report, we describe a facile solid-phase method for parallel synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones (2,3-disubstituted imidazocoumarins). Unlike the imidazocoumarin derivatives that we have previously reported, the substituent at C-2 position in this class of compounds is connected directly to the imidazole ring via a C–C bond. This combinatorial synthesis method is highly efficient. The imidazole ring closure reaction is mild and it enables one to incorporate large number of commercially available aldehydes into the final imidazocoumarin structure. We anticipate that the synthesis of the 2,3-disubstituted imidazocoumarin library will provide a rich source of highly diverse and innovative natural product-based small molecules for our anticancer drug development program.

## 2. Results and discussion

Our strategy for the solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones is illustrated in Scheme 1. 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid **2** was first tethered to Rink amide resin **1** using 1,3-diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) as the activating system. The fluorine in the resin-bound

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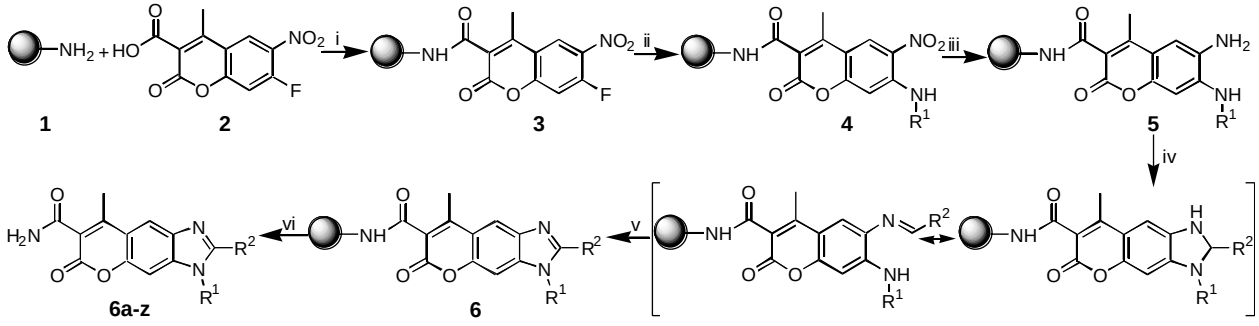


**Scheme 1.** Solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones. Reagents and conditions: **1**, Rink amide resin; (i) 2 equiv of 7-fluoro-4-methyl-6-nitro-coumarin-3-carboxylic acid, 2 equiv of DIC and 2 equiv of HOBt in DMF, rt, 16 h; (ii) 2 equiv of $R^1NH_2$ in 5% DIPEA/DMF, rt, overnight; (iii) 1 M of $SnCl_2 \cdot H_2O$ in DMF, rt, 24 h; (iv) 4 equiv of $R^2CHO$ in DMF, rt, 2 h; (v) 1 equiv of DDQ in DMF, rt, 5 h; (vi) 95% TFA/$H_2O$, rt, 2 h.

scaffold **3** was subsequently replaced by a primary amine. The optimal reaction conditions were determined to be 2 equiv of the amine in 5% *N*,*N*-diisopropylethylamine (DIPEA)/*N*,*N*-dimethylformamide (DMF), while higher concentration of the amine caused undesired side reaction on the pyranone ring. A number of structurally diverse primary amines were successfully tested for the aromatic nucleophilic substitution (see Table 1 for representative structures).

Reduction of the nitro group by treatment with tin(II) chloride (1 M solution in DMF) afforded the *o*-dianilino intermediate **5** smoothly. However, the formation of imidazole ring was problematic. The solid-phase synthesis of benzimidazoles via an *o*-dianilino intermediate have been reported by several groups.[12–14] The *o*-dianilino intermediate was usually acylated with a carboxylic acid followed by treatment with a strong mineral acid,[12] or condensed with an aldehyde under oxidative conditions or elevated temperature.[13,14] When we applied these methods to our synthesis, the results were unsatisfactory. For example, when we followed the convenient 'one-pot' solid-phase synthesis method of benzimidazoles, reported by Wu et al.,[14] by heating the polymer-bound 2-nitroaniline with an aldehyde in DMF in the presence of tin(II) chloride at 60 °C, we were able to prepare the desired products **6** from only a few simple aromatic aldehydes such as benzaldehyde and *p*-tolualdehyde. However, reactions with most of substituted aromatic aldehydes, heterocyclic aldehydes and aliphatic aldehydes all yielded complex mixtures, which were not further elucidated. We believe this is due to the electron-rich nature of 6,7-diaminocoumarin intermediate **5**, making it unstable to the harsh reaction conditions.

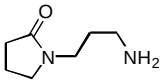
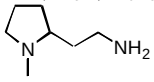
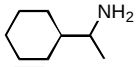
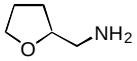
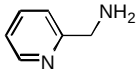
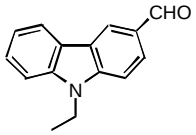
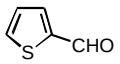
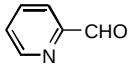
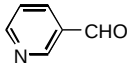
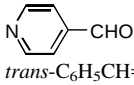
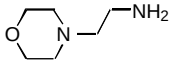
After evaluating various reagents and reaction conditions, we were finally able to establish an efficient and convenient procedure for imidazole ring formation. The resin-bound intermediate **5** was first incubated with 4 equiv of an aldehyde at room temperature for 2 h to allow the condensation, followed by the addition of 1 equiv of 2,3-dichloro-5,6-dicyanoquinone (DDQ). It is important to follow this protocol because we have found that when DDQ was added together with the aldehyde, the resin became very dark and a complex mixture was obtained after cleavage by trifluoroacetic acid (TFA). Excess DDQ should be avoided as it will form a complex with the final product causing problem in subsequent purification. Among the aldehydes we tested (see Table 1 for representative structures), aromatic aldehydes (**6a–n**), heterocyclic aldehydes (**6o–t**), and α-branched aliphatic aldehydes (**6y** and **6z**) reacted smoothly to afford the desired products in high purity. Steric hindrance and substituents on the aromatic aldehydes did not adversely affect the cyclization. Electron-rich aldehydes such as 2,4-dimethoxybenzaldehyde and 4-dimethylaminobenzaldehyde, which were known to be unstable to strong oxidants,[15] were well tolerated. Functionalities such as phenolic hydroxyl (**6h**) and carboxyl (**6i**) groups did not require protection. Cinnamaldehydes (**6u** and **6v**) and linear aliphatic aldehydes (**6w** and **6x**) also underwent the cyclization to yield the desired products but in slightly lower purity.

Using the established method, we synthesized 26 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones with diverse structures (Table 1). The final products were released from the solid support via TFA treatment, analyzed and purified by HPLC, and characterized by $^1H$, $^{13}C$ NMR and ESI-FTMS. Most of the compounds were obtained in high purity with good isolated yield.

## 3. Conclusion

To summarize, we have developed a facile solid-phase approach for parallel synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones. The desired products were obtained in high purity. The compounds prepared by this method have two sites of chemical diversity. The building blocks used for the synthesis are easily available. The methodology is ideally suited for automated high-throughput synthesis as all of the reactions were performed under ambient conditions.

**Table 1**. Preparation of compounds **6a–z** via Scheme 1

| Entry | $R^1NH_2$ | $R^2CHO$ | Yield (%)[a] | Purity (%)[b] |
|---|---|---|---|---|
| **6a** | $CH_3(CH_2)_2NH_2$ | $C_6H_5CHO$ | 81 | 92 |
| **6b** | $C_6H_5OCH_2CH_2NH_2$ | 2-$CH_3C_6H_4CHO$ | 83 | 95 |
| **6c** | 4-$ClC_6H_4CH_2CH_2NH_2$ | 4-$CH_3OC_6H_4CHO$ | 78 | 91 |
| **6d** | $(CH_3)_2CHCH_2NH_2$ | 3,4,5-$(CH_3O)_3C_6H_2CHO$ | 72 | 88 |
| **6e** |  | 2,4-$(CH_3O)_2C_6H_3CHO$ | 74 | 90 |
| **6f** | $(C_2H_5)_2CHNH_2$ | 4-$(CH_3)_2NC_6H_4CHO$ | 83 | 97 |
| **6g** | 4-$CH_3OC_6H_4CH_2CH_2NH_2$ | 4-$CH_3CONHC_6H_4CHO$ | 79 | 91 |
| **6h** | 2-$FC_6H_4CH_2CH_2NH_2$ | 4-$HOC_6H_4CHO$ | 80 | 95 |
| **6i** | 2,4-$(CH_3O)_2C_6H_3CH_2NH_2$ | 4-$HOOCC_6H_4CHO$ | 81 | 94 |
| **6j** |  | 2,6-$Cl_2C_6H_3CHO$ | 70 | 86 |
| **6k** |  | 4-$NCC_6H_4CHO$ | 77 | 92 |
| **6l** |  | 3-$O_2NC_6H_4CHO$ | 72 | 88 |
| **6m** | $(CH_3)_2CHCH_2NH_2$ | 4-$O_2NC_6H_4CHO$ | 78 | 94 |
| **6n** |  | 1-$C_{10}H_7CHO$ | 71 | 87 |
| **6o** | $(CH_3)_2CHCH_2NH_2$ |  | 73 | 84 |
| **6p** | 3,4-$(CH_2O_2)C_6H_3CH_2NH_2$ |  | 81 | 96 |
| **6q** | $C_2H_5(CH_3)CHNH_2$ |  | 75 | 91 |
| **6r** | *c*-$C_5H_9NH_2$ |  | 76 | 92 |
| **6s** | *c*-$C_6H_{11}NH_2$ |  | 81 | 97 |
| **6t** | *c*-$C_6H_{11}CH_2NH_2$ |  | 69 | 88 |
| **6u** | $CH_3(CH_2)_2NH_2$ | *trans*-$C_6H_5CH{=}CHCHO$ | 66 | 79 |
| **6v** | $CH_3(CH_2)_3NH_2$ | *trans*-4-$(CH_3)_2NC_6H_4CH{=}CHCHO$ | 70 | 84 |
| **6w** | $C_6H_5CH_2NH_2$ | $CH_3CH_2CHO$ | 55 | 72 |
| **6x** | $C_2H_5O(CH_2)_3NH_2$ | $C_6H_5CH_2CH_2CHO$ | 56 | 66 |
| **6y** | $CH_3(CH_2)_2NH_2$ | $(CH_3)_2CHCHO$ | 73 | 90 |
| **6z** |  | *c*-$C_6H_{11}CHO$ | 68 | 89 |

[a] Yields were calculated based on the purified products.
[b] Purity was determined by HPLC analysis (UV detection at 254 nm) of crude products.

## 4. Experimental

### 4.1. General

7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid was prepared using our published procedure.[9] DIC and TFA were purchased from Advanced ChemTech (Louisville, KY). Rink amide MBHA resin (0.45 mmol/g) was purchased from Nankai Hecheng (Tianjin, China). HOBt was purchased from GL Biochem (Shanghai, China). All solvents and other chemical reagents were purchased from Aldrich (Milwaukee, WI) and were analytical grade. 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). $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer

(Billerica, MA) at 25 °C. All of the experiments were carried out at room temperature unless otherwise noted.

### 4.2. General procedure for solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones

Rink amide MBHA resin (100 mg, 0.045 mmol) was swollen in DMF overnight. The supernatant was removed, and a 20% piperidine solution in DMF (1 mL) was added to the resin. The mixture was agitated for 15 min, and the supernatant was removed. This process was repeated. The resin was washed with DMF, methanol (MeOH), and DMF. To the resin was added a solution of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid (24.1 mg, 0.090 mmol), HOBt (12.2 mg, 0.090 mmol) and DIC (14.1 μL, 0.090 mmol) in DMF (1 mL). The resulting mixture was agitated for 16 h. The complete coupling was confirmed by a negative ninhydrin test. The supernatant was removed, and the resin was washed with DMF, dichloromethane (DCM), MeOH, and DMF. To the resin was added a solution of a primary amine (0.090 mmol) in 5% DIPEA/DMF (2 mL). The resulting mixture was agitated overnight. The supernatant was removed, and the resin was washed with DMF, DCM, MeOH, and DMF. To the resin was added 1 M $SnCl_2 \cdot H_2O$ solution in DMF (2 mL), and the resulting mixture was agitated for 24 h. The supernatant was removed, and the resin was washed with DMF, DCM, MeOH, and DMF. To the resin was added a solution of an aldehyde (0.180 mmol) in DMF (1 mL). The resulting mixture was agitated for 2 h, and a solution of DDQ (10.2 mg, 0.045 mmol) in DMF (1 mL) was added. After additional 5 h of agitation, the supernatant was removed. The resin was washed thoroughly with DMF, 5% DIPEA/DMF, DCM, MeOH, and DCM, and then dried in vacuo. To the dried 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 collected and the resin was washed with neat TFA (3×1 mL). The combined supernatants were concentrated to dryness under a stream of nitrogen, and further dried in vacuo. The crude product was analyzed and purified by HPLC.

**4.2.1. 8-Methyl-6-oxo-2-phenyl-3-propyl-6*H*-pyrano-[2,3-*f*]benzimidazole-7-carboxamide 6a.** Yield 81%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.20 (s, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.83 (t, 2H, $J$=3.3 Hz), 7.66 (s, 1H), 7.63 (m, 3H), 4.35 (t, 2H, $J$=7.1 Hz), 2.53 (s, 3H), 1.68 (m, 2H), 0.73 (t, 3H, $J$=7.3 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.9, 156.2, 149.7, 149.1, 138.9, 138.7, 131.3, 130.0, 129.8, 129.7, 129.1, 123.3, 116.1, 115.6, 99.1, 46.8, 23.0, 16.9, 11.5; ESI-FTMS $m/z$ calcd for $C_{21}H_{19}N_3O_3+H^+$: 362.14992; found: 362.14982.

**4.2.2. 8-Methyl-2-(2-methylphenyl)-6-oxo-3-(2-phenoxyethyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6b.** Yield 83%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.21 (s, 1H), 8.00 (s, 1H), 7.93 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1H, $J$=7.4 Hz), 7.54 (t, 1H, $J$=7.4 Hz), 7.48 (d, 1H, $J$=7.4 Hz), 7.43 (t, 1H, $J$=7.4 Hz), 7.19 (m, 2H), 6.87 (t, 1H, $J$=7.3 Hz), 6.69 (d, 2H, $J$=7.9 Hz), 4.57 (t, 2H, $J$=4.6 Hz), 4.21 (t, 2H, $J$=4.6 Hz), 2.53 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.9, 158.4, 156.1, 149.7, 149.1, 138.5, 138.0, 137.3, 131.3, 131.1, 130.2, 128.7, 126.7, 123.5, 121.7, 116.4, 115.9, 115.8, 114.8, 99.7, 65.8, 44.8, 20.1, 16.9; ESI-FTMS $m/z$ calcd for $C_{27}H_{23}N_3O_4+H^+$: 454.17614; found: 454.17608.

**4.2.3. 3-[2-(4-Chlorophenyl)ethyl]-2-(4-methoxyphenyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6c.** Yield 78%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.13 (s, 1H), 7.93 (s, 1H), 7.92 (s, 1H), 7.70 (s, 1H), 7.57 (d, 2H, $J$=8.7 Hz), 7.15 (d, 2H, $J$=8.3 Hz), 7.11 (d, 2H, $J$=8.7 Hz), 6.91 (d, 2H, $J$=8.3 Hz), 4.64 (t, 2H, $J$=6.7 Hz), 3.87 (s, 3H), 2.99 (t, 2H, $J$=6.7 Hz), 2.52 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 161.8, 158.8, 155.9, 149.8, 148.9, 137.8, 137.7, 137.0, 132.1, 131.5, 131.2, 128.9, 123.6, 120.4, 116.5, 115.1, 115.0, 99.6, 56.2, 46.8, 34.4, 16.9; ESI-FTMS $m/z$ calcd for $C_{27}H_{22}ClN_3O_4+H^+$: 488.13716; found: 488.13714.

**4.2.4. 8-Methyl-3-(2-methylpropyl)-6-oxo-2-(3,4,5-trimethoxyphenyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6d.** Yield 72%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.18 (s, 1H), 7.95 (s, 1H), 7.88 (s, 1H), 7.68 (s, 1H), 7.16 (s, 2H), 4.32 (d, 2H, $J$=7.4 Hz), 3.87 (s, 6H), 3.78 (s, 3H), 2.52 (s, 3H), 1.95 (m, 1H), 0.72 (d, 6H, $J$=6.6 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.8, 158.8, 155.9, 153.8, 149.8, 149.0, 140.1, 138.7, 137.4, 124.5, 123.5, 116.4, 115.5, 107.6, 99.6, 61.0, 57.0, 52.5, 29.1, 20.2, 16.8; ESI-FTMS $m/z$ calcd for $C_{25}H_{27}N_3O_6+H^+$: 466.19727; found: 466.19723.

**4.2.5. 2-(2,4-Dimethoxyphenyl)-8-methyl-6-oxo-3-[3-(2-oxo-1-pyrrolidinyl)propyl]-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6e.** Yield 74%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.18 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.71 (s, 1H), 7.54 (d, 1H, $J$=8.5 Hz), 6.86 (d, 1H, $J$=2.0 Hz), 6.81 (dd, 1H, $J$=8.5, 2.0 Hz), 4.14 (t, 2H, $J$=7.5 Hz), 3.12 (t, 2H, $J$=6.4 Hz), 3.05 (t, 2H, $J$=6.9 Hz), 2.52 (s, 3H), 2.09 (t, 2H, $J$=8.3 Hz), 1.83 (m, 2H), 1.74 (m, 4H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 174.7, 166.5, 164.4, 159.4, 158.6, 153.4, 150.0, 148.7, 136.5, 135.0, 133.5, 124.0, 117.1, 114.4, 107.9, 106.9, 99.8, 99.5, 56.7, 56.5, 46.6, 43.4, 39.6, 31.0, 27.1, 18.0, 16.9; ESI-FTMS $m/z$ calcd for $C_{27}H_{28}N_4O_6+H^+$: 505.20817; found: 505.20826.

**4.2.6. 2-(4-Dimethylaminophenyl)-3-(1-ethylpropyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6f.** Yield 83%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.18 (s, 1H), 8.12 (s, 1H), 7.91 (s, 1H), 7.73 (s, 1H), 7.57 (d, 2H, $J$=8.8 Hz), 6.95 (d, 2H, $J$=8.8 Hz), 4.42 (m, 1H), 3.05 (s, 6H), 2.52 (s, 3H), 2.21 (m, 2H), 2.04 (m, 2H), 0.68 (t, 6H, $J$=7.3 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.4, 158.5, 157.0, 152.9, 149.8, 148.3, 134.3, 133.5, 131.8, 124.5, 117.5, 113.3, 112.5, 111.6, 101.6, 62.8, 40.4, 25.7, 16.8, 11.3; ESI-FTMS $m/z$ calcd for $C_{25}H_{28}N_4O_3+H^+$: 433.22342; found: 433.22348.

**4.2.7. 2-(4-Acetylaminophenyl)-3-[2-(4-methoxyphenyl)-ethyl]-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6g.** Yield 79%; $^1$H NMR (DMSO-$d_6$) $\delta$ 10.29 (s, 1H), 7.92 (s, 1H), 7.89 (s, 1H), 7.76 (d, 2H, $J$=8.5 Hz), 7.69 (s, 1H), 7.55 (d, 2H, $J$=8.5 Hz), 6.80 (d, 2H, $J$=8.4 Hz), 6.67 (d, 2H, $J$=8.4 Hz), 4.59 (t, 2H, $J$=5.9 Hz), 3.67 (s, 1H), 2.93 (t, 2H, $J$=5.9 Hz), 2.52 (s, 3H), 2.11 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 169.6, 166.7, 158.8,

155.9, 149.8, 148.9, 142.2, 137.9, 137.2, 130.6, 130.4, 129.8, 123.6, 122.8, 119.8, 119.3, 116.4, 115.2, 114.5, 99.6, 55.7, 47.2, 34.2, 24.9, 16.9; ESI-FTMS *m/z* calcd for $C_{29}H_{26}N_4O_5+H^+$: 511.19760; found: 511.19763.

**4.2.8. 3-[2-(2-Fluorophenyl)ethyl]-2-(4-hydroxyphenyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6h.** Yield 80%; $^1$H NMR (DMSO-$d_6$) $\delta$ 10.2 (s, br, 1H), 8.21 (s, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.47 (d, 2H, $J$=8.6 Hz), 7.19 (m, 1H), 7.02 (m, 1H), 6.99–6.91 (m, 4H), 4.66 (t, 2H, $J$=6.8 Hz), 3.05 (t, 2H, $J$=6.8 Hz), 2.52 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.6, 161.4 (d, $^1J_{CF}$=242.5 Hz), 160.8, 158.7, 156.1, 149.8, 148.8, 137.5 (d, $^3J_{CF}$=7.3 Hz), 135.9, 132.0, 131.7, 129.8 (d, $^3J_{CF}$=7.9 Hz), 125.1, 124.5 (d, $^2J_{CF}$=15.6 Hz), 123.8, 117.8, 116.7, 116.5, 115.7 (d, $^2J_{CF}$=21.5 Hz), 114.5, 99.6, 45.7, 28.6, 16.9; ESI-FTMS *m/z* calcd for $C_{26}H_{20}FN_3O_4+H^+$: 458.15107; found: 458.15113.

**4.2.9. 4-[7-Carbamoyl-3-[(2,4-dimethoxyphenyl)-methyl]-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazol-2-yl]benzoic acid 6i.** Yield 81%; $^1$H NMR (DMSO-$d_6$) $\delta$ 13.3 (s, br, 1H), 8.21 (s, 1H), 8.11 (d, 2H, $J$=8.2 Hz), 7.92 (d, 2H, $J$=8.2 Hz), 7.85 (s, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 6.86 (d, 1H, $J$=8.4 Hz), 6.47 (s, 1H), 6.40 (dd, 1H, $J$=9.1, 1.4 Hz), 5.50 (s, 2H), 3.68 (s, 3H), 3.54 (s, 3H), 2.52 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 167.5, 166.7, 161.2, 158.9, 158.5, 156.1, 149.5, 149.2, 140.2, 139.2, 134.6, 132.7, 130.3, 130.1, 129.8, 123.2, 116.8, 116.3, 115.9, 105.3, 99.3, 56.0, 55.9, 44.9, 16.8; ESI-FTMS *m/z* calcd for $C_{28}H_{23}N_3O_7+H^+$: 514.16088; found: 514.16077.

**4.2.10. 2-(2,6-Dichlorophenyl)-8-methyl-3-[2-(1-methyl-2-pyrrolidinyl)ethyl]-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6j.** Yield 70%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.23 (s, 1H), 7.97 (s, 1H), 7.92 (s, 1H), 7.79–7.66 (m, 4H), 4.22 (m, 1H), 4.03 (m, 1H), 3.53 (m, 1H), 3.22 (m, 1H), 3.01 (m, 1H), 2.76 (d, $J$=4.1 Hz, 3H), 2.54 (s, 3H), 2.38 (m, 1H), 2.03 (m, 1H), 1.91 (m, 1H), 1.82 (m, 2H), 1.39 (m, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.9, 150.7, 149.9, 149.3, 140.3, 137.3, 135.9, 135.8, 134.3, 129.6, 128.7, 123.3, 117.7, 116.1, 98.9, 66.1, 55.8, 42.1, 39.4, 30.4, 29.3, 21.7, 16.9; ESI-FTMS *m/z* calcd for $C_{25}H_{24}Cl_2N_4O_3+H^+$: 499.12983; found: 499.12978.

**4.2.11. 2-(4-Cyanophenyl)-3-(1-cyclohexylethyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6k.** Yield 77%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.22 (s, 1H), 8.09 (s, 1H), 8.08 (m, 2H), 7.98 (s, 1H), 7.88 (m, 3H), 7.68 (s, 1H), 4.08 (m, 1H), 2.52 (s, 3H), 2.15 (m, 1H), 1.88 (m, 1H), 1.76 (d, $J$=6.7 Hz, 3H), 1.64 (m, 1H), 1.47 (m, 1H), 1.34 (m, 1H), 1.21 (m, 1H), 0.99–0.75 (m, 3H), 0.59 (m, 1H), 0.36 (m, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.8, 155.7, 149.3, 149.0, 140.1, 136.3, 134.8, 133.6, 131.3, 123.5, 119.0, 117.0, 116.2, 113.6, 100.7, 59.6, 40.4, 30.4, 29.8, 26.0, 25.8, 25.7, 17.6, 16.8; ESI-FTMS *m/z* calcd for $C_{27}H_{26}N_4O_3+H^+$: 455.20777; found: 455.20782.

**4.2.12. 8-Methyl-2-(3-nitrophenyl)-6-oxo-3-[(tetrahydro-2-furanyl)methyl]-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6l.** Yield 72%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.80 (t, 1H, $J$=1.5 Hz), 8.42 (dd, 1H, $J$=8.3, 1.5 Hz), 8.32 (d, 1H, $J$=7.9 Hz), 8.22 (s, 1H), 7.92–7.85 (m, 3H), 7.67 (s, 1H), 4.51 (dd, 1H, $J$=15.0, 2.4 Hz), 4.34 (dd, 1H, $J$=15.0, 9.2 Hz), 4.27 (m, 1H), 3.60 (dd, 1H, $J$=14.5, 6.9 Hz), 3.55 (dd, 1H, $J$=14.5, 7.3 Hz), 2.52 (s, 3H), 2.04 (m, 1H), 1.78 (m, 2H), 1.55 (m, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.9, 154.7, 149.7, 149.1, 148.6, 139.8, 139.1, 136.7, 132.0, 131.2, 125.4, 125.1, 123.3, 116.8, 116.1, 99.5, 77.2, 68.1, 49.7, 29.4, 25.9, 16.9; ESI-FTMS *m/z* calcd for $C_{23}H_{20}N_4O_6+H^+$: 449.14557; found: 449.14561.

**4.2.13. 8-Methyl-3-(2-methylpropyl)-2-(4-nitrophenyl)-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6m.** Yield 78%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.42 (d, 2H, $J$=8.8 Hz), 8.24 (s, 1H), 8.16 (d, 2H, $J$=8.8 Hz), 7.92 (s, 1H), 7.88 (s, 1H), 7.67 (s, 1H), 4.32 (d, 2H, $J$=7.5 Hz), 2.52 (s, 3H), 1.87 (m, 1H), 0.65 (d, 6H, $J$=6.6 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.9, 154.5, 149.8, 149.1, 148.9, 140.1, 139.6, 137.0, 131.3, 124.7, 123.3, 117.2, 116.1, 99.4, 52.2, 29.3, 20.1, 16.9; ESI-FTMS *m/z* calcd for $C_{22}H_{20}N_4O_5+H^+$: 421.15065; found: 421.15060.

**4.2.14. 8-Methyl-2-(1-naphthalenyl)-6-oxo-3-(2-pyridinylmethyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6n.** Yield 71%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.34–8.28 (m, 2H), 8.14 (d, 1H, $J$=8.2 Hz), 8.04 (d, 1H, $J$=8.2 Hz), 7.90 (s, 1H), 7.81–7.76 (m, 2H), 7.73 (s, 1H), 7.68 (s, 1H), 7.66–7.61 (m, 2H), 7.58 (t, 1H, $J$=7.6 Hz), 7.50 (t, 1H, $J$=7.6 Hz), 7.18 (dd, 1H, $J$=7.0, 5.4 Hz), 7.05 (d, 1H, $J$=7.8 Hz), 5.54 (s, 2H), 2.56 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.8, 155.6, 155.2, 149.8, 149.7, 149.2, 139.0, 138.6, 138.0, 133.8, 132.0, 131.5, 129.6, 129.1, 127.9, 127.3, 126.6, 125.9, 125.8, 123.7, 123.4, 122.5, 116.4, 116.3, 99.3, 49.8, 16.9; ESI-FTMS *m/z* calcd for $C_{28}H_{20}N_4O_3+H^+$: 461.16082; found: 461.16083.

**4.2.15. 2-(9-Ethyl-9*H*-carbazol-3-yl)-8-methyl-3-(2-methylpropyl)-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6o.** Yield 73%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.73 (s, 1H), 8.31 (d, 1H, $J$=7.7 Hz), 8.19 (s, 1H), 8.06 (s, 1H), 7.97 (d, 1H, $J$=8.6 Hz), 7.88 (t, 2H, $J$=7.9 Hz), 7.71 (t, 2H, $J$=7.6 Hz), 7.56 (t, 1H, $J$=7.4 Hz), 7.30 (t, 1H, $J$=7.4 Hz), 4.55 (m, 2H), 4.45 (d, 2H, $J$=7.3 Hz), 2.55 (s, 3H), 1.96 (m, 1H), 1.38 (t, 3H, $J$=7.0 Hz), 0.67 (d, 6H, $J$=6.6 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.6, 158.8, 157.0, 149.9, 148.9, 141.3, 140.9, 138.5, 136.5, 127.5, 127.4, 123.7, 123.1, 122.8, 122.7, 121.7, 120.4, 118.6, 116.6, 114.7, 110.4, 99.9, 52.5, 38.0, 28.9, 20.2, 16.9, 14.5; ESI-FTMS *m/z* calcd for $C_{30}H_{28}N_4O_3+H^+$: 493.22342; found: 493.22333.

**4.2.16. 3-(1,3-Benzodioxol-5-ylmethyl)-8-methyl-6-oxo-2-(2-thienyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6p.** Yield 81%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.20 (s, 1H), 7.85 (m, 2H), 7.73 (s, 1H), 7.65 (d, 2H, $J$=3.6 Hz), 7.24 (t, 1H, $J$=8.9 Hz), 6.82 (d, 1H, $J$=8.0 Hz), 6.70 (s, 1H), 6.46 (d, 1H, $J$=8.0 Hz), 5.97 (s, 2H), 5.74 (s, 2H), 2.51 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.8, 150.4, 149.8, 149.1, 148.5, 147.4, 139.8, 139.6, 131.9, 131.3, 130.6, 129.5, 129.4, 123.2, 120.0, 116.4, 116.3, 109.3, 107.5, 101.9, 98.6, 48.2, 16.8; ESI-FTMS *m/z* calcd for $C_{24}H_{17}N_3O_5S+H^+$: 460.09617; found: 460.09612.

**4.2.17. 8-Methyl-3-(1-methylpropyl)-6-oxo-2-(3-thienyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6q.** Yield 75%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.17 (s, 1H), 8.14 (dd,

1H, $J$=2.8, 1.2 Hz), 7.97 (s, 1H), 7.90 (s, 1H), 7.85 (dd, 1H, $J$=5.0, 2.8 Hz), 7.68 (s, 1H), 7.51 (dd, 1H, $J$=5.0, 1.2 Hz), 4.62 (m, 1H), 2.51 (s, 3H), 2.16 (m, 1H), 1.93 (m, 1H), 1.68 (d, 3H, $J$=6.9 Hz), 0.57 (t, 3H, $J$=7.3 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.8, 152.4, 149.3, 148.9, 138.5, 135.6, 130.1, 129.5, 129.1, 128.7, 123.6, 116.3, 115.7, 100.6, 56.0, 27.4, 19.6, 16.8, 11.3; ESI-FTMS $m/z$ calcd for $C_{20}H_{19}N_3O_3S+H^+$: 382.12199; found: 382.12203.

**4.2.18. 3-Cyclopentyl-8-methyl-6-oxo-2-(2-pyridinyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6r.** Yield 76%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.78 (s, 1H), 8.25 (s, 1H), 8.19 (d, 1H, $J$=7.8 Hz), 8.06 (t, 1H, $J$=7.8 Hz), 7.90 (s, 1H), 7.68 (s, 2H), 7.59 (m, 1H), 5.93 (m, 1H), 2.52 (s, 3H), 2.22 (m, 2H), 2.12 (m, 2H), 2.02 (m, 2H), 1.70 (m, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.9, 154.0, 150.1, 149.8, 149.2, 149.0, 140.2, 138.4, 136.7, 126.2, 125.6, 123.4, 117.3, 116.0, 100.1, 58.2, 30.1, 25.2, 16.8; ESI-FTMS $m/z$ calcd for $C_{22}H_{20}N_4O_3+H^+$: 389.16082; found: 389.16086.

**4.2.19. 3-Cyclohexyl-8-methyl-6-oxo-2-(3-pyridinyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6s.** Yield 81%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.95 (d, 1H, $J$=1.2 Hz), 8.19 (dd, 1H, $J$=4.8, 1.2 Hz), 8.24–8.19 (m, 2H), 8.05 (s, 1H), 7.92 (s, 1H), 7.72 (dd, 1H, $J$=7.7, 5.0 Hz), 7.68 (s, 1H), 4.24 (m, 1H), 2.52 (s, 3H), 2.31 (m, 2H), 1.96 (m, 2H), 1.83 (m, 2H), 1.60 (m, 1H), 1.47 (m, 1H), 1.30 (m, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.9, 153.5, 151.0, 149.6, 149.2, 149.0, 140.3, 138.8, 136.5, 127.1, 124.9, 123.5, 116.8, 115.9, 100.9, 58.1, 30.8, 26.1, 24.7, 16.8; ESI-FTMS $m/z$ calcd for $C_{23}H_{22}N_4O_3+H^+$: 403.17647; found: 403.17644.

**4.2.20. 3-(Cyclohexylmethyl)-8-methyl-6-oxo-2-(4-pyridinyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6t.** Yield 69%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.90 (dd, 2H, $J$=4.9, 1.1 Hz), 8.25 (s, 1H), 8.05 (dd, 2H, $J$=4.9, 1.1 Hz), 7.93 (s, 1H), 7.88 (s, 1H), 7.68 (s, 1H), 4.37 (d, 2H, $J$=7.2 Hz), 2.52 (s, 3H), 1.60 (m, 1H), 1.49 (m, 3H), 1.28 (m, 2H), 1.98 (m, 3H), 0.79 (m, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.8, 153.4, 149.9, 149.3, 149.2, 149.1, 140.3, 139.9, 139.6, 124.9, 123.4, 117.4, 116.4, 99.5, 51.1, 38.4, 30.4, 26.3, 25.6, 16.9; ESI-FTMS $m/z$ calcd for $C_{24}H_{24}N_4O_3+H^+$: 417.19212; found: 417.19208.

**4.2.21. 8-Methyl-6-oxo-2-[(*E*)-2-phenylethenyl]-3-propyl-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6u.** Yield 66%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.09 (s, 1H), 7.95 (d, 1H, $J$=15.9 Hz), 7.89 (s, 1H), 7.87–7.82 (m, 3H), 7.67 (s, 1H), 7.55 (d, 1H, $J$=15.9 Hz), 7.48 (m, 2H), 7.44 (m, 1H), 4.51 (t, 2H, $J$=7.3 Hz), 2.51 (s, 3H), 1.79 (m, 2H), 0.90 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 158.8, 153.7, 149.7, 148.9, 139.9, 138.1, 137.9, 136.0, 130.6, 129.7, 128.8, 123.4, 116.5, 114.6, 113.3, 98.8, 45.4, 23.8, 16.9, 11.6; ESI-FTMS $m/z$ calcd for $C_{23}H_{21}N_3O_3+H^+$: 388.16557; found: 388.16554.

**4.2.22. 3-Butyl-2-[(*E*)-2-(4-dimethylaminophenyl)-ethenyl]-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6v.** Yield 70%; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.99 (s, 1H), 7.94–7.87 (m, 3H), 7.72 (s, 1H), 7.66 (d, 2H, $J$=8.8 Hz), 7.17 (d, 1H, $J$=15.8 Hz), 6.76 (d, 2H, $J$=8.8 Hz), 4.52 (t, 2H, $J$=7.3 Hz), 3.02 (s, 6H), 2.50 (s, 3H), 1.75 (m, 2H), 1.34 (m, 2H), 0.89 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.5, 158.5, 153.5, 152.8, 150.1, 148.5, 144.4, 136.4, 132.7, 131.3, 124.1, 122.6, 117.5, 112.6, 111.7, 103.3, 99.6, 44.4, 40.4, 32.0, 19.9, 16.8, 14.3; ESI-FTMS $m/z$ calcd for $C_{26}H_{28}N_4O_3+H^+$: 445.22342; found: 445.22344.

**4.2.23. 3-Benzyl-2-ethyl-8-methyl-6-oxo-6*H*-pyrano-[2,3-*f*]benzimidazole-7-carboxamide 6w.** Yield 55%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.13 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 7.36 (t, 2H, $J$=7.3 Hz), 7.31 (t, 1H, $J$=7.1 Hz), 7.20 (d, 2H, $J$=7.2 Hz), 5.64 (s, 2H), 3.01 (m, 2H), 2.50 (s, 3H), 1.31 (t, 3H, $J$=7.4 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.5, 160.0, 158.7, 149.8, 148.9, 148.8, 137.4, 136.4, 129.6, 128.7, 127.6, 123.7, 116.4, 114.5, 99.1, 47.6, 20.8, 16.9, 11.6; ESI-FTMS $m/z$ calcd for $C_{21}H_{19}N_3O_3+H^+$: 362.14992; found: 362.14998.

**4.2.24. 3-(3-Ethoxypropyl)-8-methyl-6-oxo-2-(2-phenylethyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6x.** Yield 56%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.13 (s, 1H), 7.90 (s, 1H), 7.79 (s, 1H), 7.69 (s, 1H), 7.33–7.27 (m, 4H), 7.22 (m, 1H), 4.34 (t, 2H, $J$=6.3 Hz), 3.37–3.26 (m, 6H), 3.19 (t, 2H, $J$=7.5 Hz), 2.51 (s, 3H), 1.94 (m, 2H), 1.03 (t, 3H, $J$=7.0 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.6, 158.7, 158.0, 149.7, 148.8, 140.9, 137.0, 135.4, 129.2, 129.1, 127.1, 123.7, 116.4, 114.2, 99.1, 66.8, 66.1, 41.8, 33.0, 29.4, 28.5, 16.9, 15.7; ESI-FTMS $m/z$ calcd for $C_{25}H_{27}N_3O_4+H^+$: 434.20744; found: 434.20745.

**4.2.25. 8-Methyl-2-(1-methylethyl)-6-oxo-3-propyl-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6y.** Yield 73%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.11 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.69 (s, 1H), 4.34 (t, 2H, $J$=7.2 Hz), 3.51 (m, 1H), 2.49 (s, 3H), 1.79 (m, 2H), 1.41 (d, 6H, $J$=6.7 Hz), 0.94 (t, 3H, $J$=7.3 Hz); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.5, 162.9, 158.6, 149.8, 148.7, 136.6, 134.4, 123.9, 116.7, 113.8, 99.6, 46.1, 26.3, 23.3, 21.8, 16.8, 11.5; ESI-FTMS $m/z$ calcd for $C_{18}H_{21}N_3O_3+H^+$: 328.16557; found: 328.16553.

**4.2.26. 2-Cyclohexyl-8-methyl-3-[2-(4-morpholinyl)-ethyl]-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6z.** Yield 68%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.11 (s, 1H), 7.91 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 4.68 (t, 2H, $J$=7.9 Hz), 3.90 (m, 4H), 3.52 (t, 2H, $J$=7.9 Hz), 3.42 (m, 4H), 3.05 (m, 1H), 2.49 (s, 3H), 1.97 (m, 2H), 1.84 (m, 2H), 1.75 (m, 1H), 1.65 (m, 2H), 1.47 (m, 2H), 1.30 (m, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.7, 162.2, 158.8, 149.5, 149.2, 138.5, 137.2, 123.2, 115.8, 115.5, 98.5, 64.2, 53.6, 52.2, 38.4, 35.5, 32.1, 26.1, 26.0, 16.9; ESI-FTMS $m/z$ calcd for $C_{24}H_{30}N_4O_4+H^+$: 439.23399; found: 439.23406.

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## References and notes


1. (a) Cragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod.* **1997**, *60*, 52–60. (b) Newman, D. J.; Cragg, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215–234. (c) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829–837.
2. (a) Wessjohann, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 303–309. (b) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125–150. (c) Lee, M.-L.; Schneider, G. *J. Comb. Chem.* **2001**, *3*, 284–289. (d) Nielsen, J. *Curr. Opin. Chem. Biol.* **2002**, *6*, 297–305. (e) Ortholand, J.-Y.; Ganesan, A. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271–280.
3. (a) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195–214. (b) Ganesan, A. *Drug Discovery Today* **2002**, *7*, 47–55.
4. Sethna, S. M.; Shah, N. M. *Chem. Rev.* **1945**, *36*, 1–62.
5. (a) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; Wiley: New York, 1982. (b) Hoult, J. R.; Paya, M. *Gen. Pharmacol.* **1996**, *27*, 713–722. (c) *Coumarins: Biology, Applications and Mode of Action*; O'Kennedy, R., Thornes, R. D., Eds.; Wiley: Chichester, UK, 1997.
6. Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887–916.
7. (a) Hemmila, I. A. *Appl. Fluorescence Technol.* **1989**, *1*, 1–8. (b) Katerinopoulos, H. E. *Curr. Pharm. Des.* **2004**, *10*, 3835–3852.
8. (a) Zarebska, Z.; Waszkowska, E.; Caffieri, S.; Dall'Acqua, F. *Farmaco* **2000**, *55*, 515–520. (b) Bethea, D.; Fullmer, B.; Syed, S.; Seltzer, G.; Tiano, J.; Rischko, C.; Gillespie, L.; Brown, D.; Gasparro, F. P. *J. Dermatol. Sci.* **1999**, *19*, 78–88.
9. Song, A.; Zhang, J.; Lam, K. S. *J. Comb. Chem.* **2004**, *6*, 112–120.
10. Song, A.; Zhang, J.; Lebrilla, C. B.; Lam, K. S. *J. Comb. Chem.* **2004**, *6*, 604–610.
11. Song, A.; Lam, K. S. *Tetrahedron* **2004**, *60*, 8605–8612.
12. (a) Smith, J. M.; Krchňák, V. *Tetrahedron Lett.* **1999**, *40*, 7633–7636. (b) Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67–70.
13. (a) Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett.* **1998**, *39*, 6655–6658. (b) Tumelty, D.; Schwarz, M. K.; Cao, K.; Needels, M. C. *Tetrahedron Lett.* **1999**, *40*, 6185–6188. (c) Vourloumis, D.; Takahashi, M.; Simonsen, K. B.; Ayida, B. K.; Barluenga, S.; Winters, G. C.; Hermann, T. *Tetrahedron Lett.* **2003**, *44*, 2807–2811.
14. Wu, Z.; Rea, P.; Wickham, G. *Tetrahedron Lett.* **2000**, *41*, 9871–9874.
15. Beaulieu, P. L.; Haché, B.; von Moos, E. *Synthesis* **2003**, 1683–1692.