# Synthesis of Pyrazole, Isoxazole, and Aminopyrimidine Ring-Fused Benzothiocycloheptane-Derived Oxazolidinones and Their Corresponding Sulfone Derivatives

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**Abstract:** The synthesis of a series of pyrazole, isoxazole, and aminopyrimidine ring-fused benzothiocycloheptane-derived oxazolidinones and their corresponding sulfone derivatives is described.

**Key words:** antibiotics, heterocycles, fused-ring systems, oxazolidinones, bezothiocycloheptanone

There is an ongoing need to synthesize new and improved antibiotics since bacteria develop fascinating mechanisms of resistance for the existing antibiotics. Many common Gram-positive pathogens (e.g., *Staphylococcus aureus*, *Enterococcus* spp., and *Streptococcus pneumoniae*) have become increasingly resistant to antimicrobial agents, and new drugs with activity against Gram-positive bacteria are urgently needed.[1] Oxazolidinones are synthetic antibacterial agents having a novel mechanism of action that involves inhibition of bacterial protein synthesis at a very early stage, prior to chain initiation. Oxazolidinones, as exemplified by linezolid (**1**) possess excellent activity against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), and Vancomycin-resistant enterococci (VRE).[2] Strong interest in this quickly evolving area is expressed in recent publications from several research groups.[3] In our previous report,[4] we described benzocycloheptanone-derived oxazolidinone **2**, which displayed activity against Gram-positive organisms (Figure 1).

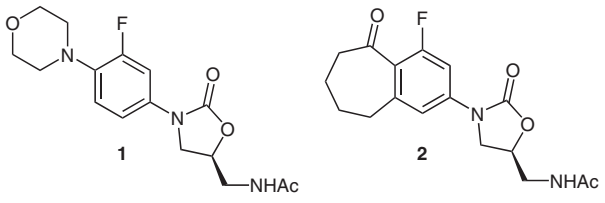


**Figure 1** Antibacterial oxazolidinones **1** and **2**

In our continued search for an oxazolidinone with broad spectrum of activity, our initial focus was to incorporate a sulfur (–S–) atom in the cycloheptanone ring of desfluoro analogue of compound **2**. In the course of our research we also investigated the influence of the oxidation state of sulfur by oxidizing to the corresponding sulfone. As further extension of the program, using compounds **9** and **10** as building blocks, we also became interested in building several heterocyclic rings such as pyrazole, isoxazole, and aminopyrimidine on the backbone of the benzothiocycloheptanone ring of compound **9** and on its sulfone analogue **10**. In this paper, we wish to report the synthesis of a series of heterocyclic-ring-fused bezothiocycloheptane derived oxazolidinones **12**, **13** and the sulfone derivatives **15**, **16**, and **17**. (*S*)-*N*-[2-Oxo-3-(1-oxo-1,2,4,5-tetrahydrobenzo[*d*]thiepin-7-yl)oxazolidin-5-ylmethyl]acetamide (**9**) and the corresponding sulfone (*S*)-*N*-[2-oxo-3-(1,3,3-trioxo-2,3,4,5-tetrahydro-1*H*-3λ$^6$-benzo[*d*]thiepin-7-yl)oxazolidin-5-ylmethyl]acetamide (**10**) were synthesized as shown in the reaction sequence reported in Scheme 1.[5]

Reaction of 3-aminophenylacetic acid (**3**) with ethyl chloroformate in the presence of aqueous NaOH gave the desired carbamate **4** in 96% yield. Subsequent reduction of the carboxylic acid with sodium borohydride in the presence of iodine in anhydrous THF furnished intermediate alcohol **5** in good yield.[6] The preparation of the mesylate **6** was carried out by stirring **5** in ethyl acetate with mesyl chloride and triethylamine as base in 90% yield, and subsequent displacement of mesylate with mercaptoacetic acid was performed in DMF in the presence of triethylamine and a stoichiometric amount of sodium iodide at 60 °C to give **7**. Alternative procedure for the preparation of **7** via the corresponding bromide instead of the mesylate **6** can also be done, but we found the mesylate route to be more convenient. Several attempts of direct cyclization of **7** to **8** in the presence of the Eaton's reagent were unsuccessful. However, the preparation of compound **8** was accomplished in good yield via a two-step and one-pot procedure. Thus, the compound **7** on treatment with thionyl chloride in dichloromethane and a catalytic amount of DMF furnished the acid chloride intermediate. After evaporation of the volatiles, the acid chloride on treatment with two molar equivalents of anhydrous aluminum chloride in dichloromethane furnished compound **8**. Next, the oxazolidinone ring formation was accomplished in a single step from compound **8** using the procedure reported by Perrault et al.[7] The carbamate **8** on treatment with (*S*)-*N*-(2-acetoxy-3-chloropropyl)acetamide in a mixture of anhydrous methanol and DMF in the presence

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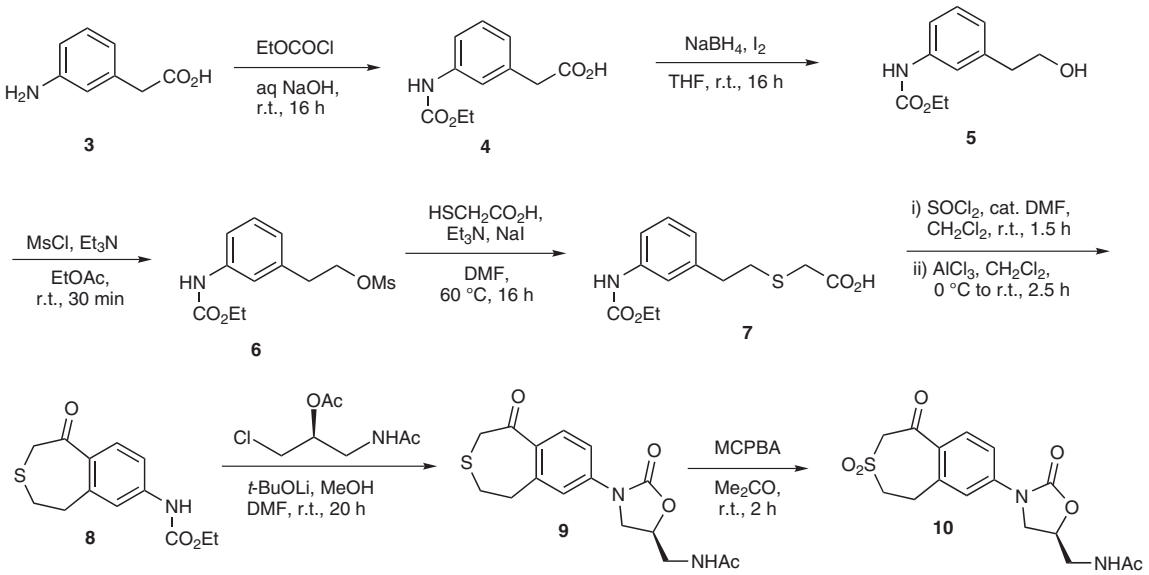
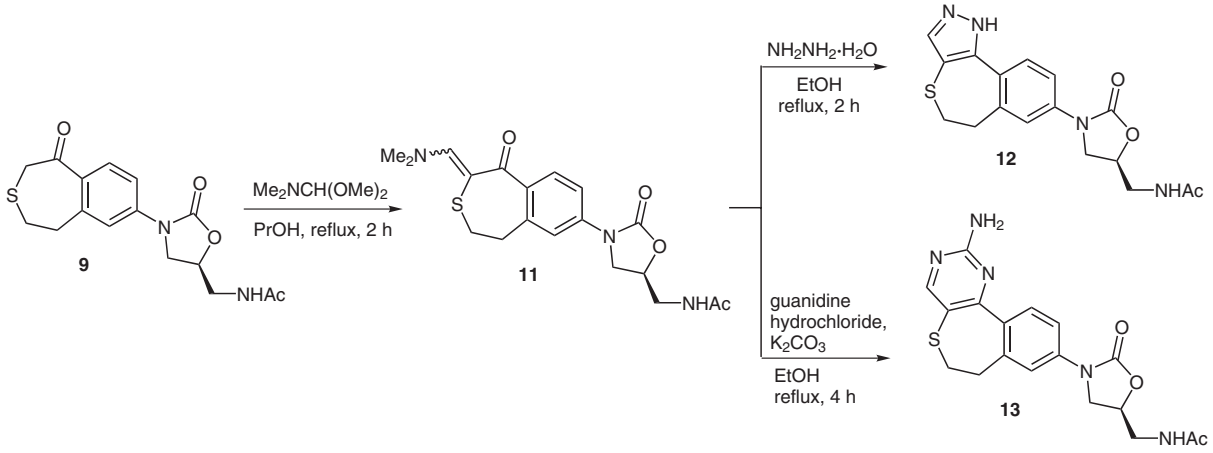


Scheme 1

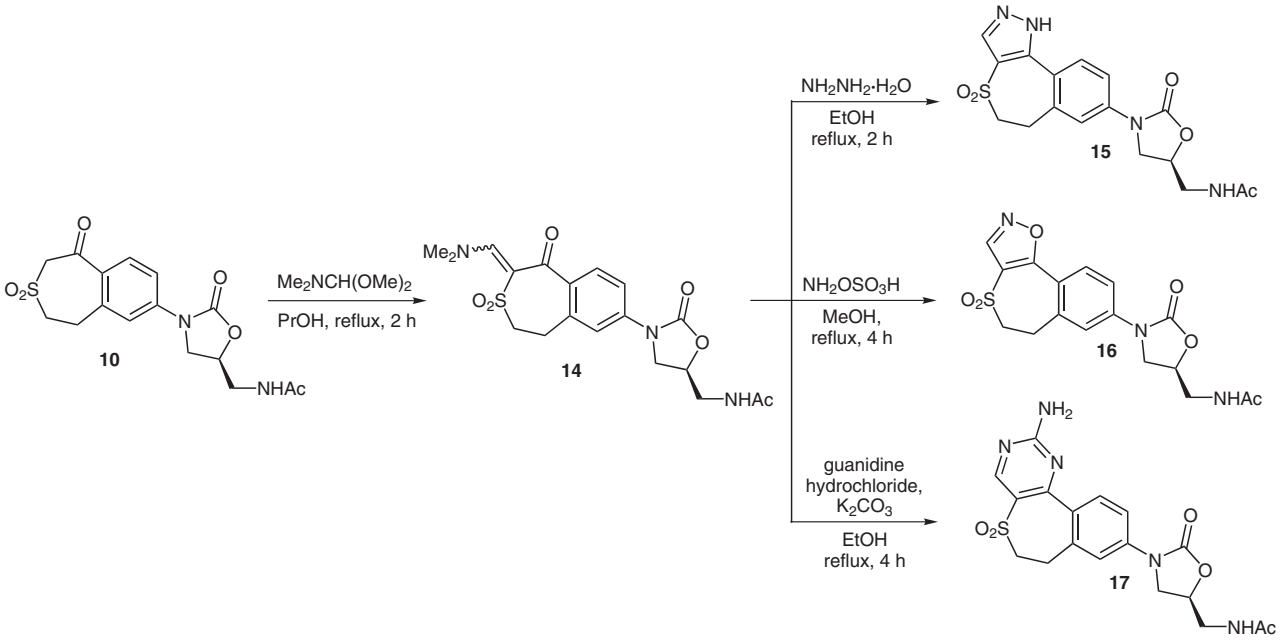
of lithium *tert*-butoxide gave the desired oxazolidinone **9** in 17% yield (not optimized). Although the reasons for the low yield in construction of oxazolidinone ring in **9** have not been carefully investigated, one can speculate that the presence of a relatively acidic proton between carbonyl group and sulfur atom could be a factor. The sulfide **9** was oxidized with MCPBA in acetone to the corresponding sulfone **10**.

The dimethylaminomethylene precursor **11** required for the synthesis of the target oxazolidinones **12** and **13** (Scheme 2) was obtained from the condensation of **9** with dimethylformamide dimethylacetal in 57% yield by refluxing in *n*-propanol. By applying the same reaction conditions as for the synthesis of compound **11**, compound **14** was obtained (Scheme 3) in almost quantitative yield, which was not surprising considering the much higher acidity of the methylene protons in **10**. Compounds **11** and **14** were then refluxed with hydrazine hydrate in ethanol to achieve the desired pyrazole-fused benzothiocycloheptane-derived oxazolidinones **12** and **15**, respectively, in excellent yields. The synthesis of aminopyrimidine-derived oxazolidinones **13** and **17** started from the same dimethylaminomethylene precursors **11** and **14**, which were treated with guanidine hydrochloride in the presence of potassium carbonate in refluxing ethanol. Finally, the isoxazole derivative **16** was synthesized in 53% yield from **14** by heating with hydroxylamine-*O*-sulfonic acid in methanol (Scheme 3). On the contrary, the similar isoxazole derivative from sulfide **11** appeared to be quite unstable, and even at room temperature the isoxazole ring underwent ring opening with formation of the corresponding cyano ketone. Therefore, we were unable to isolate the desired isoxazole ring-fused benzothiocycloheptane-derived oxazolidinone in pure form. It should also be noted that all the prepared oxazolidinones had poor solubility in common organic solvents, which made their purification very difficult.

In conclusion, (*S*)-*N*-[2-oxo-3-(1-oxo-1,2,4,5-tetrahydrobenzo[*d*]thiepin-7-yl)oxazolidin-5-ylmethyl]acetamide (**9**) has been synthesized in six steps and its sulfone ana-



Scheme 2




**Scheme 3**

logue (*S*)-*N*-[2-Oxo-3-(1,3,3-trioxo-2,3,4,5-tetrahydro-1*H*-3λ⁶-benzo[*d*]thiepin-7-yl)oxazolidin-5-ylmethyl]acetamide (**10**) in seven steps. Using these oxazolidinones **9** and **10** as key building blocks, the desired pyrazole-fused, isoxazole-fused, and aminopyrimidine-fused benzothiocycloheptane-derived oxazolidinones and their corresponding sulfone analogues have been synthesized in two steps. The biological evaluation of these oxazolidinone derivatives will be described elsewhere.

The melting points were measured on Electrothermal digital melting point apparatus and are not corrected. The $^1$H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ or DMSO-$d_6$ with Varian Mercury 400 MHz NMR spectrometer. Mass spectra were determined using Waters Micromass ZQ with electrospray ionization sources. Combustion analyses were performed on Costech ECS 4010 elemental analyzer. Column chromatography was performed using Merck Kieselgel 60 (230–400 mesh). THF was dried and distilled under $N_2$ prior to use.

**(3-Ethoxycarbonylaminophenyl)acetic Acid (4)**

To a solution of (3-aminophenyl)acetic acid (**3**; 10.6 g, 70.1 mmol) in aq 2 N NaOH (80 mL), cooled in an ice bath was added dropwise ethyl chloroformate (8.37 g, 77.1 mmol). The cooling bath was removed and the stirring was continued for 16 h at r.t. The mixture was washed with $Et_2O$ (2 × 50 mL), the aqueous layer was separated, acidified with HCl, and the mixture was extracted with EtOAc (3 × 50 mL). The EtOAc extracts were washed with brine (50 mL), dried ($Na_2SO_4$), and evaporated to give **4**; pale yellow oil, which crystallized on standing to give a low-melting waxy solid; yield: 15.1 g (96%).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 3.62 (s, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 6.71 (br s, 1 H), 6.97 (d, *J* = 7.1 Hz, 1 H), 7.22–7.36 (m, 3 H), 11.35 (br s, 1 H).

**[3-(2-Hydroxyethyl)phenyl]carbamic Acid Ethyl Ester (5)**

To a stirred suspension of $NaBH_4$ (1.27 g, 33.6 mmol) in anhyd THF (30 mL) was added a solution of **4** (5.0 g, 22.4 mmol) in anhyd THF (30 mL) at r.t. The stirring was continued for 5 min at r.t. and a solution of $I_2$ (2.84 g, 11.2 mmol) in anhyd THF (30 mL) was then added dropwise. The mixture was stirred at r.t. for 6 h, then cooled in an ice bath, and quenched with aq 2 N HCl (20 mL). The mixture was extracted with EtOAc (2 × 150 mL), the combined organic layers were washed with $H_2O$ (2 × 50 mL), aq 2 N NaOH (50 mL), brine (50 mL), dried ($Na_2SO_4$), and concentrated under vacuum. Purification by flash chromatography on silica gel (hexane–EtOAc, 1:1) gave **5**; pale yellow oil; yield: 3.49 g (74%).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 1.63 (br s, 1 H), 2.84 (t, *J* = 6.5 Hz, 2 H), 3.84 (t, *J* = 6.5 Hz, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 6.69 (br s, 1 H), 6.92 (d, *J* = 6.4 Hz, 1 H), 7.19–7.32 (m, 3 H).

**Methanesulfonic Acid 2-(3-Ethoxycarbonylaminophenyl)ethyl Ester (6)**

To a stirred solution of **5** (10.5 g, 50 mmol) and $Et_3N$ (6.10 g, 60 mmol) in anhyd EtOAc (100 mL), cooled to 0 °C was added dropwise a solution of $MeSO_2Cl$ (6.30 g, 55 mmol) in EtOAc (15 mL) via a syringe. The stirring was continued at 0 °C for 30 min, then the mixture was diluted with EtOAc (50 mL). The EtOAc solution was washed with aq 2 N HCl (2 × 30 mL), sat. aq $NaHCO_3$ (50 mL), brine (50 mL), dried ($Na_2SO_4$), and concentrated under vacuum to give **6**; colorless solid; yield: 12.97 g (90%).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 2.88 (s, 3 H), 3.02 (t, *J* = 6.8 Hz, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.41 (t, *J* = 6.8 Hz, 2 H), 6.65 (s, 1 H), 6.93 (d, *J* = 7.1 Hz, 1 H), 7.18–7.28 (m, 2 H), 7.36 (s, 1 H).

**[2-(3-Ethoxycarbonylaminophenyl)ethylsulfanyl]acetic Acid (7)**

To a stirred solution of **6** (10.0 g, 34.8 mmol) in anhyd DMF (80 mL) were added mercaptoacetic acid (3.53 g, 38.3 mmol), $Et_3N$ (7.75 g, 76.6 mmol), and NaI (5.21 g, 34.8 mmol), and the mixture was stirred for 16 h at 60 °C . The DMF was removed under vacuum and the residue was dissolved in EtOAc (150 mL). The EtOAc solution was washed with aq 2 N HCl (2 × 30 mL) and extracted with aq 5% NaOH (3 × 30 mL). The combined basic aqueous extracts were cooled, acidified with aq 6 N HCl, and the mixture was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined $CH_2Cl_2$ extracts

were washed with brine (50 mL), dried ($Na_2SO_4$), and concentrated under vacuum to give acid **7**; pale yellow oil, which crystallized on standing to give a low-melting waxy solid; yield: 4.90 g (48%).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 2.90 (m, 4 H), 3.24 (s, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 6.71 (br s, 1 H), 6.90 (d, *J* = 6.6 Hz, 1 H), 7.17–7.30 (m, 3 H), 10.34 (br s, 1 H).

**(1-Oxo-1,2,4,5-tetrahydrobenzo[*d*]thiepin-7-yl)carbamic Acid Ethyl Ester (8)**

To a stirred solution of acid **7** (4.90 g, 17.2 mmol) in anhyd $CH_2Cl_2$ (50 mL) was added $SOCl_2$ (4.1 g, 34.4 mmol) at r.t., followed by DMF (5 drops) and the stirring was continued for 1.5 h at r.t. The volatile components were removed under vacuum, the residue was dissolved in anhyd $CH_2Cl_2$ (20 mL), and added dropwise to a vigorously stirred suspension of $AlCl_3$ (4.60 g, 34.4 mmol) in anhyd $CH_2Cl_2$ (50 mL) cooled to 0 °C. The stirring was continued at r.t. for 2.5 h, the mixture was then quenched with ice and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($Na_2SO_4$), and concentrated under vacuum. Purification by flash chromatography on silica gel (hexane–EtOAc, 3:1 to 1:1) gave **8**; colorless crystals; yield: 3.02 g (66%); mp 145–146 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 2.99 (t, *J* = 6.5 Hz, 2 H), 3.18 (t, *J* = 6.5 Hz, 2 H), 3.53 (s, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 6.77 (s, 1 H), 7.22 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.51 (s, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H).

ESMS: *m*/*z* = 266 (M + 1).

**(*S*)-*N*-[2-Oxo-3-(1-oxo-1,2,4,5-tetrahydrobenzo[*d*]thiepin-7-yl)oxazolidin-5-ylmethyl]acetamide (9)**

To a stirred solution of **8** (1.50 g, 5.65 mmol) and anhyd MeOH (0.36 g, 11.3 mmol) in anhyd DMF (6.0 mL) was added dropwise a solution of *t*-BuOLi (17.0 mL of 1 M hexane solution, 17.0 mmol) during 1 h at r.t. The mixture was cooled to 0 °C and (*S*)-*N*-(2-acetoxy-3-chloropropyl)acetamide (2.19 g, 11.5 mmol) was added as a solid in one portion. The stirring was continued at r.t. for 20 h, the mixture was then quenched with sat. aq $NH_4Cl$ (20 mL) and extracted with a large amount of EtOAc (ca. 350 mL). The combined organic extracts were washed with brine (50 mL), dried ($Na_2SO_4$), and concentrated under vacuum. Purification by flash chromatography on silica gel (EtOAc–MeOH, 10:1 to 3:1), followed by recrystallization from EtOAc–MeOH gave **9**; colorless crystals; yield: 0.16 g (17%); mp 232–233 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.82 (s, 3 H), 2.90 (t, *J* = 6.5 Hz, 2 H), 3.23 (t, *J* = 6.5 Hz, 2 H), 3.41 (t, *J* = 5.5 Hz, 2 H), 3.62 (s, 2 H), 3.77 (dd, *J* = 9.3, 6.7 Hz, 1 H), 4.16 (t, *J* = 9.0 Hz, 1 H), 4.74 (m, 1 H), 7.49 (d, *J* = 2.3 Hz, 1 H), 7.63 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.83 (d, *J* = 8.7 Hz, 1 H), 8.25 (t, *J* = 5.8 Hz, 1 H).

ESMS: *m*/*z* = 335 (M + 1).

Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.42; N, 8.38. Found: C, 57.41; H, 5.37; N, 8.25.

**(*S*)-*N*-[2-Oxo-3-(1,3,3-trioxo-2,3,4,5-tetrahydro-1*H*-3λ$^6$-benzo[*d*]thiepin-7-yl)oxazolidin-5-ylmethyl]acetamide (10)**

To a stirred suspension of **9** (0.30 g, 0.9 mmol) in acetone (10.0 mL), cooled in an ice bath was added a solution of MCPBA (0.65 g of ~60% reagent, ~2.25 mmol) in acetone (2.0 mL). The cooling bath was removed and the stirring was continued for 3 h at r.t. The mixture was purified directly by flash chromatography on silica gel (EtOAc–MeOH, 10:1 to 6:1) to give **10**; colorless crystals; yield: 0.26 g (79%); mp 225–226 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.82 (s, 3 H), 3.42 (t, *J* = 4.9 Hz, 2 H), 3.56 (m, 4 H), 3.77 (t, *J* = 7.8 Hz, 1 H), 4.15 (t, *J* = 8.8 Hz, 1 H), 4.76 (m, 1 H), 4.88 (s, 2 H), 7.54 (s, 1 H), 7.66 (d, *J* = 8.7 Hz, 1 H), 7.79 (d, *J* = 8.7 Hz, 1 H), 8.25 (t, *J* = 4.9 Hz, 1 H).

ESMS: *m*/*z* = 367 (M + 1).

Anal. Calcd for $C_{16}H_{18}N_2O_6S$: C, 52.45; H, 4.95; N, 7.64. Found: C, 52.72; H, 5.16; N, 7.44.

**(*S*)-*N*-[3-(2-Dimethylaminomethylene-1-oxo-1,2,4,5-tetrahydrobenzo[*d*]thiepin-7-yl)-2-oxooxazolidin-5-ylmethyl]acetamide (11)**

To a stirred solution of **9** (0.45 g, 1.3 mmol) in *n*-propanol (15 mL) was added dropwise dimethylformamide dimethylacetal (0.62 g, 5.2 mmol) at r.t. and the stirring was continued under reflux for 2 h. Upon cooling to r.t., a precipitate appeared, which was collected by filtration, washed with *n*-propanol (5 mL), and dried to provide a first crop of **11** (0.20 g). The mother liquor was concentrated and purified by flash chromatography on silica gel (EtOAc–MeOH, 10:1 to 5:1) to give an additional amount of **11** (0.09 g); yellow crystals; combined yield: 0.29 g (57%); mp 221–222 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.83 (br s, 2 H), 2.96 (t, *J* = 6.4 Hz, 2 H), 3.35 (br s, 6 H), 3.56–3.64 (m, 1 H), 3.68–3.75 (m, 1 H), 3.79 (dd, *J* = 9.2, 7.0 Hz, 1 H), 4.08 (t, *J* = 9.0 Hz, 1 H), 4.78 (m, 1 H), 5.96 (t, *J* = 6.0 Hz, 1 H), 7.33 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.51 (d, *J* = 2.2 Hz, 1 H), 7.67 (d, *J* = 8.4 Hz, 1 H), 8.13 (s, 1 H).

ESMS: *m*/*z* = 390 (M + 1).

**(*S*)-*N*-[3-(5,6-Dihydro-1*H*-4-thia-1,2-diazabenzo[*e*]azulen-8-yl)-2-oxooxazolidin-5-ylmethyl]acetamide (12)**

To a stirred suspension of **11** (0.20 g, 0.51 mmol) in EtOH (6.0 mL) was added hydrazine hydrate (0.20 g, 4.0 mmol) and the stirring was continued for 20 h at r.t. The mixture was purified directly by flash chromatography on silica gel (EtOAc–MeOH, 10:1 to 5:1) to give **12**; colorless crystals; yield: 0.17 g (94%); mp 186–187 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.83 (s, 3 H), 2.77–2.91 (m, 2 H), 3.27 (m, 2 H), 3.41 (t, *J* = 5.2 Hz, 2 H), 3.77 (t, *J* = 7.7 Hz, 1 H), 4.15 (t, *J* = 8.9 Hz, 1 H), 4.73 (m, 1 H), 7.47–7.56 (m, 3 H), 7.58 and 7.86 (s each, 1 H), 8.26 (t, *J* = 5.1 Hz, 1 H), 13.06 and 13.32 (s each, 1 H).

ESMS: *m*/*z* = 359 (M + 1).

Anal. Calcd for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63. Found: C, 56.59; H, 4.80; N, 15.33.

**(*S*)-*N*-[3-(2-Amino-6,7-dihydro-5-thia-1,3-diazadibenzo[*a*,*c*]cyclohepten-9-yl)-2-oxooxazolidin-5-ylmethyl]acetamide (13)**

To a stirred suspension of **11** (111 mg, 0.28 mmol) in EtOH (6.0 mL) was added guanidine hydrochloride (267 mg 2.8 mmol), followed by $K_2CO_3$ (387 mg, 2.8 mmol), and the stirring was continued under reflux for 2 h. Upon cooling to r.t., the mixture solidified. Small amount of $H_2O$ (0.5–1.0 mL) was added and the mixture was purified directly by flash chromatography on silica gel (EtOAc–MeOH, 10:1 to 4:1) to give **13**; pale yellow crystals; yield: 85 mg (79%); mp 190–191 °C (dec.).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.83 (s, 3 H), 2.75 (t, *J* = 6.2 Hz, 2 H), 3.28 (t, *J* = 6.6 Hz, 2 H), 3.42 (t, *J* = 5.5 Hz, 2 H), 3.79 (dd, *J* = 9.1, 6.7 Hz, 1 H), 4.16 (t, *J* = 8.9 Hz, 1 H), 4.73 (m, 1 H), 6.94 (s, 2 H), 7.50 (d, *J* = 2.1 Hz, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 7.65 (dd, *J* = 8.5, 2.1 Hz, 1 H), 8.23 (s, 1 H), 8.25 (t, *J* = 5.8 Hz, 1 H).

ESMS: *m*/*z* = 386 (M + 1).

Anal. Calcd for $C_{18}H_{19}N_5O_3S$: C, 56.09; H, 4.97; N, 18.17. Found: C, 55.72; H, 5.20; N, 17.83.

**(*S*)-*N*-[3-(2-Dimethylaminomethylene-1,3,3-trioxo-2,3,4,5-tetrahydro-1*H*-3λ$^6$-benzo[*d*]thiepin-7-yl)-2-oxooxazolidin-5-ylmethyl]acetamide (14)**

To a stirred solution of **10** (0.52 g, 1.4 mmol) in *n*-propanol (20 mL) was added dropwise dimethylformamide dimethylacetal (0.67 g,

5.6 mmol) at r.t. and the stirring was continued under reflux for 2 h. Upon cooling to r.t., a precipitate appeared, which was collected by filtration, washed with *n*-propanol (5 mL), and dried to give **14**; yellow crystals; yield: 0.56 g (95%); mp 261–263 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 3.02 (s, 3 H), 3.30 (t, *J* = 6.4 Hz, 2 H), 3.37 (s, 3 H), 3.48 (t, *J* = 6.4 Hz, 2 H), 3.54–3.71 (m, 2 H), 3.80 (dd, *J* = 9.1, 7.1 Hz, 1 H), 4.06 (t, *J* = 9.0 Hz, 1 H), 4.76 (m, 1 H), 6.16 (t, *J* = 5.9 Hz, 1 H), 7.36 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.62 (d, *J* = 2.1 Hz, 1 H), 7.80 (s, 1 H), 7.84 (d, *J* = 8.6 Hz, 1 H).

ESMS: *m*/*z* = 422 (M + 1).

**(*S*)-*N*-[3-(4,4-Dioxo-1,4,5,6-tetrahydro-4λ$^6$-thia-1,2-diazabenzo[*e*]azulen-8-yl)-2-oxooxazolidin-5-ylmethyl]acetamide (15)**

To a stirred suspension of **14** (200 mg, 0.47 mmol) in EtOH (6.0 mL) was added hydrazine hydrate (0.20 g, 4.0 mmol) at r.t. and the stirring was continued under reflux for 2 h. Upon cooling to r.t., a precipitate appeared, which was collected by filtration, washed with EtOH (3 mL), and dried under vacuum to give **15**; colorless crystals; yield: 159 mg (87%); mp 292–293 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.83 (s, 3 H), 3.12 (m, 2 H), 3.42 (t, *J* = 5.4 Hz, 2 H), 3.70 (m, 2 H), 3.77 (dd, *J* = 9.0, 6.7 Hz, 1 H), 4.15 (t, *J* = 8.9 Hz, 1 H), 4.74 (m, 1 H), 7.56–7.65 (m, 2 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 8.25 (t, *J* = 5.7 Hz, 1 H), 8.44 (br s, 1 H), 13.88 (br s, 1 H).

ESMS: *m*/*z* = 391 (M + 1).

Anal. Calcd for $C_{17}H_{18}N_4O_5S$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.39; H, 4.55; N, 14.36.

**(*S*)-*N*-[3-(4,4-Dioxo-5,6-dihydro-4*H*-1-oxa-4λ$^6$-thia-2-azabenzo[*e*]azulen-8-yl)-2-oxooxazolidin-5-ylmethyl]acetamide (16)**

To a stirred suspension of **14** (200 mg, 0.47 mmol) in MeOH (8.0 mL) was added a solution of hydroxylamine *O*-sulfonic acid (70 mg, 0.62 mmol) in MeOH (1.0 mL) at r.t. and the stirring was continued under reflux for 4 h. Upon cooling to r.t., a precipitate appeared, which was collected by filtration, dried, and purified by chromatography on silica gel (EtOAc–MeOH, 10:1) to give **17**; colorless crystals; yield: 84 mg (53%); mp 211–212 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.82 (s, 3 H), 3.42 (m, 4 H), 3.80 (m, 3 H), 4.17 (t, *J* = 9.1 Hz, 1 H), 4.77 (m, 1 H), 7.65 (d, *J* = 2.1 Hz, 1 H), 7.77 (dd, *J* = 8.8, 2.1 Hz, 1 H), 8.03 (d, *J* = 8.8 Hz, 1 H), 8.25 (t, *J* = 5.7 Hz, 1 H), 9.39 (s, 1 H).

ESMS: *m*/*z* = 392 (M + 1).

Anal. Calcd for $C_{17}H_{17}N_3O_6S$: C, 52.17; H, 4.38; N, 10.47. Found: C, 52.33; H, 4.51; N, 10.55.

**(*S*)-*N*-[3-(2-Amino-5,5-dioxo-6,7-dihydro-5*H*-5λ$^6$-thia-1,3-diazadibenzo[*a*,*c*]cyclohepten-9-yl)-2-oxooxazolidin-5-ylmethyl]acetamide (17)**

To a stirred suspension of **14** (250 mg, 0.59 mmol) in EtOH (10.0 mL) was added guanidine hydrochloride (564 mg 5.9 mmol), followed by $K_2CO_3$ (815 mg, 5.9 mmol), and the stirring was continued under reflux for 4 h. Upon cooling to r.t., the solids were collected by filtration and suspended in $H_2O$ (10.0 mL). After stirring for 1 h at r.t., the precipitate was filtered, washed with $H_2O$ (2 × 2 mL), and dried under vacuum to give **16**; colorless crystals; yield: 215 mg (87%); mp 211–213 °C (dec.).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.83 (s, 3 H), 3.05 (t, *J* = 6.3 Hz, 2 H), 3.43 (t, *J* = 5.2 Hz, 2 H), 3.78 (m, 3 H), 4.15 (t, *J* = 8.9 Hz, 1 H), 4.75 (m, 1 H), 7.54–7.70 (m, 3 H), 7.79 (m, 2 H), 8.25 (t, *J* = 5.3 Hz, 1 H), 8.56 (s, 1 H).

ESMS: *m*/*z* = 418 (M + 1).

Anal. Calcd for $C_{18}H_{19}N_5O_5S·H_2O$: C, 49.64; H, 4.86; N, 16.08. Found: C, 49.27; H, 4.81; N, 15.92.

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