Thienopyridone Antibacterials V [1]. Synthesis of Some *N*(7)-Azacyclohexyl-4-oxothieno[2,3-*b*]pyridine-5-carboxylic Acids and Related Congeners

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Dedicated to Professor Hubert Schmidbaur on the occasion of his 75th birthday

A series of *N*(7)-azacyclohexyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxylic acids **9a** – **c**, related congeners **9d** – **g** and their methyl esters **8a** – **g** were prepared by cyclization of the respective 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-[(*N*(7)-azacyclyl/acyclic)amino]acrylates **7a** – **g**. The latter intermediates are accessible from methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-ethoxyacrylate (**6**). Of the present series, the 7-(*N,N*-dimethylamino) derivative **9d** exhibited good activity, especially against *Klebsiella pneumoniae* and *Salmonella paratyphi A* (MIC = 0.5 and 1.0 μg mL^{-1}, respectively).

Key words: 4-Oxothieno[2,3-*b*]pyridines, 7-(*N,N*-Dimethylamino), 7-Azacyclohexyl Derivatives, 7-Chiral Alaninol / Phenylethylamine Moieties, Antibacterial Activity

Introduction

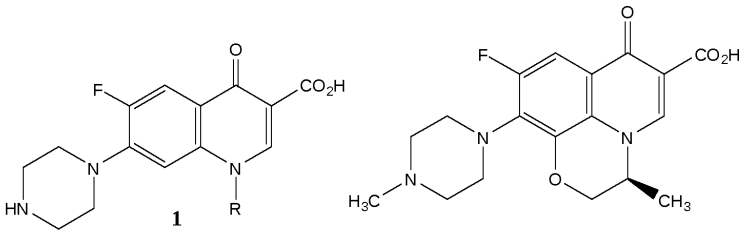
Several 4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids, potential bioisosteres of quinolone antibacterials, *e. g.* norfloxacin (**1a**) [3], ciprofloxacin (**1b**) [4] and ofloxacin (**2**) [5] (Fig. 1), were prepared and biotested [2, 6 – 13]. Substitution at the *N*(7)-position of thienopyridones has been reported for alkyl groups, *e. g.* compounds **3a** [6] and **3b** [7, 8] (Fig. 1) which exhibited a good level of activity against Gram-negative bacteria. *N*(7)-Aryl substitution has also been achieved, exemplified by compounds **4a**, **b** [2], which exhibited a good level of activity against Gram-negative and Gram-positive bacterial strains. Quite recently, *N*(7)-heteroaryl substitution, exemplified by compound **4c** [1], has also been investigated.

However, incorporation of saturated *N*(7)-azaheterocyclyl substituents has not been described in the literature for the thieno[2,3-*b*]pyridine class. Accordingly, and as a continuation of our research project directed toward structure-activity relationship (SAR) studies, we report in the present work on the synthesis and the antibacterial activity of a new series of 2-chloro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic esters **8a** – **c** and acids **9a** – **c** having selected azacyclohexyl appendages and related congeners at the *N*(7) locus (Scheme 1). Herein, the choice is confined to piperazino, morpholino, piperidino, *N,N*-dimethylamino, chiral alaninol and related biophoric amino entities.

Results and Discussion

Chemistry

The preparation of the new thieno[2,3-*b*]pyridines **9a** – **g** is achieved by utilizing 3-(2,5-dichlorothien-3-yl)-3-oxopropanoate (**5**) as starting material (accessible from 3-acetyl-2,5-dichlorothiophene) [14], and constructing the pyridone nucleus thereupon through a series of conversions, as illustrated in Scheme 1. Thus, treatment of the β-keto ester **5** with triethyl orthoformate in acetic anhydride gave the corresponding methyl 3-ethoxyacrylate derivative **6** [7] which serves as the common intermediate for the synthe-



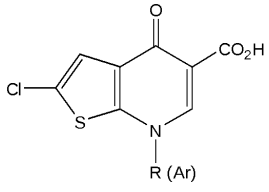


Fig. 1. Structures of some fluoroquinolones (**1a**, **b** / **2**) and thieno[2,3-*b*]pyridones (**3a**, **b** / **4a** – **c**).

sis of the target compounds **9a** – **g**. Herein, condensation of the enol ether **6** with the appropriate amino compound resulted in smooth production of the respective 3-substituted aminoacrylates **7a** – **g**. Cyclization of deprotonated **7a** – **g** (using NaH in tetrahydrofuran) yielded the respective methyl 4-oxothieno[2,3-*b*]pyridine-5-carboxylates **8a** – **g**. This intramolecular nucleophilic heteroaromatic substitution (S_N-Ar) reaction is presumably facilitated by the presence of the vicinal electron-withdrawing keto group at C-3″ and neighboring chlorine atom at C-5″. Saponification of esters **8a** – **g** furnished the desired *N*-(7)-substituted-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids **9a** – **g**.

The new compounds **7** – **9** were characterized by elemental analyses, MS and NMR spectral data. These data, detailed in the Experimental Section, are consistent with the suggested structures. Thus, their MS spectra displayed the correct molecular ions $[M]^+$ for which the *m*/*z* values are in agreement with those calculated from the respective molecular formulas.

^{1}H and ^{13}C signal assignments to the different protons and carbons in the NMR spectra of the new compounds followed from DEPT and 2D (COSY, HMQC, HMBC) experiments which showed correlations that helped in the full assignments. Each of the ^{1}H signals, belonging to the different hydrogens in the acyclic enamino-keto esters **7a** – **g**, is displayed as two sets of resonances with unequal peak areas; this feature is in accordance with the existence of *Z*/*E* diastereomeric forms in solution. Likewise, ^{13}C-signal doubling, arising from *Z*/*E* diastereomers, is also observed for a number of carbons such as C-4, C-5, C-4′, C-2″, C-3″ and ester-CH_3. Such a phenomenon is well-known and has been previously documented for related systems [2, 7].

Antibacterial activity

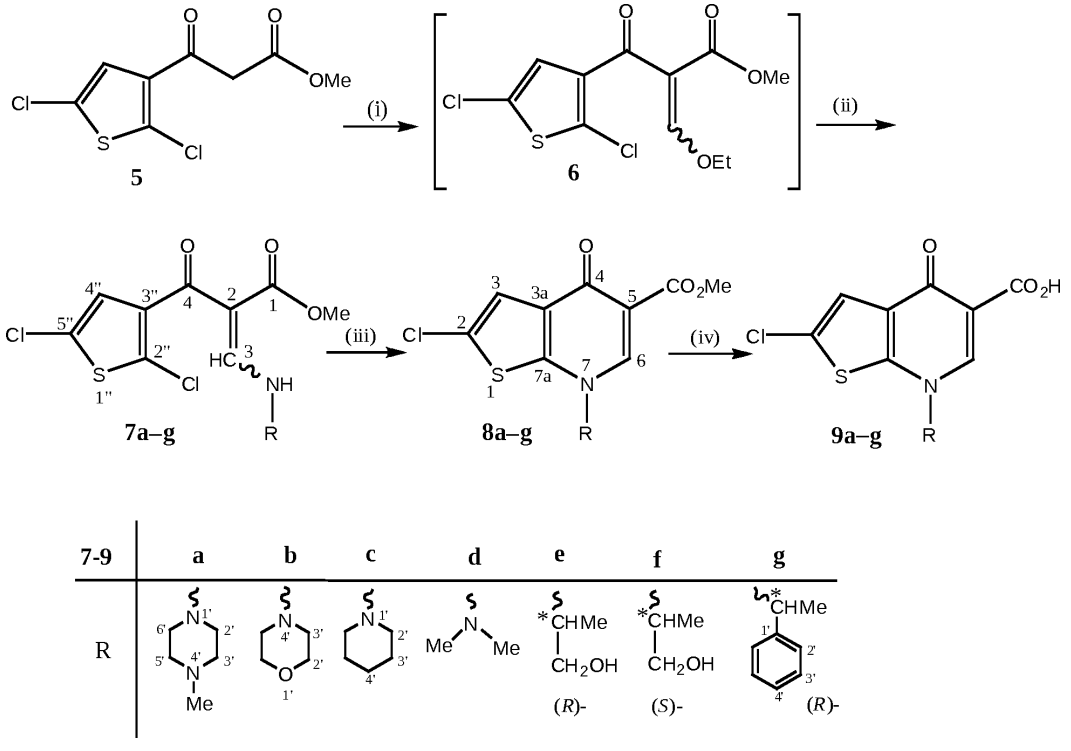
Compounds **9a** – **g** were tested *in vitro* as sodium salts in aqueous solution against eight different bacterial species (listed in Table 1) using ofloxacin (**2**, OFL) as reference. The antibacterial activity was evaluated by the minimal inhibitory concentration (MIC) technique.

Compound **9d** exhibits a moderate to low level of antibacterial activity against the test organisms except for *St. Faecalis* and *P. aeruginosa* where it is inactive at $\geq 128\ \mu g\ mL^{-1}$. Compounds **9b** – **g** did not show any significant antibacterial activity.

In conclusion, the 7-(*N*,*N*-dimethylamino) derivative **9d** might be envisaged as a lead compound for further manipulations. In particular, fluorination of va-

Table 1. *In vitro* antibacterial activity (MIC values in μg mL^{-1}) of **9d** and ofloxacin (OFL) as reference agent.

Strain	OFL	**9d**	Strain	OFL	**9d**
Staphylococcus aureus ATCC 9144	0.125	32	*Klebsiella pneumoniae* ATCC 10031	$\leq$ 0.06	0.5
Streptococcus faecalis ATCC 11700	4	$>$ 128	*Proteus mirabilis*	$\leq$ 0.06	4
Escherichia coli ATCC 10536	$\leq$ 0.06	8	*Pseudomonas aeruginosa* ATCC 27853	2	$>$ 128
Salmonella paratyphi A	0.06	1	*Salmonella paratyphi C*	$<$ 0.06	8
Shigella sonnei	$<$ 0.06	4	*Providencia rettgeri*	0.25	4



Scheme 1. (i) Ac_2O, $(EtO)_3CH$ / 130 °C, 3 – 4 h; (ii) R-NH_2, CH_2Cl_2; (iii) NaH, THF / 24 °C, 30 min, then 60 °C; (iv) 1 % ethanolic NaOH / r. t., 1 – 2 h, then 10 % aq. HCl.

cant CH-thiophene sites in **9d** might produce drugable fluorothieno[2,3-*b*]pyridones comparable in potency to marketed fluoroquinolone antibacterials.

Experimental Section

3-Acetyl-2,5-dichlorothiophene was purchased from Fluorochem (England), (*R*)-alaninol, (*S*)-alaninol, 1-amino-4-methylpiperazine and *N*-aminomorpholine were purchased from Acros. 1-Aminopiperidine was a product from Aldrich. Sodium hydride (80 % dispersion in mineral oil) was obtained from Fluka. Tetrahydrofuran (THF) and dimethyl carbonate were dried before use. Melting points were determined on an electrothermal melting temperature apparatus. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument. Chemical shifts are expressed in ppm with reference to TMS as internal standard. Mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses were preformed at M. H. W Laboratories, Arizona, USA.

Antibacterial tests

The MICs were determined by the conventional agar dilution procedures according to the method of Mueller-Hinton at pH = 7.4. Aqueous stock solutions (1000 μg mL^{-1}) of the test compounds were prepared with 0.1 N NaOH. Serial dilutions were then made to obtain test concentrations in the range 128 – 0.06 μg mL^{-1}. The agar plates were inoculated with approximately 10^5 *CFU* per spot. The agar plates were then incubated at 37 °C for 18 h. The MICs were taken as the lowest concentration of the test compounds that inhibits visible growth.

*Synthesis of compounds **5** and **6***

*Methyl 3-(2,5-dichlorothien-3-yl)-3-oxopropanoate (**5**)*

This compound was prepared from 3-acetyl-2,5-dichlorothiophene and dimethyl carbonate, following a recently reported procedure [7, 14].

*Methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-ethoxyacrylate (**6**)*

A stirred mixture of compound **5** (5.3 g, 21 mmol), triethyl orthoformate (4.6 g, 32 mmol) and acetic anhydride (9.2 g, 90 mmol) was heated at 135 – 140 °C for 3 – 4 h. The resulting solution was concentrated *in vacuo* to give **6** as a brown viscous oil in nearly quantitative yield (∼ 6.4 g), which was used as such in the next step without further purification [7, 14].

*Preparation of methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-(N-substituted amino)acrylates **7a** – **g***

General procedure

To a stirred solution of methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-ethoxyacrylate (**6**) (6.16 g, 20 mmol) in dichloromethane (50 mL) was added the particular amino compound (22 mmol) at 2 – 4 °C. The resulting reaction was then stirred at 20 °C for 24 h. In the case of compound **7a**, the particular amine (1-amino-4-methylpiperazine) was added at r. t., and the resulting reaction mixture was stirred at 40 – 45 °C for 24 h. The solvent was then evaporated and the residue recrystallized from the appropriate solvent. Yields were in the range 60 – 91 %.

*Methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-[(4-methylpiperazin-1-yl)amino]acrylate (**7a**)*

The compound was obtained as an off-white solid that was recrystallized from chloroform / petroleum ether (b. p. 40 – 60 °C). Yield: 4.9 g (65 %), m. p. 99 – 100 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3H, NCH_3), 2.57 (m, 4H, 3′-H_2 + 5′-H_2), 2.97 (m, 4H, 2′-H_2 + 6′-H_2), 3.65, 3.67 (2s, 3H, OCH_3, *Z/E*), 6.79, 6.91 (2s, 1H, H-4″, *Z/E*), 8.33, 8.10 (2d, 1H, *J* = 11.6, 11.6 Hz, 3-H, *Z/E*), 11.08, 9.67 (2d, 1H, *J* = 11.6, 11.6 Hz, NH, *Z/E*). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6 (NCH_3), 51.4 (OCH_3), 54.1 (C-3′ + C-5′), 56.5 (C-2′ + C-6′), 99.7 (C-2), 125.8 (C-3″), 126.3 (C-4″), 127.2 (C-5″), 139.6 (C-2″), 159.0 (C-3), 166.7 (C-1), 186.9, 183.9 (C-4, *Z/E*). – MS (EI, 70 eV): *m/z* (%) = 377 (23) $[M]^+$, 342 (31), 310 (61), 282 (2), 179 (14), 144 (1), 116 (2), 99 (97). – $C_{14}H_{17}N_3O_3SCl_2$ (378.28): calcd. C 44.45, H 4.53, N 11.11; found C 44.64, H 4.59, N 10.89.

*Methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-[(morpholin-4-yl)amino]acrylate (**7b**)*

The solid product was recrystallized from methanol. Yield: 5.9 g (81 %), m. p. 118 – 119 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.94 (m, 4H, 3′-H_2 + 5′-H_2), 3.80 (m, 4H, 2′-H_2 + 6′-H_2), 3.65, 3.67 (2s, 3H, OCH_3, *Z/E*), 6.79, 6.92 (2s,1H, 4″-H, *Z/E*), 8.35, 8.16 (2d, 1H, *J* = 11.4, 11.4 Hz, 3-H, *Z/E*), 11.09, 9.69 (2d, 1H, *J* = 11.4, 11.4 Hz, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.4 (OCH_3), 57.0 (C-3′ + C-5′), 66.1 (C-2′ + C-6′), 99.9 (C-2), 125.9 (C-3″), 126.2 (C-4″), 127.2 (C-5″), 139.5 (C-2″), 159.0 (C-3), 166.6, 169.0 (C-1, *Z/E*), 187.0, 183.9 (C-4, *Z/E*). – MS (EI, 70 eV): *m/z* (%) = 364 (81) $[M]^+$, 329 (63), 297 (55), 269 (2), 179 (51), 144 (48), 116 (8), 86 (41). – $C_{13}H_{14}N_2O_4SCl_2$ (365.24): calcd. C 42.75, H 3.86, N 7.67; found C 42.69, H 3.92, N 7.63.

*Methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-[(piperidin-1-yl)amino]acrylate (**7c**)*

The obtained solid product was recrystalllized from chloroform/diethyl ether. Yield: 4.5 g (62 %), m. p. 108 – 110 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (m, 2H, 4′-H_2), 1.71 (m, 4H, 3′-H_2 + 5′-H_2), 2.85 (m, 4H, 2′-H_2 + 6′-H_2), 3.64, 3.67 (2s, 3H, OCH_3, *Z/E*), 6.80, 6.90 (2s, 1H, 4″-H, *Z/E*), 8.34, 8.11 (2d, 1H, *J* = 11.7, 11.7 Hz, 3-H, *Z/E*), 11.12, 9.70 (2d, 1H, *J* = 11.7, 11.7 Hz, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (C-4′), 25.2 (C-3′ + C-5′), 51.3 (OCH_3), 58.1 (C-2′ + C-6′), 99.3, 98.9 (C-2, *Z/E*), 125.7, 124.9 (C-3″, *Z/E*), 126.3, 127.2 (C-4″, *Z/E*), 127.3 (C-5″), 139.7 (C-2″), 158.8, 159.0 (C-3, *Z/E*), 166.7, 169.0 (C-1, *Z/E*), 186.8, 183.9 (C-4, *Z/E*). – MS (EI, 70 eV): *m/z* (%) = 362 (17) $[M]^+$, 327 (46), 295 (100), 267 (3), 179 (30), 144 (2), 116 (2), 84 (34). – $C_{14}H_{16}N_2O_3SCl_2$ (363.27): calcd. C 46.29, H 4.44, N 7.71; found C 46.30, H 4.39, N 7.65.

*Methyl 2-[(2,5-dichlorothien-3-yl)carbonyl]-3-N-(2,2-dimethylhydrazino)acrylate (**7d**)*

The solid product was recrystallized from chloroform/diethyl ether. Yield: 3.3 g (51 %), m. p. 93 – 95 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.70, 2.67 (2s, 6H, $N(CH_3)_2$, *Z/E*), 3.65, 3.68 (2s, 3H, OCH_3, *Z/E*), 6.79, 6.91 (2s, 1H, 4″-H, *Z/E*), 8.33, 8.10 (2d, 1H, *J* = 11.6, 11.6 Hz, 3-H, *Z/E*), 11.08, 9.63 (2d, 1H, *J* = 11.6, 11.6 Hz, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.7 ($N(CH_3)_2$), 51.4 (OCH_3), 99.3, 100.3 (C-2, *Z/E*), 125.0 (C-3″), 125.8 (C-5″), 126.3, 127.2 (C-4″, *Z/E*), 139.6 (C-2″), 158.8, 159.1 (C-3, *Z/E*), 166.7, 169.0 (C-1, *Z/E*), 186.8, 183.9 (C-4, *Z/E*). – MS (EI, 70 eV): *m/z* (%) = 322 (67) $[M]^+$, 287 (65), 255 (100), 227 (13), 179 (41), 116 (9), 44 (19). – $C_{11}H_{12}N_2O_3SCl_2$ (323.20): calcd. C 40.88, H 3.74, N 8.67; found C 40.66, H 3.89, N 8.88.

*Methyl (R)-2-[(2,5-dichlorothien-3-yl)carbonyl]-3-N-(2-hydroxy-1-methylethylamino)acrylate (**7e**)*

The compound was obtained as an oil. Yield: 5.8 g (86 %). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32, 1.30 (2d,

3H, J = 6.4, 6.4 Hz, $CHCH_3$, *Z/E*), 3.56 (m, 3H, CH_2OH + CHMe), 3.63, 3.64 (2s, 3H, OCH_3, *Z/E*), 4.20 (br s, 1H, CH_2OH), 6.78, 6.89 (2s, 1H, 4″-H, *Z/E*), 8.17, 7.99 (2d, 1H, J = 14.4, 14.4 Hz, 3-H, *Z/E*), 10.83, 9.42 (2dd, 1H, J = 14.4, 6.4 Hz / 14.4, 6.4 Hz, NH, *Z/E*). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0 ($CHCH_3$), 51.4, 51.2 (OCH_3, *Z/E*), 57.9, 57.5 (CHMe, *Z/E*), 65.9, 66.1 (CH_2OH, *Z/E*), 100.7, 100.4 (C-2, *Z/E*), 124.6 (C-3″), 126.0 (C-5″), 126.3, 126.1 (C-4″, *Z/E*), 139.9 (C-2″), 159.9, 159.7 (C-3, *Z/E*), 167.5, 169.1 (C-1, *Z/E*), 186.8 (C-4). – MS (EI, 70 eV): m/z (%) = 337 (2) $[M]^+$, 302 (100), 270 (4), 242 (1), 179 (62), 144 (2), 116 (2), 59 (9). – $C_{12}H_{13}NO_4SCl_2$ (338.21): calcd. C 42.62, H 3.87, N 4.14; found C 42.53, H 3.78, N 4.06.

*Methyl (S)-2-[(2,5-dichlorothien-3-yl)carbonyl]-3-N-(2-hydroxy-1-methylethyl)acrylate (**7f**)*

This compound was obtained as an oil. Yield: 5.7 g (84 %). – $C_{12}H_{13}NO_4SCl_2$ (338.21): calcd. C 42.62, H 3.87, N 4.14; found C 42.45, H 3.82, N 4.11. The spectral data for this compound are in complete match with those of its (*R*)-enantiomer.

*Methyl (R)-2-[(2,5-dichlorothien-3-yl)carbonyl]-3-N-(2-phenylethylamino)acrylate (**7g**)*

The compound was recrystallized from benzene/petroleum ether. Yield: 6.5 g (85 %), m. p. 93 – 94 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67, 1.65 (2d, 3H, J = 6.9, 6.9 Hz, $CHCH_3$), 3.60, 3.64 (2s, 3H, OCH_3, *Z/E*), 4.65, 4.06 (2m, 1H, C*H*Me), 6.80, 6.87 (2s, 1H, 4″-H, *Z/E*), 7.37, 7.29 (2m, 5H, Ph), 8.13, 7.93 (2d, 1H, J = 14.3, 14.2 Hz, 3-H, *Z/E*), 11.20, 9.70 (2dd, 1H, J = 14.3, 6.9 Hz / 14.3, 6.9 Hz, NH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0 ($CHCH_3$), 51.3, 51.2 (OCH_3, *Z/E*), 59.3, 58.9 (*C*HMe, *Z/E*), 101.0, 100.8 (C-2, *Z/E*), 125.7 (C-3″), 126.0 (C-3′ + C-5′), 126.3, 125.9 (C-4″, *Z/E*), 127.1 (C-5″), 128.3 (C-4′), 129.1 (C-2′ + C-6′), 139.9 (C-2″), 141.1, 141.2 (C-1′, *Z/E*), 158.8, 159.1 (C-3, *Z/E*), 166.7, 169.0 (C-1, *Z/E*), 186.8, 183.9 (C-4, *Z/E*). – MS (EI, 70 eV): *m/z* (%) = 383 (2) $[M]^+$, 348 (51), 316 (1), 288 (2), 179 (11), 151 (2), 116 (1), 105 (100). – $C_{17}H_{15}NO_3SCl_2$ (384.28): calcd. C 53.14, H 3.93, N 3.64; found C 53.3, H 4.16, N 3.56.

*Preparation of methyl 7-(N-substituted amino)- and 7-alkyl-2-chloro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylates **8a** – **g***

General procedure

To a stirred solution of the particular methyl 3-(*N*-substituted amino)- or methyl 3-(*N*-alkylamino)-2-[(2,5-dichlorothien-3-yl)carbonyl]acrylate **7a** – **g** (16 mmol) in dry THF (70 mL) was added sodium hydride (80 % dispersion in mineral oil; 0.5 g, 20 mmol). The reaction mixture was then stirred at r. t. for 30 min. The temperature was allowed to rise to 60 – 62 °C and maintained at that temperature for 2 – 3 h. The solvent was then evaporated, and the residue was washed with water. The solid product was purified by crystallization from the appropriate solvent.

*Methyl 2-chloro-7-(4-methylpiperazin-1-yl)-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8a**)*

The obtained solid was recrystallized from chloroform/methanol. Yield: 4.5 g (82 %), m. p. 210 – 211 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, NCH_3), 2.42 (br t, 2H, J = 10.5, 3′-H + 5′-H), 2.96 (br d, 2H, J = 10.2 Hz, 3′-H + 5′-H), 3.30 (br t, 2H, J = 10.2 Hz, 2′-H + 6′-H), 3.19 (br d, 2H, J = 10.5 Hz, 2′-H + 6′-H), 3.91 (s, 3H, OCH_3), 7.40 (s, 1H, 3-H), 8.58 (s, 1H, 6-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.5 (NCH_3), 52.4 (OCH_3), 53.9 (C-3′ + C-5′), 54.6 (C-2′ + C-6′), 115.7 (C-5), 123.4 (C-3), 126.1 (C-4a), 131.5 (C-2), 139.2 (C-6), 149.2 (C-7a), 165.6 (CO_2Me), 169.6 (C-4). – MS (EI, 70 eV): *m/z* (%) = 341 (74) $[M]^+$, 242 (26), 211 (87), 183 (3), 99 (100), 56 (39), 53 (6). – $C_{14}H_{16}N_3O_3SCl$ (341.82): calcd. C 49.19, H 4.72, N 12.29; found C 48.99, H 4.69, N 11.99.

*Methyl 2-chloro-7-(morpholin-4-yl)-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8b**)*

The solid obtained was recrystallized from chloroform/petroleum ether. Yield: 4.8 g (91 %), m. p. 200 – 202 °C (dec.). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.17 (br d, 2H, J = 10.3 Hz, 3′-H + 5′-H), 3.31 (dt, 2H, J = 10.2, J = 3.0, 3′-H + 5′-H), 3.81 (dt, 2H, J = 10.3, J = 3.0 Hz, 2′-H + 6′-H), 4.07 (br d, 2H, J = 10.3 Hz, 2′-H + 6′-H), 3.93 (s, 3H, OCH_3), 7.40 (s, 1H, 3-H), 8.55 (s, 1H, 6-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.5 (OCH_3), 54.5 (C-3′ + C-5′) , 66.8 (C-2′ + C-6′), 115.9 (C-5), 123.4 (C-3), 126.1 (C-4a), 131.6 (C-2), 138.9 (C-6), 148.9 (C-7a), 165.7 (CO_2Me), 169.4 (C-4). – MS (EI, 70 eV): *m/z* (%) = 328 (43) $[M]^+$, 242 (3), 211 (14), 183 (5), 86 (35), 56 (100), 53 (11). – $C_{13}H_{13}N_2O_4SCl$ (328.78): calcd. C 47.49, H 3.99, N 8.52; found C 47.46, H 3.69, N 8.48.

*Methyl 2-chloro-4-oxo-7-(piperidin-1-yl)-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8c**)*

The obtained solid was recrystallized from a mixture of chloroform/diethyl ether. Yield: 4.6 g (88 %), m. p. 160 – 162 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (m, 6H, 3′-H_2 + 4′-H_2 + 5′-H_2), 3.01 (dt, 2H, J = 10.2, 2.1 Hz, 2′-H + 6′-H), 3.28 (br d, 2H, J = 9.3 Hz, 2′-H + 6′-H), 3.92 (s, 3H, OCH_3), 7.40 (s, 1H, 3-H), 8.54 (s, 1H, 6-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (C-4′), 26.1 (C-3′ + C-5′), 52.4 (OCH_3), 55.7 (C-2′ + C-6′), 115.6 (C-5), 123.3 (C-3), 126.1 (C-4a), 131.5 (C-2), 139.2 (C-6), 149.4 (C-7a),

166.0 (CO_2Me), 169.6 (C-4). – MS (EI, 70 eV): *m/z* (%) = 326 (5) $[M]^+$, 242 (1), 211 (5), 183 (3), 84 (18), 53 (4), 50 (100). – $C_{14}H_{15}N_2O_3SCl$ (326.80): calcd. C 51.45, H 4.63, N 8.57; found C 51.48, H 4.64, N 8.59.

*Methyl 2-chloro-7-(dimethylamino)-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8d**)*

The obtained solid was recrystallized from methanol. Yield: 1.6 g (35 %), m. p. 203 – 204 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.96 (s, 6H, $N(CH_3)_2$), 3.93 (s, 3H, OCH_3), 7.40 (s, 1H, 3-H), 8.56 (s, 1H, 6-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.2 (NCH_3), 52.5 (OCH_3), 115.9 (C-5), 123.3 (C-3), 126.2 (C-4a), 131.5 (C-2), 138.6 (C-6), 149.2 (C-7a), 166.0 (CO_2Me), 169.6 (C-4). – MS (EI, 70 eV): *m/z* (%) = 286 (96) $[M]^+$, 255 (10), 228 (100), 211 (49), 185 (39), 183 (17), 53 (23), 44 (16). – $C_{11}H_{11}N_2O_3SCl$ (286.74): calcd. C 46.08, H 3.87, N 9.77; found C 45.98, H 3.69, N 9.55.

*Methyl (R)-2-chloro-7-[N-(2-hydroxy-1-methylethyl)]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8e**)*

The obtained solid was recrystallized from chloroform/diethyl ether. Yield: 3.0 g (62 %), m. p. 180 – 181 °C (dec.). – ^{1}H NMR (300 MHz, $[D_6]$DMSO): δ = 1.65 (d, 3H, *J* = 6.9 Hz, $CHCH_3$), 3.65 (m, 2H, CH_2OH), 3.85 (s, 3H, OCH_3), 4.16 (m, 1H, C*H*Me), 7.40 (s, 1H, 3-H), 8.58 (s, 1H, 6-H). – ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 15.7 ($CHCH_3$), 52.5 (OCH_3), 62.6 (CH_2OH), 64.8 (*C*HMe), 115.9 (C-5), 122.0 (C-3), 125.5 (C-4a), 131.9 (C-2), 142.8 (C-6), 148.5 (C-7a), 165.1 (CO_2Me), 169.7 (C-4). – MS (EI, 70 eV): *m/z* (%) = 301 (24) $[M]^+$, 266 (11), 242 (26), 211 (23), 207 (67), 183 (20), 59 (94), 53 (100). – $C_{12}H_{12}NO_4SCl$ (301.75): calcd. C 47.77, H 4.01, N 4.64; found C 47.81, H 3.99, N 4.63.

*Methyl (S)-2-chloro-7-[N-(2-hydroxy-1-methylethyl)]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8f**)*

The obtained solid was recrystallized from chloroform/diethyl ether. Yield: 2.9 g (60 %), m. p. 180 – 181 °C (dec.). – $C_{12}H_{12}NO_4SCl$ (301.75): calcd. C 47.77, H 4.01, N 4.64; found C 47.72, H 3.89, N 4.61. The spectral data for this compound are in complete match with those of its (*R*)-enantiomer (compound **8e**).

*Methyl (R)-2-chloro-7-[N-(2-phenylethyl)]-4-oxo-4,7-dihydrothieno[2,3-b]-pyridine-5-carboxylate (**8g**)*

The obtained solid was purified by recrystallization from chloroform/diethyl ether. Yield: 4.7 g (85 %), m. p. 178 – 180 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (d, 3H, *J* = 7.0 Hz, $CHCH_3$), 3.90 (s, 3H, OCH_3), 5.30 (q, 1H, *J* = 7.0 Hz, C*H*Me), 7.40 (m, 5H, Ph), 7.42 (s, 1H, 3-H), 8.47 (s, 1H, 6-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 ($CHCH_3$), 52.5 (OCH_3), 65.1 (*C*HMe), 115.2 (C-5), 123.0 (C-3), 125.5 (C-4a), 126.5 (C-3′ + C-5′), 129.4 (C-4′), 129.5 (C-2′ + C-6′), 133.3 (C-2), 137.1 (C-1′), 142.4 (C-6), 147.0 (C-7a), 166.2 (CO_2Me), 169.8 (C-4). – MS (EI, 70 eV): *m/z* (%) = 347 (45) $[M]^+$, 289 (5), 243 (97), 211 (93), 185 (2), 183 (1), 105 (100), 53 (2). – $C_{17}H_{14}NO_3SCl$ (347.82): calcd. C 58.71, H 4.06, N 4.03; found C 58.49, H 3.90, N 3.83.

*Preparation of methyl 7-(N-substituted amino)- and methyl 7-alkyl-2-chloro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acids **9a** – **g**; general procedure*

The appropriate methyl 7-(*N*-substituted amino)- or methyl 7-alkyl-2-chloro-4-oxo-4,7-dihydro[2,3-*b*]pyridine-5-carboxylate **8a** – **g** (5.0 mmol) was added to an ethanolic solution of sodium hydroxide (40 mL, 2 M). The resulting solution was stirred for 1 – 2 h, filtered, diluted with H_2O (40 mL) and then acidified with 8 % aqueous hydrochloric acid. The precipitated product was collected by suction filtration, washed with water, dried and recrystallized from the appropriate solvent.

*2-Chloro-7-(4-methylpiperazin-1-yl)-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid (**9a**)*

The solid product was recrystallized from chloroform/diethyl ether. Yield: 1.36 g (83 %), m. p. 235 – 236 °C. – ^{1}H NMR (300 MHz, $[D_4]CH_3OH$): δ = 3.00 (s, 3H, NCH_3), 3.63 (m, 8H, 2′-H_2 + 3′-H_2 + 5′-H_2 + 6′-H_2)), 7.51 (s, 1H, 3-H), 9.13 (s, 1H, 6-H). – ^{13}C NMR (75 MHz, D_2O + NaOD): δ = 45.5 (NCH_3), 50.8 (C-3′ + C-5′) , 53.3 (C-2′ + C-6′), 112.9 (C-5), 121.7 (C-3), 128.6 (C-4a), 129.0 (C-2), 141.4 (C-6), 151.0 (C-7a), 166.2 (CO_2H), 173.4 (C-4). – MS (EI, 70 eV): *m/z* (%) = 327 (17) $[M]^+$, 283 (51), 229 (28), 211 (99), 185 (100), 157 (5). – $C_{13}H_{14}N_3O_3SCl$ (327.79): calcd. C 47.64, H 4.31, N 12.82; found C 47.57, H 4.29, N 11.69.

*2-Chloro-7-(morpholin-4-yl)-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid (**9b**)*

The solid compound was obtained by recrystallization from chloroform/petroleum ether. Yield: 1.37 g (87 %), m. p. 245 – 246 °C (dec.). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20 (br d, 2H, *J* = 10.0 Hz, 3′-H + 5′-H), 3.37 (dt, 2H, *J* = 10.3, *J* = 2.2 Hz, 3′-H + 5′-H), 3.82 (dt, 2H, *J* = 10.3, *J* = 2.2 Hz, 2′-H + 6′-H), 4.07 (br d, 2H, *J* = 10.0 Hz, 2′-H + 6′-H), 7.46 (s, 1H, 3-H), 8.86 (s, 1H, 6-H), 15.05 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.8 (C-3′ + C-5′) , 66.7 (C-2′ + C-6′), 113.8 (C-5), 122.2 (C-3), 128.6 (C-4a), 129.3 (C-2), 138.4 (C-6), 151.2 (C-7a), 166.0 (CO_2H), 173.2 (C-4). – MS (EI, 70 eV): *m/z* (%) = 314 (19) $[M]^+$, 270 (100), 229 (2), 211 (7), 185 (30), 157 (4), 86

(36). – $C_{12}H_{11}N_2O_4SCl$ (314.75): calcd. C 45.79, H 3.52, N 8.90; found C 45.83, H 3.60, N 8.66.

*2-Chloro-4-oxo-7-(piperidin-1-yl)-4,7-dihydrothieno-[2,3-b]pyridine-5-carboxylic acid (**9c**)*

The pure compound was obtained by recrystallization from chloroform/petroleum ether. Yield: 1.25 g (80 %), m. p. 250 – 251 °C. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.30 (m, 6H, 3′-H$_2$ + 4′-H$_2$ + 5′-H$_2$), 1.66 (br t, 2H, J = 13.0 Hz, 2′-H + 6′-H), 1.83 (br d, 2H, J = 12.0 Hz, 2′-H + 6′-H), 7.60 (s, 1H, 3-H), 9.22 (s, 1H, 6-H), 15.38 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 22.5 (C-4′), 26.4 (C-3′ + C-5′), 54.8 (C-2′ + C-6′), 112.9 (C-5), 121.9 (C-3), 127.1 (C-4a), 127.8 (C-2), 140.6 (C-6), 152.3 (C-7a), 165.2 (CO_2H), 172.6 (C-4). – MS (EI, 70 eV): *m/z* (%) = 312 (21) [M]$^+$, 268 (93), 229 (1), 211 (4), 185 (21), 183 (1), 157 (4), 84 (100). – $C_{13}H_{13}N_2O_3SCl$ (312.78): calcd. C 49.92, H 4.19, N 8.96; found C 49.91, H 4.18, N 8.94.

*2-Chloro-7-(N,N-dimethylamino)-4-oxo-4,7-dihydro-thieno[2,3-b]pyridine-5-carboxylic acid (**9d**)*

The compound was recrystallized from chloroform/ petroleum ether. Yield: 0.90 g (66 %), m. p. 210 – 211 °C (dec.). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01 (s, 6H, N(CH_3)$_2$), 7.43 (s, 1H, 3-H), 8.87 (s, 1H, 6-H), 15.17 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.5 (N(CH_3)$_2$), 113.9 (C-5), 122.0 (C-3), 128.7 (C-4a), 129.1 (C-2), 138.0 (C-6), 151.4 (C-7a), 166.2 (CO_2H), 173.1 (C-4). – MS (EI, 70 eV): *m/z* (%) = 272 (46) [M]$^+$, 228 (100), 210 (25), 185 (99), 182 (3), 157 (8), 44 (28). – $C_{10}H_9N_2O_3SCl$ (272.71): calcd. C 44.04, H 3.33, N 10.27; found C 43.81, H 3.42, N 10.07.

*(R)-2-Chloro-7-[N-(2-hydroxy-1-methylethyl)]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid (**9e**)*

The pure compound was obtained by recrystallization from chloroform/diethyl ether. Yield: 1.18 g (82 %), m. p. 249 – 250 °C. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.65 (d, 3H, J = 6.8 Hz, CHCH_3), 3.82 (m, 2H, CH_2OH), 4.46 (m, 1H, C*H*Me), 5.35 (t, 1H, J = 5.4 Hz, CH$_2$O*H*), 7.66 (s, 1H, 3-H), 8.80 (s, 1H, 6-H), 15.48 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 15.4 (CH*C*H$_3$), 62.6 (*C*H$_2$OH), 65.8 (*C*HMe), 111.8 (C-5), 121.5 (C-3), 126.0 (C-4a), 129.0 (C-2), 142.3 (C-6), 150.7 (C-7a), 165.7 (CO_2H), 172.7 (C-4). – MS (EI, 70 eV): *m/z* (%) = 287 (19) [M]$^+$, 269 (11), 243 (100), 211 (15), 185 (51), 183 (3), 157 (7), 59 (7). – $C_{11}H_{10}NO_4SCl$ (287.72): calcd. C 45.92, H 3.50, N 4.87; found C 45.89, H 3.60, N 4.88.

*(S)-2-Chloro-7-[N-(2-hydroxy-1-methylethyl)]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid (**9f**)*

The pure compound was obtained by recrystallization from chloroform/diethyl ether. Yield: 1.15 g (80 %), m. p. 249 – 250 °C. – $C_{11}H_{10}NO_4SCl$ (287.72): calcd. C 45.92, H 3.50, N 4.87; found C 45.89, H 3.60, N 4.88. The spectral data for this compound are identical to those obtained for its (*R*)-enantiomer (compound **9e**).

*(R)-2-Chloro-7-N-(2-phenylethyl)-4-oxo-4,7-dihydro-thieno[2,3-b]pyridine-5-carboxylic acid (**9g**)*

The pure compound was obtained after recrystallization from chloroform/petroleum ether. Yield: 1.47 g (88 %), m. p. 192 – 193 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (d, 3H, J = 6.9 Hz, CHCH_3), 5.43 (q, 1H, J = 6.9 Hz, C*H*Me), 7.44 (m, 5H, Ph), 7.46 (s, 1H, 3-H), 8.78 (s, 1H, 6-H), 15.12 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6 (CH*C*H$_3$), 66.3 (*C*HMe), 112.9 (C-5), 121.6 (C-3), 126.5 (C-3′ + C-5′), 127.9 (C-4a), 129.7 (C-2′ + C-6′), 129.8 (C-4′), 130.6 (C-2), 136.2 (C-1′), 141.6 (C-6), 149.0 (C-7a), 166.6 (CO_2H), 173.4 (C-4). – MS (EI, 70 eV): *m/z* (%) = 333 (32) [M]$^+$, 289 (72), 229 (99), 211 (15), 185 (23), 183 (5), 157 (3), 105 (100). – $C_{16}H_{12}NO_3SCl$ (333.80): calcd. C 57.57, H 3.62, N 4.20; found C 57.32, H 3.48, N 4.14.

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