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HYDRAZONES AND 1,3-THIAZOLIDIN-4-ONES INCORPORATING FUROXAN MOIETY SYNTHESIZED FROM EUGENOL, THE MAIN CONSTITUENT OF *OCIMUM SANTUM* L. OIL

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Abstract – Two series of new hydrazones and 1,3-thiazolidin-4-ones incorporating furoxan moiety were synthesized from eugenol, the main component of *Ocimum sanctum* L. oil. The structure of these compounds was determined by IR, MS, ^{1}H and ^{13}C NMR analysis. All resonance signals of proton and carbon in the examined compounds are assigned using HSQC, HMBC and NOESY spectra. The hydrazones and the 1,3-thiazolidin-4-ones were tested for antimicrobial activities and almost all examined thiazolidinones displayed moderate activity against *S. aureus* and *A. niger*. Among screened hydrazones only one compound exhibited a significant cytotoxicity for human cancer cell line SW620.

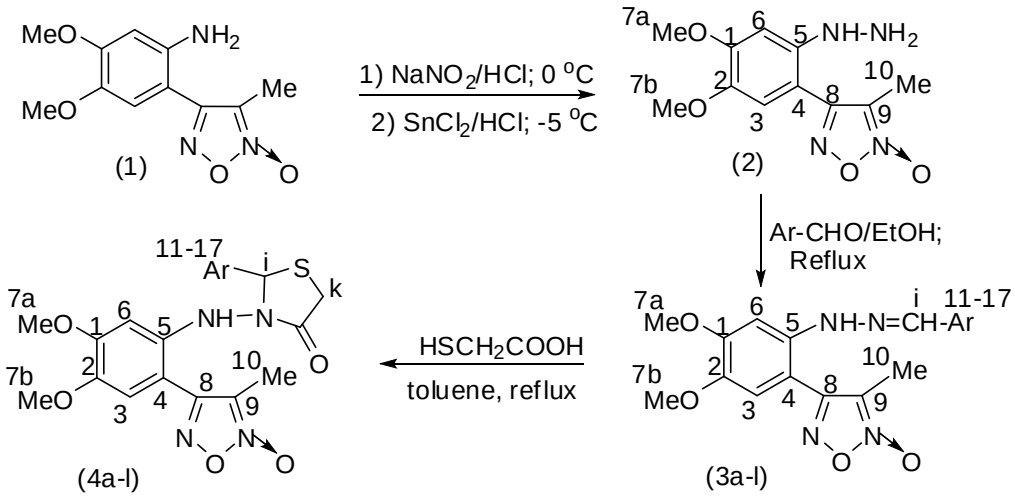
Hydrazones constitute an important class of biologically active drug molecules which has attracted attention of medicinal chemists due to their wide range of pharmacological properties. A number of hydrazones have been reported to exert notably antimicrobial, antihypertensive, anticonvulsant, anti-inflammatory, antituberculosis, anticoagulant, antimalarial and antitumor activities in two reviews.[1,2] They are also appropriate substrates for the preparation of five- or six-membered heterocyclic rings such as indole, pyrazole, pyridazin and thiazolidinone. Thiazolidinones have become among the most extensively investigated compounds due to their valuable biological activities in the areas of medicine and agriculture. They have found uses, for example, as antimalarial,[3] antimicrobial,[4,5] anti-inflammatory,[6,7] and antiviral agents, especially as anti-HIV agents.[8-11]

During recent years, furoxan derivatives were extensively studied as bioactive compounds. They possess

remarkable biological activities, such as anti-microbial and anti-parasitic properties, mutagenic, immunosuppressive and anticancer effects, anti-aggregating and vasorelaxant activity.[12] Several classes of hybrid compounds, obtained combining appropriate pharmacophoric groups with NO-releasing furoxan moiety (NO-donor), have been described.[13] A number of them, such as NO-imidazole, NO-benzimidazole, NO-aspirin,[14] NO-steroids,[15] and NO-ursodeoxycholic acid,[16] are now under clinical investigations.

In view of the above-mentioned findings, a series of new hydrazones and the corresponding 1,3-thiazolidin-4-ones incorporating furoxan moiety were synthesized from eugenol and to find out if the resulting compounds have any biological action. Eugenol is extracted from *Ocimum sanctum* L. oil. This raw material is cheap[17] and should be renewable.

4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**1**) was prepared from eugenol according to our manner.[18] Amine **1** was converted into 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylhydrazine (**2**) by diazotization and subsequent reduction with stannous chloride in concentrated hydrochloric acid. The condensation of **2** with aromatic aldehydes gave hydrazones **3a**–**l**, which on reaction with thioglycolic acid in dry toluene gave the corresponding 1,3-thiazolidin-4-ones **4a**–**l** (Figure 1, the numeration on these structures is used specifically for NMR analysis only).



Ar: Ph (3a, 4a); 2-MePh (3b, 4b); 4-MePh (3c, 4c); 2-ClPh (3d, 4d); 4-ClPh (3e, 4e); 4-HOPh (3f, 4f); 4-MeOPh (3g, 4g); 3-MeO-4-HOPh (3h, 4h); 2-O_2NPh (3i, 4i); 3-O_2NPh (3j, 4j); 4-O_2NPh (3k, 4k); 3-pyridyl (3l, 4l).

Figure 1. Synthesis of the new hydrazones and 1,3-thiazolidin-4-ones

The change in structure from hydrazine **2** to hydrazones **3a-l** and to 1,3-thiazolidin-4-ones **4a-l** is demonstrated with ^{1}H NMR spectra of **2**, **3c** and **4c** in Figure 2. The spectrum of hydrazone **3c** differs from that of hydrazine **2** in the presence of signals of aldehyde moiety (Ph, Hi, H17), the absence of NH_2 signal and also the downfield shift of NH signal. The spectrum of thiazolidinone **4c** differs from that of hydrazone

3c in the appearance of the doublet of doublets at 3.94 ppm (Hk), the doublet at 3.76 ppm (Hk'), and also the upfield shift of NH and Hi signals. These are associated with the formation of thiazolidinone ring in **4c**. 4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylhydrazine (**2**), hydrazones **3a**–**l** and thiazolidinones **4a**–**l** have not been previously reported in the literature, thus their ^{1}H NMR and ^{13}C NMR spectra were accurately analyzed on the basis of chemical shift, spin–spin splitting patterns, and 2D NMR spectra. For example, HSQC spectrum of **2** allowed to recognize singlet of HN (at 6.73 ppm, giving no cross peak with any carbon atom) among 3 singlets at 7.01, 6.86 and 6.73 ppm. The HMBC spectrum of **2** allowed to assign the signals of H3, H6 and to distinguish H7a and H7b.

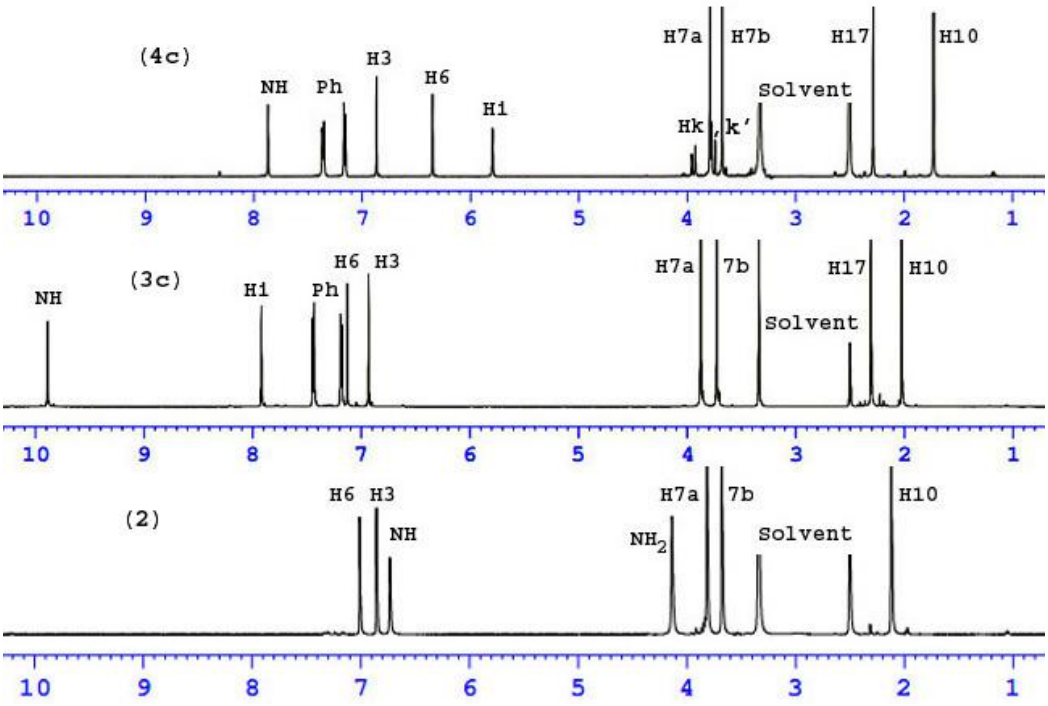


Figure 2. ^{1}H NMR spectra of hydrazine **2**, hydrazone **3c** and thiazolidin-4-one **4c**

The assignment of ^{1}H and ^{13}C signals of examined compounds using 2D NMR was illustrated as in Figure 3. For example, In ^{1}H NMR spectrum of **4f** (vertical axis in Figure 3) the singlet at 1.75 ppm (3H) is unambiguously attributed to H10; the doublet at 6.70 ppm (2H, J = 8.5 Hz) - to H13 and H15; the doublet at 7.29 ppm (2H, J = 8.5 Hz) - to H12 and H16; the doublet of doublets at 3.91 ppm (1H, J = 16 and 1 Hz) and the doublet at 3.74 ppm (1H, J = 16 Hz) are assigned to Hk and Hk' (the non-equivalent, geminal methylene protons interacting with the chiral center at position i). A singlet at 9.70 ppm (was not placed in Figure 3) was assigned to OH group because it give no cross peak with any carbon atom in both HSQC and HMBC of **4**. The singlet at 7.82 ppm was assigned to NH because it gives no cross peak with any carbon atom in HSQC spectrum of **4f** but gives cross peaks *a*, *b*, *c* in HMBC spectrum.

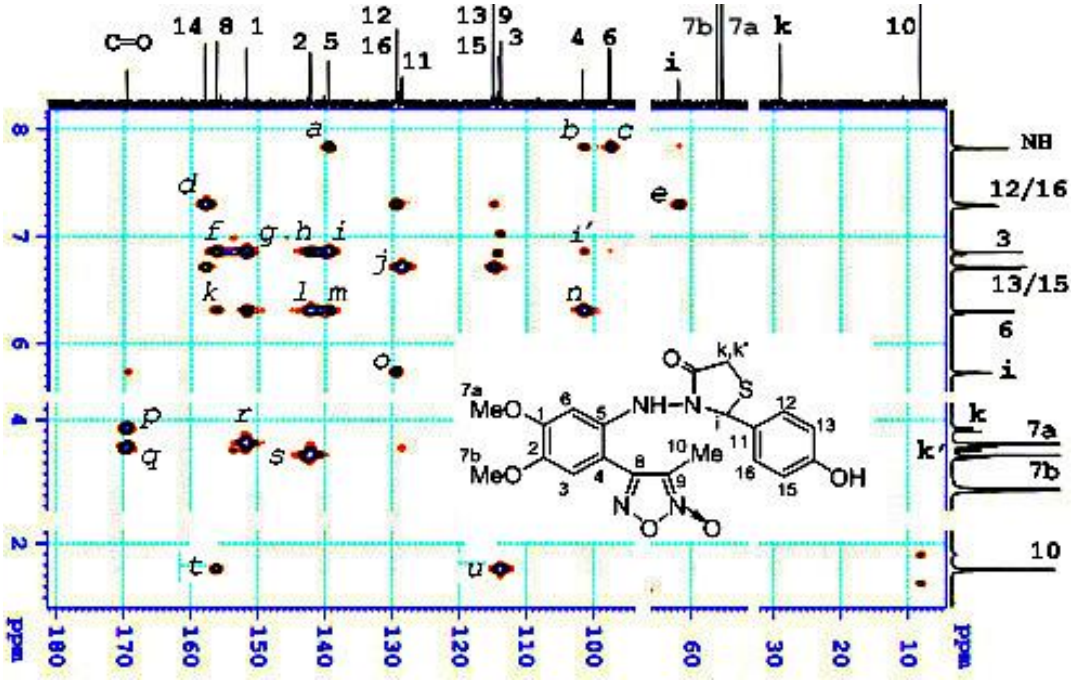


Figure 3. The HMBC spectrum of thiazolidinone **4f**

Mallory and Cammarata[19] showed that the interconversion of two isomeric methylphenylfuroxan can occur at 100 °C. Gasco and colleagues[20] indicated that the resonance signal of a ring methyl group adjacent to the N-oxide oxygen of furoxans appears at 2.30–2.33 ppm, while the resonance signal of a ring methyl group remote from it or a ring methyl group of furazan appears at 2.50–2.53 ppm. The signal of the furoxan methyl group (H10) for the hydrazones **3a-l** appears as a singlet at 2.01–2.04 ppm (Table 3), for the thiazolidinones **4a-l** - at 1.62–1.75 ppm (Table 5). These demonstrated that the methyl group is at position 3 of the furoxan ring (adjacent to the N-oxide oxygen) and the furoxan ring of examined compounds was not isomerized in the toluene reflux during 6-8 h (see the preparation below).

In ESI MS positive mode spectra of hydrazones **3a**, **3b** and **3d** relative intensity of pseudomolecular ions $[M+H]^+$ is 20, 22 and 16%, but that of ion with *m/z* = 251 is 100%. It is possible that the pseudomolecular ions $[M+H]^+$ fragmented to the more stable ion as in Figure 4.

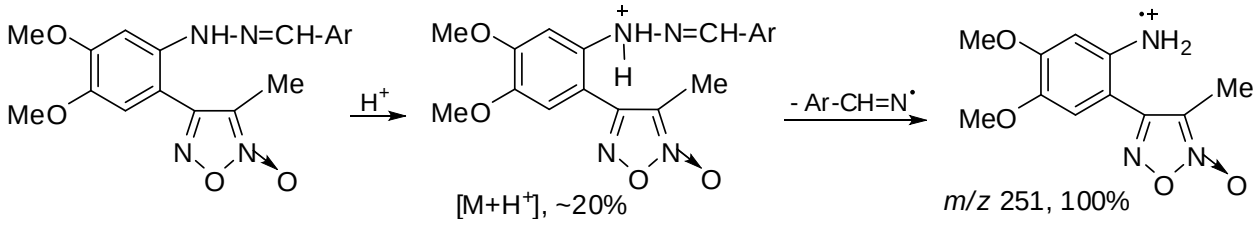


Figure 4. Possible fragmentation of pseudomolecular ions of examined hydrazones

In +MS spectra of thiazolidinones **4d**, **4e, 4f** and **4l** relative intensity of ions $[M+H]^+$ is 24, 18, 11 and 40% respectively, but that of ions $[M+Na]^+$ are 62, 100, 100 and 100 %, in addition relative intensity of ions $[2M+Na]^+$ are 50-100%. It is possible that in the thiazolidinones atom S having large polarization preferentially bond up with ion Na^+ (being as a trace in solvent for ESI MS).

The hydrazones **3a-l** and the thiazolidinones **4a-l** (except **4f** and **4h**) were tested for antimicrobial activities. The results are listed in Table 1. It is seen that almost all examined thiazolidinones displayed moderate activity against *S. aureus*.

Table 1. The minimum inhibition concentration (MIC, μg/mL) of examined compounds against some microorganism

	3a **4a**	**3b** **4b**	**3c** **4c**	**3d** **4d**	**3e** **4e**	**3f** **4f**	**3g** **4g**	**3h** **4h**	**3i** **4i**	**3j** **4j**	**3k** **4k**	**3l** **4l**
S. aureus	> 50 50*	> 50 25	> 50 > 50	> 50 25	> 50 25	> 50 -	> 50 25	> 50 -	> 50 25	> 50 25	> 50 25	> 50 50
A. niger	50 > 50	50 50	> 50 50	> 50 50	> 50 > 50	> 50 -	> 50 50	> 50 -	50 > 50	> 50 50	> 50 > 50	50 > 50
F.oxysporum	> 50 > 50	> 50 > 50	50 50	50 > 50	50 > 50	> 50 -	> 50 > 50	50 -	50 > 50	> 50 > 50	> 50 > 50	> 50 > 50

(*) MIG ≤ 50 is positive.

The hydrazones **3a-l** were also tested for cell cytotoxicity on cancer cell line SW620, the results are listed in Table 2.

Table 2. Cytotoxicity of compounds **3a-l** in human cancer cell line SW620, IC_{50} (μg/mL)

Compd.	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**
*IC_{50}**	>30	>30	16.12	>30	>30	17.45	>30	7.78	>30	>30	>30	>30

**A concentration that inhibits the growth of the cell by 50%.*

It was found that only compound **3h** bearing a 3-hydroxy-4-methoxy substituent exhibited a significant cytotoxicity against this cell line. Two compounds **3c** (with 4-methyl substitution) and **3f** (bearing a 4-hydroxy substituent) displayed moderate cytotoxic effects. Other compounds were not active up to 30 μg/mL.

EXPERIMENTAL

General

IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs at 400–4000 cm^{-1}.

ESI mass spectra were recorded using LC/MS/MS-Waters spectrometer. HR MS were recorded using Varian MS spectrometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer, in DMSO-d_6 with TMS as the internal standard, at 298–300 K. C, H, and N were analyzed in Analytical Laboratory – Institute of Chemistry of Natural Compounds (in Hanoi). The antimicrobial activities were tested at the Experimental Biological Laboratory – Institute of Chemistry of Natural Compounds (in Hanoi) by the method as described in literature,[21] the positive control for *S. aureus*: Ampicilin 50 mM, for *A. niger* and *F. oxysporum*: Nystatin 0.04 mM. The cytotoxicity against human cancer cell line SW620 was screened at College of Pharmacy, Chungbuk National University (Korea). Human cancer cell line, SW620 (colon cancer), was obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were placed at 9×10^3 cells/well in 96-well plates, incubated overnight, and treated with samples for 48 h. Compounds were dissolved in dimethyl sulfoxide (DMSO). Cytotoxicity was measured by the method as described in literature[22] with slight modifications.[23] The IC_{50} values were calculated according to the Probits method.[24] The values reported for these compounds are averages of three separate determinations.

Preparation

4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**1**) was prepared from eugenol according to the literature method.[17] Light yellow needle crystals, yield 70%, mp 174–175 °C (175 °C[17]). ^{1}H NMR, δ (ppm), J (Hz): 6.81 s (H3); 6.49 s (H6); 5.35 s (NH_2); 3.75 s (H7a); 3.62 s (H7b); 2.16 s (H10).

4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylhydrazine (2). At 0-5 °C, 12 mL of 1M $NaNO_2$ solution was slowly added to a solution of 2.51 g (10 mmol) of **1** in 10 mL of 3M HCl solution. The resulting solution was cooled to -10 °C and a solution of 5.69 g (30 mmol) $SnCl_2$ in 50 mL of concentrated hydrochloric acid was slowly added over 1 h and stirred at -5 °C for 3 h additional. The precipitate was collected and neutralized with 2M NaOH solution to pH 8-9. The solid was filtered out, washed with water and recrystallized from EtOH/$CHCl_3$ 3:1 by volume. Yellow needle crystals, yield 1.73 g (65%), mp 180-181 °C. IR (cm^{-1}): 3455, 3360, 3293 (NH); 3010, 2933, 2841 (C-H); 1598, 1525 (ring). ^{1}H NMR, δ (ppm), J (Hz): 6.86 s (H3); 7.01 s (H6); 3.82 s (H7a); 3.68 s (H7b); 2.12 s (H10), 6.73 s (NH), 4.14 s (NH_2). ^{13}C NMR, δ (ppm): 152.25 (C1), 140.25 (C2), 114.27 (C3), 99.33 (C4), 146.13 (C5), 97.46 (C6), 55.31 (C7a), 56.48 (C7b), 156.82 (C8), 113.77 (C9), 8.93 (C10). *Anal.* Calcd for $C_{11}H_{14}N_4O_4$ (M 266.25): C, 49.62; H, 5.30; N, 21.04. Found: C, 49.36; H, 5.16; N, 21.32.

*The general procedure for the preparation of hydrazones **3a–l**:*

An equimolar solution of hydrazine **2** (1 mmol) and aromatic aldehyde (1 mmol) in dry EtOH (30-50 mL) was refluxed over 4-5 h. The reaction mixture was allowed to stand at room temperature. The resulting

precipitate was collected and recrystallized.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-benzylidenhydrazine (3a)**. Yellow crystals, yield 83%, mp 195-196 °C (from EtOH/$CHCl_3$ 2/1 by volume). IR (cm^{-1}): 3286 (NH); 3000, 2943, 2900, 2829 (C-H); 1578, 1526, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. ESI +MS, m/z (au)/relative intensity (%): 355/20 $[M+H]^+$; 251/100 $[M+H-(N=CHPh)]^+$. *Anal.* Calcd for $C_{18}H_{18}N_4O_4$ (M 354.36): C, 61.01; H, 5.12; N, 15.81. Found: C, 60.75; H, 5.33; N, 16.01.

Table 3. ^{1}H NMR signals of the hydrazones **3a-l**

Compd. (Ar)	H3 H6	H7a H7b	H10 NH	H12 H16	H13 H15	H14 Hi	Other
3a (Ph)	6.94 s 7.15 s	3.88 s 3.73 s	2.02 s 9.96 s	7.55 d; J 7.5 7.55 d; J 7.5	7.38 t; J 7.5 7.38 t; J 7.5	7.30 t; J 7.5 7.95 s	-
3b (2-MePh)	6.95 s 7.16 s	3.87 s 3.73 s	2.04 s 9.94 s	- 7.66 d; J 7,5	7.19 m 7.20 m	7.21 m 8.21 s	H17: 2.41 s
3c (4-MePh)	6.93 s 7.13 s	3.87 s 3.73 s	2.02 s 9.89 s	7.44 d; J 8 7.44 d; J 8	7.18 d; J 8 7.18 d; J 8	- 7.92 s	H17: 2.31 s
3d (2-ClPh)	6.95 s 7.17 s	3.88 s 3.73 s	2.01 s 10.26 s	- 7.87 dd; J 8; 1	7.44 dd; J 8, 1 7.30 td; J 8, 1	7.35 d; J 8 8.30 s	-
3e (4-ClPh)	6.95 s 7.16 s	3.88 s 3.73 s	2.03 s 10.04 s	7.58 d; J 8.5 7.58 d; J 8.5	7.42 d; J 8.5 7.42 d; J 8.5	- 7.94 s	-
3f (4-HOPh)	6,91 s 7,11 s	3.86 s 3.72 s	2.02 s 9.69 s	7.38 d; J 8.5 7.38 d; J 8.5	6.77 d; J 8.5 6.77 d; J 8.5	- 7.86 s	OH: 9.70 s
3g (4-MeOPh)	6.92 s 7.13 s	3.87 s 3.72 s	2.03 s 9.78 s	7.50 d; J 8.5 7.50 d; J 8.5	6.95 d; J 8.5 6.95 d; J 8.5	- 7.91 s	H17: 3.78 s
3h (3-MeO-4-HOPh)	6.91 s 7.06 s	3.86 s 3.72 s	2.00 s 9.78 s	7.05 s 6.90 d; J 8	- 6.76 d; J 8	- 7.82 s	H17: 3,80 s OH: 9.25 s
3i (2-O_2NPh)	6.96 s 7.14 s	3.89 s 3.74 s	2.01 s 10.38 s	- 7.96 d; J 8	7.92 d; J 8 7.69 t; J 8	7.50 t; J 8 8.27 s	-
3j (3-O_2NPh)	6.97 s 7.16 s	3.89 s 3.74 s	2.02 s 10.28 s	8.04 s 8.11 d; J 8	- 7.66 t; J 8	8.00 d; J 8 8.31 s	-
3k (4-O_2NPh)	6.98 s 7.20 s	3.90 s 3.75 s	2.02 s 10.42 s	7.80 d; J 9 7.80 d; J 9	8.21 d; J 9 8.21 d; J 9	- 8.03 s	-
3l (3-Pyridyl)	6.95 s 7.18 s	3.89 s 3.73 s	2.02 s 10.13 s	8.73 s 8.47 d; J 4.5	- 7.40 dd; J 8, 4.5	7.96 m 7.97 s	-

Table 4. ^{13}C NMR signals of the hydrazones **3a-l**

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**
C1	152.12	152,14	152.12	152,12	152,13	152,14	152,13	152.05	152.17	152.12	152.09	152.12
C2	140.30	142,24	142.17	142,68	142,47	141,88	142,01	143.05	143.05	142.92	143.12	142.58
C3	114.03	114,03	114.02	114,02	113,98	114,05	114,02	114.00	113.84	114.03	113.89	113.70
C4	100.50	100,34	100.37	100,70	100,66	100,03	100,18	100.33	101.16	101.31	101.41	100.76
C5	138.43	137,49	137.83	138,02	138,31	139,05	138,62	138.96	137.74	137.96	137.53	138.15

C6	98.47	98,39	98.40	98,60	98,53	98,23	98,30	98.57	98.76	99.01	98.95	98.62
C7a	55.44	55,38	55.42	55,50	55,48	55,42	55,41	55.33	55.60	55.58	55.57	55.50
C7b	56.16	56,19	56.17	56,14	56,15	56,21	56,19	56.20	56.17	56.20	56.11	56.15
C8	156.99	156,79	157.06	156,71	156,86	157,10	157,04	157.52	156.58	156.96	156.61	156.77
C9	114.03	114,03	114.02	114,09	114,02	114,17	114,02	114.33	114.16	114.07	113.98	114.00
C10	8.13	8,34	8.33	8,19	8,32	8,38	8,36	8.31	8.27	8.33	8.21	8.26
Ci	138.54	138,64	138.69	133,87	137,06	139,16	138,89	139.14	132.48	137.40	135.51	135.23
C11	135.32	133.22	132.60	132,53	132,50	126,38	127,97	126.79	129.10	131.41	142.00	-
C12	128.64	135,10	129.24	131,46	128,69	127,31	127,16	115.40	147.10	122.40	126.17	147.37
C13	125.69	125.23	125.67	129,47	127,25	115,56	114,18	147.94	124.32	148.38	123.97	131.21
C14	128.26	127.93	138.64	129,73	134,32	157,98	159,55	147.48	128.59	119.88	146.28	132.03
C15	125.69	126,02	125.67	127,75	127,25	115,56	114,18	108.11	132.94	130.26	123.97	123.74
C16	128.64	130.75	129.24	127,39	128,69	127,31	127,16	120.07	127.28	135.78	126.17	148.85
C17	-	19,48	20.86	-	-	-	55,15	55.36	-	-	-	-

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(2-methylbenzyliden)hydrazine (3b)**. Yellow crystals, yield 77%, mp 184-185 °C (from EtOH/$CHCl_3$ 1/2 by volume). IR (cm^{-1}): 3286 (NH); 3010, 2965, 2900, 2837 (CH); 1579, 1526, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. ESI +MS, m/z (au)/relative intensity (%): 369/22 $[M+H]^+$; 251/100 $[M+H-(N=CHPhMe)]^{+\cdot}$. *Anal.* Calcd for $C_{19}H_{20}N_4O_4$ (M 368.39): C, 61.95; H, 5.57; N, 15.21. Found: C, 61.77; H, 5.30; N, 15.48.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(4-methylbenzyliden)hydrazine (3c)**. Yellow crystals, yield 54%, mp 186-187 °C (from EtOH/$CHCl_3$ 1/1 by volume). IR (cm^{-1}): 3286 (NH); 3001, 2929, 2900, 2843 (CH); 1580, 1529, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{19}H_{20}N_4O_4$ (M 368.39): C, 61.95; H, 5.57; N, 15.21. Found: C, 61.68; H, 5.72; N, 15.50.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(2-chlorobenzyliden)hydrazine (3d)**. Yellow crystals, yield 82%, mp 172-173 °C (from EtOH/$CHCl_3$ 1/1 by volume). IR (cm^{-1}): 3263 (NH); 3005, 2951, 2901 (C-H); 1575, 1529, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. ESI +MS, *m/z* (au)/relative intensity (%): 389/16 $[M+H]^+$; 251/100 $[M+H-(N=CHPhCl)]^+$. *Anal.* Calcd for $C_{18}H_{17}ClN_4O_4$ (M 388.80): C, 55.60; H, 4.41; N, 14.41. Found: C, 55.85; H, 4.19; N, 14.20.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(4-chlorobenzyliden)hydrazine (3e)**. Yellow crystals, yield 85%, mp 183 °C (from EtOH/$CHCl_3$ 1/1 by volume). IR (cm^{-1}): 3288 (NH); 3010, 2960, 2846 (C-H); 1581, 1527, 1495 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{18}H_{17}ClN_4O_4$ (M 388.80): C, 55.60; H, 4.41; N, 14.41. Found: C, 55.32; H, 4.66; N, 14.13.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(4-hydroxybenzyliden)hydrazine (3f)**. Yellow crystals, yield 73%, mp 196-197 °C (from EtOH). IR (cm^{-1}): 3539 (OH); 3284 (NH); 3010, 2937, 2900 (C-H); 1581, 1529, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{18}H_{18}N_4O_5$ (M 370.36): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.65; H, 4.71; N, 14.90.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(4-methoxybenzyliden)hydrazine (3g)**. Yellow crystals, yield 57%, mp 150-151 °C (from EtOH). IR (cm^{-1}): 3277 (NH); 3010, 2937, 2900 (C-H); 1581, 1529, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{19}H_{20}N_4O_5$ (M 384.39): C, 59.37; H, 5.24; N, 14.58. Found: C, 59.11; H, 5.49; N, 14.25.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(4-hydroxy-3-methoxybenzyliden)hydrazine (3h)**. Yellow crystals, yield 87%, mp 185-186 °C (from EtOH/$CHCl_3$ 1/1 by volume). IR (cm^{-1}): 3494 (OH); 3309 (NH); 3010, 2953, 2846 (C-H); 1581, 1501, 1480 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{19}H_{20}N_4O_6$ (M 400.39): C, 57.00; H, 5.03; N, 13.99. Found: C, 56.72; H, 5.27; N, 14.26.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(2-nitrobenzyliden)hydrazine (3i)**. Purple crystals, yield 90%, mp 188-189 °C (from EtOH/$CHCl_3$ 1/3 by volume). IR (cm^{-1}): 3314 (NH); 3010, 2939, 2834 (C-H); 1577, 1525, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{18}H_{17}N_5O_6$ (M 399.36): C, 54.14; H, 4.29; N, 17.54. Found: C, 54.45; H, 4.06; N, 17.30.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(3-nitrobenzyliden)hydrazine (3j)**. Deep rouge crystals, yield 89%, mp 203-204 °C (from EtOH/$CHCl_3$ 1/2 by volume). IR (cm^{-1}): 3284 (NH); 3000, 2937, 2831 (C-H); 1583, 1525, 1505 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{18}H_{17}N_5O_6$ (M 399.36): C, 54.14; H, 4.29; N, 17.54. Found: C, 53.86; H, 4.46; N, 17.26.

***N*^{1}-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(4-nitrobenzyliden)hydrazine (3k)**. Red crystals, yield 92%, mp 228-229 °C (from EtOH/$CHCl_3$ 1/3 by volume). IR (cm^{-1}): 3270 (NH); 3008, 2944, 2833 (C-H); 1590, 1527, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{18}H_{17}N_5O_6$ (M 399.36): C, 54.14; H, 4.29; N, 17.54. Found: C, 54.38; H, 4.12; N, 17.35.

***N*^{1}-[4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenyl]-*N*^{2}-(3-pyridylmethyliden)hydrazine (3l)**. Yellow crystals, yield 61%, mp 180-181 °C (from EtOH/$CHCl_3$ 1/3 by volume). IR (cm^{-1}): 3263 (NH); 3000, 2944, 2831 (C-H); 1612, 1582, 1531, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 3 and 4. *Anal.* Calcd for $C_{17}H_{17}N_5O_4$ (M 355.35): C, 57.46; H, 4.82; N, 19.71. Found: C, 57.18; H, 5.01; N, 19.46.

*The general procedure for the preparation of 1,3-thiazolidin-4-ones **4a–l**:*

A solution of 1 mmol of the hydrazone (**3a-l**) and 2 mmol (0.15 mL) of mercaptoacetic acid in 25 mL dry toluene was fluxed using a Dean–Stark trap for 6–8 h. The cooled mixture was treated with 10 mL of 0.1M NaOH solution. The resulting precipitate was collected, washed with EtOH and recrystallized.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-phenyl-1,3-thiazolidin-4-one (4a). Light yellow crystals, yield 54%, mp 95 °C (from DMF/H_2O 1/3 by volume). IR (cm^{-1}): 3288 (NH); 2990, 2932, 2848 (C-H); 1695 (C=O); 1603, 1527, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 5 and 6. HR ESI MS, calcd for $C_{20}H_{21}N_4O_5S$ ($[M+H]^+$): 429.12327. Found: 429.12281.

Table 5. ^{1}H NMR signals of the thiazolidinones **4a-l**

Compd. (Ar)	H3 H6	H7a H7b	H10 NH	H12 H16	H13 H15	H14 Hi	Hk Hk'	Other
4a	6.85 s	3.78 s	1.66 s	7.46 d; J 6.5	7.33 t; J 6.5	7.35 t; J 6.5	3.95 dd; J 16, 1	-
(Ph)	6.34 s	3.66 s	7.97 s	7.46 d; J 6.5	7.33 t; J 6.5	5.85 s	3.77 d; J 16	
4b	6.90 s	3.82 s	1.62 s	-	7.16 m	7.23 m	3.85 dd; J 16, 1	H17:
(2-MePh)	6.43 s	3.69 s	7.99 s	7.42 m	7.23 m	6.08 s	3.80 d; J 16	2.25 s
4c	6.86 s	3.79 s	1.73 s	7.36 d; J 8	7.16 d; J 8	-	3.94 dd; J 16, 1	H17:
(4-MePh)	6.35 s	3.68 s	7.87 s	7.36 d; J 8	7.16 d; J 8	5.80 s	3.76 d; J 16	2.28 s
4d	6.92 s	3.83 s	1.65 s	-	7.46 dd; J 7, 1	7.37 td; J 7, 1	3.90 dd; J 16, 1	-
(2-ClPh)	6.48 s	3.70 s	8.11 s	7.56 dd; J 7, 1	7.40 td; J 7, 1	6.12 s	3.80 d; J 16	
4e	6.88 s	3.80 s	1.72 s	7.51 d; J 8	7.43 d; J 8	-	3.96 dd; J 16, 1	-
(4-ClPh)	6.33 s	3.68 s	7.94 s	7.51 d; J 8	7.43 d; J 8	5.89 s	3.78 d; J 16	
4f	6.83 s	3.78 s	1.75 s	7.29 d; J 8.5	6.70 d; J 8.5 6.70 d;	-	3.91 dd; J 16, 1	9.60 s
(4-HOPh)	6.30 s	3.67 s	7.82 s	7.29 d; J 8.5	J 8.5	5.73 s	3.74 d; J 16	
4g	6.86 s	3.79 s	1.76 s	7.41 d; J 8.5	6.90 d; J 8.5 6.90 d;	-	3.94 d; J 16	-
(4-MeOPh)	6.33 s	3.67 s	7.84 s	7.41 d; J 8.5	J 8.5	5.79 s	3.75 d; J 16	
4h	6.98 s	3.76 s	1.69 s	6.85 s	-	-	3.91 d; J 16	HO:9.14
(3-MeO-4-HOPh)	6.30 s	3.66 s	7.89 s	6.84 d; J 8	6.69 d; J 8	5.75 s	3.65 d; J 16	H17:3.71
4i	6.91 s	3.82 s	1.76 s	-	8.08 dd; J 8, 1	7.82 td; J 8, 1	3.91 dd; J 16, 1	-
(2-O_2NPh)	6.44 s	3.67 s	8.19 s	7.64 d; J 8	7.63 td; J 8, 1	6.21 s	3.78 d; J 16	
4j	6.87 s	3.81 s	1.65 s	8.34 s	-	8.19 d; J 8	4.04 dd; J 16, 1	-
(3-O_2NPh)	6.36 s	3.67 s	8.10 s	7.97 d; J 8	7.68 t; J 8	6.10 s	3.82 d; J 16	
4k	6.90 s	3.82 s	1.69 s	7.76 d; J 8.5	8.23 d; J 8.5	-	4.02 dd; J 16, 1	-
(4-O_2NPh)	6.38 s	3.68 s	8.05 s	7.76 d; J 8.5	8.23 d; J 8.5	6.08 s	3.81 d; J 16	
4l	6.87 s	3.80 s	1.69 s	8.66 d; J 2	-	7.94 d; J 8	4.05 dd; J 16, 1	-
(3-Pyridyl)	6.32 s	3.67 s	8.00 s	8.53 dd; J 5, 1	7.41 dd; J 8, 4	5.95 s	3.79 d; J 16	

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(2-methylphenyl)-1,3-thiazolidin-4-one (4b). Yellow crystals, yield 30%, mp 126-127 ^{o}C (from EtOH/H_2O 1/1 by volume). IR (cm^{-1}): 3292 (NH); 3000, 2944, 2845 (C-H); 1686 (C=O); 1608, 1525, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 5 and 6. HR ESI MS, calcd for $C_{21}H_{23}N_4O_5S$ ($[M+H]^+$): 443.13892. Found: 443.14161.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(4-methylphenyl)-1,3-thiazolidin-4-one (4c). Yellow crystals, yield 45%, mp 103-104 ^{o}C (from EtOH/H_2O 1/1 by volume). IR (cm^{-1}): 3288 (NH); 2985, 2932, 2850 (C-H); 1701 (C=O); 1605, 1525, 1504 (ring). ^{1}H NMR and ^{13}C NMR see Tables 5 and 6. *Anal.* Calcd for $C_{21}H_{22}N_4O_5S$ (M 442.49): C, 57.00; H, 5.01; N, 12.66. Found: C, 57.27; H, 4.82; N, 12.41.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(2-chlorophenyl)-1,3-thiazolidin-4-one (4d). Yellow crystals, yield 41%, mp 125-126 ^{o}C (from EtOH/H_2O 1/1 by volume). IR (cm^{-1}): 3286 (NH); 3000, 2943, 2844 (C-H); 1698 (C=O); 1607, 1520, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Tables 5 and 6. ESI MS, *m/z* (au)/relative intensity (%): 463/24 $[M+H]^+$; 485/62 $[M+Na]^+$; 947/100 $[2M+Na]^+$.

Anal. Calcd for $C_{20}H_{19}ClN_4O_5S$ (M 462.91): C, 51.89; H, 4.14; N, 12.10. Found: C, 52.18; H, 4.35; N, 12.36.

Table 6. ^{13}C NMR signals of the thiazolidinones **4a-l**

	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**	**4l**
C1	151.96	151.99	151.93	152.05	151.95	151.87	151.91	151.93	152.03	152.01	152.01	151.94
C2	142.52	142.70	142.50	142.89	142.53	142.35	142.45	142.42	142.98	142.64	142.69	142.49
C3	113.95	113.84	113.88	113.82	113.87	113.92	113.90	113.92	113.90	113.93	113.90	113.89
C4	101.99	102.36	101.95	102.66	101.99	101.75	101.80	101.89	102.92	102.13	102.22	101.88
C5	139.43	139.21	139.46	138.97	139.33	139.62	139.54	139.60	138.84	139.23	139.14	139.27
C6	97.85	98.18	97.95	98.16	97.74	97.79	97.92	97.89	98.15	97.78	97.82	97.53
C7a	55.57	55.63	55.59	55.68	55.62	55.51	55.61	55.65	55.64	55.60	55.64	55.60
C7b	56.25	56.22	56.21	56.23	56.25	55.57	56.21	56.27	56.29	56.28	56.26	56.23
C8	156.25	156.23	156.19	156.23	156.19	156.23	156.20	156.29	156.24	156.17	156.15	156.15
C9	114.25	114.21	114.13	114.43	114.36	114.15	114.11	114.26	114.58	114.43	114.44	114.41
C10	8.14	7.93	8.19	7.96	8.13	8.20	8.23	8.13	7.85	8.07	8.14	8.08
Ci	61.92	58.50	61.81	58.57	61.10	62.01	61.71	62.18	57.20	60.76	60.57	59.60
Ck	29.04	28.76	29.05	28.64	28.90	29.10	29.09	29.11	28.13	28.93	28.81	28.89
C=O	169.69	169.78	169.63	169.83	169.52	169.54	169.57	169.57	170.00	169.57	169.53	169.43
C11	139.23	136.65	138.31	136.39	138.44	128.69	130.60	129.32	135.18	141.91	147.23	-
C12	128.52	135.94	128.97	132.09	129.70	129.48	129.41	115.09	147.40	123.72	128.87	149.10
C13	127.82	130.58	127.81	129.71	128.46	115.07	113.77	147.52	125.00	147.76	123.67	135.15
C14	128.82	128.29	136.02	130.16	133.30	157.91	159.65	147.20	127.77	122.68	147.51	135.56
C15	127.82	126.28	127.81	127.67	128.46	115.07	113.77	111.94	129.61	130.25	123.67	123.56
C16	128.52	126.28	128.97	128.59	129.70	129.48	129.41	120.85	134.46	134.54	128.87	149.90
C17	-	18.46	20.67	-	-	-	55.15	55.53	-	-	-	-

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (4e). Light yellow crystals, yield 67%, mp 174-175 °C (from EtOH/H_2O 2/1 by volume). IR (cm^{-1}): 3335 (NH); 3092, 3000, 2938, 2846 (C-H); 1702 (C=O); 1605, 1530, 1505 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. ESI MS, m/z (au)/relative intensity (%): 463/18 $[M+H]^+$; 485/100 $[M+Na]^+$; 947/83 $[2M+Na]^+$. *Anal.* Calcd for $C_{20}H_{19}ClN_4O_5S$ (M 462.91): C, 51.89; H, 4.14; N, 12.10. Found: C, 52.14; H, 4.32; N, 11.82.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one (4f). Yellow crystals, yield 62%, mp 145-146 °C (from DMF/H_2O 1/3 by volume). IR (cm^{-1}): 3480 (OH); 3319 (NH); 2995, 2944, 2850 (C-H); 1680 (C=O); 1610, 1522, 1500 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. ESI MS, m/z (au)/relative intensity (%): 445/11 $[M+H]^+$; 467/100 $[M+Na]^+$; 911/54 $[2M+Na]^+$. *Anal.* Calcd for $C_{20}H_{20}N_4O_6S$ (M 444.46): C, 54.05; H, 4.54; N, 12.61. Found: C, 53.82; H, 4.68; N, 12.32.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (4g). Light yellow crystals, yield 62%, mp 145-146 °C (from DMF/H_2O 1/3 by volume). IR (cm^{-1}): 3320 (NH); 3022, 2930, 2845 (C-H); 1704 (C=O); 1614, 1590, 1508 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. HR ESI MS, calcd. for $C_{21}H_{23}N_4O_6S$ ($[M+H]^+$): 459.13383. Found: 459.13084.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(4-hydroxy-3-methoxyphenyl)-1,3-thiazolidin-4-one (4h). Yellow crystals, yield 37%, mp 128-129 °C (from EtOH/H_2O 1/2 by volume). IR (cm^{-1}): 3414 (OH); 3380 (NH); 3000, 2928, 2837 (C-H); 1693 (C=O); 1608, 1517 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. HR ESI MS, calcd for $C_{21}H_{23}N_4O_7S$ ($[M+H]^+$): 475.12875. Found: 475.13220.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (4i). Deep rouge crystals, yield 54%, mp 114-115 °C (from EtOH/H_2O 2/1 by volume). IR (cm^{-1}): 3270 (NH); 3010, 2944, 2845 (C-H); 1702 (C=O); 1605, 1530, 1500 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. *Anal.* Calcd for $C_{20}H_{19}N_5O_7S$ (M 473.46): C, 50.74; H, 4.04; N, 14.79. Found: C, 50.45; H, 4.25; N, 14.51.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(3-nitrophenyl)-1,3-thiazolidin-4-one (4j). Yellow crystals, yield 60%, mp 118-119 °C (from EtOH/H_2O 1/2 by volume). IR (cm^{-1}): 3321 (NH); 3081, 3980, 2909, 2850 (C-H); 1708 (C=O); 1611, 1528, 1500 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. HR ESI MS, Calcd. for $C_{20}H_{20}N_5O_7S$ ($[M+H]^+$): 474.10835. Found: 474.11138.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (4k). Deep rouge crystals, yield 64%, mp 124-125 °C (from EtOH/H_2O 1/2 by volume). IR (cm^{-1}): 3324 (NH); 3092, 3000, 2938, 2846 (C-H); 1702 (C=O); 1605, 1530, 1495 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. *Anal.* Calcd for $C_{20}H_{19}N_5O_7S$ (M 473.46): C, 50.74; H, 4.04; N, 14.79. Found: C, 50.98; H, 4.22; N, 14.49.

3-[4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamino]-2-(3-pyridyl)-1,3-thiazolidin-4-one (4l). White crystals, yield 35%, mp 142-143 °C (from EtOH/H_2O 1/1 by volume). IR (cm^{-1}): 3165 (NH); 2950, 2919, 2856 (C-H); 1694 (C=O); 1605, 1535, 1485 (ring). ^1H NMR and ^{13}C NMR see Tables 5 and 6. ESI MS, *m/z* (au)/relative intensity (%): 430/40 $[M+H]^+$; 452/100 $[M+Na]^+$; 881/51 $[2M+Na]^+$. *Anal.* Calcd for $C_{19}H_{19}N_5O_5S$ (M 429.45): C, 53.14; H, 4.46; N, 16.31. Found: C, 52.88; H, 4.62; N, 16.05.

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