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Short communication

Thienopyridinone antibacterials: Synthesis and antibacterial activity of some 7-aryl-2-chloro-4,7-dihydro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids

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Abstract – A series of 7-aryl-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids **8** and their methyl esters **7** were synthesized by intramolecular cyclization of the respective 3-*N*-arylamino-2-(2,5-dichloro-3-thenoyl) acrylates **6**. The latter are accessible from methyl 3-ethoxy-2-(2,5-dichloro-3-thenoyl) acrylate **5** which, in turn, is obtained via the parent β-keto ester **4**. Of the present series, the 7-(*p*-hydroxyphenyl) and 7-(2',4'-difluorophenyl) derivatives **8e,i** possess the highest activity especially against *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus aureus* (MICs of **8e/8i** ≈ 0.06:0.25, 0.5:1.0 and 1.0:2.0 μg/mL, respectively). © Elsevier, Paris

7-aryl-4-oxothieno[2,3-*b*]pyridines / antibacterial activity

1. Introduction

Synthetic quinolones constitute an important class of therapeutically useful antiinfectious agents [1–5], especially norfloxacin **1a** [6] and ciprofloxacin **1b** [7–9]. Several studies [10–15] show that fluoroquinolone analogues with an *N*-1 aryl substituent such as difloxacin **2a** [10–12] and temafloxacin **2b** [13] are broad-spectrum agents which possess excellent antibacterial potencies (see *figure 1*).

Several 4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids, potential bioisosteres of quinolones, were prepared and biotested [16–19]. Substitution at the *N*-7-position has so far been confined to alkyl groups and for example compounds **3a** [16] and **3b** [17] have exhibited a good level of activity against Gram-negative bacteria.

However, incorporation of *N*-aryl substituents has not been described in the literature for the thienopyridinone class. Accordingly, and as a continuation of our research project directed towards structure–activity relationship (SAR) studies, we investigate in the present work the synthesis and the antibacterial activity of a new series of 2-chloro-4-oxothieno[2,3-*b*]-pyridine-5-carboxylic acids, with aryl substituents at the *N*-7-position (**8a–k**) (see *figure 2* and *table I*).

2. Chemistry

The *N*-7-substituted phenyl-4-oxothieno[2,3-*b*]pyridines **8a–k**, investigated in this study, were prepared by an efficient route as summarized in *figure 2*. This synthetic strategy is similar to that recently reported for the *N*-7 alkyl analogues (eg **3b**) [17]. Thus, the β-keto ester **4** [20] was condensed with triethyl orthoformate in acetic anhydride to produce the 3-ethoxyacrylate **5** which, in turn, was reacted smoothly with the appropriate (substituted) aniline in an addition–elimination sequence to generate the respective 3-aminoacrylates **6a–k**. These enaminoketo esters exist in (*Z*)- and (*E*)-forms in solution in which the former isomer is predominant. Cyclization of deprotonated **6** (HNa in refluxing THF) afforded the corre-

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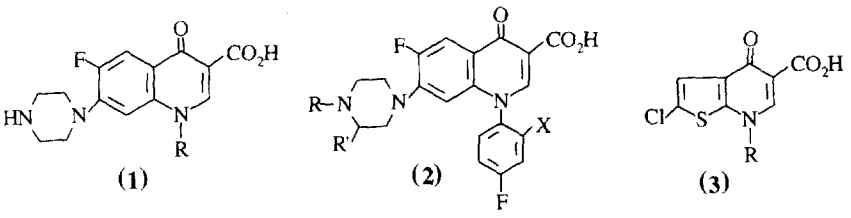


(1) (2) (3)

	R
a	Et
b	Δ

	R	R'	X
a	Me	H	H
b	H	Me	F

	R
a	Et
b	Δ

Figure 1.

sponding methyl *N*-aryl-4-oxothieno[2,3-*b*]pyridine-5-carboxylates **7**. Mild saponification of the latter esters **7** furnished the target acids, namely 7-aryl-2-chloro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids **8a–k**.

This strategy allowed us to obtain compounds **8a–k** more easily than by the Gould–Jacobs method since *N*-arylation is particularly difficult. Compounds **6–8** were characterized by elemental analyses, ^{1}H and ^{13}C-NMR spectroscopy, and electron impact mass spectrometry.

3. Results and discussion

Table II summarizes the in vitro antibacterial activity of the 7-aryl-2-chloro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids **8a–k** against microorganisms representative of Gram-positive and Gram-negative bacteria classes (ofloxacin is included for comparison). Six compounds, with 4'-chloro (**8c**), 4'-bromo (**8d**), 4'-methoxy (**8f**), 4'-methyl (**8g**), 2'-methoxy (**8j**), 2'-methyl (**8k**) as substituents on the *N*-7-phenyl ring were totally inactive during the in vitro assay. Only *Kl. pneumonia* seemed to be poorly affected by these compounds, and in a similar way by the unsubstituted compound **8a**.

Introduction of a fluorine atom at the 4'-position of the *N*-7-phenyl ring (compound **8b**) led to considerable enhancement of the antibacterial activity (4- to 8-fold) compared to **8a**. The *N*-(2'-fluorophenyl) analogue **8h** exhibited an activity comparable to **8b**. The presence of two fluorine atoms on the benzene ring (**8i**) greatly improved the antibacterial activity against the eight representative strains, and compound **8i** represents the first example of a thienopyridinone showing slight activity against *Streptococcus faecalis*.

The 4'-hydroxyphenyl derivative **8e** possessed an excellent level of potency against *Klebsiella pneumoniae* similar to ofloxacin. It exhibited good to moderate activity against the other strains tested, with the exception of Streptococcus faecalis where it is inactive.

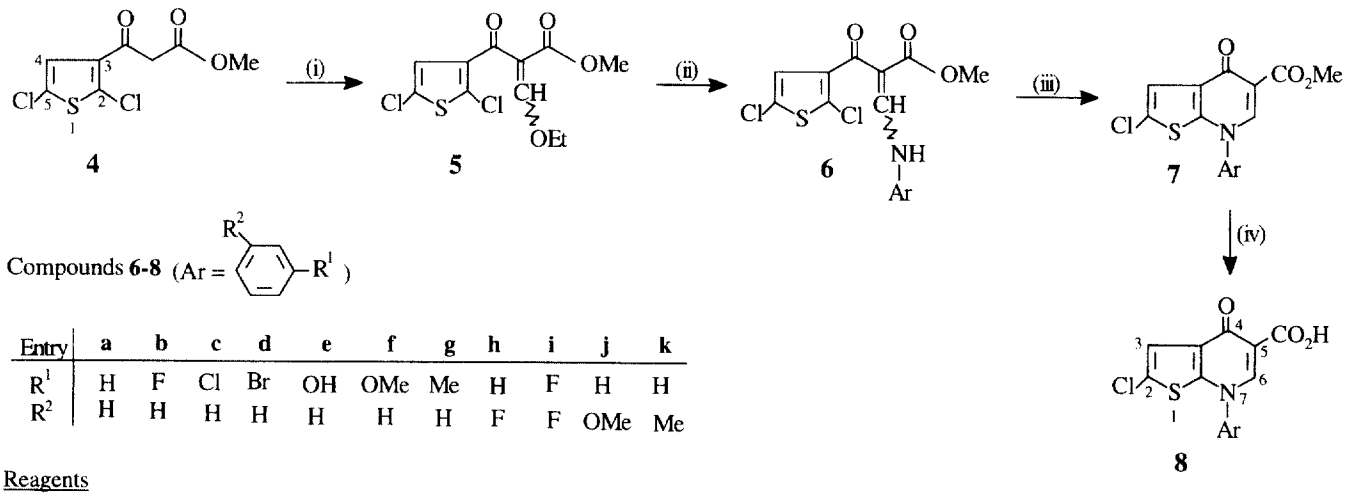
4. Conclusion

Substituents at the *N*-7-phenyl ring exert influence on the antibacterial activity of the thienopyridinones **8a–k** in the following decreasing order: 4'-OH ≥ 2',4'-F_2 > 4'-F, 2'-F > H, 2'-Me >> 4'-Cl, 4'-OMe, 2'-OMe, 4'-Me > 4'-Br. This order is in parallel with that reported for the *N*-1-arylfluoro quinolones [10–12] for which an 'active conformation', based on molecular modeling and receptor mapping analyses, has been postulated [15]. Such a receptor model approach brings new insight into three-dimensional SARs and demonstrates that both fluorine and hydroxyl, at the *para* position of the *N*-1-phenyl, occupy an optimum spatial region for increasing the activity. However, the present series of *N*-7-arylthienopyridinones **8a–k** are less potent than the respective *N*-1-substituted phenyl-quinolones.

It is probable that the 4'-OH and 2',4'-F substituents take part in the binding interactions (via hydrogen bonding) between the thienopyridinone substrate (**8b,e,h,i**) and DNA gyrase, a condition which eventually disrupts the bacterial DNA replication. This property of the polar groups, OH and F, is a result of their relatively small steric effect as compared to the other bulkier substituents that are also less polar and aprotic.

Table I. Physicochemical data for compounds (**6a–k**, **7a–k**, **8a–k**).

Compound	Yield (%)	Mp (°C)	Molecular formula	Molecular weight
6a	44	73–74	$C_{15}H_{11}Cl_2NO_3S$	356.23
6b	68	89–90	$C_{15}H_{10}Cl_2FNO_3S$	374.22
6c	58	122–123	$C_{15}H_{10}Cl_3NO_3S$	390.67
6d	80	125–126	$C_{15}H_{10}BrCl_2NO_3S$	435.13
6e	47	64–65 (dec)	$C_{15}H_{11}Cl_2NO_4S$	372.23
6f	62	78–79	$C_{16}H_{13}Cl_2NO_4S$	386.25
6g	78	105–106	$C_{16}H_{13}Cl_2NO_3S$	370.25
6h	72	91–92	$C_{15}H_{10}Cl_2FNO_3S$	374.22
6i	76	117–118	$C_{15}H_9Cl_2F_2NO_3S$	392.21
6j	63	thick oil	$C_{16}H_{13}Cl_2NO_4S$	386.25
6k	75	72–73 (dec)	$C_{16}H_{13}Cl_2NO_3S$	370.25
7a	77	200–201	$C_{15}H_{10}ClNO_3S$	319.77
7b	81	220–221	$C_{15}H_9ClFNO_3S$	337.76
7c	78	208–210	$C_{15}H_9Cl_2NO_3S$	354.21
7d	76	196–197	$C_{15}H_9BrClNO_3S$	398.67
7e	85	242–243 (dec)	$C_{15}H_{10}ClNO_4S$	335.77
7f	75	144–145	$C_{16}H_{12}ClNO_4S$	349.79
7g	82	205–206	$C_{16}H_{12}ClNO_3S$	333.79
7h	64	173–174	$C_{15}H_9ClFNO_3S$	337.76
7i	48	113–114	$C_{15}H_8ClF_2NO_3S$	355.75
7j	72	212–213	$C_{16}H_{12}ClNO_4S$	349.79
7k	78	168–169	$C_{16}H_{12}ClNO_3S$	333.79
8a	78	275–276	$C_{14}H_8ClNO_3S$	305.74
8b	84	273–274	$C_{14}H_7ClFNO_3S$	323.73
8c	88	271–272	$C_{14}H_7Cl_2NO_3S$	340.19
8d	82	280–281	$C_{14}H_7BrClNO_3S$	384.64
8e	92	297–298	$C_{14}H_8ClNO_4S$	321.74
8f	78	219–220	$C_{15}H_{10}ClNO_4S$	335.77
8g	84	243–244	$C_{15}H_{10}ClNO_3S$	319.77
8h	92	232–233	$C_{14}H_7ClFNO_3S$	323.73
8i	90	213–214	$C_{14}H_6ClF_2NO_3S$	341.72
8j	78	241–242	$C_{15}H_{10}ClNO_4S$	335.77
8k	84	244–245 (dec)	$C_{15}H_{10}ClNO_3S$	319.77



Compounds **6-8** (Ar =)

Entry	a	b	c	d	e	f	g	h	i	j	k
R^1	H	F	Cl	Br	OH	OMe	Me	H	F	H	H
R^2	H	H	H	H	H	H	H	F	F	OMe	Me

Reagents
(i) $CH(OEt)_3 + Ac_2O$
(ii) $Ar\text{-}NH_2 + CH_2Cl_2$ / reflux
(iii) NaH + THF / 60 °C
(iv) NaOH / H^+

Figure 2.

Table II. In vitro antibacterial activity (MIC values, in µg/mL) of the different thieno[2,3-*b*]pyridinones **8a–k**, and of ofloxacin (OFL) as the reference agent.

	OFL	**8a**	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**	**8h**	**8i**	**8j**	**8k**
Staphylococcus aureus ATCC 9144	0.125	64	16	> 128	> 128	1	> 128	> 128	16	2	> 128	64
Streptococcus faecalis ATCC 11700	4	> 128	> 128	> 128	> 128	> 128	> 128	> 128	>128	32	> 128	> 128
Bordetella bronchiseptica ATCC 4617	1	> 128	> 128	> 128	>128	16	> 128	> 128	>128	4	> 128	128
Escherichia coli ATCC 10536	≤ 0.06	32	4	> 128	> 128	0.5	> 128	> 128	4	1	> 128	32
Klebsiella pneumoniae ATCC 10031	≤ 0.06	1	0.125	4	> 128	≤ 0.06	8	4	≤ 0.06	0.25	32	2
Enterobacter cloacae ATCC 13047	≤ 0.06	32	8	> 128	> 128	1	> 128	> 128	16	2	> 128	32
Proteus mirabilis IP 54163	≤ 0.06	64	8	> 128	> 128	1	> 128	> 128	16	2	> 128	32
Pseudomonas aeruginosa ATCC 27853	1	> 128	> 128	> 128	>128	16	> 128	> 128	>128	16	> 128	> 128

5. Experimental protocols

The required arylamines were purchased from Acros. Melting points were determined on an electrothermal melting-temperature apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker-WM 400 and 300 MHz instrument with TMS as internal reference. Electron-impact (EI) mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses, carried out by MHW Laboratories, Arizona, USA, were within ± 0.4% of theorical values.

5.1. Pharmacological tests

The MICs were determined by conventional agar dilution procedures according to the method of Mueller–Hinton at pH 7.4. Aqueous stock solutions of the test compounds were prepared with 0.1 N NaOH. Serial dilutions were then made to obtain test concentrations ranging from 128–0.06 μg/mL. The agar plates were inoculated with approximately 10^4 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.

5.2. Syntheses

5.2.1. Methyl 2-(2,5-dichloro-3-thenoyl)-3-ethoxyacrylate 5 [17]

A stirred mixture of **4** [20] (5.3 g, 21 mmol), triethyl orthoformate (4.6 g, 32 mmol) and acetic anhydride (8.6 g, 85 mmol) was heated at 130–135 °C (oil bath) for 3 h with removal of the ethyl acetate formed during the reaction. The resulting solution was concentrated in vacuo (100 °C/1 mmHg, 1 h) to a brown mobile oil which was used as such in subsequent steps. The yield of **5** is nearly quantitative (~ 6.4 g).

*5.2.2. Methyl 3-anilino-2-(2,5-dichloro-3-thenoyl) acrylate **6a***

To a stirred solution of **5** (6.2 g, 20 mmol) in dichloromethane (80 mL) was added freshly distilled aniline (2.8 g, 30 mmol), and the resulting reaction mixture was refluxed for 2–5 h. The solvent was then evaporated to dryness, and the residue was recrystallized from methanol. Yield of **6a**: 3.1 g (44%).

By use of this procedure, compounds **6b–k** were prepared from interaction of **5** with the respective appropriately substituted anilines. Compounds **6b–d** and **6h,i,k** were likewise recrystallized from methanol. Compounds **6e–g,j** were first purified using Silica gel column chromatography, and eluting with chloroform, followed by solutions of 2–5% methanol in chloroform (**6e**); alternatively, the eluents were *n*-hexane and 5–10% solutions of chloroform in *n*-hexane (**6f,g,j**). Recrystallization was then performed from methanol (**6e**), or from chloroform/*n*-hexane (**6f,g,j**). Analytical samples of compounds **6** were obtained with preparative TLC plates, using chloroform as the developing solvent; in the case of **6e**, the eluent was 5% methanol in chloroform solution. The physical data of compounds **6a–k** are given in *table I*.

*5.2.3. Methyl 2-chloro-4,7-dihydro-4-oxo-7-phenylthieno[2,3-b]pyridine-5-carboxylate **7a***

Sodium hydride (suspension in oil, 80%) (4.3 g, 12 mmol) was portionwise added, during 30 min, to a cold solution (~ 5 °C) of **6a** (4.3 g, 12 mmol) in dry tetrahydrofuran (70 mL). The reaction mixture was heated at 62–65 °C (oil bath) for 3–4 h and then cooled. Acetic acid (0.2 mL) was added, the solvent was evaporated under reduced pressure to a small volume (1–2 mL). Water (30 mL) was then added, the precipitated solid product was collected by suction filtration, washed with water, dried and recrystallized from chloroform/n-hexane. Yield of **7a**: 3.0 g (77%). Various substituted 7-phenyl-4-oxothieno[2,3-*b*]pyridine-5-carboxylic esters (**7b–k**) were prepared in a similar fashion from the corresponding enamino keto ester precursors (**6b–k**). Compounds **7b–k** were recrystallized from chloroform/*n*-hexane (a few drops of methanol were used with compounds **7e,f** to access their solubility in chloroform).

Analytical samples of **7a–k** were obtained using preparative TLC plates, and eluting with chloroform (in the case of **7e,f,j**, the eluent was 5% methanol in chloroform solution). For the case of **6e**, two equivalents of NaH were employed, and compound **8e** was always formed along with **7e**. Hence, compound **7e** was conveniently obtained via Fischer esterification of **8e** in methanol under reflux in the presence of a catalytic amount of concentrated H_2SO_4, and usual work-up. The physical data of compounds **7a–k** are shown in *table I*.

*5.2.4. 2-Chloro-4,7-dihydro-4-oxo-7-phenylthieno[2,3-b]pyridine-3-carboxylic acid **8a***

Compound **7a** (1.6 g, 5 mmol) was stirred in ethanolic sodium hydroxide (1 N, 25 mL) at room temperature for 2 h. The resulting solution was filtered and the ethanolic filtrate was acidified with 2 N hydrochloric acid to pH 2. The precipitated solid was filtered, washed successively with water (2 x 10 mL) and ethanol (5 mL), and dried. Yield of **8a**: 1.2 g (78%). A sample of **8a** was further purified by dissolution in 1 N aqueous sodium hydroxide, and acidification of the alkaline filtrate with 2 N hydrochloric acid to pH 2.

By the above procedure, the various substituted 7-phenyl analogues (**8b–k**) were prepared via hydrolysis of the corresponding methyl esters **7b–k**. The physical data of compounds **8a–k** are provided in *table I*.

5.3. Characterization

5.3.1. Mass spectra

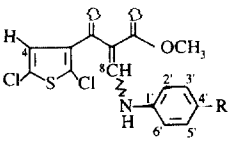
In the mass spectra of compounds **6a–k** consecutive loss of the chlorine atom and methanol from $M^{+\bullet}$ leads to the ions $[M - 35]^+$ and $[M - 67]^+$ as the base peaks. Successive elimination of two CO from $[M - 67]^+$ furnishes the ions $[M - 95]^+$ and $[M - 123]^+$. Alternatively, α-cleavage at the ketone function of $M^{+\bullet}$ gives rise to the acylium ion at *m/z* 179 which suffers loss of CO to afford the thienyl cation at *m/z* 151.

For compounds **7a–k**, the main fragmentation pathway of $M^{+\bullet}$ starts with elimination of the ester group via a process that gives ions [M – 58] as the base peaks. The latter ions eliminate the chlorine atom to produce ions [M – 93]. A less favoured mode is initiated by successive loss of a methoxy radical and CO to yield ions $[M - 31]^+$ and $[M - 59]^+$. Compounds **8a–k** eject CO_2 to give the base peak ions $[M - 44]^{+\bullet}$ which fragment further in a pattern similar to those of the respective esters.

5.3.2. ^{1}H-NMR spectral data (tables III and IV)

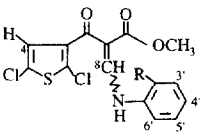
The spectra of compounds **6a–k** are dominated by signal doubling of the various resonating protons. This phenomenon features the existence of *Z/E* diastereomers of which the (*Z*)-form predominates and to which the signal sets with larger peak areas are assigned (*table III*). The exchangeable N-H and the adjacent vinyl H-8 protons are mutually coupled and resonate around δ 10.9–12.6 and δ 8.2–8.6, respectively. The H-4 (δ 6.7–7.0), N-H and H-8 protons belonging to the (*Z*)-isomer are more deshielded than their (*E*)-form. The CO_2CH_3 protons of the (*Z*)-isomer are, however, more shielded than their (*E*)-form. In compounds **6c–g**, each of the *ortho*- and *meta*-phenyl protons (Ar) appear as distinct doublet (AA', BB' system).

Table III. (a) ^{1}H-NMR spectral data of compounds **6a–g** (δ-values)[a].



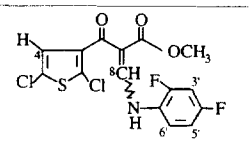
Compound	H-4 *Z/E*	H-8 *Z/E*	N–H *Z/E*	CO_2CH_3 *Z/E*	H-2'/H-6'	H-3'/H-5'R	R *Z/E*	Ratio *(Z/E)*
6a	6.86/6.98 (1H, s)	8.58/8.36 (1H, d) J = 13.8 Hz	12.44/11.05 (1H, br d) J = 13.8 Hz	3.70/3.72 (3H, s)	7.44/7.21 (5H, m)[b]			7.5/1
6b	6.84/6.94 (1H, s)	8.48/8.26 (1H, d) J = 13.7 Hz	12.45/11.03 (1H, br d) J = 13.7 Hz	3.65/3.68 (3H, s)	7.21 (2H, m)[c]	7.11 (2H, m)[c]		2.4/1
6c	6.83/6.96 (1H, s)	8.49/8.26 (1H, d) J = 13.6 Hz	12.39/11.01 (1H, br d) J = 13.6 Hz	3.69/3.72 (3H, s)	7.38 (2H, d) J = 8.4 Hz	7.17 (2H, d) J = 8.4 Hz		4.0/1
6d	6.78/6.91 (1H, s)	8.44/8.20 (1H, d) J = 13.7 Hz	12.29/10.93 (1H, br d) J = 13.7 Hz	3.63/3.65 (3H, s)	7.45 (2H, d) J = 8.8 Hz	7.05 (2H, d) J = 8.8 Hz		5.0/1
6e	6.83/6.88 (1H, s)	8.46/8.25 (1H, d) J = 13.9 Hz	12.53/11.08 (1H, br d) J = 13.9 Hz	3.72/3.75 (3H, s)	7.25 (2H, d) J = 8.8 Hz	7.05 (2H, d) J = 8.8 Hz	10.54 (1H, br s)	4.6/1
6f	6.84/6.90 (1H, s)	8.48/8.30 (1H, d) J = 13.8 Hz	12.52/11.06 (1H, br d) J = 13.8 Hz	3.68/3.70 (3H, s)	7.19 (2H, d) J = 9.0 Hz	6.95 (2H, d) J = 9.0 Hz	3.82/3.84 (3H, s)	2.7/1
6g	6.79/6.90 (1H, s)	8.47/8.27 (1H, d) J = 13.6 Hz	12.39/10.97 (1H, br d) J = 13.6 Hz	3.62/3.64 (3H, s)	7.14 (2H, d) J = 8.7 Hz	7.05 (2H, d) J = 8.7 Hz	2.28/2.30 (3H, s)	2.5/1

(b) ^{1}H-NMR spectral data of compounds **6h,j,k** (δ-values)[a].



Compound	H-4 *Z/E*	H-8 *Z/E*	N–H *Z/E*	CO_2CH_3 *Z/E*	H-6'	H-3'/H-4'/H-5'	R *Z/E*	Ratio *(Z/E)*
6h	7.00/6.89 (1H, s)	8.32/8.57 (1H, d) J = 13.6 Hz	11.16/12.44 (1H, br d) J = 13.6 Hz	3.74/3.71 (3H, s)	7.36 (1H, m)	7.17 (1H, m)	–	13/1
6j	7.03/6.90 (1H, s)	8.62/8.41 (1H, d) J = 14.1 Hz	12.59/11.32 (1H, d) J = 14.1 Hz	3.75/3.78 (3H, s)	7.24/6.95 (4H, m)		3.94/3.93 (3H, s)	2.6/1
6k	6.98/6.88 (1H, s)	8.61/8.37 (1H, d) J = 13.5 Hz	12.65/11.21 (1H, br d) J = 13.5 Hz	3.71/3.73 (3H, s)	7.29/7.20 (4H, m) (*Z/E*)		2.44/2.42 (3H, s)	3.2/1

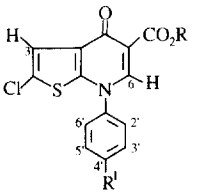
(c) ^{1}H-NMR spectral data of compound **6i** (δ-values)[a].



Compound	H-4 *Z/E*	H-8 *Z/E*	N–H *Z/E*	CO_2CH_3 *Z/E*	H-3'/H-5'	H-6'	Ratio *(Z/E)*
6i	6.88/6.98 (1H, s)	8.48/8.24 (1H, d) J = 13.5 Hz	12.40/11.09 (1H, d) J = 13.5 Hz	3.71/3.73 (3H, s)	6.99 (2H, m)	7.35 (1H, m)	1.8/1

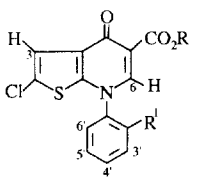
[a]NMR solvent: $CDCl_3$. [b]Including H-4' (R^1). [c]Overlapped doublets due to additional H–F coupling.

Table IV. (a) ^{1}H-NMR spectral data of compounds **7a–g** and **8–g** (δ-values)[a].



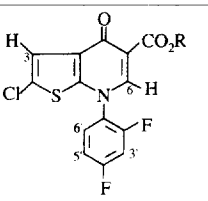
Compound	H-3	H-6	CO_2R	H-2'/H-6'	H-3'/H-5'	R^1
7a	7.43 (1H, s)	8.38 (1H, s)	3.90 (3H, s)	7.53 (5H, m)[b]		
7b	7.40 (1H, s)	8.32 (1H, s)	3.88 (3H, s)	7.59 (2H, m)	7.31 (2H, m)	–
7c	7.38 (1H, s)	8.31 (1H, s)	3.87 (3H, s)	7.60 (2H, d) J = 8.4 Hz	7.55 (2H, d) J = 8.4 Hz	–
7d	7.33 (1H, s)	8.24 (1H, s)	3.84 (3H, s)	7.69 (2H, d) J = 8.6 Hz	7.43 (2H, d) J = 8.6 Hz	–
7e	7.42 (1H, s)	8.33 (1H, s)	3.74 (3H, s)	7.58 (2H, d) J = 8.7 Hz	6.99 (2H, d) J = 8.7 Hz	10.33 (1H, br s)
7f	7.37 (1H, s)	8.33 (1H, s)	3.86 (3H, s)	7.53 (2H, d) J = 8.9 Hz	7.10 (2H, d) J = 8.9 Hz	3.92 (1H, s)
7g	7.42 (1H, s)	8.34 (1H, s)	3.89 (3H, s)	7.37 (4H, 2d)[c]		2.46 (3H, s)
8a	7.50 (1H, s)	8.66 (1H, s)	14.85 (1H, br s)	7.52 (2H, m)	7.63 (3H, m)[b]	
8b	7.51 (1H, s)	8.63 (1H, s)	14.84 (1H, br s)	7.56 (2H, m)[d]	7.33 (2H, m)[d]	–
8c	7.70 (1H, s)	8.75 (1H, s)	15.08 (1H, br s)	7.90 (2H, d) J = 8.8 Hz	7.78 (2H, d) J = 8.8 Hz	–
8d	7.72 (1H, s)	8.76 (1H, s)	15.17 (1H, br s)	7.92 (2H, d) J = 8.7 Hz	7.82 (2H, d) J = 8.7 Hz	–
8e	7.75 (1H, s)	8.68 (1H, s)	15.31 (1H, br s)	7.68 (2H, d) J = 8.8 Hz	7.06 (2H, d) J = 8.8 Hz	10.37 (1H, br s)
8f	7.49 (1H, s)	8.61 (1H, s)	14.96 (1H, br s)	7.45 (2H, d) J = 9.2 Hz	7.10 (2H, d) J = 9.2 Hz	3.92 (3H, s)
8g	7.48 (1H, s)	8.63 (1H, s)	14.94 (1H, br s)	7.43 (4H, 2d)[c]		2.51 (3H, s)

(b) ^{1}H-NMR spectral data of compounds **7h,j,k** and **8h,j,k** (δ-values)[a].



Compound	H-3	H-6	CO_2R	H-3'/H-5'	H-4'	H-6'	R^1
7h	7.42 (1H, s)	8.31 (1H, s)	3.89 (3H, s)	7.38 (2H, m)	7.68 (1H, m)	7.63 (1H, m)	–
7j	7.43 (1H, s)	8.26 (1H, s)	3.84 (3H, s)	7.14 (2H, m)	7.54 (2H, m)	7.42 (1H, dd) J = 7.9/1.5 Hz	3.92 (3H, s)
7k	7.47 (1H, s)	8.27 (1H, s)	3.89 (3H, s)	7.40 (2H, m)	7.53 (1H, m)	7.45 (1H, dd) J = 7.8/1.6 Hz	2.19 (3H, s)
8h	7.52 (1H, s)	8.61 (1H, s)	14.80 (1H, s)	7.45 (2H, m)	7.70 (1H, m)	7.57 (1H, m)	–
8j	7.42 (1H, s)	8.48 (1H, s)	14.94 (1H, s)	7.11 (2H, d)	7.56 (1H, m)	7.36 (1H, dd) J = 8.1/1.5 Hz	3.96 (3H, s)
8k	7.52 (1H, s)	8.56 (1H, s)	14.95 (1H, s)	7.47 (2H, m)	7.58 (1H, m)	7.36 (1H, dd) J = 7.9/1.6 Hz	2.17 (3H, s)

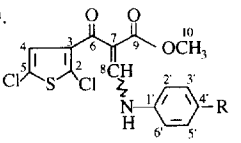
(c) ^{1}H-NMR spectral data of compounds **7i** and **8i** (δ-values)[a].



Compound	H-3	H-6	CO_2R	H-3'/H-5'	H-6'
7i	7.30 (1H, s)	8.24 (1H, s)	3.86 (3H, s)	7.25 (2H, m)	8.01 (1H, m)
8i	7.49 (1H, s)	8.56 (1H, s)	14.72 (1H, br s)	7.21 (2H, m)	7.68 (1H, m)

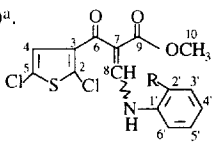
[a]NMR solvents: DMSO-d_6 (**7e**, **8c–e**); $CDCl_3$ (**7a–d,f,g/8a,b,f,g**). [b]Including H-4' (R^1). [d]Overlapped doublets due to additional H–F coupling. [c]Center of overlapped doublets.

Table V. (a) ^{13}C-NMR spectral data of compounds **6a–g** (δ-values)[a].



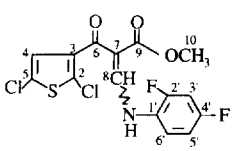
Compound	C-2	C-3	C-4 *Z/E*	C-5	C-6	C-7 *Z/E*	C-8 *Z/E*	C-9	C-10 *Z/E*	C-1' *Z/E*	C-2'/6' *Z/E*	C-3'/5' *Z/E*	C-4' *Z/E*	R *Z/E*
6a	140.0	126.5	126.8	126.7	187.9	103.2	153.2	167.4	52.2	139.0	118.5	130.5	126.2	–
			127.7			104.1	152.7		52.0	139.2	118.0	130.7		
6b	139.5	125.8	126.4	126.2	187.6	103.4	153.2	166.9	51.7	135.0	119.9(d)	116.4(d)	160.8(d)	–
			127.3			103.7	152.7		51.5	135.2	119.3(d)	117.0(d)	160.5(d)	
											$^3J_{CF}$ = 8.5 Hz	$^2J_{CF}$ = 23.6 Hz	$^1J_{CF}$ = 247 Hz	
6c	139.4	125.5	126.4	126.0	187.7	103.8	152.5	166.9	51.8	137.3	119.3	130.2	131.6	–
			127.3			104.2	151.8		51.6	137.5	118.7		131.1	
6d	140.1	125.6	126.2	126.0	187.0	103.7	152.2	166.7	51.7	137.6	119.4	133.0	119.1	–
			127.2			103.8	151.5		51.6		118.9	132.9		
6e	139.5	125.4	126.3	126.4	187.2	102.6	153.4	167.6	51.8	131.6	120.0	116.8	154.8	–
			127.2			102.3	153.2		51.6	131.8	119.6		154.5	
6f	140.3	126.5	126.8	127.7	187.7	103.1	153.7	167.5	52.1	132.4	120.1	115.6	158.6	56.1
			127.4			103.3	153.4		51.9		119.7			
6g	139.6	125.4	126.2	126.0	187.2	102.8	152.8	166.9	51.5	136.1	117.9	130.4	136.0	20.8
			127.2			103.0	152.4		51.3	136.2	117.5	130.3	135.6	20.7

(b) ^{13}C-NMR spectral data of compounds **6h,j,k** (δ-values)[a].



Compound	C-2	C-3	C-4 *Z/E*	C-5	C-6 *Z/E*	C-7 *Z/E*	C-8 *ZE*	C-9 *Z/E*	C-10 *Z/E*	C-1' *Z/E*	C-2' *Z/E*	C-3' *Z/E*	C-4' *Z/E*	C-5' *ZE*	C-6' *Z/E*	R *Z/E*
6h	139.3	127.4	127.2	127.6	184.4	104.8	151.2	168.6	51.7	126.5 (d)	153.1 (d)	116.4 (d)	125.8	126.4	125.2 (d)	–
			127.0		187.5	104.3	152.0	166.9	51.8	^2J = 10 Hz	152.9 (d)	116.6 (d)	126.6		^3J = 3.8 Hz	
											^1J = 245.6 Hz	^2J = 18.5 Hz	^3J = 7.4 Hz			
6j	139.4	127.3	126.4	127.8	185.2	103.4	151.1	167.3	51.7	128.8	149.4	111.5	127.0	116.1	121.3	56.0
			126.3		187.0	103.7	150.9	169.6	51.5	128.6	149.2	111.3	126.3	115.2	120.5	55.9
6k	139.6	127.3	126.4	128.1	187.5	103.5	153.0	167.0	51.7	137.2	125.6	116.2	131.5	127.6	126.2	17.6
			126.2		184.4	103.7	152.7	169.2	51.6	137.4	125.5	115.8	131.4	127.3	125.6	17.4

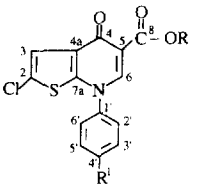
(c) ^{13}C-NMR spectral data of compound **6i** (δ-values)[a].



Compound	C-2	C-3	C-4 *Z/E*	C-5	C-6 *Z/E*	C-7 *Z/E*	C-8 *Z/E*	C-9 *Z/E*	C-10 *Z/E*	C-1' *Z/E*	C-2' *Z/E*	C-3' *Z/E*	C-4' *Z/E*	C-5' *Z/E*	C-6' *Z/E*
6i	139.2	126.2	126.3	127.3	187.5	104.4	152.4	166.8	51.8	123.8 (d)	160.1 (dd)	105.2 (dd)	153.3 (dd)	112.3 (dd)	118.6 (dd)
			127.2		184.5	104.7	151.5	168.6	51.7	124.1 (d)	159.8 (dd)	105.0 (dd)	153.0 (dd)	112.2 (dd)	117.7 (dd)
										^2J = 10 Hz	^1J = 247.6 Hz	^2J = 22.5 Hz	^1J = 249.3 Hz	^2J = 22.7 Hz	^3J = 9.6 Hz
											^3J = 11.0 Hz	^2J = 26.4 Hz	^3J = 11.8 Hz	^4J = 3.8 Hz	

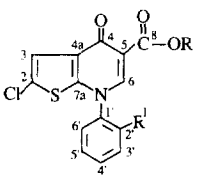
[a]NMR solvent: $CDCl_3$.

Table VI. (a) ^{13}C-NMR spectral data of compounds **7a–g** and **8a–g** (δ-values)[a].



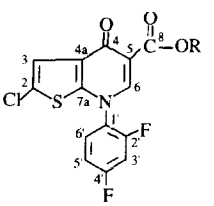
Compound	C-2	C-3	C-4a	C-4	C-5	C-6	C-7a	C-8	R	C-1'	C-2'/C-6'	C-3'/C-5'	C-4'	R^1
7a	132.9	123.4	126.1	170.2	115.9	146.0	148.8	166.2	52.8	141.9	125.5	131.2	131.1	–
7b	132.4	123.1	125.8	169.6	115.6	145.6	148.5	165.7	52.4	137.5 (d) $^4J_{CF}$ = 3.4 Hz	127.5 (d) $^3J_{CF}$ = 9.2 Hz	117.9 (d) $^2J_{CF}$ = 23.4 Hz	163.4 (d) $^1J_{CF}$= 252.6 Hz	–
7c	132.5	123.0	125.8	169.6	115.7	145.4	148.0	165.6	52.3	139.8	126.6	131.0	137.0	–
7d	132.3	122.9	125.6	169.4	115.5	145.2	147.8	165.4	52.2	140.2	126.7	133.9	124.9	–
7e	130.7	122.4	124.0	168.4	114.5	145.8	149.5	164.5	51.5	132.6	126.8	116.5	159.1	–
7f	132.0	122.8	125.7	169.6	114.9	145.9	149.2	165.6	52.2	134.2	126.6	115.6	161.0	55.8
7g	132.4	123.0	125.6	169.7	115.5	145.6	148.5	166.0	52.3	141.3	124.7	131.2	139.0	21.3
8a	128.6	122.3	125.1	174.1	113.8	145.4	148.4	166.7	–	141.4	125.3	131.5	132.0	–
8b	130.1	122.0	128.3	173.7	113.4	145.0	147.8	166.2	–	136.9 (d) $^4J_{CF}$ = 3.3 Hz	127.4 (d) $^3J_{CF}$ = 9.1 Hz	118.3 (d) $^2J_{CF}$ = 23.1 Hz	163.6 (d) $^1J_{CF}$ = 251.3 Hz	–
8c	128.7	122.2	126.6	173.1	112.1	146.5	151.3	165.2	–	139.6	128.2	131.0	135.7	–
8d	129.2	122.2	127.2	173.7	112.6	146.5	151.8	165.8	–	140.6	128.4	134.0	124.9	–
8e	132.6	121.7	126.1	173.0	112.1	146.0	148.1	165.4	–	136.1	126.8	116.6	159.4	–
8f	130.2	122.2	128.6	174.0	113.6	145.6	151.9	166.8	–	134.1	126.7	116.3	162.0	56.4
8g	129.8	121.8	128.1	173.5	113.1	145.0	151.0	166.3	–	142.1	124.6	131.5	138.5	21.3

(b) ^{13}C-NMR spectral data of compounds **7h,j,k** and **8h,j,k** (δ-values)[a].



Compound	C-2	C-3	C-4a	C-4	C-5	C-6	C-7a	C-8	R/R^1	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
7h	132.1	122.9	125.6	169.7	115.5	146.1	148.7	165.4	52.3/ –	128.5 (d) ^2J = 12.7 Hz	156.5 (d) ^1J = 253 Hz	117.9 (d) ^2J = 18.8 Hz	133.1 (d) ^3J = 7.8 Hz	128.0 (d) ^4J = 1.5 Hz	126.0 (d) ^3J = 4 Hz
7j	132.0	122.8	125.2	170.0	115.1	146.8	149.5	166.0	52.2/ 56.0	129.4	154.0	113.0	132.6	121.5	127.4
7k	132.1	123.1	125.9	169.7	115.4	145.6	149.0	165.8	52.3/ 17.0	140.0	134.8	128.2	131.4	132.4	126.6
8h	129.8	121.8	128.0	173.7	113.5	145.6	151.0	166.0	–/ –	128.1 (d) ^2J = 12.9 Hz	156.2 (d) ^1J = 254.6 Hz	113.3 (d) ^2J = 18.6 Hz	133.3 (d) ^3J = 7.7 Hz	127.4 (d) ^4J = 1.6 Hz	126.2 (d) ^3J = 4.2 Hz
8j	129.4	121.5	127.6	173.6	113.0	146.2	151.2	166.4	–/ 56.0	128.9	153.6	113.0	133.0	121.4	126.9
8k	129.6	121.5	129.4	173.6	113.2	145.0	151.6	166.3	–/ 17.0	139.6	134.3	128.4	132.0	132.6	126.2

(c) ^{13}C-NMR spectral data of compounds **7i** and **8i** (δ-values)[a].



Compound	C-2	C-3	C-4a	C-4	C-5	C-6	C-7a	C-8	R	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
7i	131.9	122.7	125.8	169.5	115.3	146.2	148.9	164.9	52.2	124.9 (dd) ^2J = 12.6 Hz ^4J = 4.3 Hz	157.1 (dd) ^2J = 25.6 Hz ^3J = 12.8 Hz	106.2 (dd) ^2J = 22.5 Hz ^2J = 22.5 Hz	163.9 (dd) ^1J = 254.6 Hz ^3J = 11 Hz	113.6 (dd) ^2J = 22.5 Hz ^4J = 3.9 Hz	130.0 (dd) ^3J = 10.3 Hz ^3J = 10.3 Hz
8i	129.8	121.9	128.1	173.7	113.5	145.7	151.1	165.8	–	124.4 (dd) ^2J = 12.8 Hz ^4J = 4.3 Hz	157.0 (dd) ^1J = 257.2 Hz ^3J = 12.8 Hz	106.8 (dd) ^2J = 22.4 Hz ^2J = 22.3 Hz	164.3 (dd) ^1J = 256.1 Hz ^3J = 11 Hz	113.8 (dd) ^2J = 24.7 Hz ^4J = 3.9 Hz	129.0 (dd) ^3J = 10.0 Hz ^3J = 10.0 Hz

[a]NMR solvents: $CDCl_3$.

In compounds **7** and **8**, the H-3 and H-6 protons of the thienopyridinone system resonate around δ 7.4–7.7 and δ 8.4–8.7, respectively (*table IV*). The exchangeable CO_2H proton of compounds **8** resonates in the range δ 14.8–15.3. Signal assignments to the different Ar-protons are straightforward.

5.3.3. ^{13}C-NMR spectral data (tables V and VI)

DEPT experiments were performed to differentiate between the different carbons of compounds **6–8**. The spectra of compounds **6, 7** display a signal around δ 52 corresponding to the CH_3- carbon of the ester group which is absent in the spectra of the respective acids **8a–g**. Compounds **6–8** exhibit two signals in the range δ 166–187 that are assigned to the carbonyl carbons. Signals in the region δ 110–160 account for the remaining thienopyridinone and phenyl carbons. The observed signal-doubling for most carbons of compounds **6a–g** is a reflection of the co-existence of *Z/E* diastereoisomers (*table V*).

Acknowledgements

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