Efficient Synthesis of 5-(2-Hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones and 5-(2-Hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones

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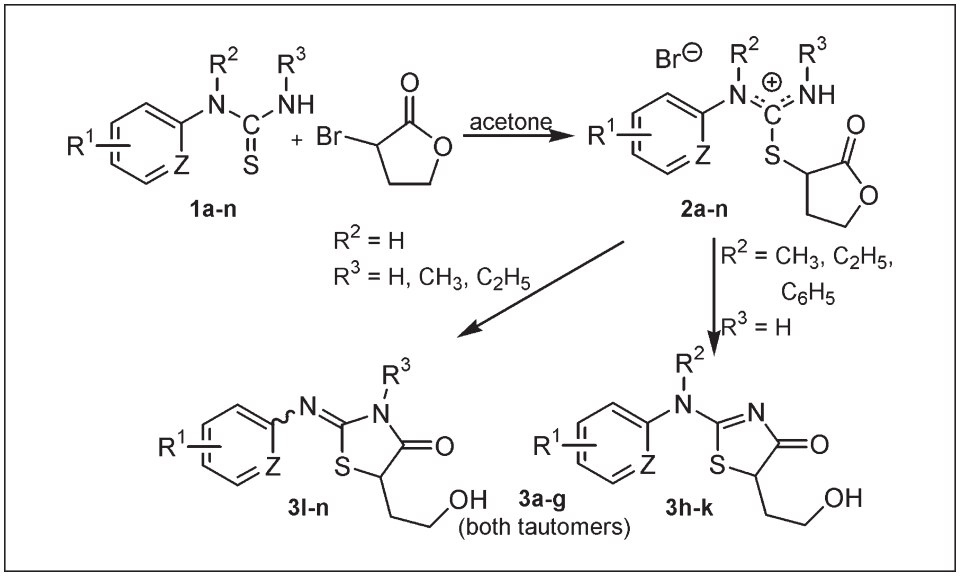
Dedicated to Professor Vladimír Macháček on the occasion of his 65th birthday.



A new method for the synthesis of substituted 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones and 5-(2-hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones is described, starting from phenylthioureas and 3-bromotetrahydrofuran-2-one. The reaction proceeds under mild conditions, is very simple to perform, and is applicable to a relatively wide range of substituents in benzene nucleus. Some 1,3-thiazolidin-4-ones show dynamic NMR behavior in solution because of prototropy tautomerism and *E*-/*Z*-stereoisomerism.

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INTRODUCTION

Natural [1] as well as synthetic heterocyclic compounds, containing a thiazole ring system often exhibit good antifungal [2], antibacterial [3], and anti-inflammatory [4] activity and are widely used in new pharmaceutical and agrochemical compounds. Also thiazolidine cycle belongs among pharmaceutically significant heterocycles representing an important group of per oral antidiabetics [5]. Thiazole skeleton is also present in many dyes and pigments [6].

There exist a lot of synthetic methods leading to thiazole or thiazolidine skeleton [7] from which those involving rearrangements of another heterocyclic rings represent new interesting alternative. Such rearrangements may provide fascinating routes to derivatives that can be obtained only with great difficulties—or not at all—by other procedures.

RESULTS AND DISCUSSION

Recently, we have found [8] that substituted *S*-(1-phenylpyrrolidin-2-on-3-yl) isothiuronium salts in weakly basic medium undergo an intramolecular transformation reaction. In this particular case, the γ-lactam ring is cleaved and a thiazolidine ring is formed, i.e. substituted 2-imino-5-[2-(phenylamino)ethyl]-1,3-thiazolidin-4-ones are obtained in very good yields. In this work, we extended the scope of this transformation replacing γ-lactam cycle by γ-lacton cycle. In the first step, we have prepared corresponding *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(subst. phenyl) isothiuronium

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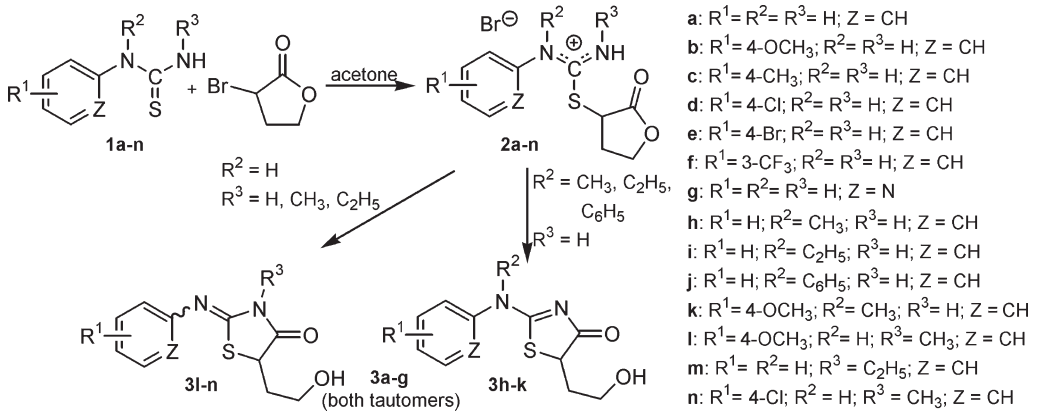
Scheme 1



bromides (**2a–n**) from substituted phenylthioureas (**1a–n**) and 3-bromotetrahydrofuran-2-one (α-bromo-γ-butyrolactone), which then underwent rearrangement in basic medium to give desired 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones (**3a–g**, **3l–n**) or 5-(2-hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones (**3h–k**) (Scheme 1). In most cases, it was impossible to characterize pure isothiuronium salts by NMR because of their spontaneous cyclization giving **3a–n** in DMSO-d_6 solution.

The only exception was *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)isothiuronium bromide (**2b**) which was prepared in a pure form and characterized by ^{1}H, ^{13}C NMR, and microanalysis. The reason for enhanced reactivity of the other derivatives lies in the presence of electron-withdrawing group in the benzene nucleus or methyl group on nitrogen(s). All of these substituents facilitate rearrangement involving bicyclic tetrahedral intermediate.

Similar method [9] starting from substituted phenylthioureas and ethyl 3-bromo-5-methyl-2-oxo-tetrahydrofuran-3-carboxylate, ethyl 3-bromo-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate, and ethyl 3-bromo-5-isobutoxymethyl-2-oxotetrahydrofuran-3-carboxylate giving spirocyclic 2-aza-3-amino or substituted amino-4-thia-7-oxa-8-methyl-8-substituted spiro[4.4]-2-nonene-1,6-diones was recently published. In this case, nitrogen atom of isothiuronium salt attacks ethoxycarbonyl group in position 3 instead of lactone carbonyl group.

Prepared 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones (**3a–g**, **3l–n**) 5-(2-hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones (**3h–k**) were characterized by ^{1}H, ^{13}C NMR, and microanalyses and some of them also by X-ray diffraction (Figs. 1, 2) and mass spectroscopy.

Compounds **3a–f** carrying hydrogen atoms on both nitrogen atoms ($R^2 = R^3 = H$) exist in the form of two tautomers differing in the position of C=N double bond. Moreover, the tautomer with exocyclic double bond exists as a mixture of *E*- and *Z*-stereoisomers in the proportion depending on substitution of the benzene nucleus and temperature. This tautomerism and stereoisomerism, which can be seen in both ^{1}H and ^{13}C NMR spectra was previously studied for C-5 unsubstituted 2-phenyliminothiazolidin-4-ones by several authors [10].

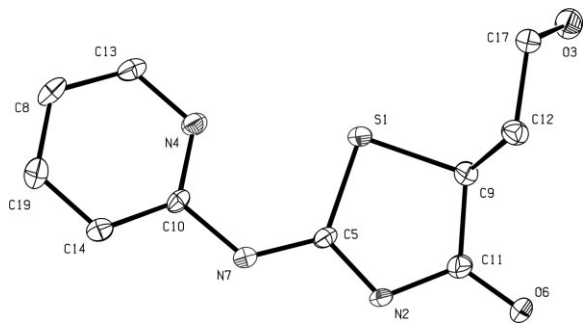


Figure 1. ORTEP view of compound **3g** (thermal ellipsoids at 40% probability).

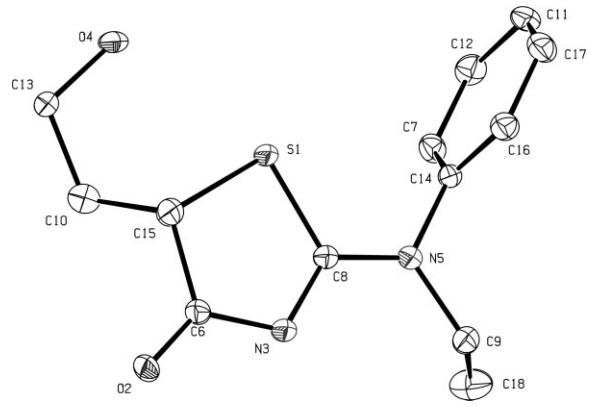


Figure 2. ORTEP view of compound **3i** (thermal ellipsoids at 40% probability).

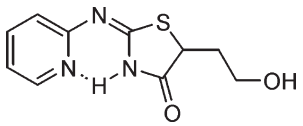


Figure 3. Intramolecular hydrogen bond in solution of **3g** in DMSO-d_6.

In the case of compounds **3h–k** (R^2 = CH_3, C_2H_5, C_6H_5; R^3 = H) and **3l–n** (R^2 = H; R^3 = CH_3, C_2H_5), prototropic tautomerism is absent due to C=N double bond fixation and stereoisomerism is possible only for **3l–n**. In both ^{1}H and ^{13}C NMR spectra of **3g**, there is only one set of signals. From this observation, it can be deduced that compound **3g** exists only as *E*-stereoisomer stabilized in solution by intramolecular hydrogen bond (Fig. 3). On the other hand, in crystal lattice two molecules of **3g** are connected by intermolecular hydrogen bonds (N_{ring}—H···N_{imino}), which constrains *Z*-configuration of C=N double bond (Fig. 1).

EXPERIMENTAL

Starting arylthioureas **1a–n** were prepared and purified by known methods [11]. All other chemicals were purchased from commercial suppliers and used as received. Before use, solvents were dried and distilled. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz instrument in DMSO-d_6 solution. Chemical shifts δ are referenced to solvent residual peak δ(DMSO-d_6) = 2.50 (^{1}H) and 39.6 ppm (^{13}C). Coupling constants *J* are quoted in Hz. ^{13}C NMR spectra were measured in a standard way and by means of the APT (attached proton test) pulse sequence to distinguish CH, CH_3, and CH_2, C_{quart}. Proton–proton connectivities were found by gs-COSY. Protonated carbon atoms were assigned by gs-HSQC spectra. All NMR experiments were performed with the aid of the manufacturer's software. The microanalyses were performed on an apparatus of Fisons Instruments, EA 1108 CHN. The mass spectra (EI) were recorded on an Agilent Technologies Co. gas chromatograph 6890N with a mass detector 5973 Network for samples dissolved in either ether or acetone.

X-ray Crystallography of 3g and 3i. The colorless single crystals of **3g** and **3i** were grown from DMSO solution. The X-ray diffraction data were collected at 150(2)K on a Nonius KappaCCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods (SIR92) [12]. All reflections were used in the structure refinement based on F2 by full-matrix least-squares technique (SHELXL97) [13].

Compound 3g. $C_{10}H_{11}N_3O_2S$; triclinic, space group P-1, *a* = 5.7500(3), *b* = 8.7980(3), *c* = 10.9290(6) (Å), α = 90.703(4)°, β = 95.787(4)°, γ = 107.550(4)°, *Z* = 2, *V* = 523.93(4) Å^3, Dc = 1.504 g·cm^{-3}. Intensity data collected with 3.0 ≤ θ ≤ 27.5°; 2404 independent reflections measured; 2000 observed [$I > 2\sigma(I)$]. Final *R* index = 0.0589 (observed reflections), Rw = 0.1329 (all reflections), *S* = 1.112. CCDC 704421.

Compound 3i. $C_{13}H_{16}N_2O_2S$; monoclinic, space group P-21/c, *a* = 9.3440(7), *b* = 18.8800(1), *c* = 7.5690(5) (Å), α = 90.000(5)°, β = 105.913(6)°, γ = 90.000(5)°, *Z* = 4, *V* = 1284.11(15) Å^3, Dc = 1.367 g·cm^{-3}. Intensity data collected with 3.0 ≤ θ ≤ 27.5°; 2849 independent reflections measured; 2406 observed [$I > 2\sigma(I)$]. Final *R* index = 0.0608 (observed reflections), Rw = 0.1481 (all reflections), *S* = 1.062. CCDC 704422.

Isothiuronium salts 2; General Procedure. To a hot solution of *N*-arylthiourea **1a–n** (5 mmol) in dry acetone 5 mmol (0.83 g) of 3-bromotetrahydrofuran-2-one was injected. Reaction mixture was refluxed for 5 min and left to stand at room temperature for 2 days. Then precipitated crystals were collected by filtration and submitted to cyclization. In the case of compounds **2d–g**, **2j**, **2l**, and **2n**, no crystals precipitated so that the solution was evaporated and resulting oil was submitted to cyclization without any further purification (yields are given only for **3d–g**, **3j**, **3l**, and **3n**). Crystalline isothiuronium salts **1a–c**, **1h**, **1i**, **1k**, and **1m** were characterized by melting point and by microanalysis. Only in the case of salt **1b**, it was possible to measure ^{1}H and ^{13}C NMR spectra immediately after its dissolution in DMSO-d_6. For all the other salts quick transformation to **3a–n** was observed during the measurement.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl isothiuronium bromide (2a). Yield: 1.24g (78%); m.p. 153–155°C. *Anal*. Calcd. for $C_{11}H_{13}BrN_2O_2S$: C, 41.65; H, 4.13; N, 8.83; S, 10.11; Br, 25.19. Found: C, 41.74; H, 4.13; N, 9.01; S, 10.16; Br, 25.05.

S-(2-Oxotetrahydrofuran-3-yl)-N-(4-methoxyphenyl) isothiuronium bromide (2b). Yield: 0.77g (44%); m.p. 154–156°C; ^{1}H NMR (500 MHz): δ = 2.29 (m, 2H, CH_2), 3.65 (m, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 4.72 (dd, *J* = 7.5 and 4.5 Hz, 1H, SCH), 7.16 (AA′XX′, *J* = 9 Hz, 2H, ArH), 7.37 (AA′XX′, *J* = 9 Hz, 2H, ArH), 10.79 (vbs, 3H, NH and NH_2).

^{13}C NMR (125 MHz): δ = 33.6 (CH_2), 47.5 (S—CH), 55.7 (OCH_3), 57.8 (O—CH_2), 115.3 (Ar C-3), 123.6 (Ar C-1), 129.6 (Ar C-2), 160.7 (Ar C-4), 174.1 (C=N), 175.0 (C=O). *Anal*. Calcd. for $C_{12}H_{15}BrN_2O_3S$: C, 41.51; H, 4.35; N, 8.07; S, 9.23; Br, 23.01. Found: C, 41.56; H, 4.29; N, 8.07; S, 9.08; Br, 22.99.

S-(2-Oxotetrahydrofuran-3-yl)-N-(4-methylphenyl) isothiuronium bromide (2c). Yield: 0.83g (50%); m.p. 160–164°C. *Anal*. Calcd. for $C_{12}H_{15}BrN_2O_2S$: C, 43.51; H, 4.56; N, 8.46; S, 9.68; Br, 24.12. Found: C, 43.71; H, 4.60; N, 8.26; S, 9.45; Br, 24.32.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl-N-methyl isothiuronium bromide (2h). Yield: 1.3g (78%); m.p. 155–159°C. *Anal*. Calcd. for $C_{12}H_{15}BrN_2O_2S$: C, 43.51; H, 4.56; N, 8.46; S, 9.68; Br, 24.12. Found: C, 43.51; H, 4.86; N, 8.35; S, 9.90; Br, 24.03.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl-N-ethyl isothiuronium bromide (2i). Yield: 1.59g (92%); m.p. 155–157°C. *Anal*. Calcd. for $C_{13}H_{17}BrN_2O_2S$: C, 45.23; H, 4.96; N, 8.11; S, 9.29; Br, 23.14. Found: C, 45.14; H, 5.11; N, 8.08; S, 9.03; Br, 23.20.

S-(2-Oxotetrahydrofuran-3-yl)-N-(4-methoxyphenyl)-N-methyl isothiuronium bromide (2k). Yield: 0.96g (53%); m.p. 164–167°C. *Anal*. Calcd. for $C_{13}H_{17}BrN_2O_3S$: C, 43.22; H, 4.74; N, 7.75; S, 8.87; Br, 22.12. Found: C, 43.06; H, 4.80; N, 7.66; S, 8.68; Br, 22.03.

S-(2-Oxotetrahydrofuran-3-yl)-N-phenyl-N′-ethyl isothiuronium bromide (2m). Yield: 1.3g (75%); m.p. 144–146°C. *Anal*. Calcd. for $C_{13}H_{17}BrN_2O_2S$: C, 45.23; H, 4.96; N, 8.11; S, 9.29; Br, 23.14. Found: C, 45.43; H, 5.08; N, 7.96; S, 9.10; Br, 23.14.

5-(2-Hydroxyethyl)-2-phenyliminothiazolidin-4-ones (3a-n); General Procedure. Isothiuronium salts (2 mmol) were dissolved in a minimum amount of aqueous ammonia (25%) and solution was stirred until precipitation of products. Crude products (yields 80–90%) were filtered off and recrystallized from water. Isothiuronium salts **2k–m** were quite insoluble in aqueous ammonia and stirring of suspension gave an oil which was extracted by dichloromethane. Extract was dried and evaporated to give oil solid which was characterized.

5-(2-Hydroxyethyl)-2-(phenylimino)-1,3-thiazolidin-4-one (3a). Yield: 0.44g (94%); m.p. 123–124°C; ^{1}H NMR (500 MHz): δ = 1.79 and 2.26 (2 × m, 2H, CH_2), 3.45 (m, 2H, OCH_2), 4.29 (m, 1H, S—CH), 4.74 (m, 1H, OH), 7.00 and 7.72 (2 × m, 2H, Ar H-2,6), 7.12 (m, 1H, Ar H-4), 7.36 (m, 2H, Ar H-3,5), 11.14, and 11.71 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 36.0 and 36.6 (CH_2), 47.7 and 52.1 (S—CH), 58.8 and 59.6 (O—CH_2), 120.5 and 121.6 (Ar C-2,6), 124.7 and 124.8 (Ar C-4), 129.1 and 129.4 (Ar C-3,5), 138.9 and 146.8 (Ar C-1), 177.5 and 178.5 (C=N), 190.6 (C=O). *Anal*. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86; S, 13.57. Found: C, 56.13; H, 5.32; N, 11.62; S, 13.35. EI-MS: *m/z* 236 [M^+], 218 [M^+—H_2O], 205, 192, 160, 151, 145, 135, 118 (100 %), 109, 101, 91, 77, 71, 65, 59, 51.

5-(2-Hydroxyethyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (3b). Yield: 0.48g (91%); m.p. 124–126°C; ^{1}H NMR (500 MHz): δ = 1.76 and 2.27 (2 × m, 2H, CH_2), 3.52 (m, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 4.26 (dt, *J* = 11.8 and 3.5 Hz, 1H, S—CH), 4.73 (m, 1H, OH), 6.94 (m, 2H, Ar H-3,5), 6.99 and 7.60 (2 × m, 2H, Ar H-2,6), 11.02 and 11.56 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 36.0 and 36.5 (CH_2), 48.4 and 52.0 (S—CH), 55.2 (OCH_3), 58.8 and 59.5 (O—CH_2), 114.0 and 114.4 (Ar C-3,5), 121.9 and 123.3 (Ar C-2,6), 131.9 (Ar C-1), 156.2 and 156.7 (Ar C-4), 176.6 (C=N), 190.3 (C=O). *Anal*. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 55.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 55.24; H, 5.26; N, 10.64; S, 12.01. EI-MS: *m/z* 266 [M^+], 248 [M—H_2O], 235, 222, 207, 191, 175, 165, 148, 133 (100%), 118, 105, 90, 78, 63, 55, 41.

5-(2-Hydroxyethyl)-2-[(4-methylphenyl)imino]-1,3-thiazolidin-4-one (3c). Yield: 0.43g (87%); m.p. 124–126°C; ^{1}H NMR (500 MHz): δ = 1.79 and 2.30 (2 × m, 2H, CH_2), 2.27 (s, 3H, CH_3), 3.52 (m, 2H, OCH_2), 4.27 (m, 1H, S—CH), 4.75 (m, 1H, OH), 6.91 and 7.14 (2 × AA′XX′, 2H, Ar H-2,6), 7.15 and 7.59 (2 × AA′XX′, 2H, Ar H-3,5), 11.08 and 11.64 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 20.3 (CH_3), 36.1 and 36.7 (CH_2), 48.1 and 52.1 (S—CH), 58.9 and 59.7 (O—CH_2), 120.4 and 121.7 (Ar C-2,6), 129.5 and 129.8 (Ar C-3,5), 134.0 (Ar C-4), 136.5 and 143.3 (Ar C-1), 177.1 and 179.4 (C=N), 190.6 (C=O). *Anal*. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.59; H, 5.69; N, 10.93; S, 12.74.

5-(2-Hydroxyethyl)-2-[(4-chlorophenyl)imino]-1,3-thiazolidin-4-one (3d). Overall yield: 1.7g (97%); m.p. 136–137°C; ^{1}H NMR (500 MHz): δ = 1.79 and 2.25 (2 × m, 2H, CH_2), 3.52 (m, 2H, OCH_2), 4.31 (m, 1H, S—CH), 4.75 (bs, 1H, OH), 6.96 and 7.37 (2 × AA′XX′, 2H, Ar H-2,6), 7.42 and 7.77 (2 × AA′XX′, 2H, Ar H-3,5), 11.26 and 11.80 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.8 and 36.5 (CH_2), 47.5 and 52.2 (S—CH), 58.7 and 59.6 (O—CH_2), 122.0 and 123.3 (Ar C-2,6), 128.6 (Ar C-4), 129.1 and 129.3 (Ar C-3,5), 137.1 and 146.7 (Ar C-1), 177.4 and 177.7 (C=N), 190.5 (C=O). *Anal*. Calcd. for $C_{11}H_{11}ClN_2O_2S$: C, 48.80; H, 4.10; N, 10.35; S, 11.84; Cl, 13.10. Found: C, 49.01; H, 4.27; N, 10.08; S, 11.60; Cl, 12.94.

5-(2-Hydroxyethyl)-2-[(4-bromophenyl)imino]-1,3-thiazolidin-4-one (3e). Overall yield: 1.21g; (61%) m.p. 140–141°C; ^{1}H NMR (500 MHz): δ = 1.81 and 2.26 (2 × m, 2H, CH_2), 3.50 (m, 2H, OCH_2), 4.31 (m, 1H, S—CH), 4.77 (bs, 1H, OH), 6.91 and 7.51 (2 × AA′XX′, 2H, Ar H-2,6), 7.56 and 7.67 (2 × AA′XX′, 2H, Ar H-3,5), 11.37 and 11.70 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.8 and 36.5 (CH_2), 47.5 and 52.1 (S—CH), 58.7 and 59.6 (O—CH_2), 116.7 (Ar C-4), 122.4 and 123.7 (Ar C-2,6), 132.0 and 132.3 (Ar C-3,5), 138.3 and 147.1 (Ar C-1), 176.6 (C=N), 190.6 (C=O). *Anal*. Calcd. for $C_{11}H_{11}BrN_2O_2S$: C, 41.92; H, 3.52; N, 8.89; S, 10.17; Br, 25.35. Found: C, 41.93; H, 3.71; N, 8.78; S, 10.40; Br, 24.98.

5-(2-Hydroxyethyl)-2-[(3-trifluoromethylphenyl)-imino]-1,3-thiazolidin-4-one (3f). Overall yield: 1.02g (53%); m.p. 130–131°C; ^{1}H NMR (500 MHz): δ = 1.83 and 2.26 (2 × m, 2H, CH_2), 3.52 (m, 2H, OCH_2), 4.34 (d, *J* = 6.0 Hz, 1H, S—CH), 4.78 (m, 1H, OH), 7.24 (m, 1H, Ar H-6), 7.48 (m, 1H, Ar H-4), 7.60 (m, 1H, Ar H-5), 7.89 and 8.22 (2 × m, 1H, Ar H-2), 11.02 and 11.56 (2 × bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.6 and 36.4 (CH_2), 47.4 and 52.2 (S—CH), 58.6 and 59.6 (O—CH_2), 124.1 (q, *J* = 272 Hz, CF_3), 130.1 (q, *J* = 31.6 Hz, Ar C-3), 116.6 and 121.1 (Ar C-2), 117.8 and 120.8 (Ar C-5), 124.0 and 130.5 (Ar C-4), 125.2 and 130.6 (Ar C-6), 139.6 and 149.1 (Ar C-1), 176.9 and 178.3 (C=N), 190.6 (C=O). *Anal*. Calcd. for $C_{12}H_{11}F_3N_2O_2S$: C, 47.37; H, 3.64; N, 9.21; S, 10.54. Found: C, 47.56; H, 3.67; N, 9.42; S, 10.31.

5-(2-Hydroxyethyl)-2-[(2-pyridyl)imino]-1,3-thiazolidin-4-one (3g). Overall yield: 1.34g (84%); m.p. 187–188°C; ^{1}H NMR (500 MHz): δ = 1.82 and 2.22 (2 × m, 2H, CH_2), 3.58 (m, 2H, OCH_2), 4.10 (d, *J* = 7.0 Hz, 1H, S—CH), 4.78 (bs, 1H, OH), 7.11 (m, 2H, Ar H-4,6), 7.82 (m, 1H, Ar H-5), 8.42 (m, 1H, Ar H-3), 11.93 (bs, 1H, NH); ^{13}C NMR (125 MHz): δ = 35.9 (CH_2), 47.2 (S—CH), 58.9 (O—CH_2), 118.2 (Ar C-6), 119.8 (Ar C-4), 138.7 (Ar C-5), 146.9 (Ar C-3), 156.2 (Ar C-1), 165.3 (C=N), 180.7 (C=O). *Anal*. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.41. Found: C, 50.52; H, 4.44; N, 17.76; S, 13.64. EI-MS: *m/z* 237 [M^+], 206, 119 (100%), 78, 55, 44.

5-(2-Hydroxyethyl)-2-[(N-phenyl-N-methyl)amino]-4,5-dihydro-1,3-thiazol-4-one (3h). Yield: 0.40g (80%); m.p. 112–115°C; ^{1}H NMR (500 MHz): δ = 1.67 and 2.24 (2 × m, 2H, CH_2), 3.44 (m, 2H, OCH_2), 3.50 (s, 3H, NCH_3), 4.21 (d, *J* = 10.9 Hz, 1H, S—CH), 4.69 (bs, 1H, OH), 7.47 (m, 5H, Ar H-2,3,4,5,6); ^{13}C NMR (125 MHz): δ = 36.5 (CH_2), 41.8 (S—CH), 54.7 (NCH_3), 59.6 (O—CH_2), 127.1 (Ar C-2,6), 129.3 (Ar C-4), 130.0 (Ar C-3,5), 142.2 (Ar C-1), 181.9 (C=N), 189.3 (C=O). *Anal*. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.53; H, 5.56; N, 10.90; S, 12.76.

5-(2-Hydroxyethyl)-2-[(N-phenyl-N-ethyl)amino]-4,5-dihydro-1,3-thiazol-4-one (3i). Yield: 0.47g (90%); m.p. 158–160°C; ^{1}H NMR (500 MHz): δ = 1.12 (t, *J* = 7.1 Hz, 3H, CH_3), 1.67 and 2.26 (2 × m, 2H, CH_2), 3.46 (m, 2H, OCH_2), 4.01 (m, 2H, NCH_2), 4.23 (dd, *J* = 10.6 and 3.1 Hz, 1H, S—CH), 4.68 (t, *J* = 4.8 Hz, 1H, OH), 7.45 (m, 2H, Ar H-2,6), 7.52 (m, 3H, Ar H-3,4,5); ^{13}C NMR (125 MHz): δ =

12.6 (CH_3), 36.5 (CH_2), 49.0 (S—CH), 54.3 (NCH_3), 59.6 (O—CH_2), 128.2 (Ar C-2,6), 129.6 (Ar C-4), 130.0 (Ar C-3,5), 140.4 (Ar C-1), 181.7 (C=N), 189.5 (C=O). *Anal*. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.84; H, 5.92; N, 10.76; S, 12.31.

5-(2-Hydroxyethyl)-2-diphenylamino-4,5-dihydro-1,3-thiazol-4-one (3j). Overall yield: 1.66g (60%); m.p. 153–155°C; ^{1}H NMR (500 MHz): δ = 1.74 and 2.27 (2 × m, 2H, CH_2), 3.47 (m, 2H, OCH_2), 4.26 (dd, J = 7.5 and 3.0 Hz, 1H, S—CH), 4.73 (t, J = 5.0 Hz, 1H, OH), 7.33-7.63 (m, 10H, Ar H); ^{13}C NMR (125 MHz): δ = 36.1 (CH_2), 54.5 (S—CH), 59.4 (O—CH_2), 126.5 (Ar C-2,6), 128.5 (Ar C-4), 129.1 (Ar C-3,5), 129.9 (Ar C-1), 183.2 (C=N), 189.7 (C=O). *Anal*. Calcd. for $C_{17}H_{16}N_2O_2$: C, 65.36; H, 5.16; N, 8.97; S, 10.26. Found: C, 65.12; H, 5.27; N, 8.79; S, 10.44.

5-(2-Hydroxyethyl)-2-[(N-(4-methoxyphenyl)-N-methyl) amino]-4,5-dihydro-1,3-thiazol-4-one (3k). Yield: 0.44g (79%); m.p. 119–120°C; ^{1}H NMR (500 MHz): δ = 1.66 and 2.23 (2 × m, 2H, CH_2), 3.36 (s, 3H, NCH_3), 3.45 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 4.18 (dd, J = 10.5 and 3.0 Hz, 1H, S—CH), 4.76 (t, J = 5.5 Hz, 1H, OH), 7.05 (AA′XX′, J = 8.5 Hz, 2H, Ar H-2,6), 7.41 (AA′XX′, J = 8.5 Hz, 2H, Ar H-3,5); ^{13}C NMR (125 MHz): δ = 35.4 (CH_2), 41.7 (S—CH), 54.6 (NCH_3), 55.4 (OCH_3), 59.5 (O—CH_2), 114.8 (Ar C-2,6), 128.3 (Ar C-3,5), 134.8 (Ar C-1), 159.4 (Ar C-4), 182.1 (C=N), 189.2 (C=O). *Anal*. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 56.03; H, 5.96; N, 10.32; S, 11.76.

5-(2-Hydroxyethyl)-2-[(4-methoxyphenyl)imino]-3-methyl-1,3-thiazolidin-4-one (3l). Overall yield: 1.03g (57%); m.p. 101–103°C; ^{1}H NMR (500 MHz): δ = 1.83 and 2.28 (2 × m, 2H, CH_2), 3.16 (s, 3H, NCH_3), 3.43 and 3.51 (2 × m, 2H, OCH_2), 3.73 (s, 3H, OCH_3), 4.33 (dd, J = 9.7 and 3.5 Hz, 1H, S—CH), 4.76 (bs, 1H, OH), 6.91 (m, 4H, Ar H-2,3,5,6); ^{13}C NMR (125 MHz): δ = 29.2 (NCH_3), 35.8 (CH_2), 45.2 (S—CH), 55.1 (OCH_3), 58.4 (O—CH_2), 114.3 (Ar C-2,6), 122.0 (Ar C-3,5), 141.2 (Ar C-1), 154.4 (C=N), 156.0 (Ar C-4), 174.6 (C=O). *Anal*. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.81; H, 5.54; N, 10.37; S, 11.21. EI-MS: *m/z* 280 [M^+] (100 %), 265, 249, 236, 221, 207, 194, 179, 162, 147, 133, 119, 106, 90, 78, 64, 55, 45, 35.

5-(2-Hydroxyethyl)-2-(4-phenylimino)-3-ethyl-1,3-thiazolidin-4-one (3m). Yield: 0.17g (33%); oil; ^{1}H NMR (500 MHz): δ = 1.18 (t, J = 7.0 Hz, 3H, CH_3), 1.84 and 2.24 (2 × m, 2H, CH_2), 3.43-3.58 (m, 2H, OCH_2), 3.77 (q, J = 7.0 Hz, 2H, NCH_2), 4.34 (dd, J = 9.6 and 3.7 Hz, 1H, S—CH), 4.75 (bs, 1H, OH), 6.96 (d, J = 7.3 Hz, 2H, Ar H-2,6), 7.11 (t, J = 7.3 Hz, 1H, Ar H-4), 7.35 (t, J = 7.4 Hz, 2H, Ar H-3,5); ^{13}C NMR (125 MHz): δ = 12.3 (CH_3), 35.7 (CH_2), 37.4 (NCH_2), 45.3 (S—CH), 58.3 (O—CH_2), 121.0 (Ar C-2,6), 124.2 (Ar C-4), 129.2 (Ar C-3,5), 148.3 (Ar C-1), 154.0 (C=N), 174.4 (C=O). *Anal*. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.71; H, 5.96; N, 10.86; S, 11.88. EI-MS: *m/z* 264 [M^+] (100 %), 233, 221, 205, 192, 177, 163, 146, 131, 118, 104, 91, 77, 65, 55, 45, 35.

5-(2-Hydroxyethyl)-2-[(4-chlorophenyl)imino]-3-methyl-1,3-thiazolidin-4-one (3n). Overall yield: 1.15g (63%); m.p. 87–89°C; ^{1}H NMR (500 MHz): δ = 1.86 and 2.27 (2 × m, 2H, CH_2), 3.16 (s, 3H, NCH_3), 3.45 and 3.54 (2 × m, 2H, OCH_2), 4.36 (dd, J = 9.8 and 3.6 Hz, 1H, S—CH), 4.75 (t, J = 5.0 Hz, 1H, OH), 6.96 (AA′XX′, J = 8.5 Hz, 2H, Ar H-2,6) 7.40 (AA′XX′, J = 8.5 Hz, 2H, Ar H-3,5); ^{13}C NMR (125 MHz): δ = 29.0 (NCH_3), 35.3 (CH_2), 45.3 (S—CH), 58.1 (O—CH_2), 122.6 (Ar C-2,6), 128.0 (Ar C-4), 128.9 (Ar C-3,5), 147.0 (C-1), 155.6 (C=N), 174.3 (C=O). *Anal*. Calcd. for $C_{12}H_{13}ClN_2O_2S$: C, 50.61; H, 4.60; N, 9.84; S, 11.26. Found: C, 50.35; H, 4.63; N, 10.15; S, 11.02.

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