SYNTHETIC STUDIES CONNECTED WITH THE PREPARATION OF 4-CYCLOPROPYL-7-FLUORO-6-(4-METHYLPIPERAZIN-1-YL)-1,2,4,9-TETRAHYDROTHIAZOLO[5,4-*b*]QUINOLINE-2,9-DIONE

Stanislav RADL

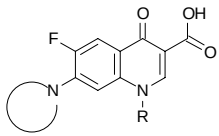
Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3, Czech Republic; e-mail: vufbchs@mbox.vol.cz

Received November 13, 1996
Accepted February 17, 1997

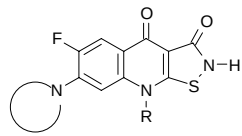
Target 4-cyclopropyl-7-fluoro-6-(4-methylpiperazin-1-yl)-1,2,4,9-tetrahydrothiazolo[5,4-*b*]quinoline-2,9-dione (**5a**) was obtained from 3-amino-1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-2-mercaptoquinolin-4(1*H*)-one (**9b**). This intermediate was obtained from 3-amino-1-cyclopropyl-6,7-difluoro-2-(methylsulfinyl)quinolin-4(1*H*)-one (**9f**) *via* 3-amino-1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-2-(methylsulfinyl)quinolin-4(1*H*)-one (**9c**). Compound **9f** was prepared from 2,4,5-trifluoroacetophenone (**6a**) in several steps. 4-Cyclopropyl-6,7-difluoro-2,3,4,9-tetrahydrothiazolo[5,4-*b*]quinoline-3,4-dione (**5b**) was prepared similarly as the target compound. Treatment of **5b** with *N*-methylpiperazine did not afford **5a** but 1-cyclopropyl-6,7-difluoro-2-mercapto-3-[(4-methylpiperazin-1-yl)carbonylamino]quinolin-4(1*H*)-one (**11**). Several unsuccessful attempts to prepare compound **5a** and/or some useful intermediates of its synthesis are also described.
Key words: Thiazolo[5,4-*b*]quinolines; Antibacterial quinolones.

Antibacterial quinolones of a general formula **1**, which exert their activity by inhibiting bacterial DNA gyrase, have attracted increasing attention as a source of clinically useful drugs[1,2]. During our research into antibacterial quinolones we were also interested in tricyclic compounds having annelated additional rings at positions 2 and 3 of the quinoline moiety. Compounds of general formula **2**, having an isothiazolone ring annelated to the 2,3-position of the quinolone moiety, have been found to be extremely active DNA gyrase inhibitors[3]. Since only compounds having an unsubstituted isothiazolone nitrogen were found to be active, we envisaged that involvement of the tautomers **3** might be important for their biological action. This tautomer could be involved in DNA gyrase-inhibitor complex with its carbonyl (hydrogen bond acceptor) and hydroxy (hydrogen bond donor) groups in accordance with the model proposed by Shen *et al.*[4]. Recently quite different type of DNA gyrase inhibitors of general formula **4** has been discovered[5]. In these compounds similar acceptor–donor pattern was suggested to be involved in a biointeraction. In this case the hydrogen donor is represented by an NH group. These findings inspired us to prepare new thiazolo[5,4-*b*]quinoline-2,9-diones represented by compound **5a**, which combine some features of both men-

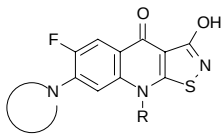
tioned groups of DNA gyrase inhibitors. For our initial study we chose a typical substitution pattern present in many potent quinolones, that is a cyclopropyl group as the *N* substituent and a 4-methylpiperazin-1-yl group as the cyclic amine residue. Synthetic studies connected with the preparation of the target compound **5a** are presented in this paper.



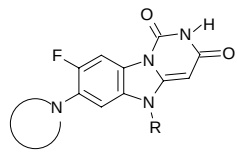
1



2



3

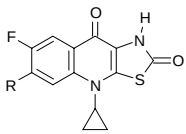


4

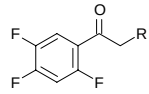
Our strategy was based on annelation of the thiazole ring onto the quinolone moiety constructed in previous steps. There are several methods for preparation of quinolones bearing various substituents[6]. For this purpose we needed a 2-mercapto-3-aminoquinolone structure. We adopted method similar to that developed by Chu[7] for preparation of similar quinoline-3-carboxylates. We chose commercially available 2,4,5-trifluoroacetophenone (**6a**) as a suitable starting compound which can be easily transformed into phthalimide derivative **6c** *via* the corresponding bromoacetyl derivative **6b**. Treatment of a mixture of **6c** and cyclopropyl isothiocyanate with one molar equivalent of sodium hydride in DMF furnished intermediate **7a** which, without isolation, was treated with iodomethane at room temperature providing **7b** as a main product. A small amount of its *N*-methyl derivative **7c** was also isolated. ^{1}H NMR spectra of **7b** and **7c** documented that both compounds were present exclusively in one isomeric form (*E* or *Z*). Since intramolecular nucleophilic cyclization of **7b**, which was easily achieved by sodium hydride in THF at room temperature, yielded **8a**, at least compound **7b** is present in its *Z* form.

Compound **8a** seemed to be an ideal intermediate for the synthesis of **5** and we proposed several ways of its preparation. First strategy was based on a reaction sequence which included introduction of the *N*-methylpiperazine substituent leading to **8b** and deprotection of its 3-amino group which then could lead to **9a**. We assumed that the key intermediate **9b** can be accessible either by a reduction of the 2-methylsulfanyl group in **9a** or *via* corresponding methylsulfinyl derivative **9c**. Though this retrosynthetic analysis was consistent with the current knowledge of the field, we were aware

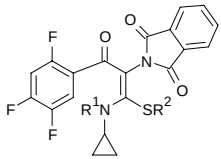
that there were some sources of potential troubles. For example, there are examples of reduction of aromatic and heteroaromatic methylsulfanyl groups into mercapto groups but none of them dealt with similar heterocycles. We also did not know if the methylsulfanyl group in **9a** would be preferentially oxidized to **9c** without oxidation of the piperazine nitrogen.



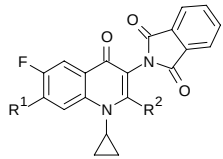
5	R
a	4MeP
b	F



6	R
a	H
b	Br
c	phthalimido

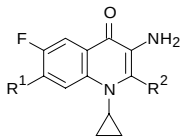


7	R^1	R^2
a	H	H
b	H	Me
c	Me	Me



8	R^1	R^2
a	F	SMe
b	4MeP	SMe
c	F	SOMe

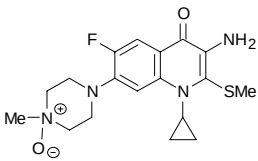
In formulae **5**, **8** and **9**, 4MeP = 4-methylpiperazinyl



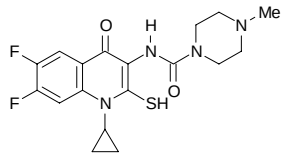
9	R^1	R^2
a	4MeP	SMe
b	4MeP	SH
c	4MeP	SOMe
d	4MeP	H
e	F	SMe
f	F	SOMe
g	F	SH

A treatment of **8a** with *N*-methylpiperazine under usual conditions really provided compound **8b**. Hydrazine hydrate was used for deprotection of the C-3 amino group in this compound and **9a** was obtained in high yield. Reduction of various aromatic and heteroaromatic methylsulfanyl derivatives, *e.g.* 2-methylsulfanyl imidazoles, with sodium in liquid ammonia is known to provide corresponding mercapto derivatives[8]. However, we applied this method to the reduction of **9a** and obtained the corresponding 2-unsubstituted derivative **9d** and not the required compound **9b**. We have previously

reported synthesis of **9d** by catalytic hydrogenation of the corresponding 3-nitro derivative[9,10]. Attempts to oxidize **9a** with 3-chloroperbenzoic acid (MCPBA) in dichloromethane or with hydrogen peroxide in acetic acid into the corresponding methylsulfinyl derivative **9c** were also unsuccessful. In both cases the *N*-oxide **10** was isolated. This finding was surprising since similar *S*-oxidation of methyl 2-[2-chloro-5-fluoro-4-(4-methylpiperazin-1-yl)phenyl]thioacetate with hydrogen peroxide was reported to provide the corresponding *S*-oxide without *N*-oxidation[11].



10



11

These results suggested that the introduction of the 4-methylpiperazin-1-yl group into the structure in a later step can be necessary. However, this strategy has also some risks. For example, relative reactivity of the C-7 fluorine and C-2 methylsulfinyl groups in the prospective intermediate **9f** toward the reaction with *N*-methylpiperazine was not known. In case the isothiazolone species **5b** is chosen as an intermediate, stability of the thiazolone ring of the tricycle in the reaction with *N*-methylpiperazine was also questionable. Therefore we decided to study these reactions. Compound **8a** was easily oxidized with MCPBA into **8c** but we failed to deprotect this compound with hydrazine hydrate to give **9f**. At room temperature no reaction occurred and prolonged reflux in ethanol provided a mixture of several compounds in which the starting material still prevailed. On the other hand compound **8a** was smoothly converted into **9e** by treating with hydrazine hydrate at room temperature. Oxidation of **9e** with MCPBA then provided the intermediate **9f** which treated with *N*-methylpiperazine at 70 °C for 5 days provided the required intermediate **9c**. This compound treated with sodium hydrogensulfite in tetrahydrofuran provided mercapto derivative **9b** which was, without isolation, treated with triphosgene. Since only a small yield of the required compound **5a** was obtained by this way, the possibility to construct the thiazolo[5,4-*b*]quinolone moiety first was also studied. Compound **9f** was treated with sodium hydrogensulfite followed by triphosgene in the same way as described above, yields about 60% of the corresponding tetrahydrothiazolo[5,4-*b*]quinolone **5b** were repeatedly obtained. Attempts to prepare **5a** by a treatment of this compound with *N*-methylpiperazine failed leading to compound **11**, a product of a cleavage of the thiazole ring.

In conclusion, several potential routes to **5a** have been studied and a small yield of the compound has been obtained. The compound exerted no significant *in vitro* antibacterial activity.

EXPERIMENTAL

Melting points were measured on Thomas Hoover capillary apparatus and are uncorrected. IR spectra were taken on a Digilab FTS 15E spectrophotometer (wavenumbers in cm^{-1}) and UV spectra on a Cary 17D spectrometer. ^1H NMR spectra were recorded on a Varian XL-200 instrument (200 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were obtained on a VG 7070 E-HF spectrometer. Flash and vacuum chromatography were done on silica gel 60 (230–400 mesh) and preparative TLC on pre-coated PLC plates (silica gel 60) from EM Science.

2-Bromo-1-(2,4,5-trifluorophenyl)ethanone (**6b**)

Bromine (4.6 g, 28.8 mmol) was added dropwise to a solution of **6a** (5.0 g, 28.7 mmol) in dry ether (7 ml) containing anhydrous aluminium chloride (0.05 g, 0.4 mmol) stirred in an ice bath. Then the solution was evaporated and triturated with a mixture of hexane (2 ml) and water (2 ml), the insoluble portion was filtered off and washed with another portion of the hexane–water mixture and dried; yield 6.3 g (87%). An analytical sample was purified by crystallization from ethanol, m.p. 56–57 °C. For $C_8H_4BrF_3O$ (253.0) calculated: 37.98% C, 1.59% H, 31.58% Br, 22.53% F; found: 37.73% C, 1.49% H, 31.52% Br, 22.23% F. ^1H NMR spectrum ($CDCl_3$): 4.48 d, 2 H, J = 3 (CH_2); 7.00–7.12 m, 1 H (H-3); 7.72–7.88 m, 1 H (H-6). IR spectrum ($CHCl_3$): 1 702, 1 687 (C=O). UV spectrum, λ_{max} (log ε): 240 (3.94), 285 (3.47). Mass spectrum, *m/z* (%): 252 (M^+, 3), 159 (100).

2-[2-Oxo-2-(2,4,5-trifluorophenyl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**6c**)

A solution of **6b** (2.5 g, 10 mmol) in *N*,*N*-dimethylformamide (5 ml) was added dropwise to a stirred suspension of potassium phthalimide (2.05 g, 11.0 mmol) in *N*,*N*-dimethylformamide (15 ml) and the mixture was stirred at room temperature for 2 h. Residue after evaporation of the mixture was triturated with water, the insoluble portion was filtered off, washed with water and dried. The crude product was purified by flash chromatography (dichloromethane) and by crystallization from ethanol; yield 2.5 g (78%) of **6c** (white crystals), m.p. 168–169 °C. For $C_{16}H_8F_3NO_3$ (319.2) calculated: 60.20% C, 2.53% H, 4.39% N, 17.85% F; found: 60.05% C, 2.45% H, 4.33% N, 17.56% F. ^1H NMR spectrum ($CDCl_3$): 5.03 d, 2 H, J = 4 (CH_2); 7.02–7.18 m, 1 H (H-3); 7.72–7.96 m, 5 H (H-6, H of phthalyl). IR spectrum ($CHCl_3$): 1 777, 1 721 (C=O). UV spectrum, λ_{max} (log ε): 217 (4.66), 231 (3.42), 239 (4.37), 285 (3.68), 290 (3.67). Mass spectrum, *m/z* (%): 319 (M^+, 8), 160 (100).

2-[2-Cyclopropylamino-2-methylsulfanyl-1-[(2,4,5-trifluorobenzoyl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**7b**) and 2-[2-(*N*-Cyclopropyl-*N*-methyl)amino]-2-methylsulfanyl-1-[(2,4,5-trifluorobenzoyl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**7c**)

Sodium hydride (80% suspension in mineral oil, 0.825 g, 27.8 mmol) was added during 30 min to a solution of **6c** (4.8 g, 15.0 mmol) and cyclopropyl isothiocyanate (1.65 g, 16.5 mmol) in *N*,*N*-dimethylformamide (50 ml) stirred under argon at 0 °C. The temperature was allowed to raise to room temperature and the stirring continued for additional 20 h. Then iodomethane (1.125 ml, 18 mmol) was added and the mixture was stirred at room temperature for 5 h and then poured into a mixture of water (200 ml) and acetic acid (2 ml). The insoluble portion was filtered off, washed with water, dried and purified by flash chromatography (dichloromethane). The first isolated fraction was crystallized from ether yielding 0.12 g (1.8%) of **7c** (yellow crystals), m.p. 123–125 °C. For $C_{22}H_{17}F_3N_2O_3S$ (446.5) calculated: 59.19% C, 3.84% H, 12.77% F, 6.27% N, 7.10% S; found: 59.26% C, 3.73% H, 12.87% F, 6.23% N, 7.38% S. ^1H NMR spectrum ($CDCl_3$): 0.72–1.03 m, 4 H (2 × CH_2); 2.14 s, 3 H (SCH_3); 2.72 m, 1 H (CH); 3.24 s, 3 H (NCH_3); 6.66–6.80 m, 1 H (H-3); 7.32–7.46 m, 1 H (H-6); 7.66–7.84 m, 4 H (H of phthalyl). IR spectrum ($CHCl_3$): 1 784, 1 720, 1 660

(C=O). UV spectrum, λ_{max} (log ε): 216 (4.65), 276 (4.09), 366 (4.11). Mass spectrum, *m/z* (%): 446 (M^+, 11), 159 (100).

The following fraction isolated by flash chromatography was crystallized from methanol providing 3.45 g (53%) of **7b** (white crystals), m.p. 178–179 °C. For $C_{21}H_{15}F_3N_2O_3S$ (432.4) calculated: 58.33% C, 3.50% H, 13.18% F, 6.48% N, 7.41% S; found: 58.30% C, 3.48% H, 13.14% F, 6.33% N, 7.55% S. ^{1}H NMR spectrum ($CDCl_3$): 0.90–1.06 m, 4 H (2 × CH_2); 2.48 s, 3 H (SCH_3); 3.12–3.22 m, 1 H (CH); 6.66–6.80 m, 1 H (H-3); 7.05–7.18 m, 1 H (H-6); 7.66–7.87 m, 4 H (H of phthalyl); 12.30 bs, 1 H (NH). IR spectrum ($CHCl_3$): 1 784, 1 725 (C=O). UV spectrum, λ_{max} (log ε): 217 (4.63), 262 (3.85), 346 (4.28). Mass spectrum, *m/z* (%): 432 (M^+, 8), 159 (100).

2-[1-Cyclopropyl-6,7-difluoro-2-(methylsulfanyl)-4-oxo-1,4-dihydroquinolin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (**8a**)

Sodium hydride (80% dispersion in mineral oil, 40 mg, 1.3 mmol) was added to a solution of **7b** (0.43 g, 1.0 mmol) in THF (5 ml) and the mixture was stirred at room temperature under nitrogen for 20 h. The mixture was evaporated, the residue was triturated with water and the insoluble portion was filtered, washed with water and dried. Crystallization from ethanol yielded 0.28 g (68%) of **8a** (white crystals), m.p. 234–236 °C. For $C_{21}H_{14}F_2N_2O_3S$ (412.4) calculated: 61.16% C, 3.42% H, 9.21% F, 6.79% N, 7.77% S; found: 58.88% C, 3.29% H, 8.88% F, 6.37% N, 7.93% S. ^{1}H NMR spectrum ($CDCl_3$): 1.05–1.56 m, 4 H (2 × CH_2); 2.47 s, 3 H (SCH_3); 3.32–3.46 m, 1 H (CH); 7.68–8.00 m, 5 H (H-8, H of phthalyl); 8.08 dd, 1 H, J = 7, J' = 10 (H-5). IR spectrum ($CHCl_3$): 1 787, 1 722 (C=O). UV spectrum, λ_{max} (log ε): 218 (4.69), 250 (4.28), 247 (4.14), 330 (4.14), 338 (4.12); λ_{infl} 303 (3.91). Mass spectrum, *m/z* (%): 412 (M^+, 39), 218 (100).

2-[1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-2-(methylsulfanyl)-4-oxo-1,4-dihydroquinolin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (**8b**)

A solution of **8a** (2.06 g, 5.0 mmol) and *N*-methylpiperazine (1 ml, 9.0 mmol) in pyridine (25 ml) was stirred at 110 °C for 12 h. The mixture was evaporated under reduced pressure and the residue was triturated with water. The insoluble portion was filtered off, washed with cold water and dried, the crude product was purified by flash chromatography (dichloromethane) and then by crystallization from ethanol yielding 1.65 g (67%) of **8b** (white crystals), m.p. 278–280 °C. For $C_{26}H_{25}FN_4O_3S$ (492.6) calculated: 63.40% C, 5.12% H, 3.86% F, 11.37% N, 6.51% S; found: 63.18% C, 5.01% H, 4.00% F, 11.04% N, 6.85% S. ^{1}H NMR spectrum ($CDCl_3$): 1.08–1.60 m, 4 H (2 × CH_2); 2.47 s, 3 H (CH_3); 2.49 s, 3 H (CH_3); 2.46–2.78 m, 4 H (2 × CH_2 of piperazine); 3.25–3.46 m, 5 H (CH, 2 × CH_2 of piperazine); 7.65–8.06 m, 6 H (H-5, H-8, H of phthalyl). IR spectrum ($CHCl_3$): 1 786, 1 720 (C=O). UV spectrum, λ_{max} (log ε): 218 (4.66), 270 (4.56) 335 (4.33). Mass spectrum, *m/z* (%): 492 (M^+, 62), 43 (100).

2-[1-Cyclopropyl-6,7-difluoro-1,4-dihydro-2-(methylsulfinyl)-4-oxoquinolin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (**8c**)

3-Chloroperbenzoic acid (80%, 0.22 g, 1.0 mmol) was added portionwise during 30 min to a solution of **8a** (0.41 g, 1.0 mmol) in dichloromethane (10 ml) stirred at 0 °C and the solution was stirred for 1 h at this temperature. The mixture was consecutively washed with dilute sodium hydrogen carbonate and sodium bisulfide solutions, the dichloromethane solution was dried with magnesium sulfate and purified by flash chromatography (dichloromethane–ethyl acetate 95 : 5). Crystallization from ethanol gave 0.33 g (77%) of **8c** (white crystals), m.p. 255–256 °C. For $C_{21}H_{14}F_2N_2O_4S$ (428.4) calculated: 58.88% C, 3.29% H, 8.87% F, 6.54% N, 7.48% S; found: 58.92% C, 3.21% H, 9.08% F,

6.52% N, 7.55% S. ^{1}H NMR spectrum ($CDCl_3$): 1.05–1.56 m, 4 H (2 × CH_2); 3.14 s, 3 H ($S(O)CH_3$); 3.32–3.44 m, 1 H (CH); 7.68–8.00 m, 5 H (H-8, H of phthalyl); 8.08 dd, 1 H, J = 7, J' = 10 (H-5). IR spectrum ($CHCl_3$): 1 789, 1 722 (C=O). UV spectrum, λ_{max} (log ε): 217 (4.76), 245 (4.37), 328 (4.09), , 339 (4.11). Mass spectrum, *m/z* (%): 429 (M^+ + 1, 65).

3-Amino-1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-2-(methylsulfanyl)quinolin-4(1*H*)-one (**9a**)

A suspension of **8b** (0.49 g, 1.0 mmol) in a mixture of 85% hydrazine hydrate (65 µl, 2.8 mmol) and ethanol (20 ml) was refluxed for 4 h and then evaporated to dryness. The residue was triturated with ethyl acetate, the insoluble phthalyl hydrazide was filtered off, the filtrate was evaporated and crystallized from toluene yielding 0.34 g (94%) of **9a** (yellow crystals), m.p. 176–179 °C. For $C_{18}H_{23}FN_4OS$ (362.5) calculated: 59.65% C, 6.40% H, 5.24% F, 15.46% N, 8.84% S; found: 59.73% C, 6.40% H, 5.32% F, 15.50% N, 8.67% S. ^{1}H NMR spectrum ($CDCl_3$): 0.84–0.92 m, 2 H (CH_2); 1.36–1.46 m, 2 H (CH_2); 2.38 s, 3 H (CH_3); 2.44 s, 3 H (CH_3); 2.60–2.75 m, 4 H (2 × CH_2 of piperazine); 3.22–3.44 m, 5 H (CH, 2 × CH_2 of piperazine); 4.44 s, 2 H (NH_2); 7.18 d, 1 H, J = 7 (H-8); 7.94 d, 1 H, J = 12 (H-5). IR spectrum ($CHCl_3$): 3 297 (NH_2), 1 630 (C=O). UV spectrum, λ_{max} (log ε): 245 (4.15), 284 (4.47), 343 (4.12), 385 (3.96); λ_{infl} 210 (4.24). Mass spectrum, *m/z* (%): 362 (M^+, 100).

3-Amino-1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)quinolin-4(1*H*)-one (**9d**)

Compound **9a** (0.10 g, 0.28 mmol) was added to a stirred liquid ammonia (300 ml) and the mixture was stirred until all the compound dissolved. Sodium (0.03 g, 1.3 mmol) was then added portionwise to the solution and the mixture was stirred under a stream of nitrogen till all ammonia evaporated. Ice (10 g) was added, the mixture was acidified with acetic acid and the suspension was extracted with dichloromethane. Purification by preparative TLC (chloroform–methanol 9 : 1) provided after crystallization from toluene 0.04 g (45%) of **9d** (yellow crystals), m.p. 207–209 °C. The compound was found to be identical (TLC, ^{1}H NMR, IR) with the sample prepared by a different method[10].

3-Amino-1-cyclopropyl-6,7-difluoro-2-(methylsulfanyl)quinolin-4(1*H*)-one (**9e**)

A mixture of **8a** (0.41 g, 1.0 mmol), 85% hydrazine hydrate (65 µl, 2.8 mmol) and ethanol (25 ml) was stirred at room temperature for 48 h and then evaporated to dryness. The residue was triturated with ethyl acetate and the insoluble phthalyl hydrazide was filtered off. The filtrate was evaporated and crystallized from toluene yielding 0.25 g (87%) of **9e** (yellow crystals), m.p. 125–128 °C. For $C_{13}H_{12}F_2N_2OS$ (282.3) calculated: 55.31% C, 4.28% H, 13.46% F, 9.92% N, 11.36% S; found: 55.39% C, 4.16% H, 13.45% F, 9.97% N, 11.56% S. ^{1}H NMR spectrum ($CDCl_3$): 0.84–0.96 m, 2 H (CH_2); 1.36–1.46 m, 2 H (CH_2); 2.42 s, 3 H (SCH_3); 3.26–3.38 m, 1 H (CH); 4.46 s, 2 H (NH_2); 7.60 dd, 1 H, J = 7 (H-8); 8.12 dd, 1 H, J = 8, J' = 11 (H-5). IR spectrum ($CHCl_3$): 3 445, 3 355 (NH_2), 1 638 (C=O). UV spectrum, λ_{max} (log ε): 269 (3.97), 323 (4.35), 491 (3.94); λ_{infl} 235 (3.97). Mass spectrum, *m/z* (%): 282 (M^+, 100).

3-Amino-1-cyclopropyl-6,7-difluoro-2-(methylsulfinyl)quinolin-4(1*H*)-one (**9f**)

3-Chloroperbenzoic acid (80%, 0.22 g, 1.0 mmol) was added portionwise during 30 min to a solution of **9e** (0.28 g, 1.0 mmol) in dichloromethane (10 ml) stirred at 0 °C, and the solution was stirred for 2 h at this temperature. The mixture was consecutively washed with dillute sodium hydrogencarbonate and sodium bisulfide solutions. The dichloromethane solution was dried with magnesium sulfate and purified by flash chromatography (dichloromethane–ethyl acetate 95 : 5). Crystallization from ethanol gave 0.22 g (74%) of **9f** (white crystals), m.p. 218–219 °C. For $C_{13}H_{12}F_2N_2O_2S$ (298.3) cal-

culated: 52.34% C, 4.05% H, 12.74% F, 9.39% N, 10.75% S; found: 52.40% C, 3.94% H, 13.06% F, 9.37% N, 10.78% S. ^{1}H NMR spectrum ($CDCl_3$): 0.82–1.54 m, 4 H (2 × CH_2); 3.18 s, 3 H ($S(O)CH_3$); 3.22–3.38 m, 1 H (CH); 5.15 s, 1 H (NH_2); 7.65 dd, 1 H, J = 8, J' = 11 (H-8); 8.11 dd, 1 H, J = 8, J' = 11 (H-5). IR spectrum ($CHCl_3$): 3 438, 3 338 (NH_2), 1 608 (C=O). UV spectrum, λ_{max} (log ε): 210 (4.17), 271 (4.36), 308 (3.26), 324 (3.18), 393 (3.90). Mass spectrum, *m/z* (%): 298 (M^+, 100).

3-Amino-1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-2-(methylsulfinyl)quinolin-4(1*H*)-one (**9c**)

A mixture of **9f** (1.49 g, 5.0 mmol), *N*-methylpiperazine (3.0 ml, 27.0 mmol) and acetonitrile (50 ml) was stirred under nitrogen at 70 °C for 5 days. Then the mixture was evaporated to dryness and the residue was triturated with water. The insoluble portion was filtered off, washed with water and dried yielding 1.65 g (87%) of **9c** (yellow crystals), not melting up to 300 °C. For $C_{19}H_{23}FN_4O_2S$ (378.5) calculated: 57.13% C, 6.13% H, 5.02% F, 14.80% N, 8.47% S; found: 56.88% C, 6.04% H, 4.65% F, 15.04% N, 8.11% S. ^{1}H NMR spectrum (CD_3SOCD_3): 0.76–1.52 m, 4 H (2 × CH_2); 2.54 s, 3 H (NCH_3); 2.80–3.00 m, 4 H (2 × CH_2 of piperazine); 3.19 s, 3 H ($S(O)CH_3$); 3.24–3.46 m, 5 H (CH, 2 × CH_2 of piperazine); 5.42 s, 2 H (NH_2); 7.08 d, 1 H, J = 7 (H-8); 7.92 d, 1 H, J = 12 (H-5); 12.15 bs, 1 H (NH). IR spectrum (KBr): 3 412, 3 316 (NH_2), 16 277 (C=O). UV spectrum, λ_{max} (log ε): 258 (4.25), 292 (4.42), 350 (4.10), 385 (3.98). Mass spectrum, *m/z* (%): 378 (M^+, 100).

3-Amino-1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-2-(methylsulfanyl)quinolin-4(1*H*)-one *N*-Oxide (**10**)

A solution of 3-chloroperbenzoic acid (80%, 0.05 g, 0.23 mmol) in dichloromethane (1 ml) was added dropwise to a cold solution (0 °C) of **9a** (0.11 g, 0.3 mmol) in dichloromethane (4 ml) and the mixture was stirred for 30 min at 0 °C. Then the solution was washed with a solution of sodium hydrogencarbonate (0.1 g) in water (3 ml) and the dichloromethane solution was dried with magnesium sulfate. The residue after evaporation of the solvent was purified by preparative TLC (chloroform–methanol 8 : 2) yielding after crystallization from toluene 42 mg (36%) of **10** (yellow crystals), m.p. 220–225 °C (decomposition). For $C_{18}H_{23}FN_4OS.H_2O$ (396.5) calculated: 54.53% C, 6.36% H, 4.79% F, 14.13% N, 8.09% S; found: 54.30% C, 6.01% H, 4.67% F, 13.47% N, 7.46% S. ^{1}H NMR spectrum ($CDCl_3$): 0.86–0.94 m, 2 H (CH_2); 1.38–1.48 m, 2 H (CH_2); 2.44 s, 3 H (SCH_3); 3.26–3.94 m, 10 H (CH, 2 × CH_2 of piperazine, $N(O)CH_3$); 4.46 s, 2 H (NH_2); 7.32 d, 1 H, J = 6 (H-8); 7.94 d, 1 H, J = 11 (H-5). IR spectrum ($CHCl_3$): 3 297 (NH_2), 1 630 (C=O). UV spectrum, λ_{max} (log ε): 242 (4.07), 284 (4.45), 340 (4.02), 386 (3.89). Mass spectrum, *m/z* (%): 379 (M^+ + H, 38).

4-Cyclopropyl-7-fluoro-6-(4-methylpiperazin-1-yl)-1,2,4,9-tetrahydrothiazolo[5,4-*b*]quinoline-2,9-dione (**5a**)

A solution of sodium hydrosulfide hydrate (0.9 g, 12.2 mmol) in water (5 ml) was added to a stirred solution of **9c** (1.2 g, 3.2 mmol) in THF (75 ml) and the mixture was stirred under nitrogen overnight. The mixture was evaporated to dryness, then water (50 ml) was added to the residue and the mixture was acidified with acetic acid and extracted with dichloromethane. Triethylamine (3 ml) was added to the water portion from the previous extraction and then triphosgene (0.60 g, 2.0 mmol) was added in several portions and the mixture was stirred at room temperature overnight. The formed solid was filtered off, washed with water and dried; yield 0.2 g (17%) of **5a** (yellow solid), decomposing without melting at 310–315 °C. For $C_{18}H_{19}FN_4O_2S$ (374.4) calculated: 57.74% C, 5.11% H, 5.07% F, 14.96% N, 8.56% S; found: 57.36% C, 5.29% H, 5.01% F, 14.74% N, 8.33% S. ^{1}H NMR spectrum (CD_3SOCD_3): 1.14–1.46 m, 4 H (2 × CH_2); 2.22 s, 3 H (CH_3); 3.10–3.40 m, 8 H (H of piperazine); 3.50–3.62 m, 1 H (CH); 7.40 d, 1 H, J = 8 (H-8); 7.76 d, 1 H, J = 12 (H-5); 11.6 bs, 1 H

(NH). IR spectrum (KBr): 1 710 (C=O). UV spectrum, λ_{max} (log ε): 213 (4.23), 252 (4.31), 261 (3.30), 284 (3.45), 337 (4.24), 357 (4.01); λ_{infl} 324 (4.13). Mass spectrum, *m/z* (%): 386 (M^+, 80).

9-Cyclopropyl-6,7-difluoro-2,3,4,9-tetrahydrothiazolo[5,4-*b*]quinoline-3,4-dione (**5b**)

A solution of sodium hydrosulfide hydrate (0.3 g, 4.1 mmol) in water (3 ml) was added to a stirred solution of **9f** (0.30 g, 1.0 mmol) in THF (25 ml) and the mixture was stirred under nitrogen overnight. Then water (25 ml) was added and the mixture was extracted with ether (25 ml), the water layer was acidified with dilluted hydrochloric acid and extracted with dichloromethane (6 × 50 ml). Triethylamine (0.5 ml) was added to the collected dichloromethane extracts and then triphosgene (0.15 g, 0.50 mmol) was added in several portions and the mixture was stirred at room temperature for 1 h. The solution was washed with water, dried with magnesium sulfate, evaporated and the residue was purified by flash chromatography (chloroform–methanol 95 : 5) yielding after crystallization from ethanol 0.18 g (61%) of **5b** (white crystals), decomposing without melting at 235–240 °C. For $C_{13}H_8F_2N_2O_2S$ (294.3) calculated: 53.06% C, 2.74% H, 12.91% F, 9.52% N, 10.89% S; found: 52.85% C, 3.04% H, 13.17% F, 9.74% N, 10.55% S. ^{1}H NMR spectrum (CD_3SOCD_3): 1.14–1.46 m, 4 H (2 × CH_2); 3.52–3.66 m, 1 H (CH); 7.98–8.18 m, 2 H (H-5, H-8); 12.15 bs, 1 H (NH). IR spectrum (KBr): 1 708 (C=O). UV spectrum, λ_{max} (log ε): 222 (4.27), 268 (4.55), 307 (3.52), 312 (3.54), 345 (3.98), 350 (3.97). Mass spectrum, *m/z* (%): 294 (M^+, 80), 279 (100).

1-Cyclopropyl-6,7-difluoro-2-mercapto-3-[(4-methylpiperazin-1-yl)carbonylamino]quinolin-4(1*H*)-one (**11**)

A mixture of **5b** (0.05 g, 0.17 mmol), *N*-methylpiperazine (0.1 ml, 0.9 mmol), triethylamine (0.3 ml) and acetonitrile (10 ml) was stirred at 50 °C under argon for 3 days. The mixture was evaporated to dryness and the residue was purified by preparative TLC (toluene–hexane 9 : 1) providing the main product which after crystallization from methanol yielded 0.03 g (45%) of **11** (yellowish crystals), decomposing without melting over 300 °C. For $C_{18}H_{20}F_2N_4O_2S$ (394.4) calculated: 54.81% C, 5.11% H, 9.63% F, 14.20% N, 8.13% S; found: 54.58% C, 4.98% H, 9.69% F, 14.44% N, 7.77% S. ^{1}H NMR spectrum ($CDCl_3$): 0.98–1.12 m, 2 H (CH_2); 1.48–1.64 m, 2 H (CH_2); 2.55 s, 3 H (CH_3); 2.80–3.00 m, 4 H (2 × CH_2 of piperazine); 3.35–3.46 m, 1 H (CH); 3.85–4.04 m, 4 H (2 × CH_2 of piperazine); 7.76–8.04 m, 2 H (H-5, H-8); 9.84 bs, 1 H (NH); 13.90 bs, 1 H (SH). Mass spectrum, *m/z* (%): 395 (M^+ + H, 18), 217 (100).

REFERENCES

1. Albrecht R.: Prog. Drug Res. *21*, 9 (1977).
2. Radl S.: Pharmacol. Ther. *48*, 1 (1990).
3. Chu D. T. W.: Drugs Fut. *17*, 1101 (1992).
4. Shen L. L., Baranowski J., Pernet A. G.: Biochemistry *28*, 3879 (1989).
5. Hubschwerlen C., Pflieger P., Specklin J.-L., Gubernator K., Gmunder H., Angehrn P., Kompis I.: J. Med. Chem. *35*, 1385 (1992).
6. Radl S., Bouzard D.: Heterocycles *34*, 2143 (1992)
7. Chu D. T. W.: J. Heterocycl. Chem. *27*, 839 (1990).
8. Sunko D. E., Wolf G.: J. Am. Chem. Soc. *80*, 4405 (1958).
9. Radl S., Chan K.-K.: J. Heterocycl. Chem. *31*, 437 (1994).
10. Radl S.: Collect. Czech. Chem. Commun *59*, 2123 (1994).
11. Cecchetti V., Fravolini A., Schiaffella F., Tabarrini O., Zhou W. C., Pagella P. G.: J. Heterocycl. Chem. *29*, 375 (1992).