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The Synthesis of Fluorinated 4*H*-1,4-Benzothiazine-2-carboxylic Acid 1,1-Dioxides—Thionated Analogues of Pefloxacin

Victor I. Vysokov, Valerii N. Charushin, Galina B. Afanasyeva and Oleg N. Chupakhin*

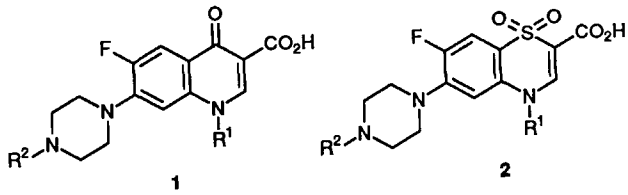
Chemical-Technological Department, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3432 44 1624

A synthetic route to 1,4-benzothiazine-2-carboxylic acid 1,1-dioxides, analogues of the 'fluoroquinolone' family of antibacterials, has been developed; unfortunately, the target compound (the thia-analogue of pefloxacin) has not revealed remarkable antibacterial activity *in vitro* against the majority of the strains tested.

The development of the so-called 'fluoroquinolone' family of antibiotics is a significant achievement in the medicinal chemistry of the last decade. In spite of the fact that a whole range of fluorinated 4-oxo-1,4-dihydroquinoline-3-carboxylic acids have already found application in practical and veterinary medicine as broad-spectrum antibacterial agents, there is still strong interest in new, more effective antibacterials. This has stimulated a stream of publications on structural modifications of the parent fluoroquinolones.[1–4]

Since fluoroquinolones exert their activity by inhibiting the DNA gyrase, a search for new inhibitors of this enzyme is currently in progress.[5]

In this communication we report on a new synthetic approach to 7-fluoro-6-piperazino-4*H*-1,4-benzothiazine-2-carboxylic acid 1,1-dioxides **2**, regarded as the thia-analogues of fluorinated quinolones of general formula **1** in which the quinolone carbonyl fragment is replaced by the sulphonyl group (Scheme 1). It has been suggested that such a replacement could satisfy the structural requirements in the putative mechanism of action.



Scheme 1

Non-fluorinated derivatives of 4*H*-1,4-benzothiazine-2-carboxylic acid 1,1-dioxide described in the literature[6] proved to possess poor antibacterial activity. The synthesis of fluorinated 1,4-benzothiazine-2-carboxylic acid 1-oxides, the close thia-analogues of quinolone antibiotics, has recently been reported; however, this group of compounds has not exhibited marked antibacterial activity.[7]

Our approach to the synthesis of 1,1-dioxides of 7-fluoro-6-piperazino-4*H*-1,4-benzothiazine-2-carboxylic acids **2** involved the following steps (Scheme 2).

(i) Regioselective conversion of 3,4-difluoroaniline **3** into the corresponding sulfonyl chloride **4** followed by the formation of sulfinic acid sodium salt **5**.

(ii) Alkylation of the latter with methyl bromoacetate followed by the intramolecular cyclization of the compounds **6** with triethylorthoformate into 6,7-difluoro-4*H*-1,4-benzothiazine-2-carboxylate 1,1-dioxides **7**.

(iii) Alkylation of **7** with ethyl iodide in DMF in the presence of potassium carbonate yielding the compounds **8**.

(iv) Nucleophilic substitution of the fluorine atom at C–6 by action of *N*-methylpiperazine and, finally, alkaline hydrolysis of the ester **9** yielding the target thia-analogue of pefloxacin **2**.

Evidence for the structure of compounds **2** and **6–9** is provided by their ^{1}H, ^{19}F NMR and mass spectroscopy data.†

† *Experimental procedure and selected spectral data for compounds* **2** and **6–9**.

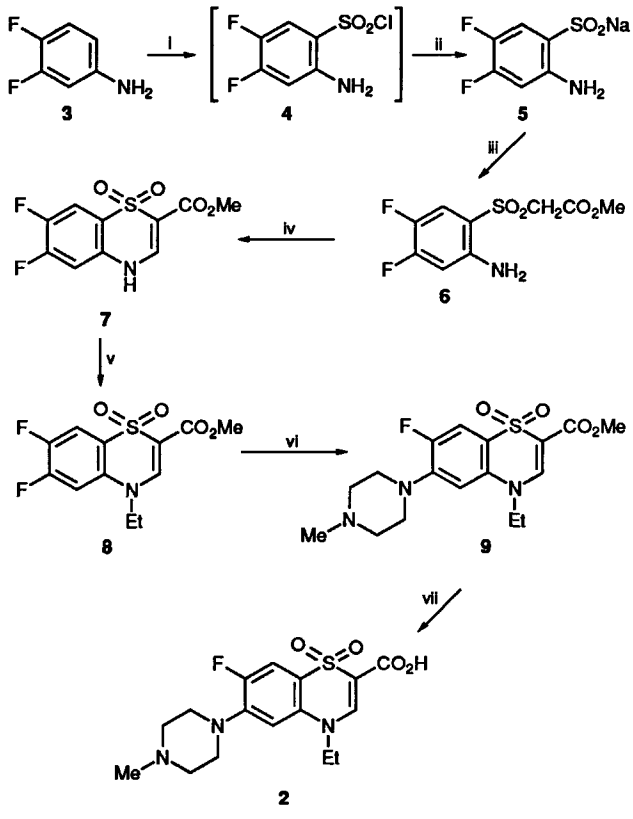
Methyl α-(2-amino-4,5-difluorophenyl)sulfonyl acetate **6** was obtained in 83% yield by a standard procedure for the alkylation of sulfinic sodium salt **5** with methyl bromoacetate in ethanol. ^{1}H NMR ([^{2}H$_6$]DMSO) 4.10 s (3H, OMe), 4.50 s (2H, $COCH_2$), 6.90 dd [1H, H–3, ^3J(H–3, F–4) 12 Hz, ^4J(H–3, F–5) 7 Hz], 7.50 dd [1H, H–6, ^3J(H–6, F–5) 10 Hz, ^4J(H–6, F–4) 7 Hz].

Methyl 6,7-difluoro-4*H*-1,4-benzothiazine-2-carboxylate 1,1-dioxide **7**. A mixture of sulfone **6** (7.9 g, 0.03 mol) and thioethylorthoformate (50 ml) was heated and kept under reflux for 1 h. The precipitate obtained after cooling to room temperature was filtered off and dried in air yielding 8 g (96%) of **7** with m.p. 238–240 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) 3.80 s (3H, OMe), 7.45 dd [1H, H–5, ^3J(H–5, F–6) 11 Hz, ^4J(H–5, F–7) 7 Hz], 8.10 dd [(1H, H–8), ^3J(H–8, F–7) 10 Hz, ^4J(H–8, F–6) 7 Hz], 8.20 s (1H, H–3).

Methyl 4-ethyl-6,7-difluoro-4*H*-1,4-benzothiazine-2-carboxylate 1,1-dioxide **8** was obtained in 90% yield by alkylation with ethyl iodide in DMF in the presence of potassium carbonate, m.p. 280–282 °C. ^{1}H NMR ([^{2}H$_6$]DMSO): 1.30 t (3H, CH_2–CH_3), 3.80 s (3H OMe), 4.20 q (2H, CH_2–CH_3), 7.9 dd [1H, H–5, ^3J(H–5, F–6) 10 Hz, ^4J(H–5, F–7) 7 Hz], 8.10 dd [1H, H–8, ^3J(H–8, F–7) 10 Hz, ^4J(H–8, F–6) 8 Hz], 8.30 s (1H, H–3).

Methyl 4-ethyl-7-fluoro-6-(4-methylpiperazino)-4*H*-1,4-benzothiazine-2-carboxylate 1,1-dioxide **9** was obtained in 80 yield, m.p. 190–192 °C.

4-Ethyl-7-fluoro-6-(4-methylpiperazino)-4*H*-1,4-benzothiazine-2-carboxylic acid 1,1-dioxide **2**. A suspension of **9** (3 g, 8 mmol) in 5% aqueous sodium hydroxide (20 ml) and DMF (20 ml) was stirred under reflux for 15 min. After being cooled to room temperaure the reaction mixture was acidified with acetic acid to pH 7. A precipitate of **2** was filtered off and recrystallized from water yielding 2 g (70%) of **2**, m.p. 210–212 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) 1.30 t (3H, CH_2–CH_3), 2.30 s (3H, N–CH_3), 3.1–3.3 m (8H, CH_2–CH_2), 4.20 q (2H, CH_2–CH_3), 6.70 d [1H, H–5, ^4J(H–5, F–7) 9 Hz], 7.70 d [1H, H–8, ^3J(H–8, F–7) 15 Hz], 8.10 s (1H, H–3).



Scheme 2 *Reagents and conditions* i, HSO_3Cl, $SOCl_2$, 130 °C; ii, Na_2SO_3, NaOH, 40 °C; iii, $BrCH_2CO_2Me$, EtOH, 20 °C; iv, $HC(OEt)_3$, 140 °C; v, EtI, K_2CO_3, DMF; vi, *N*-methylpiperazine, DMF, 120 °C; vii, 5% NaOH, DMF

The thia-analogue of pefloxacin **2** has been tested *in vitro* against representative gram-negative bacteria but has shown no activity. This can be explained by either the structural replacement made (the sulfonyl group instead of the carbonyl one) or by an easily-occurring decarboxylation reaction. Indeed, the characteristic feature of the mass spectrum of benzothiazine-2-carboxylic acid **2** is the absence (in contrast to pefloxacin) of a molecular ion peak. Instead, there is an intensive peak M − 44, which indicates easy decarboxylation of the acid **2**.

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