

# Microwave-assisted Synthesis of Some N-alkylisatin- $\beta$ -thiocarbohydrazones

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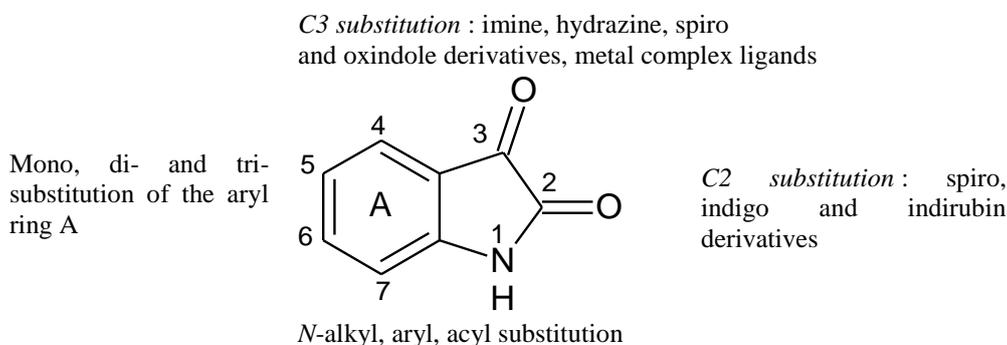
**Abstract**— The effectiveness of microwave-assisted preparation of N-alkylisatin- $\beta$ -thiocarbohydrazones, where alkyl group is methyl and ethyl, was evaluated. The corresponding N-alkylisatin- $\beta$ -thiocarbohydrazones were predominantly obtained by TCH and N-alkyl substituted isatin in molar ratio 3:1. Reactions of carbonyl-amine condensation were performed in water acidified to pH 1.5 as a solvent system. Reaction mixtures were exposed to microwave irradiation under 300W and pressure 200 psi, for a specified incubation period of 5-15 min. The yield of products obtained by microwave assisted reaction was similar to that had been obtained using conventional reflux method (about 70% to 80%), with reduction of time. The structures of synthesized N-alkylisatins and corresponding N-alkylisatin- $\beta$ -thiocarbohydrazones were established on the basis of recorded spectral data from IR, GC-MS, <sup>1</sup>H NMR and <sup>13</sup>C NMR.

**Keywords**— Microwave-assisted organic synthesis (MAOS), N-alkylisatin, N-alkylisatin- $\beta$ -thiocarbohydrazone.

## I. INTRODUCTION

Discovery of small molecules (MW < 1500 Da) play an essential role in medicinal chemistry. Some of these organic compounds derived from natural products and are endogenous, such as isatin (indoline-2,3-dione) identified in human, mammals and plants [1, 2]. Isatin was discovered by Erdmann and Laurent in 1840 as an oxidation product of indigo, and numerous of its derivatives have been synthetically obtained and characterized so far [3, 4].

Isatins are a group of organic compounds containing the heterocyclic indole nucleus, where the aryl ring (A) is mono, di-, or tri-substituted, as can be seen on Fig.1. Some of isatin analogues have been obtained by derivatization of the indole nitrogen and/or carbonyl moieties: lactam and keto group on C2 and C3, respectively.



**FIGURE 1. The various substitution types and patterns possible for the isatin scaffold**

The literature reports information about the chemistry of isatin and its derivatives, their physicochemical properties [5] and biological activities [6, 7]. Isatin, at first was detected as monoamine oxidase (MAO) and identified as tribulin, but also possess anticonvulsant, sedative and anxiogenic properties [8]. Its derivatives exhibit a wide spectrum of pharmacological actions such as antiviral, antibacterial, antifungal, anticonvulsant, and anti-inflammatory, analgesic, anticancer, anti-HIV, herbicidal, hypotensive and enzymatic inhibition [9-12]. Therefore, synthesis and investigation of novel isatin derivatives is an active area of research and has the potential for the development of pharmacologically active molecules.

Antimicrobial activity studies revealed that the presence of strong electron-donating thiocarbohydrazone group enhances biological activity in respect to the parent molecule and is consistent to proposed pharmacophoric requirements in the molecules [6, 13]. This observation encouraged us to study the reaction of some substituted isatin heterocycles with thiocarbohydrazide and synthesized new derivatives with potential biological activity.

Recently, there has been a dramatic upsurge in the use of microwave heating within the pharmaceutical industry to facilitate the chemical synthesis of new chemical entities, and some N-alkylisatin derivatives have been obtained [14, 15]. Microwave-

assisted organic synthesis (MAOS) has been shown to be an invaluable tool for medicinal chemistry and drug discovery applications since it often dramatically reduces reaction times, minimizes secondary reactions and improves yield. These advantages of microwave-assisted chemistry over conventional approaches motivated us to evaluate this approach for synthesis of thiocarbohydrazones of *N*-methyl and *N*-ethylisatins, where the incorporated alkyl groups are increasing the lipophilicity of the molecules.

## II. EXPERIMENTAL

### 2.1 General

Microwave-assisted reactions were carried out on CEM, MARS X 300W.ATR-FTIR Perkin-Elmer 2000 was used for recording IR spectra, directly from the solid samples. The mass spectra were recorded on GC-MS Shimadzu, DI-EI (70 eV). NMR spectra were recorded on Bruker-250 NMR Spectrometer determined in DMSO- $d_6$  as solvent and using tetramethylsilane as internal standard. Melting points were determined using Koffler apparatus and were uncorrected.

All chemicals used for synthesis and purification were of p.a. grade (Merck). Commercial isatin was recrystallized twice from ethanol. Preparative flash chromatography was performed using Merck silica gel 60 (230–400 mesh) and thin layer chromatography (TLC) was carried out on aluminum sheets with silica gel with fluorescent indicator (254 nm), obtained from Sigma-Aldrich. Spots were visualized using either UV-lamp at 254 nm or iodine.

### 2.2 Preparation Procedures

#### 2.2.1 General synthesis of *N*-alkylisatins (1)

Isatin (1.0 mmol) was dissolved in DMF (5 ml), and  $K_2CO_3$  (1.3 mmol) was added. The mixture was stirred under room temperature until isatin anion was obtained and hydrogen was removed. Alkyl halide ( $CH_3I$  or  $C_2H_5I$ , respectively) (4.0 mmol) was added to the reaction mixture. The reaction under reflux on 70 °C was completed after 1.5-2 hour, while the reaction time for the same reaction under microwave irradiation was 15 minutes, at 300 W and pressure 200 psi. Then the reaction mixtures were cooled overnight and the precipitates were formed in ice water. Further it was purified by recrystallization by ethanol or column chromatography (silica gel, petroleum ether / ethyl acetate = 20:1).

*N*-methylisatin (**1a**), melting point 133-134 °C (lit 130-134 [90]), yield 82 %

IR:  $cm^{-1}$   $\nu$ (CH aromatic) 3061,  $\nu$ (CH aliphatic) 2923,  $\nu$ (C=O) 1717,  $\nu$ (C=O, lactam) 1603

GS-MS: molecular ion  $m/z$  = 161, base peak at  $m/z$  = 104, fragments at  $m/z$  146, 133 and 78.

$^1H$ -NMR (600 MHz, DMSO- $d_6$ ):  $\delta$ /ppm 7.12 – 7.67 (m, 4H, Ar-H), 3.12 (s, 3 H,  $CH_3$ ).

$^{13}C$ -NMR (150,90 MHz, DMSO- $d_6$ ):  $\delta$ /ppm 183.47 (C=O, lactam), 158.63 (C=O), 110.57 ( $C_{Ar}$ ), 117.37 ( $C_{Ar}$ ) 123.21 ( $C_{Ar}$ ), 124.25 ( $C_{Ar}$ ), 138.19 ( $C_{Ar}$ ), 151.37 ( $C_{Ar}$ ), 26.02 ( $CH_3$ )

*N*-ethylisatin (**1b**), melting point 95-96 °C (lit 96) 90, yield 79 %

IR:  $cm^{-1}$   $\nu$ (CH aromatic) 3061,  $\nu$ (CH aliphatic) 2989,  $\nu$ (C=O) 1723,  $\nu$ (C=O, lactam) 1607

GS-MS: molecular ion  $m/z$  = 175, base peak at  $m/z$  = 104, fragments at  $m/z$  161, 147, 132 and 78.

$^1H$ -NMR (600 MHz, DMSO- $d_6$ ):  $\delta$ /ppm 7.10 - 7.66 (m, 4H, Ar-H), 3.70 (q, 2H,  $CH_2$ ), 1.79 (t, 3H,  $CH_3$ )

$^{13}C$ -NMR (150,90 MHz, DMSO- $d_6$ ):  $\delta$ /ppm 183.66 (C=O, lactam), 157.76 (C=O), 110.62 ( $C_{Ar}$ ), 117.50 ( $C_{Ar}$ ) 123.10 ( $C_{Ar}$ ), 124.51 ( $C_{Ar}$ ), 138.21 ( $C_{Ar}$ ), 150.39 ( $C_{Ar}$ ), 34.3 ( $CH_2$ ), 12.39 ( $CH_3$ ).

#### 2.2.2 General synthesis of *N*-alkylisatin- $\beta$ -thiocarbohydrazones (2)

*N*-alkyl substituted isatin (1.0 mmol) and thiocarbohydrazide (3.0mmol) were dissolved in 5 ml hot water acidified with HCl to pH 1.5. The mixture was refluxed for an one hour with constant stirring, while the reaction under microwave irradiation at 300 W and pressure 200 psi was completed for 10 minutes. The obtained precipitates were collected by vacuum filtration, washed with hot water and air dried. The obtained solid products were recrystallized by ethanol.

*N*-methylisatin- $\beta$ -thiocarbohydrazone (**2a**), melting point 205-207 °C, yield 83 %

IR:  $cm^{-1}$   $\nu$ (NH) 3207,  $\nu$ (CH aromatic) 3051,  $\nu$ (CH aliphatic) 2987,  $\nu$ (C=N) 1677,  $\nu$ (C=O, lactam) 1613

GS-MS: molecular ion  $m/z$  = 249, base peak at  $m/z$  = 75, fragments at  $m/z$  221, 175, 159, 146, 131, 104 and 91.

$^1\text{H-NMR}$  (600 MHz, DMSO-*d*<sub>6</sub>):  $\delta$ /ppm 12.36 (s, 1H, NH, C=NNH(CS)N-H), 9.99 (s, 1H, NH, C=NN-H), 5.12 (s, 2H, C=NNH(CS)NH-NH<sub>2</sub>), 7.09 - 7.69 (m, 4H, Ar-H), 3.20 (s, 3H, CH<sub>3</sub>)

$^{13}\text{C-NMR}$  (150,90 MHz, DMSO-*d*<sub>6</sub>):  $\delta$ /ppm 180.11 (C=S), 174.33 (C=O, lactam), 160.74 (C=N), 109.70 (C<sub>Ar</sub>), 119.34(C<sub>Ar</sub>), 122.81 (C<sub>Ar</sub>), 130.82 (C<sub>Ar</sub>), 134.71 (C<sub>Ar</sub>), 143.23 (C<sub>Ar</sub>), 25.63 (CH<sub>3</sub>)

*N*-ethylisatin- $\beta$ -thiocarbohydrazone (**2b**), melting point 190-191°C, yield 80 %

IR:  $\text{cm}^{-1}$   $\nu$ (NH) 3213,  $\nu$ (CH aromatic) 3052,  $\nu$ (CH aliphatic) 2977,  $\nu$ (C=N) 1668,  $\nu$ (C=O, lactam) 1611

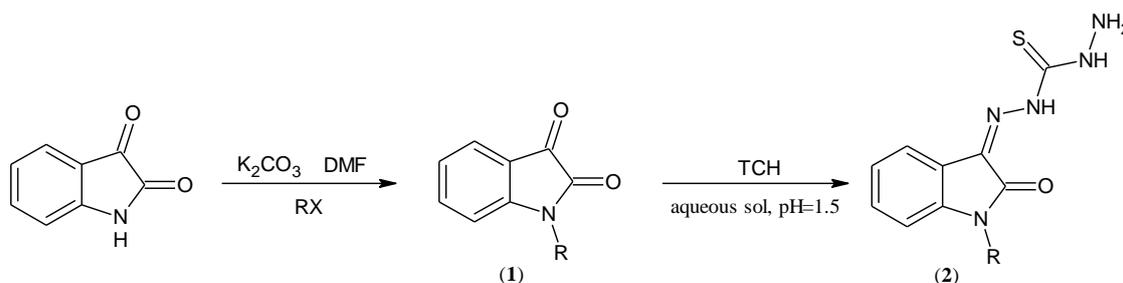
GS-MS: molecular ion  $m/z$  = 263, base peak at  $m/z$  = 146, fragments at  $m/z$  221, 175, 159, 146, 131, 104 and 91.

$^1\text{H-NMR}$  (600 MHz, DMSO-*d*<sub>6</sub>): 12.39 (s, 1H, NH, C=NNH(CS)N-H), 9.99 (s, 1H, NH, C=NN-H), 5.20 (s, 2H, C=NNH(CS)NH-NH<sub>2</sub>), 7.12 - 7.72 (m, 4H, Ar-H), 3.78 (q, 2H, CH<sub>2</sub>), 1.11 (t, 3H, CH<sub>3</sub>)

$^{13}\text{C-NMR}$  (150,90 MHz, DMSO-*d*<sub>6</sub>):  $\delta$ /ppm 180.10 (C=S), 174.26 (C=O, lactam), 160.39 (C=N), 109.76 (C<sub>Ar</sub>), 119.52 (C<sub>Ar</sub>), 122.74 (C<sub>Ar</sub>), 130.87 (C<sub>Ar</sub>), 134.75 (C<sub>Ar</sub>), 142.23 (C<sub>Ar</sub>), 33.96 (CH<sub>2</sub>), 12.63 (CH<sub>3</sub>)

### III. RESULTS AND DISCUSSION

To develop more effective small molecules with potential biological activity, the title compounds were synthesized by two step reaction as shown in Scheme 1. The first step involved *N*-substitution of isatin to obtain the corresponding *N*-alkyl derivatives. Afterward, in the carbonyl-amine condensation of the *N*-alkyl substituted isatin with TCH, *N*-alkylisatin- $\beta$ -thiocarbohydrazones were obtained. Microwave synthesis and traditional conductive heating methods were used in both reactions.



**SCHEME 1.** Synthesis of *N*-alkylisatin- $\beta$ -thiocarbohydrazones (**2**) from corresponding *N*-alkylisatins (**1**) (RX is: CH<sub>3</sub>I or C<sub>2</sub>H<sub>5</sub>I)

A variety of methods have been demonstrated for the *N*-alkylation of isatins [16]. *N*-alkyl derivatives of isatin are commonly synthesized from the reaction of the sodium salt of isatin with alkyl halides or sulphates. Some of the more general methods include the use of NaH, either in toluene under reflux or DMF (25-80 °C) or THF (-20 °C to room temperature), as well as CaH<sub>2</sub>, (40-50 °C). Other methods involve the use of potassium carbonate in DMF or in acetone. An alternative method for preparing *N*-alkylisatins consists of the reaction between isatin and alkyl halides in benzene - chloroform / 50% aq. KOH biphasic system; utilize tetrabutyl-ammonium hydrogensulfate as the phase transfer catalyst.

In this work, the reaction of *N*-alkylation of isatin was carried out in the catalytic presence of K<sub>2</sub>CO<sub>3</sub>, using DMF as solvent. In this reaction of substitution, the isatin anion is the nucleophilic reactant to the alkyl halide. Higher solvent polarity that exhibits DMF can promote the proton-transfer equilibrium and leads to the higher yields. The typical yields of obtained products after recrystallizations from ethanol, using either microwave assisted synthesis or conventional heating methods are presented in Table 1.

**TABLE 1**  
**COMPARISON BETWEEN REACTION TIME AND YIELD OF OBTAINED ISATIN DERIVATIVES BY MICROWAVE SYNTHESIS AND CONVENTIONAL HEATING**

Compound	Reagents		Catalyst	Solvent	Microwave synthesis		Conventional heating	
					Reaction time	Yield	Reaction time	Yield
<b>1a</b>	Isatin	CH <sub>3</sub> I	K <sub>2</sub> CO <sub>3</sub>	DMF	15 min	82 %	1.5 h	75 %
<b>1b</b>	Isatin	C <sub>2</sub> H <sub>5</sub> I	K <sub>2</sub> CO <sub>3</sub>	DMF	15 min	79 %	2 h	68 %
<b>2a</b>	<b>1a</b>	TCH	HCl	H <sub>2</sub> O	10 min	83 %	1 h	74 %
<b>2b</b>	<b>1b</b>	TCH	HCl	H <sub>2</sub> O	10 min	80 %	1 h	70 %

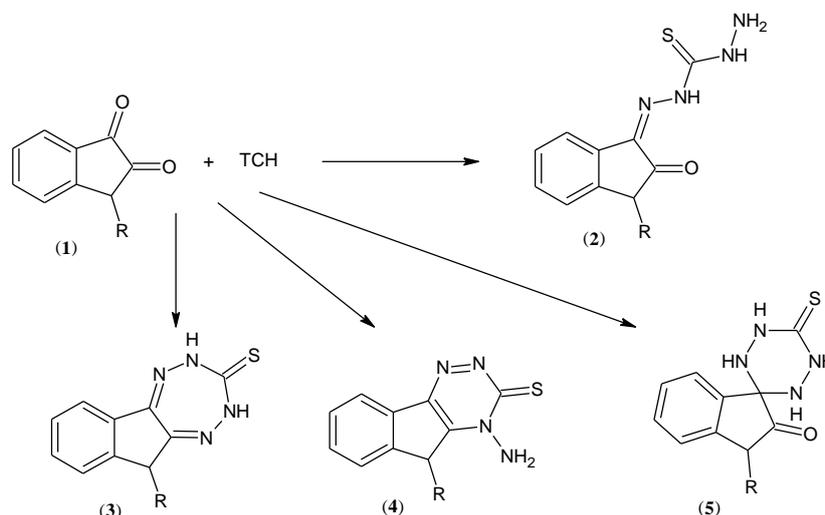
The structures of *N*-methylisatin (**1a**) and *N*-ethylisatin (**1b**) were confirmed using ATR-FTIR, GC-MS, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR. In the IR spectra of synthesized *N*-alkylisatins, the band at around 2900 cm<sup>-1</sup> can be attributed with great certainty to  $\nu(\text{CH aliphatic})$ . The most prominent bands are the ones due to the carbonyl stretching  $\nu(\text{C=O})$  of keto and lactam group at 1720 cm<sup>-1</sup> and 1605 cm<sup>-1</sup>, respectively. The method of direct sample injection into to ion source, without using gas chromatograph, was used. The mass spectra obtained by electron ionization mode demonstrated molecular ions at  $m/z$  161 (**1a**) and 175 (**1b**), that represents molecular ion radicals with formula C<sub>9</sub>H<sub>7</sub>NO<sub>2</sub> and C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub>, respectively. The base peaks were observed at  $m/z$  104 for both compounds and they due to a loss of an alkyl group and NCO fragment, which occurs in amides and lactams.

The <sup>1</sup>H-NMR spectra of (**1a**) and (**1b**) displayed characteristic multiplet at  $\delta$ 7.1 to 7.7 due to aromatic protons. The singlet at 3.12 ppm (**1a**) is attributed to protons from *N*-methyl group, while quadruplet at  $\delta$ 3.70 and triplet at  $\delta$  1.79 (**1b**) are from *N*-ethyl group CH<sub>2</sub> and CH<sub>3</sub> protons, respectively.

The <sup>13</sup>C-NMR spectrum of (**1a**) exhibits 9 signals, while (**1b**) 10 signals. Six signals belong to the aromatic carbons ( $\delta$  110 to 152 ppm). There are two more signals in <sup>13</sup>C-NMR spectra from carbons of two chemically distinct carbonyl groups, lactam and keto, at 183 and 158 ppm, respectively. The presence of *N*-methyl and *N*-ethyl group in <sup>13</sup>C-NMR spectra is confirmed by corresponding signals at 26 ppm (**1a**), and at  $\delta$  34 and 12 ppm (**1b**).

In addition, we investigated the carbonyl-aminereaction of the *N*-alkyl isatin derivatives (**1a** and **1b**) with TCH. Thiocarbohydrazone condenses easily with two molecules of carbonyl compounds on the terminated hydrazineamino groups to produce the centrosymmetric dimer. Here in, we report the optimal conditions for synthesis of monothioarbohydrazones, which may react with another carbonyl compound and gave new Schiff base.

In order to improve the yield of *N*-alkylisatin- $\beta$ -thiocarbohydrazones (**2**), the effect of molar ratio of reactants and electing of solvent system were investigated. It was found that the condensation of isatin derivative (**1**) with excess of TCH (molar ratio of TCH and *N*-alkylisatin was 3:1) in water as solvent, acidified with HCl to pH 1.5, yield thiocarbohydrazone (**2**), rather than tetrazepine (**3**), triazine (**4**) or spiro system (**5**). Structures (**3**) and (**4**) were excluded based on appearing the lactam C=O, band in the IR spectra (1611 cm<sup>-1</sup>). In ethanol with catalytic amount of acetic acid either in acetonitrile as solvents, nucleophilic addition at position C3 was followed by a spiro-annulation. The presence of this product (**5**) in a reaction mixture was confirmed by <sup>13</sup>C-NMR, since the chemical shift at 63.11 ppm is a result of sp<sup>3</sup> hybridized carbon in isatin moiety.



**FIGURE 2. Possible isatin derivatives from the reaction of *N*-alkylisatin (**1**) with TCH under microwave irradiation**

Structures of synthesized isatin derivatives (**2**) were determined by spectroscopic methods. Complex bands dominate in the 3500-2800 cm<sup>-1</sup> spectral region of synthesized *N*-alkyl- $\beta$ -thiocarbohydrazones. The band around 3207 cm<sup>-1</sup> can be attributed with great certainty to  $\nu(\text{NH})$ . The absence of carbonyl (C=O) peak at around 1750 cm<sup>-1</sup> characteristic for the keto group on C3 in (**1**) could explain the formation of a thiocarbohydrazone derivative of isatin. The obtained DI-EI mass spectra of synthesized thiocarbohydrazones demonstrated molecular ions at  $m/z$  249 (**2a**) and  $m/z$  263 (**2b**), which represent molecular formulas C<sub>10</sub>H<sub>11</sub>N<sub>5</sub>OS and C<sub>11</sub>H<sub>13</sub>N<sub>5</sub>OS, correspondingly. The base peak in MS of **2a** was observed at  $m/z$  75 and arrived from the -CSNHNH<sub>2</sub> thiocarbohydrazone part of molecule, while the base peak of **2b** at  $m/z$  146 resulted from cleavage of the

-CSNHNH<sub>2</sub> and loss of ethyl group with NCO fragment, characteristic for lactams. The further fragmentation involve the sequential loss of a same parts of isatin- $\beta$ -thiocarbohydrazone structure.

The <sup>1</sup>H-NMR spectra of (2) displayed three separate singlets at 12.36, 9.99 and 5.15 ppm, which according of the chemical shifts and signal intensities can be attributed to protons from thiocarbohydrazyde moiety C=NNH(CS)N-H, C=NN-H and C=NNH(CS)NH-NH<sub>2</sub>, respectively. The other peaks are the same as the corresponding *N*-alkylisatin (1).

The <sup>13</sup>C-NMR spectrum of 2a exhibit 10 signals, while in spectrum of 2b there are 11 signals, respectively. Of these signals, 6 belong to the aromatic carbons, (chemical shift at 109 to 143 ppm). The C2 and C3 atoms from isatin moiety and the C atom as a part of thiocarbohydrazyde were assigned on the basis of their chemical shifts at 174 ppm (C=O, lactam), 160 ppm (C=N) and 180 ppm (C=S). Other signals in the spectra belong to carbons from alkyl groups.

#### IV. CONCLUSION

*N*-alkylisatins (1) and *N*-alkylisatin- $\beta$ -thiocarbohydrazones (2), where alkyl group is methyl or ethyl, have been prepared by two-step reaction pathway including (i) nucleophilic substitution of alkyl halide with isatin anion and (ii) subsequent carbonyl-amine condensation of *N*-alkylisatin with TCH. Reactions were performed using conventional heating technique and microwave-assisted synthesis. *N*-alkylisatins (1) and title compounds (2) were obtained by microwave irradiation for 10 to 15 minutes, so one of the advantages over conventional heating is reducing the reaction time. Investigation of the effect of the mole ratio of reactants and elected solvent indicated that the monothiocarbohydrazone derivatives of isatin were predominantly obtained in acidic media in water as solvent and triple molar excess of TCH. In ethanol and acetonitrile solutions, spiro compounds were detected. Synthesized compounds were characterized using GC-MS, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR. *N*-ethylisatin- $\beta$ -thiocarbohydrazone has cytostatic activity towards malignant melanoma cells.

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