Synthesis of N,N'-Linked Bisazaheterocycles with Sulfonamide Structure via Oxidation of S,N-Heteroaromatic Cations

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Abstract: N-Phthalimidyl- and N-quinazolinyl-substituted 3-hydroperoxy-, 3-hydroxy- and 3-oxoisothiazole 1,1-dioxides have been synthesized by the sequence of oxidation reactions from N,N'-linked isothiazolium perchlorates with hydrogen peroxide, MMPP, and pyridinium dichromate. Isothiazolium salts without acceptor substituents did not give N-substituted sultams. Novel N,N'-bisaza
heterocycles were investigated as inhibitors of acetylcholinesterase (AChE) and human leukocyte elastase (HLE). Two 2,3-dihydro-3-
hydroperoxy-2-(phthalimid-1-yl)isothiazole 1,1-dioxides were found to inhibit AChE.

Key words: β-thiocyanatovinyl aldehydes, N-aminoheterocycles, isothiazolium salts, N,N'-linked bisazaheterocycles, sultams

During the last years N,N'-linked bisazaheterocycles have gained significant importance in view of their pharmacological activities as potential anticonvulsant,1 antidepressant,2 antiinflammatory,3 antimicrobial,4 and antifilarial agents,5 reductase inhibitors,6 and anti-Parkinson agents.7 They are also excellent precursors of nitrogen centered free radicals, which play an important role in the physiological processes of living organisms and in understanding the mode of action of many toxins.8

The structure of bisazaheterocycles described in the literature differs both in symmetry (identical or different rings) and in the size and nature of the heterocycles included.8a The compounds bearing a phthalimide or quinazolinone unit often possess biological activities. For example, 2-(pyrrol-1-yl)phthalimides 1 can be used as a glycine partial agonists.9 3-Triazinyl-4(3H)-quinazolino
one derivatives 2 showed anticonvulsant activity,1 whereas compounds 3 were studied for their anti-Parkin
son activity1 (Figure 1).

However, to the best of our knowledge, there is no litera
ture report on N,N'-linked bisazaheterocycles containing a fragment of saccharin (4, R = H) or its analogues. Sac
ccharin-based compounds show a broad range of biological

activities, for example, N-arylbensothiazol-3-one 1,1-dioxides 4 (R = Ar) and 2-methylene derivatives 5 are po
tent, mechanism-based inhibitors of serine proteases.10 In view of these observations we became interested in N,N'-linked bisazaheterocycles, containing an isothiazole fragment in their structure.11

Recently, the synthesis of a series of monocyclic and bi
cyclic 2-arylsultams with hydroperoxy, hydroxy, alkoxy or oxo groups in C-3 position was developed by the reaction of β-thiocyanatovinyl aldehydes with the corresponding amino compounds, followed by oxidation of the formed iminium salts.12 Some of the 3-oxo derivatives were found to inhibit human leukocyte elastase (HLE) in a time-dependent manner.10,13 Moreover, 3-hydroperoxy-
sultams can be used as renewable chemoselective electro
philic oxidants for a wide range of substrates in

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nonaqueous media, for example, with nitrogen, sulfur, and phosphorus heteroatoms.14

Herein we report on a study of the reaction of β-thiocyanatovinyl aldehydes with N-aminoheterocycles and an approach to N,N'-linked bisazaheterocycles via intramolecular cyclocondensation and oxidation reactions. The two β-thiocyanatovinyl aldehydes 6 \([\text{R}^1 = \text{R}^2 = \text{Me} ; \text{R}^1\text{R}^2 = -(\text{CH}_2)_4\text{-}]\) used in this study were synthesized by a known method from the corresponding ketones.15 Conversions were carried out with \(\text{N}\)-aminophthalimide (7), \(\text{N}\)-amino-4(3\(H\))-quinazolinones 8, and heterocycles of type 9 (Figure 2).

Thiocyanates 6 reacted with the N-aminoheterocycles 7–9 in glacial acetic acid in the presence of perchloric acid for the salt formation.12 The first stage of the reaction leads to hydrazonium salts, which then undergo intramolecular cyclocondensation giving rise to N,N'-linked isothiazolium salts 10–12 (Figure 3, Table 1). Compounds 11a–d were obtained as hygroscopic bisperchlorate salts.

The IR spectra of the isothiazolium perchlorates 10, 11 showed absorption bands of perchlorate anion at 1079–1090 cm\(^{-1}\). NMR spectra of the salts 10, 11 are compatible with the structure of isothiazolium salts. The characteristic signals in the \(^{13}\text{C}\) NMR spectra for C-5 (C-7a), C-3, and C-4 (C-3a) were elucidated by additional HMBC and HMQC experiments and were found at \(\delta = 174.8–178.2, 159.9–161.1,\) and 132.1–133.1 ppm, respectively. The diagnostic signal of the H-3 atom in the \(^1\text{H}\) NMR spectra appeared in the region \(\delta = 9.31–9.48\) ppm as usual for isothiazolium salts.

The oxidation reactions of the iminium salts 10, 11 prepared were studied using the standard system \(\text{H}_2\text{O}_2–\text{AcOH}\) and with magnesium monoperoxyphthalate (MMPP) under different reaction conditions, such as solvent, temperature, and reaction time.

The oxidation of phthalimidyl isothiazolium perchlorates 10a, b was carried out at first with hydrogen peroxide in glacial acetic acid at room temperature during 1–2 days. The oxidation occurred at both C-3 carbon and sulfur atoms of the isothiazole ring to give stable hydroperoxysultams 13a, b as colorless crystals in moderate yields (Scheme 1, Table 2).

In accordance to a previous investigation using an HPLC methodology,17 the supposed mechanism for this reaction includes an oxidation cascade with the initial nucleophilic attack of \(\text{H}_2\text{O}_2\) at C-3 of the salts 10 with the formation of 3-hydroperoxysultams 13 as colorless crystals in moderate yields (Scheme 1, Table 2).
ultrasound conditions at 50 °C. The 3-hydroxyisothiazole 1,1-dioxides 14a,b, in every respect identical to the corresponding sultams prepared using H₂O₂–DMSO, were obtained by this pathway in moderate yields (Table 2). Obviously, the mechanism of MMPP oxidation reaction in this case is similar to that described for 2-arylisothiazolium salts, where the oxidation sequence was opposite compared to the H₂O₂–AcOH system (Scheme 1).12e

To develop an alternative approach to N,N'-linked isothiazol-3(2H)-one 1,1-dioxides, the oxidation of 3-hydroxy-sultams 14 with pyridinium dichromate in CH₂Cl₂ was applied. It resulted in the preparation of 3-oxosultams 15, already obtained by H₂O₂ oxidation, in good yields (Table 2).

The structures of the compounds 13–15 were established by NMR spectroscopy and confirmed by IR spectroscopy, mass spectrometry, and elemental analysis. In the IR spectra of sultams 13–15, two absorption bands for the SO₂ groups, known to be characteristic for the 1,1-dioxides, were observed at 1299–1323 and 1161–1180 cm⁻¹ for the antisymmetric and symmetric vibrations, respectively. Phthalimide carbonyl bands together with isothiazol-3(2H)-one carbonyl signals for isothiazol-3(2H)-ones 15 could be found in the region of 1736–1754 cm⁻¹.

The ¹H NMR spectra of sultams 13 and 14 showed the typical absorption of the H-3 atom at δ = 5.73–6.04 ppm, while the OOH groups of 3-hydroperoxysultams 13 and the OH of 3-hydroxy derivatives 14 resonated at δ = 11.46–11.68 (OOH) and 6.16–7.21 (OH) ppm. In the ¹³C NMR spectra, the diagnostic C-3 signals of isothiazole 1,1-dioxides 13–15 differed significantly and were located at δ = 94.1–95.0, 83.3–83.7 and 157.8–158.7 ppm, respectively.

The oxidation reactions of quinazolinyl isothiazolium salts 11 were investigated with the same oxidants, H₂O₂ and MMPP, as in the case of compounds 10. However, the reaction of salts 11a,c,d with H₂O₂ at room temperature or at 80 °C failed to give positive results and either initial salts 11 or decomposition products were obtained after workup.

Nevertheless, oxidation of the isothiazolium salt 11b by H₂O₂ at room temperature after 48 hours furnished 3-hydroperoxysultam 16b (Scheme 2). Unexpectedly, increasing the temperature to 80 °C had a destructive effect on the quinazolinone part of the molecule, which was transformed during the oxidation process to the nitro compound 17, prepared before by H₂O₂ oxidation of 4,5-dimethyl-2-[N-(2-nitro)benzamidyl]isothiazolium perchlorate.14 Like its analogues 13, 3-hydroperoxy sultam 16b could be quantitatively converted into the 3-hydroxy derivative 18b in the presence of DMSO (Scheme 2, Table 3).

The oxidation reactions of isothiazolium salts 11a–d with MMPP were carried out in acetonitrile–water system at room temperature during 12 hours. However, after the usual workup procedure the quinazolinyl substituted 3-hydroxysultams 18 were obtained in only low yields as

Scheme 1

From the structure of hydroperoxides 13 one may expect that the peroxy oxygen atom is electron-deficient due to the strong electron-withdrawing effect of the sulfonamide function adjacent to the hydroperoxy group. Therefore, hydroperoxysultams 13 are potential oxidants, especially since the related 2-aryl-3-hydroperoxysultams were already found to be suitable and mild reagents for heteroatom oxidations.14 The hydroperoxides 13 were reduced using DMSO to give 3-hydroxyisothiazole 1,1-dioxides 14 (Scheme 1). After stirring for two hours and removal of DMSO in vacuo, 3-hydroxysultams 14a,b were isolated in almost quantitative yields (Table 2).

It has been reported that 2-aryl-3-hydroperoxysultams could be transformed into 3-oxo derivatives by heating in ethanol followed by the addition of concentrated HCl.12a Hydroperoxides 13a,b were found to be more stable under such dehydration conditions and were regenerated from the reaction mixture after refluxing for two hours. However, increasing the temperature to 80 °C in the reaction of salts 10a,b with H₂O₂ and reflux during 17 hours gave directly 3-oxosultams 15a,b as the final products of the oxidation cascade (Scheme 1, Table 2).

The oxidation reaction of isothiazolium salts 10 using MMPP in water–acetonitrile system was carried out under
colorless crystals (Scheme 3, Table 3). Unfortunately, in contrast to the increase in the yields described for N-aryl
sultams,12d,e the use of an ultrasound bath in this case was not helpful.

3-Oxosultams, containing a quinazolinyl substituent were not available by oxidation of isothiazolium salts 11 with hydrogen peroxide. Therefore, the oxidation of 3-hydroxy derivatives 18 was carried out with pyridinium dichromate. Using this procedure, the 3-oxosultams 19a, 19b, 19d were obtained in good yields in agreement with previous results for the preparation of sultams 15.

The IR spectra of the new compounds 18, 19 exhibited signals for the carbonyl group of the quinazolinone ring at 1674–1715 cm\(^{-1}\), absorption bands for C=N bonds at 1605–1614 cm\(^{-1}\) and symmetrical and antisymmetrical bands for the SO\(_2\) group at 1167–1180 and 1308–1347 cm\(^{-1}\). In the \(^{13}\)C NMR spectra of 3-hydroxyisothiazole 1,1-dioxides 18 the chemical shift corresponding to the C-3 atom occurred at \(\delta = 82.9–84.7\) ppm, while for sultams 19 the signal for the new carbonyl group appeared instead at \(\delta = 156.5–157.9\) ppm. Characteristic chemical shifts of 3-H and OH groups of compounds 18 were found at \(\delta = 5.84–6.07\) and 6.48–7.40 ppm, respectively.

Structures of the novel N,N¢-linked isothiazole 1,1-dioxides 15a, 18d, and 19b are sterically demanding compounds. The analysis of dihedral angles between two heterocyclic rings showed values of 84–88° and thus the planes of two cycles are almost perpendicularly orientated.

Unlike isothiazolium salts 10 and 11, their analogues 12 failed to undergo oxidation to N-substituted sultams. Un-
In conclusion, a series of N,N-3-hydroxy-, and 3-oxosultams have been prepared by the oxidation of N,N-3-hydroxy-, and 3-oxosultams have been prepared by the oxidation of N,N-4,5,6,7), 125.4 (2 CH arom), 130.1 (2 C arom), 132.9 (C-3a), 136.7 (2 C=O), 174.8 (C-5). MS (ESI): mlz = 259 [M – ClO₄]⁺.

The newly synthesized N,N’-linked bisazaheterocycles 13a,b, 14a,b, 15a, 17, 18b,d, and 19a,d were evaluated as inhibitors of acetylcholinesterase (AChE) from *Electrophorus electricus* and human leukocyte elastase (HLE). The hydroperoxides 13a and 13b showed inhibitory activity towards acetylcholinesterase with IC₅₀ values of 14.7 ± 2.4 μM, and 15.7 ± 0.6 μM, respectively. However, no HLE inhibition was found for the investigated sultams. In conclusion, a series of N,N’-connected 3-hydroperoxy-, 3-hydroxy-, and 3-oxosultams have been prepared by the oxidation of N,N’-linked isothiazolium perchlorates. These new isothiazolium salts were found to be less reactive in oxidation reactions with hydrogen peroxide and MMPP than their N-arylsubstituted analogues, described in the literature. Thus, the oxidation process in this case was found to depend on the nature of the cyclic substituent at the isothiazole N-atom. The presence of acceptor substituents, such as carbonyl groups in phthalimidyl or 4-oxoisothiazol-3-yl rings, assisted the oxidation reaction. The new N,N’-linked sultams were evaluated for their inhibitory activity toward HLE and AChE. Two 2,3-dihydro-3-hydroperoxy-2-(phthalimid-1-yl)isothiazole 1,1-dioxides were found to inhibit AChE.

Melting points were determined on Boetius micro-melting-point apparatus and are corrected. ¹H and ¹³C NMR spectra were recorded at 300 or 400 MHz (¹H) and 75 or 100 MHz (¹³C) with Varian Mercury Plus 300 or 400 NMR spectrometers in DMSO-d₆ or acetone-d₆ solution using TMS as internal standard. IR spectra were recorded on a spectrophotometer Genesis FTIR Unicam Analytical System (ATI Mattson) with KBr pellets; values in cm⁻¹. Elemental analyses were performed on a Heraeus CHNO Rapid Analyzer.

Mass spectra (70 eV) were determined on Quadrupol-MS VG 12-250.

**Isothiazolium Perchlorates 10, 11; General Procedure**

To a magnetically stirred solution of β-thiocyanatovinyl aldehyde 6a,b (1 mmol) in glacial AcOH (2 mL) under argon was added the N-amino compound 7, 8 (1 mmol). The mixture was stirred for 15 min and HClO₄ (0.4 mL) was added. After stirring for 50 min, the mixture was diluted with Et₂O (20 mL). The precipitate was collected by filtration, washed with Et₂O (3 ×) and air dried (for 10a,b) or dried in vacuo (for 11a-d). The salts 11a-d are hygroscopic and therefore the mps were not measured.

**4,5-Dimethyl-2-(phthalimid-1-yl)isothiazolium Perchlorate (10a)**

Yield: 333 mg (93%); white solid; mp 240–242 °C.

IR (KBr): 1753 (C=O), 1079 (ClO₄) cm⁻¹.

¹H NMR (300 MHz, DMSO-d₆): δ = 2.35 (s, 3 H, CH₃), 2.84 (s, 3 H, CH₃), 8.04 (d, J = 7.8 Hz, 2 H arom), 8.13 (d, J = 7.8 Hz, 2 H arom), 9.31 (s, 1 H, CH).

¹³C NMR (75 MHz, DMSO-d₆): δ = 11.4 (CH₃), 15.0 (CH₃), 125.4 (2 CH arom), 130.0 (2 C arom), 132.1 (C-4), 136.7 (2 CH arom), 160.4 (C-3), 162.9 (2 C=O), 174.8 (C-5).


Anal. Calcd for C₁₅H₁₂ClN₂O₆S: C, 43.64; H, 3.26; N, 7.81; S, 9.31.

**4,5,6,7-Tetrahydro-2-(phthalimid-1-yl)-1,2-benzisothiazolium Perchlorate (10b)**

Yield: 342 mg (89%); white solid; mp 247–249 °C.

IR (KBr): 1753 (C=O), 1090 (ClO₄) cm⁻¹.

¹H NMR (300 MHz, DMSO-d₆): δ = 1.90 (m, 4 H, 2 CH₂), 2.90 (m, 2 H, CH₃), 3.28 (m, 2 H, CH₃), 8.08–8.21 (m, 4 H arom), 9.36 (s, 1 H, CH).

¹³C NMR (75 MHz, DMSO-d₆): δ = 21.0, 21.7, 22.9, 27.2 (C-4,5,6,7), 125.4 (2 CH arom), 130.1 (2 C arom), 132.9 (C-3a), 136.7 (2 CH arom), 159.9 (C-3), 162.9 (2 C=O), 175.7 (C-7a).


Anal. Calcd. for C₁₅H₁₄ClN₂O₆S: C, 46.82; H, 3.41; N, 7.28; S, 8.33. Found: C, 46.50; H, 3.55; N, 8.64; S, 7.87.

**4,5-Dimethyl-2-[4-oxo-3(4H)-quinazolinyl]isothiazolium Perchlorate (11a)**

Yield: 394 mg (86%); yellow solid.

IR (KBr): 1713 (C=O), 1086 (ClO₄) cm⁻¹.

¹H NMR (300 MHz, acetone-d₆): δ = 2.55 (s, 3 H, CH₃ at C-4), 3.08 (s, 3 H, CH₃ at C-5), 8.00 (m, 1 H, H-6'), 8.08 (d, J = 8.9 Hz, 1 H, H-8'), 8.25 (m, 1 H, H-7'), 8.47 (d, J = 9.3 Hz, 1 H, H-5'), 9.48 (s, 1 H, H-3), 9.79 (s, 1 H, NH), 10.12 (s, 1 H, H-2).

¹³C NMR (75 MHz, acetone-d₆): δ = 10.5 (CH₃ at C-5), 13.8 (CH₃ at C-4), 120.3 (C-4a), 120.7 (C-8'), 128.9 (C-5'), 131.8 (C-6'), 133.1 (C-14), 138.5 (C-7'), 152.1 (C-2'), 154.5 (C-8a'), 155.8 (C=O), 160.5 (C-3), 176.5 (C-5).


**4,5-Dimethyl-2-[2-methyl-4-oxo-3(4H)-quinazolinyl]isothiazolium Perchlorate (11b)**

Yield: 397 mg (84%); yellow solid.

¹H NMR (300 MHz, acetone-d₆): δ = 1.87 (s, 3 H, CH₃ at C-2'), 2.32 (s, 3 H, CH₃ at C-4), 2.83 (s, 3 H, CH₃ at C-5) 7.60–8.70 (m, 5 H, 4 H arom + NH), 9.42 (s, 1 H, H-3).

**Benzisothiazolium Perchlorate (11d)**

Found: C, 51.27; H, 3.69; N, 7.88; S, 9.33.

IR (KBr): 1173 (SO₂), 1323 (SO₂), 1741 (C=O) cm⁻¹.

Yield: 108 mg (44%); white solid; mp 184–187 °C.

**Benzisothiazole 1,1-Dioxide (13b)**

2,3,4,5,6,7-Hexahydro-3-hydroperoxy-2-(phthalimid-1-yl)-1,2-benzisothiazolium Perchlorate (11c)

Yield: 115 mg (51%); white solid; mp 215–217 °C.

**Benzisothiazole 1,1-Dioxide (14a)**

2,3-Dihydro-3-hydroperoxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (13a)

Yield: 60 mg (98%) (from 13a); 54 mg (41%) (from 10a); white solid; mp 198–200 °C.

**Benzisothiazole 1,1-Dioxide (14b)**

2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (13b)

Yield: 62 mg (93%) (from 13b); 72 mg (36%) (from 10b); white solid; mp 185–187 °C.

**Benzisothiazole 1,1-Dioxide (14c)**

2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (13c)

Yield: 74 mg (36%) (from 10c); white solid; mp 198–200 °C.

**3-Hydroxysultams 14 from 3-Hydroperoxysultams 13; General Procedure**

DMSO (2 mL) was added to 13 (0.2 mmol). After 2 h, DMSO was evaporated in vacuum, the residue was washed with H₂O (2 mL), and air dried.

**3-Hydroxysultams 14 from 3-Hydroperoxysultams 13; General Procedure**

A stirred solution of appropriate isothiazolium salt 10 (0.6 mmol) in MeCN (13 mL) was treated in portions with MMPP (890 mg, 1.8 mmol) and the mixture was left in the ultrasound bath at 50 °C for 3 h. Then, sat. aq NaHCO₃ (5 mL) was added, the mixture extracted with EtO (3 × 25 mL) and the combined organic layers were dried (MgSO₄). The solvent was evaporated and the respective product 14 was purified by recrystallization from EtOH–H₂O.

**2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (14a)**

Yield: 62 mg (93%) (from 13a); 54 mg (41%) (from 10a); white solid; mp 198–200 °C.

**2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (14b)**

Yield: 62 mg (93%) (from 13b); 72 mg (36%) (from 10b); white solid; mp 185–187 °C.

**2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (14c)**

Yield: 62 mg (93%) (from 13c); 54 mg (41%) (from 10c); white solid; mp 198–200 °C.

**3-Oxosultams 15 from Isothiazolium Salts 10; General Procedure**

H₂O (2.8 mL, 30%) was added at r.t. to a stirred suspension of 10 (0.7 mmol) in AcOH (4.2 mL). After 24–48 h, the solution was diluted with cold H₂O (3–5 mL), and the colorless crystals of 13 were collected by filtration, and recrystallized from EtOH–H₂O.

**3-Oxosultams 15 from Isothiazolium Salts 10; General Procedure**

H₂O (2.8 mL, 30%) was added at r.t. to a stirred suspension of 10 (0.7 mmol) in AcOH (4.2 mL). After 24–48 h, the solution was diluted with cold H₂O (3–5 mL), and the colorless crystals of 13 were collected by filtration, and recrystallized from EtOH–H₂O.

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H₂O (2.8 mL, 30%) was added at r.t. to a stirred suspension of 10 (0.7 mmol) in AcOH (4.2 mL). After 24–48 h, the solution was diluted with cold H₂O (3–5 mL), and the colorless crystals of 13 were collected by filtration, and recrystallized from EtOH–H₂O.
4,5-Dimethyl-2-[phthalimid-1-yl]isothiazol-3(2H)-one, 1,1-Dioxide (15a)
Yield: 81 mg (38%) (from 10a), 61 mg (79%) (from 14a); white solid; mp 267–269 °C.
IR (KBr): 1754 (C=O), 1299 (SO2), 1161 (SO2) cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 2.18 (s, 3 H, CH₃), 2.41 (s, 3 H, CH₃), 7.85 (m, 2 H₆), 8.06 (m, 2 H₇).
13C NMR (100 MHz, DMSO-d₆): δ = 18.9 (CH₃), 19.7 (CH₃), 20.2 (CH₂), 124.7 (2 CH₆), 128.8 (2 CH₇), 134.8 (C₄), 136.2 (2 C₅), 144.6 (C₆), 158.7 (C₇), 162.7 (2 C=O).
MS (EI): m/z = 306 [M]+.
Anal. Calcd for C₁₄H₁₅N₃O₅S: C, 49.85; H, 4.48; N, 12.46; S, 9.50.

11b Oxidation of S,N-Heteroaromatic Cations to N,N-Linked Bisazaheterocycles

2.3-Hydroxy-4,5-dimethyl-2-[2-methyl-4-oxo-3(4H)-quinazolinyl]isothiazole 1,1-Dioxide (18b) from 3-Hydroperoxysultam (16b)
DMSO (2 mL) was added at r.t. to 16b (0.2 mmol). After 2 h, DMSO was evaporated in vacuo, the residue was washed with H₂O (2 mL) and air dried.

3-Hydroxy-2-[4-oxo-3(4H)quinazolinyl]sultams 18 from Isothiazolium Salts 11; General Procedure
A stirred solution of isothiazolium salts 11 (0.9 mmol) in MeCN (15 mL) was treated portionwise with MPP (1.336 g, 2.7 mmol) and the mixture was stirred during 16 h at r.t. Then, sat. aq NaHCO₃ (5 mL) was added to the mixture and it was extracted with EtO (3 × 25 mL). The combined organic layers were dried (MgSO₄). The solvent was evaporated and the products 18 were purified by recrystallization from EtOH–H₂O.

2.3-Dihydroxy-4,5-dimethyl-2-[2-methyl-4-oxo-3(4H)-quinazolinyl]isothiazole 1,1-Dioxide (18a)
Yield: 91 mg (33%) (from 11a); white solid; mp 220–223 °C.
IR (KBr): 1714 (C=O), 1307 (SO₂), 1177 (SO₂) cm⁻¹.
1H NMR (400 MHz, DMSO-d₆): δ = 1.98 (s, 3 H, CH₃), 2.07 (s, 3 H, CH₃), 5.84 (s, 1 H, H-3), 7.40 (s, 1 H, OH), 7.64 (m, 1 H₆), 7.76 (m, 1 H₇), 7.92 (m, 1 H₆), 8.17 (m, 1 H₇), 8.19 (s, 1 H, H-2).
13C NMR (100 MHz, DMSO-d₆): δ = 7.3 (CH₃), 12.2 (CH₃), 83.2 (C₃), 122.2 (C₄), 126.6 (C₅), 127.7 (C₆), 128.1 (C₇), 130.2 (C₈), 141.5 (C₉), 146.5 (C₈a), 149.3 (C₇C), 158.6 (C=O).
MS (EI): m/z = 307 [M]+.
Anal. Calcd for C₁₅H₁₂N₂O₅S: C, 54.21; H, 3.64; N, 8.43; S, 9.64.
Found: C, 54.29; H, 3.58; N, 8.47; S, 9.64.

2,3-Dihydroxy-4,5-dimethyl-2-[2-methyl-4-oxo-3(4H)-quinazolinyl]isothiazole 1,1-Dioxide (18b)
Yield: 61 mg (95%) (from 16b); 52 mg (18%) (from 11b); white solid; mp 238–240 °C.
IR (KBr): 1709 (C=O), 1608 (C=O), 1315 (SO₂), 1173 (SO₂) cm⁻¹.
1H NMR (300 MHz, DMSO-d₆): δ = 2.05 (s, 3 H, CH₃), 2.05 (s, 3 H, CH₃), 2.64 (s, 3 H, CH₃), 5.87 (d, J = 4.8 Hz, 1 H-3), 7.30 (d, J = 6.6 Hz, 1 H, OH), 7.54 (m, 1 H₆), 7.66 (m, 1 H₇), 8.08 (m, 1 H₇), 8.17 (m, 1 H₇).
13C NMR (75 MHz, DMSO-d₆): δ = 7.4 (CH₃), 12.2 (CH₃), 22.0 (CH₂ at C-2), 93.9 (C-3), 121.8 (C₄a), 126.8 (C₅), 127.1 (C₆), 133.5 (C₄), 135.3 (C₇), 137.5 (C₈), 146.1 (C₈a), 157.8 (C-2), 159.5 (C=O).
MS (EI): m/z = 321 [M]+.
Anal. Calcd for C₁₆H₁₄N₃O₇S: C, 52.33; H, 4.70; N, 13.08; S, 9.98.
Found: C, 52.21; H, 4.77; N, 13.15; S, 9.84.
1H NMR (400 MHz, DMSO-d$_6$): δ = 2.13 (s, 3 H, CH$_3$ at C-4), 2.40 (s, 3 H, CH$_3$ at C-5), 7.69 (m, 1 H$_{arom}$), 7.84 (d, J = 8 Hz, 1 H$_{arom}$), 7.99 (m, 1 H$_{arom}$), 8.20 (d, J = 8 Hz, 1 H$_{arom}$), 8.49 (s, 1 H, H-2')

1C NMR (75 MHz, acetone-d$_6$): δ = 8.3 (CH$_3$ at C-5), 9.3 (CH$_3$ at C-4), 121.4 (C-4a), 126.9 (C-5), 128.1 (C-8'), 128.7 (C-6'), 133.6 (C-4), 136.2 (C-7'), 143.6 (C-8'a), 146.4 (C-5'), 147.1 (C-2'a), 156.5 (C=O), 158.7 (C=O).

MS (EI): m/z = 305.1 [M$^+$].

Anal. Calcld for C$_{16}$H$_{13}$N$_3$O$_4$S: C, 55.61; H, 4.79; N, 12.16; S, 9.20.

2-(4-Oxo-3-(4H)-quinazolinyl)-isothiazol-3(2H)-one 1,1-Dioxide 19

Yield: 67 mg (88%); white solid; mp 191–193 °C.

IR (KBr): 1756 (C=O), 1605 (C=O), 1347 (SO$_2$), 1180 (SO$_2$) cm$^{-1}$.

1H NMR (300 MHz, acetone-d$_6$): δ = 2.12 (s, 3 H, CH$_3$ at C-4), 2.40 (s, 3 H, CH$_3$ at C-5), 7.69 (m, 1 H$_{arom}$), 7.84 (d, J = 8 Hz, 1 H$_{arom}$), 7.99 (m, 1 H$_{arom}$), 8.20 (d, J = 8 Hz, 1 H$_{arom}$), 8.49 (s, 1 H, H-2')

1C NMR (75 MHz, acetone-d$_6$): δ = 8.3 (CH$_3$ at C-5), 9.3 (CH$_3$ at C-4), 121.4 (C-4a), 126.9 (C-5), 128.1 (C-8'), 128.7 (C-6'), 133.6 (C-4), 136.2 (C-7'), 143.6 (C-8'a), 146.4 (C-5'), 147.1 (C-2'a), 156.5 (C=O), 158.7 (C=O).

MS (EI): m/z = 305.1 [M$^+$].

Anal. Calcld for C$_{16}$H$_{13}$N$_3$O$_4$S: C, 55.61; H, 4.79; N, 12.16; S, 9.20.
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