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Three isomeric substituted thienoimidazothiazoles were synthesized as thiophene analogs of the immune modulator TILOMISOL, by cyclizing appropriate β-oxothioethers of thienoimidazoles. In contrast to the benzene analog no intermediates were observed at this step.

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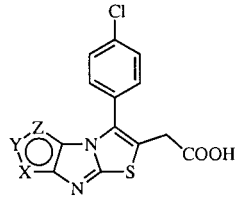
Many compounds of the class of annelated thiazoles have a marked stimulating effect on the human cellular immune system [1,2]. In particular annelated thiazole acetic acids, like TILOMISOL, turned out to be highly active, which even gained in importance as an antimetastaticum, shown by decreased growth of metastasis in mice [3]. As demonstrated by several drugs - among them BROTIZOLAM and TENOXICAM synthesized in our research group - a bioisosteric exchange of benzene by the chemically related thiophene moiety may be performed, often leading to an improved physiological effect. Therefore we decided to apply this process to TILOMISOL, comprising a new class of annelated heterocycles with three isomers being considered shown below.

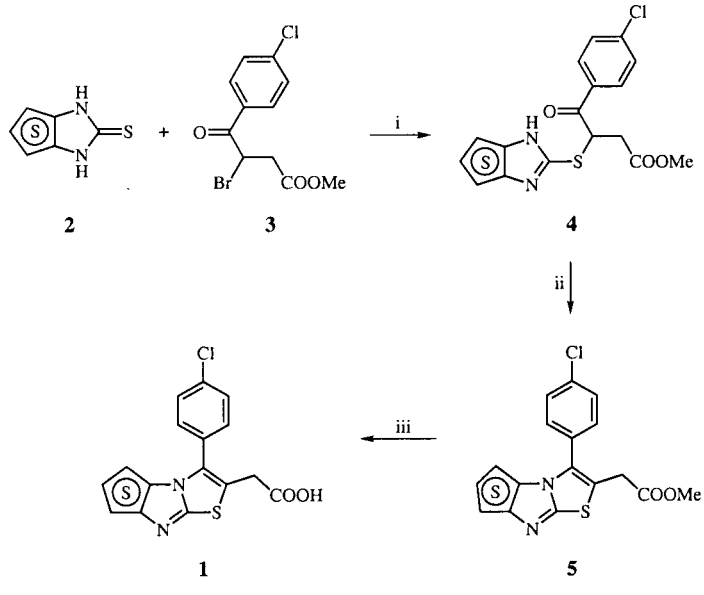


	X	Y	Z
1a	S	CH	CH
1b	CH	S	CH
1c	CH	CH	S

Thienoimidazothiazoles **1** were synthesized by alkylation of thienoimidazolones **2** with β-bromoester **3**, cyclization of intermediates **4** and subsequent hydrolysis of esters **5** (Scheme 1).

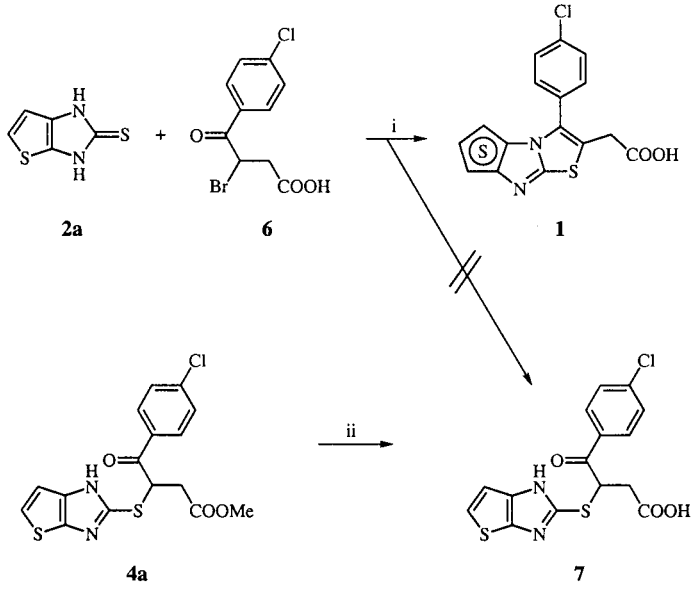
Since cyclization of the [2,3-*d*] annelated thioether **4a** yields both esters **5a** and **5c**, only two isomers of thienoimidazole **2** had to be considered. As known for isomer **2b** [4], they were obtained by reaction of freshly prepared diaminothiophenes [5] with sodium methyl xanthogenate. The β-bromoester **3** [6] was prepared by methylation of 4-(4-chlorophenyl)-4-oxo-butanoic acid [7] with dimethyl sulfate/potassium carbonate and bromination with bromine in acetic acid in 95% overall yield. Upon refluxing equimolar mixtures of the starting materials in methanol, thioethers **4** were obtained, either as the free compound **4a** after treatment with sodium bicarbonate or directly as the hydrobromide **4b**. Whereas the latter was readily cyclized in boiling phosphoryl chloride to thienoimidazothiazole **5b**, treatment of thioether **4a** with polyphosphoric acid at 80° yielded a mixture of isomeric esters **5a** and **5c**, which were obtained, however, mainly as their free acids **1a** and **1c**. As separation of the isomeric acids was not possible, neither by recrystallization nor by chromatography, they were reconverted to esters **5** with dimethyl sulfate/potassium carbonate. Ester **5a** was now isolated from the mixture of isomers by repeated recrystallization from methanol. Its isomer **5c** was then isolated by chromatography of the mother liquor. Finally all three esters **5** were hydrolyzed quantitatively in alkaline medium to acids **1**. Reacting thione **2a** with the free β-bromoacid **6** did not give thioether **7**, as expected, but a mixture of isomeric products **1a** and **1c** (Scheme 2). As the yield of the crude product was below 20% and a further purification was not possible, this method was discarded.

Scheme 1



Reagents and conditions: i, methanol, reflux; ii, Polyphosphoric acid, 80° (**4a**) or $POCl_3$, reflux (**4b**); iii, aqueous KOH, methanol, reflux

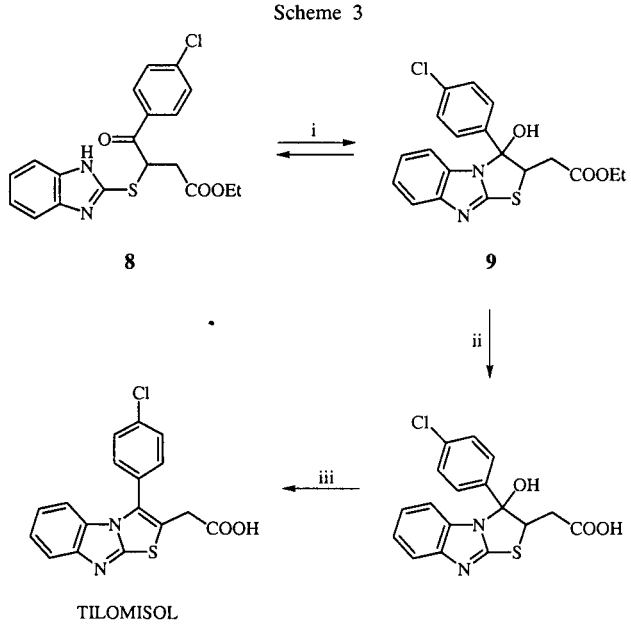
Scheme 2



Reagents and conditions: i, Acetic acid, 100°; ii, 1*N* aqueous NaOH, RT

Assignment of isomers for **4a/c** and **5a/c** was achieved by nmr-spectroscopy. In contrast to isomer **a** a mesomeric form for isomer **c** may be formulated bearing a negative charge on the α-CH of the thiophene moiety. This results in a distinct highfield shift of the corresponding hydrogen atom from 7.2 to 6.5 ppm whereas the β-CH hydrogen remains essentially unchanged. Equal effects were observed in the ^{13}C-nmr.

Scheme 3



Reagents and conditions: i, H_2O; ii, Aqueous NaOH, Δ; iii, Aqueous HCl, dioxane, reflux

A remarkable difference from the analogous synthesis of TILOMISOL was observed at the cyclization step. Whereas thieno annelated thioethers **4** and their hydrobromides directly gave thienoimidazothiazoles **5**, liberation of the free amine of the benzo annelated hydrobromide initiates an equilibrium between the ring-opened form **8** and the hydroxylated form **9**, which is then converted to TILOMISOL through hydrolysis and elimination (Scheme 3) [8].

The proof of structure of thiophene analog **4** was achieved by ir-spectroscopy, which gave two carbonyl signals (1677 cm^{-1}, 1726 cm^{-1}) not only in the solid phase (potassium bromide) but also in solution (chloroform). Just so the ^1H-nmr chemical shifts of the CH-groups at ≈5 ppm were explained by the strong electron withdrawing effect of the carbonyl group in the open form **4**. The same behavior was observed with the analogous acid **7**, which was obtained by alkaline hydrolysis of ester **4a** at room temperature.

EXPERIMENTAL

Melting points were measured on a Kofler-apparatus and are uncorrected. The ^1H-nmr spectra were recorded on a JOEL FX 90Q FT-NMR spectrometer (88.55 MHz) in deuteriochloroform (internal standard tetramethylsilane δ = 0.00 ppm) or dimethyl-d_6 sulfoxide (internal standard DMSO δ = 2.50 ppm) as the solvent; abbreviations: Ph = phenyl, Th = thiophene.

3-(4-Chlorophenyl)thieno[2',3'-4,5]imidazo[2,1-*b*]thiazole-6-acetic Acid (**1a**).

Ester **5a** (1.70 g, 4.69 mmoles) was suspended in a solution of potassium hydroxide (270 mg, 4.81 mmoles) in 8 ml of water and 20 ml of methanol and stirred under reflux until clear. After evaporation the residue was taken up in 15 ml of water and acidified with 2*N* hydrochloric acid until *p*H = 1. The precipitate was filtered, digested with water and recrystallized from ethanol, yielding carboxylic acid **1a** (1.60 g, 98%) as colorless crystals, mp 239-240° (from ethanol); ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.71 (4 H, s, Ph), 7.29-7.20 (2 H, AB, Th , ^3J = 5.5), 3.82 (2 H, s, CH_2).

Anal. Calcd. for $C_{15}H_9N_2ClO_2S_2$: C, 51.65; H, 2.60; N, 8.03. Found: C, 51.60; H, 2.67; N, 7.81.

3-(4-Chlorophenyl)thieno[3',4'-4,5]imidazo[2,1-*b*]thiazole-6-acetic Acid (**1b**).

Applying the same procedure as for **1a**, but refluxing for 15 minutes and recrystallization from methanol, ester **5b** (8.34 g, 23.0 mmoles) gave carboxylic acid **1b** (5.73 g, 72%) as colorless crystals, mp 200-210° (from methanol); ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.87 (1 H, br s, OH), 7.72 (4 H, s, Ph), 7.41-6.76 (2 H, AB, Th , ^3J = 2.4), 3.83 (2 H, s, CH_2).

Anal. Calcd. for $C_{15}H_9N_2ClO_2S_2$: C, 51.65; H, 2.60; N, 8.03. Found: C, 51.48; H, 2.67; N, 7.87.

7-(4-Chlorophenyl)thieno[3',2'-4,5]imidazo[2,1-*b*]thiazole-6-acetic Acid (**1c**).

Applying the same procedure as for **1a** ester **5c** (0.30 g, 0.83 mmoles) gave carboxylic acid **1c** (0.28 g, 97%) as colorless crystals, mp 235-238° (from ethanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.70 (4 H, s, Ph), 7.17-6.56 (2 H, AB, Th , ^{3}J = 5.6), 3.78 (2 H, s, CH_2).

Anal. Calcd. for $C_{15}H_9N_2ClO_2S_2$: C, 51.65; H, 2.60; N, 8.03. Found: C, 51.61; H, 2.66; N, 7.96.

1,3-Dihydrothieno[2,3-*d*]imidazole-2-thione (**2a**).

A freshly prepared solution of 2,3-diaminothiophene (7.91 g, 69.4 mmoles) in 300 ml of methanol and sodium methyl xanthogenate (11.8 g, 90.7 mmoles) were shaken in an autoclave for 6 hours at 80°. After removal of the solvent, the residue was diluted with 150 ml of water and 200 ml of ethyl acetate, acidified with concentrated hydrochloric acid until *p*H = 1, filtered over hyflo, and the aqueous layer extracted three times with 300 ml of ethyl acetate altogether. The combined organic layers were dried over sodium sulfate, filtered and evaporated. Digestion of the crude product with ether, yielded thione **2a** (4.20 g, 39%) as pale brown crystals, mp dec from 190°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.0-6.0 (2 H, br s, NH), 7.14-6.81 (2 H, AB, Th).

Anal. Calcd. for $C_5H_4N_2S_2 \cdot 0.12H_2O$: C, 37.92; H, 2.70; N, 17.69. Found: C, 38.20; H, 2.66; N, 17.39.

4-(4-Chlorophenyl)-4-oxo-3-(1*H*-thieno[2,3-*d*]imidazol-2-yl)thiobutanoic Acid Methyl Ester (**4a**).

A solution of thione **2a** (3.60 g, 23.0 mmoles) and 3-bromo-4-(4-chlorophenyl)-4-oxobutanoic acid methyl ester (6.40 g, 20.9 mmoles) in 100 ml of absolute methanol was refluxed for one hour. After removal of the solvent the oily residue was crystallized under 5 ml of ether, filtered, suspended in 20 ml ethyl acetate and stirred with saturated sodium bicarbonate solution until the end of gas evolution. Evaporation of the organic solvent and subsequent filtration yielded thioether **4a** (6.45 g, 81%) as pale yellow crystals, mp 170-172° (from ethanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.05-7.59 (4 H, A_2B_2, Ph , ^{3}J = 8.7), 7.37-7.01 (2 H, AB, Th , ^{3}J = 5.6), 5.31 (1 H, t, CH, ^{3}J = 5.9), 3.55 (3 H, s, OCH_3), 3.13 (2 H, d, CH_2, ^{3}J = 5.9 Hz).

Anal. Calcd. for $C_{16}H_{13}N_2ClO_3S_2$: C, 50.46; H, 3.44; N, 7.36. Found: C, 50.20; H, 3.47; N, 7.43.

4-(4-Chlorophenyl)-4-oxo-3-(1*H*-thieno[3,4-*d*]imidazol-2-yl)-thiobutanoic Acid Methyl Ester, Hydrobromide (**4b**).

A solution of 1,3-dihydrothieno[3,4-*d*]imidazol-2-thione (15.9 g, 102 mmoles) and 3-bromo-4-(4-chlorophenyl)-4-oxobutanoic acid methyl ester (28.7 g, 94.1 mmoles) in 450 ml of absolute methanol was refluxed for 2 hours. After filtration of the hot mixture and removal of the solvent the residue was digested with ether and recrystallized from dimethylformamide/acetonitrile 3:10, yielding hydrobromide **4b** (16.7 g, 36%) as beige crystals, mp 185-187° (from dimethylformamide/acetonitrile, dec); ^{1}H nmr (dimethyl-d_6 sulfate): δ 8.52 (2 H, br s, NH_2), 7.89-7.29 (6 H, m, Ph, Th), 5.03-4.73 (1 H, in, CH), 3.55 (3 H, s, OCH_3) 3.35-2.79 (2 H, m, CH_2).

Cyclization of Thioether **4a**.

A suspension of thioether **4a** (6.40 g, 16.8 mmoles) in 30 g polyphosphoric acid was heated at 80° for 2.5 hours with stirring and poured onto 100 ml water. After addition of 100 ml ethyl acetate the mixture was heated at 70°, filtered over hyflo and the hydrous layer extracted three times with 300 ml of ethyl acetate. The combined organic layers were extracted with saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and evaporated, yielding a mixture of esters **5a** and **5c** (1.20 g, 20%).

The potassium carbonate layer was filtered over charcoal, acidified with concentrated hydrochloric acid, the precipitate filtered, digested with water and dried in a vacuum, yielding a mixture of carboxylic acids **1a** and **1c** (3.10 g, 53%).

This mixture (3.10 g, 8.89 mmoles), dimethyl sulfate (1.69 g, 13.4 mmoles) and potassium carbonate (1.32 g, 9.57 mmoles) in 40 ml of absolute acetone were heated at reflux for 30 minutes. After evaporation the residue was taken up in 40 ml water, extracted four times with a total of 140 ml ethyl acetate, dried over sodium sulfate, filtered and evaporated, yielding a mixture of esters **5a** and **5c** (3.14 g, 97%) as beige crystals, which was combined with the ester, obtained from the cyclization step.

By repeated recrystallization from methanol isomer **5a** (1.70 g) was obtained as yellow crystals. The combined mother liquors were evaporated, fractionated by chromatography (silica gel KG60, chloroform:benzene = 3:1) and the residues recrystallized from methanol, yielding a second fraction of ester **5a** (0.61 g) and ester **5c** (0.32 g) as light yellow crystals.

5-(4-Chlorophenyl)thieno[2,'3'-4,5]imidazo[2,1-*b*]thiazole-6-acetic Acid Methyl Ester (**5a**).

Ester **5a** was obtained in an overall yield of 2.31 g (38%) as yellow crystals, mp 159-162° (from methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.70 (4 H, s, Ph), 7.28-7.19 (2 H, AB, Th, ^{3}J = 5.5), 3.92 (2 H, s, CH_2).

Anal. Calcd. for $C_{16}H_{11}N_2ClO_2S_2$: C, 52.96; H, 3.06; N, 7.72. Found: C, 52.94; H, 3.17; N, 7.68.

7-(4-Chlorophenyl)thieno[3',2'-4,5]imidazo[2,1-*b*]thiazole-6-acetic Acid Methyl Ester (**5c**).

Ester **5c** was obtained in an overall yield of 0.32 g (5%) as light yellow crystals, mp 131-133° (from methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.69 (4 H, s, Ph), 7.17-6.54 (2 H, AB, Th, ^{3}J = 5.6), 3.88 (2 H, s, CH_2).

Anal. Calcd. for $C_{16}H_{11}N_2ClO_2S_2$: C, 52.96; H, 3.06; N, 7.72. Found: C, 52.91; H, 3.09; N, 7.57.

3-(4-Chlorophenyl)thieno[3',4'-4,5]imidazo[2,1-*b*]thiazole-6-acetic Acid Methyl Ester (**5b**).

A suspension of hydrobromide **4b** (10.7 g, 21.7 mmoles) in 100 ml of phosphoryl chloride was refluxed for 30 minutes. The excess phosphoryl chloride was distilled, the residue dissolved in 30 ml of methanol, and 120 ml of saturated sodium carbonate solution was added until the *p*H = 9. The separating oily product was crystallized under 3 ml of ethyl acetate, filtered, digested twice with water, dried and recrystallized from ethanol, yielding ester **5b** (8.34 g, 64%) as beige crystals, mp 198-199° (from ethanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.68 (4 H, s, Ph), 7.21-6.53 (2 H, AB, Th , ^{3}J = 2.4), 3.81 (2 H, s, $CH)_2$, 3.67 (3 H, s, OCH_3).

Anal. Calcd. for $C_{16}H_{11}N_2ClO_2S_2$: C, 52.96; H, 3.06; N, 7.72. Found: C, 52.66; H, 3.16; N, 7.54.

4-(4-Chlorophenyl)-4-oxo-3-(1*H*-thieno[2,3-*d*]imidazol-2-yl)thiobutanoic Acid (**7**).

Ester **4a** (1.00 g, 2.63 mmoles) was stirred for one hour in 15 ml of 1*N* sodium hydroxide solution, the mixture washed with 5 ml of ether, filtered over hyflo and acidified with concentrated hydrochloric acid. The precipitate was filtered off and digested with water, yielding carboxylic acid **7** (0.58 g, 60%) as beige crystals, mp 164-166° (from ethanol/water 1:1); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 11.1 (1 H, br s, COOH), 8.04-7.58 (4 H, A_2B_2, Ph, ^3J = 8.5), 7.37-7.01 (2 H, AB, Th , ^3J = 5.5), 5.31 (1 H, dd, CH , $^3J_{CH_2}$ = 5.5 , $^3J_{CH_2}$ = 8.7), 3.12-3.01 (2 H, m, CH_2).

Anal. Calcd. for $C_{15}H_{11}N_2ClO_3S_2$: C, 49.11; H, 3.02; N, 7.64. Found: C, 48.85; H, 3.01; N, 7.43.

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