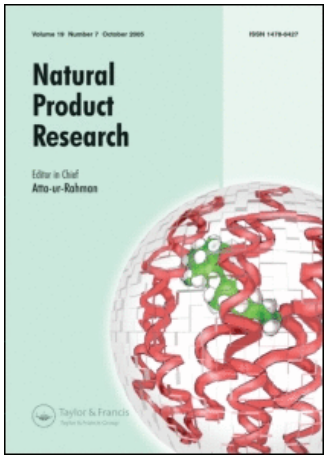

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Synthesis of some N^4-substituted isatin-3-thiosemicarbazones

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Synthesis of some N^4-substituted isatin-3-thiosemicarbazones

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In this article, we describe a simple and new method for the synthesis of some N^4-substituted isatin-3-thiosemicarbazones based on the reactions of the common intermediate, methyl 2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbodithioate, prepared by condensing isatin with methyl 1-hydrazinecarbodithioate, and the readily available amines in essentially a one-step reaction. The synthesized thiosemicarbazones were fully characterized by their physical, analytical, and spectral (IR, ^{1}H-NMR, EIMS) data.

Keywords: Thiosemicarbazones; Isatin; Isatin-3-thiosemicarbazones

1. Introduction

Thiosemicarbazones are a class of compounds which has been found to display numerous biological activities [1]. Isatins-derived thiosemicarbazones have also been found to show a variety of physiological properties [2,3]. Due to the significant pharmacological effects of isatins-thiosemicarbazones, there is still an increasing interest in synthesizing and biotesting such compounds [4–8]. Conventionally, thiosemicarbazones have been synthesized by refluxing mixture of the thiosemicarbazide and the carbonyl compound in an organic solvent, for example, ethanol [9] or methanol [10], but variations are known, such as refluxing the same mixture in 50% aqueous ethanol [11], or aqueous ethanol [12], ethanol [13] and methanol [14] containing a few drops of acetic acid, or azeotroping the mixture with dry benzene in a Dean–Stark apparatus [15]. In addition, certain 3-(*p*-substituted) phenylthiosemicarbazono-2-indolinones have been synthesized by refluxing mixtures of *p*-substituted phenylthiosemicarbazides and 3-arylimino-2-indolinones in ethanol [16]. Klayman *et al*. [17] reported the synthesis of certain potential antimalarial

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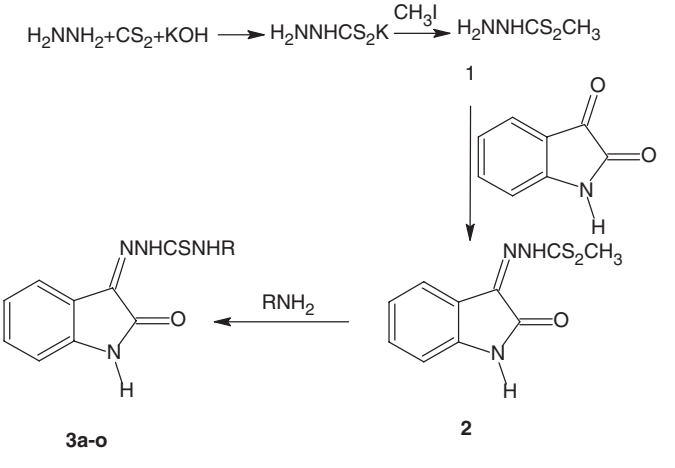
2-acetylpyridine thiosemicarbazones by a method consisting of the condensation of 2-acetylpyridine with methyl 1-hydrazinecarbodithioate to form methyl 2-[1-(2-Pyridinyl)ethylidene]-1-hydrazinecarbodithioate, the *S*-methyl group of which, upon displacement by an amine, formed the desired thiosemicarbazones. In view of the simplicity of this method and in continuation of our work [18–22] in search of medicinally important organic and metallo-organic compounds, we thought of interest to synthesize some title thiosemicarbazones according to this method. The present work, therefore, deals with the synthesis of a series of 15 N^4-substituted isatin-3-thiosemicarbazones based on the reactions of the common intermediate, methyl 2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbodithioate (prepared by condensing isatin with methyl 1-hydrazinecarbodithioate) with the readily available amines.

2. Results and discussion

Isatin was reacted with methyl 1-hydrazinecarbodithioate **1** in 2-propanol to give methyl 2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbodithioate **2**. The *S*-methyl group of **2**, upon displacement by an amine, formed the desired thiosemicarbazone (scheme 1). Through the use of the common intermediate **2** and the readily available amines, it was possible (in every instance) to form the desired compounds **3a**–**o** in essentially a one-step reaction.

As might be expected, the rate of the displacement reaction roughly paralleled the basicity of the amine, the weaker ones sometimes requiring ca a 24 h refluxing time (table 1). The structures of all the synthesized thiosemicarbazones were established through their physical, analytical, and spectral (IR, ^{1}H-NMR, EIMS) data. Satisfactory elemental analyses (±0.4% of calculated values) were obtained for all compounds, except where noted otherwise. The IR spectra of **3** showed two separate bands resulting from the NH stretchings of the indole and thioamide functions in the 3396–3207 and 3190–3147 cm^{-1} regions. The lactam C=O, azomethine C=N, and thioamide C=S stretchings were observed in the 1705–1686, 1622–1595 and 1225–1180 cm^{-1} regions, respectively [11,23,24]. The ^{1}H-NMR spectra of **3** exhibited NH protons of the



Scheme 1.

Table 1. Synthesis of N^4-substituted isatin-3-thiosemicarbazones **3a–o**.

Compounds	R	Reaction time (h)	Yield[a] (%)
3a	C_6H_5	10	72
3b	$C_6H_4CH_3$ (2-)	12	55
3c	$C_6H_4CH_3$ (3-)	16	39
3d	$C_6H_4CH_3$ (4-)	14	52
3e	$C_6H_4OCH_3$ (2-)	18	54
3f	$C_6H_4OCH_3$ (3-)	12	42
3g	$C_6H_4OCH_3$ (4-)	20	71
3h	C_6H_4Br (2-)	17	69
3i	C_6H_4Br (3-)	18	63
3j	C_6H_4Br (4-)	16	72
3k	C_6H_4Cl (2-)	24	61
3l	C_6H_4Cl (3-)	19	55
3m	C_6H_4Cl (4-)	17	66
3n	$C_6H_4NO_2$ (3-)	22	45
3o	$C_6H_4NO_2$ (4-)	24	34

[a]Without work-up of mother liquors.

thiosemicarbazone moieties at δ 8.70–11.70 and δ 13.63–14.55, and the indole NH protons at δ 12.41–12.86 as three separate singlets [11,25]. The indole C_7–H appeared as a doublet at δ 6.84–6.99, while the indole C_5–H and C_6–H appeared at δ 6.89–7.14 and δ 7.01–7.39, respectively, as a triplet or a doublet of double doublet. Indole C_4–H, experiencing a deshielding effect due to the inductive effect of the C=N function, resonated as a doublet at δ 7.51–7.72 [26–28]. In certain cases, however, overlapping of all these four signals, particularly that of indole C_5–H and C_6–H, were observed as multiplets. These signals appeared in combination with the different aromatic protons of the N^4-substituents.The EI mass spectra of **3** showed molecular ions of different intensity, which confirmed their molecular weights. The major fragmentation pathway involved the cleavage of the exocyclic N–N, NH–CS and endocyclic NH–CO bonds. The compound **3k** did not show molecular ion in its spectrum. However, the fragments corresponding to thiosemicarbazone moiety, formed by N–N and NH–CS bonds rupture, confirmed its structure. The proposed fragmentation pattern of **3n** is depicted in figure 1.

3. Experimental

3.1. *General*

Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo–Erba 1106 elemental analyzer (Milano, Italy). Infrared spectra (KBr disks) were run on a Shimadzu 8400 or a Shimadzu Prestige-21 FT-IR spectrometer. The ^{1}H-NMR spectra were recorded in C_3D_6O, $CDCl_3$, or C_5D_5N on Bruker (Rhenistetten–Forchheim, Germany) AM 300 and AM 400 spectrometers operating at 300 MHz and 400 MHz, respectively, using TMS as an internal standard. ^{1}H chemical shifts are reported in δ (ppm) and coupling constants in Hz. The electron impact mass spectra (EIMS) were determined with a Finnigan MAT-95 XP and a JEOL MSRoute mass spetrometer. The progress of the reaction and the purity of the products were checked on thin layer chromatography

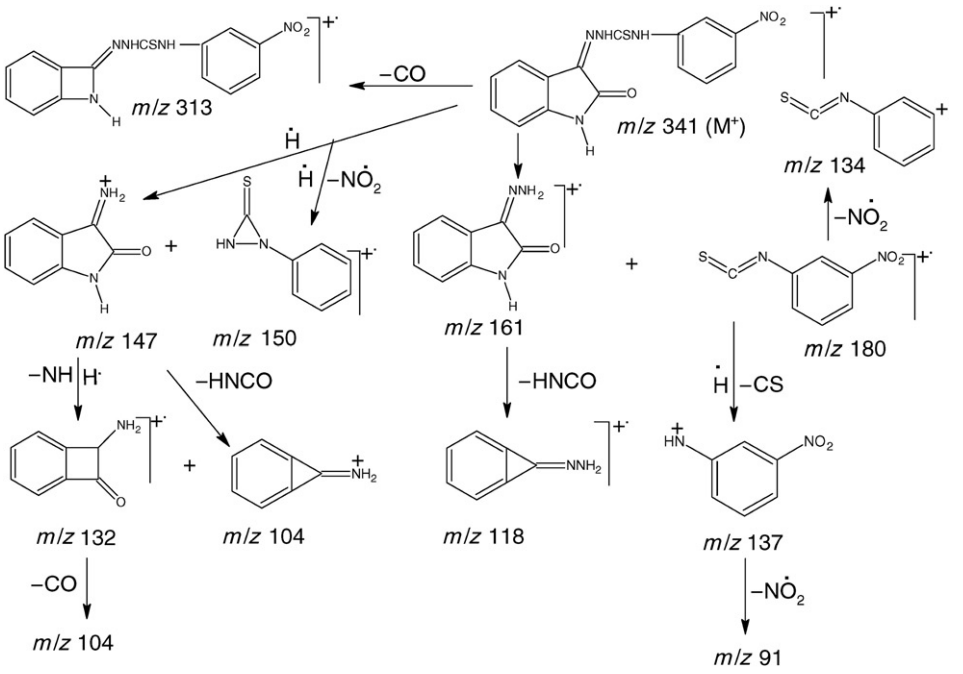


Figure 1. The proposed fragmentation pattern of the compound **3n**.

(TLC) plates coated with Merck silica gel 60 GF_{254} and the spots were visualized under ultraviolet light at 254 and 366 nm and/or spraying with iodine vapor.

3.2. *Synthetic*

3.2.1. Methyl 1-hydrazinecarbodithioate (1). This compound was synthesized using the reported method [17]. To a cooled solution of KOH (56.00 g, 1000 mmol) in water (80 mL) and 2-propanol (70 mL) was added 85% hydrazine hydrate (57 mL, 1000 mmol). Then ice-cooled solution of carbon disulphide (76.00 g, 61 mL, 1000 mmol) was added drop wise to the stirred solution, which was maintained at $<10^{\circ}C$ over about 100 min. A bright yellow solution obtained was stirred for an additional 60 min, after which ice-cooled methyl iodide (142.00 g, 62 mL, 1000 mmol) was added drop wise over a period of 120 min. The color of the mixture diminished gradually and became white. Stirring was continued for an additional 90 min. The white precipitate was collected by suction filtration, washed with ice-cold water and dried slowly at $60^{\circ}C$. Recrystallization of the crude product from dichloromethane afforded the desired compound (60.00 g, 49%), m.p. $82^{\circ}C$ (lit. [17] m.p. 81–$83^{\circ}C$); IR (KBr, cm^{-1}): 3264, 3217, 3194 (br., NH), 1153 (C=S).

3.2.2. Methyl 2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbodithioate (2). Methyl 1-hydrazinecarbodithioate **1** (24.40 g, 200 mmol), isatin (29.40 g, 200 mmol) and 2-propanol (300 mL) were mixed and stirred vigorously. The reaction mixture turned orange yellow as the compound **1** dissolved and then the orange colored product began to precipitate. The reaction mixture was stirred for an additional 120 min and

refrigerated overnight. The orange red crystals formed were collected by suction filtration. Washing with cold 2-prorpanol and drying at 80–90°C furnished the target compound (47.19 g, 94%), m.p. 228°C (lit. [9] m.p. 227°C); IR (KBr, cm^{-1}): 3212, 3185 (NH), 1695 (C=O), 1618 (C=N), 1219 (C=S); ^{1}H-NMR (C_3D_6O, δ, ppm): 2.64 (5, 3H, SCH_3, 7.04) (dt, $J = 7.9$, 1.6, 0.8 Hz, 1H, indole C_7–H), 7.13 (ddd, $J = 7.6$, 7.6, 1.0 Hz, 1H, indole C_5–H), 7.43 (ddd, $J = 7.7$, 7.7, 1.2 Hz, 1H, indole C_6–H), 7.62 (br.d, $J = 7.6$ Hz, 1H, indole C_4–H), 10.26 (s, 1H, indole NH), 14.24 (s, 1H, N–NH); EIMS (70 eV): m/z (%) 253 ([M^+] +2, 1), 252 ([M^+] +1, 2), 251 ([M^+], 26), 223 (100), 178 (16), 144 (64), 132 (26), 118 (57), 104 (17), 91(60), 76(14), 64(16); (found: C, 47.63; H, 3.60; N, 16.80%. Calcd for $C_{10}H_9N_3OS$: C, 47.80; H, 3.58; N, 16.73%).

3.2.3. General procedure for the preparation of isatin-thiosemicarbazones 3a–o. To a solution of the compound **2** (1.26 g, 0.005 mol) in warm ethanol (80 mL) was added the corresponding amine (0.005 mol) dissolved in ethanol (10 mL). The reaction mixture was then heated under reflux until the evolution of methylmercaptan almost completely ceased (10–24 h). Methylmercaptan was detected by the yellow colour it imparts to moistened lead acetate paper placed at the neck of the reaction flask. The reaction was also continuously monitored by TLC performed in petroleum ether (60–80°C) – ethyl acetate (7 : 3). The refluxate upon concentration and standing overnight at room temperature resulted into the bright yellow to reddish brown crystalline product, which was collected by suction filtration. Recrystallization from ethanol furnished the purified products **3a**–**o** in moderate to good yields.

The different compounds are characterized as follows:

2-(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)-*N*-phenyl-1-hydrazinecarbothioamide (3a). m.p. 232°C (lit. [15,16,29,30] m.p. 234–235°C, 230–231°C, 220–222°C, 239–241°C); IR (KBr, cm^{-1}): 3298, 3185 (NH), 1694 (C=O), 1620 (C=N) and 1164 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 6.91 (d, $J = 7.6$ Hz, 1H, indole C_7–H), 7.05–7.13 (m, 2H, indole C_5–H and phenyl C_4–H), 7.25–7.43 (m, 3H, indole C_6–H and phenyl C_3–H, C_5–H), 7.58–7.65 (m, 2H, phenyl C_2–H, C_6–H), 7.71 (d, $J = 7.7$ Hz, 1H, indole C_4–H), 9.48 (s, 1H, CS-NH), 12.83 (s, 1H, indole NH), 13.68 (s, 1H, N–NH); EIMS (70 eV): m/z (%) 298 ([M^+] +2, 1), 297 ([M^+] +1, 3), 296 ([M^+], 14), 268 (40), 252 (3), 161 (11), 150 (13), 147 (12), 132 (7), 118 (55), 104 (13), 93 (100), 77 (35); (found: C, 61.00; H, 4.07; N, 18.84%. Calcd for $C_{15}H_{12}N_4OS$: C, 60.81; H, 4.05; N, 18.91%).

***N*-(2-Methylphenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3b)**. m.p. 222°C (lit. [10,11] m.p. 222–223°C, 244°C); IR (KBr, cm^{-1}): 3300, 3190 (NH), 1693 (C=O), 1618 (C=N), 1207 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.35 (s, 3H, CH_3), 6.93 (d, $J = 7.7$ Hz, 1H, indole C_7–H), 7.10 (d, $J = 7.6$ Hz, 1H, phenyl C_3–H), 7.17–7.29 (m, 2H, indole C_5–H and phenyl C_4–H), 7.32–7.41 (m, 2H, indole C_6–H and phenyl C_5–H), 7.58 (d, $J = 7.5$ Hz, 1H, phenyl C_6–H), 7.72 (d, $J = 7.4$ Hz, 1H, indole C_4–H), 9.29 (s, 1H, CS–NH), 12.84 (s, 1H, indole NH), 13.64 (s, 1H, N–NH); EIMS (70 eV): m/z (%) 312 ([M^+] +2, 2), 311 ([M^+] +1, 4), 310 ([M^+], 20), 282 (61), 161 (15), 147 (21), 132 (34), 118 (49), 106 (100), 104 (41), 91 (45), 77 (33); (found: C, 61.91; H, 4.52; N, 18.00%. Calcd for $C_{16}H_{14}N_4OS$: C, 61.93; H, 4.51; N, 18.06%).

***N* -(3-Methylphenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3c).** m.p. 224°C; IR (KBr, cm^{-1}): 3305, 3184 (NH), 1690 (C=O), 1610 (C=N), 1180 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.38 (s, 3H, CH_3), 6.92 (d, $J = 7.7$ Hz, 1H,

indole C_7–H), 7.04–7.13 (m, 2H, indole C_5–H and phenyl C_2–H), 7.19 (d, $J = 8.2$ Hz, 1H, phenyl C_4–H), 7.27–7.36 (m, 2H, indole C_6–H and phenyl C_5–H), 7.52 (d, $J = 8.3$ Hz, 1H, phenyl C_6–H), 7.62 (d, $J = 7.6$ Hz, 1H, indole C_4–H), 9.44 (s, 1H, CS–NH), 12.80 (s, 1H, indole NH), 13.68 (s, 1H, N–NH); EIMS (70 eV): m/z (%) 311 ([M^+] +1, 2), 310 ([M^+], 11), 282 (36), 161 (28), 147 (5), 132 (27), 118 (38), 107 (100), 104 (29), 91 (50), 77 (27); (found: C, 61.91; H, 4.52; N, 17.98%. $C_{16}H_{14}N_4OS$ requires C, 61.93; H, 4.51; N, 18.06%).

***N*-(4-Methylphenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3d).** m.p. 236°C (lit. [11,15,16] m.p. 241–242°C, 238–239°C, 237–238°C); IR (KBr, cm^{-1}): 3310, 3150 (NH), 1695 (C=O), 1600 (C=N) 1205 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.31 (s, 3H, CH_3), 6.91 (d, $J = 7.8$ Hz, 1H, indole C_7–H), 7.07 (t, $J = 7.6$ Hz, 1H, indole C_5–H), 7.21 (d, $J = 8.1$ Hz, 2H, phenyl C_2–H, C_6–H), 7.30 (t, $J = 7.2$ Hz, 1H, indole C_6–H), 7.55 (d, $J = 8.2$ Hz, 2H, phenyl C_3–H, C_5–H), 7.64 (d, $J = 8.0$ Hz, 1H, indole C_4–H), 9.40 (s, 1H, CS–NH), 12.81 (s, 1H, indole NH), 13.68 (s, 1H, N–NH); EIMS (70 eV): m/z (%) 312 ([M^+] +2, 3), 311 ([M^+] +1, 9), 310 ([M^+], 42), 282 (100), 161 (19), 146 (9), 132 (40), 118 (49), 106 (100), 104 (31), 91 (58), 77 (32). (found: C, 61.90; H, 4.54; N, 18.10%. Calcd for $C_{16}H_{14}N_4OS$: C, 61.93; H, 4.51; N, 18.06%).

***N*-(2-Methoxyphenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3e).** m.p. 250°C; IR (KBr, cm^{-1}): 3295, 3150 (NH), 1686 (C=O), 1620 (C=N), 1184 (C=S); ^{1}H-NMR (C_5D_5N, δ, ppm): 3.77 (s, 3H, OCH_3), 6.99 (d, $J = 7.7$ Hz, 1H, indole C_7–H), 7.02–7.09 (m, 4H, indole C_5–H and phenyl C_4–H, C_5–H, C_6–H), 7.21, 7.23 (dd, $J = 7.9$, 1.6 Hz, 1H, phenyl C_3–H), 7.32 (ddd, $J = 7.7$, 7.7, 1.1 Hz, 1H, indole C_6–H), 7.51 (d, $J = 7.2$ Hz, 1H, indole C_4–H), 10.91 (s, 1H, CS–NH), 12.68 (s, 1H, indole NH), 13.63 (s, 1H, N–NH); EIMS (70 eV): m/z (%) 327 ([M^+] +1, 2), 326 ([M^+], 8), 298 (40), 267 (2), 203 (4), 165 (100), 161 (70), 150 (36), 147 (3), 132 (33), 123 (41), 122 (60), 118 (13), 108 (43), 104 (39), 77 (21); (found: C, 58.86; H, 4.31; N, 17.07%. $C_{16}H_{14}N_4O_2S$ requires C, 58.89; H, 4.29; N, 17.17%).

***N*-(3-Methoxyphenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3f).** m.p. 204°C; IR (KBr, cm^{-1}): 3207, 3186 (NH), 1692 (C=O), 1618 (C=N), 1193 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.83 (s, 3H, OCH_3), 6.79, 6.81 (dd, $J = 7.8$, 1.9 Hz, 1H, phenyl C_4–H), 6.91 (d, $J = 7.8$ Hz, 1H, indole C_7–H), 7.09–7.19 (m, 2H, indole C_5–H and phenyl C_6–H), 7.30 (t, $J = 8.0$ Hz, 1H, indole C_6–H), 7.35, 7.37 (dd, $J = 7.7$, 7.7 Hz, 1H, phenyl C_5–H), 7.52 [t (superimposed dd), 1H, phenyl C_2–H)], 7.63 (d, $J = 7.6$ Hz, 1H, indole C_4–H), 9.49 (s, 1H, CS–NH), 12.82 (s, 1H, indole NH), 13.65 (s, 1H, N–NH); EIMS (70 eV): m/z (%) 326 ([M^+], 8), 298 (100), 203 (3), 166 (15), 161 (14), 150 (25), 147 (5), 132 (20), 123 (13), 118 (20), 108 (4), 104 (48), 77 (56); (found: C, 59.00; H, 4.30; N, 7.20%. $C_{16}H_{14}N_4O_2S$ requires C, 58.89; H, 4.29; N, 17.17%).

***N*-(4-Methoxyphenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3g).** m.p. 240°C (lit. [15,16] m.p. 242–243°C, 237–238°C); IR (KBr, cm^{-1}): 3300, 3190 (NH), 1695 (C=O), 1620 (C=N), 1219 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.82 (s, 3H, OCH_3), 6.88–6.95 (m, 3H, indole C_7–H and phenyl C_2–H, C_6–H), 7.11 (t, $J = 7.4$ Hz, 1H, indole C_5–H), 7.34 (t, $J = 7.7$ Hz, 1H, indole C_6–H), 7.52–7.63 (m, 3H, indole C_4–H and phenyl C_3–H, C_5–H), 9.34 (s, 1H, CS–NH), 12.82 (br.s, 1H,

indole NH), 13.68 (s, 1H, N–NH); EIMS (70 eV): *m/z* (%), 327 ([M^+] +1, 4), 326 ([M^+], 18), 298 (71), 203 (2), 165 (100), 161 (64), 150 (82), 147 (5), 132 (18), 123 (30), 118 (19), 108 (53), 104 (56), 77 (44), 65 (35); (found: C, 58.85; H, 4.25; N, 17.00%. Calcd for $C_{16}H_{14}N_4O_2S$: C, 58.89; H, 4.29; N, 17.17%).

***N*-(2-Bromophenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3h).** m.p. 250°C; IR (KBr, cm^{-1}): 3246, 3167 (NH), 1697 (C=O), 1620 (C=N), 1593 (C=N), 1210 (C=S); ^{1}H-NMR (C_5D_5N, δ, ppm): 6.93–6.99 (m, 2H, indole C_7–H and phenyl C_4–H), 7.02–7.12 (m, 2H, indole C_5–H and phenyl C_5–H), 7.25–7.38 (m, 2H, indole C_6–H and phenyl C_6–H), 7.67–7.71 (m, 2H, indole C_4–H and phenyl C_3–H), 11.51 (s, 1H, CS–NH), 12.70 (s, 1H, indole NH), 13.73 (s, 1H, N–NH); EIMS (70 eV): *m/z* (%) 376 ([M^+] +1, 1), 375 ([M^+], 2), 348 (23), 347 (5), 295 (100), 215 (7), 171 (77), 161 (17), 150 (53), 147 (24), 132 (21), 118 (50), 108 (13), 104 (34), 92 (34), 77 (20), 65 (35); (found: C, 48.05; H, 2.91; N, 14.95%. $C_{15}H_{11}BrN_4OS$ requires C, 48.00; H, 2.93; N, 14.93%).

***N*-(3-Bromophenyl)-2(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3i).** m.p. 232°C; IR (KBr, cm^{-1}): 3340, 3185 (NH), 1705 (C=O), 1620 (C=N), 1180 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 6.91 (d, $J = 7.8$ Hz, 1H, indole C_7–H), 7.12 (t, $J = 7.4$ Hz, 1H, indole C_5–H), 7.28 (d, $J = 8.0$ Hz, 1H, phenyl C_4–H), 7.36 (ddd, $J = 7.8$, 7.8, 1.1 Hz, 1H, indole C_6–H), 7.58–7.64 (m, 2H, phenyl C_5–H, C_6–H), 7.72 (d, $J = 8.2$ Hz, 1H, indole C_4–H), 7.92 (t (superimposed dd), 1H, phenyl C_2–H), 9.47 (s, 1H, CS–NH), 12.87 (s, 1H, indole NH), 13.70 (s, 1H, N–NH); EIMS (70 eV): *m/z* (%) 376 ([M^+] +2, 5), 374 ([M^+], 5), 348 (24), 346 (23), 215 (100), 171 (25), 161 (8), 150 (13), 147 (2), 132 (19), 118 (31), 108 (5), 104 (61), 92 (81), 77 (32), 65 (99); (found: C, 48.00; H, 2.95; N, 14.91%. $C_{15}H_{11}BrN_4OS$ requires C, 48.00; H, 2.93; N, 14.93%).

***N*-(4-Bromophenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3j).** m.p. 246°C (lit. [11,15,16] m.p. 225–226°C, 242–243°C, 241–243°C); IR (KBr, cm^{-1}): 3330, 3185 (NH), 1690 (C=O), 1620 (C=N), 1205 (C=S); ^{1}H-NMR (C_5D_5N, δ, ppm): 6.89 (ddd, $J = 7.6$, 7.5, 1.0 Hz, 1H, indole C_5–H), 6.97–7.00 (m, 3H, indole C_7–H and phenyl C_2–H, C_6–H), 7.28 (ddd, $J = 7.6$, 6.3, 1.3 Hz, 1H, indole C_6–H), 7.54–7.57 (m, 3H, indole C_4–H and phenyl C_3–H, C_5–H), 11.36 (s, 1H, CS–NH), 12.41 (s, 1H, indole NH), 13.63 (s, 1H, N–NH); EIMS (70 eV): *m/z* (%) 376 ([M^+] +2, 26), 375 ([M^+] +1, 5), 374 ([M^+], 25), 346 (76), 215 (16), 171 (100), 161 (23), 150 (22), 147 (11), 132 (16), 118 (24), 108 (4), 104 (26), 92 (37), 77 (25), 65 (38); (found: C, 48.11; H, 2.95; N, 14.93%. Calcd for $C_{15}H_{11}BrN_4OS$: C, 48.00; H, 2.93; N, 14.93%).

***N*-(2-Chlorophenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3k)**. m.p. 254°C; IR (KBr, cm^{-1}): 3396, 3176 (NH), 1701 (C=O), 1622 (C=N), 1203 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 6.84 (d, $J = 8.0$ Hz, 1H, indole C_7–H), 6.88–6.93 (m, 2H, indole C_5–H and phenyl C_4–H), 7.01 (t, $J = 7.9$ Hz, 1H, indole C_6–H), 7.06–7.14 (m, 1H, phenyl C_5–H), 7.31–7.37 (m, 2H, phenyl C_3–H, C_6–H), 7.67 (d, $J = 7.9$ Hz, 1H, indole C_4–H), 9.47 (s, 1H, CS–NH), 12.86 (s, 1H, indole NH), 13.68 (s, 1H, N–NH); EIMS (70 eV): *m/z* (%) 317.2 (3), 304.2 (6), 302.2 (21), 295 (100), 267 (2), 172 (7), 171 (31), 170 (19), 161 (51), 150 (37), 147 (12), 127 (21), 118 (31), 111 (39), 104 (66), 77 (33), 75 (52), 65 (13), 63 (34); (found: C, 54.49; H, 3.33; N, 16.92%. $C_{15}H_{11}ClN_4OS$ requires C, 54.46; H, 3.32; N, 16.94%).

***N*-(3-Chlorophenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3l).** m.p. 212°C; IR (KBr, cm^{-1}): 3285, 3147 (NH), 1693 (C=O), 1618 (C=N), 1207 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 6.84–6.93 (m, 2H, indole C_7–H and phenyl C_5–H), 6.99–7.13 (m, 2H, indole C_5–H and phenyl C_6–H), 7.31–7.37 (m, 2H, indole C_6–H and phenyl C_5–H), 7.61–7.68 (m, 2H, indole C_4–H and phenyl C_2–H), 9.47 (s, 1H, CS–NH), 12.85 (s, 1H, indole NH), 13.68 (s, 1H, N-NH); EIMS (70 eV): *m*/*z* (%) 332.5 ([M^+] +2, 19), 330.4 ([M^+], 49), 302.4 (100), 243 (3), 203 (4), 185 (3), 172 (6), 171 (6), 170 (15), 169 (14), 161 (17), 150 (25), 147 (3), 132 (25), 127 (23), 118 (19), 111 (32), 104 (41), 77 (22), 75 (29), 65 (10), 63 (15); (found: C, 54.48; H, 3.33; N, 16.93%. $C_{15}H_{11}ClN_4OS$ requires C, 54.46; H, 3.32; N, 16.94%).

***N*-(4-Chlorophenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3m).** m.p. 236°C (lit. [11,15,16,31] m.p. 247–248°C, 241–242°C, 238–239°C, 238–240°C); IR (KBr, cm^{-1}): 3320, 3185 (NH), 1695 (C=O), 1620 (C=N), 1195 (C=S); ^{1}H-NMR (C_5D_5N, δ, ppm): 6.87–6.99 (m, 3H, indole C_7–H and phenyl C_2–H, C_6–H), 7.04 (ddd, $J = 7.6$, 7.6, 0.8 Hz, 1H, indole C_5–H), 7.27–7.35 (m, 3H, indole C_6–H and phenyl C_3–H, C_5–H), 7.68 (d, $J = 7.6$ Hz, 1H, indole C_4–H), 11.70 (s, 1H, CS–NH), 12.69 (br.s, 1H, indole NH), 13.75 (s, 1H, N–NH); EIMS (70 eV): *m*/*z* (%) 332.9 ([M^+] +2, 1), 332 ([M^+] +1, 6), 330.9 ([M^+], 3), 305 (4), 303.9 (24), 302.9 (11), 301.9 (63), 203 (9), 185 (1), 171.9 (6), 170.9 (38), 169.9 (18), 168.9 (100), 161(68), 150 (18), 147 (3), 132 (23), 127 (49), 118 (22), 111 (60), 77 (25), 75 (56), 65 (20), 63 (31); (found: C, 54.50; H, 3.30; N, 16.90%. Calcd for $C_{15}H_{11}ClN_4OS$: C, 54.46; H, 3.32; N, 16.94%).

***N*-(3-Nitrophenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3n).** m.p. 250°C; IR (KBr, cm^{-1}): 3380, 3185 (NH), 1690 (C=O), 1595(C=N), 1225 (C=S); ^{1}H-NMR (C_5D_5N, δ, ppm): 6.95 (d, $J = 7.7$ Hz, 1H, indole C_7–H), 6.98–7.09 (m, 2H, indole C_5–H and phenyl C_5–H) 7.24–7.33 (m, 3H, indole C_6–H and phenyl C_4–H, C_6–H), 7.68 (d, $J = 7.5$ Hz, 1H, indole C_4–H,), 8.16, 8.18 (dd, $J = 1.1$, 1.0 Hz, 1H, phenyl C_2–H), 8.70 (s, 1H, CS–NH), 12.71 (br.s, 1H, indole NH), 14.55 (s, 1H, N–NH); EIMS (70 eV): *m*/*z* (%) 342 ([M^+] +1, 3), 341 ([M^+], 19), 313 (100), 281 (5), 267 (3), 203 (6), 181 (16), 161 (72), 151 (4), 147 (3), 138 (23), 132 (45), 118 (38), 104 (88), 91 (28), 77 (45), 65 (53); (found: C, 52.70; H, 3.20; N, 20.50%. $C_{15}H_{11}N_5O_3S$ requires C, 52.78; H, 3.22; N, 20.52%).

***N*-(4-Nitrophenyl)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)-1-hydrazinecarbothioamide (3o).** m.p. 254°C; IR (KBr, cm^{-1}): 3285, 3160 (NH), 1695 (C=O), 1618 (C=N), 1222 (C=S); ^{1}H-NMR ($CDCl_3$, δ, ppm): 6.91 (d, $J = 7.6$ Hz, 1H, indole C_7–H), 7.05 (d, $J = 8.0$ Hz, 2H, phenyl C_2–H, C_6–H), 7.14 (t, $J = 7.6$ Hz, 1H, indole C_5–H), 7.39 (t, $J = 8.0$ Hz, 1H, indole C_6–H), 7.52 (d, $J = 8.0$ Hz, 1H, indole C_4–H), 8.26 (d, $J = 8.0$ Hz, 2H, phenyl C_3–H, C_5–H), 11.55 (s, 1H, CS–NH), 12.72 (br.s, 1H, indole NH), 13.84 (s, 1H, N–NH); EIMS (70 eV): *m*/*z* (%) 341([M^+], 2), 313 (13), 203 (39), 181 (3), 161 (21), 150 (12), 146 (10), 138 (87), 132 (10), 118 (22), 104 (20), 91 (16), 77 (12), 76 (25), 65 (100); (found: C, 52.75; H, 3.21; N, 20.48%. $C_{15}H_{11}N_5O_3S$ requires C, 52.78; H, 3.22; N, 20.52%).

4. Conclusions

In this contribution, we report a simple and new method for the synthesis of isatin-3-thiosemicarbazones **3a**–**o**. The striking feature of this method is the possibility of

synthesizing the desired compounds through the treatment of the common intermediate **2** with the readily available amines in essentially a one-step reaction. The proposed route could be used as an alternative to the direct synthesis of certain potential biologically active thiosemicarbazones for which the appropriate thiosemicarbazides or their respective isothiocyanates are not readily available.

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