SYNTHESIS OF 3-AMINO- AND 3-ACYLAMINO-1-CYCLOPROPYLQUINOLIN-4(1*H*)-ONES

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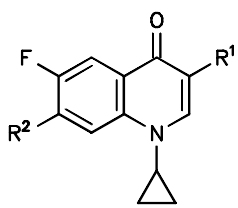
Antibacterial quinolones have attracted an increasing attention as a source of clinically useful drugs[1,2]. During our research into antibacterial quinolones we were also interested in compounds having at the position 3 various groups that could mimic the carboxylic group present in these drugs. Having our own procedure[3] for the preparation of 3-nitroquinolones, we decided to investigate the question of possible activity of 3-amino derivatives and 3-acylamino derivatives.

Compounds *Ia* and *Ib* were hydrogenated over palladium on carbon to provide 3-amino derivatives *Ic* and *Id*, respectively. These 3-amino derivatives were acetylated with acetic anhydride providing 3-acetamido derivatives *Ie* and *If*, respectively. Compound *If* was also prepared by a treatment of *Ie* with *N*-methylpiperazine. Acylation of *Id* with benzoyl chloride in pyridine provided *Ig*. Similarly, acylation of *Ic* and *Id* with ethyl oxalyl chloride provided the respective acylamino derivatives *Ih* and *Ii*. Compound *Ij* was prepared by a treatment of *Ic* with hydroxylamine hydrochloride and chloral hydrate under acidic conditions.



	R^1	R^2		R^1	R^2
Ia	NO_2	F	*If*	CH_3CONH	4-methyl-1-piperazinyl
Ib	NO_2	4-methyl-1-piperazinyl	*Ig*	C_6H_5CONH	4-methyl-1-piperazinyl
Ic	NH_2	F	*Ih*	$NHCOCOOC_2H_5$	F
Id	NH_2	4-methyl-1-piperazinyl	*Ii*	$NHCOCOOC_2H_5$	4-methyl-1-piperazinyl
Ie	CH_3CONH	F	*Ij*	NHCOCH=NOH	F

Elemental analyses and spectral data (^{1}H NMR, IR, UV, MS) of all the prepared compounds are in accordance with the proposed structures. Compound *Ic – Ij* were virtually inactive as antibacterials when tested in vitro against a variety of organisms.

EXPERIMENTAL

Melting points were measured on Thomas Hoover capillary apparatus and are uncorrected. IR spectra were taken on a Digilab FTS 15E spectrophotometer in KBr pellets (wavenumbers in cm^{-1}). UV spectra were taken on a Cary 17D spectrometer in ethanol, molar absorption coefficients (ε) are given in $m^2\ mol^{-1}$, wavelengths (λ) in nm. ^{1}H NMR spectra were recorded on a Varian XL-200 instrument (200 MHz) in deuteriochloroform, unless otherwise stated, chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were obtained on a VG 7070 E-HF spectrometer.

3-Amino-1-cyclopropyl-6,7-difluoroquinolin-4(1*H*)-one (*Ic*)

A solution of *Ia* (0.16 g, 0.6 mmol) in ethanol (50 ml) was hydrogenated over 10% Pd on carbon (0.05 g) for 2 h at room temperature, the catalyst was filtered off, the filtrate was evaporated to dryness and crystallized from ethanol to provide 0.13 g (92%) of *Ic*; m.p. 165 – 170 °C (decomp.). For $C_{12}H_{10}F_2N_2O$ (236.2) calculated: 61.02% C, 4.23% H, 16.09% F, 11.86% N; found: 61.18% C, 4.24% H, 14.26% F, 11.78% N. ^{1}H NMR spectrum: 1.05 – 1.35 m, 4 H (2 × CH_2); 3.20 bs, 2 H (NH_2); 3.45 m, 1 H (N–CH); 7.45 s, 1 H (H-2); 7.65 dd, 1 H, *J* = 11 and 7 (H-8); 8.25 dd, 1 H, *J* = 11 and 8 (H-5). IR spectrum: 3 354, 3 298 (NH_2); 1 628 (CO). Mass spectrum, *m*/*z* (%): 236 (M^+, 100), 207 (24), 167 (28).

3-Amino-1-cyclopropyl-6-fluoro-7-(4-methyl-1-piperazinyl)quinolin-4(1*H*)-one (*Id*)

Compound *Id* was prepared from *Ib* by above mentioned procedure in 91% yield, m.p. 207 – 210 °C (decomp.). For $C_{17}H_{21}FN_4O$ (316.4) calculated: 64.54% C, 6.69% H, 6.01% F, 17.71% N; found: 64.23% C, 6.63% H, 5.85% F, 17.36% N. ^{1}H NMR spectrum: 1.05 – 1.30 m, 4 H (2 × CH_2); 2.35 s, 3 H (CH_3); 2.65 t, 4 H (2 × N–CH_2); 3.30 t, 4 H (2 × N–CH_2); 3.35 m, 1 H (N–CH); 3.70 bs, 2 H (NH_2); 7.20 d, 1 H, *J*(H,F) = 7 (H-8); 7.45 s, 1 H (H-2); 8.02 d, 1 H, *J*(H,F) = 12 (H-5). IR spectrum: 3 362, 3 298 (NH_2); 1 628 (CO). UV spectrum, λ_{max} (log ε): 243 (4.23), 279 (4.56), 333 (4.05), 365 (3.86). Mass spectrum, *m*/*z* (%): 316 (M^+, 100), 70 (47), 43 (79).

The compound was converted to a water soluble hydrochloride salt decomposing over 300 °C without melting. For $C_{17}H_{21}FN_4O$. HCl . H_2O (407.3) calculated: 50.13% C, 6.19% H, 17.41% Cl, 4.66% F, 13.76% N; found: 49.65% C, 6.13% H, 17.12% Cl, 4.80% F, 13.46% N.

3-Acetamido-1-cyclopropyl-6,7-difluoroquinolin-4(1*H*)-one (*Ie*)

A mixture of *Ic* (0.1 g, 0.04 mmol) and acetic anhydride (1 ml) was stirred at room temperature for 30 min, then the mixture was evaporated in vacuo and the residue was crystallized from ethanol to provide 0.1 g (85%) of white crystals; m.p. 270 – 273 °C. For $C_{14}H_{12}F_2N_2O_2$ (278.3) calculated: 60.43% C, 4.35% H, 13.66% F, 10.07% N; found: 60.14% C, 4.44% H, 14.06% F, 10.48% N. ^{1}H NMR spectrum: 1.15 – 1.35 m, 4 H (2 × CH_2); 2.22 s, 3 H (CH_3); 3.45 m, 1 H (N–CH); 7.75 dd, 1 H, *J* = 11 and 7 (H-8); 8.22 dd, 1 H, *J* = 11 and 8 (H-5); 9.25 s, 1 H (H-2). IR spectrum: 3 312 (NH); 1 668 (CONH); 1 628 (CO). UV spectrum, λ_{max} (log ε): 213 (4.39), 257 (4.44), 266 (4.61),

294 (3.64), 306 (3.75), 346 (3.98), 362 (3.86), λ_{infl} 262 (4.47). Mass spectrum, *m*/*z* (%): 278 (M^+, 100) 236 (97), 235 (67), 43 (54), 41 (63), 32 (48), 28 (100).

3-Acetamido-1-cyclopropyl-6-fluoro-7-(4-methyl-1-piperazinyl)quinolin-4(1*H*)-one (*If*)

a) A mixture of *Id* (0.16 g, 0.5 mmol) and acetic anhydride (1.6 ml) was stirred at room temperature for 5 min, then the mixture was evaporated in vacuo and the residue was crystallized from ethanol to provide 0.15 g (84%) of white crystals; m.p. 242 – 243 °C. For $C_{19}H_{23}FN_4O_2$ (358.4) calculated: 63.67% C, 6.47% H, 5.30% F, 15.63% N; found: 63.82% C, 6.19% H, 5.53% F, 15.58% N. ^{1}H NMR spectrum: 1.05 – 1.25 m, 4 H (2 × CH_2); 2.15 s, 3 H (CH_3); 2.30 s, 3 H (CH_3); 2.55 t, 4 H (2 × N–CH_2); 3.25 t, 4 H (2 × N–CH_2); 3.38 m, 1 H (N–CH); 7.22 d, 1 H, *J*(H,F) = 7 (H-8); 7.85 d, 1 H, *J*(H,F) = 12 (H-5); 9.08 s, 1 H (H-2). IR spectrum: 3 367 (NH); 1 673 (CONH); 1 630 (CO). UV spectrum, λ_{max} (log ε): 245 (4.18), 285 (4.66), 337 (4.21). Mass spectrum, *m*/*z* (%): 358 (M^+, 100), 316 (40), 71 (34), 70 (49), 43 (62).

b) A mixture of *Ie* (56 mg, 0.2 mmol), acetonitrile (2 ml), triethylamine (0.2 ml) and *N*-methylpiperazine (0.1 ml, 0.9 mmol) was stirred at 50 °C for 50 h (monitored by TLC). Then the mixture was evaporated in vacuo and purified by preparative TLC (pre-coated silica gel TLC plates Merck, methylene chloride–methanol 95 : 5) yielding 30 mg (42%) of *If* which was identical with product prepared by procedure *a*).

3-Benzamido-1-cyclopropyl-6-fluoro-7-(4-methyl-1-piperazinyl)quinolin-4(1*H*)-one (*Ig*)

Benzoyl chloride (85 mg, 0.5 mmol) was added dropwise via syrringe to a stirred suspension of *Id* (0.16 g, 0.5 mmol) in pyridine (3.2 ml) and the mixture was stirred at room temperature for 10 min. Then the mixture was evaporated in vacuo, the residue was triturated with water, insoluble portion was filtered off, washed with water and dried to provide 0.18 g (86%) of white crystals; m.p. 237 – 238 °C. For $C_{24}H_{25}FN_4O_2$ (420.5) calculated: 68.56% C, 5.99% H, 4.52% F, 13.33% N; found: 68.08% C, 6.09% H, 6.45% F, 13.42% N. ^{1}H NMR spectrum: 1.20 – 1.40 m, 4 H (2 × CH_2); 2.40 s, 3 H (CH_3); 2.65 t, 4 H, (2 × N–CH_2); 3.35 t, 4 H (2 × N–CH_2); 3.50 m, 1 H (N–CH); 7.30 – 8.15 m, 7 H (C_6H_5CO, H-5, H-8); 9.20 s, 1 H (H-2). IR spectrum: 3 363 (NH); 1 657 (CONH); 1 628 (CO). UV spectrum, λ_{max} (log ε): 235 (4.29), 299 (4.54), 335 (4.32). Mass spectrum, *m*/*z* (%): 420 (M^+, 100), 315 (54), 105 (53), 70 (39), 43 (56).

1-Cyclopropyl-3-ethyloxalylamino-6,7-difluoroquinolin-4(1*H*)-one (*Ih*)

Ethyl oxalyl chloride (1.36 g, 10 mmol) was added dropwise via syrringe to a stirred suspension of *Ic* (2.36 g, 10 mmol) in pyridine (50 ml) an the mixture was stirred at room temperature for 10 min. Then the mixture was evaporated in vacuo, the residue was triturated with water, insoluble portion was filtered off. Crystallization from ethanol provided 2.3 g (83%) of white crystals; m.p. 225 – 227 °C. For $C_{16}H_{14}F_2N_2O_4$ (336.3) calculated: 57.15% C, 4.20% H, 11.30% F, 8.33% N; found: 57.58% C, 4.44% H, 11.52% F, 8.12% N. ^{1}H NMR spectrum spectrum: 1.15 – 1.30 m, 4 H (2 × CH_2); 1.45 t, 3 H, *J* = 7 (CH_3 of ethyl); 3.48 m, 1 H (N–CH); 4.44 q, 2 H, *J* = 7 (CH_2 of ethyl); 7.76 dd, 1 H, *J* = 11 and 6 (H-8); 8.22 dd, 1 H, *J* = 11 and 8 (H-5); 9.32 s, 1 H (H-2); 9.82 bs, 1 H (NH). IR spectrum: 3 355 (NH); 1 728 (COO); 1 697 (CONH); 1 620 (CO). UV spectrum, λ_{max} (log ε): 218 (4.19), 230 (4.21), 281 (4.17), 326 (4.15), 339 (4.19). Mass spectrum, *m*/*z* (%): 336 (M^+, 18), 263 (100), 41 (42).

1-Cyclopropyl-3-ethyloxalylamino-6-fluoro-7-(4-methyl-1-piperazinyl)quinolin-4(1*H*)-one (*Ii*)

Following the procedure for the preparation of *Ih*, *Ii* (white crystals) was prepared (reaction time 1 h) in 86% yield; m.p. 208 – 210 °C. For $C_{21}H_{25}FN_4O_4$ (416.5) calculated: 60.57% C, 6.05% H, 4.56% F, 13.45% N; found: 60.54% C, 5.93% H, 4.35% F, 13.02% N. ^{1}H NMR spectrum: 1.15 – 1.35 m, 4 H (2 × CH_2); 1.45 t, 3 H, J = 7 (CH_3 of ethyl); 2.35 s, 3 H (CH_3); 2.75 t, 4 H (2 × N–CH_2); 3.35 t, 4 H (2 × N–CH_2); 3.45 m, 1 H (N–CH); 4.40 q, 2 H, J = 7 (CH_2 of ethyl), 7.30 d, 1 H J(H,F) = 7 (H-8); 8.05 d, 1 H J(H,F) = 12 (H-5); 9.25 s, 1 H (H-2); 9.80 bs, 1 H (NH). IR spectrum: 1 731 (COO); 1 697 (CONH); 1 630 (CO). UV (ethanol): λ_{max} (log ε): 232 (4.08), 253 (3.97), 303 (4.37), 335 (4.25). Mass spectrum, *m*/*z* (%): 416 (M^+, 18), 343 (100).

1-Cyclopropyl-6,7-difluoro-3-(isonitrosoacetamido)quinolin-4(1*H*)-one (*Ij*)

Compound *Ic* (0.24 g, 1 mmol) was dissolved in concentrated hydrochloric acid (1 ml) and the mixture was stirred at room temperature for 1 h. A solution of hydroxylamine hydrochloride (0.2 g, 2.9 mmol) in water (1 ml) was added and the formed suspension was added to a solution of chloral hydrate (0.15 g, 0.9 mmol) and sodium sulfate decahydrate (2.2 g, 6.8 mmol) in water (2 ml) at 90 °C during 20 min. Then the mixture was refluxed for 5 h, cooled and the separated solid was filtered off and crystallized from ethanol; yield 0.1 g (33%) of creamy crystals; m.p. 286 – 290 °C (decomp.). For $C_{14}H_{11}F_2N_3O_3$ (307.3) calculated: 54.73% C, 3.61% H, 12.37% F, 13.68% N; found: 54.55% C, 3.34% H, 12.32% F, 14.01% N. ^{1}H NMR spectrum: 1.06 – 1.32 m, 4 H (2 × CH_2); 3.70 m, 1 H (N–CH); 8.02 – 8.25 m, 2 H (H-5, H-8); 9.25 s, 1 H (H-2); 9.45 s, 1 H (NH). IR spectrum: 3 345 (NH); 1 682 (CONH); 1 616 (CO). UV spectrum, λ_{max} (log ε): 219 (4.29), 230 (4.28), 248 (4.19), 273 (4.07), 285 (4.07), 328 (4.09), 340 (4.11). Mass spectrum, *m*/*z* (%): 308 (M^+ + H, 50), 307 (M^+, 42), 154 (100), 149 (52), 138 (48), 137 (76), 136 (96), 107 (56).

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