Scientific paper

A Convenient Synthesis of 4-Benzyl-2-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)ethyl)-2*H*-1,4-benzoxazin-3(4*H*)-ones and 5-(2-(4-Benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethylidene)thiazolidine-2,4-diones

Nace Zidar, Jure Kladnik and Danijel Kikelj*

Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, SI-1000 Ljubljana, Slovenia

** Corresponding author: E-mail: danijel.kikelj@ffa.uni-lj.si*

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

4-Benzyl-2-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)ethyl)-2*H*-1,4-benzoxazin-3(4*H*)-ones and 5-(2-(4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethylidene)thiazolidine-2,4-diones are conveniently prepared from 2-aminophenol and rhodanine or thiazolidine-2,4-dione derivatives using microwave-assisted synthesis.

Keywords: 2*H*-1,4-benzoxazin-3(4*H*)-one, rhodanine, 5-ylidene-2-thioxothiazolidin-4-one, microwave-assisted synthesis

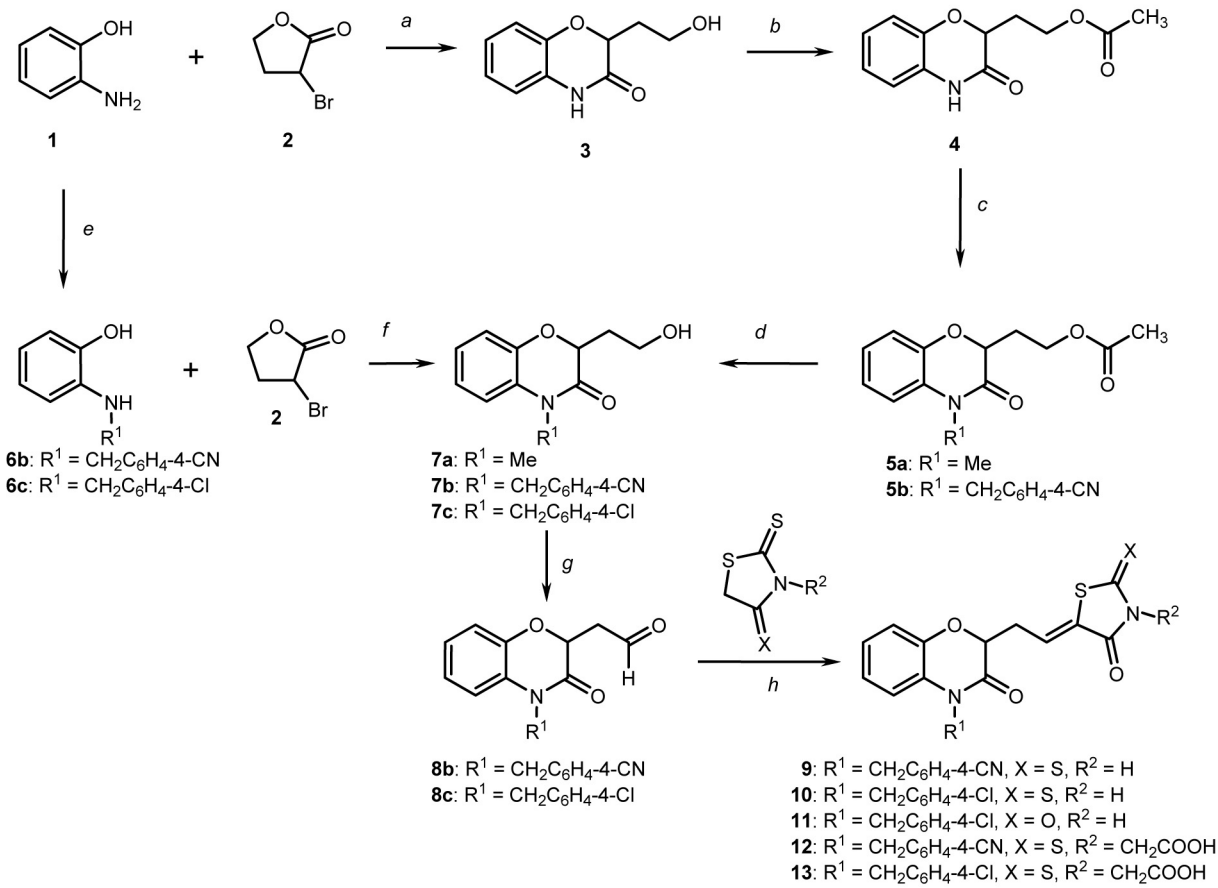
1. Introduction

Due to their manifold derivatization, functionalization and substituent-orienting possibilities, 2*H*-1,4-benzoxazin-3(4*H*)-ones have been frequently used as heterocyclic scaffolds for design of cardiovascular, antipsychotic, antidepressive and antibacterial drugs.[1] In the course of our studies toward the discovery of novel inhibitors of peptidoglycan biosynthesis targeting enzymes of the Mur ligases family (MurC-F),[2,3] recently described 2*H*-1,4-benzoxazin-3(4*H*)-one inhibitors of bacterial histidine protein kinase[4–6] attracted our attention due to similarities in structure of Mur enzymes and various kinases. Thus, histidine protein kinase inhibitors possessing a 2*H*-1,4-benzoxazin-3(4*H*)-one core were employed as a starting point for the design of inhibitors of Mur enzymes with potential antibacterial activity. On the basis of preliminary docking studies, attachment of 2-thioxothiazolidin-4-one (rhodanine) or thiazolidine-2,4-dione moiety to 2*H*-1,4-benzoxazin-3(4*H*)-one scaffold *via* a short linker, giving compounds **9**-**13**, seemed promising for interaction with enzymes MurC and MurD. 5-Benzylidenerhodanine derivatives themselves were reported to inhibit MurC[7] and MurG[8] as well as various other enzymes, *e.g.* beta lactamase,[9] aldose reductase,[10] cyclooxygenase,[11] 5-lipoxygenase[11] and phosphodiesterase.[12] In this communication we present our strategy for the synthesis of 4-benzyl-2-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)ethyl)-2*H*-1,4-benzoxazin-3(4*H*)-ones and 5-(2-(4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethylidene)thiazolidine-2,4-diones **9**-**13** using microwave-assisted synthesis. Antibacterial activity of compounds **9**-**13** is under investigation and will be reported elsewhere.

2. Results and Discussion

The synthesis of 5-ylidene-2-thioxothiazolidin-4-ones and 5-ylidene-thiazolidine-2,4-diones **9**-**13** is outlined in Scheme 1. The reaction of 2-aminophenol (**1**) with 3-bromodihydrofuran-2(3*H*)-one (**2**) in the presence of potassium carbonate in *N*,*N*-dimethylformamide afforded 2-(2-hydroxyethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one (**3**). The preferential alkylation of a hydroxyl group of 2-aminophenol is in accordance with previously established reactions of 2-aminophenols with 2-bromocarboxylates.[13] Reasonable yield of **3** could thus be obtained in a one step reaction avoiding protection and deprotection of the ami-

no group. The reaction was further improved using microwave irradiation and sodium hydride as a base, giving better yields and shortening the reaction time. Protection of the hydroxyl group of alcohol **3** with acetic anhydride, followed by *N*-alkylation of the lactam with methyl iodide or benzyl bromide under phase transfer conditions,[15] smoothly afforded *N*-methyl and *N*-benzyl derivatives **5a** and **5b**. Compounds **5a** and **5b** were deprotected by hydrolysis with aqueous sodium hydroxide in 1,4-dioxane to give alcohols **7a** and **7b**. Alternatively, 2*H*-1,4-benzoxazin-3(4*H*)-ones **7b** and **7c** were prepared by ring closure of 4-((2-hydroxyphenylamino)methyl)benzonitrile (**6b**) and 2-(4-chlorobenzylamino)-phenol (**6c**) with 3-bromodihydrofuran-2(3*H*)-one (**2**) in the presence of sodium hydride in *N*,*N*-dimethylformamide in a microwave reactor (180 °C, 30 min). Compounds **6b** and **6c** were obtained by reductive amination[16,17] of 4-cyanobenzaldehyde and 4-chlorobenzaldehyde with 2-aminophenol using sodium cyanoborohydride as a reducing agent. The synthesis of **7b** and **7c** *via* this reaction pathway is two steps shorter and gives better overall yields. Since *N*-methyl-2-aminophenol could not be obtained by reductive amination of 2-aminophenol with formaldehyde, compound **7a** was prepared by *N*-methylation of protected 2*H*-1,4-benzoxazin-3(4*H*)-one **4** followed by hydrolytic deprotection step. The Corey-Kim oxidation[18] of alcohols **7a** and **7b** afforded carbaldehydes **8b** and **8c** in high yields. Finally, the Knoevenagel condensation[19] of rhodanine, 2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid and thiazolidine-2,4-dione with aldehydes **8b** and **8c**, in a microwave reactor at 150 °C for 20 minutes, afforded 5-alkylidenerhodanines **9**, **10**, **12**, **13** and 5-alkylidenethiazolidine-2,4-dione **11** in good yields. One signal for alkylidene proton at 6.8–6.9 ppm in ^{1}H NMR spectra of **9**–**13** suggested that a single isomer was present. On the basis of literature data for similar compounds,[20–22] *Z*-configuration of the exocyclic double bond was anticipated. To prove *Z*-configuration we recorded ^{1}H-coupled ^{13}C NMR spectrum of compound **9** and examined the splitting pattern and coupling constant of the signal of the C=O group in the rhodanine system. The signal appeared as a doublet (J = 5.6 Hz) at 168.48 ppm due to a long-range coupling with alkylidene proton. According to ^{13}C and X-ray data, the structural assignment of the double bond in similar compounds is possible



Scheme 1. Reagents and conditions: (*a*) K_2CO_3, DMF, reflux, 5 h or NaH, DMF, MW: 145 °C, 40 min; (*b*) Ac_2O, 60 °C, 12 h; (*c*) 4-(bromomethyl)benzonitrile or MeI, K_2CO_3, BTEAC, CH_3CN, 60 °C, 12 h; (*d*) 1 M NaOH, 1,4-dioxane, 60 °C, 10 h; (*e*) 4-cyanobenzaldehyde or 4-chlorobenzaldehyde, $NaBH_3CN$, AcOH, MeOH, rt, 2 h; (*f*) NaH, DMF, MW: 180 °C, 30 min; (*g*) NCS, Me_2S, Et_3N, CH_2Cl_2, –25 °C; (*h*) AcOH, piperidine, EtOH, MW: 150 °C, 20 min.

on the basis of the magnitude of a coupling constant (12 Hz for *E*-configuration, 6 Hz for *Z*-configuration) in the signal of the C=O group.[22] This experiment confirmed *Z*-configuration of compound **9** which can be assumed also for products **10–13**.

In conclusion, we described a convenient synthesis of 4-benzyl-2-(2-(4-oxo-2-thioxothiazolidin-5-ylidene) ethyl)-2*H*-1,4-benzoxazin-3(4*H*)-ones and 5-(2-(4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethylidene)thiazolidine-2,4-diones from 2-aminophenol and rhodanine or thiazolidine-2,4-dione derivatives using microwave-assisted synthesis.

3. Experimental

Chemicals were obtained from Acros, Aldrich Chemical Co. and Merck and used without further purification. Analytical TLC was performed on Merck silica gel (60 F_{254}) plates (0.25 mm) and components visualized with ultraviolet light. Column chromatography was carried out on silica gel (particle size 240–400 mesh). HPLC analyses were performed on Agilent Technologies 1100 instrument with G1365B UV-VIS detector, G1316A thermostat and G1313A autosampler using Phenomenex Luna 4u C18 column (4.6 × 250 mm). Eluent consisted of 0.01% trifluoroacetic acid in water (30%) and acetonitrile (70%). Microwave assisted reactions were performed using a CEM Discover microwave reactor (CEM Corporation, USA). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX$_{300}$ spectrometer in $CDCl_3$ or DMSO-d_6 solution, with TMS as the internal standard, at 300 MHz or 75 MHz, respectively. IR spectra were obtained on a Perkin–Elmer FTIR System Spectrum BX spectrometer. Microanalyses were performed at the Faculty of Chemistry and Chemical Technology, University of Ljubljana on a Perkin–Elmer C, H, N analyzer 240 °C. Mass spectra were recorded at Jožef Stefan Institute, Ljubljana, using a VG Analytical Autospec Q mass spectrometer. All reported yields are those of the purified products.

2-(2-Hydroxyethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one (3). Method A: To a solution of **1** (0.981 g, 9.00 mmol) in anhydrous DMF (10 mL), potassium carbonate (1.244 g, 9.00 mmol) and 3-bromodihydrofuran-2(3*H*)-one (**2**) (1.06 mL, 9.90 mmol, 90%) were added. The reaction mixture was stirred under reflux for 5 hours, after which the solvent was removed under reduced pressure and 10% citric acid (40 mL) was added. Water phase was extracted with ethyl acetate (2 × 50 mL) and combined organic phase washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was crystallized from methanol, to give white solid (0.230 g, 13%), mp 72–75 °C (lit.[4] 65–69 °C); R_f = 0.31 (EtOAc/petroleum ether = 4:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75–2.01 (m, 2H, CHC<u>H</u>$_2$), 3.54–3.62 (m, 2H, CH_2O), 4.60–4.65 (m, 2H, CH, OH), 6.88–6.99 (m, 4H, ArH), 10.63 (br s, 1H, NH).

Method B: To a solution of **1** (0.730 g, 6.69 mmol) in anhydrous DMF (30 mL) in an 80 mL process vial, NaH (401 mg, 10.03 mmol, 60% dispersion in paraffin) was added by portions. After stirring for 30 minutes under an argon atmosphere, 3-bromodihydrofuran-2(3*H*)-one (**2**) (1.07 mL, 10.03 mmol, 90%) was added, the vial was sealed, placed in a microwave reactor and heated at 145 °C for 40 minutes. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (80 mL). The organic phase was washed with water (3 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound **3** (0.646 g, 50%) was isolated from the residue by flash column chromatography using ethyl acetate/petroleum ether (4:1) as eluent. The product was identical in all respects (mp, R_f, NMR) to the product obtained by method A.

2-(3-Oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethyl acetate (4). A solution of compound **3** (0.190 g, 0.983 mmol) in acetic anhydride (10mL) was stirred at 60 °C for 12 hours. Acetic anhydride was removed under reduced pressure and the product recrystallized from ethyl acetate to give yellow-white crystals (0.208 g, 90%), mp 134–136 °C; R_f = 0.55 (EtOAc/petroleum ether = 4:1); IR (KBr) 3413, 3197, 3060, 1734, 1679, 1500, 1400, 1249, 1049, 758, 748, 474 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H, CH_3), 2.00–2.23 (m, 2H, CHC<u>H</u>$_2$), 4.17–4.22 (m, 2H, CH_2O), 4.66 (dd, 1H, J_1 = 8.4 Hz, J_2 = 4.5 Hz, CH), 6.87–6.99 (m, 4H, ArH), 10.71 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.53 (CH_3), 30.00 (CH_2), 60.66 (CH_2), 74.19 (CH), 116.50 (Ar-C), 117.34 (Ar-C), 123.41 (Ar-C), 124.01 (Ar-C), 128.18 (Ar-C), 143.26 (Ar-C), 166.89 (C=O), 171.15 (C=O). MS (EI) *m/z* (%): 235 (M^+, 40), 193 (34), 175 (100), 162 (35), 148 (30), 134 (9), 130 (8), 120 (34), 109 (11), 93 (10). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; found C, 61.21; H, 5.68; N, 5.77.

3. 1. General procedure for the synthesis of compounds 5a and 5b by alkylation of 4 under phase-transfer catalysis

4-(Bromomethyl)benzonitrile or iodomethane (1.50 mmol) was added to a stirred suspension of **4** (0.235 g, 1.00 mmol), benzyltriethylammonium chloride (0.228 g, 1.00 mmol) and potassium carbonate (0.346 g, 2.50 mmol) in acetonitrile (10 mL) and the reaction mixture was heated at 60 °C for 12 hours. The suspension was filtered and the filtrate evaporated under reduced pressure. The obtained residue was dissolved in dichloromethane (20 mL) and washed successively with 10% citric acid (2

× 10 mL), saturated solution of $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography using dichloromethane/methanol (50:1) (**5a**) or dichloromethane/acetone (50:1) (**5b**) as eluent.

2-(4-Methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethyl acetate (5a). Yield: 79%; yellow-orange oil; R_f = 0.37 (dichloromethane/methanol = 50:1); IR (KBr) 3354, 2934, 2857, 1740, 1683, 1609, 1594, 1504, 1479, 1422, 1390, 1368, 1278, 1235, 1128, 1046, 752 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H, CH_3CO), 2.00–2.23 (m, 2H, CHC$\underline{H}_2$), 3.29 (s, 3H, CH_3N), 4.16–4.21 (m, 2H, CH_2O), 4.72 (dd, 1H, J_1 = 8.6 Hz, J_2 = 4.4 Hz, CH), 7.00–7.19 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.31 (CH_3), 28.86 (CH_2/CH_3), 30.06 (CH_2/CH_3), 60.50 (CH_2), 74.36 (CH), 115.06 (Ar-C), 117.59 (Ar-C), 123.25 (Ar-C), 124.38 (Ar-C), 130.01 (Ar-C), 144.30 (Ar-C), 166.29 (C=O), 171.30 (C=O). MS (EI) *m/z* (%): 249 (M^+, 84), 207 (35), 189 (100), 176 (32), 162 (50), 148 (20), 134 (44), 122 (15), 106 (5), 93 (9), 77 (7). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62; found C, 62.85; H, 6.18; N, 5.58.

2-(4-(4-Cyanobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethyl acetate (5b). Yield: 40%; white crystals; mp 98–100 °C; R_f = 0.40 (EtOAc/hexane = 1:1); IR (KBr) 3414, 2228, 1723, 1677, 1502, 1400, 1245, 1041, 753 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H, CH_3), 2.00–2.23 (m, 2H, CHC$\underline{H}_2$), 4.24 (m, 2H, CH_2O), 4.92 (dd, 1H, J_1 = 8.52 Hz, J_2 = 4.18 Hz, CH), 5.16–5.34 (AB-system, 2H, ^2J = 16.92 Hz, CH_2N), 6.90–7.05 (m, 4H, ArH), 7.46 (d, 2H, *J* = 8.20 Hz, H-2, H-6), 7.81 (d, 2H, *J* = 8.20 Hz, H-3, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.57 (CH_3), 30.01 (CH_2), 44.76 (CH_2), 60.61 (CH_2), 74.37 (CH), 110.96 (Ar-C), 116.46 (Ar-C/CN), 117.90 (Ar-C/CN), 119.53 (Ar-C/CN), 123.77 (Ar-C), 124.91 (Ar-C), 128.36 (2,6/3,5-C), 129.15 (Ar-C), 133.49 (2,6/3,5-C), 143.20 (Ar-C), 144.69 (Ar-C), 166.55 (C=O), 171.19 (C=O). MS (EI) *m/z* (%): 350 (M^+, 15), 192 (9), 174 (100), 146 (8), 116 (38), 89 (9). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00; found C, 68.48; H, 5.18; N, 7.97.

3. 2. General procedure for the preparation of 2-(benzylamino)phenols 6b and 6c

A solution of **1** (109 mg, 1.00 mmol), the corresponding benzaldehyde (1.00 mmol) and glacial acetic acid (57.2 μL, 1.00 mmol) in methanol (7 mL) was stirred under an argon atmosphere for 15 minutes. $NaBH_3CN$ (69.1 mg, 1.10 mmol) was added by portions and the reaction mixture was stirred for 2 hours at room temperature, after which the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL), washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), water (2 × 10 mL) and brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was used without further purification.

4-((2-Hydroxyphenylamino)methyl)benzonitrile (6b). Yield: 100%; brown solid; mp 100–103 °C (lit.[23] 108 °C); R_f = 0.34 (dichloromethane/methanol = 50:1); ^1H NMR (DMSO-d_6, 300 MHz) δ 4.40 (d, 2H, *J* = 6.3 Hz, CH_2), 5.52 (t, 1H, *J* = 6.3 Hz, NH), 6.27 (dd, 1H, $J_{3',4'}$ = 7.5 Hz, $J_{3',5'}$ = 1.5 Hz, H-3'), 6.39 (ddd, 1H, ^3J = 7.5 Hz, ^4J = 1.5 Hz, H-4'/5'), 6.52 (ddd, 1H, ^3J = 7.5 Hz, ^4J = 1.5 Hz, H-4'/5'), 6.67 (dd, 1H, $J_{6',5'}$ = 7.5 Hz, $J_{6',4'}$ = 1.5 Hz, H-6'), 7.52 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 7.76 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 9.28 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 47.01 (CH_2), 110.13 (Ar-C), 110.91 (Ar-C), 114.44 (Ar-C/CN), 116.96 (Ar-C/CN), 119.85 (Ar-C/CN), 120.41 (Ar-C/CN), 128.71 (2,6/3,5-C), 133.04 (2,6/3,5-C), 137.55 (Ar-C), 145.07 (Ar-C), 147.96 (Ar-C).

2-(4-Chlorobenzylamino)phenol (6c). Yield: 94%; brown solid; mp 100–103 °C (lit.[24] 109 °C); R_f = 0.55 (dichloromethane/methanol = 50:1); ^1H NMR (DMSO-d_6, 300 MHz) δ 4.30 (d, 2H, *J* = 6.0 Hz, CH_2), 5.35 (t, 1H, *J* = 6.0 Hz, NH), 6.33 (dd, 1H, $J_{3,4}$ = 7.8 Hz, $J_{3,5}$ = 1.5 Hz, H-3), 6.39 (ddd, 1H, ^3J = 7.8 Hz, ^4J = 1.5 Hz, H-4/5), 6.54 (ddd, 1H, ^3J = 7.8 Hz, ^4J = 1.5 Hz, H-4/5), 6.67 (dd, 1H, $J_{6,5}$ = 7.8 Hz, $J_{6,4}$ = 1.5 Hz, H-6), 7.36 (s, 4H, ArH), 9.25 (s, 1H, OH).

3. 3. Synthesis of compounds 7a and 7b by hydrolysis of acetates 5a and 5b (Method A)

2-(2-Hydroxyethyl)-4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one (7a). To a stirred solution of **5a** (0.655 g, 2.63 mmol) in 1,4-dioxane (15 mL), 1 M NaOH (5.00 mL, 5.00 mmol) was added and the reaction mixture heated at 60 °C for 10 hours. Then, pH was adjusted to 8 with 1H MCl, solvent was removed under reduced pressure and the residue partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous phase was extracted with ethyl acetate (4 × 20 mL), combined organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography using dichloromethane/methanol (15:1) as eluent, giving **7a** as colourless oil (0.513 g, 94%).[25] ^1H NMR (300 MHz, DMSO-d_6) δ 1.75–2.02 (m, 2H, CHC$\underline{H}_2$), 3.28 (s, 3H, CH_3N), 3.51–3.65 (m, 2H, CH_2O), 4.63 (t, 1H, *J* = 5.4 Hz, OH), 4.70 (dd, 1H, J_1 = 9.0 Hz, J_2 = 3.9 Hz, CH), 7.01–7.16 (m, 4H, ArH). MS (EI) *m/z* (%): 207 (M^+, 100), 189 (6), 176 (40), 163 (81), 148 (25), 134 (65), 122 (21), 107 (15), 94 (16), 77 (13).

4-((2-(2-Hydroxyethyl)-3-oxo-2,3-dihydro-1,4-benzoxazin-4-yl)methyl)benzonitrile (7b). To a stirred solution of **5b** (0.620 g, 1.77 mmol) in 1,4-dioxane (20 mL), 1

M NaOH (6.00 mL, 6.00 mmol) was added and the reaction mixture heated at 60 °C for 10 hours. Solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (100 mL). The solution was washed with 1 M HCl (1 × 30 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was crystallized from ethyl acetate, to give a white solid (0.350 g, 64%), mp 84–86 °C; R_f = 0.33 (ethyl acetate/petroleum ether = 2:1); IR (KBr) 3410, 2227 (CN), 1676, 1654, 1501, 1400, 1278, 1248, 1049, 751, 545 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.86–2.10 (m, 2H, CHC$\underline{H_2}$), 3.59–3.67 (m, 2H, CH_2O), 4.68 (t, 1H, J = 5.4 Hz, OH), 4.89 (dd, 1H, J_1 = 9.2 Hz , J_2 = 4.1 Hz, CH), 5.24 (s, 2H, NCH_2), 6.94–7.05 (m, 4H, Ar-H), 7.44 (d, 2H, J = 8.4 Hz, H-3, H-5), 7.81 (d, 2H, J = 8.4 Hz, H-2, H-6). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 34.06 (CH_2), 44.64 (CH_2), 57.06 (CH_2), 74.33 (CH), 110.94 (Ar-C), 116.33 (Ar-C/CN), 117.99 (Ar-C/CN), 119.53 (Ar-C/CN), 123.58 (Ar-C), 124.85 (Ar-C), 128.33 (2,6/3,5-C), 129.17 (Ar-C), 133.50 (2,6/3,5-C), 143.31 (Ar-C), 144.55 (Ar-C), 167.16 (C=O). MS (EI) *m/z* (%): 308 (M^+, 51), 264 (11), 252 (6), 235 (6), 223 (9), 192 (59), 174 (20), 162 (24), 148 (73), 120 (49), 116 (100), 108 (26), 93 (7), 89 (31), 80 (14), 65 (16). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09; found C, 70.11; H, 5.26; N, 9.04.

3. 4. General procedure for the synthesis of compounds 7b and 7c by cyclization of N-substituted 2-aminophenols 6b and 6c (Method B)

To a solution of **6b** or **6c** (6.69 mmol) in anhydrous DMF (30 mL) in an 80 mL process vial, NaH (401 mg, 10.03 mmol, 60% dispersion in paraffin) was added by portions. After 30 minutes of stirring under an argon atmosphere, 3-bromodihydrofuran-2(3*H*)-one (**2**) (1.07 mL, 10.03 mmol, 90%) was added, the vial was sealed, placed in a microwave reactor and heated at 180 °C for 30 minutes. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (80 mL). The organic phase was washed with water (3 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compounds **7b** and **7c** were isolated from the residue by flash column chromatography using ethyl acetate/petroleum ether (1:2 → 2:1) as eluent.

4-((2-(2-Hydroxyethyl)-3-oxo-2,3-dihydro-1,4-benzoxazin-4-yl)methyl)benzonitrile (7b). Yield: 68%. The product was identical in all respects (mp, IR, NMR, MS) to **7b** obtained by method A.

4-(4-Chlorobenzyl)-2-(2-hydroxyethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one (7c). Yield: 71%; white solid; mp 82–85 °C (lit.[4] 86–88 °C); R_f = 0.45 (ethyl acetate/petroleum ether = 2:1); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.84–2.10 (m, 2H, CHC$\underline{H_2}$), 3.59–3.68 (m, 2H, CH_2O), 4.69 (t, 1H, J = 5.3 Hz, OH), 4.86 (dd, 1H, J_1 = 9.2 Hz , J_2 = 4.1 Hz, CH), 5.14 (s, 2H, NCH_2), 6.93–7.05 (m, 4H, ArH), 7.28 (d, 2H, J = 8.6 Hz, H-2,6/3,5), 7.39 (d, 2H, J = 8.6 Hz, H-2,6/3,5).

3. 5. General procedure for the synthesis of aldehydes 8b and 8c by oxidation of compounds 7b and 7c

Dimethyl sulfide (0.095 mL, 1.30 mmol) was added to a stirred solution of *N*-chlorosuccinimide (130 mg, 0.973 mmol) in dichloromethane (5 mL) at 0 °C under an argon atmosphere. The resulting mixture was stirred for 30 minutes at 0 °C and then cooled down to –25 °C. A solution of alcohol **7b** or **7c** (0.649 mmol) in dichloromethane (2 mL) was added dropwise over 10 minutes. Stirring was continued for 3 hours at –25 °C and then a solution of triethylamine (0.136 mL, 0.973 mmol) in dichloromethane (0.5 mL) was added dropwise. Reaction mixture was stirred at –25 °C for another 10 minutes, after which the cooling bath was removed and the mixture was allowed to reach room temperature. After 20 minutes dichloromethane (20 mL) was added and the organic phase washed with 0.5 M HCl (1 × 10 mL), water (2 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compounds **8b** and **8c** were isolated from the residue by flash column chromatography using ethyl acetate/petroleum ether (1:2) as eluent.

4-((3-Oxo-2-(2-oxoethyl)-2,3-dihydro-1,4-benzoxazin-4-yl)methyl)benzonitrile (8b). Yield: 60%; white crystals; mp 146–148 °C; R_f = 0.38 (ethyl acetate/petroleum ether = 1:1); IR (KBr) 3429, 3054, 2922, 2832, 2734, 2231, 1720, 1676, 1610, 1594, 1503, 1467, 1405, 1374, 1303, 1283, 1248, 1106, 917, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.20 (ddd, 1H, ^2J = 17.7 Hz, $^3J_1$ = 6.6 Hz, $^3J_2$ = 1.2 Hz, H_A from CHC$\underline{H_2}$), 3.33 (ddd, 1H, ^2J = 17.7 Hz, $^3J_1$ = 4.8 Hz, $^3J_2$ = 0.9 Hz, H_B from CHC$\underline{H_2}$), 5.12 (dd, 1H, J_1 = 6.6 Hz , J_2 = 4.8 Hz, C$\underline{H}CH_2$), 5.23 (AB-system, 2H, ^2J = 16.5 Hz NCH_2), 6.78–7.04 (m, 4H, ArH), 7.39 (d, 2H, J = 8.4 Hz, H-3, H-5), 7.65 (d, 2H, J = 8.4 Hz, H-2, H-6), 9.91 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 44.68 (CH_2), 44.81 (CH_2), 72.68 (CH), 110.98 (Ar-C), 116.59 (Ar-C/CN), 117.63 (Ar-C/CN), 119.55 (Ar-C/CN), 123.79 (Ar-C), 124.88 (Ar-C), 128.44 (2,6/3,5-C), 129.18 (Ar-C), 133.45 (2,6/3,5-C), 143.13 (Ar-C), 145.14 (Ar-C), 166.32 (C=O), 200.30 (CHO). MS (ESI+) *m/z* (%): 307 (MH^+, 100), 261 (10), 214 (78), 205 (12), 166 (8), 164 (12), 158 (30), 140 (10). Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15; found C, 70.60; H, 4.47; N, 9.18.

2-(4-(4-Chlorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetaldehyde (8c). Yield: 61%; white crystals; mp 85–87 °C; R_f = 0.49 (ethyl acetate/petroleum ether = 1:1); IR (KBr) 3425, 3049, 2983, 2951, 2910, 2853,

2833, 2734, 1915, 1720, 1676, 1607, 1503, 1466, 1443, 1399, 1356, 1318, 1302, 1281, 1236, 1128, 1092, 1015, 916, 839, 794, 745 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.09 (ddd, 1H, ^2J = 17.6 Hz, $^3J_1$ = 6.6 Hz, $^3J_2$ = 1.7 Hz, H_A from CH$\underline{CH_2}$), 3.19 (ddd, 1H, ^2J = 17.6 Hz, $^3J_1$ = 5.0 Hz, $^3J_2$ = 1.4 Hz, H_B from CH$\underline{CH_2}$), 5.16 (AB-system, 2H, ^2J = 17.1 Hz NCH$_2$), 5.29 (dd, 1H, J_1 = 6.6 Hz , J_2 = 5.0 Hz, $\underline{CH}CH_2$), 6.96–7.05 (m, 4H, ArH), 7.33 (d, 2H, J = 8.7 Hz, H-2,6/3,5), 7.40 (d, 2H, J = 8.7 Hz, H-2,6/3,5), 9.75 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 44.32 (CH$_2$), 44.67 (CH$_2$), 72.68 (CH), 116.72 (Ar-C), 117.59 (Ar-C), 123.76 (Ar-C), 124.77 (Ar-C), 129.21 (Ar-C), 129.48 (4 × Ar-C), 132.70 (Ar-C), 136.28 (Ar-C), 145.14 (Ar-C), 166.19 (C=O), 200.28 (CHO). MS (ESI+) *m/z* (%): 318 ([M+2]H$^+$, 15), 316 (MH$^+$, 38), 214 (48), 164 (6), 158 (32), 141 (15), 125 (10). HRMS for $C_{17}H_{15}ClNO_3$: calculated 316.0735; found 316.0742. Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47; N, 4.44; found C, 64.38; H, 4.27; N, 4.29.

3. 6. General procedure for the synthesis of 5-ylidene-2-thioxothiazolidin-4-ones and 5-ylidene-thiazolidine-2,4-diones 9-13

To a suspension of aldehyde **8b** or **8c** (0.475 mmol) and rhodanine, thiazolidine-2,4-dione or 2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid (0.475 mmol) in ethanol (2 mL) in a 10 mL process vial, glacial acetic acid (2.72 μL, 0.048 mmol) and piperidine (4.69 μL, 0.048 mmol) were added. The vial was sealed, placed in a microwave reactor and heated at 150 °C for 20 minutes. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (30 mL). The organic phase was washed with 0.5 M solution of NaOH (10 mL), water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compounds **9–13** were isolated from the residue by flash column chromatography using ethyl acetate/petroleum ether or dichloromethane/methanol as eluent.

(*Z*)-4-((3-Oxo-2-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)ethyl)-2,3-dihydro-1,4-benzoxazin-4-yl)methyl) benzonitrile (9). Yield: 52%; yellow solid; mp 210–215 °C; R_f = 0.48 (ethyl acetate/petroleum ether = 1:1); IR (KBr) 3433, 3186, 3121, 2925, 2851, 2228, 1720, 1684, 1609, 1500, 1467, 1430, 1402, 1301, 1248, 1203, 1065, 751 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.96–3.01 (m, 2H, $\underline{CH_2}CH$), 4.85 (t, 1H, J = 5.6 Hz, O$\underline{CH}CH_2$), 5.21 (AB-system, 2H, ^2J = 16.5 Hz, NCH$_2$), 6.80 (dd, 1H, J_1 = 7.5 Hz, J_2 < 1.0 Hz, $\underline{CH}$CS), 6.95–7.09 (m, 4H, ArH), 7.36 (d, 2H, J = 8.4 Hz, H-3, H-5), 7.65 (d, 2H, J = 8.4 Hz, H-2, H-6), 9.52 (br s, 1H, NH). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 33.28 (CH$_2$), 45.74 (CH$_2$), 75.54 (OCH), 112.19, 115.65, 118.08, 118.80, 123.90, 125.23, 127.71 (2,6/3,5-C), 128.71, 131.87, 132.77, 133.21 (2,6/3,5-C), 141.60, 144.63, 165.32 (C=O), 166.61 (C=O), 193.17 (C = S). MS (ESI+) *m/z* (%): 444 (MNa$^+$, 10), 422 (MH$^+$, 80), 283 (8), 261 (20), 214 (17), 205 (85), 161 (100), 144 (28), 141 (31). Anal. Calcd for $C_{21}H_{15}N_3O_3S_2$: C, 59.84; H, 3.59; N, 9.97; found C, 59.75; H, 3.87; N, 10.17.

(*Z*)-4-(4-Chlorobenzyl)-2-(2-(4-oxo-2-thioxothiazolidin-5-ylidene)ethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one (10). Yield: 48%; yellow solid; mp 191–194 °C; R_f = 0.28 (ethyl acetate/petroleum ether = 1:2); IR (KBr) 3430, 3184, 3132, 2922, 2851, 1717, 1659, 1500, 1466, 1418, 1402, 1298, 1247, 1204, 1090, 1065, 747, 661 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.95–3.00 (m, 2H, $\underline{CH_2}CH$), 4.84 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.2 Hz, O$\underline{CH}CH_2$), 5.13 (AB-system, 2H, ^2J = 16.2 Hz, NCH$_2$), 6.88 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.5 Hz, $\underline{CH}$CS), 6.97–7.08 (m, 4H, ArH), 7.20 (d, 2H, J = 8.7 Hz, H-2,6/3,5), 7.32 (d, 2H, J = 8.7 Hz, H-2,6/3,5), 9.46 (br s, 1H, NH). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 33.30 (CH$_2$), 45.47 (CH$_2$), 75.53 (OCH), 115.93, 117.88, 123.77, 124.96, 128.46 (2,6/3,5-C), 128.91, 129.55 (2,6/3,5-C), 132.18, 132.64, 133.92, 134.67, 144.58, 165.21 (C=O), 166.63 (C=O), 193.26 (C = S). MS (ESI+) *m/z* (%): 433 ([M+2]H$^+$, 48), 431 (MH$^+$, 100), 419 (27), 399 (6), 391 (37), 372 (5), 325 (56), 312 (16), 298 (8), 279 (12). Anal. Calcd for $C_{20}H_{15}ClN_2O_3S_2$: C, 55.74; H, 3.51; N, 6.50; found C, 55.54; H, 3.60; N, 6.44.

(*Z*)-5-(2-(4-(4-Chlorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethylidene)-thiazolidine-2,4-dione (11). Yield: 44%; yellow solid; mp 70–75 °C; R_f = 0.29 (ethyl acetate/petroleum ether = 1:2); IR (KBr) 3439, 3190, 3065, 2927, 2854, 2769, 1749, 1702, 1608, 1500, 1401, 1319, 1302, 1278, 1249, 1158, 1093, 1015, 799, 750 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.94–3.01 (m, 2H, $\underline{CH_2}CH$), 4.83 (dd, 1H, J_1 = 6.8 Hz, J_2 = 5.0 Hz, O$\underline{CH}CH_2$), 5.13 (AB-system, 2H, ^2J = 16.1 Hz, NCH$_2$), 6.88 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.5 Hz, $\underline{CH}$CS), 6.94–7.06 (m, 4H, ArH), 7.20 (d, 2H, J = 8.7 Hz, H-2,6/3,5), 7.32 (d, 2H, J = 8.7 Hz, H-2,6/3,5), 8.82 (br s, 1H, NH). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 33.12 (CH$_2$), 45.44 (CH$_2$), 75.57 (OCH), 115.90, 117.89, 123.73, 124.94, 128.46 (2,6/3,5-C), 128.91, 129.54 (2,6/3,5-C), 129.70, 133.15, 133.91, 134.70, 144.57, 164.92 (C=O), 165.28 (C=O), 166.65 (C=O). MS (ESI+) *m/z* (%): 437 (MNa$^+$, 6), 417 ([M+2]H$^+$, 42), 415 (MH$^+$, 100), 391 (8), 339 (5), 318 (7), 312 (26), 296 (8), 257 (20), 241 (9), 236 (28). Anal. Calcd for $C_{20}H_{15}ClN_2O_4S$: C, 57.90; H, 3.64; N, 6.75; found C, 57.79; H, 3.84; N, 6.54.

(*Z*)-2-(5-(2-(4-(4-Cyanobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (12). Yield: 38%; yellow solid; mp 65–75 °C; R_f = 0.24 (ethyl acetate/petroleum ether/AcOH = 10:10:1); IR (KBr) 3494, 3446, 3290, 3053, 2925, 2854, 2627, 2229, 1723, 1683, 1609, 1500, 1468, 1402, 1361, 1328, 1245, 1198, 1140, 1050, 752 cm^{-1}. ^{1}H NMR (CDC-

l_3, 300 MHz) δ 2.99–3.04 (m, 2H, $\underline{CH_2}CH$), 4.85–4.89 (m, 3H, $O\underline{CH}CH_2$, CH_2CO), 5.21 (AB-system, 2H, ^2J = 16.5 Hz, NCH_2), 6.45 (br s, 1H, COOH + H_2O), 6.80 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.2 Hz, $\underline{CH}CS$), 6.95–7.19 (m, 4H, ArH), 7.36 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 7.65 (d, 2H, *J* = 8.4 Hz, H-3, H-5). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.35 (CH_2), 44.65 (CH_2), 45.72 (CH_2), 75.56 (OCH), 112.13, 115.65, 118.12, 118.84, 123.89, 125.27, 127.71 (2,6/3,5-C), 128.64, 130.20, 132.67, 133.23 (2,6/3,5-C), 141.59, 144.61, 165.41 (C=O), 165.60 (C=O), 169.88 (C=O), 193.13 (C = S). MS (ESI+) *m/z* (%): 502 (MNa^+, 34), 480 (MH^+, 70), 462 (75), 457 (12), 441 (20), 429 (18), 413 (52), 400 (29), 312 (30), 291 (53). HRMS for $C_{23}H_{18}N_3O_5S_2$: calculated 480.0682; found 480.0701. HPLC: Phenomenex Luna 5u C18 column; mobile phase: 70% acetonitrile, 30% trifluroacetic acid (0.01%), flow rate 1.0 mL/min; injection volume: 10 μL; retention time: 4.758 min (96.27% at 218 nm, 96.83% at 254 nm).

(*Z*)-2-(5-(2-(4-(4-Chlorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)ethylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (13). Yield: 42%; yellow solid; mp 65–75 °C; R_f = 0.35 (ethyl acetate/petroleum ether/AcOH = 10:10:1); IR (KBr) 3439, 3048, 2930, 2607, 1724, 1681, 1500, 1468, 1401, 1326, 1247, 1199, 1092, 1050, 1214, 798, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.98–3.03 (m, 2H, $\underline{CH_2}CH$), 4.83–4.87 (m, 3H, $O\underline{CH}CH_2$, CH_2CO), 5.13 (AB-system, 2H, ^2J = 15.9 Hz, NCH_2), 5.58 (br s, 1H, COOH + H_2O), 6.88 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz, $\underline{CH}CS$), 6.94–7.18 (m, 4H, ArH), 7.19 (d, 2H, *J* = 8.9 Hz, H-2,6/3,5), 7.32 (d, 2H, *J* = 8.9 Hz, H-2,6/3,5). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.39 (CH_2), 44.67 (CH_2), 45.49 (CH_2), 75.54 (OCH), 115.93, 117.93, 123.76, 125.01, 128.47 (2,6/3,5-C), 128.86, 129.55 (2,6/3,5-C), 130.05, 132.97, 133.91, 134.65, 144.55, 165.32 (C=O), 165.58 (C=O), 170.59 (C=O), 193.19 (C = S). MS (ESI+) *m/z* (%): 513 ($[M+2]Na^+$, 40), 511 (MNa^+, 100), 491 ($[M+2]H^+$, 30), 489 (MH^+, 62), 482 (31), 457 (23), 440 (25), 413 (58), 391 (20), 365 (19), 340 (15), 301 (25). HRMS for $C_{22}H_{18}ClN_2O_5S_2$: calculated 489.0340; found 489.0365. HPLC: Phenomenex Luna 5u C18 column; mobile phase: 70% acetonitrile, 30% trifluroacetic acid (0.01%), flow rate 1.0 mL/min; injection volume: 10 μL; retention time: 7.576 min (96.04% at 218 nm, 95.09% at 254 nm).

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5. References

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Povzetek

Opisana je enostavna sinteza 4-benzil-2-(2-(4-okso-2-tioksotiazolidin-5-iliden)etil)-2*H*-1,4-benzoksazin-3(4*H*)-onov in 5-(2-(4-benzil-3-okso-3,4-dihidro-2*H*-1,4-benzoksazin-2-il)etiliden)tiazolidin-2,4-dionov iz 2-aminofenola ter derivatov rodanina in tiazolidin-2,4-diona s pomočjo mikrovalovnega reaktorja.