

Concise Synthesis of 2, 3-Diarylpyrimido[1,2-*a*]benzimidazole Based on Isoflavones

Zun-Ting Zhang,* Li Qiu, Dong Xue, Jing Wu, and Fei-Fei Xu

Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, and School of Chemistry and Materials Science, Shaanxi Normal University, Xi'an 710062, P.R. China

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The 2,3-diarylpyrimido[1,2-*a*]benzimidazole derivatives were prepared by one-step cyclocondensation of 2-aminobenzimidazole with isoflavone in methanol. Single-crystal diffraction analysis was performed for 2-(2-hydroxyl-4-isopropoxy-phenyl)-3-phenylpyrimido[1,2-*a*]benzimidazole. The fluorescence properties of the fused 2, 3-diarylpyrimido[1, 2-*a*]benzimidazole were evaluated.

Introduction

Polysubstituted pyrimido[1,2-*a*]benzimidazoles have biological properties such as antiparasitic,¹ substance P receptor binding activity,² antibacterial drugs,³ antiarrhythmics,⁴ central nervous system-depressing agents,⁵ as well as marked herbicidal activity.⁶ Meanwhile, the pyrimido[1,2-*a*]benzimidazoles possess fluorescence properties.⁷ The structural feature of the pyrimido[1,2-*a*]benzimidazole nucleus are similar to that of the purine ring system, and therefore, we were interested in the synthesis of various substituted 2,3-diarylpyrimido[1,2-*a*]benzimidazoles. The existing methods for building up the pyrimido[1,2-*a*]benzimidazole core involve the condensation of 2-aminobenzimidazole with (i) acetylene esters;⁸ (ii) enamino esters;⁹ (iii) 1,3-diketone;^{3–5,10} (iv) α , β -unsaturated ketones;¹¹ (v) α -halogenated ketones,¹² and (vi) intramolecular condensation of *N*-(halophenyl)pyrimidin-2-amine⁷ (Scheme 1). The common feature of methods i–v is the use of 2-aminobenzimidazole **2** as the starting materials. Method vi is an intramolecular condensation which needs a special molecular structure as *N*-(halophenyl)pyrimidin-2-amine. Significantly, no syntheses of 2,3-diarylpyrimido[1,2-*a*]benzimidazoles were reported in the literature.

It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent which readily react with amidines,¹³ guanidine,¹⁴ sulfocarbamides,¹⁵ and hydrazine¹⁶ to form the corresponding 2-substituted pyrimidines and diarylpyrazoles. Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles and 4,5-biphenyl-2-pyrimidinylguanidine by using a one-pot reaction of hydrazine¹⁷ and bisguanidine¹⁸ with isoflavones, respec-

tively. Herein, we report a new strategy for the preparation of 2,3-diarylpyrimido[1,2-*a*]benzimidazole from isoflavones.

Results and Discussion

Reactions of 2-aminobenzimidazole **2** with isoflavones **1** were carried out in refluxing methanol in the presence of sodium methoxide as base to promote the ring-opening of isoflavone. Products **3** were obtained in moderate to excellent yields after refluxing for 8–15 h (Scheme 2).

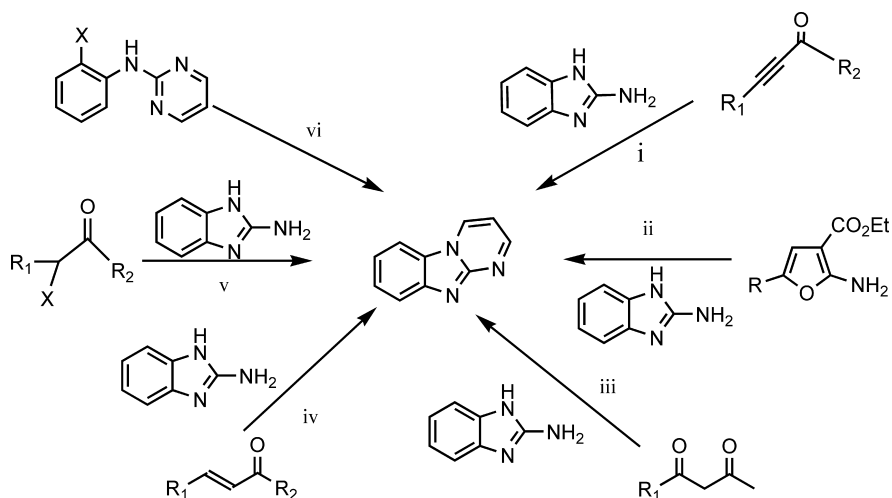
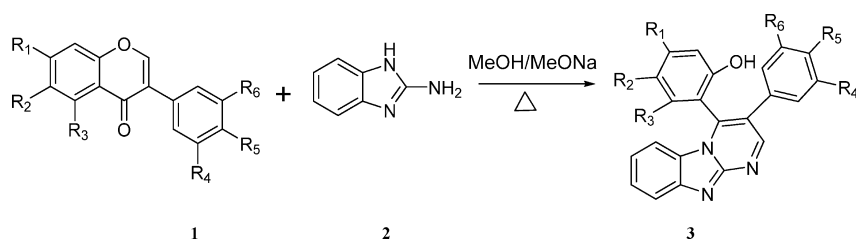
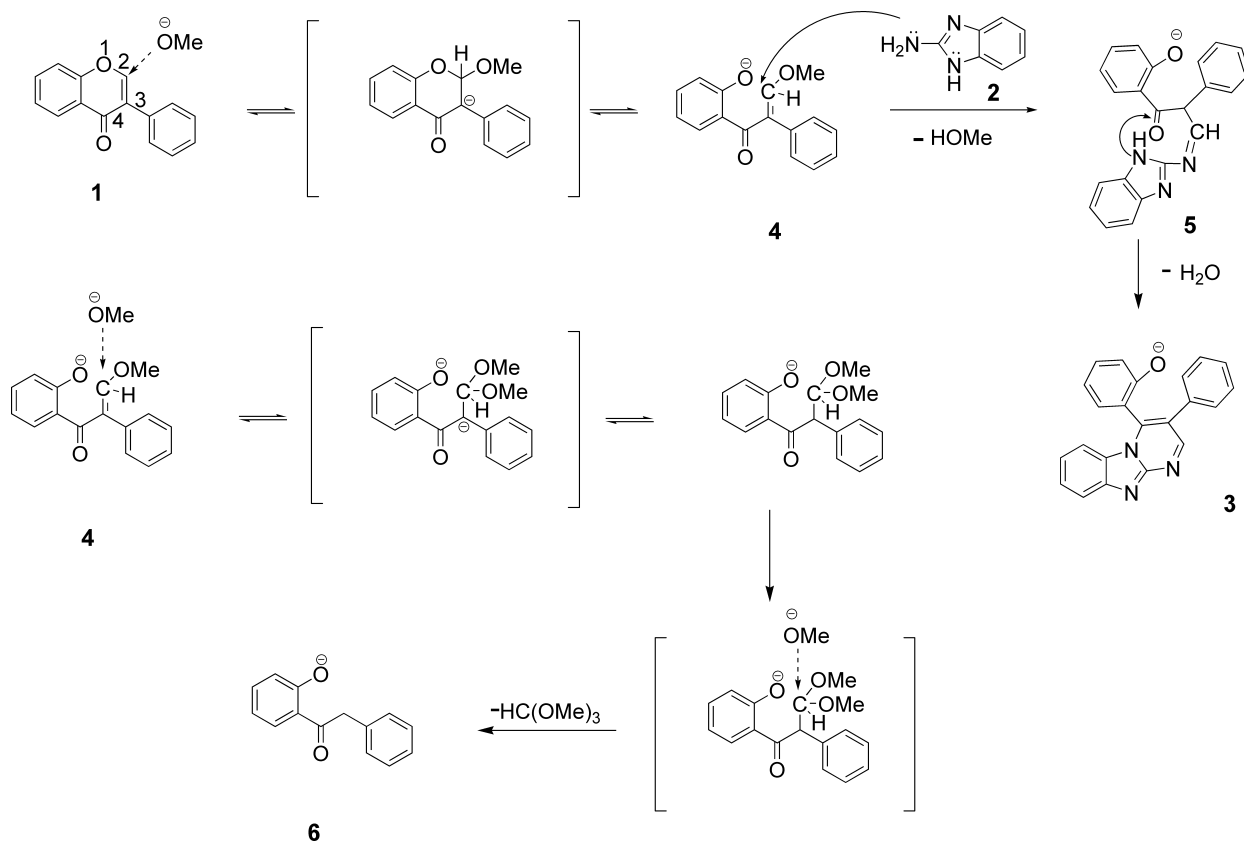
The choice of base was very important for the cyclocondensations of 2-aminobenzimidazole with isoflavone. It was reported that isoflavone will undergo ring-opening when refluxed in the presence of base forming an α , β -unsaturated ketone intermediate **4** (Scheme 3).¹⁹ Subsequent, attack of the primary amine group from the 2-aminobenzimidazole on the β -carbon in **4**, followed by a ring closure reaction between the secondary amine and the carbonyl carbon to produce **3**. Meanwhile, intermediate **4** with a high concentration of base may eliminate methylorthofoemate to generate the byproduct **6**.¹⁹ To identify the optimal variety of the base and its equivalency, a mixture of ipriflavone (2 mmol) and 2-aminobenzimidazole **2** (4 mmol) was refluxed in methanol. Under different equivalency of NaOH and NaOMe, it was found that that 3 equivalency of NaOMe gave the best results (Table 1, Entry 5). In the cyclocondensations reaction, sodium methoxide gave excellent yields, while sodium hydroxide failed to give high yields or reasonable conversion, probably because of the presence of water. In the presence

Table 1. Effects of Base and Its Amount on the Condensation of Ipriflavone with 2-Aminobenzimidazole

entry	base	amount	yield(%) ^a
1	5 mol/L NaOH	2.5 equiv	43
2	5 mol/L NaOH	5 equiv	57
3	NaOMe	1 equiv	61
4	NaOMe	2 equiv	79
5	NaOMe	3 equiv	88
6	NaOMe	4 equiv	72

^a Recrystallized from EtOH.

* To whom correspondence should be addressed. E-mail: zhangzt@snnu.edu.cn. Phone: 86-29-85303940. Fax: 86-29-85303774.

Scheme 1. Methods for Building up the Pyrimido[1,2-*a*]benzimidazole Core**Scheme 2.** Synthesis of 2,3-Diarylpyrimido[1,2-*a*]benzimidazole by the Cyclocondensations of 2-Aminobenzimidazole with Isoflavone**Scheme 3.** Proposed Mechanism for the Formation of **3** and Byproduct

of excess methoxide anions, attack of the methoxide anion on the β -carbon in **4** can produce an orthoester intermediate, which leads to byproduct **5**. It would promote **4** the conversion of **6** instead of **3**. On the other hand, it is harder

to open the isoflavone ring and produce intermediate **4** under the condition of lower concentration base.

In general isoflavone **1** substituted with alkoxy, benzyloxy groups gave high yields. In contrast, the presence of the

Table 2. Synthesis of 2, 3-Diarylpyrimido[1,2-*a*]benzimidazole by the Reaction of Various Isoflavones with 2-Aminobenzimidazole at 65°C in MeOH and Their Isolated Yield (for Details, see Experimental Section)

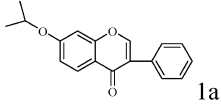
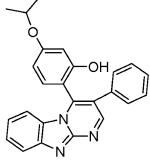
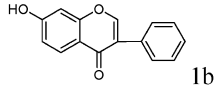
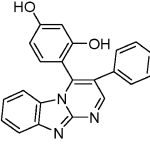
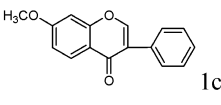
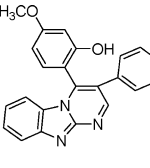
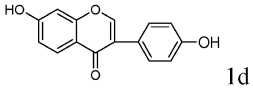
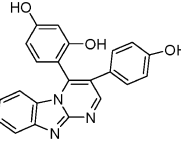
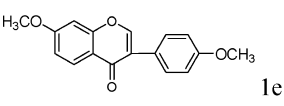
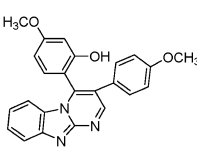
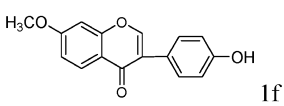
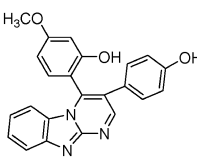
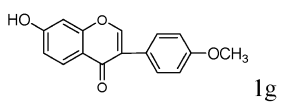
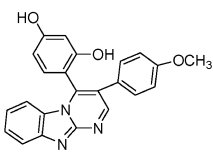
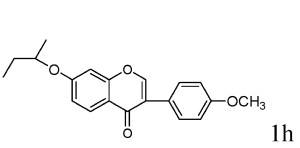
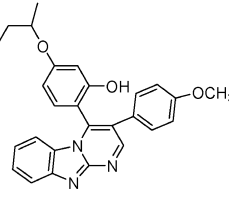
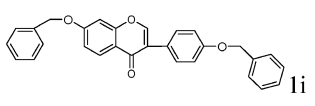
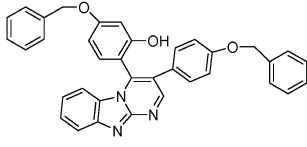
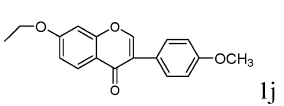
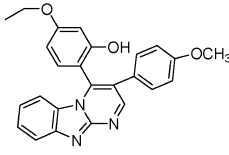
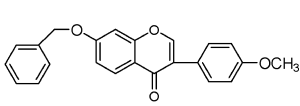
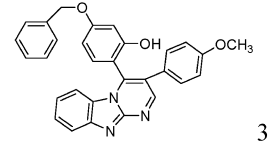
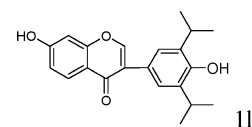
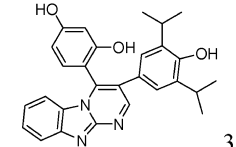
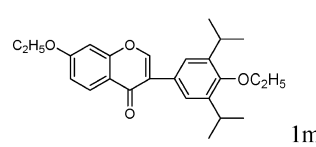
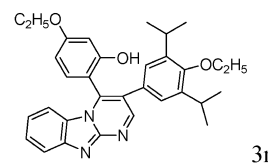
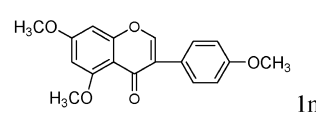
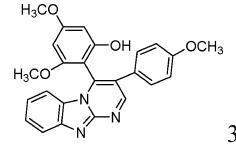
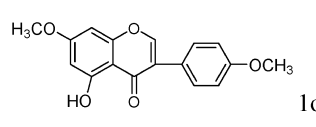
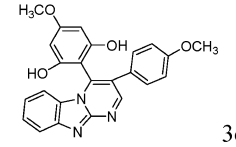
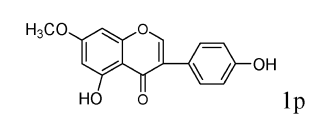
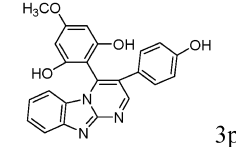
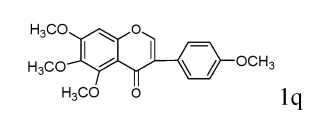
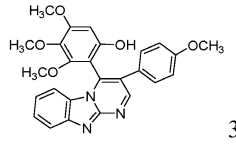
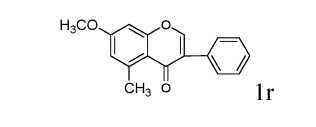
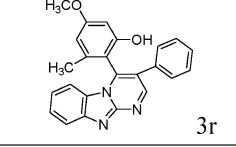
entry	substrate	product&number	time(h)	yield(%) ^a
1	 1a	 3a	8	88
2	 1b	 3b	10	74 ^b
3	 1c	 3c	8	89
4	 1d	 3d	11	71 ^b
5	 1e	 3e	8	90
6	 1f	 3f	8	86
7	 1g	 3g	8	83
8	 1h	 3h	8	92
9	 1i	 3i	8	92
10	 1j	 3j	8	93

Table 2. Continued

entry	substrate	product&number	time(h)	yield(%) ^a
11	 1k	 3k	8	91
12	 1l	 3l	13	77 ^b
13	 1m	 3m	8	95
14	 1n	 3n	8	90
15	 1o	 3o	13	72 ^b
16	 1p	 3p	15	68 ^b
17	 1q	 3q	8	89
18	 1r	 3r	8	93

^a Recrystallized from EtOH. ^b Purified by silica gel column chromatography.

hydroxyl groups gave lower yields. As shown in the Table 2, isoflavones **1a**, **1c**, **1e**, **1h**, **1i**, **1j**, **1k**, **1m**, **1n**, **1q**, and **1r** (Table 2, Entries 1, 3, 5, 8–14 and 18) which do not contain hydroxyl groups, gave yields of **3** of about 90%. Isoflavone with one hydroxyl group, **1b**, **1f**, **1g**, and **1o** (Table 2, Entries 2, 6, 7 and 12) only gave yields of **3** of about 80% while those with two free hydroxyls, **3d**, **3l** (Table 2, Entries 4 and 12) gave yields of roughly 70%. Condensation of trihydroxy isoflavone genistein (4',5,7-trihydroxy-isoflavone) and irisolidone (4',6-dimethoxy-5,7-dihydroxy-isoflavone) with **2** failed to produce product **3**. The yields of **3** are directly dependent on the number of free hydroxyl groups

present on the engaged isoflavone. Because the hydroxyls of isoflavone **1** under basic condition would be oxygen ions, which possess stronger electron donability than alkoxy and benzyloxy groups of the isoflavone, it is not favorable to the condensation reaction. Compounds **3** were characterized by ¹H and ¹³C NMR, HRMS, and IR, and the structure was further unequivocally confirmed by single crystal X-ray diffraction of **3a** which adds sharp evidence for the proposed structure (Figure 1).

The synthesized compound possesses excellent fluorescence property both in solution and solid. The fluorescence spectra of **3a** in the solution and solid are shown in Figure

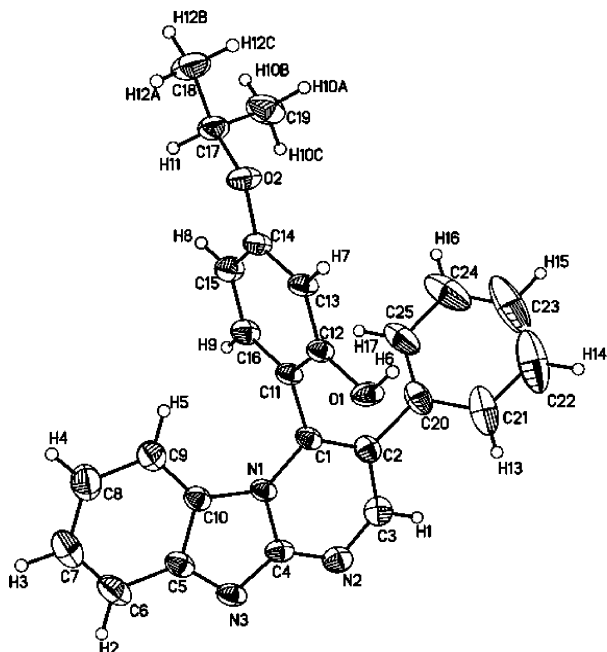


Figure 1. Single-Crystal X-ray structure of **3a**.

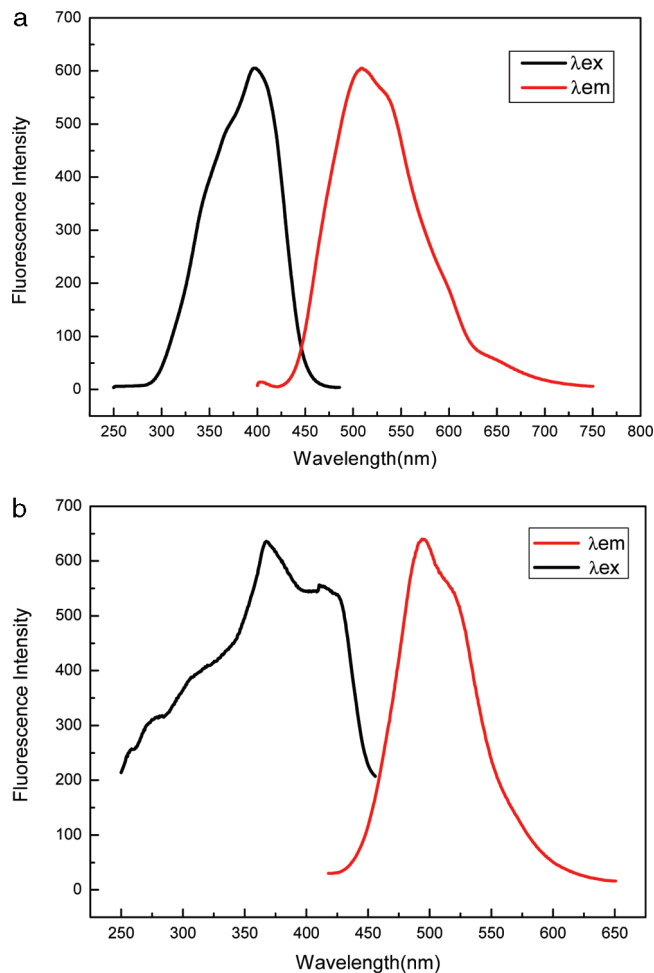


Figure 2. Fluorescence spectrum of **3a**. (a) Fluorescence spectrum of **3a** in ethanol ($c = 1 \times 10^{-4}$ mol/L). (b) Fluorescence spectrum of **3a** as a solid.

2. We found that compounds **3** emit fluorescence with $\lambda_{em} = 490\text{--}512$ nm in the range of 450–550 nm when they are irradiated at 390 nm in the solid state, and they emit

fluorescence with $\lambda_{em} = 440\text{--}445$ nm in the range of 390–470 nm when they are irradiated at 350 nm in ethanol. The structural feature of molecules that fluoresce is that they possess a first singlet excited state $S_1(\pi, \pi^*)$ in a rigid and conjugated system. The more rigid the structure and the more conjugated its system, the stronger its fluorescence.²⁰ That the fused 2,3-diarylpyrimido[1,2-*a*]benzimidazole **3** possesses excellent property of fluorescence confirms that its structure meets these requirements of rigidity and conjugation.

Conclusions

In summary, we have developed a useful method for the construction of fused pyrimido[1,2-*a*]benzimidazole derivatives by the cyclocondensation of 2-aminobenzimidazole with isoflavone in methanol and the presence of 3 equiv of sodium methoxide. It is an efficient and regioselective approach towards the synthesis 2,3-disubstituted pyrimido[1,2-*a*]benzimidazole. The yields of pyrimido[1,2-*a*]benzimidazole derivatives are excellent, most between 68%–93%. Furthermore, 2,3-diarylpyrimido[1,2-*a*]benzimidazoles exhibit excellent fluorescence. When solids of 2,3-diarylpyrimido[1,2-*a*]benzimidazoles are irradiated at 390 nm, they emit a green fluorescence.

Experimental Section

General Procedure. The corresponding isoflavones **1** (2 mmol), 2-aminobenzimidazole **2** (4 mmol), and sodium methoxide (6 mmol) were refluxed in methanol (15 mL) for 8–15 h. All reactions were monitored by TLC, which showed the disappearance of **1** that was indicative of the reaction being complete. The reaction mixture was added into water (30 mL) and adjusted to neutrality with a solution of 5% HCl. A yellow precipitate appeared and was filtered. The yellow precipitate was dissolved in a solution of 10% HCl (10 mL) and filtered. The mother liquid was neutralized with sodium hydroxide until crude product was completely precipitated. The crude product was filtered and recrystallized from ethanol or purified by column chromatography on silica gel using chloroform–methanol (10:1) to give the corresponding pure product.

2-(2-Hydroxyl-4-isopropoxyphenyl)-3-phenyl-pyrimido[1,2-*a*]benzimidazole (Entry **3a, Table 2).** Yellow solid, M.p.: 289.3–289.7 °C. ¹H NMR: 1.30 (s, 6H), 4.60 (t, 1H), 6.51 (s, 1H), 6.60 (d, 1H, $J = 8.4$ Hz), 7.08 (t, 1H), 7.11 (s, 1H), 7.36 (m, 5H), 7.47 (t, 1H), 7.88 (d, 1H, $J = 8.1$ Hz), 8.89 (s, 1H), 10.14 (s, 1H). ¹³C NMR: 21.7, 69.6, 103.1, 107.3, 110.6, 114.5, 119.3, 121.2, 121.6, 125.5, 127.4, 127.5, 127.8, 128.2, 129.6, 131.1, 134.7, 144.4, 144.7, 150.6, 157.1, 160.5. IR ν KBr max cm^{-1} : 3419.5, 2959.6, 2924.8, 1599.8, 1489.6, 1448.9, 1387.9, 1349.7, 1254.9, 1175.9, 738.8. HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{25}H_{22}N_3O_2$, 396.1707; found, 396.1718; $\lambda_{ex}/\lambda_{em} = 372/501$ (solid); $\lambda_{ex}/\lambda_{em} = 396/512$ (in ethanol, $c = 1 \times 10^{-4}$ mol/L).

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and Technology Key Project of Xi'an of Shaanxi province (No: FY07075).

Supporting Information Available. Data includes synthetic procedures; characterization data, copies of ^1H and ^{13}C NMR spectra, fluorescence spectrum of all compounds; crystal and structure refinement data for **3a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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