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Thermochemical reaction of 7-azido-1-ethyl-6,8-difluoroquinolone-3-carboxylate with heterocyclic amines. An expeditious synthesis of novel fluoroquinolone derivatives

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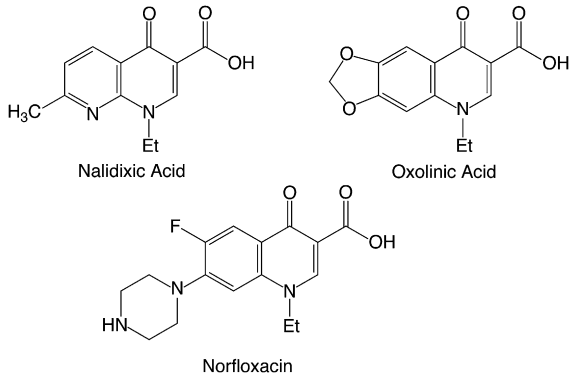
Abstract—Novel 7-hydrazino-1-ethyl-6,8-difluoroquinolone-3-carboxylate derivatives are obtained by thermochemical reaction of 7-azido-1-ethyl-6,8-difluoroquinolone-3-carboxylate with heterocyclic amines. These new fluoroquinolone carboxylates could be used as precursors in the preparation of novel fluoroquinolone carboxylic acids. These latter compounds are known to have biological activity.

1. Introduction

Since the discovery of the antibacterial penicillium, there has been a great deal of interest in finding new natural and synthetic organic compounds with antibacterial activity. Nalidixic and oxolinic acids were the first quinolones used as antibacterial agents (Scheme 1). Since these quinolones showed activity only against Gram-negative microorganisms,[1] later structural modifications on their basic scaffold led to new analogues with improved antibacterial activity.[2–4] Common structural features of the newer and more potent quinolones are a C-6 fluorine and a C-7 amino group.[5–9]



Scheme 1. Structure of antibacterial quinolones.

Fluoroquinolones such as ciprofloxacin and norfloxacin (Scheme 1) are synthetic antibacterial agents that have gained wide acceptance for use in the treatment of various bacterial infections. It is believed that their mode of action involves inhibition of bacterial DNA gyrase, which is essential for DNA replication.[10] Other fluoroquinolones have been shown to have anticancer activity since they inhibit mammalian topoisomerase-II.[11] Knowing the increasing incidence of bacterial resistance[12,13] and due to the interest to make more potent broad spectrum quinolone antibacterials, we have been involved in the synthesis of fluoroquinolone analogues.[14,15]

2. Results and discussion

Fluoroquinolone antibacterials are usually prepared by direct amination of 7-halogen-6-fluoroquinolone-3-carboxylic acids with piperazine or pyrrolidine derivatives under thermal conditions.[16] Unlike piperazine, other amino derivatives are weaker nucleophiles and are less reactive to undergo amination by nucleophilic substitution on the fluoroquinolone carboxylic acids.[16] However, we could overcome this problem by converting the precursor 1-ethyl-6,7,8-trifluoroquinolone-3-carboxylate **4** into the thermochemically reactive 7-azido-1-ethyl-6,8-difluoroquinolone-3-carboxylate **5** (Scheme 2). In a recent investigation, we reported the photochemistry of several fluorophenyl azides in diethylamine.[17] Photolysis of pentafluoro- and 2,6-difluorophenyl azides gave singlet nitrene that generated the corresponding hydrazines upon reaction with diethylamine. In this study, we investigated the thermochemical reaction of azide **5** with several heterocyclic amines **6** for the preparation of novel

Keywords: Fluoroquinolone; Antibacterial; Aryl azide; Singlet nitrene.
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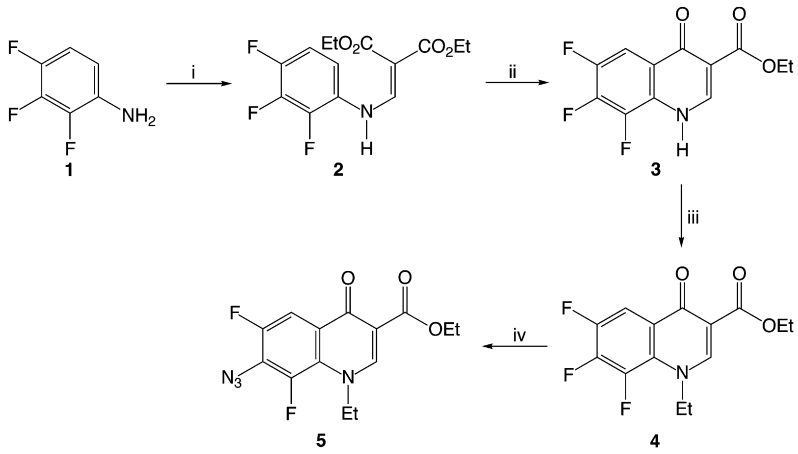
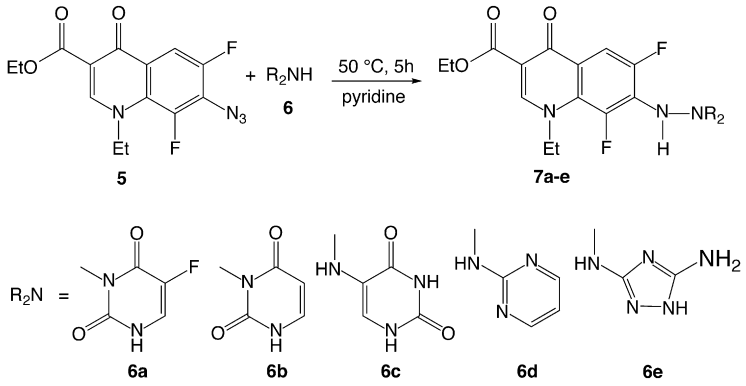


Scheme 2. Preparation of 7-azido-3-carboxylate-1-ethyl-6,8-difluoroquinolone **5**. Reagents and conditions: (i) diethyl ethoxymethylenemalonate, 100–120 °C, 2 h, 86%; (ii) diphenyl ether, 250 °C, 6 h, 83%; (iii) CH_3CH_2I, K_2CO_3, DMF, reflux, 10 h, 53%; (iv) NaN_3, acetone/H_2O, reflux, 6 h, 83%.



Scheme 3. Preparation of 7-hydrazino-1-ethyl-6,8-difluoroquinolone-3-carboxylate derivatives **7a**–**e**. Heterocyclic amine **6**: R_2NH: **a**: 5-fluorouracil, 54%; **b**: uracil, 51%; **c**: 5-aminouracil, 56%; **d**: 2-aminopyrimidine, 50%; **e**: 3,5-diamino-1,2,4-triazole, 57%.

7-hydrazino-1-ethyl-6,8-difluoroquinolone-3-carboxylate derivatives **7** (Scheme 3).

A general procedure (Scheme 2) for the synthesis of azide **5** is presented. This azide **5** was easily prepared by selective nucleophilic substitution of 1-ethyl-6,7,8-trifluoroquinolone-3-carboxylate **4** with sodium azide. The precursor trifluoroquinolone **4** was prepared by the general Gould–Jacobs procedure previously reported.[14,18,19] Thermochemical reaction of azide **5** with a heterocyclic amine **6** was performed at 50 °C in pyridine for 5 h. The corresponding hydrazino derivative **7** precipitated out of the reaction mixture upon cooling by cold water addition. The structure and yield of several 7-hydrazino derivatives **7a**–**e**, prepared by this procedure, are shown in Table 1. All compounds were obtained in greater than 50% yields and did not require further purification.

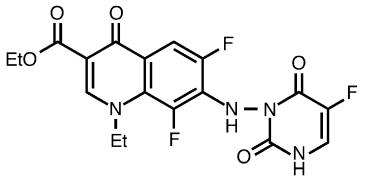
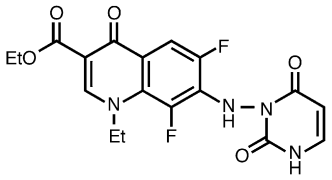
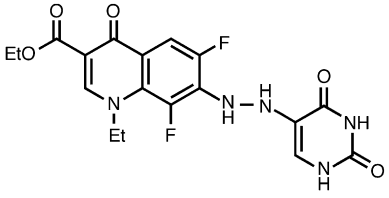
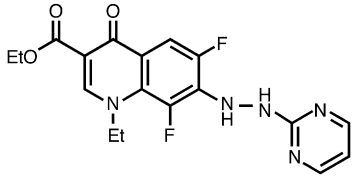
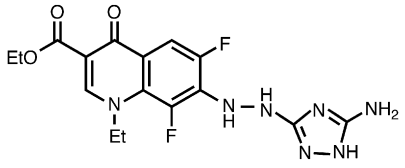
A suggested mechanism (Scheme 4) for the reaction of azide **5** with a heterocyclic amine **6** is presented, based on our previous report on the photochemistry of *ortho*-fluorophenyl azides.[17] Under moderate heating conditions, thermolysis of azide **5** gave a highly reactive singlet nitrene intermediate **5**[1] that generated the corresponding hydrazino derivative **7** upon selective N–H insertion reaction with a heterocyclic amine **6**. A singlet intermediate nitrene has been previously suggested in the thermal cyclization of *ortho*-nitrofluorophenyl azides to the corresponding fluorobenzofuroxans.[20,21]

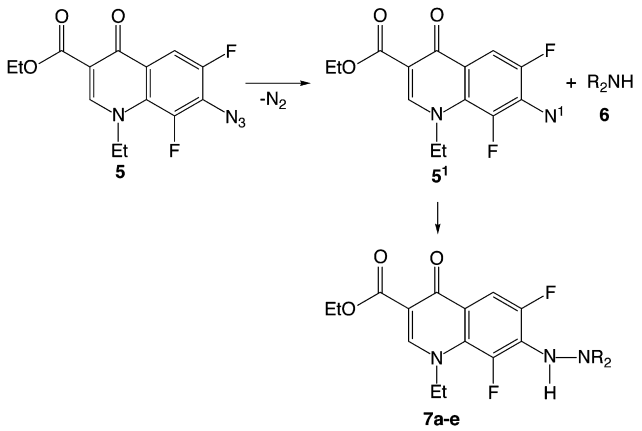
Pyridine was selected as the solvent of choice to avoid singlet nitrene insertion reactions.[22] The mixture was refluxed at 50 °C to induce thermal reaction.[21] Yields below 60% were due to some unreacted material that remained in the reaction mixture.

3. Conclusion

In conclusion, a new method to obtain novel 7-hydrazino-1-ethyl-6,8-difluoroquinolone-3-carboxylate derivatives in good yields from 7-azido-1-ethyl-6,8-difluoroquinolone-3-carboxylate is presented. This methodology could be useful for the synthesis of a variety of biologically active compounds or intermediates. The structure of the several hydrazino derivatives prepared was established on the basis of ^{1}H NMR, ^{13}C NMR, and IR spectroscopies and mass spectrometry.

Table 1. Structure and yield of hydrazino derivatives **7a–e**

	Product	Molecular formula (weight)	Yield (%)
7a		$C_{18}H_{15}F_3N_4O_5$ (424.3309)	54
7b		$C_{18}H_{16}F_2N_4O_5$ (406.3404)	51
7c		$C_{18}H_{17}F_2N_5O_5$ (421.3551)	56
7d		$C_{18}H_{17}F_2N_5O_3$ (389.3563)	50
7e		$C_{16}H_{17}F_2N_7O_3$ (393.3484)	57



Scheme 4. Mechanism for the reaction of 7-azido-1-ethyl-6,8-difluoroquinolone-3-carboxylate **5** with a heterocyclic amine **6**.

4. Experimental

4.1. General procedures

All melting points were measured with a Differential Scanning Calorimeter Pyris 6 DSC Perkin Elmer apparatus. IR spectra were recorded on GX2000 Perkin Elmer spectrometer with FT-IR as ATR. NMR spectra were recorded on a Bruker 300 MHz spectrometer. ^{1}H NMR spectra (ppm) were obtained in $CDCl_3$ or CF_3CO_2D with tetramethylsilane as an internal standard. ^{13}C NMR spectra (ppm) were measured in $CDCl_3$ or CD_3COCD_3. Mass spectra were recorded on AEI MS 902 mass spectrometer at 70 eV using methanol/tetrahydrofuran 1:1 with NaCl.

4.1.1. Diethyl 2-(2,3,4-trifluoro)-phenylaminomethylenemalonate (2). A mixture of 2,3,4-trifluoroaniline **1** (2.96 g, 20.13 mmol) and diethyl ethoxymethylenemalonate (4.39 g, 20.29 mmol) was heated at 110–120 °C in an oil bath for 2 h, the resulting EtOH was eliminated by distillation. Then, the mixture was cooled and the residue was recrystallized from *n*-hexane to yield **2** (5.49 g, 86%) as colorless needles, mp: 94–95 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 11.00 (1H, d, amine H), 8.36 (1H, d, vinyl H), 7.07 (2H, m, aromatic H), 4.31 (2H, q, CH_2), 4.25 (2H, q, CH_2), 1.38 (3H, t, CH_3), 1.33 (3H, t, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.60 and 165.42 (C=O, ester), 151.06 and 96.28 (vinyl C), 126.00, 125.91, 112.62, 112.22, 110.44 and 110.24 (aromatic C), 60.84 and 60.51 (CH_2), 14.44 and 14.31 (CH_3); IR (cm^{-1}): 3255 (N–H, secondary amine), 3170 (N–H, overtone), 2986 (C–H, aliphatic), 2940 and 2875 (CH_3), 3082 (C–H, aromatic and vinylic), 1651 (C=C, alkene), 1609 and 1505 (C=C, aromatic), 1689 (C=O, ester), 1251 and 1228 (C–O, ester).

4.1.2. Ethyl 6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (3). Compound **2** (5.30 g, 16.70 mmol) was added to diphenyl ether (35 mL) and refluxed for 6 h. After the solution was cooled, the resulting precipitate was filtered off and recrystallized from EtOH to give 3.76 g (83%) of **3** as a white solid, sublimation point: 279–280 °C. ^{1}H NMR (CF_3CO_2D, δ ppm): 9.10 (1H, s, vinyl H), 7.99 (1H, m, aromatic H), 4.43 (2H, q, CH_2), 1.30 (3H, t, CH_3); ^{13}C NMR (CF_3CO_2D, δ ppm): 171.62 (C=O, ketone), 166.50 (C=O, ester), 153.00 and 108.19 (vinyl C), 152.30, 141.00, 130.30, 125.09, 119.46 and 113.82 (aromatic C), 60.34 (CH_2), 17.04 (CH_3); IR (cm^{-1}): broad band around 3000 (N–H, secondary amine), 2986 (C–H, aliphatic), 3082 (C–H, aromatic and vinylic), 1572 (C=C, alkene), 1497 (C=C, aromatic), 1717 (C=O, ester), 1298 and 1251 (C–O, ester), 1628 (C=O, ketone).

4.1.3. Ethyl 1-ethyl-6,7,8-trifluoroquinolone-3-carboxylate (4). A mixture of **3** (2.71 g, 10 mmol), K_2CO_3 (3.45 g, 24.96 mmol), EtI (50 mmol), and DMF (20 mL) was refluxed with stirring. After 10 h, the precipitate of K_2CO_3 and $KHCO_3$ was filtered off and washed with ethanol. Then, the filtrate was cooled to yield **4** (1.58 g, 53%) as a white solid, mp: 201–202 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 8.40 (1H, s, vinyl H), 8.20 (1H, m, aromatic H), 4.43 (4H, q, $2CH_2$), 1.60 (3H, t, CH_3), 1.48 (3H, t, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 171.36 (C=O, ketone), 165.05 (C=O, ester), 151.12 and 109.79 (vinyl C), 146.16, 126.04, 125.84, 125.73, 110.87 and 110.16 (aromatic C), 61.31 and 53.42 (CH_2), 16.14 and 14.44 (CH_3); IR (cm^{-1}): 2986 (C–H, aliphatic), 3082 (C–H, aromatic and vinyl), 1680 (C=O, ester), 1323 (C–O, ester), 1611 (C=O, ketone), 1490 (C=C, aromatic), 1106 and 1100 (C–F); exact mass for $C_{14}H_{12}F_3NO_3Na^+$: 322.0667 amu, observed: 322.0647 amu.

4.1.4. Ethyl 7-azido-1-ethyl-6,8-difluoroquinolone-3-carboxylate (5). Compound **4** (0.53 g, 1.78 mmol) and sodium azide (0.12 g, 1.85 mmol) were added to acetone/water (2.5 mL/1 mL). The mixture was refluxed for 6 h and water (5 mL) was added. The precipitate was filtered, washed with water, and dried, yielding 0.47 g of **5** (83%) as a fine white solid, mp: 203–204 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 8.52 (1H, s, vinyl H), 8.30 (1H, dd, aromatic H), 4.51 (4H, br q, $2CH_2$), 1.66 (3H, br t, CH_3), 1.52 (3H, br t, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 173.93 (C=O, ketone), 167.75 (C=O, ester), 153.60 and 102.36 (vinyl C), 164.00, 153.60, 128.56, 113.74, 112.88 and 112.78 (aromatic C), 63.92 and 55.82 (CH_2), 18.70 and 17.05 (CH_3); IR (cm^{-1}): 2123 ($^-$N=N$^+$=N), 1684 (C=O, ester), 1323 (C–O, ester), 1608 (C=O, ketone), 1483 (C=C, aromatic), 1130 and 1111 (C–F); MS (EI, 70 eV) *m*/*z* 322 (100%), 317 (40%), 254 (6%); exact mass for $C_{14}H_{12}F_2N_4O_3Na^+$: 345.0775 amu, observed: 345.0764 amu.

4.1.5. Ethyl 1-ethyl-7-(5-fluoro-2,6-dioxo-3,6-dihydro-2*H*-pyrimidin-1-ylamino)-6,8-difluoroquinolone-3-carboxylate (7a). A mixture of compound **5** (0.40 g, 1.24 mmol) and 5-fluorouracil **6a** (0.16 g, 1.29 mmol) in 3.5 mL of pyridine was heated at 50 °C for 5 h. Then, the mixture was cooled and water (20 mL) was added. The residue was filtered, washed with water, and dried. The solid was recrystallized from ethanol, yielding 0.28 g of **7a** (54%) as a bright brown solid, mp: 204–205 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 8.53 (1H, s, vinyl quinolone H), 8.30 (1H, dd, vinyl uracil H), 7.37 (1H, s, aromatic H), 4.53 (4H, br q, $2CH_2$), 4.51 (1H, br s, NH), 1.66 (3H, br t, CH_3), 1.53 (3H, br t, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 174.00 (C=O, ketone), 167.82 (C=O, ester), 153.70 and 152.52 (C=O, uracil), 144.00 and 93.08 (vinyl uracil C), 153.70 and 102.42 (vinyl quinolone C), 149.26, 147.15, 128.54, 113.64, 112.90 and 112.66 (aromatic C), 63.99 and 56.09 (CH_2), 18.78 and 17.09 (CH_3); IR (cm^{-1}): 1743 (C=O, overtone uracil), 1654 and 1575 (C=O, uracil), 1483 (C–N), 1681 (C=O, ester), 1318 (C–O, ester), 1608 (C=O, ketone), 1510 (C=C, aromatic); MS (EI, 70 eV) *m*/*z* 323 (22%), 322 (100%); exact mass for $C_{18}H_{15}F_3N_4O_5$: 424.0995 amu, observed: 424.0968 amu.

4.1.6. Ethyl 7-(2,6-dioxo-3,6-dihydro-2*H*-pyrimidin-1-ylamino)-1-ethyl-6,8-difluoroquinolone-3-carboxylate (7b). A mixture of compound **5** (0.40 g, 1.24 mmol) and uracil **6b** (0.14 g, 1.29 mmol) in 3.5 mL of pyridine was heated at 50 °C for 5 h. Then, the mixture was cooled and water (20 mL) was added. The residue was filtered, washed with water, and dried. The solid was recrystallized from ethanol, yielding 0.26 g of **7b** (51%) as a sand color solid, mp: 206–207 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 8.52 (H, br s, vinyl quinolone H), 8.33 (2H, m, vinyl uracil H and aromatic H), 7.34 (1H, d, vinyl uracil H), 4.53 (4H, br q, $2CH_2$), 4.50 (1H, br s, NH), 1.66 (3H, br t, CH_3), 1.55 (3H, br t, CH_3); ^{13}C NMR (CD_3COCD_3, δ ppm): 174.00 (C=O, ketone), 167.80 (C=O, ester), 153.70 and 152.83 (C=O, uracil), 149.47 and 112.66 (vinyl uracil C), 153.70 and 102.42 (vinyl quinolone C), 146.23, 144.94, 142.59, 128.53, 113.63 and 112.90 (aromatic C), 63.98 and 55.99 (CH_2), 18.78 and 17.09 (CH_3); IR (cm^{-1}): 1653 and 1568 (C=O, uracil), 1480 (C–N), 1678 (C=O, ester), 1321 (C–O, ester), 1608 (C=O, ketone), 1514 (C=C, aromatic); MS (EI, 70 eV) *m*/*z* 323 (35%), 322 (100%), 294 (2%); exact mass for $C_{18}H_{16}F_2N_4O_5$: 406.1080 amu, observed: 406.1067 amu.

4.1.7. Ethyl 7-[*N*′-(2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-hydrazino]-1-ethyl-6,8-difluoroquinolone-3-carboxylate (7c). A mixture of compound **5** (0.40 g, 1.24 mmol) and 5-aminouracil **6c** (0.16 g, 1.29 mmol) in 3.5 mL of pyridine was heated at 50 °C for 5 h. Then, the mixture was cooled and water (15 mL) was added. The residue was filtered, washed with water, and dried, yielding 0.29 g of **7c** (56%) as a yellow crystalline solid, mp: 206–207 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 8.52 (1H, br s, vinyl quinolone), 8.30 (1H, dd, aromatic H), 7.37 (1H, br s, vinyl uracil H), 4.53 (4H, br q, $2CH_2$), 4.50 (1H, br s, NH), 1.73 (1H, br s, NH), 1.66 (3H, br t, CH_3), 1.55 (3H, br t, CH_3); ^{13}C NMR (CD_3COCD_3, δ ppm): 180.00 (C=O, ketone), 165.11 (C=O, ester), 152.22 and 151.66 (C=O, uracil), 125.00 and 123.33 (vinyl uracil C), 152.22 and 109.87 (vinyl quinolone C), 145.83, 145.00, 130.83, 120.83, 115.14 and 111.87 (aromatic C), 66.32 and 51.39 (CH_2), 16.07 and 14.68 (CH_3); IR (cm^{-1}): 1748 (C=O, overtone uracil), 1647 and 1567 (C=O, uracil), 1494 and 1480 (C–N), 1673 (C=O, ester), 1321 (C–O, ester), 1608 (C=O, ketone), 1508 (C=C, aromatic); MS (EI, 70 eV) *m*/*z* 323 (40%), 322 (100%), 319 (18%); exact mass for $C_{18}H_{17}F_2N_5O_5$: 421.1198 amu, observed: 421.1171 amu.

4.1.8. Ethyl 1-ethyl-7-(*N*′-pyrimidin-2-yl-hydrazino)-6,8-difluoroquinolone-3-carboxylate (7d). A mixture of compound **5** (0.40 g, 1.24 mmol) and 2-aminopyrimidine **6d** (0.12 g, 1.29 mmol) in 3.5 mL of pyridine was heated at 50 °C for 5 h. Then, the mixture was cooled and water (10 mL) was added. The residue was filtered, washed with water, and dried, yielding 0.24 g of **7d** (50%) as yellow needles, mp: 199–200 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 8.52 (2H, br s, aromatic H), 8.30 (2H, br s, vinyl quinolone H and aromatic H), 7.37 (1H, br s, aromatic H), 4.52 (4H, br q, $2CH_2$), 4.50 (2H, br s, NH), 1.66 (3H, br t, CH_3), 1.52 (3H, br t, CH_3); ^{13}C NMR (CD_3COCD_3, δ ppm): 174.41 (C═O, ketone), 167.78 (C═O, ester), 163.36, 153.61 and 113.69 (pyrimidine C), 153.06 and 102.35 (vinyl C), 143.57, 132.00, 128.53, 114.00, 112.65 and 112.35 (aromatic C), 63.92 and 56.02 (CH_2), 18.72 and 17.06 (CH_3); IR (cm^{-1}): 1681 (C═O, ester), 1321 (C–O, ester), 1608 (C═O, ketone), 1480 (C═C, aromatic), 1130 and 1105 (C–F); MS (EI, 70 eV) *m*/*z* 345 (9%), 323 (12%), 322 (100%), 317 (18%); exact mass for $C_{18}H_{17}F_2N_5O_3$: 389.1299 amu, observed: 389.1286 amu.

4.1.9. Ethyl 7-[*N*′-(5-amino-2*H*-1,2,4-triazol-3-yl)-hydrazino]-1-ethyl-6,8-difluoroquinolone-3-carboxylate (7e). A mixture of compound **5** (0.40 g, 1.24 mmol) and 3,5-diamino-1,2,4-triazole **6e** (0.13 g, 1.29 mmol) in 3.5 mL of pyridine was heated at 50 °C for 5 h. Then, the mixture was cooled and water (10 mL) was added. The residue was filtered, washed with water, and dried, yielding 0.28 g of **7e** (57%) as an orange crystalline solid, mp: 205–206 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 8.52 (1H, s, vinyl quinolone H), 8.30 (1H, dd, aromatic H), 6.47 (2H, br s, NH_2), 5.30 (2H, br s, NH), 4.51 (4H, br q, $2CH_2$), 1.68 (3H, br t, CH_3), 1.53 (3H, br t, CH_3); ^{13}C NMR (CD_3COCD_3, δ ppm): 173.87 (C═O, ketone), 167.97 (C═O, ester), 170.92 and 165.10 (vinyl heterocycle amine C), 153.60 and 102.36 (vinyl quinolone C), 145.61, 138.36, 128.59, 113.76, 112.88 and 112.58 (aromatic C), 63.93 and 56.01 (CH_2), 18.70 and 17.06 (CH_3); IR (cm^{-1}): 1678 (C═O, ester), 1321 (C–O, ester), 1611 (C═O, ketone), 1480 (C═C, aromatic), 1103 and 1091 (C–F); MS (EI, 70 eV) *m*/*z* 323 (92%), 321 (100%); exact mass for $C_{16}H_{17}F_2N_7O_3$: 393.1361 amu, observed: 393.1348 amu.

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