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′-bisazaheterocycles 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(3*H*)-quinazolinone derivatives **2** showed anticonvulsant activity,[1] whereas compounds **3** were studied for their anti-Parkinson activity[7] (Figure 1).

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

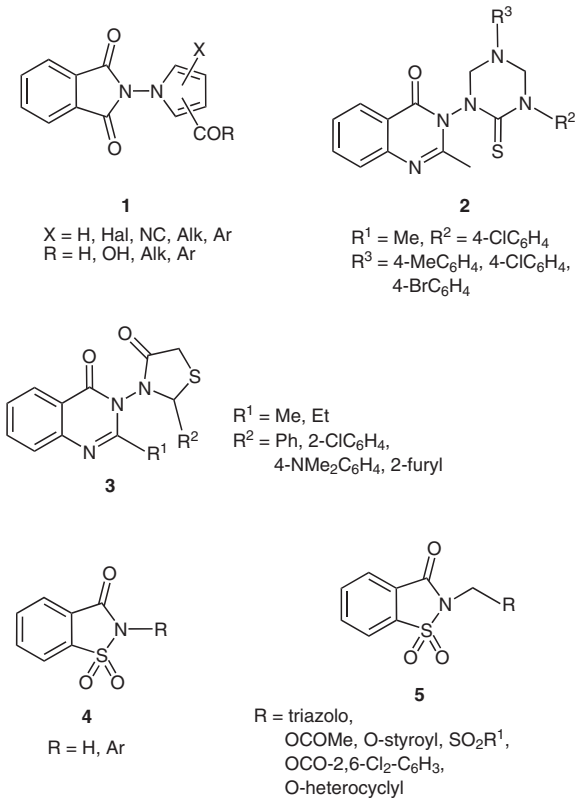

Figure 1 Some biologically active N,N′-linked bisazaheterocycles and N-substituted sultams

activities, for example, *N*-arylbenzisothiazol-3-one 1,1-dioxides **4** (R = Ar) and 2-methylene derivatives **5** are potent, 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 bicyclic 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.[10b,13] Moreover, 3-hydroperoxysultams can be used as renewable chemoselective electrophilic oxidants for a wide range of substrates in

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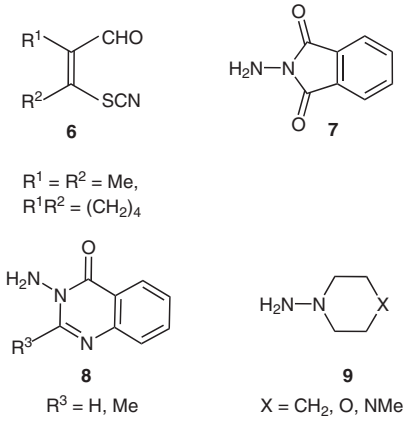


Figure 2 Starting β-thiocyanatovinyl aldehydes **6** and N-amino-heterocycles **7–9**

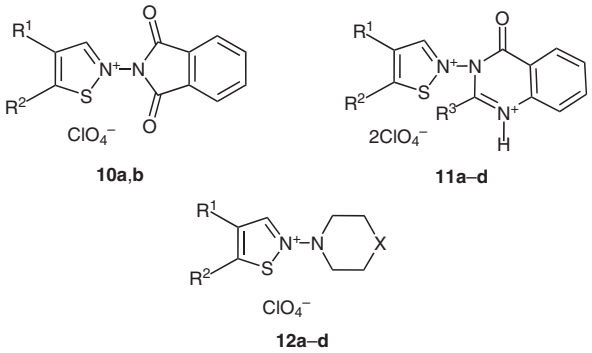


Figure 3 Isothiazolium salts, prepared by cyclocondensation reaction of β-thiocyanatovinyl aldehydes with N-amino compounds

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** [$R^1 = R^2 = Me$; $R^1R^2 = -(CH_2)_4-$] used in this study were synthesized by a known method from the corresponding ketones.[15] Conversions were carried out with *N*-aminophthalimide (**7**), *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}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 δ = 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 ^1H NMR spectra appeared in the region δ = 9.31–9.48 ppm as usual for isothiazolium salts.

Table 1 Isothiazolium Salts **10–12** Prepared

Product	R^1	R^2	R^3/X	Yield (%)
10a	Me	Me	–	93
10b	$(CH_2)_4$		–	89
11a	Me	Me	H	86
11b	Me	Me	Me	84
11c	$(CH_2)_4$		H	84
11d	$(CH_2)_4$		Me	97
12a	Me	Me	NMe	98[16]
12b	$(CH_2)_4$		CH_2	54[16]
12c	$(CH_2)_4$		O	77[16]
12d	$(CH_2)_4$		NMe	93[16]

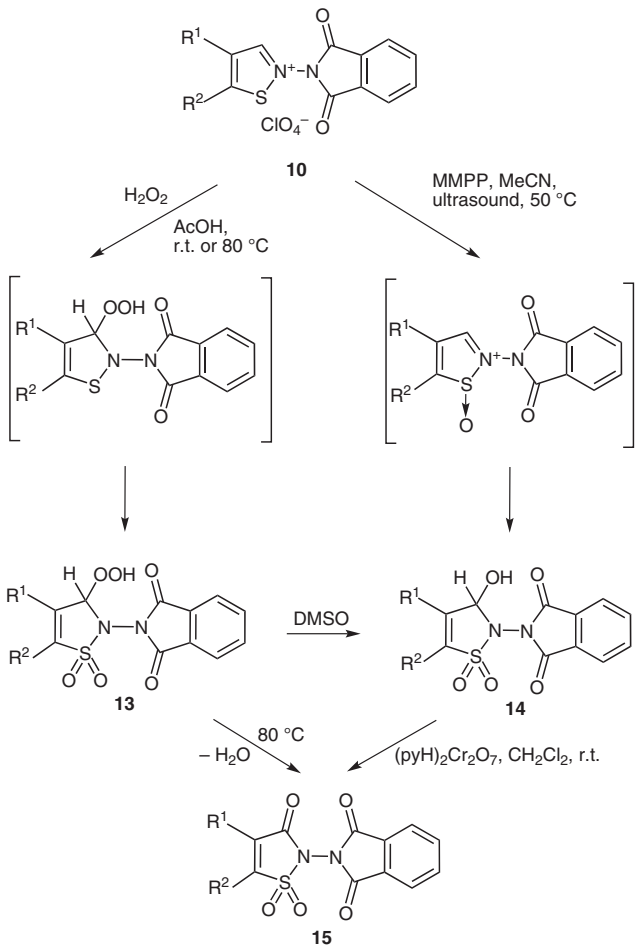
Table 2 Sultams **13–15** Prepared

Product	R^1	R^2	Isolated yield (%)
13a	Me	Me	51
13b	$(CH_2)_4$		44
14a	Me	Me	98 (from **13a**), 41 (from **10a**)
14b	$(CH_2)_4$		93 (from **13b**), 36 (from **10b**)
15a	Me	Me	38 (from **10a**), 79 (from **14a**)
15b	$(CH_2)_4$		41 (from **10b**), 82 (from **14b**)

The oxidation reactions of the iminium salts **10**, **11** prepared were studied using the standard system H_2O_2–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 H_2O_2 at C-3 of the salts **10** with the formation of 3-hydroperoxyisothiazoles (Scheme 1). The second attack of the hydrogen peroxide molecule occurs at the S-atom giving rise to *S*-oxides, which undergo further oxidation to the 3-hydroperoxysultams **13**.



Scheme 1

From the structure of hydroperoxides **13** one may expect that the peroxide 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 H_2O_2 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 ultrasound conditions at 50 °C. The 3-hydroxyisothiazole 1,1-dioxides **14a**,**b**, in every respect identical to the corresponding sultams prepared using H_2O_2–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 H_2O_2–AcOH system (Scheme 1).[12e]

To develop an alternative approach to N,N′-linked isothiazol-3(2*H*)-one 1,1-dioxides, the oxidation of 3-hydroxysultams **14** with pyridinium dichromate in CH_2Cl_2 was applied. It resulted in the preparation of 3-oxosultams **15**, already obtained by H_2O_2 oxidation, in good yields (Table 2).

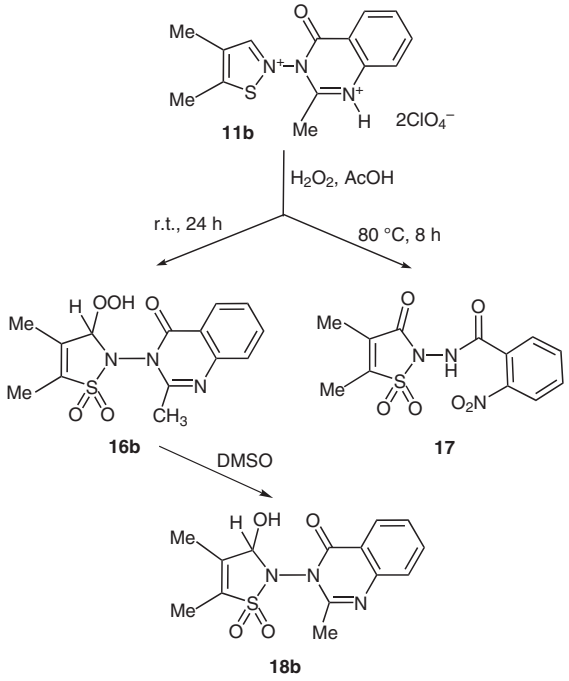
The structures of the compounds **13–15** were established by NMR spectroscopy and confirmed by IR spectroscopy, mass spectrometry, and elemental analysis. In the IR spectra of sultams **13–15**, two absorption bands for the SO_2 groups, known to be characteristic for the 1,1-dioxides, were observed at 1299–1323 and 1161–1180 cm^{-1} for the antisymmetric and symmetric vibrations, respectively. Phthalimide carbonyl bands together with isothiazole-3(2*H*)-one carbonyl signals for isothiazol-3(2*H*)-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 ^{13}C 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, H_2O_2 and MMPP, as in the case of compounds **10**. However, the reaction of salts **11a**,**c**,**d** with H_2O_2 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 H_2O_2 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 H_2O_2 oxidation of 4,5-dimethyl-2-[*N*-(2-nitro)benzamidyl]isothiazolium perchlorate.[18] 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 2

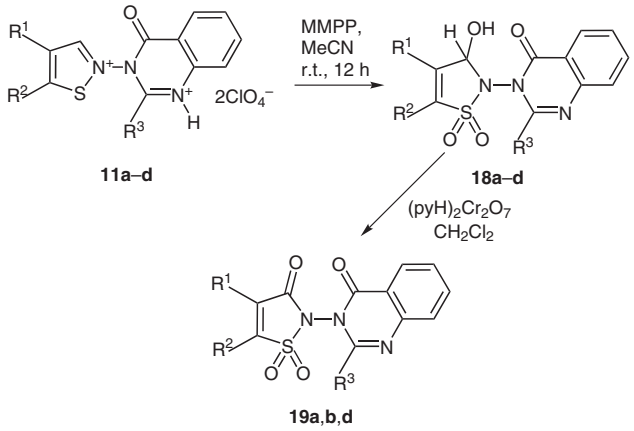
Table 3 Sultams **16**–**19** Prepared

Product	R^1	R^2	R^3	Isolated yield (%)
16b	Me	Me	Me	31
17	Me	Me	Me	28
18a	Me	Me	H	33 (from **11a**)
18b	Me	Me	Me	95 (from **16b**), 18 (from **11b**)
18c	$(CH_2)_4$		H	16 (from **11c**)
18d	$(CH_2)_4$		Me	16 (from **11d**)
19a	Me	Me	H	88
19b	Me	Me	Me	71
19d	$(CH_2)_4$		Me	73

colorless crystals (Scheme 3, Table 3). Unfortunately, in contrast to the increase in the yields described for *N*-arylsultams,[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**,**b**,**d** 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



Scheme 3

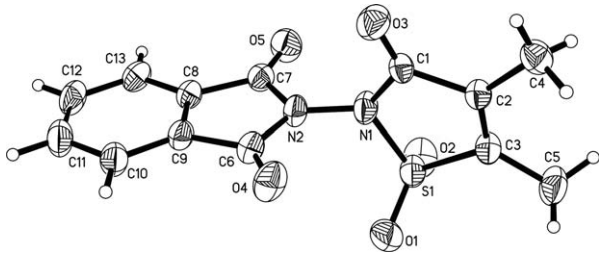


Figure 4 Molecular structure of 4,5-dimethyl-2-(phthalimid-1-yl)isothiazol-3(2*H*)-one 1,1-dioxide (**15a**)

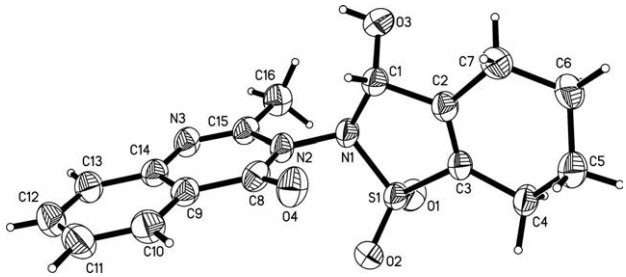


Figure 5 Molecular structure of 2,3,4,5,6,7-hexahydro-3-hydroxy-2-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]-1,2-benzisothiazole 1,1-dioxide (**18d**)

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 δ = 82.9–84.7 ppm, while for sultams **19** the signal for the new carbonyl group appeared instead at δ = 156.5–157.9 ppm. Characteristic chemical shifts of 3-H and OH groups of compounds **18** were found at δ = 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** were confirmed by X-ray crystal structure analyses (Figures 4–6).[19–21] Sultams **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-

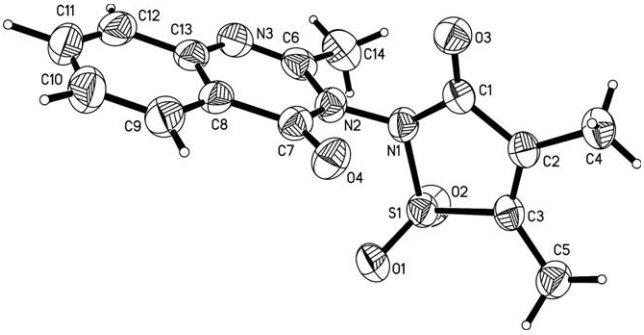


Figure 6 Molecular structure of 4,5-dimethyl-2-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]isothiazol-3(2*H*)-one 1,1-dioxide (**19b**)

der different reaction conditions either initial salts or decomposition products were isolated.

Compared to the ^{13}C NMR data of **12**,[16] the main diagnostic signals of the salts **10a**,**b**, **11a**,**c** were shifted to lower field. This can serve as further evidence for the difference in electrophilicity of the salts **12** and their acceptor substituted analogues **10**, **11**, and explain the reduced reactivity of **12** with nucleophilic reagents H_2O_2 and MMPP. The formation of decomposition products during the attempts to oxidize **12** might result from undesired N-oxidation reactions known for tertiary amines.[14,22]

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 IC_{50} 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-oxoquinazolin-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 ^{13}C NMR spectra were recorded at 300 or 400 MHz (^1H) and 75 or 100 MHz (^{13}C) with Varian Mercury Plus 300 or 400 NMR spectrometers in DMSO-d_6 or acetone-d_6 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 $HClO_4$ (0.4 mL) was added. After stirring for 50 min, the mixture was diluted with Et_2O (20 mL). The precipitate was collected by filtration, washed with Et_2O (3 ×) and air dried (for **10a**,**b**) or dried in vacuo (for **11a–d**). The salts **11a–d** are hygoscopic 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 (ClO_4) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.35 (s, 3 H, CH_3), 2.84 (s, 3 H, CH_3), 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).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.4 (CH_3), 15.0 (CH_3), 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).

MS (ESI): *m*/*z* = 259 $[M - ClO_4]^+$.

Anal. Calcd for $C_{13}H_{11}ClN_2O_6S$: C, 43.51; H, 3.07; N, 7.81; S, 8.93. Found: 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 (ClO_4) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.90 (m, 4 H, 2 CH_2), 2.90 (m, 2 H, CH_2), 3.28 (m, 2 H, CH_2), 8.08–8.21 (m, 4 H_{arom}), 9.36 (s, 1 H, CH).

^{13}C NMR (75 MHz, DMSO-d_6): 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), 175.2 (C-7a).

MS (ESI): *m*/*z* = 285 $[M - ClO_4]^+$.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_6S$: C, 46.82; H, 3.41; N, 7.28; S, 8.33. Found: C, 46.50; H, 3.55; N, 6.84; S, 7.87.

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

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

IR (KBr): 1713 (C=O), 1086 (ClO_4) cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 2.55 (s, 3 H, CH_3 at C-4), 3.08 (s, 3 H, CH_3 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′).

^{13}C NMR (75 MHz, acetone-d_6): δ = 10.5 (CH_3 at C-5), 13.8 (CH_3 at C-4), 120.3 (C-4a′), 120.7 (C-8′), 128.9 (C-5′), 131.8 (C-6′), 133.1 (C-4), 138.5 (C-7′), 152.1 (C-2′), 154.5 (C-8a′), 155.8 (C=O), 160.5 (C-3), 176.5 (C-5).

MS (ESI): *m*/*z* = 258 $[M - 2\ ClO_4 - H]^+$.

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

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

^1H NMR (300 MHz, acetone-d_6): δ = 1.87 (s, 3 H, CH_3 at C-2′), 2.32 (s, 3 H, CH_3 at C-4), 2.83 (s, 3 H, CH_3 at C-5) 7.60–8.70 (m, 5 H, 4 H_{arom} + NH), 9.42 (s, 1 H, H-3).

MS (ESI): m/z = 272 [M – 2 ClO_4 – H]$^+$.

4,5,6,7-Tetrahydro-2-[4-oxo-3(4*H*)-quinazolinyl]-1,2-benzisothiazolium Perchlorate (11c)
Yield: 407 mg (84%); yellow solid.

IR (KBr): 1731 (C=O), 1100 (ClO_4) cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 2.00 (m, 4 H, 2 CH_2), 3.03 (m, 2 H, CH_2), 3.47 (m, 2 H, CH_2), 8.00 (m, 1 H, H-6′), 8.10 (d, J = 9.0 Hz, 1 H, H-8′), 8.23 (m, 1 H, H-7′), 8.47 (d, J = 9.3 Hz, 1 H, H-5′), 9.47 (s, 1 H, H-3), 9.80 (s, 1 H, NH), 10.09 (s, 1 H, H-2′).

^{13}C NMR (75 MHz, acetone-d_6): δ = 21.9, 22.5, 23.8, 27.4 (C-4,5,6,7), 121.4 (C-4a′), 122.0 (C-8′), 129.7 (C-5′), 132.3 (C-6′), 133.0 (C-3a), 139.1 (C-7′), 151.8 (C-2′), 153.3 (C-8a′), 155.8 (C=O), 161.1 (C-3), 178.2 (C-7a).

MS (ESI): m/z = 284 [M – 2 ClO_4 – H]$^+$.

4,5,6,7-Tetrahydro-2-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]-1,2-benzisothiazolium Perchlorate (11d)
Yield: 483 mg (97%); yellow solid.

^{1}H NMR (200 MHz, DMSO-d_6: δ = 1.86 (m, 4 H, 2 CH_2), 2.39 (s, 3 H, CH_3 at C-2′), 2.84 (m, CH_2, CH_2), 3.25 (m, CH_2, CH_2), 7.60–8.18 (m, 5 H, 4 H_{arom} + NH), 9.4 (s, 1 H, H-3).

MS (ESI): m/z = 298 [M – 2 ClO_4 – H]$^+$.

2,3-Dihydro-3-hydroperoxy-2-(phthalimid-1-yl)isothiazole 1,1-Dioxides 13; General Procedure
H_2O_2 (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 H_2O (3–5 mL), and the colorless crystals of **13** were collected by filtration, and recrystallized from EtOH–H_2O.

2,3-Dihydro-3-hydroperoxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (13a)
Yield: 115 mg (51%); white solid; mp 215–217 °C.

IR (KBr): 1180 (SO_2), 1323 (SO_2), 1736 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.07 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 5.99 (s, 1 H, H-3), 7.99 (m, 4 H_{arom}), 11.68 (s, 1 H, OOH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 7.4 (CH_3), 11.8 (CH_3), 94.1 (C-3), 124.0 (CH_{arom}), 124.2 (arom. CH), 129.0 (C_{arom}), 130.0 (C_{arom}), 133.6 (C-4), 135.7 (2 CH_{arom}), 137.9 (C-5), 164.8 (C=O), 165.4 (C=O).

MS (EI): m/z = 324 [M]$^+$.

Anal. Calcd for $C_{13}H_{12}N_2O_6S$: C, 48.15; H, 3.73; N, 8.64; S, 9.89. Found: C, 48.10; H, 3.85; N, 8.60; S, 9.89.

2,3,4,5,6,7-Hexahydro-3-hydroperoxy-2-(phthalimid-1-yl)-1,2-benzisothiazole 1,1-Dioxide (13b)
Yield: 108 mg (44%); white solid; mp 184–187 °C.

IR (KBr): 1173 (SO_2), 1323 (SO_2), 1741 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 1.85 (m, 4 H, 2 CH_2), 2.47 (m, 4 H, 2 CH_2), 6.04 (s, 1 H, H-3), 7.98 (m, 4 H_{arom}), 11.46 (s, 1 H, OOH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 20.3 (CH_2), 22.2 (2 CH_2), 24.6 (CH_2), 95.0 (C-3), 125.3 (CH_{arom}), 125.5 (CH_{arom}), 131.1 (C_{arom}), 131.3 (C_{arom}), 137.0 (2 CH_{arom}), 137.6 (C-3a), 142.5 (C-7a), 166.2 (C=O), 166.9 (C=O).

MS (EI): m/z = 350 [M]$^+$.

Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00; S, 9.15. Found: C, 51.27; H, 3.69; N, 7.88; S, 9.33.

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 H_2O (2 mL), and air dried.

3-Hydroxysultams 14 by MMPP Oxidation of Isothiazolium Salts 10; 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 $NaHCO_3$ (5 mL) was added, the mixture extracted with Et_2O (3 × 25 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated and the respective product **14** was purified by recrystallization from EtOH–H_2O.

2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-(phthalimid-1-yl)isothiazole 1,1-Dioxide (14a)
Yield: 60 mg (98%) (from **13a**); 54 mg (41%) (from **10a**); white solid; mp 198–200 °C.

IR (KBr): 1752 (C=O), 1307 (SO_2), 1180 (SO_2) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.94 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 5.73 (s, 1 H, 3-H), 7.21 (s, 1 H, OH), 7.95–8.01 (m, 4 H_{arom}).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 7.4 (CH_3), 12.0 (CH_3), 83.7 (C-3), 123.9 (2 CH_{arom}), 129.0 (C_{arom}), 129.2 (C_{arom}), 129.6 (C-5), 135.6 (2 CH_{arom}), 141.8 (C-4), 164.6 (C=O), 164.8 (C=O).

MS (ESI): m/z = 331 [M + Na]$^+$.

Anal. Calcd for $C_{13}H_{12}N_2O_5S$: C, 50.64; H, 3.92; N, 9.09; S, 10.40. Found: C, 50.35; H, 3.98; N, 9.00; S, 10.47.

2,3,4,5,6,7-Hexahydro-3-hydroxy-2-(phthalimid-1-yl)-1,2-benzisothiazole 1,1-Dioxide (14b)
Yield: 62 mg (93%) (from **13b**); 72 mg (36%) (from **10b**); white solid; mp 185–187 °C.

IR (KBr): 1747 (C=O), 1283 (SO_2), 1139 (SO_2) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.82 (m, 4 H, 2 CH_2), 2.04 (m, 2 H, CH_2), 2.42 (m, 2 H, CH_2), 5.89 (s, 1 H, CH), 6.16 (s, 1 H, OH), 7.84 (m, 2 H_{arom}), 7.95 (m, 2 H_{arom}).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.1 (CH_2), 22.3 (2 CH_2), 24.3 (CH_2), 85.8 (C-3), 124.4 (2 CH_{arom}, 3′, 6′), 131.3 (C-7a), 135.7 (2 CH_{arom}, 4′, 5′), 136.7 (2 C_{arom}, 2a′,6a′), 145.6 (C-3a), 160.3 (2 C=O).

MS (ESI): m/z = 357 [M + Na]$^+$.

Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38; S, 9.59. Found: C, 53.70; H, 4.16; N, 8.61; S, 9.68.

3-Oxosultams 15 from Isothiazolium Salts 10; General Procedure
H_2O_2 (2.8 mL, 30%) was added at r.t. to a stirred suspension of **10** (0.7 mmol) in AcOH (4.2 mL). The solution was stirred for 18–20 h at 80 °C. After cooling, the product was isolated by filtration. In case when no precipitate was formed, H_2O and AcOH were removed in vacuum, cold H_2O (3 mL) was added to the mixture and the solid was isolated and recrystallized from EtOH–H_2O.

3-Oxosultams 15 from 3-Hydroxysultams 14; General Procedure
To a stirred solution of 3-hydroxysultam **14** (0.25 mmol) in CH_2Cl_2 (2 mL) was added $(pyH)_2Cr_2O_7$ (0.63 mmol) at r.t. The mixture was stirred 8 h and the product purified by column chromatography using EtOAc as eluent to give **15** as colorless crystals.

4,5-Dimethyl-2-(phthalimid-1-yl)isothiazol-3(2*H*)-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 (SO_2), 1161 (SO_2) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.18 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 7.85 (m, 2 H_{arom}), 8.06 (m, 2 H_{arom}).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 8.4 (CH_3 at C-5), 9.3 (CH_3 at C-4), 124.8 (2 CH_{arom}), 128.8 (2 C_{arom}), 133.3 (C-4), 136.3 (2 CH_{arom}), 144.6 (C-5), 158.7 (C=O), 162.7 (2 C=O).

MS (EI): *m*/*z* = 306 $[M]^+$.

Anal. Calcd for $C_{13}H_{10}N_2O_5S$: C, 50.98; H, 3.29; N, 9.15; S, 10.47. Found: C, 50.45; H, 3.39; N, 9.10; S, 10.61.

4,5,6,7-Tetrahydro-2-(phthalimid-1-yl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (15b)

Yield: 95 mg (41%) (from **10b**), 68 mg (82%) (from **14b**); white solid; mp 185–187 °C.

IR (KBr): 1751 (C=O), 1307 (SO_2), 1177 (SO_2) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.91 (m, 2 H, CH_2), 1.98 (m, 2 H, CH_2), 2.58 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 7.88 (m, 2 H_{arom}), 8.07 (m, 2 H_{arom}).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.9 (CH_2), 19.7 (CH_2), 20.2 (2 CH_2), 124.7 (2 CH_{arom}), 128.8 (2 C_{arom}), 134.8 (C-4), 136.22 (2 CH_{arom}), 147.4 (C-5), 157.8 (C=O), 162.8 (2 C=O).

MS (EI): *m*/*z* = 332 $[M]^+$.

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43; S, 9.65. Found: C, 54.29; H, 3.58; N, 8.47; S, 9.64.

2,3-Dihydro-3-hydroperoxy-4,5-dimethyl-2-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]isothiazole 1,1-Dioxide (16b)

H_2O_2 (2.8 mL, 30%) was added at r.t. to a stirred suspension of **11b** (0.7 mmol) in AcOH (4.2 mL). After 48 h, H_2O and AcOH were removed in vacuum and the residue was washed with a mixture of H_2O–EtOH (3 mL, 2:3) to give a white precipitate; yield: 73 mg (31%); white solid; mp 108–111 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.15 (s, 3 H, CH_3), 2.72 (s, 3 H, CH_3), 2.81 (s, 3 H, CH_3), 6.12 (s, 1 H, H-3), 7.52 (m, 1 H_{arom}, H-6′), 7.63 (d, *J* = 8.6 Hz, 1 H_{arom}, H-8′), 7.87 (m, 1 H_{arom}, H-7′), 8.13 (d, *J* = 8.8 Hz, 1 H_{arom}, H-5′), 11.74 (s, 1 H, OOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 7.4 (CH_3), 11.9 (CH_3), 22.0 (CH_3 at C-2′), 93.9 (C-3), 121.8 (C-4a′), 126.8 (C-5′), 127.1 (C-8′), 127.5 (C-6′), 133.5 (C-4), 135.3 (C-7′), 137.5 (C-5), 146.1 (C-8a′), 157.8 (C-2′), 159.5 (C=O).

MS (EI): *m*/*z* = 337 $[M]^+$.

Anal. Calcd for $C_{14}H_{15}N_3O_5S$: C, 49.85; H, 4.48; N, 12.46; S, 9.50. Found: C, 49.11; H, 4.23; N, 12.61; S, 9.08.

4,5-Dimethyl-2-[*N*-(2-nitro)benzamidyl]isothiazol-3(2*H*)-one 1,1-Dioxide (17)

H_2O_2 (2.8 mL, 30%) was added at r.t. to a stirred suspension of **11b** (0.7 mmol) in AcOH (4.2 mL). The solution was stirred for 18–20 h at 80 °C. After cooling, H_2O and AcOH were removed in vacuum. Cold H_2O (3 mL) was added to the residue and the precipitated solid was isolated and recrystallized from EtOH–H_2O; yield: 64 mg (28%); white solid; mp 242–244 °C.

IR (KBr): 1758 (C=O), 1690 (C=O), 1533 (NO_2), 1351 (NO_2), 1329 (SO_2), 1186 (SO_2) cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 2.12 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 7.85–7.82 (m, 2 H_{arom}), 7.91 (d, *J* = 8 Hz, 1 H_{arom}), 8.16 (d, *J* = 8 Hz, 1 H_{arom}), 10.40 (s, 1 H, NH).

^{13}C NMR (75 MHz, acetone-d_6): δ = 7.7 (CH_3), 8.6 (CH_3), 129.4 (C_{arom}), 129.8 (CH_{arom}), 129.9 (CH_{arom}), 132.4 (CH_{arom}), 133.1 (C-4), 134.1 (CH_{arom}), 143.3 (CNO_2), 147.7 (C-5), 159.3 (C-3), 164.5 (C=O).

MS (EI): *m*/*z* = 325 $[M]^+$.

Anal. Calcd for $C_{12}H_{11}N_3O_6S$: C, 44.31; H, 3.41; N, 12.92; S, 9.86. Found: C, 43.89; H, 3.56; N, 12.81; S, 10.04.

2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-[2-methyl-4-oxo-3(4*H*)-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 H_2O (2 mL) and air dried.

3-Hydroxy-2-[4-oxo-3(4*H*)-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 MMPP (1.336 g, 2.7 mmol) and the mixture was stirred during 16 h at r.t. Then, sat. aq $NaHCO_3$ (5 mL) was added to the mixture and it was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried ($MgSO_4$). The solvent was evaporated and the products **18** were purified by recrystallization from EtOH–H_2O.

2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-[4-oxo-3(4*H*)-quinazolinyl]isothiazole 1,1-Dioxide (18a)

Yield: 91 mg (33%) (from **11a**); white solid; mp 220–223 °C.

IR (KBr): 1714 (C=O), 1613 (C=N), 1325 (SO_2), 1178 (SO_2) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.98 (s, 3 H, CH_3 at C-4), 2.07 (s, 3 H, CH_3 at C-5), 5.84 (s, 1 H, H-3), 7.40 (s, 1 H, OH), 7.64 (m, 1 H_{arom}, H-6′), 7.76 (m, 1 H_{arom}, H-8′), 7.92 (m, 1 H_{arom}, H-7′), 8.17 (m, 1 H_{arom}, H-5′), 8.19 (s, 1 H, H-2′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 7.3 (CH_3 at C-5), 12.2 (CH_3 at C-4), 83.2 (C-3), 122.2 (C-4a′), 126.6 (C-5′), 127.7 (C-8′), 128.1 (C-6′), 129.4 (C-5), 135.5 (C-7′), 141.5 (C-4), 146.5 (C-8a′), 149.3 (C-2′), 158.6 (C=O).

MS (EI): *m*/*z* = 307 $[M]^+$.

Anal. Calcd for $C_{13}H_{13}N_3O_4S$: C, 50.81; H, 4.26; N, 13.67; S, 10.43. Found: C, 50.69; H, 4.35; N, 13.65; S, 10.47.

2,3-Dihydro-3-hydroxy-4,5-dimethyl-2-[2-methyl-4-oxo-3(4*H*)-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=N), 1315 (SO_2), 1173 (SO_2) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.05 (s, 3 H, CH_3 at C-4), 2.05 (s, 3 H, CH_3 at C-5), 2.64 (s, 3 H, CH_3 at C-2′), 5.87 (d, *J* = 4.8 Hz, 1 H, H-3), 7.30 (d, *J* = 6.6 Hz, 1 H, OH), 7.54 (m, 1 H_{arom}, H-6′), 7.66 (m, 1 H_{arom}, H-8′), 7.87 (m, 1 H_{arom}, H-7′), 8.08 (m, 1 H_{arom}, H-5′).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 7.4 (CH_3 at C-5), 12.2 (CH_3 at C-4), 22.0 (CH_3 at C-2′), 83.7 (C-3), 121.1 (C-4a′), 126.5 (C-5′), 127.1 (C-8′), 127.2 (C-6′), 129.6 (C-5), 135.5 (C-7′), 141.5 (C-4), 146.1 (C-8a′), 157.7 (C-2′), 159.0 (C=O).

MS (EI): *m*/*z* = 321 $[M]^+$.

Anal. Calcd for $C_{14}H_{15}N_3O_4S$: 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.

2,3,4,5,6,7-Hexahydro-3-hydroxy-2-[4-oxo-3(4*H*)-quinazolinyl]-1,2-benzisothiazole 1,1-Dioxide (18c)

Yield: 48 mg (16%) (from **11c**); white solid; mp 217–220 °C.

IR (KBr): 1674 (C=O), 1609 (C=N), 1308 (SO_2), 1182 (SO_2) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.75 (m, 4 H, 2 CH_2), 2.38 (m, 2 H, CH_2), 2.48 (m, 2 H, CH_2), 5.89 (d, *J* = 6.8 Hz, 1 H, H-3), 7.39 (d, *J* = 7.2 Hz, 1 H, OH), 7.61 (m, 1 H_{arom}, H-6′), 7.72 (m, 1 H_{arom}, H-8′), 7.91 (m, 1 H_{arom}, H-7′), 8.16 (m, 1 H_{arom}, H-5′), 8.22 (s, 1 H, H-2′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.17, 21.5, 20.6, 22.7 (4 CH_2), 82.9 (C-3), 122.0 (C-4a′), 126.4 (C-5′), 127.7 (C-8′), 128.1 (C-6′), 132.2 (C-7a), 135.0 (C-7′), 144.6 (C-3a), 147.2 (C-8a′), 150.0 (C-2′), 158.5 (C=O).

MS (EI): *m*/*z* = 333 $[M]^+$.

Anal. Calcd for $C_{15}H_{15}N_3O_4S$: C, 54.04; H, 4.54; N, 12.60; S, 9.62. Found: C, 54.18; H, 4.52; N, 12.67; S, 9.68.

2,3,4,5,6,7-Hexahydro-3-hydroxy-2-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]-1,2-benzisothiazole 1,1-Dioxide (18d)

Yield: 50 mg (16%) (from **11d**); white solid; mp 233–235 °C.

IR (KBr): 1691 (C=O), 1609 (C=N), 1314 (SO_2), 1173 (SO_2) cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 1.83 (m, 2 H, CH_2), 2.36 (m, 2 H, CH_2), 2.70 (s, 3 H, CH_3 at C-2′), 2.90 (m, 4 H, 2 CH_2), 6.07 (d, *J* = 7.5 Hz, 1 H, H-3), 6.48 (d, *J* = 8.1 Hz, 1 H, OH), 7.51 (m, 1 H_{arom}, H-6′), 7.64 (d, *J* = 8.33 Hz, 1 H_{arom}, H-8′), 7.87 (m, 1 H_{arom}, H-7′), 8.13 (d, *J* = 9.0 Hz, 1 H_{arom}, H-5′).

^{13}C NMR (75 MHz, acetone-d_6): δ = 19.4 (CH_2), 21.7 (CH_3), 21.9 (3 CH_2), 22.7, 23.7, 84.7 (C-3), 122.6 (C-4a′), 127.4 (C-5′), 127.7 (C-8′), 128.2 (C-6′), 134.2 (C-7a), 135.9 (C-7′), 144.8 (C-3a), 147.6 (C-8a′), 158.8 (C-2′), 160.3 (C=O).

MS (EI): *m*/*z* = 347 $[M]^+$.

Anal. Calcd for $C_{16}H_{17}N_3O_4S$: C, 55.32; H, 4.93; N, 12.10; S, 9.23. Found: C, 55.61; H, 4.79; N, 12.16; S, 9.20.

2-[4-Oxo-3(4*H*)-quinazolinyl]isothiazol-3(2*H*)-one 1,1-Dioxides 19; General Procedure

To a stirred solution of 3-hydroxysultam **18** (0.25 mmol) in CH_2Cl_2 (2 mL) was added $(pyH)_2Cr_2O_7$ (0.63 mmol) at r.t. The mixture was stirred 8 h and purified by column chromatography using EtOAc as eluent. After removal of the solvent, the colorless crystals were washed with EtOH (2 mL) and collected by filtration.

4,5-Dimethyl-2-[4-oxo-3(4*H*)-quinazolinyl]isothiazol-3(2*H*)-one 1,1-Dioxide (19a)

Yield: 67 mg (88%); white solid; mp 188–190 °C.

IR (KBr): 1756 (C=O), 1712 (C=O), 1605 (C=N), 1347 (SO_2), 1180 (SO_2) cm^{-1}.

^1H NMR (300 MHz, acetone-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′)

^{13}C 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-8a′), 146.4 (C-5), 147.1 (C-2a′), 156.5 (C=O), 158.7 (C=O).

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

Anal. Calcd for $C_{13}H_{11}N_3O_4S$: C, 51.14; H, 3.63; N, 13.76; S 10.50. Found: C, 50.85; H, 3.51; N, 13.49; S, 10.36.

4,5-Dimethyl-2-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]isothiazol-3(2*H*)-one 1,1-Dioxide 19b

Yield: 57 mg (71%); white solid; mp 205–208 °C.

IR (KBr): 1758 (C=O), 1708 (C=O), 1608 (C=N), 1342 (SO_2), 1176 (SO_2) cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 2.43 (s, 3 H, CH_3 at C-4), 2.61 (s, 3 H, CH_3 at C-5), 2.87 (s, 3 H, CH_3 at C-2′), 7.57 (d, *J* = 8 Hz, 1 H_{arom}), 7.70 (m, 1 H_{arom}), 7.92 (m, 1 H_{arom}), 8.16 (d, *J* = 8 Hz, 1 H_{arom}).

^{13}C NMR (75 MHz, acetone-d_6): δ = 8.6 (CH_3 at C-5), 9.5 (CH_3 at C-4), 21.7 (CH_3 at C-2′), 121.5 (C-4a′), 127.8 (C-5′), 128.4 (C-8′), 128.6 (C-6′), 134.6 (C-4), 136.6 (C-7′), 145.2 (C-8a′), 147.4 (C-5), 156.1 (C-2a′), 157.8 (C=O), 160.4 (C=O).

MS (EI): *m*/*z* = 319.1 $[M]^+$.

Anal. Calcd for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.10; N, 13.16; S, 10.04. Found: C, 52.28; H, 4.11; N, 13.31; S, 10.20.

4,5,6,7-Tetrahydro-2-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide 19d

Yield: 63 mg (73%); white solid; mp 135–137 °C.

IR (KBr): 1765 (C=O), 1702 (C=O), 1612 (C=N), 1238 (SO_2), 1173 (SO_2) cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 1.9 (m, 2 H, CH_2), 1.98 (m, 2 H, CH_2), 2.58 (m, 2 H, CH_2), 2.61 (s, 3 H, CH_3 at C-2′), 2.72 (m, 2 H, CH_2), 7.58 (d, *J* = 8 Hz, 1 H_{arom}), 7.70 (m, 1 H_{arom}), 7.91 (m, 1 H_{arom}), 8.16 (d, *J* = 8 Hz, 1 H_{arom}).

^{13}C NMR (100 MHz, acetone-d_6): δ = 19.9 (CH_2), 20.9 (CH_2), 21.2 (CH_2), 21.3 (CH_3 at C-2′), 21.7 (CH_2), 121.5 (C-4a′), 127.8 (C-5′), 128.4 (C-8′), 128.6 (C-6′), 136.6 (C-7′), 137.4 (C-3a), 147.4 (C-8a′), 148.2 (C-7a), 156.2 (C-2a′), 157.9 (C=O), 159.7 (C=O).

MS (EI): *m*/*z* = 345.1 $[M]^+$.

Anal. Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17; S, 9.28. Found: C, 55.37; H, 4.51; N, 12.01; S, 9.33.

X-ray Crystal Structure Analysis

Crystals of compounds **15a**, **18b**, **19d** were obtained from acetone-d_6. The intensities were measured on an IPDS1 diffractometer (STOE). The structures were solved by direct methods, and refinement was performed with SHELX-97.[23,24]

Enzyme Inhibition

Acetyl cholinesterase from *Electrophorus electricus* was assayed spectrophotometrically at 412 nm at 25 °C in duplicate experiments.[25,26] Assay buffer was 100 mM Na_3PO_4 in 100 mM NaCl, pH 7.3. Acetyl thiocholine (ATCh) (10 mM) and 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) (7 mM) were dissolved in the assay buffer. Stock solutions of the inhibitors were prepared in MeCN. Into a cuvette containing 825 μL of assay buffer were added 50 μL of the DTNB solution, 55 μL MeCN, 10 μL of an inhibitor solution, and 10 μL of an enzyme solution (~3 U/mL), and the contents were thoroughly mixed. After incubation for 15 min at 25 °C, the reaction was initiated by adding 50 μL of the ATCh solution and was followed over 5 min. IC_{50} values were calculated from the linear steady-state turnover of the substrate using the four-parametric logistic equation. Compounds **13a** and **13b** were measured at six different concentrations between 5 and 30 μM.

Human leukocyte elastase (HLE) was assayed spectrophotometrically at 405 nm at 25 °C in duplicate experiments.[13] Assay buffer was 50 mM sodium phosphate buffer in 500 mM NaCl, pH 7.8. Inhibitor stock solutions were prepared in DMSO. A stock solution of the chromogenic substrate MeOSuc-Ala-Ala-Pro-ValpNA was prepared in DMSO and diluted with assay buffer. Final concentration of the chromogenic substrate MeOSuc-Ala-Ala-Pro-ValpNA was 100 μM, final concentration of DMSO was 1.5%. Assays were performed with a final HLE concentration of 50 ng/mL. Into a cuvette containing 890 μL of assay buffer were added 10 μL of an inhibitor solution, 50 μL of the substrate solution, and the contents were thoroughly mixed. The reaction was initiated by adding 50 μL of the HLE solution and was followed over 10 min.

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(19) Crystal data for **15a**: $C_{13}H_{16}N_2O_5S$; M = 306,3: T = 213 (2) K; λ = 0.71073 Å; Colorless prism; 0.3 × 0.3 × 0.2 mm^3; Triclinic; space group P–1; Unit cell dimensions a = 8.030 (2) Å, b = 8.624 (3) Å, c = 10.148 (2) Å, α = 86.81 (2)°, β = 76.02 (2)°, γ = 77.43 (2)°, V = 665.6 (3) Å^3, Z = 2, D_{calcd} = 1.528 gcm^{-3}; F(000) = 316, μ = 0.267 mm^{-1}; Theta range for data collection 2.4° to 28.2°; Index ranges $-10 \le h \le 10, -11 \le k \le 11, -13 \le l \le 13$; Reflections collected 6555; Independent reflections 2997 [R_{int} = 0.052]; Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0463, $wR2$ = 0.0626; R indices (all data) $R1$ = 0.0626, $wR2$ = 0.1283; Largest diff. Peak/hole 0.335/–0.471 e Å^{-3}.

(20) Crystal data for **18d**: $C_{16}H_{17}N_3O_4S \cdot H_2O$; M = 365.4; T = 213 (2) K; λ = 0.71073 Å; Colorless prism; 0.2 × 0.2 × 0.2 mm^3; Triclinic; Space group P–1; Unit cell dimensions a = 8.163 (2) Å, b = 8.906 (2) Å, c = 11.862 (4) Å, α = 83.76 (2)°, β = 87.82 (2)°, γ = 81.28 (2)°, V = 847.1 (4) Å^3, Z = 2, D_{calcd} = 1.433 gcm^{-3}; F(000) = 384, μ = 0.224 mm^{-1}; Theta range for data collection 2.5° to 28.1°; Index ranges $-10 \le h \le 10, -11 \le k \le 11, -15 \le l \le 15$; Reflections collected 8243; Independent reflections 3779 [R_{int} = 0.033]; Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0363, $wR2$ = 0.0982; R indices (all data) $R1$ = 0.0463, $wR2$ = 0.1018; Largest diff. Peak/hole 0.262/–0.266 e Å^{-3}.

(21) Crystal data for **19b**: $C_{14}H_{13}N_3O_4S$; M = 319.3; T = 213 (2) K; λ = 0.71073 Å; Colorless prism; 0.3 × 0.2 × 0.2 mm^3; Orthorhombic; Space group $Pna2_1$; Unit cell dimensions a = 10.811 (1) Å, b = 12.632 (1) Å, c = 10.654 (1) Å, V = 1455.0(2) Å^3, Z = 4, D_{calcd} = 1.458 gcm^{-3}; F(000) = 664, μ = 0.245 mm^{-1}; Theta range for data collection 2.5° to 26.0°; Index ranges $-13 \le h \le 13, -15 \le k \le 15, -13 \le l \le 13$; Reflections collected 10986; Independent reflections 2828 [R_{int} = 0.038]; Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0259, $wR2$ = 0.0673; R indices (all data) $R1$ = 0.0281, $wR2$ = 0.0681; Largest diff. Peak/hole 0.183/–0.136 e Å^{-3}.

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(24) The details of the structure analyses for compounds **15a**, **18d**, and **19b** have been deposited at the Cambridge Crystallographic Data Centre with the numbers CCDC-651832, -651831 and -651833, respectively. The copies of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge, CB2 1EZ UK (fax: +44 1233 336033; e-Mail: deposit@ccdc.cam.ac.uk, internet: http://www.ccdc.cam.ac.uk).

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