

Article

Microwave-Assisted Synthesis of New N_1,N_4 -Substituted Thiosemicarbazones

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Abstract: We present an efficient procedure for the synthesis of thirty-six N_1,N_4 -substituted thiosemicarbazones, including twenty-five ones that are reported for the first time, using a microwave-assisted methodology for the reaction of thiosemicarbazide intermediates with aldehydes in the presence of glacial acetic acid in ethanol and under solvent free conditions. Overall reaction times (20–40 min when ethanol as solvent, and 3 min under solvent free conditions) were much shorter than with the traditional procedure (480 min); satisfactory yields and high-purity compounds were obtained. The thiosemicarbazide intermediates were obtained from alkyl or aryl isothiocyanates and hydrazine hydrate or phenyl hydrazine by stirring at room temperature for 60 min or by microwave irradiation for 30 min, with lower yields for the latter. The preliminary *in vitro* antifungal activity of thiosemicarbazones was evaluated against *Aspergillus parasiticus* and *Candida albicans*.

Keywords: thiosemicarbazone; thiosemicarbazide; microwave irradiation; antifungal activity

1. Introduction

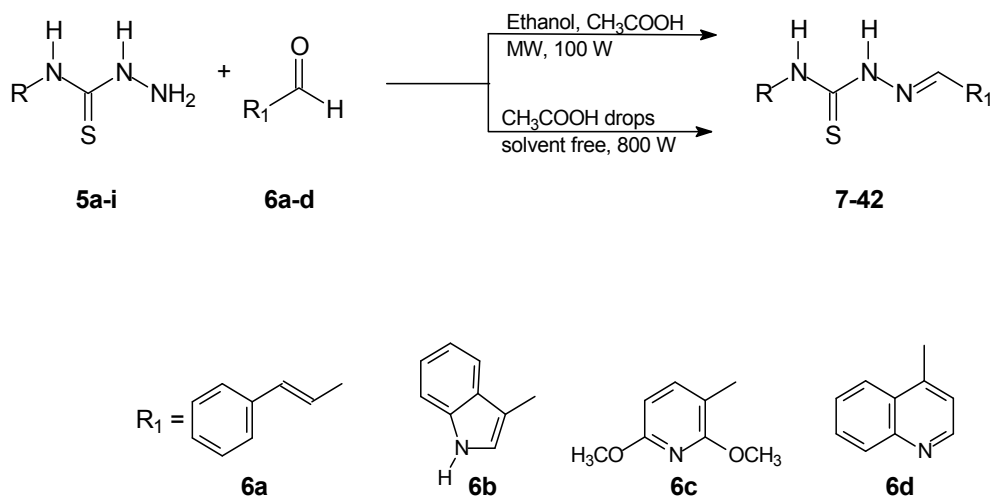
Thiosemicarbazones and thiosemicarbazides are now well established as an important class of sulfur/nitrogen donor ligands, particularly for transition metal ions [1,2], because of the remarkably diverse biological activities observed for these compounds. These activities include antiviral [3-5], antitumor [6,7], and antimicrobial properties [8], as well as other industrially important activities, including anticorrosion [9] and antifouling [10] effects. Considering all of these properties, it is important to be able to synthesize new series of thiosemicarbazones.

The increasing demand for clean and efficient chemical procedures has been a target for the synthesis of organic compounds. The combined use of microwave irradiation and solvent-free conditions has shown advantages from economic and environmental standpoints [11,12]. Furthermore, microwave-assisted organic reactions generally provide high yields of pure products, minimize the use of organic solvents, and allow for a simplified work-up and shorter reaction times [13].

Our research group has been working on more efficient and cleaner synthetic methods, focusing on microwave irradiation and solvent-free conditions [14-17]. To extend our investigation and considering the special importance of thiosemicarbazone class, in this paper we report the synthesis of thirty six thiosemicarbazones N_1, N_4 -substituted from thiosemicarbazides with low reaction times and good yields by microwave-assisted reactions. Furthermore, the evaluation of antifungal activity against the *Aspergillus parasiticus* and *Candida albicans* was realized.

2. Results and Discussion

Thirty-six thiosemicarbazones were synthesized using a microwave-assisted methodology; twenty-five are new compounds. The synthetic procedure was performed in two steps starting with aryl thiosemicarbazides **5a–d** or alkyl thiosemicarbazides **5e–i**, also prepared in this work, and cinnamaldehyde (**6a**), 3-methyl-indolcarboxaldehyde (**6b**), 2,6-dimethoxy-pyridincarboxaldehyde (**6c**) or 4-quinolinecarboxaldehyde (**6d**) in ethanol as a solvent, and under solvent free conditions, with a few drops of added glacial acetic acid, as outlined in Scheme 1. The reaction mixtures were irradiated in a scientific microwave reactor for 20–40 min at 100 W when ethanol used as solvent, and for 3 min at 800 W in the absence of solvent. The products, a cinnamaldehyde series (compounds **7–15**), a 3-methyl-indolcarboxaldehyde series (compounds **16–24**), a 2,6-dimethoxypyridincarboxaldehyde series (compounds **25–33**) and a 4-quinolinecarboxaldehyde series (compounds **34–42**), were obtained with both procedures as fine crystals in high-purity and satisfactory yields after a short time, when compared with the reaction time for the traditional procedure (480 min). The best yields (88–98%) and the short reaction times (3 min) were obtained when the solvent free conditions were used. The thiosemicarbazones **7–10** and **16–19** were also prepared using a reflux method; after 8 h under reflux in ethanol, lower yields were obtained for all the compounds than in the microwave-assisted synthesis. Table 1 shows the reaction times and yields for the target compounds, **7–42**.

Scheme 1. Synthesis of thiosemicarbazones by microwave irradiation.

- | | | | |
|---|---|---|---|
| 7: R = C ₆ H ₅ ; R ₁ = 6a | 16: R = C ₆ H ₅ ; R ₁ = 6b | 25: R = C ₆ H ₅ ; R ₁ = 6c | 34: R = C ₆ H ₅ ; R ₁ = 6d |
| 8: R = <i>p</i> -CH ₃ -C ₆ H ₄ ; R ₁ = 6a | 17: R = <i>p</i> -CH ₃ -C ₆ H ₄ ; R ₁ = 6b | 26: R = <i>p</i> -CH ₃ -C ₆ H ₄ ; R ₁ = 6c | 35: R = <i>p</i> -CH ₃ -C ₆ H ₄ ; R ₁ = 6d |
| 9: R = <i>p</i> -CH ₃ O-C ₆ H ₄ ; R ₁ = 6a | 18: R = <i>p</i> -CH ₃ O-C ₆ H ₄ ; R ₁ = 6b | 27: R = <i>p</i> -CH ₃ O-C ₆ H ₄ ; R ₁ = 6c | 36: R = <i>p</i> -CH ₃ O-C ₆ H ₄ ; R ₁ = 6d |
| 10: R = <i>p</i> -NO ₂ -C ₆ H ₄ ; R ₁ = 6a | 19: R = <i>p</i> -NO ₂ -C ₆ H ₄ ; R ₁ = 6b | 28: R = <i>p</i> -NO ₂ -C ₆ H ₄ ; R ₁ = 6c | 37: R = <i>p</i> -NO ₂ -C ₆ H ₄ ; R ₁ = 6d |
| 11: R = CH ₃ CH ₂ ; R ₁ = 6a | 20: R = CH ₃ CH ₂ ; R ₁ = 6b | 29: R = CH ₃ CH ₂ ; R ₁ = 6c | 38: R = CH ₃ CH ₂ ; R ₁ = 6d |
| 12: R = (CH ₃) ₂ CH; R ₁ = 6a | 21: R = (CH ₃) ₂ CH; R ₁ = 6b | 30: R = (CH ₃) ₂ CH; R ₁ = 6c | 39: R = (CH ₃) ₂ CH; R ₁ = 6d |
| 13: R = CH ₃ (CH ₂) ₂ CH ₂ ; R ₁ = 6a | 22: R = CH ₃ (CH ₂) ₂ CH ₂ ; R ₁ = 6b | 31: R = CH ₃ (CH ₂) ₂ CH ₂ ; R ₁ = 6c | 40: R = CH ₃ (CH ₂) ₂ CH ₂ ; R ₁ = 6d |
| 14: R = CH ₃ (CH ₂) ₄ CH ₂ ; R ₁ = 6a | 23: R = CH ₃ (CH ₂) ₄ CH ₂ ; R ₁ = 6b | 32: R = CH ₃ (CH ₂) ₄ CH ₂ ; R ₁ = 6c | 41: R = CH ₃ (CH ₂) ₄ CH ₂ ; R ₁ = 6d |
| 15: R = C ₆ H ₁₁ ; R ₁ = 6a | 24: R = C ₆ H ₁₁ ; R ₁ = 6b | 33: R = C ₆ H ₁₁ ; R ₁ = 6c | 42: R = C ₆ H ₁₁ ; R ₁ = 6d |

Table 1. Thiosemicarbazone yields and reaction times obtained under microwave irradiation using ethanol as solvent and in solvent free conditions (7–42), and under traditional reflux (7–10 and 16–19).

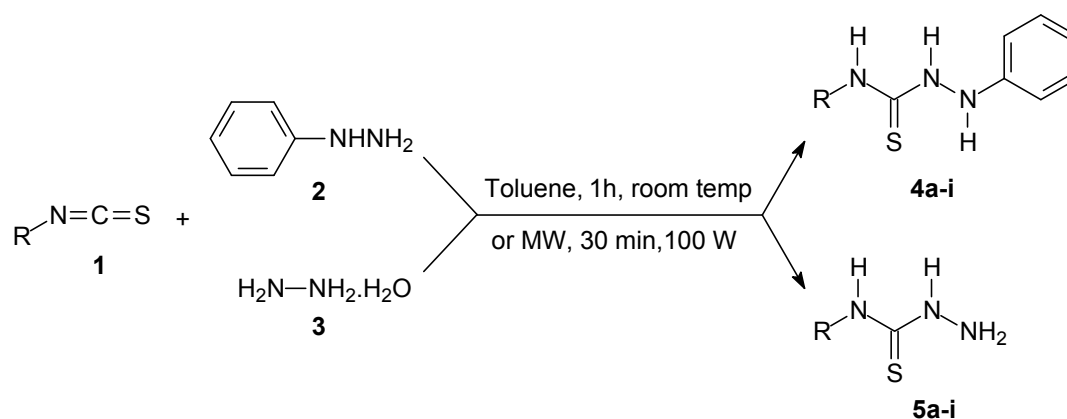
Compound	Time (min)	Yield (%)	Compound	Time (min)	Yield (%)
7	3 ^a /40 ^b /480 ^c	96 ^a /86 ^b /83 ^c	25	3 ^a /40 ^b	93 ^a /82 ^b
8	3 ^a /40 ^b /480 ^c	92 ^a /79 ^b /74 ^c	26	3 ^a /40 ^b	86 ^a /70 ^b
9	3 ^a /40 ^b /480 ^c	97 ^a /71 ^b /70 ^c	27	3 ^a /40 ^b	91 ^a /78 ^b
10	3 ^a /40 ^b /480 ^c	90 ^a /88 ^b /68 ^c	28	3 ^a /40 ^b	90 ^a /82 ^b
11	3 ^a /20 ^b	89 ^a /54 ^b	29	3 ^a /20 ^b	96 ^a /99 ^b
12	3 ^a /20 ^b	96 ^a /83 ^b	30	3 ^a /20 ^b	97 ^a /99 ^b
13	3 ^a /20 ^b	94 ^a /71 ^b	31	3 ^a /20 ^b	92 ^a /94 ^b
14	3 ^a /20 ^b	92 ^a /70 ^b	32	3 ^a /20 ^b	91 ^a /88 ^b
15	3 ^a /20 ^b	95 ^a /83 ^b	33	3 ^a /20 ^b	94 ^a /97 ^b
16	3 ^a /40 ^b /480 ^c	91 ^a /62 ^b /49 ^c	34	3 ^a /40 ^b	89 ^a /77 ^b
17	3 ^a /40 ^b /480 ^c	97 ^a /93 ^b /78 ^c	35	3 ^a /40 ^b	88 ^a /84 ^b
18	3 ^a /40 ^b /480 ^c	88 ^a /76 ^b /67 ^c	36	3 ^a /40 ^b	90 ^a /57 ^b
19	3 ^a /40 ^b /480 ^c	96 ^a /82 ^b /63 ^c	37	3 ^a /40 ^b	96 ^a /79 ^b
20	3 ^a /20 ^b	98 ^a /73 ^b	38	3 ^a /20 ^b	95 ^a /70 ^b
21	3 ^a /20 ^b	93 ^a /52 ^b	39	3 ^a /20 ^b	93 ^a /75 ^b
22	3 ^a /20 ^b	94 ^a /78 ^b	40	3 ^a /20 ^b	91 ^a /81 ^b
23	3 ^a /20 ^b	87 ^a /52 ^b	41	3 ^a /20 ^b	89 ^a /79 ^b
24	3 ^a /20 ^b	95 ^a /85 ^b	42	3 ^a /20 ^b	93 ^a /62 ^b

^a Solvent free conditions; ^b using ethanol as solvent; ^c using traditional reflux.

The thiosemicarbazone structures **7–42** were fully characterized by ^1H - and ^{13}C -NMR and IR spectroscopy. The ^1H - and ^{13}C -NMR shifts (δ) were assigned based on literature data [18–22] and were consistent with the structures proposed. The ^1H chemical shifts of $\text{H}-\text{C}=\text{N}$ for the thiosemicarbazone cinnamaldehyde series products **7–15** showed lower values than for the other series. In contrast, the ^{13}C chemical shifts of $\text{C}=\text{N}$ were assigned with lower and similar values for the 2,6-dimethoxy-3-pyridinecarboxaldehyde and 4-quinolinecarboxaldehyde series products **25–33** and **34–42**. The values ranged from $\delta = 137.02$ to 138.62 for the cinnamaldehyde ones **7–15** and from $\delta = 140.10$ to 146.93 for the 3-indolecarboxaldehyde series **16–24**. The electronic substituent effects were as expected. The Figures 1–4 show the numbered structures.

The aryl thiosemicarbazides **5a–d** or alkyl thiosemicarbazides **5e–i** used as intermediates in thiosemicarbazone preparation were prepared by both traditional and microwave-assisted procedures. Scheme 2 shows the reactions and the conditions for both procedures.

Scheme 2. Synthesis of thiosemicarbazides.



R = C_6H_5 (**a**), $p\text{-CH}_3\text{-C}_6\text{H}_4$ (**b**), $p\text{-CH}_3\text{O-C}_6\text{H}_4$ (**c**), $p\text{-NO}_2\text{-C}_6\text{H}_4$ (**d**), CH_3CH_2 (**e**), $(\text{CH}_3)_2\text{CH}$ (**f**), $\text{CH}_3(\text{CH}_2)_2\text{CH}_2$ (**g**), $\text{CH}_3(\text{CH}_2)_4\text{CH}_2$ (**h**), C_6H_{11} (**i**)

Table 2. Thiosemicarbazide yields and reaction times using microwave irradiation and stirring at room temperature.

Compound	Traditional Procedure (%) 60 min	Microwave Irradiation (%) 30 min	Compound	Traditional Procedure (%) 60 min	Microwave Irradiation (%) 30 min
4a	93	83	5a	79	65
4b	92	78	5b	85	71
4c	92	80	5c	80	67
4d	95	73	5d	89	77
4e	97	25	5e	97	36
4f	99	35	5f	99	30
4g	94	22	5g	94	28
4h	94	31	5h	94	34
4i	93	83	5i	98	41

Different from the thiosemicarbazones, thiosemicarbazide preparation via the traditional methodology with toluene as the solvent under stirring at room temperature was more efficient than the microwave-assisted procedure, affording very good yields in comparison, especially for the alkyl isothiosemicarbazides. This performance may be due to the higher volatility of the alkyl isothiocyanates (**1e–i**). However, the reaction times using the microwave irradiation method were 30 minutes, whereas stirring at room temperature required 60 minutes. Table 2 lists the yields in the preparation of **5a–i**. The thiosemicarbazides were identified by comparison with analytical data found in the literature [23].

The preliminary *in vitro* antimicrobial activity of all thiosemicarbazones synthesized on *Aspergillus parasiticus* and *Candida albicans* was evaluated. The thiosemicarbazones showed weak or moderate activity as compared to the standard fungicide itroconazole. However, the observed antimicrobial effects do not exclude from further investigations of these compounds against other fungal strains. Table 3 lists the MIC ($\mu\text{g/mL}$) values obtained for active thiosemicarbazones.

Table 3. MIC ($\mu\text{g/mL}$) values of thiosemicarbazones against *C. albicans* and *A. parasiticus* isolates.

Compound	<i>C. albicans</i>	<i>A. parasiticus</i>	Compound	<i>C. albicans</i>	<i>A. parasiticus</i>
11	250	500	20	NI	500
13	250	500	21	250	500
14	500	NI	22	500	500
16	500	500	23	NI	500
17	NI	500	24	500	500
18	250	500	41	NI	500
19	500	500			

NI: no inhibition up to 500 $\mu\text{g/mL}$.

3. Experimental

3.1. General

Melting points were determined with a Meltemp II apparatus and were uncorrected. Infrared spectra (KBr pellets) were recorded on a Bruker Vertex 70 spectrophotometer. The ^1H - and ^{13}C -NMR spectra were obtained on a Bruker Avance II 400 spectrometer (^1H , 400 MHz; ^{13}C , 100 MHz) using tetramethylsilane TMS as the internal standard and acetone- d_6 and pyridine- d_5 as the solvent. Elemental analyses were performed on a Perkin-Elmer Model 2400 instrument. The microwave-assisted organic reactions were performed in a CEM Discovery System reactor.

3.2. General Procedure for the Preparation of Thiosemicarbazides **5a–i**

The thiosemicarbazides were prepared according to methods described elsewhere [23]. Briefly, the alkyl or aryl isothiocyanate (25 mmol) and hydrazine hydrate or phenyl hydrazine (25 mmol) were mixed in the presence of toluene (20 mL). The reaction mixture was kept under stirring for 1 hour at room temperature. The solid obtained was filtered and washed with ice-cold toluene. All thiosemicarbazides were identified by the comparison of analytical data (melting points and NMR) with literature reports.

3.3. General Procedure for the Preparation of Thiosemicarbazides 5a–i Using Microwave Irradiation

The alkyl or aryl isothiocyanate (0.74 mmol) and hydrazine hydrate or phenyl hydrazine (0.74 mmol) were mixed in the presence of toluene (2 mL) and submitted to microwave irradiation for 30 min at 100 W. The solid obtained was filtered and washed with ice-cold toluene. All thiosemicarbazides were identified by comparing their melting points with those previously obtained.

3.4. General Procedure for the Preparation of Thiosemicarbazones 7–42 Using Microwave Irradiation and Ethanol as Solvent

The aldehyde (0.84 mmol) and alkyl or aryl thiosemicarbazide (0.84 mmol) were mixed in the presence of ethanol (5 mL) and few drops of glacial acetic acid and submitted to microwave irradiation for 20–40 min at 100 W. The solid obtained was filtered and washed with ice-cold ethanol several times.

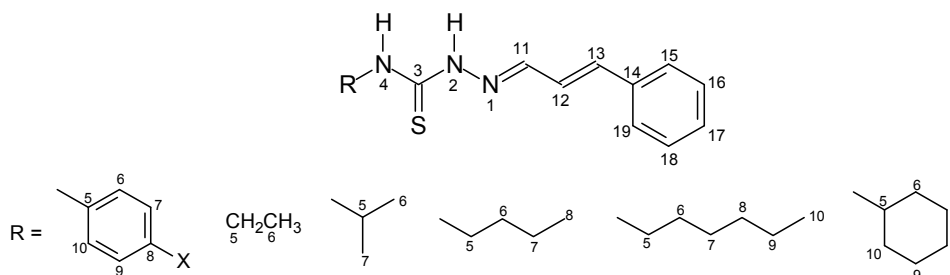
3.5. General Procedure for the Preparation of Thiosemicarbazones 7–42 Using Microwave Irradiation in Solvent-Free Conditions

The aldehyde (0.84 mmols) and alkyl or aryl thiosemicarbazide (0.84 mmols) were mixed in an agate mortar with few drops of glacial acetic acid and submitted to microwave irradiation for 3 min at 800 W. The solid obtained was extracted and recrystallized from ethanol to furnish the pure products.

3.6. General Procedure for the Preparation of Thiosemicarbazones 7–10 and 16–19 Using Traditional Reflux

The aldehyde (1.19 mmol) and aryl thiosemicarbazide (1.19 mmol) were mixed in the presence of ethanol (10 mL) and few drops of glacial acetic acid. The reaction mixture was kept under reflux for 8 hours. The solid obtained was filtered and washed with ice-cold ethanol several times.

Figure 1. Cinnamaldehyde series 7–15.



Cinnamaldehyde-4-phenyl-thiosemicarbazone (7). Yellow solid; m.p. 174–176 °C (lit. [18] 176 °C); yield 86%; FT-IR (KBr, ν cm⁻¹): 3,271 (N-H), 3,107 (N-H), 1,552 (C=C), 1,517 (C=N), 1,068 (C=S), 991 (C=C); ¹H-NMR (acetone-*d*₆) δ 11.80 (s, 1H, H-4), 9.93 (s, 1H, H-2), 7.98 (d, 1H, H-11), 7.60 (d, 2H, H-15 to 19), 7.56 (d, 2H, H-6, H-10), 7.39 (t, 2H, H-7 to 9), 7.30–7.35 (m, 1H, H-17), 7.30–7.35 (m, 2H, H-16, H-18), 7.16 (t, 1H, H-8), 7.06 (d, 1H, H-13), 6.94 (dd, 1H, H-12); ¹³C-NMR (acetone-*d*₆) δ 177.42 (C-3), 145.81 (C-11), 141.04 (C-17), 140.54 (C-5), 129.62 (C-6, C-10), 128.41 (C-7, C-9), 126.45 (C-8), 126.40 (C-13), 125.24 (C-12), 137.64 (C-14), 130.33 (C-15, C-19), 130.28 (C-16, C-18).

Cinnamaldehyde-4-(p-methyl-phenyl)-thiosemicarbazone (8). Yellow solid; m.p. 178–180 °C (lit. [19] 176 °C); yield 79%; FT-IR (KBr, ν cm⁻¹): 3,340 (N-H), 3,118 (N-H), 2,981 (C-H), 1,556 (C=C), 1,517 (C=N), 1,068 (C=S), 981 (C=C); ¹H-NMR (acetone-*d*₆) δ 11.85 (s, 1H, H-4), 9.84 (s, 1H, H-2), 7.96 (d, 1H, H-11), 7.55 (d, 2H, H-15, H-19), 7.44 (d, 2H, H-6, H-10), 7.12 (d, 2H, H-7, H-9), 7.32 (t, 1H, H-17), 7.39 (t, 2H, H-16, H-18), 7.05 (d, 1H, H-13), 6.94 (dd, 1H, H-12), 2.28 (s, 3H, CH₃); ¹³C-NMR (acetone-*d*₆) δ 175.41 (C-3), 144.77 (C-11), 139.14 (C-17), 136.35 (C-8), 135.90 (C-5), 134.18 (C-14), 128.89 (C-15, C-19), 128.55 (C-16, C-18), 126.91 (C-6, C-10), 125.12 (C-13), 124.74 (C-7, C-9), 20.52 (CH₃).

Cinnamaldehyde-4-(p-methoxy-phenyl)-thiosemicarbazone (9). Yellow solid; m.p. 152–154 °C (lit. [19] 155 °C); yield: 71%; FT-IR (KBr, ν cm⁻¹): 3,319 (N-H), 3,143 (N-H), 2,985 (C-H), 1,537 (C=C), 1,514 (C=N), 1,247 (C-O), 1,201 (O-CH₃), 1,026 (C=S), 964 (C=C); ¹H-NMR (acetone-*d*₆) δ 11.72 (s, 1H, H-4), 9.80 (s, 1H, H-2), 7.96 (d, 1H, H-11), 7.55 (d, 2H, H-15, H-19), 7.41 (d, 2H, H-6, H-10), 6.88 (d, 2H, H-7, H-9), 7.32 (t, 1H, H-17), 7.39 (t, 2H, H-16, H-18), 7.04 (d, 1H, H-13), 6.93 (dd, 1H, H-12), 3.74 (s, 3H, OCH₃); ¹³C-NMR (acetone-*d*₆) δ 177.95 (C-3), 158.86 (C-8), 145.60 (C-11), 140.81 (C-17), 137.72 (C-14), 133.45 (C-5), 126.57 (C-12), 127.37 (C-6, C-10), 127.26 (C-13), 130.30 (C-15, C-19), 128.41 (C-16, C-18), 114.82 (C-7, C-9), 56.25 (OCH₃).

Cinnamaldehyde-4-(p-nitro-phenyl)-thiosemicarbazone (10). Yellow solid; m.p. 198–199 °C; yield 88%; FT-IR (KBr, ν cm⁻¹): 3,263 (N-H), 3,149 (N-H), 1,598 (C=C), 1,562 (C=N), 1,332 (N=O), 1,207 (C=S), 970 (C=C), 850 (C-N); ¹H-NMR (acetone-*d*₆) δ 12.12 (s, 1H, H-4), 10.40 (s, 1H, H-2), 8.02 (d, 1H, H-11), 7.58 (d, 2H, H-15, H-19), 8.07 (d, 2H, H-6, H-10), 8.20 (d, 2H, H-7, H-9), 7.34 (t, 1H, H-17), 7.40 (t, 2H, H-16, H-18), 7.11 (d, 1H, H-13), 6.96 (dd, 1H, H-12); ¹³C-NMR (acetone-*d*₆) δ 176.88 (C-3), 146.93 (C-11), 146.64 (C-8), 145.36 (C-5), 141.98 (C-17), 137.57 (C-14), 130.58 (C-15, C-19), 130.36 (C-16, C-18), 128.53 (C-7, C-9), 126.21 (C-13), 125.35 (C-6, C-10), 124.00 (C-12). Anal. Calcd. for C₁₆H₁₄N₄O₂S (326.37); C, 58.88; H, 4.32; N, 17.17%. Found: C, 58.84; H, 4.39; N, 17.23%.

Cinnamaldehyde-4-ethyl-thiosemicarbazone (11). White solid; m.p. 166–168 °C; yield 54%; FT-IR (KBr, ν cm⁻¹): 3,315 (N-H), 3,134 (N-H), 3,001 (C-H), 1,554 (C=N), 1,523 (C=C), 1,085 (C=S), 977 (C=C); ¹H-NMR (acetone-*d*₆) δ 10.28 (s, 1H, H-2), 7.97 (s, 1H, H-4), 7.94 (d, 1H, H-11), 7.55 (d, 2H, H-15, H-19), 7.38 (t, 2H, H-16, H-18), 7.31 (t, 1H, H-17), 6.99 (d, 1H, H-13), 6.88 (dd, 1H, H-12), 3.69 (q, 2H, H-5), 1.21 (t, 3H, H-6); ¹³C-NMR (acetone-*d*₆) δ 178.57 (C-3), 144.51 (C-11), 140.31 (C-12), 137.05 (C-14), 130.28 (C-16, C-18), 130.19 (C-17), 129.01 (C-15, C-19), 125.31 (C-13), 39.42 (C-5), 14.20 (C-6). Anal. Calcd. for C₁₂H₁₅N₃S (233.33); C, 61.77; H, 6.48; N, 18.01%. Found: C, 61.83; H, 6.44; N, 18.11%.

Cinnamaldehyde-4-isopropyl-thiosemicarbazone (12). White solid; m.p. 195–196 °C; yield 83%; FT-IR (KBr, ν cm⁻¹): 3,296 (N-H), 3,126 (N-H), 2,993 (C-H), 1,556 (C=N), 1,546 (C=C), 1,072 (C=S), 974 (C=C); ¹H-NMR (acetone-*d*₆) δ 10.25 (s, 1H, H-2), 7.99 (s, 1H, H-4), 7.94 (d, 1H, H-11), 7.55 (d, 2H, H-15, H-19), 7.38 (t, 2H, H-16, H-18), 7.32 (t, 1H, H-17), 6.99 (d, 1H, H-13), 6.88 (dd, 1H, H-12), 6.64 (s, 1H, H-4), 4.56 (m, 1H, H-5), 1.26 (s, 3H, H-7), 1.25 (s, 3H, H-6); ¹³C-NMR (acetone-*d*₆) δ 177.62 (C-3), 144.59 (C-11), 139.72 (C-12), 137.11 (C-14), 129.67 (C-18), 129.65

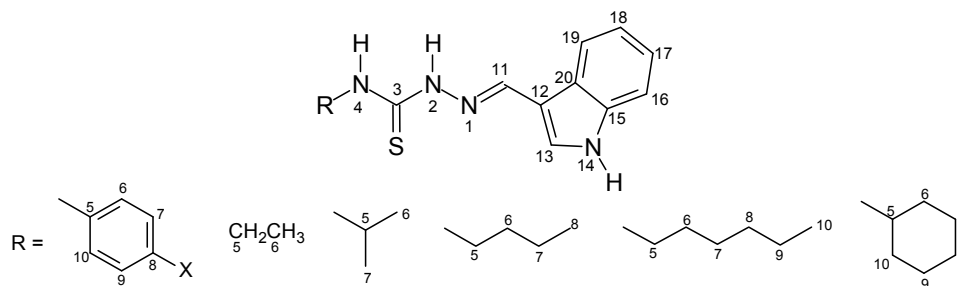
(C-16), 129.59 (C-17), 127.75 (C-15, C-19), 125.97 (C-13), 46.58 (C-5), 22.36 (C-6 to 7). Anal. Calcd. for $C_{13}H_{17}N_3S$ (247.36); C, 63.12; H, 6.93; N, 16.99%. Found: C, 63.16; H, 6.89; N, 17.04%.

Cinnamaldehyde-4-butyl-thiosemicarbazone (13). Yellow solid; m.p. 105–107 °C; yield 71%; FT-IR (KBr, ν cm^{-1}): 3,278 (N-H), 3,155 (N-H), 2,997 (C-H), 1,552 (C=N), 1,517 (C=C), 1,091 (C=S), 974 (C=C); 1H -NMR (acetone- d_6) δ 10.28 (s, 1H, H-2), 7.98 (s, 1H, H-4), 7.94 (d, 1H, H-11), 7.54 (d, 2H, H-15, H-19), 7.38 (t, 2H, H-16, H-18), 7.31 (t, 1H, H-17), 6.99 (d, 1H, H-13), 6.89 (dd, 1H, H-12), 3.65 (q, 2H, H-5), 1.63 (m, 2H, H-6), 1.37 (m, 2H, H-7), 0.93 (t, 3H, H-8); ^{13}C -NMR (acetone- d_6) δ 178.76 (C-3), 144.56 (C-11), 139.63 (C-12), 137.73 (C-19), 137.10 (C-14), 129.59 (C-17), 129.26 (C-16, C-18), 127.73 (C-15), 125.97 (C-13), 44.38 (C-5), 30.04 (C-6), 19.76 (C-7), 14.10 (C-8). Anal. Calcd. for $C_{14}H_{19}N_3S$ (261.38); C, 64.33; H, 7.33; N, 16.08%. Found: C, 64.28; H, 7.38; N, 7.39%.

Cinnamaldehyde-4-hexyl-thiosemicarbazone (14). Yellow solid; m.p. 95–97 °C; yield 70%; FT-IR (KBr, ν cm^{-1}): 3,346 (N-H), 3,132 (N-H), 2,927 (C-H), 1,560 (C=N), 1,527 (C=C), 1,099 (C=S), 972 (C=C); 1H -NMR (acetone- d_6) δ 10.28 (s, 1H, H-2), 7.97 (s, 1H, H-4), 7.94 (d, 1H, H-11), 7.54 (d, 2H, H-15, H-19), 7.38 (t, 2H, H-16, C-18), 7.31 (t, 1H, H-17), 6.99 (d, 1H, H-13), 6.89 (dd, 1H, H-12), 3.64 (q, 2H, H-5), 1.67 (m, 2H, H-6), 1.33 (m, 6H, H-7, H-9), 0.88 (t, 3H, H-10); ^{13}C -NMR (acetone- d_6) δ 178.74 (C-3), 144.55 (C-11), 139.62 (C-12), 137.10 (C-14), 129.67 (C-16, C-18), 129.61 (C-17), 127.72 (C-15, C-19), 125.96 (C-13), 44.68 (C-5), 32.26 (C-8), 29.87 (C-6), 27.22 (C-7), 22.20 (C-9), 17.27 (C-10). Anal. Calcd. for $C_{16}H_{23}N_3S$ (289.44); C, 66.40; H, 8.01; N, 14.52%. Found: C, 66.47; H, 7.94; N, 14.59%.

Cinnamaldehyde-4-cyclohexyl-thiosemicarbazone (15). White solid; m.p. 225–226 °C; yield 83%; FT-IR (KBr, ν cm^{-1}): 3,275 (N-H), 3,122 (N-H), 2,925 (C-H), 1,546 (C=N), 1,517 (C=C), 1,068 (C=S), 974 (C=C); 1H -NMR (pyridine- d_5) δ 12.58 (s, 1H, H-2), 8.38 (s, 1H, H-4), 8.10 (dd, 1H, H-11), 7.47 (d, 2H, H-15, H-19), 7.35 (t, 2H, H-16, H-18), 7.28 (t, 1H, H-17), 6.99 (d, 1H, H-13), 6.86 (dd, 1H, H-12), 4.75 (m, 1H, H-5), 1.64–1.04 (m, 10H, H-6 to H-10); ^{13}C -NMR (pyridine- d_5) δ 177.57 (C-3), 143.60 (C-11), 138.87 (C-12), 136.80 (C-14), 129.26 (C-16, C-18), 129.14 (C-17), 127.36 (C-15, C-19), 125.87 (C-13), 55.39 (C-5), 32.94 (C-6, C-10), 25.81 (C-8), 25.44 (C-7, C-9). Anal. Calcd. for $C_{16}H_{21}N_3S$ (287.42); C, 66.86; H, 7.36; N, 14.62%. Found: C, 66.81; H, 7.31; N, 14.71%.

Figure 2. Indole carboxaldehyde series 16–24.



Indole-3-carboxaldehyde-4-phenyl-thiosemicarbazone (16). Beige solid; m.p. 201–203 °C (lit. [20] 197–199 °C); yield: 62%; FT-IR (KBr, ν cm^{-1}): 3,410 (N-H), 3,317 (N-H), 3,314 (N-H), 1,554 (C=N), 1,105 (C=S); 1H -NMR (acetone- d_6) δ 11.60 (s, 2H, H-2, H-14), 9.61 (s, 1H, H-4), 8.40 (s, 1H, H-11),

8.23 (d, 1H, H-19), 7.90 (d, 1H, H-13), 7.63 (d, 2H, H-6, H-10), 7.42 (d, 1H, H-16), 7.37 (t, 2H, H-7, H-9), 7.20 (t, 1H, H-18), 7.14 (t, 1H, H-17); ^{13}C -NMR (acetone- d_6) δ 176.82 (C-3), 141.99 (C-11), 140.83 (C-15), 138.95 (C-5), 132.05 (C-13), 129.60 (C-6, C-10), 126.17 (C-8), 125.96 (C-20), 125.24 (C-7, C-9), 124.38 (C-17), 123.08 (C-18), 122.42 (C-19), 113.21 (C-12), 113.25 (C-16).

Indole-3-carboxaldehyde-4-(p-methyl-phenyl)-thiosemicarbazone (17). Beige solid; m.p. 198–199 °C (lit. [21] 200 °C); yield 93%; FT-IR (KBr, ν cm^{-1}): 3,404 (N-H), 3,309 (N-H), 3,165 (N-H), 2,920 (C-H), 1,544 (C=N), 1,197 (C=S); ^1H -NMR (acetone- d_6) δ 11.67 (s, 1H, H-14), 11.54 (s, 1H, H-2), 9.52 (s, 1H, H-4), 8.39 (s, 1H, H-11), 8.20 (d, 1H, H-19), 7.89 (d, 1H, H-13), 7.48 (d, 2H, H-6, H-10), 7.42 (d, 1H, H-16), 7.20 (t, 1H, H-18), 7.15 (d, 2H, H-7, H-9), 7.13 (t, 1H, H-17), 2.30 (s, 3H, CH_3); ^{13}C -NMR (acetone- d_6) δ 176.88 (C-3), 141.81 (C-11), 138.89 (C-15), 138.21 (C-8), 135.71 (C-5), 131.91 (C-13), 130.05 (C-6, C-10), 126.90 (C-20), 126.38 (C-7 to 9), 124.31 (C-17), 123.00 (C-18), 122.33 (C-19), 113.20 (C-16), 113.05 (C-12), 21.38 (CH_3).

Indole-3-carboxaldehyde-4-(p-methoxy-phenyl)-thiosemicarbazone (18). Beige solid; m.p. 202–203 °C (lit. [20] 207–209 °C); yield: 76%; FT-IR (KBr, ν cm^{-1}): 3,435 (N-H), 3,315 (N-H), 3,203 (N-H), 2,972 (C-H), 1,548 (C=N), 1,245 (C-O), 1,110 (C=S), 1,029 (O- CH_3); ^1H -NMR (acetone- d_6) δ 11.67 (s, 1H, H-14), 11.49 (s, 1H, H-2), 9.47 (s, 1H, H-4), 8.39 (s, 1H, H-11), 8.23 (d, 1H, H-19), 7.88 (d, 1H, H-13), 7.44 (d, 2H, H-6, H-10), 7.42 (d, 1H, H-16), 7.19 (t, 1H, H-18), 7.13 (t, 1H, H-17), 6.92 (d, 2H, H-7 to 9), 3.76 (s, 3H, OCH_3); ^{13}C -NMR (acetone- d_6) δ 177.37 (C-3), 158.77 (C-8), 141.78 (C-11), 138.97 (C-15), 133.80 (C-5), 131.90 (C-13), 127.52 (C-6, C-10), 126.00 (C-20), 124.37 (C-17), 123.16 (C-18), 122.37 (C-19), 114.79 (C-7, C-9), 113.24 (C16), 113.22 (C12), 58.25 (OCH_3).

Indole-3-carboxaldehyde-4-(p-nitro-phenyl)-thiosemicarbazone (19). Orange solid; m.p. 210–212 °C; Yield: 82%; FT-IR (KBr, ν cm^{-1}): 3,367 (N-H), 3,296 (N-H), 3,124 (N-H), 1,550 (C=N), 1,334 (N=O), 1,107 (C=S), 844 (C-N); ^1H -NMR (acetone- d_6) δ 11.97 (s, 1H, H-14), 11.74 (s, 1H, H-2), 10.08 (s, 1H, H-4), 8.44 (s, 1H, H-11), 8.23 (d, 2H, H-6, H-10), 8.18 (d, 1H, H-19), 8.09 (d, 2H, H-7, H-9), 7.95 (d, 1H, H-13), 7.43 (d, 1H, H-16), 7.21 (t, 1H, H-18), 7.15 (t, 1H, H-17); ^{13}C -NMR (acetone- d_6) δ 175.97 (C-3), 146.97 (C-8), 145.16 (C-5), 143.17 (C-11), 139.03 (C-15), 132.67 (C-13), 126.99 (C-20), 125.38 (C-7, C-9), 124.55 (C-17), 123.82 (C-6, C-10), 123.16 (C-18), 122.62 (C-19), 113.38 (C-6), 113.04 (C-12). Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}_2\text{S}$ (339.37); C, 56.63; H, 3.86; N, 20.64%. Found: C, 56.68; H, 3.91; N, 20.69%.

Indole-3-carboxaldehyde-4-ethyl-thiosemicarbazone (20). Beige solid; m.p. 226–228 °C [22]; yield: 73%; FT-IR (KBr, ν cm^{-1}): 3,352 (N-H), 3,238 (N-H), 3,184 (N-H), 2,972 (C-H), 1,546 (C=N), 1,109 (C=S); ^1H -NMR (pyridine- d_5) δ 12.83 (s, 1H, H-14), 12.29 (s, 1H, H-2), 8.76 (s, 1H, H-11), 8.62 (d, 1H, H-19), 8.51 (s, 1H, H-4), 7.89 (d, 1H, H-13), 7.57 (d, 1H, H-16), 7.32 (t, 1H, H-18), 7.23 (t, 1H, H-17), 3.99 (m, 2H, H-5), 1.26 (t, 3H, H-6); ^{13}C -NMR (pyridine- d_5) δ 178.10 (C-3), 140.32 (C-11), 138.37 (C-15), 130.85 (C-13), 125.35 (C-20), 123.36 (C-17), 122.44 (C-18), 121.20 (C-19), 112.63 (C-12), 112.45 (C-16), 39.32 (C-5), 15.15 (C-6).

Indole-3-carboxaldehyde-4-isopropyl-thiosemicarbazone (21). Beige solid; m.p. 156–158 °C (lit. [21] 160 °C); yield: 52%; FT-IR (KBr, ν cm^{-1}): 3,346 (N-H), 3,307 (N-H), 3,157 (N-H), 2,922 (C-H),

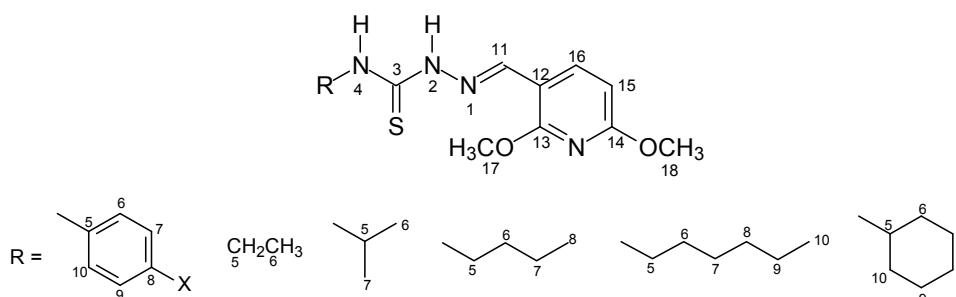
1,548 (C=N), 1,056 (C=S); $^1\text{H-NMR}$ (pyridine- d_5) δ 12.86 (s, 1H, H-14), 12.34 (s, 1H, H-2), 8.75 (s, 1H, H-11), 8.55 (d, 1H, H-19), 7.95 (s, 1H, H-4), 7.91 (d, 1H, H-13), 7.59 (d, 1H, H-16), 7.39 (t, 1H, H-18), 7.35 (t, 1H, H-17), 5.00 (m, 1H, H-5), 1.33 (s, 3H, H-6), 1.32 (s, 3H, H-7); $^{13}\text{C-NMR}$ (pyridine- d_5) δ 177.21 (C-3), 140.19 (C-11), 130.89 (C-13), 138.46 (C-15), 125.46 (C-20), 123.47 (C-17), 122.03 (C-18), 121.45 (C-19), 112.68 (C-16), 112.62 (C-12), 42.35 (C-5), 22.70 (C-6, C-7).

Indole-3-carboxaldehyde-4-butyl-thiosemicarbazone (22). Beige solid; m.p. 172–178 °C (lit. [21] 170 °C); yield: 78%; FT-IR (KBr, ν cm^{-1}): 3,410 (N-H), 3,365 (N-H), 3,138 (N-H), 2,954 (C-H), 1,537 (C=N), 1,105 (C=S); $^1\text{H-NMR}$ (pyridine- d_5) δ 12.84 (s, 1H, H-14), 12.34 (s, 1H, H-2), 8.77 (s, 1H, H-11), 8.64 (d, 1H, H-19), 8.45 (s, 1H, H-4), 7.90 (d, 1H, H-13), 7.34 (t, 1H, H-18), 7.58 (d, 1H, H-16), 7.28 (t, 1H, H-17), 3.97 (q, 2H, H-5), 1.71 (m, 2H, H-7), 1.36 (m, 2H, H-6), 0.84 (t, 3H, H-8); $^{13}\text{C-NMR}$ (pyridine- d_5) δ 178.31 (C-3), 140.29 (C-11), 130.94 (C-13), 138.45 (C-15), 125.41 (C-20), 123.44 (C-17), 122.45 (C-18), 121.29 (C-19), 112.71 (C-16), 112.56 (C-12), 44.26 (C-5), 32.05 (C-6), 20.43 (C-7), 14.01 (C-8).

Indole-3-carboxaldehyde-4-hexyl-thiosemicarbazone (23). Beige solid; m.p. 170–172 °C [22]; yield: 52%; FT-IR (KBr, ν cm^{-1}): 3354 (N-H), 3,259 (N-H), 3,195 (N-H), 2,925 (C-H), 1,544 (C=N), 1,105 (C=S); $^1\text{H-NMR}$ (pyridine- d_5) δ 12.84 (s, 1H, H-14), 12.34 (s, 1H, H-2), 8.77 (s, 1H, H-11), 8.65 (d, 1H, H-19), 8.47 (s, 1H, H-4), 7.90 (d, 1H, H-13), 7.58 (d, 1H, H-16), 7.34 (t, 1H, H-18), 7.29 (t, 1H, H-17), 3.99 (q, 2H, H-5), 1.75 (m, 2H, H-6), 1.35 (m, 2H, H-7), 1.21 (m, 4H, H-8, H-9), 0.8 (t, 3H, H-10); $^{13}\text{C-NMR}$ (pyridine- d_5) δ 178.25 (C-3), 140.30 (C-11), 138.42 (C-15), 130.96 (C-13), 125.36 (C-20), 123.42 (C-17), 122.43 (C-19), 121.25 (C-18), 112.68 (C-12), 112.53 (C-16), 44.54 (C-5), 31.75 (C-8), 29.60 (C-6), 26.95 (C-7), 22.85 (C-9), 14.06 (C-10).

Indole-3-carboxaldehyde-4-cyclohexyl-thiosemicarbazone (24). Beige solid; m.p. 203–205 °C; yield: 84%; FT-IR (KBr, ν cm^{-1}): 3,410 (N-H), 3,354 (N-H), 3,219 (N-H), 2,923 (C-H), 1544 (C=N), 1,105 (C=S); $^1\text{H-NMR}$ (pyridine- d_5) δ 12.88 (s, 1H, H-14), 12.39 (s, 1H, H-2), 8.75 (s, 1H, H-11), 8.60 (d, 1H, H-19), 8.03 (s, 1H, H-4), 7.92 (d, 1H, H-13), 7.60 (d, 1H, H-16), 7.44 (t, 1H, H-18), 7.37 (t, 1H, H-17), 4.77 (m, 1H, H-5), 1.65–1.10 (m, 10H, H-6 to H-10); $^{13}\text{C-NMR}$ (pyridine- d_5) δ 177.04 (C-3), 140.10 (C-11), 130.98 (C-13), 138.47 (C-15), 123.47 (C-17), 125.41 (C-20), 122.04 (C-18), 121.44 (C-19), 112.69 (C-16), 112.63 (C-12), 52.58 (C-5), 32.96 (C-6, C-10), 25.74 (C-7), 25.02 (C-7, C-9). Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{S}$ (300.42); C, 63.97; H, 6.71; N, 18.65%. Found: C, 63.94; H, 6.68; N, 18.71%.

Figure 3. 2,6-Dimethoxypyridinecarboxaldehyde series **25–33**.



2,6-Dimethoxypyridine-3-carboxaldehyde-4-phenylthiosemicarbazone (25). Yellow solid; m.p. 211–212 °C; yield: 82%; FT-IR (KBr, ν cm⁻¹): 3,307 (N-H), 3,128 (N-H), 2,978 (C-H), 1,595 (C=N), 1,326 (C-O), 1,205 (O-CH₃), 1,004 (C=S); ¹H-NMR (acetone-*d*₆) δ 11.77 (s, 1H, H-4), 10.06 (s, 1H, H-2), 8.58 (d, 1H, H-16), 8.32 (s, 1H, H-11), 7.53 (d, 2H, H-6, H-10), 7.35 (t, 2H, H-7, H-9), 7.19 (t, 1H, H-8), 6.45 (d, 1H, H-15), 3.95 (s, 3H, H-17), 3.90 (s, 3H, H-18); ¹³C-NMR (acetone-*d*₆) δ 175.52 (C-3), 163.64 (C-13), 160.53 (C-14), 139.08 (C-5), 138.62 (C-16), 137.31 (C-11), 127.95 (C-7, C-9), 125.70 (C-6, C-10), 125.14 (C-8), 108.34 (C-12), 102.39 (C-15), 53.52 (C-17), 53.47 (C-18). Anal. Calcd. for C₁₅H₁₆N₄O₂S (316.38); C, 56.95; H, 5.10; N, 17.71%. Found: C, 56.98; H, 5.06; N, 17.79%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-(p-methylphenyl)-thiosemicarbazone (26). Yellow solid; m.p. 187–188 °C; yield: 70%; FT-IR (KBr, ν cm⁻¹): 3,286 (N-H), 3,140 (N-H), 2,983 (C-H), 1,598 (C=N), 1,126 (C=S); ¹H-NMR (acetone-*d*₆) δ 11.72 (s, 1H, H-4), 9.99 (s, 1H, H-2), 8.58 (d, 1H, H-16), 8.31 (s, 1H, H-11), 7.38 (d, 2H, H-6, H-10), 7.14 (d, 2H, H-7, H-9), 6.45 (d, 1H, H-15), 3.94 (s, 3H, H-17), 3.90 (s, 3H, H-18), 2.49 (s, 3H, CH₃); ¹³C-NMR (acetone-*d*₆) δ 175.60 (C-3), 163.61 (C-13), 160.50 (C-14), 138.61 (C-16), 137.15 (C-11), 136.53 (C-8), 134.32 (C-5), 128.45 (C-6), 128.43 (C-10), 125.68 (C-7, C-9), 108.38 (C-12), 102.39 (C-15), 53.52 (C-17), 53.46 (C-18), 20.53 (CH₃). Anal. Calcd. for C₁₆H₁₈N₄O₂S (330.40); C, 58.16; H, 5.49; N, 16.96%. Found: C, 58.21; H, 5.44; N, 17.02%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-(p-methoxyphenyl)-thiosemicarbazone (27). Yellow solid; m.p. 189–190 °C; yield: 78%; FT-IR (KBr, ν cm⁻¹): 3,329 (N-H), 3,134 (N-H), 2,981 (C-H), 1,604 (C=N), 1,326 (C-O), 1,213 (O-CH₃), 1,114 (C=S); ¹H-NMR (acetone-*d*₆) δ 11.69 (s, 1H, H-4), 9.96 (s, 1H, H-2), 8.58 (d, 1H, H-16), 8.30 (s, 1H, H-11), 7.35 (d, 2H, H-6, H-10), 6.90 (t, 2H, H-7, H-9), 6.44 (d, 1H, H-15), 3.94 (s, 3H, H-17), 3.90 (s, 3H, H-18), 3.75 (s, 3H, OCH₃); ¹³C-NMR (acetone-*d*₆) δ 175.94 (C-3), 163.59 (C-13), 160.48 (C-14), 156.86 (C-8), 138.59 (C-16), 137.02 (C-11), 132.00 (C-5), 127.45 (C-6, C-10), 113.20 (C-7, C-9), 108.43 (C-12), 102.38 (C-15), 55.20 (OCH₃), 53.53 (C-17), 53.46 (C-18). Anal. Calcd. for C₁₆H₁₈N₄O₃S (346.40); C, 55.48; H, 5.24; N, 16.17%. Found: C, 55.41; H, 5.21; N, 16.23%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-(p-nitrophenyl)-thiosemicarbazone (28). Yellow solid; m.p. 209–211 °C; yield: 82%; FT-IR (KBr, ν cm⁻¹): 3,257 (N-H), 3,122 (N-H), 2,968 (C-H), 1,598 (C=N), 1,332 (N=O), 1,107 (C=S), 844 (C-N); ¹H-NMR (acetone-*d*₆) δ 12.12 (s, 1H, H-4), 10.37 (s, 1H, H-2), 8.56 (d, 1H, H-16), 8.37 (s, 1H, H-11), 8.21 (d, 2H, H-7, H-9), 8.04 (d, 2H, H-6, H-10), 6.49 (d, 1H, H-15), 3.95 (s, 3H, H-17), 3.90 (s, 3H, H-18); ¹³C-NMR (acetone-*d*₆) δ 174.71 (C-3), 163.92 (C-13), 160.79 (C-14), 145.41 (C-8), 143.32 (C-5), 138.69 (C-16), 138.62 (C-11), 124.17 (C-6, C-10), 123.64 (C-7, C-9), 107.99 (C-12), 102.52 (C-5), 53.58 (C-17), 53.54 (C-18). Anal. Calcd. for C₁₅H₁₅N₅O₄S (361.38); C, 49.86; H, 4.18; N, 19.38%. Found: C, 49.81; H, 4.23; N, 19.42%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-ethylthiosemicarbazone (29). White solid; m.p. 218–220 °C; yield: 99%; FT-IR (KBr, ν cm⁻¹): 3,276 (N-H), 3,138 (N-H), 2,976 (C-H), 1,604 (C=N), 1,380 (C-O), 1,236 (O-CH₃), 1,012 (C=S); ¹H-NMR (pyridine-*d*₅) δ 12.49 (s, 1H, H-2), 8.99 (s, 1H, H-4), 8.61 (s, 1H, H-11), 7.92 (d, 1H, H-16), 6.24 (d, 1H, H-15), 3.98 (m, 2H, H-5), 3.83 (s, 3H, H-17), 3.80 (s, 3H,

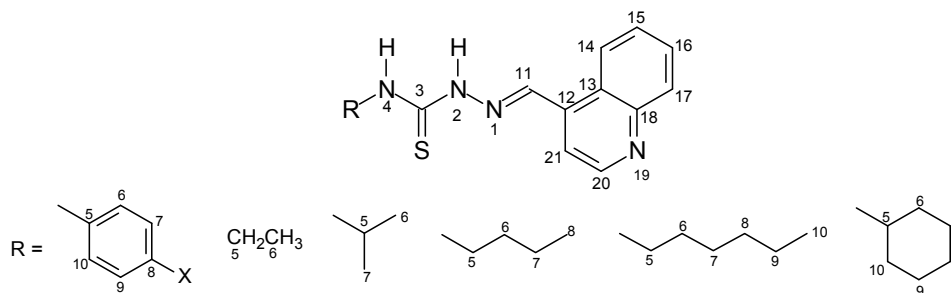
H-18), 1.28 (t, 3H, H-6); ^{13}C -NMR (pyridine- d_5) δ 178.48 (C-3), 164.21 (C-13), 161.15 (C-14), 137.49 (C-16), 137.17 (C-11), 109.01 (C-12), 102.99 (C-15), 53.55 (C-17), 53.51 (C-18), 39.36 (C-5), 15.06 (C-6). Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$ (268.33); C, 49.24; H, 6.01; N, 20.88%. Found: C, 49.28; H, 5.93; N, 20.92%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-isopropylthiosemicarbazone (30). White solid; m.p. 216–218 °C; yield: 99%; FT-IR (KBr, $\nu\text{ cm}^{-1}$): 3,315 (N-H), 3,151 (N-H), 2,970 (C-H), 1,597 (C=N), 1,325 (C-O), 1,240 (O-CH₃), 1,018 (C=S); ^1H -NMR (pyridine- d_5) δ 12.45 (s, 1H, H-2), 8.63 (s, 1H, H-11), 8.43 (s, 1H, H-4), 7.93 (d, 1H, H-16), 6.24 (d, 1H, H-15), 5.09 (m, 1H, H-5), 3.82 (s, 3H, H-17), 3.79 (s, 3H, H-18), 1.32 (s, 3H, H-6), 1.30 (s, 3H, H-7); ^{13}C -NMR (pyridine- d_5) δ 177.49 (C-3), 164.23 (C-13), 161.18 (C-14), 137.57 (C-16), 137.40 (C-11), 108.88 (C-12), 102.98 (C-15), 53.54 (C-17), 53.51 (C-18), 46.48 (C-5), 22.39 (C-6, C-7). Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ (282.36); C, 51.05; H, 6.43; N, 19.84%. Found: C, 51.12; H, 6.40; N, 19.89%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-butylthiosemicarbazone (31). White solid; m.p. 204–206 °C; yield: 94%; FT-IR (KBr, $\nu\text{ cm}^{-1}$): 3,334 (N-H), 3,132 (N-H), 2,987 (C-H), 1,604 (C=N), 1,332 (C-O), 1,215 (O-CH₃), 1,008 (C=S); ^1H -NMR (acetone- d_6) δ 10.28 (s, 1H, H-2), 8.29 (s, 1H, H-11), 8.21 (s, 1H, H-4), 6.36 (d, 1H, H-15), 3.98 (s, 3H, H-17), 3.93 (s, 3H, H-18), 3.65 (q, 2H, H-5), 1.91 (m, 2H, H-7), 1.80 (m, 2H, H-6), 0.92 (t, 3H, H-8); ^{13}C -NMR (acetone- d_6) δ 178.84 (C-3), 167.93 (C-13), 160.83 (C-14), 141.43 (C-16), 137.29 (C-11), 109.45 (C-12), 104.42 (C-15), 53.92 (C-16, C-18), 44.39 (C-5), 32.17 (C-6), 20.67 (C-7), 14.14 (C-8). Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$ (296.39); C, 52.68; H, 6.80; N, 19.90%. Found: C, 52.72; H, 6.76; N, 19.96%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-hexylthiosemicarbazone (32). Yellow solid; m.p. 130–132 °C; yield: 88%; FT-IR (KBr, $\nu\text{ cm}^{-1}$): 3,309 (N-H), 3,126 (N-H), 2,952 (C-H), 1,602 (C=N), 1,328 (C-O), 1,238 (O-CH₃), 1,012 (C=S); ^1H -NMR (acetone- d_6) δ 10.28 (s, 1H, H-2), 8.87 (t, 3H, H-10), 8.29 (s, 1H, H-11), 8.25 (s, 1H, H-4), 8.21 (d, 1H, H-16), 6.36 (d, 1H, H-15), 3.97 (s, 3H, H-17), 3.93 (s, 3H, H-18), 3.64 (q, 2H, H-5), 1.65 (m, 2H, H-6), 1.32 (m, 6H, H-7 to H-9); ^{13}C -NMR (acetone- d_6) δ 178.79 (C-3), 164.96 (C-14), 161.81 (C-13), 138.37 (C-16), 137.26 (C-11), 109.49 (C-12), 103.42 (C-15), 53.92 (C-17, C-18), 44.68 (C-5), 32.39 (C-8), 32.22 (C-9), 29.97 (C-6), 27.24 (C-7), 14.27 (C-10). Anal. Calcd. for $\text{C}_{15}\text{H}_{24}\text{N}_4\text{O}_2\text{S}$ (324.44); C, 55.53; H, 7.46; N, 17.27%. Found: C, 55.57; H, 7.42; N, 17.34%.

2,6-Dimethoxypyridine-3-carboxaldehyde-4-cyclohexylthiosemicarbazone (33). Yellow solid; m.p. 241–243 °C; yield: 97%; FT-IR (KBr, $\nu\text{ cm}^{-1}$): 3,332 (N-H), 3,113 (N-H), 2,978 (C-H), 1,602 (C=N), 1,328 (C-O), 1,222 (O-CH₃), 1,014 (C=S); ^1H -NMR (pyridine- d_5) δ 12.49 (s, 1H, H-2), 8.63 (s, 1H, H-11), 8.37 (s, 1H, H-4), 8.01 (d, 1H, H-16), 6.29 (d, 1H, H-15), 4.79 (m, 1H, H-5), 3.83 (s, 3H, H-18), 3.80 (s, 3H, H-17), 1.62–0.99 (m, 10H, H-6 to H-10); ^{13}C -NMR (pyridine- d_5) δ 177.40 (C-3), 164.27 (C-13), 161.21 (C-14), 137.41 (C-11), 137.70 (C-16), 108.90 (C-12), 103.04 (C-15), 53.56 (C-17), 53.53 (C-18), 53.49 (C-5), 32.88 (C-6, C-10), 25.76 (C-8), 25.48 (C-7, C-9). Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ (322.43); C, 55.88; H, 6.88; N, 17.38%. Found: C, 55.94; H, 6.82; N, 17.42%.

Figure 4. 4-Quinolinecarboxaldehyde series **34–42**.

Quinoline-4-carboxaldehyde-4-phenylthiosemicarbazone (34). Yellow solid; m.p. 195–198 °C (lit. [24] 200 °C); yield: 77%; FT-IR (KBr, ν cm⁻¹): 3,338 (N-H), 3,132 (N-H), 1,525 (C=N), 1,195 (C=S); ¹H-NMR (pyridine-*d*₅) δ 13.28 (s, 1H, H-2), 11.02 (s, 1H, H-4), 9.09 (s, 1H, H-11), 8.38 (d, 1H, H-14), 8.34 (d, 1H, H-17), 8.06 (d, 2H, H-6, H-10), 7.73 (t, 1H, H-16), 7.72 (d, 1H, H-20), 7.54 (t, 1H, H-15), 7.41 (t, 2H, H-7, H-9), 7.22 (t, 1H, H-8), 8.39 (d, 1H, H-19); ¹³C-NMR (pyridine-*d*₅) δ 178.16 (C-3), 150.39 (C-19), 149.49 (C-18), 140.04 (C-5), 137.79 (C-11), 137.77 (C-12), 130.85 (C-16), 129.74 (C-4), 128.79 (C-9), 128.78 (C-7), 127.52 (C-15), 125.98 (C-6, C-10), 125.95 (C-8), 125.92 (C-13), 123.79 (C-17), 118.53 (C-20).

Quinoline-4-carboxaldehyde-4-(*p*-methylphenyl)-thiosemicarbazone (35). Yellow solid; m.p. 203–205 °C; yield: 84%; FT-IR (KBr, ν cm⁻¹): 3,319 (N-H), 3,211 (N-H), 2,985 (C-H), 1,544 (C=N), 1,188 (C=S); ¹H-NMR (pyridine-*d*₅) δ 13.22 (s, 1H, H-2), 11.00 (s, 1H, H-4), 9.09 (s, 1H, H-11), 8.39 (d, 1H, H-19), 8.38 (d, 1H, H-14), 8.34 (d, 1H, H-17), 7.91 (d, 1H, H-6), 7.88 (d, 1H, H-10), 7.73 (t, 1H, H-16), 7.72 (d, 1H, H-20), 7.54 (t, 1H, H-15), 7.03 (d, 2H, H-7, H-9), 2.19 (s, 1H, H-20); ¹³C-NMR (pyridine-*d*₅) δ 178.68 (C-3), 150.39 (C-19), 149.51 (C-18), 137.86 (C-8), 137.63 (C-11), 137.46 (C-12), 132.96 (C-5), 130.85 (C-16), 129.74 (C-14), 129.37 (C-6, C-10), 127.97 (C-7), 127.50 (C-15), 126.10 (C-9), 125.94 (C-13), 123.79 (C-17), 118.47 (C-20), 20.87 (CH₃). Anal. Calcd. for C₁₈H₁₆N₄S (320.41); C, 67.48; H, 5.03; N, 17.49%. Found: C, 67.44; H, 4.98; N, 17.54%.

Quinoline-4-carboxaldehyde-4-(*p*-methoxyphenyl)-thiosemicarbazone (36). Yellow solid; m.p. 186–189 °C; yield: 57%; FT-IR (KBr, ν cm⁻¹): 3,309 (N-H), 3,201 (N-H), 2,929 (C-H), 1,550 (C=N), 1,247 (C-O), 1,184 (C=S), 1,035 (O-CH₃); ¹H-NMR (pyridine-*d*₅) δ 13.23 (s, 1H, H-2), 11.02 (s, 1H, H-4), 9.10 (s, 1H, H-11), 8.87 (d, 1H, H-19), 8.39 (d, 4H, H-14, OCH₃), 8.34 (d, 1H, H-17), 7.88 (d, 2H, H-7, H-9), 7.72 (d, 1H, H-20), 7.71 (t, 1H, H-16), 7.53 (t, 1H, H-15), 7.01 (d, 2H, H-6, H-10); ¹³C-NMR (pyridine-*d*₅) δ 178.73 (C-3), 158.12 (C-8), 150.43 (C-19), 149.54 (C-18), 137.90 (C-12), 137.60 (C-11), 132.97 (C-5), 130.89 (C-16), 129.79 (C-14), 128.05 (C-6, C-10), 127.57 (C-15), 126.00 (C-13), 123.52 (C-17), 118.28 (C-20), 114.13 (C-7, C-9), 55.37 (OCH₃). Anal. Calcd. for C₁₈H₁₆N₄OS (336.41); C, 64.27; H, 4.79; N, 16.65%. Found: C, 64.32; H, 4.76; N, 16.72%.

Quinoline-4-carboxaldehyde-4-(*p*-nitrophenyl)-thiosemicarbazone (37). Yellow solid; m.p. 220–223 °C; yield: 79%; FT-IR (KBr, ν cm⁻¹): 3,296 (N-H), 3,082 (N-H), 1,552 (C=N), 1,330 (N=O), 1,193 (C=S), 852 (C-N); ¹H-NMR (pyridine-*d*₅) δ 13.65 (s, 1H, H-2), 11.35 (s, 1H, H-4), 9.13 (s, 1H, H-11), 8.87 (d, 1H, H-19), 8.38 (d, 2H, H-7, H-14), 8.34 (d, 2H, H-9, H-17), 8.26 (d, 1H, H-10), 8.06 (d, 1H, H-6),

7.73 (t, 1H, H-16), 7.65 (d, 1H, H-20), 7.58 (t, 1H, H-15); ^{13}C -NMR (pyridine- d_5) δ 177.67 (C-3), 150.39 (C-19), 149.51 (C-18), 146.03 (C-8), 138.97 (C-11), 137.46 (C-12), 130.92 (C-16), 129.83 (C-14), 127.64 (C-15), 125.92 (C-13), 124.73 (C-7, C-10), 124.36 (C-6, C-9), 123.80 (C-17), 118.66 (C-20). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_2\text{S}$ (351.38); C, 58.11; H, 3.73; N, 19.93%. Found: C, 58.19; H, 3.68; N, 20.01%.

Quinoline-4-carboxaldehyde-4-ethylthiosemicarbazone (38). Yellow solid; m.p. 175–177 °C; yield: 70%; FT-IR (KBr, ν cm^{-1}): 3,373 (N-H), 3,149 (N-H), 2,958 (C-H), 1,533 (C=N), 1,230 (C=S); ^1H -NMR (pyridine- d_5) δ 12.86 (s, 1H, H-2), 9.31 (s, 1H, H-4), 9.01 (s, 1H, H-11), 8.84 (d, 1H, H-19), 8.35 (d, 1H, H-14), 8.32 (d, 1H, H-17), 7.69 (t, 1H, H-16), 7.66 (d, 1H, H-20), 7.50 (t, 1H, H-15), 4.01 (m, 2H, H-5), 1.32 (t, 3H, H-6); ^{13}C -NMR (pyridine- d_5) δ 179.08 (C-3), 150.34 (C-19), 149.50 (C-18), 138.04 (C-12), 136.94 (C-11), 130.82 (C-16), 129.68 (C-14), 127.41 (C-15), 125.91 (C-13), 123.47 (C-7), 118.22 (C-20), 39.62 (C-5), 14.83 (C-6). Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{S}$ (258.34); C, 60.44; H, 5.46; N, 21.69%. Found: C, 60.47; H, 5.41; N, 21.73%.

Quinoline-4-carboxaldehyde-4-isopropylthiosemicarbazone (39). White solid; m.p. 193–195 °C; yield: 75%; FT-IR (KBr, ν cm^{-1}): 3,303 (N-H), 3,136 (N-H), 2,976 (C-H), 1,541 (C=N), 1,236 (C=S); ^1H -NMR (pyridine- d_5) δ 12.86 (s, 1H, H-2), 9.28 (s, 1H, H-4), 8.99 (s, 1H, H-11), 8.83 (d, 1H, H-19), 8.72 (s, 1H, H-4), 8.32 (d, 2H, H-14, H-17), 7.70 (t, 1H, H-16), 7.63 (d, 1H, H-20), 7.54 (t, 1H, H-15), 5.09 (m, 1H, H-5), 1.37 (d, 3H, H-7), 1.35 (d, 3H, H-6); ^{13}C -NMR (pyridine- d_5) δ 178.15 (C-3), 150.37 (C-18), 149.48 (C-19), 137.97 (C-12), 137.04 (C-11), 130.87 (C-16), 129.69 (C-14), 127.44 (C-15), 125.91 (C-13), 123.42 (C-7), 118.28 (C-20), 46.84 (C-5), 22.23 (C-6, C-7). Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{S}$ (272.37); C, 61.74; H, 5.92; N, 20.57%. Found: C, 61.77; H, 5.87; N, 20.64%.

Quinoline-4-carboxaldehyde-4-butylthiosemicarbazone (40). Yellow solid; m.p. 104–108 °C; yield: 81%; FT-IR (KBr, ν cm^{-1}): 3,379 (N-H), 3,205 (N-H), 2,927 (C-H), 1,529 (C=N), 1,211 (C=S); ^1H -NMR (pyridine- d_5) δ 12.89 (s, 1H, H-2), 9.26 (s, 1H, H-4), 9.01 (s, 1H, H-11), 8.86 (d, 1H, H-19), 8.38 (d, 1H, H-14), 8.33 (d, 1H, H-17), 7.70 (t, 1H, H-16), 7.69 (d, 1H, H-20), 7.50 (t, 1H, H-15), 4.00 (m, 2H, H-5), 1.79 (m, 2H, H-7), 1.37 (m, 2H, H-6), 0.85 (t, 2H, H-8); ^{13}C -NMR (pyridine- d_5) δ 179.24 (C-3), 150.36 (C-19), 149.50 (C-18), 138.05 (C-12), 137.02 (C-11), 130.82 (C-16), 129.69 (C-14), 127.41 (C-15), 125.88 (C-13), 123.55 (C-17), 118.35 (C-20), 44.56 (C-5), 31.75 (C-6), 20.41 (C-7), 14.00 (C-8). Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{S}$ (286.39); C, 62.91; H, 6.33; N, 19.56%. Found: C, 62.97; H, 6.28; N, 19.61%.

Quinoline-4-carboxaldehyde-4-hexylthiosemicarbazone (41). Yellow solid; m.p. 158–160 °C; yield: 57%; FT-IR (KBr, ν cm^{-1}): 3,271 (N-H), 3,153 (N-H), 2,927 (C-H), 1,543 (C=N), 1,224 (C=S); ^1H -NMR (pyridine- d_5) δ 12.89 (s, 1H, H-2), 9.27 (s, 1H, H-4), 9.00 (s, 1H, H-11), 8.85 (d, 1H, H-19), 8.38 (d, 1H, H-14), 8.32 (d, 1H, H-17), 7.70 (t, 1H, H-16), 7.69 (d, 1H, H-20), 7.52 (t, 1H, H-15), 4.00 (q, 2H, H-5), 1.82 (m, 2H, H-6), 1.35 (m, 2H, H-7), 1.20 (m, 4H, H-8, H-9), 0.78 (t, 3H, H-10); ^{13}C -NMR (pyridine- d_5) δ 179.28 (C-3), 150.41 (C-19), 149.56 (C-18), 137.10 (C-11), 138.08 (C-12), 130.89 (C-16), 129.73 (C-14), 127.46 (C-15), 125.93 (C-13), 123.60 (C-17), 118.42 (C-20), 44.95 (C-5), 31.80 (C-8), 26.98 (C-7), 22.86 (C-9), 29.70 (C-6), 14.18 (C-10). Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{S}$ (314.45); C, 64.93; H, 7.05; N, 17.82%. Found: C, 65.02; H, 6.98; N, 17.89%.

Quinoline-4-carboxaldehyde-4-cyclohexylthiosemicarbazone (**42**). Yellow solid; m.p. 208–210 °C; yield: 62%; FT-IR (KBr, ν cm^{-1}): 3,255 (N-H), 3,174 (N-H), 2,925 (C-H), 1,527 (C=N), 1,207 (C=S); ^1H -NMR (pyridine- d_5) δ 12.86 (s, 1H, H-2), 9.26 (s, 1H, H4), 8.98 (s, 1H, H-11), 8.90 (d, 1H, H-19), 8.62 (s, 1H, H-4), 8.38 (d, 1H, H-14), 8.34 (d, 1H, H-17), 7.70 (d, 1H, H-20), 7.69 (t, 1H, H-16), 7.56 (t, 1H, H-15), 3.85 (m, 1H, H-5), 1.66–1.04 (m, 10H, H-6 to H-10); ^{13}C -NMR (pyridine- d_5) δ 178.05 (C-3), 150.43 (C-19), 149.51 (C-18), 137.95 (C-11), 137.21 (C-12), 130.88 (C-16), 129.72 (C-14), 127.47 (C-15), 125.87 (C-13), 123.55 (C-17), 118.54 (C-20), 53.73 (C-5), 32.64 (C-6, C-10), 35.39 (C-9), 25.74 (C-8), 25.39 (C-7). Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{S}$ (312.43); C, 65.35; H, 4.45; N, 17.93%. Found: C, 65.41; H, 4.38; N, 18.02%.

3.7. Antifungal Activity

Determination of antifungal activity was performed as described in the M27-A2 document of Clinical and Laboratory Standards Institute (CLSI, 2002) for the yeast *Candida albicans* (ATCC 24433) and M38-A for the filamentous fungus *Aspergillus parasiticus* CMT 0334 provided by Mycological Collection of *Trichocomaceae* at IOC/FIOCRUZ-RJ, Brazil. Briefly, the broth microdilution method was performed by 96-well microtiter assay plate containing RPMI 1640 medium (Invitrogen, USA) at pH 7.0 buffered with MOPS 0.16 M. The 36 thiosemicarbazones were diluted in DMSO: Tween 20 (1:1 v/v) to obtain final concentrations ranging from 3.90 to 500 $\mu\text{g/mL}$ and maximum concentration of organic solvent at 2.5%. Next, the yeast *C. albicans* and conidia of *A. parasiticus* suspensions were inoculated into the appropriate well at a final concentration of $0.5\text{--}2.5 \times 10^3$ CFU mL^{-1} and $0.4\text{--}5.0 \times 10^4$ CFU mL^{-1} , respectively. The minimum inhibitory concentration (MIC) of each drug was determined visually after incubation at 35 °C for 48 h. The lowest concentration inhibiting growth of the organism was recorded as the MIC. Itraconazole (ITC, Sigma Chemical Co., St Louis, MO, USA) was used as reference compound. Each experiment was performed in triplicate.

4. Conclusions

In summary, four series of thiosemicarbazones derived from cinnamaldehyde, 3-indole-carboxaldehyde, 2,6-dimethoxypyridinecarboxaldehyde and 4-quinolinecarboxaldehyde and the corresponding thiosemicarbazides were prepared using microwave-assisted reactions in the presence of ethanol as solvent and under solvent free conditions, resulting in good yields, high purity and lower reaction times in comparison with the traditional reflux method, especially when solvent free conditions were utilized.

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Conflict of Interest

The authors declare that no conflicts of interest exist in this work.

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Sample Availability: Samples of the compounds are available from the authors.

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