Synthesis of Some Series of 1,3-Thiazolidin-4-ones and Indoles Incorporating Furoxan Moiety Starting with Anethole Isolated from Star Anise Oil

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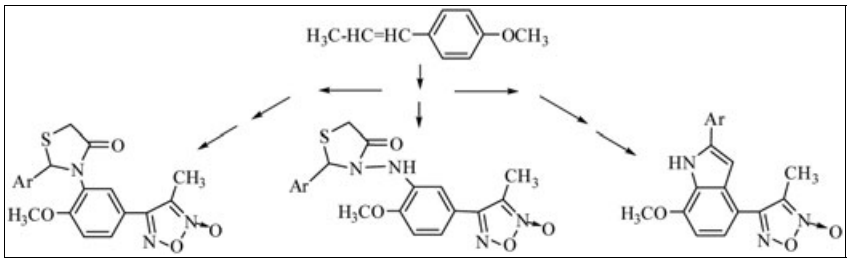

Some series of 1,3-thiazolidin-4-ones and indoles incorporating furoxan moiety were synthesized from anethole, a main component of star anise oil. The structure of these compounds and the intermediates was examined by elemental and spectral data. Ten compounds were screened against some bacteria and fungi.

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INTRODUCTION

Anethole, a main component of star anise (*Illicium verum* Hook f) oil, is *trans*-1-methoxy-4-(prop-1-enyl)-benzene being a flavoring substance of commercial value. Anethole has potent antimicrobial properties, against bacteria, yeast, and fungi [1]. Antifungal activity includes increasing the effectiveness of some other phytochemicals (e.g., polygodial) against *Saccharomyces cerevisiae* and *Candida albicans,* this synergistic effect has potential medicinal uses [2]. Pharmaceutical drugs derived from or related to anethole include anisyldithiolthione, anethole dithione (ADT), and anethole trithione (ATT) [3]. Also, anethole is an inexpensive chemical precursor for paramethoxyamphetamine (PMA) [4].

In our previous article [5], anethole was treated with nitrous acid to give 3-methyl-4-(4-methoxyphenyl)furoxan which was nitrated and subsequently reduced to 2-methoxy-5-(3-methylfuroxan-4-yl)phenylamine (**1**). Compounds **1** exhibit inhibition activity toward *P. aeruginosa* at concentration 25 μg/mL. Several imines and azo compounds derived from **1** have antimicrobial properties at concentrations 12.5–25.0 μg/mL.

Nowadays, thiazolidinones and their derivatives have become among the most extensively investigated compounds. They constitute an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine and agriculture. They have found uses, for example, as antimalarial [6], antimicrobial [7, 8] anti-inflammatory [9, 10], and antiviral agents, especially as anti-HIV agents [11, 12].

As already seen, the investigation of the chemistry of indoles has been, and continues to be, one of the most active of heterocyclic chemistry since many natural and synthetic indoles and related compounds are used as pharmaceuticals and agrochemicals [13, 14].

During recent years, there is a widespread interest in several classes of "hybrid" compounds, obtained combining appropriate pharmacophoric groups with NO-releasing furoxan moiety [15]. A number of them, such as NO-aspirin [16], NO-steroids [17], and NO-ursodeoxycholic acid [18], are now under clinical investigations.

In view of the aforementioned findings, some series of new compounds containing furoxan ring incorporating thiazolidinone or indole moieties were synthesized from anethole and to find out if the resulting compounds have any biological action.

RESULTS AND DISCUSSION

2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamine (**1**) was prepared from anethole according to the literature method [5]. Amine **1** was converted into thiazolidin-4-ones **4a–e** by condensation with appropriate aromatic aldehydes and mercaptoacetic acid, and into 2-methoxy-5-(3-methylfuroxan-4-yl)phenylhydrazine (**2**) by diazotization and subsequent

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reduction. The condensation of **2** with aromatic aldehydes gave hydrazones **3a–j**, with substituted acetophenones gave hydrazones **3k–m** (Fig. 1, the numeration on these structures is used specifically for NMR analysis only).

To our knowledge, the 2-methoxy-5-(3-methylfuroxan-4-yl)phenylhydrazine (**2**), hydrazones **3a–m**, thiazolidin-4-ones **4a–e**, thiazolidin-4-ones **5a–j**, and indoles **6a–c** have not been previously reported in the literature, thus besides elemental and IR spectral data, 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. The IR and ^{13}C-NMR of **2** are similar to those of **1** (see Experimental). In ^{1}H-NMR spectrum of **1**, there is a singlet at 5.06 ppm (2H) associated with the NH_2 group but in ^{1}H-NMR spectrum of **2** beside a singlet at 4.05 ppm (2H) associated with the NH_2 group there is also a singlet at 6.28 ppm (1H) due to NH group. EI MS of **1** and **2** displayed molecular ion at *m/z* 221 and 236 which confirmed their molecular weights, respectively. The ^{1}H-NMR and ^{13}C-NMR spectra of hydrazones **3a–m** displayed the signals of hydrazine moiety: H3–H10, C1–C10 and signals of carbonyl moiety: Hi or Hk, H12–H17, Ci, Ck, C11–C17 (Table 1, Experimental). For example, the resonance of methin proton Hi of aldohydrazones **3a–j** appeared as a singlet at 8.0–8.6 ppm, and the resonance methin Ci of these aldohydrazones appeared at 133.6–143.0 ppm.

The main synthetic routes to 1,3-thiazolidin-4-ones involve three components (an amine, an aldehyde, and mercaptoacetic acid), either in a one- or two-step process [19]. The one-pot reaction of 1 equiv of amine **1**, 1 equiv of appropriated aromatic aldehyde with 3 equiv of mercaptoacetic acid in toluene using a Dean–Stark trap for 6–8 h, gave the thiazolidinones **4a–e** in good yields. Unfortunately, in the same condition the one-pot reaction using 4-dimethylaminobenzaldehyde, 4-bromobenzaldehyde or 4-hydroxy-3-methoxybenzaldehyde as the carbonyl precursor did not produce the expected thiazolidin-4-ones, but rather the mercaptoacetamide **4f** (Fig. 2).

In ^{1}H-NMR and ^{13}C-NMR spectra of thiazolidin-4-ones **4a–e** beside signals of amine moiety (H3–H10 and C1–C10) and signals of aldehyde moiety (Hi, H12–H17, and Ci, C11–C17) there were also signals of CH_2 and C=O of the thiazolidinone ring (Table 2, Experimental). Moreover, two methylene protons of thiazolidinone ring are unequivalent (denoted Hk, Hk'). Proton Hk gave rise to a doublet of doublets at 3.99–4.10 ppm with geminal coupling constant $^2J_{Hk,Hk'}$ = 15.5–16 Hz and long-range coupling constant $^4J_{Hk,Hi}$ = 1.5 Hz, while Hk' appeared as a doublet at 3.86–3.93 ppm with $^2J_{Hk,Hk'}$ =16 Hz ($^4J_{Hk',Hi}$ = 0). Proton Hi of thiazolidin-4-ones **4a–e** theoretically give rise to a doublet with $^4J_{Hk,Hi} \approx 1.5$ Hz but in fact its signal often appeared as a singlet, only Hi of **4b** appeared as a doublet at 6.65 ppm with $^4J_{Hk,Hi}$ = 1.3 Hz (Table 2). In ^{1}H-NMR spectrum of mercaptoacetamide **4f** beside signals of amine moiety (H3, H5, H6, H7, and H10), there also were a singlet at 3.89 ppm (2H) due to the methylene group (Hk) and another singlet at 3.57 ppm associated with HS proton. Amide HN proton displayed a singlet at 9.59 ppm (1H) instead of the singlet at 5.06 ppm (2H) belonging to NH_2 group of amine **1**.

Because the one-pot reaction some time could give unexpected product as mentioned earlier, to prepare thiazolidin-4-ones **5a–j**, the two-step process was used: aldohydrazones **3a–j** which were obtained from hydrazine **2** were refluxed with mercaptoacetic acid in toluene using a Dean–Stark trap for 6–7 h.

The distinctive features for NMR spectra of thiazolidin-4-ones **5a–j** in comparison to those of the hydrazone precursor **3a–j** are as following. First, it can be seen that the signals of Hi and HN in **5a–j** (Table 3) are shifted by about 2.0 ppm as compared to those in **3a–j** (Table 1). Second, in ^{1}H-NMR spectra of **5a–j** beside the signals of H3–H10, Hi, and H12–H17, there are also a doublet of doublets at 3.86–3.92 ppm (1H) with germinal coupling constant $^2J_{Hk,Hk'}$ = 16 Hz and long-range coupling constant $^4J_{Hk,Hi}$ = 1.5 Hz (denoted Hk) and a doublet at 3.70–3.75 ppm (1H, denoted Hk') with $^2J_{Hk,Hk'}$ =16 Hz (Table 3). In ^{13}C-NMR spectra of **5a–j** beside the signals of

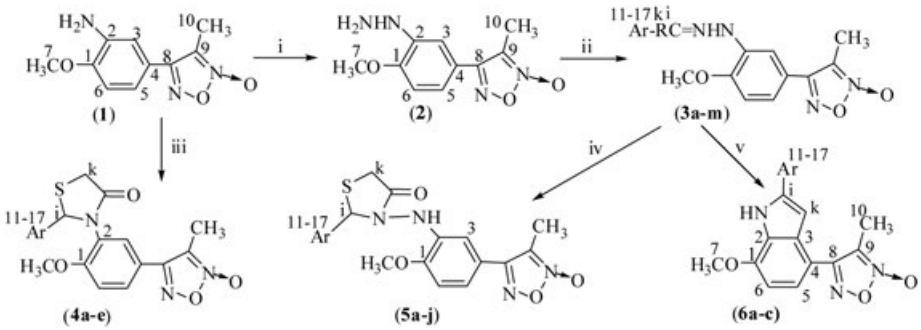
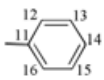
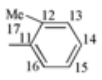
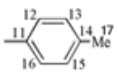
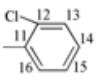
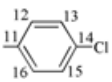
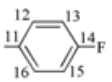
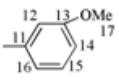
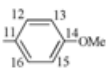
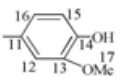


Figure 1. Synthesis of 1,3-thiazolidi-4-ones and indoles from anethole. i: (1) HNO_2, 0–5°C, (2) $SnCl_2$/HCl, 0°C; ii: ArCH=O, reflux or $ArCO–CH_3$, reflux; iii: ArCH=O, $HSCH_2COOH$, reflux; iv: $HSCH_2COOH$, reflux; v: polyphosphoric acid, 120°C.

Table 1

^{1}H-NMR signals of the hydrazones **3a-j**, δ (ppm), J (Hz).

Com.	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
Ar										
H3	7.74 d	7.77 d	7.74 d	7.77 d	7.76 d	7.75 d	7.77 d	7.73 d	7.75 d	7.66 d
	J: 2	J: 2	J: 2	J: 2	J: 2	J: 2	J: 2	J: 2	J: 2	J: 2
H5	7.15 dd	7.16 dd	7.14 dd	7.17 dd	7.17 dd	7.15 dd	7.17 dd	7.11 dd	7.14 dd	7.15 dd
	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5	J: 2; 8.5
H6	7.13 d	7.14 d	7.12 d	7.13d	7.14 d	7.13 d	7.13 d	7.09 d	7.11 d	7.12 d
	J: 8.5	J: 8.5	J: 8.5	J: 8.5	J: 8.5	J: 8.5	J: 8.5	J: 8.5	J: 8.5	J: 8.5
H7	3.94 s	3.95 s	3.94 s	3.93s	3.94 s	3.94 s	3.94 s	3.91 s	3.93 s	3.93 s
H10	2.33 s	2.32 s	2.29 s	2.31	2.29 s	2.33 s	2.33 s	2.30 s	2.34 s	2.32 s
N–H	9.95 s	9.89 s	9.84 s	10.36 s	10.04 s	9.95 s	9.97 s	9.71 s	9.66 s	10.00 s
Hi	8.23 s	8.52 s	8.19 s	8.60 s	8.21 s	8.22 s	8.19 s	8.15 s	8.11 s	8.39 s
H12	7.64 d	—	7.53 d	—	7.65 d	7.69 dd	7.20 s	7.58 d	7.26 d	—
	J: 7.5		J: 8		J: 8.5	J: 8.5; 5.5		J: 8.5	J: 1.5	
H13	7.41 t	7.20 d	7.21 d	7.44 dd	7.45 d	7.24 t	—	6.96 d	—	7.21 d
	J: 7.5	J: 7.5	J: 8	J: 8; 1.5	J: 8.5	J: 9		J: 8.5		J: 3.5
H14	7.32 t	7.22 t	—	7.37 t	—	—	6.90 dd	—	HO: 9.21	7.06 t
	J: 7.5	J: 7.5		J: 8			J: 8			J: 4
H15	7.41 t	7.21 t	7.21 d	7.31 td	7.45 d	7.24 t	7.21 d	6.96 d	6.81 d	7.48 d
	J: 7.5	J: 7.5	J: 8	J: 8; 1.5	J: 8.5	J: 9	J: 8; 2	J: 8.5	J: 8	J: 4.5
H16	7.64 d	7.78 d	7.53 d	8.00 dd	7.45 d	7.69 dd	7.19 dd	7.58 d	7.01 dd	—
	J: 7.5	J: 7.5	J: 8	J: 8; 1.5	J: 8.5	J: 8.5; 5.5	J: 8; 2	J: 8.5	J: 8; 1.5	
H17	—	2.44 s	2.32	—	—	—	3.80 s	3.77 s	3.83 s	—

C1–C10, Ci, and C11–C17, there are also signals of Ck (28.5–29.7 ppm) and C=O (169.1–169.9 ppm) associated with the methylene and carbonyl groups, respectively. These confirmed the formation of the thiazolidin-4-one ring. The ^{1}H-NMR spectra of **5a–j** differ from those of **4a–e** on the presence of the singlet at 7.60–8.02 ppm due to NH group.

The indoles **6a–c** were prepared according to the Fischer synthesis by heating ketohydrazones **5k–m** with polyphosphoric acid at 120°C for 2 h. ^{1}H-NMR and ^{13}C-NMR spectra of indoles **6a–c** quite differ from those of the hydrazone precursors **3k–m** (Table 4). Particularly, in ^{1}H-NMR spectra of indoles **6a–c**, there was no signal of H3; proton Hk give rise to a signal at 6.96–7.16 ppm (1H) instead of the singlet at 2.24–2.32 ppm (3H) in the spectra of **3k–m**; the indole HN proton displayed singlet at 11.67–11.91 ppm instead of the singlet at 8.26–8.24 ppm belonging to hydrazone NH group in precursors **3k–m**. The signals of Ck in **3k–m** appeared at 12.38, 12.36, 12.39 ppm, but in **6a–c**, they appeared at 98.5, 97.76, 97.92 ppm, respectively, the signal of Ci in **6a–c** is upfield shifted by about 5 ppm as compared to those in **3k–m**, and so all (see Experimental).

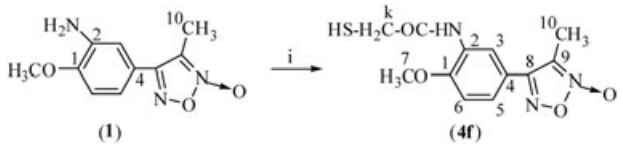


Figure 2. Mercaptoacetamide derived from amine **1**. (i) $HSCH_2COOH$, 4-Me_2NPhCH=O (or 4-BrPhCH=O, 4-HO-3-MeOPhCH=O), reflux.

The HMBC spectra of **6a–c** clearly demonstrated the indole cyclization. For example, in Figure 3, proton HN give rise to not only cross peak *b* and *c* with C3 and Ci but also cross peaks *a* with Ck; proton Hk give rise to not only cross peak *f* with C11 of 4-methylphenyl group but also cross peaks *d* and *e* with C2 and C3 of the indole ring respectively.

ESI MS of **6a–c** shown molecular weights of 321, 335, 337 au corresponding with their molecular formula.

It has been pointed out that furoxans could be undergone a isomerization to isomeric furoxans under heating condition and a reduction to furazans by stannous chloride [20]. Gasco et al. [21] showed that the chemical shift of a ring methyl group adjacent to the *N*-oxide oxygen of furoxans occurs at 2.30–2.33 ppm, while a ring methyl group remote from it (i.e. in isomeric furoxans) or a ring methyl group of furazan appears at 2.50–2.53 ppm. The signal of the ring methyl group (H10) of all examined compounds appears as a singlet at 2.10–2.34 ppm (Tables 1–4) indicating that during the reported synthesis the furoxan ring was not isomerized, and was not reduced by stannous chloride.

Table 2

^{1}H-NMR signals of 1,3-thiazolidin-4-one **4a-e**, δ (ppm), J (Hz).

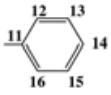
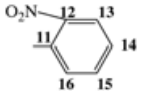
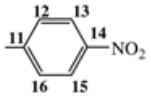
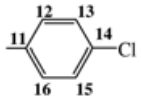
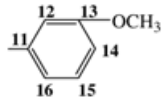
Com.	**4a**	**4b**	**4c**	**4d**	**4e**
Ar					
H3	7.43 d J: 2.0	7.64 d J: 2	7.54 d J: 2	7.45 d J: 2	7.46 dJ: 2
H5	7.61 dd J: 2; 9	7.66 dd J: 2; 8.5	7.64 dd J: 2; 8.5	7.64 dd J: 2; 8.5	7.61 dd J: 2; 9
H6	7.23 d J: 9	7.28 d J: 8	7.26 d J: 8.5	7,25 d J: 8.5	7.23 d J: 9
H7	3.88 s	3.88 s	3.88 s	3.87 s	3.88 s
H10	2.10 s	2.15 s	2.14 s	2.13 s	2.10 s
Hi	6.25 s	6.65 d J: 1.3	6.44 s	6.27 s	6.23 s
Hk	4.01 dd J: 16; 1.5	4.05 dd J: 16; 1.5	4.10 dd J: 16; 1.5	4.02 dd J: 16; 1.5	3.99 dd J: 16; 1.5
Hk'	3.88 d J: 16	3.86 d J: 16	3.93 d J: 16	3.90 d J: 16	3.86 d J: 16
H12	7.44 d J: 7	—	7.76 d J: 8.5	7.47 d J: 8.5	6.99 d J: 1.5
H13	7.28 t J: 7	8.06 dd J: 8; 1	8.13 d J: 8,5	7.34 d J: 8.5	H17: 3.69 s
H14	7.24 t J: 7	7.53 td J: 8; 1	—	—	6.78 dd J: 1.5; 8
H15	7.28 t J: 7	7.77 t J: 8	8.13 d J: 8,5	7.34 d J: 8.5	7.17 t J: 8
H16	7.44 d J: 7	7.91 dd J: 8; 1	7.76 d J: 8.5	7.47 d J: 8.5	6,98 d J: 8

Table 3

^{1}H-NMR signals of 1,3-thiazolidin-4-one **5a-j**, δ (ppm), J (Hz).

	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**
Ar	Ph	2-MePh	4-MePh	2-ClPh	4-ClPh	4-FPh	3-MeO-Ph	4-MeO-Ph	4-HO-3-MeO-Ph	2-Thienyl
H3	6.95 d J: 2	7.01 d J: 2	6.94 d J: 2	7.04 d J: 2	6.91 d J: 2	6.92 d J: 2	6.95 d J: 2	6.91 d J: 2	6.94 d J: 2	6.87 d J: 2
H5	7.13 dd J: 8.5; 2	7.16 dd J: 8.5; 2	7.13 dd J: 8.5; 2	7.19 dd J: 8.5; 2	7.14 dd J: 8.5; 2	7.17 d J: 8.5	7.13 dd J: 8.5; 2	7.11 dd J: 8.5; 2	7.10 dd J: 8.5; 2	7.12 dd J: 8.5; 2
H6	7.04 d J: 8.5	7.07 d J: 8.5	7.04 d J: 8.5	7.09 d J: 8.5	7.05 d J: 8.5	7.05 d J: 8.5	7.05 d J: 8.5	7.03 d J: 8.5	7.03 d J: 8.5	7.05 d J: 8.5
H7	3.82 s	3.84 s	3.83 s	3.85 s	3.83 s	3.83 s	3.83 s	3.82 s	3.83 s	3.87 s
H10	2.27 s	2.29 s	2.27 s	2.29 s	2.27 s	2.27 s	2.27 s	2.26 s	2.24 s	2.24 s
HN	7.71 s	7.79 s	7.64 s	8.02 s	7.64 s	7.76 s	7.77 s	7.60 s	7.63 s	7.62 s
Hi	5.88 s	6.12 s	5.83 s	6.17 s	5.90 s	5.91 s	5.86 s	5.82 s	5.77 s	6.13 s
Hk	3.91 dd J:16; 1.5	3.82 dd J:16; 1.5	3.89 dd J:16; 1.5	3.86 dd J:16; 1.5	3.92 dd J:16; 1.5	3.92 d J: 16	3.92 d d J:16; 1.5	3.88 d d J:16; 1.5	3.88 d d J:16; 1.5	3.88 d d J:16; 1.5
Hk'	3.73 d J: 16	3.74 d J: 16	3.72 d J: 16	3.75 d J: 16	3.73 d J: 16	3.73 d J: 16	3.72 d J: 16	3.71 d J: 16	3.70 d J: 16	3.74 d J: 16
H12	7.50 d J: 8	—	7.39 d J: 8	—	7.54 d J: 8.5	7.57 m	7.06 d J: 8	7.43 d J: 9	7.06 d J: 2	—
H13	7.34 t J: 8	7.15 dd J: 8.5; 2	7.14 d J: 8	7.47 dd J: 7.5; 1.5	7.40 d J: 8.5	7.14 t J: 9	—	6.87 d J: 9	—	7.24 dd J: 4; 1
H14	7.31 t J: 8	7.20 td J: 8.5; 2	—	7.37 td J: 7.5; 1.5	—	—	6.87 d d J: 8; 2	—	HO: 9.07 s	6.93 dd J: 5; 4
H15	7.34 t J: 8	7,21 td J: 8.5; 2	7.14 d J: 8	7.40 td J: 7.5; 1.5	7.40 d J: 8.5	7.14 t J: 9	7.24 t J: 8	6.87 d J: 9	6.67 d J: 8.5	7.54 d J: 5
H16	7.50 d J: 8	7.59 dd J: 8.5; 2	7.39 d J: 8	7.74 dd J: 7.5; 2	7.54 d J: 8.5	7.57 m	7.04 d J: 8	7.43 d J: 9	6.84 dd J: 8.5; 2	—
H17	—	2.29 s	2.29 s	—	—	—	3.73 s	3.72 s	3.73 s	—

Some reported compounds were tested for their *in vitro* antimicrobial activities; the results are listed in Table 5. It is seen that the examined compounds showed low activities toward the tested microorganism.

EXPERIMENTAL

General. IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs at 400–4000 cm^{-1}. The EI mass spectra of examined compounds were recorded using a

Table 4

^{1}H-NMR signals of hydrazone **3k-m** and indoles **6a-c**, δ (ppm), J (Hz).

Com.	3k	3l	3m	6a	6b	6c
Ar	Ph	4-MePh	4-HOPh	Ph	4-MePh	4-HOPh
H3	7.81 d; J: 2	7.80 d; J: 2	7.76 d; J: 2	—	—	—
H5	7.22 dd; J: 8.5; 2	7.19 dd; J: 8.5; 2	7.18 dd; J: 8.5; 2	7.33 d; J: 8	7.31 d; J: 8	7.29 d; J: 8
H6	7.17 d; J: 8.5	7.16 d; J: 8.5	7.14 d; J: 8.5	6.89 d; J: 8	6.86 d; J: 8	6.82 d; J: 8
H7	3.97 s	3.96 s	3.95 s	4.05 s	4.04 s	4.03 s
H10	2.32 s	2.32 s	2.32 s	2.32 s	2.32 s	2.31 s
N–H	8.24 s	8.18 s	8.06 s	11.91 s	11.83 s	11.67 s
Hk	2.31 s	2.32 s	2.24 s	7.16 d; J: 2.5	7.11 d; J: 2.5	6.96 s
H12	7.82 d; J: 7.5	7.71 d; J: 8	7.65 d; J: 8.5	7.99 d; J: 8	7.88 d; J: 8	7.80 d; J: 8
H13	7.41 t; J: 7.5	7.22 d; J: 8	6.79 d; J: 8.5	7.44 t; J: 8	7.25 d; J: 8	6.83 d; J: 8
H14	7.34 t; J: 7.5	H17: 2.32 s	HO: 9.62 s	7.33 t; J: 8	H17: 2.34 s	HO: 9.65
H15	7.41 t; J: 7.5	7.22 d; J: 8	6.79 d; J: 8.5	7.44 t; J: 8	7.25 d; J: 8	6.83 d; J: 8
H16	7.82 d; J: 7.5	7.71 d; J: 8	7.65 d; J: 8.5	7.99 d; J: 8	7.88 d; J: 8	7.80 d; J: 8

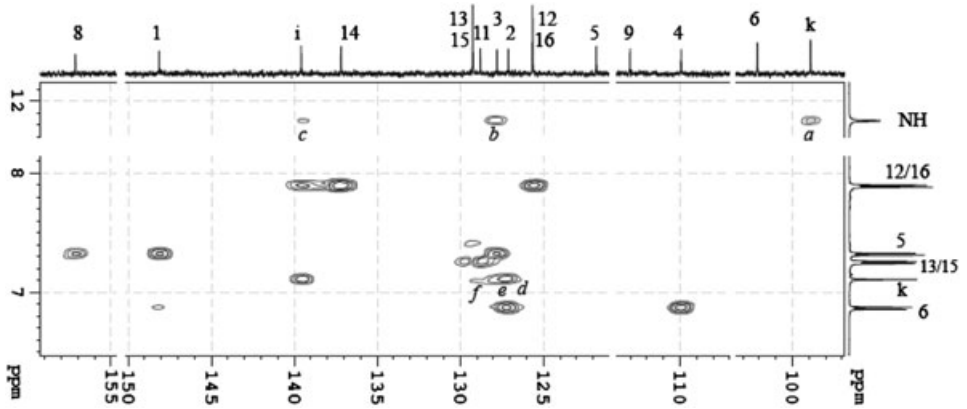


Figure 3. Partial HMBC spectrum of indole **6b** (the formula in Fig. 1, compd. **6b**, Ar = 4-MePh).

5989B Hewlett–Packard mass spectrometer. ESI mass spectra were recorded using Agilent LC-MSD-Trap-SL series 1100 spectrometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer, in d_6-DMSO 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 anti microbial activities were tested at the Experimental Biological Laboratory – Institute of Chemistry of Natural Compounds (in Hanoi), according to the method described in reference [22].

Preparation ***2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamine (1)*** is prepared from anethole according to the literature method [5, 23]. Light yellow needle crystals, yield 60%, mp 119–120°C. IR (cm^{-1}): 3468; 3371 (NH); 3075; 2934 (C–H), 1603, 1582 (ring). ^{1}H-NMR, δ(ppm), J (Hz): 7.06 (1H, d, $^4J_{HH}$ = 1.5, H3), 6.90 (1H, dd, $^3J_{HH}$ = 8, $^4J_{HH}$ = 1.5, H5), 6.96 (1H, d, $^3J_{HH}$ = 8, H6), 3.83 (3H, s, H7), 2.28 (3H, s, H10), 5.06 (2H, s, NH_2). ^{13}C-NMR, δ (ppm): 148.69 (C1), 138.70 (C2), 111.89 (C3), 119.01 (C4), 116.02 (C5), 110.68 (C6), 55.59 (C7), 157.49 (C8), 112.98 (C9), 9.38 (C10). EI ms, *m/z* (%) = 221 (M^+, 32), 205 (M^+- O, 5),

Table 5

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

Compounds	4b	4c	4d	5e	5f	5i	5j	6a	6b	6c
E. coli	32	88.2	88.2	91.5	64	91.5	50	50	>128	>128
B. subtillis	88.2	>128	32	88.2	64	>128	64	91.5	>128	88.2
S. aureus	>128	20.3	20.3s	32	20.3	32	20.3	20.3	32	88.2
P. aeruginosa	>128	88.2	88.2	64	>128	>128	50	32	64	32
C. albicans	64	32	91.5	32	64	91.5	88.2	91.5	64	32

161 (M^+- 2NO, 56), 146 (M^+- 2NO – CH_3, 100). *Anal.* Calcd. for $C_{10}H_{11}N_3O_3$ (M 221.22): C, 54.29; H, 5.01; N, 18.99. Found: C, 54.61; H, 4.88; N, 18.65.

2-Methoxy-5-(3-methylfuroxan-4-yl)phenylhydrazine (2). At 0–5°C, 12 mL of 1 *M* $NaNO_2$ solution was slowly added to a solution of 10 mmol of **1** in 10 mL of 3 *M* HCl solution. The resulting solution was cooled to −10°C and a solution of 6.78g (30 mmol) $SnCl_2$ in 100 mL of concentrated hydrochloric acid was slowly added over an hours and stirred at −5°C for 2 hours additional. The precipitate was collected and neutralized with 2 *M* NaOH solution. The white solid was filtered out, washed with water and recrystallized from ethanol/chloroform 3:1 by volume.

White needle crystals, yield 85%, mp 126°C. IR (cm^{-1}): 3447; 3318; 3230 (NH); 3096; 3030; 2931; 2852 (C–H), 1591, 1531 (ring). ^{1}H-NMR, δ(ppm), J (Hz): 7.39 (1H, d, $^4J_{HH}$ = 2, H3), 7.00 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 2, H5), 6.96 (1H, d, $^3J_{HH}$ = 8.5, H6), 3.84 (3H, s, H7), 2.31 (3H, s, H10), 6.28 (1H, s, NH), 4.05 (2H, s, NH_2). ^{13}C-NMR, δ (ppm): 147.86 (C1), 141.94 (C2), 108.74 (C3), 118.78 (C4), 116.19 (C5), 109.74 (C6), 55.48 (C7), 157.51 (C8), 112.68 (C9), 9.04 (C10). EI ms, *m/z* (%) = 236 (M^+, 100), 220 (M^+- O, 8), 175 ($M^{+\cdot}$ - 2NO, 83). *Anal.* Calcd. for $C_{10}H_{12}N_4O_3$ (M 236.23): C, 50.84; H, 5.12; N, 23.72. Found: C, 51.08; H, 5.38; N, 23.47.

The general procedure for the preparation of hydrazones 3a–m. An equimolar solution of hydrazine **2** (1 mmol) and aromatic aldehyde (1 mmol) or ketone (1 mmol) in dry ethanol was refluxed over 2–4 h. The reaction mixture was allowed to stand at room temperature. The resulting precipitate was collected and recrystallized.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-benzylidenhydrazine (3a). White crystals, yield 65%, mp 138°C (from EtOH). IR (cm^{-1}): 3307 (NH); 3060; 3032; 2932; 2855 (C–H), 1590, 1539, 1500 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.78 (C1), 135.66 (C2), 110.44 (C3), 119.74 (C4), 118.77 (C5), 111.62 (C6), 55.36 (C7), 157.95 (C8), 113.45 (C9), 9.66 (C10), 140.14 (Ci), 136.09 (C11), 126.36 (C12/16), 129.23 (C13/15), 128.84 (C14). *Anal.* Calcd. for $C_{17}H_{16}N_4O_3$ (M 324.32): C, 62.95; H, 4.97; N, 17.28. Found: C, 63.29; H, 4.68; N, 17.57.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(2-methylbenzyliden)hydrazine (3b). White crystals, yield 77%, mp 175°C (from EtOH). IR (cm^{-1}): 3321 (NH); 3050; 3020; 2979; 2843 (C–H), 1582, 1540, 1511 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.21 (C1), 135.28 (C2), 109.80 (C3), 119.26 (C4), 118.10 (C5), 111.08 (C6), 55.83 (C7), 157.37 (C8), 112.84 (C9), 9.12 (C10), 135.23 (Ci), 133.45 (C11), 138.95 (C12), 125.40 (C13), 127.97 (C14), 126.04 (C15), 130.74 (C16), 19.50 (C17). *Anal.* Calcd. for $C_{18}H_{18}N_4O_3$ (M 338.35): C, 63.89; H, 5.36; N, 16.52. Found: C, 63.56; H, 5.68; N, 16.17.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(4-methylbenzyliden)hydrazine (3c). White needle crystals, yield 57%, mp 168–170°C (from EtOH). IR (cm^{-1}): 3313 (NH); 3050; 3026; 2970; 2855 (C–H), 1582, 1538, 1511 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.18 (C1), 135.23 (C2), 109.78 (C3), 119.18 (C4), 118.03 (C5), 111.01 (C6), 55.79 (C7), 157.42 (C8), 112.90 (C9), 9.11 (C10), 139.81 (Ci), 132.83 (C11), 129.28 (C12/C16), 125.80 (C13/C15), 137.86 (C14), 20.87 (C17). *Anal.* Calcd. for $C_{18}H_{18}N_4O_3$ (M 338.35): C, 63.89; H, 5.36; N, 16.52. Found: C, 64.09; H, 5.09; N, 16.21.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(2-chlorobenzyliden)hydrazine (3d). Yellow needle crystals, yield 66%, mp 196°C (from EtOH). IR (cm^{-1}): 3293 (NH); 3095; 3060; 2968; 2840 (C–H), 1599, 1538, 1500 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.45 (C1), 134.81 (C2), 110.16 (C3), 119.24 (C4), 118.81 (C5), 111.26 (C6), 55.88 (C7), 157.40 (C8), 112.98 (C9), 9.14 (C10), 135.39 (Ci), 131.68 (C11), 132.91 (C12), 125.54 (C13), 129.77 (C14), 126.03 (C15), 127.45 (C16). *Anal.* Calcd. for $C_{17}H_{15}N_4O_3Cl$ (M 358.76): C, 56.91; H, 4.21; N, 13.38. Found: C, 57.25; H, 4.39; N, 13.05.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(4-chlorobenzyliden)hydrazine (3e). White crystals, yield 50%, mp 179°C (from EtOH). IR (cm^{-1}): 3301 (NH); 3060; 3024; 2960; 2853 (C–H), 1582, 1548, 1500 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.24 (C1), 134.87 (C2), 109.98 (C3), 119.16 (C4), 118.40 (C5), 111.10 (C6), 55.77 (C7), 157.29 (C8), 112.76 (C9), 9.01 (C10), 134.45 (Ci), 132.45 (C11), 128.64 (C12/C16), 127.27 (C13/C15), 138.14 (C14). *Anal.* Calcd. for $C_{17}H_{15}N_4O_3Cl$ (M 358.76): C, 56.91; H, 4.21; N, 13.38. Found: C, 57.22; H, 4.49; N, 13.09.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(4-fluobenzyliden)hydrazine (3f). White crystals, yield 62%, mp 167–168°C (from EtOH). IR (cm^{-1}): 3317 (NH); 3064; 3040; 2945; 2853 (C–H), 1599, 1540, 1488 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.28 (C1), 135.09 (C2), 110.44 (C3), 119.25 (C4), 118.67 (C5), 111.18 (C6), 55.02 (C7), 157.34 (C8), 112.86 (C9), 9.11 (C10), 138.50 (Ci), 132.17 (C11), 122.75 d ; $^3J_{FC}$ 8 Hz (C12/C16), 115.70 d ; $^2J_{FC}$ 22 Hz (C13/C15), 162.08 d ; $^1J_{FC}$ 245 Hz (C14). *Anal.* Calcd. for $C_{17}H_{15}N_4O_3F$ (M 342.31): C, 59.64; H, 4.42; N, 16.37. Found: C, 59.28; H, 4.29; N, 16.08.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(3-methoxybenzyliden)hydrazine (3g). White needle crystals, yield 68%, mp 140°C (from EtOH/dioxan 1:1). IR (cm^{-1}): 3277 (NH); 3080; 3040; 2958; 2840 (C–H), 1587, 1560, 1503 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.21 (C1), 135.28 (C2), 109.80 (C3), 119.26 (C4), 118.10 (C5), 111.08 (C6), 55.83 (C7), 157.37 (C8), 112.84 (C9), 9.12 (C10), 139.42 (Ci), 137.05 (C11), 110.10 (C12), 159.56 (C13), 114.28 (C14), 129.76 (C15), 118.24 (C16), 55.84 (C17). *Anal.* Calcd. for $C_{18}H_{18}N_4O_4$ (M 354.35): C, 61.04; H, 5.12; N, 15.81. Found: C, 61.42; H, 4.88; N, 15.49.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(4-methoxybenzyliden)hydrazine (3h). Pale orange crystals, yield 75%, mp 184°C (from EtOH). IR (cm^{-1}): 3341 (NH); 3078; 3015; 2970; 2852 (C–H), 1603, 1536, 1497 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.18 (C1), 135.43 (C2), 109.67 (C3), 119.22 (C4), 117.85 (C5), 110.92 (C6), 55.19 (C7), 157.45 (C8), 112.94 (C9), 9.16 (C10), 139.79 (Ci), 128.26 (C11), 127.34 (C12/C16), 114.27 (C13/C15), 159.65 (C14), 55.80 (C17). *Anal.* Calcd. for $C_{18}H_{18}N_4O_4$ (M 354.35): C, 61.04; H, 5.12; N, 15.81. Found: C, 60.74; H, 5.29; N, 16.05.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-(4-hydroxy-3-methoxybenzyliden)-hydrazine (3i). White needle crystals, yield 88%, mp 209°C (from EtOH). IR (cm^{-1}): 3380 (OH); 3337 (NH); 3060; 3031; 2974; 2845 (C–H), 1586, 1520, 1494 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.01 (C1), 135.39 (C2), 109.73 (C3), 119.14 (C4), 117.46 (C5), 110.92 (C6), 55.69 (C7), 157.28 (C8), 112.76 (C9), 9.04 (C10), 140.26 (Ci), 127.09 (C11), 108.69 (C12), 147.89 (C13), 147.49 (C14), 115.48 (C15), 120.01 (C16), 55.44 (C17). *Anal.* Calcd. for $C_{18}H_{18}N_4O_5$ (M 370.35): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.06; H, 4.68; N, 15.45.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-[(thien-2-yl)methyliden]hydrazine (3j). Pale orange crystals, yield 89%, mp 178°C (from EtOH). IR (cm^{-1}): 3321 (NH); 3100; 3050;

2970; 2836 (C–H), 1595, 1504, 1500 (ring). ^{1}H-NMR: see Table 1. ^{13}C-NMR, δ (ppm): 147.23 (C1), 134.86 (C2), 109.71 (C3), 119.19 (C4), 118.15 (C5), 111.06 (C6), 55.81 (C7), 157.26 (C8), 112.86 (C9), 9.19 (C10), 134.83 (Ci), 140.79 (C12), 127.09 (C13), 126.28 (C14), 127.64 (C15). *Anal.* Calcd. for $C_{15}H_{14}N_4O_3S$ (M 330.35): C, 54.53; H, 4.27; N, 16.96. Found: C, 54.21; H, 4.48; N, 17.27.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-[1-(phenyl) ethyliden]hydrazine (3k). White crystals, yield 56%, mp 131°C (from EtOH). IR (cm^{-1}): 3389 (NH); 3060; 3006; 2980; 2934 (C–H), 1591, 1539, 1490 (ring). ^{1}H-NMR: see Table 4. ^{13}C-NMR, δ (ppm): 147.75 (C1), 135.35 (C2), 110.65 (C3), 119.20 (C4), 118.85 (C5), 111.02 (C6), 56.01 (C7), 157.38 (C8), 112.88 (C9), 9.12 (C10), 144.76 (Ci), 12.38 (Ck), 138.66 (C11), 125.43 (C12/C16), 128.35 (C13/C15), 128.12 (C14). +ms, *m/z* = 339 (M+H$^+$). *Anal.* Calcd. for $C_{18}H_{18}N_4O_3$ (M 338.35): C, 63.89; H, 5.36; N, 16.55. Found: C, 64.04; H, 5.09; N, 16.26.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-[1-(4-methylphenyl)ethyliden]-hydrazine (3l). White crystals, yield 67%, mp 161–162°C (from EtOH). IR (cm^{-1}): 3382 (NH); 3041; 3000; 2949; 2850 (C–H), 1590, 1537, 1497 (ring). ^{1}H-NMR: see Table 4. ^{13}C-NMR, δ (ppm): 147.71 (C1), 135.45 (C2), 110.57 (C3), 119.19 (C4), 118.69 (C5), 110.97 (C6), 55.99 (C7), 157.39 (C8), 112.88 (C9), 9.12 (C10), 144.77 (Ci), 12.36 (Ck), 135.93 (C11), 125.37 (C12/C16), 128.95 (C13/C15), 137.59 (C14), 20.72 (C17). EI ms, *m/z* (%) = 352 (M$^{+\cdot}$, 50), 336 (M$^{+\cdot}$- O, 10), 292 (M$^{+\cdot}$ - 2NO, 24). *Anal.* Calcd. for $C_{19}H_{20}N_4O_3$ (M 352.37): C, 64.76; H, 5.72; N, 15.90. Found: C, 64.44; H, 5.98; N, 16.21.

N^1-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-N^2-[1-(4-hydroxyphenyl)ethyliden]-hydrazine (3m). White needle crystals, yield 76%, mp 186°C (from EtOH). IR (cm^{-1}): 3363 (NH); 3300 (OH), 3062; 3000; 2970; 2848 (C–H); 1605, 1579, 1514 (ring). ^{1}H-NMR: see Table 4. ^{13}C-NMR, δ (ppm): 147.61 (C1), 135.65 (C2), 110.31 (C3), 119.13 (C4), 118.37 (C5), 110.79 (C6), 55.93 (C7), 157.45 (C8), 112.97 (C9), 9.16 (C10), 145.19 (Ci), 12.39 (Ck), 129.63 (C11), 126.91 (C12/C16), 115.16 (C13/C15), 157.92 (C14). *Anal.* Calcd. for $C_{18}H_{18}N_4O_4$ (M 354.45): C, 61.01; H, 5.12; N, 15.81. Found: C, 61.42; H, 4.98; N, 16.11.

The one-pot procedure for the preparation of thiazolidin-4-ones 4a–e. To a solution of 1 mmol (0.221 g) of amine **1** and 1 mmol of an appropriated aromatic aldehyde in 15 mL dry toluene 3.5 mmol (2.5 mL) of mercaptoacetic acid was slowly added. The reaction mixture was fluxed using a Dean–Stark trap for 8–10 hours. The cooled mixture was neutralized with 0.1 *M* NaOH solution and then was evaporated in vacuo. The residue was recrystallized from suitable solvents.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-2-phenyl-1,3-thiazolidin-4-one (4a). White crystals, yield 86%, mp 173°C (from EtOH/H_2O 1:1). IR (cm^{-1}): 3070, 3036, 2973, 2924, 2846 (C–H); 1688 (C=O); 1598, 1524 (ring). ^{1}H-NMR: see Table 2. ^{13}C-NMR, δ (ppm): 156.94 (C1), 126.27 (C2), 129.16 (C3), 118.34 (C4), 128.85 (C5), 113.25 (C6), 56.21 (C7), 156.24 (C8), 112.69 (C9), 8.68 (C10), 63.23 (Ci), 32.23 (Ck), 170.77 (C=O), 139.16 (C11), 127.61 (C12/C16), 128.47 (C13/C15), 128.79 (C14). +ms, *m/z* = 384 (M+H$^+$). *Anal.* Calcd. for $C_{19}H_{17}N_3O_4S$ (M 383.42): C, 59.52; H, 4.47; N, 10.96. Found: C, 59.20; H, 4.24; N, 11.28.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (4b) White crystals, yield 79%, mp 198–200°C (from EtOH/H_2O 1:1). IR (cm^{-1}): 3097, 3040, 2985, 2935, 2865 (C–H); 1696 (C=O); 1604, 1576, 1522 (ring). ^{1}H-NMR: see Table 2. ^{13}C-NMR, δ (ppm): 156.66 (C1), 125.53 (C2), 129.03 (C3), 118.48 (C4), 128.85 (C5), 113.25 (C6), 56.21 (C7), 156.23 (C8), 112.69 (C9), 8.66 (C10), 57.62 (Ci), 31.18 (Ck), 171.21 (C=O), 134.80 (C11), 147.56 (C12), 124.47 (C13), 129.11 (C14), 134.16 (C15), 129.65 (C16). *Anal.* Calcd. for $C_{19}H_{16}N_4O_6S$ (M 428.42): C, 53.27; H, 3.76; N, 13.08. Found: C, 53.59; H, 3.48; N, 13.41.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (4c). White crystals, yield 90%, mp 203–204°C (from EtOH). IR (cm^{-1}): 3086, 2965, 2945, 2859 (C–H); 1692 (C=O); 1605, 1523 (ring). ^{1}H-NMR: see Table 2. ^{13}C-NMR, δ (ppm): 156.80 (C1), 125.83 (C2), 129.07 (C3), 118.50 (C4), 128.86 (C5), 113.36 (C6), 56.23 (C7), 156.15 (C8), 112.66 (C9), 8.67 (C10), 61.91 (Ci), 31.95 (Ck), 170.70 (C=O), 147.05 (C11), 128.77 (C12/C16), 123.66 (C13/C15), 147.45 (C14). +ms, *m/z* = 429 (M+H$^+$). *Anal.* Calcd. for $C_{19}H_{16}N_4O_6S$ (M 428.42): C, 53.27; H, 3.76; N, 13.08. Found: C, 53.60; H, 3.45; N, 13.38.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (4d). White crystals, yield 56%, mp 176°C (from EtOH). IR (cm^{-1}): 3067, 2989, 2931, 2850 (C–H); 1684 (C=O); 1606, 1564 (ring). ^{1}H-NMR: see Table 2. ^{13}C-NMR, δ (ppm): 156.85 (C1), 126.05 (C2), 129.02 (C3), 118.40 (C4), 128.94 (C5), 113.26 (C6), 56.19 (C7), 156.20 (C8), 112.67 (C9), 8.63 (C10), 62.37 (Ci), 32.12 (Ck), 170.60 (C=O), 133.25 (C11), 129.54 (C12/C16), 128.46 (C13/C15), 138.33 (C14). *Anal.* Calcd. for $C_{19}H_{16}N_3O_4ClS$ (M 417.85): C, 54.61; H, 3.86; N, 10.06. Found: C, 54.92; H, 3.59; N, 9.78.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenyl]-2-(3-methoxyphenyl)-1,3-thiazolidin-4-one (4e). White crystals, yield 74%, mp 178–179°C (from EtOH). IR (cm^{-1}): 3022, 2970, 2937, 2845 (C–H); 1692 (C=O); 1616, 1520, 1495 (ring). ^{1}H-NMR: see Table 2. ^{13}C-NMR, δ (ppm): 156.88 (C1), 126.28 (C2), 129.01 (C3), 118.33 (C4), 128.78 (C5), 113.22 (C6), 56.19 (C7), 156.22 (C8), 112.66 (C9), 8.61 (C10), 63.03 (Ci), 32.16 (Ck), 170.70 (C=O), 140.79 (C11), 112.79 (C12), 159.27 (C13), 114.36 (C14), 129.57 (C15), 119.63 (C16), 55.03 (C17). *Anal.* Calcd. for $C_{20}H_{19}N_3O_5S$ (M 413.43): C, 58.10; H, 4.63; N, 10.16. Found: C, 57.82; H, 4.39; N, 10.42.

2-Mercaptoacetamido-1-methoxy-4-(3-methylfuroxan-4-yl) benzene (4f). White crystals, yield 56%, mp 115–117°C (from EtOH/H_2O 1:1). IR (cm^{-1}): 3389, 3277 (NH); 3097, 2928, 2844 (C–H); 1672 (C=O); 1600, 1549 (ring). ^{1}H-NMR, δ(ppm), J (Hz): 8.50 (1H, d, $^4J_{HH}$ = 1.5, H3), 7.49 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 1.5, H5), 7.24 (1H, d, $^3J_{HH}$ = 8.5, H6), 3.91 (3H, s, H7), 2.28 (3H, s, H10), 3.89 (2H, s, Hk). ^{13}C-NMR, δ (ppm): 167.41 (C=O),151.12 (C1), 127.69 (C2), 119.83 (C3), 118.23 (C4), 123.84 (C5), 111.676 (C6), 56.08 (C7), 156.70 (C8), 112.75 (C9), 8.98 (C10), 66.32 (Ck). +ms, *m/z* = 296 (M+H$^+$). *Anal.* Calcd. for $C_{12}H_{13}N_3O_4S$ (M 295.31): C, 48.81; H, 4.44; N, 14.23. Found: C, 49.52; H, 4.19; N, 13.88.

The general procedure for the preparation of 1,3-thiazolidin-4-ones 5a–j. A solution of 1 mmol of the hydrazone (**3a-j**) and 2 mmol (0.15 mL) of mercaptoacetic acid in 25 mL dry toluene was fluxed using a Dean–Stark trap for 7–8 hours. The cooled mixture was treated with 10 mL of 0.1 M NaOH solution. The resulting precipitate was collected, washed with ethanol and recrystallized.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-phenyl-1,3-thiazolidin-4-one (5a). White crystals, yield 46%, mp 141°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3334 (NH); 3060; 2930; 2859 (C–H), 1691 (C=O), 1600, 1522 (ring). ^{1}H-NMR: see Table 3. *Anal.* Calcd. for $C_{19}H_{18}N_4O_4S$ (M 398.42): C, 55.27; H, 4.55; N, 14.06. Found: C, 54.94; H, 4.69; N, 14.37.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(2-methylphenyl)-1,3-thiazolidin-4-one (5b). White crystals, yield 80%, mp 168–170°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3295 (NH); 3060; 2960; 2931, 2853 (C–H), 1706 (C=O), 1596, 1530 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.53 (C1), 135.73 (C2), 110.06 (C3), 118.63 (C4), 119.39 (C5), 111.08 (C6), 55.65 (C7), 157.23 (C8), 112.91 (C9), 9.02 (C10), 58.62 (Ci), 28.78 (Ck), 169.61 (C=O), 136.84 (C11), 135.82 (C12), 130.42 (C13), 128.11 (C14), 126.27 (C15), 126.59 (C16), 18.48 (C17). *Anal.* Calcd. for $C_{20}H_{20}N_4O_4S$ (M 412.44): C, 58.24; H, 4.89; N, 13.58. Found: C, 58.51; H, 4.69; N, 13.27.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(4-methylphenyl)-1,3-thiazolidin-4-one (5c). White crystals, yield 56%, mp 170–171°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3326 (NH); 3060; 3015, 2923; 2858 (C–H), 1697 (C=O), 1600, 1594, 1520 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.34 (C1), 136.00 (C2), 109.77 (C3), 118.56 (C4), 119.21 (C5), 110.96 (C6), 55.61 (C7), 157.23 (C8), 112.89 (C9), 9.02 (C10), 61.98 (Ci), 29.11 (Ck), 169.44 (C=O), 138.09 (C11), 128.97 (C12/C16), 127.66 (C13/C15), 133.70 (C14), 20.66 (C17). *Anal.* Calcd. for $C_{20}H_{20}N_4O_4S$ (M 412.44): C, 58.24; H, 4.89; N, 13.58. Found: C, 57.94; H, 5.12; N, 13.79.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(2-chlorophenyl)-1,3-thiazolidin-4-one (5d). White crystals, yield 58%, mp 177°C (from DMF/H_2O 1:2). IR (cm^{--1}): 3311 (NH); 3070, 3040, 2931, 2852 (C–H), 1706 (C=O), 1602, 1528 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.68 (C1), 135.58 (C2), 109.88 (C3), 118.71 (C4), 119.68 (C5), 111.23 (C6), 55.67 (C7), 157.21 (C8), 112.95 (C9), 9.03 (C10), 58.65 (Ci), 28.55 (Ck), 169.53 (C=O), 136.66 (C11), 131.89 (C12), 129.58 (C13), 129.96 (C14), 127.70 (C15), 128.22 (C16). *Anal.* Calcd. for $C_{19}H_{17}N_4O_4ClS$ (M 432.86): C, 52.72; H, 3.96; N, 12.94. Found: C, 53.01; H, 4.24; N, 12.65.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (5e). White crystals, yield 62%, mp 173–174°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3335 (NH); 3095; 3060, 2932; 2862 (C–H), 1699 (C=O), 1595, 1535 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.44 (C1), 135.90 (C2), 109.74 (C3), 118.60 (C4), 119.38 (C5), 111.06 (C6), 55.68 (C7), 157.23 (C8), 112.93 (C9), 9.04 (C10), 61.26 (Ci), 29.01 (Ck), 169.27 (C=O), 138.38 (C11), 128.45 (C12/C16), 129.64 (C13/C15), 133.20 (C14). *Anal.* Calcd. for $C_{19}H_{17}N_4O_4ClS$ (M 432.86): C, 52.72; H, 3.96; N, 12.94. Found: C, 52.41; H, 4.21; N, 13.25.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(4-fluophenyl)-1,3-thiazolidin-4-one (5f). White crystals, yield 71%, mp 165°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3326 (NH); 3086; 3022, 2979; 2859 (C–H), 1686 (C=O), 1602, 1540, 1511 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.40 (C1), 135.96 (C2), 109.76 (C3), 118.58 (C4), 119.32 (C5), 111.02 (C6), 55.66 (C7), 157.23 (C8), 112.92 (C9), 9.04 (C10), 61.34 (Ci), 29.05 (Ck), 169.28 (C=O), 135.37 (C11), 129.98 ($^3J_{FC}$ = 9 Hz, C12/C16), 115.26 ($^2J_{FC}$ = 22 Hz, C13/C15), 162.00 ($^1J_{FC}$ = 230 Hz, C14). *Anal.* Calcd. for $C_{19}H_{17}N_4O_4FS$ (M 416.41): C, 54.80; H, 4.12; N, 13.46. Found: C, 55.09; H, 4.22; N, 13.12.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(3-methoxyphenyl)-1,3-thiazolidin-4-one (5g). White crystals, yield 71%, mp 165°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3302 (NH); 3080, 3020, 2960, 2931, 2853 (C–H), 1706 (C=O), 1598, 1525 (ring). ^{1}H-NMR: see Table 3. *Anal.* Calcd. for $C_{20}H_{20}N_4O_5S$ (M 428.44): C, 56.06; H, 4.71; N, 13.08. Found: C, 56.34; H, 4.39; N, 13.34.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (5h). White crystals, yield 82%, mp 190–191°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3314 (NH); 3090; 3012, 2972; 2845 (C–H), 1703 (C=O), 1591, 1520 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.86 (C1), 136.61 (C2), 110.32 (C3), 119.09 (C4), 119.73 (C5), 111.48 (C6), 56.18 (C7), 157.78 (C8), 113.44 (C9), 9.56 (C10), 62.44 (Ci), 29.70 (Ck), 169.92 (C=O), 131.13 (C11), 129.81 (C12/C16), 114.32 (C13/C15), 160.08 (C14). *Anal.* Calcd. for $C_{20}H_{20}N_4O_5S$ (M 428.44): C, 56.06; H, 4.71; N, 13.08. Found: C, 55.78; H, 4.45; N, 13.40.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(4-hydroxy-3-methoxyphenyl)-1,3-thiazolidin-4-one (5i). White crystals, yield 90%, mp 212°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3440 (OH), 3256 (NH); 3064; 3020, 2960; 2852 (C–H), 1689 (C=O), 1601, 1513 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.28 (C1), 136.15 (C2), 110.88 (C3), 118.50 (C4), 119.06 (C5), 111.38 (C6), 56.62 (C7), 157.18 (C8), 112.86 (C9), 9.00 (C10), 62.50 (Ci), 29.19 (Ck), 169.00 (C=O), 132.90 (C11), 114.84 (C12), 147.54 (C13), 147.09 (C14), 109.68 (C15), 120.77 (C16). *Anal.* Calcd. for $C_{20}H_{20}N_4O_6S$ (M 444.44): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.32; H, 4.25; N, 12.33.

3-[2-Methoxy-5-(3-methylfuroxan-4-yl)phenylamino]-2-(thien-2-yl)-1,3-thiazolidin-4-one (5j). White crystals, yield 55%, mp 168°C (from DMF/H_2O 1:2). IR (cm^{-1}): 3316 (NH); 3081; 3010, 2914; 2853 (C–H), 1691 (C=O), 1600, 1532 (ring). ^{1}H-NMR: see Table 3. ^{13}C-NMR, δ (ppm): 148.32 (C1), 136.21 (C2), 109.89 (C3), 118.49 (C4), 119.25 (C5), 110.95 (C6), 55.73 (C7), 157.10 (C8), 112.78 (C9), 9.06 (C10), 57.97 (Ci), 29.34 (Ck), 169.14 (C=O), 142.40 (C12), 127.71 (C13), 126.78 (C14), 128.38 (C15). *Anal.* Calcd. for $C_{17}H_{16}N_4O_4S_2$ (M 404.45): C, 50.48; H, 3.99; N, 13.85. Found: C, 50.22; H, 4.14; N, 14.13.

The general procedure for the preparation of indoles 6a–c. To a stirring solution of 5 mL polyphosphoric acid at 120°C 1 mmol of an appropriated hydrazone (3 **k**–**m**) was slowly added and stirred for 2 h. The reaction mixture was allowed to cool to room temperature, and was poured into 40 mL ice-water and then was neutralized with 1 *M* NaOH solution. The resulting precipitate was collected and recrystallized from ethanol/dioxin 4:1 by volume.

7-Methoxy-4-(3-methylfuroxan-4-yl)-2-phenylindole (6a). Dark brown crystals, yield 57%, mp 164–164°C. IR (cm^{-1}): 3325 (NH); 3074; 3000; 2938, 2852 (C–H), 1598, 1573, 1539 (ring). ^{1}H-NMR: see Table 4. ^{13}C-NMR, δ (ppm): 148.75 (C1), 127.83 (C2), 128.24 (C3), 110.62 (C4), 122.51 (C5), 102.84 (C6), 56.06 (C7), 157.70 (C8), 113.64 (C9), 10.00 (C10), 139.94 (Ci), 100.04 (Ck), 132.10 (C11), 126.26 (C12/C16), 129.27 (C13/C15), 128.31 (C14). -MS, *m/z* = 320 ($M-H^+$). *Anal.* Calcd. for $C_{18}H_{15}N_3O_3$ (M 321.33): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.54; H, 4.56; N, 12.86.

7-Methoxy-4-(3-methylfuroxan-4-yl)-2-(4-methylphenyl)indole (6b). Dark brown crystals, yield 62%, mp 186–187°C. IR (cm^{-1}): 3379 (NH); 3070, 3015, 2979, 2852 (C–H), 1601, 1569 (ring). ^{1}H-NMR: see Table 4. ^{13}C-NMR, δ (ppm): 148.13 (C1), 127.11 (C2), 127.80 (C3), 109.95 (C4), 121.84 (C5), 102.13 (C6), 55.48 (C7), 157.16 (C8), 113.03 (C9), 9.43 (C10), 139.58 (Ci), 98.92 (Ck), 128.81 (C11), 125.65 (C12/C16), 129.26 (C13/C15), 137.18 (C14). -MS, *m/z* = 334 ($M-H^+$). *Anal.* Calcd. for $C_{19}H_{17}N_3O_3$ (M 335.34): C, 68.05; H, 5.11; N, 12.53. Found: C, 67.84; H, 5.28; N, 12.81.

7-Methoxy-4-(3-methylfuroxan-4-yl)-2-(4-hydroxyphenyl) indole (6c) Dark brown crystals, yield 46%, mp 192°C. IR (cm^{-1}): 3345 (NH); 3250 (OH); 3060, 3020, 2939, 2830 (C–H), 1595, 1571

(ring). ^{1}H-NMR: see Table 4. ^{13}C-NMR, δ (ppm): 148.02 (C1), 126.87 (C2), 128.07 (C3), 109.69 (C4), 121.69 (C5), 101.83 (C6), 55.47 (C7), 157.25 (C8), 113.04 (C9), 9.47 (C10), 140.15 (Ci), 97.76 (Ck), 122.69 (C11), 127.28 (C12/C16), 115.52 (C13/C15), 157.43 (C14). +ms, *m/z* = 338 ($M+H^+$). *Anal.* Calcd. for $C_{18}H_{15}N_3O_4$ (M 337.31): C, 64.09; H, 4.48; N, 12.46. Found: C, 64.34; H, 4.27; N, 12.73.

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REFERENCES AND NOTES

[1] Minakshi, D.; Krishna A. D.; Parimal, S.; Banerjee, A. B. Phytother Res 2002, 16, 94.

[2] Fujita, K.; Fujita, T.; Kubo, I. Phytother Res 2007, 21, 47.

[3] Mansuy, D.; Sassi, A.; Dansette, P. M.; Plat, M. Biochem Biophys Res Commun 1986, 135, 1015.

[4] Waumans, D.; Bruneel, N.; Tytgat, J. Forensic Sci Int 2003, 133, 159.

[5] Nguyen, H. D.; Ngo T. L.; Trinh, T. H. J Chem 2005, 43, 128.

[6] Solomon, V. R.; Haq, W.; Srivastava, K.; Puri, S. K.; Katti, S. B. J Med Chem 2007, 50, 394.

[7] Kavitha, C. V.; Basappa, B.; Swamy, S. N.; Mantelingu, K.; Doreswamy, S.; Sridhar, M. A.; Prasad, J. S.; Rangappa, K. S. Bioorg Med Chem 2006, 14, 2290.

[8] Tejaskumar, J. S.; Vikas, A. D. Arkivoc 2007, 14, 218.

[9] Kumar, A.; Sharma, S.; Archana, A.; Bajaj, K.; Sharma, S.; Panwar, H.; Singh, T.; Srivastava, V. K. Bioorg Med Chem 2003, 11, 5293.

[10] Sharma, S.; Singh, T.; Mittal, R.; Saxena, K. K.; Srivastava, V. K.; Kumar, A. Arch Pharm Chem Life Sci 2006, 339, 145.

[11] Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. Eur J Med Chem 2008, 43, 2800.

[12] Ravichandran, V.; Prashantha Kumar, B. R.; Sankar, S.; Agrawal, R. K. Eur J Med Chem 2009, 44, 1180.

[13] Sharma, V.; Kumar, P.Pathak, D. J Heterocycl Chem,2010, 47, 491.

[14] Regina, G. L.; Silvestri, R.; Gatti, V.; Lavecchia, A.; Novellino, E.; Befani, O.; Turini, P.; Agostinelli, E. Bioorg Med Chem 2008, 16, 9729.

[15] Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wan, Z.; Cai, T.; Janczuk, A. J Chem Rev 2002, 102, 1109.

[16] Freduzzi, S.; Mariucci, G.; Tantucci, M.; del Soldato, P.; Ambrosini, M. V. Neurosci Lett 2001, 302, 121.

[17] Tallet, D.; del Soldato, P.; Oudart, N.; Burgaud, J. L. Biochem Biophys Res Commun 2002, 290, 125.

[18] Fiorucci, S.; Antonelli, E.; Morelli, O.; Mencarelli, A.; Casini, A.; Mello, T.; Palazzetti, B.; Tallet, D.; del Soldato, P.; Morelli, A. Proc Natl Acad Sci USA 2001, 98, 8897.

[19] Cunico, W.; Gomes, C. R. B.; Vellasco, W. T. J Mini-Rev Org Chem 2008, 5, 336.

[20] Gasco, A. Adv Heterocycl Chem 1981, 29, 251.

[21] Gasco, A; Mortarini, G. R.; Menziani, E. J Heterocycl Chem 1972, 9, 837.

[22] Hadacek, F.; Greger, H. Phytochem Anal 2000, 90, 137.

[23] Nguyen, H. D.; Ngo, T. L.; Le, T. T. V. J Heterocycl Chem 2004, 41, 1015.