Novel Chemical Transformations of Tenoxicam

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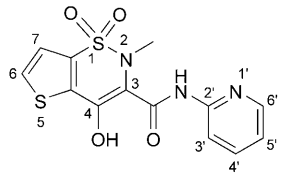
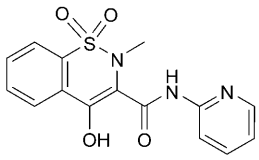
Both *N*- and *O*-substituted derivatives of the anti-inflammatory drug tenoxicam (= 4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide 1,1-dioxide; **1**) were synthesized, and various chemical transformations were investigated. Both selective hydrolysis and reaction of 1′-*N*-methyltenoxicam (**5**) with a variety of N-nucleophiles were performed (*Scheme 1*). Also, five new 4-*O*-acyl derivatives **10** were prepared as potential prodrugs (*Scheme 2*). The 4-chloro derivatives of **1** and its analog **8** could be successfully transformed into the novel tetra- and tricyclic ring systems **12** and **13**, respectively, the latter being a conformationally restricted 1,5-diaryl-pyrazole designed as a potential COX-2 inhibitor.

Introduction. – The dynamic structural features and electronic properties of conjugated enolic acids have recently received considerable interest. These types of compounds often consist of heteroaromatic components, and several fused-ring systems based on benzothiazine or thienothiazine moieties have been investigated as therapeutic anti-inflammatory agents [1][2].

Tenoxicam (= 4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide 1,1-dioxide; **1**) is a member of the nonsteroidal oxicam drug family with potent anti-inflammatory, analgetic, and antipyretic effects based on the combined inhibition of lipoxygenase (LX) and cyclooxygenase (COX), which catalyze the formation of prostaglandins [3]. Tenoxicam (**1**) is structurally related to piroxicam (**2**), which contains a fused benzene rather than a thiophene ring. Both compounds are inhibitors of COX-1. Compound **1** also inhibits COX-2, an enzyme responsible for inducing inflammatory mediators under pathological conditions. The drug has long been used in the treatment of rheumatic diseases [4][5].



1



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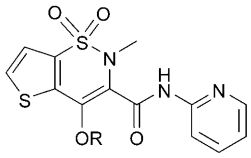


3 R = *t*-BuCO
4 R = EtOC(O)OCH(Me)

While the preparation of thieno[2,3-*e*][1,2]thiazine was described in 1987 by *Binder et al.* [6], neither experimental data on its chemical reactivity nor the molecular properties of analogues of **1** have been published. Only few papers deal with the synthesis and structural modification of the thieno[2,3-*e*][1,2]thiazine bicyclic system

[7][8], despite the fact that several synthetic modifications of other oxicam drugs have been published.

Prodrugs of piroxicam (**2**) such as pivoxicam (**3**) [9], ampiroxicam (**4**) [10], and other analogous structures [11][12] were synthesized by transforming the 4-OH group to an enol ether, enol ester, and enol carbamate, respectively. The prodrugs do not possess detectable piroxicam-like *in vitro* inhibitory activities regarding prostaglandin synthesis, but they suppress inflammation in arthritis *in vivo*.

The quaternization of the amino group of the oxicams greatly increases their affinity towards articular cartilage, without loss of their primary pharmacological activity, which results in a significant decrease of the required dosage and, consequently, an attenuation of adverse effects such as digestive toxicity [13].

Here, we report synthetic modifications of the two main functional groups of tenoxicam (**1**), leading to new analogues and possible prodrug forms. Also, **1** and its derivatives were transformed by cyclocondensation into new heterocondensed compounds. The syntheses of a new tetracyclic ring system and a conformationally restricted tricyclic 1,5-diarylpyrazole derivative as a potential COX-2 inhibitor are described.

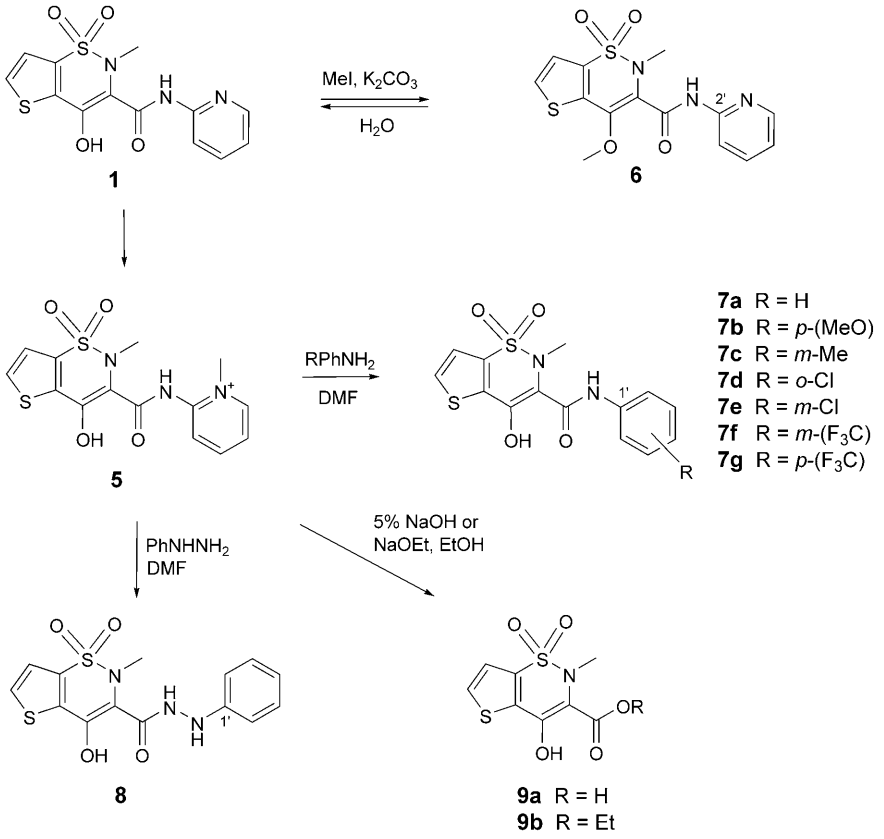
Results and Discussion. – Methylation of **1** was carried out under heterogeneous reaction conditions employing MeI and K_2CO_3 in acetone (*Scheme 1*) [14]. The *N*-methylated compound **5** was the major product, the corresponding 4-*O*-methyl derivative **6** being a side product, which could be separated from **5** by crystallization, based on a large solubility difference. In contrast to the stable 4-MeO derivative of **2**, **6** undergoes spontaneous hydrolysis in H_2O. The vinylogous carboxylate character of **6** and the formation of a strong intramolecular H-bond between the 4-OH and the 3-(C=O) groups of **1** must account for this fast hydrolysis. In addition, neighboring-group participation between the 4-MeO group and the large S-atom of the thiophene ring should further accelerate hydrolysis.

The positively charged pyridine N-atom of **5** polarizes the 3-carboxamido group considerably, increasing its reactivity towards nucleophilic agents. Supposedly, the 2-amino-1-methylpyridinium moiety now has the character of a leaving group. Hence, **5** could be transformed into various aromatic tenoxicam analogues, **7a**–**g** and **8** (*Scheme 1*), by reaction with substituted anilines or phenylhydrazine, respectively, in moderate-to-good yields, depending on the nucleophilicity of the anilines.

This method has an advantage over ester amidation: the reactions of **5** could be successfully performed with anilines having strong electron-withdrawing substituents. The structures of the products **7** were confirmed by UV/VIS and ^{1}H-NMR spectroscopy. Both the extended conjugation throughout the system and an additional RAHB (resonance-assisted H-bond) stabilization effect between the 4-OH group and the amide C=O group influence the physico-chemical properties of **1** and its analogues **7**. These effects result in the coplanarity of the bicyclic moiety and the pyridine or substituted phenyl ring(s).

Semi-empirical PM3 calculations with HYPERCHEM 6.0 for compound **7** supported the assumption of coplanarity, indicating H-bonds between the 4-OH and the amide C=O groups, with C(3)–C(O)–N–C(1′) dihedral angles in the range 0.6–8.9°. Concerning the UV/VIS data of **7**, the 4-(trifluoromethyl)-substituted derivative

Scheme 1



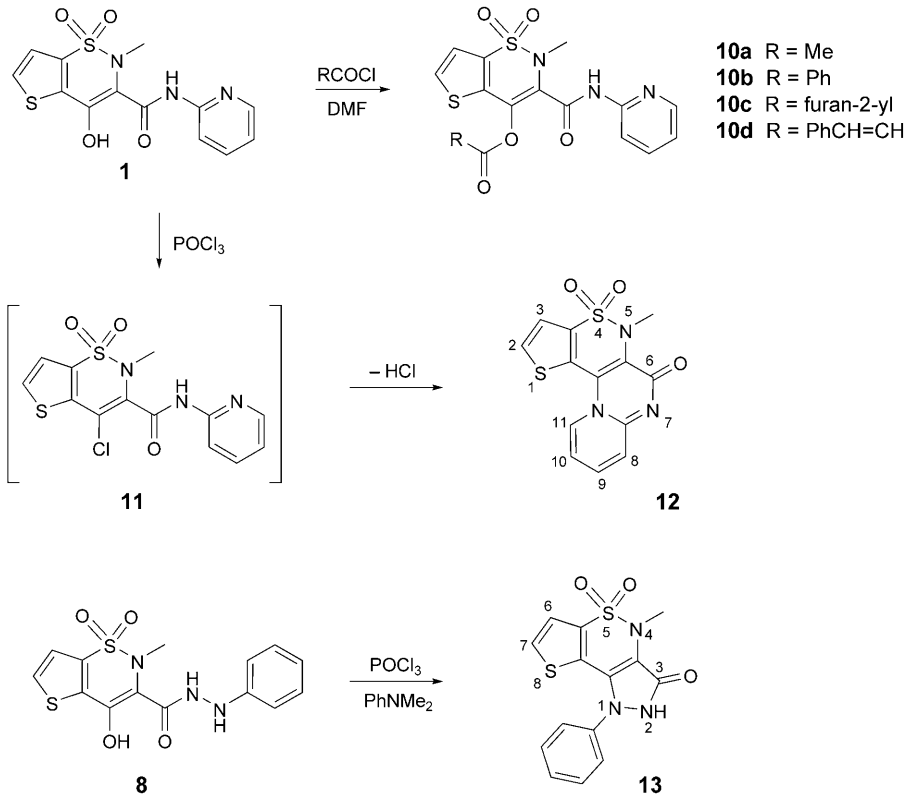
7g showed the highest similarity to **1**, with absorption maxima in MeOH at 372 nm for both compounds. This indicates that the influence of the 4-CF_3 substituent on the acidity of the 4-OH group in **7g** is similar to that of the unprotonated pyridyl group in **1**. The UV/VIS maxima in the spectra of the other tenoxicam analogues **7** showed various shifts, indicating changes in electron density in the conjugated system.

The hydrolysis of **1** has been investigated earlier by *Özer et al.* under both acidic (pH 1) and alkaline (pH 10) conditions at 100° [15]. They reported that **1** is hydrolyzed at low pH within 2 h under complete degradation of the fused-ring system. Because of the sensitivity of **5** towards nucleophiles, we next investigated its hydrolytic propensity (*Scheme 1*). Due to the poor solubility of **5** in acidic solutions, the hydrolysis was investigated under alkaline conditions (pH 10). We also assumed that the polarized amide bond would result in an enhanced hydrolytic reactivity. And, indeed, we could hydrolyze **5** in a mixture of 5% aq. NaOH/EtOH without any degradation. The resulting, stable carboxylic acid **9a** was then esterified under acid catalysis to yield ethyl 4-hydroxythieno[2,3-*e*][1,2]thiazine-3-carboxylate 1,1-dioxide (**9b**), a key intermediate for the preparation of further tenoxicam analogues *via* the *Binder* method [6]. In the

case of selective alcoholysis of **5** with EtONa/EtOH, **9b** could also be obtained directly (see *Exper. Part*).

Because of the highly unstable nature of the 4-MeO congener **6**, we investigated the preparation of 4-*O*-acyl derivatives as possible prodrug forms of **1** (*Scheme 2*). In these cases, we expected the acyl C=O group to improve the hydrolytic stability by conjugation. Reaction of **1** with various acid chlorides provided a range of 4-acylated products of type **10** as colorless, moisture-sensitive, crystalline substances.

Scheme 2



The acidic 4-OH group of **1** is essential for COX-1 anti-inflammatory activity, but it is not necessarily important for other biological activities. The replacement of the 4-OH group with an amino group was effected *via* the intermediary 4-Cl derivative **11**, obtained by halogenation with $POCl_3$, followed by intramolecular reaction with the pyridine N-atom of the 3-carboxamido group. The resulting ring-closure product **12** is the first member of a novel tetracyclic ring system.

Applying the above procedure, we could also perform the cyclization of the phenylhydrazide analogue **8**, leading to the formation of the new tricyclic derivative **13**, which was isolated by chromatographic separation. This compound contains the structural elements of selective COX-2 inhibiting 1,5-diaryl-pyrazoles [16–18], but the

condensed thiazine ring restricts the conformational mobility by linking the pyrazole ring to the thiophene ring.

Conclusions. – We have developed new synthetic pathways for the direct conversion of tenoxicam (**1**) to the substituted benzene analogs **7** by quaternization of the pyridine N-atom followed by nucleophilic substitution with different anilines. We also performed the selective hydrolysis of the amide bond of **1** without the degradation of the bicyclic system. In alkaline solution, mild hydrolysis and solvolysis of **5** yielded the stable carboxylic acid **9a** and its ethyl ester **9b**. To obtain derivatives of **1** with improved bio-availability, we also synthesized various types of 4-*O*-acyl derivatives of **1** as possible prodrug candidates. Moreover, the 4-OH group was successfully replaced with a Cl-atom, and the resulting intermediate **11** underwent a consecutive intramolecular ring closure to the new tetracyclic ring system **12**. In a similar manner, cyclization of the 3-phenylhydrazide derivative **8** provided the new fused heterocyle **13** as a conformationally restricted 1,5-diaryl-pyrazole derivative with similar structural elements as the selective COX-2 inhibiting agents. The biological properties of these new compounds are under study now, and will be reported elsewhere.

Experimental Part

General. All reagents and solvents were purchased from *Aldrich*, and were used as received. Tenoxicam (**1**) was a generous gift of *Mihály Kata*, Department of Pharmaceutical Technology, University of Szeged. Reactions were monitored by thin-layer chromatography (TLC) on silica-gel plates (*Merck 5554*) using benzene/MeOH 4:1 as eluent. pK_a Values were measured by UV/pH titrations with an accuracy of $\pm$ 0.03 pK_a units. Melting points (m.p.) were measured on a *Boetius* apparatus; uncorrected. UV Spectra were recorded in MeOH on a *UNICAM SP-800* instrument; λ_{max} (log ε) in nm. IR Spectra were recorded on a *PYE UNICAM SP-1100* apparatus, with KBr disks; in cm^{-1}. ^{1}H-NMR Spectra were recorded on a *Bruker* 500-MHz spectrometer in $CDCl_3$ and (D_6)DMSO solns.; chemical shifts δ in ppm rel. to Me_4Si as internal standard, coupling constants *J* in Hz. Mass spectra were recorded on a *Shimadzu GC/MS-QP 1000EX* instrument; in *m*/*z*. Elemental analyses were performed on a *Perkin-Elmer 2400 CHN Analyzer*; compounds yielded satisfactory combustion analyses, with C $\pm$ 0.30, H $\pm$ 0.21, and N $\pm$ 0.16% of the calculated values (see the *Table*).

1′-N-*Methyltenoxicam* (= *2-[[(4-Hydroxy-2-methyl-1,1-dioxido-2*H-*thieno[2,3-*e*][1,2]thiazin-3-yl)carbonyl]amino}-1-methylpyridinium*; **5**) *and 4*-O-*Methyltenoxicam* (= *4-Methoxy-2-methyl*-N-*(pyridin-2-yl)-2*H-*thieno[2,3-*e*][1,2]thiazine-3-carboxamide 1,1-Dioxide*; **6**). To a suspension of **1** (3.47 g; 10 mmol) in acetone (50 ml), K_2CO_3 (2.78 g, 20 mmol) and MeI (3.74 ml, 8.52 g, 60 mmol) were added. The mixture was stirred for 5 d at r.t. The resulting precipitate was removed by filtration, washed with acetone (15 ml), and purified from inorg. impurities by heating in H_2O (25 ml). After cooling, the precipitate was filtered off, and washed with EtOH to afford **5** (2.6 g, 72%). The above acetone filtrate was evaporated to dryness, and the residue was suspended in anh. Et_2O (20 ml). The insoluble materials were filtrated off, and washed with anh. Et_2O (2 $\times$ 10 ml). Evaporation of the combined etheral solns. yielded a solid residue, which was suspended in Et_2O/hexane 1:1, and filtered to afford **6** (0.4 g, 12%).

Data of **5**. Yellow crystals. M.p. 227°. UV (MeOH): 384 (3.54), 296 (3.40). ^{1}H-NMR ((D_6)DMSO): 2.95 (*s*, MeN); 3.75 (*s*, MeN^+); 7.28 (*dd*, *J* = 7.2, 6.8, H–C(5′)); 7.38 (*d*, *J* = 5.0, H–C(7)); 7.80 (*d*, *J* = 5.0, H–C(6)); 8.19 (*dd*, *J* = 7.8, 7.2, H–C(4′)); 8.52 (*d*, *J* = 7.8, H–C(3′)); 8.96 (*d*, *J* = 6.8, H–C(6′)). Anal.: see the *Table.*

Data of **6**. Colorless crystals. M.p. 174°. UV (MeOH): 332 (3.04), 280 (2.82). ^{1}H-NMR ($CDCl_3$): 3.04 (*s*, MeN); 4.06 (*s*, MeO); 7.07 (*dd*, *J* = 7.4, 6.5, H–C(5′)); 7.35 (*d*, *J* = 5.3, H–C(7)); 7.72 (*d*, *J* = 5.3, H–C(6)); 7.76 (*dd*, *J* = 8.1, 7.4, H–C(4′)); 8.14 (*d*, *J* = 8.1, H–C(3′)); 8.30 (*d*, *J* = 6.5, H–C(6′)). Anal.: see the *Table.*

General Procedure (*GP 1*) *for the Synthesis of Compounds* **7**. Compound **5** (1.20 g, 3.4 mmol) was suspended in DMF (10 ml), excess of substituted aniline (8.5 mmol) was added, and the mixture was heated under N_2 atmosphere for 3–20 h at 130–150° (oil bath). After 1 h of heating, **5** had dissolved completely, and the mixture slowly became dark. The end point of the reaction was determined by TLC. The mixture was cooled

Table. *Elemental-Analyses Data of Tenoxicam* (**1**) *and Its Derivatives* **5**–**13**

	Formula	M_r [g/mol]	Calculated [%]			Found [%]		
			C	H	N	C	H	N
1	$C_{13}H_{13}N_3O_4S_2$	339.39	46.11	3.86	12.38	46.25	3.92	12.30
5	$C_{14}H_{15}N_3O_4S_2$	353.42	47.58	4.28	11.89	47.34	4.24	11.74
6	$C_{14}H_{15}N_3O_4S_2$	353.42	47.58	4.28	11.89	47.53	4.25	11.79
7a	$C_{14}H_{14}N_2O_4S_2$	338.43	49.69	4.17	8.28	49.65	4.02	8.24
7b	$C_{15}H_{16}N_2O_5S_2$	368.43	48.90	4.38	7.60	48.70	4.24	7.68
7c	$C_{15}H_{16}N_2O_4S_3$	352.43	51.12	4.58	7.95	50.97	4.63	8.01
7d	$C_{14}H_{13}ClN_2O_4S_2$	372.85	45.10	3.51	7.51	45.02	3.60	7.54
7e	$C_{14}H_{13}ClN_2O_4S_2$	372.85	45.10	3.51	7.51	44.83	3.33	7.41
7f	$C_{15}H_{13}F_3N_2O4S_3$	406.41	44.33	3.22	6.89	44.37	3.27	6.80
7g	$C_{15}H_{13}F_3N_2O4S_2$	406.41	44.33	3.22	6.89	44.40	3.30	6.77
8	$C_{14}H_{13}N_3O_4S_2$	351.40	47.85	3.73	11.96	48.12	3.52	11.99
9a	$C_8H7NO_5S_2$	261.28	36.78	2.70	5.36	36.71	2.82	5.47
9b	$C_{10}H_{13}NO_5S_2$	291.35	41.23	4.50	4.81	41.27	4.64	4.87
10a	$C_{15}H_{13}N_3O_5S_2$	379.41	47.48	3.45	11.08	47.19	3.35	11.17
10b	$C_{20}H_{15}N_3O_5S_2$	441.48	54.41	3.42	9.52	54.42	3.40	9.53
10c	$C_{18}H_{13}N_3O_6S_2$	431.44	50.11	3.04	9.74	50.40	3.09	9.60
10d	$C_{22}H_{17}N_3O_5S_2$	467.52	56.52	3.67	8.99	56.32	3.59	8.78
12	$C_{13}H_9N_3O_3S_2$	319.36	48.89	2.84	13.16	48.81	2.72	13.20
13	$C_{14}H_{11}N_3O_3S_2$	333.39	50.44	3.33	12.60	50.28	3.20	12.66

and diluted with H_2O (40 ml). A dark-yellow oily product separated. After decantation of the solvent, the residue was taken up in $CHCl_3$ (20 ml). The soln. was washed with 10% aq. HCl (3×10 ml) and H_2O (2×10 ml), dried (Na_2SO_4), decolorized over charcoal, and evaporated *in vacuo*. The resulting residue was crystallized from an appropriate solvent.

4-Hydroxy-2-methyl-N-*phenyl-2*H-*thieno[2,3*-e*][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**7a**). Prepared according to *GP 1*: 3 h at 130°, recrystallization from AcOEt/Et_2O. Yield: 74%. Colorless solid. pK_a 1.88. M.p. 250–252°. UV (MeOH): 376 (3.32), 264 (3.25). ^{1}H-NMR ($CDCl_3$): 2.96 (*s*, MeN); 4.06 (*s*, MeO); 7.18–7.32 (*m*, H–C(2′), H–C(3′), H–C(4′), H–C(5′), H–C(6′)); 7.39 (*d*, $J = 5.3$, H–C(7)); 7.85 (*d*, $J = 5.3$, H–C(6)). Anal.: see the *Table*.

4-Hydroxy-N-*(4-methoxyphenyl)-2-methyl-2*H-*thieno[2,3*-e*][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**7b**). Prepared according to *GP 1*: 3 h at 130°, recrystallized from i-PrOH/Et_2O. Yield: 82%. Light-yellow crystals. M.p. 265–267°. UV (MeOH): 366 (3.55), 272 (3.31). ^{1}H-NMR ($CDCl_3$): 2.98 (*s*, MeN); 3.76 (*s*, MeO); 7.41 (*d*, $J = 5.3$, H–C(7)); 7.47 (*d*, $J = 8.5$, H–C(2′), H–C(6′)); 7.61 (*d*, $J = 8.5$, H–C(3′), H–C(5′)); 7.88 (*d*, $J = 5.3$, H–C(6)). Anal.: see the *Table*.

4-Hydroxy-2-methyl-N-*(3-methylphenyl)-2*H-*thieno[2,3*-e*][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**7c**). Prepared according to *GP 1*: 6 h at 130°, recrystallized from (i-PrO)$_2$O. Yield: 65%. Light-yellow crystals. M.p. 196–198°. UV (MeOH): 374 (3.58), 268 (3.40). ^{1}H-NMR ($CDCl_3$): 2.36 (*s*, Me); 3.08 (*s*, MeN); 7.22–7.39 (*m*, H–C(2′), H–C(4′), H–C(5′), H–C(6′)); 7.37 (*d*, $J = 5.2$, H–C(7)); 7.86 (*d*, $J = 5.2$, H–C(6)). Anal.: see the *Table*.

N-*(2-Chlorophenyl)-4-hydroxy-2-methyl-2*H-*thieno[2,3*-e*][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**7d**). Prepared according to *GP 1*: 10 h at 140°, recrystallized from benzene. Yield: 51%. Light-yellow crystals. M.p. 181–182°. UV (MeOH): 382 (3.22), 268 (3.10). ^{1}H-NMR ($CDCl_3$): 3.08 (*s*, MeN); 7.24–7.32 (*m*, H–C(3′), H–C(4′), H–C(5′), H–C(6′)); 7.39 (*d*, $J = 5.3$, H–C(7)); 7.85 (*d*, $J = 5.3$, H–C(6)). Anal.: see the *Table*.

N-*(3-Chlorophenyl)-4-hydroxy-2-methyl-2*H-*thieno[2,3*-e*][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**7e**). Prepared according to *GP 1*: 10 h at 140°, purified by CC (SiO_2; AcOEt) and recrystallization from Et_2O/benzene. Yield: 78%. Light-yellow crystals. M.p. 240–243°. UV (MeOH): 354 (3.58), 258 (3.40). ^{1}H-NMR ($CDCl_3$): 2.97 (*s*, MeN); 7.21–7.42 (*m*, H–C(2′), H–C(4′), H–C(5′), H–C(6′)); 7.38 (*d*, $J = 5.1$, H–C(7)); 7.89 (*d*, $J = 5.1$, H–C(6)). Anal.: see the *Table*.

4-Hydroxy-2-methyl-N-*[3-(trifluoromethyl)phenyl]-2*H-*thieno[2,3*-e*][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**7f**). Prepared according to *GP 1*: 20 h at 150°, crystallized from Et_2O/benzene, and recrystallized from

i-PrOH. Yield: 37%. Light-yellow crystals. M.p. 258–261°. UV (MeOH): 404 (3.58), 296 (3.34). ^{1}H-NMR ((D$_6$)DMSO): 3.04 (*s*, MeN); 7.32–8.04 (*m*, H–C(2′), H–C(4′), H–C(5′), H–C(6′)); 7.37 (*d*, *J* = 5.1, H–C(7)); 7.78 (*d*, *J* = 5.1, H–C(6)). Anal.: see the *Table*.

4-Hydroxy-2-methyl-N-*[4-(trifluoromethyl)phenyl]-2*H-*thieno[2,3-e][1,2]thiazine-3-carboxamide 1,1-Dioxide* (**7g**). Prepared according to *GP 1*: 18 h at 150°, recrystallized from i-PrOH/Et$_2$O and i-PrOH. Yield: 44%. Light-yellow crystals. M.p. 272–275°. UV (MeOH): 372 (3.68), 258 (3.48). pK_a 1.08. ^{1}H-NMR (CDCl$_3$): 2.95 (*s*, MeN); 7.38 (*d*, *J* = 5.0, H–C(7)); 7.67 (*d*, *J* = 8.6 , H–C(2′), H–C(6′)); 7.89 (*d*, *J* = 5.0, H–C(6)); 7.91 (*d*, *J* = 8.6 , H–C(3′), H–C(5′)). Anal.: see the *Table*.

*4-Hydroxy-2-methyl-2*H-*thieno[2,3-*e*][1,2]thiazine-3-carboxylic Acid 2-Phenylhydrazide 1,1-Dioxide* (**8**). To a suspension of **5** (1.20 g, 3.4 mmol) in DMF (10 ml), phenylhydrazine (0.67 ml, 6.8 mmol) was added, and the mixture was heated under N$_2$ atmosphere for 8 h at 100° (oil bath). The mixture was cooled and diluted with H$_2$O (40 ml). A dark-yellow oily product separated. After decantation of the solvent, the residue was taken up in CHCl$_3$ (20 ml), and washed with 5% aq. HCl (3 × 10 ml) and H$_2$O (2 × 10 ml), dried (Na$_2$SO$_4$), decolorized over charcoal, and evaporated *in vacuo*. The resulting residue was crystallized from EtOH to afford **8** in 57% yield. Colorless crystals. M.p. 248–249°. UV (MeOH): 420 (4.10), 298 (3.78). ^{1}H-NMR ((D$_6$)DMSO): 3.02 (*s*, MeN); 7.16–8.38 (*m*, H–C(2′), H–C(3′), H–C(4′), H–C(5′), H–C(6′)); 7.41 (*d*, J = 5.4, H–C(7)); 7.88 (*d*, *J* = 5.4, H–C(6)); 8.83 (*s*, HN–CO); 13.86 (*s*, HN–Ph). Anal.: see the *Table*.

*4-Hydroxy-2-methyl-2*H-*thieno[2,3-e][1,2]thiazine-3-carboxylic Acid 1,1-Dioxide* (**9a**). Compound **5** (3.53 g, 10 mmol) was suspended in a mixture of 5% aq. NaOH soln. (20 ml) and EtOH (10 ml). The mixture was heated for 3 h at 80° (water bath). After removal of the EtOH *in vacuo*, the cold aq. soln. was adjusted to pH 3 with conc. HCl. A white precipitate started to form and was allowed to fully crystallize in a refrigerator overnight. The crystals were filtered, washed with a small amount of cold H$_2$O and EtOH, and dried in a vacuum desiccator at r.t. to afford 1.52 g (57%) of **9a**. Colorless crystals. M.p. 242°. pK_a 4.27. UV (MeOH): 330 (3.02), 256 (2.78). ^{1}H-NMR ((D$_6$)DMSO): 2.95 (*s*, MeN); 7.38 (*d*, *J* = 5.4, H–C(7)); 7.79 (*d*, *J* = 5.4, H–C(6)). Anal.: see the *Table*.

*Ethyl 4-Hydroxy-2-methyl-2*H-*thieno[2,3-e][1,2]thiazine-3-carboxylate 1,1-Dioxide* (**9b**). *Method A* (acid-catalyzed esterification). Compound **9a** (2.63 g, 10 mmol) was dissolved in EtOH (40 ml) containing a cat. amount of H$_2$SO$_4$ (0.4 g). The soln. was heated for 3 h at 80° (water bath), and then evaporated *in vacuo*. The residue was dissolved in EtOH (40 ml), and this process was repeated twice. The residue was then dissolved in CHCl$_3$ (30 ml), and washed with 5% aq. Na$_2$CO$_3$ soln. (2 × 15 ml) and H$_2$O (2 × 15 ml). The reddish-black org. layer was separated and dried (Na$_2$SO$_4$), decolorized over charcoal, and evaporated *in vacuo*. The crude product was recrystallized from EtOH to afford 1.32 g (45%) of **9b**. Light-yellow crystals. M.p. 160–163°. UV (MeOH): 310 (2.98), 256 (2.85). ^{1}H-NMR (CDCl$_3$): 1.19 (*t*, *J* = 7.4, Me); 3.06 (*s*, MeN); 4.42 (*q*, *J* = 7.4, CH$_2$); 7.39 (*d*, *J* = 5.3, H–C(7)); 7.85 (*d*, *J* = 5.3, H–C(6)). Anal.: see the *Table*.

Method B (Alcoholysis). Compound **5** (3.53 g, 10 mmol) was suspended in EtOH (40 ml) containing EtONa (1.7 g, 25 mmol). The mixture was heated under N$_2$ atmosphere for 12 h at 80° (water bath). The solvent was evaporated under reduced pressure, the residue was diluted with 10% aq. HCl, and extracted with CHCl$_3$ (3 × 25 ml). The combined org. layer was washed with 5% aq. Na$_2$CO$_3$ soln. (2 × 15 ml) and H$_2$O (2 × 15 ml), and the org. layer was dried (Na$_2$SO$_4$) *in vacuo*. The resulting residue was purified by CC (SiO$_2$; AcOEt) and recrystallization from EtOH to afford 1.71 g (58%) of **9b**.

General Procedure (*GP 2*) *for the Preparation of Compounds* **10**. To a suspension of **1** (0.16 g, 0.5 mmol) in anh. DMF (1 ml), the appropriate acid chloride (0.55 mmol) was added at 0°. Then, the mixture was kept for 3 h at r.t., and the progress of the reaction was monitored by TLC (SiO$_2$; benzene/MeOH 4:1). After cooling, the hydrochloride salts of the products precipitated from the mixture. They were filtered off, washed with AcOEt or Et$_2$O, and dried *in vacuo* to afford the pure products. A faint yellow color indicated some trace amount of **1** as a hydrolytic product.

4-O-*Acetyltenoxicam Hydrochloride* (*= 2-Methyl-1,1-dioxido-3-[(pyridin-2-ylamino)carbonyl]-2*H-*thieno[2,3-e][1,2]thiazin-4-yl Acetate Hydrochloride*; **10a**). According to *GP 2*. Yield: 39%. Yellowish-white crystals. M.p. 208°. UV (MeOH): 354 (3.85), 270 (2.82). ^{1}H-NMR (CDCl$_3$): 2.51 (*s*, MeCO); 2.89 (*s*, MeN); 7.34 (*dd*, *J* = 7.2, 5.8, H–C(5′)); 7.45 (*d*, *J* = 5.1, H–C(7)); 7.74 (*d*, *J* = 8.2, H–C(3′)); 8.04 (*d*, *J* = 5.1, H–C(6)); 8.20 (*dd*, *J* = 8.2, 7.2, H–C(4′)); 8.34 (*d*, *J* = 5.8, H–C(6′)); 8.59 (*s*, HN–CO); 13.50 (s, HN$^+$). Anal.: see the *Table*.

4-O-*Benzoyltenoxicam Hydrochloride* (*= 2-Methyl-1,1-dioxido-3-[(pyridin-2-ylamino)carbonyl]-2*H-*thieno[2,3-e][1,2]thiazin-4-yl Benzoate Hydrochloride*; **10b**). According to *GP 2*. Yield: 43%. Yellowish-white crystals. M.p. 199°. UV (MeOH): 352 (3.20), 272 (2.65). ^{1}H-NMR (CDCl$_3$): 2.92 (*s*, MeN); 7.41 (*dd*, *J* = 7.1, 6.0, H–C(5′)); 7.49 (*d*, *J* = 5.1, H–C(7)); 7.62 (*t*, *J* = 5.2, H–C(4″)); 7.67 (*t*, *J* = 5.2, H–C(3″), H–C(5″)); 7.83 (*d*,

J = 8.2, H–C(3′)); 7.95 (*d*, J = 5.2, H–C(2″), H–C(6″)); 8.08 (*d*, J = 5.1, H–C(6)); 8.25 (*dd*, J = 8.2, 7.1, H–C(4′)); 8.39 (*d*, J = 6.0, H–C(6′)); 8.51 (*s*, HN–CO); 13.47 (*s*, HN^+). Anal.: see the *Table*.

4-O-*Furoyltenoxicam Hydrochloride* (= *2-Methyl-1,1-dioxido-3-[(pyridin-2-ylamino)carbonyl]-2*H-*thieno[2,3-*e*][1,2]thiazin-4-yl 2-Furoate*; **10c**). According to *GP 2*. Yield: 24%. Yellowish-white crystals. M.p. 184°. UV (MeOH): 352 (3.08), 248 (3.25). ^{1}H-NMR ($CDCl_3$): 2.90 (*s*, MeN); 6.66 (*dd*, J = 3.4, 1.7, H–C(4″)); 7.22 (*dd*, J = 3.4, 0.9, H–C(3″)); 7.36 (*dd*, J = 7.2, 5.6, H–C(5′)); 7.46 (*d*, J = 5.2, H–C(7)); 7.76 (*d*, J = 8.4, H–C(3′)); 7.92 (*dd*, J = 1.7, 0.9, H–C(5″)); 8.05 (*d*, J = 5.2, H–C(6)); 8.21 (*dd*, J = 8.4, 7.2, H–C(4′)); 8.36 (*d*, J = 5.6, H–C(6′)); 8.52 (*s*, HN–CO); 13.54 (*s*, HN^+). Anal.: see the *Table*.

4-O-*Cinnamoyltenoxicam Hydrochloride* (= *2-Methyl-1,1-dioxido-3-[(pyridin-2-ylamino)carbonyl]-2*H-*thieno[2,3-*e*][1,2]thiazin-4-yl 3-Phenylprop-2-enoate*; **10d**). According to *GP 2*. Yield: 39%. Yellowish-white crystals. M.p. 206°. UV (MeOH): 352 (3.28), 272 (2.75). ^{1}H-NMR ($CDCl_3$): 2.91 (*s*, MeN); 6.53 (*s*, H–C(1″)); 7.18–7.27 (*m*, H–C(4″) H–C(5″) H–C(6″) H–C(7″) H–C(8″)); 7.38 (*dd*, J = 6.6, 6.2, H–C(5′)); 7.47 (*d*, J = 5.2, H–C(7)); 7.79 (*d*, J = 8.6, H–C(3′)); 7.95 (*s*, H–C(2″)); 8.08 (*d*, J = 5.2, H–C(6)); 8.23 (*dd*, J = 8.6, 6.6, H–C(4′)); 8.39 (*d*, J = 6.2, H–C(6′)); 8.54 (*s*, HN–CO); 13.50 (*s*, HN^+). Anal.: see the *Table*.

*5-Methyl-5*H,*6*H-*pyrido[2′,1′:2,3]pyrimido[5,4-*c*]thieno[2,3-*e*][1,2]thiazin-6-one 4,4-Dioxide* (**12**). A soln. of **1** (0.34 g, 1 mmol) in $POCl_3$ (1 ml) was heated for 3 h at 100° under N_2 atmosphere. The mixture was slowly poured onto H_2O (15 ml). The resulting precipitate was neutralized with Na_2CO_3, suction-filtered, thoroughly washed with H_2O, dried at r.t., and recrystallized from EtOH to afford 0.18 g (56%) of **12**. Yellowish-green solid. M.p. 256–258°. UV (MeOH): 352 (3.88), 260 (3.52). IR (KBr): 1638*w*, 1615*w*, 1333*m*, 1166*m*. ^{1}H-NMR ($CDCl_3$): 3.05 (*s*, MeN); 7.20 (*d*, J = 5.1, H–C(3)); 7.35 (*dd*, J = 8.6, 1.2, H–C(8)); 7.69 (*d*, J = 5.1, H–C(2)); 7.88 (*ddd*, J = 7.6, 6.7, 1.7, H–C(10)); 8.37 (*ddd*, J = 8.6, 6,7, 1.7, H–C(9)); 9.07 (*dd*, J = 7.6, 1.7, H–C(11)). QP-MS: 319 (M^+). Anal.: see the Table.

*4-Methyl-1-phenyl-1,4-dihydropyrazolo[4,3-*c*]thieno[2,3-*e*][1,2]thiazin-3(2*H*)-one 5,5-Dioxide* (**13**). To a suspension of **8** (0.7 g, 2 mmol) in toluene (8 ml), *N*,*N*-dimethylaniline (1 ml) and $POCl_3$ (2 ml) were added. The mixture was heated for 7 h at 100° under N_2 atmosphere. After cooling, the reaction was quenched with ice-cold H_2O (25 ml). The mixture was diluted with toluene (22 ml), the layers were separated, the aq. layer was adjusted to pH 3 with conc. aq. NH_4OH soln., and extracted with $CHCl_3$ (3 × 15 ml). The combined org. layers were washed with 10% aq. Na_2CO_3 soln. (2 × 10 ml) and H_2O (2 × 10 ml), dried (Na_2SO_4), decolorized over charcoal, and evaporated *in vacuo*. The residue was purified by CC (SiO_2; AcOEt/CH_2Cl_2 1:1) and recrystallization (i-PrOH) to afford 0.31 g (47%) of **13**. Yellow solid. M.p. 209–211°. UV (MeOH): 362 (4.22), 265 (4.06). IR (KBr): 3253*w*, 1648*w*, 1623*m*, 1336*m*, 1157*m*. ^{1}H-NMR ($CDCl_3$): 3.17 (*s*, MeN); 6.66–7.10 (*m*, H–C(2′), H–C(3′), H–C(4′), H–C(5′), H–C(6′)); 7.45 (*d*, J = 5.1, H–C(6)); 7.71 (*d*, J = 5.1, H–C(7)); 9.75 (*s*, H–N). QP-MS: 333 (M^+). Anal.: see the *Table*.

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