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 μ g 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 Gramnegative bacteria. N(7)-Aryl substitution has also been achieved, exemplified by compounds **4a**, **b** [2], which exhibited a good level of activity against Gramnegative 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 2chloro-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 $9\mathbf{a} - \mathbf{g}$ is achieved by utilizing 3-(2,5-dichlorothien-3yl)-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-

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4-(OH)-C₆H₄) 4c (Ar = 2-thienyl)

sis of the target compounds 9a - g. Herein, condensation of the enol ether $\mathbf{6}$ 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[2,3b]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-4oxothieno[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.

¹H and ¹³C 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 ¹H signals, belonging to the different hydrogens in the acyclic

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

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, ¹³C-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-CH₃. 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 $\geq 128 \ \mu g \ m L^{-1}$. 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 vaStrain

9d

OFL

Staphylococcus aureus A Streptococcus faecalis A Escherichia coli ATCC	XTCC 9144 TCC 11700 10536	0.125 4 ≤ 0.06	32 > 128 8	Klebsiella Proteus mi Pseudomo	pneumoniae irabilis nas aeruginos	ATCC 10031 sa ATCC 27853	$ \leq 0.06 \\ \leq 0.06 \\ 2 $	0.5 4 > 12
Salmonella paratyphi A Shigella sonnei		0.06 < 0.06	4	Salmonella Providenci	a paratyphi C ia rettgeri		< 0.06 0.25	8 4
		OMe				OMe	0120	<u>.</u>
	eg R	OMe (iii) Ch	2 S 1 8a-g	a b d b d	6 CO 2Me	Ci-Ci-S- 9a-g		1
7-9	a t) С	d	e	f	g		
R	$\int_{0}^{6} \left(\bigvee_{\substack{4^{\prime} \\ N \\ Me}}^{N^{1}} \right)_{3^{\prime}}^{2^{\prime}} \int_{0}^{N} \int_{1^{\prime}}^{N}$	$\int_{2^{\prime}}^{3^{\prime}} \bigcup_{4^{\prime}}^{\mathbf{S}} \int_{3^{\prime}}^{2^{\prime}}$	S Me ^N Me	\$ CHMe CH ₂ OH (<i>R</i>)-	*СНМе СН ₂ ОН (S)-	² CHMe ² CHMe ² CHMe ² CHMe ² CHMe		

Table 1. In vitro antibacterial activity (MIC values in $\mu g m L^{-1}$) of **9d** and ofloxacin (OFL) as reference agent.

Strain

9d

OFL

Scheme 1. (i) Ac_2O , (EtO)₃CH / 130 °C, 3–4 h; (ii) R-NH₂, CH₂Cl₂; (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.

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.

Experimental Section

3-Acetyl-2,5-dichlorothiophene was purchased from Fluorochem (England), (*R*)-alaninol, (*S*)-alaninol, 1-amino-4methylpiperazine 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. ¹H and ¹³C NMR spectra were measured on a Bruker DPX-300 instrument. Chemical shifts are expressed in ppm with

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 μ g 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 μ g mL⁻¹. The agar plates were inoculated with approximately 10⁵ *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-methyl-piperazin-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. – ¹H NMR (300 MHz, CDCl₃): δ = 2.32 (s, 3H, NCH₃), 2.57 (m, 4H, 3'-H₂ + 5'-H₂), 2.97 (m, 4H, 2'-H₂ + 6'-H₂), 3.65, 3.67 (2s, 3H, OCH₃, *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*). – ¹³C NMR (75 MHz, CDCl₃): δ = 45.6 (NCH₃), 51.4 (OCH₃), 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). – C₁₄H₁₇N₃O₃SCl₂ (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, CDCl₃): δ = 2.94 (m, 4H, 3'-H₂ + 5'-H₂), 3.80 (m, 4H, 2'-H₂ + 6'-H₂), 3.65, 3.67 (2s, 3H, OCH₃, *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). – ¹³C NMR (75 MHz, CDCl₃): δ = 51.4 (OCH₃), 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). – C₁₃H₁₄N₂O₄SCl₂ (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. – ¹H NMR (300 MHz, CDCl₃): δ = 1.45 (m, 2H, 4'-H₂), 1.71 (m, 4H, 3'-H₂ + 5'-H₂), 2.85 (m, 4H, 2'-H₂ + 6'-H₂), 3.64, 3.67 (2s, 3H, OCH₃, *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). – ¹³C NMR (75 MHz, CDCl₃): δ = 22.8 (C-4'), 25.2 (C-3' + C-5'), 51.3 (OCH₃), 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). – C₁₄H₁₆N₂O₃SCl₂ (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. – ¹H NMR (300 MHz, CDCl₃): δ = 2.70, 2.67 (2s, 6H, N(CH₃)₂, Z/E), 3.65, 3.68 (2s, 3H, OCH₃, 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). – ¹³C NMR (75 MHz, CDCl₃): δ = 48.7 (N(CH₃)₂), 51.4 (OCH₃), 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). – C₁₁H₁₂N₂O₃SCl₂ (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-(2hydroxy-1-methylethylamino)acrylate (7e)

The compound was obtained as an oil. Yield: 5.8 g (86 %). - ¹H NMR (300 MHz, CDCl₃): δ = 1.32, 1.30 (2d,

3H, J = 6.4, 6.4 Hz, CHCH₃, Z/E), 3.56 (m, 3H, CH₂OH + CHMe), 3.63, 3.64 (2s, 3H, OCH₃, Z/E), 4.20 (br s, 1H, CH₂OH), 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). – ¹³C NMR (75 MHz, CDCl₃): $\delta = 17.0$ (CHCH₃), 51.4, 51.2 (OCH₃, Z/E), 57.9, 57.5 (CHMe, Z/E), 65.9, 66.1 (CH₂OH, 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). – C₁₂H₁₃NO₄SCl₂ (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-(2hydroxy-1-methylethyl)acrylate (7f)

This compound was obtained as an oil. Yield: 5.7 g (84%). – C₁₂H₁₃NO₄SCl₂ (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. -¹H NMR (300 MHz, CDCl₃): $\delta = 1.67$, 1.65 (2d, 3H, J =6.9, 6.9 Hz, CHCH₃), 3.60, 3.64 (2s, 3H, OCH₃, Z/E), 4.65, 4.06 (2m, 1H, CHMe), 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). – ¹³C NMR (75 MHz, CDCl₃): δ = 23.0 (CHCH₃), 51.3, 51.2 (OCH₃, Z/E), 59.3, 58.9 (CHMe, 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). -C₁₇H₁₅NO₃SCl₂ (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-5carboxylates 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. – ¹H NMR (300 MHz, CDCl₃): δ = 2.39 (s, 3H, NCH₃), 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, OCH₃), 7.40 (s, 1H, 3-H), 8.58 (s, 1H, 6-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 45.5 (NCH₃), 52.4 (OCH₃), 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 (CO₂Me), 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). – C₁₄H₁₆N₃O₃SCl (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.). – ¹H NMR (300 MHz, CDCl₃): 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, OCH₃), 7.40 (s, 1H, 3-H), 8.55 (s, 1H, 6-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 52.5 (OCH₃), 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 (CO₂Me), 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). – C₁₃H₁₃N₂O₄SCI (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. – ¹H NMR (300 MHz, CDCl₃): δ = 1.84 (m, 6H, 3'-H₂ + 4'-H₂ + 5'-H₂), 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, OCH₃), 7.40 (s, 1H, 3-H), 8.54 (s, 1H, 6-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 22.8 (C-4'), 26.1 (C-3' + C-5'), 52.4 (OCH₃), 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 (CO₂Me), 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). – C₁₄H₁₅N₂O₃SCl (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. – ¹H NMR (300 MHz, CDCl₃): δ = 2.96 (s, 6H, N(CH₃)₂), 3.93 (s, 3H, OCH₃), 7.40 (s, 1H, 3-H), 8.56 (s, 1H, 6-H). – ¹³C NMR (75 MHz, CDCl₃): δ = 46.2 (NCH₃), 52.5 (OCH₃), 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 (CO₂Me), 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). – C₁₁H₁₁N₂O₃SCI (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)]-4oxo-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.). – ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.65 (d, 3H, *J* = 6.9 Hz, CHC*H*₃), 3.65 (m, 2H, C*H*₂OH), 3.85 (s, 3H, OCH₃), 4.16 (m, 1H, C*H*Me), 7.40 (s, 1H, 3-H), 8.58 (s, 1H, 6-H). – ¹³C NMR (75 MHz, [D₆]DMSO): δ = 15.7 (CHCH₃), 52.5 (OCH₃), 62.6 (CH₂OH), 64.8 (CHMe), 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 (CO₂Me), 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). – C₁₂H₁₂NO₄SCI (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)]-4oxo-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. – ¹H NMR (300 MHz, CDCl₃): δ = 1.99 (d, 3H, J = 7.0 Hz, CHCH₃), 3.90 (s, 3H, OCH₃), 5.30 (q, 1H, J = 7.0 Hz, CHMe), 7.40 (m, 5H, Ph), 7.42 (s, 1H, 3-H), 8.47 (s, 1H, 6-H). $-{}^{13}$ C NMR (75 MHz, CDCl₃): δ = 20.4 (CHCH₃), 52.5 (OCH₃), 65.1 (CHMe), 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 (CO₂Me), 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). – C₁₇H₁₄NO₃SCl (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-5carboxylic 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 H₂O (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. – ¹H NMR (300 MHz, [D₄]CH₃OH): δ = 3.00 (s, 3H, NCH₃), 3.63 (m, 8H, 2'-H₂ + 3'-H₂ + 5'-H₂ + 6'-H₂)), 7.51 (s, 1H, 3-H), 9.13 (s, 1H, 6-H). – ¹³C NMR (75 MHz, D₂O + NaOD): δ = 45.5 (NCH₃), 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 (CO₂H), 173.4 (C-4). – MS (EI, 70 eV): *m/z* (%) = 327 (17) [M]⁺, 283 (51), 229 (28), 211 (99), 185 (100), 157 (5). – C₁₃H₁₄N₃O₃SCI (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[2,3b]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.). – ¹H NMR (300 MHz, CDCl₃): 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, CO₂H). – ¹³C NMR (75 MHz, CDCl₃): 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 (CO₂H), 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. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.30 (m, 6H, 3'-H₂ + 4'-H₂ + 5'-H₂), 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, CO₂H). – ¹³C NMR (75 MHz, [D₆]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 (CO₂H), 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). – C₁₃H₁₃N₂O₃SCl (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-dihydrothieno[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.). – ¹H NMR (300 MHz, CDCl₃): δ = 3.01 (s, 6H, N(CH₃)₂), 7.43 (s, 1H, 3-H), 8.87 (s, 1H, 6-H), 15.17 (s, 1H, CO₂H). – ¹³C NMR (75 MHz, CDCl₃): δ = 46.5 (N(CH₃)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 (CO₂H), 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). – C₁₀H₉N₂O₃SCI (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-4,7dihydrothieno[2,3-b]pyridine-5-carboxylic acid (**9***e*)

The pure compound was obtained by recrystallization from chloroform/diethyl ether. Yield: 1.18 g (82%), m. p. 249–250 °C. – ¹H NMR (300 MHz, [D₆]DMSO): δ = 1.65 (d, 3H, *J* = 6.8 Hz, CHC*H*₃), 3.82 (m, 2H, C*H*₂OH), 4.46 (m, 1H, C*H*Me), 5.35 (t, 1H, *J* = 5.4 Hz, CH₂O*H*), 7.66 (s, 1H, 3-H), 8.80 (s, 1H, 6-H), 15.48 (s, 1H, CO₂H). – ¹³C NMR (75 MHz, [D₆]DMSO): δ = 15.4 (CHCH₃), 62.6 (CH₂OH), 65.8 (CHMe), 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 (CO₂H), 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). – C₁₁H₁₀NO₄SCI (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-4,7dihydrothieno[2,3-b]pyridine-5-carboxylic acid (**9**f)

The pure compound was obtained by recrystallization from chloroform/diethyl ether. Yield: 1.15 g (80%), m. p. 249–250 °C. – $C_{11}H_{10}NO_4SCI$ (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-dihydrothieno[2,3-b]pyridine-5-carboxylic acid (**9**g)

The pure compound was obtained after recrystallization from chloroform/petroleum ether. Yield: 1.47 g (88 %), m. p. 192–193 °C. – ¹H NMR (300 MHz, CDCl₃): δ = 2.04 (d, 3H, *J* = 6.9 Hz, CHCH₃), 5.43 (q, 1H, *J* = 6.9 Hz, CHMe), 7.44 (m, 5H, Ph), 7.46 (s, 1H, 3-H), 8.78 (s, 1H, 6-H), 15.12 (s, 1H, CO₂H). – ¹³C NMR (75 MHz, CDCl₃): δ = 20.6 (CHCH₃), 66.3 (CHMe), 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 (CO₂H), 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). – C₁₆H₁₂NO₃SCl (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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