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Synthesis and properties of *N*-substituted saccharin derivatives

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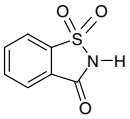
Dedicated to Prof. Dr. Dr. h.c. Peter Pflegel, Greifswald, on the occasion of his 65th birthday

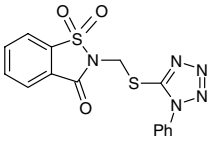
Four different routes for the synthesis of saccharin containing peptids were studied. While reactions between saccharin sodium and α-halogeno acids were limited to two examples, reactions of sulfobenzoic anhydride (**4**) or saccharin-*N*-carboxylate (**6**) with amino acid esters yielded the ring opened products **5** and **7**. Finally, we found, that the reaction between the benzoxathiol derivative **8** and amino acid derivatives represents a versatile route to the peptidic compounds **9** and **11**. Hydrolysis and hydrogenolysis were studied, and by combination of the different routes the "saccharin tripeptides" **18** were obtained. Structures and stereochemistry were elucidated by spectroscopic and chromatographic methods. Selected compounds were tested as sweeteners or as inhibitors of elastase, but no exiting results were found.

1. Introduction

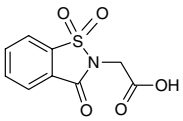
Saccharin, 3-oxo-2,3-dihydrobenzo[1,2]thiazol 1,1-dioxide (**I**), was first prepared by Remsen and Fahlberg [1], and its sodium salt has been used as a sweetener since 1885. Attempts to modify the structure to develop other sweeteners were unsuccessful until today [2], but some derivatives exhibited different biological activities. Structure **II** represents an example for derivatives acting as inhibitors of human leukocyte elastase (HLE) [3, 4]. Also, by long chain fatty acids N-acylated derivatives show good inhibitory activity [5]. Finally, some derivatives of saccharin like **III** inhibit aldose reductase [6].



I



II



III

In preceding papers, we have reported about the inhibitory activity of peptidyl ß-lactams against elastase [7]. From these results we developed the concept of constructing saccharin derivatives from amino acids and peptides, using the N-terminal as the nitrogen of the saccharin moiety. Here we report about synthesis, and properties of these compounds.

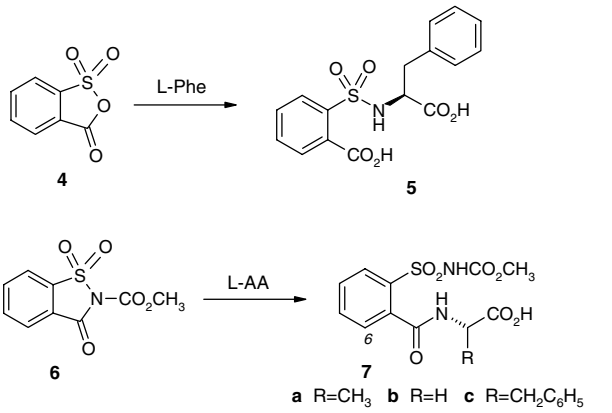
2. Investigations, results and discussion

2.1. Chemistry

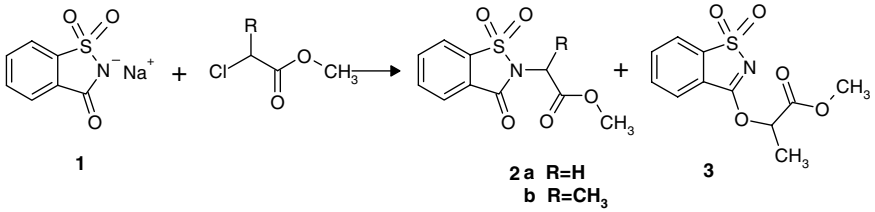
Examples for the reaction of saccharin sodium (**1**) with alkyl 2-haloalkanoates are described [8–10]. Repeating these experiments with methyl 2-chloropropionate, we isolated, depending on the reaction conditions, either the N-alkylated derivative **2b** or the O-alkylated (pseudosaccharin) derivative **3** (Scheme 1). From the reaction with methyl 2-chloroacetates only structure **2a** was isolated. The racemic compounds **2b** and **3** were separated by HPLC, but experiments with other alkanoic acids failed, and even from the reaction between **1** and (*R*)-2-chloropropionate the racemic **2b** was isolated.

N-Substituted maleinimides were obtained in high yields by a reaction between maleinic anhydride and amines [11, 12]. In analogy to this reaction we tried to obtain N-substituted derivatives of saccharin by a reaction between 2-sulfobenzoic anhydride (**4**) and amino acid ester. No products could be isolated, only from the reaction between **4** and L-Phe the ring opened sulfonamide **5** was isolated (Scheme 2). Cyclization of **5** [13] was not possible, indicating that this route is not appropriate for the synthesis of our targets. Similar problems arose during the reaction between *N*-methoxycarbonyl saccharin (**6**) and amino

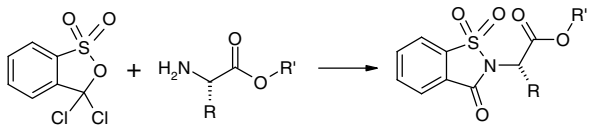
Scheme 2



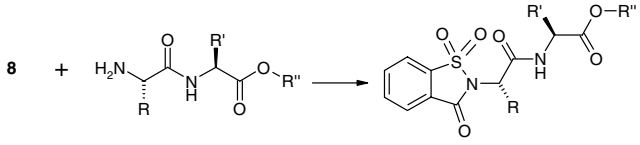
Scheme 1



Scheme 3



Scheme 4



acids. Different from the analogue reaction of maleinimides [14] we isolated with high yields the ring opened products, the carboxamide acids **7**, demonstrating that in this reaction not the sulfonyl but the carbonyl group was attacked by the amino group. The structure of **7** was clearly established by NMR spectroscopic methods. $^{13}C,^{1}H$ coupling experiments, and C,H-COSY long range experiments showed couplings between the aryl substituted carbonyl C, the nitrogen, and 6-H, and on the other hand, a coupling between that nitrogen atom and CH of the alanine moiety.

As a very versatile substrate for reactions with amino acid and dipeptide ester we finally found 3,3-dichloro-3*H*-benz[*c*][1,2]oxathiol 1,1-dioxide (**8**), first prepared by Holmes in 1901 [15]. Reactions of **8** with amino acids failed, but when we reacted amino acid ester with **8** in DMF at maximal 0 °C the saccharin derivatives **9a**–**p** were obtained with yields between 35 and 80% (Table 1).

Amino acid ester were prepared according to literature procedures [16, 17], then reacted with Boc-amino acids forming the Boc-dipeptide ester using the DCC/NHS method [18], which were finally N-deprotected by reaction with trifluoroacetic acid [19]. The dipeptide ester **10**, used as triflates, were reacted with **8** forming the "saccharin dipeptides" **11**, which were isolated as solid compounds with yields between 30 and 60% (Table 2).

Hydrolysis of the ester **9n** with equimolar amounts of 0.1 N NaOH in acetone at room temperature was not successful as the ester group was not hydrolyzed but the amide bond of the ring was opened yielding compound **12**. A similar result was found, when we tried to hydrolyze **2a** with NaOH at 50 °C. We isolated the glycine derivative **13** with 66% yield [20]. However, when **2a** or **2b** were refluxed with conc. HCl the ester groups were completely hydrolyzed yielding the acids **14a** and **14b**. Hydrolysis of (*S*)-**9a** under these conditions resulted in (*S*)-**14b**, while the hydrolysis of (*RS*)-**2b** yielded (*RS*)-**14b**, as could be shown by HPLC on ChiraSpher, demonstrating that during acidic hydrolysis no razemisation occurred. Probably, a big group R inhibits the acidic hydrolysis, as most other ester either gave only very poor yields for the acid or did not react at all. As a result we found that the most eary way to obtain the acids is the hydrogenation of the benzyl ester in the presence of Pd-C at normal pressure and room temperature. By this method we obtained the acids **15** with isolated yields between 80 and 100% (Scheme 5, Table 3).

The saccharin acetic acid **14a**, a N-protected glycine, was an appropriate target for the elongation with amino acid or peptide ester. When we reacted it with amino acid ester using the DCC/NHS method, we isolated the "saccharin dipeptides" **16** in yields up to 50%. The benzyl ester derivatives **16a** and **16b** were hydrogenated yielding the free acids **17a** and **17b** in yields of 68 and 79%. Under similar conditions two dipeptide esters, **10e** and **10f** were reacted with **14a**, yielding the "saccharin tripeptides" **18** as solid compounds (Scheme 6).

All saccharin derivatives were characterized by their IR spectra. Two strong bands represent the sulfonyl group. The SO_{2as} band usually appeared between 1330 and 1350 cm^{-1}, while SO_{2sym} was found between 1175 and 1190 cm^{-1}. Furthermore, all spectra showed a strong carbonyl bond around 1730–1740 cm^{-1}, indicating the carbonyl group of the five membered ring. In the spectra of compounds **9** usually a second carbonyl band around 1750 cm^{-1} was found indicating the ester group, the amid bond in **11** caused a band around 1660–1680 cm^{-1} and a N-H band around 3200–3300 cm^{-1}, while the acid group in compounds **15** could be detected by the carbonyl absorption band around 1710 cm^{-1}, and the hydroxyl band around 3300 cm^{-1}.

The NMR spectra were congruent with all structures. ^{13}C NMR spectra show the expected signals for all carbon atoms (Fig.), and were completely resolved. The spectra

Table 1: Saccharin derivatives 9

Compd.	R	R′	Yield (%)	M.p. (°C)	$[\alpha]_D^{20}$
9a	CH_3	CH_3	46	115	−20.65
9b	CH_3	C_2H_5	35	40	−24.83
9c	CH_3	$CH_2C_6H_5$	60	65	−9.5
9d	$CH_2(CO_2Bn)$	$CH_2C_6H_5$	54	112	−2.16
9e	H	$CH_2C_6H_5$	60	125	–
9f	$CH(CH_3)C_2H_5$	CH_3	53	75	−38.6
9g	$CH(CH_3)C_2H_5$	$CH_2C_6H_5$	53	70	−18.0
9h	$CH_2CH(CH_3)_2$	CH_3	47	72	−62.16
9i	$CH_2CH_2SCH_3$	CH_3	37	–	−70.10
9j	CH_2OH	CH_3	40	130	−4.3
9k	$CH_2C_6H_5$	CH_3	50	120	−175.0
9l	$CH_2C_6H_5$	C_2H_5	59	75	−85.0
9m	$CH_2C_6H_5$	$CH_2C_6H_5$	80	143	−100.66
9n	$CH(CH_3)_2$	CH_3	75	105	−65.0
9o	$CH(CH_3)_2$	C_2H_5	48	60	−65.5
9p	$CH(CH_3)_2$	$CH_2C_6H_5$	68	80	−30.16

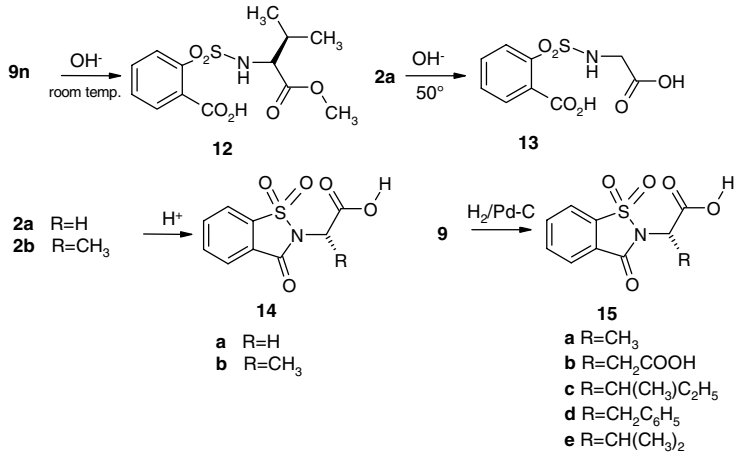
Table 2: Saccharin derivatives 11

Compd.	R	R′	R″	Yield (%)	M.p. (°C)	$[\alpha]_D^{20}$
11a	CH_3	$CH_2C_6H_5$	CH_3	54	130	+18.8
11b	CH_3	$CH(CH_3)_2$	CH_3	37	140	+8.0
11c	$CH_2C_6H_5$	CH_3	CH_3	33	115	−28.0
11d	$CH_2C_6H_5$	$CH_2C_6H_5$	CH_3	45	125	−58.6

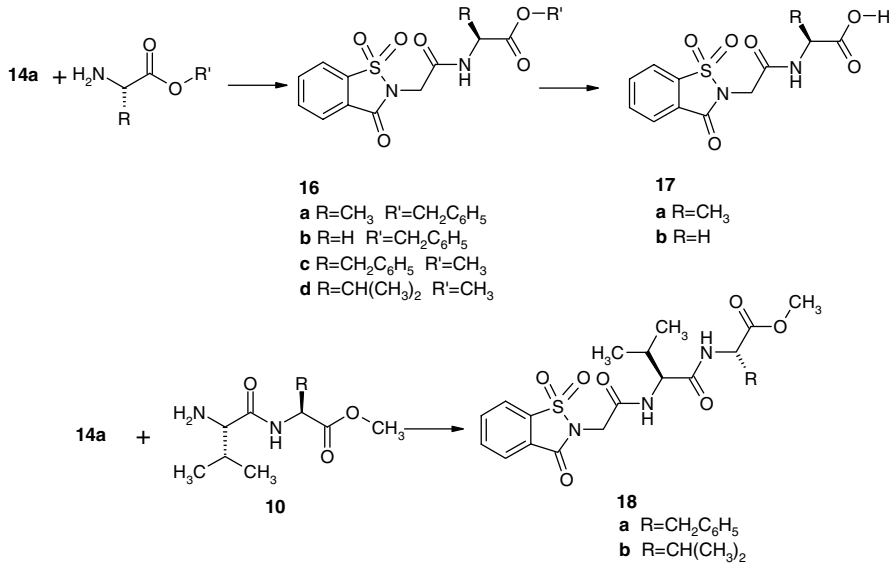
Table 3: Saccharin derivatives 15

Compd.	R	Yield (%)	M.p. (°C)	$[\alpha]_D^{20}$
15a	CH_3	98	165	−13.83
15b	CH_2COOH	78	220	+3.0
15c	$CH(CH_3)C_2H_5$	85	115	−28.5
15d	$CH_2C_6H_5$	82	170	−142.5
15e	$CH(CH_3)_2$	80	120	−49.8

Scheme 5



Scheme 6



of all other compounds were similar. All ^{1}H NMR spectra were completely resolved, and were congruent with the postulated structures. As can be deduced from the ^{1}H NMR spectra the amount of racemization is smaller than 5%. These results were in good agreement with those from HPLC experiments. All compounds were checked either by CE [21] or by HPLC using RP-18 and (S,S)-Whelk-O1 columns. Results and parameters for compounds **11** are summarized in Table 4. Parameters for other compounds are documented in the Experimental part.

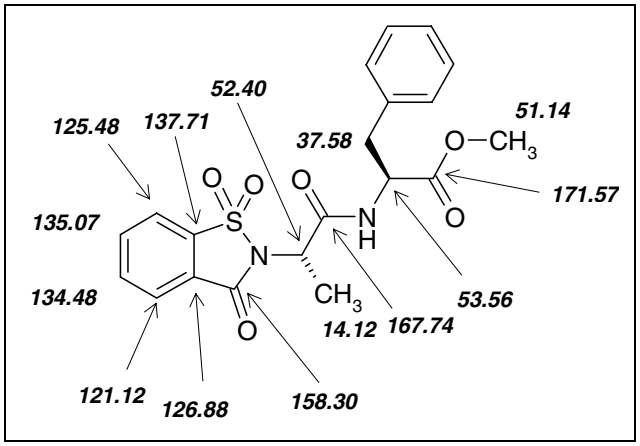


Fig.: ^{13}C NMR data ($CDCl_3$, 75 MHz) of **11a**

2.2. Biological evaluation

Different theories about sweetness are discussed, but until today, there is no exact knowledge about a receptor for sweetness [22, 23]. Therefore, it seems to be difficult to predict if a compound is a sweetener or not. Sensorial tests may give a first hint. We compared a number of selected compounds, dissolved in water, with the sweetness of a solution of saccharose (10 mg/ml). The results are summarized in Table 5.

None of the water soluble compounds exhibited a sweet taste. The water insoluble compounds, ester, were tested as solids. Nevertheless, none of them tasted sweet.

Using the standard procedure [7], the compounds **5**, **7a**–**c**, **9c**, **9e**, **9k**, **9m**, **9n**, **12**, **13**, **14a**, **15d**, **16b**, and **16c** were tested for inhibition of PPE. No remarkable activity could be detected.

Table 4: HPLC parameters for compounds 11

Compd.	t_R	k′	Phase	Column	λ (nm)	Flow (ml/min)
11a	12.35	4.62	MeCN/H_2O 1 : 1	RP-18	210	1.0
	7.02	2.90	*n*-hexane/EtOH 1 : 1	(S,S)-Whelk-O1	220	0.8
11b	8.87	3.17	MeCN/H_2O 1 : 1	RP-18	225	1.0
	5.43	1.84	*n*-hexane/EtOH 1 : 1	(S,S)-Whelk-O1	220	1.0
11c	9.39	3.91	MeCN/H_2O 1 : 1	RP-18	220	1.0
	6.45	2.38	*n*-hexane/EtOH 1 : 1	(S,S)-Whelk-O1	220	1.0
11d	31.29	13.22	MeCN/H_2O 1 : 1	RP-18	210	0.8
	7.07	2.93	*n*-hexane/EtOH 1 : 1	(S,S)-Whelk-O1	220	1.0

Table 5: Taste of selected saccharin derivatives

Compd.	Concentration	Taste
14a	10 mg/ml	acidic
14b	10 mg/ml	acidic, bitter
15a	10 mg/ml	acidic, bitter
15b	10 mg/ml	neutral
15c	10 mg/ml	bitter
15d	5 mg/ml	bitter
15e	5 mg/ml	bitter
17a	10 mg/ml	neutral
17b	10 mg/ml	bitter

3. Experimental

3.1. General

M.p.: PHMK 80/2747 (Küstner, Dresden) apparatus, not corrected. IR Spectra: Perkin-Elmer FTIR 1600; in KBr (cm^{-1}), if not noted otherwise. NMR Spectra: Bruker DPX 200/300 (200/300 MHz), for ^1H; Bruker DPX 200/300 (50/75 MHz) for ^{13}C; δ (ppm) rel. to TMS as internal standard, J in Hz; ^1H-values and ^{13}C-values from spectra in $CDCl_3$, if not noted otherwise. Mass Spectra: Intectra AMD 402/3. Optical rotation: Polatronic D (Schmidt Haensch GmbH). Elementary analyses: Perkin-Elmer Analyzer 2400 CHN, Pharmazeutisches Institut der Universität Greifswald. All the results were in an acceptable range. TLC on Merck DC-Alufolien, Silica Gel 60 F_{254}, Nr. 5554. CC with Silica Gel 60 Merck Nr. 7734 or 9385. HPLC with LaChrom apparatus series 7000 Merck Hitachi, columns: LiChrospher 250–4, RP-18,5 µm, and LiChroCART 250–4, (S,S)-Whelk-O1, 5 µm. HPLC: (S,S)-Welk-O1, n-hexane/EtOH 1 : 1, if not noted otherwise.

PPE (EC 3.4.21.36, ≈200 U/mg) was purchased from Serva, Suc-$(Ala)_3$-pNA from Bachem, 2-Sulfobenzoic anhydride (**4**) from Fluka, Nr. 86130, and saccharin sodium was obtained from Merck-Schuchardt, Nr. 814114.

Tetrahydrofuran (THF) was stored with $CaCl_2$, then refluxed with Na and benzophenone, and distilled prior to use. Dimethylformamide was distilled from P_4O_{10} and stored with molecular sieve 4Å. Other solvents were dried/purified according to literature procedures.

Abbreviations: CC = Column chromatography; DCC = Dicyclohexyl Carbodiimide; DMF = Dimethylformamide; EtOAc = Ethyl acetate; MeCN = Acetonitril; NHS = N-Hydroxysuccinimide; TEA = Triethylamine; TFA = Trifluoroacetic acid; ar = aromatic.

3.2. Methyl 3-oxo-2,3-dihydrobenzo[d][1,2]thiazol-2-acetate 1,1-dioxide (**2a**)

A mixture of 2.9 g (0.012 mol) of **1**, 0.86 g (0.08 mol) of methyl chloroacetate, and 5 ml of DMF was refluxed at 120 °C for 6 h with stirring. Then, the mixture was pored into ice/water, the precipitate was separated, washed with water and dried. Yield: 2.2 g (73%). Colorless crystals. – M.p. 118 °C (EtOH), (Lit 118 °C) [10]. – IR: ν = 3093, 3036, 2965, 2936 (CH), 1761, 1737 (CO), 1340, 1191 (SO_2). – ^1H NMR: δ = 3.76 (s, 3 H, OCH_3), 4.54 (s, 2 H, CH_2), 8.12 (m, 4 H, ar H).
$C_{10}H_9NO_5S$ (255.2)

3.3. Methyl (RS)-2-(3-oxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)propionate 1,1-dioxide (**2b**)

From 1.0 g (0.08 mol) of methyl (*RS*)-2-chloropropionate as described for **2a**. Yield: 1.7 g (51%). Colorless crystals. – M.p. 115 °C (EtOH). – IR: ν = 3094, 2991, 2961 (CH), 1759, 1738 (CO) 1381, 1185 (SO_2). – ^1H NMR: δ = 1.87 (d, J = 7.4, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), (q, J = 7.4, 1 H, CH), 7.8–8.1 (m, 4 H, ar H). – ^{13}C NMR: δ = 14.80 (CH_3), 49.58 (CH), 53.11 (OCH_3), 121.01 (C-4), 125.36 (C-7), 126.94 (C-3a), 134.45 (C-5), 135.04 (C-6), 137.89 (C-7a), 158.78 (C-3) 169.14 (CO). – HPLC: $k_1' = 1.81$, $k_2' = 1.95$, $t_o = 2.77$, (S,S)-Whelk-O1, n-hexane/propan-2-ol 1 : 1.
$C_{11}H_{11}NO_5S$ (269.3)

3.4. (RS)-3-[1-(Methoxycarbonyl)ethoxy]benzo[d][1,2]thiazol 1,1-dioxide (**3**) [24]

A mixture of 3.1 g (0.015 mol) of **1**, 0.86 g (0.007 mol) of methyl (*RS*)-2-chloropropionate, and 0.55 g of hexadecyltrimethylammonium bromide in 15 ml of toluene was heated to 100–105 °C for 4 h. Then, the mixture was cooled to room temp., filtered, and the solvent was evaporated in vacuo. Yield: 0.79 g (20%). Colorless crystals. – M.p. 145 °C (EtOH). – IR: ν = 3090, 3060, 3028, 2998 (CH), 1759 (CO), 1615 (C=N), 1336, 1133 (SO_2). – ^1H NMR ([d_6]acetone): δ = 1.76 (d, J = 7.0, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 5.56 (q, J = 7.0, 1 H, CH), 7.9–8.1 (m, 4 H, ar H). – ^{13}C NMR ([d_6]acetone): δ = 17.4 (CH_3), 53.0 (OCH_3), 76.0 (CH), 122.6 (C-4), 124.5 (C-7), 125.0 (C-3a), 134.9 (C-5), 135.8 (C-6), 144.6 (C-7a), 168.0 (C-3), 170.1 (CO). – HPLC: $k_1' = 3.16$, $k_2' = 3.82$, $t_o = 2.77$, (S,S)-Whelk-O1, n-hexane/propan-2-ol 1 : 1.
$C_{11}H_{11}NO_5S$ (269.3)

3.5. N-(2-Carboxyphenylsulfonyl)-L-phenylalanine (**5**)

1.65 g (0.1 mol) of L-Phe, and 1.84 g (0.1 mol) of **4** were suspended in 6 ml of glacial acetic acid and stirred for 24 h. Then, the precipitate was separated, washed with diethyl ether, and dried. Yield: 2.1 g (60%). – M.p.: 170 °C (MeOH/diethyl ether). – $[\alpha]_D^{20} = +9.7$ (c = 1.9, EtOH). – IR: ν = 3418 (NH), 3028, 2932 (CH), 1723 (CO), 1275, 1188 (SO_2). – ^1H NMR: δ = 3.12 (d, 2 H, CH_2), 4.20 (m, 1 H, CH), 7.2–7.5, 7.5–7.9 (2 m, 9 H, ar H), 8.23 (bs, 1 H, OH).
$C_{16}H_{15}NO_6S$ (349.4)

3.6. 2-Methoxycarbonyl-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**6**) [14]

9.15 g (50 mmol) of **1** and 5.05 g (50 mmol) of *N*-methylmorpholine were dissolved with stirring in 250 ml of EtOAc. At 0 °C, 4.5 g (50 mmol) of methyl chloroformiate were dropwise added. After 30 min, the precipitate was filtered off and washed with EtOAc. The filtrate was washed with a satd. NaCl solution (~100 ml), the combined organ. layers were dried (Na_2SO_4), the solvent was evaporated in vacuo, and the residue was recrystallized from EtOAc/petroleum ether. Yield: 0.47 g (20%). – M.p. 180 °C. – IR: ν = 3089, 2971 (CH), 1792 (CO), 1363, 1186 (SO_2). – ^1H NMR: δ = 4.08 (s, 3 H, OCH_3), 7.8–8.2 (m, 4 H, ar H). – ^{13}C NMR: δ = 54.94 (OCH_3), 121.34 (C-4), 125.61 (C-3a), 126.32 (C-7), 134.97 (C-5), 136.35 (C-6), 137.19 (C-7a), 147.57 (C-3), 156.02 (CO).
$C_9H_7NO_5S$ (241.2)

3.7. N-[2-(N-Methoxycarbonylsulfamoyl)benzoyl]-L-alanine (**7a**)

With stirring, 0.25 g (2.9 mmol) of L-Ala, and 0.7 g (2.9 mmol) of **6** were dissolved in 15 ml of a satd. solution of $NaHCO_3$, cooled to 0 °C, and 29 ml of THF was added. The mixture was stirred for 2 h at 40 °C, and then adjusted with sulfuric acid to pH = 6–7, concentrated in vacuo to half of the volume, and acidified to pH = 1–2. Then, it was extracted with EtOAc, the organic layer was washed with a satd. solution of NaCl, dried (Na_2SO_4), and evaporated. The residue was purified from excess of **6** by extraction with diethyl ether (soxhlet). Yield: 0.85 g (90%). – M.p. 175 °C. – $[\alpha]_D^{20} = +21$ (c = 1, MeOH). – IR: ν = 3189 (NH), 3070, 2966, 2930 (CH), 1746, 1712, 1666 (CO), 1255, 1164 (SO_2). – ^1H NMR ([d_6]DMSO): δ = 1.35 (d, J = 7.3, 3 H, CH_3), 3.56 (s, 3 H, OCH_3), 4.41 (m, 1 H, CH), 7.5–8.1 (m, 4 H, ar H), 8.79 (d, J = 7.17, 1 H, NH). – ^{13}C NMR ([d_6]DMSO): δ = 16.65 (CH_3), 47.84 (CH), 52.69 (OCH_3), 128.84, 129.28, 130.17, 133.40, 135.69, 136.31 (ar C), 151.55, 166.15, 174.18 (CO).
$C_{12}H_{14}N_2O_7S$ (330.3)

3.8. N-[2-(N-Methoxycarbonylsulfamoyl)benzoyl]glycine (**7b**)

From 0.15 g (2.1 mmol) of Gly, 0.5 g (2.1 mmol) of **6**, 10 ml of a satd. $NaHCO_3$ solution, and 30 ml of water as described for **7a**. Yield: 0.35 g (56%). – M.p. 115 °C. – IR: ν = 3456 (OH), 3392, 3229 (NH), 3077 (CH), 1723, 1673, 1644 (CO), 1336, 1167 (SO_2). – ^1H NMR ([d_6]DMSO): δ = 3.56 (s, 3 H, OCH_3), 3.94 (d, J = 5.8, 2 H, CH_2), 7.5–8.1 (m, 4 H, ar H), 8.82 (t, J = 5.8, 1 H, NH). – ^{13}C NMR ([d_6]DMSO):

δ = 44.34 (CH_2), 52.70 (OCH_3), 129.02, 129.78, 130.73, 133.47, 134.91, 136.09 (ar C), 151.33, 166.86, 171.05 (CO).
$C_{11}H_{12}N_2O_7S$ (316.3)

3.9. N-[2-(N-Methoxycarbonylsulfamoyl)benzoyl]-L-phenylalanine (**7c**)

From 0.5 g (2.9 mmol) of L-Phe, 0.7 g (2.9 mmol) of **6**, 15 ml of a satd. $NaHCO_3$ solution, and 29 ml of THF as described for **7a**. Yield: 0.77 g (65%). – M.p. 70 °C. – $[\alpha]_D^{20} = +34.0$ (c = 2, MeOH). – IR: ν = 3183 (NH), 3061, 2930, 2868 (CH), 1726, 1660, 1637 (CO), 1257, 1166 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 3.01, 3.14, 4.67 (ABX, $J_{AX} = 7.9$, $J_{BX} = 4.7$, $J_{AB} = 13.9$, 3 H, CH–CH_2), 3.55 (s, 3 H, OCH_3), 7.3, 7.6–8.0 (2 m, 9 H, ar H), 8.87 (d, J = 7.51, 1 H, NH). – ^{13}C NMR ([d_6]DMSO): δ = 44.34 (CH_2), 52.70 (OCH_3), 126.34, 128.06, 128.83, 129.0, 129.33, 130.34, 133.28, 135.74, 136.19, 137.42 (ar C), 151.54, 166.33, 172.99 (CO).
$C_{18}H_{18}N_2O_7S$ (406.4)

3.10. 3,3-Dichloro-3H-benz[c][1,2]oxathiol 1,1-dioxide (**8**) [15]

From 68 g of ammonium o-sulfobenzoate as described in the reference [15]. Yield: 25.4 g (51%). Colorless solid. M.p. 76 °C (Lit 79 °C) (petroleum ether).

3.11. Synthesis of 9. General procedure

Equimolar amounts of the amino acid ester salt and of **8** were stirred in DMF at 0 °C, 3 eq. of TEA were added dropwise, and stirring was continued for 16 h. Then, the precipitate was separated, washed with water, and dried.

3.11.1. 2-[(S)-1-(Methoxycarbonyl)ethyl]-3-oxo-2,3-dihydrobenzo[d][1,2]-thiazol 1,1-dioxide (**9a**)

From 0.66 g (4.8 mmol) of L-Ala-OMe-HCl in 10 ml of DMF. Yield: 0.58 g (46%). – M.p. 115 °C (MeOH/H_2O). – $[\alpha]_D^{20} = -20.65$ (c = 2, MeOH). – IR: ν = 3093, 3006, 2954 (CH) 1728 (CO), 1335, 1189 (SO_2). – ^{1}H NMR: δ = 1.84 (d, J = 7.4, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 4.85 (q, J = 7.4, 1 H, CH), 7.95 (m, 4 H, ar H). – ^{13}C NMR: δ = 14.83 (CH_3), 49.64 (CH), 53.03 (OCH_3), 121.04 (C-4), 125.37 (C-7), 127.08 (C-3a), 134.42 (C-5), 135.04 (C-6), 138.05 (C-7a), 158.80 (C-3), 169.08 (CO). – HPLC: k′ = 1.78, t_o = 1.81.
$C_{11}H_{11}NO_5S$ (269.3)

3.11.2. 2-[(S)-1-(Ethoxycarbonyl)ethyl]-3-oxo-2,3-dihydrobenzo[d][1,2]-thiazol 1,1-dioxide (**9b**)

From 0.5 g (4.1 mmol) of L-Ala-OEt-HCl in 8 ml of DMF. Yield: 0.4 g (35%). – M.p. 40 °C (MeOH/H_2O). – $[\alpha]_D^{20} = -24.83$ (c = 2, MeOH). – IR: ν = 3090, 2988, 2952 (CH), 1753, 1729 (CO), 1334, 1189 (SO_2). – ^{1}H NMR: δ = 1.25 (t, J = 7.1, 3 H, CH_3), 1.87 (d, J = 7.5, 3 H, CH_3), 4.24 (q, J = 7.1, 2 H, CH_2), 4.84 (q, J = 7.5, 1 H, CH), 7.95 (m, 4 H, ar H). – ^{13}C-NMR: δ = 14.04, 14.73 (CH_3), 49.88 (CH), 62.26 (CH_2), 120.99 (C-4), 125.32 (C-7), 127.37 (C-3a), 134.38 (C-5), 134.95 (C-6), 138.42 (C-7a), 158.84 (C-3), 168.52 (CO). – HPLC: k′ = 1.41, t_o = 1.91.
$C_{12}H_{13}NO_5S$ (283.3)

3.11.3. 2-[(S)-1-(Benzyloxycarbonyl)ethyl]-3-oxo-2,3-dihydrobenzo[d][1,2]-thiazol 1,1-dioxide (**9c**)

From 1.47 g (4.18 mmol) of L-Ala-OBn-p-tosylate in 10 ml of DMF. Yield: 0.86 g (60%). – M.p. 65 °C (EtOH). – $[\alpha]_D^{20} = -9.5$ (c = 2, MeOH). – IR: ν = 3097, 3025, 3000, 2948 (CH), 1759, 1732 (CO), 1328, 1186 (SO_2). – ^{1}H NMR: δ = 1.90 (d, J = 7.4, 3 H, CH_3), 4.89 (q, J = 7.4, 1 H, CH), 5.20 (m, 2 H, OCH_2), 7.30 [s, 5 H, ar H(Bn)], 7.92 (m, 4 H, ar H). – ^{13}C NMR: δ = 14.69 (CH_3), 49.96 (CH), 67.79 (OCH_2), 120.98 (C-4), 125.32 (C-7), 126.95 (C-3a), 128.0, 128.31, 128.50 [ar-C(Bn)], 134.37 (C-5), 134.97 (C-6), 137.91 (C-7a), 158.91 (C-3), 168.44 (CO). – HPLC: k′ = 4.38, t_o = 2.53, (S,S)-Welk-O1, n-hexane/propan-2-ol 1 : 1.
$C_{17}H_{15}NO_5S$ (345.4)

3.11.4. 2-[(S)-1-Benzyloxycarbonyl-2-(benzyloxycarbonyl)ethyl]-3-oxo-2,3-dihydrobenzo[d][1,2] thiazol 1,1-dioxide (**9d**)

From 3 g (6.3 mmol) of dibenzyl L-aspartate p-tosylate in 15 ml of DMF. Yield: 1.6 g (54%). – M.p. 112 °C (EtOH). – $[\alpha]_D^{20} = -2.16$ (c = 2, CH_2Cl_2). – IR: ν = 3059, 3027, 2949 (CH), 1736 (CO), 1340, 1190 (SO_2). – ^{1}H NMR: δ = 3.19, 3.52, 5.39 (AMX, $J_{AX} = 7.3$, $J_{MX} = 7.4$, $J_{AM} = 16.7$, 3 H, CH–CH_2), 5.08 (m, 2 H, OCH_2), 5.21 (m, 2 H, OCH_2), 7.28 [m, 10 H, ar H(Bn)], 7.85 (m, 4 H, ar H). – ^{13}C NMR: δ = 34.29 (CH_2), 50.02 (CH), 67.09 (OCH_2), 68.18 (OCH_2), 121.05 (C-4), 125.43 (C-7), 126.72 (C-3a), 128.0, 128.31, 128.37, 128.45, 128.48, 134.42, 135.26 (ar C), 134.7 (C-5), 135.09 (C-6), 137.72 (C-7a), 158.79 (C-3), 166.90, 169.21 (CO). – HPLC: k′ = 11.21, t_o = 2.53, (S,S)-Welk-O1, n-hexane/propan-2-ol 1 : 1.
$C_{25}H_{21}NO_7S$ (479.5)

3.11.5. 2-Benzyloxycarbonylmethyl-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9e**)

From 1.41 g (4.2 mmol) of Gly-OBn-p-tosylate in 10 ml of DMF. Yield: 0.9 g (65%). – M.p. 125 °C (EtOH). – IR: ν = 3090, 3060, 3027, 2978 (CH), 1768, 1732 (CO), 1334, 1185 (SO_2). – ^{1}H NMR: δ = 4.50 (s, 2 H, NCH_2), 5.33 (s, 2 H, OCH_2), 7.45 [s, 5 H, ar H(Bn)], 7.95 (m, 4 H, ar H). – ^{13}C NMR: δ = 39.12 (CH_2), 67.95 (CH_2), 121.25 (C-4), 125.50 (C-7), 127.06 (C-3a), 128.41, 128.85, 134.52 [ar C (Bn)], 134.77 (C-5), 135.10 (C-6), 137.76 (C-7a), 158.80 (C-3), 165.83 (CO). – HPLC: k′ = 6.38, t_o = 1.89, RP-18, MeCN/water 1 : 1.
$C_{16}H_{13}NO_5S$ (331.3)

3.11.6. 2-[(1S,2S)-1-(Methoxycarbonyl)-2-methylbutyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9f**)

From 1.86 g (10.3 mmol) of L-Ile-OMe-HCl in 25 ml of DMF. Yield: 1.68 g (53%). – M.p. 75 °C (MeOH/H_2O). – $[\alpha]_D^{20} = -38.6$ (c = 2, MeOH). – IR: ν = 3102, 2973, 2951 (CH), 1737 (CO), 1334, 1178 (SO_2). – ^{1}H NMR: δ = 0.94 (t, J = 7.3, 3 H, CH_3), 1.15 (d, J = 6.6, 3 H, CH_3), 1.23 (m, 1 H, CH_2), 1.67 (m, 1 H, CH_2), 2.68 (m, 1 H, CH), 3.76 (s, 3 H, OCH_3), 4.49 (d, J = 9.4, 1 H, CH), 7.96 (m, 4 H, ar H). – ^{13}C NMR: δ = 10.89, 16.61 (CH_3), 25.86 (CH_2), 34.11 (CH), 52.71 (OCH_3), 59.31 (CH), 120.97 (C-4), 125.48 (C-7), 126.88 (C-3a), 134.44 (C-5), 135.0 (C-6), 137.51 (C-7a), 159.01 (C-3), 168.44 (CO). – HPLC: k′ = 1.52, t_o = 2.97, (S,S)-Welk-O1, n-hexane/propan-2-ol 4 : 6.
$C_{14}H_{17}NO_5S$ (311.4)

3.11.7. 2-[(1S,2S)-1-(Benzyloxycarbonyl)-2-methylbutyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9g**)

From 32.4 g (6.1 mmol) of L-Ile-OBn-p-tosylate in 15 ml of DMF. Yield: 2.36 g (53%). – M.p. 70 °C (EtOH). – $[\alpha]_D^{20} = -18.0$ (c = 2, dioxane). – IR: ν = 3095, 3035, 2979, 2954 (CH), 1735 (CO), 1334, 1180 (SO_2). – ^{1}H NMR: δ = 0.92 (t, J = 7.3, 3 H, CH_3), 1.12 (d, J = 6.7, 3 H, CH_3), 1.24 (m, 1 H, CH_2), 1.64 (m, 1 H, CH_2), 2.70 (m, 1 H, CH), 4.53 (d, J = 9.3, 1 H, CH), 5.19 (m, 2 H, OCH_2), 7.29 [s, 5 H, ar H(Bn)], 7.90 (m, 4 H, ar H). – ^{13}C NMR: δ = 10.77, 16.53 (CH_3), 25.92 (CH_2), 34.04 (CH), 59.61 (CH), 67.41 (OCH_2), 120.85 (C-4), 125.33 (C-7), 126.82 (C-3a), 128.06, 128.18, 128.37, 134.89 [ar C(Bn)], 134.31 (C-5), 135.06 (C-6), 137.45 (C-7a), 159.03 (C-3), 167.81 (CO). – HPLC: k′ = 1.29, t_o = 1.91.
$C_{20}H_{21}NO_5S$ (387.5)

3.11.8. 2-[(S)-1-(Methoxycarbonyl)-3-methylbutyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9h**)

From 1 g (5.5 mmol) of L-Leu-OMe-HCl in 12 ml of DMF. Yield: 0.8 g (47%). - M.p. 72 °C (MeOH/H_2O). – $[\alpha]_D^{20} = -62.16$ (c = 2, MeOH). – IR: ν = 3101, 3081, 2952, 2932 (CH), 1740 (CO), 1334, 1178 (SO_2). – ^{1}H NMR: δ = 0.97 (d, J = 6.5, 3 H, CH_3), 1.00 (d, J = 6.5, 3 H, CH_3), 1.80 (m, 1 H, CH), 2.04 (m, 1 H, CH_2), 2.40 (m, 1 H, CH_2), 3.76 (s, 3 H, OCH_3), 4.80 (dd, 1 H, CH), 7.95 (m, 4 H, ar H). – ^{13}C NMR: δ = 21.01, 22.97 (CH_3), 24.80 (CH), 37.03 (CH_2), 52.79 (OCH_3), 53.01 (CH), 120.98 (C-4), 125.38 (C-7), 127.05 (C-3a), 134.38 (C-5), 134.96 (C-6), 137.73 (C-7a), 159.31 (C-3), 169.10 (CO). – HPLC: k′ = 1.03, t_o = 1.91.
$C_{14}H_{17}NO_5S$ (311.4)

3.11.9. 2-[(S)-1-(Methoxycarbonyl)-3-methylthiopropyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9i**)

From 2.48 g (12.5 mmol) of L-Met-OMe-HCl in 30 ml of DMF. CC (cyclohexane/EtOAc 1 : 1.5). Yield: 1.5 g (37%). Viscous liquid. – $[\alpha]_D^{20} = -70.10$ (c = 2, MeOH). – IR: ν = 3093, 2954, 2918 (CH), 1734 (CO), 1339, 1184 (SO_2). – ^{1}H NMR: δ = 2.04 (s, 3 H, SCH_3), 2.49–2.72 (m, 4 H, CH_2-CH_2), 3.69 (s, 3 H, OCH_3), 4.99 (m, 1 H, CH), 7.99 (m, 4 H, ar H). – ^{13}C NMR: δ = 14.33, 26.62 (CH_2), 29.55 (SCH_3), 51.32 (CH), 52.16 (OCH_3), 120.10 (C-4), 125.10 (C-7), 127.77 (C-3a), 133.55 (C-5), 134.20 (C-6), 136.30 (C-7a), 158.17 (C-3), 167.49 (CO). – MS (EI, 70eV): m/z = 329 [M^+], 298, 270, 255. – HPLC: k′ = 1.62, t_o = 1.83, (S,S)-Welk-O1, n-hexane/EtOH/acetic acid 50 : 50 : 0.5.
$C_{13}H_{15}NO_5S_2$ (329.4).

3.11.10. 2-[(S)-1-(Methoxycarbonyl)-2-hydroxyethyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9j**)

From 0.5 g (3.2 mmol) of L-Ser-OMe-HCl in 8 ml of DMF. Yield: 0.36 g (40%). – M.p. 130 °C (MeOH). – $[\alpha]_D^{20} = -4.3$ (c = 1, CH_2Cl_2). – IR: ν = 3550 (OH), 3096, 3021, 2963, 2908 (CH), 1752, 1723 (CO), 1339, 1184 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 3.67 (s, 3 H, OCH_3), 4.09 (m, 2 H, CH_2), 4.91 (m, 1 H, CH), 5.19 (t, J = 6.2, 1 H, OH), 8.18 (m, 4 H, ar H). – ^{13}C NMR ([d_6]DMSO): δ = 52.57 (OCH_3), 55.43 (CH_2), 57.58 (CH), 121.57 (C-4), 124.97 (C-7), 125.97 (C-3a), 135.23 (C-5), 135.90 (C-6), 136.82 (C-7a), 158.59 (C-3), 166.92 (CO). – HPLC: k′ = 1.57, t_o = 1.73.
$C_{11}H_{11}NO_6S$ (285.3)

3.11.11. 2-[(S)-1-(Methoxycarbonyl)-2-phenylethyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9k**)

From 2.2 g (10.2 mmol) of L-Phe-OMe-HCl in 25 ml of DMF. Yield: 1.8 g (50%). – M.p. 120 °C (EtOH/H_2O). – $[\alpha]_D^{20} = -175$ (c = 2, MeOH). – IR: ν = 3095, 3059, 3027 (CH), 1747, 1723 (CO), 1341, 1187 (SO_2). – ^{1}H NMR: δ = 3.59, 3.72, 4.93 (ABX, $J_{AX} = 10.6$, $J_{BX} = 8.9$, $J_{AB} = 14.3$, 3 H, CH–CH_2-Ph), 3.78 (s, 3 H, OCH_3), 7.25 [m, 5 H, ar H(Phe)], 7.93 (m, 4 H, ar H). – ^{13}C NMR: δ = 34.79 (CH_2), 49.36 (OCH_3), 54.06 (CH), 121.08 (C-4), 123.90 (C-7), 125.37 (C-3a), 128.58, 129.24, 136.36 [ar C(Phe)], 134.38 (C-5), 134.96 (C-6), 137.58 (C-7a), 159.11 (C-3), 168.22 (CO). – HPLC: k′ = 2.64, t_o = 2.97, (S,S)-Welk-O1, n-hexane/propan-2-ol 4 : 6.
$C_{17}H_{15}NO_5S$ (345.4)

3.11.12. 2-[(S)-1-(Ethoxycarbonyl)-2-phenylethyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9l**)

From 1.3 g (5.7 mmol) of L-Phe-OEt-HCl in 15 ml of DMF. Yield: 1.2 g (59%). – M.p. 75 °C (EtOH/H_2O). – $[\alpha]_D^{20} = -85.0$ (c = 2, MeOH). – IR: ν = 3094, 3062, 2985, 2943 (CH), 1734 (CO), 1331, 1181 (SO_2). – ^{1}H NMR: δ = 1.24 (t, J = 7.1, 3 H, CH_3), 3.60, 3.68, 4.92 (ABX, $J_{AX} = 10.1$, $J_{BX} = 5.7$, $J_{AB} = 14.4$, 3 H, CH–CH_2-Ph), 4.25 (q, J = 7.1, 2 H, CH_2), 7.26 [m, 5 H, ar H(Phe)], 7.91 (m, 4 H, ar H). – ^{13}C NMR: δ = 14.0 (CH_3), 34.77 (CH_2), 55.83 (CH), 62.40 (CH_2), 121.05 (C-4), 125.32 (C-7), 126.92 (C-3a), 127.05, 128.55, 129.23, 136.46 [ar C(Phe)], 134.34 (C-5), 134.92 (C-6), 137.63 (C-7a), 159.18 (C-3), 167.64 (CO). – HPLC: k′ = 1.43, t_o = 1.91.
$C_{18}H_{17}NO_5S$ (359.4)

3.11.13. 2-[(S)-1-(Benzyloxycarbonyl)-2-phenylethyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9m**)

From 3.58 g (8.4 mmol) of L-Phe-OBn-p-tosylate in 20 ml of DMF. Yield: 2.8 g (80%). – M.p. 143 °C (EtOH). – $[\alpha]_D^{20} = -100.66$ (c = 2, dioxane). – IR: ν = 3090, 3063, 3031 (CH), 1745, 1723 (CO), 1342, 1188 (SO_2). – ^{1}H NMR: δ = 3.62, 3.70, 4.98 (ABX, $J_{AX} = 10.5$, $J_{BX} = 5.4$, $J_{AB} = 14.3$, 3 H, CH–CH_2-Ph), 5.28 (m, 2 H, OCH_2), 7.91 (m, 4 H, ar H). – ^{13}C NMR: δ = 34.71 (CH_2), 55.87 (CH), 67.95 (OCH_2), 121.05 (C-4), 125.32 (C-7), 127.07 (C-3a), 128.09, 128.34, 128.49, 128.56, 129.20, 134.33 [ar C(Phe)], 134.33 (C-5), 134.93 (C-6), 137.58 (C-7a), 159.50 (C-3), 167.57 (CO). – HPLC: k′ = 3.80, t_o = 2.41, (S,S)-Welk-O1, n-hexane/propan-2-ol 1 : 1.
$C_{23}H_{19}NO_5S$ (421.5)

3.11.14. 2-[(S)-1-(Methoxycarbonyl)-2-methylpropyl]-3-oxo-2,3-dihydrobenzo[d][1,2] thiazol 1,1-dioxide (**9n**)

From 1.7 g (10.2 mmol) of L-Val-OMe-HCl in 25 ml of DMF. Yield: 2.3 g (75%). – M.p. 105 °C (MeOH/H_2O). – $[\alpha]_D^{20} = -65.0$ (c = 2, MeOH). – IR: ν = 3102, 2988, 2974 (CH), 1751, 1740 (CO), 1336, 1179 (SO_2). – ^{1}H NMR: δ = 1.05 (d, J = 6.6, 3 H, CH_3), 1.19 (d, J = 6.6, 3 H, CH_3), 2.89 (m, 1 H, CH), 3.75 (s, 3 H, OCH_3), 4.39 (d, J = 9.4, 1 H, CH), 7.96 (m, 4 H, ar H). – ^{13}C NMR: δ = 19.71, 20.74 (CH_3), 28.24 (CH), 52.74 (OCH_3), 59.97 (CH), 121.03 (C-4), 125.47 (C-7), 126.81 (C-3a), 134.50 (C-5), 135.10 (C-6), 137.52 (C-7a), 158.95 (C-3), 168.29 (CO). – HPLC: k′ = 1.59, t_o = 2.97, (S,S)-Welk-O1, n-hexane/propan-2-ol 4 : 6.
$C_{13}H_{15}NO_5S$ (297.3)

3.11.15. 2-[(S)-1-(Ethoxycarbonyl)-2-methylpropyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9o**)

From 0.6 g (3.4 mmol) of L-Val-OEt-HCl in 10 ml of DMF. Yield: 0.49 g (48%). – M.p. 60 °C (MeOH/H_2O). – $[\alpha]_D^{20} = -65.5$ (c = 2, MeOH). – IR: ν = 3090, 2988, 2974 (CH), 1751, 1740 (CO), 1336, 1186 (SO_2). – ^{1}H NMR: δ = 1.05 (d, J = 6.7, 3 H, CH_3), 1.19 (d, J = 6.6, 3 H, CH_3), 1.25 (t, J = 7.1, 3 H, CH_3), 2.90 (m, 1 H, CH), 4.23 (q, J = 7.1, 2 H, CH_2), 4.36 (d, J = 9.4, 1 H, CH), 7.96 (m, 4 H, ar H). – ^{13}C NMR: δ = 13.89, 19.72, 20.64 (CH_3), 28.12 (CH), 60.30 (CH_2), 61.79 (CH), 120.88 (C-4), 125.30 (C-7), 126.77 (C-3a), 134.33 (C-5), 134.92 (C-6), 137.49 (C-7a), 158.90 (C-3), 167.66 (CO). – HPLC: k′ = 1.10, t_o = 1.89.
$C_{14}H_{17}NO_5S$ (311.4)

3.11.16. 2-[(S)-1-(Benzyloxycarbonyl)-2-methylpropyl]-3-oxo-2,3-dihydrobenzo[d][1,2]thiazol 1,1-dioxide (**9p**)

From 1.58 g (4.18 mmol) of L-Val-OBn-p-tosylate in 10 ml of DMF. Yield: 1.05 g (68%). – M.p. 80 °C (EtOH). – $[\alpha]_D^{20} = -30.16$ (c = 2, dioxane). – IR: ν = 3101, 3065, 3035, 2989, 2973 (CH), 1741 (CO), 1333, 1178 (SO_2). – ^{1}H NMR: δ = 1.06 (d, J = 6.7, 3 H, CH_3), 1.17 (d, J = 6.6, 3 H, CH_3), 2.92 (m, 1 H, CH), 4.42 (d, J = 9.3, 1 H, CH), 5.23 (m, 2 H, OCH_2), 7.35 [m, 5 H, ar H(Bn)], 7.92 (m, 4 H, ar H). – ^{13}C NMR: δ = 19.8, 20.7 (CH_3), 28.2 (CH), 60.4 (CH), 67.5 (OCH_2), 120.92 (C-4), 125.37 (C-7), 126.82 (C-3a), 128.03, 128.18, 128.51, 128.57, 134.33 (ar C), 134.92 (C-5), 135.09 (C-6), 137.53 (C-7a), 159.0 (C-3), 167.66 (CO). – HPLC: k′ = 2.10, t_o = 2.41, (S,S)-Welk-O1, n-hexane/propan-2-ol 1 : 1.
$C_{19}H_{19}NO_5S$ (373.4)

3.12. Boc-L-alanyl-L-phenylalanine methyl ester (**10a**)

From 1.89 g of Boc-L-Ala, and 2.68 g of L-Phe-OMe-HCl. Yield: 2.33 g (67%). Colorless solid. M.p. 75 °C. – $[\alpha]_D^{20} = -19.5$ (c = 2, MeOH).
$C_{18}H_{26}N_2O_5$ (350.41)

3.13. Boc-L-alanyl-L-valine methyl ester (**10b**)

From 1.89 g of Boc-L-Ala, and 2.08 g of L-Val-OMe-HCl. Yield: 1.6 g (53%). Colorless solid. M.p. 85 °C. – $[\alpha]_D^{20} = -49$ (c = 2, MeOH).
$C_{14}H_{25}N_2O_5$ (301.4)

3.14. Boc-L-phenylalanyl-L-alanine methyl ester (**10c**)

From 2.65 g of Boc-L-Phe, and 1.73 g of L-Ala-OMe-HCl. Yield: 2.3 g (52%). Colorless solid. M.p. 100 °C. – $[\alpha]_D^{20} = -20.83$ (c = 2, MeOH).
$C_{18}H_{26}N_2O_5$ (350.4)

3.15. BOC-L-phenylalanyl-L-phenylalanine methyl ester (**10d**)

From 2.65 g of Boc-L-Phe, and 2.68 g of L-Phe-OMe-HCl. Yield 2.3 g (54%). Colorless solid. M.p. 112 °C. – $[\alpha]_D^{20} = -12.5$ (c = 2, MeOH).
$C_{24}H_{30}N_2O_5$ (426.5)

3.16. Boc-L-valyl-L-phenylalanine methyl ester (**10e**)

From 2.17 g of Boc-L-Val, and 2.68 g of L-Phe-OMe-HCl. Yield: 1.96 g (52%). Colorless solid. M.p. 100 °C. – $[\alpha]_D^{20} = -29.66$ (c = 2, MeOH).
$C_{20}H_{30}N_2O_5$ (378.5)

3.17. Boc-L-valyl-L-valine methyl ester (**10f**)

From 2.17 g of Boc-L-Val, and 2.08 g of L-Val-OMe-HCl. Yield: 2.55 g (77%). Colorless solid. M.p. 166 °C (Lit 167–168) [25]. – $[\alpha]_D^{20} = -45.8$ (c = 2, MeOH).
$C_{16}H_{30}N_2O_5$ (378.5)

3.18. Reaction of 8 with dipeptide methyl ester 10. General procedure

The Boc-dipeptide ester **10** was deprotected by stirring with TFA at 0 °C for 1 h (2 ml of TFA for 1 mmol Boc), then diethyl ether was added, and the precipitate separated and dried, yielding the dipeptide methyl ester triflate. Equimolar amounts of this triflate and **8** were stirred at 0 °C in DMF, the threefold amount of TEA was added dropwise, After 16 h of stirring, water was added, and the precipitate was separated, washed with water, and dried.

3.18.1. N-[(S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-propionyl]-L-phenylalanine methyl ester (**11a**)

From 4.6 mmol of **10a** in 12 ml of DMF. Yield: 1.1 g (54%). – M.p. 130 °C (EtOAc/n-hexane). – $[\alpha]_D^{20} = +18.8$ (c = 2, MeOH). – IR: ν = 3318 (NH), 3062, 2991, 2949 (CH), 1741, 1660 (CO), 1337, 1191 (SO_2). – ^{1}H NMR: δ = 1.78 (d, J = 7.3, 3 H, CH_3), 3.02, 3.13, 4.82 (ABX, $J_{AX} = 6.7$, $J_{BX} = 5.5$, $J_{AB} = 13.9$, 3 H, CH–CH_2-Ph), 3.76 (s, 3 H, OCH_3), 4.71 (q, J = 7.3, 1 H, CH), 6.59 (d, J = 7.2, 1 H, NH), 6.99 [s, 5 H, ar H(Phe)], 7.95 (m, 4 H, ar H). – ^{13}C NMR: δ = 14.12 (CH_3), 37.58 (CH_2), 51.14 (OCH_3), 52.40 (CH), 53.56 (CH), 121.12 (C-4), 125.48 (C-7), 126.88 (C-3a), 126.93, 128.31, 129.18, 135.54 [ar C(Phe)], 134.48 (C-5), 135.07 (C-6), 137.71 (C-7a), 158.30 (C-3), 167.74, 171.57 (CO).
$C_{20}H_{20}N_2O_6S$ (416.5)

3.18.2. N-[(S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-propionyl]-L-valine methyl ester (**11b**)

From 2.8 mmol of **10b** in 8 ml of DMF. Yield: 0.39 g (37%). – M.p. 140 °C (MeOH/H_2O). – $[\alpha]_D^{20} = +8.0$ (c = 1, MeOH). – IR: ν = 3391 (NH), 3082, 3057, 2984, 2960 (CH), 1739, 1716, 1678 (CO), 1341, 1185 (SO_2). – ^{1}H NMR: δ = 0.81, 0.89 (2 d, each J = 6.9, 3 H, CH_3), 1.87 (d, J = 7.3, 3 H, CH_3), 2.17 (m, 1 H, CH), 3.70 (s, 3 H, OCH_3), 4.56 (dd, 1 H, CH), 4.79 (q, J = 7.3, 1 H, CH), 6.73 (d, J = 8.5, 1 H, NH), 7.96 (m, 4 H, ar H). – ^{13}C NMR: δ = 14.49, 17.47, 18.90 (CH_3), 31.28 (CH), 51.89 (OCH_3), 52.18 (CH), 57.46 (CH), 121.20 (C-4), 125.46 (C-7), 126.84 (C-3a), 134.66 (C-5), 135.19 (C-6), 137.86 (C-7a), 158.57 (C-3), 168.30, 172.03 (CO).
$C_{16}H_{20}N_2O_6S$ (368.4)

3.18.3. N-[(S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-3-phenylpropionyl]-L-alanine methyl ester (**11c**)

From 1.1 mmol of **10c** in 6 ml of DMF. Yield: 0.18 g (33%). – M.p. 115 °C (EtOAc/n-hexane). – $[\alpha]_D^{20} = -28.0$ (c = 2, MeOH). – IR:

ν = 3325 (NH), 3030, 2951 (CH), 1739, 1682 (CO), 1339, 1185 (SO_2). – ^{1}H NMR: δ = 1.35 (d, J = 7.2, 3 H, CH_3), 3.57, 3.71, 4.82 (ABX, J_{AX} = 9.1, J_{BX} = 6.6, J_{AB} = 14.2, 3 H, CH–CH_2-Ph), 3.71 (s, 3 H, OCH_3), 4.56 (m, 1 H, CH), 6.79 (d, J = 6.6, 1 H, NH), 7.23 (m, 5 H, ar H), 7.96 (m, 4 H, ar H). – ^{13}C NMR: δ = 18.08 (CH_3), 34.15 (CH_2), 48.59 (OCH_3), 52.47 (CH), 57.09 (CH), 121.17 (C-4), 125.35 (C-7), 126.61 (C-3a), 127.0, 128.54, 129.27, 136.40 [ar C(Phe)], 134.53 (C-5), 135.06 (C-6), 137.22 (C-7a), 158.73 (C-3), 166.40, 172.81 (CO).
$C_{26}H_{24}N_2O_6S$ (416.5)

3.18.4. N-[(S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-3-phenylpropionyl]-L-phenylalanine methyl ester (**11d**)

From 2.04 mmol of **10d** in 6 ml of DMF. Yield: 0.45 g (45%). – M.p. 125 °C (EtOAc/n-hexane). – $[\alpha]_D^{20}$ = –58.6 (c = 2, MeOH). – IR: ν = 3272 (NH), 3086, 3065, 2958 (CH), 1735, 1660 (CO), 1333, 1185 (SO_2). – ^{1}H NMR: δ = 2.98, 3.11, 4.72 (ABX, J_{AX} = 6.5, J_{BX} = 5.2, J_{AB} = 13.85, 3 H, CH–CH_2-Ph), 3.53, 3.63, 4.83 (ABX, J_{AX} = 10.1, J_{BX} = 6.1, J_{AB} = 14.2, 3 H, CH–CH_2-Ph), 3.70 (s, 3 H, OCH_3), 6.62 (d, J = 7.1, 1 H, NH), 6.93 (s, 5 H, ar H), 7.20 (s, 5 H, ar H), 7.95 (m, 4 H, ar H). – ^{13}C NMR: δ = 33.80, 37.47 (CH_2-Ph), 52.41 (OCH_3), 53.65, 56.73 (CH), 121.21 (C-4), 125.41 (C-7), 126.85 (C-3a), 127.00, 128.22, 128.58, 129.05, 135.48 [ar C(Phe)], 134.47 (C-5), 135.04 (C-6), 136.46 (C-7a), 158.50 (C-3), 166.67, 171.42 (CO).
$C_{26}H_{24}N_2O_6S$ (492.5)

3.19. N-(2-Carboxyphenylsulfonyl)-L-valine methyl ester (**12**)

250 mg (0.8 mmol) of **9n** was dissolved in 15 ml of acetone, 2.5 ml of 0.1 N NaOH was added, the pH was adjusted to 10.45, the mixture was stirred for about 16 h while the pH was kept at 10.45 by dropwise adding of 0.1 N NaOH. The mixture was extracted with EtOAc, the aqueous layer was acidified with dil. HCl, and the precipitate was separated and dried in vacuo over P_4O_{10}. Yield: 0.1 g (39%). – M.p. 100 °C (H_2O). – $[\alpha]_D^{20}$ = –1.0 (c = 2, MeOH). – IR: ν = 3239 (NH), 3024, 2986, 2971 (CH), 1736 (CO), 1347, 1172 (SO_2). – ^{1}H NMR: δ = 0.93, 0.98 (2 d, each J = 6.9, 3 H, CH_3), 2.10 (m, 1 H, CH), 3.38 (s, 3 H, OCH_3), 3.95 (dd, 1 H, CH), 6.77 (d, J = 9.7, 1 H, NH), 7.6–8.1 (m, 4 H, ar H). – ^{13}C NMR: δ = 17.61, 18.55 (CH_3), 30.46 (CH), 51.52 (OCH_3), 61.02 (CH), 128.10, 129.04, 130.62, 132.30, 132.48, 137.94 (ar C), 168.86, 170.89 (CO). – HPLC: k′ = 1.32, t_o = 2.09, ChiraSpher, n-hexane/propan-2-ol 1 : 1.
$C_{13}H_{17}NO_6S$ (315.3)

3.20. N-(2-Carboxyphenylsulfonyl)glycine (**13**) [20]

1.5 g of **2a** was dissolved in 15 ml of acetone, 60 ml of 0.1 N NaOH was added, and the mixture was refluxed for about 50 min. After cooling to room temp., the mixture was extracted with EtOAc, the aqueous layer was acidified with dil. HCl, and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4), and the solvent was removed in vacuo. Yield: 1.0 g (66%). – M.p. 140 °C (H_2O). – IR: ν = 3283 (NH), 3026, 2963 (CH), 1737, 1713 (CO), 1341, 1164 (SO_2). – ^{1}H NMR: δ = 3.73 (d, J = 5.75, 2 H, CH_2), 7.46 (t, J = 5.8, 1 H, NH), 7.7–7.95 (m, 4 H, ar H).
$C_9H_9NO_6S$ (259.2)

3.21. (1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetic acid (**14a**) [9]

2 g of **2a** was refluxed with 8 ml of conc. HCl for 1 h. After cooling to room temp., the precipitate was separated, washed with water, and dried in vacuo over P_4O_{10}. Yield: 1.05 g (56%). – M.p. 210 °C (Lit 212 °C). – IR: ν = 3102, 2987, 2940 (CH), 1749 (CO), 1340, 1187 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 4.49 (s, 2 H, CH_2), 8.0–8.4 (m, 4 H, ar H). – ^{13}C NMR ([d_6]DMSO): δ = 41.69 (CH_2), 121.72 (C-4), 125.12 (C-7), 126.01 (C-3a), 135.31 (C-5), 136.0 (C-6), 136.94 (C-7a), 158.50 (C-3), 167.49 (CO).
$C_9H_7NO_5S$ (241.2)

3.22. (RS)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)propionic acid (**14b**)

0.81 g of (RS)-**2b** was refluxed with 9 ml of conc. HCl for 5 h. The precipitate was separated, washed with water, and dissolved in a mixture of $NaHCO_3$ solution and methyl isobutyl ketone. The aqueous phase was separated, acidified with HCl, the precipitate was separated, and washed with H_2O. Yield 0.46 g (61%). – M.p. 177 °C (H_2O), (Lit. 177–179 °C) [6]. – IR: ν = 3444 (OH), 3097, 3002, 2916 (CH), 1715 (CO), 1336, 1187 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 1.66 (d, J = 7.31, 3 H, CH_3), 4.98 (q, J = 7.3, 1 H, CH), 7.9–8.4 (m, 4 H, ar H). – ^{13}C NMR ([d_6]DMSO): δ = 14.61 (CH_3), 48.82 (CH), 121.49 (C-4), 125.01 (C-7), 125.83 (C-3a), 135.27 (C-5), 135.95 (C-6), 136.92 (C-7a), 158.31 (C-3), 169.74 (CO). – HPLC: k_1' = 5.53, k_2' = 5.84, t_o = 2.10, ChiraSpher, n-hexane/propan-2-ol 3 : 1.
$C_{10}H_9NO_5S$ (255.2)

3.23. Hydrogenolysis of the benzyl ester. General procedure

The benzyl ester was dissolved in THF (50 ml), 0.1 g of Pd-C (10%) was added, and the mixture was hydrogenated (1 atm) at room temp. until the ester was completely hydrogenated (TLC control, ~2–3 h). The catalyst was filtered off, and the solvent removed in vacuo. The residue was recrystallized from water.

3.23.1. (S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)propionic acid (**15a**)

From 0.25 g (0.7 mmol) of **9c**. Yield: 0.17 g (98%). Colorless solid. – M.p. 165 °C. – $[\alpha]_D^{20}$ = –13.83 (c = 2, MeOH). – IR: ν = 3275 (OH), 3097 (CH), 1762, 1709 (CO), 1334, 1186 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 1.67 (d, J = 7.3, 3 H, CH_3), 4.98 (q, J = 7.2, 1 H, CH), 7.95–8.4 (m, 4 H, ar H). – ^{13}C NMR ([d_6]DMSO): δ = 14.64 (CH_3), 48.91 (CH), 121.50 (C-4), 125.03 (C-7), 125.92 (C-3a), 135.25 (C-5), 135.95 (C-6), 137.02 (C-7a), 158.36 (C-3), 169.77 (CO). – HPLC: k′ = 5.58, t_o = 2.08, ChiraSpher, n-hexane/propan-2-ol 3 : 1.
$C_{10}H_9NO_5S$ (255.2)

3.23.2. (S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)succinic acid (**15b**)

From 0.35 g (0.7 mmol) of **9d**. Yield: 0.17 g (78%). – M.p. 220 °C. – $[\alpha]_D^{20}$ = +3.0 (c = 2, DMF). – IR: ν = 2953 (CH), 1740, 1707 (CO), 1335, 1181 (SO_2). – ^{1}H NMR: δ = 2.88, 3.25, 5.03 (AMX, J_{AX} = 7.9, J_{MX} = 6.4, J_{AM} = 16.6, 3 H, CH–CH_2), 8.0–8.4 (m, 4 H, ar H). – ^{13}C NMR: δ = 34.39 (CH_2), 49.68 (CH), 121.54 (C-4), 124.49 (C-7), 125.9 (C-3a), 135.31 (C-5), 136.0 (C-6), 137.11 (C-7a), 158.2 (C-3), 168.52, 170.89 (CO).
$C_{11}H_9NO_7S$ (299.3)

3.23.3. (2S,3S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-3-methylpentanoic acid (**15c**)

From 0.25 g (0.65 mmol) of **9g**. Yield: 0.16 g (85%). – M.p. 115 °C. – $[\alpha]_D^{20}$ = –28.5 (c = 2, MeOH). – IR: ν = 3098, 2973, 2932, 2877 (CH), 1732 (CO), 1344, 1190 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 0.86 (t, J = 7.1, 3 H, CH_3), 1.10 (d, J = 6.4, 3 H, CH_3), 1.56 (m, 2 H, CH_2), 2.51 (m, 1 H, CH), 4.35 (d, J = 8.2, 1 H, CH), 7.95–8.35 (m, 4 H, ar H). – ^{13}C NMR ([d_6]DMSO): δ = 10.89, 16.57 (CH_3), 25.54 (CH_2), 33.72 (CH), 59.07 (CH), 121.47 (C-4), 125.12 (C-7), 125.94 (C-3a), 135.28 (C-5), 135.91(C-6), 136.67 (C-7a), 158.74 (C-3), 168.98 (CO).
$C_{13}H_{15}NO_5S$ (297.3)

3.23.4. (S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-3-phenylpropionic acid (**15d**)

From 0.5 g (1.2 mmol) of **9m**. Yield: 0.32 g (82%). – M.p. 170 °C. – $[\alpha]_D^{20}$ = –142.5 (c = 2, MeOH). – IR: ν = 3292 (OH), 3086, 3065, 3028, 2911 (CH), 1747, 1730 (CO), 1318, 1185 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 3.42, 3.53, 5.08 (ABX, J_{AX} = 4.7, J_{BX} = 6.1, J_{AB} = 14.1, 3 H, CH–CH_2-Ph), 7.21, 8.09 (2 m, 9 H, ar H). – ^{13}C NMR ([d_6]DMSO): δ = 33.93 (CH_2), 54.99 (CH), 121.47 (C-4), 125.0 (C-7), 125.68 (C-3a), 126.50, 128.10, 129.02, 136.67 [ar C(Phe)], 135.23 (C-5), 135.96 (C-6), 136.80 (C-7a), 158.87 (C-3), 168.82 (CO).
$C_{16}H_{13}NO_5S$ (331.4)

3.23.5. (2S)-2-(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-3-methylbutyric acid (**15e**)

From 0.1 g (0.3 mmol) of **9p**. Yield: 60 mg (80%). – M.p. 120 °C. – $[\alpha]_D^{20}$ = –49.8 (c = 2, MeOH). – IR: ν = 3349 (OH), 3102, 2988, 2971, 2929 (CH), 1765, 1745 (CO), 1328, 1181 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 0.95, 1.13 (2 d, each J = 6.6, 3 H, CH_3), 2.66 (m, 1 H, CH), 4.35 (d, J = 8.5, 1 H, CH), 8.0–8.35 (m, 4 H, ar H), 12.7 (s, 1 H, OH). – ^{13}C NMR ([d_6]DMSO): δ = 19.54, 20.55 (CH_3), 27.64 (CH), 59.17 (CH), 121.53 (C-4), 125.15 (C-7), 125.73 (C-3a), 135.31 (C-5), 135.98 (C-6), 136.63 (C-7a), 158.67 (C-3) 168.71 (CO).
$C_{12}H_{13}NO_5S$ (283.3)

3.24. Reaction of **14a** *with amino acid ester or dipeptide ester. General procedure*

The amino acid ester or the dipeptide ester, **14a**, and NHS were dissolved in CH_2Cl_2, cooled to –10 °C, then TEA and DCC were added. The mixture was stirred for 1 h at –10 °C, then 3 d at room temp. The mixture was filtered, and the solvent concentrated in vacuo. EtOAc was added to the residue, the mixture was filtered again, then, the filtrate was washed with 1 N HCl (2 × 20 ml), a satd. $NaHCO_3$ solution (25 ml), and a satd. NaCl solution (25 ml). The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was purified by CC (EtOAc/cyclohexane 3 : 1).

3.24.1. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]-L-alanine benzyl ester (**16a**)

From 2 g (8.3 mmol) of **14a**, 3.5 g (9.9 mmol) of L-Ala-OBn-p-tosylate, 2 g (16.5 mmol) of NHS, 0.9 g (9.5 mmol) of TEA, and 2.4 g (10.3 mmol) of DCC. Yield: 1.7 g (51%). – M.p. 62 °C. – $[\alpha]_D^{20} = +2.66$ (c = 2, CH_2Cl_2). – IR: ν = 3287 (NH), 3071, 3032, 2984, 2939 (CH), 1737, 1666 (CO), 1330, 1186 (SO_2) – ^{1}H NMR: δ = 1.43 (d, J = 7.2, 3 H, CH_3), 4.43 (s, 2 H, CH_2), 4.66 (m, 1 H, CH), 5.16 (m, 2 H, OCH_2), 6.83 (d, J = 7.5, 1 H, NH), 7.29 [m, 5 H, ar H(Bn)], 7.98 (m, 4 H, ar H). – ^{13}C NMR: δ = 18.27 (CH_3), 41.22 (NCH_2), 48.56 (CH), 67.28 (OCH_2), 121.34 (C-4), 125.66 (C-7), 126.89 (C-3a), 128.11, 128.44, 128.59, 135.27 [ar C(Bn)], 134.68 (C-5), 135.12 (C-6), 137.57 (C-7a), 158.82 (C-3), 164.66, 172.21 (CO). – HPLC: k′ = 3.28, t_o = 1.89, RP-18, MeCN/H_2O 1 : 1; k′ = 3.86, t_o = 1.90.
$C_{19}H_{18}N_2O_6S$ (402.4)

3.24.2. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]glycine benzyl ester (**16b**)

From 1 g (4.14 mmol) of **14a**, 1.66 g (4.9 mmol) of Gly-OBn-p-tosylate, 1 g (8.3 mmol) of NHS, 0.5 g (4.8 mmol) of TEA, and 1.2 g (5.2 mmol) of DCC. Yield: 0.35 g (22%). – M.p. 150 °C . – IR: ν = 3290 (NH), 3089, 3031, 2962, 2928 (CH), 1740, 1662 (CO), 1335, 1189 (SO_2). – ^{1}H NMR: δ = 4.12 (d, J = 4.9, 2 H, CH_2), 4.46 (s, 2 H, CH_2), 5.17 (s, 2 H, OCH_2), 6.74 (d, 1 H, NH), 7.34 [s, 5 H, ar H(Bn)], 7.99 (m, 4 H, ar H). – ^{13}C NMR: δ = 41.21 (CH_2), 41.76 (CH_2), 121.4 (C-4), 125.14 (C-7), 127.51 (C-3a), 128.43, 128.51, 128.67, 135.01 (ar C), 134.74 (C-5), 135.32 (C-6), 137.66 (C-7a), 158.95 (C-3), 165.45, 169.15 (CO). – HPLC: k′ = 2.68, t_o = 1.81, RP-18, MeCN/H_2O 1 : 1.
$C_{18}H_{16}N_2O_6S$ (388.4)

3.24.3. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]-L-phenylalanine methyl ester (**16c**)

From 0.5 g (2.1 mmol) of **14a**, 0.55 g (2.5 mmol) of L-Phe-OMe-HCl, 0.5 g (4 mmol) of NHS, 0.3 g (2.4 mmol) of TEA, and 0.6 g (2.5 mmol) of DCC. Yield: 0.41 g (49%). – M.p. 90 °C. – $[\alpha]_D^{20} = +53.8$ (c = 2, CH_2Cl_2). – IR: ν = 3315 (NH), 3102, 3028, 2953 (CH), 1738, 1667 (CO), 1332, 1186 (SO_2). – ^{1}H NMR: δ = 3.05, 3.14, 4.86 (ABX, J_{AX} = 5.7, J_{BX} = 5.7, J_{AB} = 13.8, 3 H, CH–CH_2-Ph), 3.70 (s, 3 H,OCH_3), 4.3–4.5 (m, 2 H, NCH_2), 6.75 (d, J = 7.4, 1 H, NH), 7.11 [m, 5 H, ar H(Phe)], 7.8–8.1 (m, 4 H, ar H). – ^{13}C NMR: δ = 37.58 (CH_2-Ph), 41.02 (NCH_2), 52.46 (OCH_3), 53.54 (CH), 121.35 (C-4), 125.55 (C-7), 126.93 (C-3a), 127.07, 128.46, 129.36, 134.64 [ar C(Phe)], 135.25 (C-5), 135.46 (C-6), 137.58 (C-7a), 158.81 (C-3), 164.86, 171.45 (CO). – HPLC: k′ = 2.93, t_o = 1.89, RP-18, MeCN/water 1 : 1; k′ = 3.09, t_o = 1.91.
$C_{19}H_{18}N_2O_6S$ (402.4)

3.24.4. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]-L-valine methyl ester (**16d**)

From 1 g (4.14 mmol) of **14a**, 0.82 g (4.9 mmol) of L-Val-OMe-HCl, 1 g (8.3 mmol) of NHS, 0.5 g (4.8 mmol) of TEA, and 1.2 g (5.2 mmol) of DCC. Yield: 0.47 g (32%). – M.p. 130 °C. – $[\alpha]_D^{20} = +17.66$ (c = 2, CH_2Cl_2). – IR: ν = 3311 (NH), 3079, 3034, 2968 (CH), 1740, 1669 (CO), 1333, 1187 (SO_2). – ^{1}H NMR: δ = 0.87, 0.93 (2 d, each J = 6.8, 3 H, CH_3), 2.17 (m, 1 H, CH), 3.72 (s, 3 H, OCH_3), 4.45 (s, 2 H, NCH_2), 4.60 (dd, 1 H, NH-CH), 6.68 (d, J = 8.1, 1 H, NH), 7.8–8.2 (m, 4 H, ar H). – ^{13}C NMR: δ = 17.52, 18.68 (CH_3), 31.37 (CH), 41.32 (NCH_2), 52.23 (OCH_3), 57.44 (NCH), 121.45 (C-4), 125.71 (C-7), 126.86 (C-3a), 134.75 (C-5), 135.34 (C-6), 137.65 (C-7a), 158.86 (C-3), 165.04, 171.77 (CO). – HPLC: k′ = 1.76, t_o = 1.89, RP-18, MeCN/H_2O 1 : 1; k′ = 2.48, t_o = 1.91.
$C_{15}H_{18}N_2O_6S$ (354.4)

*3.25. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]-L-alanine (***17a***)*

From 0.36 g (0.9 mmol) of **16a** as described for **15**. Yield: 0.19 g (68%). – M.p. 170 °C. – $[\alpha]_D^{20} = +7.0$ (c = 2, dioxane). – IR: ν = 3351 (NH), 3093, 2944 (CH), 1737, 1702, 1667 (CO), 1345, 1185 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 1.29 (d, J = 7.2, 3 H, CH_3), 4.25 (m, 1 H, CH), 4.36 (s, 2 H, CH_2), 8.0–8.35 (m, 4 H, ar H), 8.57 (d, J = 7.2, 1 H, NH). – ^{13}C NMR ([d_6]DMSO): δ = 17.34 (CH_3), 47.74 (CH), 121.59 (C-4), 125.02 (C-7), 126.41 (C-3a), 135.20 (C-5), 135.78 (C-6), 136.89 (C-7a), 158.55 (C-3), 164.23, 173.61 (CO).
$C_{12}H_{12}N_2O_6S$ (312.3)

*3.26. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]glycine (***17b***)*

From 0.1 g (0.25 mmol) of **16b** as described for **15**. Yield: 60 mg (79%). – M.p. 212 °C. – IR: ν = 3377 (NH), 3089, 2930 (CH), 1747, 1636 (CO), 1339, 1182 (SO_2). – ^{1}H NMR ([d_6]DMSO): δ = 3.82 (d, J = 5.6, 2 H, NCH_2), 4.38 (s, 2 H, CH_2), 7.9–8.4 (m, 4 H, ar H), 8.57 (t, J = 5.6, 1 H, NH). – ^{13}C NMR ([d_6]DMSO): δ = 25.15, 25.37 (CH_2), 121.51 (C-4), 124.97 (C-7), 126.35 (C-3a), 135.18 (C-5), 135.75 (C-6), 136.79 (C-7a), 158.34 (C-3), 164.88, 170.69 (CO).
$C_{11}H_{10}N_2O_6S$ (298.3)

3.27. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]-L-valyl-L-phenylalanine methyl ester (**18a**)

From 0.13 g (0.5 mmol) of **14a**, 0.25 g (0.6 mmol) of L-Val-L-Phe-OMe-triflate (from **10e**), 0.13 g (1.1 mmol) of NHS, 0.1 g (0.7 mmol) of TEA, and 2.4 g (10.3 mmol) of DCC. Yield: 50 mg (16%). – M.p. 165 °C. – $[\alpha]_D^{20} = +11.3$ (c = 1, dioxane). – IR: ν = 3315 (NH), 3107, 2927, 2850 (CH), 1743, 1733, 1672, 1650 (CO), 1347, 1193 (SO_2). – ^{1}H NMR: δ = 0.84, 0.91 (2 d, each J = 6.8, 3 H, CH_3), 2.09 (m, 1 H, CH), 3.11 (d, 2 H, CH_2Ph), 3.71 (s, 3 H, OCH_3), 4.28 (dd, 1 H, NCH), 4.43 (s, 2 H, CH_2), 4.84 (dd, 1 H, CH), 6.18 (d, J = 7.7, 1 H, NH), 6.73 (d, J = 7.8, 1 H, NH), 7.05–7.3 [m, 5 H, ar H(Ph)], 7.85–8.15 (m, 4 H, ar H). – ^{13}C NMR: δ = 17.74, 18.95 (CH_3), 31.18 (CH), 37.78 (CH_2Ph), 41.24 (NCH_2), 52.34 (OCH_3), 53.18 (CH), 58.63 (CH), 121.41 (C-4), 125.75 (C-7), 127.04 (C-3a), 127.31, 128.76, 129.27, 134.70 [ar C(Ph)], 135.31 (C-5), 135.51 (C-6), 137.77 (C-7a), 158.89 (C-3), 165.14, 169.98, 171.53 (CO). – HPLC: k′ = 1.60, t_o = 1.91.
$C_{24}H_{26}N_3O_7S$ (500.6)

3.28. N-[(1,1,3-Trioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)acetyl]-L-valyl-L-valine methyl ester (**18b**)

From 0.15 g (0.6 mmol) of **14a**, 0.25 g (0.7 mmol) of L-Val-L-Val-OMe-triflate (from **10f**), 0.15 g (1.2 mmol) of NHS, 0.1 g (0.7 mmol) of TEA, and 0.17 g (0.7 mmol) of DCC. Yield: 55 mg (17%). – M.p. 185 °C. – $[\alpha]_D^{20} = -15.55$ (c = 0.5, dioxane). – IR: ν = 3293 (NH), 3092, 2967, 2931 (CH), 1731, 1671, 1646 (CO), 1345, 1191 (SO_2). – ^{1}H NMR: δ = 0.89, 0.97 (2 d, each 6 H, CH_3), 2.17 (m, 2 H, CH), 3.73 (s, 3 H, OCH_3), 4.34 (dd, 1 H, NCH), 4.45 (s, 2 H, CH_2), 4.51 (dd, 1 H, NCH), 6.23 (d, 1 H, NH), 6.74 (d, 1 H, NH), 7.85–8.15 (m, 4 H, ar H). – ^{13}C NMR: δ = 17.87, 18.93 (CH_3), 30.96, 33.94 (CH), 41.05 (NCH_2), 52.12 (OCH_3), 57.39, 58.84 (CH), 121.33 (C-4), 125.63 (C-7), 127.06 (C-3a), 134.66 (C-5), 135.24 (C-6), 137.67 (C-7a), 158.92 (C-3), 165.32, 170.63, 172.03 (CO). – HPLC: k′ = 1.24, t_o = 1.91.
$C_{20}H_{27}N_3O_7S$ (453.5)

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References

1 Remsen, I.; Fahlberg, C.: Chem. Ber. **12**, 469 (1879)
2 Ager, D. J.; Pantaleone, D. P.; Henderson, S. A.; Katritzky, A. R.; Prakash, I.; Walters, D. E.: Angew. Chem. **110**, 1900 (1998)
3 Groutas, W. C.; Houser-Archield, N.; Chong, L. S.; Venkataraman, R. K.; Epp, J. B.; Huang, H.; McClenahan, J. J.: J. Med. Chem. **36**, 3178 (1993)
4 Hlasta, D. J.; Subramanyam, C.; Bell, M. R.; Carabateas, P. M.; Court, J. J.; Desai, R. C.; Drozd, M. L.; Eickhoff, W. M.; Ferguson, E. W.; Gordon, R. J.; Johnson, J. A.; Kumar, V.; Maycock, A. L.; Mueller, K. R.; Pagani, E. D.; Robinson, D. T.; Saindane, M. T.; Silver, P. J.; Subramanian, S.: J. Med. Chem. **38**, 739 (1995)
5 Kerneur, C.; Hornebeck, W.; Robert, L.; Moczar, E.: Biochem. Pharmacol. **45**, 1889 (1993)
6 Da Settimo, A.; Primofiore, G.; Motta, C. L.; Settimo, F. D.; Simorini, F.: Farmaco **51**, 261 (1996)
7 Achilles, K.; Schirmeister, T.; Otto, H.-H.: Arch. Pharm. **333**, 243 (2000)
8 Pettit, G. R.; Kadunce, R. E.: J. Org. Chem. **27**, 4566 (1962)
9 Magidson, O. J.; Gorbatschow, S. W.: Chem. Ber. **56**, 1810 (1923)
10 Schapira, C. B.; Perillo, I. A.; Lamdan, S.: J. Heterocycl. Chem. **17**, 1281 (1980)
11 Reddy, Y. P.; Kondo, S.; Toru, T.; Ueno, Y.: J. Org. Chem. **62**, 2652 (1997)
12 Bodtke, A. Ph.D. Thesis, University of Greifswald 2001, in preparation
13 Paul, L.; Dittmar, A.; Rusch, C.: Chem. Ber. **100**, 2757 (1967)
14 Keller, O.; Rudinger, J.: Helv. Chem. Acta. **58**, 532 (1975)
15 Holmes, W. B.: J. Am. Chem. Soc. **25**, 203 (1901)
16 Bernner, M.; Huber, W.: Helv. Chim. Acta **36**, 1109 (1953)
17 Deimer, K. H.; Thamm, P. T.; Stelzel, P.: in Houben-Weyl, Methoden der organischen Chemie, Thieme, Stuttgart 1974, vol. XV/1, page 315
18 Wendleberger, G.: in Houben-Weyl, Methoden der organischen Chemie, Thieme, Stuttgart 1974, vol. XV/2, page 111.

19 Schwyzer, R.; Rittel, W.; Kappeler, H.; Iselin, B.: Angew. Chem. **72**, 915 (1960).
20 Abe, K.; Tsukamoto, Y.; Ishimura, A.: J. Pharm. Soc. Japan **73**, 1319 (1953).
21 Salami, M.; Otto, H.-H.; Jira, T.: Electrophoresis **22**, 3291 (2001)
22 Yamazaki, T.; Benedetti, E.; Kent, D.; Goodman, M.: Angew. Chem. **106**, 1502 (1994)
23 Walters, D. E.; Prakash, I.; Desai, N.: J. Med. Chem. **43**, 1242 (2000)
24 Svoboda, J.; Palecek, J.; Jaroslav, J.; Kubelka, V.; Dedek, V.; Mostecky, J.; Dranovsky, J.; Hampel, F.; Stanek, J.; Votava, V.: Czech CS 248,909, 15 Jan **1988**, C.A. **110**, 38983a (1989)
25 Schafer, D. J.: J. Chem. Soc. Perkin Trans.I. **12**, 1452 (1972)

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