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RING TRANSFORMATION OF THE *S*-(2-OXO-2,3-DIHYDRO-1-BENZOFURAN-3-YL)ISOTHIURONIUM BROMIDES TO 5-(2-HYDROXY-PHENYL)-2-IMINO-1,3-THIAZOLIDIN-4-ONES

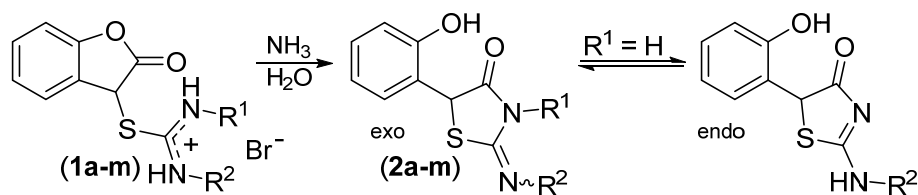
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Abstract – Synthesis of thirteen substituted 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones is described starting from easily available and stable *S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromides. The transformation proceeds under mild conditions, is very simple to perform, and is applicable to a wide range of substituents on isothiuronium moiety. Some 1,3-thiazolidin-4-ones show dynamic NMR behavior in solution because of prototropy tautomerism and *E/Z*-stereoisomerism. Thermochromic behavior was observed for all synthesized compound.

INTRODUCTION

Thiazolidin-4-ones and 2-iminothiazolidin-4-ones represent widely studied heterocyclic scaffolds which still attract attention especially for their occurrence in biologically active substances.¹ For instance they are known to possess antibacterial,² anti-inflammatory³ (darbufelone) and anti-protozoal⁴ activity and some of them are used as important per oral antidiabetics⁵ (glitazones). The synthesis of the 2-iminothiazolidin-4-one ring routinely starts from substituted thioureas and 2-halocarboxylic acid esters or halides⁵ but several novel methods or improvements have appeared during the last decade.⁶ In our group we developed new method involving rearrangements of another heterocyclic rings such as lactams⁷ and lactones⁸ and intensively studied the kinetics and mechanism of these ring transformations.⁹ Although such transformation giving 2-iminothiazolidin-4-ones appears to be expectable, in some cases completely different products were formed¹⁰ (e.g. 2*H*-isoindole-2-carbothioamides or *N,N'*-dimethyl-*N*-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)thiourea). In this work we applied our protocol for synthesis of novel 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones (**2a-m**) from easily available *S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromides (**1a-m**) (Scheme 1).



a: R¹, R² = H; **b:** R¹ = H, R² = Me; **c:** R¹ = H, R² = CH(Me)₂; **d:** R¹ = H, R² = C(Me)₃;
e: R¹ = H, R² = C₆H₅; **f:** R¹ = H, R² = 4-MeOC₆H₄; **g:** R¹ = H, R² = 4-MeC₆H₄; **h:** R¹ = H,
R² = 4-BrC₆H₄; **i:** R¹ = H, R² = 2-C₅H₄N; **j:** R¹, R² = Me; **k:** R¹, R² = C₆H₅; **l:** R¹ = Me,
R² = 4-MeOC₆H₄; **m:** R¹-R² = CH₂CH₂.

Scheme 1. Transformation reaction of isothiuronium salts **1a-m**

RESULTS AND DISCUSSION

In the first step, we have prepared and characterized corresponding *S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromides (**1a-m**) from commercially available 3-bromo-1-benzofuran-2(3*H*)-one and appropriately substituted thiourea or imidazolidine-2-thione. In contrast to our previous experience⁸ it was now possible to characterize pure isothiuronium salts by ¹H and ¹³C-NMR because their spontaneous cyclization giving **2a-m** was not observable in DMSO-*d*₆ solution during measurement. This enhanced stability is quite surprising because phenoxide which is cleaved during transformation of **1a-m** to give **2a-m** is better leaving group than alkoxide.⁸ On the other hand the salts are still unstable in polar protic solvents – especially in water – where slow rearrangement to **2a-m** takes place. In order to accelerate this transformation the addition of one equivalent of some moderately strong base (ammonia seems to be the best option) is beneficial. Stronger bases (e.g. triethylamine, carbonate or hydroxide) have negative influence on the overall yield as well as on the purity of the product. In some cases a very complex mixture of unidentified products was observed in ¹H NMR spectrum. After transformation of unsymmetrically substituted isothiuronium salts **1b-i** one would expect the formation of two constitutional isomers i.e. 2-(substituted-imino)thiazolidin-4-one or 3-substituted-2-iminothiazolidin-4-one. From the past studies¹¹ it is well known that both constitutional isomers are mutually interconvertible by treatment with a base and an acid and under basic conditions 2-(substituted-imino/amino)thiazolidin-4-one is favored. Our observations were completely consistent with the previous results. Prototropy tautomerism and *E*-/*Z*-stereoisomerism are another typical structural features of 2-iminothiazolidin-4-ones. This tautomerism was studied for both alkyl/aryl-amino/imino substituted thiazolidinones/thiazolinones by several authors^{8,12} in solid state as well as in solution and the results can be generalized as follows. Exo *N*-unsubstituted and *N*-alkyl substituted compounds exist in solution preferentially as 2-(alkyl)aminothiazolin-4-ones whereas *N*-aryl substituted compounds prefer 2-aryliminothiazolidin-4-one arrangement although some exception to this rule was also published.⁷

In ^1H NMR spectrum of freshly prepared compound **2c** (see Experimental part) at 25 °C there are three signals for proton N–CH of the isopropyl group whose integral intensities are 0.76, 0.18 and 0.06 (Figure 1a). Similar, but less resolved signals can be seen for isopropyl CH_3 groups (one well resolved doublet and one multiplet composed of the two doublets - Figure 1a) and for Ar–CH (two singlets). When is the sample heated to 60 °C for 10 min and then cooled to 25 °C the relative abundance of tautomers/stereoisomers changes as seen from integral intensity for proton N–CH (i.e. 0, 0.85 and 0.15) but the chemical shift of the individual signals remain virtually the same (Figure 1b). The two close singlets for Ar–CH changes to one singlet and broad NH singlet at 9.1 ppm changes to broad doublet at the same time. Final solution of **2c** in $\text{DMSO-}d_6$ is completely stable and the ratio of individual isomers (as depicted in Figure 1b) does not change in time.

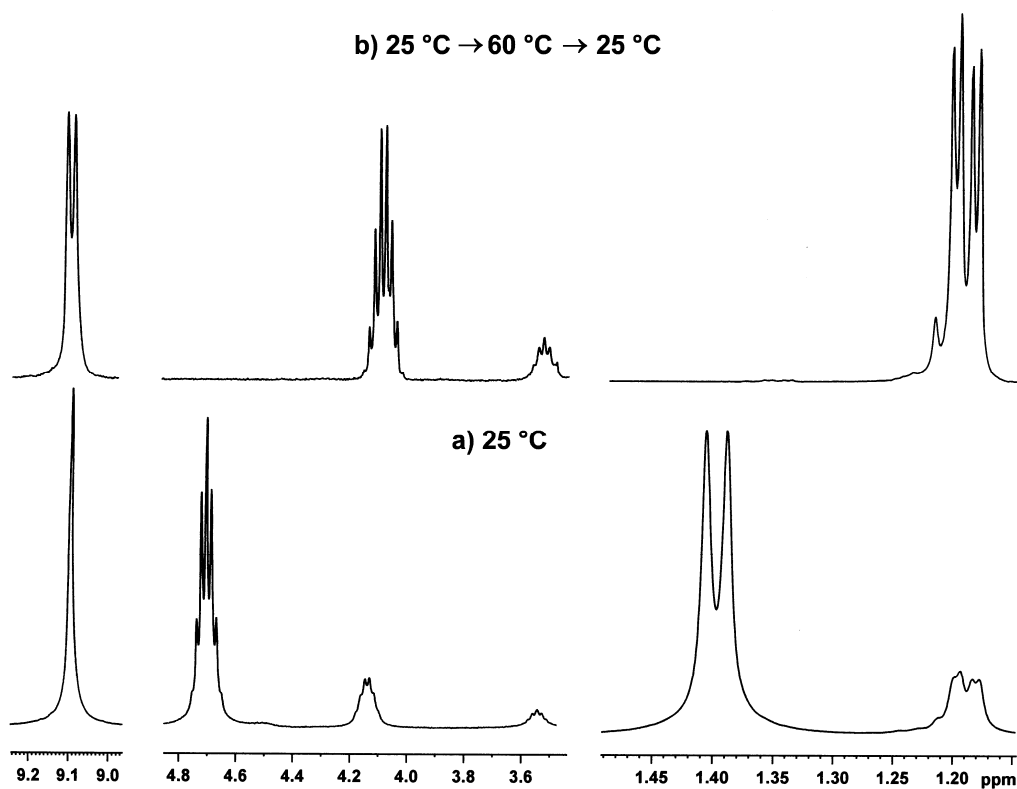


Figure 1. Peaks of NH and N–CH(CH_3) $_2$ group in NMR spectra of compound **2c**

This observation can be interpreted as mutual interconversion of all possible isomers which is slow on the NMR time scale. From the inspection of the line shape of N–CH proton it is clear that two septets at 3.55 and 4.73 belong to *E/Z*-isomers of 2-isopropylimino-5-(2-hydroxyphenyl)thiazolidin-4-one whereas the octet at 4.12 ppm belongs to 2-isopropylamino-5-(2-hydroxyphenyl)thiazolin-4-one. From this spectrum it can be also concluded that the initially formed (but thermodynamically less stable) imino form changes to much stable amino form, which is in accordance with previous general claims.^{8,12} Similar situation can be observed for compound **2b**. In this case the initial spectrum at 25 °C contains only one set of signals. From

the lineshape of N-CH₃ at 3.08 ppm (singlet) it can be concluded that only one methylimino stereoisomer is preferred. After heating to 60 °C and cooling back to 25 °C the spectrum contains all three possible isomers in the ratio 32% : 52.6% : 15.4% as seen from integrals of NCH₃ protons at 3.08 ppm (singlet), 2.98 ppm (doublet) and 2.86 ppm (singlet).

Completely different situation was observed for compounds **2e-h** derived from substituted phenylthioureas. For these compounds imino form composed of the two *E/Z*-isomers is clearly preferred^{8,12} as evidenced by ¹H NMR spectrum. At 25 °C, there are two almost equally populated forms of **2e** characterized by the two sets of signals (Figure 2a). When is the same sample gradually heated these signals mutually approaches and at 70 °C (Figure 2b) only one set of signals is observable. After cooling the original population of both *E/Z*-isomers is restored.

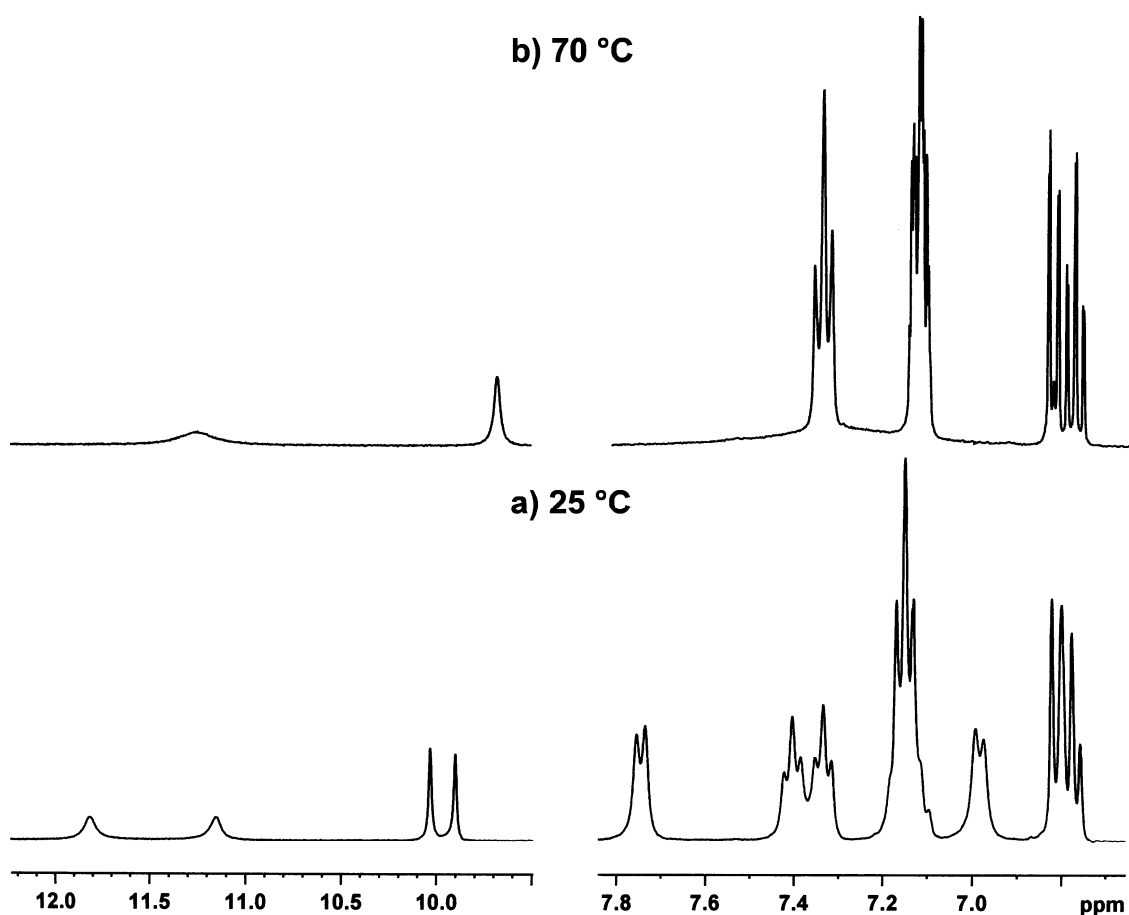


Figure 2. Peaks of NH, OH and aromatic region in NMR spectra of compound **2e**

In the case of 2-pyridyl derivative **2i** only one set of signals was observed at 25 °C. From this observation, it can be deduced that compound **2i** exists only as *E*-stereoisomer stabilized in solution by intramolecular hydrogen bond like in the case of structurally similar 5-(2-hydroxyethyl)-2-(2-pyridylimino)-1,3-thiazolidin-4-one.¹⁰

Our further interests concerned thermochromism¹⁵ of prepared compounds. Solutions of all pure compounds **2a-m** in polar protic (e.g. methanol) or aprotic solvents (e.g. DMSO) turn red slightly ($\lambda_{\max} = 470$ nm) when heated and then reversibly decolorize after cooling. In one case white compound **2j** even crystallized as pink crystals from hot solution. One would expect that the change in color is directly connected with above-mentioned prototropy or *E/Z*-isomerism. Such suggestion was previously published for structurally similar 5-arylidene-2-iminothiazolidin-4-ones.¹⁶ However, in our case the solution of **2a-m** always decolorizes after cooling although the population of individual isomers remains the same. Moreover for compounds **2j-m** prototropic tautomerism is absent due to C=N double bond fixation and *E/Z*-isomerism cannot explain change in color because compounds **2j-l** prefer *Z*-configuration whereas **2m** is fixed in its *E*-configuration. We also excluded formation of some colored complex with metal ions like Zn^{2+} and $\text{Fe}^{2+}/\text{Fe}^{3+}$ which can be present as contaminant originating from charcoal or steel spatula. On the other hand, the addition of a base (a few drops of concentrated ammonium hydroxide) causes very quick decolorization even at elevated temperature. From this observation it appears that the thermochromism could be connected with intramolecular or intermolecular hydrogen bonds causing self aggregation. Unfortunately we have no definite experimental evidence for this suggestion.

EXPERIMENTAL

The ^1H and ^{13}C -NMR spectra were recorded on a Bruker Avance 3 - 400 MHz instrument in $\text{DMSO-}d_6$ solution. Chemical shifts δ are referenced to the solvent residual peaks $\delta(\text{DMSO-}d_6) = 2.50$ (^1H) and 39.6 (^{13}C) ppm. Coupling constants J are quoted in Hz. ^{13}C NMR spectra were also 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} . All NMR experiments were performed with the aid of the manufacturer's software. Mass spectra were recorded on a MALDI LTQ Orbitrap XL (Thermo Fisher Scientific, Bremen, Germany) equipped with nitrogen UV laser (337 nm, 60 Hz, 8–20 μJ) in positive ion mode. For the CID experiment using the linear trap quadrupole (LTQ) helium was used as the collision gas and 2,5-dihydroxybenzoic acid (DHB) or *trans*-2-[3-(4-*tert*-butylphenyl)-2-methylprop-2-en-1-ylidene]malononitrile (DCTB) as the MALDI matrix. Starting arylthioureas¹³ and 3-bromo-1-benzofuran-2(3*H*)-one¹⁴ (if not purchased) were prepared and purified by known methods. All other chemicals were purchased from commercial suppliers and used as received.

General procedure for the preparation of isothiuronium salts **1a-m**

3-Bromo-1-benzofuran-2(3*H*)-one (0.5 g, 2.35 mmol) was dissolved in 4 mL of MeCN and the saturated solution of corresponding thiourea (2.35 mmol) in MeCN was added in one portion. Reaction mixture was left to stand for several hours (1-24 h) at room temperature and then precipitated crystals of isothiuronium salts were filtered-off and washed with 2 mL of MeCN and well dried in a vacuum desiccator.

S-(2-Oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1a): white solid, yield: 0.59 g (87%), mp 233-237 °C (decomp.); ¹H NMR: δ 5.73 (s, 1H); 6.80 (t, ³J = 7.6 Hz, 1H), 6.87 (d, ³J = 8.0 Hz, 1H), 7.20-7.27 (m, 2H), 10.26 and 10.58 (2×bs, 4H); ¹³C NMR: δ_C: 52.3, 115.7, 119.3, 120.7, 130.6, 131.5, 155.7, 176.7, 178.1; Anal. Calcd for C₉H₉BrN₂O₂S: C, 37.38; H, 3.14; N, 9.69; S, 11.09; Br, 27.63. Found: C, 37.18; H, 3.05; N, 9.57; S, 10.97; Br, 27.45. HRMS (MALDI) Calcd. for C₉H₉BrN₂O₂S [M-Br⁻]⁺ 209.0379. Found: 209.0375.

N-Methyl-S-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1b): white solid, yield: 0.59 g (83%), mp 181-183 °C; ¹H NMR: δ 3.31 (s, 3H), 5.86 (s, 1H), 6.83 (dt, ³J = 7.2 Hz and ⁵J = 0.8 Hz, 1H), 6.87 (d, 1H, ³J = 8.0 Hz, 1H); 7.25 (dt, 1H, ³J = 8.0 Hz, ⁴J = 1.6 Hz); 7.37 (dd, 1H, ³J = 7.6 Hz, ⁴J = 1.6 Hz); 10.33 (bs, 1H); 11.28 (vbs, 2H); ¹³C NMR: δ_C: 30.3, 49.7, 115.7, 119.4, 119.8, 131.0, 131.7, 155.5, 172.9, 174.1, Anal. Calcd for C₁₀H₁₁BrN₂O₂S: C, 39.62; H, 3.66; N, 9.24; S, 10.58; Br, 26.36; Found: C, 39.33; H, 3.48; N, 9.04; S, 10.55; Br, 26.42. HRMS (MALDI) Calcd for C₁₀H₁₁BrN₂O₂S [M-Br⁻]⁺ 223.0536. Found: 223.0529.

N-Isopropyl-S-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1c): white solid, yield: 0.64 g (83%); mp 223-233 °C (decomp.); ¹H NMR (two tautomeric forms in the ratio 1 : 9): δ_H: 1.21, 1.42 and 1.44 (3×d, ³J = 6.4 Hz, 6H); 4.14 and 4.69 (m and sept, ³J = 6.8 Hz, 1H); 5.53 and 5.71 (2×s, 1H); 6.75-6.89 (m, 2H); 7.11-7.17 and 7.24 (m and dt, ³J = 7.6 Hz, ⁴J = 1.2 Hz, 1H); 7.11-7.17 and 7.34 (m and d, ³J = 6.8 Hz, 1H); 9.92 and 10.36 (2×bs, 1H); 11.41 (vbs, 2H); ¹³C-NMR: δ_C: 17.8, 18.1, 49.1, 49.6, 115.7, 119.3, 120.2, 130.9, 132.1, 155.5, 173.5, 173.8; Anal. Calcd for C₁₂H₁₅BrN₂O₂S: C, 43.51; H, 4.56; N, 8.46; S, 9.68; Br, 24.12. Found: C, 43.40; H, 4.45; N, 8.56; S, 9.45; Br, 24.34. HRMS (MALDI) Calcd for C₁₂H₁₅BrN₂O₂S [M-Br⁻]⁺ 251.0849. Found: 251.0842.

N-tert-Butyl-S-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1d): white solid, yield: 0.54 g (67%); mp 207-219 °C (decomp.); ¹H NMR (two tautomeric forms in the ratio 6.25 : 1): δ_H: 1.40 and 1.44 (2×s, 9H); 5.40 and 5.84 (2×s, 1H); 6.75 and 6.81 (2×t, ³J = 7.6 Hz, 1H); 6.83 and 6.90 (2×d, ³J = 8.0 Hz, 1H); 7.08 and 7.32 (2×d, ³J = 7.2 Hz, 1H); 7.12 and 7.23 (2×t, ³J = 8.0 Hz, 1H), 9.5 (bs, 1H); 9.81 (vbs, 2H); ¹³C NMR: δ_C: 28.0 and 28.4, 52.0, 55.7 and 56.7, 115.5 and 115.8, 119.3 and 119.6, 123.4, 129.4 and 131.0, 130.0 and 131.9, 155.6 and 155.9, 175.7, 185.6; Anal. Calcd for C₁₃H₁₇BrN₂O₂S: C, 45.22; H, 4.96; N, 8.11; S, 9.29; Br, 23.14%. Found: C, 45.24; H, 4.97; N, 7.94; S, 9.22; Br, 22.90. HRMS (MALDI) Calcd for C₁₃H₁₇BrN₂O₂S [M-Br⁻]⁺ 265.1005. Found: 265.0999.

N-Phenyl-S-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1e): white solid, yield: 0.56 g (65%); mp 209-213 °C (decomp.); ¹H-NMR : δ_H: 5.94 (s, 1H); 6.86 (t, ³J = 7.2 Hz, 1H); 6.95 (d, ³J = 8.0 Hz, 1H); 7.28 (m, 1H); 7.45-7.49 (m, 3H); 7.63-7.71 (m, 3H); 10.62 (bs, 1H); 10.95 (vbs, 2H). ¹³C-NMR: δ_C: 50.2; 115.9; 119.4; 120.2; 128.2; 130.6; 131.1; 131.2; 131.7; 132.2; 155.5; 172.8; 174.1;

Anal. Calcd for $C_{15}H_{12}BrN_2O_2S$: C, 49.33; H, 3.59; N, 7.67; S, 8.78; Br, 21.88. Found: C, 49.44; H, 3.54; N, 7.76; S, 8.75; Br, 21.76. HRMS (MALDI) Calcd for $C_{15}H_{12}BrN_2O_2S[M-Br]^{+}$ 285.0692. Found: 285.0693.

***N*-(4-Methoxyphenyl)-*S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1f)**: white solid, yield: 0.79 g (85%); mp 211-232 °C (decomp.); 1H -NMR: δ_H : 3.85 (s, 3H); 5.90 (s, 1H); 6.86 (t, $^3J = 7.6$ Hz, 1H); 6.93 (d, $^3J = 8.0$ Hz, 1H); 7.22 (AA'XX', $^3J = 9.2$ Hz, 2H); 7.28 (dt, $^3J = 7.6$ Hz, $^4J = 1.2$ Hz, 1H); 7.36 (AA'XX', $^3J = 7.6$ Hz, 2H); 7.46 (dd, $^3J = 7.6$ Hz, $^4J = 1.2$ Hz, 1H); 10.59 (bs, 1H); 10.92 (vbs, 2H). ^{13}C -NMR: δ_C : 50.0; 55.8; 115.8; 119.4; 120.2; 123.9; 129.5; 131.0; 132.1; 155.5; 161.0; 172.9; 174.4;

Anal. Calcd for $C_{16}H_{15}BrN_2O_3S$: C, 48.62; H, 3.82; N, 7.09; S, 8.11; Br, 20.22. Found: C, 48.70; H, 3.67; N, 7.04; S, 8.26; Br, 20.11. HRMS (MALDI) Calcd for $C_{16}H_{15}BrN_2O_3S[M-Br]^{+}$ 315.0798. Found: 315.0789.

***N*-(4-Methylphenyl)-*S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1g)**: white solid, yield: 0.63 g (71%); mp 215-233 °C (decomp.); 1H -NMR δ_H : 2.42 (s, 3H); 5.91 (s, 1H); 6.86 (t, $^3J = 7.2$ Hz, 1H); 6.93 (AA'XX', $^3J = 8.0$ Hz, 1H); 7.25-7.40 (m, 3H); 7.44-7.51 (m, 3H); 10.59 (bs, 1H); 10.93 (vbs, 2H). ^{13}C -NMR: δ_C : 21.0; 50.1; 115.8; 119.4; 120.2; 127.9*; 129.1; 131.1; 132.2; 141.0; 155.5; 172.8; 174.2; Anal. Calcd for $C_{16}H_{15}BrN_2O_2S$: C, 50.67; H, 3.99; N, 7.39; S, 8.45; Br, 21.07. Found: C, 50.76; H, 3.83; N, 7.35; S, 8.62; Br, 21.18. HRMS (MALDI) Calcd for $C_{16}H_{15}BrN_2O_2S[M-Br]^{+}$ 299.0849. Found: 299.0841. *Broad signal probably contains two carbons of the same chemical shift.

***N*-(4-Bromophenyl)-*S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1h)**: white solid, yield: 0.88 g (85%); mp 199-222 °C (decomp.); 1H -NMR: δ_H : 5.92 (s, 1H); 6.86 (dt, $^3J = 7.6$ Hz, $^4J = 0.8$ Hz, 1H); 6.93 (d, $^3J = 8.0$ Hz, 1H); 7.28 (dt, $^3J = 8.0$ Hz, $^5J = 0.8$ Hz, 1H); 7.41 (AA'XX', $^3J = 8.0$ Hz, 2H); 7.47 (dd, $^3J = 7.6$ Hz, $^4J = 1.6$ Hz, 1H); 7.92 (AA'XX', $^3J = 8.8$ Hz, 2H); 10.60 (bs, 1H); 10.92 (vbs, 2H). ^{13}C -NMR: δ_C : 50.1; 115.8; 119.4; 120.1; 124.7; 130.4; 131.0; 131.1; 132.1; 133.7; 155.5; 172.6; 173.8; Anal. Calcd for $C_{15}H_{12}Br_2N_2O_2S$: C, 40.56; H, 2.72; N, 6.31; S, 7.22; Br, 35.98. Found: C, 40.73; H, 2.59; N, 6.32; S, 7.31; Br, 35.89. HRMS (MALDI) Calcd for $C_{15}H_{12}Br_2N_2O_2S[^{79}M-Br]^{+}$ 362.9797. Found: 362.9800. $[^{81}M-Br]^{+}$ 364.9777. Found: 364.9777.

***N*-(Pyridin-2-yl)-*S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1i)**: white solid; yield: 0.70 g (82%); mp 166-169 °C; 1H -NMR: δ_H : 5.60 (s, 1H); 4.00-7.00 (vbs, 2H + H₂O) 6.79 (t, $^3J = 7.6$ Hz, 1H); 6.86 (d, 1H, $^3J = 8.0$ Hz); 7.14-7.24 (m, 2H); 7.35-7.45 (m, 2H); 8.14 (t, 1H, $^3J = 7.6$ Hz); 8.48 (d, 1H, $^3J = 5.2$ Hz); 10.06 (bs, 1H). ^{13}C -NMR: δ_C : 50.4; 115.7; 118.3; 119.3; 120.5; 121.9; 130.0; 130.7; 143.3; 143.9; 155.2; 155.7; 165.8; 177.0. Anal. Calcd for $C_{14}H_{12}BrN_3O_2S$: C, 45.91; H, 3.30; N, 11.47; S, 8.76; Br, 21.82. Found: C, 45.64; H, 3.42; N, 11.70; S, 8.52; Br, 21.69. HRMS (MALDI) Calcd for $C_{14}H_{12}BrN_3O_2S[M-Br]^{+}$ 286.0645. Found: 286.0640.

***N,N'*-Dimethyl-*S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1j)**: white solid, yield: 0.65 g (87%); mp 231-238 °C (decomp.); 1H -NMR: δ_H : 3.15 (s, 3H); 3.32 (s, 3H); 5.92 (s, 1H); 6.83

(dt, $^3J = 7.6$ Hz, $^4J = 0.8$ Hz, 1H); 6.89 (d, $^3J = 8.4$ Hz, 1H); 7.24 (dt, $^3J = 8.0$ Hz, $^4J = 1.6$ Hz, 1H); 7.37 ($^3J = 7.6$ Hz, 1H); 10.33 (s, 2H); $^{13}\text{C-NMR}$: δ_{C} : 30.7; 33.2; 49.7; 115.7; 119.4; 119.8; 131.0; 131.5; 155.6; 171.2; 172.6. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{BrN}_2\text{O}_2\text{S}$: C, 41.65; H, 4.13; N, 8.83; S, 10.11; Br, 25.19. Found: C, 41.62; H, 4.08; N, 8.79; S, 10.03; Br, 24.94. HRMS (MALDI) Calcd for $\text{C}_{11}\text{H}_{13}\text{BrN}_2\text{O}_2\text{S} [\text{M}-\text{Br}]^+$ 237.0692. Found: 237.0688.

***N,N'*-Diphenyl-*S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1k)**: white solid; yield: 0.77 g (75%); mp 219-224 °C; $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} : 5.71 (s, 1H); 6.79 (t, $^3J = 7.2$ Hz, 1H); 6.85-6.90 (m, 3H); 7.06 (t, $^3J = 7.2$ Hz, 1H); 7.18 (dt, $^3J = 7.2$ Hz, $^4J_{\text{H,H}} = 1.2$ Hz, 1H); 7.25-7.33 (m, 3H); 7.44-7.45 (m, 3H); 7.51-7.58 (m, 2H); 8.90-10.30 (vbs, 2H); $^{13}\text{C-NMR}$: δ_{C} : 48.3; 115.9; 119.3; 121.0; 122.9; 124.4; 128.6; 128.8; 129.3; 129.4; 130.1; 130.9; 136.0; 148.2; 155.6; 173.2; Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S}$: C, 57.15; H, 3.88; N, 6.35; S, 7.27; Br, 18.10. Found: C, 57.30; H, 3.86; N, 6.49; S, Br, 18.10. HRMS (MALDI) Calcd for $\text{C}_{21}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S} [\text{M}-\text{Br}]^+$ 361.1005. Found: 361.1001.

***N*-Methyl-*N'*-(4-methoxyphenyl)-*S*-(2-oxo-2,3-dihydro-1-benzofuran-3-yl)isothiuronium bromide (1l)**: white solid; yield: 0.79 g (82%); mp 175-207 °C; $^1\text{H-NMR}$: δ_{H} : 3.08 (s, 3H); 3.85 (s, 3H); 5.00 (vbs H_2O , 1H); 5.97 (s, 1H); 6.87 (dt, $^3J = 7.2$ Hz, $^4J = 0.8$ Hz, 1H); 6.95 (d, $^3J = 8.4$ Hz, 1H); 7.20 (AA'XX', = 9.2 Hz, 2H); 7.28 (dt, $^3J = 8.0$ Hz, $^4J = 1.6$ Hz, 1H); 7.36 (AA'XX', $^3J = 8.8$ Hz, 2H); 7.48 (dd, $^3J = 8.0$ Hz, $^4J = 1.6$ Hz, 1H); 10.59 (s, 1H). $^{13}\text{C-NMR}$: δ_{C} : 33.6; 50.0; 55.8; 115.6; 115.8; 119.4; 120.3; 124.6; 129.6; 131.0; 131.9; 155.6; 160.8; 171.5; 172.7. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}_3\text{S}$: C, 49.89; H, 4.19; N, 6.84; S, 7.83; Br, 19.52. Found: C, 49.95; H, 4.10; N, 6.87; S, 7.64; Br, 19.40. HRMS (MALDI) Calcd for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}_3\text{S} [\text{M}-\text{Br}]^+$ 329.0954. Found: 329.0962.

2-[(2-Oxo-2,3-dihydro-1-benzofuran-3-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium bromide (1m): white solid; yield: 0.64 g (86%); mp 181-185 °C; $^1\text{H-NMR}$: δ_{H} : 3.98-4.12 (m, 2H); 4.35-4.49 (m, 2H); (s, 1H); 6.84 (dt, $^3J = 7.6$ Hz, $^4J = 1.2$ Hz, 1H); 6.92 (d, $^3J = 8.4$ Hz, 1H); 7.25 (dt, $^3J = 7.6$ Hz, $^4J = 1.6$ Hz, 1H); 7.37 (dd, $^3J = 7.2$ Hz, $^4J = 1.6$ Hz, 1H); 8.50 (vbs, 1H); 10.41 (bs, 1H). $^{13}\text{C-NMR}$ δ_{C} : 42.5; 53.0; 115.7; 119.3; 119.8; 131.1; 131.3; 155.8; 168.1; 173.9. Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{BrN}_2\text{O}_2\text{S}$: C, 42.19; H, N, 8.94; S, 10.24%; Br, 25.51. Found: C, 41.92; H, 3.17; N, 8.73; S, 10.09; Br, 25.27. HRMS (MALDI) Calcd for $\text{C}_{11}\text{H}_{11}\text{BrN}_2\text{O}_2\text{S} [\text{M}-\text{Br}]^+$ 235.0536. Found: 235.0528.

General procedure for the transformation of isothiuronium salts 1a-m to 2a-m

To a suspension of corresponding isothiuronium salt (2 mmol) in 25 mL of water one equivalent (2 of aqueous ammonia was added. After stirring for 2 h the solid residue was filtered, washed with 25 mL of water and dried on air. Crude product can be recrystallized from MeOH.

5-(2-Hydroxyphenyl)-2-imino-1,3-thiazolidin-4-one (2a): white solid; yield: 0.35 g (83%); mp 212-214 °C; $^1\text{H-NMR}$: δ_{H} : 5.44 (s, 1H); 6.74-6.84 (m, 2H); 7.04 (d, $^3J = 7.6$ Hz, 1H); 7.12 (dt, $^3J = 8.0$ Hz, $^4J_{\text{H,H}} = 0.8$ Hz, 1H); 8.74 (bs, 1H); 9.00 (bs, 1H); 9.81 (s, 1H); $^{13}\text{C-NMR}$ δ_{C} : 54.7; 115.4; 119.2; 124.0; 129.2; 129.6; 155.5; 181.6; 188.4. Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S}$: C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 51.99; H, 3.89; N, 13.32; S, 15.52. HRMS (MALDI) Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S} [\text{M}+\text{H}]^+$ 209.0379. Found: 209.0374.

5-(2-Hydroxyphenyl)-2-(methylamino)-1,3-thiazolin-4-one (2b): white solid; yield: 0.30 g (68%); mp 154-156 °C; $^1\text{H NMR}$ (after crystallization or heating three forms *endo* : *exo-Z* : *exo-E* in the ratio 3 : 2 : 1 are visible; underlined signals correspond to non-crystallized product): δ_{H} : 2.98 and 3.07 and 2.86 (d, $J = 4.6$ Hz, s, s, 3H); 5.45 and 5.53 and 5.41 (3×s, 1H); 6.73-6.81 (m, 2H); 7.01-7.17 (m, 2H); 9.10 and 9.14 and 9.14 and 9.51 (q, $J = 4.6$ Hz, bs, bs, 1H); 9.82 and 9.87 and 9.95 (3×bs, 1H); $^{13}\text{C NMR}$ (non-crystallized): δ_{C} : 28.4; 48.5; 115.7; 119.2; 123.2; 129.7; 130.3; 155.5; 157.6; 173.3. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: 54.04% C; 4.53% H; 12.60% N; 14.40% O; 14.43% S. Found: 54.08% C; 4.66% H; 12.51% N; 14.27% S. HRMS (MALDI+) Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{S} [\text{M}+\text{H}]^+$ 223.0536. Found: 223.0531.

5-(2-Hydroxyphenyl)-2-(isopropylamino)-1,3-thiazolin-4-one (2c): white solid; yield: 0.34 g (68%); mp 200-201 °C; $^1\text{H-NMR}$ (after crystallization or heating two forms *endo* : *exo-Z* or *E* in the ratio 17 : 3 are visible): δ_{H} : 1.16-1.48 (m, 6H); 3.54 and 4.13 (septet $J = 5.9$ Hz and octet $J = 6.8$ Hz); 5.40 (s, 1H); 6.73-6.83 (m, 2H); 7.00-7.15 (m, 2H); 9.08 (bd, $J = 7.2$ Hz, 1H); 9.80 (bs, 1H); $^{13}\text{C-NMR}$ (major *endo* form underlined): δ_{C} : 18.0 and 18.3; 21.8 and 22.2; 45.8 and 46.8; 53.1; 115.3 and 115.5; 118.9 and 119.0; 124.0; 128.7 and 128.9; 129.2 and 129.5; 155.3; 177.6; 187.3. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.55; H, 5.51; N, 11.02; S, 12.69. HRMS (MALDI) Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{S} [\text{M}+\text{H}]^+$ 251.0849. Found: 251.0842.

2-(tert-Butylamino)-5-(2-hydroxyphenyl)-1,3-thiazolin-4-one (2d): white solid; yield: 0.50 g (95%); mp 136-139 °C; $^1\text{H-NMR}$: δ_{H} : 1.45 and 1.49 (2×s, 9H); 5.37 (s, 1H); 6.78-6.87 (m, 2H); 7.04 (dd, $^3J = 7.6$ Hz, $^4J = 1.6$ Hz, 1H); 7.13-7.18 (m, 1H); 8.96 (bs, 1H); 9.78 (bs, 1H). $^{13}\text{C-NMR}$: δ_{C} : 28.4; 52.6; 54.9; 115.4; 119.2; 124.2; 129.0; 129.4; 155.5; 177.1; 188.2. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.89; H, 6.02; N, 10.56; S, 11.93. HRMS (MALDI) Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{S} [\text{M}+\text{H}]^+$ 265.1005. Found: 265.1003.

5-(2-Hydroxyphenyl)-2-(phenylimino)-1,3-thiazolidin-4-one (2e):

Yield: 47 g (82%); mp 203-205 °C; $^1\text{H-NMR}$ (*E/Z*-isomers in the ratio 1 : 1): δ_{H} : 5.52 (s, 1H); 6.76-6.83 (m, 2H); 6.98 and 7.74 (2×d, $^3J = 7.6$ Hz, 2H); 7.08-7.20 (m, 3H); 7.33 and 7.40 (2×t, $^3J = 7.4$ Hz, 2H); 9.90 and 10.03 (2×bs, 1H); 11.15 and 11.81 (2×bs, 1H). $^{13}\text{C-NMR}$: δ_{C} : 49.7 and 53.6; 115.5; 115.6; 119.2; 120.4; 121.6; 122.8; 123.3; 124.8; 129.2; 129.4; 129.5; 130.2; 138.9; 155.6; 173.7; 176.9; 188.9.

Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; S, 11.28. Found: C, 63.21; H, 4.11; N, 9.69; S, 11.01. HRMS (MALDI) Calcd for $C_{15}H_{12}N_2O_2S$ $[M+H]^+$ 285.0692. Found: 285.0696.

5-(2-Hydroxyphenyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (2f): white solid; yield: 0.54 g (86%); mp 166-168 °C; 1H -NMR (*E/Z*-isomers in the ratio 1 : 1): δ_H : 3.72 and 3.75 (2×s, 3H); 5.49 and 5.51 (2×s, 1H); 6.74-6.84 (m, 2H); 6.88-7.02 (m, 3H); 7.10-7.17 (m, 2H); 7.62-7.68 (m, 1H); 9.89 and 9.99 (2×bs, 1H); 11.04 and 11.66 (2×bs, 1H). ^{13}C -NMR: δ_C : 50.4 and 53.6; 55.4; 114.2 and 114.6; 115.5 and 115.6; 119.2; 122.0; 123.0; 123.4; 129.4 and 129.7; 130.1; 132.2; 155.6; 156.3 and 156.8; 176.2; 188.7. Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 61.11; H, 4.53; N, 8.99; S, 10.19. HRMS (MALDI) Calcd for $C_{16}H_{14}N_2O_3S$ $[M+H]^+$ 315.0798. Found: 315.0787.

5-(2-Hydroxyphenyl)-2-[(4-methylphenyl)imino]-1,3-thiazolidin-4-on (2g): white solid; yield: 0.54 g (91%); mp 197-201 °C; 1H -NMR (*E/Z*-isomers in the ratio 1 : 1): δ_H : 2.26 a 2.29 (2×s, 3H); 5.51 and 5.52 (2×s, 1H); 6.75-6.85 (m, 2H); 6.90 (½AA'XX', $^3J = 8.0$ Hz, 1H); 7.10-7.24 (m, 4H); 7.64 (½AA'XX', $^3J = 8.0$ Hz, 1H); 9.90 and 10.01 (s, 1H); 11.08 and 11.72 (s, 1H); ^{13}C -NMR: δ_C : 20.6; 50.0 and 53.6; 115.5 and 115.6; 119.2; 120.4 and 121.7; 122.9 and 123.4; 129.4 and 129.5; 129.7 and 129.8; 130.1; 133.9; 136.6; 155.6; 176.5; 188.8; Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.40; H, 4.87; N, 9.31; S, 10.65. HRMS (MALDI) Calcd for $C_{16}H_{14}N_2O_2S$ $[M+H]^+$ 299.0849. Found: 299.0838.

5-(2-Hydroxyphenyl)-2-[(4-bromophenyl)imino]-1,3-thiazolidin-4-one (2h): white crystals; yield: 0.64 g (88%); mp 138-142 °C; 1H -NMR (*E/Z*-isomers in the ratio 1 : 1): δ_H : 5.55 (s, 1H); 6.74-6.86 (m, 2H); 6.92 (m, 1H); 7.10-7.22 (m, 2H); 7.49 (m, 1H); 7.60 (m, 1H); 7.72 (m, 1H); 9.90 and 10.20 (2×bs, 1H); 11.20 and 11.84 (2×bs, 1H); ^{13}C -NMR (70 °C) δ_C : 48.3; 115.4; 116.2; 118.9; 122.7; 122.8; 129.1; 129.4; 131.6; 155.2; 175.4; 188.4; Anal. Calcd for $C_{15}H_{11}N_2BrO_2S$: C, 49.60; H, 3.05; N, 7.71; S, 8.83; Br, 22.00. Found: C, 49.32; H, 3.29; N, 7.50; S, 8.64; Br, 22.27. HRMS (MALDI) Calcd for $C_{15}H_{11}N_2BrO_2S$ $[M+H]^+$ 362.9797. Found: 362.9788.

5-(2-Hydroxyphenyl)-2-(pyridin-2-ylimino)-1,3-thiazolidin-4-one (2i): white solid; yield: 0.43 g (75%); mp 219-222 °C; 1H -NMR: δ_H : 5.32 (s, 1H); 6.75-6.85 (m, 2H); 7.05-7.22 (m, 4H); 7.79 (t, $^3J = 7.2$ Hz, 1H); 8.33 (d, $^3J = 4.0$ Hz, 1H); 9.91 (bs, 1H); 11.94 (bs, 1H). ^{13}C -NMR δ_C : 49.8; 115.6; 118.4; 119.2; 123.0; 129.4; 130.3; 138.7; 146.6; 155.5; 156.4; 164.8; 178.7. Anal. Calcd for $C_{14}H_{11}N_3O_2S$: C, 58.93; H, 3.89; N, 14.73; S, 11.24. Found: C, 58.74; H, 3.80; N, 14.59; S, 11.11. HRMS (MALDI) Calcd for $C_{14}H_{11}N_3O_2S$ $[M+H]^+$ 286.0645. Found: 286.0638.

5-(2-Hydroxyphenyl)-3-methyl-2-(methyylimino)-1,3-thiazolidin-4-one (2j): white or off-pink solid; yield: 0.38 g (80%); mp 136-161 °C (decomp.); 1H -NMR: δ_H : 3.04 (s, 3H); 3.11 (s, 3H); 5.58 (s, 1H); 6.77-6.83 (m, 2H); 7.16-7.20 (m, 2H); 10.04 (bs, 1H). ^{13}C -NMR: δ_C : 29.4; 37.5; 47.7; 115.7; 119.3; 122.7; 130.0; 130.5; 155.5; 156.0; 173.0. Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86; S,

13.57. Found: C, 55.90; H, 5.09; N, 11.81; S, 13.50. HRMS (MALDI) Calcd for $C_{11}H_{12}N_2O_2S$ $[M+H]^+$ 237.0692. Found: 237.0686.

5-(2-Hydroxyphenyl)-3-phenyl-2-(phenylimino)-1,3-thiazolidin-4-on (2k): white solid; yield: 0.63 g (88%); mp 217-219 °C; 1H -NMR: δ_H : 5.70 (s, 1H); 6.80 (dt, 1H, $^3J = 7.2$ Hz, $^4J = 0.8$ Hz); 6.87 (m, 1H); 7.07 (t, $^3J = 8.4$ Hz, 1H); 7.2 (dt, $^3J = 8.0$ Hz, $^4J = 1.6$ Hz, 1H); 7.28-7.32 (m, 3H); 7.44-7.48 (m, 3H); 7.54 (m, 2H); 10.30 (bs, 1H). ^{13}C -NMR: δ_C : 48.1; 115.8; 119.2; 120.9; 122.9; 124.3; 128.5; 128.7; 129.2; 129.3; 130.1; 130.8; 136.0; 148.3; 155.4; 155.6; 173.1. Anal. Calcd for $C_{21}H_{16}N_2O_2S$: C, 69.98; H, 4.47; N, 7.77; S, 8.90. Found: C, 70.10; H, 4.36; N, 7.61; S, 8.82. HRMS (MALDI) Calcd for $C_{21}H_{16}N_2O_2S$ $[M+H]^+$ 361.1005. Found: 361.0998.

5-(2-Hydroxyphenyl)-3-methyl-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (2l): white solid; yield: 0.45 g (69%); mp 150-153 °C; 1H -NMR δ_H : 3.24 (s, 3H); 3.72 (s, 3H); 5.55 (s, 1H); 6.74-6.82 (m, 2H); 6.86-6.93 (m, 4H); 7.13-7.21 (m, 2H); 10.03 (bs, 1H). ^{13}C -NMR: δ_C : 29.6; 47.5; 55.3; 114.5; 115.6; 119.1; 122.1; 122.7; 129.8; 130.2; 141.2; 154.7; 155.4; 156.1; 173.2. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 61.95; H, 4.88; N, 8.33; S, 9.63. HRMS (MALDI) Calcd for $C_{16}H_{14}N_2O_2S$ $[M+H]^+$ 329.0954. Found: 329.0957.

2-(2-Hydroxyphenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3(2H)-one (2m): white solid, yield: 0.33 g (70%); mp 181-185 °C; 1H -NMR: δ_H : 3.61-3.76 (m, 2H); 4.15-4.28 (m, 2H); 5.93 (s, 1H); 6.75-6.87 (m, 2H); 7.17-7.25 (m, 2H); 10.11 (bs, 1H). ^{13}C -NMR: δ_C : 41.7; 55.3; 60.8; 115.7; 119.1; 122.8; 130.1; 130.3; 155.6; 160.1; 166.6. Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.12; H, 4.15; N, 11.79; S, 13.48. HRMS (MALDI) Calcd for $C_{11}H_{10}N_2O_2S$ $[M+H]^+$ 235.0536. Found: 235.0539.

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