Quinolone Analogs 11: Synthesis of Novel 4-Quinolone-3-carbohydrazide Derivatives with Antimalarial Activity

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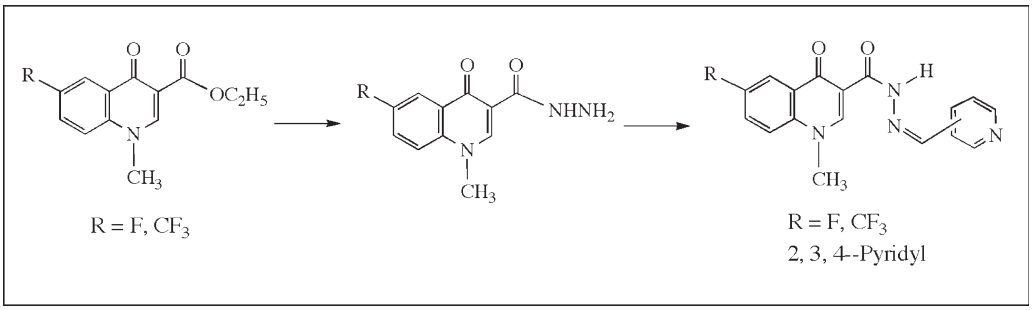

The reaction of the 6-substituted 1-methyl-4-quinolone-3-carboxylates **10a,b** with hydrazine hydrate gave the 3-carbohydrazides **7a,b**, respectively, whose reaction with 2-, 3-, and 4-pyridinecarbaldehydes afforded the 3-(N^2-pyridylmethylene)carbohydrazides **8a–c** and **9a–c**. The Curtius rearrangement of compound **7b** provided the *N*,*N*′-bis(4-quinolon-3-yl)urea **14** presumably *via* the 3-carboazide **11** and then 3-isocyanate **12**. Compounds **7a**, **8a**, and **9a** were found to possess antimalarial activity from the *in vitro* screening data.

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INTRODUCTION

In previous papers [1–9], we reported the synthesis of the 1-alkyl-4-oxopyridazino[3,4-*b*]quinoxalines **1** (Chart 1) as candidates of antibacterial quinolone analogs [1–10], which were found to have antibacterial, antifungal, and/or algicidal activities [3–6]. Thereafter, we changed the target ring system from the pyridazino[3,4-*b*]quinoxalin-4(1*H*)-one to 4-quinolone such as new quinolones **2** to search for novel biologically active compounds. In literature [11], quinolones and new quinolones **2** have been known as antibacterial agents inhibiting DNA gyrase and clinically used in the world. In addition, quinolones have also been studied on the application to antiviral agent, as quinolones interact with DNA topoisomerase. In fact, the 4-quinolone-3-carboxamide **3** was reported to show antiviral activity [12]. This is an example for the activity conversion by the substituent change of the 3-carboxyl into 3-carboxamide group in quinolones. Moreover, the 4-quinolone-3-[*N*-(4-chlorobenzyl)]carboxamide **4** is a non-nucleoside antiviral agent inhibiting herpesvirus polymerase [13], and the 4-quinolone-3-[*N*-(4-chlorobenzyl)]carboxamide **5** is an antiviral agent for the treatment of infections caused by viruses belonging to the herpesvirus family [14].

In this context, we also tried to modify the structure of new quinolones **2**, following the above examples for the activity conversion. At first, we transferred the base moiety of new quinolones **2** from the C7-position to the N1-side chain, leading to the production of the quinolones **6** [10] (Chart 2). As the result, we found that the 4-pyridyl derivative of quinolones **6** (X = H, $R^1 = R^2 = C_2H_5$) exhibited antimalarial activity. Some antimalarial quinolones [15–17] as well as quinine and chloroquin have been introduced in a recent review [18], which also includes 4-aminoquinolines, 8-aminoquinolines, isoquinolines, 9-aminoacridines, and many other related compounds. Moreover, pyridinium dimers [19–21] and carbocyclic adenine nucleosides [22–25] were synthesized as candidates of antimalarial agents.

In continuation of our works, we further synthesized the quinolones **8** and **9** *via* the quinolone-3-carbohydrazides **7** based on the concept shifting a pyridyl moiety from the N1-side chain to C3-side chain. Subsequently,

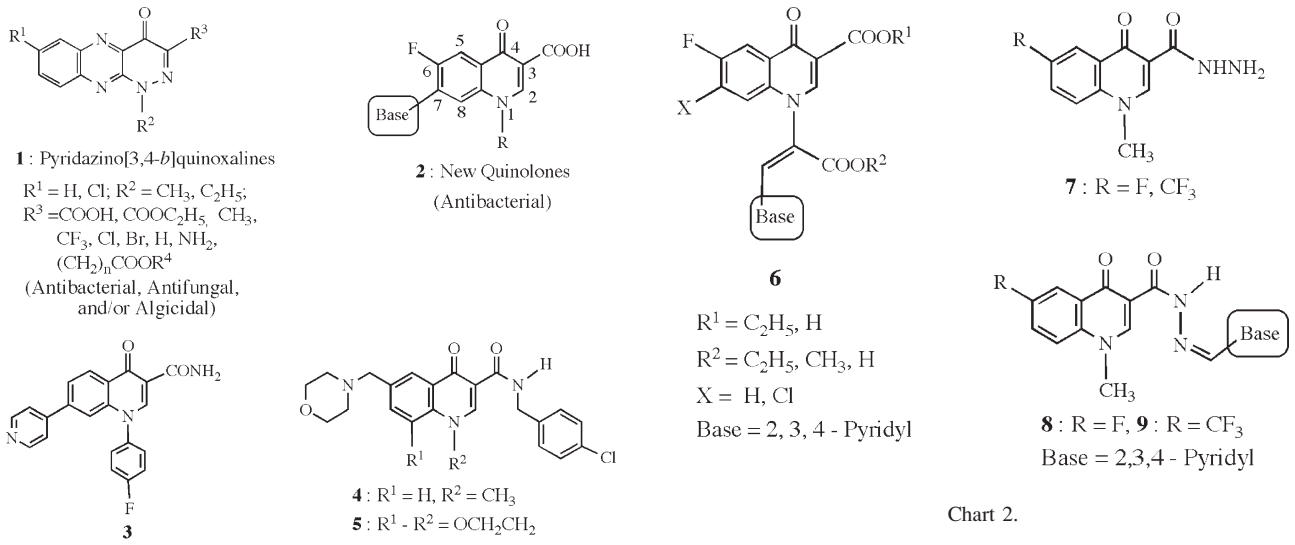
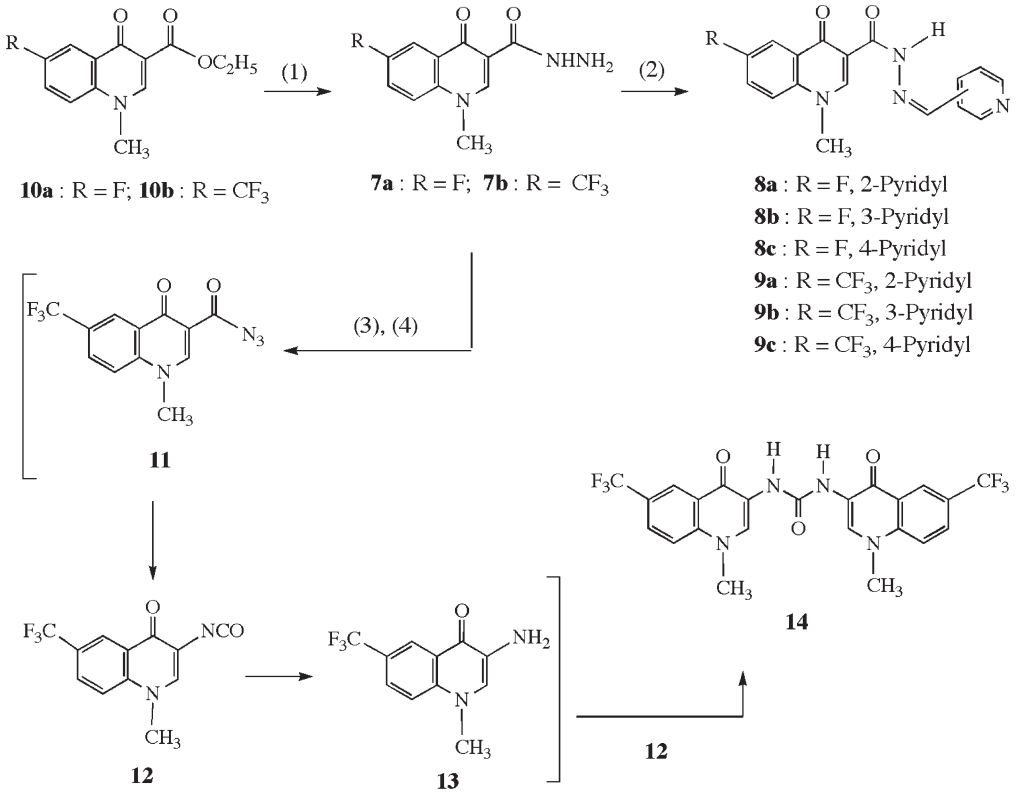


Chart 1.

Chart 2.

we evaluated the *in vitro* antimalarial activity for compounds **7**, **8**, and **9**, wherein compounds **7a**, **8a**, and **9a** (Scheme 1) were found to possess inhibitory activity to *Plasmodium falciparum* (Table 2). In our extended works, this antimalarial activity was clarified to diminish remarkably when the N1-methyl group of compounds **7a**, **8a**, and **9a** was substituted with the acrylate moiety included in compounds **6** [26]. Thus, we have accomplished the serial synthesis of antimalarial quinolones by shifting the basic moiety from the C6-position of new

Scheme 1



Reagent and reaction condition: (1) $NH_2NH_2 \bullet H_2O$ in ethanol; (2) pyridine-2-, 3-, 4-carbaldehyde in *N*,*N*-dimethylformamide; (3) $NaNO_2$ / H_2O / acetic acid at room temperature; (4) heat

Table 1

^{13}C-NMR spectral data for compounds **7a** and **8a**.[a]

Carbon	Compound **7a**	**8a**
2-C	148.2	149.7
3-C	109.7	109.5
4-C	174.1	174.7
4a-C	128.3	128.6
5-C	110.2	110.6
6-C	159.2	159.8
7-C	121.3	121.9
8-C	120.6	121.2
8a-C	136.6	137.0
3-CONN	163.5	161.5
CH_3	41.3	41.9
Pyridyl 2-C	–	154.3
Pyridyl 3-C	–	120.6
Pyridyl 4-C	–	136.9
Pyridyl 5-C	–	124.6
Pyridyl 6-C	–	149.7

[a] Measured in deuteriodimethyl sulfoxide.

quinolone to N1-position of compound **6** and then to C3-position of compounds **7**, **8**, and **9** (Chart 2), successively. This article describes the synthesis and antimalarial activity of the 4-quinolones **7a,b**, **8a–c**, and **9a–c**.

RESULTS AND DISCUSSION

Synthesis of quinolone derivatives. The 6-substituted 1-methyl-4-quinolone-3-carboxylates **10a,b** were synthesized from 6-substituted 4-hydroxyquinoline-3-carboxylates by known methods [27,28]. The reaction of compounds **10a,b** with hydrazine hydrate gave the 3-carbohydrazides **7a,b**, whose reaction with 2-, 3-, and 4-pyridinecarbaldehydes afforded the 3-[N^2-(2-, 3-, and 4-pyridylmethylene)]carbohydrazides **8a–c** and **9a–c**, respectively (Scheme 1).

The Curtius rearrangement of compound **7b** provided the *N*,*N*′-bis(6-trifluoromethyl-4-quinolon-3-yl)urea **14**, wherein 3-amino intermediate **13** was not isolated presumably due to the slow hydrolysis of 3-isocyanate intermediate **12** and due to the fast addition of 3-amino intermediate **13** to 3-isocyanate intermediate **12**. The isolation of the *N*,*N*′-bis(6-trifluoromethyl-4-quinolon-3-yl)urea **14**, but not the 3-amino derivative **13**, may be attributed to an electron donating character of the N1 moiety.

The structural assignment of new compounds **7**, **8**, **9**, and **14** was based on the analytical and spectral data. Table 1 shows the carbon chemical shifts for our typical quinolones **7a** and **8a** assigned by the gHSQC and gHMBC spectral data.

Antimalarial activity. The *in vitro* screening to antimalarial activity was carried out for compounds **7a,b**, **8a–c**, **9a–c**, and **14** according to a method described in previous papers [10,29], and the data are shown in Table 2. The IC_{50} values in micromolar concentraton for our 3-carbohydrazides **7a**, **8a**, and **9a**, and reference compounds (quinine and chloroquin) are 8.7, 3.3, 6.2, and (0.110, 0.018) to *P. falciparum* FCR-3 strain, respectively, and the above values of our 3-carbohydrazides are referred as effective level. The 2-pyridyl moiety results in a good antimalarial activity. The IC_{50} values in micromolar concentration for compounds **8b** and **9b** (3-pyridyl), **8c** and **9c** (4-pyridyl), and **14** (dimer) are above 100, which is referred as not effective level.

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The IR spectra (potassium bromide) were recorded with a JASCO FT/IR-200 spectrometer. The NMR spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The gHSQC and gHMBC spectra were measured with Varian INOVA 600 spectrometer. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

6-Fluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carbohydrazide 7a. A solution of compound **10a** (5.0 g) and an excess amount of hydrazine hydrate (100% purity, 10.0 g) in ethanol (150 mL) was refluxed with stirring for 5 h to precipitate colorless needles **7a**, which were collected by filtration and washed with ethanol to give an analytically pure sample (4.2 g, 89%); mp 273–274°; IR: ν 3220, 3040, 1660 cm^{-1}; ms: *m*/*z* 235 (M^+); NMR (deuteriodimethyl sulfoxide): 10.56 (s, 1H, NH), 8.83 (s, 1H, 2-H), 7.95 (dd, J = 3.0, 9.0 Hz, 1H, 5-H), 7.90 (dd, J = 4.5, 10.0 Hz, 1H, 8-H), 7.75 (ddd, J = 3.0, 8.0, 10.0 Hz, 1H, 7-H), 5.57 (s, 2H, NH_2), 4.01 (s, 3H, CH_3). Anal. Calcd. For $C_{11}H_{10}FN_3O_2$: C, 56.17; H, 4.29; N, 17.86. Found: C, 56.28; H, 4.47; N, 17.80.

Table 2

In vitro antimalarial activity of compounds **7**, **8**, **9**, and **14**.[a]

Compound	R	Base position	IC_{50} (μmol)
Quinine			0.110
Chloroquin			0.018
7a	F	–	8.7
7b	CF_3	–	>100
8a	F	2-Pyridyl	3.3
8b	F	3-Pyridyl	>100
8c	F	4-Pyridyl	>100
9a	CF_3	2-Pyridyl	6.2
9b	CF_3	3-Pyridyl	>100
9c	CH_3	4-Pyridyl	>100
14	CH_3	–	>100

[a] Antimalarial activity was examined to chloroquin-sensitive *P. falciparum* FCR-3 strain.

1,4-Dihydro-1-methyl-4-oxo-6-trifluoromethylquinoline-3-carbohydrazide 7b. A solution of compound **10b** (5.0 g) and an excess amount of hydrazine hydrate (100% purity, 10.0 g) in ethanol (150 mL) was refluxed with stirring for 5 h. Cooling of the solution to room temperature precipitated colorless needles **7b**, which were collected by filtration and washed with ethanol to give an analytically pure sample (4.4 g, 92%); mp 262–263°; IR: ν 3320, 3280, 1680, 1655 cm^{-1}; ms: *m/z* 285 (M^+); NMR (deuteriodimethyl sulfoxide): 10.46 (s, 1H, NH), 8.90 (s, 1H, 2-H), 8.52 (d, J = 2.0 Hz, 1H, 5-H), 8.13 (dd, J = 9.0, 2.0 Hz, 1H, 7-H), 8.01 (d, J = 9.0 Hz, 1H, 8-H), 4.62 (s, 2H, NH_2), 4.03 (s, 3H, CH_3). Anal. Calcd. For $C_{12}H_{10}F_3N_3O_2$: C, 50.53; H, 3.53; N, 14.73. Found: C, 50.27; H, 3.64; N, 14.44.

6-Fluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-[N^2-(2-, 3-, and 4-pyridylmethylene)]carbohydrazides 8a–c and 1,4-dihydro-1-methyl-4-oxo-6-trifluoromethylquinoline-3-[N^2-(2-, 3-, and 4-pyridylmethylene)]carbohydrazides 9a–c. ***General procedure.*** A solution of the 3-carbohydrazide **7a** (1.0 g, 4.26 mmol) or **7b** (1.0 g, 3.51 mmol) and 2-, 3-, or 4-pyridinecarbaldehyde (0.68 g, 6.30 mmol for **7a**; 0.56 g, 5.27 mmol for **7b**) in *N,N*-dimethylformamide (30 mL) was refluxed for 2 h. Cooling of the solution to room temperature precipitated colorless crystals **8a–c** or **9a–c**, which were collected by filtration and washed with ethanol to give an analytically pure sample. Evaporation of the filtrate *in vacuo* afforded additional product, which was recrystallized from *N,N*-dimethylformamide to provide colorless needles.

2-Pyridyl derivative **8a** was obtained in 80% yield (1.10 g); mp 263–264°; IR: ν 3060, 1665 cm^{-1}; ms: *m/z* 324 (M^+); NMR (deuteriotrifluoroacetic acid): 9.20 (s, 1H, 2-H), 8.67 (d, J = 8.0, 1H, pyridine 6-H), 8.58 (dd, J = 8.0, 8.0 Hz, 1H, pyridine 4-H), 8.54 (s, 1H, hydrazone CH), 8.03 (dd, J = 8.0, 3.0 Hz, 1H, 5-H), 8.20 (d, J = 8.0 Hz, 1H, pyridine 3-H), 7.98 (dd, J = 8.0, 8.0 Hz, 1H, pyridine 5-H), 7.88 (dd, J = 9.0, 3.5 Hz, 1H, 8-H), 7.69 (ddd, J = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 4.18 (s, 3H, CH_3). Anal. Calcd. For $C_{17}H_{13}FN_4O_2{\cdot}H_2O$: C, 59.65; H, 4.42; N, 16.37. Found: C, 59.81; H, 4.35; N, 16.23.

3-Pyridyl derivative **8b** was obtained in 97% yield (1.34 g); mp above 300°; IR: ν 3060, 1675 cm^{-1}; ms: *m/z* 324 (M^+); NMR (deuteriotrifluoroacetic acid): 9.24 (s, 1H, 2-H), 9.08 (s, 1H, pyridine 2-H), 9.02 (d, J = 8.0 Hz, 1H, pyridine 6-H), 8.67 (d, J = 6.0 Hz, 1H, pyridine 4-H), 8.49 (s, 1H, hydrazone CH), 8.05 (dd, J = 8.0, 2.5 Hz, 1H, 5-H), 7.99 (dd, J = 8.0, 6.0 Hz, 1H, pyridine 5-H), 7.91 (dd, J = 9.0, 4.0 Hz, 1H, 8-H), 7.72 (ddd, J = 9.0, 7.0, 2.5 Hz, 1H, 7-H), 4.21 (s, 3H, CH_3). Anal. Calcd. For $C_{17}H_{13}FN_4O_2$: C, 62.96; H, 4.04; N, 17.28. Found: C, 63.02; H, 4.11; N, 17.18.

4-Pyridyl derivative **8c** was obtained in 93% yield (1.29 g); mp above 300°; IR: ν 3065, 1680 cm^{-1}; ms: *m/z* 324 (M^+); NMR (deuteriotrifluoroacetic acid): 8.80 (s, 1H, 2-H), 8.47 (d, J = 7.0 Hz, 2H, pyridine 2,6-H), 8.23 (s, 1H, hydrazone CH), 8.09 (d, J = 7.0 Hz, 2H, pyridine 3,5-H), 7.68 (dd, J = 10.0, 3.5 Hz, 1H, 5-H), 7.59 (dd, J = 11.0, 5.0 Hz, 1H, 8-H), 7.72 (ddd, J = 11.0, 9.0, 3.5 Hz, 1H, 7-H), 3.87 (s, 3H, CH_3). Anal. Calcd. For $C_{17}H_{13}FN_4O_2$: C, 62.96; H, 4.04; N, 17.28. Found: C, 63.13; H, 4.21; N, 17.15.

2-Pyridyl derivative **9a** was obtained in 86% yield (1.13 g); mp above 300°; IR: ν 3140, 3055, 1675 cm^{-1}; ms: *m/z* 374 (M^+); NMR (deuteriotrifluoroacetic acid): 9.14 (s, 1H, 2-H), 8.58 (d, J = 7.0 Hz, 1H, pyridine 6-H), 8.56 (s, 1H, 5-H), 8.49 (dd, J = 8.0, 8.0 Hz, 1H, pyridine 4-H), 8.45 (s, 1H, hydrazone CH), 8.10 (d, J = 8.0 Hz, 1H, pyridine 3-H), 8.02 (d, J = 9.0 Hz, 1H, 7-H), 7.89 (dd, J = 8.0, 7.0 Hz, 1H, pyridine 5-H), 7.82 (d, J = 9.0 Hz, 1H, 8-H), 4.07 (s, 3H, CH_3). Anal. Calcd. For $C_{18}H_{13}F_3N_4O_2$: C, 57.76; H, 3.50; N, 14.97. Found: C, 57.67; H, 3.57; N, 14.85.

3-Pyridyl derivative **9b** was obtained in 80% yield (1.05 g); mp above 300°; IR: ν 3050, 1670 cm^{-1}; ms: *m/z* 374 (M^+); NMR (deuteriotrifluoroacetic acid): 9.21 (s, 1H, 2-H), 9.05 (s, 1H, pyridine 2-H), 9.00 (d, J = 8.0 Hz, 1H, pyridine 6-H), 8.63 (d, J = 8.0 Hz, 1H, pyridine 4-H), 8.62 (d, J = 2.0 Hz, 1H, 5-H), 8.44 (s, 1H, hydrazone CH), 8.06 (dd, J = 9.0, 2.0 Hz, 7-H), 7.95 (dd, J = 8.0, 8.0 Hz, 1H, pyridine 5-H), 7.87 (d, J = 9.0 Hz, 1H, 8-H), 4.11 (s, 3H, CH_3). Anal. Calcd. For $C_{18}H_{13}F_3N_4O_2$: C, 57.76; H, 3.50; N, 14.97. Found: C, 57.69; H, 3.57; N, 14.69.

4-Pyridyl derivative **9c** was obtained in 82% yield (1.08 g); mp above 300°; IR: ν 3060, 1680 cm^{-1}; ms: *m/z* 374 (M^+); NMR (deuteriotrifluoroacetic acid): 9.19 (s, 1H, 2-H), 8.60 (d, J = 2.0 Hz, 1H, 5-H), 8.59 (d, J = 7.0 Hz, 2H, pyridine 2,6-H), 8.42 (s, 1H, hydrazone CH), 8.34 (d, J = 7.0 Hz, 2H, pyridine 3,5-H), 8.04 (d, J = 9.0, 2.0 Hz, 1H, 7-H), 7.84 (d, J = 9.0 Hz, 1H, 8-H), 4.09 (s, 3H, CH_3). Anal. Calcd. For $C_{18}H_{13}F_3N_4O_2$: C, 57.76; H, 3.50; N, 14.97. Found: C, 57.66; H, 3.57; N, 14.86.

***N,N′*-Bis(1,4-dihydro-1-methyl-4-oxo-6-trifluoromethylquinolin-3-yl) urea 14.** A solution of sodium nitrite (0.36 g, 5.26 mmol) in water (10 mL) was added to a solution of compound **7b** (1.0 g, 3.50 mmol) in acetic acid (20 mL) with stirring for 30 min at room temperature to precipitate colorless crystals. Then, the reaction mixture was refluxed for 1 h to precipitate pale yellow needles **14**, which were collected by filtration and washed with ethanol to afford an analytically pure sample (0.51 g, 57%). Herein, compounds **11**, **12**, and **13** were not isolated from the above filtrate. Compound **14** had mp above 300°; IR: ν 3450, 3320, 3100, 1640, 1580 cm^{-1}; ms: *m/z* 510 (M^+); NMR (deuteriotrifluoroacetic acid): 8.97 (s, 2H, 2-H), 8.83 (d, J = 2.0 Hz, 2H, 5-H), 8.17 (dd, J = 9.0, 2.0 Hz, 2H, 7-H), 8.09 (d, J = 9.0 Hz, 2H, 8-H), 4.33 (s, 6H, CH_3). Anal. Calcd. For $C_{23}H_{16}F_6N_4O_3{\cdot}1.5H_2O$: C, 51.40; H, 3.56; N, 10.43. Found: C, 51.66; H, 3.56; N, 10.41.

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