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**Short communication**

# Dibenzo[1,6]naphthyridindiones as modified quinolone antibacterials

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**Abstract** – A series of dibenzo[1,6]naphthyridindiones, synthesized as modified quinolones, in which the usual carboxylic group was replaced by a heterocyclic amide function, was evaluated for antibacterial activity. None of the target compounds showed any significant antibacterial activity. Semiempirical molecular orbital AM1 calculations allowed us to hypothesize that the lack of activity could depend on amide tautomeric equilibrium. © Elsevier, Paris

**dibenzonaphthyridindiones / tetracyclic modified quinolones / antibacterials**

## 1. Introduction

Quinolones are a very important class of extremely potent and broad-spectrum antibacterial agents which are widely used in the treatment of infections [1–3]. These synthetic antibacterial agents target the bacterial topoisomerase II (DNA-gyrase) [4–6], a key enzyme in DNA replication, and are structurally characterized by a combination of 1-substituted-1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety, the pharmacophoric unit responsible for its intrinsic activity, linked to an aromatic or heteroaromatic ring. In recent manipulations of the quinolone structure, the carboxylic group of the pharmacophoric unit has been modified to provide a surrogate such as the heterocyclic amide in the isothiazoloquinoline derivatives **1** [7, 8]. These modified quinolones showed excellent activity against various bacteria [9]. The replacement of the carboxylic acid moiety with a hydroxyl function, such as in benzonaphthyridine derivative **2** (AT 5755) [10] and benzoxazinonaphthyridine derivatives **3** [11] resulted in good antibacterial activity (*figure 1*). These successful modifications of the carboxylic moiety led us to speculate whether replacing the carboxylic group with a heterocyclic amide function, by annelling the 1,2-dihydroquinolone moiety at C-2 and C-3 positions of the basic quinolone structure, would give compounds which maintain antimicrobial activity.

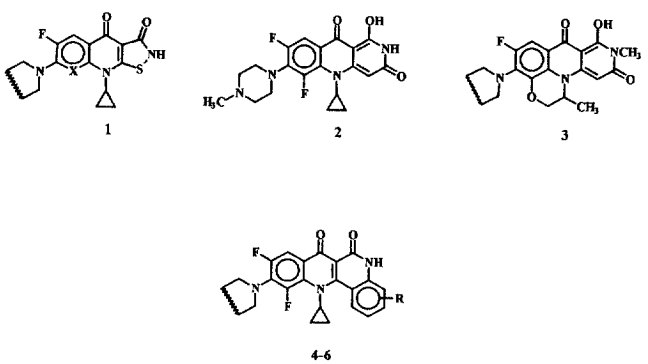


**Figure 1.**

In this paper we report the synthesis and antimicrobial activity of a series of dibenzo[1,6]naphthyridindione derivatives **4a**, **5a–d** and **6a** (*figure 2*).

## 2. Chemistry

The synthetic strategy, depicted in *figure 2*, first involved the preparation of the key ethyl cyclopropylamineacrylates **10–12** which were obtained by reacting

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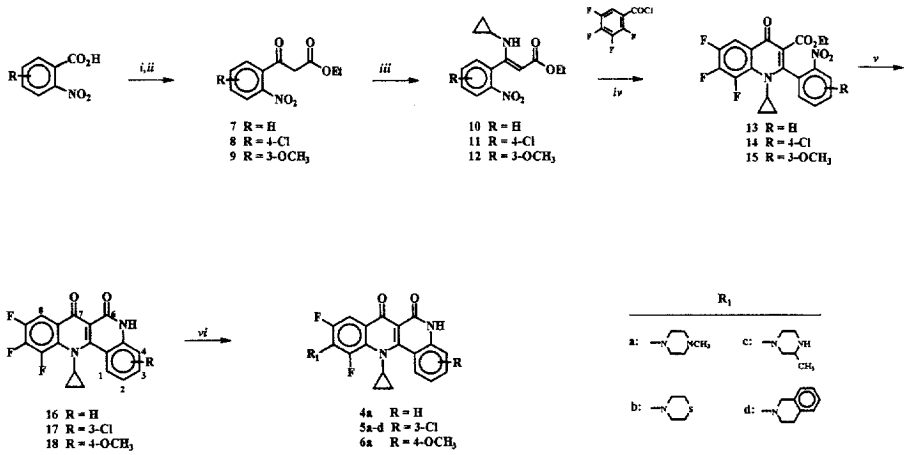


**Figure 2.** Reagents: (i) $SOCl_2$, reflux; (ii) $Li_2(O_2CCHCO_2Et)$; (iii) cyclopropylamine; (iv) DBU; (v) Ni-Raney, $H_2$, EtOH; (vi) $R_1H$, $CH_3CN$.

cyclopropylamine with suitable β-ketoesters **7–9**. The target compounds **4a**, **5a–d**, **6a** were then obtained by a subsequent three-step sequence involving: the reaction of acrylate **10–12** with tetrafluorobenzoyl chloride in the presence of DBU to obtain 2-phenylquinolones **13–15**, intramolecular cyclization of these by Ni-Raney reduction to give tetracyclic dibenzo[1,6]naphthyridindiones **16–18**, and finally, nucleophylic substitution at C-10 with selected heterocyclic bases.

## 3. Results and discussion

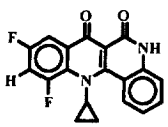
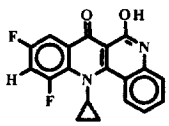
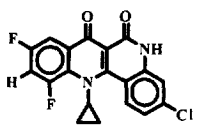
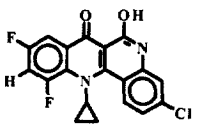
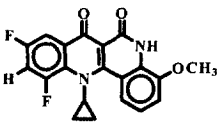
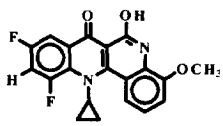
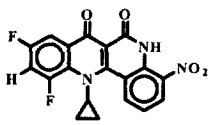
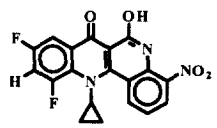
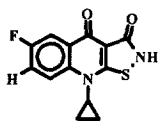
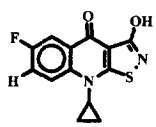
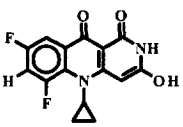
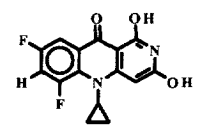
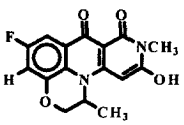
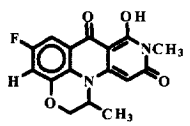
The antibacterial activity of synthesized compounds **4a**, **5a–d** and **6a** was tested against seven Gram-negative strains (*E. coli, E. cloacae, P. vulgaris, P. stuardii, K. pneumoniae, S. enteritidis* and *P. aeruginosa*) and three Gram-positive strains (*S. faecalis, S. aureus* and *D. epidermidis*). *In vitro* bacterial susceptibility (MIC) was determined by conventional agar dilution procedure [12].

None of the target derivatives showed any antibacterial activity against the strain tested (MIC > 128 μg/mL) with the exception of **5d** which showed a modest activity against Gram-positive bacteria (MIC = 4 and 16 μg/mL against *S. epidermidis* and *S. aureus*, respectively). All compounds were also inactive to inhibit the supercoiling activity of DNA-gyrase with $IC_{50}$ values ranging from 100 to >140 μg/mL. Based on these results, we hypothesize that the lack of activity of these modified quinolones is due to the very limited ability of amide linkage to enolize, and it therefore fails to mimic the carboxylic group in the interaction with cleavable-complex (DNA/DNA-gyrase) identified in the proposed quinolone mode of action [13–17].

For all synthesized naphthyridindiones, the $^1$H-NMR spectra showed only one proton, as an exchangeable broad singlet, at chemical shift > 10 ppm, which did not allow us to discriminate between the amide or enol form. In their IR spectra, two absorption bands which could be assigned to the stretching vibrations of enolic OH and amidic NH were observed, one ranging from 3585 to 3550 $cm^{-1}$ and the other from 3550 to 3500 $cm^{-1}$. This indicates the presence of both tautomeric forms.

In order to investigate the tautomeric equilibrium of the amide linkage, the amide derivatives **4–6** were compared with the active isothiazoloquinoline **1**, benzonaphthyridine **2** and benzoxazinonaphthyridine **3** optimizing the geometries and calculating the heats of formation ($\Delta H_f$) of each tautomer by means semiempirical molecular orbital AM1 method, both in gas phase and in acqueous solution [18]. Since the heterocyclic bases would not affect the calculations of amide tautomeric linkage, they were replaced by a hydrogen atom; the study was therefore carried out on their relative models. In order to evaluate the effect on tautomeric equilibrium of amide linkage also due to the presence in C-4 position of an electron-withdrawing substituent, the heats of formation were also calculated for the 4-nitroderivative model [19]. The calculated $\Delta H_f$ values, reported in *table I*, show that, while for the isothiazoloquinoline,

**Table I.** Calculated AM1 heats of formation ($\Delta H_f$) in gas phase and aqueous solution for tautomeric forms of modified quinolones.

| Keto form | $\Delta H_f$ [a] (kcal/mol) | | Enol form | $\Delta H_f$ [a] (kcal/mol) | |
|---|---|---|---|---|---|
| | aq. phase | gas phase | | aq. phase | gas phase |
|  | –60.680 | –35.230 |  | –57.010 | –30.320 |
|  | –67.219 | –41.519 |  | –63.962 | –36.710 |
|  | –101.690 | –71.795 |  | –94.464 | –63.957 |
|  | –48.820 | –29.431 |  | –41.202 | –21.700 |
|  | –22.348 | –9.937 |  | –24.087 | –11.538 |
|  | –126.365 | –98.461 |  | –130.388 | –100.289 |
|  | –143.591 | –115.417 |  | –149.451 | –123.428 |

[a] The heats of formation $\Delta H_f$ of each tautomer were calculated with $\varepsilon = 1$ (corresponding to the gas phase) and $\varepsilon = 78$ (water).

benzonaphthyridine and benzoxazinonaphthyridine models the enol form is the major tautomer, for dibenzonaphtyridine models the keto-form is the more stable tautomer. The presence of electron-donating group ($OCH_3$) or electron-withdrawing group ($NO_2$) at C-4 position did not affect the acidity of nitrogen proton. These results strenghten the hypothesis that, to ensure antimicrobial activity, the amide group should be predominantly in the enolic form in order to mimic the acid function as happens in isothiazoloquinoline derivatives **1**, benzonaphthyridine **2** and benzoxazinonaphthyridine **3**, but not in the dibenzonaphthyridindione derivatives **4–6**.

## 4. Experimental protocols

Melting points were determined in capillary tubes (Büchi melting point apparatus) and are uncorrected. Elemental analyses were performed on a Carlo Erba elemental analyzer, Model 1106, and the data for C, H,

and N are within ±0.4% of the theoretical values. $^1$H-NMR spectra were recorded at 200 MHz (Bruker AC-200 spectrometer) with $Me_4Si$ as internal standard. Chemical shifts are given in ppm (δ) and the spectral data are consistent with the assigned structures. The IR spectra were recorded on a Perkin-Elmer 1725X FT infrared spectrometer. Reagents and solvents were purchased from common commercial suppliers and used as received. Column chromatography separations were carried out on Merck silica gel 40 (mesh 70–230). Organic solutions were dried over anhydrous $Na_2SO_4$ and concentrated with a Büchi rotary evaporator at low pressure. Yields are of purified product and were not optimized. All starting materials were commercially available unless otherwise indicated.

*4.1. Ethyl 4-chloro-2-nitro-β-oxobenzenepropanoate* ***8***

A mixture of 4-chloro-2-nitrobenzoic acid (5 g, 25 mmol) and thionyl chloride (10 mL) was refluxed for 4 h. The excess thionyl chloride was removed by distillation under reduced pressure to give 4-chloro-2-nitrobenzoyl chloride as a mobile oil residue.

In a separate vessel, BuLi 1.6 M solution in hexanes (100 mL) was added at rate into a solution of malonic acid monoethyl ester (9.9 g, 75 mmol) in THF (150 mL) while keeping the temperature between –60 °C and –70 °C. The mixture was then cooled to –78 °C, and 4-chloro-2-nitrobenzoyl chloride, as prepared above, in THF (50 mL) was added over 20 min. After raising the temperature to –45 °C, the reaction mixture was stirred for 1 h and then poured into water containing 36% HCl (6 mL). The mixture was extracted with $CH_2Cl_2$ and the combined extracts were then washed with a saturated solution of $NaHCO_3$. The organic layers were dried, and the resulting residue was purified by column chromatography eluting with EtOAc/cyclohexane (5:95) to give oil **8** (5.3 g, 78%) as a 60:40 mixture of keto and enol isomers based on $^1$H-NMR spectrum.

*Major isomer*: $^1$H-NMR ($CDCl_3$) δ 1.25 (3 H, t, $J$ = 7.1 Hz, $CH_2CH_3$), 3.85 (2 H, s, $CH_2$), 4.15 (2 H, q, $J$ = 7.1 Hz, $CH_2CH_3$), 7.50 (1 H, d, $J$ = 8.3 Hz, H-6), 7.74 (1 H, dd, $J$ = 8.3 and 2.0 Hz, H-5), 8.15 (1 H, d, $J$ = 2.0 Hz, H-3). Anal. ($C_{11}H_{10}ClNO_5$) C, H, N.

*Minor isomer*: $^1$H-NMR ($CDCl_3$) δ 1.35 (3 H, t, $J$ = 7.1 Hz, $CH_2CH_3$), 4.30 (2 H, q, $J$ = 7.1 Hz, $CH_2CH_3$), 5.40 (1 H, s, CH), 7.50 (1 H, d, $J$ = 8.3 Hz, H-6), 7.62 (1 H, dd, $J$ = 8.3 and 2.0 Hz, H-5), 7.88 (1 H, d, $J$ = 2.0 Hz, H-3), 12.10 (1 H, s, OH). Anal. ($C_{11}H_{10}ClNO_5$) C, H, N.

*4.2. Ethyl 3-(4-chloro-2-nitrophenyl)-3-(cyclopropylamino)-2-propenoate* ***11***

Compound **8** (1.08 g, 4 mmol) was added into a mixture of cyclopropylamine (1.16 g, 20 mmol) and acetic acid (1.20 g, 20 mmol) in EtOH (5 mL). After refluxing 10 h, the solvent was removed by distillation and the residue poured into water, extracted with $CHCl_3$ and purified by column chromatography eluting with EtOAc/cyclohexane (5:95) to give **11** (0. 95 g, 76.5%) as a yellow solid, m.p. 96–100 °C. $^1$H-NMR ($CDCl_3$) δ 0.30–0.70 (4 H, m, cyclopropyl $CH_2$), 1.20 (3 H, t, $J$ = 7.0 Hz, $CH_2CH_3$), 2.20–2.40 (1 H, m, cyclopropyl CH), 4.10 (2 H, q, $J$ = 7.0 Hz, $CH_2CH_3$), 4.50 (1 H, s, CH), 7.34 (1 H, d, $J$ = 8.2 Hz, H-6), 7.55 (1 H, dd, $J$ = 8.2 and 2.0 Hz, H-5), 8.00 (1 H, d, $J$ = 2.0 Hz, H-3), 8.55 (1 H, bs). Anal. ($C_{14}H_{15}ClN_2O_4$) C, H, N.

*4.3. Ethyl 1-cyclopropyl-2-(4-chloro-2-nitrophenyl)-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate* ***14***

A mixture of 2,3,4,5-tetrafluorobenzoic acid (1 g, 5.1 mmol) and thionyl chloride (5 mL) was refluxed for 6 h. The excess thionyl chloride was removed by distillation under reduced pressure to give a mobile oil which was dissolved in dry toluene (8 mL) and added to a mixture of **11** (1 g, 3.2 mmol) and dry $Et_3N$ (0.97 g, 9.6 mmol) in toluene (7 mL). The resulting mixture was refluxed for 3 h, then DBU (1.5 g, 9.8 mmol) was added and refluxed for another 3 h. The solvent was evaporated to dryness and the residue was purified by column chromatography, eluting with a gradient of cyclohexane to EtOAc/cyclohexane (20:80) to give unreacted **11** (0.5 g, 50%) and the desired **14** (0.32 g, 21.5%) as white solid, m.p. 222–225 °C. $^1$H-NMR ($CDCl_3$) δ 0.60–0.95 (4 H, m, cyclopropyl $CH_2$), 1.04 (3 H, t, $J$ = 7.1 Hz, $CH_2CH_3$), 3.20–3.35 (1 H, m, cyclopropyl CH), 4.02 (2 H, q, $J$ = 7.1 Hz, $CH_2CH_3$), 7.58 (1 H, d, $J$ = 8.5 Hz, H-6'), 7.80 (1H, dd, $J$ = 8.5 and 2.1 Hz, H-5'), 8.30 (1 H d, $J$ = 2.1 Hz, H-3'), 7.95 (1 H, ddd, $J$ = 9.7, 8.2, and 1.9 Hz, H-5). Anal. ($C_{21}H_{14}ClF_3N_2O_5$) C, H, N.

*4.4. 3-Chloro-12-cyclopropyl-9,10,11-trifluoro-5,6,7,12-tetrahydrodibenzo[b,h]-[1,6]-naphthyridine-6,7-dione* ***17***

A stirred solution of **14** (0.1 g, 0.214 mmol) in EtOH (30 mL) was hydrogenated over Ni-Raney (0.4 g) at room temperature and atmospheric pressure for 2 h. The mixture was then filtered over Celite, and the filtrate was concentrated to about 10 mL and refluxed for 4 h. The resulting precipitate was filtered and washed with EtOH to give **17** (0.045 g, 54%), m.p. 330–334 °C. $^1$H-NMR (DMSO-$d_6$) δ 0.25–0.50 and 0.80–1.05 (each 2 H, m, cyclopropyl $CH_2$), 4.10–4.35 (1 H, m, cyclopropyl CH), 7.10 (1 H, dd, $J$ = 9.0 and 2.1 Hz, H-2), 7.30 (1 H, d, $J$ = 2.1 Hz, H-4), 7.70–7.85 (1 H, m, H-8), 8.30 (1 H, d, $J$ = 9.0 Hz, H-1), 11.85 (1 H, s). Anal. ($C_{19}H_{10}ClF_3N_2O_2$) C, H, N.

*4.5. 3-Chloro-12-cyclopropyl-9,11-difluoro-10-(4-methyl-1-piperrazinyl)-5,6,7,12-tetrahydrodibenzo[b,h][1,6]naphthyridine-6,7-dione* ***5a***

The mixture of amide **17** (0.072 g, 0.18 mmol) and 1-methylpiperazine (0.5 mL, 4.5 mmol) in $CH_3CN$ (4 mL) was refluxed for 5 h. After cooling, the precipitate was filtered, washed with EtOH, and dried to give **5a** (0.04 g, 47%), m.p. 267–269 °C. IR ($CHCl_3$) ν 3585, 3550, 1698, 1605 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 0.30–0.55 and 0.70–1.0 (each 2 H, m, cyclopropyl $CH_2$), 2.25 (3 H, s, $CH_3$), 2.40–2.50 and 3.20–3.50 (each 4 H, m, piperazine $CH_2$), 4.35–4.50 (1 H, m, cyclopropyl CH), 7.20 (1 H, dd, $J$ = 9.0 and 2.0 Hz, H-2), 7.35 (1 H, d, $J$ = 2.0 Hz, H-4), 7.55 (1 H, dd, $J$ = 12 and 2.1 Hz, H-8), 8.55 (1 H, d, $J$ = 9.0 Hz, H-1), 11.50 (1 H, bs). Anal. ($C_{24}H_{21}ClF_2N_4O_2$) C, H, N.

In an analogous procedure, amide derivatives **5b–d** were obtained by reaction with the appropiate heterocyclic amine. Their physical properties and spectral data are enumerated below.

***5b***: (55%), m.p. 288–291 °C. IR ($CHCl_3$) ν 3583, 3550, 1695, 1600 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$) δ 0.25–0.50 and 0.80–1.50 (each

2 H, m, cyclopropyl $CH_2$), 2.75–2.95 and 3.50–3.65 (each 4H, m, thiomorpholine $CH_2$), 4.15–4.35 (1 H, m, cyclopropyl CH), 7.25 (1 H, dd, $J$ = 8.8 and 1.8 Hz, H-2), 7.35 (1 H, d, $J$ = 1.8 Hz, H-4), 7.55 (1 H, dd, $J$ = 12 and 1.5 Hz, H-8), 8.25 (1 H, d, $J$ = 8.8 Hz, H-1). Anal. ($C_{23}H_{18}ClF_2N_3O_2S$) C, H, N.

***5c***: (65%), m.p. 277–279 °C. IR ($CHCl_3$) ν 3560, 3550, 1695, 1620, 1600 $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$/$CDCl_3$) δ 0.30–0.50 and 0.85–1.05 (each 2 H, m, cyclopropyl $CH_2$), 1.10 (1 H, d, $J$ = 2.0 Hz, $CH_3$), 2.95–3.50 (8 H, m, piperazine $CH_2$ and NH), 4.10–4.30 (1 H, m, cyclopropyl CH), 7.15 (1 H, dd, $J$ = 9.0 and 2.0 Hz, H-2), 7.45 (1 H, d, $J$ = 2.0 Hz, H-4), 7.65 (1 H, dd, $J$ = 12 and 1.5 Hz, H-8), 8.35 (1 H, d, $J$ = 9.0 Hz, H-1), 11.5 (1 H, bs). Anal. ($C_{24}H_{21}ClF_2N_4O_2$) C, H, N.

***5d***: (45%), m.p. 258–262 °C. IR ($CHCl_3$) ν 3550, 3540, 1680, 1630 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.20–0.50 and 0.80–1.20 (each 2 H, m, cyclopropyl $CH_2$), 2.85–3.20 and 3.55–3.80 (each 2 H, m, isoquinoline $CH_2$), 4.20–4.40 (1 H, m, cyclopropyl CH), 4.45–4.80 (2 H, m, isoquinoline $CH_2$), 7.10–7.30 (6 H, m, isoquinoline aromatic H and H-2 and H-4), 7.80 (1 H, dd, $J$ = 12 and 1.5 Hz, H-8), 8.40 (1 H, bd, H-1), 14.20 (1 H, bs). Anal. ($C_{28}H_{20}ClF_2N_3O_2$) C, H, N.

### *4.6. 12-Cyclopropyl-9,11-difluoro-10-(4-methyl-1-piperazinyl)-5,6,7,12-tetrahydrodibenzo[b,h][1,6]naphthyridine-6,7-dione **4a***

It was obtained by the same synthetic procedure used to prepare compound **5a** but starting with 2-nitrobenzoic acid instead of 4-chloro-2-nitrobenzoic acid, m.p. 256–260 °C. IR ($CHCl_3$) ν 3585, 3550, 1695, 1610 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.30–0.50 and 0.80–1.10 (each 2 H, m, cyclopropyl $CH_2$), 2.20 (3 H, s, $CH_3$), 2.38–2.45 and 3.16–3.48 (each 4 H, m, piperazine $CH_2$), 4.25–4.45 (1 H, m, cyclopropyl CH), 7.26 and 8.55 (each 1 H, dd, $J$ = 6.7 and 2.0 Hz, H-1 and H-4), 7.55–7.70 (2 H, m, H-2 and H-3), 7.85 (1 H, dd, $J$ = 11.8 and 2.0 Hz, H-8). Anal. ($C_{24}H_{22}F_2N_4O_2$) C, H, N.

### *4.7. 12-Cyclopropyl-4-methoxyl-9,11-difluoro-10-(4-methyl-1-piperazinyl)-5,6,7,12-tetrahydrodibenzo[b,h][1,6]naphthyridine-6,7-dione **6a***

It was obtained by the same synthetic procedure used to prepare compound **5a** but starting with 3-methoxy-2-nitrobenzoic acid instead of 4-chloro-2-nitrobenzoic acid, m.p. 298–301 °C. IR ($CH_2Cl_2$) ν 3520, 3500, 1675, 1625, 1619 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.35–0.50 and 0.85–1.05 (each 2 H, m, cyclopropyl $CH_2$), 2.40 (3 H, s, $CH_3$), 2.50–2.70 and 3.30–3.60 (each 4 H, m, piperazine $CH_2$), 4.05 (3 H, s, $OCH_3$), 4.15–4.35 (1 H, m, cyclopropyl CH), 7.05 and 7.80 (each 1 H, dd, $J$ = 7.7 and 1.0 Hz, H-1 and H-3), 7.20 (1 H, t, $J$ = 7.7 Hz, H-2), 7.75 (1 H, dd, $J$ = 12.7 and 1.3 Hz, H-8), 9.20 (1 H, bs). Anal. ($C_{25}H_{24}F_2N_4O_3$) C, H, N.

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[19] It was impossible to obtain the hypothesized 4-nitro derivative by the synthetic route described for the dibenzonaphthyridindiones **4–6** since it entails a reductive cyclization step. An alternative route by direct nitration of intermediate **16** or target compound **4a**, under various conditions, likewise did not give the 4-nitro derivative but unpurified mixtures were always obtained.